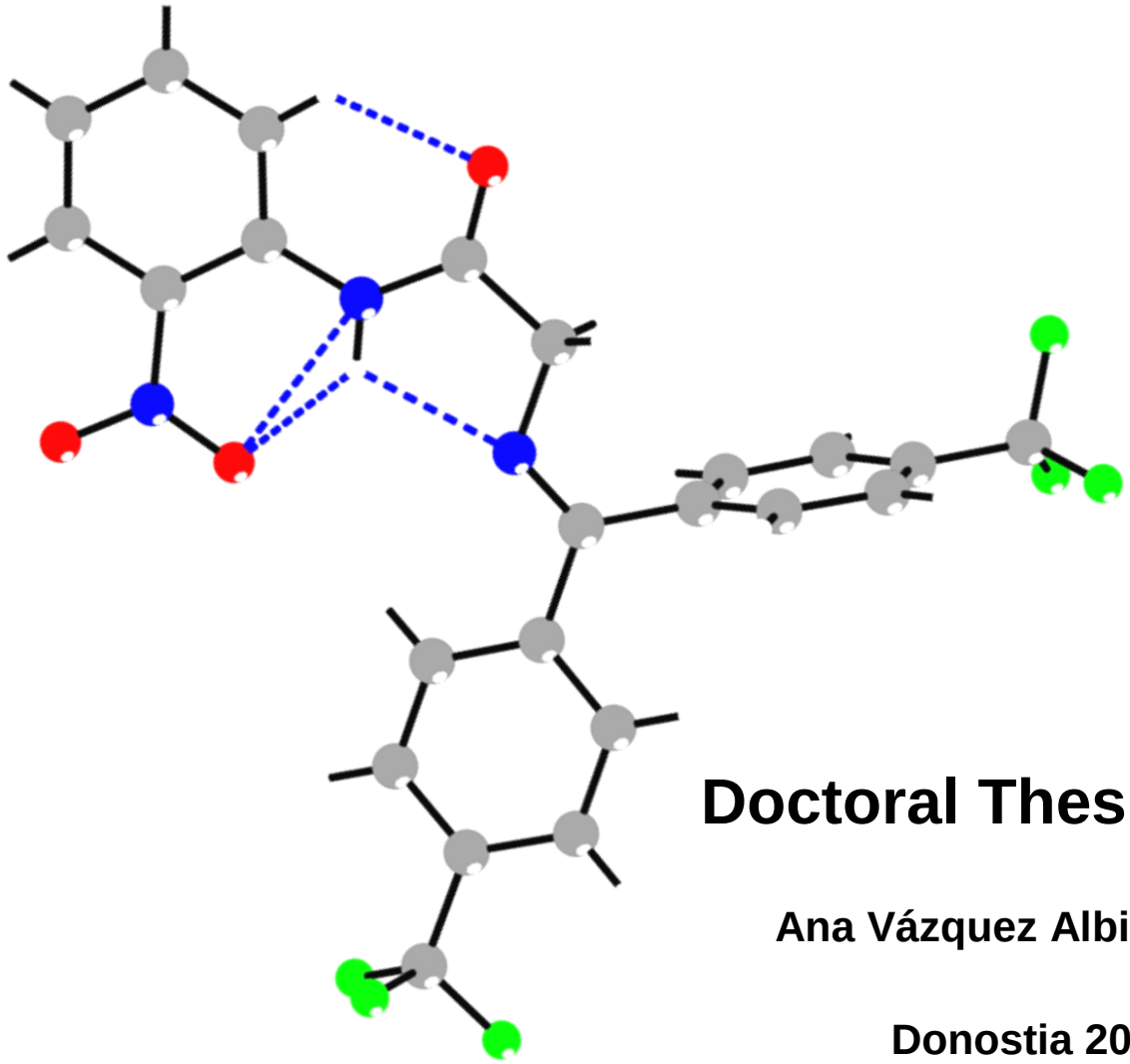
eman ta zabal zazu

Universidad del País Vasco

Euskal Herriko Unibertsitatea

Asymmetric Catalytic Approach to α-Functionalized Amides



Doctoral Thesis

Ana Vázquez Albisu

Donostia 2020

AUTORIZACIÓN DEL DEPARTAMENTO

El Consejo del Departamento de Química Orgánica I en reunión celebrada el día 24 de enero de 2020 ha acordado dar la conformidad a la admisión a trámite de presentación de la Tesis Doctoral titulada: Asymmetric Catalytic Approach to α-Functionalized Amides, dirigida por el Dr Claudio Palomo Nicolau y la Dra Mª Antonia Mielgo Vicente y presentada por Doña. Ana Vázquez Albisu ante este Departamento.

En Vitoria-Gasteiz a 24 de enero de 2020

VºBº DIRECTOR DEL DEPARTAMENTO SECRETARIA DEL DEPARTAMENTO

Fdo.: Francisco Palacios Gambra Fdo.: Ana Mª Ochoa de Retana Mendibil

Eskerrak

Esta Tesis Doctoral ha sido realizada en el Departamento de Química Orgánica I de la Facultad de Ciencias Químicas de Donostia de la Universidad del País Vasco (UPV/EHU), bajo la dirección del Dr. Claudio Palomo y la Dra. Mª Antonia Mielgo, a quienes expreso mi gratitud por haberme dado la oportunidad de incorporarme a este grupo de investigación y por la formación tan completa y de calidad que me habéis ofrecido. Por otro lado, querría agradecer a Aitor por su implicación, interés y apoyo en la última etapa de mi tesis. Debo agradecer, además, la financiación de este trabajo, que ha provenido de una beca predoctoral del Gobierno Vasco.

My sincere thanks go to Dr. Gilles Guichard for giving me the opportunity to realize a four-month stay in the Institut Européen de Chimie et Biologie (IECB) in Pessac (Bordeaux). I would also like to thank Diane for all the French lessons before my departure, for all your help, support and motivation. I am also thankful to Stéphanie, Christophe and Céline for helping with all the chemistry with the oligoureas, and all the funny moments we have had. I am also deeply thankful to the other members of the lab.

Bihotzez eskertu nahi diet laborategian nirekin egon direnei. Bertan emandako lehen pausoetan gidatu eta laguntzegatik, zure dinamismo eta laguntasunagatik, eskerrik asko Eider. Iurre eta Sandrarekin batera ere lan egitea gozada bat izan da niretzako. Mon ami Julien, Donostian zein Burdeosen zure profesionaltasuna, eskuzabaltasuna eta laguntasuna bihotzez eskertzen ditut. Laborategitik pasatakoekin eta daudenekin igarotako uneak (sagardotegiak, hondartza, taper bazkariak, juergak eta Potesera egindako ihesaldia), zuen alaitasun eta humoreak eguneroko erronkei aurre egiten lagundu didate. Aigor, Laino eta Olaf, nire familia bihurtu zarete urte hauetan eta elkarrekin sortutako laguntasun honek aurrera jarraitzea espero dut. Nutrizio, muskulito, one piece, karretera, industrialdea, konpetenzia, TIC, BOPV, telenovela eta txamanen inguruan asko irakatsi didazue, eta horregatik ez ahaztu Ordizian lagun on bat duzuela.

Kuadrilla eta familiari eskerrik asko nire kezkak, urduritasunak eta bildurrak kontatzean aurrera jarraitzeko animoak eman eta hitz egokiak aukeratzeagatik. Fakultatetik irten naizen bakoitzean eta zuekin elkartzean, nire errealitatea erabat aldatu eta bizitzan benetan garrantzitsuena dena zer den ikustarazi didazue, nire zailtasun profesionalak ahaztuz. Aita, aunque lleves toda la vida haciéndote un lio con mis estudios y no consigas aclararte, tengo la suerte de poder decir que siempre tendré una familia que me apoyará en todas las decisiones que tome y que estará a mi lado cuando lo necesite. Inguruan ditudan emakume guztiei eredugarri zaretela esan nahi dizuet. Hala ere, nire bizitzako erreferenterik onena, entzule eta sostengua bizitzako arlo guztietan, nire ama da. Bidean aurkitutako oztopo eta erronka guztiei aurre egiteko gai naizela eta borrokatzeko indarra soberan dudala ikustarazteagatik, eskerrik asko. Azkenik, urte guzti hauetan eta bereziki etapa aldapatsu honetan jaso dudan goxotasun, pazientzia eta maitasun guzti hori eskertu nahi dizkizut, bihotza.

Summary

The objective of this PhD Thesis has been the introduction of two novel pronucleophiles (Figure A) for catalytic reactions under Brønsted base (BB) catalysis: 4-substituted pyrrolidin-2,3-diones (A) and *o*-nitroanilides (B).

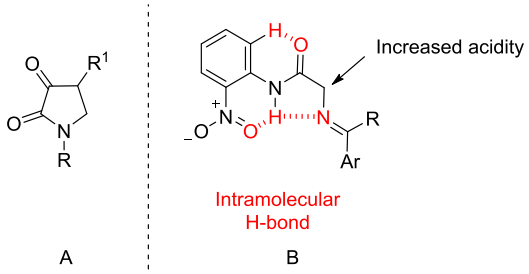
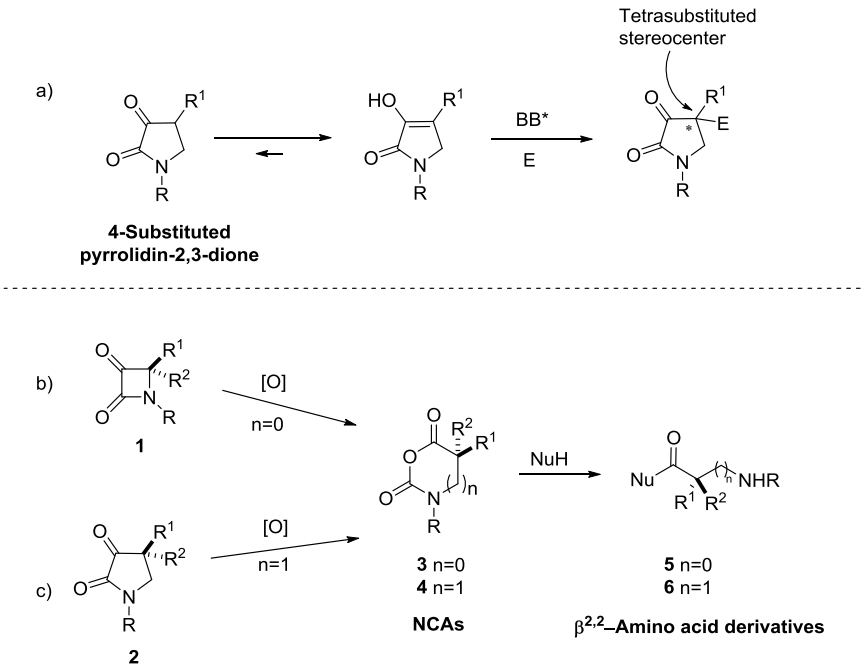


Figure A. Novel pronucleophiles developed in this Thesis: 4-Substituted pyrrolidin-2,3-diones A, and b) Schiff bases of glycine *o*-nitroanilide B.

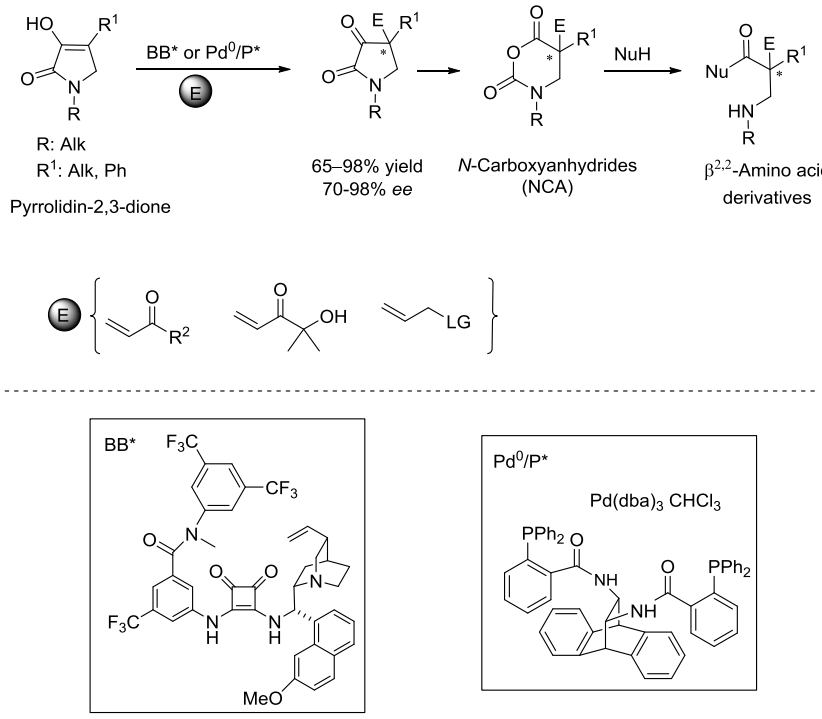
4-Substituted pyrrolidin-2,3-diones (A, Figure A) exhibit two important features which render them efficient substrates for BB catalysis. Firstly, they are enolized to a large extent, what facilitates deprotonation by soft bases and subsequent reaction with an electrophile under catalytic conditions (a, Scheme A.). And, secondly, the rigidity of their cyclic structure, provides an efficient platform for stereocontrol during the C-C bond forming step.

Given the precedents from this laboratory for the synthesis of amino acid *N*-carboxyanhydrides (NCAs) **3** containing a quaternary stereocenter starting from disubstituted β-lactams **1** (b, Scheme A), it has been proven that the same methodology can be applied to pyrrolidin-2,3-diones **2** (c, Scheme A). These *N*-carboxyanhydrides constitute very attractive intermediates as the structure offers simultaneously both, *N*-protection and carbonyl activation. Subsequent ring-opening of **4** by a nucleophile affords $\beta^{2,2}$-amino acid derivatives with different functionalities at the newly created stereocenter.



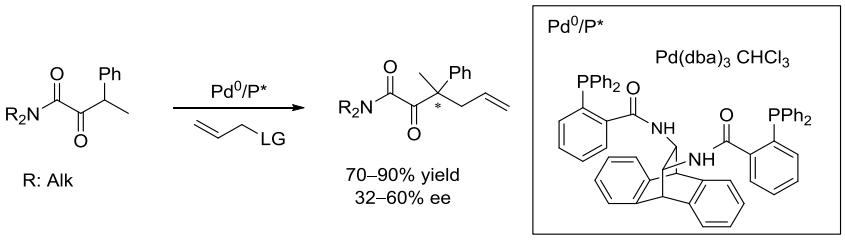
Scheme A. a) Enolization of 4-substituted pyrrolidin-2,3-diones and their reaction with an electrophile under BB catalysis. b) Previous work from the group with disubstituted β-lactams **1**. c) Our approach for the synthesis of $\beta^{2,2}$-amino acid derivatives with 4,4-disubstituted pyrrolidin-2,3-diones **2**.

These heterocycles had never been used in asymmetric catalysis in spite of their biological and pharmaceutical interest, but in this thesis they have been employed in different organocatalytic and metal-catalyzed asymmetric allylic alkylation reactions with high efficiency and stereoselectivity, in the presence of bifunctional chiral Brønsted base catalysts (BB*) or palladium chiral phosphine (Pd^0/P*) catalytic systems with generation of a tetrasubstituted stereocenter (Scheme B). More specifically, the use of pyrrolidin-2,3-diones as Michael donors in BB-catalyzed conjugate additions to α-oxy enones and vinyl ketones and Pd-catalyzed asymmetric α-allyation has been explored and it has been observed that the reactions proceed well in terms of reactivity and enantioselectivity, and as it has been mentioned, their transformation into NCAs followed by ring opening, provides $\beta^{2,2}$-amino acid derivatives. This protocol represents a new catalytic approach to $\beta^{2,2}$-amino acids, that allows for the first time their direct coupling with nucleophiles.



Scheme B. Our approach to acces β^{22}-amino acid derivatives through asymmetric catalytic processes, followed by ring expansion (NCA) and subsequent ring opening by a nucleophile.

Given the good results in the asymmetric allylic alkylation with cyclic α-substituted ketoamides, we then focused our interest on the allylation of the more challenging acyclic α-ketoamides to generate tetrasubstituted stereocenters. The Pd-catalyzed AAA worked efficiently with acyclic ketoamides, but the enantioselectivity values were not as high as with pyrrolidin-2,3-diones (Scheme C).

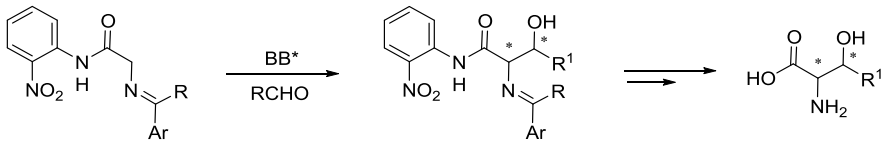


Scheme C. Pd-Catalyzed AAA of acyclic α-ketoamides.

With the previously mentioned strategy, β^{22}-amino acid derivatives can be obtained, including highly functionalized amides, whose direct catalytic access is challenging. Other strategy to afford α-functionalized amides is the introduction of activating groups into the structure that enhance the acidity of the α-carbon. Therefore,

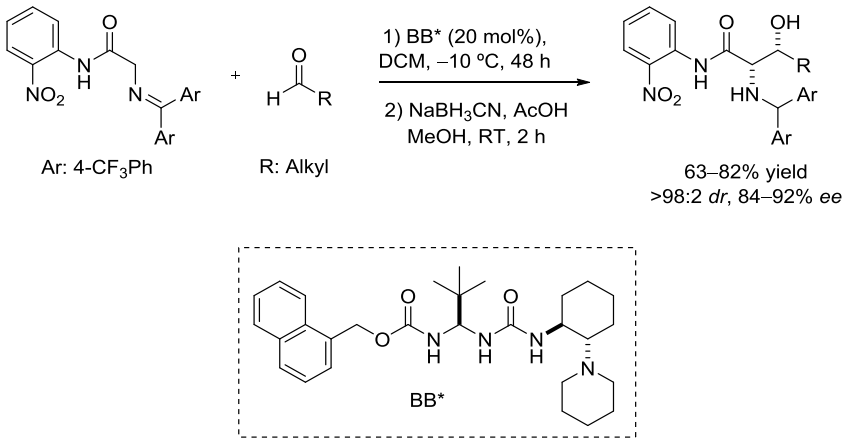
based on the literature precedents that make use of intramolecular hydrogen bonds that lower the pK_a (higher acidity) of the α-carbon, we designed Schiff bases of glycine *o*-nitroanilide (B, Figure A) as efficient reagents for bifunctional Brønsted base promoted stereoselective aldol reactions.

In this design, we expected that the presence of the *o*-nitroanilide framework, which provides an efficient hydrogen-bonding platform, would result in higher acidity of the α-carbon and, efficient stereoselectivity control. Furthermore, after simple modifications, the *o*-nitroanilide moiety should be easily displaced by different nucleophiles thus providing and efficient entry to peptide derivatives and other interesting building blocks (Scheme D).



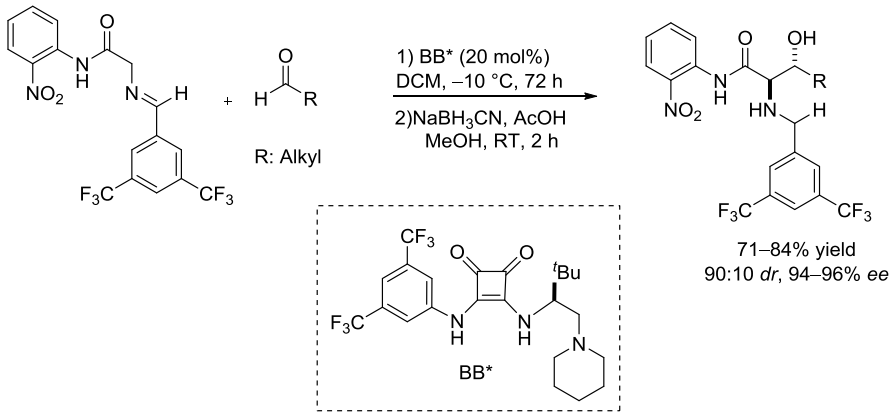
Scheme D. BB-Catalyzed aldol reaction of *o*-nitroanilides and subsequent transformation into α-amino β-hydroxy acids.

With the newly designed *o*-nitroanilide, their aldol reaction in which two contiguous tertiary stereocenters are generated has been studied. The optimal conditions were found using the new ureidopeptide type catalyst as depicted in Scheme E, and after reductive work-up, the adducts were isolated as their corresponding *syn* aminoalcohols in good yields and excellent stereoselectivity.



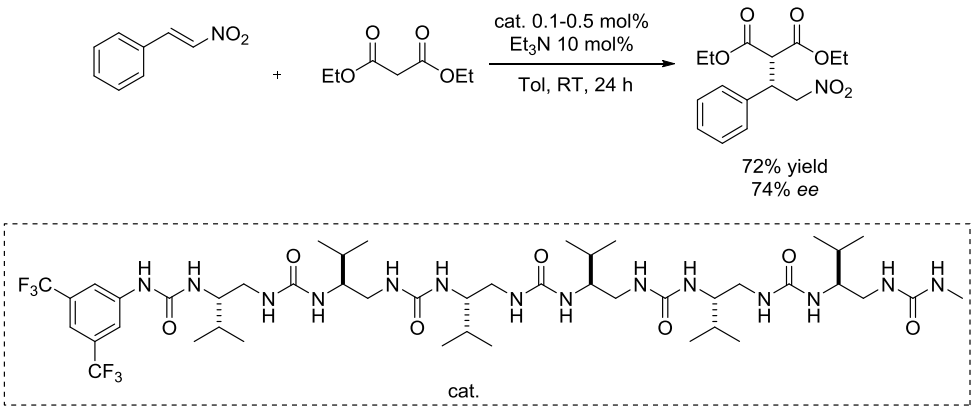
Scheme E. *syn*-Selective BB-catalyzed aldol reaction of ketimines of glycine nitroanilides.

In addition, the equivalent aldimines have also been explored in the aldol reaction and in contrast to ketimines, a squaramide-based organocatalyst afforded the reaction *anti*- adducts with the highest diastereo- and enantioselectivity (Scheme F).



Scheme F. *anti*-Selective BB-catalyzed aldol reaction of aldimines of glycine nitroanilides.

Finally, under the supervision of Prof. Gilles Gichard in the European Institute of Chemistry and Biology (IECB) at Bordeaux-Pessac campus in the Peptidomimetic Chemistry Group, synthesis of different chain-length valine-based oligoureas and their evaluation as H-bonding chiral organocatalysts in the well-known Michael addition of diethyl malonate to nitrostyrene has been performed (Scheme G). It has been observed that the hexamer containing valine residues promotes the reaction with highest enantioselectivity, comparing to shorter chain oligoureas. However, this result does not improve the ones previously obtained in the group with the oligourea bearing the valine-alanine-leucine sequence.



Scheme G. Conjugate addition of diethyl malonate to nitrostyrene promoted by valine-based oligoureas.

Resumen

El objetivo de la presente Tesis Doctoral ha sido introducir dos nuevos pronucleófilos (Figura A) para reacciones catalíticas promovidas por bases de Brønsted (BB): Las pirrolidin-2,3-dionas 4-sustituídas A y *o*-nitroanilidas de tipo B, basados en su alta reactividad, debido a distintos factores, tal y como se muestra a continuación.

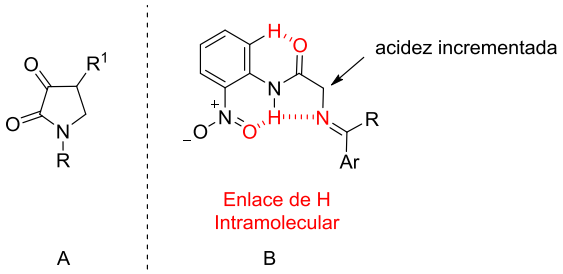
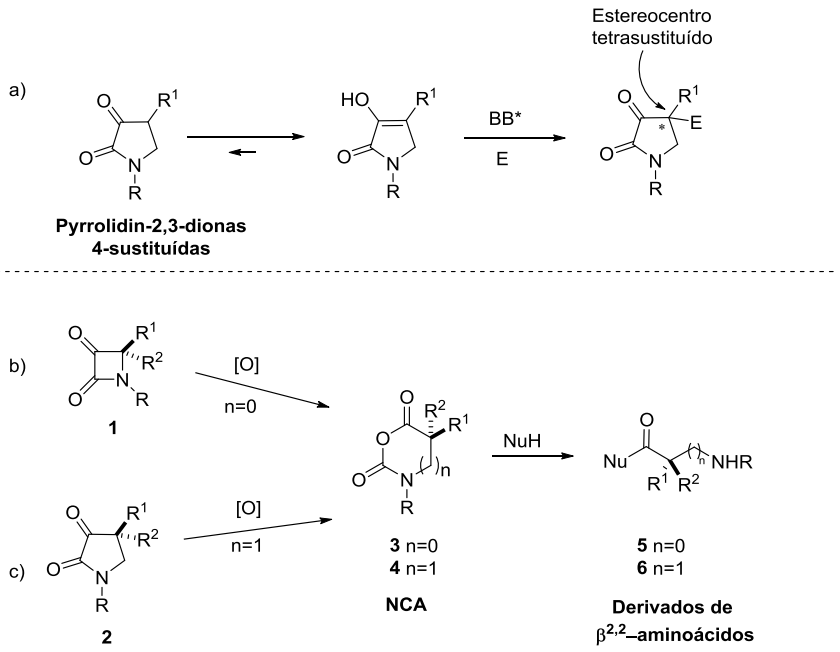


Figura A. Nuevos pronucleófilos desarrollados en esta Tesis: Pirrolidin-2,3-dionas 4-sustituídas (A), y *o*-nitroanilidas (B).

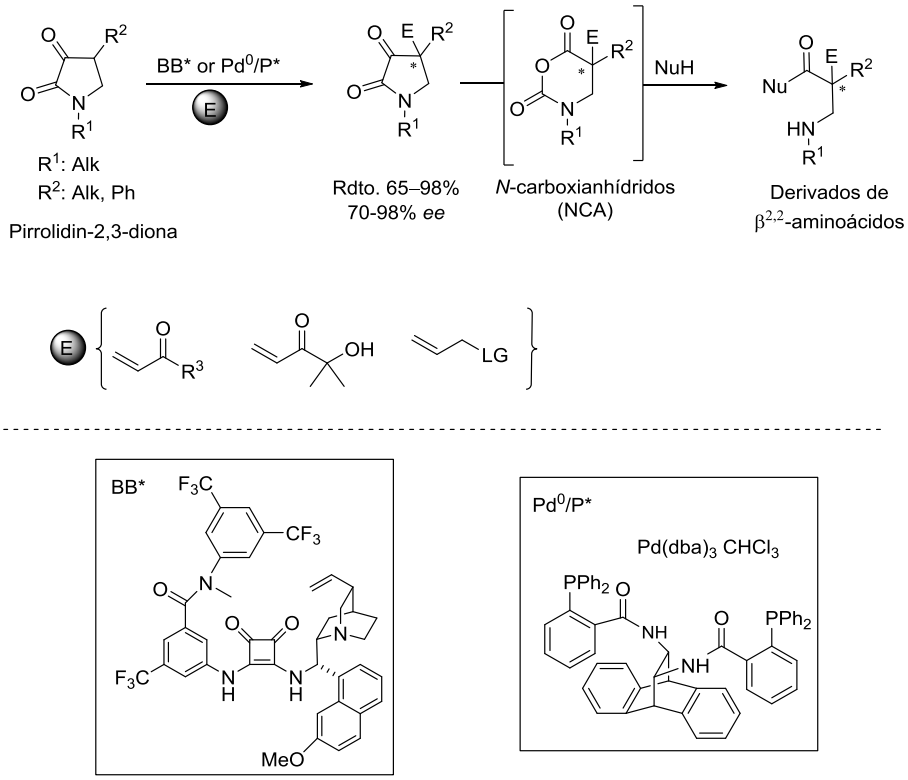
Las pirrolidin-2,3-dionas 4-sustituídas (A, Figura) tienen distintas características que las hacen eficientes para catálisis por BB. Por un lado, están enolizadas, lo que facilita su desprotonación por bases débiles y la reacción posterior con un electrófilo en condiciones catalíticas (a, Esquema A). Además, debido a la rigidez de su estructura cíclica, el estereocontrol durante la formación del enlace C-C está favorecido.

Basándonos en los precedents de nuestro grupo de investigación sobre la síntesis de *N*-carboxyanhídridos de tipo **3** con un centro stereogénico tetrasustituído, a partir de β-lactamas disustituídas **1** (b, Esquema A), se ha aplicado la misma metodología a las pirrolidin-2,3-dionas **2** (c, Esquema A). Estos *N*-carboxyanhídridos constituyen intermedios de gran interés, debido a que su estructura ofrece simultáneamente protección de la amina y activación del carbonilo. La posterior apertura del ciclo por un nucleófilo, genera derivados de $\beta^{2,2}$-aminoácidos con distintas funcionalidades en el estereocentro creado.



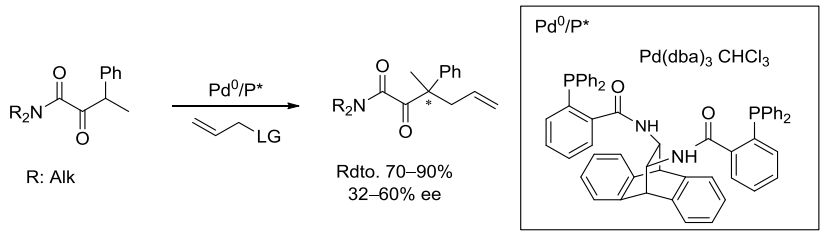
Esquema A. a) Enolización de las pirrolidin-2,3-dionas 4-sustituídas y su reacción con electrófilos bajo catálisis por BB. b) Trabajo previo del grupo con β-lactamas disustituídas **1**. c) Nuestra aproximación a derivados de $\beta^{2,2}$-aminoácidos partiendo de pirrolidin-2,3-dionas 4,4-disustituídas **2**.

En la presente Tesis Doctoral, se ha demostrado que las pirrolidin-2,3-dionas, que no se habían empleado previamente en catálisis asimétrica a pesar del interés biológico y farmacéutico que presentan, pueden ser utilizadas en distintas reacciones de adición conjugada organocatalíticas y en la alquilación alílica asimétrica, promovida por catálisis metálica con buen rendimiento y estereoselectividad (Scheme A). Dichas reacciones han sido catalizadas por bases bifuncionales de Brønsted quirales (BB*) y por el sistema catalítico de complejos de paladio y fosfina quiral (Pd^0/P*), con generación de un estereocentro tetrasustituído. Más específicamente, se han estudiado las pirrolidin-2,3-dionas como dadores de Michael en la adición organocatalítica y enantioselectiva a α-oxy enonas y a vinil cetonas promovida por bases de Brønsted bifuncionales y la alquilación alílica asimétrica catalizada por paladio (Pd-AAA). Los aductos obtenidos por medio de las reacciones mencionadas, además de ser estructuras de interés biológico, son también precursores de $\beta^{2,2}$-aminoácidos (Esquema B). Más específicamente, su transformación a NCAs por expansión de anillo, seguido de apertura del mismo por distintos nucleófilos, da lugar a derivados de $\beta^{2,2}$-aminoácidos. Esta metodología supone una nueva estrategia catalítica para acceder a $\beta^{2,2}$-aminoácidos.



Esquema B. Nuestra estrategia para accede a derivados de β^{22}-aminoácidos por preocesos asimétricos cataíticos, seguido de expansion de anillo (NCA) y posterior apertura del ciclo por un nucleófilo.

Debido a los buenos resultados obtenidos en la AAA con cetoamidas cíclicas α-sustituídas, se propuso estudiar la misma reacción con las cetoamidas acíclicas α-sustituídas, para generar estereocentros tetrasustituídos en sistemas menos rígidos. La reacción transcurrió eficientemente con las cetoamidas acíclicas, pero los niveles de enantioselectividad no fueron tan altos como con las cetoamidas cíclicas (Esquema C).

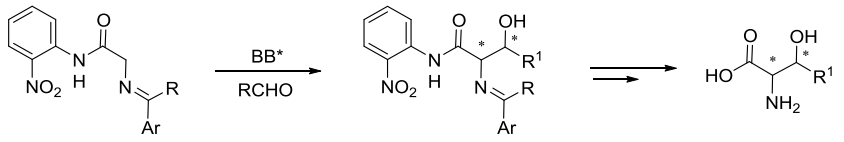


Esquema C. Alquílación alílica asimétrica de α-cetoamidas acíclicas promovida por Pd.

Tal y como se ha mencionado anteriormente, otra estrategia para acceder a amidas α-funcionalizadas, es la incorporación de grupos activantes en la estructura, de manera que aumente la acidez del carbono en alfa. Así, basándonos en los precedentes de la

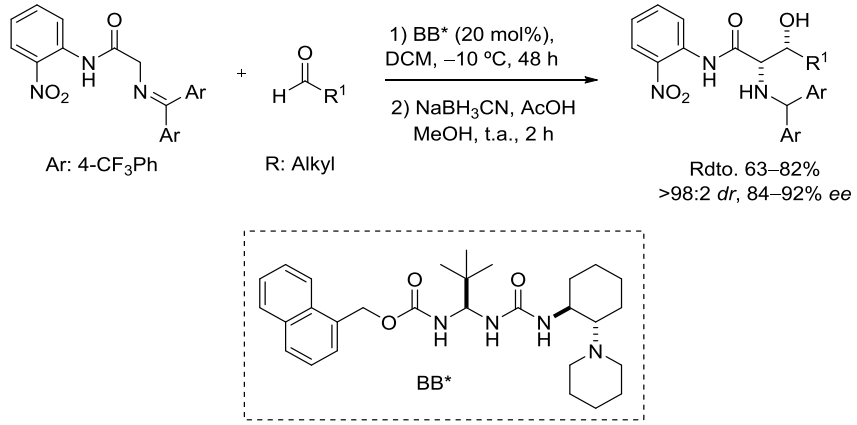
bibliografía que hacen uso de enlaces de hidrógeno intramoleculares para aumentar la acidez (bajando el valor de pK_a), se diseñaron bases de Schiff de la glicina (B, Figura A) como pronucleófilos en la reacción aldólica promovida por bases bifuncionales de Brønsted.

En este diseño, se predijo que la presencia de la unidad *o*-nitroanilida, la cual contribuye a un sistema eficiente de enlaces de hidrógeno, daría lugar a una mayor acidez del carbono en alfa y a un mayor estereocontrol, actuando como un auxiliar. Además, tras simples transformaciones, la unidad *o*-nitroanilida, debería desprenderse por medio de distintos nucleófilos, dando lugar a derivados de péptidos y estructuras de interés sintético (Esquema D).



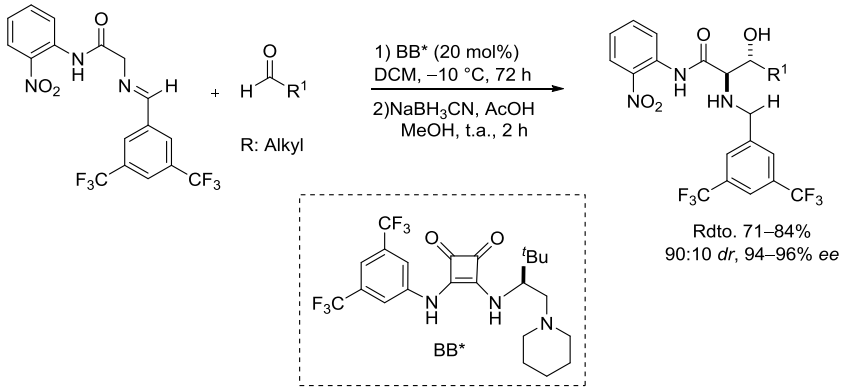
Esquema D. Reacción aldólica de *o*-nitroanilidas promovida por BB y posterior transformación a α-amino β-hidroxiácidos.

Así, se ha estudiado la reacción aldólica de las *o*-nitroanilidas en la que se generan dos estereocentros terciarios adyacentes. Las condiciones óptimas de reacción con las cetiminas se consiguieron con el ureidopéptido mostrado en el Esquema E, siendo mayoritario el diastereoisómero *sin*. Tras la reacción aldólica, se aislaron los aductos de reacción en forma de amino alcoholes, tras aminación reductora con buen rendimiento y estereoselectividad.



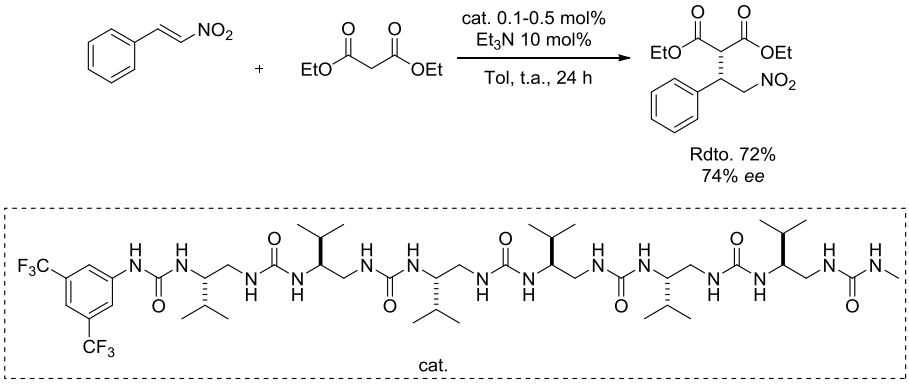
Esquema E. Reacción aldólica *sin*-selectiva de cetiminas de la glicina promovida por BB.

En paralelo, también se ha estudiado la reacción aldólica de las aldiminas equivalentes, y al contrario que con las cetiminas, el catalizador bifuncional de tipo escuaramida mostrado en el Esquema F, dio lugar mayoritariamente a aductos *anti* con altos niveles de diastero- y enantioselectividad.



Esquema F. Reacción aldólica *anti*-selectiva de aldiminas de la glicina promovida por BB.

Por último, bajo supervisión del Prof. Gilles Guichard en el Instituto Europeo de Química y Biología (IECB) en el Departamento de Química Peptidomimética del campus de Burdeos-Pessac, se ha llevado a cabo la síntesis de oligoureas formadas de distintos número de residuos de valina y se han evaluado como organocatalizadores quirales de enlace de hidrógeno en la conocida adición conjugada de dietil malonato al nitroestireno (Esquema G). En este estudio, se ha observado que la oligourea de seis unidades de valina promueve la reacción con mayor rendimiento y estereoselectividad. Sin embargo, esta oligourea no llega a los niveles de enantioselectividad obtenidos por el grupo con el hexámero formado por unidades de valina-alanina-leucina.



Esquema G. Adición conjugada de dietíl malonato a nitroestireno promovida por la oligourea derivada de la valina.

Abbreviations and acronyms

Standard abbreviations and acronyms have been used as recommended in "Guidelines for authors" (J. Org. Chem., January 2017). Additionally, the following abbreviations and acronyms have been employed:

Alk	Alkyl
B	Base
BA	Brønsted Acid
BB	Brønsted Base
BHT	2,6-Di-*tert*-butyl-4-methylphenol
Cat.	Catalyst
Conv.	Conversion
CSA	Camphorsulphonic acid
DIAD	Diisopropyl azodicarboxylate
DIPEA	Diisopropylethylamine
DMBA	Dimethoxybenzyl
DMP	Dimethoxypropane
DSC	*N*, *N*'-Disuccinimidyl dicarbonate
E	*Electrophile*
EDC HCl	*N*-(3-Dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride
ee	Enantiomeric excess
EWG	Electron withdrawing group
HATU	O-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N*,*N*-tetramethyluroniumhexafluorophosphate
HOBT	1-Hydroxybenzotriazole
IBCF	Isobutyl chloroformate
KHMDS	Potassium bis(trimethylsilyl)amide
LG	Leaving group
LiHMDS	Lithium bis(trimethylsilyl)amide
MS	Molecular sieves
NaHMDS	Sodium bis(trimethylsilyl)amide
Napht	Naphtyl
ND	Not determined
NMM	*N*-methyl morpholine
n.r.	No reaction
o-	ortho-
ORTEP	Oak ridge thermal ellipsoid plot
p-	para-

PMP	p-methoxyphenyl
PTC	Phase transfer catalysis
Rac	Racemic
RAMP	(*R*)-1-amino-2-methoxymethylpyrrolidine
Ref.	Reference
SAMP	(*S*)-1-amino-2-methoxymethylpyrrolidine
TBTU	2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
Tol	Toluene
Val	Valine

INDEX

Chapter 1

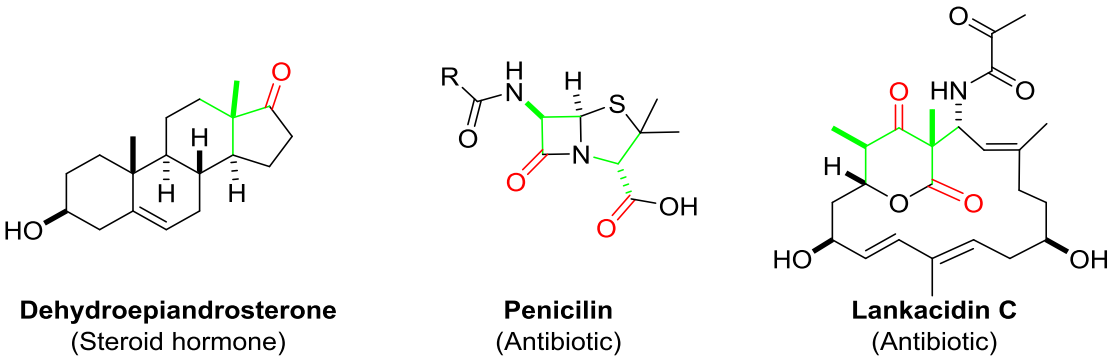
Introduction

1. Introduction

1.1. α-Functionalized carbonyl compounds

1.1.1. Relevance of α-functionalized carbonyl compounds.

Many biologically active compounds contain a stereogenic center attached to a carbonyl unit (Figure 1),[1] a feature that makes enantiopure molecules bearing this structure of great interest. Historically, the best way to obtain biologically active enantiomerically pure compounds has been to isolate them from natural sources. However, due to the limitation of natural sources, great efforts have been made in synthesis, in order to develop new and more efficient protocols to obtain enantiomerically enriched compounds.



Dehydroepiandrosterone
(Steroid hormone)

Penicilin
(Antibiotic)

Lankacidin C
(Antibiotic)

Figure 1. Biologically active compounds containing α-functionalized carbonyl units.

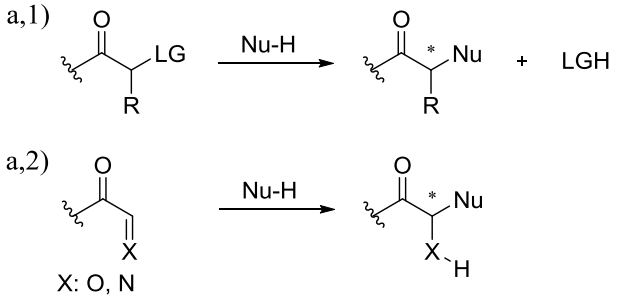
Two main strategies can be considered for the introduction of a stereogenic center at the α-position of a carbonyl compound (Scheme 1). The first consists on the employment of a carbonyl compound as an electrophile (a, Scheme 1). In this context, one possibility involves the nucleophilic α-substitution on a carbonyl compound bearing a leaving group at the alpha position (a1, Scheme 1). A second approach involves the addition of a nucleophile to a C= X double bond (X: O, N) placed at the α-position of the carbonyl group in a 1,2-dicarbonyl or equivalent compound (a2, Scheme 1) .

Another approach is the use of carbonyl compounds as nucleophiles (b, Scheme 1). In this case, the reaction occurs between an electrophile and an enolate anion or equivalent, generated from an enolizable carbonyl compound. In this context, two

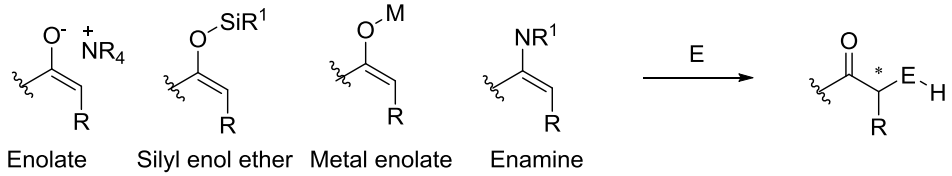
[1] Dehydroepiandrosterone: a) D. Freilich, S. Ferris, M. Wallace, L. Leach, A. Kallen, J. Frincke, C. Ahlem, M. Hacker, D. Nelson, J. Hebert, *Am. J. Trop. Med. Hyg*. **2000**, *63*, 280-283. Penicilin: b) A. Fleming, *Br. J. Exp. Pathol.* **1929**, *10*, 226-236. Lankacidin c) C: K. Ootsu, T. Matsumoto, S. Harada, T. Kishi, *Cancer Chemoteraphy Reports* **1975**, *59*, 919-928.

possibilities exist. Indirect methods in which preformation of the enolate (or silyl enol ether) is carried out, or direct methods in which the enolate (or equivalent) is generated *in situ*. This methodology is very versatile among others due to different aspects. First, there are many options to generate enolates or their equivalents (enolate, silyl enol ether, metal enolate or enamine). Secondly, enolates and equivalents are highly nucleophilic, enabling the reaction with many electrophiles.

a) Carbonyl containing compounds as electrophiles

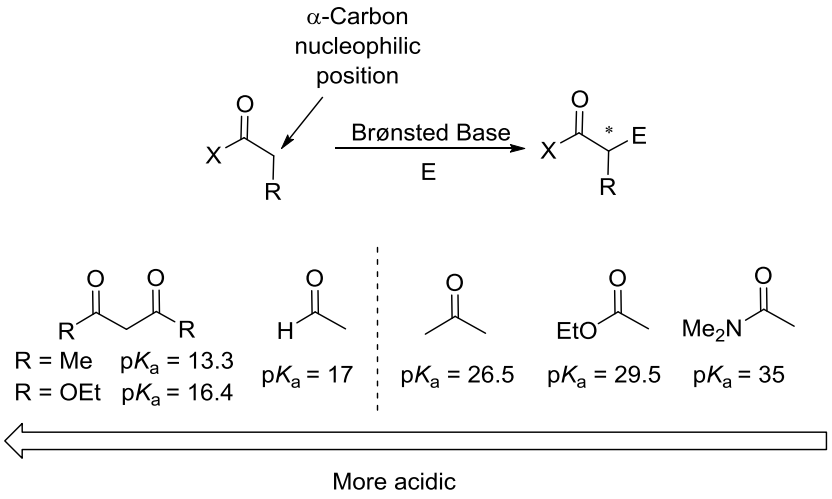


b) Carbonyl compounds as nucleophiles



Scheme 1. Main approaches for the stereoselective formation of a stereogenic center at the α-position of carbonyl compounds.

The most general means of generating carbon nucleophiles involves removal of a proton from a carbon by a Brønsted base, to provide enolates or equivalents (b, Scheme 1). A quantitative measure of the acidity of these carbonyl substrates in solution is given by the dissociation constant (K_a), which is usually expressed as pK_a. This factor influences the aptitude of a compound to generate the corresponding enolate and accept electrophiles. A classification of carbonyl compounds regarding their carbon acidity would include 1,3-dicarbonyl compounds (pK_a in DMSO ≈ 13-16) and aldehydes (pK_a in DMSO ≈ 17), as more easily enolizable compounds, in contrast to ketones (pK_a in DMSO ≈ 27), esters (pK_a in DMSO ≈ 30) and amides (pK_a in DMSO ≈ 35), which are less acidic as it is shown in Scheme 2. In this context, unactivated carbonyl compounds display higher pK_a values, thus they are more challenging substrates for deprotonation and their α-functionalization is more difficult. As a consequence, amides and esters have been the most challenging substrates in this strategy.



Scheme 2. pk_a values of the α-carbons in carbonyl compounds in DMSO.[2]

In all the above options (Scheme 1) at least one new stereocenter is created. Therefore, the control of its configuration is of great relevance, and for this purpose asymmetric synthesis offers the optimal tools. In this context, the use of carbonyl compounds as nucleophiles has been the most developed strategy involving the use of chiral auxiliaries, metal catalysts and organocatalysts. The main contributions are summarized below.

1.1.2. Strategies for the enantioselective α-functionalization of carbonyl compounds

Asymmetric synthesis,[3] that is formation of new bonds in a diastereo- and enantiocontrolled manner, is a good tool for the obtention of enantiopure products. Here, achiral substrates are employed in the reaction, while the asymmetric induction comes from a chiral ligand,[4] a chiral auxiliary[5] or a chiral catalyst.[6] The two formers require the

[2] Based on the Bordwell pKa table (See: http://www.chem.wisc.edu/areas/reich/pkatable/index.htm).

[3] For more information about asymmetric synthesis, see: a) Gawley, R. E.; Aube, J. *Principles of Asymmetric Synthesis 2nd Edition*, **2012**, Pergamon Press, Oxford. b) *Asymmetric Synthesis II: More Methods and Applications*, Eds. Christmann, M.; Bräse, S., **2012**, Wiley-VHC, Weinheim, Germany. c) Christmann, M.; Bräse, S. *Asymmetric Synthesis: The Essentials*, **2007**, Wiley-VCH, New York.

[4] For more information about chiral ligands, see: a) *Privileged chiral ligands and catalyst*, Ed. Zhou, Q.-L. **2011**, Wiley-VCH, Weinheim. For the use of (–)-sparteine as chiral ligand in asymmetric synthesis, see: b) Schütz, T. *Synlett* **2003**, *6*, 901–902.

[5] For more information about chiral auxiliaries, see: a) G. Roos, *Key Chiral Auxiliary Applications*, **2014**, Academic Press, New York; b) S. G. Davies, A. M. Fletcher, J. E. Thomson, *Chem. Commun.* **2013**, *49*, 8586-8598; c) F. Glorious, Y. Gnass, *Syntesis*, **2006**, *12*, 1899–1930; d) G. Roos, *Compendium of Chiral Auxiliary Applications*, **2002**, Academic Press, New York; e) S. Jones, *J. Chem. Soc. Perkin Trans.* **2002**, *1*, 1-21.

[6] For general references on asymmetric catalysis, see: a) K. Mikami, M. Lautens, *New Frontiers in Asymmetric Catalysis*, **2007**, Wiley-VCH, Weinhelm; b) B. M. Trost, *Proc. Natl. Acad. Sci. USA*, **2004**, *101*, 5348–5355.

use of stoichiometric amounts of chiral compounds, whereas substoichiometric quantities of catalysts are employed in asymmetric catalysis. Chiral auxiliaries were initially developed for the α-functionalization of carbonyl compounds. This methodology is based on the formation of a covalent bond between a substrate and the chiral auxiliary, which controls the stereoselectivity of the process, and it is removed and recovered after the reaction (Figure 2).

Since Enders reported in 1976 SAMP and RAMP auxiliaries[7] for the asymmetric α-alkylation of ketones, these chiral auxiliaries have proven to be very useful for the α-functionalization of aldehydes and ketones. Further examples made use of substrates in the carboxylic acid oxidation state, and, after the asymmetric reaction afforded the corresponding carboxylic acid derivative, aldehyde or ketone, depending on the scission conditions. In this context, following Evans's contribution with chiral oxazolidinones as auxiliaries for the asymmetric formation of a stereogenic center at the α-position of acyl systems,[8] other chiral auxiliaries were reported[9] including Oppolzer[10] and Myers[11] auxiliaries (Figure 2).

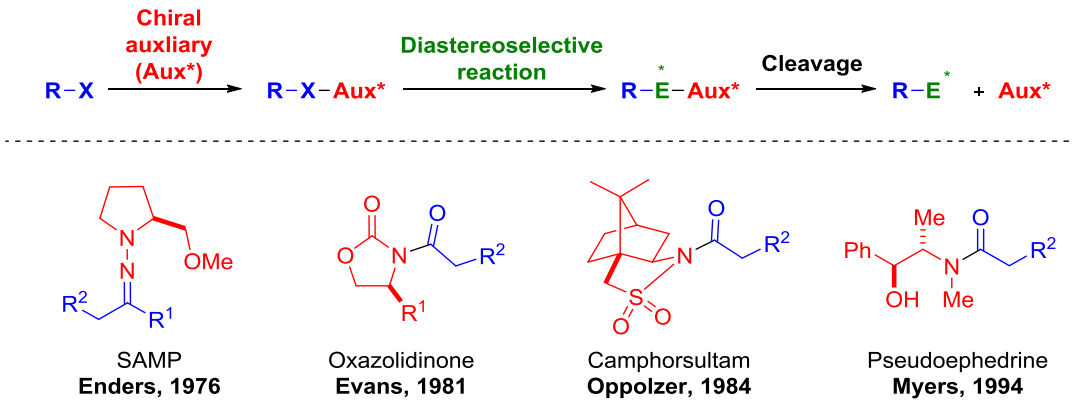


Figure 2. Some representative chiral auxiliaries.

However, the use of substoichiometric quantities of a chiral enantiopure catalyst, known as *asymmetric catalysis*, which avoids the additional steps of attachement and

[7] For the first example, see: a) D. Enders, H. Eichenauer, *Angew. Chem.* **1976**, *88*, 579-581. For a review, see: b) A. Job, C. F. Janeck, W. Bettray, R. Peters, D. Enders, *Tetrahedron*, **2002**, 58, 2253-2329.
[8] For the first example, see: D. A. Evans, J. Bartroli, T. L Shih, *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.
[9] For further information on the subject see: a) M. M. Heravi, V. Zadsirjan, *Tetrahedron: Asymmetry* **2014**, *25*, 1061–1090; b) L. M. Geary, P. G. Hultin, *Tetrahedron: Asymmetry* **2009**, *20*, 131–173; c) C. Palomo, M. Oiarbide, J. M. García, *Chem. Soc. Rev*. **2004**, *33*, 65–75; d) P. Arya, H. Qin, *Tetrahedron* **2000**, *56*, 917–947.
[10] For the first example, see: W. Oppolzer, C. Chapuis, G. Bernardielli, *Helv. Chim. Acta* **1984**, *67*, 1397-1401.
[11] For the first example, see: A. G. Myers, B. H. Yang, H. Chen, J. L. Gleason, *J. Am. Chem. Soc.* **1994**, *116*, 9361-9362.

dettachmement of the chiral source, remains more attractive due to step economy. As a result, this strategy has experienced a great development during the last decades.

The field of asymmetric catalysis has been classified into three categories: *biocatalyisis*, *organocatalysis* and *metal catalysis*. Biocatalysis[12] was the first pioneering methodology developed in this field and it makes use of enzymes to catalyze reactions. However, due to the the high specificity between the substrate and the biocatalyst, the strategy turns limited for obtaining enantiopure compounds. In contrast, metal catalysis[13] and organocatalysis (which uses small organic molecules to catalyze organic transformations)[14] have emerged as attractive synthetic alternatives.

Both strategies, metal based catalysis and organocatalysis, have been deeply investigated and applied to the direct α-functionalization of carbonyl compounds. The main results and characteristics of these methodologies are described below.

1.1.2.1. Metal catalysis

In the field of asymmetric catalysis, metal-catalysis has played a significant role in allowing synthetic access to biologically interesting molecules.[15] Regarding direct methods for enolate generation, introduction of new bifunctional Lewis acid/Brønsted base metal catalysts by Shibasaki[16] and Trost,[17] represented a considerable progress in the field (Figure 3).[18] Thus, these catalysts can simultaneously bind and activate the

[12] For general reviews on enzymatic catalysis, see: a) X. Garrrabou, D. S. Macdonald, B. I. M. Wicky, D. Hilbert *Angew. Chem. Int. Ed.* **2018**, *57*, 5288-5291; b) G. De Gonzalo, I. Lavandera, V. Gotor, *Catalytic Methods in Asymmetric Synthesis. Advanced material, techniques, and applications*, **2011**, 391–527, Ed. M. Gruttadauria, F. Giacalone, John Wiley & Sons; c) N. Zagrebelny, *Russ. Chem. Rev*. **2005**, *74*, 285–296; d) M. T. Reetz, B. Brunner, F. Schnerider, C. M. Schulz, M. M. Clouthier, M. Kayser, *Angew. Chem. Int. Ed*. **2004**, *43*, 4075–4078.

[13] For general reviews on organometallic catalysis, see: a) S. H. A. M. Leenders, R. Gramage-Doria, B. de Bruin, J. N. H. Reek, *Chem. Soc. Rev*. **2015**, *44*, 433–448; b) D. Steinborn, *Fundamentals of Organometallic Catalysis*, **2011**, Wiley-VCH, Germany; c) D. Astruc, *Organometallic Chemistry and Catalysis*, **2007**, Springer-Verlag Berlin Heidelberg

[14] a) *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications*, Ed. Dalko, P. I. **2013**. Wiley-VCH; b) *Enantioselective Organocatalysis*, Ed. Dalko, P. I. **2007**. Wiley-VCH; c) *Asymmetric Organocatysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*, Ed. Berkessel, A.; Gröger, H. **2005**. Wiley-VCH.

[15] a) M. Beller, C. Bolm, *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals*, 2nd ed., Vol. 1-2; Wiley-VCH: Weinheim, **2004**; b) G.-Q. Lin, Y.-M. Li, A. C. S. Chan, *Principles and Applications of Asymmetric Synthesis*; JohnWiley & Sons: New York, **2001**; c) E. N. Jacobsen, A. Pfaltz, H. Yamamoto, *Comprehensive Asymmetric Catalysis*, Vol. I-III; Springer:Berlin, **1999**.

[16] Y. M. A. Yamada, N. Yoshikawa, H. Sasai, M. Shibasaki, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1871-1872.

[17] B. M. Trost, H. Ito, *J. Am. Chem. Soc.* **2000**, *122*, 12003-12004.

[18] For the concept of bifunctional metal complexes see: a) J. Ito, H. Nishiyama, *Bifunctional Molecular Catalysis. Topics in organometallic Chemistry*, Ed. Springer, Berlin **2011**, vol. 37; b) M. Shibasaki, M. Kanai, S. Matsunaga, *Acc. Chem. Res.* **2009**, *42*, 1117–1127; c) T. Ikariya, K. Murata, R. Noyori, *Org. Biomol. Chem.* **2006**, *4*, 393–406.

pronucleophile and the electrophile, improving the efficiency and the stereoselectivity of the reaction, compared with conventional (monofunctional) catalysts.[19]

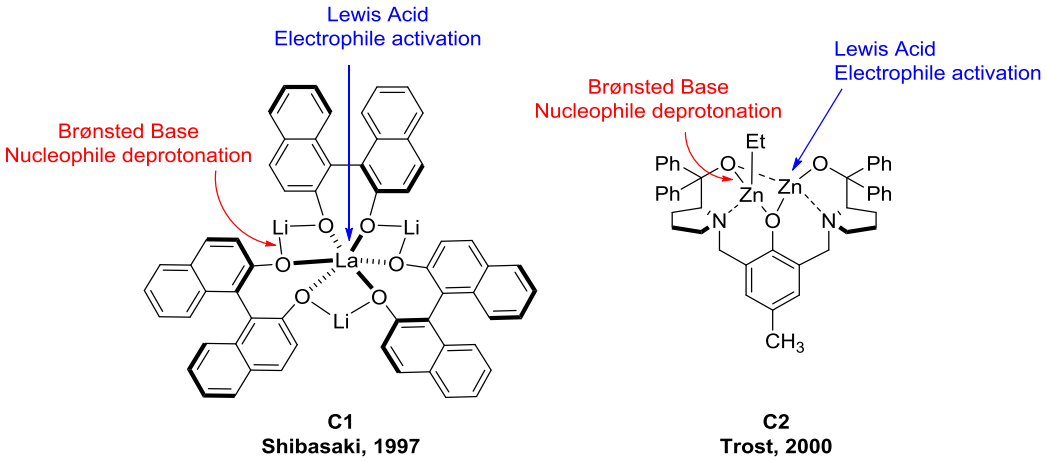


Figure 3. Most representative bifunctional metal catalysts.

However, as each carbonyl containing compound has a different reactivity, a deeper insight on their most significant reactions is described below.

a) More reactive carbonyl compounds

In this section, 1,3-dicarbonyl compounds (active methylenes; pK_a = 13-16) and aldehydes (pK_a = 17), which are carbonyl compounds with lower pK_a values, have been considered.

Starting with the first ones, the two carbonyl groups can chelate the metal center to form a stable six-membered structure, thus facilitating their functionalization. Hence, 1,3-dicarbonyl compounds have been widely investigated as nucleophiles in Mannich, aldol, Michael and allylic alkylation reaction as described below.

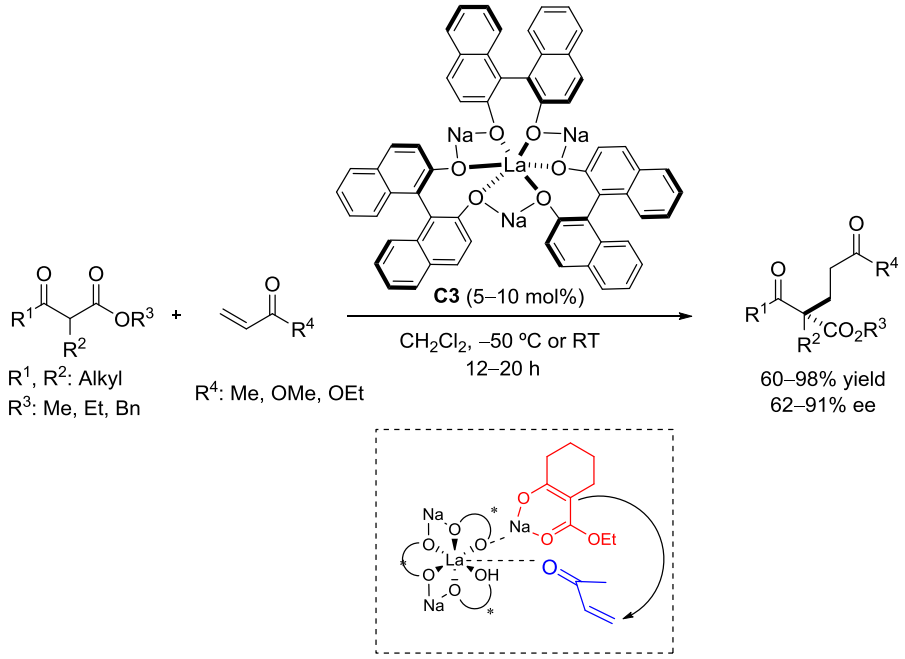
Since the pioneering work of Jørgensen and co-workers involving the first direct asymmetric Mannich reaction of substituted and unmodified malonates and β-ketoesters with *N*-tosyl-α-imino esters,[20] other contributions have been reported.[21]

However, the use of 1,3-dicarbonyl compounds in aldol reactions has been limited due to the retroaldol reaction that can occur under proton-transfer conditions.[22] In spite of

[19] M. Shibasaki, M. Kanai, S. Matsunaga, *Acc. Chem. Res.* **2009**, *42*, 1117-1127.
[20] M. Marigo, A. Kjaersgaard, K. Juhl, N. Gathergood, K. A. Jørgensen, *Chem. Eur. J.* **2003**, 9, 2359-2367.
[21] A. Córdova, *Acc. Chem. Res.* **2004**, *37*, 102-112.
[22] Y. Yamashita, T. Yasukawa, W-J. Yoo, T. Kitanosono, S. Kobayashi, *Chem. Soc. Rev.* **2018**, *47*, 4388-4480.

that, some examples of aldol reactions of dicarbonyl compounds promoted by metal catalysis have been reported by Sodeoka's group, and Matsunaga/Shibasaki.[23]

Conjugate additions of 1,3-dicarbonyl compounds have been widely explored in the presence of various well-defined metal catalyst systems.[24] In this context, many contributions in the conjugate addition of cyclic and acyclic β-ketoesters, β-diketones, β-ketoacids and 2-fluoro or bromomalonates to various nitroalkenes and enones affording excellent yields and enantioselectivities have been reported. A representative example described by Shibasaki and co-workers[25] in the conjugate addition of cyclic β-ketoesters to methyl vinyl ketone and acrylates, afforded reaction adducts with high enantioselectivity promoted by their bifunctional catalyst (Scheme 3). As postulated by the authors, the ketoester is activated by the basic unit (R-ONa) through generation of the corresponding sodium enolate, and the enone is activated by the Lewis acid, La(III).



Scheme 3. Michael addition of β-ketoesters to vinyl ketone and acrylates promoted by a bifunctional metal catalyst. **Shibasaki, 1996**.

1,3-Dicarbonyl compounds have also shown to be very efficient substrates for enantioselective palladium-catalyzed asymmetric allylic alkylations (Pd-AAA). The main contributions in this field will be mentioned in the following chapter.

[23] a) S. Mouri, Z. H. Chen, S. Matsunaga and M. Shibasaki, *Chem. Commun.*, **2009**, 5138; b) N. Umebayashi, Y. Hamashima, D. Hashizume and M. Sodeoka, *Angew. Chem., Int. Ed.*, **2008**, 47, 4196; c) I. Fukuchi, Y. Hamashima, M. Sodeoka, *Adv. Synth. Catal.*, **2007**, *349*, 509.
[24] K. Zheng, X. Liu, X. Feng, *Chem. Rev.* **2018**, *118*, 7586-7656.
[25] H. Sasai, E. Emori, T. Arai, M. Shibasaki, *Tetrahedron Lett.* **1996**, *37*, 5561–5564

In contrast to the vast number of examples involving the metal catalyzed α-functionalization of 1,3-dicarbonyl compounds, aldehyde α-functionalization has been more challenging due to additional problems associated with aldol and self-aldol reaction, polyaldolization, dehydration of the product enabling Michael-type additions, Tishchenko-type processes and oligomerization.[26] As a result, these substrates have been little explored in this strategy.

Following these representative examples, other contributions to the α-functionalization of 1,3-dicarbonyl compounds promoted by chiral metal catalysis have been published.[27]

b) Less reactive carbonyl compounds

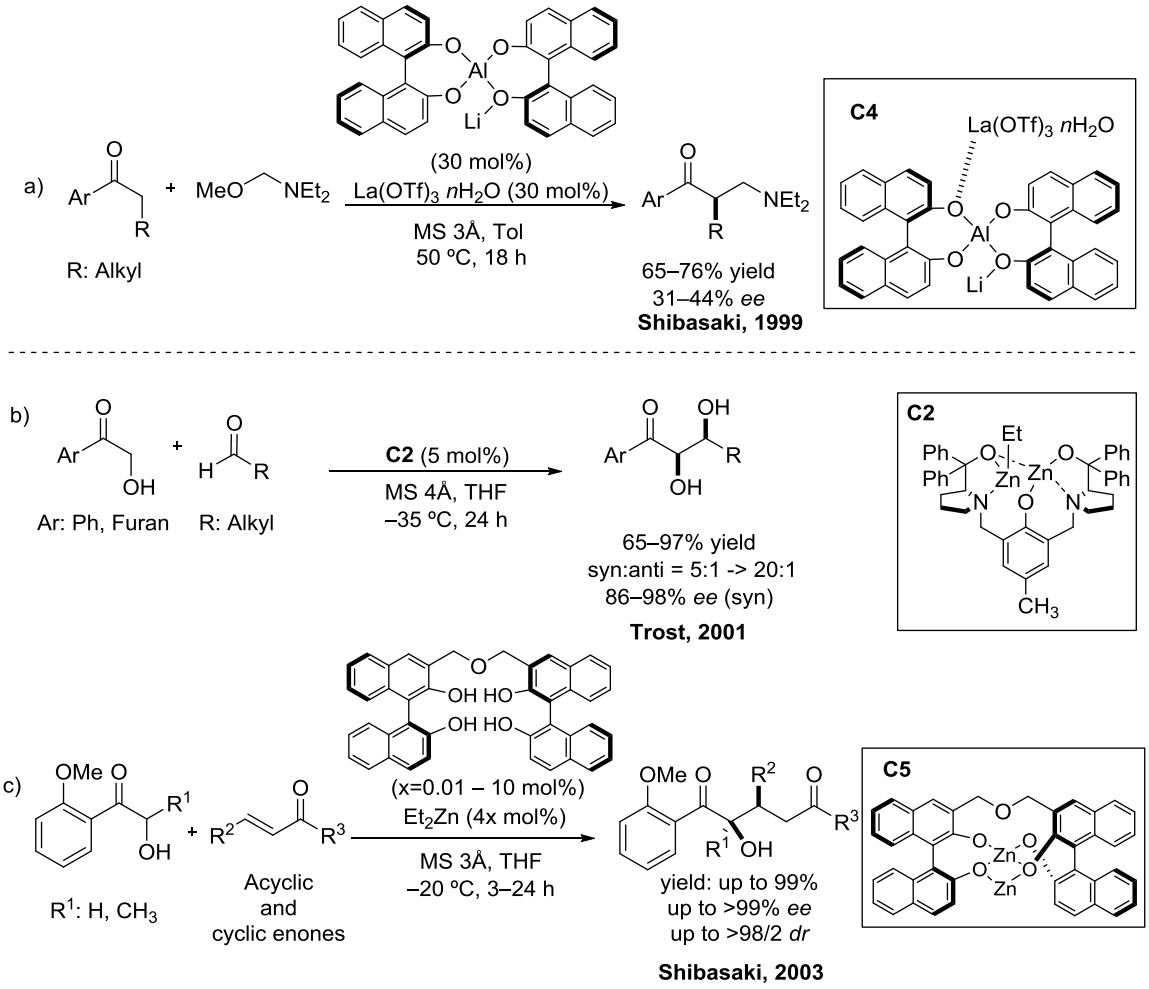
Going back to the α-carbon acidity classification, less acidic compounds include ketones (pK_a in DMSO ≈ 26.5), and carbonyl compounds in the carboxylic acid oxidation state such as esters (pK_a in DMSO ≈ 29.5) and amides (pK_a in DMSO ≈ 35). As mentioned before, the low acidity of the α-carbon in these substrates complicates efficient protocols for their α-functionalization using metal catalysts, compared to the more reactive 1,3-dicarbonyl compounds.

In this context, ketones do not inherently experiment the self-condensation due to their lower electrophilicity and their α-functionalization via metal-catalysis has been investigated in Mannich, aldol and Michael reactions as well as in Pd-catalyzed asymmetric allylic alkylations. Some representative examples are depicted in Scheme 4.

In 1999, Shibasaki's group used a bifunctional heterobimetallic catalyst for the first report of a direct catalytic asymmetric Mannich reaction between aromatic ketones and aminoethyl ethers (a, Scheme 4) with high catalyst loading (30 mol %) obtaining the adducts in good yield but low enantioselectivities.[28] In this context, an improvement in the α-functionalization of ketones came with hydroxyketones.[29] These substrates provide excellent stereoselectivity compared to simple ketones due to the possibility of acting as bidentate ligands. This feature can enhance the reactivity and stereoselectivity of the reaction, compared to simple ketones. Many contributions by Shibasaki[30] and Trost,

[26] B. Alcaide, P. Almendros, *Angew. Chem. Int. Ed.* **2003**, *42*, 858-859.
[27] For reviews on some representative metal-catalyzed reactions including α-functionalization reactions, see: a) see ref: 22; b) N. Kumagai, M. Kanai, H. Sasai, *ACS Catal.*, **2016**, *6*, 4699-4709; c) S. Matsunaga, M. Shibasaki, *Chem. Commun*., **2014**, *50*, 1044-1057; d) A. M. R. Smith. K. K. Hii, *Chem. Rev.* **2011**, *111*, 1637-1656; e) H. Yamamoto, K. Futatsugi, *Angew. Chem. Int. Ed*., **2005**, *44*, 1924-1942.
[28] S. Yamasaki, T. Iida, M. Shibasaki, *Tetrahedron Lett.* **1999**, *40*, 307–310.
[29] C. Palomo, M. Oiarbide, J. M. García, *Chem. Soc. Rev.* **2012**, *41*, 4150-4164.
[30] N. Yoshikawa, N. Kumagai, S. Matsunaga, G. Moll, T. Ohshima, T. Suzuki, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 2466–2467.

among others, have been described involving these substrates and affording the corresponding adducts with high enantioselectivity.[21] For instance, Trost and co-workers[31] employed their dinuclear zinc catalyst **C2** to promote aldol reactions of α-hydroxyketones with aliphatic linear and branched aldehydes, with excellent yields and stereocontrol (b, Scheme 4). Another contribution that is worth mentioning was reported by Shibasaki and co-workers[32c] with the bifunctional catalyst **C5** that proved to be excellent for the conjugate addition of hydroxyketones to enones (c, Scheme 4).



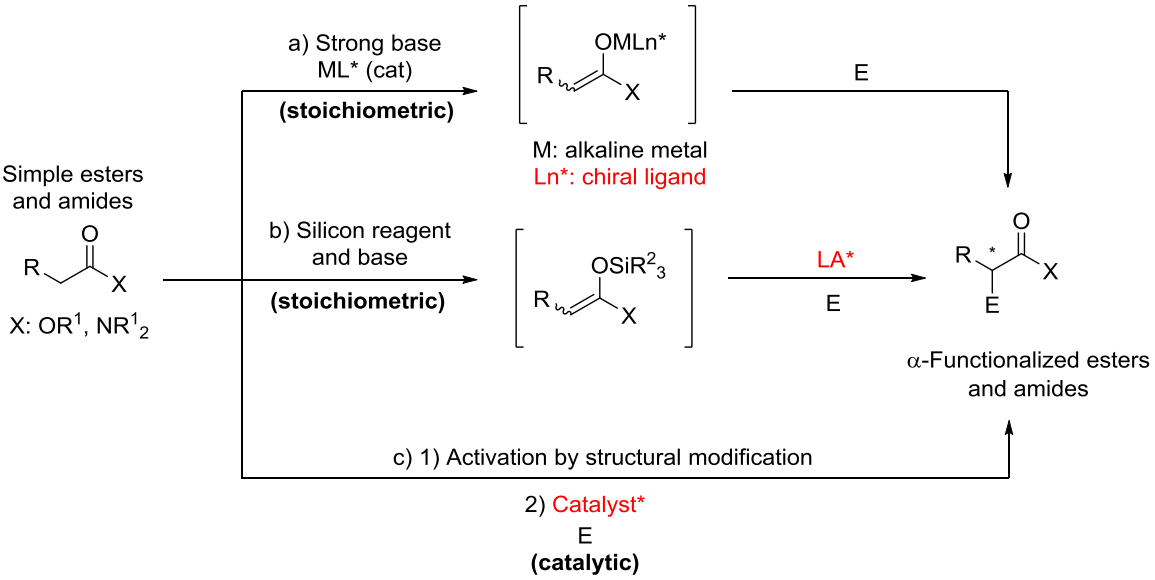
Scheme 4. Some representative examples of α-functionalization of ketones via metal catalysis.

[31] a) B. M. Trost, H. Ito, E. R. Silcoff, *J. Am. Chem. Soc.* **2001**, *123*, 3367-3368. For Mannich reactions of α-hydroxyketones promoted by the same catalyst, see: b) B. M. Trost, L. M. Terrell, *J. Am. Chem. Soc.* **2003**, *125*, 338–339.

[32] Mannich reaction: a) S. Matsunaga, N. Kumagai, S. Harada, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 4712-4713. Aldol reaction: b) N. Kumagai, S. Matsunaga, T. Kinoshita, S. Harada, S. Okada, S. Sakamoto, K. Yamaguchi, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 2169-2178. Michael addition: c) S. Harada, N. Kumagai, T. Kinoshita, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 2582-2590.

Following these representative examples, other contributions to the metal-catalyzed α-functionalization of ketones have been reported.[33]

Regarding esters and amides, the standard procedure for their α-functionalization involves irreversible generation of metal enolates using stoichiometric amounts of strong bases such as lithium diisopropylamide (LDA), potassium hexamethyldisilazide (KHMDS) (a, Scheme 5), or alternatively isolable silyl enolates generated from stoichiometric amounts of silicon reagents and bases (b, Scheme 5),[34] in both cases in the presence of a chiral catalyst (ML*, in a or LA* in b).

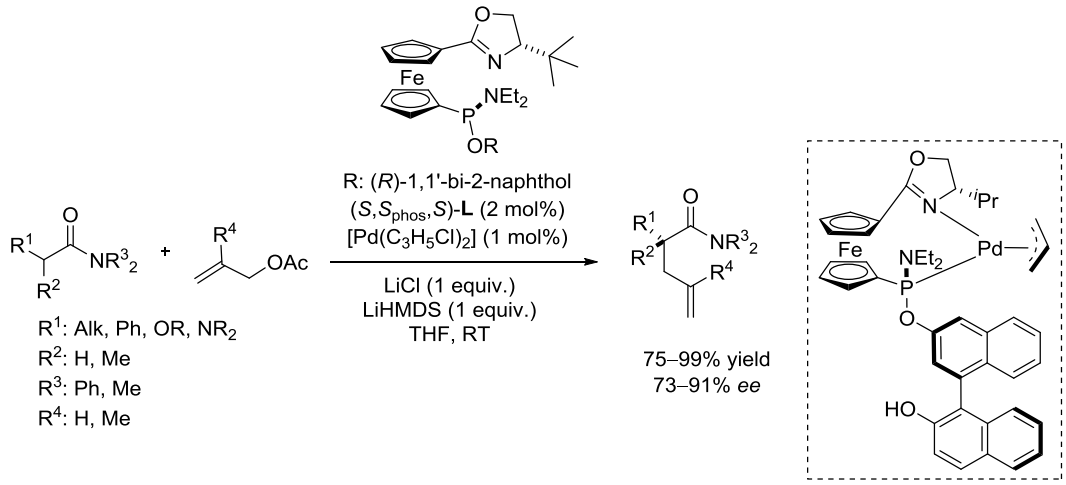


Scheme 5. Standard procedures for the α-functionalization of amides and esters: a) and b) stoichiometric approaches, and c) catalytic procedure for activated amides or esters.

An example of this approach, which involves stoichiometric enolate formation and subsequent catalytic α-allylation of unactivated amides in the presence of a chiral palladium catalyst with a ferrocene ligand, was reported by Hou in 2008, as depicted in Scheme 6.[34c]

[33] a) B. M. Trost, J. S. Tracy, T. Saget, *Chem. Sci.*, **2018**, *9*, 2975-2980; b) B. M. Trost, M. J. Bartlett, *Acc. Chem. Res.*, **2015**, *48*, 688-701.

[34] For general examples of C-C bond formation using amides and esters, see: a) Y.-J. Yiang, G.-P. Zhang, J.-Q. Huang, D. Chen, C.-H. Ding, X.-L. Hou, *Org. Lett.* **2017**, *19*, 5932-5935; b) Y. Yamamoto, H. Suzuki, Y. Yasuda, A. Iida, K. Tomioka, *Tetrahedron Lett.* **2008**, *49*, 4582; c) K. Zhang, Q. Peng, X.-L. Hou, Y.-D. Wu, *Angew. Chem. Int. Ed.* **2008**, *47*, 1741-1744; d) D.A. Oare, M. A. Henderson, M. A. Sanner, C. H. Heathcock, *J. Org. Chem.* **1990**, *55*, 132–157; e) H. Fujieda, M. Kanai, T. Kambara, A. Iida, K. Tomioka, *J. Am. Chem. Soc*. **1997**, *119*, 2060–2061.



Scheme 6. Pd-Catalyzed asymmetric allylic alkylation of unactivated amides with stoichoimetric enolate formation. **Hou, 2008**.

However, the catalytic variants are limited to some modified and activated amides or esters[35] (c, Scheme 5). The main contributions of this approach are summarized below.

Heterocyclic donors

The use of activated heterocyles is a very useful tool to access α-functionalized substrates in the carboxylic acid oxidation state. For this purpose, some specific examples have been reported.

The heterocyclic systems developed for this purpose (Figure 4) posses interesting characteristics,[36] such as their easy deprotonation under soft enolization conditions (aromaticity is generated after enolate formation in some cases). Additionally, the stereoselectivity control is easier due to the rigidity of the cyclic structure. Moreover, most of them are substituted at the α-position and after reaction with an electrophile, a tetrasubstituted stereocenter is formed. Finally, these cycles (1a,1b and 1c) can be opened under appropriate conditions after the enantioselective reaction to afford α- hydroxy, α-mercapto and α- or β-amino acid derivatives with a tetrasubstituted stereocenter.

[35] a) N. Kumagai, M. Shibasaki, *Synthesis*, **2019**, *51*, 185-193; b) N. Kumagai, M. Shibasaki, *Chem. Eur. J.* **2016**, *22*, 15192-15200; c) H. Suzuki, I. Sato, Y. Yamashita, S. Kobayashi, *J. Am. Chem. Soc.* **2015**, *137*, 4336-4339.
[36] A. Mielgo, C. Palomo, *Beilstein J. Org. Chem.* **2016**, *12*, 918-936.

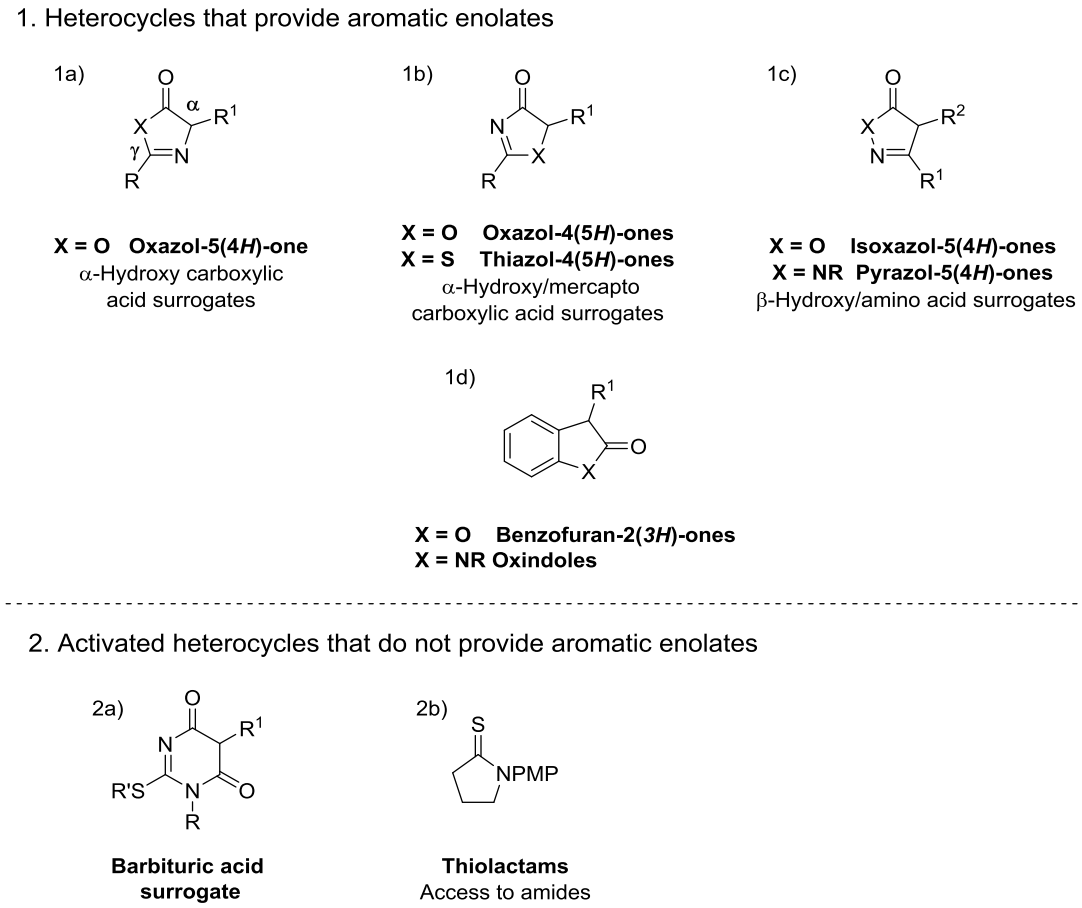


Figure 4. Some representative activated heterocycles employed in asymmetric metal catalysis, for their α-functionalization.

In this context, oxazol-5-(4*H*)-ones (1a, Figure 4) have been widely explored[37] in asymmetric transformations involving their α-functionalizalization. However, upon enolization the reaction can occur either at the α- or γ-position, thus regioselectivity problems can arise.[38] In this case, the reaction adducts are precursors of α-hydroxy carboxylic acids. In contrast, oxazol-4-(5*H*)-ones[39] (1b (X=O), Figure 4) and their sulphur[40] analogues (1b (X=S), Figure 4) (developed in our research group), which upon reaction provide α-hydroxy or α-mercapto derivatives, only exhibit one nucleophilic position at the α-carbon to the carbonyl. Both structures provide access to α-substituted

[37] a) N. M. Hewlett, C. D. Hupp, J. J. Tepe, *Synthesis* **2009**, *17*, 2825-2839; b) J. S. Fisk, R. A. Mosey, J. J. Tepe, *Chem. Soc. Rev.* **2007**, *36*, 1432-1440.
[38] J. Alemán, A. Minelli, S. Cabrera, E. Reyes, K. A. Jørgensen, *Chem. Eur. J.* **2008**, *14*, 10958-10966.
[39] a) B. M. Trost, K. Hirano, *Angew. Chem. Int. Ed.* **2012**, *51*, 6480–6483; b) D. Zhao, L. Wang, D. Yang, Y. Zhang, R. Wang, *Angew. Chem. Int. Ed.* **2012**, *51*, 7523–7527; c) B. M. Trost, K. Dogra, M. J. Franzini, *J. Am. Chem. Soc.* **2004,** *126*, 1944–1945.
[40] T.-C. Wang, Z.-Y. Han, P.-S. Wang, H.-C. Lin, S.-W. Luo, L.-Z. Gong, *Org. Lett.* **2018**, *20*, 4740-4744. For oxazol-4-(5*H*)-ones and thiazol-4-(5*H*)-ones, see: b) W. Chen, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 377–382;

carboxylic acid surrogates. Similarly, isoxazol-5(4*H*)-ones[41] (1c (X=O), Figure 4) and their analogues pyrazol-5(4*H*)-ones[42] (1c (X=NR), Figure 4) can be employed to access β-hydroxy/amino acid surrogates. In addition, other interesting nucleophiles with low pK_a values are benzofuran-2(3*H*)-ones[43] (1d (X=O), Figure 4) and oxindoles (1d (X=NR), Figure 4),[44] which also generate aromatic enolates.

Barbituric acid derivatives (2a, Figure 4)[45] and thiolactams[46] (2b, Figure 4) are very attractive reactants for asymmetric catalysis in the synthesis of a wide variety of bioactive compounds and big efforts have been made to expand their scope. Other cycles employed in asymmetric metal catalysis, though mainly for their γ-functionalization or as electrophiles, are γ-butenolides,[47] β-unsaturated γ-butyrolactams[48] and γ-substituted deconjugated butenolides.[49]

Acyclic donors

Similarly, acyclic activated structures have also been employed in asymmetric metal catalysis to access α-functionalized carboxylic acid derivatives (Figure 5). These include 2-acylimidazoles (a, Figure 5), which are known to be excellent ester surrogates due to the enhanced reactivity and stereoselectivity compared to simple esters or amides, on account of the privileged modes of coordination with metal complexes, thus facilitating soft enolization.[50] In addition they can be easily transformed into ketones or carboxylic acid derivatives.

A key step in the biosynthesis of polyketides and fatty acids is the *in situ* generation of the nucleophile through decarboxylation followed by a C-C bond forming reaction. This has served as inspiration to chemists, and malonic acid half thioesters (MAHT) and oxoesters (MAHO) have emerged as ester enolate analogues for catalytic

[41] T. Hellmuth, W. Frey, R. Peters, *Angew. Chem. Int. Ed.* **2015**, *54*, 2788-2791.
[42] Z. Wang, Z. Yang, D. Chen, X. Liu, L. Lin, X. Feng, *Angew. Chem. Int. Ed.* **2011**, *50*, 4928-4932.
[43] Y. Jie, Y.-L. Ding, S.-S. Niu, J.-T. Ma, Y. Chen, *J. Org. Chem.* **2018**, *83*, 1913-1923.
[44] a) Z.-Y. Cao, J. Zhou, *Org. Chem. Front.* **2015**, *2*, 849-858; b) K. Shen, X. Liu, L. Lin, X. Feng, *Chem. Sci.* **2012**, *3*, 327-334.
[45] C. Segovia, A. Lebrêne, V. Levacher, S. Oudeyer, J.-F. Brière, *Catalysis*, **2019**, 131.
[46] D. Sureshkumar, Y. Kawato, M. Iwata, N. Kumagai, M. Shibasaki, *Org. Lett.* **2012**, *14*, 3108-3111.
[47] L. Yan, X. Wu, H. Liu, L. Xie, Z. Jiang, *Mini-Reviews Med. Chem.* **2013**, *13*, 845-853.
[48] a) X. Jusseau, L. Chabaud, C. Guillou, *Tetrahedron* **2014**, *70*, 2595-2615; b) C. Schneider, F. Abels, *Org. Biomol. Chem.* **2014**, *12*, 3531-3543; c) G. Casiraghi, L. Battistini, C. Curti, G. Rassu, F. Zanardi, *Chem. Rev.* **2011**, *111*, 3076-3154; d) S. E. Denmark, J. R. Heemstra, G. L. Beutner, *Angew. Chem. Int. Ed.* **2005**, *44*, 4682-4698.
[49] L. Zhou, L. Lin, J. Ji, M. Xie, X. Liu, X. Feng, *Org. Lett.* **2011**, *13*, 3056-3059.
[50] For a review, see: J. Lauberteaux, D. Pichon, O. Baslé, M. Mauduit, R. Marcia de Figuereido, J.-M. Campagne *ChemCatChem*, **2019**, *11*, 5705-5722.

asymmetric reactions (b, Figure 5).[51] Furthermore, the thioester unit can be transformed into the corresponding ester under methanolic conditions.[52]

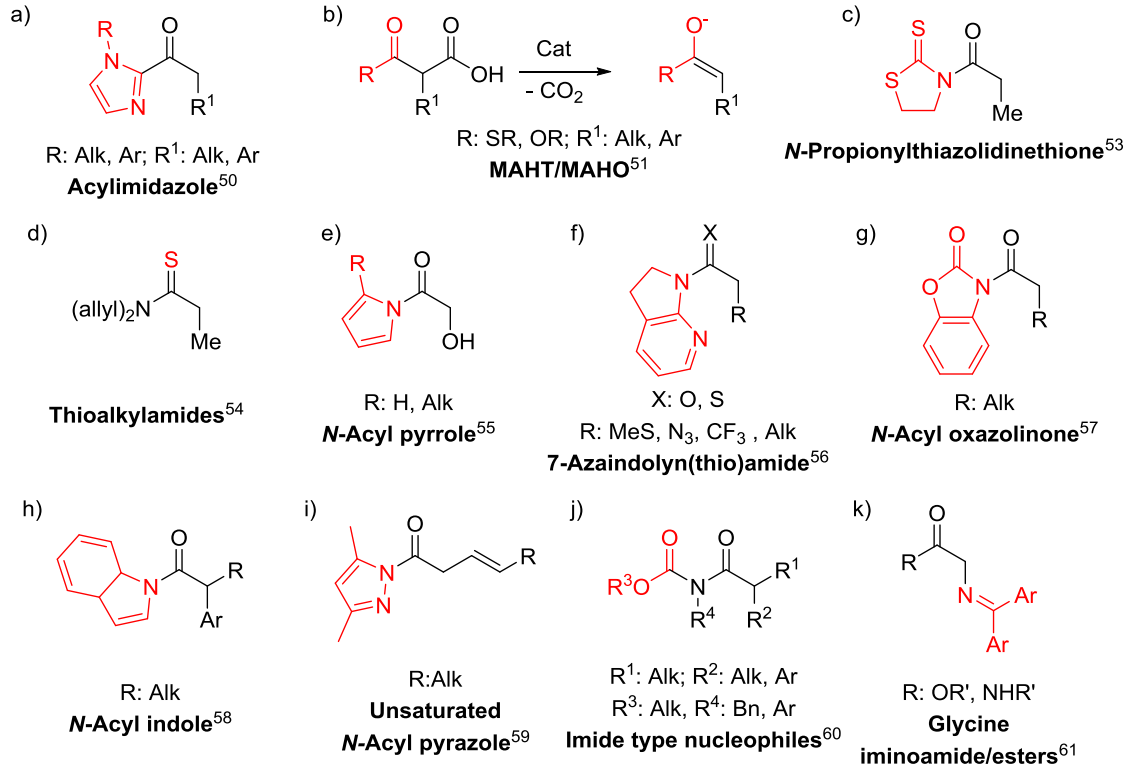


Figure 5. Some representative acyclic activated structures employed in asymmetric metal catalysis, for their α-functionalization.

Thioesters contain a more acidic α-carbon than their equivalent esters and therefore, their α-functionalization is facilitated. On this basis, Evans[53] described in 2003 the aldol reaction of *N*-propionylthiazolidinethione (c, Figure 5) and Shibasaki and Kumagai reported thioalkylamides (d, Figure 5) for their direct enantioselective aldol reaction.[54] It is noteworthy that all the mentioned structures can be transformed into different carboxylic acid derivatives.

Because the lone pair on the nitrogen atom is delocalized in heterocyclic aromatic systems, the properties of the adjacent carbonyl groups are similar to those of a phenyl

[51] For reviews, see: a) S. Nakamura, M. Sano, A. Toda, D. Nakane, H. Masuda *Chem. Eur. J.* **2015**, *21*, 3929-3932; b) S. Nakamura, *Org. Biomol. Chem.* **2014**, *12*, 394-405; c) Z.-L. Wang, *Adv. Synth. Catal.* **2013**, *355*, 2745-2755; d) L. Bernardi, M. Fochi, M. Comer Franchini, A. Ricci, *Org. Biomol. Chem.* **2012**, *10*, 2911-2922; e) C.-H. Tan, Y. Pan *Synthesis* **2011**, *13*, 2044-2053.
[52] J. Wang, J. Chen, C. W. Kee, C.-H. Tan, *Angew. Chem. Int. Ed.* **2012**, *51*, 2382-2386.
[53] D. A. Evans, C. W. Downey, J. L Hubbs, *J. Am. Chem. Soc.* **2003**, *125*, 8706-8707.
[54] M. Iwata, R. Yazaki, I. H. Chen, D. Sureshkumar, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2011**, *133*, 5554-5560.

ketone regarding the enhanced acidity of the α-carbon. In this context, *N*-acyl pyrrole,[55] 7-azaindolyn(thio)amide derivatives,[56] *N*-acyl oxazolidindiones,[57] *N*-acyl indoles[58] and unsaturated *N*-acyl pyrazoles[59] (e, f, g, h and i, Figure 5) are considered activated amide structures and have been successfully employed for α-functionalization reactions.

Other strategies for amide activation involve the introduction of electron withdrawing groups either at the amide nitrogen,[60] providing imide type substrates (j, Figure 5), or at the α-carbon of the amide (k, Figure 5). Examples of the latter are glycine iminoesters or iminoamides which are activated through introduction of the imine moiety at the α-carbon, thus increasing its acidity.[61] Even though most examples of asymmetric catalysis involving these substrates have been performed by phase transfer catalysis (PTC), metal-catalyzed approaches have also been reported with excellent yield and stereocontrol, and after imine hydrolysis, the corresponding β-substituted-α-amino derivatives can be obtained.

In summary, different reactions for the α-functionalization of carbonyl compounds promoted by metal catalysis have been reported. However, there are still limitations due to the problems associated with aldehyde functionalization, the inherent low reactivity of ketones (hydroxyketones are required for optimal reactivity and stereocontrol), esters and amides (introduction of activating groups is required for their catalytic functionalization).

---

[55] For Mannich reaction, see: a) S. Harada, S. Handa, S. Matsunaga, M. Shibasaki, *Angew. Chem. Int. Ed.* **2005**, *44*, 4365-4368. For Aldol reaction, see: b) B. M. Trost, D. J. Michaelis, M. I. Truica, *Org. Lett.* **2013**, *15*, 4516-4519; c) B. M. Trost, W. M. Seganish, C. K. Chung, D. Amans, *Chem. Eur. J.* **2012**, *18*, 2948-2960.

[56] A recent contribution involving 7-azaindolynthioamides: a) R. Pluta, Z. Li, N. Kumagai, M. Shibasaki, DOI: 10.1021/acs.orglett.9b04120. For aldol reactions, see: b) K. Weidner, N. Kumagai, M. Shibasaki, *Angew. Chem. Int. Ed.* **2014**, *53*, 6150-6154; c) K. Weidner, Z. Sun, N. Kumagai, M. Shibasaki, *Angew. Chem. Int. Ed.* **2015**, *54*, 6236-6240; d) H. Noda, F. Amemiya, K. Weidner, N. Kumagai, M. Shibasaki, *Chem. Sci.* **2017**, *8*, 3260-3269; e) A. Matsuzawa, H. Noda, N. Kumagai, M. Shibasaki, *J. Org. Chem.* **2017**, *82*, 8304-8308; f) Z. Liu, T. Takeuchi, R. Pluta, F. Arteaga, N. Kumagai, M. Shibasaki, *Org. Lett.* **2017**, *19*, 710-713. For Mannich reactions, see: g) Z. Sun, K. Weidner, N. Kumagai, M. Shibasaki *Chem. Eur. J.* **2015**, *21*, 17574-17577; h) L. Brewitz, F. Arteaga, L. Yin, K. Akigiri, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2015**, *137*, 15929-15939.

[57] For α-allylation, see: B. M. Trost, D. K. Michaelis, J. Charpentier, J. Xu, *Angew. Chem. Int. Ed.* **2012**, *51*, 204-208.

[58] For α-allylation, see: E. J. Alexy, T. J. Fulton, H. Zhang, B. M. Stolz, *Chem. Sci.* **2019**, *10*, 5996-6000.

[59] For α-amination, see: a) S. Lin, Z. Lin, *J. Org. Chem.* **2019**, *84*, 12399-12407; b) X. Fu, H.-Y. Bai, G.-D. Zhu, Y. Huang, S.-Y. Zhang, *Org. Lett.* **2018**, *20*, 3469-3472.

[60] For α-allylation, see: P. Starkov, J. T. Moore, D. C. Duquette, B. M. Stolz, I. Marek, *J. Am. Chem. Soc.* **2017**, *139*, 9615-9620.

[61] For aldol reactions, see: a) N. Yoshikawa, M. Shibasaki, *Tetrahedron* **2002**, *58*, 8289. b) B. M. Trost, F. Miege *J. Am. Chem. Soc.* **2014**, *136*, 3016-3019. For Mannich reaction, see: c) E. Hernando, R. Gómez Arrayás, J. C. Carretero *Chem. Commun.* **2012**, *48*, 9622-9624. For Michael reaction, see: d) X.-F. Bai, L. Li, Z. Xu, Z.-J. Zheng, C.-G. Xia, Y.-M. Cui, L.-W. Xu *Chem. Eur. J.* **2016**, *22*, 10399-10404. For α-allylation, see: e) X. Huo, J. Fu, X. He, J. Chen, F. Xie, W. Zhang, *Chem. Comm.* **2018**, *54*, 599-602; f) X. Huo, J. Zhang, J. Fu, R. He, W. Zhang, *J. Am. Chem. Soc.* **2018**, *140*, 2080-2084; g) X. Huo, R. He, J. Fu, J. Zhang, G. Yang, W. Zhang, *J. Am. Chem. Soc.* **2017**, *139*, 9819-9822.

1.1.2.2. Organocatalysis

With the growth of organocatalysis at the beginning of this millennium, two metal free main pathways for the activation of enolizable carbonyl substrates were developed which have been classified as covalent and non-covalent catalysis.[62]

Covalent catalysis comprises catalysts which are bound to the substrates covalently in a reversible manner to generate a reactive intermediate that participate in organic reactions. In contrast, non-covalent catalysis relies on weak attractive interactions between the catalyst and the substrate to promote the reaction through reactive intermediates. The main strategies for covalent and non covalent catalysis are summarized below.

1.1.2.2.1. *Covalent catalysis*

In this strategy, the strong interaction between the catalyst and the substrate allows an effective and well-defined influence of the former in the stereochemistry and reaction rate. Among catalysts working through this model, primary and secondary amines (also called aminocatalysts) stand out. In addition, *N*-heterocyclic carbenes[63] and chiral isothioureas[64] have emerged as very useful catalysts to promote asymmetric reactions. Other covalent organocatalytic systems are tertiary amines,[65] pyridines,[66] trialquilphosphines and trialquilamines,[67] and chiral oxyranes[68] but their characteristics will not be discussed in this thesis.

---

[62] Classification proposed by Langebek in 1994. For more information, see: a) A. Berkessel, H. Groger, *Asymmetric Organocatalysis. From Biomimetic Concepts to Applications in Asymmetric Synthesis (Chapter 2)*, **2005**, Wiley-VHC; b) J. L. Vicario, D. Badia, L. Carrillo, E. Reyes, *Organocatalytic Enantioselective Conjugate Addition Reactions. A Powerful Tool for the Stereocontrolled Synthesis of Complex Molecules*, **2010**, RSC. For a classification based on the acid/base character of the catalysts, see: c) J. Seayad, B. List, *Org. Biomol Chem.* **2005**, *3*, 719-724.

[63] a) X. Bugaut, F. Glorius, *Chem. Soc. Rev.* **2012**, *41*, 3511-3522; b) D. Enders, O. Niemeier, A. Henseler, *Chem.Rev.* **2007**, *107*, 5606-5655; c) N. Marion, S. Diez-Gonzalez, S. P. Nolan, *Angew. Chem. Int. Ed.* **2007**, *46*, 2988-3000.

[64] For the pioneering work with chiral isothioureas, see: a) J. Merad, J.-M. Pong, O. Chuzel, C. Bressy, *Eur. J. Org. Chem.* **2016**, 5589-5610; b) V. B. Birman, X. Li, *Org. Lett.* **2006**, *8*, 1351-1354;

[65] a) E. L. Myers, O. Illa, M. A. Shaws, S. L. Riches, V. K. Aggarwal, *Chem. Rev.* **2007**, *107*, 5841-5883; b) M. J. Gaunt, C. C. C. Johanson, *Chem. Rev.* **2007**, *107*, 5596-5605; c) S. France, D. J. Guerin, S. J. Miller, T. Lectka, *Chem. Rev.* **2003**, *103*, 2985-3012.

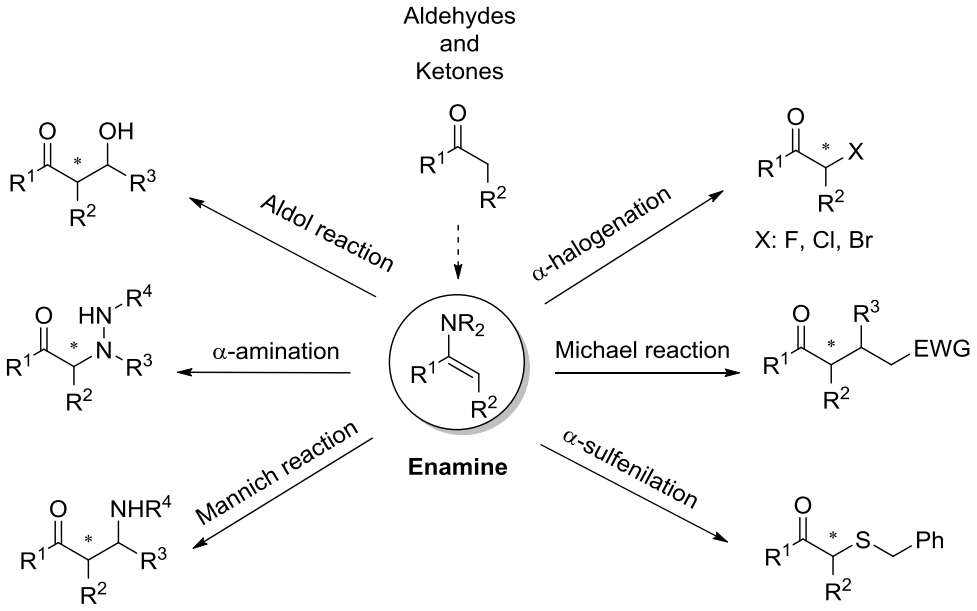
[66] a) V. Declerck, J. Martínez, F. Lamaty, *Chem. Rev.* **2009**, *109*, 1-48; b) P. R. Krishna, R. Sachwani, P. S. Reddy, *Synlett*, **2008**, 2897-2912; c) G. Masson, C. Housseman, J. Zhu, *Angew. Chem. Int. Ed.* **2007**, *46*, 4614-4628; d) Y.-L. Shi, *Eur. J. Org. Chem.* **2007**, 2905-2916; e) D. Basavaiah, K. V. Rao, R. J. Reddy, *Chem. Soc. Rev.* **2007**, *36*, 1581-1588.

[67] a) V. Declerck, J. Martinez, F. Lamaty, *Chem. Rev.* **2009**, *109*, 1-48; b) P. R. Krishna, R. Sachwani, P. S. Reddy, *Synlett*, **2008**, 2897-2912; c) G. Masson, C. Housseman, J. Zhu, *Angew. Chem. Int. Ed.* **2007**, *46*, 4614-4628; d) Y.-L. Shi, M. Shi, *Eur. J. Org. Chem.* **2007**, 2905-2916; e) D. Basavaiah, K. V. Rao, R. J. Reddy, *Chem. Soc. Rev.* **2007**, *36*, 1581-1588.

With respect to aminocatalysis, different activation strategies have been reported. On the one hand, enamine activation, works through HOMO orbital activation,[69] while SOMO activation[70] makes use of radicals through a radical cation intermediate formation, and both strategies are useful for the synthesis of α-functionalized compounds. The HOMO-activation concept was extended to the use of α,β-unsaturated aldehydes and ketones, which after condensation with a chiral amine, generate a dienamine species capable of undergoing stereoselective α or γ-functionalization of the starting carbonyl compound.[71] Trienamines, which are formed upon the condensation of organocatalysts with dienals or dienones, react at β,ε-positions leading to functionalized cyclohexenes.[72] In addition, iminium ion activation[73] of α,β-unsaturated compounds through LUMO orbital activation, provides β-functionalized compounds.

Regarding α-functionalization of carbonyl compounds, List, Lerner and Barbas III,[74] pioneered enamine catalysis for aldol reactions in 2000 followed by many other contributions as it is shown in Scheme 7. Here, the enamine intermediate generated from a primary or secondary amine and an enolizable aldehyde or ketone, posses and increased nucleophilicity compared with the starting carbonyl compound, thus enabling different reactions. The adducts obtained in the reaction (bonded to the catalyst) are hydrolized *in situ*, leading to the desired α-substituted adduct and recovering the starting chiral amine catalyst, which can re-enter the catalytic cycle.[75]

[68] a) M. Frohn, Y.Shi, *Synthesis*, **2000**, 1979-2000; b) S. E. Denmark, Z. Wu, *Synlett*, **1999**, 847-859.
[69] For reviews on aminocatalysis see: a) B. M. Paz, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2015**, *21*, 1846–1853; b) M. Nielsen, D. Worgull, T. Zweifel, B. Gschwend, S. Bertelsen, K. A. Jørgensen, *Chem. Commun.* **2011**, *47*, 632–649; c) A. Dondoni, A. Massi, *Angew. Chem. Int. Ed.* **2008**, *47*, 4638–4660. d) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem. Int. Ed.* **2008**, *47*, 6138–6171. e) S. Mukherjee, J. W. Yang, S. Hoffman, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569.
[70] a) P. Melchiorre, *Angew. Chem. Int. Ed.* **2009**, *48*, 1360-1363; b) H.-Y. Young, J.-B. Hung, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2007**, *129*, 7004-7005; c) T. D. Beeson, A. Mastracchio, J.-B. Hong, K. Ashton, D. W. C. MacMillan, *Science*, **2007**, *322*, 77-80.
[71] For the first example of dienamine catalysis, see: S. Bertelsen, M. Marigo, S. Brandes, P. Diner, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 12973-12980.
[72] For the first example of trienamine catalysis, see: Z.-J. Jia, H. Jiang, J.-L. Li, B. Gschwend, Q.-Z. Li, X. Yin, J. Grouleff, Y. C. Chen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2011**, *133*, 5053-5061.
[73] For general reviews of iminium ion catalysis, see: a) J. B. Brazier, N. C. O. Tomkinson, *Top. Curr. Chem.* **2010**, *291*, 281-347; b) G. Bartoli, P. Melchiorre, *Synlett*, **2008**, *12*, 1759-1772; c) P. M. Pihko, I. Majander, A. Erkkila, *Chem. Rev.* **2007**, *107*, 5416- 5470; d) G. Lelais, D. W. C. MacMillan, *Aldrichimica Acta*, **2006**, *39*, 79-87.
[74] B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.
[75] I. Ojima, *Catalytic Asymmetric Synthesis*, Ed. John Wiley & Sons, New York, **2010**.



Scheme 7. Representative examples of α-functionalization of aldehydes and ketones via enamine catalysis.

As earlier mentioned, enamine catalysis has enabled many protocols for the direct α-functionalization of aldehydes and ketones, but until recently, alkylation reactions using this methodology were lacking, due to the preferential alkylation of the amine catalyst with the alkyl electrophiles. Hence, these challenges were overcome by SOMO catalysis, where aldehyde and ketone α-alkylation has been carried out with excellent stereoselectivity.[76]

Many contributions have been made in the field of asymmetric α-functionalization of carbonyl compounds promoted by aminocatalysis. However, the procedures are limited to aldehydes and ketones, and the use of sterically hindered ketones still remains a challenge. In addition, unsymmetrical ketones have been barely used due to the bad regiocontrol and low diastereomeric ratios. Moreover, in cross aldol reactions chemoselectivity is still hard to control.

1.1.2.2.2. *Non-covalent catalysis*

Enolizable carbonyl compounds can also be activated in a non-covalent manner by cooperative, weak attractive interactions between the catalyst and the substrate. Although the catalyst-substrate interactions are generally weaker and less directional than with covalent catalysis, non-covalent interactions operate in concert to ensure a high level of transition state organization. This way, efficient activation and a high degree of

[76] *Science of Synthesis: Asymmetric Organocatalysis 1 Lewis Base and Acid Catalysis*, Ed. B. List **2012**. Thieme.

enantioselectivity is obtained. The strategies included in this type of catalysis involve hydrogen bonding,[77] Brønsted acid,[78] ion-pairing,[79] and Brønsted base catalysis.[80]

Hydrogen bonding and Brønsted acid (BA) activation of carbonyl compounds have attracted much attention. The first one is based on the activation of carbonyl compounds by hydrogen bonds, whereas Brønsted acids activate carbonyl compounds through protonation (enol). However, although in some cases there is no clear borderline between H-bonding catalysis and BA catalysis, in general Brønsted acid catalysis is considered an extreme case of H-bonding wherein the shared hydrogen is completely transferred to the substrate. Hydrogen bonding catalysts include (thio)ureas and squaramides among others, and this strategy has resulted efficient for electrophilic activation, but their main contributions in the α-functionalization of carbonyl compounds have been carried out in combination with other catalytic systems forming a bifunctional catalyst as it will be exaplained later in more detail.

Since the first introduction of phosphoric acids as asymmetric BA catalysts independently by Akiyama[81] and Terada[82] in 2004, enantioselective Brønsted acid catalysis has attracted much attention for asymmetric synthesis. Numerous variations of mostly BINOL-derived phosphoric acids have been developed.[83] List and co-workers reported in 2015 the first enatioselective conjugate addition of α-branched cyclic ketones

[77] For general reviews on hydrogen-bonding catalysis: a) Y. Nishikawa *Tetrahedron Lett.* **2018**, *59*, 216–223; b) A. Doyle, E. N. Jacobsen *Chem. Rev*. **2007**, *107*, 5713–5743; c) P. R. Schreiner *Chem. Soc. Rev.* **2003**, *32*, 289–296; d) M. S. Taylor, E. N. Jacobsen *Angew. Chem. Int. Ed*. **2006**, *45*, 1520–1543.

[78] For general reviews on Brønsted acid catalysis: a) C. Min, D. Seidel, *Chem. Soc. Rev.* **2017**, *46*, 5889-5902; b) D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev*. **2014**, *114*, 9047–9153; c) T. Akiyama, J. Itoh, K. Fuchibe *Adv. Synth. Catal.* **2006**, *348*, 999-1010; d) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe *Angew. Chem. Int. Ed.* **2004**, *43*, 1566–1568.

[79] For a general review on Ion-Pairing catalysis that includes anion binding, phase transfer, cation binding and chiral anion directed catalysis, see: a) K. Brak, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2013**, *52*, 534-561; For a general review on anion-binding catalysis, see: b) M. D. Visco, J. Attard, Y. Guan, A. E. Matson, *Tetr. Lett.* **2017**, *58*, 2623-2628.

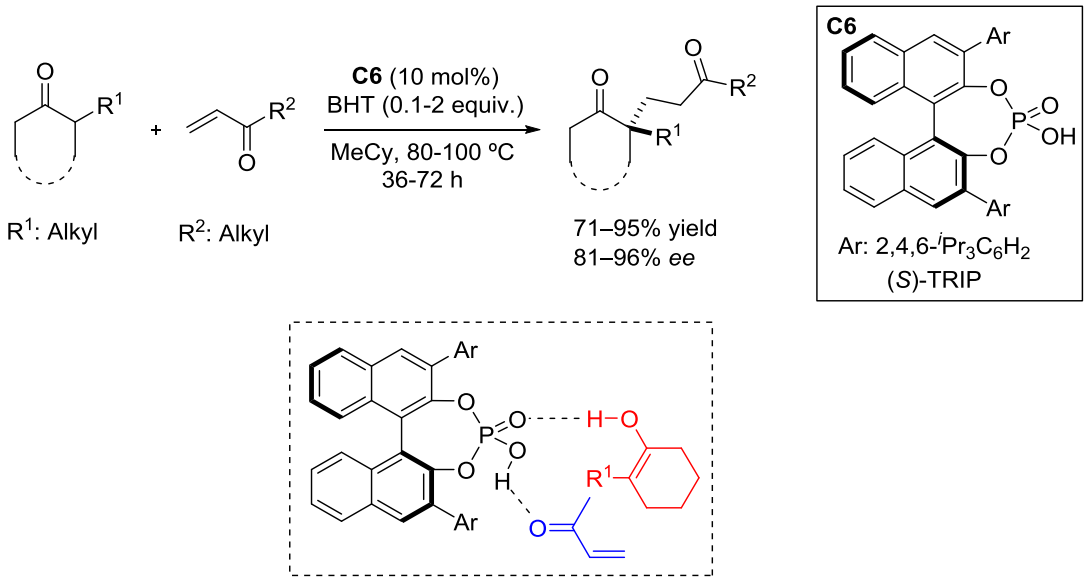
[80] For general reviews on Brønsted base catalysis: a) B. Teng, W. C. Lim, C. H. Tan *Synlett*, **2017**, *28*, 1272–1277; b) *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications*; (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, Vol. 1-3, **2013**; c) *Asymmetric Organocatalysis 1, Brønsted Base and Acid Catalysis, and Additional Topics* (Ed: K. Maruoka), Thieme, Stuttgart, **2012**; d) *Asymmetric Organocatalysis 2, Brønsted Base and Acid Catalysis, and Additional Topics* (Ed.: B. List), Thieme, Stuttgart, **2012**; e) A. Ting, J. M. Gross, N, T. McDougal, S. E. Schaus, *Top. Curr. Chem*. **2010**, *291*, 145–200; f) I. Ojima, *Catalytic Asymmetric Synthesis*, Ed. John Wiley and Sons, New York, **2010**; g) C. Palomo, M. Oiarbide, R. Lopez, *Chem. Soc. Rev.* **2009**, *38*, 632.

[81] T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem. Int. Ed.* **2004**, *126*, 5356-5357.

[82] D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356-5357.

[83] a) T. Akiyama and K. Mori, *Chem. Rev.* **2015**, *115*, 9277–9306; b) M. Rueping, D. Parmar and E. Sugiono, *Asymmetric Brønsted Acid Catalysis*, Wiley-VCH Verlag GmbH & Co.KGaA, **2015**, pp. 5–86.
c) M. Rueping, A. Kuenkel and I. Atodiresei, *Chem. Soc. Rev.* **2011**, *40*, 4539–4549; d) M. Terada, *Synthesis* **2010**, 1929–1982; e) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744–5758.40; f) H. Yamamoto and K. Futatsugi, *Angew. Chem., Int. Ed*. **2005**, *44*, 1924–1942.39.

to enones via a concerted acid-base mechanism with **C6** (Scheme 8).[84] The authors suggest that the chiral phosphoric acid could activate the enol nucleophile through the Brønsted base (P=O) moiety and the electrophile through the BA (P-OH) site. However, there is a limitation in the methodology that involves the need of a bulky R^1 group in the ketone to obtain high enantioselectivities.



Scheme 8. Conjugate addition of branched cyclic ketones to enones promoted by a chiral Brønsted acid. **List, 2015**.

The fact that ion-pairing interactions are less directional than covalent or hydrogen-bonding interactions, underlies the challenge in designing stereoselective catalysts that operate efficiently with this methodology. However, several powerful approaches have been developed for asymmetric catalysis of transformations that involve charged intermediates. Among them, phase-transfer catalysis[85] has been widely explored in asymmetric catalysis. Here, an enolate-ion, formed *in situ* is paired with an enantiopure quaternary ammonium cation. Partitioning to the organic phase is thus facilitated, allowing the enolate to selectively react with an organic soluble electrophile. PTC has promoted a wide number of stereoselective transformations. The most representative phase transfer catalysts are quaternary ammonium salts derived from cinchones[86] and binaftilamines (a, Figure 6).[87]

[84] I. Felker, G. Pupo, B. List, *Angew. Chem. Int. Ed.* **2015**, *54*, 1960-1964.
[85] For general reviews on phase transfer catalysis: a) J. Tan, N. Yasuda, *Org. Process Res. Dev.* **2015**, *19*, 1731–1746; b) S. Shirakawa, S, K. Maruoka, *Angew. Chem. Int. Ed.* **2013**, *52*, 4312–4348; c) O. Takashi, K. Maruoka, *Angew. Chem. Int. Ed.* **2007**, *23*, 4222–4266; d) K. Maruoka, O. Takashi, *Chem. Rev.* **2003**, *103*, 3013–3028.
[86] U.-H. Dolling, P. Davis, E. J. J. Grabowski, *J. Am. Chem. Soc.* **1984**, *106*, 446-447.
[87] K. Maruoka, T. Ooi, T. Kano, *Chem. Commun.* **2007**, 1487-1495.

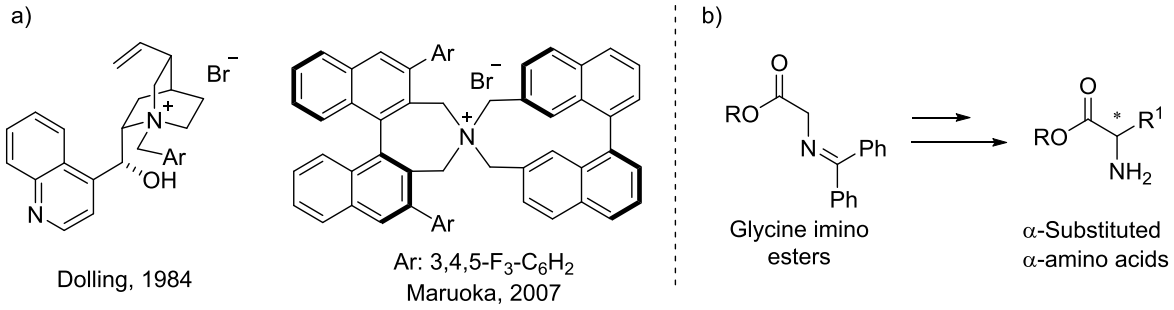


Figure 6. a) Most representative chiral ammonium phase transfer catalysts. b) Glycine imino esters and α-substituted α-amino acids.

More specifically, the most studied substrates in PTC include compounds bearing active methylene groups. Thus, β-ketoesters[85c] and ketones[88] α-functionalization has been successfully performed by PTC. However, reactions involving glycine imino esters (b, Figure 6) stand out. Moreover, due to their easy transformation into α-substituted α-amino acids,[89] transformations involving these substrates (activated ester structure) are of great interest and PTC has proven to be an outstanding tool for that purpose as it will be explained in more detail in chapter 3.

Another approach for the α-functionalization of carbonyl compounds is Brønsted Base catalysis which is outlined in the following section.

1.2. **Direct enantioselective α-functionalization of carbonyl compounds promoted by chiral Brønsted Bases**

A Brønsted base (BB) is defined as a molecular entity capable of accepting a hydron (or proton) from an acid or the corresponding chemical species.[90] This proton transfer is often considered from the organic synthesis point of view, key for activation of one of the reaction components that precedes the new bond formation. Enolizable carbonyl compounds with relatively small pK_a value (10-17 pK_a range in DMSO)[2] are the

[88] a) M. B. Andrus, E. J. Hicken, J. C. Stephens, *Org. Lett.* **2004**, *6*, 2289-2292. b) A. E. Nibbs, A.-L. Baize, R. M. Herter, K. A. Scheidt, *Org. Lett.* **2009**, *11*, 4010-4013.
[89] Enantioselective Amino Acid Synthesis by Chiral PTC, see: a) S. Shirakawa, K. Maruoka, *Angew. Chem. Int. Ed.* **2013**, *52*, 4312.4348; b) K. Maruoka, *Chem. Rec.* **2010**, *10*, 254-259; c) K. Maruoka, *Chem. Rec.* **2010**, *10*, 254-259; d) T. Hashimoto, K. Maruoka, *Chem Rev.* **2007**, *107*, 5656-5682; e) T. Ooi, K. Maruoka, *Angew. Chem. Int. Ed.* **2007**, *46*, 4222-4266; f) M. J. O'Donnell, *Acc. Chem. Res.* **2004**, *37*, 506-517; g) K. Maruoka, T. Ooi, *Chem. Rev.* **2003**, *103*, 3013-3028.
[90] For reviews on organocatalytic reactions promoted by chiral Brønsted bases, see ref 80.

most exploited substrates in soft enolization.[91] In this strategy, a relatively weak chiral amine is usually employed to reversively and catalytically deprotonate a relatively acidic substrate.

A simplified catalytic cycle involving carbonyl compounds is shown in Figure 7. Deprotonation of the carbonyl compound by the basic catalyst initiates the catalytic cycle forming a chiral ion pair. The enolate reacts with the electrophile in an enantioselective manner to afford a Nu-E adduct as reaction product and the free basic catalyst is released for a new catalytic cycle.

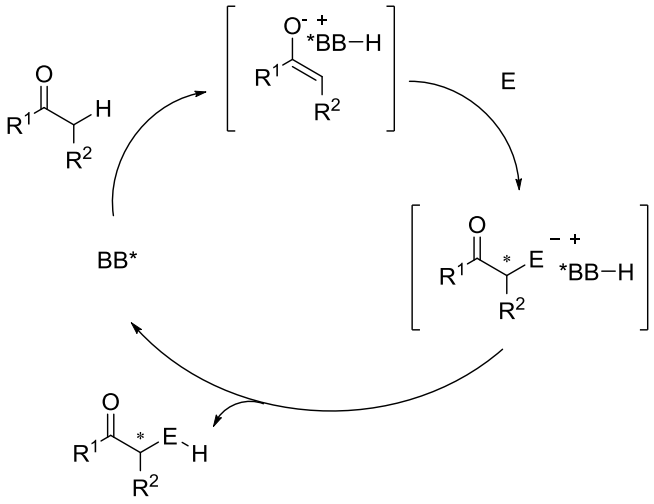


Figure 7. Catalytic cycle promoted by a chiral Brønsted base (BB*).

In the design of chiral BB catalysts, different nitrogen containing functionalities have been employed. Among them, tertiary amines, guanidines,[92] amidines and imidazoles[93] are the most prominent (Figure 8). Cinchona alkaloids constitute a very popular source of enantiopure BB, but their use in asymmetric catalysis has been limited to relatively acidic compounds with small pK_a values, like 1,3-dicarbonyl compounds (β-cyanoesters, malonitriles, nitroalkanes) in Mannich-type and 1,4-conjugate additions. Simple ketones, aldehydes, esters and other carboxylic acid derivatives remain elusive subtrates in BB catalysis.

[91] For pioneering examples of soft enolization, see: a) M. W. Rathke, P. J. Cowan, *J. Org. Chem.* **1985**, *50*,2622–2624; b) M. W. Rathke, M. Nowak, *J. Org. Chem*. **1985**, *50*, 2624–2626; c) R. E. Tirpak, R. S. Olsen, M. W. Rathke, *J. Org. Chem.* **1985**, *50*, 4877–4879.

[92] Guanidines are considered superbases, due to the stability of their conjugate acids. For reviews on guanidines in asymmetric synthesis, see: a) D. Leow, C.-H. Tan, *Chem. Asian J.* **2009**, *4*, 488–507; b) T. Ishikawa, T. Kumamoto, *Synthesis* **2006**, 737–752; c) T. Ishikawa, T. Isobe, *Chem. Eur. J.* **2002**, *8*, 553–557; d) D. Mailhol, M. M. Coquerel, J. Rodriguez, *Adv. Synth. Catal.* **2012**, *354*, 3523–3532.

[93] For a review on imidazole catalysts in asymmetric synthesis, see: Z. Zhang, F. Xie, J. Jia, W. Zhang, *J.Am. Chem. Soc.* **2010**, *132*, 15939–15941 and references therein.

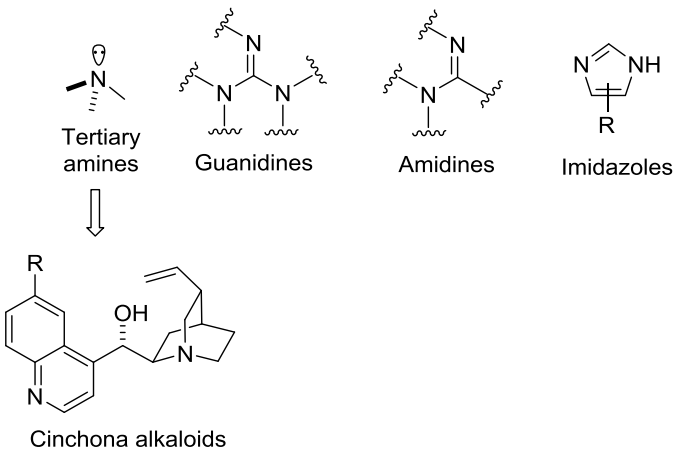
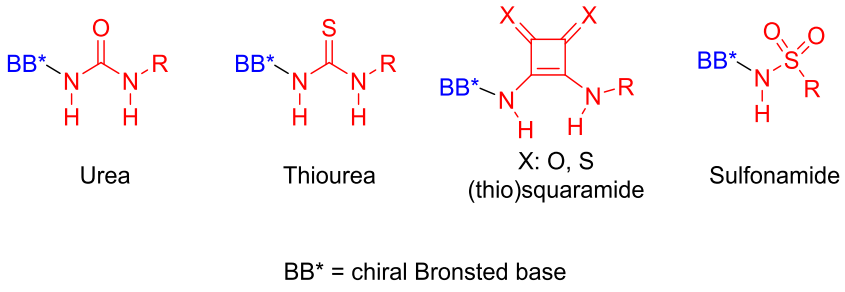


Figure 8. Monofunctional chiral BB catalysts.

As it has been mentioned before, in this kind of processes, chirality transfer from the chiral catalyst to the product occurs during the key C_{α}-E bond forming reaction. This step implies information transfer throughout a non-covalent substrate-catalyst ion-pairing complex, and due to the intrinsic nondirectional nature of these electrostatic interactions in ion-pairing complexes, prediction of the stereoinduction exerted from the catalyst is difficult to make. In order to form bonds in the correct orientation, dual activation is considered the best tool. In this case, both the nucleophile and electrophile are activated simultaneously by two catalytic units, improving the reaction efficiency and/or chemoselectivity.

The close proximity of both catalytic units, could facilitate asymmetric induction the same way enzymes do. In this context, the most successful strategies consist of a chiral amine (BB) and an efficient H-bond donor group, such as urea, thiourea, (thio)squaramide or sulphonamide (Scheme 9). These modifications have given rise to more active and selective bifunctional BB catalysts.[94]



Scheme 9. General structure of chiral bifunctional BB catalysts.

[94] a) S. Nagy, G. Dargó, P. Kisszéleky, Z. Fehrér, A. Simon, J. Barabás, T. Höltzl, B. Mátravölgyi, L. Kárpáti, L. Drahos, P. Huszthy, J. Kupai, *New. J. Chem.* **2019**, *43*, 5948-5959; b) Y. Nishikawa, *Tetrahedron Lett.* **2018**, *59*, 216-223.

The most representative bifunctional Brønsted base catalysts are shown below (Figure 9).

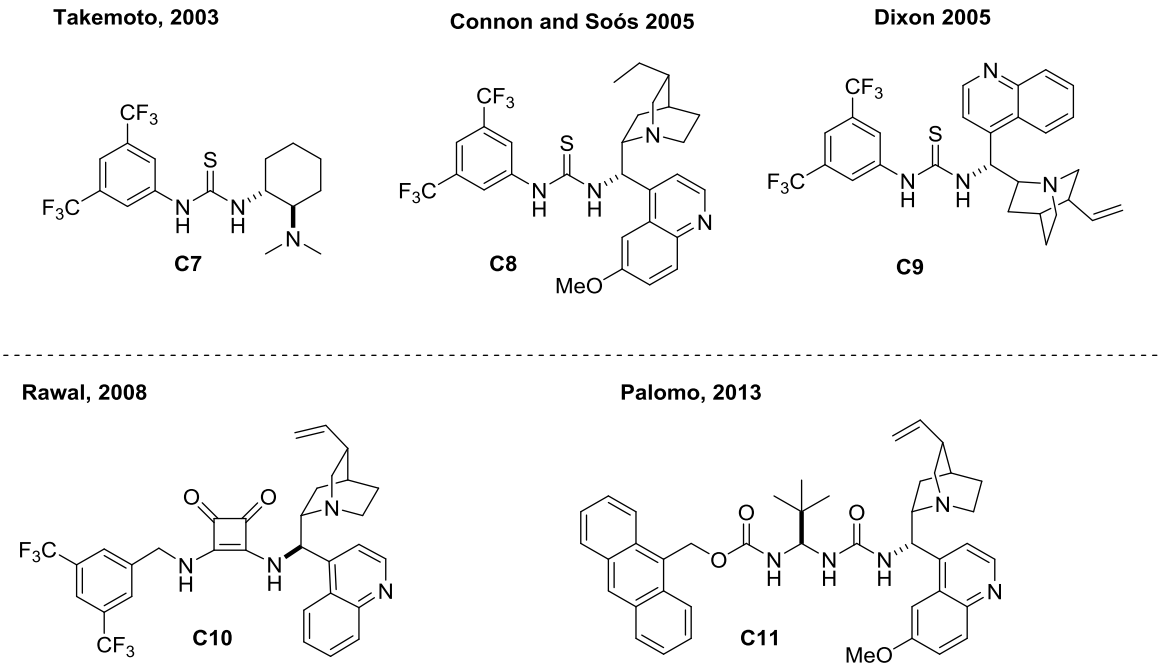


Figure 9. Representative bifunctional Brønsted Bases.

In 2003, Takemoto *et al.*[95] developed the first highly enantioselective bifunctional Brønsted base **C7**, which consisted of a 1,2-diaminocyclohexane derived thiourea which worked efficiently in the Michael addition of malonates to nitroalkenes. According to the authors proposal, the nucleophile would be activated by the amino group, whereas the thiourea moiety would activate the electrophile (a, Figure 10). This way, the approach of both components occurs in a stereoselective manner.[96] However, later Pápai and co-workers proposed and alternative substrate-catalyst combination for the same transformation (b, Figure 10).[97]

[95] T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.
[96] T. Okino, Y. Hoashi, T. Furakawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119–125.
[97] Pápai proposed that the nucleophile coordinates to the NH-bonds of the thiourea moiety and the nitrostyrene is activated by the protonated tertiary amine, based on DFT studies: a) A. Hamza, G. Schubert, T. Soós, I. Pápai *J. Am. Chem. Soc.* **2006**, *128*, 13151-13160. Later Zhong reported a modified proposal based on DFT studies, stating that the proton in ortho position of the aromatic ring in a similar thiourea type catalyst also participates in the activation of the nucleophile in the conjugate addition of a cyclic ketoester to nitrosyrenes, see Figure 12, B2. Further evidence of the participation of this proton was provided by Schreiner and co-workers, based on IR, NMR, ESI and DFT studies: b) K. M. Lippert, K. Hof, D. Gerbig, D. Ley, H. Hausmann, S. Guenther, P. R. Schreiner, *Eur. J. Org. Chem.* **2012**, 5919-5927.

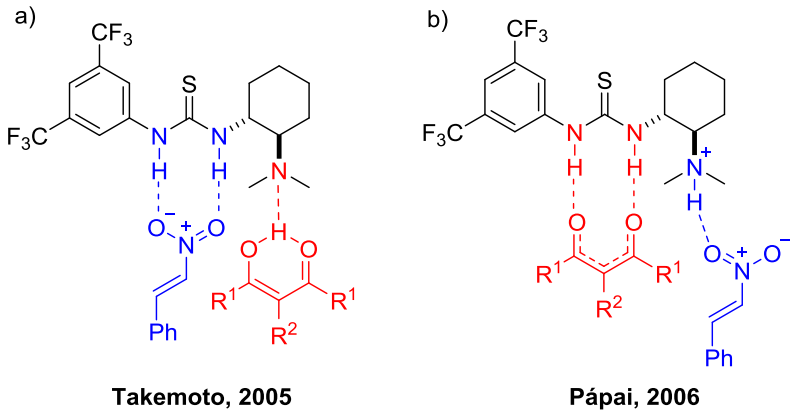


Figure 10. Two proposals for the catalyst-substrate interactions in the conjugate addition of malonates to nitrostyrene promoted by thiourea **C7**.

After this pioneering work, many other chiral tertiary amine derived thioureas were developed and efficiently used in enantioselective catalytic reactions. Connon, Dixon and Soós independent work[98] reported simultaneously bifunctional (thio)urea-tertiary amine catalysts **C8-C9** (Figure 9) to promote Michael reactions efficiently.

Rawal and co-workers[99] introduced in 2008 the squaramide containing structure **C10** (Figure 9) bearing a squaramide group as efficient H-bond donor unit in asymmetric catalysis. The first reaction employing this type of catalysts was the conjugate addition of 2,4-pentanediones to β-nitrostyrene with excellent results at even low catalyst loading (0.1 mol%). Since then, other groups have employed squaramide type Brønsted base catalysts in many other transformations,[100] with special success in tandem and domino reactions,[101] including the thiosquaramide-derived variant.[102]

Both (thio)urea and squaramide functions are structurally rigid. Nevertheless, unlike (thio)ureas, squaramides contain two (N-H) and two carbonyl (C=O) units showing one more acceptor than thioureas (Figure 11). Besides, the distance between both hydrogen units attached to the nitrogen atom is larger in the case of squaramides (2.71 A vs 2.13 A).[103] Both units are able to delocalize the nitrogen lone pair through the carbon heteroatom double bond, but squaramides can delocate the lone pair through the

[98] a) S. H. McCoey, S. J. Connon *Angew. Chem. Int. Ed.* **2005**, *44*, 6367-6370. b) J. Ye, D. J. Dixon, P. S. Hynes *Chem. Commun.* **2005**, 4481-4483. c) B. Vakulya, S. Varga, A. Csámpai, T. Soós *Org. Lett.* **2005**, *7*, 1967-1969.
[99] J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416–14417.
[100] For reviews on squaramide-based catalysts see: a) B.-L. Zhao, J.-H. Li, S.-M. Du, *Chem. Rec.* **2017**, *17*, 994–1018; b) X. Han, H.-B. Zhou, C. Dong, *Chem. Rec.* **2016**, *16*, 897–906; c) J. Alemán, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 6890–6899.
[101] For a review on squaramide-catalyzed domino and tandem reactions see: P. Chauhan, S. Mahajan, U. Kaya, D. Hack, D. Enders, *Adv. Synth. Catal.* **2015**, *357*, 254–281.
[102] M. Rombola, V.-H. Rawal, *Org. Lett.* **2018**, *20*, 514-517.
[103] T. Okino, Y. Hoashi, T. Fukurawa, X. N. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119–125

partially aromatic cyclobutenedione, thus increasing the acidity of N-H unit, compared to the thiourea analogs.[104] Consequently, squaramides can form stronger hydrogen bonds, which may explain their higher reactivity, even at lower catalyst loadings.

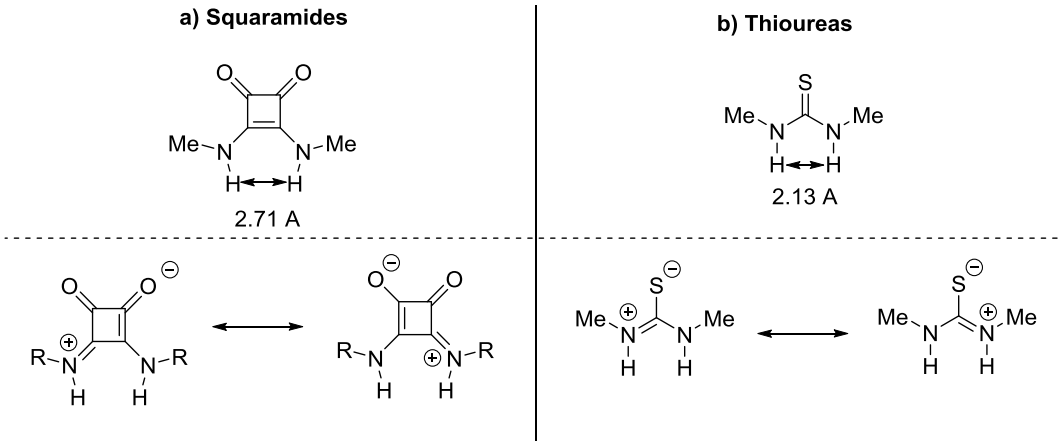


Figure 11. Comparison between squaramides and thioureas.

In 2013, our research group introduced a new variant of bifunctional BB catalyst containing a ureidopeptide unit as H bond donor site[105] which bears three tunable parts for stereoinduction. In this first work, catalyst **C11** (Figure 9) was employed in the Michael reaction of 5*H*-thiazol-4-ones with nitroolefins with high diastereo- and enantioselectivity and it proved to be more effective than Takemoto's thiourea in the reaction. These catalysts are easily tunable in the carbamate group, the amino acid rest and in the chiral BB site for improving the efficiency, and they have been employed in our research group in different reactions providing the reaction adducts with excellent diastereo- and enantioselectivities.[106]

In general, when bifunctional BB catalysts are employed, three possible and different mechanistic proposals (including the previously mentioned proposals of Takemoto and Pápai/Zhong) can be considered, as depicted in Figure 12.[107]

[104] a) S. Tomàs, R. Prohens, M. Vega, M. C. Rotger, P. M. Deyá, A. Costa, *J. Org. Chem.* **1996**, *61*, 9394 9401. b) T. Okino, Y. Hoashi, T. Fukurawa, X. N. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119-125.

[105] a) S. Diosdado, J. Etxabe, J. Izquierdo, A. Landa, A. Mielgo, I. Olaizola, R. López, C. Palomo, *Angew. Chem. Int. Ed.* **2013**, *52*, 11846–11851.

[106] For further utility of these catalysts, see: a) I. Bastida, M. San Segundo, R. López, C. Palomo *Chem. Eur. J.* **2017**, *23*, 13332-13336; b) H. Echave, R. López, C. Palomo *Angew. Chem Int. Ed.* **2016**, *55*, 3364-3368; c) S. Diosdado, R. López, C. Palomo, *Chem. Eur. J.* **2014**, *20*, 6526–6531.

[107] For Model A, see a) ref. 96; For Model B1, see: b) see ref. 97a; For Model B2, see: c) B. Tan, Y. Lu, X. Zeng, P. J. Chua, G. Zhong *Org. Lett.* **2010**, *12*, 2682-2695 (based on DFT studies). For Model C (based on DFT and NMR studies), see: d) J.-L. Zhu, Y. Zhang, C. Liu, A.-M. Zheng, W. Wang, *J. Org. Chem.* **2012**, *77*, 9813-9825.

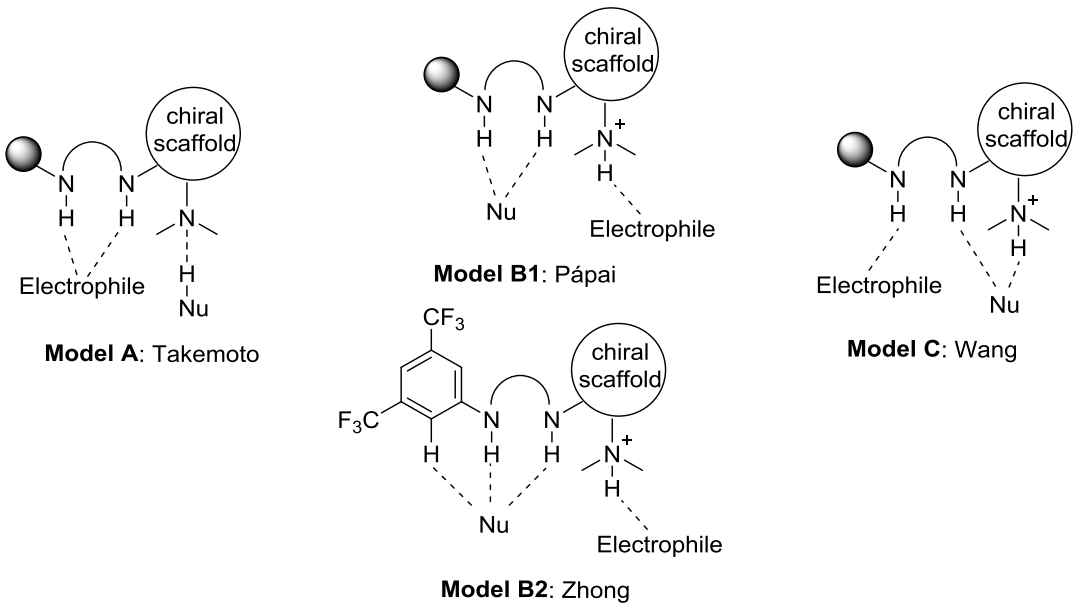


Figure 12. Three alternative substrate-catalyst combinations in reactions promoted by bifunctional BBs.

The development of new types of bifunctional BBs has enabled different transformations at the α-position of carbonyl compounds. The main contributions are explained below.

a) More reactive carbonyl compounds

The α-functionalization of carbonyl compounds promoted by BBs has been mainly focused on 1,3-dicarbonyl compounds, while no examples of aldehydes have been reported to the best of our knowledge.

In this context, mono thiomalonates (MTMs) have been explored as efficient substrates for catalytic asymmetric Michael[108] and Mannich[109] reactions in BB catalysis. Other 1,3-dicarbonyl compounds (malonates, β-diketones, β-ketoesters) have been subjected to the conjugate addition to nitroolefins[110] and enones,[111] promoted by

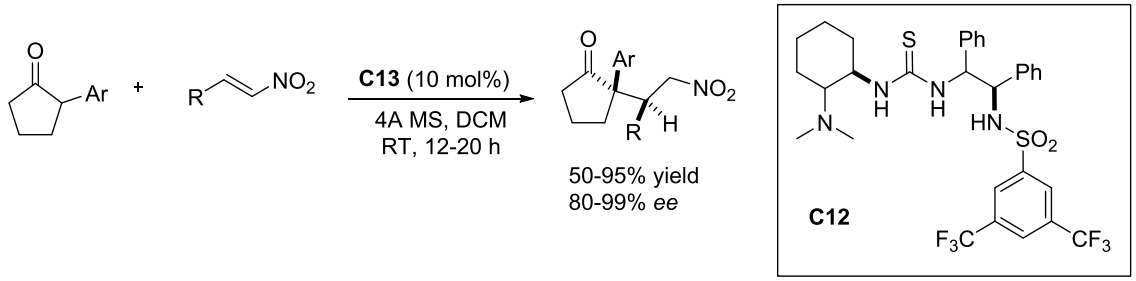
[108] a) A. Kolarovic, A. Käslin, H. Wennemers, *Org. Lett.* **2014**, *16*, 4236–4239; b) Y. Arakawa, S. P. Fritz, H. Wennemers, *J. Org. Chem.***2014**, *79*, 3937–3945; c) O. D. Eng, S. P. Fritz, A. Käsling, H. Wennemers, *Org. Lett.* **2014**, *16*, 5454–5457.
[109] a) O. D. Engl, S. P. Fritz, H. Wennemers, *Angew. Chem. Int. Ed.* **2015**, *54*, 8193–8197; b) A. Bahlinger, S. P. Fritz, H. Wennemers, *Angew. Chem. Int. Ed.* **2014**, *53*, 8779–8783.
[110] a) H.Y Bae, S. Some, J. S. Oh, Y. S. Lee, C. E. Song, *Chem. Commun.* **2011**, *47*, 9621-9623; b) J. Luo, L.-W. Xu, R.A.S. Hay, Y. Lu, *Org. Lett.* **2009**, *11*, 437-440; c) Z.-H. Zhang, X.-Q. Dong, D. Chen, C.-J. Wang, *Chem. Eur. J.* **2008**, *14*, 8780-8783; d) S. H. McCooey, S. J. Connon, *Angew. Chem. Int. Ed.* **2005**, *44*, 6367-6370; e) J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481-4483.
[111] J. Wang, H. Li,L. Zu,W. Jiang, H. Xie, W. Duan, W. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 12652-12653.

bifunctional BBs, as well as to Mannich reactions,[112] α-aminations[113] and aldol-lactonizations[114] with excellent stereoselectivity.

b) Less reactive carbonyl compounds

As previously mentioned, the α-functionalization of less reactive carbonyl compounds (ketones, esters and amides) promoted by BBs is challenging due to the low acidity of the α-carbon, and activation of the nucleophile is required for their use in BB catalysis.

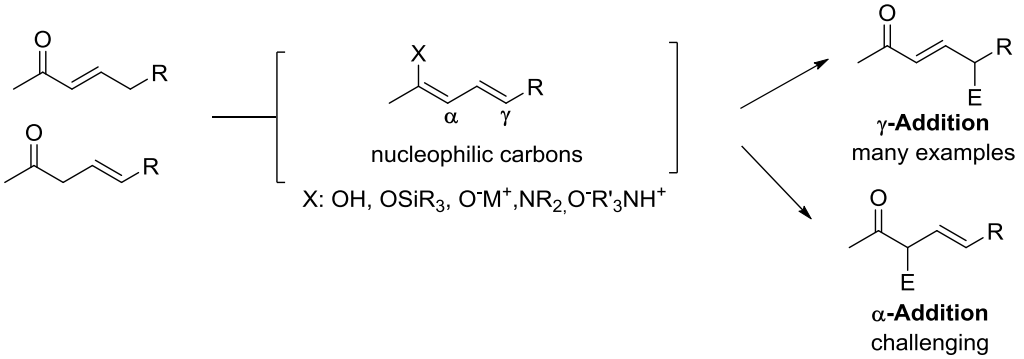
In this context, few protocols for the α-functionalization of ketones via BB have been published[115] and, as mentioned, they all include activating groups at the α-position. Wang and co-workers[116] reported the first asymmetric conjugate addition of α-aryl cyclopentanones to nitroolefins promoted by the bifunctional organocatalyst **C12** which bear multiple H-bond donors (Scheme 10). In this case, the aromatic substituent at the α-position of the starting ketone enhances the acidity of that carbon. Following this work, Zhao and co-workers[117] performed the first enantioselective Mannich reaction of ketones bearing electron withdrawing groups at the α-position with excellent diastereo- and enantioselectivity using bifunctional BBs.



Scheme 10. Michael addition of α-aryl cyclopentanones to nitroolefins promoted by **C12**. **Wang, 2010**.

[112] a) A. L. Tillman, J. Ye, D. J. Dixon, *Chem. Commun.* **2006**, 1191-1193. b) J. Song, Y. Wang, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 6048-6049.
[113] a) H. Konishi, T. Y. Lam, J. P. Lamerich, V. H. Rawal, *Org. Lett.* **2010**, *12*, 2028-2031; b) S. Saaby, M. Bella, K.A. Jørgensen, *J. Am. Chem. Soc.* **2004**, *126*, 8120-8121.
[114] S. Meninno, T. Fuoco, C. Tedesco, A. Lattanzi, *Org. Lett.* **2014**, *16*, 4746-4749.
[115] R. Cano, A. Zakarian, G. P. McGlacken, *Angew. Chem. Int. Ed.* **2017**, *56*, 9278-9290.
[116] X.-Q. Dong, H.-L.Teng, M.-C. Tong, H. Huang, H.-Y. Tao, C.-J. Wang, *Chem. Commun.* **2010**, *46*, 6840-6842.
[117] Q. Guo, J C.-G. Zhao, *Org. Lett.* **2013**, *5*, 508-511.

In addition, dienolate (or equivalent dienamine) intermediates are considered particular ketones and their use as nucleophiles[118] involves the control of the α- vs ϒ-competitive reaction pathways (Scheme 11).

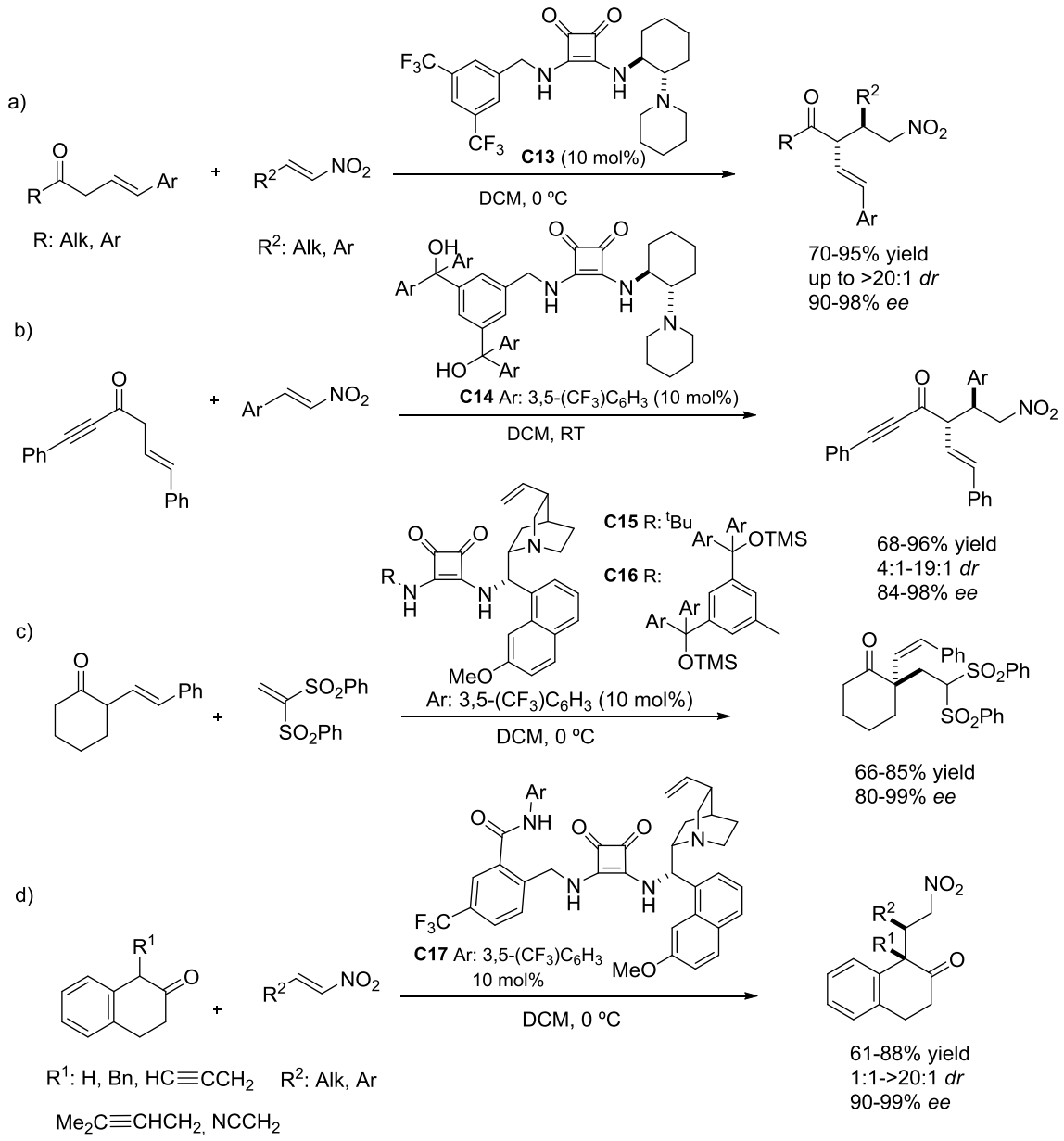


Scheme 11. Competitive pathways in the functionalization of dienolate intermediates.

The resulting adducts are of great synthetic versatility. While γ-addition products have been obtained by enamine (dienamine/trienamine)[119] and metal catalysis,[120] the alternative α-reaction is less favoured due to the disruption of the π-conjugation at some point of the reaction. In this context, Brønsted base catalyzed α-functionalization of vinylogous enolates remains little explored, and the few examples described provide the adducts with moderate enantioselectivities or are restricted to specific substrates. Hence, our research group has reported the catalytic asymmetric α-selective conjugate addition of vinylogous ketone enolates[121a] (Scheme 12a), alkynyl ketones[121b] (Scheme 12b), cyclic and acyclic α-substituted ketones[121c] (Scheme 12c) and tetralones[121d] (Scheme 12d) with excellent stereoselectivity. In addition, conjugate addition of α-hydroxy ketones (h, Figure 14)[122a] (activated ketones, masked ester donors) to nitroalkenes under bifunctional BB catalysis, afforded reaction adducts with excellent stereoselectivity and their

[118] For reviews on vinylogous addition reactions, see: a) C. Schneider, F. Abels, *Org. Biomol. Chem.* **2014**, *12*, 3531–3543; b) G. Casiraghi, L. Battistini, C. Curti, G. Rassu, F. Zanardi, *Chem. Rev.* **2011**, *111*, 3076–3154. c) S. E. Denmark, J. R. Heemstra, G. L. Beuter, *Angew. Chem. Int. Ed.* **2005**, *44*, 4682–4698.
[119] For reviews, see: a) V. Marcos, J. Alemán, *Chem. Soc. Rev.* **2016**, *45*, 6812-6832; b) I. D. Jurberg, I. Chatterjee, R. Tannerta, P. Melchiorre, *Chem. Commun.* **2013**, *49*, 4869-4883.
[120] For reviews, see: a) X. Jusseau, L. Chabaud, C. Guillou, *Tetrahedron* **2014**, *70*, 2595-2615. b) Q. Zhang, X. Liu, X. Feng, *Curr. Org. Synth.* **2013**, *10*, 764-785.
[121] a) I. Iriarte, O. Olaizola, S. Vera, I. Gamboa, M. Oiarbide, C. Palomo, *Angew. Chem. Int. Ed.* **2017**, *56*, 8860-8864; b) T. Campano, I. Iriarte, O. Olaizola, J. Etxabe, A. Mielgo, I. Ganboa, J. M. Odriozola, J. M. Garcia, M. Oiarbide, C. Palomo, *Chem. Eur. J.* **2019**, *25*, 4390-4397; c) I. Urruzuno, O. Mugica, G. Zanella, S. Vera, E. Gómez-Bengoa, M. Oiarbide, C. Palomo, *Chem. Eur. J.* **2019**, *25*, 9701-9709; d) I. Urruzuno, O. Mugica, M. Oiarbide, C. Palomo, *Angew. Chem. Int. Ed.* **2017**, *56*, 2059-2063.
[122] a) I. Olaizola, T. E. Campano, I. Iriarte, S. Vera, A. Mielgo, J. M. Garcia, J. M. Odriozola, M. Oiarbide, C. Palomo, *Chem. Eur. J.* **2018**, *24*, 3893-3901. Another example involving α-hydroxyketones as nucleophiles in organocatalysis: b) P. Wang, H.-F. Li, J.-Z. Zhao, Z.-H. Du, C.-S. Da, *Org. Lett.* **2017**, *19*, 2634-2637.

elaboration provided the corresponding enantioenriched α-branched carboxylic acids and aldehydes.



Scheme 12. Some examples from our research group of α-selectivity in the conjugate addition of ketones.

With respect to carboxylic acid derivatives, as well as for metal-catalysis, more reactive heterocyclic and acyclic donors have been developed for BB-catalyzed reactions in order to access through posterior transformation, α-functionalized esters and amides.

Heterocyclic donors

As mentioned before in the metal catalysis section, different heterocycles whose pK_a is lower due to the formation of aromatic enolates and whose hydrolysis gives rise to α- or β-amino acid derivatives have been also applied in organocatalysis. Oxazol-5-(4*H*)-

ones[123] (or azlactones), their analogues thiazol-5-(4*H*)-ones[124] (1a, Figure 13) and oxazol-4-(5*H*)-ones[125] and their thiazolone[105] and imidazolone[126] analogues (1b, Figure 13) have been also explored in the field. As mentioned, thiazolones were developed in our research group and employed in different reactions.[127] Likewise, the conjugate addition of related hydantoins (1c, Figure 13) to nitroolefins and vinyl ketones has been reported in our group.[128]

Regarding substrates which do not generate aromatic enolates, but which bear more acidic α-carbons, rhodanines,[129] piperazin-2,3,6-triones[130] and barbituric acid derivatives[131] (2a, 2b and 2c, Figure 13) have also been reported in different organocatalytic reactions with excellent stereoselectivity.

[123] a) A.-N. Alba, R- Ríos, *Chem.-Asian J.* **2011**, *6*, 720-734; b) R. A. Mosey, J. S. Fisk, J. J. Tepe, *Tetrahedron: Asymmetry* **2008**, *19*, 2755-2762.

[124] For the first organocatalytic asymmetric reaction with these substrates, see: a) D. Uraguchi, K. Koshimoto, T. Ooi, *Chem. Commun.* **2010**, *46*, 300-302. Other organocatalytic reactions: b) X. Liu, L. Deng, H. Song, H. Jia, R. Wang, *Org. Lett.* **2011**, *13*, 1494-1497; c) X. Liu, H. Song, Q. Chen, W. Li, W. Yin, M. Kai, R. Wang, *Eur. J. Org. Chem.* **2012**, 6647-6655; d) D. Uraguchi, K. Yamada, T. Ooi, *Angew. Chem. Int. Ed.* **2015**, *54*, 9954-9957

[125] Applications in organocatalysis: a) A. Morita, T. Misaki, T. Sugimura *Tetrahedron. Lett.* **2015**, *56*, 264-267; b) T. Wang, Z. Yu, D.-L. Hoon, K.-W. Huang, Y. Lan, Y. Lu *Chem. Sci.* **2015**, *6*, 4912-4922; c) S. Duan. S. Li, N.-N. Du, C.-H. Tan, Z. Jiang *J. Org. Chem.* **2015**, *80*, 7770-7778; d) Q. Liu, B. Qiao, K. F. Chin, C.-H. Tan, Z. Jiang *Adv. Synth. Catal.* **2014**, *356*, 3777-3783; e) A. Morita, T. Misaki, T. Sugimura *Chem. Lett.* **2014**, *43*, 1826-1828; f) M. Xu, B. Qiao, S. Duan, H. Liu, Z. Jiang *Tetrahedron* **2014**, *70*, 8696-8702; g) B. Qiao, Y. An, Q. Liu, W. Yang, H. Liu, J. Shen, L. Yan, Z. Jiang *Org. Lett.* **2013**, *15*, 2358-2361; h) N. Lu, H. Wang Int. *J. Quantum Chem* **2013**, *113*, 2267-2276; i) Z. Han, W. Yang, C.-H. Tan *Adv. Synth. Catal.* **2013**, *355*, 1505-1511; j) N. Jin, T. Misaki, T. Sugimura *Chem. Lett.* **2013**, *42*, 894-896; k) H. Huang, K. Zhu, W. Wu, Z. Jin, J. Ye *Chem. Commun.* **2012**, *48*, 461-463; l) T. Misaki, N. Jin, K. Kawano, T. Sugimura *Chem. Lett.* **2012**, 1675-1677; m) T. Misaki, N. Jin, K. Kawano, T. Sugimura *J. Am. Chem. Soc.* **2011**, *133*, 5695-5697; n) T. Misaki, G. Takimoto, T. Sugimura *J. Am. Chem. Soc.* **2010**, *132*, 6286-6287.

[126] J. Etxabe, J. Izquierdo, A. Landa, M. Oiarbide, C. Palomo, *Angew. Chem. Int. Ed.* **2015**, *54*, 6883-6886.

[127] T. Wang, Z. Yu, D. L. Hoon, K.-W. Huang, Y. Lan, Y. Lu, *Chem. Sci.* **2015**, *6*, 4912-4922.

[128] a) J. Izquierdo, N. Demurget, A. Landa, T. Brinck, J. M. Mercero, P. Dinér, M. Oiarbide, C. Palomo, *Chem. Eur. J.* **2019**, *25*, 12431-12438; b) J. Izquierdo, J. Etxabe, E. Duñabeitia, A. Landa, M. Oiarbide, C. Palomo, *Chem. Eur. J.* **2018**, *24*, 7217-7227.

[129] H. Xu, T.-C. Kang, F. Sha, X.-Y. Wu, *Org. Biomol. Chem.* **2018**, *16*, 5780-5787.

[130] a) R. W. Foster, E. N. Lenz, N. S. Simpkins, D. Stead, *Chem. Eur. J.* **2017**, *23*, 8810-8813; b) A. Cabanillas, C. D. Davies, L. Male, N. S. Simpkins, *Chem. Sci.* **2015**, *6*, 1350-1354.

[131] a) see Ref 45; b) S. Del Pozo, S. Vera, M. Oiarbide, C. Palomo, *J. Am. Chem. Soc.* **2017**, *139*, 15308-15311

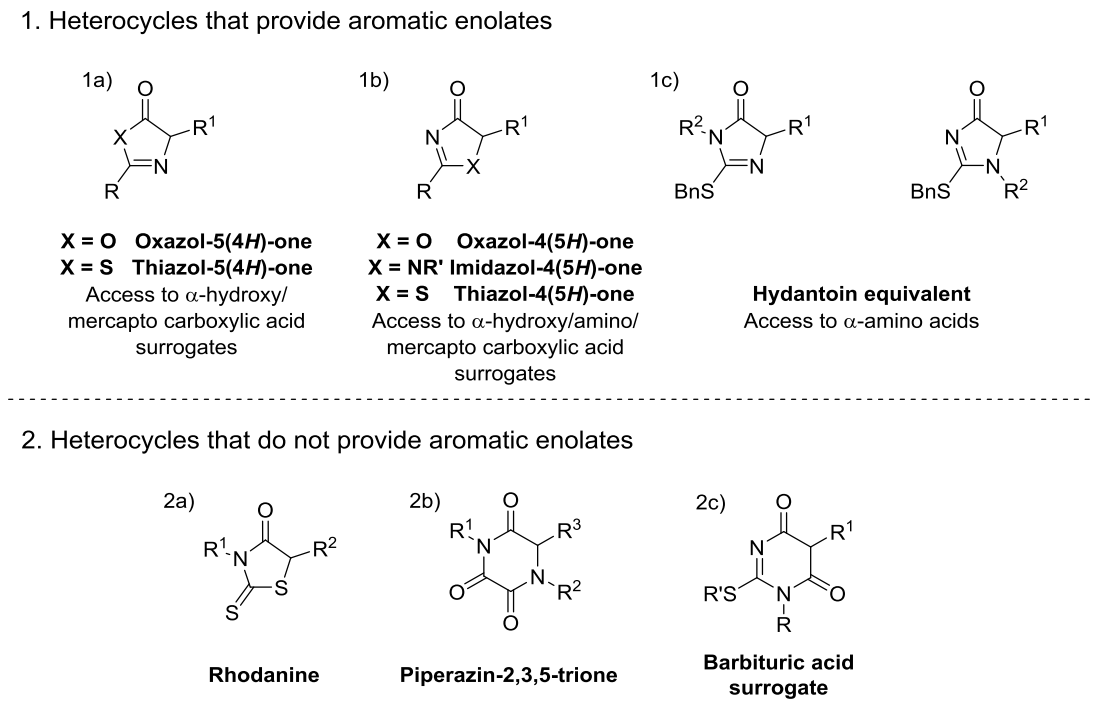


Figure 13. Some representative activated heterocycles employed in BB catalysis for their asymmetric α-functionalization.

Acyclic donors

As mentioned in section 1.1.2.1., malonic acid half esters and thioesters (MAHOs and MAHTs) have been successfully employed as more reactive ester surrogates not only in metal catalysis, but also in organocatalysis (a, Figure 14).[51] However, a more atom economical approach, avoiding decarboxylation as a driving force is the use of arylacetic thioesters (b, Figure 14). These reagents have been applied in asymmetric Michael[132] and Mannich[133] reactions. Thioesters were also employed in our group as more reactive ester analogues,[121a] where β,γ-unsaturated thioesters (c (X=S), Figure 14) were found to be more reactive and regioselective to α-addition than their parent esters (c (X=O), Figure 14).[134]

[132] a) D. A. Alonso, S. Kitagaki, N. Utsumi, C. F. Barbas III, *Angew. Chem. Int. Ed.* **2008**, *47*, 4588–4591; b) S. Duce, M. Jorge, I. Alonso, J. L. G. Ruano, M. B. Cid, *Eur. J. Org. Chem.* **2013**, 7067–7075; c) P.-Y. Géant, M. Urban, M. Remes, I. Císarova, J. Veselý, *Eur. J. Org. Chem.* **2013**, 7979–7988; d) A. Claraz, G. Sahoo,D. Berta, A. Madarász, I. Pápai, P. M. Pikho, *Angew. Chem. Int. Ed.* **2016**, *55*, 669–673; e) S. Li, E. Zhang, J. Feng, X. Li, *Org. Chem. Front.* **2017**, *4*, 2301–2305.

[133] a) J. Guang, A. J. Larson, J. C. G. Zhao, *Adv. Synth. Catal.* **2015**, *357*, 523–529; b) M. C. Kohler, J. M. Yost, M. R. Garnsey, D. M. Caltart, *Org. Lett.* **2010**, *12*, 3376–3379..

[134] Mannich reaction involving α-Styrylacetates: Guang, S. Rout, M. Bihani, A. J. Larson, H. D. Arman, J. C.-G. Zhao, *Org. Lett.* **2016**, *18*, 2648-2651.

In addition, pyrazoleamides (d, Figure 14), which are considered activated amide structures, are the only example of direct α-functionalization of amides,[135] and were first reported in organocatalysis by Barbas III.[135d] This functional group increases the acidity of the α-carbon and also improves the steoreocontrol through hydrogen bonding. Moreover, the pyrazol group can be displaced by nucleophiles such as alcohols and amines, affording different esters and amides.

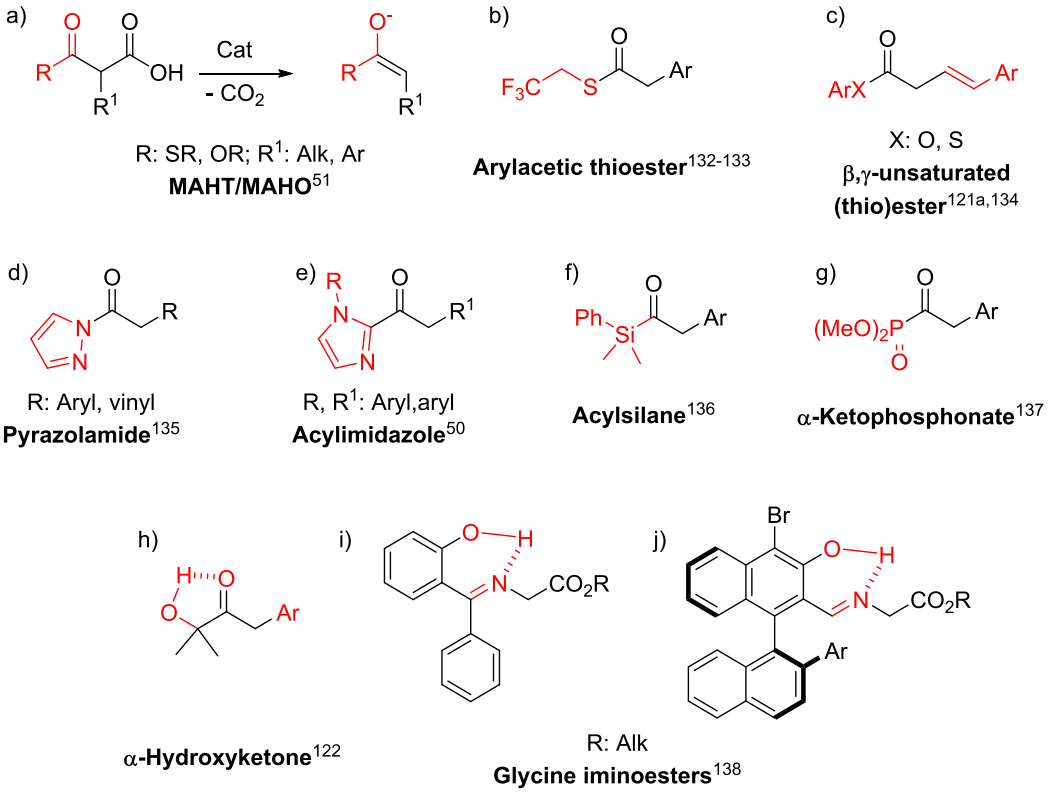


Figure 14. Some representative activated acyclic donors employed for their BB catalyzed asymmetric α-functionalization.

Acylimidazoles (e, Figure 14),[50] acylsilanes (f, Figure 14)[136] and α-ketophosphonates (g, Figure 14)[137] have also been explored in organocatalytic reactions. After reaction, these groups can be easily converted into carboxylic acids, esters or amides. Another strategy involves the activation of the substrates through intramolecular

[135] A recent example in Diels-Alder reaction: a) J. Quin, Y. Zhang, C. Liu, J. Zhou, R. Zhan, W. Chen, H. Huang, *Org. Lett.* **2019**, *21*, 7337-7341; b) S. Agrawal, N. Molleti, V. K. Singh, *Chem. Commun.* **2015**, *51*, 9793-9796 ; c) T. Ze, X.-B. Wang, F. Sha, X.-Y. Wu, *J. Org. Chem.* **2014**, *79*, 4332-4339; d) B. Tan, G. Hernández-Torrez, C. F. Barbas III, *Angew. Chem. Int. Ed.* **2012**, *51*, 5381-5385.
[136] L. Wu, G. Li, Q. Fu, L. Yu, Z. Tang, *Org. Biomol. Chem.* **2013**, *11*, 443-447.
[137] a) J. Guang, J. C.-G. Zhao, *Tetrahedron Lett.* **2013**, *54*, 5703-5706. b) J. Guang, Q. Guo, J. C.-G. Zhao, *Org. Lett.* **2012**, *14*, 3174-3177.

hydrogen bonds, a feature that can increase the acidity of the methylenic carbon as in α-hydroxyketones (h, Figure 14)[122] and iminoesters i and j in Figure 14.[138]

The limitations in catalysis of less reactive carbonyl compounds are evident. More specifically, the described procedures for the α-functionalization of esters and amides involve stoichiometric enolization, while metal catalyzed and organocatalytic methods are scarce. In spite of that, enantiopure α-functionalized amides are of great interest due to their presence in pharmaceuticals, natural products and biologically active compounds. Therefore, renewing or developing new activation modes (that make α-carbon more acidic), to access these compounds in an catalytic manner is required.

1.3. **Objectives**

The previous precedents show that, due to the low acidity of the α-carbon in amides, their asymmetric organocatalytic α-functionalization has been scarcely developed. There is only one example of α-functionalization promoted by BBs, which involves the use of pyrazoleamides as activated amide substrates.

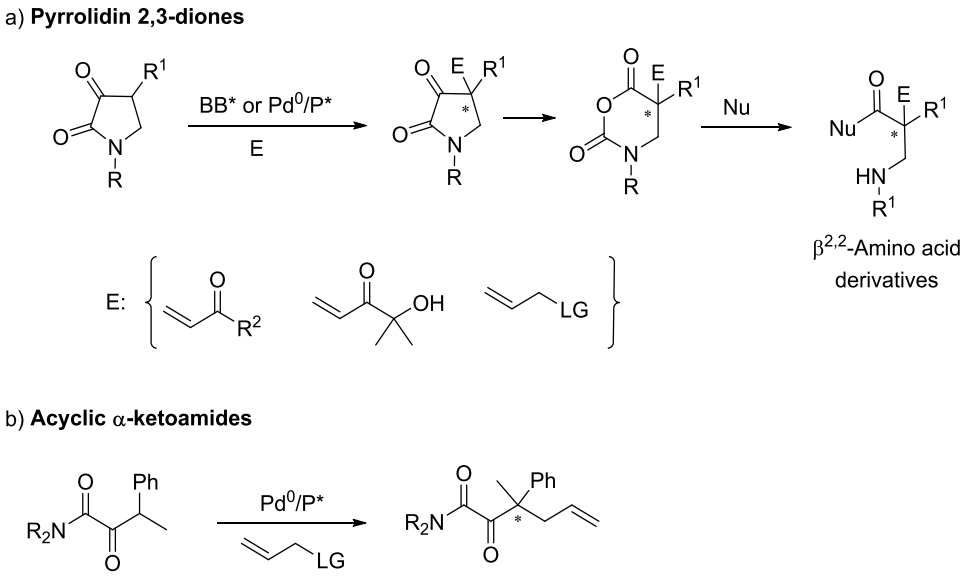
The limitations in the direct catalytic functionalization of amides render interesting approaches involving functionalization starting from more reactive heterocyclic surrogates and further transformation into amides. In this context, our first goal has been the introduction of a new and efficient heterocycle for catalytic reactions and for subsequent transformation into different functionalities with generation of tetrasubstituted stereocenters, particularly all-cabon quaternary stereocenters[139] which is still challenging in asymmetric organocatalysis.

With this purpose in mind, we selected pyrrolidin 2,3-diones (a, Scheme 13) as promising pronucleophiles for two reasons. First, because the corresponding reaction adducts could be transformed under mild conditions into $\beta^{2,2}$-amino acid derivatives; and secondly, because their heterocyclic scaffold is present in molecules of biological interest. To evaluate the usefulness of these cyclic ketoamides as pronucleophiles in catalytic

[138] a) W. Wen, L. Chen, M.-J. Luo, Y. Zhang, Y.-C. Chen, Q. Ouyang, Q.-X. Guo, *J. Am. Chem. Soc.* **2018**, *140*, 9774-9780; b) A. Guerrero-Corella, F. Esteban, M. Iniesta, A. Martín-Somer, M. Parra, S. Díaz.Tendero, A. Fraile, J. Alemán, *Angew. Chem. Int. Ed.* **2018**, *57*, 5350-5354.

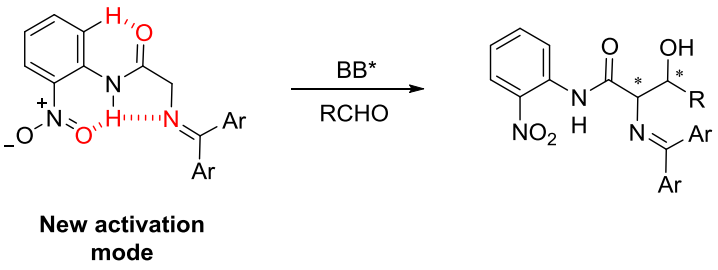
[139] For reviews, see: a) A. Y. Hong, B. M. Stoltz, *Eur. J. Org. Chem.* **2013**, 2745 –2759; b) J. P. Das, I. Marek, *Chem. Commun.* **2011**, *47*, 4593– 4623; c) M. Bella, T. Caspery, *Synthesis* **2009**, 1583 –1614; d) P. G. Cozzi, R. Hilgraf, N. Zimmerman, *Eur. J. Org. Chem.* **2007**, 5969– 5614; e) B. M. Trost, C. Jiang, *Synthesis* **2006**, 369– 396; f) *Quaternary Stereocenters* (Eds: J. Christoffers, A. Baro) Wiley-VCH, Weinheim, **2005**; g) C. J. Douglas, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363 –5367.

reactions, conjugate additions and Pd-catalyzed asymmetric allylic alkylation (Pd-AAA) were selected. As an additional challenge, the investigation of acyclic ketoamides in the Pd-AAA was also considered (b, Scheme 13). The corresponding results are explained in Chapter 2.



Scheme 13. a) Transformation of pyrrolidin-2,3-diones into $\beta^{2,2}$-amino acid derivatives. b) Pd-catalyzed AAA of acyclic α-ketoamides.

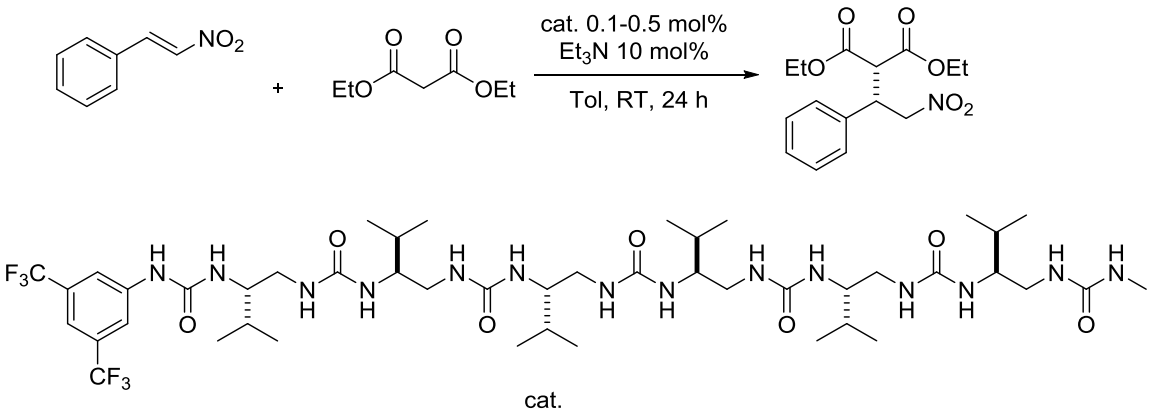
Another objective of this Thesis has been the development of a new activation mode for amides in order to overtake their inherent low reactivity and to access enantiopure amide containing reaction adducts leaving behind old fashioned stoichiometric and metallic procedures. Therefore, an activated amide bearing an intramolecular hydrogen bonding system has been designed for aldol reactions promoted by bifunctional BBs (Scheme 14). These results are collected in Chapter 3.



Scheme 14. Novel activation mode in amides for BB catalysis.

Finally, a short stay was carried out under supervision of Prof. Gilles Gichard in the European Institute of Chemistry and Biology (IECB) at Bordeaux-Pessac campus in the Peptidomimetic Chemistry Group. The research project has focused on the synthesis

of valine-based oligoureas and their evaluation as H-bonding chiral organocatalysts in the well-known conjugate addition of diethyl malonate to nitrostyrene (Scheme 15). Chapter 4 deals with the corresponding results.



Scheme 15. Conjugate addition of diethyl malonate to nitrostyrene promoted by valine-based oligoureas.

Chapter 2

Pyrrolidin-2,3-diones as intermediates in the synthesis of α-functionalized amides

2. Pyrrolidin-2,3-diones as useful intermediates in the synthesis of enantiopure α-functionalized amides

2.1. General considerations

Construction of tetrasubstituted carbon stereocenters, particularly all-carbon quaternary stereogenic centers is an important challenging goal in asymmetric catalysis. However, the direct approach to structurally interesting molecules is often limited, due to the low reactivity and the difficulty in controlling the stereoselectivity of the process.[140] In this context, as mentioned in the introduction, direct catalytic α-functionalization of amides is challenging, due to the low acidity of the α-carbon. Therefore, the search of new and more efficient pronucleophiles that upon reaction with an electrophile, can be converted into different structures, is of great interest. Pyrrolidin-2,3-diones (Figure 15a) exhibit rich reactivity due to the combination of both nucleophilic and electrophilic characteristics, which can enable various types of reactions and sequential or cascade transformations with suitable nucleophiles and electrophiles. Furthermore, they are structural motifs that are present in a wide variety of biologically important compounds (Figure 15b).[141]

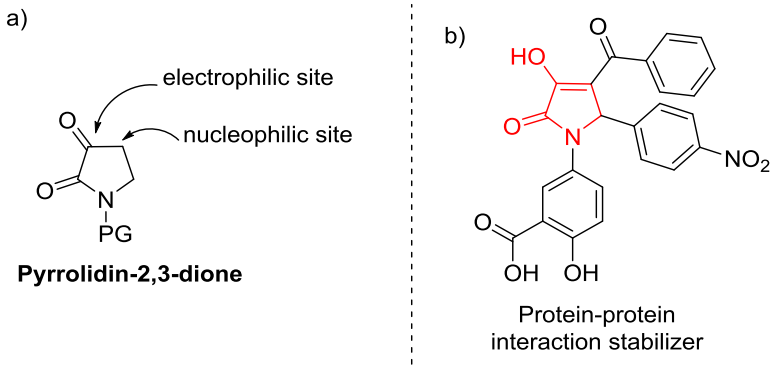


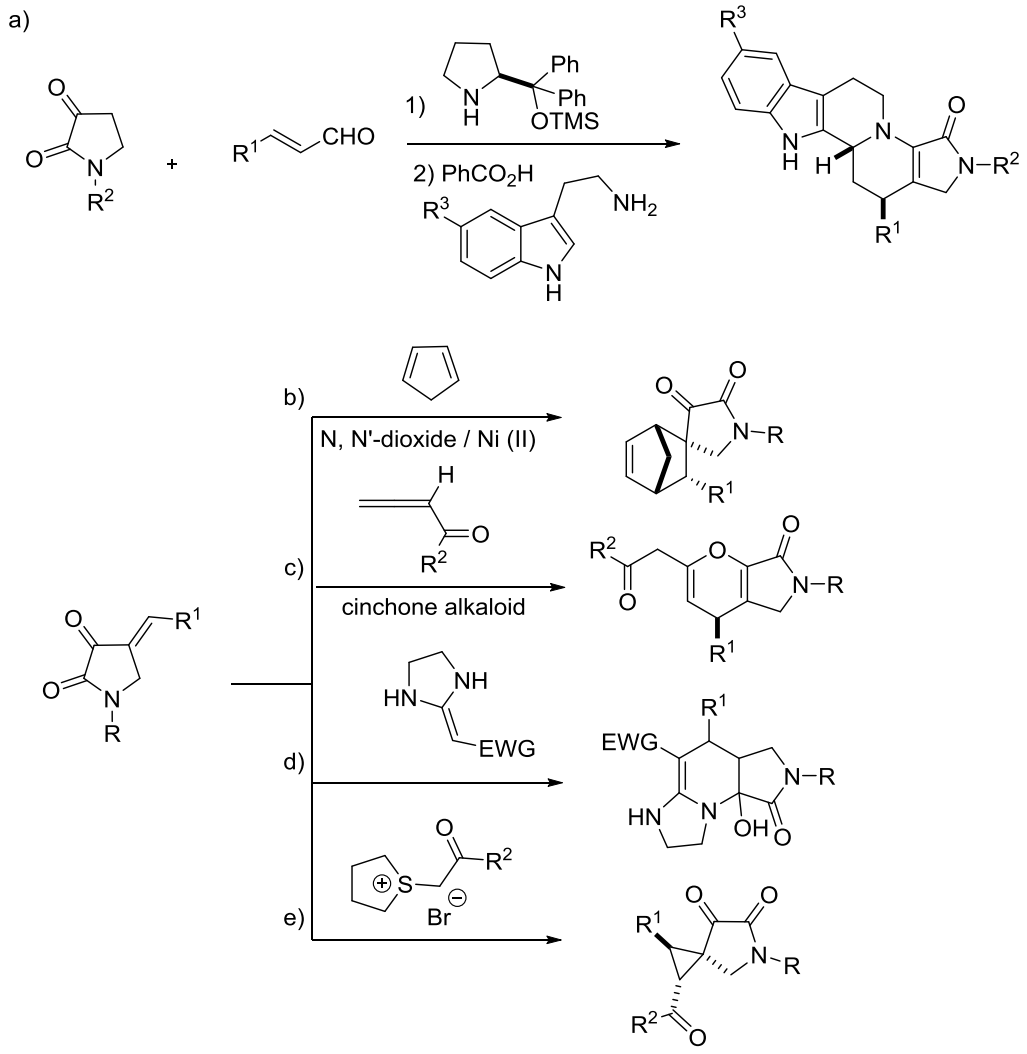
Figure 15. a) General structure of pyrrolidin-2,3-diones, and their reactive sites. b) An example of a biologically relevant compound bearing the above structure.

[140] For reviews, see: a) A. Y. Hong, B. M. Stoltz, *Eur. J. Org. Chem.* **2013**, 2745 –2759; b) J. P. Das, I. Marek, *Chem. Commun.* **2011**, *47*, 4593– 4623; c) M. Bella, T. Caspery, *Synthesis* **2009**, 1583 –1614; d) P. G. Cozzi, R. Hilgraf, N. Zimmerman, *Eur. J. Org. Chem.* **2007**, 5969– 5614; e) B. M. Trost, C. Jiang, *Synthesis* **2006**, 369– 396; f) *Quaternary Stereocenters* (Eds: J. Christoffers, A. Baro) Wiley-VCH, Weinheim, **2005**; g) C. J. Douglas, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363 –5367.

[141] a) A. I. Meyers, L. Snyder, *J. Org. Chem.* **1993**, *58*, 36–42; b) C. M. Moody, D. W. Young, *Tetrahedron Lett.* **1994**, *35*, 7277–7280; c) B. Rigo, D. Fasseur, N. Cherepy, D. Couturier, *Tetrahedron Lett.* **1989**, *30*, 7057–7060; d) G. Poli, S. C. Baffoni, G. Giambastiani, G. Renginato, *Tetrahedron* **1998**, *54*, 10403–10418.

However, in spite of the biological and pharmaceutical interest in this family of compounds, the asymmetric synthesis of chiral pyrrolidin-2,3-diones and reactions involving them have been barely explored. When we started this project and, to our knowledge, there was only one organocatalytic example involving the use of 4-unsubstituted pyrrolidin-2,3-diones as nucleophiles, developed by Xu and co-workers, in a one pot Michael/Pictet-Spengler sequence (a, Scheme 16).[142] The products obtained are synthetically and medicinally important, and are efficiently constructed in a highly stereocontrolled manner. Other examples of the use of pyrrolidin-2,3-diones as electrophiles had been published. For example, Ling and Fen described a Diels-Alder reaction of C(4)-alkylidene pyrrolidin-2,3-diones with cyclopentadiene promoted by a chiral *N*,*N*'-dioxide/Ni^{II} complex to furnish bridged C(4)-spiro pyrrolidin-2,3-diones (b, Scheme 16).[143] Besides, the reaction with allene ketones catalyzed by cinchona alkaloid could not afford quaternary stereocenters at the C4 position of the ring (c, Scheme 16).[144] In this context, other examples were reported in racemic form (d, Scheme 16) to provide fused rings and spirocyclopropanes (e, Scheme 16).[145]

[142] H.-L. Zhu, J.-B. Ling, P.-F. Xu, *J. Org. Chem*. **2012**, *77*, 7737–7743.
[143] Y. Lu, Y. Zhou, L. Lin, H. Zheng, K. Fu, X. Liu, X. Feng, *Chem. Commun.* **2016**, *52*, 8255-8258.
[144] S. Zhang, Y.-C. Luo, X.-Q. Hu, Z.-Y. Wang, Y.-M. Liang, P.-F. Xu, *J. Org. Chem.* **2015**, *80*, 7288-7294.
[145] a) S. Zhang, X.-Q. Hu, Z.-Y. Wang, P.-F. Xu, *Synthesis* **2015**, *47*, 2529–2537; b) X. B. Chen, L. Zhu, L. Fanf, S. Y. Yan, J. Lin, *RSC Adv.* **2014**, *4*, 9926-9934.



Scheme 16. Catalytic reactions of pyrrolidin-2,3-diones.

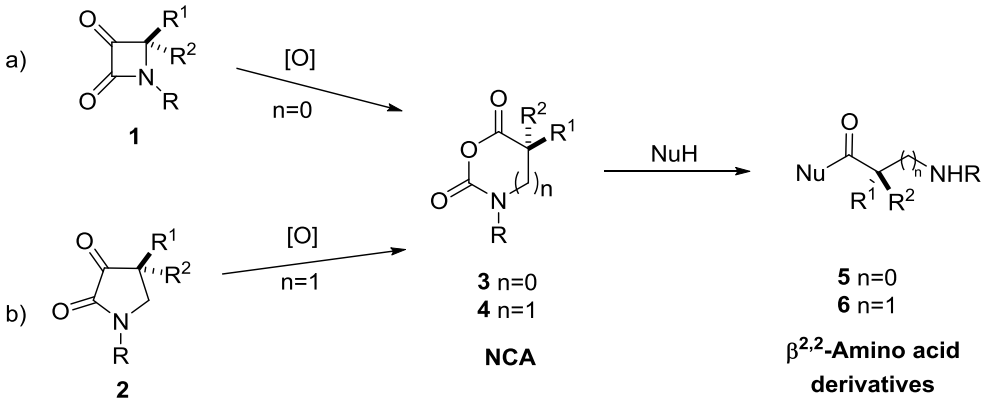
2.2. **Access to enantiopure amides through pyrrolidin-2,3-diones**

Pyrrolidin-2,3-diones were selected as pronucleophiles for different asymmetric reactions in order to access highly functionalized enantiopure amides. Given the precedents from this laboratory for the synthesis of amino acid *N*-carboxyanhydrides of type **3** containing a quaternary stereocententer starting from disubstituted β-lactams **1** (Scheme 17),[146] we envisaged that the same methodology could be applied to 4-substituted pyrrolidin-2,3-diones **2**. In this instance, β-amino acid *N*-carboxyanhydrides of type **4** could be produced, which would be of interest in β-peptide coupling reactions.

These *N*-carboxyanhydrides constitute very attractive intermediates as this structure offers simultaneously both, *N*-protection and carbonyl activation. Hence, this

[146] For a review on the use of β-lactams in α- and β-amino acid synthesis, see: C. Palomo, J. M. Aizpurua, I. Gamboa, M. Oiarbide, *Synlett* **2001**, *12*, 1813–1826.

approach would involve the transformation of the corresponding reaction adducts into the corresponding *N*-carboxyanhydrides and subsequent ring-opening by an amine (or other nucleophiles), thus affording $\beta^{2,2}$-amino acid derivatives bearing a quaternary stereocenter at the alpha position.



Scheme 17. a) Previous work from the group with β-lactams. b) Our approach for the synthesis of $\beta^{2,2}$-amino acid derivatives from pyrrolidin-2,3-diones.

After catalytic enantioselective reaction of these pyrrolidin-2,3-diones with an appropriate electrophile, a tetrasubstituted stereocenter would be generated (**2**). Their ring expansion would provide the corresponding NCA **4**, and sybsequent nucleophilic attack of an alcohol, amine or an amino acid would give rise to $\beta^{2,2}$-amino acid derivatives **6**. Performing the ring opening reaction with an amine, α-functionalized amides would be obtained (Figure 16). This would constitute an excellent alternative method to access α-functionalized amides containing a quaternary stereocenter in a not straightforward manner.

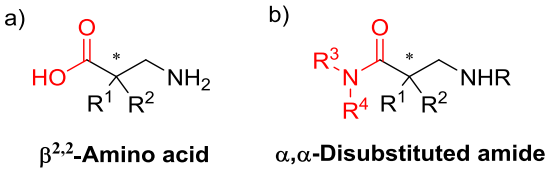


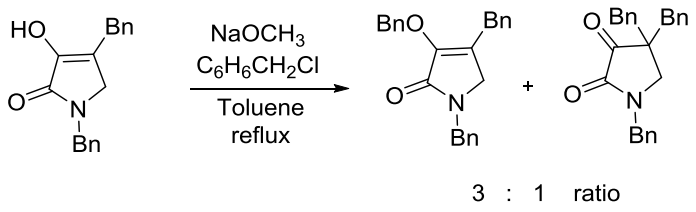
Figure 16. a) General structure of a $\beta^{2,2}$-amino acid. b) An amide bearing a quaternary stereocenter at the α-position.

Moreover, the enantioselective synthesis of β-amino acids has focused much attention over the years, not only because they are important building blocks for a wide variety of natural products and pharmaceutical agents, but also because they are mimics

of protein structural motifs.[147] On this basis, we envisaged that our approach would be useful for that purpose.

2.3. **Synthetic plan**

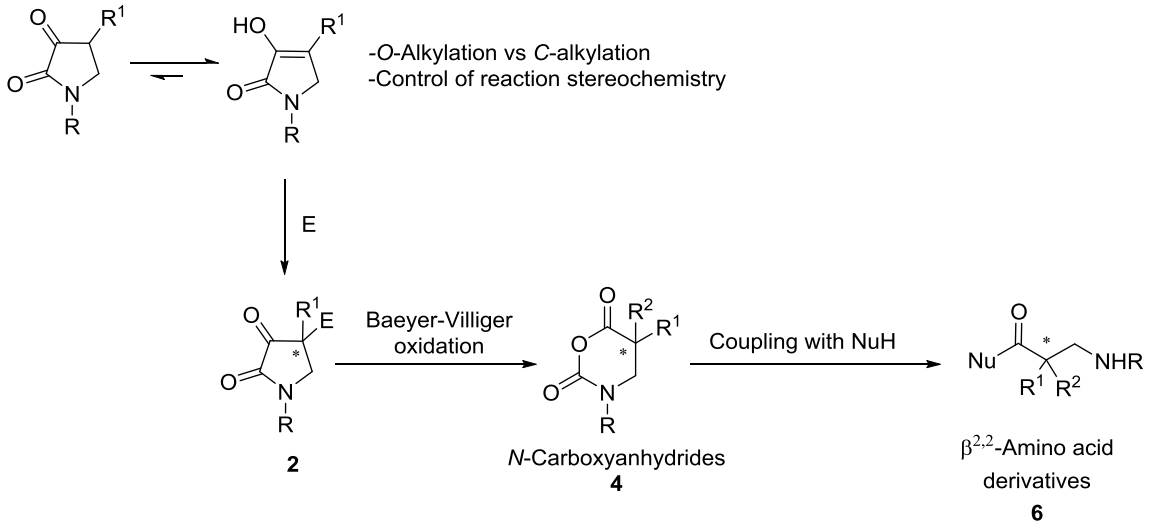
Construction of pyrrolidin-2,3-diones bearing an all-carbon quaternary stereocenter at C-4 in a catalytic enantioselective manner has not yet been described in the literature. One reason could be that the direct alkylation of pyrrolidin 2,3-diones by alkyl halides provides mainly *O*-alkylated products (Scheme 18).[148] Southwick and Barnas observed a 3:1 mixture of *O*-alkylated and *C*-alkylated products in the alkylation of sodium enolates obtained from 4-benzyl pyrrolidin-2,3-diones.



Scheme 18. Alkylation reaction of sodium enolates of 4-substituted pyrrolidin-2,3-diones

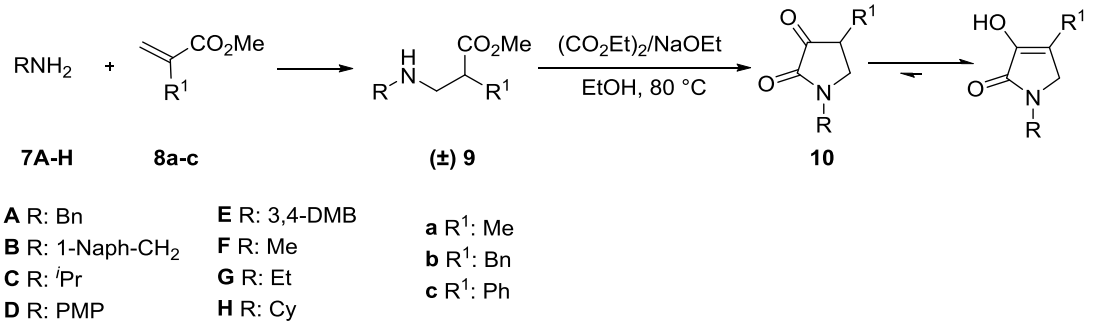
On the other hand, experimental data show that C(4)-substituted pyrrolidin-2,3-diones exist almost exclusively as the enolic form.[148] In this context, we envisaged that a weak Brønsted base might be sufficient for enolate generation and promotion of the reaction with an electrophile under catalytic conditions. The main problems associated to this proposal would be firstly the control of reaction stereochemistry, and secondly the control of C-alkylation vs O-alkylation. Furthermore, and as previously mentioned, the resultant 4,4-disubstituted adducts could be transformed, on the basis of previous work from this laboratory,[146] into *N*-carboxyanhydrides **4**, thereby enabling subsequent couplings with nucleophiles, affording this way highly functionalized amides, esters or $\beta^{2,2}$-amino acids **6** (Scheme 19).

[147] For reviews, see: a) D. Seebach, J. Gardiner, *Acc. Chem. Res.* **2008**, *41*,1366 –1375; b) R. P. Cheng, S. H. Gellman, W. F. DeGrado, *Chem. Rev.* **2001**, *101*, 3219 – 3232.
[148] P. L. Southwick, E. F. Barnas, *J. Org. Chem.* **1962**, 27, 98– 106.



Scheme 19. Our approach for the synthesis of $\beta^{2,2}$-amino acid derivatives.

The required pyrrolidin-2,3-diones **10** were prepared following the protocol shown in Scheme 20, adapting a literature procedure which involves the aza-Michael addition of the corresponding amine **7** to the appropiate acrylate **8**, followed by cyclization of the corresponding β-amino ester **9** with ethyl oxalate and further *in situ* decarboxylation (Scheme 20).



Scheme 20. Synthesis of pyrrolidin-2,3-diones **10**.

Southwick and Barnas demonstrated by IR spectroscopy that these compounds, in contrast to non-substituted pyrrolidin-2,3-diones, are essentially in their enolic form. This fact was corroborated by IR analysis and by ^{1}H-NMR spectra in $CDCl_3$ solution of our synthesized pyrrolidin-2,3-diones. Figure 17 and 18 show the IR and ^{1}H-NMR spectra, respectively for of compound **10Aa**.

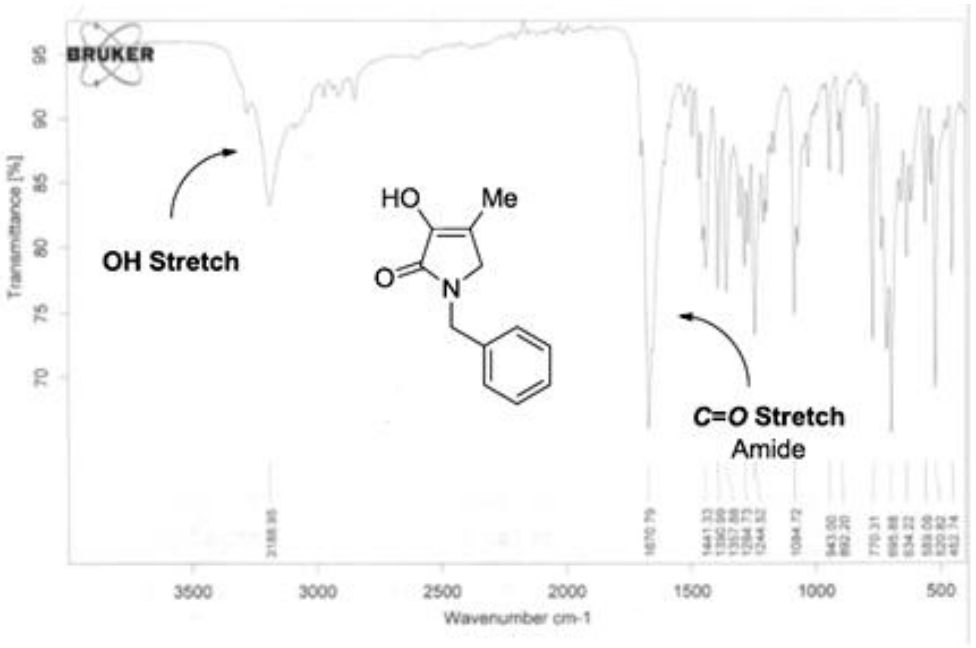


Figure 17. IR spectrum of **10Aa**.

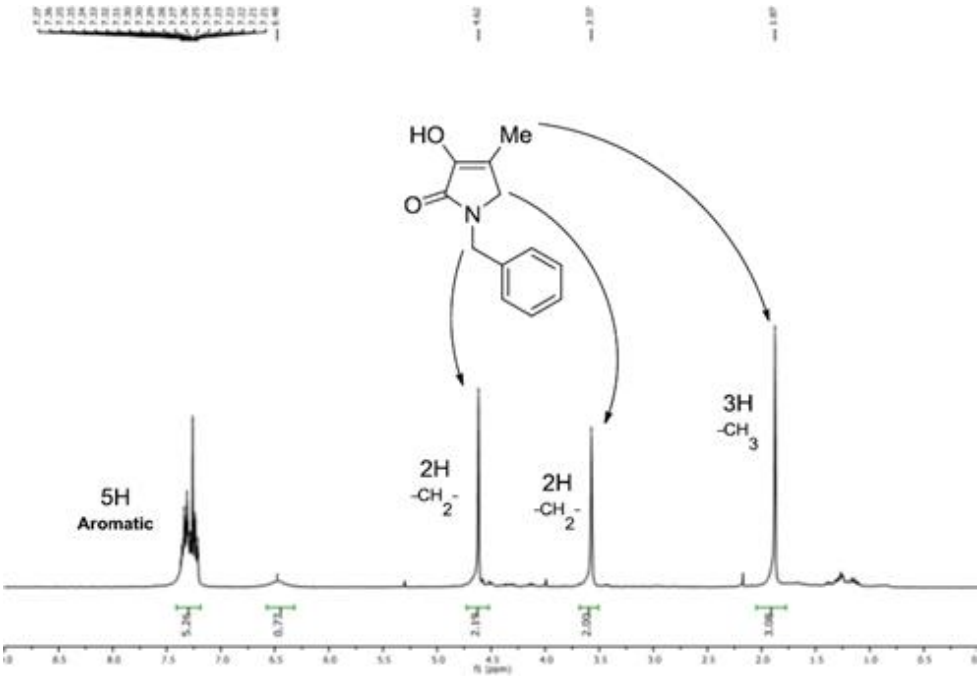


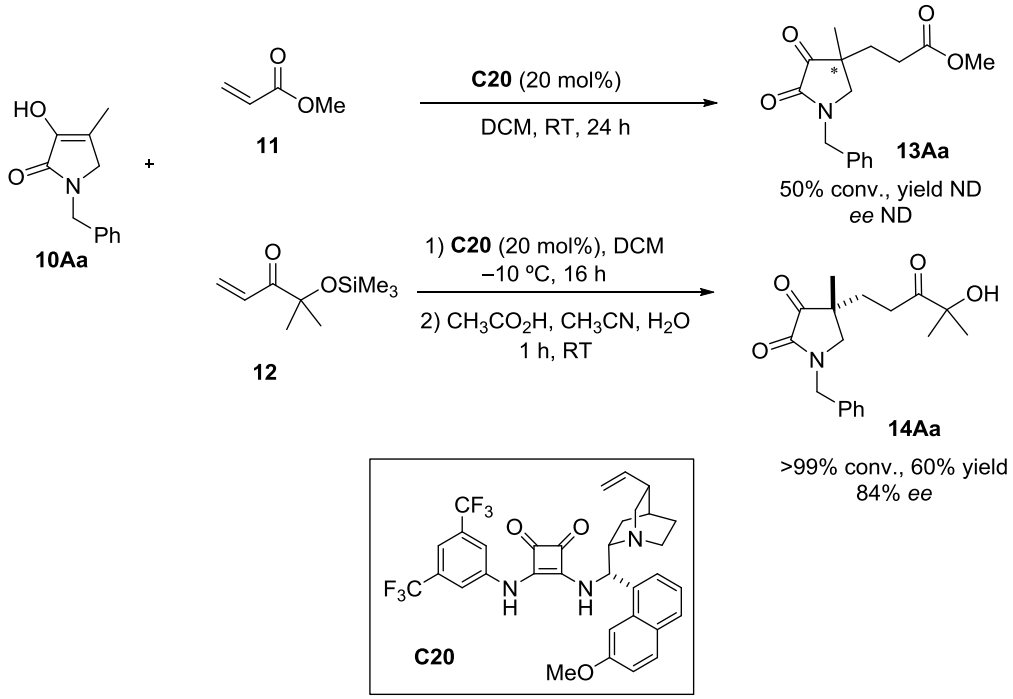
Figure 18. ^{1}H- NMR spectrum of **10Aa**.

2.4. **Results and discussion**

2.4.1. Organocatalytic conjugate addition to enones

In order to explore the reactivity of these 4-substituted pyrrolidinones, the conjugate addition of **10Aa** to methyl acrylate **11** promoted by the squaramide based, bifunctional Bronsted base catalyst **C20** was first explored at room temperature (Scheme 21). However, only 50% of conversion was obtained in 24 h, thus corroborating the low reactivity of acrylates as Michael acceptors in these reactions.

Based on the precedents of our research group with α'-oxy enones as more reactive ester surrogates, the reaction with enone **12** was also explored, and full conversion and 84% *ee* were obtained.[149]



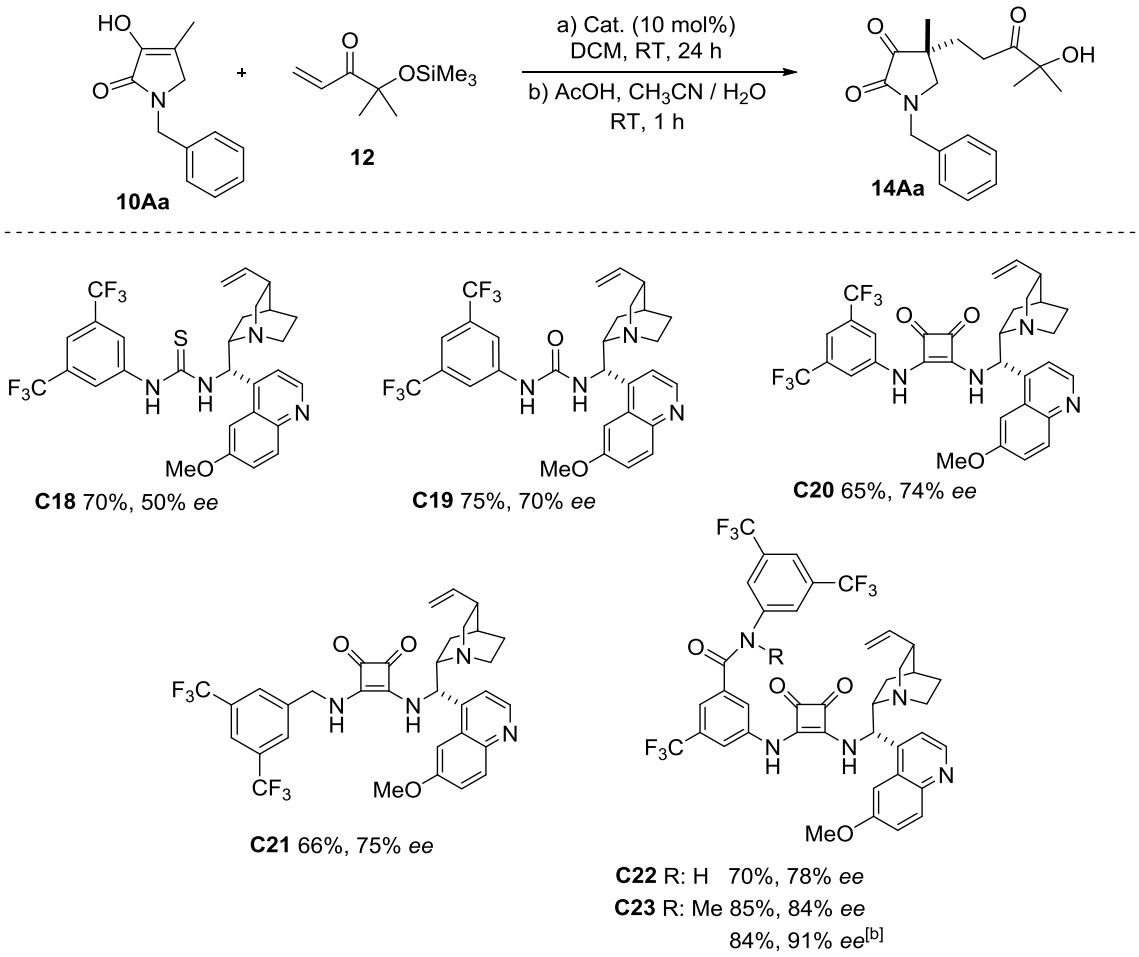
Scheme 21. Preliminary experiments on the catalytic asymmetric conjugate addition of pyrrolidin-2,3-dione **10Aa** to methyl acrylate **11** and α'-oxy enone **12**.

On this basis and with the aim of improving the enantioselectivity, other bifunctional BBs were evaluated in the reaction of 4-methyl-pyrrolidin 2,3-dione **10Aa** with silyloxy enone **12**. First, as Table 1 ilustrates, the conjugate additions promoted by urea **C18** and thiourea **C19** were explored, but both catalysts afforded lower enantioselectivity than **C20**. In addition, the derived analogue squaramide **C21**, provided

[149] This part is described in: E. Badiola, Doctoral Thesis, "*α-Oxy enones and pyrrolidin-2,3-diones as efficient new templates in asymmetric organocatalytic Michael reactions*", EHU/UPV, **2016**, 142.

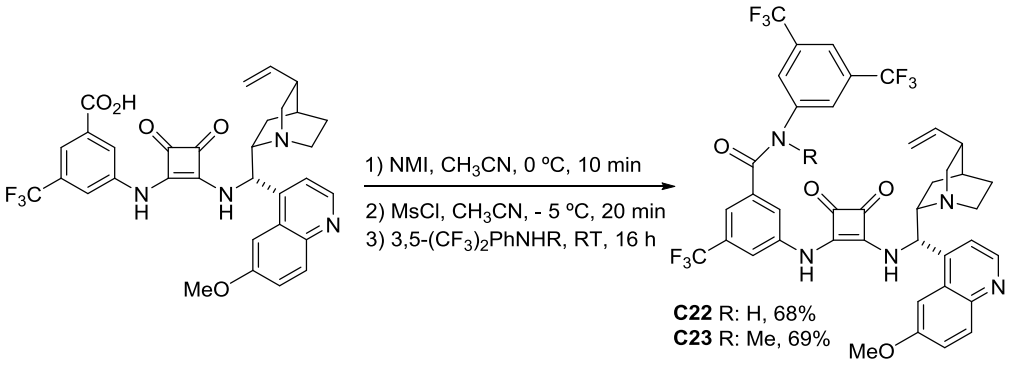
similar enantioselectivity level (75% *ee*). Therefore we decided to modify the structure of **C20** in order to optimize the process. Hence, an amide unit was installed in the catalyst providing **C22**, and in the presence of this promoter, a slight increase in the enantiocontrol was observed. Furthermore, the *N*-methyl derivative **C23**, allowed an increase in enantioselectivity and lowering the temperature to 0 °C, the enantiomeric excess reached 91%.

Table 1. Catalyst screening in the reaction of **10Aa** with **12**.[a]



[a] Reactions performed on a 0.2 mmol scale in 0.4 mL of DCM by using 2 equiv. of silyloxy enone **12**. Isolation of **14Aa** was effected by desilylation with AcOH in CH_3CN/H_2O; see experimental section for more details. Enantioselectivities were determined by HPLC analysis on a chiral stationary phase. [b] The reaction was carried out at 0 ºC.

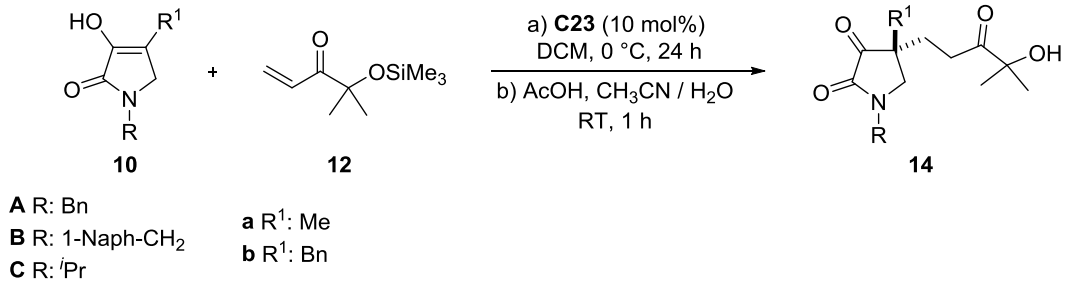
The advantages of this new modular subfamily of squaramide catalysts when compared to more common catalysts like **C20** are evident, as the catalyst can be easily modulable tuning the carboxamide function in order to improve catalyst/substrate interaction. These catalysts are easily obtained from the carboxylic acid intermediate through peptide coupling with the corresponding amine (Scheme 22).

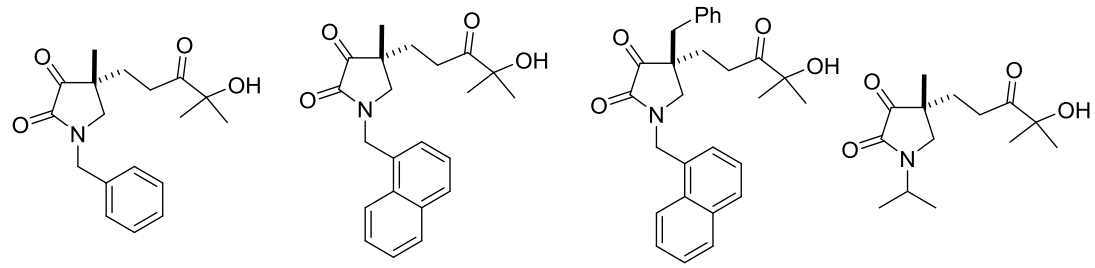


Scheme 22. Preparation of catalysts **C22** and **C23**.

Next, we explored the substrate scope varying the substituents at the nitrogen atom and at the C4 position of the pyrrolidin-2,3-dione ring (R and R^1). As depicted in Table 2, switching the benzyl group to 1-naphtylmethyl, the resulting product **14Ba** increased the enantiomeric excess to 96% *ee*, and similar levels were maintained when a benzyl group was installed at C4 position, leading to **14Bb** with 92% *ee*. Both yield and enantioselectivity were also high when *N*-isopropyl **14Ca** was employed as pronucleophile.

Table 2. Conjugate additions to α'-silyloxy enone **12**.[a]

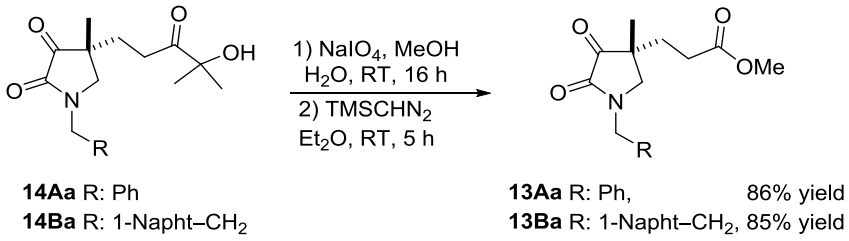




14Aa	**14Ba**	**14Bb**	**14Ca**
84%, 91% *ee*	86%, 96% *ee*	80%, 92% *ee*	84%, 88% *ee*

[a] Reactions performed on a 0.2 mmol scale in 0.4 mL of DCM by using 2 equiv. of silyloxy enone **12**. Isolation of **14** was effected by desilylation with AcOH in CH_3CN/H_2O; see experimental section for more details. Enantioselectivities were determined by HPLC analysis on a chiral stationary phase.

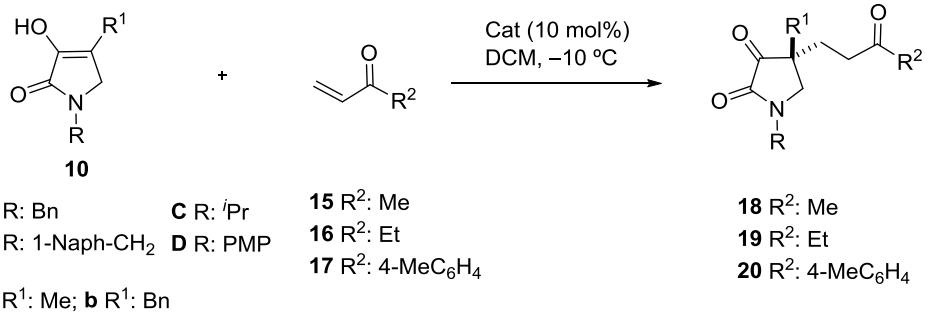
Compounds **14Aa** and **14Ba** were then transformed into their corresponding esters by simple oxidative cleavage of the acyloin moiety with $NaIO_4$ and subsequent esterification (Scheme 23), showing the utility of the α-hydroxy carbonyl motif as carboxylic acid derivatives surrogates,[149] since the reaction of **10Aa** with methyl acrylate **11** (Scheme 21) failed (50% conversion after 24 h at room temperature).



Scheme 23. Transformation of adducts **14Aa** and **14Ba** into the corresponding methyl ester derivatives.

The reaction with enones further illustrates the feasibility of the proposal. Thus reaction of **10Aa** with methyl vinyl ketone (MVK) **15** carried out at – 10 ºC in the presence of **C22** led to product **18Aa** in 75% yield and 88% *ee* (Table 3). For this reaction, however, both **C20** and **C23** were found to be equally effective affording enantioselectivities of 92 and 90% *ee*, respectively. Likewise **18Ab** was obtained from **10Ab** and MVK **15** in good yield and 93% *ee* using catalyst **C23** whilst catalyst **C20** led to adduct **18Ab** with almost the same enantioselectivity level. Further experiments revealed that with both catalysts (**C20** and **C23**) the stereochemical outcome of the reaction appears to be independent upon the *N*-substitution pattern of the nucleophile employed. Derivatives **10Ba**, **10Bb**, **10Ca** and **10Da**, respectively reacted with MVK **15** to afford the corresponding adducts **18Ba**, **18Bb**, **18Ca** and **18Da** with *ee* values between 91-98%. Furthermore, the reaction seems to be general with respect to the enone component, as reaction of compound **10Ab** with ethyl vinyl ketone **16** and 4-methylphenyl vinyl ketone **17** promoted by catalyst **C23** provided under the same conditions, the corresponding adducts **19Ab** and **20Ab** with 88 and 87% *ee*, respectively.

Table 3. Catalytic conjugate addition of pyrrolidin-2,3-diones **10** to enones **15-17**.[a]



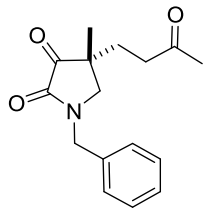
10

A R: Bn
B R: 1-Naph-CH_2
C R: ^{i}Pr
D R: PMP

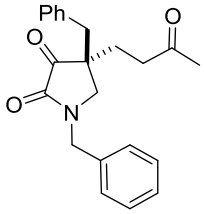
a R^1: Me; **b** R^1: Bn

15 R^2: Me
16 R^2: Et
17 R^2: 4-MeC_6H_4

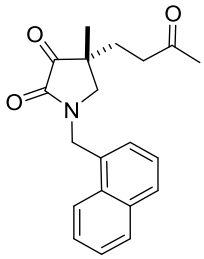
18 R^2: Me
19 R^2: Et
20 R^2: 4-MeC_6H_4



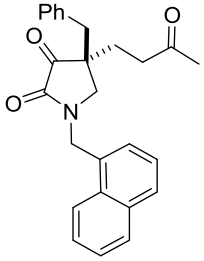
18Aa
C20 75%, 92% ee
C22 75%, 88% ee
C23 92%, 90% ee



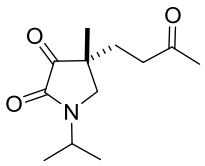
18Ab
C20 78%, 92% ee
C23 86%, 93% ee



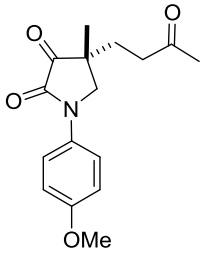
18Ba
C23 95%, 93% ee



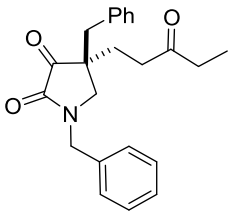
18Bb
C23 97%, 91% ee



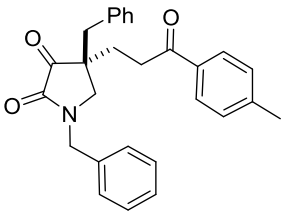
18Ca
C23 98%, 98% ee



18Da
C23 98%, 91% ee



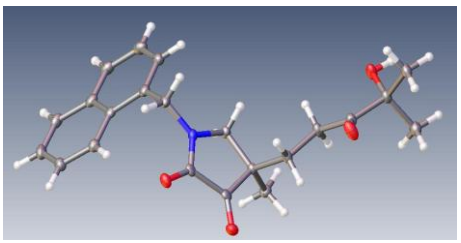
19Ab
C23 94%, 88% ee

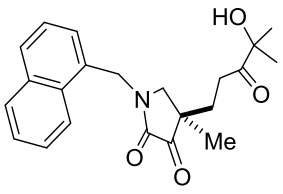


20Ab
C23 73%, 87% ee

[a] Reactions performed on a 0.2 mmol scale in 0.4 mL of DCM by using 2 equiv. of enone **15-17**. Yield of isolated product after chromatography. Enantioselectivity determined by chiral HPLC.

The absolute configuration of the products from these reactions was determined[149] by X-ray single crystal structure analysis of adducts **14Ba** and that of the remaining adducts was established by assuming a uniform reaction mechanism (Figure 19).





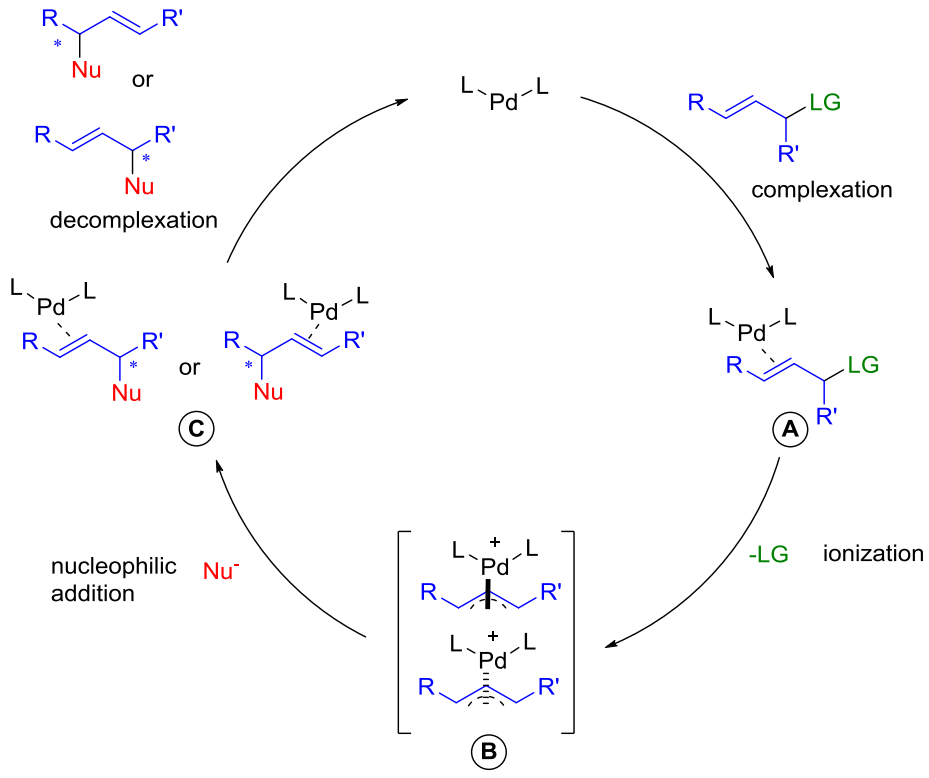
14Ba

Figure 19. X-ray structure for compound **14Ba**.

2.4.2. Palladium-catalyzed asymmetric allylic alkylation

Following the good results obtained in the conjugate addition of pyrrolidin-2,3-diones to α'-oxy enones and vinyl ketones, and with the aim of expanding the scope of reactions involving these substrates, the asymmetric allylic alkylation (AAA) was selected.

The insertion of allylic groups at the α-position of carbonyl-containing compounds is of great interest, and palladium-catalyzed asymmetric allylic alkylation constitutes a very useful tool for that purpose. The general catalytic cycle of the reaction consists of four steps (Scheme 24). The first one involves coordination of the transition metal to the electrophilic olefin (A complex), followed by ionization of the allylic leaving group to generate the Pd^{II} π-allyl transition metal complex B. Further alkylation of the nucleophile (enolate) generates a new transition metal olefin complex (C), whose decomplexation provides the allylated product and returns the transition metal Pd^{0} so that it can re-enter the catalytic cycle (Scheme 24). When this reaction is performed in the presence of a chiral ligand, asymmetric induction can be achieved.[150]



Scheme 24. Catalytic cycle in Pd-catalyzed allylic alkylation.

[150] A. Y. Hong, B. M. Stolz, *Eur. J. Org. Chem.* **2013**, 2745-2759.

The most employed ligands in Pd-AAA are phosphines, and a variety of scaffolds have arisen from the different contributions in the field. Figure 20 shows the most representative chiral ligands in this area.[151]

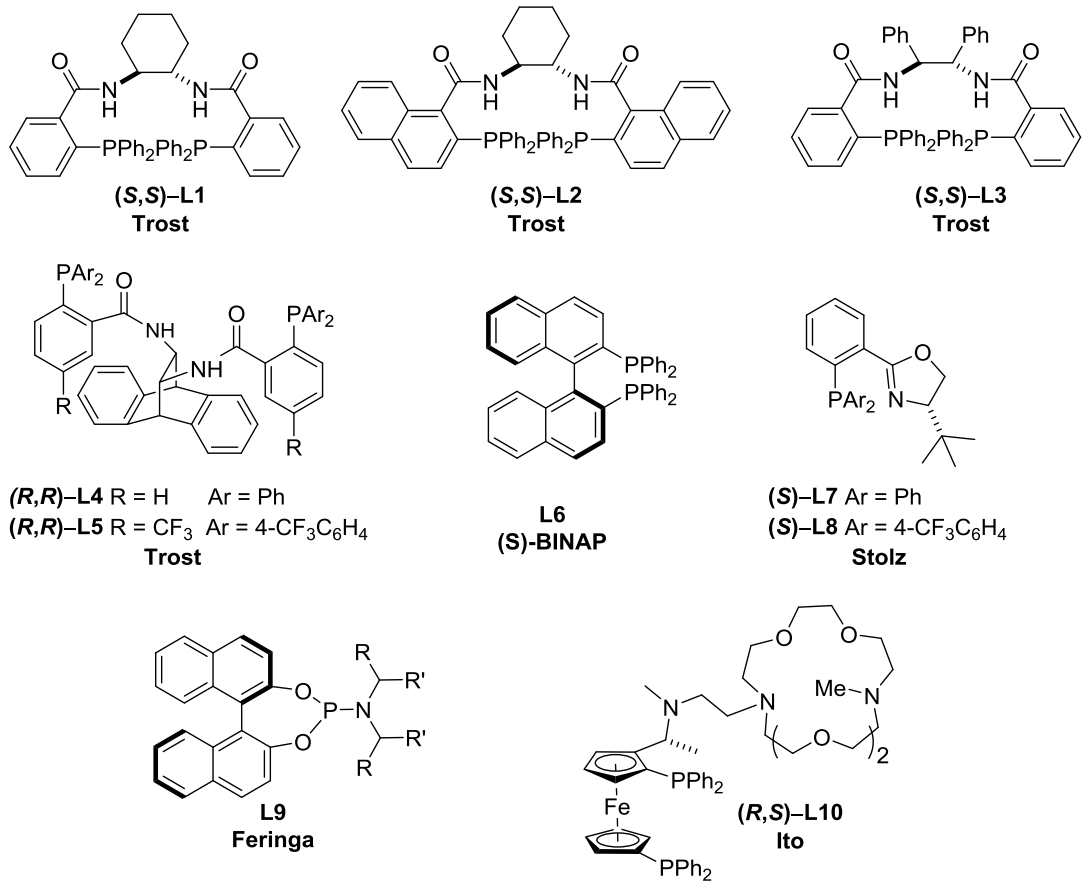
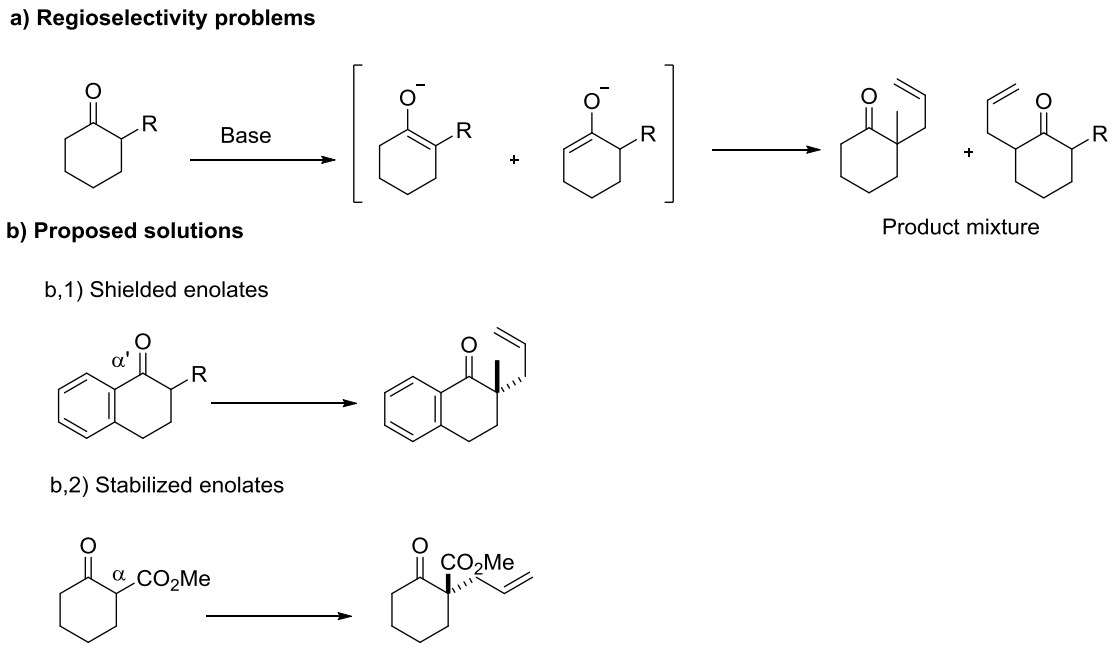


Figure 20. Representative chiral ligands used in Pd-AAA reactions.

For two decades, the reaction had been limited to stabilized carbanions that function as soft nucleophiles (pK_a<20) like anions of malonic esters, β-keto esters, α-imino esters and sulfones. But less reactive nucleophiles (hard nucleophiles) have also been proven to be efficient in the reaction after formation of enolates. As mentioned, the Pd^{II} π-allyl complex reacts with an enolate, and for their generation, different methods have been employed. Nevertheless, an unavoidable and general problem in the allylation of differentially substituted ketones with multiple acidic sites is the formation of isomeric enolates, which can lead to the generation of different regioisomeric products (a, Scheme 25). The first solutions to circunvent this problem involved the use of substrates with α-blocking groups to shield undesired deprotonation sites (b1, Scheme 25), or to install electron withdrawing groups at the α position to reduce the pK_a of the desired deprotonation sites (b2, Scheme 25). In all of the above cases, as the such generated

[151] B. M. Trost, J. E. Schultz, *Synthesis*, **2019**, *51*, 1-30.

enolate reacts with an external electrophile, this approach is usually referred as intermolecular AAA.



Scheme 25. a) Regioselectivity problem in enolate alkylation. b) Proposed solutions: b,1) α' blocking strategy. b,2) α-EWG to provide reduction in pK_a.

Even though both proposed strategies (b1 and b2 in Scheme 25) have resulted in high regiocontrol in AAA,[152] these approaches involve the introduction of functional groups into the starting ketone that can be unwanted, reducing the applications of these compounds in total synthesis. Despite these limitations, many nucleophiles have been successfully α-allylated following these approaches and the most representative ones are depicted in Figure 21.

On the other hand, organocatalysis has also been combined in an efficient manner with palladium catalysis in AAA. In this context, α-allylation of enamines of 1,3-dicarbonyl compounds,[153] aldehydes[154] and ketones[155] has been achieved in an efficient

[152] a) B. M. Trost, G. M. Schroeder, *Chem. Eur. J.* **2005**, *11*, 174–184; b) R. Kuwano, K. Uchida, Y. Ito, *Org. Lett.* **2003**, *5*, 2177–2179; c) B. M. Trost, G. M. Schroeder, J. Kristensen, *Angew. Chem. Int. Ed.* **2002**, *41*, 3492–3495; d) S.-L. You, X.-L. Hou, L.-X. Dai, X.-Z. Zhu, *Org. Lett.* **2001**, *3*, 149–151; e) S.-L. You, X.-L. Hou, L.-X. Dai, B.-X. Cao, J. Sun, *Chem. Commun.* **2000**, 1933–1934; f) R. Kuwano, Y. Ito, *J. Am. Chem. Soc.* **1999**, *121*, 3236–3237; g) B. M. Trost, G. M. Schroeder, *J. Am. Chem. Soc.* **1999**, *121*, 6759–6760; h) B. M. Trost, X. Ariza, *Angew. Chem.* **1997**, *109*, 2749–2751; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2635–2637; i) B. M. Trost, R. Radinov, E. M. Grenzer, *J. Am. Chem. Soc.* **1997**, *119*, 7879–7880; j) M. Sawamura, M. Sudoh, Y. Ito, *J. Am. Chem. Soc.* **1996**, *118*, 3309–3310; k) M. Sawamura, H. Nagata, H. Sakamoto, Y. Ito, *J. Am. Chem. Soc.* **1992**, *114*, 2586–2592; l) T. Hayashi, K. Kanehira, T. Hagihara, M. Kumada, *J. Org. Chem.* **1988**, *53*, 113–120.
[153] M. Yoshida, *J. Org. Chem.* **2017**, *82*, 12821-12826.

and stereoselective manner. Likewise, Brønsted acid[156] and phase-tranfer catalysis[157] have also been combined with Pd catalysis.

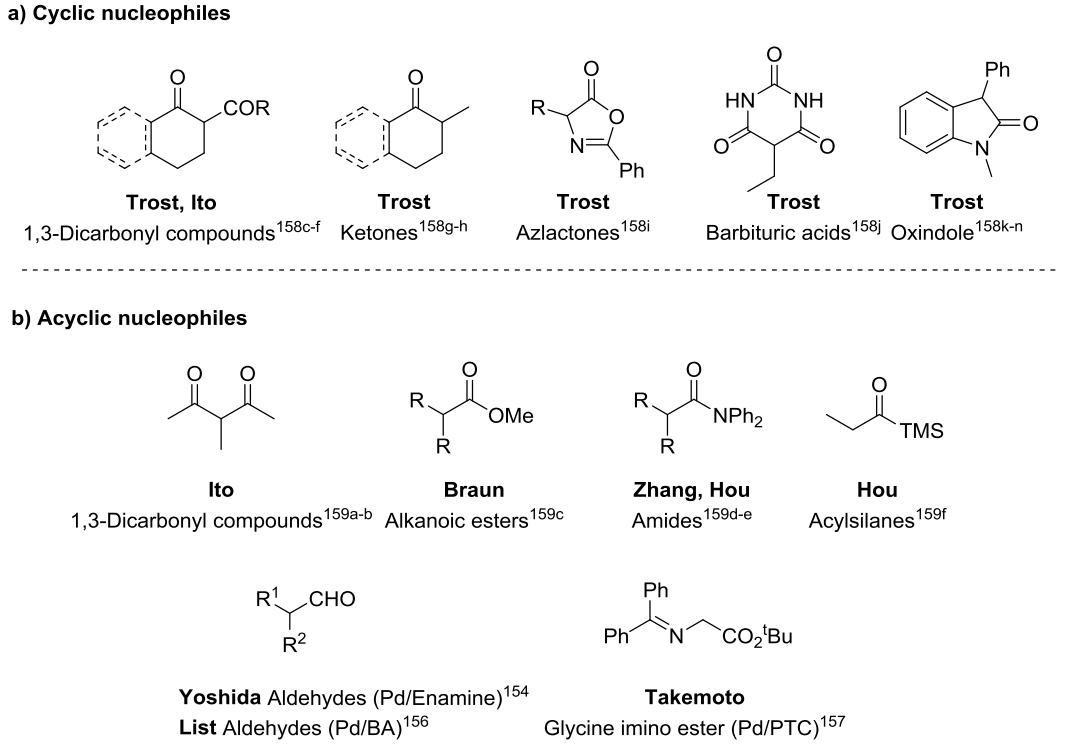


Figure 21. Representative pronucleophiles employed in the Pd-AAA. a) Cyclic nucleophiles.[158] b) Acyclic nucleophiles.[159]

[154] a) F. Bihelovic, R. Matovic, B. Vulovic, R. N. Saicic, *Org. Lett.* **2007**, *9*, 5063-5066; b) X. Zhao, D. Liu, F. Xie, Y. Liu, W. Zhang, *Org. Biomol. Chem.* **2011**, *9*, 1871-1875; c) S. Afewerki, I. Ibrahem, J. Rydfjord, P. Breinstein, A. Córdova, *Chem. Eur. J.* **2012**, *18*, 2972-2977; d) M. Yoshida, T. Terumine, E. Masaki, S. Hara, *J. Org. Chem.* **2013**, *78*, 10853-10859.

[155] a) S. Yasuda, N. Kumagai, M. Shibasaki, *Heterocycles*, **2012**, *86*, 745-757; b) X. Zhao, D. Liu, F. Xie, Y. Liu, W. Zhang, *Org. Biomol. Chem.* **2011**, *9*, 1871-1875.

[156] For some representative examples, see: a) G. Pupo, R. Properzi, B. List, *Angew. Chem. Int. Ed.* **2016**, *55*, 6099-6102; b) S. Mukherjee, B. List, *J. Am. Chem. Soc.* **2007**, *129*, 11336; c) G. Jiang, B. List, *Angew. Chem. Int. Ed.* **2011**, *50*, 9471.

[157] For some representative examples, see: a) M. Nakoji, T. Kanayama, T. Okino, I. Takemoto, *Org. Lett.* **2001**, *3*, 3329-3331; b) M. Nakoji, T. Kanayama, T. Okino, I. Takemoto, *J. Org. Chem.* **2002**, *67*, 7418-7423.

[158] For reviews, see: a) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921-2943; b) J. D. Weaver, A. Recio, A. J. Grenning, J. A. Tunge, *Chem. Rev.* **2011**, *111*, 1846-1912; B. M. Trost J. E. Schiltz, *Synthesis* **2019**, *51*, 1-30. For 1,3-dicarbonyl compounds, see: c) B. M. Trost, R. Radinov, E. M. Grenzer, *J. Am. Chem. Soc.* **1997**, *119*, 7879-7880; d) R. Kuwano, K-I. Uchida, Y. Ito, *Org. Lett.* **2003**, 5, 2177-2179; e) B. M. Trost, E. J. Doncklete, D. A. Thaisrivongs, M. Osipov, J. T. Master, *J. Am. Chem. Soc.* **2015**, *137*, 2776-2784; f) B. M. Trost, B. Schäffner, M. Osipov, D. A. A. Wilton, *Angew. Chem. Int. Ed.* **2011**, *50*, 3548-3551. For the first example involving ketones, see: g) B. M. Trost, G. M. Schröder *J. Am. Chem. Soc.* **1999**, *121*, 6759-6760; h) B. M. Trost, G. M. Schröder *Chem. Eur. J.* **2005**, *11*, 174-184. For the first example with azlactones, see: i) B. M. Trost *Angew. Chem. Int Ed. Engl.* **1997**, *36*, 2635-2637. For barbituric acids, see: j) B. M. Trost, G. M. Schroeder *J. Org. Chem.* **2000**, *65*, 1569. For oxindoles, see: k) B. M. Trost, S. Malhotra, W. H. Chan, *J. Am. Chem. Soc.* **2011**, *133*, 7328; l) B. M. Trost, J. Xie, J. D. Sieber, *J. Am.*

In spite of this progress, the regioselectivity in enolate generation was still an issue in some cases. An alternative solution for that problem came by Tsuji and co-workers when they introduced in the 80s some alternative methods for the selective enolate generation. Using silyl enol ether[160] (a, Scheme 26) or enol acetate[161] (b, Scheme 26) substrates in the presence of appropriate additives, the latent enolates were unmasked as single isomers. Subsequent allylic alkylation of these derivatives provided the corresponding reaction adducts without the need of additional functional groups unlike the first approaches. Besides, Tsuji's group[162a] and Saegusa's[162b] group also showed that allyl fragments could also be introduced into cyclic ketones by the use of allyl enol carbonates[163] or allyl β-keto esters[164] (c, Scheme 26). The loss of CO_2 after palladium complexation, replaces the need to selectively prepare preformed enolate equivalents. This way, both the allyl electrophile and the enolate nucleophile are formed *in situ* by Pd^0. Although the exact mechanism of this reaction remains unclear, recently it has been postulated that it may occur through the formation of a palladium enolate.[165] This methodology is known as the decarboxylative (Pd-DAAA) or Tsuji-Trost asymmetric allylic alkylation (AAA). With all of these methods explored by Tsuji, the enolates are formed with high regioselectivity and providing the products in high regiocontrol and in a straightforward manner.

Chem. Soc. **2011**, *133*, 20611; m) B. M. Trost, J. T. Masters, A. C. Burns, *Angew. Chem. Int. Ed.* **2013**, *52*, 2260; n) B. M. Trost, M. Osipov, *Angew. Chem. Int. Ed.* **2013**, *52*, 9176.

[159] For 1,3-dicarbonyl compounds, see: a) M. Sawamura, H. Nagata, H. Sakamoto, Y. Ito, *J. Am. Chem. Soc.* **1992**, *114*, 2586-2592; b) R. Kuwano, Y. Ito *J. Am. Chem. Soc.* **1999**, *121*, 3236-3237. For alkanoic esters, see: c) R. Visse, M.-A Möllemann, M. Braun, *Eur. J. Org. Chem.* **2019**, 4604-4608. For amides, see: d) K. Zhang, Q. Peng, X. L. Hou, Y. D. Wu, *Angew. Chem. Int. Ed.* **2008**, *47*, 1741-1744; e) Y.-J. Jiang, G.-P. Zhang, J.-Q. Huang, D. Chen, C.-H. Ding, X.-L. Hou, *Org. Lett.* **2017**, *19*, 5932-5935. For acylsilanes, see: f) J.-P. Chen, C.-H. Ding, W. Liu, X.-L. Hou, L.-X. Da, *J. Am. Chem. Soc.* **2010**, *132*, 15493-15495.

[160] J. Tsuji, I. Minami, I. Shimizu, *Chem. Lett.* **1983**, 1325–1326.

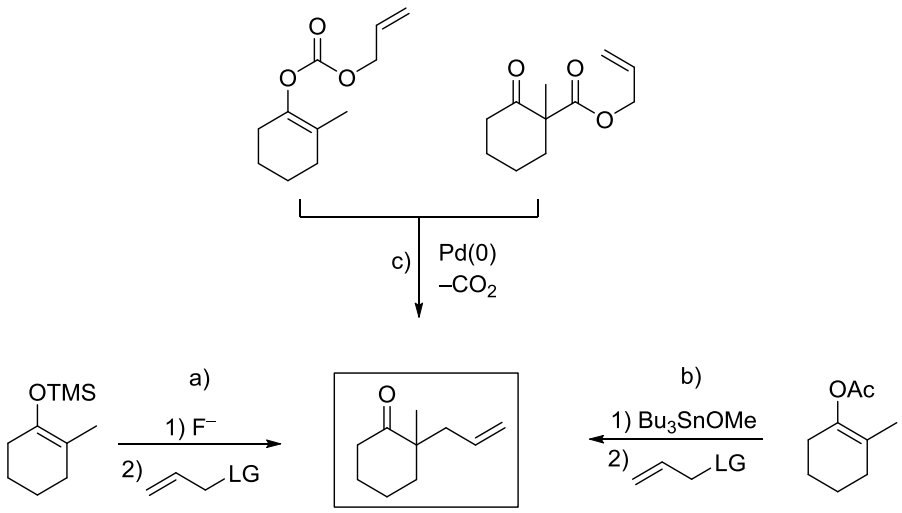
[161] J. Tsuji, I. Minami, I. Shimizu, *Tetrahedron Lett.* **1983**, *24*, 4713–4714.

[162] a) I. Shimizu, T. Yamada, J. Tsuji, *Tetrahedron Lett.***1980**,21,3199; b) T. Tsuda, Y. Chujo, S. Nishi, K. Tawara, T. Saegusa, *J. Am.Chem. Soc.* **1980**,102, 6381.

[163] J. Tsuji, I. Minami, I. Shimizu, *Tetrahedron Lett.* **1983**, *24*, 1793–1796.

[164] a) I. Shimizu, T. Yamada, J. Tsuji, *Tetrahedron Lett.* **1980**, *21*, 3199–3202; b) Saegusa published a very similar work with β-keto esters simultaneously with Tsuji's work, see: T. Tsuda, Y. Chujo, S. Nishi, K. Tawara, T. Saegusa, *J. Am. Chem. Soc.* **1980**, *102*, 6381–6384.

[165] J. James, M. Jackson, P. J. Guiry, *Adv. Synth. Catal.* **2019**, *361*, 3016-3049.



Scheme 26. Different approaches for the regioselective enolate formation.

Although these methods provided promising strategies for regioselective enolate generation, asymmetric variants of the Pd-DAAA were not reported until the 2000s. Figure 22 shows the representative pronucleophiles used following the Pd-DAAA developed by Tsuji, which has allowed to broaden the scope and synthetic potential of this transformation.[165]

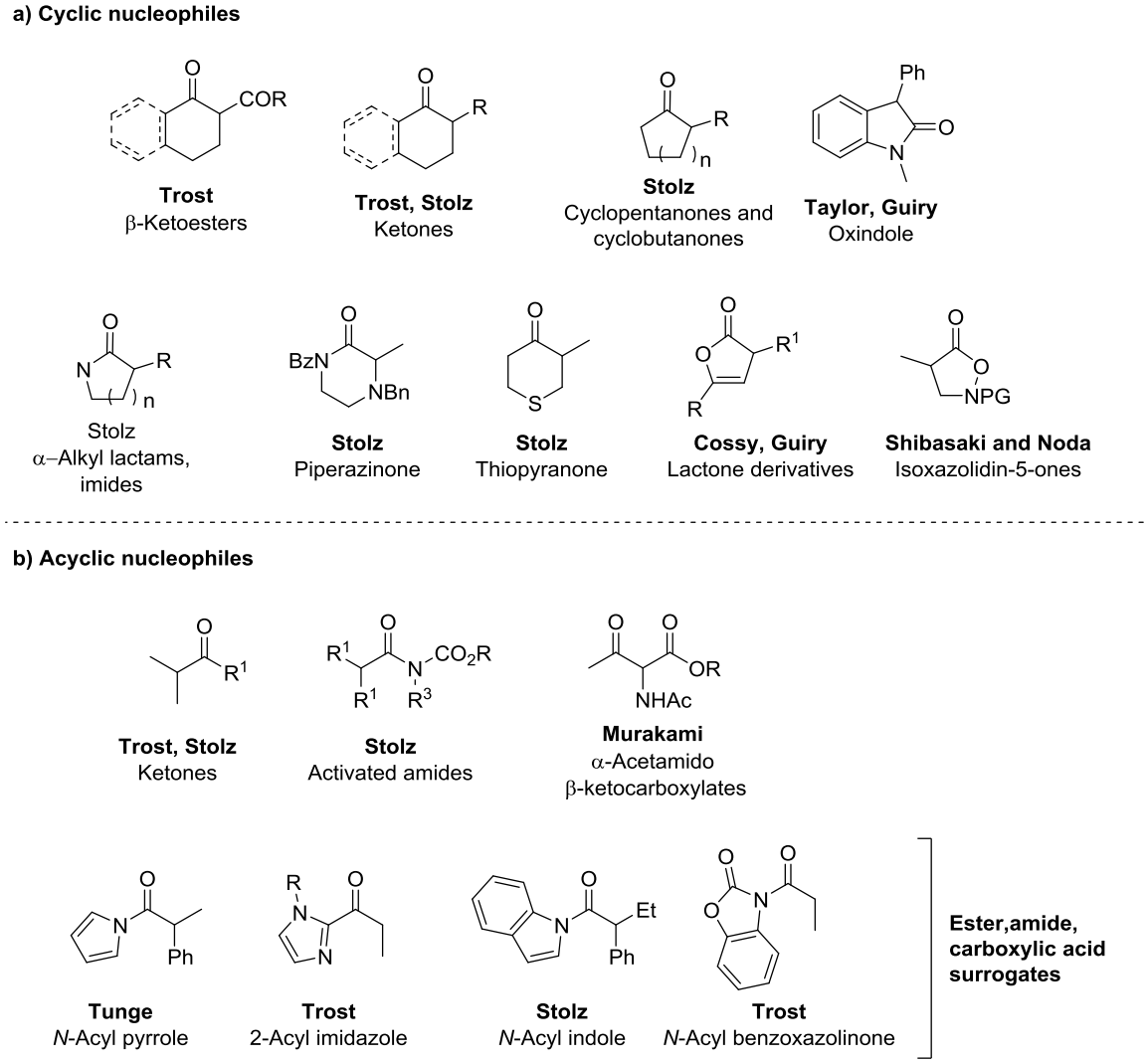
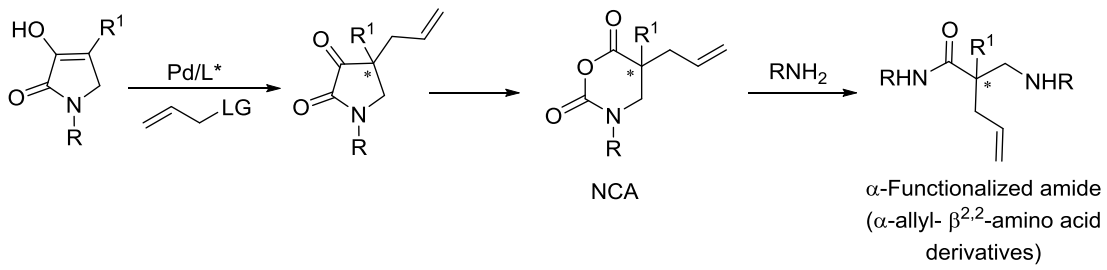


Figure 22. Representative pronucleophiles employed in the Pd-DAAA.[165] a) Cyclic nucleophiles. b) Acyclic nucleophiles.

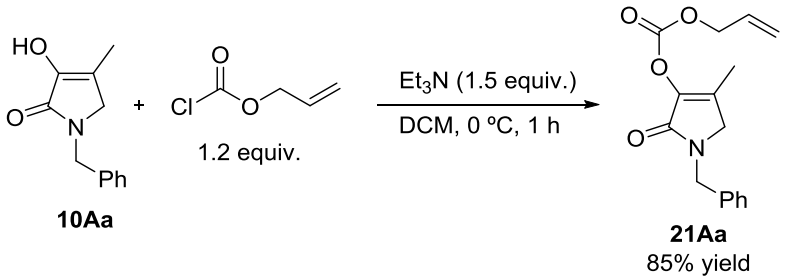
2.4.2.1. Pd-catalyzed AAA of pyrrolidin-2,3-diones

Given the success in the conjugate addition of pyrrolidin-2,3-diones to α-oxy enones and vinyl ketones, we wondered whether these promising pronucleophiles would generate enantiopure allyl derivatives through a Pd-catalyzed AAA. The resulting adducts could also follow ring expansion (NCA formation) and ring opening after reaction with a nucleophile to afford α-tetrasubstituted derivatives bearing an allyl group at the α-position (Scheme 27), thus providing α-allyl $\beta^{2,2}$-amino acid derivatives (α-functionalized amides when using an amine as a nucleophile). As far as we know, ketoamides have not been employed as pronucleophiles in asymmetric allylic alkylation.



Scheme 27. Proposed synthetic plan to obtain α-allyl $\beta^{2,2}$-amino acid derivatives.

In a first instance, the decarboxylative asymmetric allylic alkylation approach via allyl enol carbonates was selected, attracted by the mild and neutral reaction conditions that are employed in this methodology. It was gratifying to observe that pyrrolidin **10Aa** reacted with allyl chloroformate to afford **21Aa** without generation of side products and with good yield after column chromatography (Scheme 28).



Scheme 28. Synthesis of the allyl enol carbonate **21Aa**.

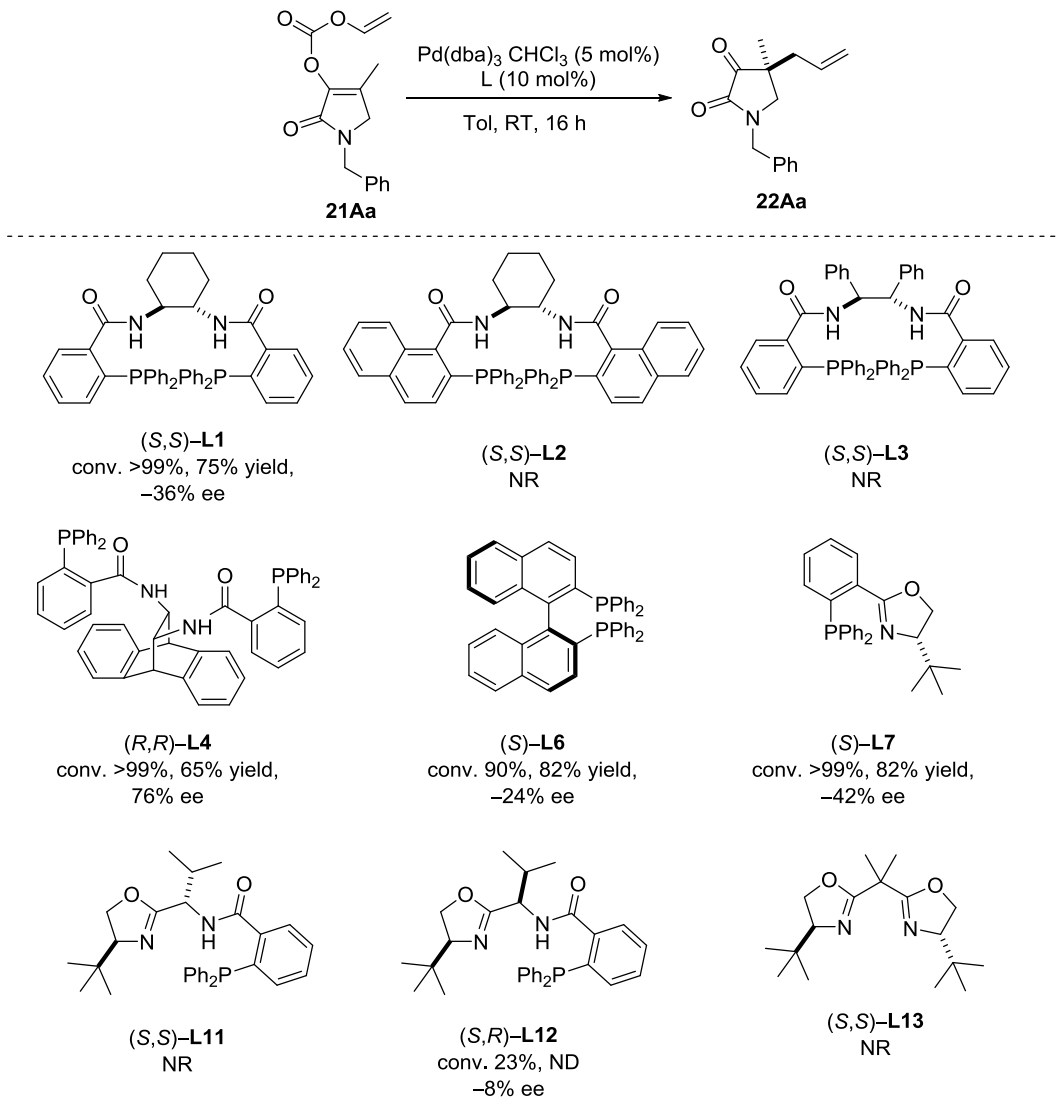
Then, the allyl enol carbonate **21Aa** was subjected to allylation conditions in the presence of different phosphine ligands in order to check both the reactivity and the enantioselectivity of the reaction products. For that purpose, toluene was selected as the solvent and $Pd(dba)_3$ $CHCl_3$ (5 mol%) as palladium source to perform the reaction at room temperature (Table 4).

Trost ligands **L1**-**L4** were firstly checked and it was observed that **L1** afforded the reaction adduct with full conversion, but with poor enantioselectivity (–36% *ee*). In contrast, when employing **L2** and **L3**, the reation did not proceed. However, it was gratifying to see that structurally similar **L4** provided the allyl derivative **22Aa** in total conversion, 65% yield and with 76% *ee*. **L6** provided the reaction adduct in good conversion but with low enantiocontrol. Next, we decided to switch to Stolz ligand **L7**, but despite the good reactivity, the enantiocontrol was low (–42% *ee*). Structurally similar **L11** and **L12** were synthesized in the laboratory, following literature protocols,[166] but results were not satisfactory as **L11** did not promote the allylation and **L12** afforded **22Aa**

[166] Adapted from: J.-Y. Lee, J.J. Miller, S.S. Hamilton, M.S. Sigman, *Org. Lett.* **2005**, *7*, 1837-1839.

with low conversion and enantioselectivity. Finally, **L13** was also investigated but no reaction was observed.

Table 4. Catalyst screening for the DAAA of **21Aa**.[a]

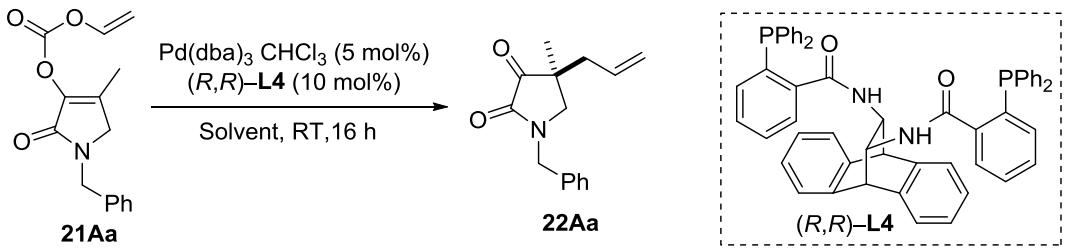


[a] Reactions performed on a 0.2 mmol scale and in 0.8 mL of toluene. Conversion related to the disappearance of the starting material. Yield of isolated product after chromatography. Enantioselectivity determined by chiral HPLC. NR: Not reaction. ND: Not determined.

It should be noted that the reaction is very sensitive to air and moisture, thus the reactions had to be perfomed under inert conditions. This implies the use of freshly distilled and degassed solvents in previously dried vials under Ar atmosphere. Oxidation of the ligands to the corresponding phosphine oxides had to be prevented. This can be easily checked by ^{31}P-NMR experiments and purified by column chromatography (explained in more detail in the experimental section).

With the optimal ligand **L4** in hand, a solvent screening was performed under the same reaction conditions (Table 5). As it can be seen in the table, increasing the polarity of the solvents, the enantioselectivity was enhanced. Compared to toluene which provides **22Aa** with 76% ee (entry 1), with THF the enantioselectivity increases up to 90% (entry 2), a value which does not improve at 0 ºC (91% *ee*), and in dioxane the reaction adduct is provided with 92% *ee* (entry 3). However, when acetonitrile was used (entry 4), the enantiocontrol dropped dramatically up to 18% *ee*. Thus, dioxane was chosen as the optimal solvent for the reaction and for further experiments.

Table 5. Solvent screening for the DAAA of **21Aa**.[a]



Entry	Solvent	Polarity index[167]	Conv. (%)[b]	Yield (%)[c]	*ee* (%)[d]
1	Toluene	2.4	>99	65	76
2	THF[e]	4.0	90	88	90
3	Dioxane	4.8	>99	78	92
4	CH_3CN	5.8	>99	74	18

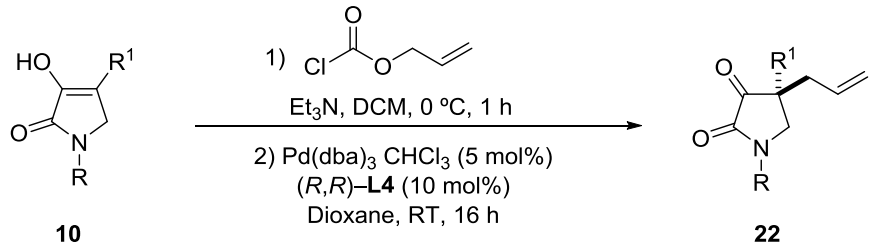
[a] Reactions performed on a 0.2 mmol scale and in 0.8 mL of solvent. [b] Related to the disappearance of the starting material. [c] Yield of isolated product after chromatography. [d] Enantioselectivity determined by chiral HPLC. [e] Same results were obtained at 0 ºC.

Next, the reaction scope was explored with pyrrolidinones bearing different substituents at the *N*- and C4- positions under optimized reaction conditions (Table 6). The synthesis of the starting allyl enol carbonates and the subsequent allylation proved to be general for different substitution patterns. Switching to 1-naphthylmethyl group in the nitrogen, the reaction adduct **22Ba** was generated with high conversion and enantioselectivity. Variation of the C4 substituent, showed that with benzyl group in C4, the corresponding adducts were afforded in high conversion and enantioselectivity **22Ab** and **22Bb**, but when changing to a phenyl group, enantioselectivity dropped below 60% *ee* in both **22Ac** and **22Bc**. In addition, **22Ea** and **22Da** were afforded with enantioselectivity values up to 90% ee. Small alkyl chains at the the nitrogen atom, (**22Fa**

[167] http://macro.lsu.edu/howto/solvents/Polarity%20index.htm

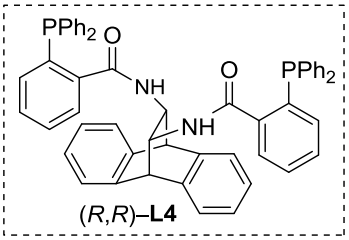
and **22Ga)** lowered enantioselectivity to 70 and 76% respectively, whereas sterically more hindered **22Ca** and **22Ha** were produced with high enantioselectivity.

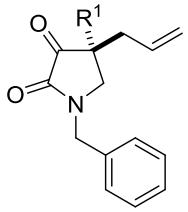
Table 6. Scope of the allylation reaction.[a]



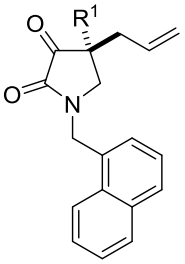
A R: Bn
B R: 1-Naph-CH_2
C R: ^{i}Pr
D R: PMP
E R: 3,4-DMB
F R: Me
G R: Et
F R: Cy

a R^1: Me
b R^1: Bn
c R^1: Ph

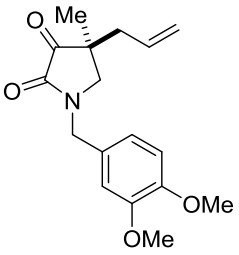




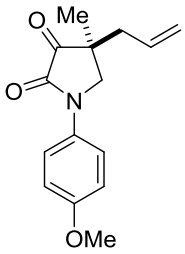
22Aa R^1: Me 78%, 92% *ee*
22Ab R^1: Bn 96%, 96% *ee*
22Ac R^1: Ph 85%, 55% *ee*



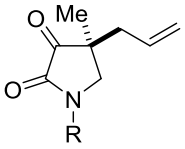
22Ba R^1: Me 77%, 93% *ee*
22Bb R^1: Bn 78%, 96% *ee*
22Bc R^1: Ph 84%, 42% *ee*



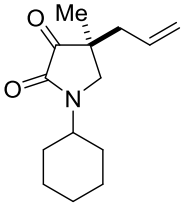
22Ea 73%, 88% *ee*



22Da 96%, 90% *ee*



22Fa R: Me 81%, 70% *ee*
22Ga R: Et 83%, 76% *ee*
22Ca R: ^{i}Pr 77%, 92% *ee*



22Ha 80%, 90% *ee*

[a] Reactions performed on a 0.2 mmol scale and in 0.8 mL of solvent. Yield of isolated product after chromatography. Enantioselectivity determined by chiral HPLC.

The absolute configuration of adduct **22Aa** was established by a single crystal X-ray analysis and the configuration of the remaining adducts was assigned by assuming a uniform reaction mechanism.

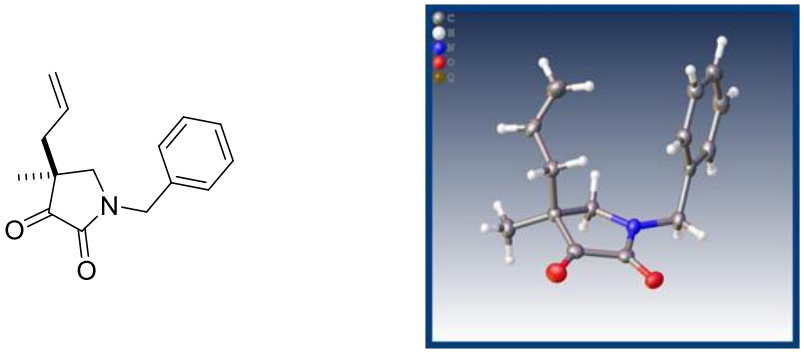
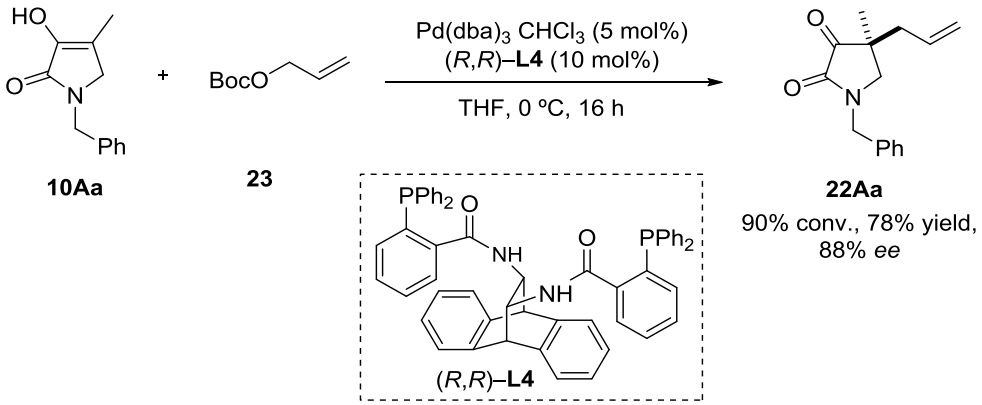


Figure 23. ORTEP diagram of compound **22Aa**.

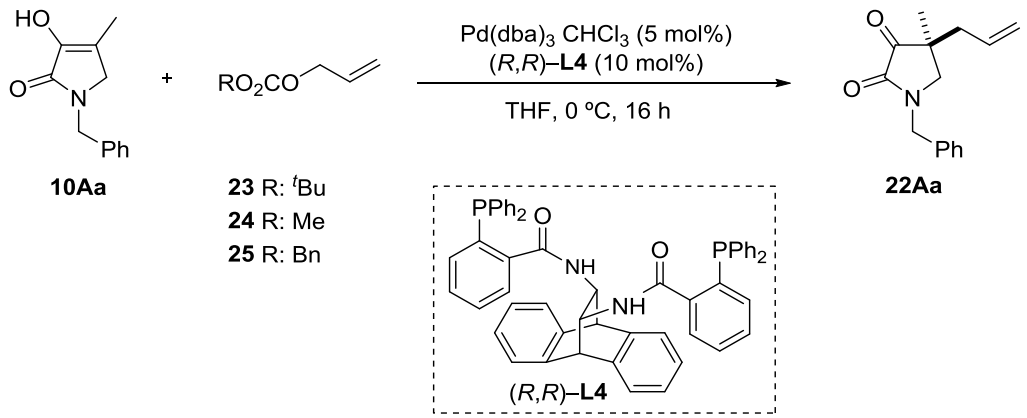
Once the decarboxylative asymmetric allylic alkylation (DAAA) was proven to be a good methodology to obtain allyl derived tetrasubstituted pyrrolidin-2,3-diones, a more direct approach (intermolecular AAA) was explored in order to check the feasibility of the methodology. For this purpose, allyl *tert*-butyl carbonate **23** was added to the palladium species followed by the addition of **10Aa** and **L4** at 0 ºC (Scheme 29). No external base was required for the reaction to work, probably due to the *in situ* enolization of the nucleophile. The reaction worked well under the described conditions, and enantioselectivity was also in the range of the previous methodology. Thus both approaches seem to be valid for the enantioselective α-allylation reaction of pyrrolidin-2,3-diones.



Scheme 29. Intermolecular allylation of pyrrolidin-2,3-dione **10Aa**.

The influence of the nature of the carbonate group was also checked in this reaction and the results are shown in Table 7. The screening showed that the results are independent on the nature of the leaving group. The enantioselectivity values were in the same range, all comparable to the decarboxylative version (92% *ee*).

Table 7. Carbonate screening in the allylation reaction of **10Aa**.[a]

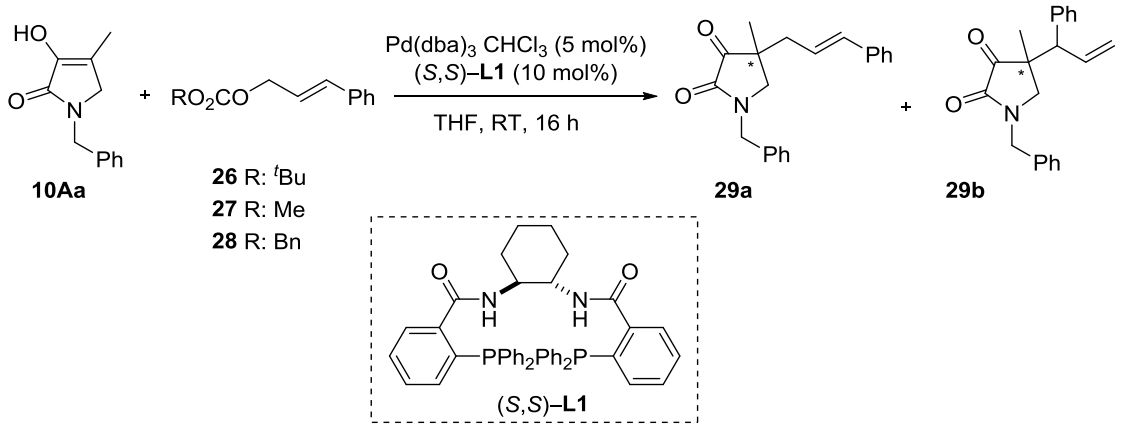


Entry	R	Conv. (%)[b]	Yield (%)[c]	*ee* (%)[d]
1	**23**	90	79	88
2	**24**	90	82	91
3	**25**	90	70	93

[a] Reactions performed on a 0.2 mmol scale and in 0.8 mL of solvent (mol ratio **10**/allyl carbonate of 1:1.2). [b] Related to the disappearance of the starting material. [c] Yield of isolated product after chromatography. [d] Enantioselectivity determined by chiral HPLC.

As a major challenge, the intermolecular allylation of **10Aa** with phenyl substituted allyl carbonates was also explored (Table 8). This reaction is challenging since it provides the possibility to access both regioisomers, linear **29a** or branched **29b**. Different carbonates (**26**-**28**) were explored under the usual reaction conditions. When the reaction was carried out with *tert*-butyl cinnamyl carbonate **26** for 16 h at room temperature, the linear product **29a** was detected with 50-55% conversion, but no trace of the branched product was observed. However, after 4 days at the same temperature, the branched product was detected in 20%. Thus we can conclude that under these reaction conditions, branched product generation is slower. When using carbonates **27** and **28**, similar conversion was observed after 16 h for the linear product, with no branched product generation, also checked in the crude of the reaction. However, after column chromatography purification, the branched regioisomer **29b** was detected (**29a**/**29b** 57:43 with **27**, and **29a**/**29b** 67:33 with **28**, entries 2 and 3).

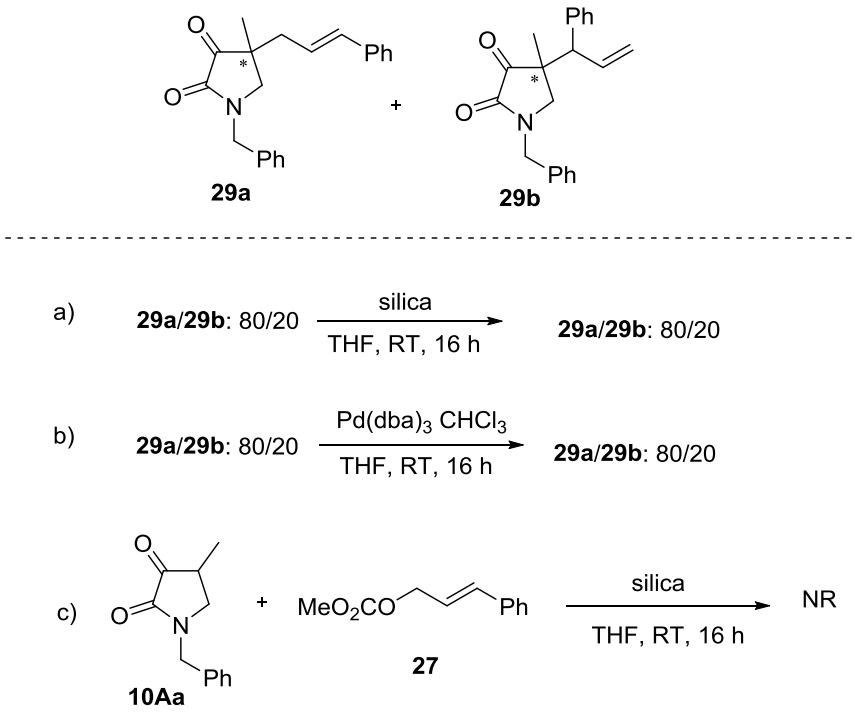
Table 8. Asymmetric Allylic Alkylation of **10Aa** with alkyl cinnamyl carbonates **26**-**28**.



Entry	R	t (h)	Total conv. (%)[b]	Conv. 29a (%)[b]	Conv. 29b (%)[b]	29a/29b[c]	*ee* (%)[d]
1	**26**	16	52	52	0		
		4d	63	43	20	n.d.	23
2	**27**	16	55	55	0	57/43	20
3	**28**	16	50	50	0	67/33	24

[a] Reactions performed on a 0.2 mmol scale and in 0.8 mL of solvent (mol ratio pyrrolidin/allyl carbonate of 1:2). [b] Related to the disappearance of the starting material. [c] **29a**:**29b** ratio after column chromatography. [d] Enantioselectivity determined by chiral HPLC for **29a**.

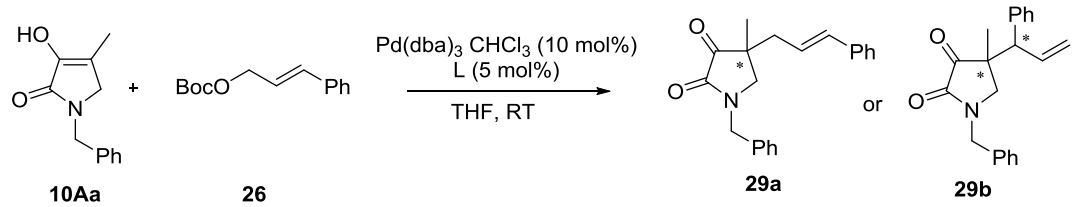
The generation of the branched product after column chromatography made us wonder whether the acid silica would promote the isomerisation of the linear product. Therefore, the stability of the linear adduct was checked under different conditions (Scheme 30). Thus a mixture of compounds **29a**/**29b** in a 80:20 ratio was treated with silica in THF at room temperature for 16 h and it was observed that the product ratio did not vary (a, Scheme 30). In addition, the same mixture was treated with the palladium source in THF at room temperature and the product ratio was also maintained after 16 h (b, Scheme 30). Finally, it was observed that the allylation of **10Aa** with **27** did not proceed in the absence of the catalyst and in the presence of silica in THF at room temperature (c, Scheme 30). Therefore, further information is required to have a better understanding of the reaction pathway.

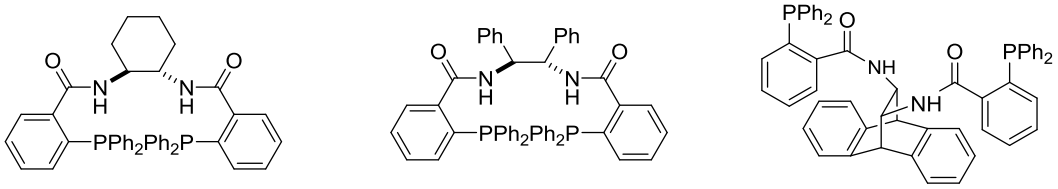


Scheme 30. Stability experiments with the reaction adducts.

The addition of a base (TEA, DIPEA, DBU, Li_2CO_3, and chiral bifunctional BB) did not improve the reactivity nor the regioselectivity. Finally, other chiral ligands were also explored (0). Ligand **L1** afforded the reaction adducts in 63% conversion after 4 days with 23% *ee* (entry 1). In contrast, when **L3** was employed, the reaction did not proceed (entry 2), and as happened with unsubstituted carbonates, **L4** afforded the reaction adduct with the highest enantioselectivity (50% *ee*, entry 3), although still poor.

Table 9. Ligand screening of **10Aa** with *tert*-butyl cinnamyl carbonate **26**.[a]



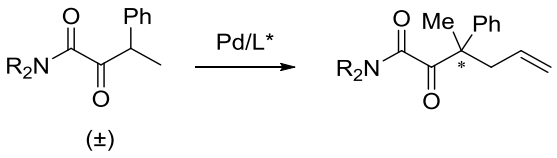


Entry	Ligand (5 mol%)	t (h)	Total. Conv. (%)[b]	Conv. 29a (%)[b]	Conv. 29b (%)[b]	*ee* (%)[c]
1	**L1**	16	52	52	0	
		4d	63	43	20	23
3	**L3**	16	0	-	-	-
2	**L4**	16	56	56	0	
		4d	64	42	22	50

[a] Reactions performed on a 0.2 mmol scale and in 0.8 mL of solvent (mol ratio pyrrolidin **10Aa**/allyl carbonate **26** of 1:2). [b] Related to the disappearance of the starting material. [c] Enantioselectivity determined by chiral HPLC.

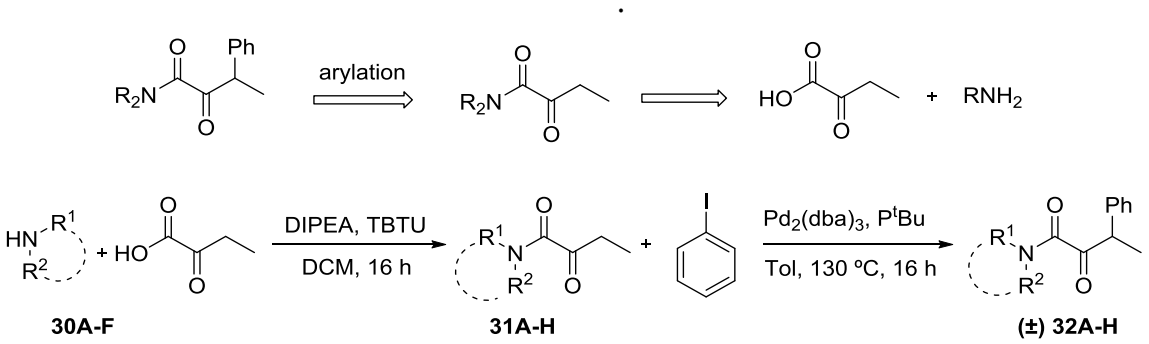
2.4.2.2. Pd-catalyzed AAA of acyclic ketoamides

Given the good results of asymmetric allylic alkylation with cyclic α-substituted ketoamides, we focused our interest on the allylation of the more challenging acyclic α-ketoamides to generate tetrasubstituted stereocenters (Scheme 31). For a first exploration, α-phenyl ketoamides were selected, expecting that the reactivity and stereoselectivity control would be favoured. Therefore, ketoamides bearing different substituents at the amide nitrogen were explored in the AAA.



Scheme 31. Assymmetric allylic alkylation of acyclic α-ketoamides.

Due to the lower rigidity of the acyclic structure, control of enantioselectivity seems a more difficult task with these substrates. The acyclic ketoamides were prepared following the protocol shown in Scheme 32.[168] The commercially available (di)amines **30A-30F** were coupled with 2-oxobutyric acid in presence of DIPEA and TBTU followed by the arylation of the α-carbon with a palladium-phosphine catalyst at high temperature in a sealed tube.



30A R^1, R^2: Bn	**31A** (84%)	**(±) 32A** (70%)
30B R^1, R^2: Et	**31B** (92%)	**(±) 32B** (60%)
30C R^1, R^2: ^{i}Bu	**31C** (98%)	**(±) 32C** (58%)
30D R^1, R^2: 1-Napht-CH_2	**31D** (77%)	**(±) 32D** (83%)
30E R^1, R^2: $-(CH_2)_5-$	**31E** (84%)	**(±) 32E** (80%)
30F R^1, R^2: $-(CH_2)_2-O-(CH_2)_2$	**31F** (92%)	**(±) 32F** (80%)
30G R^1: OMe, R^2: Me	**31G** (60%)	**(±) 32G** (83%)
30H R^1: Ph, R^2: Me	**31H** (85%)	**(±) 32H** (68%)

Scheme 32. Synthesis of α-phenyl ketoamides **32A-F**

In a first instance, the decarboxylative asymmetric allylic alkylation was considered. Following a procedure from the literature, the enol carbonate of compound **32A** was formed at – 78ºC in THF, in the presence of NaHMDS, TMEDA followed by the addition of allyl chloroformate (Figure 24).[169] It was gratifying to observe that only one isomer was formed (checked by ^{1}H-NMR) and its geometry was determined by X-ray analysis (Figure 24).

[168] For the first step: a) M. R. Davis, E. K. Singh, H. Wahyudi, L. D. Alexander, J. B. Kunicki, L. A. Nazarova, K. A. Fairweather, A. M. Giltrap, K. A. Jolliffe, S. R. McAlpine, *Tetrahedron* **2012**, *68*, 1029-1051; b) M. M. Zhao, W. F. Li, X. Ma, W. Z. Fan, X. M. Tao, X. M. Li, X. M. Xie, Z. G. Zhang, *Sci.China. Chem.* **2013**, *56*, 342-348. For the second step: B. P. Zavesky, S. L. Bartlett, J. S. Johnson, *Org. Lett.* **2017**, *19*, 2126-2129.

[169] B. M. Trost, J. Xi, *J. Am. Chem. Soc.* **2005**, *127*, 17180-17181.

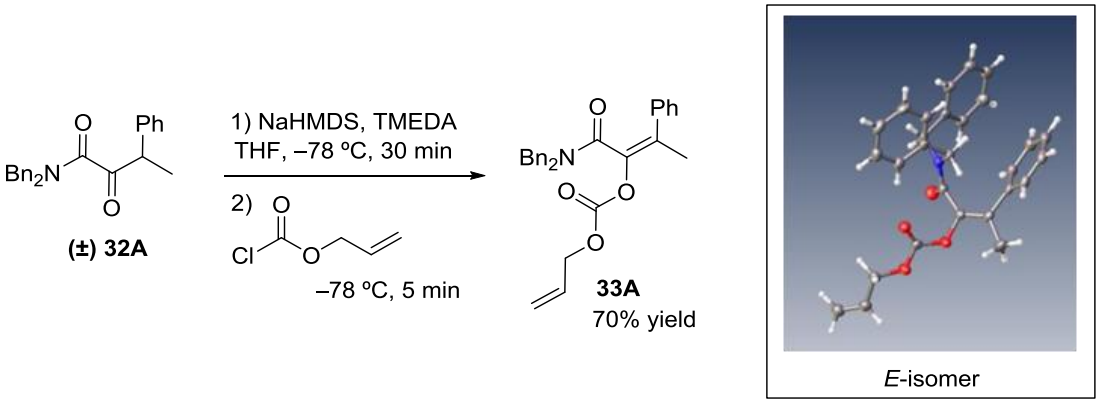
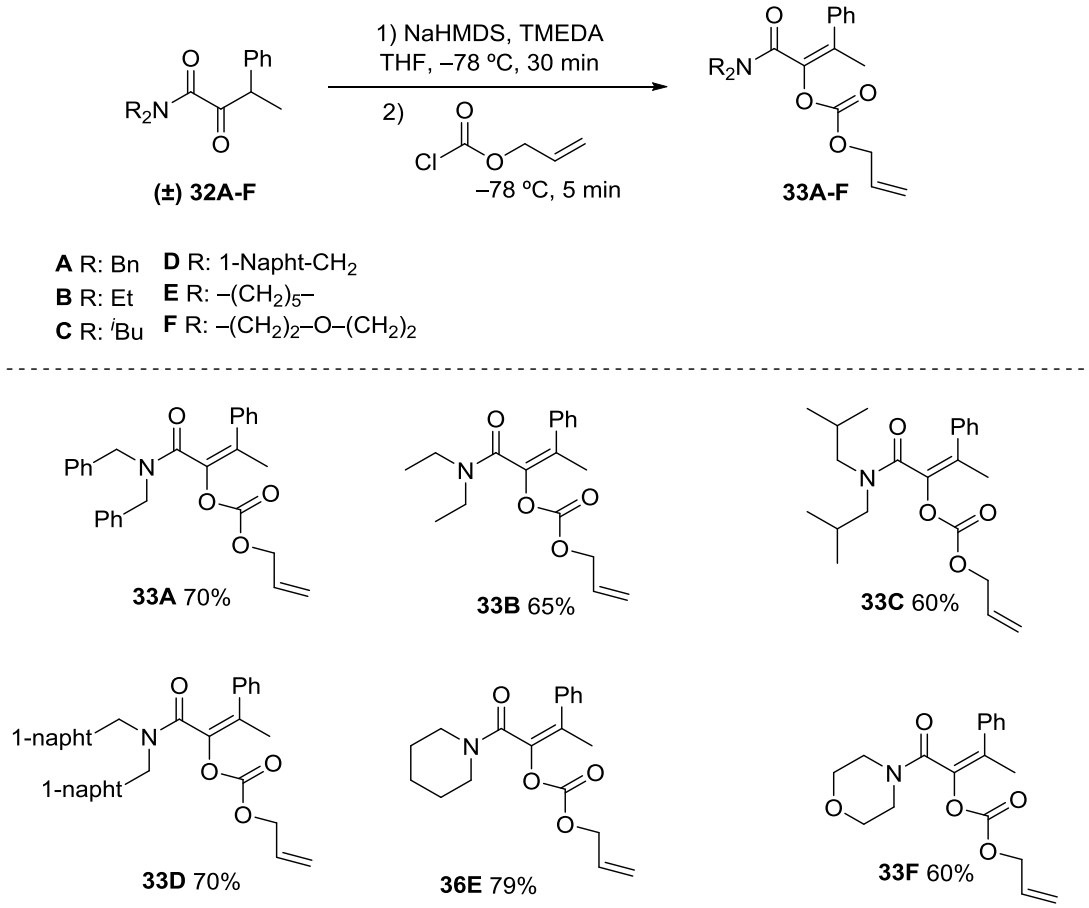


Figure 24. Enol carbonate formation of ketoamide **32A** and X-ray structure of enol carbonate **33A**.

Then, enol carbonates of ketoamides **32B-F** were prepared following the same procedure and the final adducts were obtained with same selectivity and similar conversion (Table 10). As mentioned, the substituents of the nitrogen atom of the amide were varied to explore their influence in the enantioselectivity.

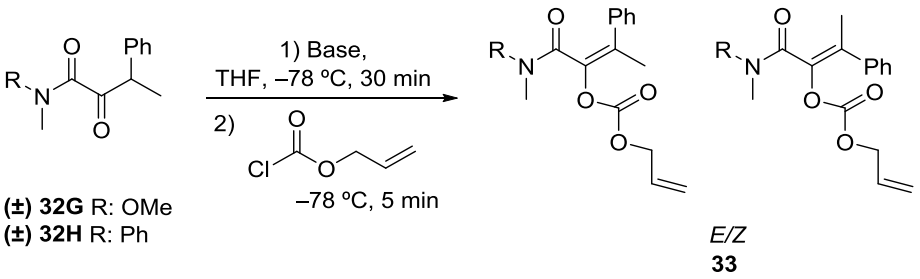
Table 10. Enol carbonate formation of acyclic α-ketoamides **32A-F**.



[a] Reactions performed on a 0.2 mmol scale and in 0.8 mL of. Yield of isolated product after chromatography.

However, with amides not symmetrically substituted at the nitrogen, isomeric mixtures of the enol carbonates were detected, even under different reaction conditions (Table 11). These substrates were discarded (ketoamides **32G** and **32H**) and their allylation was not performed.

Table 11. Enol carbonate formation with ketoamides **32G** and **32H**.[a]

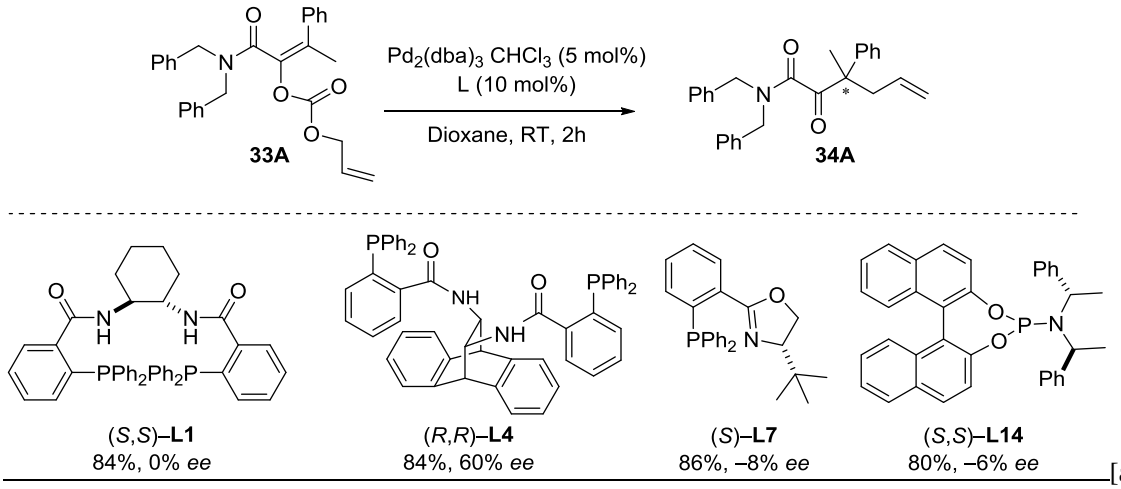


Entry	Product	Base	Yield[b]	Mixture[c]
1	**33G**	NaHMDS in THF, TMEDA	58	46:54
2		KHMDS in Tol, TMEDA	67	32:68
3		LiHMDS in THF, TMEDA	65	74:26
4		$(PhMe_2Si)_2NLi$ in hexane, TMEDA	70	30:70
5	**33H**	NaHMDS in THF, TMEDA	69	84:16

[a] Reactions performed on a 0.2 mmol scale and in 0.8 mL of. [b] Yield of isolated product after chromatography. [c] Mixture of *E/Z* isomers, which were not identified.

The study of the asymmetric allylation began with the ligand screening of compound **33A** in dioxane at room temperature. As happened with pyrrolidin-2,3-diones, **L4** promoted the allylation with the highest enantioselectivity. Despite providing the reaction adducts in good yields, no control of enantioselectivity was observed with **L1**, **L7** and **L14**.

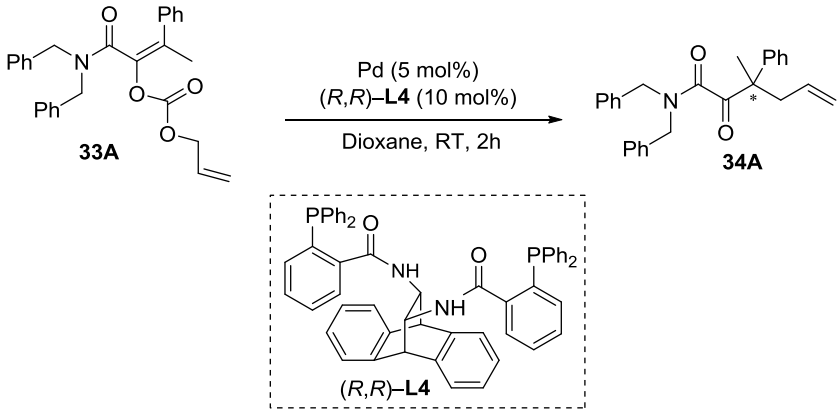
Table 12. Ligand screening in DAAA of acyclic ketoamide **33A**.[a]



[a] Reactions performed on a 0.2 mmol scale and in 0.8 mL of solvent. Yield of isolated product after chromatography. Enantioselectivity determined by chiral HPLC.

With the best ligand in hand, the palladium source was varied to explore the influence in enantioselectivity (Table 13). Thus, when switching to $Pd(dmdba)_2$ (entry 2) or $Pd(dba)_2$ (entry 3), same reactivity and lower enantioselectivity than with $Pd_2(dba)_3$ $CHCl_3$ was observed. Hence, $Pd_2(dba)_3$ $CHCl_3$ and ligand **L4** were selected for the next studies.

Table 13. Palladium screening with **33A**.[a]

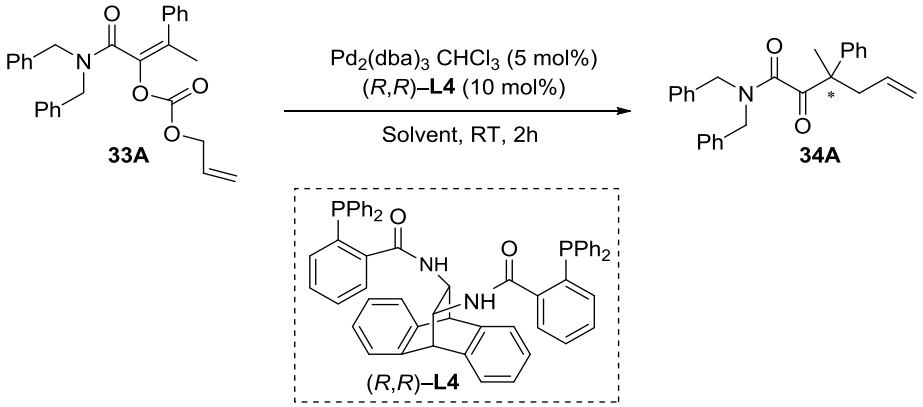


Entry	Pd	Conv. (%)[b]	Yield (%)[c]	*ee* (%)[d]
1	$Pd_2(dba)_3$ $CHCl_3$	>99	84	60
2	$Pd(dmdba)_2$	>99	76	53
3	$Pd(dba)_2$	>99	68	52

[a] Reactions performed on a 0.2 mmol scale and in 0.8 mL of solvent. [b] Conversion after 2 h, related to the disappearance of the starting material. [c] Yield of isolated product after chromatography. [d] Enantioselectivity determined by chiral HPLC.

With the aim of increasing the enantioselectivity values, a solvent screening was also carried out whose results are depicted in Table 14. Performing the reaction in THF, the same value of enantioselectivity than with dioxane was observed (entry 2), and when using toluene as the solvent, the enantioselectivity dropped to 45% *ee* (entry 3). Therefore, dioxane was the solvent of choice for the next experiments.

Table 14. Solvent screening of **33A**.[a]

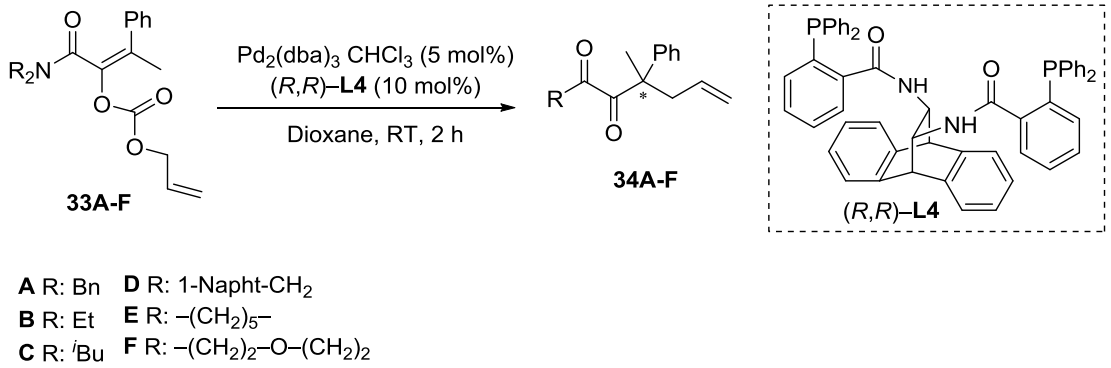


Entry	Solvent	Conv. (%)[b]	Yield (%)[c]	*ee* (%)[d]
1	Dioxane	>99	84	60
2	THF	>99	76	60
3	Toluene	>99	80	45

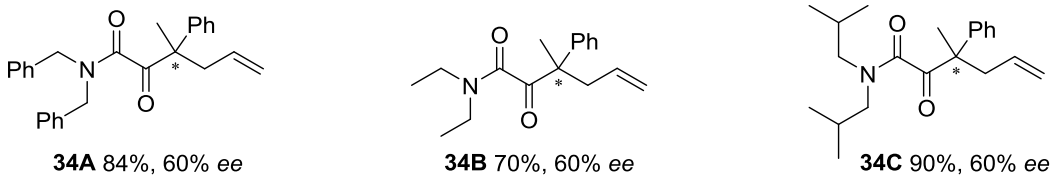
[a] Reactions performed on a 0.2 mmol scale and in 0.8 mL of solvent. [b] Conversion after 2 h, related to the disappearance of the starting material. [c] Yield of isolated product after chromatography. [d] Enantioselectivity determined by chiral HPLC.

With the optimized reaction conditions, an amide screening was carried out in order to check the influence of the amide substituents in enantioselectivity (Table 15). Changing the amide substituent to diethyl (**33B**) or diisobutyl (**33C**) groups, the corresponding adducts were afforded with the same enantioselectivity level (60% *ee*). However, the enantiocontrol was slightly lower when 1-naphtylmethyl derivative **33D**, or cyclic amides **33E** and **33F** were employed.

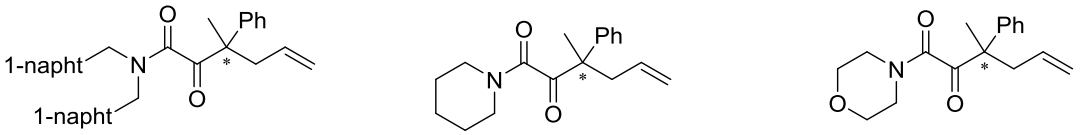
Table 15. Amide screening of the allylation reaction with acyclic ketoamides.[a]



A R: Bn **D** R: 1-Napht-CH_2
B R: Et **E** R: $-(CH_2)_5-$
C R: ^{i}Bu **F** R: $-(CH_2)_2-O-(CH_2)_2$



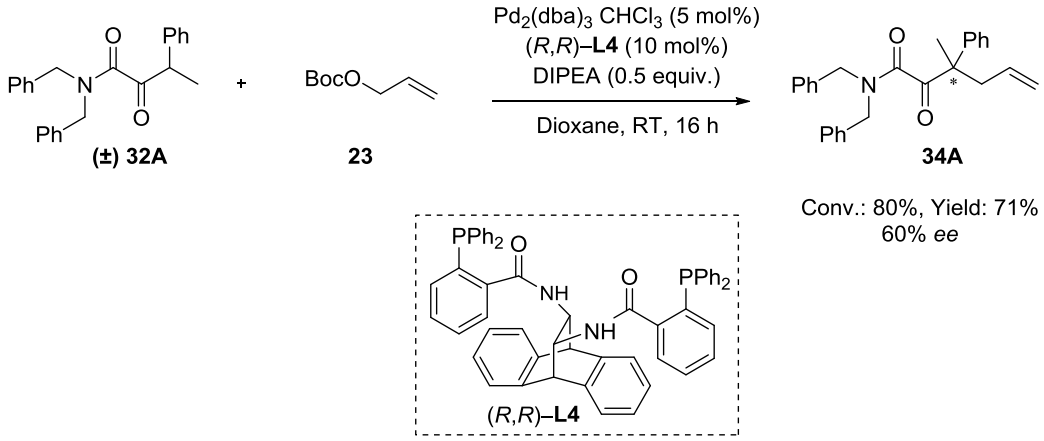
34A 84%, 60% *ee* **34B** 70%, 60% *ee* **34C** 90%, 60% *ee*



34D 80%, 56% *ee* **34E** 81%, 54% *ee* **34F** 73%, 48% *ee*

[a] Reactions performed on a 0.2 mmol scale and in 0.8 mL of solvent. Yield of isolated product after chromatography. Enantioselectivity determined by chiral HPLC.

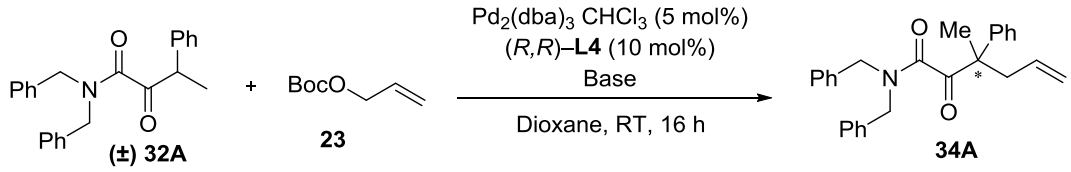
The intermolecular version of the reaction was also investigated with acyclic ketoamides. Here, longer reaction times were required, compared to the decarboxylative version, but enantioselectivity remained unaltered (Scheme 33).

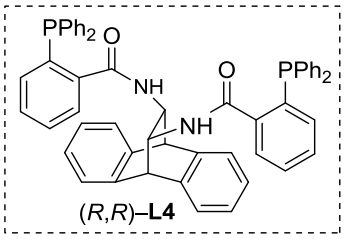


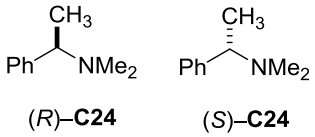
Scheme 33. Intermolecular AAA of **32A** with **23**.

A base screening was also performed (Table 16) and it was observed that the reaction proceeds without the need of the base, but its addition increases the reaction rate (entry 1 and 2). In addition, the enantioselectivity value decreased significantly to 10% when NaHMDS was employed instead of DIPEA (entry 2). Besides, both enantiomers of the chiral base **C24** were checked, but it was observed that the configuration had no influence in stereoselectivity as the same enantiocontrol was obtained with both of them (entries 3 and 4).

Table 16. Base screening of AAA of α-phenyl ketoamide **32A.**[a]





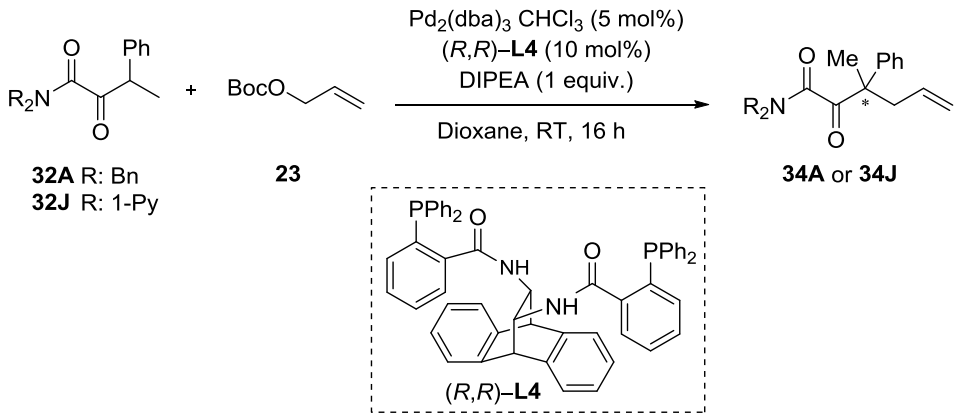


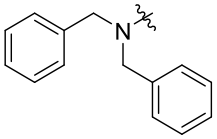
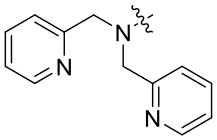
Entry	Base	Conv. (%)[b]	Yield (%)[c]	*ee* (%)[d]
1	-	68	-	-
	DIPEA (0.5 equiv.)	80	68	60
2	NaHMDS (1 equiv.)	>99	72	10
3	(*R*)-**C24**	>99	75	52
4	(*S*)-**C24**	>99	73	52

[a] Reactions performed on a 0.2 mmol scale and in 0.8 mL of solvent (mol ratio ketoamide **32A**/allyl *tert*-butyl carbonate **23** of 1:2). [b] Conversion after 16 h, related to the disappearance of the starting material. [c] Yield of isolated product after chromatography. [d] Enantioselectivity determined by chiral HPLC.

With these results in hand, improvement of the enantioselectivity was pursued with the variation of the amide group from dibenzyl- to dipyridine (Table 17). We hypothesized that the nitrogen of the aromatic ring could have an influence in the enantiocontrol. However, enantioselectivity with **32I** decreased up to 32% *ee* (entry 2).

Table 17. Intermolecular allylation.[a]



Entry	Product	R	Conv. (%)[b]	Yield (%)[c]	*ee* (%)[d]
1	**34A**		>99	80	60
2	**34J**		>99	73	32

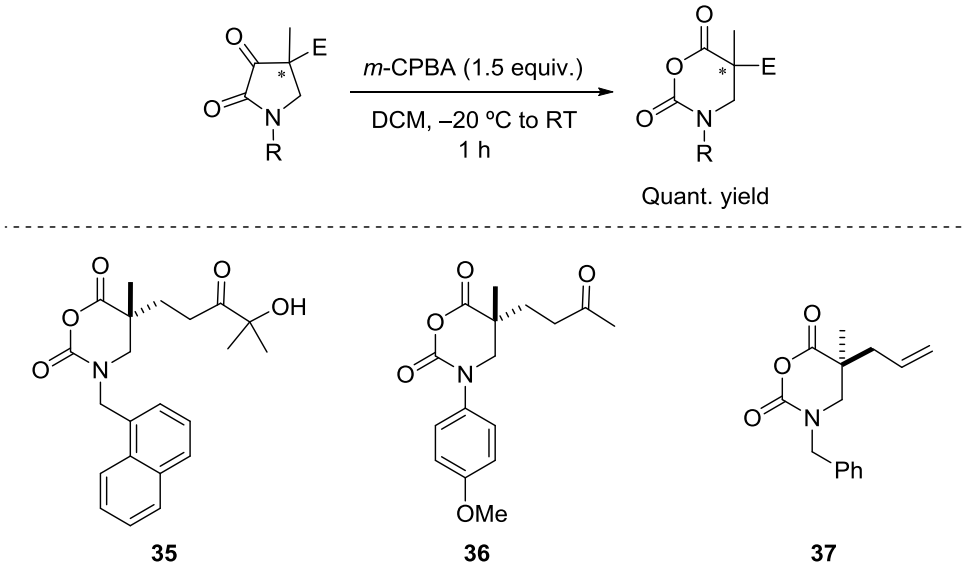
[a] Reactions performed on a 0.2 mmol scale and in 0.8 mL of solvent (mol ratio ketoamide/allyl *tert*-butyl carbonate **23** of 1:2). [b] Conversion after 16 h, related to the disappearance of the starting material. [c] Yield of isolated product after chromatography. [d] Enantioselectivity determined by chiral HPLC.

To conclude, the asymmetric allylic alkylation of pyrrolidin 2,3-diones has proven an excellent procedure for the generation of quaternary stereocenters bearing an allyl group at the alpha position with high enantioselectivity. In contrast, the enantiocontrol when using acyclic ketoamides was not so good as higher levels than 60% *ee* were not obtained. Hence, further studies in this field are at the moment underway in our research group, pursuing an improvement in the enantiocontrol in the α-allylation of acyclic α-ketoamides.

2.4.3. Elaboration of the adducts

As mentioned at the beginning of the chapter, based on the precedents of this laboratory, we questioned whether these 4,4-disubstituted pyrrolidin-2,3-diones upon Baeyer-Villiger oxidation could be regioselectively transformed into the respective *N*-carboxyanhydrides, that is, a carboxyl activated form of $\beta^{2,2}$-amino acids which would provide the opportunity to perform further couplings. Thus, we were pleased to find that reaction of **14Ba**, **18Da**, and **22A** with m-chloroperbenzoic acid (*m*-CPBA) at –20 °C in DCM proceeds with complete regio- and chemoselectivity to give the respective β-amino

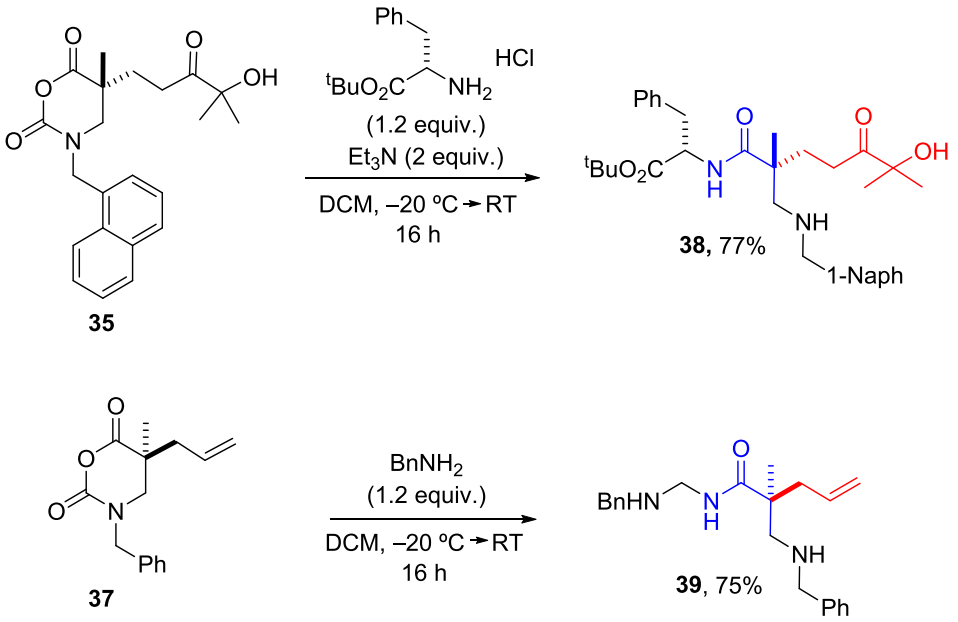
acid derived *N*-carboxyanhydrides ($\beta^{2,2}$-NCAs) **35-37** almost quantitatively and without products from oxidation of the exocyclic carbonyl group or epoxidation of the allyl group (Scheme 34). To the best of our knowledge, this is the first approach to carboxyl activated forms of α,α-disubstituted β-amino acids instead of the most common free acids or esters,[170] and therefore products of more complexity may be made readily feasible by coupling of these NCAs with appropriate nucleophiles.



Scheme 34. Transformation of the reaction adducts into the corresponding NCAs **35-37**.

With the NCAs in hand, the last step would be the nucleophilic reaction with an amine, to afford highly functionalized amides. Hence, coupling of **39** with L-phenylalanine *tert*-butyl ester, furnished product **38** in 77% yield. Similarly, **37** reacted with benzylamine to afford **39** in 75% yield.

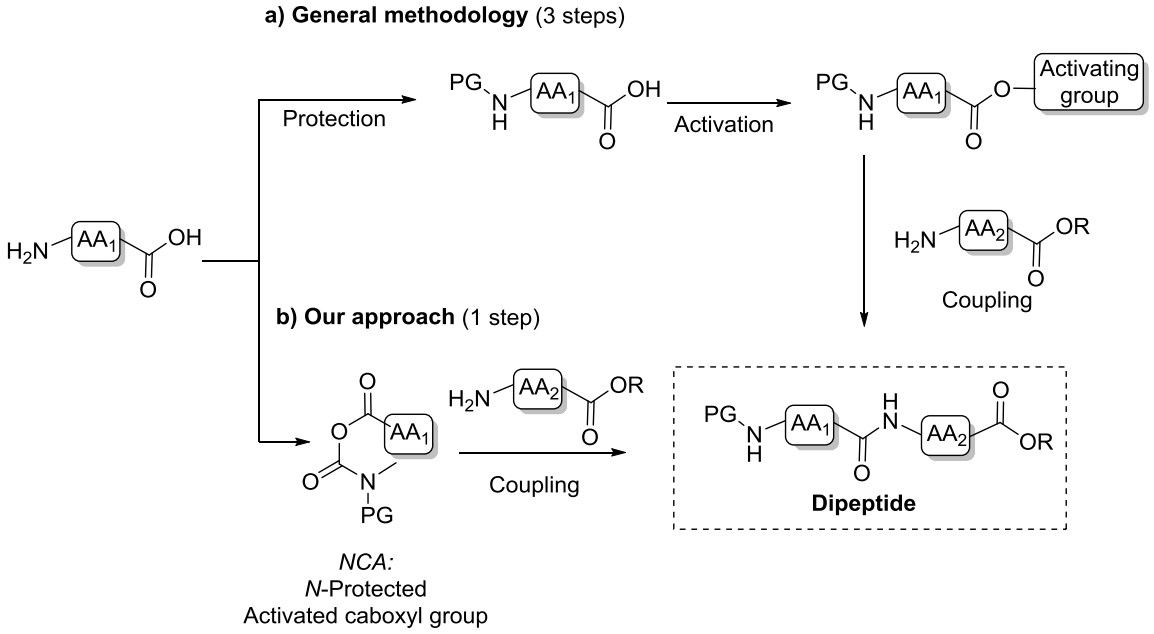
[170] a) H. Kricheldorf, *α-Amino Acid-N-Carboxyanhydrides and related Heterocycles*, Springer, **1997**. For recent examples from b-amino acids, see: b) J. G. Hernández, E. Juaristi, *J. Org. Chem.* **2010**, *75*, 7107 – 7111.



Scheme 35. Reactions of the amines and amino acids with NCAs.

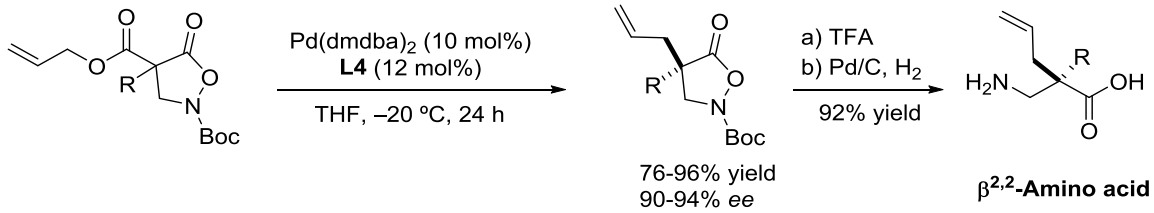
Despite the interest in $\beta^{2,2}$-amino acids, the procedures for their catalytic and enantioselective synthesis are very limited.[171] Besides the narrow range of the existing enantioselective methods for the synthesis of $\beta^{2,2}$-amino acids, it is noteworthy that these methodologies generally involve several steps including *N*-protection, subsequent carbonyl group activation and final coupling (a, Scheme 36), thus complicating the process. Therefore, our methodology (b, Scheme 36) has proven to be a very efficient tool to access $\beta^{2,2}$-amino acid derivatives with good reactivity and high enantioselectivity, containing functionalized groups at the alpha position to the carbonyl unit.[172]

[171] a) S. Abele, D. Seebach, *Eur. J. Org. Chem.* **2000**, 1 –15; b) B. Weiner, W. Szymánsky, D. B. Janssen, A. J. Minnaand, B. L. Feringa, *Chem. Soc. Rev.* **2010**, 39, 1656– 1691.
[172] E. Badiola, I. Olaizola, A. Vázquez, S. Vera, A. Mielgo, C. Palomo *Chem. Eur. J.* **2017**, *23*, 8185-8195.



Scheme 36. a) General procedure for the incorporation and/or derivatization of amino acids into peptidic sequences and b) Our approach based on *N*-carboxyanhydrides.

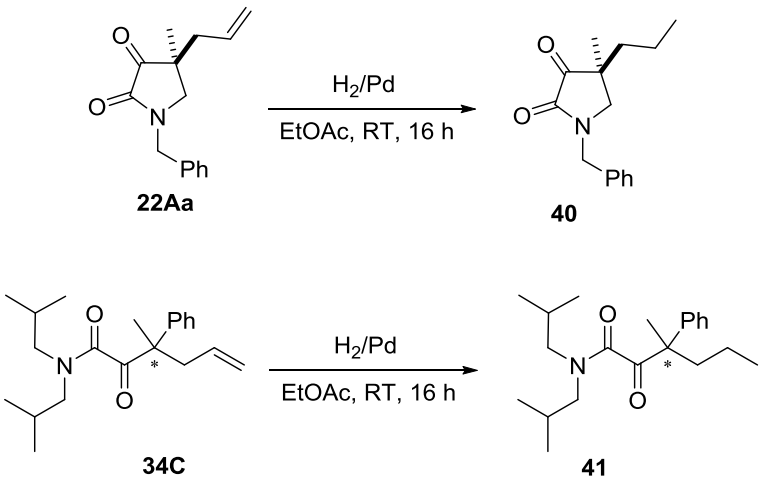
When this research work started, there were no examples of the synthesis of $\beta^{2,2}$-amino acids through Pd-dAAA. However, Noda and Shibasaki[173] published in 2018, the decarboxylative allylation of substituted isoxazolidin-5-ones and their hydrolysis to afford $\beta^{2,2}$-amino acids bearing an allyl group (Scheme 37). In addition, a similar approach was reported by Pierce and co-workers.[174]



Scheme 37. Pd-catalyzed AAA of isoxazolidin-5-ones and their hydrolysis to afford $\beta^{2,2}$-amino acids.

Finally, hydrogenation of the allyl group afforded the corresponding alkyl derivatives in an easy manner for both cyclic **22Aa** and acyclic ketoamides **34C**.

[173] J.-S. Yu, H. Noda, M. Shibasaki, *Angew. Chem. Int. Ed.* **2018**, *57*, 818-822.
[174] a) N. V. Shymanska, J. G. Pierce, *Org. Lett.* **2017**, *19*, 2961-2964. b) A. Q. Cusumano, M. W. Boudreau, J. G. Pierce, *J. Org. Chem.* **2017**, *82*, 13714-13721.



Scheme 38. Hydrogenation of **22Aa** and **34C**.

Chapter 3

Activated amides in aldol reaction

3. Activated amides in aldol reaction

3.1. α-Functionalization of amides via BB catalysis

α-Functionalized amides are structural units present in pharmaceuticals, natural products and biologically active compounds, as well as in many industrial materials such as polymers, detergents and lubricants (Figure 25), and therefore amide α-functionalization reactions are significant transformations in organic chemistry and biochemistry.[175]

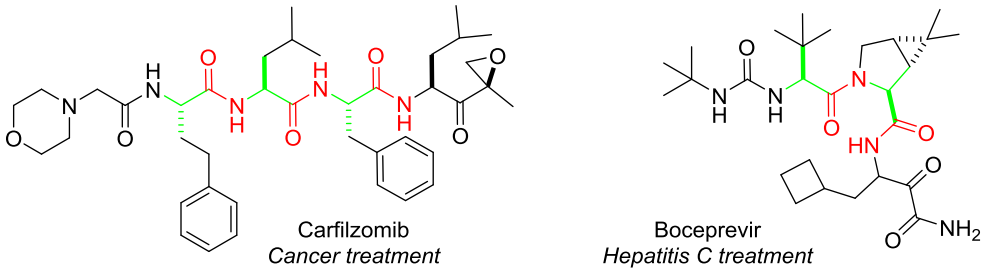


Figure 25. Biologically active compounds bearing an amide unit.

In spite of the huge importance of α-functionalized amides in organic chemistry, well-established methods for their asymmetric synthesis are limited. Most examples are promoted via stoichiometric approaches, and catalytic strategies (metal catalysis, and Brønsted base catalysis) involving α-functionalization of amides remains challenging, due to the low acidity of their α-carbon. As mentioned in the introduction, the strategies that have been reported in this context involve the use of activated amides.

Additionally, there is a great interest in the enantioselective synthesis of α-amino acids due to their presence in many natural and non-natural products as well as useful scaffolds for asymmetric catalysis.[176] Therefore, different approaches for their enantioselective synthesis have been reported, mostly relying on the use of glycine as starting material (Figure 26).[177]

---

[175] P. Rajput, A. Sharma, *J. Pharmacol. Med. Chem*. **2018**, 2, 22-31.
[176] a) *Amino Acids, Peptides and Proteins in Organic Chemistry: Building Blocks, Catalysis and Coupling Chemistry*, A. B. Hughes Ed.; Wiley-VCH, 2011; b) *Asymmetric Synthesis and Application of α-Amino Acids;* Soloshonok, V. A.; Izawa, K., Eds.; American Chemical Society: Washington DC, **2009**.
[177] a) R. Saladino, G. Bot-taa, M. Crucianelli, *Mini-Rev. Med. Chem*. **2012**, *12*, 277–300; b) C. Nájera, J. M. Sansano, Chem. Rev. **2007**, *107*, 4584–4671.

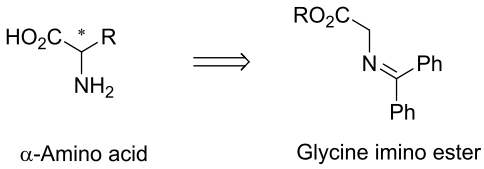


Figure 26. Approach to α-amino acids through benzophenone imine glycine esters.

In this context, benzophenone imines of glycine esters, introduced by O'Donnel and Eckrich[178] in 1978, have shown to be very useful bench stable pronucleophiles for this goal.[179] However, their use in enantioselective synthesis has been mainly limited to metal[180] and phase transfer catalysis[181] while application in BB/H-bonding catalysis remains essentially underexplored.[182]

α-Amino β-hydroxy acids are of interest in medicinal chemistry[183] and useful starting materials for synthesis. One approach for their asymmetric synthesis is the aldol reaction of glycine iminoesters. The first catalytic direct aldol reaction of benzophenone imines of glycine esters was reported in 1991 by Miller and Gasparski using phase-transfer catalysis, but the major *anti*-adducts were produced in low diastereoselectivity and negligible enantiomeric excess.[184] Maruoka achieved a significant improvement through the development of the *N*-spiro, binaphtyl-based ammonium phase transfer catalysts **C25** (a, Scheme 39), which provided the *anti* isomers in excellent stereoselectivity for aliphatic aldehydes but very poor with aromatic aldehydes.[185] In the same context Shibasaki described the use of the heterobimetallic $Li_3[La(S\text{-}BINOL)_3]$

[178] a) M. J. O'Donnell, T. M. Eckrich, *Tetrahedron Lett.* **1978**, *19*, 4625-4628. For reviews, see: b) M. K. O'Donnel, *Tetrahedron* **2019**, *75*, 3667-3696; c) A. Jakubowska, K. Kulig, *Current Org. Synthesis* **2013**, *10*, 547-563.

[179] For nucleophilic reactivities of Schiff base derivatives of amino acids, see: D. S. Timofeeva, A. R. Ofial, H. Mayr, *Tetrahedron* **2019**, *75*, 459-463.

[180] For enantioselective amino acid synthesis by metal catalysis: a) Y. Wang, X. Song, J. Wang, H. Moriwaki, V. A. Soloshonok, H. Liu, *Amino Acids* **2017**, *49*, 1487-1520; b) J. Adrio, J. C. Carretero, *Chem. Commun.* **2011**, *47*, 6784-6794.

[181] Enantioselective amino acid synthesis by chiral PTC, see: a) S. Shirakawa, K. Maruoka, *Angew. Chem. Int. Ed.* **2013**, *52*, 4312.4348; b) K. Maruoka, *Chem. Rec.* **2010**, *10*, 254-259; c) K. Maruoka, *Chem. Rec.* **2010**, *10*, 254-259; d) T. Hashimoto, K. Maruoka, *Chem Rev.* **2007**, *107*, 5656-5682; e) T. Ooi, K. Maruoka, *Angew. Chem. Int. Ed.* **2007**, *46*, 4222-4266; f) M. J. O'Donnell, *Acc. Chem. Res.* **2004**, *37*, 506-517; g) K. Maruoka, T. Ooi, *Chem. Rev.* **2003**, *103*, 3013-3028.

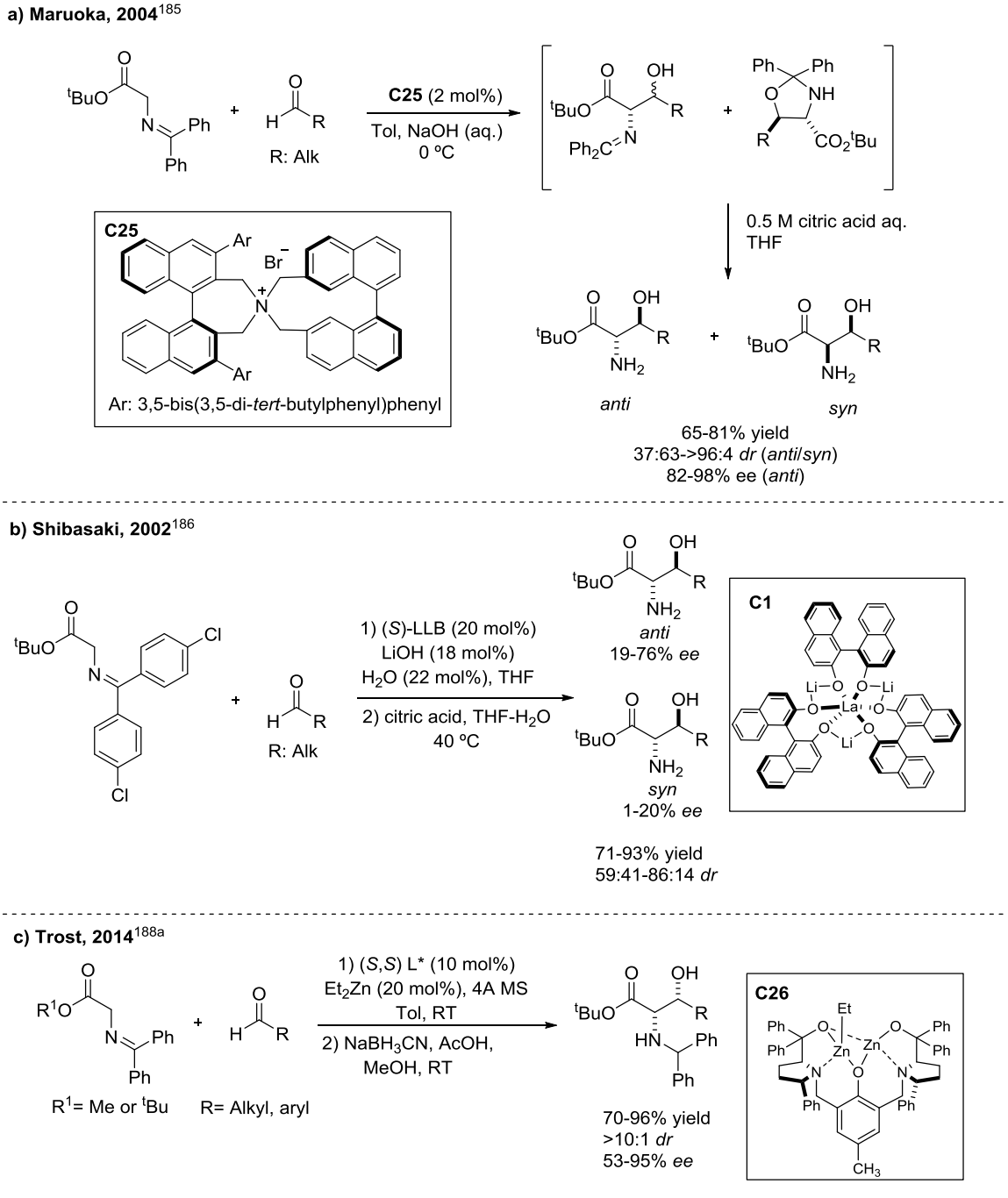
[182] A 1,3-dipolar cycloaddition of azomethyine ylides with nitroalkenes promoted by a bifunctional BB with low enantiocontrol: M.-X. Xue, X.-M Zhang, L.-Z. Gong, *Synlett*, **2008**, 691-694.

[183] Z. Ziora, M. Skwarczynski, Y. Kiso, Amino Acids, Peptides and Proteins in Organic Chemistry (Ed.: A. B. Hughes), Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, **2011**, *4*, 189-245.

[184] C. M. Gasparski, M. J. Miller, *Tetrahedron* **1991**, *47*, 5367-5378.

[185] a) T. Ooi, M. Taniguchi, M. Kaweda, K. Maruoka, *Angew. Chem. Int. Ed.* **2002**, *41*, 4542-4647; b) T. Ooi, M. Kaweda, M. Taniguchi, K. Maruoka, *J. Am. Chem. Soc.* **2004**, *126*, 9685-9694; c) S. Mettath, G. S. C. Srikanth, B. S. Dangerfields, S. L. Castle, *J. Org. Chem.* **2004**, *69*, 6489-6492.

catalysts to access the *anti*- aldols, but poor to only moderate stereoselectivities were observed (b, Scheme 39).[186]



Scheme 39. Representative literature precedents involving aldol reaction of glycinate Schiff bases.

Poor diastereo- and enantioselectivities were also produced in the aldol reaction of the corresponding lithium enolate of the iminoester with aldehydes in the presence of

[186] N. Yoshikawa, M. Shibasaki, *Tetrahedron* **2002**, *58*, 8289-8298.

(–)–sparteine.[187] The only report concerning the synthesis of *syn*- isomers was described by Trost using a zinc-ProPhenol-catalyst (c, Scheme 39).[188] The reaction works well for α-substituted aldehydes but provides less satisfactory enantioselectivities for aromatic or linear alkyl aldehydes. To the best of our knowledge, no organocatalytic *syn*-selective protocols for the direct aldol reaction of these iminoesters have been reported to date. In addition Brønsted base/H-bonding catalysis with benzophenone iminoesters is underexplored. The main reason that may account for this observation is the relatively low acidity of the methylenic carbon, which precludes enolate generation through deprotonation by soft Brønsted bases.

3.2. **Activation of imino esters/amides through intramolecular H-bonding**

Only recently, three examples of stereoselective α-functionalization of imino esters promoted by BBs have been documented in which the low reactivity problem has been solved by using the more acidic structural analogs **42**, **43** and **44** (Figure 27). The increased acidity of these compounds is the result of the structural modification of the imine function of the iminoester as in compound **42** developed by Kobayashi and co-workers[189] whose fluorenyl moiety stabilizes the resulting enolate by more extensive charge delocalization, or as in compound **43**[190] and **44**[191] wherein the acidity of the methylenic carbon is increased through intramolecular hydrogen bonding of the previously installed *o*-hydroxylaryl motif at the imine function.

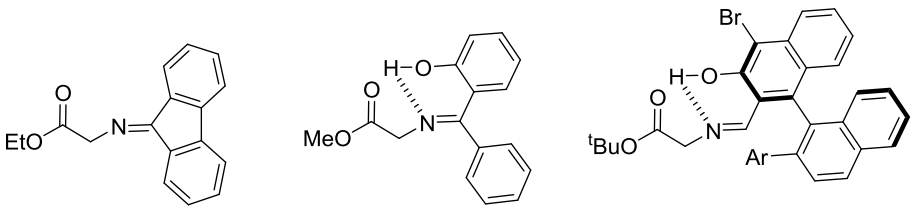


Figure 27. Glycine ester derived imines used in BB asymmetric catalysis.

[187] J. B. MacMillan, T. F. Molinski, *Org. Lett.* **2002**, *4*, 1883-1886.
[188] a) B. M. Trost, F. Miege, *J. Am. Chem. Soc.* **2014**, *136*, 3016-3019. For racemic syn-selective aldol reaction, see: b) S. Lou, A. Ramirez, D. A. Conlon, *Adv. Synth. Catal.* **2015**, *357*, 28-34.
[189] S. Kobayashi, R. Yazaki, K. Seki, Y. Yamashita, *Angew. Chem. Int. Ed.* **2008**, *47*, 5613-5615.
[190] A. Guerrero-Corella, F. Esteban, M. Iniesta, A. Martín-Somer, M. Parra, S. Díaz-Tendero, A. Fraile, J. Alemán, *Angew. Int. Chem. Ed.* **2018**, *57*, 5350–5354
[191] W. Wen, L. Chen, M.-J. Luo, Y. Zhang, Y.-C. Chen, Q. Ouyang, Q.-X. Guo, *J. Am. Chem. Soc.* **2018**, *140*, 9774-9780.

In this context, there are a few examples in the literature documenting the intramolecular hydrogen bond activation of substrates for catalytic reactions, as it will be explained below. In addition to the recent works by Aleman and Guo (Figure 27, compounds **43** and **44**), different research groups,[192] have reported the increased reactivity of different substrates through intramolecular hydrogen bonding, which also provide the reaction adducts in good stereoselectivity (Figure 28). Takemoto and co-workers designed an activated Michael acceptor with enhanced reactivity due to the intramolecular hydrogen bonding between the imide N-H moiety and the methoxy group of the benzamide (a, Figure 28), and Kim designed a similar activated Michael acceptor (b, Figure 28). Following this work, Vicario reported an activated nitroalkene (c, Figure 28), based on the same strategy, and in our research group, α-hydroxy enones (d, Figure 28) were reported as useful templates for conjugate additions. Regarding nucleophilic activation through intramolecular hydrogen bonding, Da employed *o*-hydroxyacetophenone (e, Figure 28) as nucleophile for the cross-aldol reaction with trifluoromethyl ketones promoted by bifunctional BB catalysis and, as mentioned in the introduction, our research group reported hydroxyketones (f, Figure 28) for the conjugate addition to nitroalkenes.

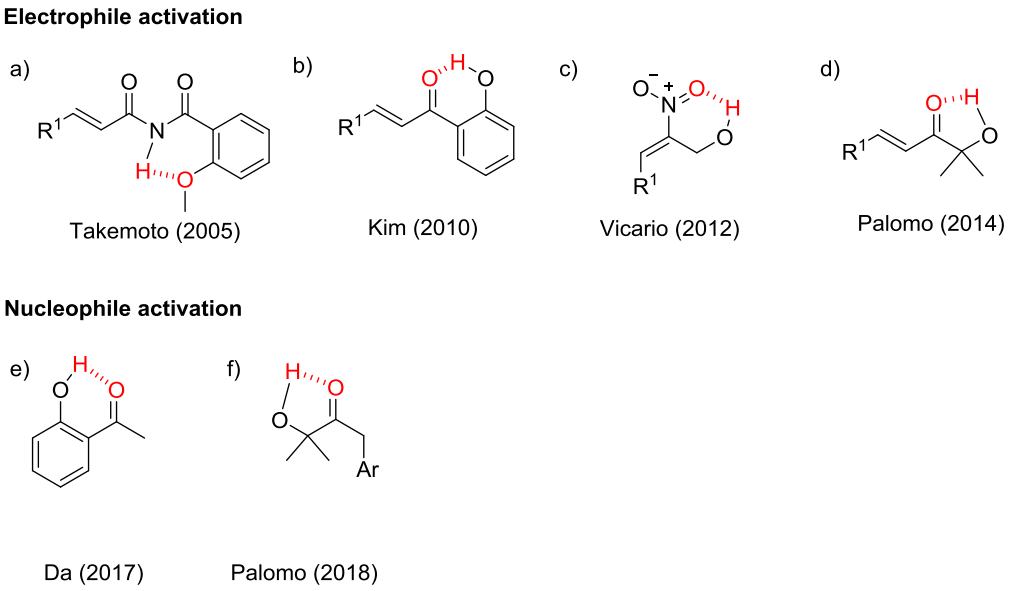


Figure 28. Examples of intramolecular H-bond activation for electrophiles and nucleophiles in asymmetric catalysis.

[192] For electrophile activation, see: a) T. Inokuma, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc*. **2006**, *128*, 9413–9419; b) G. Talavera, E. Reyes, J. L. Vicario, L. Carrillo, *Angew. Chem. Int. Ed*. **2012**, *51*, 4104–4107; c) E. Badiola, B. Fiser, E. Gómez-Bengoa, A. Mielgo, I. Olaizola, I. Urruzuno, J. M. Garcia, J. M. Odriozola, J. Razkin, M. Oiarbide, C. Palomo, *J. Am. Chem. Soc*. **2014**, *136*, 17869–17881. For nucleophile activation, see: a) P. Wang, H.-F. Li, J.-Z. Zhao, Z.-H. Du, C.-S. Da, *Org. Lett*. **2017**, *19*, 2634-2637; b) I. Olaizola, T. E. Campano, I. Iriarte, S. Vera, A. Mielgo, J. M. García, J. M. Odriozola, M. Oiarbide, C. Palomo, *Chem. Eur. J*. **2018**, *24*, 3893-3901.

Based on these examples in which intramolecular hydrogen bond preactivate the pronucleophile for the subsequent reaction, we decided to evaluate a conceptually new option for iminoesters in which the activation of the glycine derived benzophenone imine proceeds from the carboxylic acid terminus by formation of an *o*-nitroanilide (Figure 29).

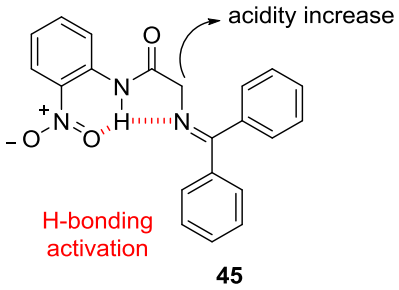
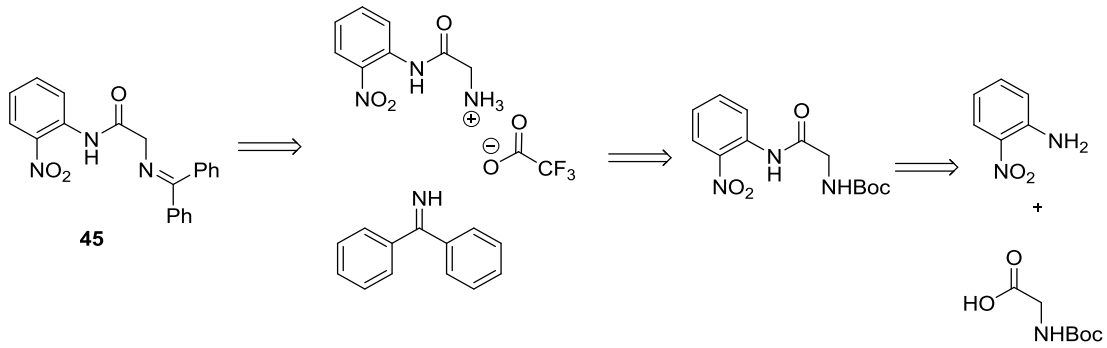


Figure 29. New glycine derived benzophenone imine **45** for BB asymmetric catalysis.

It has been reported that *o*-nitroanilides of simple carboxylic acids exhibit intramolecular hydrogen bonding between the oxygen of the nitro group and the hydrogen of the amide moiety,[193] a feature that facilitates hydrolysis by enzymes.[194] Therefore, we hypothesized that benzophenone imine **45**, besides this H-bond pattern, should also exhibit an additional H-bonding with the imine function increasing the acidity of the methylenic carbon thus allowing enolization with a weak tertiary amine base.

3.3. **Synthetic plan**

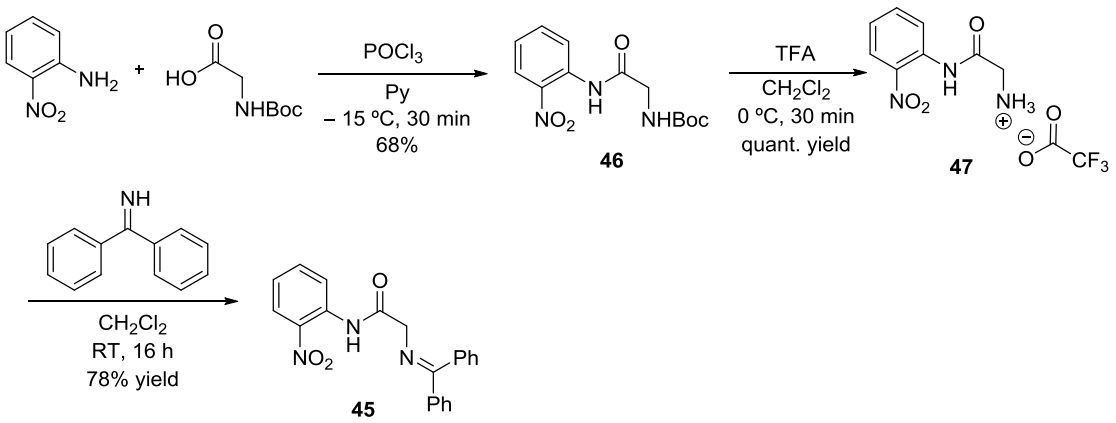
Preparation of **45** was carried out following the protocol shown in Scheme 40.



Scheme 40. Retrosynthesis of nitroanilide **45**.

[193] a) L. Skulski, *J. Org. Chem.* **1963**, *28*, 3565-3567; b) J. R. Bartel-Keith, R. F. W. Cieciuch, *Can. J. Chem.* **1968**, *46*, 2593-2600.
[194] S. Darvesh, R. S. McDonald, K. V. Darvesh, D. Mataija, S. Mothana, H. Cook, K. M. Carneiro, N. Richard, R. Walsh, E. Martinic, *Bioorg. Med. Chem.* **2006**, *14*, 4586-4599.

The first step is the coupling of *N*-(*tert*-butoxycarbonyl)glycine with 2-nitroaniline. For this reaction pyridine was used as solvent and phosphorus oxychloride as the condensing agent, following a procedure developed by Tesser.[195] Under these conditions, **46** was obtained in 68% yield (Scheme 41). Removal of the Boc- group and condensation with benzophenone imine in dichloromethane, led to *o*-nitroanilide **45** in good yield.



Scheme 41. Synthesis of nitroanilide **45**.

The previously mentioned H-bonding interactions could be confirmed in the X-ray structure analysis of compound **45**, which revealed hydrogen bond lengths of 1,987 Å and 2,149 Å that fit well with the proposed bifurcated hydrogen bond motif[196] (Figure 30). Interestingly, the X-Ray analysis also showed an additional hydrogen bonding (2.234 Å) between the *o*-aromatic hydrogen and the carbonyl oxygen. Therefore, while amides are known to be reluctant to enolization,[197] we expected these structural features should render substrate **45** quite promising for Brønsted base promoted stereoselective transformations.

[195] D. T. S. Rijkers, H.P.H.M. Adams, H. Coenraad Hemker, G. I. Tesser, Tetrahedron **1995**, *51*, 11235-11250.
[196] The hydrogen bond in the solid state: T. Steiner, *Angew. Chem. Int. Ed.* **2002**, *41*, 48−76.
[197] First amide donor in organocatalysis: a) B. Tan, G. Hernández-Torres, C. F. Barbas III, *Angew. Chem. Int. Ed.* **2012**, *51*, 5381–5385; *Angew. Chem.* **2012**, *124*, 5477-5481. For amides in metal catalysis: b) N. Kumagai, M. Shibasaki, *Chem. Eur. J.* **2016**, *22*, 15192–15200; c) N. Kumagai, M. Shibasaki, *Synthesis*, **2019**, *51*, 185–193.

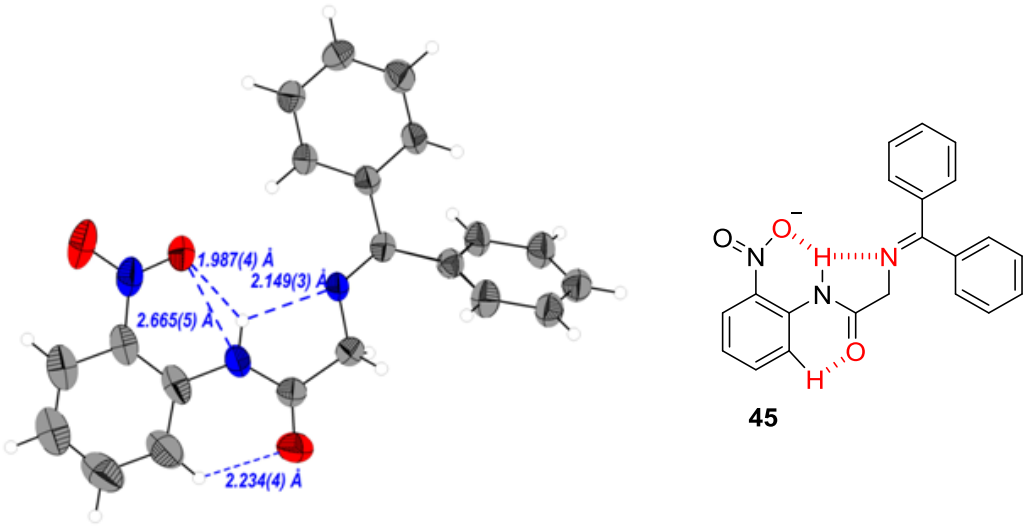


Figure 30. X-ray structure for compound **45**.

The previous precedents on organocatalytic aldol reactions of iminoesters clearly show the need of protocols to access the *syn* aldol isomers. Therefore, with pronucleophile **45** in hand, we selected the aldol reaction to check our hypothesis on the higher reactivity on nitroanilides **45** in BB bifunctional catalysis in order to explore both the reactivity and dioastereoselectivity of this transformation.

3.4. Results and discussion

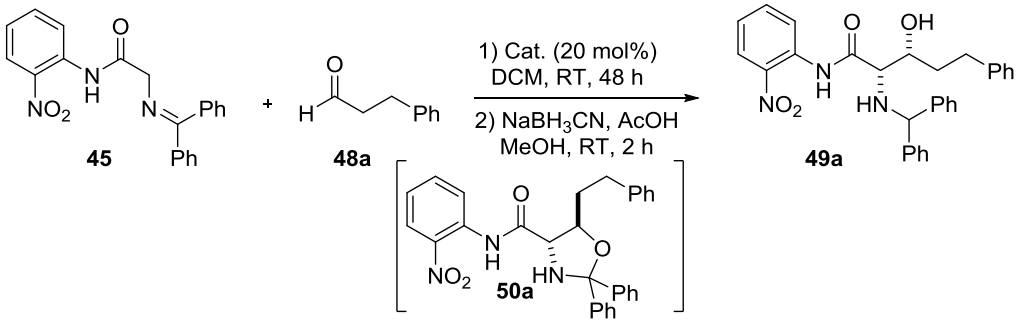
3.4.1. Organocatalytic aldol reaction of glycine derived ketiminoamides

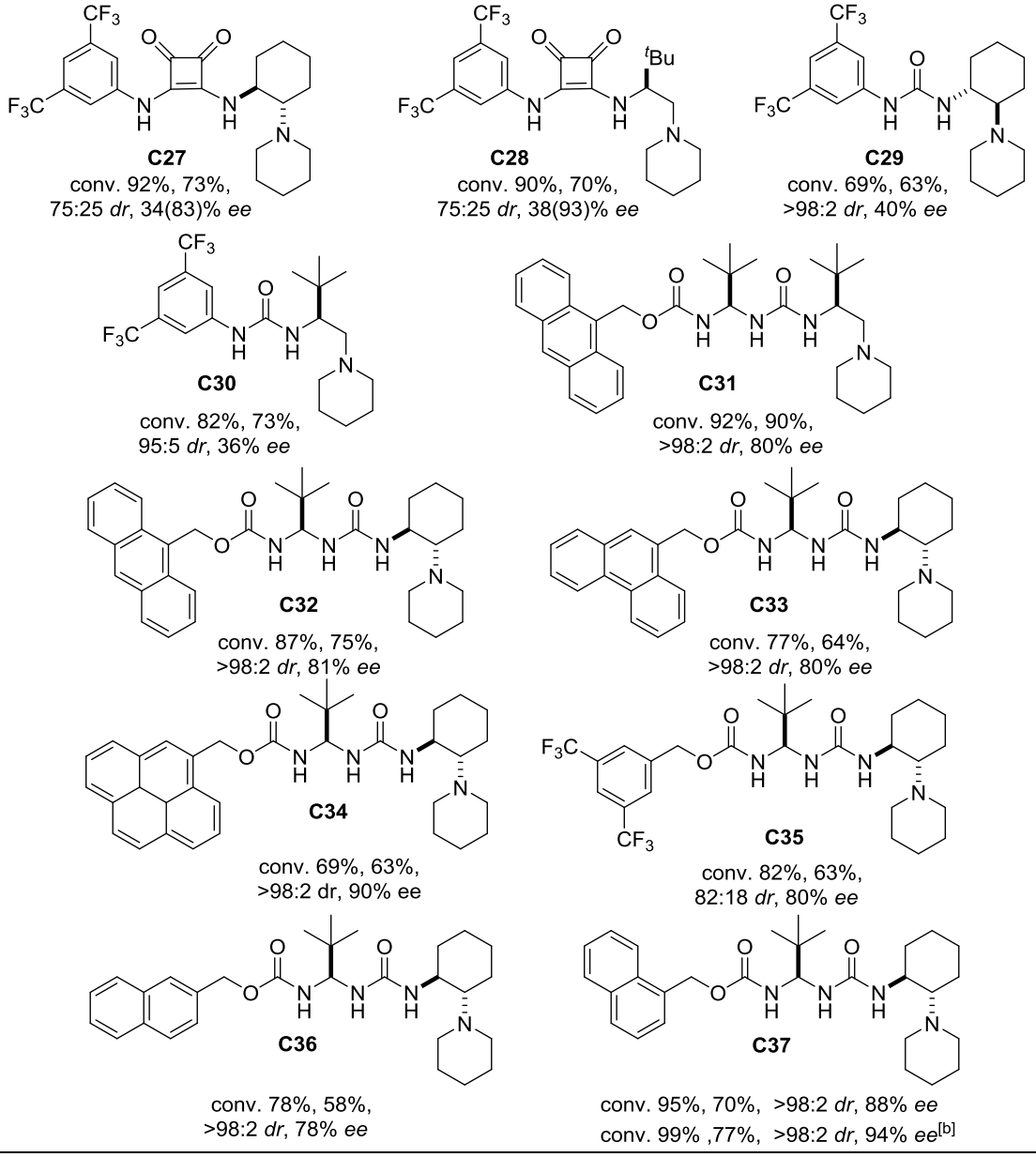
3.4.1.1. Catalyst screening

Initially, the approach was evaluated from the reaction of benzophenone imine **45** with hydrocinnamaldehyde **48a** (Table 18) mediated by different bifunctional BBs at room temperature. Under these reaction conditions, formation of small amounts (10-15%) of the cyclisized product **50a** were also observed.[198] However, after one-pot reductive work up with $NaBH_3CN$/AcOH, both the aldol adduct and the cyclisized product were transformed into amino alcohol derivative **49a** with no loss of stereoselectivity. Therefore, the same procedure was followed in all of the studies in order to avoid product mixture generation. Using squaramides **C27** and **C28**, the reaction, indeed proceeded to give the aldol product **49a** after one-pot reductive work up, but with very poor diastereoselectivity and negligible enantioselectivity, albeit very good for the minor

[198] The formation of this product was not observed at 0 °C or lower.

Table 18. Catalyst screening for the aldol reaction of **45** and hydrocinnamaldehyde **48a**.[a]



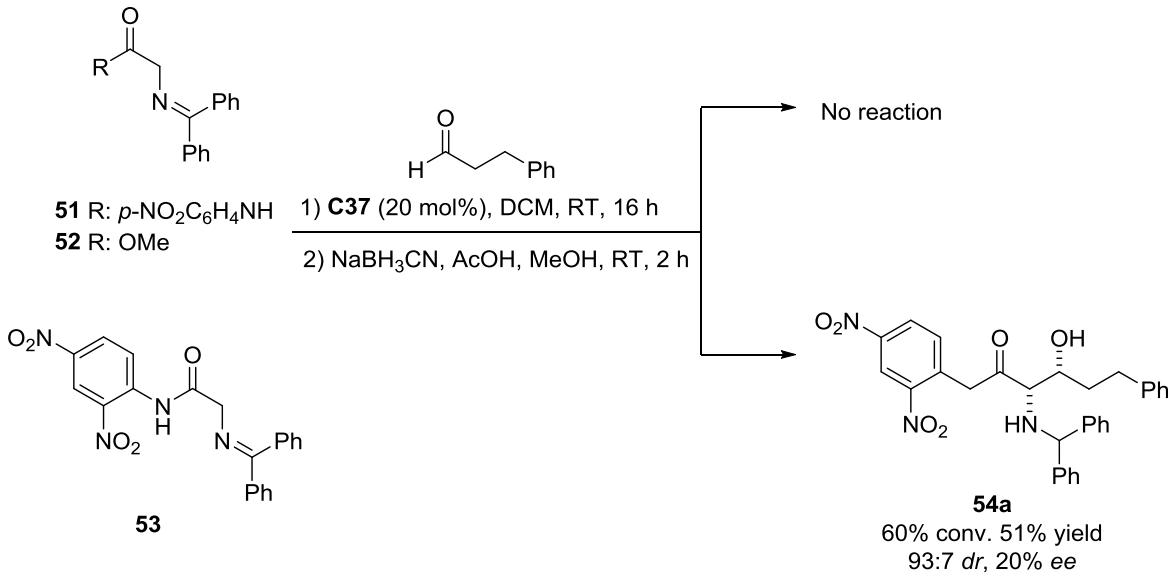


[a] Reaction conditions: Nitroanilide **45** (0.2 mmol, 1 equiv.) in 0.6 mL of CH_2Cl_2 and hydrocinnamaldehyde **48a** (0.6 mmol, 3 equiv.). Conversion determined by the disappearance of the starting material by ^{1}H-NMR before reduction. The dr values were determined by ^{1}H-NMR before reduction and corrobotared in the reaction crude after reduction. The *ee* values were determined for the major diastereiomer by chiral HPLC. [b] Reaction carried out at 0 ºC in 64 h.

isomer. Using the parent ureas **C29** and **C30** much better diastereocontrol was achieved, but the enantioselectivity of the product was still poor. To improve the stereocontrol through the incorporation of additional H-bond donors, we focused on ureidopeptide derived Brønsted bases, previously developed in our research group. It was gratifying to observe that with exception of **C35**, the new catalysts **C31**-**C37** provided diastereomeric ratios greater than 98:2 in each case with good enantioselectivity. **C34** was mostly unsoluble and conversion was lower than with **C37**. Therefore, further improvement was achieved using catalyst **C37** and lowering the reaction temperature to 0 ºC **49a** was afforded in 77% isolated yield and 94% *ee*.

3.4.1.2. Control experiments

To further show the relevance of the intramolecular hydrogen bonding in *o*-nitroanilide **45**, benzophenone imines **51** and **52** were prepared and subjected to treatment with hydrocinnamaldehyde under the above reaction conditions (Scheme 42). The reaction with **51** did not proceed. This observation suggests the inability of the NO_2 group in *para* position to participate in intramolecular H-bond, thus corroborating the potential of the designed nucleophile **45**. The same result was obtained with α-imino ester **52**. Likewise, in an attempt to strengthen the hydrogen bonding, compound **53** bearing an additional nitro group at the para position was also prepared. In this case, the reaction proceeded in poor yield, with a slight loss in diastereoselectivity, but with a dramatic decrease in enantioselectivity.

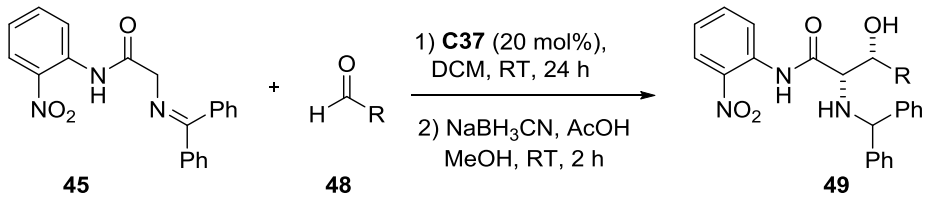


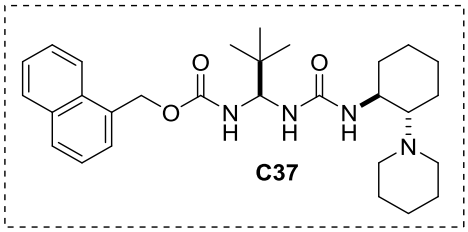
Scheme 42. Control experiments.

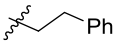
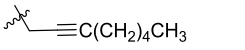
3.4.1.3. Aldehyde scope

With the optimal reaction conditions in hand, the scope of aldehydes was then investigated with **45**, in order to show the generality of the reaction. The study was performed with other enolizable aldehydes. When hexanal was used (entry 2), it was noticed that longer reaction timers were required, but high diastereoselectivity (>98:2) and high enantioselectivity were observed. When using 2-octynal (entry 3), total conversion was obtained after 24 h, but diastereoselectivity lowered to 77:23 and enantioselectivity was reduced to 4% *ee*. Sterically more demanding aldehydes (isopropanal, cyclohexanecarboxaldehyde, entries 4-6), did not provide the corresponding reaction adducts, even at high temperatures. Aromatic aldehydes were also unreactive towards nucleophile **45** (entries 7 and 8) under those reaction conditions.

Table 19. Aldehyde scope of **45**.[a]





Entry	R	Prod	t (h)	Conv. (%)[c]	Yield (%)	*dr* [d]	*ee* (%)[e]
1		**49a**	48	95	70	>98:2	88
2	^{n}Pent	**49b**	48	46	35	>98:2	90
3		**49c**	24	100	85	77:23	4
4	^{i}Pr	**49d**	24	0	-	-	-
5[b]			24	0	-	-	-
6		**49e**	24	0	-	-	-
7	*p*-Tolualdehyde	**49f**	24	<5	-	-	-
8	Ph	**49g**	24	15	-	-	-

[a] Reaction conditions: **45** (0.2 mmol, 1 equiv.), $NaHCO_3$ (20 mol%) and the corresponding aldehyde (0.6 mmol, 3 equiv.) in dichloromethane (0.6 mL). [b] The reaction was carried out at 50 ºC in dichloroethane. [c] Determined by the disappearance of the starting material by ^{1}H-NMR, before reduction. [d] Determined before reduction by ^{1}H-NMR and corroborated after reduction. [e] Determined by chiral HPLC for the major diastereioisomer.

In order to broad the scope of the aldol reaction, further activation of the pronucleophile was investigated. Therefore, two pathways were considered: 1) the introduction of an electronwithdrawing group at the aromatic ring of the imine, and 2) switching from ketiminoamides to aldiminoamides. The corresponding results of these two alternatives are summarized below.

3.4.1.4. More reactive ketiminoamides for the aldol reaction.

In this context and, as mentioned before, we first considered the introduction of CF_3- groups in the imine unit (Figure 31).[186]

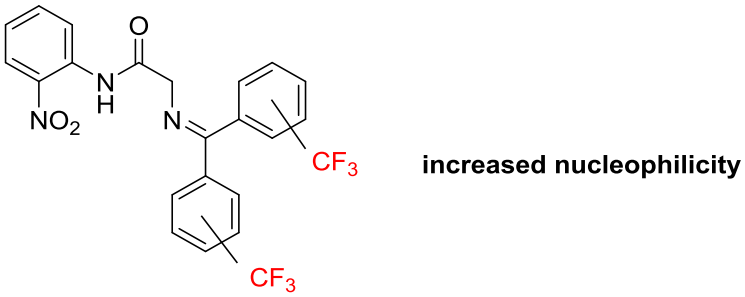
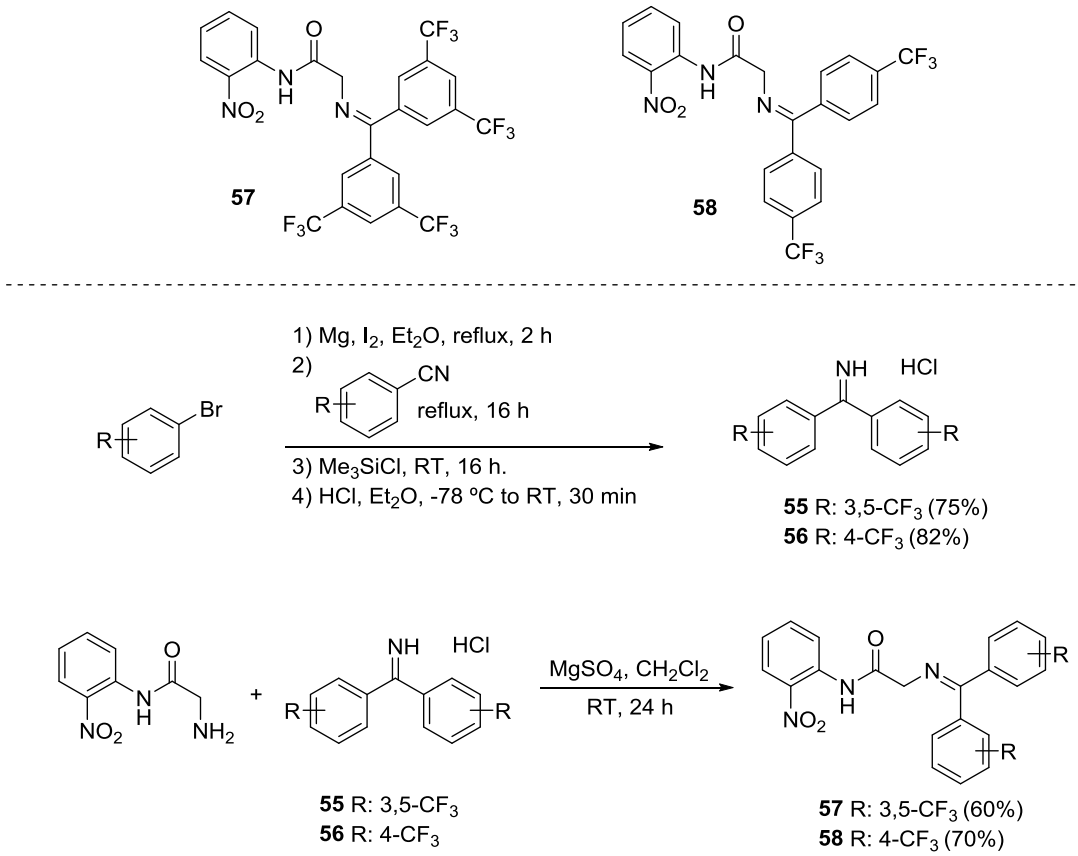


Figure 31. Proposal for increasing the nucleophilicity.through EWG introduction.

Hence, two different pronucleophiles were prepared **57** and **58** (Scheme 43). The corresponding imines were not commercially available, therefore imine hydrochlorides **55** and **56** were prepared adapting the described procedures, and compounds **57** and **58** were obtained in good yields.[199]

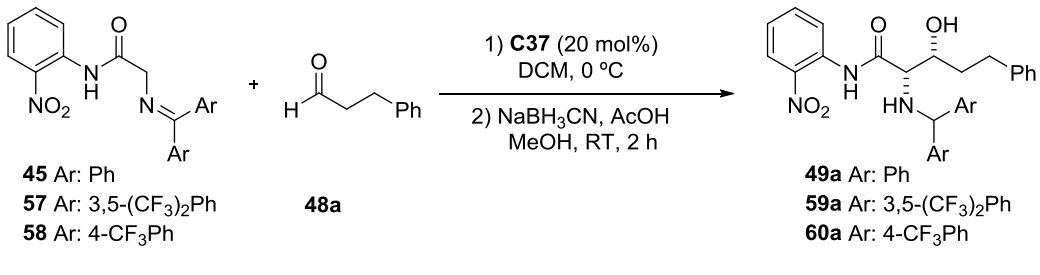
[199] Adapted from: a) Á. Pintér, G. Haberhauer, I. Hyla-Kryspin, S. Grimme, *Chem. Commun.* **2007**, 3711–3713; b) L.-H. Chan, E. G. Roschow, *J. Organomet. Chem.* **1967**, *9*, 231–250 c) S. Zhang, W. E. Piers, X. Gao, M. Parvez, *J. Am. Chem. Soc.* **2000**, *122*, 5499–5509.

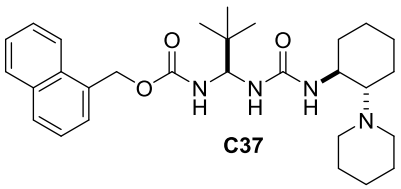


Scheme 43. Synthesis of pronucleophiles **56** and **57**.

The aldol reaction of compounds **57** and **58** with hydrocinnamaldehyde **48a** was then explored in the presence of **C37** at 0 ºC (Table 20). Compound **57** afforded the reaction adduct with full conversion in 16 h, but with lower stereoselectivity values (entry 2). Compound **58** (entry 3) also showed increased reactivity with respect to **45** and provided the reaction adduct with excellent diastereo and enantioselectivity (Entry 2). With these results in hand, **58** was selected for the study of the reaction scope with different aldehydes.

Table 20. Imine screening with hydrocinnamaldehyde **48a**.[a]



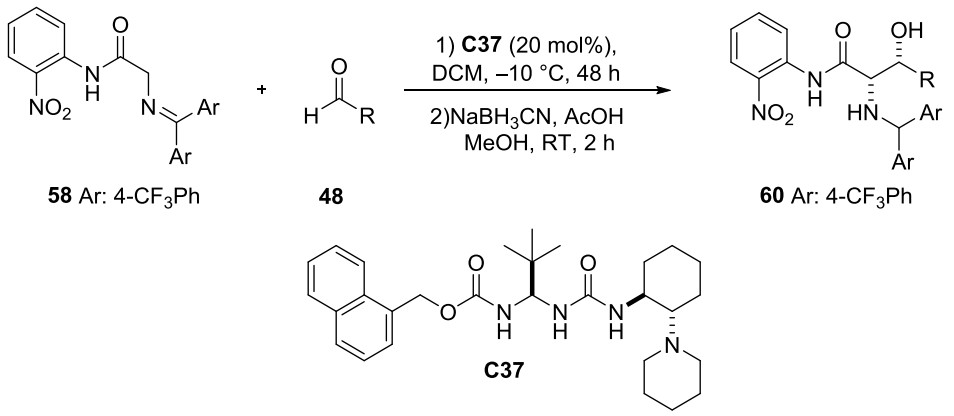


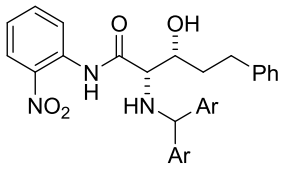
Entry	Ar	Prod	t (h)	Conv. (%)[b]	Yield (%)	*dr*[c]	*ee* (%)[d]
1	Ph	**49a**	64	99	77	>98:2	94
2	3,5-$(CF_3)_2$Ph	**59a**	16	100	84	88:12	76
3	4-CF_3Ph	**60a**	16	80	64	>98:2	92

[a] Reaction conditions: Nitroanilide (0.2 mmol) in CH_2Cl_2 (0.4 mL) and hydrocinnamaldehyde (0.6 mmol, 3 equiv.) [b] Determined by the disappearance of the starting material by ^{1}H-NMR before reduction. [c] Determined by ^{1}H-NMR before reduction and corroborated after reduction. [d] Determined for the major diastereiomer by chiral HPLC.

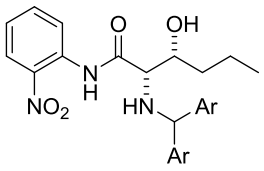
p-Trifluoromethyl derivative **58** was therefore subjected to the general reaction conditions with different enolizable aldehydes at – 10 ºC (Table 21). With the exception of the α-branched aldehyde cyclohexane carboxaldehyde **48e** which was inert also to this system, results were consistently good. As data in Table 21 show, short and long alkyl chains (butanal, hexanal, heptanal), β-branched isovaleraldehyde, and even aldehydes bearing side chains with functional groups (carbamate, ether) participate satisfactorily in this reaction. Chemical yields were generally good and essentially a single diastereoisomer was produced with high enantiomeric excess. Importantly, in every case under these reaction conditions self aldol products from the corresponding enolizable aldehyde **48** were not detected.

Table 21. Scope of the catalytic aldol reaction of nitroanilide **58** with enolizable aldehydes.[a]

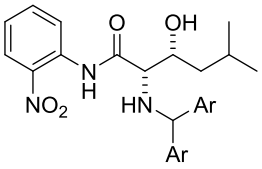




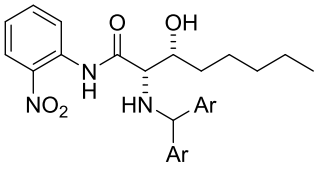
60a
58%, >98:2 *dr*, 92% *ee*[b]



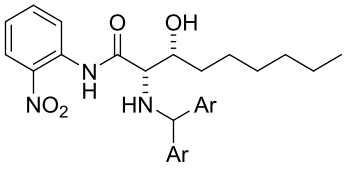
60h
72%, >98:2 *dr*, 92% *ee*



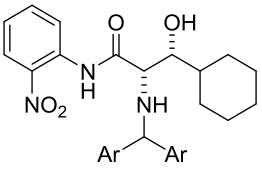
60i
78%, >98:2 *dr*, 84% *ee*



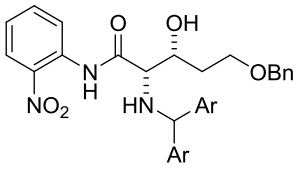
60b
82%, >98:2 *dr*, 90% *ee*



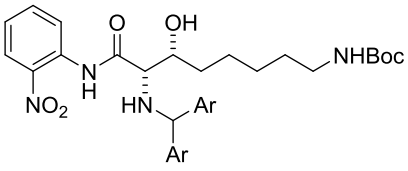
60j
76%, 91:9 *dr*, 90% *ee*



60e
<10% conv. ND[c]



60k
69%, >98:2 *dr*, 90% *ee*



60l
69%, >98:2 *dr*, 90% *ee*

[a] Reaction conditions: **58** (0.2 mmol, 1 equiv.) and the corresponding aldehyde (0.6 mmol, 3 equiv.) in CH_2Cl_2 (0.6 mL) Yields refer to isolated adducts after reduction of the imine. The *dr* values were determined by ^{1}H-NMR before reduction and corroborated after reduction. The *ee* values determined for the major diastereiomer by chiral HPLC after reduction. [b] Reaction carried out at 0 ºC. [c] The reaction was also tried at 40 ºC, but conversion remained negligible.

The absolute configuration of the adducts was determined by X-Ray analysis of compound **61** after transformation of **59a** through imine hydrolysis and further coupling with 4-bromobenzoyl chloride, and that of the remaining adducts was established by assumption of a uniform reaction mechanism (Figure 32).

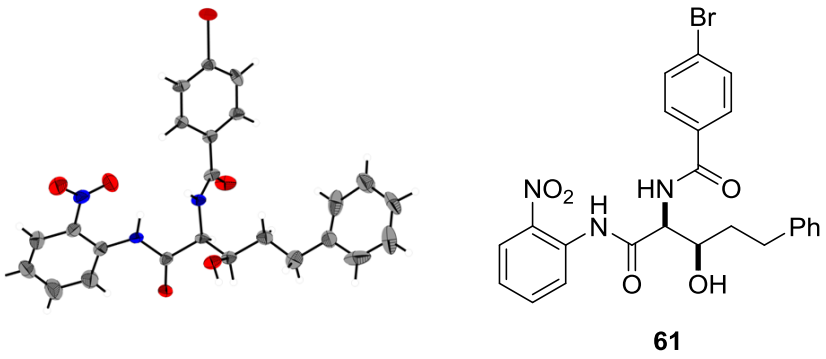
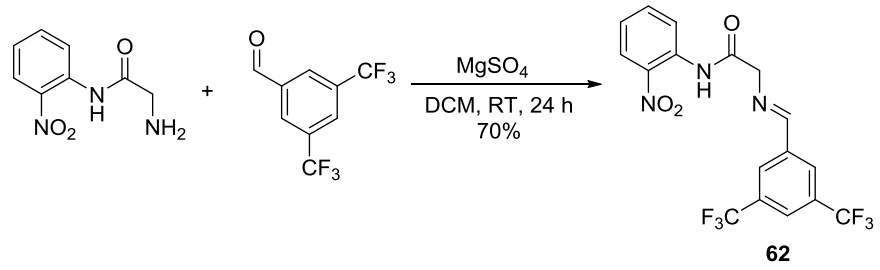
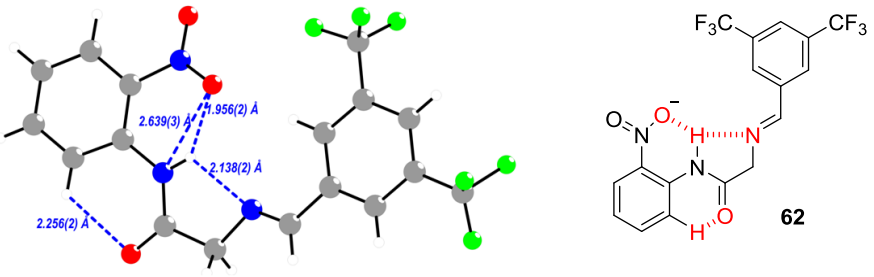


Figure 32. X-Ray structure of compound **61**.

3.4.2. Organocatalytic aldol reaction of glycine derived aldiminoamides

As a second possibility for the improvement of the reactivity of **45** in the aldol reaction, glycine aldimino amide **62** was prepared following the general procedure (Scheme 44). The X-ray analysis of **62** confirmed the existence of the same intramolecular hydrogen bond network than in **45** and the *E* geometry of the imine



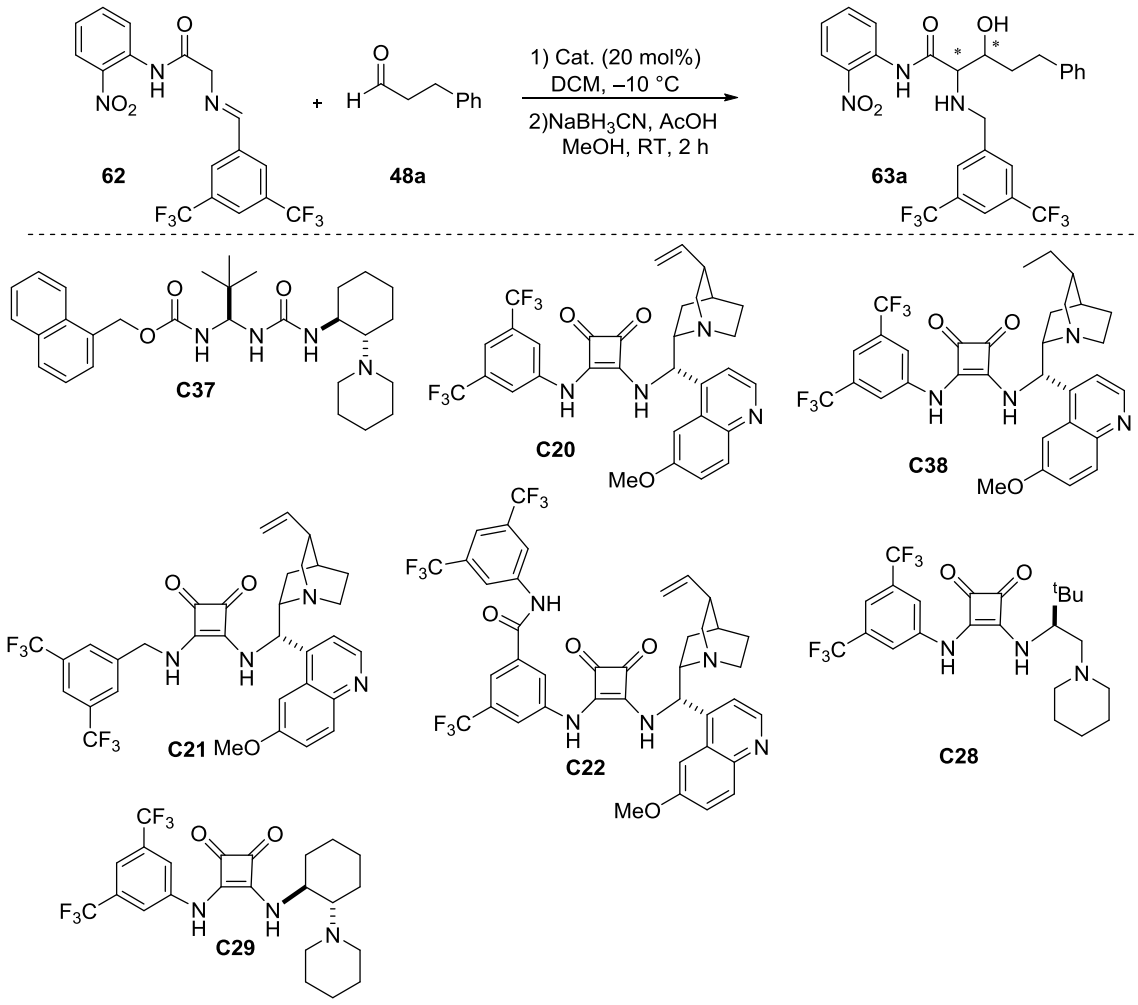


Scheme 44. Preparation and X-Ray structure of compound **62**.

3.4.2.1. Catalyst screening

The aldol reaction of **62** with hydrocinnamaldehyde **48a** was then investigated at room temperature in the presence of different catalysts (Table 22). **C37** afforded **63a** with complete conversion in 3 h revealing that the reactivity of **62** was much higher than that of **45** (16 h, 84% conv.). However, diastereoselectivity and enantioselectivity were very low (55:45 *dr*, 24% and 25% *ee* for each diastereoisomer, respectively). Lowering the temperature to – 10 ºC, did not significantly improve the stereocontrol (entry 2). Hence, a catalyst screening was performed. Switching to quinine-derived squaramides **C20** and **C38**, inversion of the diastereoselectivity was observed and enantioselectivity values improved to 93% in both cases (entries 3 and 4). Looking for an improvement in diastereoselectivity, catalysts **C21** and **C22** which differ in the aromatic unit were checked, but the reaction did not proceed at -10 ºC, and RT and 0 ºC were respectively required for conversion improvement. Diastereoselectivity was low in both cases and enantioselectivity was moderate. Therefore as **C38** and **C20** had provided the best results, structural modifications in **C38** and **C20** were then considered, and in a first instance the basic unit was varied. **C28** and **C29** were then screened under the same reaction conditions. As a result, both catalysts afforded excellent enantioselectivity and improved diastereoselectivity up to 90:10 (entryies 7 and 8).

Table 22. Catalyst screening in the reaction of **62** with hydrocinnamaldehyde **48a**.

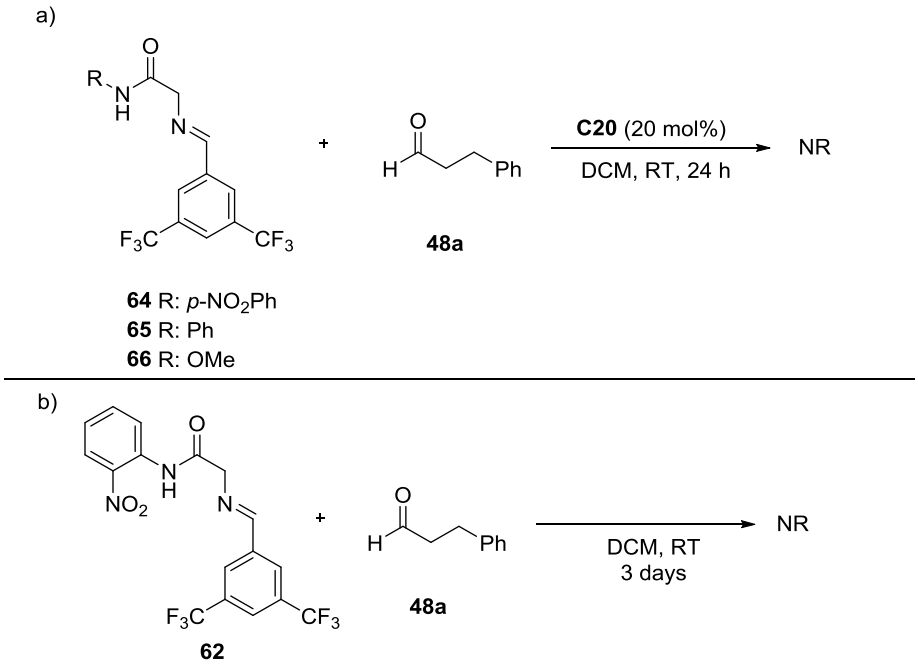


Entry	Cat.	t (h)	Conv.(%) [b]	Yield (%)	*dr*[c] *syn*:*anti*	*ee* syn (%)[d]	*ee* anti (%)[d]
1[e]	**C37**	3	>99	70	55:45	24	25
2		24	>99	65	68:32	54	26
3	**C20**	16	70	61	20:80	18	93
4	**C38**	20	>99	78	20:80	18	93
5[e]	**C21**	40	>99	80	55:45	44	12
6[f]	**C22**	72	72	60	30:70	24	84
7	**C28**	72	>99	85	9:91	50	97
8	**C29**	20	87	76	15:85	48	94

[a] Reaction conditions: **62** (0.2 mmol, 1 equiv.) and hydrocinnamaldehyde **48a** (0.6 mmol, 3 equiv.) in dry dichloromethane (0.6 mL). [b] Determined by the disappearance of the starting material by ^{1}H-NMR before reductive work-up. [c] Determined by ^{1}H-NMR before reduction (*syn*/*anti*) and corroborated after reduction. [d] Determined by chiral HPLC. [e] Reaction carried out at room temperature. [f] Reaction carried out at 0 ºC.

3.4.2.2. Control experiments

Control experiments were also performed in this case, and it was gratifying to observe the significance of the intramolecular hydrogen bonding network in *o*-nitroanilides for success. Compounds **64**, **65** and **66** were prepared and none of them afforded the corresponding adduct under the standard reaction conditions (a, Scheme 45). In addition, when the reaction was carried out with **62** in the absence of catalyst under the same reaction conditions, no reaction was observed after 3 days (b, Scheme 45).

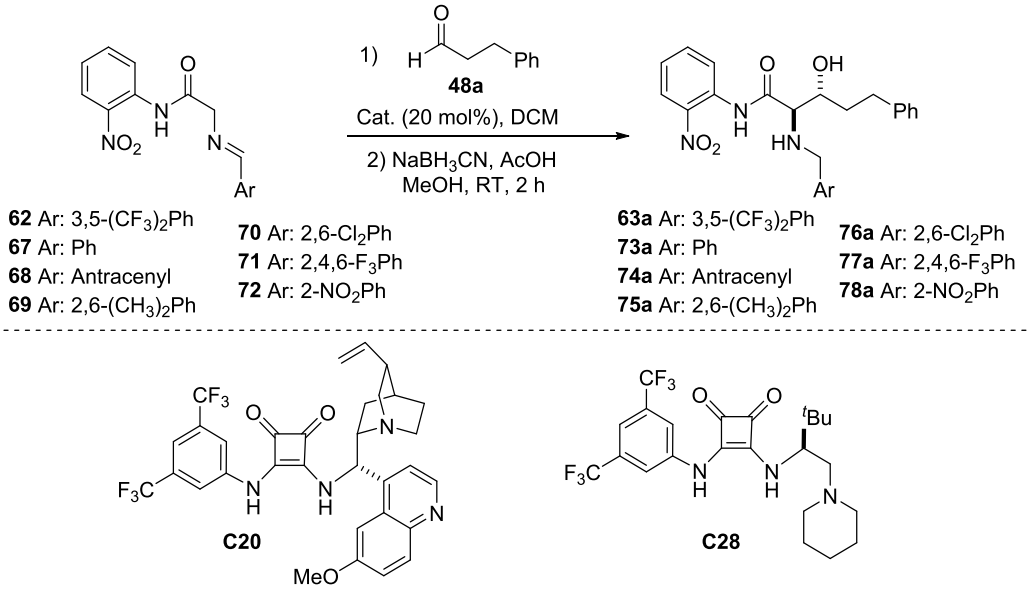


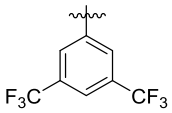
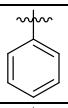
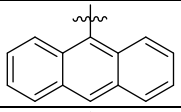
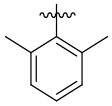
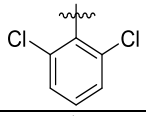
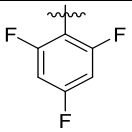
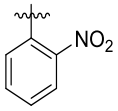
Scheme 45. Control experiments: a) Reactivitiy of aldimines **64**, **65** and **66** in the aldol reaction with **48a**. b) Reaction of the starting **62** in the absence of catalyst. NR: no reaction.

3.4.2.3. Aldimine screening

On the other hand, an in order to improve the diastereoselectivity values obtained with **62**, variations in the imine structure were also considered. Therefore, amides bearing different imine substituents were prepared (**67**-**72**, Table 23) and screened under the previously optimized reaction conditions. The phenyl- derivative **67** (entry 3) did not react at -10 ºC, and only 20% conversion was obtained at room temperature in four days. When the reaction was performed with the antracenyl derivative **68** (entry 4), the temperature had to be increased to 0 ºC for the reaction to proceed, but the diastereo and enantiocontrol were poor. With the ortho-substituted derivatives **69**, **70**, **71** and **72** (entries 5, 6, 7, 8) the aldol reactions were run at room temperature, as conversion at – 10 ºC was very low. As a result, diastereoselectivity and enantioselectivity dropped. After these results aldimine **62** was selected for the study of the aldehyde scope.

Table 23. Imine screening of glycine aldimines with hydrocinnamaldehyde **48a**.[a]



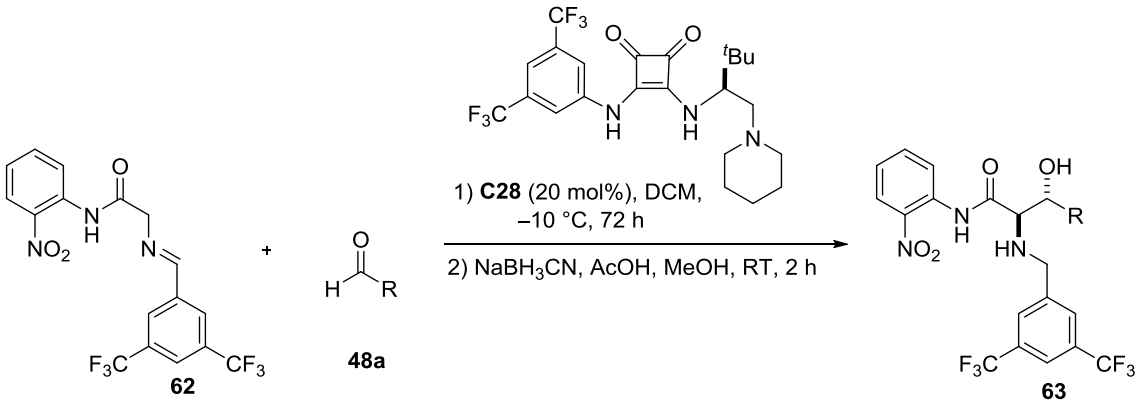
Entry	Ar	Prod	Cat.	T (ºC)	t (h)	Conv. (%)[b]	Yield (%)	*dr*[c]	*ee* (%)[d]
1		**63a**	**C20**	-10	16	70	61	80:20	93/(18)
2			**C28**	-10	4d	100	80	91:9	97/(50)
3		**73a**	**C28**	RT	4d	20	n.d.	n.d.	n.d.
4		**74a**	**C20**	0	3d	100	56	70:30	12/(30)
5		**75a**	**C20**	RT	24	83	67	87:13	66/(55)
6		**76a**	**C28**	RT	16	100	76	88:12	66/(26)
7		**77a**	**C28**	RT	16	100	77	82:18	80/(14)
8[e]		**78a**	**C28**	RT	16	90	75	70:30	80/(30)

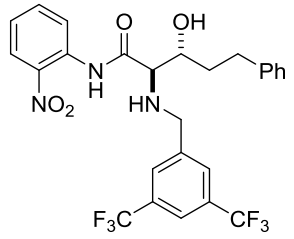
[a] Reaction conditions: The corresponding nitroanilide (0.2 mmol) and hydrocinnamaldehyde **48a** (0.6 mmol, 3 equiv.) in CH_2Cl_2 (0.6 mL). [b] Determined by the disappearance of the starting material before reduction by ^{1}H-NMR. [c] *anti*/*syn* ratio determined before reduction by ^{1}H-NMR and corroborated after reductive work up. [d] Determined by chiral HPLC for the major and minor (*anti*/*syn*) diastereomers respectively. [e] Precipitates at – 10 ºC.

3.4.2.4. Aldehyde scope

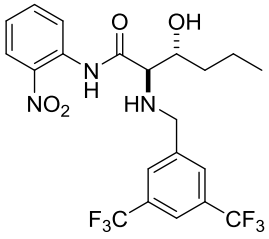
With the best imine group in hand, the aldehyde scope was studied with **62** in the presence of **C28**. The corresponding results are shown in Table 24. Reaction of **62** with aliphatic aldehydes (butanal, hexanal, isovaleraldehyde), provided the reaction adduct with 90:10 *anti*/*syn* ratio and *ee* values up to 96%. 4-Pentenal also reacted affording the adduct in 90:10 dr and 96% *ee*. The reaction with sterically more hindered aldehydes as cyclohexane carboxaldehyde, afforded **63e** with 85:15 *dr* and 93% *ee*. In all of the investigated cases, the low solubility of catalyst **C28** under the reaction conditions longered reaction time to 72 h.

Table 24. Scope of aldehydes with **62**.[a]

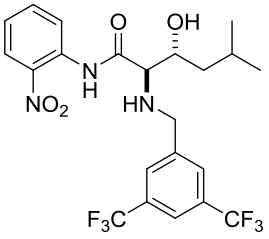




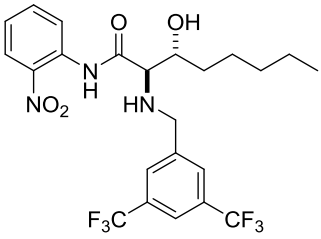
63a
conv. >99%, 80%, 90:10 *dr*,
97% *ee*



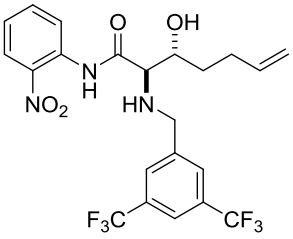
63h
conv. >99%, 71%, 90:10 *dr*,
95% *ee*



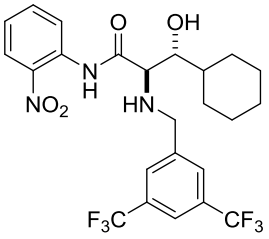
63i
conv. >99%, 76%, 90:10 *dr*,
96% *ee*



63b
conv. >99%, 82%, 90:10 *dr*,
95% *ee*



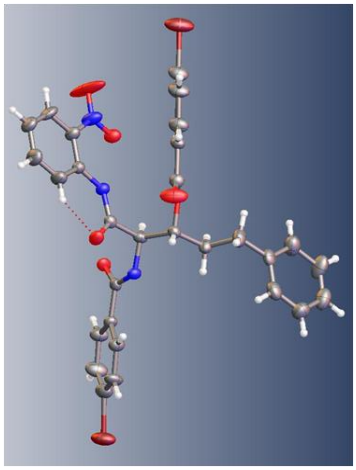
63m
conv. >99%, 84%, 90:10 *dr*,
96% *ee*

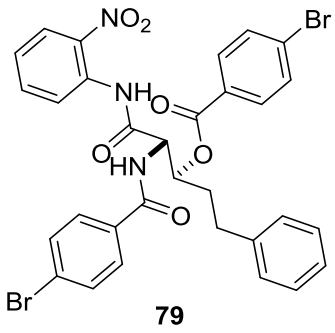


63e
conv. 80%, 77%, 85:15 *dr*,
93% *ee*[b]

[a] Reaction conditions: Nitroanilide **62** (0.2 mmol) and the corresponding aldehyde (0.6 mmol, 3 equiv.) in CH_2Cl_2 (0.6 mL). Conversion determined by the disappearance of the starting material by ^{1}H-NMR before reduction. The *dr* values were determined before reduction by ^{1}H-NMR and corroborated after reduction. The *ee* values were determined by chiral HPLC for the major *anti* diastereoisomer. [b] The reaction was carried out at 0 ºC.

The absolute configuration of the reaction adducts was determined for compound **79** by X-Ray single crystal structure analysis after transformation of **63a** through imine hydrolysis and further coupling with 4-bromobenzoyl chloride in the presence of DMAP, and that of the remaining adducts was established by assuming a uniform reaction mechanism.





79

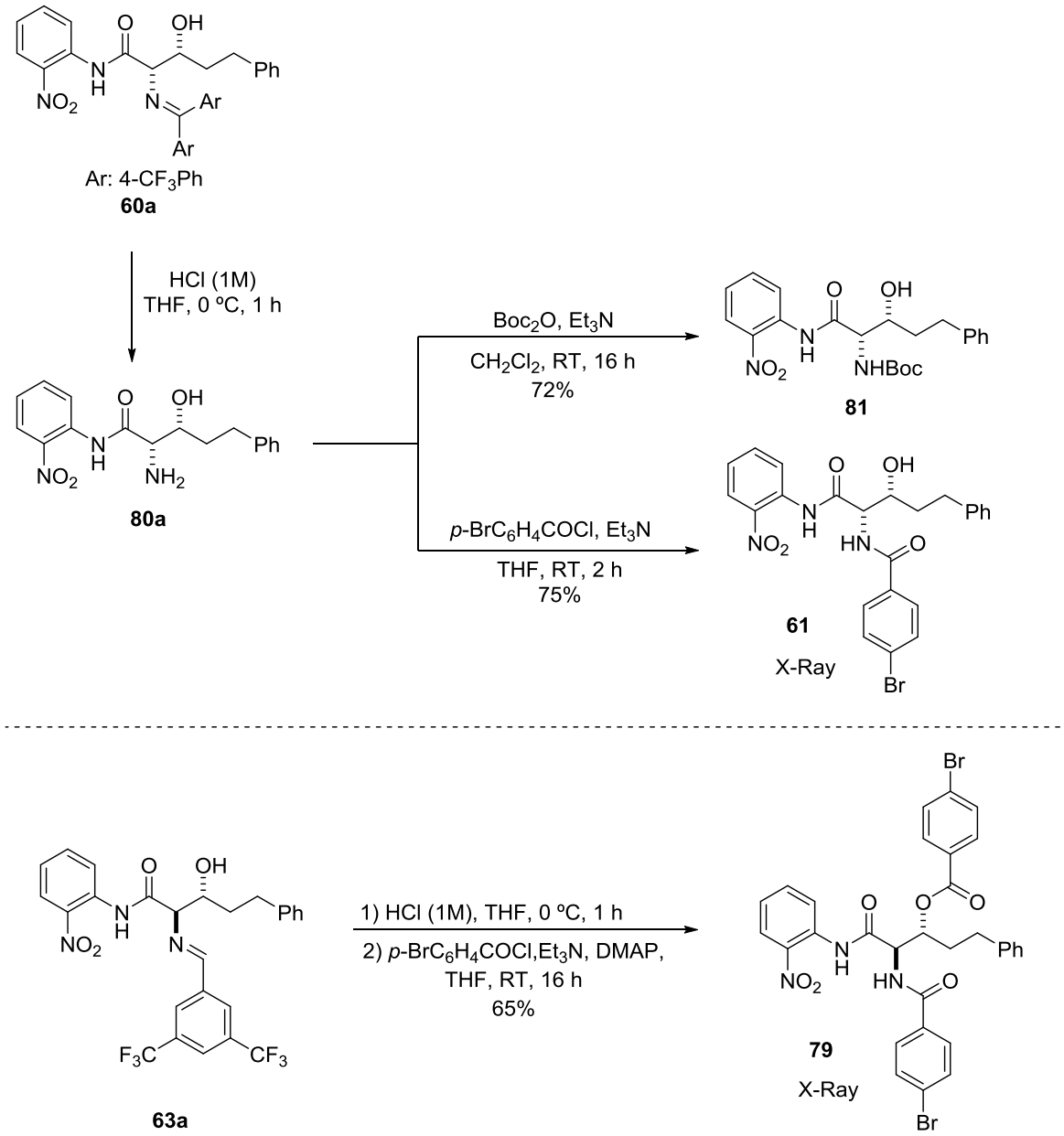
Figure 33. X-Ray structure of **79**.

3.4.3. Elaboration of the adducts

These densely functionalized adducts are of interest for further reactions and can therefore be transformed into different functionalities, as summarized below.

3.4.3.1. Imine hydrolysis

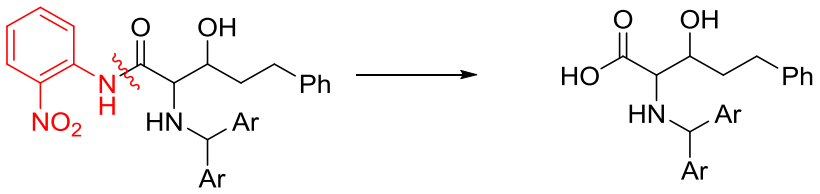
Hydrolysis of the imine moiety of the aldol adduct **60a** provided β-hydroxy-α-amino amide **80a** with the same initial diastereoselecivity as showed the treatment of **60a** with HCl in THF at 0 ºC for one hour. Subsequent Boc protection of **80a** rendered **81**. This way, the optimal imine structure can be employed in the organocatalytic reaction, regardless the synthetic utility, as it is easily eliminated under mild reaction conditions. Additionally, coupling of **80a** with 4-bromo benzoyl chloride, afforded **61**, which enabled crystallization for X-Ray analysis and determination of the absolute configuration. Following the same methodology, hydrolysis and further coupling of **63a** with 4-bromo benzoyl chloride in presence of DMAP, afforded **79** with good yield, also enabling crystallization for X-Ray analysis and determination of the absolute configuration.



Scheme 46. Hydrolysis of the imine moiety and amine-protection.

3.4.3.2. Removal of the nitroanilide unit

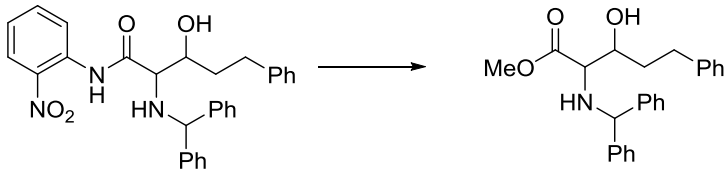
One of the most synthetically interesting transformation consists on the removal of the nitroanilide (Scheme 47), which can be considered as an auxiliary that enhances the reactivity of the nucleophile. For this goal different reaction conditions were explored, which are summarized below.



Scheme 47. Removal of the nitroanilide unit.

The first efforts were directed towards the direct esterification of the amide of compound **49a** under acidic conditions in MeOH. However, the starting material did not react under any of the conditions shown in Table 25.

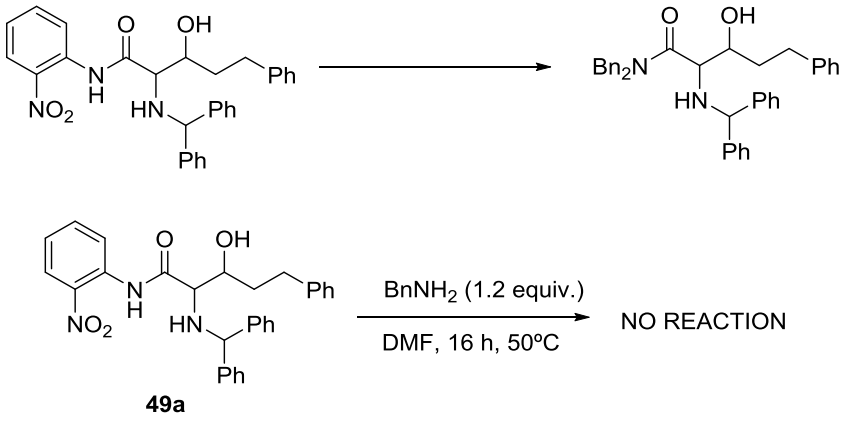
Table 25. First efforts towards removal of the nitroanilide unit in adduct **49a**.



49a

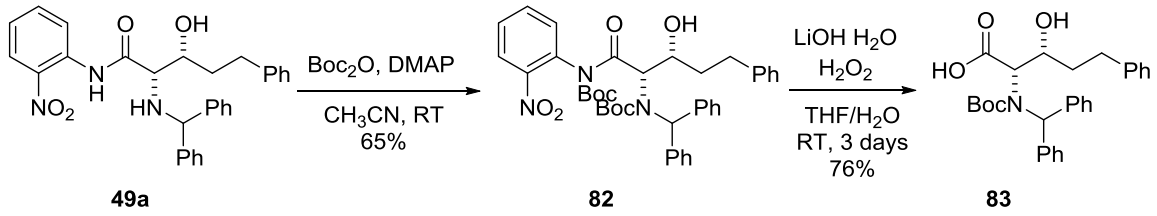
Entry	Solvent	Acid (M)	Equiv.	T (ºC)	t (h)	Conv. (%)
1	MeOH	HCl (3M)	1.3	RT	16	0
2	MeOH	HCl (3M)	6.7	RT	16	0
3	MeOH	HCl (3M)	10	40	4	0
4	MeOH	HCl conc	66	RT	48	0
5	MeOH	HCl (1.25M)	3	RT	16	0
6	MeOH	HCl (6M)	20	RT	4	0
7		H_2SO_4 conc	38	RT	48	0
8	-	HCl conc	230	100	4	0
9	MeOH	$BF_3O(C_2H_5)_2$	1	65	3	0

Transamidation of the reaction adducts was also tried, by treatment of adduct **49a** with 1.2 equiv. of benzylamine in DMF at 50 ºC, but no reaction was observed after 16 h, probably due to the nature of the nitroanilide as a bad leaving group or to the stabilization of the group through hydrogen bonding.



Scheme 48. Transamidation.efforts **49a**.

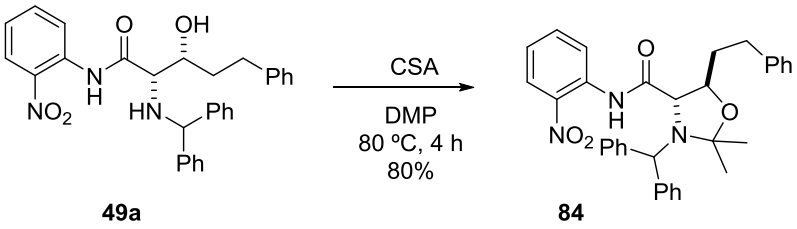
Other strategy that enables milder hydrolysis conditions involves the *N*-methylation or the Boc-protection of the amide, in order to create a more labile leaving group. On this basis, following a procedure described by Verho and co-workers,[200] β-hydroxy-α-amino amide **49a** was Boc-protected (**82**) and converted into the corresponding carboxylic acid **83** using $LiOH/H_2O_2$ with good yield (Scheme 49).



Scheme 49. Boc protection and further hydrolysis of **49a**.

3.4.3.3. Other transformations

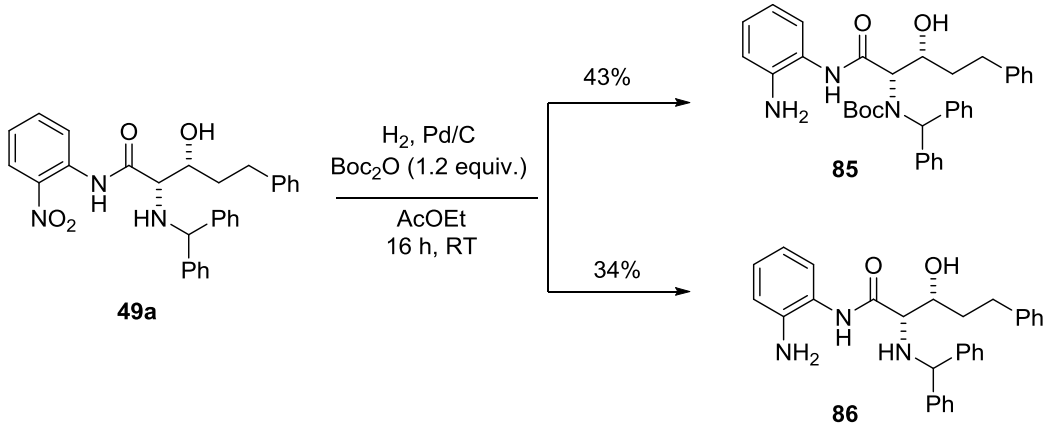
Protection of **49a** with camphorsulphonic acid and dimethoxy propane afforded **84** with good yield.



Scheme 50. Protection of amino alcohol **49a** with CSA and DPM.

[200] O. Verho, M. Pourghasemi Lati, M. Oschmann, *J. Org. Chem.* **2018**, *83*, 4464-4476.

We were surprised to find that the benzhydryl moiety was not cleaved under hydrogenation conditions when **49a** was used with the aim of obtaining the *N*-Boc derivative **81**, in the presence of *tert*-butyl dicarboxylate. Alternatively, the nitro group was reduced to the amine, and a mixture of **85** and **86** was obtained.



Scheme 51. Hydrogenation of **49a**.

In summary, we have reported a highly diastereo- and enantioselective direct aldol reaction of Schiff bases of glycine *o*-nitroanilide triggered by an intramolecular hydrogen bonding as key activation element. In this way both *anti*- and *syn*-β-hydroxy α-amino acids may be accessed from the same strategy by simple using a glycine *o*-nitroanilide derived ketimine or aldimine and their corresponding optimal catalysts, respectively. This realization constitutes the first synthetic application of this type of amides that will clearly found further utility in asymmetric catalysis.

Chapter 4

New Oligoureas for their evaluation in organocatalysis

4. New oligoureas for their evaluation in organocatalysis.

4.1. Synthetic foldamers to mimic protein features

In nature, there are large molecules that perform diverse functions such as catalysis, tight and specific binding, directed flow of electrons or molecular recognition among others. The polymers that fulfil these functions, mostly proteins or RNA, are unique compared to other biological and synthetic polymers because of their ability to adopt specific compact conformations that are kinetically and thermodynamically stable. In other words, there is a strong relationship between folding and function among proteins.[201] These folding patterns generate "active sites" via precise three dimensional arrangements of functional groups.

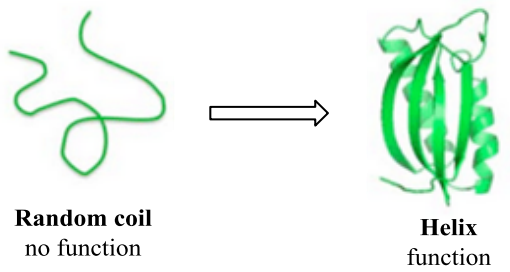


Figure 34. Folding of a random coil forming a helix.

On this basis, the design of discrete non-natural oligomers (foldamers) with predictable and well-characterized folding patterns has attracted considerable attention in the last decade.[202] The term foldamer refers to a synthetic polymer with a strong tendency to adopt a specific compact conformation. The ability to synthesize sequence-based oligomers that fold with high fidelity (foldamers) raises interesting prospects for mimicking biopolymers and for creating molecules with functions.

[201] L. Fischer, G. Guichard *Org. Biomol. Chem.* **2010**, *8*, 3101-3117.
[202] a) I. Saraogi, A. D. Hamilton *Chem. Soc. Rev.* **2009**, *38*, 1726-1743; b) *Foldamers: Structure, Properties and Applications*, ed. S. Hecht, I. Huc Wiley-VCH, Weinheim, **2007**; c) C. M. Goodman, S. Choi, S. Shandler, W. F. DeGrado *Nat. Chem. Biol.* **2007**, *3*, 252-262; d) I. Huc Eur. *J. Org. Chem.* **2004**, 17-29; e) D. Seebach, A. K. Beck, D. J. Bierbaum *Chem. Biodiversity* **2004**, *1*, 1111-1239; f) D. J. Hill, M. J. Mio, R. B. Prince, T. S. Hughes, J. S. Moore *Chem. Rev.* **2001**, *101*, 3893-4012g) S. H. Gellman *Acc. Chem. Res.* **1998**, *31*, 173-180.

In addition, the possibility to integrate and convert high resolution structural data into a functional outcome is being explored for biomedical applications (antimicrobials, cell penetrating agents and inhibitors of protein-protein interactions).[203]

It has been demonstrated that some non-natural oligoamide backbones exhibit protein-like conformational behaviour. This is of great interest for chemists.[204] On this basis, many research groups have focused on the synthesis of new oligoureas for different purposes. The applications of foldamers are being explored in different fields. In this context, Zuckermann and co-workers[205] studied peptoid sequences that form supramolecular assembles of nanosheets and nanotubes (Figure 35).

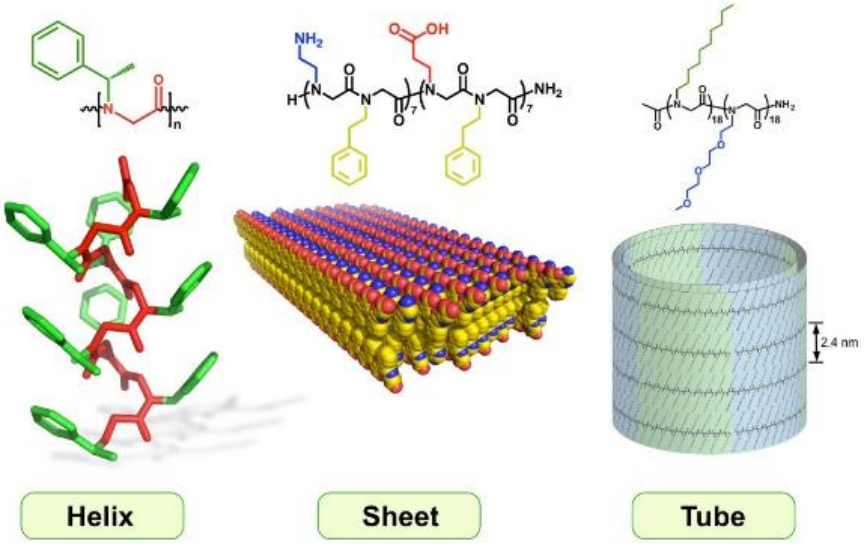


Figure 35. Applications of peptoid polymers in materal science.

Biomedical applications of foldamers have also been studied by different groups. Based on the difficulties of proteins to penetrate human cells, different cell-penetrating agents have been synthesized. More specifically, Amblard and co-workers[206] designed the oligomer shown in Figure 36, through a straightforward conversion of peptide sequences into γ-lactam containing oligomers, that adopt a ribbon-like secondary structure which enables cell penetration.

[203] a) B. Baptiste, F. Godde, I. Huc *ChemBioChem* **2009**, *10*, 1765-1767; b) A. D. Bautista, C. J. Craig, E. A. Harker, A. Scherpartz *Curr. Opin. Chem. Biol.* **2007**, *11*, 685-692
[204] W. S. Horne, S. H. Gellman *Acc. Chem. Res.* **2008**, *41*, 1399-1408.
[205] a) E. J. Robertson, A. Battigelli, C. Proulx, R. V. Mannige, T. K. Haxton, L. Yun, S. Whitelam, R. N. Zuckermann *Acc. Chem. Res.* **2016**, *49*, 379- 389; b) J. Sun, X. Jiang, R. Lund, K. H. Downing, N. P. Balsara, R. N. Zuckerman *Proc. Natl. Sci. U.S.A.*, **2016**, ASAP Online (2016); c) R. V. Mannige, T. K. Haxton, C. Proulx, E. J. Robertson, A. Battigelli, G. L. Butterfoss, R. N. Zuckermann, S. Whitelam, *Nature*, **2015**, *526*, 415-420.
[206] V. Martin, B. Legrand, L. Vezenkov, M. Berthet, G. Subra, M. Calmès, J. L. Bantignies, J. Martinez, M. Amblard *Angew. Chem. Int. Ed.* **2015**, *54*, 13966-13970.

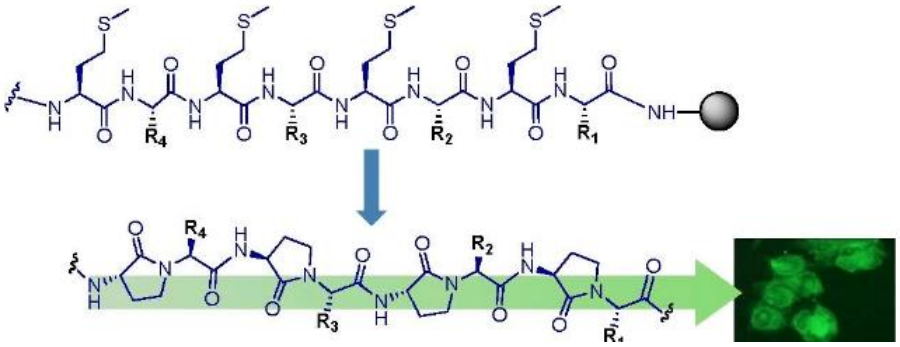


Figure 36. Conversion of peptides into cell-penetrating α-amino γ-lactam foldamers.

Recently, organocatalysis has emerged as an additional application of foldamers. Similar to enzymes, preorganization of the catalyst through H-bonding may contribute to enhance catalyst efficiency through stabilization of charged and transition-state intermediates. Even though peptides have been described as catalysts in a wide number of stereoselective transformations,[207] little progress has been made in this direction with foldamers.

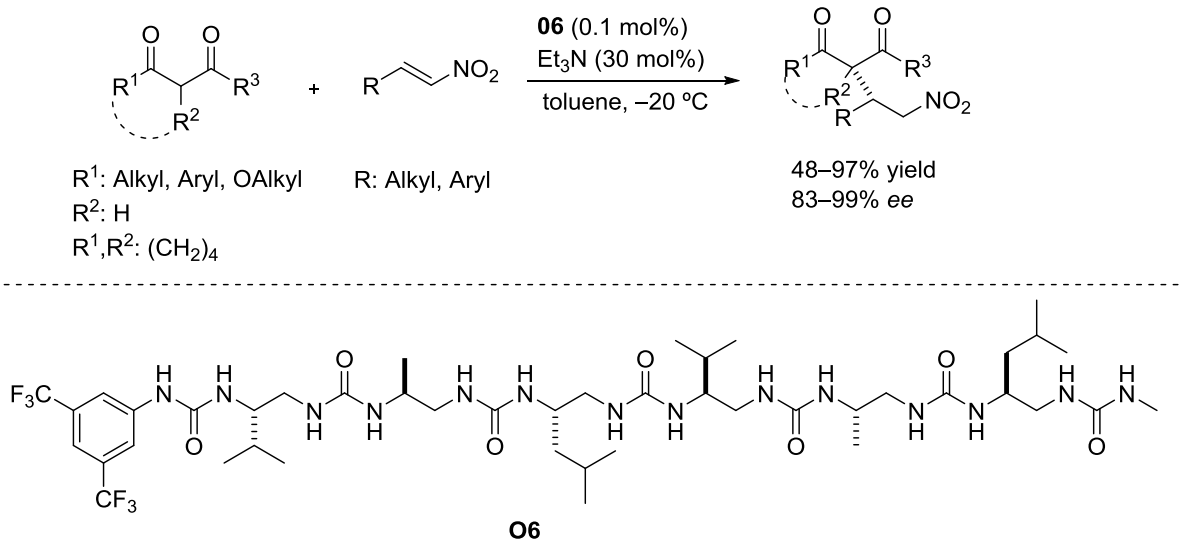
4.2. **Oligoureas as hydrogen bonding catalysts for enantioselective reactions**

Preorganization of a catalyst through folding would be expected to contribute to enhanced catalytic efficiency through cooperative substrate binding, specific stabilization of charged transition-states and intermediates and minimization of the entropic cost of transition-state binding.

Based on the idea that oligourea foldamers could be useful in hydrogen bonding catalysis, the group of Guichard and our own group investigated for the first time enantiopure helical oligo(thio)urea foldamers for enantioselective carbon-carbon bond forming reactions (Scheme 52).[208] In this context, a potential oligourea foldamer catalyst that is known to be long enough (hexamer) to form a stable helix **O6** was designed (a and b in Figure 37). More specifically, the valine-alanine-leucine sequence was combined with a classical activating electron withdrawing group forming the final organocatalyst. As mentioned, the H-bond network provides the helical conformation leaving the first two ureas free, ready to interact with substrates and anions.

[207] a) B. Lewandowski, H. Wennemers *Curr. Opin. Chem. Biol.* **2014**, *22*, 40-46; b) E. A. Colby Davie, S. M. Mennen, Y. Xu, S. J. Miller *Chem. Rev.* **2007**, *107*, 5759-5812.
[208] D. Bécart, V. Diemer, A. Salaün, M. Oiarbide, Y. Reddy Nelli, B. Kauffmann, L. Fischer, C. Palomo, G. Guichard *J. Am. Chem. Soc.* **2017**, *139*, 12524-12532.

Then, the conjugate addition of malonate esters to different nitroolefins promoted by **O6** in combination with triethylamine as Brønsted base cocatalyst was performed. It is noteworthy that even at low catalyst loading, the reactivity and stereoselectivity were high. Thus the catalytic system proved to be valid for different substitution patterns.



Scheme 52. Conjugate addition of malonate esters to nitroolefins, promoted by **O6**.

The reaction was performed employing a very low catalyst loading, leading to high yields and excellent enantioselectivity. A study on the effect of the oligourea chain length was performed, observing that the ability to form a stable helix influences the enantioselectivity. As it is known, the helix forming propensity of a specific compound can be measured by electronic circular dichroism (ECD) spectroscopy (c, Figure 37). As Figure 37 ilustrates, the tetramer, pentamer and hexamer, displayed the characteristic ECD signature with a positive maximum whose intensity increases with the number of residues in the chain.

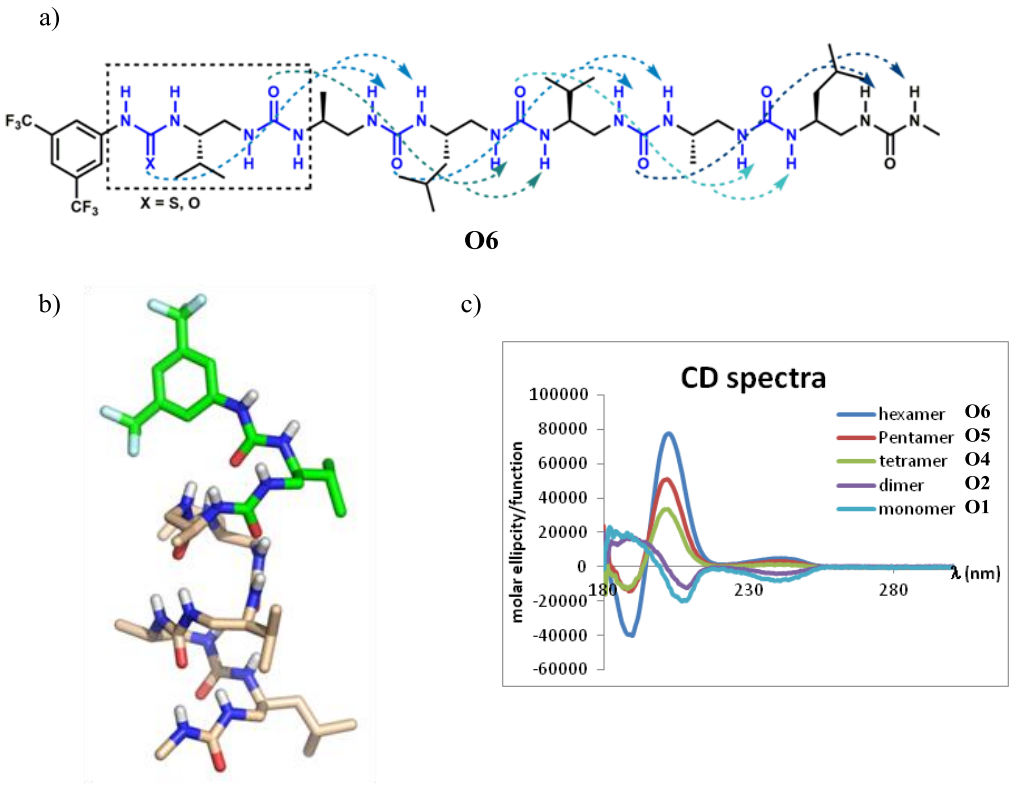


Figure 37. a) Representation of the extended chain of the *N,N'*.linked oligourea **O6**. b) X-Ray crystal structure of **O6**. c) Electronic circular dichroism (ECD) analysis of oligoureas **O1**-**O6**.

All foldamers were tested in the conjugate addition, and it was observed that all of the oligoureas catalyzed the reaction even at low catalyst loading. There was almost no enantiocontrol in the presence of monomer and dimer. Therefore, it can be stated that well-defined helical conformation is required for efficient stereocontrol in catalysis. Moreover, it was proven that the activity of the catalytic system persists at high temperature, with a slight decrease in enantioselectivity.

With these precedents in mind, additional studies in the ability of different oligoureas to catalyze asymmetric reactions were proposed. In this context, the aim of my research work was the synthesis of different chain-length (L)-valine-based oligoureas and their evaluation in organocatalysis.

4.2.1. Valine-based oligourea for organocatalysis

The interest in having a valine-based oligourea relies on the structure. Unlike alanine and leucine, valine is β-branched. Same as isoleucine and threonine, valine contains two non-hydrogen substituents in β position (Figure 38).

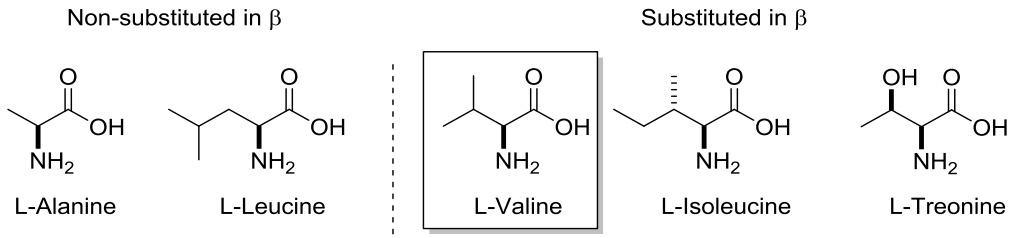
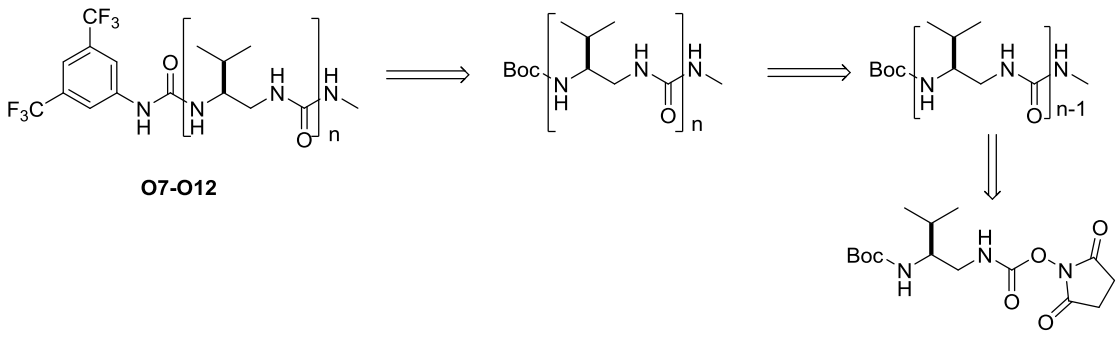


Figure 38. Amino acids

Hence, the interest relies on the bulkyness around the amino acid unit. We wondered whether this fact would restrict the conformations that the main chain may adopt and influence the enantioselectivity outcome of the reaction.

4.3. **Synthetic plan**

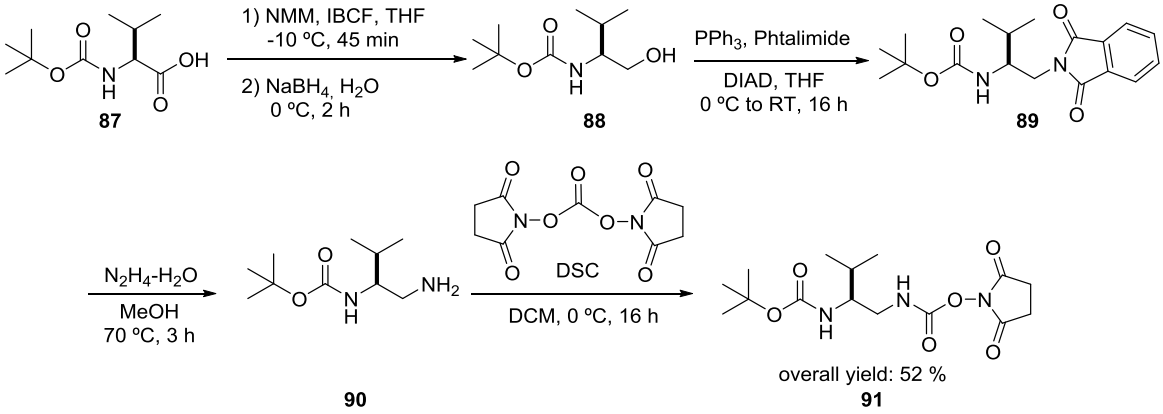
Preparation of valine-based oligoureas was carried out following the described procedures.



Scheme 53. Retrosynthesis of oligoureas **O7**-**O12**.

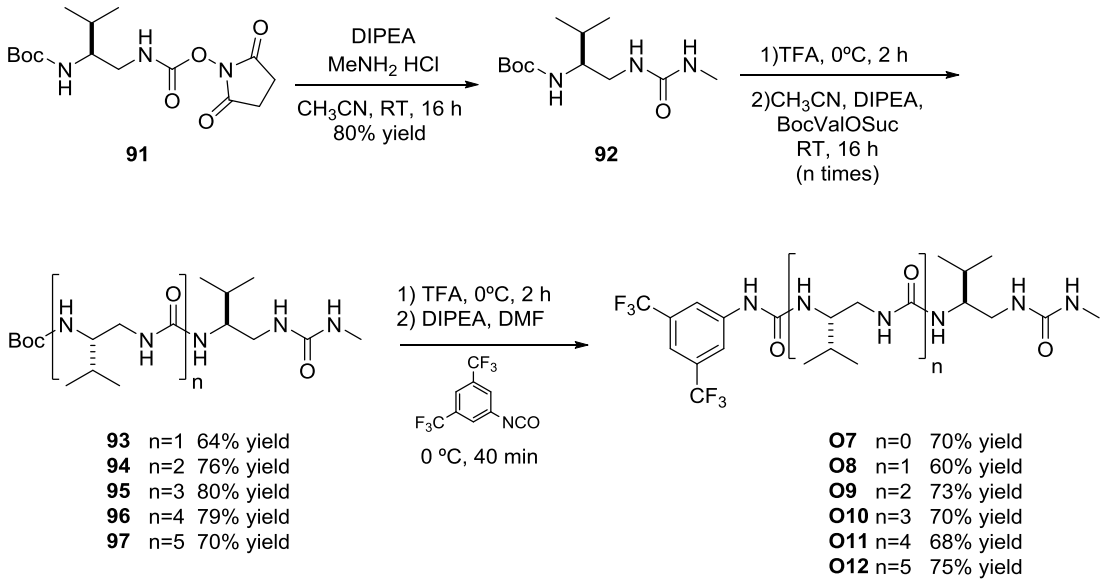
The valine-based building block was prepared as shown in Scheme 54.[209] First, the Boc-protected valine was reduced to the corresponding alcohol **88**, followed by the Mitsunobu reaction, in the presence of phthalimide. The phthalimide derivative **89** was then reduced to the corresponding amine **90** and this was activated by reaction with *N*,*N*'-disuccinimidyl carbonate affording **91** with an overall yield of 52%.

[209] C.Aisenbrey, N. Pendem, G. Guichard, B. Bechinger, *Org. Biomol. Chem.*, **2012**, 10, 1440–1447.



Scheme 54. Synthesis of valine building block.

After preparation of building block **91**, different chain-length oligoureas were synthesised in solution according to the method shown in Scheme 55.[210] Firstly, the C-terminal residue of the oligourea chain **92** was prepared by methylation of the *N*-Boc protected and DSC activated building block **91**. Then, a synthetic pathway that involves successive deprotection/coupling sequences allowed the introduction of each residue of the oligomer in a stepwise manner with good yield. Final coupling of the amino group of the chain with 3,5-bis(trifluoromethyl)phenyl isocyanate, afforded the corresponding oligoureas **O7**-**O12** with good yield.



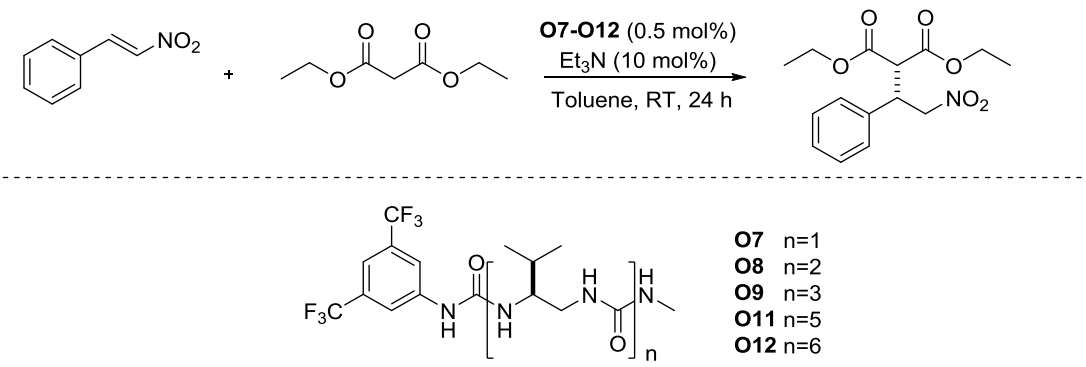
Scheme 55. Synthesis of oligoureas **O7**-**O12**.

[210] a) V. Diemer, L. Fischer, B. Kauffmann, G. Guichard, *Chem. Eur. J.* **2016**, *22*, 15684-15692; b) N. Pendem, C. Douat, P. Claudon, M. Laguerre, S. Castano, B. Desbat, D. Cavagnat, E. Ennifar, B. Kauffmann, G. Guichard, *J. Am. Chem. Soc.* **2013**, *135*, 4884-4892.

4.4. Results and discussion

With all the oligoureas in hand, their screening in the conjugate addition of dimethylmalonate with nitrostyrene was performed. Catalysis with **O10** (tetramer) was not performed due the impurities found on the oligourea and its low solubility. All catalytic experiments were carried out twice, in order to check the reproducibility of the reaction. As it can be seen in Table 26, all the oligoureas promote the reaction though the reactivity is much lower when short chains **O7** and **O8** are employed. Regarding enatioselectivity, the stereocontrol with monomer **O7** and dimer **O8** is very low. The enantiomeric excess increases to higher values (up to 75% *ee*) with longer chains. It has been proven that even at low catalyst loading (0.3 and 0.1 mol%), the reactivity and the enantiocontrol is mantained (entries 6 and 7).

Table 26. Oligourea screening in the conjugate addition of diethyl malonate to nitrostyrene, promoted by oligoureas **O7**-**O12**.[a]

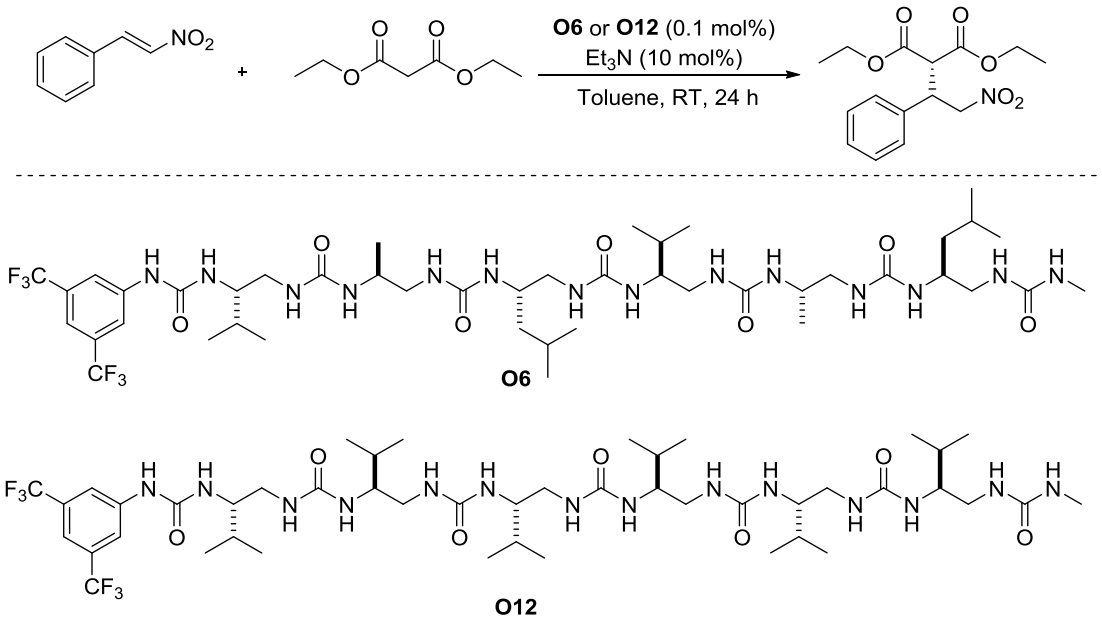


Entry	O	Conv. (%)[b]	Yield (%)	*ee* (%)[c]
1	**O7**	47	30	2
		47	32	5
2	**O8**	53	40	16
		53	37	17
3	**O9**	81	60	63
		81	62	60
4	**O11**	92	70	70
		92	72	68
5	**O12**	92	70	75
		93	73	73
6[d]		92	70	72
7[e]		90	72	70

[a] Reaction conditions: Nitrostyrene (0.5 mmol), the corresponding oligourea **O7-O12** (0.0005 mmol, 0.01 equiv.) and diethyl malonate (1 mmol, 2 equiv.). [b] Conversion determined by the disappearance of the starting material by ^{1}H-NMR. [c]The *ee* values were determined by chiral HPLC. [d] Reaction performed with 0.3 mol% of **O12**. [e] Reaction performed with 0.1 mol% of **O12**.

If we compare the result obtained with valine-base hexamer **O12**, with the previous one from the group using **O6**, it is clear that with valine-alanine-leucine sequence, higher enantioselectivity level than with **O12** is induced. (Table 27).

Table 27. Comparison in the conjugate addition of diethyl malonate to nitrostyrene, promoted by oligoureas **O6** and **O12.**[a]



Entry	O (%)	Conv. (%)[b]	Yield (%)	*ee* (%)[c]
1	**O6**	98	75	89
2	**O12**	90	72	70

[a] Reaction conditions: Nitrostyrene (0.5 mmol), the corresponding oligourea **O7**-**O12** (0.0005 mmol, 0.01 equiv.) and diethyl malonate (1 mmol, 2 equiv.). [b] Conversion determined by the disappearance of the starting material by ^{1}H-NMR. [c]The *ee* values were determined by chiral HPLC.

In summary, we have observed that with the valine-based monomer **O7** and dimer **O8**, do not provide reaction adducts enantioselectively. However, when trimer **O9** is employed, moderate values are obtained. This enantiomeric excess increases with the pentamer **O11** and with the hexamer **O12**, which affords values up to 70% ee. Although the results do not improve the previous ones obtained with the sequence valine-alanine-leucine **O6**, these new oligoureas induce stereoselectivity, as well even at low catalyst loading (0.1 mol%). Further studies on the structure-activity should give extra information in the correlation between the oligomer catalyst efficiency and its folding propensity.

Chapter 5

Conclusions

5. CONCLUSIONS

Two Brønsted base promoted highly stereoselective approaches have been developed in order to access enantiopure α-functionalized amides, thereby overcoming the low acidity problem associated to these substrates. In this context, 4-substituted pyrrolidin-2,3-diones have been employed as efficient new donor templates in Brønsted base catalyzed conjugate additions to α'-silyloxy enones and vinyl ketones with high enantioselectivity. The palladium-catalyzed asymmetric allylic alkylation (AAA) has also been successfully performed with these potential heterocycles. The corresponding enantioenriched reaction adducts bearing a tetrasubstituted stereocenter, have been transformed into $\beta^{2,2}$-amino acid derivatives, following a strategy that involves the transformation of the adducts into *N*-carboxyanhydrides and subsequent ring opening with different nucleophiles. When the nucleophile employed for the reaction is an amine, highly functionalized amides with a quaternary stereocenter in α-position can be obtained.

On the other hand, Schiff bases of glycine *o*-nitroanilide as efficient donors for the Brønsted Base catalyzed *syn*-selective aldol reaction have been designed. The presence of the *o*-nitroanilide framework provides an efficient hydrogen-bonding platform that accounts for both, the higher acidity of the α-carbon and efficient stereoselectivity control. This constitutes the first application of this type of amides in asymmetric catalysis. The equivalent aldimines, provide *anti* adducts, thus enabling the access to *syn*- or *anti*- adducts depending on the substrate. Besides, the *o*-nitroanilide unit can be removed to obtain the corresponding α-amino β-hydroxy acids.

Finally, new valine-based oligoureas have been synthesized during the international stay at the European Institut of Chemistry and Biology (IECB) at Bordeaux-Pessac campus under the supervision of Prof. Gilles Guichard, and their evaluation as hydrogen-bonding organocatalysts with an achiral cocatalyst has been performed in the conjugate addition of diethyl malonate to nitrostyrene. Enantioselectivity proved to be oligourea chain length dependant. Thus, the valine-based hexamer oligourea promotes the reaction with higher, but moderate enantioselectivity. Although more information is needed, this study helps to understand the main elements for stereocontrol in urea based oligomers.

Chapter 6

Experimental section

6. EXPERIMENTAL SECTION

6.1. MATERIALS AND TECHNIQUES

6.1.1. Reagents and solvents

Reagents were purchased from different commercial suppliers (Aldrich, Across, Alfa Aesar, Fluka, TCI, Merck, Fluorochem, etc.), stored as specified by the manufactured and used without previous purification unless otherwise stated.

Triethylamine, DBU, and DIPEA were purified by distillation. Liquid aldehydes were purified by distillation before usage and stored in the fridge at – 30 °C under nitrogen. When anhydrous solvents were required, they were dried following established procedures.[211] Dichloromethane was dried over CaH_2, tetrahydrofuran, toluene and dioxane were dried over sodium and diethyl ether was dried by filtration through activated alumina (powder 150 mesh, pore size 58 Å, basic Sigma Aldrich) columns.

6.1.2. General experiments

All non-aqueous reactions were performed under inert atmosphere using oven-dried glassware and were magnetically stirred. Yields refer to chromatographically purified and spectroscopically pure compounds, unless otherwise stated.

Heat requiring reactions were performed using a hotplate with a sand or an oil bath and a condenser. Reactions requiring low temperatures were performed using cooling bath circulators *Huber* T100E and acetone or isopropanol baths.

Organic layers washed with aqueous phases were dried over $MgSO_4$ or Na_2SO_4 and filtered through cotton. Organic solvents were evaporated under reduced pressure using Büchi R-100, R-200 and R-210 rotavapors, the latter equipped with a Büchi V-700 vacuum pump and a Büchi V-850 vacuum controller, appropriate for the evaporation of solvents when products were volatile compounds. For the complete removal of solvents vacuum pump Telstar Top-3 (≈ 0.5 mmHg) was employed.

6.1.3. Chromatography

Reactions and flash chromatographic columns were monitored by thin layer chromatography (TLC) using Merck silica gel 60 F254 plates and visualized by

[211] Armanego, W. L. F.; Perrin, D. D. *Purification of laboratory Chemicals*, 3rd Edition Butterworth-Heinemann, Oxford, **1988**.

fluorescence quenching under UV light, Fisher Biolock lamp VL-4LC, λ = 254 and 365 nm. In addition, TLC plates were stained with a dipping solution of potassium permanganate (1g) in 100 ml of water (limited lifetime), followed by heating and charring with 1% w/w ninhydrin in ethanol followed by heating.

Chromatographic purification was performed on Merck ROCC 60 silica gel 40-63 μm as stationary phase and a suitable mixture of solvents (typically hexane: ethyl acetate, pentane: diethyl ether or dichloromethane: methanol) as eluent.

Non acid silica gel was prepared by mixing silica gel with a saturated aqueous solution of sodium bicarbonate (300 mL of solution for 100 g of silica gel) during 24 h and subsequent evaporation of water in an oven at 80 ºC for 72 hours.

6.1.4. Optical rotation

Optical rotations were recorded using a Jasco P-2000 polarimeter; specific rotations (SR) ($[\alpha]_D$) are reported in 10^{-1} deg.cm^2.g^{-1}; concentrations (*c*) are quoted in g/100 mL; $_D$ refers to the D-line of sodium (589 nm); temperatures (T) are given in degree Celsius (°C).

6.1.5. Melting points

Melting points were determined in open capillaries in a Stuart SHP3 melting point apparatus and microscope and were uncorrected.

6.1.6. NMR spectra

NMR spectra were recorded using a Bruker Avance 300 (300 MHz for ^{1}H, 75 MHz for ^{13}C) spectrometer, Bruker 400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C) or Bruker AV-500 spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C). Chemical shifts (δ) are quoted in parts per million referenced to the residual solvent peak, usually $CDCl_3$, ^{1}H (δ = 7.26) and ^{13}C (δ = 77.0). The multiplicity of each signal is designated using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; brs, broad singlet. Coupling constants (*J*) are reported in Hertz (HZ). MestrReNova Mnova 8.1 program was used to process and edit the registered spectra.

6.1.7. Mass spectra

Ms spectra were recorded on an ESI-ion trap Mass spectrometer (Agilent 1100 series LC/MSD, SL model) on a UPLC-DAD-QTOF, Ultra High Performance Liquid Chromatography-Mass spectrometer, Waters UPLC ACQUITY, Waters PDA detector,

Waters Sunapt G2 or on an Agilent Thermoquest LCT spectrometer. Mass spectrometry analyses were performed in the General Research Service (SGIker) of the University of the Basque Country (UPV/EHU) and ESI-MS analyses in Bordeaux, were carried out with a ThermoElectron LCQ Advantage spectrometer equipped with an ion-trap mass analyzer.

6.1.8. Infrared spectra

Infrared spectra were recorded on a Bruker Alpha FT-IR spectrometer as a thin film.

6.1.9. Determination of enantiomeric excesses

Enantiomeric excesses were determined using analytical high performance liquid chromatography (HPLC) performed on Waters 600-E (equipped with 2996 and 2998 photodiode array UV detector) employing Daicel columns (IA, IB, IC, ID, IF, AD-H, AY-H, AS-H, OD-H, OJ-H) and phenomenex Lu-xi (cellulose 3µm, amylose 3µm).

6.1.10. X-Ray diffraction analysis

The X-ray diffraction analysis experiments were conducted in the General Research Service (SGIker) of the University of the Basque Country (UPV/EHU) using difractometers for monocrystals.

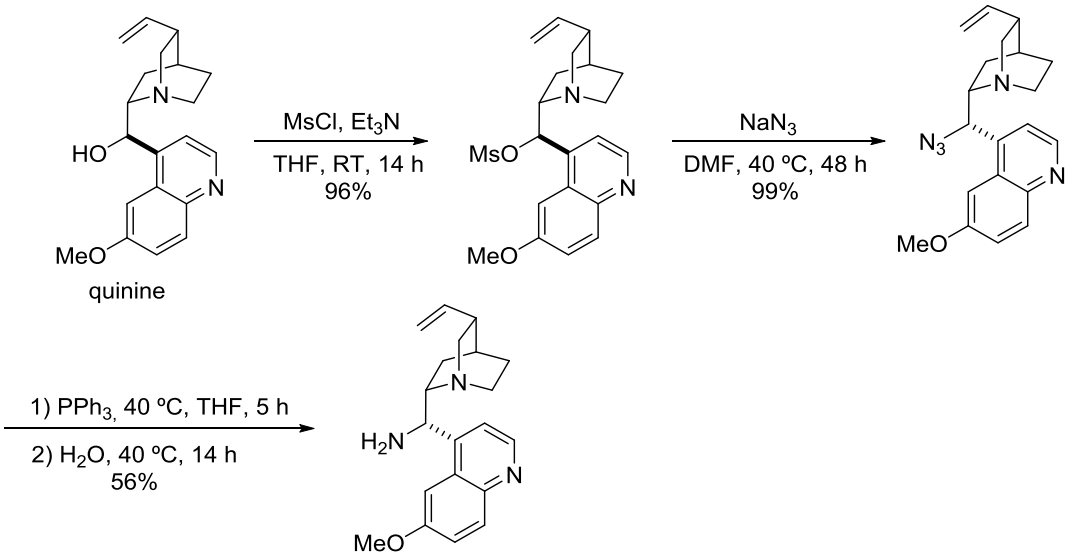
6.2. PREPARATION OF CATALYSTS

Organocatalysts **C18**,[212] **C19**,[213] **C20**,[214] **C21**,[215] **C22,**[216] **C27,**[217] **C28,**[218] **C29**,[219] **C30,**[220] **C31** and **C32**,[221] **C33**,[222] and **C38**,[223] and **C39**[224] were prepared following reported procedures. Catalysts **C23**, **C34**-**37** were synthesized as follows:

[212] B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett*. **2005**, *7*, 1967–1969.
[213] K. Greenaway, P. Dambruoso, A. Ferrali, A. J. Hazelwood, F. Sladojevich, D. J. Dixon, *Synthesis* **2011**, *12*, 1880–1886 .
[214] W. Yang, M. U. Du, *Org. Lett*. **2010**, *12*, 5450–5453.
[215] J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416–14417.
[216] I. Urruzuno, O. Mugica, M. Oiarbide, C. Palomo, *Angew. Chem. Int. Ed.* **2017**, *56*, 2059-2063.
[217] W. Yang, D.-M. Du, *Adv. Synth. Catal.* **2011**, *353*, 1241-1246.
[218] K. Hu, A. Lu, Y. Wang, Z. Zhou, C. Tang, *Tetrahedron: Asymm* **2013**, *24*, 953-957.
[219] Y. Kurimoto, T. Nasu, Y. Fuji, K. Asano, S. Matsubara, *Org. Lett.* **2019**, *21*, 2156-2160.
[220] L. Jiao, X. Zhao, H. Liu, X. Ye, Y. Li, Z. Jiang, *Org. Chem. Front.* **2016**, *3*, 470-474.
[221] Prepared following the methodology described for ureidopeptide catalysts. For more details, see: S. Rodriguez, doctoral thesis, *Asymmetric α-Functionalization of Barbituric Acids via Brønsted Base Catalysis.* EHU/UPV, **2018** (https://www.ehu.eus/es/web/gicas/tesiak).

6.2.1. Preparation of chiral amines

6.2.1.1. Synthesis of 9-amino-(9-deoxy)epiquinine[225]



Step 1: A mixture of quinine (16.2 g, 50 mmol, 1 equiv.) and triethylamine (25.1 mL, 180 mmol, 3.6 equiv.) in dry THF (250 mL) was cooled to 0 ºC and then methanesulfonyl chloride (7.0 mL, 90 mmol, 1.8 equiv.) was added dropwise. The mixture was stirred overnight at room temperature. The reaction was quenched with water (40 mL) and then THF was removed under vacuum. The residue was dissolved in dichloromethane (40 mL) and washed with water (30 mL) and saturated sodium bicarbonate (30 mL). The organic layer was dried over $MgSO_4$, filtered and concentred under vacuum to afford the crude product in 96 % yield, which was used in the next step without further purification.

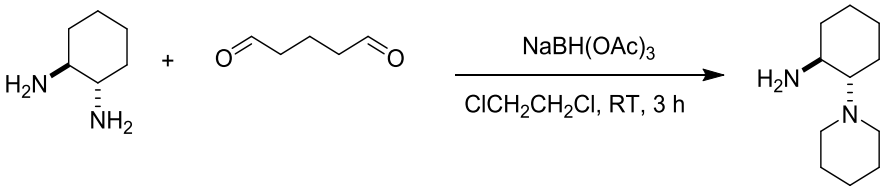
Step 2: The crude product (19.3 g, 48 mmol, 1 equiv.) was dissolved in DMF (150 mL). The solution was cooled to 0 °C and NaN_3 (6.2 g, 96 mmol, 2 equiv.) was added portionwise. The mixture was stirred at 40 °C for 48 h and after this time the reaction was quenched with water (80 mL) and then ethyl acetate (150 mL) was added. The organic layer was separated and washed with saturated NaCl (5 x 60 mL), dried over $MgSO_4$,

[222] Prepared following the methodology described for ureidopeptide catalysts. For more details, see: H. Echave, doctoral thesis, *α-Keto Amides in Brønsted-Base Mediated Stereoselective Aldol and Mannich reactions: Access to Chiral Polyfunctionalized Scaffolds*. EHU/UPV, **2017** (https://www.ehu.eus/es/web/gicas/tesiak).
[223] H. Y. Bae, S. Some, J. H. Lee, J.-Y. Kim, M. J. Song, S. Lee, Y. J. Zhang, C. E. Song, *Adv. Synth. Catal.* **2011**, *353*, 3196-3202.
[224] Z. Zhang, Z. Bao, H. Xing, *Chem. Eur. J.* **2012**, *18*, 8464-8473.
[225] Adapted from: H. Brunner, J. Büegler, B. Nuber, *Tetrahedron: Asymmetry*, **1995**, *6*, 1699–1702.

filtered and evaporated under reduced pressure to obtain the crude product in quantitative yield, which was used in the next step without further purification.

Step 3: The crude product was dissolved in THF (250 mL) and PPh_3 (12.6 g, 48 mmol, 1 equiv.) was added. The reaction mixture was heated to 40 °C and stirred until the gas evolution ceased (~5 h). Then H_2O (8 mL) was added and the mixture was stirred overnight at 40 °C. The solvent was removed under vacuum and the residue was dissolved in dichloromethane (150 mL). HCl 6 M (250 mL) was added and the aqueous phase was separated and washed with dichloromethane (2 x 100 mL). Then the aqueous layer was cooled to 0 °C and basified until pH > 10 with NaOH 40%. The aqueous phase was then extracted with dichloromethane (3 x 150 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford 9-amino-(9-deoxy)*epi*quinine as a yellow viscous oil. Yield: 56% (8.7 g, 26.9 mmol). All data were consistent with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$), δ 8.75 (d, *J* = 4.6 Hz, 1H), 7.36 – 8.05 (m, 4H), 5.79 – 5.75 (m, 1H), 4.97 (m, 2H), 4.57 (d, *J* = 10.4 Hz, 1H), 3.97 (s, 3H), 3.02 – 3.34 (m, 3H), 2.75 – 2.77 (m, 2H), 2.27 – 2.24 (m, 1H), 2.08 (s, 2H), 1.26 – 1.63 (m, 4H), 0.80 – 0.78 (m, 1H).

6.2.1.2. Preparation of (1S,2S)-2-(piperidin-1-yl)cyclohexan-1-amine[226]

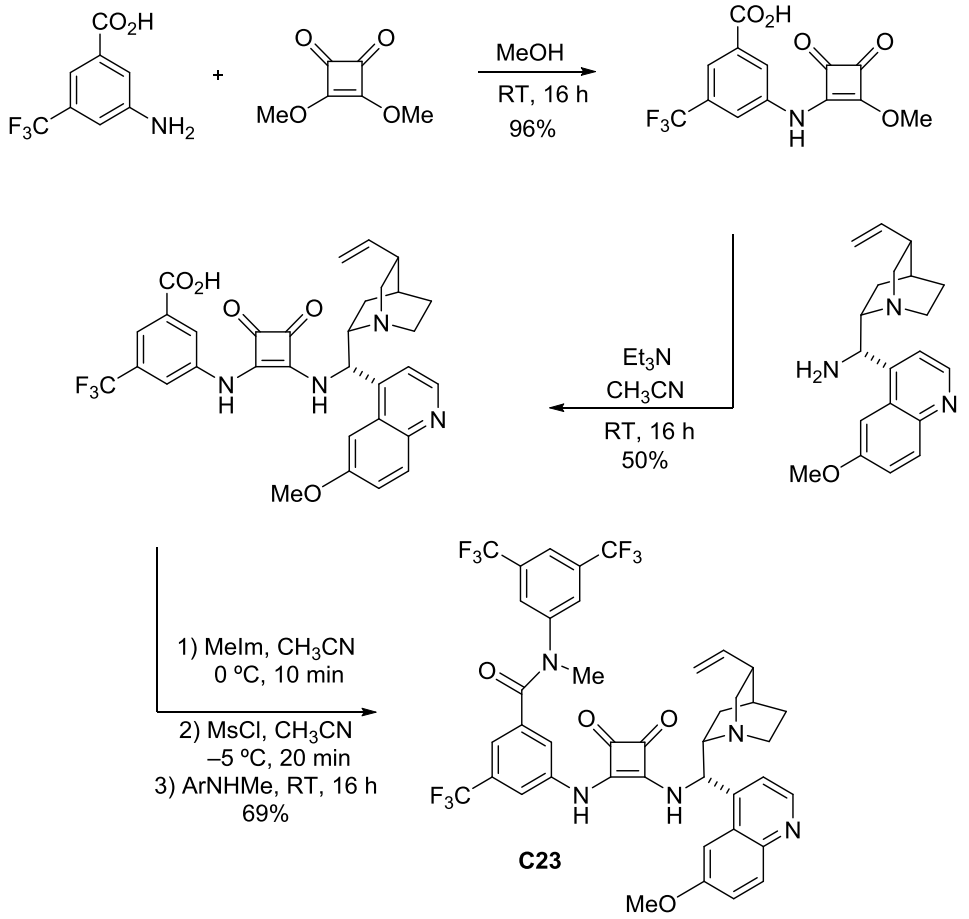


Glutaraldehyde (50 wt % H_2O, 0.93 mL, 5.1 mmol, 1.05 equiv.) was added dropwise to a mixture of (1*S*,2*S*)-(+)-1,2-diaminocyclohexane (560 mg, 4.9 mmol, 1.0 equiv.) and $NaBH(OAc)_3$ (4.16 g, 19.6 mmol, 4.0 equiv.) in $ClCH_2CH_2Cl$ (30 mL) at room temperature. The mixture was stirred at room temperature for 3 h, and quenched with NaOH 6.0 M (15 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 twice (2x15 mL). The organic layers were combined and washed with brine (1 x 15 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the product as brown oil. Yield: 80% (715 mg, 3.92 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.71 – 2.51 (m, 3H), 2.40 – 2.19 (m, 2H), 1.87 – 1.59 (m, 5H), 1.60 – 1.35 (m, 6H), 1.25 – 0.99 (m, 4H). Spectral data were in agreement with the data described in the literature.

6.2.2. Synthesis of squaramide-based catalyst C23

Squaramide based catalysts **C23** was synthesized according to the protocol shown below. 3-Amino-5-(trifluoromethyl)benzoic acid was prepared following procedures described in the literature.[227]

[226] J. Gonzalez-Sabin, V. Gotor, F. Rebolledo, *Chem. Eur. J.* **2004**, 10, 5788-5794.
[227] J. Shirai, S. Morimoto,H. Sugiyama, N. Sakauchi, T. Yoshikawa *PCT Int. Appl*., 2008133344, 06 Nov **2008**.



1st step:[228] To a solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (710 mg, 5 mmol, 1 equiv.) in MeOH (5 mL) aminobenzoic acid (5 mmol, 1.03 g, 1 equiv.) was added and the mixture was stirred at room temperature for 15 h. The white precipitate was filtered, washed with MeOH and dried *in vacuo* to give the title product as a yellow solid. Yield: 96% (1.51 g, 4.8 mmol). ^{1}H NMR (300 MHz, Acetone-*d*6) δ 9.88 (s, 1H), 8.38 (s, 1H), 8.16 (s, 1H), 8.00 (s, 1H), 4.50 (s, 3H).

2nd step: Triethylamine (0.67 mL, 4.8 mmol, 1 equiv.) and (*R*,*R*)-9-deoxy-9-epiaminoquinine (1.55 g, 4.8 mmol, 1 equiv.) were added to a suspension of the squarate (1.51 g, 4.8 mmol, 1 equiv.) in CH_3CN (5 mL) at room temperature. The reaction mixture was stirred at room temperature for 16 h and then was directly purified by flash column chromatography (DCM/ MeOH, 99:1) to give the title product as a yellow solid. Yield: 50% (1.46 g, 2.4 mmol). ^{1}H NMR (300 MHz, Acetonitrile-*d*3) δ 11.51 (bs, 1H), 10.17 (bs, 1H), 8.85 (d, *J* = 4.5 Hz, 1H), 8.38 (s, 1H), 8.07 – 7.56 (m, 5H), 7.32 (dd, *J* = 9.2, 2.5 Hz, 1H), 6.40 (bs, 1H), 5.86 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.32 – 4.97 (m, 2H), 4.50 (s, 1H), 4.05 – 3.53 (m, 5H), 3.51 – 3.11 (m, 2H), 2.84 (d, *J* = 9.0 Hz, 1H), 2.25 – 1.97

[228] Adapted from: Y. Qian, G. Ma, A. Lv, H.-L. Zhu, J. Zhao and V. H. Rawal, *Chem. Commun.* **2010**, *46*, 3004–3006.

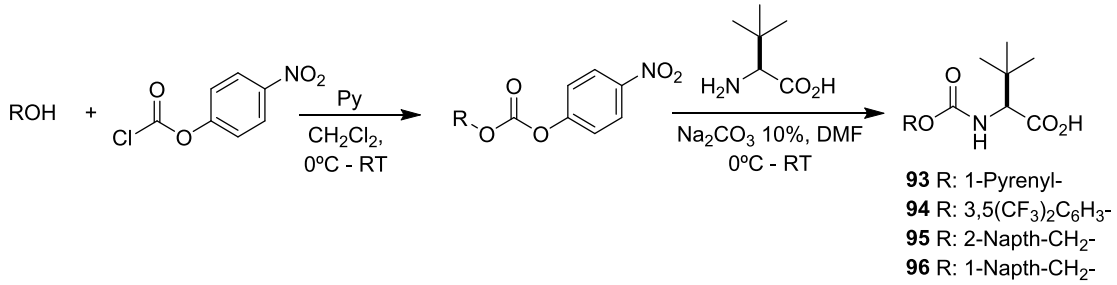
(m, 4H), 1.78 (t, *J* = 12.4 Hz, 1H), 1.22 (d, *J* = 13.9 Hz, 1H). ^{13}C NMR (75 MHz, Acetonitrile-*d*3) δ 185.7, 181.9, 171.9, 169.0, 166.5, 159.5, 149.0, 145.6, 142.4, 140.6, 139.6, 138.4, 132.8, 131.7 (q), 127.9, 127.0, 123.2, 122.7, 120.7, 120.6, 117.4, 117.0, 102.2, 60.4, 56.3, 55.3, 54.3, 42.2, 37.3, 27.6, 24.7, 24.2. UPLC-DAD-QTOF: $C_{32}H_{30}N_4O_5F_3$ $[M+H]^+$ calcd.: 607.2168, found: 607.2175.

3rd Step: C6[229]**:** 1-Methylimidazole (0.2 mL, 2.5 mmol, 2.5 equiv.) was added to a slurry of the benzoic acid derivative obtained in the previous step (606 mg, 1 mmol, 1 equiv.) in CH_3CN (2.5 mL) at 0 °C, and the mixture was stirred for 10 min. MsCl (0.12 mL, 1.5 mmol, 1.5 equiv) in CH_3CN (0.5 mL) was added to the mixture under –5 °C. After stirring at that temperature for 20 min, the corresponding amine (1 mmol, 1 equiv.) was added. The mixture was then stirred at room temperature overnight. H_2O (10 mL) was added to the mixture and a solid was formed. This solid was solved in EtOAc (10 mL) and the organic layer was washed with brine (3 x 50 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the crude was purified by silica flash column chromatography to afford the desired catalyst (CH_2Cl_2/MeOH, 98:2). Yellow solid. Yield: 95% (1.4 g, 1.7 mmol). $[\alpha]_D^{25}$ = – 115.89° (c=1.0, CH_2Cl_2). ^{1}H NMR (300 MHz, Acetone-d_6) δ 8.77 (d, *J* = 4.5 Hz, 1H), 8.01 (d, *J* = 9.6 Hz, 4H), 7.93 (s, 2H), 7.86 (s, 1H), 7.77 (s, 1H), 7.69 (d, *J* = 4.0 Hz, 1H), 7.42 (dd, *J* = 9.2, 2.5 Hz, 1H), 7.23 (s, 1H), 6.31 (s, 1H), 5.87 (m , 1H), 4.97 (m, 2H), 4.04 (s, 3H), 3.59 (s, 3H), 3.36 – 3.20 (m, 1H), 2.82 (d, *J* = 12.4 Hz, 2H), 2.36 (s, 1H), 2.08 (m, 1H), 1.65 (d, *J* = 15.0 Hz, 4H), 0.89 (s, 1H). ^{13}C NMR (75 MHz, Acetone-d_6) δ 185.8, 181.4, 169.7, 169.1, 164.1, 159.3, 148.4, 146.8, 145.8, 143.9, 142.4, 141.1, 138.9, 132.6, 132.4, 131.9, 129.3, 128.8, 128.5, 126.1, 125.7, 123.0, 122.5, 122.1, 120.7, 119.3, 118.4, 116.6, 114.8, 102.2, 60.7, 56.7, 56.3, 54.9, 41.5, 40.4, 38.3, 30.3, 28.5, 28.1, 26.7. UPLC-DAD-QTOF: $C_{42}H_{36}N_4O_4F_9$ $[M+H]^+$ calcd.: 831.2593, found: 831.2596.

[229] Adapted from: L. Mao, Z. Wang, Y. Li, X. Han, W. Zhou *Synlett* **2011**, *1*, 129–133.

6.2.3. Ureidopeptide-like Brønsted base catalysts

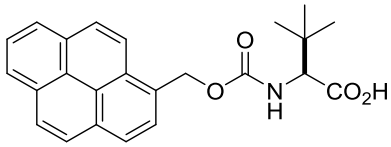
6.2.3.1. Preparation of N-protected amino acids **93-96**[230]



1st step: Pyridine (0.9 mL, 11 mmol, 1.1 equiv.) was added to a stirred solution of *p*-nitrophenyl chloroformate (2.2 g, 11 mmol, 1.1 equiv.) in dichloromethane (13.6 mL). The white slurry was cooled to 0 ^{o}C and the corresponding alcohol (10 mmol, 1 equiv.) was slowly added at the same temperature. After addition, the mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was diluted with CH_2Cl_2 (40 mL) and washed with HCl 1M (20 mL), water (20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$ and concentred under reduced pressure. The residue was used in the next step without further purification.

2nd step: To a stirred solution of *L*-tert-leucine (1.31 g, 10 mmol, 1 equiv.) in 10% Na_2CO_3 (26 mL), and dimethylformamide (10 mL), a solution of the corresponding carbonate (10 mmol, 1 equiv.) in dimethylformamide (30 mL) was slowly added at 0 ^{o}C. The mixture was stirred at the same temperature for 1 h and at room temperature for 16 h. The reaction mixture was poured into H_2O (100 mL) and washed with Et_2O (3 x 50 mL). The aqueous layer was cooled in an ice bath and acidified with concentrated HCl, followed by extraction with EtOAc (3 x 50 mL). The combined organic phases were washed with brine (5 x 50 mL), dried over $MgSO_4$ and concentrated under reduced pressure.

(*S*)-3,3-Dimethyl-2-(((pyren-1-ylmethoxy)carbonyl)amino)butanoic acid 93

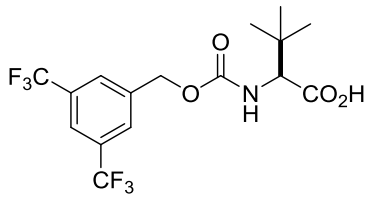


The title compound was prepared from 1-pyrenemethanol (2.32 g, 10 mmol) according to the general procedure. Purification by column chromatography (hexane/EtOAc, 70:30) afforded **93** as

[230] P. Lan, Jr. J. A. Porco, M. S. South, J. J. Parlow, *Comb. Chem*. **2003**, *5,* 660 –669.

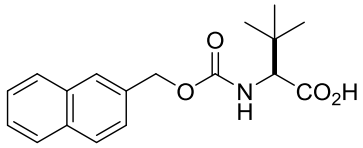
white solid. Yield: 74% (2.9 g, 7.4 mmol). m.p.= 93–97 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 – 7.96 (m, 9H), 5.80 (d, *J* = 12.8 Hz, 2H), 5.58 – 5.55 (m, 1H), 4.33 – 4.40 (m, 1H), 2.86 – 2.82 (m, 1H), 1.03 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1 , 156.5 , 131.7 , 131.2 , 130.7 , 129.5 , 128.2 , 127.8 , 127.6 , 127.4 , 126.0 , 125.5 , 124.8 , 124.6 , 122.9 , 65.6 , 62.4 , 34.7 , 26.6 . UPLC-DAD-QTOF: $C_{24}H_{23}NO_4Na$* *$[M+Na]^+$ calcd.: 412.1525, found: 412.1529.

(*S*)-2-((((3,5-Bis(trifluoromethyl)benzyl)oxy)carbonyl)amino)-3,3-dimethylbutanoic acid 94[231]



The title compound was prepared from 3,5-bis(trifluoromethyl)benzyl alcohol (2.44 g, 10 mmol) according to the general procedure. Removal of the remaining fenol was not possible by column chromatography, so after the work up described in the general procedure, the crude was dissolved in Et_2O (20 mL) and basified with NaOH 20%. The aqueous phase was washed with Et_2O (3 x 20 mL), acidified with concentrated HCl and extracted with EtOAc (3 x 25 mL). The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure to afford **94** as white solid. Yield: 91% (3.65 g, 9.1 mmol). All spectroscopic data were consistent with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.80 (s, 2H), 5.56 (d, *J* = 9.6 Hz, 1H), 5.36 – 5.09 (m, 2H), 4.20 (d, *J* = 9.6 Hz, 1H), 1.03 (s, 9H).

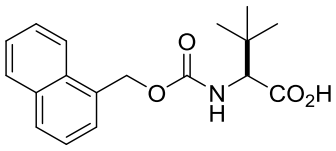
(*S*)-3,3-Dimethyl-2-(((naphthalen-2-ylmethoxy)carbonyl)amino)butanoic acid 95 [232]



The title compound was prepared from 2-naphthalenemethanol (1.58 g, 10 mmol) according to the general procedure. Removal of the remaining fenol was not possible by column chromatography. After the work up described in the general procedure, the crude was dissolved in Et_2O (30 mL) and basified with saturate $NaHCO_3$ (1 x 20 mL). The aqueous phase was washed with Et_2O (3 x 20 mL), acidified with concentrated HCl and extracted with EtOAc (3 x 25 mL). The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure to afford **95** as white solid. Yield 48% (1.5 g, 4.8 mmol). All the spectroscopic data were coincident with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 – 7.74 (m, 4H), 7.58 – 7.36 (m, 3H), 5.47 (d, *J* = 9.4 Hz, 1H), 5.30 (s, 2H), 4.26 (d, *J* = 9.6 Hz, 1H), 1.04 (s, 9H).

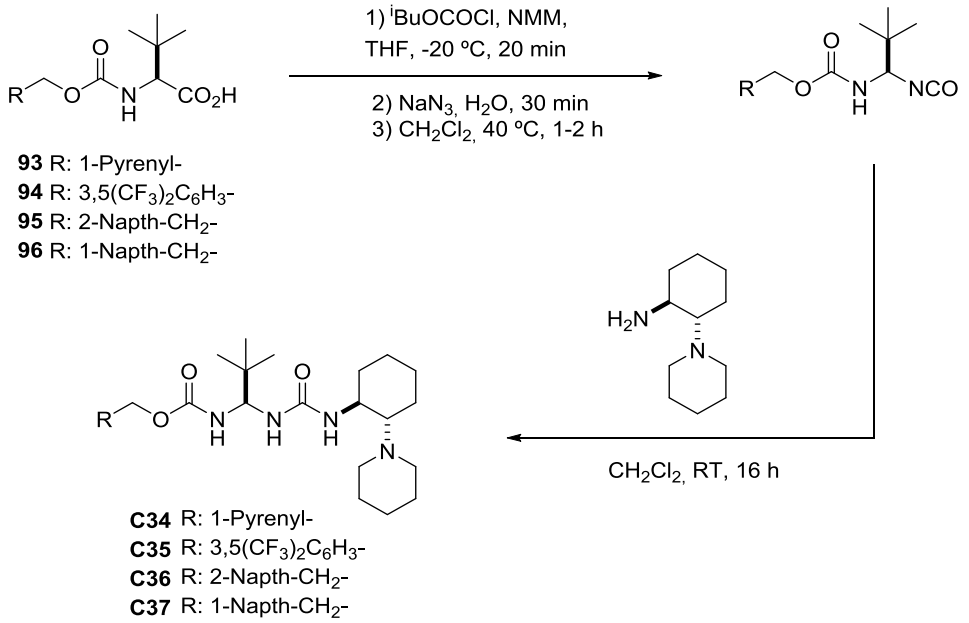
[231] I. Bastida, M. San Segundo, R. López, C. Palomo, *Chem. Eur. J.* **2017**, *23*, 13332-13336.
[232] S. Diosdado J. Etxabe, J. Izquierdo, A. Landa, A. Milego, I. Olaizola, R. López, C. Palomo, *Angew. Chem. Int. Ed.* **2013**, *52*, 11846-11851.

(*S*)-3,3-Dimethyl-2-(((naphthalen-1-ylmethoxy)carbonyl)amino)butanoic acid 96



The title compound was prepared from 1-naphthalenemethanol (1.58 g, 10 mmol) according to the general procedure. Purification by column chromatography (hexane/EtOAc, 80:20) afforded **96** as white solid. Yield: 88% (2.8 g, 8.8 mmol). m.p. = 131-135 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.10 (s,1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.87 (t, *J* = 8.8 Hz, 2H), 7.49 (dt, *J* = 27.2, 7.3 Hz, 4H), 5.60 (q, *J* = 12.3 Hz, 2H), 5.40 (d, *J* = 9.5 Hz, 1H), 4.26 (d, *J* = 9.6 Hz, 1H), 1.02 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 156.4, 133.8, 131.7, 129.5, 128.8, 127.6, 126.7, 126.07, 125.4, 123.7, 65.6, 62.3, 34.7, 26.6. UPLC-DAD-QTOF: $C_{18}H_{21}NO_4Na$* *$[M+Na]^+$ calcd.: 338.1368, found: 338.1369.

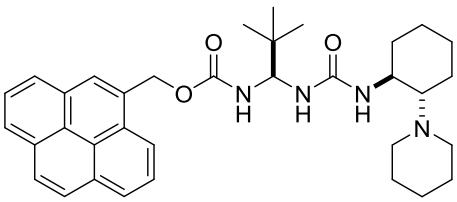
6.2.3.2. Isocyanate synthesis and coupling with the amine[232]



To a cooled solution of the corresponding *N*-protected α-amino acid (5 mmol, 1 equiv.) in dry THF (20 mL), isobutyl chloroformate (0.65 mL, 5 mmol, 1 equiv.) and *N*-methylmorpholine (0.6 mL, 5 mmol, 1 equiv.) were added at –20 ^{o}C. The mixture was stirred at the same temperature for 20 min. Then, a suspension of NaN_3 (0.48 g, 7.5 mmol, 1.5 equiv.) in 5 mL of H_2O was added and the reaction mixture stirred at the same temperature for 30 min. The organic layer was separated, evaporated and the residue was dissolved in CH_2Cl_2 (30 mL), and washed with water (15 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated in *vacuo* to give a yellow oil which was dissolved in dry CH_2Cl_2 (10 mL). The resulting solution was stirred at 40 ^{o}C under nitrogen for 1-2 h. The reaction was monitored by IR analysis until disappearance of the azide band (from azide ≈ 2136 cm^{-1} to isocyanate ≈ 2239 cm^{-1})

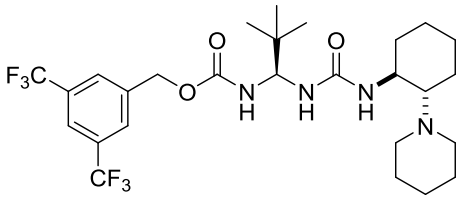
After isocyanate generation, the corresponding amine was added (638 mg, 3.5 mmol, 0.7 equiv.) and the reaction mixture was stirred for 16 h at room temperature. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on non acidic silica gel to afford the desired catalysts.

Pyren-4-ylmethyl ((*S*)-2,2-dimethyl-1-(3-((1*S*,2*S*)-2-(piperidin-1-yl)cyclohexyl)ureido)propyl)carbamate C34



Prepared according to the general procedure starting from **93** (1.94 g, 5 mmol) according to the general procedure. Purified by column chromatography (hexane/EtOAc, 70:30). White solid. Yield: 48% (1.36 g, 2.4 mmol). m.p.= 178-180 ºC. $[\alpha]_D^{23}$ = –9.64º (*c*=1, CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6, 70 ºC) δ 8.37 (d, *J* = 9.2 Hz, 1H), 8.34 – 8.28 (m, 2H), 8.24 (d, *J* = 9.6 Hz, 2H), 8.17 (d, *J* = 2.4 Hz, 2H), 8.14 (d, *J* = 7.8 Hz, 1H), 8.08 (t, *J* = 7.6 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 2H), 5.85 (d, *J* = 9.2 Hz, 1H), 5.79 (s, 2H), 5.63 (d, *J* = 6.3 Hz, 1H), 5.16 (t, *J* = 9.2 Hz, 1H), 3.35 (br s, 1H), 2.61 – 2.51 (m, 2H), 2.33 – 2.25 (m, 2H), 2.16 – 2.07 (m, 1H), 2.07 – 1.98 (m, 1H), 1.78 – 1.69 (m, 1H), 1.71 – 1.63 (m, 1H), 1.59 – 1.49 (m, 1H), 1.45 – 1.36 (m, 4H), 1.32 – 1.22 (m, 3H), 1.21 – 1.07 (m, 3H), 0.89 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 157.1 , 155.5 , 130.8 , 130.7 , 130.6 , 130.2 , 128.6 , 127.8 , 127.5 , 127.3 , 126.3 , 125.5 , 125.4 , 124.6 , 123.9 , 123.8 , 123.2 , 67.4 , 65.0 , 63.5 , 49.8 , 49.0 , 40.4 , 36.0 , 33.9 , 26.2 , 25.5 , 25.1 , 24.6 , 24.6 , 23.6 . UPLC-DAD-QTOF: $C_{35}H_{45}N_4O_3$ $[M+H]^+$ calcd.: 569.3492, found: 569.3501.

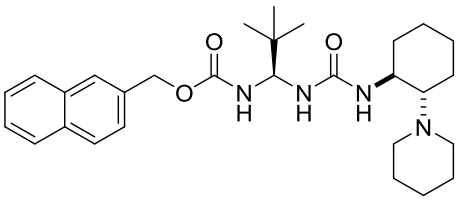
3,5-Bis(trifluoromethyl)benzyl ((1*S*)-2,2-dimethyl-1-(3-((2*S*)-2-(piperidin-1-yl)cyclohexyl)ureido)propyl)carbamate C35



Prepared according to the general procedure starting from **94** (2 g, 5 mmol). Purified by column chromatography by non-acid silica gel (hexane/EtOAc, 80:20). White solid. Yield: 58% (1.68 g, 2.8 mmol). $[\alpha]_D^{25}$ = –3.50° (c=1, CH_2Cl_2). m.p.= 170-174 ºC. ^{1}H NMR (500 MHz, DMSO-d_6, 70 ºC) δ 8.05 (s, 2H), 7.96 (s, 1H), 7.05 (s, 1H), 5.94 (d, *J* = 9.1 Hz, 1H), 5.70 (d, *J* = 6.2 Hz, 1H), 5.29 – 5.19 (m, 2H), 5.13 (t, *J* = 9.1 Hz, 1H), 3.39 (s, 1H), 2.59 (br s, 2H), 2.34 (br s, 2H), 2.19 (d, *J* = 10.3 Hz, 1H), 2.05 (d, *J* = 12.6 Hz, 1H), 1.78 (s, 1H), 1.71 (d, *J* = 8.5 Hz, 1H), 1.58 (d, *J* = 10.1 Hz, 1H), 1.46 (s, 4H), 1.32 (d, *J* = 11.7 Hz, 3H), 1.22 – 1.13 (m, 3H), 0.90 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.1 , 155.0 , 141.2 , 130.2 (q, *J* = 32.6 Hz), 127.8 , 125.1

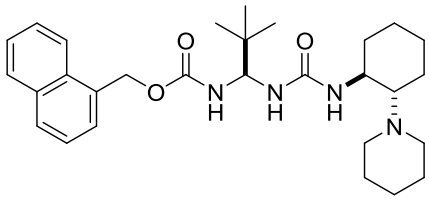
, 121.5 , 121.3 , 67.7 , 65.1 , 63.4 , 49.7 , 49.1 , 35.8 , 33.8 , 25.9 , 25.4 , 25.0 , 24.6 , 24.5 , 23.6 . UPLC-DAD-QTOF: $C_{27}H_{39}N_4O_3F_6$ $[M+H]^+$ calcd.: 581.2926, found: 581.2881.

Naphthalen-2-ylmethyl ((1*S*)-2,2-dimethyl-1-(3-((2*S*)-2-(piperidin-1-yl)cyclohexyl)ureido)propyl)carbamate C36



Prepared according to the general procedure starting from **95** (1.57 g, 5 mmol). Purified by column chromatography by non-acid silica gel (hexane/EtOAc, 70:30). White solid. Yield: 61% (1.06 g, 2.14 mmol). m.p.= 170-172 ºC. $[\alpha]_D^{23}$ = –15.6º (*c*=1, CH_2Cl_2) ^{1}H NMR (500 MHz, DMSO-d_6, 70 ºC) δ 7.99 – 7.80 (m, 4H), 7.65 – 7.41 (m, 3H), 6.88 (s, 1H), 5.91 (d, *J* = 9.2 Hz, 1H), 5.69 (d, *J* = 6.3 Hz, 1H), 5.21 (s, 2H), 5.15 (t, *J* = 9.2 Hz, 1H), 3.48 – 3.31 (m, 1H), 2.60 – 2.55 (m, 2H), 2.39 – 2.27 (m, 2H), 2.24 – 2.11 (m, 1H), 2.09 – 2.03 (m, 1H), 1.82 – 1.74 (m, 1H), 1.72 – 1.64 (m, 1H), 1.64 – 1.52 (m, 1H), 1.52 – 1.39 (m, 4H), 1.39 – 1.25 (m, 3H), 1.24 – 1.12 (m, 3H), 0.91 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 157.2 , 155.5 , 134.9 , 132.7 , 132.5 , 127.9 , 127.7 , 127.6 , 126.3 , 126.2 , 126.1 , 125.7 , 67.5 , 65.2 , 49.7 , 49.0 , 35.9 , 33.8 , 25.9 , 25.5 , 25.0 , 24.6 , 23.6 . UPLC-DAD-QTOF: $C_{29}H_{43}N_4O_3$ $[M+H]^+$ calcd.: 495.3335, found: 495.3348.

Naphthalen-1-ylmethyl ((1*S*)-2,2-dimethyl-1-(3-((2*S*)-2-(piperidin-1-yl)cyclohexyl)ureido)propyl)carbamate C37



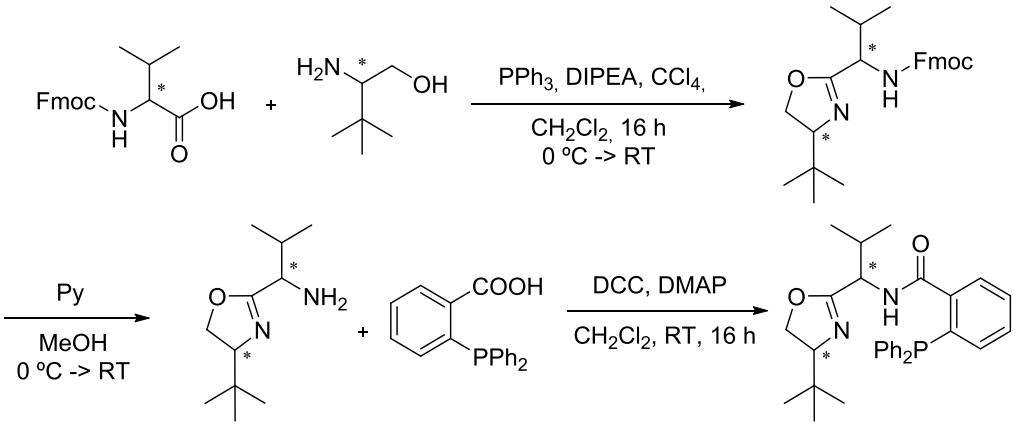
Prepared according to the general procedure starting from **96** (1.57 g, 5 mmol). Purified by column chromatography by non-acid silica gel (hexane/EtOAc, 90:10). White solid. Yield: 60% (1.42 g, 3 mmol). m.p.= 174–179 ºC. $[\alpha]_D^{23}$ = –19.1º (*c*=0.5, CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6, 70 ºC) δ 8.32 – 8.27 (m, 1H), 8.21 – 8.18 (m, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.85 – 7.77 (m, 3H), 7.76 – 7.69 (m, 1H), 7.19 (br s, 1H), 6.16 (d, *J* = 9.1 Hz, 1H), 6.00 – 5.95 (m, 1H), 5.75 (q, 2H), 5.39 (t, *J* = 9.2 Hz, 1H), 3.63 (br s, *J* = 6.7, 5.6 Hz, 1H), 2.85 (br s, 2H), 2.60 (br s, 2H), 2.43 (s, 1H), 2.28 (d, *J* = 12.5 Hz, 1H), 2.04 (d, *J* = 11.0 Hz, 1H), 1.94 (d, *J* = 11.4 Hz, 1H), 1.82 (d, *J* = 10.1 Hz, 1H), 1.74 – 1.66 (m, 5H), 1.64 – 1.53 (m, 3H), 1.47 – 1.36 (m, 3H), 1.12 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.3 , 155.5 , 133.2 , 132.7 , 131.0 , 128.5 , 126.6 , 126.4 , 125.9 , 125.3 , 123.6 , 65.2 , 63.4 , 49.5 , 49.3 , 35.8 , 33.6 , 25.5 , 24.5 , 23.8 . UPLC-DAD-QTOF: $C_{29}H_{43}N_4O_3$ $[M+H]^+$ calcd.: 495.3335, found: 495.3349.

6.3. EXPERIMENTAL SECTION OF CHAPTER 2

6.3.1. Preparation of chiral ligands

Ligands **L1**, **L2**, **L6**, **L7**, **L13 and L14** are commercially available and were purchased from commercial suppliers. Ligands **L3** and **L4** were prepared following synthetic sequences described in the literature.[233] **L11** and **L12** were prepared as follows. ^{31}P-NMR spectra were carried out to check the stability of the phosphine towards oxidation. Oxidazed phosphine chemical shifts ≈ 30 ppm, not oxidized ≈ – 8-11 ppm. In the cases where oxidation of the phosphine was detected, the oxidized compound was removed by column chromatography. For non oxidized (*S*,*S*)-**L3** ^{31}P NMR (162 MHz, $CDCl_3$) δ -9.90; for non oxidized (*R*,*R*)-**L4** ^{31}P NMR (162 MHz, $CDCl_3$) δ -10.87 .

*6.3.1.1. New phosphine ligands **L11** and **L12**[234]*



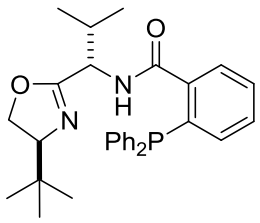
1st step: The corresponding aminoalcohol (586 mg, 5 mmol, 1 equiv.), the corresponding Fmoc protected amino acid (1.697 g, 5 mmol, 1 equiv.) and PPh_3 (3.934 g, 15 mmol, 3 equiv.) were dissolved in dry dichloromethane (100 mL) and DIPEA (2.61 mL, 15 mmol, 3 equiv.) was added at 0 ºC. To the previous mixture, CCl_4 (1.59 mL, 25 mmol, 5 equiv.) was added dropwise at the same temperature and the mixture was allowed to stir at room temperature for 16 h. Toluene (60 mL) was added to the reaction mixture and the solvent evaporated ca. (80 mL). Hexane was then added and the flask was allowed to stand for 30 min. The precipitate was removed by eluting through a pad of celite and washed with a mixture of toluene/hexane. (3:4). The filtrate was concentrated and purified by flash column chromatography.

[233] B. M. Trost, D. L. Van Vranken, C. Bingel *J. Am. Chem. Soc.* **1992**, *114*, 9327-9343.
[234] Adapted from: J.-Y. Lee, J.J. Miller, S.S. Hamilton, M.S. Sigman *Org. Lett.* **2005**, *7*, 1837-1839.

2nd step: The Fmoc-protected oxazoline (1 mmol) was dissolved in MeOH (8 mL) and pyridine (8 mL) was added dropwise at 0 °C. The reaction was allowed to warm to room temperature and it was monitored by TLC. After completion, the solvents were evaporated and the crude was purified by column chromatography.

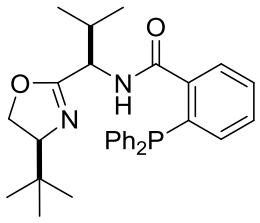
3rd step: DCC (921 mg, 4.46 mmol, 2.2 equiv.) and DMAP (25 mg, 203 mmol, 5 mol%) were added to a suspension of 2-(diphenylphosphino)benzoic acid (1.243 g, 4.06 mmol, 2 equiv.) in dry dichloromethane (14 mL) at 0 °C under argon atmosphere. After solubilisation of the reagents, the corresponding oxazoline (403 mg, 2.03 mmol, 1 equiv.) was added and the mixture stirred at room temperature for 16 h. Then, water was added to the reaction mixture and it was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$, and the crude was purified by column chromatography.

***N*-((*S*)-1-((*R*)-4-(*tert*-butyl)-4,5-dihydrooxazol-2-yl)-2-methylpropyl)-2-(diphenylphosphaneyl)benzamide L11**



The intermediate from the 1st step was purified eluting with (hexane/EtOAc, 95:5) and the intermediate from the 2nd step with (DCM/MeOH, 90:10). The crude from the 3rd step was purified by column chromatography (hexane/EtOAc, 80:20) to afford **L11** as a white solid. Yield: 55% (543 mg, 1.12 mmol). m.p. = 121–123 ºC. $[\alpha]_D^{23}$ = – 39.3° (c=1, CH_2Cl_2) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (ddd, *J* = 7.5, 3.7, 1.5 Hz, 1H), 7.38 (td, *J* = 7.5, 1.4 Hz, 1H), 7.29 (dtt, *J* = 10.6, 6.7, 2.4 Hz, 12H), 6.99 (ddd, *J* = 7.6, 3.9, 1.3 Hz, 1H), 6.64 (d, *J* = 8.6 Hz, 1H), 4.72 (dd, *J* = 8.6, 4.5 Hz, 1H), 4.24 – 4.00 (m, 2H), 3.89 – 3.70 (m, 1H), 2.17 – 1.96 (m, 1H), 1.00 – 0.74 (m, 15H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 166.1, 141.7, 137.6, 136.6, 134.5, 134.1, 133.8, 130.3, 128.8, 128.7, 128.7, 128.6, 128.5, 127.6, 75.4, 69.3, 53.2, 33.8, 31.6, 26.0, 18.9, 18.1. ^{31}P NMR (162 MHz, $CDCl_3$) δ -11.83. UPLC-DAD-QTOF: $C_{30}H_{36}N_2O_2P$ $[M+H]^+$ calcd.: 486.2544, found: 486.2563.

***N*-((*R*)-1-((*R*)-4-(*tert*-butyl)-4,5-dihydrooxazol-2-yl)-2-methylpropyl)-2-(diphenylphosphaneyl)benzamide L12**



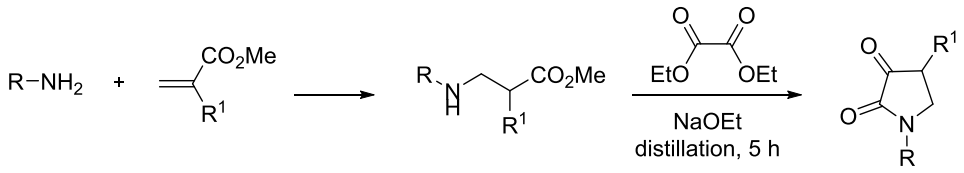
The intermediate from the 1st step was purified eluting with (hexane/EtOAc, 90:10) and the intermediate from the 2nd step with (DCM/MeOH, 95:5). The crude from the 3rd step was purified by column chromatography (hexane/EtOAc, 80:20) to afford **L12** as a yellow oil. Yield: 65% (642 mg, 1.31 mmol). $[\alpha]_D^{25}$ = –12.15° (c=2, CH_2Cl_2).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (ddd, *J* = 7.5, 3.8, 1.5 Hz, 1H), 7.38 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.34 – 7.20 (m, 10H), 6.99 (ddd, *J* = 7.7, 3.9, 1.3 Hz, 1H), 6.68

(d, *J* = 8.3 Hz, 1H), 4.67 (ddd, *J* = 8.3, 4.7, 1.5 Hz, 1H), 4.21 (dd, *J* = 10.2, 8.6 Hz, 1H), 4.01 (t, *J* = 8.7 Hz, 1H), 3.89 – 3.74 (m, 1H), 2.17 – 1.97 (m, 1H), 0.99 – 0.58 (m, 15H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 166.0, 141.7, 137.8, 137.6, 136.6, 134.6, 134.1, 133.8, 130.3, 128.8, 128.7, 128.7, 128.6, 128.6, 128.5, 127.8, 75.6, 69.3, 53.3, 33.6, 31.7, 26.2, 18.8, 18.3. ^{31}P NMR (162 MHz, $CDCl_3$) δ -10.12. UPLC-DAD-QTOF: $C_{30}H_{36}N_2O_2P$ $[M+H]^+$ calcd.: 486.2545, found: 486.2560.

6.3.2. Preparation of pronucleophiles

6.3.2.1. Synthesis of pyrrolidin-2,3-diones

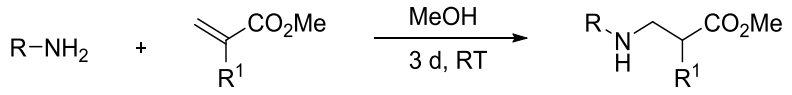
General procedure for the synthesis of 4-substituted pyrrolidin-2,3-diones:



6.3.2.1.1. *Addition of amines to acrylates: Synthesis of β-amino esters*

β-Amino esters were synthesized by the addition of the corresponding amine to the the corresponding α-substituted acrylate and these were prepared according to literature protocols.[235] In the case of less hindered amines mild reaction conditions were applied (METHOD A) in MeOH at room temperature without catalyst. However, the conjugate addition of hindered amines to substituted acrylates did not procceed under the above mentioned reaction conditions and this was successfully achieved by ruthenium activation. With ruthenium (III) chloride as catalyst and poly ethylene glycol as solvent (METHOD B), single addition products are obtained with very high yield.

6.3.2.1.1.1. *Method A*[236]



7

7F R: Me
7G R: Et

8a: R^1: Me

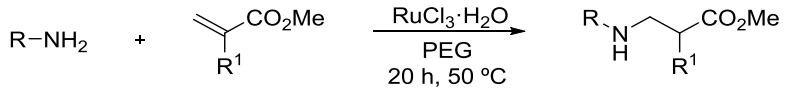
(±) 9

(±) 9Fa R: Me; R^1: Me
(±) 9Ga R: Et; R^1: Me

[235] J. E. Beddow, S. G. Davies, K. B. Ling, P. M. Roberts, A. J. Russell, A. D. Smith, J. E. Thomson, *Org. Biomol. Chem*. **2007**, *5*, 2812–2825.
[236] D. Howton, *J. Org. Chem* **1945**, 10, 4, 277-282.

To a solution of the amine (1 equiv.) in MeOH (0.2 mL/mmol), a solution of methyl methacrylate (1.5 equiv.) in MeOH (0.15 mL/mmol) was added at 0 ºC. The mixture was stirred at room temperature for 3 days. After completion of the reaction, methanol was evaporated and the crude product was purified by flash column chromatography on silica gel.

6.3.2.1.1.2. *Method B*[237]



7A-H **8a-c** **(±) 9**

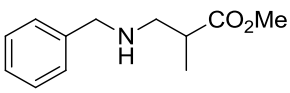
A R: Bn
B R: 1-Napht-CH_2
C R: ^{i}Pr
D R: PMP
E R: 3,4-DMB
H R: Cy

a R^1: Me
b R^1: Bn
c R^1: Ph

(±) **9Aa** R: Bn, R^1: Me
(±) **9Ab** R: Bn, R^1: Bn
(±) **9Ac** R: Bn, R^1: Ph
(±) **9Ba** R: 1-Napht-CH_2, R^1: Me
(±) **9Bb** R: 1-Napht-CH_2, R^1: Bn
(±) **9Bc** R: 1-Napht-CH_2, R^1: Ph
(±) **9Ca** R: ^{i}Pr, R^1: Me
(±) **9Da** R: PMP; R^1: Me
(±) **9Ea** R: 3,4-DMB, R^1: Me
(±) **9Ha** R: Cy, R^1: Me

$RuCl_3 \cdot H_2O$ (0.022 g, 0.1 mmol, 0.5 mol%) was added to a mixture of PEG (average MW 2000, 8 g), the amine (20 mmol, 1 equiv.) and methyl acrylate (20 mmol, 1 equiv.). The reaction mixture was kept at 50 °C for 16 h by magnetic stirring and then cooled to room temperature. The mixture was poured into Et_2O (40 mL) and then it was kept cooling in a refrigerator for 30 min to aid precipitation. The precipitate was filtered and washed with further portions of Et_2O, and the washings were combined with the initial filtrate. The combined organic phases were washed several times with H_2O and dried ($MgSO_4$). After filtration and removal of the solvent, the product was purified by flash column chromatography.

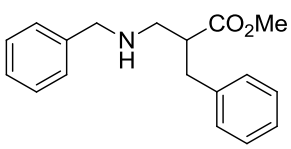
(±) Methyl 3-(benzylamino)-2-methylpropanoate 9Aa[238]



Prepared according to METHOD B starting from benzylamine **7A** (2.18 mL, 20 mmol) and methyl methacrylate **8a** (2.13 mL, 20 mmol). The title compound was purified by flash column chromatography (hexane/EtOAc, 80:20) and isolated as a yellow oil. Yield: 80% (3.32 g, 16.0 mmol). All the spectroscopic data were coincident with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 3H), 7.27 – 7.19 (m, 2H), 3.79 (s, 2H), 3.69 (s, 3H), 2.88 (td, *J* = 9.9, 3.6 Hz, 1H), 2.75 – 2.61 (m, 2H), 1.17 (d, *J* = 6.9 Hz, 3H).

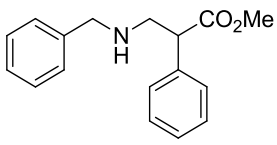
[237] H. Zhang, Y. Zhang, L. Liu, H. Xu, Y. Wang, *Synthesis* **2005**, *13*, 2129-2136.
[238] J. Escalante, M. Carrillo-Morales, I. Linzaga, *Molecules* **2008**, *13*, 340–347.

(±) Methyl 2-benzyl-3-(benzylamino)propanoate 9Ab[239]



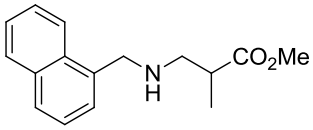
Prepared according to METHOD B starting from benzylamine **7A** (2.18 mL, 20 mmol) and methyl 2-benzylacrylate **8b** (3.52 g, 20 mmol). The title compound was purified by flash column chromatography (hexane/EtOAc, 80:20) and isolated as a yellow oil. Yield: 61% (3.46 g, 12.2 mmol). All the spectroscopic data were coincident with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.16 (m, 10H), 3.90 – 3.82 (m, 2H), 3.67 (s, 3H), 3.29 (dd, *J* = 12.0, 8.6 Hz, 4H), 2.93 (dd, *J* = 12.0, 6.5 Hz, 1H.

(±) Methyl 3-(benzylamino)-2-phenylpropanoate 9Ac[240]



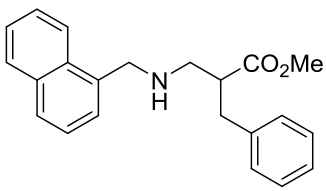
Prepared according to METHOD B starting from benzylamine **7A** (2.18 mL, 20 mmol) and methyl 2-phenylacrylate **8c** (3.244 g, 20 mmol). The title compound was purified by flash column chromatography (hexane/EtOAc, 80:20) and isolated as a yellow oil. Yield: 65% (3.501 g, 13.0 mmol). All the spectroscopic data were coincident with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.16 (m, 10H), 3.90 – 3.82 (m, 1H), 3.81 (s, 2H), 3.67 (s, 3H), 3.29 (dd, *J* = 12.0, 8.6 Hz, 1H), 2.93 (dd, *J* = 12.0, 6.5 Hz, 1H).

(±) Methyl 2-methyl-3-((naphthalen-1-ylmethyl)amino)propanoate 9Ba



Prepared according to METHOD B starting from 1-naphthylmethylamine **7B** (2.93 mL, 20 mmol) and methyl methacrylate **8a** (2.13 mL, 20 mmol). The title compound was purified by flash column chromatography (hexane/EtOAc, 80:20) and isolated as a yellow oil. Yield: 58% (2.98 g, 11.6 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 – 8.11 (m, 1H), 7.89 – 7.82 (m, 1H), 7.80 – 7.73 (m, 1H), 7.56 – 7.37 (m, 4H), 4.24 (s, 2H), 3.66 (s, 3H), 3.01 (dd, *J* = 11.6, 8.0 Hz, 1H), 2.85 – 2.63 (m, 3H), 1.19 (d, *J* = 6.9 Hz, 3H).

(±) Methyl 3-((naphthalen-1-yl)methylamino)-2-benzylpropanoate 9Bb

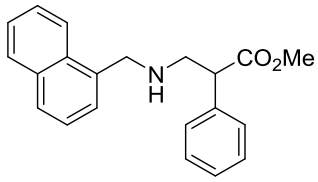


Prepared according to METHOD B starting from 1-naphtylmethylamine **7B** (2.2 g, 14 mmol, 1 eq) and methyl 2-benzylacrylate **8b** (3.5 g, 20 mmol, 1 eq.) The title compound was purified by flash column chromatography

[239] H. E. Bartrum, H. Adams, L. Caggiano, R. F. W. Jackson, *Tetrahedron* **2008**, *64*, 3701–3712.
[240] H. Rangel, M. Carrillo-Morales, J. M. Galindo, E. Castillo, A. Obregón-Zúñiga, E. Juaristi, J. Escalante, *Tetrahedron: Asymmetry* **2015**, *26*, 325–332.

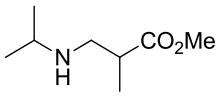
(hexane/EtOAc, 80:20) and isolated as a yellow oil. Yield: 68% (1.5 g, 13.5 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 – 8.06 (m, 1H), 7.92 – 7.81 (m, 1H), 7.77 (dd, *J* = 8.6, 3.8 Hz, 1H), 7.58 – 7.44 (m, 2H), 7.42 – 7.38 (m, 2H), 7.31 – 7.19 (m, 3H), 7.17 – 7.10 (m, 2H), 4.29 – 4.05 (m, 2H), 3.60 (s, 3H), 3.06 – 2.75 (m, 5H).

(±) Methyl 3-((naphthalen-1-ylmethyl)amino)-2-phenylpropanoate 9Bc



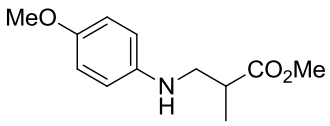
Prepared according to METHOD B starting from 1-naphthylmethylamine **7B** (3.34 mL, 20 mmol) and methyl 2-phenylacrylate **8c** (3.4 g mL, 20 mmol). Purified by column chromatography (hexane/EtOAc, 80:20) and isolated as yellow oil. Yield: 70% (4.45 g, 14 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, *J* = 9.7 Hz, 1H), 7.87 (d, *J* = 5.4 Hz, 1H), 7.77 (d, *J* = 7.2 Hz, 1H), 7.53 – 7.47 (m, 2H), 7.45 – 7.40 (m, 2H), 7.37 – 7.24 (m, 5H), 4.33 – 4.18 (m, 2H), 3.95 – 3.84 (m, 1H), 3.66 (s, 3H), 3.43 (dd, *J* = 12.0, 8.7 Hz, 1H), 3.07 (dd, *J* = 12.0, 6.5 Hz, 1H).

(±) Methyl 3-(isopropylamino)-2-methylpropanoate 9Ca[241]



Prepared according to METHOD B starting from isopropylamine **7C** (1.72 mL, 20 mmol) and methyl methacrylate **8a** (2.13 mL, 20 mmol). The title compound was isolated as a yellow oil. Yield: 76% (2.420 g, 15.2 mmol). All the spectroscopic data were coincident with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.69 (s, 3H), 2.91 – 2.82 (m, 1H), 2.82 – 2.72 (m, 1H), 2.68 – 2.55 (m, 2H), 1.17 (d, *J* = 6.7 Hz, 3H), 1.03 (dd, *J* = 6.2, 1.1 Hz, 6H).

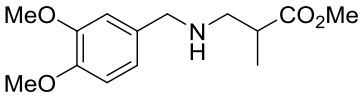
(±) Methyl 3-((4-methoxyphenyl)amino)-2-methylpropanoate 9Da



Prepared according to METHOD B starting from *p*-anisidine (2.46 g, 20 mmol) **7D** and methyl methacrylate **9a** (2.13 mL, 20 mmol). The title compound was purified by flash column chromatography (hexane/EtOAc, 80:20) and isolated as a yellow oil (2.68 g, 12.0 mmol, 60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 – 6.72 (m, 2H), 6.62 – 6.49 (m, 2H), 3.74 (s, 3H), 3.69 (s, 3H), 3.37 (dd, *J* = 12.9, 7.9 Hz, 1H), 3.17 (dd, *J* = 12.9, 5.4 Hz, 1H), 2.86 – 2.72 (m, 1H), 1.23 (d, *J* = 7.1 Hz, 3H).

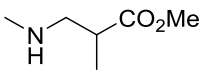
[241] See ref 237

(±) Methyl 3-((3,4-dimethoxybenzyl)amino)-2-methylpropanoate 9Ea[242]



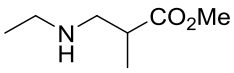
Prepared according to METHOD B starting from veratrylamine **7E** (3.01 mL, 20 mmol) and methyl methacrylate **8a** (2.13 mL, 20 mmol). Purified by column chromatography (hexane/EtOAc, 50:50) and isolated as yellow oil. Yield: 70% (3.74 g, 14 mmol). All the spectroscopic data were coincident with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (m, 1H), 6.82 (m, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.73 (s, 2H), 3.68 (s, 3H), 2.96 – 2.81 (m, 1H), 2.77 – 2.57 (m, 2H), 1.16 (d, *J* = 6.9 Hz, 3H).

(±) Methyl 2-methyl-3-(methylamino)propanoate 9Fa[243]



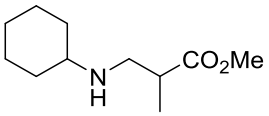
Prepared according to METHOD A starting from 33% methylamine **7F** in EtOH (2.5 mL, 20 mmol) and methyl methacrylate **8a** (3.2 mL, 30 mmol). The title compound was purified by flash column chromatography (hexane/EtOAc, 90:10) and isolated as yellow oil. Yield: 75% (1.95 g, 15 mmol). All the spectroscopic data were coincident with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (s, 3H), 2.92 – 2.74 (m, 1H), 2.72 – 2.52 (m, 2H), 2.40 (s, 3H), 1.15 (d, *J* = 6.9 Hz, 3H).

(±) Methyl 3-(ethylamino)-2-methylpropanoate 9Ga[244]



Prepared according to METHOD A starting from 70% ethylamine in water **7G** (1.89 mL, 20 mmol) and methyl methacrylate **8a** (3.2 mL, 30 mmol). The title compound was purified by flash column chromatography (hexane/EtOAc, 90:10) and isolated as yellow oil. Yield: 80% (2.3 g, 15.8 mmol). All the spectroscopic data were coincident with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (s, 3H), 2.90 – 2.76 (m, 1H), 2.69 – 2.53 (m, 4H), 1.15 (d, *J* = 6.9 Hz, 3H), 1.07 (t, *J* = 7.1 Hz, 3H).

(±) Methyl 3-(cyclohexylamino)-2-methylpropanoate 9Ha[245]

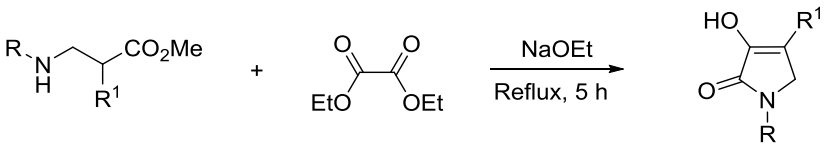


Prepared according to METHOD B starting from cyclohexylamine **7H** (2.28 mL, 20 mmol) and methyl methacrylate **8a** (2.13 mL, 20 mmol). The title compound was purified by flash column chromatography (hexane/EtOAc, 90:10) and isolated as yellow oil. Yield: 65% (2.56 g, 13 mmol). All the spectroscopic data were coincident with those previously reported. ^{1}H

[242] P. Steunenberg, M. Sijm, H. Zuilhof, J. P. M. Sanders, E. L. Scott, M. C. R. Franssen, *J. Org. Chem.* **2013**, 78, 3802-3813.
[243] O. I. Lukashov, P. V. Kazakov, N. S. Mirzabekova, *Pharmaceut. Chem. J.* **2015**, 49, 51-54.
[244] Y. Guindon, Z. Liu, Z. Jung, *J. Am. Chem. Soc.* **1997**, 119, 9289-9290.
[245] J. Včelák, J. Čermák, M. Czakóová, J. Storch, *J. Mol. Catal. A-Chem.* **2006**, 259, 41-45.

NMR (300 MHz, $CDCl_3$) δ 3.68 (s, 3H), 2.96 – 2.80 (m, 1H), 2.78 – 2.54 (m, 2H), 2.45 – 2.29 (m, 1H), 1.90 – 1.76 (m, 3H), 1.74 – 1.64 (m, 3H), 1.64 – 1.54 (m, 2H), 1.45 – 1.34 (m, 2H), 1.15 (d, *J* = 6.8 Hz, 3H).

6.3.2.1.2. *Cyclization and in situ decaboxilation*

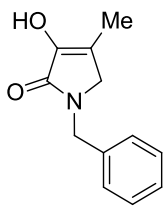


(±) **9Aa** R: Bn, R^1: Me
(±) **9Ab** R: Bn, R^1: Bn
(±) **9Ac** R: Bn, R^1: Ph
(±) **9Ba** R: 1-Napht-CH_2, R^1: Me
(±) **9Bb** R: 1-Napht-CH_2, R^1: Bn
(±) **9Bc** R: 1-Napht-CH_2, R^1: Ph
(±) **9Ca** R: ^{i}Pr, R^1: Me
(±) **9Da** R: PMP; R^1: Me
(±) **9Ea** R: 3,4-DMB, R^1: Me
(±) **9Fa** R: Me, R^1: Me
(±) **9Ga** R: Et, R^1: Me
(±) **9Ha** R: Cy, R^1: Me

10Aa R: Bn, R^1: Me
10Ab R: Bn, R^1: Bn
10Ac R: Bn, R^1: Ph
10Ba R: 1-Napht-CH_2, R^1: Me
10Bb R: 1-Napht-CH_2, R^1: Bn
10Bc R: 1-Napht-CH_2, R^1: Ph
10Ca R: ^{i}Pr, R^1: Me
10Da R: PMP; R^1: Me
10Ea R: 3,4-DMB, R^1: Me
10Fa R: Me, R^1: Me
10Ga R: Et, R^1: Me
10Ha R: Cy, R^1: Me

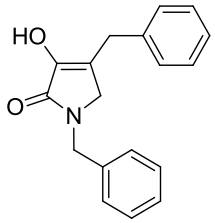
To a solution of the corresponding β-amino ester **9** (10 mmol, 1 equiv.) and ethyl oxalate (1.6 mL, 12 mmol, 1.2 equiv.), sodium ethoxide (817 mg, 12 mmol, 1.3 equiv.) was added. The mixture was heated under reflux for 5 h (except for **10Fa** and **10Ga**) and ethanol was removed by distillation leaving a liquid residue which was dissolved in a 50 mL of warm water. Acidification with 3M HCl precipitated a solid and the resulting decarboxilated product was collected by filtration and then purified. The ^{1}H-NMR spectra of the obtained products in $CDCl_3$ showed that they were essentially in their enolic form.

1-Benzyl-3-hydroxy-4-methyl-1*H*-pyrrol-2(5*H*)-one 10Aa



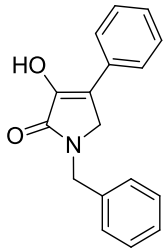
Prepared according to the general procedure starting from methyl 3-(benzylamino)-2-methylpropanoate **9Aa** (2.073 g, 10 mmol) and purified by flash silica column chromatography (hexane/EtOAc, 80:20). The title compound was isolated as a white solid. Yield: 86% (2.75 g, 8.6 mmol). m.p. = 140–144 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 – 7.06 (m, 5H), 6.48 (s, 1H), 4.62 (s, 2H), 3.57 (s, 2H), 1.87 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 142.0, 137.0, 128.9, 128.2, 127.8, 118.2, 50.7, 46.9, 10.3. UPLC-DAD-QTOF: $C_{12}H_{14}NO_2$ $[M+H]^+$ calcd.: 204.1025, found: 204.1023.

1,4-Dibenzyl-3-hydroxy-1*H*-pyrrol-2(5*H*)-one 10Ab



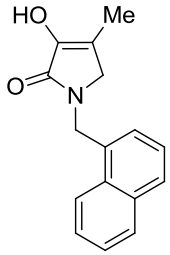
Prepared according to the general procedure starting from methyl 2-benzyl-3-(benzylamino)propanoate **9Ab** (2.79 g, 10 mmol) and purified by flash silica column chromatography (hexane/EtOAc, 1:1). The title compound was isolated as a yellow solid. Yield: 93% (2.60 g, 9.32 mmol). m.p. = 149–151 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.11 (m, 10H), 4.59 (s, 2H), 3.66 (s, 2H), 3.51 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 142.1, 138.9, 136.9, 129.0, 128.9, 128.8, 128.2, 127.9, 126.7, 120.8, 49.1, 47.0, 31.6. UPLC-DAD-QTOF: $C_{18}H_{18}NO_2$ [M+H]+ calcd.: 280.1338, found: 280.1335.

1-Benzyl-3-hydroxy-4-phenyl-1*H*-pyrrol-2(5*H*)-one 10Ac



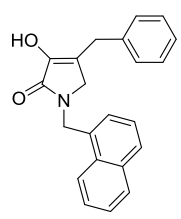
Prepared according to the general procedure starting from methyl 3-(benzylamino)-2-phenylpropanoate **9Ac** (2.693 g, 10 mmol) and purified by flash silica column chromatography (hexane/EtOAc, 1:1). The title compound was isolated as a white solid. Yield: 92% (2.43 g, 9.2 mmol). m.p. = 240–244 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.79 – 7.47 (m, 2H), 7.41 – 7.01 (m, 8H), 4.63 (s, 2H), 4.12 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.7, 143.2, 137.5, 132.7, 128.7, 128.5, 127.6, 127.4, 127.1, 125.7, 116.6, 47.1, 45.8. UPLC-DAD-QTOF: $C_{28}H_{36}NO_5$ $[M+H]^+$ calcd.: 266.1181, found: 266.1173.

3-Hydroxy-4-methyl-1-(naphthalen-1-ylmethyl)-1*H*-pyrrol-2(5*H*)-one 10Ba



Prepared according to the general procedure starting from methyl 2-methyl-3-((naphthalen-1-ylmethyl)amino)propanoate **9Ba** (2.573 g, 10 mmol) and purified by flash silica column chromatography (hexane/EtOAc, 80:20). The title compound was isolated as a white solid. Yield: 65% (1.65 g, 6.5 mmol). m.p. = 158–161 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 – 8.09 (m, 1H), 7.92 – 7.79 (m, 2H), 7.60 – 7.35 (m, 4H), 6.73 (s, 1H), 5.07 (s, 2H), 3.45 (s, 2H), 1.82 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 141.8, 134.1, 132.3, 131.6, 129.1, 128.8, 127.5, 127.1, 126.3, 125.4, 123.9, 118.2, 50.7, 45.1, 10.3. UPLC-DAD-QTOF: $C_{16}H_{16}NO_2$ [M+H]+ calcd.: 254.1181, found: 254.1181.

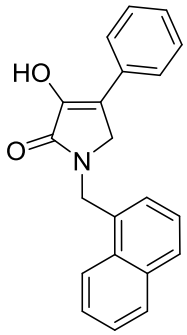
4-Benzyl-3-hydroxy-1-((naphthalen-1-yl)methyl)-1H-pyrrol-2(5*H*)-one 10Bb



Prepared according to the general procedure starting from methyl 3-((naphthalen-1-yl)methylamino)-2-benzylpropanoate **9Bb** (2.7 g, 8 mmol) and purified by flash silica column chromatography (hexane/EtOAc, 1:1). The title compound was isolated as a white solid. Yield: 70% (1.8 g, 5.6 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.85 (m, *J* = 15.4, 8.5, 5.8 Hz, 2H), 7.62 – 7.46 (m, 3H), 7.45 – 7.29

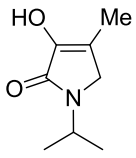
(m, 3H), 7.16 – 7.08 (m, 2H), 5.02 (s, 2H), 3.58 (s, 2H), 3.41 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 141.9, 138.7, 133.7, 132.1, 131.5, 129.1, 128.7, 128.7, 127.3, 127.0, 126.5, 126.2, 125.3, 123.7, 120.7, 49.0, 45.1, 31.2. UPLC-DAD-QTOF: $C_{12}H_{14}NO_3$ $[M+H]^+$ calcd.: 330.1494, found: 330.1495. m.p. = 178–180 ºC.

3-Hydroxy-1-(naphthalen-1-ylmethyl)-4-phenyl-1,5-dihydro-2H-pyrrol-2-one 10Bc



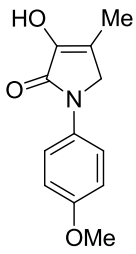
Prepared according to the general procedure starting from methyl 3-((naphthalen-1-ylmethyl)amino)-2-phenylpropanoate **9Bc** (3.19 g, 10 mmol) and purified by flash silica column chromatography (hexane/EtOAc, 70:30). The title compound was isolated as an orange solid. Yield: 55% (1.73 g, 5.5 mmol). T_{dec} = 168–170ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, *J* = 7.9 Hz, 1H), 7.86 (t, *J* = 7.7 Hz, 2H), 7.63 – 7.50 (m, 4H), 7.49 – 7.37 (m, 2H), 7.30 (d, *J* = 7.7 Hz, 2H), 7.22 (d, *J* = 7.2 Hz, 1H), 5.14 (s, 2H), 3.91 (s, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ 202.9 , 160.6 , 134.9 , 132.8 , 132.4 , 130.1 , 129.7 , 129.6 , 128.4 , 128.1 , 127.3 , 127.1 , 126.3 , 124.6 , 49.0 , 46.2 , 30.8 . UPLC-DAD-QTOF: $C_{21}H_{18}NO_2$ $[M+H]^+$ calcd.: 316.1338, found: 316.1340.

3-Hydroxy-1-isopropyl-4-methyl-1*H*-pyrrol-2(5*H*)-one 10Ca



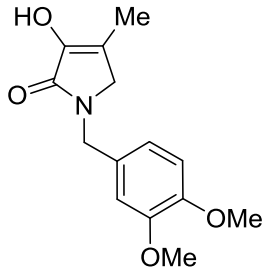
Prepared according to the general procedure starting from methyl 3-(isopropylamino)-2-methylpropanoate **9Ca** (1.59 g, 10 mmol) purified by flash silica column chromatography (hexane/EtOAc, 80:20). The title compound was isolated as a yellow solid. Yield: 71% (1.11 g, 7.13 mmol). m.p. = 138–140 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.39 (hept, *J* = 6.8 Hz, 1H), 3.61 (s, 2H), 1.89 (s, 3H), 1.16 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 142.2, 117.2, 46.4, 43.3, 21.0, 10.3. UPLC-DAD-QTOF: $C_8H_{14}NO_2$ $[M+H]^+$ calcd.: 156.1025, found: 156.1011.

3-Hydroxy-1-(4-methoxyphenyl)-4-methyl-1*H*-pyrrol-2(5*H*)-one 10Da



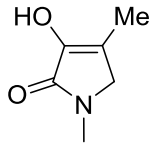
Prepared according to the general procedure starting from methyl 3-((4-methoxyphenyl)amino)-2-methylpropanoate **9Da** (2.233 g, 10 mmol) and purified by flash silica column chromatography (hexane/EtOAc, 1:1). The title compound was isolated as a yellow solid. Yield: 71% (1.55 g, 7.1 mmol). m.p. = 173–175 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 – 7.49 (m, 2H), 6.93 – 6.82 (m, 2H), 6.32 (s, 1H), 4.08 (s, 2H), 3.77 (s, 3H), 1.96 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 156.7, 141.8, 132.6, 120.5, 116.2, 114.6, 55.7, 51.9, 10.4. UPLC-DAD-QTOF: $C_{12}H_{14}NO_3$ $[M+H]^+$ calcd.: 220.0974, found: 220.0973.

1-(3,4-Dimethoxybenzyl)-3-hydroxy-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one 10Ea



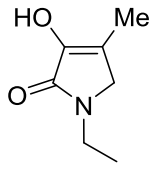
Prepared according to the general procedure starting from methyl 3-((3,4-dimethoxybenzyl)amino)-2-methylpropanoate **9Ea** (2.67 g, 10 mmol) and purified by flash silica column chromatography (hexane/EtOAc, 70:30). The title compound was isolated as a white solid. Yield: 70% (1.8 g, 7 mmol). m.p. 115–117 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76 (m, 3H), 4.52 (s, 2H), 3.84 (s, 6H), 3.54 (s, 2H), 1.85 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.05 , 149.21 , 148.54 , 141.73 , 129.32 , 120.40 , 117.86 , 111.26 , 110.99 , 55.83 , 50.30 , 46.43 , 10.05. UPLC-DAD-QTOF: $C_{14}H_{18}NO_4$ $[M+Na]^+$ calcd.: 264.1236, found: 264.1229.

3-Hydroxy-1,4-dimethyl-1,5-dihydro-2*H*-pyrrol-2-one 10Fa



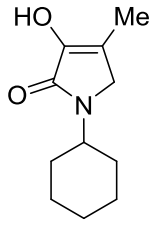
Prepared according to the general procedure starting from methyl 2-methyl-3-(methylamino)propanoate **9Fa** (1.31 g, 10 mmol) performing the addition in an ice bath and stirring at room temperature, and purified by flash silica column chromatography (EtOAc). The title compound was isolated as yellow solid. Yield: 70% (1.27 g, 7 mmol) m.p. 140–142 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65 (s, 2H), 3.00 (s, 3H), 1.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5 , 142.0 , 118.0 , 53.2 , 29.8 , 10.1 . UPLC-DAD-QTOF: $C_6H_{10}NO_2$ $[M+H]^+$ calcd.: 128.0712, found: 128.0716.

1-Ethyl-3-hydroxy-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one 10Ga



Prepared according to the general procedure starting from methyl 3-(ethylamino)-2-methylpropanoate **9Ea** (1.45 g, 10 mmol) performing the addition in an ice bath and stirring at room temperature, and purified after crushing with diethyl ether. The title compound was isolated as a white solid. Yield: 85% (1.19 g, 8.5 mmol). m.p. 144–147 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.66 (s, 2H), 3.46 (q, *J* = 7.3 Hz, 2H), 1.89 (s, 2H), 1.15 (t, *J* = 7.3 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0 , 142.1 , 117.5 , 50.4 , 37.5 , 13.7 , 10.2 . UPLC-DAD-QTOF: $C_7H_{12}NO_2$ $[M+H]^+$ calcd.: 142.0868, found: 142.0871.

1-Cyclohexyl-3-hydroxy-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one 10Ha

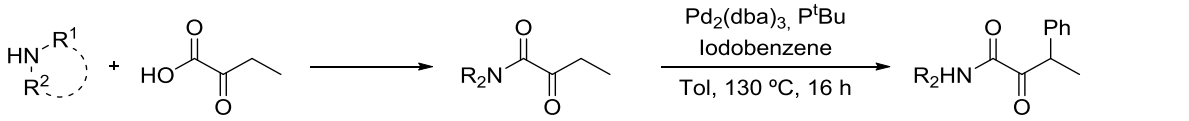


Prepared according to the general procedure starting from methyl 3-(cyclohexylamino)-2-methylpropanoate **9Ha** (1.99 g, 10 mmol) and purified by flash silica column chromatography (hexane/EtOAc, 80:20). The title compound was isolated as a white solid. Yield: 76% (1.48 g, 7.6 mmol). m.p. 167–169 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05 – 3.92 (m,

1H), 3.63 (s, 2H), 1.90 (s, 3H), 1.85 – 1.64 (m, 5H), 1.43 – 1.24 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.0 , 51.1 , 47.3 , 31.6 , 25.6 , 10.3 .UPLC-DAD-QTOF: $C_{11}H_{18}NO_2$ $[M+H]^+$ calcd.: 196.1338, found: 196.1340.

6.3.2.2. Synthesis of acyclic ketoamides

6.3.2.2.1. *Method A*



30A	R^1, R^2: Bn	**31A**	R^1, R^2: Bn	**(±) 32A**	R^1, R^2: Bn
30B	R^1, R^2: Et	**31B**	R^1, R^2: Et	**(±) 32B**	R^1, R^2: Et
30C	R^1, R^2: ^{i}Bu	**31C**	R^1, R^2: ^{i}Bu	**(±) 32C**	R^1, R^2: ^{i}Bu
30D	R^1, R^2: 1-Napht-CH_2	**31D**	R^1, R^2: 1-Napht-CH_2	**(±) 32D**	R^1, R^2: 1-Napht-CH_2
30E	R^1, R^2: $-(CH_2)_5-$	**31E**	R^1, R^2: $-(CH_2)_5-$	**(±) 32E**	R^1, R^2: $-(CH_2)_5-$
30F	R^1, R^2: $-(CH_2)_2-O-(CH_2)_2-$	**31F**	R^1, R^2: $-(CH_2)_2-O-(CH_2)_2-$	**(±) 32F**	R^1, R^2: $-(CH_2)_2-O-(CH_2)_2-$
30G	R^1: OMe, R^2: Me	**31G**	R^1: OMe, R^2: Me	**(±) 32G**	R^1: OMe, R^2: Me
30H	R^1: Ph, R^2: Me	**31H**	R^1: Ph, R^2: Me	**(±) 32H**	R^1: Ph, R^2: Me

1st step: Amide bond formation **31A-31H**

Method A1[246]: To a solution of 2-oxobutyric acid (598 mg, 5.85 mmol, 1 equiv.) in CH_2Cl_2 (50 mL), the corresponding amine (6.43 mmol, 1.1 equiv.) was added followed by DIPEA (4.07 mL, 23.4 mmol, 4 equiv.) and TBTU (2.06 g, 6.43 mmol, 1.1 equiv.). The reaction mixture was stirred at room temperature for 16 h. Then, TBTU (0.47 g, 1.46 mmol, 0.25 equiv.) was added and the mixture was stirred for 3 h, and then washed with HCl 3M (2 x 100 mL). The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by flash column chromatography.

Method A2[247]**:** To a solution of 2-oxobutyric acid (510 mg, 5 mmol, 1 equiv.) in CH_3CN (13 mL), *N,O*-dimethylhydroxylamine hydrochloride (7.5 mmol, 1.5 equiv.) was added followed by EDCI hydrochloride (1.24 g, 6.5 mmol, 1.3 equiv.) at room temperature. The mixture was cooled to 0 °C and Et_3N (1.04 mL, 7.5 mmol, 1.5 equiv.) was added dropwise. After addition, the mixture was stirred at room temperature for 16 h. The solvent was evaporated and the residue was redissolved in CH_2Cl_2 (15 mL) and

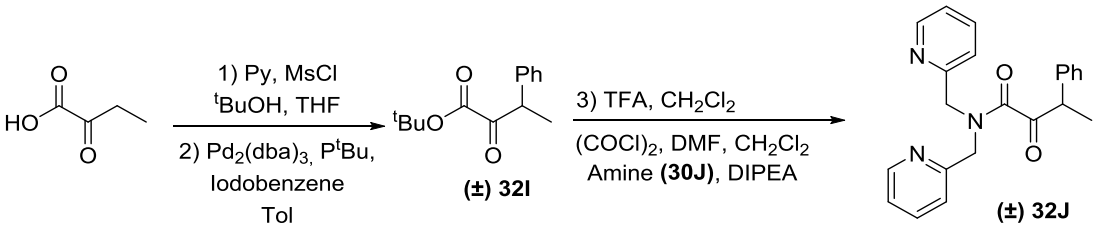
[246] M. R. Davis, E. K. Singh, H. Wahyudi, L. D. Alexander, J. B. Kunicki, L. A. Nazarova, K. A. Fairweather, A. M. Giltrap, K. A. Jolliffe, S. R. McAlpine, *Tetrahedron* **2012**, *68*, 1029-1051
[247] M.-M. Zhao, W.F. Li, X. Ma, W. Z. Fan, X. M. Tao, X. M. Li, X. M. Xie, Z.G. Zhang, *Sci. China. Chem.* **2013**, *56*, 342-348.

washed with brine (1 x 10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was purified by flash column chromatography.

2nd step: α-Arilation of ketoamides **32A-32H**[248]

A flame-dried sealing tube was cooled under a steam of Ar and charged with $Pd(dba)_3$ (0.04 mmol, 0.02 equiv.) and tri-*tert*-butylphosphonium tetrafluoroborate (0.08 mmol, 0.08 equiv.). Dry toluene (5 mL) was added followed by K_2CO_3 (3 mmol, 3 equiv.). The mixture stirred at room temperature for 2 h. The corresponding ketoamide (1 mmol, 1 equiv.) and benzyl iodide (2 mmol, 2 equiv.) were added and stirred at 130 ºC for 16 h. The reaction was quenched with NH_4Cl (sat) and extracted with dichloromethane. The organic phase was dried over $MgSO_4$ and evaporated in *vacuo* to afford the crude which was purified by flash column chromatography.

6.3.2.2.2. *Method B*[249]



1st step: 2-Oxobutanoic acid (1.02 g, 10 mmol, 1 equiv.), *tert*-butyl alcohol (1.9 mL, 20 mmol, 2 equiv.) and pyridine (2 mL, 25 mmol, 2.5 equiv.) were dissolved in dry THF (10 mL) at 0 °C. Mesyl chloride (0.93 mL, 12 mmol, 1.2 equiv.) was then added dropwise, and the reaction was warmed to room temperature and stirred for 16 h. The reaction was quenched with water (20 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo. The crude was used in the next step without further purification. All spectroscopic data were coincident with those previously described. Yellow oil. Yield: 75% (1.18 g, 7.5 mmol). ^1H NMR (300 MHz, $CDCl_3$) δ 2.79 (q, J = 7.2 Hz, 2H), 1.54 (s, 9H), 1.10 (t, J = 7.2 Hz, 3H).

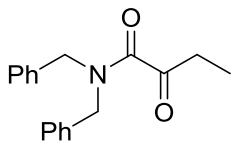
2nd step: A flame-dried sealing tube was cooled under a steam of Ar and charged with $Pd_2(dba)_3$ (25 mg, 0.02 mmol, 0.02 equiv.) and tri-*tert*-butylphosphonium

[248] B. P. Zavesky, S. L. Bartlett, J. S. Johnson, *Org. Lett.* **2017**, *19*, 2126-2129.
[249] For ketoester synthesis: D. Becerra, W. Raimondi, T. Constantieux, D. Bonne, J. Rodriguez, *Synthesis* **2017**, *49*, 195-201.

tetrafluoroborate (23 mg, 0.08 mmol, 0.08 equiv.). Dry toluene (5 mL) was added followed by K_2CO_3 (415 mg, 6 mmol, 3 equiv.) and the mixture stirred at room temperature for 2 h. Then, *tert*-butyl 2-oxo-3-phenylbutanoate (1 mmol, 1 equiv.) and benzyl iodide (0.16 mL, 1.5 mmol, 1.5 equiv.) were added and the mixture stirred at 110 ºC for 16 h. The reaction was quenched with NH_4Cl (sat) and extracted with dichloromethane (3 x 10 mL). The organic phase was dried over $MgSO_4$ and evaporated *in vacuo* to afford crude **32I**. The title compound was purified by flash column chromatography (hexane/EtOAc, 95:5) and isolated as a colourless oil. Yield: 67% (238 mg, 0.67 mmol). All the spectroscopic data were coincident with those previously reported.[250] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.09 (m, 5H), 4.34 (q, J = 7.0 Hz, 1H), 1.45 (d, J = 7.0 Hz, 3H), 1.33 (s, 9H).

3rd step: To a solution of **32I** (234 mg, 1 mmol, 1 equiv.) in dry dichloromethane (1 mL), TFA (1 mL) was slowly added at room temperature and the mixture was stirred at the same temperature for 3 h until consumption of the starting material (followed by TLC). Then, the acid was co-evaporated with EtOAc until dryness and the crude was used in the next step without further purification. To a solution of the acid (178 mg, 1 mmol, 1 equiv.) in DCM (1 mL), a catalytic amount of DMF (1 drop) and oxalyl chloride (0.1 mL, 1.2 mmol, 1.2 equiv.) were added at 0 °C and it was stirred at room temperature until generation of gasses stopped (2 h). The mixture was cooled in an ice bath, amine **30J** and DIPEA (2 mmol, 2 equiv.) were added and the mixture was allowed to stir at room temperature for 4 h. Then the reaction was quenched by the addition of water (3 mL) and the organic materials were extracted with DCM (3 x 10 mL). The combined extracts were washed with brine (1 x 15 mL) and dried over $MgSO_4$. The crude material was purified by flash silica gel column chromatography to afford **32J** as a yellow oil.

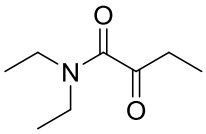
***N,N*-Dibenzyl-2-oxobutanamide 31A**[251]



Prepared according to General Method A1 starting from dibenzylamine **30A** (1.24 mL, 6.43 mmol). Purified by column chromatography (hexane/EtOAc, 90:10) to afford X as a white solid. Yield: 84% (1.38 g, 4.9 mmol). All the spectroscopic data were coincident with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 10H), 4.55 (s, 2H), 4.36 (s, 2H), 2.83 – 2.74 (m, 2H), 1.09 (t, *J* = 7.3 Hz, 3H).

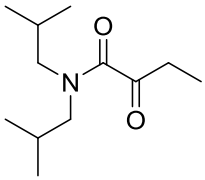
[250] S. L. Bartlett, K. M. Keiter, B. P. Zavesky, J. S. Johnson, *Synthesis* **2019**, *51*, 203-212.
[251] D. Tejedor, L. Cotos, F. García-Tellado *Org.Lett.* **2011**, 13, 4422-4425.

***N,N*-Diethyl-2-oxobutanamide 31B**[252]



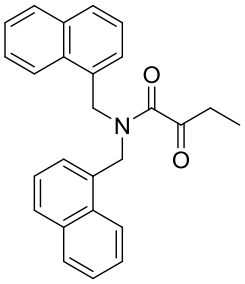
Prepared according to General Method A1 starting from diethylamine **30B** (0.66 mL, 6.43 mmol). Purified by flash column chromatography (hexane/EtOAc, 80:20) and isolated as a colourless oil. Yield: 92% (0.84 g, 5.36 mmol). All the spectroscopic data were coincident with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.22 (q, *J* = 7.2 Hz, 2H), 3.07 (q, *J* = 7.1 Hz, 2H), 2.59 (q, *J* = 7.3 Hz, 2H), 0.99 (q, *J* = 7.1 Hz, 6H), 0.93 (t, *J* = 7.3 Hz, 3H).

***N,N*-Diisobutyl-2-oxobutanamide 31C**



Prepared according to General Method A1 starting from diisobutylamine **30C** (1.12 mL, 6.43 mmol). Purified by flash column chromatography (hexane/EtOAc, 95:5) and isolated as a colourless oil. Yield: 98% (1.22 g, 5.73 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.20 (d, *J* = 7.6 Hz, 2H), 3.07 (d, *J* = 7.6 Hz, 2H), 2.76 (q, *J* = 7.3 Hz, 2H), 2.01 (d, *J* = 28.3 Hz, 1H), 1.85 (d, *J* = 27.6 Hz, 1H), 1.11 (t, *J* = 7.3 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 6H), 0.85 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (75 MHz, , $CDCl_3$) δ 202.0 , 168.3 , 54.7 , 51.5 , 33.6 , 27.2 , 26.3 , 20.2 , 19.9 , 7.2 . UPLC-DAD-QTOF: $C_{12}H_{24}NO2$ $[M+H]^+$ calcd.: 213.1785, found: 213.1701.

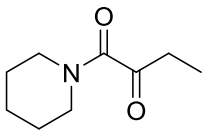
***N,N*-Bis(naphthalen-1-ylmethyl)-2-oxobutanamide 31D**



Prepared according to General Method A1 starting from bis(naphthalen-1-ylmethyl)amine[253] **30D** (2.49 g, 6.43 mmol). Purified by column chromatography (hexane/EtOAc, 90:10) and isolated as a white solid. Yield 77% (1.71 g, 4.5 mmol). m.p. = 118-180 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 – 7.98 (m, 1H), 7.93 – 7.86 (m, 2H), 7.83 (d, *J* = 8.3 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.55 – 7.46 (m, 4H), 7.43 – 7.36 (m, 2H), 7.35 – 7.30 (m, 1H), 7.17 (d, *J* = 7.0 Hz, 1H), 5.20 (s, 2H), 4.87 (s, 2H), 2.79 (q, *J* = 7.3 Hz, 2H), 1.01 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.9 , 168.2 , 133.4 , 129.1 , 129.0 , 127.9 , 127.7 , 127.1 , 126.7 , 126.5 , 126.5 , 126.3 , 125.4 , 50.2 , 47.4 , 33.7 , 7.0 . UPLC-DAD-QTOF: $C_{26}H_{24}NO_2$ $[M+H]^+$ calcd.: 382.1752, found: 383.1780.

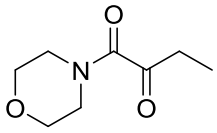
[252] R. Peters, M. Althaus, A.-L. Nagy *Org. Biomol. Chem.* **2006**, 4, 498–509.
[253] Prepared according to the described procedures: a) M. Lüthy, K. Schenk, P. Renaud *Chem. Eur. J.* **2010**, *16*, 10171-10177; b) X. Wang, B. List *Angew. Chem. Int. Ed*. **2008**, *47*, 1119-1122

1-(Piperidin-1-yl)butane-1,2-dione 31E[254]



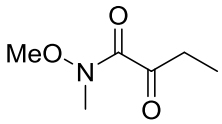
Prepared according to General Method A1 starting from piperidine **30E** (0.64 mL, 6.43 mmol). Purified by flash column chromatography (hexane/EtOAc, 80:20) and isolated as a colourless oil. Yield: 84% (0.83 g, 4.91 mmol). All the spectroscopic data were coincident with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.61 – 3.48 (m, 2H), 3.38 – 3.22 (m, 2H), 2.77 (q, *J* = 7.3 Hz, 2H), 1.73 – 1.49 (m, 6H), 1.13 (t, *J* = 7.3 Hz, 3H).

1-Morpholinobutane-1,2-dione 31F[255]



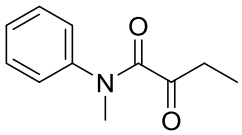
Prepared according to General Method A1 starting from morpholine **30F** (0.55 mL, 6.43 mmol). Purified by flash column chromatography (hexane/EtOAc, 80:20) and isolated as a colourless oil. Yield: 92% (0.84 g, 5.36 mmol). All the spectroscopic data were coincident with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.61 – 3.35 (m, 6H), 3.35 – 3.16 (m, 2H), 2.59 (q, *J* = 7.3 Hz, 2H), 0.91 (t, *J* = 7.3 Hz, 3H).

***N*-Methoxy-*N*-methyl-2-oxobutanamide 31G**



Prepared according to General Method A2 starting from *N*,*O*-dimethylhydroxylamine hydrochloride **30G** (731.5 mg, 7.5 mmol). Purified by flash column chromatography (hexane/EtOAc, 70:30) and isolated as a colourless oil. Yield: 60% (370 mg, 2.55 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.60 (s, 3H), 3.14 (s, 3H), 2.63 (q, *J* = 7.3 Hz, 2H), 1.06 (t, *J* = 7.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.2, 168.2 , 62.2 , 32.9 , 31.4 , 6.5 . UPLC-DAD-QTOF: $C_6H_{12}NO_3$ $[M+H]^+$ calcd.: 146.0817, found: 146.0820.

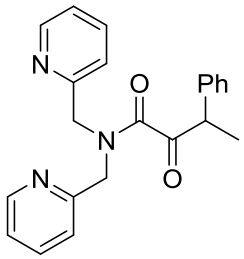
***N*-Methyl-2-oxo-*N*-phenylbutanamide 31H**[256]



Prepared according to General Method A2 starting from *N*-methylaniline (10.69 mL, 6.43 mmol) **30H**. Purified by flash column chromatography (hexane/EtOAc, 90:10) and isolated as a colourless oil. Yield: 85% (1.04 g, 5.46 mmol). All the spectroscopic data were coincident with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (m, 3H), 6.91 m, 2H), 3.02 (s, 1H), 2.28 (q, *J* = 7.3 Hz, 2H), 0.59 (t, *J* = 7.3 Hz, 3H).

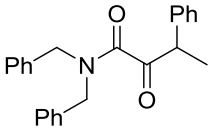
[254] R. Newton, S. P. Marsden *Synthesis* **2005**, 19, 3263–3270.
[255] P. Duhamel, L. Duhamel, J.L. Klein *Bulletin de la Societe Chimique de France* **1973**, 2, 2517-2521.
[256] M. Baode, T. Miao, Y. Sun, Y. He, J. Liu, Y. Feng, H. Chen, Q.-H. Fan *Chem. Eur. J.* **2014**, 20, 9969 – 9978.

(±) 2-Oxo-3-phenyl-*N*,*N*-bis(pyridin-2-ylmethyl)butanamide 32J



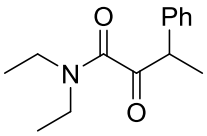
Prepared according to General Method B starting from di-(2-picolyl)amine **30J** (0.27 mL, 1.5 mmol, 1.5 equiv.). Purified by column chromatography (hexane/EtOAc, 1:1) to afford the pure amide as a yellow oil. Yield: 71% (254 mg, 0.71 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (m, 1H), 7.56 (m, 1H), 7.44 (m, 1H), 7.29 – 7.20 (m, 6H), 7.10 (m, 3H), 6.62 (d, *J* = 7.8 Hz, 1H), 4.86 (d, *J* = 15.4 Hz, 1H), 4.65 (q, *J* = 7.0 Hz, 1H), 4.43 (d, *J* = 16.5 Hz, 1H), 4.29 (d, *J* = 15.4 Hz, 1H), 4.16 (d, *J* = 16.4 Hz, 1H), 1.48 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.8 , 167.5 , 155.7 , 149.3 , 136.8 , 136.7 , 129.1 , 128.8 , 128.6 , 128.3 , 127.7 , 127.1 , 122.5 , 122.3 , 121.5 , 52.6 , 49.9 , 48.9 . UPLC-DAD-QTOF: $C_{22}H_{22}N_3O_2$ $[M+H]^+$ calcd.: 360.1674, found: 360.1684.

(±) *N*,*N*-Dibenzyl-2-oxo-3-phenylbutanamide 32A



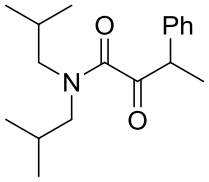
Prepared according to the General Procedure A starting from *N*,*N*-dibenzyl-2-oxobutanamide **31A** (357 mg, 1 mmol). Purified by column chromatography (hexane/EtOAc, 95:5) to afford **32A** as a colourless oil. Yield: 70% (250 mg, 0.7 mmol). m.p. = 78-81 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 – 7.17 (m, 11H), 7.08 (m, 2H), 6.82 (m, 2H), 4.77 (m, 2H), 4.20 (d, *J* = 15.4 Hz, 1H), 3.98 (d, *J* = 14.9 Hz, 1H), 3.71 (d, *J* = 15.4 Hz, 1H), 1.58 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.7 , 167.2 , 136.9 , 135.3 , 134.9 , 130.0 , 129.1 , 128.8 , 128.5 , 128.3 , 128.3 , 128.0 , 127.8 , 127.8 , 127.3 , 49.4 , 48.9 , 45.8 , 15.1 . UPLC-DAD-QTOF: $C2_4H_{24}NO_2$ $[M+H]^+$ calcd.: 358.1807, found: 358.1810.

(±) *N*,*N*-Diethyl-2-oxo-3-phenylbutanamide 32B



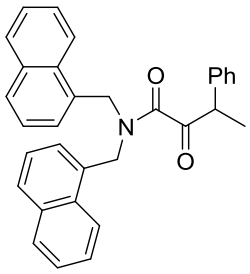
Prepared according to the General Procedure A starting from *N*,*N*-diethyl-2-oxobutanamide **31B** (157 mg, 1 mmol). Purified by flash column chromatography (hexane/EtOAc, 90:10) to afford **32B** as colourless oil. Yield: 60% (140 mg, 0.6 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.04 (m, 5H), 4.47 (q, *J* = 7.0 Hz, 1H), 3.40 – 3.21 (m, 1H), 3.19 – 3.00 (m, 1H), 2.85 – 2.60 (m, 2H), 1.44 (d, *J* = 7.0 Hz, 2H), 0.90 (t, *J* = 7.2 Hz, 3H), 0.79 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.5 , 166.9 , 144.9 , 137.2 , 129.1 , 128.8 , 128.3 , 127.8 , 127.3 , 48.8 , 41.7 , 38.9 , 15.0 , 13.9 , 12.3 . UPLC-DAD-QTOF: $C_{14}H_{20}NO_2$ $[M+H]^+$ calcd.: 234.1494, found: 234.1498.

(±) *N,N*-Diisobutyl-2-oxo-3-phenylbutanamide 32C



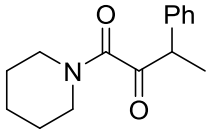
Prepared according to the General Procedure A starting from *N,N*-diisobutyl-2-oxobutanamide **31C** (157 mg, 1 mmol). Purified by flash column chromatography (hexane/EtOAc, 98:2) to afford **32C** as yellow oil. Yield: 58% (168 mg, 0.58 mmol)^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.18 (m, 5H), 4.55 (q, *J* = 7.0 Hz, 1H), 3.21 (dd, *J* = 13.5, 7.6 Hz, 1H), 3.00 (dd, *J* = 13.5, 7.5 Hz, 1H), 2.82 – 2.71 (m, 1H), 2.61 (dd, *J* = 14.1, 7.2 Hz, 1H), 1.90 – 1.77 (m, 1H), 1.69 (m, 1H), 1.50 (d, *J* = 7.0 Hz, 3H), 0.74 (d, *J* = 6.7 Hz, 6H), 0.69 (d, *J* = 6.7 Hz, 3H), 0.58 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9 , 167.5 , 137.3 , 128.8 , 128.6 , 127.5 , 53.9 , 51.0 , 48.6 , 26.4 , 25.6 , 19.9 , 19.7 , 19.4 , 19.2 , 15.8 . UPLC-DAD-QTOF: $C_{18}H_{28}NO_2$ $[M+H]^+$ calcd.: 290.2054, found: 290.2062.

(±) *N,N*-Bis(naphthalen-1-ylmethyl)-2-oxo-3-phenylbutanamide 32D



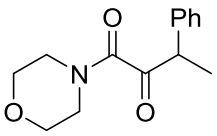
Prepared according to the General Procedure A starting from *N,N*-bis(naphthalen-1-ylmethyl)-2-oxobutanamide **31D** (381 mg, 1 mmol). Purified by column chromatography (hexane/EtOAc, 95:5) to afford **32D** as a white solid. Yield: 83% (379 mg, 0.83 mmol). m.p. = 121-124 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 – 7.65 (m, 5H), 7.60 – 7.02 (m, 13H), 6.79 – 6.47 (m, 1H), 5.24 (d, *J* = 15.1 Hz, 1H), 4.81 (td, *J* = 11.3, 9.8, 5.9 Hz, 2H), 4.68 – 4.54 (m, 1H), 4.54 – 4.35 (m, 1H), 1.54 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.6 , 167.9 , 137.1 , 133.8 , 133.7 , 131.4 , 130.6 , 129.2 , 128.9, 128.7 , 128.4 , 128.2 , 127.9 , 126.5 , 126.3 , 125.9 , 125.8 , 125.6 , 125.2 , 124.7 , 123.3 , 122.1 , 49.0 , 46.9 , 44.9 , 15.6 . UPLC-DAD-QTOF: $C_{32}H_{28}NO_2$ $[M+H]^+$ calcd.: 458.5760, found: 458.5788.

(±) 3-Phenyl-1-(piperidin-1-yl)butane-1,2-dione 32E



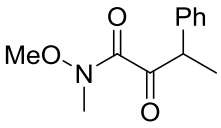
Prepared according to the General Procedure A starting from 1-(piperidin-1-yl)butane-1,2-dione **31E** (169 mg, 1 mmol). Purified by flash column chromatography (hexane/EtOAc, 90:10) to afford **32D** as a yellow oil. Yield: 80% (196 mg, 0.8 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.15 (m, 5H), 4.52 (q, *J* = 7.0 Hz, 1H), 3.69 – 3.49 (m, 1H), 3.19 (ddd, *J* = 13.1, 8.6, 3.2 Hz, 1H), 2.97 (ddd, *J* = 13.5, 8.7, 3.5 Hz, 1H), 2.81 (dddd, *J* = 13.5, 6.3, 4.0, 0.9 Hz, 1H), 1.51 (d, *J* = 7.0 Hz, 3H), 1.48 – 1.40 (m, 3H), 1.34 – 1.19 (m, 2H), 0.64 (tq, *J* = 12.5, 4.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.3, 165.8, 136.8, 129.0, 128.7, 127.7, 48.8, 46.5, 42.1, 25.6, 25.1, 24.1, 14.8. UPLC-DAD-QTOF: $C_{15}H_{20}NO_2$ $[M+H]^+$ calcd.: 246.1494, found: 246.1503.

(±) 1-Morpholino-3-phenylbutane-1,2-dione 32F



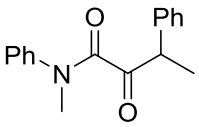
Prepared according to the General Procedure A starting from 1-morpholinobutane-1,2-dione **31F** (171 mg, 1 mmol). Purified by flash column chromatography (hexane/EtOAc, 80:20) to afford **32F** as a white solid. Yield: 80% (196 mg, 0.79 mmol). m.p. = 91-95 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 – 7.08 (m, 5H), 4.39 (q, *J* = 7.0 Hz, 1H), 3.55-3.48 (m, 1H), 3.44-3.39 (m, 1H), 3.24 – 3.15 (m, 1H), 3.17-3.03 (m, 1H), 3.02 – 2.94 (m, 1H), 2.67 – 2.60 (m, 1H), 2.47-2.40 (m, 1H), 1.34 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0 , 165.2 , 136.2 , 128.8 , 128.3 , 127.6 , 65.8 , 48.3 , 45.4 , 41.10 , 14.1. UPLC-DAD-QTOF: $C_{14}H_{18}NO_3$ $[M+H]^+$ calcd.: 248.1287, found: 248.1292.

(±) *N*-Methoxy-*N*-methyl-2-oxo-3-phenylbutanamide 32G



Prepared according to the General Procedure A starting from *N*-methoxy-*N*-methyl-2-oxobutanamide **31G** (145 mg, 1 mmol). Purified by flash column chromatography (hexane/EtOAc, 90:10) to afford **32G** as a colourless oil. Yield: 83% (183 mg, 0.83 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.08 (m, 5H), 4.13 (q, *J* = 7.1 Hz, 1H), 3.40 (s, 3H), 2.87 (s, 3H), 1.42 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.8 , 167.9 , 128.7 , 128.5 , 128.1 , 127.6 , 127.1 , 62.2 , 49.2 , 31.5 , 16.0 . UPLC-DAD-QTOF: $C_{12}H_{16}NO_3$ $[M+H]^+$ calcd.: 222.1123, found: 222.1145.

(±) *N*-Methyl-2-oxo-*N*,3-diphenylbutanamide 32H



Prepared according to the General Procedure A starting from *N*-Methyl-2-oxo-*N*-phenylbutanamide **31H** (191 mg, 1 mmol). Purified by flash column chromatography (hexane/EtOAc, 95:5) to afford **32H** as a colourless oil. Yield: 68% (181 mg, 0.68 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 – 6.92 (m, 9H), 6.74 – 6.50 (m, 1H), 4.40 (q, *J* = 7.0 Hz, 1H), 3.21 (s, 3H), 1.33 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8 , 143.6 , 141.2 , 129.4 , 129.2 , 128.6 , 128.5 , 127.9 , 127.0 , 126.7 , 125.4 , 36.5 , 28.4 , 26.1 . UPLC-DAD-QTOF: $C_{17}H_{18}NO_2$ $[M+H]^+$ calcd.: 267.1376, found: 267.1365.

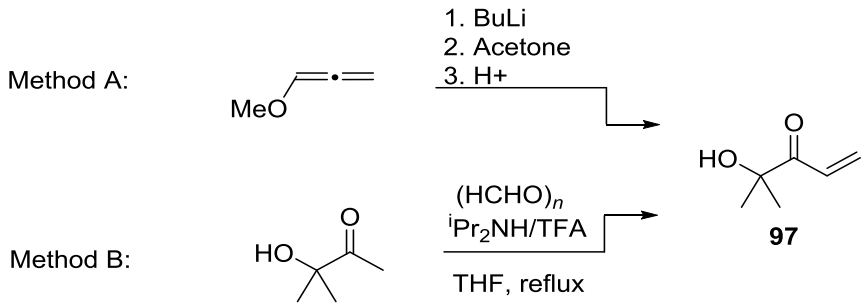
6.3.3. Preparation of electrophiles

6.3.3.1. Preparation of enones

Enones **15** and **16** were commercially available and were used in the reaction after distillation, and **12** and **17** were prepared as follows:

6.3.3.1.1. *Synthesis of α'-hydroxy enone **12***

The two procedures (method A and B) described below are efficient for the obtention of enone **12**.



METHOD A:[257]

To a solution of methoxypropadiene (3.5 g, 50 mmol) in dry Et_2O (100 mL) at –40 °C, *n*BuLi (2.5 M in hexanes, 22 mL, 55 mmol) was added under nitrogen and the reaction was stirred at –40 °C for 10 min. Then, acetone (4.0 mL, 55 mmol) in dry Et_2O (55 mL) was added within 5 min. The reaction was stirred at the same temperature for 0.5 h and quenched with H_2O (100 mL). The resulting mixture was allowed to warm to room temperature and extracted with Et_2O (3 x 100 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to afford 2-methyl-3-methoxy-3,4-pentadien-2-ol as a yellow liquid that was employed in the next step without further purification. Yield: 82% (5.6 g, 41.0 mmol).

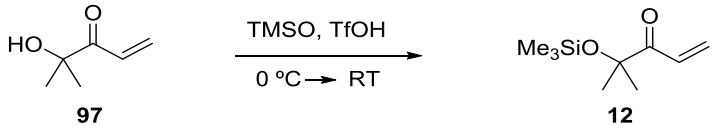
The material from the previous step (2-methyl-3-methoxy-3,4-pentadien-2-ol, 5.6 g, 41.0 mmol) was added dropwise to 5% aq H_2SO_4 (110 mL) at 0 °C and the mixture was stirred for 1.5 h. After this time the reaction was allowed to warm to room temperature and the solution was saturated with solid NaCl. The mixture was extracted with Et_2O (5 x 60 mL) and the combined organic extracts were washed with brine and dried over Na_2SO_4. The solvent was removed to give a yellow oil which upon distillation afforded the enone **97** as a colorless liquid. Yield: 88% (4.4 g, 38.7 mmol) b.p. 45 ºC (13 mmHg); IR (neat, cm^{-1}) 3445 (OH), 1693 (C=O); ^{1}H NMR ($CDCl_3$) δ 6.73 (dd, *J* = 9.5, 16.8 Hz, 1H), 6.50 (dd, *J* = 2.2, 16.8 Hz, 1H), 5.82 (dd, *J* = 2.2, 10.3 Hz, 1H), 1.38 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 202.3, 131.1, 128.8, 75.4, 26.1.

[257] C. Palomo, M. Oiarbide, J. M. García, A. González, E. Arceo *J. Am. Chem. Soc.* **2003**, *125*, 13942–13943.

METHOD B:[258]

Commercially available 3-hydroxy-3-methyl-2-butanone (5.3 mL, 50 mmol, 1 equiv.) and paraformaldehyde (3 g, 100 mmol, 2 equiv.) were added to a solution of $^{i}Pr_2NH$ (14.0 mL, 100 mmol, 2 equiv.) and TFA (9.6 mL, 125 mmol, 2.5 equiv.) in THF (250 mL). The mixture was refluxed and paraformaldehyde (3 g, 100 mmol, 2 equiv.) was added every 2 h three times. The mixture was stirred at reflux overnight and then was cooled to room temperature. CH_2Cl_2 (100 mL) was added and the mixture was washed with 1N HCl (75 mL), 1N NaOH (75 mL) and brine (75 mL), and the organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure (230 mbar/ bath 40 ºC). The residue was purified by flash column chromatography on silica gel (eluting with diethyl ether) to afford 4-hydroxy-4-methylpent-1-en-3-one **97** as colorless oil. Yield: 5.0 g, 44.5 mmol, 89%.

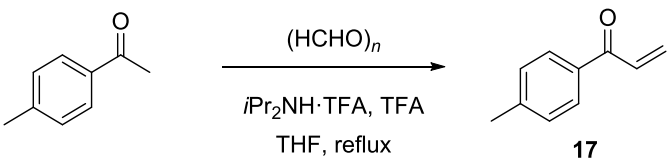
6.3.3.1.2. *Silylation of α'-hydroxy enone*[259]



97 **12**

3-(Trimethylsilyl)-2-oxazolidinone (TMSO) (3.4 mL, 22.5 mmol, 1.5 equiv.) and 3 drops of trifluoromethanesulfonic acid were added to enone **97** (1.7 g, 15 mmol, 1 equiv.). The reaction mixture was stirred at room temperature for 2 h, diluted with pentane (20 mL) and subsequently washed with water (20 mL) and $NaHCO_3$ sat. (20 mL). The organic phase was then dried over with $MgSO_4$ and concentred under reduced pressure to afford the title compound **12** as a colorless oil. Yield: 93% (2.6 g, 14.0 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (dd, *J* = 17.3, 10.4 Hz, 1H), 6.38 (dd, *J* = 17.3, 2.1 Hz, 1H), 5.72 (dd, *J* = 10.4, 2.1 Hz, 1H), 1.37 (s, 6H), 0.14 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 130.7, 129.2, 79.3, 27.2, 2.3.

6.3.3.1.3. *Synthesis of 1-(p-tolyl)prop-2-en-1-one* ***17***[260]



17

[258] Adapted from: A. Bugarin, K. D. Jones, B. T. Connell *Chem. Commun*. **2010**, *46*, 1715–1717.
[259] Adapted from: J. M. Aizpurua, C. Palomo, A. L. Palomo *Can. J. Chem*. **1984**, *62*, 336–340.
[260] S. H. Guo, S. Z. Xing, S. Mao, Y. R. Gao, W. L. Chen, Y. Q. Wang, *Tetrahedron Lett*. **2014**, *55*, 6718–6720.

To a solution of 1-(*p*-tolyl)ethan-1-one (2.0 mL, 15 mmol, 1 equiv.) and paraformaldehyde (0.9 g, 30 mmol, 2 equiv.) in dry THF (15 mL) was added diisopropylammonium trifluoroacetate (2.2 g, 15 mmol, 1 equiv.) and trifluoroacetic acid (0.1 mL, 1.5 mmol, 0.1 equiv.). The reaction mixture was stirred at reflux for 2 h, then cooled down to room temperature and a second addition of paraformaldehyde (0.9 g, 30 mmol, 2 equiv.) and diisopropylammonium trifluoroacetate (2.2 g, 15 mmol, 1 equiv.) was performed. The reaction mixture was then stirred at reflux overnight, then cooled down and the solvent was removed under reduced pressure. The residue was dissolved in Et_2O and washed with 1M HCl and 1M MaOH. The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude was purified by flash column chromatography on silica gel eluting with hexane/ethyl acetate 95/5 to give the title compound as colorless oil. Yield: 76% (1.7 g, 11.4 mmol). All data were consistent with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 7.16 (dd, *J* = 17.1, 10.6 Hz, 1H), 6.43 (dd, *J* = 17.1, 1.8 Hz, 1H), 5.90 (dd, *J* = 10.6, 1.8 Hz, 1H), 2.43 (s, 3H).

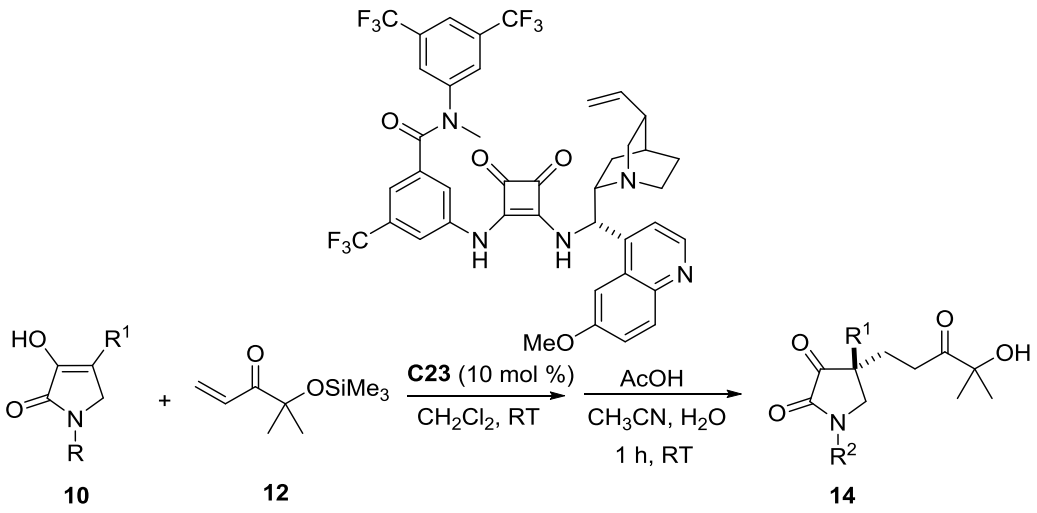
6.3.3.2. Preparation of allyl carbonates

Carbonates **23-25** and **26-28** were prepared according to the procedures described in the literature.[261]

[261] a) P. Vertelsaljai, P. V. Navaratne, A. J. Grenning, *Angew. Chem. Int. Ed.* **2016**, *55*, 317-320; b) N. Kagawa, H. Takabatake, Y. Masuda, *Tetrahedron Lett.* **2014**, *55*, 6427-6431.

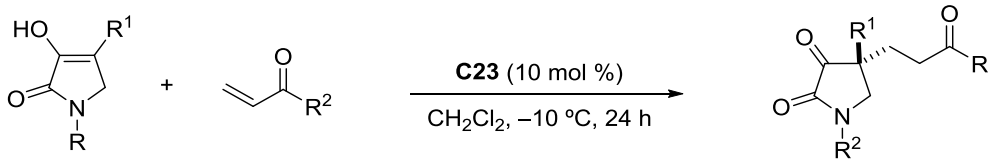
6.3.4. Organocatalytic conjugate addition to enones

6.3.4.1. Asymmetric addition to α'-oxy enones



To a mixture of the corresponding pyrrolidin-2,3-dione (0.2 mmol, 1 equiv.) and the α'-silyloxyenone **12** (74 mg, 0.4 mmol, 2 equiv.) in dichloromethane (0.4 mL) catalyst **C23** (0.02 mmol, 10 mol%) was added. The mixture was stirred until consumption of the α-ketoamide (monitored by ^{1}H-NMR). The reaction mixture was then quenched with 1M HCl (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. For the desilylation step, the reaction crude was dissolved in CH_3CN (1mL) and, H_2O (0.5 mL) and glacial acetic acid (0.3 mL) were added. The reaction mixture was stirred for 1 h at room temperature and was then quenched with $NaHCO_3$ saturated aqueous solution (20 mL). The organic layer was separated and evaproated under reduced pressure and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude was purified by flash column chromatography on silica gel to afford the expected adducts.

6.3.4.2. Asymmetric addition to vinyl ketones



10

A R: Bn
B R: 1-Napht-CH_2
C R: ^{i}Pr
D R: PMP

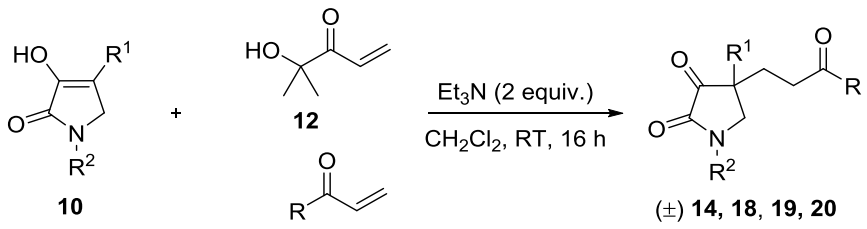
a R^1: Me
b R^1: Bn

15 R^2: Me
16 R^2: Et
17 R^2: 4-MeC_6H_4

18 R^2: Me
19 R^2: Et
20 R^2: 4-MeC_6H_4

To a mixture of the corresponding enol **10** (0.2 mmol, 1 equiv.) and the corresponding vinyl ketone **15–17** (0.4 mmol, 2 equiv.) in dichloromethane (0.4 mL) catalyst **C23** (17 mg, 0.02 mmol, 10 mol%) was added. The mixture was stirred until consumption of the enol **9** (monitored by ^{1}H-NMR). The reaction mixture was then quenched with 1M HCl (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude was purified by flash column chromatography on silica gel to afford the expected adducts.

6.3.4.3. Racemic reaction



10

12

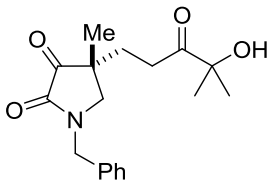
15-17

(±) **14, 18, 19, 20**

To a mixture of the corresponding α-ketoamide **10** (0.2 mmol, 1 equiv.) the corresponding enone **12** or **15-17** (0.3 mmol, 1.5 equiv.) in dichloromethane (0.4 mL) triethylamine (56 µL, 0.4 mmol, 2 equiv.) was added at room temperature. The mixture was stirred at the same temperature, until consumption of the α-ketoamide (monitored by ^{1}H-NMR). The reaction mixture was then quenched with 1M HCl (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude was purified by flash column chromatography on silica gel to afford the expected adducts.

6.3.4.4. Characterization data for compounds

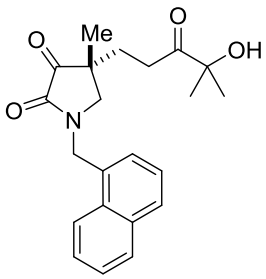
1-Benzyl-4-(4-hydroxy-4-methyl-3-oxopentyl)-4-methylpyrrolidine-2,3-dione 14Aa



The title compound was prepared from 1-benzyl-3-hydroxy-4-methyl-1*H*-pyrrol-2(5*H*)-one **10Aa** (41 mg, 0.2 mmol) and 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one **12** (75 mg, 0.4 mmol) following the general procedure. The crude was purified by flash column chromatography on silica gel (hexane/EtOAc, 80:20) to give the title compound as a white foam. Yield: 84% (53 mg, 0.17 mmol). $[\alpha]_D^{23}$ = + 18.9° (c=1.15, 90% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 – 7.22 (m, 5H), 4.77 (d, *J* = 14.3 Hz, 1H), 4.61 (d, *J* = 14.3 Hz, 1H), 3.34 (s, 1H), 3.31 (d, *J* = 10.9 Hz, 1H), 3.24 (d, *J* = 10.9 Hz, 1H), 2.53 – 2.43 (m, 2H), 1.92 – 1.82 (m, 2H), 1.32 (s, 3H), 1.28 (s, 3H), 1.20 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.6, 203.5, 159.2, 134.6, 129.3, 128.7, 128.6, 76.6, 53.9, 48.6, 42.5, 31.1, 30.2, 26.7, 21.9. UPLC-DAD-QTOF: $C_{18}H_{24}NO_4$ $[M+H]^+$ calcd.: 318.1705, found: 318.1705.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 40/60, flow rate= 0.7 mL/min, retention times: 23 min (major.) and 28 min (minor.)).

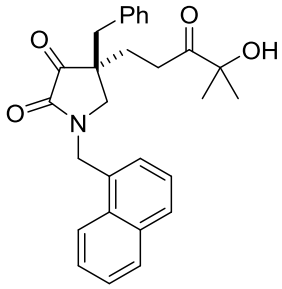
4-(4-Hydroxy-4-methyl-3-oxopentyl)-4-methyl-1-(naphthalen-1-ylmethyl)pyrrolidine-2,3-dione 14Ba



The title compound was prepared from 3-hydroxy-4-methyl-1-(naphthalen-1-ylmethyl)-1*H*-pyrrol-2(5*H*)-one **10Ba** (51 mg, 0.2 mmol) and 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one **12** (75 mg, 0.4 mmol) following the general procedure. The crude was purified by flash column chromatography on silica gel (hexane/EtOAc, 80:20) to give the title compound as a white foam. Yield: 86% (63 mg, 0.17 mmol). $[\alpha]_D^{23}$ = + 18.3° (c=1.6, 96% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 – 7.97 (m, 1H), 7.96 – 7.76 (m, 2H), 7.67 – 7.36 (m, 4H), 5.31 (d, *J* = 14.4 Hz, 1H), 4.98 (d, *J* = 14.4 Hz, 1H), 3.32 (s, 1H), 3.19 – 3.04 (m, 2H), 2.40 – 2.09 (m, 2H), 1.85 – 1.61 (m, 2H), 1.16 (s, 3H), 1.09 (s, 3H), 1.07 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.2, 203.6, 158.8, 134.1, 131.5, 130.0, 129.9, 129.1, 128.9, 127.6, 126.7, 125.3, 123.5, 76.5, 53.6, 46.9, 42.5, 31.2, 23.0, 26.6, 22.2.UPLC-DAD-QTOF: $C_{22}H_{26}NO_4$ $[M+H]^+$ calcd.: 368.1862, found: 368.1861.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/ethanol 50/50, flow rate= 0.5 mL/min, retention times: 14 min (minor.) and 16 min (major.)).

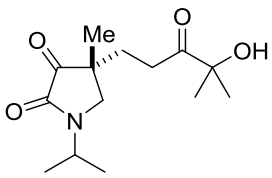
(*S*)-4-Benzyl-4-(4-hydroxy-4-methyl-3-oxopentyl)-1-((naphthalen-1-yl)methyl) pyrrolidine-2,3-dione 14Bb



The title compound was prepared from 4-benzyl-3-hydroxy-1-(naphthalen-1-ylmethyl)-1,5-dihydro-2*H*-pyrrol-2-one **10Bb** (66 mg, 0.2 mmol) and 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one **12** (75 mg, 0.4 mmol) following the general procedure. The crude was purified by flash column chromatography on silica gel (hexane/EtOAc, 1:1) to give the title compound as a white solid. Yield: 80% (70 mg, 0.16 mmol). m. p. = 118–120 ºC. $[\alpha]_D^{25}$ = + 13.6° (c=2.9, 92% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 – 7.82 (m, 3H), 7.54 – 7.47 (m, 2H), 7.45 – 7.37 (m, 1H), 7.31 – 7.24 (m, 1H), 7.04 (d, *J* = 5.9 Hz, 3H), 6.79 – 6.71 (m, 2H), 5.08 (d, *J* = 14.4 Hz, 1H), 4.81 (d, *J* = 14.4 Hz, 1H), 3.38 (d, *J* = 11.4 Hz, 1H), 2.97 (d, *J* = 12.2 Hz, 2H), 2.56 (d, *J* = 13.6 Hz, 1H), 2.46 – 2.29 (m, 1H), 2.23 – 2.09 (m, 1H), 2.04 – 1.87 (m, 1H), 1.82 – 1.68 (m, 1H), 1.17 (s, 3H), 1.06 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.0, 204.2, 158.6, 134.5, 134.1, 131.4, 129.8, 129.7, 128.9, 128.6, 128.6, 127.5, 126.6, 125.2, 123.5, 49.3, 46.7, 42.2, 30.7, 26.5. UPLC-DAD-QTOF: $C_{18}H_{24}NO_4$ $[M+H]^+$ calculated.: 444.2175, found: 444.2173.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC hexane/isopropanol 60/40, flow rate= 1.0 mL/min, retention times: 23 min (minor.) and 26 min (major.)).

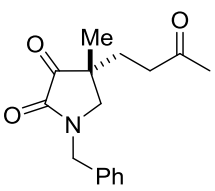
(*R*)-4-(4-hydroxy-4-methyl-3-oxopentyl)-1-isopropyl-4-methylpyrrolidine-2,3-dione 14Ca



The title compound was prepared from 3-hydroxy-1-isopropyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one **10Ca** (31 mg, 0.2 mmol) and 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one **12** (75 mg, 0.4 mmol) following the general procedure. The crude was purified by flash column chromatography on silica gel (hexane/EtOAc, 1:1) to give the title compound as a white solid. Yield: 84% (45 mg, 0.17 mmol). m. p. = 90–92 ºC. $[\alpha]_D^{25}$ = – 2.1° (c=0.9, 88% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.65 – 4.56 (m, 1H), 3.39 (d, *J* = 10.8 Hz, 1H), 3.29 (d, *J* = 10.8 Hz, 1H), 2.60 (ddd, *J* = 8.2, 6.4, 2.8 Hz, 2H), 1.91 (td, *J* = 8.0, 3.0 Hz, 2H), 1.34 (d, *J* = 5.3 Hz, 6H), 1.28 – 1.21 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.6, 203.9, 158.6, 49.8, 44.6, 42.5, 31.0, 30.2, 26.7, 21.7, 19.4. UPLC-DAD-QTOF: $C_{18}H_{24}NO_4$ $[M+H]^+$ calculated.: 270.1705, found: 270.1713.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H hexane/isopropanol 50/50, flow rate= 0.5 mL/min, retention times: 34 min (major.) and 44 min (minor.)).

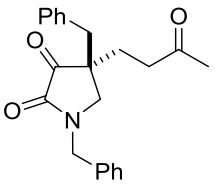
(*R*)-1-Benzyl-4-methyl-4-(3-oxobutyl)pyrrolidine-2,3-dione 18Aa



The title compound was prepared from 1-benzyl-3-hydroxy-4-methyl-1*H*-pyrrol-2(5*H*)-one **10Aa** (41 mg, 0.2 mmol) and but-3-en-2-one **15** (28 mg, 0.4 mmol) following the general procedure. The crude was purified by flash column chromatography on silica gel (hexane/EtOAc, 80:20) to give the title compound as a white foam. Yield: 75% (41 mg, 0.15 mmol). $[\alpha]_D^{23}$ = – 1.0° (c=1.75, 92% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) 7.40 – 7.18 (m, 5H), 4.71 (d, *J* = 14.3 Hz, 1H), 4.61 (d, *J* = 14.3 Hz, 1H), 3.29 (d, *J* = 10.9 Hz, 1H), 3.20 (d, *J* = 10.9 Hz, 1H), 2.33 (dd, *J* = 8.7, 6.8 Hz, 2H), 2.05 (s, 3H), 1.86 – 1.73 (m, 2H), 1.15 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.0, 203.6, 159.2, 134.6, 129.2, 128.7, 128.6, 54.0, 48.6, 42.5, 37.8, 30.9, 30.1, 21.8. UPLC-DAD-QTOF: $C_{16}H_{20}NO_3$ $[M+H]^+$ calcd.: 274.1443, found: 274.1453.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak OD-H, hexane/isopropanol 80/20, flow rate= 0.7 mL/min, retention times: 38 min (minor.) and 41 min (major.)).

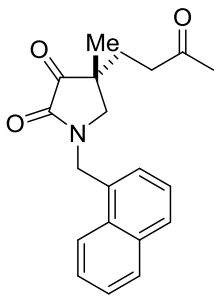
(*S*)-1,4-Dibenzyl-4-(3-oxobutyl)pyrrolidine-2,3-dione 18Ab



The title compound was prepared from 1,4-dibenzyl-3-hydroxy-1*H*-pyrrol-2(5*H*)-one **10Bb** (59 mg, 0.2 mmol) and but-3-en-2-one **15** (28 mg, 0.4 mmol) following the general procedure. The crude was purified by flash column chromatography on silica gel (hexane/EtOAc, 80:20) to give the title compound as a white foam. Yield: 84% (59 mg, 0.17 mmol). $[\alpha]_D^{23}$ = – 15.3° (c=2.0, 92% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.24 (m, 3H), 7.24 – 7.15 (m, 3H), 7.05 – 6.98 (m, 2H), 6.95 – 6.89 (m, 2H), 4.50 (s, 2H), 3.48 (d, *J* = 11.2 Hz, 1H), 3.17 – 3.06 (m, 2H), 2.64 (d, *J* = 13.6 Hz, 1H), 2.49 – 2.22 (m, 2H), 2.08 (s, 3H), 2.04 – 1.80 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.7, 204.4, 159.1, 135.0, 134.4, 129.9, 129.2, 128.9, 128.4, 128.4, 127.5, 49.8, 48.4, 46.9, 41.9, 37.6, 30.8, 30.1. UPLC-DAD-QTOF: $C_{22}H_{24}NO_3$ $[M+H]^+$ calcd.: 350.1756, found: 350.1769.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak OD-H, hexane/isopropanol 50/50, flow rate= 0.5 mL/min, retention times: 21 min (minor.) and 40 min (major.)).

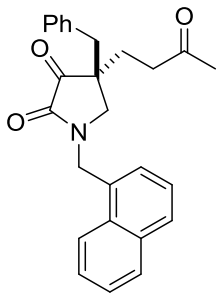
(*R*)-4-Methyl-1-((naphthalen-1-yl)methyl)-4-(3-oxobutyl)pyrrolidine-2,3-dione 18Ba



The title compound was prepared from 3-hydroxy-4-methyl-1-(naphthalen-1-ylmethyl)-1,5-dihydro-2*H*-pyrrol-2-one **10Ba** (51 mg, 0.2 mmol) and but-3-en-2-one **15** (28 mg, 0.4 mmol) following the general procedure. The crude was purified by flash column chromatography on silica gel (hexane/EtOAc, 1:1) to give the title compound as a white foam. Yield: 95% (60 mg, 0.19 mmol). $[\alpha]_D^{25}$ = – 0.2° (c=1.0, 93% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 – 7.95 (m, 1H), 7.90 – 7.74 (m, 2H), 7.63 – 7.50 (m, 2H), 7.49 – 7.39 (m, 2H), 5.33 (d, *J* = 14.4 Hz, 1H), 4.98 (d, *J* = 14.4 Hz, 1H), 3.15 – 3.01 (m, 2H), 2.16 (ddd, *J* = 17.8, 10.2, 5.9 Hz, 1H), 2.05 – 1.90 (m, 1H), 1.85 (s, 3H), 1.78 – 1.59 (m, 2H), 1.08 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.7, 203.8, 158.8, 134.1, 131.4, 129.9, 129.9, 129.1, 128.9, 127.4, 126.6, 125.3, 123.6, 53.4, 46.9, 42.4, 37.6, 31.1, 29.8, 22.0. UPLC-DAD-QTOF: $C_{18}H_{24}NO_4$ $[M+H]^+$ calcd.: 324.1600, found: 324.1606.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel OD-H hexane/ isopropanol 80/20, flow rate= 0.5 mL/min, retention times: 61 min (major.) and 76 min (minor.)).

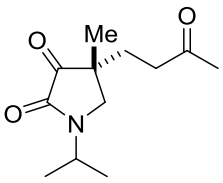
(*S*)-4-Benzyl-1-((naphthalen-1-yl)methyl)-4-(3-oxobutyl)pyrrolidine-2,3-dione 18Bb



The title compound was prepared from 4-benzyl-3-hydroxy-1-(naphthalen-1-ylmethyl)-1,5-dihydro-2*H*-pyrrol-2-one **10Bb** (66 mg, 0.2 mmol) and but-3-en-2-one **15** (28 mg, 0.4 mmol) following the general procedure. The crude material was purified by flash column chromatography on silica gel (hexane/EtOAc, 1:1) to give the title compound as a white solid. Yield: 97% (77 mg, 0.19 mmol). m. p. = 146–147 ºC. $[\alpha]_D^{25}$ = – 8.0° (c=1.0, 91% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 – 7.81 (m, 3H), 7.58 – 7.47 (m, 2H), 7.44 – 7.37 (m, 1H), 7.27 (d, *J* = 6.9 Hz, 1H), 7.05 – 6.99 (m, 3H), 6.76 (dd, *J* = 6.4, 2.8 Hz, 2H), 5.09 (d, *J* = 14.4 Hz, 1H), 4.81 (d, *J* = 14.4 Hz, 1H), 3.36 (d, *J* = 11.4 Hz, 1H), 3.04 – 2.89 (m, 2 H), 2.54 (d, *J* = 13.6 Hz, 1H), 2.33 – 2.15 (m, 1H), 2.10 – 1.88 (m, 2H), 1.84 (s, 3H), 1.77 – 1.63 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.4, 204.3, 158.6, 134.6, 133.9, 131.2, 129.6, 128.9, 128.5, 127.2, 126.4, 125.2, 123.5, 49.2, 46.8, 46.5, 41.8, 37.3, 30.6, 29.8. UPLC-DAD-QTOF: $C_{18}H_{24}NO_4$ $[M+H]^+$ calcd.: 400.1913, found: 400.1913.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel OD-H hexane/isopropanol 50/50, flow rate= 0.5 mL/min, retention times: 38 min (minor.) and 50 min (major.)).

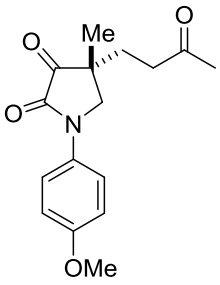
(*R*)-1-Isopropyl-4-methyl-4-(3-oxobutyl)pyrrolidine-2,3-dione 18Ca



The title compound was prepared from 3-hydroxy-1-isopropyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one **10Ca** (31 mg, 0.2 mmol) and but-3-en-2-one **15** (28 mg, 0.4 mmol) following the general procedure. he crude material was purified by flash column chromatography on silica gel (hexane/EtOAc, 1:1) to give the title compound as a white foam. Yield: 98% (45 mg, 0.19 mmol). $[\alpha]_D^{25}$ = + 18.7° (c=1.0, 98% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.60 (p, *J* = 6.8 Hz, 1H), 3.38 (d, *J* = 10.8 Hz, 1H), 3.27 (d, *J* = 10.8 Hz, 1H), 2.45 (dd, *J* = 8.9, 6.7 Hz, 2H), 2.13 (s, 3H), 1.88 (td, *J* = 8.1, 2.1 Hz, 2H), 1.24 (dd, *J* = 6.8, 4.1 Hz, 6H), 1.21 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.0, 204.0, 158.6, 49.7, 44.5, 42.4, 37.8, 30.7, 30.1, 21.7, 19.4. UPLC-DAD-QTOF: $C_{12}H_{20}NO_3$ $[M+H]^+$ calcd.: 226.1443, found: 226.1450.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel OJ-H hexane/isopropanol 80/20, flow rate= 1.0 mL/min, retention times: 19 min (minor.) and 21 min (major.)).

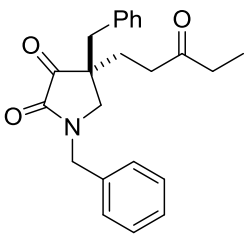
(*R*)-1-(4-Methoxyphenyl)-4-methyl-4-(3-oxobutyl)pyrrolidine-2,3-dione 18Da



The title compound was prepared from 3-hydroxy-1-(4-methoxyphenyl)-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one **10Da** (44 mg, 0.2 mmol) and but-3-en-2-one **15** (28 mg, 0.4 mmol) following the general procedure. The crude was purified by flash column chromatography on silica gel (hexane/EtOAc, 1:1) to give the title compound as a white foam. Yield: 98% (55 mg, 0.19 mmol). $[\alpha]_D^{25}$ = + 2.5° (c=1.4, 91% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 9.0 Hz, 2H), 6.93 (d, *J* = 9.0 Hz, 2H), 3.98 – 3.62 (m, 5H), 2.63 – 2.39 (m, 2H), 2.11 (s, 3H), 1.95 (t, *J* = 7.8 Hz, 2H), 1.29 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.8, 202.7, 158.1, 157.4, 131.6, 120.8, 114.3, 55.6, 55.4, 42.1, 37.7, 30.8, 30.0, 21.6. UPLC-DAD-QTOF: $C_{16}H_{20}NO_4$ $[M+H]^+$ calculated.: 290.1392, found: 290.1393.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel OD-H hexane/isopropanol 70/30, flow rate= 1 mL/min, retention times: 29 min (minor.) and 34 min (major.)).

(*S*)-1,4-Dibenzyl-4-(3-oxopentyl)pyrrolidine-2,3-dione 19Ab

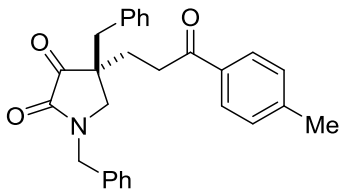


The title compound was prepared from 1,4-dibenzyl-3-hydroxy-1*H*-pyrrol-2(5*H*)-one **10Ab** (59 mg, 0.2 mmol) and pent-1-en-3-one **16** (34 mg, 0.4 mmol) following the general procedure. The crude was purified by flash column chromatography on silica gel

(hexane/EtOAc, 1:1) to give the title compound as a white foam. Yield: 94% (68 mg, 0.19 mmol). $[\alpha]_D^{25}$ = – 11.3° (c=1.4, 88% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.10 (m, 6H), 7.06 – 6.82 (m, 4H), 4.48 (s, 2H), 3.45 (d, *J* = 11.3 Hz, 1H), 3.09 (dd, *J* = 12.5, 4.9 Hz, 2H), 2.62 (d, *J* = 13.6 Hz, 1H), 2.44 – 2.18 (m, 4H), 2.07 – 1.80 (m, 2H), 0.99 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.3, 204.2, 158.9, 134.8, 134.1, 129.7, 128.9, 128.7, 128.2, 128.1, 127.3, 49.6, 48.2, 46.7, 41.7, 36.0, 30.6, 7.7. UPLC-DAD-QTOF: $C_{23}H_{26}NO_3$ $[M+H]^+$ calculated.: 364.1913, found: 364.1918.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel IC hexane/isopropanol 50/50, flow rate= 1 mL/min, retention times: 35 min (minor.) and 51 min (major.)).

(*S*)-1,4-Dibenzyl-4-(3-oxo-3-(*p*-tolyl)propyl)pyrrolidine-2,3-dione 20Ab



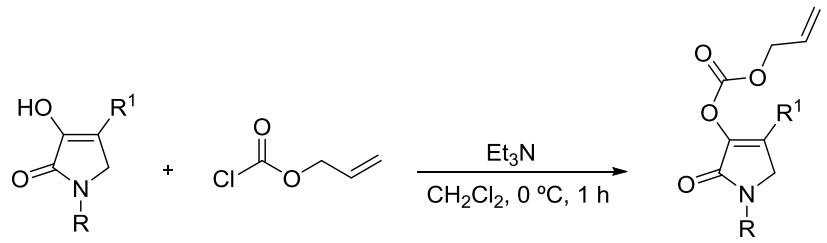
The title compound was prepared from 1-benzyl-3-hydroxy-4-phenyl-1*H*-pyrrol-2(5*H*)-one **10Ab** (59 mg, 0.2 mmol) and 1-(*p*-tolyl)prop-2-en-1-one **17** (59 mg, 0.4 mmol) following the general procedure. The crude was purified by flash column chromatography on silica gel (hexane/EtOAc, 1:1) to give the title compound as a yellow solid. Yield: 73% (62 mg, 0.15 mmol). m. p. = 144–145 ºC. $[\alpha]_D^{25}$ = – 38.5° (c=1.8, 87% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 – 7.70 (m, 2H), 7.30 – 7.13 (m, 8H), 7.06 – 6.98 (m, 2H), 6.97 – 6.90 (m, 2H), 3.51 (d, *J* = 11.3 Hz, 1H), 3.25 – 3.11 (m, 2H), 2.94 (ddd, *J* = 16.9, 10.5, 5.5 Hz, 1H), 2.85 – 2.74 (m, 1H), 2.70 (d, *J* = 13.5 Hz, 1H), 2.41 (s, 3H), 2.18 (ddd, *J* = 14.2, 10.2, 5.6 Hz, 1H), 2.04 (ddd, *J* = 14.2, 10.5, 5.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.6, 198.0, 159.2, 144.5, 135.1, 134.4, 134.0, 130.0, 129.5, 129.2, 128.9, 128.4, 128.4, 128.3, 127.5, 49.8, 48.5, 47.2, 42.2, 32.6, 31.5, 21.8. UPLC-DAD-QTOF: $C_{28}H_{28}NO_3$ $[M+H]^+$ calculated.: 426.2069, found: 426.2075.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel IA hexane/isopropanol 80/20, flow rate= 1 mL/min, retention times: 22.1 min (major.) and 26.7 min (minor.)).

6.3.5. Pd-catalyzed AAA of pyrrolidin-2,3-diones

6.3.5.1. Decarboxylative AAA of pyrrolidin-2,3-diones

6.3.5.1.1. *Carbonate formation*

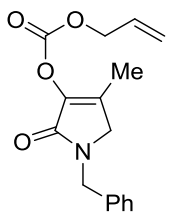


10Aa R: Bn, R^1: Me
10Ab R: Bn, R^1: Bn
10Ac R: Bn, R^1: Ph
10Ba R: 1-Napht-CH_2, R^1: Me
10Bb R: 1-Napht-CH_2, R^1: Bn
10Bc R: 1-Napht-CH_2, R^1: Ph
10Ca R: ^{i}Pr, R^1: Me
10Da R: PMP; R^1: Me
10Ea R: 3,4-DMB, R^1: Me
10Fa R: Me, R^1: Me
10Ga R: Et, R^1: Me
10Ha R: Cy, R^1: Me

21Aa R: Bn, R^1: Me
21Ab R: Bn, R^1: Bn
21Ac R: Bn, R^1: Ph
21Ba R: 1-Naph-CH_2, R^1: Me
21Bb R: 1-Naph-CH_2, R^1: Bn
21Bc R: 1-Naph-CH_2, R^1: Ph
21Ca R: ^{i}Pr, R^1: Me
21Da R: PMP; R^1: Me
21Ea R: 3,4-DMB, R^1: Me
21Fa R: Me, R^1: Me
21Ga R: Et, R^1: Me
21Ha R: Cy, R^1: Me

The corresponding 2,3-dioxopyrrolidine (0.5 mmol, 1 equiv.) was dissolved in dry dichloromethane (2 mL/mmol) at 0 °C. To this solution allyl chloroformate (64 μL, 0.6 mmol, 1.2 equiv.) was added followed by slow addition of triethylamine (0.11 mL, 0.75 mmol, 1.5 equiv.). Then, the reaction was stirred at room temperature for 1 h until complete conversion (followed by TLC). The reaction was quenched with HCl (1M) and extracted with dichloromethane (3 x 20 mL). The combined organic phases were dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography afforded the corresponding allyl carbonates and the crude was purified by column chromatography.

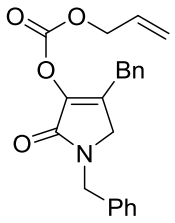
1-Benzyl-2,5-dihydro-4-methyl-2-oxo-1*H*-pyrrol-3-yl vinyl carbonate 21Aa



Prepared according to the general procedure starting from 1-benzyl-3-hydroxy-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one **10Aa** (101 mg, 0.5 mmol). Purification by column chromatography (hexane/EtOAc, 1:1) led to the title compound as white solid. Yield: 85% (122 mg, 0.42 mmol). m.p. 78–79 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (m, 5H), 6.03 – 5.74 (m, 1H), 5.40 – 5.14 (m, 2H), 4.64 (d, *J* = 5.7 Hz, 2H), 4.50 (s, 2H), 3.61 (s, 2H), 1.82 (s,

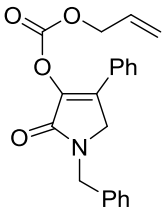
3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5 , 151.5 , 138.4 , 136.5 , 135.7 , 130.6 , 128.5 , 127.8 , 127.4 , 119.1 , 69.3 , 50.1 , 46.1 , 10.7 . UPLC-DAD-QTOF: $C_{16}H_{18}NO_4$ $[M+H]^+$ calcd.: 288.1236, found: 288.1243.

1,4-Dibenzyl-2-oxo-2,5-dihydro-1*H*-pyrrol-3-yl vinyl carbonate 21Ab



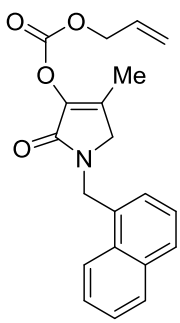
Prepared according to the general procedure starting from 1,4-dibenzyl-3-hydroxy-1,5-dihydro-2*H*-pyrrol-2-one **10Ab** (140 mg, 0.5 mmol). Purification by column chromatography (hexane/EtOAc 1:1) led to the title compound as white foam. Yield: 70% (125 mg, 0.35 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.05 (m, 10H), 6.12 – 5.87 (m, 1H), 5.43 (d, *J* = 16.1 Hz, 1H), 5.33 (d, *J* = 10.5 Hz, 1H), 4.75 (d, *J* = 5.8 Hz, 2H), 4.56 (s, 2H), 3.66 (s, 2H), 3.60 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7 , 151.9 , 139.0 , 138.4 , 136.7 , 136.5 , 130.9 , 129.0 , 128.9 , 128.7 , 128.1 , 127.8 , 127.1 , 119.7 , 69.9 , 48.9 , 46.7 , 32.1 . UPLC-DAD-QTOF: $C_{22}H_{22}NO_4$ $[M+H]^+$ calcd.: 364,1471, found: 364,1486.

Allyl (1-benzyl-2-oxo-4-phenyl-2,5-dihydro-1H-pyrrol-3-yl) carbonate 21Ac



Prepared according to the general procedure starting from 1-benzyl-3-hydroxy-4-phenyl-1,5-dihydro-2H-pyrrol-2-one **10Ac** (133 mg, 0.5 mmol). Purification by column chromatography (hexane/EtOAc, 70:30) led to the title compound as a white foam. Yield: 60% (105 mg, 0.3 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 – 7.47 (m, 2H), 7.45 – 7.21 (m, 8H), 6.14 – 5.88 (m, 1H), 5.57 – 5.22 (m, 2H), 4.84 – 4.75 (m, 2H), 4.71 (s, 2H), 4.16 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0 , 151.5 , 136.6 , 134.3 , 130.9 , 130.0 , 129.1 , 129.0 , 128.3 , 128.0 , 127.0 , 119.8 , 70.1 , 48.1 , 46.8 . UPLC-DAD-QTOF: $C_{21}H_{20}NO_4$ $[M+H]^+$ calcd.: 350.1392, found: 350.1406.

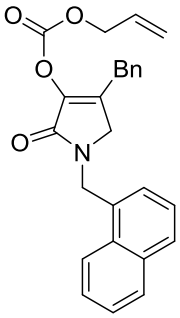
Allyl (4-methyl-1-(naphthalen-1-ylmethyl)-2-oxo-2,5-dihydro-1*H*-pyrrol-3-yl) carbonate 21Ba



Prepared according to the general procedure starting from 3-hydroxy-4-methyl-1-(naphthalen-1-ylmethyl)-1,5-dihydro-2*H*-pyrrol-2-one **10Ba** (127 mg, 0.5 mmol). Purification by column chromatography (hexane/EtOAc, 70:30) led to the title compound as yellow oil. Yield: 95% (160 mg, 0.47 mmol). m.p. 102–104 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 – 8.07 (m, 1H), 7.90 – 7.75 (m, 2H), 7.61 – 7.33 (m, 4H), 5.98 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.52 – 5.26 (m, 2H), 5.03 (s, 2H), 4.75 (dt, *J* = 5.8, 1.4 Hz, 2H), 3.54 (s, 2H), 1.83 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4, 151.8, 138.8, 135.9, 133.9, 132.1, 131.4, 130.9, 129.0, 128.6, 127.5, 127.0, 126.2,

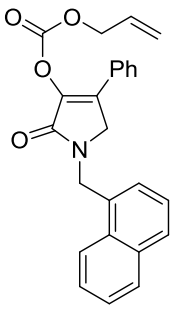
125.2, 123.8, 119.6, 69.7, 50.4, 44.7, 11.0. UPLC-DAD-QTOF: $C_{26}H_{24}NO_4$ $[M+H]^+$ calcd.: 414.1705, found: 414.1700.

Allyl (4-benzyl-1-(naphthalen-1-ylmethyl)-2-oxo-2,5-dihydro-1*H*-pyrrol-3-yl) carbonate 21Bb



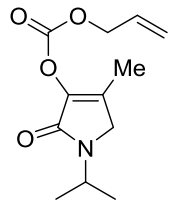
Prepared according to the general procedure starting from 4-benzyl-3-hydroxy-1-(naphthalen-1-ylmethyl)-1,5-dihydro-2H-pyrrol-2-one **10Bb** (165 mg, 0.5 mmol). Purification by column chromatography (hexane/EtOAc, 70:30) led to the title compound as yellow foam. Yield: 82% (170 mg, 0.41 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (dt, *J* = 8.4, 1.2 Hz, 1H), 7.90 – 7.78 (m, 2H), 7.60 – 7.47 (m, 2H), 7.43 – 7.29 (m, 2H), 7.29 – 7.18 (m, 4H), 7.08 (dd, *J* = 7.8, 1.7 Hz, 1H), 5.99 (ddt, *J* = 17.1, 10.4, 5.8 Hz, 1H), 5.58 – 5.17 (m, 2H), 5.02 (s, 2H), 4.76 (dt, *J* = 5.8, 1.3 Hz, 2H), 3.59 (s, 2H), 3.49 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 151.7, 138.8, 138.4, 136.4, 133.8, 131.9, 131.3, 130.8, 128.9, 128.8, 128.5, 127.3, 126.9, 126.9, 126.1, 125.1, 123.6, 119.5, 69.7, 48.7, 44.7, 31.8. UPLC-DAD-QTOF: $C_{20}H_{20}NO_4$ $[M+H]^+$ calcd.: 338.1392, found: 338.1396.

Allyl (1-(naphthalen-1-ylmethyl)-2-oxo-4-phenyl-2,5-dihydro-1*H*-pyrrol-3-yl) carbonate 21Bc



Prepared according to the general procedure starting from 3-hydroxy-1-(naphthalen-1-ylmethyl)-4-phenyl-1,5-dihydro-2*H*-pyrrol-2-one **10Bc** (158 mg, 0.5 mmol). Purification by column chromatography (hexane/EtOAc, 80:20) led to the title compound as white solid. Yield: 50% (100 mg, 0.25 mmol). m.p. 131–133 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.5 Hz, 1H), 7.87 (m, 2H), 7.59 (m, 2H), 7.46 (d, *J* = 8.7 Hz, 4H), 7.33 (m, 3H), 6.12 – 5.92 (m, 1H), 5.46 (m, 1H), 5.35 (m, 1H), 5.15 (s, 2H), 4.80 (m, 1H), 4.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6 , 151.5 , 134.5 , 134.0 , 132.0 , 131.5 , 130.9 , 130.0 , 129.3 , 129.0 , 128.8 , 127.7 , 127.2 , 127.0 , 126.4 , 125.3 , 123.8 , 119.8 , 70.1 , 48.1 , 45.1 . UPLC-DAD-QTOF: $C_{25}H_{22}NO_4$ $[M+H]^+$ calcd.: 400.1549, found: 400.1551.

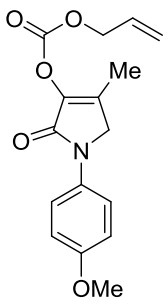
Allyl (1-isopropyl-4-methyl-2-oxo-2,5-dihydro-1*H*-pyrrol-3-yl) carbonate 21Ca



Prepared according to the general procedure starting from 3-hydroxy-1-isopropyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one **10Ca** (78 mg, 0.5 mmol). Purification by column chromatography (hexane/EtOAc, 50:50) led to the title compound as a yellow foam. Yield: 77% (92 mg, 0.39 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.45 – 5.12 (m,

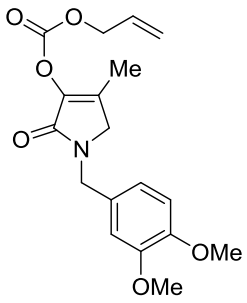
2H), 4.65 (dt, *J* = 5.8, 1.4 Hz, 2H), 4.33 (hept, *J* = 6.8 Hz, 1H), 3.71 (s, 2H), 1.90 (s, 3H), 1.12 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 151.8, 138.9, 135.0, 130.8, 119.3, 69.5, 46.3, 42.9, 20.6, 11.0. UPLC-DAD-QTOF: $C_{12}H_{18}NO_4$ $[M+H]^+$ calcd.: 240.1236, found: 240.1239.

1-(4-Methoxyphenyl)-4-methyl-2-oxo-2,5-dihydro-1*H*-pyrrol-3-yl vinyl carbonate 21Da



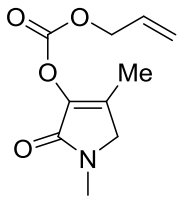
Prepared according to the general procedure starting from 3-hydroxy-1-(4-methoxyphenyl)-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one **10Da** (110 mg, 0.5 mmol). Purification by column chromatography (hexane/EtOAc, 1:1) led to the title compound as a white solid. Yield: 72% (108 mg, 0.36 mmol). m.p. 93–95 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 9.2 Hz, 2H), 6.90 (d, *J* = 9.2 Hz, 2H), 6.13 – 5.90 (m, 1H), 5.44 (d, *J* = 18.6 Hz, 1H), 5.33 (d, *J* = 10.4 Hz, 1H), 4.76 (d, *J* = 5.8 Hz, 2H), 4.24 (s, 2H), 3.80 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2 , 156.5 , 151.9 , 139.2 , 134.9 , 132.3 , 130.9 , 120.3 , 119.8 , 114.3 , 69.8 , 55.5 , 51.6 , 11.1 . UPLC-DAD-QTOF: $C_{16}H_{18}NO_5$ $[M+H]^+$ calcd.: 304.1185, found: 304.1190.

Allyl (1-(3,4-dimethoxybenzyl)-4-methyl-2-oxo-2,5-dihydro-1*H*-pyrrol-3-yl) carbonate 21Ea



Prepared according to the general procedure starting from 1-(3,4-dimethoxybenzyl)-3-hydroxy-4-methyl-1,5-dihydro-2H-pyrrol-2-one **10Ea** (132 mg, 0.5 mmol). Purification by column chromatography (hexane/EtOAc, 1:1) led to the title compound as a white solid. Yield: 70% (120 mg, 0.35 mmol). m.p. 99–101 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 – 6.70 (m, 3H), 6.03 – 5.87 (m, 1H), 5.39 (d, *J* = 17.2 Hz, 1H), 5.29 (d, *J* = 11.6 Hz, 1H), 4.71 (dt, *J* = 7.1 Hz, 2H), 4.50 (s, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.66 (s, 2H), 1.89 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.87 , 151.9 , 149.4 , 148.7 , 138.9 , 135.9 , 130.9 , 129.3 , 120.6 , 119.6 , 111.3 , 111.1 , 69.7 , 56.0 , 50.4 , 46.4 , 11.1 .UPLC-DAD-QTOF: $C_{18}H_{22}NO_6$ $[M+H]^+$ calcd.: 348.1447, found: 348.1456.

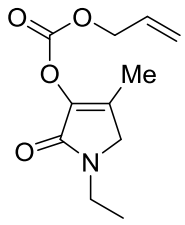
1,4-Dimethyl-2-oxo-2,5-dihydro-1*H*-pyrrol-3-yl vinyl carbonate 21Fa



Prepared according to the general procedure starting from 3-hydroxy-1,4-dimethyl-1,5-dihydro-2*H*-pyrrol-2-one **10Fa** (64 mg, 0.5 mmol). Purification by column chromatography (EtOAc) led to the title compound as colourless oil. Yield: 70% (72 mg, 0.35 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.00 – 5.81 (m, 1H), 5.38 – 5.32 (m, 1H), 5.27-5.23

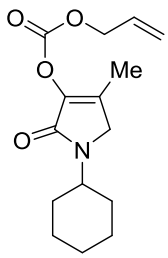
(m, 1H), 4.66 (d, *J* = 5.8 Hz, 2H), 3.77 (s, 2H), 2.95 (s, 3H), 1.89 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9 , 151.8 , 139.0 , 135.3 , 130.8 , 119.5 , 69.6 , 52.9 , 29.5 , 10.9 . UPLC-DAD-QTOF: $C_{10}H_{14}NO_4$ $[M+H]^+$ calcd.: 212.0923, found: 212.0930.

Allyl (1-ethyl-4-methyl-2-oxo-2,5-dihydro-1*H*-pyrrol-3-yl) carbonate 21Ga



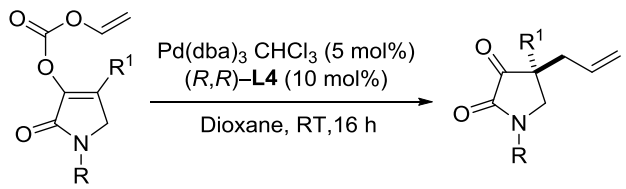
Prepared according to the general procedure starting from 1-ethyl-3-hydroxy-4-methyl-1,5-dihydro-2H-pyrrol-2-one **10Ga** (70 mg, 0.5 mmmol). Purification by column chromatography (hexane/EtOAc, 50:50) led to the title compound as colourless oil. Yield: 76% (86 mg, 0.38 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.14 – 5.85 (m, 1H), 5.51 – 5.22 (m, 2H), 4.73 (d, *J* = 5.8 Hz, 2H), 3.81 (s, 2H), 3.48 (q, *J* = 7.3 Hz, 2H), 1.96 (s, 3H), 1.18 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6 , 152.0 , 139.2 , 131.0 , 119.6 , 69.7 , 50.4 , 37.3 , 13.7 , 11.1 . UPLC-DAD-QTOF: $C_{11}H_{16}NO_4$ $[M+H]^+$ calcd.: 226.1079, found: 226.1090.

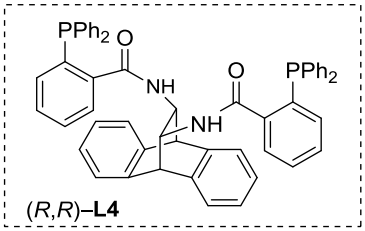
Allyl (1-cyclohexyl-4-methyl-2-oxo-2,5-dihydro-1*H*-pyrrol-3-yl) carbonate 21Ha



Prepared according to the general procedure starting from 1-cyclohexyl-3-hydroxy-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one **10Ha** (98 mg, 0.5 mmol). Purification by column chromatography (hexane/EtOAc, 80:20) led to the title compound as a colourless oil. Yield: 88% (123 mg, 0.44 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.12 – 5.80 (m, 1H), 5.48 – 5.07 (m, 2H), 4.70 (d, *J* = 5.8 Hz, 2H), 4.09 – 3.85 (m, 1H), 3.76 (s, 2H), 1.94 (s, 3H), 1.84 – 1.72 (m, 5H), 1.45 – 1.21 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3 , 152.0 , 139.1 , 135.1 , 131.0 , 119.5 , 69.7 , 50.9 , 47.3 , 31.4 , 25.6 , 11.1 . UPLC-DAD-QTOF: $C_{15}H_{22}NO_4$ $[M+H]^+$ calcd.: 280.1549, found: 280.1559.

6.3.5.1.2. *Asymmetric reaction*[262]



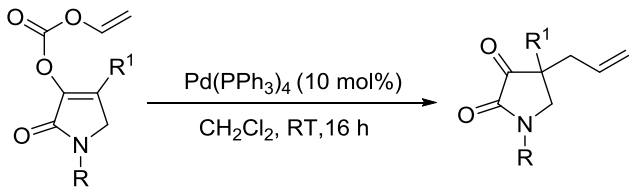


21Aa	R: Bn, R^1: Me	**22Aa**	R: Bn, R^1: Me
21Ab	R: Bn, R^1: Bn	**22Ab**	R: Bn, R^1: Bn
21Ac	R: Bn, R^1: Ph	**22Ac**	R: Bn, R^1: Ph
21Ba	R: 1-Napht-CH_2, R^1: Me	**22Ba**	R: 1-Napht-CH_2, R^1: Me
21Bb	R: 1-Napht-CH_2, R^1: Bn	**22Bb**	R: 1-Napht-CH_2, R^1: Bn
21Bc	R: 1-Napht-CH_2, R^1: Ph	**22Bc**	R: 1-Napht-CH_2, R^1: Ph
21Ca	R: ^{i}Pr, R^1: Me	**22Ca**	R: ^{i}Pr, R^1: Me
21Da	R: PMP; R^1: Me	**22Da**	R: PMP; R^1: Me
21Ea	R: 3,4-DMB, R^1: Me	**22Ea**	R: 3,4- DMBA, R^1: Me
21Fa	R: Me, R^1: Me	**22Fa**	R: Me, R^1: Me
21Ga	R: Et, R^1: Me	**22Ga**	R: Et, R^1: Me
21Ha	R: Cy, R^1: Me	**22Ha**	R: Cy, R^1: Me

In an oven dried vial, $Pd(dba)_3 \cdot CHCl_3$ (11 mg, 0.01 mmol, 5 mol%) and (*R*,*R*)–**L4** (10 mol%) were placed under argon atmosphere. Freshly distilled and degassed solvent (1 mL) was then added and the solution was stirred at the corresponding temperature for ca. 15 min until the reaction turned from heterogeneous deep red to homogeneous orange-green in colour. To this mixture, a premixed solution of allyl carbonate **21** (0.2 mmol, 1 equiv.) in the same solvent (1 mL) was slowly added. The reaction mixture stirred at the same temperature until complete conversion of the starting material (monitored by ^{1}H-NMR). Then, a saturated aqueous solution of brine (15 mL) was added and the aqueous phase was extracted with DCM (3 x 10 mL/mmol). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude material was purified by column chromatography.

[262] Adapted from: B. M. Trost, J. Xu, *J. Am. Chem. Soc.* **2005**, *127*, 2846-2847.

6.3.5.1.3. *Racemic reaction*

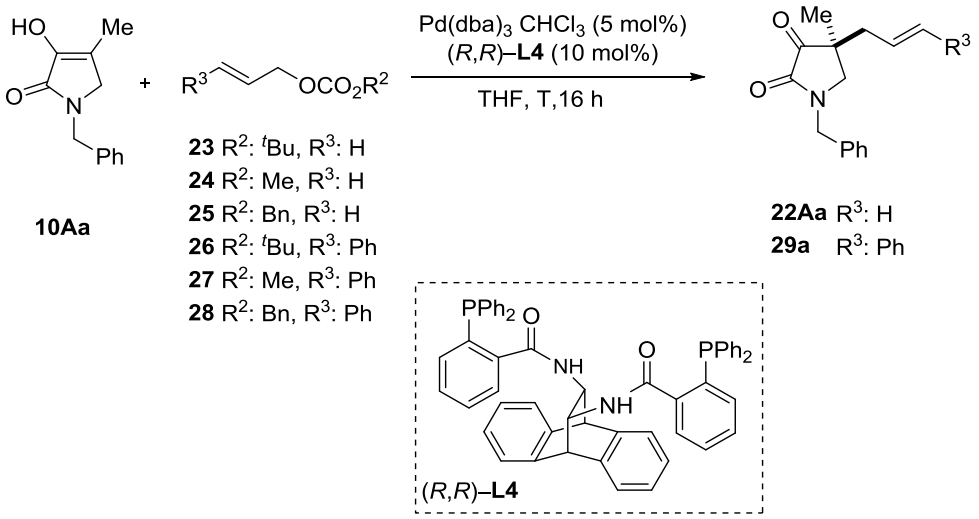


21Aa	R: Bn, R^1: Me	**(±) 22Aa**	R: Bn, R^1: Me
21Ab	R: Bn, R^1: Bn	**(±) 22Ab**	R: Bn, R^1: Bn
21Ac	R: Bn, R^1: Ph	**(±) 22Ac**	R: Bn, R^1: Ph
21Ba	R: 1-Napht-CH_2, R^1: Me	**(±) 22Ba**	R: 1-Napht-CH_2, R^1: Me
21Bb	R: 1-Napht-CH_2, R^1: Bn	**(±) 22Bb**	R: 1-Napht-CH_2, R^1: Bn
21Bc	R: 1-Napht-CH_2, R^1: Ph	**(±) 22Bc**	R: 1-Napht-CH_2, R^1: Ph
21Ca	R: ^{i}Pr, R^1: Me	**(±) 22Ca**	R: ^{i}Pr, R^1: Me
21Da	R: PMP; R^1: Me	**(±) 22Da**	R: PMP; R^1: Me
21Ea	R: 3,4-DMB, R^1: Me	**(±) 22Ea**	R: 3,4-DMB, R^1: Me
21Fa	R: Me, R^1: Me	**(±) 22Fa**	R: Me, R^1: Me
21Ga	R: Et, R^1: Me	**(±) 22Ga**	R: Et, R^1: Me
21Ha	R: Cy, R^1: Me	**(±) 22Ha**	R: Cy, R^1: Me

To a mixture of allyl carbonate **21** (0.2 mmol, 1 equiv.) in dichloromethane (1 mL), $Pd(PPh_3)_4$ (11 mg, 0.01 mmol, 5 mol%) was added at room temperature. The reaction mixture stirred until complete conversion of the starting material (monitored by ^{1}H-NMR). Then, a saturated aqueous solution of brine (15 mL) was added and the aqueous phase was extracted with DCM (3 x 10 mL/mmol). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude material was purified by column chromatography.

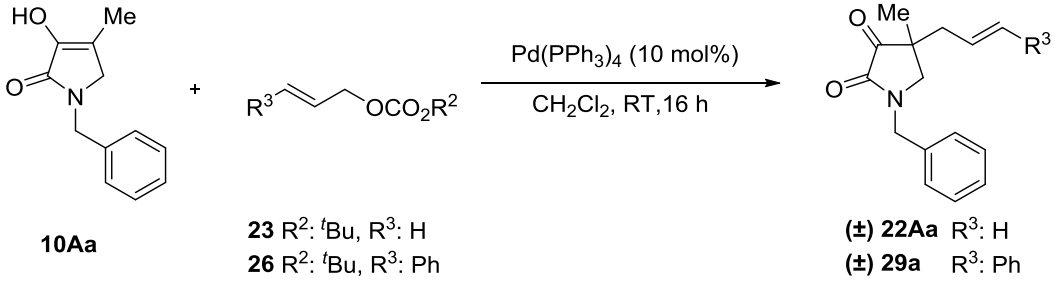
6.3.5.2. Intermolecular AAA of pyrrolidin-2,3-diones

6.3.5.2.1. *Asymmetric reaction*[263]



A mixture of $Pd_2(dba)_3$ $CHCl_3$ (11 mg, 0.01 mmol, 5 mol %) and (*R*,*R*)-**L4** (16.2 mg, 0.02 mmol, 10 mol %) was dissolved in degassed dioxane (1 mL) and the mixture was stirred under argon atmosphere for 10 min for complexation (observed by a change in colour from dark red to green, approx 10 min). Then, the corresponding allyl carbonate **23-28** (0.4 mmol, 2 equiv.) and a solution of the ketoamide **10 Aa** (0.2 mmol, 1 equiv.) in the corresponding solvent (1 mL) was slowly added. The reaction mixture was stirred at the same temperature until complete conversion of the starting material (monitored by ^{1}H-NMR). Then, a saturated aqueous solution of brine (10 mL) was added and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude material was purified by flash column chromatography to afford the pure reaction adducts.

6.3.5.2.2. *Racemic reaction*

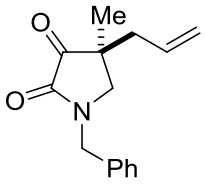


[263] Adapted from: a) M. Hayashi, L. E. Brown, J. A. Porco, *Eur. J. Org. Chem.* **2016**, 4800-4804; b) C.-X. Zhuo, S.-L. You, *Angew. Chem. Int. Ed.* **2013**, *52*, 10056-10059.

To a solution of the ketoamide **10Aa** (0.2 mmol, 1 equiv.) and the corresponding carbonate **23** or **26** (0.4 mmol, 2 equiv.) in dry dichloromethane (0.5 mL), $Pd(PPh_3)_4$ (0.02 mmol, 10 mol%) was added in one portion under argon atmosphere at room temperature. The reaction mixture was stirred until complete conversion of the starting material (16 h). Then, the solvent was evaporated and the crude was purified by column chromatography

6.3.5.3. Characterization of compounds

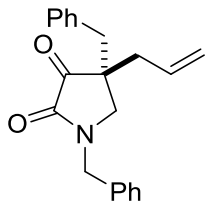
(*S*)-4-Allyl-1-benzyl-4-methylpyrrolidine-2,3-dione 22Aa



Prepared according to the general procedure starting from 1-benzyl-2,5-dihydro-4-methyl-2-oxo-1*H*-pyrrol-3-yl vinyl carbonate **21Aa** (43 mg, 0.15 mmol). Purification by column chromatography (hexane/EtOAc, 80:20) led to the title compound as a white solid. Yield: 78% (28 mg, 0.12 mmol). m.p. 68–69 ºC. $[\alpha]_D^{25}$ = – 38.3° (c=0.5, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (m, 3H), 7.25 (m, 2H), 5.64 – 5.42 (m, 1H), 5.08 – 4.92 (m, 2H), 4.74 – 4.60 (m, 2H), 3.40 (d, *J* = 10.9 Hz, 1H), 3.13 (d, *J* = 10.9 Hz, 1H), 2.32 (m, 1H), 2.17 (m, 1H), 1.17 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.7, 159.3, 134.6, 131.4, 129.1, 128.7, 128.5, 120.4, 52.4, 48.6, 43.3, 41.7, 22.0. UPLC-DAD-QTOF: $C_{16}H_{16}NO_2$ $[M+H]^+$ calculated: 244.1338, found: 244.1341.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel IC hexane/isopropanol 80/20, flow rate= 1 mL/min, retention times: 41 min (minor.) and 44 min (major.)).

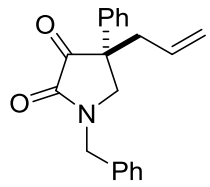
(*R*)-4-Allyl-1,4-dibenzylpyrrolidine-2,3-dione 22Ab



Prepared according to the general procedure starting from 1,4-dibenzyl-2-oxo-2,5-dihydro-1*H*-pyrrol-3-yl vinyl carbonate **21Ab** (55 mg, 0.15 mmol). Purification by column chromatography (hexane/EtOAc, 1:1) led to the title compound as a white solid. Yield: 96% (46 mg, 0.14 mmol). m.p. 99–100 ºC. $[\alpha]_D^{25}$ = + 1.8° (c=0.1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.13 (m, 6H), 7.03 – 6.81 (m, 4H), 5.72 – 5.40 (m, 1H), 5.15 – 4.94 (m, 2H), 4.55 (d, *J* = 14.5 Hz, 1H), 4.39 (d, *J* = 14.5 Hz, 1H), 3.39 (d, *J* = 11.2 Hz, 1H), 3.25 (d, *J* = 11.2 Hz, 1H), 3.10 (d, *J* = 13.6 Hz, 1H), 2.65 (d, *J* = 13.6 Hz, 1H), 2.56 – 2.42 (m, 1H), 2.31 – 2.12 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.5 , 159.2 , 135.1 , 134.3 , 131.1 , 129.9 , 129.0 , 128.8 , 128.4 , 128.2 , 127.4 , 120.8 , 48.5 , 48.3 , 47.6 , 42.2 , 41.8 . UPLC-DAD-QTOF: $C_{21}H_{22}NO_2$ $[M+H]^+$ calcd.: 320.1651, found: 320.1661.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel ADH hexane/isopropanol 90/10, flow rate= 1 mL/min, retention times: 18 min (minor.) and 19 min (major.)).

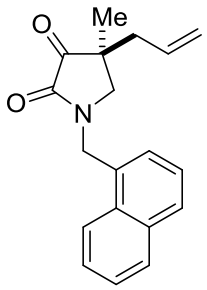
_(R)_-4-Allyl-1-benzyl-4-phenylpyrrolidine-2,3-dione 22Ac



Prepared according to the general procedure starting from Allyl (1-(naphthalen-1-ylmethyl)-2-oxo-4-phenyl-2,5-dihydro-1*H*-pyrrol-3-yl) carbonate **21Ac** (52 mg, 0.15 mmol). Purification by column chromatography (hexane/EtOAc, 70:30) led to the title compound as a white solid. Yield: 85% (39 mg, 0.13 mmol). m.p. 111–113 ºC. $[\alpha]_D^{25}$ = + 122.2° (c=0.5, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 – 7.11 (m, 10H), 5.49 – 5.33 (m, 1H), 5.08 – 4.87 (m, 2H), 4.71 (s, 2H), 3.83 (d, *J* = 11.1 Hz, 1H), 3.67 (d, *J* = 11.1 Hz, 1H), 2.78 – 2.54 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.2 , 159.0 , 138.0 , 134.5 , 131.4 , 129.1 , 128.9 , 128.6 , 129.0 , 127.9 , 126.4 , 120.6 , 51.9 , 48.7 , 43.9 , 42.8 . UPLC-DAD-QTOF: $C_{20}H_{20}NO_2$ $[M+H]^+$ calcd.: 306.1494, found: 306.1503.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel ADH hexane/isopropanol 80/20, flow rate= 1 mL/min, retention times: 10 min (major.) and 13 min (minor.)).

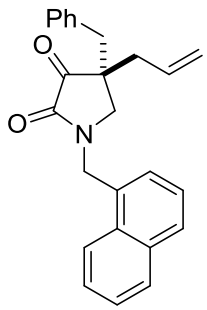
(_S_)-4-Allyl-4-methyl-1-(naphthalen-1-ylmethyl)pyrrolidine-2,3-dione 22Ba



Prepared according to the general procedure starting from allyl (4-methyl-1-(naphthalen-1-ylmethyl)-2-oxo-2,5-dihydro-1*H*-pyrrol-3-yl) carbonate **21Ba** (51 mg, 0.15 mmol). Purification by column chromatography (silica, (hexane/EtOAc, 70:30) led to the title compound as a white solid. Yield: 82% (34 mg, 0.12 mmol). m.p. 83–85 ºC. $[\alpha]_D^{25}$ = + 2.4° (c=1.7, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 – 7.98 (m, 1H), 7.87 (dq, *J* = 5.8, 2.0 Hz, 2H), 7.58 – 7.37 (m, 4H), 5.38 – 5.26 (m, 1H), 5.22 (d, *J* = 14.4 Hz, 1H), 5.02 (d, *J* = 14.4 Hz, 1H), 4.80 – 4.53 (m, 2H), 3.21 (d, *J* = 10.9 Hz, 1H), 2.98 (d, *J* = 11.0 Hz, 1H), 2.17 (ddt, *J* = 13.7, 7.0, 1.1 Hz, 1H), 2.01 (ddt, *J* = 13.7, 7.7, 1.1 Hz, 1H), 1.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.8, 158.9, 134.0, 131.5, 131.1, 130.0, 129.7, 128.9, 128.7, 127.2, 126.5, 125.1, 123.7, 120.1, 51.9, 46.7, 43.3, 41.8, 21.8. UPLC-DAD-QTOF: $C_{19}H_{20}NO_2$ $[M+H]^+$ calcd.: 294.1494, found: 294.1501.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel IC hexane/isopropanol 70/30, flow rate= 1 mL/min, retention times: 25 min (minor.) and 27 min (major.)).

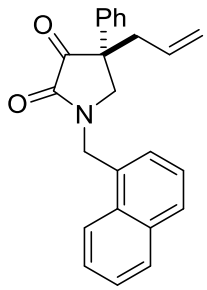
(*R*)-4-Allyl-4-benzyl-1-(naphthalen-1-ylmethyl)pyrrolidine-2,3-dione 22Bb



Prepared according to the general procedure starting from allyl (4-benzyl-1-(naphthalen-1-ylmethyl)-2-oxo-2,5-dihydro-1*H*-pyrrol-3-yl) carbonate **21Bb** (62 mg, 0.15 mmol). Purification by column chromatography (hexane/EtOAc, 70:30) led to the title compound as a white solid. Yield: 78% (43 mg, 0.12 mmol). m.p. 103–104 ºC. $[\alpha]_D^{25}$ = – 8.1° (c=2.25, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (ddt, *J* = 7.7, 4.9, 2.0 Hz, 3H), 7.58 – 7.33 (m, 3H), 7.22 (dd, *J* = 7.0, 1.2 Hz, 1H), 6.98 (dd, *J* = 5.0, 2.0 Hz, 3H), 6.79 – 6.61 (m, 2H), 5.36 (dddd, *J* = 16.8, 10.0, 8.1, 6.6 Hz, 1H), 5.01 – 4.59 (m, 4H), 3.28 (d, *J* = 11.2 Hz, 1H), 3.11 (d, *J* = 11.2 Hz, 1H), 2.96 (d, *J* = 13.6 Hz, 1H), 2.54 (d, *J* = 13.6 Hz, 1H), 2.44 – 2.32 (m, 1H), 2.10 (dd, *J* = 13.6, 8.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.3, 158.7, 134.8, 133.9, 131.4, 130.9, 129.8, 129.6, 129.5, 128.7, 128.4, 128.2, 127.2, 127.1, 126.4, 125.0, 123.6, 120.5, 48.0, 47.7, 46.5, 41.9, 41.5. UPLC-DAD-QTOF: $C_{25}H_{24}NO_2$ $[M+H]^+$ calcd.: 370.1807, found: 370.1808.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel AS-H hexane/isopropanol 50/50, flow rate= 0.5 mL/min, retention times: 34 min (major.) and 47 min (minor.)).

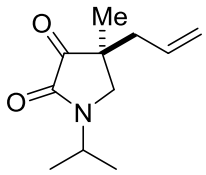
***(R)*-4-Allyl-1-(naphthalen-1-ylmethyl)-4-phenylpyrrolidine-2,3-dione 22Bc**



Prepared according to the general procedure starting from allyl (1-(naphthalen-1-ylmethyl)-2-oxo-4-phenyl-2,5-dihydro-1*H*-pyrrol-3-yl) carbonate **21Bc** (60 mg, 0.15 mmol). Purification by column chromatography (hexane/EtOAc, 80:20) led to the title compound as a yellow foam. Yield: 84% (45 mg, 0.13 mmol). $[\alpha]_D^{25}$ = + 36.2° (c=1.5, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 – 7.93 (m, 1H), 7.99 – 7.82 (m, 2H), 7.59 – 7.33 (m, 4H), 7.21 – 7.09 (m, 3H), 7.10 – 7.01 (m, 2H), 5.36 – 5.19 (m, 2H), 5.12 (d, *J* = 14.4 Hz, 1H), 4.81 – 4.51 (m, 2H), 3.67 (d, *J* = 11.2 Hz, 1H), 3.50 (d, *J* = 11.2 Hz, 1H), 2.54 (d, *J* = 7.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.2 , 158.7 , 137.8 , 134.1 , 131.6 , 131.1 , 129.9 , 129.0 , 128.9 , 127.7 , 127.4 , 126.6 , 126.3 , 125.2 , 123.9 , 120.4 , 51.6 , 50.8 , 46.9 , 42.6 . UPLC-DAD-QTOF: $C_{24}H_{22}NO_2$ $[M+H]^+$ calcd.: 356.1651, found: 356.1653.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel AS-H hexane/isopropanol 60/40, flow rate= 1 mL/min, retention times: 30 min (major.) and 45 min (minor.)).

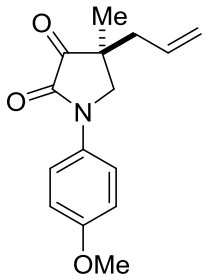
(*S*)-4-Allyl-1-isopropyl-4-methylpyrrolidine-2,3-dione 22Ca



Prepared according to the general procedure starting from allyl (1-isopropyl-4-methyl-2-oxo-2,5-dihydro-1*H*-pyrrol-3-yl) carbonate **21Ca** (36 mg, 0.15 mmol). Purification by column chromatography (hexane/EtOAc, 50:50) led to the title compound as a white solid. Yield: 77% (23 mg, 0.12 mmol). m.p. 80–82 ºC. $[\alpha]_D^{25}$ = + 12.2° (c=0.5, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71 – 5.52 (m, 1H), 5.15 (d, *J* = 1.2 Hz, 1H), 5.11 (dt, *J* = 6.4, 1.2 Hz, 1H), 4.60 (p, *J* = 6.8 Hz, 1H), 3.48 (d, *J* = 10.8 Hz, 1H), 3.20 (d, *J* = 10.8 Hz, 1H), 2.50 – 2.30 (m, 1H), 2.24 (ddt, *J* = 13.7, 7.8, 1.1 Hz, 1H), 1.35 – 1.05 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.3, 158.9, 131.7, 120.3, 47.9, 44.6, 43.1, 42.0, 22.2, 19.5. UPLC-DAD-QTOF: $C_{11}H_{18}NO_2$ $[M+H]^+$ calcd.: 196.1338, found: 196.1341.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel AS-H hexane/isopropanol 90/10, flow rate= 1 mL/min, retention times: 41 min (major.) and 49 min (minor.)).

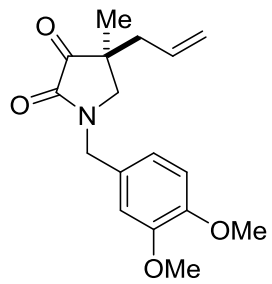
(*S*)-4-Allyl-1-(4-methoxyphenyl)-4-methylpyrrolidine-2,3-dione 22Da



Prepared according to the general procedure starting from 1-(4-methoxyphenyl)-4-methyl-2-oxo-2,5-dihydro-1*H*-pyrrol-3-yl vinyl carbonate **21Da** (45 mg, 0.15 mmol). Purification by column chromatography (hexane/EtOAc, 1:1) led to the title compound as a white solid. Yield: 96% (37 mg, 0.14 mmol). m.p. 90–91 ºC. $[\alpha]_D^{25}$ = + 5.1° (c=0.8, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 9.1 Hz, 2H), 6.95 (d, *J* = 9.1 Hz, 2H), 5.78 – 5.61 (m, 1H), 5.23 – 5.06 (m, 2H), 3.95 (d, *J* = 10.5 Hz, 1H), 3.82 (s, 3H), 3.71 (d, *J* = 10.5 Hz, 1H), 2.51 – 2.41 (m, 1H), 2.40 – 2.25 (m, 1H), 1.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.1 , 158.2 , 157.7 , 131.9 , 131.5 , 121.1 , 120.6 , 114.5 , 55.7 , 54.3 , 43.1 , 41.9 , 22.3 . UPLC-DAD-QTOF: $C_{15}H_{17}NO_3$ $[M+H]^+$ calcd.: 260.1287, found: 260.1299.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel ADH hexane/isopropanol 90/10, flow rate= 1 mL/min, retention times: 39 min (major.) and 42 min (minor.)).

***(S)*-4-Allyl-1-(3,4-dimethoxybenzyl)-4-methylpyrrolidine-2,3-dione 22Ea**

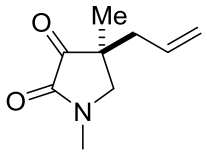


Prepared according to the general procedure starting from allyl(1-(3,4-dimethoxybenzyl)-4-methyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl) carbonate **22Ea** (52 mg, 0.15 mmol). Purification by column chromatography (hexane/EtOAc, 70:30) led to the title compound as yellow oil. Yield: 84% (38 mg, 0.13 mmol). $[\alpha]_D^{25}$ = + 49.7°

(c=1.5, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (d, *J* = 1.1 Hz, 2H), 6.76 (s, 1H), 5.61 – 5.40 (m, 1H), 5.08 – 4.91 (m, 2H), 4.57 (s, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.37 (d, *J* = 10.9 Hz, 1H), 3.11 (d, *J* = 10.9 Hz, 1H), 2.29 (dd, *J* = 14.2, 6.6 Hz, 1H), 2.15 (dd, *J* = 13.7, 7.7 Hz, 1H), 1.14 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.8 , 159.2 , 149.6 , 149.3 , 131.4 , 127.1 , 121.3 , 120.4 , 111.6 , 111.2 , 56.1, 52.3 , 48.4 , 43.3 , 41.7 , 22.1 . UPLC-DAD-QTOF: $C_{17}H_{22}NO_4$ $[M+H]^+$ calcd.: 304.1549, found: 304.1564.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel ASH hexane/isopropanol 50/50, flow rate= 1 mL/min, retention times: 17 min (major.) and 19 min (minor.)).

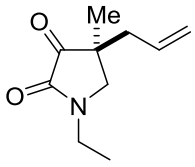
***(S)*-4-Allyl-1,4-dimethylpyrrolidine-2,3-dione 22Fa**



Prepared according to the general procedure starting from Allyl (1-ethyl-4-methyl-2-oxo-2,5-dihydro-1*H*-pyrrol-3-yl) carbonate **21Fa** (32 mg, 0.15 mmol). Purification by column chromatography (hexane/EtOAc, 1:1) led to the title compound as a yellow oil. Yield: 81% (20 mg, 0.12 mmol). $[\alpha]_D^{25}$ = + 2.9° (c=1.5, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 – 5.47 (m, 1H), 5.27 – 5.00 (m, 2H), 3.55 (d, *J* = 10.9 Hz, 1H), 3.30 (d, *J* = 10.9 Hz, 1H), 3.10 (s, 3H), 2.52 – 2.31 (m, 1H), 2.31 – 2.15 (m, 1H), 1.24 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.5 , 159.6 , 131.6 , 120.4 , 55.5 , 51.5 , 41.8 , 31.8 , 22.2 . UPLC-DAD-QTOF: $C_9H_{14}NO_2$ $[M+H]^+$ calcd.: 168.1025, found: 168.1033.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel ASH hexane/isopropanol 80/20, flow rate= 1 mL/min, retention times: 26 min (major.) and 36 min (minor.)).

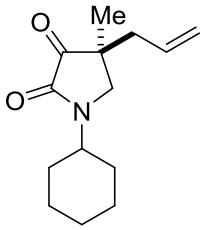
***(S)*-4-Allyl-1-ethyl-4-methylpyrrolidine-2,3-dione 22Ga**



Prepared according to the general procedure starting from Allyl (1-ethyl-4-methyl-2-oxo-2,5-dihydro-1*H*-pyrrol-3-yl) carbonate **21Ga** (34 mg, 0.15 mmol). Purification by column chromatography (hexane/EtOAc, 1:1) led to the title compound as a yellow oil. Yield: 83% (23 mg, 0.12 mmol). $[\alpha]_D^{25}$ = + 8.4° (c=0.8, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 – 5.48 (m, 1H), 5.16 (s, 1H), 5.14 – 5.06 (m, 1H), 3.64 – 3.46 (m, 3H), 3.28 (d, *J* = 10.8 Hz, 1H), 2.50 – 2.31 (m, 1H), 2.32 – 2.15 (m, 1H), 1.30 – 1.14 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.9 , 159.2 , 131.7 , 120.3 , 52.6 , 43.2 , 41.9 , 39.3 , 22.3 , 12.2 . UPLC-DAD-QTOF: $C_{10}H_{16}NO_2$ $[M+H]^+$ calcd.: 182.1181, found: 182.1186.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel ASH hexane/isopropanol 80/20, flow rate= 1 mL/min, retention times: 25 min (major.) and 31 min (minor.)).

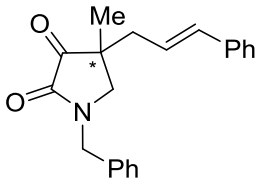
(*S*)-4-Allyl-1-cyclohexyl-4-methylpyrrolidine-2,3-dione 22Ha



Prepared according to the general procedure starting from Allyl (1-cyclohexyl-4-methyl-2-oxo-2,5-dihydro-1*H*-pyrrol-3-yl) carbonate **21Ha** (42 mg, 0.15 mmol). Purification by column chromatography (hexane/EtOAc, 80:20) led to the title compound as a white solid. Yield: 80% (28 mg, 0.12 mmol). m.p. 75–77 ºC. $[\alpha]_D^{25}$ = + 21.9° (c=0.5, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71 – 5.50 (m, 1H), 5.22 – 5.00 (m, 2H), 4.35 – 4.03 (m, 1H), 3.50 (d, *J* = 10.8 Hz, 1H), 3.22 (d, *J* = 10.8 Hz, 1H), 2.48 – 2.31 (m, 1H), 2.32 – 2.13 (m, 1H), 1.95 – 1.62 (m, 6H), 1.53 – 1.36 (m, 4H), 1.22 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.4 , 159.0 , 131.7 , 120.3 , 52.5 , 49.1 , 43.3 , 42.0 , 29.8 , 25.3 , 22.2 . UPLC-DAD-QTOF: $C_{14}H_{22}NO_2$ $[M+H]^+$ calcd.: 236.1651, found: 236.1656.

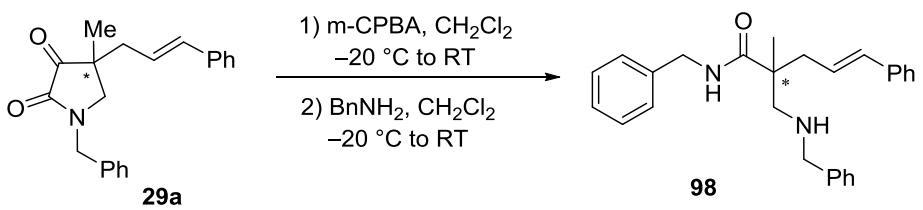
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel AS-H hexane/isopropanol 50/50, flow rate= 0.5 mL/min, retention times: 44 min (major.) and 56 min (minor.)).

1-Benzyl-4-cinnamyl-4-methylpyrrolidine-2,3-dione 29a



Prepared according to the general procedure starting from 1-benzyl-3-hydroxy-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one **10Aa** (40.6 mg, 0.2 mmol) and (*E*)-(tert-butyl carbonic) cinnamic anhydride **26** (99 mg, 0.4 mmol). Purified by column chromatography (hexane/EtOAc, 1:1). Yield: 35% (22 mg, 0.07 mmol). Yellow oil. $[\alpha]_D^{25}$ = –2.30° (c=1, CH_2Cl_2).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.04 (m, 10H), 6.30 (d, *J* = 15.7 Hz, 1H), 6.02 – 5.81 (m, 1H), 4.77 (d, *J* = 14.4 Hz, 1H), 4.55 (d, *J* = 14.4 Hz, 1H), 3.47 (d, *J* = 10.9 Hz, 1H), 3.16 (d, *J* = 10.9 Hz, 1H), 2.64 – 2.42 (m, 1H), 2.42 – 2.20 (m, 1H), 1.23 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 203.8 , 159.3 , 136.5 , 135.3 , 134.6 , 129.1 , 128.7 , 128.6 , 128.4 , 127.9 , 126.4 , 122.6 , 119.7 , 119.3 , 52.4 , 48.6 , 43.8 , 41.1 , 22.3 . UPLC-DAD-QTOF: $C_{21}H_{22}NO_2$ $[M+H]^+$ calcd.: 320.1657, found: 320.1652.

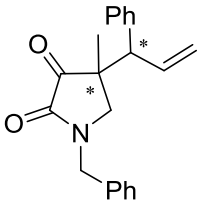
The enantiomeric purity was determined by HPLC analysis after transformation of **29a** into **98**.



To a solution of **29a** (0.03 mmol, 1 equiv.) in CH_2Cl_2 (0.2 mL), *m*CPBA (12 mg, 0.05 mmol, 1.5 equiv.) was slowly added at –20 ºC. The reaction mixture was stirred at –20 ºC and warmed up to room temperature. The reaction was quenched with aqueous 10% $NaHSO_3$ and the mixture was extracted with CH_2Cl_2 (2 x 3 mL). All organic phases were combined, washed with NaOH 1 N, dried over $MgSO_4$ and evaporated under reduced pressure to afford the NCAs. Benzylamine (4 µL, 1.2 equiv.) was added to a solution of the crude NCA (1 equiv.) in CH_2Cl_2 (0.1 mL) at –20 ºC. The reaction mixture was warmed to room temperature and stirred overnight. The reaction was then quenched with HCl 1N, and the mixture extracted with CH_2Cl_2 (3 x 3 mL), washed with $NaHCO_3$ (1 x 5 mL) and dried over $MgSO_4$.The combined organic layers were evaporated under reduced pressure. The crude was purified by column chromatograpy (hexane/EtOAc, 1:1) to afford **98** as a yellow oil. Yield: 66% (7 mg, 0.02 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.18 (m, 13H), 7.09 – 7.02 (m, 2H), 6.41 (d, *J* = 15.8 Hz, 1H), 6.23 – 6.08 (m, 1H), 4.52 – 4.35 (m, 2H), 3.69 (s, 2H), 2.85 (d, *J* = 12.4 Hz, 1H), 2.67 (d, *J* = 12.4 Hz, 1H), 2.63 – 2.57 (m, 1H), 2.47 – 2.31 (m, 1H), 1.21 (s, 3H).

HPLC analysis (Daicel Chiralcel IC hexane/isopropanol 80/20, flow rate= 1 mL/min, retention times: 17 min (major.) and 18 min (minor.)).

1-Benzyl-4-methyl-4-(1-phenylallyl)pyrrolidine-2,3-dione 29b

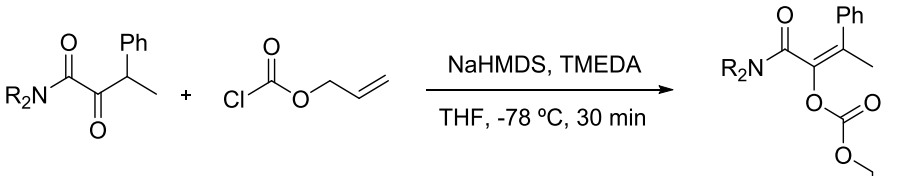


Prepared according to the general procedure starting from 1-benzyl-3-hydroxy-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one **10Aa** (40.6 mg, 0.2 mmol) and (*E*)-(*tert*-butyl carbonic) cinnamic anhydride **26** (99 mg, 0.4 mmol). Purified by column chromatography (hexane/EtOAc, 70:30). Yield: 18% (11 mg, 0.036 mmol). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, 5H), 7.22 – 7.14 (m, 2H), 7.10 – 7.02 (m, 1H), 7.00 – 6.92 (m, 2H), 6.13 – 5.84 (m, 1H), 5.30 – 5.08 (m, 2H), 4.57 (d, *J* = 14.4 Hz, 1H), 4.50 (d, *J* = 6.2 Hz, 2H), 4.38 (d, *J* = 14.4 Hz, 1H), 3.80 – 3.52 (m, 2H), 3.08 (d, *J* = 11.2 Hz, 1H), 1.23 (s, 3H). UPLC-DAD-QTOF: $C_{21}H_{22}NO_2$ $[M+H]^+$ calcd.: 320.1657, found: 320.1650.

6.3.6. Pd-catalyzed AAA of acyclic ketoamides

6.3.6.1. Decarboxylative AAA of acyclic ketoamides

6.3.6.1.1. *Carbonate formation*[263]

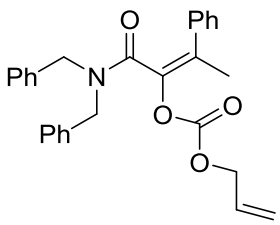


(±) 32A R: Bn
(±) 32B R: Et
(±) 32C R: ^{i}Bu
(±) 32D R: 1-CH_2-Napht
(±) 32E R: Piperidine
(±) 32F R: Morpholine
(±) 32G R: OMe, Me
(±) 32H R: Ph, Me

33A R: Bn
33B R: Et
33C R: ^{i}Bu
33D R: 1-CH_2-Napht
33E R: Piperidine
33F R: Morpholine
33G R: OMe, Me
33H R: Ph, Me

Sodium hexamethyldisilazane 1M (0.6 mL, 0.6 mmol, 1.2 equiv.) was dissolved in dry THF (2 mL) at -78 ºC under argon atmosphere. The flask was warmed to 0 ºC and TMEDA (90 µL, 0.6 mmol, 1.2 equiv.) was added. The solution was cooled to -78 ºC and a solution of the corresponding ketoamide (0.5 mmol, 1 equiv.) in THF (0.5 mL) was slowly added. The reaction mixture turned dark red and the mixture was allowed to stir for 30 min at the same temperature for enolate formation. Allyl chloroformate (71 µL, 0.6 mL, 1.2 equiv.) was then added and the mixture was stirred at the same temperature for 5 minutes. Then it was allowed to reach room temperature and quenched with a saturated solution of NH_4Cl. The mixture was then diluted with diethyl ether and the organic phase was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. The crude was purified by column chromatography.

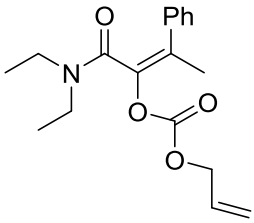
_(E)_-Allyl (1-(dibenzylamino)-1-oxo-3-phenylbut-2-en-2-yl) carbonate 33A



Prepared according to the general procedure starting from *N*,*N*-dibenzyl-2-oxo-3-phenylbutanamide **32A** (179 mg, 0.5 mmol,). Purified by column chromatography (hexane/EtOAc, 90:10) to afford **33A** as a white solid. Yield 70% (150 mg, 0.35 mmol). m.p. = 110-112 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.09 (m, 12H), 6.94 – 6.81 (m, 3H), 6.03-5.90 (m, 1H), 5.45 – 5.30 (m, 2H), 4.72 (dt, *J* = 5.7, 1.4 Hz, 2H), 4.31 (s, 2H), 4.13 (s, 2H), 2.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3 , 152.7 , 137.8 , 136.7 , 135.9 , 135.7 , 131.2 , 129.9 , 129.3 , 128.7

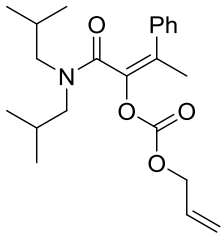
, 128.6 , 128.3 , 128.3 , 128.1 , 127.6 , 127.3 , 119.5 , 69.5 , 51.3 , 46.2 , 18.3 . UPLC-DAD-QTOF: $C_{28}H_{28}NO_4$ $[M+H]^+$ calcd.: 442.2018, found: 442.2019.

***(E)*-Allyl (1-(diethylamino)-1-oxo-3-phenylbut-2-en-2-yl) carbonate 33B**



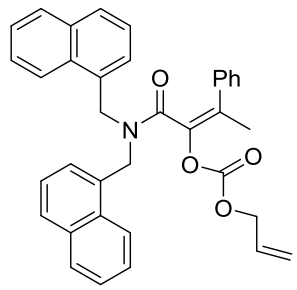
Prepared according to the general procedure starting from *N*,*N*-diethyl-2-oxo-3-phenylbutanamide **32B** (117 mg, 0.5 mmol). Purified by flash column chromatography (hexane/EtOAc, 95:5) to afford **33B** as a colourless oil. Yield: 60% (95 mg, 0.3 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (s, 5H), 6.02 – 5.89 (m, 1H), 5.50 – 5.22 (m, 2H), 4.69-4.67 (m, 2H), 3.25 (q, *J* = 7.1 Hz, 2H), 3.06 (q, *J* = 7.1 Hz, 2H), 2.11 (s, 3H), 0.89 (t, *J* = 7.2 Hz, 3H), 0.62 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1 , 152.7 , 137.9 , 137.1 , 131.1 , 128.4 , 128.3 , 128.1 , 127.3 , 119.2 , 69.2 , 42.4 , 37.8 , 17.5 , 12.4 , 11.5 .UPLC-DAD-QTOF: $C_{18}H_{24}NO_4$ $[M+H]^+$ calcd.: 318.1705, found: 318.1714.

***(E)*-Allyl (1-(diisobutylamino)-1-oxo-3-phenylbut-2-en-2-yl) carbonate 33C**



Prepared according to the general procedure starting from *N*,*N*-diisobutyl-2-oxo-3-phenylbutanamide **32C** (145 mg, 0.5 mmol). Purified by column chromatography (hexane/EtOAc, 95:5) to afford **33C** as a colourless oil. Yield: 58% (104 mg, 0.29 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (m, 5H), 6.08 – 5.86 (m, 1H), 5.43 – 5.19 (m, 2H), 4.68 (m, 2H), 3.01 (d, *J* = 7.2 Hz, 2H), 2.84 (d, *J* = 7.6 Hz, 2H), 2.02 (s, 3H), 1.80-1.68 (m, 2H), 0.72 (d, *J* = 6.6 Hz, 6H), 0.56 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.3 , 152.4 , 138.3 , 137.0 , 131.4 , 129.6 , 129.2 , 128.7 , 128.3 , 128.3 , 119.5 , 69.4 , 56.1 , 51.8 , 29.8 , 26.7 , 26.2 , 20.6 , 20.0 , 18.4. UPLC-DAD-QTOF: $C_{22}H_{32}NO_4$ $[M+H]^+$ calcd.: 373.5905, found: 373.5966.

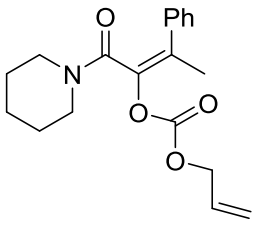
***(E)*-Allyl (1-(bis(naphthalen-1-ylmethyl)amino)-1-oxo-3-phenylbut-2-en-2-yl) carbonate 33D**



Prepared according to the general procedure starting from *N*,*N*-bis(naphthalen-1-ylmethyl)-2-oxo-3-phenylbutanamide **32D** (228 mg, 0.5 mmol). Purified by flash column chromatography (hexane/EtOAc, 90:10) to afford **33D** as a colourless oil. Yield: 83% (217 mg, 0.4 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.82 (t, *J* = 8.9 Hz, 2H), 7.73 (t, *J* = 8.7 Hz, 2H), 7.40 (dd, *J* = 29.6, 8.4 Hz, 6H), 7.21 – 7.08 (m, 5H), 6.91 (t, *J* = 8.0 Hz, 2H), 6.70 (d, *J* = 6.9 Hz, 1H), 5.89 (m, 1H), 5.47 – 5.21 (m, 2H), 5.04 (s, 2H), 4.66 (s, 2H), 4.62 – 4.48 (m, 2H), 2.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6 , 152.5 ,

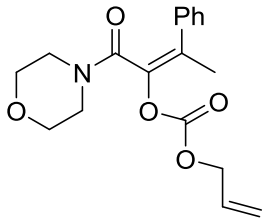
137.7 , 136.8 , 133.9 , 132.1 , 128.9 , 128.4 , 128.3 , 128.2 , 127.7 , 126.4 , 126.2 , 125.8 , 125.1 , 124.6 , 124.3 , 122.3 , 119.4 , 69.4 , 47.6 , 44.1 , 18.5 . UPLC-DAD-QTOF: $C_{36}H_{32}NO_4$ $[M+H]^+$ calcd.: 541.7483, found: 541.7470.

(*E*)-Allyl (1-oxo-3-phenyl-1-(piperidin-1-yl)but-2-en-2-yl) carbonate 33E



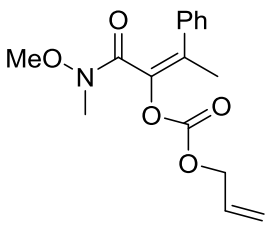
Prepared according to the general procedure starting from 3-phenyl-1-(piperidin-1-yl)butane-1,2-dione **32E** (123 mg, 0.5 mmol). The crude product was purified by flash column chromatography (hexane/EtOAc, 80:20) to afford **33E** as a colourless oil. Yield: 80% (130 mg, 0.4 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) 7.34 – 7.11 (m, 5H), 5.86 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.41 – 5.08 (m, 2H), 4.58 (dt, *J* = 5.7, 1.4 Hz, 2H), 3.35 – 3.11 (m, 2H), 2.92 (t, *J* = 5.6 Hz, 2H), 2.03 (s, 3H), 1.46 – 0.88 (m, 4H), 0.91 – 0.51 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2, 152.7, 137.8, 136.6, 131.0, 128.2, 128.2, 127.9, 127.2, 119.1, 69.0, 47.4, 42.0, 24.6, 24.5, 24.0, 17.2. UPLC-DAD-QTOF: $C_{19}H_{24}NO_4$ $[M+H]^+$ calcd.: 330.1705, found: 330.1711.

***(E)*-Allyl (1-morpholino-1-oxo-3-phenylbut-2-en-2-yl) carbonate 33F**



Prepared according to the general procedure starting from 1-morpholino-3-phenylbutane-1,2-dione **32F** (124 mg, 0.5 mmol). The crude product was purified by flash column chromatography (hexane/EtOAc, 70:30) to afford **33F** as a colourless oil. Yield: 76% (127 mg, 0.38 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.32 (m, 3H), 7.31 – 7.21 (m, 2H), 6.14 – 5.82 (m, 1H), 5.46 – 5.22 (m, 2H), 4.67 (d, *J* = 5.7 Hz, 2H), 3.38 (s, 4H), 3.14 – 2.93 (m, 2H), 2.98 – 2.76 (m, 2H), 2.12 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7 , 153.0 , 137.7 , 136.0 , 131.0 , 128.8 , 128.6 , 128.0 , 119.5 , 69.4 , 65.8 , 47.0 , 41.8 , 17.4 . UPLC-DAD-QTOF: $C_{18}H_{22}NO_5$ $[M+H]^+$ calcd.: 331.2405, found: 331.2411.

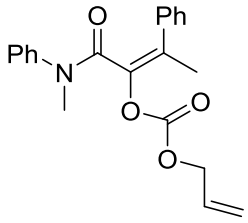
***(E)*-Allyl (1-(methoxy(methyl)amino)-1-oxo-3-phenylbut-2-en-2-yl) carbonate 33G**



Prepared according to the general procedure starting from *N*-methoxy-*N*-methyl-2-oxo-3-phenylbutanamide **32G** (111 mg, 0.5 mmol). Purified by column chromatography (hexane/EtOAc, 90:10) to afford **33G** as a colourless oil. Yield: 80% (122 mg, 0.4 mmol). Isolated as a 45:55 E/Z mixture. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.19 (m, 10H), 5.99 – 5.81 (m, 1H), 5.81 – 5.63 (m, 1H), 5.44 – 5.27 (m, 2H), 5.26 – 5.08 (m, 2H), 4.65 (d, *J* = 5.7 Hz, 2H), 4.49 (d, *J* = 5.7 Hz, 2H), 3.73 (s, 3H), 3.41 (s, 3H), 3.29 (s, 3H), 2.10 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.7 , 152.4 , 137.8 , 135.2 , 130.9 , 128.3 , 128.2 , 127.9 , 127.6 , 127.5 , 119.3 , 118.9 , 69.2 ,

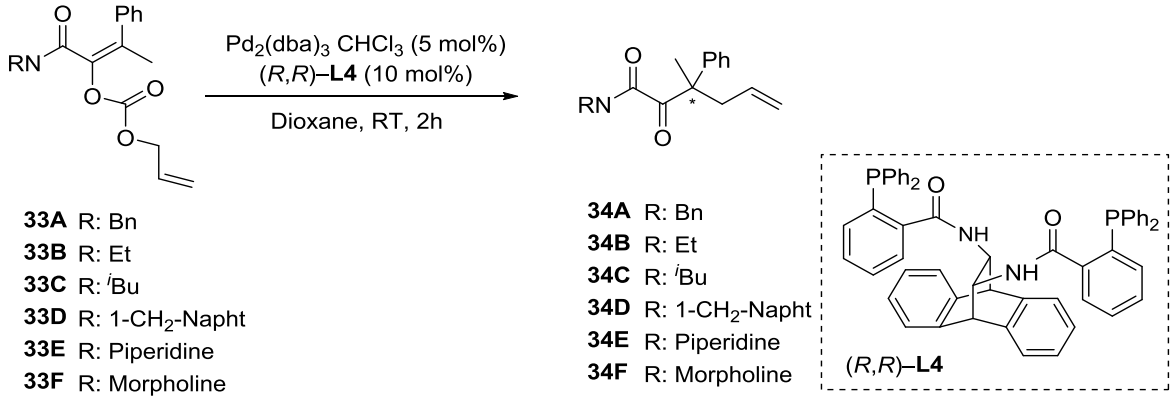
69.0 , 61.2 , 59.5 , 35.9 , 33.6 , 19.1 , 17.8 . UPLC-DAD-QTOF: $C_{16}H_{20}NO_5$ $[M+H]^+$ calcd.: 306.2205, found: 306.2269.

***(E)*-Allyl (1-(methyl(phenyl)amino)-1-oxo-3-phenylbut-2-en-2-yl) carbonate 33H**



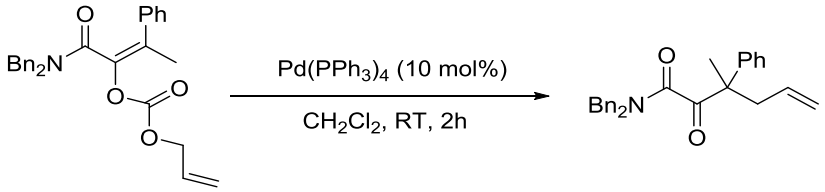
Prepared according to the general procedure starting from *N*-methyl-2-oxo-N,3-diphenylbutanamide **32H** (134 mg, 0.5 mmol). Purified by flash column chromatography (hexane/EtOAc, 90:10) to afford **33H** as a colourless oil. Yield: 71% (124 mg, 0.36 mmol). *Major isomer*: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.16 (m, 9H), 7.06 (s, 1H), 5.82 – 5.62 (m, 1H), 5.30 – 5.07 (m, 2H), 4.47 (d, *J* = 5.4 Hz, 2H), 3.44 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2 , 152.6 , 142.8 , 137.8 , 136.8 , 131.0 , 128.0 , 125.6 , 125.0 , 119.2 , 69.2 , 36.8 , 17.7 . UPLC-DAD-QTOF: $C_{21}H_{21}NO_4$ $[M+H]^+$ calcd.: 351.1570, found: 351.1564.

6.3.6.1.2. *Asymmetric reaction*[262]



A solution of $Pd_2(dba)_3$ $CHCl_3$ (10 mg, 0.01 mmol, 5 mol %) and (*R*,*R*)-**L4** (16 mg, 0.02 mmol, 10 mol %) was stirred in degassed dioxane (1 mL) under argon atmosphere for 10 min for complexation (observed by a change in colour from dark red to green, approx 10 min). A solution of the enol carbonate **33** (0.2 mmol, 1 equiv.) in dioxane (1 mL) was slowly added. The reaction mixture was then stirred at the same temperature until complete conversion of the starting material (monitored by ^{1}H-NMR). Then, a saturated aqueous solution of brine (10 mL) was added and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude material was purified by flash column chromatography to afford the pure reaction adducts.

6.3.6.1.3. *Racemic reaction*



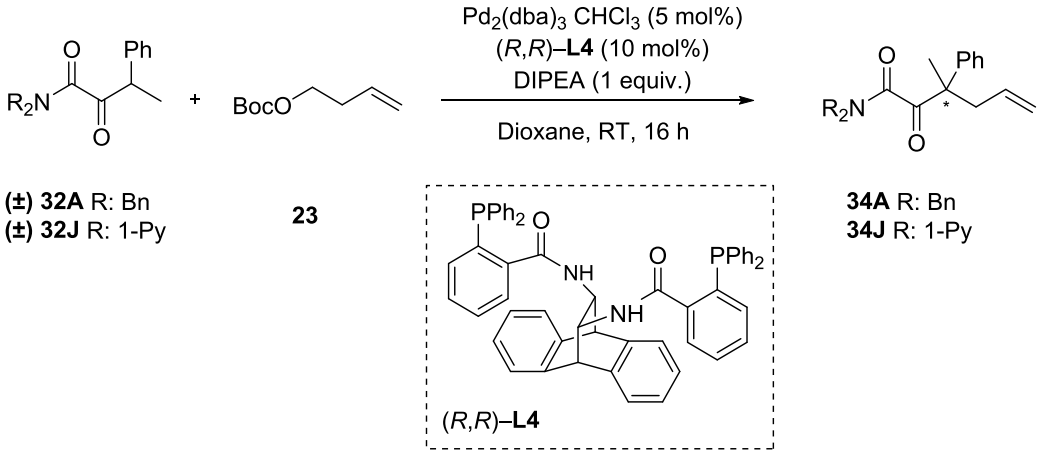
33A R: Bn
33B R: Et
33C R: ^{i}Bu
33D R: 1-CH_2-Napht
33E R: Piperidine
33F R: Morpholine

(±) 34A R: Bn
(±) 34B R: Et
(±) 34C R: ^{i}Bu
(±) 34D R: 1-CH_2-Napht
(±) 34E R: Piperidine
(±) 34F R: Morpholine

To a solution of the corresponding enol carbonate **33** (0.2 mmol, 1 equiv.) in dry dichloromethane (0.5 mL), $Pd(PPh_3)_4$ (0.02 mmol, 10 mol%) was added in one portion under argon atmosphere at room temperature. The reaction mixture stirred until complete conversion of the starting material. Then, the solvent was evaporated and the crude was purified by column chromatography.

6.3.6.2. Intermolecular AAA of acyclic ketoamides

6.3.6.2.1. *Asymmetric reaction*[263]



(±) 32A R: Bn
(±) 32J R: 1-Py

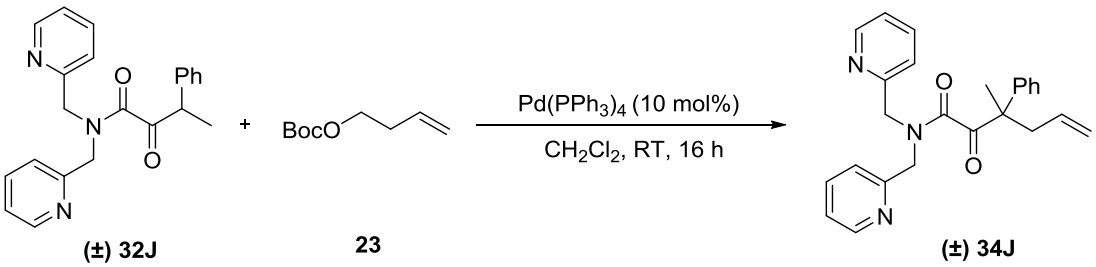
23

34A R: Bn
34J R: 1-Py

A solution of $Pd_2(dba)_3$ $CHCl_3$ (10 mg, 0.01 mmol, 5 mol %) and (*R*,*R*)-**L4** (16 mg, 0.02 mmol, 10 mol %) in degassed dioxane (1 mL) under argon atmosphere was stirred for 10 min for complexation (observed by a change in colour from dark red to green, approx 10 min). A solution of the corresponding ketoamide **32** (0.2 mmol, 1 equiv.) in dioxane (1 mL) was slowly added followed by *tert*-butyl allyl carbonate (0.4 mmol, 2 equiv.) and DIPEA (0.2 mmol, 1 equiv.). The reaction mixture was stirred at the same temperature until complete conversion of the starting material (monitored by ^{1}H-NMR). Then, a saturated aqueous solution of brine (10 mL) was added and the aqueous phase was

extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude material was purified by flash column chromatography to afford the pure reaction adducts.

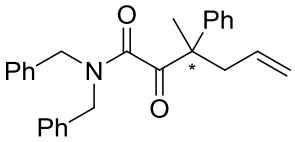
6.3.6.2.2. *Racemic reaction*



To a solution of the corresponding ketoamide (0.2 mmol, 1 equiv.) and allyl *tert*-butyl carbonate (0.4 mmol, 2 equiv.) in dry dichloromethane (0.5 mL), $Pd(PPh_3)_4$ (0.02 mmol, 10 mol%) was added in one portion under argon atmosphere at room temperature. The reaction mixture was stirred until complete conversion of the starting material. Then, the solvent was evaporated and the crude was purified by column chromatography.

6.3.6.3. Characterization of compounds

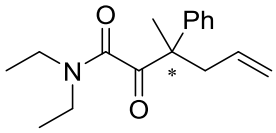
***N,N*-Dibenzyl-3-methyl-2-oxo-3-phenylhex-5-enamide 34A**



The title compound was prepared according to the general procedure starting from *(E)*-allyl (1-(dibenzylamino)-1-oxo-3-phenylbut-2-en-2-yl) **33A** (88 mg, 0.2 mmol). Purified by column chromatography (hexane/EtOAc, 95:5) to afford **34A** as a white solid. Yield: 84% (66 mg, 0.17 mmol). m.p. = 63-65 ºC. $[\alpha]_D^{25}$ = + 11.7° (c=1.5, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (m, 2H), 7.40 – 7.29 (m, 6H), 7.28 – 7.14 (m, 5H), 6.77 (m, 2H), 5.61 (s, 1H), 5.15-5.04 (m, 2H), 4.29 (s, 2H), 3.87 (s, 2H), 3.09-3.02 (m, 1H), 2.98-2.91 (m, 1H), 1.75 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.9 , 167.9 , 141.0 , 136.6 , 136.0 , 134.5 , 130.0 , 129.8 , 129.6 , 129.4 , 129.6 , 129.2 , 128.5 , 128.5 , 128.5 , 120.0 , 55.0 , 50.6 , 46.5 , 44.1 , 22.8 .UPLC-DAD-QTOF: $C_{24}H_{24}NO_2$ $[M+H]^+$ calcd.: 398.2120, found: 398.2113.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel AD-H hexane/isopropanol 90/10, flow rate= 1 mL/min, retention times: 10 min (major.) and 12 min (minor.)).

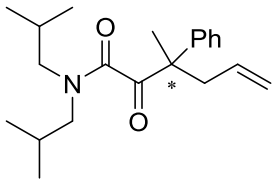
***N,N*-Diethyl-3-methyl-2-oxo-3-phenylhex-5-enamide 34B**



The title compound was prepared according to the general procedure starting from *(E)*-allyl (1-(diethylamino)-1-oxo-3-phenylbut-2-en-2-yl) carbonate **33B** (63 mg, 0.2 mmol). Purified by flash column chromatography (hexane/EtOAc, 95:5) to afford **34B** as colourless oil. Yield: 80% (44 mg, 0.16 mmol). $[\alpha]_D^{25}$ = + 10.3° (c=1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 – 7.11 (m, 1H), 5.71 – 5.42 (m, 0H), 5.24 – 4.96 (m, 1H), 3.37 – 3.06 (m, 1H), 3.01 – 2.86 (m, 1H), 2.82 – 2.69 (m, 1H), 1.64 (s, 1H), 1.18 – 0.59 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.5 , 166.2 , 140.2 , 133.6 , 128.7 , 127.4 , 118.8 , 53.7 , 43.3 , 41.7 , 38.2 , 21.1 , 13.7 , 12.2 .UPLC-DAD-QTOF: $C_{17}H_{24}NO_2$ $[M+H]^+$ calcd.: 274.1807, found: 274.1807.

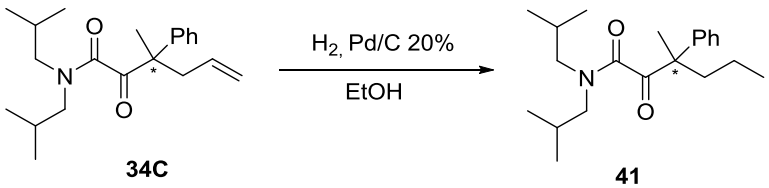
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel AY-H hexane/isopropanol 95/5, flow rate= 1 mL/min, retention times: 16 min (major.) and 30 min (minor.)).

***N,N*-Diisobutyl-3-methyl-2-oxo-3-phenylhex-5-enamide 34C**



The title compound was prepared according to the general procedure starting from *(E)*-allyl (1-(diisobutylamino)-1-oxo-3-phenylbut-2-en-2-yl) carbonate **33C** (75 mg, 0.2 mmol). Purified by column chromatography (hexane/EtOAc, 95:5) to afford **34C** as colourless oil. Yield: 90% (59 mg, 0.19 mmol). $[\alpha]_D^{25}$ = + 11.3° (c=1.5, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5H), 5.55 (m, 1H), 5.07 (m, 2H), 3.14 (m, 1H), 3.03 (m, 1H), 2.89 (m, 2H), 2.57 (d, *J* = 7.6 Hz, 2H), 1.86-1.77 (m, 1H), 1.67 (s, 3H), 0.75 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.2 , 167.5 , 140.5 , 133.8 , 128.7 , 127.3 , 118.8 , 54.2 , 53.4 , 50.7 , 43.8 , 26.5 , 25.9 , 21.0 , 20.3 , 19.7 . UPLC-DAD-QTOF: $C_{21}H_{31}NO_2$ $[M+H]^+$ calcd.: 329.4950, found: 329.4956.

The enantiomeric purity was determined in compound 41, obtained after hydrogenation of the allyl group in **34C**.



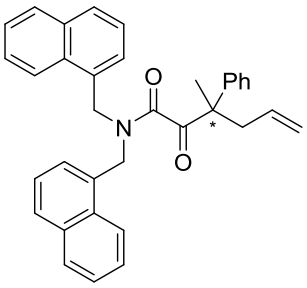
34C **41**

To a solution of **34C** (36 mg, 0.1 mmol) in EtOH (0.4 mL) under argon atmosphere, Pd on carbon (8 mg) was carefully added. The mixture was stirred under H_2 for 16 h and then filtered through celite. Evaporation of the solvent under reduced

pressure provided **41** as a yellow oil. Quantitative yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 5H), 3.10 (m, 1H), 3.03 (m, 1H), 2.54 (d, *J* = 7.6 Hz, 2H), 2.16-2.06 (m, 2H), 1.85-1.76 (m, 2H), 1.67 (s, 3H), 1.33-1.20 (m, 1H), 1.15-1.05 (m, 1H), 0.90 (t, *J* = 13.8 Hz, 3H), 0.74 (m, 12H).

HPLC analysis (Daicel Chiralcel IC hexane/isopropanol 90/10, flow rate= 1 mL/min, retention times: 5 min (major.) and 6 min (minor.)).

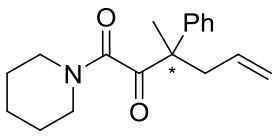
3-Methyl-*N*,*N*-bis(naphthalen-1-ylmethyl)-2-oxo-3-phenylhex-5-enamide 34D



The title compound was prepared according to the general procedure starting from *(E)*-allyl (1-(bis(naphthalen-1-ylmethyl)amino)-1-oxo-3-phenylbut-2-en-2-yl) carbonate (108 mg, 0.2 mmol) **33D**. Purified by column chromatography (hexane/EtOAc, 95:5) to afford **34D** as colourless oil. Yield: 80% (79 mg, 0.16 mmol). $[\alpha]_D^{25}$ = - 2.9° (c=2.5, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 – 7.71 (m, 6H), 7.57 – 7.41 (m, 4H), 7.42 – 7.32 (m, 4H), 7.30 – 7.10 (m, 4H), 6.66 (d, *J* = 6.9 Hz, 1H), 5.70 – 5.41 (m, 1H), 5.15 – 4.86 (m, 4H), 4.32 (d, *J* = 3.7 Hz, 2H), 3.09 – 2.84 (m, 2H), 1.73 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.4 , 167.5 , 139.9 , 133.9 , 133.6 , 131.6 , 130.3 , 129.0 , 128.9 , 128.8 , 128.6 , 128.4 , 127.5 , 127.4 , 126.8 , 126.6 , 126.3 , 126.1 , 125.9 , 125.6 , 125.3 , 124.9 , 123.7 , 122.2 , 118.9 , 53.9 , 46.7 , 44.3 , 43.1 , 21.3 . UPLC-DAD-QTOF: $C_{35}H_{32}NO_2$ $[M+H]^+$ calcd.: 498.3376, found: 498.3356.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel IC hexane/isopropanol 90/10, flow rate= 1 mL/min, retention times: 9 min (major.) and 11 min (minor.)).

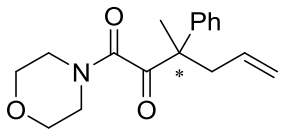
3-Methyl-3-phenyl-1-(piperidin-1-yl)hex-5-ene-1,2-dione 34E



The title compound was prepared according to the general procedure starting from (*E*)-allyl (1-oxo-3-phenyl-1-(piperidin-1-yl)but-2-en-2-yl) carbonate **33E** (66 mg, 0.2 mmol). Purified by column chromatography (hexane/EtOAc, 90:10) to afford **34E** as colourless oil. Yield: 81% (46 mg, 0.16 mmol). $[\alpha]_D^{25}$ = + 0.7° (c=1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 – 7.12 (m, 5H), 5.56 (ddt, *J* = 17.2, 10.1, 7.2 Hz, 1H), 5.18 – 4.94 (m, 2H), 3.36 (t, *J* = 5.4 Hz, 2H), 3.08 – 2.64 (m, 4H), 1.65 (s, 3H), 1.56 – 1.31 (m, 4H), 1.28 – 0.97 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.6, 165.2, 140.0, 133.6, 128.7, 127.5, 127.4, 118.8, 53.6, 46.7, 43.2, 41.8, 25.8, 25.2, 24.3, 20.9. UPLC-DAD-QTOF: $C_{18}H_{24}NO_2$ $[M+H]^+$ calcd.: 286.1807, found: 286.1809.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel IC hexane/isopropanol 90/10, flow rate= 1 mL/min, retention times: 30 min (major.) and 32 min (minor.)).

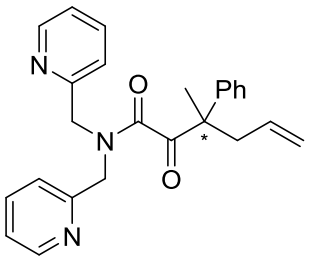
3-Methyl-1-morpholino-3-phenylhex-5-ene-1,2-dione 34F



The title compound was prepared according to the general procedure starting from *(E)*-allyl (1-morpholino-1-oxo-3-phenylbut-2-en-2-yl) carbonate **33F** (67 mg, 0.2 mmol). Purified by column chromatography (hexane/EtOAc, 90:10) to afford **34F** as colourless oil. Yield: 73% (42 mg, 0.14 mmol). $[\alpha]_D^{25}$ = - 3.1° (c=1.5, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.13 (m, 5H), 5.70 – 5.41 (m, 1H), 5.32 – 4.91 (m, 2H), 3.55 – 3.33 (m, 4H), 3.32 – 3.19 (m, 1H), 3.19 – 3.08 (m, 1H), 3.03 – 2.80 (m, 4H), 1.66 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.5 , 165.2 , 139.5 , 133.4 , 129.0 , 127.8 , 127.6 , 119.1 , 66.3 , 53.9 , 46.0 , 42.7 , 41.3 , 21.0 . UPLC-DAD-QTOF: $C_{17}H_{22}NO_3$ $[M+H]^+$ calcd.: 288.1600, found: 288.1605

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel IC hexane/isopropanol 80/20, flow rate= 1 mL/min, retention times: 11 min (major.) and 13 min (minor.)).

3-Methyl-2-oxo-3-phenyl-*N*,*N*-bis(pyridin-2-ylmethyl)hex-5-enamide 34J

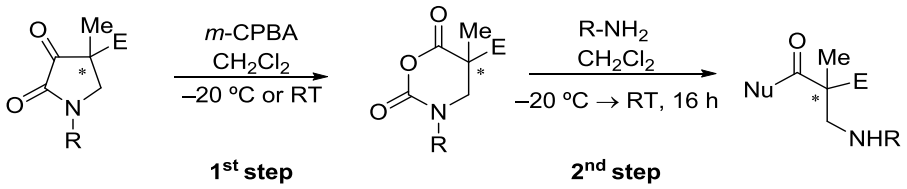


The title compound was prepared according to the general procedure starting from 2-oxo-3-phenyl-*N*,*N*-bis(pyridin-2-ylmethyl)butanamide **32J** (72 mg, 0.2 mmol). The solvent was evaporated and the crude was purified by column chromatography (hexane/EtOAc, 30:70) to afford **34J** as colourless oil. Yield: 68% (54 mg, 0.14 mmol). $[\alpha]_D^{25}$ = + 10.9° (c=1.5, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 – 8.48 (m, 1H), 8.48 – 8.39 (m, 2H), 7.76 – 7.61 (m, 2H), 7.58 – 7.41 (m, 3H), 7.19 – 7.04 (m, 3H), 6.90 – 6.82 (m, 1H), 6.71 – 6.58 (m, 1H), 5.70 – 5.49 (m, 1H), 5.20 – 4.98 (m, 1H), 4.89 (d, *J* = 15.5 Hz, 1H), 4.45 (d, *J* = 16.6 Hz, 1H), 4.31 (d, *J* = 13.7 Hz, 1H), 4.26 – 4.14 (m, 1H), 3.12 – 2.95 (m, 1H), 2.95 – 2.84 (m, 1H), 1.73 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.9 , 167.9 , 141.0 , 136.6 , 136.0 , 134.5 , 130.0 , 129.8 , 129.6 , 129.4 , 129.2 , 128.5 , 128.5 , 128.5 , 120.0 , 55.0 , 50.6 , 46.5 , 44.1 , 22.8 .UPLC-DAD-QTOF: $C_{25}H_{26}N_3O_2$ $[M+H]^+$ calcd.: 400.2154, found: 400.2166

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel IA hexane/isopropanol 70/30, flow rate= 1 mL/min, retention times: 14 min (major.) and 18 min (minor.)).

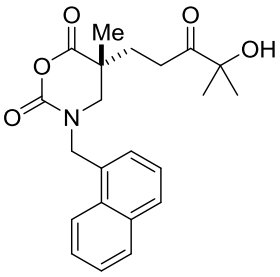
6.3.7. Elaboration of adducts

6.3.7.1. To NCAs and ring opening with amines



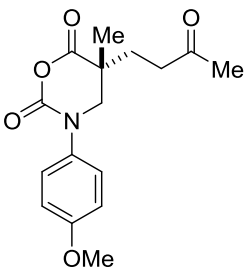
1st step: To a solution of the reaction adduct (0.2 mmol, 1 equiv.) in CH_2Cl_2 (1 mL), *m*CPBA (67 mg, 0.3 mmol, 1.5 equiv.) was slowly added at –20 ºC. The reaction mixture was stirred at –20 ºC or warmed up to room temperature for 1 h. The reaction was quenched with aqueous 10% $NaHSO_3$ and the mixture extracted with CH_2Cl_2 (2 x 3 mL). All organic phases were combined, washed with NaOH 1 N (1 x 4 mL), dried over $MgSO_4$ and evaporated under reduced pressure to afford the corresponding pure NCAs.

(*R*)-5-(4-Hydroxy-4-methyl-3-oxopentyl)-5-methyl-3-(naphthalen-1-ylmethyl)-1,3-oxazinane-2,6-dione 35



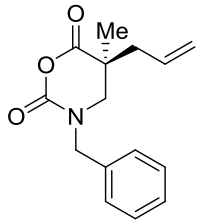
The title compound was prepared starting from (*R*)-4-(4-hydroxy-4-methyl-3-oxopentyl)-4-methyl-1-(naphthalen-1-yl-methyl)pyrrolidine-2,3-dione **14Ba** (73 mg, 0.2 mmol) and following the general procedure at –20 ºC for 1 h. The crude material was pure enough for the next step (77 mg, 0.2 mmol, quantitative). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 – 8.05 (m, 1H), 8.03 – 7.84 (m, 2H), 7.67 – 7.35 (m, 4H), 5.15 (d, *J* = 14.5 Hz, 1H), 5.08 (d, *J* = 14.5 Hz, 1H), 3.04 – 2.92 (m, 2H), 2.41 (ddd, *J* = 18.1, 9.3, 5.9 Hz, 1H), 2.26 (ddd, *J* = 18.1, 9.1, 5.8 Hz, 1H), 1.79 (ddd, *J* = 14.9, 9.1, 6.0 Hz, 1H), 1.50 (ddd, *J* = 14.7, 9.2, 5.7 Hz, 1H), 1.25 (s, 3H), 1.24 (s, 3H), 0.99 (s, 3H).

(*R*)-3-(4-Methoxyphenyl)-5-methyl-5-(3-oxobutyl)-1,3-oxazinane-2,6-dione 36



The title compound was prepared starting from (*R*)-1-(4-methoxyphenyl)-4-methyl-4-(3-oxobutyl)pyrrolidine-2,3-dione **18Da** (58 mg, 0.2 mmol) and following the general procedure at –20 ºC for 1 h. The crude material was pure enough for the next step (61 mg, 0.2 mmol, quantitative). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.18 (m, 2H), 7.03 – 6.88 (m, 2H), 3.81 (s, 3H), 3.57 (q, *J* = 12.9 Hz, 2H), 2.59 (t, *J* = 7.7 Hz, 2H), 2.25 – 2.18 (m, 1H), 2.17 (s, 3H), 2.03 – 1.85 (m, 1H), 1.35 (s, 3H).

(*S*)-5-Allyl-3-benzyl-5-methyl-1,3-oxazinane-2,6-dione 37



The title compound was prepared starting from (*S*)-4-allyl-1-benzyl-4-methylpyrrolidine-2,3-dione (49 mg, 0.2 mmol) **22Aa** and following the general procedure at –20 ºC for 1 h. The crude material was pure enough for the next step (51 mg, 0.2 mmol, quantitative). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.30 (m, 5H), 5.65 – 5.44 (m, 1H), 5.24 – 4.91 (m, 2H), 4.66 (d, *J* = 14.6 Hz, 1H), 4.52 (d, *J* = 14.6 Hz, 1H), 3.13 (d, *J* = 12.8 Hz, 1H), 3.02 (d, *J* = 12.9 Hz, 1H), 2.29 (d, *J* = 6.3 Hz, 2H), 1.16 (s, 3H).

2nd step:

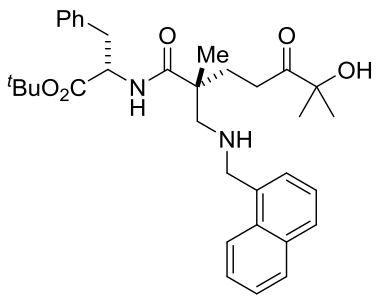
METHOD A: Amino ester hydrochlorides as nucleophiles

A suspension of the amino ester hydrochloride (1.2 equiv.) in CH_2Cl_2 (2 mL/mmol) was treated with Et_3N (2.0 equiv.) for 30 min. The mixture was then cooled to –20 ºC and the corresponding NCA (1.0 equiv.) solution in CH_2Cl_2 (1 mL/mmol) was added at this temperature. The reaction mixture was warmed to room temperature and stirred overnight. The reaction was quenched with HCl 1N, and the mixture extracted with CH_2Cl_2 (3 x 2 mL/mmol), washed with $NaHCO_3$ (1 x 4 mL/mmol and dried over $MgSO_4$. The organic layer was evaporated under reduced pressure to provide the reaction product.

METHOD B: Amines as nucleophiles

The amine nucleophile (1.2 equiv.) was added to a solution of the crude NCA (1 equiv.) in CH_2Cl_2 (2 mL/mmol) at –20 ºC. The reaction mixture was warmed to room temperature and stirred overnight. The reaction was quenched with HCl 1N, and the mixture extracted with CH_2Cl_2 (3 x 2 mL/mmol), washed with $NaHCO_3$ (1 x 4 mL/mmol) and dried over $MgSO_4$. The organic layer was evaporated under reduced pressure to provide the reaction product.

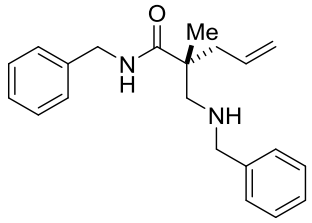
(*S*)-*tert*-Butyl 2-((*R*)-6-hydroxy-2,6-dimethyl-2-(((naphthalen-1-ylmethyl)amino) methyl)-5-oxoheptanamido)-3-phenylpropanoate 38



The title compound was prepared from (*R*)-5-(4-hydroxy-4-methyl-3-oxopentyl)-5-methyl-3-(naphthalene-1-ylmethyl)-1,3-oxazinane-2,6-dione **35** (77 mg, 0.2 mmol), (*S*)-*tert*-butyl 2-amino-3-phenylpropanoate hydrochloride (62 mg, 0.24 mmol) and triethylamine (56 μL, 0.4 mmol) following METHOD A. The reaction mixture was stirred for 16 h until completion of reaction. The crude material

was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 80/20) to give the title compound as a white foam (86 mg, 0.15 mmol, 77% yield). $[\alpha]_D^{25}$ = + 1.8° (c=0.8, 96% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.93 (d, *J* = 8.4 Hz, 1H), 8.12 (dt, *J* = 7.4, 1.4 Hz, 1H), 7.94 – 7.75 (m, 2H), 7.56 – 7.34 (m, 5H), 7.12 – 7.03 (m, 2H), 6.89 – 6.79 (m, 2H), 4.70 – 4.59 (m, 1H), 4.32 (d, *J* = 13.0 Hz, 1H), 4.05 (d, *J* = 13.0 Hz, 1H), 2.98 (dd, *J* = 13.8, 5.4 Hz, 1H), 2.76 (d, *J* = 12.2 Hz, 1H), 2.70 (d, *J* = 12.2 Hz, 1H), 2.54 (dd, *J* = 13.8, 8.8 Hz, 1H), 2.43 – 2.15 (m, 3H), 1.72 – 1.61 (m, 2H), 1.44 (s, 9H), 1.26 (s, 3H), 1.23 (s, 3H), 1.09 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 214.7, 176.0, 171.3, 137.2, 134.2, 132.0, 129.4, 129.1, 128.5, 128.3, 127.0, 126.8, 126.7, 126.0, 125.6, 123.9, 81.8, 76.5, 56.6, 53.5, 52.3, 44.2, 38.0, 31.8, 28.2, 26.7, 26.6, 22.1. UPLC-DAD-QTOF: $C_{34}H_{45}N_2O_5$ [M+H]+ calcd.: 561.3328, found: 561.3331.

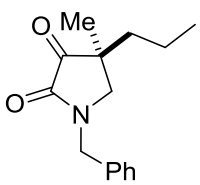
(*R*)-*N*-Benzyl-2-((benzylamino)methyl)-2-methylpent-4-enamide 39



The title compound was prepared from (*S*)-5-allyl-3-benzyl-5-methyl-1,3-oxazinane-2,6-dione **37** (52 mg, 0.2 mmol), benzylamine (28 µL, 0.24 mmol) following METHOD B. The reaction mixture was stirred for 16 h until completion of reaction. The crude material was purified by flash column chromatography on silica gel (hexane/EtOAc, 50:50) to give the title compound as a yellow oil. Yield: 70% (45 mg, 0.14 mmol). $[\alpha]_D^{23}$ = 11.2° (c=0.5, 92% *ee*, CH_2Cl_2).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.15 (m, 8H), 7.06 (m, 2H), 5.97 – 5.57 (m, 1H), 5.18 – 5.07 (m, 2H), 4.41 (d, *J* = 5.4 Hz, 2H), 3.69 (s, 2H), 2.79 (d, *J* = 12.4 Hz, 1H), 2.62 (d, *J* = 12.4 Hz, 1H), 2.45 (d, *J* = 13.8 Hz, 1H), 2.26 (dd, *J* = 13.8, 7.6 Hz, 1H), 1.16 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8 , 134.3 , 128.7 , 128.6 , 128.3 , 127.9 , 127.4 , 127.3 , 118.1 , 55.7 , 54.6 , 44.6 , 43.5 , 42.3 , 22.2 . UPLC-DAD-QTOF: $C_{21}H_{27}N_2O$ $[M+H]^+$ calcd.: 323.2126, found: 323.2123.

6.3.7.2. Hydrogenation

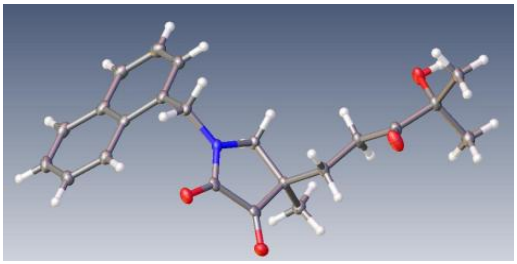
(*S*)-1-Benzyl-4-methyl-4-propylpyrrolidine-2,3-dione 40

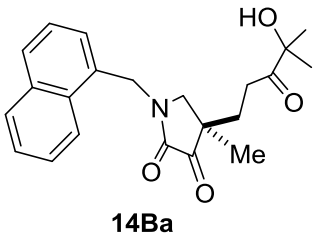


To a solution of **22Aa** (49 mg, 0.2 mmol) in EtOH (0.6 mL) under argon atmosphere, Pd on carbon (8 mg) was carefully added. The mixture was stirred under H_2 for 16 h and then filtered through celite. Purification by column chromatography (hexane/EtOAc, 80:20) led to the title compound as white foam. Yield: 80% (39 mg, 0.16 mmol). $[\alpha]_D^{25}$ = 22.14° (c=0.5, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.19 (m, 5H), 4.68 (s, 2H), 3.34 (d, *J* = 10.8 Hz, 1H), 3.15 (d, *J* = 10.8 Hz, 1H), 1.62 – 1.40 (m, 2H), 1.15 (s, 3H), 1.22 – 0.99 (m, 2H), 0.83 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.2 ,

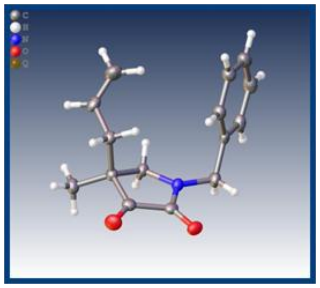
159.5 , 134.7 , 129.2 , 128.7 , 128.5 , 128.0 , 53.5 , 48.6 , 43.6 , 39.9 , 22.3 , 17.5 , 14.5 .
UPLC-DAD-QTOF: $C_{15}H_{20}NO_2$ $[M+H]^+$ calcd.: 246.1502, found: 246.1494.

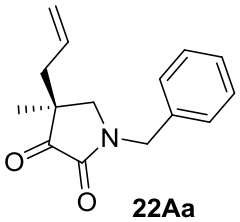
6.3.8. ORTEP diagram for compounds 14Ba, 22Aa and 33A.



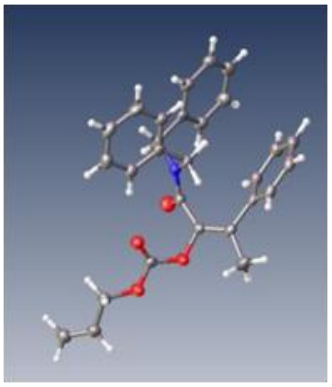


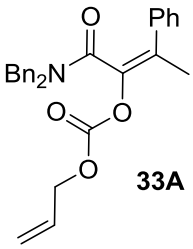
14Ba





22Aa





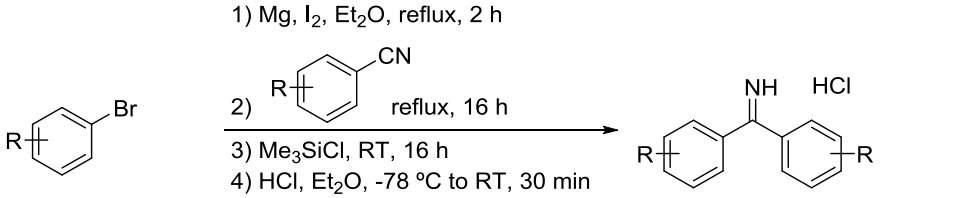
33A

6.4. EXPERIMENTAL SECTION OF CHAPTER 3

6.4.1. Preparation of pronucleophiles

6.4.1.1. Preparation of ketimine hydrochlorides

Imine hydrochlorides **55** and **56** were prepared adapting literature procedures.[264]



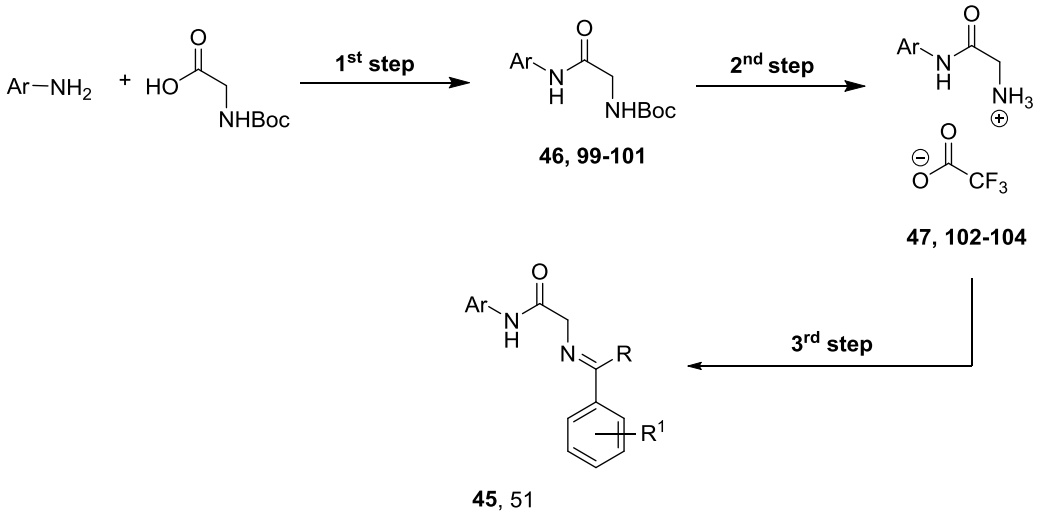
55 R: 3,5-$(CF_3)_2$Ph (70% yield)
56 R: 4-CF_3Ph (82% yield)

Dry diethyl ether (50 mL) was added to a three-necked round bottom flask equipped with a reflux condenser containing magnesium powder (434 mg, 20 mmol, 1 equiv.) and iodine (20 mg). The resulting suspension was heated to mild reflux and the corresponding bromobenzene was added dropwise (20 mmol, 1 equiv.). The resulting mixture was stirred at the same temperature for 2 h, the magnesium was dissolved and the solution darkened.

The corresponding benzonitrile (20 mmol, 1 equiv.) was then added dropwise to the solution and the mixture was allowed to stir at the same temperature for 16 h, resulting in the formation of a white salt. Thus, Me_3SiCl (2.5 mL, 20 mmol, 1 equiv.) was added dropwise with vigorous stirring after removing the heating, and the resulting mixture was stirred at room temperature for 16 h. A brown solid formed as a result, and the mixture was concentrated under reduced pressure and dissolved in benzene in order to filter off the salts. Benzene was then removed under reduced pressure and the resulting crude was dissolved in dry diethyl ether (10 mL) and the mixture was cooled to –78 °C. Then, HCl (2 M in Et_2O, 10 mL, 20 mmol, 1 equiv.) was added, the resulting suspension was allowed to warm to room temperature over 30 minutes and the solid was filtered and washed with diethyl ether and dried under an IR lamp affording the desired product.

[264] Adapted from: a) Á. Pintér, G. Haberhauer, I. Hyla-Kryspin, S. Grimme, *Chem. Commun.* **2007**, 3711–3713; b) L.-H. Chan, E. G. Roschow, *J. Organomet. Chem.* **1967**, *9*, 231–250 c) S. Zhang, W. E. Piers, X. Gao, M. Parvez, *J. Am. Chem. Soc.* **2000**, *122*, 5499–5509.

6.4.1.2. Preparation of Ketimines and Aldimines of Glycine Nitroanilides



6.4.1.2.1. *1st step: Amide formation*

Method A1[265]**:** Boc-Gly-OH (1.38 g, 10 mmol, 1 equiv.) and the corresponding nitroaniline (10 mmol, 1 equiv.) were dissolved in dry pyridine (30 mL). The solution was cooled to – 15 °C and phosphorus oxychloride (1 mL, 11 mmol, 1.1 equiv.) was added dropwise with vigorous stirring. During addition, the reaction mixture coloured deeply red and slowly changed to brown. The reaction was complete after 30 minutes (monitored by TLC). The reaction was quenched with ice water (100 mL) and the mixture extracted with EtOAc (4 x 60 mL). The organic phase was dried over $MgSO_4$, and the solvent was evaporated in *vacuo*. The residue was coevaporated successively with hexane and diethyl eter, and the resulting solid was crushed with diethyl ether and hexane.

Method A2: Boc-Gly-OH (1.05 g, 6 mmol, 1.2 equiv.) was disolved in dry DMF (7 mL) and DIPEA (5.2 mL, 30 mmol, 6 equiv.) was added at room temperature. 2,5-Dinitroaniline (920 mg, 5 mmol, 1 equiv.) was added, followed by HATU (2.09 g, 5.5 mmol, 1.1 equiv.). The mixture stirred at room temperature for 16 h. Then, a solution of EtOAc/H_2O (1:1) was added to the reaction mixture and it was extracted with EtOAc (3 x 50 mL), washed with brine (5 x 30 mL), dried over $MgSO_4$ and evaporated under reduced pressure.

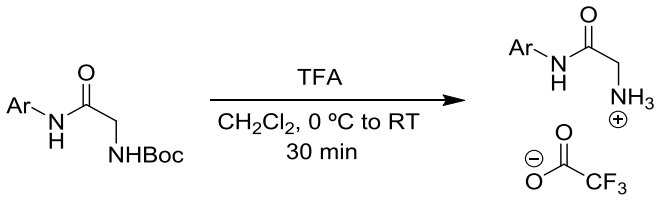
Method A3[266]: Boc-Gly-OH (5 mmol, 1 equiv.) was dissolved in dry THF (10 mL), and isobutyl chloroformate (0.8 mL, 6 mmol, 1.2 equiv.) and NMM (0.66 mL, 6

[265] Rijkers, D. T. S.; Adams, H.; Hemker, C.; Tesser, G. I. *Tetrahedron*, **1995**, *51*, 11235–11250.

[266] P. Gisbert, P. Trillo, I. M. Pastor, *Chemistry Select* **2018**, 3, 887-893.

mmol, 1.2 equiv.) were added at – 15 ºC to form the mixed anhydride. The mixture was stirred at the same temperature for 45 minutes. Then, aniline (5 mmol, 1 equiv.) was added and the mixture stirred for 3 h at room temperature. The reaction mixture was filtered through a plug of silica, eluting with EtOAc. Ethyl acetate was removed under reduced pressure and X was purified after recrystallization with CH_2Cl_2/*n*-pentane.

6.4.1.2.2. *2nd step: Amine deprotection*



46 Ar: *o*-NO_2Ph
99 Ar: *p*-NO_2Ph
100 Ar: 2,4-$(NO_2)_2$Ph
101 Ar: Ph

47 Ar: *o*-NO_2Ph
102 Ar: *p*-NO_2Ph
103 Ar: 2,4-$(NO_2)_2$Ph
104 Ar: Ph

To a solution of the corresponding aminoamide (3 mmol) in CH_2Cl_2 (12 mL) trifluoroacetic acid (4.5 mL) was added at 0 °C. The mixture was stirred at room temperature for 30 min until full conversion (monitored by TLC). The solvents were evaporated under vacuum and the residue was coevaporated successively with a mixture of ether and pentane. Then it was dried *in vacuo* and the resulting solid was used in the next step without further purification. Quantitative yield.

6.4.1.2.3. *3rd step: Imine formation*

Method B1: The synthesis of the diaryl iminoamides **45**, **51** and **53** derived from benzophenone imine was carried out starting from the corresponding aminoamide salt.

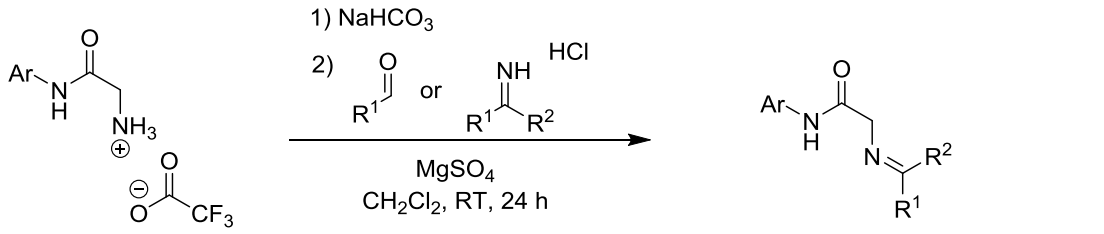
47 Ar: *o*-NO_2Ph
102 Ar: *p*-NO_2Ph
103 Ar: o, *p*-$(NO_2)_2$Ph

45 Ar: *o*-NO_2Ph
51 Ar: *p*-NO_2Ph
53 Ar: o, *p*-$(NO_2)_2$Ph

To a suspension of the corresponding aminoamide salt (3 mmol, 1 equiv.) in CH_2Cl_2 (11 mL) benzophenone imine (3 mmol, 1 equiv.) and anhydrous $MgSO_4$ (903 mg, 7.5 mmol, 2.5 equiv.) were added. The reaction was stirred at room temperature for 24 h. The reaction mixture was filtered to remove the salt and evaporated *in vacuo*. The crude

was crushed in diethyl ether/hexane to afford pure solids, which were used as such in the next step.

Method B2: In cases when hydrochloride imines or aldehydes were employed, the corresponding amine salt was neutralized by the addition of a saturate solution of $NaHCO_3$ and successive extractions with dichloromethane (≈70% yield in the extraction).

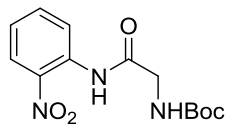


47 Ar: *o*-NO_2Ph
101 Ar: Ph
102 Ar: *p*-NO_2Ph

57 Ar: *o*-NO_2, R^1, R^2: 3,5-$(CF_3)_2$Ph
58 Ar: *o*-NO_2, R^1, R^2: 4-CF_3Ph
62 Ar: *o*-NO_2, R^1: 3,5-$(CF_3)_2$Ph, R^2: H
64: Ar: *p*-NO_2, R^1: 3,5-$(CF_3)_2$Ph, R^2: H
65: Ar: Ph, R^1: 3,5-$(CF_3)_2$Ph, R^2: H
67 Ar: *o*-NO_2, R^1: Ph, R^2: H
68 Ar: *o*-NO_2, R^1: Antracenyl, R^2: H
69 Ar: *o*-NO_2, R^1: 2,6-$(CH_3)_2$Ph, R^2: H
70 Ar: *o*-NO_2, R^1: 2,6-Cl_2Ph, R^2: H
71 Ar: *o*-NO_2, R^1: 2,4,6-F_3Ph, R^2: H
72 Ar: *o*-NO_2, R^1: 2-NO_2Ph, R^2: H

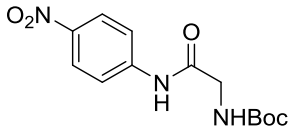
To a solution of the aminoamide (3 mmol, 1 equiv.) in CH_2Cl_2 (11 mL), the corresponding imine hydrochloride or aldehyde (3 mmol, 1 equiv.) and anhydrous $MgSO_4$ (903 mg, 7.5 mmol, 2.5 equiv.) were added. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was filtered then to remove the salt and evaporated to dryness *in vacuo*. The crude was crushed in diethyl ether/hexane to afford pure iminoamide derivatives which were used as such in the next step.

***Tert*-butyl (2-((2-nitrophenyl)amino)-2-oxoethyl)carbamate 46**



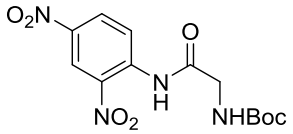
Prepared according to method A1 starting from *o*-nitroaniline (1.38 g, 10 mmol). Yellow solid. Yield: 68% (2.01 g, 6.8 mmol). m.p. = 128-130 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.02 (brs, 1H), 8.84 (dd, *J* = 8.6, 1.3 Hz, 1H), 8.25 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.69 (ddd, *J* = 8.7, 7.2, 1.6 Hz, 1H), 7.26 – 7.10 (m, 1H), 5.19 (brs, 1H), 4.05 (d, *J* = 6.1 Hz, 2H), 1.57 (s, 3H), 1.53 (s, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 136.6, 134.9, 127.0, 126.5, 124.2, 122.7, 81.8, 46.4, 28.9.UPLC-DAD-QTOF: $C_{13}H_{17}N_3O_5$ $[M+H]^+$ calcd.: 296.1168, found: 296.1274.

***Tert*-butyl (2-((4-nitrophenyl)amino)-2-oxoethyl)carbamate 99**[265]



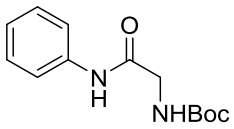
Prepared according to method A1 starting from *p*-nitroaniline (1.38 g, 10 mmol). White solid. Yield: 69% (1.27 g, 3.9 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, *J* = 9.2 Hz, 2H), 7.70 (d, *J* = 9.2 Hz, 2H), 3.95 (d, *J* = 6.1 Hz, 2H), 1.49 (s, 9H). All data were consistent with those previously reported.

***Tert*-butyl (2-((2,4-dinitrophenyl)amino)-2-oxoethyl)carbamate 100**



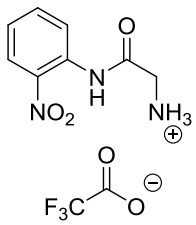
Prepared according to method A2 starting from 2,5-dinitroaniline (1.83 g, 10 mmol). Purified by column chromatography (hexane/EtOAc, 90:10) to afford **100** as a yellow solid. Yield: 77% (2.62 g, 7.7 mmol). m.p. = 186-188 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.29 (s, 1H), 9.12 – 9.02 (m, 2H), 8.43 (dd, *J* = 9.4, 2.6 Hz, 1H), 5.53 (t, *J* = 5.7 Hz, 1H), 4.01 (d, *J* = 6.1 Hz, 2H), 1.45 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8 , 156.2 , 142.0 , 139.2 , 135.3 , 130.2 , 122.3 , 122.1 , 81.5 , 46.0 , 28.3 . UPLC-DAD-QTOF: $C_{13}H_{16}N_4O_7Na$* *$[M+Na]^+$ calcd.: 363.0917, found: 363.0911.

***Tert*-butyl (2-oxo-2-(phenylamino)ethyl)carbamate 101**[266]



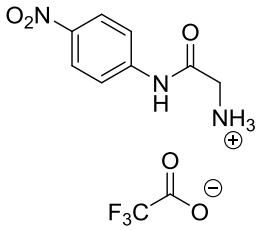
Prepared according to method A3. Purified by column chromatography (hexane/EtOAc, 90:10) to afford X as a yellow solid. Yield: 75% (1.05 g, 4.2 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.60 – 7.47 (m, 2H), 7.32 (dd, *J* = 15.4, 7.2 Hz, 2H), 7.21 – 7.07 (m, 1H), 5.43 (s, 1H), 3.96 (d, J = 5.6 Hz, 2H), 1.50 (s, 9H). All data were consistent with those previously reported.

2-((2-Nitrophenyl)amino)-2-oxoethan-1-aminium 2,2,2-trifluoroacetate 47



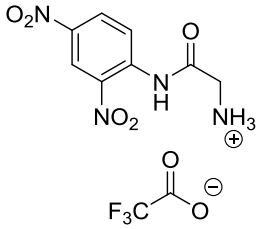
Prepared according to the general procedure starting *tert*-butyl (2-((2-nitrophenyl)amino)-2-oxoethyl)carbamate **46** (885 mg, 3 mmol). Yellow solid. m.p. = 148-152 ºC. ^{1}H NMR (300 MHz, D_2O) δ 8.15 – 7.93 (m, 1H), 7.84 – 7.59 (m, 2H), 7.41 (ddd, *J* = 8.6, 6.6, 2.3 Hz, 1H), 4.03 (s, 3H).^{13}C NMR (75 MHz, D_2O) δ 166.4, 135.1, 129.6, 127.1, 126.4, 125.6, 41.2. UPLC-DAD-QTOF (measured after neutralization): $C_8H_{10}N_3O_3$ $[M+H]^+$ calcd.: 196.0722, found: 196.0723.

2-((4-Nitrophenyl)amino)-2-oxoethan-1-aminium 2,2,2-trifluoroacetate 102



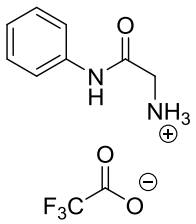
Prepared according to the general procedure starting from *tert*-butyl (2-((4-nitrophenyl)amino)-2-oxoethyl)carbamate **99** (885 mg, 3 mmol). Yellow solid. m.p. = 153-155 ºC. ^{1}H NMR (300 MHz, D_2O) δ 8.15 (d, *J* = 9.2 Hz, 2H), 7.61 (d, *J* = 9.2 Hz, 2H), 3.97 (s, 2H). ^{13}C NMR (75 MHz, D_2O) δ 165.8, 143.7, 142.9, 127.4, 125.1, 120.1, 114.4, 41.2. UPLC-DAD-QTOF (measured after neutralization): $C_8H_{10}N_3O_3$ $[M+H]^+$ calcd.: 196.0722, found: 196.0727.

2-((2,4-Dinitrophenyl)amino)-2-oxoethan-1-aminium 2,2,2-trifluoroacetate 103



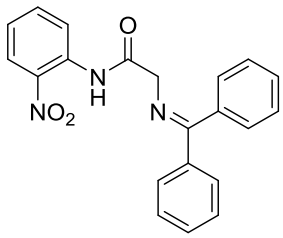
Prepared according to the general procedure starting from *tert*-butyl (2-((2,4-dinitrophenyl)amino)-2-oxoethyl)carbamate **100** (1.02 g, 3 mmol). White solid. m.p. = 146-150 ºC. ^{1}H NMR (300 MHz, D_2O) δ 8.97 (d, *J* = 2.6 Hz, 1H), 8.57 – 8.42 (m, 1H), 8.25 (d, *J* = 9.2 Hz, 1H), 4.11 (s, 2H). ^{13}C NMR (75 MHz, D_2O) δ 166.4 , 143.5 , 139.3 , 136.3 , 129.4 , 125.4 , 121.9 , 41.7 . UPLC-DAD-QTOF (measured after neutralization): $C_8H_8N_4O_5Na$* *$[M+Na]^+$ calcd.: 263.0392, found: 263.0403.

2-Oxo-2-(phenylamino)ethan-1-aminium 2,2,2-trifluoroacetate 104



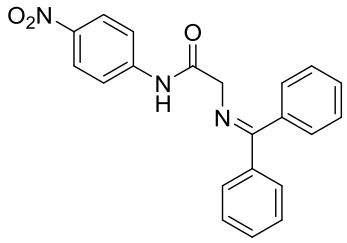
The title compound was prepared from *tert*-butyl (2-oxo-2-(phenylamino)ethyl)carbamate **101** (750 mg, 3 mmol). White solid. m.p. = 165-168 ºC. ^{1}H NMR (300 MHz, D_2O) δ 7.80 – 7.38 (m, 4H), 7.38 – 7.20 (m, 1H), 4.01 (s, 2H). ^{13}C NMR (75 MHz, D_2O) δ 165.4 , 136.2 , 129.3 , 125.8 , 121.4 , 40.9 . UPLC-DAD-QTOF (measured after neutralization): $C_8H_{11}N_2O$ $[M+H]^+$ calcd.: 151.0874, found: 151.0879.

2-((Diphenylmethylene)amino)-*N*-(2-nitrophenyl)acetamide 45



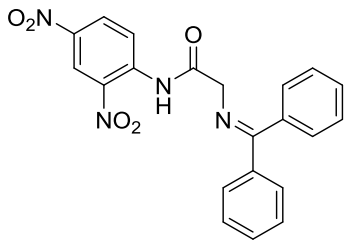
Prepared according to method B1 starting from 2-((2-nitrophenyl)amino)-2-oxoethan-1-aminium **47** (927 mg, 3 mmol) and benzophenone imine (0.5 mL, 3 mmol). Yellow solid. Yield: 78% (840 mg, 2.34 mmol). m.p. = 111-114 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.15 (s, 1H), 8.93 (dd, *J* = 8.6, 1.3 Hz, 1H), 8.29 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.97 – 7.79 (m, 2H), 7.69 (ddd, *J* = 8.7, 7.4, 1.6 Hz, 1H), 7.64 – 7.39 (m, 5H), 7.31 – 7.16 (m, 3H), 4.17 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 171.6, 139.4, 137.4, 136.7, 135.5, 132.2, 130.2, 130.1, 129.9, 129.5, 128.2, 126.9, 124.5, 123.5, 58.6. UPLC-DAD-QTOF: $C_{21}H_{17}N_3O_3$ $[M+H]^+$ calcd.: 360.1270, found: 360.1274.

2-((Diphenylmethylene)amino)-*N*-(4-nitrophenyl)acetamide 51



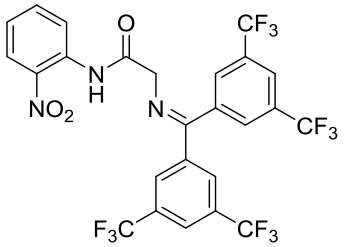
Prepared according to method B1 starting from 2-((4-nitrophenyl)amino)-2-oxoethan-1-aminium 2,2,2-trifluoroacetate **102** (927 mg, 3 mmol) and benzophenone imine (0.5 mL, 3 mmol). White solid. Yield: 82% (883 mg, 2.5 mmol). m.p. = 183-188 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (brs, 1H), 8.43 – 8.15 (m, 2H), 7.96 – 7.81 (m, 2H), 7.71 (dd, *J* = 8.2, 1.5 Hz, 2H), 7.61 – 7.39 (m, 5H), 7.39 – 7.08 (m, 3H), 4.13 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 170.0, 144.3, 144.0, 139.0, 136.5, 131.9, 130.1, 129.8, 129.2, 127.8, 125.9, 119.8, 57.4. UPLC-DAD-QTOF: $C_{21}H_{17}N_3O_3$ $[M+H]^+$ calcd.: 360.1270, found: 360.1372.

***N*-(2,4-Dinitrophenyl)-2-((diphenylmethylene)amino)acetamide 53**



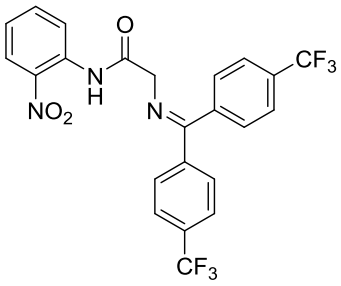
Prepared according to method B1 starting from 2-((2,4-dinitrophenyl)amino)-2-oxoethan-1-aminium **103** (1.06 mg, 3 mmol) and benzophenone imine (0.5 mL, 3 mmol). Yellow solid. Yield: 66% (800 mg, 1.98 mmol). m.p. = 175-180 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.53 (s, 1H), 9.24 (d, *J* = 9.4 Hz, 1H), 9.18 (d, *J* = 2.7 Hz, 1H), 8.48 (dd, *J* = 9.4, 2.7 Hz, 1H), 7.87 (dd, *J* = 8.1, 1.6 Hz, 2H), 7.60 – 7.38 (m, 6H), 7.23 – 7.12 (m, 2H), 4.18 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0 , 171.1 , 139.5 , 138.1 , 136.2 , 132.5 , 131.4 , 130.2 , 130.0 , 129.4 , 129.3 , 128.97 , 128.6 , 128.4 , 127.1 , 122.7 , 122.2 , 57.6 . UPLC-DAD-QTOF: $C_{21}H_{17}N_4O_5$ $[M+H]^+$ calcd.: 405.1199, found: 405.1192.

2-((Bis(3,5-bis(trifluoromethyl)phenyl)methylene)amino)-*N*-(2-nitrophenyl)acetamide 57



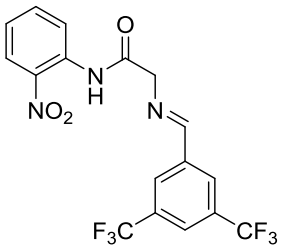
Prepared according to method B2 starting from 2-amino-*N*-(2-nitrophenyl)acetamide **47** (585 mg, 3 mmol) and 3,5-bis(trifluoromethyl)phenyl)methaniminehydrochloride **55** (1.47 g, 3 mmol). Yellow solid. Yield: 66% (1.25 g, 1.98 mmol). m.p. = 178-180 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.07 (s, 1H), 8.88 (d, *J* = 9.6 Hz, 0H), 8.31 – 8.22 (m, 2H), 8.13 (s, 1H), 8.06 (s, 1H), 7.76 – 7.59 (m, 2H), 7.24 (t, *J* = 9.1 Hz, 0H), 4.16 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2 , 165.3 , 139.0 , 137.2 , 136.4 , 136.0 , 133.2 (q), 128.7 , 127.5 , 126.0 , 125.4 , 124.4 , 124.0 , 122.3 , 57.9 .UPLC-DAD-QTOF: $C_{25}H_{14}F_{12}N_3O_3$ $[M+H]^+$ calcd.: 632.0842, found: 632.0844.

2-((Bis(4-(trifluoromethyl)phenyl)methylene)amino)-*N*-(2-nitrophenyl)acetamide 58



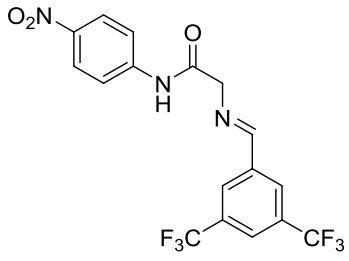
Prepared according to method B2 starting from 2-amino-*N*-(2-nitrophenyl)acetamide **47** (585 mg, 3 mmol) and bis(4-(trifluoromethyl)phenyl)methaniminium **5** (1.06 g, 3 mmol). Yellow solid. Yield: 75% (1.1 g, 2.25 mmol). m.p. = 165-168 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.94 (s, 1H), 8.85 (dd, *J* = 8.5, 1.2 Hz, 1H), 8.26 – 8.16 (m, 1H), 7.91 (d, *J* = 8.1 Hz, 4H), 7.78 (d, *J* = 8.2 Hz, 4H), 7.70 – 7.60 (m, 1H), 7.23 – 7.16 (m, 1H), 3.57 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.28, 168.50, 140.50, 139.03, 136.91, 135.82, 134.17, 129.00, 127.53, 126.45, 126.40, 125.86, 125.59, 125.54, 123.62, 122.29, 57.61.UPLC-DAD-QTOF: $C_{23}H_{16}N_3O_3F_6$ $[M+H]^+$ calcd.: 496.1096, found: 496.1102.

(*E*)-*N*-(2-Nitrophenyl)-2-((4-(trifluoromethyl)benzylidene)amino)acetamide 62



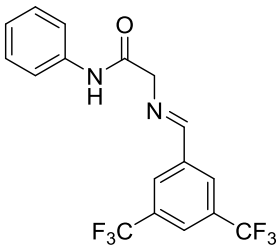
Prepared according to method B2 starting from 2-amino-*N*-(2-nitrophenyl)acetamide **47** (588 mg, 3 mmol) and 3,5-bis(trifluoromethyl)benzaldehyde (0.48 mL, 3 mmol). Yellow solid. Yield 60% (75.5 mg, 1.8 mmol). m.p. = 155-158 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.79 (s, 1H), 8.91 (d, *J* = 9.8 Hz, 1H), 8.50 (t, *J* = 1.6 Hz, 1H), 8.44 (s, 2H), 8.24 (d, *J* = 10.0 Hz, 1H), 8.01 (s, 1H), 7.72 – 7.62 (m, 1H), 7.26 – 7.18 (m, 1H), 4.55 (d, *J* = 1.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8 , 161.0 , 137.1 , 135.9 , 134.2 , 132.6 (q, *J* = 33.9 Hz), 128.7 , 128.6 , 125.9 , 125.05 (d, *J* = 7.3 Hz), 123.7 , 122.1 , 62.8 . UPLC-DAD-QTOF: $C_{17}H_{12}N_3O_3F_6$ $[M+H]^+$ calcd.: 420.0783, found: 420.0786.

(*E*)-2-((3,5-Bis(trifluoromethyl)benzylidene)amino)-*N*-(4-nitrophenyl)acetamide 64



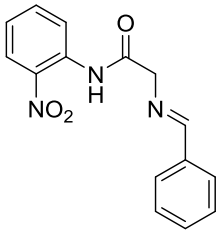
Prepared according to method B2 starting from 2-amino-*N*-(4-nitrophenyl)acetamide **102** (585 mg, 3 mmol) and 3,5-bis(trifluoromethyl)benzaldehyde (0.48 mL, 3 mmol). Yellow solid. Yield: 75% (943 mg, 2.25 mmol) m.p. = 144-148 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.52 (s, 1H), 8.26 (s, 2H), 8.22 (s, 1H), 8.03 (s, 1H), 7.80 (d, *J* = 9.2 Hz, 2H), 4.52 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7 , 161.7 , 144.0 , 143.0 , 136.9 , 132.8 (q, *J* = 33.8 Hz), 128.4 , 125.3 , 119.5 , 63.1 . UPLC-DAD-QTOF: $C_{17}H_{12}F_6N_3O_3$ $[M+H]^+$ calcd.: 420.1087, found: 420.1099.

(*E*)-2-((3,5-Bis(trifluoromethyl)benzylidene)amino)-*N*-phenylacetamide 65



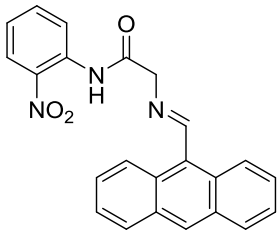
Prepared according to method B2 starting from 2-amino-*N*-phenylacetamide **104** (450 mg, 3 mmol) and 3,5-bis(trifluoromethyl)benzaldehyde (0.48 mL, 3 mmol). Yellow solid Yield: 73% (820 mg, 2.19 mmol). m.p. = 141-144 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.49 (s, 1H), 8.26 (s, 2H), 8.01 (s, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.36 (t, *J* = 7.9 Hz, 2H), 7.15 (t, *J* = 6.9 Hz, 1H), 4.48 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2 , 161.0 , 137.3 , 137.1 , 132.7 (q, *J* = 33.9 Hz), 129.2 , 128.3 , 125.1 , 125.1 , 124.9 , 120.2 , 63.3 . UPLC-DAD-QTOF: $C_{17}H_{13}F_6N_2O$ $[M+H]^+$ calcd.: 375.0932, found: 375.0930.

(*E*)-2-(Benzylideneamino)-*N*-(2-nitrophenyl)acetamide 67



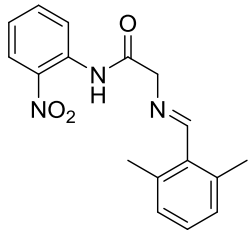
Prepared according to method B2 starting from 2-amino-*N*-(2-nitrophenyl)acetamide **47** (585 mg, 3 mmol) and benzaldehyde (0.3 mL, 3 mmol). White solid. Yield: 77% (654 mg, 2.31 mmol). m.p. = 214-218 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.81 (s, 1H), 8.92 (d, *J* = 9.7 Hz, 1H), 8.37 (s, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 8.06 – 7.86 (m, 1H), 7.65 (t, *J* = 8.6 Hz, 1H), 7.52 – 7.44 (m, 1H), 7.18 (t, 1H), 4.45 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0 , 164.3 , 135.8 , 135.3 , 134.5 , 131.8 , 129.0 , 128.8 , 125.9 , 123.5 , 122.2 , 63.1 . UPLC-DAD-QTOF: $C_{15}H_{14}N_3O_3$ $[M+H]^+$ calcd.: 284.1035, found: 284.1031.

(*E*)-2-((Anthracen-9-ylmethylene)amino)-*N*-(2-nitrophenyl)acetamide 68



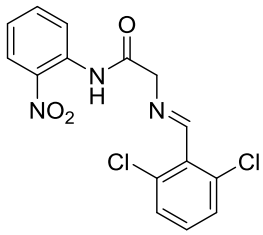
Prepared according to method B2 starting from 2-amino-*N*-(2-nitrophenyl)acetamide **47** (588 mg, 3 mmol) and 9-anthracenecarboxaldehyde (619 mg, 3 mmol). Aldehyde residue was removed by column chromatography (hexane/EtOAc, 90:10), followed by a washing with a saturate $NaHCO_3$ solution. Yellow solid. Yield: 75% (862 mg, 2.25 mmol). m.p. = 142-145 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.61 (s, 1H), 9.66 (s, 1H), 8.89 (d, *J* = 7.2 Hz, 1H), 8.75 (d, *J* = 9.7 Hz, 2H), 8.59 (s, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 8.07 (d, *J* = 9.7 Hz, 2H), 7.69 (t, 1H), 7.66 – 7.46 (m, 4H), 7.20 (t, 1H), 4.81 (d, *J* = 1.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8 , 163.9 , 135.7 , 131.3 , 129.3 , 127.60 , 125.6 , 124.7 , 123.7 , 122.8 , 65.5 .UPLC-DAD-QTOF: $C_{23}H_{17}N_3O_3Na$* *$[M+Na]^+$ calcd.: 406.1168, found: 406.1160.

(*E*)-2-((2,6-Dimethylbenzylidene)amino)-N-(2-nitrophenyl)acetamide 69



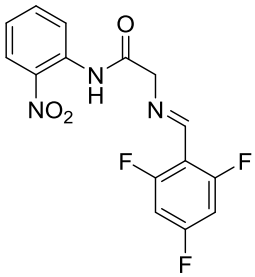
Prepared according to method B2 starting from 2-amino-*N*-(2-nitrophenyl)acetamide **47** (588 mg, 3 mmol) and 2,6-dimethylbenzaldehyde (403 mg, 3 mmol). Yellow solid. Yield: 70% (653 mg, 2.1 mmol). m.p. = 130-132 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.43 (s, 1H), 8.85 (d, *J* = 9.8 Hz, 1H), 8.78 (s, 1H), 8.19 (d, *J* = 10.0 Hz, 1H), 7.65 (t, *J* = 8.6 Hz, 1H), 7.33 – 7.15 (m, 2H), 7.09 (d, *J* = 7.6 Hz, 2H), 4.51 (s, 2H), 2.55 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0 , 164.5 , 138.6 , 135.7 , 134.2 , 132.4 , 130.1 , 129.1 , 127.9 , 125.8 , 123.6 , 122.7 , 65.1 , 21.2 . UPLC-DAD-QTOF: $C_{17}H_{18}N_3O_3$ $[M+H]^+$ calcd.: 312.1348, found: 312.1354.

(*E*)-2-((2,6-Dimethylbenzylidene)amino)-*N*-(2-nitrophenyl)acetamide 70



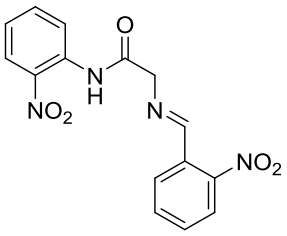
Prepared according to method B2 starting from 2-amino-*N*-(2-nitrophenyl)acetamide **47** (585 mg, 3 mmol) and 2,6-dichlorobenzaldehyde (525 mg, 3 mmol). Yellow solid. Yield: 65% (685 mg, 1.95 mmol). m.p. = 140-143 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.39 (s, 1H), 8.78 (d, *J* = 9.6 Hz, 1H), 8.62 (s, 1H), 8.16 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.63 (t, *J* = 8.6 Hz, 1H), 7.38 (d, *J* = 1.3 Hz, 1H), 7.35 (s, 1H), 7.30 – 7.22 (m, 1H), 7.19 (dd, *J* = 7.3, 1.1 Hz, 1H), 4.55 (d, *J* = 1.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1 , 160.1 , 137.2 , 135.5 , 135.1 , 134.0 , 131.1 , 129.0 , 128.3 , 125.7 , 123.7 , 122.8 , 64.0 . UPLC-DAD-QTOF: $C_{15}H_{12}Cl_2N_3O_3$ $[M+H]^+$ calcd.: 351.0280, found: 351.0266.

(*E*)-*N*-(2-Nitrophenyl)-2-((2,4,6-trifluorobenzylidene)amino)acetamide 71



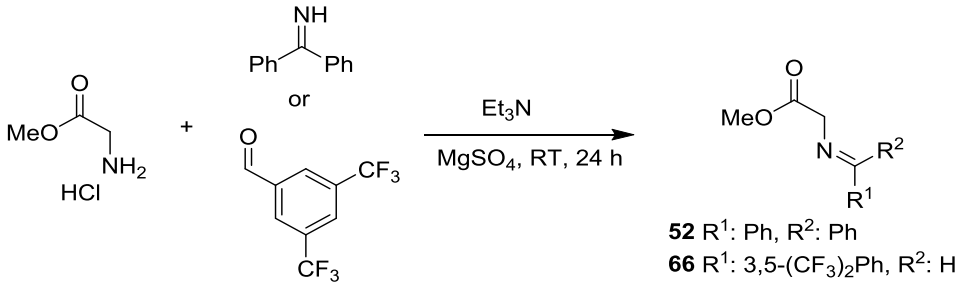
Prepared according to method B2 starting from 2-amino-*N*-(2-nitrophenyl)acetamide **47** (585 mg, 3 mmol) and 2,4,6-trifluorobenzaldehyde (1.01 g, 3 mmol). White solid. Yield: 70% (708 mg, 2.1 mmol). m.p. = 138-141 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.42 (s, 1H), 8.83 (d, *J* = 9.8 Hz, 1H), 8.55 (s, 1H), 8.21 (d, *J* = 10.0 Hz, 1H), 7.66 (t, *J* = 8.5 Hz, 1H), 7.39 – 7.09 (m, 1H), 6.78 (t, *J* = 8.6 Hz, 2H), 4.50 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2 , 164.3 (dt, *J* = 257.1 Hz, 17.1 Hz), 162.8 (ddd, *J* = 260.3, 23.9, 12.0 Hz), 154.5 , 135.6 , 134.1 , 125.8 , 123.7 , 122.7 , 101.4 (dd, *J* = 25.2 Hz, 4.1 Hz), 65.0 . UPLC-DAD-QTOF: $C_{15}H_{11}N_3O_3F_3$ $[M+H]^+$ calcd.: 338.0753, found: 338.0754.

(*E*)-2-((2-Nitrobenzylidene)amino)-N-(2-nitrophenyl)acetamide 72



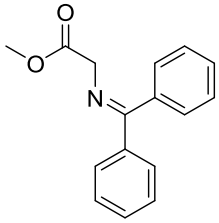
Prepared according to method B2 starting from 2-amino-*N*-(2-nitrophenyl)acetamide **47** (585 mg, 3 mmol) and 2-nitrobenzaldehyde (453 mg, 3 mmol). Yellow solid. Yield: 80% (787 mg, 2.4 mmol). m.p. = 160-163 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.75 (s, 11H), 8.93 (d, *J* = 8.5 Hz, 1H), 8.88 (s, 1H), 8.49 (d, *J* = 7.8 Hz, 1H), 8.24 (d, *J* = 9.9 Hz, 1H), 8.06 (d, *J* = 8.1 Hz, 1H), 7.83 (t, *J* = 7.4 Hz, 1H), 7.67 (q, *J* = 9.1, 8.7 Hz, 2H), 7.21 (t, *J* = 7.8 Hz, 1H), 4.55 (d, *J* = 1.5 Hz, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1 , 160.0 , 136.0 , 134.1 , 131.9 , 129.7 , 125.9 , 124.6 , 123.7 , 122.4 , 63.3 . UPLC-DAD-QTOF: $C_{15}H_{12}N_4O_5Na$* *$[M+Na]^+$ calcd.: 351.0705, found: 352.0707.

6.4.1.3. Preparation of Ketimines and Aldimines of Glycine Esters



To a suspention of glycine ester hydrochloride (377 mg, 3 mmol, 1 equiv.) in DCM (6 mL), the corresponding imine or aldehyde (2.4 mmol, 0.8 equiv.) was added. Triethylamine was added dropwise (0.42 mL, 3 mmol, 1 equiv.) and the reaction was stirred at room temperature for 24 h. The mixture was then diluted with Et_2O (6 mL), filtered and washed with H_2O (3 x 10 mL), brine (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to dryness. The crude was obtained with quantitative yield and was used without further purification.

Methyl 2-((diphenylmethylene)amino)acetate[267] 52

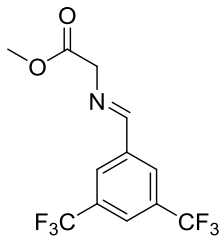


Prepared according to the general procedure starting with glycine ester hydrochloride (377 mg, 3 mmol) and benzophenone imine (0.5 mL, 3 mmol, 1 equiv.). Yield: >99%. All the spectroscopic data were coincident with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 – 7.61 (m, 2H), 7.56 – 7.42 (m, 4H), 7.43 – 7.29 (m,

[267] P. Nun,P, V. Prez, M. Calms, J. Martinez, F. Lamaty, *Chem. Eur. J.* **2012**, *18*, 3773-3779

3H), 7.25 – 7.14 (m, 1H), 4.25 (s, 2H), 3.77 (s, 3H).

Methyl (*E*)-2-((3,5-bis(trifluoromethyl)benzylidene)amino)acetate[268] 66



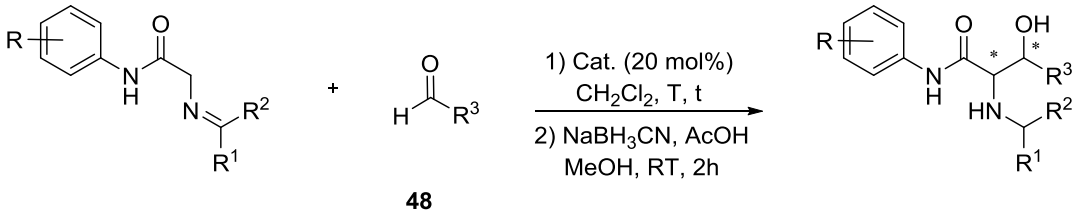
Prepared according to the general procedure starting with glycine ester hydrochloride (377 mg, 3 mmol) and 3,5-bis(trifluoromethyl)benzaldehyde (0.38 mL, 2.4 mmol). Yield: 65% (488 mg, 1.56 mmol). All the spectroscopic data were coincident with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.23 (s, 2H), 7.94 (s, 1H), 4.47 (d, *J* = 1.3 Hz, 2H), 3.78 (s, 3H).

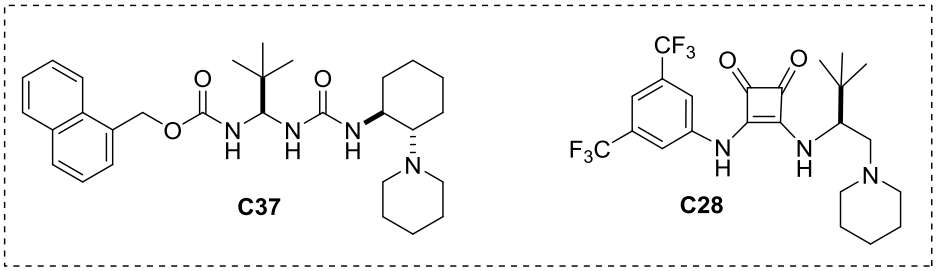
6.4.2. Preparation of aldehydes

Aliphatic aldehydes **48a**, **48b**, **48d**, **48e**, **48h**, **48i**, **48j**, **48k**, **48m** aromatic aldehydes **48f-g** and propargylic aldehyde **48c** are commercially available. They were purchased from commercial suppliers and distilled before their use in aldol reaction. Aldehyde **48l** was prepared following the literature procedure.[269]

6.4.3. Aldol reaction of nitroanilides

6.4.3.1. Asymmetric reaction



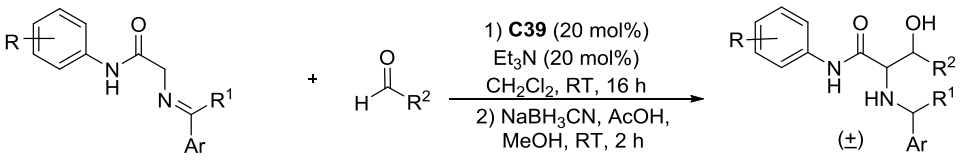


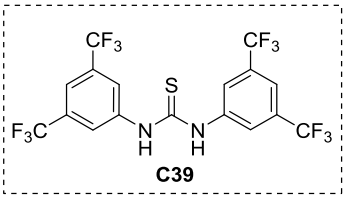
The corresponding nitroanilide (0.2 mmol, 1 equiv.) and the corresponding catalyst (0.02 mmol, 20 mol%) were dissolved in dry dichloromethane (0.5 mL) at the

[268] Z. Chen, N. Ren, X. Ma, J. Nie, F.-G. Zhang, J.-A Ma, *ACS Catal.* **2019**, *9*, 4600-4608.
[269] X. Xiao, S. Anthony, G. Kohlagen, Y. Pommier, M. Cushman, *Bioorg. Med. Chem.* **2004**, *126*, 5147-5160.

corresponding temperature. To the mixture, $NaHCO_3$ (0.02 mmol, 20 mol%) was added in one portion, followed by the corresponding aldehyde (0.6 mmol, 3 equiv.) The reaction mixture was stirred at the indicated temperature until consumption of the starting material (followed by ^{1}H-NMR). Then, MeOH (0.4 mL) was added, followed by $NaBH_3CN$ (32 mg, 0.5 mmol, 2.5 equiv.) and AcOH (24 µL, 0.4 mmol, 2 equiv.) and the mixture stirred for 2 h at room temperature (reduction of the imine can be followed by ^{1}H-NMR), the solvents were evaporated under reduced pressure, the resulting residue was redissolved in dichloromethane and washed with a saturated $NaHCO_3$ solution (1 x 4 mL). The organic phase was dried over $MgSO_4$ and evaporated in vacuo. The crude was purified by column chromatography.

6.4.3.2. Racemic reaction

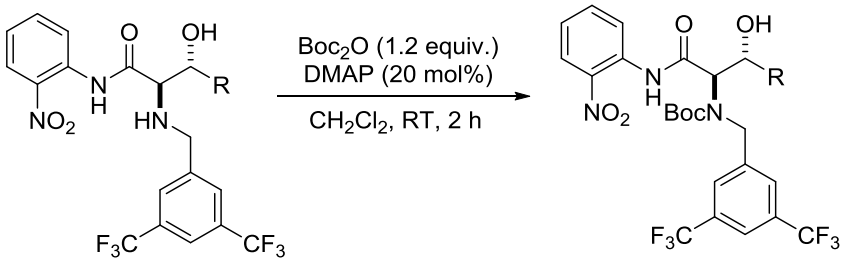




The corresponding nitroanilide (0.2 mmol, 1 equiv.) and **C39** (0.02 mmol, 20 mol%) were dissolved in dry dichloromethane (0.5 mL) at room temperature. To the mixture, Et_3N (0.02 mmol, 20 mol%) was added, followed by the corresponding aldehyde (0.6 mmol, 3 equiv.) The reaction was stirred at room temperature until consumption of the starting material (followed by ^{1}H-NMR). To the reaction mixture MeOH (0.4 mL) was added, followed by $NaBH_3CN$ (32 mg, 0.5 mmol, 2.5 equiv.) and AcOH (24 µL, 0.4 mmol, 2 equiv.). The reaction mixture stirred for 2 h at room temperature (the reduction of the imine can be followed by ^{1}H-NMR), the solvents were evaporated under reduced pressure, the resulting crude was redissolved in dichloromethane and washed with a saturate $NaHCO_3$ solution (1 x 4 mL). The organic phase was dried over $MgSO_4$ and evaporated in vacuo. The crude was purified by column chromatography.

General procedure for the Boc-protection of the aldol adducts

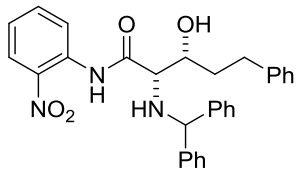
In some cases, Boc-protection of the secondary amine was carried out in order to find appropriate HPLC conditions for enantiomer separation. This was performed following the general procedure indicated below.



The purified compound (1 equiv.) was dissolved in dry dichloromethane (5 mL/mmol) and Boc_2O (1.2 equiv.) was added followed by DMAP (20 mol%). (The quantities have to be measured accurately to avoid amide Boc-protection). The reaction was followed by TLC, and when finished, the mixture was filtered through a small silica plug and evaporated under reduced pressure.

6.4.3.3. Characterization of compounds

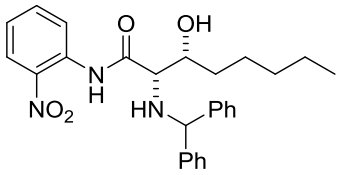
(2*S*,3*R*)-2-(Benzhydrylamino)-3-hydroxy-*N*-(2-nitrophenyl)-5-phenylpentanamide 49a



Prepared according to the general procedure starting from 2-((diphenylmethylene)amino)-*N*-(2-nitrophenyl)acetamide **45** (72 mg, 0.2 mmol) and hydrocinnamaldehyde **48a** (80 µL, 0.6 mmol). Purified by column chromatography (hexane/EtOAc, 90:10). Yellow oil. Yield: 71% (70 mg, 0.14 mmol). $[\alpha]_D^{23} = -1.3^o$ (*c*=1.35, 94% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.77 (s, 1H), 8.72 (d, *J* = 8.5 Hz, 1H), 8.20 (d, *J* = 10.0 Hz, 1H), 7.60 (t, *J* = 8.6 Hz, 1H), 7.52 – 7.45 (m, 2H), 7.46 – 7.31 (m, 4H), 7.31 – 7.05 (m, 9H)., 4.91 (s, 12H), 4.07 (m, 1H), 3.32 (d, *J* = 3.9 Hz, 1H), 2.86 (m, 1H), 2.67 (m, 1H), 1.88 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6 , 143.0 , 142.4 , 141.4 , 137.1 , 135.7 , 134.0 , 129.0 , 128.8 , 128.7 , 128.6 , 127.8 , 127.6 , 127.4 , 126.2 , 125.9 , 123.7 , 122.2 , 72.1 , 66.8 , 65.0 , 35.4 , 32.4 . UPLC-DAD-QTOF: $C_{30}H_{30}N_3O_4$ $[M+H]^+$ calcd.: 496.2233, found: 496.2236.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel IA hexane/ethanol 90/10, flow rate= 1 mL/min, retention times: 18 min (major) and 40 min (minor)).

(2*S*,3*R*)-2-(Benzhydrylamino)-3-hydroxy-*N*-(2-nitrophenyl)octanamide 49b

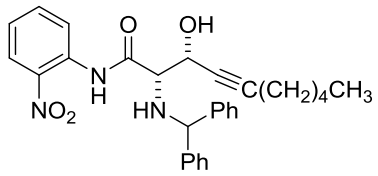


Prepared according to the general procedure starting from 2-((diphenylmethylene)amino)-*N*-(2-nitrophenyl)acetamide **45** (72 mg, 0.2 mmol) and hexanal **48b** (74 µL, 0.6 mmol).

Purified by column chromatography (hexane/EtOAc, 90:10). Yellow oil. Yield: 71% (65.5 mg, 0.14 mmol). $[\alpha]_D^{23}$ = –8.2º (*c*=2, 90% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.86 (s, 1H), 8.75 (d, *J* = 8.5 Hz, 1H), 8.21 (d, 1H), 7.60 (t, *J* = 8.7 Hz, 1H), 7.57 – 7.07 (m, 11H), 4.97 (s, 1H), 4.15 – 3.99 (m, 1H), 3.29 (d, *J* = 3.7 Hz, 1H), 1.67 – 1.51 (m, 3H), 1.37 – 1.24 (m, 5H), 1.05 – 0.68 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8 , 143.1 , 142.6 , 137.0 , 135.7 , 134.1 , 129.0 , 128.9 , 128.7 , 127.8 , 127.7 , 127.6 , 127.5 , 127.3 , 125.9 , 123.6 , 122.1 , 72.9 , 67.0 , 65.0 , 33.9 , 31.8 , 25.8 , 22.7 , 14.2 . UPLC-DAD-QTOF: $C_{27}H_{32}N_3O_4$ $[M+H]^+$ calcd.: 462.2390, found: 462.2393.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel IA hexane/ethanol 90/10, flow rate= 1 mL/min, retention times: 16 min (minor) and 17 min (major)).

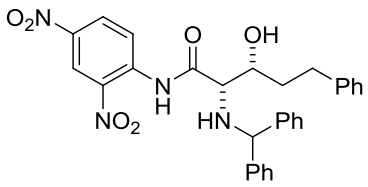
(2*S*,3*R*)-2-(Benzhydrylamino)-3-hydroxy-*N*-(2-nitrophenyl)dec-4-ynamide 49c



Prepared according to the general procedure starting from 2-((diphenylmethylene)amino)-*N*-(2-nitrophenyl)acetamide **45** (71.8 mg, 0.2 mmol) and 2-octynal **48c** (86 µL, 0.6 mmol). Purified by column chromatography (hexane/EtOAc, 92:8). Yellow oil. Yield: 85% (82 mg, 0.17 mmol). Both diastereoisomers were separated by column chromatography. *Major diastereoisomer*: ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.20 (s, 1H), 8.79 (d, 1H), 8.26 (d, *J* = 10.0 Hz, 1H), 7.70 – 7.57 (m, 3H), 7.52 (d, *J* = 8.6 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.33 – 7.24 (m, 3H), 7.24 – 7.12 (m, 2H), 5.24 (s, 1H), 4.98 – 4.85 (m, 1H), 3.89 (d, 1H), 3.51 (s, 1H), 2.70 (s, 1H), 2.29 – 2.00 (m, 2H), 1.54 – 1.36 (m, 2H), 1.32 – 1.07 (m, 4H), 0.90 – 0.59 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1 , 143.3 , 142.0 , 137.2 , 135.8 , 133.9 , 129.0 , 129.0 , 127.9 , 127.7 , 127.1 , 125.9 , 123.9 , 122.3 , 88.1 , 78.1 , 66.2 , 63.2 , 62.7 , 31.1 , 28.2 , 22.2 , 18.8 , 14.0 . *Minor diastereoisomer:* ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.94 (s, 1H), 8.74 (d, *J* = 8.5 Hz, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 7.67 – 7.53 (m, 3H), 7.53 – 7.43 (m, 2H), 7.37 (t, *J* = 7.4 Hz, 2H), 7.32 – 7.09 (m, 5H), 5.26 (s, 1H), 5.01 (d, *J* = 2.3 Hz, 1H), 3.56 (d, *J* = 4.5 Hz, 1H), 2.28 – 2.02 (m, 2H), 1.51 – 1.01 (m, 6H), 0.78 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6 , 143.3 , 142.5 , 137.1 , 135.7 , 134.1 , 128.9 , 128.8 , 128.1 , 127.6 , 127.4 , 125.85 , 123.6 , 122.3 , 89.4 , 76.9 , 66.8 , 65.4 , 65.2 , 31.0 , 28.2 , 22.2 , 18.8 , 13.9. UPLC-DAD-QTOF: $C_{29}H_{32}N_3O_4$ $[M+H]^+$ calcd.: 486.2393, found: 486.2402.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel IA hexane/isopropanol 90/10, flow rate= 0.5 mL/min, retention times: *Major diastereoisomer* 24 min (major) and 27 min (minor); *Minor diastereioisomer* 27 min (major) and 38 min (major)).

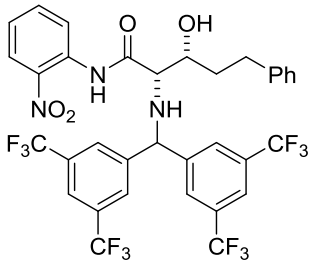
(2*S*,3*R*)-2-(Benzhydrylamino)-*N*-(2,4-dinitrophenyl)-3-hydroxy-5-phenylpentanamide 54a



Prepared according to the general procedure starting from *N*-(2,4-dinitrophenyl)-2-((diphenylmethylene)amino)acetamide (81 mg, 0.2 mmol) **53** and hydrocinnamaldehyde **48a** (80 µL, 0.6 mmol). Purified by column chromatography (hexane/EtOAc, 95:5). Yellow oil. Yield: 51% (55 mg, 0.1 mmol). $[\alpha]_D^{23}$ = –9.0 (*c*=2, 20% *ee*, CH_2Cl_2) ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.29 (s, 1H), 9.16 – 9.06 (m, 1H), 9.02 (d, *J* = 9.4 Hz, 1H), 8.46 – 8.35 (m, 1H), 7.54 – 7.44 (m, 3H), 7.43 – 7.07 (m, 12H), 4.93 (s, 1H), 3.39 (d, *J* = 3.6 Hz, 1H), 2.83 (d, *J* = 14.4 Hz, 1H), 2.68 (d, *J* = 11.3 Hz, 1H), 1.99 – 1.82 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2 , 142.7 , 142.0 , 141.0 , 139.1 , 129.9 , 129.1 , 128.8 , 128.8 , 128.6 , 127.9 , 127.5 , 127.2 , 126.4 , 122.2 , 72.3 , 67.3 , 65.4 , 35.7 , 32.4 .UPLC-DAD-QTOF: $C_{30}H_{29}N_4O_6$ $[M+H]^+$ calcd.: 541.2087, found: 541.2076.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel IF hexane/ethanol 90/10, flow rate= 1 mL/min, retention times: 16 min (minor) and 17 min (major)).

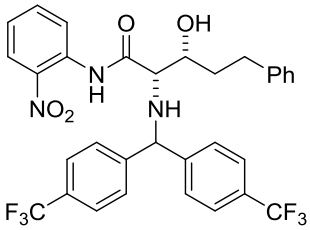
(2*S*,3*R*)-2-((Bis(3,5-bis(trifluoromethyl)phenyl)methyl)amino)-3-hydroxy-*N*-(2-nitrophenyl)-5-phenylpentanamide 59a



Prepared according to the general procedure starting from 2-((Bis(3,5-bis(trifluoromethyl)phenyl)methylene)amino)-*N*-(2-nitrophenyl)acetamide **57** (126 mg, 0.2 mmol) and hydrocinnamaldehyde **48a** (80 µL, 0.6 mmol). Purified by column chromatography (hexane/EtOAc, 90:10). Yellow oil. Yield: 84% (129 mg, 0.17 mmol). $[\alpha]_D^{24}$ = –10.5 (*c*=1, 76% *ee*, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.75 (s, 1H), 8.75 (d, *J* = 9.5 Hz, 1H), 8.26 (d, *J* = 9.9 Hz, 1H), 8.00 (s, 2H), 7.88 (s, 3H), 7.71 – 7.63 (m, 1H), 7.33 – 7.27 (m, 2H), 7.23 – 7.14 (m, 4H), 5.13 (s, 1H), 4.21 – 4.11 (m, 1H), 3.24 – 3.14 (m, 1H), 2.93 – 2.85 (m, 1H), 2.80 – 2.67 (m, 1H), 2.01 – 1.89 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8 , 143.8 , 143.6 , 140.8 , 136.1 , 133.8 , 133.5 – 132.2 (m), 128.9 , 128.6 , 127.8 , 127.4 , 126.6 , 126.1 , 121.8 , 72.1 , 65.8 , 65.4 , 35.5 , 32.3 , 29.9 . UPLC-DAD-QTOF: $C_{34}H_{25}F_{12}N_3O_4$ $[M+H]^+$ calcd.: 768.1746, found: 768.1732.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IAIA) hexane/isopropanol 98:2, flow rate= 0.5 mL/min. Retention times: *Minor diastereoisomer*: 30 min (major) and 36 min (minor); *Major diastereoisomer:* 49 min (major) and 56 min (minor).

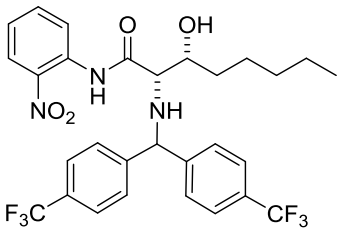
(2*S*,3*R*)-2-((Bis(4-(trifluoromethyl)phenyl)methyl)amino)-3-hydroxy-*N*-(2-nitrophenyl)-5-phenylpentanamide 60a



Prepared according to the general procedure starting from 2-((bis(4-(trifluoromethyl)phenyl)methylene)amino)-*N*-(2-nitrophenyl)acetamide (99 mg, 0.2 mmol) **58** and hydrocinnamaldehyde **48a** (80 µL, 0.6 mmol). Purified by column chromatography (hexane/EtOAc, 90:10). Yellow oil. Yield: 60% (76 mg, 0.12 mmol). $[\alpha]_D^{24}$ = –20.8 (*c*=1, 92% *ee*, CH_2Cl_2). H NMR (300 MHz, $CDCl_3$) δ 11.76 (s, 1H), 8.83 – 8.60 (m, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 7.71 – 7.58 (m, 5H), 7.52 (d, *J* = 1.8 Hz, 4H), 7.36 – 7.23 (m, 3H), 7.24 – 7.12 (m, 4H), 5.04 (s, 1H), 4.19 – 4.06 (m, 1H), 3.28 (d, 1H), 4.12 (m, 1H), 3.38 – 3.18 (m, 1H), 3.00 – 2.83 (m, 1H), 2.67 (m, 1H), 1.93 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8 , 146.0 , 145.6 , 141.2 , 136.9 , 136.0 , 133.9 , 130.6 (q), 128.8 , 128.6 , 128.1 , 127.7 , 124.0 , 122.1 , 72.0 , 66.1 , 65.2 , 35.5 , 32.4 . UPLC-DAD-QTOF: $C_{32}H_{28}F_6N_3O_4$ $[M+H]^+$ calcd.: 632.1992, found: 632.1984.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IF) hexane/isopropanol 98:2, flow rate= 0.5 mL/min. Retention times: *Minor diastereoisomer*: 32 min (minor) and 37 min (major); *Major diastereoisomer:* 40 min (minor) and 45 min (major).

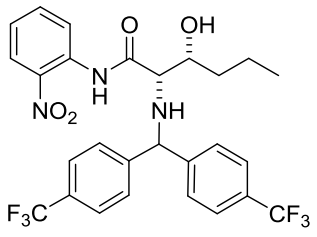
(2*S*,3*R*)-2-((Bis(4-(trifluoromethyl)phenyl)methyl)amino)-3-hydroxy-*N*-(2-nitrophenyl)octanamide 60b



Prepared according to the general procedure starting from 2-((bis(4-(trifluoromethyl)phenyl)methylene)amino)-N-(2-nitrophenyl)acetamide (99 mg, 0.2 mmol) **58** and hexanal **48b** (74 µL, 0.6 mmol). Purified by column chromatography (hexane/EtOAc, 95:5). Yellow oil. Yield: 82% (98 mg, 0.16 mmol). $[\alpha]_D^{24}$ = –2.4 (*c*=1, 90% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.80 (s, 1H), 8.75 (dd, *J* = 8.5, 1.2 Hz, 1H), 8.23 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.66 (s, 4H), 7.65 – 7.60 (m, 1H), 7.54 (q, *J* = 8.5 Hz, 4H), 7.21 (t, 1H), 5.10 (s, 1H), 4.23 – 4.04 (m, 1H), 3.25 (d, *J* = 3.7 Hz, 1H), 1.69 – 1.51 (m, 2H), 1.40 – 1.20 (m, 4H), 0.99 – 0.81 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9 , 146.2 , 145.8 , 136.9 , 136.0 , 134.0 , 130.3 (q, *J* = 32.6, 10.5 Hz), 128.1 , 127.7 , 126.2 , 126.2 , 126.0 , 123.8 , 122.0 , 72.8 , 66.3 , 65.3 , 34.0 , 31.8 , 25.8 , 22.7 , 14.1 . UPLC-DAD-QTOF: $C_{29}H_{30}F_6N_3O_4$ $[M+H]^+$ calcd.: 598.2138 found: 598.2141.

The enantiomeric purity was determined by HPLC analysis (Phenomenex-Lux 3µm i-Amilose-1 (00G-4729-E0)) hexane/isopropanol 95:5, flow rate= 0.5 mL/min. Retention times: *Minor diastereoisomer* 31 min (major) and 39 min (minor); *Major diastereoisomer* 43 min (minor) and 46 min (major).

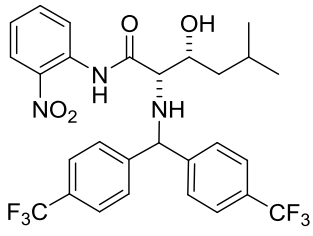
(2*S*,3*R*)-2-((Bis(4-(trifluoromethyl)phenyl)methyl)amino)-3-hydroxy-*N*-(2-nitrophenyl)hexanamide 60h



Prepared according to the general procedure starting from 2-((bis(4-(trifluoromethyl)phenyl)methylene)amino)-*N*-(2-nitrophenyl)acetamide (99 mg, 0.2 mmol) **58** and butyraldehyde **48h** (54 µL, 0.6 mmol). Purified by column chromatography (hexane/EtOAc, 95:5). Yellow oil. Yield: 72% (80 mg, 0.14 mmol). $[\alpha]_D^{24}$ = –13.9 (*c*=0.5, 92% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.80 (s, 1H), 8.76 (d, *J* = 8.4 Hz, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 7.71 – 7.66 (m, 4H), 7.66 – 7.62 (m, 1H), 7.54 (q, *J* = 8.3 Hz, 4H), 7.22 (t, *J* = 7.6 Hz, 1H), 5.10 (s, 1H), 4.31 – 3.97 (m, 1H), 3.44 – 2.99 (m, 1H), 1.72 – 1.51 (m, 3H), 1.46 – 1.31 (m, 1H), 1.10 – 0.65 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9 , 146.1 , 145.7 , 136.0 , 134.0 , 130.56 (q), 128.1 , 127.7 , 126.3 , 126.2 , 126.0 , 123.9 , 122.0 , 72.6 , 66.3 , 65.3 , 36.1 , 19.3 , 14.0 . UPLC-DAD-QTOF: $C_{27}H_{26}F_6N_3O_4$ $[M+H]^+$ calcd.: 570.1836 found: 570.1828.

The enantiomeric purity was determined by HPLC analysis (Phenomenex-Lux 3µm i-Amilose-1 (00G-4729-E0)) hexane/isopropanol 95:5, flow rate= 0.5 mL/min. Retention times: *Minor diastereoisomer* 31 min (major) and 41 min (minor); *Major diastereoisomer* 45 min (minor) and 49 min (major).

(2*S*,3*R*)-2-((Bis(4-(trifluoromethyl)phenyl)methyl)amino)-3-hydroxy-5-methyl-*N*-(2-nitrophenyl)hexanamide 60i

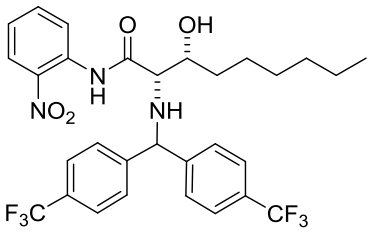


Prepared according to the general procedure starting from 2-((bis(4-(trifluoromethyl)phenyl)methylene)amino)-*N*-(2-nitrophenyl)acetamide (99 mg, 0.2 mmol) **58** and isovaleraldehyde **48i** (64 µL, 0.6 mmol). Purified by column chromatography (hexane/EtOAc, 95:5). Yellow oil. Yield: 78% (91 mg, 0.16 mmol). $[\alpha]_D^{24}$ = –6.9 (*c*=0.5, 84% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.80 (s, 1H), 8.75 (d, *J* = 8.5 Hz, 1H), 8.24 (d, *J* = 1.4 Hz, 1H), 7.66 (s, 4H), 7.65 – 7.60 (m, 1H), 7.54 (q, *J* = 8.5 Hz, 3H), 7.21 (td, *J* = 7.9, 7.4, 1.3 Hz, 1H), 5.10 (s, 6H), 4.31 – 4.18 (m, 1H), 3.23 (d, *J* = 3.6 Hz, 1H), 1.79 (s, 0H), 1.56 (d, *J* = 4.1 Hz, 1H), 1.37 (d, *J* = 8.9 Hz, 1H), 1.01 – 0.88 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9 , 146.2 , 145.8 , 137.0 , 136.0 , 134.0 , 129.6 , 128.1 , 127.7 , 126.2

, 126.0 , 123.9 , 122.1 , 70.9 , 66.3 , 65.5 , 42.9 , 24.9 , 23.6 , 21.8 . UPLC-DAD-QTOF: $C_{28}H_{28}F_6N_3O_4$ $[M+H]^+$ calcd.: 584.1980 found: 584.1987.

The enantiomeric purity was determined by HPLC analysis (Phenomenex-Lux 3µm i-Amilose-1 (00G-4729-E0)) hexane/isopropanol 95:5, flow rate= 0.5 mL/min. Retention times: *Minor diastereoisomer* 18 min (major) and 26 min (minor); *Major diastereoisomer* 30 min (major) and 36 min (minor).

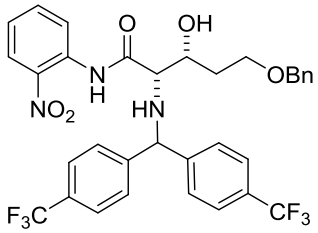
(2*S*,3*R*)-2-((Bis(4-(trifluoromethyl)phenyl)methyl)amino)-3-hydroxy-*N*-(2-nitrophenyl)nonanamide 60j



Prepared according to the general procedure starting from 2-((bis(4-(trifluoromethyl)phenyl)methylene)amino)-N-(2-nitrophenyl)acetamide (99 mg, 0.2 mmol) **58** and heptanal **48j** (84 µL, 0.6 mmol) Purified by column chromatography (hexane/EtOAc, 94:6). Yellow oil. Yield: 76% (93 mg, 0.15 mmol). $[\alpha]_D^{24} = -9.6$ (*c*=1, 90% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.80 (s, 1H), 8.75 (d, *J* = 8.5 Hz, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 7.66 (s, 4H), 7.62 (t, *J* = 8.6 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 4H), 7.22 (t, *J* = 7.8 Hz, 1H), 5.10 (s, 1H), 4.13 (s, 1H), 3.37 – 3.19 (m, 1H), 1.71 – 1.47 (m, 2H), 1.41 – 1.20 (m, 8H), 1.04 – 0.76 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5 , 146.7 , 146.3 , 137.5 , 136.5 , 134.6 , 131.0 (q, *J* = 32.4 Hz), 128.6 , 128.2 , 126.8 , 126.7 , 126.5 , 126.5 , 124.4 , 122.6 , 73.4 , 66.9 , 65.8 , 34.6 , 32.4 , 29.8 , 26.6 , 23.2 , 14.7 . UPLC-DAD-QTOF: $C_{30}H_{32}F_6N_3O_4$ $[M+H]^+$ calcd.: 612.2298 found: 612.2297.

The enantiomeric purity was determined by HPLC analysis (Phenomenex-Lux 3µm i-Cellulose) hexane/isopropanol 95:5, flow rate= 0.5 mL/min. Retention times: *Minor diastereoisomer* 19 min (major) and 21 min (minor); *Major diastereoisomer* 23 min (major) and 29 min (minor).

(2*S*,3*R*)-5-(Benzyloxy)-2-((bis(4-(trifluoromethyl)phenyl)methyl)amino)-3-hydroxy-*N*-(2-nitrophenyl)pentanamide 60k

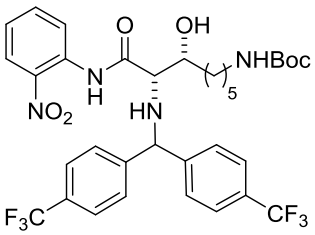


Prepared according to the general procedure starting from 2-((bis(4-(trifluoromethyl)phenyl)methylene)amino)-N-(2-nitrophenyl)acetamide (99 mg, 0.2 mmol) **58** and (benzyloxy)acetaldehyde **48k** (84 µL, 0.6 mmol). Purified by column chromatography (hexane/EtOAc, 85:15). Yellow oil. Yield: 70% (91 mg, 0.14 mmol). $[\alpha]_D^{24} = -13.2$ (*c*=0.5, 90% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.74 (s, 1H), 8.71 (d, *J* = 9.7 Hz, 1H), 8.22 (d, *J* = 9.9 Hz, 1H), 7.64 (s, 5H), 7.50 (d, *J* = 1.6 Hz, 4H), 7.38 – 7.25 (m, 5H), 7.26 – 7.13 (m, 1H), 5.08 (s, 1H), 4.47

(s, 2H), 4.37 – 4.24 (m, 1H), 3.80 – 3.61 (m, 2H), 3.30 (d, *J* = 4.9 Hz, 1H), 2.06 – 1.84 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5 , 146.0 (q), 135.8 , 134.1 , 129.6 , 128.7 , 128.2 , 127.9 , 127.8 , 126.1 , 126.1 , 125.9 , 125.9, 123.7 , 122.1 , 73.8 , 72.9 , 69.2 , 66.2 , 65.6 , 33.2 . UPLC-DAD-QTOF: $C_{33}H_{30}F_6N_3O_4$ $[M+H]^+$ calcd.: 662.2083 found: 662.2090.

The enantiomeric purity was determined by HPLC analysis (Phenomenex-Lux 3µm i-Amilose-1 (00G-4729-E0)) hexane/isopropanol 95:5, flow rate= 0.5 mL/min. Retention times: *Minor diastereoisomer* 31 min (major) and 37 min (minor); *Major diastereoisomer* 37 min (minor) and 45 min (major).

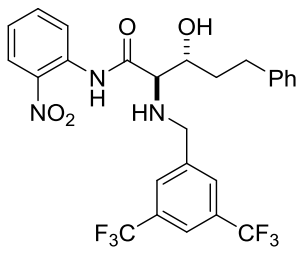
tert-Butyl ((2*R*,3*S*)-(3-((bis(4-(trifluoromethyl)phenyl)methyl)amino)-2-hydroxy-4-((2-nitrophenyl)amino)-4-oxobutyl)carbamate 60l



The title compound was prepared according to the general procedure starting from 2-((bis(4-(trifluoromethyl)phenyl)methylene)amino)-N-(2-nitrophenyl)acetamide (99 mg, 0.2 mmol) **58** and *tert*-butyl (6-oxohexyl)carbamate **48l** (130 mg, 0.6 mmol). The crude was purified by column chromatography (hexane/EtOAc, 80:20). Yellow oil. Yield: 63% (88 mg, 0.13 mmol). $[\alpha]_D^{24}$ = –1.8 (*c*=1.5, 88% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.77 (s, 1H), 8.73 (d, 1H), 8.22 (d, *J* = 9.8 Hz, 1H), 7.65 (s, 4H), 7.61 (t, *J* = 7.3 Hz, 1H), 7.58 – 7.47 (m, 4H), 7.20 (t, *J* = 8.4 Hz, 1H), 5.09 (s, 1H), 4.66 – 4.44 (m, 1H), 4.08 (s, 1H), 3.07 (s, 2H), 1.68 – 1.55 (m, 3H), 1.41 (s, 9H), 1.36 – 1.12 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9 , 156.4 , 146.2 , 145.8 , 136.9 , 135.9 , 135.8 , 134.1 , 130.3 (q, *J* = 42.7 Hz), 128.1 , 127.7 , 126.2 , 126.1 , 125.9 , 123.7 , 122.0 , 72.1 , 66.1 , 55.7 , 40.0 , 33.9 , 30.2 . UPLC-DAD-QTOF: $C_{34}H_{39}F_6N_4O_6$ $[M+H]^+$ calcd.: 713.2774 found: 713.2774.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel IA hexane/isopropanol 90/10, flow rate= 0.5 mL/min, retention times: 26 min (minor) and 29 min (major).

(2*R*,3R)-2-((3,5-Bis(trifluoromethyl)benzyl)amino)-3-hydroxy-N-(2-nitrophenyl)-5-phenylpentanamide 63a

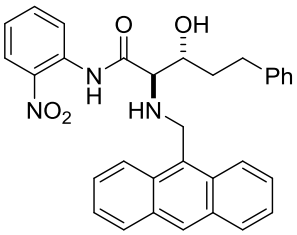


Prepared according to the general procedure starting from (E) *N*-(2-nitrophenyl)-2-((4-(trifluoromethyl)benzylidene)amino)acetamide **62** (82 mg, 0.2 mmol) and hydrocinnamaldehyde **48a** (80 µL, 0.6 mmol).

Purified column chromatography (hexane/EtOAc, 85:15), separable diastereoisomers. Yellow oil. Yield (including both diastereoisomers): 80% (89 mg, 0.16 mmol). $[\alpha]_D^{23} = -1.675^o$ (*c*=2, 97% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.72 (s, 1H), 8.78 (dd, *J* = 8.5 Hz, 1H), 8.40 – 8.15 (m, 1H), 7.90 (s, 2H), 7.78 (s, 1H), 7.73 – 7.58 (m, 1H), 7.35 – 7.09 (m, 5H), 4.09 (s, 1H), 3.98 (q, *J* = 12.9 Hz, 2H), 3.39 (d, *J* = 4.7 Hz, 1H), 2.92 – 2.83 (m, 1H), 2.80 – 2.66 (m, 1H), 2.07 – 1.78 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7 , 141.5 , 141.2 , 135.9 , 134.0 , 128.7 , 128.6 , 126.4 , 126.0 , 123.9 , 122.2 , 121.7 , 72.0 , 68.0 , 52.5 , 34.6 , 32.2 . UPLC-DAD-QTOF: $C_{26}H_{24}N_3O_4F_6$ $[M+H]^+$ calcd.: 556.1671, found: 556.1693.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel IA hexane/isopropanol 95/5, flow rate= 1 mL/min, retention times: *Major diastereoisomer* 14 min (minor) and 17 min (major); *Minor diastereoisomer* 23 min (major) and 30 min (minor).

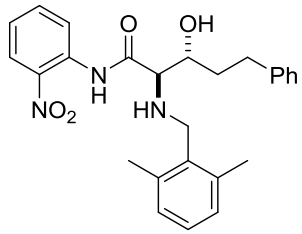
2-((Anthracen-9-ylmethyl)amino)-3-hydroxy-*N*-(2-nitrophenyl)-5-phenylpentanamide 74a



Prepared according to the general procedure starting from (*E*)-2-((anthracen-9-ylmethylene)amino)-*N*-(2-nitrophenyl)acetamide **68** (77 mg, 0.2 mmol) and hydrocinnamaldehyde **48a** (80 µL, 0.6 mmol). Purified by column chromatography (hexane/EtOAc, 90:10). Yellow solid. Yield: 56% (58 mg, 0.11 mmol). $[\alpha]_D^{24} = -15.7^o$ (*c*=1, 12% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.60 (s, 1H), 8.78 (d, *J* = 9.6 Hz, 1H), 8.41 (s, 1H), 8.30 (d, *J* = 8.4 Hz, 2H), 8.04 – 7.95 (m, 2H), 7.54 – 7.41 (m, 4H), 7.30 – 7.13 (m, 7H), 7.08 – 7.01 (m, 1H), 4.93 (d, *J* = 12.9 Hz, 1H), 4.76 (d, *J* = 13.0 Hz, 1H), 3.97 – 3.89 (m, 1H), 3.58 (d, *J* = 4.9 Hz, 1H), 3.01 – 2.90 (m, 1H), 2.71 – 2.60 (m, 1H), 1.83 – 1.71 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.4 , 141.4 , 135.8 , 134.2 , 131.6 , 130.5 , 129.4 , 128.5 , 128.0 , 126.6 , 126.1 , 125.2 , 123.9 , 122.3 , 71.9 , 68.3 , 44.8 , 34.6 , 29.9 . UPLC-DAD-QTOF: $C_{32}H_{30}N_3O_4$ $[M+H]^+$ calcd.: 520.2236, found: 520.2238.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel ID hexane/isopropanol 90/10, flow rate= 1 mL/min, retention times: *Minor diastereoisomer* 30 min (minor) and 34 min (major); *Major diastereoisomer* 41 min (minor) and 48 min (major).

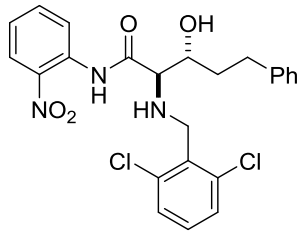
2-((2,6-Dimethylbenzyl)amino)-3-hydroxy-*N*-(2-nitrophenyl)-5-phenylpentanamide 75a



Prepared according to the general procedure starting from (*E*)-2-((2,6-dimethylbenzylidene)amino)-*N*-(2-nitrophenyl)acetamide **69** (62 mg, 0.2 mmol) and hydrocinnamaldehyde **48a** (80 µL, 0.6 mmol). Purified by column chromatography (hexane/EtOAc, 95:5). Yield: 67% (60 mg, 0.13 mmol). Yellow oil. $[\alpha]_D^{24}$ = –6.2º (*c*=0.5, 66% *ee*, CH_2Cl_2) ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.57 (s, 1H), 8.80 (d, *J* = 1.2 Hz, 1H), 8.21 (d, *J* = 10.0 Hz, 1H), 7.65 (t, *J* = 7.9 Hz, 1H), 7.39 – 7.11 (m, 6H), 7.11 – 6.97 (m, 3H), 4.02 – 3.94 (m, 1H), 3.95 – 3.83 (m, 2H), 3.34 (d, *J* = 5.1 Hz, 1H), 2.95 – 2.77 (m, 2H), 2.74 – 2.58 (m, 2H), 2.36 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4 , 141.4 , 137.2 , 135.8 , 134.0 , 128.6 , 127.7 , 126.2 , 125.9 , 123.8 , 122.4 , 72.0 , 68.2 , 47.1 , 35.4 , 32.1 , 19.8 . UPLC-DAD-QTOF: $C_{26}H_{30}N_3O_4$ $[M+H]^+$ calcd.: 448.2236, found: 448.2253.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel IC hexane/isopropanol 90/10, flow rate= 0.5 mL/min, retention times: *Major diastereoisomer* 25 min (major) and 27 min (minor); *Minor diastereoisomer* 30 min (major) and 44 min (minor).

2-((2,6-Dichlorobenzyl)amino)-3-hydroxy-*N*-(2-nitrophenyl)-5-phenylpentanamide 76a

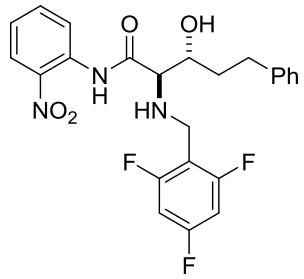


Pprepared according to the general procedure starting from (*E*)-2-((2,6-dimethylbenzylidene)amino)-N-(2-nitrophenyl)acetamide **70** (70 mg, 0.2 mmol) and hydrocinnamaldehyde **48a** (80 µL, 0.6 mmol). Purified by column chromatography (hexane/EtOAc, 90:10). Yield: 76% (74 mg, 0.15 mmol). White solid. m.p. = 181-184 ºC. $[\alpha]_D^{24}$ = –9.3º (*c*=1, 66% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.82 (s, 1H), 8.81 (d, *J* = 9.8 Hz, 1H), 8.22 (d, *J* = 10.0 Hz, 1H), 7.65 (t, *J* = 8.6 Hz, 1H), 7.44 – 6.96 (m, 9H), 4.19 (d, *J* = 3.2 Hz, 2H), 3.68 (t, *J* = 6.4 Hz, 1H), 3.36 (d, *J* = 5.4 Hz, 1H), 2.92 – 2.62 (m, 2H), 1.98 – 1.67 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3 , 141.5 , 136.1 , 135.7 , 129.6 , 128.5 , 126.0 , 125.9 , 123.6 , 122.2 , 71.7 , 67.0 , 47.4 , 34.3 , 31.9 . UPLC-DAD-QTOF: $C_{24}H_{24}N_3O_4Cl_2$ $[M+H]^+$ calcd.: 488.1144, found: 488.1165.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel IF hexane/isopropanol 90/10, flow rate= 0.6 mL/min, retention times: *Major*

diastereoisomer 27 min (major) and 30 min (minor); *Minor diastereoisomer* 33 min (major) and 40 min (minor).

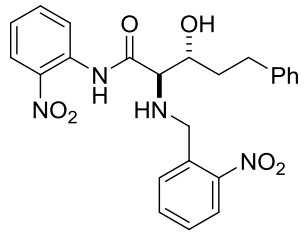
3-Hydroxy-*N*-(2-nitrophenyl)-5-phenyl-2-((2,4,6-trifluorobenzyl)amino)pentanamide 77a



Prepared according to the general procedure starting from (*E*) *N*-(2-nitrophenyl)-2-((2,4,6-trifluorobenzylidene)amino)acetamide **71** (67 mg, 0.2 mmol) and hydrocinnamaldehyde **48a** (80 µL, 0.6 mmol). Purified by column chromatography (hexane/EtOAc, 92:8). Isolated as a 73:27 diastereomeric mixture. Yield: 77% (73 mg, 0.15 mmol). White solid. m.p. = 190-192 ºC. $[\alpha]_D^{24}$ = –12.3º (*c*=1.5, 80% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.91 (s, 1H), 11.81 (s, 0H), 8.84 (d, *J* = 9.8 Hz, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 7.73 – 7.61 (m, 1H), 7.43 – 7.06 (m, 9H), 6.82 – 6.46 (m, 2H), 4.13 – 3.82 (m, 5H), 3.39 (d, *J* = 5.1 Hz, 0H), 3.31 (d, *J* = 4.2 Hz, 1H), 2.99 – 2.81 (m, 2H), 2.80 – 2.58 (m, 2H), 1.97 – 1.76 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0 , 172.0 , 162.0 (m) , 161.9 (m) , 141.3 , 137.0 , 135.8 , 134.0 , 128.7 , 128.5 , 126.2 , 125.9 , 123.7 , 122.1 , 100.5 (dd, *J* = 26.3 Hz, 2.7 Hz) , 72.0 , 71.8 , 67.4 , 67.2 , 39.9 , 39.7 , 35.5 , 34.3 , 32.2 , 32.0 . UPLC-DAD-QTOF: $C_{24}H_{23}N_3O_4F_3$ $[M+H]^+$ calcd.: 474.1641, found: 474.1663.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel ID hexane/isopropanol 90/10, flow rate= 0.5 mL/min, retention times: *Major diastereoisomer* 29 min (minor) and 36 min (major); *Minor diastereoisomer* 44 min (major) and 51 min (minor).

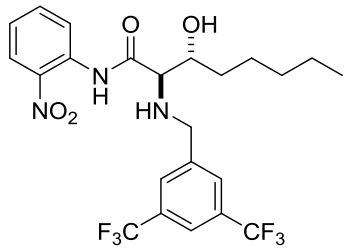
3-Hydroxy-2-((2-nitrobenzyl)amino)-*N*-(2-nitrophenyl)-5-phenylpentanamide 78a



Prepared according to the general procedure starting from (*E*)-2-((2-nitrobenzylidene)amino)-*N*-(2-nitrophenyl)acetamide **72** (66 mg, 0.2 mmol) and hydrocinnamaldehyde **48a** (80 µL, 0.6 mmol). Purified by column chromatography (hexane/EtOAc, 85:15). Yield: 75% (70 mg, 0.15 mmol) Yellow oil. $[\alpha]_D^{24}$ = –3.6º (*c*=1, 80% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.78 (s, 1H), 8.79 (d, *J* = 8.5 Hz, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 7.76 – 7.58 (m, 2H), 7.45 (d, *J* = 2.2 Hz, 1H), 7.39 – 6.97 (m, 7H), 4.15 (d, *J* = 10.5 Hz, 2H), 4.02 (m, 1H), 3.37 (d, *J* = 4.2 Hz, 1H), 2.87 (m, 1H), 2.78 – 2.60 (m, 1H), 2.01 – 1.65 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9 , 141.3 , 135.8 , 133.8 , 132.0 , 128.8 , 128.7 , 128.6 , 126.2 , 125.9 , 125.3 , 123.8 , 122.3 , 72.2 , 67.5 , 50.7 , 35.5 , 32.3 . UPLC-DAD-QTOF: $C_{24}H_{25}N_4O_6$ $[M+H]^+$ calcd.: 465.1174, found: 465.1178.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel IF hexane/isopropanol 80/20, flow rate= 1 mL/min, retention times: *Major diastereoisomer* 18 min (major) and 20 min (minor); *Minor diastereoisomer* 23 min (major) and 33 min (minor).

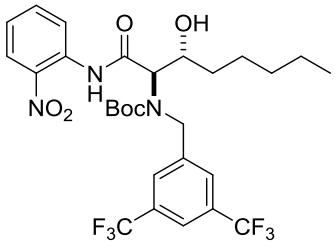
2-((3,5-Bis(trifluoromethyl)benzyl)amino)-3-hydroxy-*N*-(2-nitrophenyl)octanamide 63b



Prepared according to the general procedure starting from (*E*)-*N*-(2-nitrophenyl)-2-((4-(trifluoromethyl)benzylidene)amino)acetamide **62** (82 mg, 0.2 mmol) and hexanal **48b** (74 µL, 0.6 mmol). Purified by column chromatography (hexane/EtOAc, 90:10). Yield: 82% (85 mg, 0.16 mmol). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.74 (s, 1H), 8.77 (dd, 1H), 8.23 (dd, 1H), 7.92 (s, 2H), 7.78 (s, 1H), 7.65 (t, *J* = 8.6 Hz, 1H), 7.21 (t, *J* = 7.9 Hz, 1H), 4.09 – 4.07 (m, 1H), 4.04 (q, 2H), 3.42 (d, *J* = 4.6 Hz, 1H), 1.69 – 1.45 (m, 2H), 1.45 – 1.17 (m, 6H), 1.01 – 0.62 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8 , 141.6 , 137.0 , 135.9 , 134.0 , 132.0 (q, *J* = 33.3 Hz), 128.6 , 126.0 , 123.9 , 122.2 , 121.6 , 72.8 , 68.1 , 52.6 , 32.8 , 31.7 , 25.7 , 22.7 , 14.1 . UPLC-DAD-QTOF: $C_{23}H_{26}N_3O_4F_6$ $[M+H]^+$ calcd.: 522.1828, found: 522.1853.

The enantiomeric purity was determined by HPLC analysis after boc-protection of the amine.

***tert*-Butyl (3,5-Bis(trifluoromethyl)benzyl)(3-hydroxy-1-((2-nitrophenyl)amino)-1-oxooctan-2-yl)carbamate 104b**

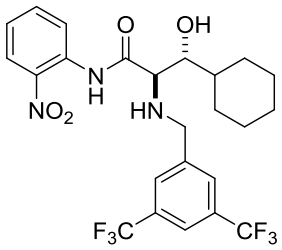


Prepared according to the general procedure. $[\alpha]_D^{24}$ = –9.1º (*c*=1, 95% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.78 (s, 1H), 8.83 (d, *J* = 9.8 Hz, 1H), 8.21 (d, *J* = 10.0 Hz, 1H), 7.90 (s, 2H), 7.77 (s, 1H), 7.68 – 7.58 (m, 1H), 7.19 (dd, 1H), 5.19 – 5.00 (m, 1H), 3.99 (d, *J* = 6.9 Hz, 2H), 3.60 (s, 1H), 1.70 (s, 1H), 1.49 (s, 9H), 1.33 – 1.22 (m, 5H), 0.92 – 0.66 (m, 3H).^{13}C NMR (75 MHz, $CDCl_3$)) δ 169.8 , 153.8 , 141.4 , 135.8 , 134.1 , 132.0 (q, *J* = 33.2 Hz), 128.4 , 125.9 , 123.6 , 121.9 , 121.6 , 83.3 , 77.2 , 67.3 , 52.5 , 31.4 , 30.5 , 27.7 , 25.5 , 22.6 , 14.0 . UPLC-DAD-QTOF: $C_{28}H_{34}N_3O_6F_6$ $[M+H]^+$ calcd.: 622.2352, found: 622.2363.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel IF and ID hexane/isopropanol 98/2, flow rate= 0.5 mL/min, retention times: *Major diastereoisomer*

52 min (minor) and 56 min (major); *Minor diastereoisomer* 79 min (minor) and 90 min (major).

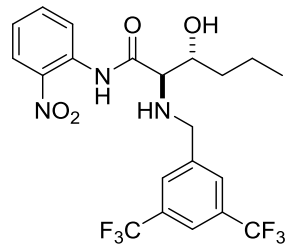
2-((3,5-Bis(trifluoromethyl)benzyl)amino)-3-cyclohexyl-3-hydroxy-*N*-(2-nitrophenyl)propanamide 63e



Prepared according to the general procedure starting from 2-((diphenylmethylene)amino)-*N*-(2-nitrophenyl)acetamide **62** (83.8 mg, 0.2 mmol) and cyclohexanecarbaldehyde **48e** (72 µL, 0.6 mmol). Purified by column chromatography (hexane/EtOAc, 90:10). Yield: 77% (82 mg, 0.15 mmol). Yellow oil. $[\alpha]_D^{23}$ = – 4.6º (*c*=2, 88% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.66 (s, 1H), 8.77 (dd, *J* = 8.5, 1.2 Hz, 1H), 8.22 (dd, 1H), 7.91 (s, 2H), 7.78 (s, 1H), 7.64 (t, *J* = 8.7 Hz, 1H), 7.24 – 7.13 (m, 1H), 4.02 (s, 2H), 3.71 – 3.60 (m, 1H), 3.44 (d, *J* = 4.7 Hz, 1H), 1.85 – 1.59 (m, 6H), 1.17 – 0.96 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4 , 141.7 , 135.8 , 132.0 (q, *J* = 33.4 Hz), 128.6 , 126.0 , 123.8 , 122.3 , 121.6 , 77.5 , 64.9 , 52.0 , 40.6 , 29.9 , 28.3 , 26.3 , 26.1 , 25.9 . UPLC-DAD-QTOF: $C_{24}H_{26}N_3O_4F_6$ $[M+H]^+$ calcd.: 534.1828, found: 534.1841.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel two columns IAIA hexane/isopropanol 80/20, flow rate= 0.5 mL/min, retention times: *Major diastereoisomer* 40 min (minor) and 47 min (major); *Minor diastereoisomer* 44 min (minor) and 60 min (major).

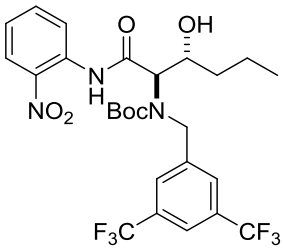
2-((3,5-Bis(trifluoromethyl)benzyl)amino)-3-hydroxy-*N*-(2-nitrophenyl)hexanamide 63h



Prepared according to the general procedure starting from (*E*)-*N*-(2-nitrophenyl)-2-((4-(trifluoromethyl)benzylidene)amino)acetamide **62** (82 mg, 0.2 mmol) and butyraldehyde **48h** (54 µL, 0.6 mmol). Purified by column chromatography (hexane/EtOAc, 90:10). Yield: 71% (70 mg, 0.14mmol). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.75 (s, 1H), 8.78 (d, *J* = 8.5 Hz, 1H), 8.23 (d, *J* = 8.5 Hz, 1H), 7.93 (s, 2H), 7.78 (s, 1H), 7.65 (td, *J* = 1.2 Hz, 1H), 7.21 (td, *J* = 7.2 Hz, 1H), 4.18 – 4.07 (m, 1H), 4.07 – 3.94 (m, 2H), 3.42 (d, *J* = 4.6 Hz, 1H), 1.69 – 1.46 (m, 4H), 0.92 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8 , 141.6 , 135.9 , 134.0 , 132.0 (q, *J* = 33.3 Hz), 128.6 , 126.0 , 123.9 , 122.2 , 121.6 , 72.5 , 68.2 , 52.6 , 34.9 , 19.2 , 13.9 . UPLC-DAD-QTOF: $C_{21}H_{22}N_3O_4F_6$ $[M+H]^+$ calcd.: 494.1515, found: 494.1532.

The enantiomeric purity was determined by HPLC analysis after Boc-protection of the amine.

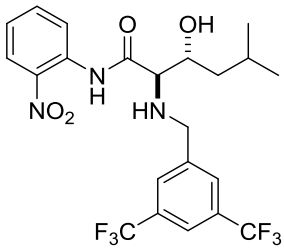
***tert*-Butyl (3,5-bis(trifluoromethyl)benzyl)(3-hydroxy-1-((2-nitrophenyl)amino)-1-oxohexan-2-yl)carbamate 104h**



Prepared according to the general procedure. $[\alpha]_D^{23}$ = -5.1º (*c*=1.5, 95% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.79 (s, 1H), 8.84 (d, *J* = 8.5 Hz, 1H), 8.20 (d, *J* = 1.6 Hz, 1H), 7.91 (s, 2H), 7.77 (s, 1H), 7.64 (t, *J* = 9.1 Hz, 1H), 7.25 – 7.10 (m, 1H), 5.25 – 5.06 (m, 1H), 3.99 (s, 2H), 3.61 (d, *J* = 3.7 Hz, 1H), 1.85 – 1.55 (m, 3H), 1.49 (s, 9H), 1.40 (s, 1H), 0.91 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0 , 154.0 , 141.5 , 136.0 , 134.3 , 132.2 (q, *J* = 33.4 Hz), 128.6 , 126.1 , 123.8 , 122.1 , 121.8 , 118.5 , 83.5 , 77.8 , 67.5 , 52.7 , 32.7 , 27.9 , 19.3 , 13.9 . UPLC-DAD-QTOF: $C_{26}H_{30}N_3O_6F_6$ $[M+H]^+$ calcd.: 594.2039, found: 594.2031.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel IF and ID hexane/isopropanol 98/2, flow rate= 0.5 mL/min, retention times: *Major diastereoisomer* 56 min (minor) and 59 min (major); *Minor diastereoisomer* 73 min (minor) and 91 min (major).

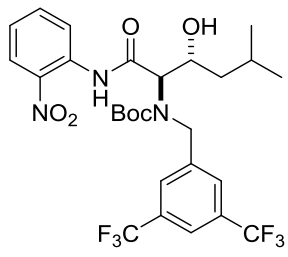
2-((3,5-Bis(trifluoromethyl)benzyl)amino)-3-hydroxy-5-methyl-*N*-(2-nitrophenyl)hexanamide 63i



Prepared according to the general procedure starting from (*E*)-*N*-(2-nitrophenyl)-2-((4-(trifluoromethyl)benzylidene)amino)acetamide **62** (82 mg, 0.2 mmol) and isovaleraldehyde **48i** (64 µL, 0.6 mmol). Purified by column chromatography (hexane/EtOAc, 90:10). Yield: 76% (77mg, 0.15 mmol). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.72 (s, 1H), 8.79 (dd, *J* = 9.8 Hz, 1H), 8.24 (dd, *J* = 9.9 Hz, 1H), 7.93 (s, 2H), 7.78 (s, 1H), 7.66 (t, 1H), 7.22 (t, 1H), 4.18 (d, *J* = 13.5 Hz, 1H), 4.03 (q, *J* = 13.9 Hz, 2H), 3.40 (d, *J* = 4.5 Hz, 1H), 1.79 (d, *J* = 11.1 Hz, 1H), 1.70 – 1.46 (m, 1H), 1.41 – 1.20 (m, 1H), 0.92 (dd, *J* = 12.3, 6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7 , 141.6 , 135.9 , 134.0 , 132.0 (d, *J* = 33.4 Hz), 128.7 , 126.0 , 123.9 , 122.2 , 121.6 , 70.8 , 68.4 , 52.6 , 41.7 , 24.7 , 23.7 , 21.5 . UPLC-DAD-QTOF: $C_{22}H_{24}N_3O_4F_6$ $[M+H]^+$ calcd.: 508.1671, found: 508.1672.

The enantiomeric purity was determined by HPLC analysis after Boc-protection of the amine.

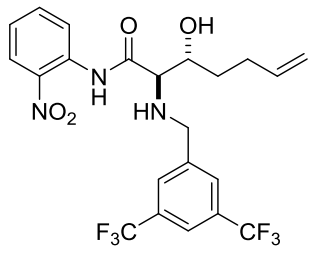
***tert*-Butyl (3,5-bis(trifluoromethyl)benzyl)(3-hydroxy-5-methyl-1-((2-nitrophenyl)amino)-1-oxohexan-2-yl)carbamate 104i**



Prepared according to the general procedure. $[\alpha]_D^{23}$ = –14.05º (*c*=0.75, 95% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.79 (s, 1H), 8.84 (d, *J* = 9.7 Hz, 1H), 8.21 (d, *J* = 10.0 Hz, 1H), 7.90 (s, 2H), 7.77 (s, 1H), 7.69 – 7.52 (m, 1H), 7.19 (t, *J* = 7.9 Hz, 1H), 5.34 – 5.06 (m, 1H), 4.00 (s, 2H), 3.58 (d, *J* = 3.1 Hz, 1H), 1.87 – 1.62 (m, 2H), 1.50 (s, 9H), 1.44 – 1.35 (m, 1H), 0.91 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8 , 153.8 , 141.4 , 135.8 , 134.2 , 132.0 (q, *J* = 33.4 Hz), 128.4 , 125.9 , 123.6 , 121.9 , 121.6 , 83.3 , 75.5 , 67.7 , 52.6 , 39.2 , 27.7 , 24.8 , 23.2 , 21.7 . UPLC-DAD-QTOF: $C_{27}H_{32}N_3O_6F_6$ $[M+H]^+$ calcd.: 608.2195, found: 608.2195.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel IF and ID hexane/isopropanol 98/2, flow rate= 0.5 mL/min, retention times: *Major diastereoisomer* 46 min (minor) and 51 min (major); *Minor diastereoisomer* 55 min (minor) and 60 min (major).

2-((3,5-Bis(trifluoromethyl)benzyl)amino)-3-hydroxy-N-(2-nitrophenyl)hept-6-enamide 63m



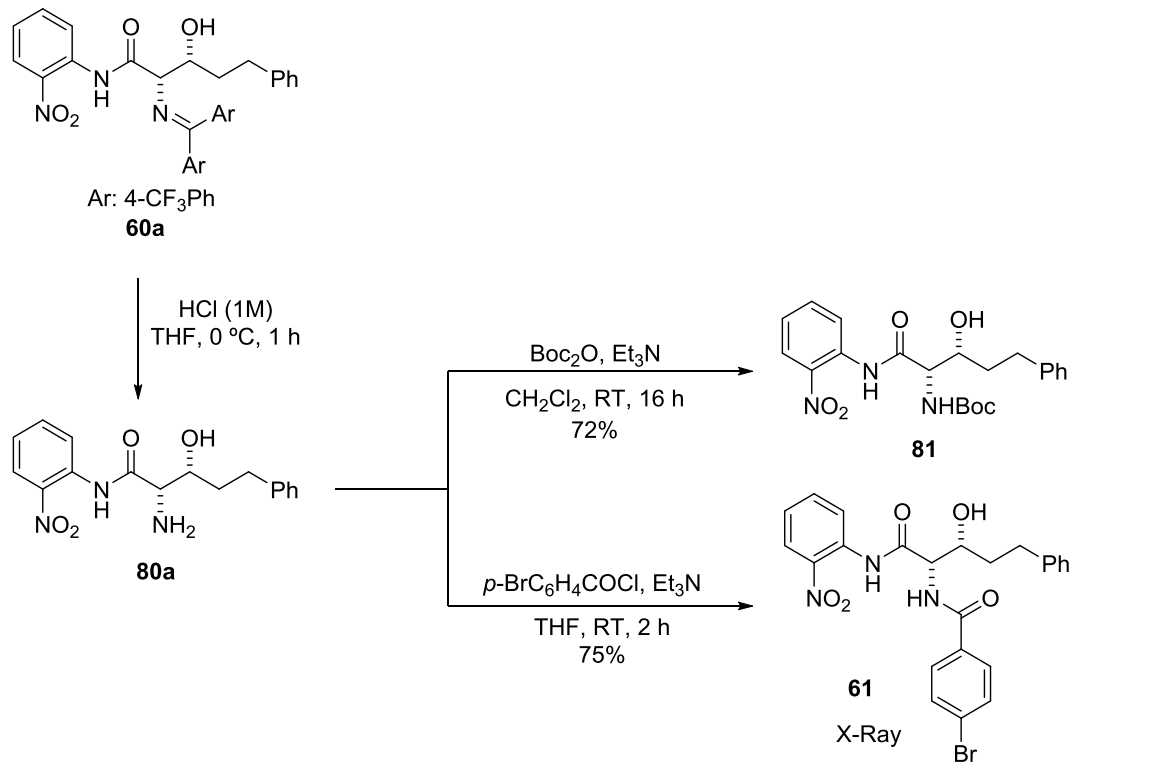
Prepared according to the general procedure starting from 2-((diphenylmethylene)amino)-*N*-(2-nitrophenyl)acetamide **62** (82 mg, 0.2 mmol) and 4-pentenal **48m** (60 µL, 0.6 mmol). Purified by column chromatography (hexane/EtOAc, 90:10). Yield: 84% (85 mg, 0.17 mmol). Yellow oil. $[\alpha]_D^{23}$ = +5.2º (*c*=1.5, 95% *ee*, CH_2Cl_2)^{1}H NMR (300 MHz, $CDCl_3$) δ 11.75 (s, 1H), 8.79 (dd, *J* = 8.5, 1.3 Hz, 1H), 8.24 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.00 – 7.86 (m, 1H), 7.79 (s, 1H), 7.66 (ddd, *J* = 8.6, 7.2, 1.6 Hz, 1H), 7.22 (ddd, 0H), 5.94 – 5.69 (m, 1H), 5.16 – 4.92 (m, 1H), 4.03 (q, *J* = 13.8 Hz, 2H), 3.42 (d, *J* = 4.6 Hz, 1H), 2.32 – 2.12 (m, 1H), 1.88 – 1.64 (m, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7 , 141.6 , 137.8 , 135.9 , 132.0 (q, *J* = 33.3 Hz), 128.6 , 126.0 , 123.9 , 122.2 , 121.1 , 115.8 , 72.2 , 68.2 , 52.6 , 31.8 , 30.3 . UPLC-DAD-QTOF: $C_{22}H_{22}N_3O_4F_6$ $[M+H]^+$ calcd.: 506.1515, found: 505.1539.

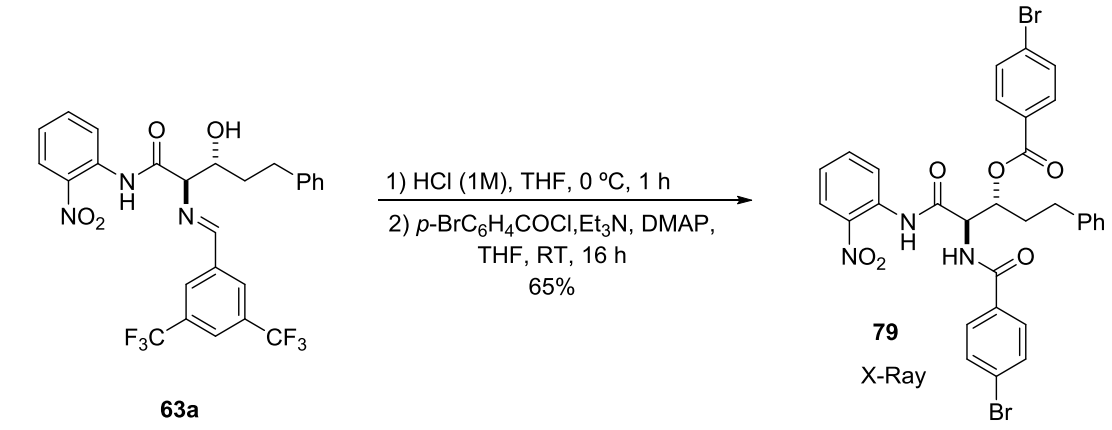
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel IF hexane/isopropanol 97/3, flow rate= 0.5 mL/min, retention times: *Major diastereoisomer*

32 min (minor) and 37 min (major); *Minor diastereoisomer* 51 min (minor) and 54 min (major).

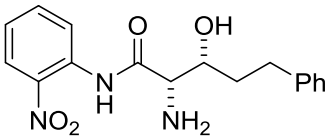
6.4.4. Elaboration of adducts

6.4.4.1. Imine hydrolysis and amine protection



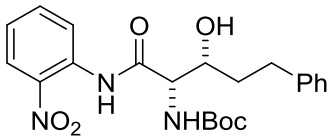


(2*S*,3*R*)-2-amino-3-hydroxy-N-(2-nitrophenyl)-5-phenylpentanamide 80a



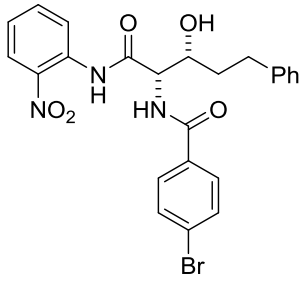
60a (0.2 mmol, 1 equiv.) was dissolved in THF (5 mL) and HCl 1M (0.68 mL, 0.68 mmol, 3.4 equiv.) was added at 0 ºC. The mixture stirred at the same temperature for 2 h. Then, when the reaction was finished (monitored by TLC), the solvent was evaporated under reduced pressure and $NaHCO_3$ (sat) was added until pH 8-9. The mixture was extracted with DCM (3 x 10 mL), brine (10 mL) was added to the aqueous phase and this was extracted again with DCM (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude was used in the next step without further purification. Yield: 80% (52 mg, 0.16 mmol). Yellow oil. $[\alpha]_D^{23}$ = –8.1º (*c*=2, 94% *ee*, CH_2Cl_2) ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.06 (s, 1H), 8.79 (dd, *J* = 8.5 Hz, 1H), 8.18 (dd, 1H), 7.63 (td, *J* = 7.6 Hz, 1H), 7.46 – 7.01 (m, 5H), 4.41 – 4.22 (m, 1H), 3.46 (d, *J* = 2.5 Hz, 1H), 2.95 – 2.83 (m, 1H), 2.83 – 2.61 (m, 1H), 2.01 – 1.72 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8 , 141.6 , 135.7 , 134.2 , 128.7 , 128.6 , 126.3 , 125.9 , 123.6 , 122.2 , 71.3 , 60.0 , 35.4 , 32.4 . UPLC-DAD-QTOF: $C_{17}H_{20}N_3O_4$ $[M+H]^+$ calcd.: 330.1454, found: 330.1462.

***tert*-Butyl ((2*S*,3*R*)-3-hydroxy-1-((2-nitrophenyl)amino)-1-oxo-5-phenylpentan-2-yl)carbamate 81**



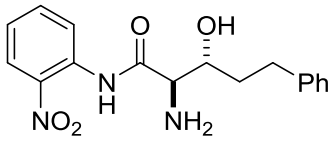
Aminoalcohol **80a** (0.2 mmol, 1 equiv.) was dissolved in dry dichloromethane (1.8 mL), di-*tert*-butyl dicarbonate (48 mg, 0.22 mmol, 1.1 equiv.) was added at room temperature and the mixture stirred for 16 h. The reaction was quenched with 1M HCl (0.6 mL) and the mixture extracted with DCM (3 x 6 mL). The combined organic phases were dried over $MgSO_4$ and evaporated under reduced pressure. The crude was purified by column chromatography (hexane/EtOAc, 88:12) to afford **81** as yellow oil. Yield: 67% (0.094 mmol). $[\alpha]_D^{23}$ = –20.1º (*c*=1, 88% *ee*, CH_2Cl_2) ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.17 (s, 1H), 8.76 (dd, 1H), 8.21 (dd, *J* = 9.9 Hz, 1H), 7.64 (td, *J* = 8.6 Hz, 1H), 7.35 – 7.15 (m, 5H), 5.57 (d, 1H), 4.47 – 4.36 (m, 2H), 2.91 – 2.63 (m, 2H), 1.89 (d, *J* = 15.0 Hz, 2H), 1.50 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1 , 156.2 , 141.3 , 136.1 , 135.9 , 128.7 , 128.6 , 126.3 , 125.9 , 123.9 , 123.7 , 122.2 , 81.2 , 70.4 , 59.6 , 35.0 , 32.1 , 28.4 . UPLC-DAD-QTOF: $C_{22}H_{27}N_3O_6Na$* *$[M+Na]^+$ calcd.: 452.1798, found: 452.1804.

4-Bromo-*N*-((2*S*,3*R*)-3-hydroxy-1-((2-nitrophenyl)amino)-1-oxo-5-phenylpentan-2-yl)benzamide 61



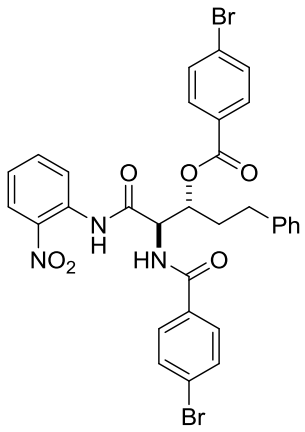
Aminoalcohol **80a** (0.2 mmol, 1 equiv.) was dissolved in dry THF (1 mL) and 4-bromobenzoyl chloride (0.2 mmol, 1 equiv.) was added in one portion, followed by slow addition of triethylamine (0.65 mL). The reaction mixture was stirred at room temperature for 2 h until complete conversion of the starting material. Then the solvent was evaporated, and the residue was redisolved in dichloromethane (5 mL), washed with water (3 mL), and extracted with dichloromethane (2 x 5 mL). The combined organic phases were dried over $MgSO_4$ and evaporated in vacuo. The crude was purified by column chromatography (hexane/EtOAc, 90:10) and afforded **61** as a white solid. Yield: 75% (76 mg, 0.15 mmol). m.p. = 145-147 ºC. $[\alpha]_D^{23}$ = –7.4º (*c*=2, 92% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.07 (s, 1H), 8.66 (dd, 1H), 8.16 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.77 (d, *J* = 8.5 Hz, 2H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.38 – 7.12 (m, 6H), 4.92 (d, *J* = 9.7 Hz, 1H), 4.54 – 4.39 (m, 1H), 2.86 (s, 1H), 2.78 – 2.60 (m, 1H), 1.86 (q, *J* = 8.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1 , 167.5 , 141.1 , 137.2 , 135.8 , 133.7 , 132.2 , 129.1 , 128.7 , 128.5 , 127.3 , 126.3 , 125.9 , 124.1 , 122.6 , 70.3 , 58.7 , 34.8 , 32.1 . UPLC-DAD-QTOF: $C_{24}H_{23}BrN_3O_5$ $[M+H]^+$ calcd.: 512.0826, found: 512.0821.

(2*R*,3*R*)-2-amino-3-hydroxy-N-(2-nitrophenyl)-5-phenylpentanamide 105a



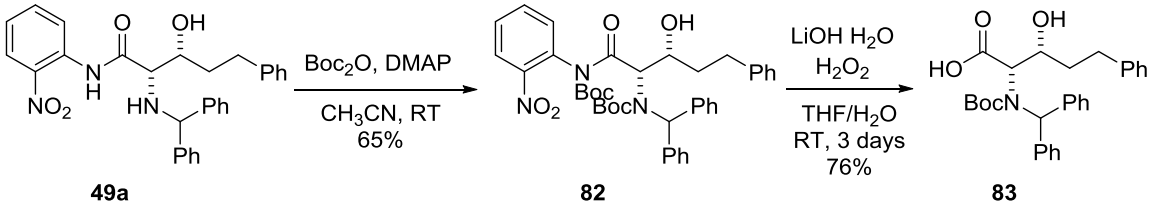
63a (0.2 mmol, 1 equiv.) was dissolved in THF (5 mL) and HCl 1M (0.68 mL, 0.68 mmol, 3.4 equiv.) was added at 0 ºC. The mixture stirred at the same temperature for 2 h. Then, when the reaction was finished (monitored by TLC), the solvent was evaporated under reduced pressure and $NaHCO_3$ (sat) was added until pH 8-9. The mixture was extracted with DCM (3 x 10 mL), brine (10 mL) was added to the aqueous phase and this was again extracted with DCM (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude was used in the next step without further purification. Yield: 70% (46 mg, 0.14 mmol). $[\alpha]_D^{23}$ = –2.6º (*c*=0.5, 97% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.92 (s, 1H), 8.77 (d, *J* = 9.7 Hz, 1H), 8.21 (d, *J* = 9.9 Hz, 1H), 7.65 (t, *J* = 7.1 Hz, 1H), 7.39 – 7.14 (m, 6H), 4.03 – 3.88 (m, 1H), 3.54 (d, *J* = 6.2 Hz, 1H), 2.97 – 2.78 (m, 1H), 2.71 (d, *J* = 7.5 Hz, 1H), 2.02 – 1.82 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0 , 141.7 , 135.7 , 133.9 , 128.6 , 126.2 , 125.9 , 123.8 ,122.4 , 73.1 , 60.08 , 34.8 , 31.9 . UPLC-DAD-QTOF: $C_{17}H_{20}N_3O_4$ $[M+H]^+$ calcd.: 330.1454, found: 330.1462.

(2*R*,3*R*)-2-(4-Bromobenzamido)-1-((2-nitrophenyl)amino)-1-oxo-5-phenylpentan-3-yl 4-bromobenzoate 79



Aminoalcohol **105a** (0.2 mmol, 1 equiv.) was dissolved in dry THF (1 mL) and 4-bromobenzoyl chloride (0.4 mmol, 2 equiv.) was added in one portion, followed by slow addition of triethylamine (0.65 mL) and DMAP (30 mol%). The reaction mixture stirred at room temperature for 16 h until complete conversion of the starting material. Then the solvent was evaporated, and the residue was redisolved in dichloromethane, washed with water, and extracted with dichloromethane (2 x 5 mL). The combined organic phases were dried over $MgSO_4$ and evaporated in vacuo. The crude was purified by column chromatography (hexane/EtOAc, 80:20) and afforded **79** as a white solid. Yield: 65% (90 mg, 0.13 mmol). m.p. = 88-93 ºC. $[\alpha]_D^{23}$ = –2.3º (*c*=0.5, 97% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.93 (s, 1H), 8.73 (d, *J* = 8.5 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 5.9 Hz, 1H), 7.81 (d, *J* = 7.7 Hz, 2H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.57 – 7.48 (m, 2H), 7.19 (d, *J* = 6.1 Hz, 6H), 5.42 – 5.29 (m, 1H), 5.16 – 4.95 (m, 1H), 2.82 (d, *J* = 23.3 Hz, 2H), 2.55 (d, *J* = 17.8 Hz, 1H), 2.28 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4 , 166.8 , 163.8 , 140.2 , 136.2 , 133.9 , 132.3 , 132.1 , 131.8 , 131.4 , 129.0 , 128.8 , 128.5 , 128.2 , 126.5 , 125.9 , 124.0 , 122.1 , 76.0 , 59.3 , 33.3 , 32.1 . UPLC-DAD-QTOF: $C_{31}H_{26}Br_2N_3O_6$ $[M+H]^+$ calcd.: 694.0195, found: 694.0198.

6.4.4.2. Removal of the nitroanilide unit[270]



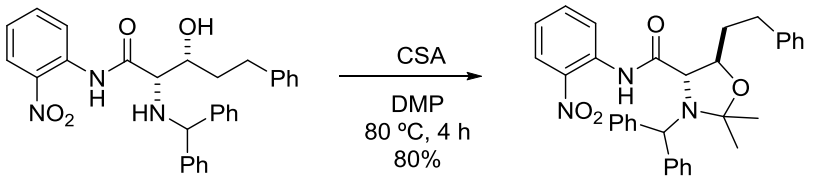
Compound **49a** (0.2 mmol) was dissolved in dry acetonitrile (0.3 mL) and DMAP (8 mg, 0.06 mmol, 30 mol%) was added, followed by and di-*tert*-butyl dicarbonate (280 mg, 1.2 mmol, 6 equiv.). The solution stirred at room temperature for 16 h. Then, the solution was evaporated and the resulting residue purified by column chromatography (hexane/EtOAc, 95:5) to afford **82** as yellow oil. Yield: 65% (90 mg, 0.13 mmol). $[\alpha]_D^{23}$ = –7.9º (*c*=2, 92% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.0 Hz, 1H),

[270] Adapted from: a) S.-Y. Zhang, Q. Li, G. He, W. A. Nack, G. Chen, *J. Am. Chem. Soc.* **2013**, *135*, 12135-12141. b) O. Verho, M. Pourghasemi Lati, M. Oschmann, *J. Org. Chem.* **2018**, *83*, 4464-4476.

7.60 (d, *J* = 7.3 Hz, 2H), 7.56 – 7.48 (m, 1H), 7.47 – 7.39 (m, 2H), 7.37 – 7.07 (m, 13H), 5.25 (t, 1H), 4.73 (s, 1H), 4.68 (s, 1H), 2.79 – 2.66 (m, 1H), 2.62 – 2.44 (m, 2H), 2.24 – 1.98 (m, 1H), 1.41 (s, 9H), 1.19 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0 , 153.8 , 150.6 , 145.9 , 144.5 , 143.1 , 141.6 , 134.0 , 131.7 , 129.1 , 128.6 , 128.5 , 127.3 , 127.0 , 126.0 , 125.2 , 84.9 , 82.3 , 76.9 , 65.4 , 62.2 , 33.5 , 31.8 , 27.9 , 27.5 . UPLC-DAD-QTOF: $C_{40}H_{46}N_3O_8$ $[M+H]^+$ calcd.: 696.3285, found: 696.3285.

Compound **82** (139 mg, 0.2 mmol) was dissolved in THF/H_2O 3:1 (2 mL). Then, LiOH H_2O (9 mg, 0.4 mmol, 2 equiv.) and 30% H_2O_2 (22 µL, 1 mmol, 5 equiv.) were added at 0 ºC. The reaction mixture was stirred at room temperature for 48 h, and Na_2SO_3 (252 mg, 2 mmol, 10 equiv.) was added. The mixture was then diluted with EtOAc, acidified with 0.5 M HCl, and extracted with EtOAc (3 x 10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting residue was purified by column chromatography (hexane/EtOAc, 80:20) to afford **83** as a yellow oil. Yield: 76% (71 mg, 0.15 mmol). $[\alpha]_D^{23}$ = –9.1º (*c*=1, 91% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 – 7.34 (m, 3H), 7.33 – 6.85 (m, 12H)., 5.12 – 5.02 (m, 1H), 4.88 (s, 1H), 3.33 (d, *J* = 3.1 Hz, 1H), 2.76 – 2.58 (m, 1H), 2.58 – 2.45 (m, 1H), 2.32 – 2.15 (m, 1H), 2.14 – 1.90 (m, 1H), 1.46 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2 , 153.1 , 143.4 , 142.3 , 141.0 , 128.9 , 128.8 , 128.6 , 128.5 , 127.8 , 127.6 , 127.3 , 126.6 , 126.3 , 82.8 , 65.69 , 61.0 , 33.3 , 31.8 , 29.9 , 27.8 . UPLC-DAD-QTOF: $C_{29}H_{34}NO_5$ $[M+H]^+$ calcd.: 476.2437, found: 476.2437.

6.4.4.3. Protection of the amino alcohol

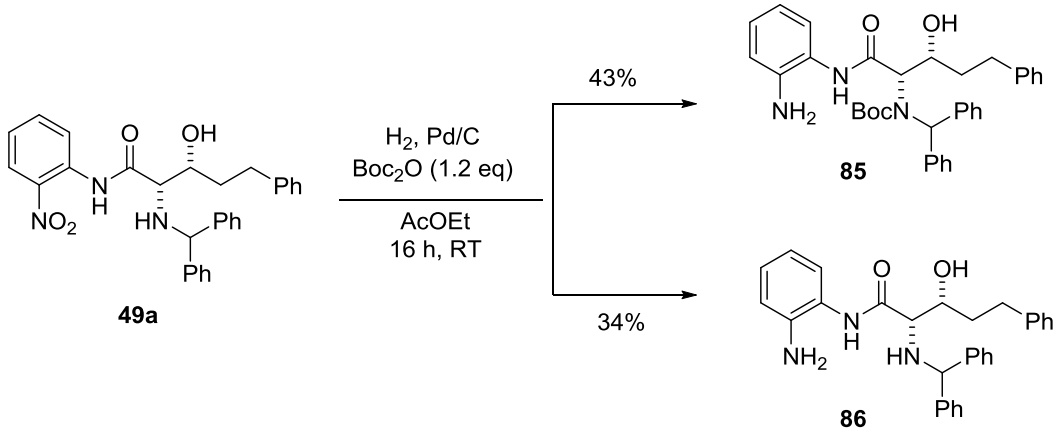


49a **84**

2-amino-3-hydroxy-*N*-(2-nitrophenyl)-5-phenylpentanamide **49a** (100 mg, 0.2 mmol, 1 equiv.) was disolved in dimethoxypropane (2 mL) and camphorsulfonic acid (CSA) (9 mg, 0.04 mmol, 20 mol%) was added at room temperature. The mixture was stirred at 80 ºC for 4 h (followed by TLC). Then, the solvent was evaporated and the crude was purified by column chromatography (hexane/EtOAc, 90:10) to afford **84** as yellow oil. Yield: 67% (73 mg, 0.13 mmol). $[\alpha]_D^{23}$ = –12.1º (*c*=1, 92% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.59 (s, 1H), 8.48 (dd, *J* = 8.6, 1.2 Hz, 1H), 8.25 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.57 (t, *J* = 8.6 Hz, 1H), 7.41 – 7.07 (m, 15H), 5.24 (s, 1H), 4.16 – 4.04 (m, 1H), 3.60 (d, *J* = 7.6 Hz, 1H), 3.01 – 2.81 (m, 1H), 2.81 – 2.64

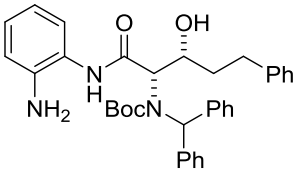
(m, 1H), 2.27 – 2.11 (m, 1H), 2.11 – 1.98 (m, 1H), 1.58 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2 , 143.5 , 141.7 , 141.4 , 136.8 , 135.7 , 134.3 , 129.9 , 128.8 , 128.5 , 128.5 , 128.4 , 127.7 , 127.6 , 127.2 , 125.9 , 125.8 , 125.3 , 123.2 , 122.0 , 77.2 , 73.6 , 70.9 , 36.5 , 32.3 , 29.6 , 25.5 . UPLC-DAD-QTOF: $C_{33}H_{34}N_3O_4$ $[M+H]^+$ calcd.: 536.2549, found: 536.2556.

6.4.4.4. Hydrogenation of the amino alcohol



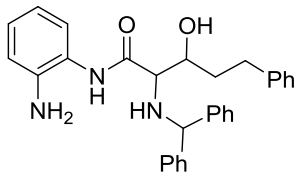
To a solution of **49a** (69 mg, 0.14 mmol) in EtOAc (1.5 mL), Boc_2O (37 mg, 0.17 mmol, 1.2 equiv.) was added at room temperature. The mixture stirred under argon and Pd/C (7 mg) was added in one portion and it was stirred under H_2 atmosphere for 16 h. The reaction mixture was filtered through a celite pad and concentrated *in vacuo*.

Tert-butyl ((2*S*,3*R*)-1-((2-aminophenyl)amino)-3-hydroxy-1-oxo-5-phenylpentan-2-yl)(benzhydryl)carbamate 85



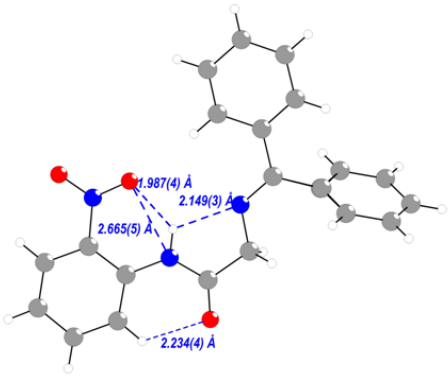
Observation in the crude NMR: 73%. Purified by column chromatography (hexane/EtOAc, 80:20) to afford **85** as a white foam. Yield: 43% (34 mg, 0.06 mmol). $[\alpha]_D^{23}$ = –9.6º (*c*=2, 92% *ee*, CH_2Cl_2) ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.17 (s, 1H), 7.54 (d, *J* = 7.9 Hz, 1H), 7.43 – 7.06 (m, 18H), 6.94 (s, 1H), 4.91 (s, 1H), 4.09 – 3.94 (m, 1H), 3.25 (d, *J* = 4.2 Hz, 1H), 2.97 – 2.76 (m, 1H), 2.75 – 2.49 (m, 1H), 1.96 – 1.75 (m, 2H), 1.44 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6 , 153.9 , 142.8 , 141.6 , 131.3 , 129.2 , 129.0 , 128.9 , 128.7 , 128.6 , 127.8 , 127.7 , 127.6 , 127.5 , 126.8 , 126.2 , 125.4 , 124.8 , 124.7 , 81.0 , 72.2 , 66.4 , 64.6 , 35.2 , 32.2 , 28.4 . UPLC-DAD-QTOF: $C_{35}H_{40}N_3O_4$ $[M+H]^+$ calcd.: 566.3019, found: 566.3022.

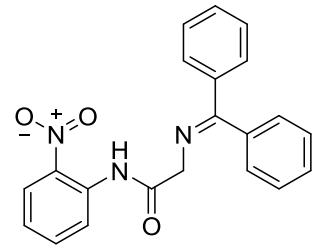
_N_-(2-Aminophenyl)-3-benzhydryl-2,2-dimethyl-5-phenethyloxazolidine-4-carboxamide 86



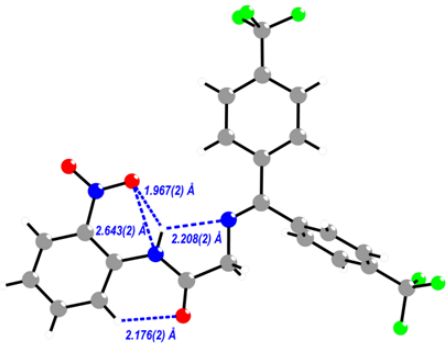
Observation in the crude NMR: 27%. Purified by column chromatography (hexane/EtOAc, 80:20) to afford **86** as a white foam. Yield: 34% (23 mg, 0.05 mmol). $[\alpha]_D^{23} = -8.2^o$ (*c*=2, 92% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (s, 1H), 7.55 – 7.10 (m, 67H), 7.06 (t, *J* = 6.9 Hz, 1H), 6.87 – 6.70 (m, 2H), 4.93 (s, 1H), 4.13 – 3.92 (m, 1H), 3.29 (d, *J* = 4.0 Hz, 1H), 2.96 – 2.78 (m, 1H), 2.78 – 2.58 (m, 1H), 1.89 (q, *J* = 7.8, 7.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0 , 142.8 , 141.6 , 140.5 , 129.0 , 128.9 , 128.7 , 127.8 , 127.7 , 127.6 , 127.5 , 127.3 , 126.2 , 125.0 , 124.1 , 119.7 , 118.3 , 72.1 , 66.3 , 64.4 , 35.2 , 32.3 . UPLC-DAD-QTOF: $C_{30}H_{32}N_3O_2$ $[M+H]^+$ calcd.: 466.2495, found: 466.2498.

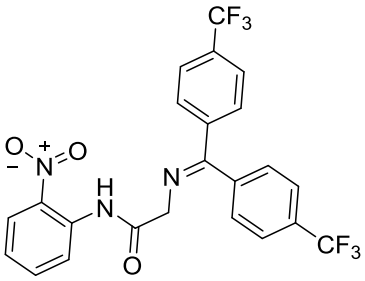
6.4.5. ORTEP diagram for compounds 45, 58, 62, 61 and 79.



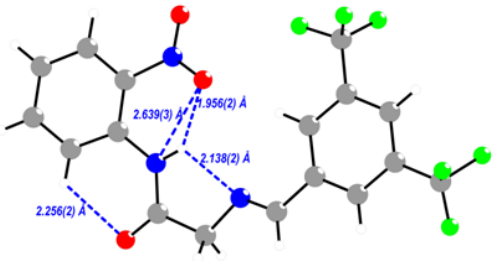


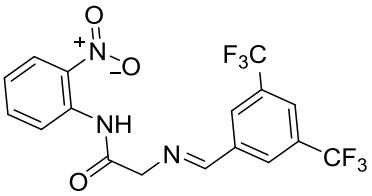
45



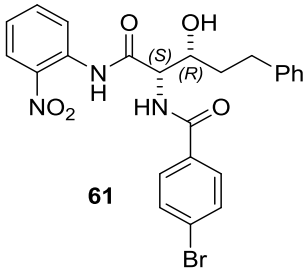


58

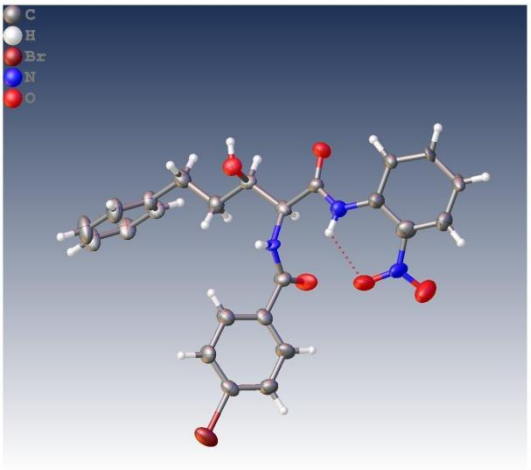


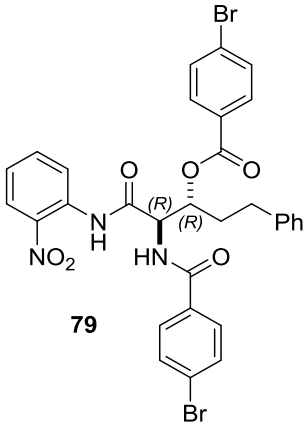


62

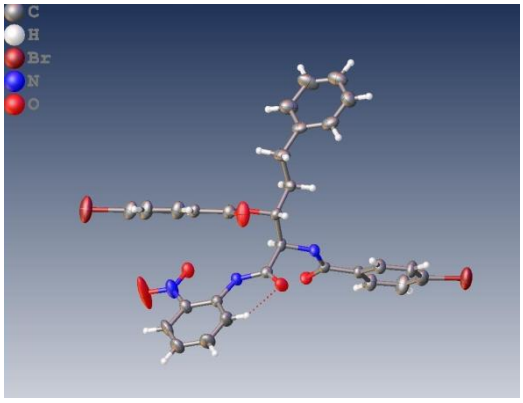


61





79



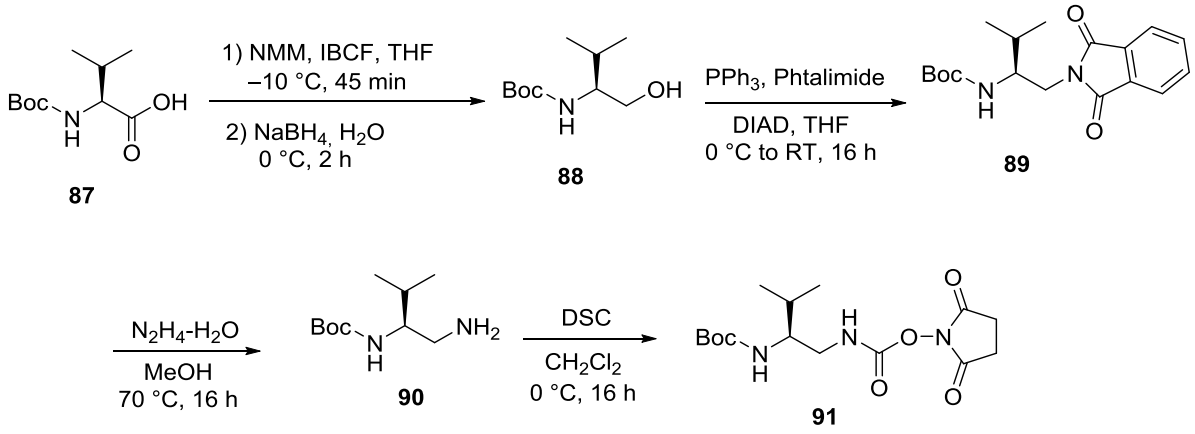
6.5. EXPERIMENTAL SECTION OF CHAPTER 4

6.5.1. Synthesis of oligoureas O7-O12

Oligomers **O7-O12** were synthesized in solution using a stepwise approach and *N*-Boc protected succinimidyl carbamate building block following previously reported procedures.[271]

6.5.1.1. Synthesis of building block 91

The valine-based building block **91** was synthesized according to a procedure described in the literature.[272]



Step 1: Boc-(L)-valine **87** (7 g, 32 mmol, 1 equiv) was dissolved in dry THF (60 mL) at 0 °C under nitrogen atmosphere. Then, *N*-methylmorpholine (3.75 mL, 35.2 mmol, 1.1 equiv.) was added, followed by isobutyl chloroformate (4.56 mL, 35.2 mmol, 1.1 equiv.) which was added dropwise at the same temperature. The reaction mixture was stirred at room temperature for 45 minutes (followed by TLC), while a white precipitate formed. This was removed by filtration (rinsed with THF) and the filtrate was added dropwise to an opened flask containing a suspension of $NaBH_4$ (2.44 g, 64 mmol, 2 equiv.) in distilled water (9.6 mL) at 0 °C. Then, THF was evaporated and the residue, redissolved in EtOAc (45 mL) and washed with 1M $KHSO_4$ (24 mL). The organic phase was washed with 1M $KHSO_4$ (3 x 16 mL), a saturated solution of $NaHCO_3$ (3 x 16 mL)

[271] a) V. Diemer, L. Fischer, B. Kauffmann, G. Guichard, *Chem. Eur. J.* **2016**, *22*, 15684-15692.; b) N. Pendem, C. Douat, P. Claudon, M. Laguerre, S. Castano, B. Desbat, D. Cavagnat, E. Ennifar, B. Kauffmann, G. Guichard, *J. Am. Chem. Soc.* **2013**, *135*, 4884-4892.
[272] C.Aisenbrey, N. Pendem, G. Guichard, B. Bechinger, *Org. Biomol. Chem.*, **2012**, 10, 1440–1447.

and brine (1 x 16 mL). The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. Crude **2** was used without further purification.

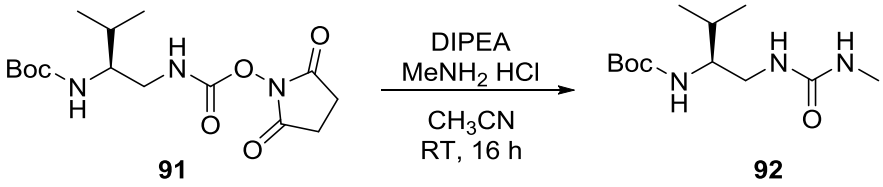
Step 2: Triphenyl phosphine (10 g, 38.7 mmol, 1.2 equiv.) was dissolved in dry THF (60 mL) at 0 °C and phtalimide (5.65 g, 38.7 mmol, 1.2 equiv.) was added, followed by slow addition of DIAD (7.6 mL, 38.7 mmol, 1.2 equiv.) at the same temperature. Alcohol **2** (32 mmol, 1 equiv.) was then added in dry THF (12 mL) and the mixture was allowed to stir at room temperature for 16 h (followed by TLC). The mixture was then concentrated and the resulting crude **89** was used in the next step without any further purification.

Step 3: Phtalimide **89** (32 mmol, 1 equiv.) was dissolved in MeOH (150 mL) and monohydrated hydrazine (6.1 mL, 80 mmol, 2.5 equiv.) was added. The mixture was refluxed for 16 h, while a big amount of precipitate was formed. The mixture was then filtered to remove the solid. The solvent was evaporated and the crude was dissolved in CH_2Cl_2 (32 mL) and washed with a saturated solution of $NaHCO_3$ (1 x 20 mL). The aqueous phase was extracted with EtOAc (3 x 16 mL) and CH_2Cl_2 (3 x 16 mL), and the combined organic phases were dried over $MgSO_4$ and evaporated under reduced pressure. Crude **90** was used in the next step without further purification.

Step 4: To a solution of disuccinidimyl carbonate (9.8 g, 38.4 mmol, 1.2 equiv.) in dry dichloromethane (38 mL), a solution of **90** (32 mmnol, 1 equiv.) in dichloromethane (38 mL) was slowly added at 0 °C and the resulting mixture was stirred for 16 hours. Then, the mixture was filtered to remove the precipitate. The solution was washed with a solution of 1M $KHSO_4$ (3 x 20 mL), and brine (1 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford **91**. Trituration with diethyl ether led to the title compound as a white solid. Overall yield: 64% (5.05 g, 14.7 mmol). All the spectroscopic data were identical to the reported in literature.[273] ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.09 (brs, 1H), 4.58 (brd, J = 16.4 Hz, 1H), 3.56 (brs, 1H), 3.41 (brd, J = 13.4 Hz, 1H), 3.26 (brs, 1H), 2.81 (s, 4H), 1.87 – 1.72 (m, 1H), 1.46 (s, 9H), 0.95 (t, J = 6.9 Hz, 6H).

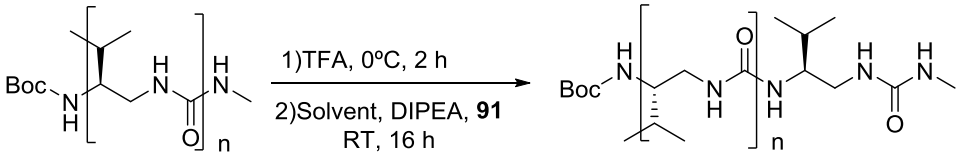
[273] G. Guichard, V. Semetey, C. Didierjean, A. Aubry, J.-P. Briand , M. Rodriguez, *J. Org. Chem.* **1999**, *64*, 8702-8705.

6.5.1.2. Methylation



To a cooled suspension of $MeNH_2$-HCl (7 mmo, 2.5 equiv.) in acetonitrile (2.3 mL) at 0 °C, DIPEA (14 mmol, 5 equiv.) was added, followed by a solution of **91** (2.8 mmol, 1 equiv.) in acetonitrile (34 mL) and the reaction mixture was stirred at room temperature for 16 h. Then, acetonitrile was evaporated under reduced pressure and the residue was solubilized in EtOAc. The mixture was washed with a 1N solution of $KHSO_4$ (1 x 5 mL/mmol), saturated $NaHCO_3$ solution (1 x 15 mL), brine (1 x 15 mL), dried over $MgSO_4$ and evaporated under reduced pressure. Trituration in diethyl ether led to the title compound **92** as a white solid. Yield: 80% (0.58 g, 2.24 mmol). All the spectroscopic data were identical to the reported in literature.[272] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.93 (s, 1H), 4.62 (s, 1H), 3.44 (m, *J* = 34.9, 14.9 Hz, 1H), 3.24 (m, *J* = 13.5 Hz, 2H), 2.76 (s, 3H), 1.86 – 1.71 (m, 1H), 1.43 (s, 9H), 0.94 (dd, *J* = 8.4, 6.9 Hz, 6H).

6.5.1.3. Coupling[274]



92 n=1
93 n=2
94 n=3
95 n=4
96 n=5

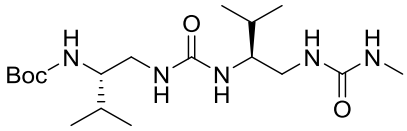
93 n=1
94 n=2
95 n=3
96 n=4
97 n=5

The Boc-protected compound **92-96** (1 mmol, 1 equiv.) was dissolved in trifluoroacetic acid (6 mL) at 0 ºC under N_2 atmosphere and the resulting mixture was stirred at room temperature for 2 h. After complete conversion, the reaction mixture was concentrated under reduced pressure and coevaporated 3 times with cyclohexane. The obtained residue was redisolved in the corresponding solvent (4 mL), and DIPEA (3 mmol, 3 equiv.) was added at 0 ºC. Then, **91** (1.5 mmol, 1.5 equiv.) was added in one portion and the mixture was stirred for 16 h at room temperature (pH was checked after succinimide addition, basic conditions are required for the addition). After reaction

[274] L. Fischer, P. Claudon, N. Pendem, E. Miclet, C. Didierjean, E. Ennifar, G. Guichard, *Angew. Chem. Int. Ed.* **2010**, *49*, 1067-1070.

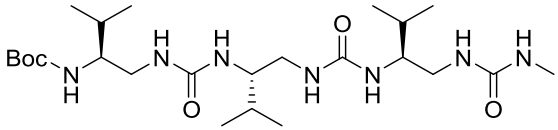
completion (monitored by TLC), the solvent was evaporated and the residue was dissolved in AcOEt (5 mL). The resulting solution was washed with a 1N solution of $KHSO_4$ (3 x 5 mL), H_2O (1 x 5 mL), a saturated $NaHCO_3$ solution (2 x 5 mL) and H_2O (1 x 5 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The reaction crudes were crushed with Et_2O.

(Boc(Val^u)$_2$NHMe) 93



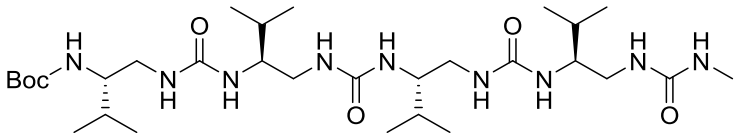
Prepared according to the general procedure starting from **92** (259 mg, 1 mmol) in acetonitrile. White solid. Yield: 64% (248 mg, 0.64 mmol). ^{1}H NMR (300 MHz, CD_3OH) δ 6.37 (d, *J* = 9.5 Hz, 1H), 6.00 – 5.75 (m, 4H), 3.65 – 3.52 (m, 1H), 3.49 – 3.35 (m, 1H), 3.05 – 2.79 (m, 1H), 2.69 (d, *J* = 4.5 Hz, 1H), 1.82 – 1.63 (m, 1H), 1.43 (s, 1H), 0.92 (dd, *J* = 10.8, 6.8 Hz, 1H).

(Boc(Val^u)$_3$NHMe) 94



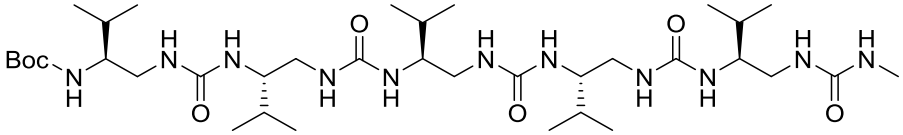
Prepared according to the general procedure starting from **93** (387 mg, 1 mmol) in acetonitrile. White solid Yield: 76% (391, 0.76 mmol). ^{1}H NMR (300 MHz, CD_3OH δ 6.57 (d, *J* = 10.0 Hz, 1H), 6.29 (d, *J* = 8.0 Hz, 1H), 6.18 (d, *J* = 4.4 Hz, 1H), 6.12 – 5.99 (m, 1H), 5.99 (dd, *J* = 16.1, 10.8 Hz, 1H), 5.78 (d, *J* = 10.0 Hz, 1H), 5.67 (d, *J* = 6.5 Hz, 1H), 3.80 – 3.42 (m, 6H), 2.70 (d, *J* = 4.1 Hz, 3H), 2.63 – 2.50 (m, 2H), 2.41 (dd, *J* = 18.8, 8.1 Hz, 1H), 1.62 (ddq, *J* = 20.7, 13.8, 7.0 Hz, 3H), 1.46 (s, 9H), 1.04 – 0.81 (m, 18H).

(Boc(Val^u)$_4$NHMe) 95



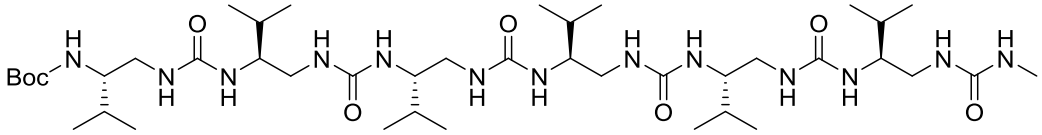
Prepared according to the general procedure starting from **94** (515 mg, 1 mmol) in DMF (4 mL). White solid. Yield: 80% (516 mg, 0.8 mmol). ^{1}H NMR (300 MHz, CD_3OH) δ 6.65 (d, *J* = 10.0 Hz, 1H), 6.40 (d, *J* = 10.5 Hz, 1H), 6.34 – 6.21 (m, 3H), 6.03 (d, *J* = 10.5 Hz, 2H), 5.81 (d, *J* = 10.1 Hz, 1H), 5.73 (d, *J* = 6.4 Hz, 1H), 3.94 – 3.45 (m, 8H), 2.71 (d, *J* = 3.9 Hz, 3H), 2.54 – 2.29 (m, 4H), 1.62 (ddd, *J* = 19.4, 12.3, 6.0 Hz, 4H), 1.48 (s, 9H), 0.99 – 0.85 (m, 24H).

(Boc(Val^u)$_5$NHMe) 96



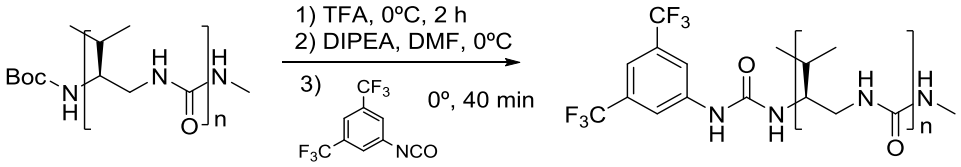
Prepared according to the general procedure starting from **95** (643 mg, 1 mmol) in DMF (4 mL). White solid. Yield: 79% (609 mg, 0.79 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.94 (d, *J* = 9.6 Hz, 1H), 6.25 – 6.12 (m, 2H), 6.08 (d, *J* = 10.4 Hz, 2H), 6.03 – 5.96 (m, 3H), 5.94 – 5.87 (m, 2H), 5.72 – 5.58 (m, 1H), 3.68 – 3.41 (m, 12H), 2.60 – 2.54 (m, 3H), 2.25 (s, 4H), 1.56 – 1.51 (m, 4H), 1.42 (s, 3H), 0.95 – 0.68 (m, 30H).

(Boc(Val^{u})$_6$NHMe) 97



Prepared according to the general procedure starting from **96** (771 mg, 1 mmol) in DMF (4 mL). The solid was triturated with pentane. White solid. Yield: 70% (629 mg, 0.7 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.20 (s, 1H), 6.93 (d, *J* = 9.5 Hz, 2H), 6.09 (m, 10H), 5.72 (d, *J* = 6.3 Hz, 1H), 3.73 – 3.20 (m, 25H), 2.57 (d, *J* = 4.6 Hz, 5H), 2.42 – 2.26 (m, 4H), 1.55 (s, 4H), 1.42 (s, 9H), 0.92 – 0.66 (m, 36H).

6.5.1.4. Boc deprotection

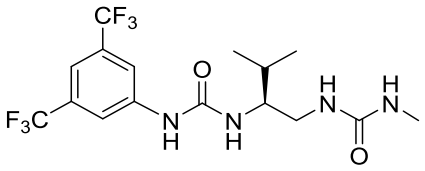


92 n=1
93 n=2
94 n=3
95 n=4
96 n=5
97 n=6

O7 n=1
O8 n=2
O9 n=3
O10 n=4
O11 n=5
O12 n=6

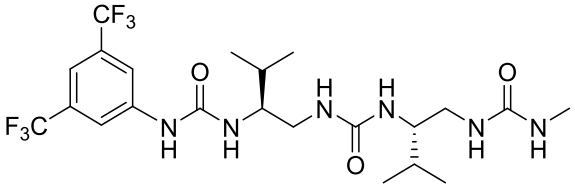
The Boc-protected compound **92-97** (1 mmol, 1 equiv.) was dissolved in trifluoroacetic acid (6 mL) at 0 ºC under N_2 atmosphere.[272] After complete conversion (2 h, followed by TLC), the reaction mixture was concentrated under reduced pressure and coevaporated 3 times with cyclohexane. The residue was redissolved in DMF (4 mL) and DIPEA (3 mmol, 3 equiv.) was added at 0 ºC. Bis-trifluorophenylisocyanate (1.2 mmol, 1.2 equiv.) was added dropwise and the mixture was stirred at 0 ºC for 40 minutes. When the reaction finished, the mixture was dissolved in EtOAc (5 mL) and the organic phase was washed with $KHSO_4$ (2 x 5 mL), water (5 x 5 mL), $NaHCO_3$ (1 x 5 mL) and water (1 x 5 mL). The combined organic phases were dried over $MgSO_4$ and evaporated under reduced pressure.

$(CF_3)_2$PhNHCO-Val^u-NHMe O7[275]



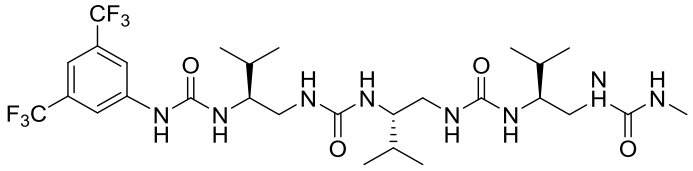
Prepared according to the general procedure starting from **92** (259 mg, 1 mmol). Purification by column chromatography (CH_2Cl_2/MeOH, 95:5) afforded the title compound as a white solid. Yield: 70% (289 mg, 0.7 mmol). All spectroscopic data were coincident with those previously reported. ^{1}H NMR (400 MHz, CD_3OH) δ 7.99 (s, 2H), 7.47 (s, 1H), 6.05 (d, *J* = 9.3 Hz, 1H), 5.98 (brs, 1H), 5.89 (brs, 1H), 3.70 – 3.61 (m, 1H), 3.36 – 3.16 (m, 2H), 2.65 (d, *J* = 4.6 Hz, 3H), 1.88 – 1.76 (m, 1H), 0.98 (dd, *J* = 9.6, 6.8 Hz, 6H).

$(CF_3)_2$PhNHCO-(Val^u)$_2$NHMe O8



Prepared according to the general procedure starting from **93** (387 mg, 1 mmol). Purification by column chromatography (CH_2Cl_2/MeOH, 97:3) afforded the title compound as a white solid. Yield: 60% (325 mg, 0.6 mmol). ^{1}H NMR (400 MHz, CD_3OH) δ 8.00 (s, 2H), 7.45 (s, 1H), 6.31 (brs, 1H), 6.07 (brs, 1H), 5.94 (brs, 1H), 3.77 – 3.63 (m, 1H), 3.60 – 3.47 (m, 1H), 3.36 – 3.26 (m, 1H), 3.24 – 3.12 (m, 1H), 3.00 – 2.86 (m, 1H), 2.66 (d, *J* = 4.5 Hz, 3H), 1.87 – 1.71 (m, 1H), 1.73 – 1.57 (m, 1H), 0.98 (t, *J* = 7.1 Hz, 3H), 0.82 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OH) δ 162. , 161.5 , 157.8 , 143.6 , 132.9 (q, *J* = 32.9 Hz), 126.1 , 123.4 , 118.9 , 115.1 , 57.0 , 56.8 , 43.5 , 43.4 , 43.2 , 43.1 , 31.6 , 27.1 , 26.9 , 19.9 , 19.8 , 18.4 , 18.2 . ^{19}F NMR (376 MHz, CD_3OH) δ -64.6 . MS (ESI): $C_{22}H_{33}F_6N_6O_3$ $[M+H]^+$ calcd.: 543.25128, found: 543.24932.

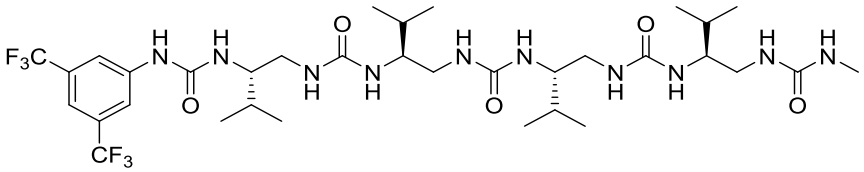
$(CF_3)_2$Ph(Val^u)$_3$NHMe O9



[275] D. Bécart, V. Diemer, A, Salaun, M. Oiarbide, Y. Reddy Nelly, B. Kauffmann, L. Fischer, C. Palomo, G. Guichard, *J. Am. Chem. Soc.* **2017**, *139*, 12524-12532.

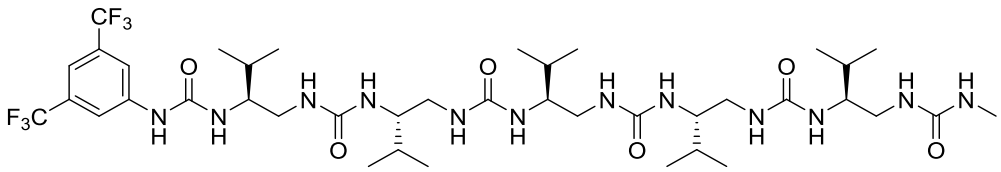
Prepared according to the general procedure starting from **94** (515 mg, 1 mmol). Trituration in diethyl ether led to the title compound as a white solid. Yield: 73% (489 mg, 0.73 mmol). ^{1}H NMR (300 MHz, CD_3OH) δ 8.00 (s, 2H), 7.50 (s, 1H), 6.13 (m, *J* = 24.5, 14.8, 7.3 Hz, 4H), 5.90 – 5.76 (m, 2H), 3.94 – 3.44 (m, 6H), 2.82 (m, 2H), 2.73 (dd, *J* = 12.0, 3.4 Hz, 3H), 2.50 (dd, *J* = 19.0, 8.2 Hz, 1H), 1.82 – 1.50 (m, 3H), 1.04 – 0.77 (m, 18H). ^{13}C NMR (101 MHz, CD_3OH) δ 162.0 , 161.7 , 161.6 , 161.6 , 158.2 , 143.4 , 133.1 (q, *J* = 32.8 Hz), 126.1 , 123.4 , 119.0 , 115.4 , 56.6 , 56.3 , 56.1 , 44.5 , 44.1 , 43.7 , 32.3 , 31.9 , 31.6 , 26.9 , 20.1 , 20.0 , 19.9 , 18.4 , 18.4 , 18.1 . ^{19}F NMR (376 MHz, CD_3OH) δ -64.6 . MS (ESI): $C_{28}H_{45}F_6N_8O_4$ $[M+H]^+$ calcd.: 671.34625, found: 671.34370.

$(CF_3)_2$Ph(Val^{u})$_4$NHMe O10



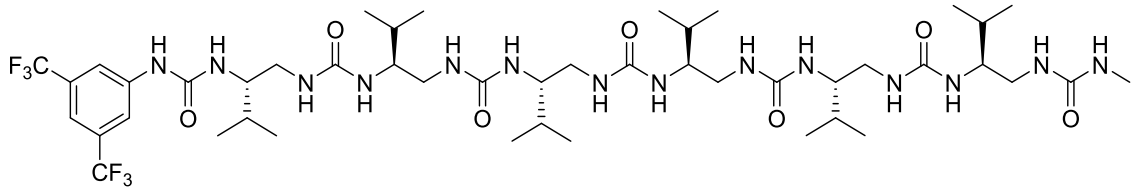
Prepared according to the general procedure starting from **95** (643 mg, 1 mmol). Trituration in diethyl ether afforded the title compound as a white solid. Yield: 70% (558 mg, 0.7 mmol). There were some impurities that could not be separated by column chromatography nor trituration with different solvents. MS (ESI): $C_{34}H_{57}F_6N_{10}O_5$ $[M+H]^+$ calcd.: 799.44121, found: 799.43802.

$(CF_3)_2$Ph(Val^{u})$_5$NHMe O11



Prepared according to the general procedure starting from **96** (771 mg, 1 mmol). Trituration in diethyl ether afforded the title compound as a white solid. Yield: 68% (629 mg, 0.68 mmol). ^{1}H NMR (300 MHz, CD_3OH) δ 8.27 (s, 2H), 7.76 (s, 1H), 6.76 – 6.44 (m, 5H), 6.37 (dd, *J* = 11.1, 6.3 Hz, 2H), 6.11 (d, *J* = 10.2 Hz, 2H), 4.21 – 3.69 (m, 9H), 3.03 – 2.91 (m, 3H), 2.92 – 2.81 (m, 2H), 2.66 (ddd, *J* = 25.4, 19.2, 8.2 Hz, 3H), 2.08 – 1.70 (m, 5H), 1.36 – 1.02 (m, 30H). ^{13}C NMR (101 MHz, CD_3OH) δ 162.4 , 162.3 , 161.5 , 161.4 , 158.3 , 143.2 , 133.24 (q, *J* = 33.1 Hz), 126.0 , 123.3 , 119.0 , 115.7 , 56.8 , 56.7 , 56.6, 56.2 , 56.1 , 55.5 , 55.4 , 44.9 , 44.8 , 44.7 , 44.5 , 43.7 , 43.6 , 32.7 , 31.9 , 31.8 , 26.8 , 26.7 , 20.1 , 20.0 , 19.9 , 18.9 , 18.7 , 18.5 , 18.2 , 18.0 . ^{19}F NMR (376 MHz, CD_3OH) δ -64.6. MS (ESI): $C_{40}H_{69}F_6N_{12}O_6$ $[M+H]^+$ calcd.: 927.53617, found: 927.53265.

$(CF_3)_2Ph(Val^u)_6NHMe$ O12



Prepared according to the general procedure starting from **97** (899 mg, 1 mmol). Trituration in diethyl ether afforded the title compound as a white solid. Yield: 75% (790 mg, 0.75 mmol). ^{1}H NMR (400 MHz, CD_3OH) δ 8.01 (s, 2H), 7.53 (s, 1H), 6.44 (brs, 3H), 6.27 (brs, 5H), 6.10 (s, 2H), 5.86 (d, *J* = 9.9 Hz, 2H), 3.85-3.47 (m, 12H), 2.72 (s, 3H), 2.70-2.64 (m, 2H), 2.44 (dt, *J* = 29.1, 19.0 Hz, 4H), 1.79 – 1.54 (m, 6H), 1.16 – 0.74 (m, 36H). ^{13}C NMR (101 MHz, CD_3OH) δ 162.4 , 162.2 , 162.0 , 162.0 , 161.5 , 158.3 , 143.2 , 133.4 , 133.1 , 119.0 , 115.8 , 115.7 , 115.6 , 56.7 , 56.7 , 56.6 , 56.4 , 56.2 , 56.2 , 56.0 , 55.9 , 55.6 , 55.5 , 54.7 , 44.9 , 44.8 , 44.7 , 44.5 , 43.7 , 43.6 , 32.7 , 31.9 , 31.8 , 31.8 , 26.8 , 26.7 , 20.2 , 20.1 , 20.0 , 19.9 , 18.9 , 18.7 , 18.5 , 18.3 , 18.3 . ^{19}F NMR (376 MHz, CD_3OH) δ -64.6 . MS (ESI): $C_{46}H_{81}F_6N_{14}O_7$ $[M+H]^+$ calcd.: 1055.63114, found: 1055.62655.

6.5.2. Catalysis promoted by oligoureas O7-O12

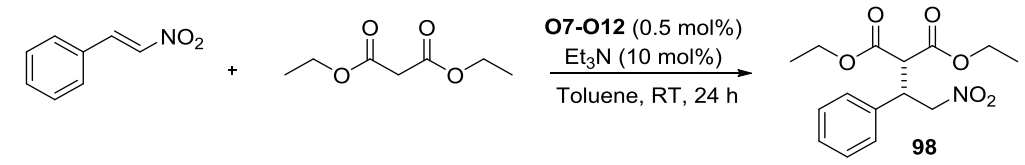
6.5.2.1. Preparation of catalyst and base solution

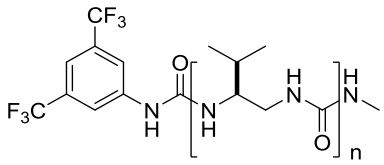
First, a stock solution of the catalyst in CH_2Cl_2/MeOH (1:1) was prepared. The oligourea catalyst **O7-O12** (0.01 mmol) was dissolved in 2 mL of a solution of CH_2Cl_2/MeOH, and each reaction vial was charged with 500 μL of this solution.[276] The catalyst was then concentrated with Genetac Evaporator (method: medium BP).

Then, a stock solution of triethylamine in toluene was prepared, dissolving triethylamine (139 μL, 101 mg, 1 mmol) in dry toluene (10 mL) in a volumetric flask.

[276] For reactions with 0.3 mol% catalyst loading, 300 μL were measured, and for reactions in 0.1 mol% catalyst loading 100 μL.

6.5.2.2. Asymmetric reaction

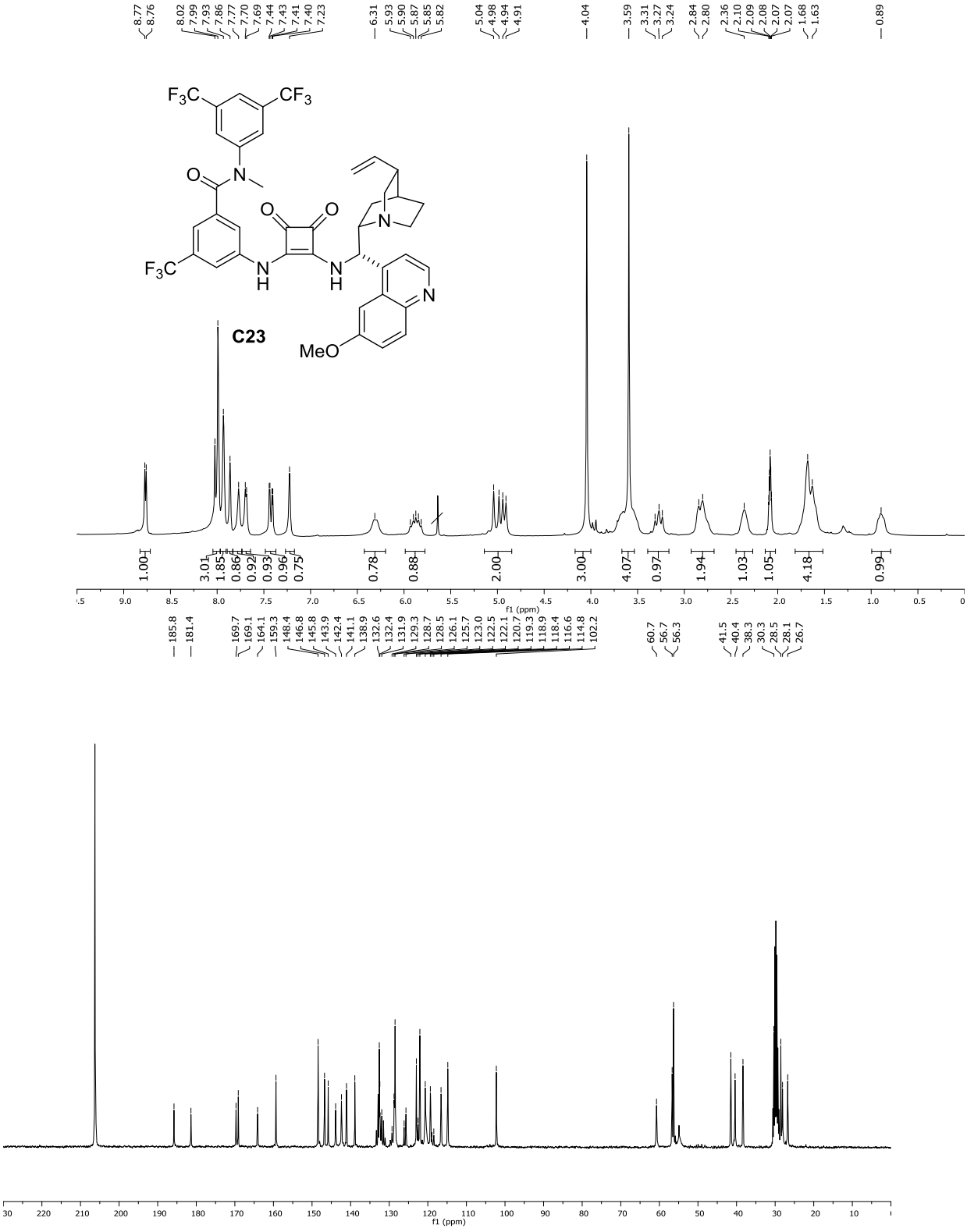


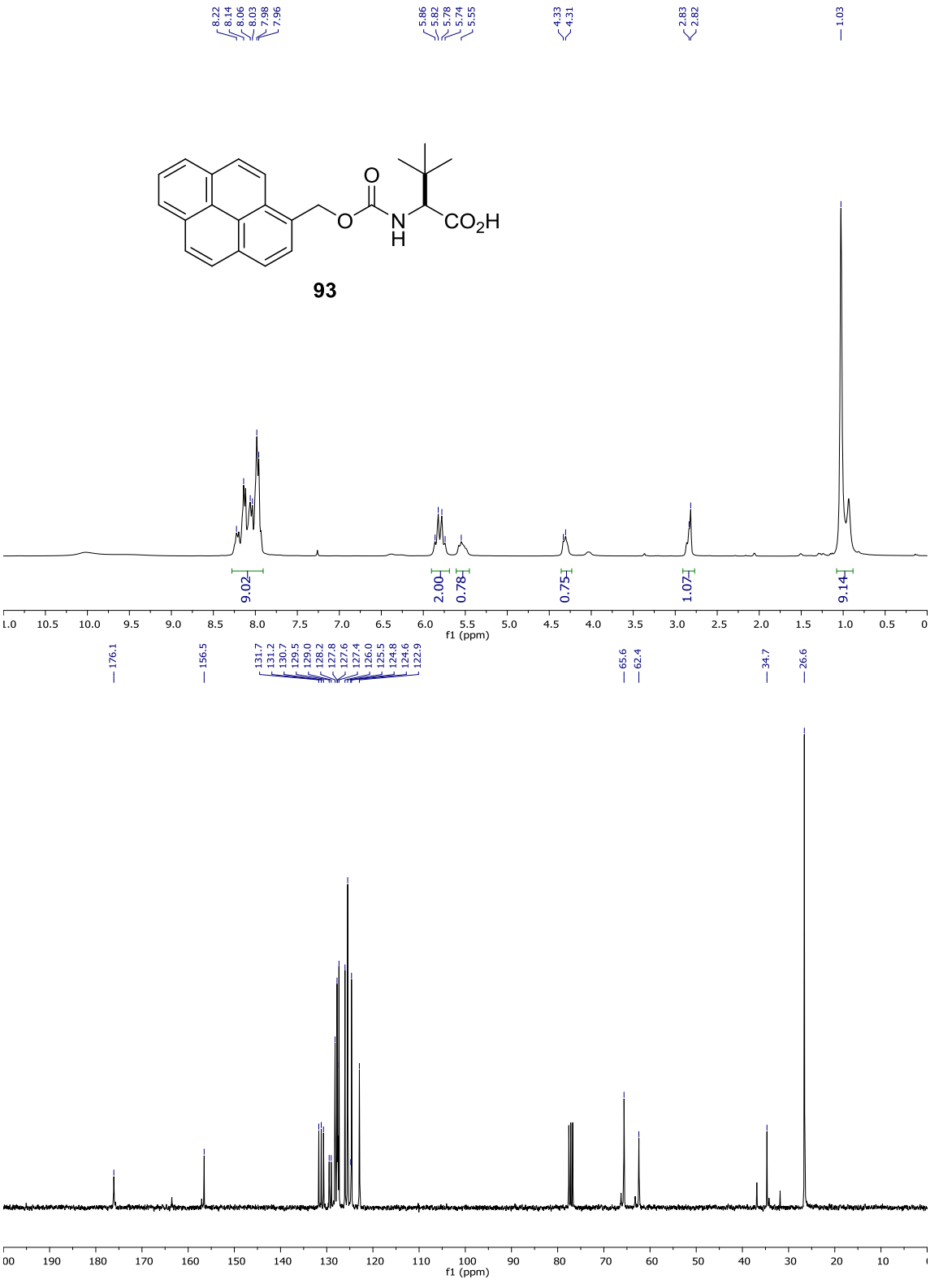


O7 n=1
O8 n=2
O9 n=3
O11 n=5
O12 n=6

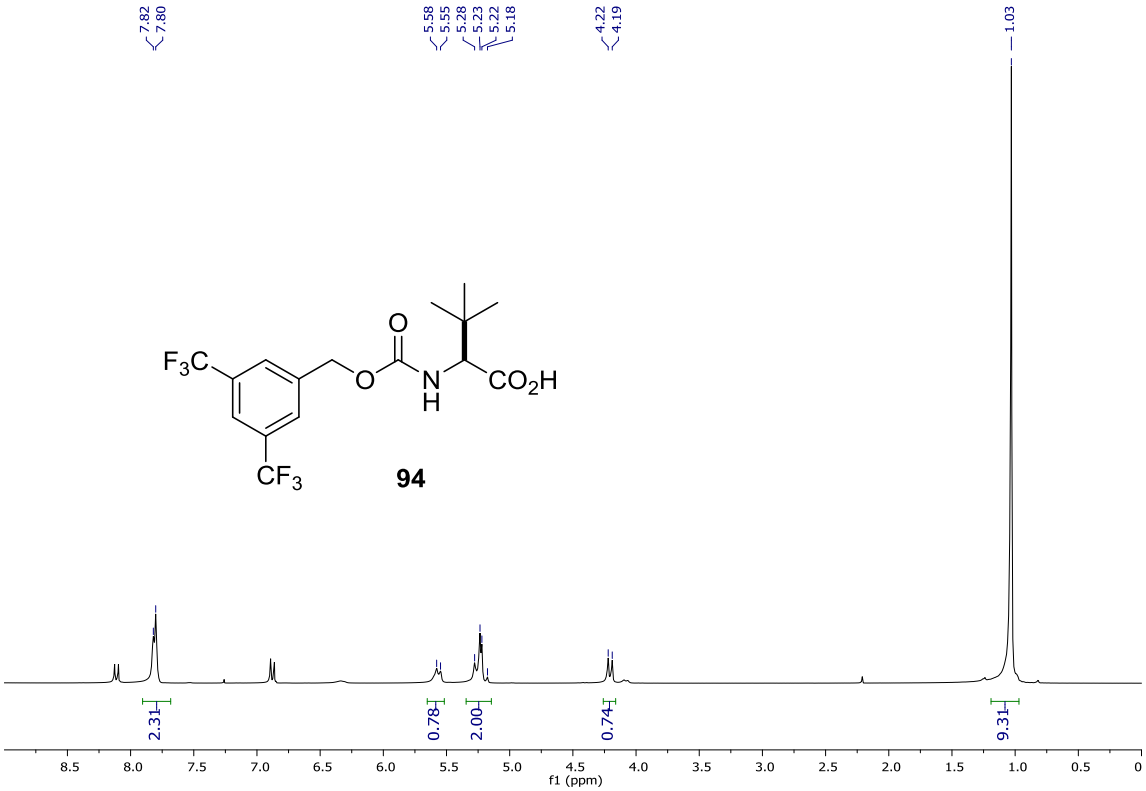
Nitrostyrene (75 mg, 0.5 mmol, 1 equiv.) was added to the vial loaded with the corresponding oligourea catalyst (0.0025 mmol, 0.5 mol%) and it was dissolved after addition of the base solution (0.5 mL). Then, diethyl malonate (152 μL, 1 mmol, 2 equiv.) was added and the mixture was vigorously stirred at room temperature for 48 h. Then, the reaction was quenched with HCl (1M) or $KHSO_4$ (1M) and the mixture was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phases were washed with brine (1 x 20 mL), dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (cyclohexane/EtOAc, 95:5) led to the title compound as a transparent oil. All the spectroscopic data were coincident with those described in the literature.[275]

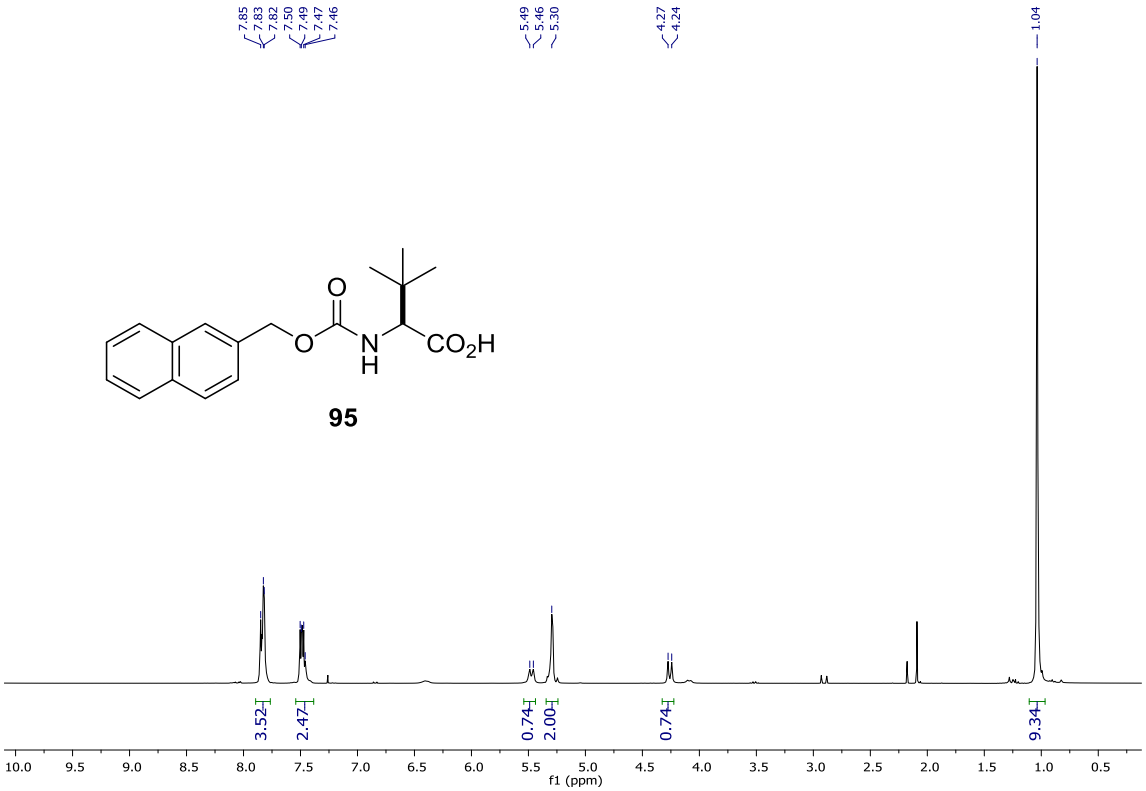
6.6. **Representative NMR spectra**

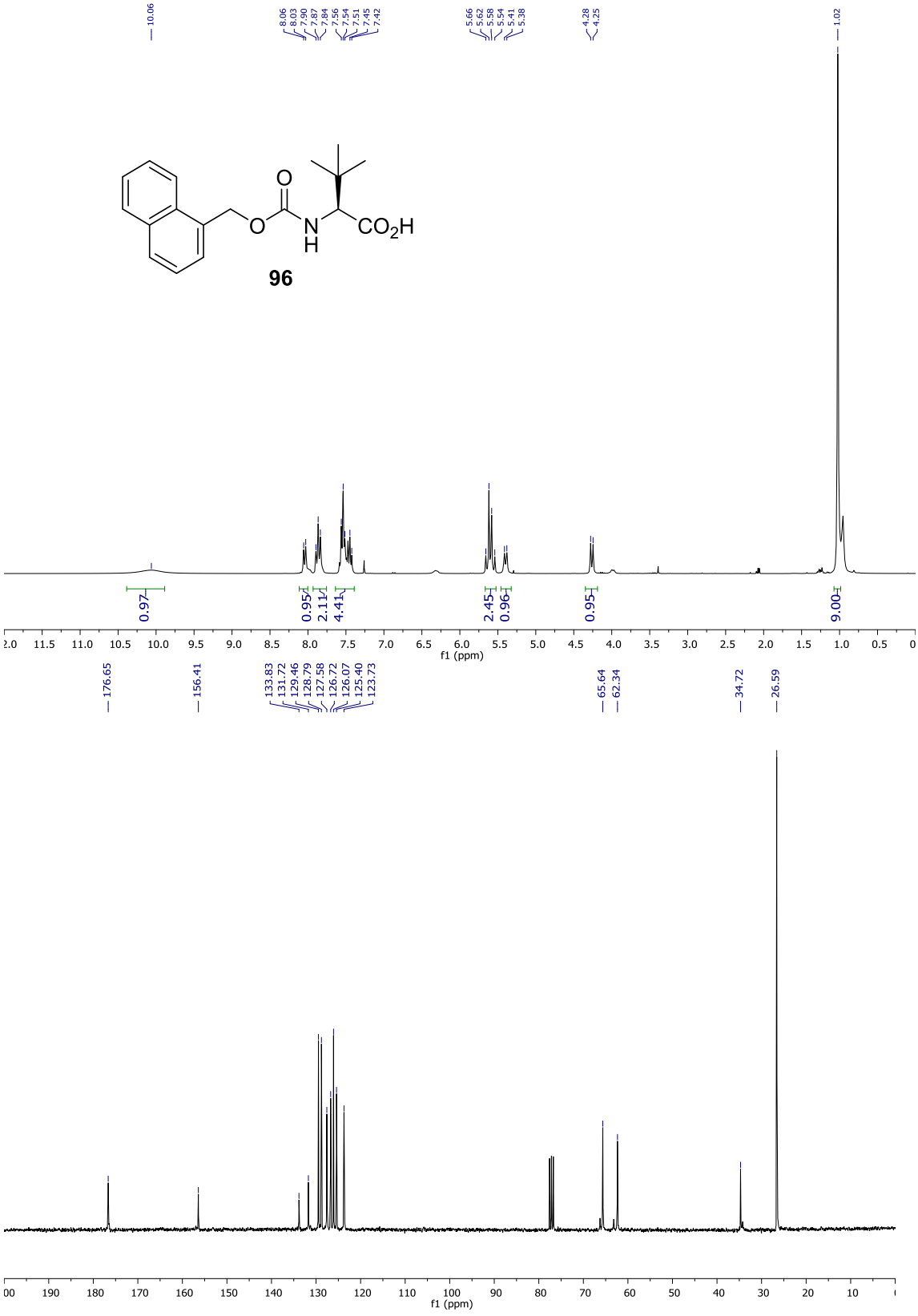


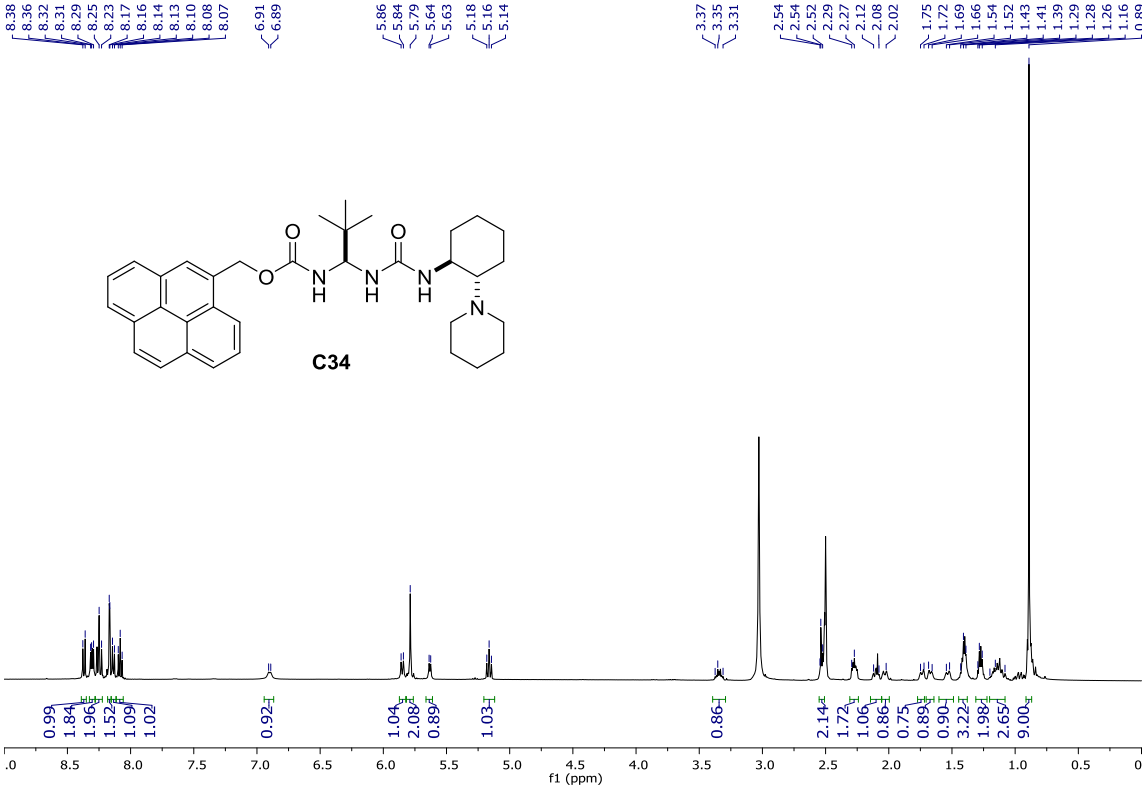

8.22
8.14
8.06
8.03
7.98
7.96
5.86
5.82
5.78
5.74
5.55
4.33
4.31
2.83
2.82
1.03
O
O
N
H
CO2H
9.02
2.00
0.78
0.75
1.07
9.14
f1 (ppm)
176.1
156.5
131.7
131.2
130.7
129.5
129.0
128.2
127.8
127.6
127.4
126.0
125.5
124.8
124.6
122.9
65.6
62.4
34.7
26.6
f1 (ppm)

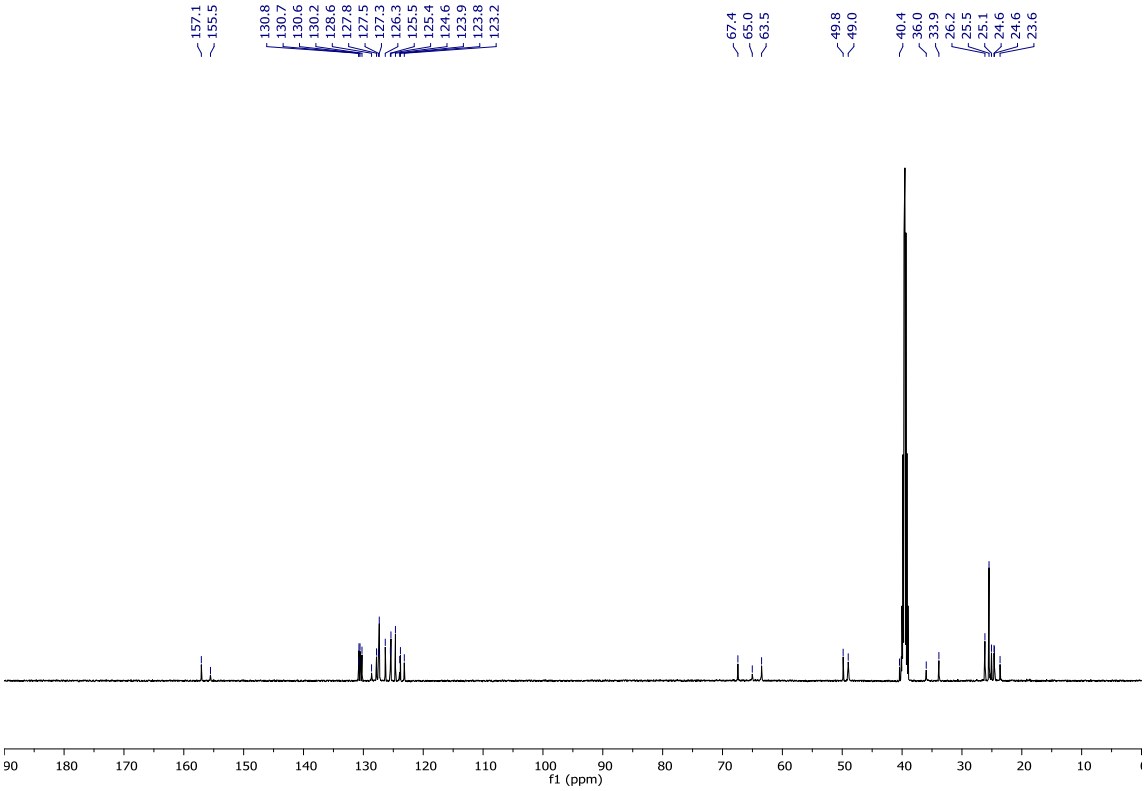
93

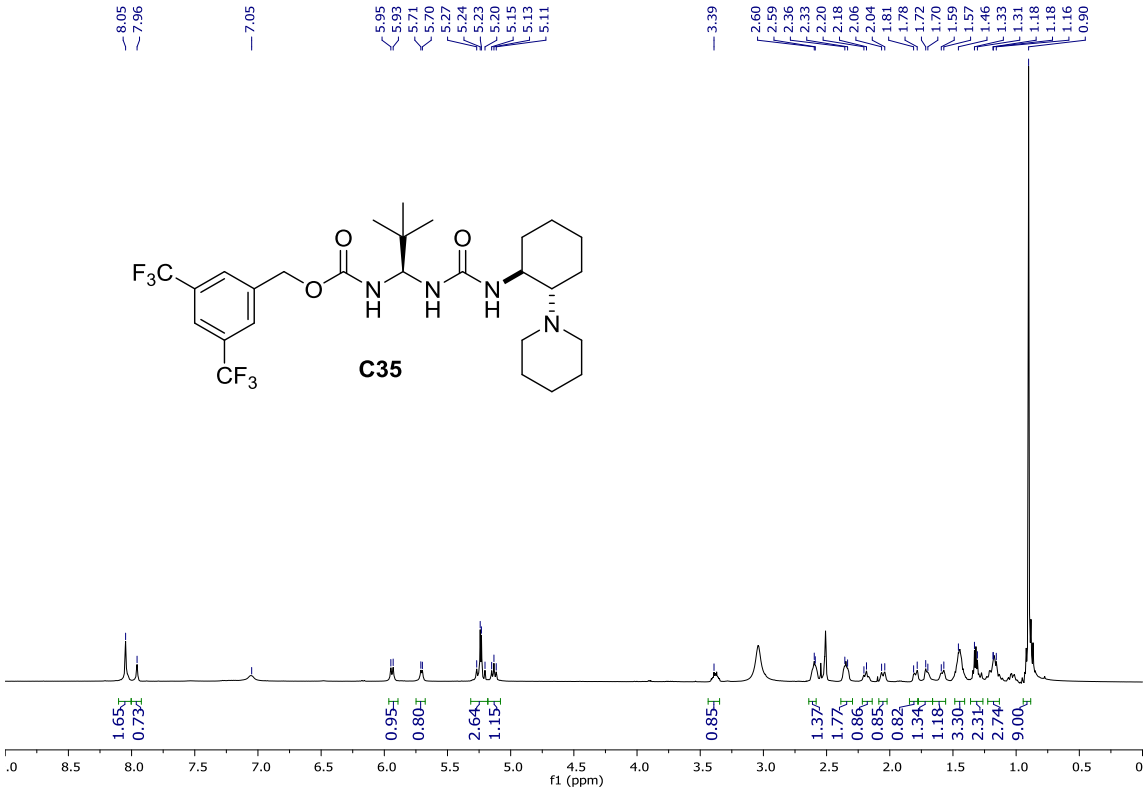

7.82
7.80
5.58
5.55
5.28
5.23
5.22
5.18
4.22
4.19
1.03
F3C
O
O
N
H
CO2H
CF3
94
2.31
0.78
2.00
0.74
9.31
f1 (ppm)

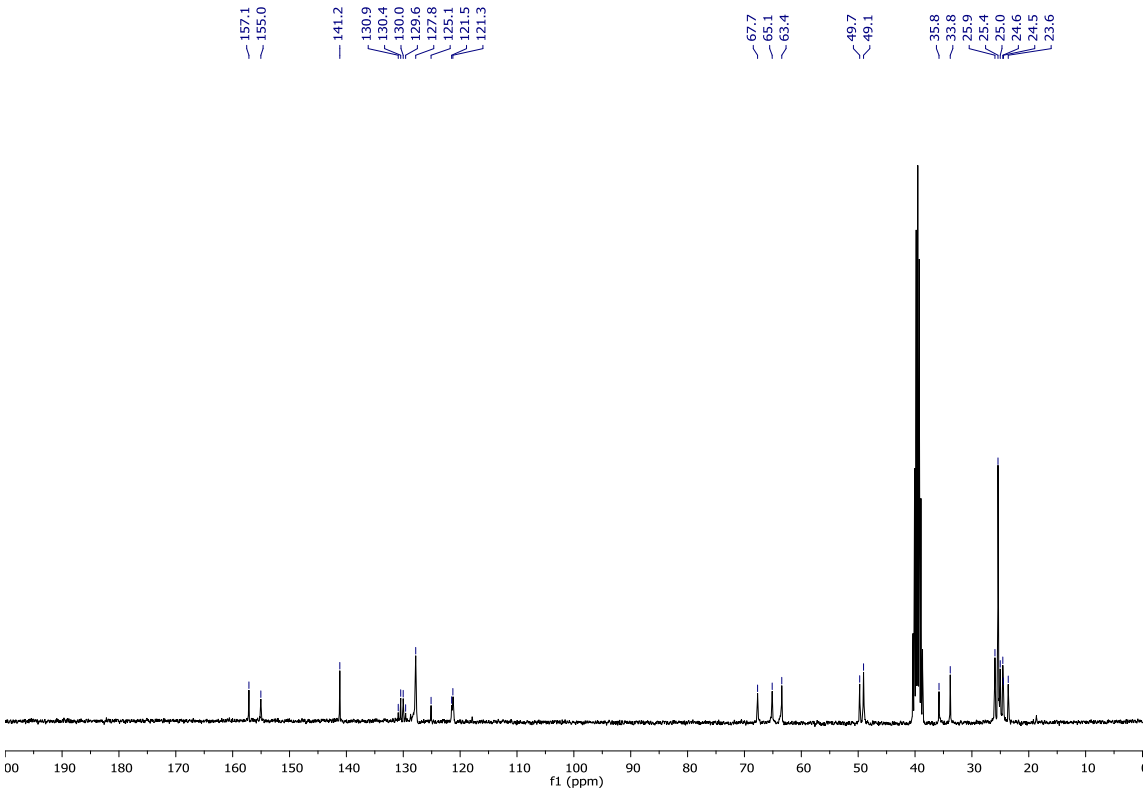

7.85
7.83
7.82
7.50
7.49
7.47
7.46
5.49
5.46
5.30
4.27
4.24
1.04
O
O
N
H
CO2H
95
3.52
2.47
0.74
2.00
0.74
9.34
f1 (ppm)

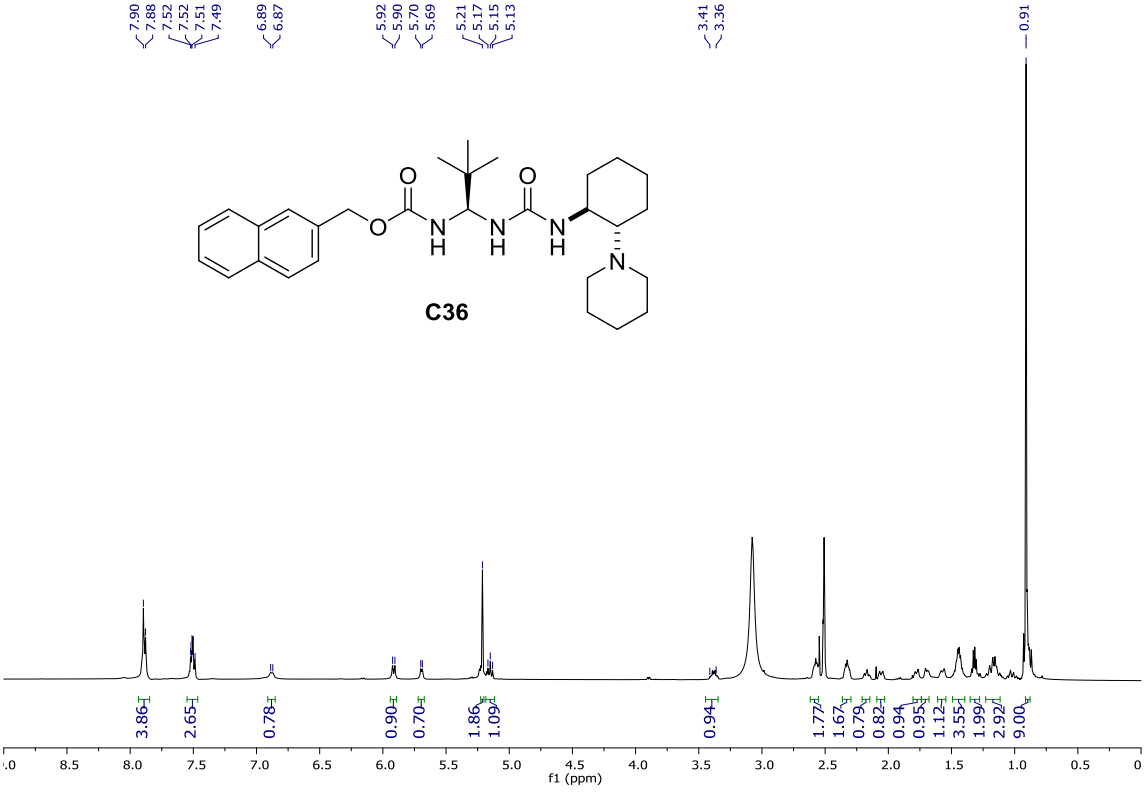

10.06
8.06
8.03
7.90
7.87
7.84
7.56
7.54
7.51
7.45
7.42
5.66
5.62
5.58
5.54
5.41
5.38
4.28
4.25
1.02
O
O
N
H
CO2H
96
0.97
0.95
2.11
4.41
2.45
0.96
0.95
9.00
f1 (ppm)
176.65
156.41
133.83
131.72
129.46
128.79
127.58
126.72
126.07
125.40
123.73
65.64
62.34
34.72
26.59
f1 (ppm)

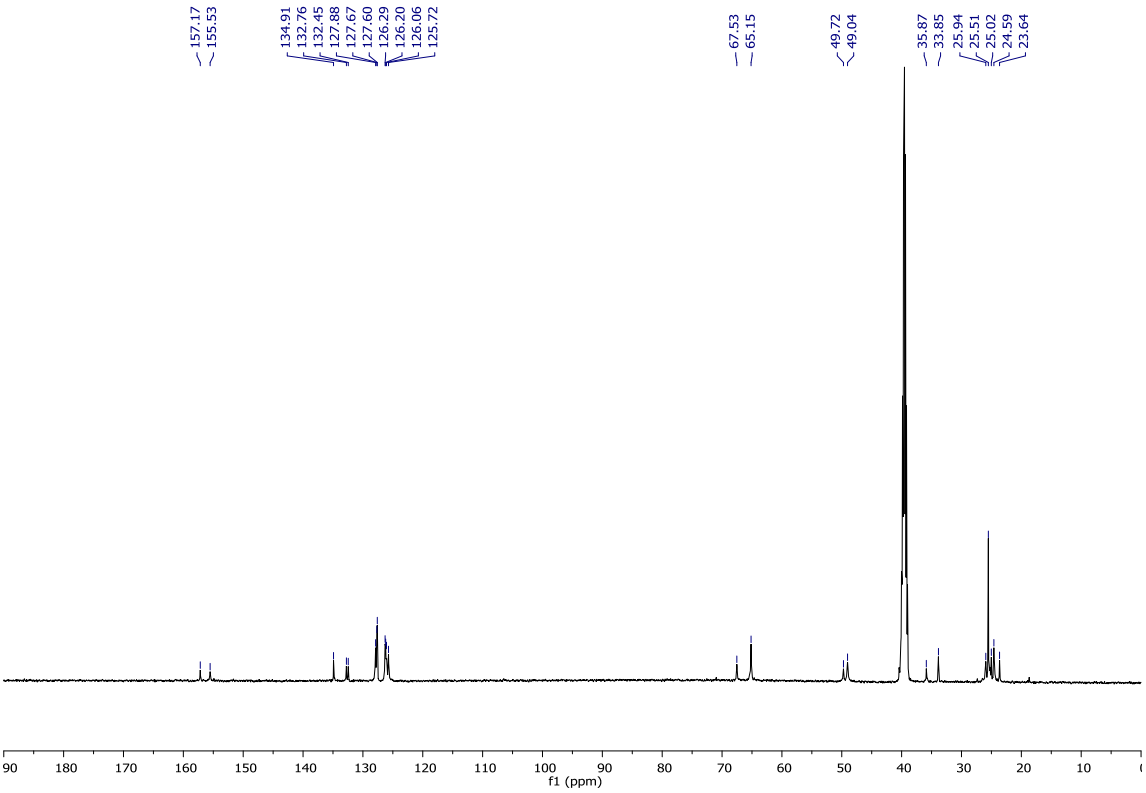

C34
f1 (ppm)

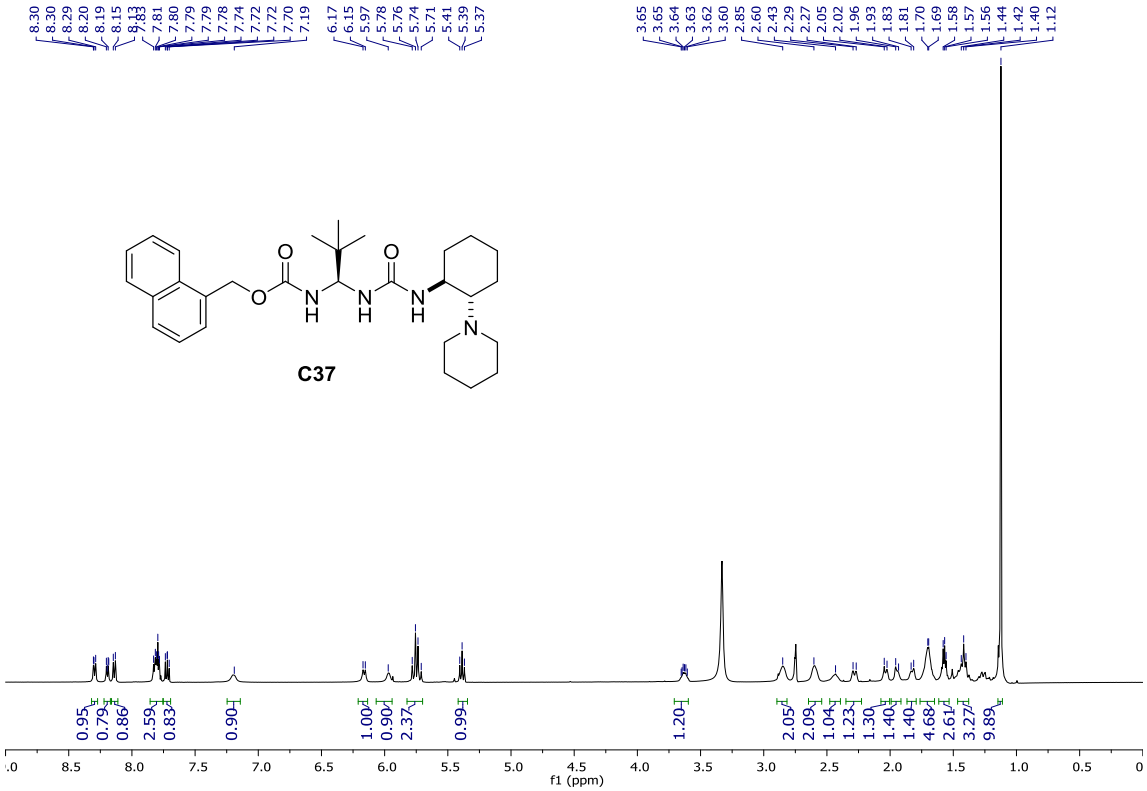

f1 (ppm)

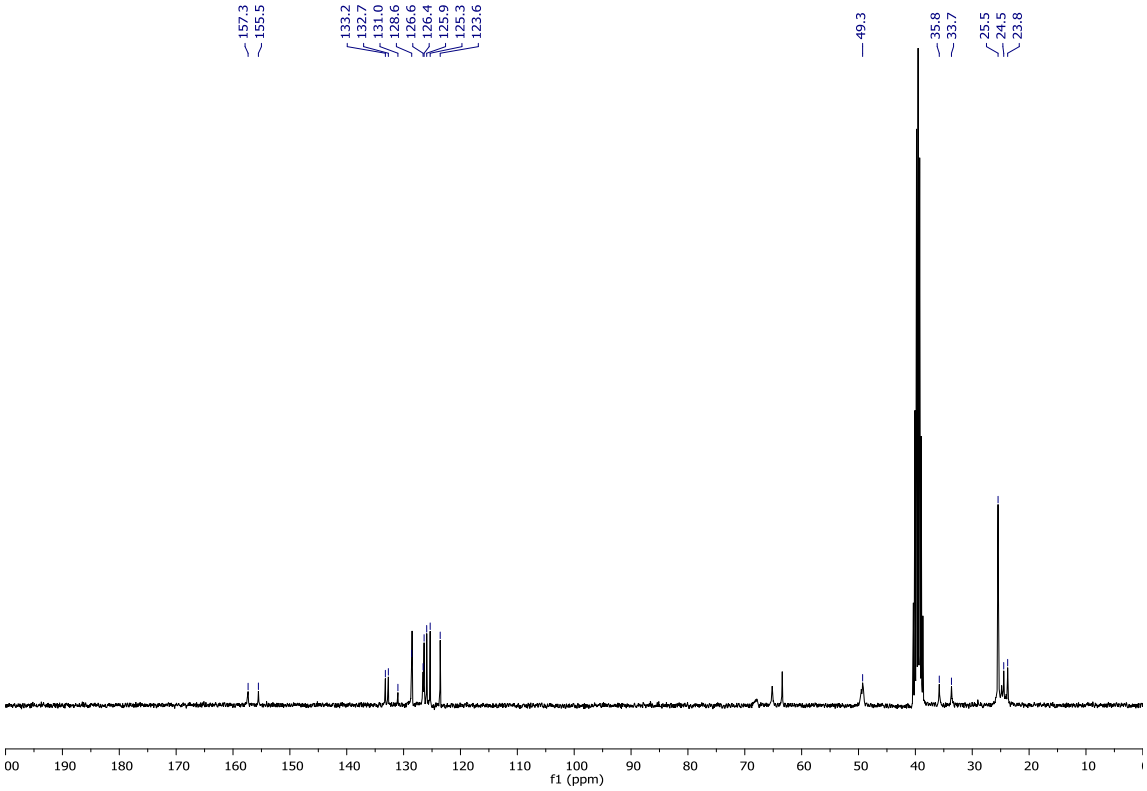

8.05
7.96
7.05
5.95
5.93
5.71
5.70
5.27
5.24
5.23
5.20
5.15
5.13
5.11
3.39
2.60
2.59
2.36
2.33
2.20
2.18
2.06
2.04
1.81
1.78
1.72
1.70
1.59
1.57
1.46
1.33
1.31
1.18
1.18
1.16
0.90
F3C
CF3
O
O
O
N
H
N
H
N
H
N
C35
1.65
0.73
0.95
0.80
2.64
1.15
0.85
1.37
1.77
0.86
0.85
0.82
1.34
1.18
3.30
2.31
2.74
9.00
f1 (ppm)

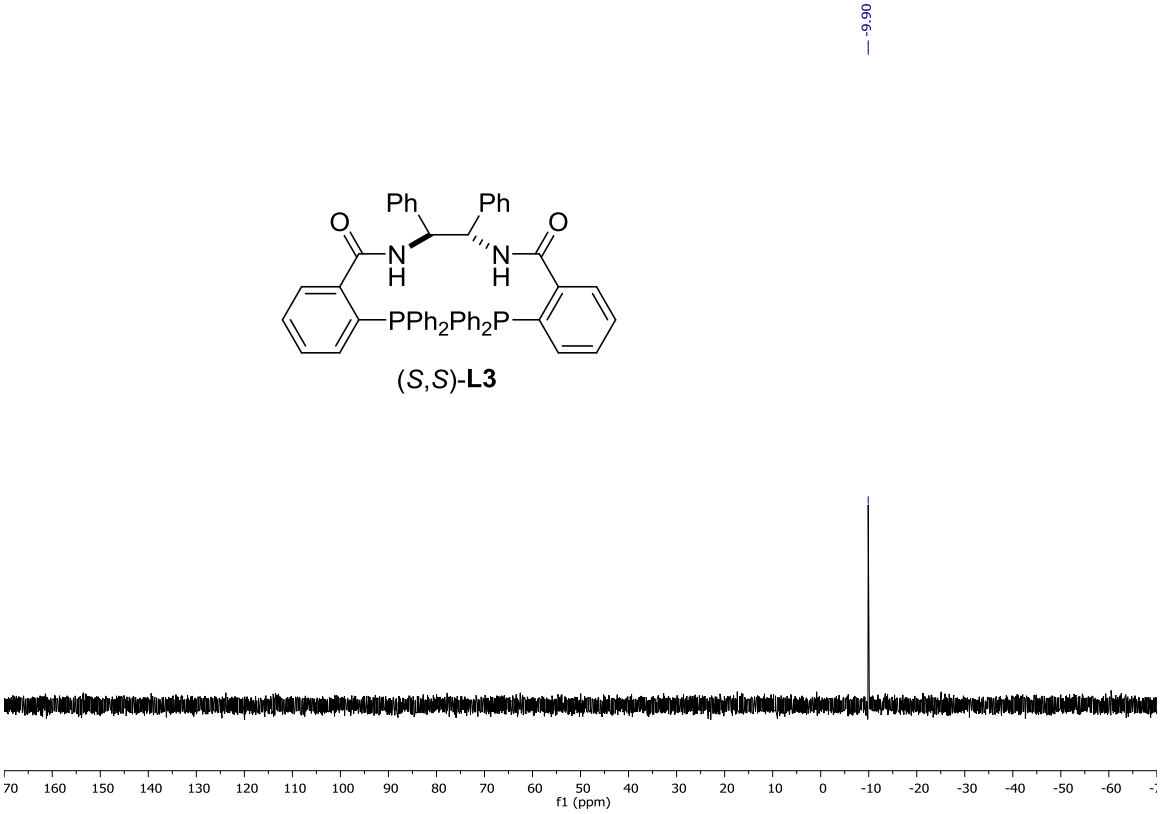

157.1
155.0
141.2
130.9
130.4
130.0
129.6
127.8
125.1
121.5
121.3
67.7
65.1
63.4
49.7
49.1
35.8
33.8
25.9
25.4
25.0
24.6
24.5
23.6
f1 (ppm)


7.90
7.88
7.52
7.52
7.51
7.49
6.89
6.87
5.92
5.90
5.70
5.69
5.21
5.17
5.15
5.13
3.41
3.36
0.91
O
O
O
N
H
N
H
N
H
N
C36
3.86
2.65
0.78
0.90
0.70
1.86
1.09
0.94
1.77
1.67
0.79
0.82
0.94
0.95
1.12
3.55
1.99
2.92
9.00
f1 (ppm)

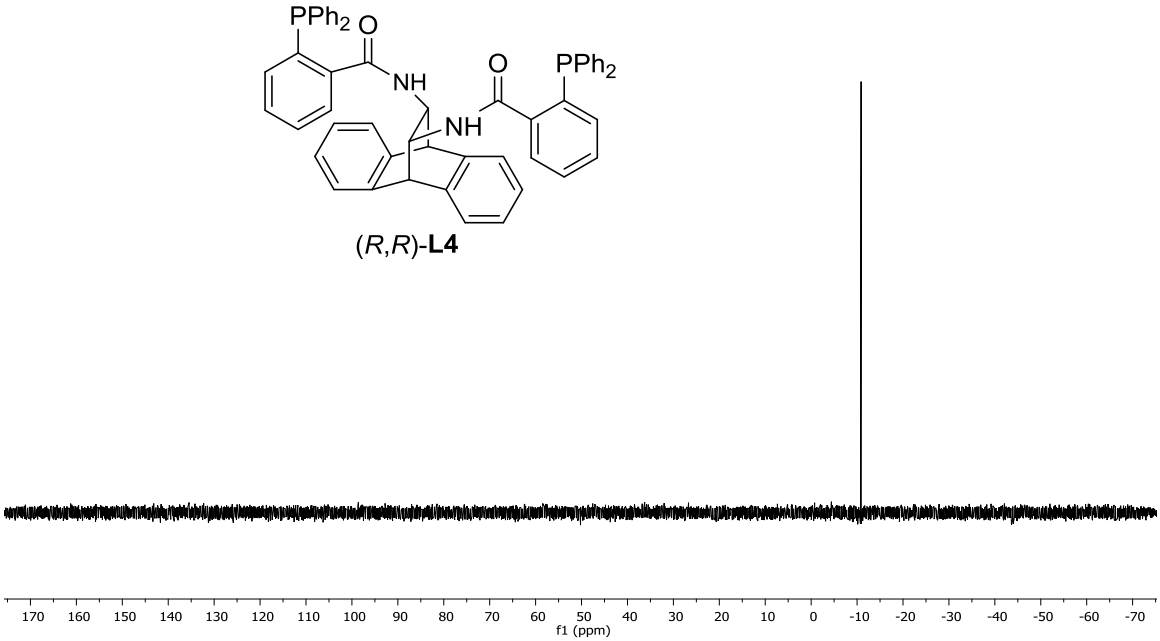

157.17
155.53
134.91
132.76
132.45
127.88
127.67
127.60
126.29
126.20
126.06
125.72
67.53
65.15
49.72
49.04
35.87
33.85
25.94
25.51
25.02
24.59
23.64
f1 (ppm)


C37
f1 (ppm)

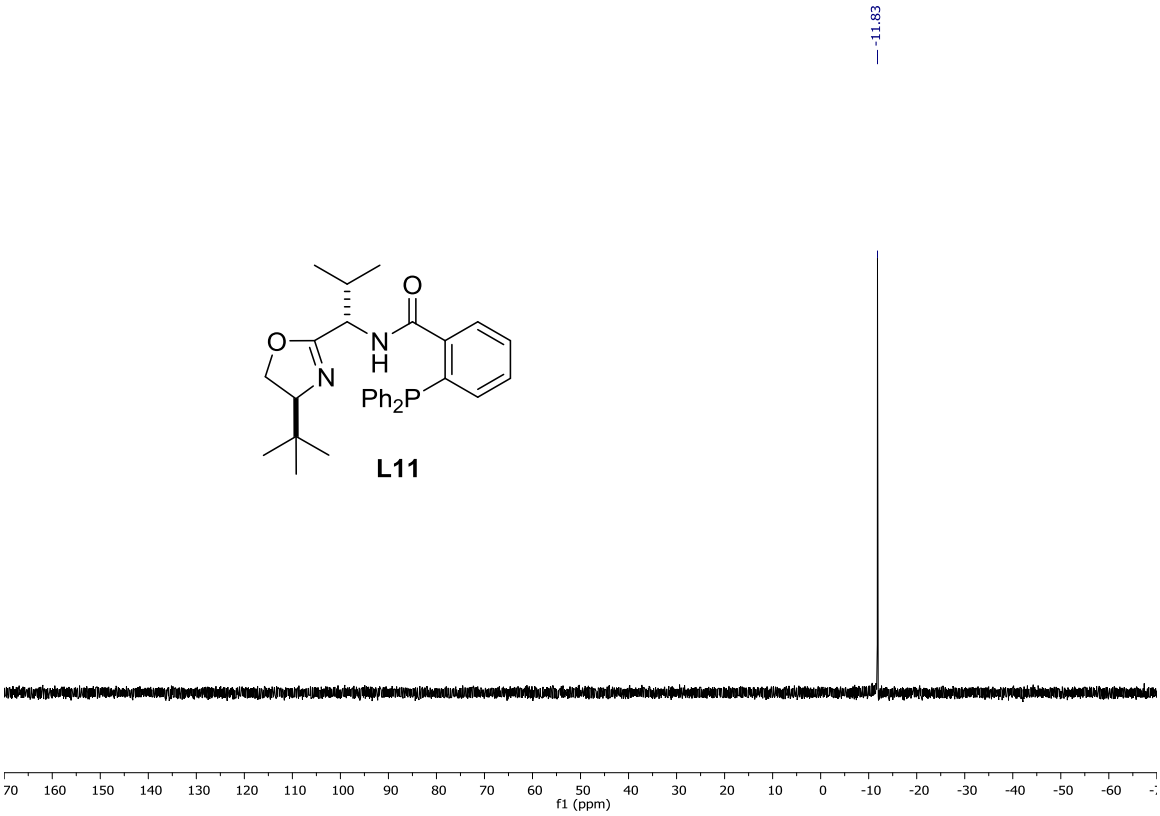

f1 (ppm)

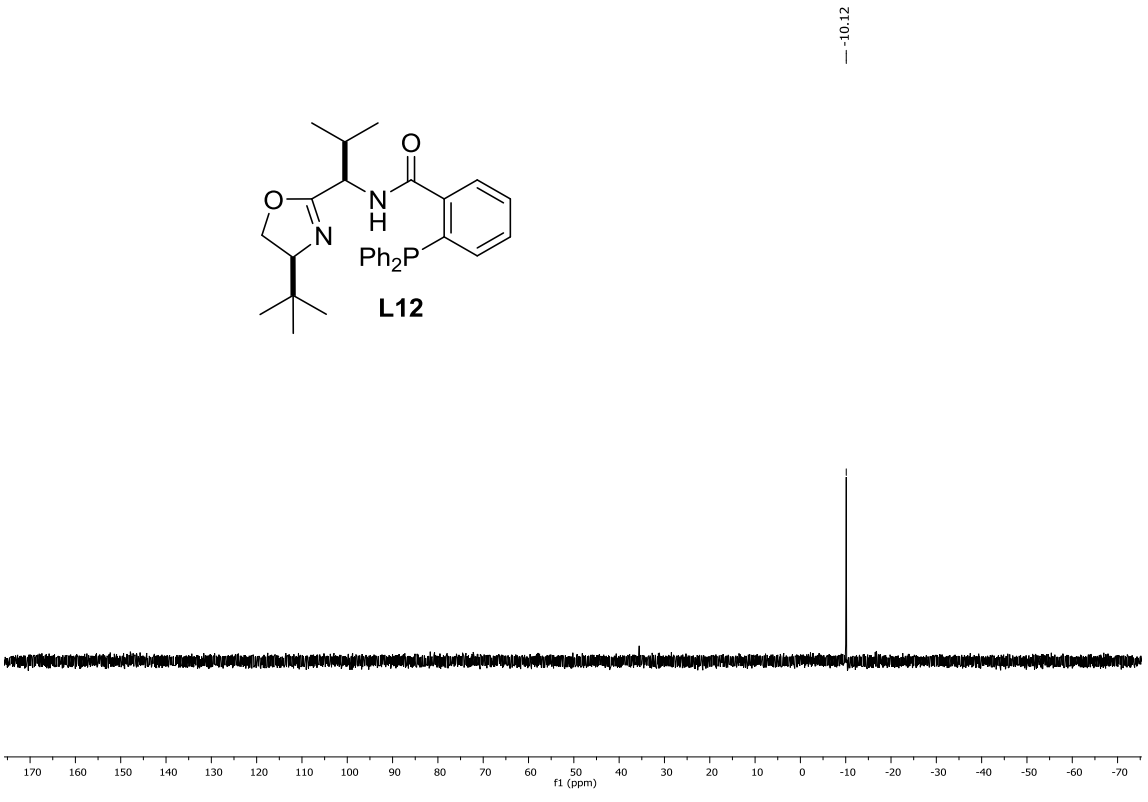


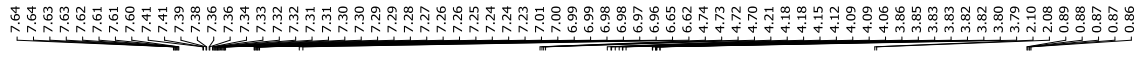
(*S*,*S*)-**L3**

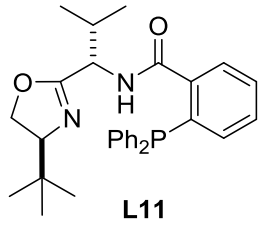


(*R*,*R*)-**L4**


-11.83
O
O
N
H
N
Ph2P
L11
70 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60
f1 (ppm)


-10.12
O
O
N
H
N
Ph2P
L12
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70
f1 (ppm)

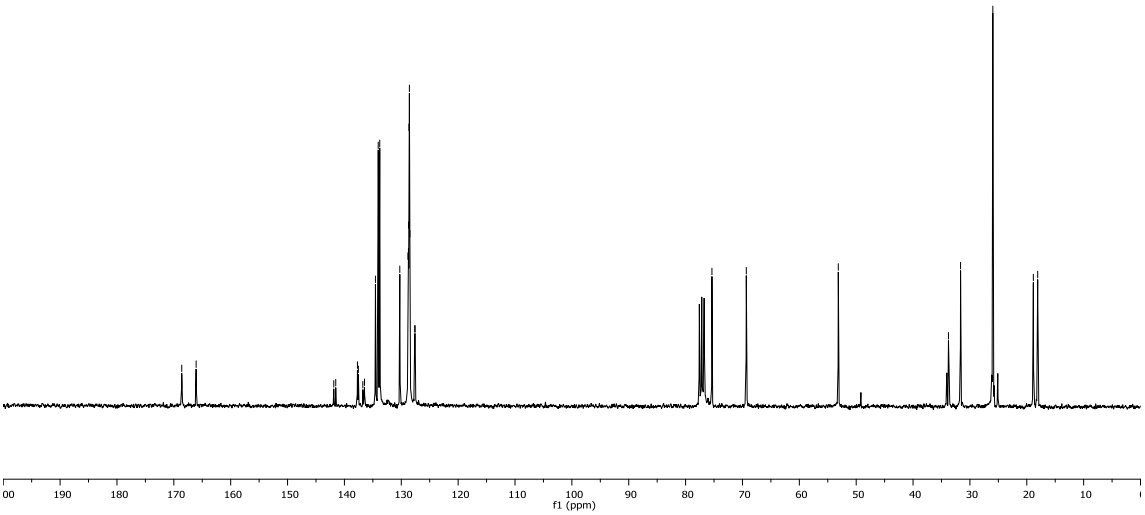

7.64 7.64 7.63 7.63 7.62 7.61 7.61 7.60 7.41 7.41 7.39 7.38 7.36 7.36 7.34 7.33 7.32 7.32 7.31 7.31 7.30 7.30 7.29 7.29 7.28 7.27 7.26 7.26 7.25 7.24 7.24 7.23 7.01 7.00 6.99 6.99 6.98 6.98 6.97 6.96 6.65 6.62 4.74 4.73 4.72 4.70 4.21 4.18 4.15 4.12 4.09 4.09 4.06 3.86 3.85 3.83 3.83 3.82 3.82 3.80 3.79 2.10 2.08 0.89 0.88 0.87 0.87 0.86

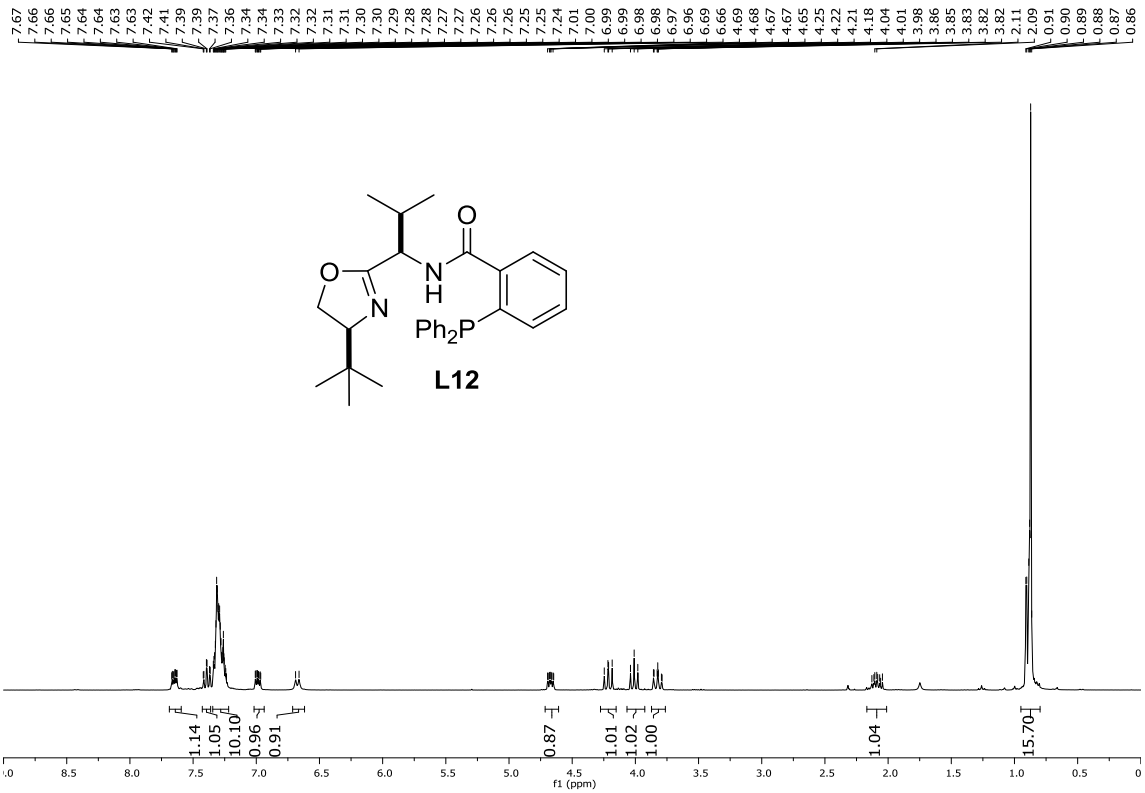

O
N
H
O
N
Ph2P

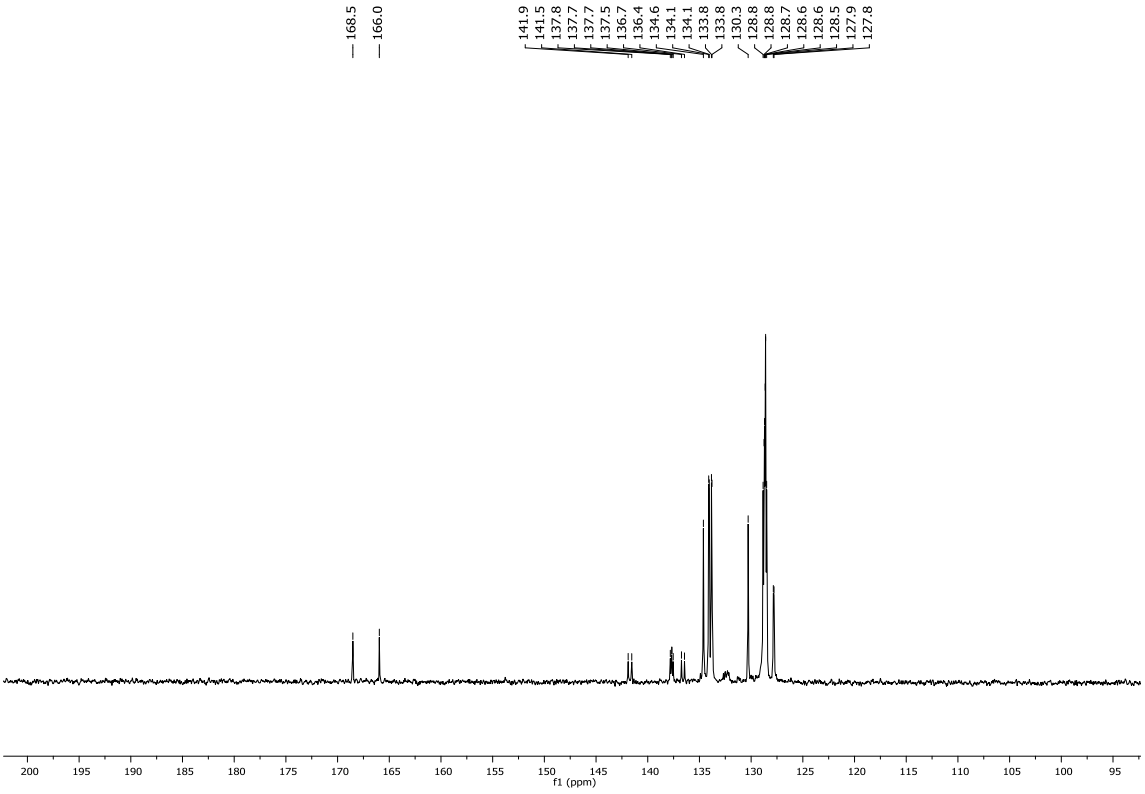
L11

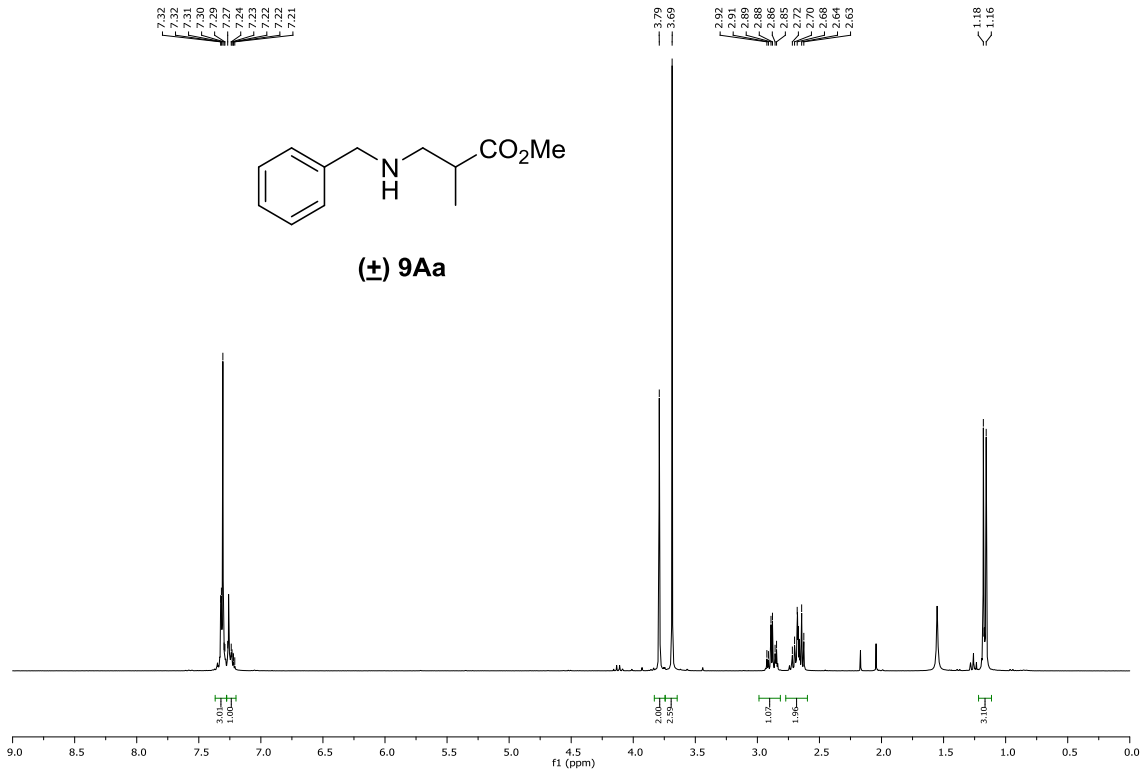
1.00
10.53
0.89
0.88
0.81
2.02
0.94
0.97
14.71
f1 (ppm)

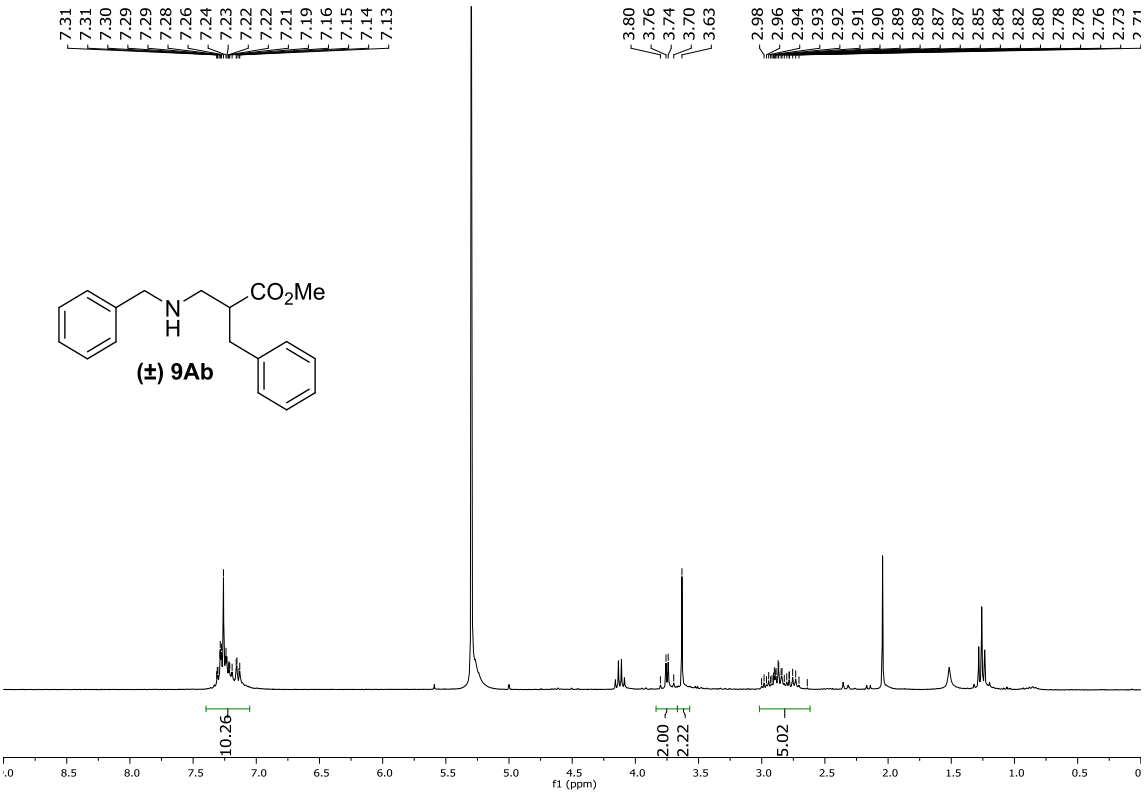

168.6
166.1
141.9
141.5
137.7
137.6
136.8
136.5
134.5
134.1
133.8
130.3
128.8
128.7
128.7
128.6
128.5
127.6
127.6
75.4
69.3
53.1
33.8
31.6
26.0
18.8
18.1

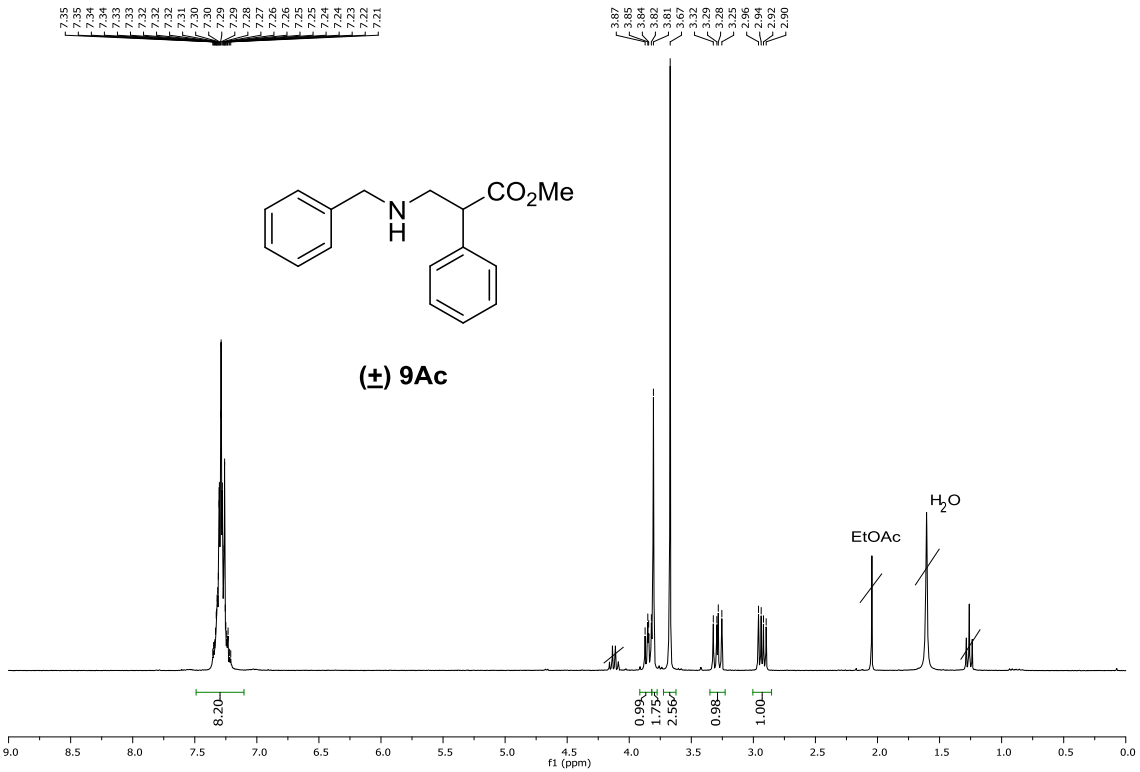

f1 (ppm)

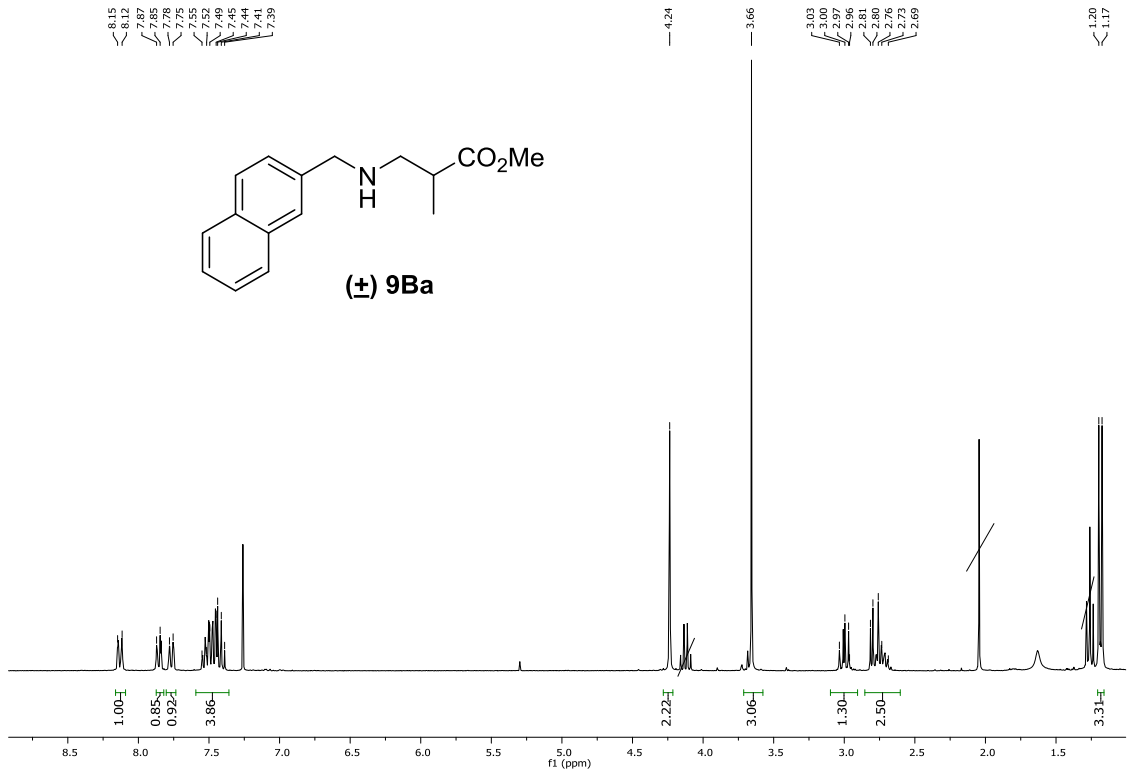

7.67 7.66 7.66 7.65 7.64 7.64 7.63 7.63 7.42 7.41 7.39 7.39 7.37 7.36 7.34 7.34 7.33 7.32 7.32 7.31 7.31 7.30 7.30 7.29 7.28 7.28 7.27 7.27 7.26 7.26 7.25 7.25 7.24 7.01 7.00 6.99 6.99 6.98 6.98 6.97 6.96 6.69 6.66 4.69 4.68 4.67 4.67 4.65 4.25 4.22 4.21 4.18 4.04 4.01 3.98 3.86 3.85 3.83 3.82 3.82 2.11 2.09 0.91 0.90 0.89 0.88 0.87 0.86
O
N
H
O
N
Ph2P
L12
1.14
1.05
10.10
0.96
0.91
0.87
1.01
1.02
1.00
1.04
15.70
f1 (ppm)

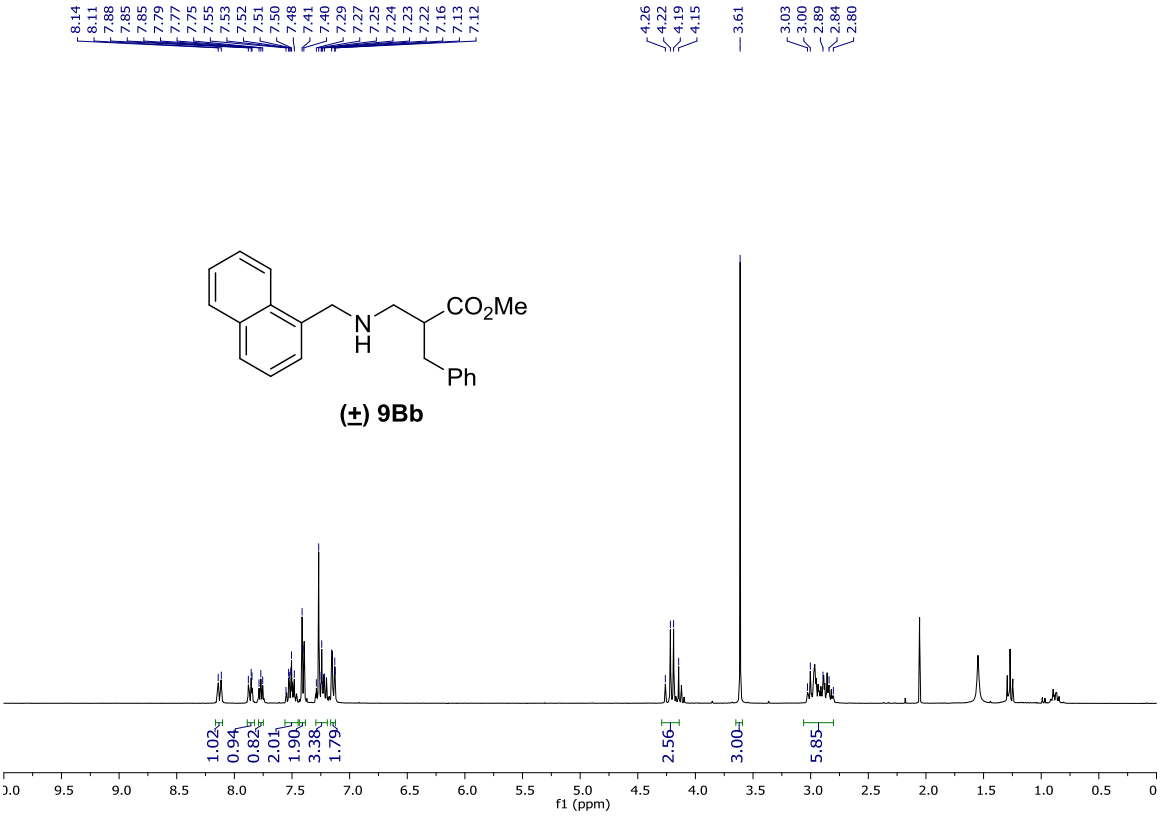

168.5
166.0
141.9
141.5
137.8
137.7
137.7
137.5
136.7
136.4
134.6
134.1
134.1
133.8
133.8
130.3
128.8
128.8
128.7
128.6
128.6
128.5
127.9
127.8
f1 (ppm)

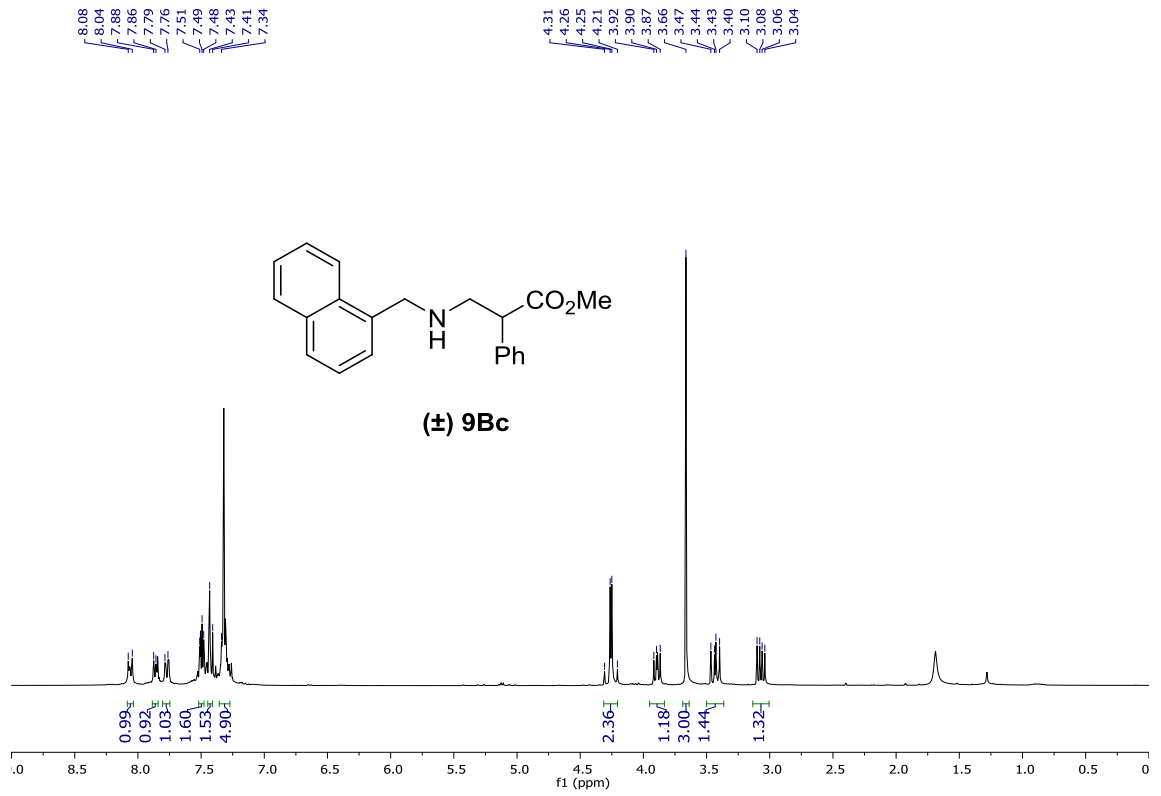

7.32
7.32
7.31
7.31
7.30
7.29
7.27
7.24
7.23
7.22
7.22
7.21
3.79
3.69
2.92
2.91
2.89
2.88
2.86
2.85
2.72
2.70
2.68
2.64
2.63
1.18
1.16
CO2Me
N
H
(±) 9Aa
3.01
1.00
2.00
2.59
1.07
1.96
3.10
f1 (ppm)

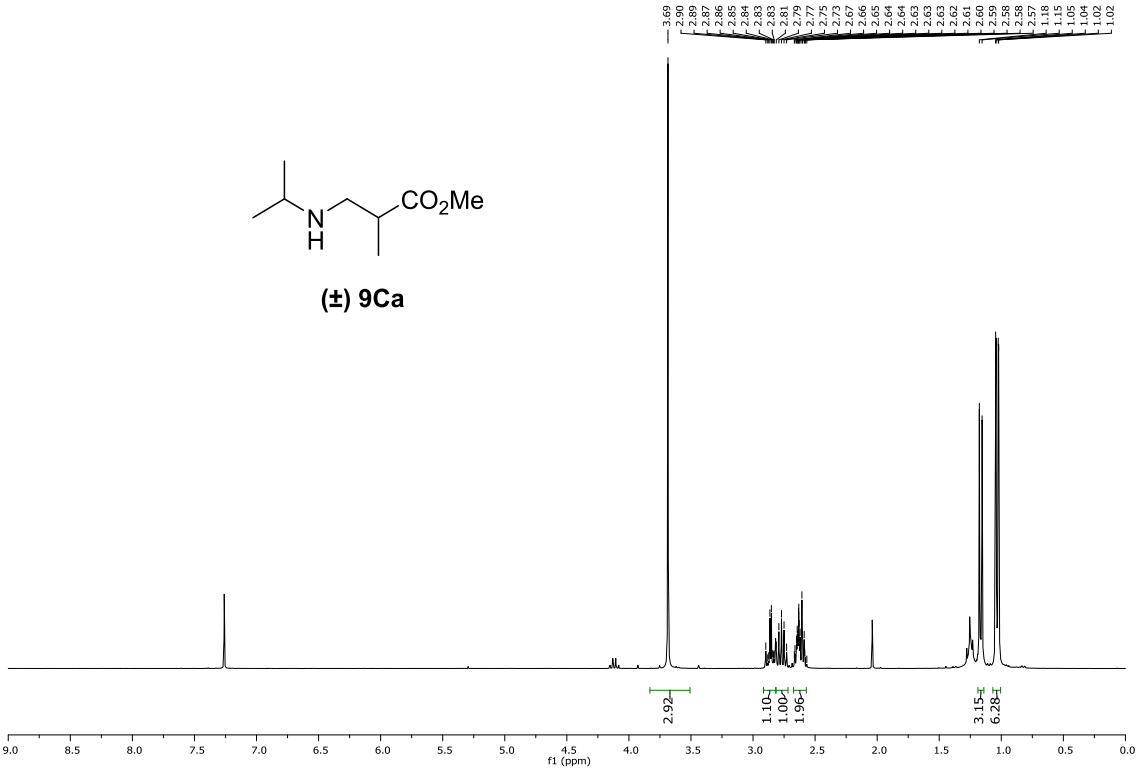

7.31
7.31
7.30
7.29
7.29
7.28
7.26
7.24
7.23
7.22
7.22
7.21
7.19
7.16
7.15
7.14
7.13
3.80
3.76
3.74
3.70
3.63
2.98
2.96
2.94
2.93
2.92
2.91
2.90
2.89
2.89
2.87
2.87
2.85
2.84
2.82
2.80
2.78
2.78
2.76
2.73
CO2Me
N
H
(±) 9Ab
10.26
2.00
2.22
5.02
f1 (ppm)

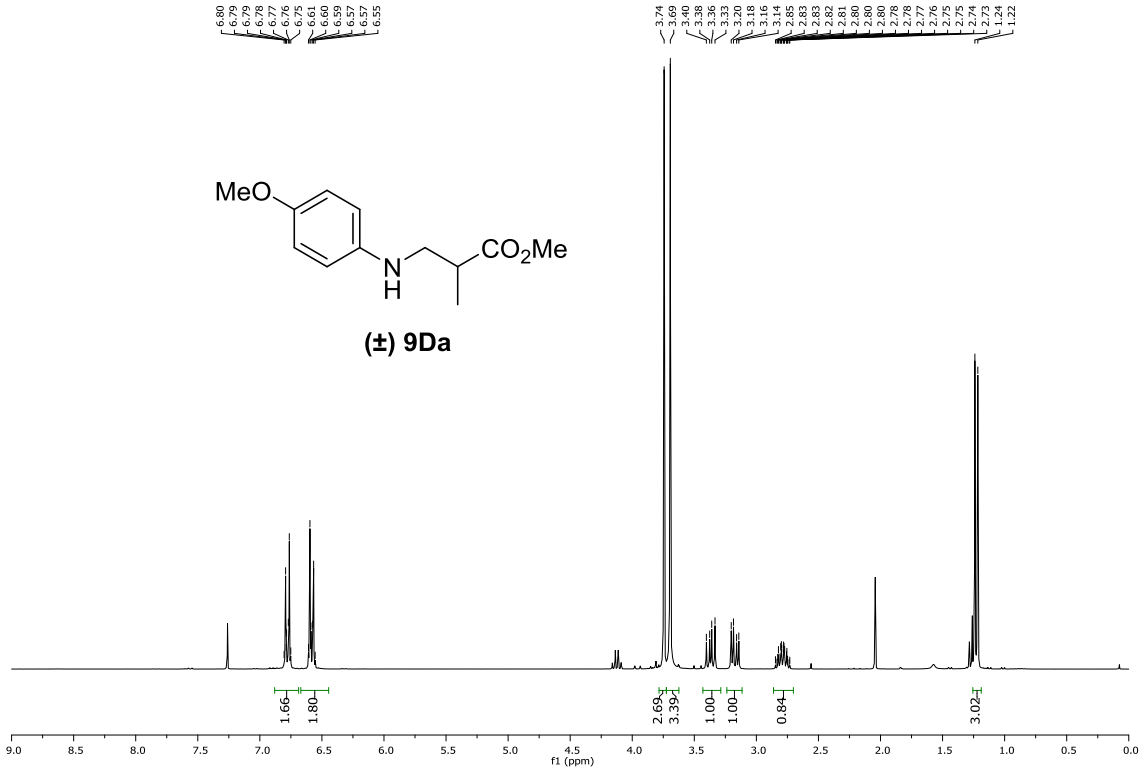

CO2Me
N
H
(±) 9Ac
EtOAc
H2O
f1 (ppm)

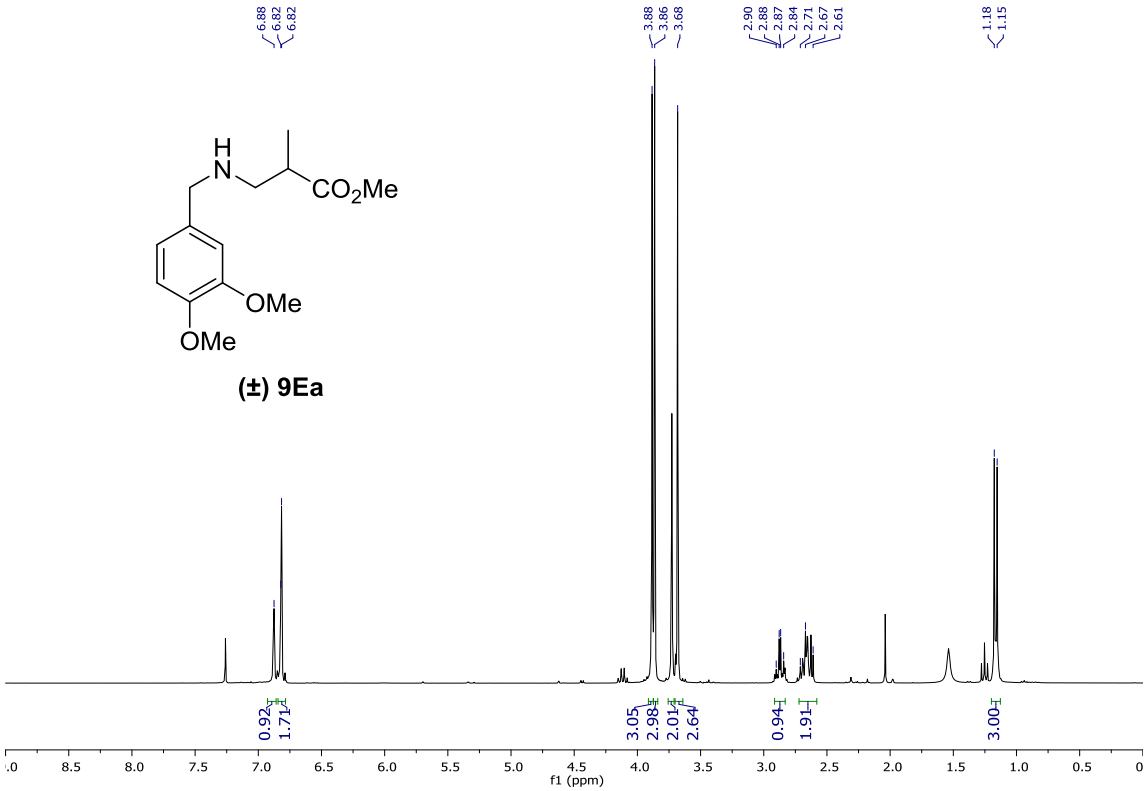

CO2Me
N
H
(±) 9Ba
f1 (ppm)


8.14
8.11
7.88
7.85
7.85
7.79
7.77
7.75
7.55
7.53
7.52
7.51
7.50
7.48
7.41
7.40
7.29
7.27
7.25
7.24
7.23
7.22
7.16
7.13
7.12
4.26
4.22
4.19
4.15
3.61
3.03
3.00
2.89
2.84
2.80
CO2Me
N
H
Ph
(±) 9Bb
1.02
0.94
0.82
2.01
1.90
3.38
1.79
2.56
3.00
5.85
f1 (ppm)

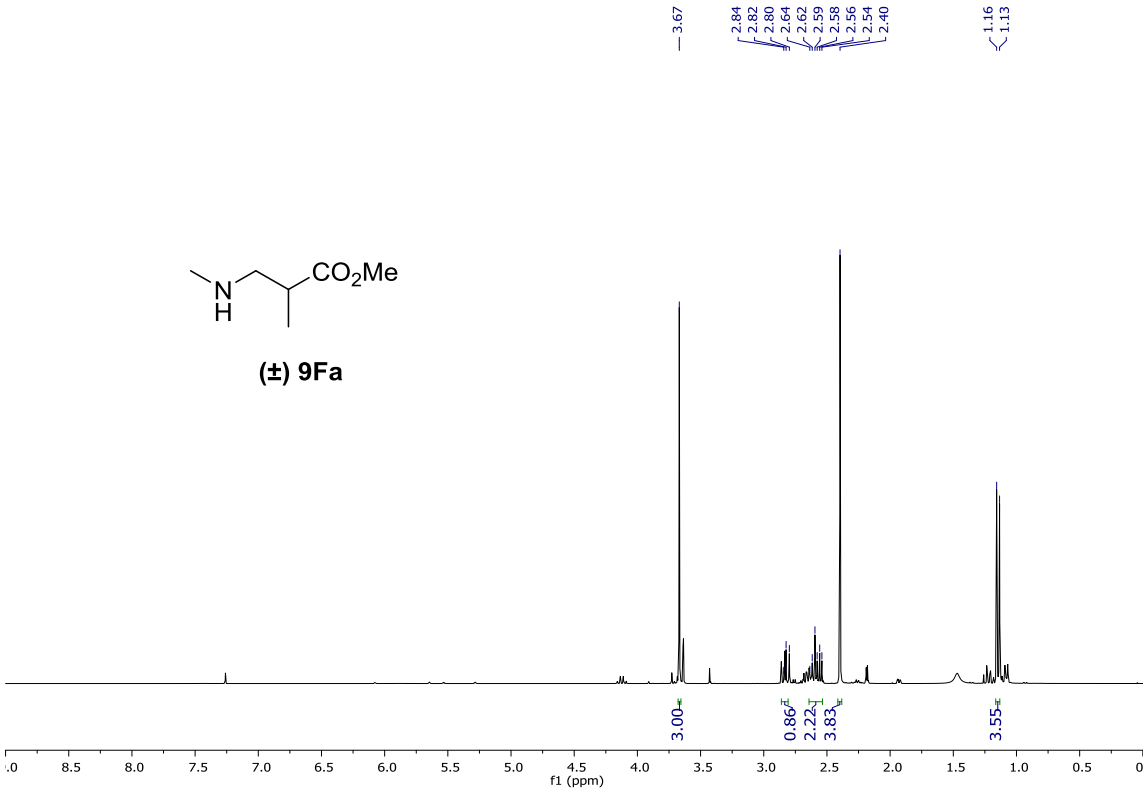

8.08
8.04
7.88
7.86
7.79
7.76
7.51
7.49
7.48
7.43
7.41
7.34
4.31
4.26
4.25
4.21
3.92
3.90
3.87
3.66
3.47
3.44
3.43
3.40
3.10
3.08
3.06
3.04
CO2Me
N
H
Ph
(±) 9Bc
0.99
0.92
1.03
1.60
1.53
4.90
2.36
1.18
3.00
1.44
1.32
f1 (ppm)


CO2Me
N
H
(±) 9Ca
f1 (ppm)

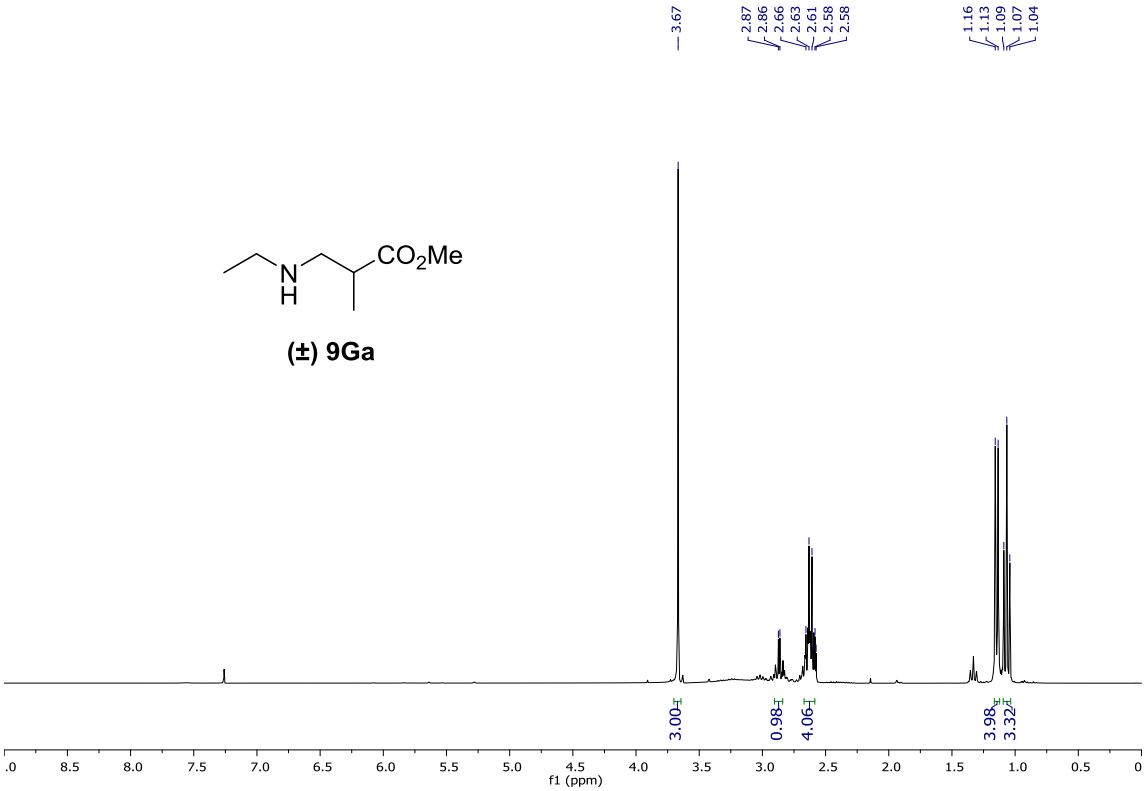

MeO
CO2Me
N
H
(±) 9Da
f1 (ppm)


6.88
6.82
6.82
3.88
3.86
3.68
2.90
2.88
2.87
2.84
2.71
2.67
2.61
1.18
1.15
H
N
CO2Me
OMe
OMe
0.92
1.71
3.05
2.98
2.01
2.64
0.94
1.91
3.00
f1 (ppm)

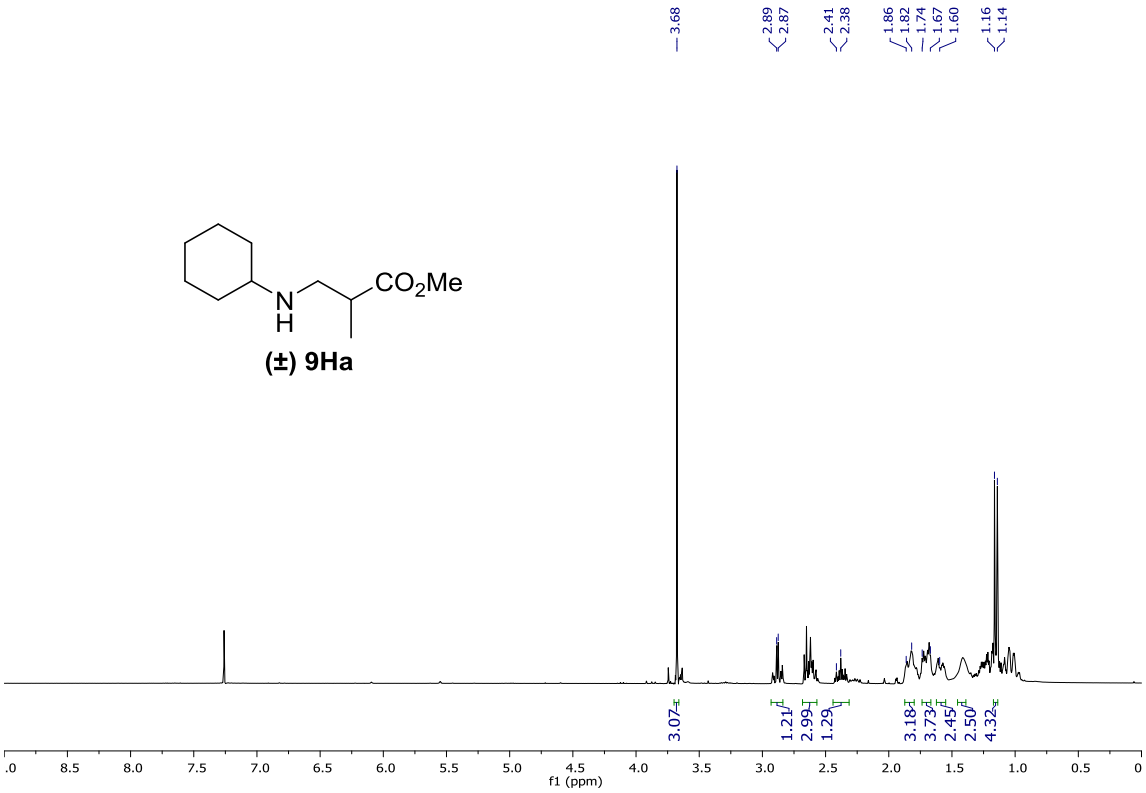
(±) 9Ea


3.67
2.84
2.82
2.80
2.64
2.62
2.59
2.58
2.56
2.54
2.40
1.16
1.13
N
H
CO2Me
3.00
0.86
2.22
3.83
3.55
f1 (ppm)

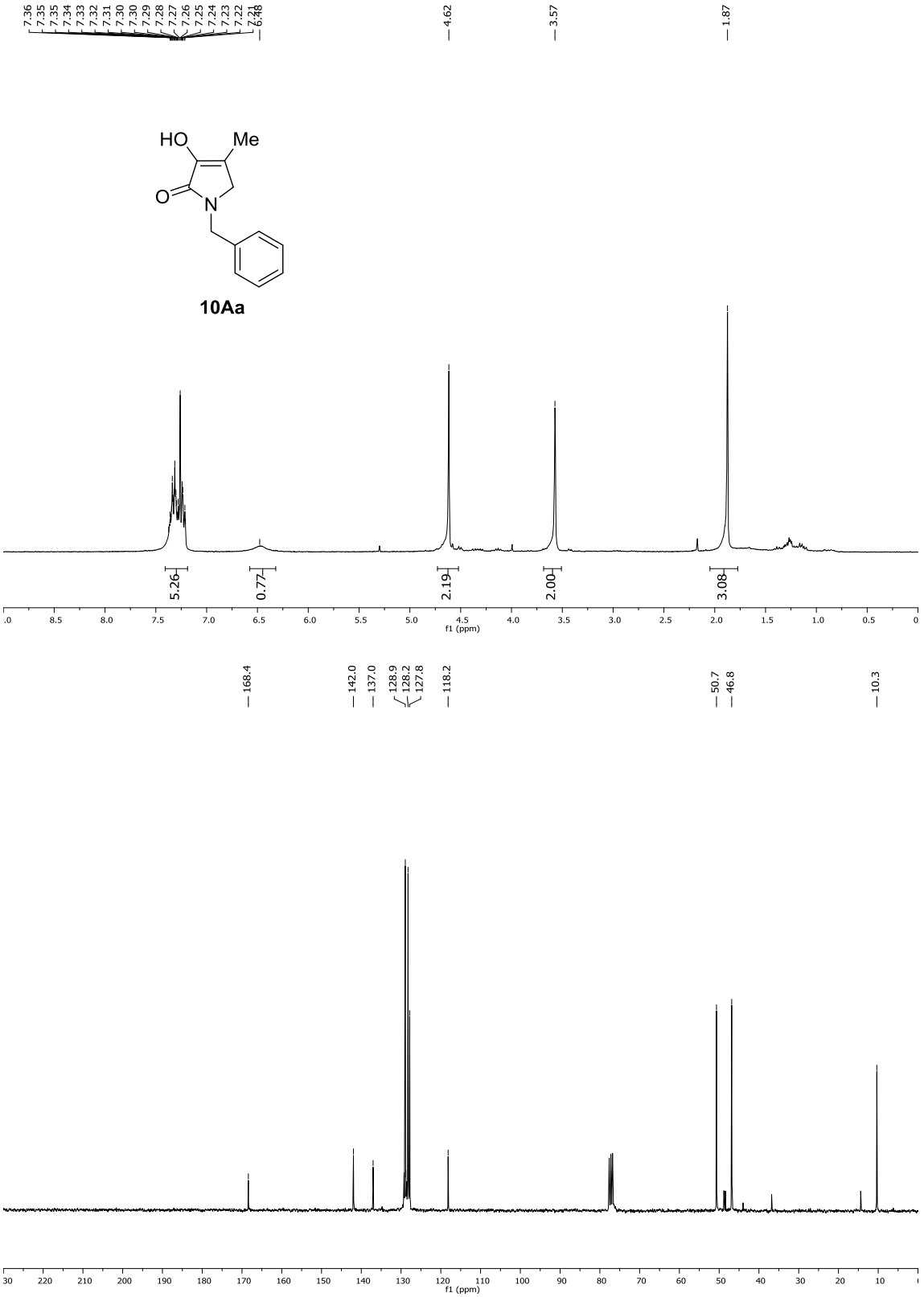
(±) 9Fa

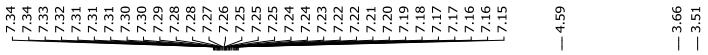

3.67
2.87
2.86
2.66
2.63
2.61
2.58
2.58
1.16
1.13
1.09
1.07
1.04
CO2Me
N
H
3.00
0.98
4.06
3.98
3.32
f1 (ppm)

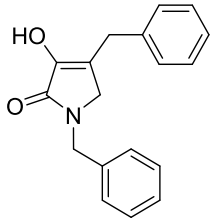
(±) 9Ga


3.68
2.89
2.87
2.41
2.38
1.86
1.82
1.74
1.67
1.60
1.16
1.14
CO2Me
N
H
3.07
1.21
2.99
1.29
3.18
3.73
2.45
2.50
4.32
f1 (ppm)

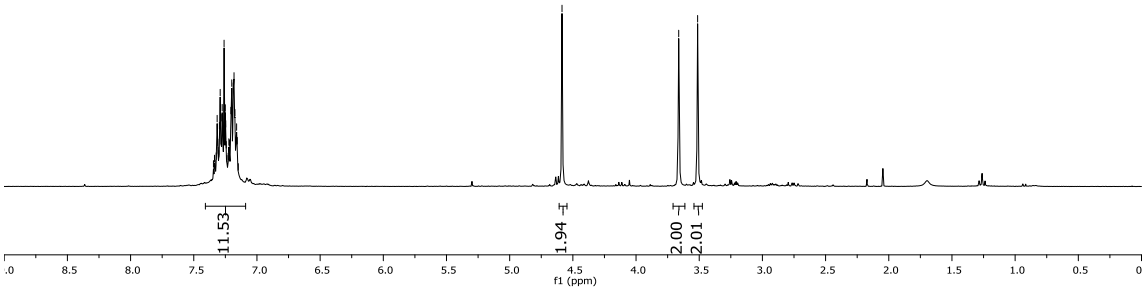
(±) 9Ha

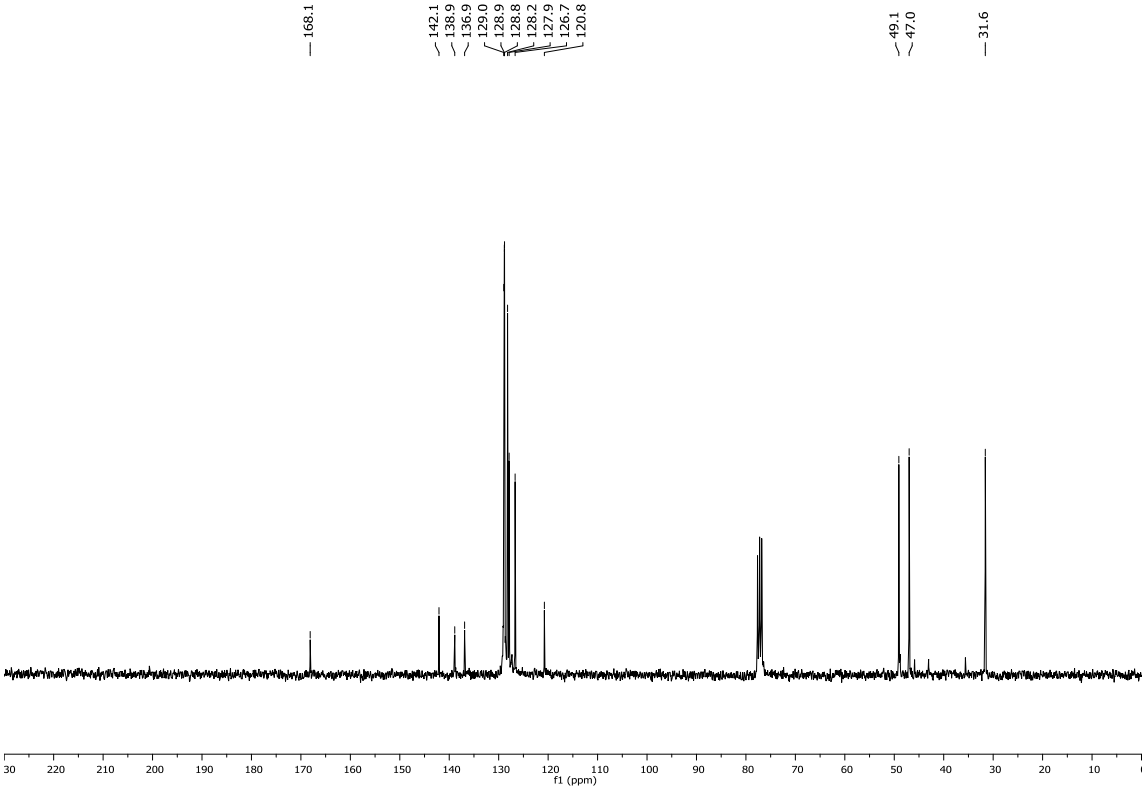

7.36
7.35
7.35
7.34
7.33
7.32
7.31
7.30
7.30
7.29
7.28
7.27
7.26
7.25
7.24
7.23
7.22
6.48
4.62
3.57
1.87
HO
Me
O
N
10Aa
5.26
0.77
2.19
2.00
3.08
f1 (ppm)
168.4
142.0
137.0
128.9
128.2
127.8
118.2
50.7
46.8
10.3
f1 (ppm)

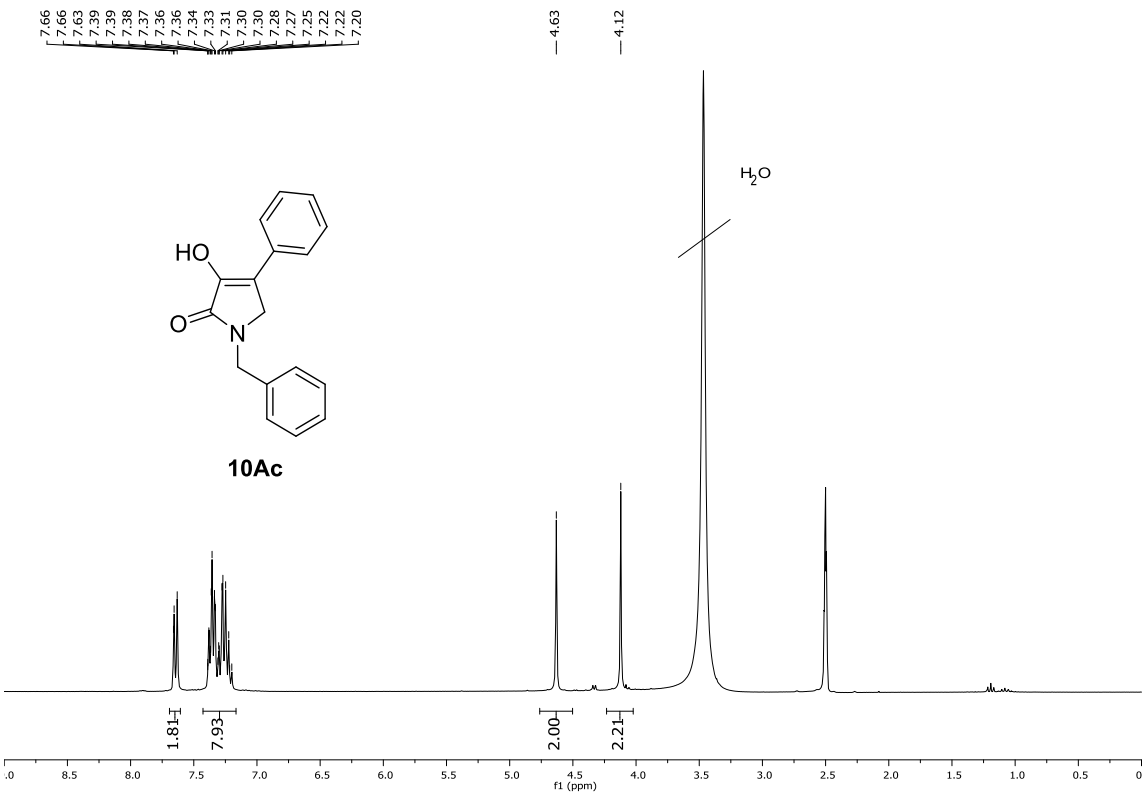

7.34
7.34
7.33
7.32
7.31
7.31
7.31
7.30
7.30
7.29
7.28
7.28
7.27
7.26
7.25
7.25
7.25
7.24
7.24
7.23
7.22
7.22
7.21
7.20
7.19
7.18
7.17
7.17
7.16
7.16
7.15
4.59
3.66
3.51

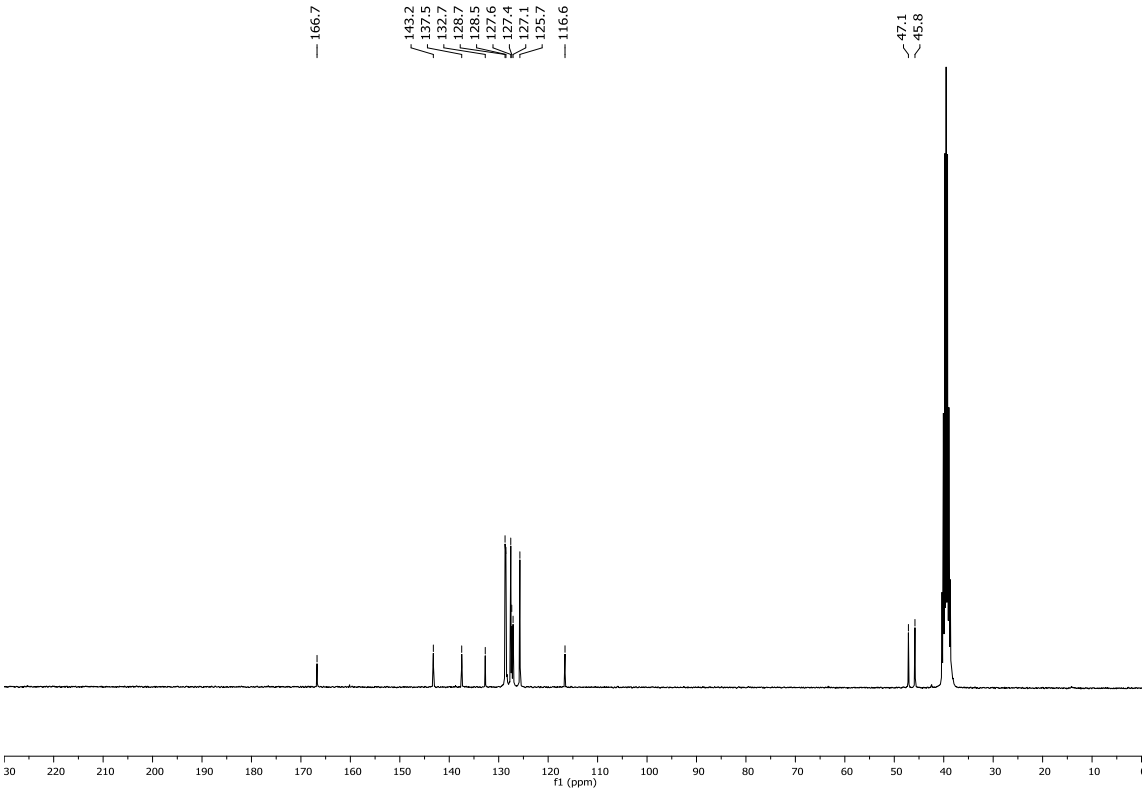

HO
O
N

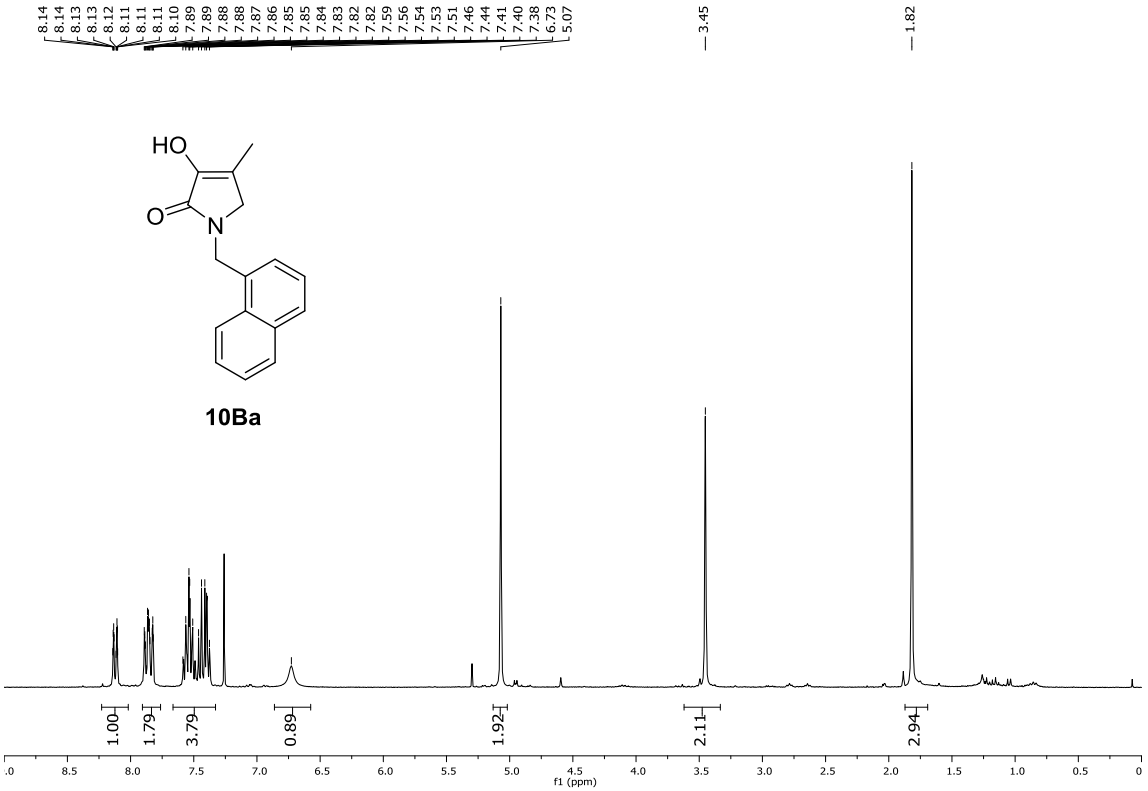
10Ab


11.53
1.94
2.00
2.01
f1 (ppm)

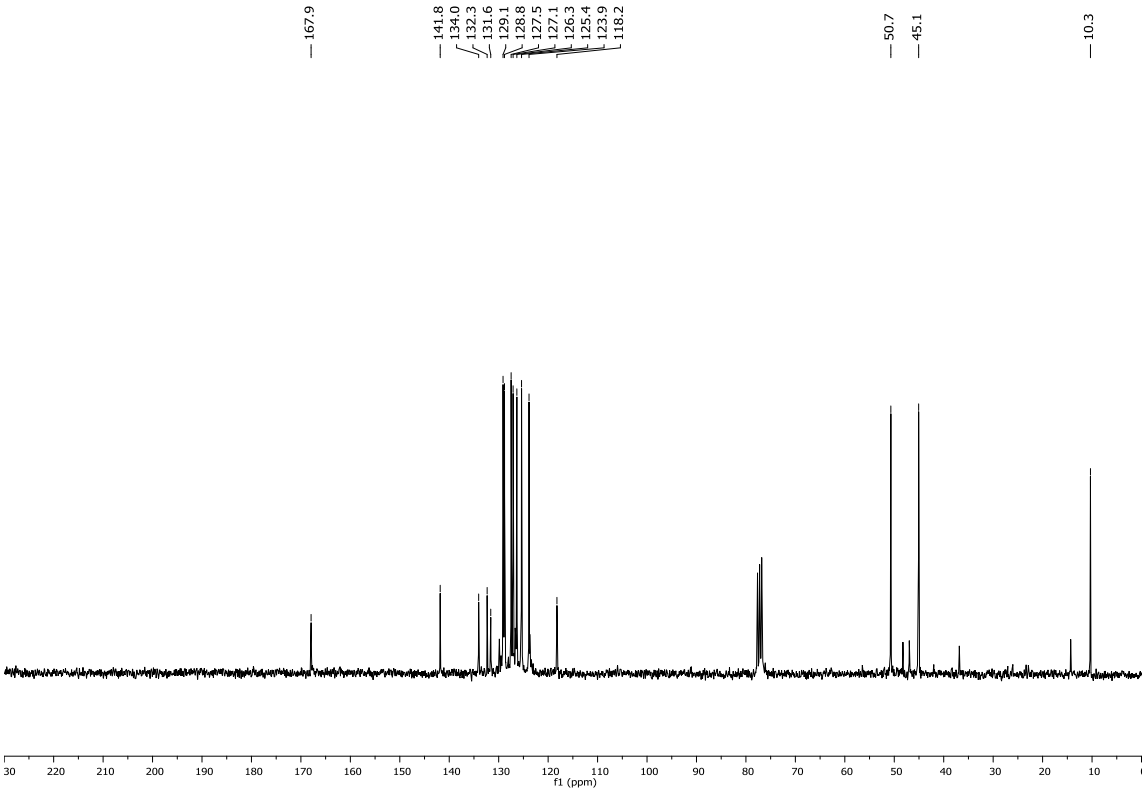

168.1
142.1
138.9
136.9
129.0
128.9
128.8
128.2
127.9
126.7
120.8
49.1
47.0
31.6
f1 (ppm)

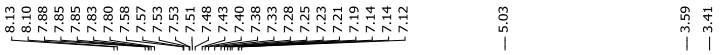

7.66
7.66
7.63
7.39
7.39
7.38
7.37
7.36
7.36
7.34
7.33
7.31
7.30
7.30
7.28
7.27
7.25
7.22
7.22
7.20
4.63
4.12
H2O
HO
O
N
10Ac
1.81
7.93
2.00
2.21
f1 (ppm)

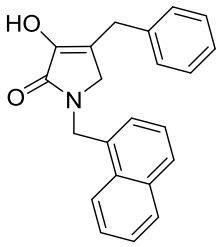

166.7
143.2
137.5
132.7
128.7
128.5
127.6
127.4
127.1
125.7
116.6
47.1
45.8
f1 (ppm)


8.14
8.14
8.13
8.13
8.12
8.11
8.11
8.11
8.10
7.89
7.89
7.88
7.88
7.87
7.86
7.85
7.85
7.84
7.83
7.82
7.82
7.59
7.56
7.54
7.53
7.51
7.46
7.44
7.41
7.40
7.38
6.73
5.07
3.45
1.82
HO
O
N
1.00
1.79
3.79
0.89
1.92
2.11
2.94
f1 (ppm)

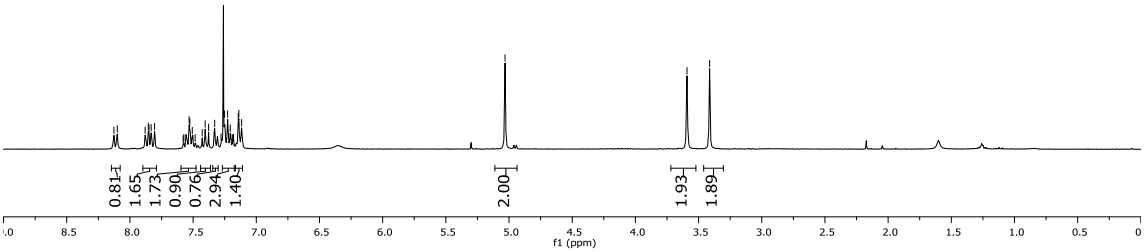
10Ba

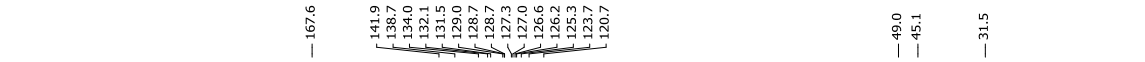

167.9
141.8
134.0
132.3
131.6
129.1
128.8
127.5
127.1
126.3
125.4
123.9
118.2
50.7
45.1
10.3
f1 (ppm)

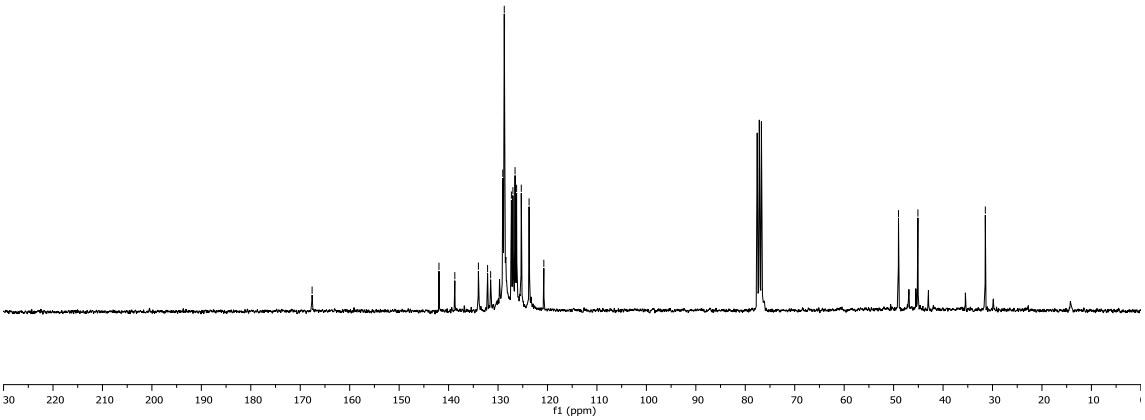

8.13
8.10
7.88
7.85
7.85
7.83
7.80
7.58
7.57
7.53
7.53
7.51
7.48
7.43
7.40
7.38
7.33
7.28
7.25
7.23
7.21
7.19
7.14
7.14
7.12
5.03
3.59
3.41

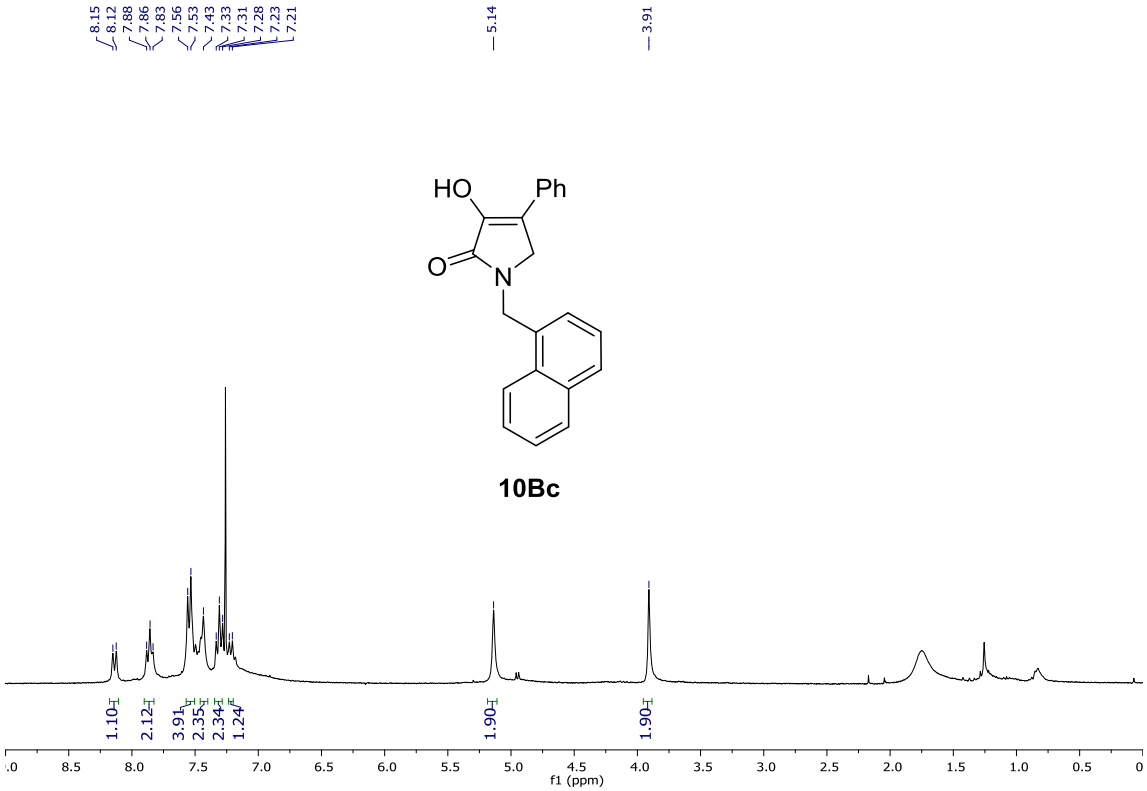

HO
O
N

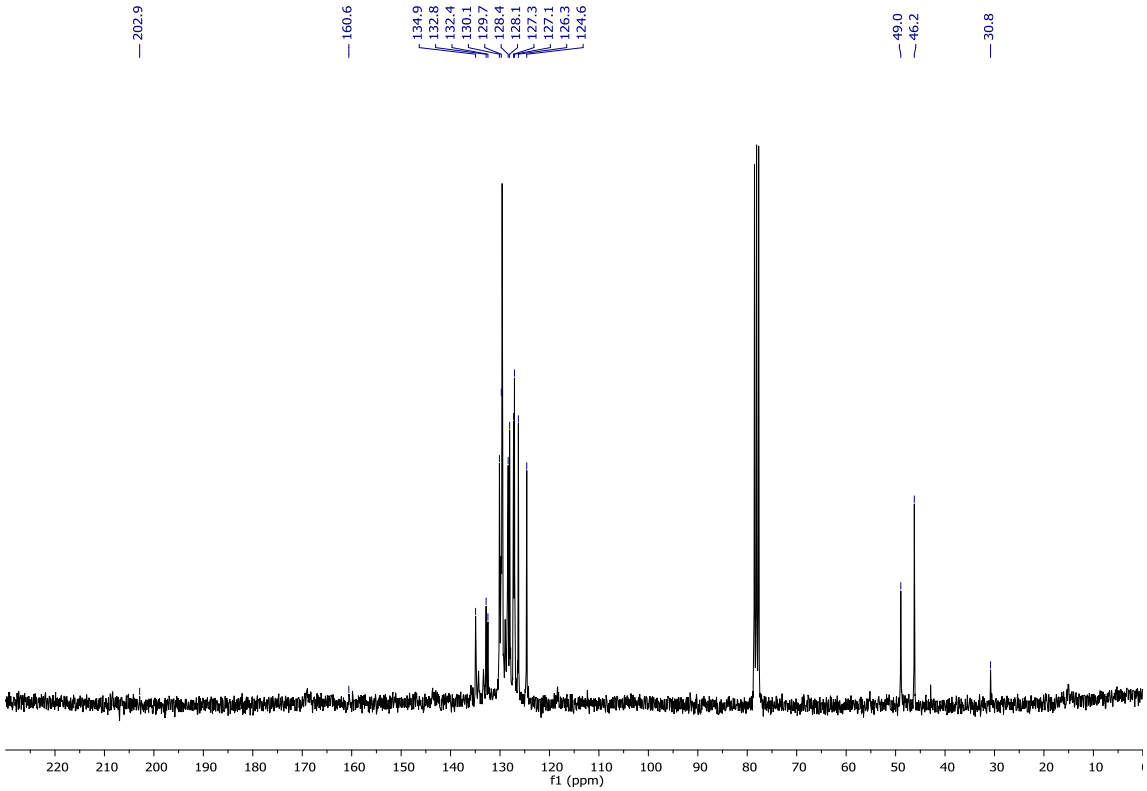
10Bb

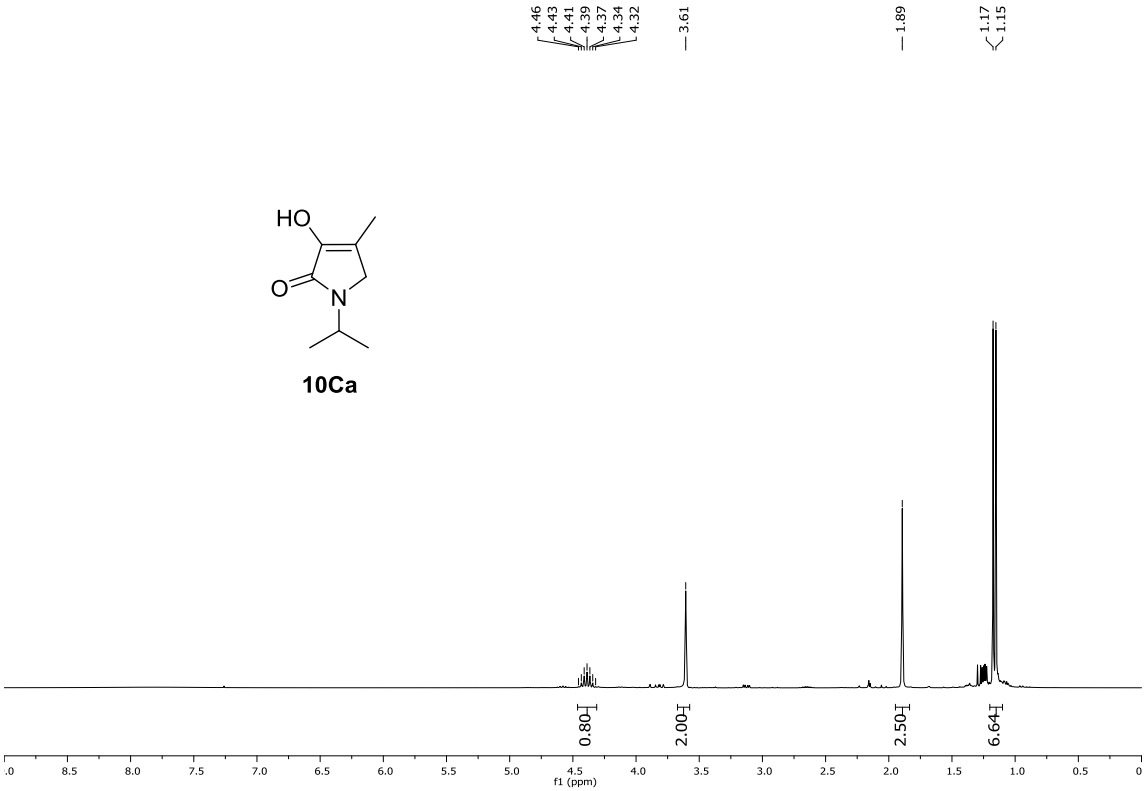

0.81
1.65
1.73
0.90
0.76
2.94
1.40
2.00
1.93
1.89
f1 (ppm)


167.6
141.9
138.7
134.0
132.1
131.5
129.0
128.7
128.7
127.3
127.0
126.6
126.2
125.3
123.7
120.7
49.0
45.1
31.5

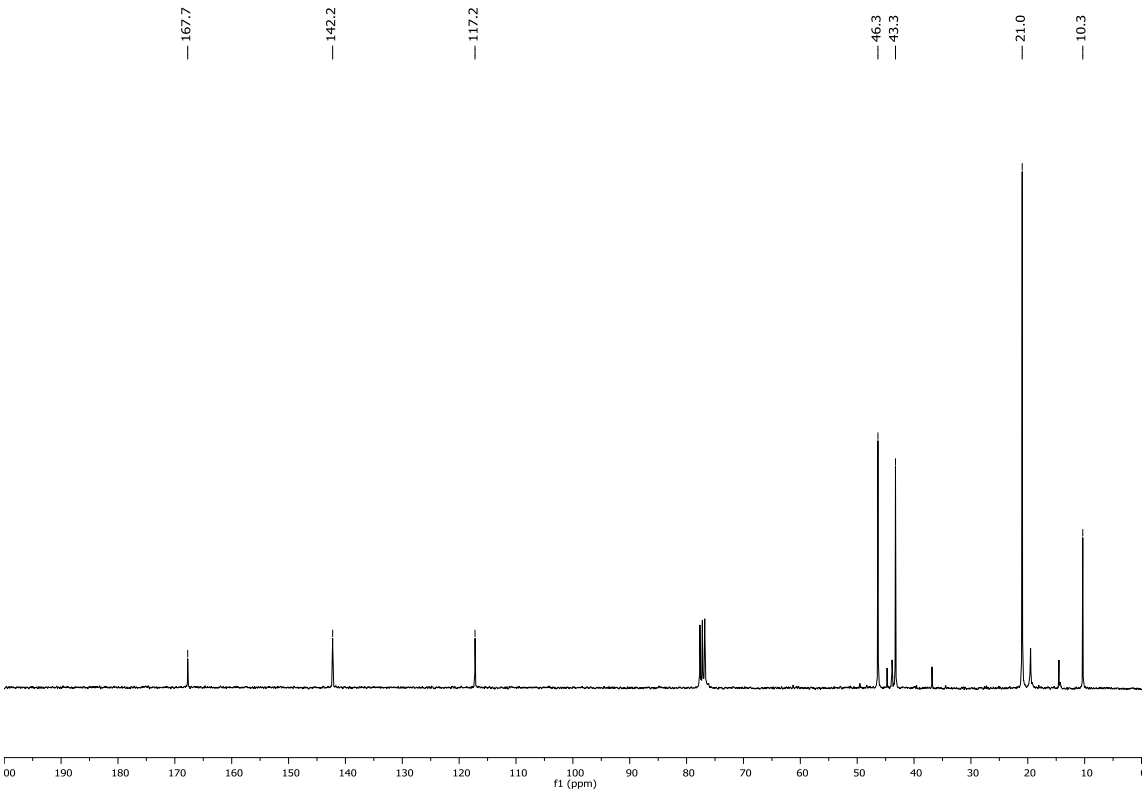

f1 (ppm)

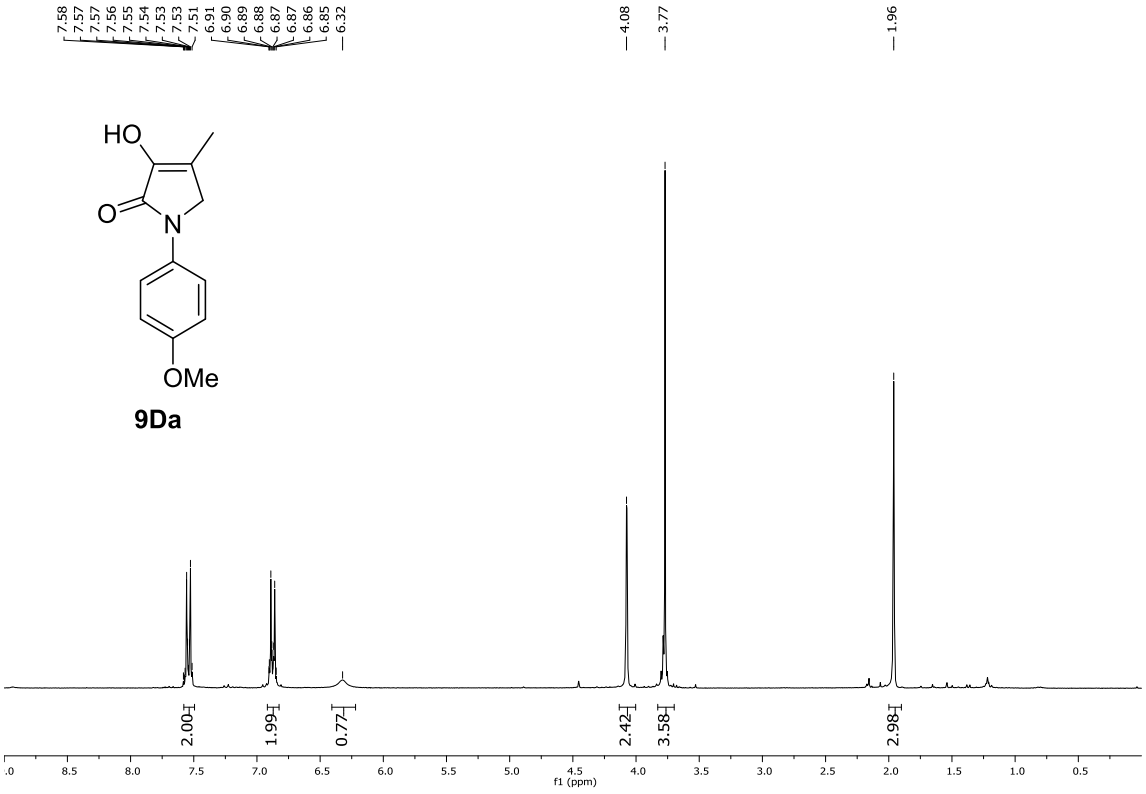

8.15
8.12
7.88
7.86
7.83
7.56
7.53
7.43
7.33
7.31
7.28
7.23
7.21
5.14
3.91
HO
Ph
O
N
10Bc
1.10
2.12
3.91
2.35
2.34
1.24
1.90
1.90
f1 (ppm)

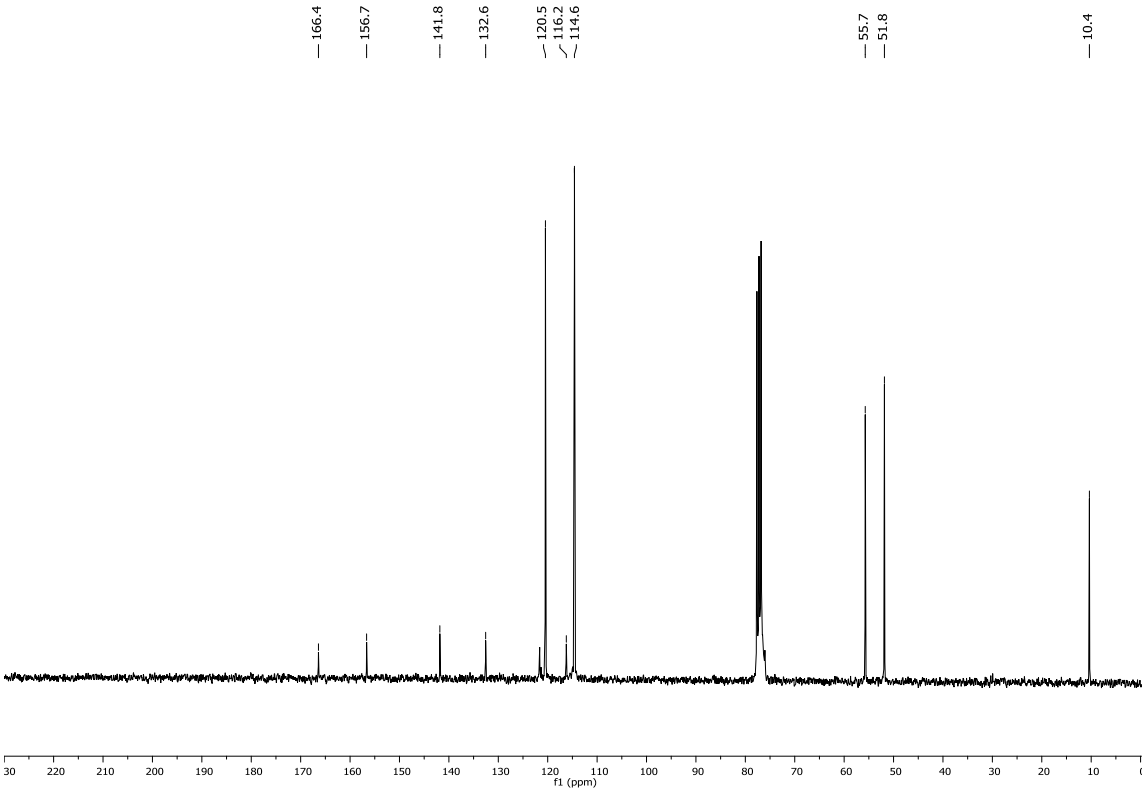

202.9
160.6
134.9
132.8
132.4
130.1
129.7
128.4
128.1
127.3
127.1
126.3
124.6
49.0
46.2
30.8
f1 (ppm)

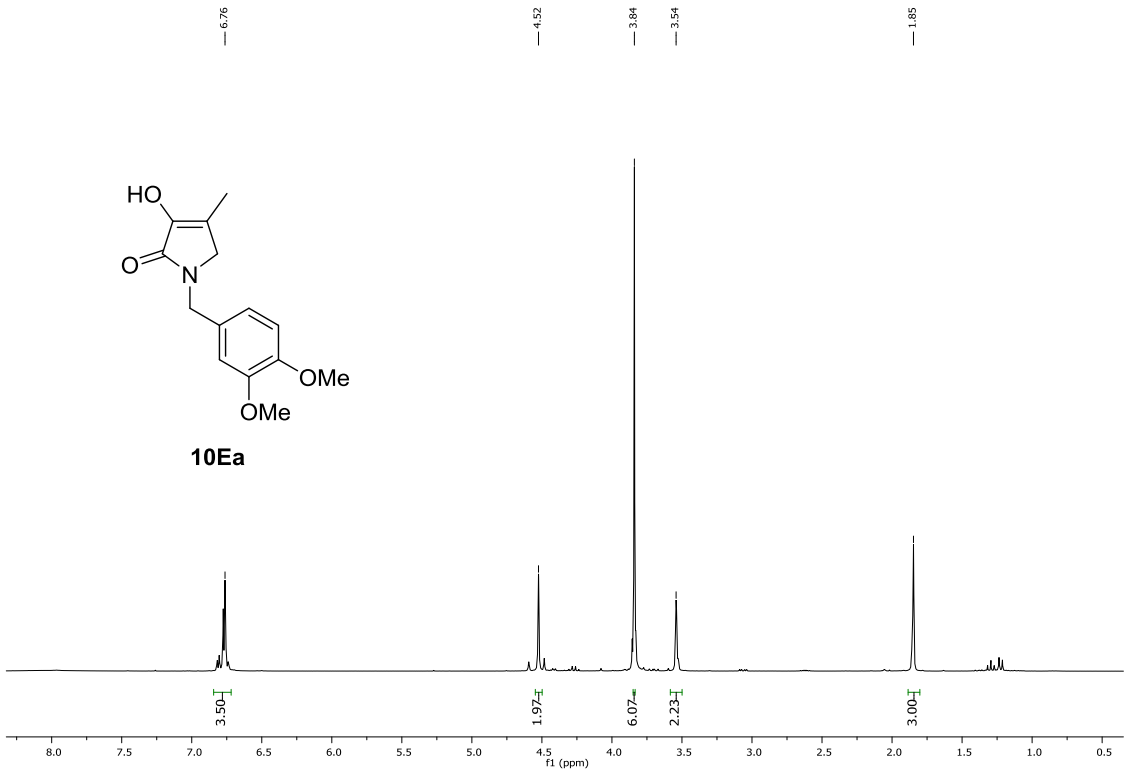

4.46
4.43
4.41
4.39
4.37
4.34
4.32
3.61
1.89
1.17
1.15
HO
O
N
0.80
2.00
2.50
6.64
f1 (ppm)

10Ca

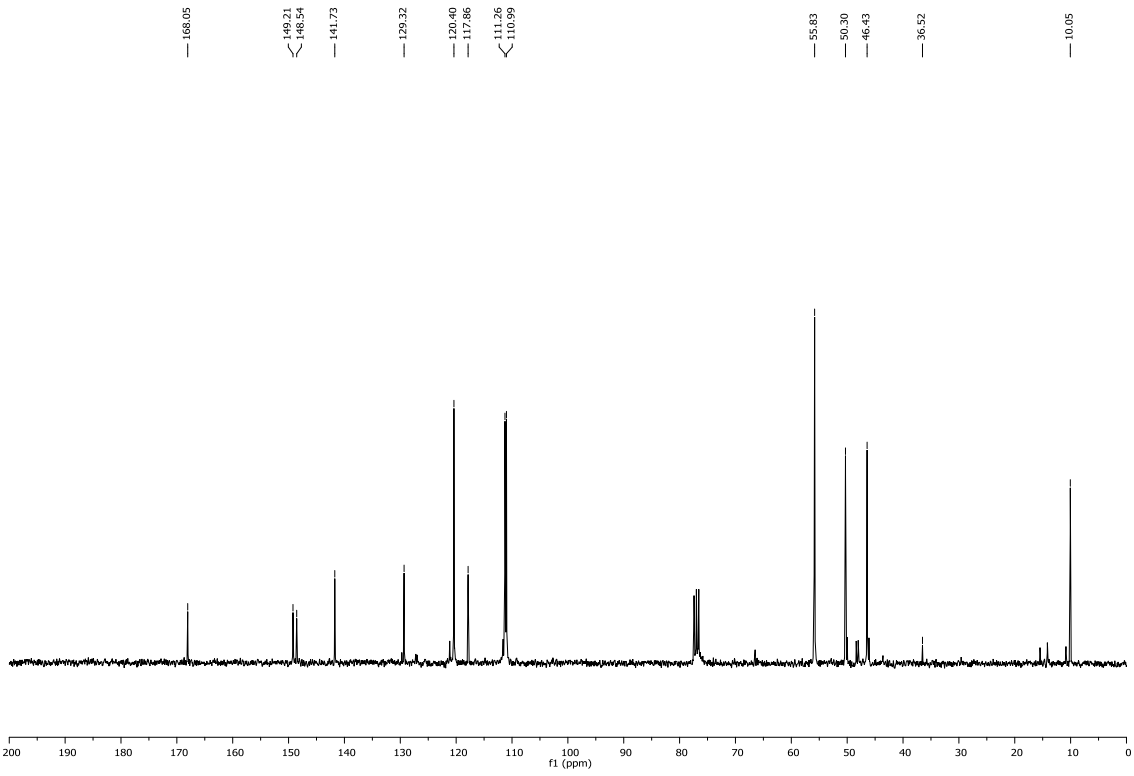

167.7
142.2
117.2
46.3
43.3
21.0
10.3
f1 (ppm)

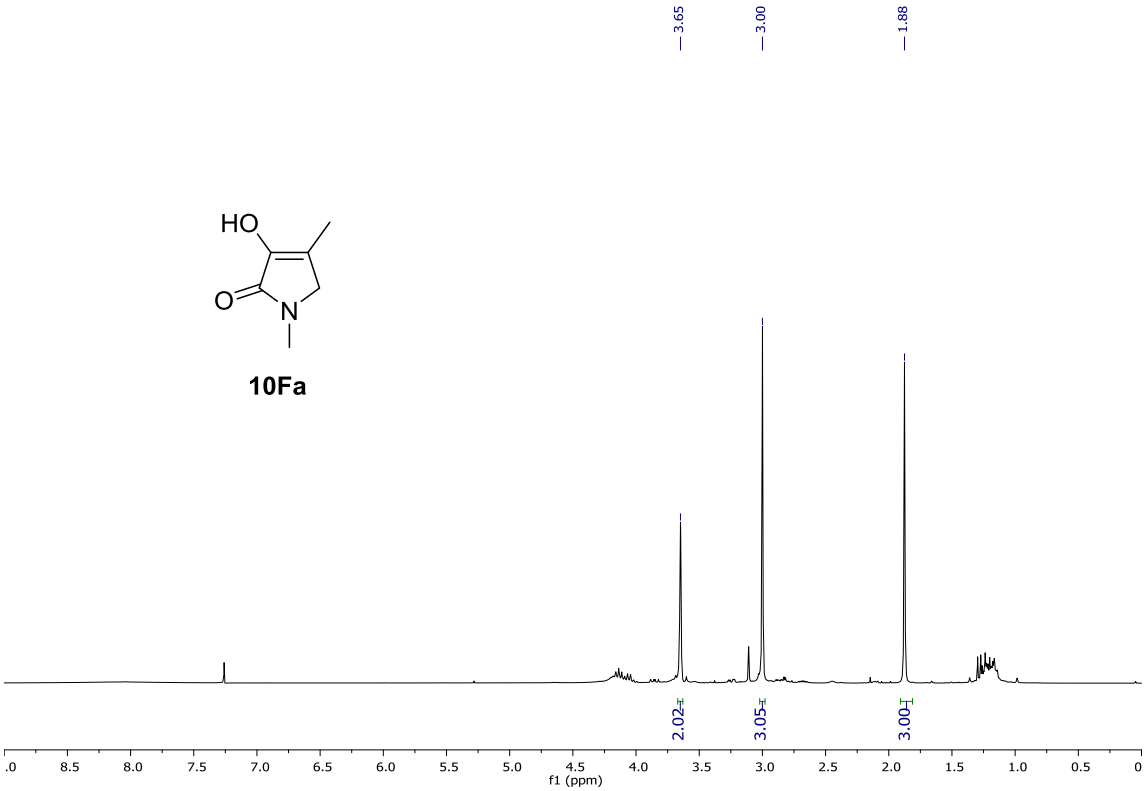

7.58
7.57
7.57
7.56
7.55
7.54
7.53
7.53
7.51
6.91
6.90
6.89
6.88
6.87
6.87
6.86
6.85
6.32
4.08
3.77
1.96
HO
O
N
OMe
9Da
2.00
1.99
0.77
2.42
3.58
2.98
f1 (ppm)


166.4
156.7
141.8
132.6
120.5
116.2
114.6
55.7
51.8
10.4
f1 (ppm)

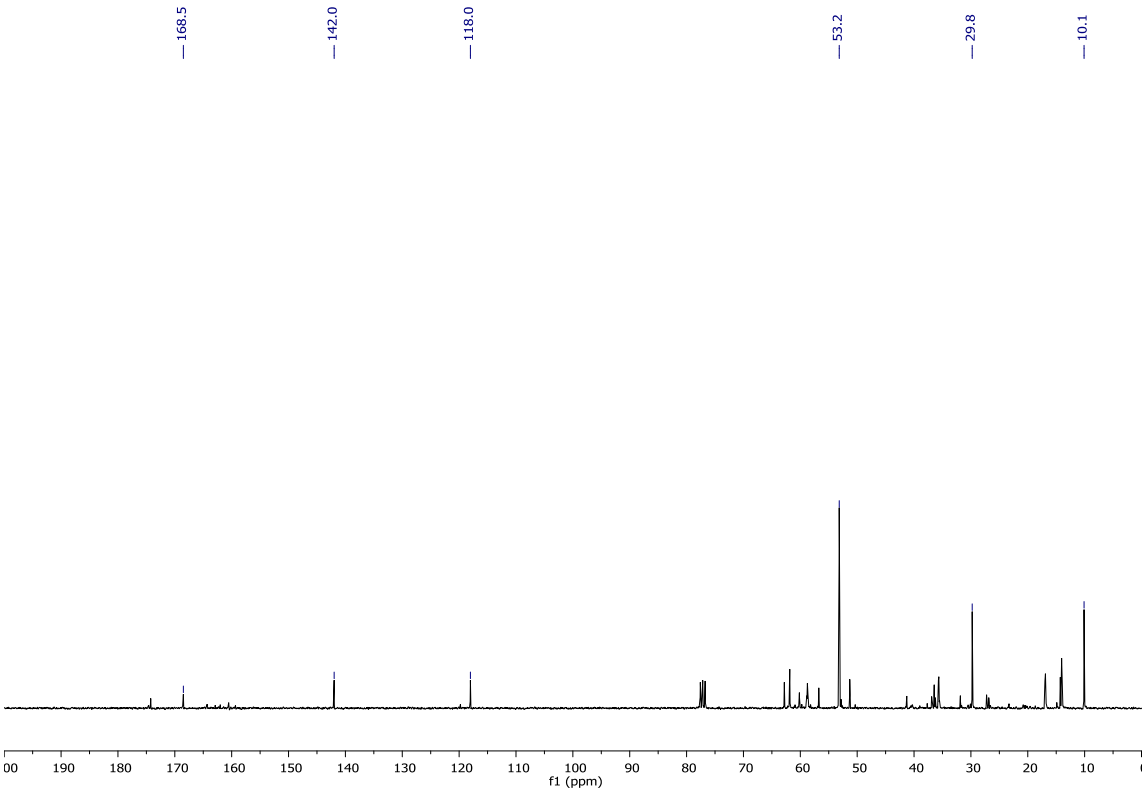

6.76
4.52
3.84
3.54
1.85
HO
O
N
OMe
OMe
3.50
1.97
6.07
2.23
3.00
f1 (ppm)

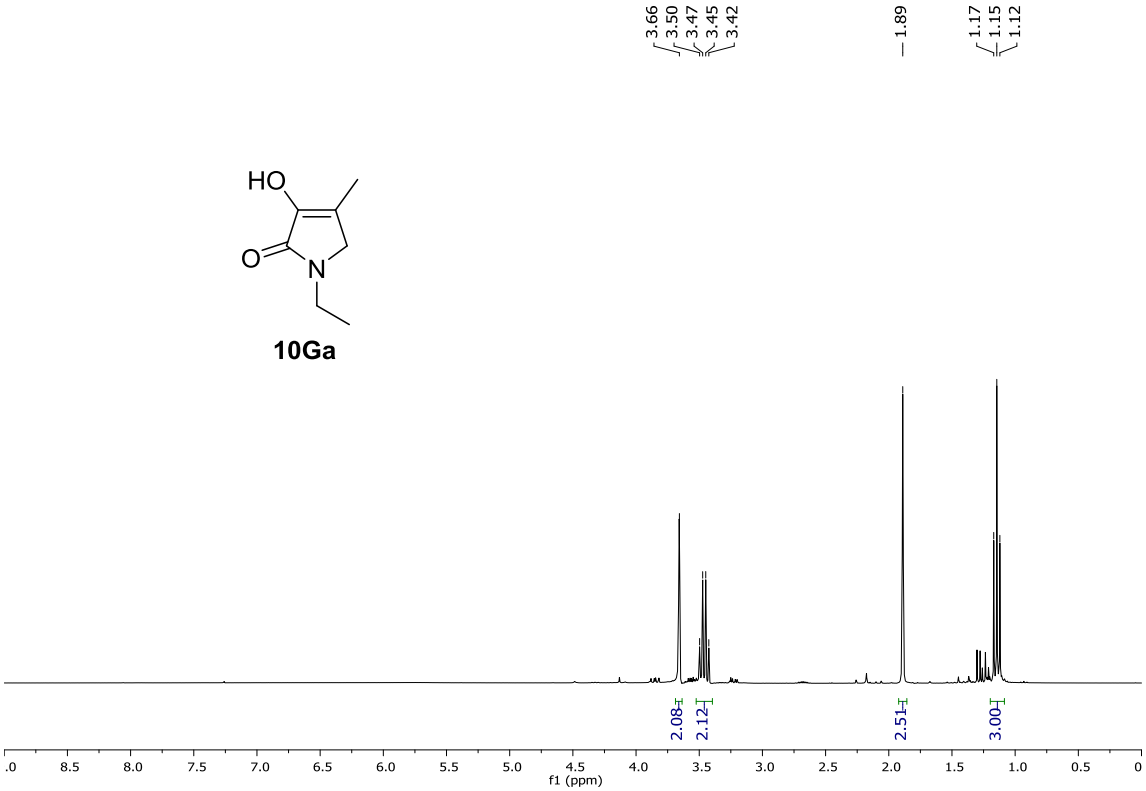
10Ea


168.05
149.21
148.54
141.73
129.32
120.40
117.86
111.26
110.99
55.83
50.30
46.43
36.52
10.05
f1 (ppm)

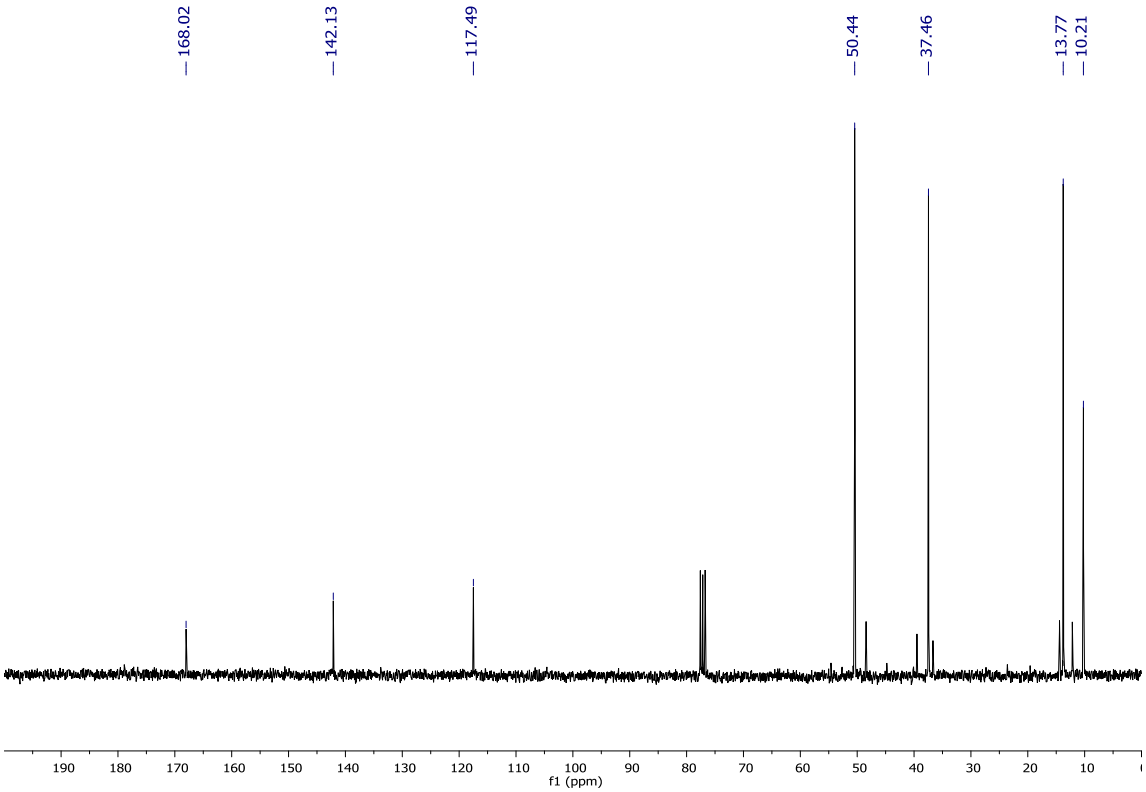

3.65
3.00
1.88
HO
O
N
2.02
3.05
3.00
f1 (ppm)

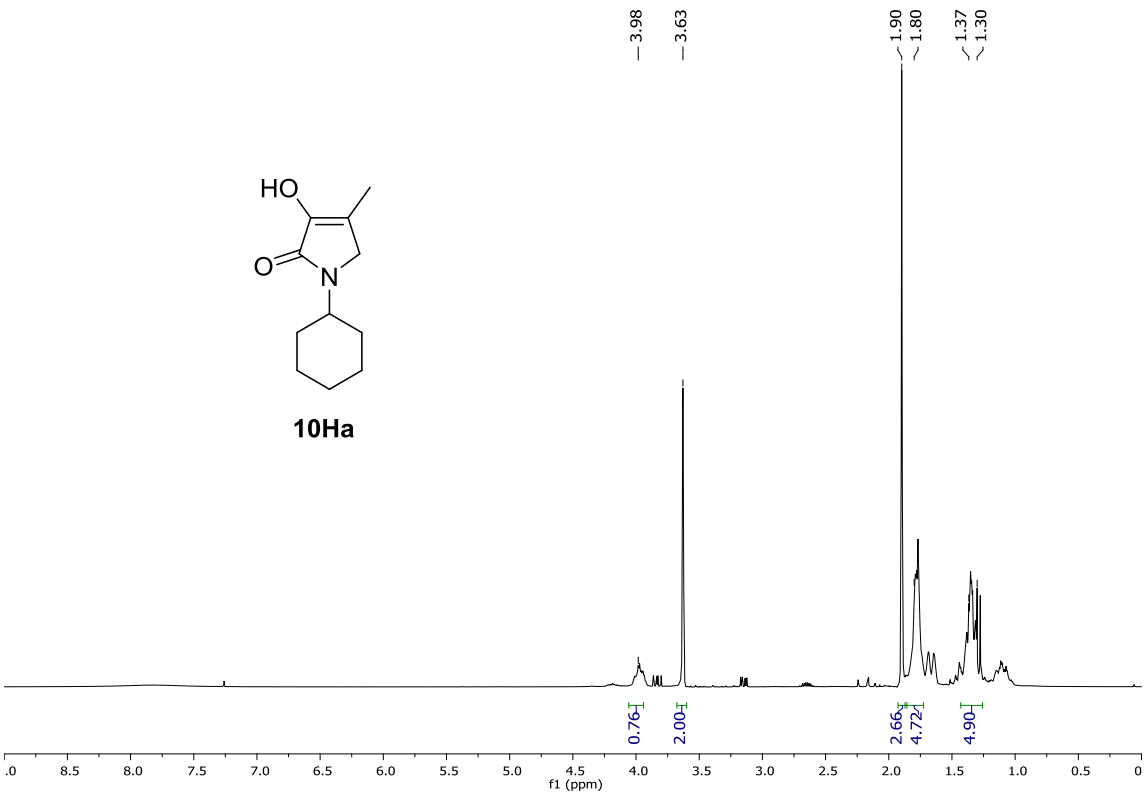
10Fa


168.5
142.0
118.0
53.2
29.8
10.1
f1 (ppm)

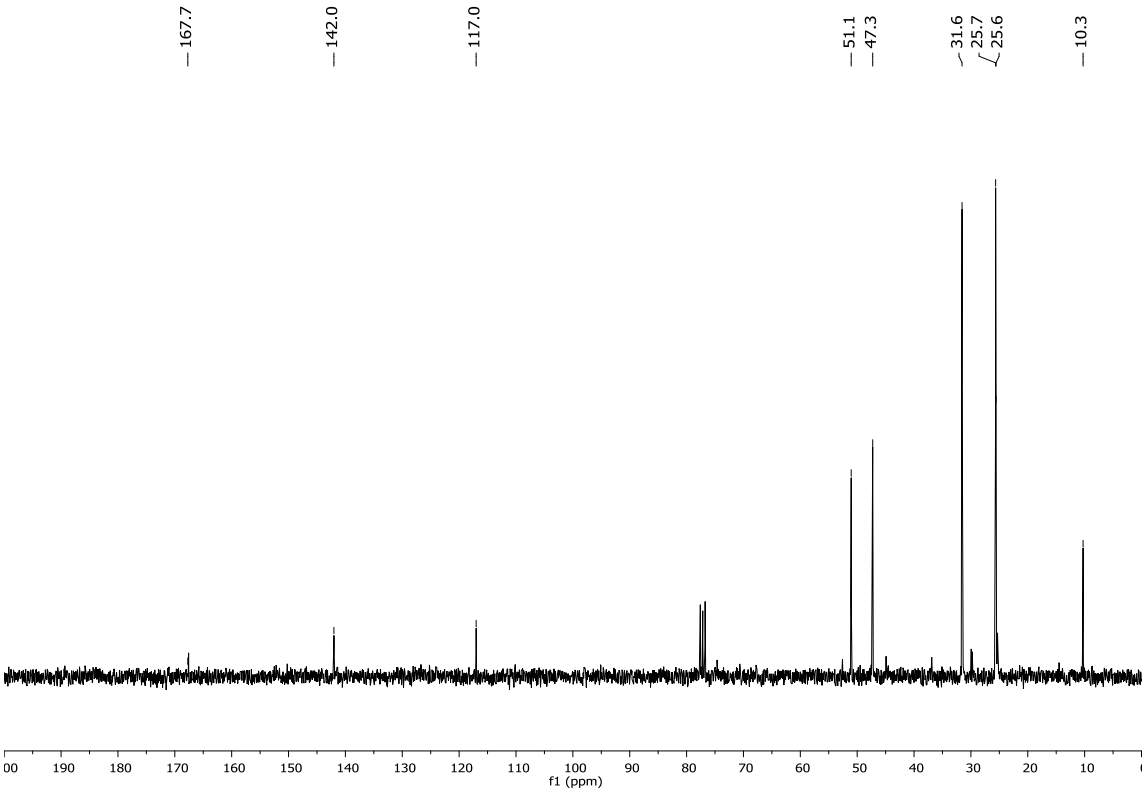

3.66
3.50
3.47
3.45
3.42
1.89
1.17
1.15
1.12
HO
O
N
2.08
2.12
2.51
3.00
f1 (ppm)

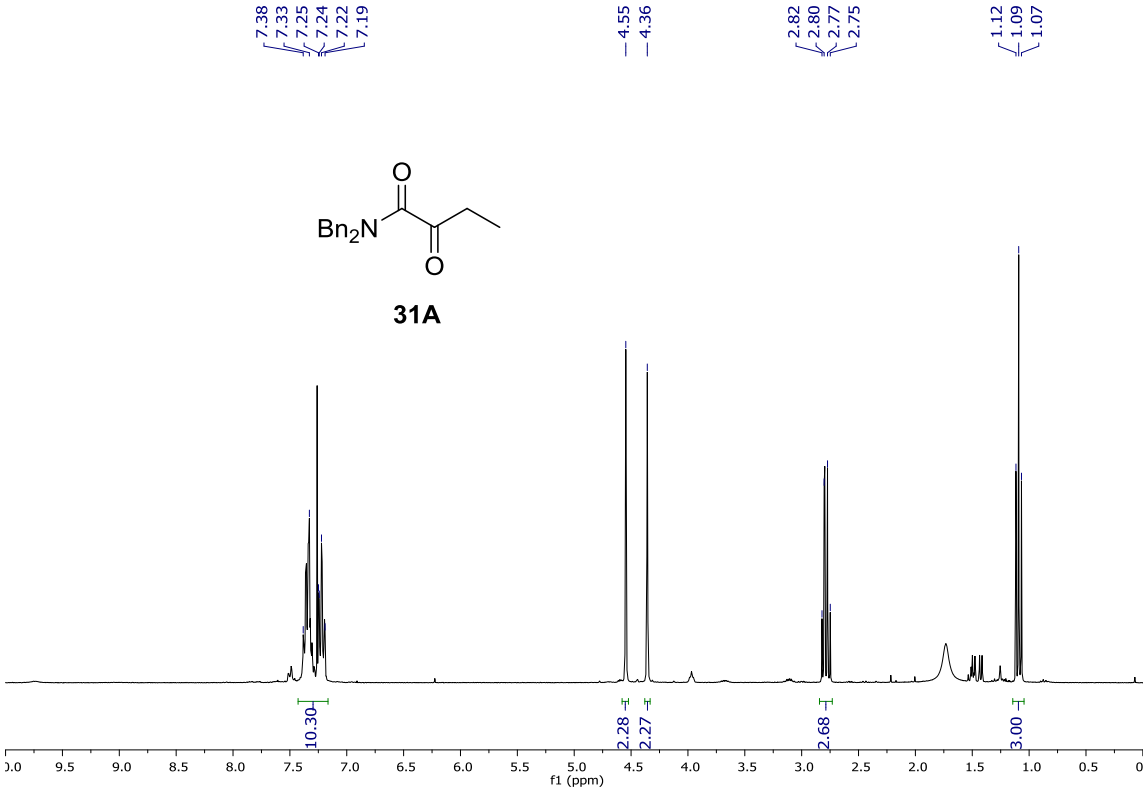
10Ga


168.02
142.13
117.49
50.44
37.46
13.77
10.21
f1 (ppm)

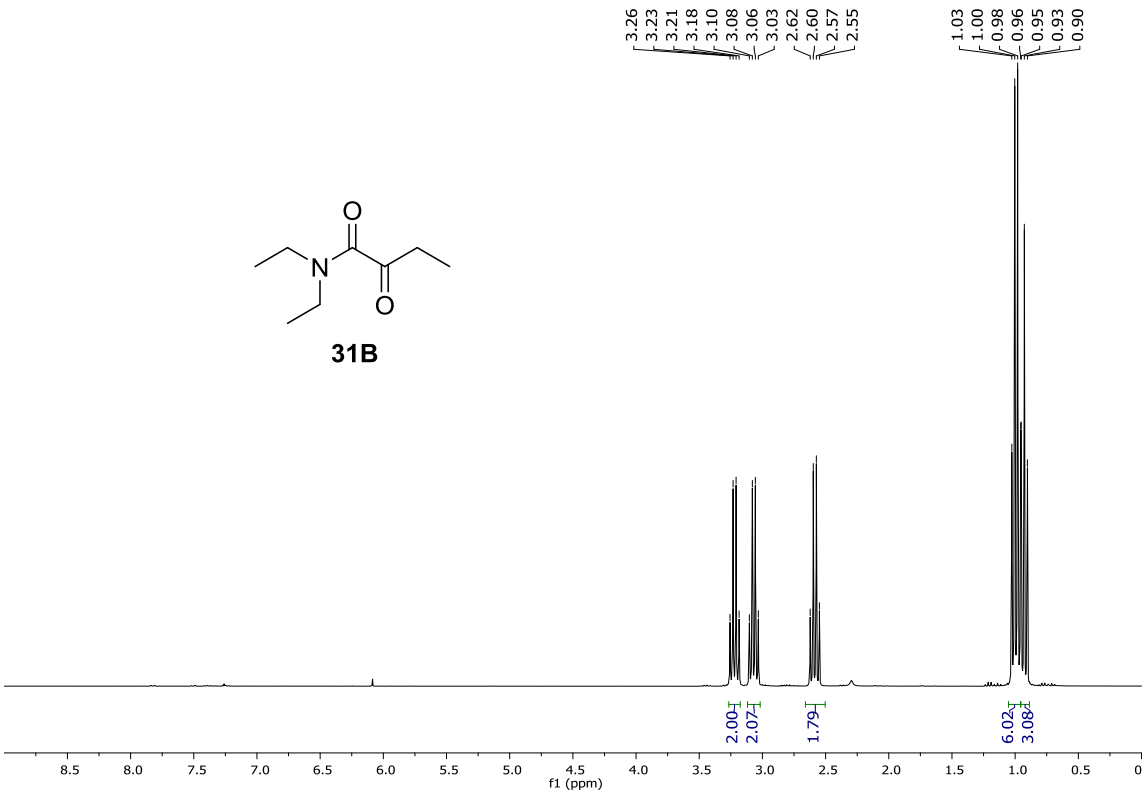

3.98
3.63
1.90
1.80
1.37
1.30
HO
O
N
0.76
2.00
2.66
4.72
4.90
f1 (ppm)

10Ha

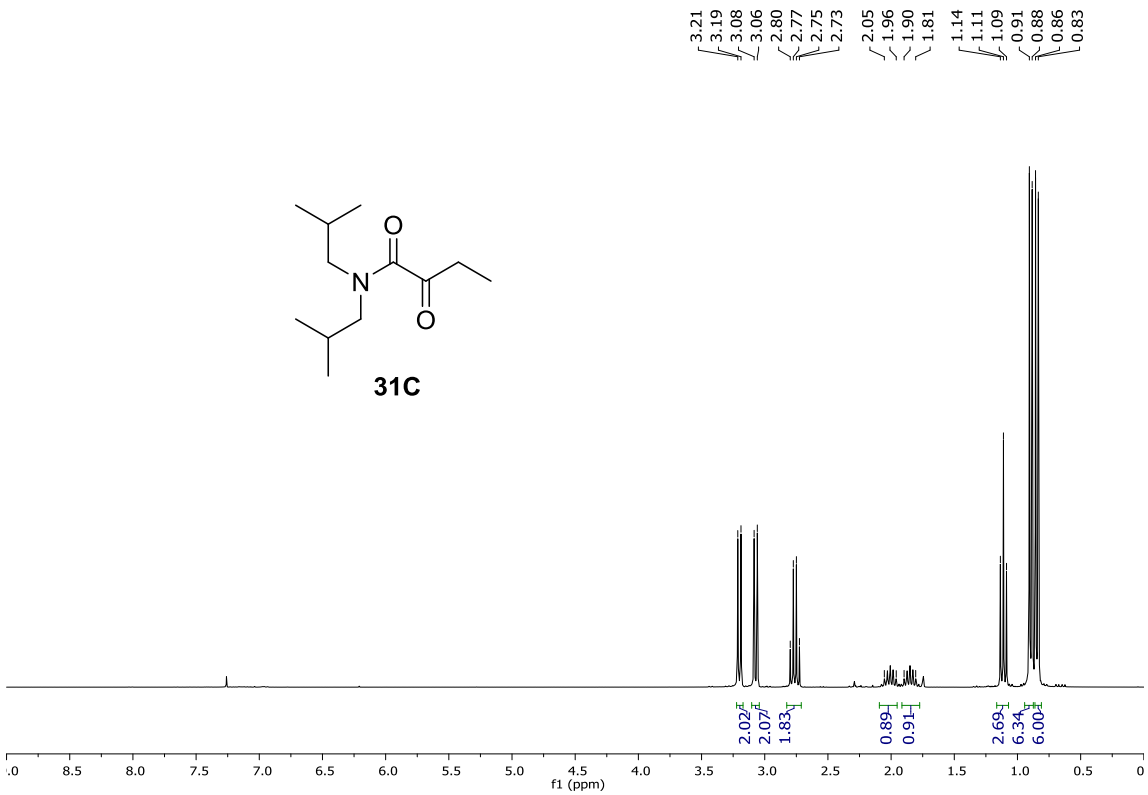

167.7
142.0
117.0
51.1
47.3
31.6
25.7
25.6
10.3
f1 (ppm)

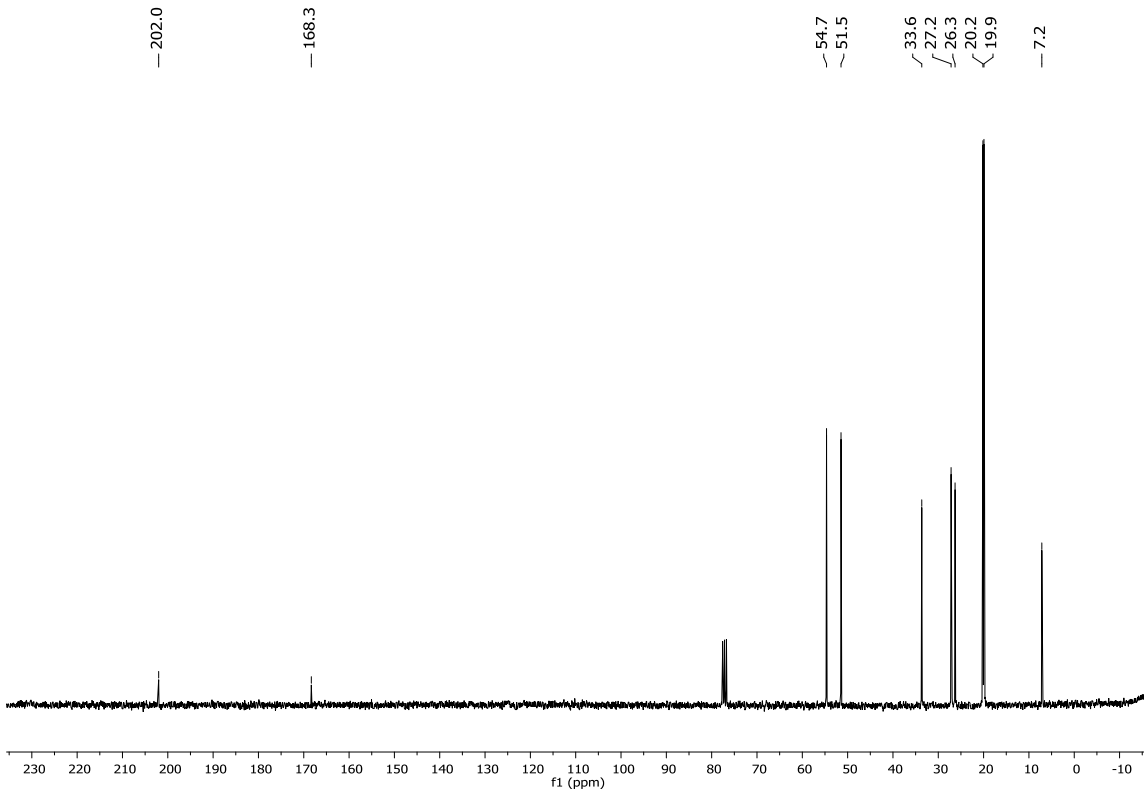

7.38
7.33
7.25
7.24
7.22
7.19
4.55
4.36
2.82
2.80
2.77
2.75
1.12
1.09
1.07
Bn2N
O
O
10.30
2.28
2.27
2.68
3.00
f1 (ppm)

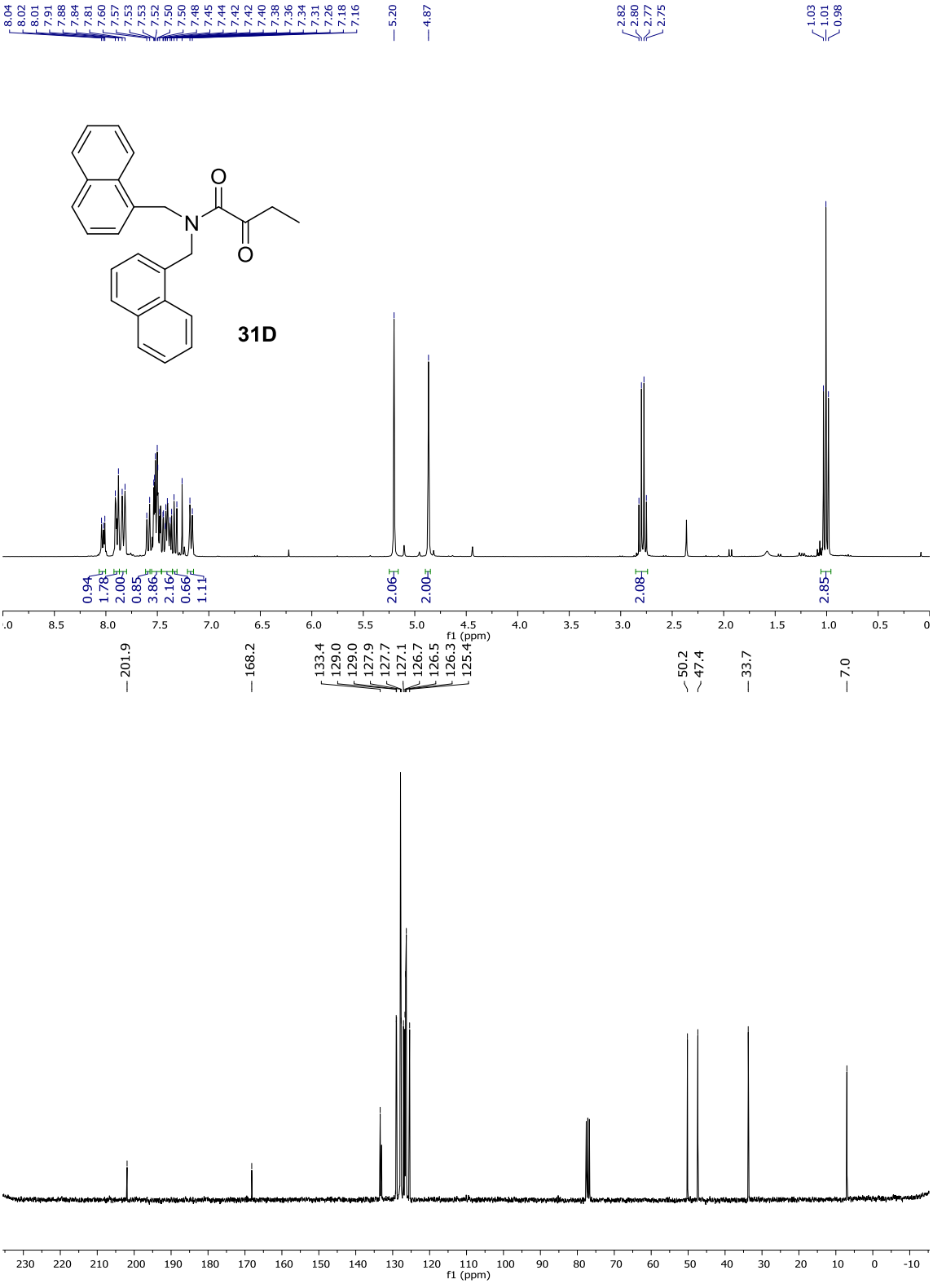
31A

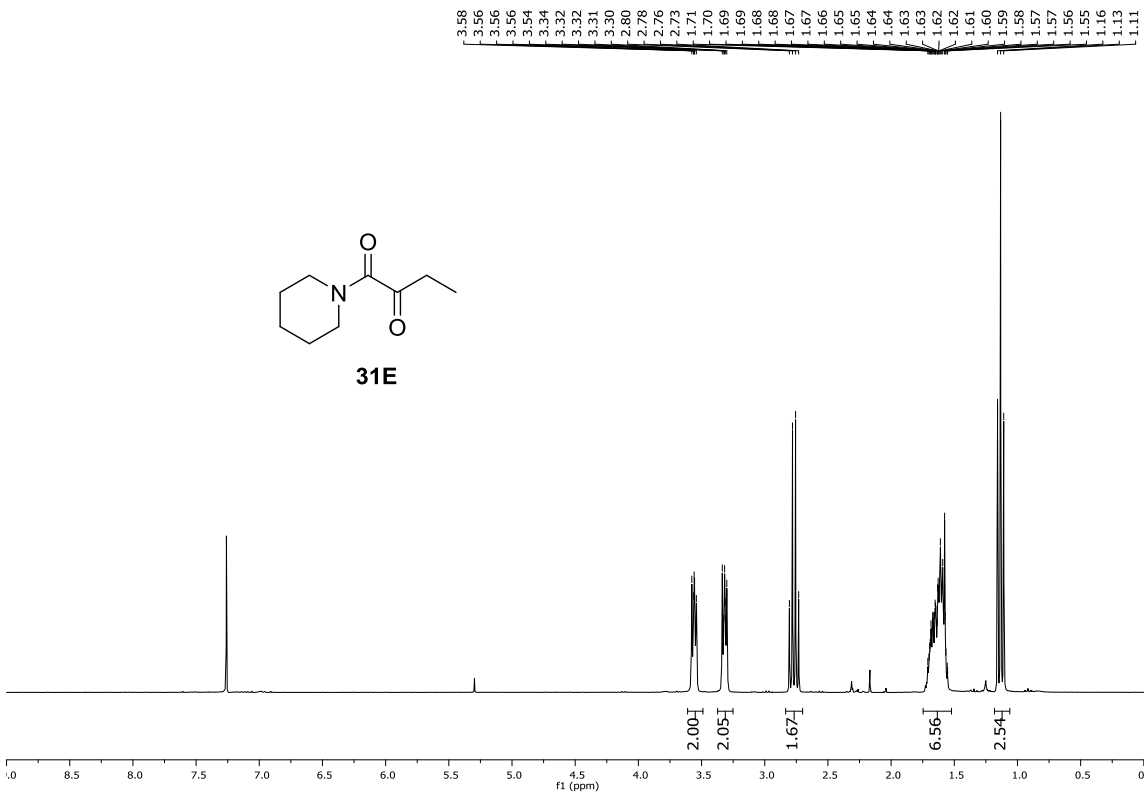

3.26
3.23
3.21
3.18
3.10
3.08
3.06
3.03
2.62
2.60
2.57
2.55
1.03
1.00
0.98
0.96
0.95
0.93
0.90
N
O
O
2.00
2.07
1.79
6.02
3.08
f1 (ppm)

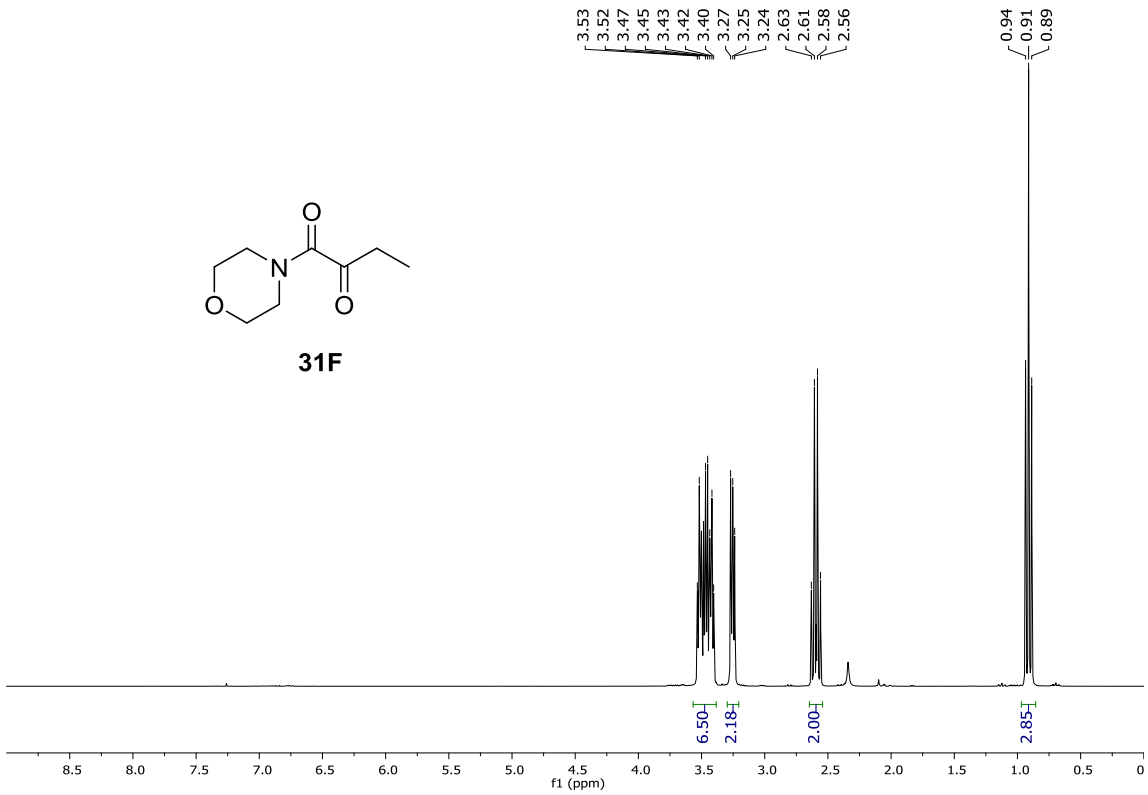
31B

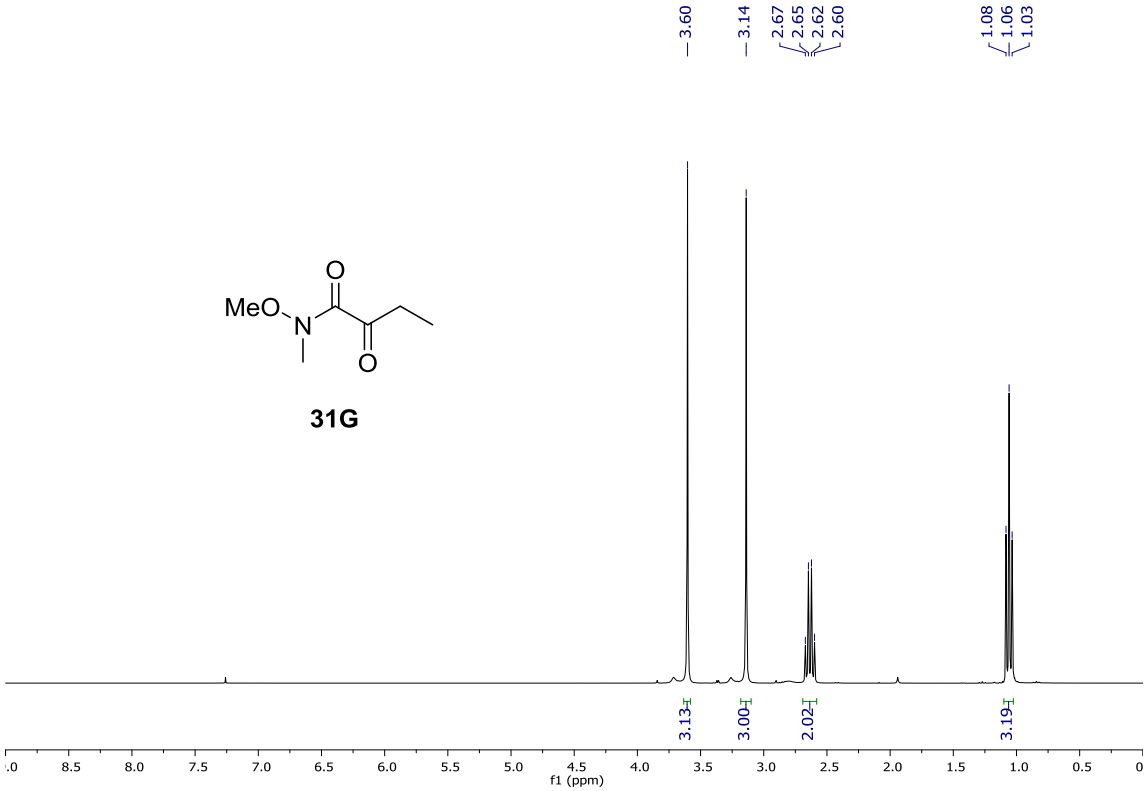

3.21
3.19
3.08
3.06
2.80
2.77
2.75
2.73
2.05
1.96
1.90
1.81
1.14
1.11
1.09
0.91
0.88
0.86
0.83
O
N
O
31C
2.02
2.07
1.83
0.89
0.91
2.69
6.34
6.00
f1 (ppm)


202.0
168.3
54.7
51.5
33.6
27.2
26.3
20.2
19.9
7.2
f1 (ppm)

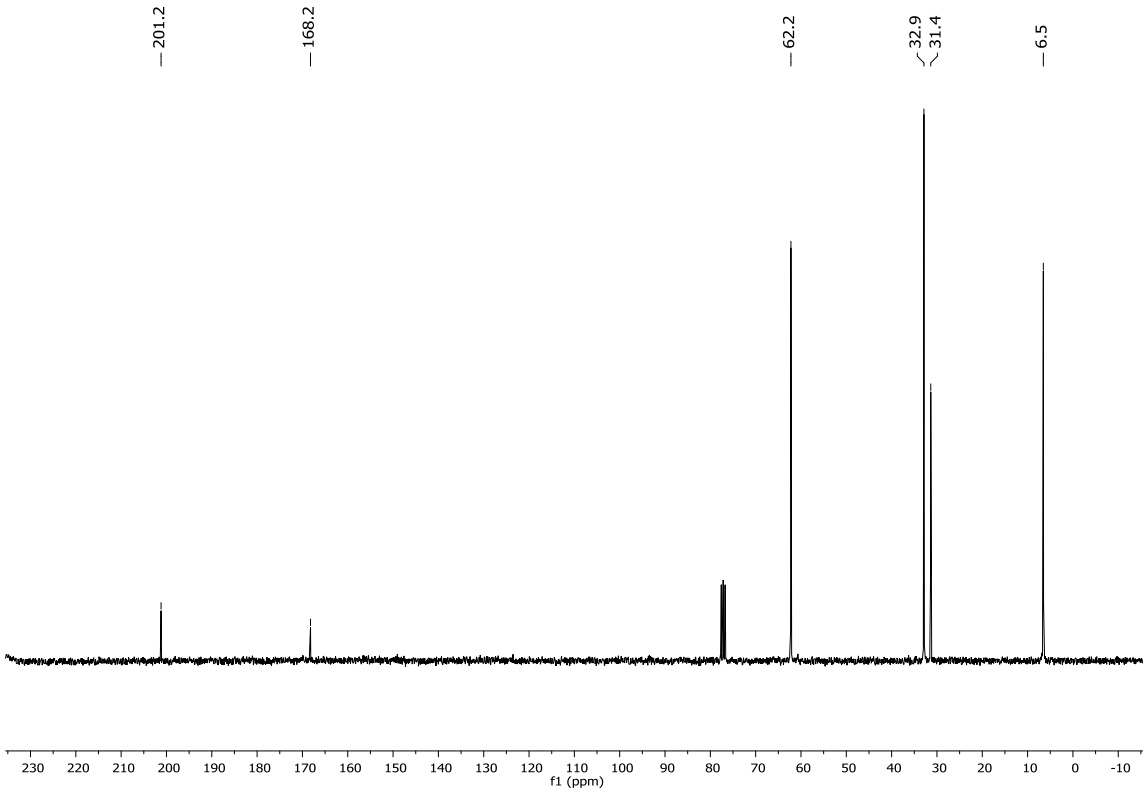

8.04
8.02
8.01
7.91
7.88
7.84
7.81
7.60
7.57
7.53
7.53
7.52
7.50
7.50
7.48
7.45
7.44
7.42
7.42
7.40
7.38
7.36
7.34
7.31
7.26
7.18
7.16
5.20
4.87
2.82
2.80
2.77
2.75
1.03
1.01
0.98
O
N
O
31D
0.94
1.78
2.00
0.85
3.86
2.16
0.66
1.11
2.06
2.00
2.08
2.85
f1 (ppm)
201.9
168.2
133.4
129.0
129.0
127.9
127.7
127.1
126.7
126.5
126.3
125.4
50.2
47.4
33.7
7.0
f1 (ppm)

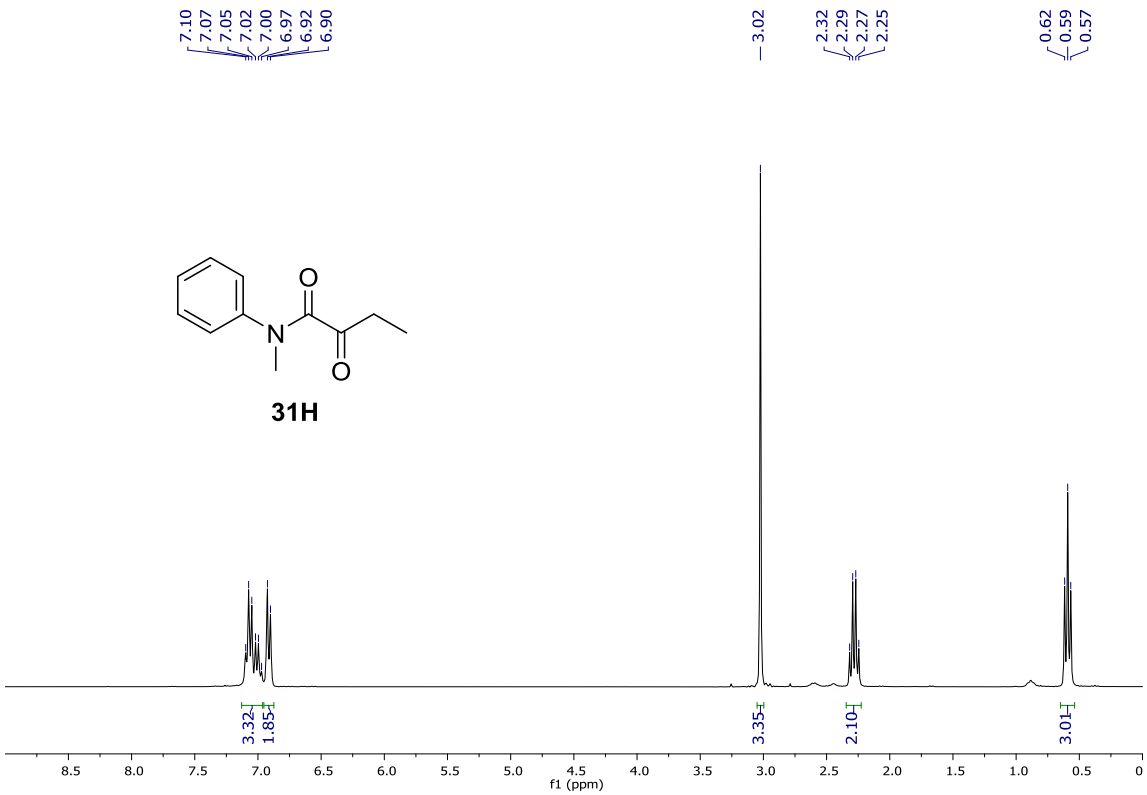

3.58
3.56
3.56
3.56
3.54
3.34
3.32
3.32
3.31
3.30
2.80
2.78
2.76
2.73
1.71
1.70
1.69
1.69
1.68
1.68
1.67
1.67
1.66
1.65
1.65
1.64
1.64
1.63
1.63
1.62
1.62
1.61
1.60
1.59
1.58
1.57
1.57
1.56
1.55
1.16
1.13
1.11
O
N
O
31E
2.00
2.05
1.67
6.56
2.54
f1 (ppm)

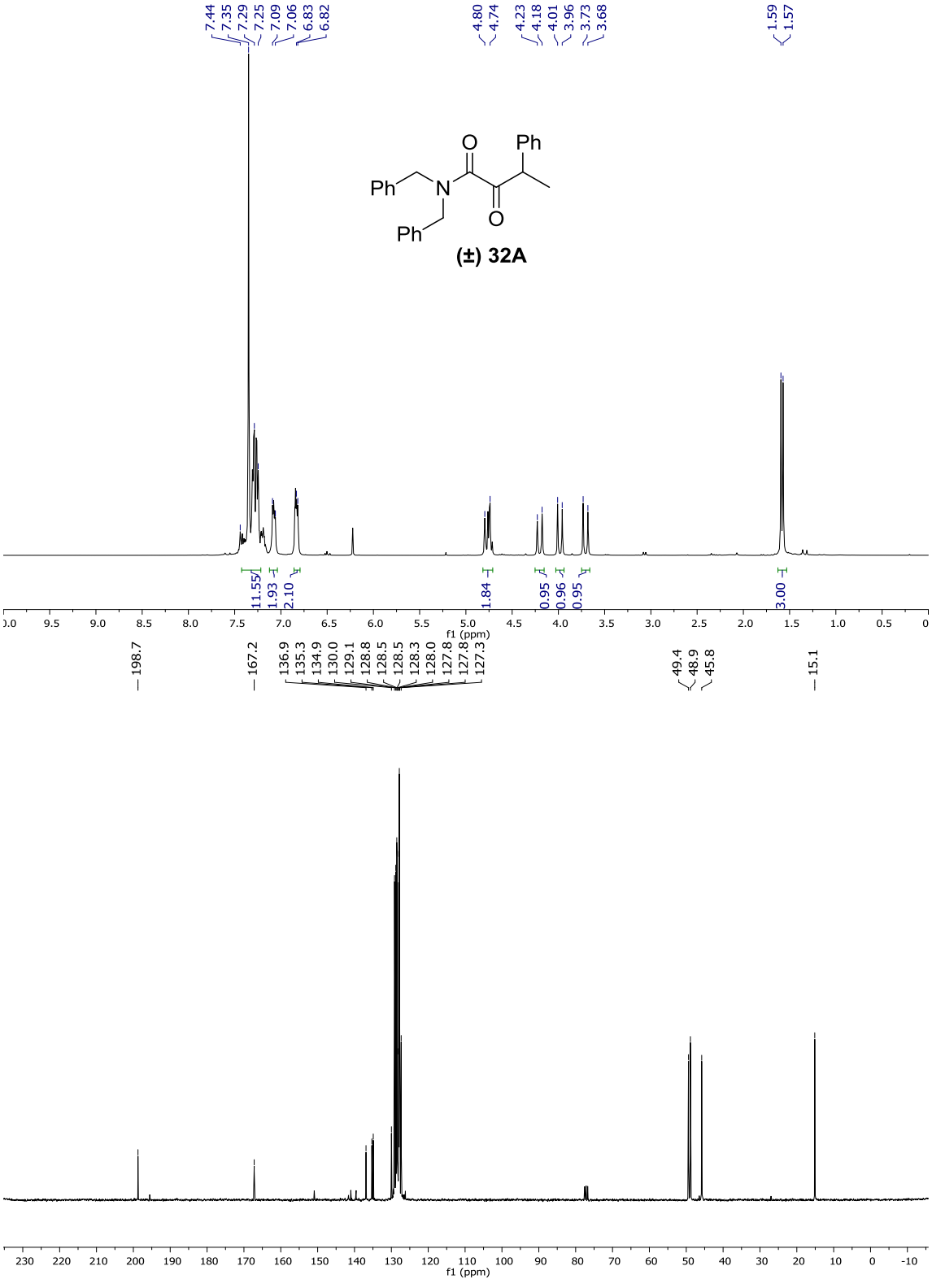

3.53
3.52
3.47
3.45
3.43
3.42
3.40
3.27
3.25
3.24
2.63
2.61
2.58
2.56
0.94
0.91
0.89
O
N
O
O
31F
6.50
2.18
2.00
2.85
f1 (ppm)

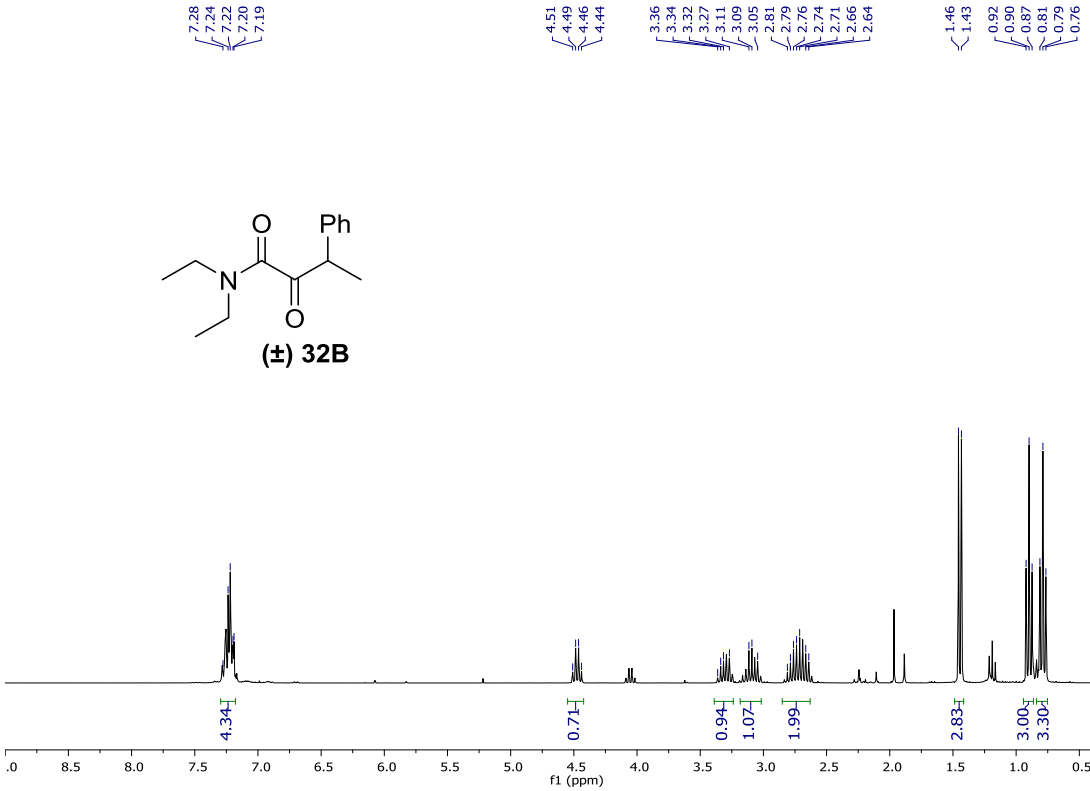

3.60
3.14
2.67
2.65
2.62
2.60
1.08
1.06
1.03
MeO
N
O
O
3.13
3.00
2.02
3.19
f1 (ppm)

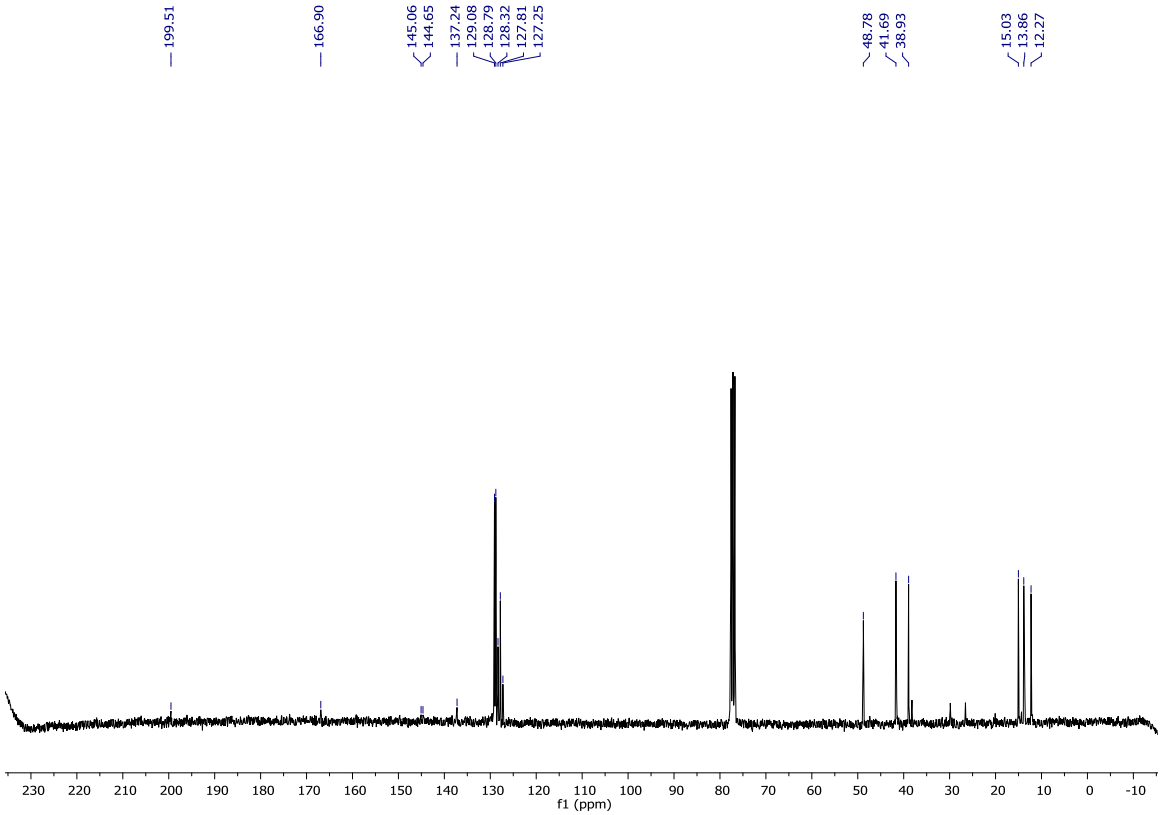
31G

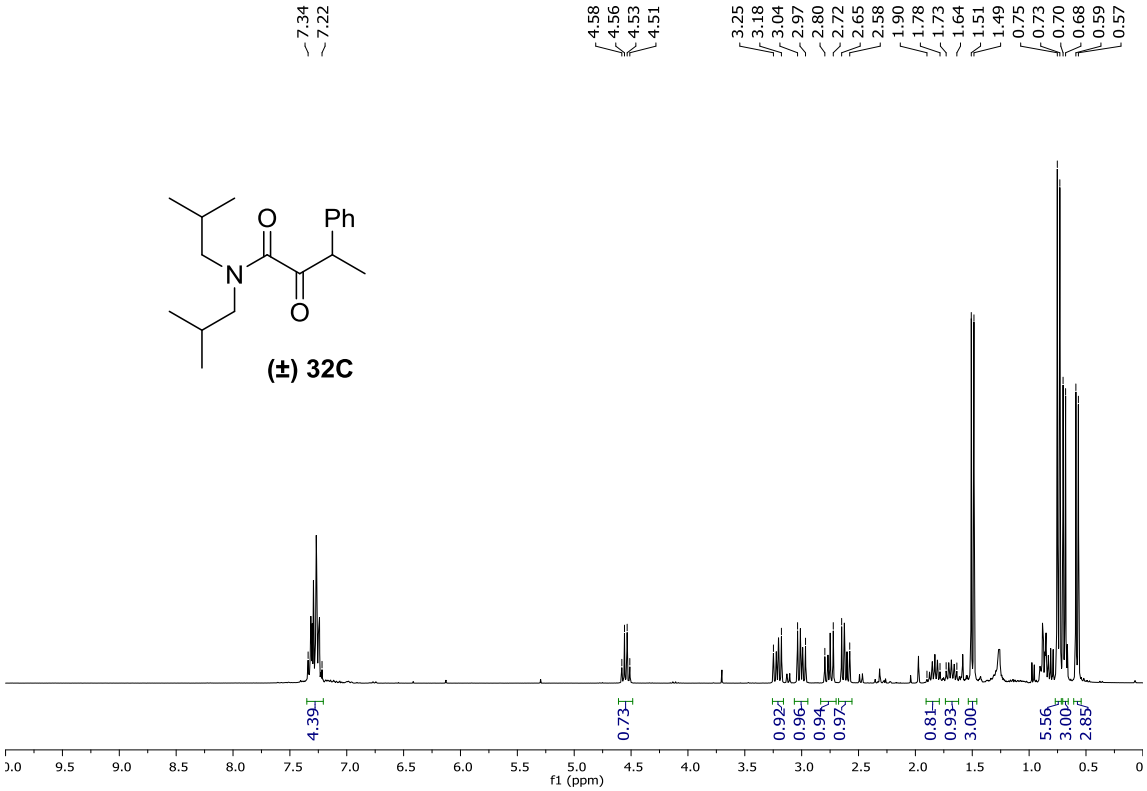

201.2
168.2
62.2
32.9
31.4
6.5
f1 (ppm)

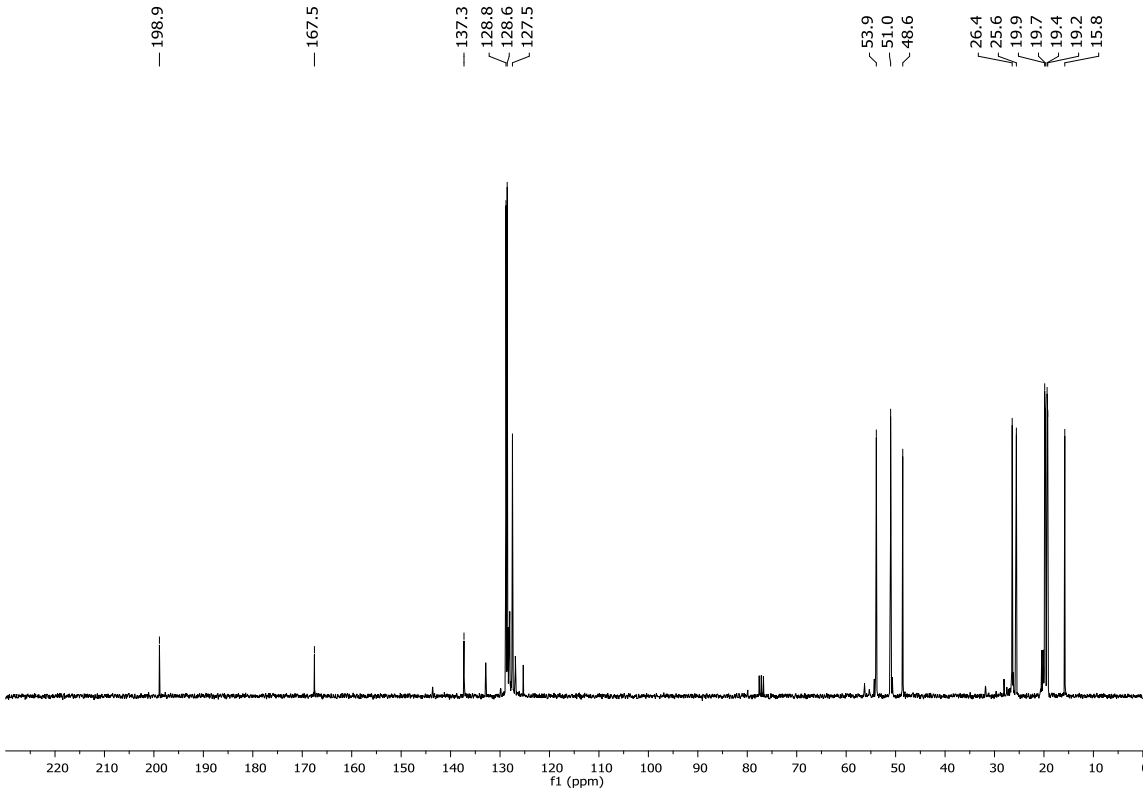

7.10
7.07
7.05
7.02
7.00
6.97
6.92
6.90
3.02
2.32
2.29
2.27
2.25
0.62
0.59
0.57
O
N
O
31H
3.32
1.85
3.35
2.10
3.01
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

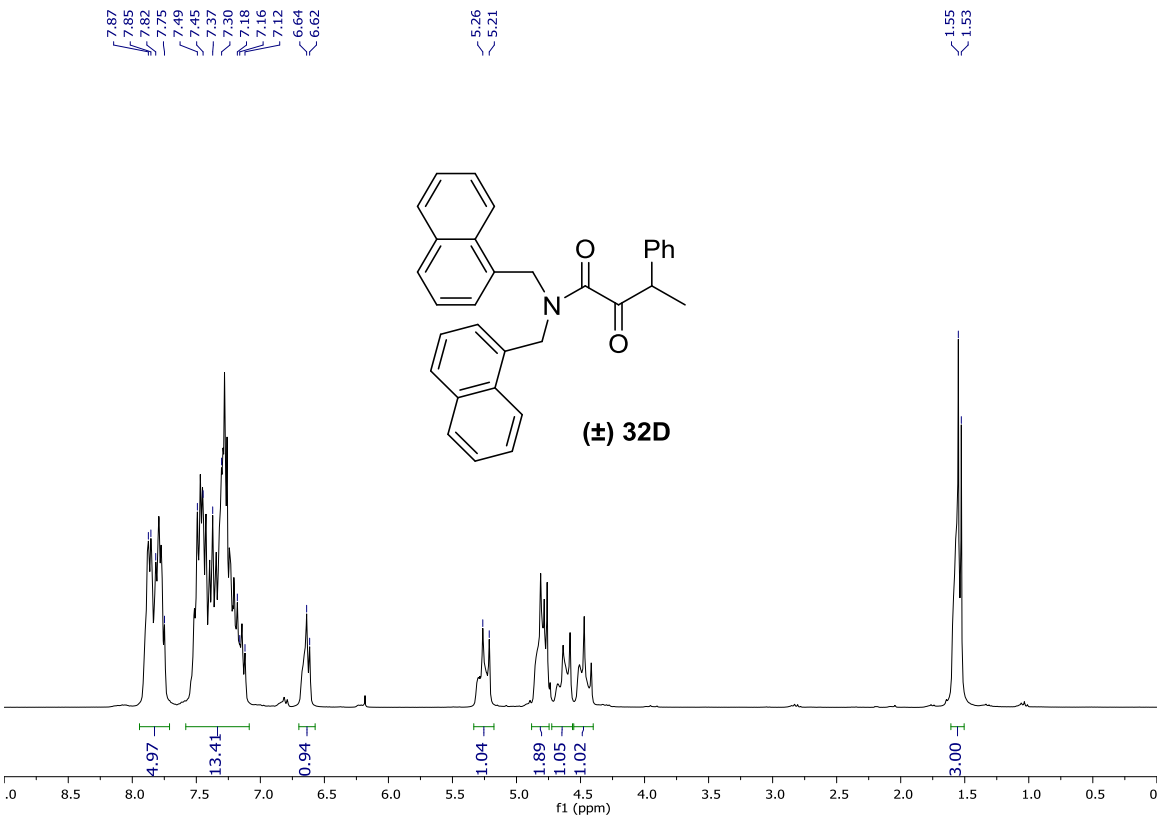

7.44
7.35
7.29
7.25
7.09
7.06
6.83
6.82
4.80
4.74
4.23
4.18
4.01
3.96
3.73
3.68
1.59
1.57
O
Ph
Ph
N
O
Ph
(±) 32A
11.55
1.93
2.10
1.84
0.95
0.96
0.95
3.00
f1 (ppm)
198.7
167.2
136.9
135.3
134.9
130.0
129.1
128.8
128.5
128.5
128.3
128.0
127.8
127.8
127.3
49.4
48.9
45.8
15.1
f1 (ppm)

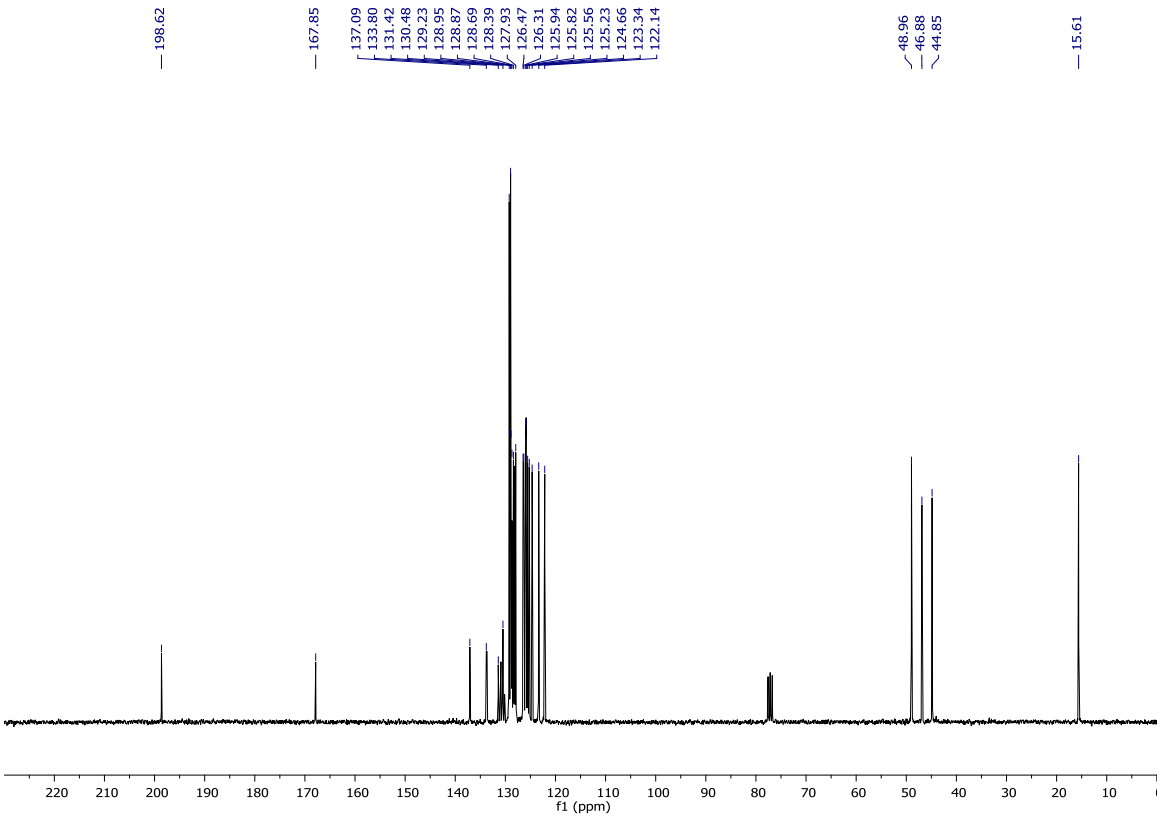

7.28
7.24
7.22
7.20
7.19
4.51
4.49
4.46
4.44
3.36
3.34
3.32
3.27
3.11
3.09
3.05
2.81
2.79
2.76
2.74
2.71
2.66
2.64
1.46
1.43
0.92
0.90
0.87
0.81
0.79
0.76
O
Ph
N
O
(±) 32B
4.34
0.71
0.94
1.07
1.99
2.83
3.00
3.30
f1 (ppm)

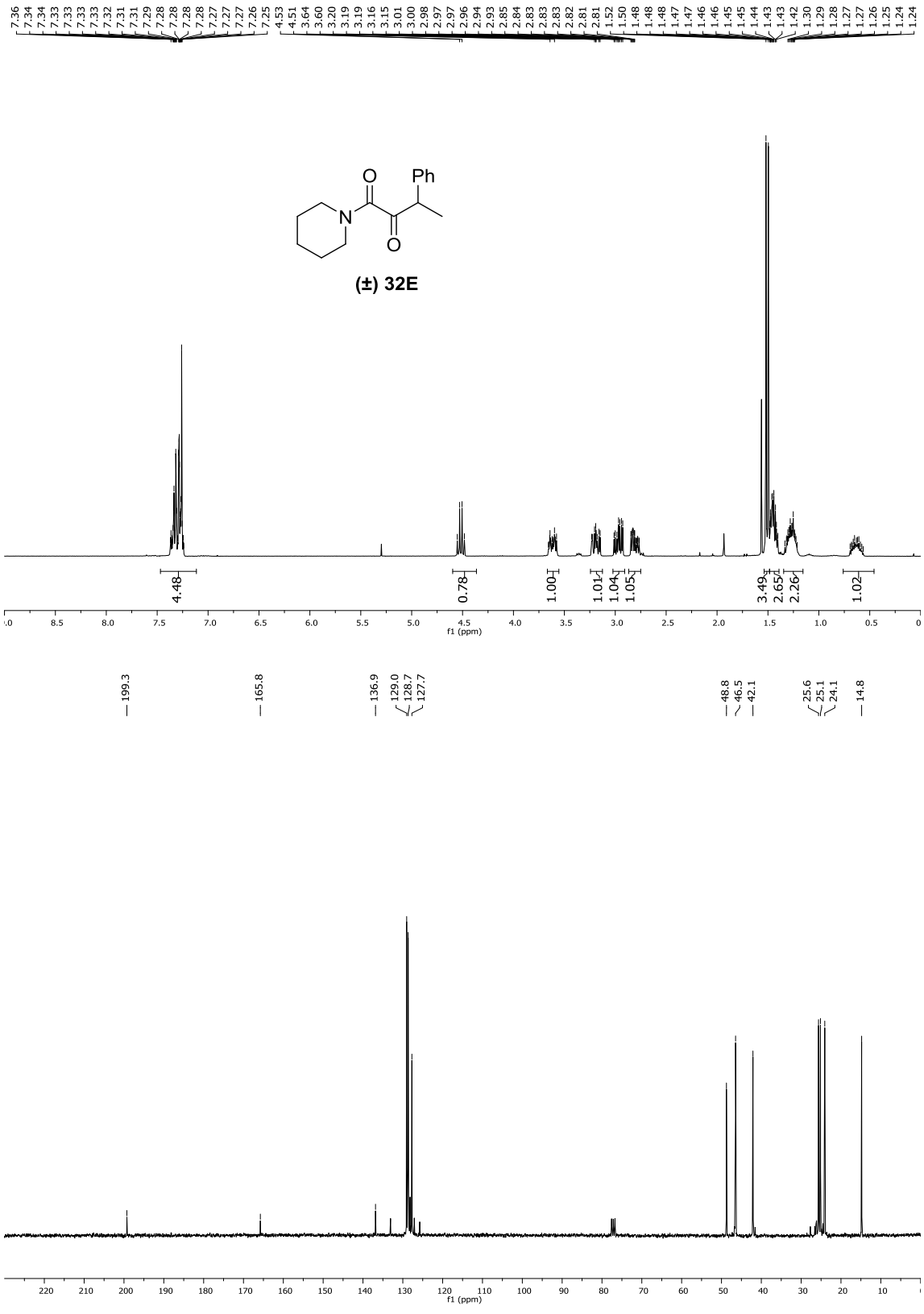

199.51
166.90
145.06
144.65
137.24
129.08
128.79
128.32
127.81
127.25
48.78
41.69
38.93
15.03
13.86
12.27
f1 (ppm)

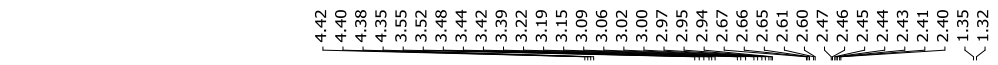

7.34
7.22
4.58
4.56
4.53
4.51
3.25
3.18
3.04
2.97
2.80
2.72
2.65
2.58
1.90
1.78
1.73
1.64
1.51
1.49
0.75
0.73
0.70
0.68
0.59
0.57
O
Ph
N
O
(±) 32C
4.39
0.73
0.92
0.96
0.94
0.97
0.81
0.93
3.00
5.56
3.00
2.85
f1 (ppm)

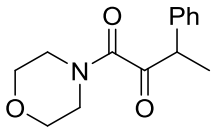

198.9
167.5
137.3
128.8
128.6
127.5
53.9
51.0
48.6
26.4
25.6
19.9
19.7
19.4
19.2
15.8
f1 (ppm)


7.87
7.85
7.82
7.75
7.49
7.45
7.37
7.30
7.18
7.16
7.12
6.64
6.62
5.26
5.21
1.55
1.53
O
Ph
N
O
(±) 32D
4.97
13.41
0.94
1.04
1.89
1.05
1.02
3.00
f1 (ppm)


198.62
167.85
137.09
133.80
131.42
130.48
129.23
128.95
128.87
128.69
128.39
127.93
126.47
126.31
125.94
125.82
125.56
125.23
124.66
123.34
122.14
48.96
46.88
44.85
15.61
f1 (ppm)

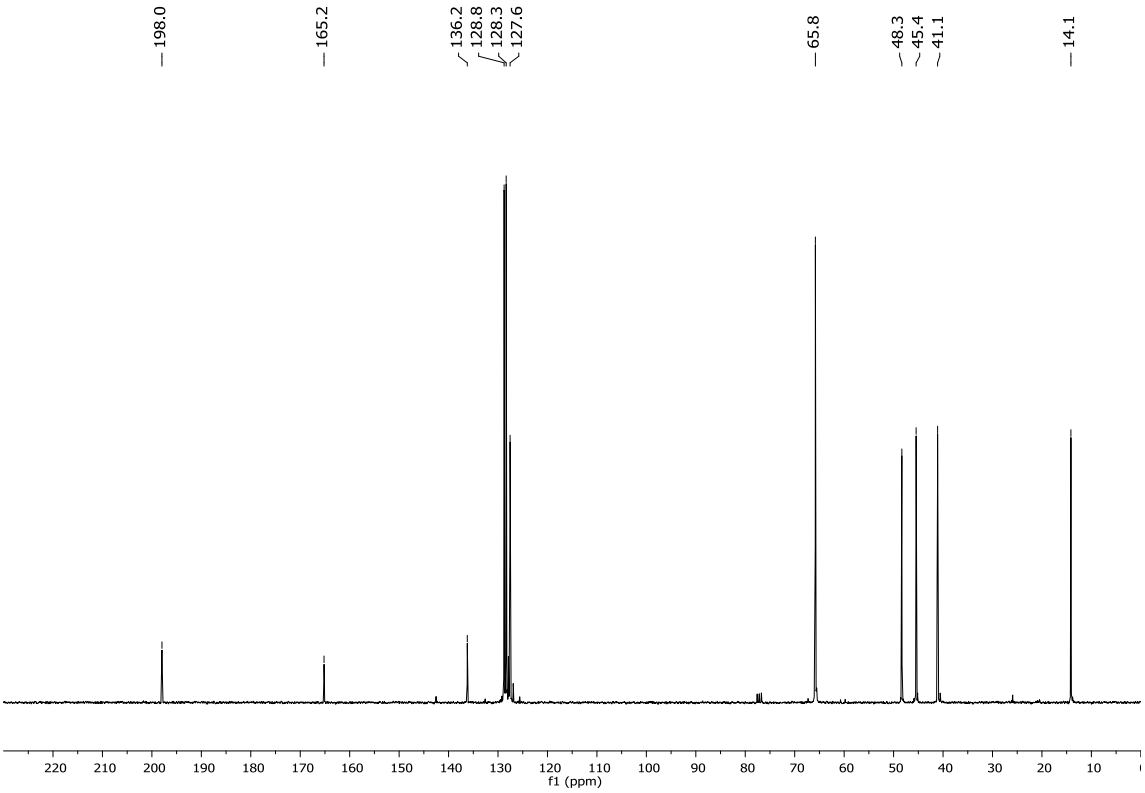

7.36 7.34 7.34 7.33 7.33 7.33 7.32 7.31 7.31 7.29 7.28 7.28 7.28 7.27 7.27 7.27 7.26 7.25
4.53 4.51 3.64 3.60 3.20 3.19 3.19 3.16 3.15 3.01 3.00 2.98 2.97 2.97 2.96 2.94 2.93 2.85 2.84 2.83 2.83 2.83 2.82 2.81 2.81 1.52 1.50 1.48 1.48 1.48 1.47 1.47 1.46 1.46 1.45 1.45 1.44 1.43 1.43 1.42 1.30 1.29 1.28 1.27 1.27 1.26 1.25 1.24 1.24
O
Ph
N
O
(±) 32E
4.48
0.78
1.00
1.01
1.04
1.05
3.49
2.65
2.26
1.02
f1 (ppm)
199.3
165.8
136.9
129.0
128.7
127.7
48.8
46.5
42.1
25.6
25.1
24.1
14.8
f1 (ppm)

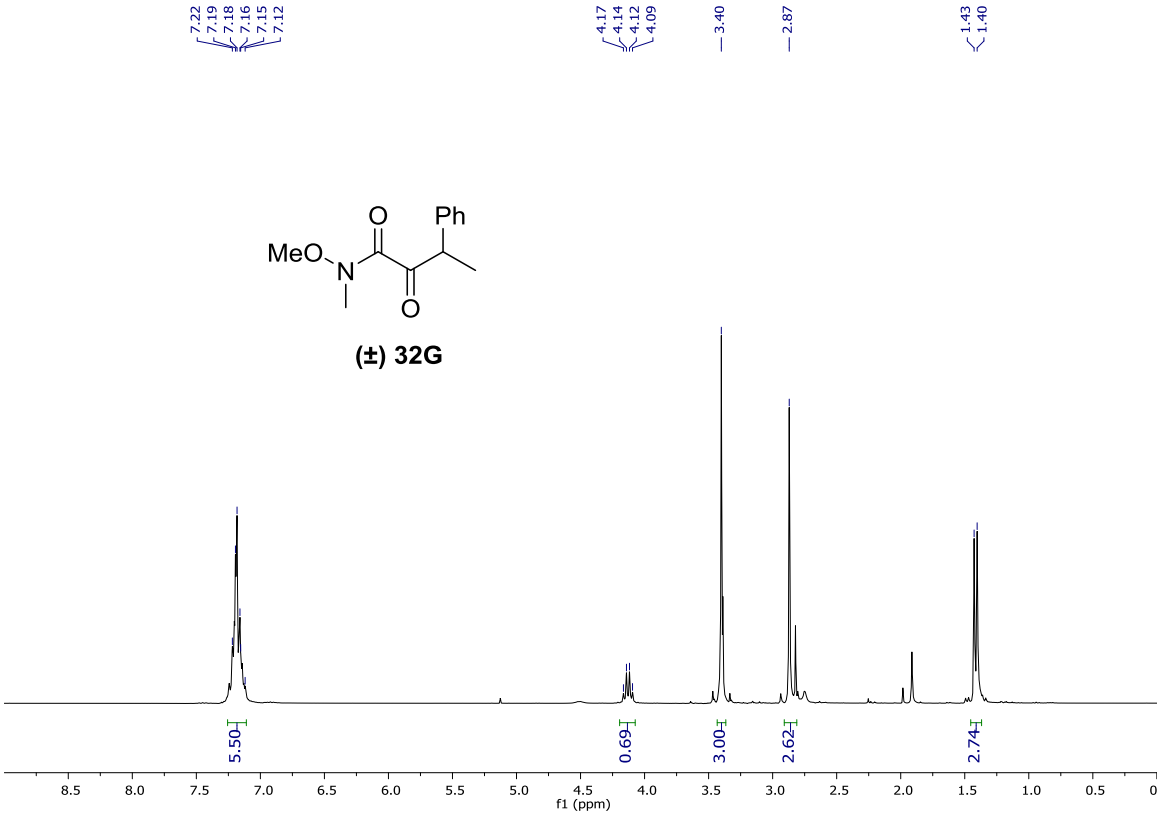

4.42
4.40
4.38
4.35
3.55
3.52
3.48
3.44
3.42
3.39
3.22
3.19
3.15
3.09
3.06
3.02
3.00
2.97
2.95
2.94
2.67
2.66
2.65
2.61
2.60
2.47
2.46
2.45
2.44
2.43
2.41
2.40
1.35
1.32


O
Ph
N
O
O

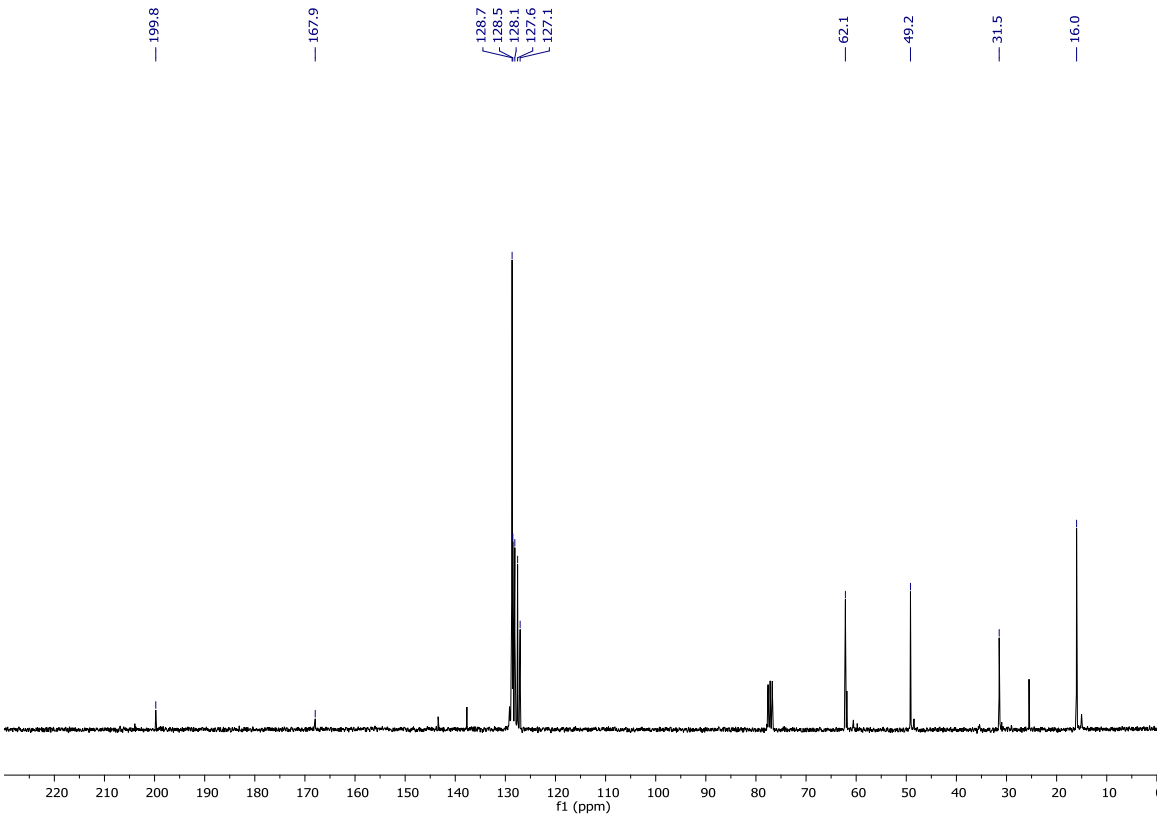
(±) 32F

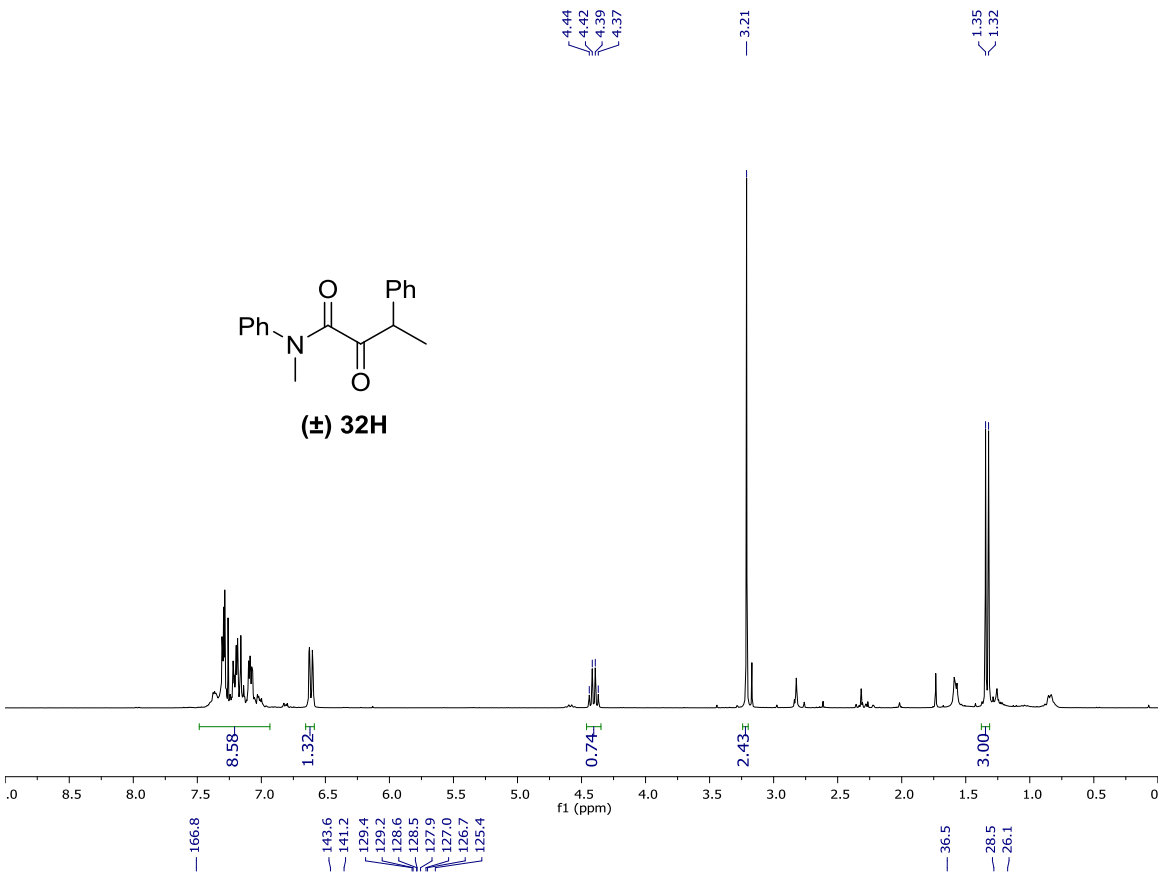
4.49
0.84
1.05
1.08
1.04
1.99
1.14
1.11
1.07
3.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

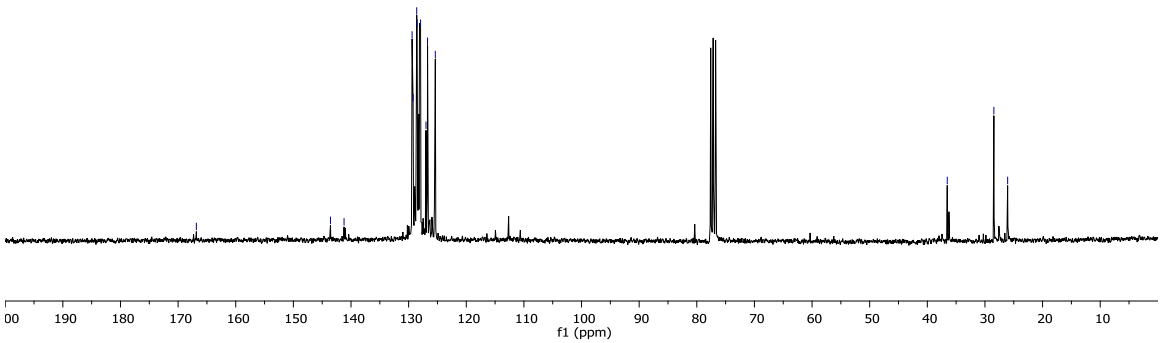

198.0
165.2
136.2
128.8
128.3
127.6
65.8
48.3
45.4
41.1
14.1
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

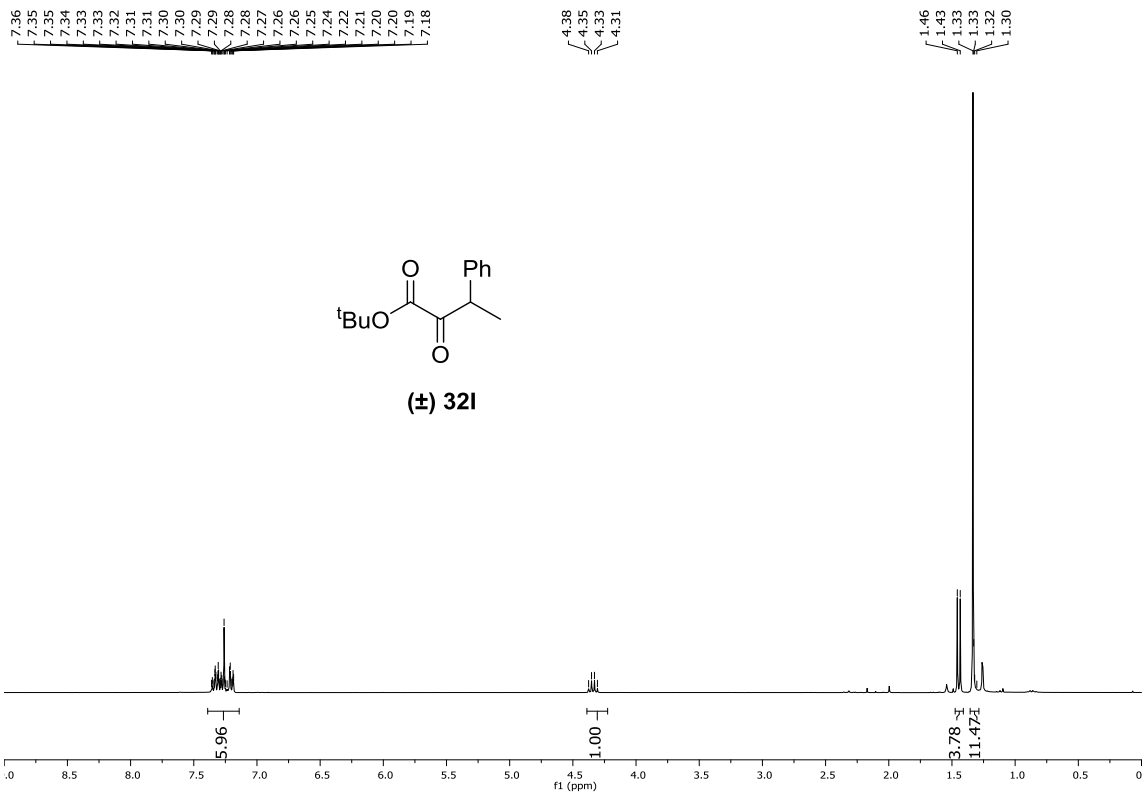

7.22
7.19
7.18
7.16
7.15
7.12
4.17
4.14
4.12
4.09
3.40
2.87
1.43
1.40
MeO
N
O
O
Ph
5.50
0.69
3.00
2.62
2.74
f1 (ppm)

(±) 32G


199.8
167.9
128.7
128.5
128.1
127.6
127.1
62.1
49.2
31.5
16.0
f1 (ppm)

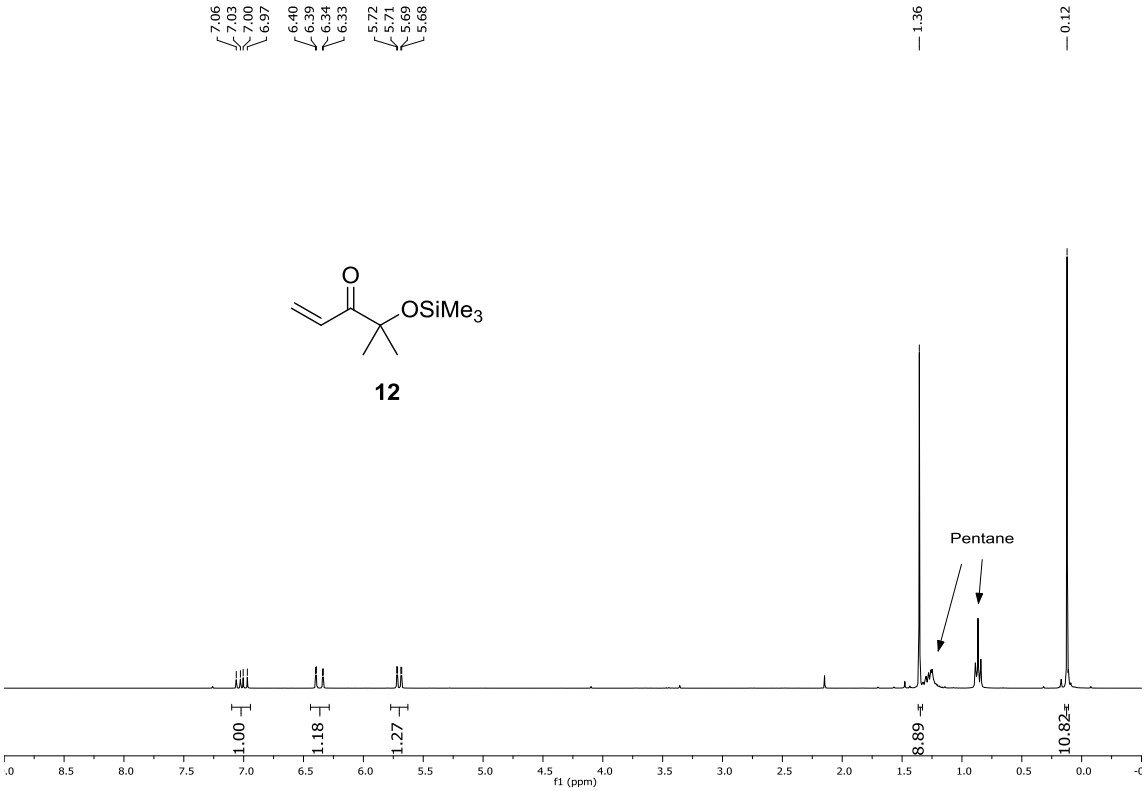

4.44
4.42
4.39
4.37
3.21
1.35
1.32
O
Ph
Ph
N
O
(±) 32H
8.58
1.32
0.74
2.43
3.00
f1 (ppm)
166.8
143.6
141.2
129.4
129.2
128.6
128.5
127.9
127.0
126.7
125.4
36.5
28.5
26.1

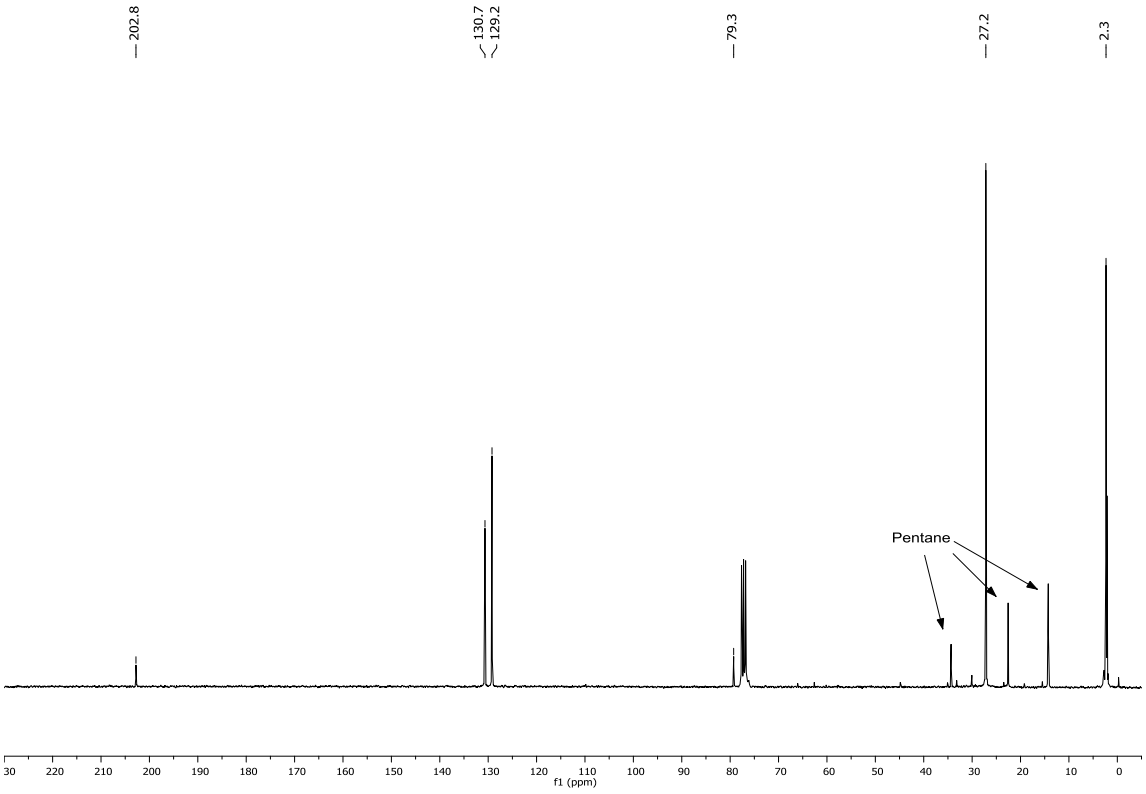

f1 (ppm)

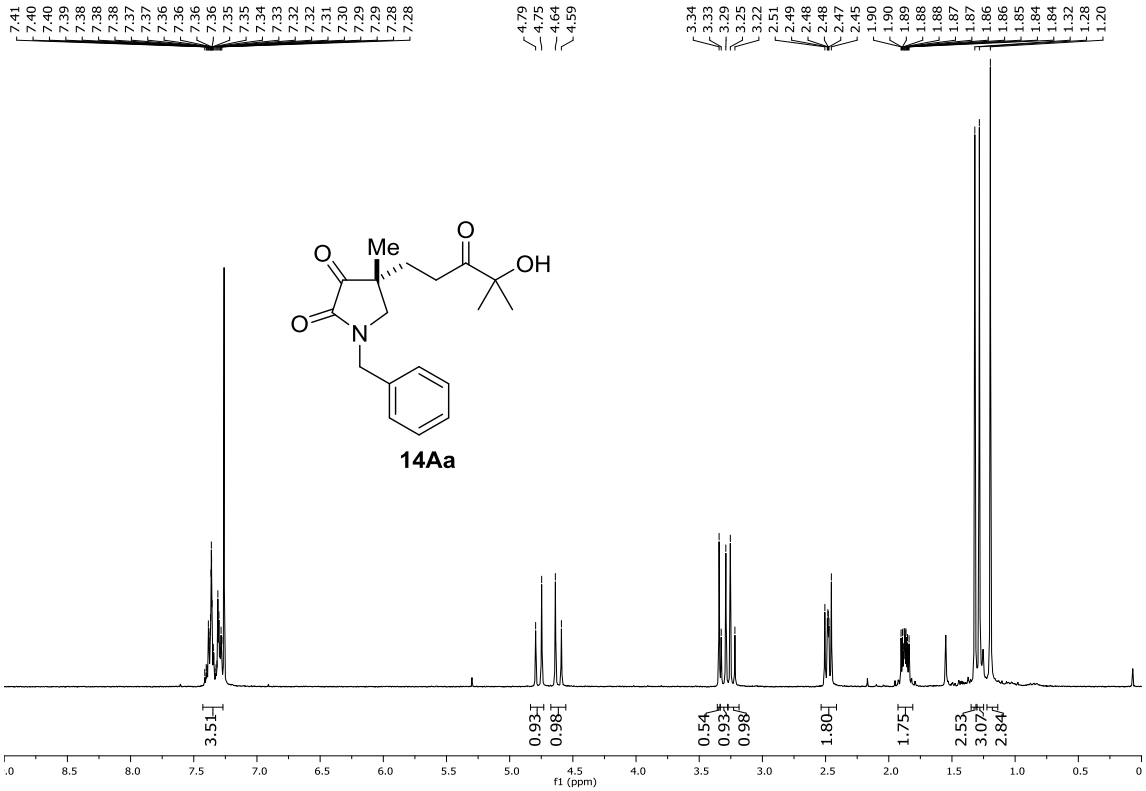

7.36
7.35
7.35
7.34
7.33
7.33
7.32
7.31
7.31
7.30
7.30
7.29
7.29
7.28
7.28
7.27
7.26
7.26
7.25
7.24
7.22
7.21
7.20
7.20
7.19
7.18
4.38
4.35
4.33
4.31
1.46
1.43
1.33
1.33
1.32
1.30
O
Ph
tBuO
O
5.96
1.00
3.78
11.47
f1 (ppm)

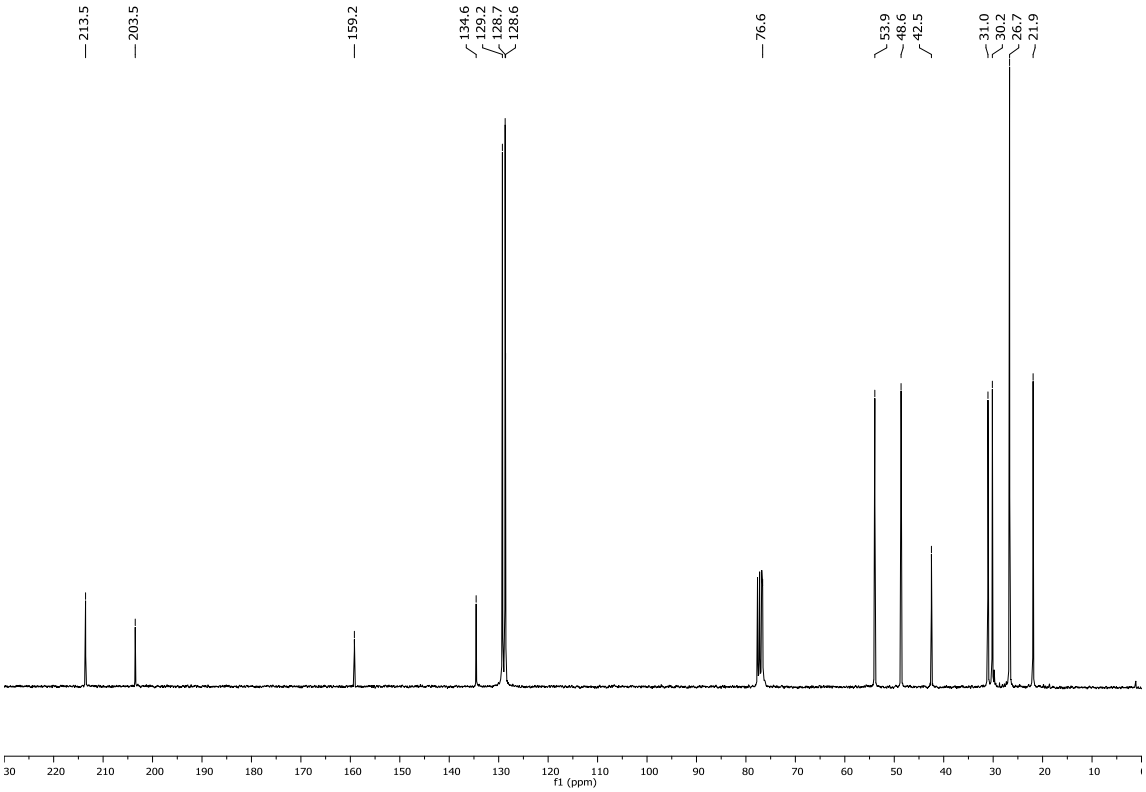
(±) 32l

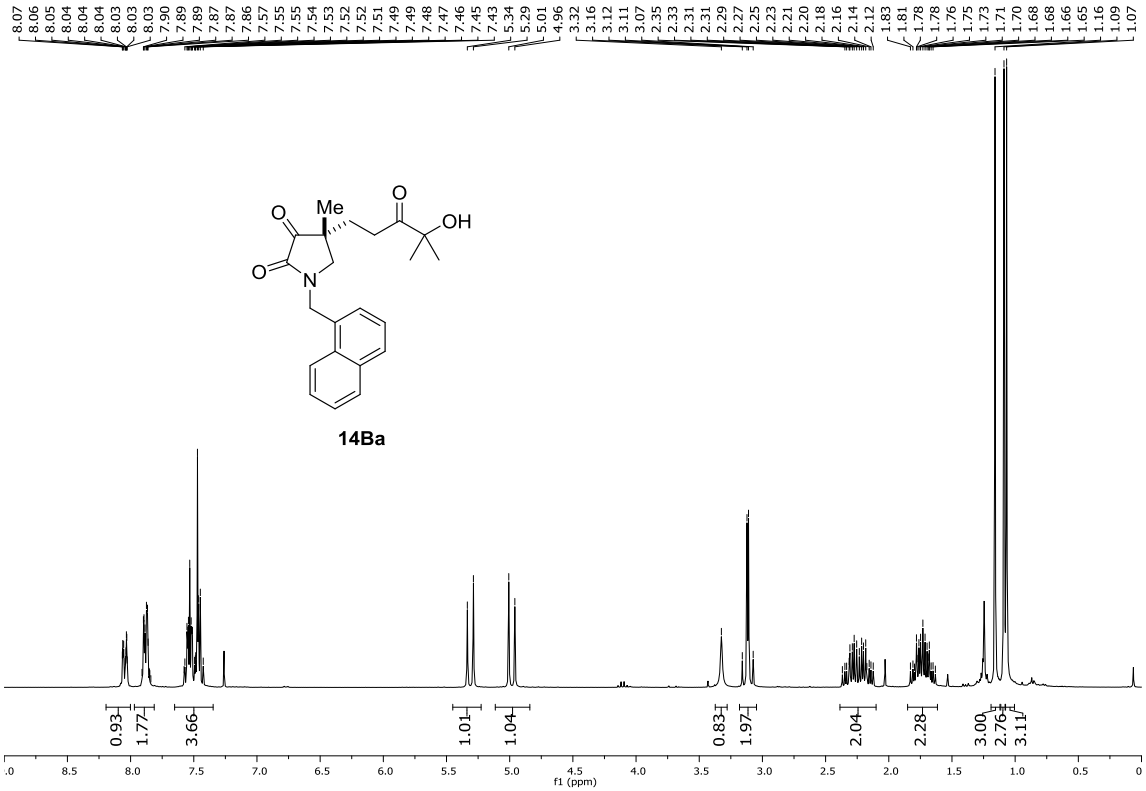

8.41
7.59
7.53
7.47
7.42
7.20
7.10
7.09
7.05
6.64
6.61
4.88
4.83
4.68
4.66
4.63
4.61
4.45
4.40
4.32
4.27
4.18
4.13
1.50
1.47
N
N
N
O
O
Ph
(±) 32J
1.46
1.09
0.97
5.61
2.75
0.81
1.03
0.92
1.02
1.03
1.22
3.00
f1 (ppm)
198.81
167.50
155.69
149.28
136.81
136.70
129.11
128.82
128.66
128.26
127.69
127.12
122.55
122.28
121.62
121.45
52.58
49.85
48.85
15.64
f1 (ppm)

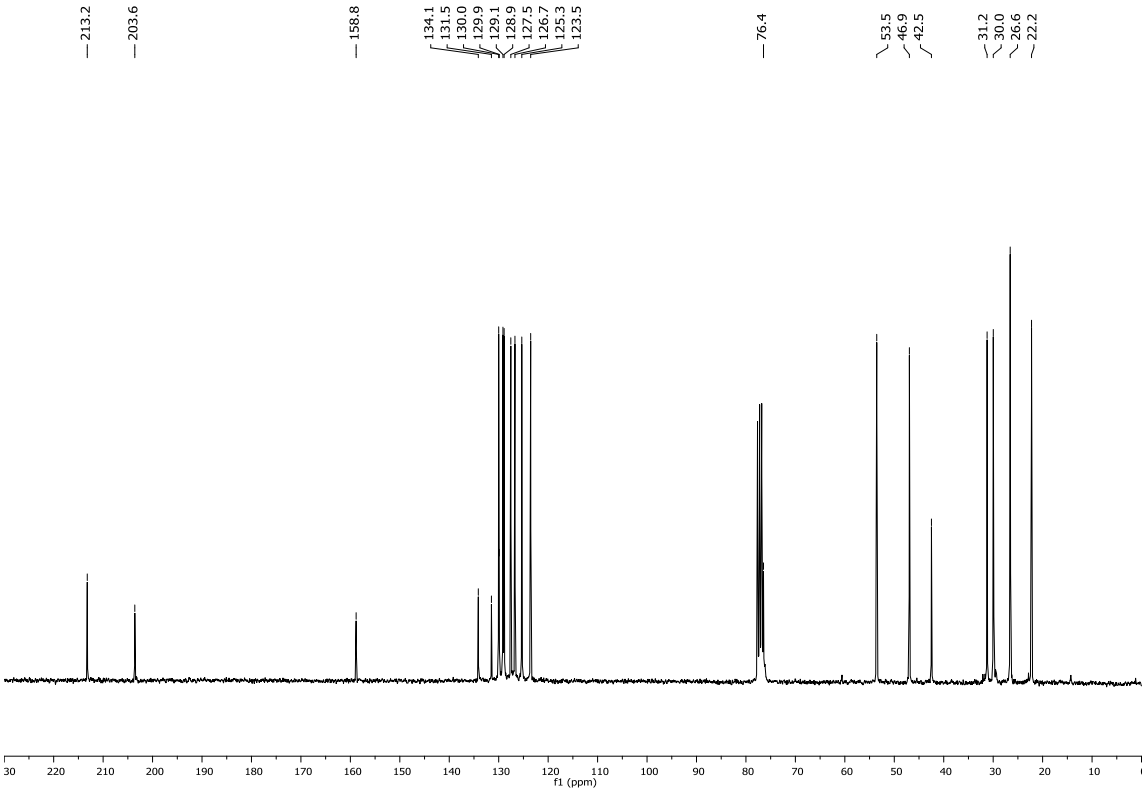

7.06
7.03
7.00
6.97
6.40
6.39
6.34
6.33
5.72
5.71
5.69
5.68
1.36
0.12
O
OSiMe3
12
Pentane
1.00
1.18
1.27
8.89
10.82
f1 (ppm)

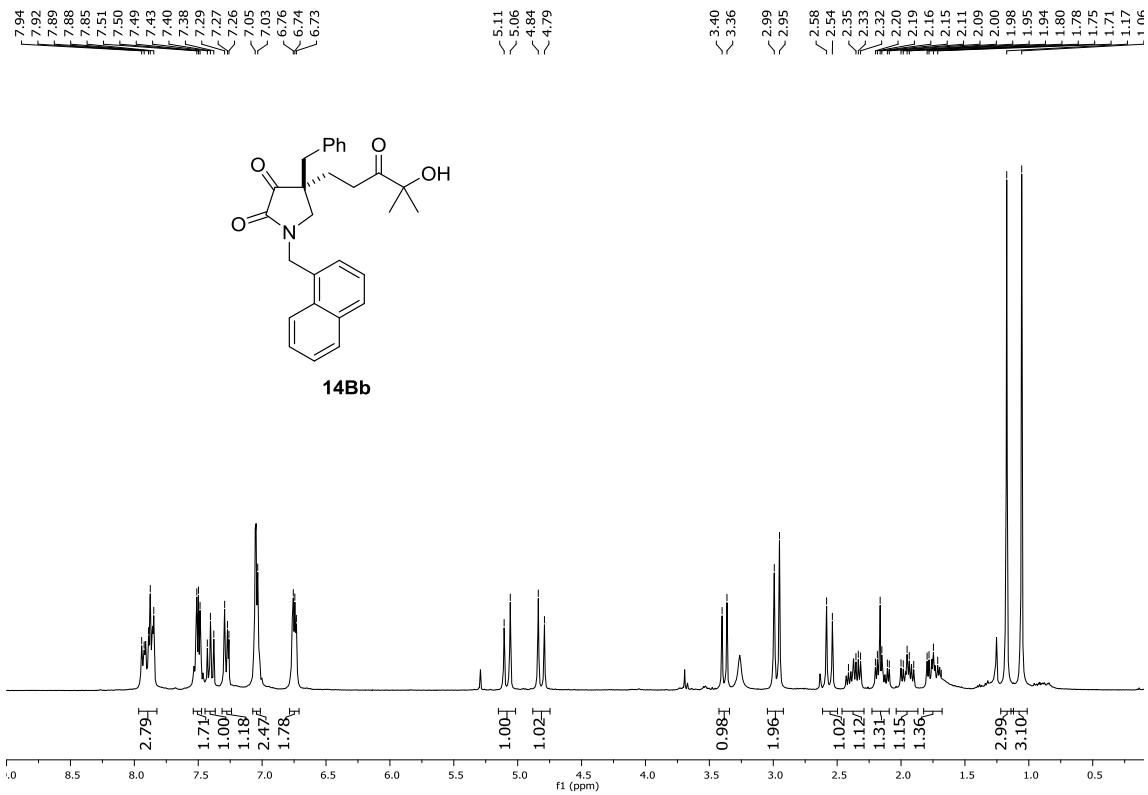

202.8
130.7
129.2
79.3
27.2
2.3
Pentane
f1 (ppm)

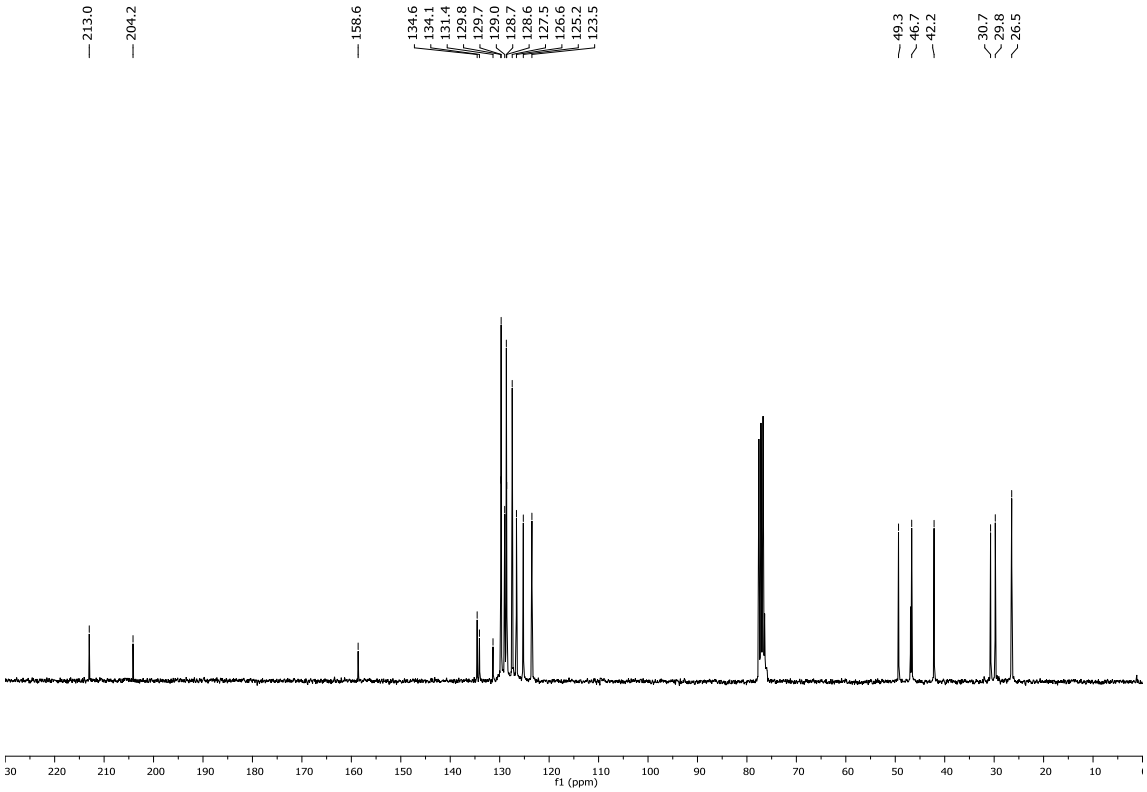

7.41 7.40 7.40 7.39 7.38 7.38 7.38 7.37 7.37 7.36 7.36 7.36 7.35 7.35 7.34 7.33 7.32 7.32 7.31 7.30 7.29 7.29 7.28 7.28
4.79 4.75 4.64 4.59
3.34 3.33 3.29 3.25 3.22 2.51 2.49 2.48 2.48 2.47 2.45 1.90 1.90 1.89 1.88 1.88 1.87 1.87 1.86 1.86 1.85 1.84 1.84 1.32 1.28 1.20
O
Me
O
OH
O
N
14Aa
3.51
0.93
0.98
0.54
0.93
0.98
1.80
1.75
2.53
3.07
2.84
f1 (ppm)

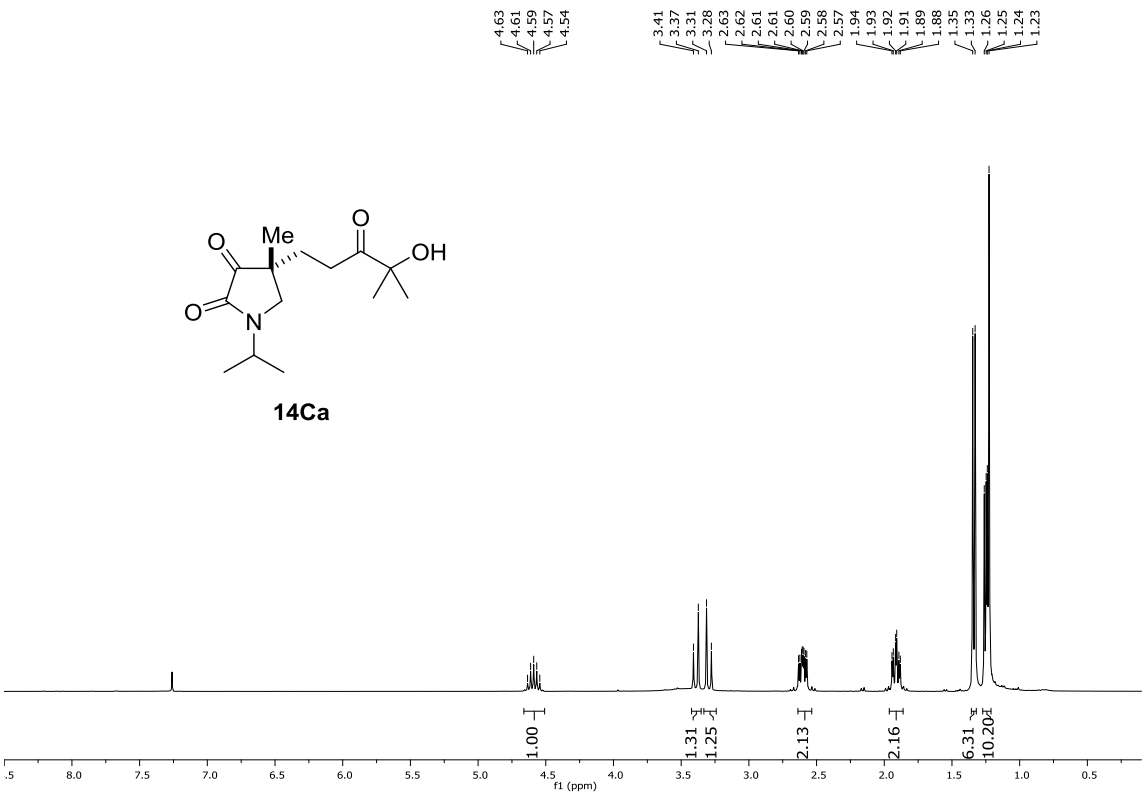

213.5
203.5
159.2
134.6
129.2
128.7
128.6
76.6
53.9
48.6
42.5
31.0
30.2
26.7
21.9
f1 (ppm)

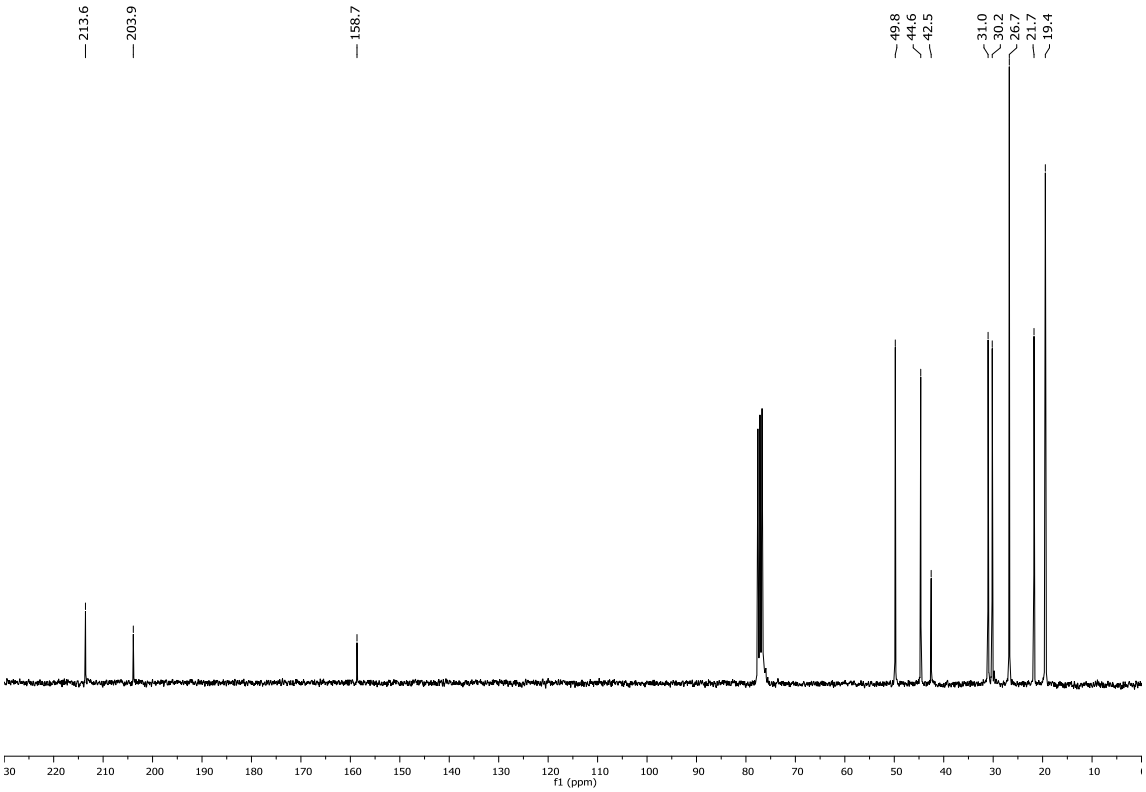

8.07 8.06 8.05 8.04 8.04 8.04 8.03 8.03 8.03 7.90 7.89 7.89 7.87 7.87 7.86 7.57 7.55 7.55 7.54 7.53 7.52 7.52 7.51 7.49 7.49 7.48 7.47 7.46 7.45 7.43 5.34 5.29 5.01 4.96 3.32 3.16 3.12 3.11 3.07 2.35 2.33 2.31 2.31 2.29 2.27 2.25 2.23 2.21 2.20 2.18 2.16 2.14 2.12 1.83 1.81 1.78 1.78 1.76 1.75 1.73 1.71 1.70 1.68 1.68 1.66 1.65 1.16 1.09 1.07
Me
O
O
O
OH
N
14Ba
0.93 1.77 3.66 1.01 1.04 0.83 1.97 2.04 2.28 3.00 2.76 3.11
f1 (ppm)

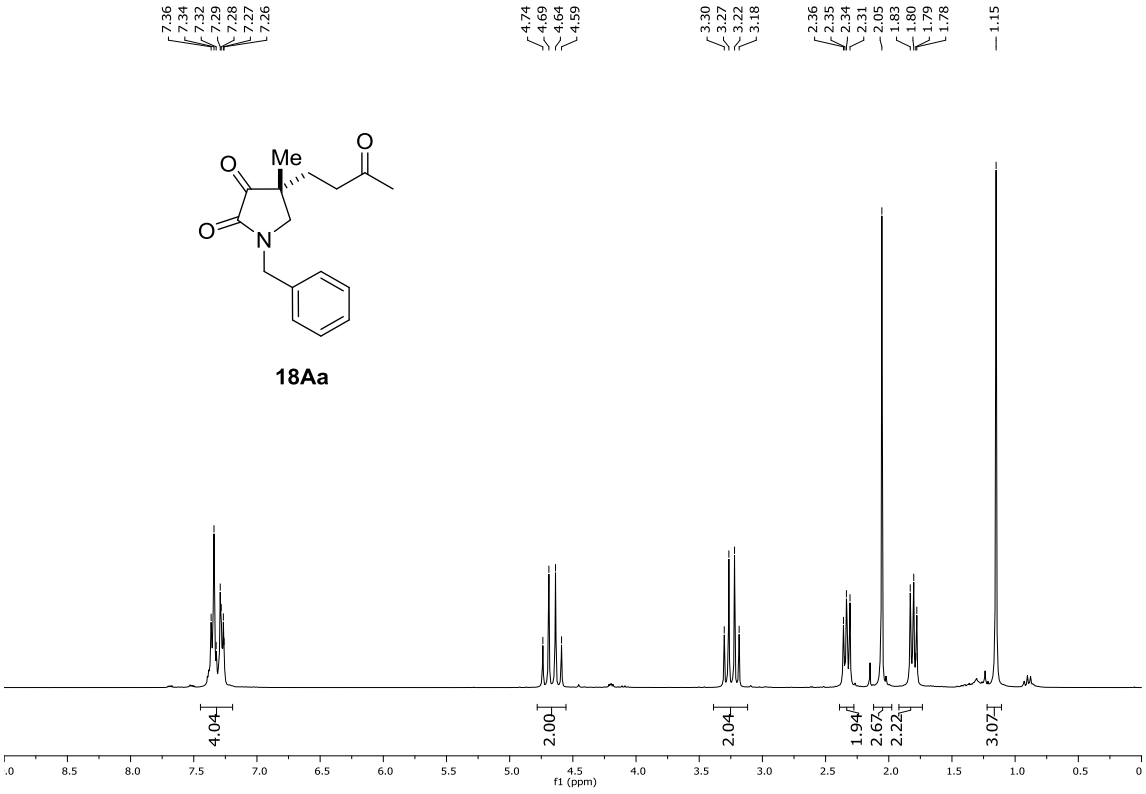

213.2 203.6 158.8 134.1 131.5 130.0 129.9 129.1 128.9 127.5 126.7 125.3 123.5 76.4 53.5 46.9 42.5 31.2 30.0 26.6 22.2
f1 (ppm)

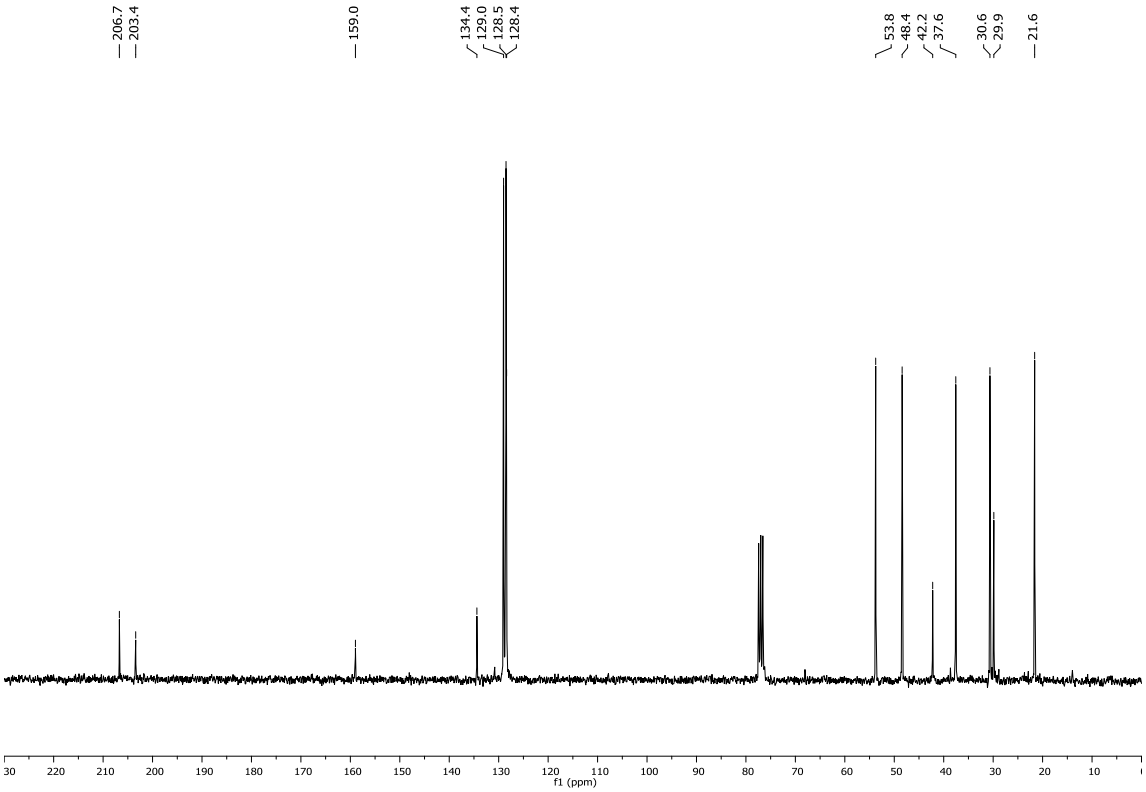

Ph
O
O
OH
O
N
14Bb
f1 (ppm)

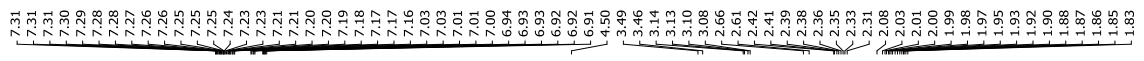

f1 (ppm)

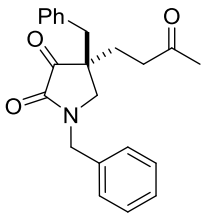

4.63
4.61
4.59
4.57
4.54
3.41
3.37
3.31
3.28
2.63
2.62
2.61
2.61
2.60
2.59
2.58
2.57
1.94
1.93
1.92
1.91
1.89
1.88
1.35
1.33
1.26
1.25
1.24
1.23
Me
O
O
OH
O
N
14Ca
1.00
1.31
1.25
2.13
2.16
6.31
10.20
f1 (ppm)


213.6
203.9
158.7
49.8
44.6
42.5
31.0
30.2
26.7
21.7
19.4
f1 (ppm)


7.36
7.34
7.32
7.29
7.28
7.27
7.26
4.74
4.69
4.64
4.59
3.30
3.27
3.22
3.18
2.36
2.35
2.34
2.31
2.05
1.83
1.80
1.79
1.78
1.15
Me
O
O
O
N
18Aa
4.04
2.00
2.04
1.94
2.67
2.22
3.07
f1 (ppm)


206.7
203.4
159.0
134.4
129.0
128.5
128.4
53.8
48.4
42.2
37.6
30.6
29.9
21.6
f1 (ppm)

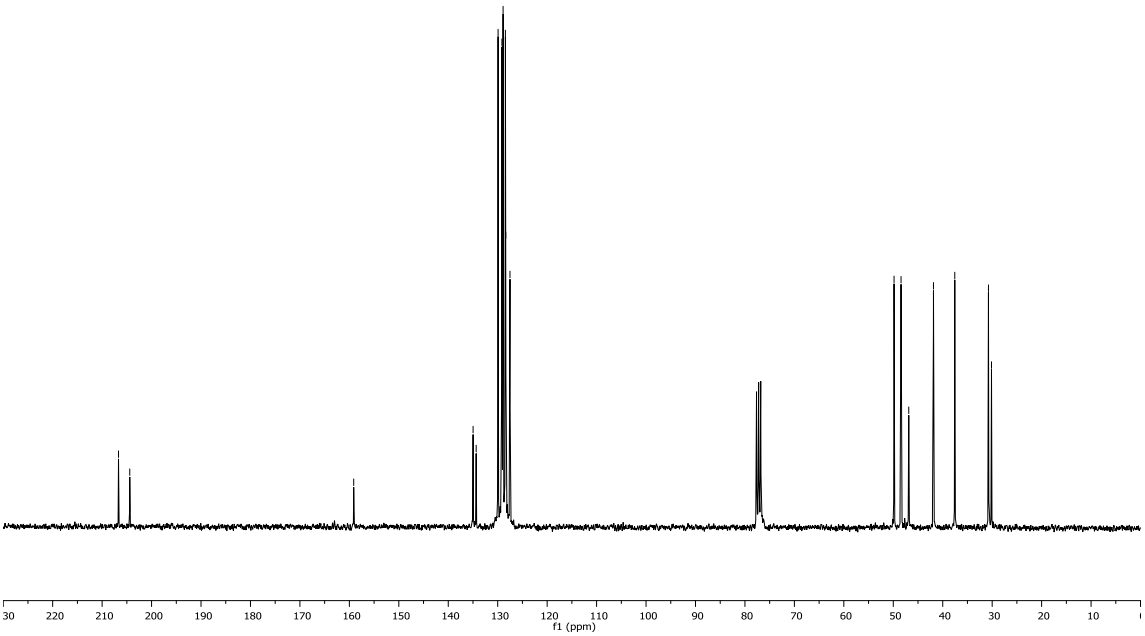

7.31
7.31
7.31
7.30
7.29
7.28
7.28
7.27
7.26
7.26
7.25
7.25
7.25
7.24
7.23
7.23
7.21
7.21
7.20
7.20
7.19
7.18
7.17
7.17
7.16
7.03
7.03
7.01
7.01
7.00
6.94
6.93
6.93
6.92
6.92
6.91
4.50
3.49
3.46
3.14
3.13
3.10
3.08
2.66
2.61
2.42
2.41
2.39
2.38
2.36
2.35
2.33
2.31
2.08
2.03
2.01
2.00
1.99
1.98
1.97
1.95
1.93
1.92
1.90
1.88
1.87
1.86
1.85
1.83

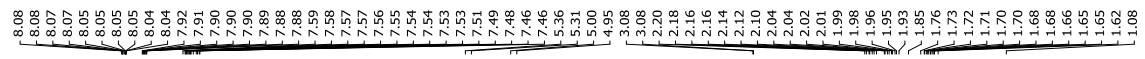

Ph
O
O
O
N

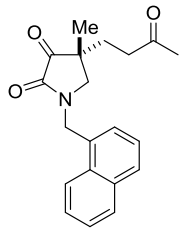
18Ab

2.90
2.93
1.76
1.90
2.00
0.97
1.96
0.98
2.13
2.60
2.19
f1 (ppm)


206.7
204.4
159.1
135.0
134.4
129.9
129.2
128.9
128.4
128.4
127.5
49.8
48.4
46.9
41.9
37.6
30.7
30.1


f1 (ppm)

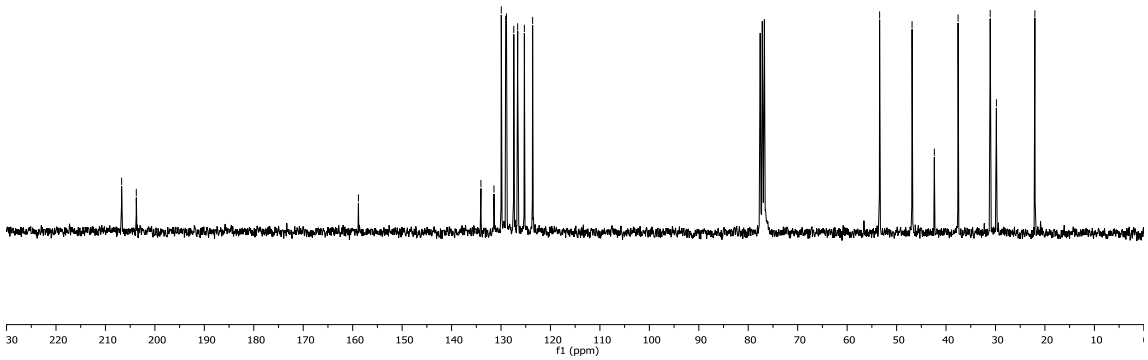


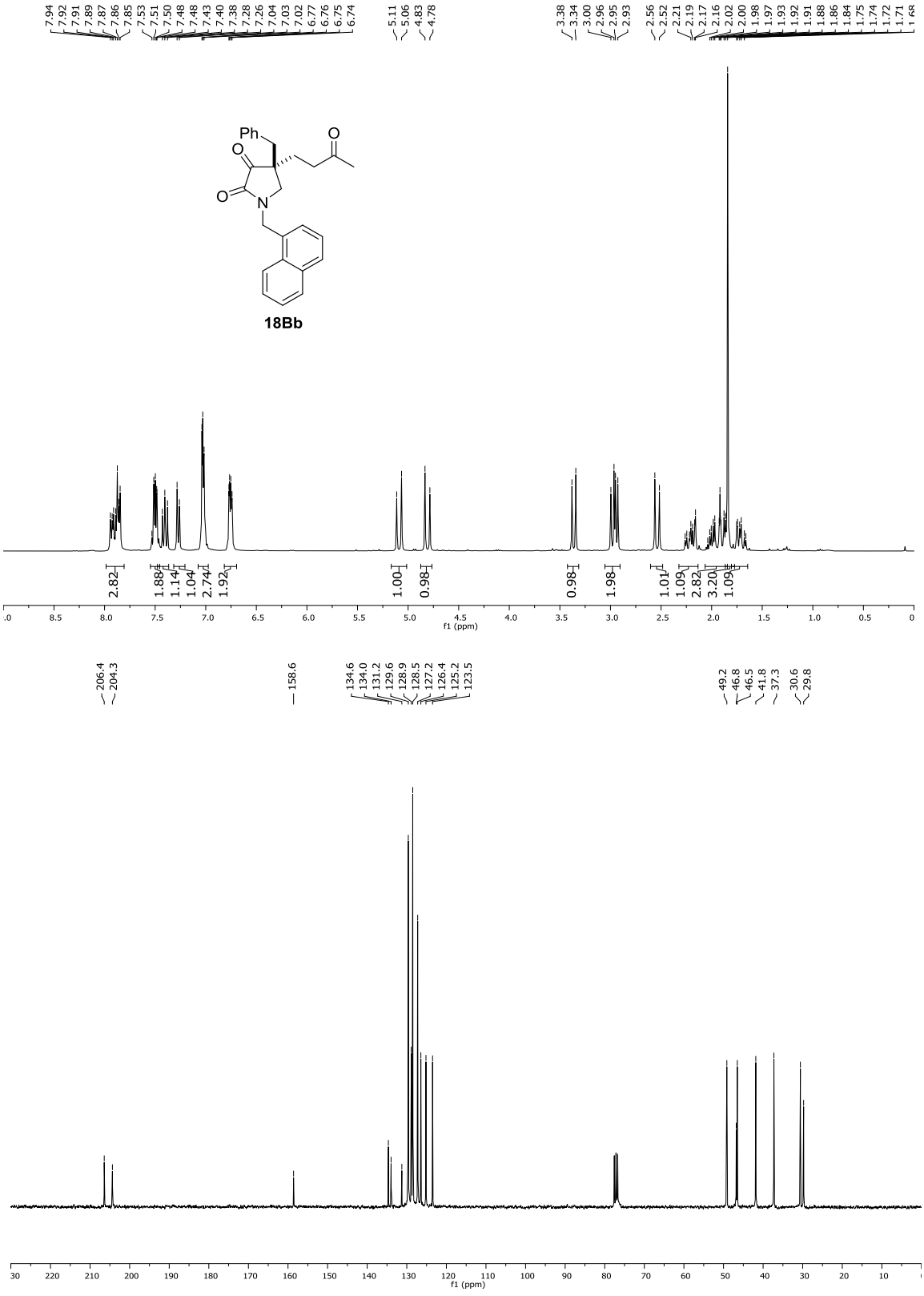

O
Me
O
O
N

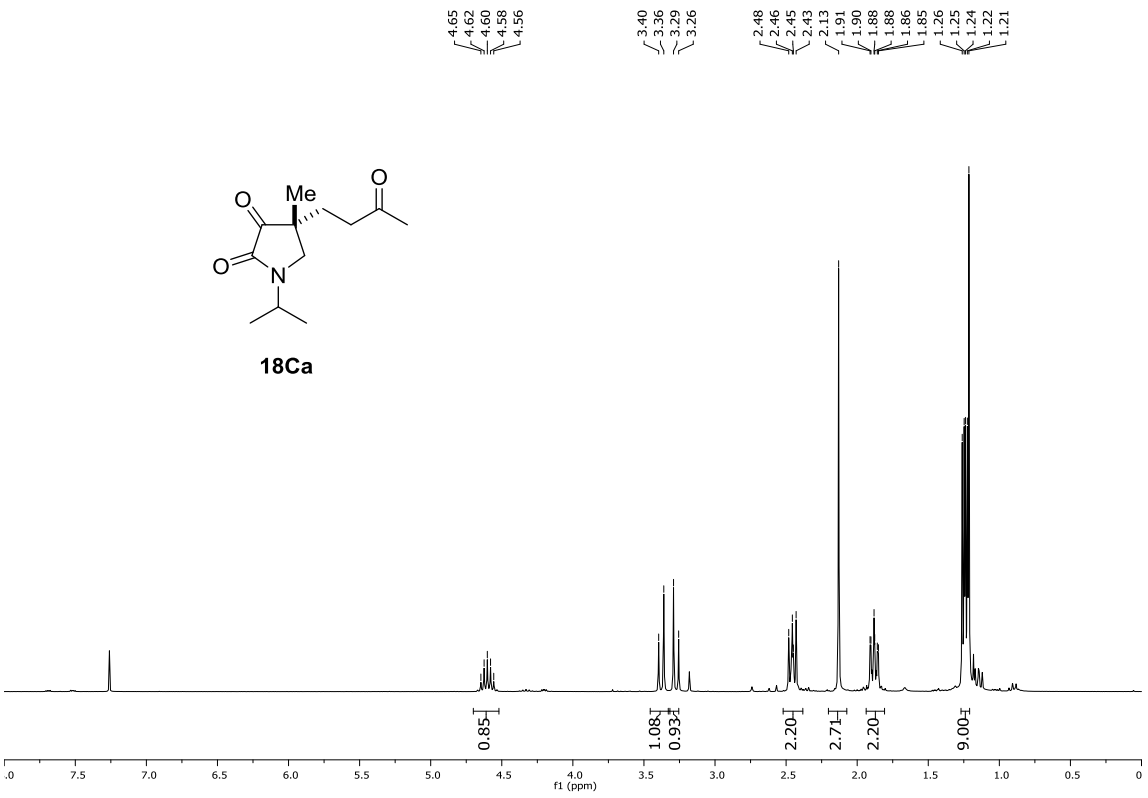
18Ba

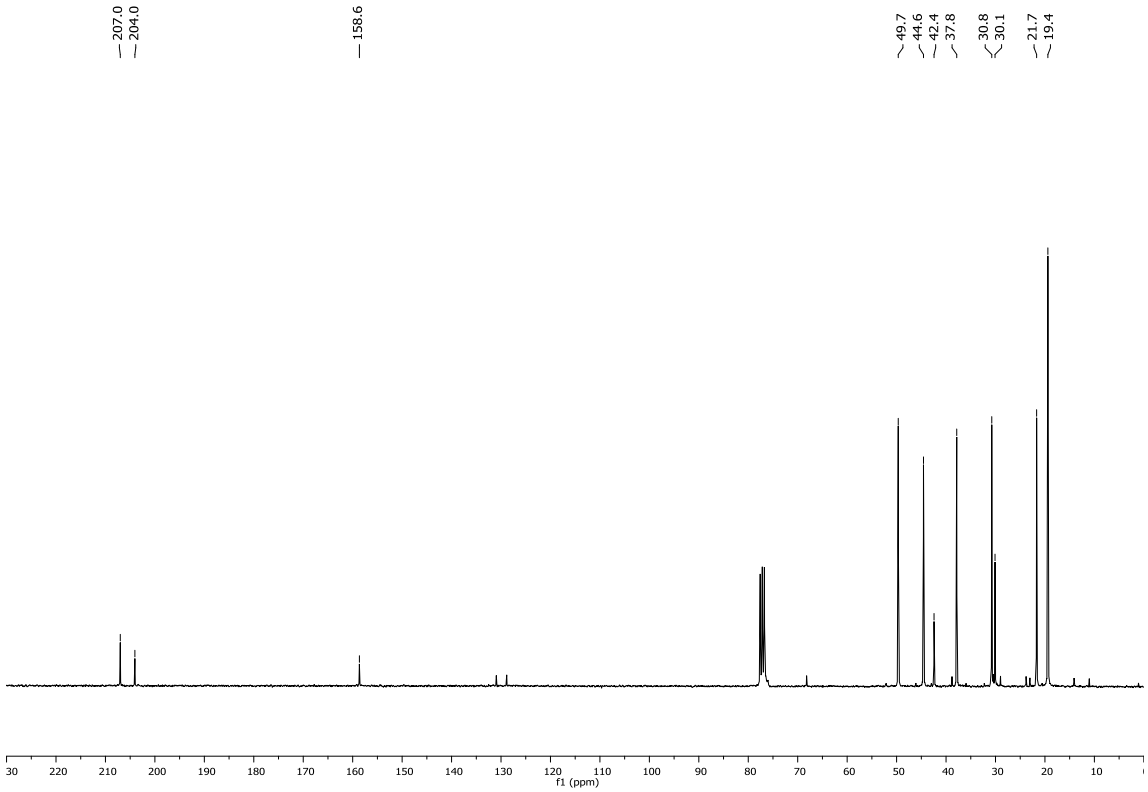
0.75
1.42
1.53
1.47
1.06
1.08
2.00
1.04
1.04
2.18
1.95
2.51
f1 (ppm)

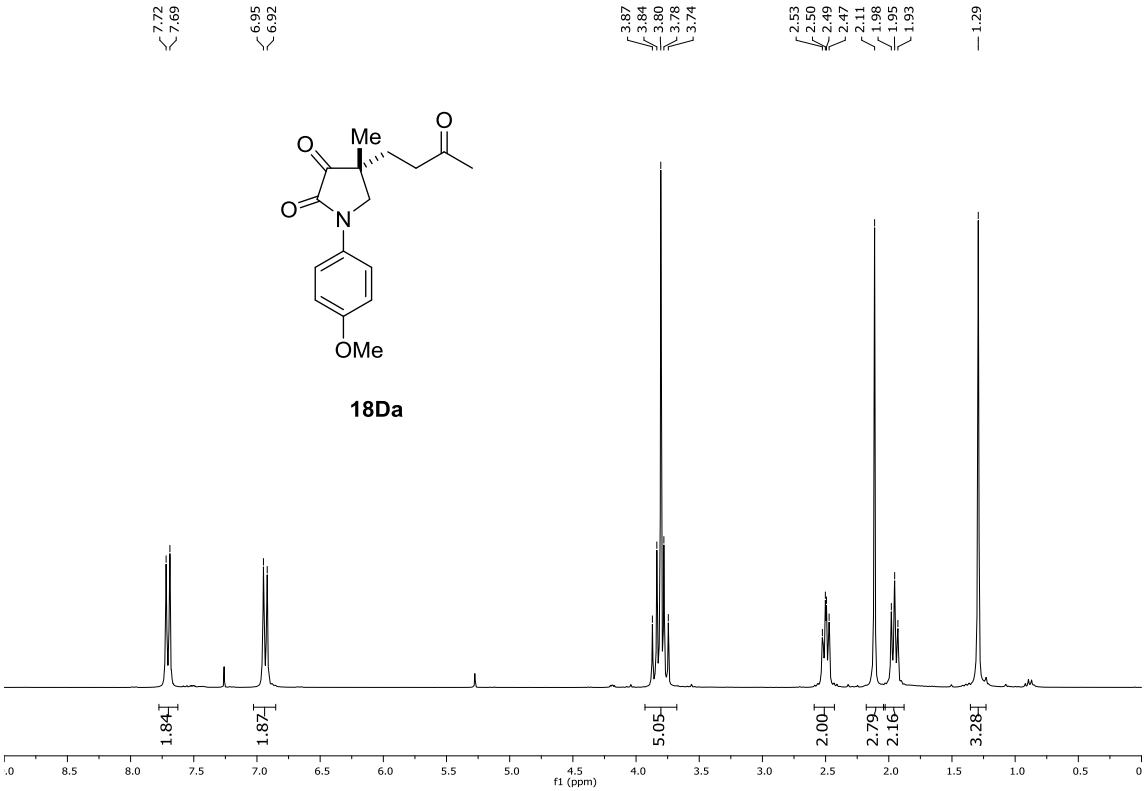

206.7
203.8
158.8
134.1
131.4
129.9
129.9
129.1
128.9
127.4
126.6
125.3
123.6
53.4
46.9
42.4
37.6
31.1
29.8
22.0

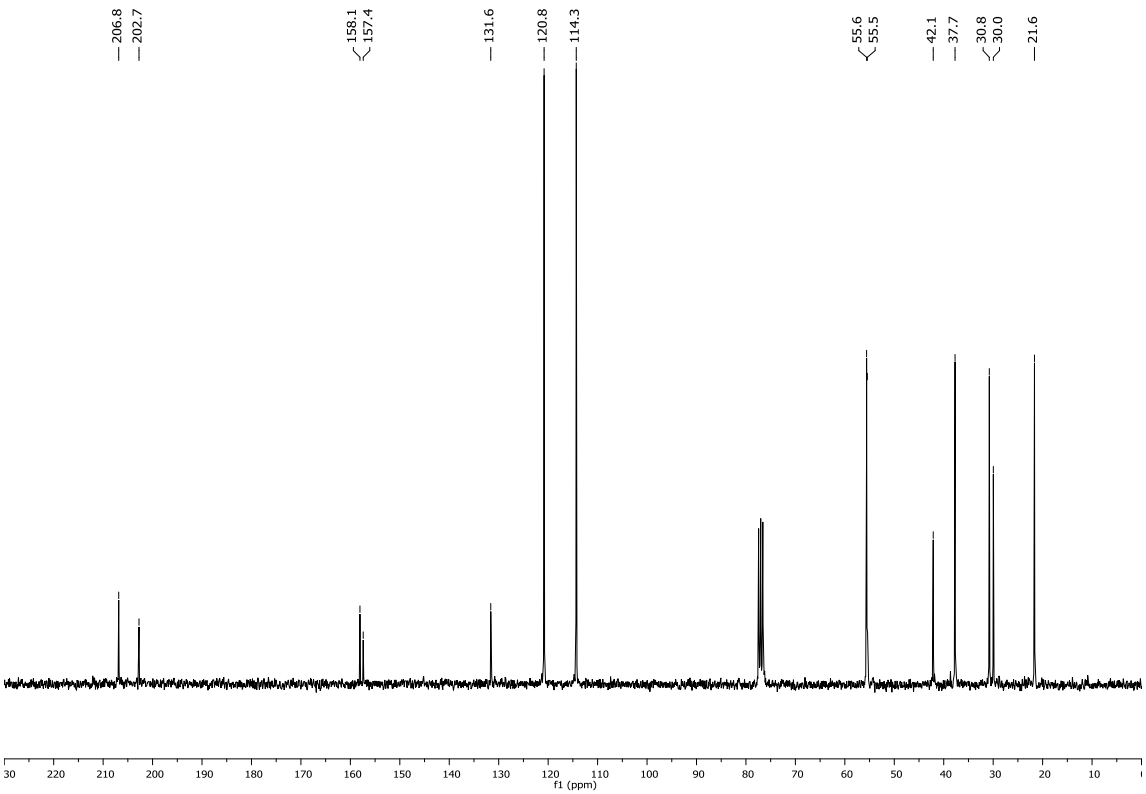

f1 (ppm)

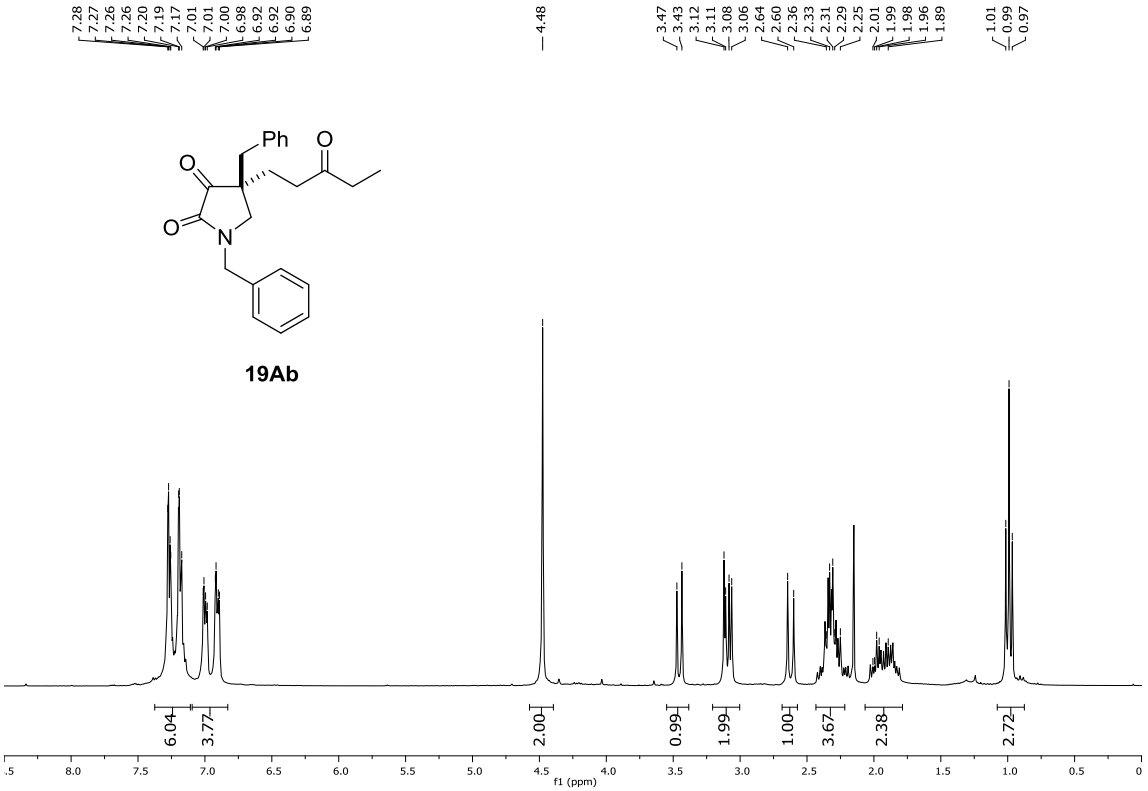

7.94
7.92
7.91
7.89
7.87
7.86
7.85
7.53
7.51
7.50
7.48
7.48
7.43
7.40
7.38
7.28
7.26
7.04
7.03
7.02
6.77
6.76
6.75
6.74
5.11
5.06
4.83
4.78
3.38
3.34
3.00
2.96
2.95
2.93
2.56
2.52
2.21
2.19
2.17
2.16
2.02
2.00
1.98
1.97
1.93
1.92
1.91
1.88
1.86
1.84
1.75
1.74
1.72
1.71
Ph
O
O
O
N
18Bb
2.82
1.88
1.14
1.04
2.74
1.92
1.00
0.98
0.98
1.98
1.01
1.09
2.82
3.20
1.09
f1 (ppm)
206.4
204.3
158.6
134.6
134.0
131.2
129.6
128.9
128.5
127.2
126.4
125.2
123.5
49.2
46.8
46.5
41.8
37.3
30.6
29.8
f1 (ppm)

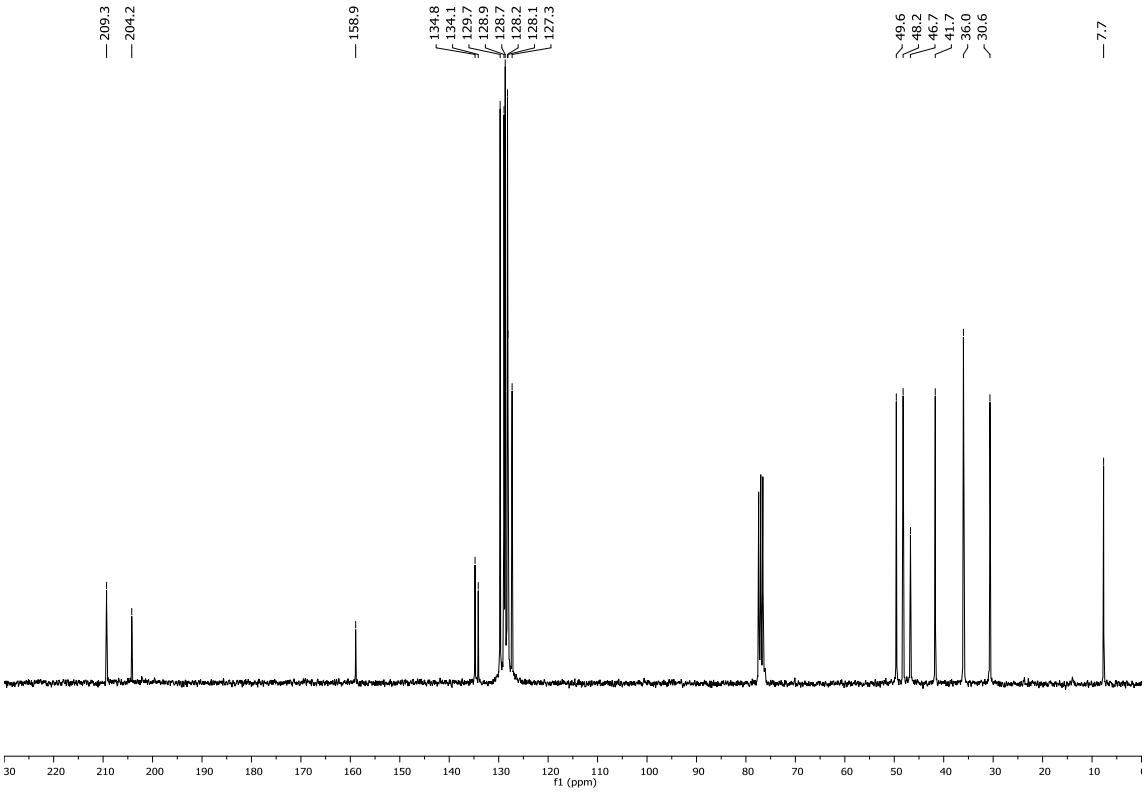

4.65
4.62
4.60
4.58
4.56
3.40
3.36
3.29
3.26
2.48
2.46
2.45
2.43
2.13
1.91
1.90
1.88
1.88
1.86
1.85
1.26
1.25
1.24
1.22
1.21
O
Me
O
O
N
18Ca
0.85
1.08
0.93
2.20
2.71
2.20
9.00
f1 (ppm)

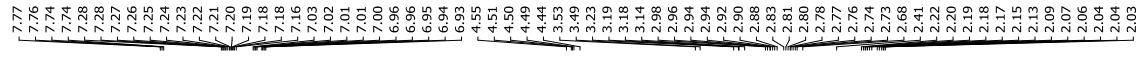

207.0
204.0
158.6
49.7
44.6
42.4
37.8
30.8
30.1
21.7
19.4
f1 (ppm)

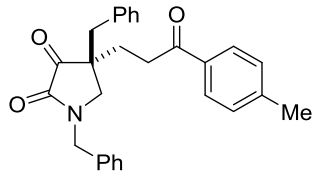

7.72
7.69
6.95
6.92
3.87
3.84
3.80
3.78
3.74
2.53
2.50
2.49
2.47
2.11
1.98
1.95
1.93
1.29
Me
O
O
O
N
OMe
18Da
1.84
1.87
5.05
2.00
2.79
2.16
3.28
f1 (ppm)


206.8
202.7
158.1
157.4
131.6
120.8
114.3
55.6
55.5
42.1
37.7
30.8
30.0
21.6
f1 (ppm)


7.28
7.27
7.26
7.26
7.20
7.19
7.17
7.01
7.01
7.00
6.98
6.92
6.92
6.90
6.89
4.48
3.47
3.43
3.12
3.11
3.08
3.06
2.64
2.60
2.36
2.33
2.31
2.29
2.25
2.01
1.99
1.98
1.96
1.89
1.01
0.99
0.97
Ph
O
O
O
N
19Ab
6.04
3.77
2.00
0.99
1.99
1.00
3.67
2.38
2.72
f1 (ppm)

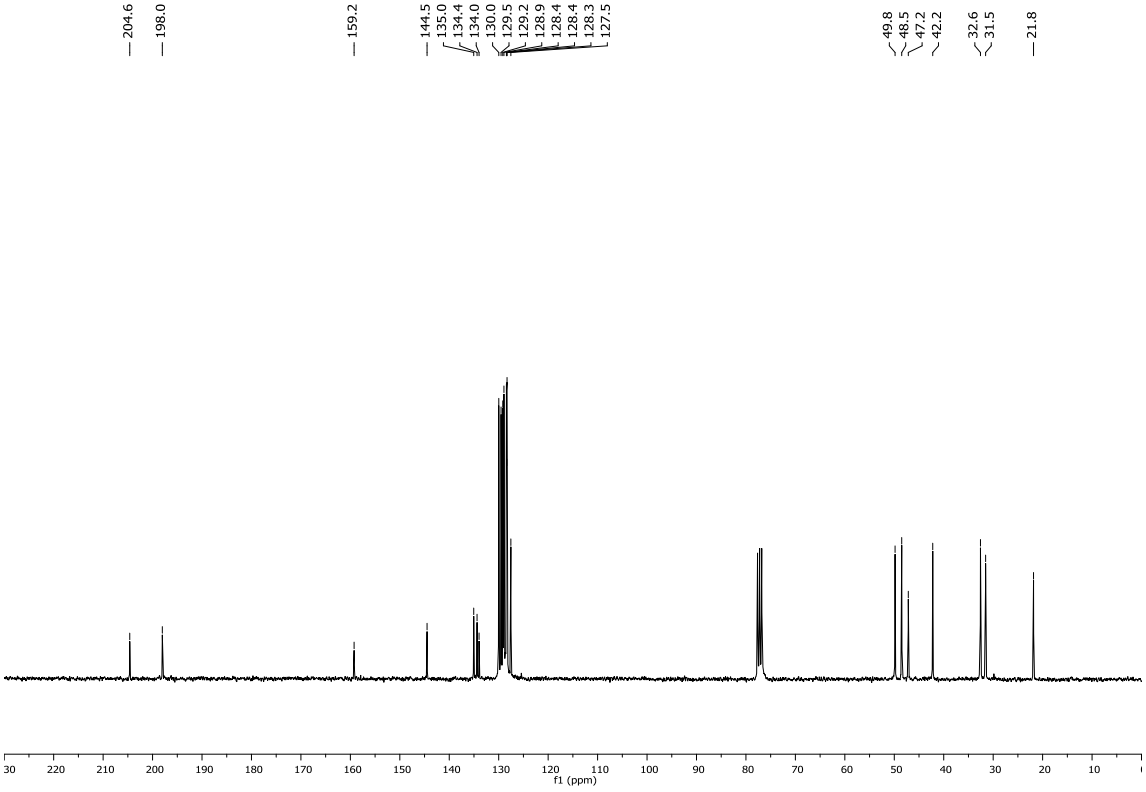

209.3
204.2
158.9
134.8
134.1
129.7
128.9
128.7
128.2
128.1
127.3
49.6
48.2
46.7
41.7
36.0
30.6
7.7
f1 (ppm)

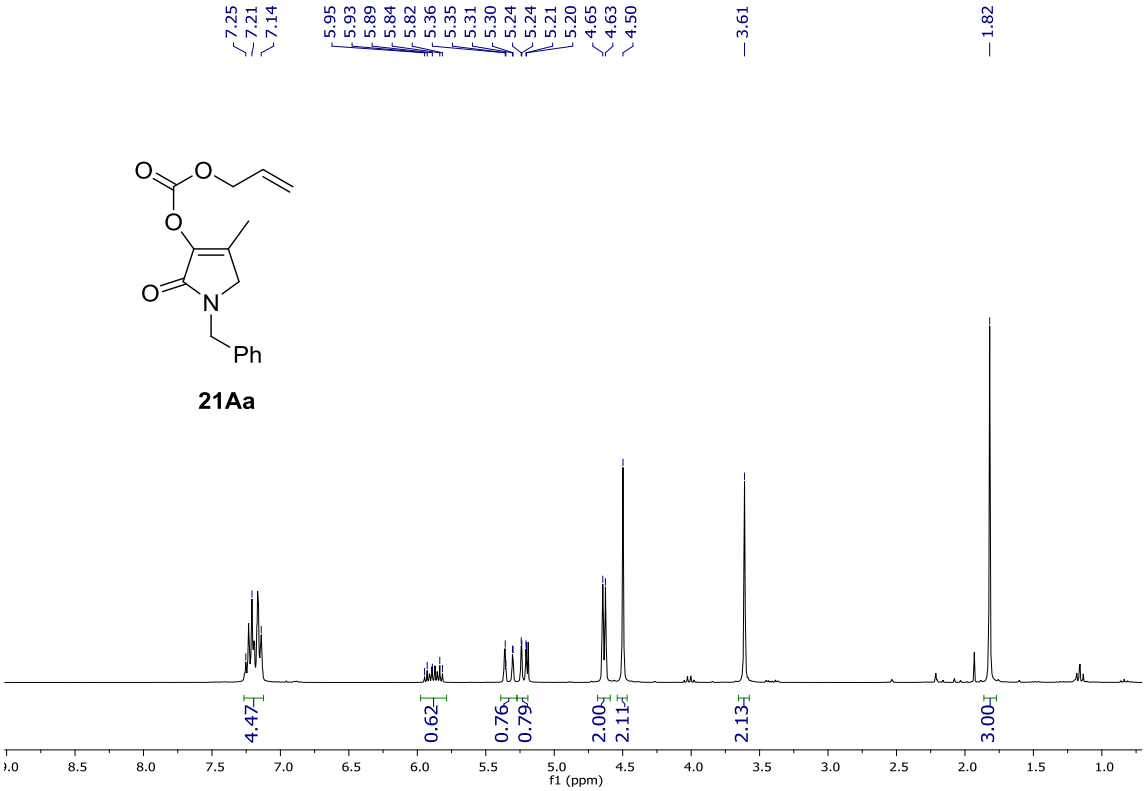

7.77 7.76 7.74 7.74 7.28 7.28 7.27 7.26 7.25 7.24 7.23 7.22 7.21 7.20 7.19 7.18 7.18 7.16 7.03 7.02 7.01 7.01 7.00 6.96 6.96 6.95 6.94 6.93
4.55 4.51 4.50 4.49 4.44 3.53 3.49 3.23 3.19 3.18 3.14 2.98 2.96 2.94 2.94 2.92 2.90 2.88 2.83 2.81 2.80 2.78 2.77 2.76 2.74 2.73 2.68 2.41 2.22 2.20 2.19 2.18 2.17 2.15 2.13 2.09 2.07 2.06 2.04 2.04 2.03

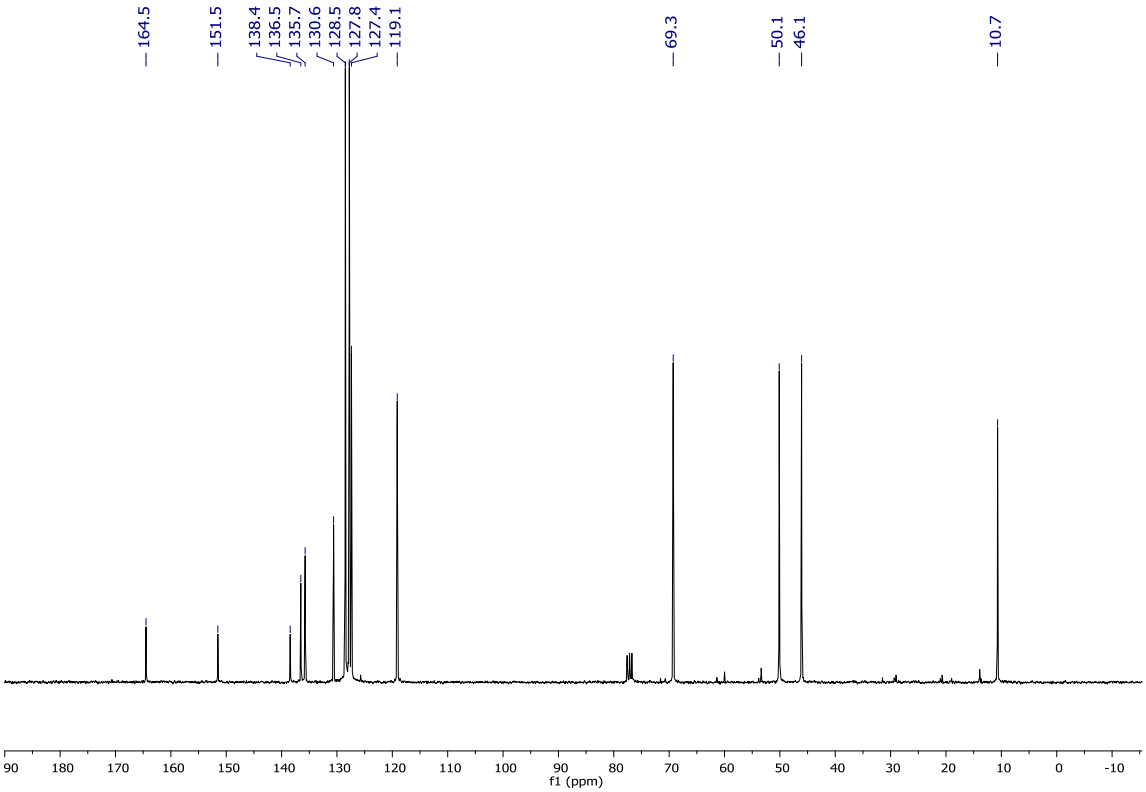

Ph
O
O
O
N
Ph
Me

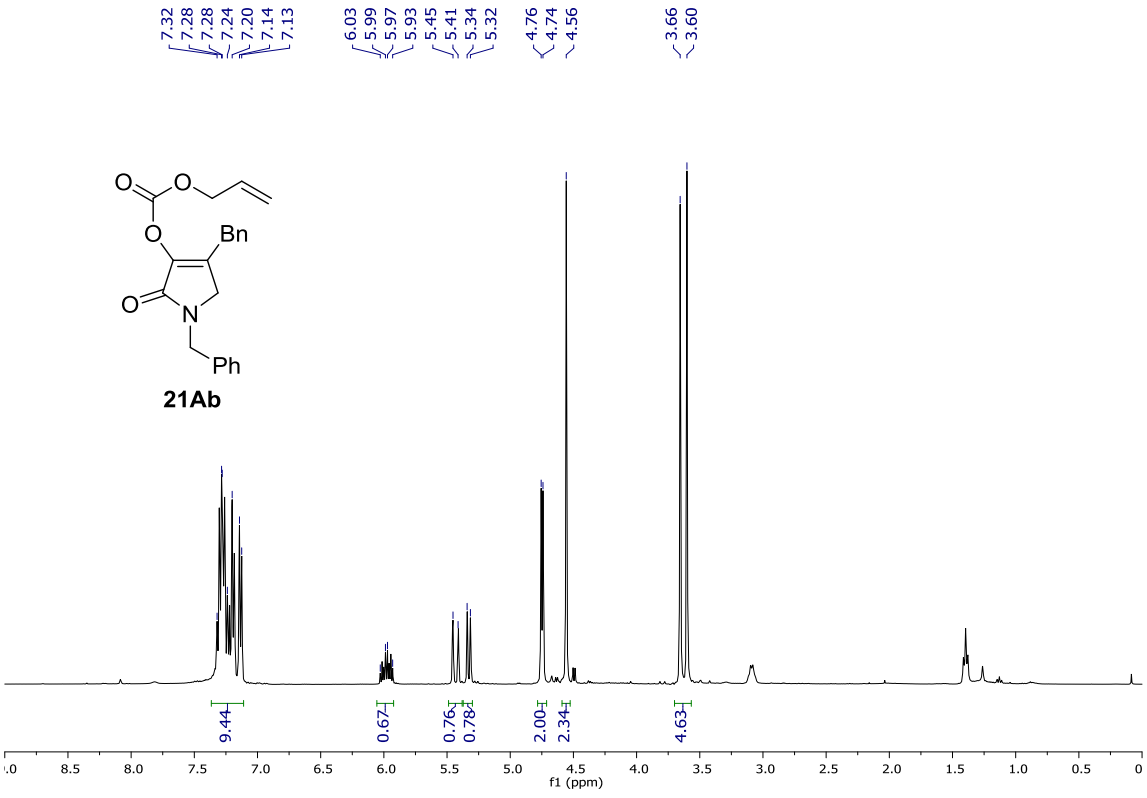
20Ab

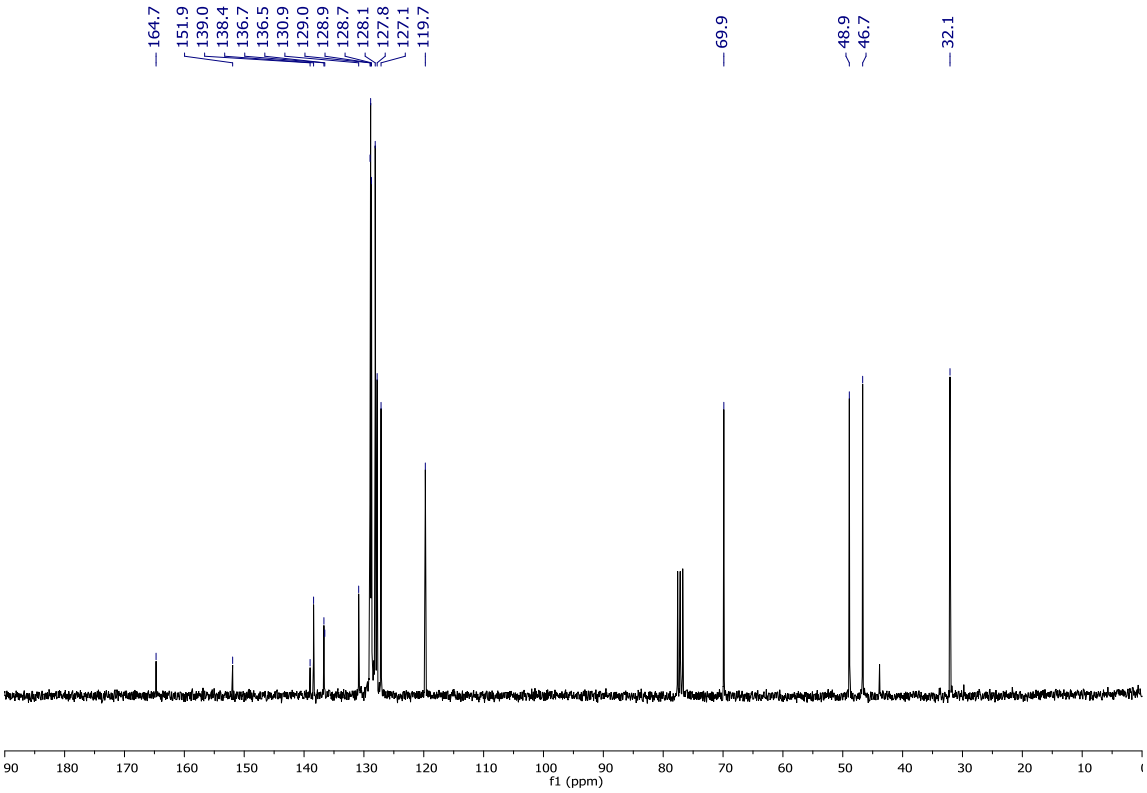
1.63
7.15
1.83
1.77
1.97
0.93
1.90
1.00
0.92
1.05
2.66
0.96
0.94
f1 (ppm)

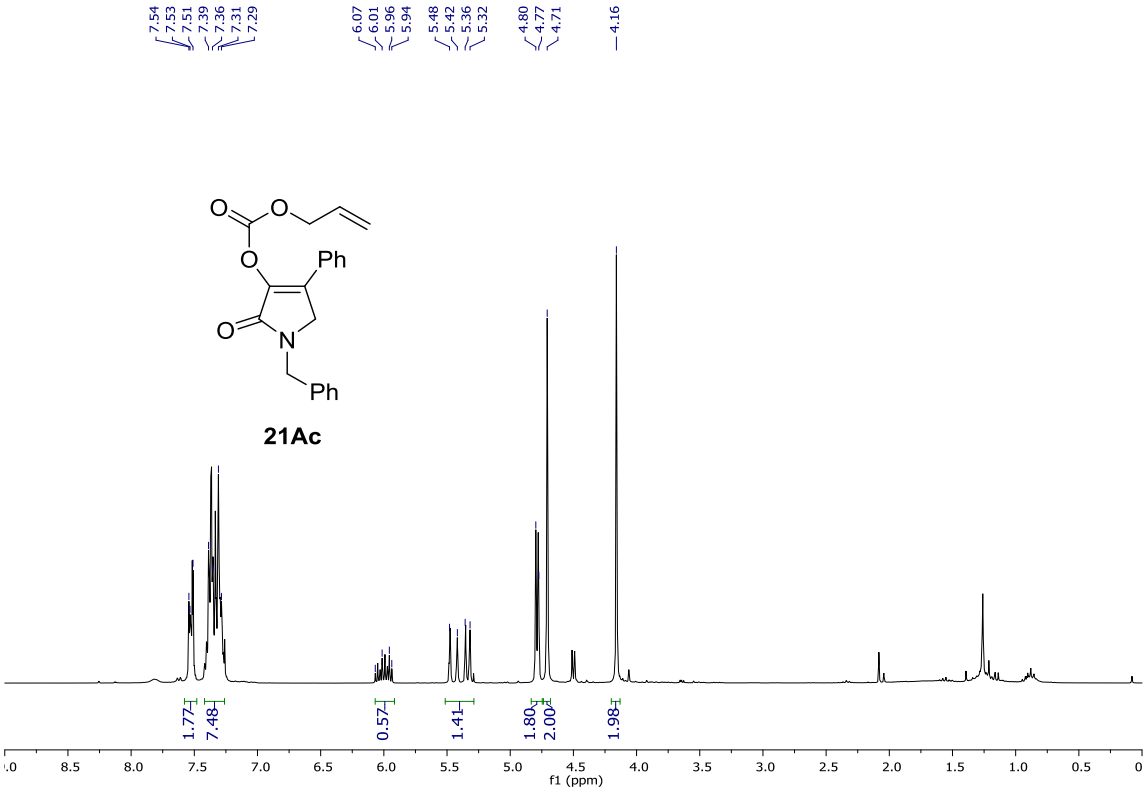

204.6
198.0
159.2
144.5
135.0
134.4
134.0
130.0
129.5
129.2
128.9
128.4
128.4
128.3
127.5
49.8
48.5
47.2
42.2
32.6
31.5
21.8
f1 (ppm)

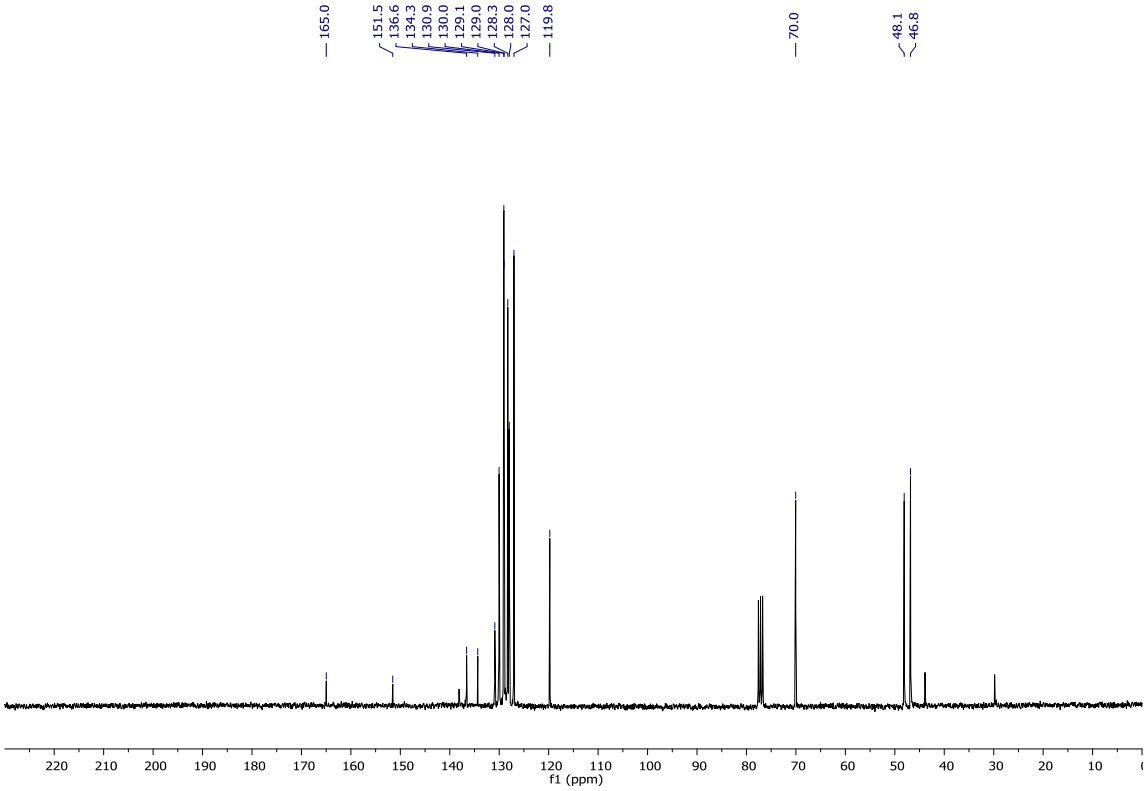

7.25
7.21
7.14
5.95
5.93
5.89
5.84
5.82
5.36
5.35
5.31
5.30
5.24
5.24
5.21
5.20
4.65
4.63
4.50
3.61
1.82
O
O
O
O
N
Ph
21Aa
4.47
0.62
0.76
0.79
2.00
2.11
2.13
3.00
f1 (ppm)

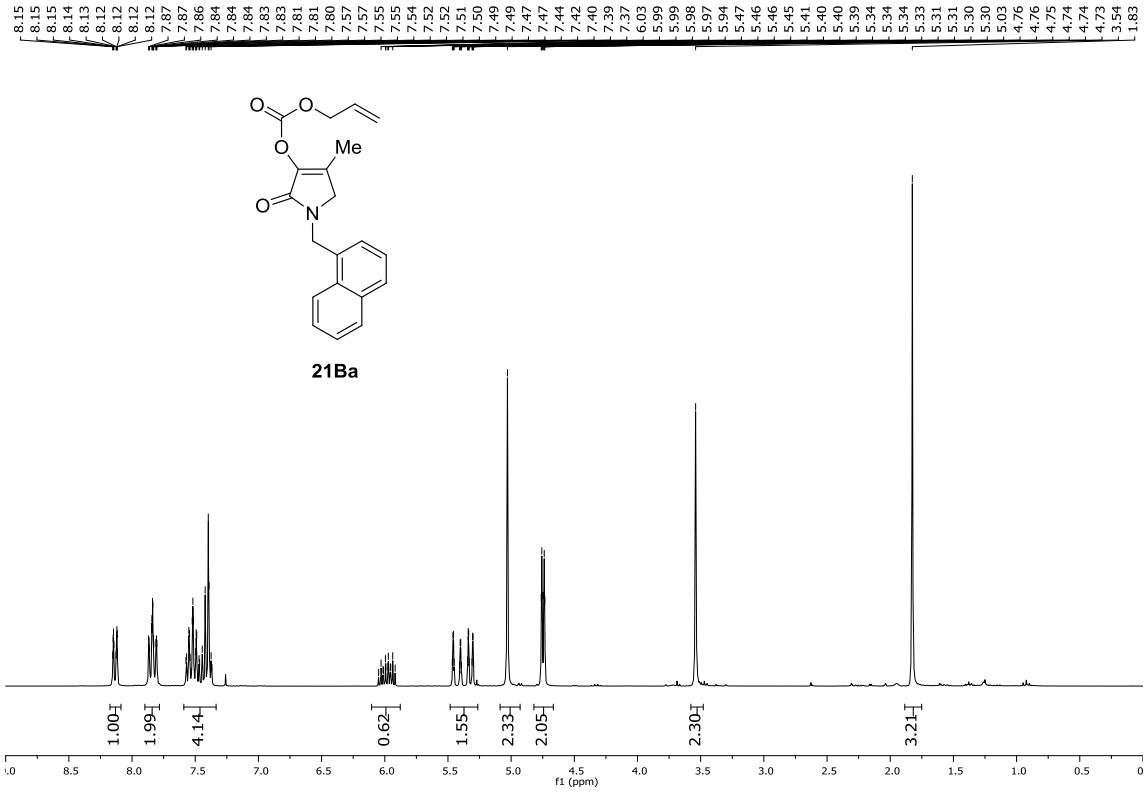

164.5
151.5
138.4
136.5
135.7
130.6
128.5
127.8
127.4
119.1
69.3
50.1
46.1
10.7
f1 (ppm)

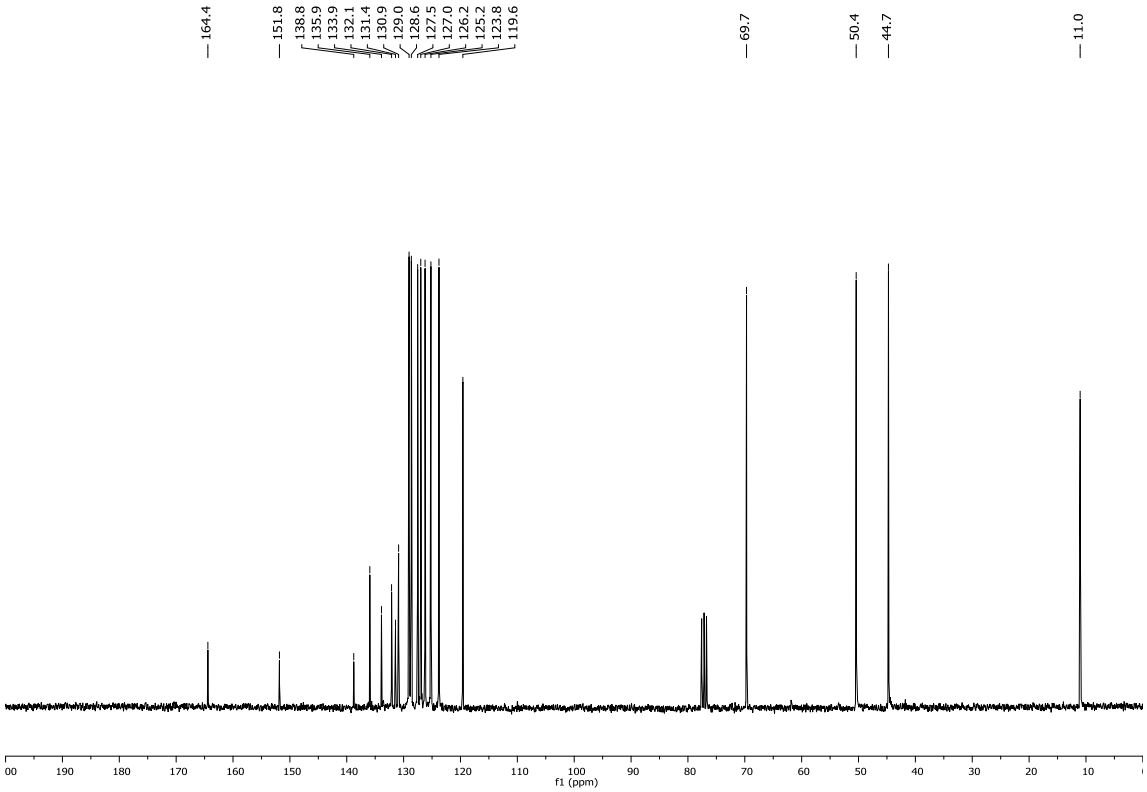

7.32
7.28
7.28
7.24
7.20
7.14
7.13
6.03
5.99
5.97
5.93
5.45
5.41
5.34
5.32
4.76
4.74
4.56
3.66
3.60
Bn
Ph
21Ab
9.44
0.67
0.76
0.78
2.00
2.34
4.63
f1 (ppm)


164.7
151.9
139.0
138.4
136.7
136.5
130.9
129.0
128.9
128.7
128.1
127.8
127.1
119.7
69.9
48.9
46.7
32.1
f1 (ppm)

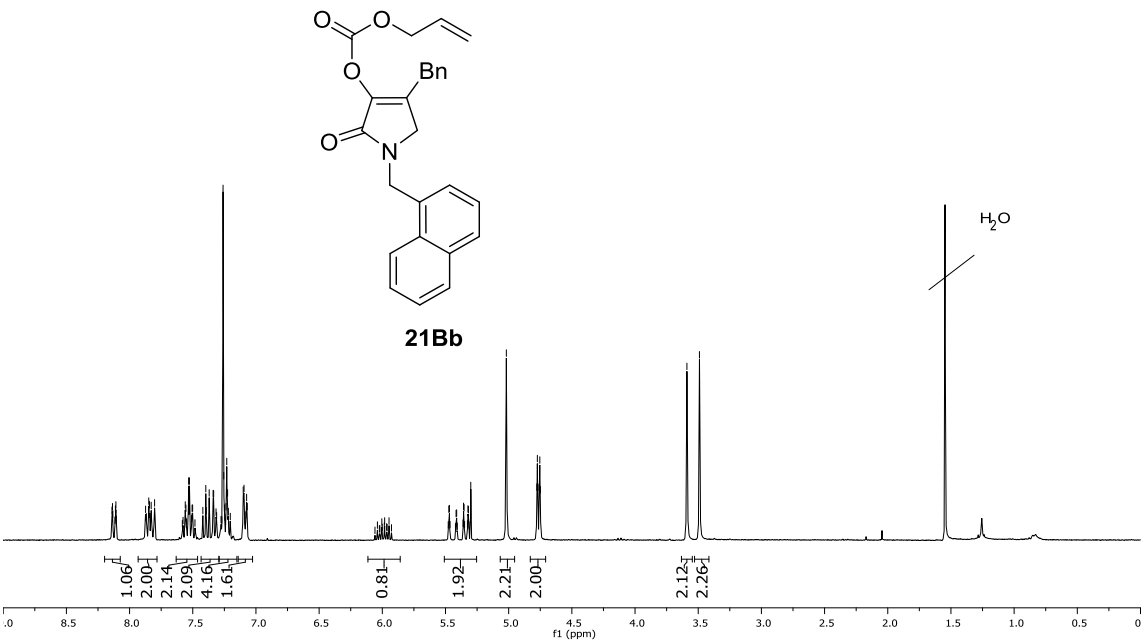

7.54
7.53
7.51
7.39
7.36
7.31
7.29
6.07
6.01
5.96
5.94
5.48
5.42
5.36
5.32
4.80
4.77
4.71
4.16
Ph
Ph
21Ac
1.77
7.48
0.57
1.41
1.80
2.00
1.98
f1 (ppm)

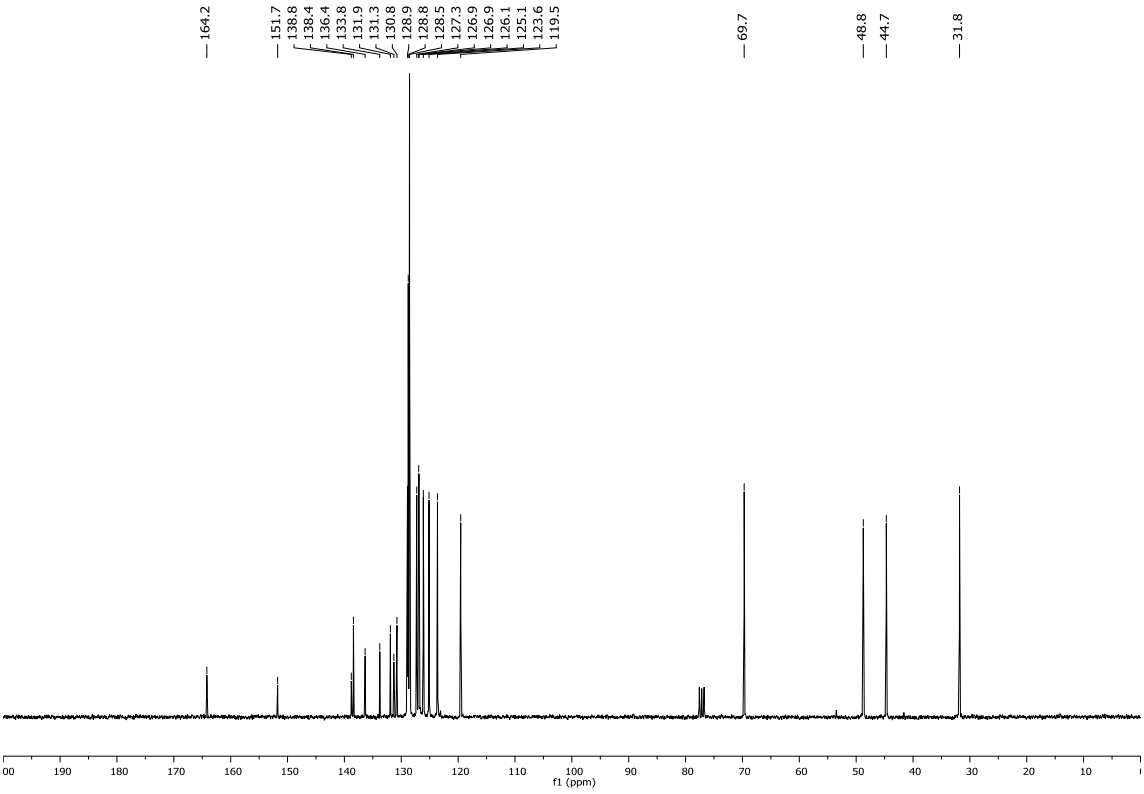

165.0
151.5
136.6
134.3
130.9
130.0
129.1
129.0
128.3
128.0
127.0
119.8
70.0
48.1
46.8
f1 (ppm)

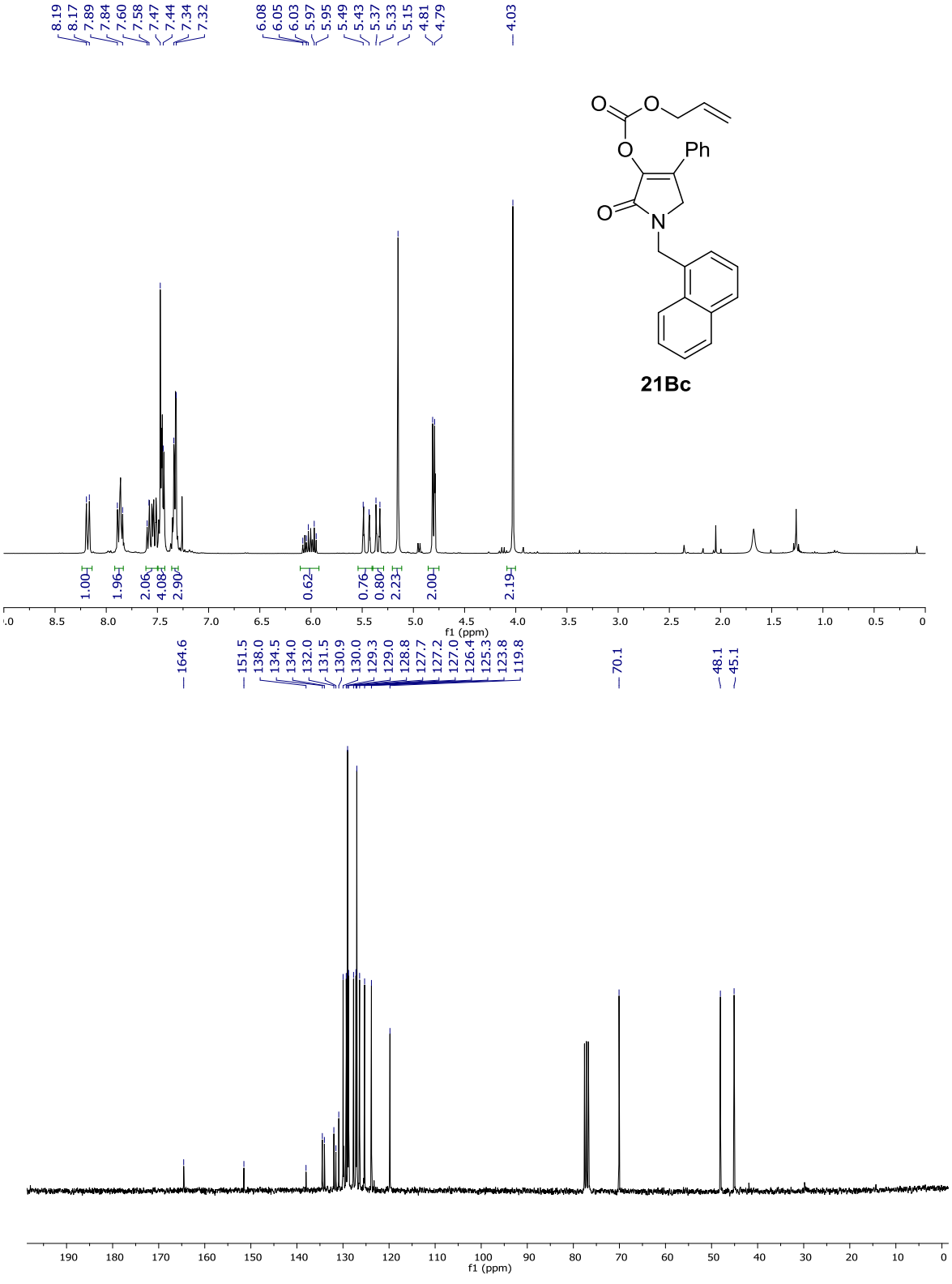

8.15 8.15 8.15 8.14 8.13 8.12 8.12 8.12 8.12 7.87 7.87 7.86 7.84 7.84 7.84 7.83 7.83 7.81 7.81 7.80 7.57 7.57 7.55 7.55 7.54 7.52 7.52 7.51 7.50 7.49 7.49 7.47 7.47 7.44 7.42 7.40 7.39 7.37 6.03 5.99 5.99 5.98 5.97 5.94 5.47 5.46 5.46 5.45 5.41 5.40 5.40 5.39 5.34 5.34 5.34 5.33 5.31 5.31 5.30 5.30 5.03 4.76 4.76 4.75 4.74 4.74 4.73 3.54 1.83
O
O
O
Me
O
N
21Ba
1.00
1.99
4.14
0.62
1.55
2.33
2.05
2.30
3.21
f1 (ppm)

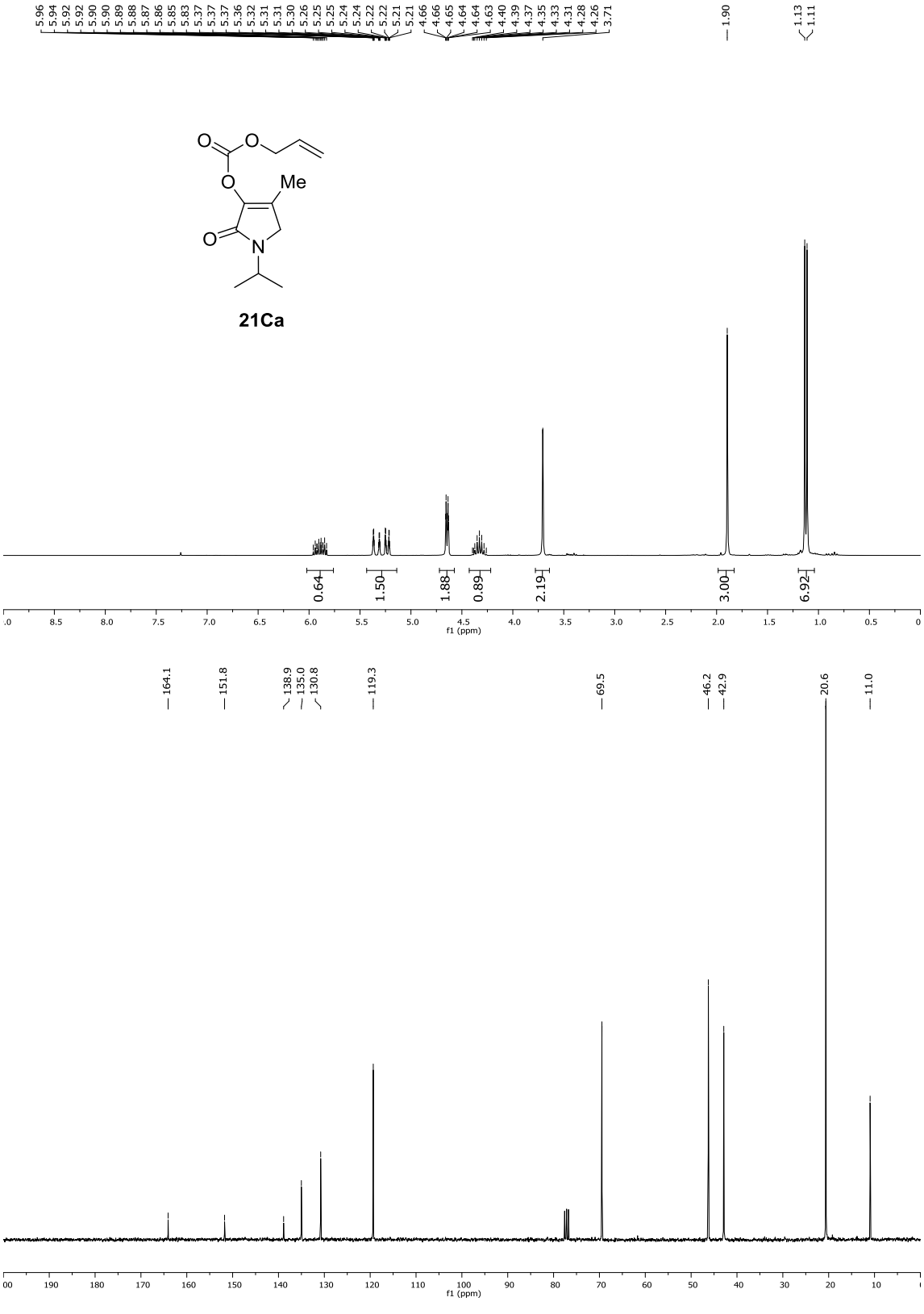

164.4
151.8
138.8
135.9
133.9
132.1
131.4
130.9
129.0
128.6
127.5
127.0
126.2
125.2
123.8
119.6
69.7
50.4
44.7
11.0
f1 (ppm)

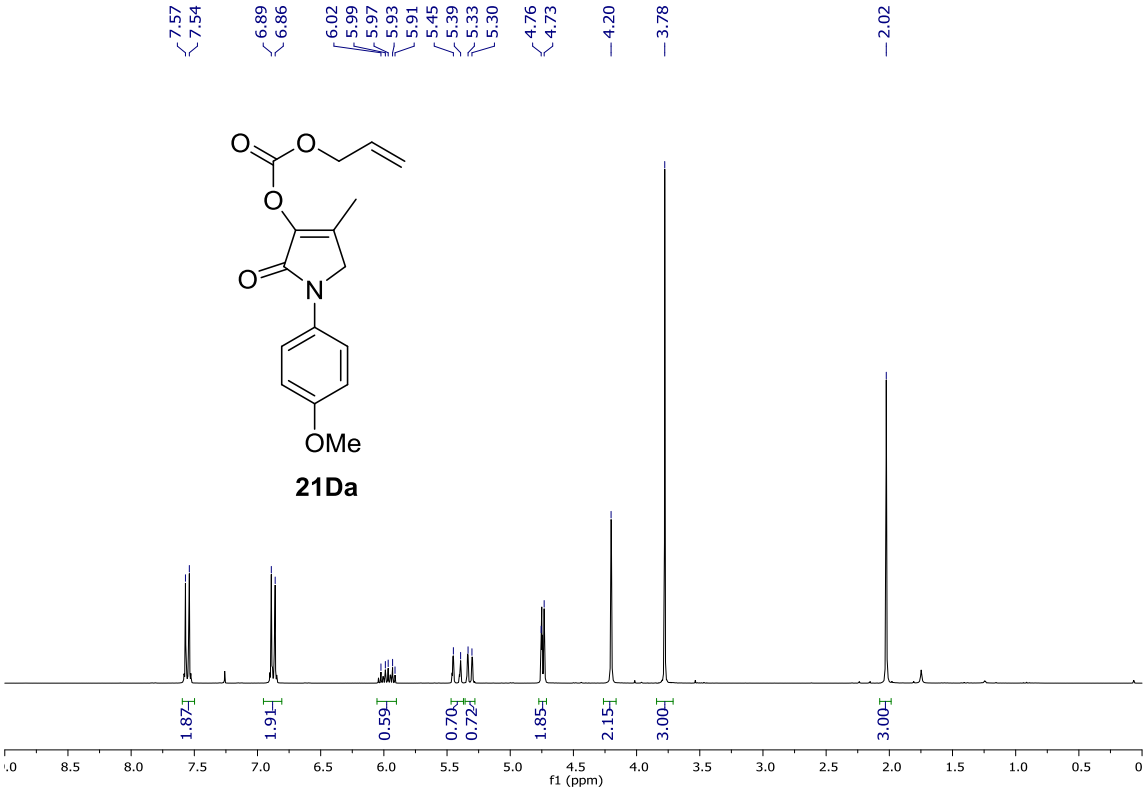

8.14
8.14
8.13
8.12
8.11
8.11
8.10
7.87
7.87
7.85
7.84
7.83
7.80
7.58
7.56
7.55
7.55
7.53
7.53
7.51
7.51
7.50
7.48
7.42
7.40
7.39
7.37
7.34
7.33
7.32
7.31
7.28
7.27
7.26
7.25
7.25
7.24
7.23
7.22
7.22
7.20
7.10
7.09
7.09
7.08
7.07
7.07
6.00
5.98
5.95
5.47
5.47
5.42
5.41
5.36
5.35
5.32
5.32
5.30
5.02
4.78
4.77
4.77
4.76
4.75
4.75
3.59
3.49

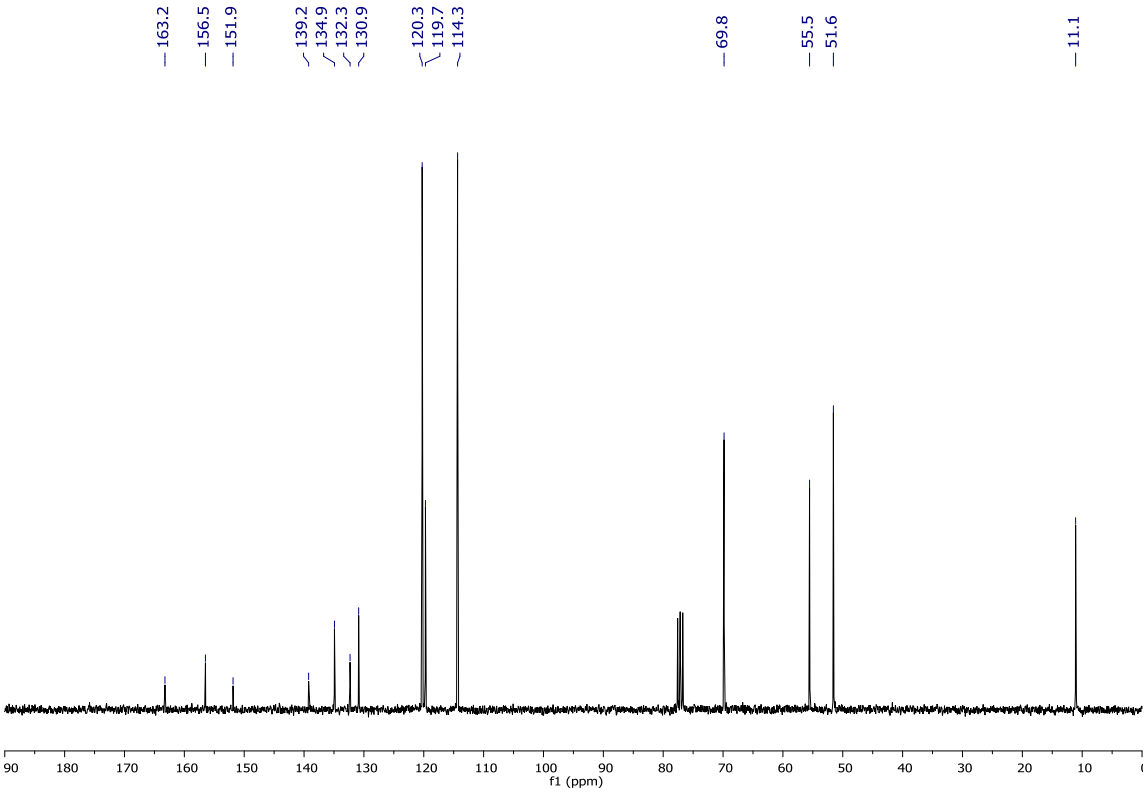

O
O
O
Bn
O
N
21Bb
H2O
1.06
2.00
2.14
2.09
4.16
1.61
0.81
1.92
2.21
2.00
2.12
2.26
f1 (ppm)

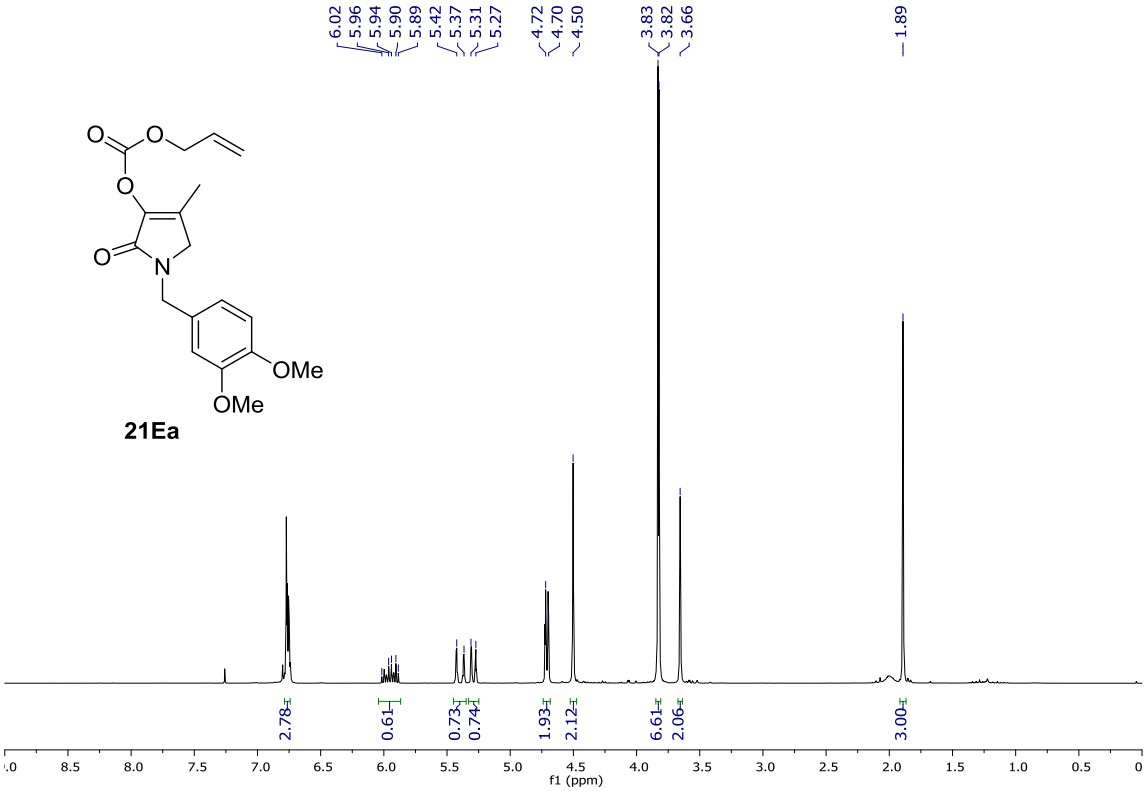

164.2
151.7
138.8
138.4
136.4
133.8
131.9
131.3
130.8
128.9
128.8
128.5
127.3
126.9
126.9
126.1
125.1
123.6
119.5
69.7
48.8
44.7
31.8
f1 (ppm)

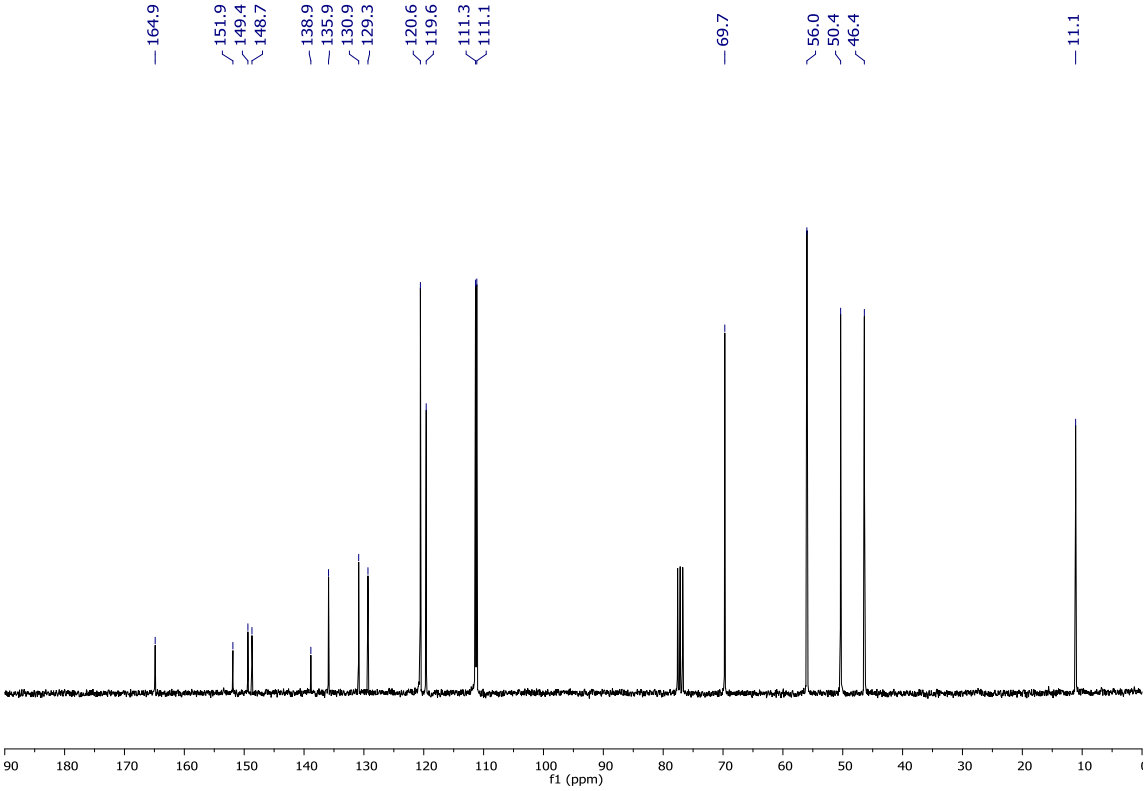

8.19
8.17
7.89
7.84
7.60
7.58
7.47
7.44
7.34
7.32
6.08
6.05
6.03
5.97
5.95
5.49
5.43
5.37
5.33
5.15
4.81
4.79
4.03
O
O
O
Ph
O
N
21Bc
1.00
1.96
2.06
4.08
2.90
0.62
0.76
0.80
2.23
2.00
2.19
f1 (ppm)
164.6
151.5
138.0
134.5
134.0
132.0
131.5
130.9
130.0
129.3
129.0
128.8
127.7
127.2
127.0
126.4
125.3
123.8
119.8
70.1
48.1
45.1
f1 (ppm)

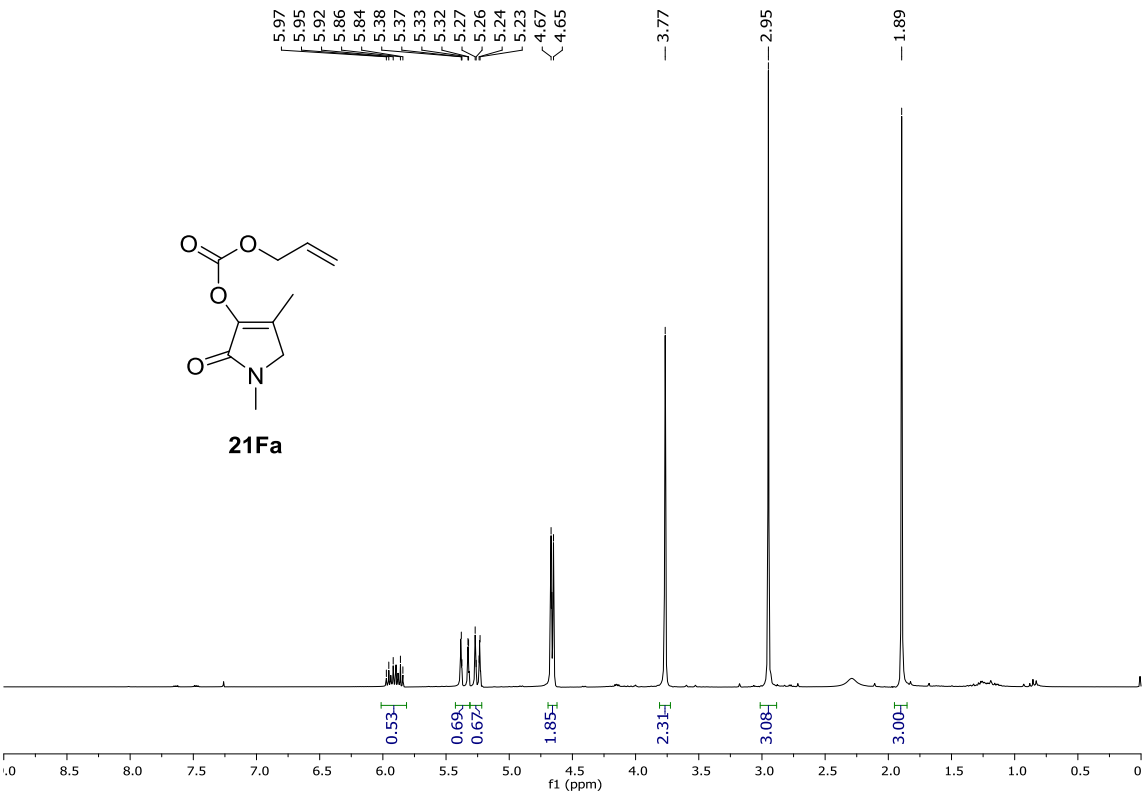

5.96
5.94
5.92
5.92
5.90
5.90
5.89
5.88
5.87
5.86
5.85
5.83
5.37
5.37
5.36
5.32
5.31
5.31
5.30
5.26
5.25
5.25
5.24
5.24
5.22
5.22
5.21
5.21
4.66
4.65
4.64
4.64
4.63
4.40
4.39
4.37
4.35
4.33
4.31
4.28
4.26
3.71
1.90
1.13
1.11
O
O
O
Me
O
N
21Ca
0.64
1.50
1.88
0.89
2.19
3.00
6.92
f1 (ppm)
164.1
151.8
138.9
135.0
130.8
119.3
69.5
46.2
42.9
20.6
11.0
f1 (ppm)

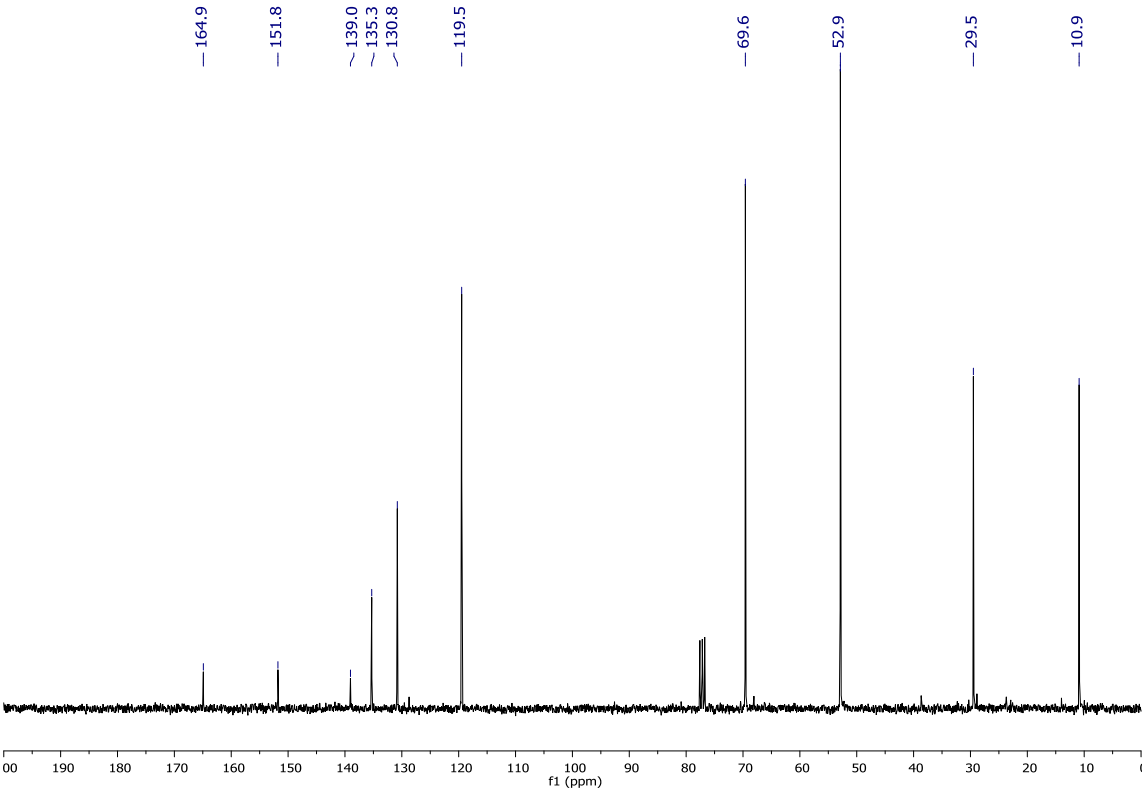

7.57
7.54
6.89
6.86
6.02
5.99
5.97
5.93
5.91
5.45
5.39
5.33
5.30
4.76
4.73
4.20
3.78
2.02
OMe
21Da
1.87
1.91
0.59
0.70
0.72
1.85
2.15
3.00
3.00
f1 (ppm)

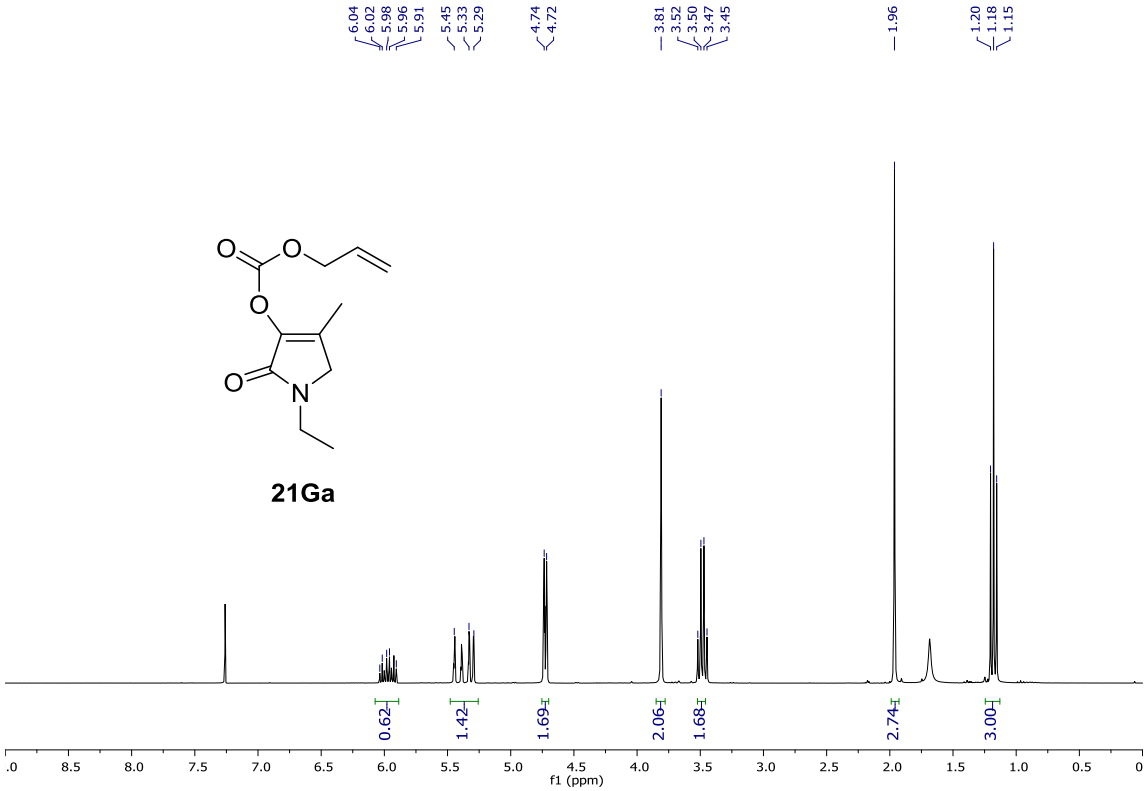

163.2
156.5
151.9
139.2
134.9
132.3
130.9
120.3
119.7
114.3
69.8
55.5
51.6
11.1
f1 (ppm)

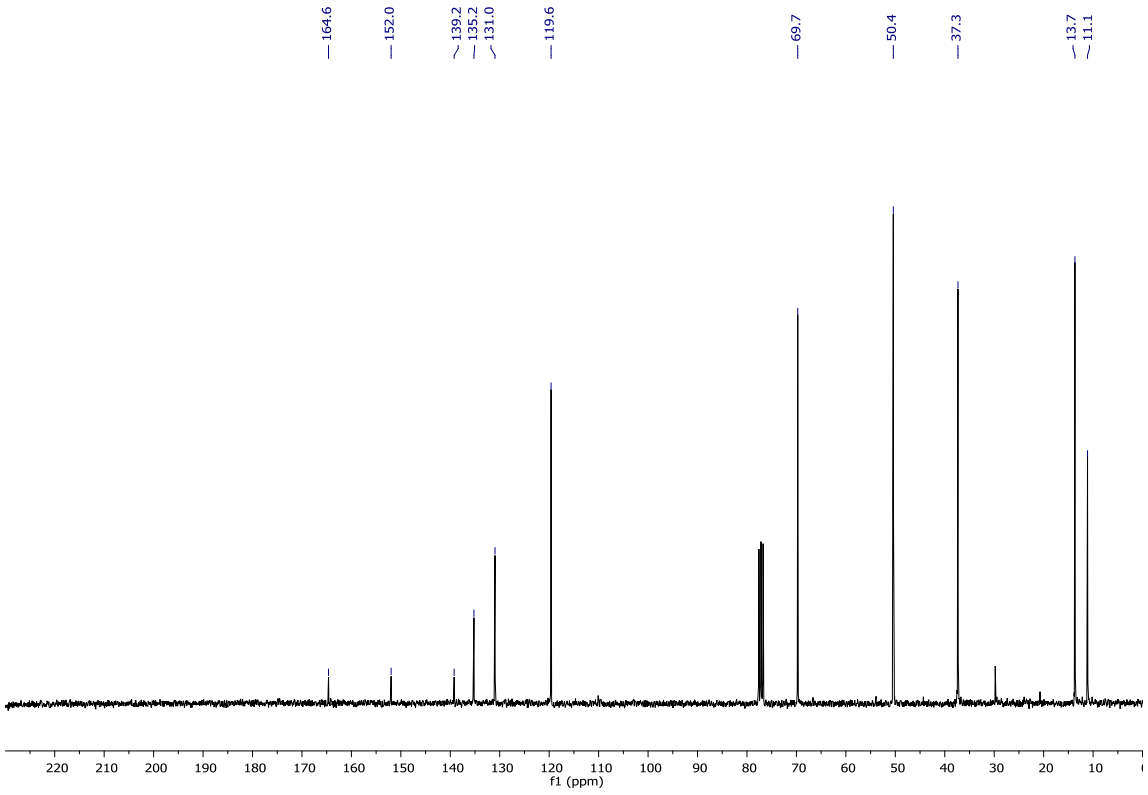

6.02
5.96
5.94
5.90
5.89
5.42
5.37
5.31
5.27
4.72
4.70
4.50
3.83
3.82
3.66
1.89
OMe
OMe
21Ea
2.78
0.61
0.73
0.74
1.93
2.12
6.61
2.06
3.00
f1 (ppm)

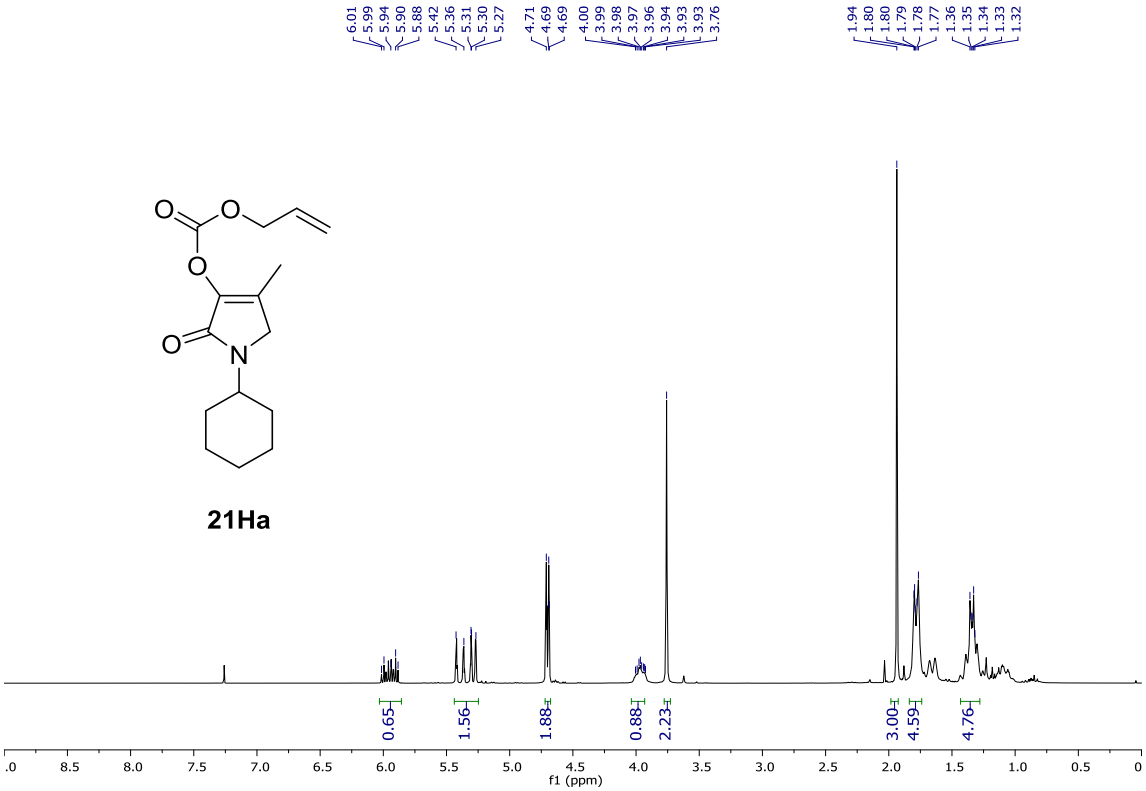

164.9
151.9
149.4
148.7
138.9
135.9
130.9
129.3
120.6
119.6
111.3
111.1
69.7
56.0
50.4
46.4
11.1
f1 (ppm)

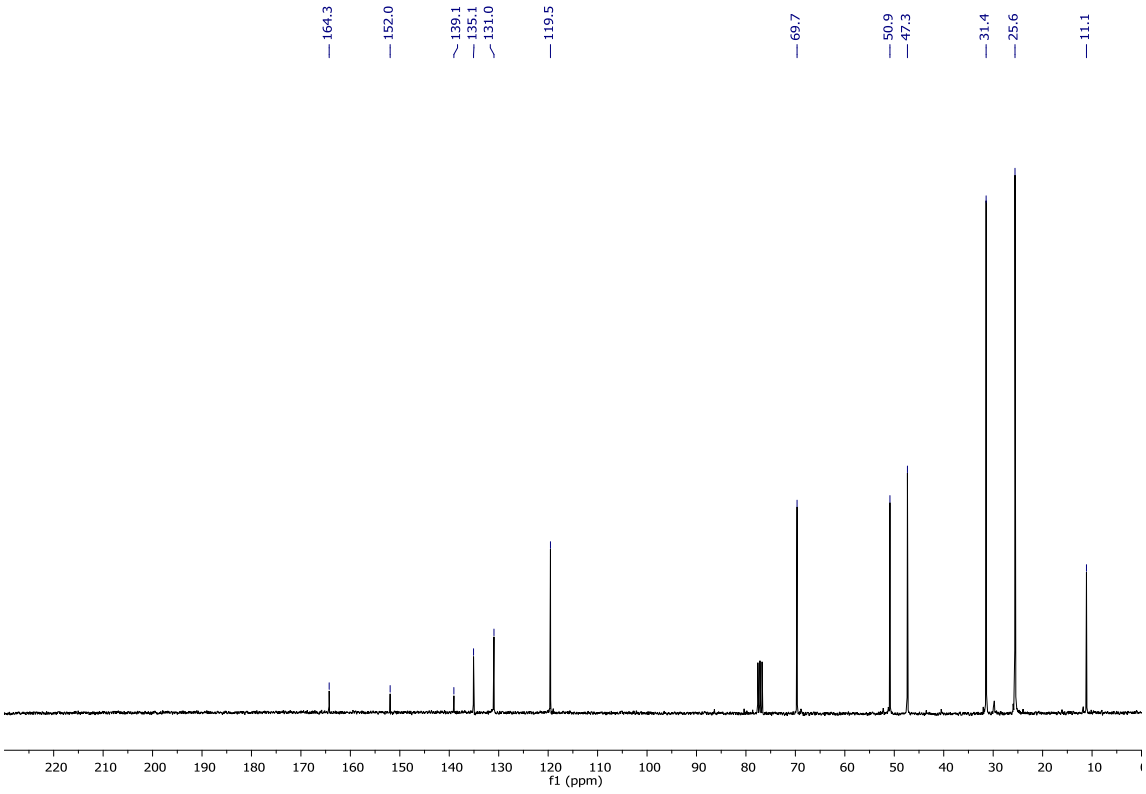

5.97
5.95
5.92
5.86
5.84
5.38
5.37
5.33
5.32
5.27
5.26
5.24
5.23
4.67
4.65
3.77
2.95
1.89
O
O
O
O
N
21Fa
0.53
0.69
0.67
1.85
2.31
3.08
3.00
f1 (ppm)

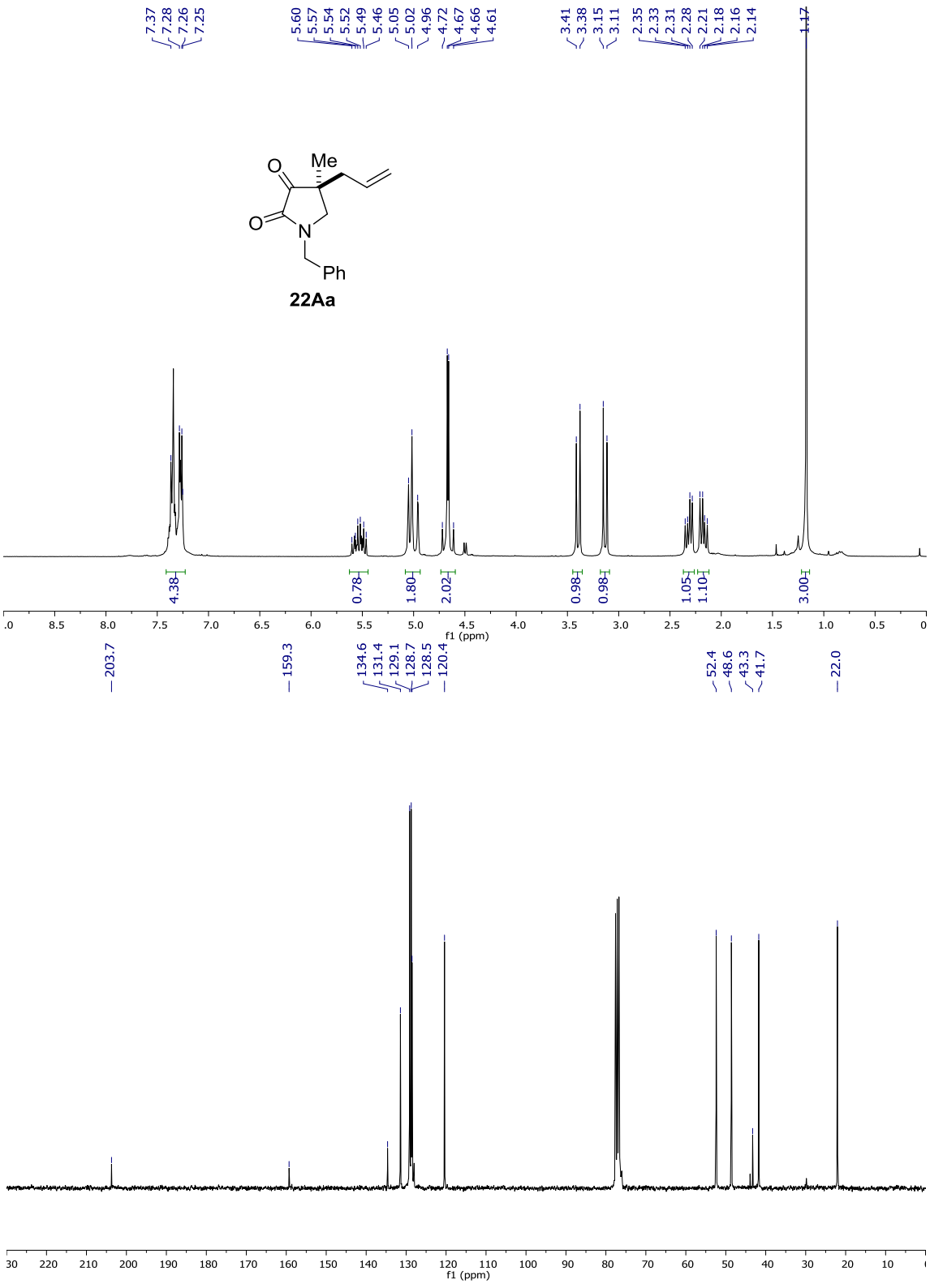

164.9
151.8
139.0
135.3
130.8
119.5
69.6
52.9
29.5
10.9
f1 (ppm)

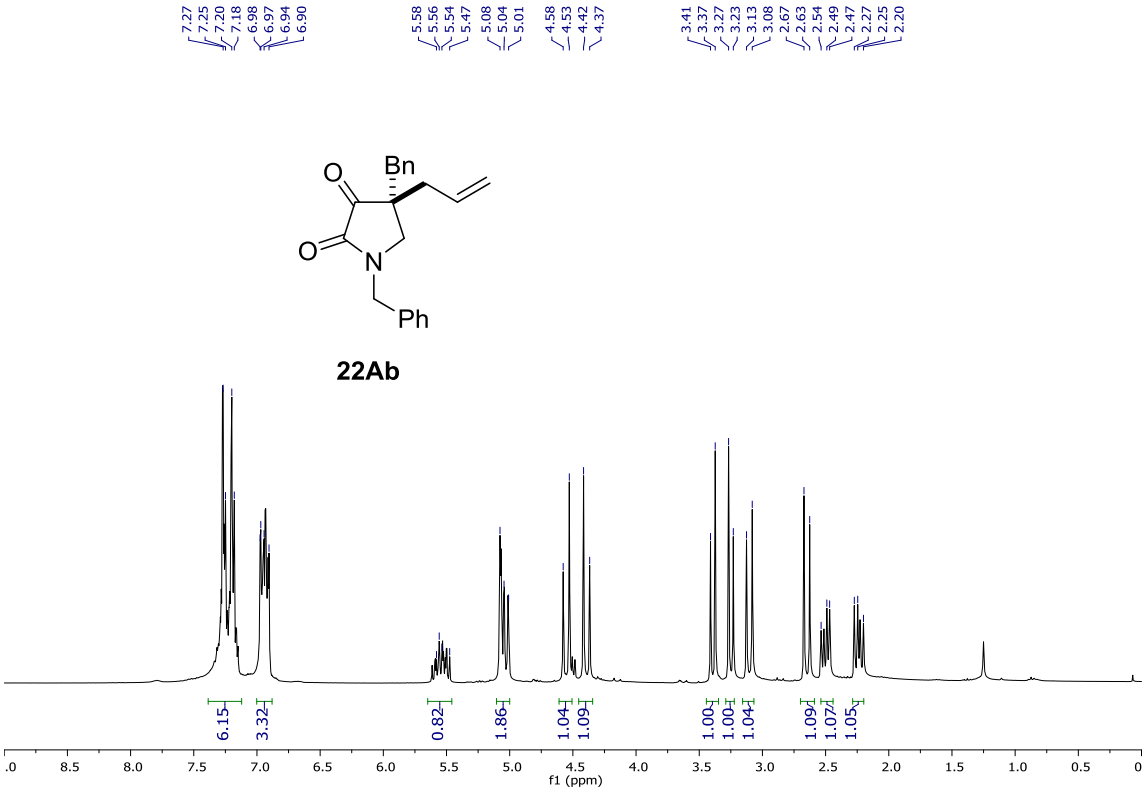

6.04
6.02
5.98
5.96
5.91
5.45
5.33
5.29
4.74
4.72
3.81
3.52
3.50
3.47
3.45
1.96
1.20
1.18
1.15
21Ga
0.62
1.42
1.69
2.06
1.68
2.74
3.00
f1 (ppm)

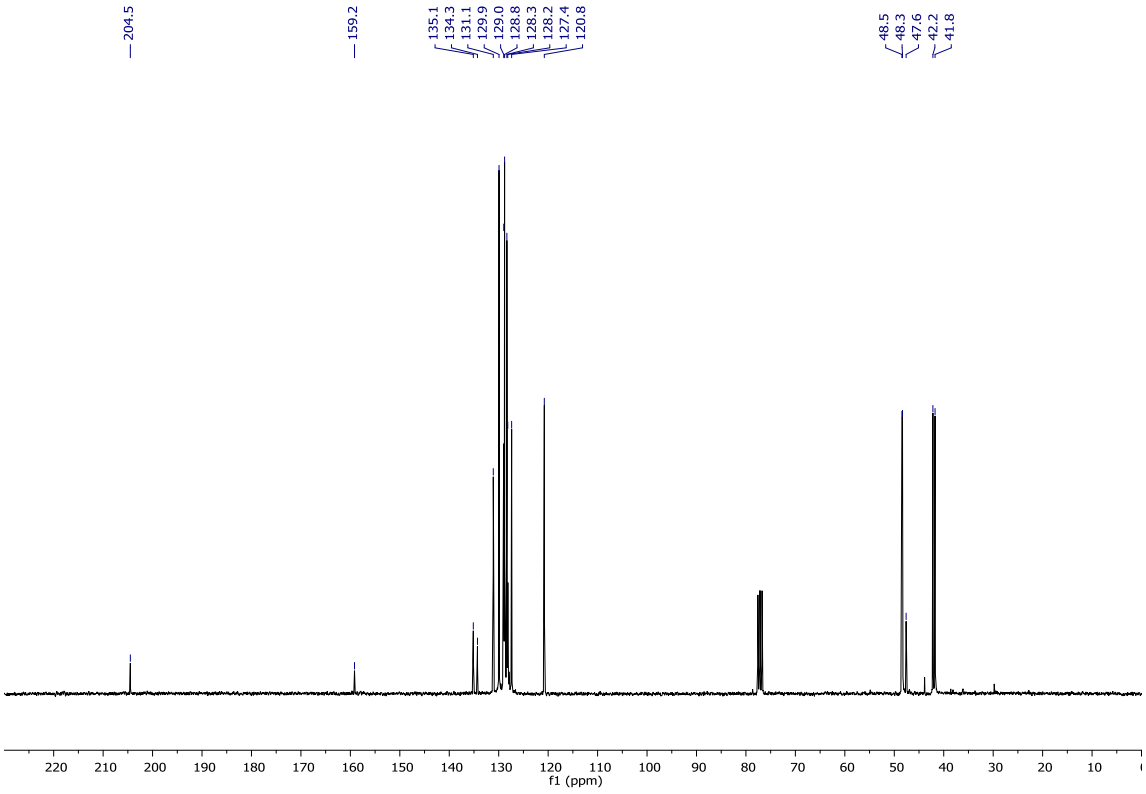

164.6
152.0
139.2
135.2
131.0
119.6
69.7
50.4
37.3
13.7
11.1
f1 (ppm)

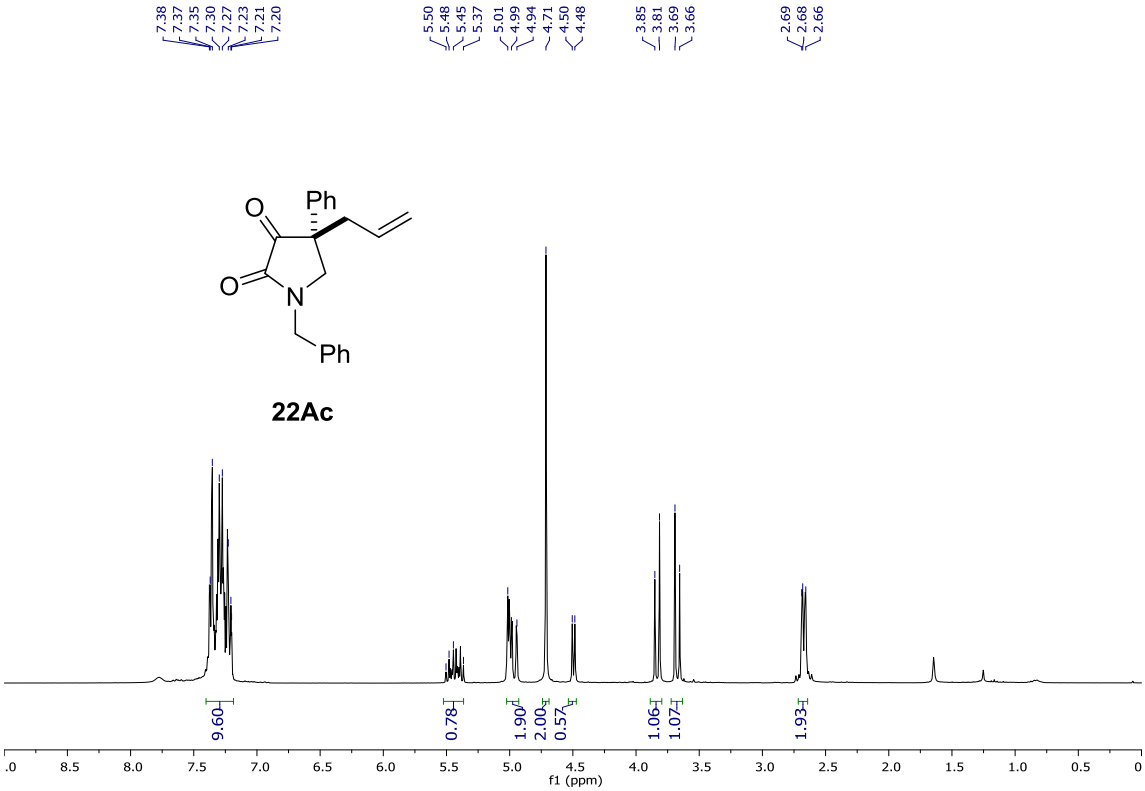

6.01
5.99
5.94
5.90
5.88
5.42
5.36
5.31
5.30
5.27
4.71
4.69
4.69
4.00
3.99
3.98
3.97
3.96
3.94
3.93
3.93
3.76
1.94
1.80
1.80
1.79
1.78
1.77
1.36
1.35
1.34
1.33
1.32
21Ha
0.65
1.56
1.88
0.88
2.23
3.00
4.59
4.76
f1 (ppm)

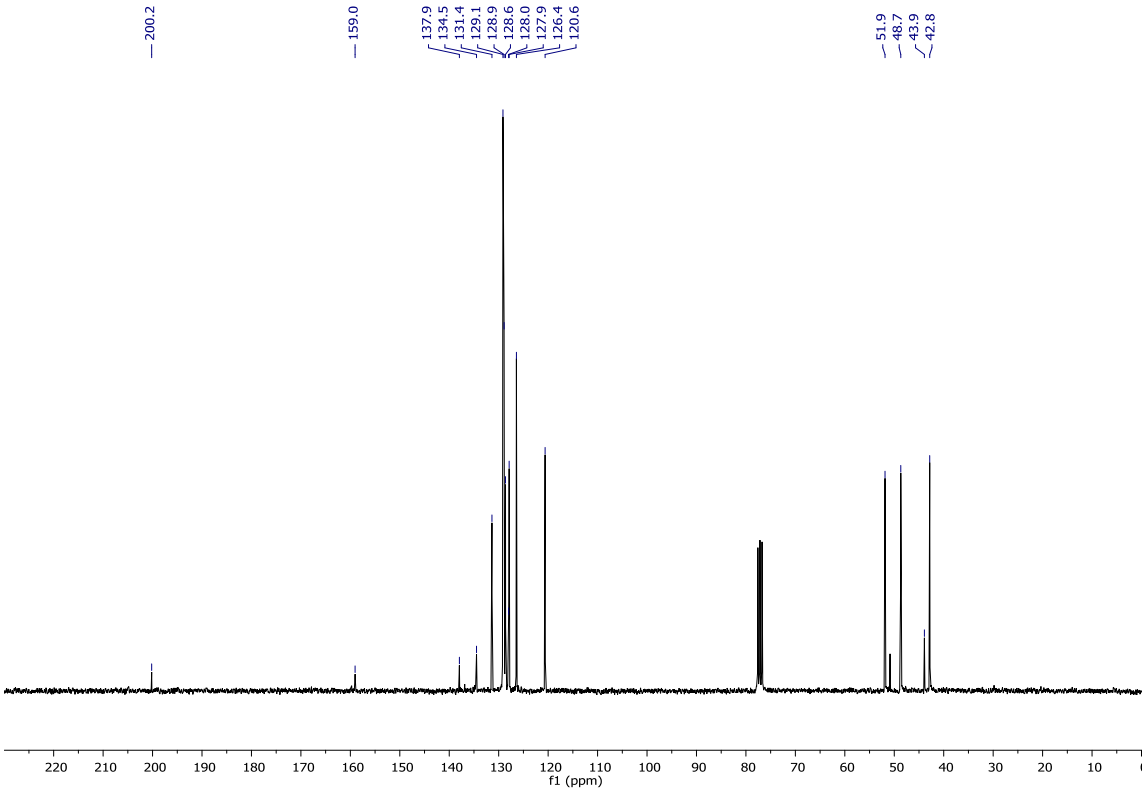

164.3
152.0
139.1
135.1
131.0
119.5
69.7
50.9
47.3
31.4
25.6
11.1
f1 (ppm)

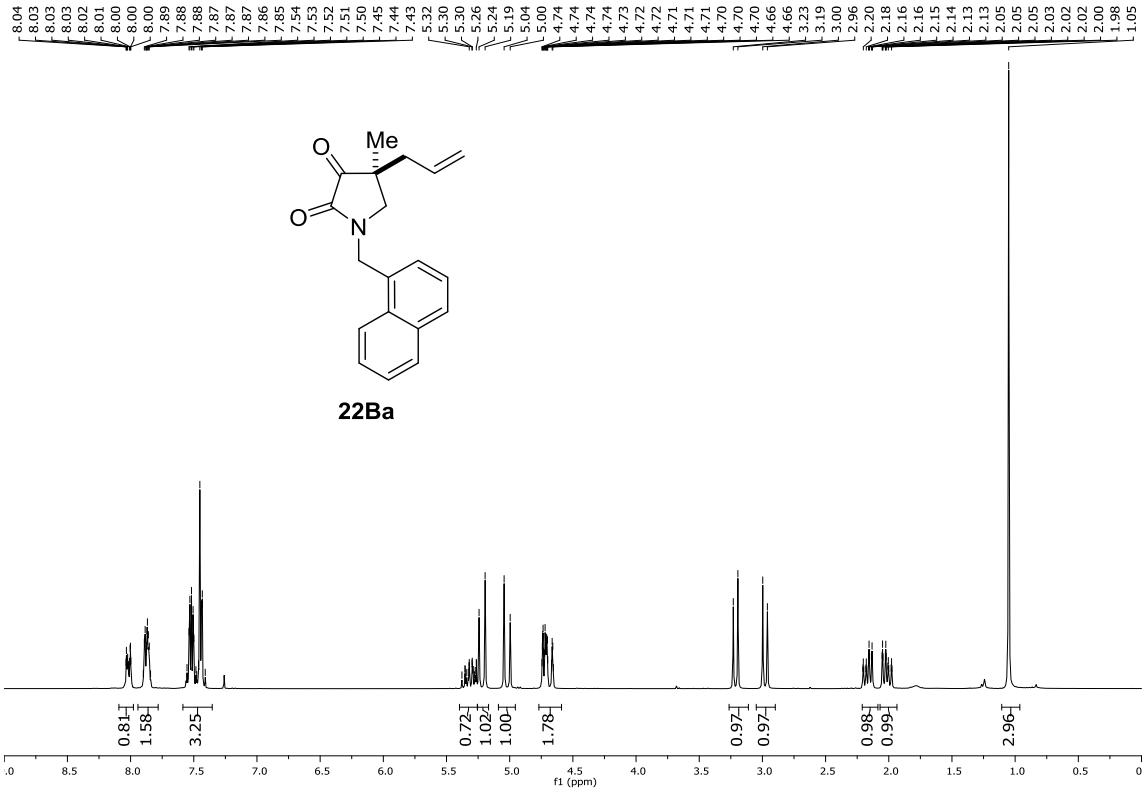

7.37
7.28
7.26
7.25
5.60
5.57
5.54
5.52
5.49
5.46
5.05
5.02
4.96
4.72
4.67
4.66
4.61
3.41
3.38
3.15
3.11
2.35
2.33
2.31
2.28
2.21
2.18
2.16
2.14
1.17
Me
O
O
N
Ph
22Aa
4.38
0.78
1.80
2.02
0.98
0.98
1.05
1.10
3.00
f1 (ppm)
203.7
159.3
134.6
131.4
129.1
128.7
128.5
120.4
52.4
48.6
43.3
41.7
22.0
f1 (ppm)

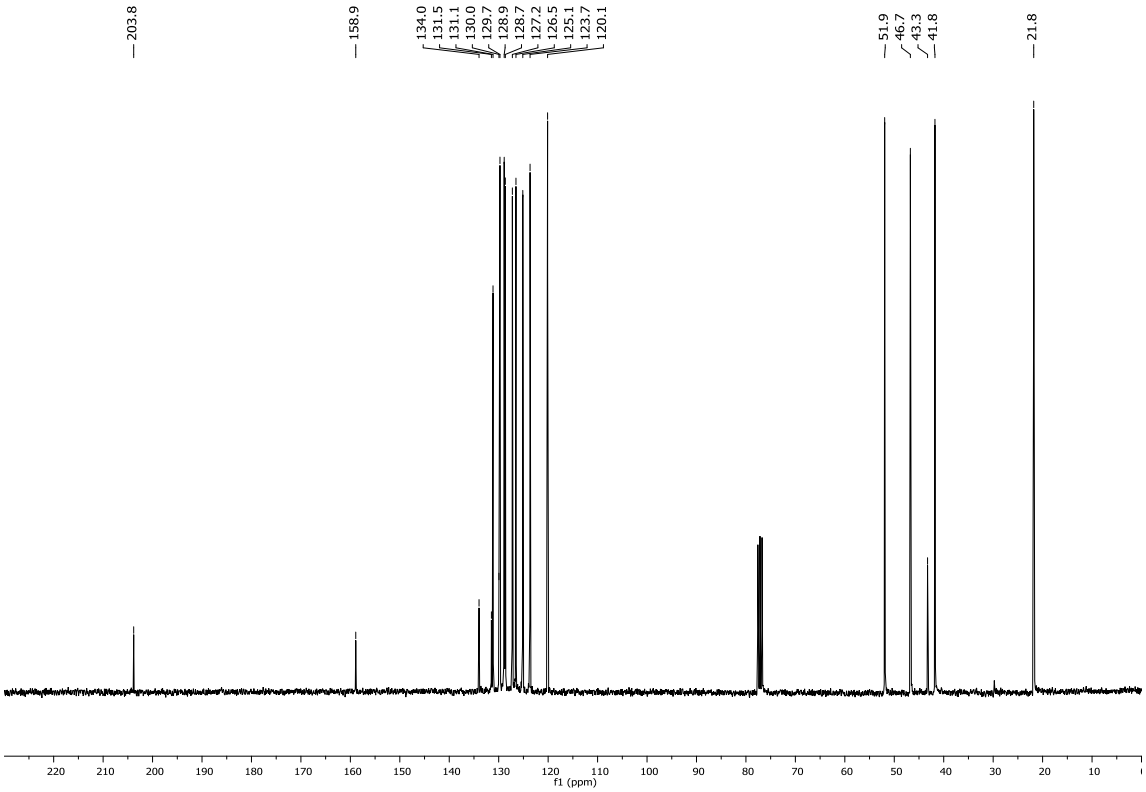

7.27
7.25
7.20
7.18
6.98
6.97
6.94
6.90
5.58
5.56
5.54
5.47
5.08
5.04
5.01
4.58
4.53
4.42
4.37
3.41
3.37
3.27
3.23
3.13
3.08
2.67
2.63
2.54
2.49
2.47
2.27
2.25
2.20
O
Bn
O
N
Ph
22Ab
6.15
3.32
0.82
1.86
1.04
1.09
1.00
1.00
1.04
1.09
1.07
1.05
f1 (ppm)

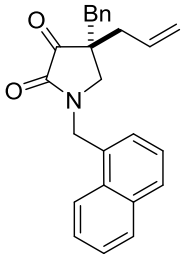

204.5
159.2
135.1
134.3
131.1
129.9
129.0
128.8
128.3
128.2
127.4
120.8
48.5
48.3
47.6
42.2
41.8
f1 (ppm)


7.38
7.37
7.35
7.30
7.27
7.23
7.21
7.20
5.50
5.48
5.45
5.37
5.01
4.99
4.94
4.71
4.50
4.48
3.85
3.81
3.69
3.66
2.69
2.68
2.66
O
Ph
O
N
Ph
22Ac
9.60
0.78
1.90
2.00
0.57
1.06
1.07
1.93
f1 (ppm)

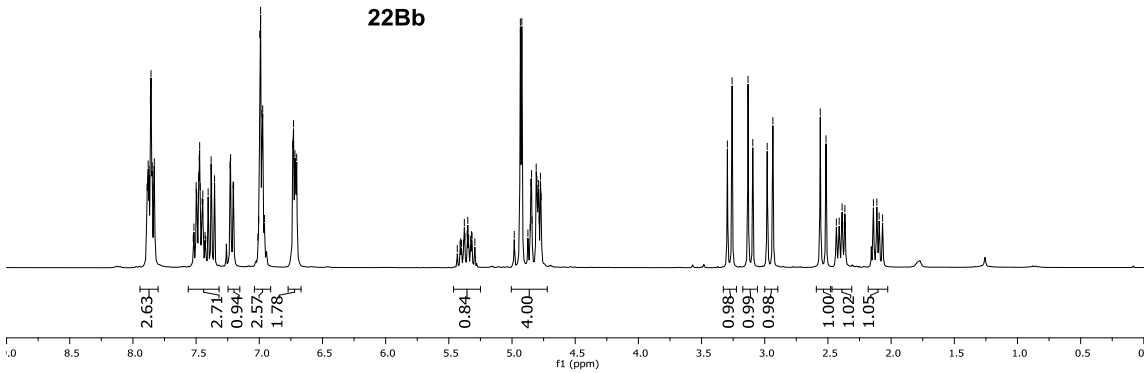

200.2
159.0
137.9
134.5
131.4
129.1
128.9
128.6
128.0
127.9
126.4
120.6
51.9
48.7
43.9
42.8
f1 (ppm)

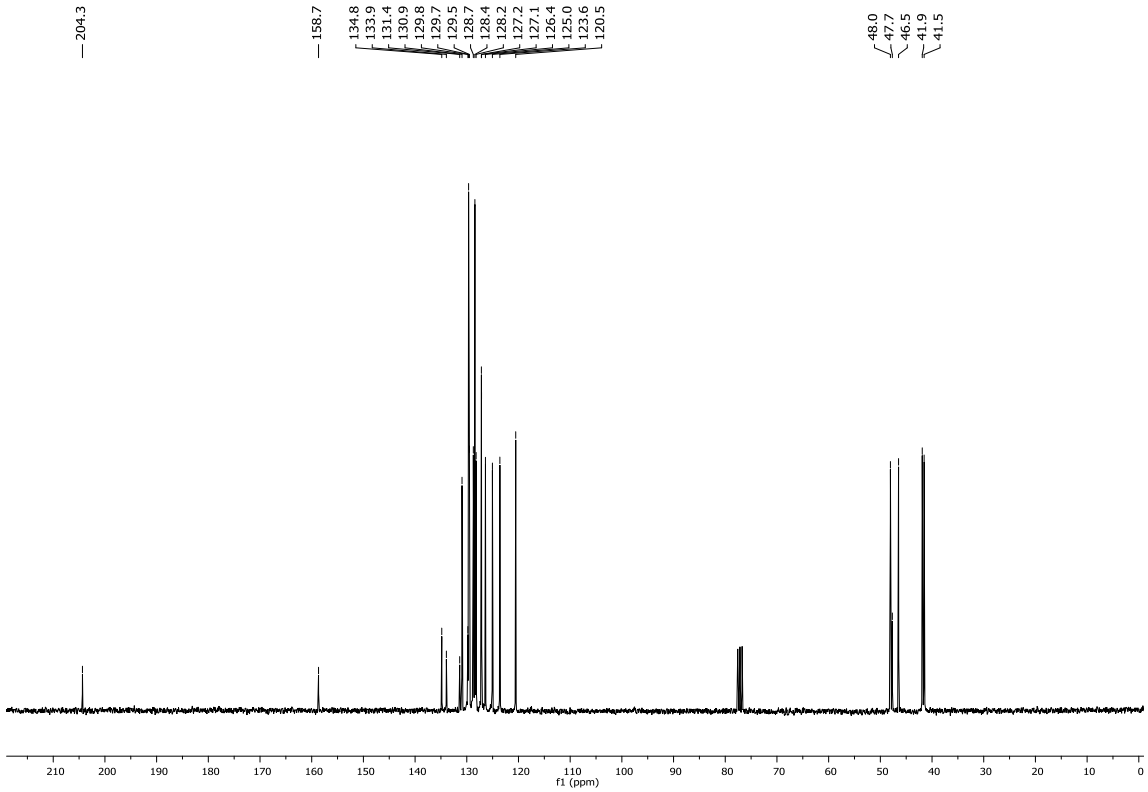

Me
O
O
N
22Ba
0.81
1.58
3.25
0.72
1.02
1.00
1.78
0.97
0.97
0.98
0.99
2.96
f1 (ppm)

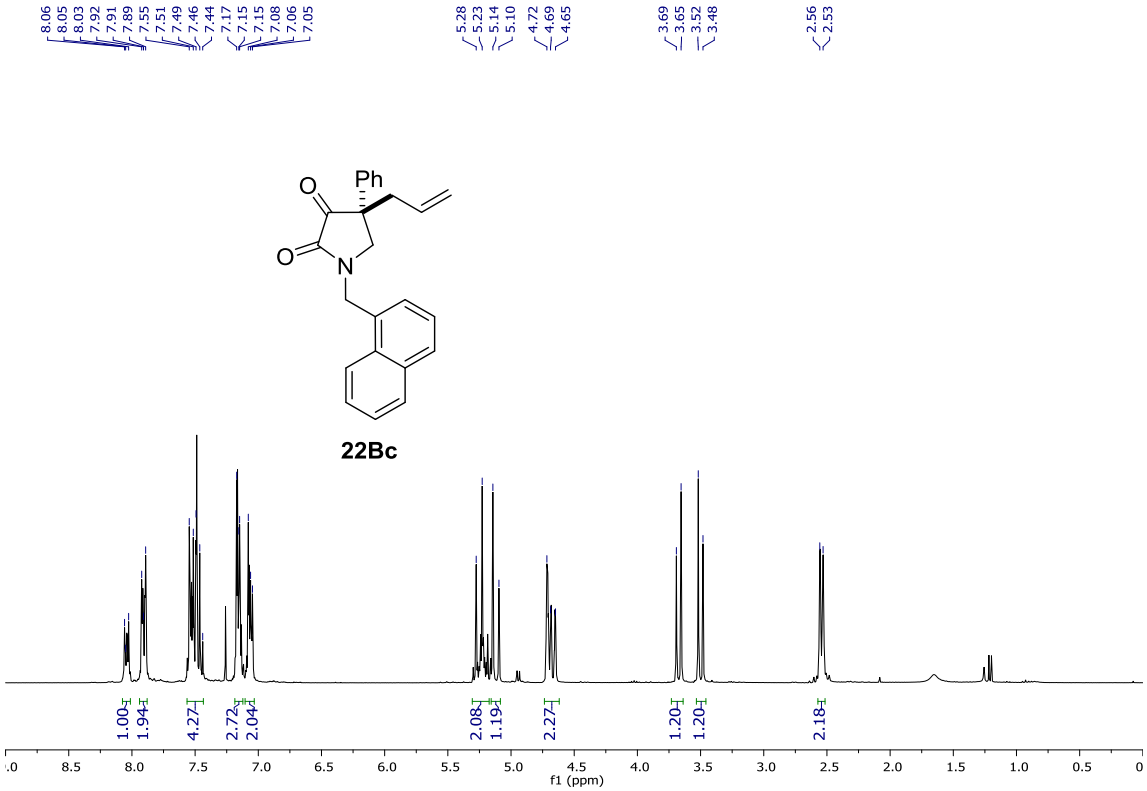

203.8
158.9
134.0
131.5
131.1
130.0
129.7
128.9
128.7
127.2
126.5
125.1
123.7
120.1
51.9
46.7
43.3
41.8
21.8
f1 (ppm)

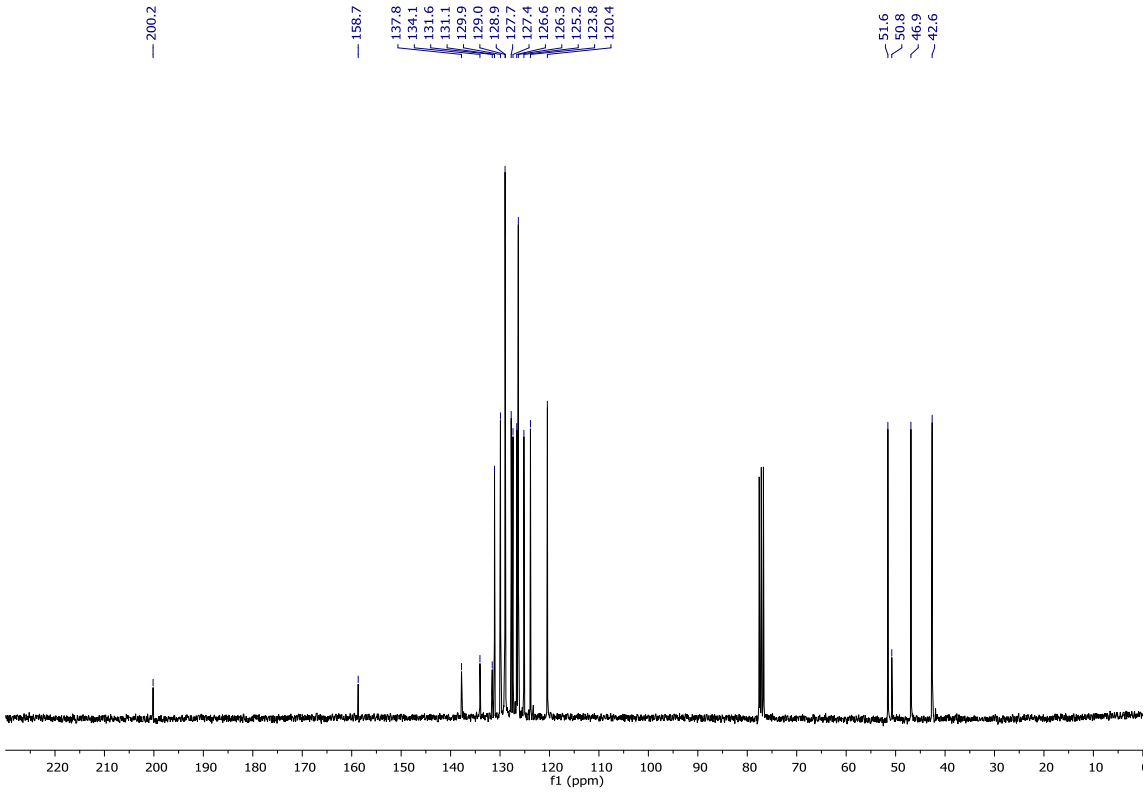


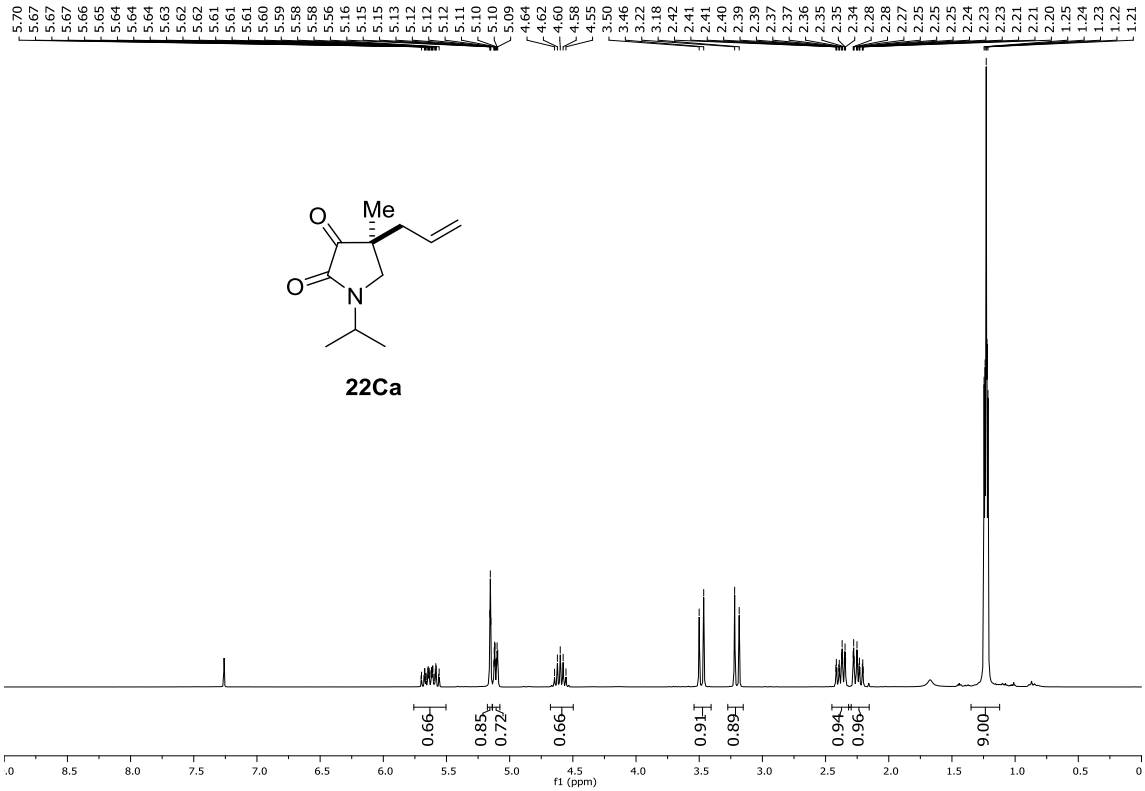
22Bb



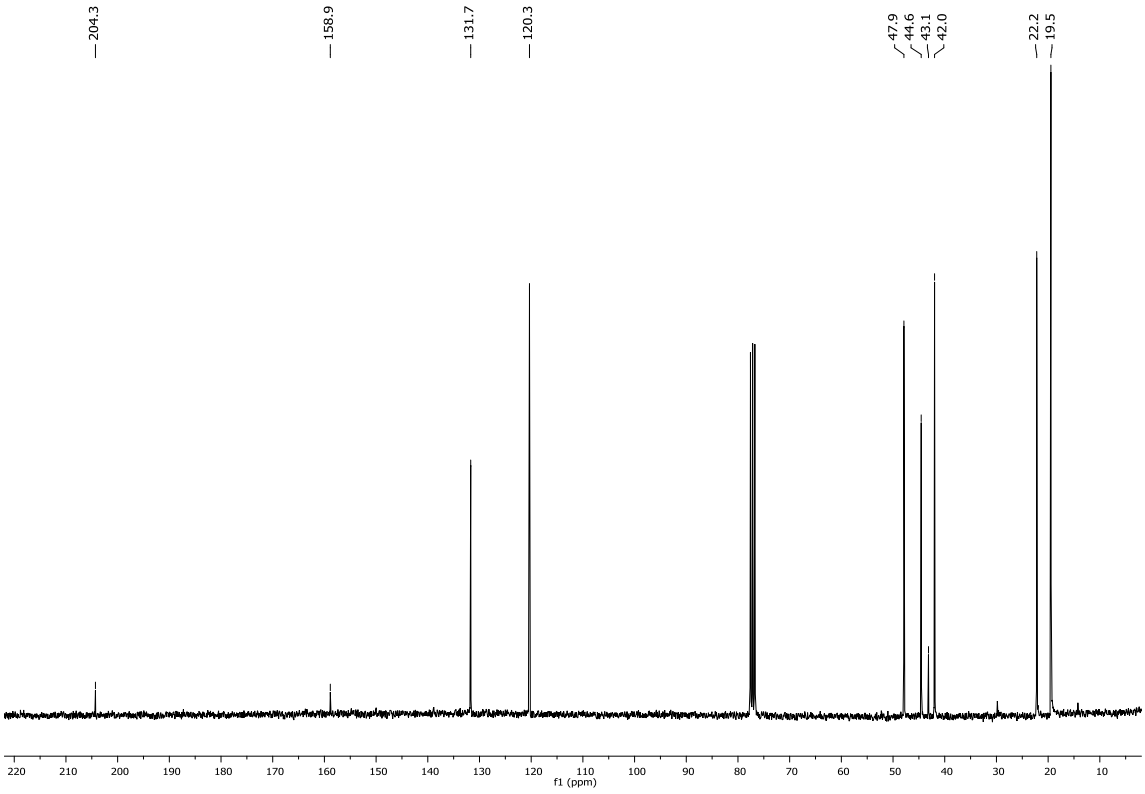


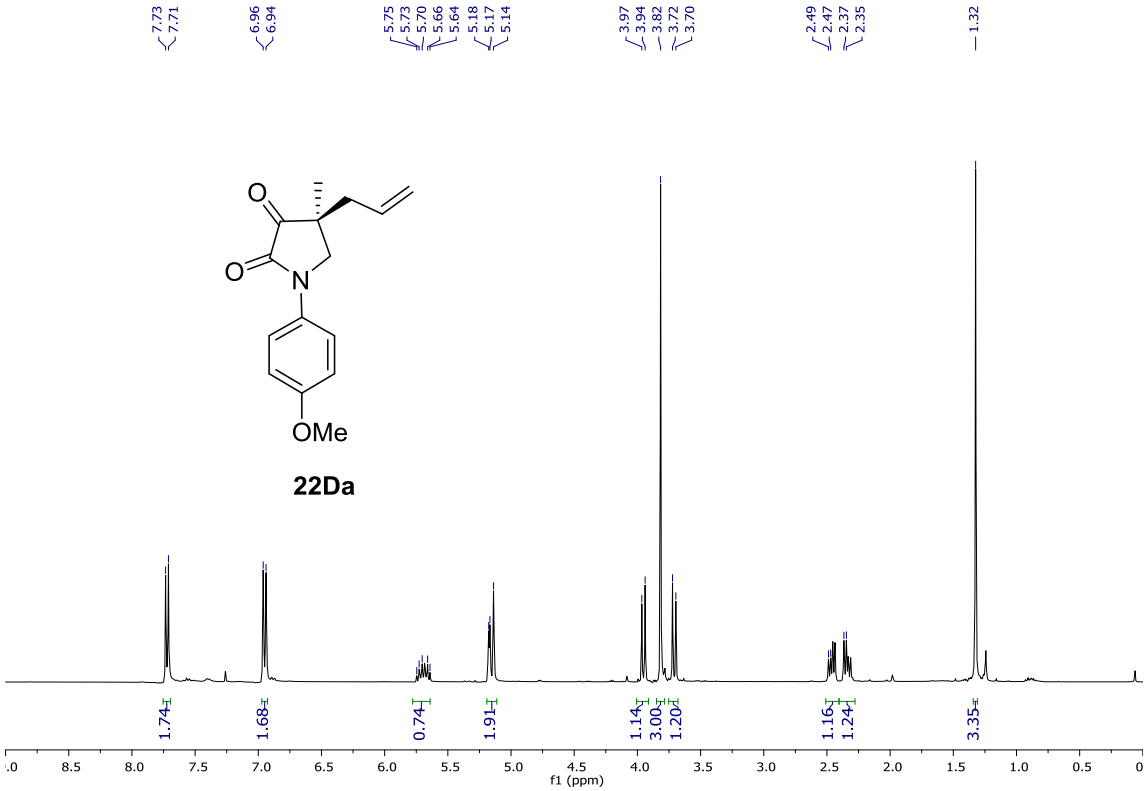

8.06
8.05
8.03
7.92
7.91
7.89
7.55
7.51
7.49
7.46
7.44
7.17
7.15
7.15
7.08
7.06
7.05
5.28
5.23
5.14
5.10
4.72
4.69
4.65
3.69
3.65
3.52
3.48
2.56
2.53
O
Ph
O
N
22Bc
1.00
1.94
4.27
2.72
2.04
2.08
1.19
2.27
1.20
1.20
2.18
f1 (ppm)

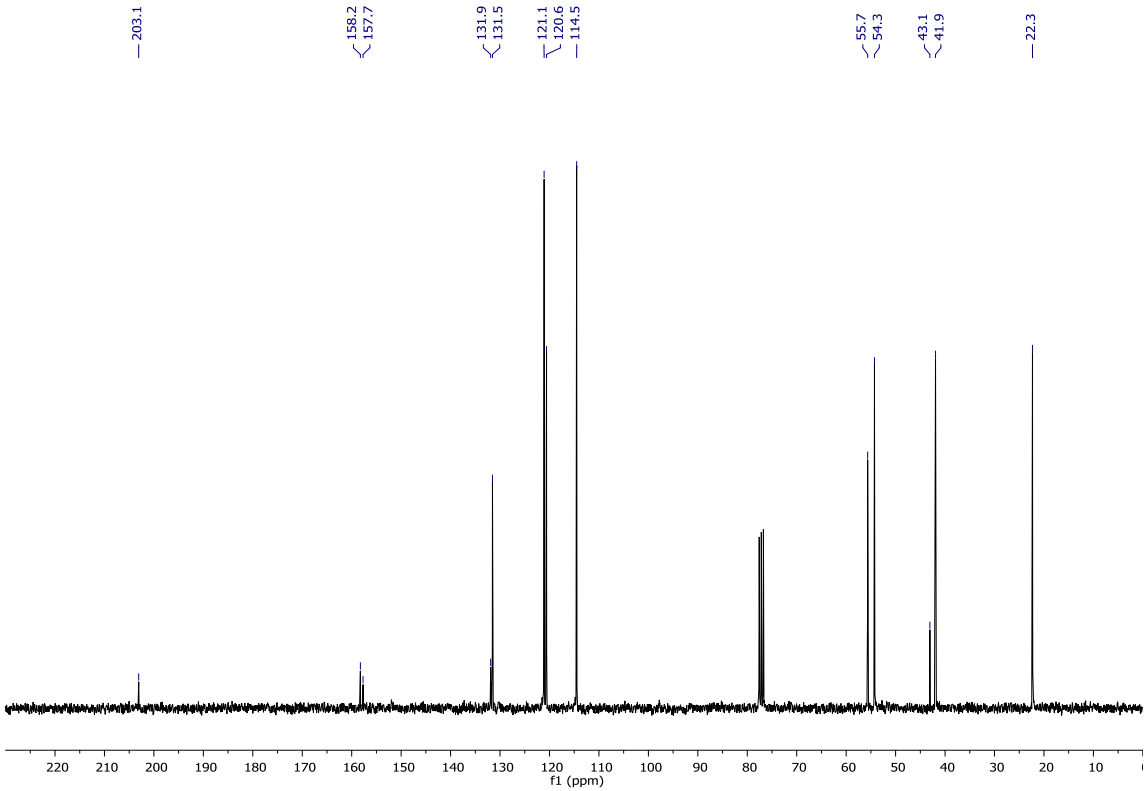

200.2
158.7
137.8
134.1
131.6
131.1
129.9
129.0
128.9
127.7
127.4
126.6
126.3
125.2
123.8
120.4
51.6
50.8
46.9
42.6
f1 (ppm)

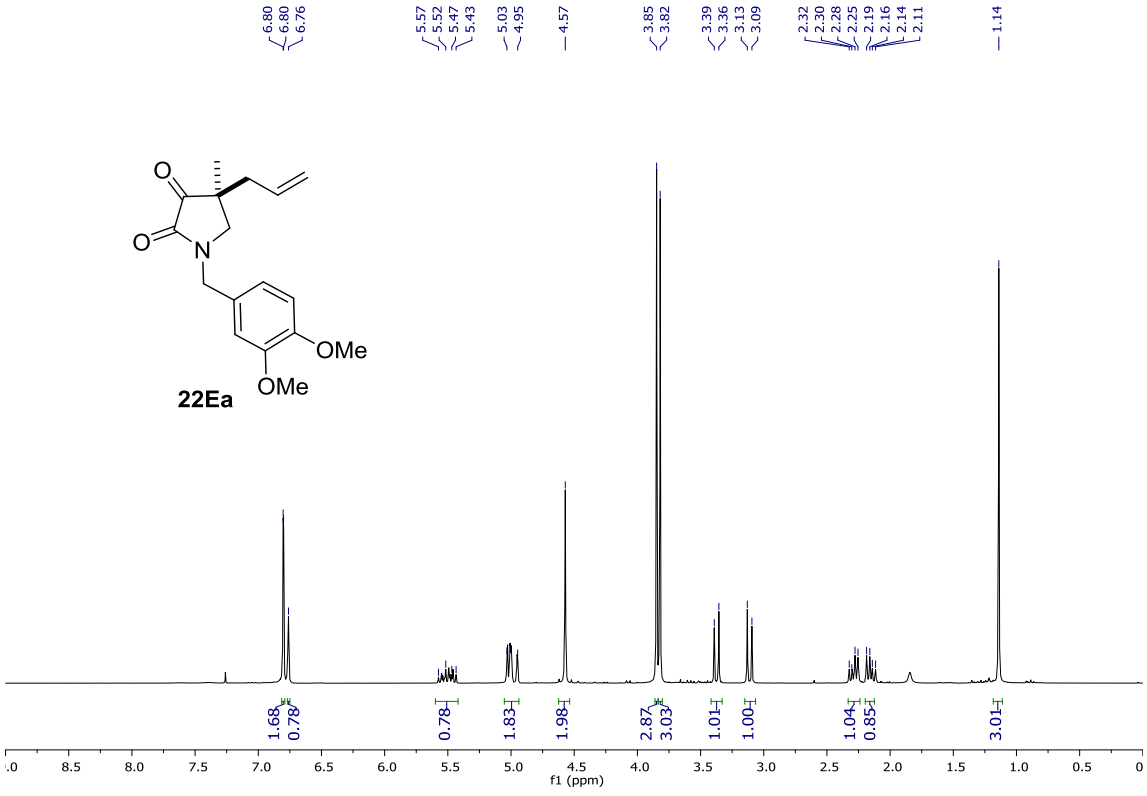

5.70 5.67 5.67 5.67 5.66 5.65 5.64 5.64 5.64 5.63 5.62 5.62 5.61 5.61 5.61 5.60 5.59 5.58 5.58 5.56 5.16 5.15 5.15 5.13 5.12 5.12 5.12 5.11 5.10 5.10 5.09 4.64 4.62 4.60 4.58 4.55 3.50 3.46 3.22 3.18 2.42 2.41 2.41 2.40 2.39 2.39 2.37 2.37 2.36 2.35 2.35 2.34 2.28 2.28 2.27 2.25 2.25 2.25 2.24 2.23 2.23 2.21 2.21 2.20 1.25 1.24 1.23 1.22 1.21
Me
O
O
N
0.66 0.85 0.72 0.66 0.91 0.89 0.94 0.96 9.00
f1 (ppm)

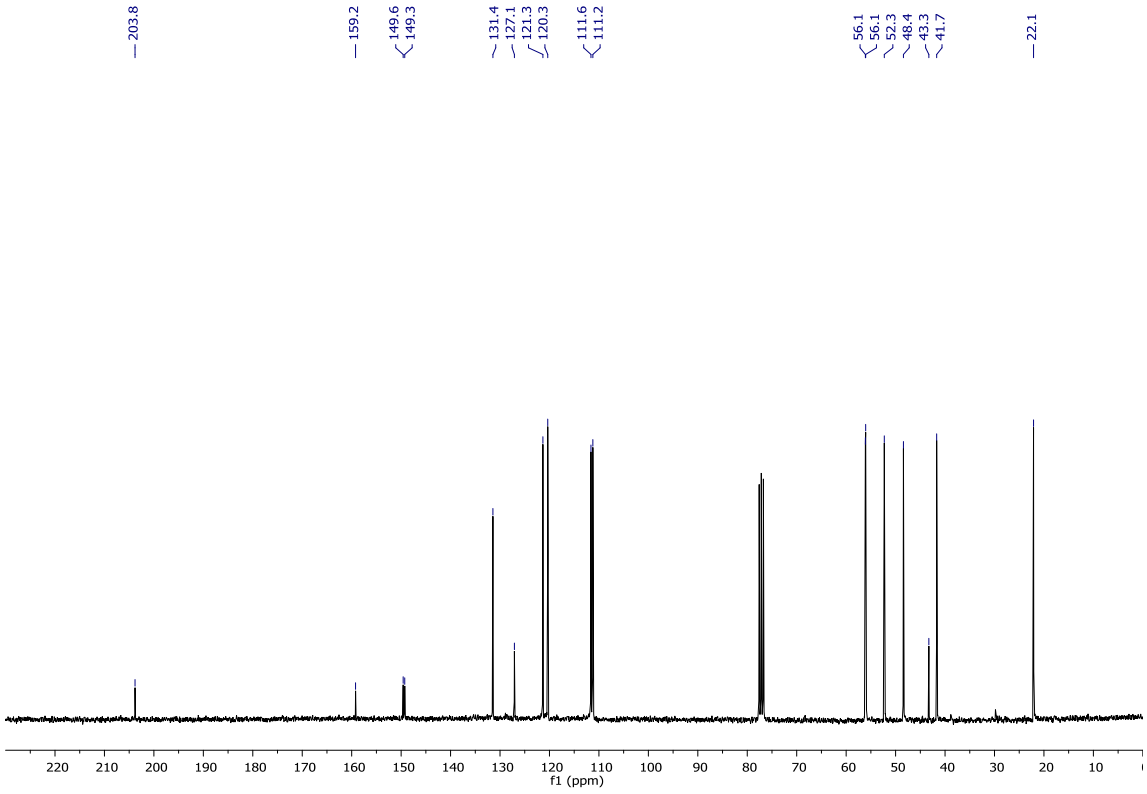
22Ca

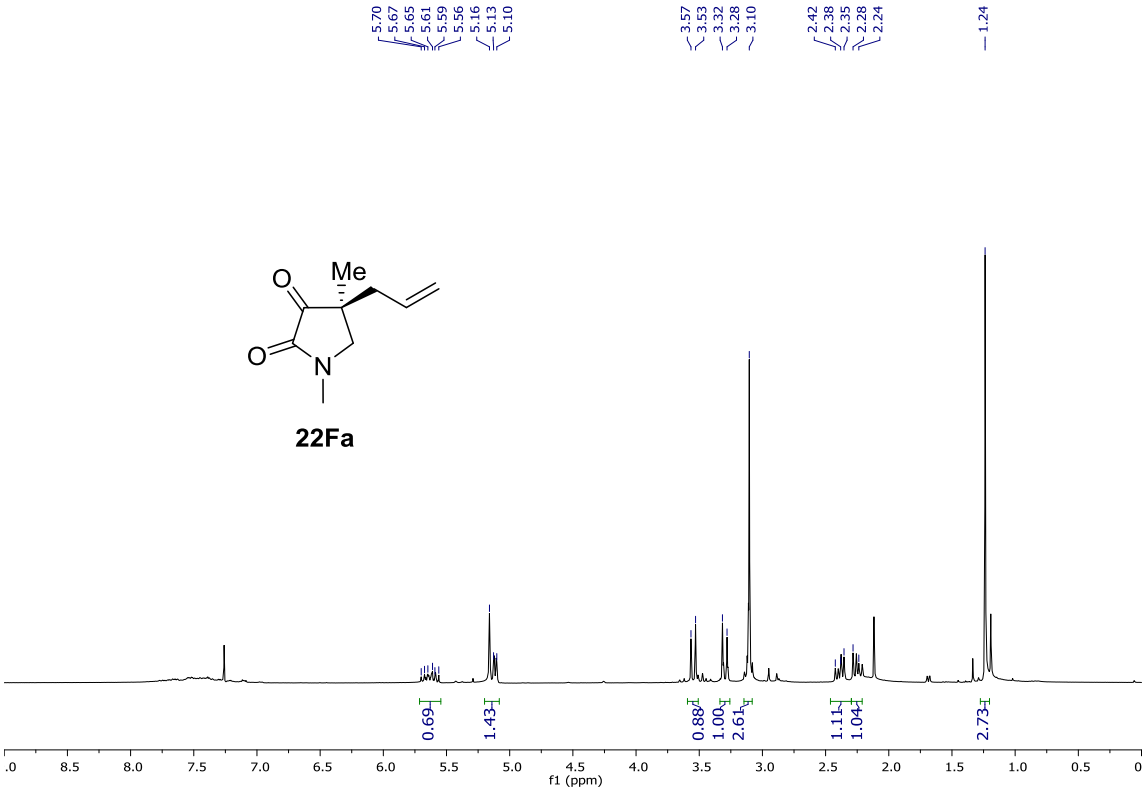

204.3
158.9
131.7
120.3
47.9
44.6
43.1
42.0
22.2
19.5
f1 (ppm)

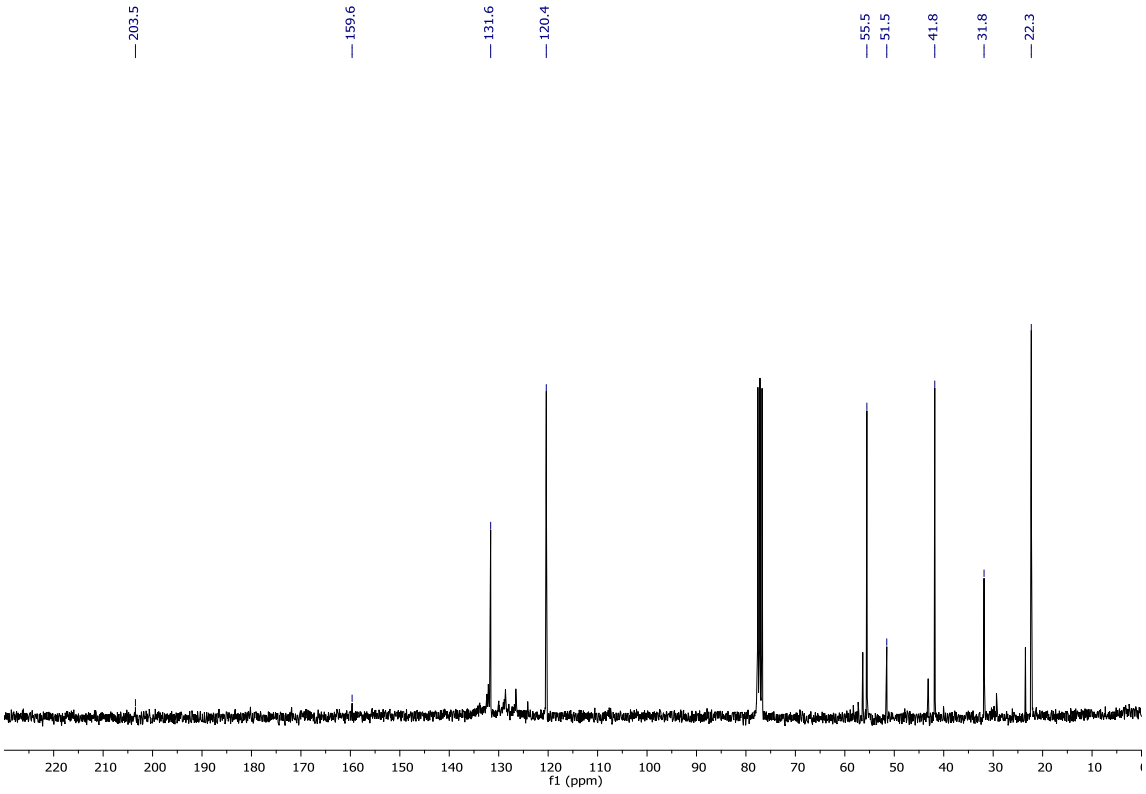

7.73
7.71
6.96
6.94
5.75
5.73
5.70
5.66
5.64
5.18
5.17
5.14
3.97
3.94
3.82
3.72
3.70
2.49
2.47
2.37
2.35
1.32
O
O
N
OMe
22Da
1.74
1.68
0.74
1.91
1.14
3.00
1.20
1.16
1.24
3.35
f1 (ppm)

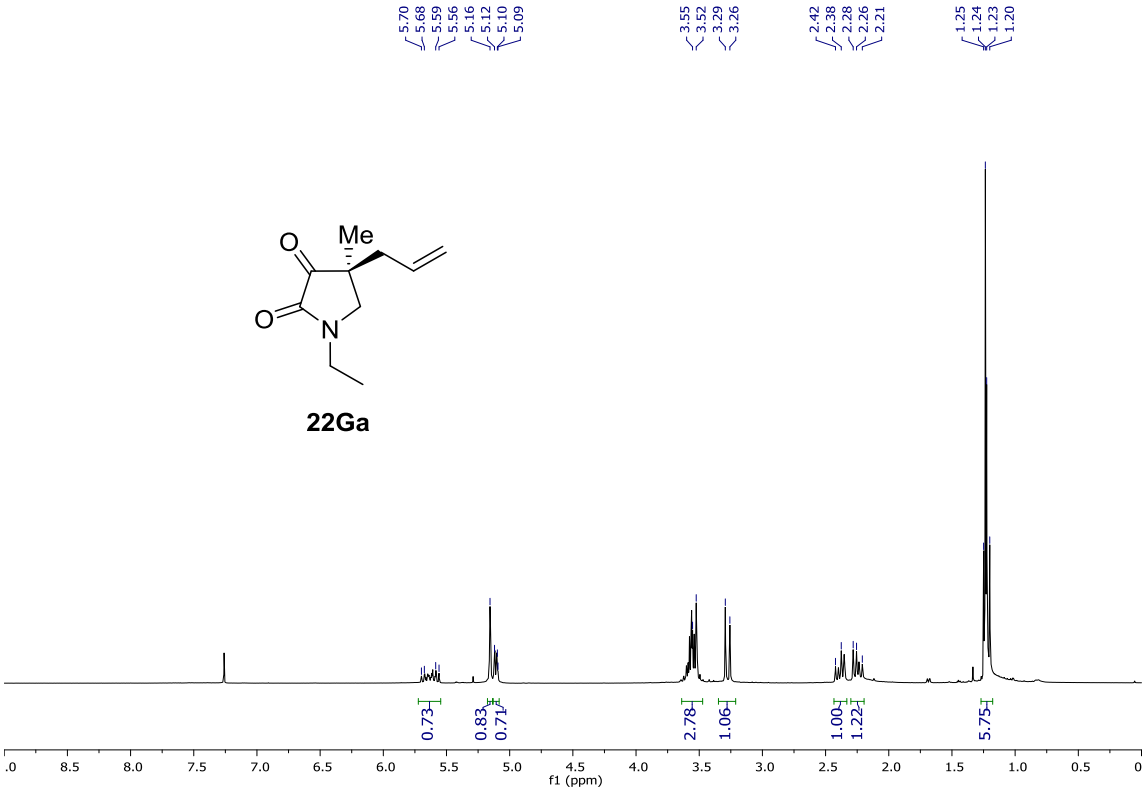

203.1
158.2
157.7
131.9
131.5
121.1
120.6
114.5
55.7
54.3
43.1
41.9
22.3
f1 (ppm)


6.80
6.80
6.76
5.57
5.52
5.47
5.43
5.03
4.95
4.57
3.85
3.82
3.39
3.36
3.13
3.09
2.32
2.30
2.28
2.25
2.19
2.16
2.14
2.11
1.14
O
O
N
OMe
OMe
22Ea
1.68
0.78
0.78
1.83
1.98
2.87
3.03
1.01
1.00
1.04
0.85
3.01
f1 (ppm)

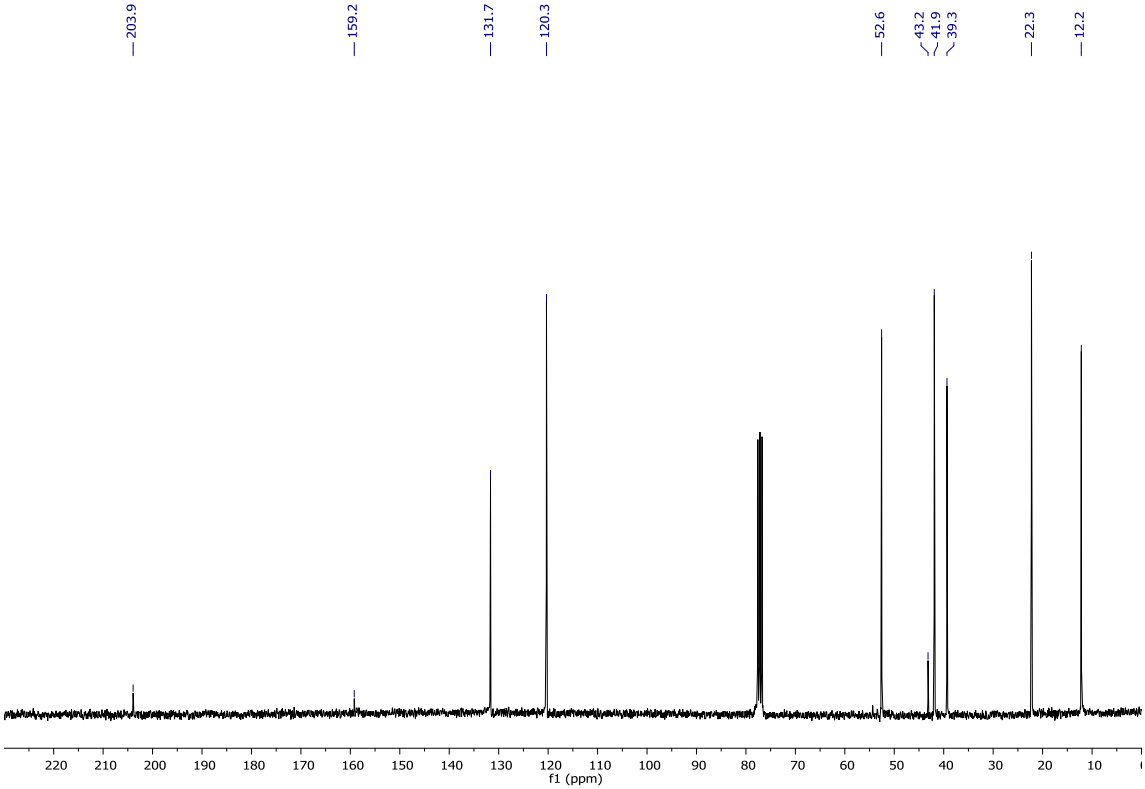

203.8
159.2
149.6
149.3
131.4
127.1
121.3
120.3
111.6
111.2
56.1
56.1
52.3
48.4
43.3
41.7
22.1
f1 (ppm)

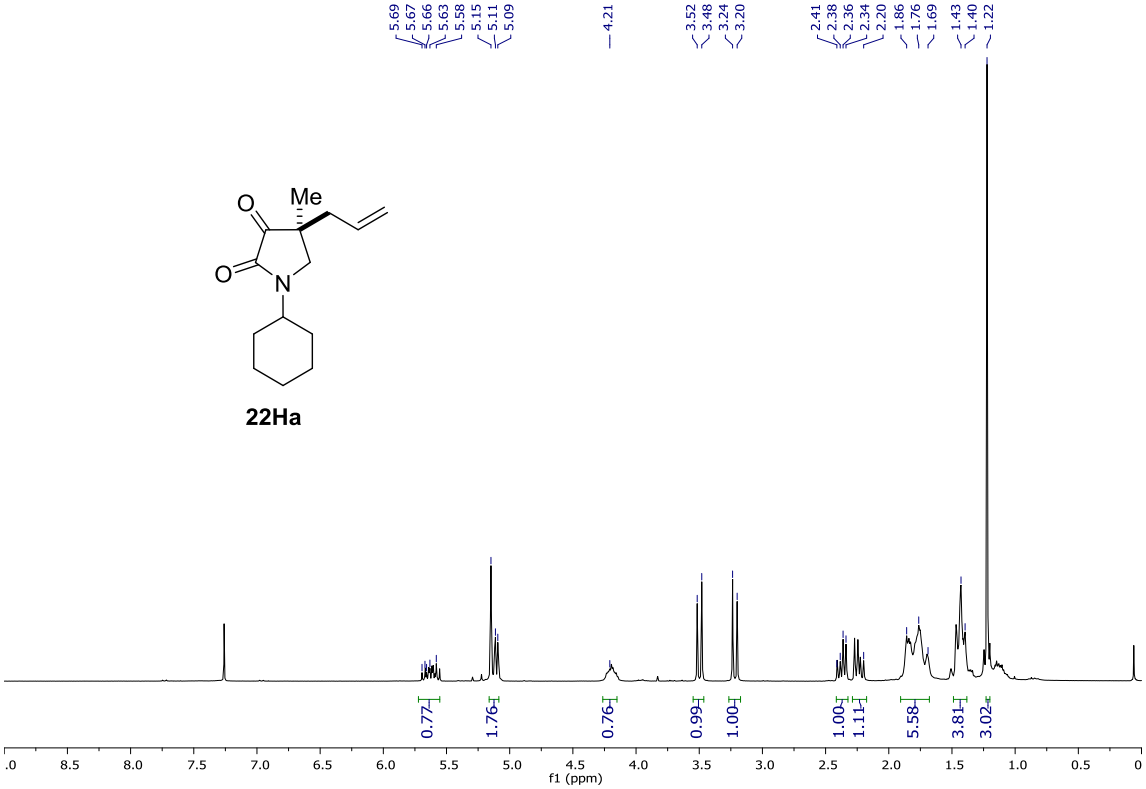

5.70
5.67
5.65
5.61
5.59
5.56
5.16
5.13
5.10
3.57
3.53
3.32
3.28
3.10
2.42
2.38
2.35
2.28
2.24
1.24
Me
O
O
N
22Fa
0.69
1.43
0.88
1.00
2.61
1.11
1.04
2.73
f1 (ppm)


203.5
159.6
131.6
120.4
55.5
51.5
41.8
31.8
22.3
f1 (ppm)

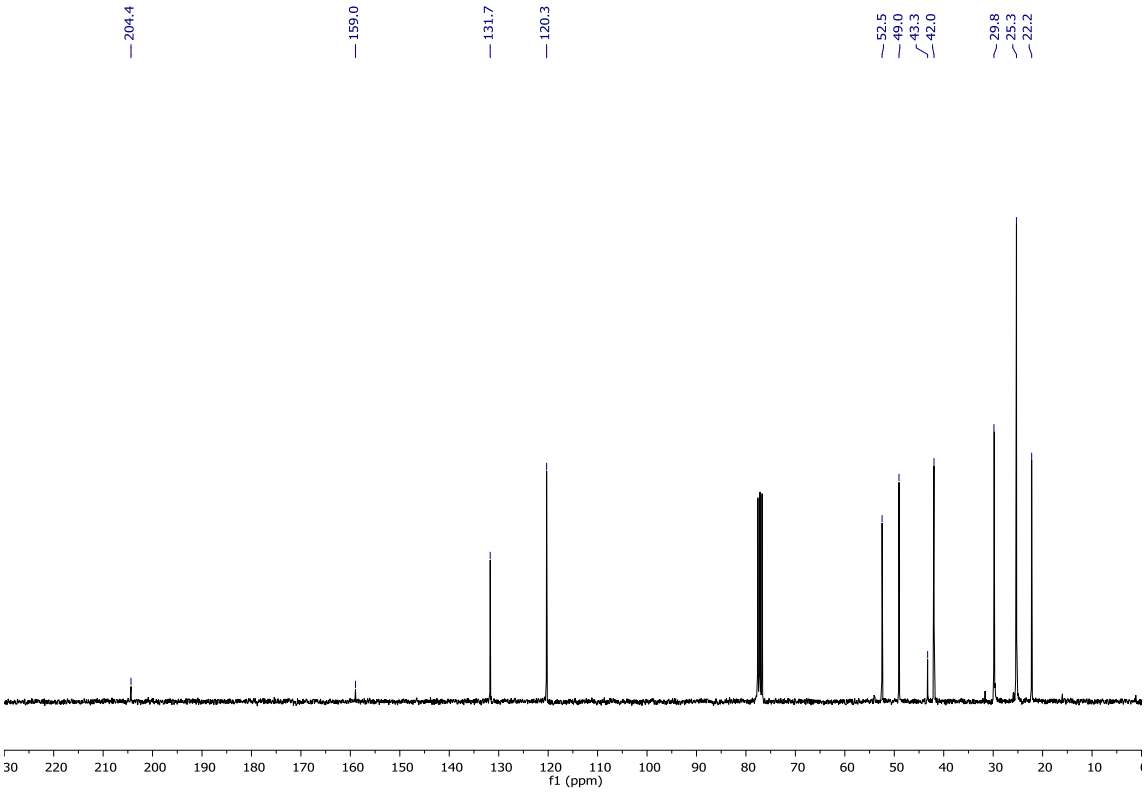

5.70
5.68
5.59
5.56
5.16
5.12
5.10
5.09
3.55
3.52
3.29
3.26
2.42
2.38
2.28
2.26
2.21
1.25
1.24
1.23
1.20
Me
O
O
N
0.73
0.83
0.71
2.78
1.06
1.00
1.22
5.75
f1 (ppm)

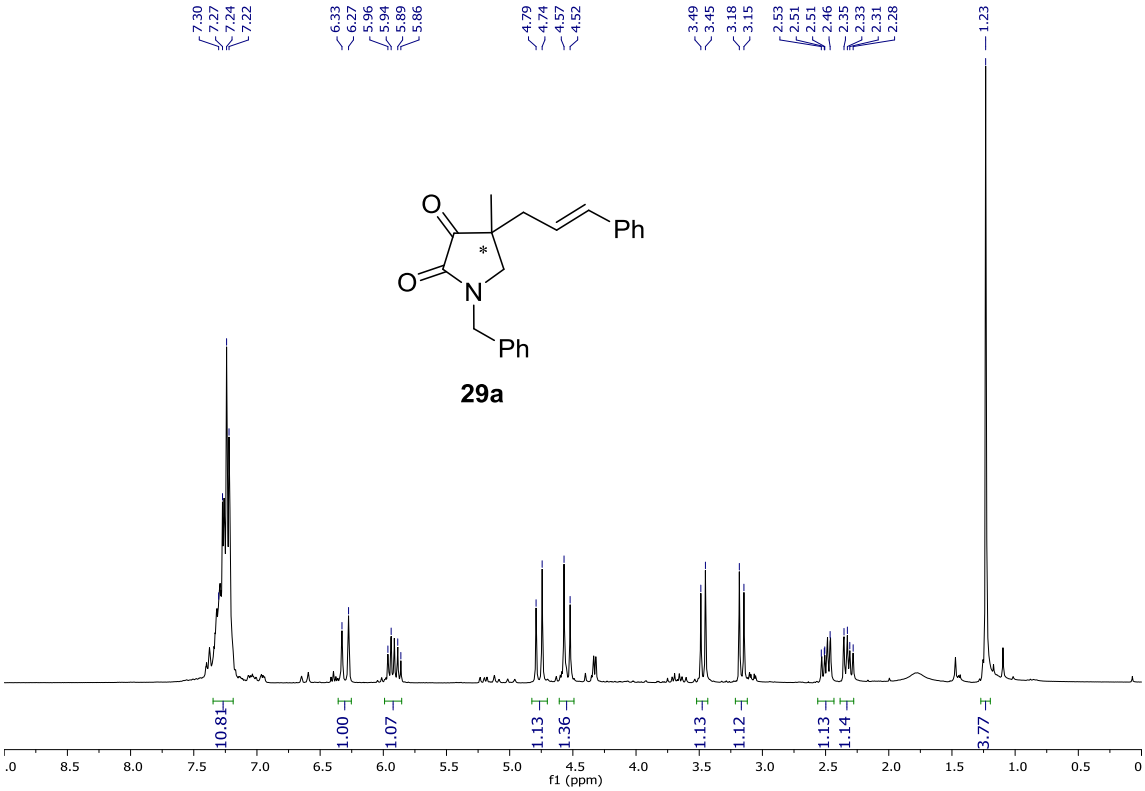
22Ga

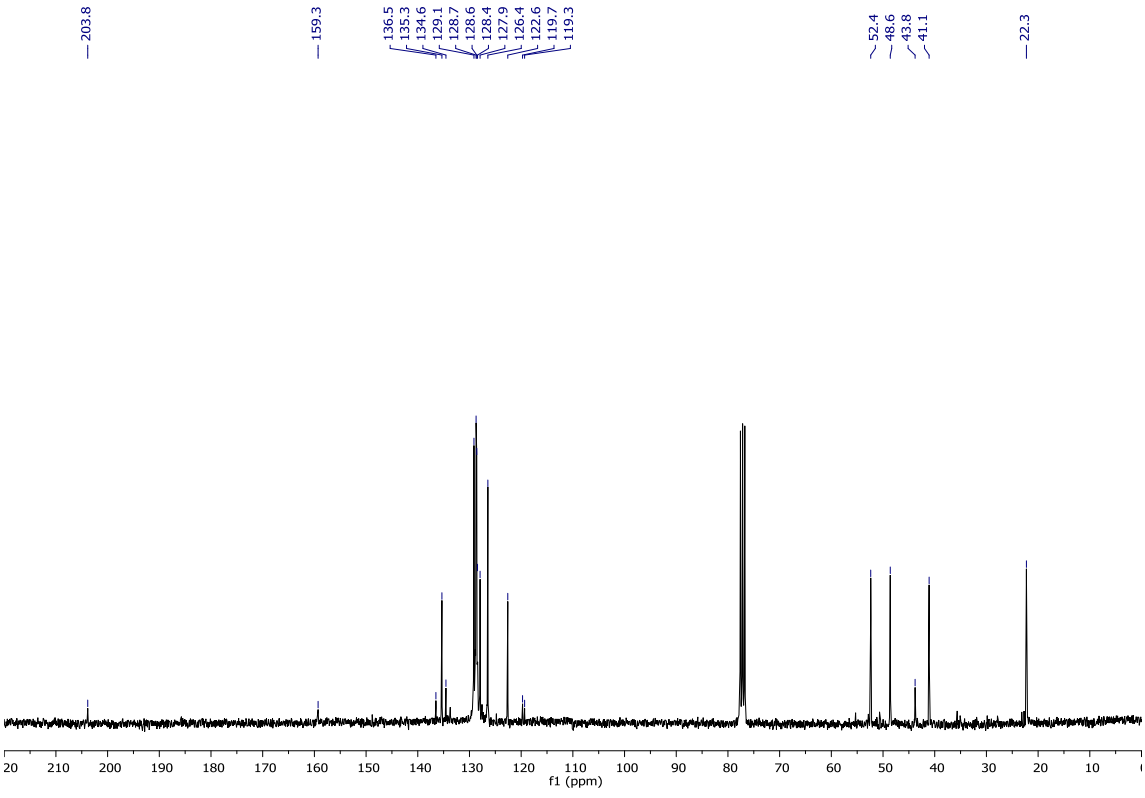

203.9
159.2
131.7
120.3
52.6
43.2
41.9
39.3
22.3
12.2
f1 (ppm)

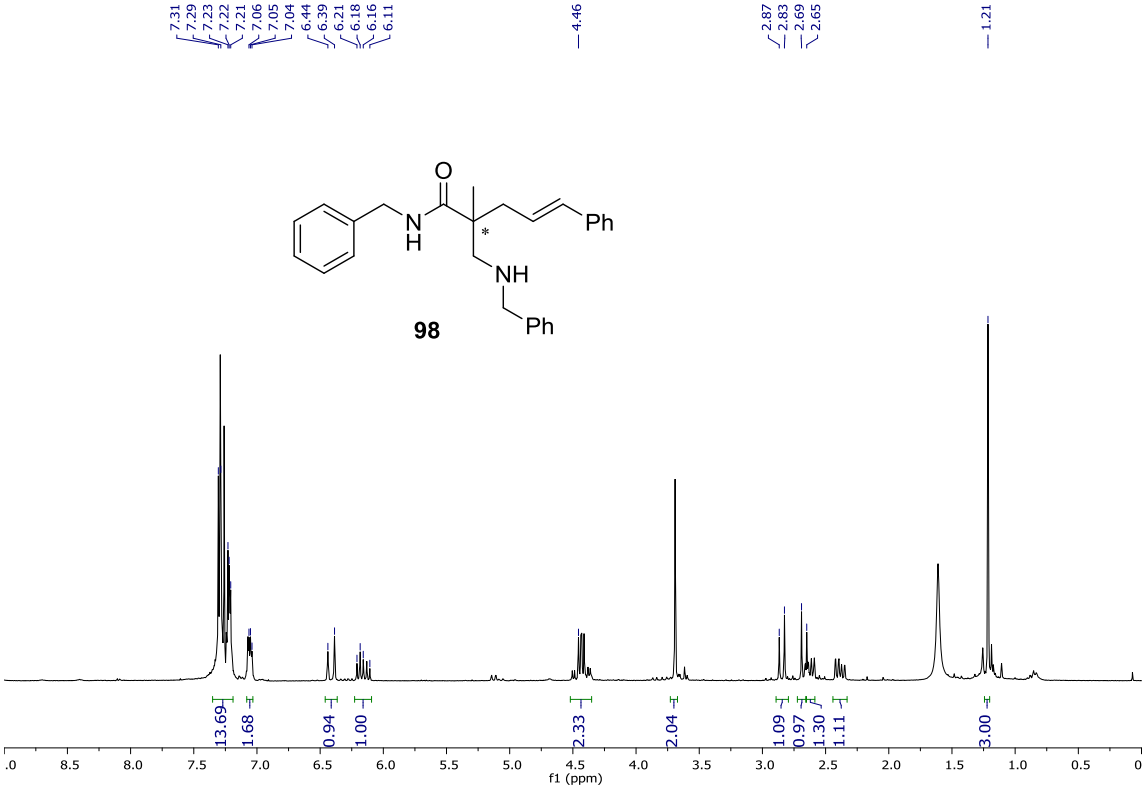

5.69
5.67
5.66
5.63
5.58
5.15
5.11
5.09
4.21
3.52
3.48
3.24
3.20
2.41
2.38
2.36
2.34
2.20
1.86
1.76
1.69
1.43
1.40
1.22
Me
O
O
N
0.77
1.76
0.76
0.99
1.00
1.00
1.11
5.58
3.81
3.02
f1 (ppm)

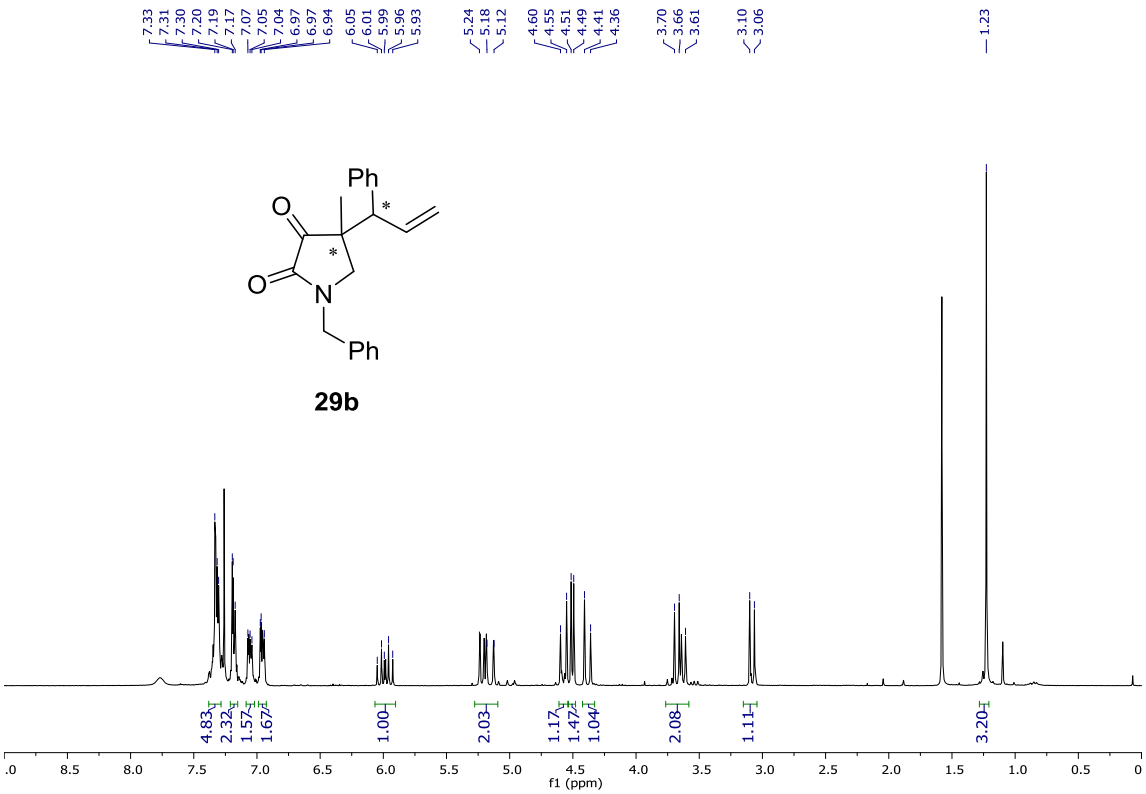
22Ha

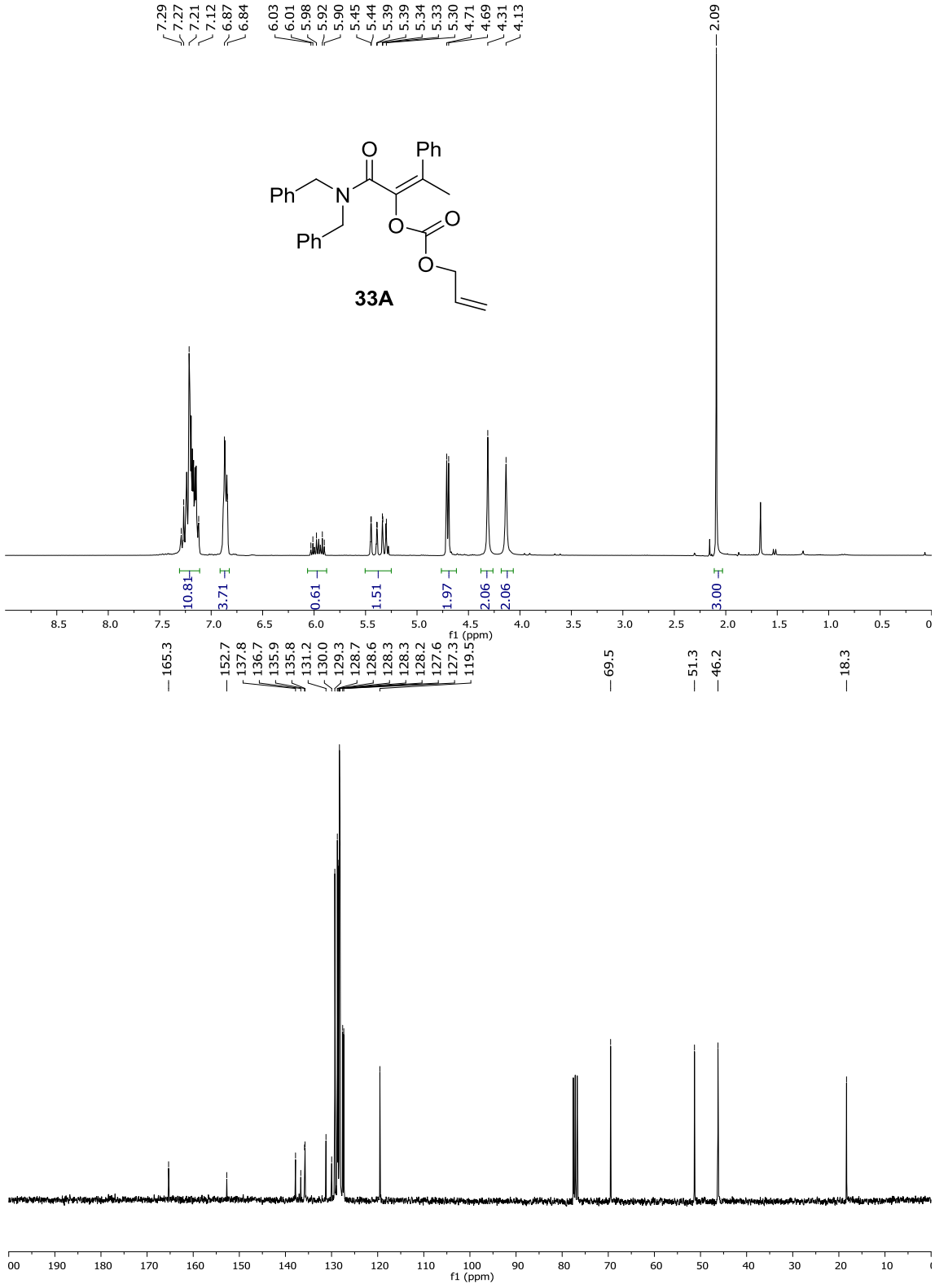

204.4
159.0
131.7
120.3
52.5
49.0
43.3
42.0
29.8
25.3
22.2
f1 (ppm)

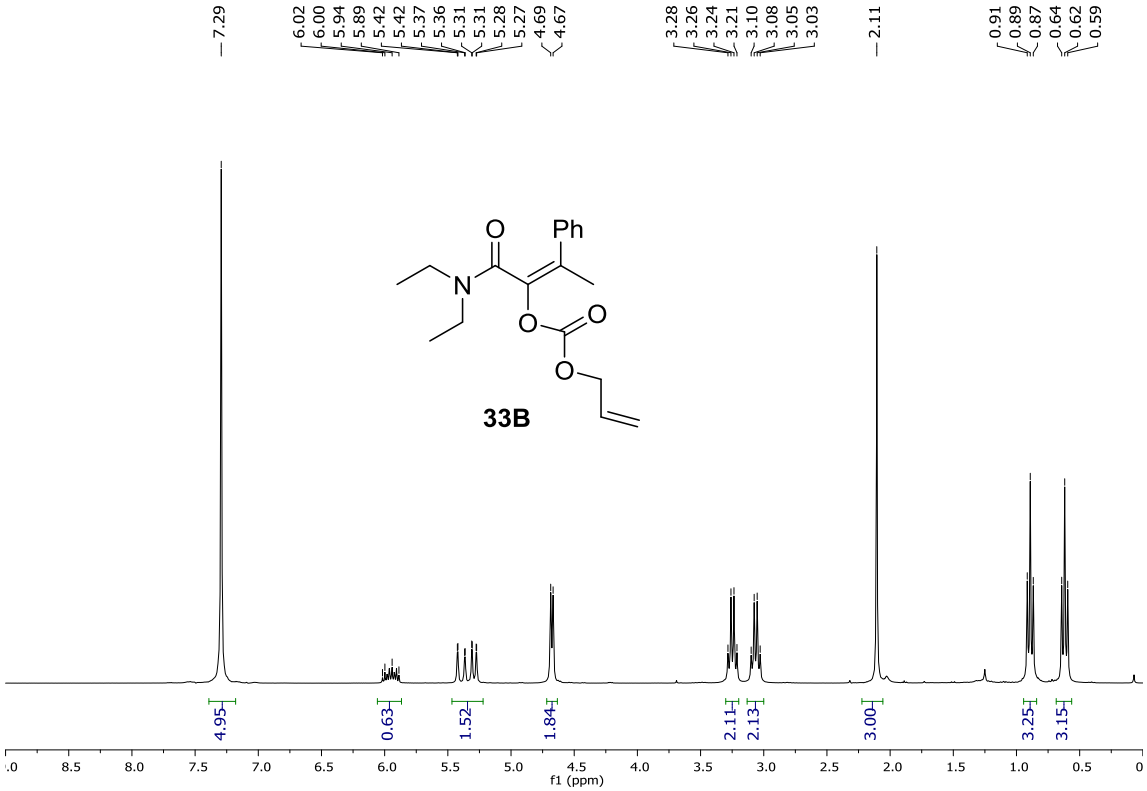

7.30
7.27
7.24
7.22
6.33
6.27
5.96
5.94
5.89
5.86
4.79
4.74
4.57
4.52
3.49
3.45
3.18
3.15
2.53
2.51
2.51
2.46
2.35
2.33
2.31
2.28
1.23
O
O
N
*
Ph
Ph
29a
10.81
1.00
1.07
1.13
1.36
1.13
1.12
1.13
1.14
3.77
f1 (ppm)

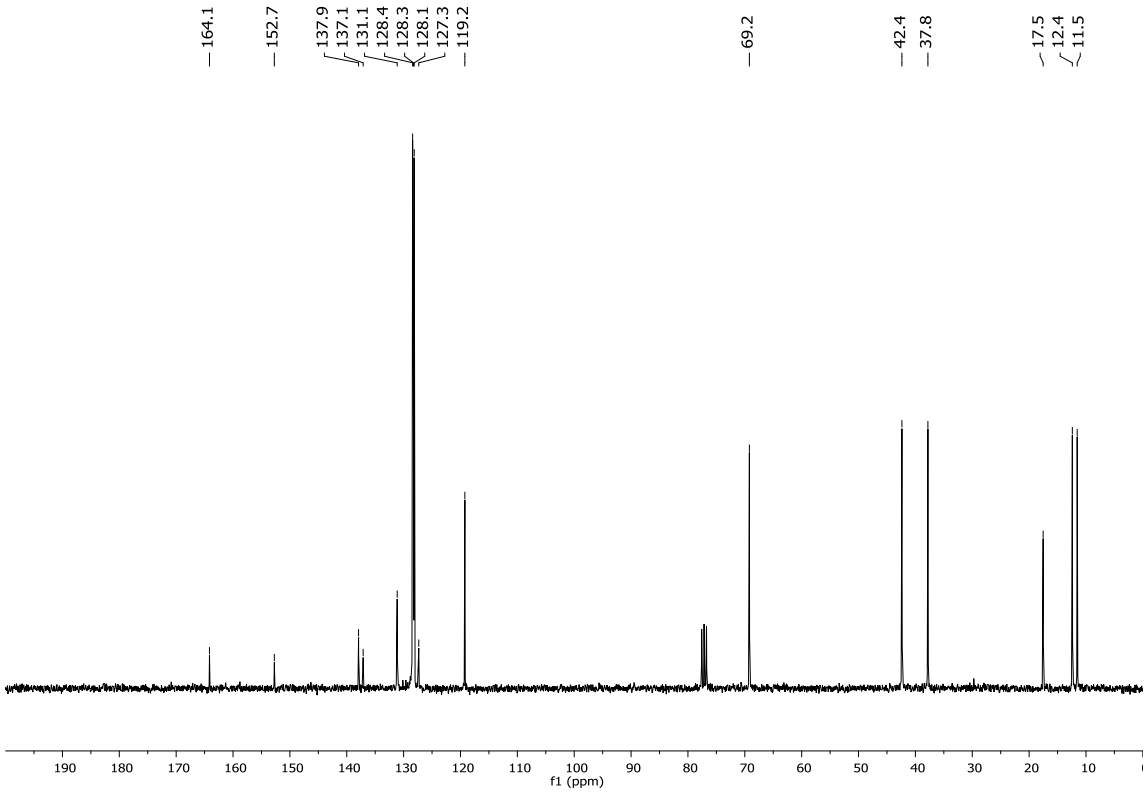

203.8
159.3
136.5
135.3
134.6
129.1
128.7
128.6
128.4
127.9
126.4
122.6
119.7
119.3
52.4
48.6
43.8
41.1
22.3
f1 (ppm)

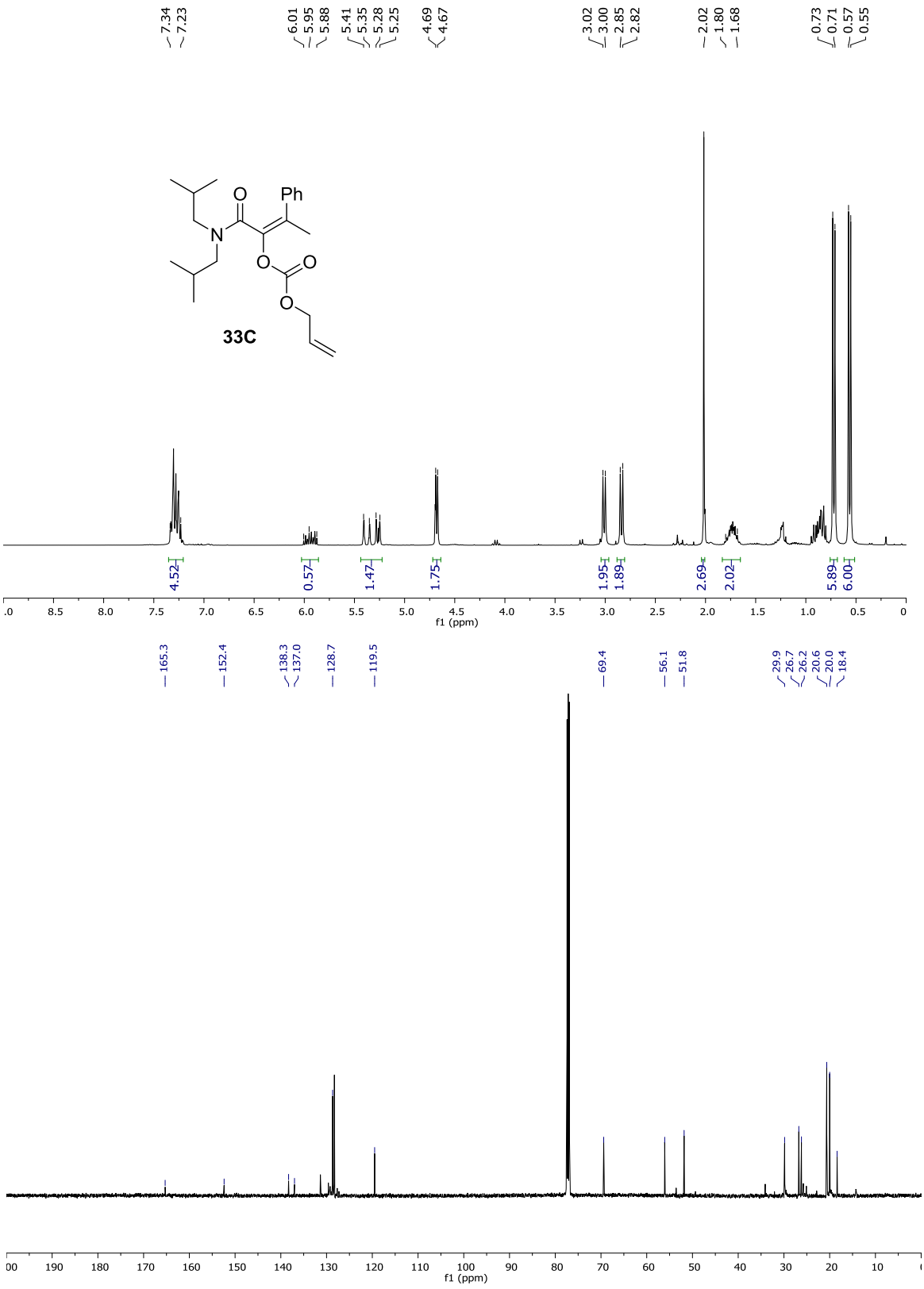

7.31
7.29
7.23
7.22
7.21
7.06
7.05
7.04
6.44
6.39
6.21
6.18
6.16
6.11
4.46
2.87
2.83
2.69
2.65
1.21
O
N
H
*
Ph
NH
Ph
98
13.69
1.68
0.94
1.00
2.33
2.04
1.09
0.97
1.30
1.11
3.00
f1 (ppm)

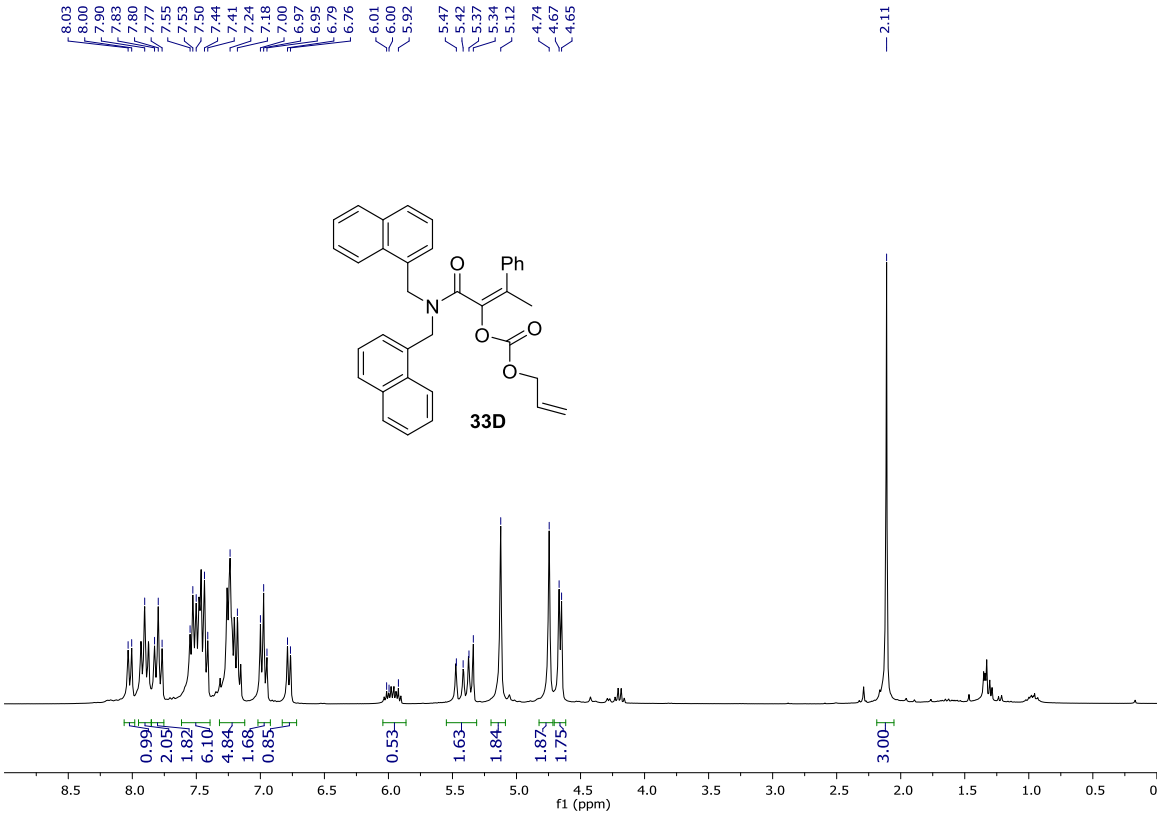

7.33
7.31
7.30
7.20
7.19
7.17
7.07
7.05
7.04
6.97
6.97
6.94
6.05
6.01
5.99
5.96
5.93
5.24
5.18
5.12
4.60
4.55
4.51
4.49
4.41
4.36
3.70
3.66
3.61
3.10
3.06
1.23
Ph
*
O
*
O
N
Ph
29b
4.83
2.32
1.57
1.67
1.00
2.03
1.17
1.47
1.04
2.08
1.11
3.20
f1 (ppm)

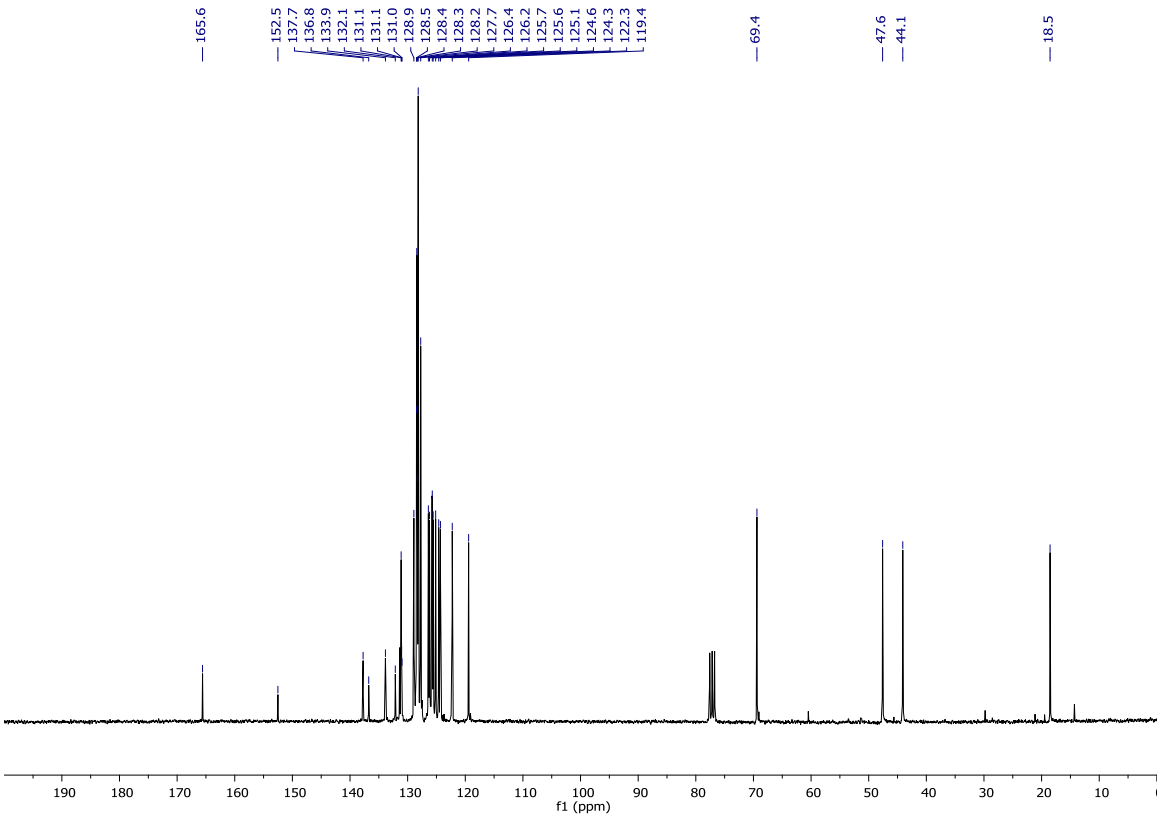

7.29
7.27
7.21
7.12
6.87
6.84
6.03
6.01
5.98
5.92
5.90
5.45
5.44
5.39
5.39
5.34
5.33
5.30
4.71
4.69
4.31
4.13
2.09
O
Ph
Ph
N
Ph
O
O
O
33A
10.81
3.71
0.61
1.51
1.97
2.06
2.06
3.00
f1 (ppm)
165.3
152.7
137.8
136.7
135.9
135.8
131.2
130.0
129.3
128.7
128.6
128.3
128.3
128.2
127.6
127.3
119.5
69.5
51.3
46.2
18.3
f1 (ppm)

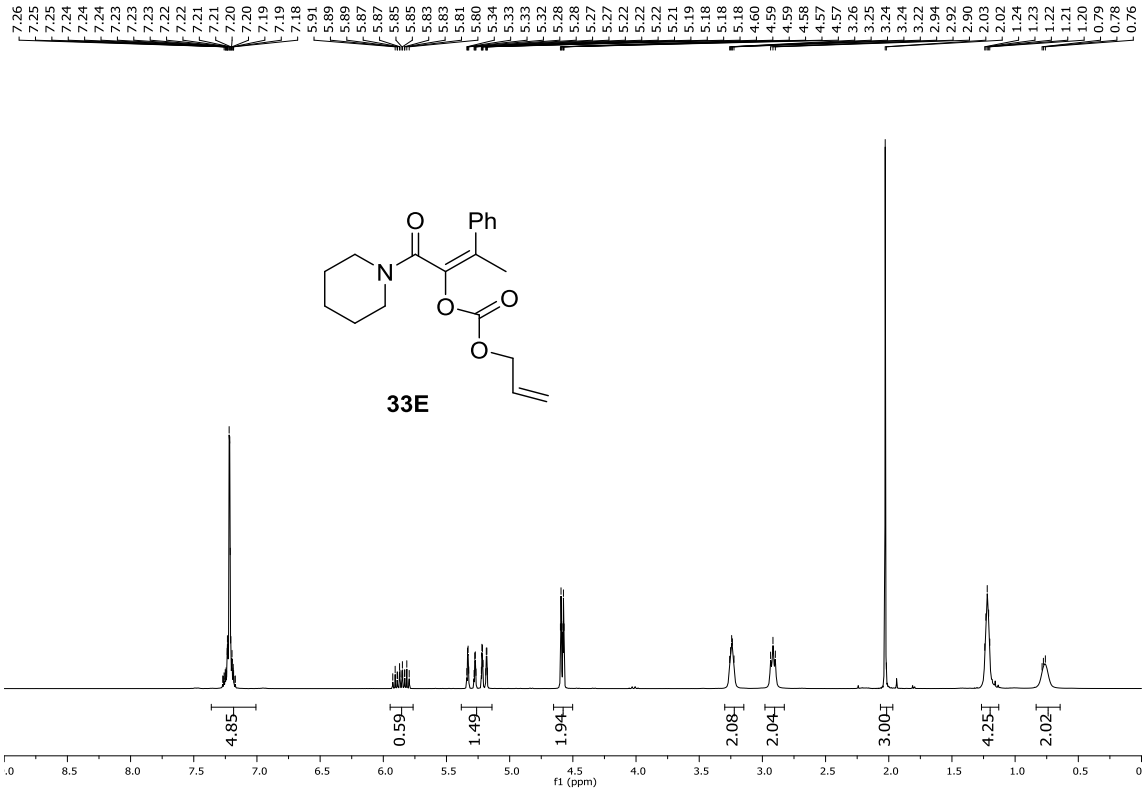

7.29
6.02
6.00
5.94
5.89
5.42
5.42
5.37
5.36
5.31
5.31
5.28
5.27
4.69
4.67
3.28
3.26
3.24
3.21
3.10
3.08
3.05
3.03
2.11
0.91
0.89
0.87
0.64
0.62
0.59
O
Ph
N
O
O
O
33B
4.95
0.63
1.52
1.84
2.11
2.13
3.00
3.25
3.15
f1 (ppm)

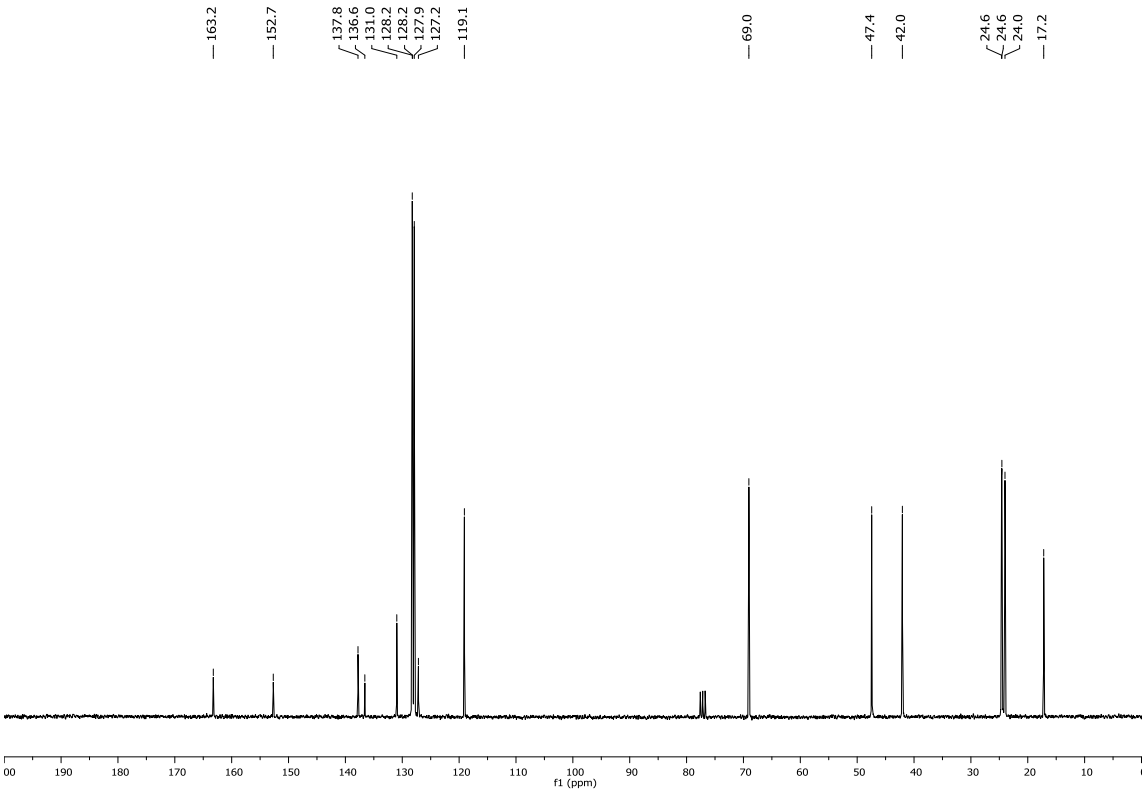

164.1
152.7
137.9
137.1
131.1
128.4
128.3
128.1
127.3
119.2
69.2
42.4
37.8
17.5
12.4
11.5
f1 (ppm)

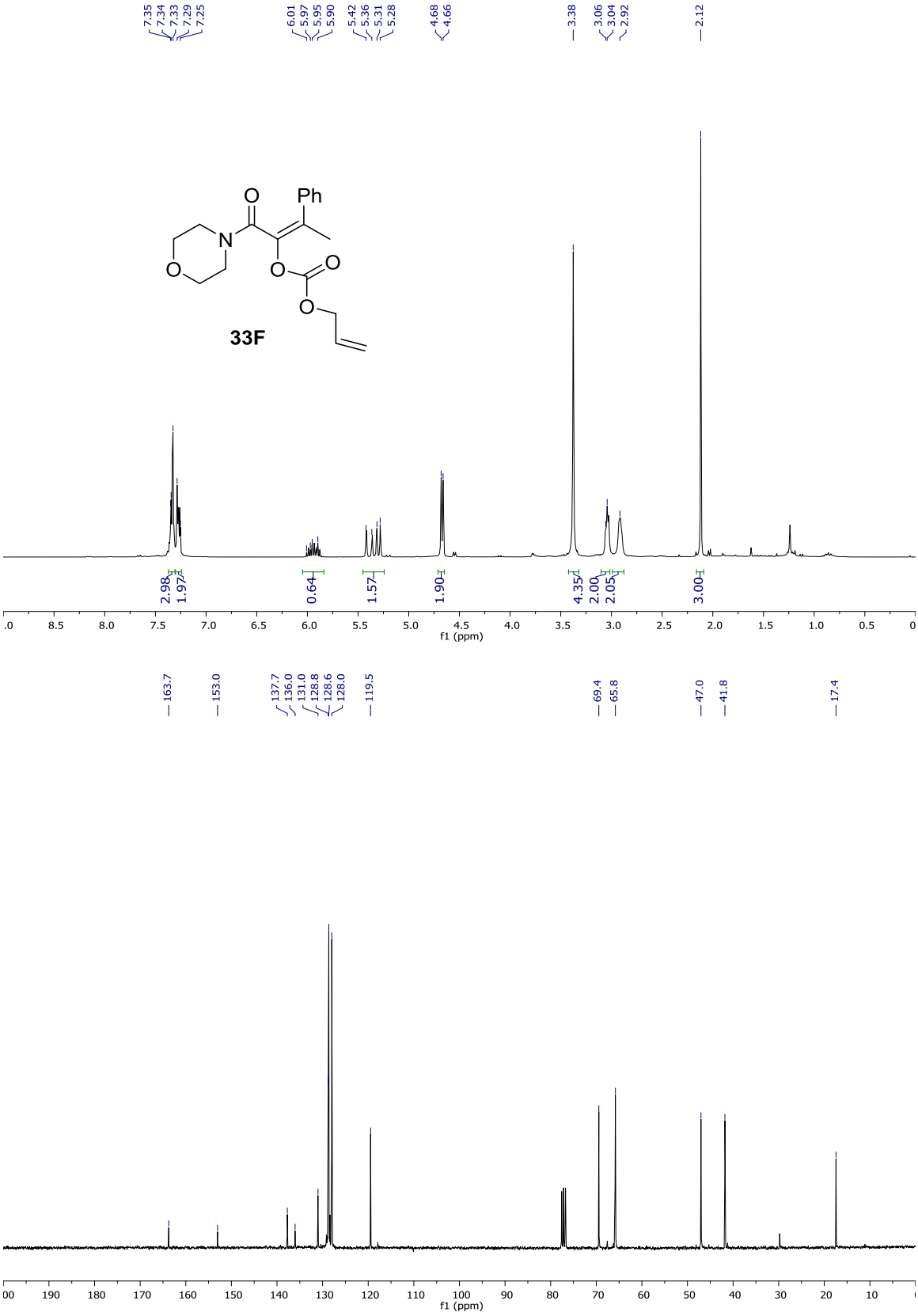

7.34
7.23
6.01
5.95
5.88
5.41
5.35
5.28
5.25
4.69
4.67
3.02
3.00
2.85
2.82
2.02
1.80
1.68
0.73
0.71
0.57
0.55
O
Ph
N
O
O
O
O
33C
4.52
0.57
1.47
1.75
1.95
1.89
2.69
2.02
5.89
6.00
f1 (ppm)
165.3
152.4
138.3
137.0
128.7
119.5
69.4
56.1
51.8
29.9
26.7
26.2
20.6
20.0
18.4
f1 (ppm)

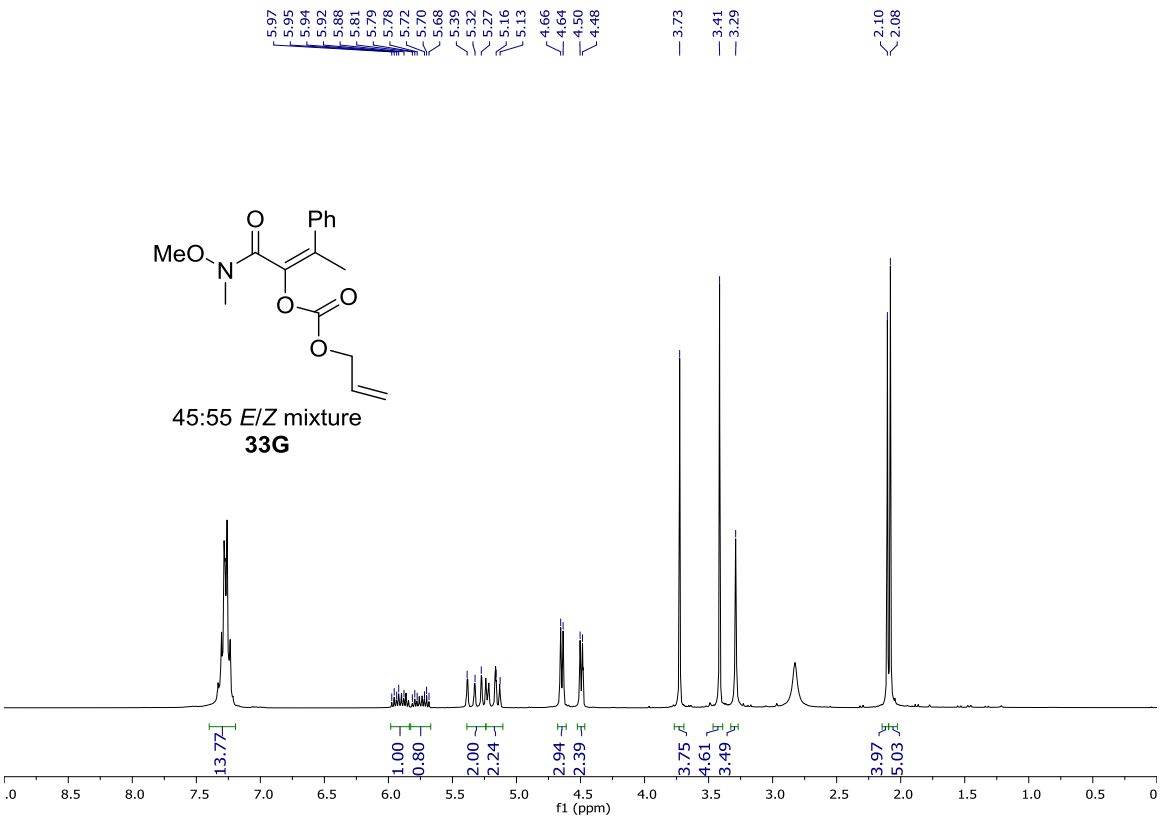

8.03
8.00
7.90
7.83
7.80
7.77
7.55
7.53
7.50
7.44
7.41
7.24
7.18
7.00
6.97
6.95
6.79
6.76
6.01
6.00
5.92
5.47
5.42
5.37
5.34
5.12
4.74
4.67
4.65
2.11
Ph
O
N
O
O
O
33D
0.99
2.05
1.82
6.10
4.84
1.68
0.85
0.53
1.63
1.84
1.87
1.75
3.00
f1 (ppm)


165.6
152.5
137.7
136.8
133.9
132.1
131.1
131.1
131.0
128.9
128.5
128.4
128.3
128.2
127.7
126.4
126.2
125.7
125.6
125.1
124.6
124.3
122.3
119.4
69.4
47.6
44.1
18.5
f1 (ppm)


7.26 7.25 7.25 7.24 7.24 7.24 7.23 7.23 7.22 7.22 7.21 7.21 7.20 7.20 7.19 7.19 7.18
5.91 5.89 5.89 5.87 5.87 5.85 5.85 5.85 5.83 5.83 5.81 5.80 5.34 5.33 5.33 5.32 5.28 5.28 5.27 5.27 5.22 5.22 5.22 5.21 5.19 5.18 5.18 5.18 4.60 4.59 4.59 4.58 4.57 4.57 3.26 3.25 3.24 3.24 3.22 2.94 2.92 2.90 2.03 2.02 1.24 1.23 1.22 1.21 1.20 0.79 0.78 0.76
O
Ph
N
O
O
O
O
33E
4.85
0.59
1.49
1.94
2.08
2.04
3.00
4.25
2.02
f1 (ppm)

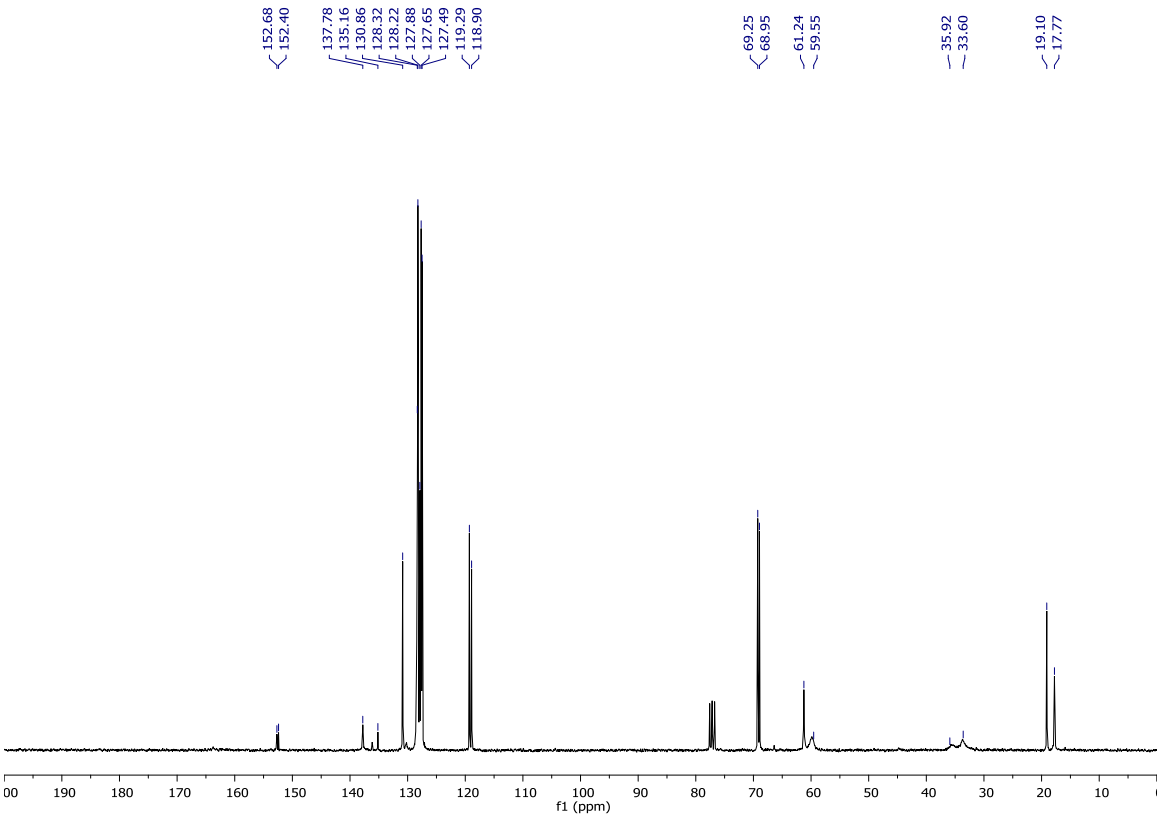

163.2
152.7
137.8
136.6
131.0
128.2
128.2
127.9
127.2
119.1
69.0
47.4
42.0
24.6
24.6
24.0
17.2
f1 (ppm)

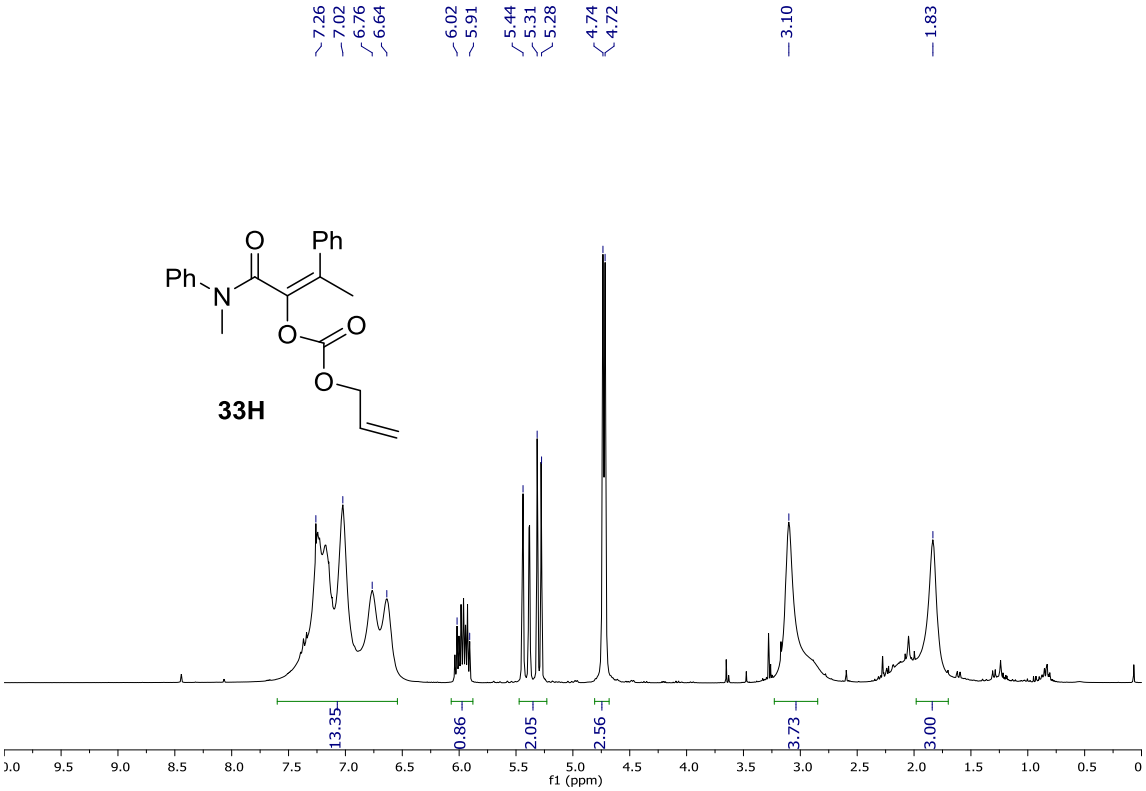

7.35
7.34
7.33
7.29
7.25
6.01
5.97
5.95
5.90
5.42
5.36
5.31
5.28
4.68
4.66
3.38
3.06
3.04
2.92
2.12
O
Ph
N
O
O
O
O
33F
2.98
1.97
0.64
1.57
1.90
4.35
2.00
2.05
3.00
f1 (ppm)
163.7
153.0
137.7
136.0
131.0
128.8
128.6
128.0
119.5
69.4
65.8
47.0
41.8
17.4
f1 (ppm)

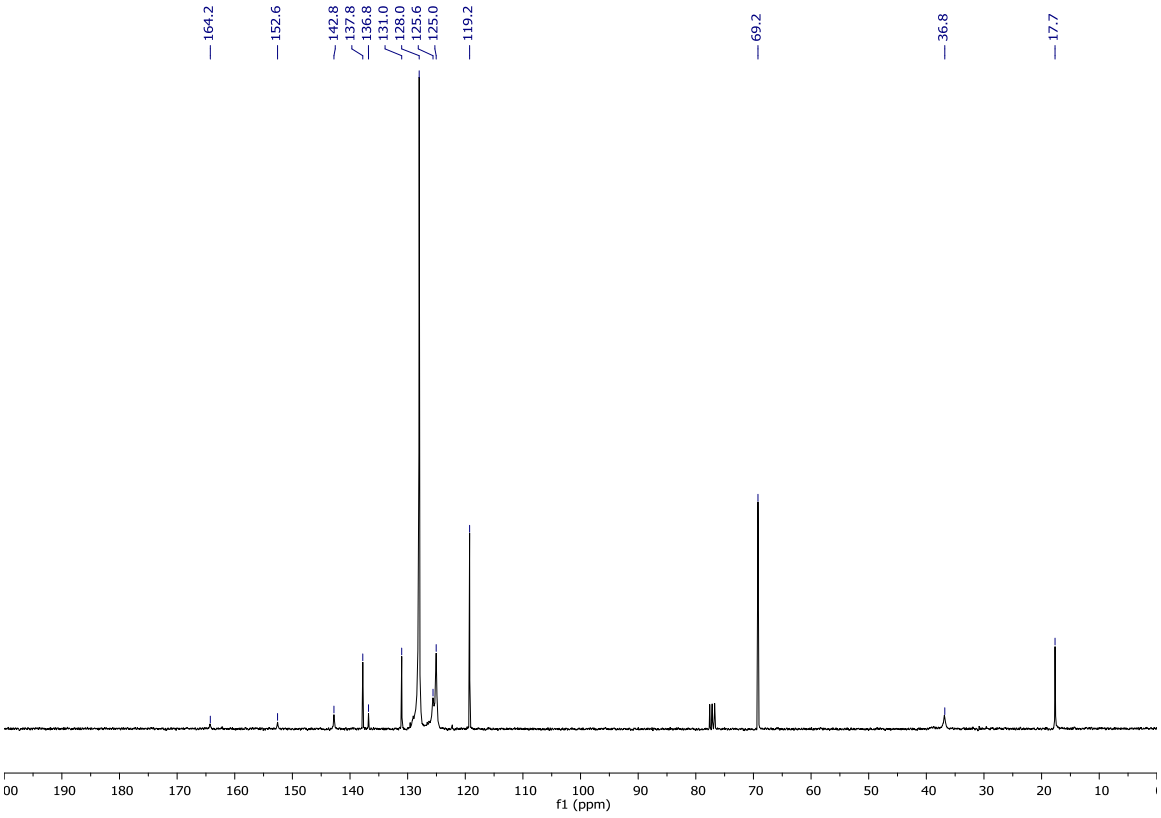


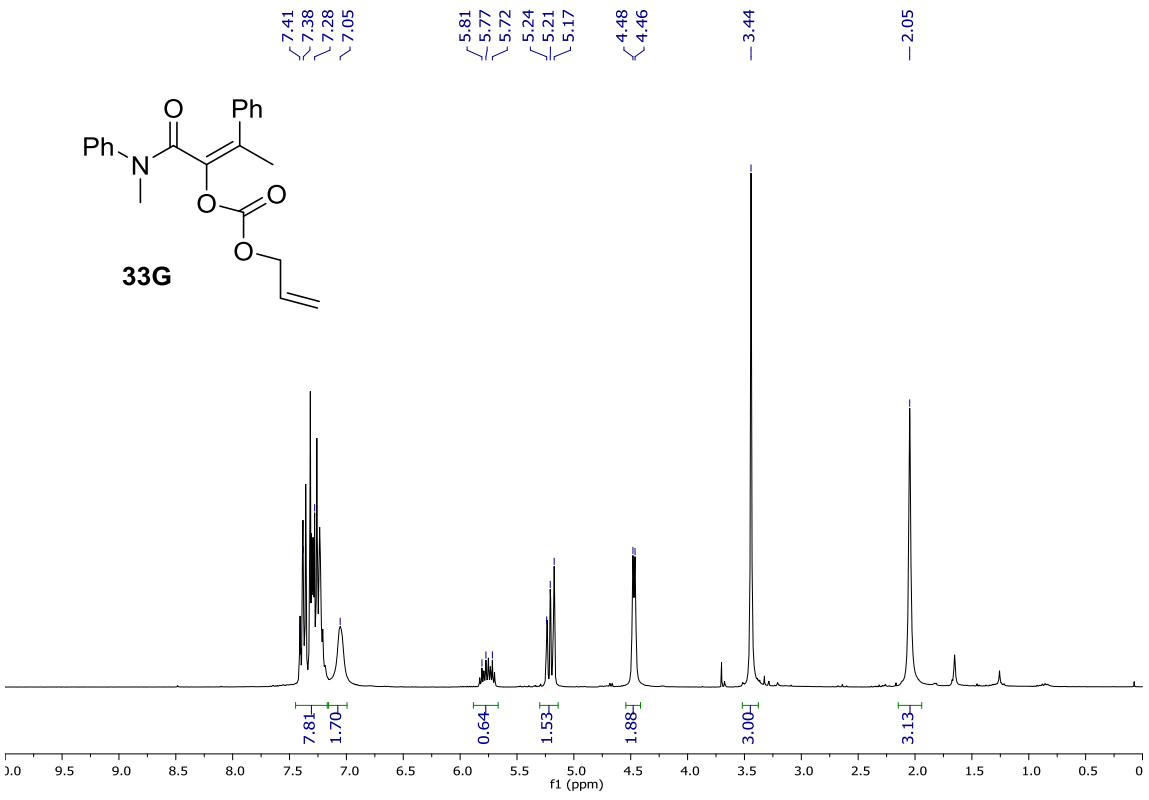
45:55 *E*/*Z* mixture

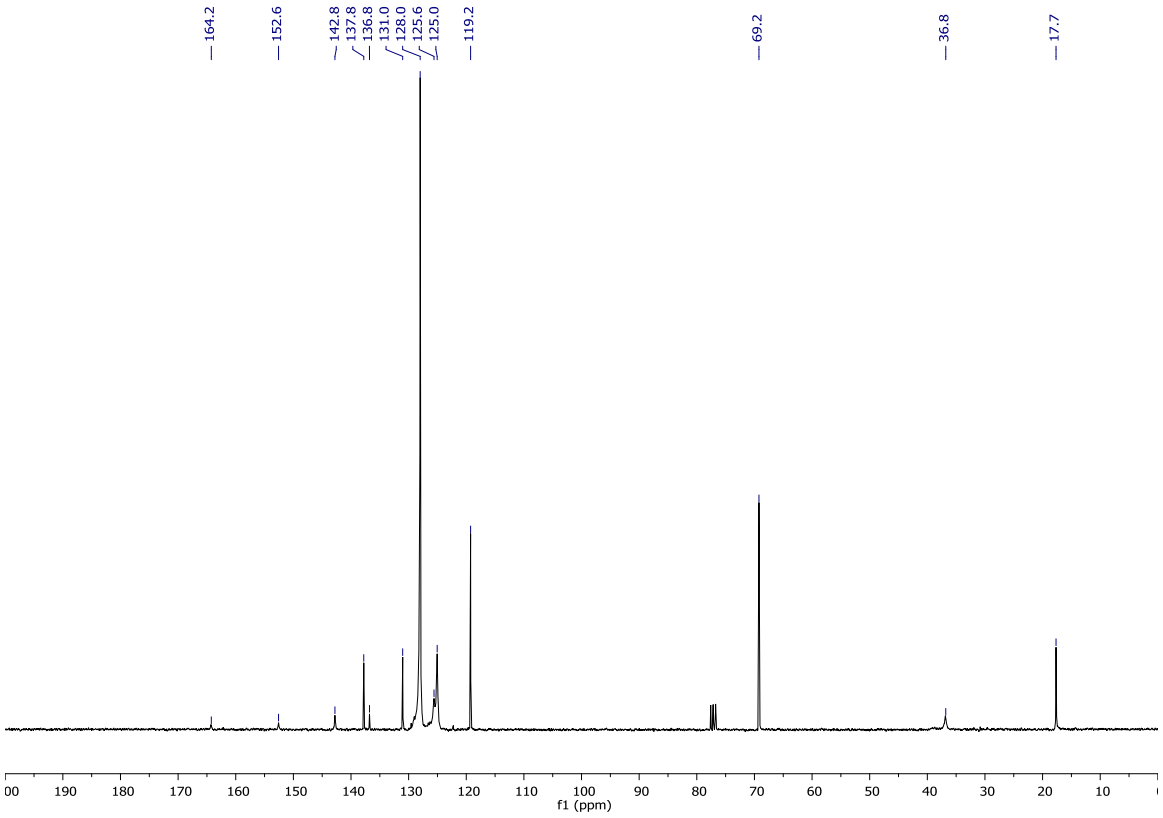
33G

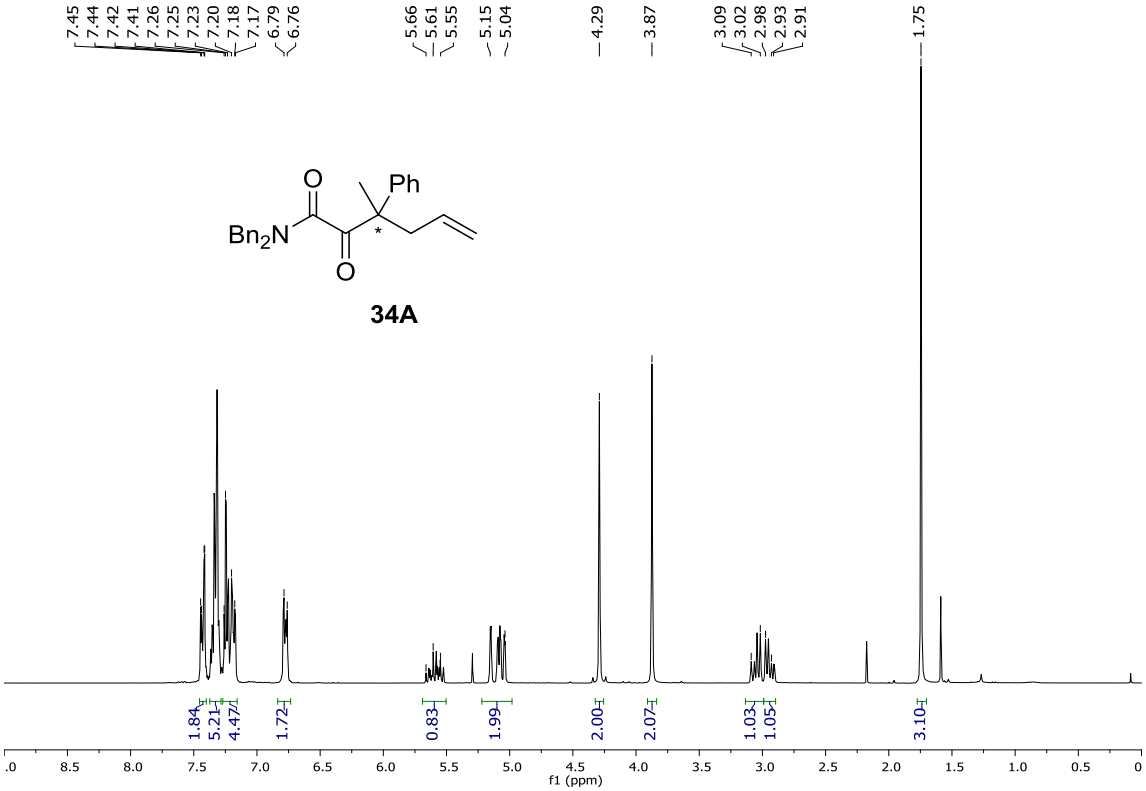


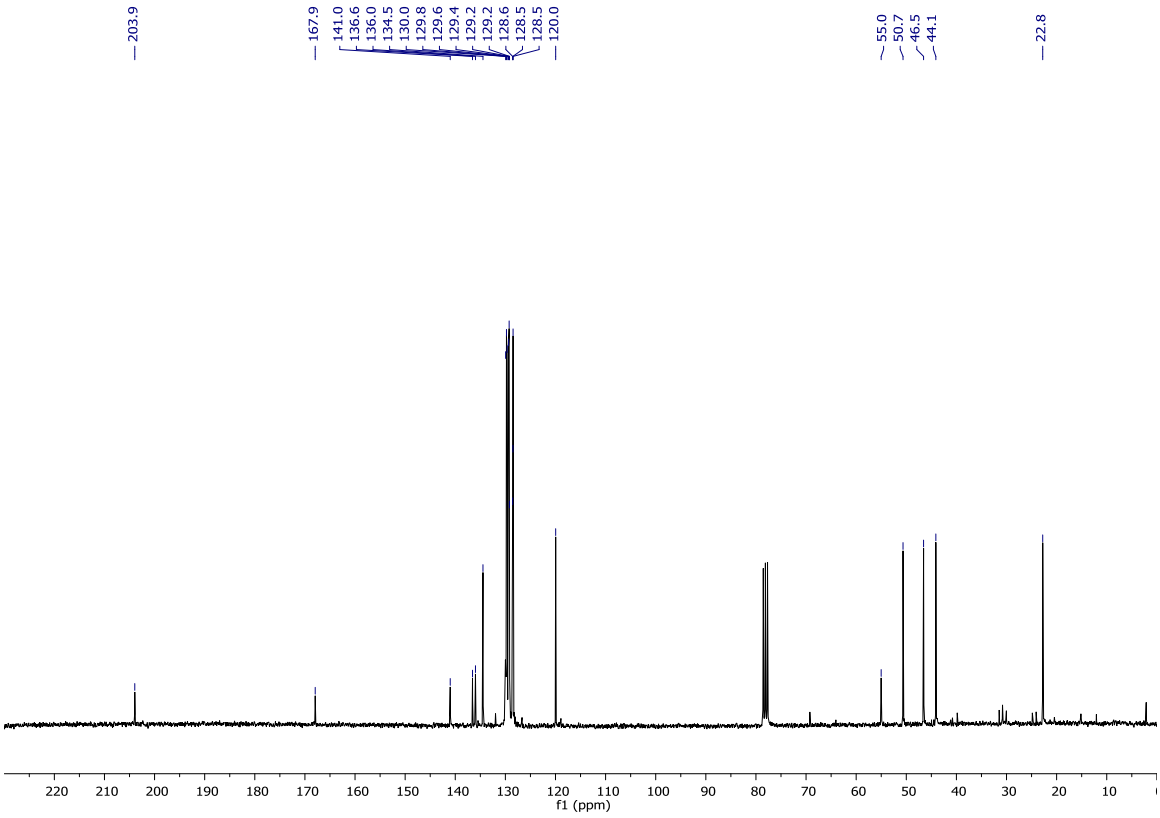

7.26
7.02
6.76
6.64
6.02
5.91
5.44
5.31
5.28
4.74
4.72
3.10
1.83
Ph
O
Ph
N
O
O
O
33H
13.35
0.86
2.05
2.56
3.73
3.00
f1 (ppm)

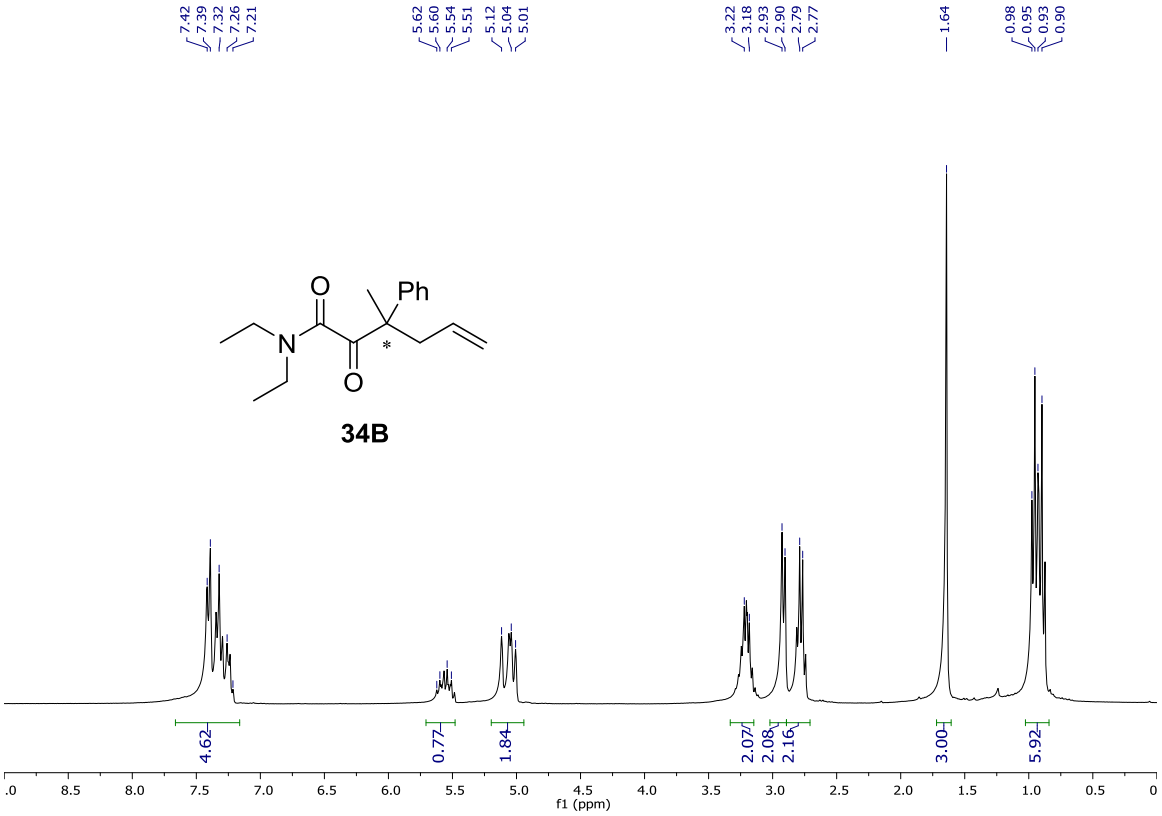

164.2
152.6
142.8
137.8
136.8
131.0
128.0
125.6
125.0
119.2
69.2
36.8
17.7
f1 (ppm)

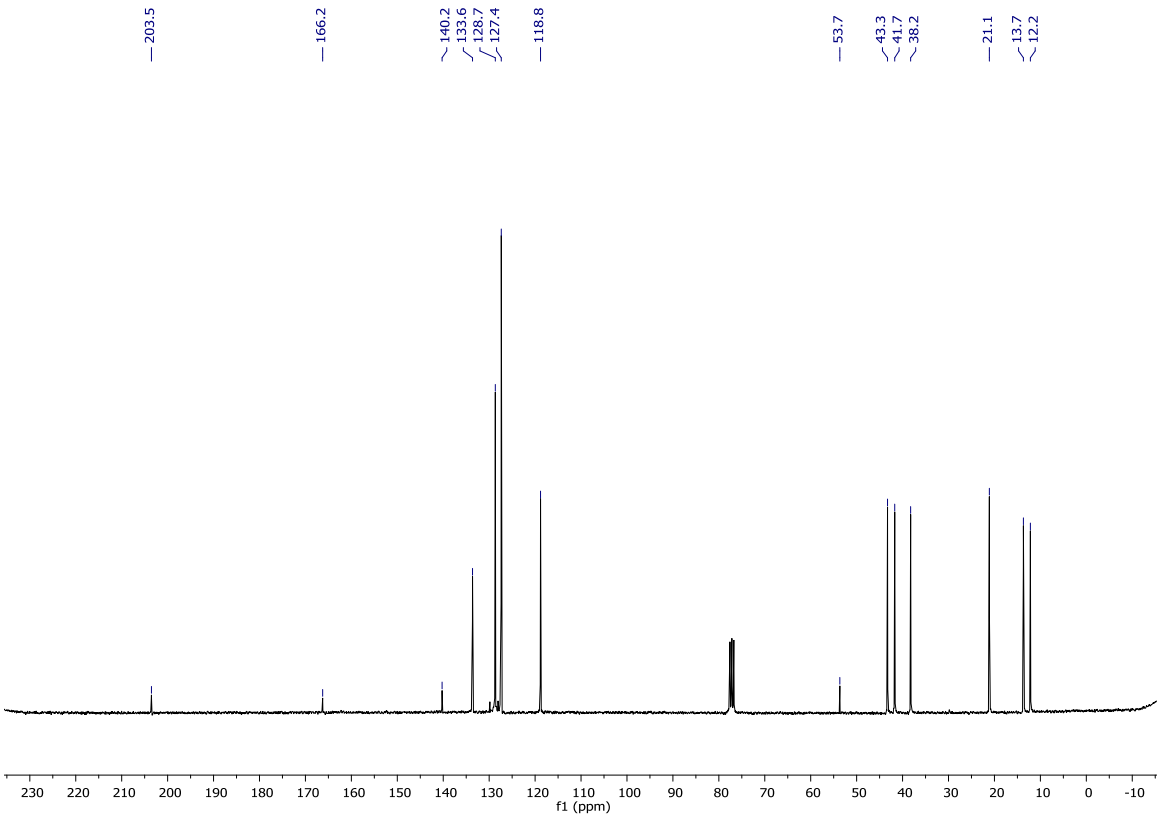

7.41
7.38
7.28
7.05
5.81
5.77
5.72
5.24
5.21
5.17
4.48
4.46
3.44
2.05
Ph
O
Ph
N
O
O
O
33G
7.81
1.70
0.64
1.53
1.88
3.00
3.13
f1 (ppm)

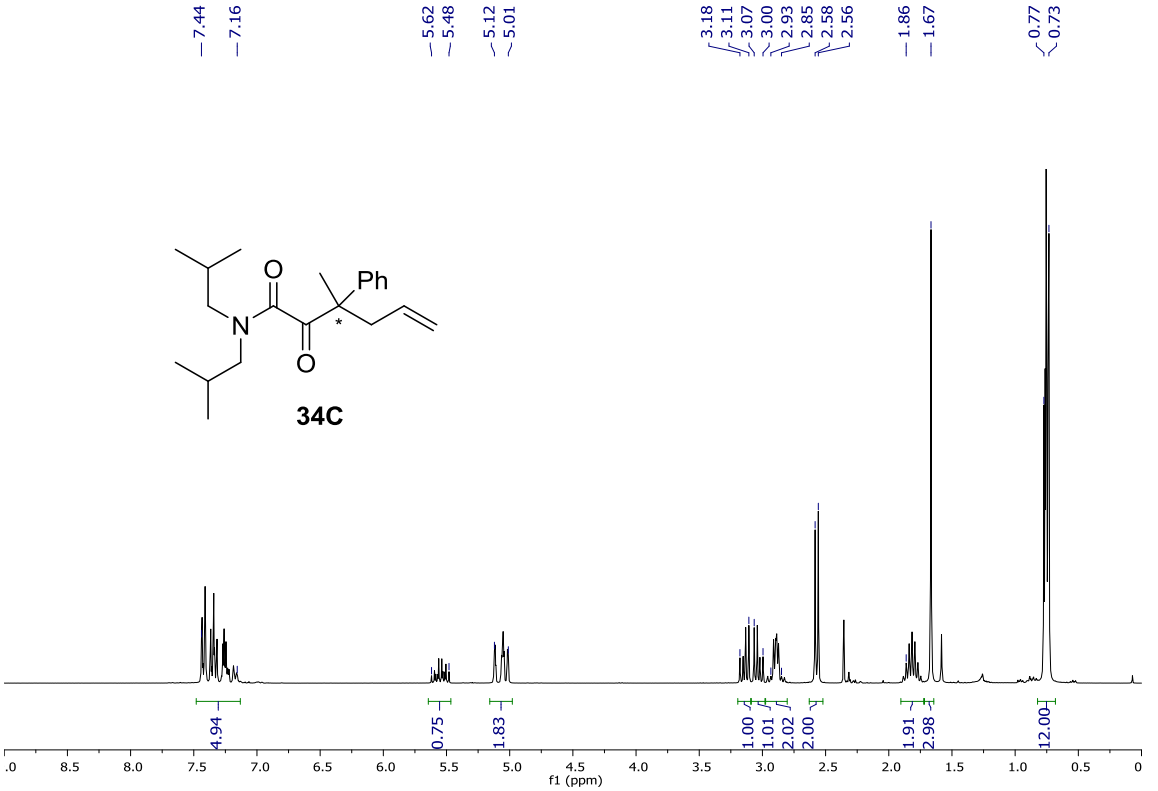

164.2
152.6
142.8
137.8
136.8
131.0
128.0
125.6
125.0
119.2
69.2
36.8
17.7
f1 (ppm)

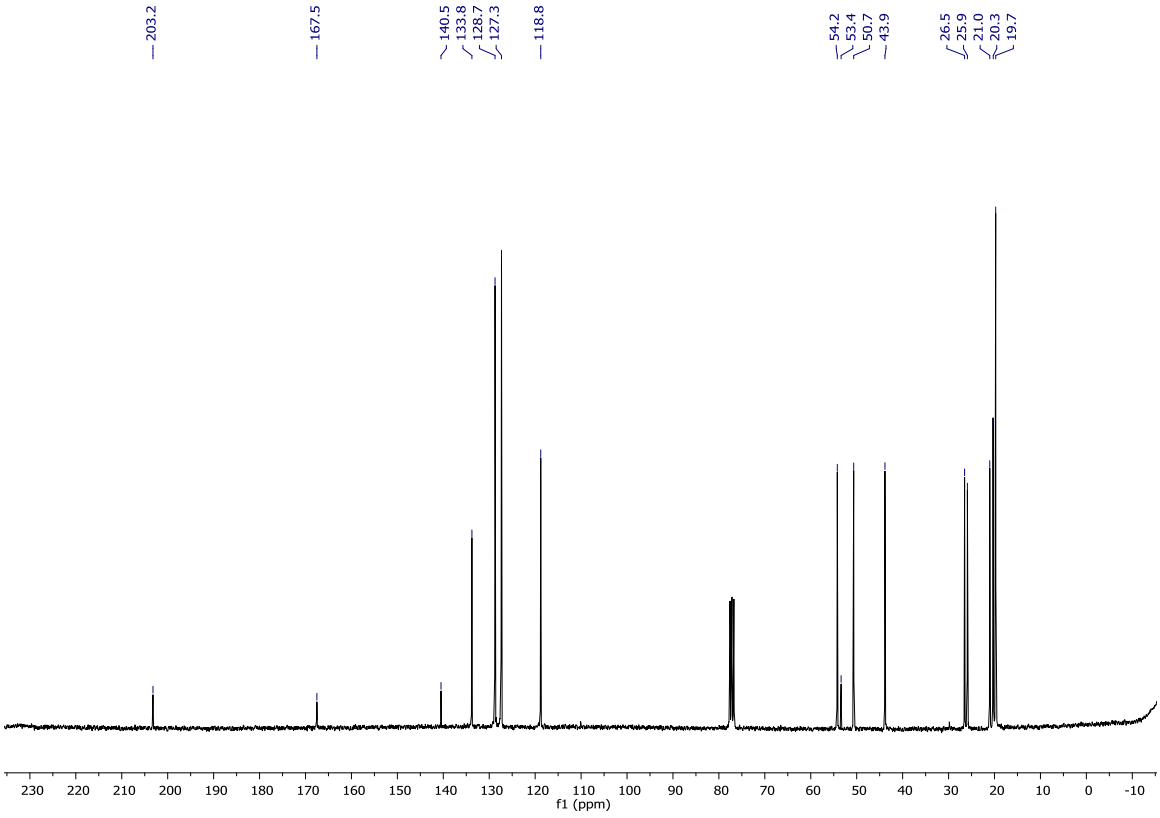

7.45
7.44
7.42
7.41
7.26
7.25
7.23
7.20
7.18
7.17
6.79
6.76
5.66
5.61
5.55
5.15
5.04
4.29
3.87
3.09
3.02
2.98
2.93
2.91
1.75
O
Ph
Bn2N
*
O
34A
1.84
5.21
4.47
1.72
0.83
1.99
2.00
2.07
1.03
1.05
3.10
f1 (ppm)

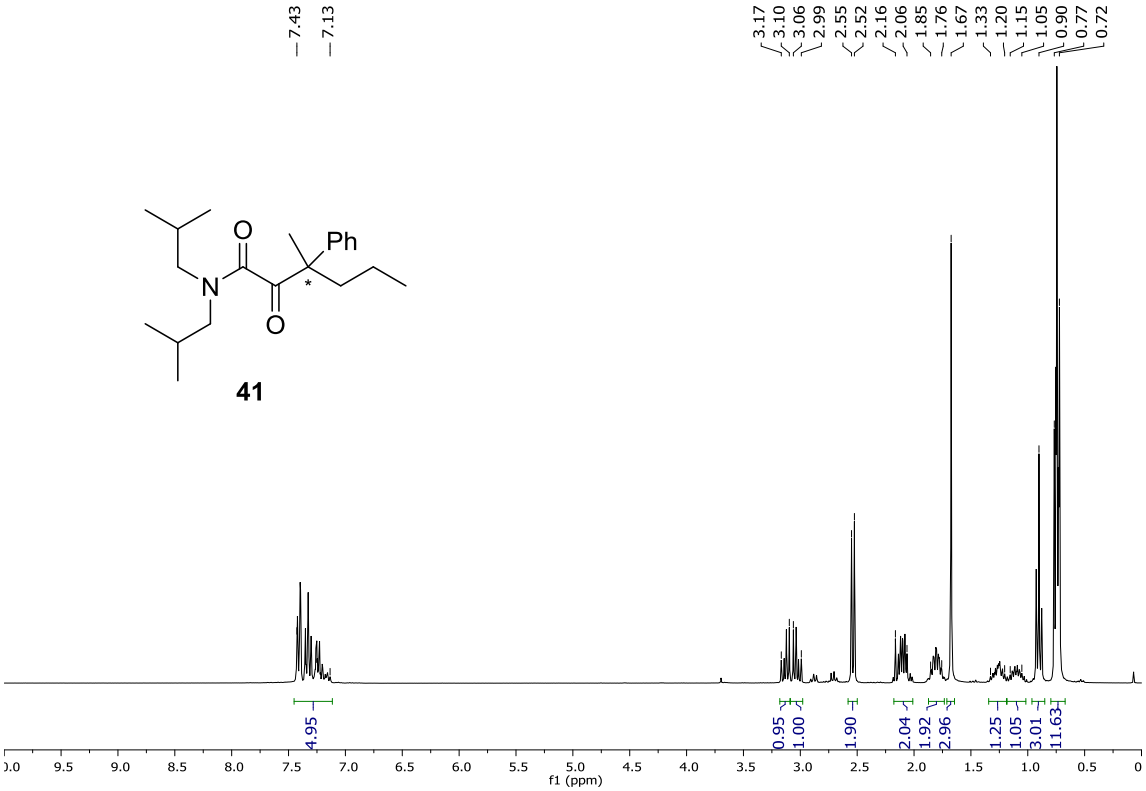

203.9
167.9
141.0
136.6
136.0
134.5
130.0
129.8
129.6
129.4
129.2
129.2
128.6
128.5
128.5
120.0
55.0
50.7
46.5
44.1
22.8
f1 (ppm)

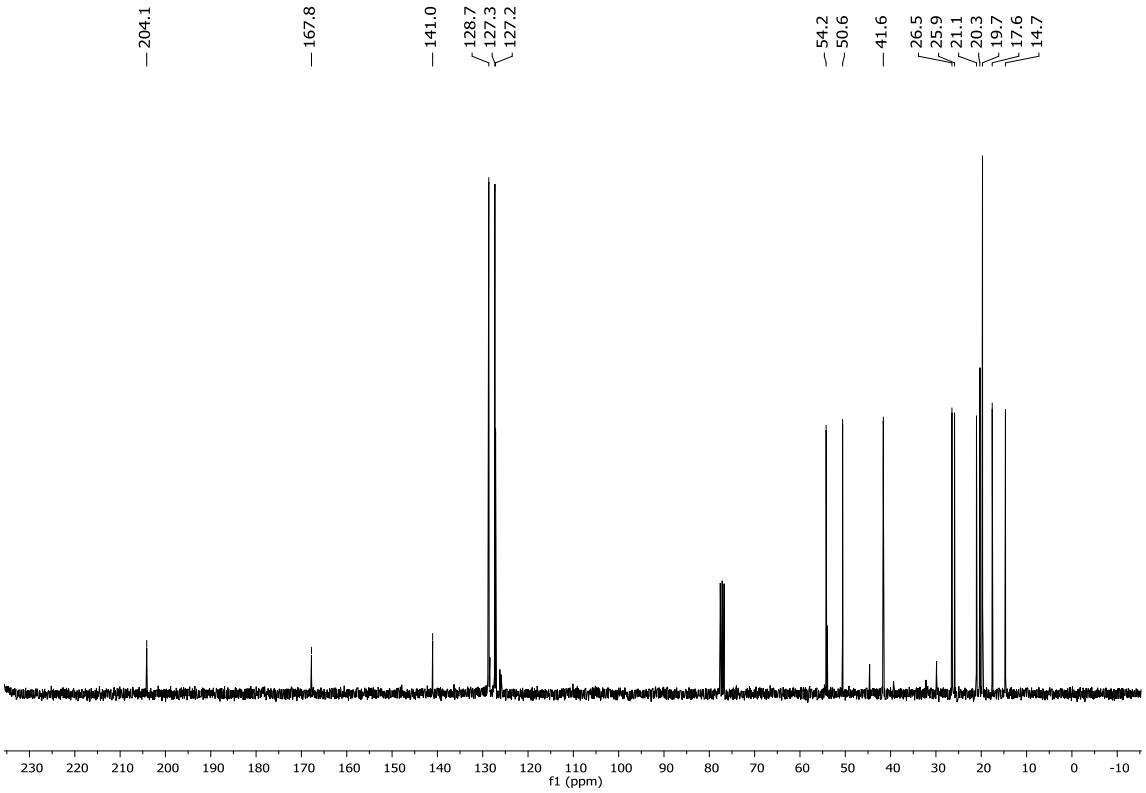

7.42
7.39
7.32
7.26
7.21
5.62
5.60
5.54
5.51
5.12
5.04
5.01
3.22
3.18
2.93
2.90
2.79
2.77
1.64
0.98
0.95
0.93
0.90
O
Ph
N
*
O
34B
4.62
0.77
1.84
2.07
2.08
2.16
3.00
5.92
f1 (ppm)

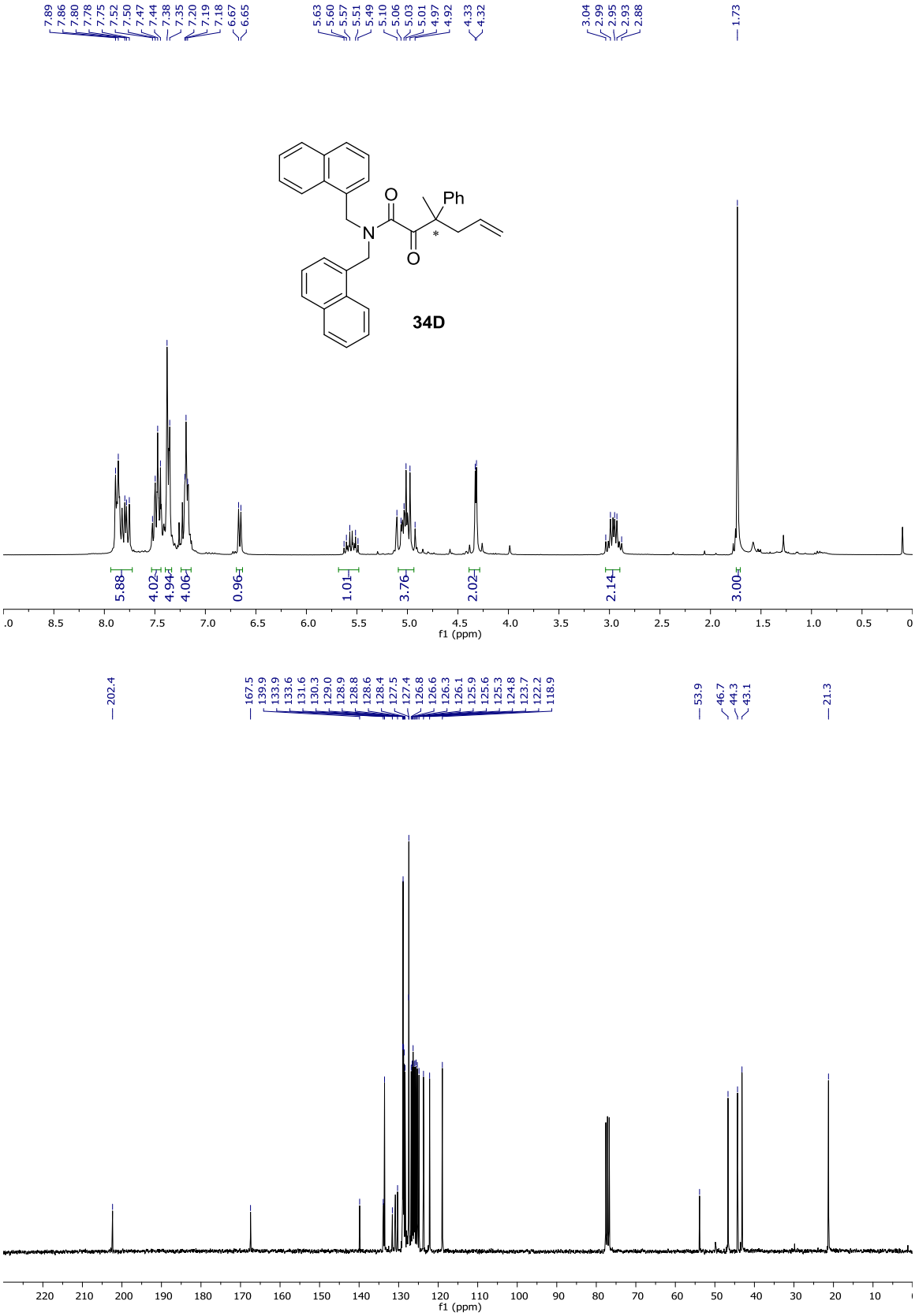

203.5
166.2
140.2
133.6
128.7
127.4
118.8
53.7
43.3
41.7
38.2
21.1
13.7
12.2
f1 (ppm)

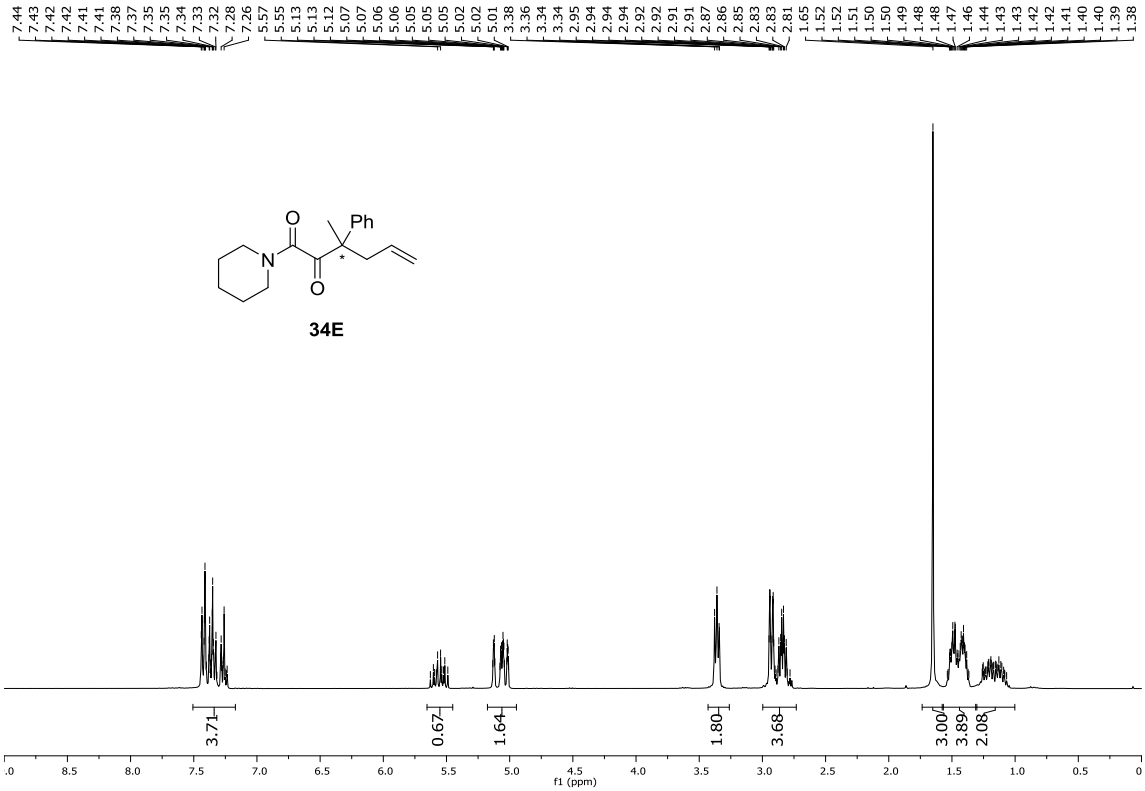

7.44
7.16
5.62
5.48
5.12
5.01
3.18
3.11
3.07
3.00
2.93
2.85
2.58
2.56
1.86
1.67
0.77
0.73
O
N
O
Ph
*
34C
4.94
0.75
1.83
1.00
1.01
2.02
2.00
1.91
2.98
12.00
f1 (ppm)

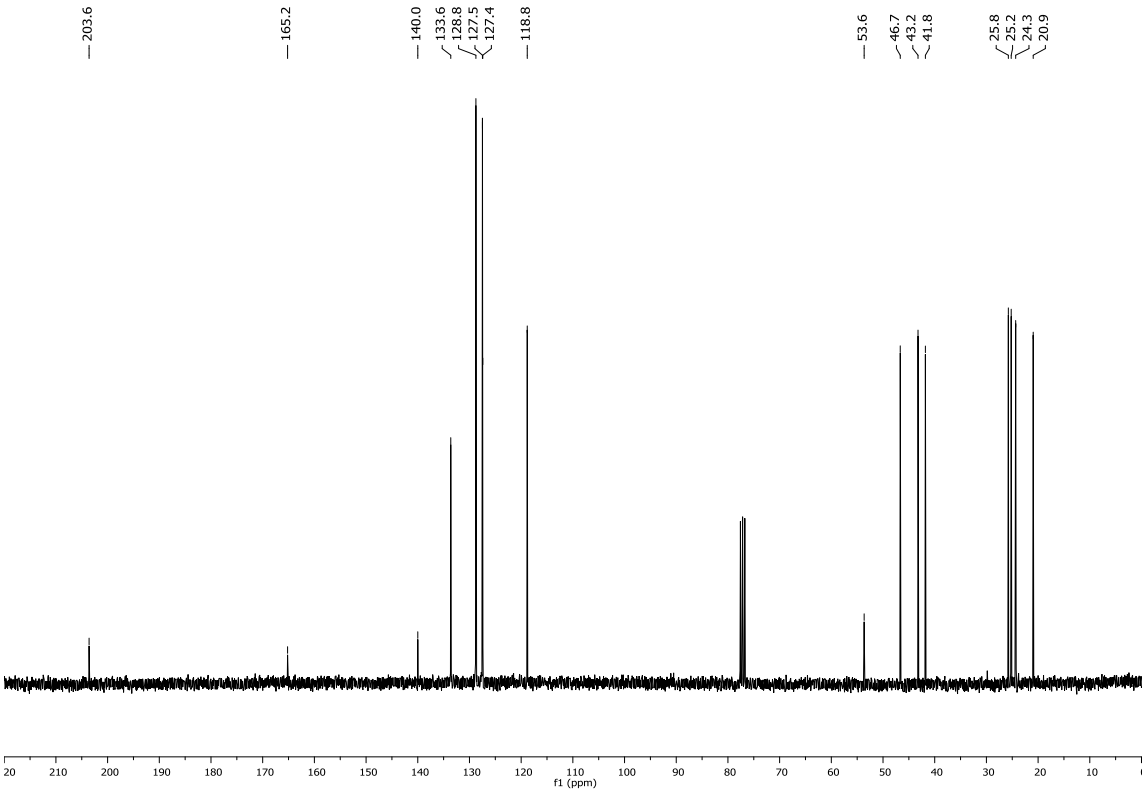

203.2
167.5
140.5
133.8
128.7
127.3
118.8
54.2
53.4
50.7
43.9
26.5
25.9
21.0
20.3
19.7
f1 (ppm)

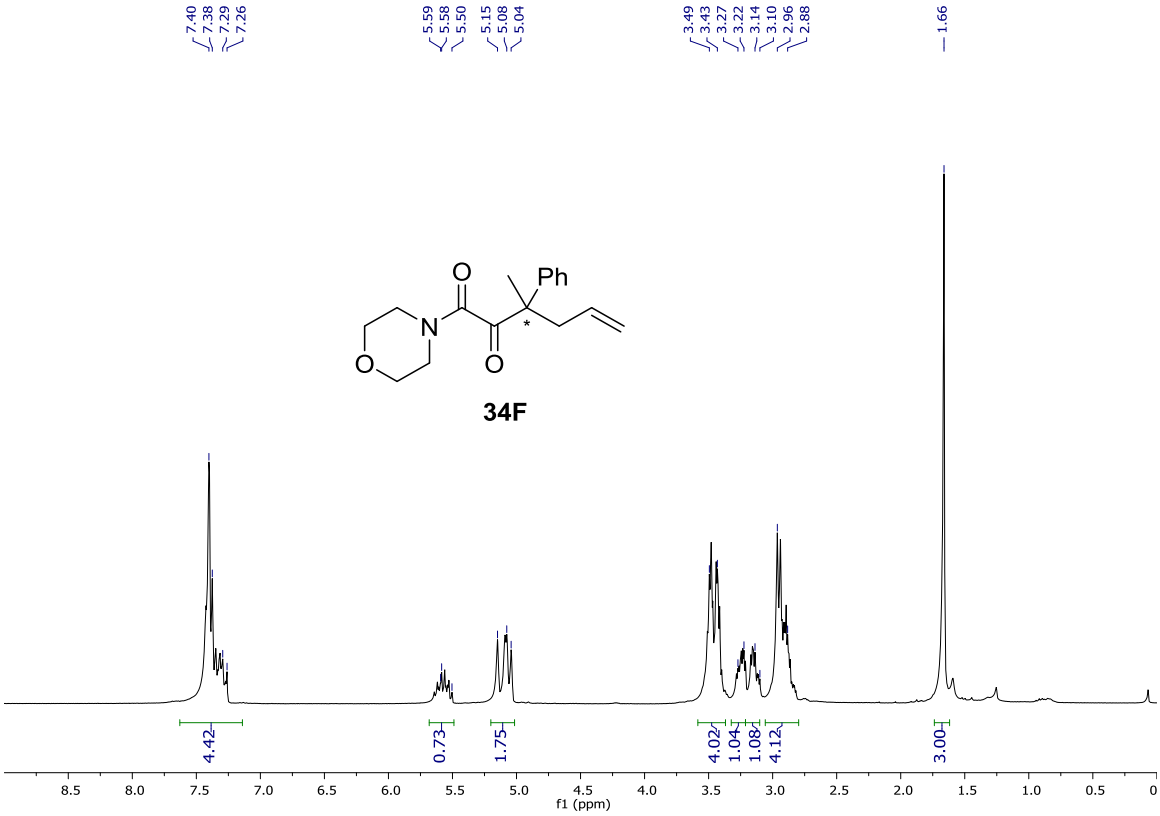

7.43
7.13
3.17
3.10
3.06
2.99
2.55
2.52
2.16
2.06
1.85
1.76
1.67
1.33
1.20
1.15
1.05
0.90
0.77
0.72
O
Ph
N
*
O
41
4.95
0.95
1.00
1.90
2.04
1.92
2.96
1.25
1.05
3.01
11.63
f1 (ppm)

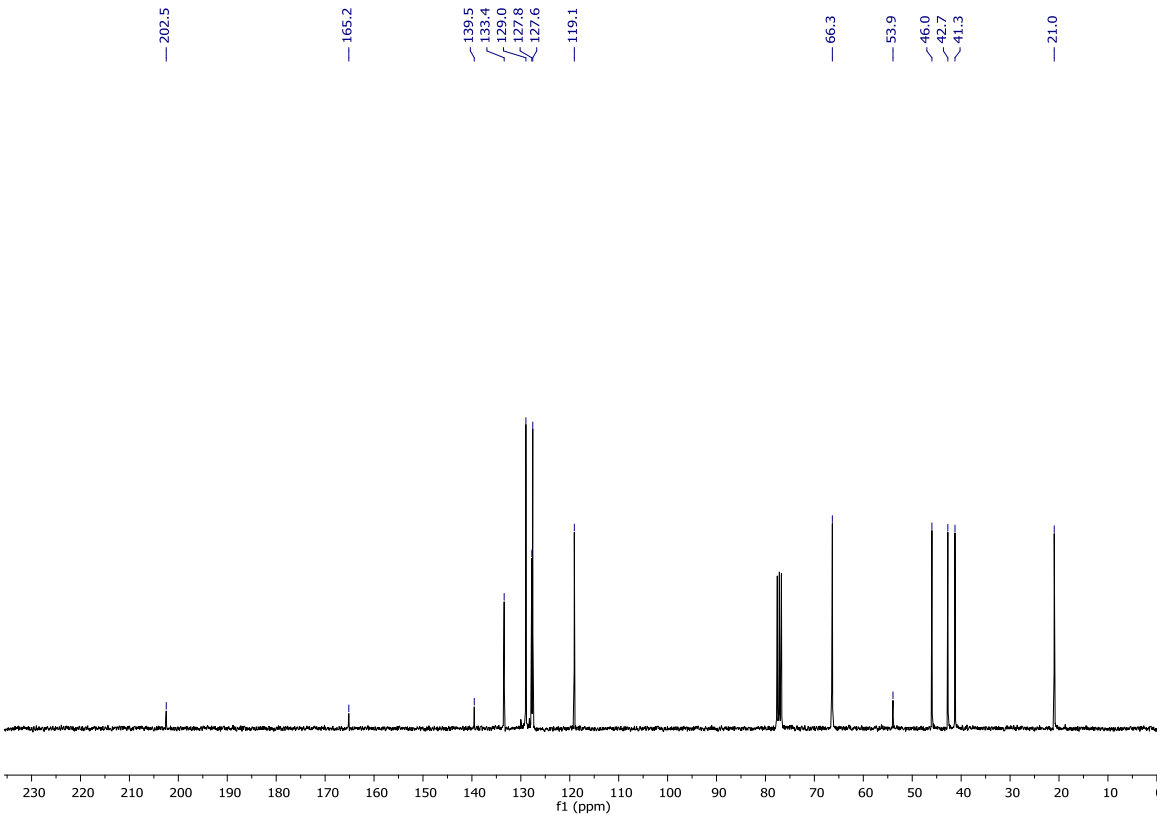

204.1
167.8
141.0
128.7
127.3
127.2
54.2
50.6
41.6
26.5
25.9
21.1
20.3
19.7
17.6
14.7
f1 (ppm)

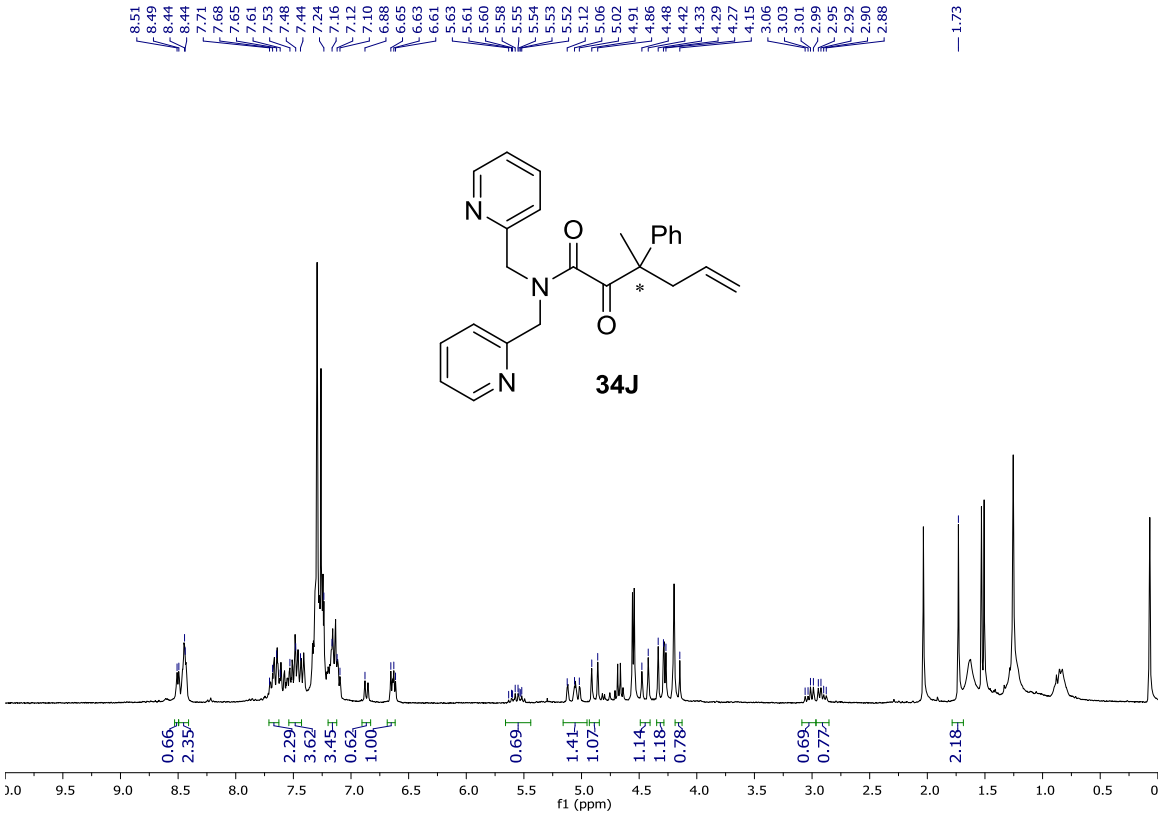

7.89
7.86
7.80
7.78
7.75
7.52
7.50
7.47
7.44
7.38
7.35
7.20
7.19
7.18
6.67
6.65
5.63
5.60
5.57
5.51
5.49
5.10
5.06
5.03
5.01
4.97
4.92
4.33
4.32
3.04
2.99
2.95
2.93
2.88
1.73
O
Ph
N
*
O
34D
5.88
4.02
4.94
4.06
0.96
1.01
3.76
2.02
2.14
3.00
f1 (ppm)
202.4
167.5
139.9
133.9
133.6
131.6
130.3
129.0
128.9
128.8
128.6
128.4
127.5
127.4
126.8
126.6
126.3
126.1
125.9
125.6
125.3
124.8
123.7
122.2
118.9
53.9
46.7
44.3
43.1
21.3
f1 (ppm)

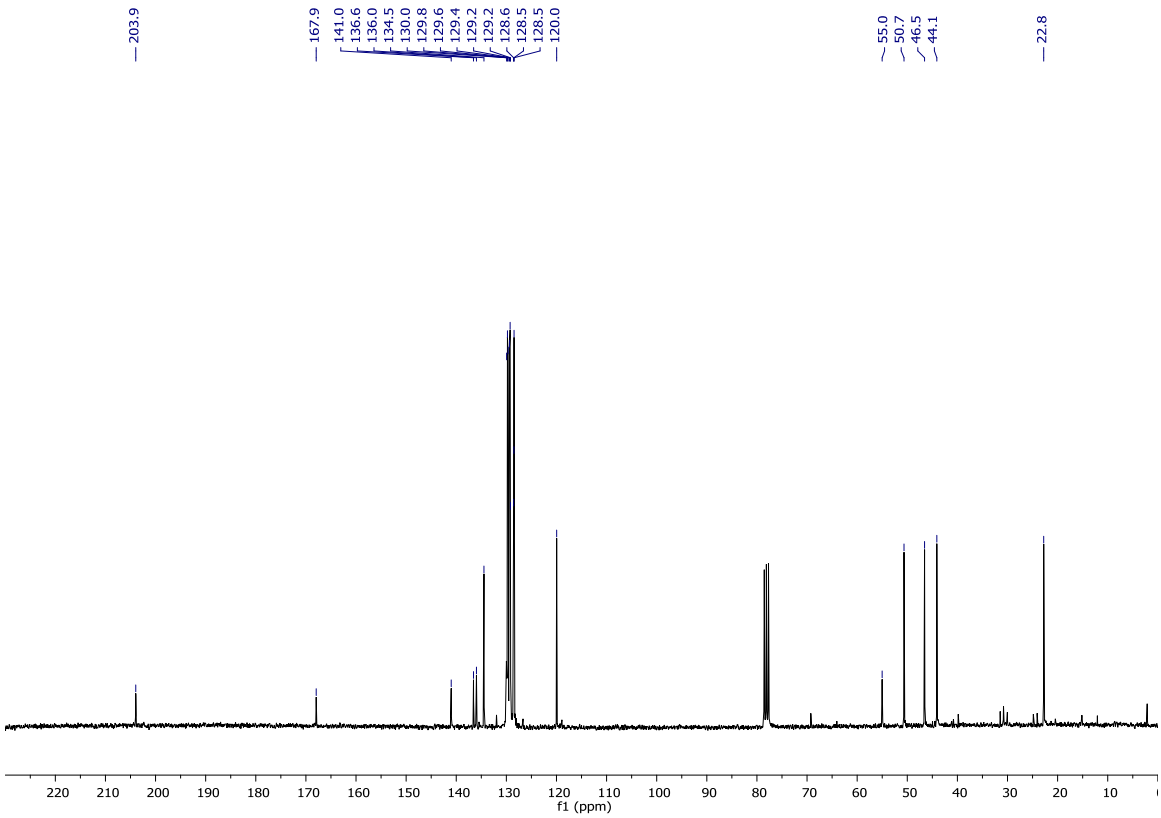

7.44 7.43 7.42 7.42 7.41 7.41 7.38 7.37 7.35 7.35 7.34 7.33 7.32 7.28 7.26
5.57 5.55 5.13 5.13 5.12 5.07 5.07 5.06 5.06 5.05 5.05 5.05 5.02 5.02 5.01
3.38 3.36 3.34 3.34 2.95 2.94 2.94 2.94 2.92 2.92 2.91 2.91 2.87 2.86 2.85 2.83 2.83 2.81
1.65 1.52 1.52 1.51 1.50 1.50 1.49 1.48 1.48 1.47 1.46 1.44 1.43 1.43 1.42 1.42 1.41 1.40 1.40 1.39 1.38
O
Ph
N
*
O
34E
3.71
0.67
1.64
1.80
3.68
3.00
3.89
2.08
f1 (ppm)

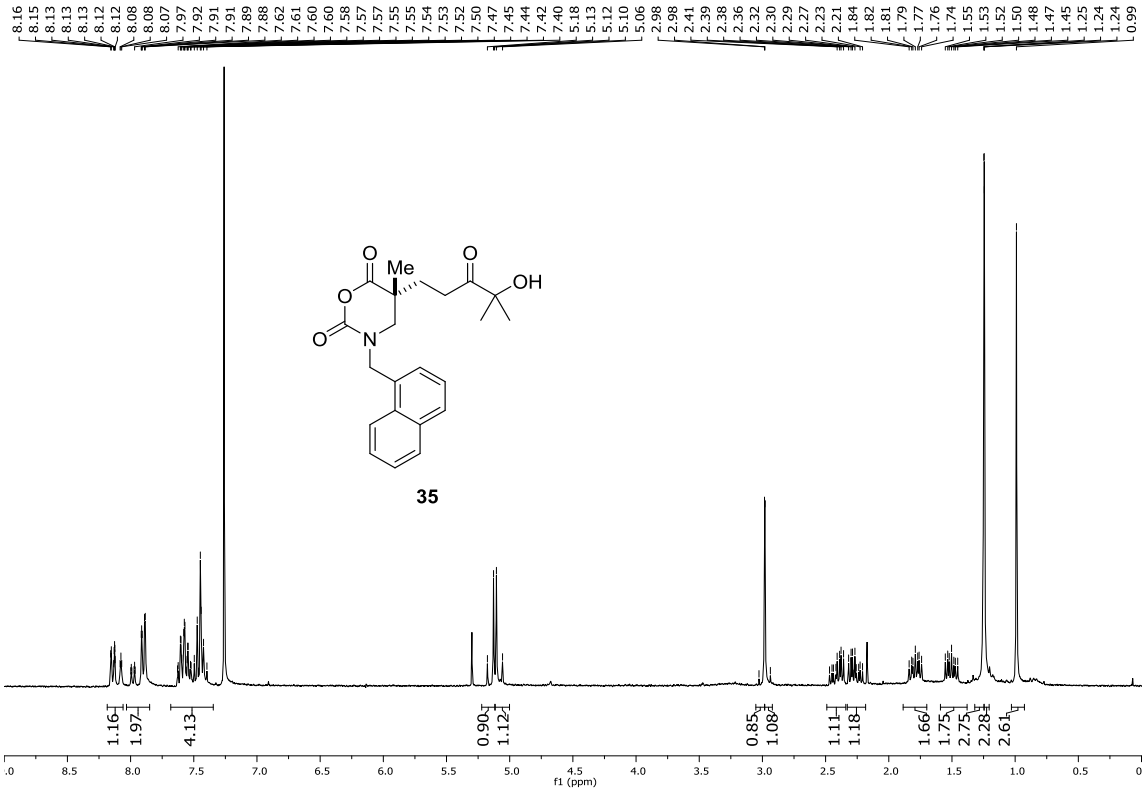

203.6
165.2
140.0
133.6
128.8
127.5
127.4
118.8
53.6
46.7
43.2
41.8
25.8
25.2
24.3
20.9
f1 (ppm)

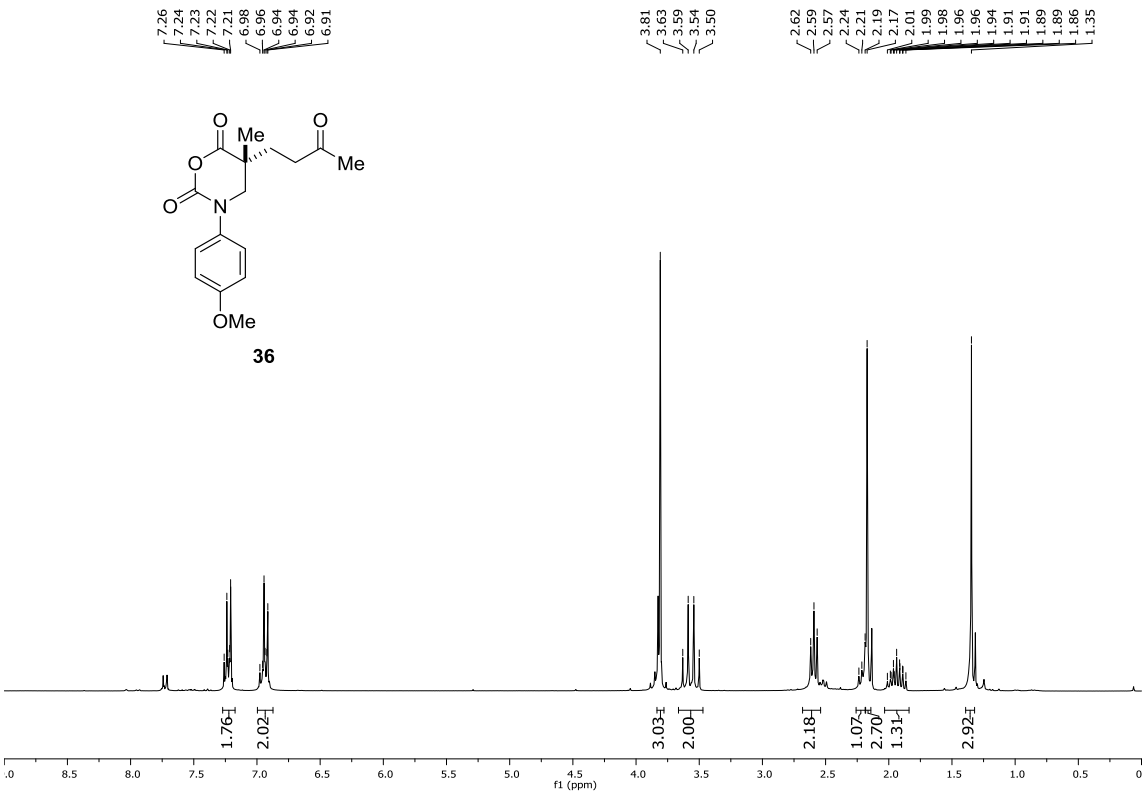

7.40
7.38
7.29
7.26
5.59
5.58
5.50
5.15
5.08
5.04
3.49
3.43
3.27
3.22
3.14
3.10
2.96
2.88
1.66
O
Ph
N
*
O
O
34F
4.42
0.73
1.75
4.02
1.04
1.08
4.12
3.00
f1 (ppm)

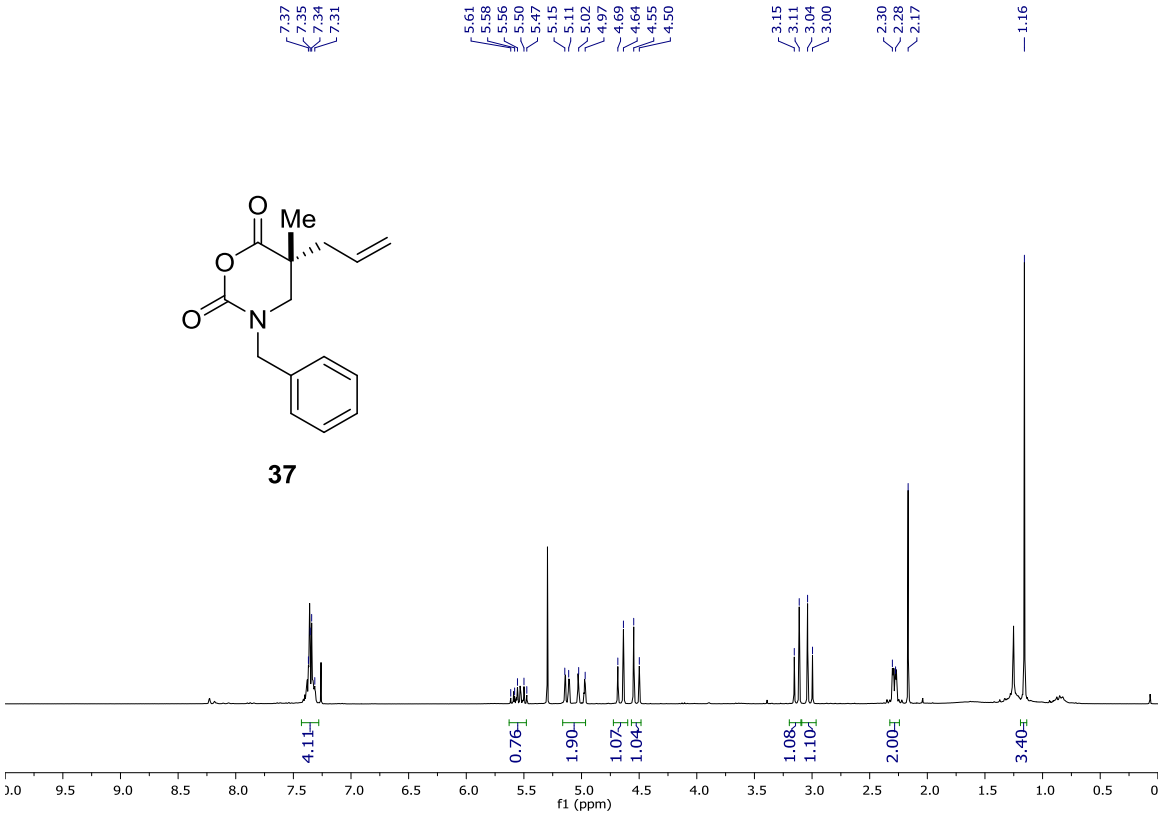

202.5
165.2
139.5
133.4
129.0
127.8
127.6
119.1
66.3
53.9
46.0
42.7
41.3
21.0
f1 (ppm)


8.51
8.49
8.44
8.44
7.71
7.68
7.65
7.61
7.53
7.48
7.44
7.24
7.16
7.12
7.10
6.88
6.65
6.63
6.61
5.63
5.61
5.60
5.58
5.55
5.54
5.53
5.52
5.12
5.06
5.02
4.91
4.86
4.48
4.42
4.33
4.29
4.27
4.15
3.06
3.03
3.01
2.99
2.95
2.92
2.90
2.88
1.73
N
O
Ph
N
*
O
N
34J
0.66
2.35
2.29
3.62
3.45
0.62
1.00
0.69
1.41
1.07
1.14
1.18
0.78
0.69
0.77
2.18
f1 (ppm)

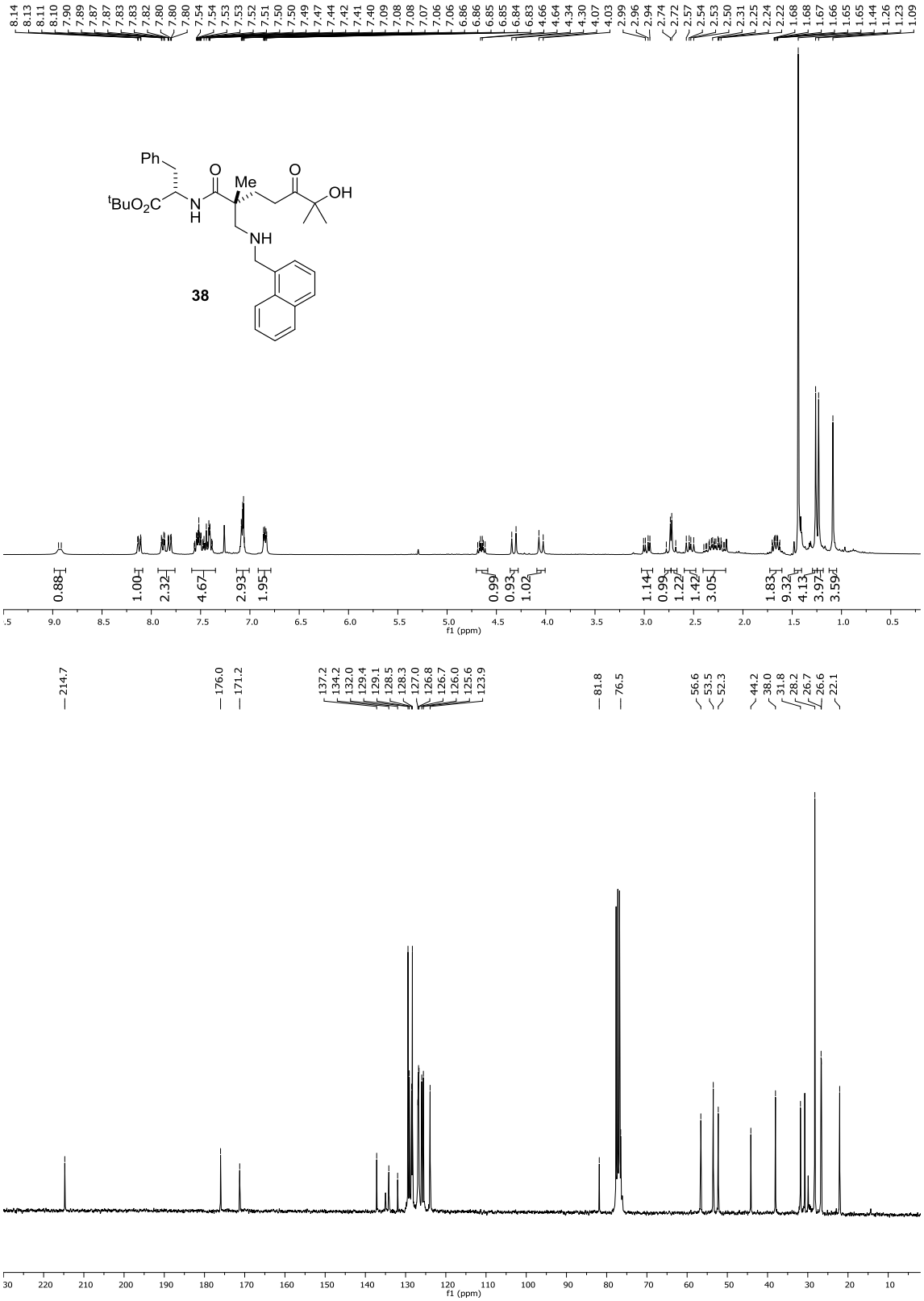

203.9
167.9
141.0
136.6
136.0
134.5
130.0
129.8
129.6
129.4
129.2
129.2
128.6
128.5
128.5
120.0
55.0
50.7
46.5
44.1
22.8
f1 (ppm)

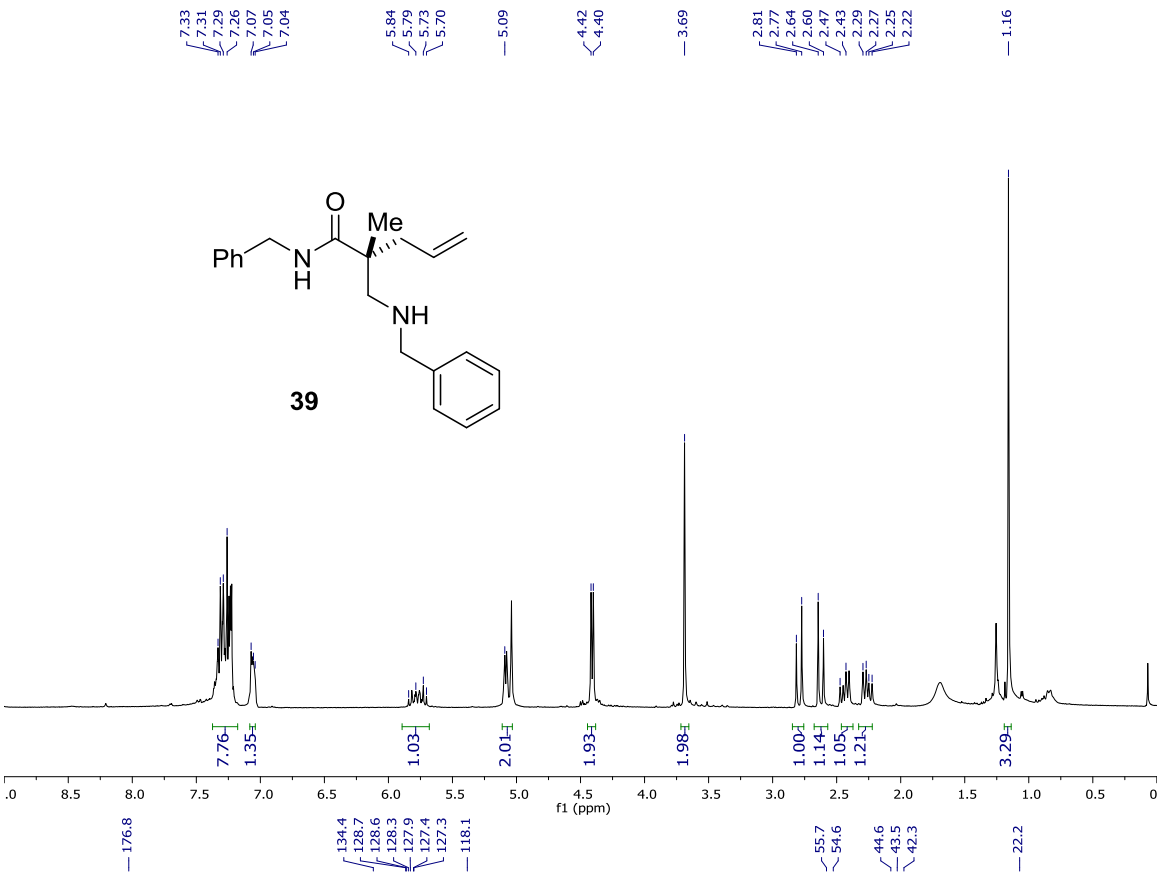

8.16 8.15 8.13 8.13 8.13 8.12 8.12 8.08 8.08 8.07 7.97 7.92 7.91 7.91 7.89 7.88 7.62 7.61 7.60 7.60 7.58 7.57 7.57 7.55 7.55 7.54 7.53 7.52 7.50 7.47 7.45 7.44 7.42 7.40 5.18 5.13 5.12 5.10 5.06 2.98 2.98 2.41 2.39 2.38 2.36 2.32 2.30 2.29 2.27 2.23 2.21 1.84 1.82 1.81 1.79 1.77 1.76 1.74 1.55 1.53 1.52 1.50 1.48 1.47 1.45 1.25 1.24 1.24 0.99
O
Me
O
O
OH
O
N
35
1.16 1.97 4.13 0.90 1.12 0.85 1.08 1.11 1.18 1.66 1.75 2.75 2.28 2.61
f1 (ppm)

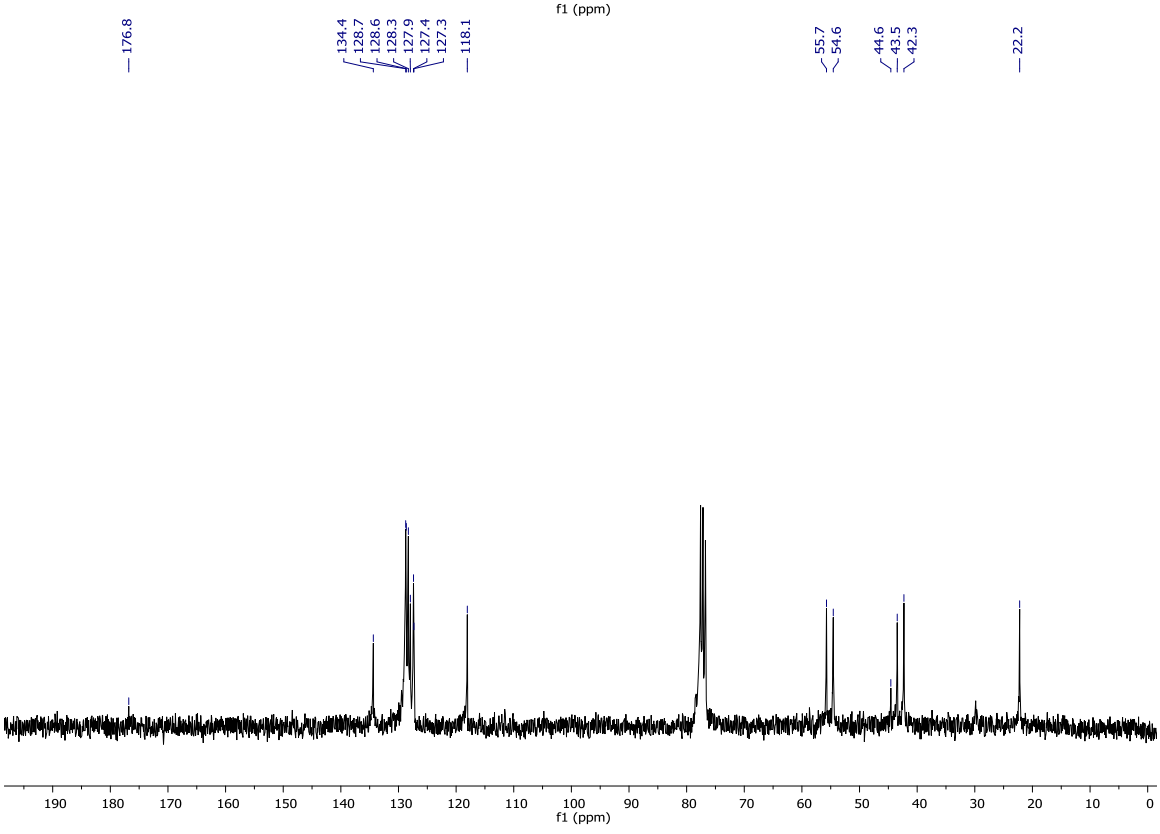

7.26 7.24 7.23 7.22 7.21 6.98 6.96 6.94 6.94 6.92 6.91 3.81 3.63 3.59 3.54 3.50 2.62 2.59 2.57 2.24 2.21 2.19 2.17 2.01 1.99 1.98 1.96 1.96 1.94 1.91 1.91 1.89 1.89 1.86 1.35
O
Me
O
O
Me
O
N
OMe
36
1.76 2.02 3.03 2.00 2.18 1.07 2.70 1.31 2.92
f1 (ppm)

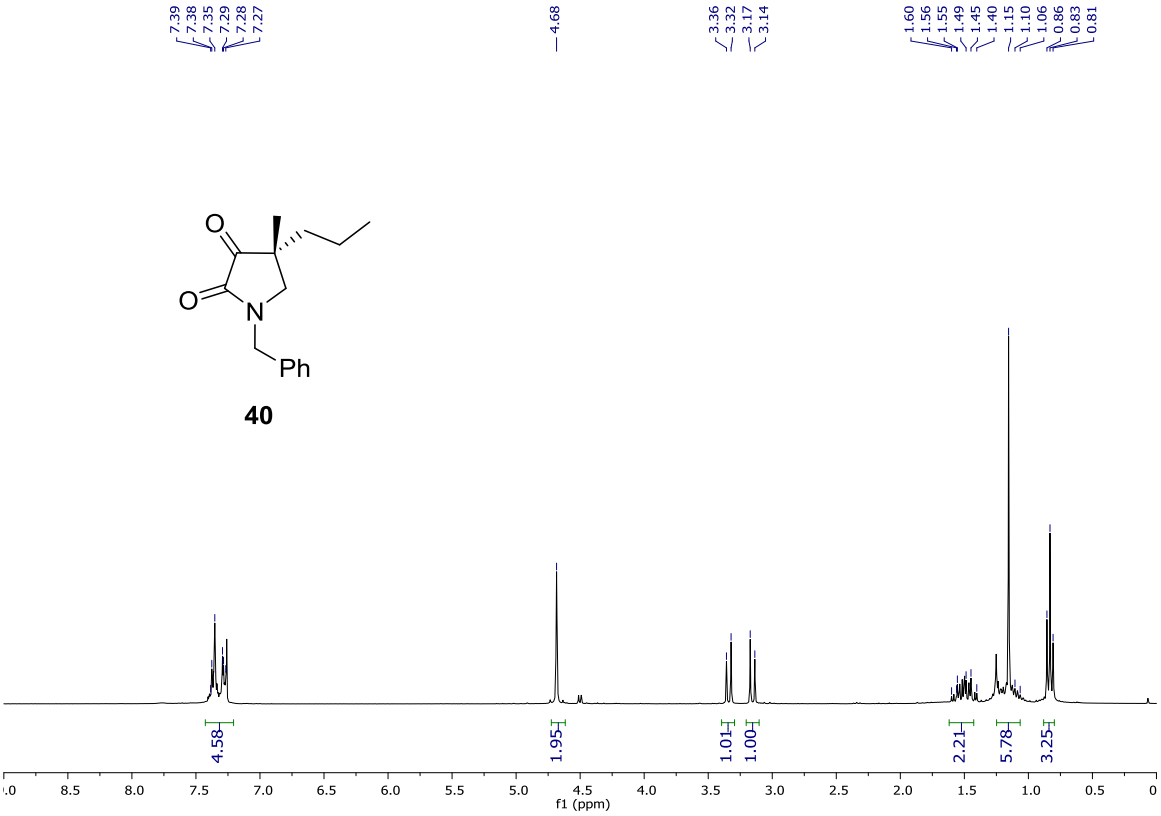

7.37
7.35
7.34
7.31
5.61
5.58
5.56
5.50
5.47
5.15
5.11
5.02
4.97
4.69
4.64
4.55
4.50
3.15
3.11
3.04
3.00
2.30
2.28
2.17
1.16
O
Me
O
O
N
4.11
0.76
1.90
1.07
1.04
1.08
1.10
2.00
3.40
f1 (ppm)

37

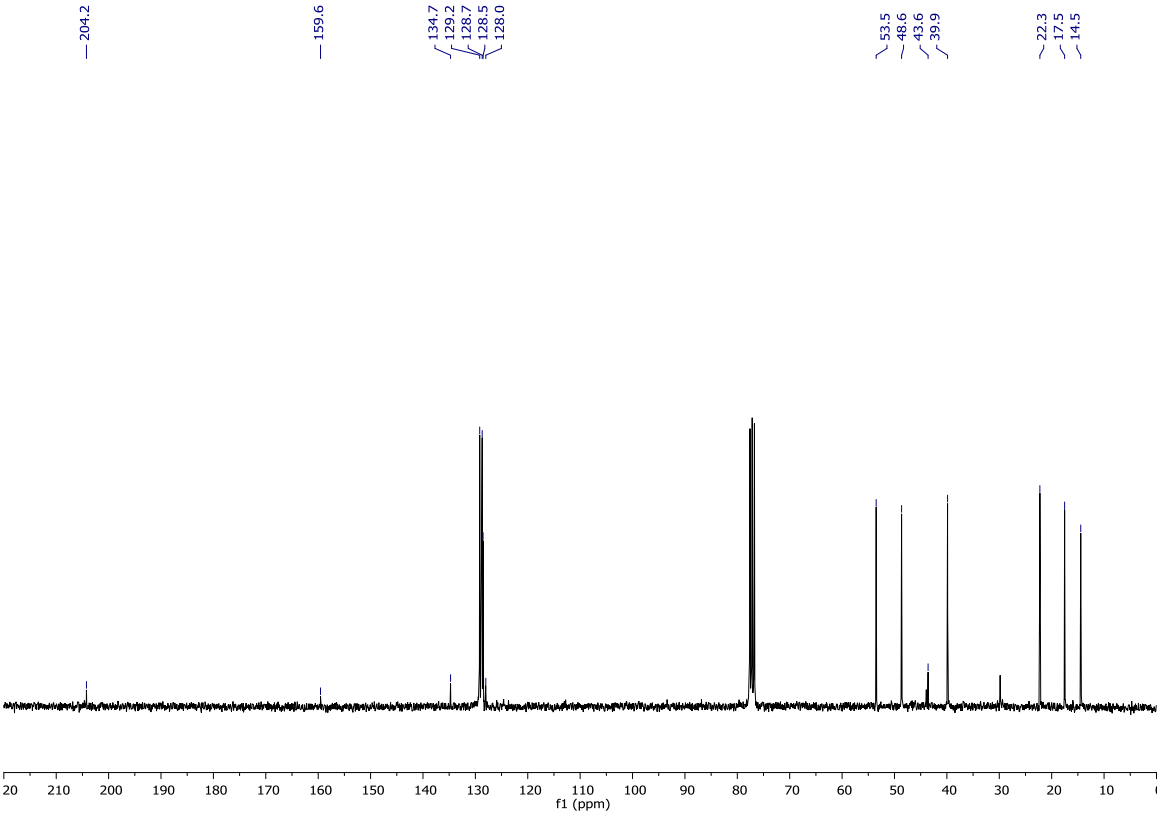

Ph
O
Me
O
OH
tBuO2C
N
H
NH
38
f1 (ppm)

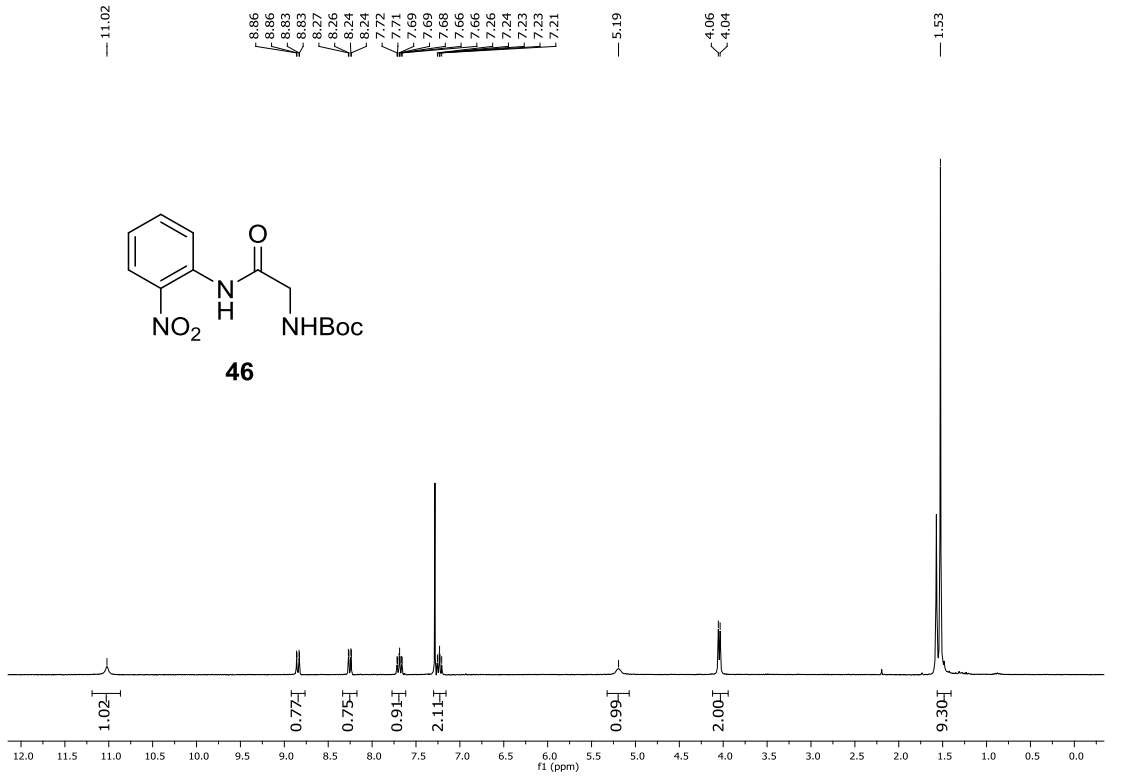

7.33
7.31
7.29
7.26
7.07
7.05
7.04
5.84
5.79
5.73
5.70
5.09
4.42
4.40
3.69
2.81
2.77
2.64
2.60
2.47
2.43
2.29
2.27
2.25
2.22
1.16
O
Me
Ph
N
H
NH
39
7.76
1.35
1.03
2.01
1.93
1.98
1.00
1.14
1.05
1.21
3.29
f1 (ppm)

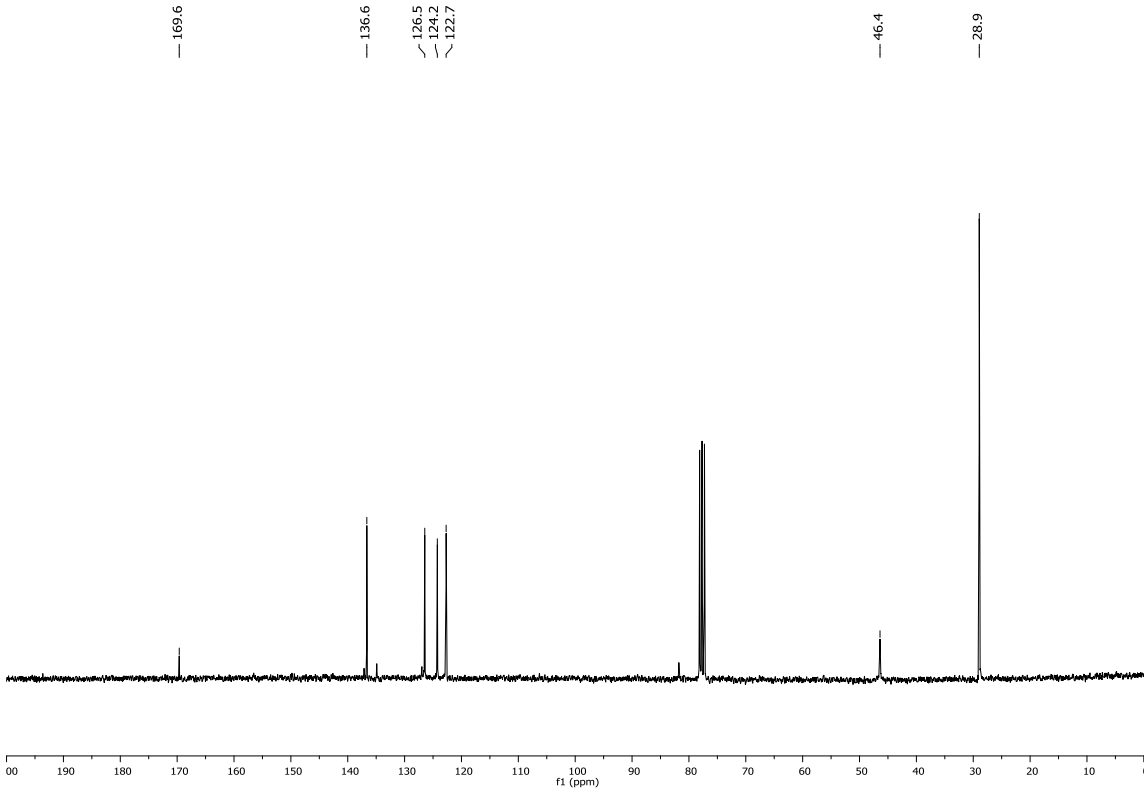

176.8
134.4
128.7
128.6
128.3
127.9
127.4
127.3
118.1
55.7
54.6
44.6
43.5
42.3
22.2
f1 (ppm)

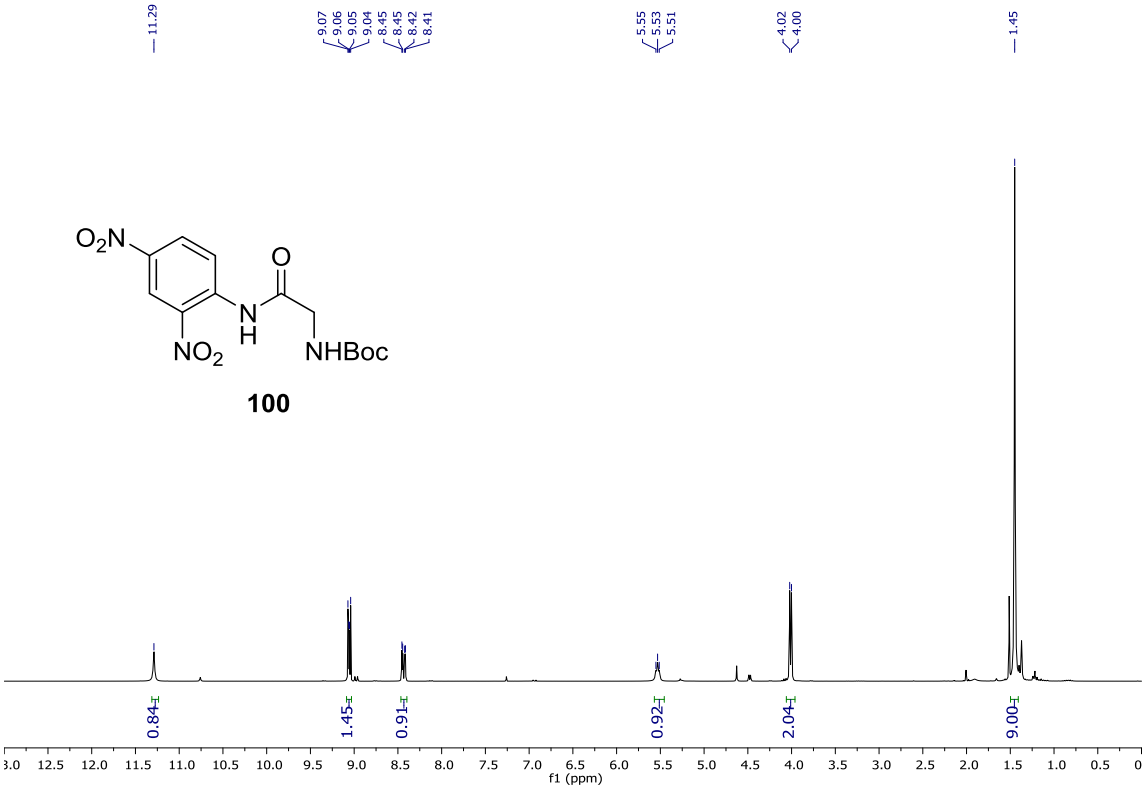

7.39
7.38
7.35
7.29
7.28
7.27
4.68
3.36
3.32
3.17
3.14
1.60
1.56
1.55
1.49
1.45
1.40
1.15
1.10
1.06
0.86
0.83
0.81
O
O
N
Ph
4.58
1.95
1.01
1.00
2.21
5.78
3.25
f1 (ppm)

40

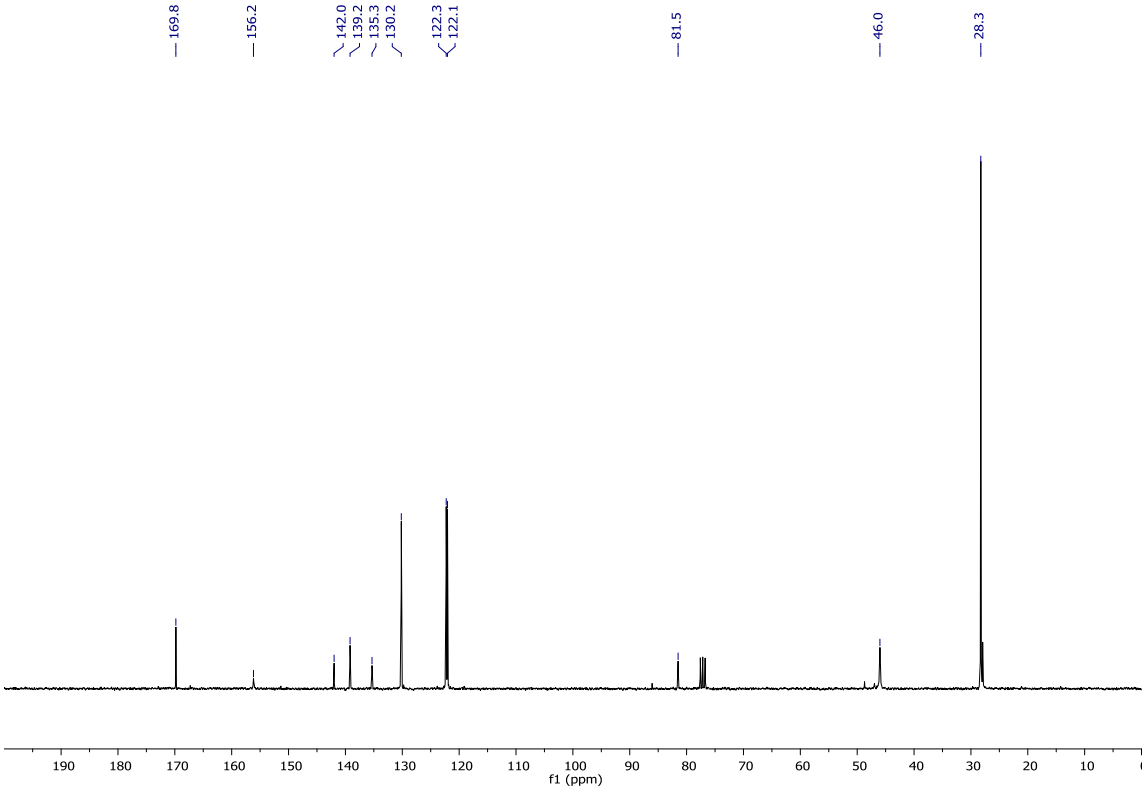

204.2
159.6
134.7
129.2
128.7
128.5
128.0
53.5
48.6
43.6
39.9
22.3
17.5
14.5
f1 (ppm)

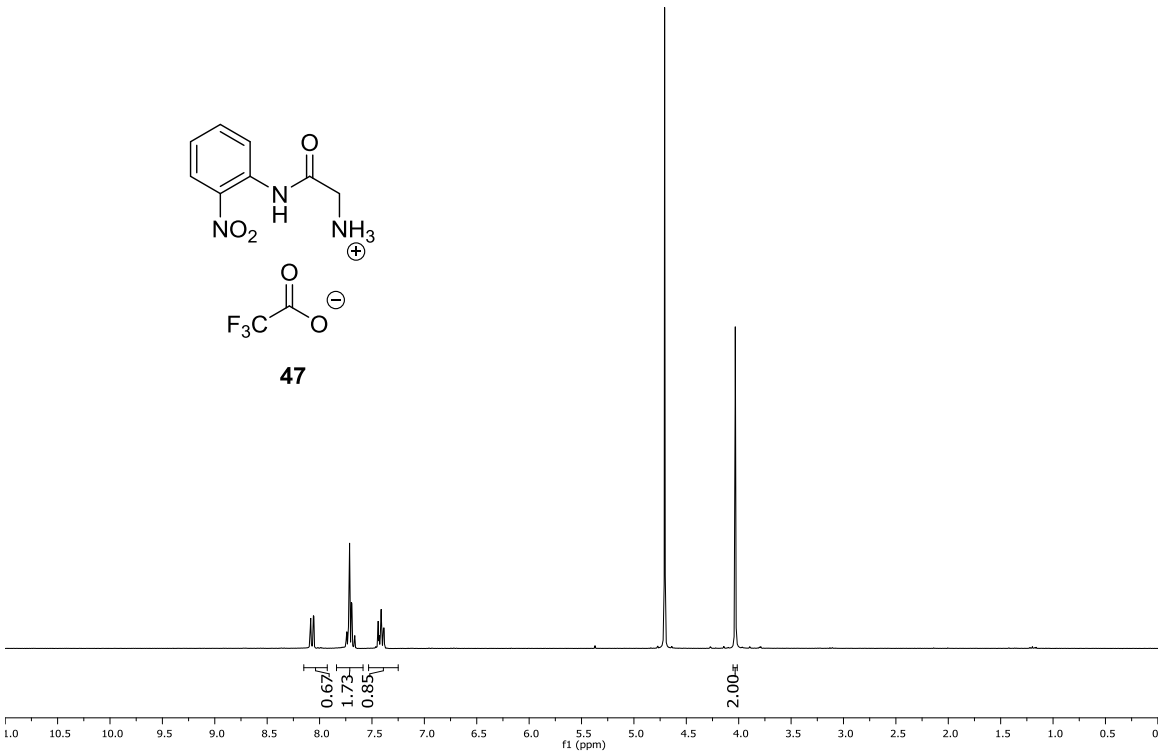

11.02
8.86
8.86
8.83
8.83
8.27
8.26
8.24
8.24
7.72
7.71
7.69
7.69
7.68
7.66
7.66
7.26
7.24
7.23
7.23
7.21
5.19
4.06
4.04
1.53
O
N
H
NO2
NHBoc
46
1.02
0.77
0.75
0.91
2.11
0.99
2.00
9.30
f1 (ppm)


169.6
136.6
126.5
124.2
122.7
46.4
28.9
f1 (ppm)

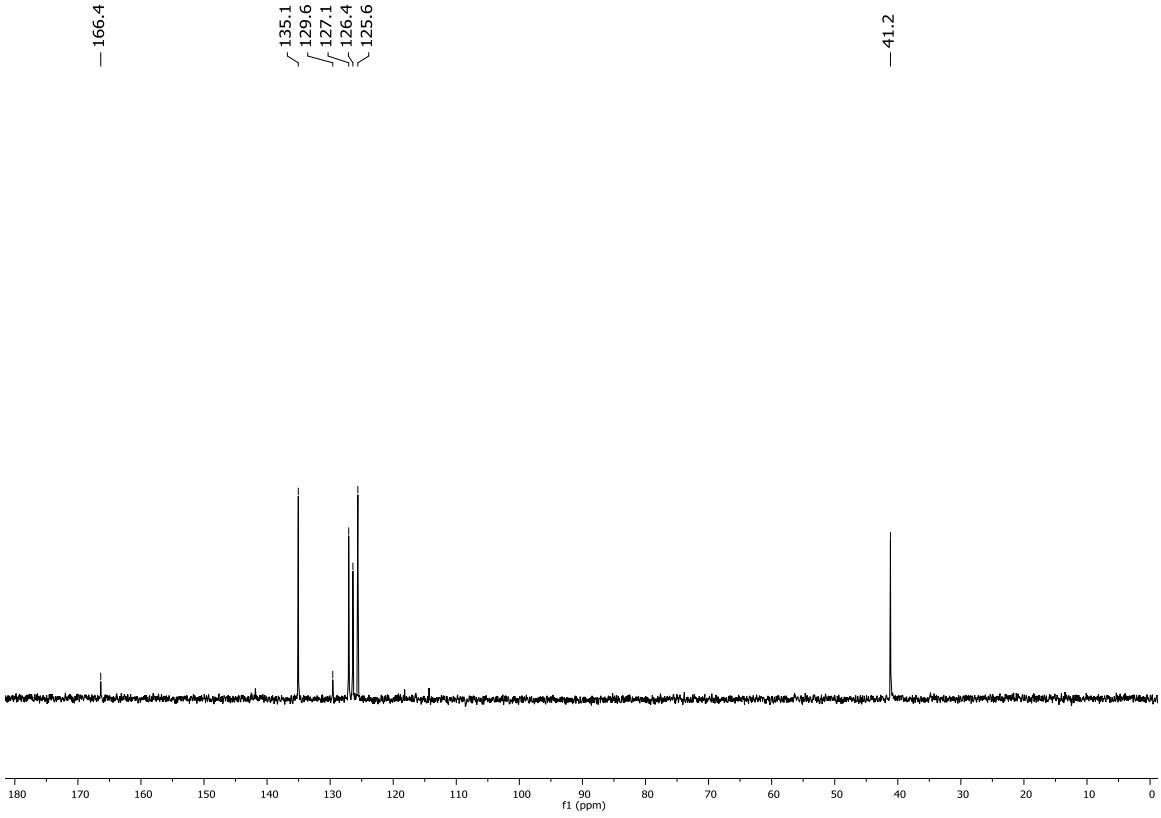

11.29
9.07
9.06
9.05
9.04
8.45
8.45
8.42
8.41
5.55
5.53
5.51
4.02
4.00
1.45
O2N
NO2
N
H
O
NHBoc
0.84
1.45
0.91
0.92
2.04
9.00
f1 (ppm)

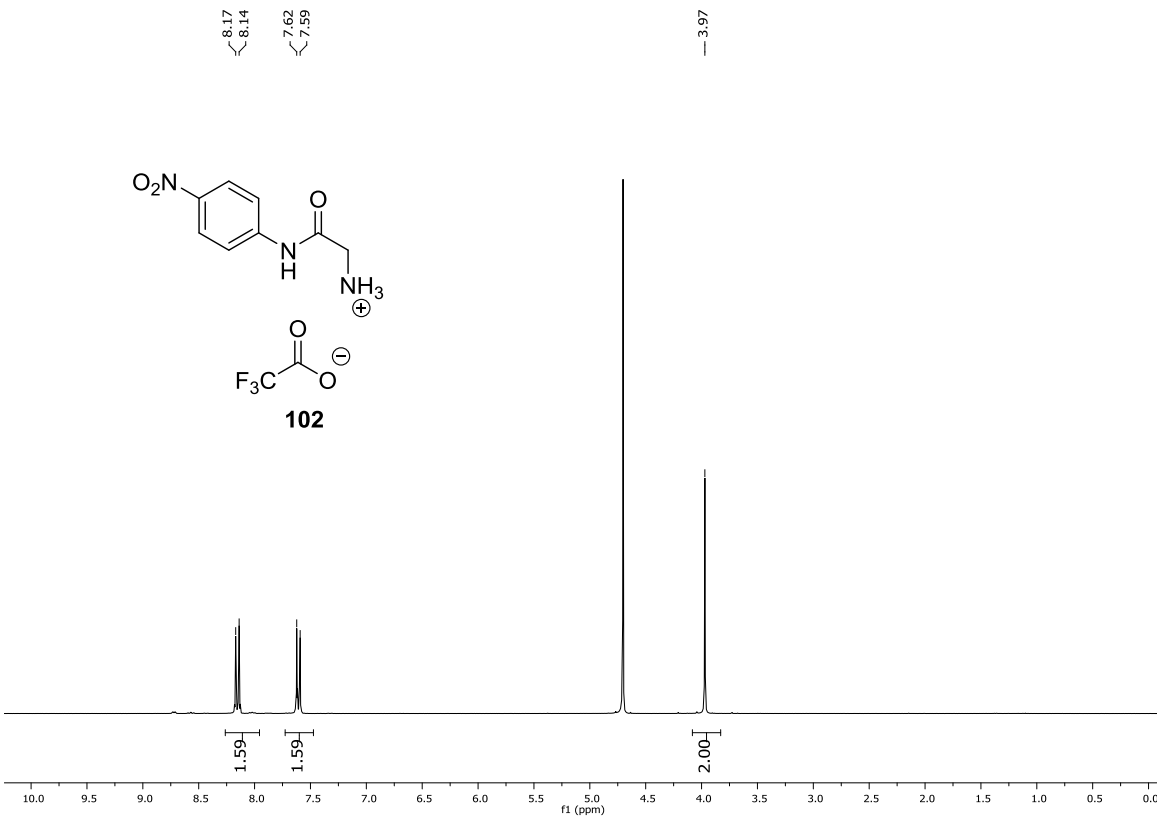
100


169.8
156.2
142.0
139.2
135.3
130.2
122.3
122.1
81.5
46.0
28.3
f1 (ppm)

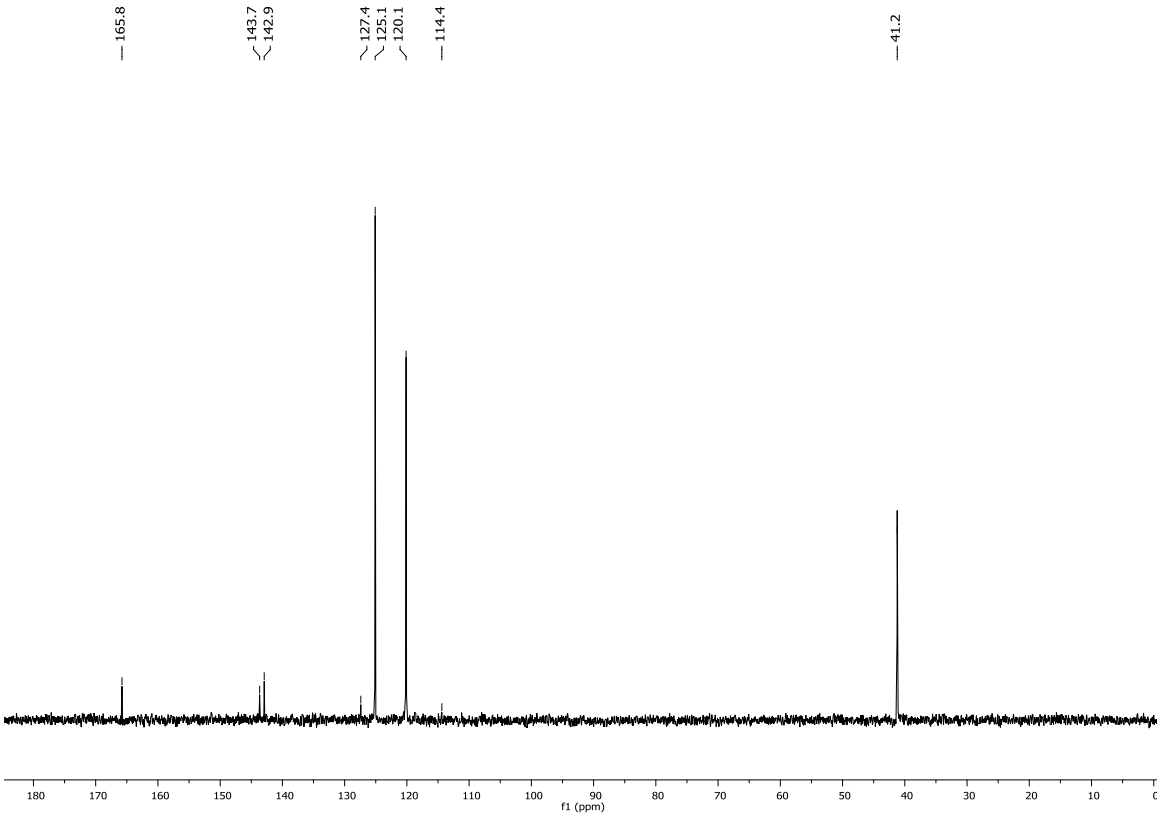

O
N
H
NO2
NH3
O
F3C
O
0.67
1.73
0.85
2.00
f1 (ppm)

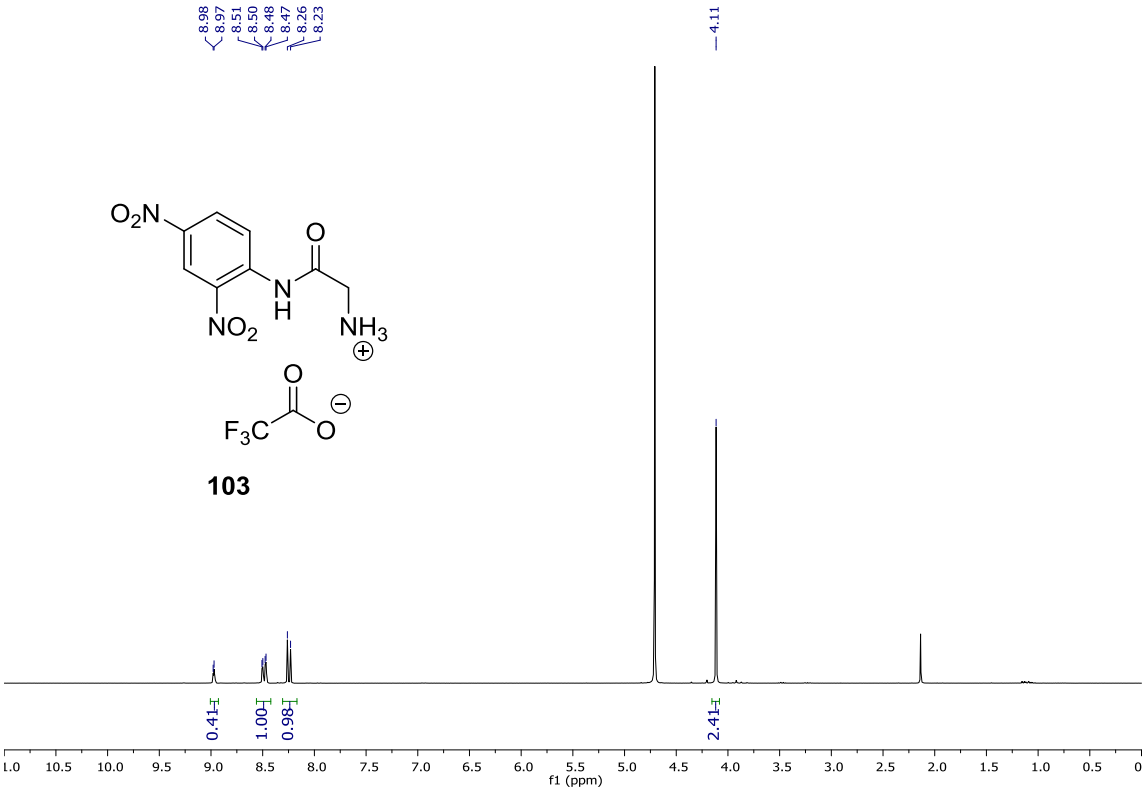
47


166.4
135.1
129.6
127.1
126.4
125.6
41.2
f1 (ppm)

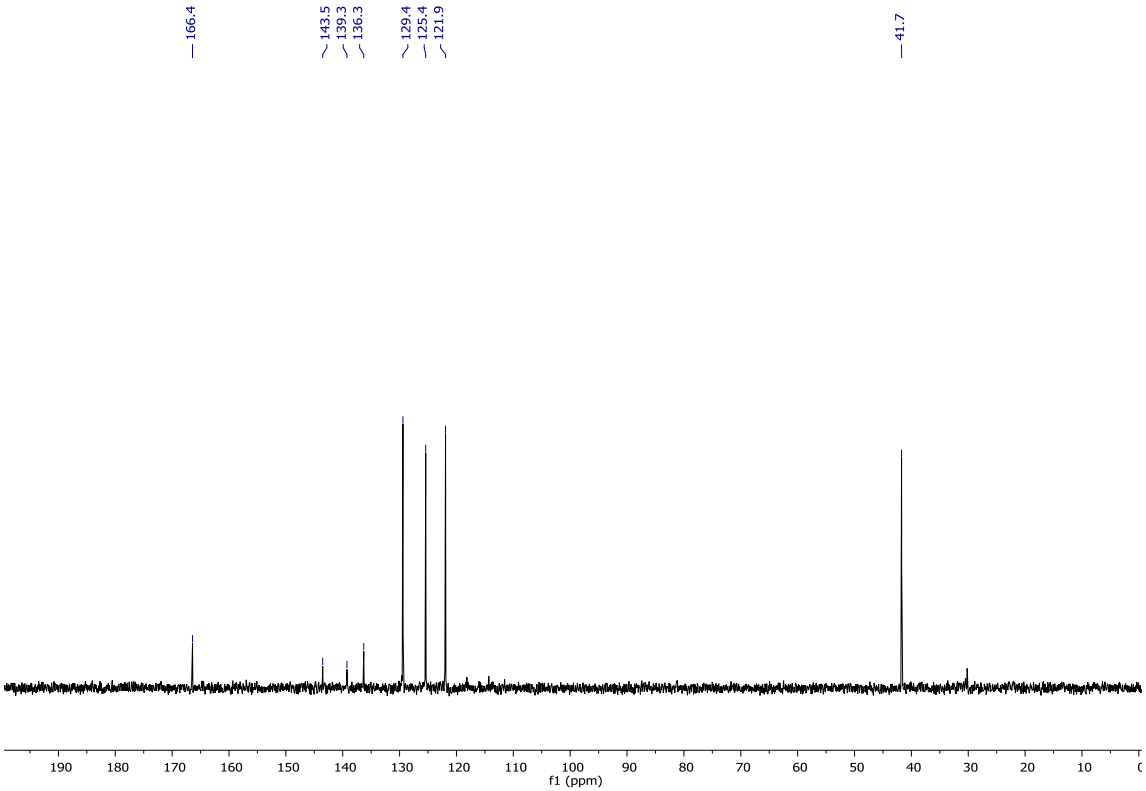

8.17
8.14
7.62
7.59
3.97
O2N
O
N
H
NH3
O
F3C
O
1.59
1.59
2.00
f1 (ppm)

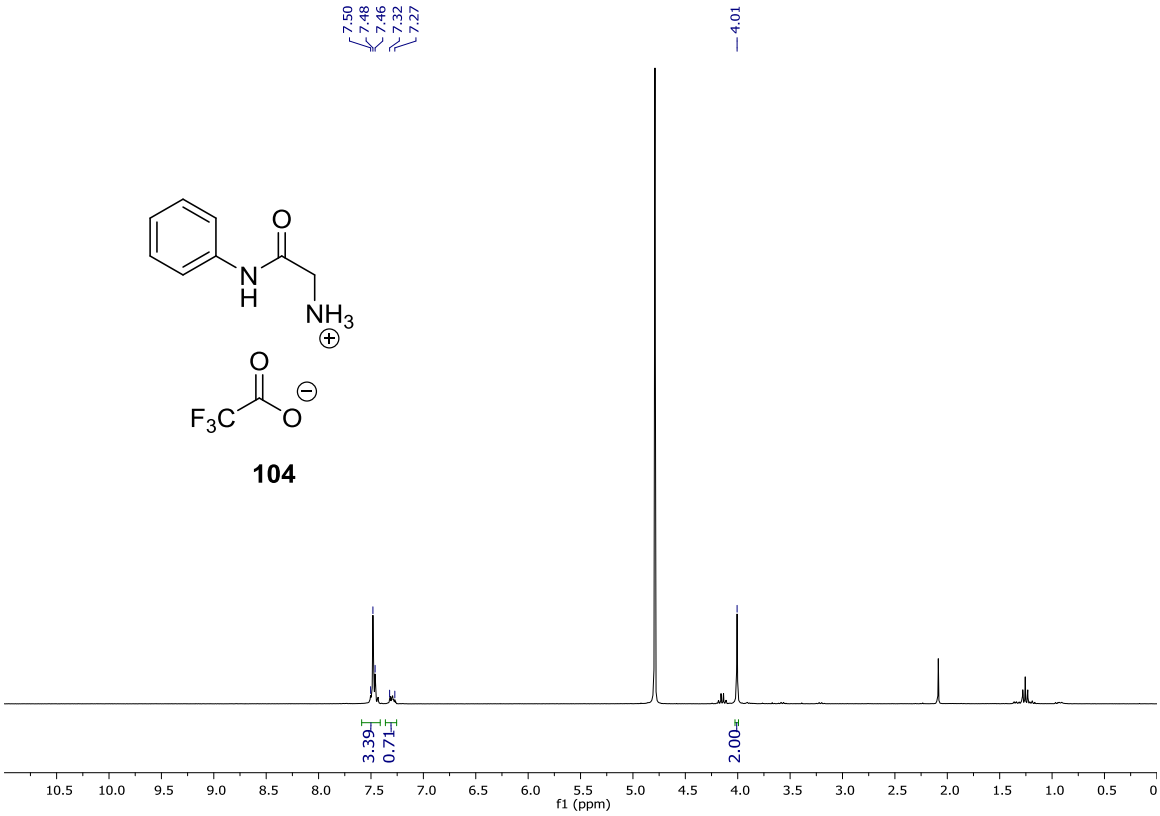
102


165.8
143.7
142.9
127.4
125.1
120.1
114.4
41.2
f1 (ppm)

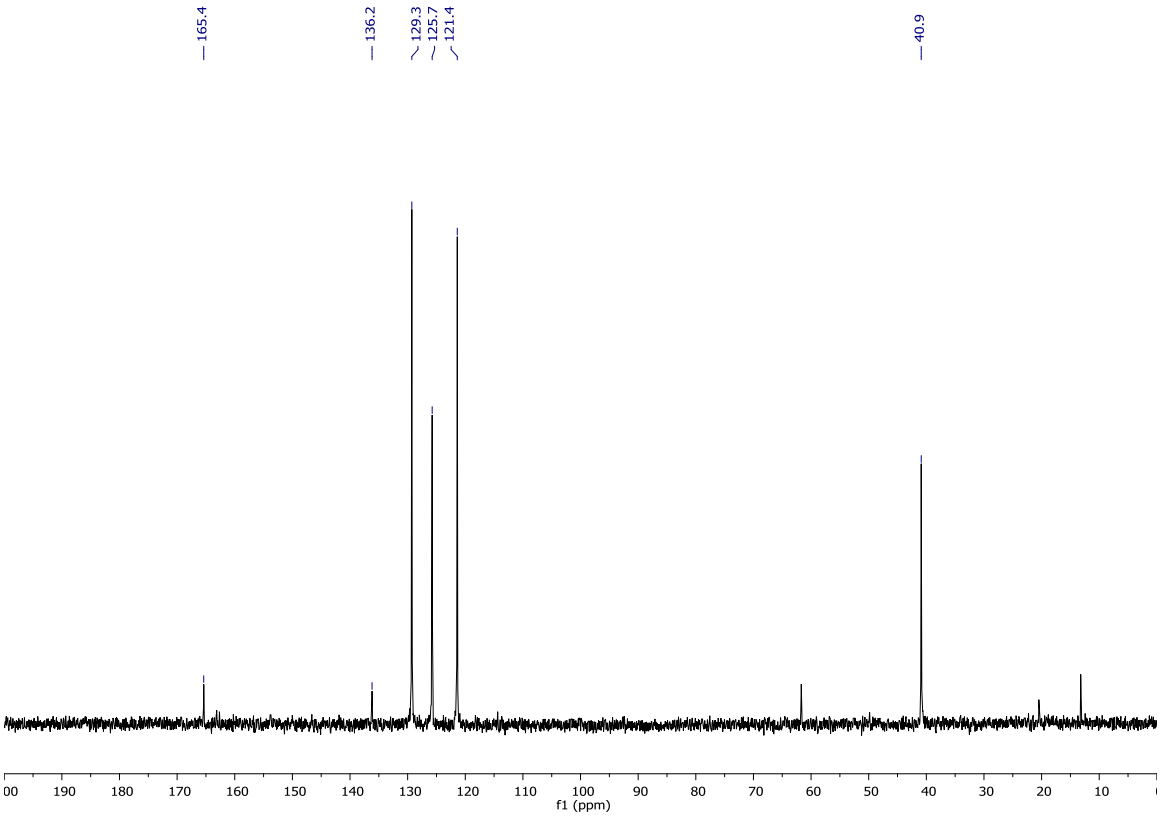

8.98
8.97
8.51
8.50
8.48
8.47
8.26
8.23
4.11
O2N
NO2
N
H
O
NH3
F3C
O
O
0.41
1.00
0.98
2.41
f1 (ppm)

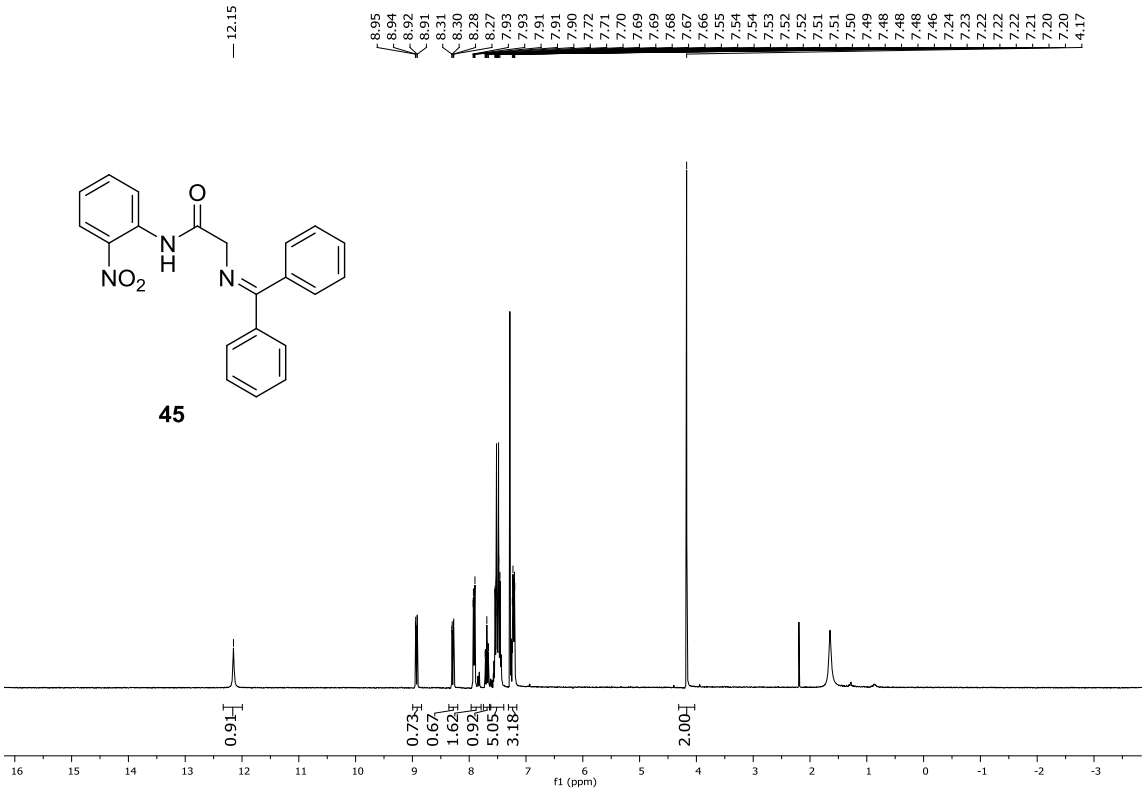
103

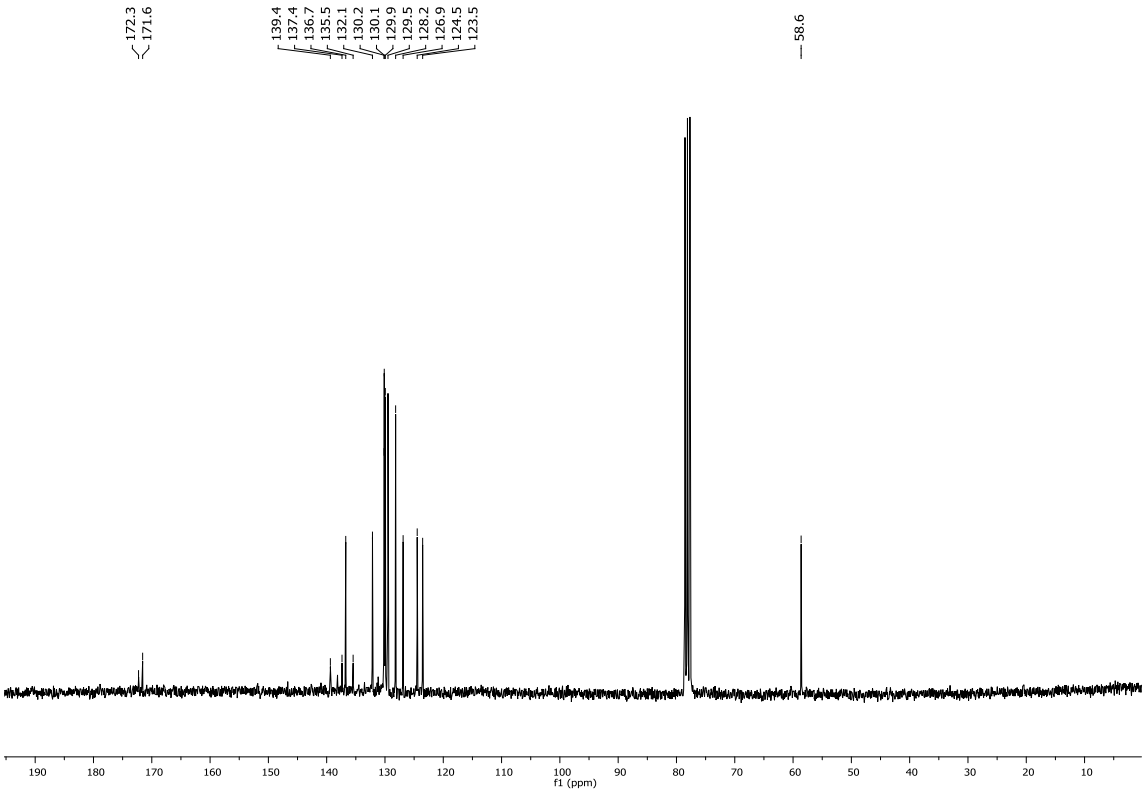

166.4
143.5
139.3
136.3
129.4
125.4
121.9
41.7
f1 (ppm)

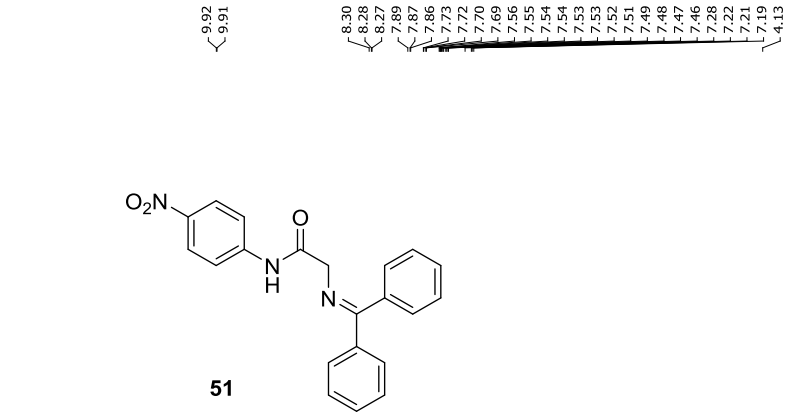

7.50
7.48
7.46
7.32
7.27
4.01
3.39
0.71
2.00
f1 (ppm)

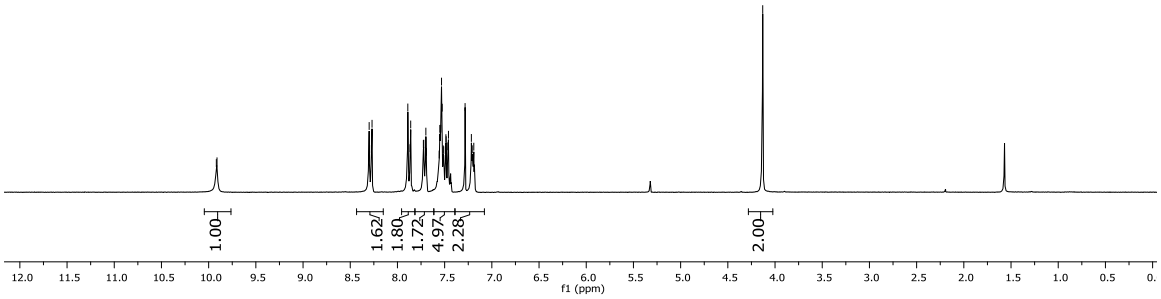
104

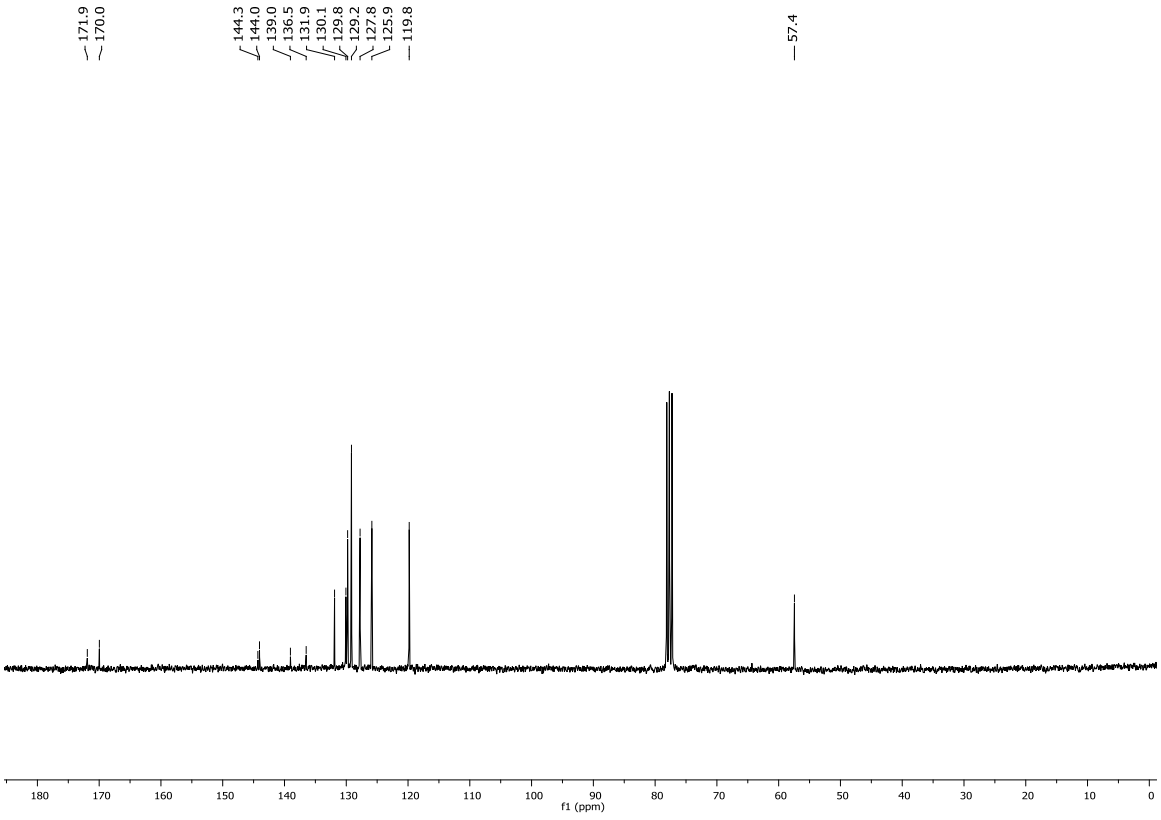

165.4
136.2
129.3
125.7
121.4
40.9
f1 (ppm)

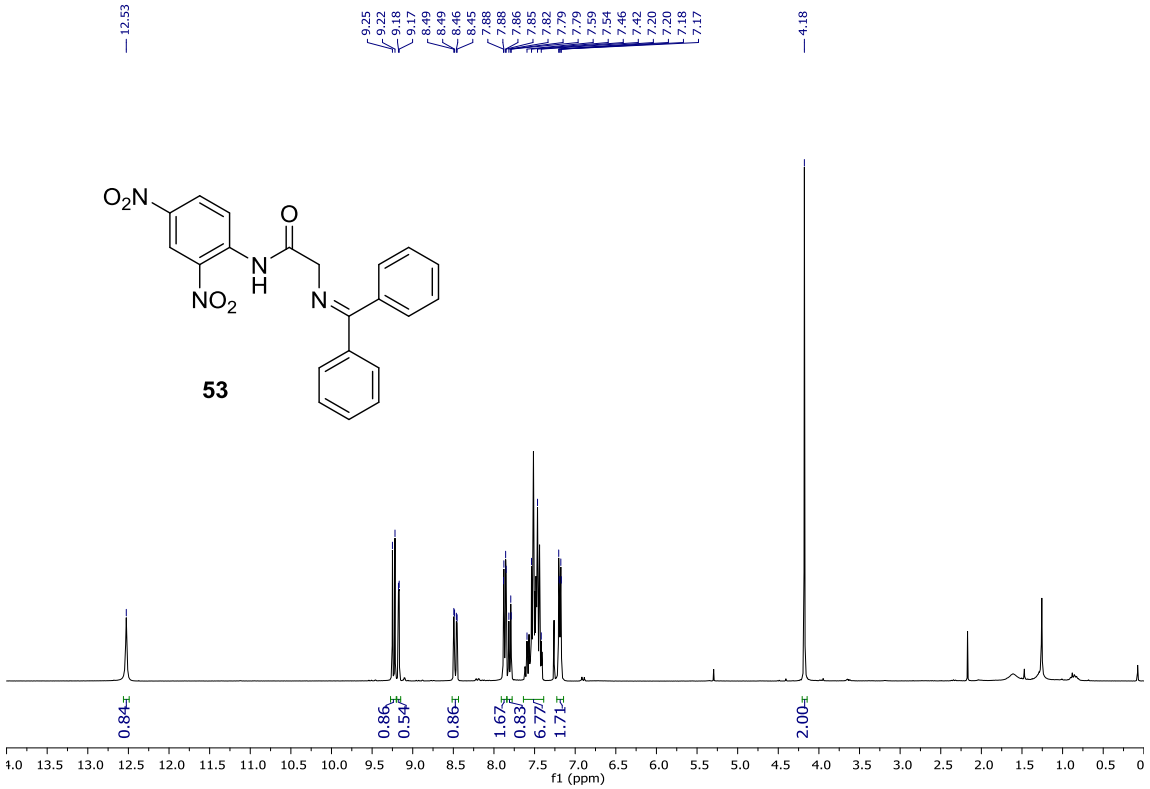

12.15
8.95
8.94
8.92
8.91
8.31
8.30
8.28
8.27
7.93
7.93
7.91
7.91
7.90
7.72
7.71
7.70
7.69
7.69
7.68
7.67
7.66
7.55
7.54
7.54
7.53
7.52
7.52
7.51
7.51
7.50
7.49
7.48
7.48
7.48
7.46
7.24
7.23
7.22
7.22
7.22
7.21
7.20
7.20
4.17
O
N
H
N
NO2
45
0.91
0.73
0.67
1.62
0.92
5.05
3.18
2.00
f1 (ppm)

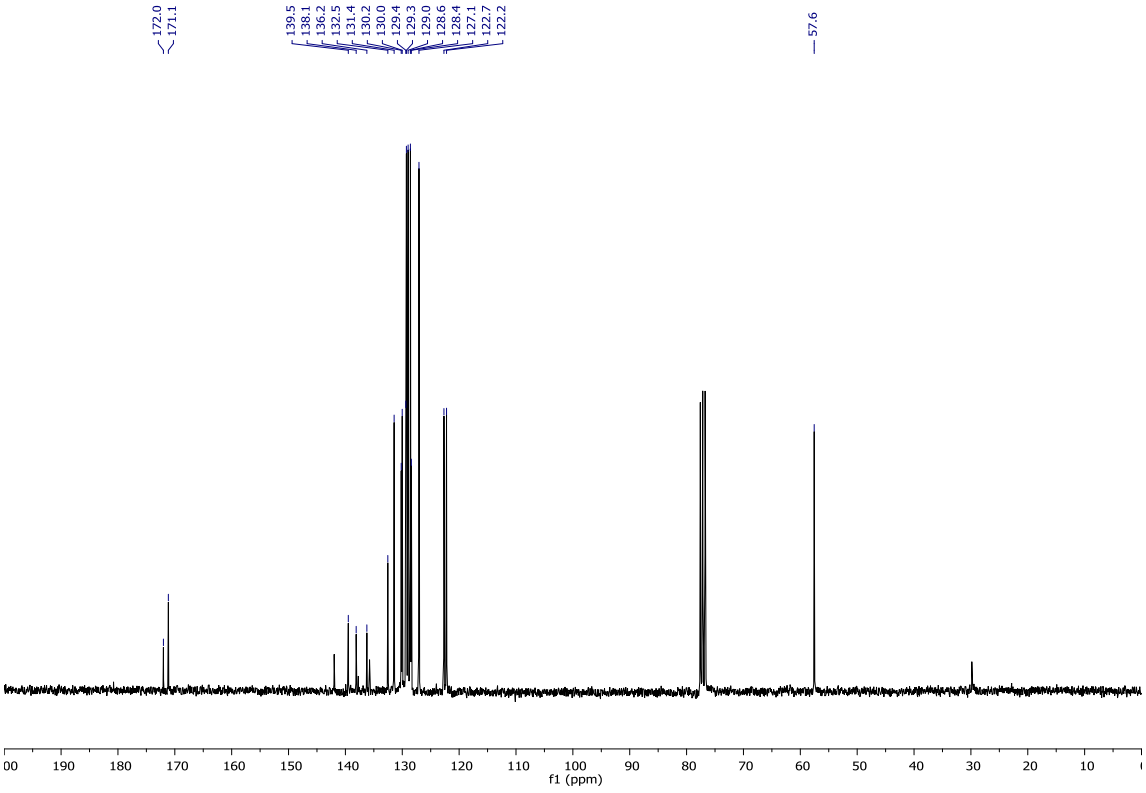

172.3
171.6
139.4
137.4
136.7
135.5
132.1
130.2
130.1
129.9
129.5
128.2
126.9
124.5
123.5
58.6
f1 (ppm)

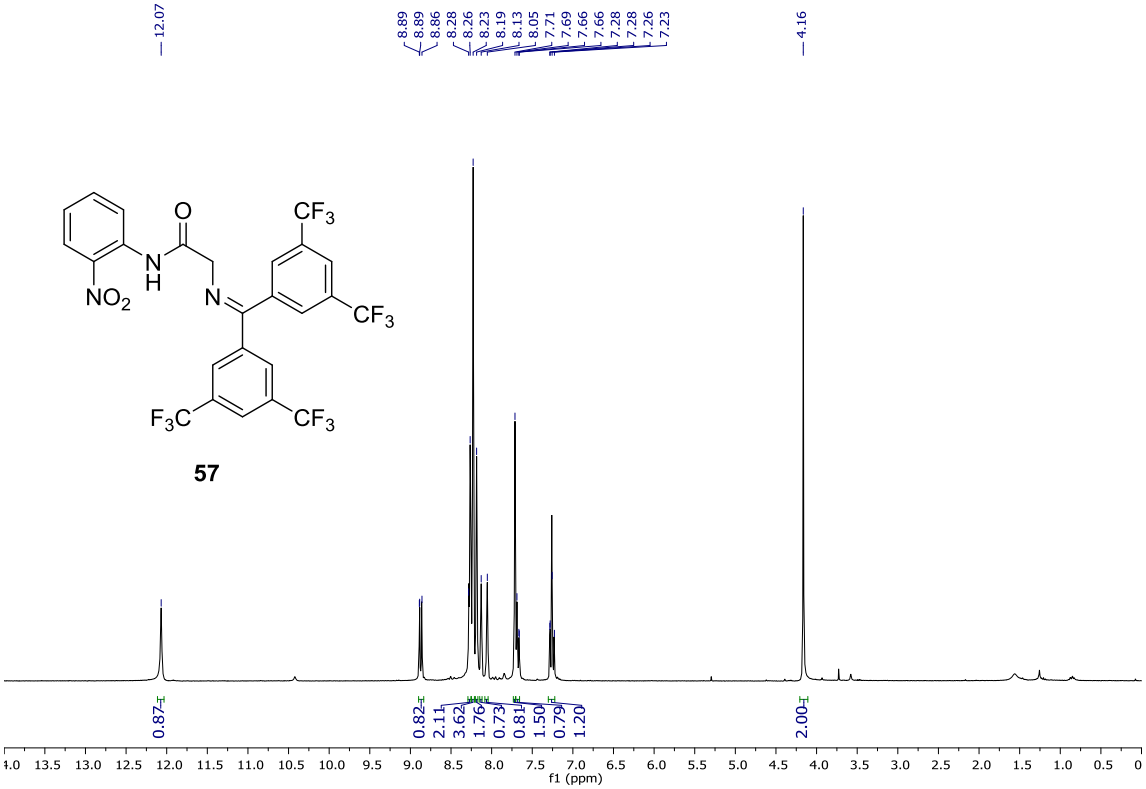

9.92
9.91
8.30
8.28
8.27
7.89
7.87
7.86
7.73
7.72
7.70
7.69
7.56
7.55
7.54
7.54
7.53
7.53
7.52
7.51
7.49
7.48
7.47
7.46
7.28
7.22
7.21
7.19
4.13
O2N
O
N
H
N
51

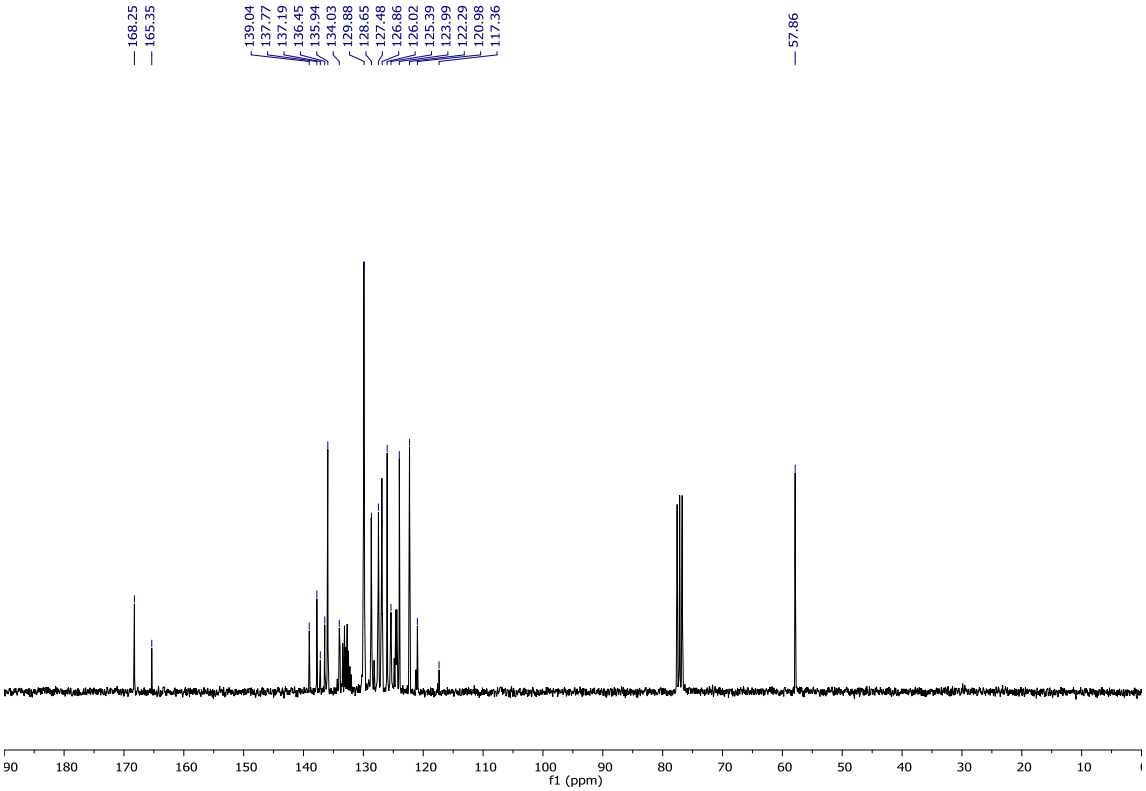

1.00
1.62
1.80
1.72
4.97
2.28
2.00
f1 (ppm)

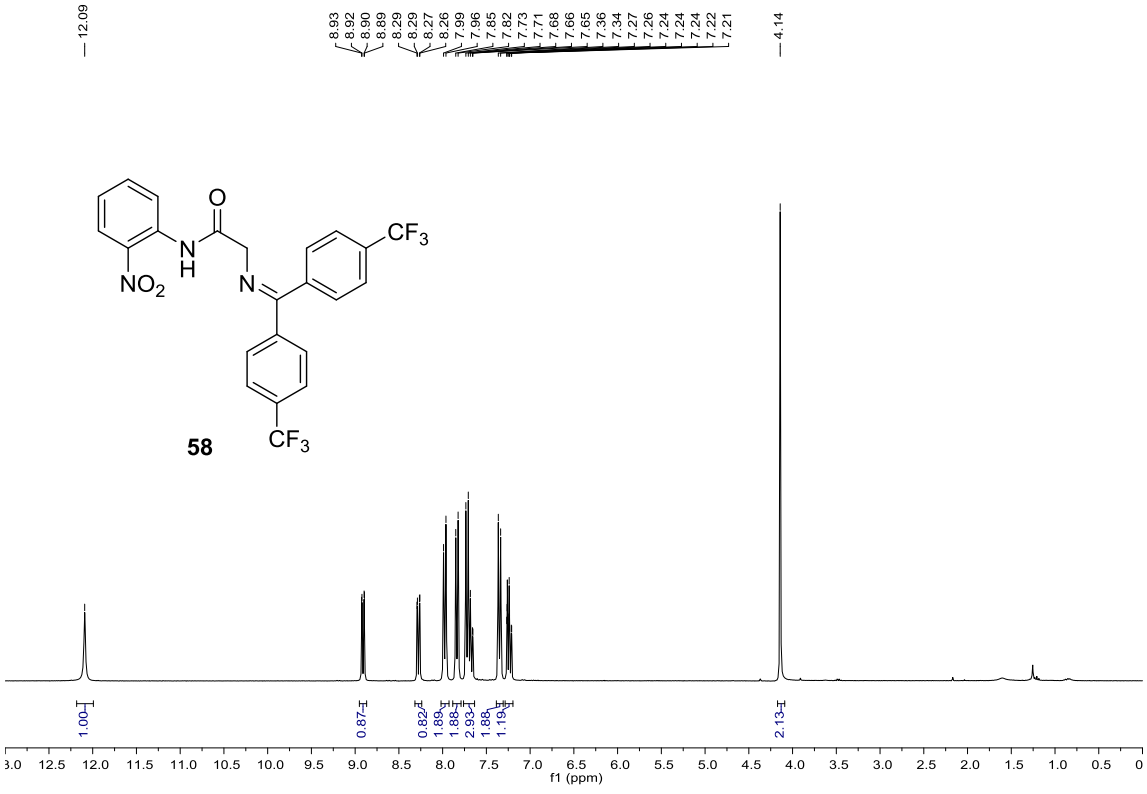

171.9
170.0
144.3
144.0
139.0
136.5
131.9
130.1
129.8
129.2
127.8
125.9
119.8
57.4
f1 (ppm)

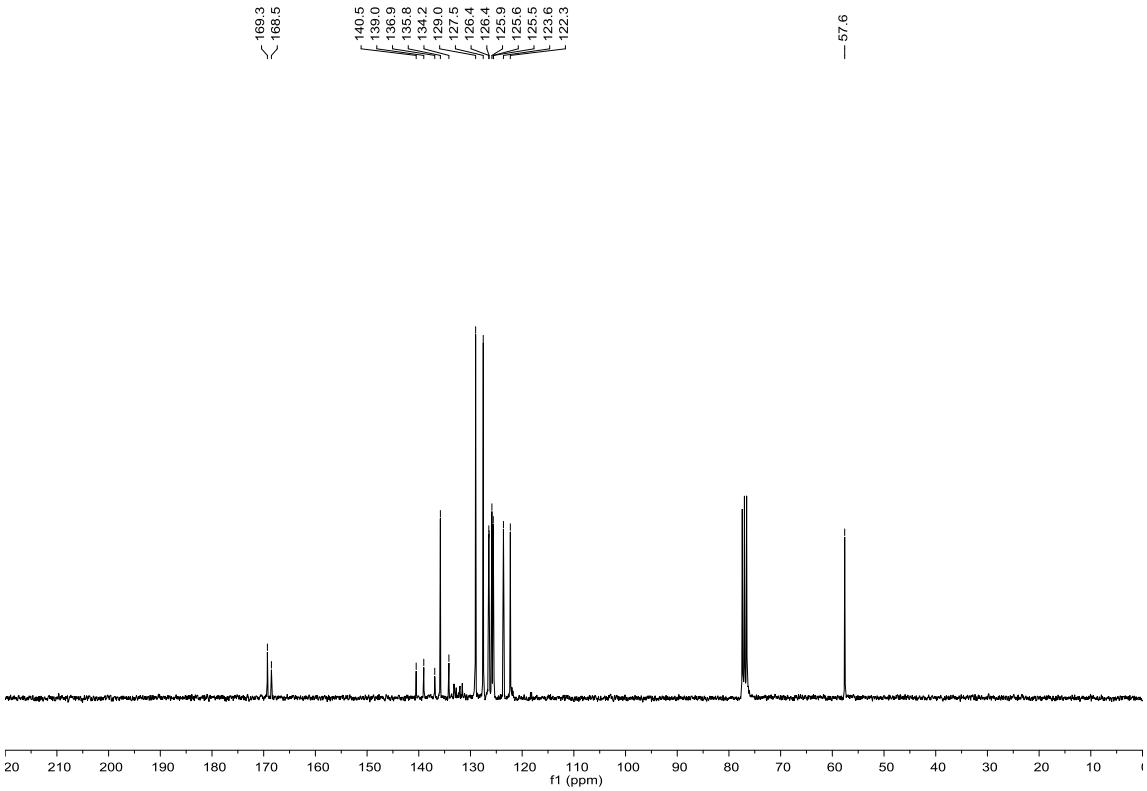

12.53
9.25
9.22
9.18
9.17
8.49
8.49
8.46
8.45
7.88
7.88
7.86
7.85
7.82
7.79
7.79
7.79
7.59
7.54
7.46
7.42
7.20
7.20
7.18
7.17
4.18
O2N
NO2
N
H
O
N
53
0.84
0.86
0.54
0.86
1.67
0.83
6.77
1.71
2.00
f1 (ppm)

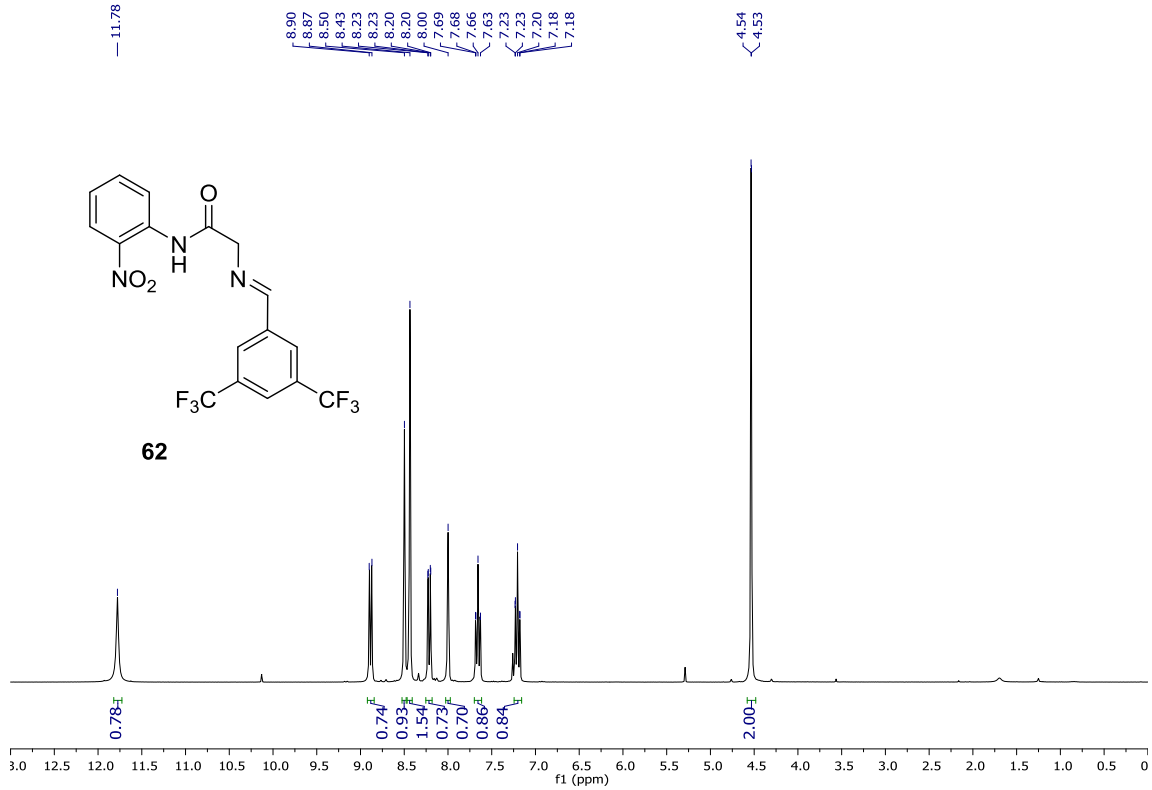

172.0
171.1
139.5
138.1
136.2
132.5
131.4
130.2
130.0
129.4
129.3
129.0
128.6
128.4
127.1
122.7
122.2
57.6
f1 (ppm)

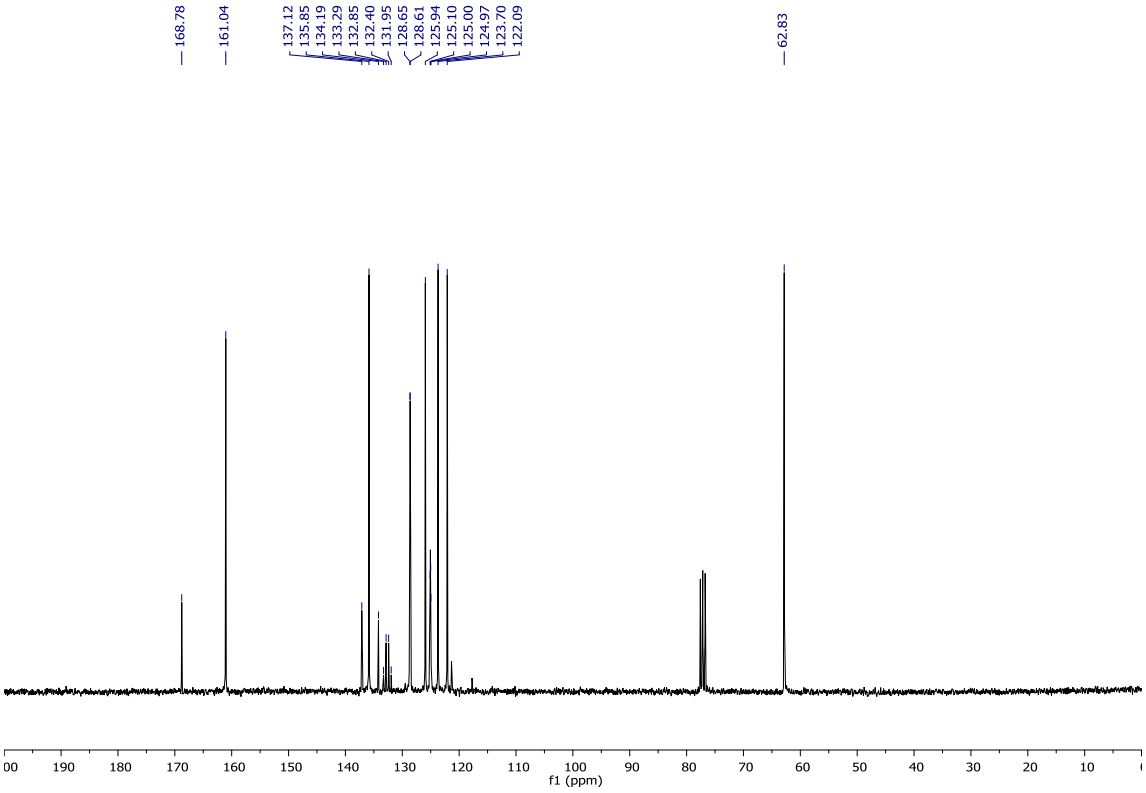

12.07
8.89
8.89
8.86
8.28
8.26
8.23
8.19
8.13
8.05
7.71
7.69
7.66
7.66
7.28
7.28
7.26
7.23
4.16
O
N
H
NO2
N
CF3
CF3
F3C
CF3
57
0.87
0.82
2.11
3.62
1.76
0.73
0.81
1.50
0.79
1.20
2.00
f1 (ppm)

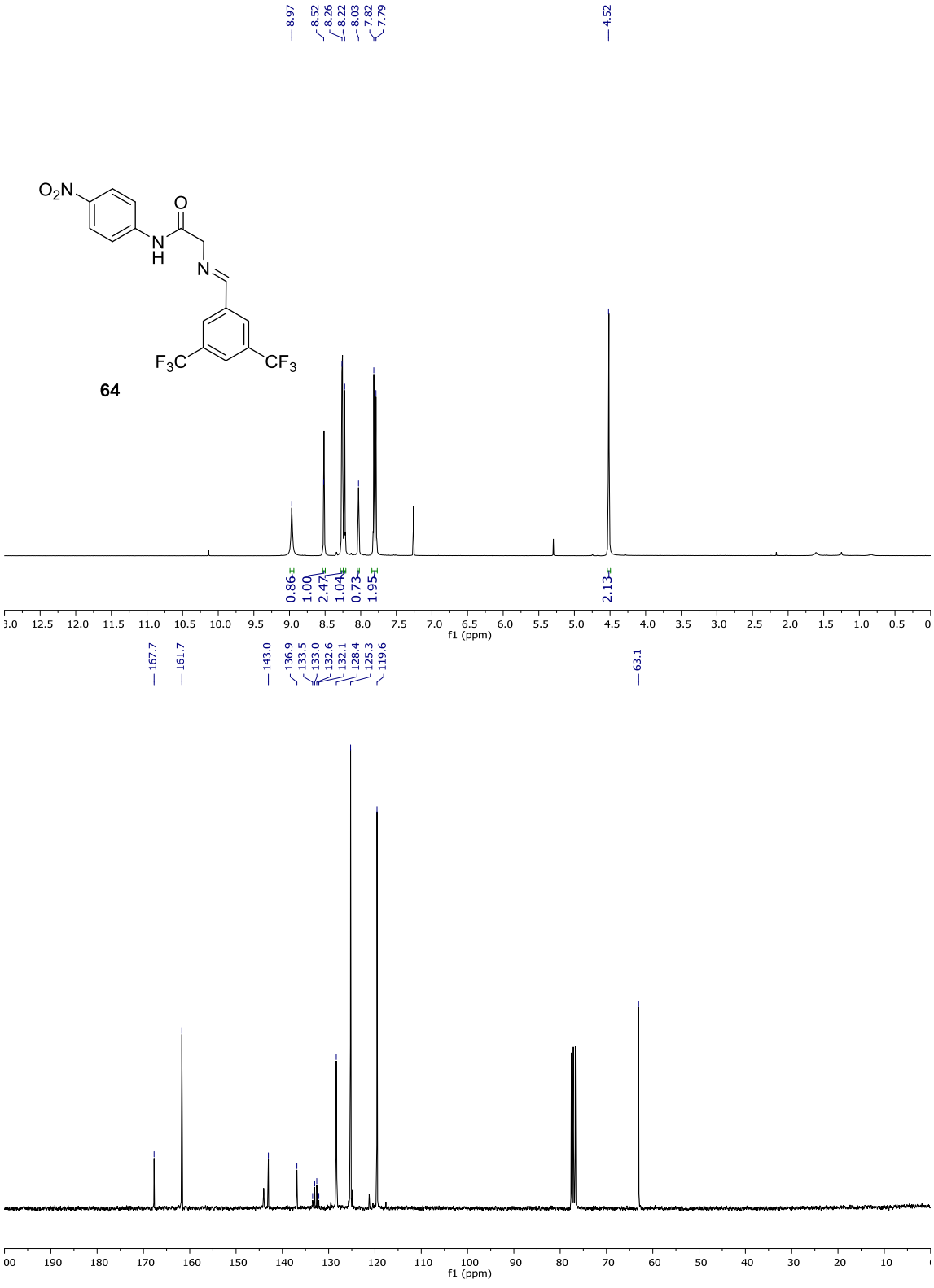

168.25
165.35
139.04
137.77
137.19
136.45
135.94
134.03
129.88
128.65
127.48
126.86
126.02
125.39
123.99
122.29
120.98
117.36
57.86
f1 (ppm)

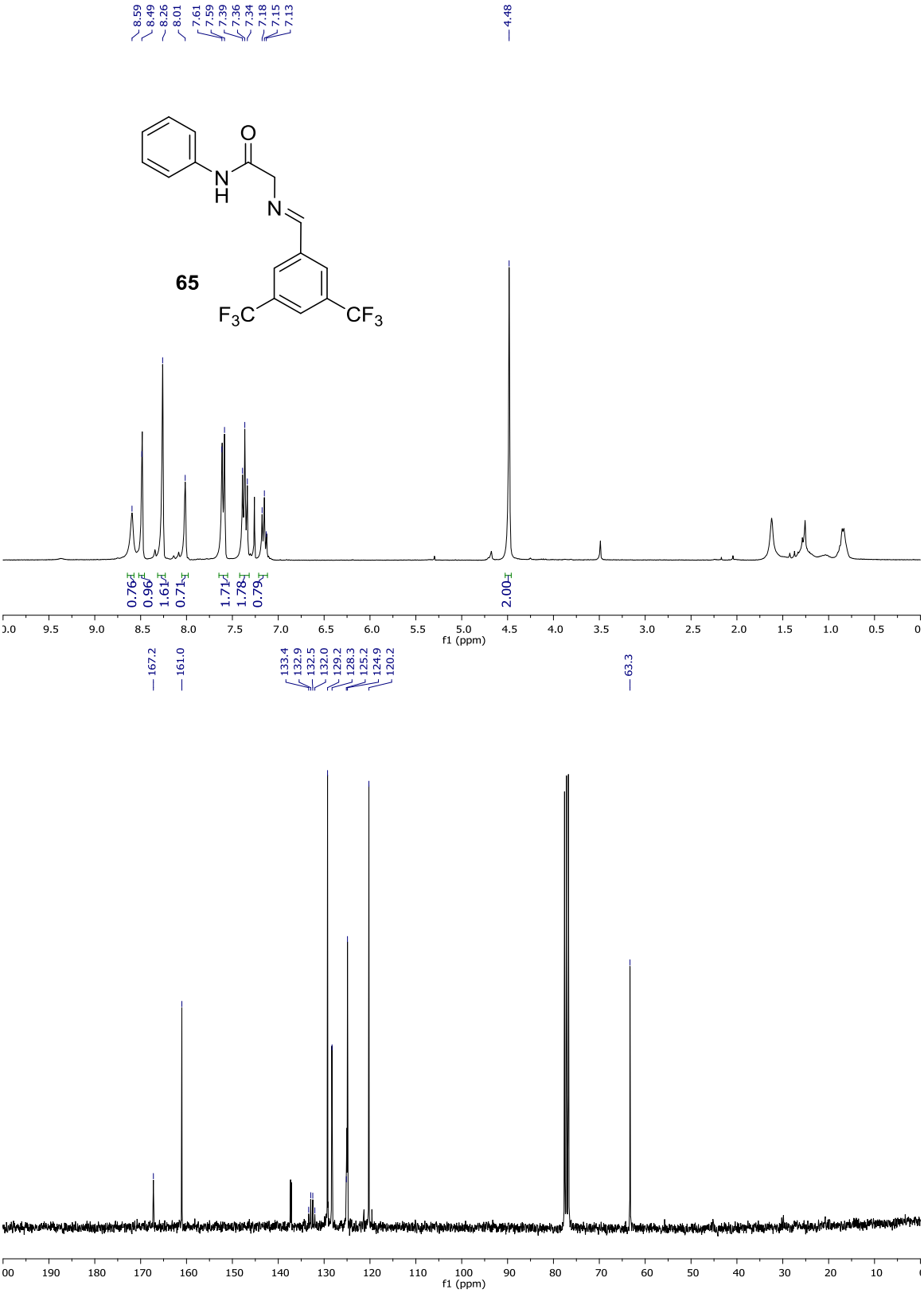

12.09
8.93
8.92
8.90
8.89
8.29
8.29
8.27
8.26
7.99
7.96
7.85
7.82
7.73
7.71
7.68
7.66
7.65
7.36
7.34
7.27
7.26
7.24
7.24
7.24
7.22
7.21
4.14
O
N
H
N
NO2
CF3
CF3
58
1.00
0.87
0.82
1.89
1.88
2.93
1.88
1.19
2.13
f1 (ppm)

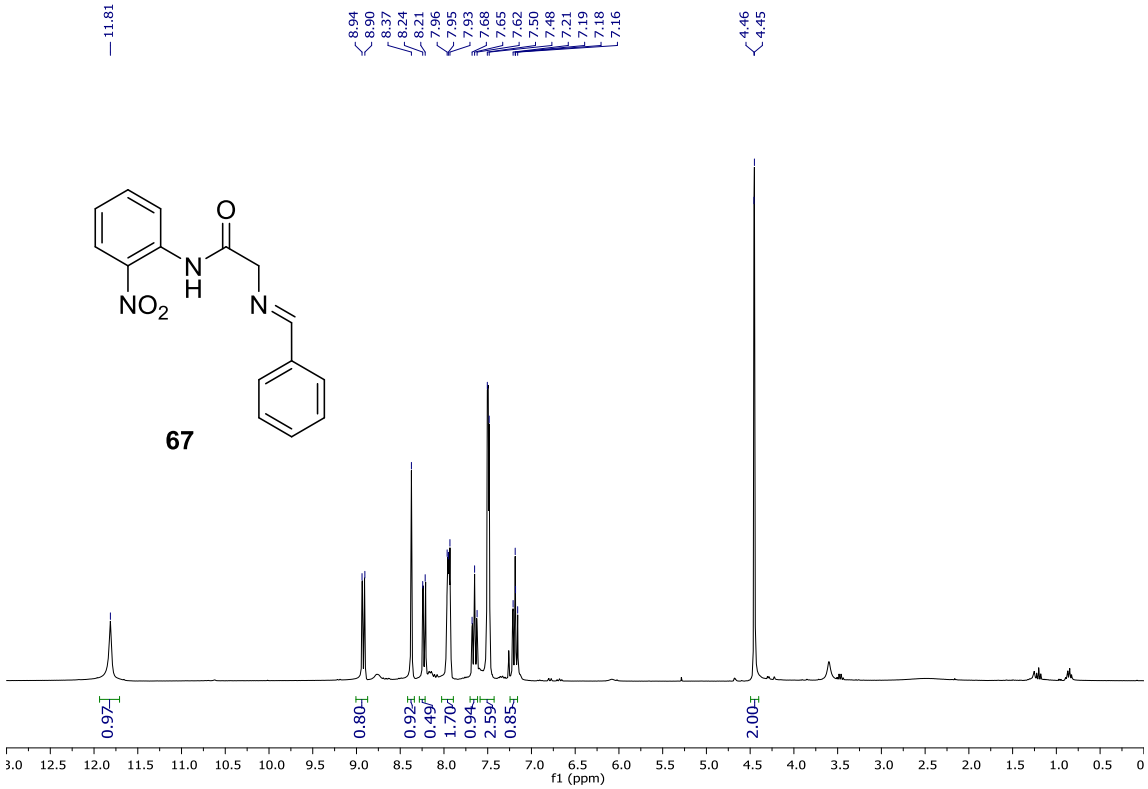

169.3
168.5
140.5
139.0
136.9
135.8
134.2
129.0
127.5
126.4
126.4
125.9
125.6
125.5
123.6
122.3
57.6
f1 (ppm)

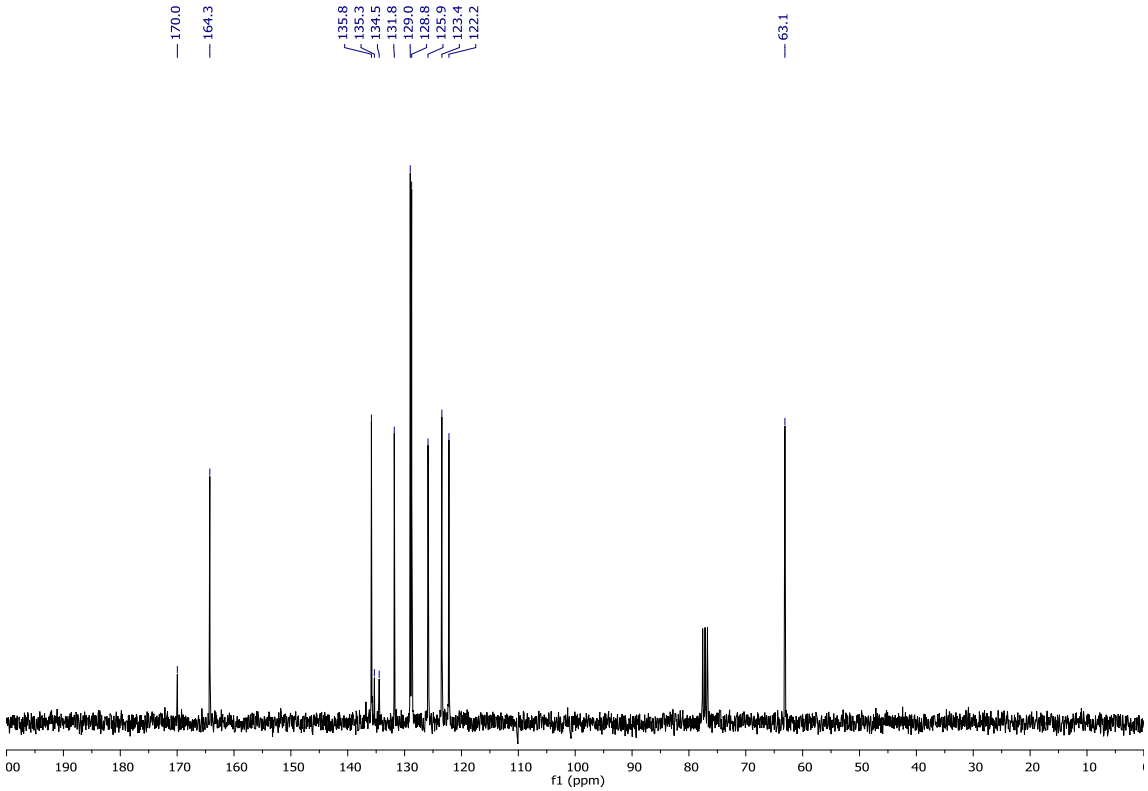

11.78
8.90
8.87
8.50
8.43
8.23
8.23
8.20
8.20
8.00
7.69
7.68
7.66
7.63
7.23
7.23
7.20
7.18
7.18
4.54
4.53
O
N
H
NO2
N
F3C
CF3
62
0.78
0.74
0.93
1.54
0.73
0.70
0.86
0.84
2.00
f1 (ppm)

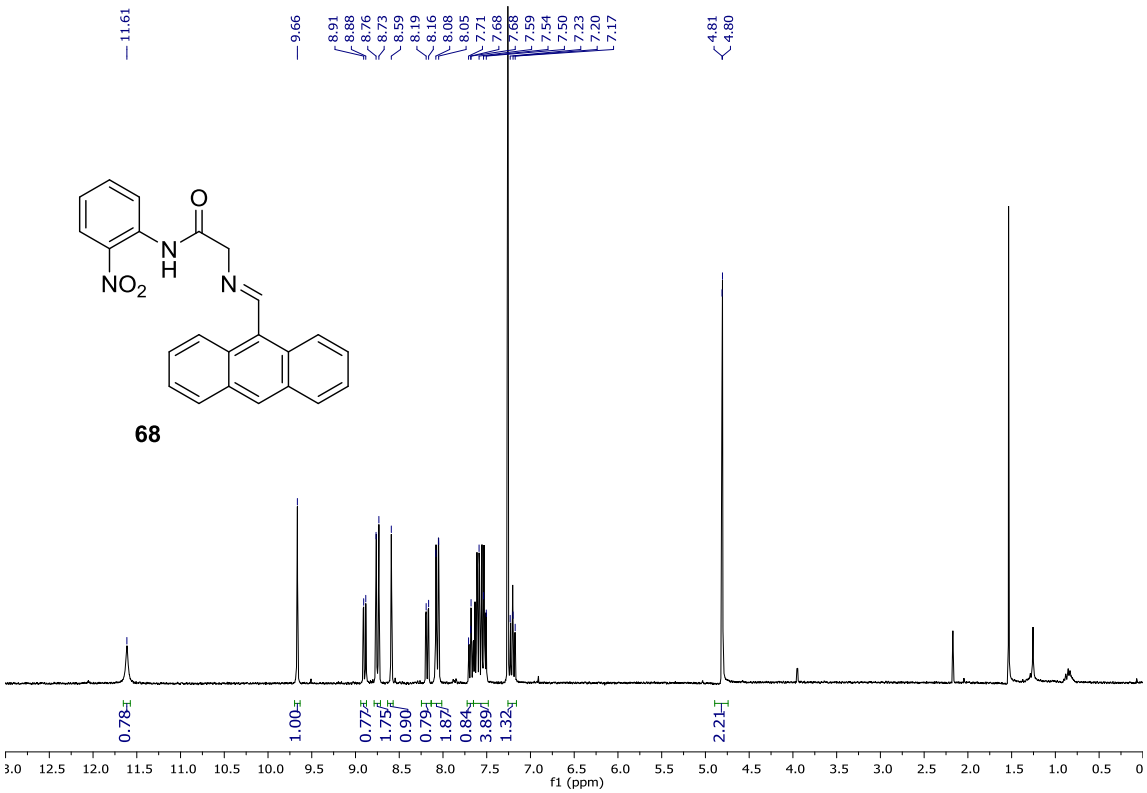

168.78
161.04
137.12
135.85
134.19
133.29
132.85
132.40
131.95
128.65
128.61
125.94
125.10
125.00
124.97
123.70
122.09
62.83
f1 (ppm)


8.97
8.52
8.26
8.22
8.03
7.82
7.79
4.52
O2N
O
N
H
N
F3C
CF3
64
0.86
1.00
2.47
1.04
0.73
1.95
2.13
f1 (ppm)
167.7
161.7
143.0
136.9
133.5
133.0
132.6
132.1
128.4
125.3
119.6
63.1
f1 (ppm)

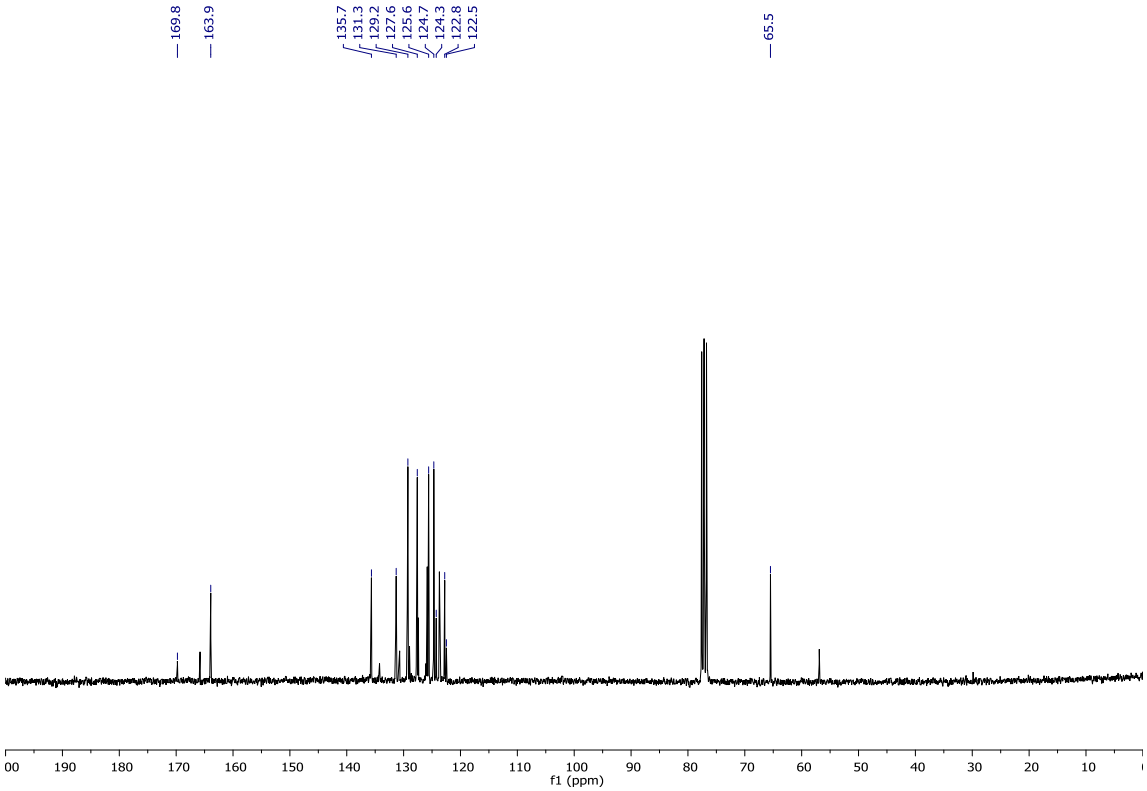

8.59
8.49
8.26
8.01
7.61
7.59
7.39
7.36
7.34
7.18
7.15
7.13
4.48
O
N
H
N
65
F3C
CF3
0.76
0.96
1.61
0.71
1.71
1.78
0.79
2.00
f1 (ppm)
167.2
161.0
133.4
132.9
132.5
132.0
129.2
128.3
125.2
124.9
120.2
63.3
f1 (ppm)

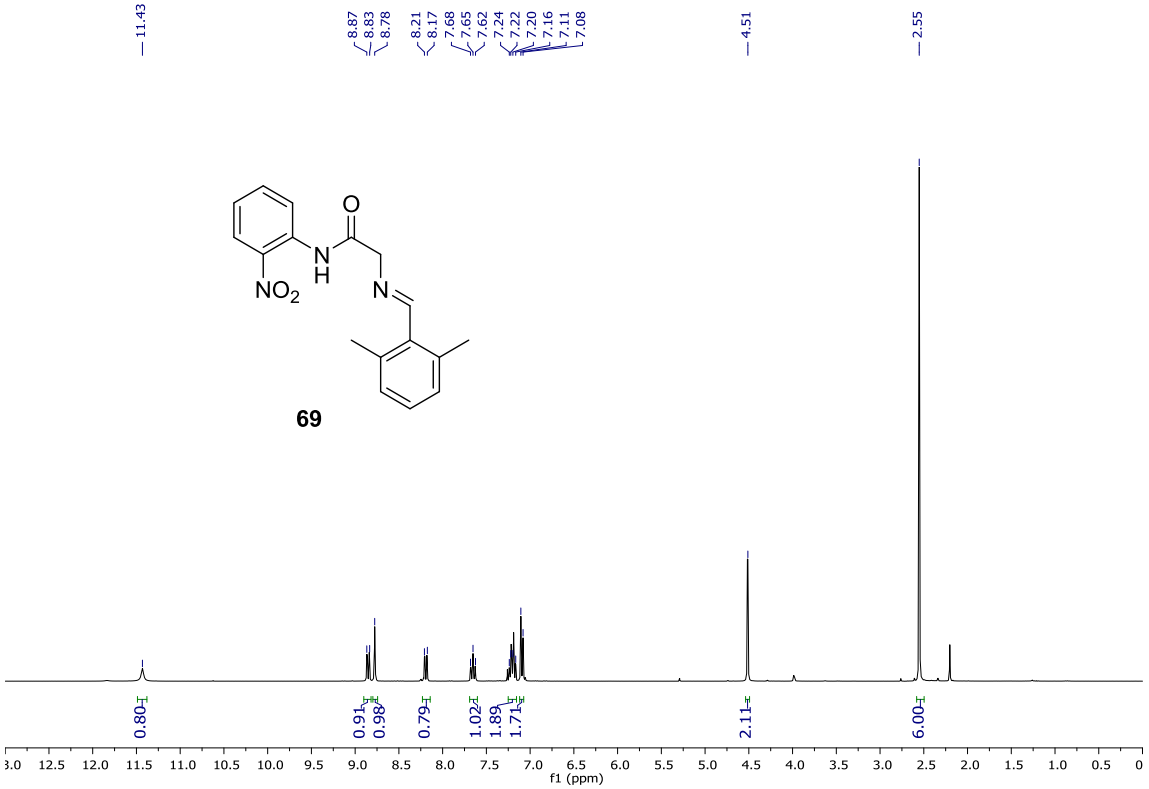

11.81
8.94
8.90
8.37
8.24
8.21
7.96
7.95
7.93
7.68
7.65
7.62
7.50
7.48
7.21
7.19
7.18
7.16
4.46
4.45
O
N
H
NO2
N
67
0.97
0.80
0.92
0.49
1.70
0.94
2.59
0.85
2.00
f1 (ppm)


170.0
164.3
135.8
135.3
134.5
131.8
129.0
128.8
125.9
123.4
122.2
63.1
f1 (ppm)

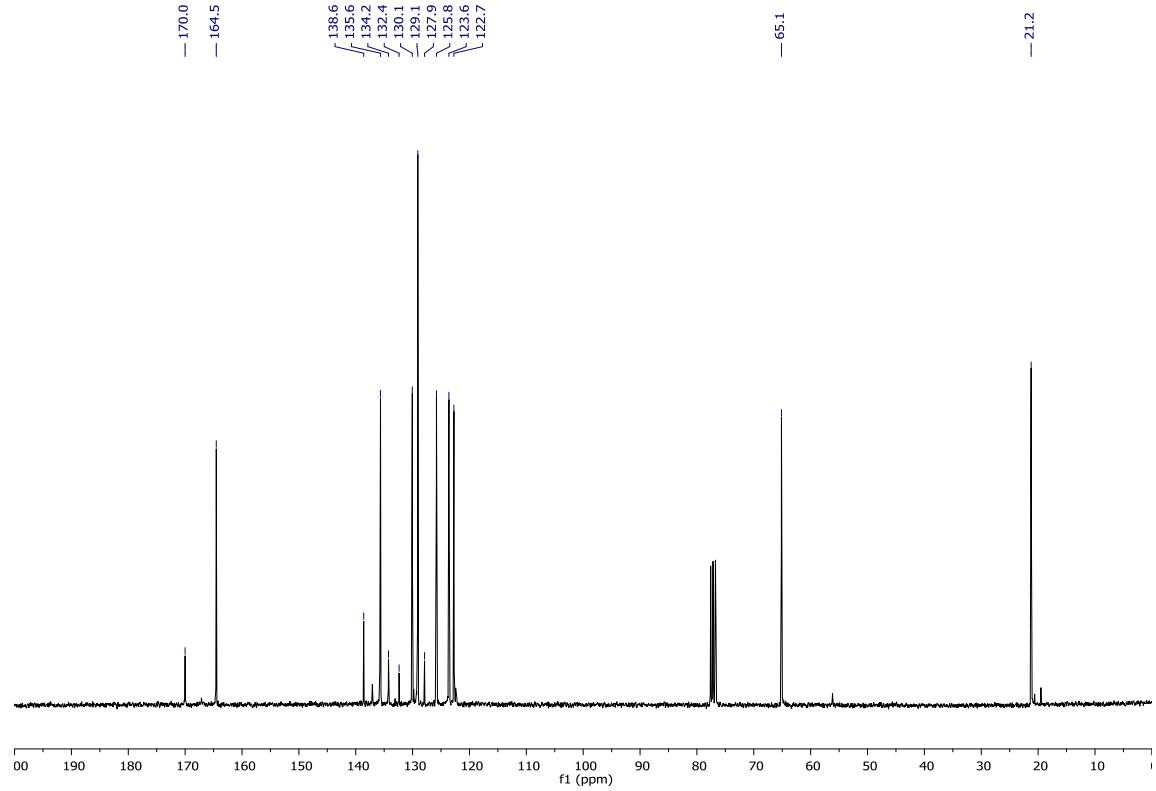

11.61
9.66
8.91
8.88
8.76
8.73
8.59
8.19
8.16
8.08
8.05
7.71
7.68
7.68
7.59
7.54
7.50
7.23
7.20
7.17
4.81
4.80
O
N
H
NO2
N
0.78
1.00
0.77
1.75
0.90
0.79
1.87
0.84
3.89
1.32
2.21
f1 (ppm)

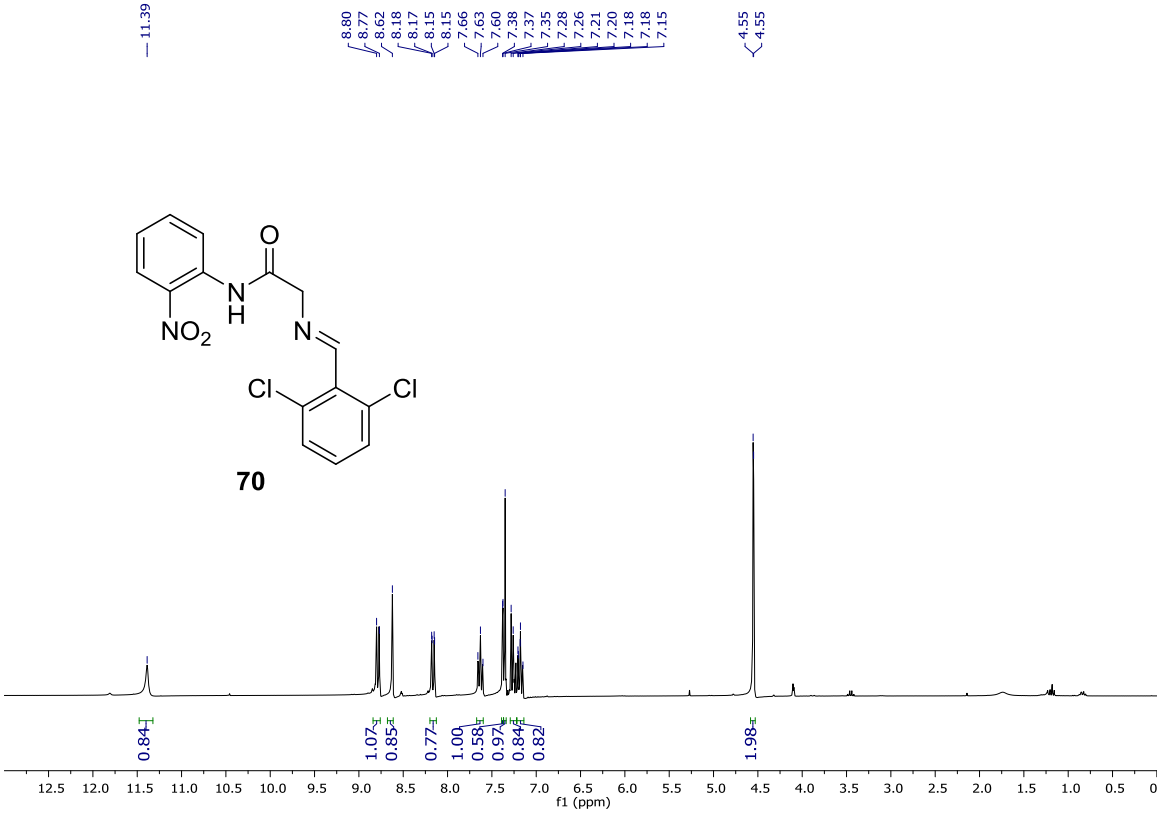
68

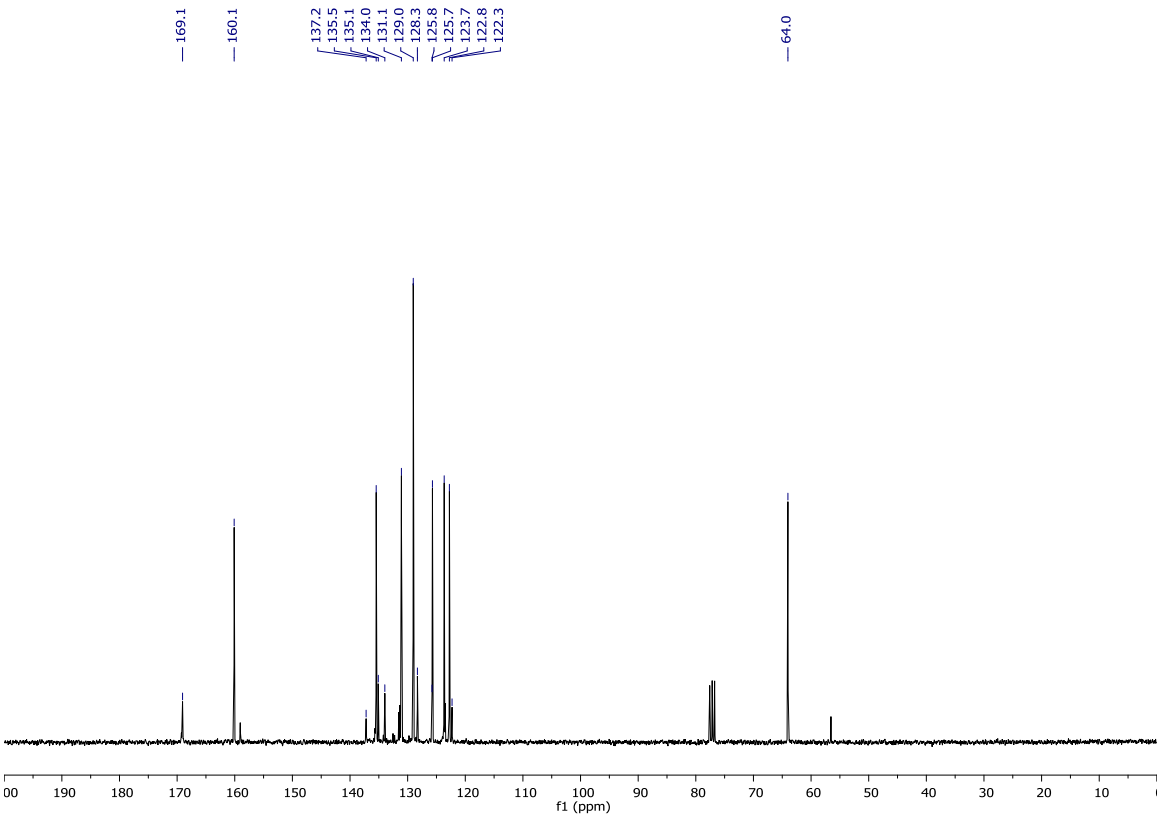

169.8
163.9
135.7
131.3
129.2
127.6
125.6
124.7
124.3
122.8
122.5
65.5
f1 (ppm)

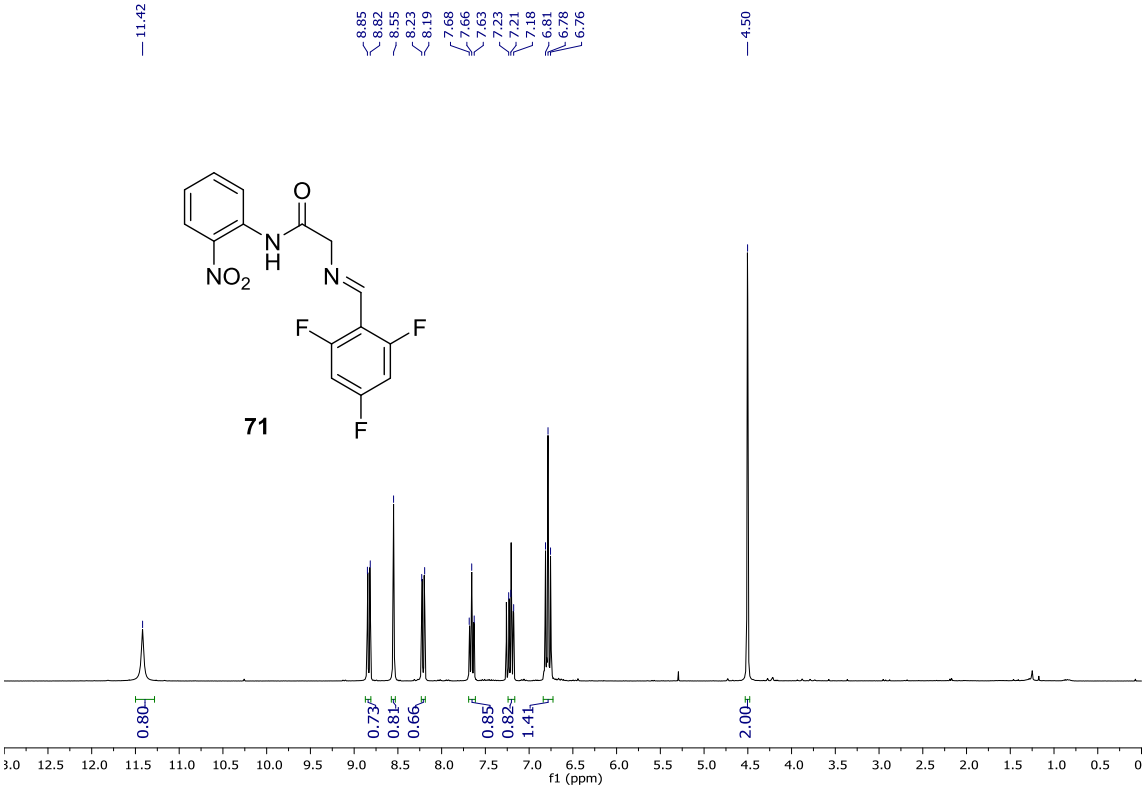

11.43
8.87
8.83
8.78
8.21
8.17
7.68
7.65
7.62
7.24
7.22
7.20
7.16
7.11
7.08
4.51
2.55
O
N
H
NO2
N
0.80
0.91
0.98
0.79
1.02
1.89
1.71
2.11
6.00
f1 (ppm)

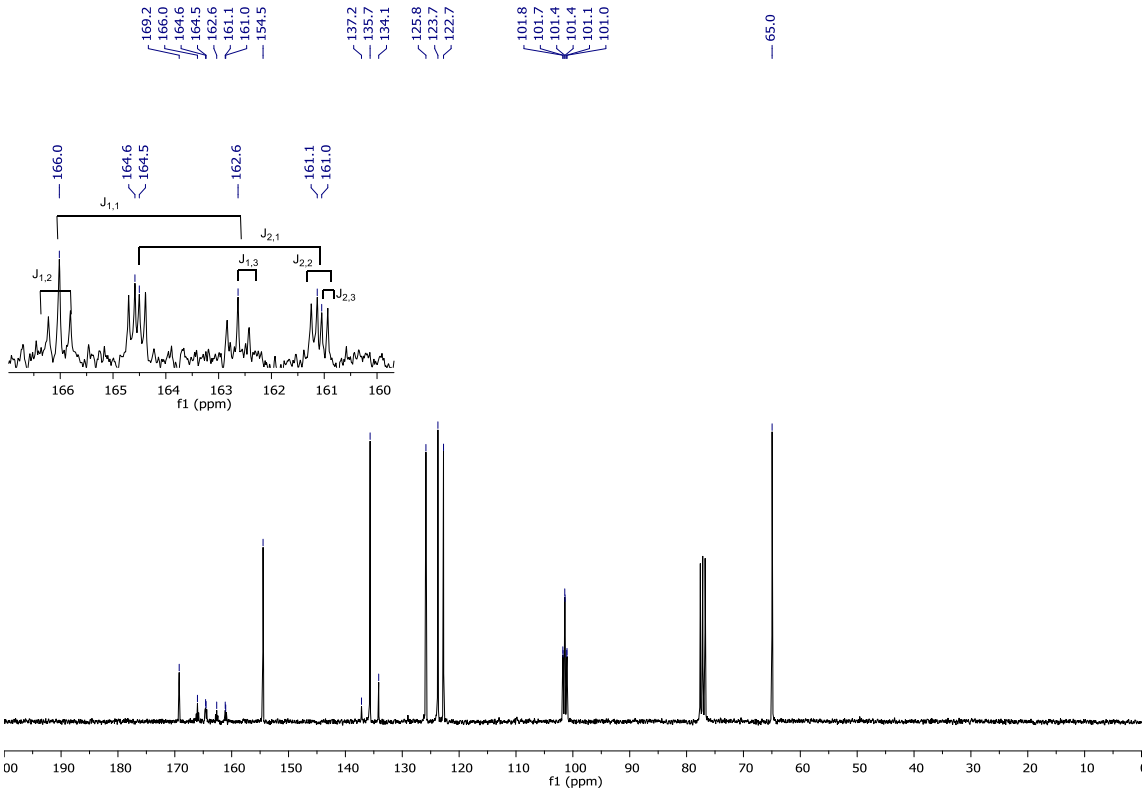
69

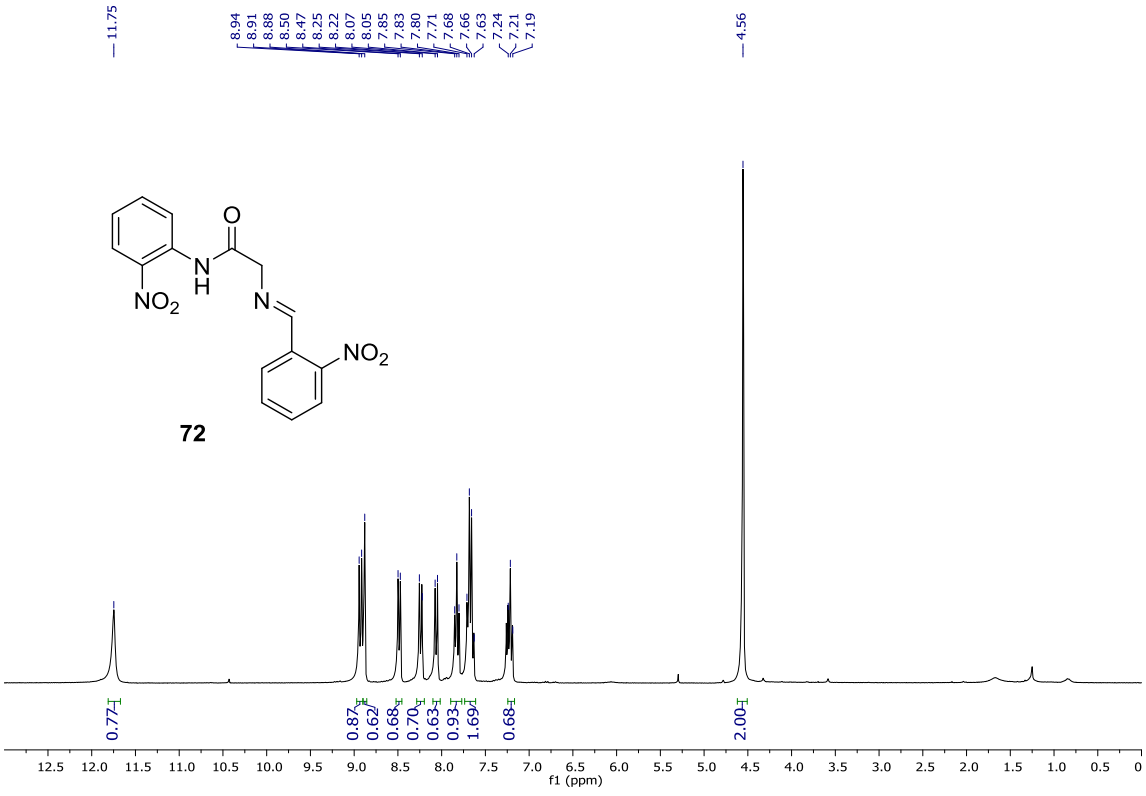

170.0
164.5
138.6
135.6
134.2
132.4
130.1
129.1
127.9
125.8
123.6
122.7
65.1
21.2
f1 (ppm)

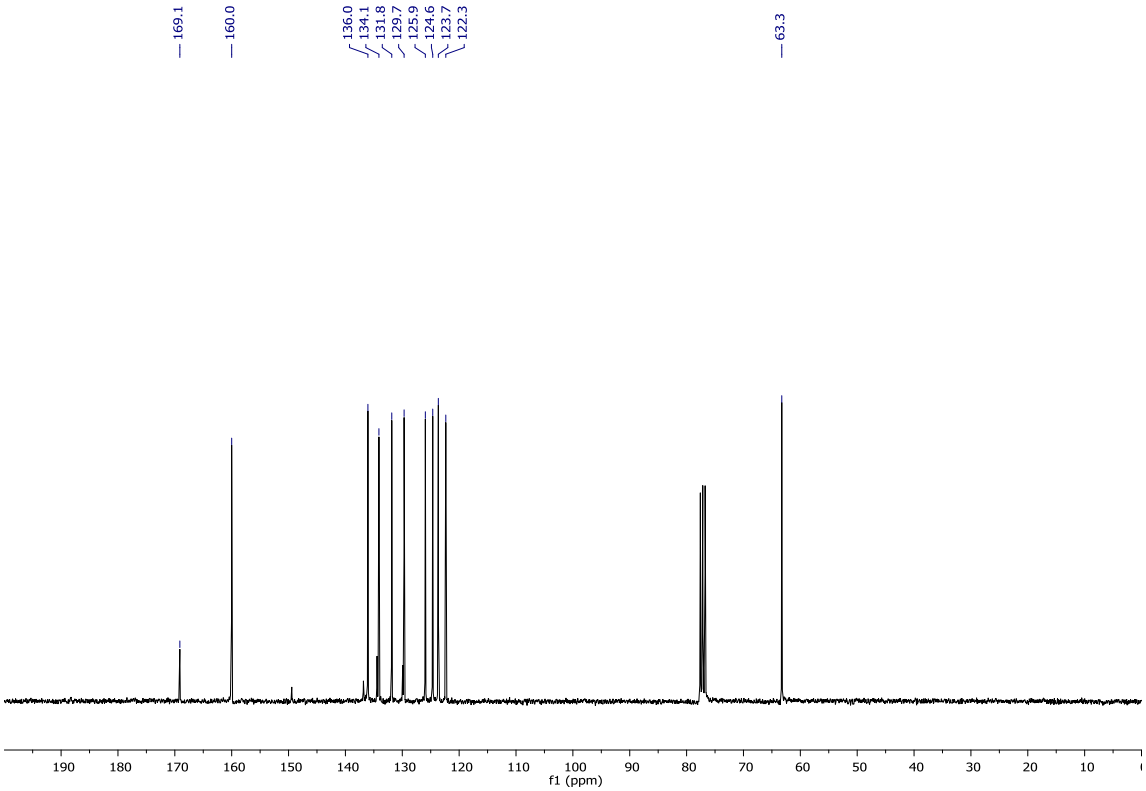

11.39
8.80
8.77
8.62
8.18
8.17
8.15
8.15
7.66
7.63
7.60
7.38
7.37
7.35
7.28
7.26
7.21
7.20
7.18
7.18
7.15
4.55
4.55
O
N
H
NO2
N
Cl
Cl
70
0.84
1.07
0.85
0.77
1.00
0.58
0.97
0.84
0.82
1.98
f1 (ppm)

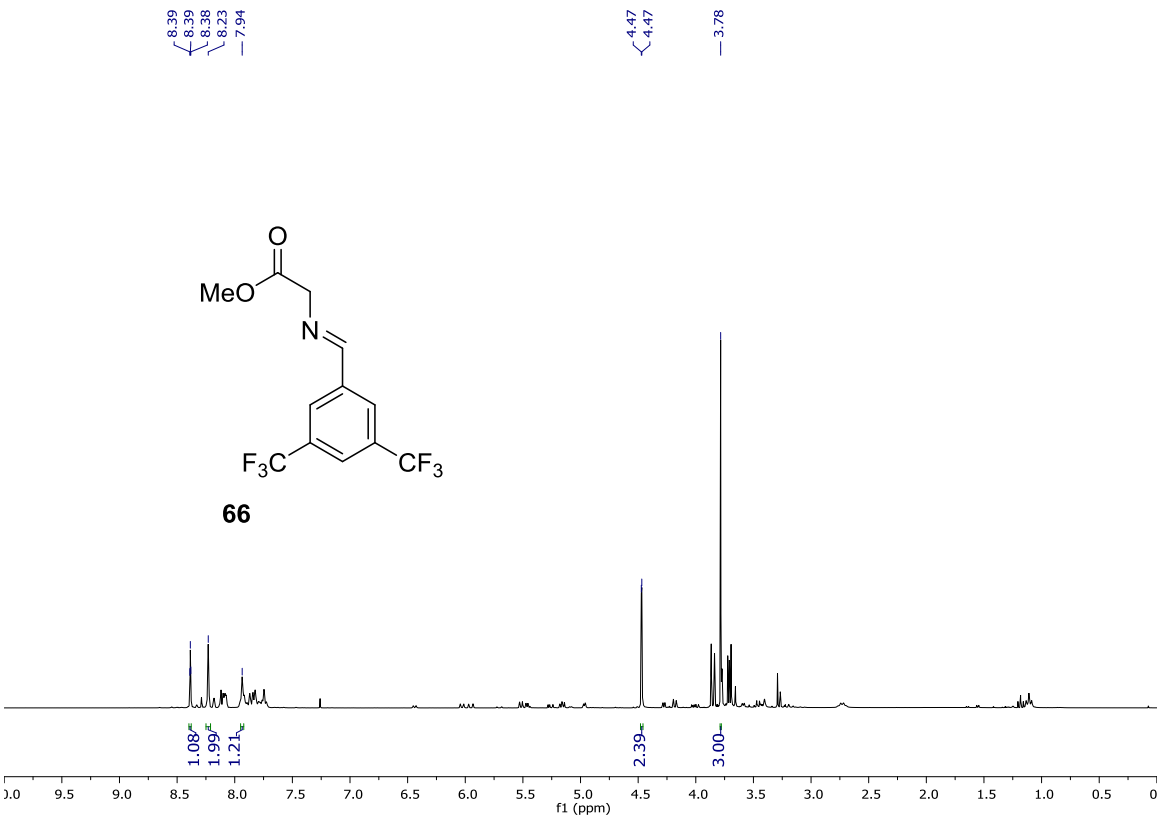

169.1
160.1
137.2
135.5
135.1
134.0
131.1
129.0
128.3
125.8
125.7
123.7
122.8
122.3
64.0
f1 (ppm)

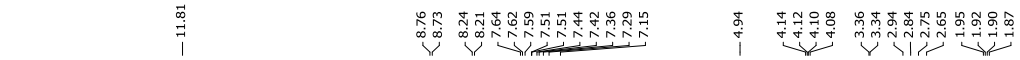

11.42
8.85
8.82
8.55
8.23
8.19
7.68
7.66
7.63
7.23
7.21
7.18
6.81
6.78
6.76
4.50
O
N
H
N
NO2
F
F
F
71
0.80
0.73
0.81
0.66
0.85
0.82
1.41
2.00
f1 (ppm)

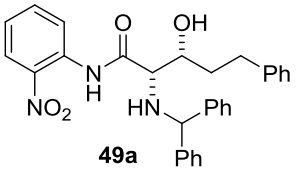

169.2
166.0
164.6
164.5
162.6
161.1
161.0
154.5
137.2
135.7
134.1
125.8
123.7
122.7
101.8
101.7
101.4
101.4
101.1
101.0
65.0
J1,1
J2,1
J1,3
J2,2
J1,2
J2,3
f1 (ppm)


11.75
8.94
8.91
8.88
8.50
8.47
8.25
8.22
8.07
8.05
7.85
7.83
7.80
7.71
7.68
7.66
7.63
7.24
7.21
7.19
4.56
O
N
H
N
NO2
NO2
72
0.77
0.87
0.62
0.68
0.70
0.63
0.93
1.69
0.68
2.00
f1 (ppm)

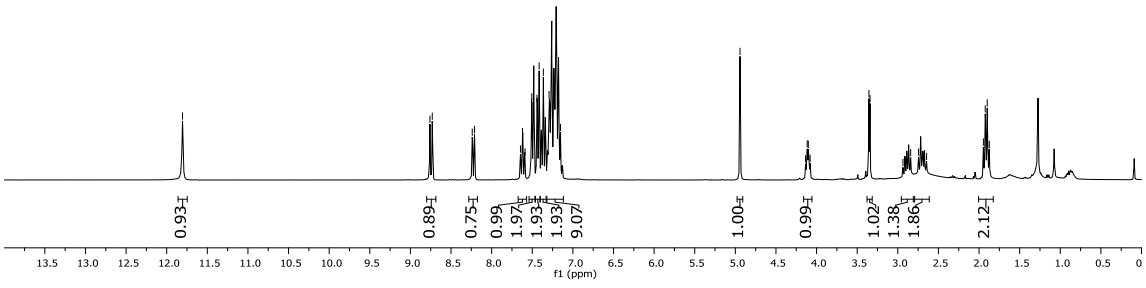

169.1
160.0
136.0
134.1
131.8
129.7
125.9
124.6
123.7
122.3
63.3
f1 (ppm)


8.39
8.39
8.38
8.23
7.94
4.47
4.47
3.78
O
MeO
N
F3C
CF3
66
1.08
1.99
1.21
2.39
3.00
f1 (ppm)

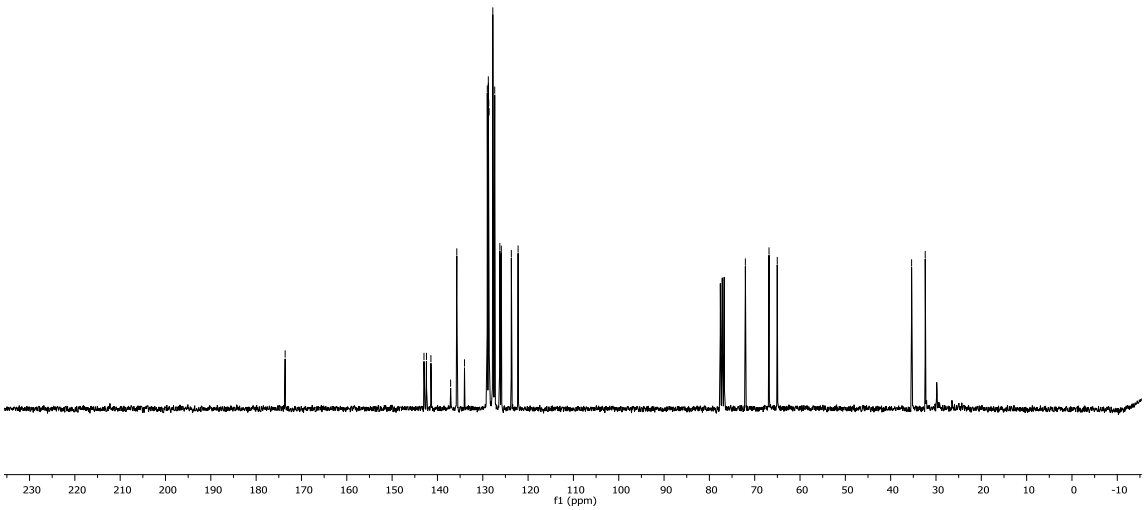

11.81
8.76
8.73
8.24
8.21
7.64
7.62
7.59
7.51
7.51
7.44
7.42
7.36
7.29
7.15
4.94
4.14
4.12
4.10
4.08
3.36
3.34
2.94
2.84
2.75
2.65
1.95
1.92
1.90
1.87

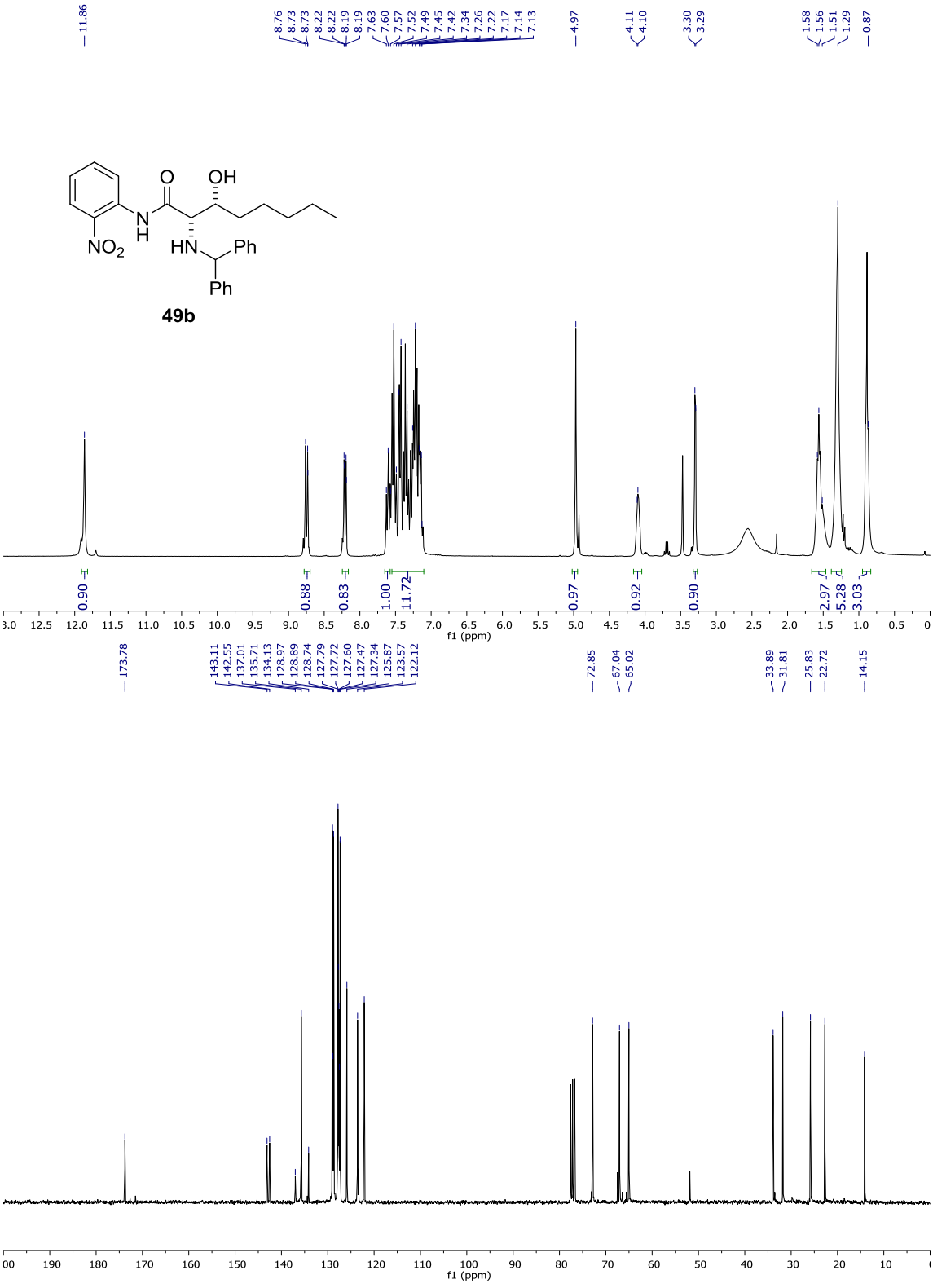

O
OH
N
H
Ph
NO2
HN
Ph
Ph

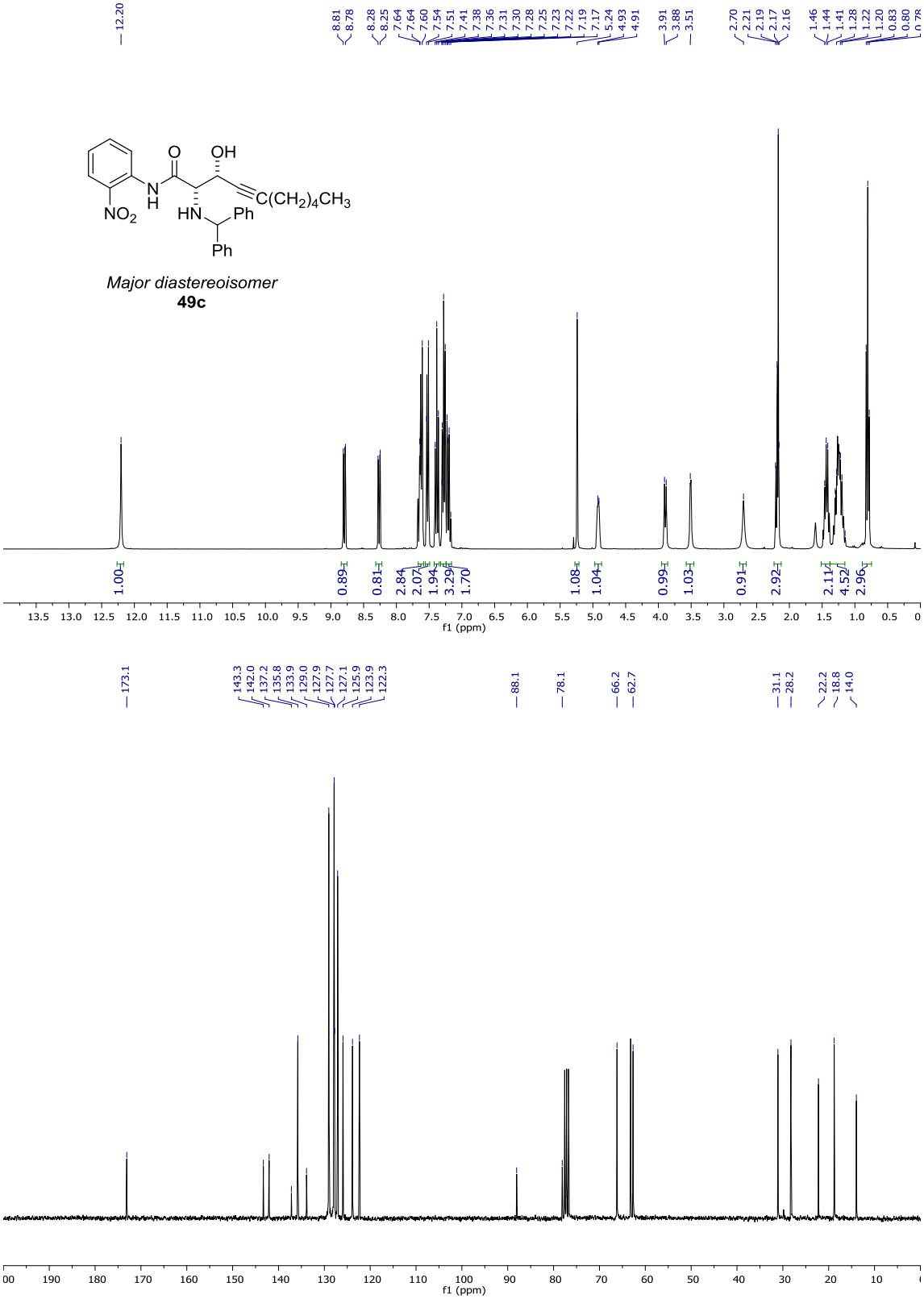
49a

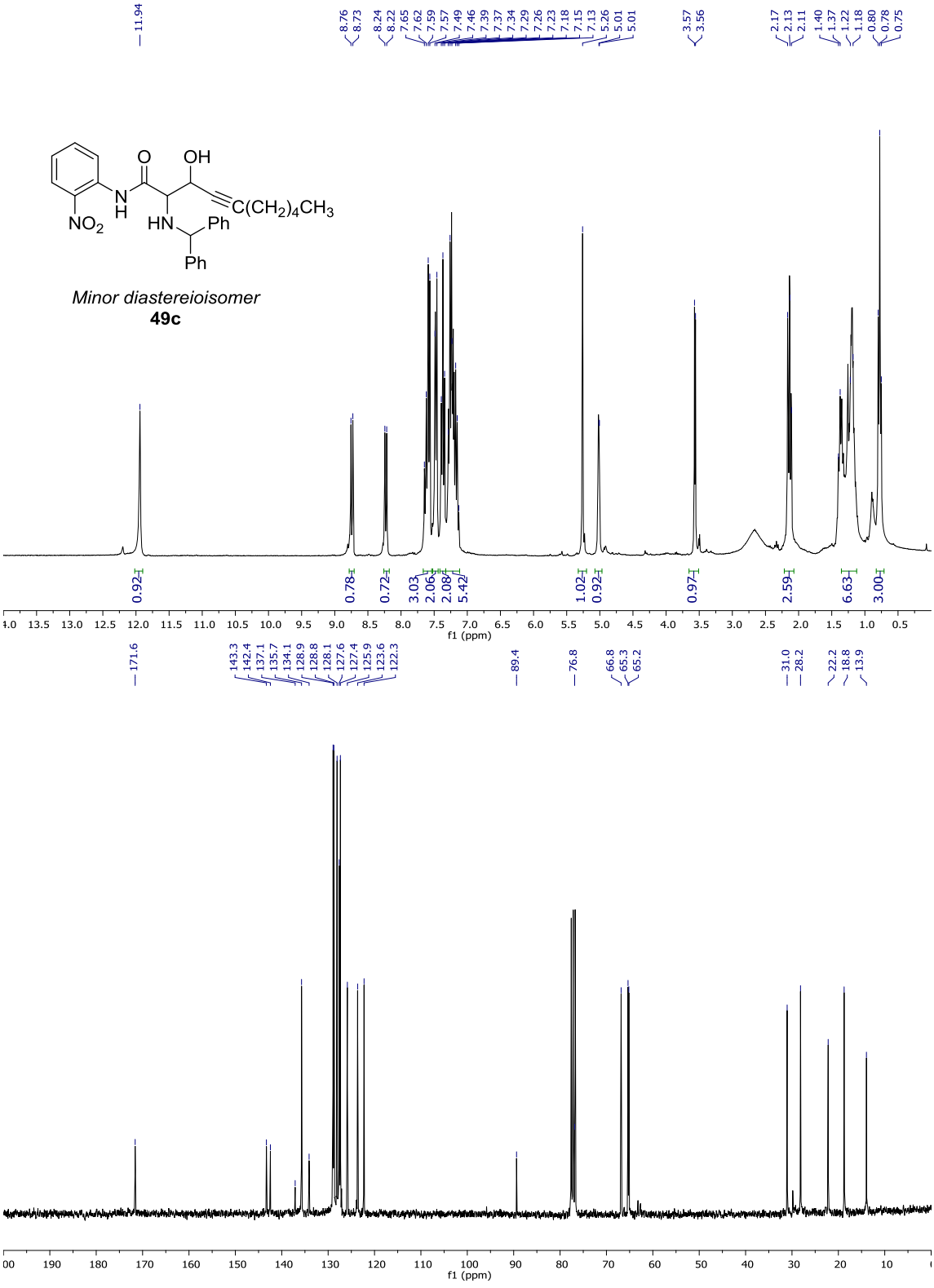

0.93
0.89
0.75
0.99
1.97
1.93
1.93
9.07
1.00
0.99
1.02
1.38
1.86
2.12
f1 (ppm)

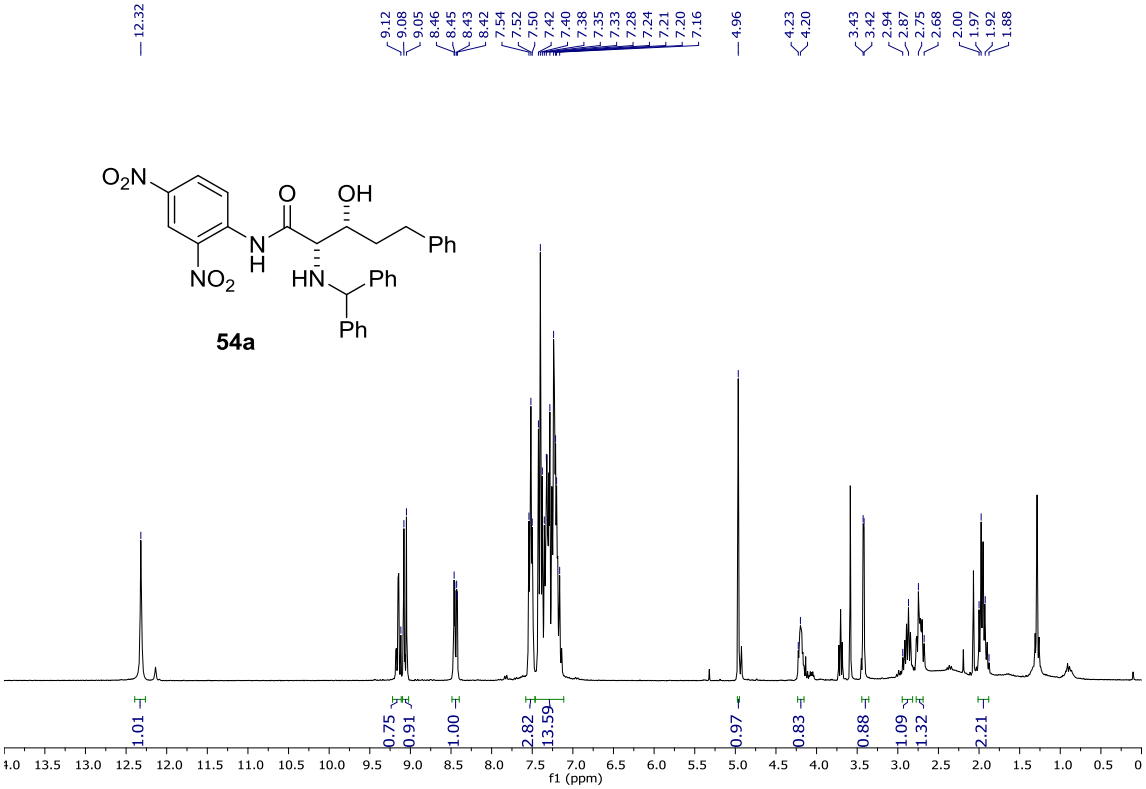

173.6
143.0
142.4
141.4
137.1
135.7
134.0
129.0
128.8
128.7
128.6
127.8
127.6
127.4
126.2
125.9
123.7
122.2
72.1
66.8
65.0
35.4
32.4

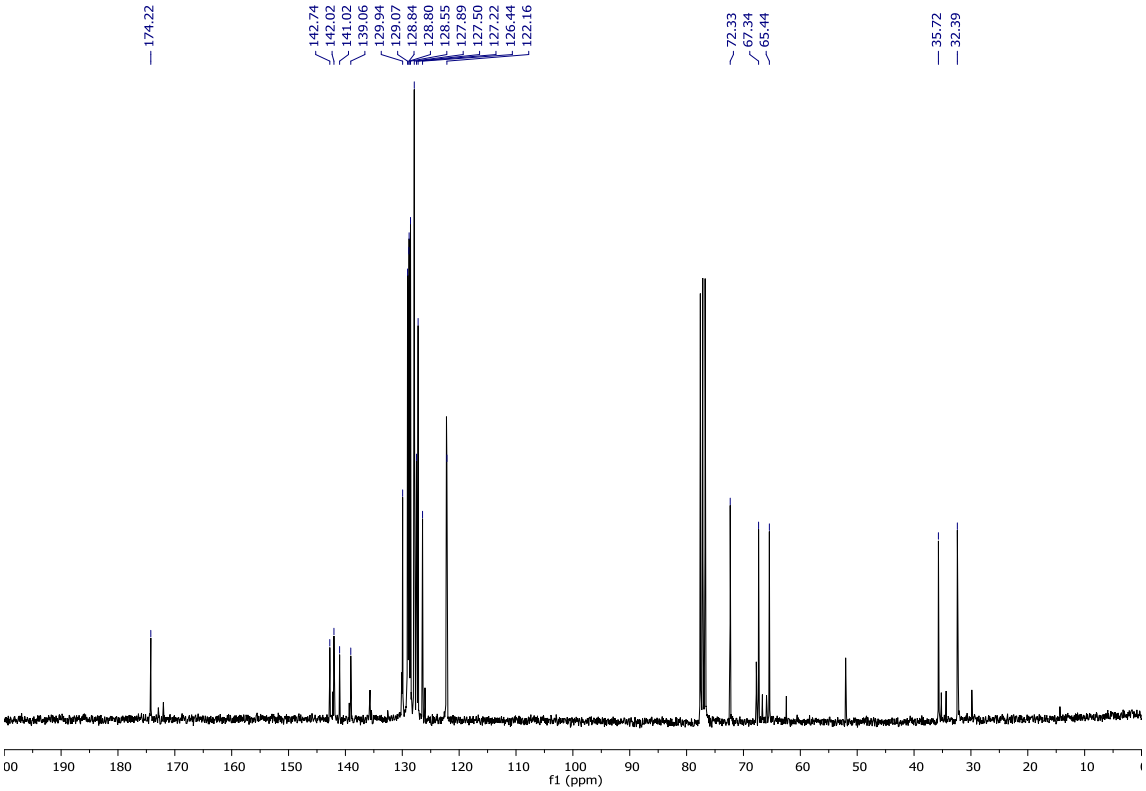

f1 (ppm)

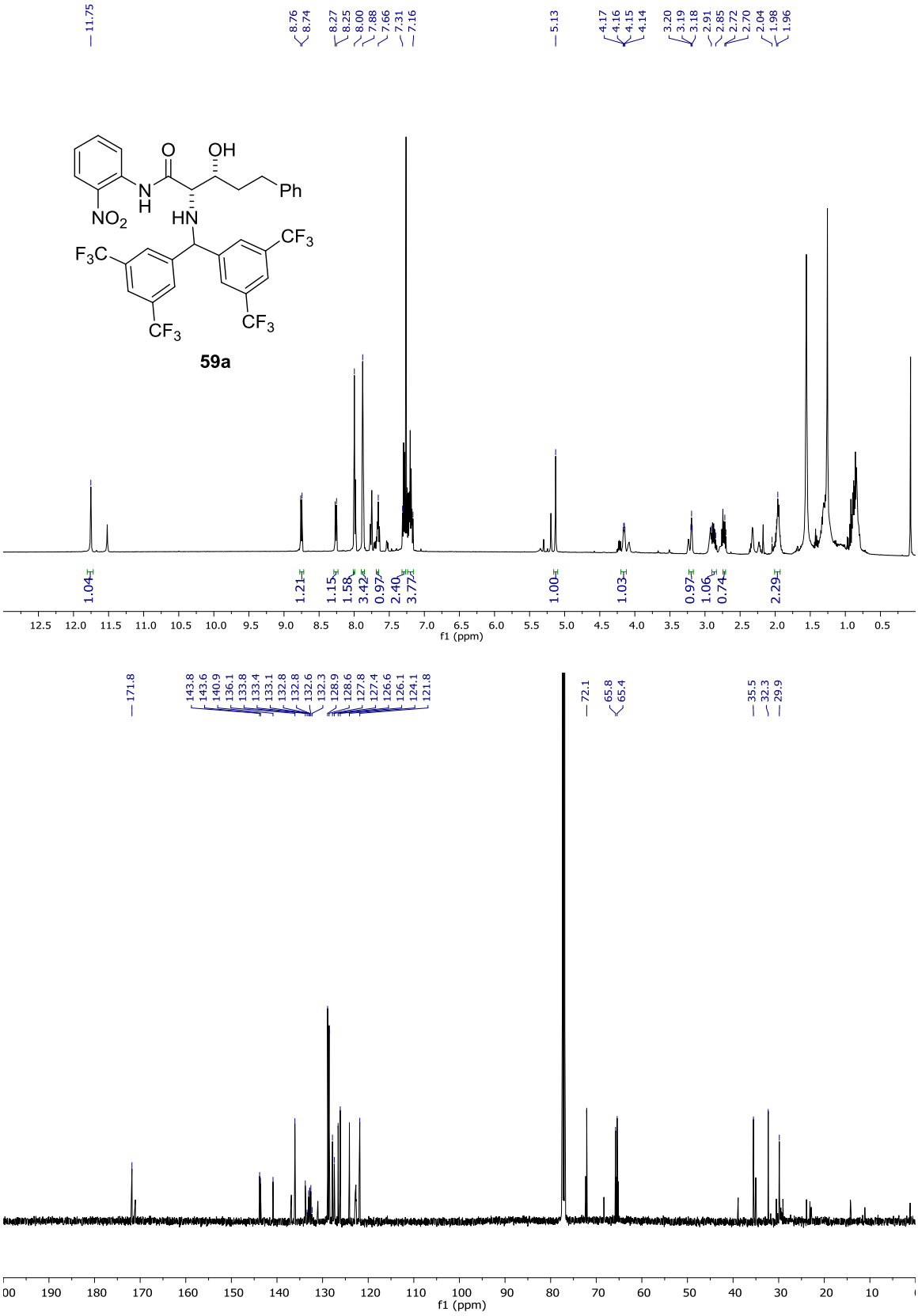

11.86
8.76
8.73
8.73
8.22
8.22
8.19
8.19
7.63
7.60
7.57
7.52
7.49
7.45
7.42
7.34
7.26
7.22
7.17
7.14
7.13
4.97
4.11
4.10
3.30
3.29
1.58
1.56
1.51
1.29
0.87
O
OH
N
H
NO2
HN
Ph
Ph
49b
0.90
0.88
0.83
1.00
11.72
0.97
0.92
0.90
2.97
5.28
3.03
f1 (ppm)
173.78
143.11
142.55
137.01
135.71
134.13
128.97
128.89
128.74
127.79
127.72
127.60
127.47
127.34
125.87
123.57
122.12
72.85
67.04
65.02
33.89
31.81
25.83
22.72
14.15
f1 (ppm)

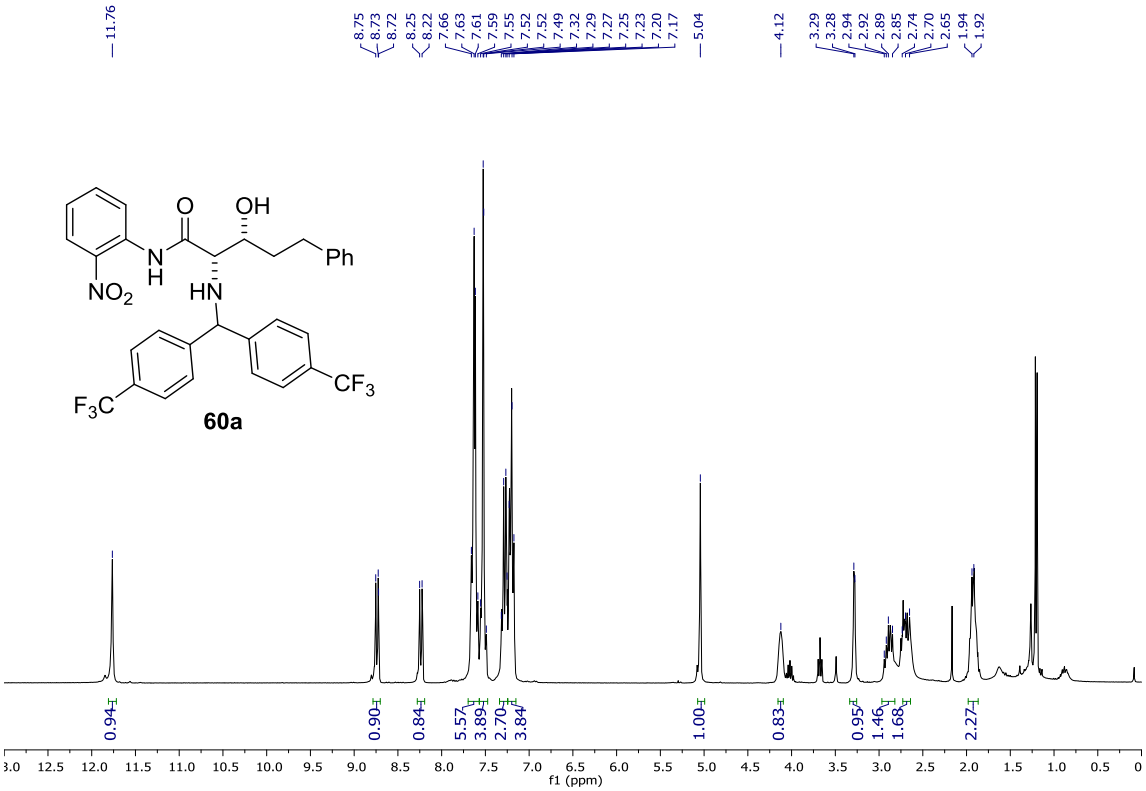

12.20
8.81
8.78
8.28
8.25
7.64
7.64
7.60
7.54
7.51
7.41
7.38
7.36
7.31
7.30
7.28
7.25
7.23
7.22
7.19
7.17
5.24
4.93
4.91
3.91
3.88
3.51
2.70
2.21
2.19
2.17
2.16
1.46
1.44
1.41
1.28
1.22
1.20
0.83
0.80
O
OH
N
H
NO2
HN
Ph
Ph
C(CH2)4CH3
Major diastereoisomer
49c
1.00
0.89
0.81
2.84
2.07
1.94
3.29
1.70
1.08
1.04
0.99
1.03
0.91
2.92
2.11
4.52
2.96
f1 (ppm)
173.1
143.3
142.0
137.2
135.8
133.9
129.0
127.9
127.7
127.1
125.9
123.9
122.3
88.1
78.1
66.2
62.7
31.1
28.2
22.2
18.8
14.0
f1 (ppm)

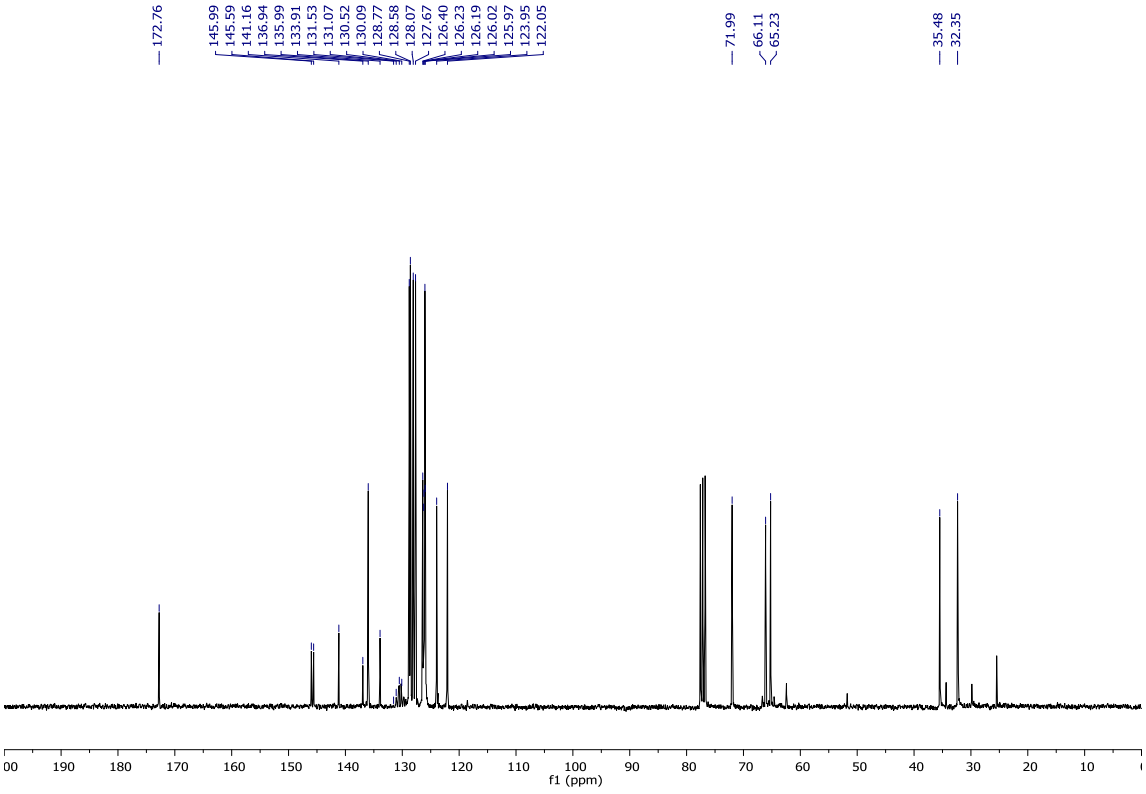

11.94
8.76
8.73
8.24
8.22
7.65
7.62
7.59
7.57
7.49
7.46
7.39
7.37
7.34
7.29
7.26
7.23
7.18
7.15
7.13
5.26
5.01
5.01
3.57
3.56
2.17
2.13
2.11
1.40
1.37
1.22
1.18
0.80
0.78
0.75
O
OH
N
H
C(CH2)4CH3
NO2
HN
Ph
Ph
Minor diastereioisomer
49c
0.92
0.78
0.72
3.03
2.06
2.08
5.42
1.02
0.92
0.97
2.59
6.63
3.00
f1 (ppm)
171.6
143.3
142.4
137.1
135.7
134.1
128.9
128.8
128.1
127.6
127.4
125.9
123.6
122.3
89.4
76.8
66.8
65.3
65.2
31.0
28.2
22.2
18.8
13.9
f1 (ppm)

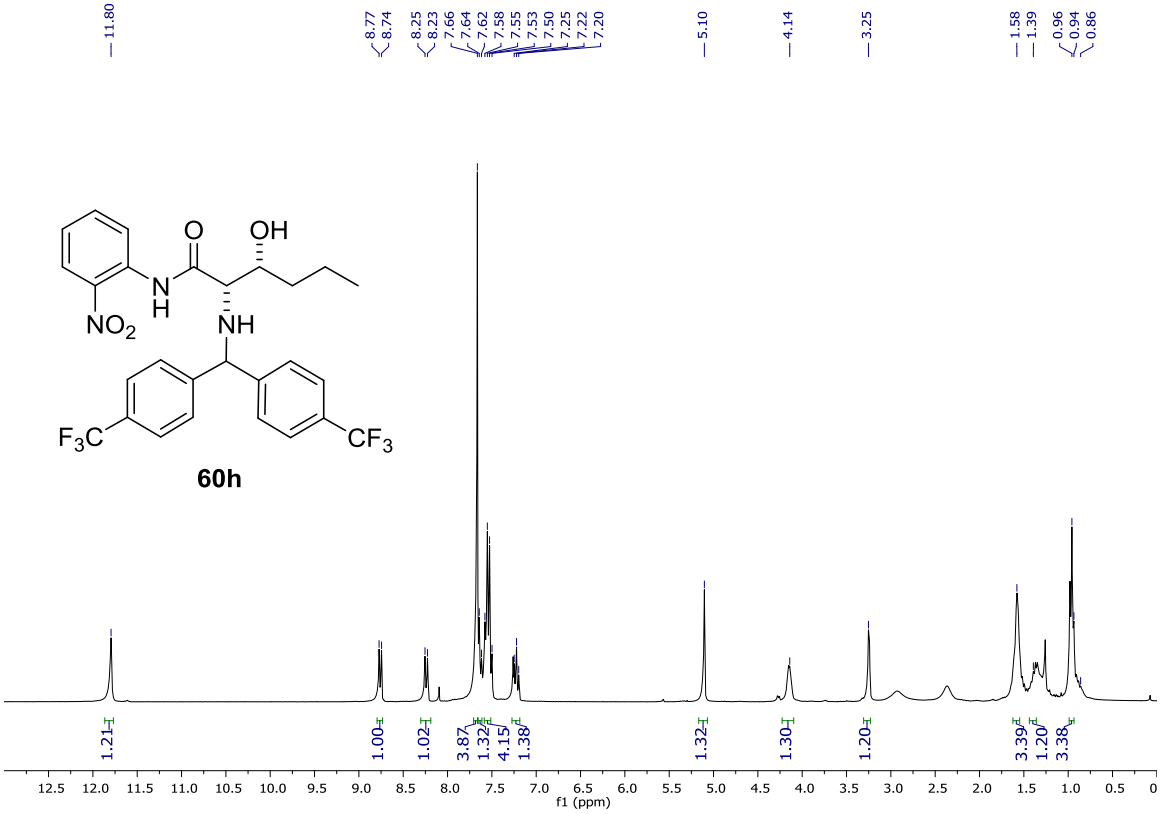

12.32
9.12
9.08
9.05
8.46
8.45
8.43
8.42
7.54
7.52
7.50
7.42
7.40
7.38
7.35
7.33
7.28
7.24
7.21
7.20
7.16
4.96
4.23
4.20
3.43
3.42
2.94
2.87
2.75
2.68
2.00
1.97
1.92
1.88
O2N
NO2
O
OH
N
H
HN
Ph
Ph
Ph
54a
1.01
0.75
0.91
1.00
2.82
13.59
0.97
0.83
0.88
1.09
1.32
2.21
f1 (ppm)

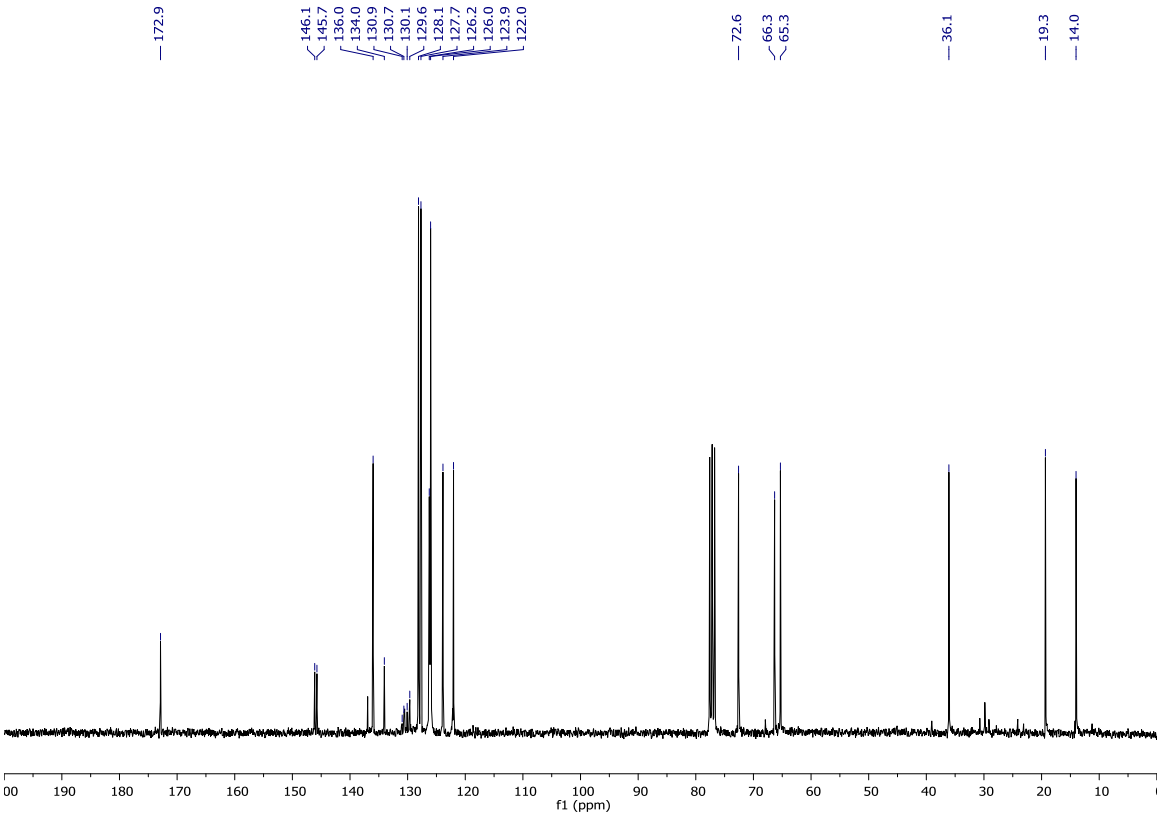

174.22
142.74
142.02
141.02
139.06
129.94
129.07
128.84
128.80
128.55
127.89
127.50
127.22
126.44
122.16
72.33
67.34
65.44
35.72
32.39
f1 (ppm)

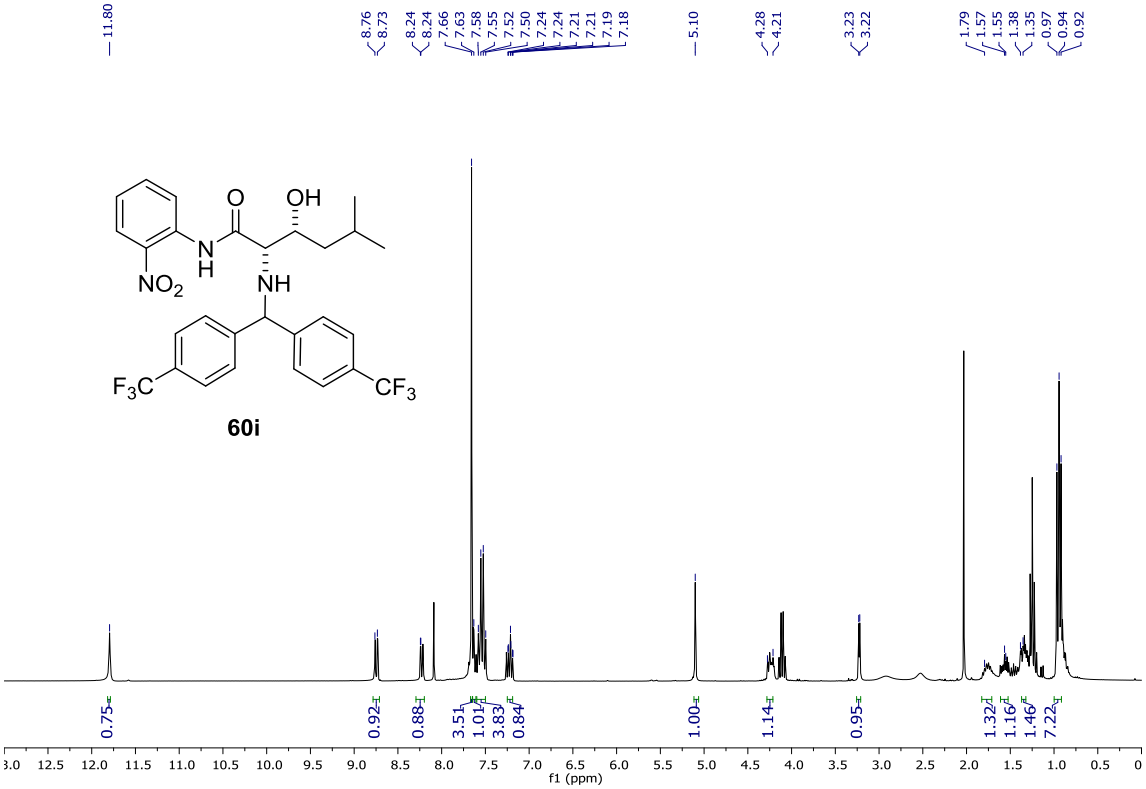

11.75
8.76
8.74
8.27
8.25
8.00
7.88
7.66
7.31
7.16
5.13
4.17
4.16
4.15
4.14
3.20
3.19
3.18
2.91
2.85
2.72
2.70
2.04
1.98
1.96
O
OH
N
H
Ph
NO2
HN
CF3
F3C
CF3
CF3
59a
1.04
1.21
1.15
1.58
3.42
0.97
2.40
3.77
1.00
1.03
0.97
1.06
0.74
2.29
f1 (ppm)
171.8
143.8
143.6
140.9
136.1
133.8
133.4
133.1
132.8
132.8
132.6
132.3
128.9
128.6
127.8
127.4
126.6
126.1
124.1
121.8
72.1
65.8
65.4
35.5
32.3
29.9
f1 (ppm)

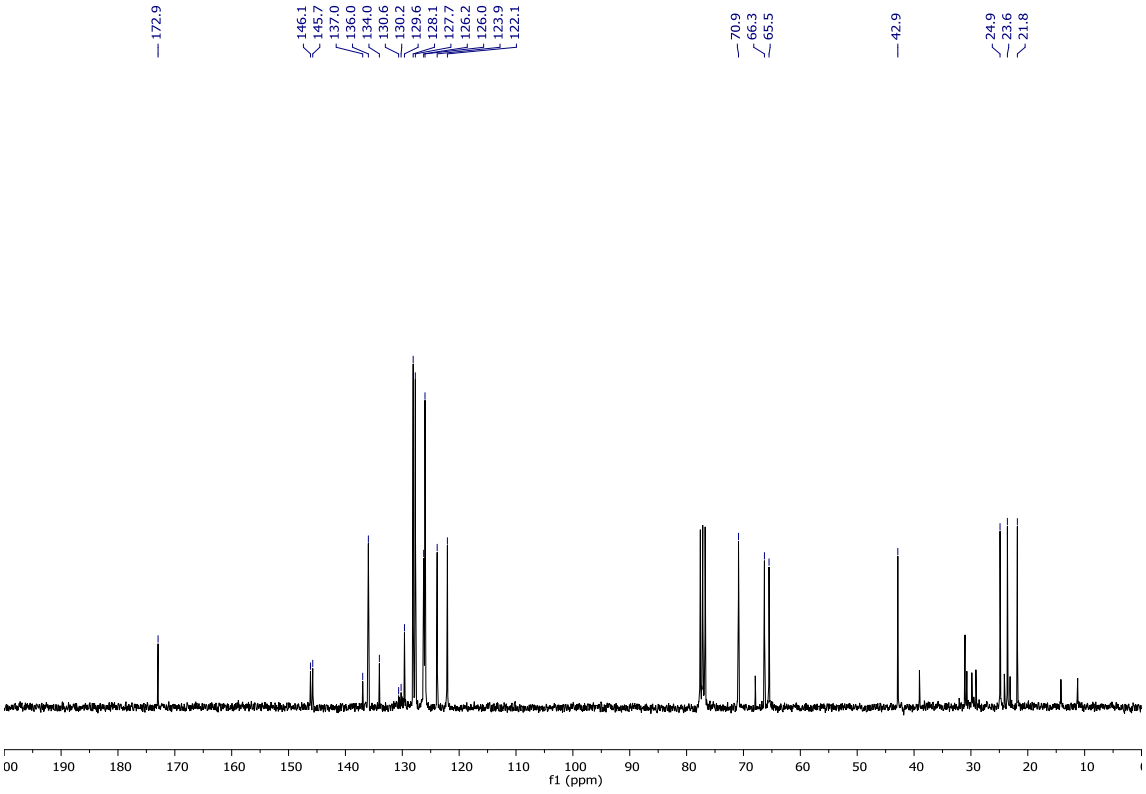

11.76
8.75
8.73
8.72
8.25
8.22
7.66
7.63
7.61
7.59
7.55
7.52
7.52
7.49
7.32
7.29
7.27
7.25
7.23
7.20
7.17
5.04
4.12
3.29
3.28
2.94
2.92
2.89
2.85
2.74
2.70
2.65
1.94
1.92
O
OH
N
H
Ph
NO2
HN
F3C
CF3
60a
0.94
0.90
0.84
5.57
3.89
2.70
3.84
1.00
0.83
0.95
1.46
1.68
2.27
f1 (ppm)

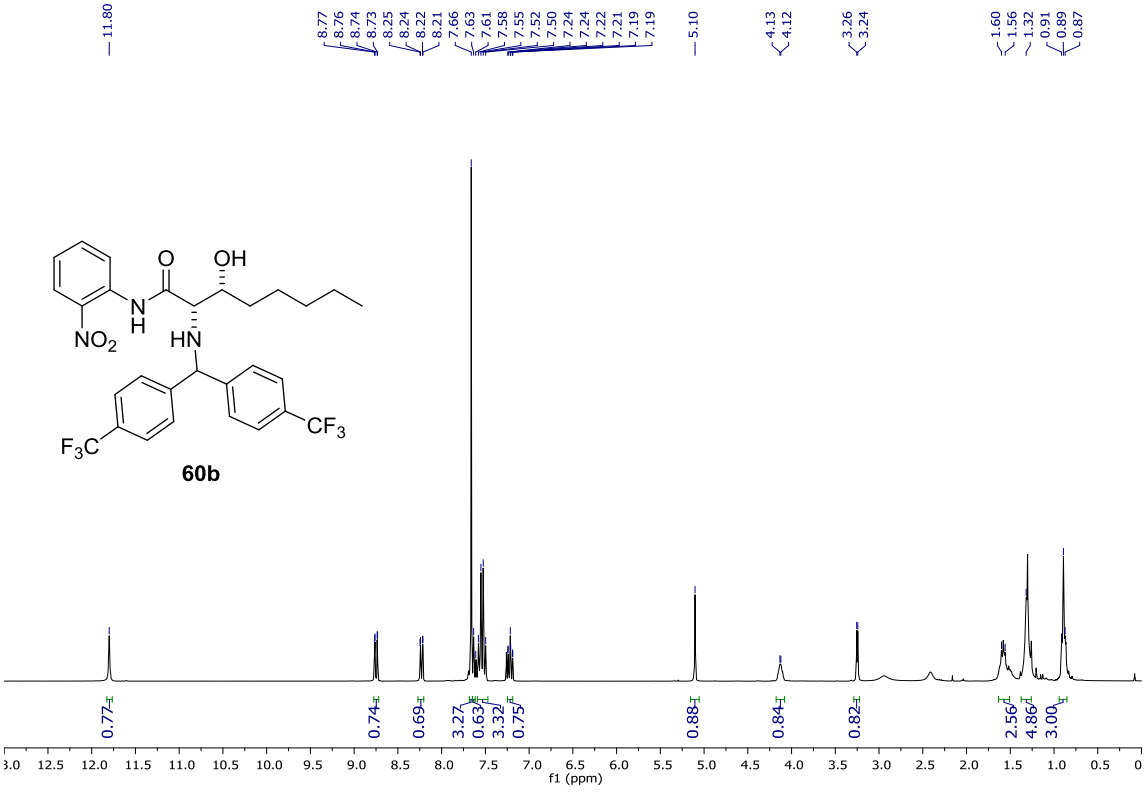

172.76
145.99
145.59
141.16
136.94
135.99
133.91
131.53
131.07
130.52
130.09
128.77
128.58
128.07
127.67
126.40
126.23
126.19
126.02
125.97
123.95
122.05
71.99
66.11
65.23
35.48
32.35
f1 (ppm)

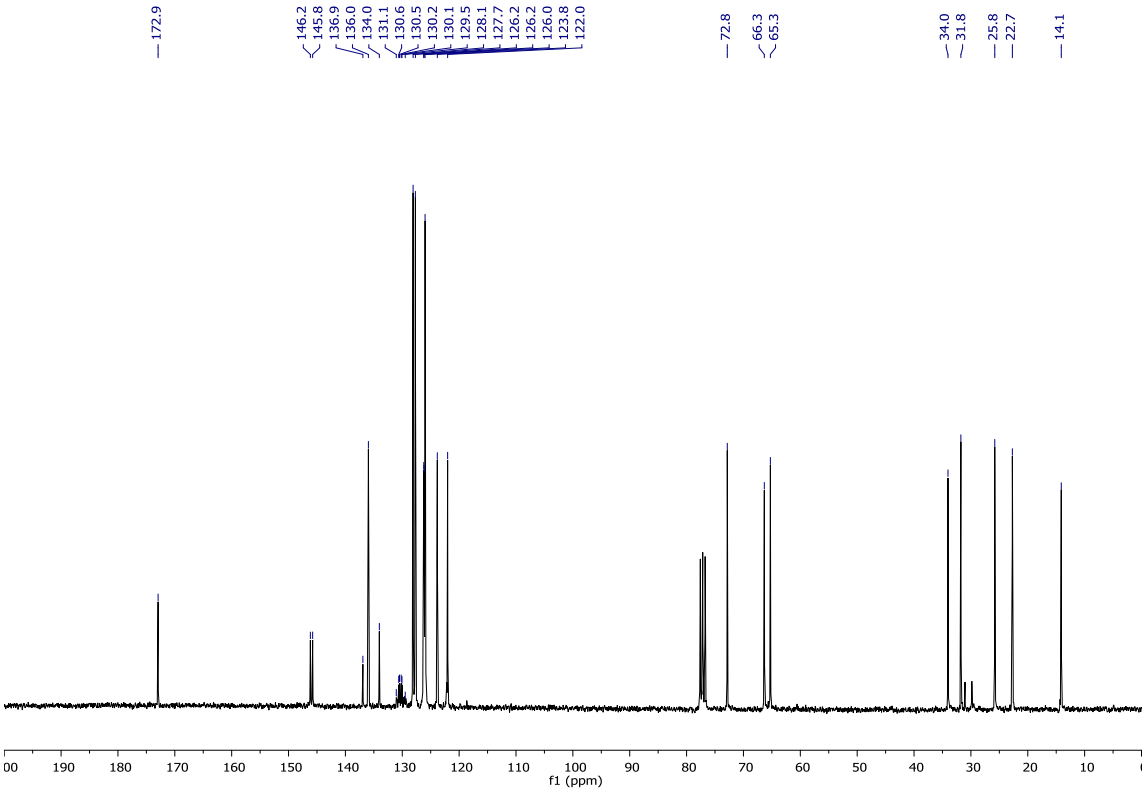

11.80
8.77
8.74
8.25
8.23
7.66
7.64
7.62
7.58
7.55
7.53
7.50
7.25
7.22
7.20
5.10
4.14
3.25
1.58
1.39
0.96
0.94
0.86
O
OH
N
H
NH
NO2
F3C
CF3
60h
1.21
1.00
1.02
3.87
1.32
4.15
1.38
1.32
1.30
1.20
3.39
1.20
3.38
f1 (ppm)

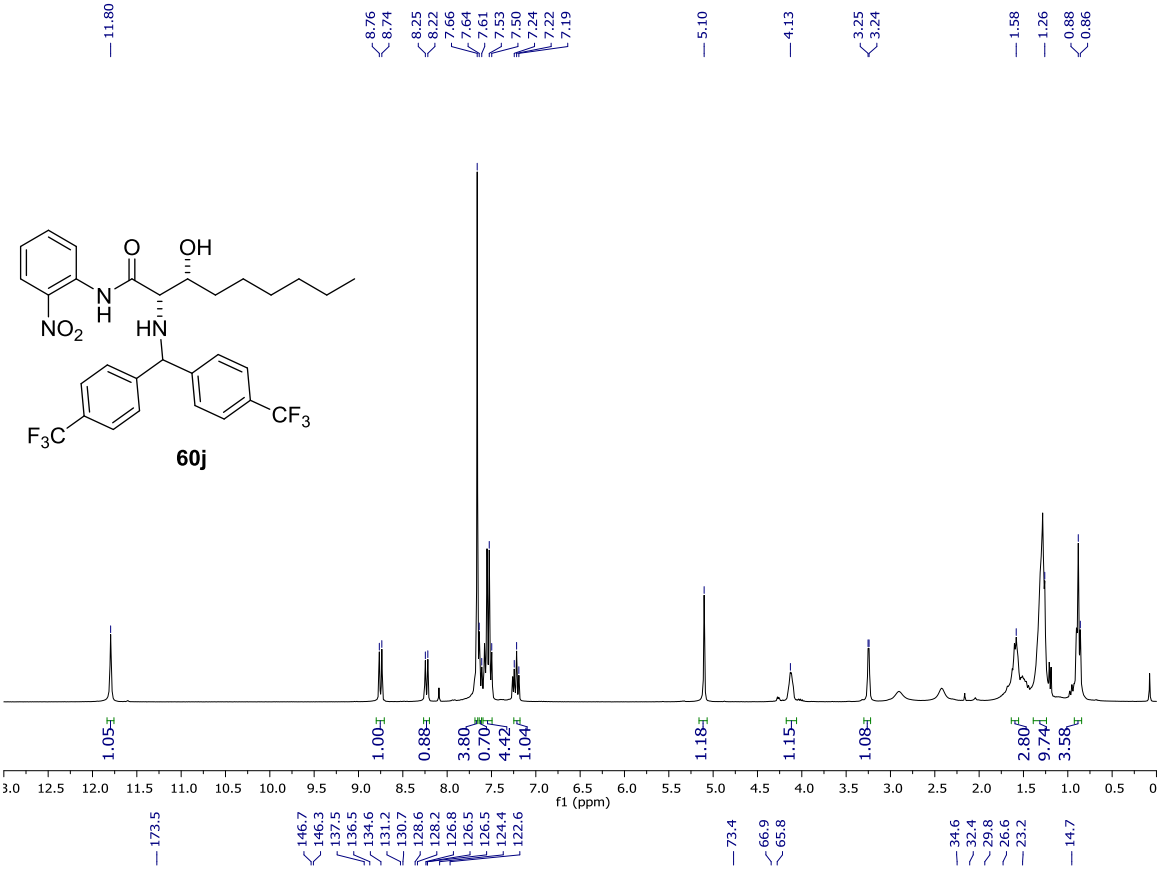

172.9
146.1
145.7
136.0
134.0
130.9
130.7
130.1
129.6
128.1
127.7
126.2
126.0
123.9
122.0
72.6
66.3
65.3
36.1
19.3
14.0
f1 (ppm)

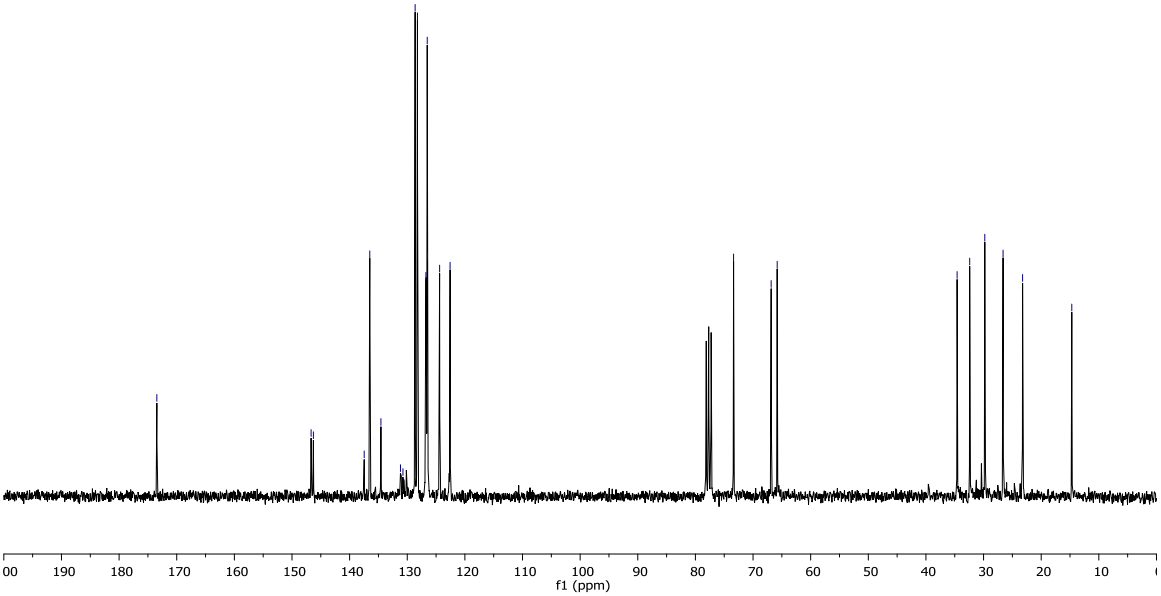

11.80
8.76
8.73
8.24
8.24
7.66
7.63
7.58
7.55
7.52
7.50
7.24
7.24
7.21
7.21
7.19
7.18
5.10
4.28
4.21
3.23
3.22
1.79
1.57
1.55
1.38
1.35
0.97
0.94
0.92
O
OH
N
H
NO2
NH
F3C
CF3
60i
0.75
0.92
0.88
3.51
1.01
3.83
0.84
1.00
1.14
0.95
1.32
1.16
1.46
7.22
f1 (ppm)

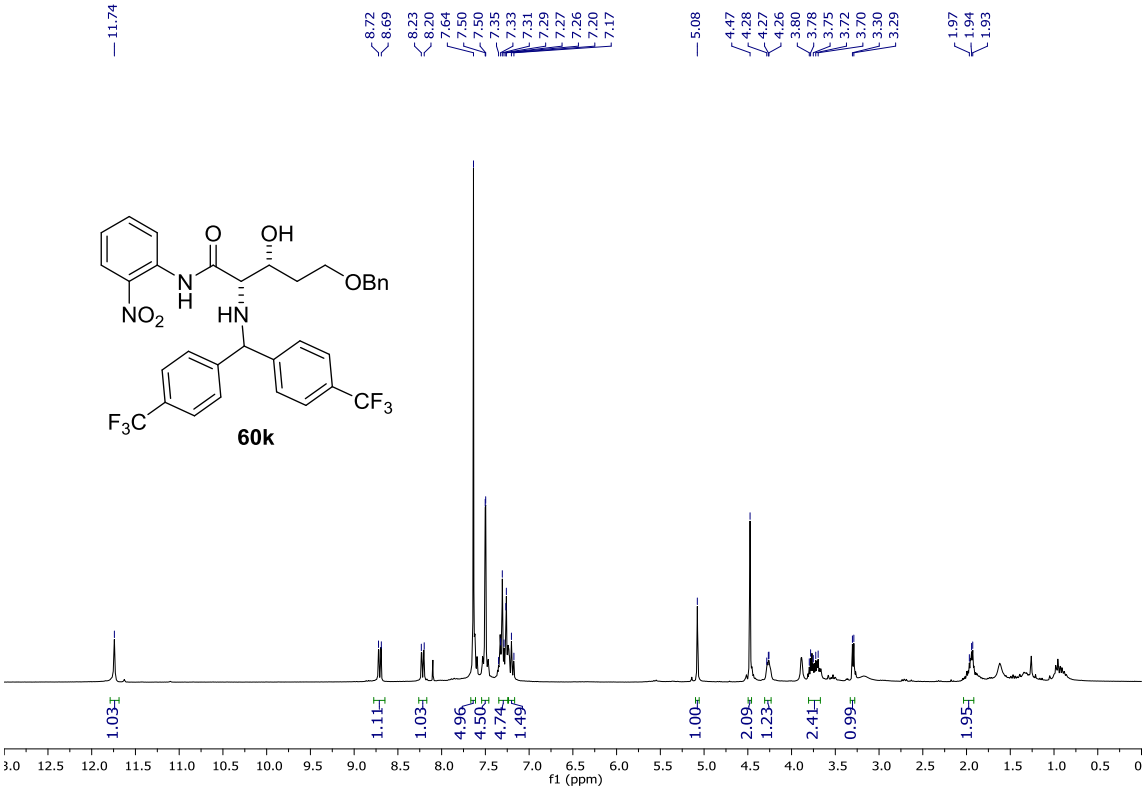

172.9
146.1
145.7
137.0
136.0
134.0
130.6
130.2
129.6
128.1
127.7
126.2
126.0
123.9
122.1
70.9
66.3
65.5
42.9
24.9
23.6
21.8
f1 (ppm)

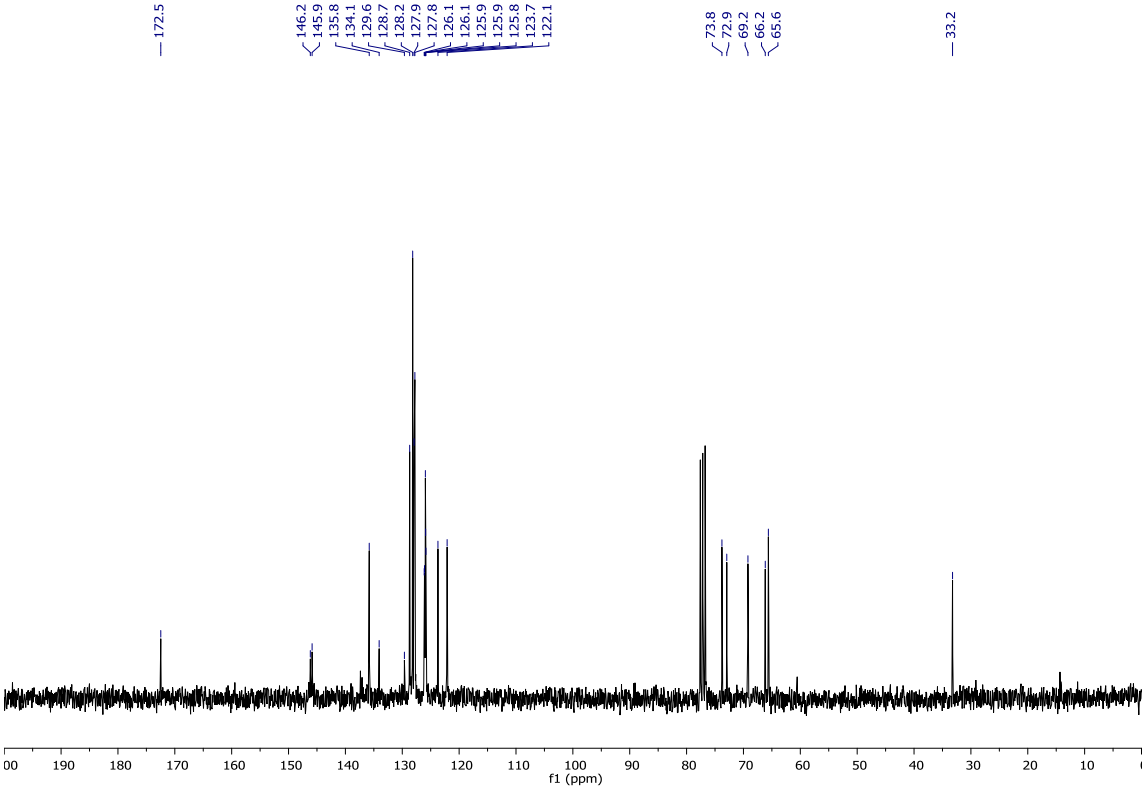

11.80
8.77
8.76
8.74
8.73
8.25
8.24
8.22
8.21
7.66
7.63
7.61
7.58
7.55
7.52
7.50
7.24
7.24
7.22
7.21
7.19
7.19
5.10
4.13
4.12
3.26
3.24
1.60
1.56
1.32
0.91
0.89
0.87
O
OH
N
H
HN
NO2
F3C
CF3
60b
0.77
0.74
0.69
3.27
0.63
3.32
0.75
0.88
0.84
0.82
2.56
4.86
3.00
f1 (ppm)

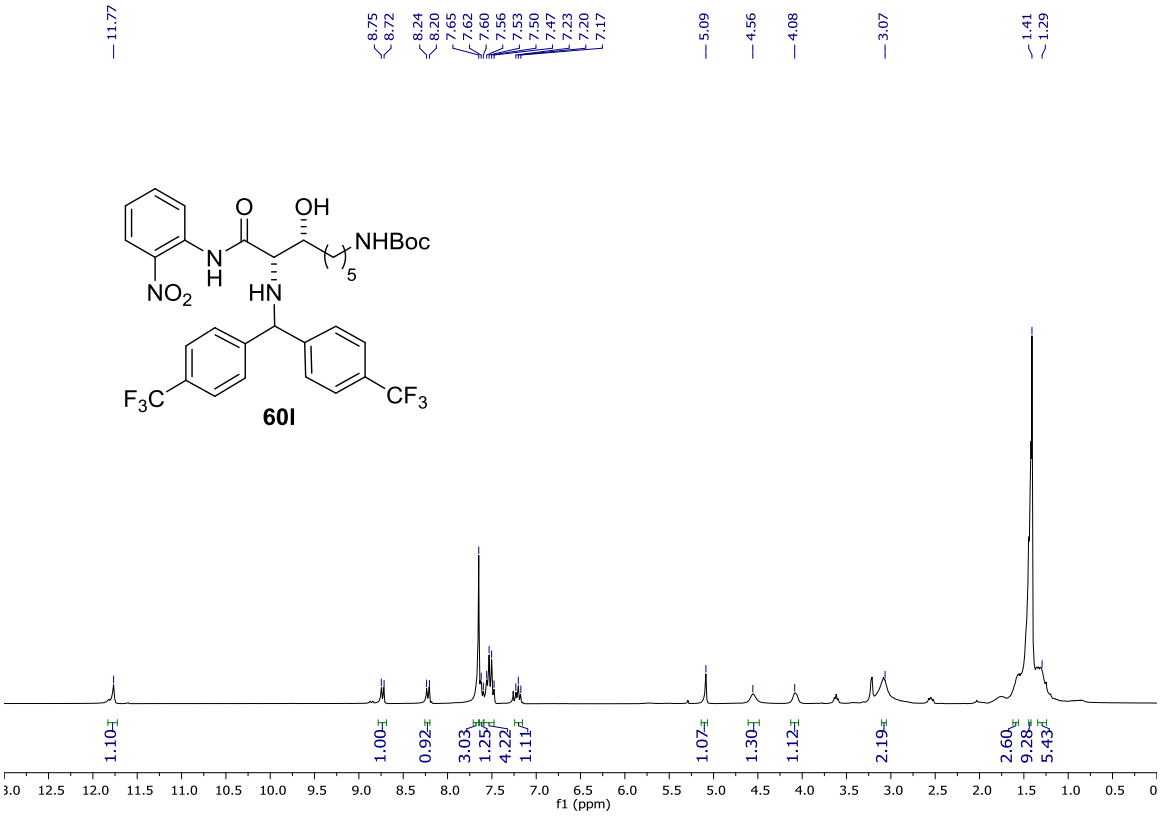

172.9
146.2
145.8
136.9
136.0
134.0
131.1
130.6
130.5
130.2
130.1
129.5
128.1
127.7
126.2
126.2
126.0
123.8
122.0
72.8
66.3
65.3
34.0
31.8
25.8
22.7
14.1
f1 (ppm)

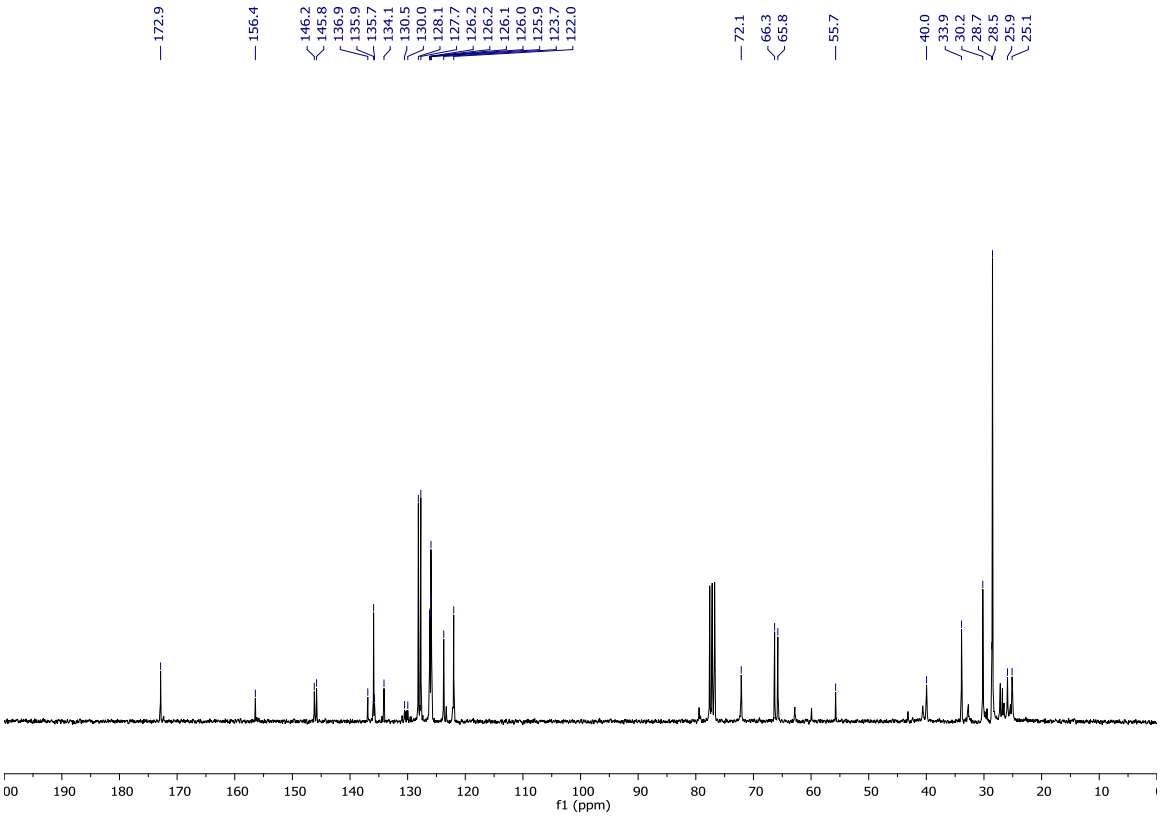

11.80
8.76
8.74
8.25
8.22
7.66
7.64
7.61
7.53
7.50
7.24
7.22
7.19
5.10
4.13
3.25
3.24
1.58
1.26
0.88
0.86
O
OH
N
H
HN
NO2
F3C
CF3
60j
1.05
1.00
0.88
3.80
0.70
4.42
1.04
1.18
1.15
1.08
2.80
9.74
3.58
f1 (ppm)

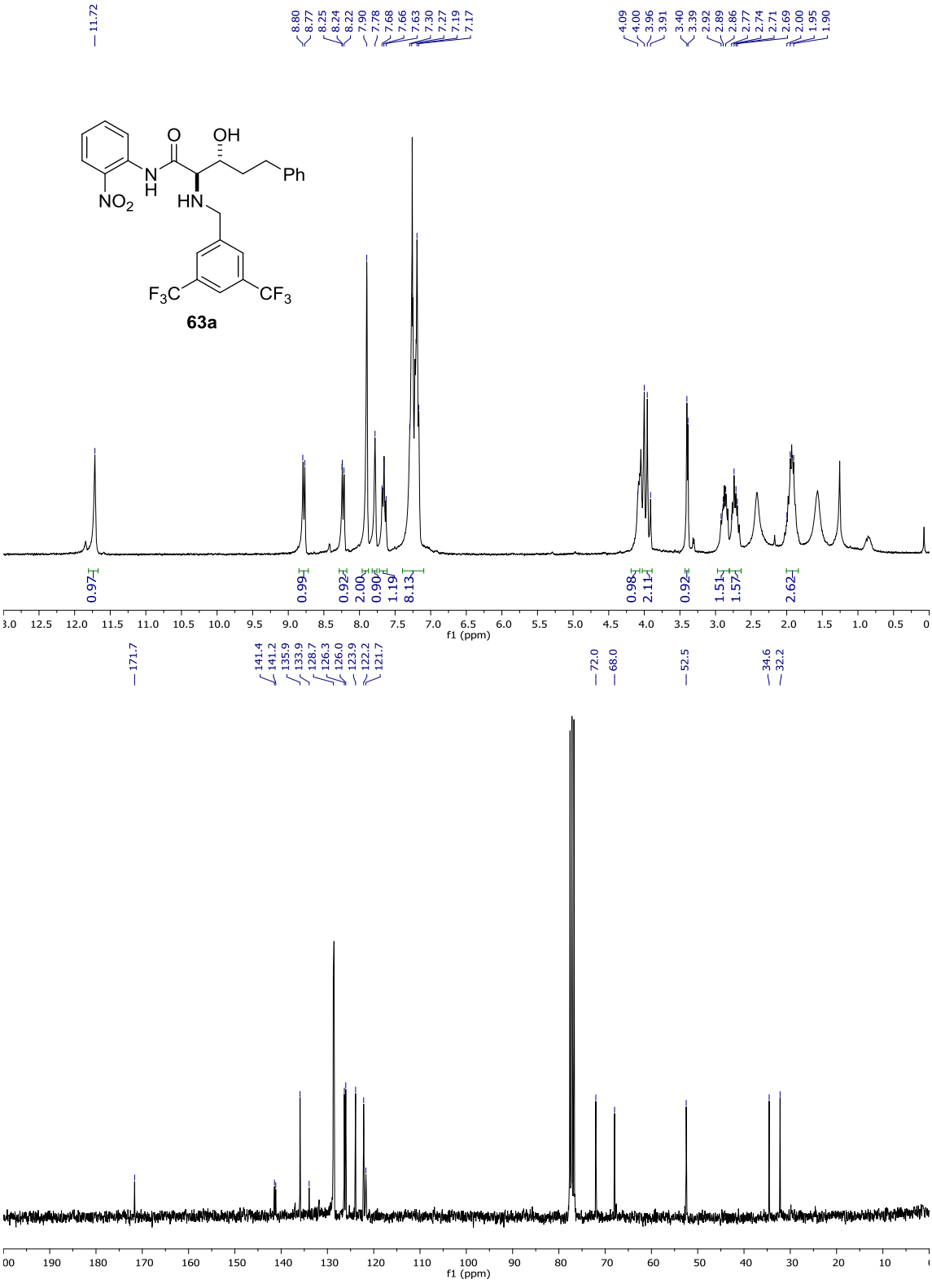

173.5
146.7
146.3
137.5
136.5
134.6
131.2
130.7
128.6
128.2
126.8
126.5
126.5
124.4
122.6
73.4
66.9
65.8
34.6
32.4
29.8
26.6
23.2
14.7
f1 (ppm)

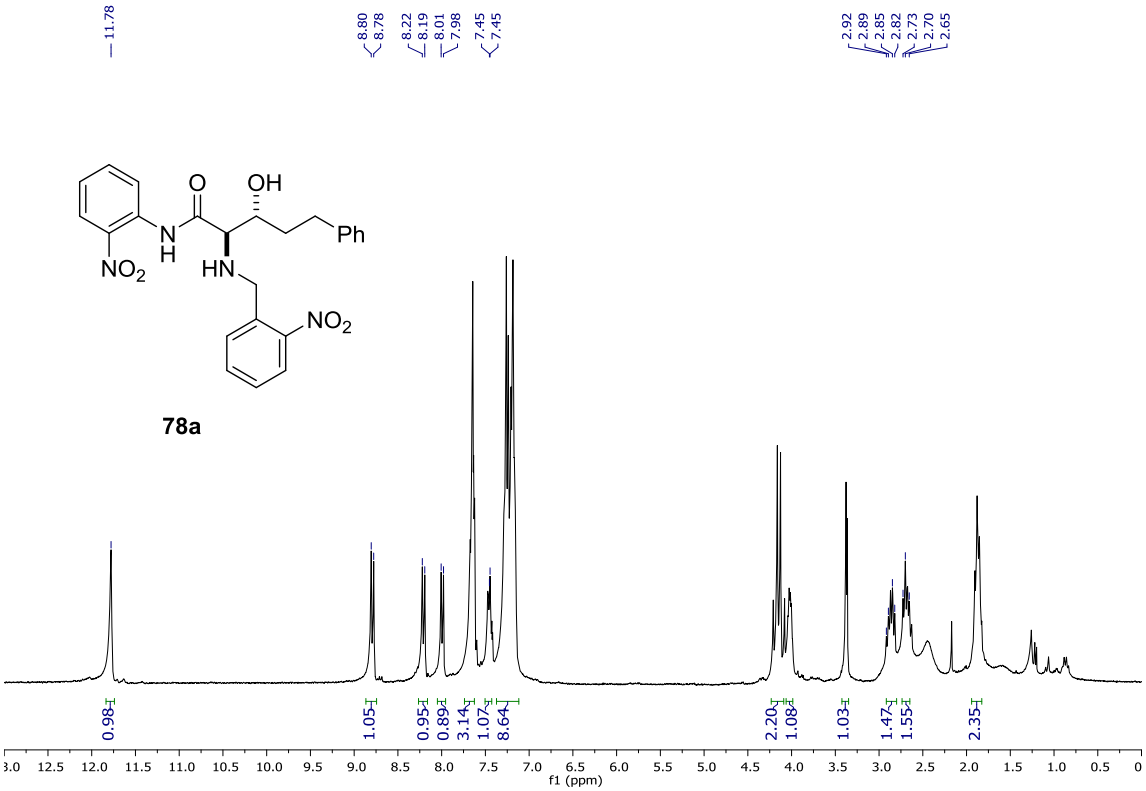

11.74
8.72
8.69
8.23
8.20
7.64
7.50
7.50
7.35
7.33
7.31
7.29
7.27
7.26
7.20
7.17
5.08
4.47
4.28
4.27
4.26
3.80
3.78
3.75
3.72
3.70
3.30
3.29
1.97
1.94
1.93
O
OH
N
H
OBn
NO2
HN
F3C
CF3
60k
1.03
1.11
1.03
4.96
4.50
4.74
1.49
1.00
2.09
1.23
2.41
0.99
1.95
f1 (ppm)

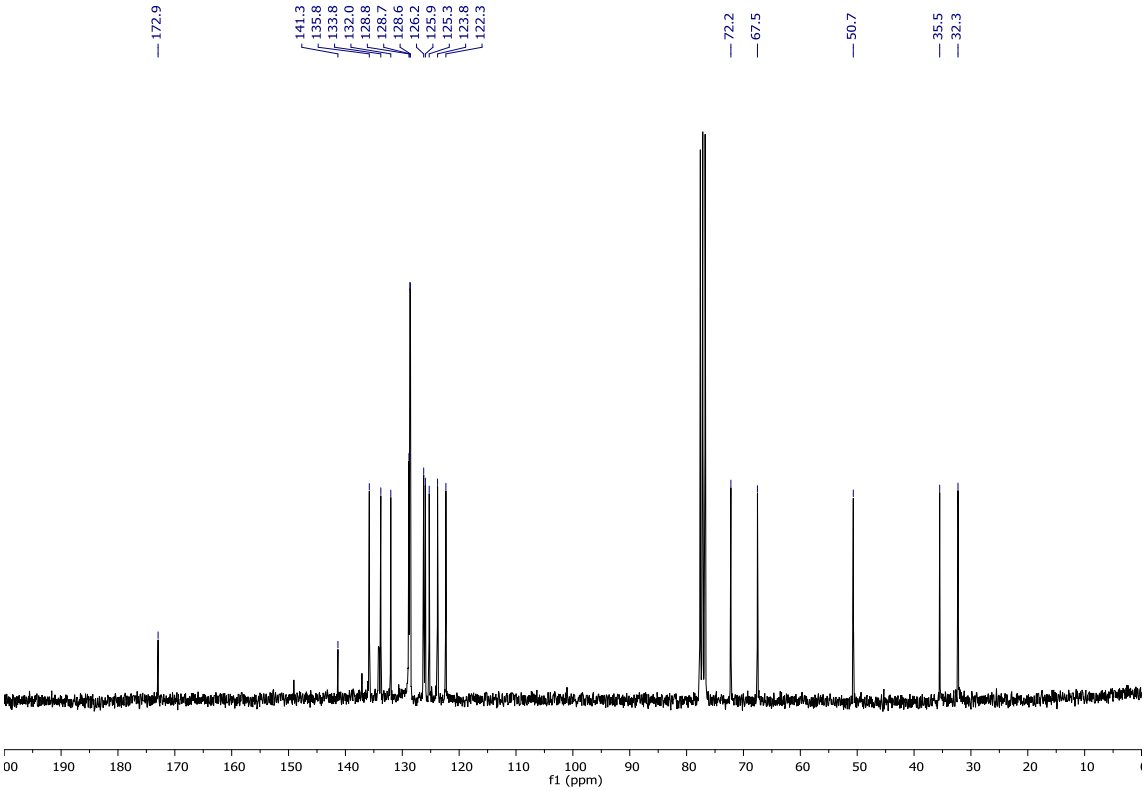

172.5
146.2
145.9
135.8
134.1
129.6
128.7
128.2
127.9
127.8
126.1
126.1
125.9
125.9
125.8
123.7
122.1
73.8
72.9
69.2
66.2
65.6
33.2
f1 (ppm)

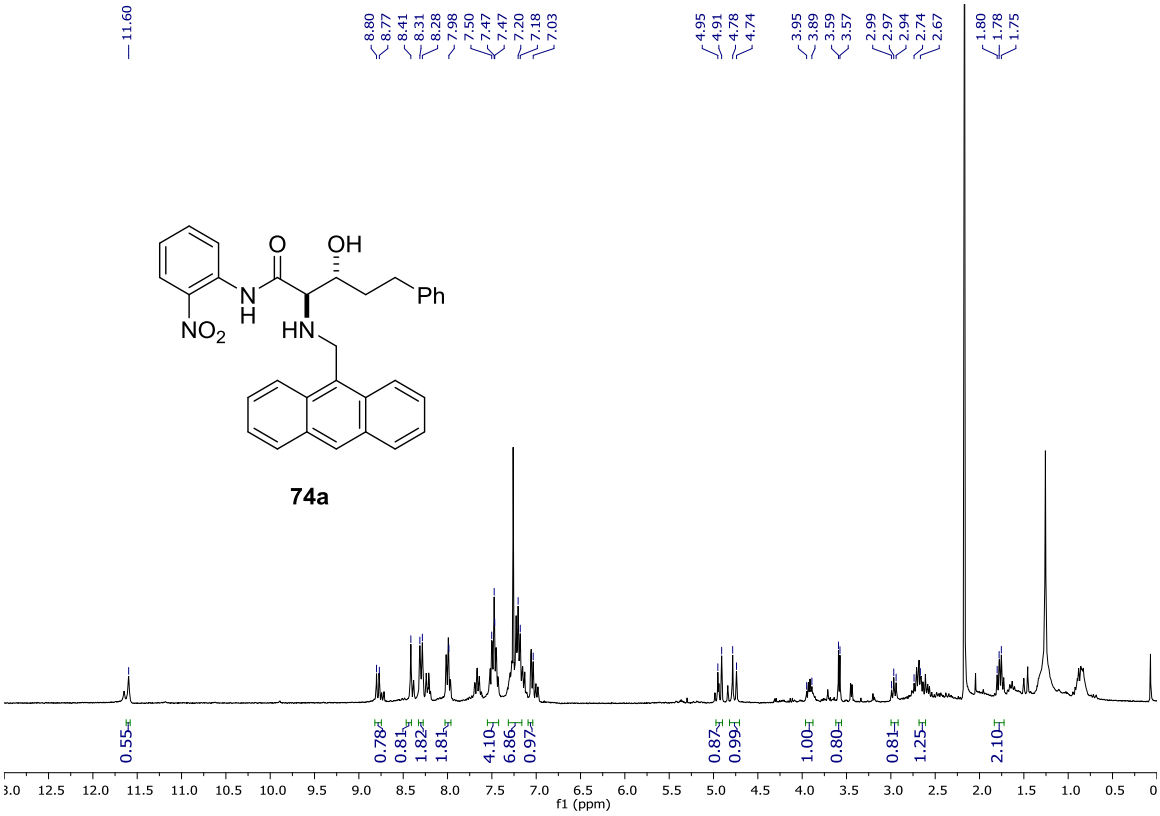

11.77
8.75
8.72
8.24
8.20
7.65
7.62
7.60
7.56
7.53
7.50
7.47
7.23
7.20
7.17
5.09
4.56
4.08
3.07
1.41
1.29
O
OH
NHBoc
N
H
5
NO2
HN
F3C
CF3
60l
1.10
1.00
0.92
3.03
1.25
4.22
1.11
1.07
1.30
1.12
2.19
2.60
9.28
5.43
f1 (ppm)


172.9
156.4
146.2
145.8
136.9
135.9
135.7
134.1
130.5
130.0
128.1
127.7
126.2
126.2
126.1
126.0
125.9
123.7
122.0
72.1
66.3
65.8
55.7
40.0
33.9
30.2
28.7
28.5
25.9
25.1
f1 (ppm)

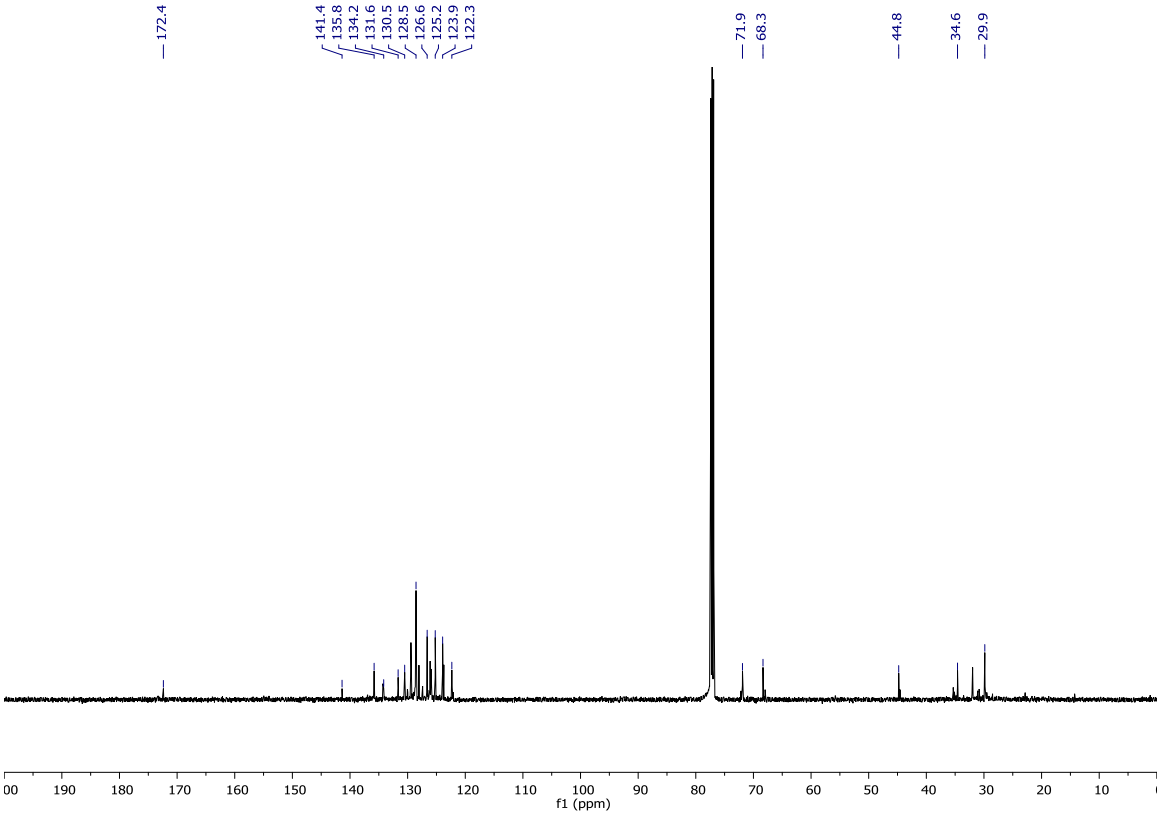

11.72
8.80
8.77
8.25
8.24
8.22
7.90
7.78
7.68
7.66
7.63
7.30
7.27
7.19
7.17
4.09
4.00
3.96
3.91
3.40
3.39
2.92
2.89
2.86
2.77
2.74
2.71
2.69
2.00
1.95
1.90
O
OH
N
H
Ph
NO2
HN
F3C
CF3
63a
0.97
0.99
0.92
2.00
0.90
1.19
8.13
0.98
2.11
0.92
1.51
1.57
2.62
f1 (ppm)
171.7
141.4
141.2
135.9
133.9
128.7
126.3
126.0
123.9
122.2
121.7
72.0
68.0
52.5
34.6
32.2
f1 (ppm)

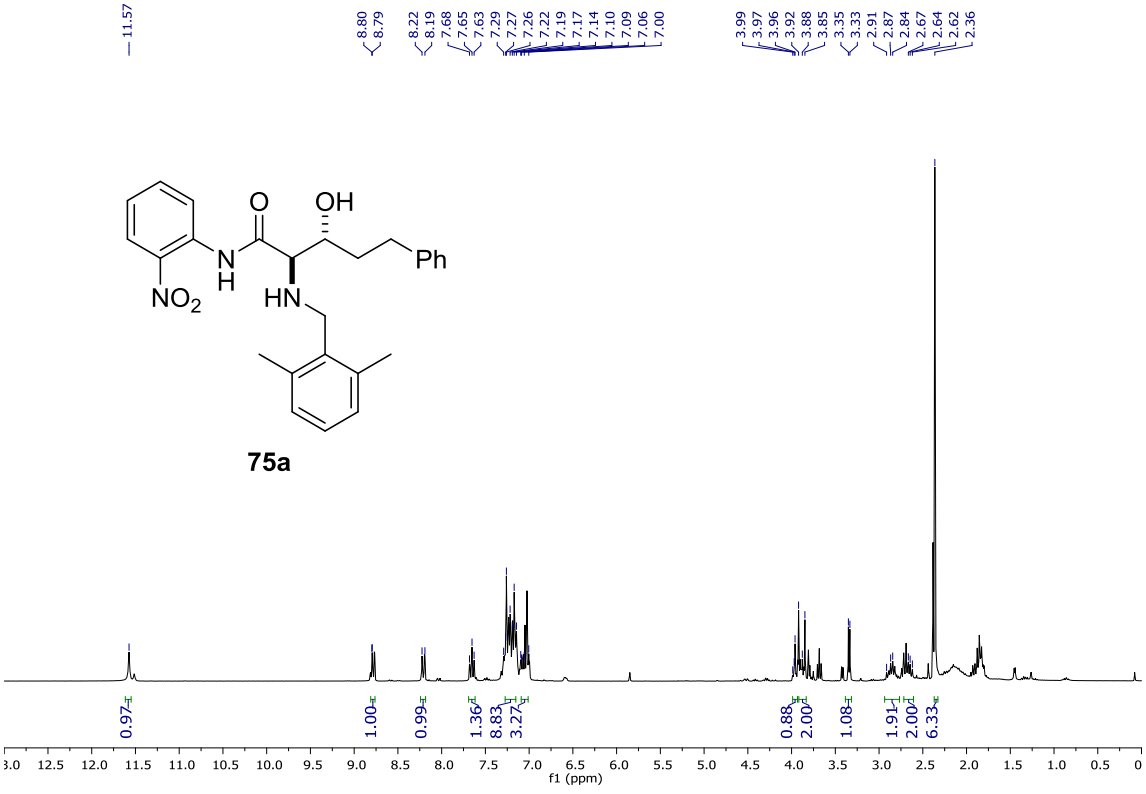

11.78
8.80
8.78
8.22
8.19
8.01
7.98
7.45
7.45
2.92
2.89
2.85
2.82
2.73
2.70
2.65
O
OH
N
H
Ph
NO2
HN
NO2
78a
0.98
1.05
0.95
0.89
3.14
1.07
8.64
2.20
1.08
1.03
1.47
1.55
2.35
f1 (ppm)


172.9
141.3
135.8
133.8
132.0
128.8
128.7
128.6
126.2
125.9
125.3
123.8
122.3
72.2
67.5
50.7
35.5
32.3
f1 (ppm)

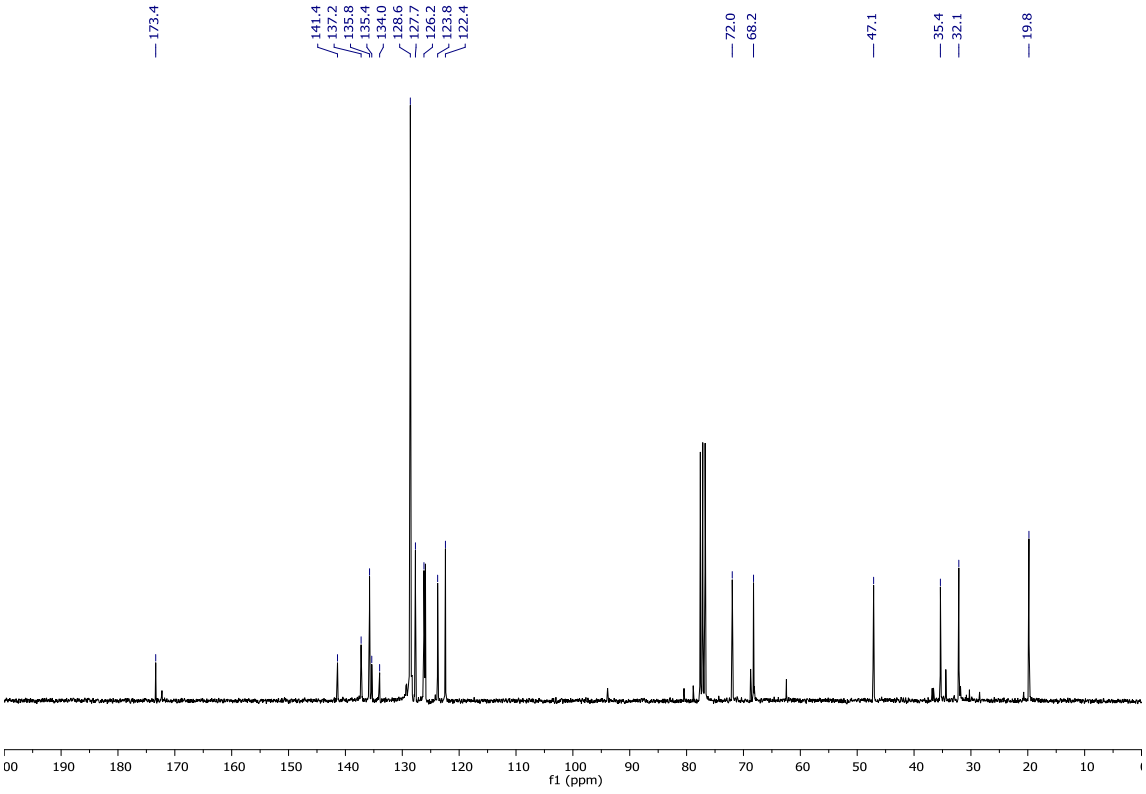

11.60
8.80
8.77
8.41
8.31
8.28
7.98
7.50
7.47
7.47
7.20
7.18
7.03
4.95
4.91
4.78
4.74
3.95
3.89
3.59
3.57
2.99
2.97
2.94
2.74
2.67
1.80
1.78
1.75
O
OH
N
H
Ph
NO2
HN
0.55
0.78
0.81
1.82
1.81
4.10
6.86
0.97
0.87
0.99
1.00
0.80
0.81
1.25
2.10
f1 (ppm)

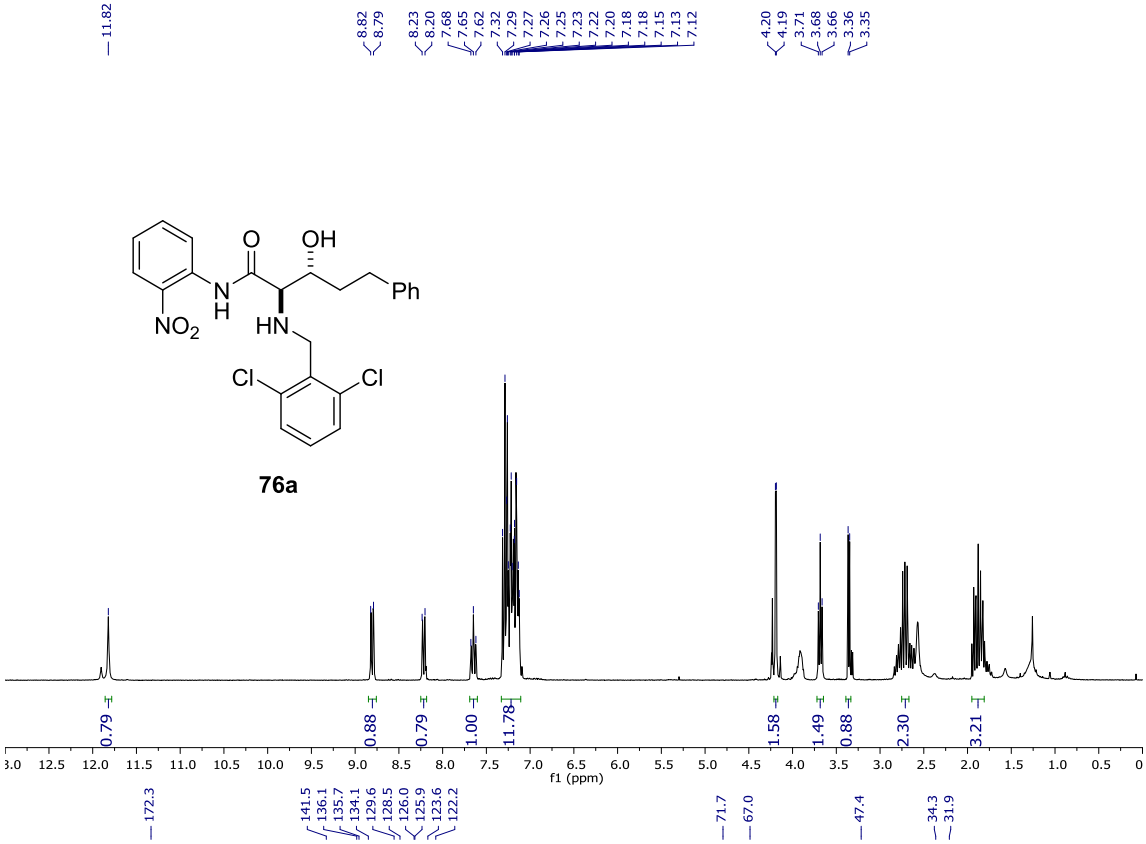
74a

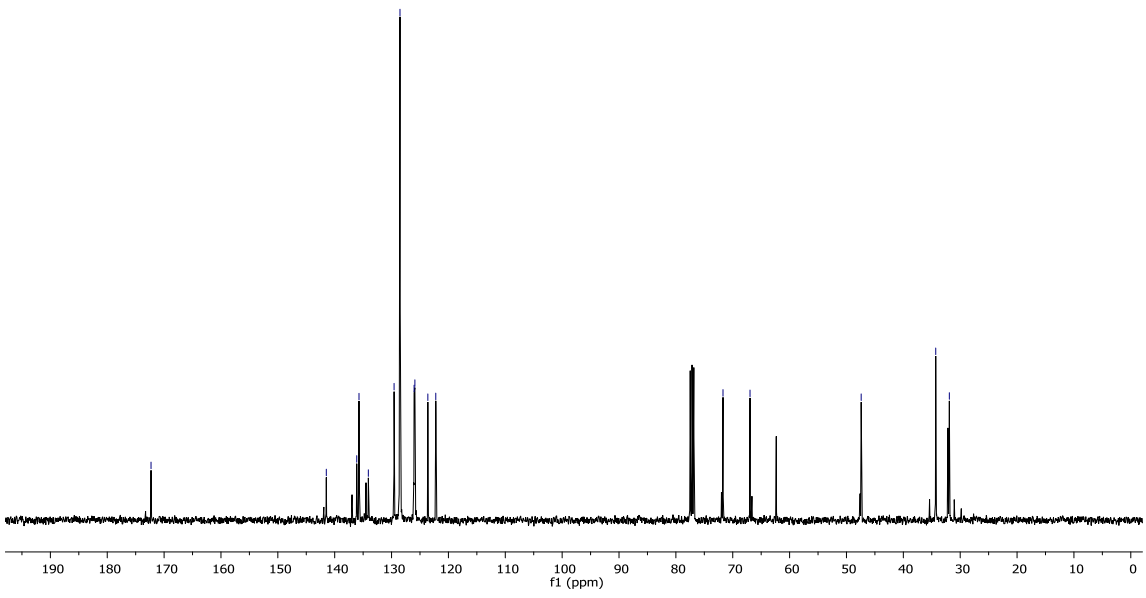

172.4
141.4
135.8
134.2
131.6
130.5
128.5
126.6
125.2
123.9
122.3
71.9
68.3
44.8
34.6
29.9
f1 (ppm)

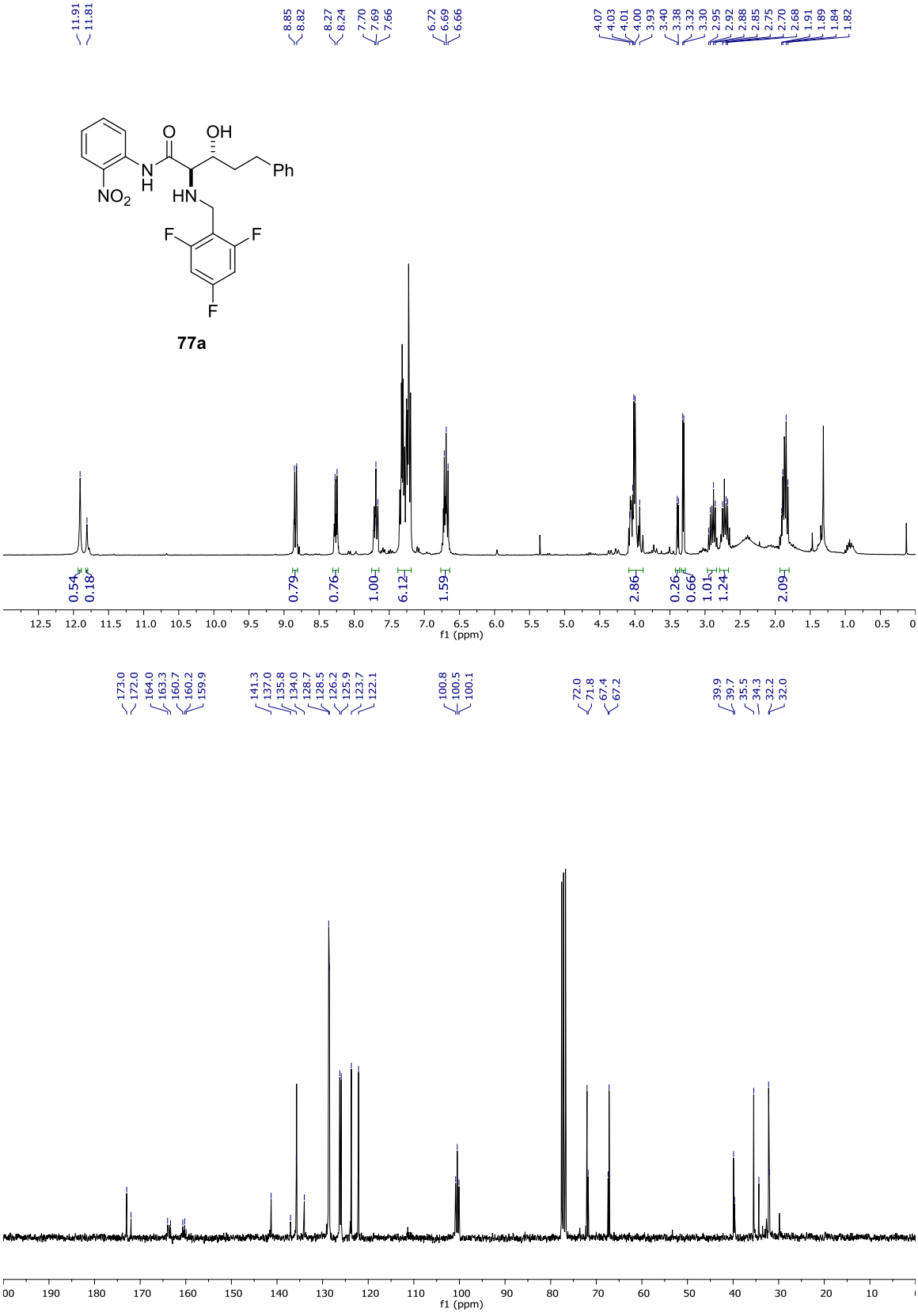

11.57
8.80
8.79
8.22
8.19
7.68
7.65
7.63
7.29
7.27
7.26
7.22
7.19
7.17
7.14
7.10
7.09
7.06
7.00
3.99
3.97
3.96
3.92
3.88
3.85
3.35
3.33
2.91
2.87
2.84
2.67
2.64
2.62
2.36
O
OH
N
H
Ph
NO2
HN
0.97
1.00
0.99
1.36
8.83
3.27
0.88
2.00
1.08
1.91
2.00
6.33
f1 (ppm)

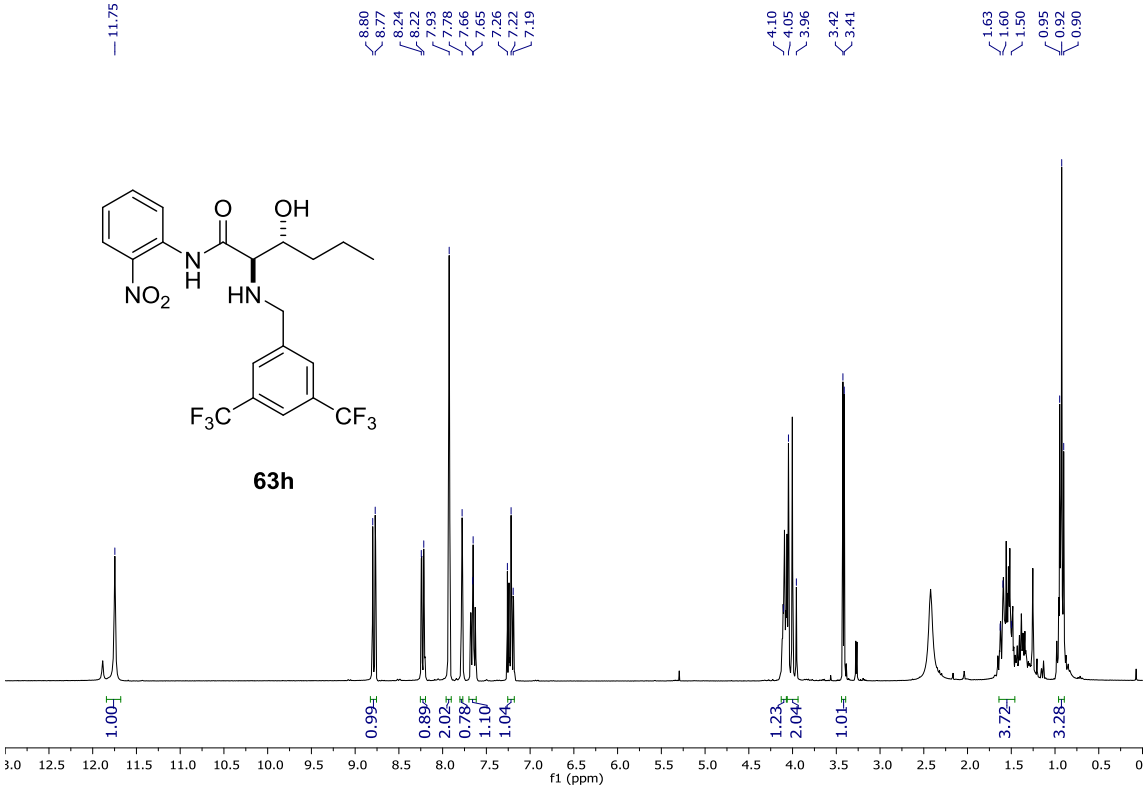
75a

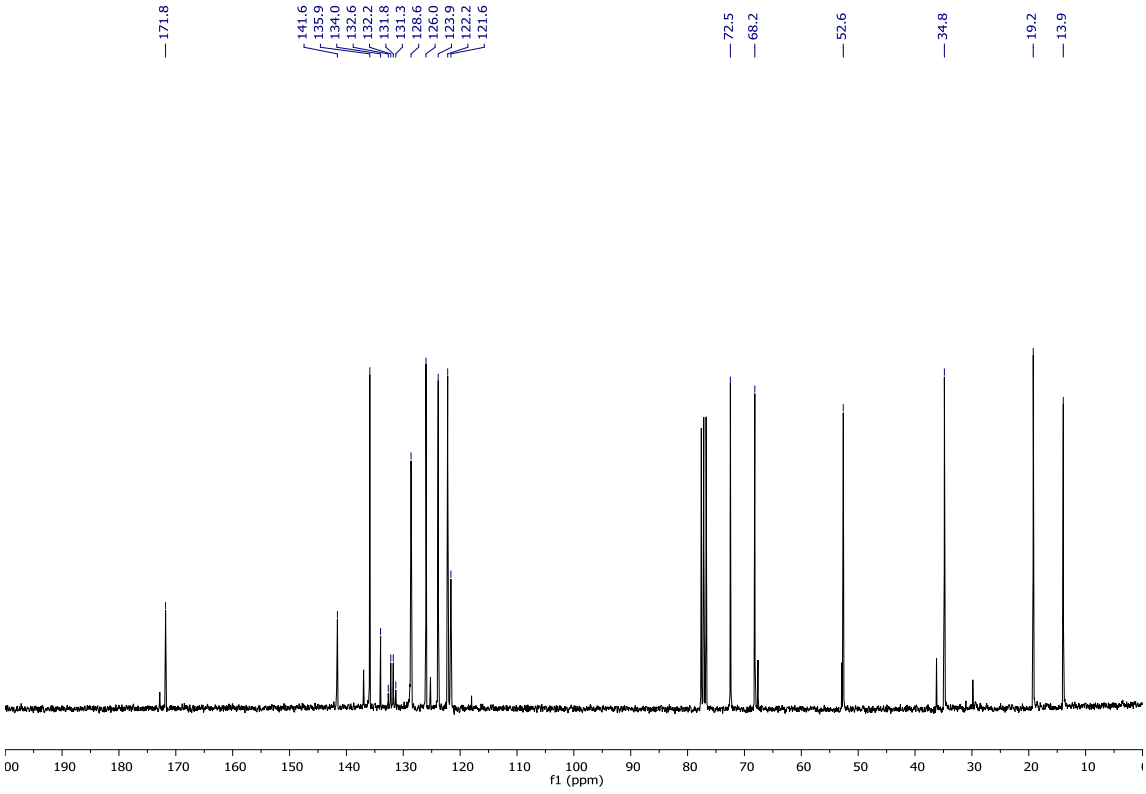

173.4
141.4
137.2
135.8
135.4
134.0
128.6
127.7
126.2
123.8
122.4
72.0
68.2
47.1
35.4
32.1
19.8
f1 (ppm)

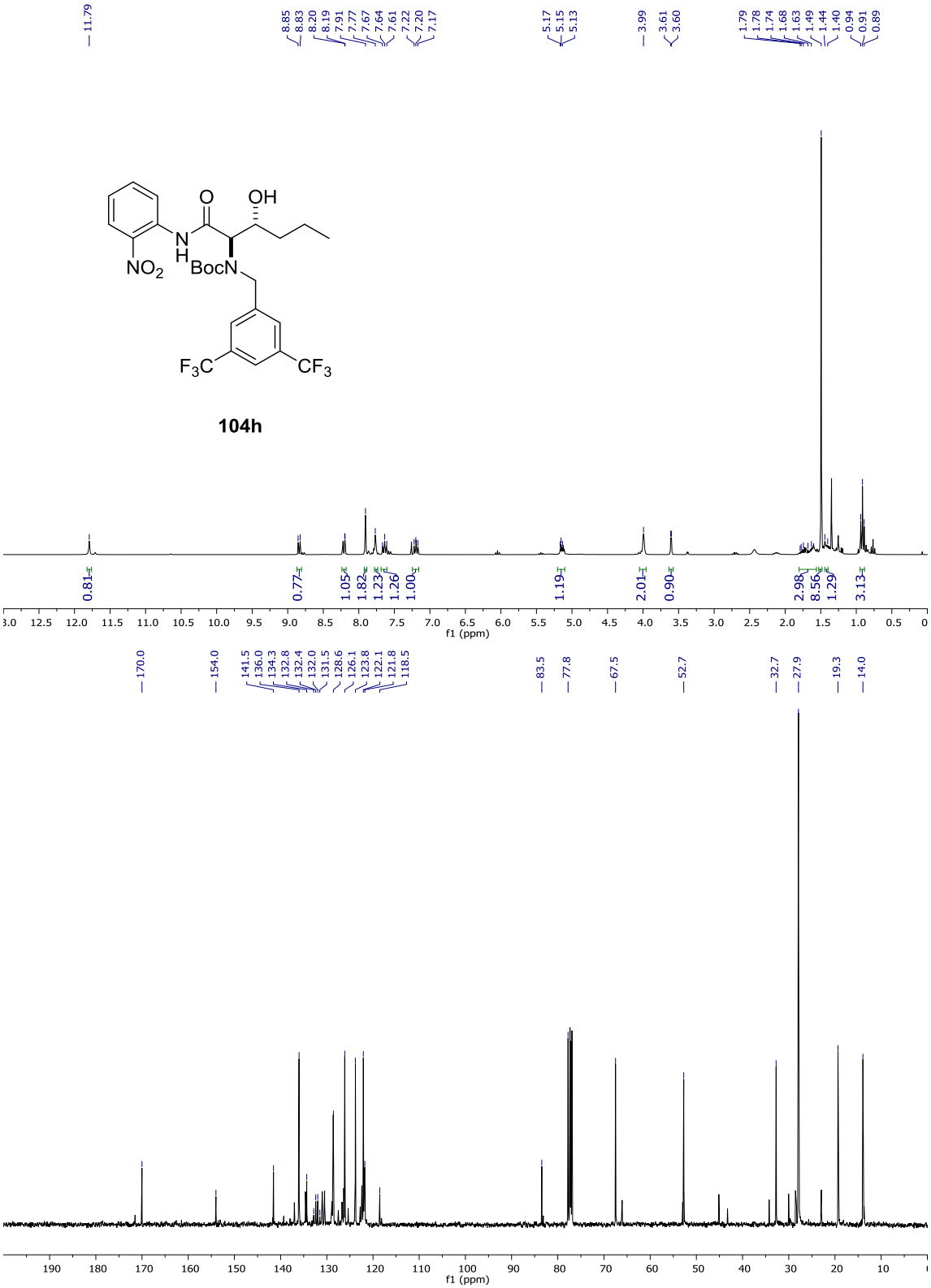

11.82
8.82
8.79
8.23
8.20
7.68
7.65
7.62
7.32
7.29
7.27
7.26
7.25
7.23
7.22
7.20
7.18
7.18
7.15
7.13
7.12
4.20
4.19
3.71
3.68
3.66
3.36
3.35
O
OH
N
H
Ph
NO2
HN
Cl
Cl
76a
0.79
0.88
0.79
1.00
11.78
1.58
1.49
0.88
2.30
3.21
f1 (ppm)

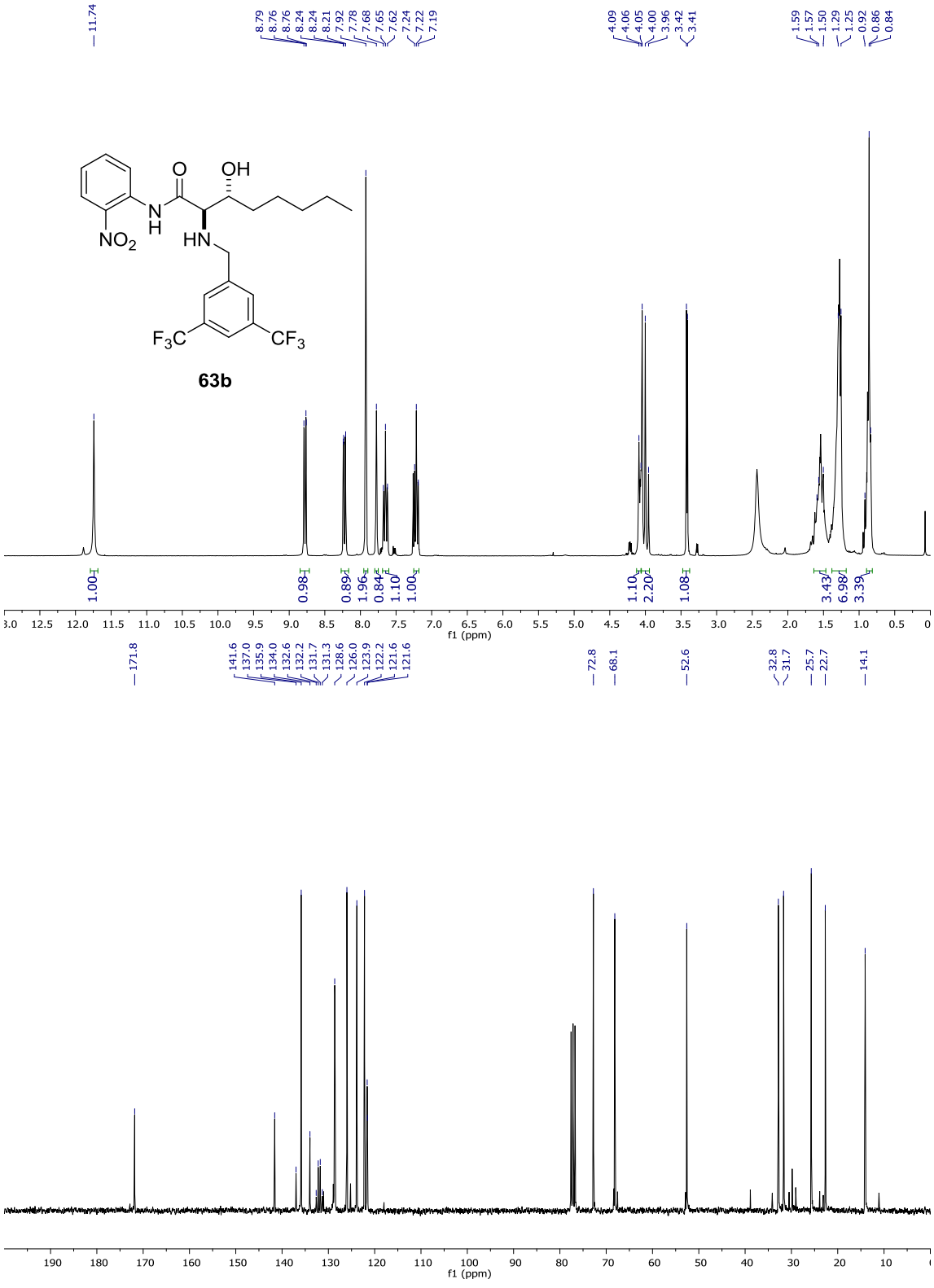

172.3
141.5
136.1
135.7
134.1
129.6
128.5
126.0
125.9
123.6
122.2
71.7
67.0
47.4
34.3
31.9
f1 (ppm)

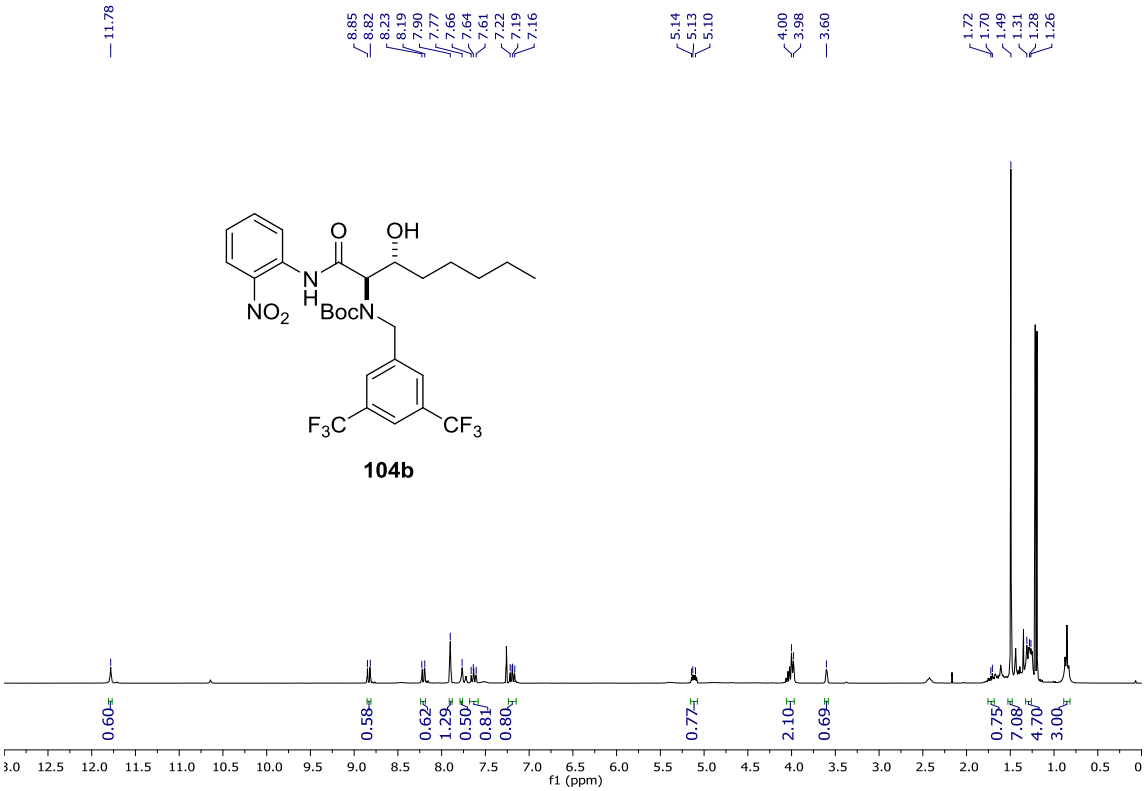

11.91
11.81
8.85
8.82
8.27
8.24
7.70
7.69
7.66
6.72
6.69
6.66
4.07
4.03
4.01
4.00
3.93
3.40
3.38
3.32
3.30
2.95
2.92
2.88
2.85
2.75
2.70
2.68
1.91
1.89
1.84
1.82
O
OH
N
H
Ph
NO2
HN
F
F
F
77a
0.54
0.18
0.79
0.76
1.00
6.12
1.59
2.86
0.26
0.66
1.01
1.24
2.09
f1 (ppm)
173.0
172.0
164.0
163.3
160.7
160.2
159.9
141.3
137.0
135.8
134.0
128.7
128.5
126.2
125.9
123.7
122.1
100.8
100.5
100.1
72.0
71.8
67.4
67.2
39.9
39.7
35.5
34.3
32.2
32.0
f1 (ppm)


11.75
8.80
8.77
8.24
8.22
7.93
7.78
7.66
7.65
7.26
7.22
7.19
4.10
4.05
3.96
3.42
3.41
1.63
1.60
1.50
0.95
0.92
0.90
O
OH
N
H
HN
NO2
F3C
CF3
63h
1.00
0.99
0.89
2.02
0.78
1.10
1.04
1.23
2.04
1.01
3.72
3.28
f1 (ppm)

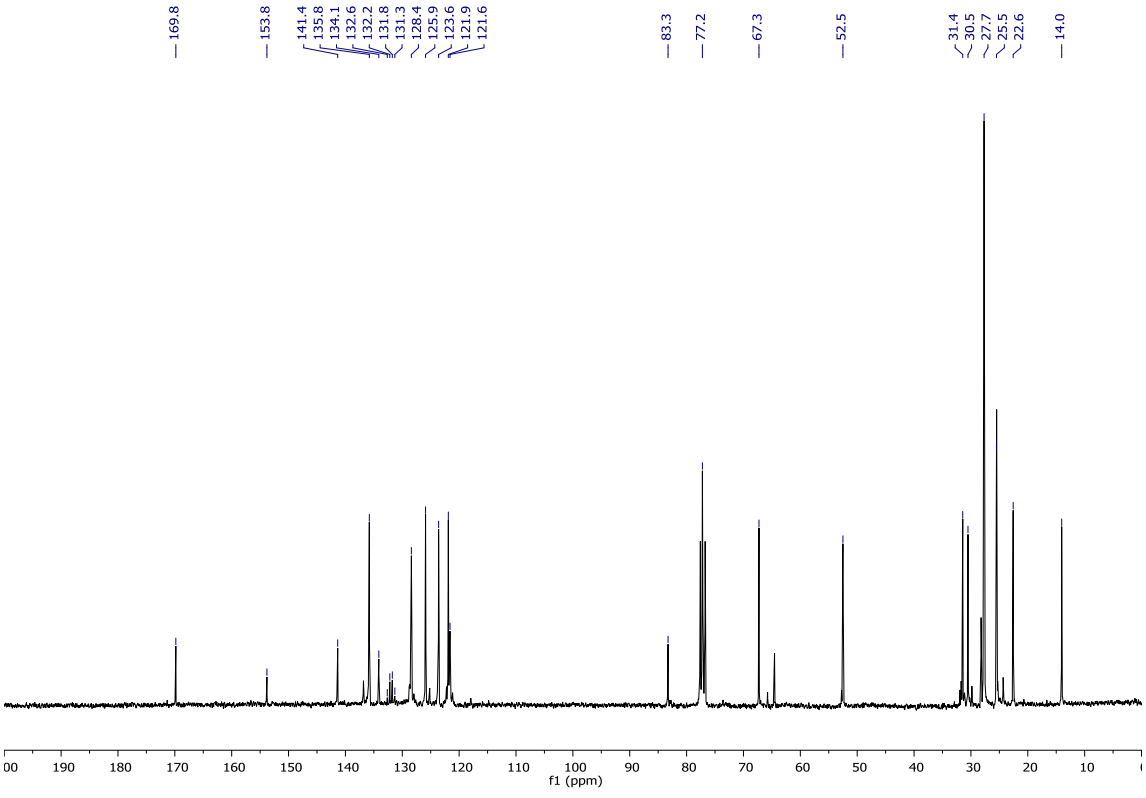

171.8
141.6
135.9
134.0
132.6
132.2
131.8
131.3
128.6
126.0
123.9
122.2
121.6
72.5
68.2
52.6
34.8
19.2
13.9
f1 (ppm)

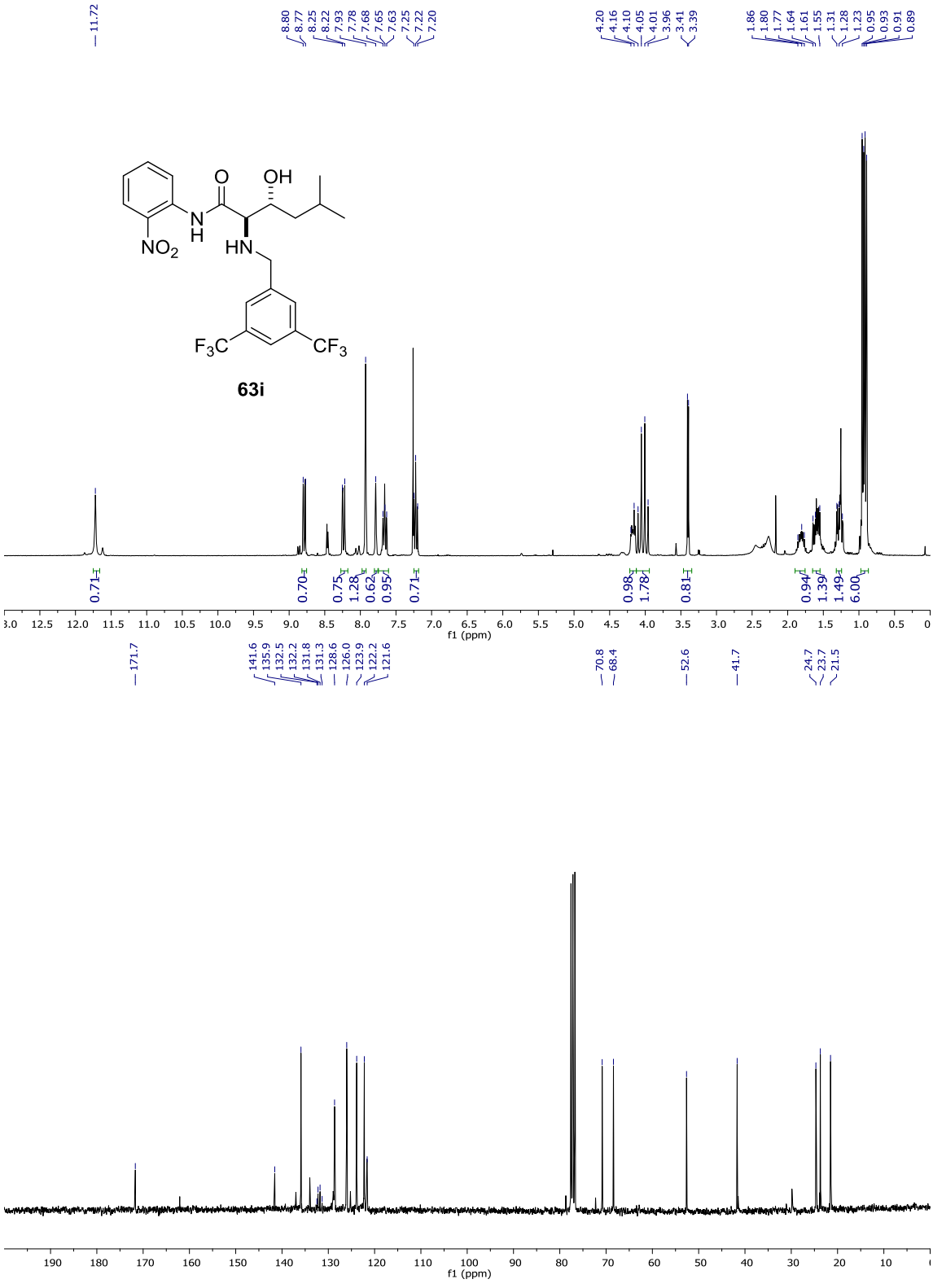

11.79
8.85
8.83
8.20
8.19
7.91
7.77
7.67
7.64
7.61
7.22
7.20
7.17
5.17
5.15
5.13
3.99
3.61
3.60
1.79
1.78
1.74
1.68
1.63
1.49
1.44
1.40
0.94
0.91
0.89
O
OH
N
H
NO2
BocN
F3C
CF3
104h
0.81
0.77
1.05
1.82
1.23
1.26
1.00
1.19
2.01
0.90
2.98
8.56
1.29
3.13
f1 (ppm)
170.0
154.0
141.5
136.0
134.3
132.8
132.4
132.0
131.5
128.6
126.1
123.8
122.1
121.8
118.5
83.5
77.8
67.5
52.7
32.7
27.9
19.3
14.0
f1 (ppm)

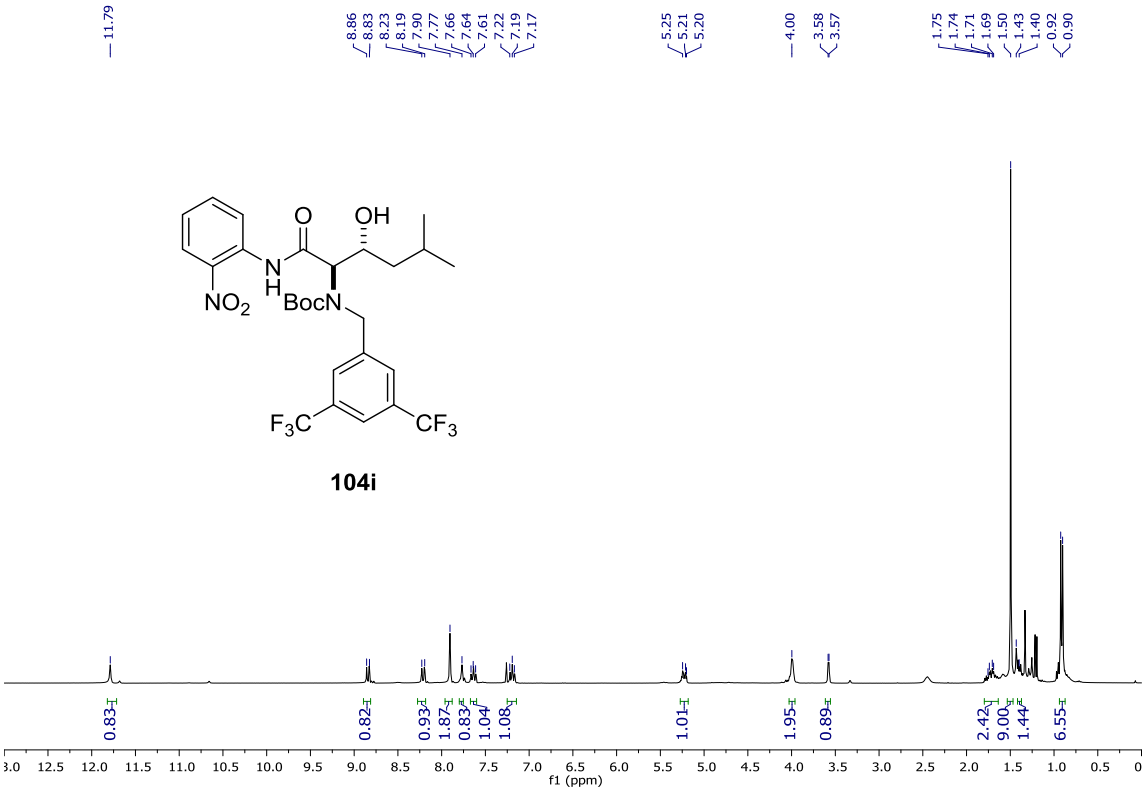

11.74
8.79
8.76
8.76
8.24
8.24
8.21
7.92
7.78
7.68
7.65
7.62
7.24
7.22
7.19
4.09
4.06
4.05
4.00
3.96
3.42
3.41
1.59
1.57
1.50
1.29
1.25
0.92
0.86
0.84
O
OH
N
H
NO2
HN
F3C
CF3
63b
1.00
0.98
0.89
1.96
0.84
1.10
1.00
1.10
2.20
1.08
3.43
6.98
3.39
f1 (ppm)
171.8
141.6
137.0
135.9
134.0
132.6
132.2
131.7
131.3
128.6
126.0
123.9
122.2
121.6
121.6
72.8
68.1
52.6
32.8
31.7
25.7
22.7
14.1
f1 (ppm)

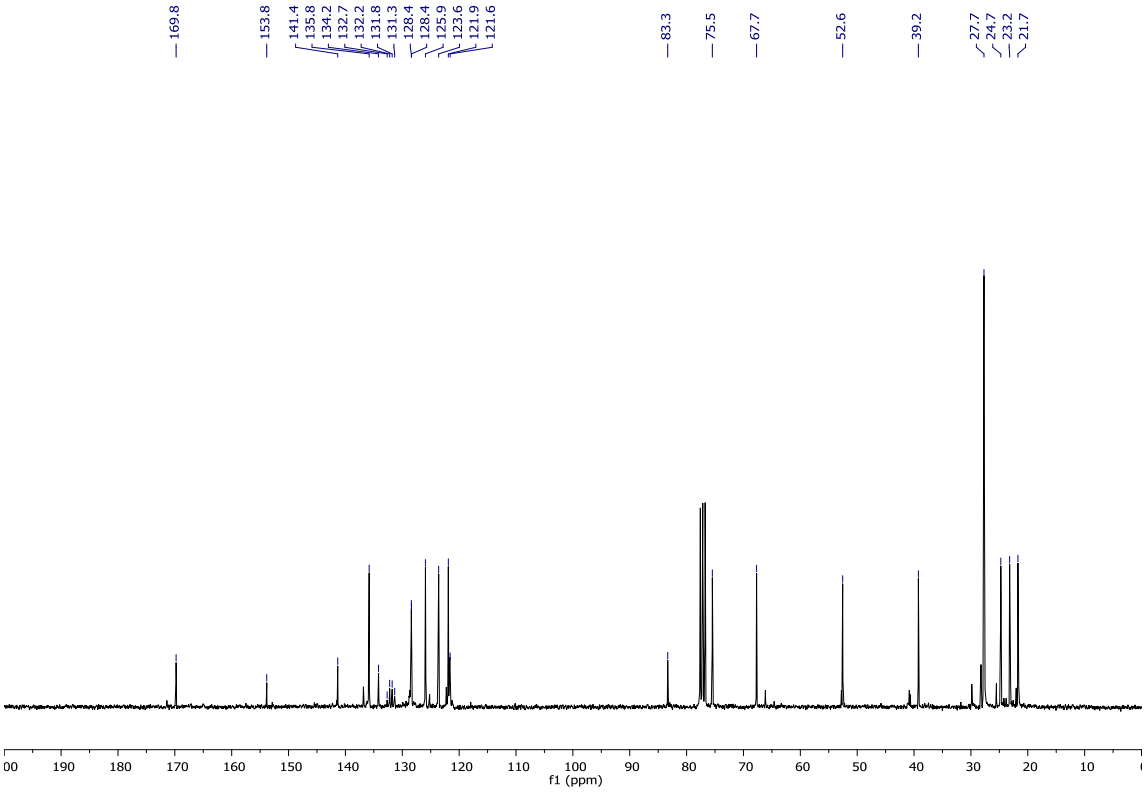

11.78
8.85
8.82
8.23
8.19
7.90
7.77
7.66
7.64
7.61
7.22
7.19
7.16
5.14
5.13
5.10
4.00
3.98
3.60
1.72
1.70
1.49
1.31
1.28
1.26
O
OH
N
H
NO2
BocN
F3C
CF3
0.60
0.58
0.62
1.29
0.50
0.81
0.80
0.77
2.10
0.69
0.75
7.08
4.70
3.00
f1 (ppm)

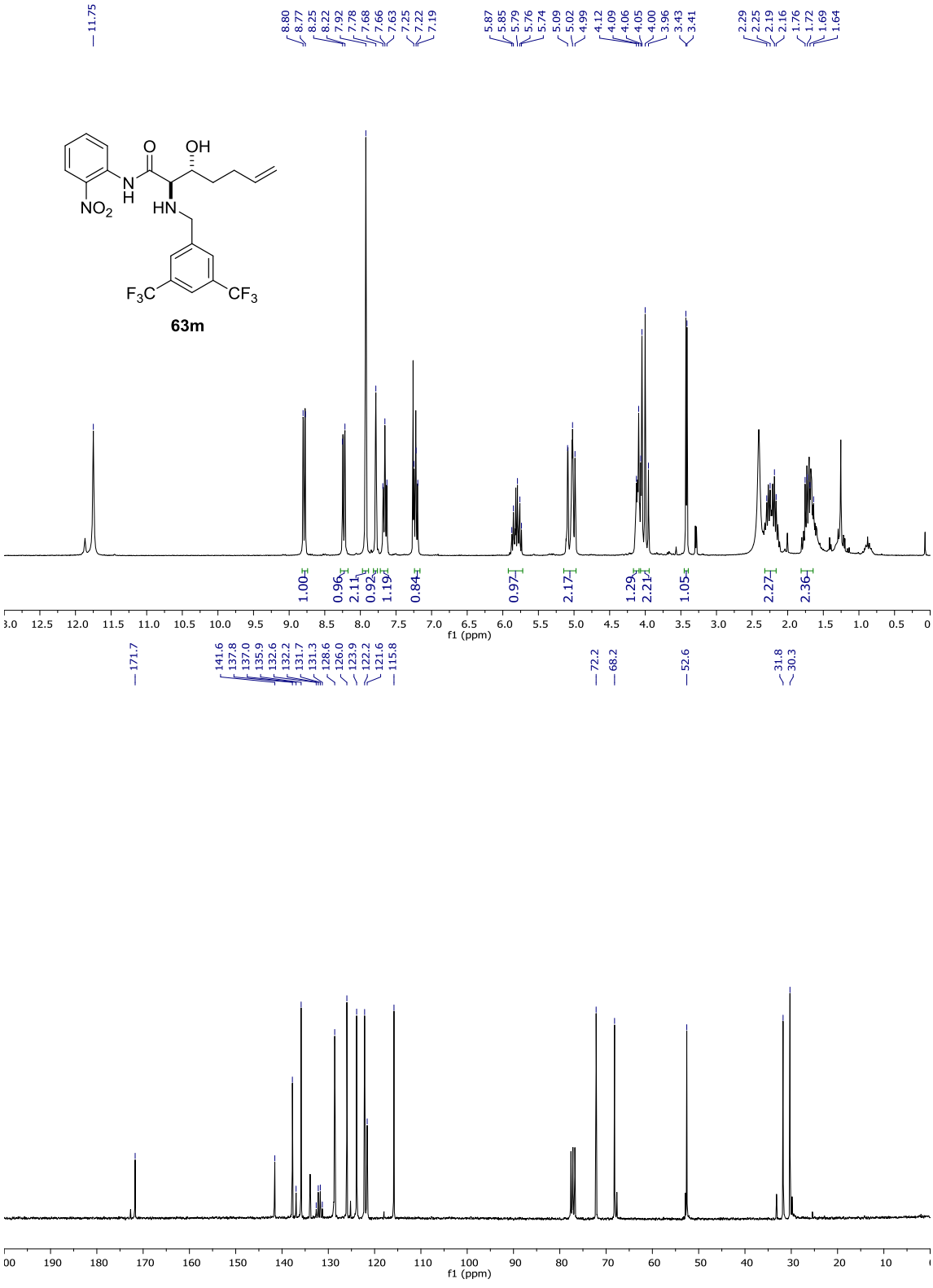
104b

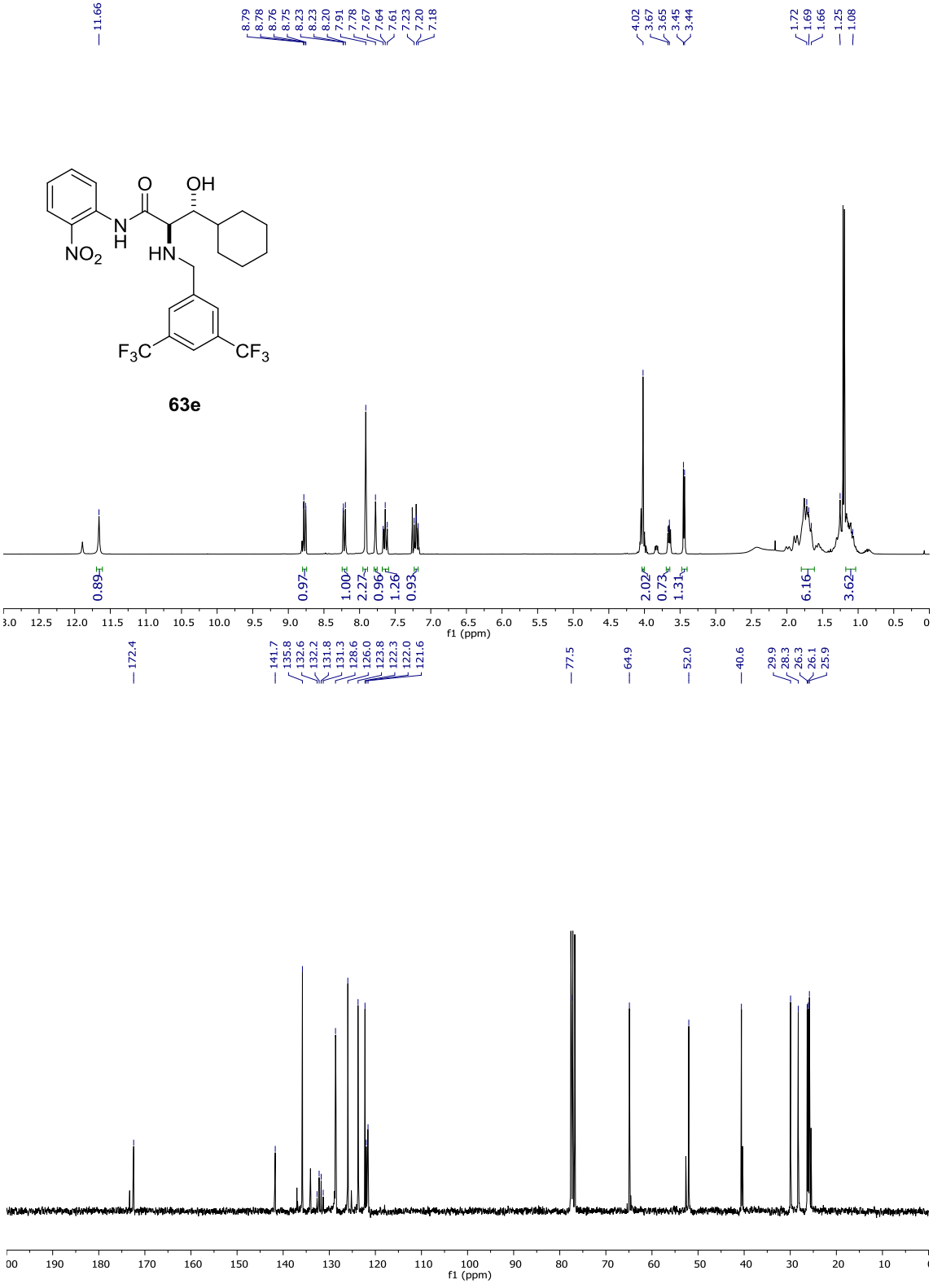

169.8
153.8
141.4
135.8
134.1
132.6
132.2
131.8
131.3
128.4
125.9
123.6
121.9
121.6
83.3
77.2
67.3
52.5
31.4
30.5
27.7
25.5
22.6
14.0
f1 (ppm)

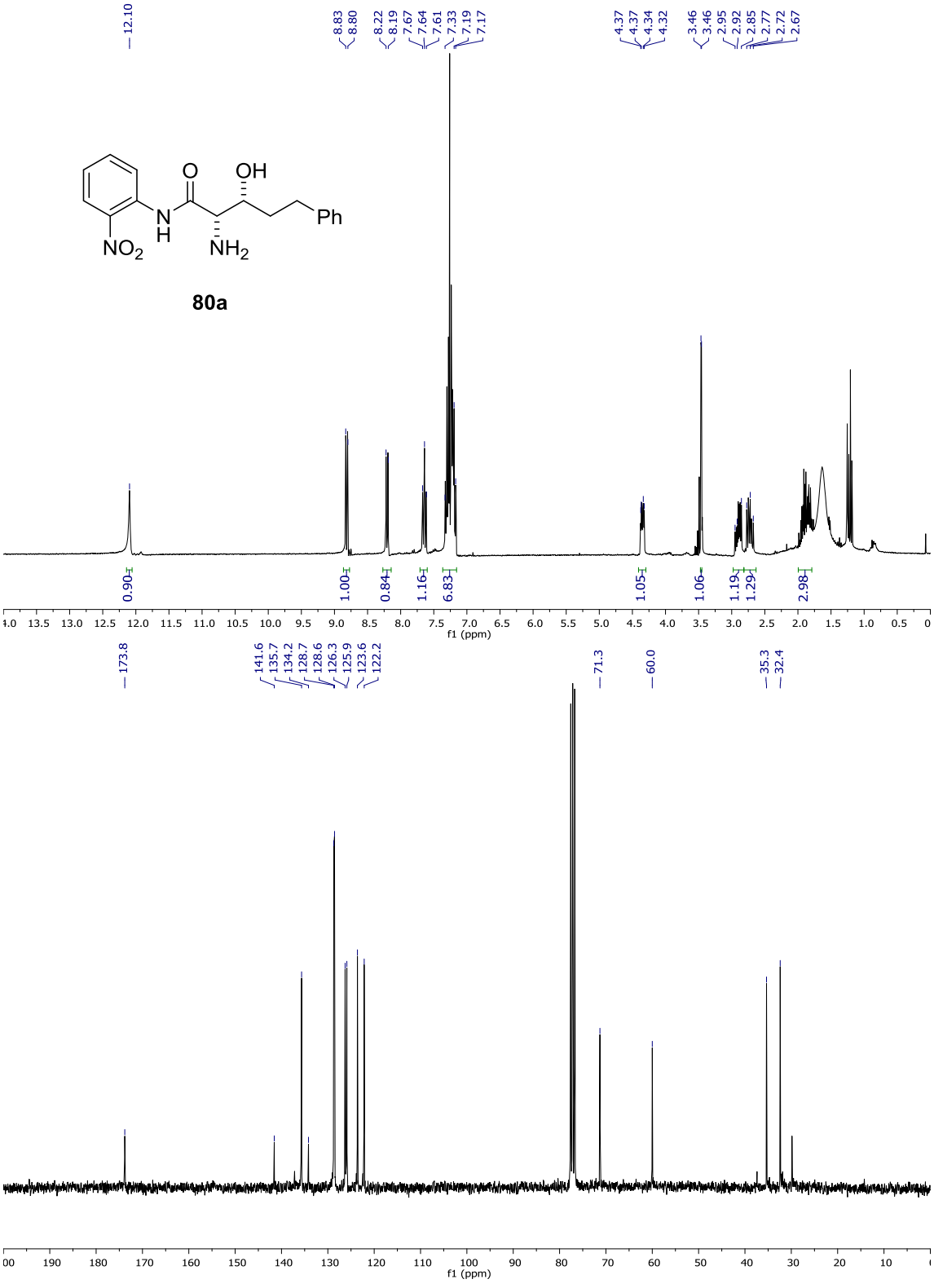

11.72
8.80
8.77
8.25
8.22
7.93
7.78
7.68
7.65
7.63
7.25
7.22
7.20
4.20
4.16
4.10
4.05
4.01
3.96
3.41
3.39
1.86
1.80
1.77
1.64
1.61
1.55
1.31
1.28
1.23
0.95
0.93
0.91
0.89
O
OH
N
H
HN
NO2
F3C
CF3
63i
0.71
0.70
0.75
1.28
0.62
0.95
0.71
0.98
1.78
0.81
0.94
1.39
1.49
6.00
f1 (ppm)
171.7
141.6
135.9
132.5
132.2
131.8
131.3
128.6
126.0
123.9
122.2
121.6
70.8
68.4
52.6
41.7
24.7
23.7
21.5
f1 (ppm)

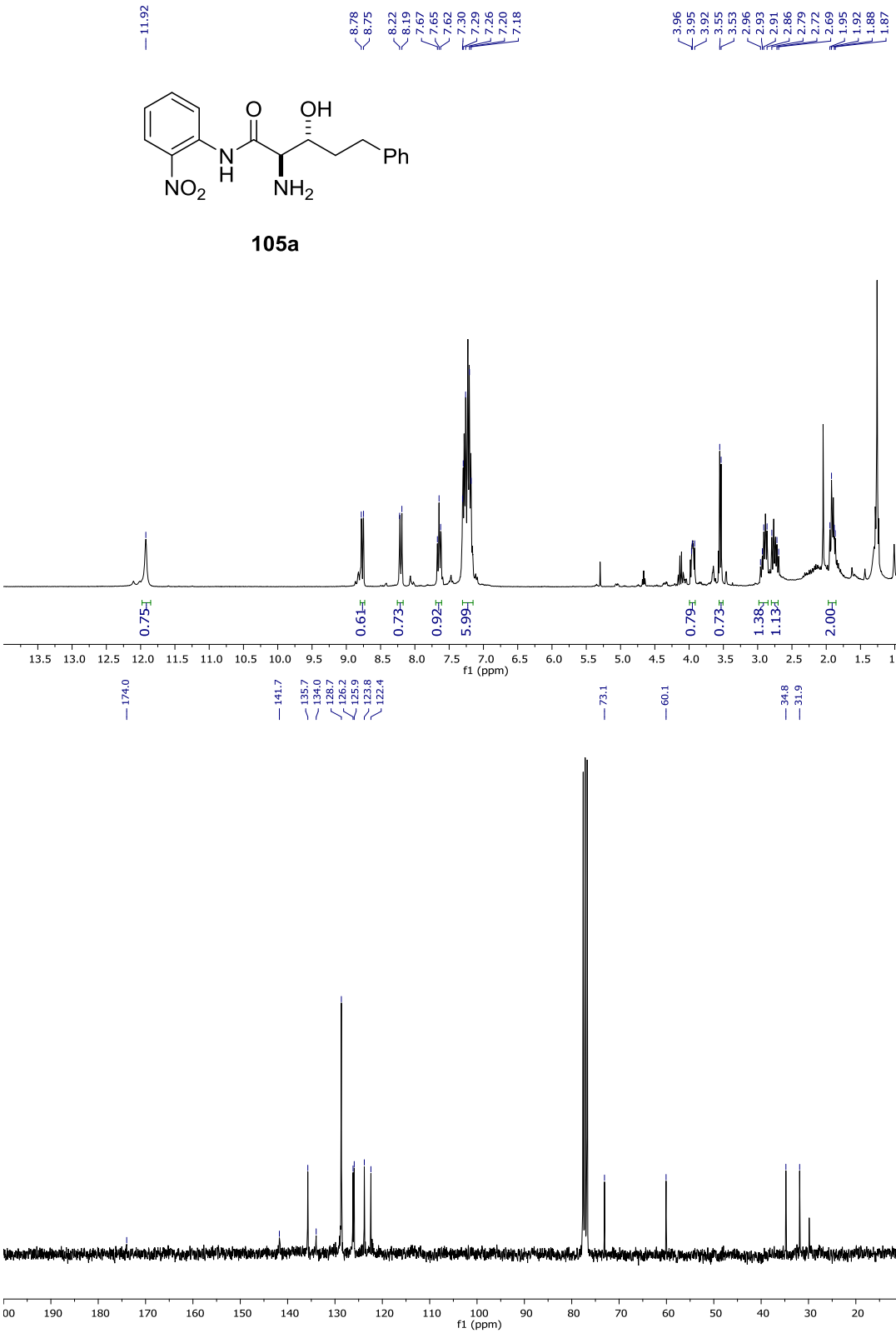

11.79
8.86
8.83
8.23
8.19
7.90
7.77
7.66
7.64
7.61
7.22
7.19
7.17
5.25
5.21
5.20
4.00
3.58
3.57
1.75
1.74
1.71
1.69
1.50
1.43
1.40
0.92
0.90
O
OH
N
H
NO2
BocN
F3C
CF3
104i
0.83
0.82
0.93
1.87
0.83
1.04
1.08
1.01
1.95
0.89
2.42
9.00
1.44
6.55
f1 (ppm)

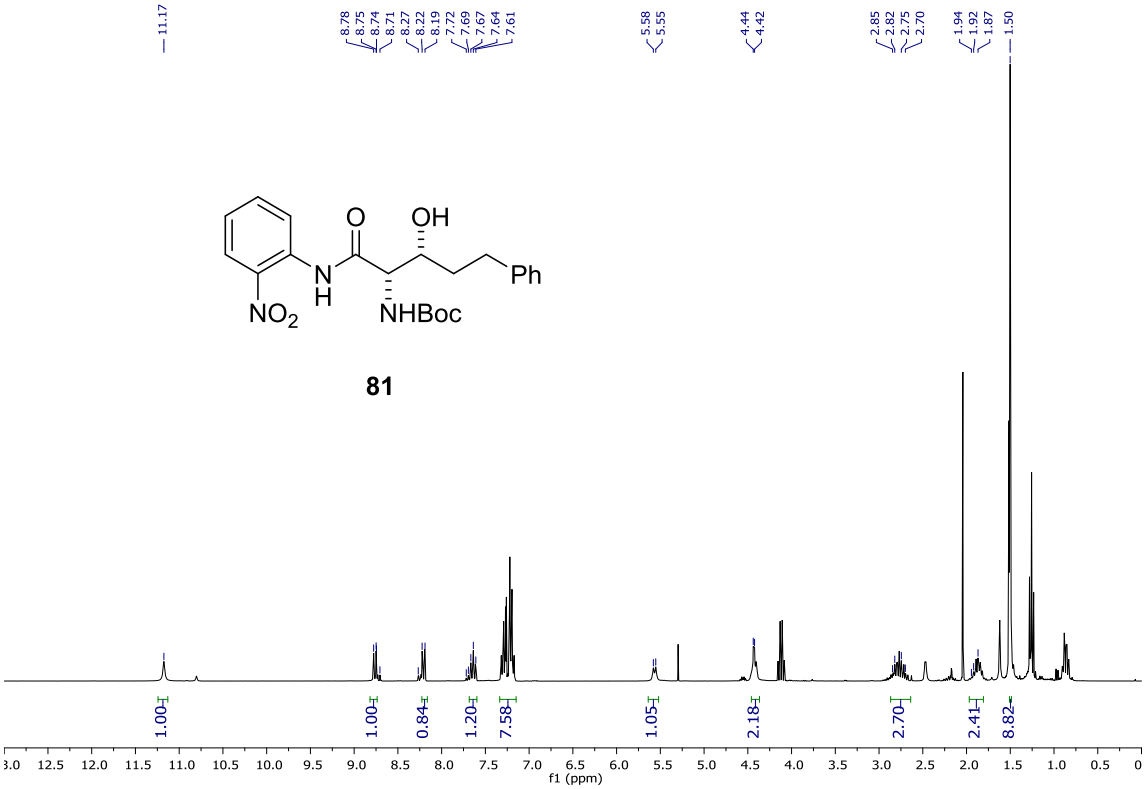

169.8
153.8
141.4
135.8
134.2
132.7
132.2
131.8
131.3
128.4
128.4
125.9
123.6
121.9
121.6
83.3
75.5
67.7
52.6
39.2
27.7
24.7
23.2
21.7
f1 (ppm)


11.75
8.80
8.77
8.25
8.22
7.92
7.78
7.68
7.66
7.63
7.25
7.22
7.19
5.87
5.85
5.79
5.76
5.74
5.09
5.02
4.99
4.12
4.09
4.06
4.05
4.00
3.96
3.43
3.41
2.29
2.25
2.19
2.16
1.76
1.72
1.69
1.64
O
OH
N
H
NO2
HN
F3C
CF3
63m
1.00
0.96
2.11
0.92
1.19
0.84
0.97
2.17
1.29
2.21
1.05
2.27
2.36
f1 (ppm)
171.7
141.6
137.8
137.0
135.9
132.6
132.2
131.7
131.3
128.6
126.0
123.9
122.2
121.6
115.8
72.2
68.2
52.6
31.8
30.3
f1 (ppm)

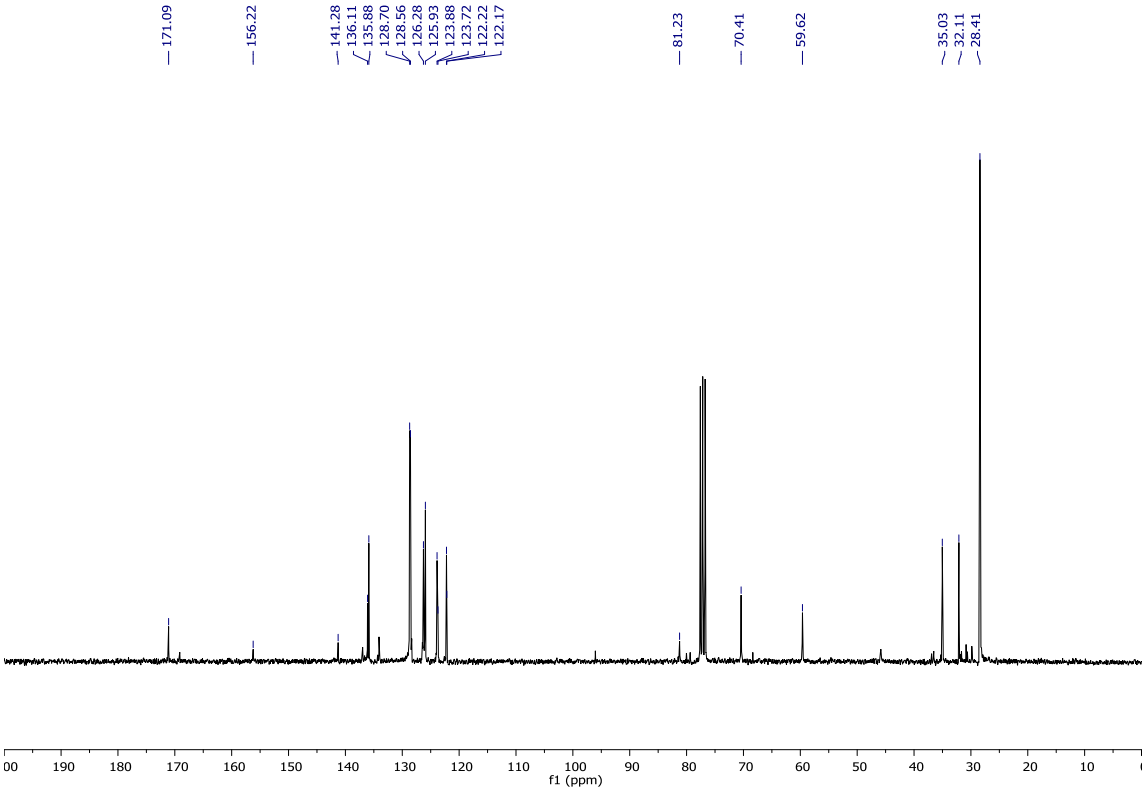

11.66
8.79
8.78
8.76
8.75
8.23
8.23
8.20
7.91
7.78
7.67
7.64
7.61
7.23
7.20
7.18
4.02
3.67
3.65
3.45
3.44
1.72
1.69
1.66
1.25
1.08
O
OH
N
H
HN
NO2
F3C
CF3
63e
0.89
0.97
1.00
2.27
0.96
1.26
0.93
2.02
0.73
1.31
6.16
3.62
f1 (ppm)
172.4
141.7
135.8
132.6
132.2
131.8
131.3
128.6
126.0
123.8
122.3
122.0
121.6
77.5
64.9
52.0
40.6
29.9
28.3
26.3
26.1
25.9
f1 (ppm)

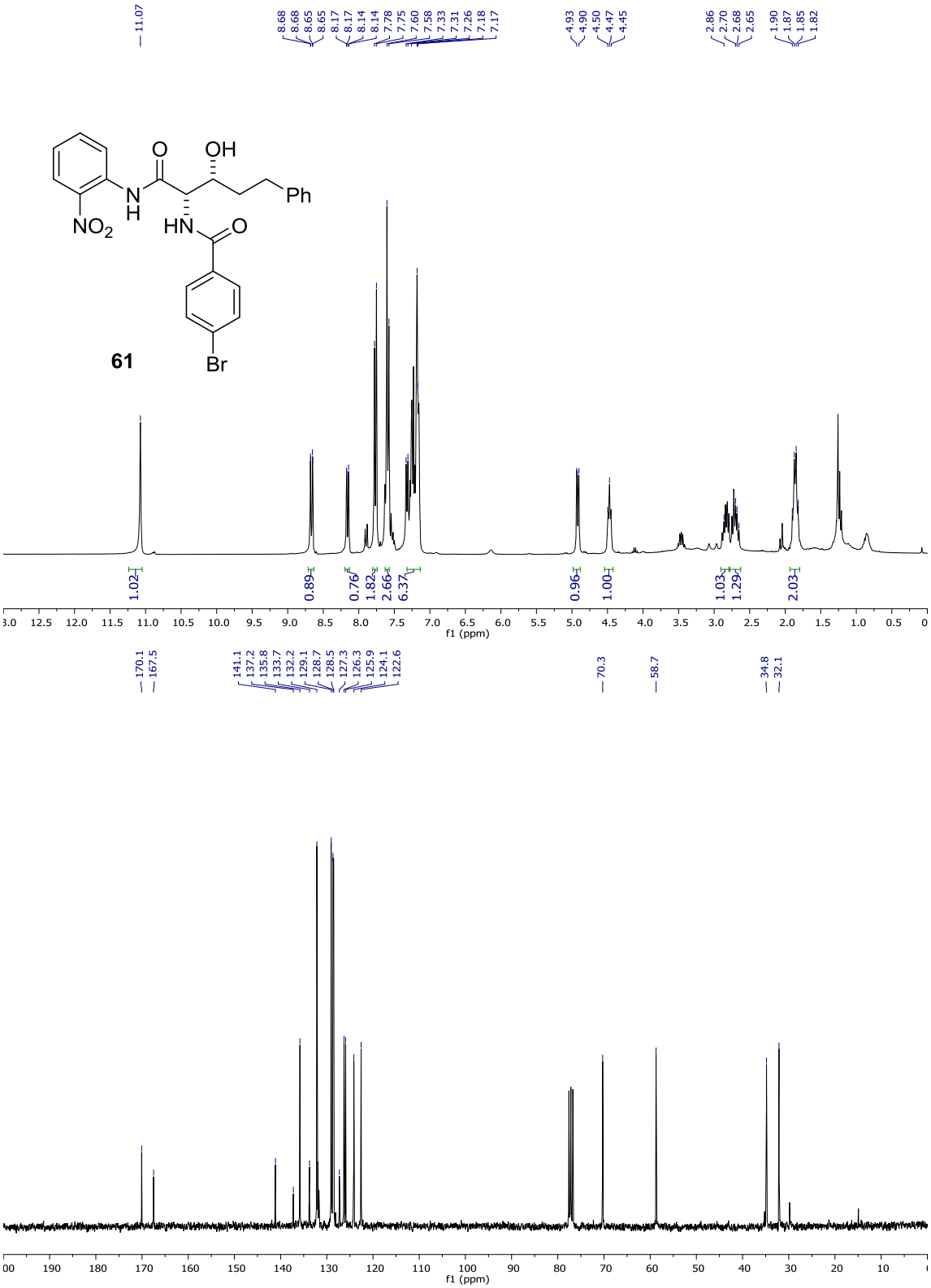

12.10
8.83
8.80
8.22
8.19
7.67
7.64
7.61
7.33
7.19
7.17
4.37
4.37
4.34
4.32
3.46
3.46
2.95
2.92
2.85
2.77
2.72
2.67
O
OH
N
H
Ph
NO2
NH2
80a
0.90
1.00
0.84
1.16
6.83
1.05
1.06
1.19
1.29
2.98
f1 (ppm)
173.8
141.6
135.7
134.2
128.7
128.6
126.3
125.9
123.6
122.2
71.3
60.0
35.3
32.4
f1 (ppm)

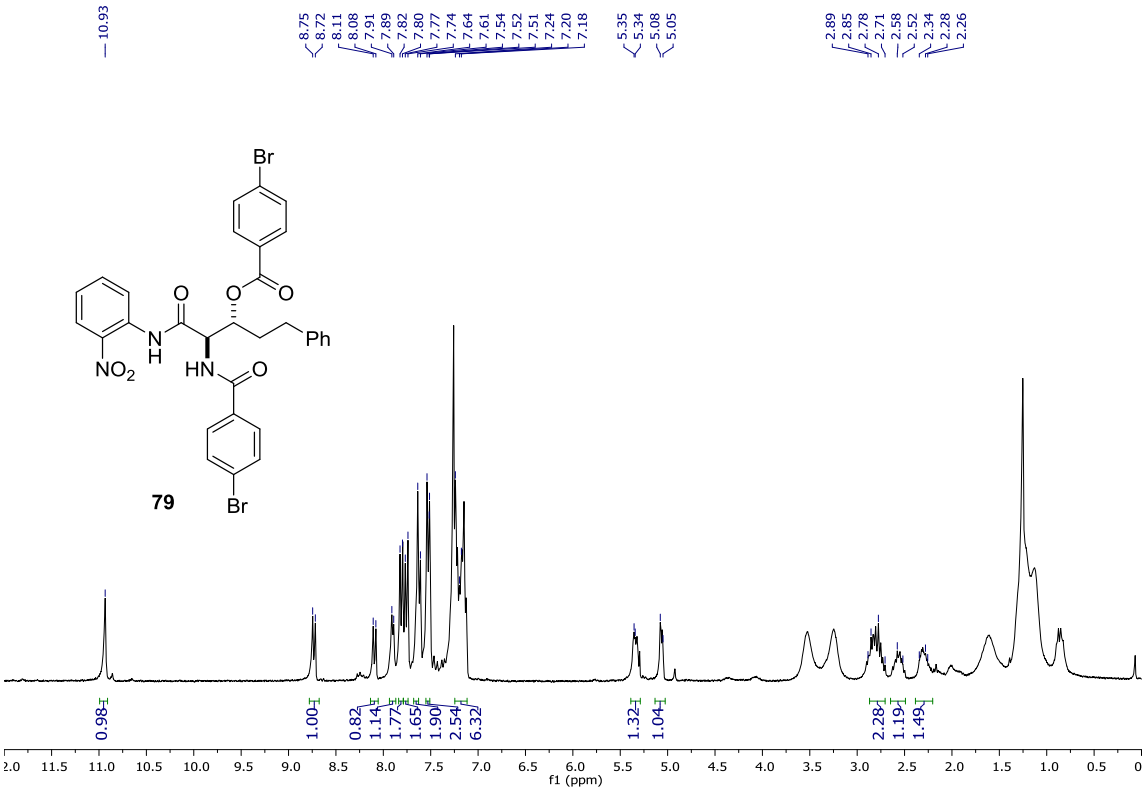

11.92
8.78
8.75
8.22
8.19
7.67
7.65
7.62
7.30
7.29
7.26
7.20
7.18
3.96
3.95
3.92
3.55
3.53
2.96
2.93
2.91
2.86
2.79
2.72
2.69
1.95
1.92
1.88
1.87
O
OH
N
H
Ph
NO2
NH2
105a
0.75
0.61
0.73
0.92
5.99
0.79
0.73
1.38
1.13
2.00
f1 (ppm)
174.0
141.7
135.7
134.0
128.7
126.2
125.9
123.8
122.4
73.1
60.1
34.8
31.9
f1 (ppm)

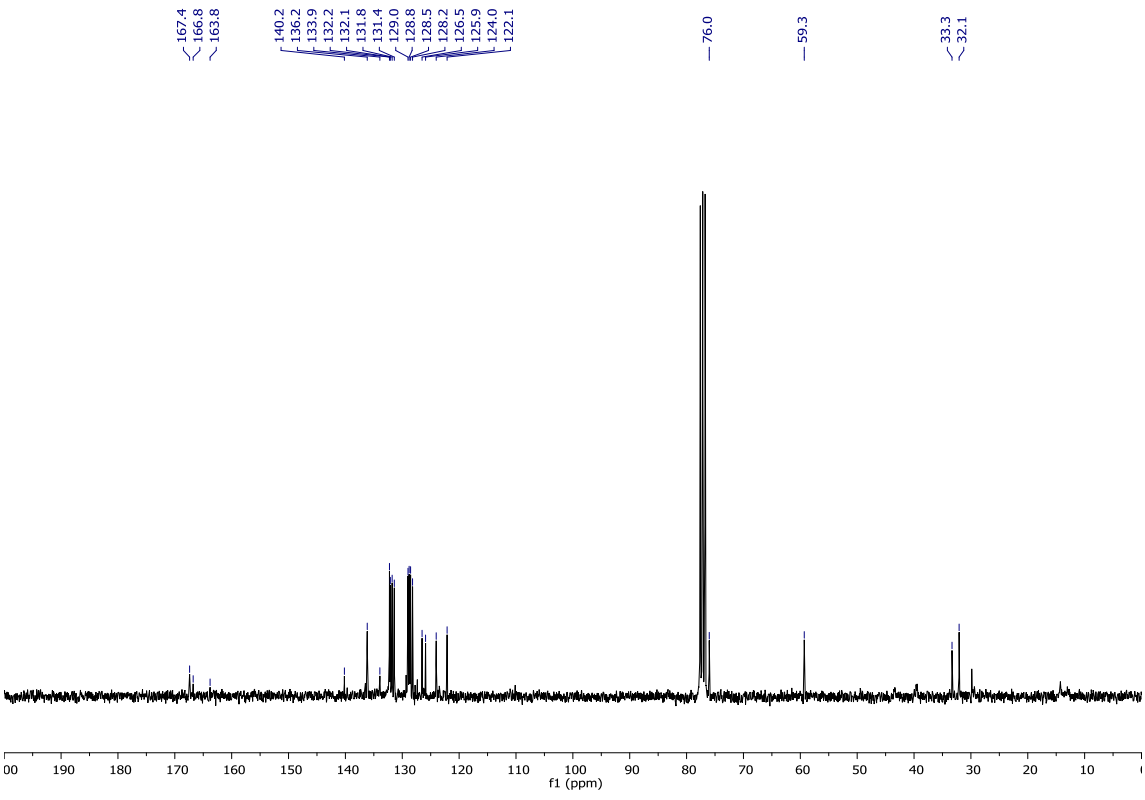

11.17
8.78
8.75
8.74
8.71
8.27
8.22
8.19
7.72
7.69
7.67
7.64
7.61
5.58
5.55
4.44
4.42
2.85
2.82
2.75
2.70
1.94
1.92
1.87
1.50
O
OH
N
H
Ph
NO2
NHBoc
1.00
1.00
0.84
1.20
7.58
1.05
2.18
2.70
2.41
8.82
f1 (ppm)

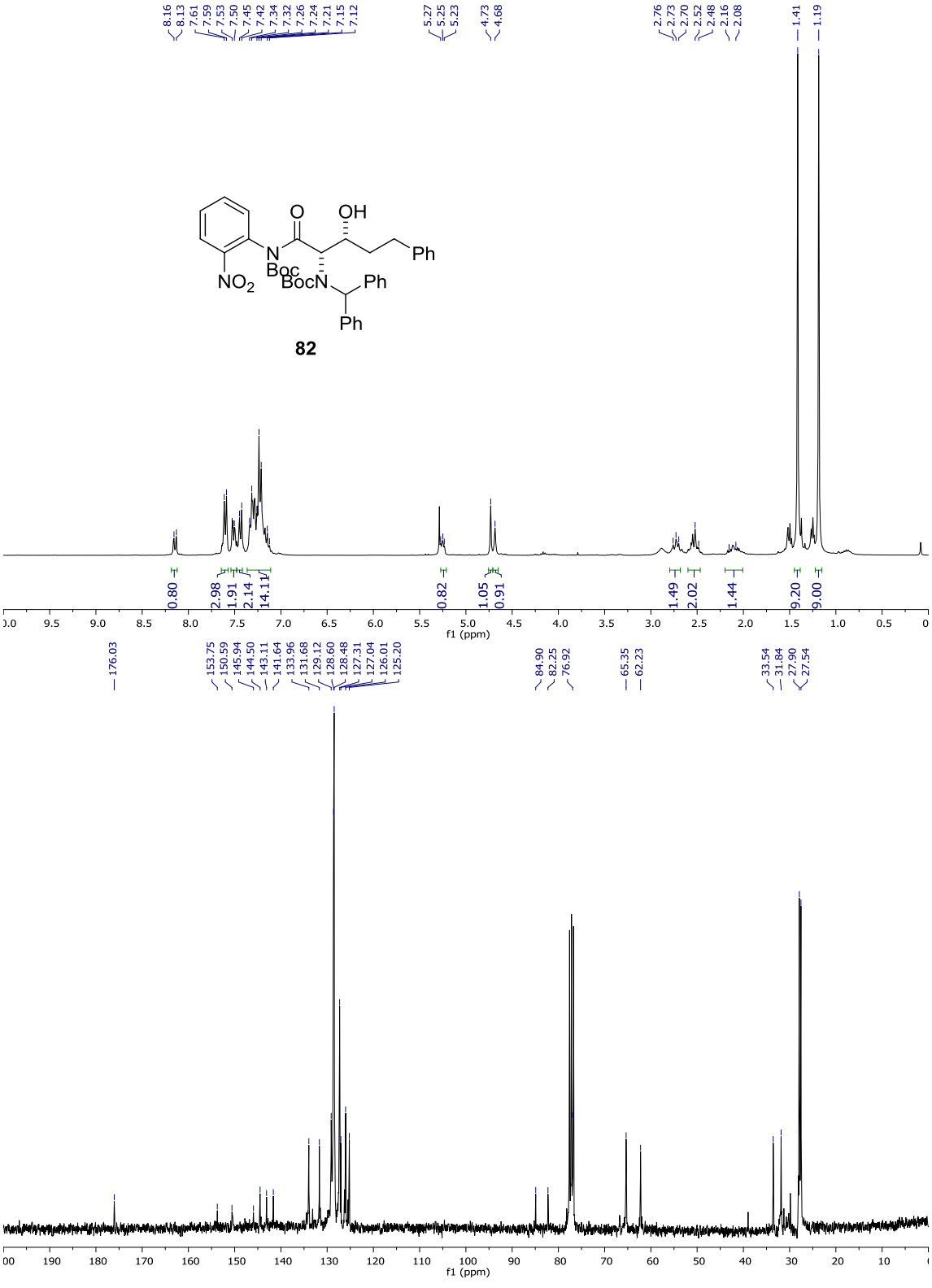
81

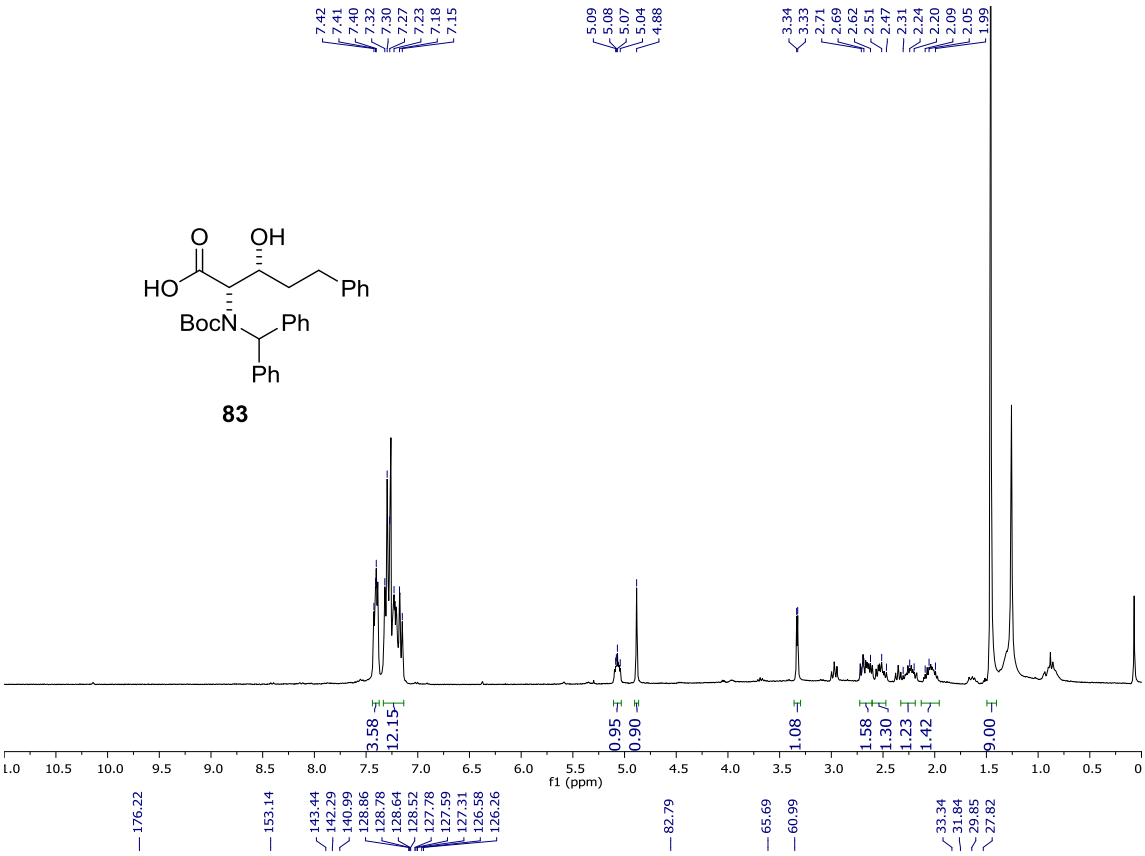

171.09
156.22
141.28
136.11
135.88
128.70
128.56
126.28
125.93
123.88
123.72
122.22
122.17
81.23
70.41
59.62
35.03
32.11
28.41
f1 (ppm)

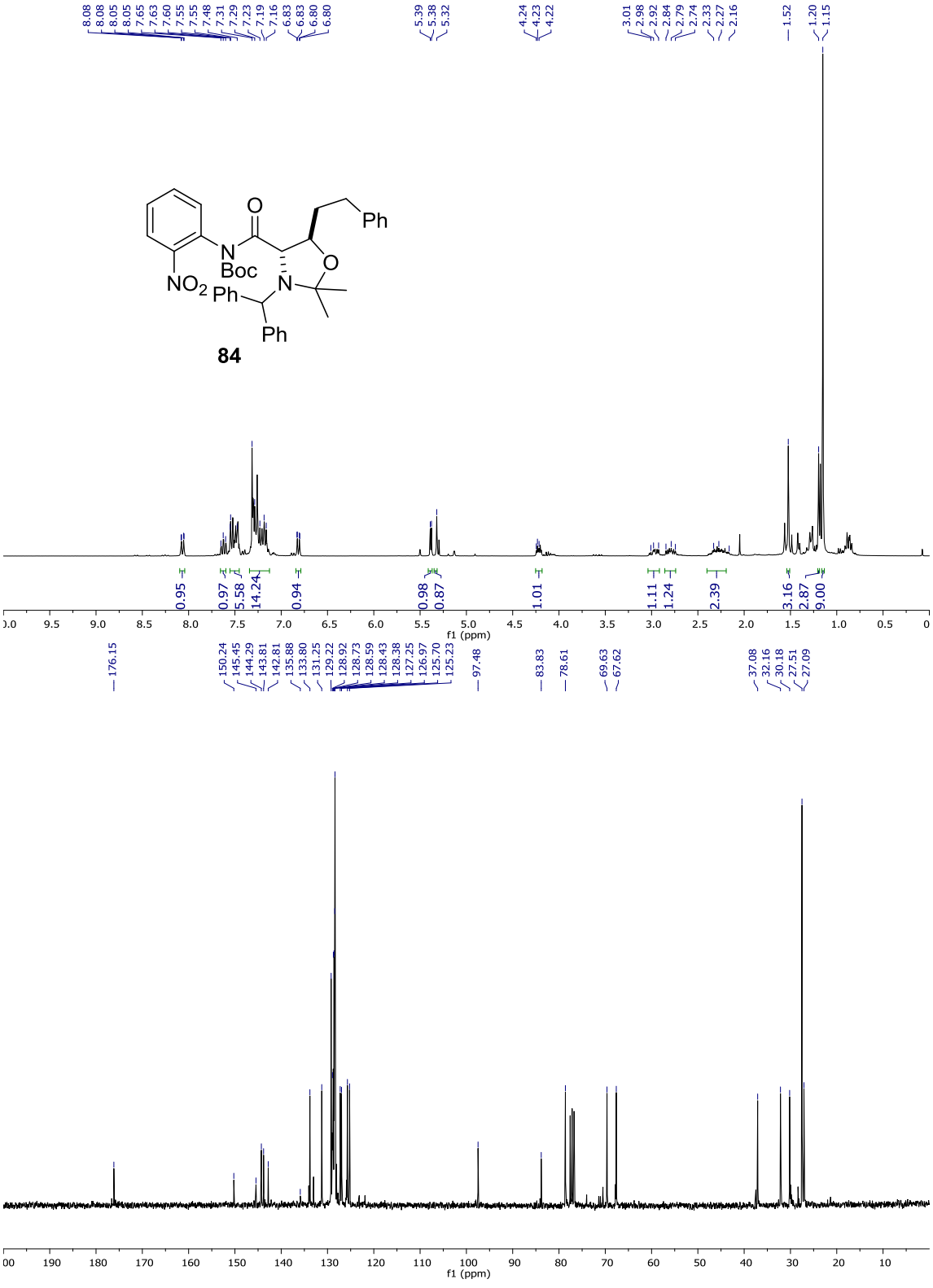

11.07
8.68
8.68
8.65
8.65
8.17
8.17
8.14
8.14
7.78
7.75
7.60
7.58
7.33
7.31
7.26
7.18
7.17
4.93
4.90
4.50
4.47
4.45
2.86
2.70
2.68
2.65
1.90
1.87
1.85
1.82
O
OH
N
H
Ph
NO2
HN
O
Br
61
1.02
0.89
0.76
1.82
2.66
6.37
0.96
1.00
1.03
1.29
2.03
f1 (ppm)
170.1
167.5
141.1
137.2
135.8
133.7
132.2
129.1
128.7
128.5
127.3
126.3
125.9
124.1
122.6
70.3
58.7
34.8
32.1
f1 (ppm)

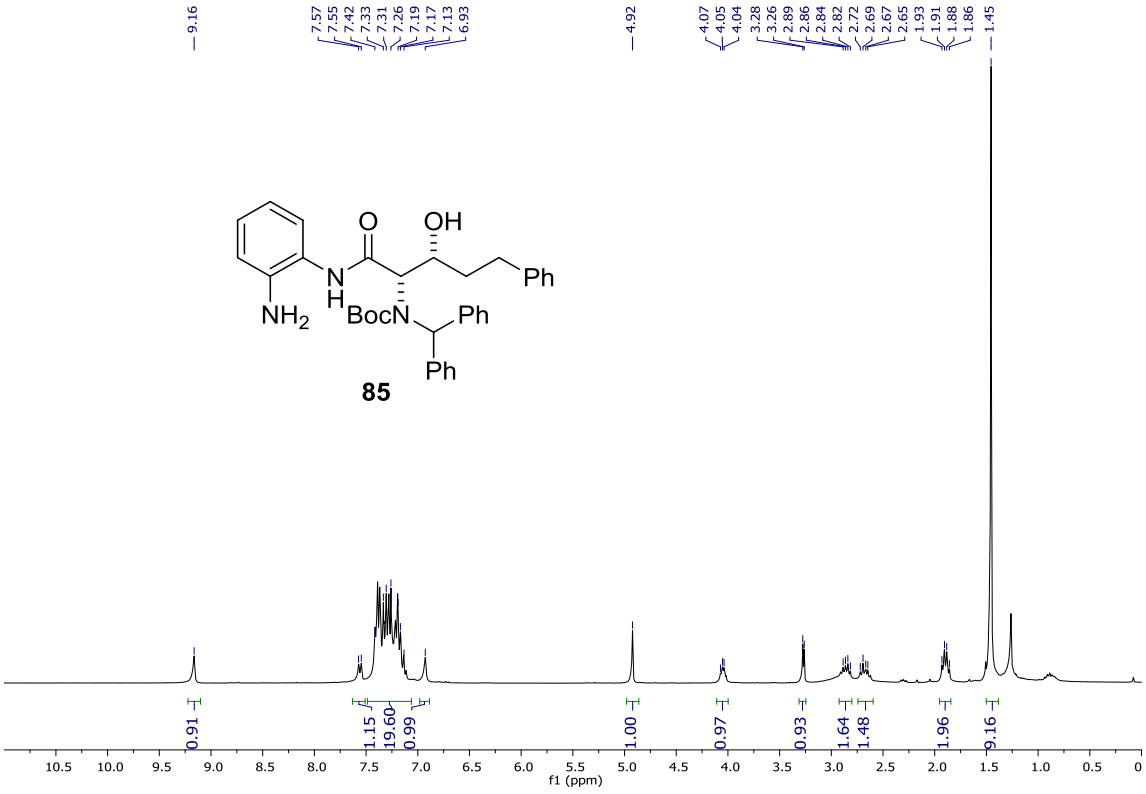

10.93
8.75
8.72
8.11
8.08
7.91
7.89
7.82
7.80
7.77
7.74
7.64
7.61
7.54
7.52
7.51
7.24
7.20
7.18
5.35
5.34
5.08
5.05
2.89
2.85
2.78
2.71
2.58
2.52
2.34
2.28
2.26
Br
O
O
O
N
H
Ph
NO2
HN
O
Br
79
0.98
1.00
0.82
1.14
1.77
1.65
1.90
2.54
6.32
1.32
1.04
2.28
1.19
1.49
f1 (ppm)

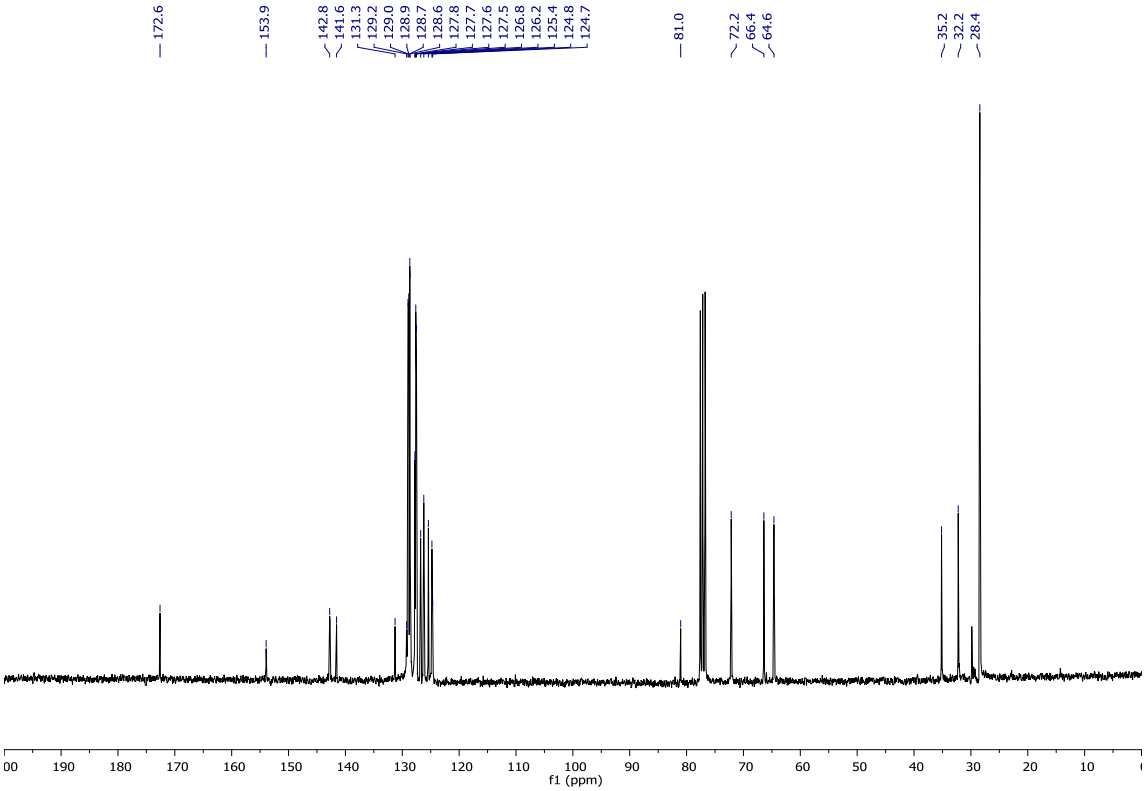

167.4
166.8
163.8
140.2
136.2
133.9
132.2
132.1
131.8
131.4
129.0
128.8
128.5
128.2
126.5
125.9
124.0
122.1
76.0
59.3
33.3
32.1
f1 (ppm)

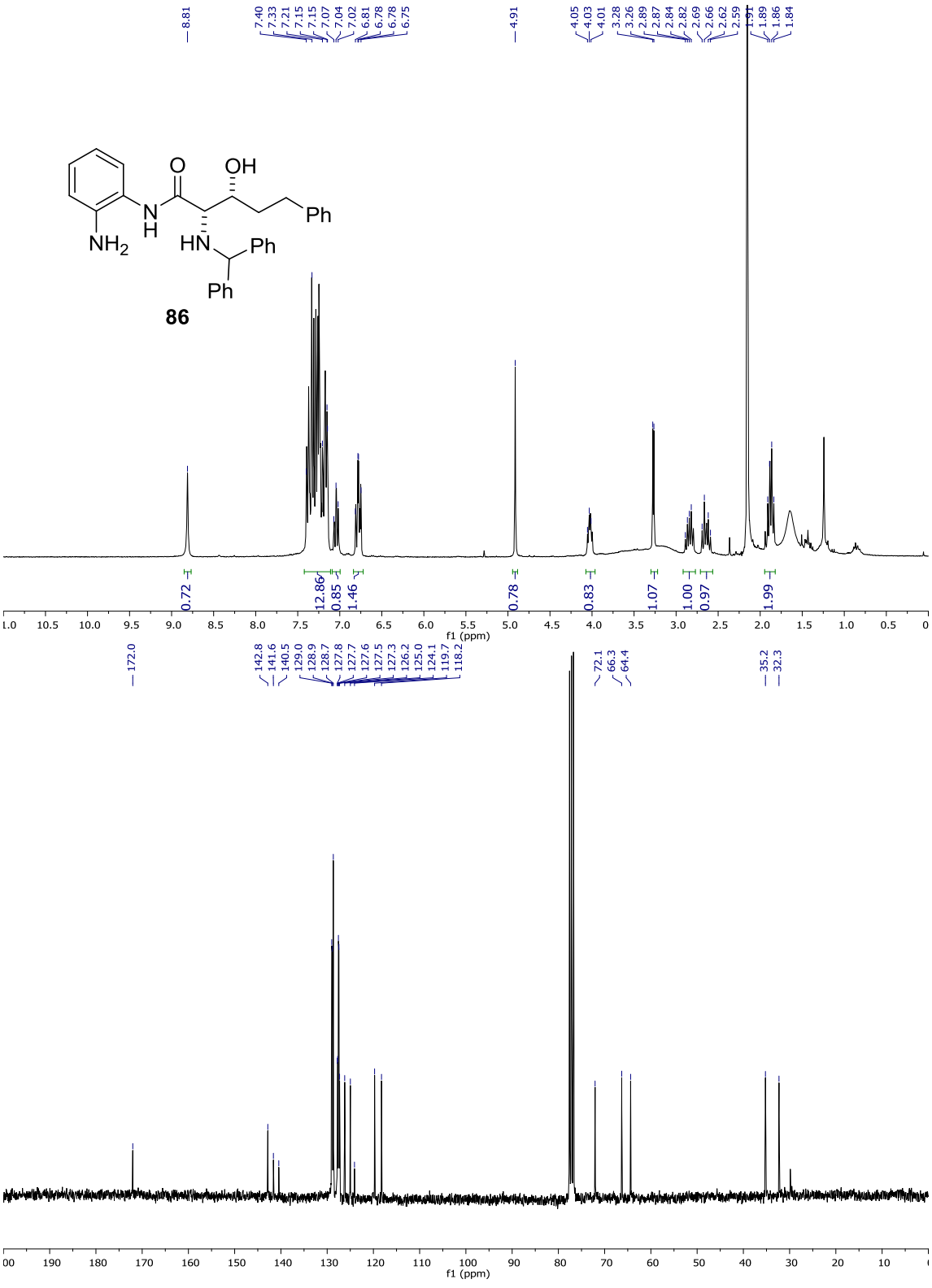

8.16
8.13
7.61
7.59
7.53
7.50
7.45
7.42
7.34
7.32
7.26
7.24
7.21
7.15
7.12
5.27
5.25
5.23
4.73
4.68
2.76
2.73
2.70
2.52
2.48
2.16
2.08
1.41
1.19
O
OH
N
Boc
Ph
NO2
BocN
Ph
Ph
82
0.80
2.98
1.91
2.14
14.11
0.82
1.05
0.91
1.49
2.02
1.44
9.20
9.00
f1 (ppm)
176.03
153.75
150.59
145.94
144.50
143.11
141.64
133.96
131.68
129.12
128.60
128.48
127.31
127.04
126.01
125.20
84.90
82.25
76.92
65.35
62.23
33.54
31.84
27.90
27.54
f1 (ppm)

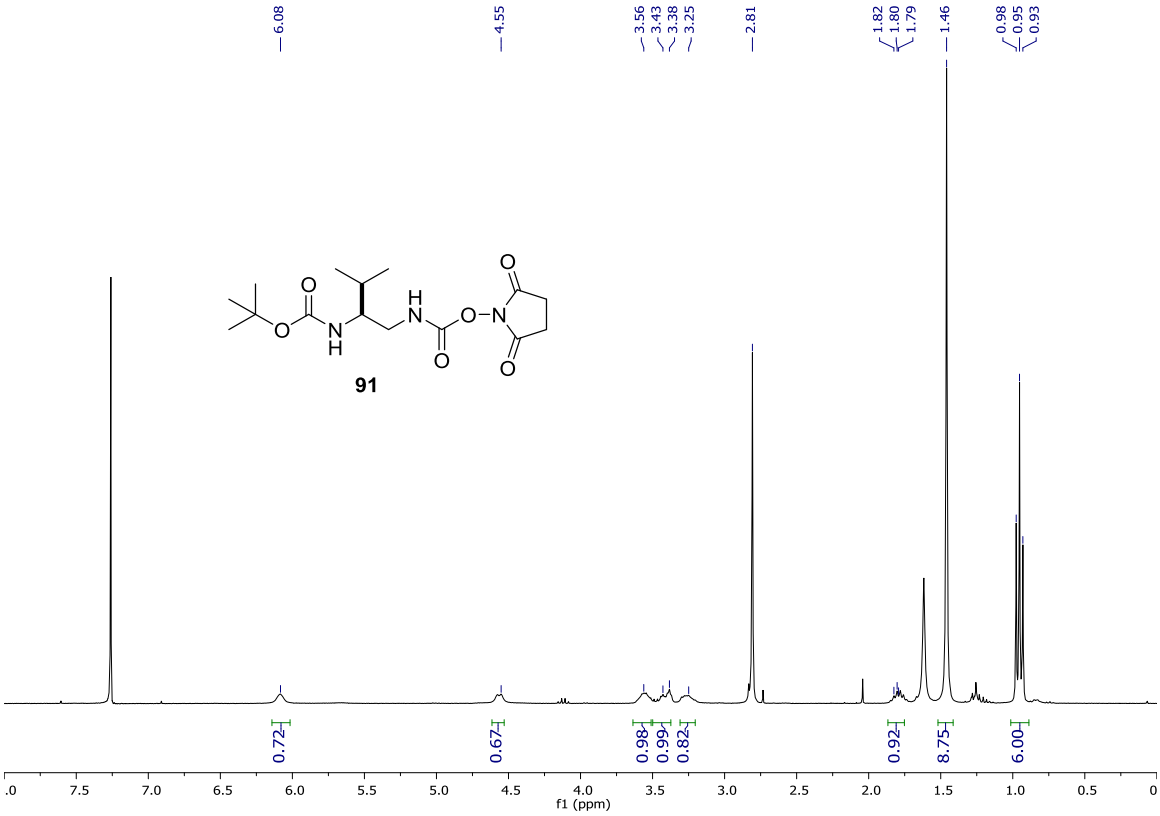

7.42
7.41
7.40
7.32
7.30
7.27
7.23
7.18
7.15
5.09
5.08
5.07
5.04
4.88
3.34
3.33
2.71
2.69
2.62
2.51
2.47
2.31
2.24
2.20
2.09
2.05
1.99
O
OH
HO
Ph
BocN
Ph
Ph
83
3.58
12.15
0.95
0.90
1.08
1.58
1.30
1.23
1.42
9.00
f1 (ppm)
176.22
153.14
143.44
142.29
140.99
128.86
128.78
128.64
128.52
127.78
127.59
127.31
126.58
126.26
82.79
65.69
60.99
33.34
31.84
29.85
27.82
f1 (ppm)


8.08
8.08
8.05
8.05
7.65
7.63
7.60
7.55
7.55
7.48
7.31
7.29
7.23
7.19
7.16
6.83
6.83
6.80
6.80
5.39
5.38
5.32
4.24
4.23
4.22
3.01
2.98
2.92
2.84
2.79
2.74
2.33
2.27
2.16
1.52
1.20
1.15
O
Ph
N
Boc
O
NO2
Ph
N
Ph
84
0.95
0.97
5.58
14.24
0.94
0.98
0.87
1.01
1.11
1.24
2.39
3.16
2.87
9.00
f1 (ppm)
176.15
150.24
145.45
144.29
143.81
142.81
135.88
133.80
131.25
129.22
128.92
128.73
128.59
128.43
128.38
127.25
126.97
125.70
125.23
97.48
83.83
78.61
69.63
67.62
37.08
32.16
30.18
27.51
27.09
f1 (ppm)

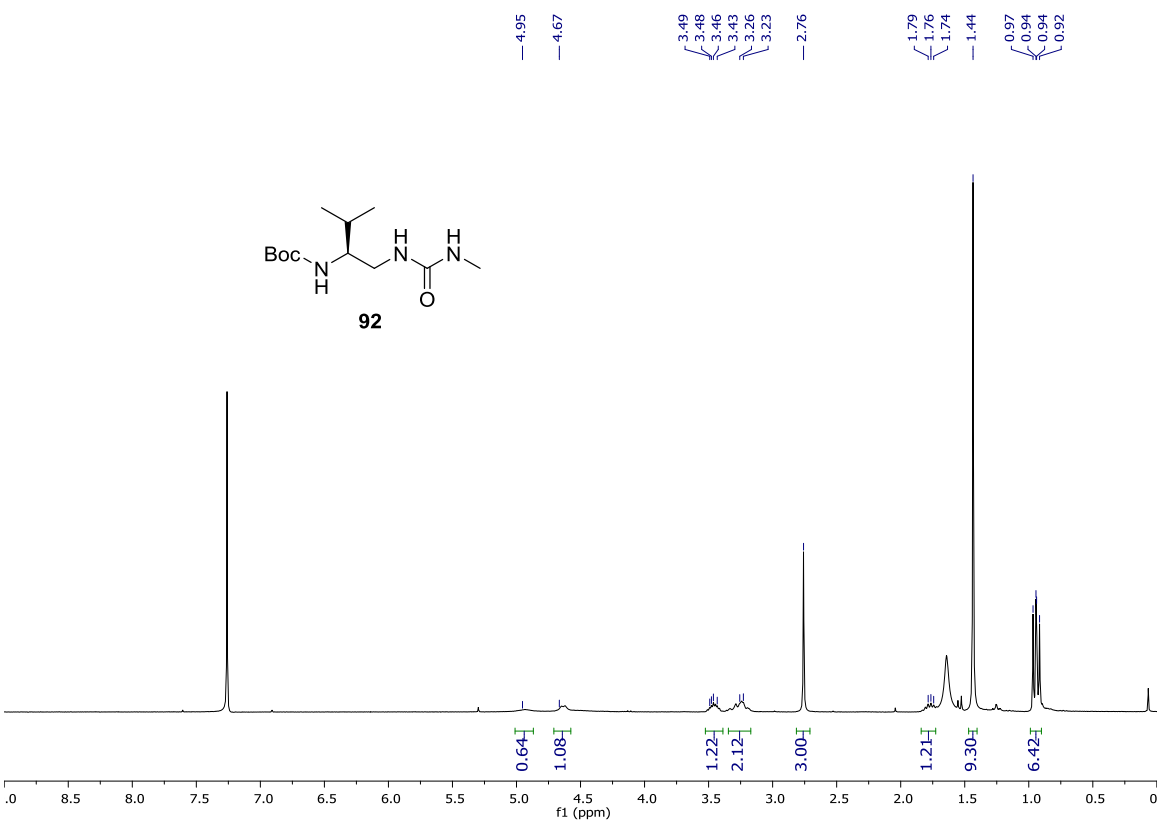

9.16
7.57
7.55
7.42
7.33
7.31
7.26
7.19
7.17
7.13
6.93
4.92
4.07
4.05
4.04
3.28
3.26
2.89
2.86
2.84
2.82
2.72
2.69
2.67
2.65
1.93
1.91
1.88
1.86
1.45
O
OH
N
H
Ph
NH2
BocN
Ph
Ph
85
0.91
1.15
19.60
0.99
1.00
0.97
0.93
1.64
1.48
1.96
9.16
f1 (ppm)


172.6
153.9
142.8
141.6
131.3
129.2
129.0
128.9
128.7
128.6
127.8
127.7
127.6
127.5
126.8
126.2
125.4
124.8
124.7
81.0
72.2
66.4
64.6
35.2
32.2
28.4
f1 (ppm)

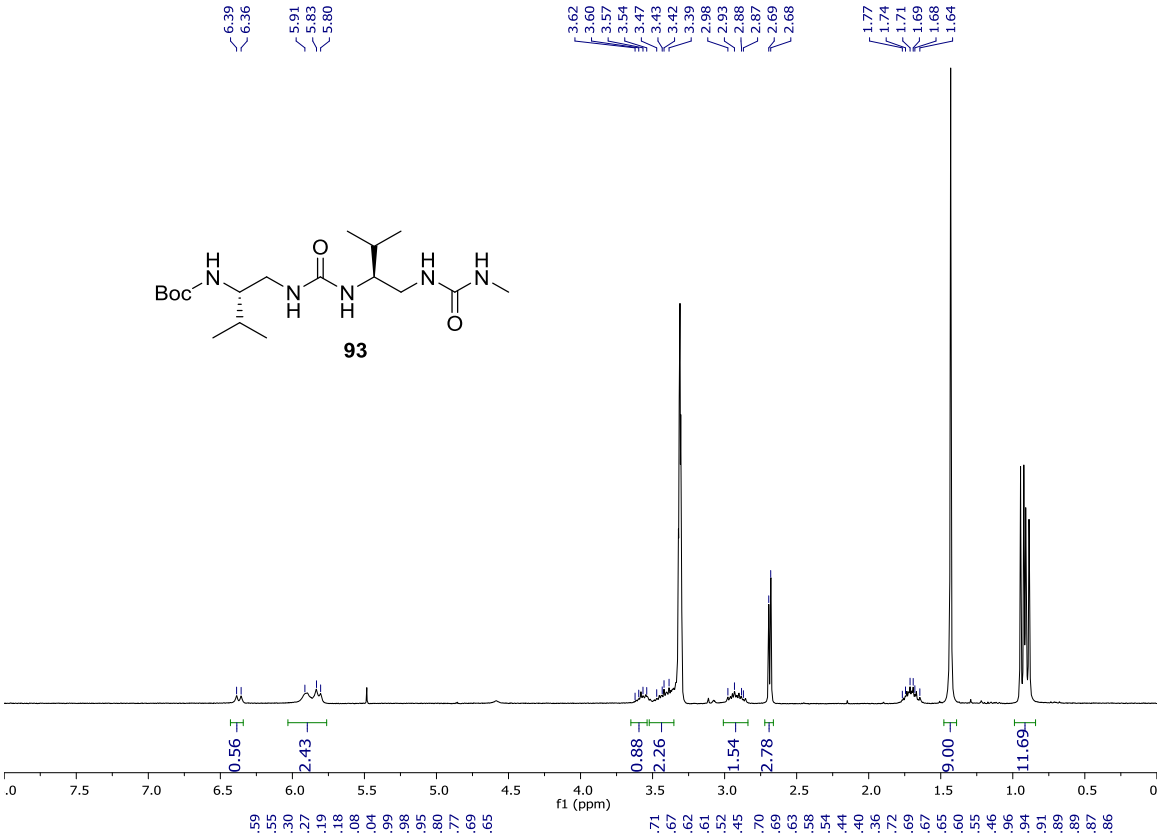

8.81
7.40
7.33
7.21
7.15
7.07
7.04
7.02
6.81
6.78
6.75
4.91
4.05
4.03
4.01
3.28
3.26
2.89
2.87
2.84
2.82
2.69
2.66
2.62
2.59
1.91
1.89
1.86
1.84
O
OH
N
H
Ph
NH2
HN
Ph
Ph
86
0.72
12.86
0.85
1.46
0.78
0.83
1.07
1.00
0.97
1.99
f1 (ppm)
172.0
142.8
141.6
140.5
129.0
128.9
128.7
127.8
127.7
127.6
127.5
127.3
126.2
125.0
124.1
119.7
118.2
72.1
66.3
64.4
35.2
32.3
f1 (ppm)

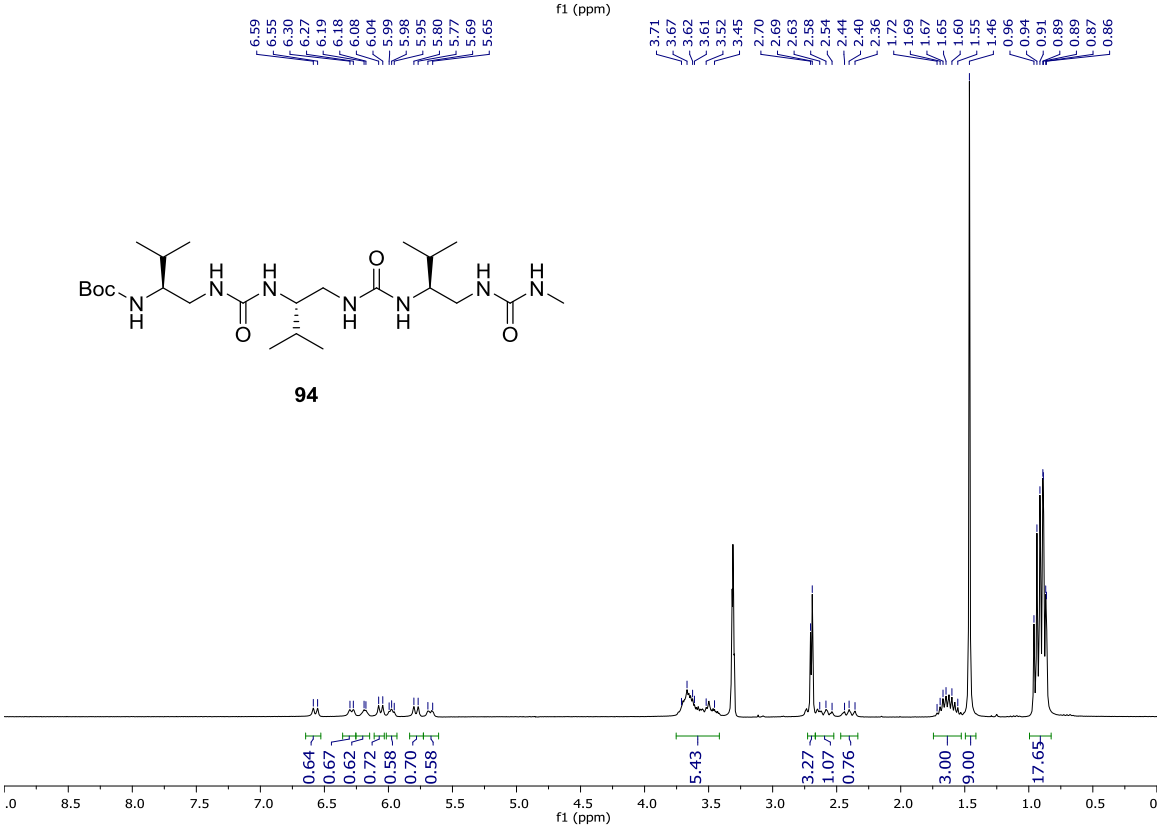

6.08
4.55
3.56
3.43
3.38
3.25
2.81
1.82
1.80
1.79
1.46
0.98
0.95
0.93
0.72
0.67
0.98
0.99
0.82
0.92
8.75
6.00
f1 (ppm)

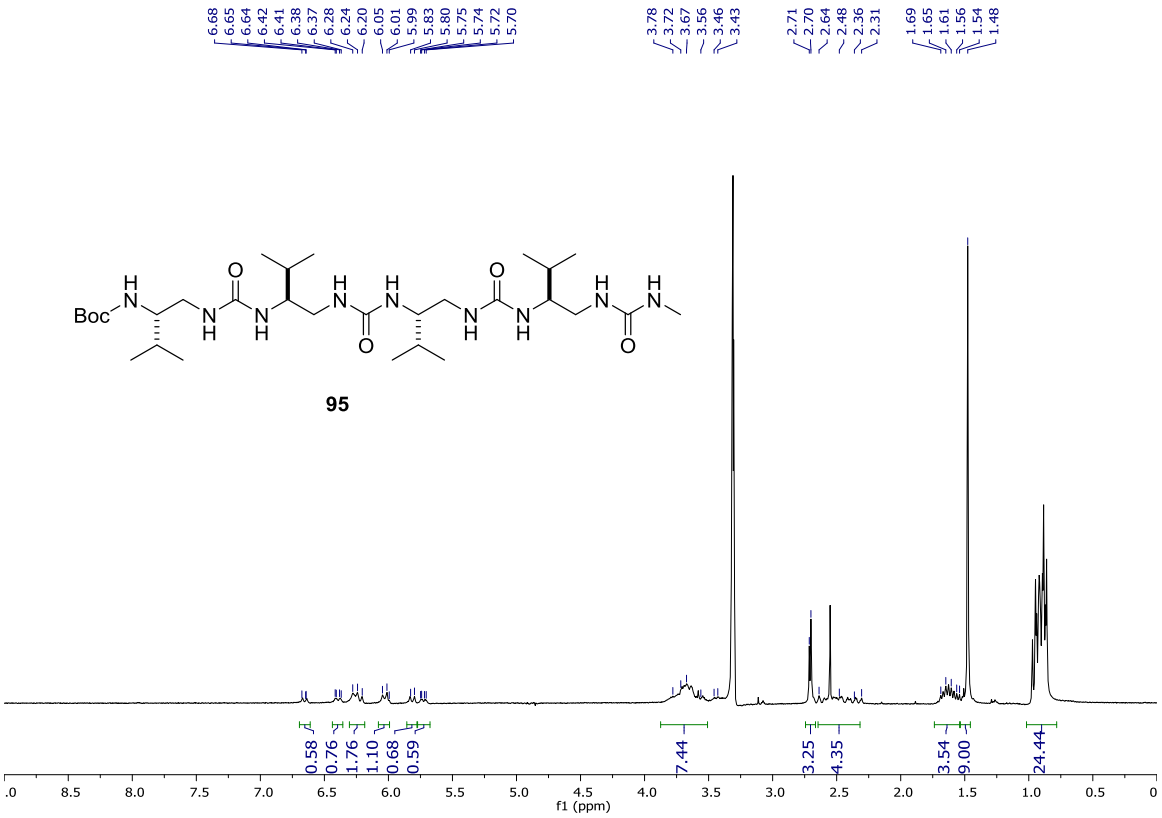
91

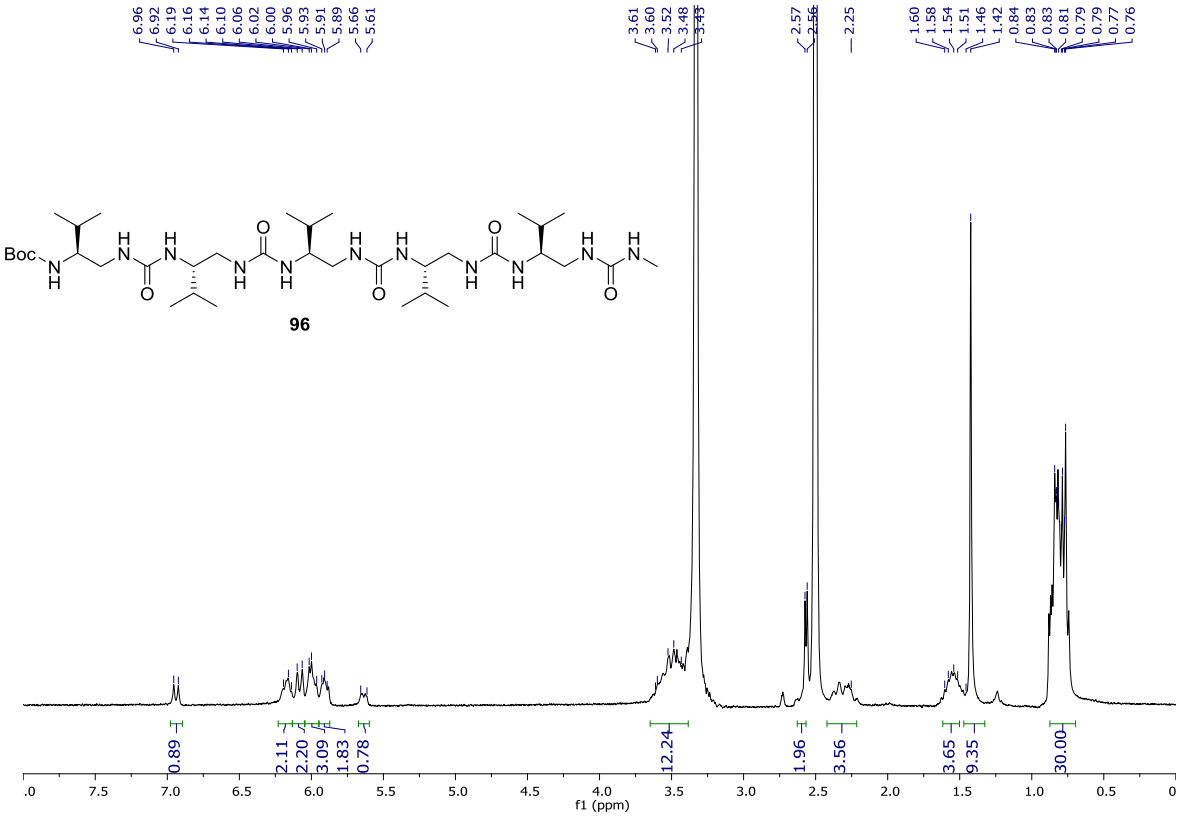

4.95
4.67
3.49
3.48
3.46
3.43
3.26
3.23
2.76
1.79
1.76
1.74
1.44
0.97
0.94
0.94
0.92
0.64
1.08
1.22
2.12
3.00
1.21
9.30
6.42
f1 (ppm)

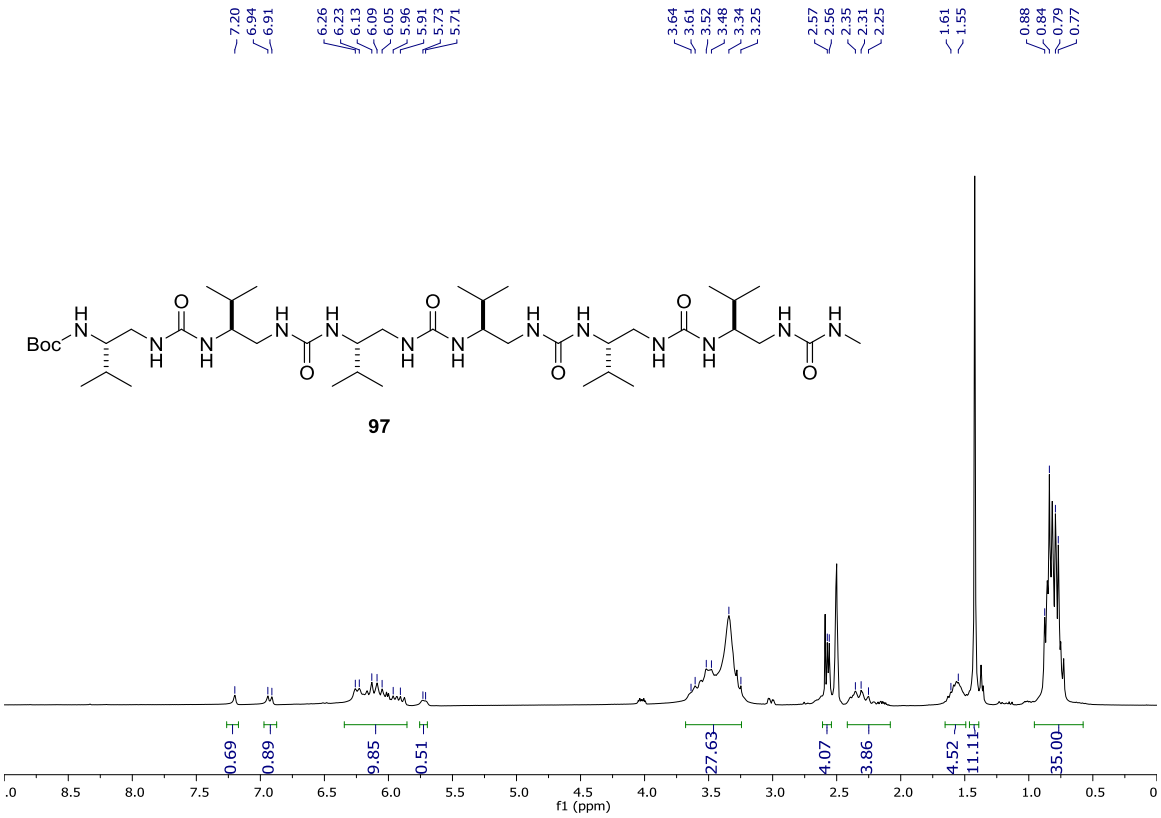
92


6.39
6.36
5.91
5.83
5.80
3.62
3.60
3.57
3.54
3.47
3.43
3.42
3.39
2.98
2.93
2.88
2.87
2.69
2.68
1.77
1.74
1.71
1.69
1.68
1.64
Boc
93
0.56
2.43
0.88
2.26
1.54
2.78
9.00
11.69
f1 (ppm)

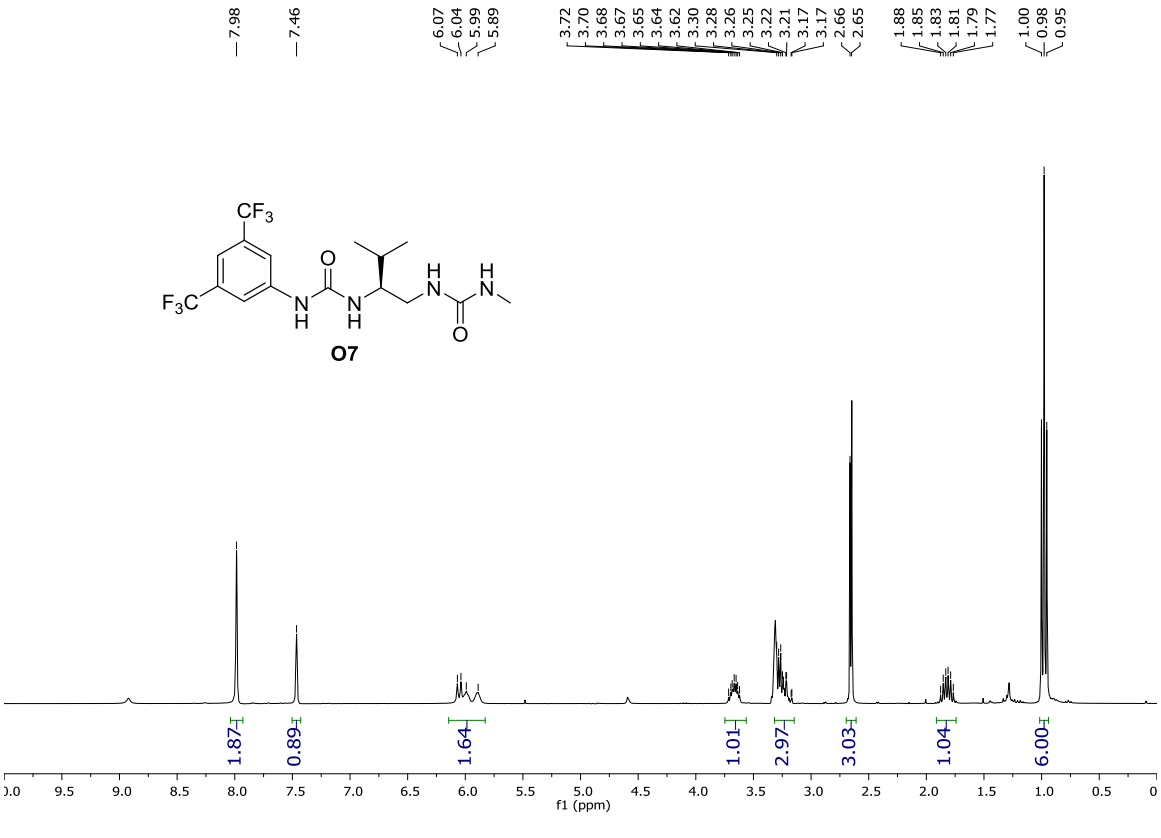

6.59
6.55
6.30
6.27
6.19
6.18
6.08
6.04
5.99
5.98
5.95
5.80
5.77
5.69
5.65
3.71
3.67
3.62
3.61
3.52
3.45
2.70
2.69
2.63
2.58
2.54
2.44
2.40
2.36
1.72
1.69
1.67
1.65
1.60
1.55
1.46
0.96
0.94
0.91
0.89
0.89
0.87
0.86
Boc
94
0.64
0.67
0.62
0.72
0.58
0.70
0.58
5.43
3.27
1.07
0.76
3.00
9.00
17.65
f1 (ppm)


6.68
6.65
6.64
6.42
6.41
6.38
6.37
6.28
6.24
6.20
6.05
6.01
5.99
5.83
5.80
5.75
5.74
5.72
5.70
3.78
3.72
3.67
3.56
3.46
3.43
2.71
2.70
2.64
2.48
2.36
2.31
1.69
1.65
1.61
1.56
1.54
1.48
Boc
95
0.58
0.76
1.76
1.10
0.68
0.59
7.44
3.25
4.35
3.54
9.00
24.44
f1 (ppm)

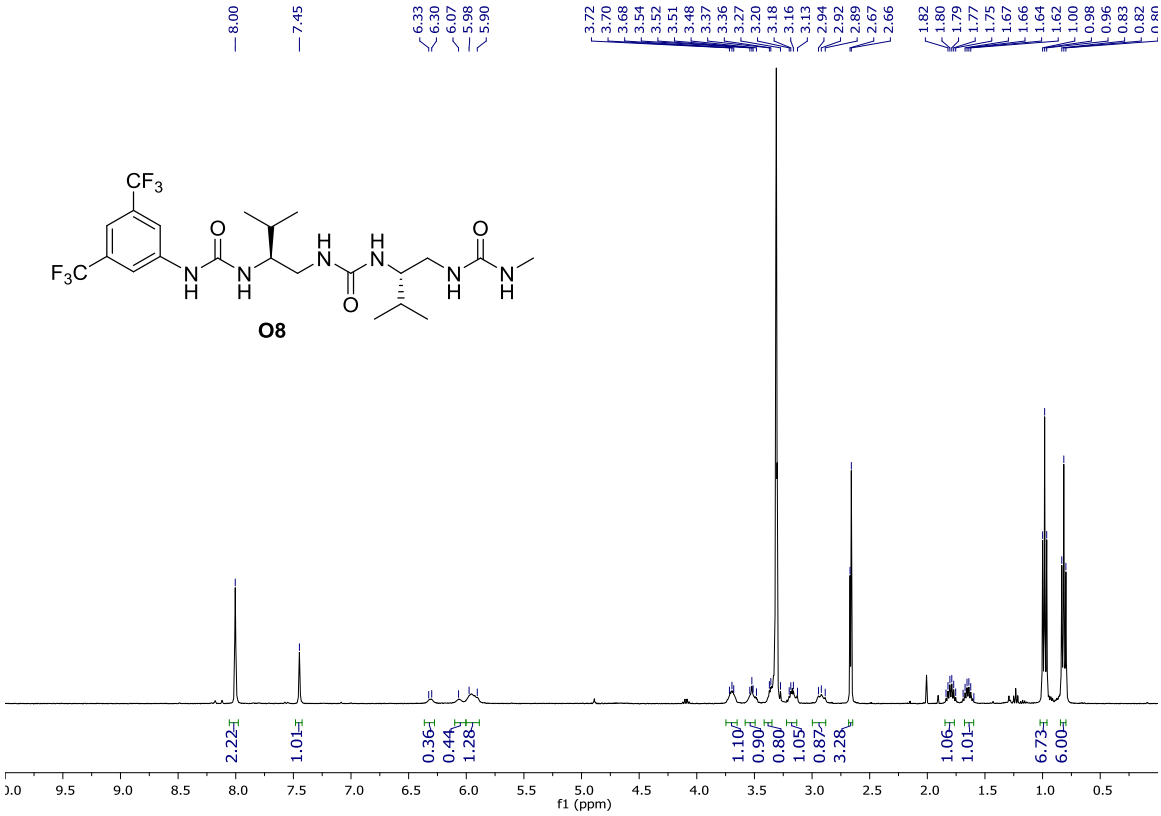

6.96
6.92
6.19
6.16
6.14
6.10
6.06
6.02
6.00
5.96
5.93
5.91
5.89
5.66
5.61
3.61
3.60
3.52
3.48
3.43
2.57
2.56
2.25
1.60
1.58
1.54
1.51
1.46
1.42
0.84
0.83
0.83
0.81
0.79
0.79
0.77
0.76
Boc
96
0.89
2.11
2.20
3.09
1.83
0.78
12.24
1.96
3.56
3.65
9.35
30.00
f1 (ppm)


7.20
6.94
6.91
6.26
6.23
6.13
6.09
6.05
5.96
5.91
5.73
5.71
3.64
3.61
3.52
3.48
3.34
3.25
2.57
2.56
2.35
2.31
2.25
1.61
1.55
0.88
0.84
0.79
0.77
Boc
0.69
0.89
9.85
0.51
27.63
4.07
3.86
4.52
11.11
35.00
f1 (ppm)

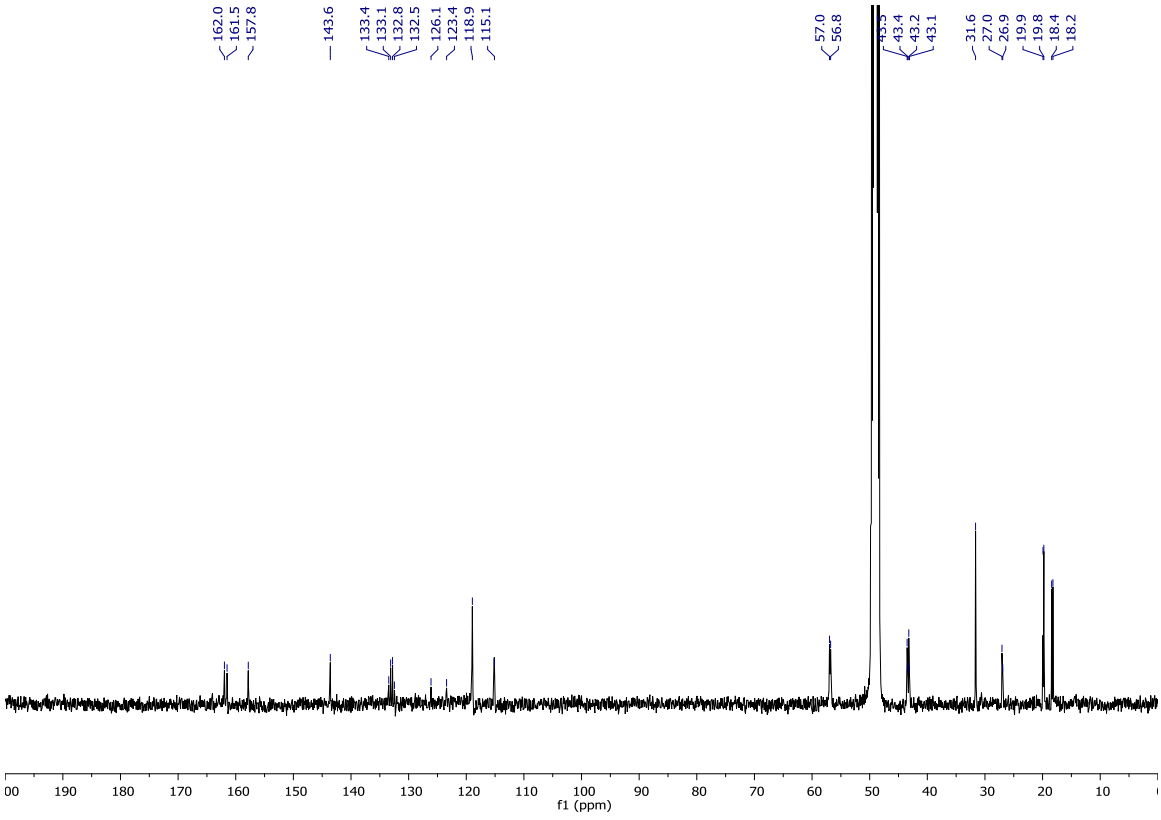
97

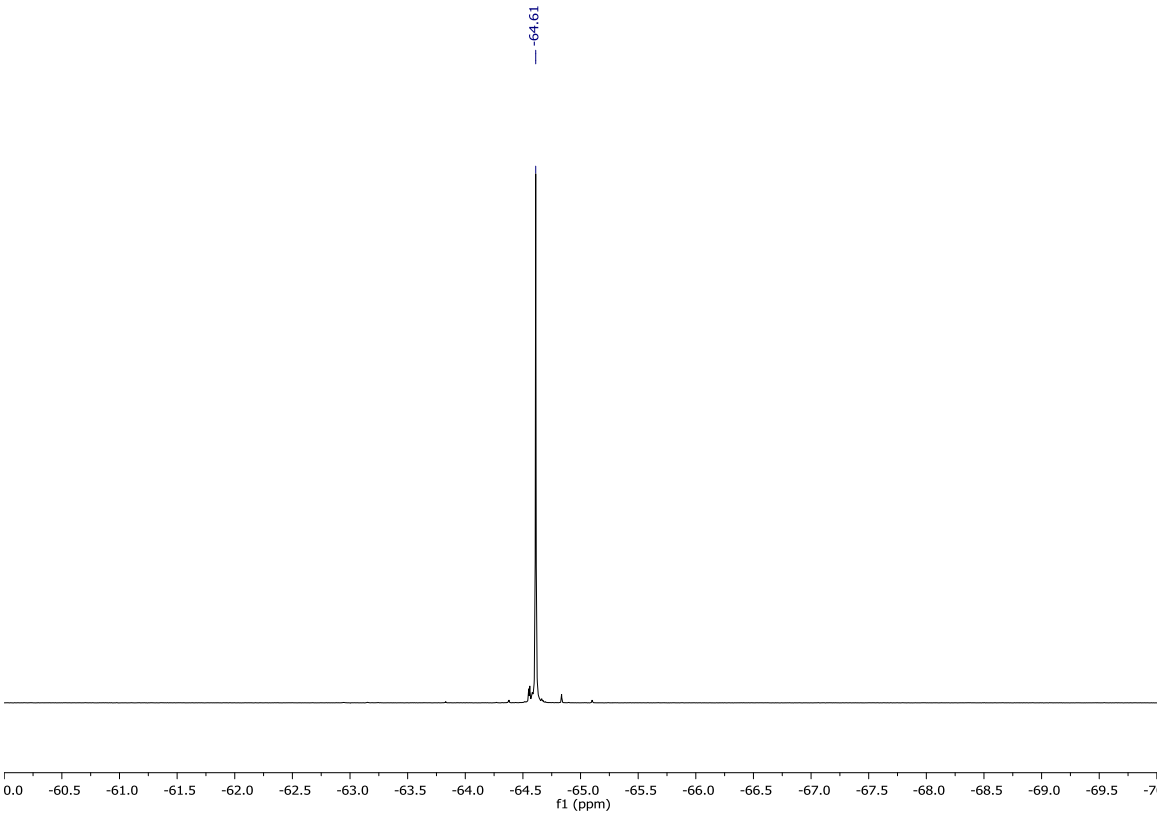

7.98
7.46
6.07
6.04
5.99
5.89
3.72
3.70
3.68
3.67
3.65
3.64
3.62
3.30
3.28
3.26
3.25
3.22
3.21
3.17
3.17
2.66
2.65
1.88
1.85
1.83
1.81
1.79
1.77
1.00
0.98
0.95
CF3
F3C
1.87
0.89
1.64
1.01
2.97
3.03
1.04
6.00
f1 (ppm)

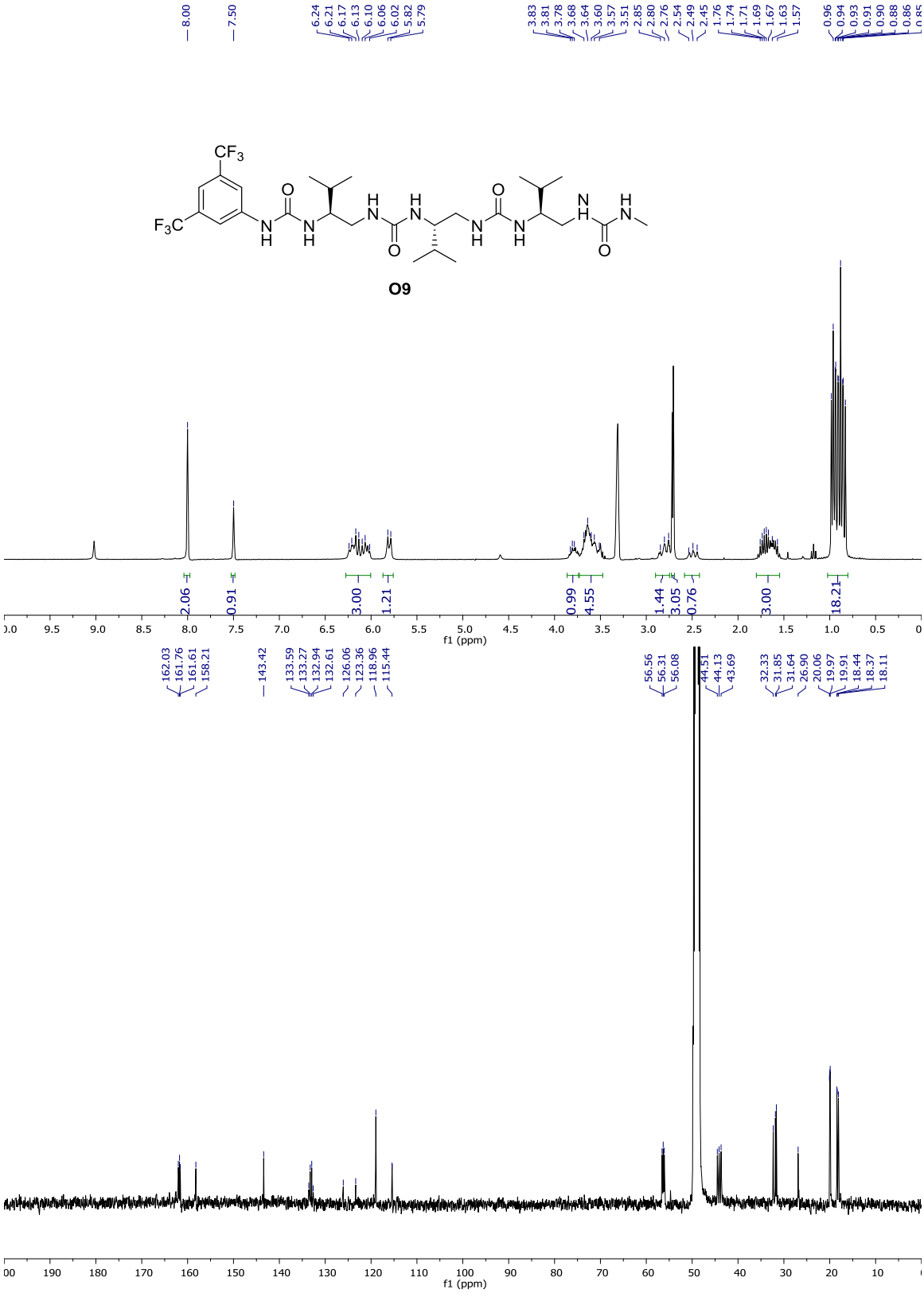
O7

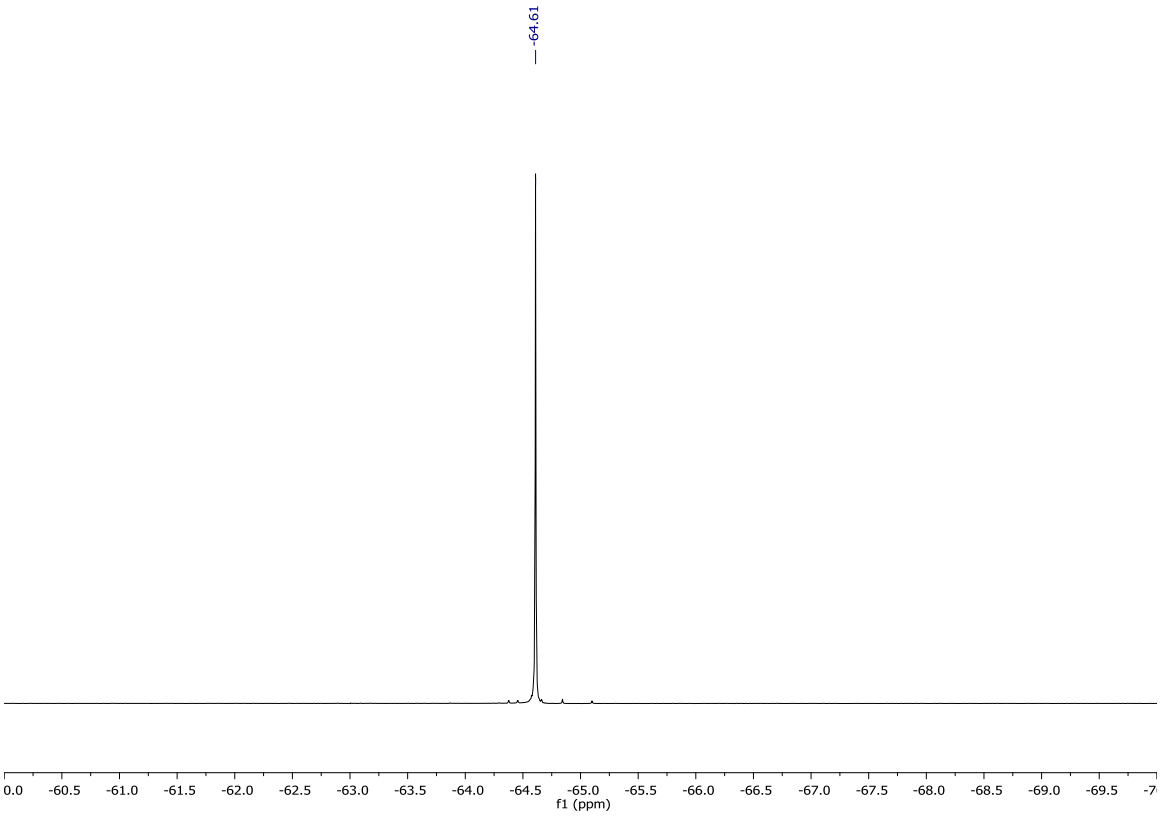

8.00
7.45
6.33
6.30
6.07
5.98
5.90
3.72
3.70
3.68
3.54
3.52
3.51
3.48
3.37
3.36
3.27
3.20
3.18
3.16
3.13
2.94
2.92
2.89
2.67
2.66
1.82
1.80
1.79
1.77
1.75
1.67
1.66
1.64
1.62
1.00
0.98
0.96
0.83
0.82
2.22
1.01
0.36
0.44
1.28
1.10
0.90
0.80
1.05
0.87
3.28
1.06
1.01
6.73
6.00
f1 (ppm)

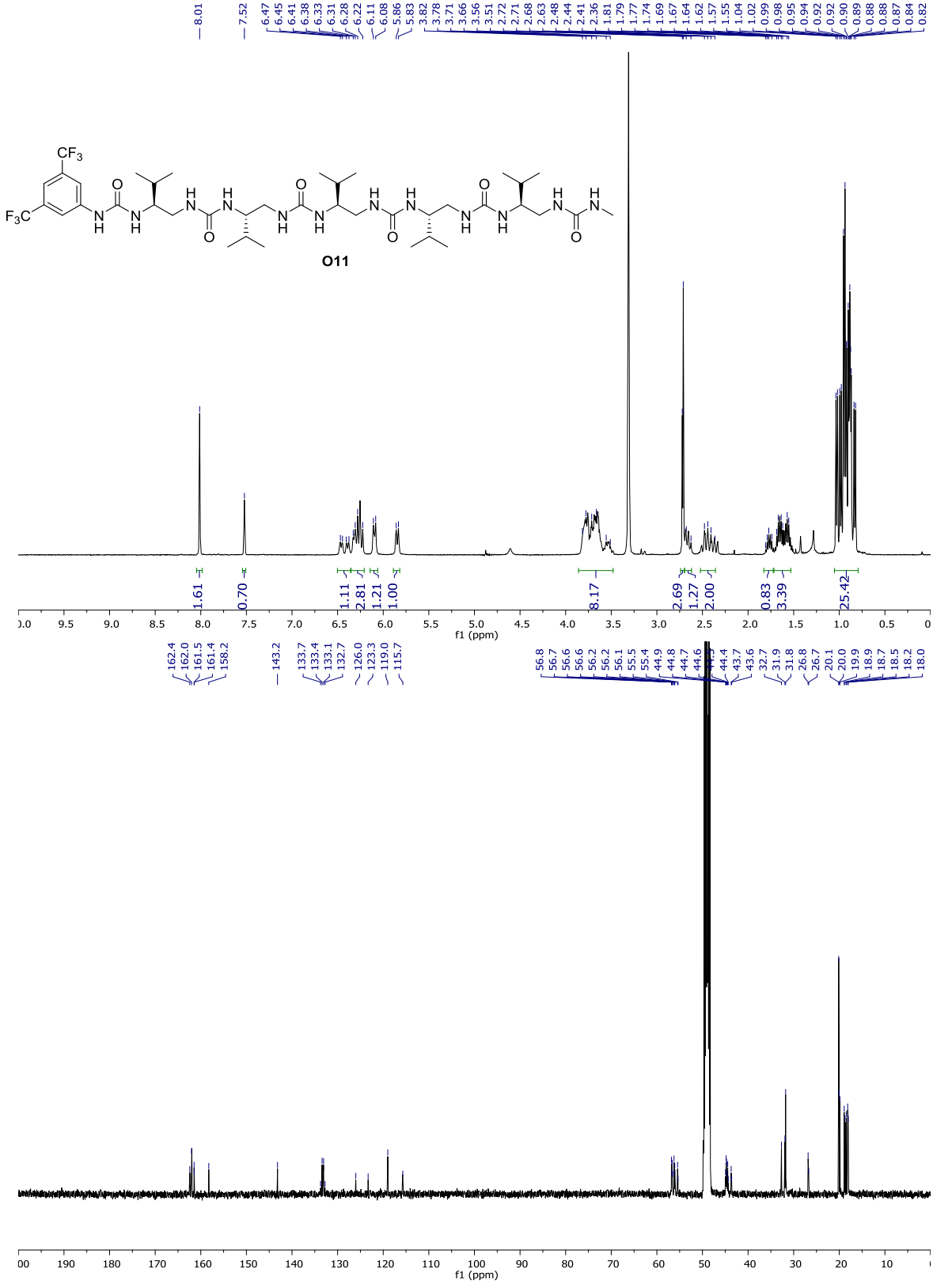
O8

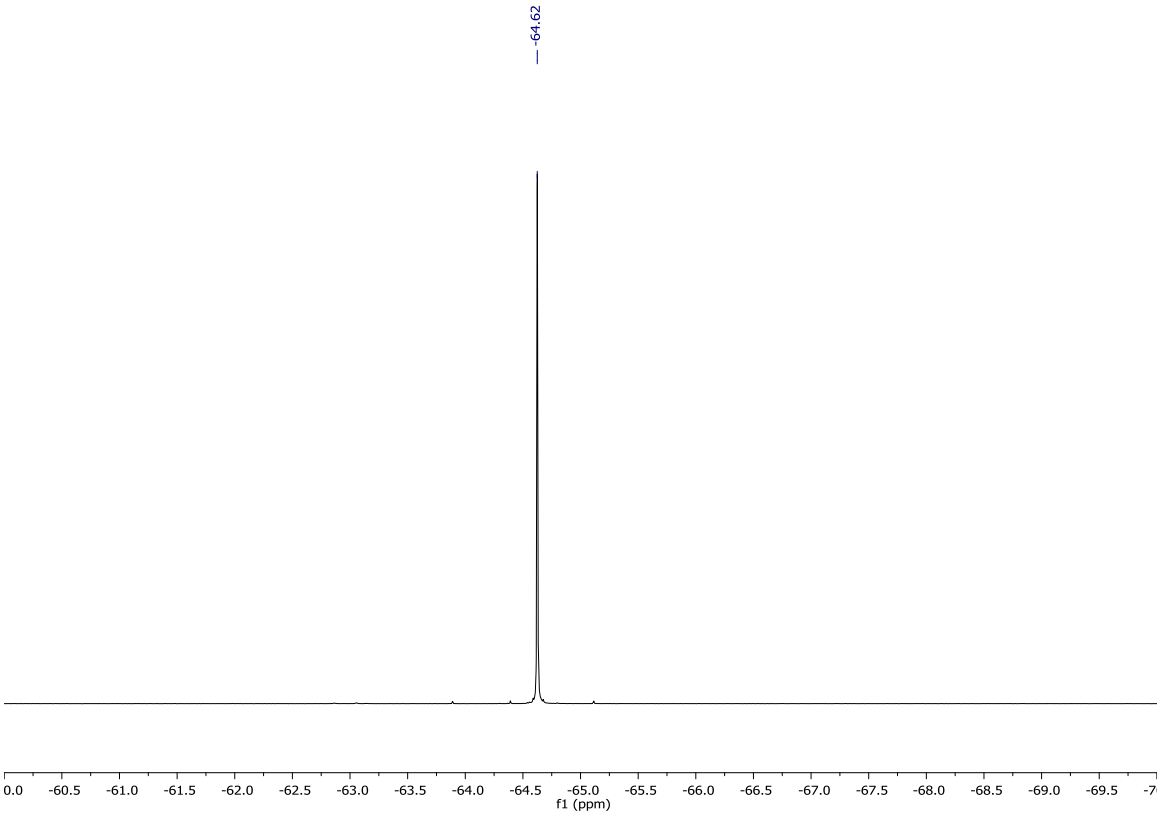

162.0
161.5
157.8
143.6
133.4
133.1
132.8
132.5
126.1
123.4
118.9
115.1
57.0
56.8
43.5
43.4
43.2
43.1
31.6
27.0
26.9
19.9
19.8
18.4
18.2
f1 (ppm)


-64.61
0.0
-60.5
-61.0
-61.5
-62.0
-62.5
-63.0
-63.5
-64.0
-64.5
-65.0
-65.5
-66.0
-66.5
-67.0
-67.5
-68.0
-68.5
-69.0
-69.5
f1 (ppm)

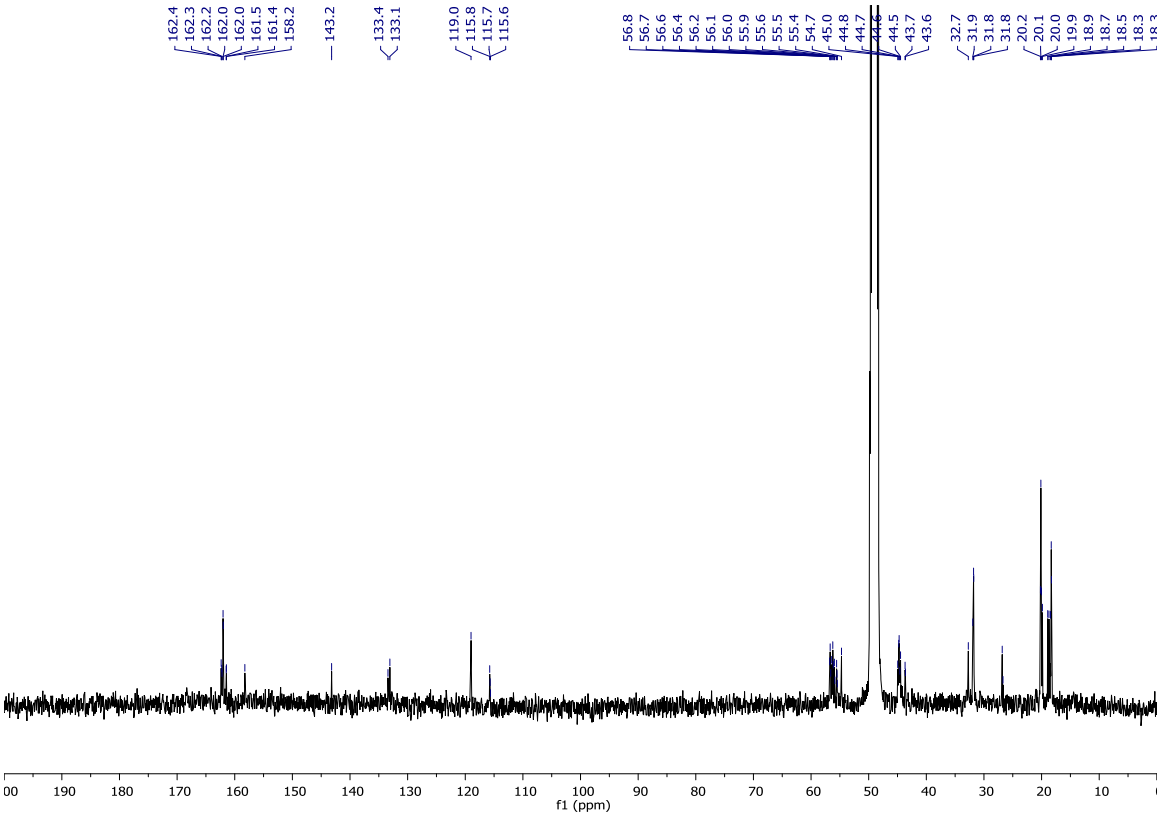

8.00
7.50
6.24
6.21
6.17
6.13
6.10
6.06
6.02
5.82
5.79
3.83
3.81
3.78
3.68
3.64
3.60
3.57
3.51
2.85
2.80
2.76
2.54
2.49
2.45
1.76
1.74
1.71
1.69
1.67
1.63
1.57
0.96
0.94
0.93
0.91
0.90
0.88
0.86
CF3
F3C
O9
2.06
0.91
3.00
1.21
0.99
4.55
1.44
3.05
0.76
3.00
18.21
f1 (ppm)
162.03
161.76
161.61
158.21
143.42
133.59
133.27
132.94
132.61
126.06
123.36
118.96
115.44
56.56
56.31
56.08
44.51
44.13
43.69
32.33
31.85
31.64
26.90
20.06
19.97
19.91
18.44
18.37
18.11
f1 (ppm)

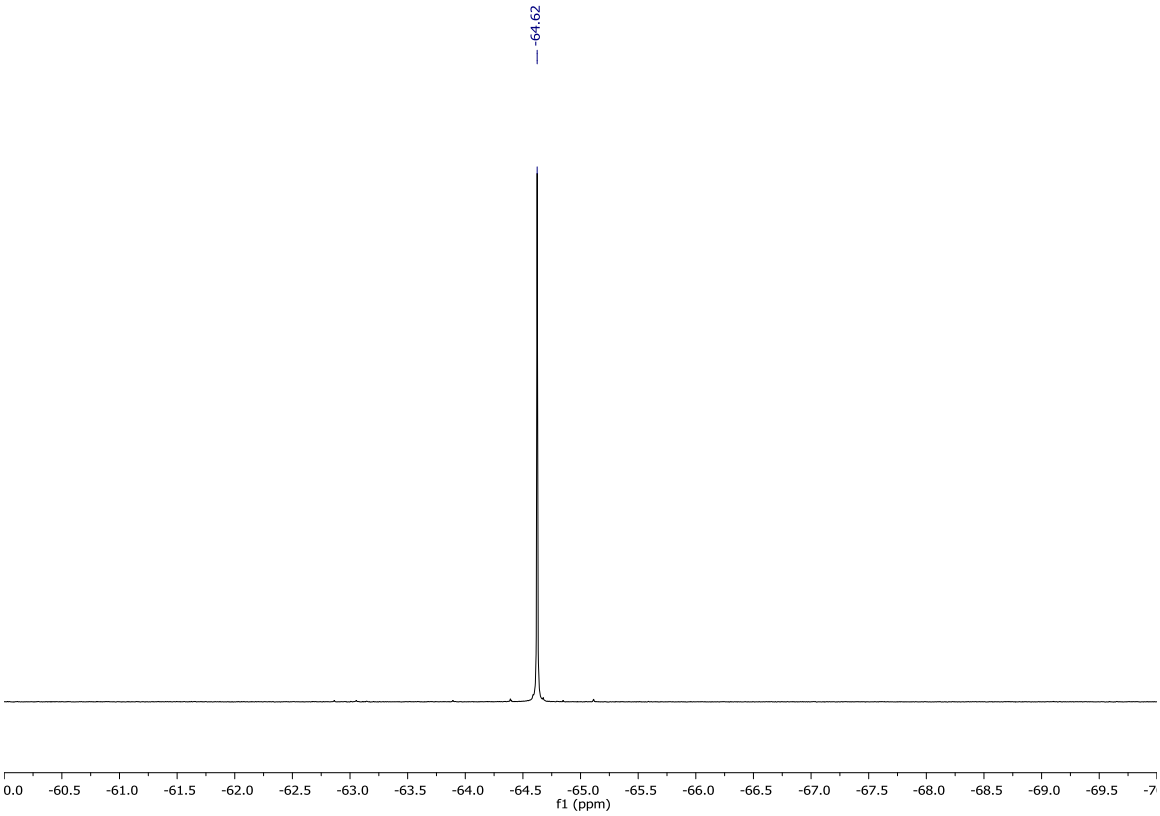

-64.61
0.0
-60.5
-61.0
-61.5
-62.0
-62.5
-63.0
-63.5
-64.0
-64.5
-65.0
-65.5
-66.0
-66.5
-67.0
-67.5
-68.0
-68.5
-69.0
-69.5
f1 (ppm)


O11
f1 (ppm)
f1 (ppm)

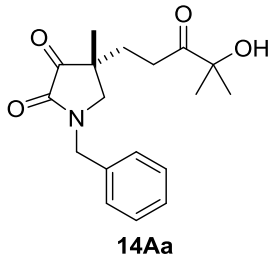

-64.62
0.0
-60.5
-61.0
-61.5
-62.0
-62.5
-63.0
-63.5
-64.0
-64.5
-65.0
-65.5
-66.0
-66.5
-67.0
-67.5
-68.0
-68.5
-69.0
-69.5
f1 (ppm)


8.02
7.53
6.45
6.43
6.34
6.31
6.26
6.23
6.13
6.10
5.87
5.85
5.49
3.79
3.78
3.72
3.66
3.57
3.49
2.72
2.71
F3C
CF3
O12
1.92
0.85
1.98
4.12
1.16
1.19
1.35
11.74
3.00
1.00
3.63
1.09
4.98
36.21
f1 (ppm)


162.4
162.3
162.2
162.0
162.0
161.5
161.4
158.2
143.2
133.4
133.1
119.0
115.8
115.7
115.6
56.8
56.7
56.6
56.4
56.2
56.1
56.0
55.9
55.6
55.5
55.4
54.7
45.0
44.8
44.7
44.5
43.7
43.6
32.7
31.9
31.8
31.8
20.2
20.1
20.0
19.9
18.9
18.7
18.5
18.3
f1 (ppm)



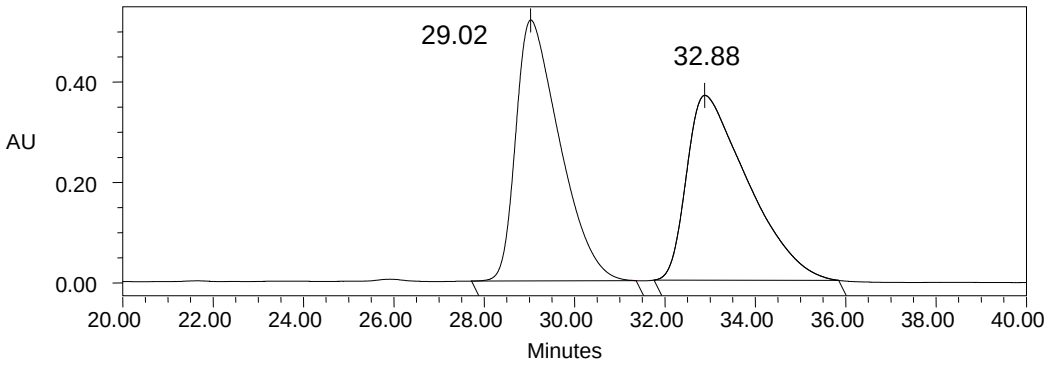
6.7. **HPLC chromatograms**



14Aa

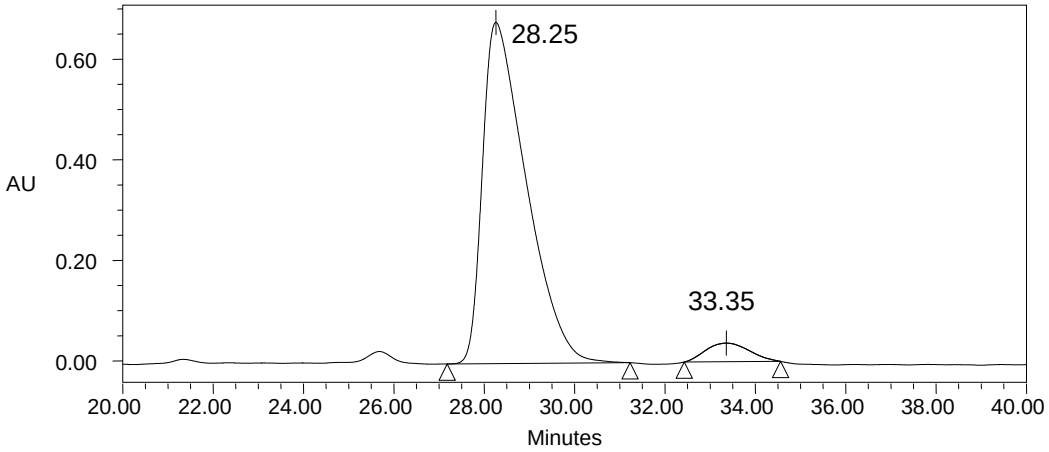
Column: AY-H
Eluent: 40:60 Hx:iPrOH
Flow rate: 0.6 mL/min
λ: 210 nm

rac-**14Aa**



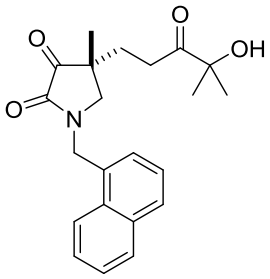
	Retention Time	% Area
1	29.02	50.30
2	32.88	49.70

14Aa



	Retention Time	% Area
1	28.25	95.64
2	33.35	4.36

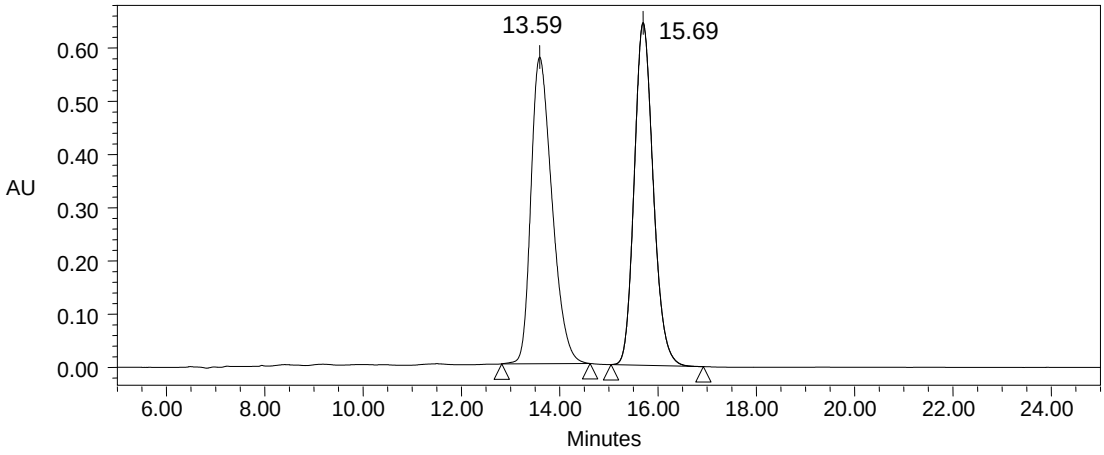
91% *ee*



14Ba

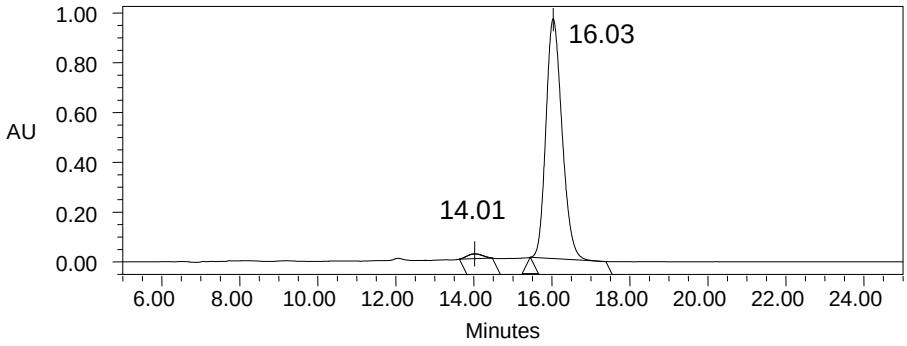
Column: AY-H
Eluent: 50:50 Hx:EtOH
Flow rate: 0.5 mL/min
λ: 210 nm

rac-**14Ba**



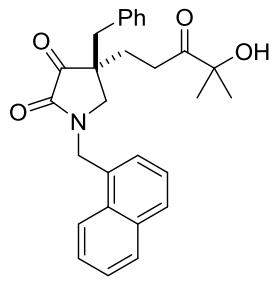
	Retention Time	% Area
1	13.59	50.18
2	15.69	49.82

14Ba



	Retention Time	% Area
1	14.01	1.89
2	16.03	98.11

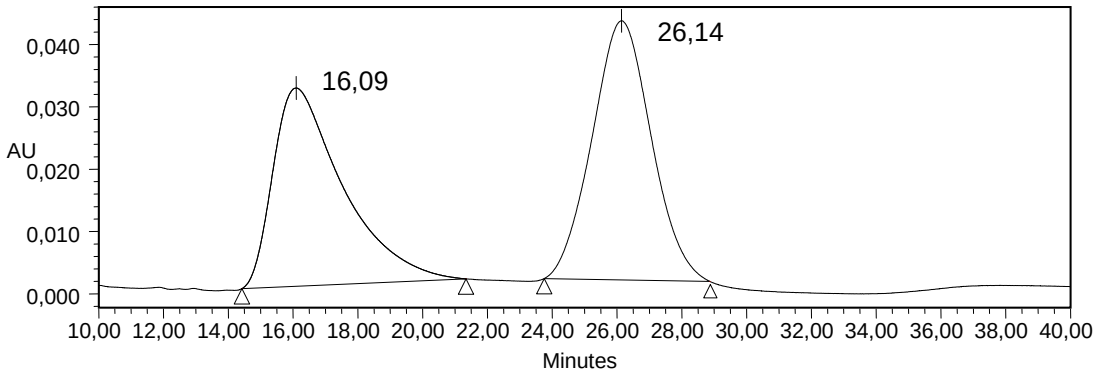
96% *ee*



14Bb

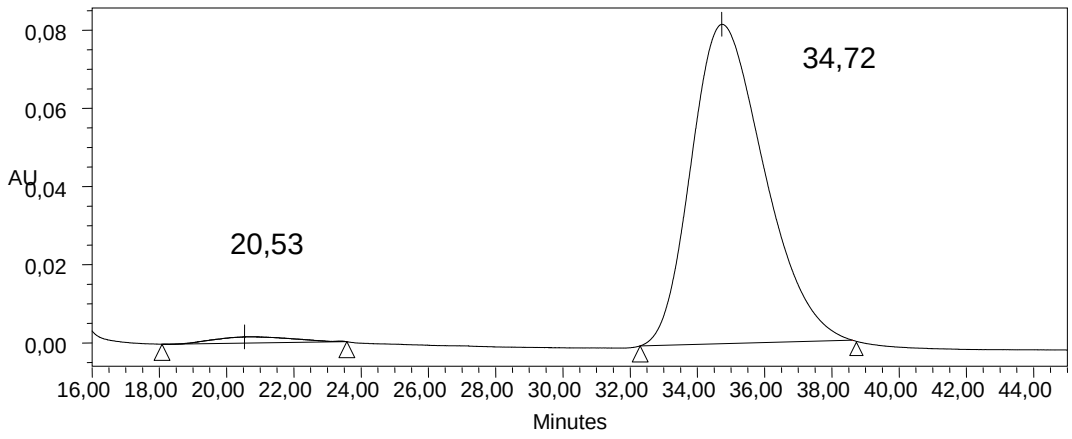
Column: AY-H
Eluent: 40:60 Hx:iPrOH
Flow rate: 0.6 mL/min
λ: 210 nm

rac-**14Bb**



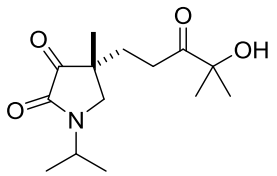
	Retention Time	% Area
1	16.09	50.47
2	26.14	49.53

14Bb



	Retention Time	% Area
1	20.53	3.65
2	34.72	96.35

92% *ee*



14Ca

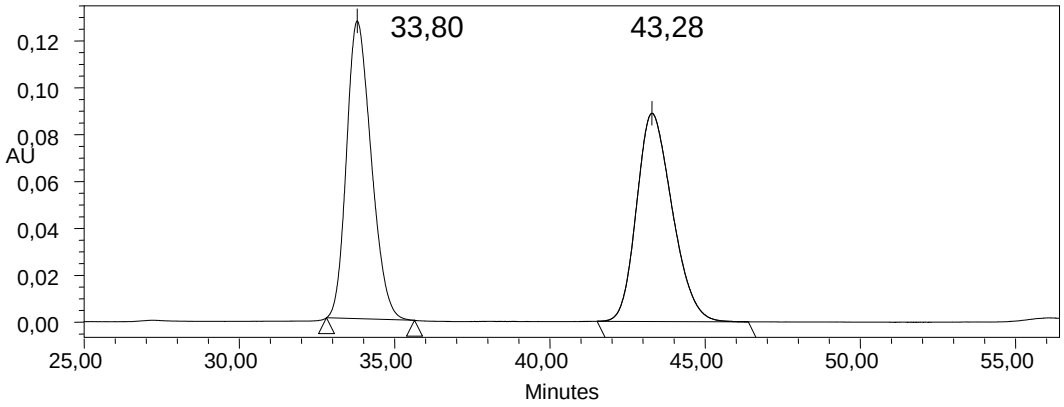
Column: AY-H

Eluent: 50:50

Hx:iPrOH

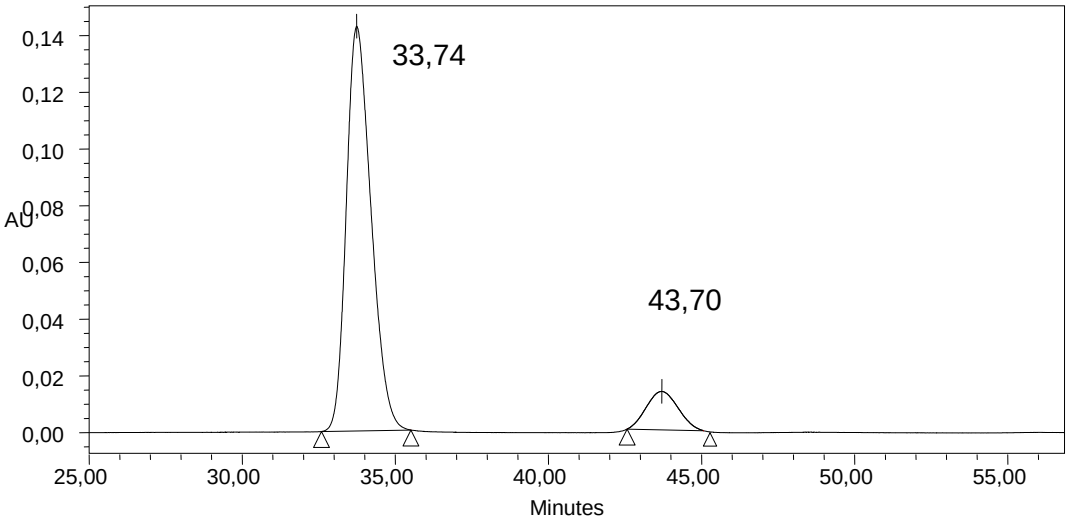
Flow rate: 0.5 mL/min

rac-**14Ca**



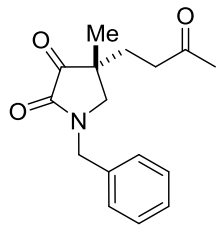
	Retention Time	% Area
1	33.80	50.12
2	43.28	49.88

14Ca



	Retention Time	% Area
1	33.74	6.29
2	43.7	93.71

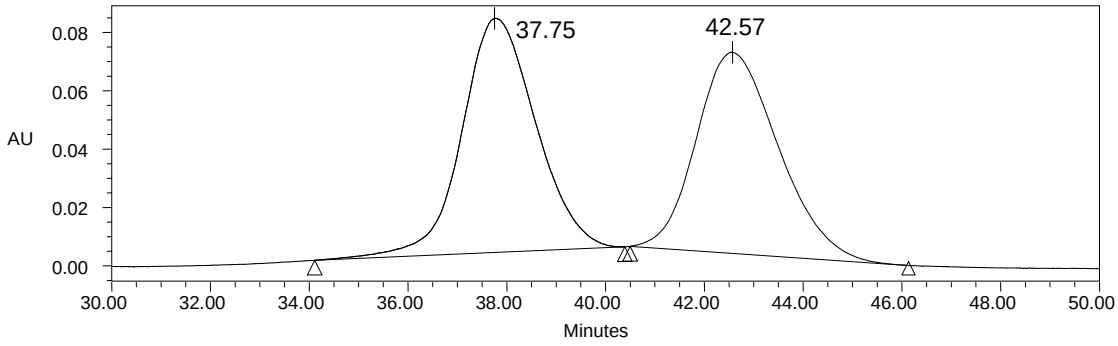
88% *ee*



18Aa

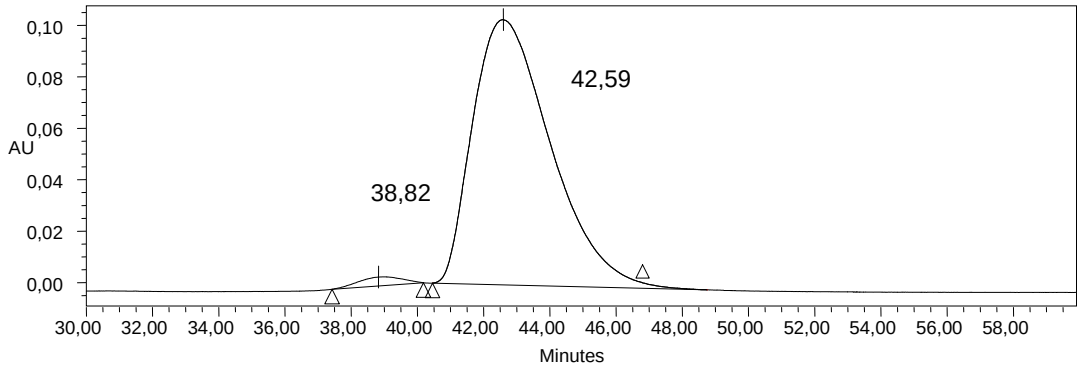
Column: ODH
Eluent: 80:20 Hx:iPrOH
Flow rate: 0.5 mL/min
λ: 210 nm

rac-**18Aa**



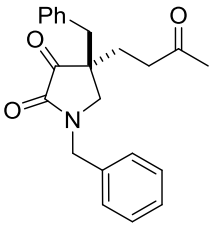
	Retention Time	% Area
1	37.75	50.58
2	42.57	49.42

18Aa



	Retention Time	% Area
1	38.82	1.83
2	42.59	98.17

96% *ee*



18Ab

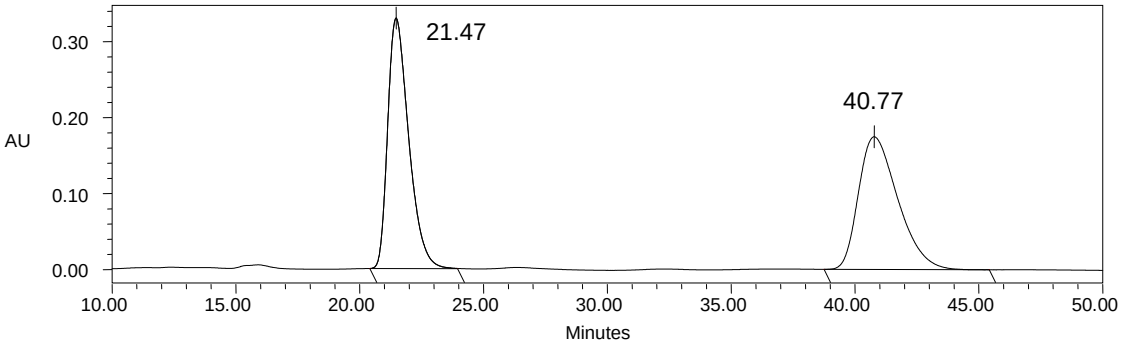
Column: ODH

Eluent: 50:50 Hx:iPrOH

Flow rate: 0.5 mL/min

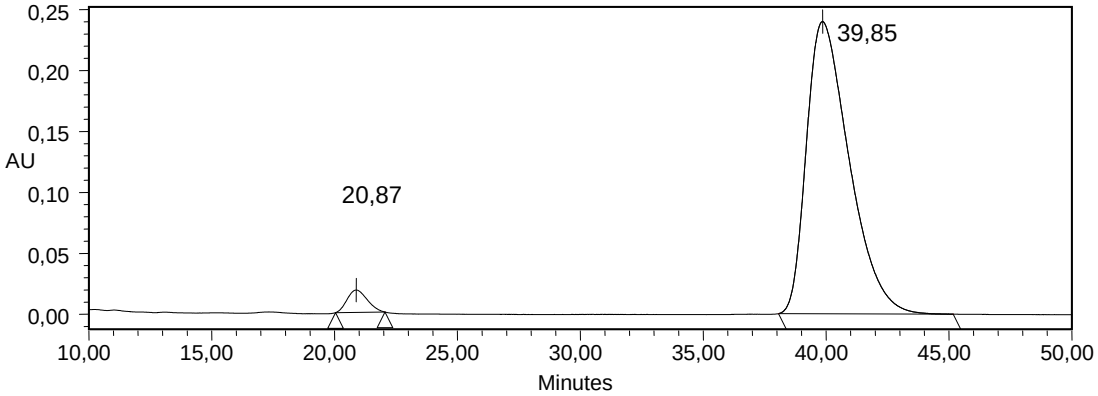
λ: 210 nm

rac-**18Ab**



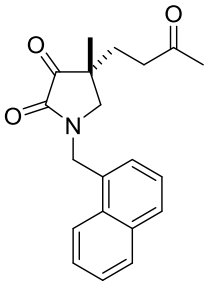
	Retention Time	% Area
1	21.47	50.72
2	40.77	49.28

18Ab



	Retention Time	% Area
1	20.87	3.46
2	39.85	96.54

94% *ee*



18Ba

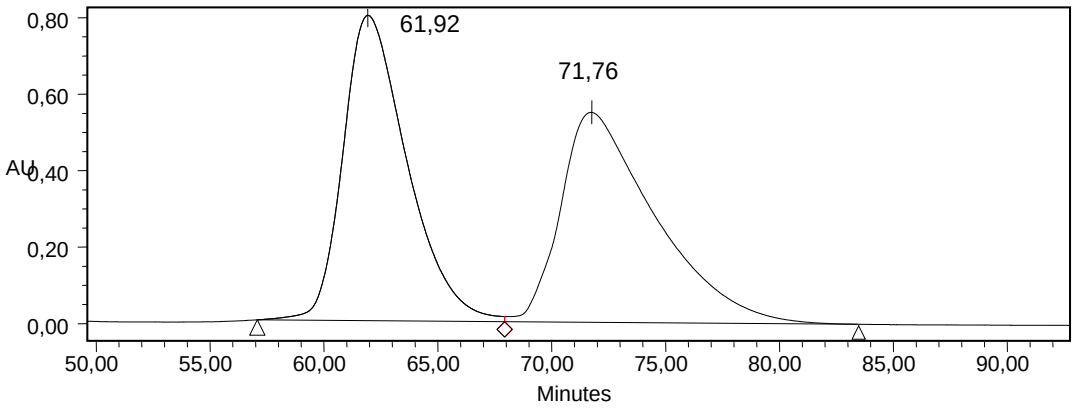
Column: ODH

Eluent: 80:20 Hx: iPrOH

Flow rate: 0.5 mL/min

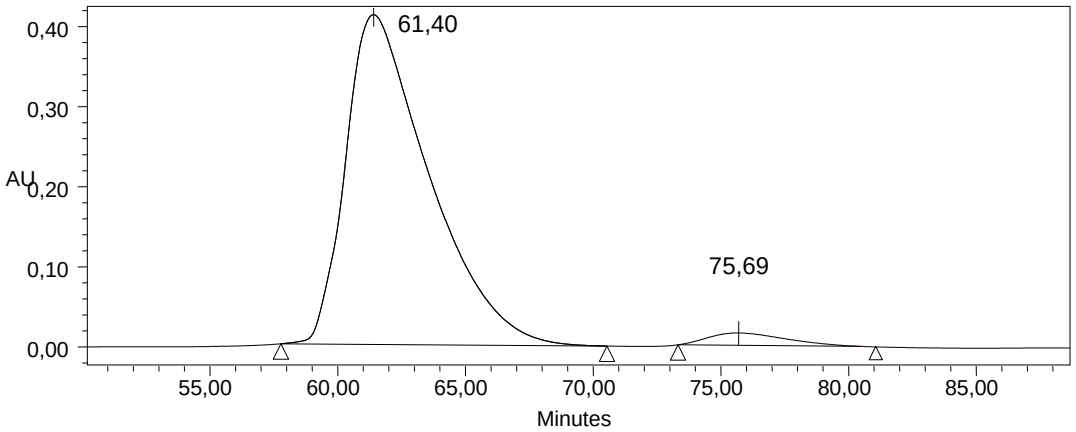
λ: 254 nm

rac-**18Ba**



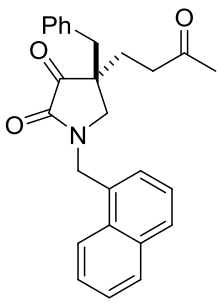
	Retention Time	% Area
1	61,92	49.77
2	71.76	50.23

18Ba



	Retention Time	% Area
1	61.40	96.64
2	75.69	3.36

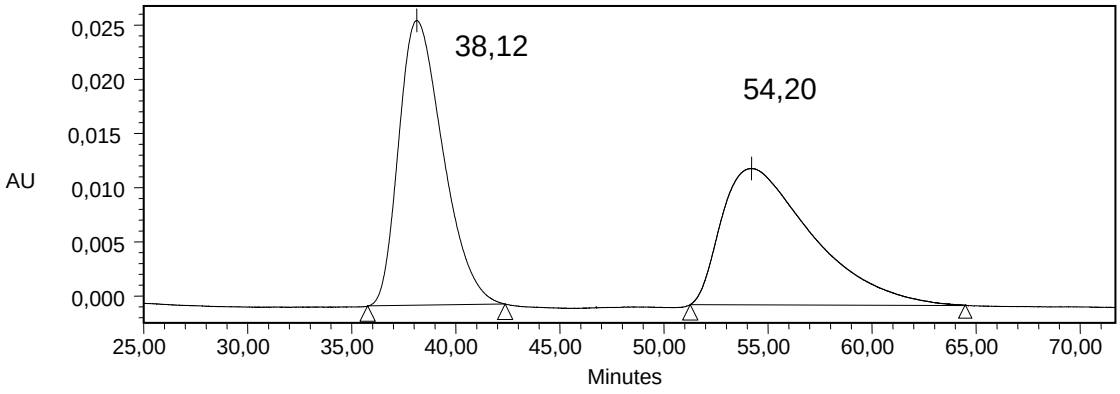
92% *ee*



18Bb

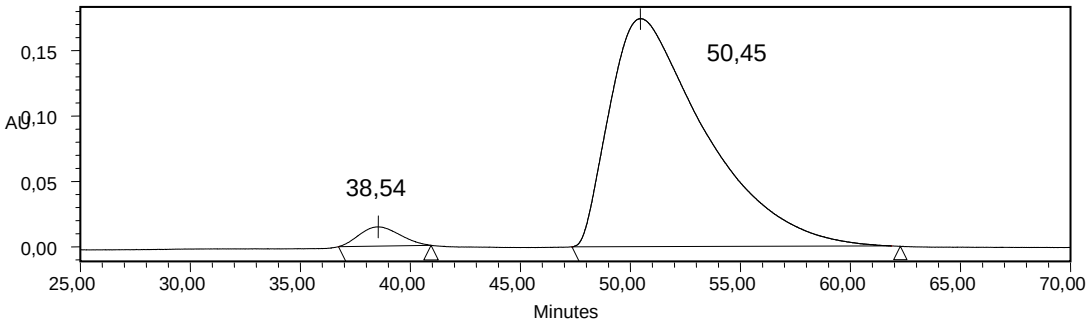
Column: ODH
Eluent: 50:50 Hx:iPrOH
Flow rate: 0.5 mL/min
λ: 210 nm

rac-**18Bb**



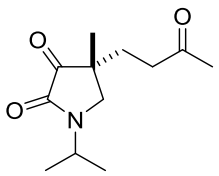
	Retention Time	% Area
1	38.12	49.84
2	54.20	50.16

18Bb



	Retention Time	% Area
1	38.54	3.42
2	50.45	96.58

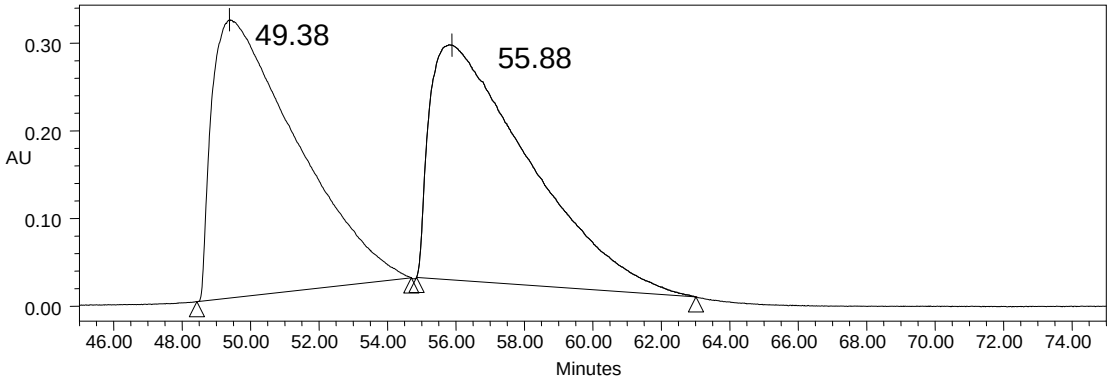
94% *ee*



18Ca

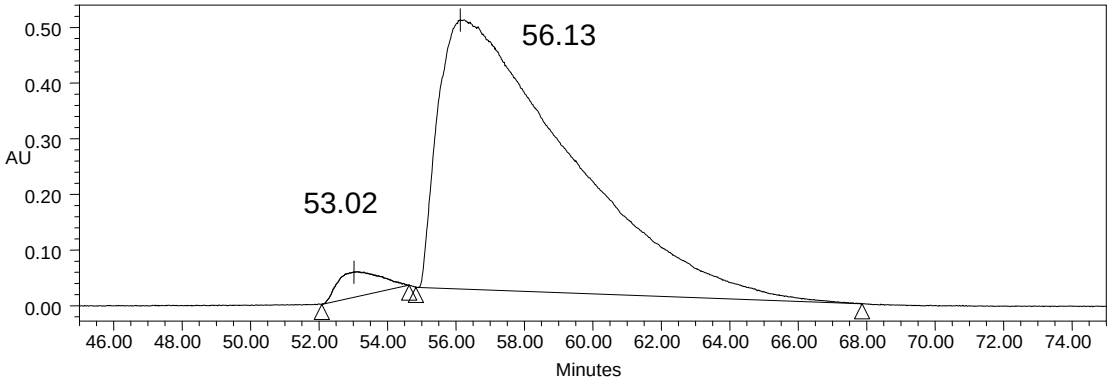
Column: OJ-H
Eluent: 80:20 Hx:iPrOH
Flow rate: 0.5 mL/min
λ: 254 nm

rac-**18Ca**



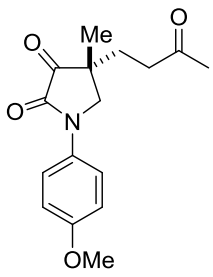
	Retention Time	% Area
1	49.38	49.65
2	55.88	50.35

18Ca



	Retention Time	% Area
1	53.02	2.03
2	56.13	97.97

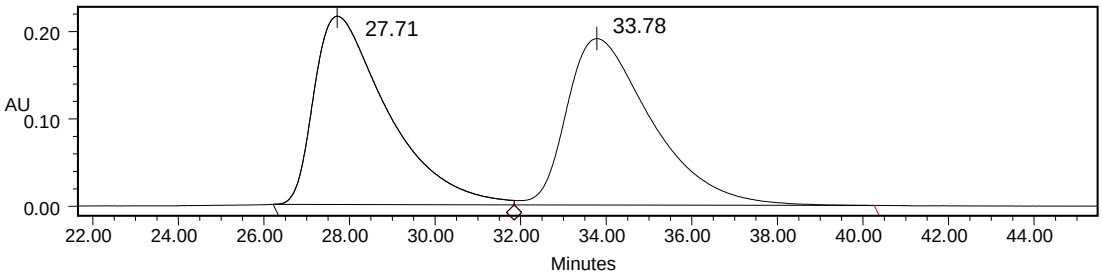
96% *ee*



18Da

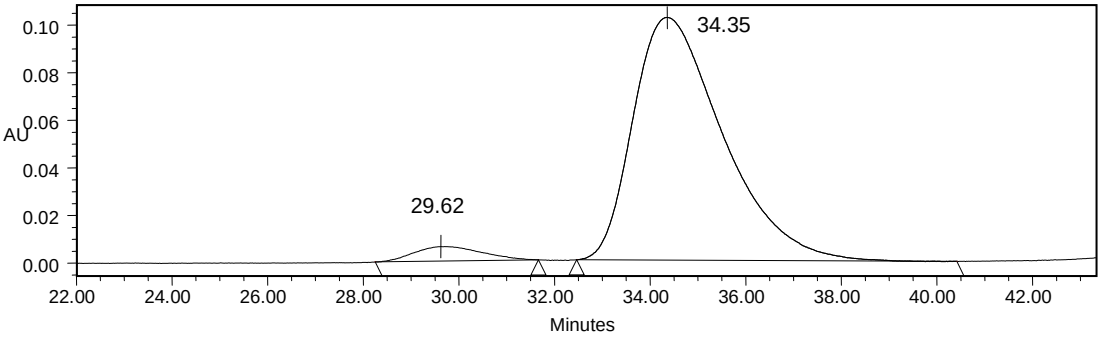
Column: OD-H
Eluent: 70:30 Hx:iPrOH
Flow rate: 1.0 mL/min
λ: 210 nm

rac-**18Da**



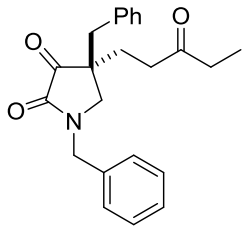
	Retention Time	% Area
1	27.71	49.60
2	33.78	50.40

18Da



	Retention Time	% Area
1	29.62	4.31
2	34.35	95.69

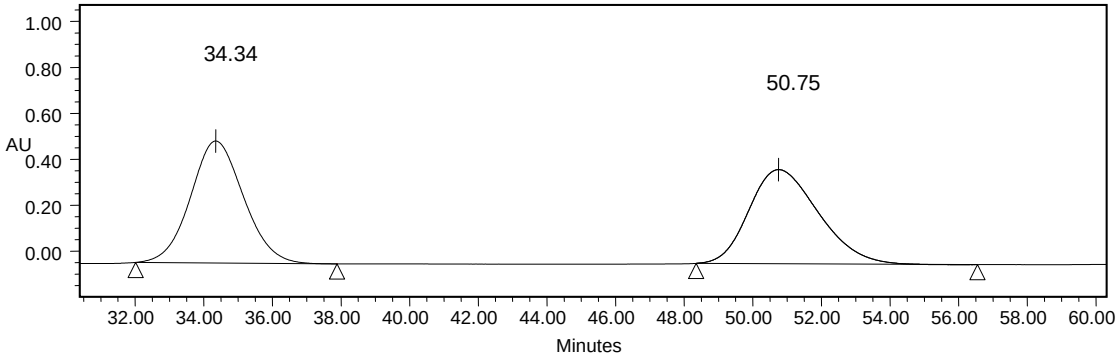
91% *ee*



19Ab

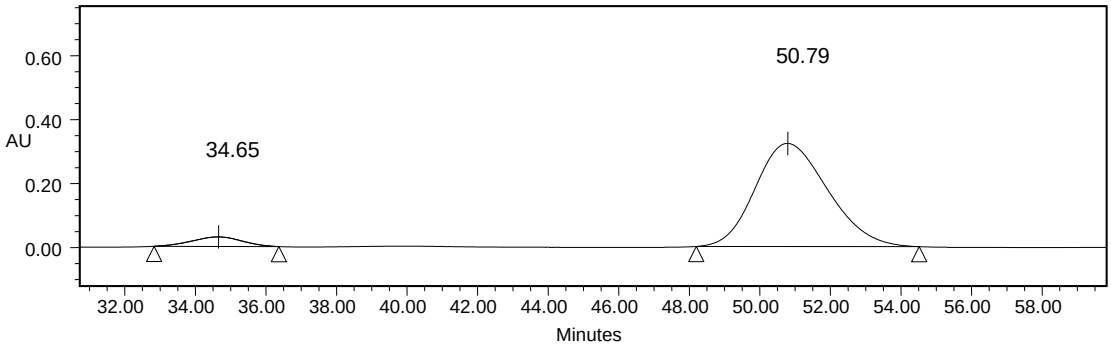
Column: IC
Eluent: 50:50 Hx:iPrOH
Flow rate: 1.0 mL/min
λ: 210 nm

rac-**19Ab**



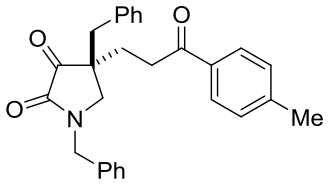
	Retention Time	% Area
1	34.34	49.79
2	50.75	50.21

19Ab



	Retention Time	% Area
1	34.65	6.00
2	50.79	94.00

88% *ee*



20Ab

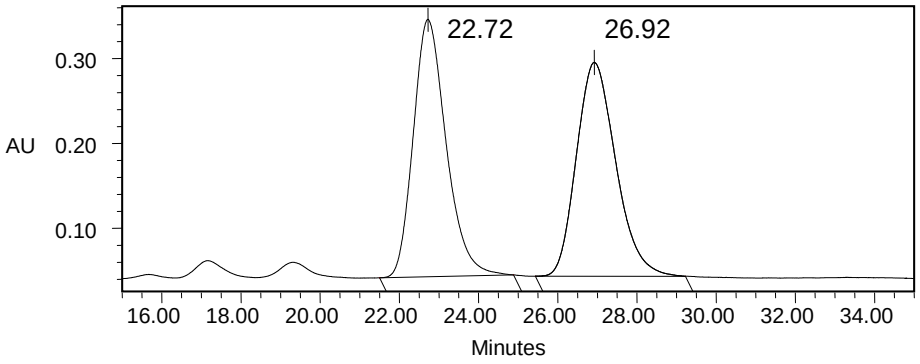
Column: IA

Eluent: 80:20 Hx:iPrOH

Flow rate: 1 mL/min

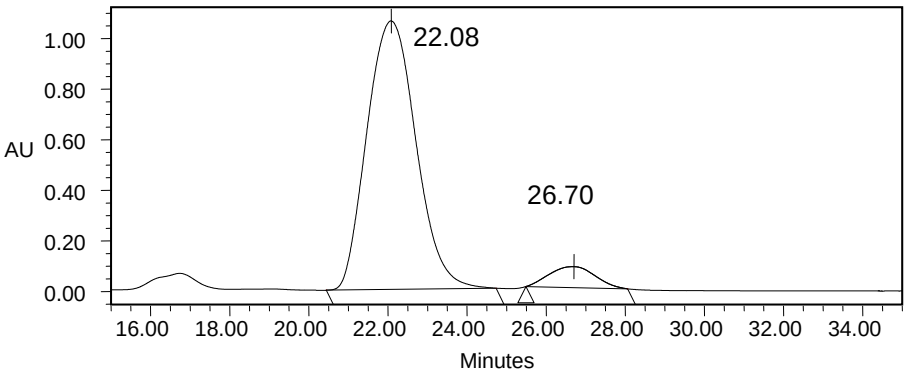
λ: 210 nm

rac-**20Ab**



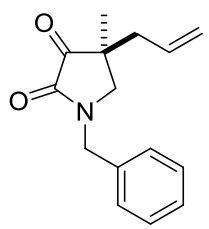
	Retention Time	% Area
1	22.72	50.15
2	26.92	49.85

20Ab



	Retention Time	% Area
1	22.08	93.43
2	26.70	6.57

87% *ee*



22Aa

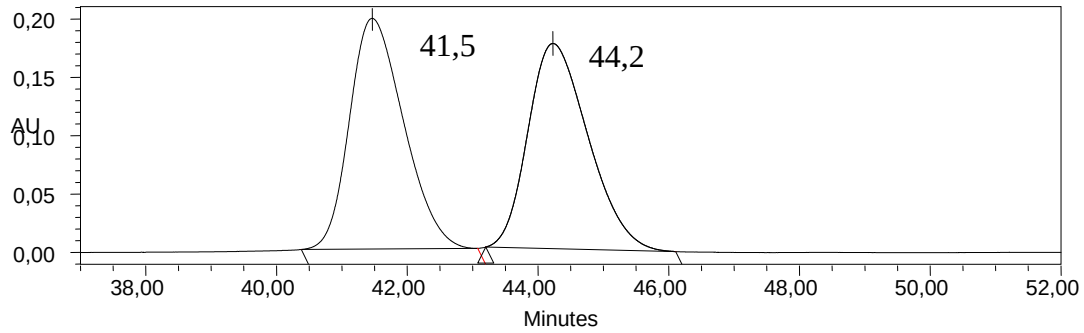
Column: IC

Eluent: 80:20 Hex/*i*PrOH

Flow rate = 1 mL/min

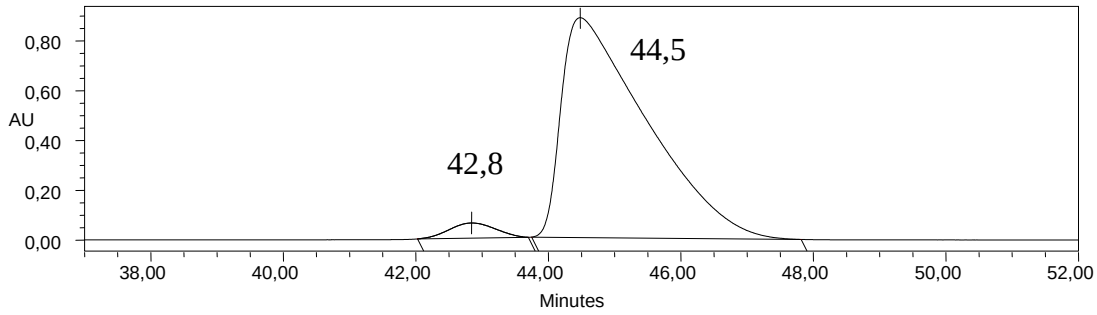
λ: 254 nm

rac-**22Aa**



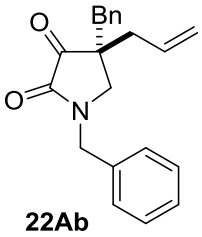
Retention Time	% Area
41,5	50,49
44,2	49,51

22Aa



Retention Time	% Area
42,8	3,58
44,5	96,42

92% *ee*



22Ab

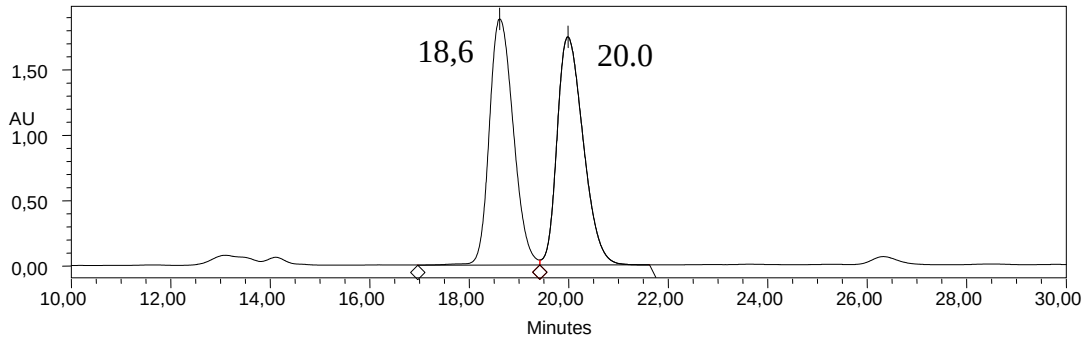
Column: ADH

Eluent: 90:10 Hex/*i*PrOH

Flow rate = 1 mL/min

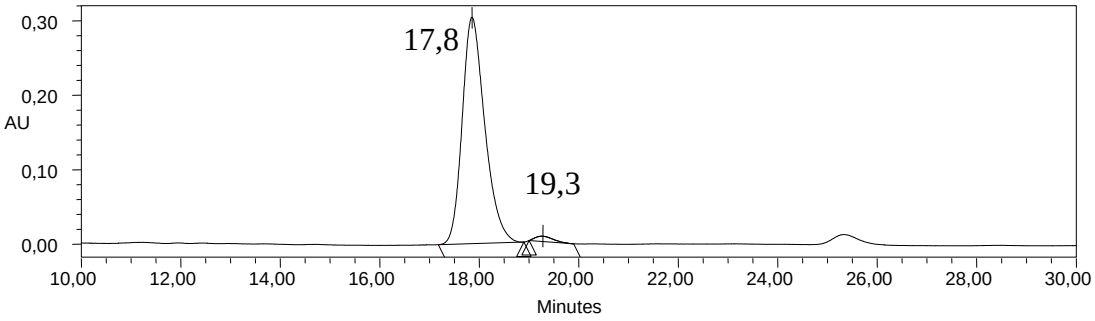
λ: 254 nm

rac-**22Ab**



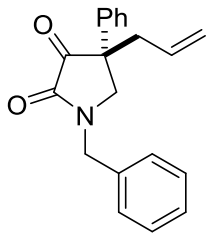
Retention Time	% Area
18,6	49,83
20.0	50,17

22Ab



Retention Time	% Area
17,8	98,19
19,3	1,81

96% *ee*



22Ac

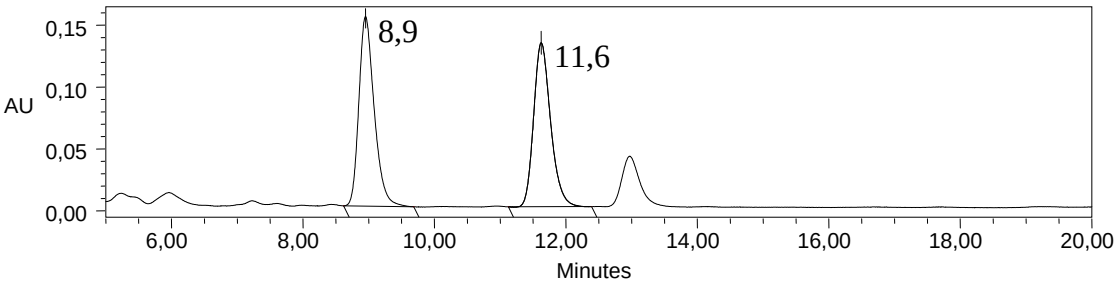
Column: ADH

Eluent: 80:20 Hex/*i*PrOH

Flow rate = 1 mL/min

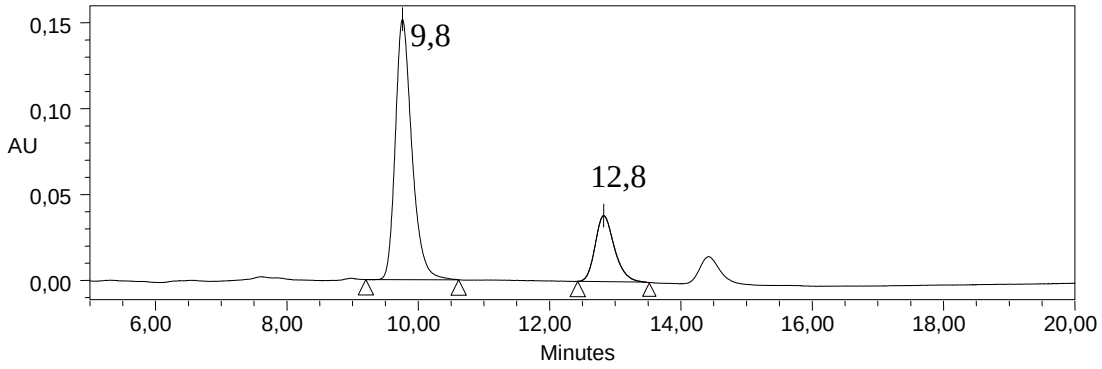
λ: 210 nm

rac-**22Ac**



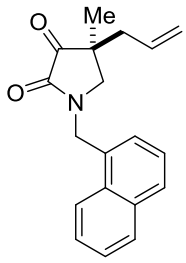
Retention Time	% Area
8,9	51,09
11,6	48,91

22Ac



Retention Time	% Area
9,8	77,28
12,8	22,72

55% *ee*



22Ba

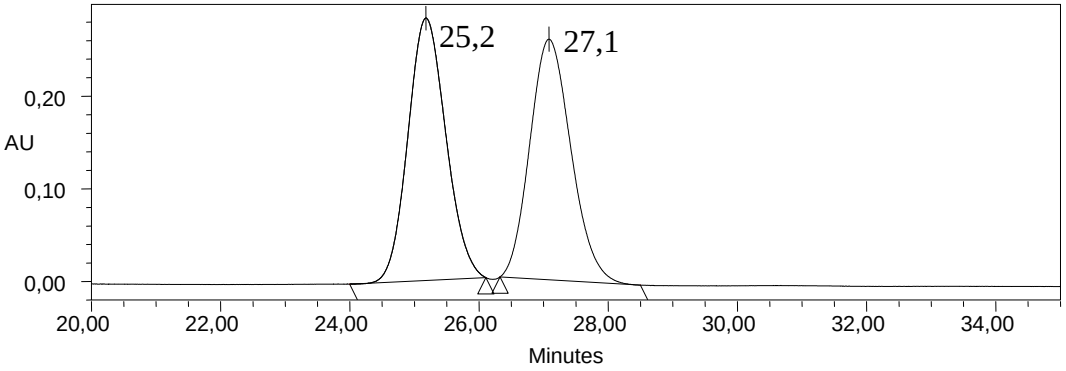
Column: IC

Eluent: 70:30 Hex/*i*PrOH

Flow rate = 1 mL/min

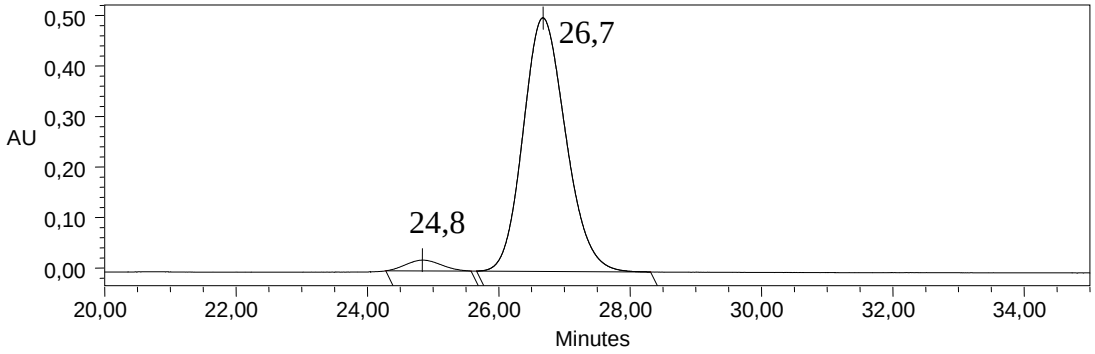
λ: 210 nm

rac-**22Ba**



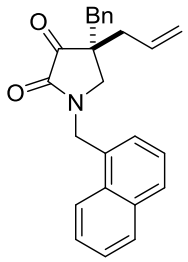
Retention Time	% Area
25,2	50,11
27,1	49,89

22Ba



Retention Time	% Area
24,8	3,39
26,7	96,61

93% *ee*



22Bb

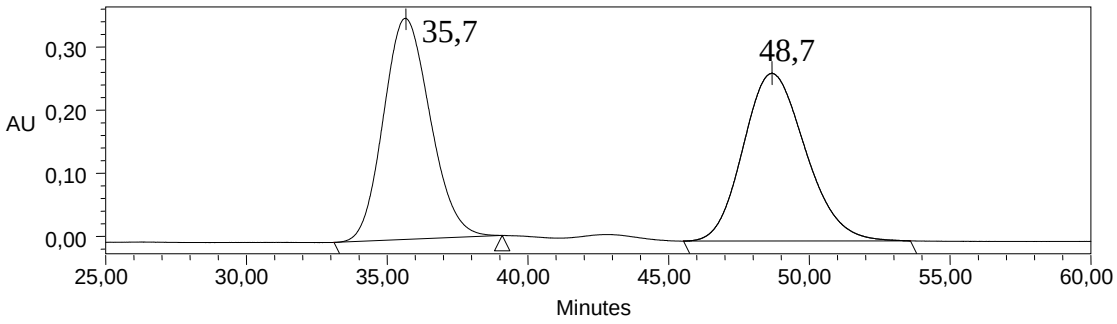
Column: AS-H

Eluent: 50:50 Hex/*i*PrOH

Flow rate = 0.5 mL/min

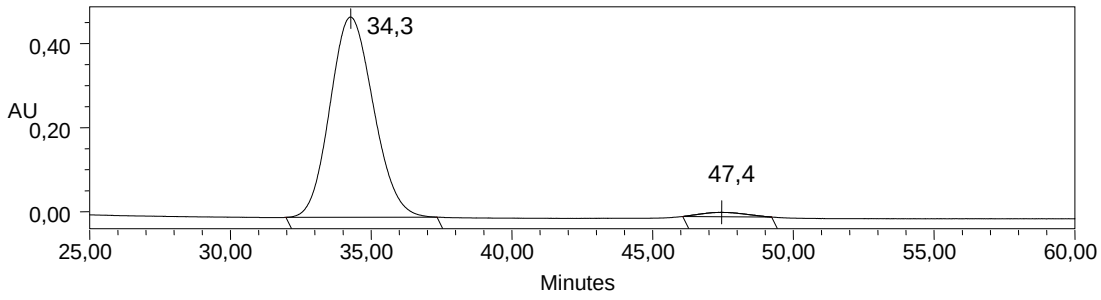
λ: 210 nm

rac-**22Bb**



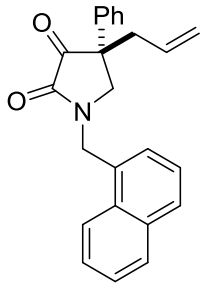
Retention Time	% Area
35,7	49,79
48,7	50,21

22Bb



Retention Time	% Area
34,3	97,85
47,4	2,15

96% *ee*



22Bc

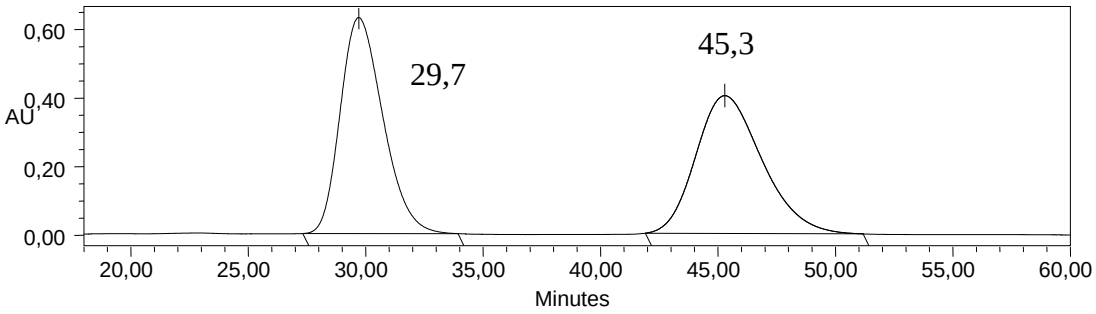
Column: ASH

Eluent: 60:40 Hex/*i*PrOH

Flow rate = 1 mL/min

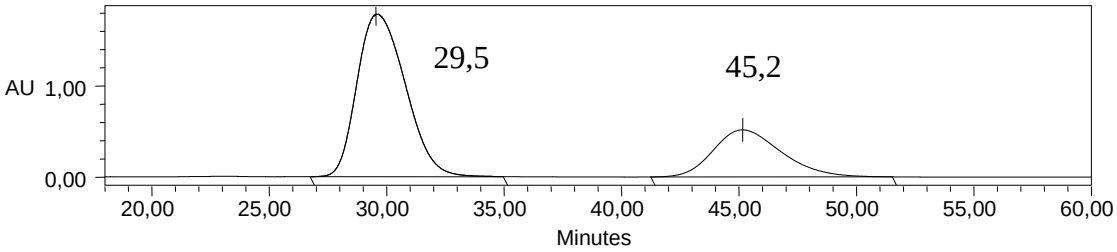
λ: 254 nm

rac-**22Bc**



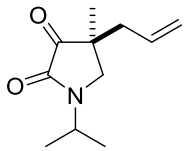
Retention Time	% Area
29,7	50,29
45,3	49,71

22Bc



Retention Time	% Area
29,5	70,95
45,2	29,05

42% *ee*



22Ca

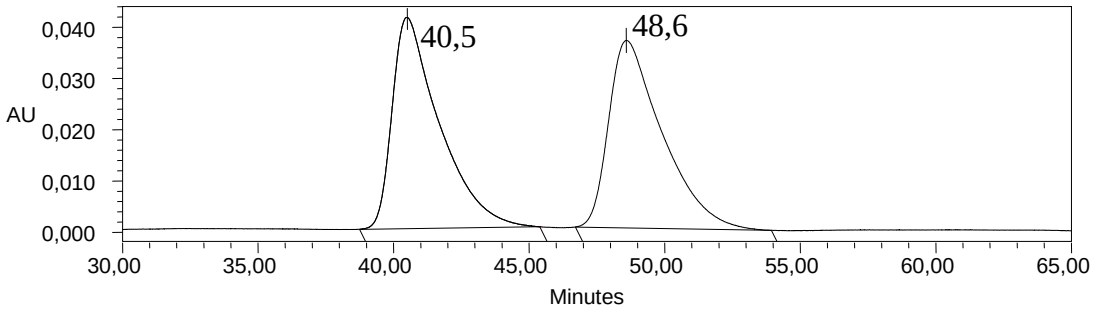
Column: AS-H

Eluent: 90:10 Hex/*i*PrOH

Flow rate = 1 mL/min

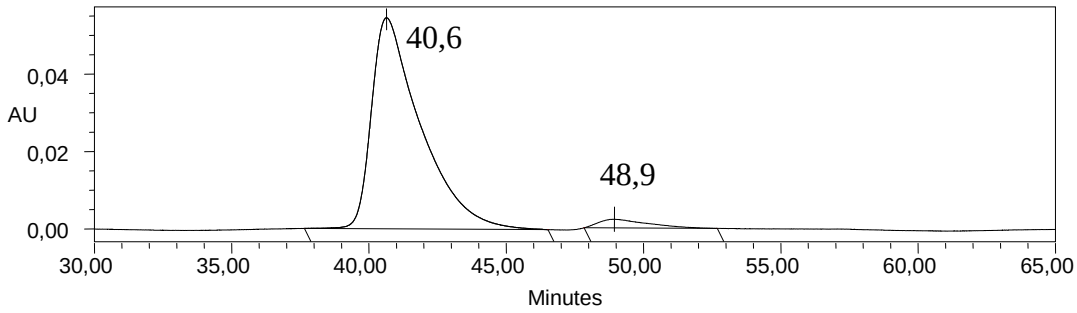
λ: 210 nm

rac-**22Ca**



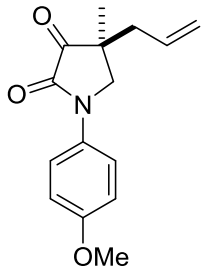
Retention Time	% Area
40,5	49,84
48,6	50,16

22Ca



Retention Time	% Area
40,6	96,06
48,9	3,94

92% *ee*



22Da

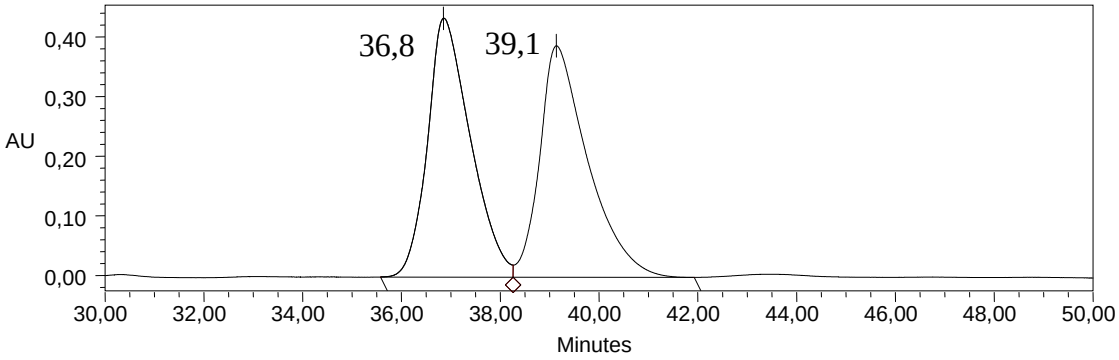
Column: ADH

Eluent: 90:10 Hex/*i*PrOH

Flow rate = 1 mL/min

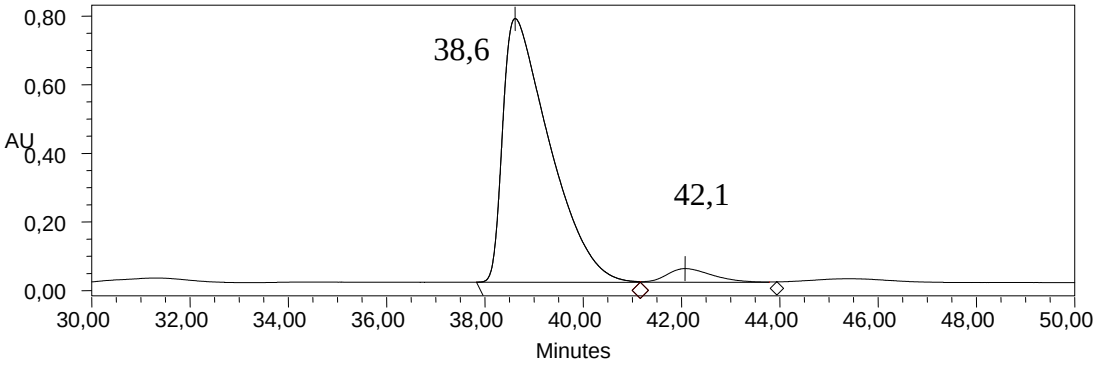
λ: 210 nm

rac-**22Da**



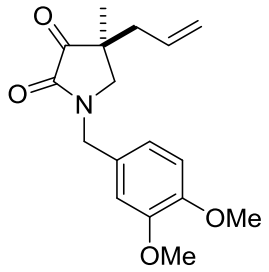
Retention Time	% Area
36,8	50,2
39.1	49,8

22Da



Retention Time	% Area
38,6	95,24
42,1	4,76

90% *ee*



22Ea

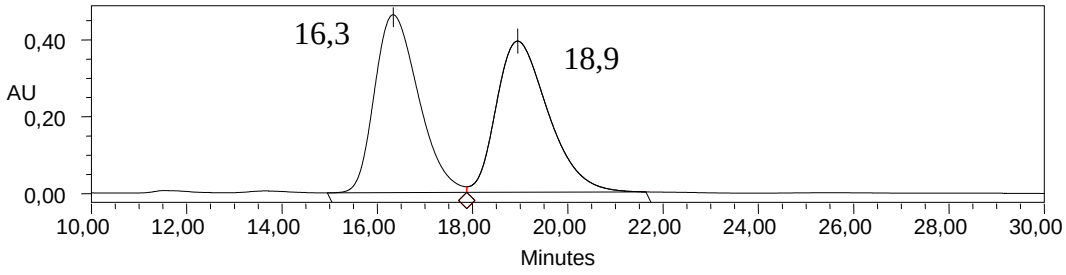
Column: ASH

Eluent: 50:50 Hex/*i*PrOH

Flow rate = 1 mL/min

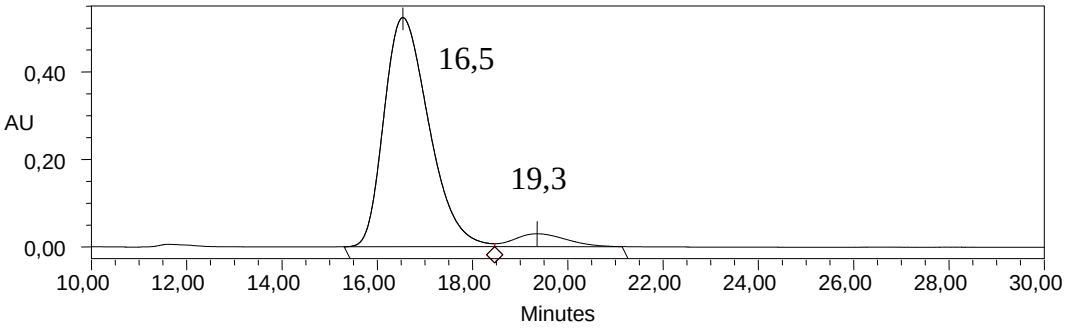
λ: 254 nm

rac-**22Ea**



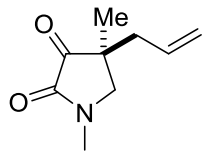
Retention Time	% Area
16,3	49,95
18,9	50,05

22Ea



Retention Time	% Area
16,5	93,87
19,3	6,13

88% *ee*



22Fa

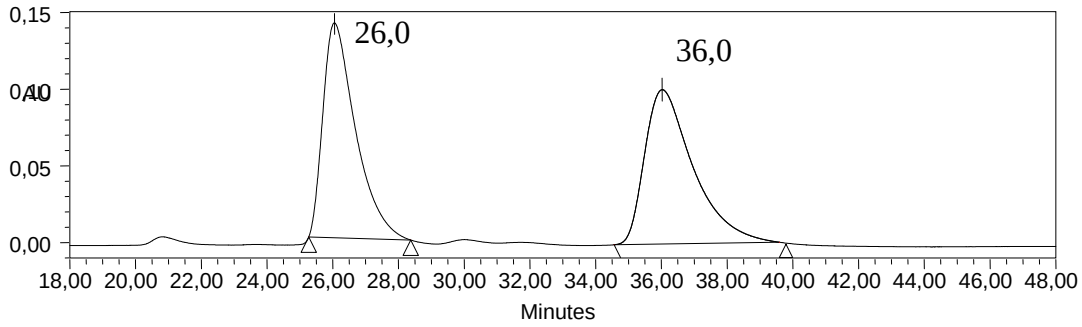
Column: ASH

Eluent: 80:20 Hex/*i*PrOH

Flow rate = 1 mL/min

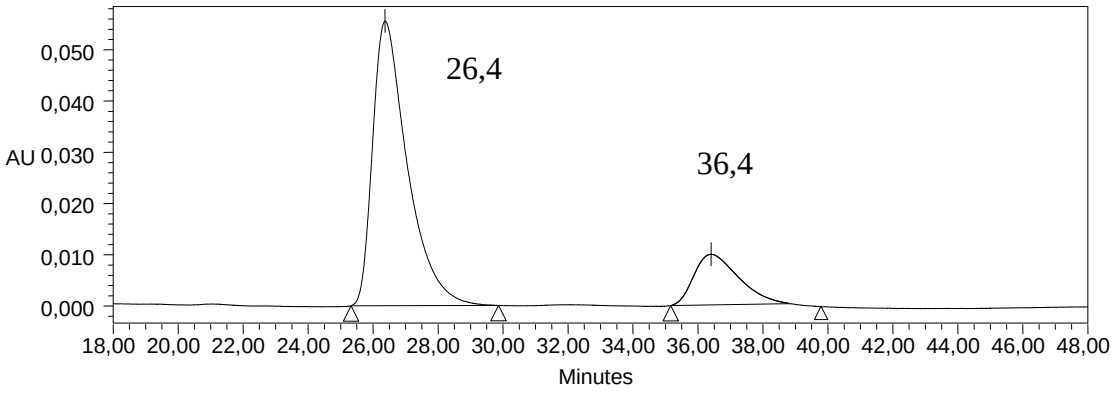
λ: 254 nm

rac-**22Fa**



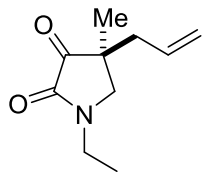
Retention Time	% Area
26,0	50,12
36,0	49,88

22Fa



Retention Time	% Area
26,4	82,70
36,4	17,30

66% *ee*



22Ga

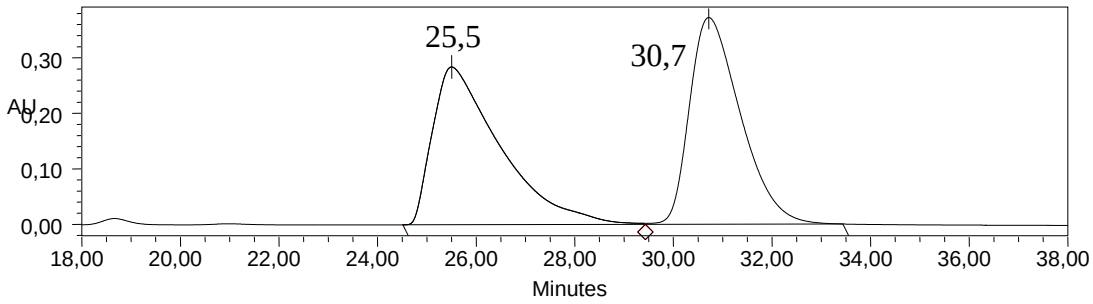
Column: ASH

Eluent: 80:20 Hex/*i*PrOH

Flow rate = 1 mL/min

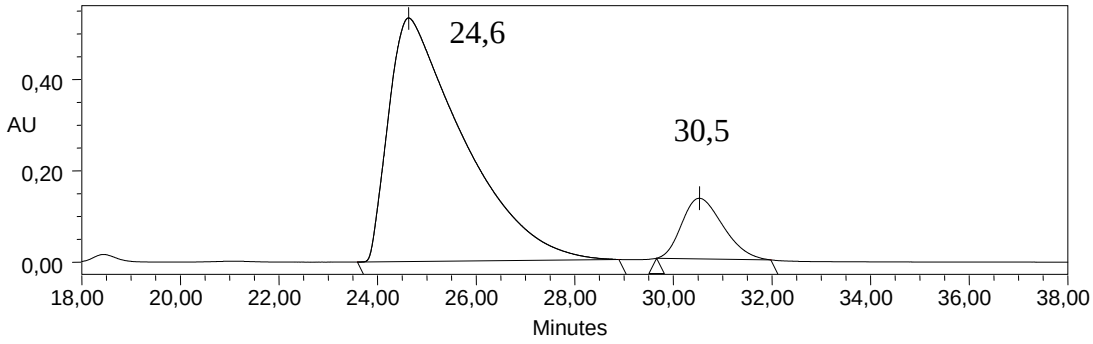
λ: 254 nm

rac-**22Ga**



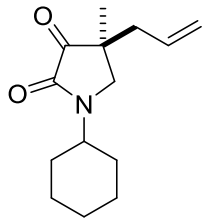
Retention Time	% Area
25,5	50,36
30,7	49,64

22Ga



Retention Time	% Area
24,6	87,89
30,5	12,11

76% *ee*



22Ha

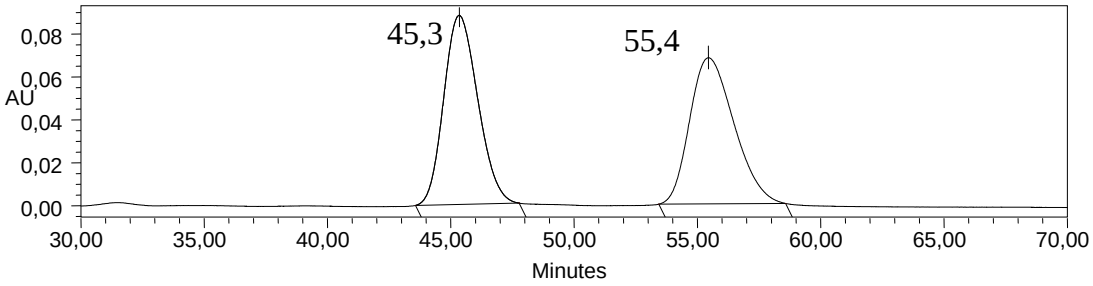
Column: ASH

Eluent: 50:50 Hex/*i*PrOH

Flow rate = 0.5 mL/min

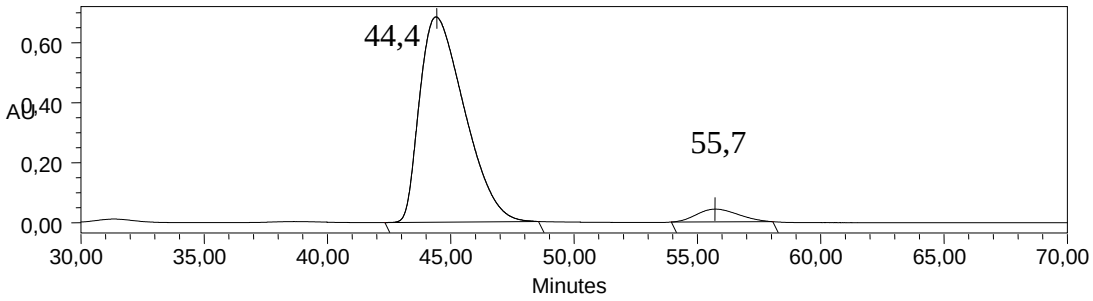
λ: 254 nm

rac-**22Ha**



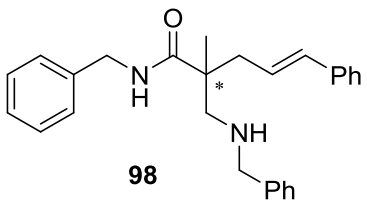
Retention Time	% Area
45,350	49,93
55,448	50,07

22Ha



Retention Time	% Area
44,4	95,49
55,7	4,51

90% *ee*



98

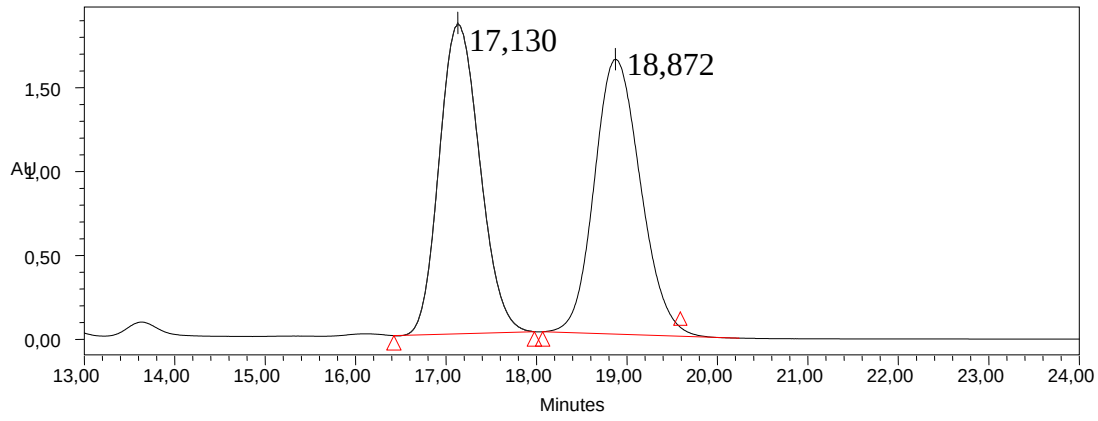
Column: IC

Eluent: 80:20 Hex/*i*PrOH

Flow rate = 1 mL/min

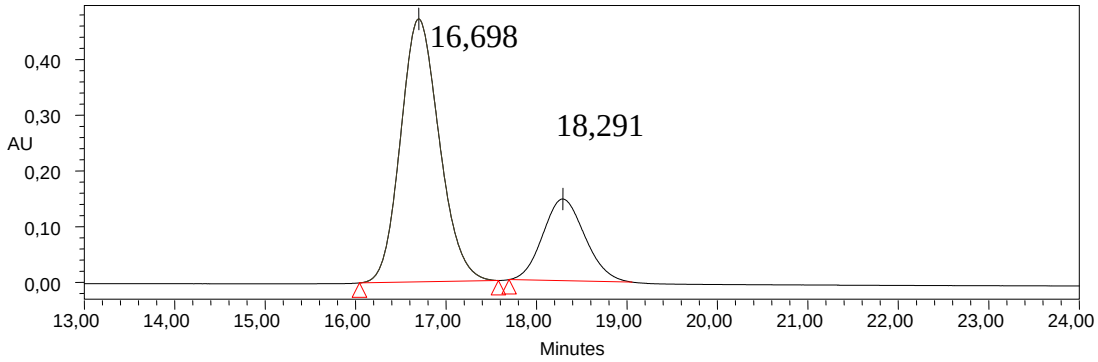
λ: 254 nm

rac-**98**



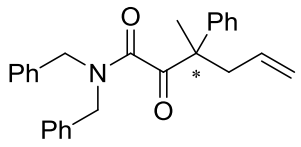
Retention Time	% Area
17,130	49,60
18,872	50,40

98



Retention Time	% Area
16,698	74,78
18,291	25,22

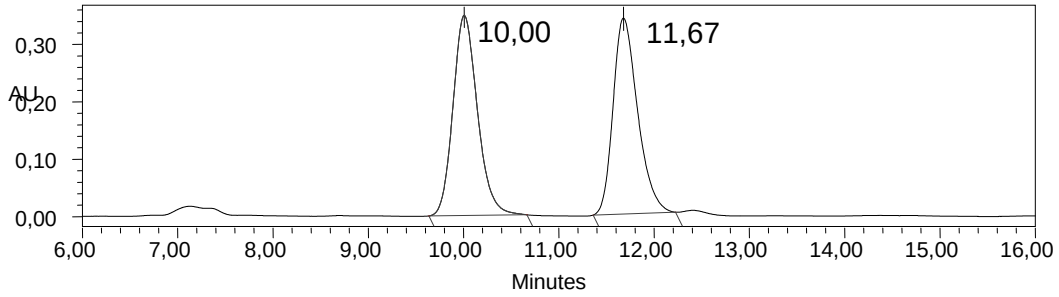
50% *ee*



34A

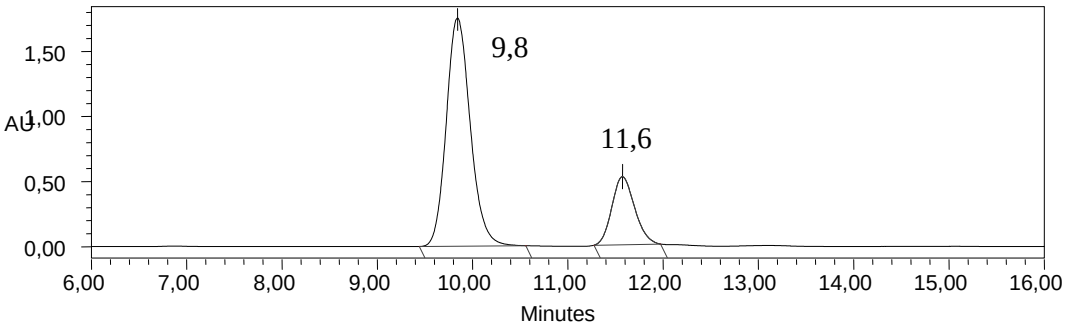
Column: ADH
Eluent: 90:10 Hex/*i*PrOH
Flow rate = 1 mL/min
λ: 254 nm

rac-**34A**



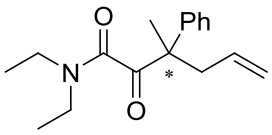
Retention Time	% Area
10,00	50,47
11,67	49,53

34A



Retention Time	% Area
9,8	79,85
11,6	20,15

60% *ee*



34B

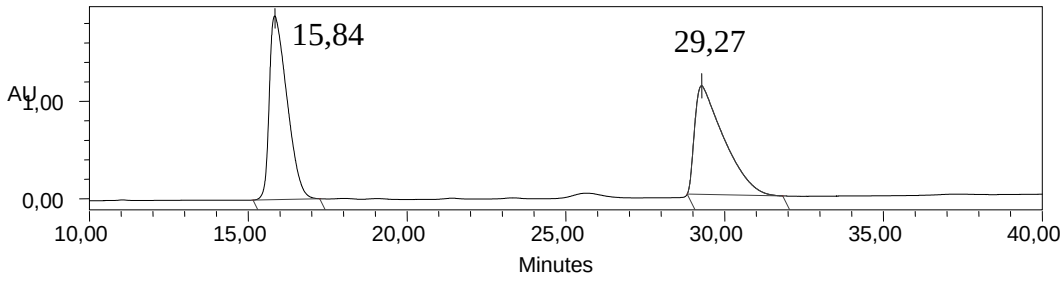
Column: AYH

Eluent: 95:5 Hex/*i*PrOH

Flow rate = 1 mL/min

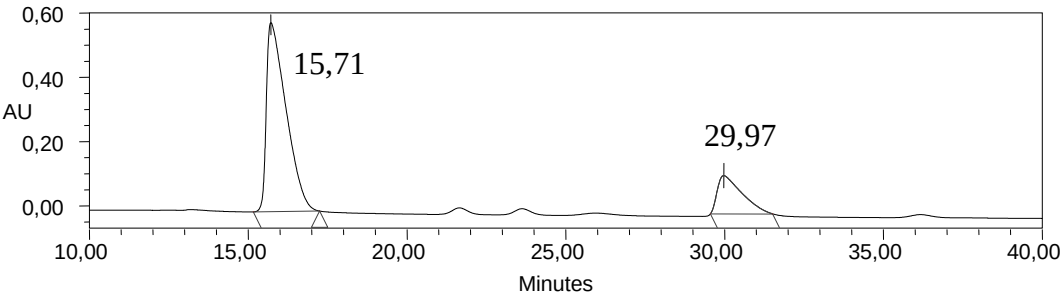
λ: 254 nm

rac-**34B**



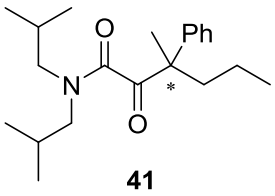
Retention Time	% Area
15,84	50,63
29,37	49,37

34B



Retention Time	% Area
15,71	79,76
29.97	20,24

60% *ee*



41

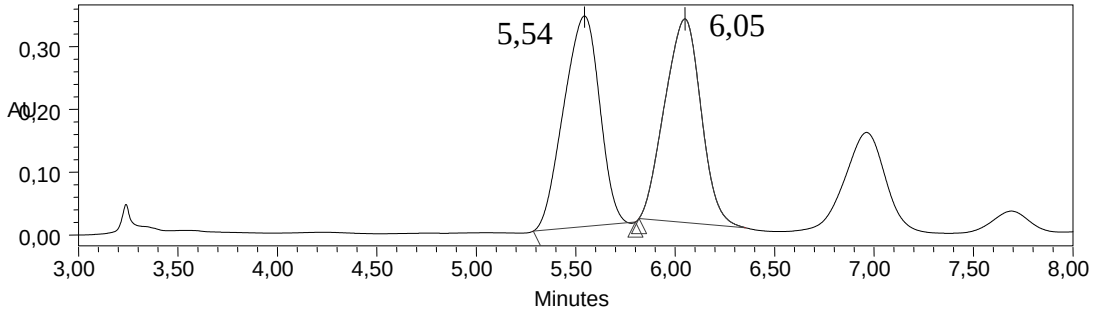
Column: IC

Eluent: 90:10 Hex/*i*PrOH

Flow rate = 1 mL/min

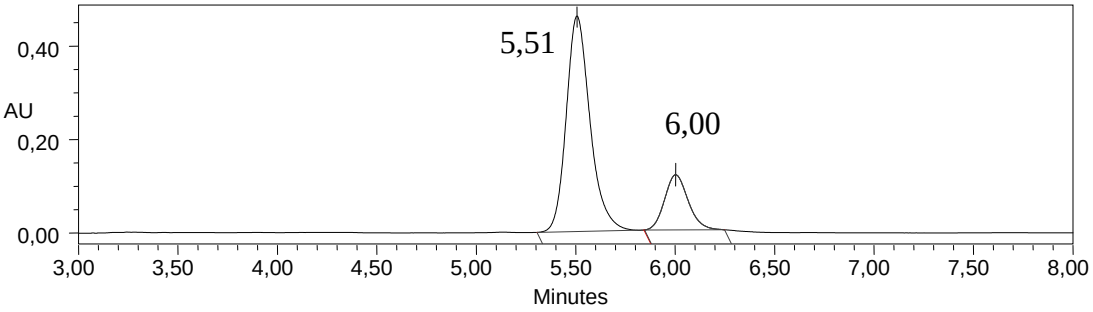
λ: 254 nm

rac-**41**



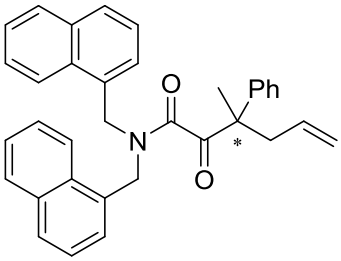
Retention Time	% Area
6,05	49,43
5,54	50,57

41



Retention Time	% Area
5,51	79,84
6,00	20,16

60% *ee*



34D

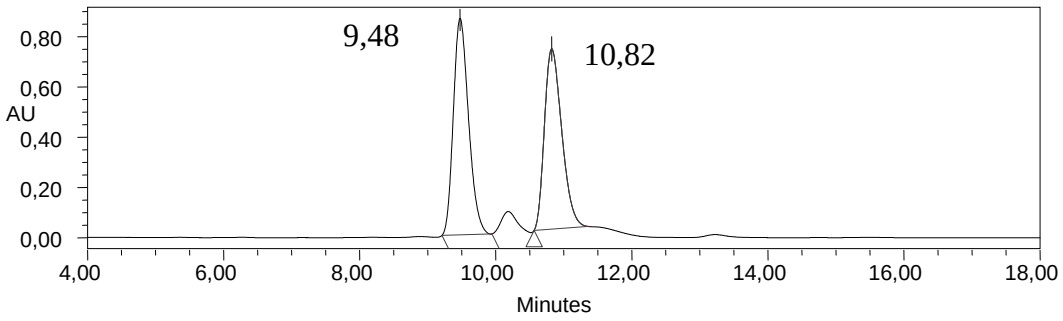
Column: IC

Eluent: 90:10 Hex/*i*PrOH

Flow rate = 1 mL/min

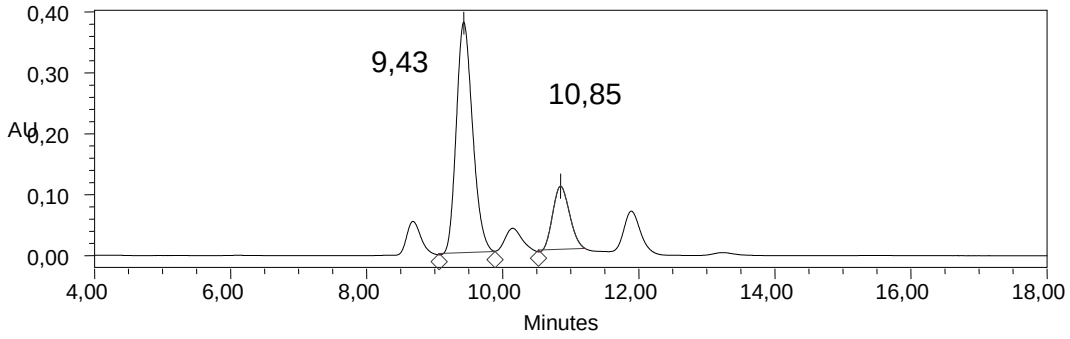
λ: 254 nm

rac-**34D**



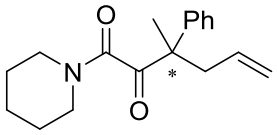
Retention Time	% Area
9,48	51,34
10,82	48,66

34D



Retention Time	% Area
9,43	78,03
10,85	21,97

60% *ee*



34E

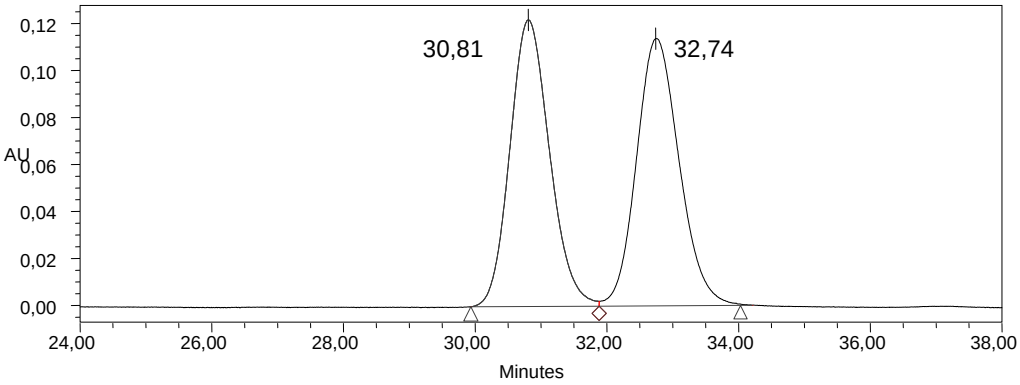
Column: IC

Eluent: 90:10 Hex/*i*PrOH

Flow rate = 1 mL/min

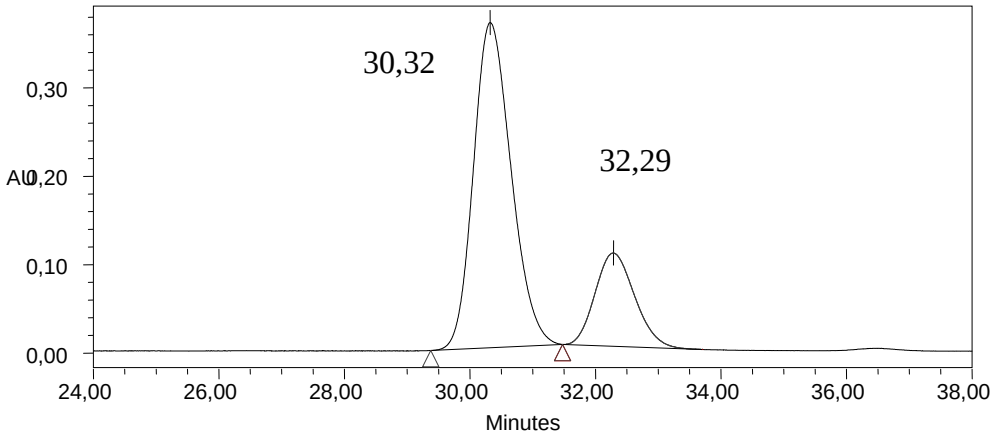
λ: 254 nm

rac-**34E**



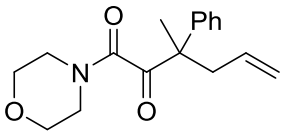
Retention Time	% Area
30,81	49,86
32,74	50,14

34E



Retention Time	% Area
30,32	76,89
32,29	23,11

54% *ee*



34F

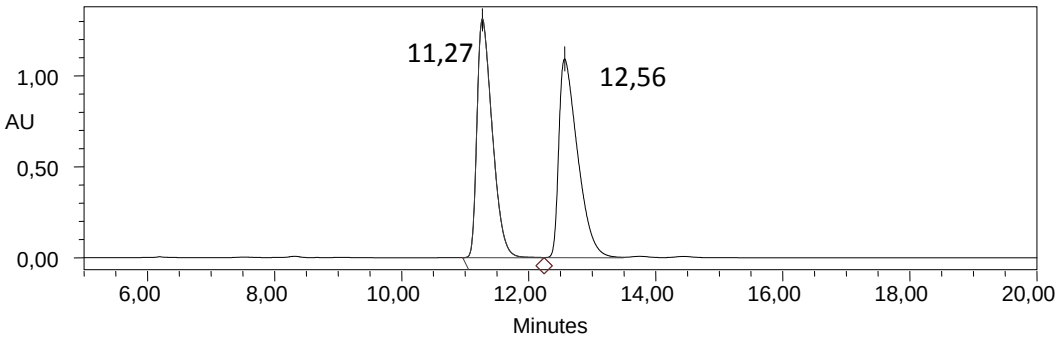
Column: IC

Eluent: 80:20 Hex/*i*PrOH

Flow rate = 1 mL/min

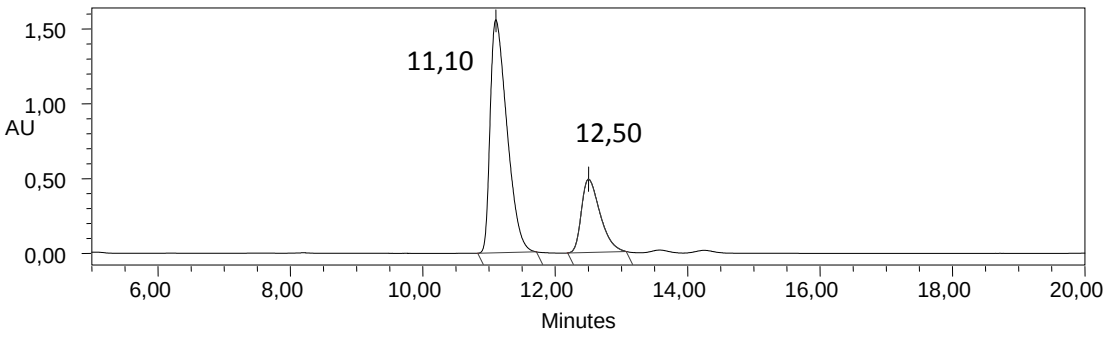
λ: 254 nm

rac-**34F**



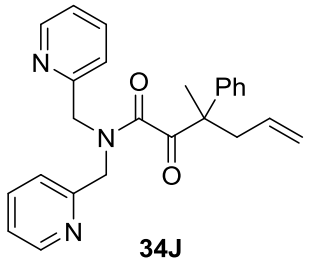
Retention Time	% Area
11,27	49,49
12,56	50,51

34F



Retention Time	% Area
11,10	74,12
12,50	25,88

48% *ee*



34J

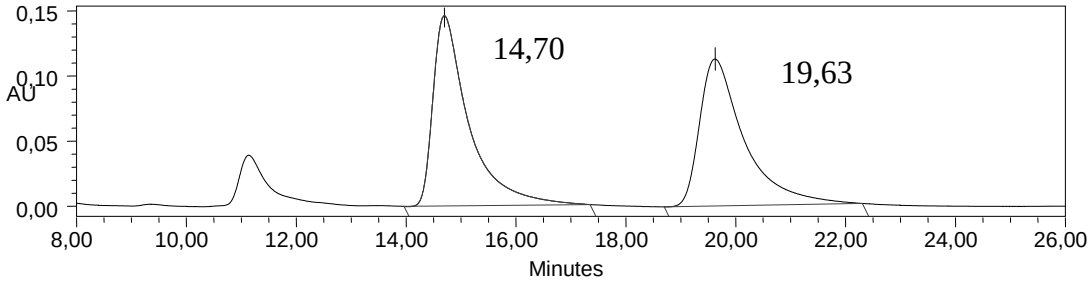
Column: IA

Eluent: 70:30 Hex/*i*PrOH

Flow rate = 1 mL/min

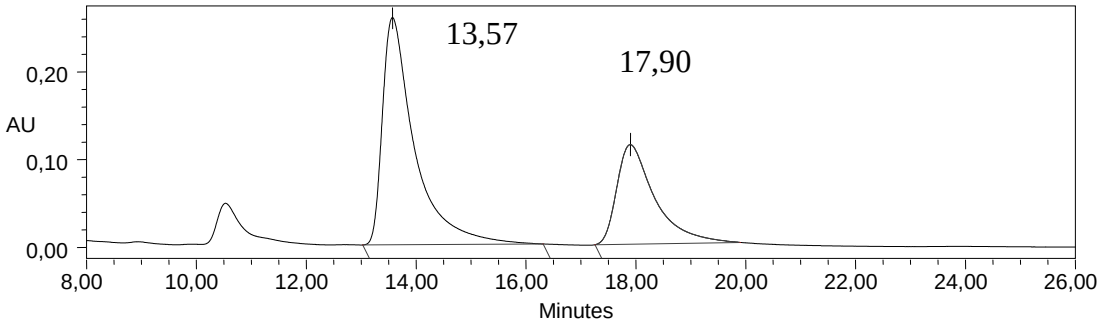
λ: 254 nm

rac-**34J**



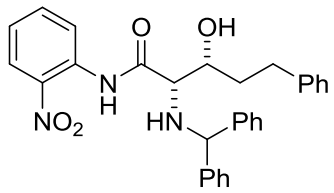
Retention Time	% Area
14,70	65,93
19,63	34,07

34J



Retention Time	% Area
13,57	65,93
17,90	34,07

32% *ee*



49a

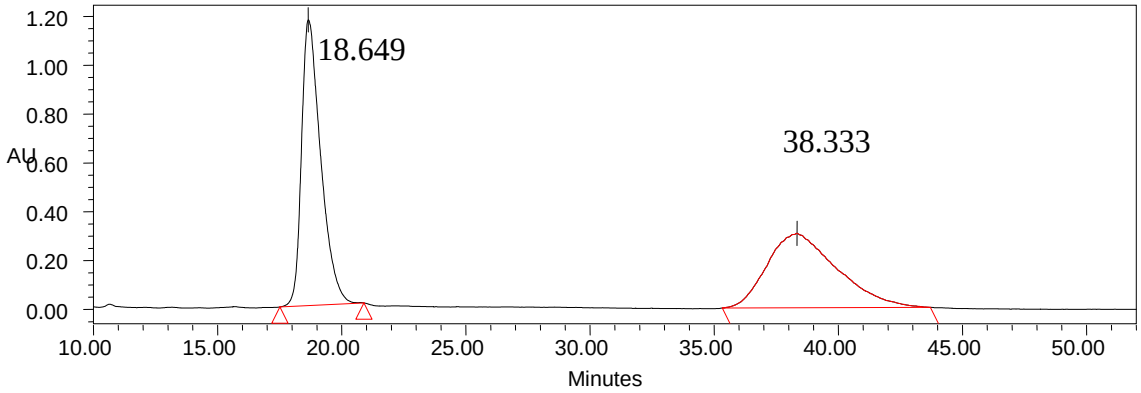
Eluent: Hx/EtOH, 90/10

Flow: 1 mL/min

Column: IA

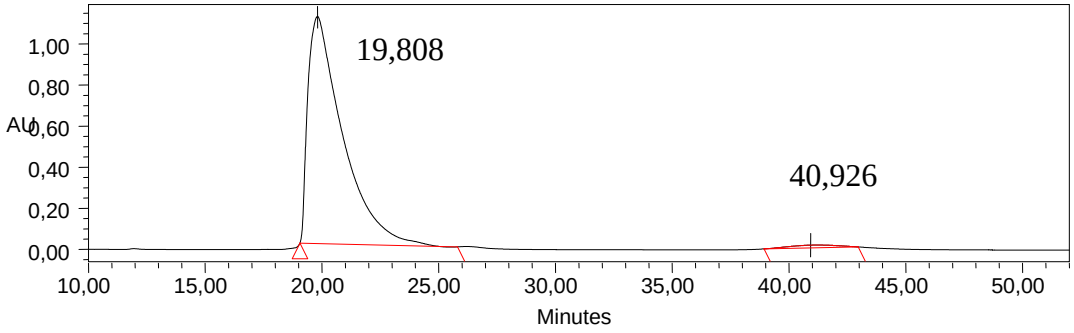
λ: 254 nm

rac-**49a**



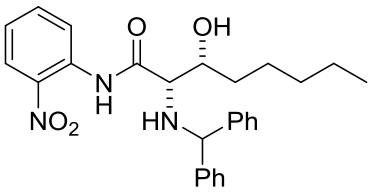
	Retention Time	% Area
1	18.649	50.47
2	38.333	49.53

49a



	Retention Time	% Area
1	19,808	97,12
2	41,228	2,88

94% *ee*



49b

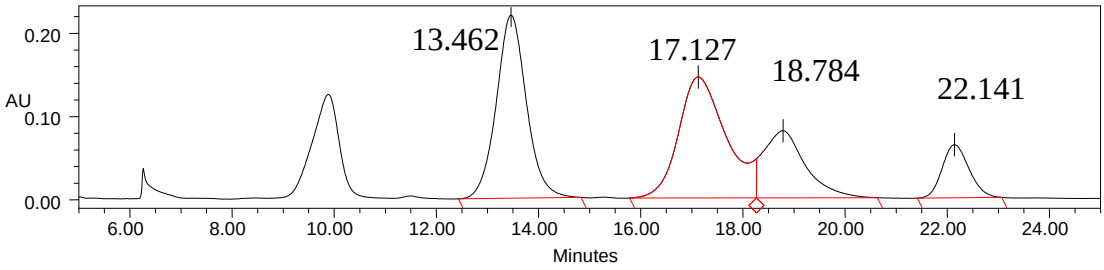
Eluent: Hx/EtOH, 90/10

Flow: 1 mL/min

Column: IA

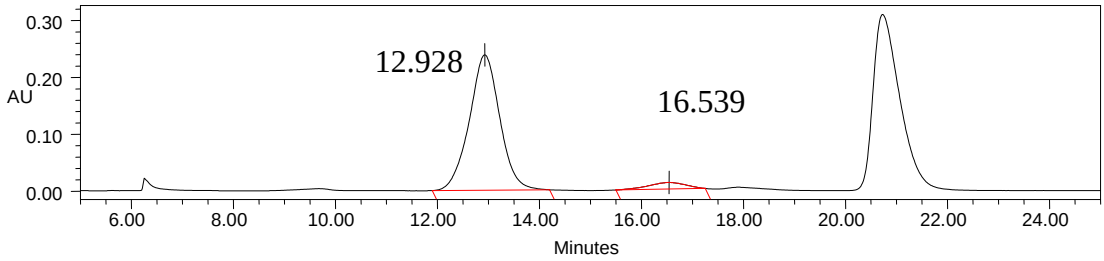
λ: 254 nm

rac-**49b**



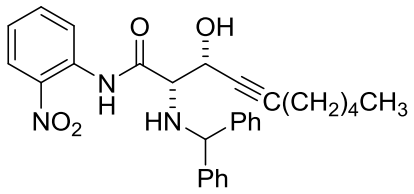
	Retention Time	% Area
1	13.462	35.59
2	17.127	37.27
3	18.784	17.93
4	22.141	9.21

49b



	Retention Time	% Area
1	12.928	94.39
2	16.539	5.61

89% *ee*



Major diastereoisomer
49c

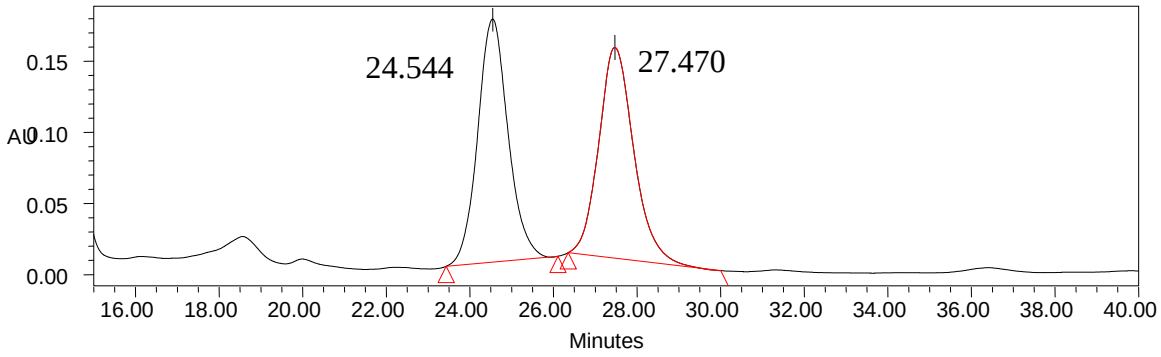
Eluent: Hx/EtOH, 90/10

Flow: 0.5 mL/min

Column: IA

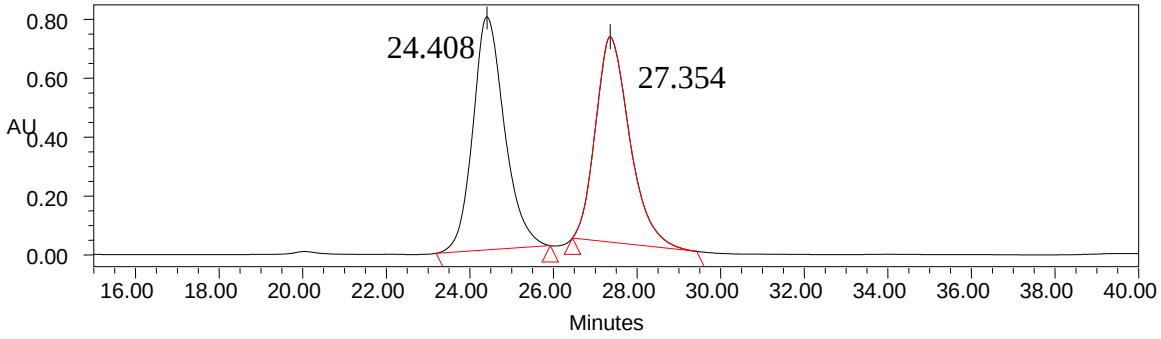
λ: 254 nm

rac-**49c**



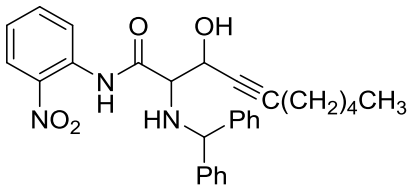
	Retention Time	% Area
1	24.544	49.98
2	27.470	50.02

49c



	Retention Time	% Area
1	24.408	51.22
2	27.354	48.78

2% *ee*



Minor diastereoisomer
49c

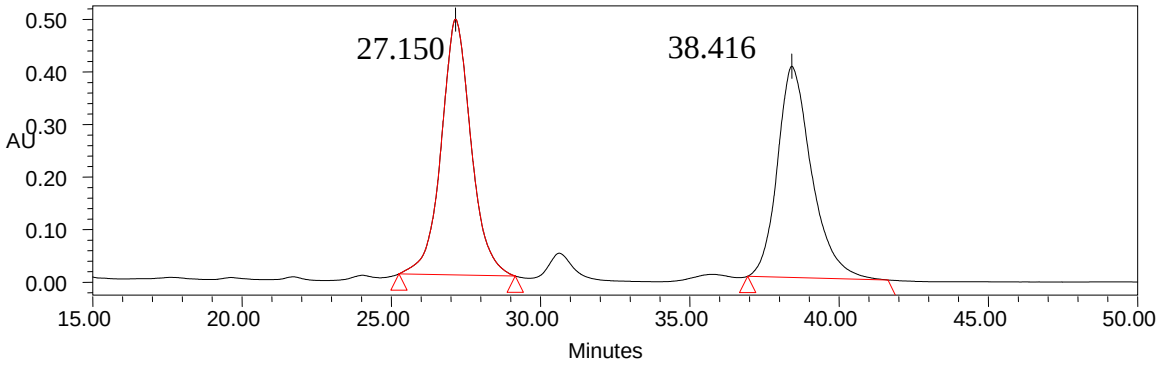
Eluent: Hx/EtOH, 90/10

Flow: 0.5 mL/min

Column: IA

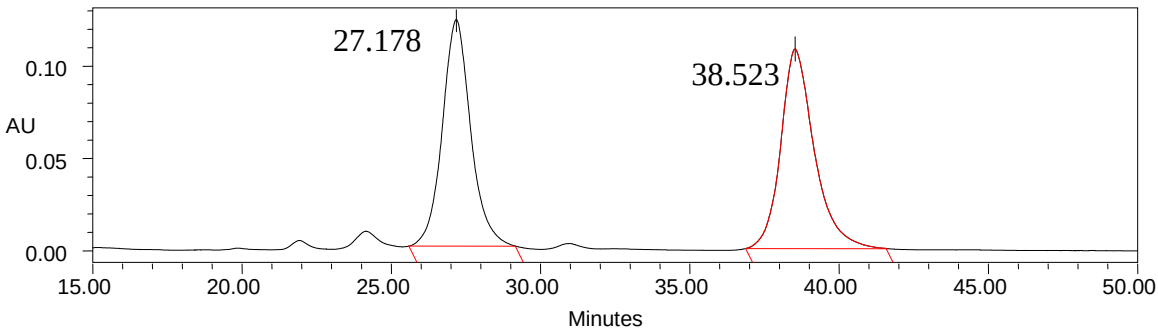
λ: 254 nm

Rac-**49c**



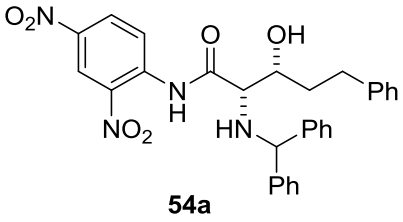
	Retention Time	% Area
1	27.150	51.37
2	38.416	48.63

49c



	Retention Time	% Area
1	27.178	49.03
2	38.523	50.97

2% *ee*



54a

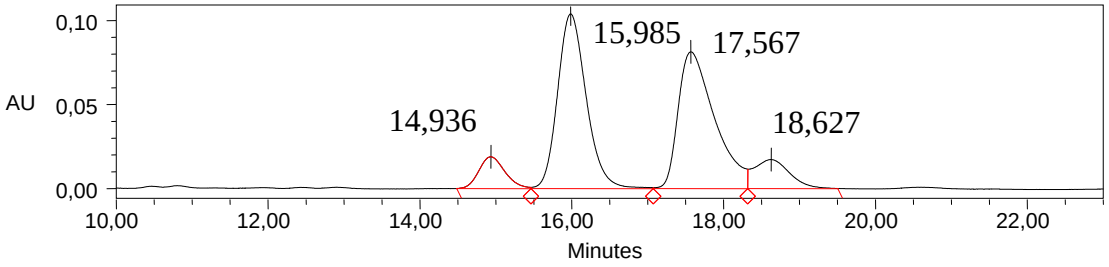
Eluent: Hx/EtOH, 90/10

Flow: 1 mL/min

Column: IF

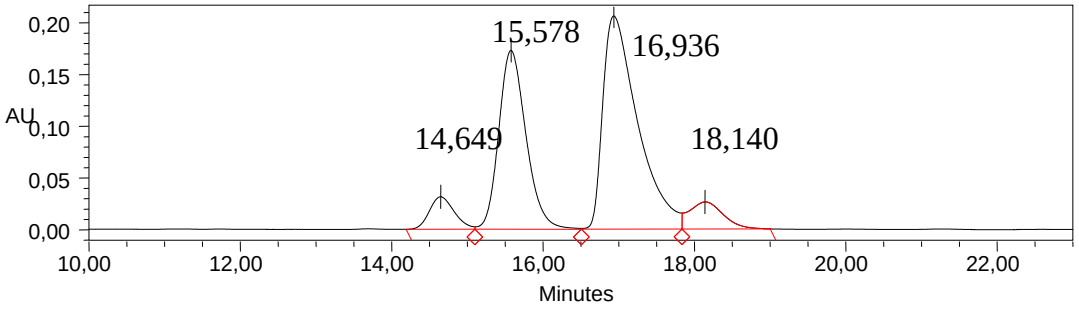
λ: 254 nm

rac-**54a**



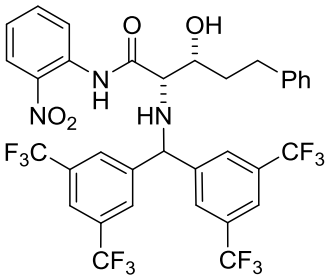
	Retention Time	% Area
1	14,936	6,98
2	15,985	42,26
3	17,567	42,09
4	18,627	8,68

54a



	Retention Time	% Area
1	14,649	5,76
2	15,578	34,74
3	16,936	52,97
4	18,140	6,53

20% *ee*



59a

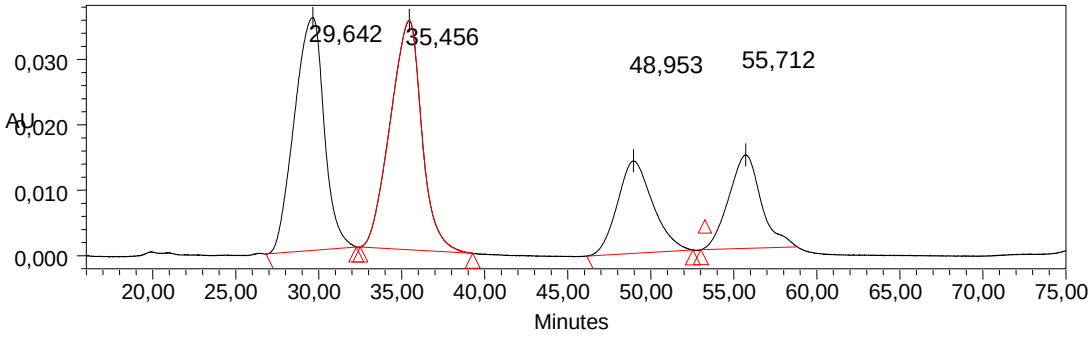
Eluent: Hx/*i*PrOH, 98/2

Flow: 0.5 mL/min

Column: IAIA

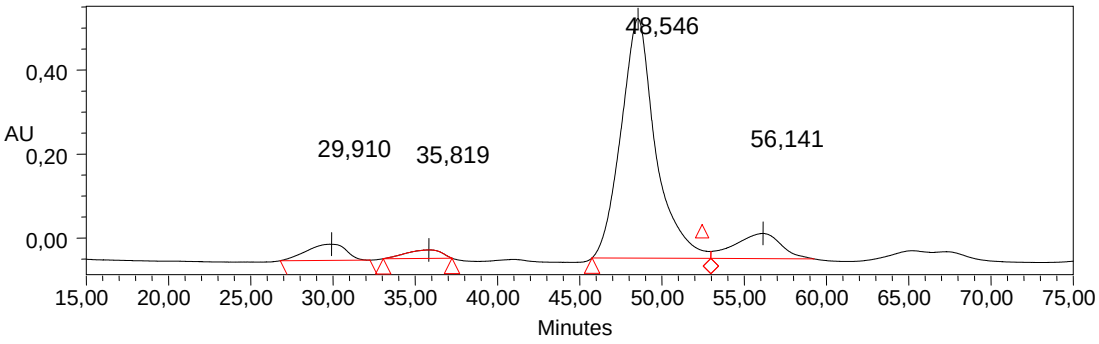
λ: 254 nm

rac-**59a**



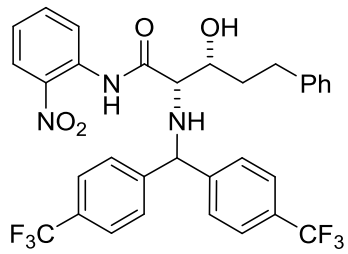
	Retention Time	% Area
1	29,642	33,89
2	35,456	35,33
3	48,953	15,97
4	55,712	14,81

59a



	Retention Time	% Area
1	48,546	87,65
2	56,141	12,35

76% *ee*



60a

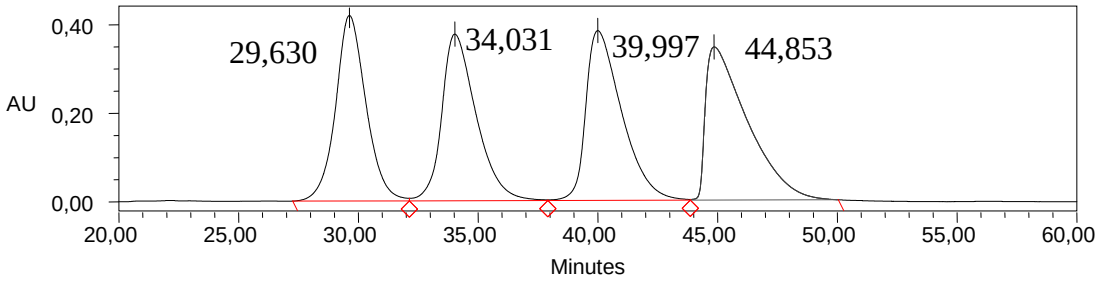
Eluent: Hx/EtOH, 98/2

Flow: 0.5 mL/min

Column: IF

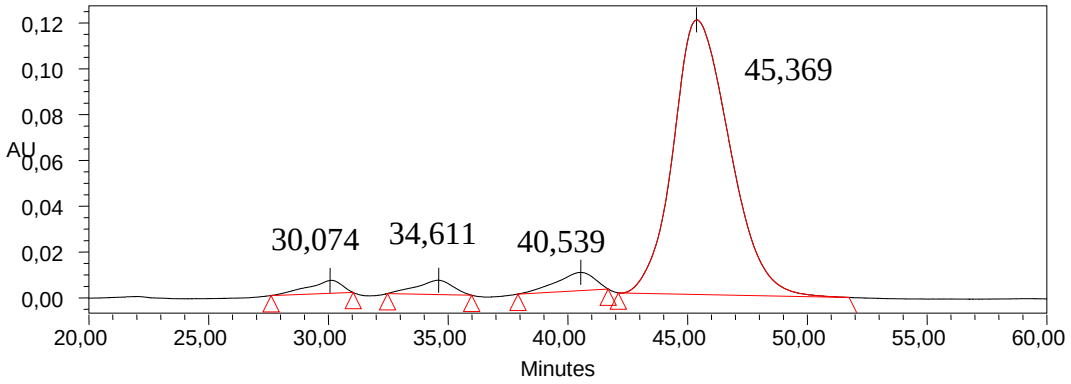
λ: 254 nm

Rac-**60a**



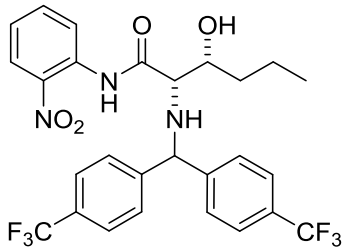
	Retention Time	% Area
1	29,630	23,67
2	34,031	24,00
3	39,997	25,50
4	44,853	26,82

60a



	Retention Time	% Area
1	40,539	4,29
2	45,369	95,71

92% *ee*



60h

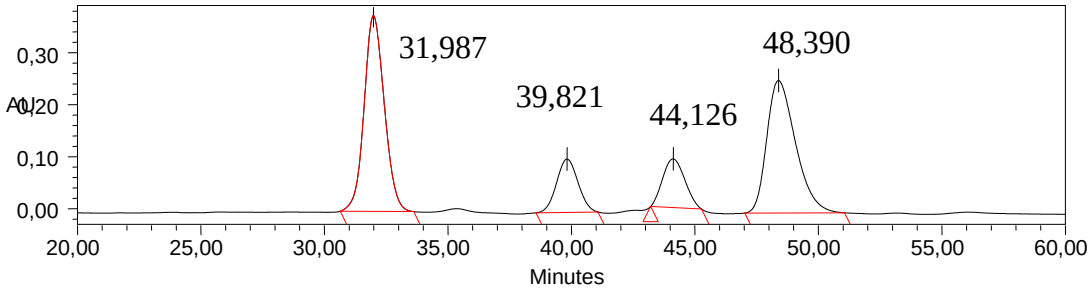
Eluent: Hx/*i*PrOH, 95/5

Flow: 0.5 mL/min

Column: Phenomenex-Lux 3µm Amylose-1

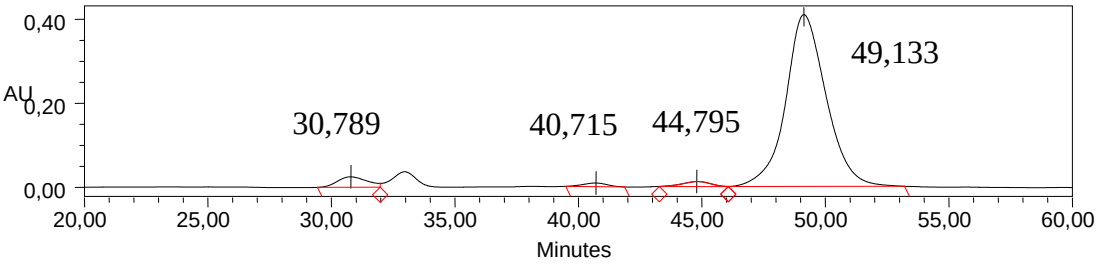
λ: 254 nm

Rac-**60h**



	Retention Time	% Area
1	31,987	39,71
2	39,821	11,48
3	44,126	10,76
4	48,390	38,06

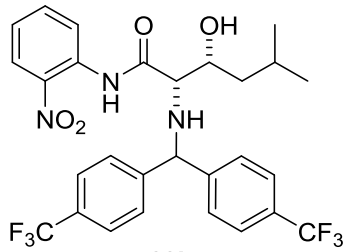
60h



	Retention Time	% Area
1	30,789	4,18
2	40,715	1,16
3	44,795	1,89
4	49,133	92,78

	Retention Time	% Area
1	30,789	4,31
2	49,133	95,69

92% *ee*



60i

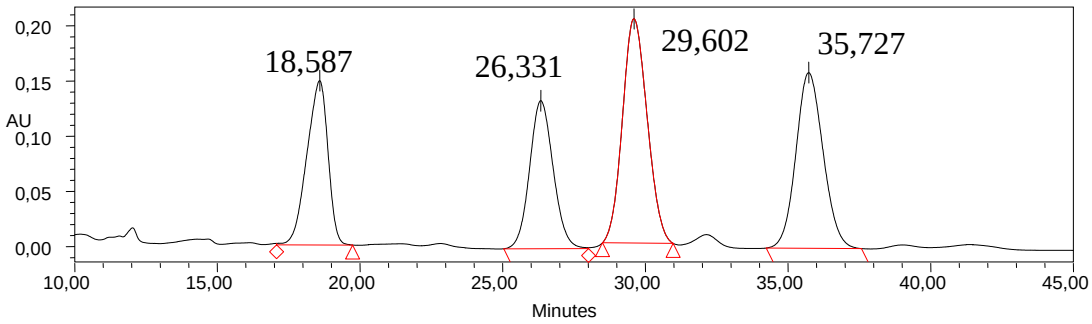
Eluent: Hx/*i*PrOH, 98/2

Flow: 0.5 mL/min

Column: Phenomenex-Lux 3µm Amylose-1

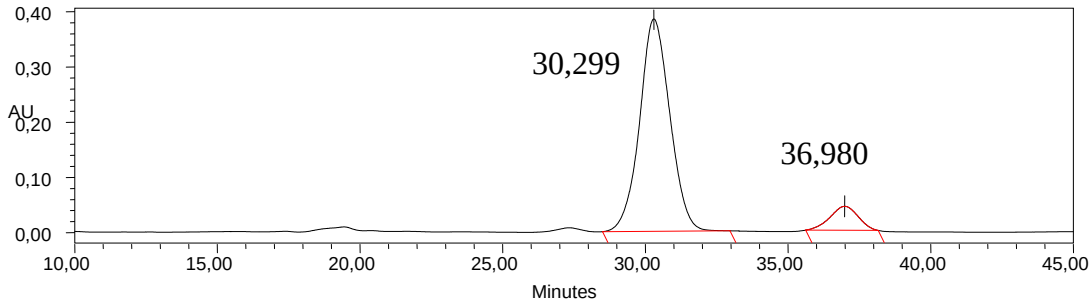
λ: 254 nm

Rac-**60i**



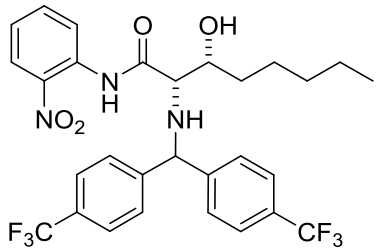
	Retention Time	% Area
1	18,587	20,01
2	26,331	20,19
3	29,602	32,13
4	35,727	27,68

60i



	Retention Time	% Area
1	30,299	92,49
2	36,980	7,51

84% *ee*



60b

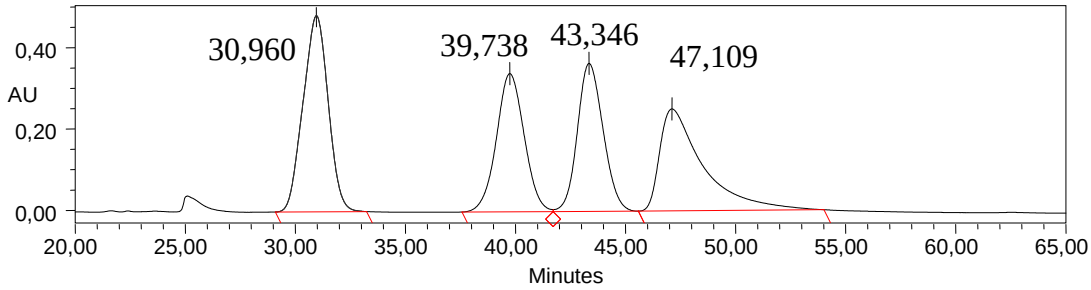
Eluent: Hx/*i*PrOH, 95/5

Flow: 0.5 mL/min

Column: Phenomenex-Lux 3µm Amylose-1

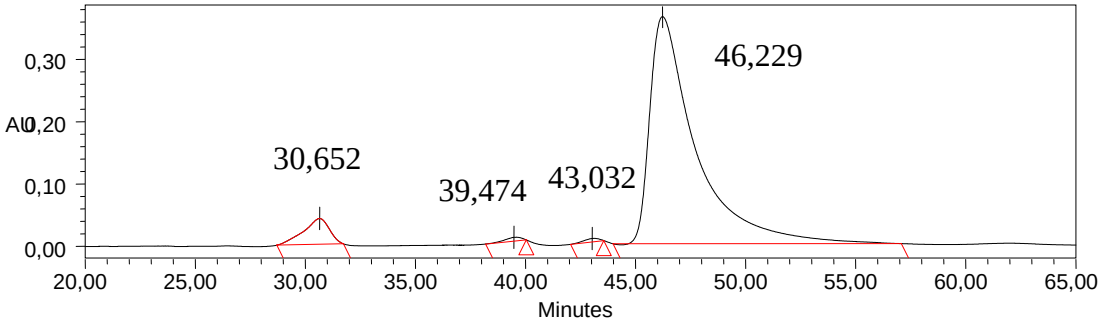
λ: 254 nm

Rac-**60b**



	Retention Time	% Area
1	30,961	28,36
2	39,738	22,59
3	43,346	22,38
4	47,109	26,67

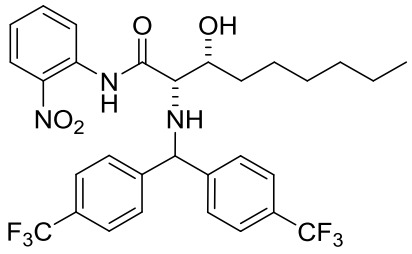
60b



	Retention Time	% Area
1	30,652	5,13
2	39,474	0,56
3	43,032	0,47
4	46,229	93,84

	Retention Time	% Area
1	30,652	5,18
2	46,229	94,82

90% *ee*



60j

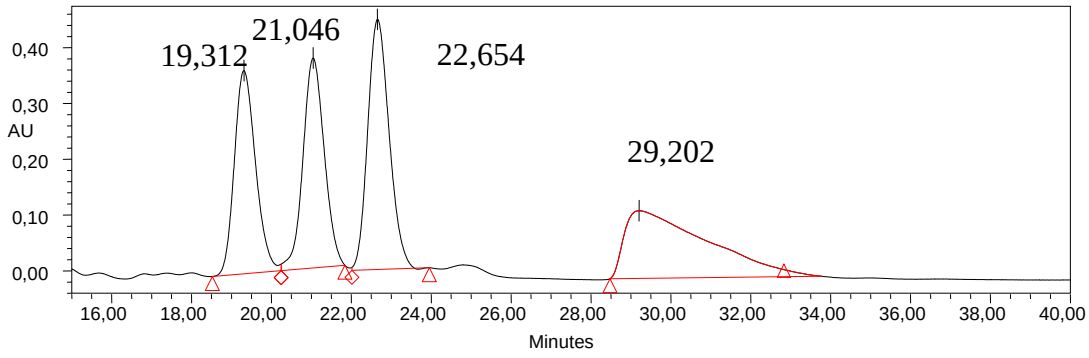
Eluent: Hx/*i*PrOH, 95/5

Flow: 0.5 mL/min

Column: Phenomenex-Lux 3 µm Cellulose-1

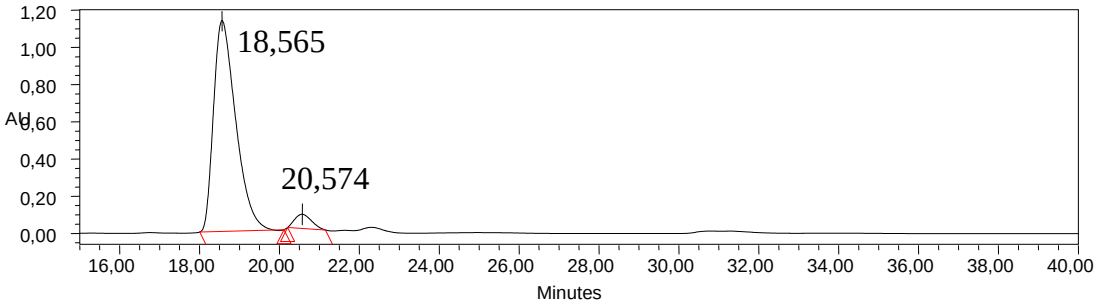
λ: 254 nm

Rac-**60j**



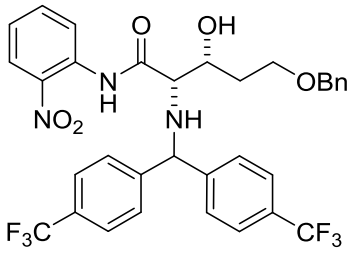
	Retention Time	% Area
1	19,312	21,87
2	21,046	22,64
3	22,654	27,16
4	29,202	28,33

60j



	Retention Time	% Area
1	18,565	95,14
2	20,574	4,86

90% *ee*



60k

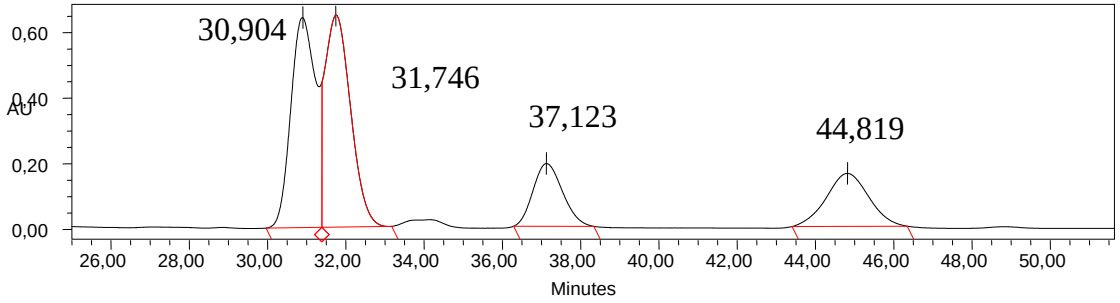
Eluent: Hx/*i*PrOH, 95/5

Flow: 0.5 mL/min

Column: Phenomenex-Lux 3 µm Cellulose-1

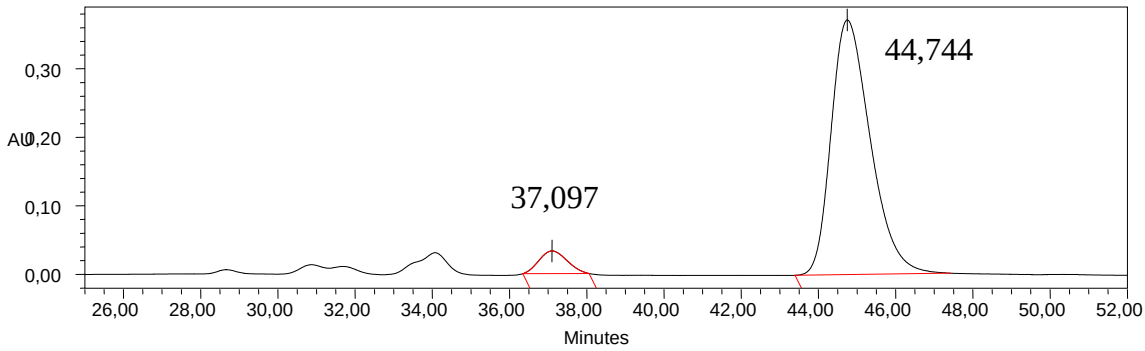
λ: 254 nm

Rac-**60k**



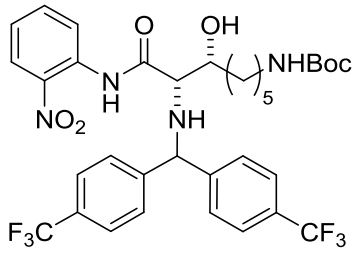
	Retention Time	% Area
1	30,904	35,84
2	31,746	36,45
3	37,123	12,52
4	44,819	15,20

60k



	Retention Time	% Area
1	37,106	5,31
2	44,744	94,69

90% *ee*



60l

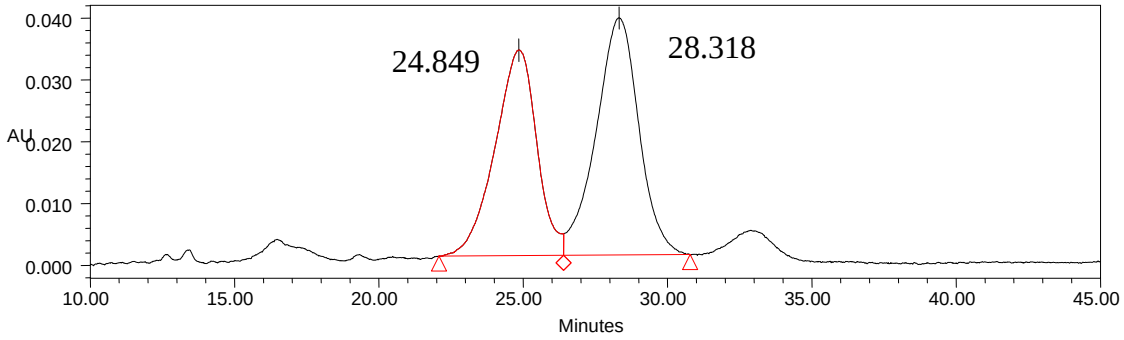
Eluent: Hx/*i*PrOH, 90/10

Flow: 0.5 mL/min

Column: IA

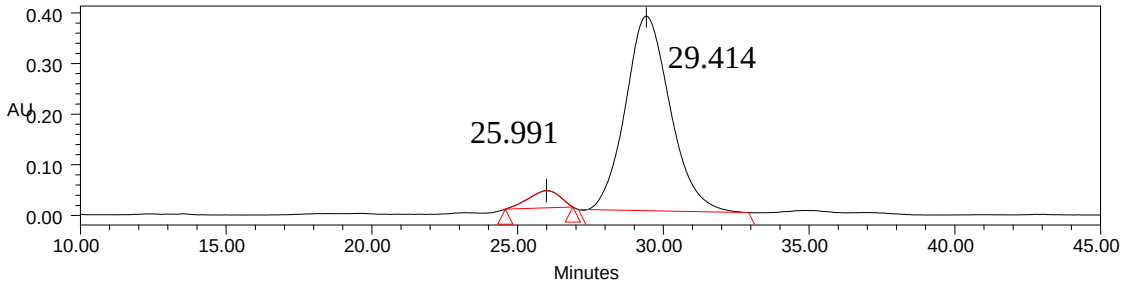
λ: 254 nm

Rac-**60l**



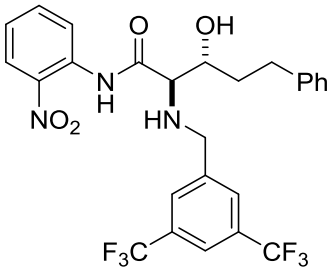
	Retention Time	% Area
1	24.861	45.25
2	28.333	54.75

60l



	Retention Time	% Area
1	25.991	5.85
2	29.414	94.15

88%*ee*



63a

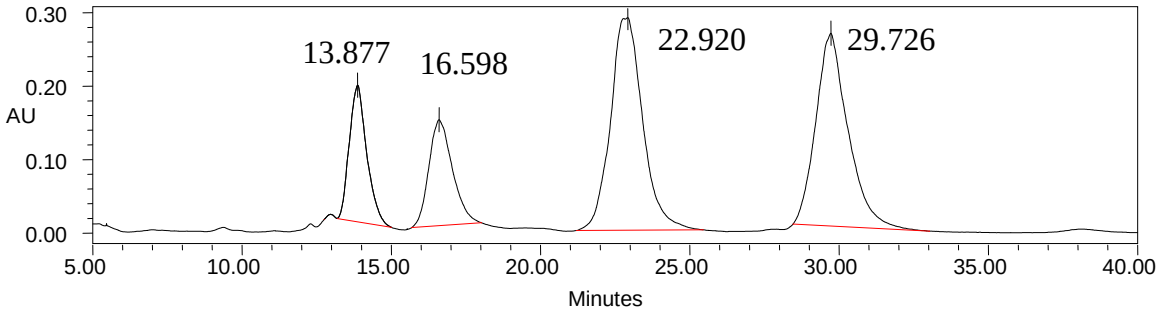
Eluent: Hx/*i*PrOH, 95/5

Flow: 1 mL/min

Column: IA

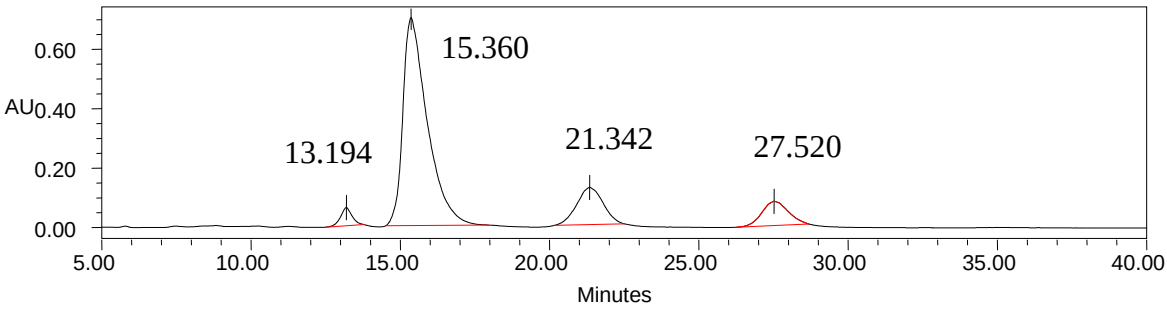
λ: 254 nm

Rac-**63a**



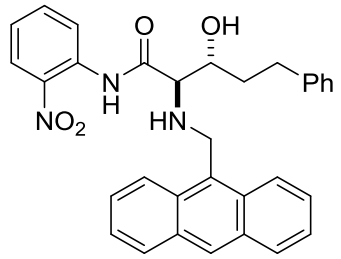
	Retention Time	% Area
1	13.877	13.31
2	16.598	13.62
3	22.920	37.47
4	29.726	35.60

63a



	Retention Time	% Area
1	13.194	2.99
2	15.360	73.58
3	21.342	14.22
4	27.520	9.21

97%*ee*



74a

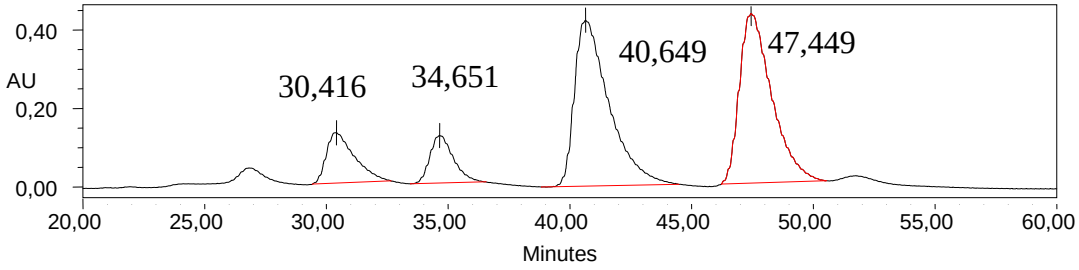
Eluent: Hx/*i*PrOH, 90/10

Flow: 1 mL/min

Column: IB

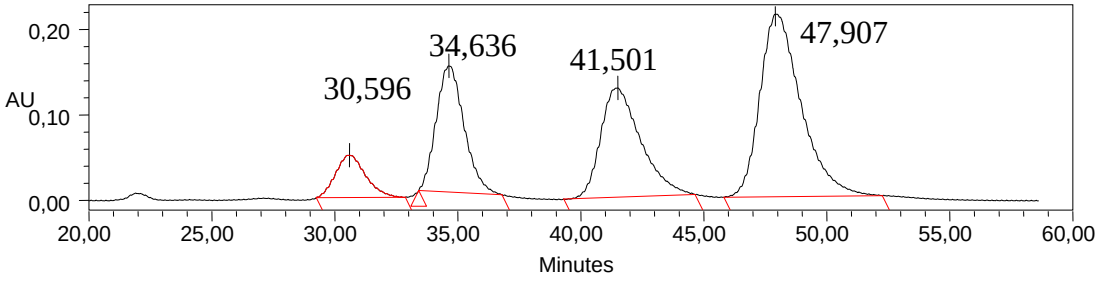
λ: 254 nm

Rac-**74a**



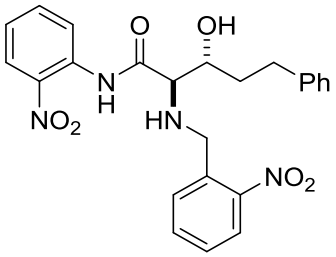
	Retention Time	% Area
1	30,416	9,85
2	34,651	9,07
3	40,649	41,45
4	47,449	39,64

74a



	Retention Time	% Area
1	30,595	7,74
2	34,629	21,09
3	41,504	26,26
4	47,907	44,91

12% *ee*



78a

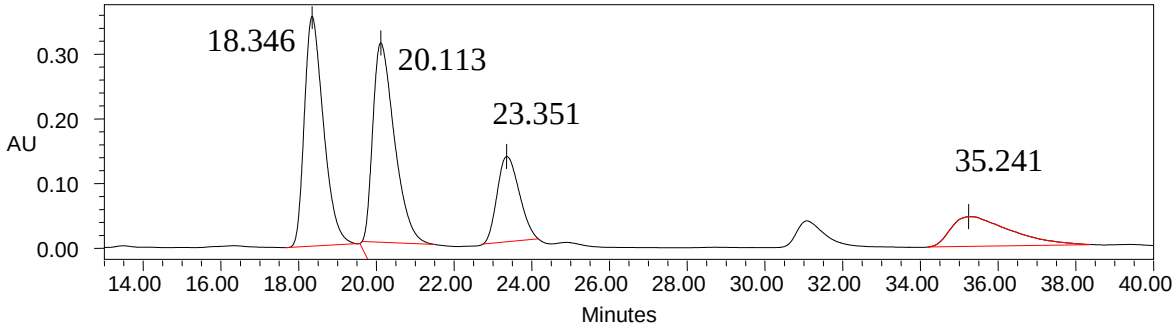
Eluent: Hx/*i*PrOH, 80/20

Flow: 1 mL/min

Column: IF

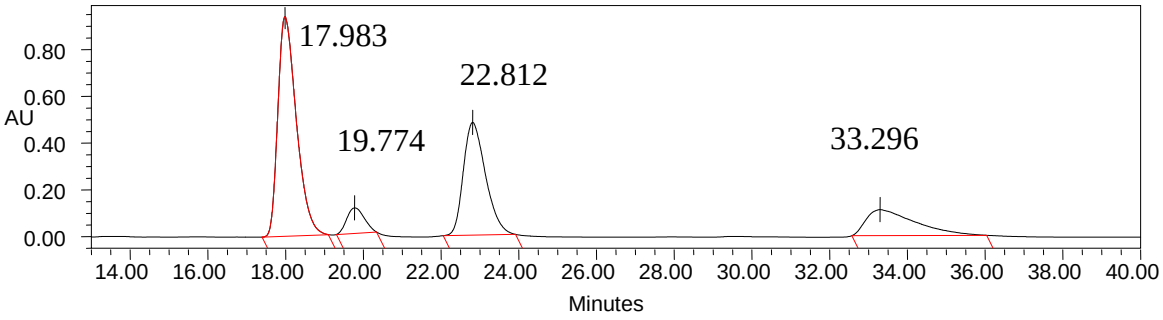
λ: 254 nm

Rac-**78a**



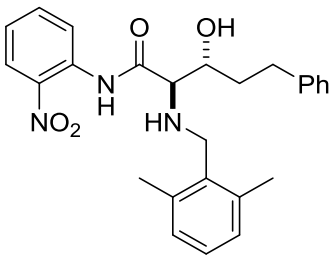
	Retention Time	% Area
1	18.346	35.69
2	20.113	34.88
3	23.351	15.26
4	35.241	14.17

78a



	Retention Time	% Area
1	17.983	49.10
2	19.774	5.38
3	22.812	30.20
4	33.296	15.33

80% *ee*



75a

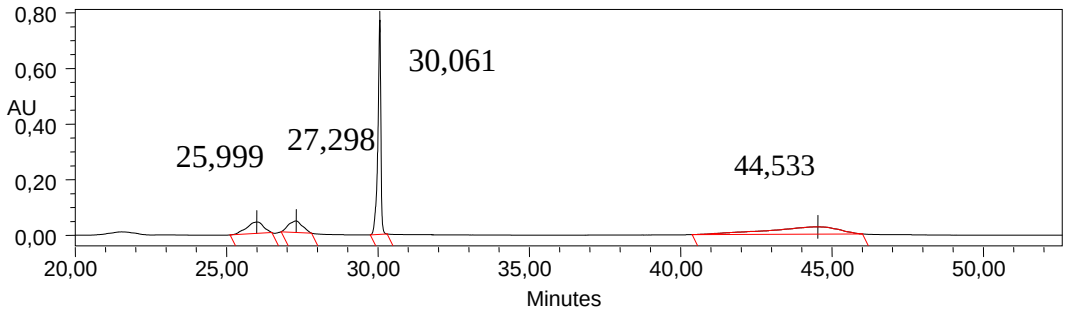
Eluent: Hx/*i*PrOH, 90/10

Flow: 0.5 mL/min

Column: IC

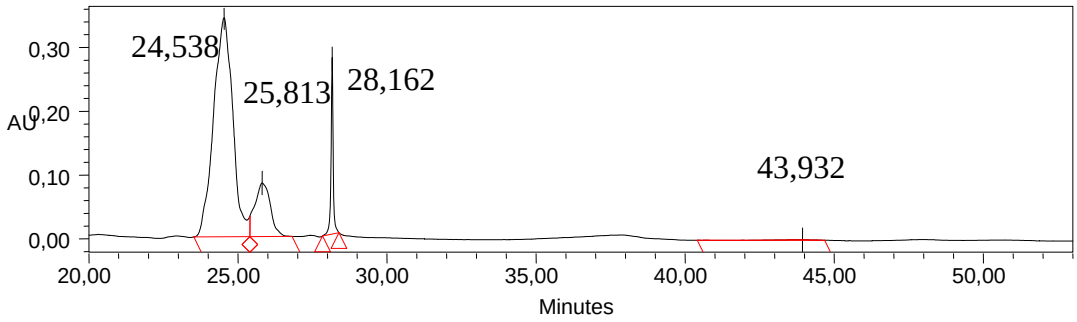
λ: 254 nm

Rac-**75a**



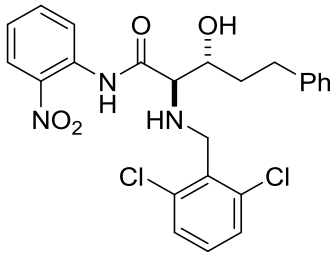
	Retention Time	% Area
1	25,995	12,64
2	27,294	12,09
3	30,061	39,81
4	44,547	35,46

75a



	Retention Time	% Area
1	24,538	77,32
2	25,813	15,36
3	28,162	6,93
4	43,932	0,39

66% *ee*



76a

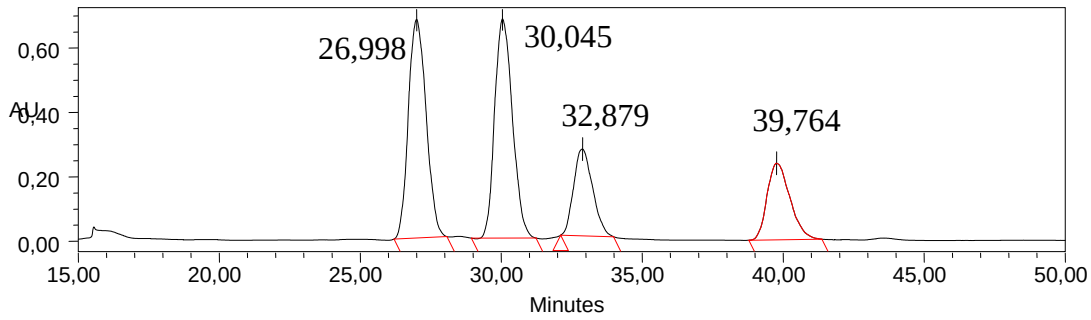
Eluent: Hx/*i*PrOH, 80/20

Flow: 0.6 mL/min

Column: IF

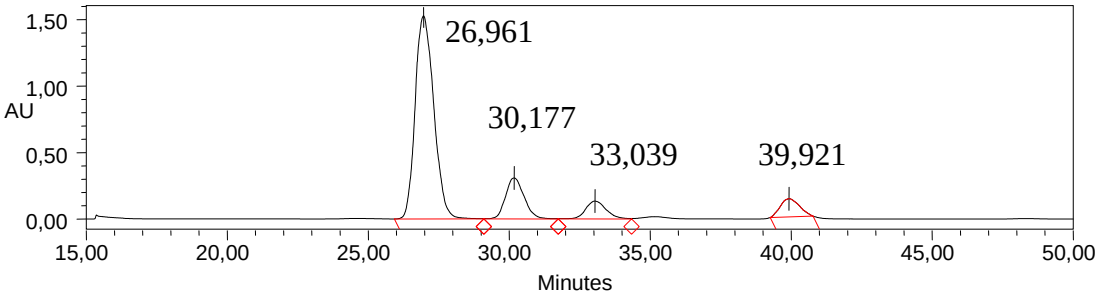
λ: 254 nm

Rac-**76a**



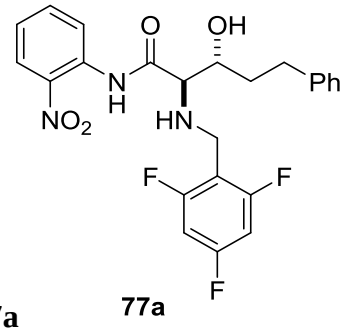
	Retention Time	% Area
1	26,998	34,74
2	30,045	34,91
3	32,879	14,73
4	39,764	15,62

76a



	Retention Time	% Area
1	26,961	71,90
2	30,177	14,50
3	33,039	6,98
4	39,921	6,62

66% *ee*



77a

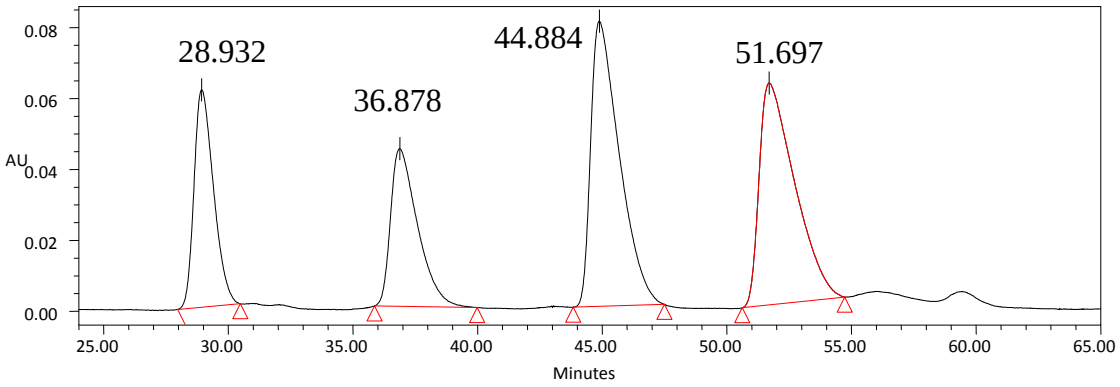
Eluent: Hx/*i*PrOH, 90/10

Flow: 0.5 mL/min

Column: ID

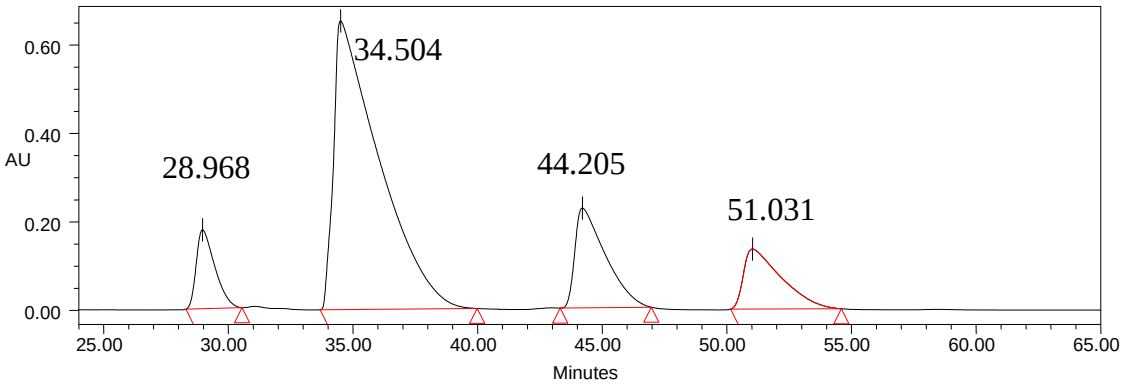
λ: 254 nm

Rac-**77a**



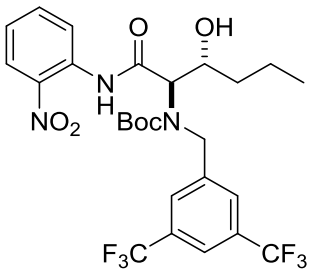
	Retention Time	% Area
1	28.933	17.32
2	36.872	16.18
3	44.886	34.53
4	51.704	31.97

77a



	Retention Time	% Area
1	28.968	7.33
2	34.504	66.05
3	44.205	15.27
4	51.031	11.35

80% *ee*



104b

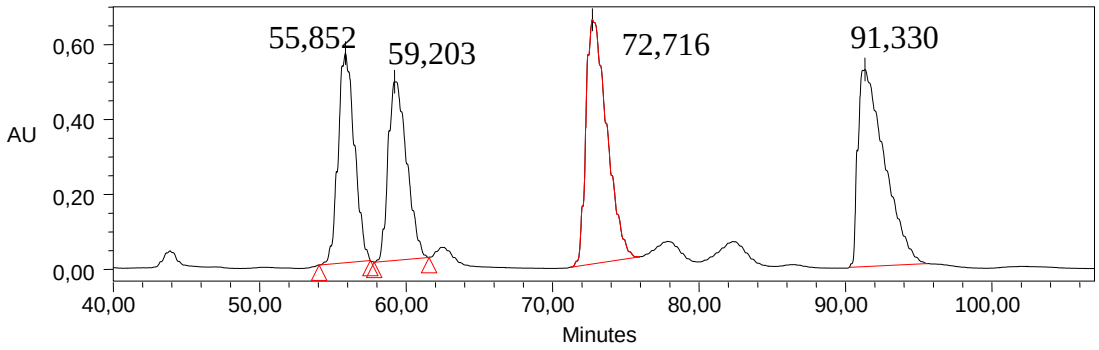
Eluent: Hx/*i*PrOH, 98/2

Flow: 0.5 mL/min

Column: IFID

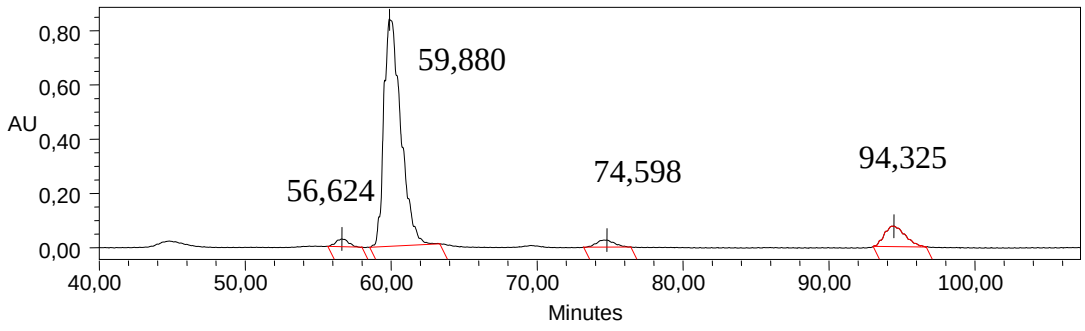
λ: 254 nm

Rac-**104b**



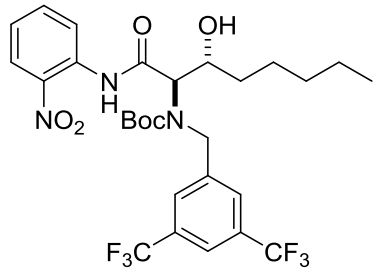
	Retention Time	% Area
1	55,852	19,99
2	59,203	19,37
3	72,716	29,87
4	91,330	30,77

104b



	Retention Time	% Area
1	56,624	2,17
2	59,880	85,22
3	74,598	2,52
4	94,325	10,09

95% *ee*



104b

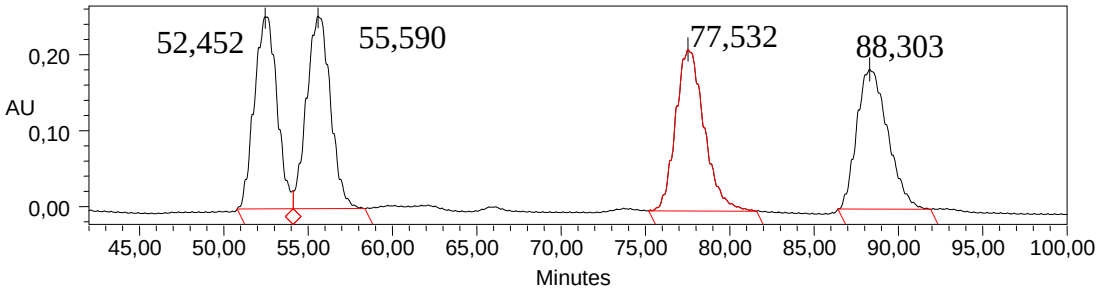
Eluent: Hx/*i*PrOH, 98/2

Flow: 0.5 mL/min

Column: IFID

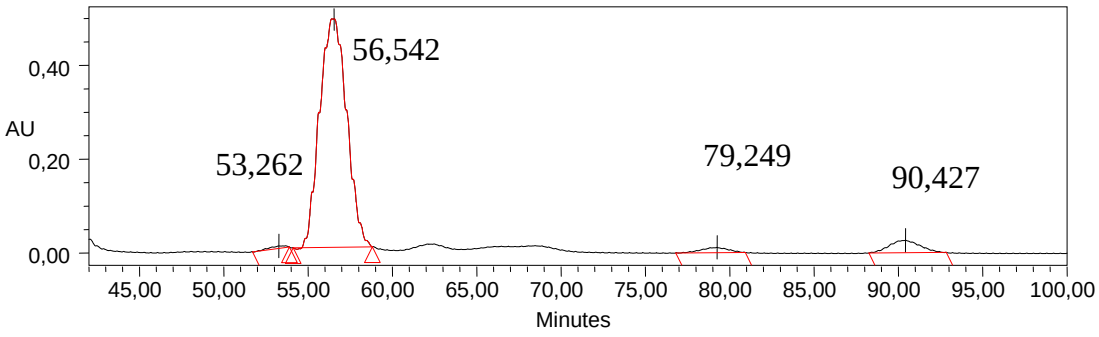
λ: 254 nm

Rac-**104b**



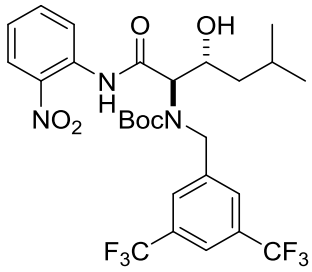
	Retention Time	% Area
1	52,469	24,63
2	55,592	25,41
3	77,537	24,92
4	88,303	25,03

104b



	Retention Time	% Area
1	53,682	1,48
2	56,542	91,84
3	79,249	0,78
4	90,427	5,91

95% *ee*



104h

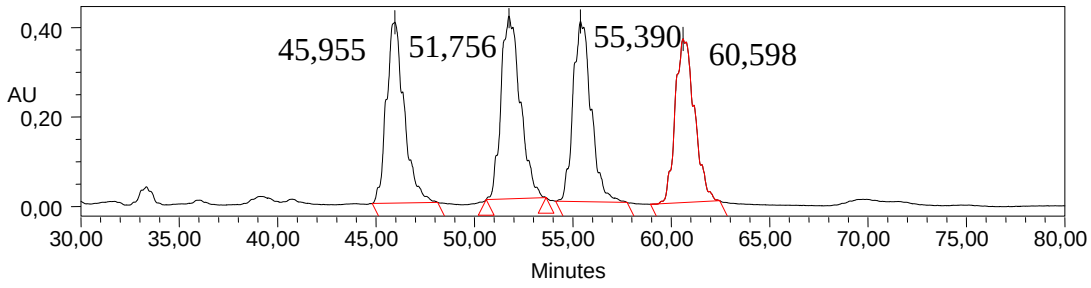
Eluent: Hx/*i*PrOH, 98/2

Flow: 0.5 mL/min

Column: IFID

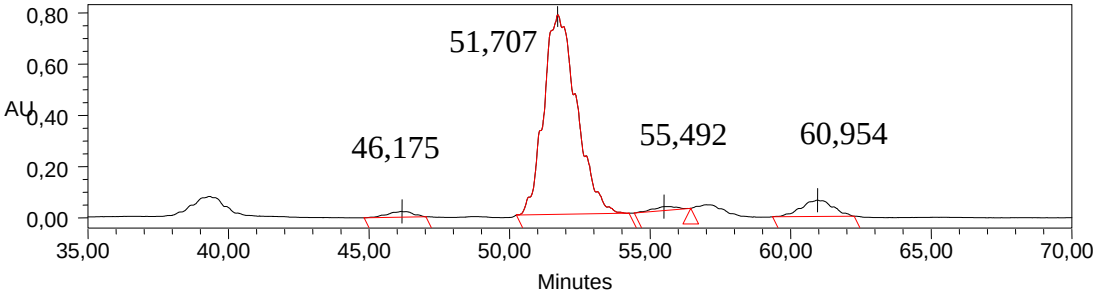
λ: 254 nm

Rac-**104h**



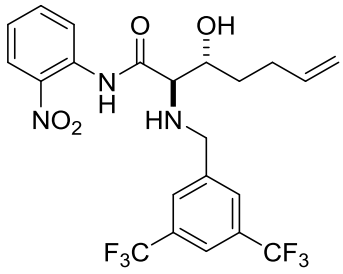
	Retention Time	% Area
1	45,955	24,50
2	51,756	26,74
3	55,390	24,79
4	60,598	23,97

104h



	Retention Time	% Area
1	46,175	1,99
2	51,707	89,68
3	55,492	1,23
4	60,954	7,10

96% *ee*



63m

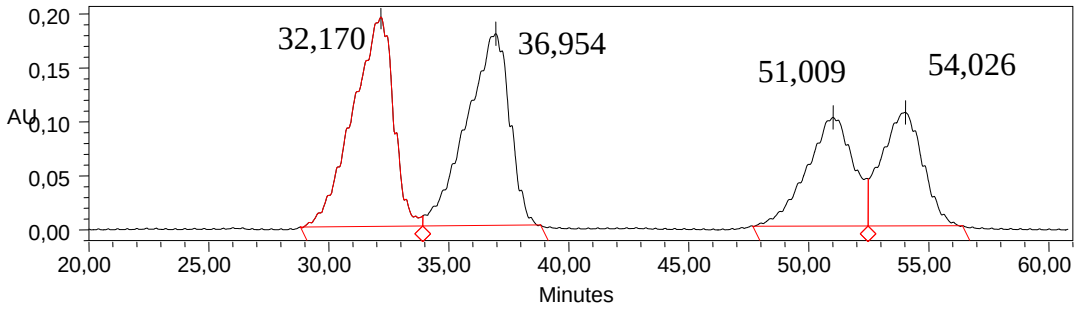
Eluent: Hx/*i*PrOH, 97/3

Flow: 0.5 mL/min

Column: IF

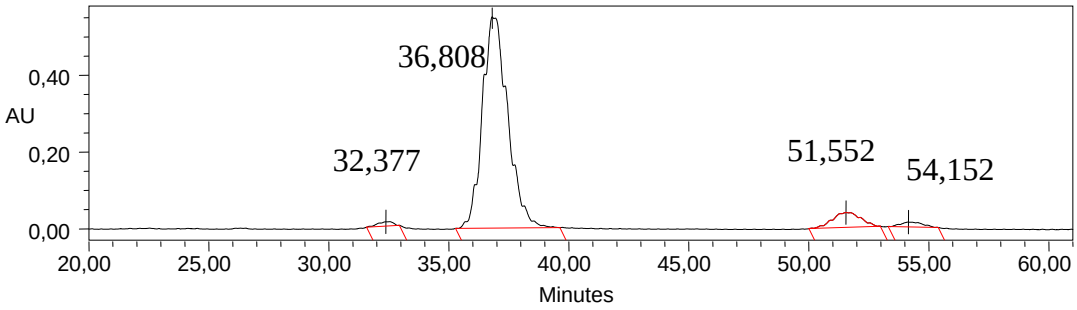
λ: 254 nm

rac-**63m**



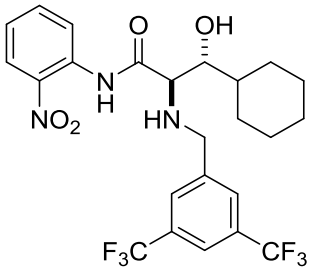
	Retention Time	% Area
1	32,170	32,10
2	36,954	31,17
3	51,009	19,14
4	54,026	17,60

63m



	Retention Time	% Area
1	32,543	2,10
2	36,807	89,14
3	51,551	6,80
4	54,151	1,96

96% ee



63e

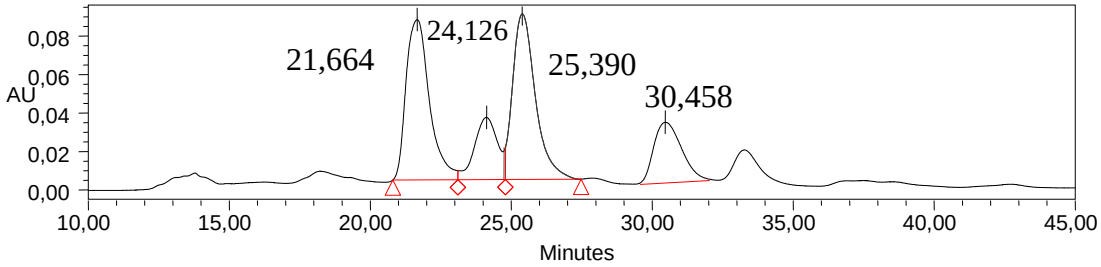
Eluent: Hx/*i*PrOH, 80/20

Flow: 0.5 mL/min

Column: IAIA

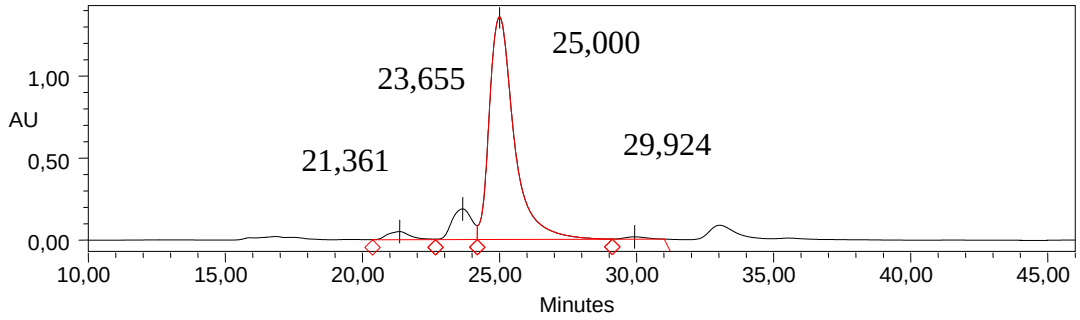
λ: 254 nm

Rac-**63e**



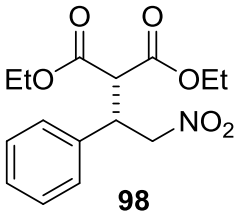
	Retention Time	% Area
1	21,664	35,92
2	24,126	13,96
3	25,390	36,04
4	30,458	14,08

63e



	Retention Time	% Area
1	21,361	2,89
2	23,655	9,53
3	25,000	86,79
4	29,924	0,80

94% *ee*



98

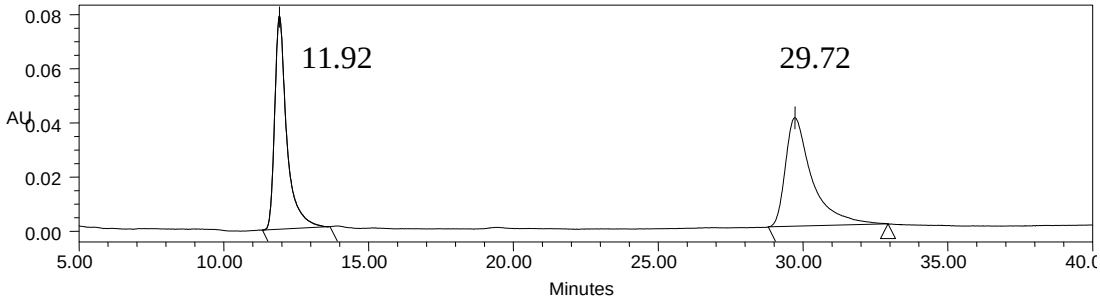
Eluent: Hx/*i*PrOH, 90/10

Flow: 0.5 mL/min

Column: IA

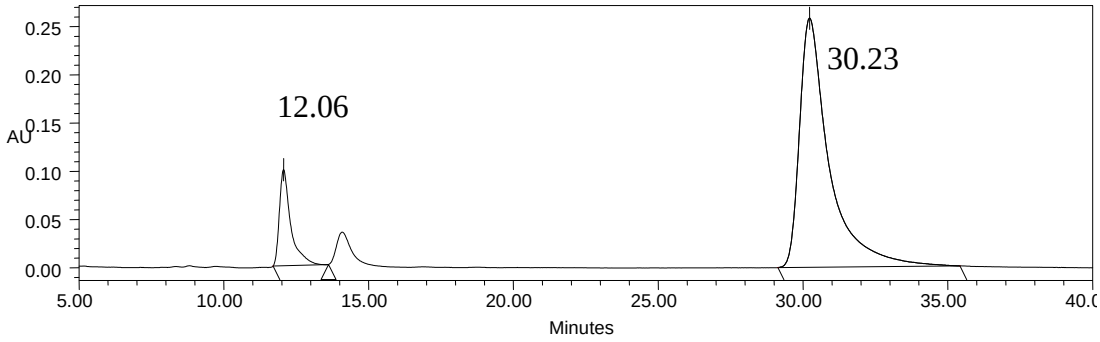
λ: 254 nm

rac-**98**



Retention Time	% Area
11.921	48.33
29.719	51.67

98



Retention Time	% Area
12.06	12.91
30.23	87.09

74% *ee*