CHIRAL BICYCLIC GUANIDINE CATALYZED MICHAEL REACTIONS

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To my parents, sisters, and Junye,

for their love, support, and encouragement

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Table of Contents

Chapter 6

Experimental Procedures

Summary

The aim of this study is to develop a highly enantioselective Michael reaction catalyzed by chiral bicyclic guanidines.

1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD), a bicyclic guanidine base, was found to be an excellent catalyst for Michael and Michael-type reactions. A wide variety of Michael donors and acceptors can participate in these reactions using 10 - 20 mol% of TDB. These reactions are mild, fast, easy to perform, and proceed with high yields. They can occur in several solvents without the need for strictly anhydrous conditions.

A series of chiral bicyclic guanidines, both symmetrical and non-symmetrical, were synthesized using a concise and efficient aziridine-based synthetic methodology. One of the synthesized chiral bicyclic guanidine was found to be a highly enantioselective organocatalyst for the Michael reactions between 2-cyclopenten-1-one and various 1,3-dicarbonyl compounds, including dialkyl malonates, benzoylactetates, and *S*,*S'*-dialkyl dithiomalonates. The enantioselectivities generally range from 86-96%, with yields between 84-99%.

The substrate scope of the chiral bicyclic guanidine catalyzed Michael reaction was expanded to include *N*-alkyl maleimides. The enantioselectivities generally range from 90-96%, with yields between 91-99%. The methodology has been applied to the first enantioselective synthesis of (*S*)-(+)-homo-β-proline, which is a potent GABA agonist and uptake inhibitor.

A stereochemical model was proposed to explain the origin of the high enantioselectivity obtained.

List of Schemes

List of Tables

List of Figures

List of Abbreviations

AcOH	acetic acid
Ac	acetyl
[α]	optical rotation
aq.	aqueous
Bn	benzyl
*i*Bu	*iso*-butyl
*t*Bu	*tert*-butyl
c	concentration
Cbz	benzyloxycarbonyl
^{o}C	degrees (Celcius)
δ	chemical shift in parts per million
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMAP	4-dimethylaminopyridine
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
dd	doublet of doublet
dr	diastereomeric ratio
ee	enantiomeric excess
EI	electron impact ionization
ESI	electro spray ionization

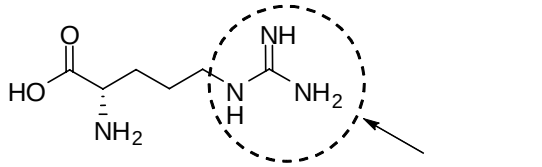
Et	ethyl
FAB	fast atom bombardment ionization
FTIR	fourier transformed infrared spectroscopy
g	grams
h	hour(s)
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
i.d.	internal diameter
IR	infrared
J	coupling constant
LRMS	low resolution mass spectroscopy
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mg	milligram
MHz	megahertz
min.	minute(s)
ml	milliliter
μl	microliter
mmol	millimole
MS	mass spectroscopy
MTBD	1,3,4,6,7,8-hexahydro-1-methyl-2*H*-pyrimido[1,2-a]pyrimidine

NMR	nulcear magnetic resonance
NOE	nuclear Overhauser enhancement
ppm	parts per million
*i*Pr	isopropyl
rt	room temperature
S_{N2}	nucleophilic substitution, second order
TBD	1,5,7-Triazabicyclo[4.4.0]dec-5-ene
THF	tetrahydrofuran
TLC	thin layer chromatography
Tol.	Toluene
T.S.	transition state
TsCl	*para*-toluenesulfonyl chloride
TsOH	*para*-toluenesulfonic acid

Chapter 1

Chiral Guanidines and Guanidinium Derivatives as Asymmetric Catalysts

Arginine **1** is found in the active site of many enzymes and its guanidine side chain typically exists in the protonated form as a guanidinium ion, which is known to interact with phosphates, nucleotide bases, and carboxylate containing biomolecules through double hydrogen bonding.[1] Guanidine is one of the most basic forms of neutral nitrogen compounds and guanidine derivatives are widely used as strong bases in synthetic organic chemistry.[2]

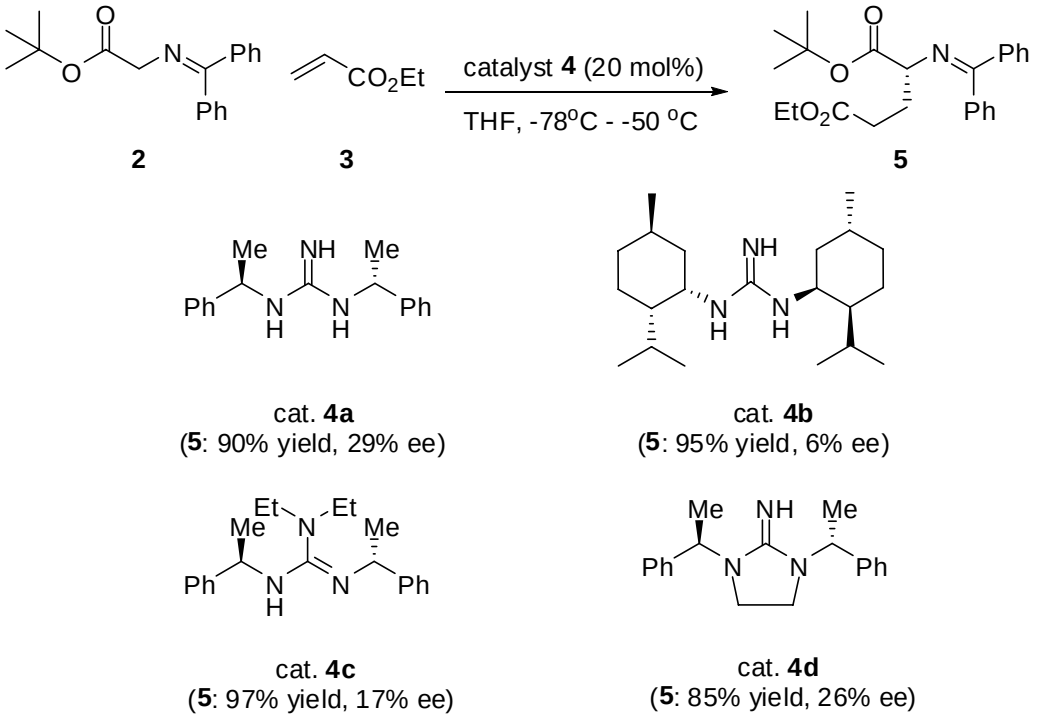


1 Arginine guanidine group

It is anticipated that chiral guanidine derivatives can function as asymmetric catalysts by utilizing the great basicity of the guanidine group and the special hydrogen bonding pattern of the guanidinium ion.[3] This research topic has increasingly attracted great interest and the asymmetric catalytic ability of chiral guanidine or guanidinium has been demonstrated in several reactions, including the Michael reaction, Strecker reaction, enone epoxidation, asymmetric silylation of secondary alcohol, TMS cyanation, azidation, Henry reaction, and phase transfer alkylation.

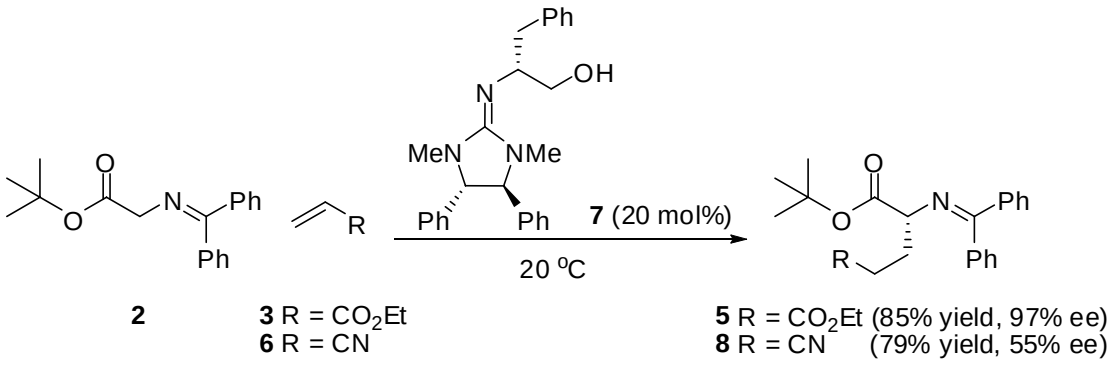
Michael reactions:

In 1999, Ma reported that chiral guanidines **4a-b** catalyze the Michael reaction of glycinate **2** to ethyl acrylate **3** (Scheme 1.1).[4] Although the yield was high, the ee obtained from the four different catalysts only ranged within 6-29%.



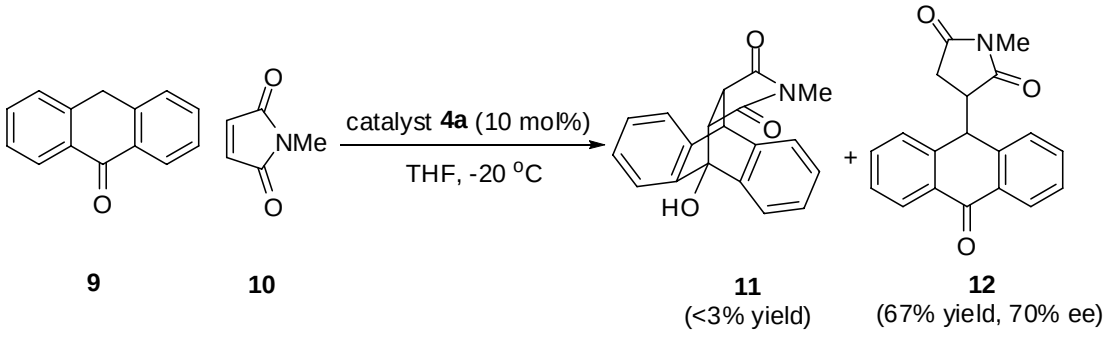
Scheme 1.1. Ma and Cheng's chiral guanidine catalyzed Michael reaction of glycinate.

In 2001, Ishikawa used the modified guanidine **7** to catalyze the Michael reaction of glycinate **2** under solvent free condition (Scheme 1.2).[5] Good yield (85%) and high ee (97%) were obtained with the reaction of ethyl acrylate **3**. It seems that this reaction only works well for acrylates. The reaction of acrylonitrile **6** only gave the product in moderate yield (79%) and ee (55%). In addition, the typical reaction time was 3-5 days.

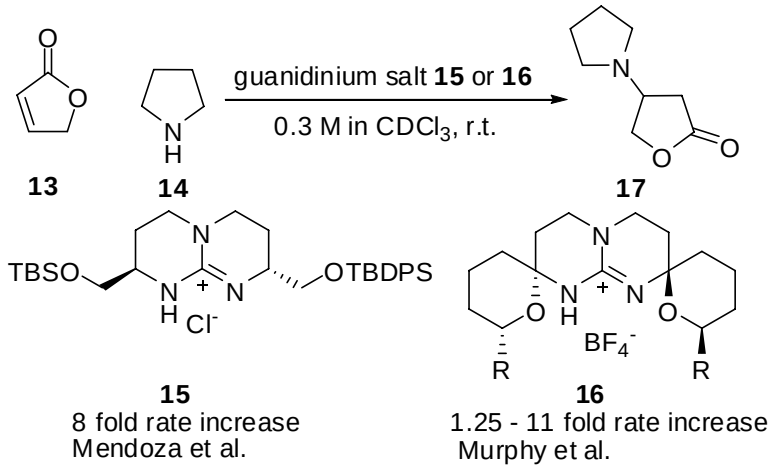


Scheme 1.2. Ishikawa's chiral guanidine catalyzed Michael reaction of glycinate.

Ma also reported that chiral guanidine **4a** catalyzed the Michael reaction and Diels-Alder reaction between anthrone **9** and *N*-methylmaleimide **10** (Scheme 1.3).[6] Up to 70% ee and 67% yield was obtained for the Michael addition product **12**, while the Diels-Alder product **11** was obtained in minimal yield (<3%), with no ee determined.



Scheme 1.3. Ma's chiral guanidine catalyzed Michael reaction and Diels-Alder reaction between anthrone and maleimide.

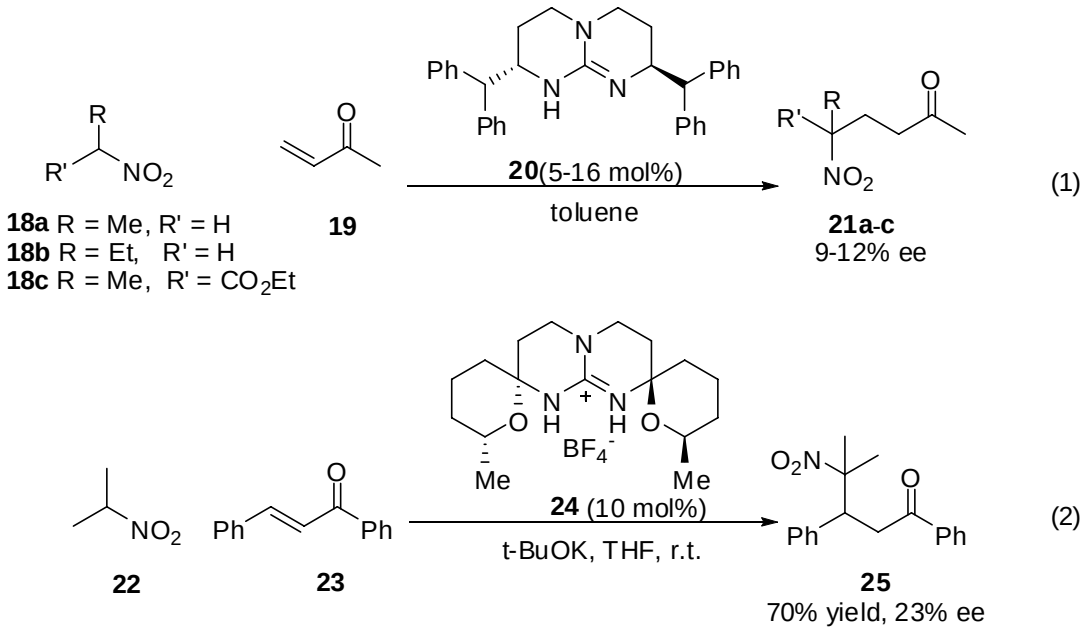


Scheme 1.4. Chiral bicyclic guanidinium salt catalyzed aza-Michael reaction.

Knowing that guanidinium ions interact well with carboxylate ion, both Mendoza[7] and Murphy[8] studied the Michael reaction between unsaturated lactone **13** and pyrrolidine **14**, hoping that the guanidinium ion would interact with the lactone in a similar manner as with a carboxylate ion (Scheme 1.4). Mendoza used bicyclic

guanidinium **15** as catalyst and Murphy used tetracyclic guanidinium **16** instead. However, in both cases, there was no enantioselectivity, though the reaction rates were increased.

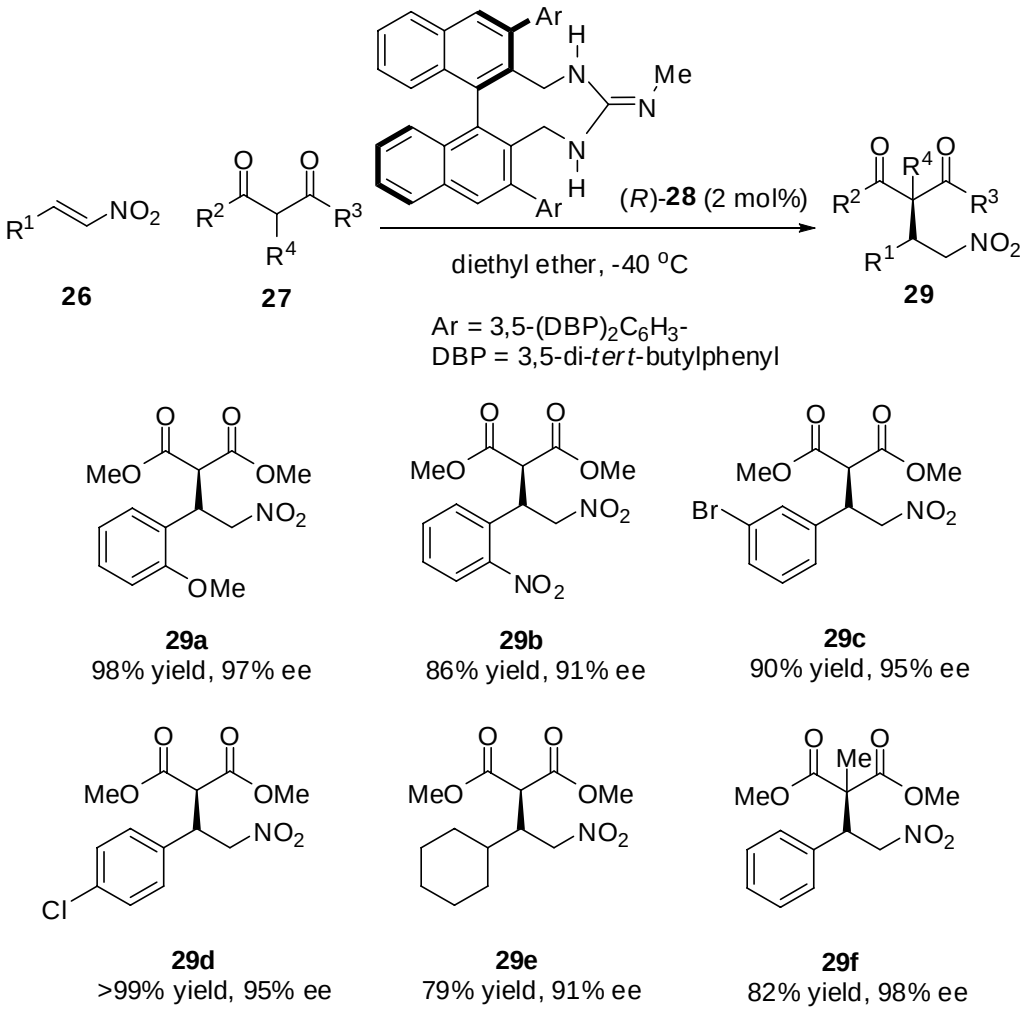
In 1995, Davis reported that chiral bicyclic guanidine **20** catalyzed the nitro Michael reaction of **18a-c** to **19**, giving products **21a-c** in 9-12% ee (Eq. (1), Scheme 1.5).[9] Similar reaction between 2-nitro propane **22** and chalcone **23** was catalyzed by Murphy's tetraguanidinium salt **24**, albeit with moderate yield (70%) and unsatisfactory ee (23%) (Eq. (2), Scheme 1.5).[8]



Scheme 1.5. Chiral guanidine or guanidinium catalyzed nitro Michael reaction.

The chiral guanidine catalysts discussed above are either acyclic guanidine (eg. **4a-c**) with chiral side chains or mono-to-polycyclic systems (eg. **4d**, **7**, **15**, **16**, **20**, and **24**) with central chiralities. Recently, Terada[3] et al. developed a new type of chiral guanidine catalysts, such as (*R*)-**28**, which introduced an axially chiral binaphthyl backbone. This axially chiral guanidine was found to be a highly efficient catalyst for

the Michael reaction between a variety of conjugated nitroalkenes **26** and several 1,3-dicarbonyl compounds **27**, featuring both high yielding and excellent enantioselectivity, with catalyst loading as low as 0.4-2 mol% (Scheme 1.6).

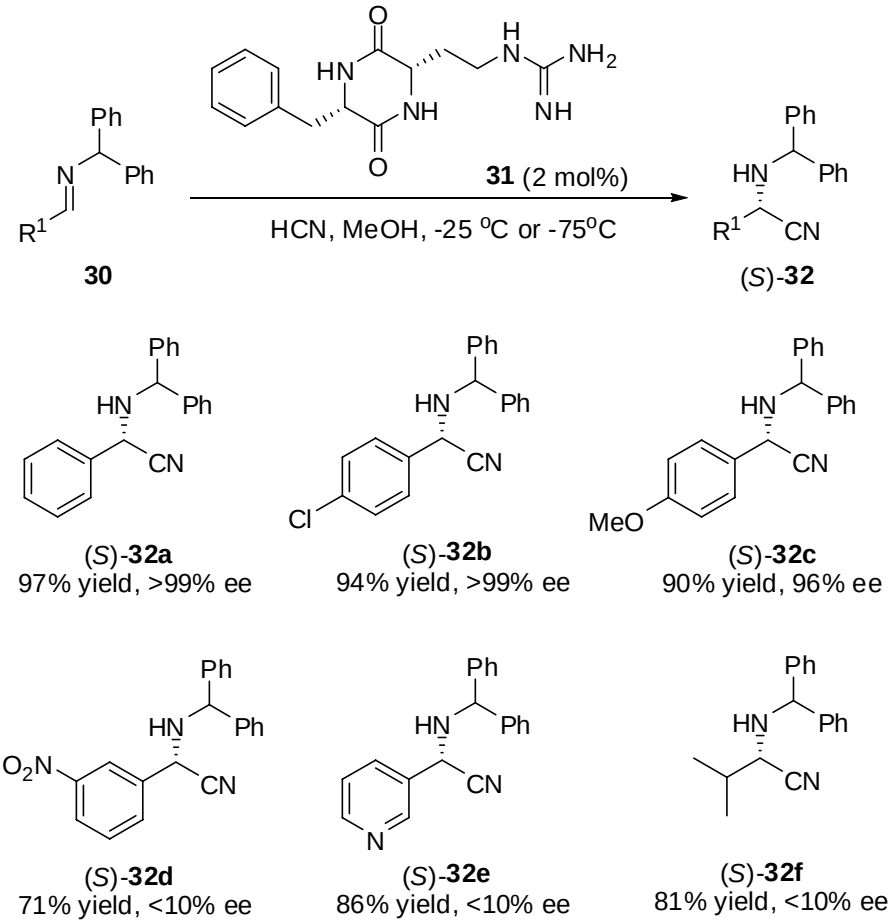


Scheme 1.6. Terada's axially chiral guanidine catalyzed Michael reaction of nitroalkene.

Strecker reaction:

In 1996, the Lipton group reported the first catalytic asymmetric Strecker reaction using the cyclic dipeptide **31** as the catalyst (Scheme 1.7).[10] The guanidine side-chain of **31** was found to be a prerequisite for asymmetric induction as replacing the

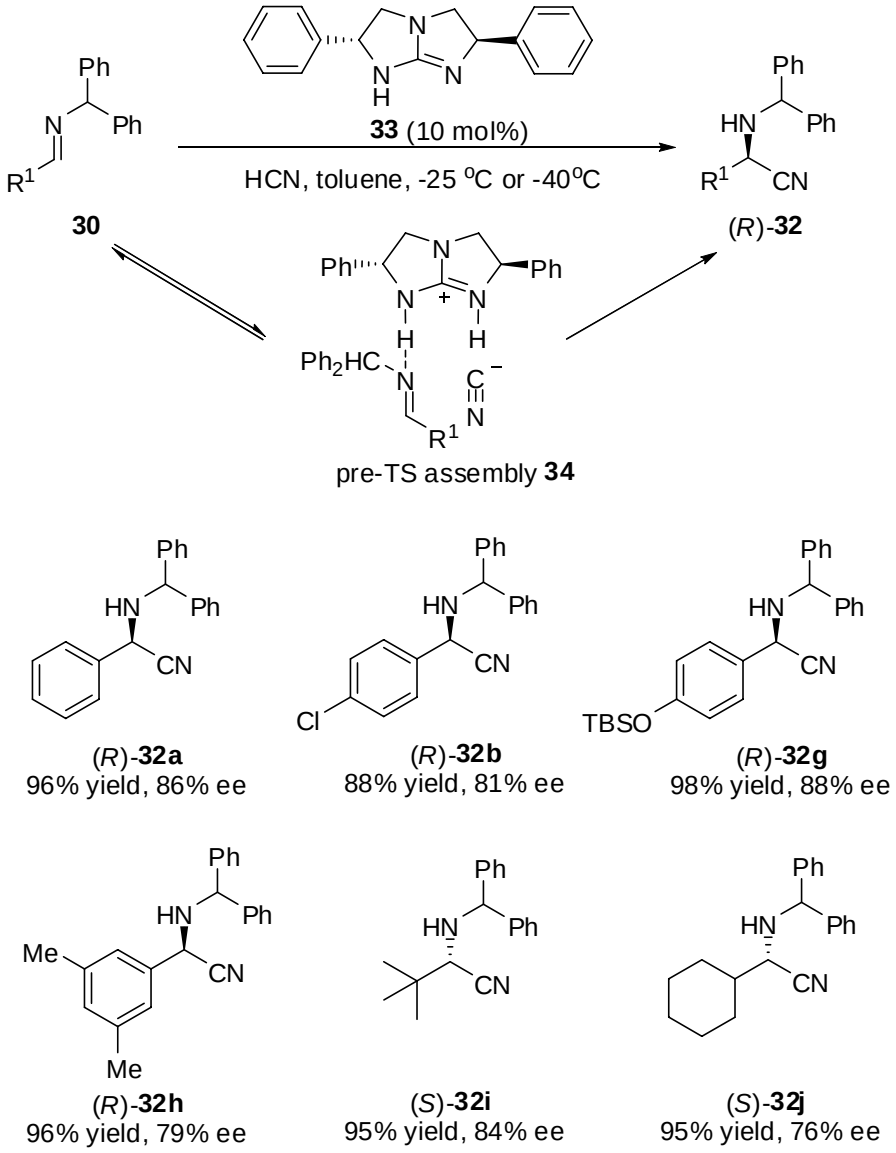
guanidine group with an imidazole group resulted in a non-enantioselective reaction. It was proposed that the more basic guanidine group enabled the catalyst to accelerate proton transfer in the Strecker reaction. Using only 2 mol% catalyst **31**, good to excellent enantioselectivities (80->99% ee) were usually obtained with the reaction of imines derived from benzaldehyde or electron-deficient aldehydes (eg. (*S*)-**32a-c**), except (*S*)-**32d**. However, unsatisfactory enantioselectivities were obtained with the heteroaromatic (eg. (*S*)-**32e**) or aliphatic ((*S*)-**32f**) Strecker products.



Scheme 1.7. Lipton's cyclic dipeptide catalyzed Strecker reaction.

In 1999, Corey and Grogan developed an efficient asymmetric Strecker reaction using the C_2-symmetric bicyclic guanidine **33** as the catalyst (Scheme 1.8).[11] The

N-benzhydryl substituent of the imine substrate **30** was found to be critical to obtain good enantioselectivity (up to 88%), as *N*-benzyl or *N*-(9'-fluorenyl)-substituted imines gave poor ee (0-25%). In contrast with Lipton's diketopiperazine-catalyzed Strecker reaction, the reactions of aliphatic imines gave high yields (ca. 95%) and good enantioselectivities (63-84%).

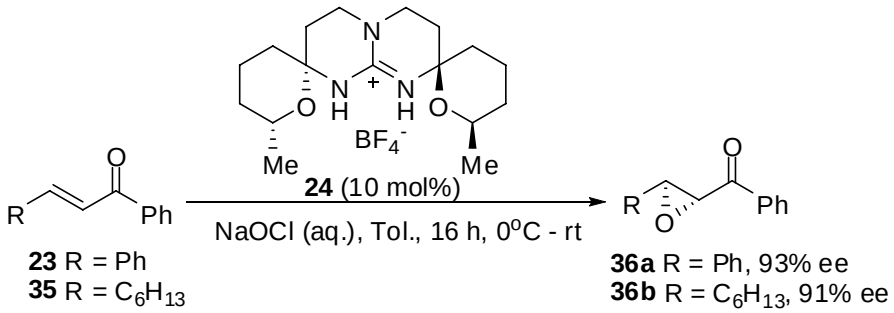


Scheme 1.8. Corey's bicyclic guanidine catalyzed Strecker reaction.

In the reaction mechanism proposed by the Corey group, a complex **34** was formed, in which both imine and cyanide attach to the guanidinium ion through

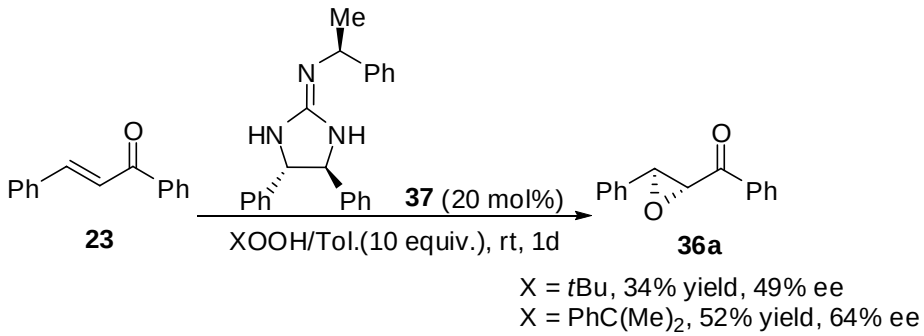
hydrogen bonds. The pre-transition state assembly modeling also explained the opposite configuration obtained for aromatic (eg. (*R*)-**32a**-**h**) and aliphatic (eg. (*S*)-**32i**-**j**) Strecker products.

Enone epoxidation:



Scheme 1.9. Guanidinium slat catalyzed phase transfer epoxidation.

In 2003, Murphy[8] reported that tetracyclic guanidinium salt **24** catalyzed the phase transfer epoxidation of chalcones **23** and **35**. High enantioselectivities were obtained for the two examples (93% ee for **36a**, 91% ee for **36b**) shown in Scheme 1.9. These results are comparable with existing phase transfer catalysts for these processes.

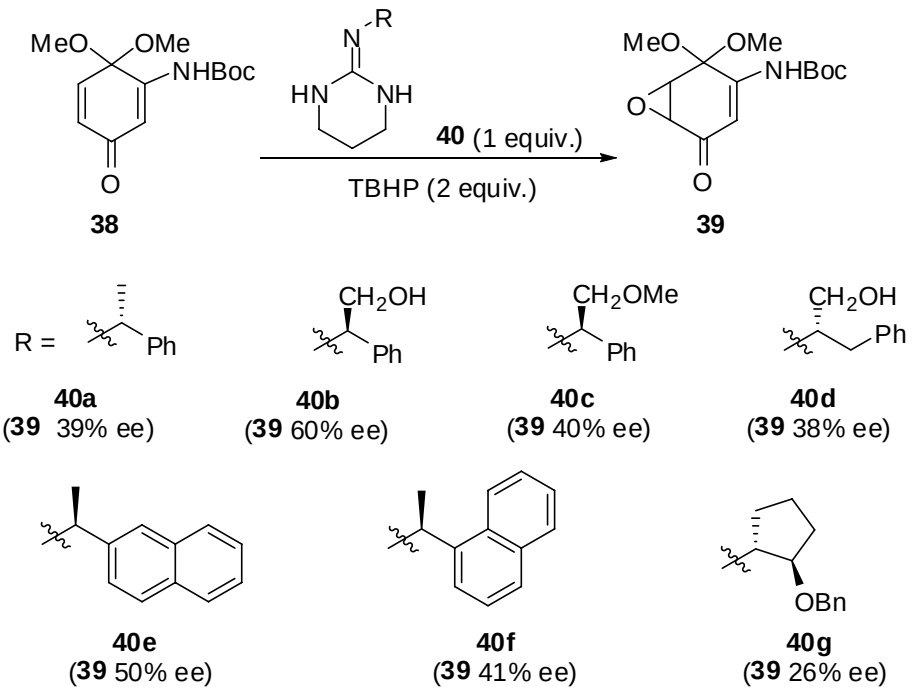


Scheme 1.10. Guanidine promoted epoxidation of chalcone.

This reaction was also catalyzed by Ishikawa's monocyclic guanidine **37** (Scheme 1.10).[5a] With 20 mol% of the guanidine **37**, epoxide **36a** was obtained in 49% and

64% ee respectively when two different hydroperoxides were used.

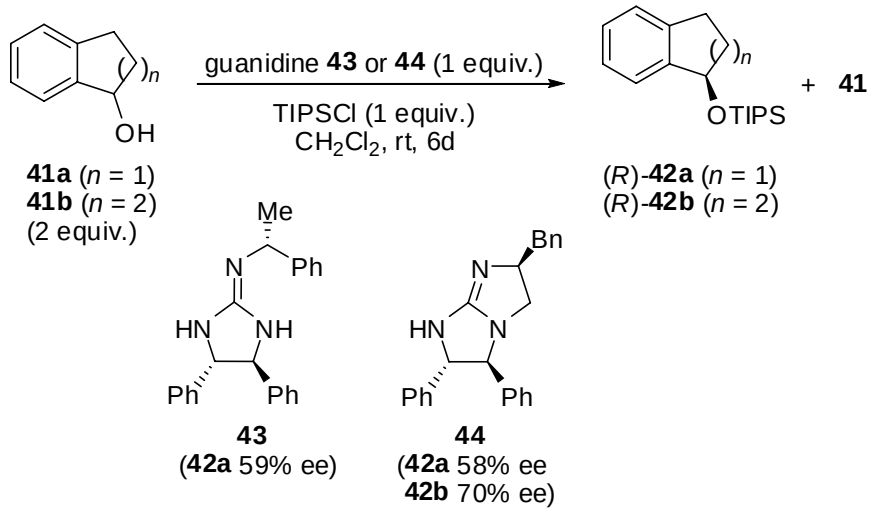
Chiral monocyclic guanidines **40a-g** were also found to promote the *tert*-butylhydroperoxide (TBHP)-mediated enantioselective epoxidation of enone **38**.[12] A stoichiometric amount of **40** was required to obtain moderate yields. With various chiral *N*-substituents on the guanidine **40**, epoxide **39** was obtained in moderate enantioselectivities ranging from 26-60% (Scheme 1.11).



Scheme 1.11. Guanidine promoted epoxidation.

Asymmetric silylation of secondary alcohols:

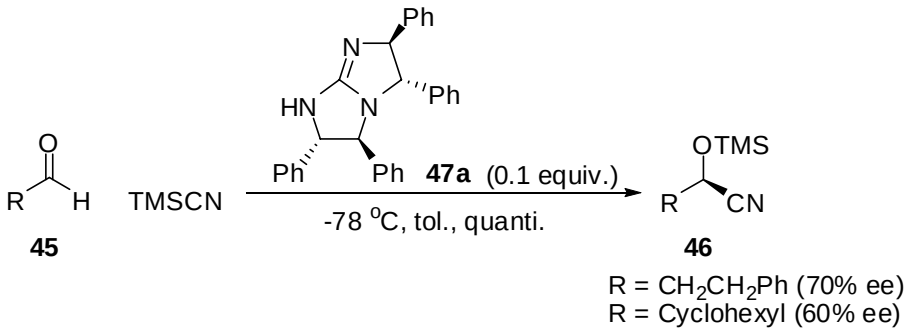
Ishikawa's modified guanidines **43** and **44** were also used as an asymmetric reagent for the kinetic silylation of secondary alcohols.[5b] Using guanidine **43**, **42a** was obtained in 59% ee and 36% yield (Scheme 1.12). While guanidine **44** was used, **42a** and **42b** were obtained in 58% and 70% ee respectively. In both cases, 1 equiv. of the guanidine was required.



Scheme 1.12. Chiral guanidine catalyzed asymmetric silylation of secondary alcohol.

TMS cyanation:

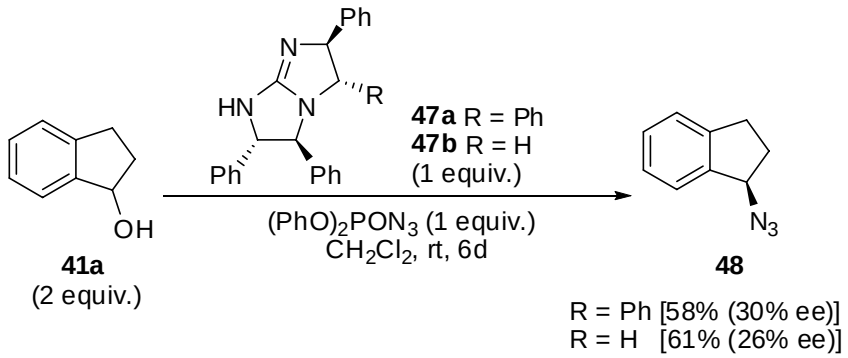
Ishikawa[5a] also reported that the C_2-symmetrical bicyclic guanidine **47a** catalyzed the TMS cyanation of aliphatic aldehydes **45**, affording the products **46** in quantitative yield and moderate ee (Scheme 1.13). However, low yield and ee were obtained when ketone was used in place of aldehyde.



Scheme 1.13. Chiral guanidine catalyzed TMS cyanation of aliphatic aldehydes **45**.

Azidation reaction:

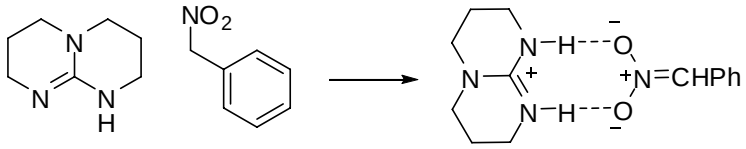
Chiral bicyclic guanidines **47a-b** were also found to promote the kinetic azidation of (±)-1-indanol **41a** (Scheme 1.14).[5a] Stoichiometric amount of the guanidine was used and the product was obtained in 26-30% ee.



Scheme 1.14. Chiral guanidine mediated azidation of (±)-1-indanol **41a**.

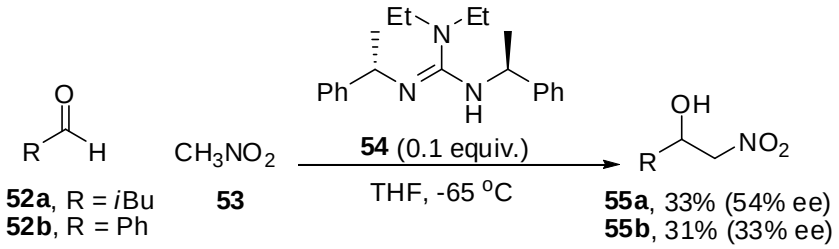
Henry reaction:

Since the isolation of complex **51**, formed between the guanidine 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) **49** and phenyl nitromethane **50**, it was anticipated that this type of intermediate could be a good model for an enantioselective guanidine-catalyzed Henry (nitroaldol) reaction.[13]

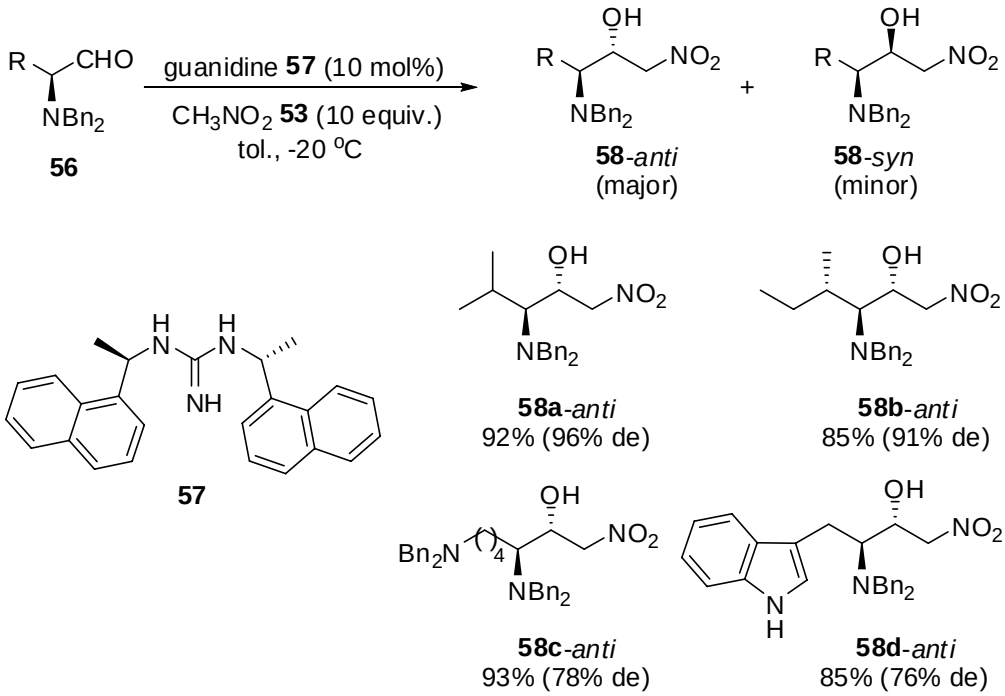


Scheme 1.15. Isolated complex between TBD and phenyl nitromethane.

The Nájera group tested the Henry reaction between aldehyde **52** and nitromethane **53** using a series of homochiral guanidines as the catalyst.[14] The best enantioselectivity was achieved with guanidine **54** with C_2-symmetry, affording **55a** in 54% ee and **55b** in 33% ee. However, yields were compromised due to the low reaction temperature required for satisfactory enantioselectivity.

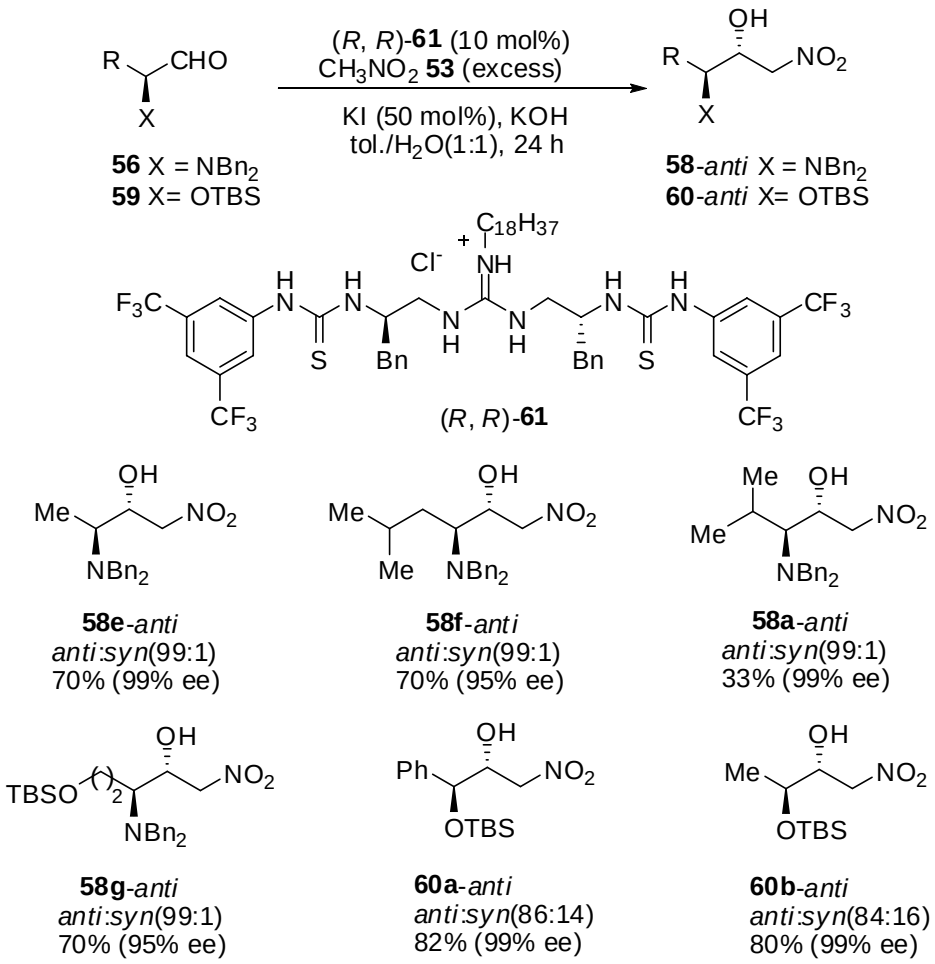


Scheme 1.16. Henry reaction catalyzed by homochiral guanidine.



Scheme 1.17. Diastereoselective Henry reaction catalyzed by chiral guanidines.

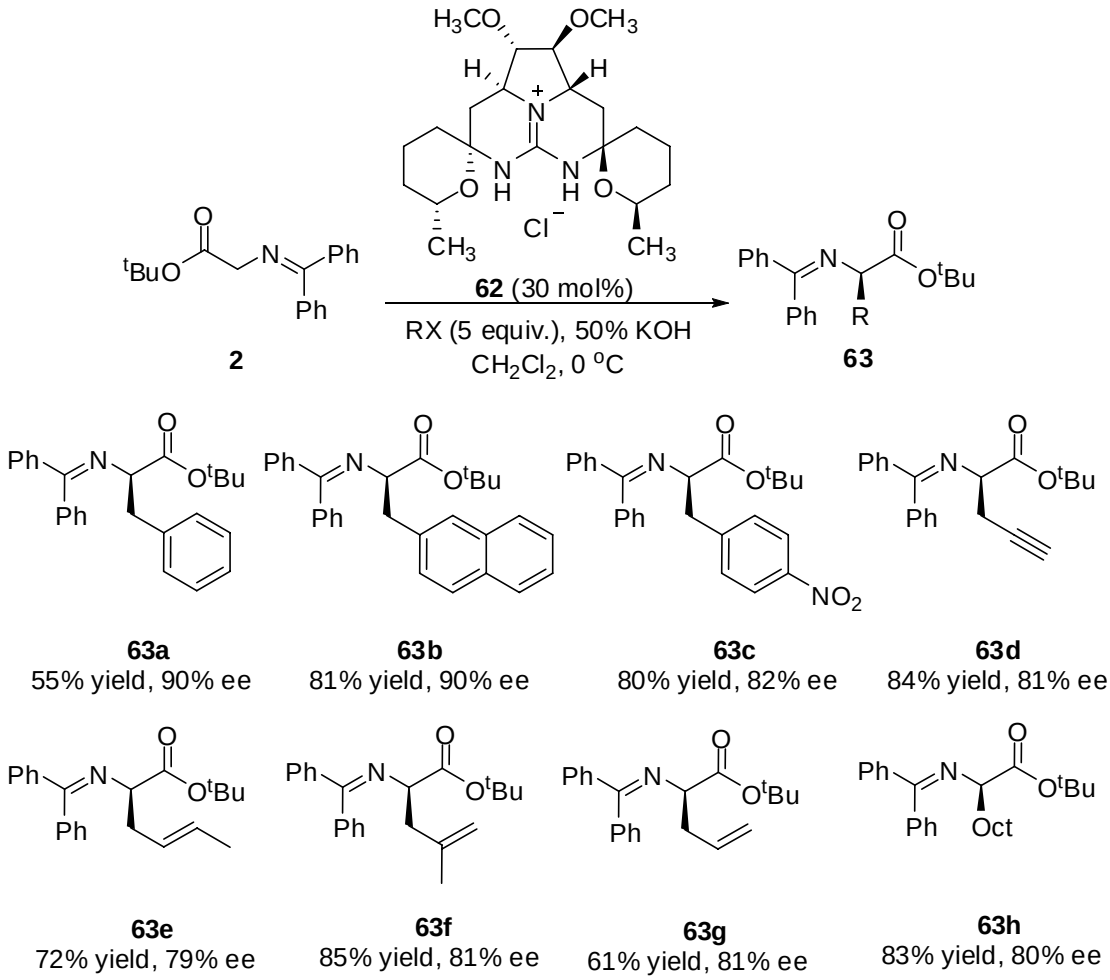
Ma also studied the diastereoselective Henry reactions of *N*,*N*-dibenzyl α-amino aldehydes **56** with nitromethane **53** catalyzed by guanidines (Scheme 1.17).[15] Among the various chiral guanidines tested, including acyclic, monocyclic, and bicyclic ones, acyclic guanidine **57** afforded the product **58**-*anti* with the best diastereoselectivity. While the reaction was generally high yielding, the diastereoselectivity was highly dependent on the substrates. Good diastereoselectivities (96% and 91% respectively) were observed with products **58a** and **58b**. Only moderate or poor diastereoselectivities were obtained with other products (eg. **58c**, **58d**).



Scheme 1.18. Diastereoselective Henry reaction catalyzed by a guanidine-thiourea catalyst.

Nagasawa[16] recently developed a highly diastereoselective Henry reaction. Under phase transfer conditions, (*R*,*R*)-**61**, a guanidinium salt with two thiourea groups, effectively catalyzed the Henry reaction between various α-substituted aldehydes **56** or **59** with nitromethane **53** (Scheme 1.18). In the reactions of *N*,*N*-dibenzyl α-amino aldehydes **56**, the *anti*-nitro alcohols (eg. **58e**, **f**-**g**) were obtained with high diastereoselectivity. Low yield was obtained with the bulky β-branched aldehyde **56a** (R = *i*Pr). Reactions with **59** proceeded to give the products with good diastereoselectivities and high yields (eg. **60a**, **b**).

Phase transfer alkylation:

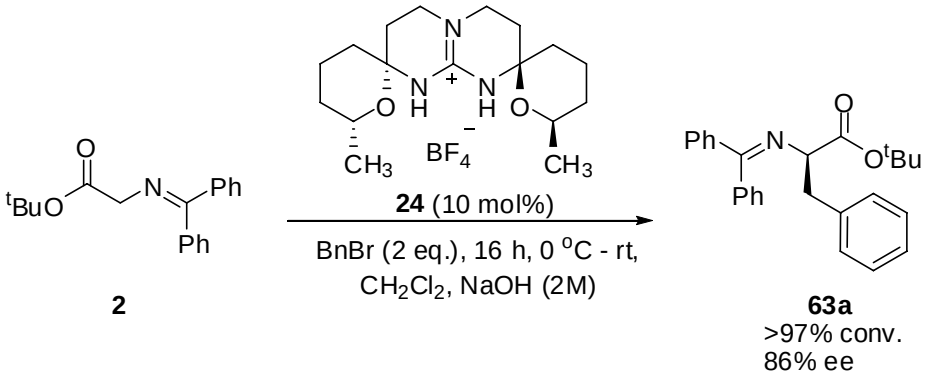


Scheme 1.19. Chiral pentacyclic guanidinium salt catalyzed phase transfer alkylation.

Based on the marine natural product ptilomycalin A and related products, Nagasawa designed a series of C_2-symmetrical pentacyclic guanidiniums, including **62** as catalyst.[17] In the presence of 30 mol% of **62** and under phase transfer conditions, glycinate **2** underwent alkylation reaction with various alkyl halides (Scheme 1.19). (*R*)-**63** were generated as the major product, with ee in the range of 80 - 90%. The yields were generally moderate to good (55 – 85%), although the reaction usually took 95 - 140 h to complete. It was observed that the stereochemical outcome was controlled by the configuration of the spiro-ether rings of the guanidinium

catalyst. The substituent (methyl group) on the spiro ether rings of **62** was found to play a key role in effective asymmetric induction.

Murphy[8] also reported that tetracyclic guanidinium **24**, which is a subunit of **62**, catalyzed the phase transfer alkylation of glycinate **2** with benzyl bromide, to afford (*R*)-**63a** in 86% ee and >97% conversion (Scheme 1.20). The catalyst was found to be robust and recyclable.



Scheme 1.20. Chiral tetracyclic guanidinium salt catalyzed phase transfer alkylation.

Summary:

Chiral guanidines function as effective Brønsted base catalyst for a variety of reactions. It is best demonstrated in Terada's axially chiral guanidine (*R*)-**28** catalyzed Michael reaction of nitroalkenes, Lipton's dipeptide **31** and Corey's bicyclic guanidine **33** catalyzed Strecker reaction. Chiral guanidinium salts are also effective phase transfer catalysts, as represented by Nagasawa's pentacyclic guanidinium **62** catalyzed phase transfer alkylation of glycinate **2**.

There are less successful examples that utilize acyclic guanidines, which are structurally less rigid than mono-polycyclic guanidines. However, currently available

methods for the preparation of chiral bicyclic, tetracyclic and pentacyclic guanidines are generally lengthy, which tends to impede catalyst supply for methodology studies.

Chapter 2

1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD) Catalyzed Michael Reactions

2.1 The Synthetic Utility of TBD

Non-chiral bicyclic guanidine bases[18] such as 1,5,7-triazabicyclo[4.4.0]dec-5-ene (**49**, TBD, $pKa_{(MeCN)}$ = 26, Fig. 2.1) and 1,3,4,6,7,8-hexahydro-1-methyl-2*H*-pyrimido-[1,2-a]-pyrimidine (7-methyl-TBD or MTBD, $pKa_{(MeCN)}$ = 25, Fig. 2.1) are known as superbases due to their high pKa values.[19] They have been shown to promote various reactions including the Wittig reaction,[20] nitroaldol (Henry) reaction,[21] dialkyl phosphite addition to carbonyl compounds[21] and the addition of azoles to α,β-unsaturated nitriles and esters.[22]

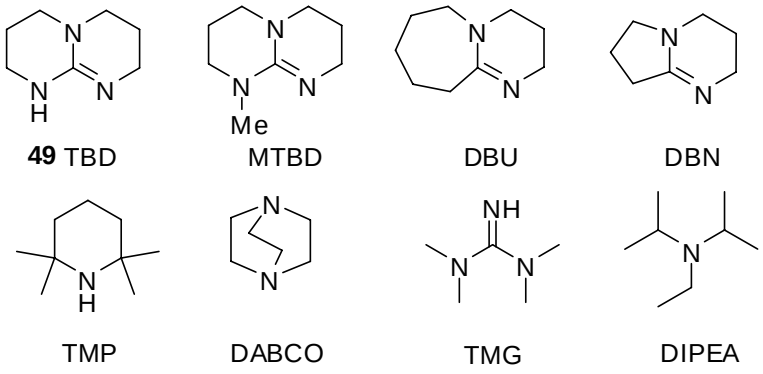


Fig. 2.1. Various organobases.

Stoichiometric amounts of MTBD have been shown to be moderately active towards the Baylis-Hillman reaction.[23] Immobilised MTBD, in siliceous MCM-41, can promote the Knoevenagel condensation, epoxidation[24] and the formation of thioureas.[25] Polystyryl supported-TBD (PSTBD) can catalyze 1,2-epoxide ring-opening, aldol-type condensation and the Michael addition of nitroethane to benzylidene acetone.[26] Nucleophilic ring opening reactions of 2,2-dialkyl-1,2,3,4-tetrahydro-γ-carbolinium salts with thiols can also be mediated by polymer-supported TBD.[27]

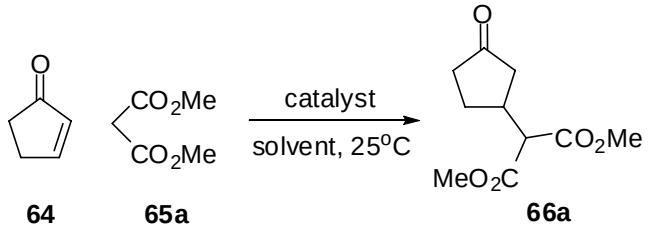
Carbon-carbon bond formation is central to organic synthesis. Direct Michael addition and Michael-type conjugate reactions are amongst the most simple, efficient and atom-economical ways to achieve this transformation. These reactions are typically performed with stoichiometric amounts of inorganic bases such as sodium ethoxide (NaOEt), potassium *tert*-butoxide (*t*BuOK), potassium hydroxide (KOH), sodium metal, LDA, sodium hydride (NaH) or *n*-butyllithium (*n*BuLi).[28] Strong basic conditions can, however, lead to side reactions. Recently, excellent enantioselective Michael reactions have been developed using transition metal catalysts.[29] A quaternary ammonium salt,[30] proline lithium salt,[31] L-proline,[32] cinchona alkaloids[33] and imidazolidine[34] have also been shown to exhibit catalytic activity in several conjugate addition reactions. In contrast, organobases such as DBU[35] (Fig. 2.1) and TBD[26, 36] are less extensively documented as catalysts for Michael reactions. We embarked on a search for the range of substrates and carbon nucleophiles that are suitable for Michael and Michael-type reactions using TBD as the catalyst.

2.2 TBD Catalyzed Michael Reactions

2.2.1 Various organobases catalyzed Michael reaction of cyclopentenone and dimethyl malonate.

As a reliable starting point, dimethyl malonate **65a** was used as the Michael donor to the cyclic enone, 2-cyclopenten-1-one **64** (Scheme 2.1, Table 2.1). With 10 mol% of TBD, the reaction proceeded smoothly at room temperature (25 ^{o}C) with toluene as the solvent. The reaction completed in 5 minutes and, after flash chromatography, gave the product in an excellent isolated yield of 95% (Table 2.1,

entry 1). The amount of catalyst could be reduced to 5 mol% (entry 2) without affecting the yield. With only 2 mol% or 1 mol% TBD, the reaction proceeded to 60% conversion in 2 h (entry 3, 4). This protocol neither requires strictly anhydrous condition nor low reaction temperature. It is more convenient and operationally simpler to perform than the reported methodology using sodium methoxide (NaOMe) to generate the same product.[37]



Scheme 2.1. Organobase catalyzed Michael reaction between 2-cyclopenten-1-one **64** and dimethyl malonate **65a**.

Table 2.1. The influence of catalyst amount and solvents on the reaction between 2-cyclopenten-1-one **64** and dimethyl malonate **65a**.

entry	catalyst/mol%	solvent	time	yield/%[a]
1	TBD (10)	Toluene	5 min	95
2	TBD (5)	Toluene	30 min	95
3	TBD (2)	Toluene	2 h	60[b]
4	TBD (1)	Toluene	2 h	60[b]
5	TBD (10)	DMF	15 min	90
6	TBD (10)	MeOH	15 min	90
7	TBD (10)	MeCN	30 min	90
8	TBD (10)	Et_2O	30 min	90
9	TBD (10)	THF	30 min	90
10	TBD (10)	CH_2Cl_2	1 h	70[b]
11	TBD (20)	Tol:H_2O (99:1)	30 min	90

[a]Isolated yield. Conversion estimated to be 100% by TLC. No side products observed. [b]Conversion estimated by TLC.

Under the same conditions, a variety of solvents such as DMF (Table 2.1, entry 5), methanol (entry 6), acetonitrile (entry 7), diethyl ether (entry 8) and THF (entry 9) were found to be suitable solvents for this reaction. These reactions typically completed within 15 to 30 minutes, giving isolated yields of ≥90%. However, in CH_2Cl_2, which is a mid-polarity solvent, the reaction reached only 70% conversion in 1 h (entry 10). We also discovered that this reaction is not sensitive to moisture. For example, the reaction in toluene containing 1% water with 20 mol% of the catalyst was completed in 30 minutes and the yield was 90% (entry 11).

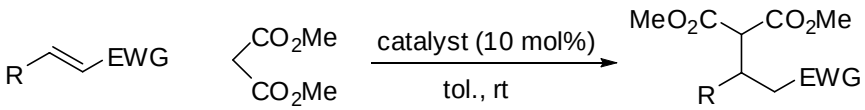
Next, we were keen to find out if it is a general phenomenon for organobases to act as catalysts in Michael reactions. We compared the results obtained with TBD against a variety of organobases such as MTBD, DBU, DBN, 1,1,3,3-tetramethylguanidine (TMG, Fig. 2.1), tetramethylpiperidine (TMP, Fig. 2.1), DABCO and diisopropylethylamine (DIPEA, Fig. 2.1). MTBD (Table 2.2, entry 1), DBU (entry 3) and DBN (entry 4) are all effective for this reaction. However, they catalyzed the reaction at a much slower rate than TBD. It is interesting to note the difference in reaction time between TBD and MTBD (entry 2). Such differences were much reduced in polar solvents such as MeOH and MeCN. The guanidinium intermediate that is generated when TBD is protonated may play a role as a hydrogen bond donor in the catalytic cycle. As such, this type of interaction would be enhanced in non-polar solvents such as toluene. The TMG catalyzed reaction (entry 5) was not able to reach completion. Other organobases such as TMP, DABCO and DIPEA were ineffective as catalyst for this reaction (entries 6-8). No products were observed after

46 h of reaction time. This was expected as the conjugate acids of these bases have relatively low pKa values.

Table 2.2. The influence of different organobases (10 mol%) on the reaction between 2-cyclopenten-1-one **64** and dimethyl malonate **65a** in toluene as solvent.

entry	catalyst	pKa[a] (solvent)[lit]	time	yield/%[b]
1	TBD	26.0 (MeCN)[19a] 21.0 (THF)[19b]	5 min	95
2	MTBD	25.4 (MeCN)[19a] 17.9 (THF)[19b]	6 h	91
3	DBU	16.8 (THF)[19b]	24 h	93
4	DBN	NA	24 h	90
5	TMG	23.3 (MeCN)[19a] 15.5 (THF)[19b]	37 h	85[c]
6	TMP	NA	46 h	0
7	DABCO	8.9 (DMSO)[i]	46 h	0
8	DIPEA	NA	46 h	0

[a]Values for conjugate acids of the respective bases. [b]Isolated yield. No side products observed. [c]Reaction did not complete.



67 **65a** **68**

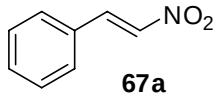
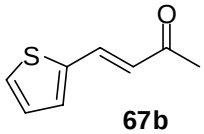
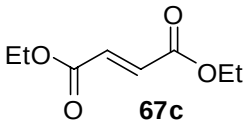
Scheme 2.2. Several organobase catalyzed Michael reaction between Michael acceptors **67** and dimethyl malonate **65a**.

We next investigated whether TBD was also advantageous on other reactions of different Michael acceptors. We compared TBD against MTBD, DBU, and TMP in the reactions of **67a-c** with dimethyl malonate **65a** in toluene as solvent at rt (Scheme 2.2). In the case of highly reactive β-nitrostyrene **67a**, MTBD and DBU were comparable with TBD in terms of reaction rate and conversion (Table 2.3, entries 1-3),

[i] Bordwell pKa Table (Acidity in DMSO): http://www.chem.wisc.edu/areas/reich/pkatable/index.htm

while TMP only gave a conversion of 10% after 19 h (entry 4). In the reactions of both **67b** and **67c**, TBD was considerably more effective than MTBD and DBU (entries 5-7, 9-11). TMP was ineffective in the reactions of **67b-c** (entries 8, 12). Thus, it could be concluded that TBD was a generally more effective organobase for Michael reactions.

Table 2.3. Comparison of TBD with other organobases as catalyst (10 mol%) in the reactions of various substrates **67** and dimethyl malonate **65a** (Scheme 2.2).

entry	substrate	catalyst	time	conv./%[a]
1	 **67a**	TBD	5 min	96[b]
2		MTBD	5 min	100
3		DBU	5 min	95
4		TMP	19 h	10
5	 **67b**	TBD	2 h	50
6		MTBD	90 h	40
7		DBU	45 h	30
8		TMP	19 h	0
9	 **67c**	TBD	1 h	90
10		MTBD	28 h	100
11		DBU	45 h	80
12		TMP	19 h	0

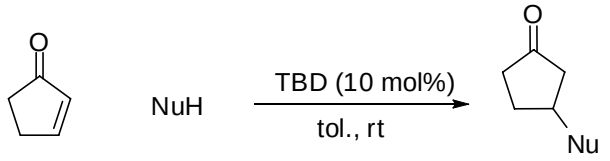
[a]Estimated reaction conversion based on TLC. [b]Isolated yield, also see Table 2.5, entry 1.

2.2.2 Suitable Michael donors for the reaction with cyclopentenone

Subsequently, we investigated a range of carbon nucleophiles suitable for this reaction using 2-cyclopenten-1-one **64** as the substrate (Scheme 2.3). Diethyl malonate **65b** (Table 2.4, entry 1) and di-*tert*-butyl malonate **65c** (entry 2) were both effective donors for the reaction. Compared with the reaction of dimethyl malonate **65a**, it was observed that as the alcohol groups of the malonate became bulkier, the

reaction rate decreased, though it did not affect the yield. Ethyl acetoacetate **65d** (entry 3), *N*,*N*-dimethylacetoacetamide **65e** (entry 4) and 2-acetylcyclopentanone **65f** (entry 5) were also found to be useful donors. These three reactions were slower than that of dimethyl malonate and the reaction of **65f** required 20 mol% TBD (entry 5). The reactions of nucleophiles **65b-f** proceeded smoothly, giving high isolated yields of the Michael adducts **66b-f**. It is interesting to note that the reaction with 2-acetylcyclopentanone had no side products even though it contained multiple enolizable protons (entry 5). This demonstrates the mildness and chemoselectivity of this reaction. The quaternary carbon of the product was identified using DEPT NMR experiments.

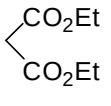
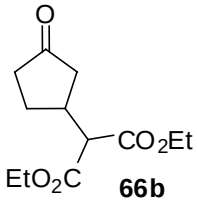
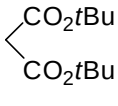
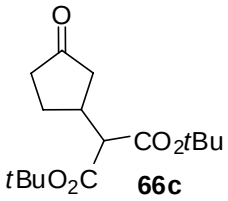
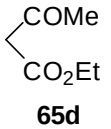
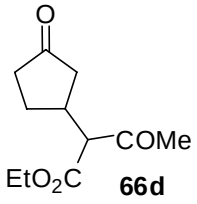
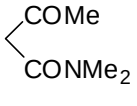
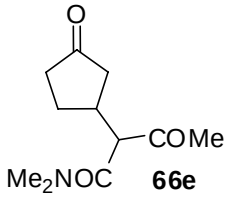
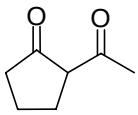
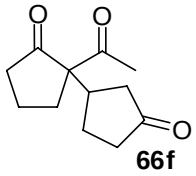
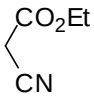
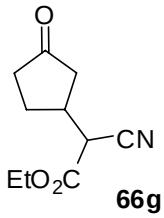
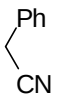
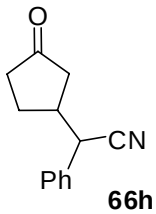
Ethyl cyanoacetate **65g** was a highly reactive donor and has side products in the reaction with 2-cyclopenten-1-one **64**. The expected product **66g** was isolated in 43% yield after 15 min reaction time (entry 6). Phenyl acetonitrile **66h** was also an effective donor for the reaction and gave the Michael adduct **67h** in a moderate yield of 82% after 18 h (entry 7).

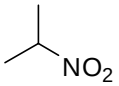
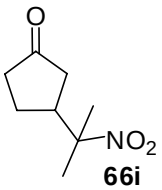


64 **65** **66**

Scheme 2.3. TBD (10 mol%) catalyzed Michael addition of various carbon nucleophiles to 2-cyclopenten-1-one **64** in toluene at rt.

Table 2.4. TBD catalyzed Michael addition of various carbon nucleophiles to 2-cyclopenten-1-one **64** (Scheme 2.3).

entry	donors	products	time	yield/%[a]
1	 **65b**	 **66b**	30 min	90
2	 **65c**	 **66c**	1 h	99
3	 **65d**	 **66d**	10 h	99
4	 **65e**	 **66e**	6 h	95
5	 **65f**	 **66f**	6 h	94[b]
6	 **65g**	 **66g**	15 min	43
7	 **65h**	 **66h**	18 h	82

8	 **22**	 **66i**	6 h	80[b]

[a]Isolated yield. [b]20 mol % of catalyst used.

Nitroalkanes are another important class of stabilized carbanions and were also tested as the Michael donor. The reaction of nitromethane with 2-cyclopenten-1-one **64** resulted in unidentified side products and the expected product was obtained in low yield. With 20 mol% TBD, the reaction of the more hindered nitroalkane **22** went smoothly to give **66i** in 80% yield after 6 h (entry 9).

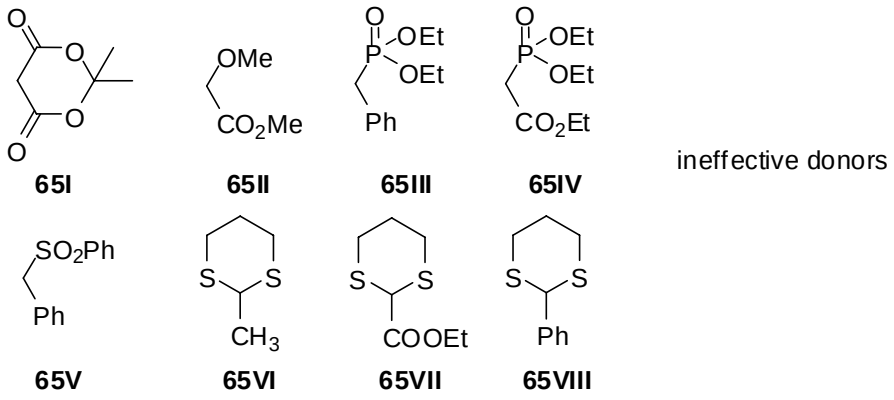


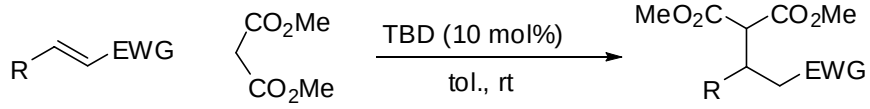
Fig. 2.2. Michael donors **65I-VIII** that do not react with 2-cyclopenten-1-one **64** in toluene at rt in the presence of TBD (10 mol%).

In our survey on Michael donors, compounds **65I-VIII** (Fig. 2.2) were found to be ineffective as donors in the reaction with 2-cyclopenten-1-one **64** in toluene at rt. Amongst these donors, **65I** and **65IV** are most unexpected to be ineffective as they have similar pKa values and structures as dimethyl malonate.

Thus, it can be concluded that TBD is generally an effective base catalyst for the Michael reactions of 1,3-dicarbonyl compounds with cyclopentenone. The Michael addition of nitroalkanes to cyclopentenone can also be catalyzed by TBD.

2.2.3 Suitable Michael acceptors for the reaction catalyzed by TBD

Using dimethyl malonate **65a** as the donor, we decided to investigate other suitable Michael acceptors (Scheme 2.4). We found that with 10 mol% of TBD, various β-nitrostyrenes **67a** and **67d-g** (Table 2.5, entry 1-5) underwent Michael addition with dimethyl malonate **65a** smoothly, featuring high yields in short reaction times (5 min). In the case of **67g**, MeCN was used as the solvent due to the poor solubility of **67g** in toluene (entry 5).



67 **65a** **68**

Scheme 2.4. TBD catalyzed Michael reaction between various Michael acceptors **67** and dimethyl malonate **65a**.

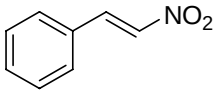
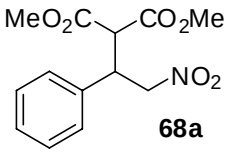
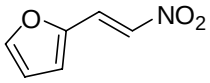
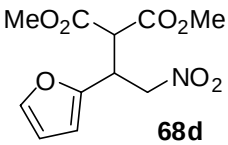
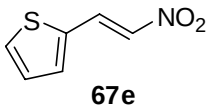
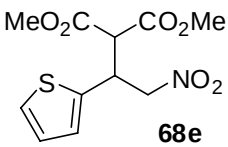
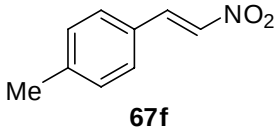
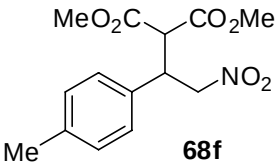
Various *trans*-chalcones **67h-l** (Table 2.5, entry 6-10) were also suitable substrates, giving the corresponding products in high yields. We realized that electron deficient chalcones were more active substrates and gave shorter reaction time. The electron rich chalcones **67k** and **67l** required 20 mol% TBD to complete the reaction. However, the difference in reaction time did not affect the yield of the reactions.

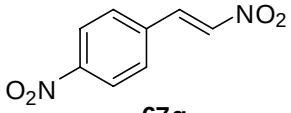
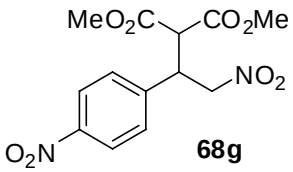
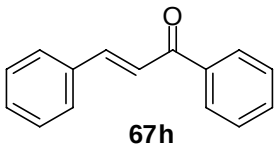
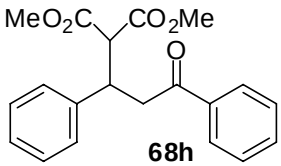
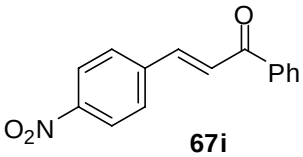
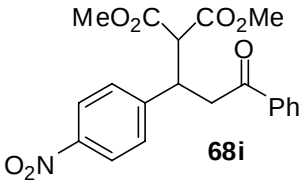
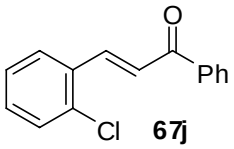
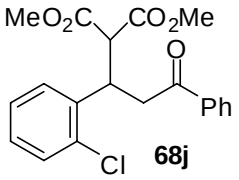
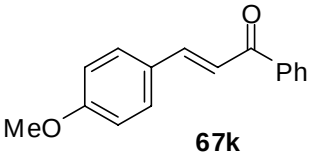
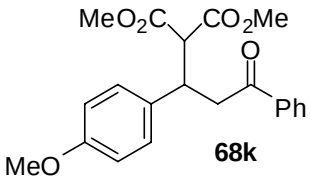
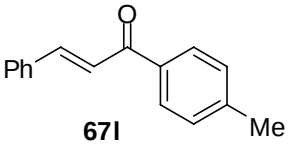
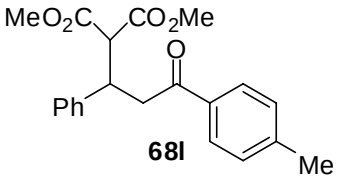
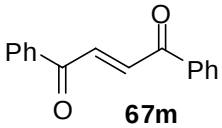
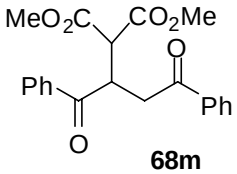
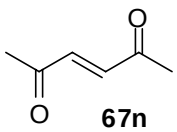
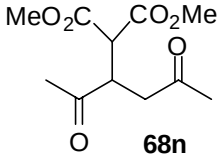
Trans-1,2-dibenzoylethylene **67m** (entry 11) and *trans*-1,2-diacetylethylene **67n** (entry 12) turned out to be very reactive and both of the reactions completed within 5 min, giving good to high yields. The reactions of diethyl fumarate **67c** (entry 13)

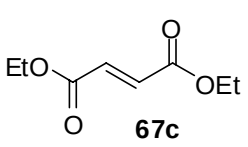
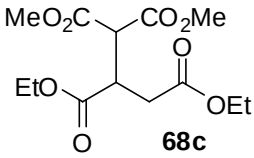
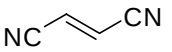
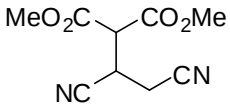
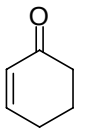
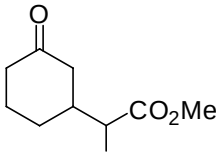
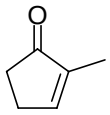
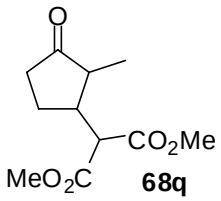
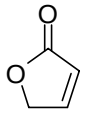
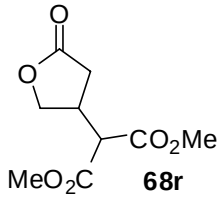
and fumaronitrile **67i** (entry 14) were relatively slower and required 15 mol% and 20 mol% TBD respectively to complete.

It is interesting to note that the reaction of 2-cyclohexen-1-one **67p** was considerably slower than that of 2-cyclopenten-1-one **64** and required 25 mol% catalyst to reach 83% yield after 10 h (Table 2.5, entry 15). The hindered cyclopentenone derivative, 2-methyl-2-cyclopenten-1-one **67q** was even less reactive than **67p** and only 20% conversion was achieved after 19 h (entry 16). Lactone **67r**, which is structurally similar to 2-cyclopenten-1-one **64**, was also less reactive and after 53 h, only 30% conversion was indicated by TLC (entry 17).

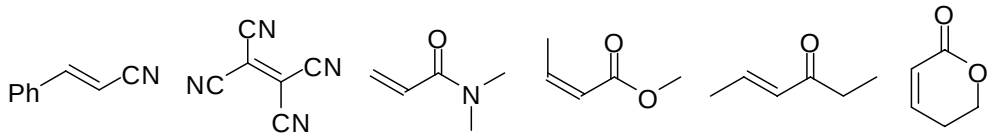
Table 2.5. TBD (10 mol%) catalyzed Michael reaction between dimethyl malonate and various substrates in toluene.

Entry	substrates	products	time	yield/%[a]
1	 **67a**	 **68a**	5 min	96
2	 **67d**	 **68d**	5 min	94
3	 **67e**	 **68e**	5 min	90
4	 **67f**	 **68f**	5 min	93

5	 **67g**	 **68g**	5 min	81[b]
6	 **67h**	 **68h**	1 h	92
7	 **67i**	 **68i**	5 min	98
8	 **67j**	 **68j**	30 min	98
9	 **67k**	 **68k**	2 h	95[c]
10	 **67l**	 **68l**	2 h	91[c]
11	 **67m**	 **68m**	5 min	96
12	 **67n**	 **68n**	5 min	84

13	 **67c**	 **68c**	30 min	91[d]
14	 **67o**	 **68o**	2 h	93[c]
15	 **67p**	 **68p**	10 h	83[e]
16	 **67q**	 **68q**	19 h	20[f]
17	 **67r**	 **68r**	53 h	30[f]

[a]Isolated yield. [b]MeCN used as solvent. [c]20 mol % of catalyst used. [d]15 mol% catalyst used. [e]25 mol % of catalyst used. [f]Estimated conversion indicated by TLC.



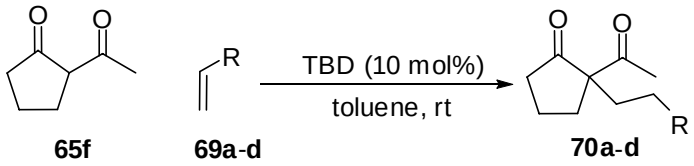
67I **67II** **67III** **67IV** **67V** **67VI**

Unreactive substrates

Fig. 2.3. Michael acceptors **67I-VI** that do not react with dimethyl malonate **65a** in toluene at rt in the presence of TBD (10 mol%).

Michael acceptors **67I-VI** (Fig. 2.3) were found to be ineffective as substrates in the reaction with dimethyl malonate **65a** in toluene at rt in the presence of TBD (10 mol%). Considering the fact that fumaronitrile **67o** was a suitable substrate under the

same conditions, it was unexpected to see **67II** as ineffective substrate for the reaction. One of the reasons might be the steric hindrance caused by the tetra-substitution.



Scheme 2.5. TBD (10 mol%) catalyzed Michael reactions between 2-acetyl-cyclopentanone **65f** and various activated terminal alkenes **69a-d**.

Table 2.6. The reaction times and yields of the reactions in Scheme 2.5.

entry	substrates	R	products	time	yield/%[a]
1	**69a**	CN	**70a**	1 h	83
2	**69b**	CO_2Me	**70b**	30 min	93
3	**69c**	CO_2Ph	**70c**	30 min	97
4	**69d**	SO_2Ph	**70d**	1.5 h	87
5	**69e**	SO_3Ph	**70e**	5 min	85

[a]Isolated yield. Conversion estimated to be 100% by TLC. No side products observed.

One-step construction of a quaternary carbon is often a difficult task, especially under catalytic conditions and this area has attracted the interest of many chemists.[38] Using our methodology, we therefore focused on broadening the range of suitable acceptors for the donor 2-acetylcyclopentanone **65f** (Scheme 2.5). We tested various activated terminal alkenes and found several suitable acceptors; for example acrylonitrile **69a** (Table 2.6, entry 1), acrylates **69b**,**c** (entry 2, 3), phenyl vinyl sulfone **69d** (entry 4) and phenyl vinylsulfonate **69e** (entry 5). All reactions completed within a short reaction time, giving moderate to excellent isolated yields of previously unreported Michael adducts **70a-d**. These Michael products are unreported previously.

The quaternary carbons of the products were identified using DEPT NMR experiments.

In conclusion, we have discovered a mild, catalytic, high yielding and efficient methodology for Michael and Michael-type reactions using TBD. This type of reaction is easy to perform, fast and the purification protocol is simple. No side products were observed for most reactions. As the reaction is not sensitive to moisture, the solvents used and reaction conditions need not be absolutely anhydrous. This methodology can accommodate a wide range of substrates and donors, making it a useful addition to the chemists' toolbox. Using this protocol, we have synthesized a series of Michael adducts containing quaternary carbon centers that were previously unreported. Moreover, TBD is inexpensive and commercially available.

Chapter 3

Chiral Bicyclic Guanidines

Catalyzed Michael Reaction

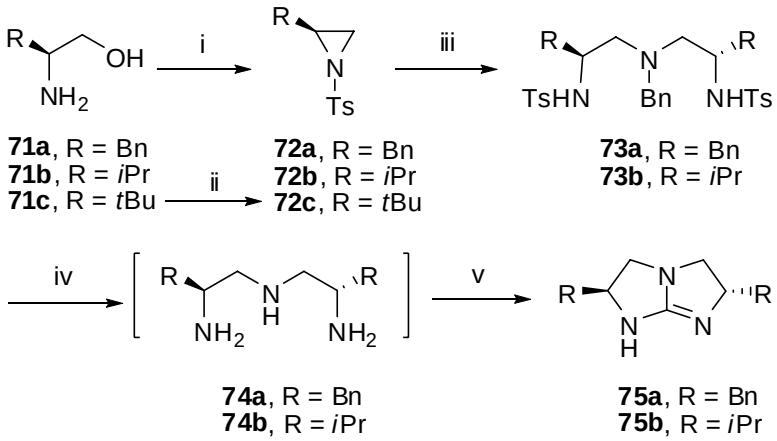
3.1 An Aziridine-Based Synthesis of Chiral Bicyclic Guanidines[ii]

To achieve an efficient asymmetric version of the 1,5,7-triazabicyclo [4.4.0]dec-5-ene (TBD) catalyzed Michael reactions, we embarked on the development of an efficient synthesis of chiral bicyclic guanidines. The current synthetic approaches to these guanidines include the coupling of two amino acid derivatives and the reduction of the resulting amide to obtain the triamine backbone.[39] Another strategy is to go through a thiourea intermediate, followed by 1,3-dimethy-imidazolinium chloride induced step-wise cyclization.[40] However, a more efficient synthetic protocol will be needed if this class of catalyst is to gain widespread usage. We envisioned that an effective synthesis will be achieved if we take advantage of the C_2 symmetric nature of the catalyst.

Aziridines can undergo regio- and stereoselective ring opening reactions, making them useful synthetic intermediates.[41] *N*-Tosyl aziridine **72** (Scheme 3.1) was readily prepared from their corresponding commercially available α-amino alcohols **71**.[42] Triamine unit **73** was easily obtained by treating **72** with 0.5 equivalent of benzyl amine.[43] The nucleophilic attack preferentially occurs at the sterically least hindered carbon atom. The subsequent removal of tosyl groups were achieved by using sodium in liquid ammonia and was immediately subjected to catalytic hydrogenation without further purification. The crude triamine **74** was subjected to the final cyclization step, leading to the expected guanidines **75a** and **75b** in 71% and 43% total yield

[ii] Mr. Leow Dasheng and Miss Serena Goh are acknowledged for providing the first few batches of the catalysts.

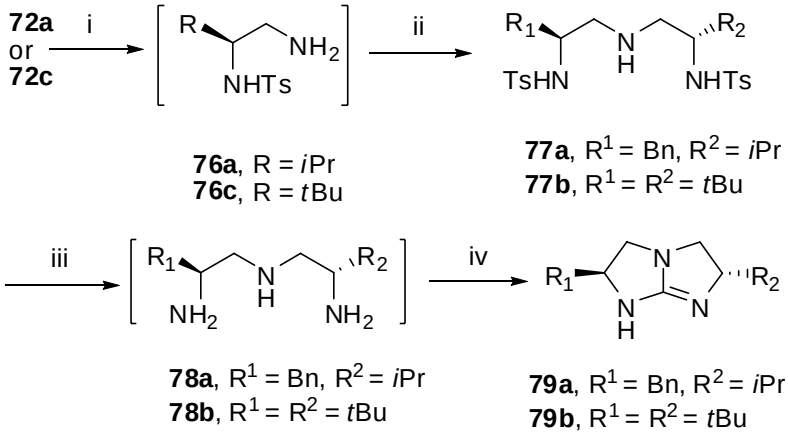
respectively from their amino alcohols. We have utilized five chemical steps with only three requiring chromatographic purification.



Scheme 3.1 Synthesis of symmetrical chiral bicyclic guanidines. *Reagents and conditions.* (i) TsCl, Et_3N, MeCN[18], 92% for **72a**, 94% for **72b**; (ii) TsCl, Et_3N, CH_3CN, MS(4A), 0 ^oC then MsCl, Et_3N, DMAP, CH_2Cl_2, rt, 80%; iii) 0.5 equiv. $BnNH_2$, MeOH, 60 ^oC, 3 days[19b], 92% for **73a**, 75% for **73b**; (iv) a) Na/NH_3(l), -78 ^oC, THF; b) H_2, Pd/C, MeOH; (v) $(MeS)_2C{=}S$, MeI/AcOH, $MeNO_2$, reflux, 84% for **75a**, 61% for **75b**.

The formation of **72c** (Scheme 3.1) did not proceed as expected using this usual protocol. The tosylation of the hydroxyl group was poor after the formation of the *N*-sulfonamide intermediate. We found that if mesyl chloride was used as a replacement, the *O*-sulfonate was formed more easily and it also facilitated the S_N2 ring-closing reaction. In our attempt to prepare guanidine **79b** (Scheme 3.2), we met with another obstacle. The aziridine double ring-opening reaction with $BnNH_2$ turned out to be slow and low yielding, giving mainly the mono-opening product. The problem was circumvented by treating **72c** with NH_3 to form diamine **76c**, which was used without purification to open another equivalent of aziridine **72c**, leading to the backbone **77b** in 84% yield (from **72c**). Detosylation and cyclization resulted in the guanidine **79b** (overall 50% yield from **71c**). A step-wise approach to construct the

triamine backbone provides us with an opportunity to prepare non-symmetrical chiral bicyclic guanines such as **79a** through the use of two different aziridines. By stirring aziridine **72a** in MeOH saturated with NH_3 gas in a sealed vessel, single ring-opening product **76a** was obtained and used as a nucleophile for the ring-opening of aziridine **72b**, leading to backbone **77a** in 80% yield (based on **72a**). After removal of the tosyl group and final cyclization step, guanidine **79a** was obtained in 71% yield (from **72a**).



Scheme 3.2 Synthesis of non-symmetrical or hindered chiral bicyclic guanidines. *Reagents and conditions.* (i) NH_3/MeOH, 0 ^oC to rt; (ii) CH_3CN, 90 ^oC, 3 days, **72b** or **72c**, 80% for **77a** from **72a**, 84% for **77b** from **72c**; (iv) $(MeS)_2C{=}S$, MeI/AcOH, $MeNO_2$, reflux, 89% for **79a** from **77a**, 75% for **79b** from **77b**.

3.2 Michael Reaction between 2-Cyclopenten-1-one and 1,3-Dicarbonyl Compounds

3.2.1 Recent advances in asymmetric catalytic Michael reactions

Organocatalytic methods have gained widespread popularity in recent years.[44] Lewis bases are particularly useful and operate through an iminium[45] or enamine intermediate.[46] The activation of a stabilized carbanion using a Brønsted base for conjugate addition is a classical approach. There are many successful examples using

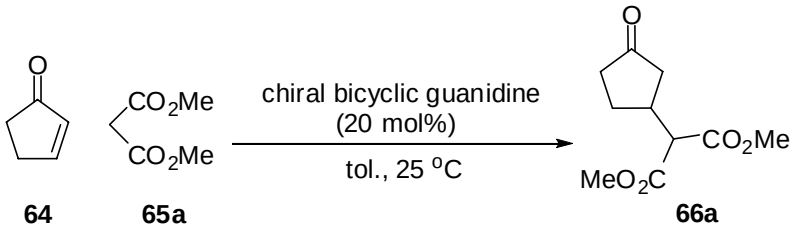
Cinchona alkaloids and its derivatives.[47] Many of these act as bifunctional catalysts; activating the electrophile with hydroxyl or phenolic group. Other bifunctional catalysts, such as those containing the thiourea moiety, activate nitro compounds for the Michael reaction using hydrogen bonding.[48] Chiral quaternary ammonium salts and *Cinchona* alkaloid derivatives are also well known to participate in Michael reactions as phase transfer catalysts.[49]

Addition reaction of 1,3-dicarbonyl compounds to 2-cyclopenten-1-one provides an easy and direct approach to chiral cyclopentanones. Successful examples typically utilize metal catalysts such as Al-Li-BINOL,[50] Al-Li-aminodiols,[51] La-linked-BINOL[52] and Ru-amido complexes.[53] Organocatalytic methods include the use of (2-pyrrolidyl)alkyl ammonium hydroxide derivatives[54] and *Cinchona* alkaloid derivatives.[55] L-Proline, with *trans*-2,5-dimethylpiperazine as an additive, has been shown to catalyze the reaction between nitroalkanes and 2-cyclopenten-1-one.[56]

3.2.2 The effect of the catalyst structure on the enantioselectivity

With an efficient synthesis of the chiral bicyclic guanidines in hand, we embarked on the study of the Michael reaction between 2-cyclopenten-1-one **64** and dimethyl malonate **65a** (Scheme 3.3). We found that with 20 mol% of **75a**, the reaction between dimethyl malonate **65a** and 2-cyclopenten-1-one **64** completed in 24 h at 25 ^{o}C in toluene (Table 3.1, entry 1). The product **66a** was obtained in an isolated yield of 95% and 30% ee. Under the same conditions, the ee of 44%, 66% and 78% (entries 2-4) were obtained for the reactions catalyzed by guanidine catalysts **79a**, **75b**, and **79b**, respectively. As the appendage of the catalysts became bulkier, the

enantioselectivity improved while the reaction rate slowed down, though yields remained high.

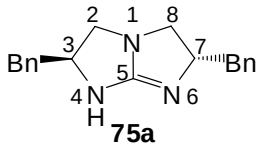
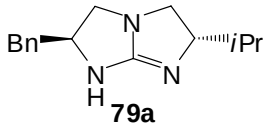
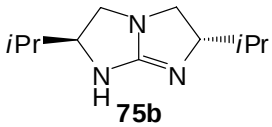


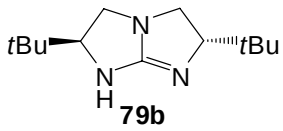
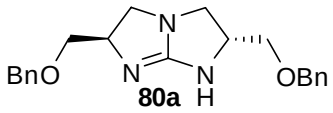
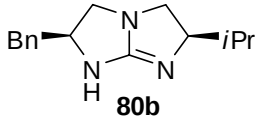
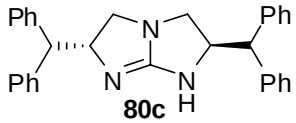
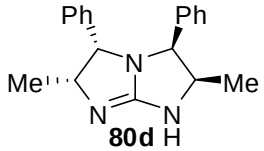
64 **65a** **66a**

Scheme 3.3. Various chiral bicyclic guanidines catalyzed Michael reaction of 2-cyclopenten-1-one **64** and dimethyl malonate **65a**.

Lowering reaction temperature is a general approach to improve enantioselectivity. However, the reaction time of 4 days to obtain 78% ee (Table 3.1, entry 4) makes conducting the experiment at lower temperatures not practical. Therefore, we designed and synthesized several other chiral bicyclic guanidine catalysts **80a-d**, hoping that by tuning the electronic and steric properties of the catalyst, both the reaction rate and enantioselectivity could be improved.

Table 3.1. Various chiral bicyclic guanidines catalyzed Michael addition of dimethyl malonate **65a** to 2-cyclopenten-1-one **64** (Scheme 3.3).

entry	catalyst (mol%)	time /day	yield/%[a]	ee/%[b]	product **66a** absolute config.
1	 **75a** (20)	1	95	30	*R*-(+)
2	 **79a** (20)	1.5	93	44	*R*-(+)
3	 **75b** (20)	2	93	66	*R*-(+)

4	 **79b** (20)	4	92	78	*R*-(+)
5	 **80a** (20)	2	56	34	*R*-(+)
6	 **80b** (20)	1.5	84	17	*R*-(+)
7	 **80c** (10)	6	55	45	*S*-(-)
8	 **80d** (20)	3	54	38	*S*-(-)

[a]Isolated yield. [b]Chiral HPLC.

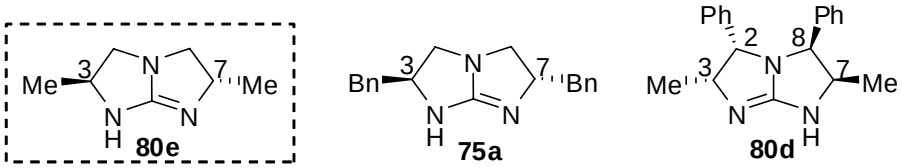
In the reaction catalyzed by guanidine **80a**, with a heteroatom-containing side chain, there was only a slight improvement in ee (34%, Table 3.1, entry 5) compared with guanidine **75a**. However, the reaction was obviously slower than that catalyzed by **75a**, giving the product in 56% yield after 2 days.

Catalyst **80b** was also tested and 17% ee (Table 3.1, entry 6) was obtained, which was inferior to both **75a** and **79a**. As the only difference between **80b** and **79a** was the relative configuration of the two appendages at *C3* and *C7* of the catalyst, it was concluded that the *anti* relative configuration was important for the effective asymmetric induction.

We designed catalyst **80c**, hoping that the bulky -$CHPh_2$ side chain would increase the enantioselectivity. However, with 10 mo% **80c**, only a moderate ee of

45% was obtained and the reaction was very slow, giving the product in 55% yield after 6 days (Table 3.1, entry 7).

As all the catalysts discussed above only have chiral centers on *C3* and *C7*, we were curious whether installation of chiral centers on *C2* and *C8* would affect the enantioselectivity. Therefore, catalyst **80d** (Fig. 3.1), with *C2*, *C3*, *C7*, and *C8* chiral centers, was synthesized and tested. 38% ee and 54% yield were obtained (Table 3.1, entry 8). From the trend of ee obtained with catalysts **75a**, **75b**, **79a**, and **79b**, we have realized that the enantioselectivity improves as the alkyl chains at *C3* and *C7* become bulkier. We envisioned that if catalyst **80e**, with a methyl group appendage that is less hindered than a benzyl group, was applied to the reaction, the ee obtained should be less than that obtained with catalyst **75a** (30% ee). Thus, the 38% ee obtained with catalyst **80e** implied that the installed *C2* and *C8* chiral centers are conducive for the asymmetric induction. However, due to the unavailability of other similar catalysts with all *C2*, *C3*, *C7*, and *C8* chiral centers, we were unable to further study the effects of the *C2* and *C8* chiral centers.



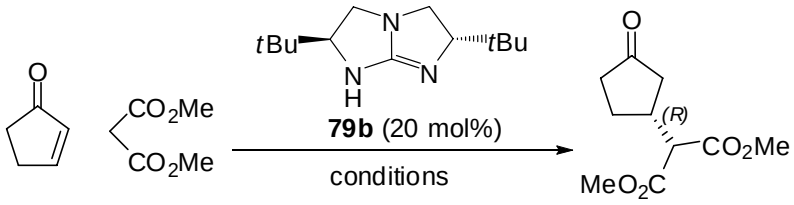
(**66a**: < 30% ee ?) **66a**: 30% ee **66a**: 38% ee

Fig. 3.1. The effect of *C2* and *C8* chiral centers.

By comparing the optical rotation and HPLC trace of the product **66a** with literature data,[50-52] it was found that (*R*)-(+)-**66a** was the major isomer obtained in the reactions catalyzed by **75a-b**, **79a-b**, and **80a-b**, while (*S*)-(-)-**6a** was the major

isomer obtained in the reactions catalyzed by **80c-d**. It was not unexpected since the absolute configuration of **80c-d** was opposite to those in **75a-b**, **79a-b**, and **80a-b**.

3.2.3 Optimization studies on the reaction of 2-cyclopenten-1-one 64 with dimethyl malonate 65a catalyzed by catalyst 79b



64 **65a** **66a**

Scheme 3.4. Chiral bicyclic guanidines **79b** catalyzed Michael reaction of 2-cyclopenten-1-one **64** and dimethyl malonate **65a** in different conditions.

Table 3.2. Solvent effect on the Michael addition of dimethyl malonate **65a** to 2-cyclopenten-1-one **64** catalyzed by **79b** (Scheme 3.4).[a]

entry	solvent	time/days	yield/%[a]	ee/%[b]
1	THF	6	91	73
2	CH_2Cl_2	4	82	58
3	PhF	2	73	57
4	$PhCF_3$	4	80	70
5	1,2-Dichlorobenzene	4	44	70
6	Nitrobenzene	4.5	52	47
7	*p*-Xylene	6	77	77
8	Xylenes	4	44	70
9	Neat in **64**	4	77	73
10	Neat in **65a**	10	33	59

[a]25 °C. [b]Isolated yield. [b]Chiral HPLC.

With **79b** as the optimal catalyst, the reaction was optimized by changing other variables of the reaction conditions (Scheme 3.4).

Solvent effect was first studied by screening various solvents at rt (Table 3.2). We found that protic (eg. MeOH) and highly polar solvents (eg. DMSO, DMF) usually caused low enantioselectivities. Solvents such as THF and CH_2Cl_2 (entries 1-2) were found to be inferior to toluene. Since toluene gave the best results so far, we tested several other aromatic solvents. Fluorobenzene (entry 3), $PhCF_3$ (entry 4), 1,2-dichlorobenzene (entry 5), and nitrobenzene (entry 6) were found unsuitable as the solvent, as they gave both lower ee and yields than in toluene. Although the reaction in *p*-xylene gave an ee of 77% (entry 7), which is close to that in toluene, only 77% yield was obtained after 6 days. A mixture of xylenes as solvent gave a lower ee of 70% and 44% yield after 4 days (entry 8). In order to improve the reaction rate, we also conducted the experiments under neat conditions. 73% ee was obtained when the reaction was in 2-cyclopenten-1-one **64** as solvent, while no obvious rate increase was observed (entry 9). Slow reaction rate (33% yield, 10 days) and low ee (59%) was resulted when dimethyl malonate **65a** was used as the solvent (entry 10). Therefore, toluene was chosen as the solvent for further optimization.

Concentration and temperature effects were studied using toluene as the solvent (Table 3.3). It was found that 78% ee and 92% yield was obtained when the concentration of **64** was 0.25 M (entry 1). When the concentration was diluted to 0.05 M, the ee decreased dramatically to 27% and the reaction obviously slowed down to reach a yield of 72% in 16 days (entry 2). When concentration was increased to 0.6 M and 1.0 M, the ee of 74% (entry 3) and 76% (entry 4) was obtained respectively, without obvious rate acceleration observed. At a concentration of 2.5 M, the ee

decreased to 68% and 89% yield was obtained in 4 days (entry 5). Thus, the concentration of **64** was maintained at 0.25 M in the study of temperature effect. Lowering the temperature to 0 ^{o}C and -20 ^{o}C slowed the reaction rate considerably without an improvement in ee (entry 6-7). To our surprise, when the reaction temperature was increased to 50 ^{o}C, the ee only decreased slightly to 76%, without obvious increase in reaction rate (entry 8).

Table 3.3. Concentration and temperature effects on the Michael addition of dimethyl malonate **65a** to 2-cyclopenten-1-one **64** catalyzed by **79b** in toluene as solvent.

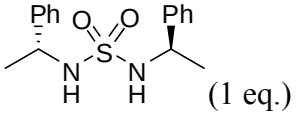
entry	temp./ ^{o}C	concentration [**64**]/M	time/days	yield/%[a]	ee/%[b]
1	25	0.25	4	92	78
2	25	0.05	16	72	27
3	25	0.6	2	75	74
4	25	1.0	4	60	76
5	25	2.5	4	89	68
6	0	0.25	10	72	79
7	-20	0.25	14	98	76
8	50	0.25	4	75	76

[a]Isolated yield. [b]Chiral HPLC.

It is known that in many cases of asymmetric catalysis, the addition of small amounts of very simple achiral compounds can be beneficial for both the yields and enantioselectivities obtained.[57] We therefore tested a few compounds as additives in the reaction (Table 3.4). Addition of 1 eq. *t*BuOH decreased both the ee (70%) and the yield (73%, entry 1). Hoping that compounds such sulfonamides or thioureas could activate the Michael acceptor through double hydrogen bonding,[58] we tested a chiral sulfonamide (1 eq.) as the additive. Though a high yield of 95% was obtained after

4.5 days, the ee was decreased to 67% (entry 2).

Table 3.4. Additive effect on the Michael addition of dimethyl malonate **65a** to 2-cyclopenten-1-one **64** catalyzed by **79b**.[a]

entry	solvent	Additive	temp/ °C	time/day	yield/%[b]	ee/%[c]
1	Tol	*t*BuOH (1 eq.)	25	4.5	73	70
2	Tol	 (1 eq.)	25	4.5	95	67
3	Tol	Et_3N (1 eq.)	25	3	99	79
4	Tol	Et_3N (10 v%)	25	0.5	86	80
5	Et_3N	Nil[d]	25	0.5	92	81
6	Et_3N	Nil[d]	-20	5	95	91

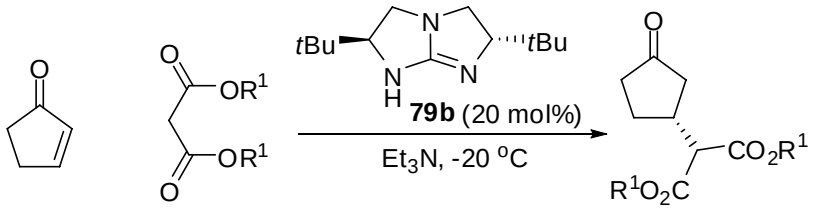
[a][**64**] = 0.25 M. [b]Isolated yield. [c]Chiral HPLC. [d]No additive.

We suspected that the possible formation of a zwitterion between the guanidine catalyst with CO_2[59] from atmosphere might have slowed down the reaction. We envisioned that addition of an extra base, like Et_3N, may speed up the reaction. Several amines were tested including trimethylamine, pyridine, Et*N*iPr_2 and *N,N,N',N'*-tetramethyl diaminomethane, but Et_3N gave the best results. Addition of 1 eq. Et_3N drove the reaction to completion within 3 days, giving the product in an excellent yield of 99% and 79% ee (entry 3). As the amount of Et_3N added to the reaction increased to 10 v%, the reaction rate accelerated significantly and completed within 12 h, with a slight improvement in ee (80%, entry 4). Using Et_3N as the solvent afforded the product in 92% yield in 12 h and an improved ee of 81% (entry 5). This dramatic rate acceleration provided us with an opportunity to conduct the experiment at a lower temperature. With Et_3N as solvent at -20 °C, the reaction completed within 5 days, giving the product in 95% yield and 91% ee (entry 6).). As the boiling point

of Et_3N is normal (88.9 ^oC), it was treated as a normal solvent during workup and no extra procedure was needed. This condition was used for expanding the substrate scope.

3.2.4 Highly enantioselective Michael reaction between cyclopentenone and 1,3-dicarbonyl compounds catalyzed by chiral bicyclic guanidine 79b

Table 3.5. Chiral guanidine **79b** catalyzed Michael addition of various dialkyl malonates to 2-cyclopenten-1-one **64**.[a]



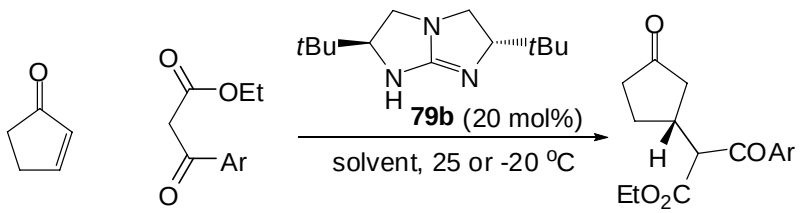
64 **65b-c, j-k** **66b-c, j-k**

entry	Donor	R^1	time/day	yield/%[b]	ee/%[c]
1	**65b**	Et	5.5	93	92
2	**65j**	Bn	5.5	99	92
3	**65k**	*i*Pr	8	84	96
4	**65c**	*t*Bu	10	36	36

[a]At -20 ^oC. [b]Isolated yield after 6 days. [c]Chiral HPLC.

With suitable conditions determined, various dialkyl malonates **65b-c**, and **65j-k** were tested as donors for the Michael addition to **64**. With Et_3N as solvent at -20 ^oC, the reactions of diethyl malonate **65b**, dibenzyl malonate **65j** completed within 5.5 days and gave the respective desired Michael adducts with high enantioselectivities and yields (Table 3.5, entry 1-2). The reaction of the more hindered malonate, diisopropyl malonate **65k**, reached a yield of 84% in 8 days and gave an excellent ee of 96% (entry 3). The reaction of di-*tert*-butyl malonate **65c** was extremely slow and only reached a yield of 36% after 10 days, with a low ee of 36% (entry 4).

Table 3.6. Chiral guanidine **79b** catalyzed Michael addition of various ethyl benzoylacetates **65l-r** to 2-cyclopenten-1-one **64**.



64 **65l-r** **66l-r**

entry	Donor	Ar	temp/ °C	solvent	time	yield/%[a]	ee/%[b]
1	**65l**	Ph	25	Et_3N	30 h	93	82; 82
2	**65l**	Ph	25	Tol	43 h	28	77; 77
3	**65l**	Ph	-20	Et_3N	7 d	98	93; 90
4	**65l**	Ph	-20	Tol	8 d	25[c]	92; 88
5	**65m**	*m*-MePh	25	Tol	20 h	67	81; 81
6	**65m**	*m*-MePh	25	Et_3N	20 h	96	77; 77
7	**65m**	*m*-MePh	-20	Tol	8 d	85	91; 90
8	**65m**	*m*-MePh	-20	Et_3N	60 h	89	87; 86
9	**65n**	*p*-CF_3Ph	-20	Tol	6 d	90	96; 92
10	**650**	*m*-CF_3Ph	-20	Tol	6 d	84	89; 88
11	**65p**	*p*-ClPh	-20	Tol	6 d	99	93; 92
12	**65q**	*m*-ClPh	-20	Tol	6 d	99	90; 90
13	**65r**	*p*-NO_2Ph	-20	Tol	6 d	91	94; 93

[a]Isolated yield. [b]Ee determined by chiral HPLC, 1:1 d.r. of **66l-r** determined by ^{1}H-NMR and chiral HPLC. [c]30 mol% catalyst **79b** used.

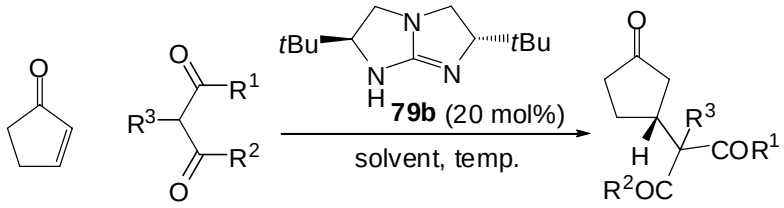
We next examined the suitability of ethyl benzoylacetate **65l** and its analogues **65m-r** as donors for the reaction. At rt, in terms of both reaction rate and enantioselectivity, Et_3N was found to be a better solvent than toluene for the reaction of ethyl benzoylacetate **65l** (Table 3.6, entry 1 *vs.* entry 2). At -20 °C, although the ee obtained in the reaction of **65l** in Et_3N (93% and 90% ee, entry 3) as solvent was close to that in toluene (92% and 88% ee, entry 4) as solvent, much higher yield (98%,

entry 3) was obtained in Et_3N than in toluene (25%, entry 4). However, for the reaction of **65m** at both rt (entry 5 and 6) and -20 ^oC (entry 7 and 8), Et_3N turned out to be inferior to toluene in terms of enantioselectivity. In the reactions of other ethyl benzoylacetate analogues **65n-r**, toluene was also found to be the better solvent than Et_3N, giving the products in high yields (84-99%) and ee (88-96%) (entries 9-13).

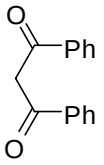
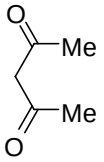
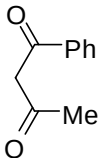
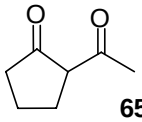
In later studies, we found out that using Et_3N as solvent, the addition of benzoylacetates **65m-r** to **64** occurred without catalyst at room temperature. This might be the reason that other than **65l**, Et_3N did not improve the enantioselectivities of the reaction compared to toluene. These reactions of **65l-r** gave the respective products in diastereomeric ratios of 1:1 (Table 3.6). All diastereomers can be distinguished using chiral HPLC.

Various 1,3-diketones **65s-u** and **65f** were also tested as the Michael donors for the reaction with 2-cyclopenten-1-one **64** (Table 3.7). Similar to the benzoylacetates, additives like Et_3N did not improve the ee of these reactions. Compared with the reaction of dibenzoylmethane **65s** in toluene at rt (83% ee, entry 1), addition of 1 eq. of Et_3N resulted in an inferior ee (72%, entry 2), though with faster reaction rate. By using 40 mol% catalyst at -20 ^oC, the reaction of **65s** in toluene afforded the product in 91% ee and 61% yield in 6 days (entry 3). In the reaction of acetyl acetone **65t** at rt, toluene gave a better ee of 61% (entry 4) than that in Et_3N (44% ee, entry 5). The reaction of **65u** at -20 ^oC gave the product in a moderate ee (80 and 81%) and yield (62%, entry 6). The reaction of the hindered 1,3-diketone **65f** was conducted at rt and the product was obtained in modest yield and ee (entry 7).

Table 3.7. Chiral guanidine **79b** catalyzed Michael addition of various 1,3-diketones **65s-u** and **65f** to 2-cyclopenten-1-one **64**.



64 **65s-u, f** **66s-u, f**

entry	donor	temp/ °C	solvent	time	yield/%[a]	ee/%[b]
1	 **65s**	25	Tol	3 d	87	83
2		25	Tol (1 eq. Et_3N)	24 h	80	72
3		-20	Tol	6 d	61	91[c]
4	 **65t**	25	Tol	7 d	67	61
5		25	Et_3N	88 h	77	44
6	 **65u**	-20	Tol	72 h	62	80; 81[d]
7	 **65f**	25	Tol	72 h	71	65; 56[d]

[a]Isolated yield. [b]Ee determined by chiral HPLC. [c]40 mol% catalyst **79b** used. [d]1:1 d.r. of **66s-u** and **66f** determined by ^{1}H-NMR and chiral HPLC.

3.2.5 *S,S'*-dialkyl dithiomalonates: novel Michael donors in the highly enantioselective Michael reaction

While the enantioselectivities obtained for the Michael addition of dialkyl malonates and benzoylacetates were high, the reaction times were long. In order to overcome this disadvantage and broaden the scope of this methodology, we started searching for other 1,3-dicarbonyl compounds with higher reactivity. It is known that the α-hydrogen acidity of thioesters is usually higher than their corresponding

esters.[60] It is because the S(3p) orbitals are too large to efficiently overlap with the C(2p) orbitals of the carbonyl group (Fig. 3.2).[60] Therefore the thioesters have less conjugation than ordinary esters and this enhances the acidity of their α-hydrogens. It makes thioester a useful enol equivalent in the laboratory[61] as well as in nature (as acyl coenzyme A).[62] We envisioned that *S,S'*-dialkyl dithiomalonates should also have lower pKa values than dialkyl malonates and so could be more reactive in Michael reactions. Thus, a series of *S,S'*-dialkyl dithiomalonates **65v-y** were synthesized and tested as the Michael donor (Table 3.8).

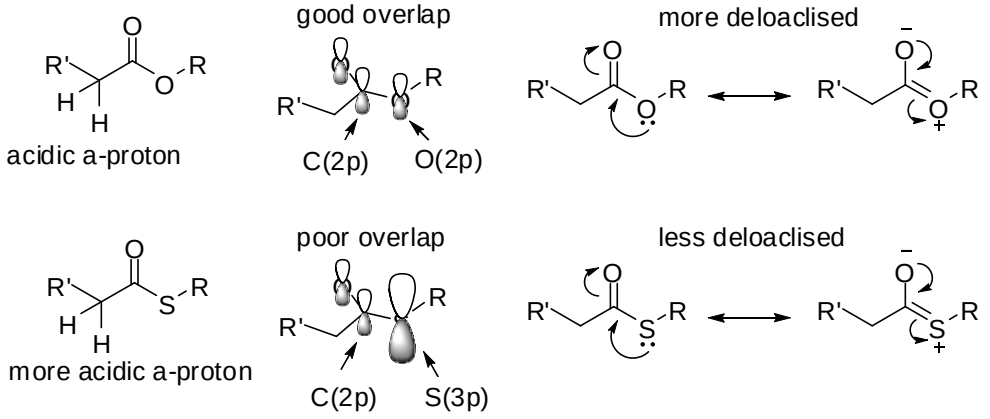
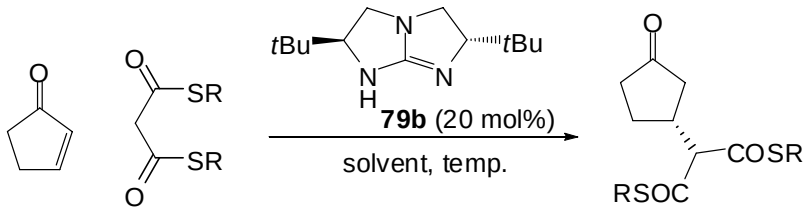


Fig. 3.2. Difference between thioester and ordinary ester.

At rt in toluene as solvent, the addition of *S,S'*-di-*n*-propyl dithiomalonate **65v** to 2-cyclopenten-1-one **64** completed within 36 h to give the product **66v** in 99% yield and 78% ee (Table 3.8, entry 1). This reaction rate was significantly faster than both the dialkyl malonates and benzoylacetates. The enantioselectivity of the reaction of **65v** was improved to 87% (entry 2) by lowering the reaction temperature at -20 ^{o}C, while the yield remained excellent (99%, entry 2). Similar to the benzoylacetates, using Et_3N as solvent at -20 ^{o}C caused inferior ee (47%, entry 3). By conducting the reactions of **65v-y** at -40 ^{o}C in toluene as solvent, all the desired Michael adducts were

obtained in good enantioselectivities (entries 4-7, 89-93% ee) and good yields (92-99%). The highest enantioselectivity was obtained with the more hindered *S,S'*-di-*tert*-butyl dithiomalonate **65y** (entry 7). At -70 °C, the reaction rate slowed considerably with a slight improvement in the ee while the yields remained high.

Table 3.8. Chiral guanidine **79b** catalyzed Michael addition of *S,S'*-dialkyl dithiomalonates **65v-y** to 2-cyclopenten-1-one **64**.



64 **65v-y** **66v-y**

entry	donor	R	temp/ °C	solvent	time/h	yield/%[a]	ee/%[b]
1	**65v**	*n*Pr	25	Tol	36	99	78
2	**65v**	*n*Pr	-20	Tol	96	99	87
3	**65v**	*n*Pr	-20	Et_3N	96	58	47
4	**65v**	*n*Pr	-40	Tol	72	95	89
5	**65w**	Et	-40	Tol	72	92	90
6	**65x**	*i*Pr	-40	Tol	80	99	90
7	**65y**	*t*Bu	-40	Tol	80	92	93

[b]Isolated yield. [b]Chiral HPLC.

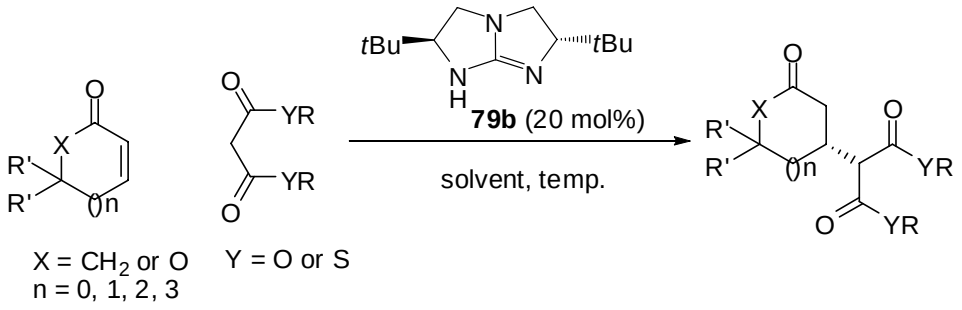
Thiol esters offer a versatile handle in organic synthesis. They can be easily hydrolyzed or conveniently transformed to ketones, aldehydes or β-ketoesters.[63] The dithiomalonate group can also be directly reduced to a saturated alcohol using Raney nickel.[64] These reactions may facilitate the modification of the Michael adducts and allow *S,S'*-dialkyl dithiomalonates to be good alternatives for the construction of chiral cyclopentanones. This is also the first example of *S,S'*-dialkyl dithiomalonates

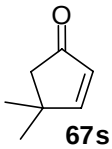
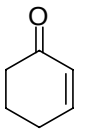
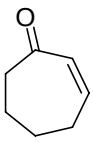
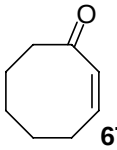
used in the highly enantioselective catalytic Michael reactions.

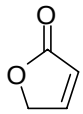
3.2.6 The Michael reaction of other cyclic enones with 1,3-dicarbonyl compounds

From the studies above, we have developed a highly enantioselective Michael reaction of 2-cyclopenten-1-one **64**. To expand the substrate scope of this methodology, we tested other cyclic enones as Michael acceptors with 1,3-dicarbonyl compounds (Table 3.9).

Table 3.9. Chiral guanidine **79b** catalyzed Michael addition between other cyclic enones and 1,3-dicarbonyl compounds.



entry	substrate	-YR	solvent	temp/ ^{o}C	time/d	yield/%[a]	ee/%[b]
1	 **67s**	OEt	Et_3N	25	3	9	96
2	 **67p**	OMe	Et_3N	25	3.5	81	68
3	**67p**	OEt	Et_3N	-20	10	-[c]	-[c]
4	 **67t**	OEt	Et_3N	25	3	-[c]	-[c]
5	 **67u**	OEt	Et_3N	25	3	-[c]	-[c]

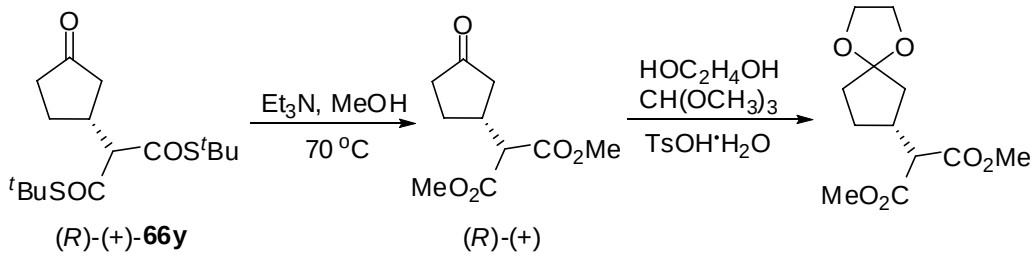
6	**67p**	SEt	Tol	25	1	64	68
7	**67p**	SBn	Tol	25	4	46	70
8	**67t**	SBn	Tol	25	4	13	56
9	**67u**	SBn	Tol	25	4	16	50
10	 **67r**	SBn	Tol	25	4	16	56

[a]Isolated yield. [b]Chiral HPLC. [c]No reaction observed.

As shown in Table 3.9, this asymmetric catalytic system is sensitive to the structure of the Michael acceptor. Thus far, only the reactions of 2-cyclopenten-1-one **64** achieved high enantioselectivities and yields. The steric hindrance of substituted cyclopentenone **67s** is likely the reason of its low reactivity. The 6, 7, and 8-membered cyclic enones **67p**, **67t**, and **67u** were also less reactive than the **64**. It might be due to the increased steric hindrance of the ring and the decreased ring strain compared with the 5-membered ring.

3.2.7 Determination of the absolute configuration of the Michael adducts

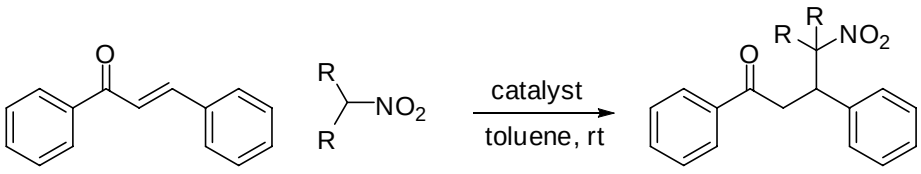
Michael adducts **66a-d, k** were determined to be (*R*)-(+) by comparing with literature reports.[50-52] Michael adduct **66l** was determined to be (*R*) by comparing with literature reports[4]. Michael adducts **66m-r** were assumed to have the same absolute configuration as **66l**. Product **66y** was converted to its *O*-ester analog, which was determined to be (*R*)-(+) by using optical rotation and HPLC (Scheme 3.5). Similar Michael adducts **66v-x** were assumed to have the same absolute configuration as **66y**.



Scheme 3.5. Determination of the absolute configuration of **65y**.

3.3 Michael Reactions of Acyclic Michael Acceptors

3.3.1 Nitroalkanes as Michael donor



Scheme 3.6. Bicyclic guanidines catalyzed Michael reaction of nitroalkanes with *trans*-chalcone **35a**.

It is known that amidine and guanidine bases can interact with nitroalkanes in non-polar solvents and form tightly bound ion pair complexes.[65] Nitroalkanes are a valuable source of stablized carbanions and are widely used as carbon nucleophiles for conjugate addition to enones.[66] The Michael adducts retaining a nitro group can undergo a variety of transformations, making it a versatile building block for organic synthesis.[57] Chiral spirocyclic guanidines have also been shown to catalyze the Michael reaction of nitroalkanes to chalcone with modest enantioselectivity.[8] In addition, there are relatively limited satisfactory examples of catalytic enantioslective Michael reaction of nitroalkanes to chalcone derivatives.[67] Thus, the synthesized chiral bicyclic guanidines were tested as catalysts in the Michael reactions between

nitroalkanes and *trans*-chalcone **35a** (Scheme 3.6).

Table 3.10. The influence of different guanidine catalysts on the Michael reaction of nitroalkanes with *trans*-chalcone **35a** (Scheme 3.6).

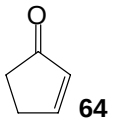
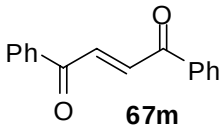
entry	Michael donor	catalyst (mol%)	time	yield/%[a]	e.e./%[b]
1	**53**	TBD (20)	1.5 h	99	NA
2	**53**	**75a** (10)	7 d	60[c]	13
3	**53**	**75b** (20)	4 d	42[c]	32
4	**53**	**79b** (20)	7 d	35[c]	56
5	**22**	**75b** (20)	4 d	23[c]	61
6	**22**	**80a** (20)	5 d	40[c]	10
7	**22**	**79b** (20)	5 d	20[c]	54
8[d]	**22**	**79b** (10)	2 d	42[c]	40

[a]Isolated yield. [b]Chiral HPLC. [c]Reaction was not completed. [d]Et_3N as solvent.

With 20 mol% TBD, the conjugate addition of nitromethane **53** to chalcone **35a** completed within 1.5 h, giving **81** in 99% yield (Table 3.10, entry 1). In the presence of 10-20 mol% **75a**, **75b**, and **79b**, 13%, 32%, and 56% e.e. (entries 2-4) were obtained respectively. It was shown that as the appendage of the catalyst became bulkier, the enantioselectivity improved. However, both the reaction rate and yields decreased. The enantioselectivity was also affected by the nature of the nitroalkanes. With the more hindered 2-nitropropane **22** and **75b** as catalyst (entry 5), higher enantioselectivity (61% e.e.) was obtained than with **53** (entry 3). Using **80a** as the catalyst, only 10% ee was obtained in the reaction of **22** (entry 6). Unexpectedly, the ee of product obtained with the more hindered catalyst **79b** (54%, entry 7) was lower

than that obtained with catalyst **75b** (61%, entry 5). Using Et_3N as solvent resulted in an inferior ee (40%, entry 8).

Table 3.11. Chiral bicyclic guanidines catalyzed Michael reaction of nitroalkanes with **64** and **67m**.

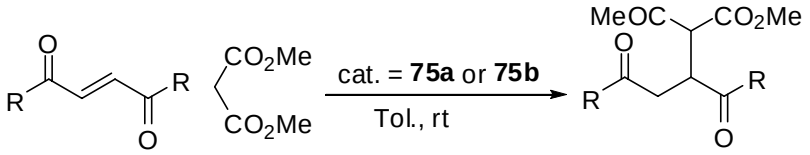
entry	substrate	Michael donor	catalyst (mol%)	time	yield/%[a]	e.e./%
1	 **64**	**53**	**75b** (10)	4 d	59	24[b]
2	 **67m**	**22**	**75b** (20)	8 d	59	41[c]
3		**22**	**79b** (20)	5 d	54	11[c]

[a]Isolated yield, reactions was not completed. [b]Ee determined by ^{13}C-NMR after conversion to a diastereomeric acetal with (2*R*, 3*R*)-2,3-butandiol. [c]Ee determined by chiral HPLC.

The Michael reactions of nitroalkanes to other Michael acceptors were also tested. The reaction of nitromethane **53** with 2-cyclopenten-1-one **64** was catalyzed by 10 mol% **75b**, giving the product in 24% ee and 59% yield after 4 days (Table 3.11, entry 1). With 20 mol% **75b**, the reaction of 1,2-dibenzoyl ethylene **67m** with 2-nitropropane **22** reached a yield of 59% and gave the product with 41% ee (entry 2). It was interesting to note that using catalyst **79b**, which was a better catalyst in the Michael reaction of 2-cyclopenten-1-one **64** with 1,3-dicarbonyl compounds, the ee (11%, entry 3) obtained was considerably lower than that obtained with **75b** (41% ee, entry 2). This trend was also observed in the reaction of trans-chalcone **35a** with **22**, where higher ee was obtained with **75b** than with **79b**. These results implied that the mode of interaction between nitroalkanes with the catalysts might be different from that between 1,3-dicarbonyl compounds and the catalysts.

3.3.2 The Michael reaction between dimethyl malonate and fumaric derivatives

In our survey on TBD catalyzed Michael reactions, we have found that fumarate and fumaric derivatives were good substrates of the reactions with dimethyl malonate. Using either **75a** or **75b** as catalyst, poor enantioselectivities (12% ee or less) were observed when 1,2-dibenzoylethylene **67m** and dimethyl fumarate **82** were reacted with dimethyl malonate **65a** (Scheme 3.7). It was observed that the reaction of **67m** gave a much higher yield and occurred at a much faster rate than **82**. This implies that α,β-unsaturated ketones are more electrophilic than α,β-unsaturated esters.



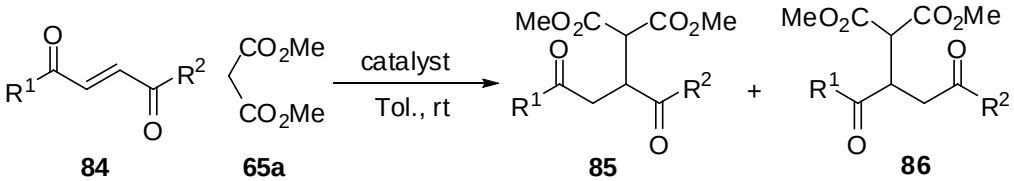
67m, R=Ph
82, R=OMe

65a

68m, R=Ph
83, R=OMe

Scheme 3.7. Bicyclic guanidines catalysed Michael reaction of dimethyl malonate with fumaric derivatives.

The observed difference in reactivity prompted us to study the regioselectivity of Michael reactions of malonate to unsymmetrical conjugated compounds such as methyl *trans*-4-oxo-2-pentenoate **84a** and ethyl *trans*-3-benzoylacrylate **84b** (Scheme 3.8).



84 **65a** **85** **86**

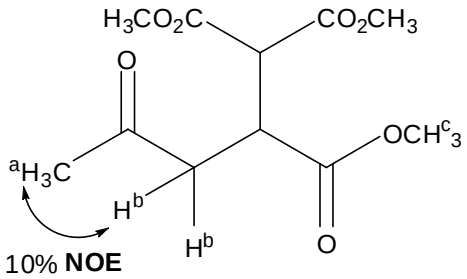
84a, R^1 = Me, R^2 = OMe
84b, R^1 = Ph, R^2 = OEt

85a, R^1 = Me, R^2 = OMe
85b, R^1 = Ph, R^2 = OEt

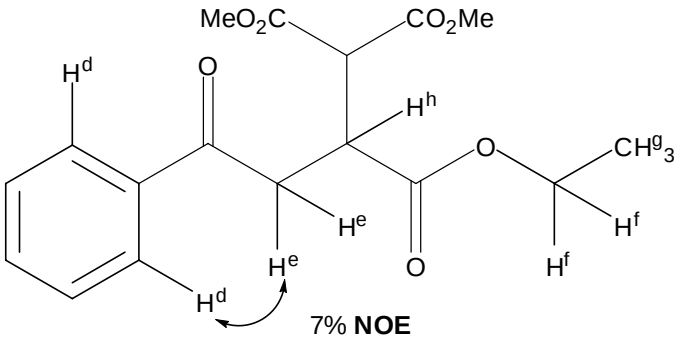
86a, R^1 = Me, R^2 = OMe
86b, R^1 = Ph, R^2 = OEt

Scheme 3.8. Bicyclic guanidines catalyzed Michael reaction of dimethyl malonate **65a** with fumaric derivatives **84**.

With various bicyclic guanidine catalysts, only one regioisomer was observed for both of the reactions. NOE experiments of the product obtained from **84a** showed that there was obvious NOE (10%) between H^a and H^b. No NOE was observed between H^b and H^c. Thus the product obtained from **84a** was confirmed to be regioisomer **85a** instead of **86a**.



85a



85b

Similarly, in the NOE experiments of the product obtained from **84b**, a clear NOE (7%) was observed between H^d and H^e. No NOE was observed between H^d and H^h, H^e and H^f, H^e and H^g. Thus the product obtained from **84b** was confirmed to be regioisomer **85b** instead of **86b**.

As expected, the formation of regioisomer **85** is directed by the ketone carbonyl group instead of the ester group. It was not unexpected since a ketone carbonyl group

is generally more electro-withdrawing than an ester carbonyl group. To the best of our knowledge, this is the first example of absolutely regioselective Michael reaction of malonates to fumaric derivatives.[68]

Table 3.12. The influenece of different guanidine catalysts on the reaction in Scheme 3.8.

entry	substrate	catalyst (mol%)	time/h	**85** : **86**	yield[a]/%	e.e./%[b]
1	**84a**	TBD (20)	0.5	100 : 0	90	NA
2	**84a**	**75a** (20)	120	100 : 0	40[c]	41
3	**84a**	**75b** (10)	90	100 : 0	41[c]	33
4	**84a**	**79a** (10)	93	100 : 0	46[c]	35
5	**84b**	**75b** (20)	120	100 : 0	86[c]	23

[a]Not optimized isolated yield. [b]Chiral HPLC. [c]Reaction not completed.

The enantioselectivity of this reaction was also studied. With catalysts **75a**, **75b**, and **79b**, 41%, 33%, and 35% e.e. (Table 3.12, entries 2-4) were obtained respectively for the reactions of **84a**. Though the e.e. of the reaction of **84b** catalyzed by **75b** was lower, the yield was improved to 86% (entry 5).

In conclusion, in this Chapter, we have developed a highly enantioselective Michael reaction between 2-cyclopenten-1-one and various 1,3-dicarbonyl compounds.

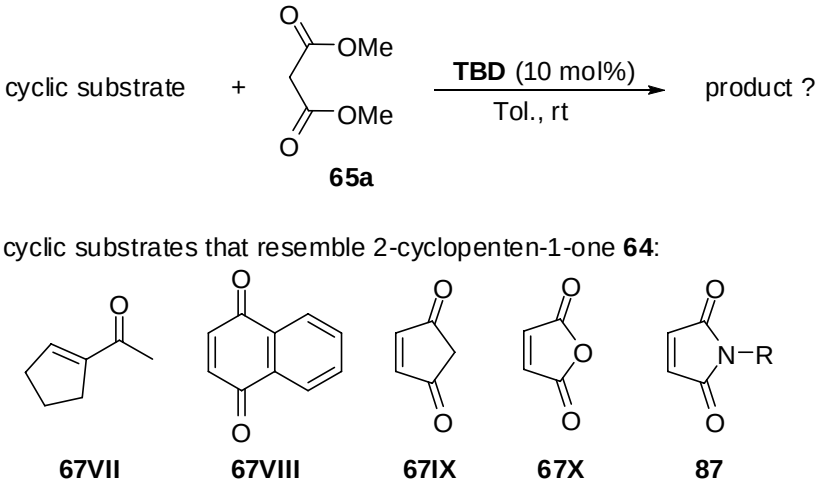
Chapter 4

Michael Reaction between N-Alkyl Maleimides and 1,3-Dicarbonyl Compounds

4.1 Michael Reaction of *N*-alkyl Maleimides

4.1.1 Michael reaction between maleimides and *S,S'*-dialkyl dithiomalonates

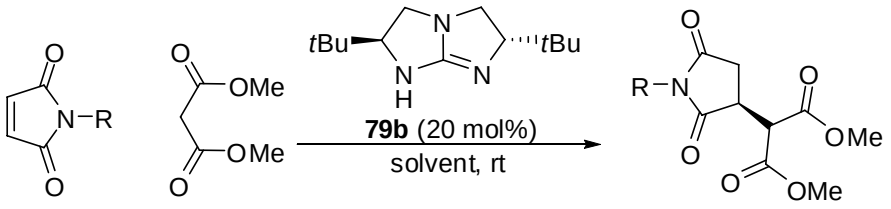
In order to expand the substrate scope of the methodology developed for 2-cyclopenten-1-one **64**, we tested other cyclic Michael acceptors that structurally resemble **64** in the reaction with dimethyl malonate **65a** in the presence of 10 mol% TBD in toluene at rt (Scheme 4.1). Enone **67VII**, 1,4-Naphthoquinone **67VIII**, dione **67IX**, and maleic anhydride **67X** were found ineffective in this reaction. Only the reaction of *N*-substituted maleimides **87** proceeded smoothly to give the products in high yields.



Scheme 4.1. Cyclic Michael acceptors that resemble 2-cyclopenten-1-one **64** tested in the reaction with dimethyl malonate **65a** in the presence of 10 mol% TBD in toluene.

Subsequent asymmetric experiments revealed that with 20 mol% of guanidine **79b**, dimethyl malonate **65a** underwent Michael addition to maleimides **87a** and **87b** (Scheme 4.2). Both these two reactions in toluene were relatively slow, giving the Michael adducts **88a** and **88b** in low yields and modest ee (39% and 47%). Conducting the reaction of **87b** in Et_3N as solvent decreased the ee to 24%, and a high

yield (99%) was obtained.



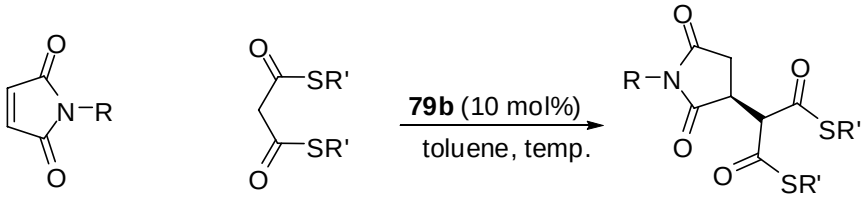
87a, R = Ph
87b, R = Et

65a

88a, R = Ph
88b, R = Et

product	solvent	time/h	yield/%	ee/%
88a	Tol	38	10	39
88b	Tol	96	20	47
88b	Et_3N	120	99	24

Scheme 4.2. Chiral guanidine **79b** catalyzed Michael reaction between *N*-substituted maleimides **87a-b** and dimethyl malonate **65a**.



87b, R = Et
87c, R = Me
87d, R = *n*-C_6H_{13}
87e, R = Bn
87f, R = *i*Bu
87g, R = *t*Bu

65x, **R'** = i*Pr*
65y, R' = *t*Bu

89

Scheme 4.3. Chiral guanidine **79b** catalyzed Michael reaction between *N*-alkyl maleimides and *S,S*'-dialkyl dithiomalonates.

To improve the reaction rate, the more reactive *S,S*'-dialkyl dithiomalonates were tested in place of dimethyl malonate (Scheme 4.3). We were pleased to find that with 10 mol% catalyst **79b** at rt, the reaction between *S,S*'-di-*tert*-butyl dithiomalonate **65y** and *N*-ethyl maleimide **87b** completed within 1 h, giving the Michael adduct **89a** in 97% yield and 78% ee (Table 4.1, entry 1). This dramatic rate improvement allowed us to conduct the reaction at lower temperatures. At -20 °C, the enantioselectivity improved to 90% ee (entry 2). By further lowering the temperature to -50 °C, the ee

was improved to 95% and the reaction was completed with an excellent yield of 98% (entry 3).

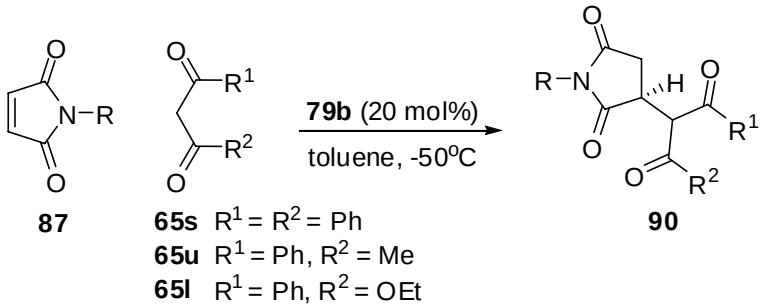
Table 4.1. Michael addition of *S*,*S*'-dialkyl dithiomaloates to *N*-alkyl maleimides catalyzed by **79b** (Scheme 4.3).

entry	substrate		product	temp/ ^{o}C	time/h	yield/%[a]	ee/%[b]
1	**87b**	**65y**	**89a**	25	1	97	78
2	**87b**	**65y**	**89a**	-20	4	99	90
3	**87b**	**65y**	**89a**	-50	6	98	95
4	**87c**	**65y**	**89b**	-50	6	94	95
5	**87d**	**65y**	**89c**	-50	6	99	95
6	**87e**	**65y**	**89d**	-50	6	99	92
7[c]	**87c**	**65x**	**89e**	-70	48	96	93
8[c]	**87b**	**65x**	**89f**	-70	48	99	93

[a]Isolated yield. [b]Chiral HPLC. [c]20 mol% **79b**.

Under these conditions, various *N*-alkyl maleimides (**87c-e**) were found to participate in the reaction with **65y**, giving the Michael adducts **89b-d** in excellent yields (94-99%) and good ee (92-95%, Table 4.1, entries 4-6). With the less hindered *S*,*S*'-diisopropyl dithiomalonate **65x**, reactions with **87c** or **87b** needed to be conducted at -70 ^{o}C to obtain satisfactory ee of 93% (entries 7, 8).

4.1.2 Michael reaction between maleimides and 1,3-diketones



Scheme 4.4. Chiral Guanidine **79b** catalyzed Michael reaction between *N*-alkyl maleimides and 1,3-diketones.

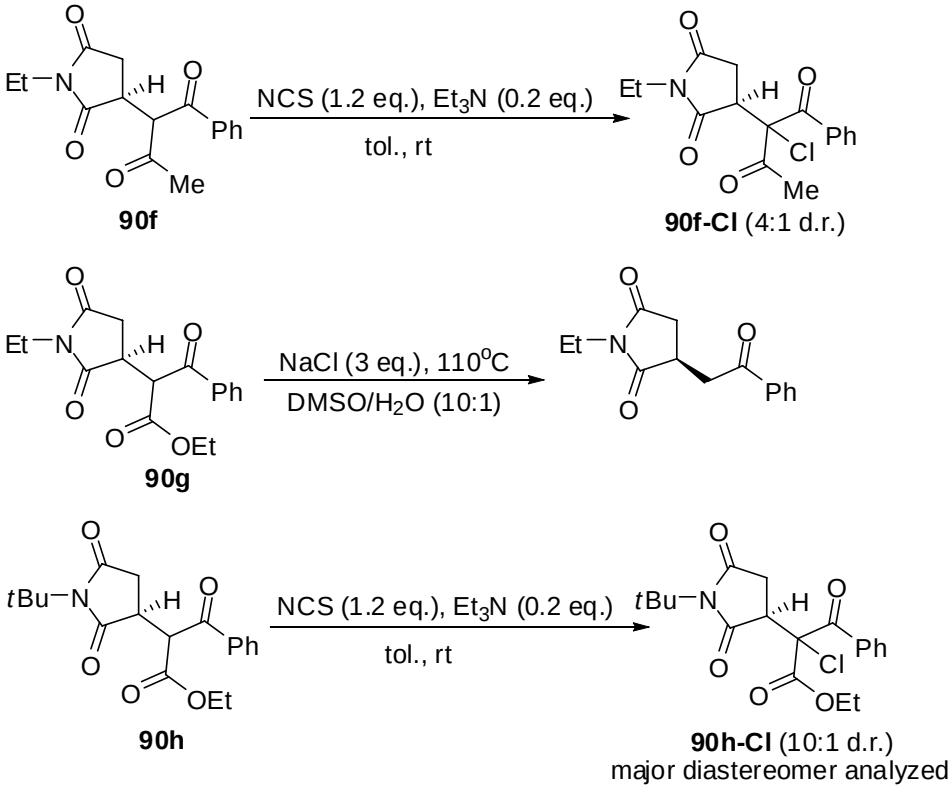
Table 4.2. Michael addition of 1,3-diketones to *N*-alkyl maleimides catalyzed by **79b**.

entry	substrate		product	time/h	yield/%[a]	ee/%[b]
1	**87b**	**65s**	**90a**	60	99	92
2	**87c**	**65s**	**90b**	72	99	93
3	**87d**	**65s**	**90c**	72	99	92
4	**87e**	**65s**	**90d**	96	99	90
5	**87f**	**65s**	**90e**	144	72	92
6	**87b**	**65u**	**90f**	120	99[c]	95;96[d]
7	**87b**	**65l**	**90g**	60	99	88[e]
8	**87g**	**65l**	**90h**	72	91	94[d]

[a]Isolated yield. [b]Chiral HPLC. [c]**65u** diluted to 0.1 M, due to low solubility at -50 °C. [d]1:1 d.r. (^{1}H NMR), ee determined after α-chlorination. [e]1:1 d.r. (^{1}H NMR), ee determined after decarboxylation.

Further studies revealed that 1,3-diketones **65y** can function as the donor for the Michael addition with the maleimides (Scheme 4.4). It was observed that the reactions with **65y** were generally slower than those with *S*,*S*'-dialkyl dithiomalonates which have relatively similar pKa values. At -50 °C, the reactions between maleimides **87b-e** and dibenzoylmethane **65s** completed between 60-96 h, giving the corresponding Michael adducts **90a-d** with >90% ee and 99% yield (Table 4.2, entries 1-4). A compromised yield (72%) was obtained for the reaction between the more hindered *N*-isobutyl maleimide **87f** and **65s**, while the ee remained high (92%, entry 5). Various other 1,3-diketones including **65u** (Table 4.2, entry 6) and benzoylacetates including **65l** (entries 7, 8) were tested using the established protocols. We observed that many of these 1,3-diketones including **65u** have poor solubility in toluene at -50 °C. We were also unable to find suitable HPLC conditions to determine the ee of

many Michael adducts of benzoylacetate derivatives. We were successful with 3 examples (entries 6-8) after the Michael adducts **90f-h** were derivatized either through decarboxylation or α-chlorination reaction (Scheme 4.5). Eventually, we were able to conclude that **65u** and **65l** were also good substrates for this reaction, giving high yields and enantioselectivities.



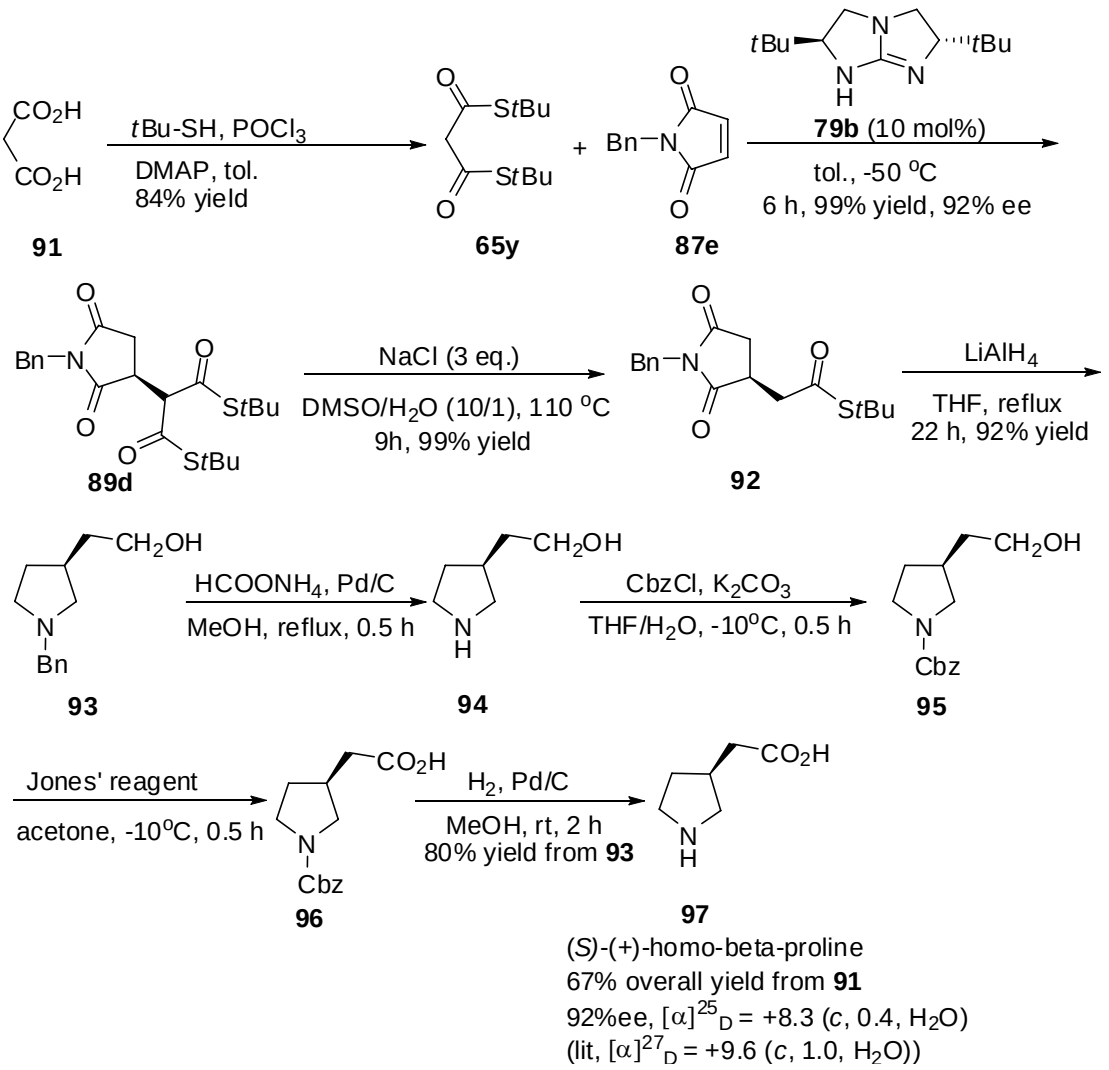
Scheme 4.5. Derivatization of Michael adducts **90f-h** for HPLC analyses.

4.1.3 Potential synthetic utility of the maleimide-based Michael adducts

While maleimides are commonly used in cycloaddition reactions, they are not well documented as acceptors in asymmetric catalytic Michael reactions.[69] A large number of biologically interesting α-substituted succinimides[70] and functionalized pyrrolidines,[71] can potentially be obtained *via* asymmetric Michael reaction. Methodology based on maleimides should provide easy access to these enantiopure

heterocycles. Simple ring opening procedures[72] could also mean rapid entry to functionalized open chain derivatives. Coupled with the versatility of thioesters, these maleimide-based Michael adducts should have good potential synthetic utility.

4.1 Enantioselective Synthesis of (*S*)-(+)-homo-β-Proline



Scheme 4.6. The first enantioselective synthesis of (*S*)-(+)-homo-β-proline.

The synthetic utility of this methodology was demonstrated in the first enantioselective synthesis of (*S*)-(+)-homo-β-proline **97** (Scheme 4.6), a potent γ-aminobutyric acid (GABA) agonist and uptake inhibitor.[73] γ-Aminobutyric acid is a neurotransmitter present in 60-70% of all synapses and has been implicated to several

neurological disorders such as anxiety, pain, Parkinson's disease and epilepsy.[74] Current syntheses include the resolution of racemic homo-β-proline using pig liver esterase,[75] the use of (*S*)-(-)-1-phenylethylamine as a chiral auxiliary,[64a, 76] and the use of aspartic acid as the chiral starting material.[77]

To realize this multistep synthesis, an efficient preparation of the novel Michael donor, *S*,*S'*-di-*tert*-butyl dithiomalonate **65y**, was desired. After surveying a few ester formation conditions, it was found that using $POCl_3$ as the carboxylic acid activating reagent and DMAP as the catalyst, malonic acid **91** and 2-methyl-2-propanethiol afforded the product **65y** in 3 h with 93% yield. Subsequently, the developed enantioselective Michael reaction between **65y** and *N*-benzyl maleimide **87e** was carried out at a 1 mmol scale without compromising the yield (99%) and enantioselectivity (92%) of the product **89d**.

Through the decarboxylation of one of the thioesters of **89d**, mono-thioester **92** was obtained in 99% yield. No recemization was observed when **92** was analyzed using chiral HPLC. Reduction of **92** with $LiAlH_4$ went smoothly to generate the *N*-benzyl-homo-β-prolinol **93** in a yield of 92%. Jones' oxidation of **93** was capricious and gave side products on some occasions. This problem was circumvented by exchanging the protecting group to Cbz group. This was followed by Jones' oxidation and hydrogenolysis. These few steps were carried out efficiently, without the need of chromatography purification and were achieved with a yield of 80% yield from **93**. This efficient enantioselective synthesis of (*S*)-(+)-homo-β-proline **97** (overall yield of 67% from **91**) also allowed the unambiguous assignment of the

absolute configuration of the substituted succinimides obtained *via* the guanidine catalyzed Michael reaction.

Chapter 5

Proposed Stereochemical Model for the Origin of Enantioselectivity

In the highly enantioselective Michael reactions catalyzed by chiral bicyclic guanidine, we believe that two key features of guanidine and guanidinium groups are important: 1) The high basicity of the guanidine group is required to initiate the base catalyzed Michael reaction by generating the carbanion; 2) The special double hydrogen bonding pattern between a guanidinium group and oxoanions.

The crystal structures of guanidinium groups with phosphates (**I**), carboxylates (**II**), or nitrates (**III**), have revealed the typical arrangement of hydrogen bonds to oxoanions (Fig. 5.1).[78] In all these three arrangements, a guanidinium-oxoanion complex was formed through double hydrogen bonding. The complexes were also stabilized by electrostatic attraction between the ion pairs.[1]

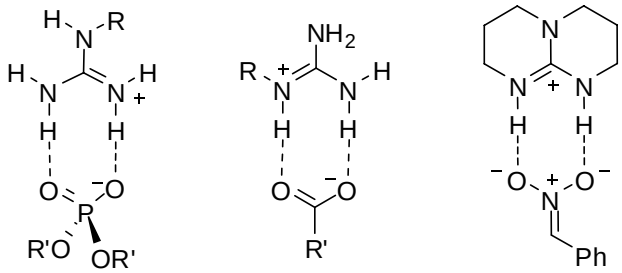
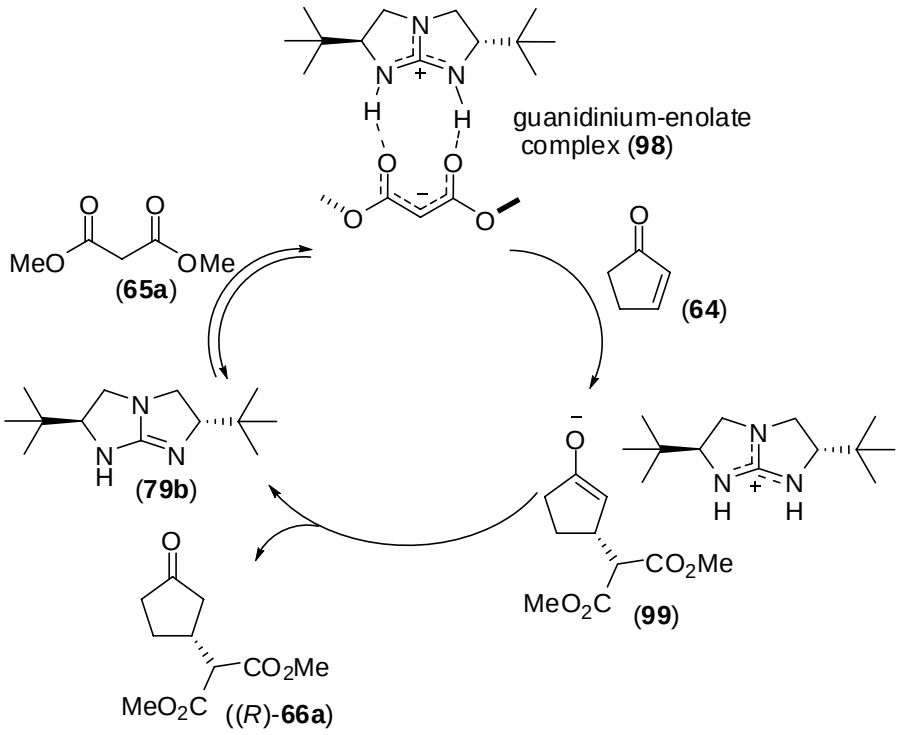


Fig. 5.1. Hydrogen bonding motifs between guanidinium groups and oxoanions revealed by crystal X-ray structures: **I**) guanidinium with phosphates; **II**) guanidinium with carboxylates; **III**) guanidinium with nitrates.

Based on these observations and speculations, the catalytic cycle of the chiral bicyclic guanidine **79b** catalyzed Michael reaction between 2-cyclopenten-1-one **64** and dimethyl malonate **65a** is proposed as in Scheme 5.1. In the first step of the cycle, deprotonation of dimethyl malonate **65a** by guanidine **79b** generates a guanidinium cation and an enolate anion. The positive charge on the guanidinium is spread among the three nitrogens by resonance, with two –NH groups as potential hydrogen bonding

donors. The negative charge on the enolate is also delocalized, rendering the two carbonyl oxygens anionic. An ion pair guanidinium-enolate complex **98** is presumably formed through double hydrogen bonding, maintaining co-planarity between the guanidinium and the enolate. The Michael addition occurs while 2-cyclopenten-1-one **64** approaches the complex to generate the enolate intermediate **99**, which in turn gains back a proton from the guanidinium ion to release the catalyst **79b** and to give the product (*R*)-**66a**.



Scheme 5.1. Proposed catalytic cycle in the chiral bicyclic guanidine catalyzed Michael reaction.

The origin of the enantioselectivity lies in the selective approach of **64** to the well-defined guanidinium-enolate complex **98**. Due to the steric repulsion by the proximal *tert*-butyl group of the guanidinium, each of the two methyl groups of the malonate enolate is tilted away from the co-plane, leaving the bottom left corner

(viewing above the co-plane of the complex **98**) more accessible by the enone **64**. The four possible ways of 2-cyclopenten-1-one **64** approaching the enolate ion are depicted as four pre-transition-state assemblies in Fig. 5.2. The difference in the steric hindrance between the alkenic side (bearing H^a and H^b) and the aliphatic side (bearing H^c and H^d) of 2-cyclopenten-1-one **64** is presumed to play a key role in the stereo control. In assemblies **A** and **B**, the more hindered aliphatic side of **64** tends to be repulsed by both the *tert*-butyl group of the guanidinium and the methyl group of the enolate on the same side of the co-plane, making **A** and **B** disfavoured. Assembly **C** is also disfavoured as the α proton of **64**, H^a, is blocked by the proximal methyl group of the enolate. Assembly **D**, with the least steric repulsion, is favoured and **64** is attacked from its *re*-face to give the observed major isomer (*R*)-**66a**.

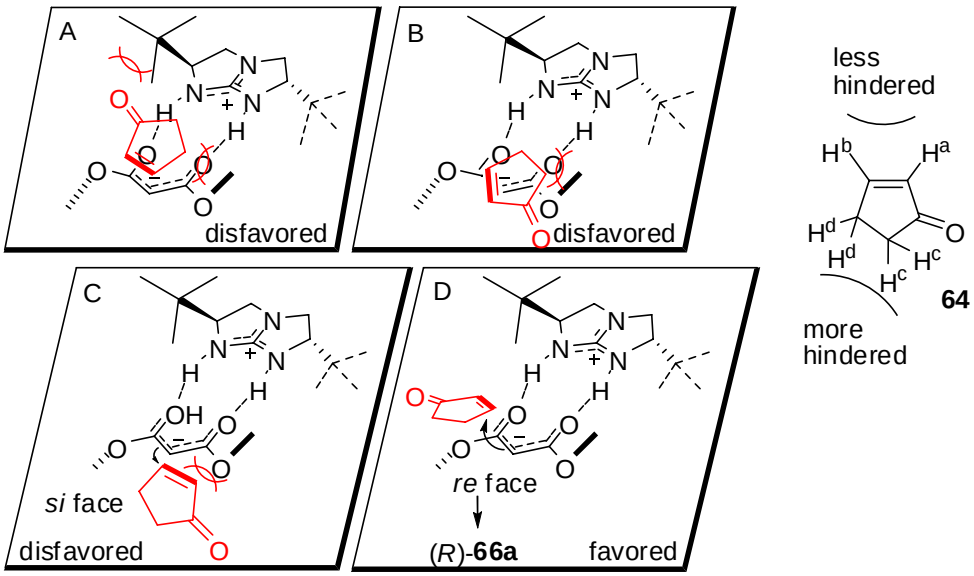


Fig. 5.2. Proposed pre-transition-state assemblies for the Michael reaction between **65a** and **64** catalyzed by **79b**.

This working hypothesis receives support from three observations:

1) As shown in Table 3.1 (Chapter 3, p51-52), the enantioselectivity of the

reaction between **64** and **65a** increased as the appendage of the catalyst became bulkier. The increased steric hindrance of the guanidinium appendage would cause more repulsion to the aliphatic side of **64**, which disfavours the pre-transition-state assemblies **A** and **B**.

2) Among various dialkyl malonates, the reaction with diisopropyl malonate **65k**, which has the bulkiest ester chain, obtained highest enantioselectivity. The bulkier malonate side chains tend to be tilted further away from the guanidinium appendage and subsequently add to the repulsion indicated in assemblies **A**, **B**, and **C**, favouring assembly **D**.

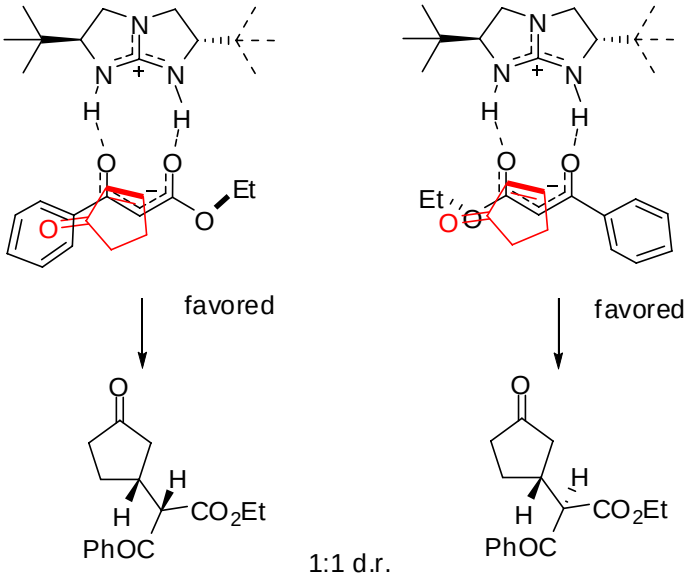


Fig. 5.3. The reason of 1:1 d.r. obtained using benzoylacetates as the donors.

3) 1:1 Diastereomeric ratios were obtained in all the reactions of various benzoylacetates as donors. As shown in Fig. 5.3, due to the C_2-symmetry of the catalyst and the co-planarity between the guanidinium group and the enolate, there is no facial selectivity over the central sp^2 carbon of the enolate, giving the two diastereomers in equal amounts.

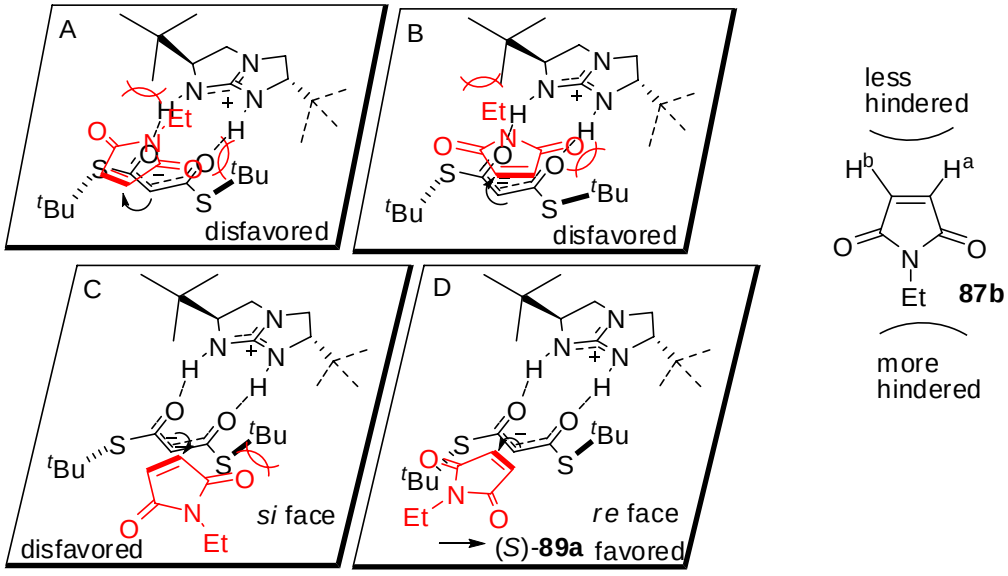
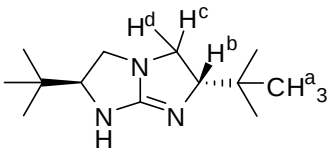


Fig. 5.4. Proposed pre-transition-state assemblies for the Michael reaction between **65y** and **87b** catalyzed by **79b**.

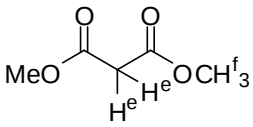
In the reactions of *N*-alkyl maleimides with 1,3-dicarbonyl compounds, we believe that the asymmetric induction was similar to the reactions using 2-cyclopenten-1-one **64** as the substrate. The catalytic cycle should also follow as in Scheme 5.1. A guanidinium-enolate complex is presumed to form between the catalyst and the donor **65y**, creating a chiral environment (Fig. 5.4). Similar to **64**, the different steric hindrance of the alkenic side (bearing H^a and H^b) and the *N*-Et side of the maleimide **87b** allowed the selective approach of **87b** to the guanidinium-enolate complex. In pre-transition-state assemblies **A** and **B** (Fig. 5.4), the bulky *N*-Et side of **87b** is repulsed by both the *tert*-butyl group of the guanidinium and the *tert*-butyl group of the enolate on the same side of the co-plane, making **A** and **B** disfavoured. In assembly **C**, the proximal carbonyl group is blocked by the *tert*-butyl group of the enolate and disfavours the attack on the *si*-face of **87b**. Assembly **D** is favoured as it has the least steric repulsion and the attack on the *re*-face gave the major isomer

(*S*)-**89a**.

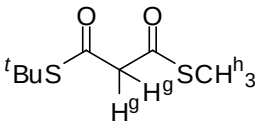
To prove the proposed stereochemical model and gain further insights, NMR study of the catalyst **79b**, Michael donors **65a** and **65y**, and their mixtures was carried out. The ^{1}H NMR spectrums of **79b**, **65a**, and **65y** were recorded respectively in toluene-D8 as solvent. The ^{1}H NMR spectra of the 1:1 mixture of **79b** with **65a** or **65y** were also taken and the change in chemical shift of characteristic protons was calculated.



79b



65a



65y

As shown in Table 5.1, when **79b** and **65a** was in a 1:1 mixture, there was no obvious change in the chemical shift of all the protons. In the NMR spectrum of the mixture, protons H^e were still present and the integration ratio of H^e:H^f was also maintained at 1:3, which means protons H^e were not completely deprotonated.

Table 5.1. ^{1}H NMR study of **79b**, **65a**, and their mixture in Tolune-D8 at 25 ^{o}C.[a]

sample / proton	**79b**	**65a**	**79b**:**65a** (1:1)[a]	$\Delta\delta$[b]/ppm
H^a/ppm	0.83	-	0.84	+0.01
H^b/ppm	3.69	-	3.72	+0.03
H^c,H^d/ppm	2.62, 2.68	-	2.67, 2.77	+0.05, +0.09
H^e/ppm	-	2.95	2.92	-0.03
H^f/ppm	-	3.27	3.25	-0.02

[a]The concentration of **79b** and **65a** was 0.02 M in toluene-D8, the 1:1 mixture of **79b** and **65a** was stirred at rt before ^{1}H NMR was recorded.
[b]$\Delta\delta$ refers to the change of a certain proton's chemical shift when in a

mixture form compared with in a pure single component form, eg. $\Delta\delta(H^a)=\delta(H^a$, **79b**:**65a**(1:1)) - $\delta(H^a$, **79b**).

Table 5.2. ^{1}H NMR study of **79b**, **65y**, and their mixture in Toluene-D8.[a]

sample / proton	**79b**	**65y**	**79b**:**65y** (1:1)			Δδ[b]/ppm
			25 °C	-20 °C	-50 °C	
H^a/ppm	0.83	-	0.82	0.90	0.93	-0.01
H^b/ppm	3.69	-	3.70	3.70	3.84	+0.01
H^c,H^d/ppm	2.62, 2.68	-	2.66, 2.73	2.69, 2.76	2.70, 2.75	+0.04, +0.05
H^g/ppm	-	1.31	1.31	1.30	1.30	0
H^h/ppm	-	3.25	3.25 (bs)	3.17	3.08	0

[a]The concentration of **79b** and **65y** was 0.02 M in toluene-D8, the 1:1 mixture of **79b** and **65y** was stirred at rt before ^{1}H NMR was recorded. [b]Δδ refers to the change of a certain proton's chemical shift when in a mixture form compared with in a pure single component form, eg. $\Delta\delta(H^a)=\delta(H^a$, **79b**:**65y**(1:1)) - $\delta(H^a$, **79b**).

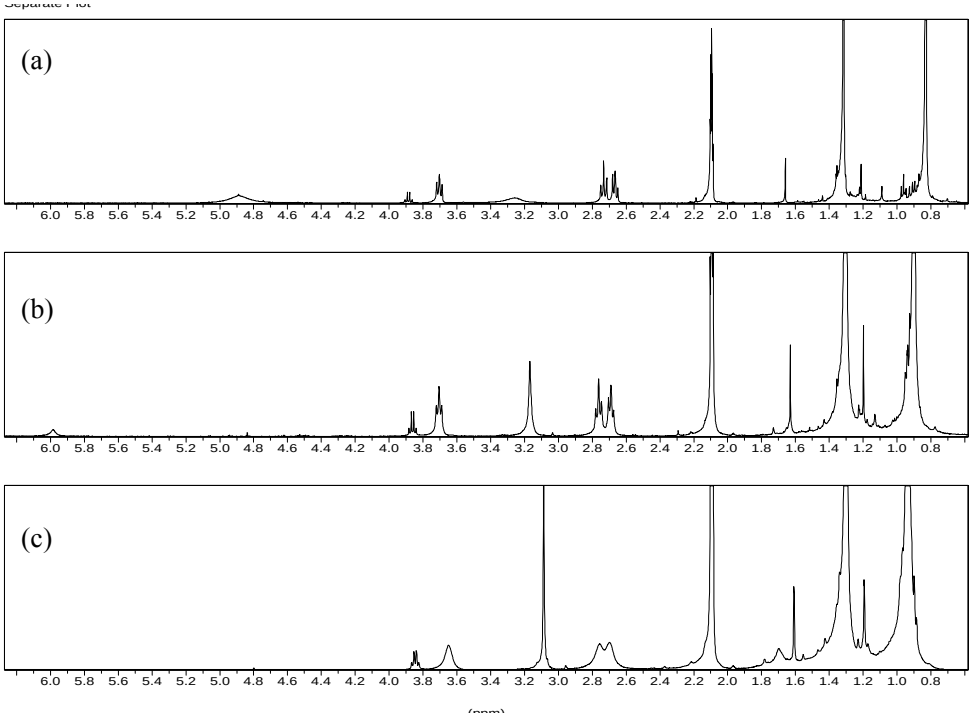


Fig. 5.5. ^{1}H NMR spectrum of the mixture (1:1) of **79b** and **65y** at 25 °C (a), -20 °C (b), and -50 °C (c).

Similarly, the ^{1}H NMR spectra of the mixture of **79b** and **65y** was also recorded.

As shown in Table 5.2, there was no clear change in the chemical shift of all the protons. However, in the mixture spectrum, the peak belonging to H^h became a broad singlet, while it reverted back to a sharp singlet when the NMR was taken at -20 ^oC or -50 ^oC (as shown in Fig. 5.5). It implied that the deprotonation of H^g was fast at rt and reversible. It also showed that the deprotonation of **65y** is faster than **65a** and may explain why the reactions with **65y** was faster than those with **65a** as donor.

In an attempt to find proof for the existence of a guanidinium-enolate complex, NOE study of the mixture of **79b** and **65y** was carried out at both rt and -50 ^oC. However, no obvious NOE was found between the protons of **79b** and those of **65y**.

In conclusion, based on the experimental results and literature study, a stereochemical model for the origin of the enantioselectivity in the chiral bicyclic guanidine catalyzed Michael reactions is proposed. NMR studies neither give positive nor negative proof for this proposal. Further studies by other techniques, such as computational simulation and crystal X-ray diffraction may give greater insights and help elucidate the mechanism of the asymmetric induction.

Chapter 6

Experimental Procedures

6.1 General Procedures

^{1}H and ^{13}C NMR spectra were recorded on a Bruker ACF300 (300MHz) or AMX500 (500MHz) spectrometer. Chemical shifts are reported in parts per million (ppm). The residual solvent peak was used as an internal reference. Low resolution mass spectra were obtained on a VG Micromass 7035 spectrometer in EI mode, a Finnigan/MAT LCQ spectrometer in ESI mode, and a Finnigan/MAT 95XL-T mass spectrometer in FAB mode. All high resolution mass spectra were obtained on a Finnigan/MAT 95XL-T spectrometer. Infrared spectra were recorded on a BIO-RAD FTS 165 FTIR spectrometer. Enantiomeric excess values were determined by chiral HPLC analysis on a set of Jasco HPLC units, including a Jasco DG-980-50 Degasser, a LG-980-02 Ternary Gradient Unit, a PU-980 Intelligent HPLC Pump, UV-975 Intelligent UV/VIS Detectors, and an AS-950 Intelligent Sampler. Optical rotations were recorded on Jasco DIP-1000 polarimeter. Melting points were determined on a BÜCHI B-540 melting point apparatus. Analytical thin layer chromatography (TLC) was performed with Merck pre-coated TLC plates, silica gel 60F-254, layer thickness 0.25 mm. Flash chromatography separations were performed on Merck 60 (0.040 - 0.063mm) mesh silica gel. Toluene was distilled from sodium/benzophenone and stored under N_2 atmosphere. THF was freshly distilled from sodium/benzophenone before use. CH_2Cl_2 was distilled from CaH_2 and stored under N_2 atmosphere. MeOH was refluxed over magnesium turnings together with a small amount of iodine until the iodine disappeared and then distilled off. All distilled solvents were stored under N_2. All other reagents and solvents are commercial grade and were used as

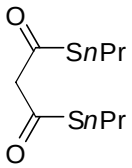
supplied without further purification, unless otherwise stated.

6.2 Preparation of *S,S'*-Dialkyl Dithiomalonates.

Typical procedure: To the mixture of malonic acid (104 mg, 1 mmol) and 4-DMAP (49 mg, 0.4 mmol, 0.4 equiv.) in dry toluene (4 ml) was added $POCl_3$ (0.21 ml, 2.2 mmol, 2.2 equiv.) dropwise, followed by addition of alkylthiol (2.2 mmol, 2.2 equiv.). The reaction flask was equipped with a condenser and heated at 70 °C until no obvious release of HCl (2-3 h). The reaction was quenched by pouring into cold water (5 ml), followed by extraction with ether (3x10 ml). The combined organic layer was washed with brine, followed by removal of solvent and chromatography on silica gel, to give the desired *S,S'*-dialkyl dithiomalonate as an oil.

(65v) *S,S'*-dipropyl propanebis(thioate)

Pale yellow oil. 35% yield. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.97 (t, J = 7.4 Hz, 6H), 1.57-1.66 (m, 4H), 2.91 (t, J = 7.2 Hz, 4H), 3.77 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 13.5, 22.8, 31.7, 58.0, 190.9. IR (film): 2965, 1673, 1457, 1287, 991 cm^{-1}. LRMS(EI) m/z 220.0 (M^+), HRMS(EI) m/z 220.0585 (M^+), calc. for $C_9H_{16}O_2S_2$ 220.0592.

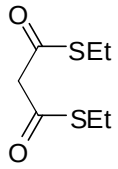


65v

(65w) *S,S'*-diethyl propanebis(thioate)

Pale yellow oil. 30% yield. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.27 (t, J = 7.4 Hz,

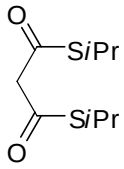
6H), 2.93 (q, J = 7.3 Hz, 4H), 3.76 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 14.3, 24.0, 57.7, 190.6. LRMS(EI) m/z 192.0 (M^+).



65w

(**65x**) ***S,S'*-Diisopropyl propanebis(thioate)**

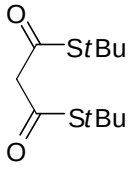
Colorless oil. 78% yield. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.26 (d, J = 3.6 Hz, 6H), 1.28 (d, J = 3.6 Hz, 6H), 3.60-3.70 (m, 2H), 3.66 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.6, 35.5, 57.8, 190.6. IR (film): 2986, 2928, 2868, 1677, 1453, 1051, 990 cm^{-1}. LRMS(EI) m/z 220.0 (M^+), HRMS(EI) m/z 220.0591 (M^+), calc. 220.0592 for $C_9H_{16}O_2S_2$.



65x

(**65y**) ***S,S'*-Di-*tert*-butyl propanebis(thioate)**[79]

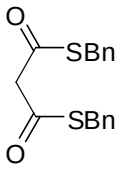
Colorless oil. 93% yield. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.46 (s, 18H), 3.58 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 29.6, 49.0, 59.0, 191.2. LRMS(EI) m/z 248.1 (M^+), HRMS(EI) m/z 248.0901 (M^+), calc. 248.09047 for $C_{11}H_{20}O_2S_2$.



65y

(**65z**) ***S,S'*-dibenzyl propanebis(thioate)**[79]

Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 2.52 (s, 2H), 2.89 (s, 4H), 5.99 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 34.1, 57.2, 127.7, 128.9, 129.0, 136.7, 189.9. LRMS(EI) m/z 315.9 (M^+).



65z

6.3 General Procedures for the Synthesis of Chiral Bicyclic Guanidines

6.3.1 General procedure for the removal of *p*-toluenesulfonyl (Ts) group: (**73b** as an example)

Na (793 mg, 100 equiv.) was washed with hexane and transferred into a 25 ml flame dried two-necked round-bottom flask equipped with a magnetic bar and an ammonium condenser. The reaction flask and the condenser were cooled to -78 ^{o}C. NH_3 gas was condensed through the condenser into the reaction flask until a dark blue solution (around 10 ml) was formed. While stirring, a THF solution (1 ml) of the triamine backbone **73b** (202 mg, 0.345 mmol) was added dropwise into the dark blue solution at -78 ^{o}C. Stirring was continued at -78 ^{o}C and more Na was added whenever the dark blue color fades. After 4 h, the reaction flask was opened to the air and brought to room temperature. Solid NH_4Cl was added slowly with vigorous stirring until a white heterogeneous mixture was formed. After all NH_3 evaporated off,

CH_2Cl_2 (5 ml) was added to the resulted white solid and stirred for a half hour. The solid was then removed by suction filtration and was washed with CH_2Cl_2 (3 x 5 ml). The filtrate was combined and the solvent was removed under reduced pressure, giving a pale yellow oil in quantitative yield. The crude product was used directly for next reaction.

6.3.2 General procedure for Pd/C catalyzed hydrogenation: (**73b** as an example)

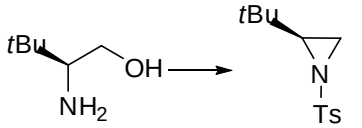
After **73b** (202 mg, 0.345 mmol) underwent removal of tosyl group in $Na/NH_3(l)$, the crude product was dissolved in dry methanol (3 ml) and added to a dry round-bottom flask containing 10% Pd/C (50 mg, 50% w/w). The reaction mixture was purged with H_2 gas for a half hour and kept stirring under H_2 balloon. The reaction was monitored by TLC. Upon completion of reaction, the Pd/C was removed by suction filtration and the solvent was evaporated off under reduced pressure, affording **74b** as a pale yellow oil, which was used for next step without further purification.

6.3.3 General procedure for final cyclization step: (**75b** as an example)

(This procedure mainly followed the protocol reported by Davis and Dempsey[80] with a slight modification during work-up). The crude free triamine **74b** (50 mg, 0.26 mmol) was dissolved in nitromethane (1 ml). Dimethyl trithiocarbonate (36 µl, 0.33 mmol, 1.25 equiv.) in nitromethane (0.1 ml) was added to the mixture slowly, followed by refluxing at 110 ^oC for 2 h, and then was cooled to room temperature. Acetic acid (61 µl, 1.06 mmol, 4 equiv.) and MeI (49 µl, .53 mmol, 2 equiv.) were

added. It was refluxed at 110 °C for 3 h and left stirring at room temperature overnight. CH_2Cl_2 (1 ml) was added to dilute the reaction mixture and the solvent was removed under reduced pressure. CH_2Cl_2 (1 ml) was added and the solution was loaded onto a plug of silica gel. It was eluted with copious CH_2Cl_2 to flush out the dark colored portion and then CH_2Cl_2/MeOH (19:1) to recover the product, which was assumed to be a HI salt. The product was basified with K_2CO_3 in CH_2Cl_2, giving the guanidine **75b** in free amine form as a pale yellow oil (31 mg, 61 % yield from **73b**).

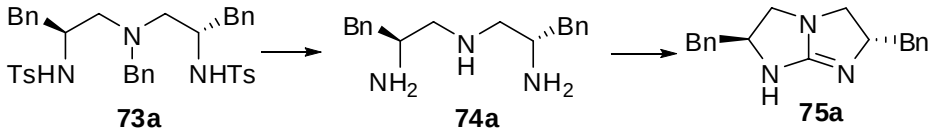
6.3.4 Preparation and characterization data of compound 72c, 75a, 75b, 77a, 77b, 79a, 79b.



71c **72c**

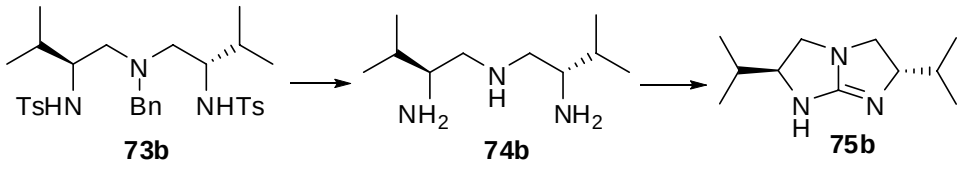
(**72c**): To a flame dried round-bottom flask containing 4Å molecular sieves and a magnetic bar was added L-*tert*-leucinol (**71c**, 100 mg, 0.85 mmol), Et_3N (0.48 ml, 3.4 mmol, 4 equiv.), and dry MeCN (2.4 ml). It was cooled to 0 °C and then TsCl (179 mg, 0.94 mmol, 1.1 equiv.) was added in one portion. After stirring at 0 °C for 20 min, the reaction mixture was brought to room temperature and stirred for another 1 h. The solvent was removed under reduced pressure and ethyl acetate (5 ml) was added. The resulted precipitate and molecular sieves were removed by suction filtration and washed thoroughly with ethyl acetate. The solvent of the filtrate was removed and the residual oil was subjected to a solution of Et_3N (0.48 ml, 3.4 mmol, 4 equiv.) and DMAP (104 mg, 0.85 mmol, 1 equiv) in dry CH_2Cl_2 (2.4 ml). MsCl (0.13ml, 1.7

mmol, 2 equiv) was added slowly and then the reaction mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure, followed by addition of ethyl acetate (5 ml). The resulted precipitate was removed by suction filtration and washed thoroughly with ethyl acetate. After removing the solvent of the filtrate and chromatography on silica gel, **72c** was obtained as a white solid (172 mg, 80% yield). mp 51.9-52.7 °C. $[\alpha]_D^{27}$ = +18.2 (*c* 6.2, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 0.78 (s, 9H), 2.16 (d, *J* = 4.6 Hz, 1H), 2.43 (s, 3H), 2.51 (d, *J* = 6.9 Hz, 1H), 2.55 (dd, *J* = 4.6, 7.4 Hz, 1H), 7.32 (d, *J* = 4.8 Hz, 2H), 7.83 (d, *J* = 4.8 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 21.6, 26.2, 30.1, 30.2, 48.8, 128.1, 129.5, 135.2, 144.3. IR (film): 3039, 2961, 1921, 1601, 1477, 1322, 1162, 1098 cm^{-1}. LRMS(FAB) m/z 254.1 ($M+H^+$), HRMS(FAB) m/z 254.1215 ($M+H^+$), calc. for $C_{13}H_{20}SNO_2$ 254.1215.

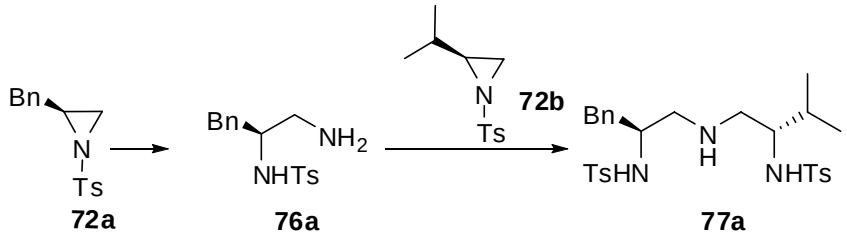


(**75a**): As described above, **73a** underwent detosylation and hydrogenolysis, followed by the final cyclization step, to give **75a** as a pale yellow oil in 84% yield (based on **73a**). $[\alpha]_D^{25}$ = -22.3 (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 2.77 (dd, *J* = 7.5, 13.5 Hz, 2H), 2.83 (dd, *J* = 6.0, 8.0 Hz, 2H), 2.95 (dd, *J* = 7.0, 13.5 Hz, 2H), 3.09 (t, *J* = 7.5 Hz，2H), 4.27 (quintet, *J* = 7.0 Hz, 2H), 7.21-7.33 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 42.1, 53.6, 65.9, 126.6, 128.7, 129.3, 138.5, 168.3. IR (film): 3069, 3020, 2929, 2857, 1776, 1707, 1667, 1600, 1499, 1459, 1386, 1316, 1187 cm^{-1}. LRMS(ESI) m/z 291.8 ($M+H^+$), HRMS(ESI) m/z 292.1816 ($M+H^+$), calc. for

$C_{19}H_{22}N_3$ 292.1814.

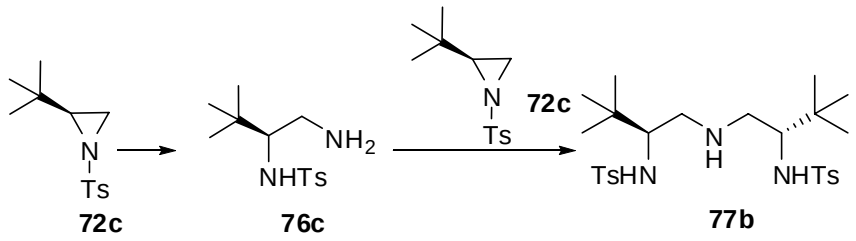


(**75b**): As described in the general procedures, **75b** was also obtained as pale yellow oil in 61% yield from **73b**. $[\alpha]_D^{26}$ = -9.0 (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.88 (d, *J* = 6.4 Hz, 6H), 0.96 (d, *J* = 6.4 Hz, 6H), 1.77 (m, 2H), 2.94 (dd, *J* = 6.4, 8.4 Hz, 2H), 3.24 (t, *J* = 8.2 Hz, 2H), 3.90 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 18.3, 18.9, 32.8, 50.9, 69.7, 167.1. IR (film): 3186, 2962, 2404, 1682, 1598, 1468, 1218 cm^{-1}. LRMS(ESI) m/z 196.3 ($M+H^+$), HRMS(ESI) m/z 196.1811 ($M+H^+$), calc. for $C_{11}H_{22}N_3$ 196.1814.

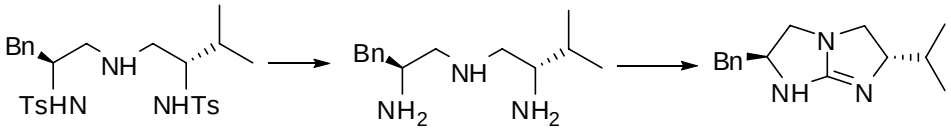


(**77a**): NH_3 gas was continuously bubbled into MeOH (3 ml) at 0 °C for 30 min. A solution of aziridine **72a** (230 mg, 0.84 mmol) in MeOH (3 ml) was added into the saturated NH_3 solution in MeOH at 0 °C. The reaction vessel was sealed up tightly and brought to room temperature slowly. After stirring over night, the solvent was removed under reduced pressure, giving a pale yellow oil. It was added to a solution of aziridine **72b** (297 mg, 1.24 mmol, 1.5 equiv.) in dry MeCN (2 ml). The reaction mixture was refluxed at 95 °C for 2 days. After removing solvent under reduced pressure and flash chromatography, **77a** was obtained as a white foamy solid in 80%

yield (based on **72a**). $[\alpha]_D^{29}$ = -20.7 (*c* 3.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.72 (m, 6H), 1.65 (m, 1H), 2.35 (m, 1H), 2.38 (s, 6H), 2.51-2.63 (m, 4H), 2.70 (dd, *J* = 6.0, 13.7 Hz, 1H), 3.03 (m, 1H), 3.45 (m, 1H), 6.97 (m, 2H), 7.16-7.27 (m, 7H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.76 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 18.2, 18.4, 21.4, 30.2, 39.2 49.3, 51.3, 53.8, 58.0, 126.5, 127.0, 127.1, 128.4, 129.1, 129.4, 129.5, 129.6, 136.8, 137.3, 137.9, 143.2. IR (film): 3027, 2964, 2867, 1723, 1643, 1598, 1449, 1326, 1158, 1090 cm^{-1}. LRMS(ESI) m/z 544.2 ($M+H^+$), HRMS(ESI) m/z 544.2299 ($M+H^+$), calc. for $C_{28}H_{38}S_2N_3O_4$ 544.2304.

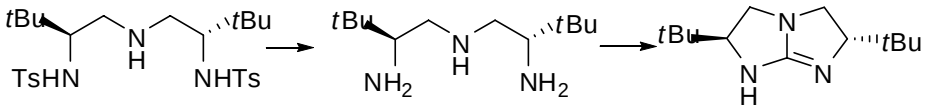


(**77b**): Using the procedure used to make compound **77a**, aziridine **72c** was converted to diamine **76c**, which was used to open aziridine **72c** (1.2 equiv). After flash chromatography, **77b** was obtained as a white solid in 84% yield (from **72c**). Mp 187.3-189.2 ^{o}C. $[\alpha]_D^{31}$ = +4.3 (*c* 1.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.76 (s, 18H), 2.33 (m, 2H), 2.39 (s, 6H), 2.63 (dd, *J* = 7.0, 13.0 Hz, 2H), 3.09 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 21.4, 26.9, 34.4, 49.0, 61.6, 126.9, 129.4, 139.0, 142.9. IR (film): 3023, 1692, 1601, 1327, 1216, 1156, 1091 cm^{-1}. LRMS(FAB) m/z 524.4 ($M+H^+$), HRMS(FAB) m/z 524.2611 ($M+H^+$), calc. for $C_{26}H_{42}S_2N_3O_4$ 524.2617.



77a **78a** **79a**

(**79a**): The crude free triamine **78a** was obtained by removing the tosyl group of **77a** and was cyclized using the general procedure to give guanidine **79a** as pale yellow oil in 89% yield from **77a**. $[\alpha]_D^{32}$ = -18.8 (*c* 3.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.85 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 1.72 (m, 1H), 2.79 (m, 2H), 2.89-3.07 (m, 3H), 3.20 (m, 1H), 3.79 (dd, *J* = 7.6, 14.9 Hz, 1H), 4.22 (m, 1H), 5.63 (bs, 2H), 7.17-7.29 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 18.7, 19.4, 33.2, 42.1, 51.7, 53.4, 66.5, 69.6, 126.5, 128.6, 129.3, 138.7, 168.4. IR (film): 3214, 3021, 2963, 1653, 1496, 1260, 1217 cm^{-1}. LRMS(ESI) m/z 243.7 ($M+H^+$), HRMS(ESI) m/z 244.1818 ($M+H^+$), calc. for $C_{15}H_{22}N_3$ 244.1814.



77b **78b** **79b**

(**79b**): The crude free triamine **78b** was obtained by removing the tosyl group of **77b** and was cyclized using the general procedure to give guanidine **79b** as pale yellow oil in 75% yield (from **77b**). $[\alpha]_D^{31}$ = -5.4 (*c* 1.7, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.92 (s, 18H), 3.10 (dd, *J* = 6.8, 8.8 Hz, 2H), 3.26 (t, *J* = 8.4 Hz, 2H), 4.00 (dd, *J* = 6.8, 8.4 Hz, 2H), 5.54 (bs, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 25.8, 33.8, 48.6, 72.8, 167.2. IR (film): 2963, 2869, 1652, 1401, 1370, 1219, 1019 cm^{-1}. LRMS(FAB) m/z 224.3 ($M+H^+$), HRMS(FAB) m/z 224.2125 ($M+H^+$), calc. for $C_{13}H_{26}N_3$ 224.2127.

6.4 Typical Experimental Procedures for the Michael Reactions

6.4.1 Typical experimental procedure for Michael reaction catalyzed by TBD

Toluene (0.4 mL) was added to a 5 mL round-bottom flask followed by 2-cyclopenten-1-one **64** (8.2 mg, 0.1 mmol) and dimethyl malonate **65a** (66 mg, 0.5 mmol). A toluene solution of TBD (0.01 mmol TBD in 0.1 mL toluene; 10 mol% catalyst) was then added to start the reaction. The reaction mixture was stirred for 5 min at room temperature, filtered through a plug of silica and washed several times with ethyl acetate (EtOAc). After removing the solvents with lower boiling points, the product was kept under high vacuum to remove excess dimethyl malonate. The product **66a** was obtained as colorless oil in 95% yield (20.3 mg). No further purification is necessary. For all reactions, control experiments containing no catalyst were performed simultaneously. For the time frame of the experiments, no product was observed for any of the controls.

For Michael donors with high boiling point, column chromatography was used to remove them after the reaction was completed and this resulted in slightly lower yields.

6.4.2 A typical procedure of the chiral guanidine catalyzed enantioselective Michael reaction:

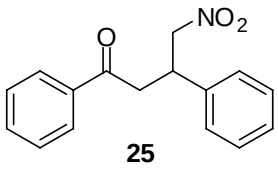
N-Ethyl maleimide **87b** (3.2 mg, 0.025 mmol) and *S*,*S*'-di-*tert*-butyl dithiomalonate **65y** (7.5 mg, 0.03 mmol, 1.2 equiv.) was dissolved in toluene (0.09 ml) and stirred at -50 ^{o}C. A pre-cooled toluene solution of catalyst **79b** (0.58 mg in 0.01

ml toluene, 0.0025 mmol, 10 mol%; pre-treated by passing through a plug of K_2CO_3 using CH_2Cl_2) was injected into the reaction mixture. It was stirred at -50 ^oC and monitored by TLC. Upon complete consumption of **87b** (6 h), the reaction mixture was directly loaded onto a short silica gel column, followed by gradient elution with hexane/EA mixtures (9/1-4/1 ratio). After removing the solvent, product **89a** was obtained as a white solid (Mp 122 ^oC) in 98% yield (9.1 mg).

6.5 Characterization of Michael Adducts

(25) 4-Nitro-1,3-diphenylbutan-1-one

White solid. Structure was confirmed by comparing with literature spectra data[81]. The enantiomeric excess was determined by HPLC analysis. HPLC separation conditions: column CHIRALPAK AS-H (4.6 mm i.d. x 250 mm); Hexane/2-propanol = 90/10; flow rate 1.2 ml/min; temp 25 ^oC; detection UV 254 nm; retention time:15.6 min (major) and 21.0 min (minor).

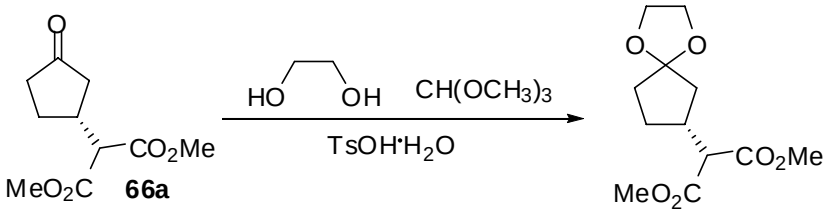


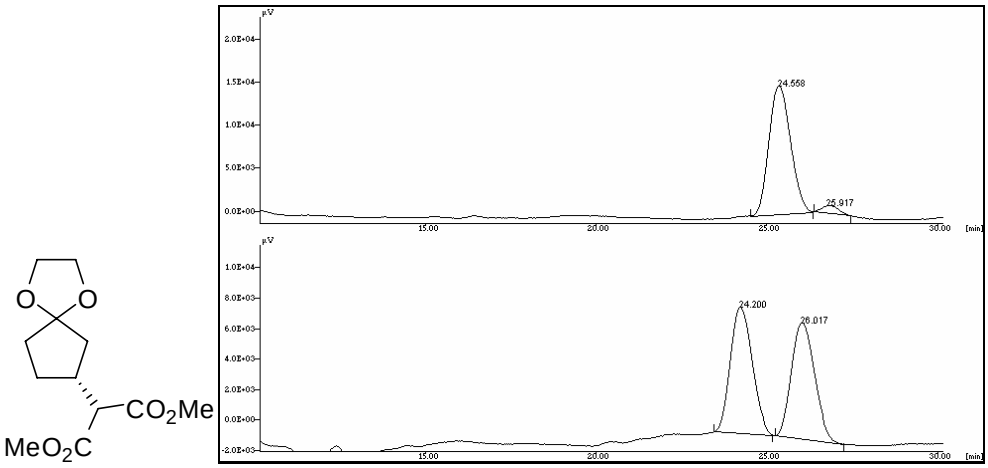
25

(66a) (*R*)-(+)-Dimethyl 2-(3-oxocyclopentyl)malonate[82]

Colorless oil. 91% ee, $[\alpha]_D^{26}$ = +132.8 (*c* 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.51-1.62 (m, 1H), 1.94 (dd, *J* = 10.8, 18.1 Hz, 2H), 2.03-2.33 (m, 3H), 2.43 (dd, *J* = 8.0, 18.1 Hz, 1H), 2.72-2.87 (m, 1H), 3.33 (d, *J* = 9.2 Hz), 3.67 (s, 3H), 3.70 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 27.3, 36.2, 38.0, 42.7, 52.4, 55.9, 168.3,

168.4, 216.7. LRMS (ESI) m/z 231.9 ($M+NH_4^+$), HRMS(ESI) m/z 213.0762 (M-H), calc. for $C_{10}H_{13}O_5$ 213.0763. The ee was determined by a HPLC analysis after conversion to ethylene ketal. CHIRALCEL OD-H (4.6 mm i.d. x 250 mm); Hexane/2-propanol = 97/3; flow rate 0.5 ml/min; 25 ^oC; 210 nm; retention time: 24.6 min (major) and 25.9 min (minor).

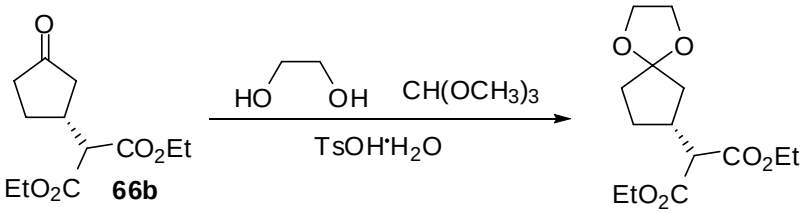


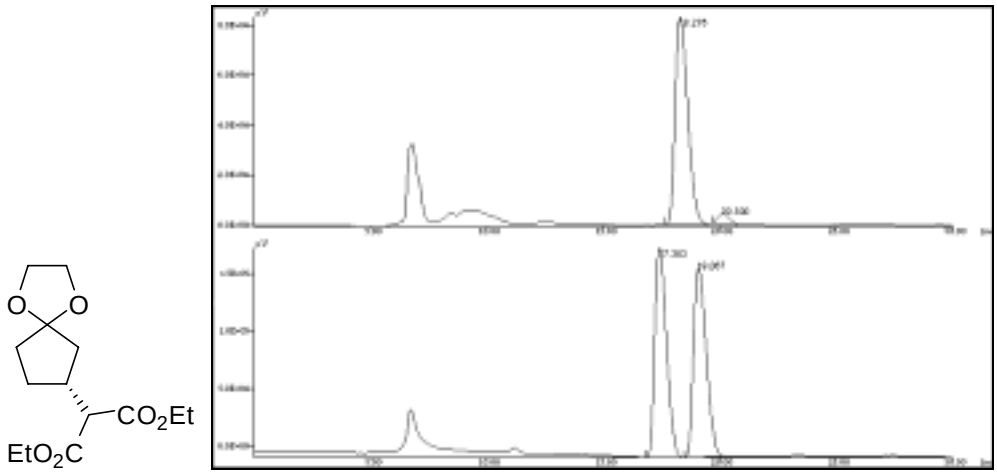


(**66b**) **(*R*)-(+)-3-Di(ethoxycarbonyl)methyl-1-cyclopentanone**[83]

Colorless oil. 92% ee, $[\alpha]_D^{26}$ = +50.4 (*c* 0.56, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.21-1.26 (m, 6H), 1.56-1.67 (m, 1H), 1.94-2.04 (m, 1H), 2.10-2.35 (m, 3H), 2.47 (dd, *J* = 7.6, 18.0 Hz, 1H), 2.75-2.90 (m, 1H), 3.30 (d, *J* = 9.6 Hz, 1H), 4.14-4.23 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 13.9, 27.3, 36.2, 38.0, 42.8, 56.4, 61.5, 167.9, 168.0, 217.0. LRMS (EI) m/z 242.2 (M^+), HRMS(EI) m/z 242.1165, (M^+), calc. for $C_{12}H_{18}O_5$ 242.1154. The ee was determined by a HPLC analysis after conversion to ethylene ketal. CHIRALCEL OD-H (4.6 mm i.d. x 250 mm); Hexane/2-propanol =

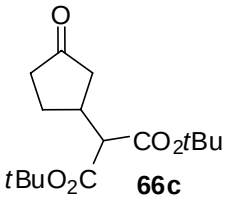
97/3; flow rate 0.5 ml/min; 25 °C; 210 nm; retention time: 18.3 min (major) and 20.1 min (minor).





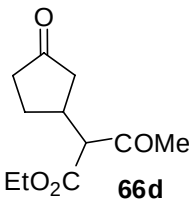
(66c) Di-tert-butyl 2-(3-oxocyclopentyl)malonate

As reported in lit.[84]



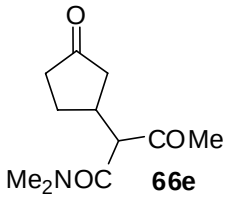
(66d) Ethyl 3-oxo-2-(3-oxocyclopentyl)butanoate

As reported in lit.[85]



(**66e**) ***N,N'*-Dimethyl-3-oxo-2-(3-oxocyclopentyl) butanamide**

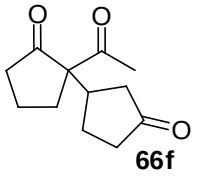
Colorless oil. A 1:1 mixture of two diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 1.42 (m, 1H), 1.56 (m, 1H), 1.75 (m, 1H), 1.85 (m, 1H), 2.07 (m, 1H), 2.15 (s, 3H), 2.18 (s, 3H), 2.15-2.36 (m, 8H), 2.54 (m, 1H), 2.97 (s, 3H), 3.00 (s, 3H), 3.04 (s, 3H), 3.07 (s, 3H), 3.50 (d, J = 6.5 Hz, 1H), 3.48 (d, J = 6.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 26.5, 26.9, 28.2, 36.0, 36.7, 36.8, 37.4, 37.5, 37.9, 38.0, 42.3, 43.5, 64.2 (2 peaks), 167.2, 203.5, 203.7, 216.9, 217.1. IR (film): 1740, 1635, 1496, 1402, 1360 cm^{-1}. LRMS (FAB) m/z 212.1 (M+H$^+$), HRMS (FAB) m/z 212.1291 (M+H$^+$), calc. for $C_{11}H_{18}NO_3$ 212.1287.



66e

(**66f**) **3-(1-acetyl-2-oxocyclopentyl)cyclopentanone**

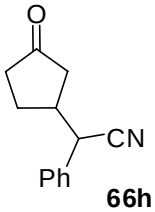
Colorless oil. A 1:1 mixture of two diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 1.47 (m, 1H), 1.61-2.02 (m, 11H), 2.11-2.27 (m, 6H), 2.22 (s, 3H) and 2.23 (s, 3H), 2.31- 2.41 (m, 4H), 2.62-2.67 (m, 2H), 2.98-3.07 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 19.3, 19.4, 24.4, 25.0, 25.7, 25.8, 26.3, 26.4, 38.0, 38.2, 38.9, 39.3, 39.8, 40.3, 40.4, 40.6, 71.1 (quaternary carbon), 71.2 (quaternary carbon), 202.7 (2 peaks), 215.2, 215.3, 216.0, 216.3. IR (film): 1740, 1708, 1592, 1464, 1377 cm^{-1}. LRMS (FAB) m/z 207.1 (M-H), HRMS (FAB) m/z 207.10217 (M-H), calc. for $C_{12}H_{15}O_3$ 207.10212.



66f

(**66h**) **2-[3'-Oxocyclopentyl]2-phenylacetonitrile**

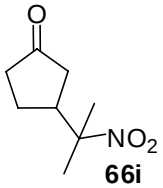
As reported in lit.[86]



66h

(**66i**) **3-(2-Nitropropan-2-yl)cyclopentanone**

As reported in lit.[87]

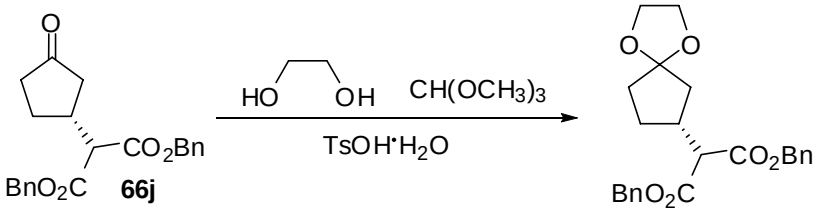


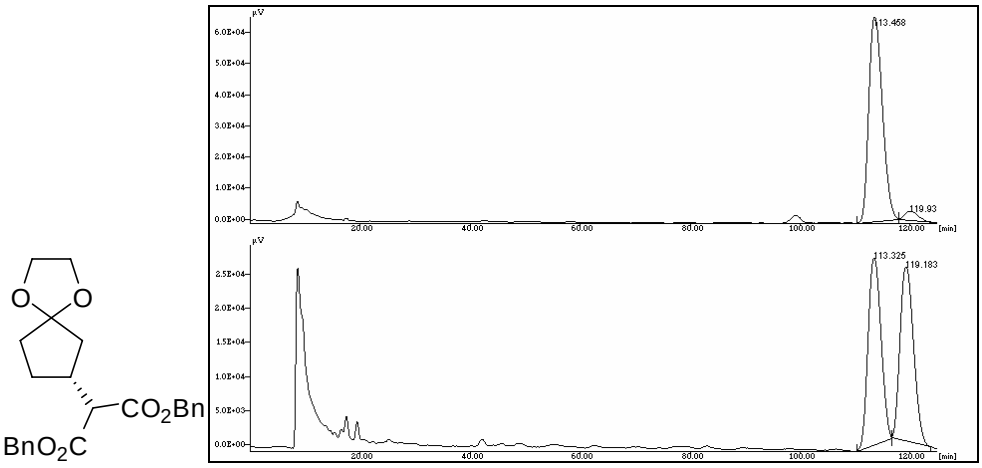
66i

(**66j**) **(*R*)-(+)-Dibenzyl 2-(3-oxocyclopentyl)malonate**

Colorless oil. 92% ee, $[\alpha]_D^{26}$= (*c* 0.91, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.54-1.72 (m, 1H), 1.94-2.04 (dd, *J* = 10.1, 18.5 Hz, 1H), 2.08-2.36 (m, 3H), 2.41-2.50 (dd, *J* = 8.0, 18.5 Hz, 1H), 2.82-2.95 (m, 1H), 3.45 (d, *J* = 9.6 Hz, 1H), 5.14 (s, 2H), 5.17 (s, 2H), 7.25-7.33 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 27.3, 36.3, 38.0, 42.7, 56.4, 67.2, 67.3, 128.2, 128.5, 135.0 (two peaks), 167.6, 167.7, 216.8. LRMS(EI) m/z 367.1 ($M+H^+$), HRMS(EI) m/z 367.1545 ($M+H^+$), calc. for $C_{22}H_{23}O_5$ 367.1545. The ee was determined by a HPLC analysis after conversion to ethylene ketal. CHIRALCEL OJ-H (4.6 mm i.d. x 250 mm); Hexane/2-propanol = 90/10; flow

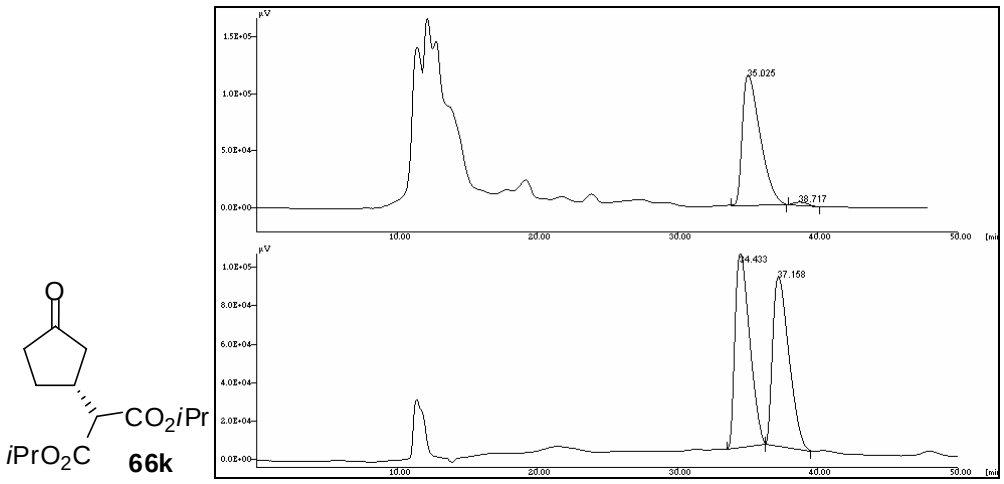
rate 0.4 ml/min; 25 ^{o}C; 210 nm; retention time: 113.5 min (major) and 119.9 min (minor).





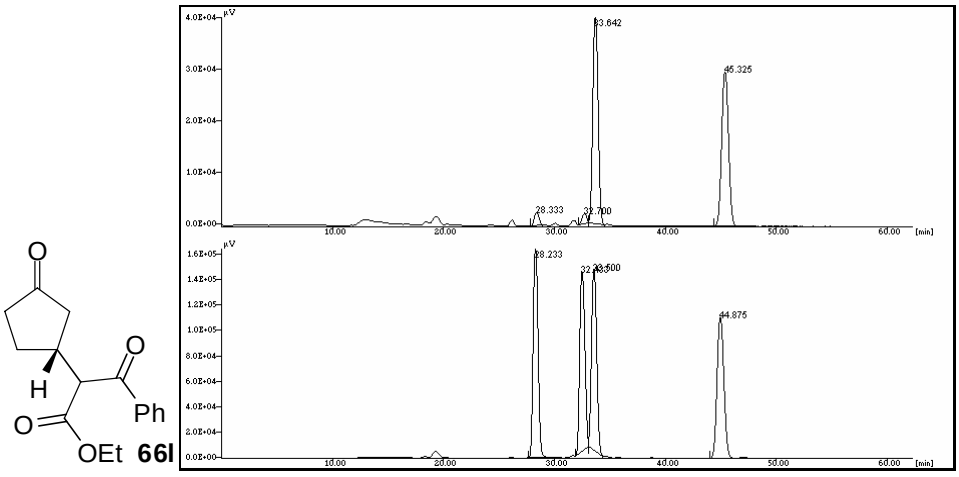
(66k) (*R*)-(+)-diisopropyl 2-(3-oxocyclopentyl)malonate

Colorless oil. 96% ee, $[\alpha]_D^{26}$ = +100.5 (*c* 0.57, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.20-1.25 (m, 12H), 1.59-1.73 (m, 1H), 1.95-2.04 (dd, *J* = 10.8, 18.1 Hz, 1H), 2.10-2.35 (m, 3H), 2.43-2.51 (dd, *J* = 6.8, 18.1 Hz, 1H), 2.77-2.84 (m, 1H), 3.24 (d, *J* = 9.2 Hz, 1H), 4.96-5.05 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 21.5, 21.6, 27.4, 36.1, 38.1, 42.8, 56.9, 69.1 (two peaks), 167.5, 167.6, 217.3. LRMS (EI) m/z 271.1 ($M+H^+$), HRMS (EI) m/z 271.1547 ($M+H^+$), calc. for $C_{14}H_{23}O_5$ 271.1545. The ee was determined by HPLC analyses of the Michael adduct. CHIRALCEL OD-H (4.6 mm i.d. x 250 mm); Hexane/2-propanol 97/3; flow rate 0.3 ml/min; 25 ^{o}C; 210 nm; retention time: 35.0 min (major) and 38.7 min (minor).



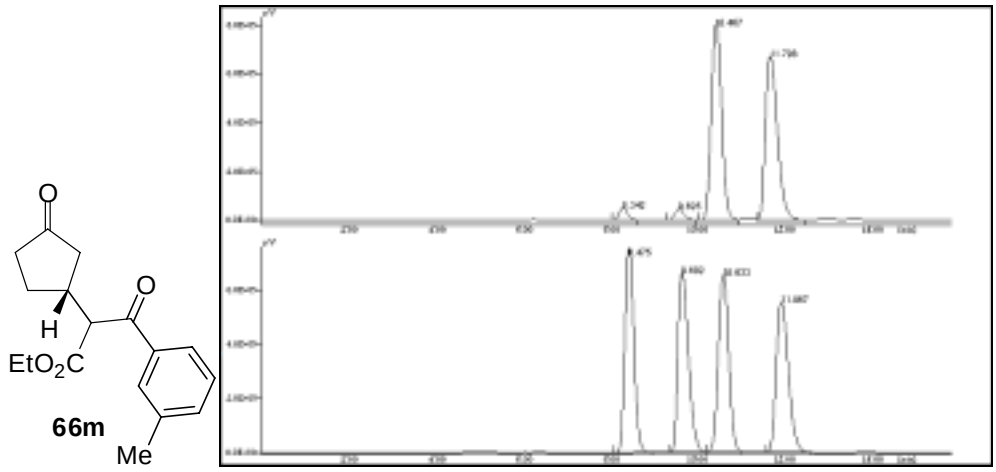
(66l) (*R*)-(+)-ethyl 3-oxo-2-(3-oxocyclopentyl)-3-phenylpropanoate

Colorless oil. A 1:1 mixture of diastereomers. 90% and 93% ee. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.14-1.20 (m, 6H), 1.42-1.54 (m, 1H), 1.71-1.86 (m, 2H), 2.04-2.38 (m, 7H), 2.50-2.58 (m, 2H), 3.06-3.15 (m, 2H), 4.10-4.20 (m, 4H), 4.26 (d, J = 6.6 Hz, 1H), 4.29 (d, J = 6.3 Hz, 1H), 7.46-7.52 (m, 4H), 7.58-7.62 (m, 2H), 7.99-8.04 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 14.0, 27.4, 28.0, 36.4, 36.6, 38.1, 38.3, 42.8, 43.3, 59.1, 59.4, 61.7 (two peaks), 128.6, 128.8, 133.8, 136.1, 136.3, 168.4, 168.5, 193.4, 193.6, 193.4, 193.6, 217.3. LRMS (EI) m/z 274.1 (M^+), HRMS (EI) m/z 274.1207 (M^+), calc. 274.1205 for $C_{16}H_{18}O_4$. The ee was determined by HPLC analyses of the Michael adduct. Double columns, CHIRALPAK (AD-H)-(AD-H) (4.6 mm i.d. x 250 mm); Hexane/2-propanol 80/20; flow rate 0.5 ml/min; 25 ^{o}C; 254 nm; retention time: 28.3 min (minor) and 45.3 min (major), 90% ee; 32.7 min (minor) and 33.6 min (major), 93% ee.



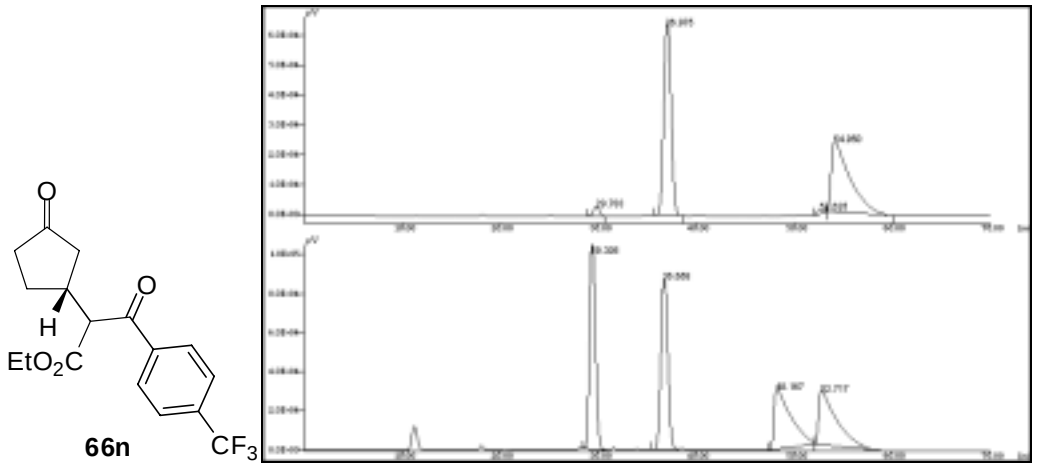
(66m) Ethyl 3-oxo-2-((R)-3-oxocyclopentyl)-3-m-tolylpropanoate

Colorless oil. A 1:1 mixture of diastereomers. 90% and 91% ee. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 1.17 (m, 6H), 1.45-1.54 (m, 1H), 1.71-1.81 (m, 2H), 2.08 (dd, *J* = 11.4, 18.3 Hz, 1H), 2.18-2.37 (m, 6H), 2.41 (s, 3H), 2.42 (s, 3H), 2.47-2.55 (m, 2H), 3.05-3.14 (m, 2H), 4.09-4.19 (m, 4H), 4.27 (m, 2H), 7.34-7.42 (m, 4H), 7.78-7.82 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 14.0, 21.3, 27.4, 27.9, 36.4, 36.6, 38.1, 38.2, 42.8, 43.3, 59.0, 59.3, 61.6 (two peaks), 125.8, 128.7, 129.0, 134.6, 136.2, 136.4, 138.7, 168.5 (two peaks), 193.6, 193.8, 217.3. IR (film): 3019, 2981, 1740, 1686, 1603, 1024, 754 cm^{-1}. LRMS(EI) m/z 288.1 (M^+), HRMS(EI) m/z 288.1360 (M^+), calc. 288.1362 for $C_{17}H_{20}O_4$. The ee was determined by HPLC analyses of the Michael adduct. CHIRALPAK AD-H (4.6 mm i.d. x 250 mm); Hexane/2-propanol 90/10; flow rate 1.0 ml/min; 25 ^{o}C; 254 nm; retention time: 8.5 min (minor), 12.0 min (major); 9.7 min (minor), 10.6 min (major).



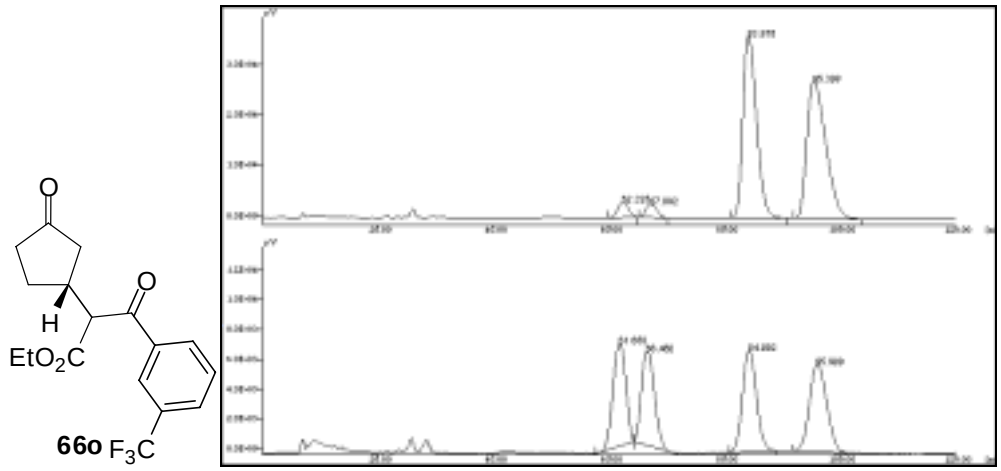
(66n) (*R*)-ethyl 3-oxo-2-(3-oxocyclopentyl)-3-(4-(trifluoromethyl)phenyl)propanoate

Colorless oil. A 1:1 mixture of diastereomers. 92% and 96% ee. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 1.17 (m, 6H), 1.46-1.55 (m, 1H), 1.73-1.84 (m, 2H), 2.08 (dd, *J* = 11.4, 18.3 Hz, 1H), 2.18-2.40 (m, 6H), 2.53 (m, 2H), 3.06-3.18 (m, 2H), 4.11-4.19 (m, 4H), 4.25 (d, *J* = 11.4 Hz, 1H), 4.27 (d, *J* = 10.7 Hz, 1H), 7.74-7.77 (m, 4H), 8.10-8.13 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 14.1, 14.2, 27.5, 28.2, 36.4, 36.6, 38.3, 38.4, 42.8, 43.5, 59.7, 60.0, 62.1, 62.2, 122.5, 124.7, 126.1 (five peaks, C-F coupling), 129.1, 135.1, 135.4, 138.9, 139.1, 168.2 (two peaks), 192.7, 192.9, 217.0 (two peaks). IR (film): 2980, 1743, 1696, 1513, 1465, 997 cm^{-1}. LRMS(EI) m/z 342.2 (M^+), HRMS(EI) m/z 342.1079 (M^+), calc. 342.1079 for $C_{17}H_{17}F_3O_4$. The ee was determined by HPLC analyses of the Michael adduct. CHIRALPAK (4.6 mm i.d. x 250 mm); Hexane/2-propanol 95/5; flow rate 0.5 ml/min; 25 ^{o}C; 254 nm; retention time: 29.8 min (minor), 37.0 min (major), 92% ee; and 52.5 min (minor), 54.1 min (major), 96% ee.



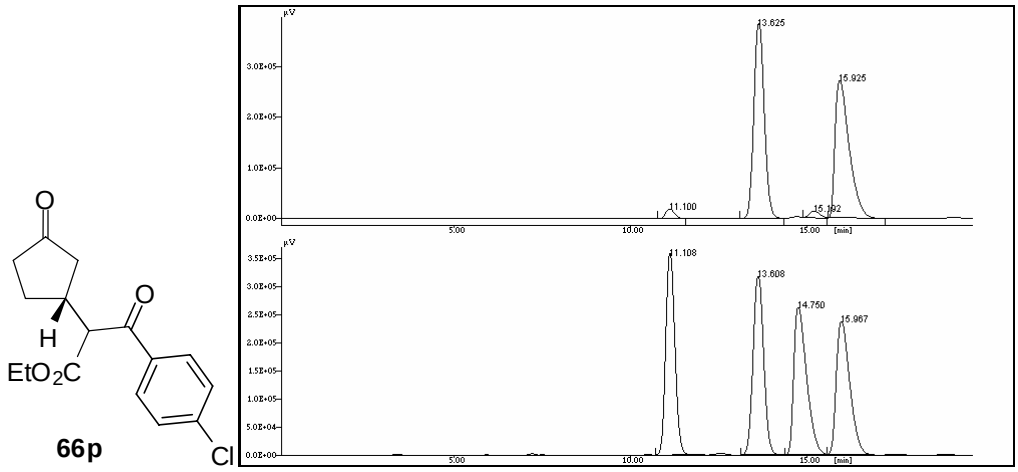
(66o) (R)-(+)-Ethyl 3-oxo-2-(3-oxocyclopentyl)-3-(3-(trifluoromethyl)phenyl)-propanoate

Colorless oil. A 1:1 mixture of diastereomers. 88% and 89% ee ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 1.18 (m, 6H), 1.46-1.56 (m, 1H), 1.70-1.84 (m, 2H), 2.09 (dd, *J* = 11.3, 18.3 Hz, 1H), 2.21-2.41 (m, 6H), 2.54 (dd, *J* = 7.6, 18.3 Hz, 2H), 3.08-3.19 (m, 2H), 4.11-4.22 (m, 4H), 4.27 (t, *J* = 10.4 Hz, 2H), 7.63-7.67 (m, 2H), 7.85-7.87 (m, 2H), 8.18-8.21 (m, 2H), 8.28 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 13.9 (two peaks), 27.3, 28.0, 36.3, 36.4, 38.1, 38.2, 42.6, 43.3, 59.4, 59.7, 62.0 (two peaks), 123.5 (q, C-F coupling, *J* = 273.1 Hz), 125.4 (three peaks), 129.6, 130.2 (four peaks), 131.2-132.0 (six peaks), 136.6, 136.8, 168.0 (two peaks), 192.1, 192.3, 216.8, 216.9. IR (film): 3021, 2984, 1735, 1692, 1333, 1137, 770 cm^{-1}. LRMS(EI) m/z 342.1 (M^+), HRMS(EI) m/z 342.1065 (M^+), calc. 342.1079 for $C_{17}H_{17}F_3O_4$. The ee was determined by HPLC analyses of the Michael adduct. CHIRALPAK AS-H (4.6 mm i.d. x 250 mm); Hexane/2-propanol 95/5; flow rate 0.5 ml/min; temp 25 ^{o}C; detection UV 254 nm; retention time: 62.3 min (minor) and 95.3 min (major), 88% ee; 67.1 min (minor), 84.0 min (major), 89% ee



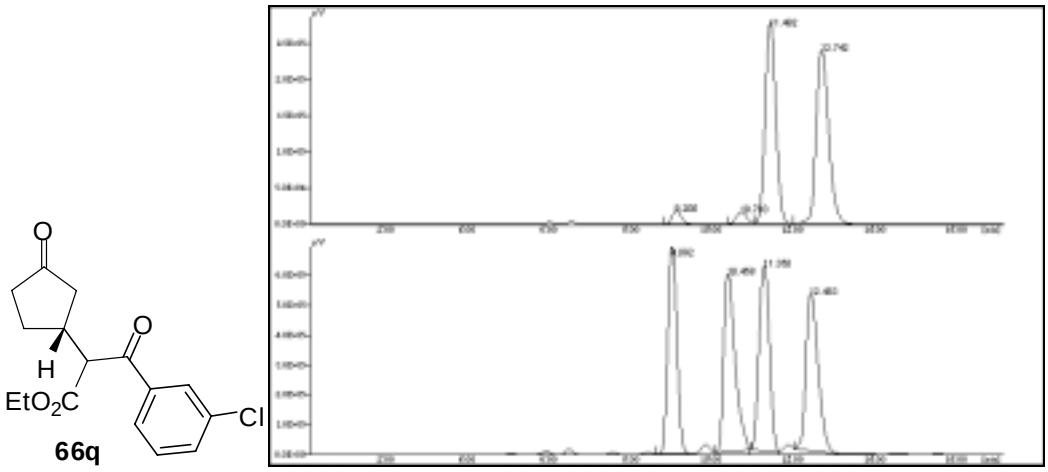
(66p) (*R*)-Ethyl 3-(4-chlorophenyl)-3-oxo-2-(3-oxocyclopentyl)propanoate

Colorless oil. A 1:1 mixture of diastereomers. 92% and 93% ee. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 1.17 (m, 6H), 1.44-1.53 (m, 1H), 1.70-1.82 (m, 2H), 2.06 (dd, *J* = 11.0, 18.5 Hz, 1H), 2.17-2.39 (m, 6H), 2.49-2.54 (m, 2H), 3.05-3.15 (m, 2H), 4.10-4.18 (m, 4H), 4.21 (t, *J* = 10 Hz, 2H), 7.44-7.47 (m, 4H), 7.93-7.97 (m, 4H).. ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 14.0 (two peaks), 27.3, 28.0, 36.3, 36.5, 38.1, 38.2, 42.7, 43.3, 59.2, 59.5, 61.9 (two peaks), 129.2 (two peaks), 130.0, 134.4, 134.6, 140.5, 168.2, 168.3, 192.2, 192.4, 217.0 (two peaks). IR (film): 3020, 1737, 1686, 1591, 1216, 1094, 760 cm^{-1}. LRMS(EI) m/z 308.1 (M^+), HRMS(EI) m/z 308.0804 (M^+), calc. 308.0815 for $C_{16}H_{17}ClO_4$. The ee was determined by HPLC analyses of the Michael adduct. CHIRALPAK AD-H (4.6 mm i.d. x 250 mm); Hexane/2-propanol 90/10; flow rate 1.0 ml/min; 25 ^{o}C; 254 nm; retention time: 11.1 min (minor) and 15.9 min (major), 92% ee; 13.6 min (major), 15.2 min (minor), 93% ee.



(66q) (*R*)-(+)-Ethyl 3-(3-chlorophenyl)-3-oxo-2-(3-oxocyclopentyl)propanoate

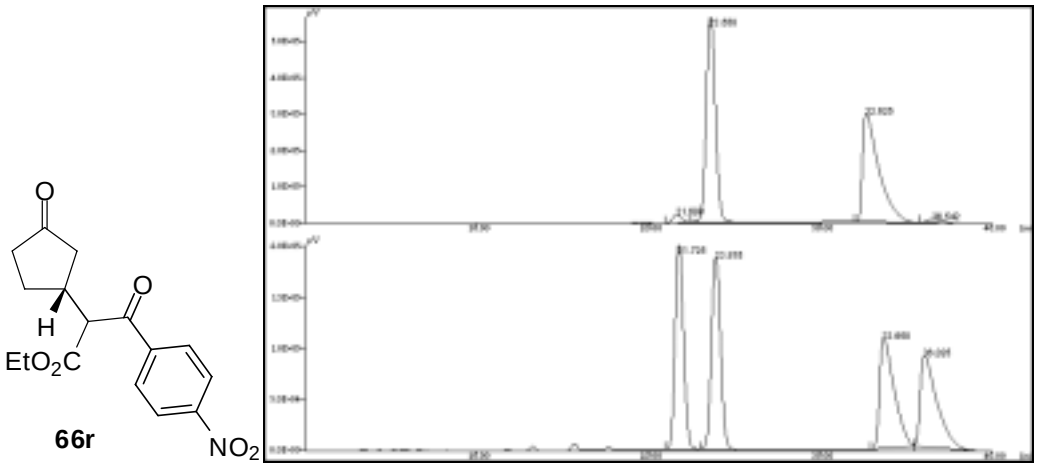
Colorless oil. A 1:1 mixture of diastereomers. 90% and 90% ee. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 1.16-1.22 (m, 6H), 1.47-1.55 (m, 1H), 1.70-1.85 (m, 2H), 2.08 (dd, *J* = 11.2, 18.1 Hz, 1H), 2.18-2.33 (m, 6H), 2.53 (dd, *J* = 7.3, 18.1 Hz, 2H), 3.08-3.12 (m, 2H), 4.12-4.24 (m, 6H), 7.41-7.47 (m, 2H), 7.58 (m, 2H), 7.86-7.91 (m, 2H), 7.98-7.80 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 14.0, 27.3, 28.0, 36.3, 36.5, 38.1, 38.2, 42.7, 43.3, 59.3, 59.6, 61.9 (two peaks), 126.6, 128.6, 130.2, 133.8, 135.3, 137.6, 137.8, 168.1 (two peaks), 192.2, 192.4, 217.0 (two peaks). IR (film): 2965, 1739, 1690, 1572, 1470, 1370, 999 cm^{-1}. LRMS(EI) m/z 307.9 (M^+), HRMS(EI) m/z 308.0814 (M^+), calc. 308.0815 for $C_{16}H_{17}ClO_4$. The ee was determined by HPLC analyses of the Michael adduct. CHIRALPAK AD-H (4.6 mm i.d. x 250 mm); Hexane/2-propanol 90/10; flow rate 1.0 ml/min; 25 ^{o}C; 254 nm; retention time: 9.2 min (minor) and 12.7 min (major); 10.8 min (minor), 11.5 min (major).



66q

(**66r**) **(*R*)-(+)-Ethyl 3-(4-nitrophenyl)-3-oxo-2-(3-oxocyclopentyl)propanoate**

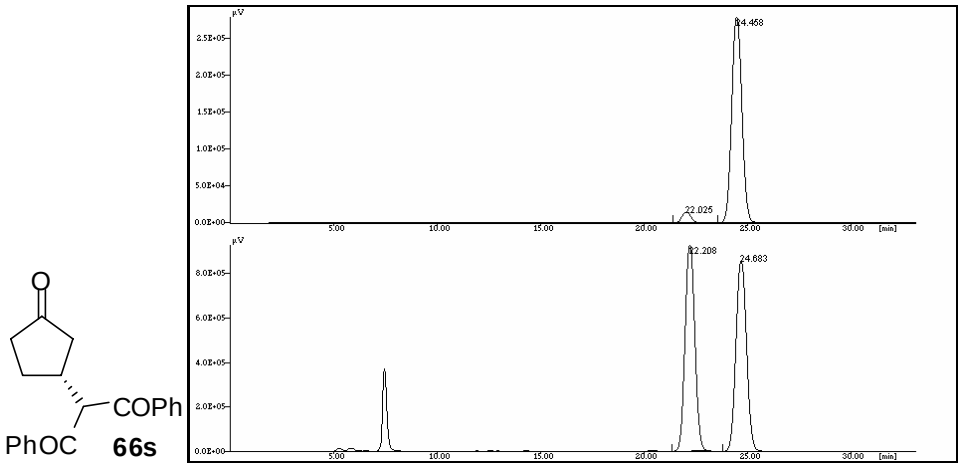
Colorless oil. A 1:1 mixture of diastereomers. 93% and 94% ee. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.15-1.21 (m, 6H), 1.51 (m, 1H), 1.71-1.87 (m, 2H), 2.09 (dd, *J* = 11.2, 18.8 Hz, 1H), 2.20-2.41 (m, 6H), 2.56 (dd, *J* = 7.7, 18.1 Hz, 2H), 3.05-3.16 (m, 2H), 4.12-4.21 (m, 4H), 4.26 (dd, *J* = 7.7, 9.4 Hz, 2H), 8.15-8.20 (m, 4H), 8.32-8.36 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 14.0 (two peaks), 27.2, 28.0, 36.1, 36.3, 38.0, 38.2, 42.5, 43.3, 59.8, 60.1, 62.1, 62.2, 124.1, 129.6, 140.3, 140.5, 150.6, 167.7, 167.8, 192.0, 192.2, 216.6, 216.7. IR (film): 1735, 1688, 1648, 1528, 1405, 1351, 1153, 999 cm^{-1}. LRMS(EI) m/z 318.9 (M^+), HRMS(EI) m/z 319.1062 (M^+), calc. 319.1056 for $C_{16}H_{17}NO_6$. The ee was determined by HPLC analyses of the Michael adduct. CHIRALPAK AD-H (4.6 mm i.d. x 250 mm); Hexane/2-propanol 90/10; flow rate 1.0 ml/min; 25 ^{o}C; 254 nm; retention time: 21.6 min (minor), 23.6 min (major); 32.6 min (major), 36.5 min (minor).



66r

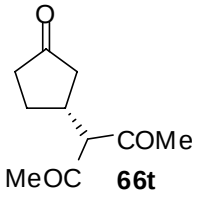
(**66s**) **3-(1,3-Dioxo-1,3-diphenylpropan-2-yl)cyclopentanone**

Colorless oil. Mp 84 ^{o}C. 61% yield, 91% ee. $[\alpha]_{D}^{27}$ = +47.1 (*c* 0.24, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.63-1.73 (m, 1H), 1.96 (dd, *J* = 11.5, 18.5 Hz, 1H), 2.12-2.37 (m, 3H), 2.49 (dd, *J* = 7.3, 18.5 Hz, 1H), 3.22-3.37 (m, 1H), 5.19 (d, *J* = 9.4 Hz, 1H), 7.41-7.49 (m, 4H), 7.56-7.61 (m, 2H), 7.95-8.03 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 28.3, 37.9, 38.4, 43.5, 63.2, 128.9, 129.2, 134.0 (two peaks), 136.5, 136.6, 194.8, 195.0, 217.1. LRMS(ESI) m/z 305.1172 (M-H), HRMS(ESI) m/z 305.3472 (M-H), calc. for $C_{20}H_{17}O_3$. The enantiomeric excess was determined by HPLC analysis of the Michael adduct without derivatization. HPLC separation conditions: column CHIRALPAK AD-H (4.6 mm i.d. x 250 mm); Hexane/2-propanol 90/10 min; flow rate 1.0 ml/min; temp 25 ^{o}C; detection UV 254 nm; retention time: 22.0 min (minor) and 24.5 min (major).



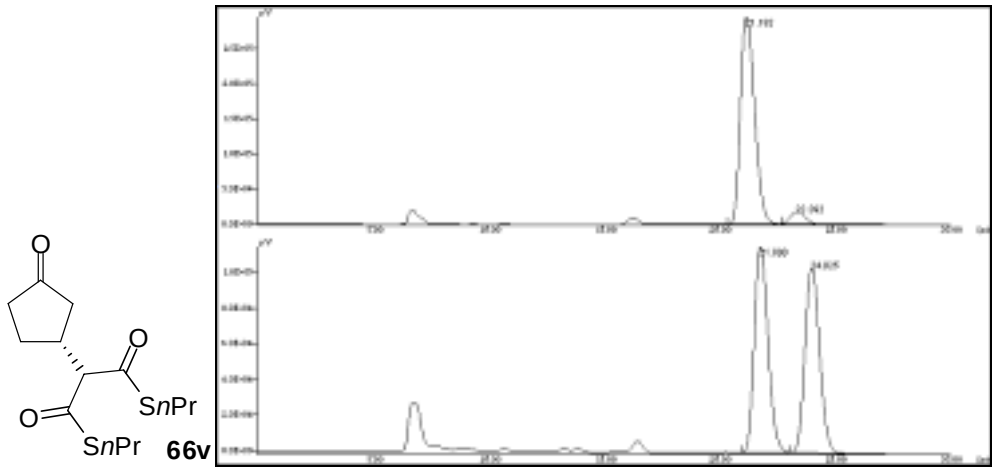
(66t) (R)-3-(3-oxocyclopentyl)pentane-2,4-dione

As reported in lit.[88]



(66v) (*R*)-(+)-*S,S'*-dipropyl 2-(3-oxocyclopentyl)propanebis(thioate)

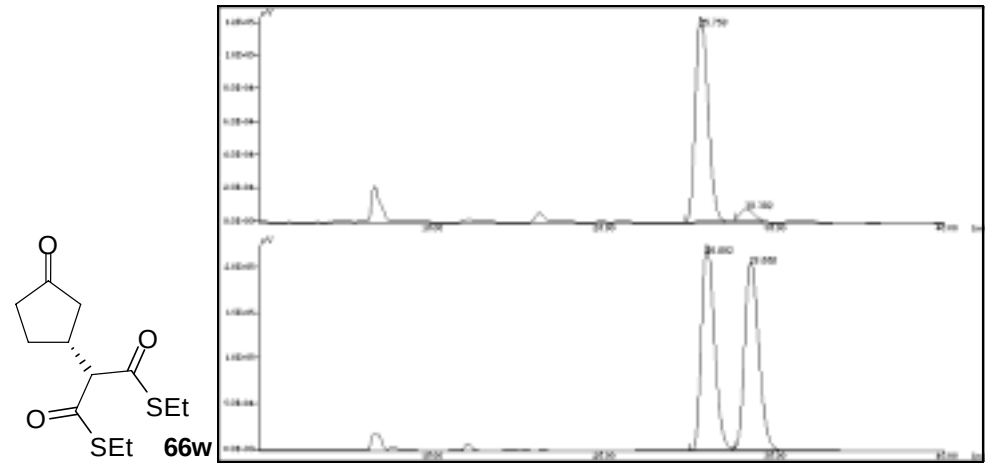
Colorless oil. 89% ee, $[\alpha]_D^{26}$= +50.3 (*c* 0.67, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 0.95 (m, 6H), 1.54-1.68 (m, 5H), 1.92 (dd, *J* = 10.8, 18.1 Hz, 1H), 2.14-2.24 (m, 2H), 2.31 (m, 1H), 2.41 (dd, *J* = 7.7, 18.5 Hz, 1H), 2.91 (q, *J* = 7.3 Hz, 4H), 3.01-3.09 (m, 1H), 3.72 (d, *J* = 10.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 13.2, 22.6, 27.3, 31.5, 37.7, 38.0, 42.4, 73.4, 192.5, 216.5. IR (film): 2965, 1744, 1696, 1287, 1240, 1153, 986 cm^{-1}. LRMS(EI) m/z 301.9 (M^+), HRMS(EI) m/z 302.1005 (M^+), calc. 302.1010 for $C_{14}H_{22}O_3S_2$. The ee was determined by HPLC analyses of the Michael adduct. CHIRALCEL OD-H (4.6 mm i.d. x 250 mm); Hexane/2-propanol 95/5 min; flow rate 0.5 ml/min; 25 ^oC; 210 nm; retention time: 21.2 min (major) and 23.4 min (minor).



66v

(**66w**) **(*R*)-(+)- *S,S'*-Diethyl 2-(3-oxocyclopentyl)propanebis(thioate)**

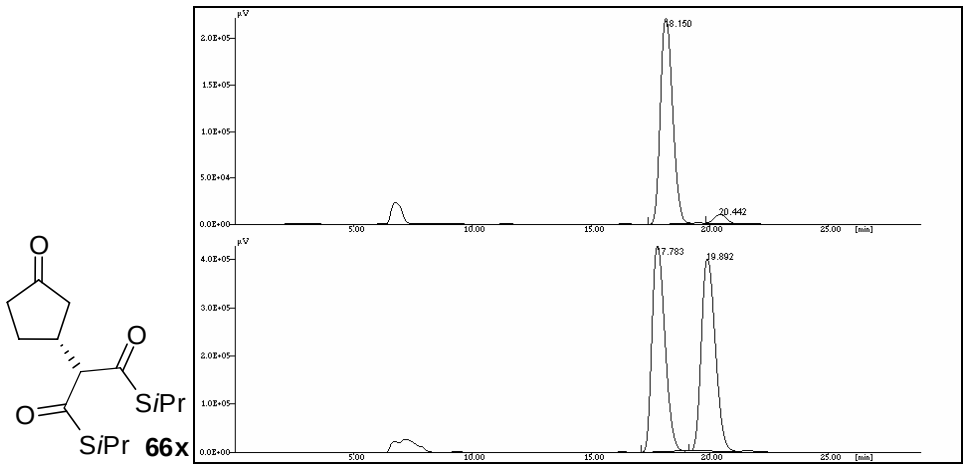
Colorless oil. 90% ee, $[\alpha]_D^{25}$= +54.3 (*c* 0.6, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.26 (m, 6H), 1.57-1.67 (m, 1H), 1.92 (dd, *J* = 10.6, 18.3 Hz, 1H), 2.14-2.46 (m, 4H), 2.88-3.01 (m, 4H), 3.03-3.06 (m, 1H), 3.70 (d, *J* = 10.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 14.3, 24.1, 27.3, 37.8, 38.0, 42.4, 73.3, 192.5, 216.5. IR (film): 2970, 1744, 1693, 1454, 1409, 1263, 1155, 974 cm^{-1}. LRMS(EI) m/z 274.1 (M^+), HRMS(EI) m/z 274.0699 (M^+), calc. 274.0697 for $C_{12}H_{18}O_3S_2$. The ee was determined by HPLC analyses of the Michael adduct. CHIRACEL OD-H (4.6 mm i.d. x 250 mm); Hexane/2-propanol 95/5; flow rate 0.5 ml/min; 25 ^oC; 210 nm; retention time: 25.8 min (major) and 28.4 min (minor).



66w

(66x) (*R*)-(+)- *S,S'*-Diisopropyl 2-(3-oxocyclopentyl)propanebis(thioate)

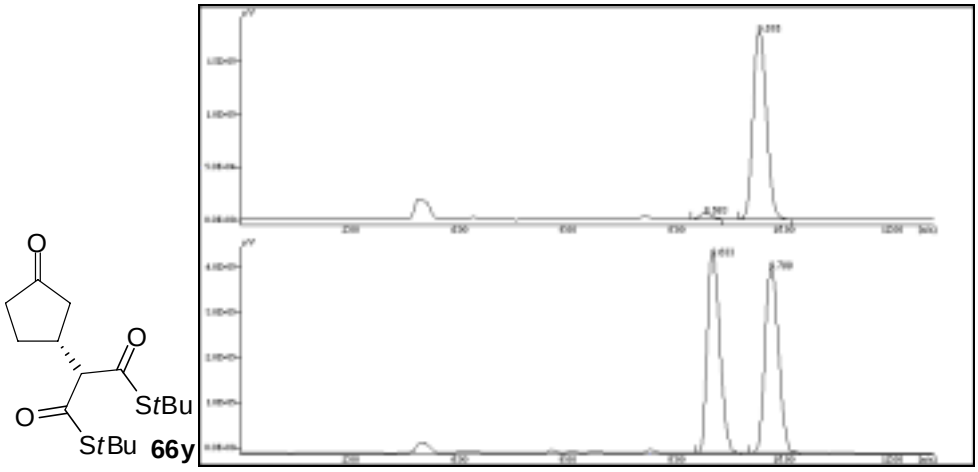
Colorless oil. 92% ee, $[\alpha]_D^{26}$= +87.6 (*c* 0.25, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.28-1.33 (m, 12H), 1.50-1.65 (m, 1H), 1.87-1.96 (m, 1H), 2.10-2.45 (m, 4H), 2.94-3.05 (m, 1H), 3.61 (d, *J* = 10.5 Hz, 1H), 3.63-3.76 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.5, 22.6, 22.7, 27.3, 35.7 (two peaks), 38.0, 42.4, 73.3, 192.5, 216.6. IR (film): 3021, 2969, 2930, 1744, 1692, 1216, 988, 764 cm^{-1}. LRMS(EI) m/z 302.1 (M^+), HRMS(EI) m/z 302.1006 (M^+), calc. 302.1010 for $C_{14}H_{22}O_3S_2$. The ee was determined by HPLC analyses of the Michael adduct. CHIRALCEL OD-H (4.6 mm i.d. x 250 mm); Hexane/2-propanol 95/5 min; flow rate 0.5 ml/min; 25 ^{o}C; 210 nm; retention time: 18.2 min (major) and 20.4 min (minor).



(66y) (*R*)-(+)- *S,S'*-Di-tert-butyl 2-(3-oxocyclopentyl)propanebis(thioate)

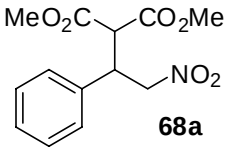
White solid. Mp 104 ^{o}C. 95% ee, $[\alpha]_D^{26}$= +44.7 (*c* 0.43, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.46 (s, 9H), 1.48 (s, 9H), 1.60 (m, 1H), 1.91 (dd, *J* = 11.0, 18.1 Hz, 1H), 2.13-2.45 (m, 4H), 2.91-3.02 (m, 1H), 3.51 (d, *J* =10.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 27.3, 29.5 (two peaks), 37.8, 38.0, 42.4, 49.4, 74.2, 192.8, 216.8. IR (film): 3024, 1741, 1655, 1457, 1364, 1222, 1157, 972 cm^{-1}. LRMS(EI) m/z

330.0 (M^+), HRMS(EI) m/z 330.1315 (M^+), calc. 330.1323 for $C_{16}H_{26}S_2O_3$. The ee was determined by HPLC analyses of the Michael adduct. CHIRALPAK AD-H (4.6 mm i.d. x 250 mm); Hexane/2-propanol 95/5; flow rate 1.0 ml/min; 25 ^oC; 210 nm; retention time: 8.6 min (minor) and 9.6 min (major).



(**68a**) **Methyl 2-carbomethoxy-4-nitro-3-phenylbutyrate**

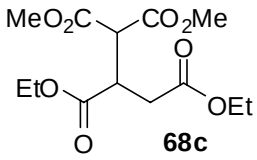
As reported in lit.[89]



68a

(**68c**) **2,3-Diethyl 1,1-dimethyl propane-1,1,2,3-tetracarboxylate**

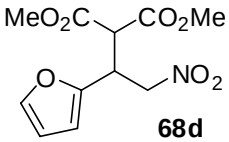
Colorless oil. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.22 (t, J = 7.2 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H), 2.67 (dd, J = 5.2, 16.9 Hz, 1H), 2.79 (dd, J = 7.6, 16.9 Hz, 1H), 3.56 (td, J = 5.2, 7.2 Hz, 1H), 3.73 (s, 3H), 3.74 (s, 3H), 3.92 (d, J = 7.2 Hz, 1H), 4.14 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 13.8, 14.0, 33.4, 40.4, 51.9, 52.6, 60.7, 61.3, 168.0, 168.1, 171.0, 171.5. IR (film): 1741, 1643, 1463, 1377 cm^{-1}. LRMS (FAB) m/z 305.2 ($M+H^+$), HRMS (FAB) m/z 305.1229 ($M+H^+$), calc. for $C_{13}H_{21}O_8$ 305.1236.



68c

(**68d**) **Dimethyl 2-(1-(furan-2-yl)-2-nitroethyl)malonate**

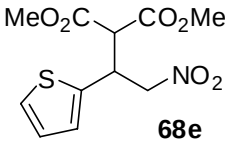
As reported in lit.[90]



68d

(**68e**) **Dimethyl 2-(2-nitro-1-(thiophen-2-yl)ethyl)malonate**

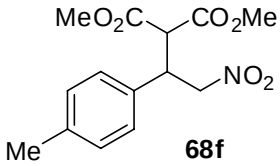
As reported in lit.[90]



68e

(**68f**) **Dimethyl 2-(2-nitro-1-p-tolylethyl)malonate**

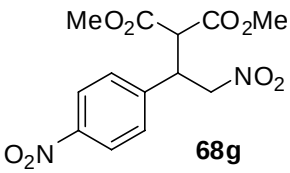
As reported in lit.[91]



68f

(**68g**) **Dimethyl 2-[2-nitro-1-(4-nitrophenyl)ethyl]malonate**

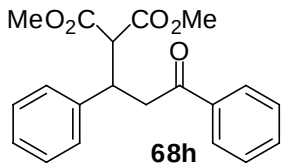
As reported in lit.[91]



68g

(**68h**) **Methyl 3,5-Diphenyl-2-methoxycarbonyl-5-oxopentanoate**

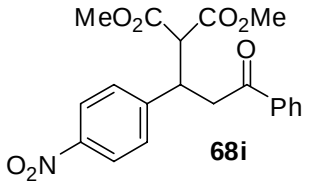
As reported in lit.[92]



68h

(**68i**) **Dimethyl 2-(1-(4-nitrophenyl)-3-oxo-3-phenylpropyl)malonate**

Brown oil. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 3.55 (s, 3H), 3.56 (m, 2H), 3.74 (s, 3H), 3.89 (d, J = 9.3 Hz, 1H), 4.30 (td, J = 5.1, 9.3 Hz, 1H), 7.42-7.56 (m, 5H), 7.88 (m, 2H), 8.12 (d, J = 8.8 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 40.3, 41.7, 52.6, 52.8, 56.5, 123.6, 128.0, 128.7, 129.2, 133.4, 136.3, 147.0, 148.3, 167.7, 168.1, 196.6. IR (film): 1647, 1524, 1458, 1215 cm^{-1}. LRMS (FAB) m/z 386.1 ($M+H^+$), HRMS (FAB) m/z 386.1257 ($M+H^+$), calc. for $C_{20}H_{20}NO_7$ 386.1240.

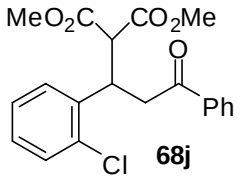


68i

(**68j**) **Dimethyl 2-(1-(2-chlorophenyl)-3-oxo-3-phenylpropyl)malonate**

Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 3.52 (s, 3H), 3,53-3.66 (m, 2H), 3.61 (s, 3H), 4.02 (d, J = 8.8 Hz, 1H), 4.59 (td, J = 4.6, 8.8 Hz, 1H), 7.07 (m, 2 H), 7.21 (dd, J = 2.3, 7.4 Hz, 1H), 7.27 (dd, J = 1.8, 7.4 Hz, 1H), 7.35 (m, 2H), 7.46 (m, 1H), 7.85 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 37.3, 40.2, 41.1, 52.5, 54.8, 126.8, 128.1, 128.3, 128.5, 129.1, 130.1, 133.1, 134.0, 136.7, 137.7, 168.2, 168.6,

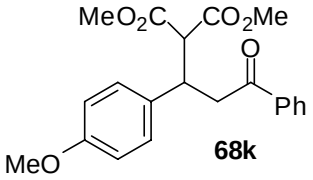
197.3. IR (film): 1737, 1642, 1459, 1377 cm^{-1}. LRMS (FAB) m/z 375.1 ($M+H^+$), HRMS (FAB) m/z 375.1016 ($M+H^+$), calc. for $C_{20}H_{20}ClO_5$ 375.0999.



68j

(**68k**) **Dimethyl 2-(1-(4-methoxyphenyl)-3-oxo-3-phenylpropyl)malonate**

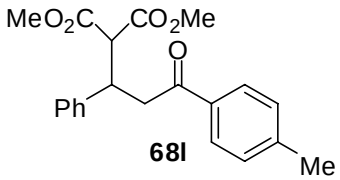
As reported in lit.[93]



68k

(**68l**) **Dimethyl 2-(3-oxo-1-phenyl-3-p-tolylpropyl)malonate**

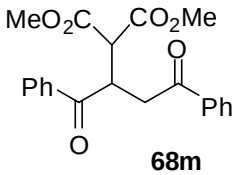
White solid. Mp 93 ^oC. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 2.38 (s, 3H), 3.38-3.56 (m, 2H), 3.50 (s, 3H), 3.72 (s, 3H), 3.85 (d, J = 9.2 Hz, 1H), 4.18 (td, J = 5.6, 9.2 Hz, 1H), 7.19-7.25 (m, 7H), 7.79 (d, J = 8.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 21.5, 40.7, 42.1, 52.2, 52.5, 57.2, 127.1, 128.0, 128.1, 128.4, 129.1, 134.3, 140.4, 143.7, 168.1, 168.6, 197.0. IR (KBr): 1759, 1681, 1497, 1436 cm^{-1}. LRMS (EI) m/z 354.1 (M+), HRMS(EI) m/z 354.1469 (M^+), calc. for $C_{21}H_{22}O_5$ 354.1467.



68l

(**68m**) **Dimethyl 2-(1,4-dioxo-1,4-diphenylbutan-2-yl)malonate**

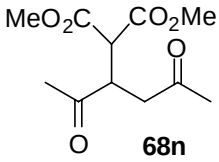
As reported in lit.[94]



68m

(**68n**) **Dimethyl 2-(2, 5-dioxohexan-3-yl)malonate**

Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 2.13 (s, 3H), 2.28 (s, 3H), 2.75 (dd, J = 4.6, 8.4 Hz, 1H), 2.86 (dd, J = 7.2, 8.4 Hz, 1H), 3.70 (s, 6H), 3.68-3.74 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 29.5, 29.7, 42.8, 45.4, 52.2, 52.7 (2 peaks), 168.3, 168.4, 205.3, 208.0. IR (film): 1647, 1459, 1377, 1216, 1161 cm^{-1}. LRMS (FAB) m/z 245.3 (M+H$^+$), HRMS(FAB) m/z 245.1036 (M+H$^+$), calc. for $C_{11}H_{17}O_6$ 245.1025.

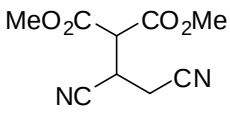


68n

The starting material, **1,2-diacetyl ethylene**, was prepared according to the method reported in the literature.[95]

(**68o**) **Methyl 2-methoxycarbonyl-3,4-dicyanobutanoate**

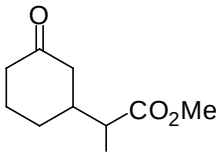
Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 2.96 (d, J = 6.5 Hz, 2H), 3.63 (dd, J = 6.5, 7.4 Hz, 1H), 3.84 (s, 3H), 3.86 (s, 3H), 3.84(d, J = 7.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 19.1, 28.0, 51.4, 53.7, 114.8, 116.3, 165.6, 165.7. IR (film): 1761, 1630, 1439, 1363 cm^{-1}. LRMS(FAB) m/z 211.2 (M+H$^+$), HRMS(FAB) m/z 211.0709 (M+H$^+$), calc. for $C_9H_{11}N_2O_4$ 211.0719.



68o

(**68p**) **3-[Bis(methoxycarbonyl)methyl]cyclohexanone**

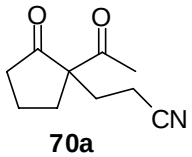
As reported in lit.[82]



68p

(**70a**) **3-(1-Acetyl-2-oxocyclopentyl)propanenitrile**

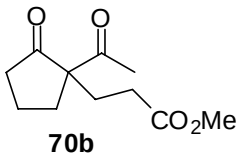
Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.72-1.81 (m, 1H), 1.93-2.11 (m, 3H), 2.16 (s, 3H), 2.19-2.39 (m, 5H), 2.55-2.64 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 13.2, 19.6, 26.4, 29.6, 31.6, 38.3, 67.2 (quaternary carbon), 118.9, 203.3, 215.1. IR (film): 1699, 1436, 1360, 1233 cm^{-1}. LRMS (FAB) m/z 180.1 ($M+H^+$), HRMS (FAB) m/z 180.1017 ($M+H^+$), calc. for $C_{10}H_{14}NO_2$ 180.1025.



70a

(**70b**) **Methyl 3-(1-acetyl-2-oxocyclopentyl)propanoate**

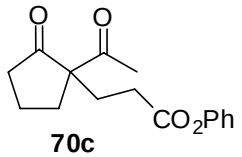
Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.61-1.71 (m, 1H), 1.79-2.02 (m, 3H), 2.17 (s, 3H), 2.19-2.29 (m, 5H), 2.55-2.63 (m, 1H), 3.65 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 19.5, 26.2, 29.5, 29.7, 31.1, 38.5, 51.9, 68.0 (quaternary carbon), 173.1, 204.2, 215.7. IR (film): 1739, 1700, 1458, 1364 cm^{-1}. LRMS(ESI) m/z 212.9 ($M+H^+$), HRMS(ESI) m/z 213.1135 ($M+H^+$), calc. $C_{11}H_{17}O_4$ for 213.1127.



70b

(**70c**) **Phenyl 3-(1-acetyl-2-oxocyclopentyl)propanoate**

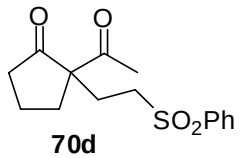
Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.71-1.80 (m, 1H), 1.86-2.01 (m, 2H), 2.07-2.17 (m, 1H), 2.22 (s, 3H), 2.31-2.38 (m, 2H), 2.47-2.52 (m, 2H), 2.60-2.68 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 19.3, 26.1, 28.9, 29.8, 31.2, 38.3, 67.6 (quaternary carbon), 121.3, 125.8, 129.3, 150.5, 171.1, 204.0, 215.6. IR (film): 1697, 1654, 1489, 1363 cm^{-1}. LRMS(EI) m/z 274.0 (M^+), HRMS(EI) m/z 274.1203 (M^+), calc. for $C_{16}H_{18}O_4$ 274.1205.



70c

(**70d**) **2-Acetyl-2-(2-(phenylsulfonyl)ethyl)cyclopentanone**

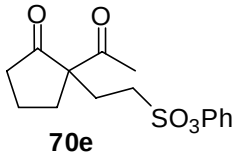
Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.62-1.70 (m, 1H), 1.82-1.97 (m, 3H), 1.99 (s, 3H), 2.06-2.35 (m, 3H), 2.47-2.56 (m, 1H), 2.94-3.05 (m, 2H), 7.55-7.60 (m, 2H), 7.64 (m, 1H), 7.88 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 19.6, 26.2, 26.8, 31.9, 38.3, 52.0, 66.6 (quaternary carbon), 128.2, 129.6, 134.2, 138.9, 203.7, 215.1. IR (film): 1701, 1590, 1448, 1409, 1323 cm^{-1}. LRMS(EI) m/z 294.1 (M^+), HRMS(EI) m/z 294.0923 (M^+), calc. for $C_{15}H_{18}O_4S$ 294.0926.



70d

(**70e**) **Phenyl 2-(1-acetyl-2-oxocyclopentyl)ethanesulfonate**

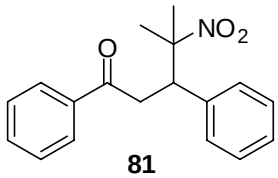
Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.74-1.84 (m, 1H), 1.95-2.04 (m, 2H), 2.17 (s, 3H), 2.33-2.44 (m, 4H), 2.53-2.59 (m, 1H), 3.20 (m, 2H), 7.27 (m, 3H), 7.39 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 19.7, 26.5, 27.5, 32.2, 38.4, 46.4, 66.3 (quaternary carbon), 122.2, 127.5, 130.2, 149.2, 203.7, 215.2. IR (film): 1741, 1707, 1653, 1592, 1488, 1353 cm^{-1}. LRMS(EI) m/z 309.9 (M^+), HRMS(EI) m/z 310.0861 (M^+), calc. for $C_{15}H_{18}O_5S$ 310.0875.



70e

(**81**) **4-Methyl-4-nitro-1,3-diphenylpentan-1-one**

White solid. Structure was confirmed by comparing with literature spectra data[81]. The enantiomeric excess was determined by HPLC analysis. HPLC separation conditions: column CHIRALCEL OJ-H (4.6 mm i.d. x 250 mm); Hexane/2-propanol = 90/10; flow rate 1.2 ml/min; temp 25 ^{o}C; detection UV 254 nm; retention time: 20.0 min (minor) and 26.8 min (major).

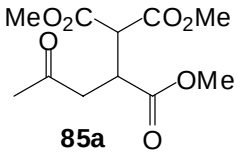


81

(**85a**) **Trimethyl 4-oxopentane-1,1,2-tricarboxylate**

Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 2.17 (s, 3H), 2.80 (dd, J = 5.0, 8.5 Hz, 1H), 3.04 (dd, J = 7.0, 8.5 Hz, 1H), 3.63 (m, 1H), 3.69 (s, 3H), 3.73 (s, 3H), 3.74 (s, 3H), 3.92 (dd, J = 6.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 29.8, 39.2,

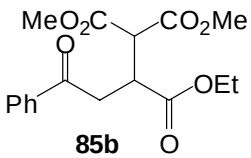
41.9, 51.8, 52.5, 52.7, 52.8, 168.2, 168.4, 172.4, 205.4. LRMS(FAB) m/z 261.1 ($M+H^+$), HRMS(FAB) m/z 261.0967 ($M+H^+$), calc. 261.0974 for $C_{11}H_{17}O_7$. The enantiomeric excess was determined by HPLC analysis. HPLC separation conditions: column CHIRALCEL OD-H (4.6 mm i.d. x 250 mm); Hexane/2-propanol = 90/10; flow rate 1.0 ml/min; temp 25 ^oC; detection UV 210 nm; retention time:14.4 min (minor) and 18.3 min (major).



85a

(**85b**) **2-Ethyl 1,1-dimethyl 4-oxo-4-phenylbutane-1,1,2-tricarboxylate**

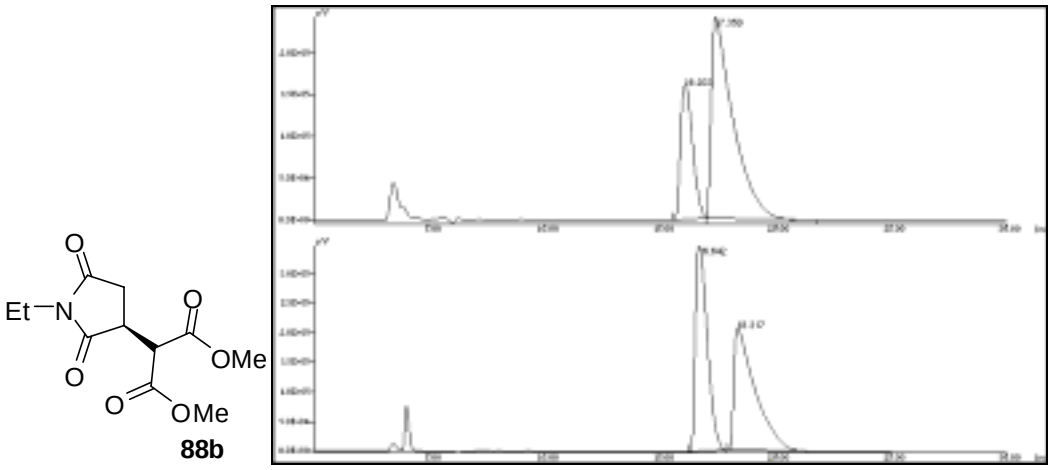
Colorless oil. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.21 (t, J = 7.3 Hz, 3H), 3.33 (dd, J = 5.0, 18.0 Hz, 1H), 3.63 (dd, J = 6.8, 18.0 Hz, 1H), 3.72 (s, 3H), 3.75 (s, 3H), 3.84 (m, 1H), 4.04 (d, J = 6.3 Hz, 1H), 4.15 (q, J = 7.3 Hz, 2H), 7.45 (m, 2H), 7.57 (m, 1H), 7.96 (d, J = 7.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 13.9, 37.3, 39.6, 52.0, 52.7, 52.8, 61.4, 128.1, 128.6, 133.3, 136.4, 168.5, 172.0, 197.2. LRMS(EI) m/z 336.0 (M^+), HRMS(EI) m/z 336.1211 (M^+), calc. 336.1209 for $C_{17}H_{20}O_7$. The enantiomeric excess was determined by HPLC analysis. HPLC separation conditions: column CHIRALCEL OD-H (4.6 mm i.d. x 250 mm); Hexane/2-propanol = 95/5; flow rate 1.0 ml/min; temp 25 ^oC; detection UV 254 nm; retention time:18.7 min (major) and 21.9 min (minor).



85b

(88b) (*S*)-Dimethyl 2-(1-ethyl-2,5-dioxopyrrolidin-3-yl)malonate

Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.17 (t, J = 7.3 Hz, 3H), 2.72 (dd, J = 5.6, 18.5 Hz, 1H), 2.86 (dd, J = 9.1, 18.5 Hz, 1H), 3.28 (m, 1H), 3.57 (q, J = 7.3 Hz, 2H), 3.73 (s, 3H), 3.79 (s, 3H), 4.10 (d, J = 4.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 12.6, 32.3, 34.0, 39.2, 50.5, 52.9, 53.0, 167.4, 168.0, 175.6, 176.9. IR (film): 3023, 2956, 1739, 1701, 1439, 1408, 1227, 754 cm^{-1}. LRMS(EI) m/z 257.0 (M^+), HRMS(EI) m/z 257.0894 (M^+), calc. 257.0899 for $C_{11}H_{15}NO_6$. The ee was determined by HPLC analyses of the Michael adduct. CHIRALPAK AD-H (4.6 mm i.d. x 250 mm); Hexane/2-propanol 90/10; flow rate 1.0 ml/min; 25 ^{o}C; 210 nm; retention time:16.0 min (minor) and 17.4 min (major).

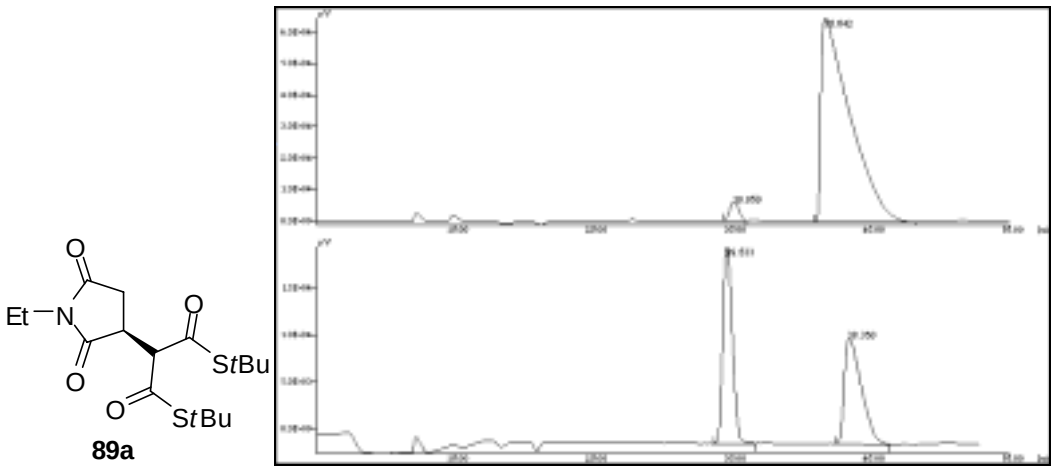


88b

(89a) (*S*)-*S*,*S*'-Di-*tert*-butyl 2-(1-ethyl-2,5-dioxopyrrolidin-3-yl)propanebis(thioate)

White solid. Mp 122 ^{o}C. 95% ee, $[\alpha]_D^{27}$= -46.6 (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.15 (t, J = 7.3 Hz, 3H), 1.43 (s, 9H), 1.50 (s, 9H), 2.77 (dd, J = 9.4, 18.5 Hz, 1H), 2.89 (dd, J = 5.6, 18.5 Hz, 1H), 3.28-3.35 (m, 1H), 3.55 (q, J = 7.3 Hz, 2H), 4.20 (d, J = 5.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 12.7, 29.5, 32.0, 33.9, 40.5, 49.8, 50.0, 66.2, 175.8, 176.8, 192.8. IR (film): 3020, 2968, 1777, 1703,

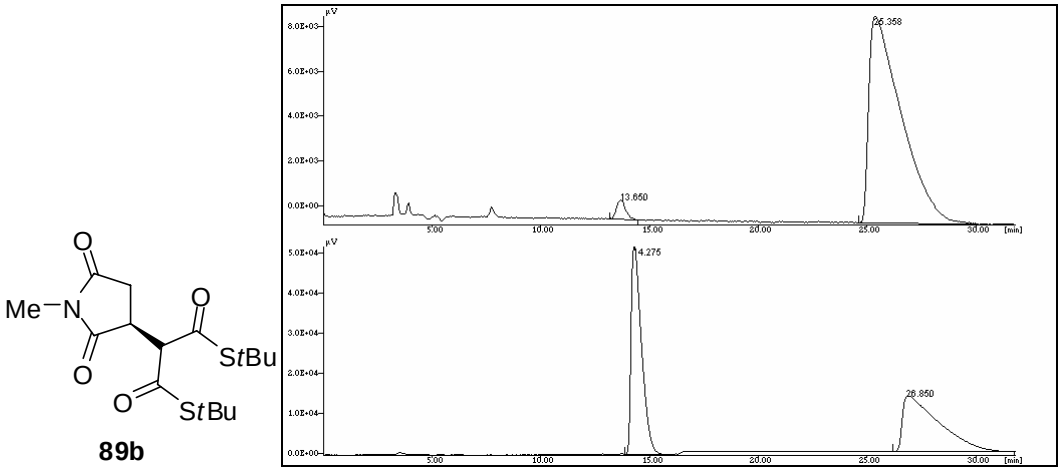
1406, 1216, 1130, 967, 776 cm^{-1}. LRMS(ESI) m/z 396.1 ($M+Na^+$), HRMS(ESI) m/z 396.1276 ($M+Na^+$), calc. 396.1279 for $C_{17}H_{27}NaNS_2O_4$. The ee was determined by HPLC analyses of the Michael adduct. CHIRALPAK AD-H (4.6 mm i.d. x 250 mm); Hexane/2-propanol 95/5; flow rate 0.5 ml/min; 25 ^oC; 254 nm; retention time: 30.1 min (minor) and 36.6 min (major).



89a

(89b) (*S*)-*S*,*S*'-Di-*tert*-butyl 2-(1-methyl-2,5-dioxopyrrolidin-3-yl)propanebis(thioate)

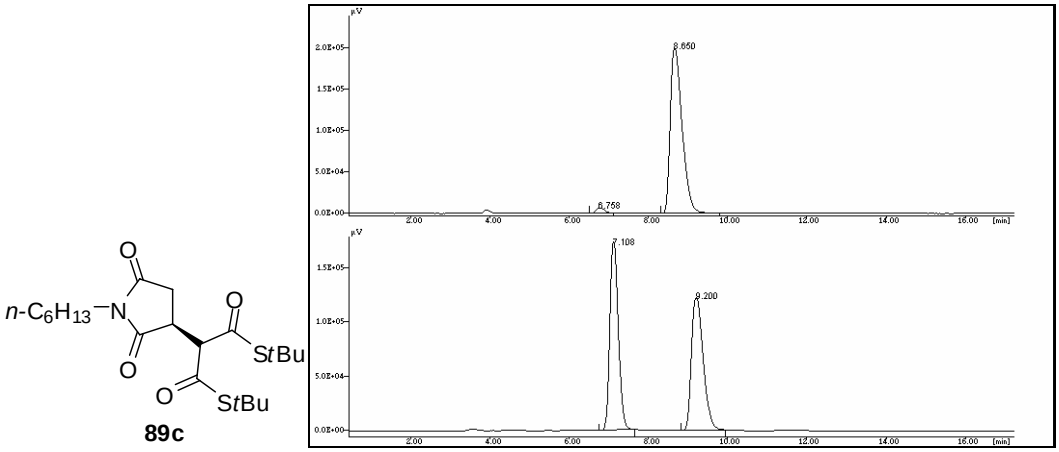
White solid. Mp 98 ^oC. 95% ee, $[\alpha]_D^{26}$= -9.3 (*c* 0.9, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.44 (s, 9H), 1.51 (s, 9H), 2.75-2.86 (m, 2H), 2.99 (s, 3H), 3.33-3.40 (m, 1H), 4.18 (d, *J* = 5.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 25.0, 29.5, 32.1, 40.5, 49.8, 50.0, 66.3, 175.9, 177.0, 192.7, 192.8. IR (film): 3020, 2965, 2400, 1780, 1706, 1439, 1217, 759 cm^{-1}. LRMS(ESI) m/z 382.0 ($M+Na^+$), HRMS(EI) m/z 382.1128 ($M+Na^+$), calc. 382.1123 for $C_{16}H_{25}NaNS_2O_4$. The ee was determined by HPLC analyses of the Michael adduct. CHIRALPAK AD-H (4.6 mm i.d. x 250 mm); Hexane/2-propanol 90/10; flow rate 1.0 ml/min; 25 ^oC; 254 nm; retention time:13.7 min (minor) and 25.4 min (major).



89b

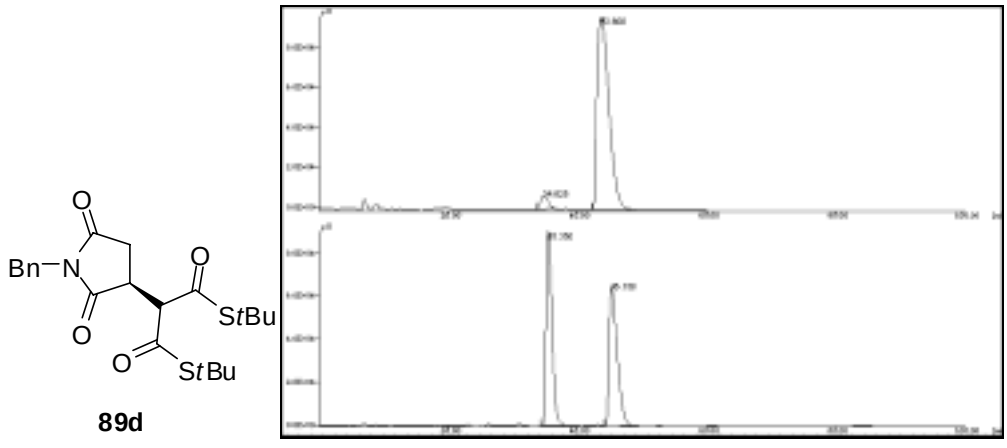
(**89c**) **(*S*)-*S*,*S'*-Di-*tert*-butyl 2-(1-hexyl-2,5-dioxopyrrolidin-3-yl)propanebis(thioate)**

White solid. Mp 62 °C. 95% ee, $[\alpha]_D^{26}$= -15.6 (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 0.84-0.87 (m, 3H), 1.27 (m, 8H), 1.44 (s, 9H), 1.50 (s, 9H), 2.77 (dd, *J* = 9.4, 18.3 Hz, 1H), 2.91 (dd, *J* = 5.6, 18.3 Hz, 1H), 3.27-3.34 (m, 1H), 3.48 (t, *J* = 7.3 Hz, 2H), 4.21 (d, *J* = 5.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 14.0, 22.4, 26.4, 27.5, 29.5, 31.3, 32.0, 39.1, 40.5, 49.8, 50.0, 66.1, 176.0, 177.0, 192.9. IR (film): 2963, 2929, 1778, 1703, 1404, 1366, 1217, 1172, 967 cm^{-1}. LRMS(ESI) m/z 452.1 ($M+Na^+$), HRMS(ESI) m/z 452.1893 ($M+Na^+$), calc. 452.1905 for $C_{21}H_{35}NaNS_2O_4$. The ee was determined by HPLC analyses of the Michael adduct. CHIRALPAK AD-H (4.6 mm i.d. x 250 mm); Hexane/2-propanol 90/10; flow rate 1.0 ml/min; 25 °C; 254 nm; retention time: 6.8 min (minor) and 8.7 min (major).



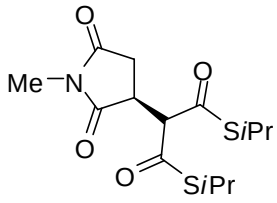
(89d) (*S*)-*S,S'*-Di-*tert*-butyl 2-(1-benzyl-2,5-dioxopyrrolidin-3-yl)propanebis(thioate)

Sticky solid. 90% ee, $[\alpha]_D^{27}$= -14.1 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.39 (s, 9H), 1.49 (s, 9H), 2.79 (dd, *J* = 9.4, 18.5 Hz, 1H), 2.94 (dd, *J* = 5.6, 18.5 Hz, 1H), 3.30-3.37 (m, 1H), 4.22 (d, *J* = 5.6 Hz, 1H), 4.63 (d, *J* = 14.3 Hz, 1H), 4.68 (d, *J* = 14.3 Hz, 1H), 7.24-7.38 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 29.7 (two peaks), 32.3, 40.8, 42.8, 50.0, 50.2, 66.2, 128.0, 128.7, 128.9, 135.7, 175.8, 176.8, 193.1. IR (film): 3020, 2967, 2925, 2402, 1777, 1707, 1400, 1216, 1168 cm^{-1}. LRMS(ESI) m/z 458.1 ($M+Na^+$), HRMS(ESI) m/z 436.1612 ($M+H^+$), calc. 436.1616 for $C_{22}H_{30}NS_2O_4$. The ee was determined by HPLC analyses of the Michael adduct. CHIRALPAK AD-H (4.6 mm i.d. x 250 mm); Hexane/2-propanol 95/5; flow rate 0.5 ml/min; 25 ^oC; 254 nm; retention time: 34.6 min (minor) and 43.5 min (major).

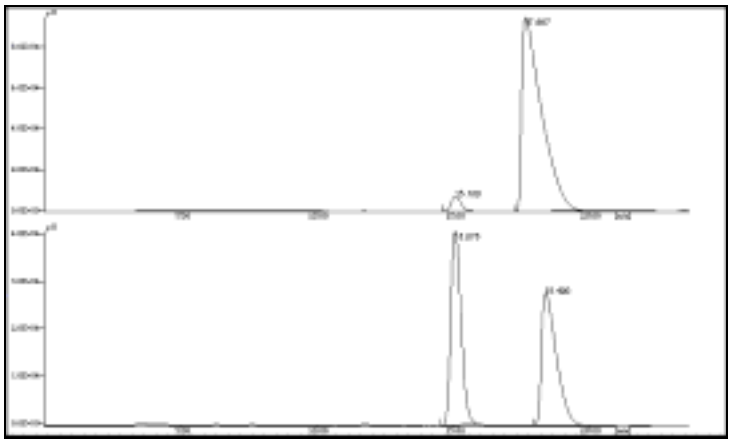


(89e) (*S*)-*S*,*S*'-Diisopropyl 2-(1-methyl-2,5-dioxopyrrolidin-3-yl)propanebis-(thioate)

White solid. Mp 78 °C. 93% ee, $[\alpha]_D^{26}$= -19.6 (*c* 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.26-1.37 (m, 12H), 2.81 (dd, *J* = 9.1, 18.5 Hz, 1H), 2.90 (dd, *J* = 5.9, 18.5 Hz, 1H), 2.99 (s, 3H), 3.32-3.39 (m, 1H), 3.62-3.79 (m, 2H), 4.30 (d, *J* =5.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.5, 25.0, 32.1, 36.0, 36.2, 40.5, 65.3, 175.9, 176.9, 192.6. IR (film): 2966, 2930, 1781, 1704, 1440, 1386, 1284, 1121, 978 cm^{-1}. LRMS(ESI) m/z 354.1 ($M+Na^+$), HRMS(ESI) m/z 354.0812 ($M+Na^+$), calc. 354.0810 for $C_{14}H_{21}NaNS_2O_4$. The ee was determined by HPLC analyses of the Michael adduct. CHIRALPAK AD-H (4.6 mm i.d. x 250 mm); Hexane/2-propanol 90/10; flow rate 1.0 ml/min; 25 °C; 254 nm; retention time:15.1 min (minor) and 17.7 min (major).



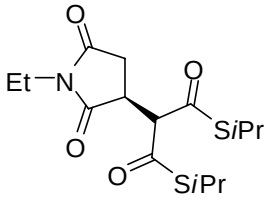
89e



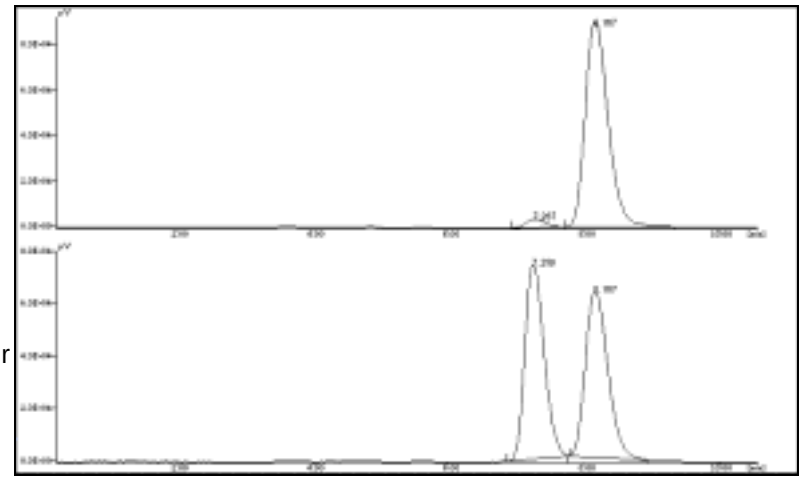
(89f) (*S*)-*S*,*S*'-Diisopropyl 2-(1-ethyl-2,5-dioxopyrrolidin-3-yl)propanebis(thioate)

White solid. Mp 65 °C. 93% ee, $[\alpha]_D^{25}$= -24.4 (*c* 0.6, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.16 (t, *J* = 7.3 Hz, 3H), 1.26-1.37 (m, 12H), 2.78 (dd, *J* = 9.4, 18.5 Hz, 1H), 2.89 (dd, *J* = 5.9, 18.5 Hz, 1H), 3.29-3.36 (m, 1H), 3.55 (q, *J* = 7.3 Hz, 3H), 3.61-3.79 (m, 2H), 4.31 (d, *J* = 5.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 12.7, 22.5, 22.6, 32.1, 33.9, 36.0, 36.1, 40.4, 65.3, 175.7, 176.7, 192.5, 192.6. IR (film):

2968, 2932, 1777, 1703, 1444, 1406, 1228, 1129, 973 cm^{-1}. LRMS(ESI) m/z 367.9 ($M+Na^+$), HRMS(ESI) m/z 368.0966 ($M+Na^+$), calc. 368.0966 for $C_{15}H_{23}NaNS_2O_4$. The ee was determined by HPLC analyses of the Michael adduct. CHIRALCEL OJ-H (4.6 mm i.d. x 250 mm); Hexane/2-propanol 80/20; flow rate 1.0 ml/min; 25 ^oC; 254 nm; retention time: 7.3 min (minor) and 8.2 min (major).



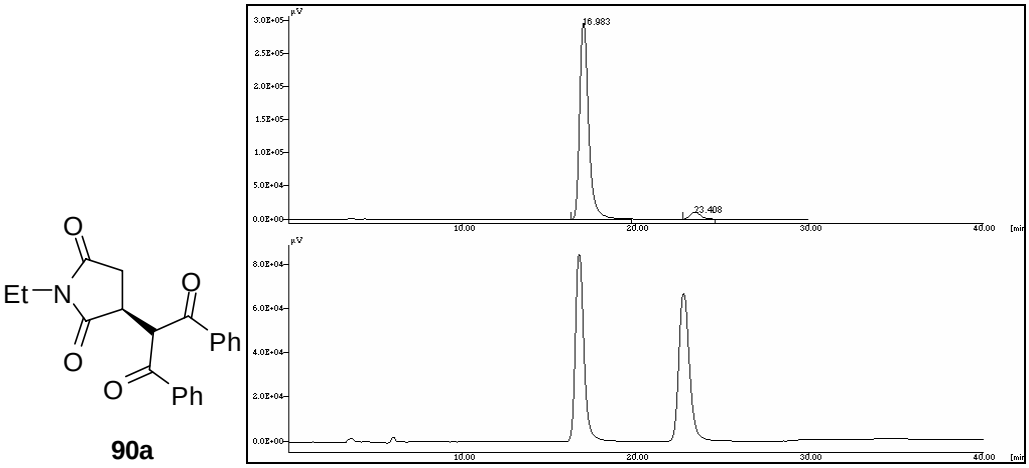
89e



(90a) (*S*)-3-(1,3-Dioxo-1,3-diphenylpropan-2-yl)-1-ethylpyrrolidine-2,5-dione

Colorless oil. 92% ee, $[\alpha]_D^{27}$ = -196.9 (*c* 0.9, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.13 (t, *J* = 7.3 Hz, 3H), 2.60 (dd, *J* = 9.4, 18.3 Hz, 1H), 2.99 (dd, *J* = 5.4, 18.3 Hz, 1H) 3.34-3.41 (m, 1H), 3.57 (q, *J* = 7.3 Hz, 2H), 6.01 (d, *J* = 4.2 Hz, 1H), 7.36-7.42 (m, 2H), 7.51-7.59 (m, 3H), 7.66-7.71 (m, 1H), 7.80-7.83 (m, 2H), 8.06-8.08 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 12.6, 31.5, 34.0, 39.9, 54.3, 128.4, 128.7, 128.8, 129.4, 133.8, 134.5, 135.4, 176.0, 177.7, 194.7, 195.1. IR (film): 3020, 2940, 2400, 1776, 1704, 1597, 1448, 1351, 1227, 1131, 777 cm^{-1}. LRMS(EI) m/z 348.7 (M^+), HRMS(EI) m/z 349.1315 (M^+), calc. 349.1314 for $C_{21}H_{19}NO_4$. The ee was determined by HPLC analyses of the Michael adduct. CHIRALPAK AD-H (4.6 mm i.d. x 250 mm); Hexane/2-propanol 90/10; flow rate 1.0 ml/min; 25 ^oC; 254

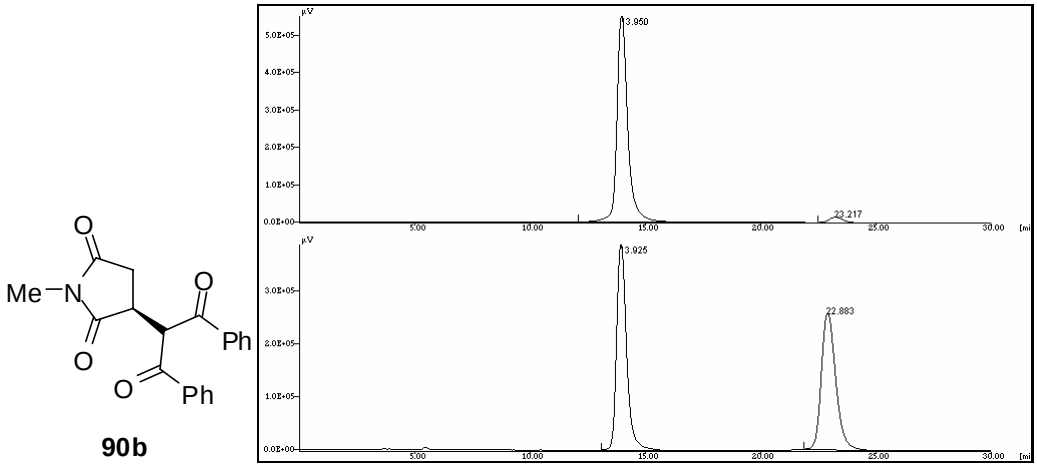
nm; retention time:17.0 min (major) and 23.4 min (minor).



90a

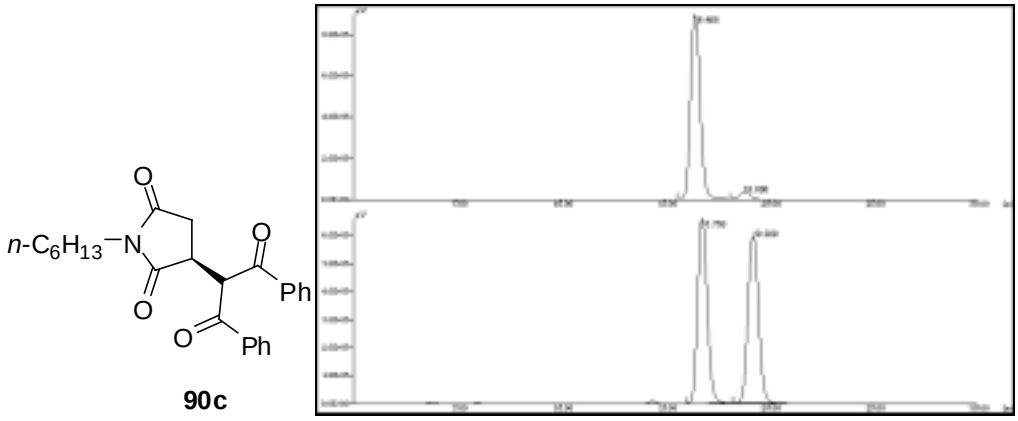
(**90b**) **(*S*)-3-(1,3-Dioxo-1,3-diphenylpropan-2-yl)-1-methylpyrrolidine-2,5-dione**

Colorless oil. 93% ee, $[\alpha]_D^{25}$ = -260.3 (*c* 0.8, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 2.64 (dd, *J* = 9.4, 18.1 Hz, 1H), 2.99 (s, 3H), 3.01 (dd, *J* = 5.5, 18.1 Hz, 1H), 3.36-3.42 (m, 1H), 6.01 (d, *J* = 4.1 Hz, 1H), 7.36-7.41 (m, 2H), 7.50-7.59 (m, 3H), 7.66-7.71 (m, 1H), 7.78-7.81 (m, 2H), 8.06-8.09 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 25.1, 31.5, 40.0, 54.3, 128.4, 128.7, 128.9, 129.5, 133.9, 134.5, 134.6, 135.3, 176.2, 178.0, 194.9, 195.2. IR (film): 3020, 2949, 2400, 1779, 1717, 1597, 1449, 1349, 1119, 1001, 839 cm^{-1}. LRMS(EI) m/z 335.0 (M^+), HRMS(EI) m/z 335.1160 (M^+), calc. 335.1158 for $C_{20}H_{17}NO_4$. The ee was determined by HPLC analyses of the Michael adduct. CHIRALPAK AD-H (4.6 mm i.d. x 250 mm); Hexane/2-propanol 80/20; flow rate 1.0 ml/min; 25 ^oC; 254 nm; retention time:14.0 min (major) and 23.2 min (minor).



(**90c**) **(*S*)-3-(1,3-Dioxo-1,3-diphenylpropan-2-yl)-1-hexylpyrrolidine-2,5-dione**

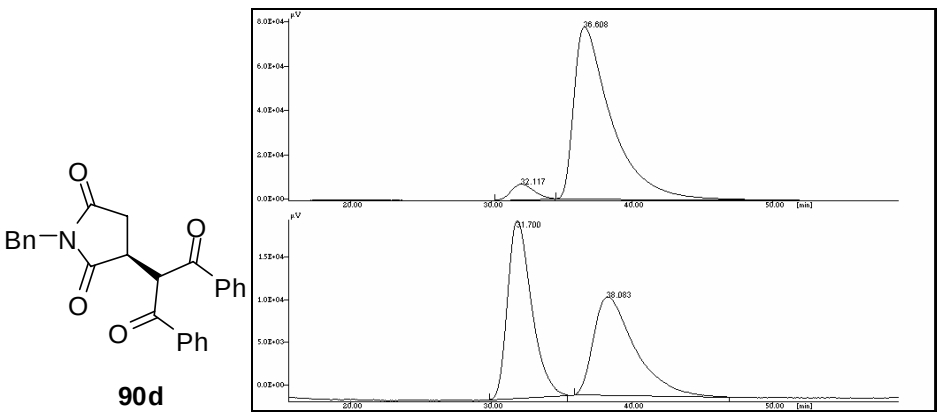
Colorless oil. 92% ee, $[\alpha]_D^{25}$ = -197.5 (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 0.87 (t, *J* = 6.0 Hz, 3H), 1.26 (bs, 6H), 1.50-1.52 (m, 2H), 2.61 (dd, *J* = 9.5, 18.3 Hz, 1H), 3.00 (dd, *J* = 5.6, 18.3 Hz, 1H), 3.34-3.41 (m, 1H), 3.50 (t, *J* = 7.4 Hz, 2H), 6.01 (d, *J* = 4.1 Hz, 1H), 7.36-7.41 (m, 2H), 7.51-7.58 (m, 3H), 7.65-7.70 (m, 1H), 7.81-7.83 (m, 2H), 8.05-8.08 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 13.9, 22.4, 26.3, 27.3, 31.3, 31.4, 39.1, 39.8, 54.2, 128.4, 128.6, 128.8, 129.3, 133.8, 134.4, 134.5, 135.4, 176.1, 177.8, 194.6, 195.0. IR (film): 3020, 2932, 2400, 1776, 1699, 1406, 1216, 776 cm^{-1}. LRMS(EI) m/z 405.0 (M^+), HRMS(EI) m/z 405.1943 (M^+), calc. 405.1940 for $C_{25}H_{27}NO_4$. The ee was determined by HPLC analyses of the Michael adduct. CHIRALPAK AD-H (4.6 mm i.d. x 250 mm); Hexane/2-propanol 90/10; flow rate 1.0 ml/min; 25 ^oC; 254 nm; retention time:16.4 min (major) and 18.8 min (minor).



90c

(**90d**) **(*S*)-1-Benzyl-3-(1,3-dioxo-1,3-diphenylpropan-2-yl)pyrrolidine-2,5-dione**

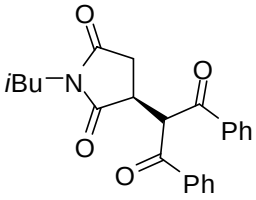
Colorless oil. 90% ee, $[\alpha]_D^{25}$ = -167.2 (*c* 0.9, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 2.63 (dd, *J* = 9.4, 18.1 Hz, 1H), 3.05 (dd, *J* = 5.6, 18.1 Hz, 1H), 3.38-3.44 (m, 1H), 4.64 (d, *J* = 14.3 Hz, 1H), 4.75 (d, *J* = 14.3 Hz, 1H), 6.01 (d, *J* = 4.2 Hz, 1H), 7.25- 7.41 (m, 7H), 7.51-7.57 (m, 3H), 7.65-7.70 (m, 1H), 7.78-7.81 (m, 2H), 8.03-8.06 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 31.5, 40.0, 42.6, 54.1, 127.7, 128.4, 128.5 (two peaks), 128.7, 128.8, 129.4, 133.9, 134.5, 135.3, 135.6, 175.7, 177.5, 194.6, 195.0. IR (film): 3023, 2403, 1777, 1700, 1597, 1402, 1218 cm^{-1}. LRMS(EI) m/z 410.8 (M^+), HRMS(EI) m/z 411.1462 (M^+), calc. 411.1471 for $C_{26}H_{21}NO_4$. The ee was determined by HPLC analyses of the Michael adduct. CHIRALCEL OD-H (4.6 mm i.d. x 250 mm); Hexane/2-propanol 90/10; flow rate 1.0 ml/min; 25 ^oC; 254 nm; retention time: 32.1 min (minor) and 36.6 min (major).



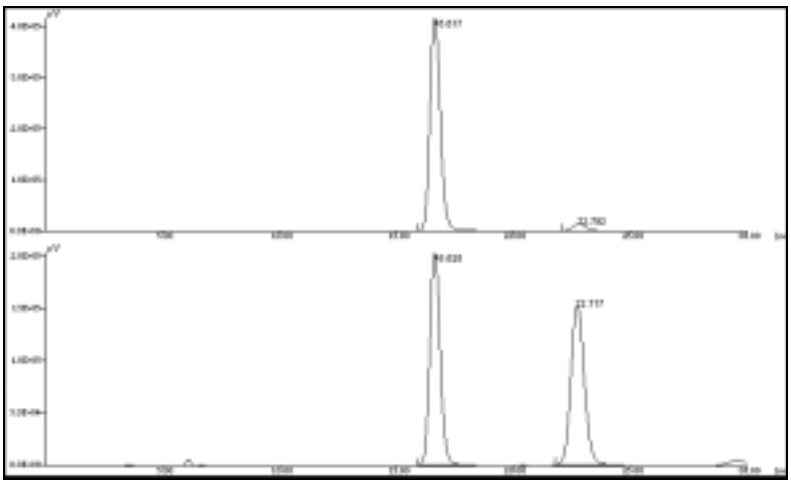
90d

(**90e**) **(*S*)-3-(1,3-Dioxo-1,3-diphenylpropan-2-yl)-1-isobutylpyrrolidine-2,5-dione**

Colorless oil. 72% yield, 92% ee, $[\alpha]_D^{24}$ = -185.6 (*c* 0.7, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 0.87 (d, *J* = 6.3 Hz, 3H), 0.89 (d, *J* = 6.3 Hz, 3H), 1.97-2.06 (m, 1H), 2.61 (dd, *J* = 9.5, 18.3 Hz, 1H), 3.04 (dd, *J* = 5.7, 18.3 Hz, 1H), 3.34 (d, *J* = 7.6 Hz, 2H), 3.37-3.41 (m, 1H), 6.02 (d, *J* = 3.8 Hz, 1H), 7.38-7.41 (m, 2H), 7.52-7.58 (m, 3H), 7.67-7.70 (m, 1H), 7.82-7.83 (m, 2H), 8.06-8.08 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 20.0, 20.1, 27.1, 31.4, 39.9, 46.5, 54.1, 128.5, 128.7, 128.9, 129.4, 133.8, 134.5, 134.6, 135.5, 176.3, 178.1, 194.6, 195.2. IR (film): 3020, 2966, 2400, 1777, 1699, 1597, 1406, 1215, 1139, 760 cm^{-1}. LRMS(EI) m/z 376.9 (M^+), HRMS(EI) m/z 377.1622 (M^+), calc. 377.1627 for $C_{23}H_{23}NO_4$. The ee was determined by HPLC analyses of the Michael adduct. CHIRALPAK AD-H (4.6 mm i.d. x 250 mm); Hexane/2-propanol 90/10; flow rate 1.0 ml/min; 25 ^oC; 254 nm; retention time:16.6 min (major) and 22.8 min (minor).



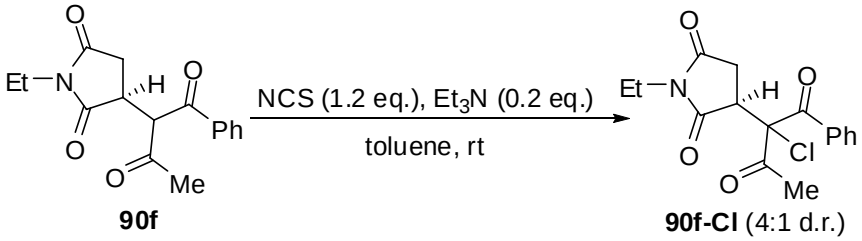
90e

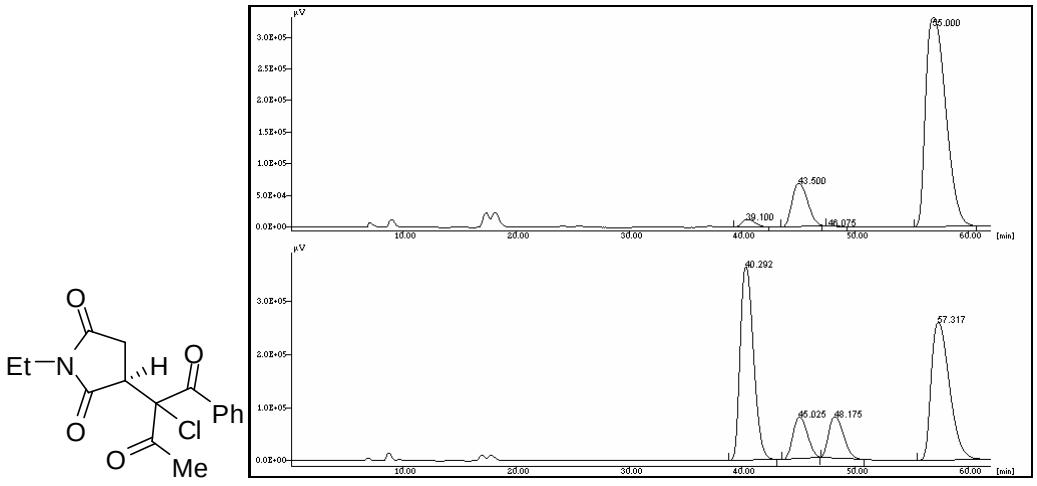


(**90f**) **(3*S*)-3-(1,3-Dioxo-1-phenylbutan-2-yl)-1-ethylpyrrolidine-2,5-dione**

Colorless oil. A 1:1 mixture of diastereomers determined by ^1H NMR. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.03 (t, *J* = 7.3 Hz, 3H), 1.17 (t, *J* = 7.3 Hz, 3H), 2.14 (s, 3H), 2.28 (s, 3H), 2.50-2.90 (m, 4H), 3.13-3.19 (m, 1H), 3.43-3.50 (m, 1H), 3.53-3.60 (m,

4H), 5.04 (d, J = 5.9 Hz, 1H), 5.20 (d, J = 7.2 Hz, 1H), 7.44-7.69 (m, 6H), 7.89-7.92 (m, 2H), 7.80-7.82 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 12.6 (two peaks), 29.2, 29.5, 31.5, 32.4, 33.9, 34.0, 39.4, 39.7, 59.1, 61.2, 128.7 (two peaks), 129.0, 129.3, 134.3, 134.6, 135.1, 135.9, 175.6, 175.8, 177.7 (two peaks), 194.8, 195.8, 201.7, 202.3. IR (film): 3021, 1774, 1700, 1448, 1407, 1353, 1227, 1131, 756 cm^{-1}. LRMS(EI) m/z 287.1 (M^+), HRMS(EI) m/z 287.11677 (M^+), calc. 287.1158 for $C_{16}H_{17}NO_4$. The ee was determined by HPLC analyses after chlorination of the Michael adduct. The chlorination product **90f-Cl** was obtained as a 4:1 mixture of diastereomers. CHIRALPAK AD-H (4.6 mm i.d. x 250 mm); Hexane/2-propanol 95/5; flow rate 0.5 ml/min; 25 ^{o}C; 254 nm; retention time: 39.1 min (minor), and 55.0 min (major), 95% ee; 43.5 min (major), and 45.6 min (minor), 96% ee.

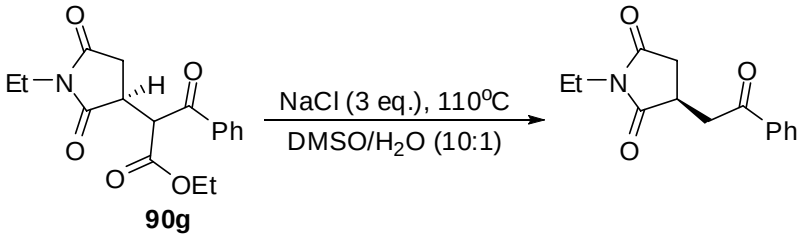




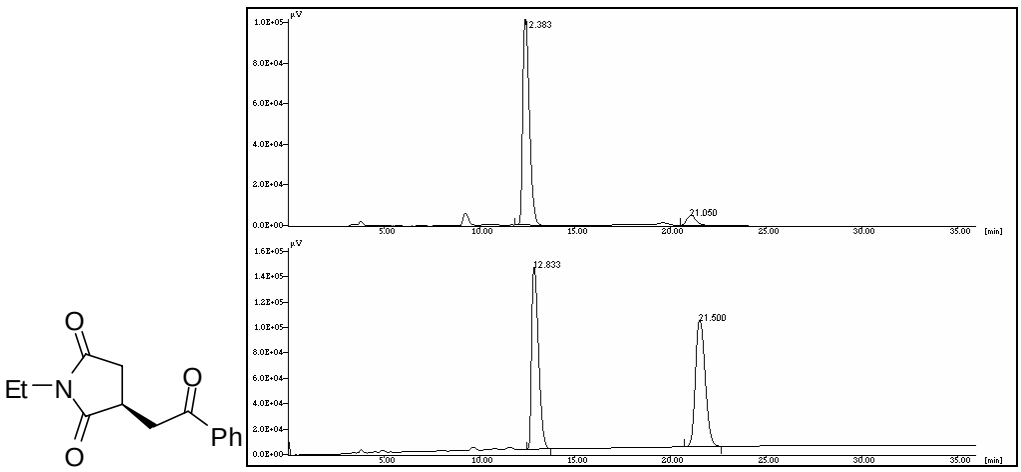
(**90g**) **(3*S*)-Ethyl 2-(1-ethyl-2,5-dioxopyrrolidin-3-yl)-3-oxo-3-phenylpropanoate**

Colorless oil. A 1:1 mixture of diastereomers, determined by ^{1}H NMR, 88% ee

determined after decarboxylation of the Michael adduct. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.12-1.21 (m, 12H), 2.77-2.94 (m, 4H), 3.26-3.32 (m, 1H), 3.41-3.48 (m,1H), 3.52-3.63 (m, 4H), 4.11-4.21 (m, 4H), 4.89 (d, *J* = 5.2 Hz, 1H), 5.12 (d, *J* = 4.2 Hz, 1H), 7.43-7.65 (m, 6H), 7.90-7.99 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 12.7 (two peaks), 13.8 (two peaks), 32.2, 32.4, 34.0, 39.4, 39.6, 52.0, 53.3, 62.1, 62.2, 128.5, 128.7, 128.8, 128.9, 134.0, 134.1, 135.5, 135.7, 167.8, 168.2, 175.9, 176.0, 177.5, 177.7, 193.2, 194.0. IR (film): 3021, 2984, 2401, 1777, 1735, 1704, 1598, 1448, 1380, 1219, 1027, 780 cm^{-1}. LRMS(EI) m/z 317.2 (M^+), HRMS(EI) m/z 317.1269 (M^+), calc. 317.1263 for $C_{17}H_{19}NO_5$. The ee was determined by HPLC analyses after removing the ester group of the Michael adduct. CHIRALPAK AD-H (4.6 mm i.d. x 250 mm); Hexane/2-propanol 80/20; flow rate 10 ml/min; 25 ^{o}C; 254 nm; retention time:12.4 min (major) and 21.1 min (minor).

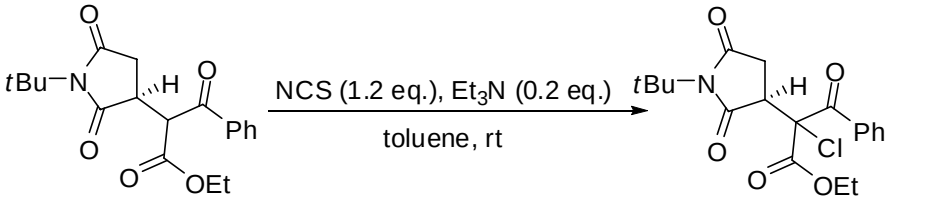


90g

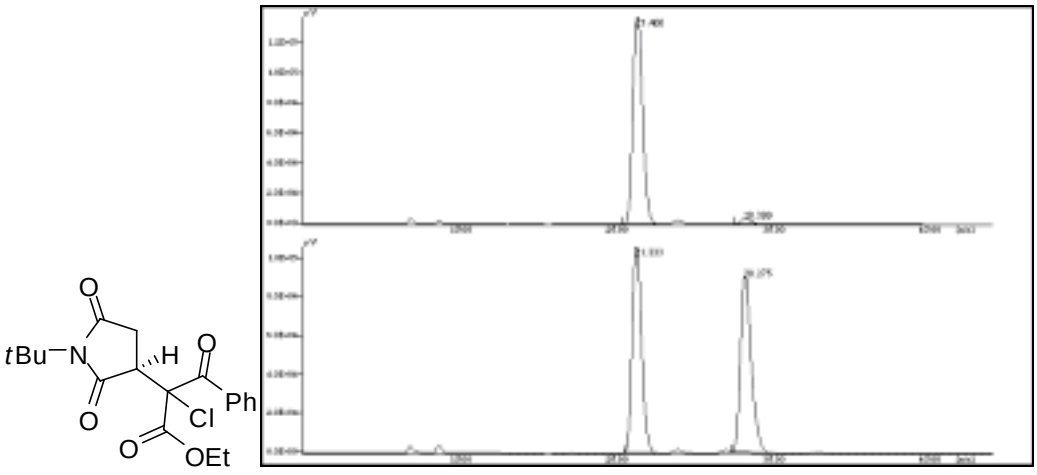


(90h) 3*S*)-Ethyl 2-(1-*tert*-butyl-2,5-dioxopyrrolidin-3-yl)-3-oxo-3-phenylpropanoate

Colorless oil. A 1:1 mixture of diastereomers determined by ^{1}H NMR. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.14-1.18 (m, 6H), 1.55 (s, 9H), 1.59 (s, 9H), 2.68-2.83 (m, 4H), 3.18-3.23 (m, 1H), 3.31-3.36 (m, 1H), 4.14-4.19 (m, 4H), 4.86 (d, *J* = 5.1 Hz, 1H), 5.08 (d, *J* = 4.4 Hz, 1H), 7.44-7.52 (m, 4H), 7.55-7.63 (m, 2H), 7.91-8.01 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 13.9 (two peaks), 28.2 (two peaks), 32.4, 32.7, 39.4, 39.6, 52.3, 53.4, 58.6, 61.9, 62.1, 128.5, 128.7 (two peaks), 128.9, 133.8, 134.0, 135.5, 135.9, 167.9, 168.4, 177.1, 178.6, 178.7, 193.4, 194.2. IR (film): 2980, 2938, 1770, 1736, 1700, 1352, 1265, 1165 cm^{-1}. LRMS(EI) m/z 345.2 (M^+), HRMS(EI) m/z 345.1581 (M^+), calc. 345.1576 for $C_{19}H_{23}NO_5$. The ee was determined by HPLC analyses after α-chlorination of the Michael adduct. The chlorination product **90h-Cl** was obtained as a 10:1 mixture of diastereomers. The major diastereomer was separated and analyzed by HPLC. CHIRALPAK AD-H (4.6 mm i.d. x 250 mm); Hexane/2-propanol 95/5; flow rate 0.5 ml/min; 25 ^{o}C; 254 nm; retention time: 21.4 min (major) and 28.3 min (minor), 94% ee.

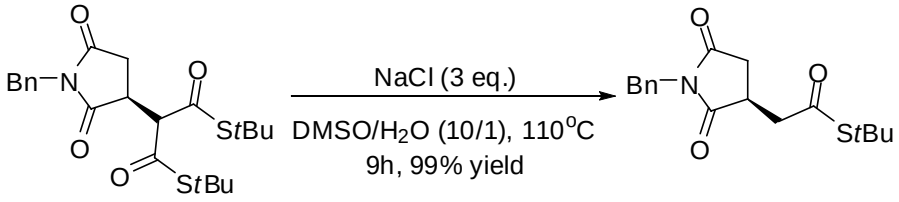


90h **90h-Cl** (10:1 d.r.)
major diastereomer analyzed



6.6 Synthesis of (S)-(+)-β-Proline

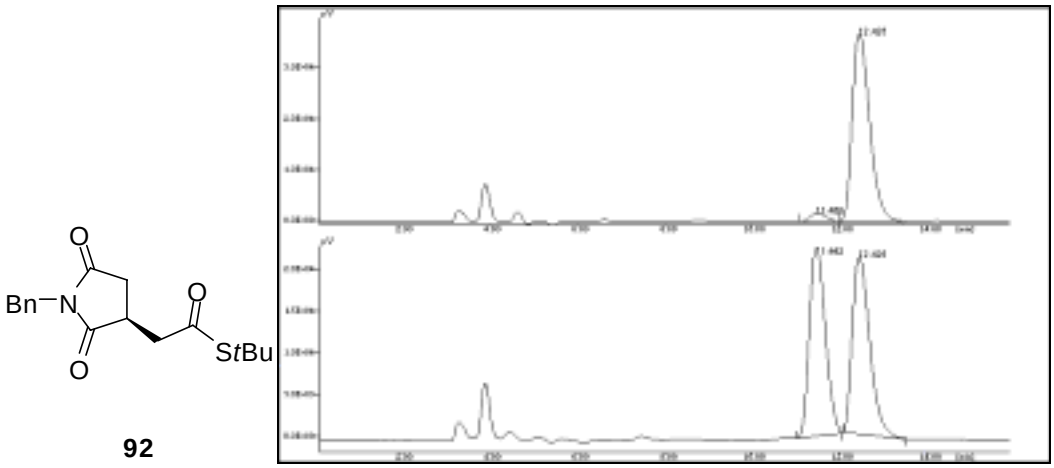
(92) (*S*)-(+)-*S*-*tert*-Butyl 2-(1-benzyl-2,5-dioxopyrrolidin-3-yl)ethanethioate



89d **92**

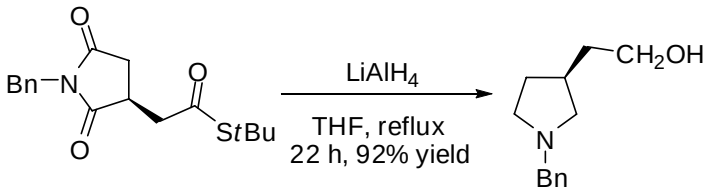
The Michael adduct **89d** (300 mg, 0.69 mmol, 90% ee) and NaCl (121 mg, 2.7 mmol, 3 equiv.) was dissolved in DMSO/H_2O (10:1) solvent mixture (11 ml) and heated to 110 ^oC. Upon complete consumption of **89d** (9h), the reaction mixture was diluted with H_2O (20 ml) and extracted with ether (3 x 30 ml). The combined organic layer was washed with brine, followed by removal of solvent and chromatography on silica gel, to give the desired mono thioester **92** as a colorless oil in 99% yield. 92% ee, $[\alpha]_D^{25}$ = +41.3 (*c* 0.8, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.44 (s, 9H), 2.50 (dd, *J* = 4.9, 18.1 Hz, 1H), 2.80-2.94 (m, 2H), 3.02-3.15 (m, 2H), 4.64 (d, *J* = 14.3 Hz, 1H), 4.70 (d, *J* = 14.3 Hz, 1H), 7.28-7.39 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 29.7, 34.0, 36.5, 42.6, 43.8, 48.9, 127.9, 128.6, 128.7, 135.6, 175.6, 178.3, 197.1. IR

(film): 3022, 2966, 2403, 1776, 1705, 1679, 1348, 1217, 1168 cm^{-1}. LRMS(ESI) m/z 342.1 ($M+Na^+$), HRMS(ESI) m/z 342.1136 ($M+Na^+$), calc. 342.1140 for $C_{17}H_{21}SNO_3Na$. The ee was determined by HPLC analyses of the Michael adduct. CHIRALPAK AD-H (4.6 mm i.d. x 250 mm); Hexane/2-propanol 90/10; flow rate 1.0 ml/min; 25 ^oC; 254 nm; retention time:11.5 min (minor) and 12.4 min (major).



92

(93) (*S*)-2-(1-Benzylpyrrolidin-3-yl)ethanol

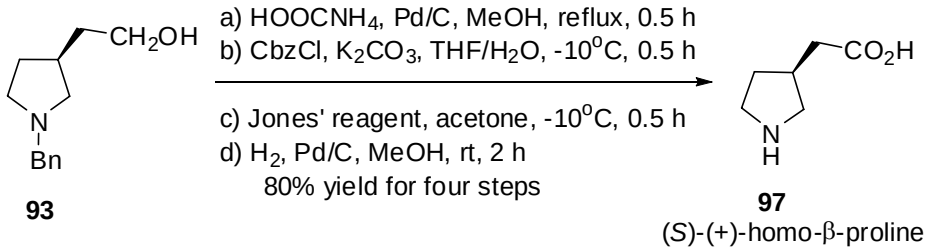


92 **93**

The mono thioester **92** (200 mg, 0.63 mmol) was dissolved in dry THF (9 ml) and refluxed with $LiAlH_4$ (470 mg, 12.5 mmol, 20 equiv.) for 22 h. The reaction was diluted with ether (45 ml) and stirred vigorously at 0 ^oC. Water (0.5 ml) was added dropwise, followed by aqueous NaOH (0.5 ml, 1M), and water (0.5 ml). After stirring vigorously at rt for 2 h, the mixture was filtered through celite and the residue solid was washed with copious ether. The combined filtrate was washed with brine and

dried over $MgSO_4$, followed by removal of solvent and chromatography on basified silica gel, to give the desired *N*-benzyl homo-β-prolinol **93** as colorless oil in 92% yield. 92% ee, $[\alpha]_D^{25}$ = -3.9 (*c* 3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.45-1.70 (m, 3H), 1.93-2.04 (m, 1H), 2.30-2.37 (m, 2H), 2.45-2.54 (m, 1H), 2.60-2.69 (m, 2H), 3.48-3.61 (m, 4H), 7.22-7.30 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 29.0, 34.3, 37.7, 53.5, 60.1, 60.2, 60.4, 127.2, 128.3, 129.0, 138.1. IR (film): 3362, 2928, 1450, 1217, 1064 cm^{-1}. LRMS(EI) m/z 205.0 (M^+), HRMS(EI) m/z 205.1467 (M^+), calc. 205.1467 for $C_{13}H_{19}NO$.

(97) (*S*)-(+)-homo-β-Proline



a) *N*-Benzyl-homo-β-prolinol **93** (33 mg, 0.16 mmol) and ammonium formate (51 mg, 0.8 mmol, 5 equiv.) was dissolved in MeOH (2 ml). Pd/C (10%, 36 mg) was added and the reaction mixture was refluxed for 0.5 h, followed by filtration through celite. The solvent was removed to give free homo-β-prolinol as thick oil in quantitative yield.

b) The product obtained above was dissolved in THF/H_2O (10/1, 1.1 ml), followed by addition of K_2CO_3 (12 mg, 0.55 equiv.). The reaction mixture was stirred in an ice-salt bath (-10 ^{o}C) and CbzCl (28 mg, 1 equiv.) was added dropwise. After stirring in ice-salt bath for another 10 min, the reaction was brought to 0 ^{o}C and stirred for 0.5 h.

The reaction mixture was poured into ice-water (3 ml) and solid NaCl was added until saturation, followed by extraction with EA (3 x 6 ml). The combined organic layer was washed with 5% HCl, water, and brine. After drying over $MgSO_4$, solvent was removed, giving *N*-Cbz homo-β-prolinol as thick oil.

c) The product obtained above was dissolved in acetone (2 ml) and stirred in an ice-salt bath (-10 ^oC). The Jones' reagent[iii] (1 ml) was diluted with acetone (3 ml) and cooled in the ice-salt bath for 10 min, followed by dropwise addition to the reaction mixture until the orange-red color persisted for more than 5 min. The reaction was further stirred in the ice-salt bath until complete consumption of the starting material indicated by TLC (about 0.5 h). Isopropanol (0.1 ml) was added to quench the reaction and the solvent was removed. The residue was diluted with brine (3 ml) and extracted with EA (3 x 6 ml). Solvent was removed and the residue was dissolved in toluene (3 ml) and washed with aqueous KOH (1 M, 3 ml). The organic layer was acidified with concentrated HCl to pH1 and extracted with EA (3 x 6 ml). The combined organic layer was washed with brine and dried over $MgSO_4$. Solvent was removed to give *N*-Cbz homo-β-proline as thick oil.

d) The product obtained above was dissolved in MeOH (1 ml) and stirred with Pd/C (10%, 6 mg) under H_2 for 2 h, before filtration through Celite to give the pure (*S*)-(+)-homo-β-proline **97** as an amorphous white solid. 92% ee, $[\alpha]_D^{25}$ = +8.3 (*c* 0.4, H_2O), (lit[73d], $[\alpha]_D^{27}$= +9.6 (*c* 1.0, H_2O)). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.45-1.70 (m, 3H), 1.93-2.04 (m, 1H), 2.30-2.37 (m, 2H), 2.45-2.54 (m, 1H),

[iii] Prepared by dissolving CrO_3 (26.7 g) in concentrated H_2SO_4 (23 ml) and dilution to 100 ml with water.

2.60-2.69 (m, 2H), 3.48-3.61 (m, 4H), 7.22-7.30 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 29.0, 34.3, 37.7, 53.5, 60.1, 60.2, 60.4, 127.2, 128.3, 129.0, 138.1. LRMS(FAB) m/z 130.0 ($M+H^+$), HRMS(FAB) m/z 130.0866 ($M+H^+$), calc. 130.0868 for $C_6H_{12}NO_2$.

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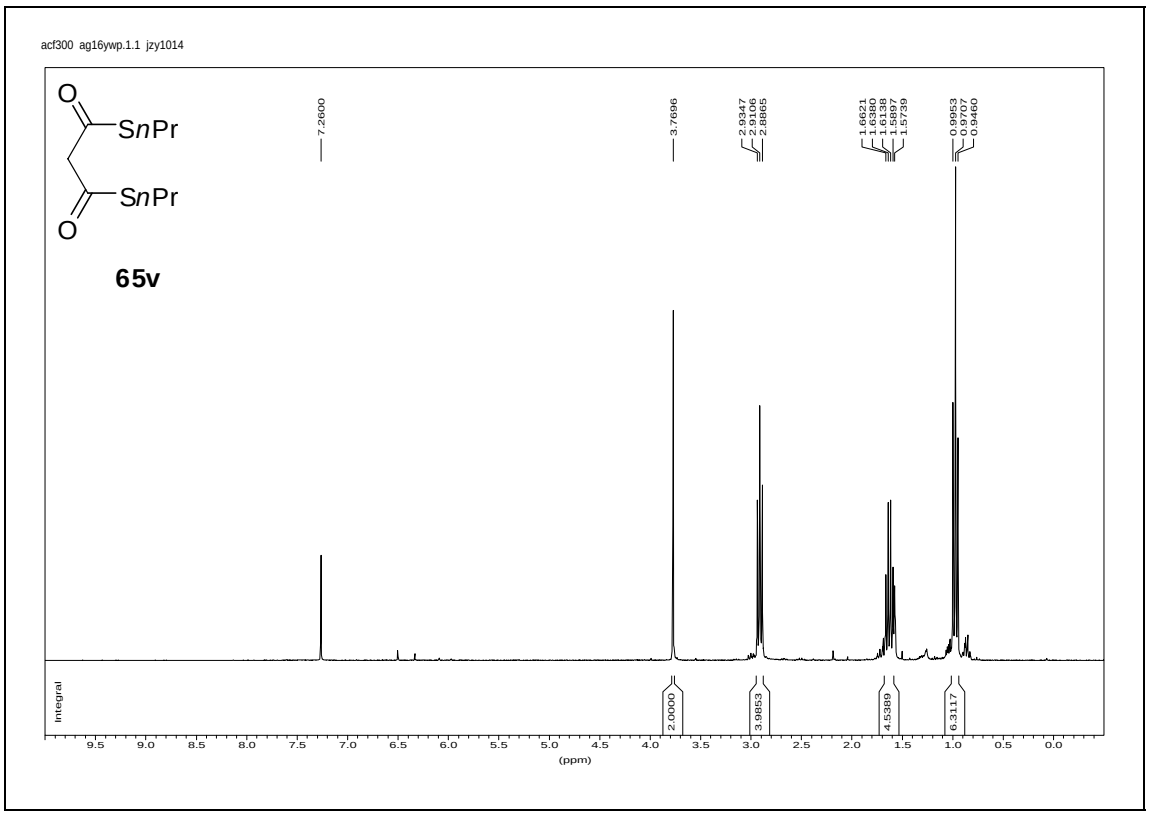
Appendices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2.9106
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1.6621
1.6380
1.6138
1.5897
1.5739
0.9953
0.9707
0.9460
Integral
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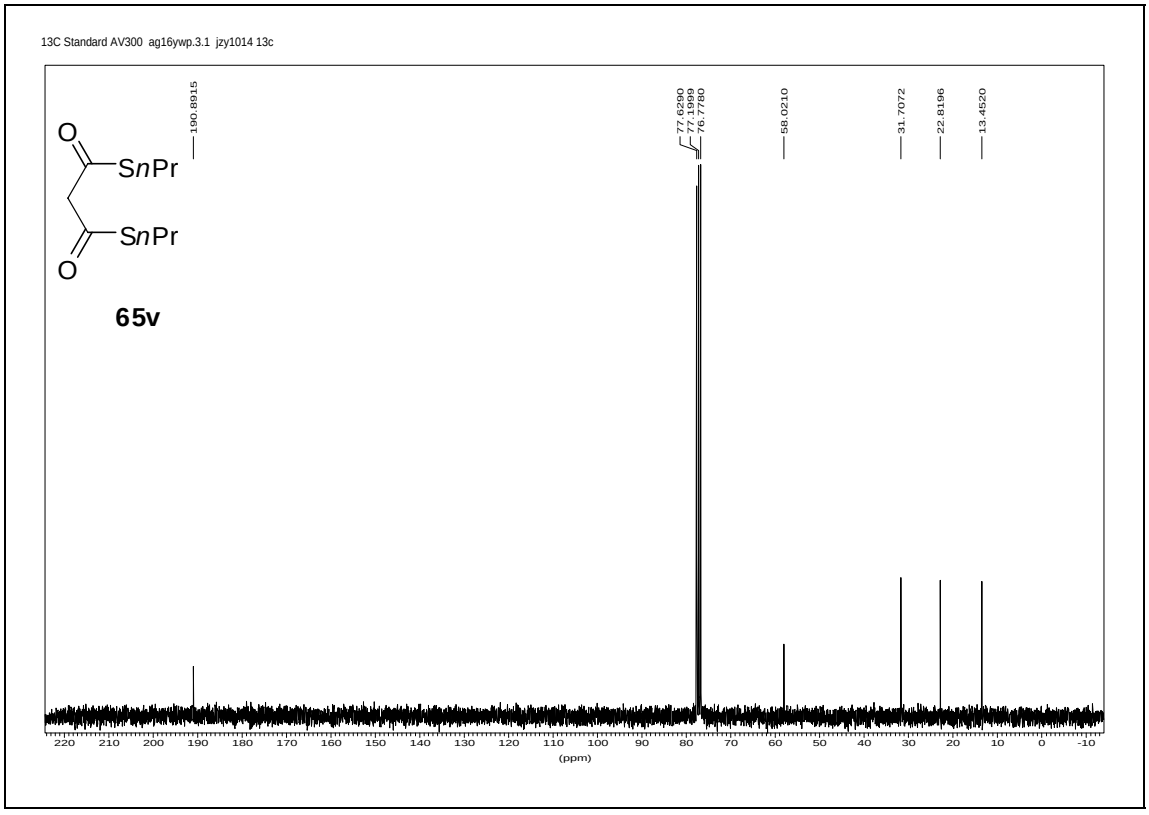
(ppm)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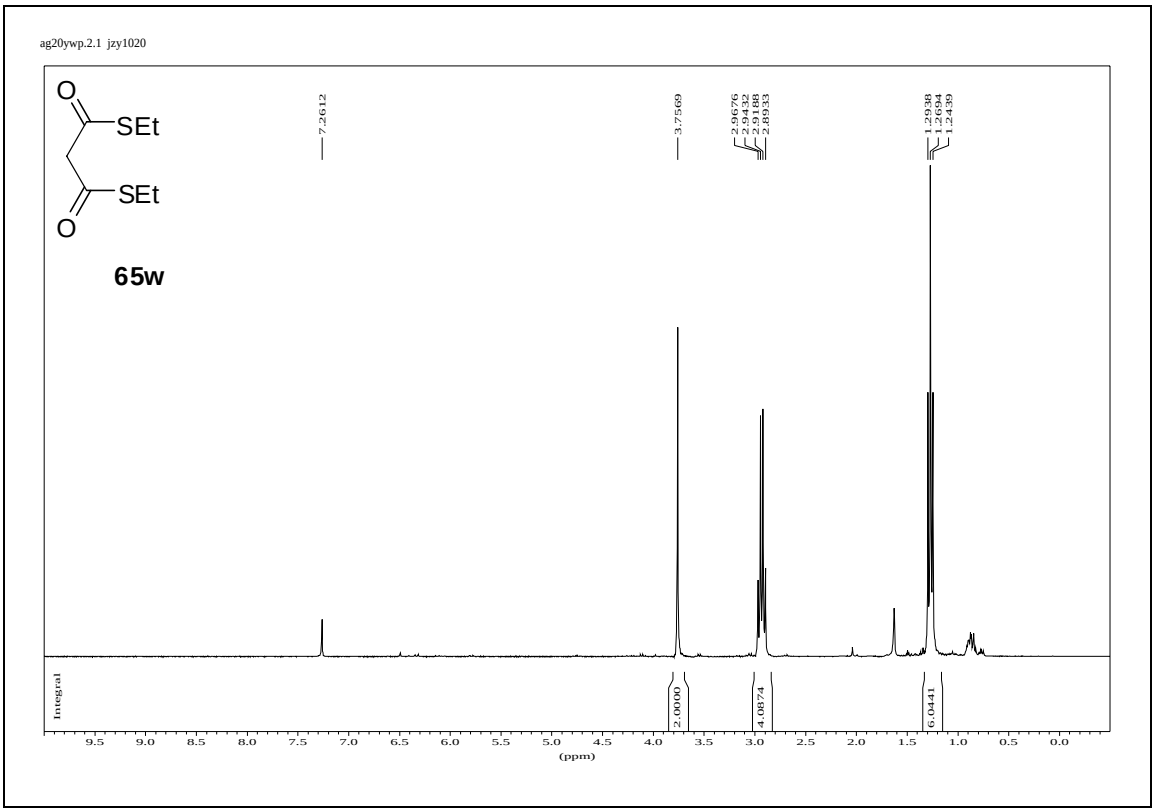
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SEt
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Integral
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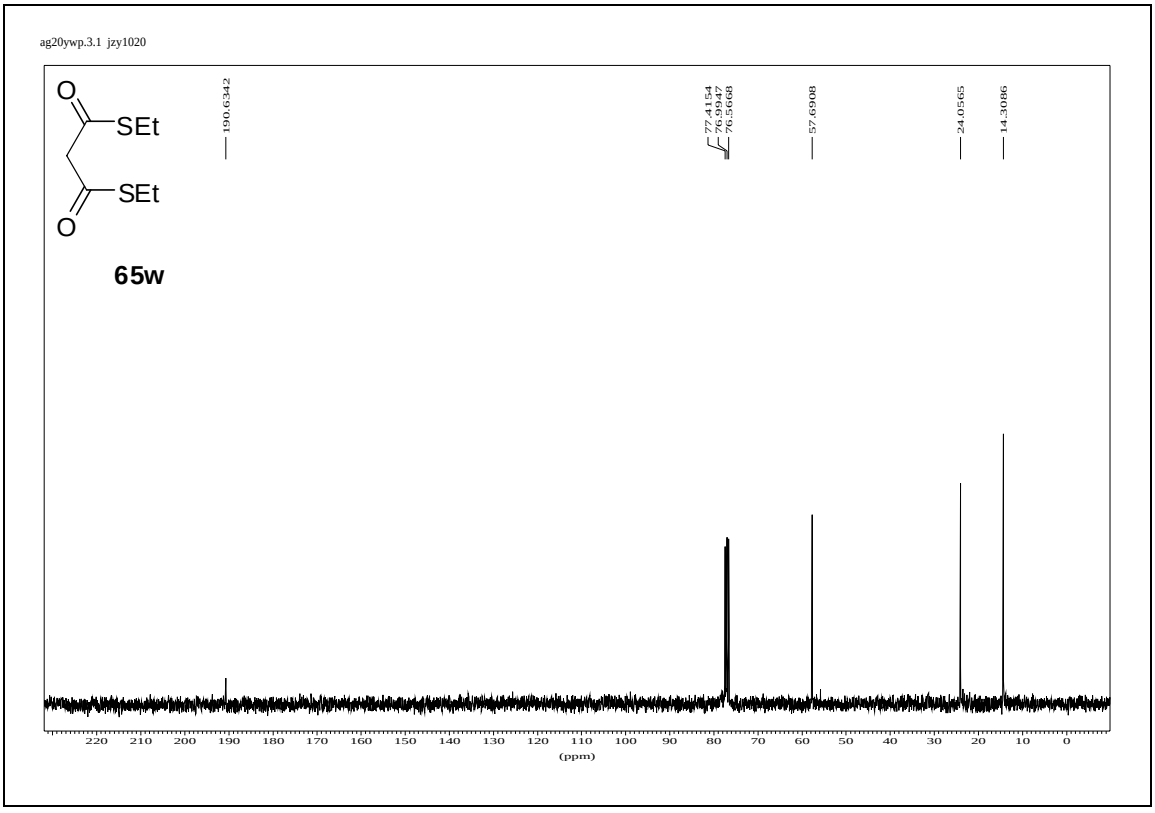
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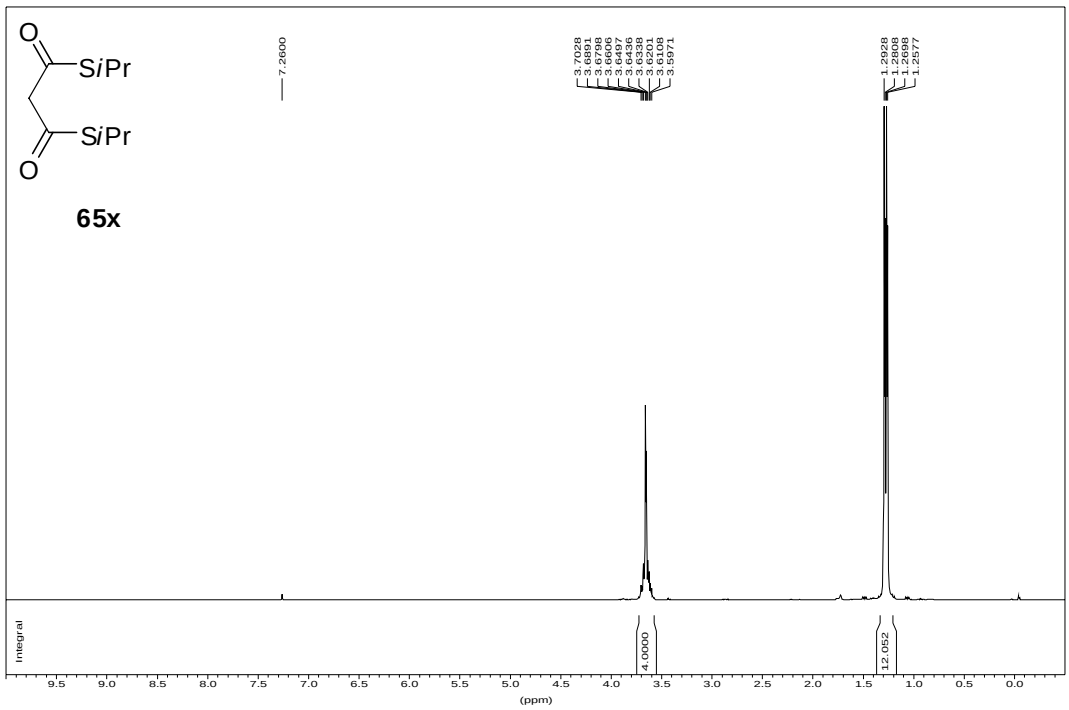

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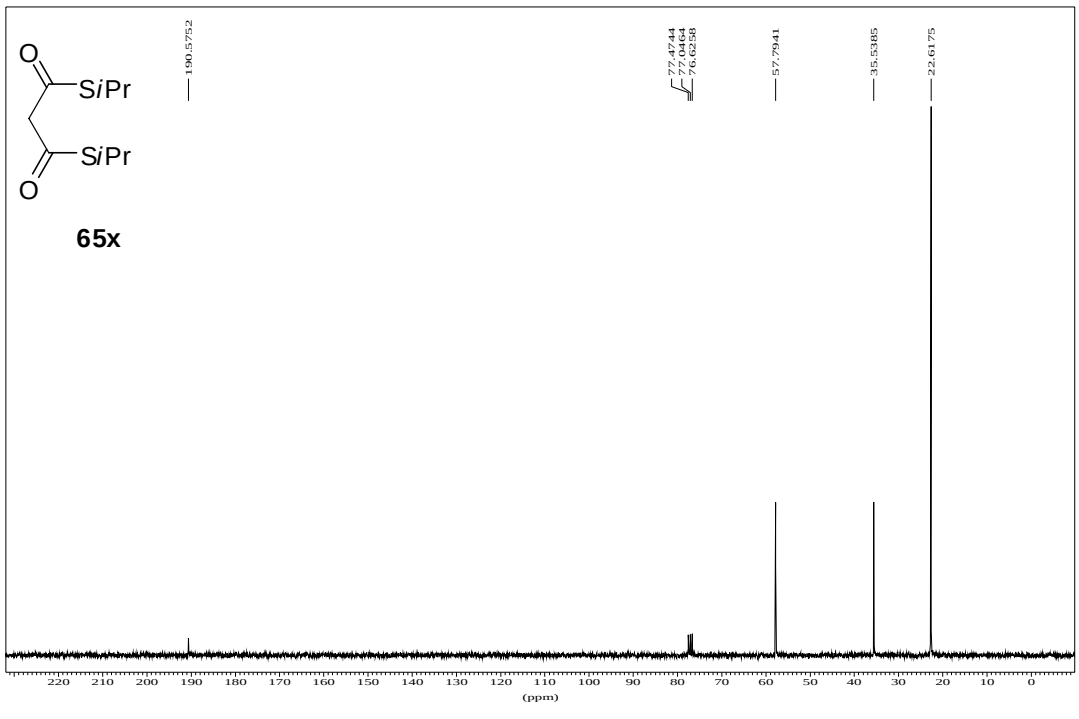

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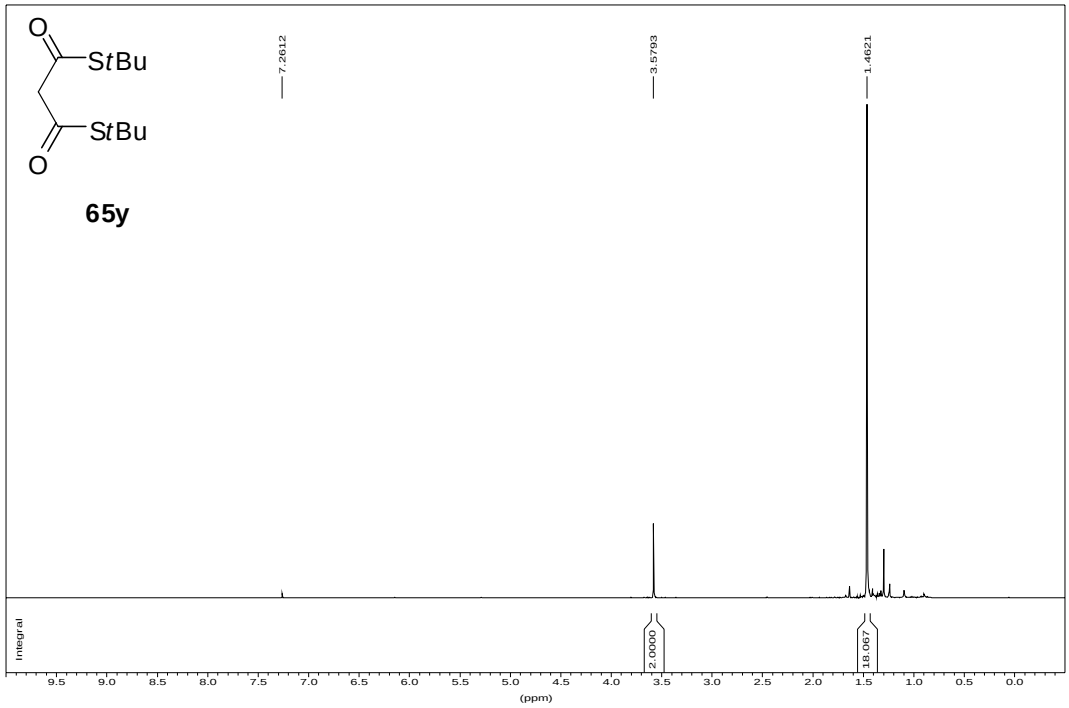

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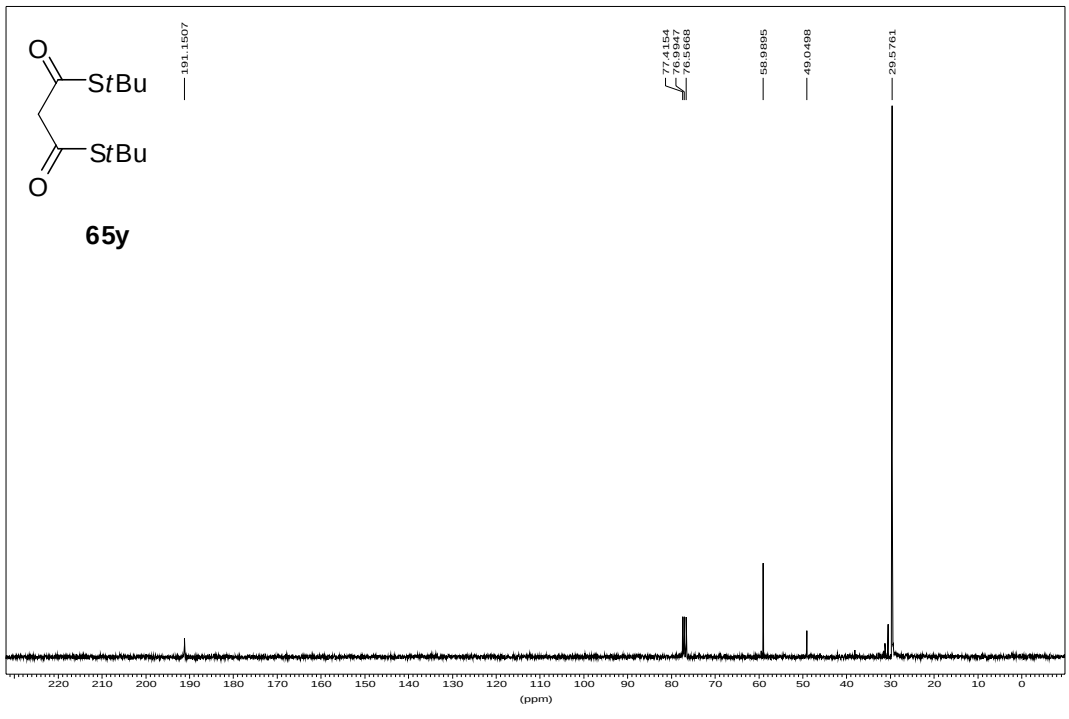

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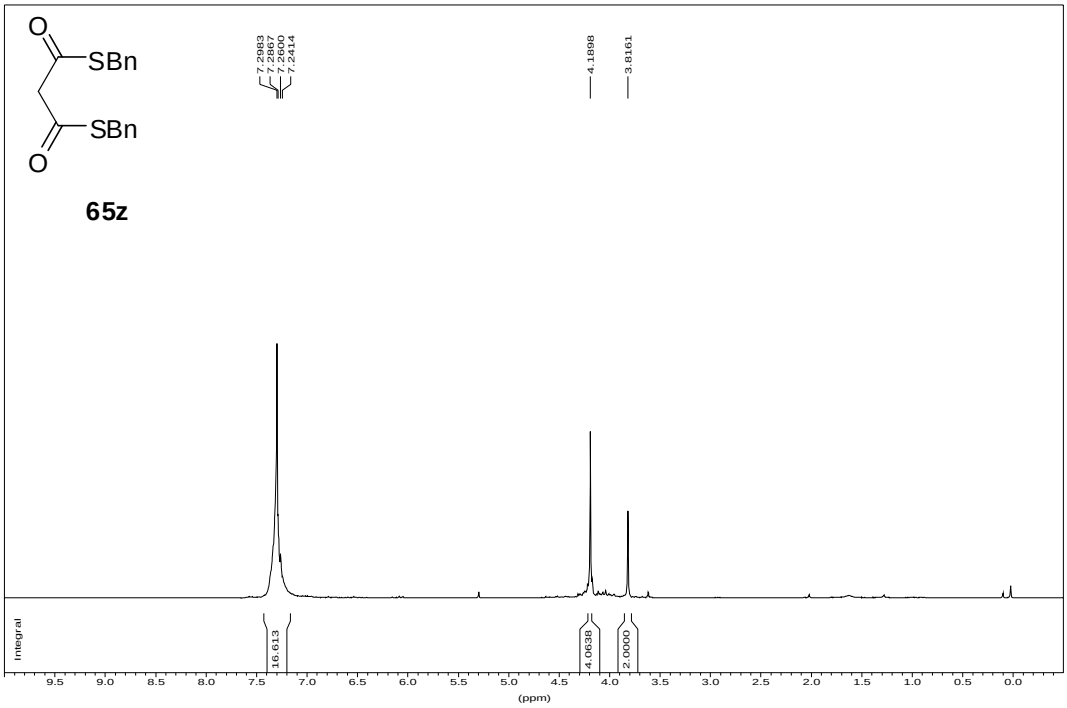

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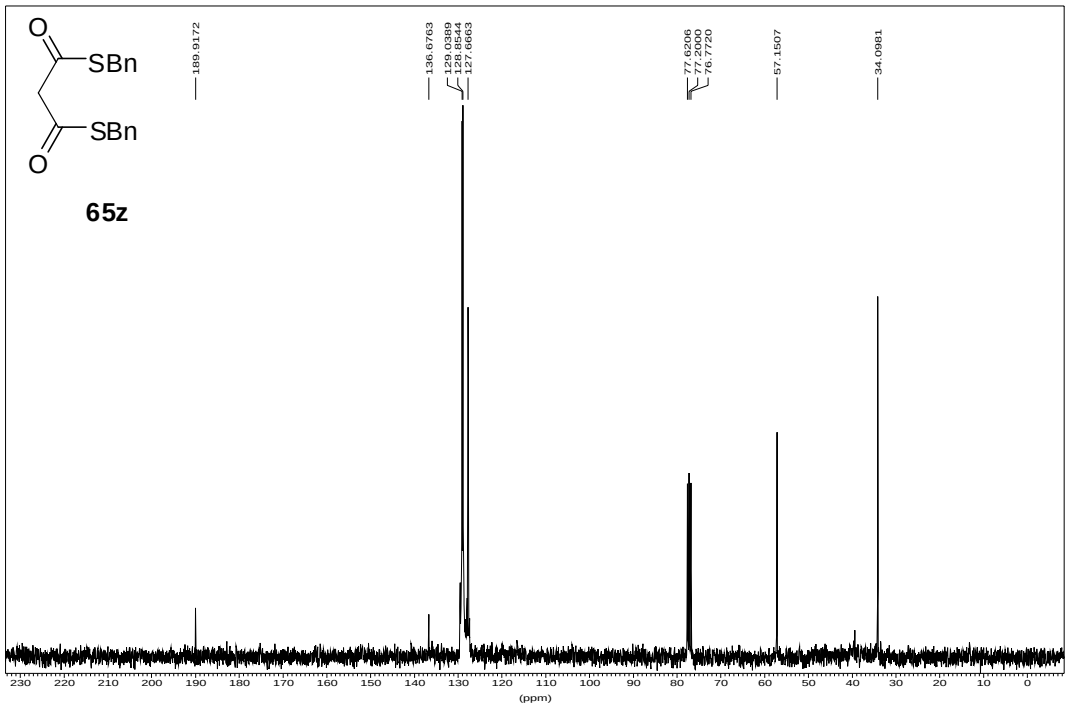

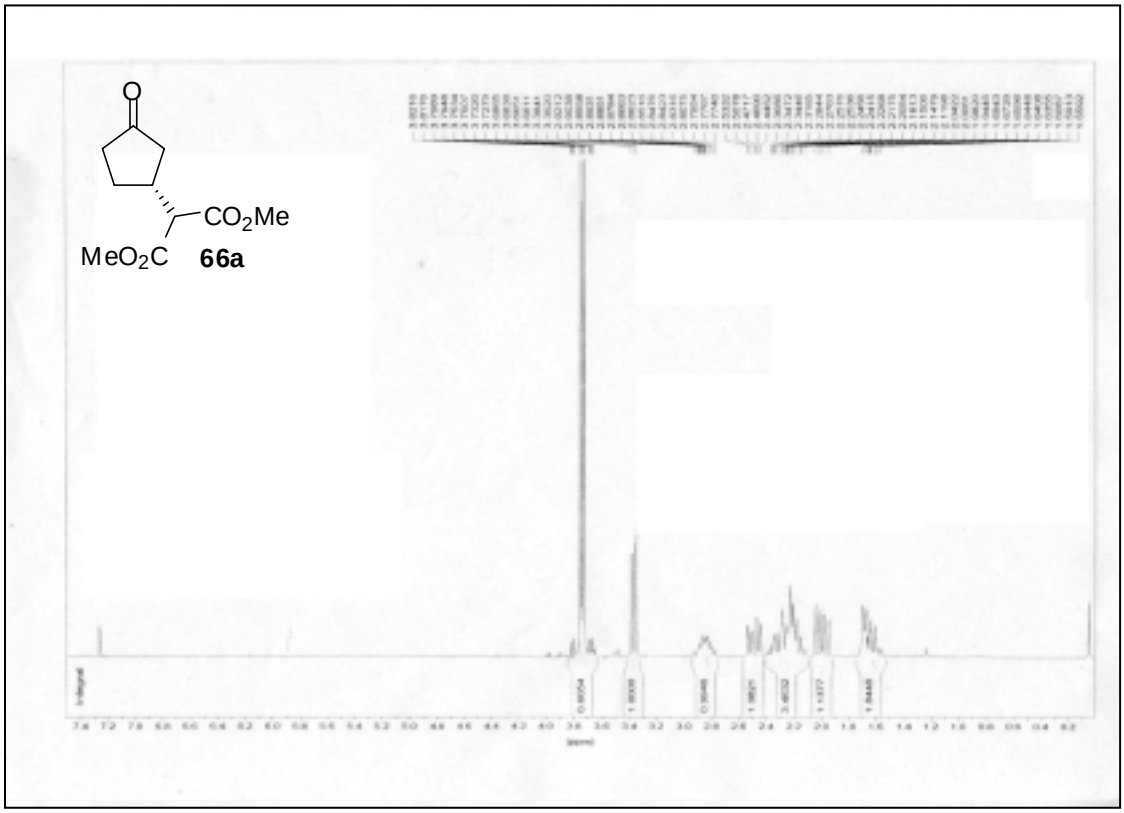
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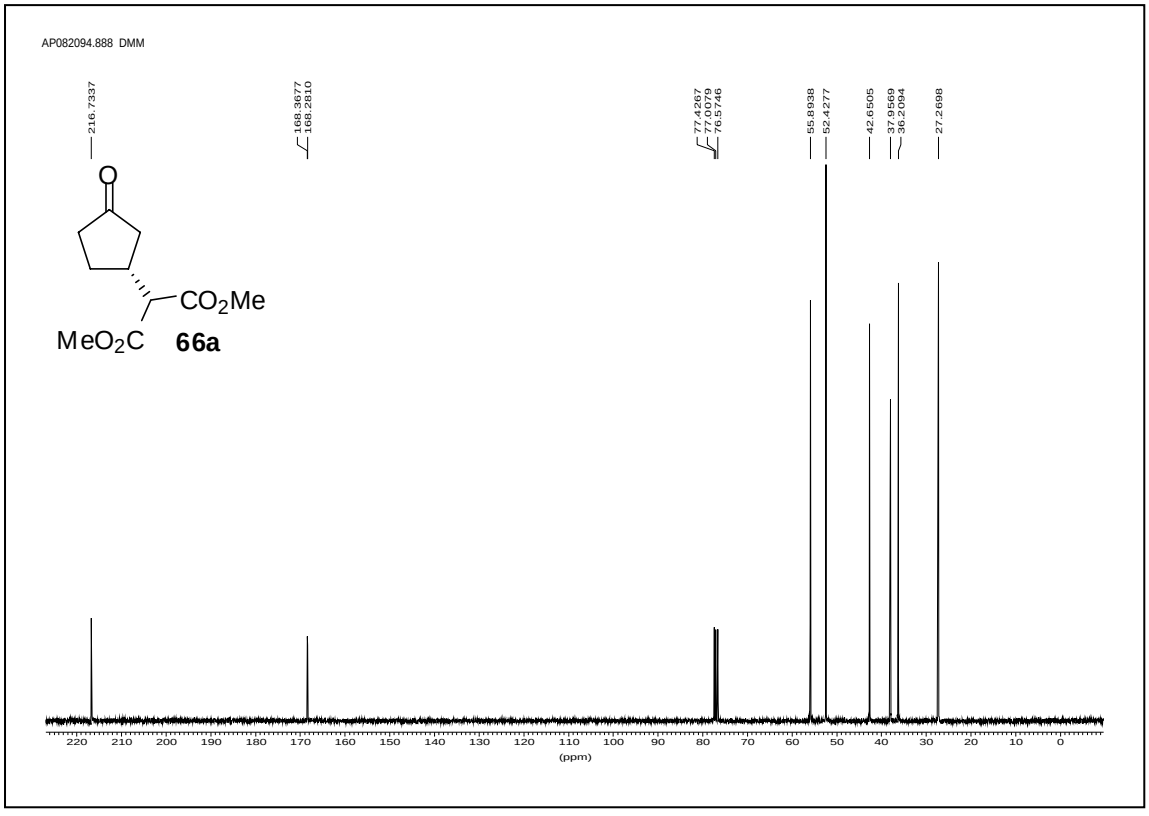
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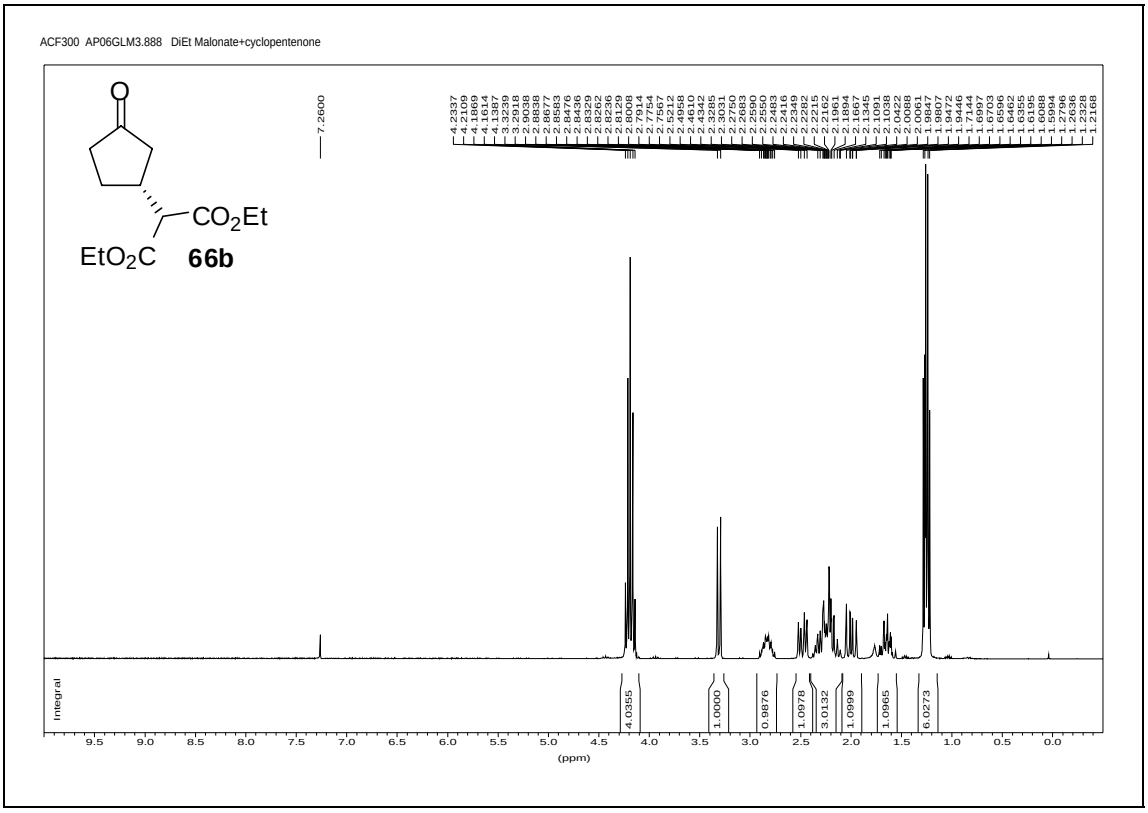
O
CO2Me
MeO2C
66a
(ppm)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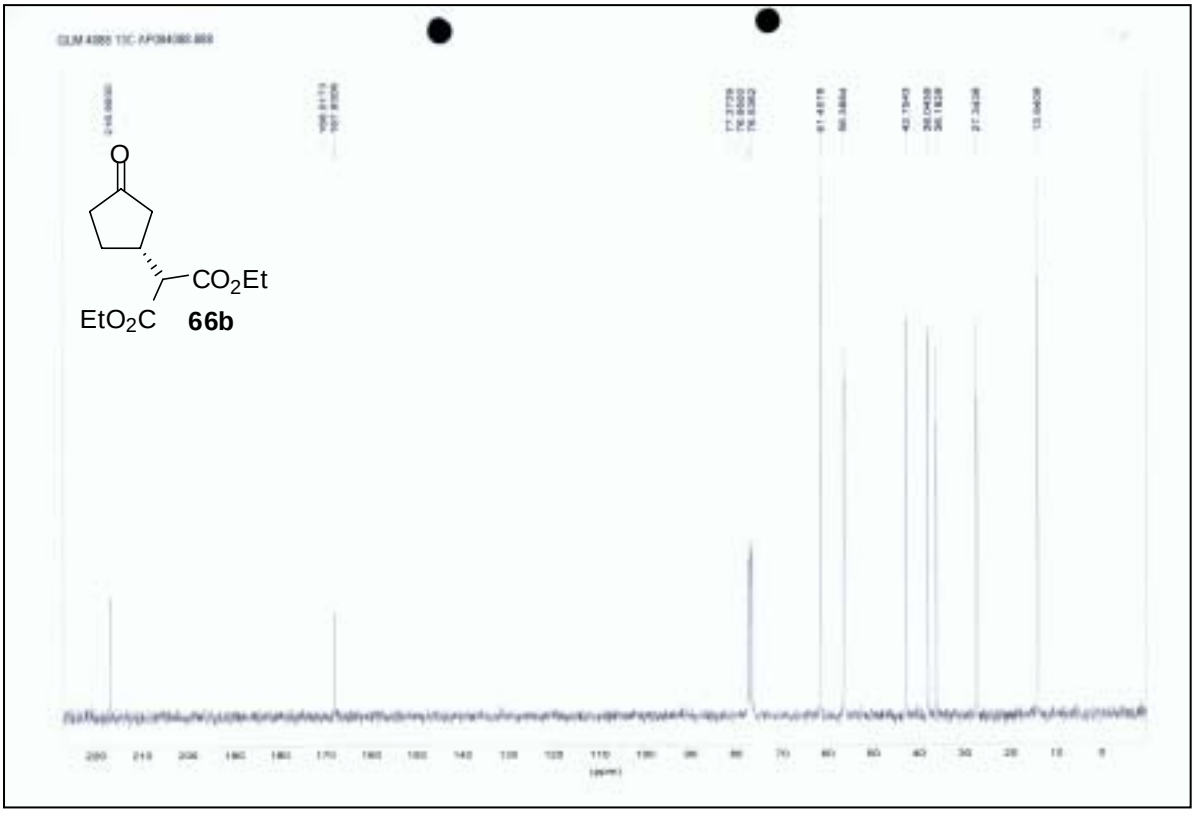
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66b

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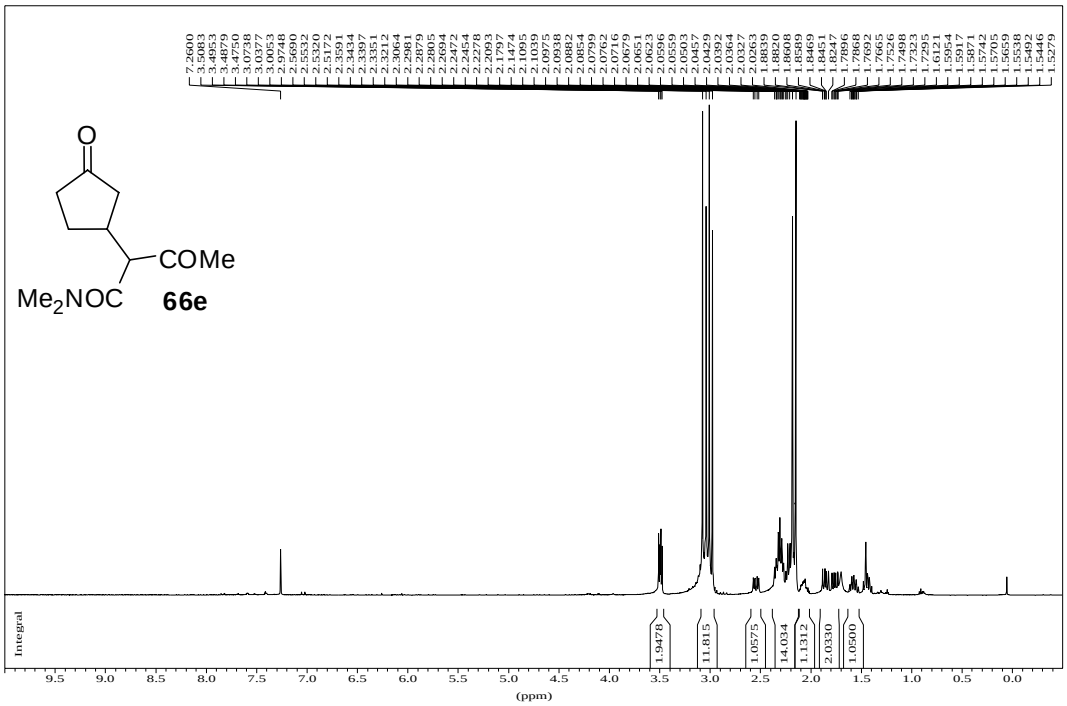

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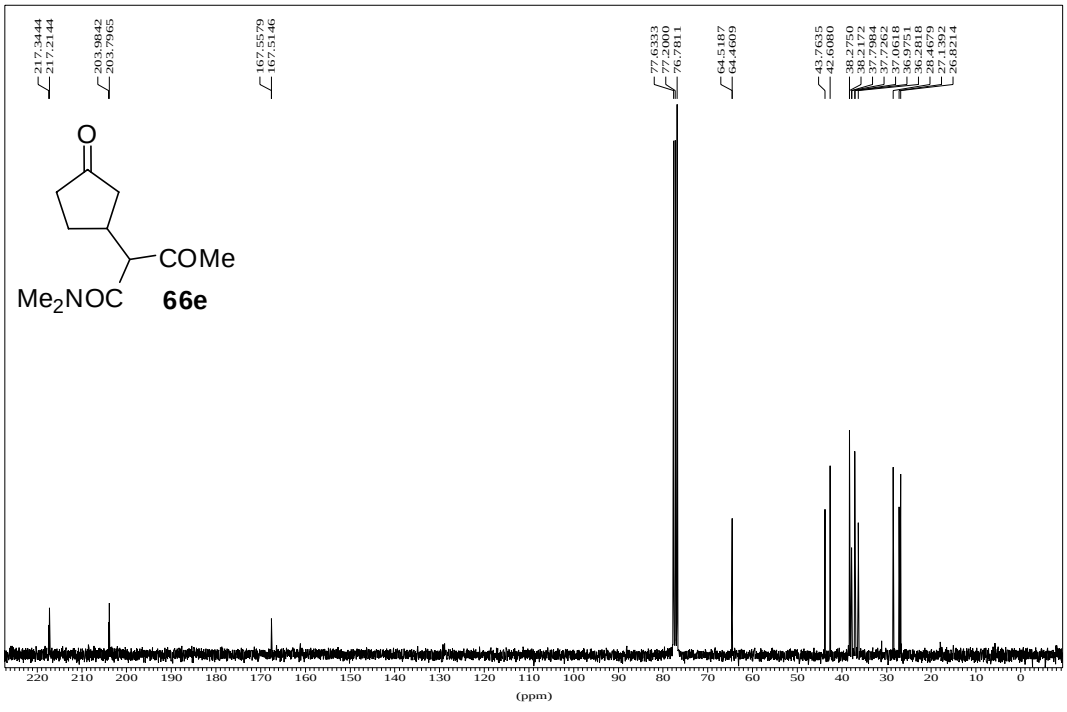

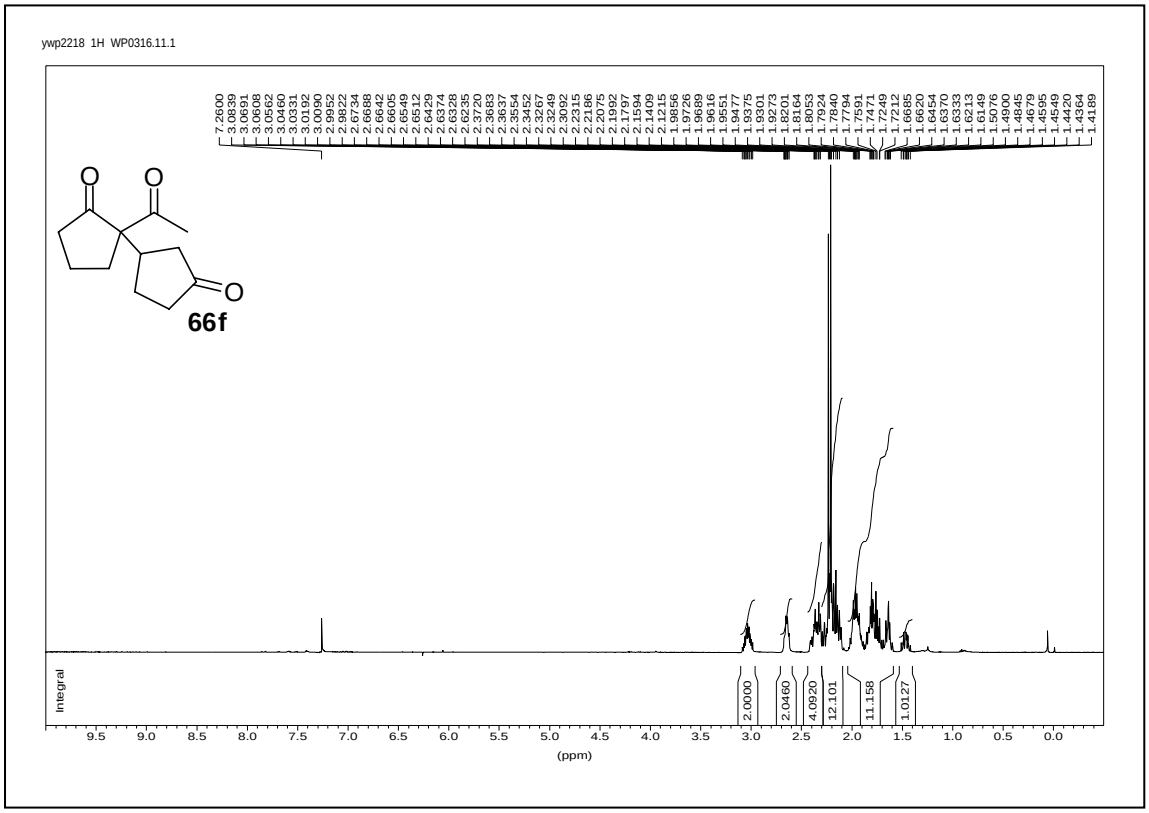
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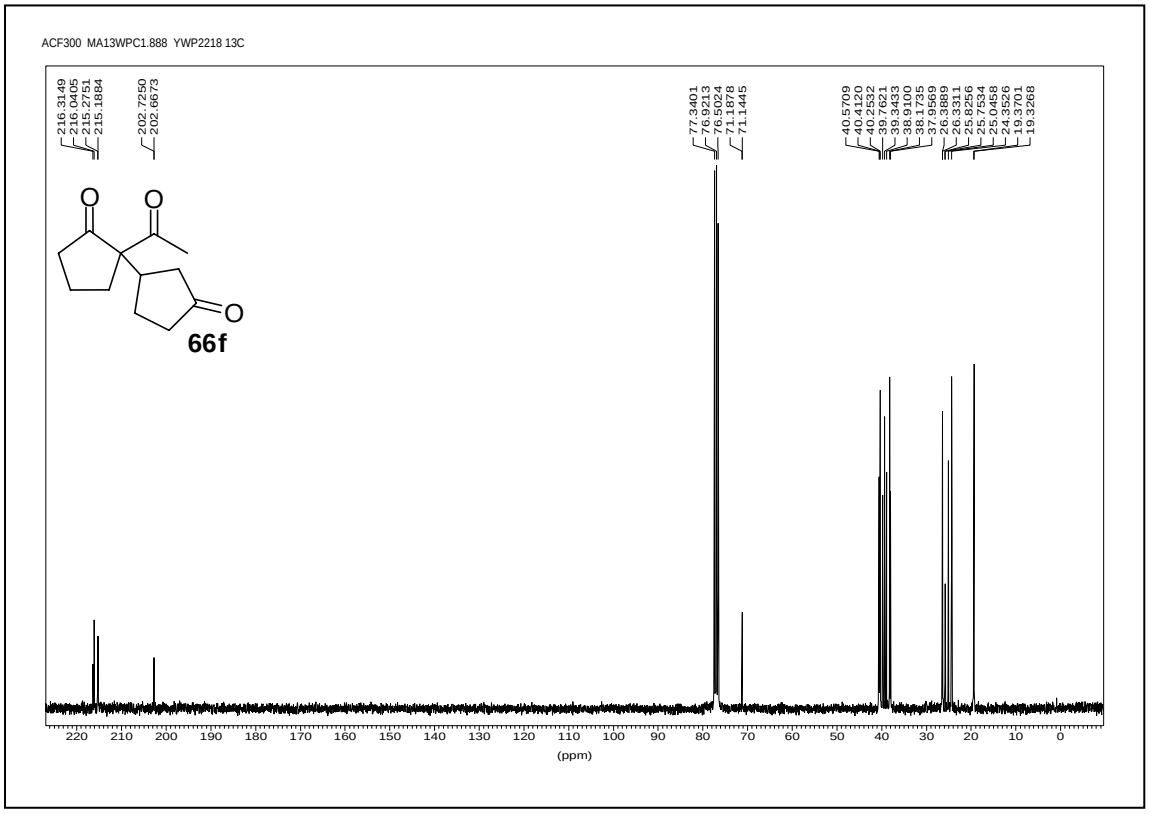
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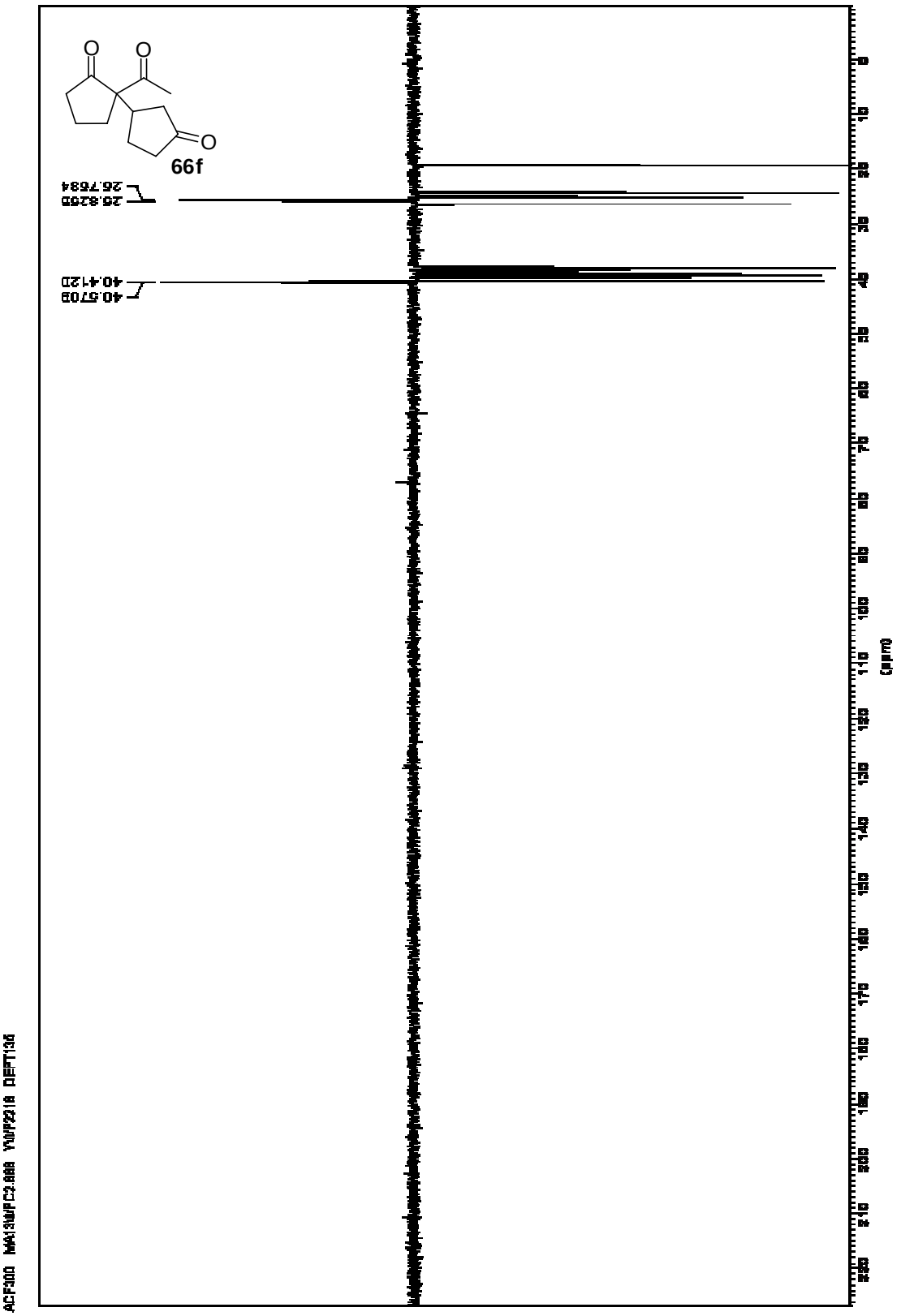
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O
O
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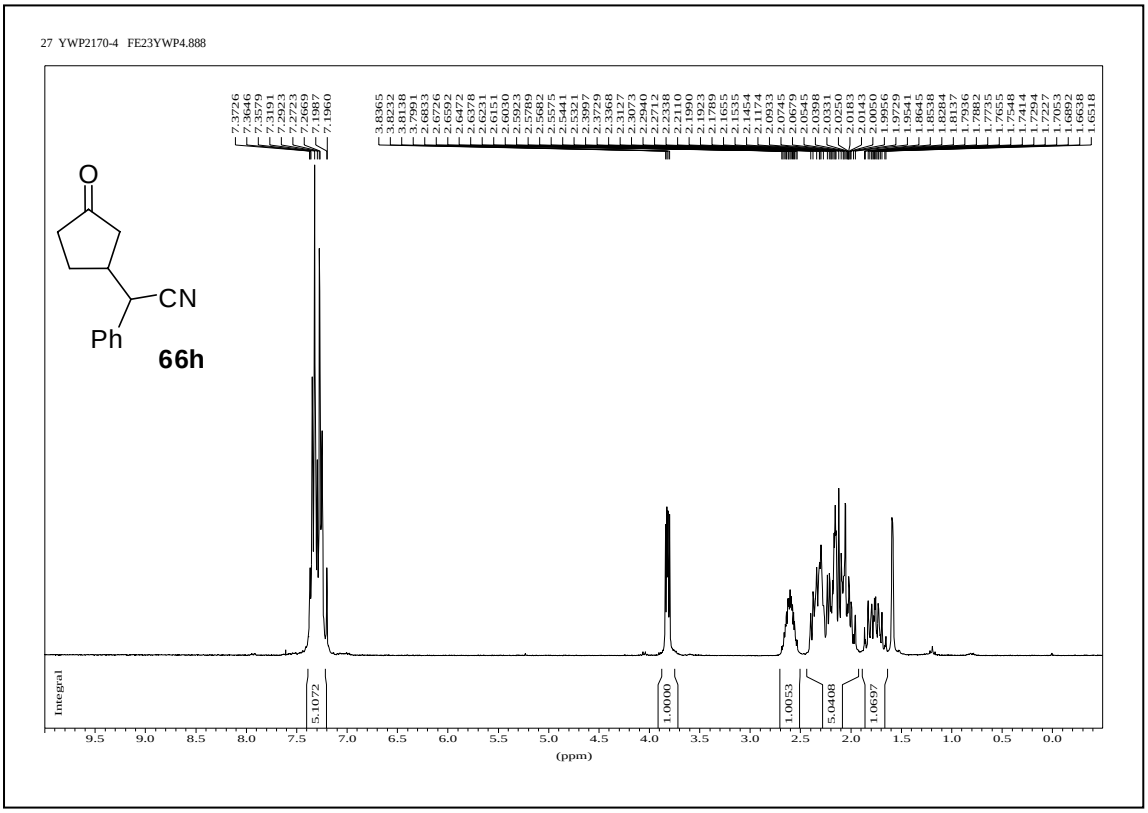
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Ph
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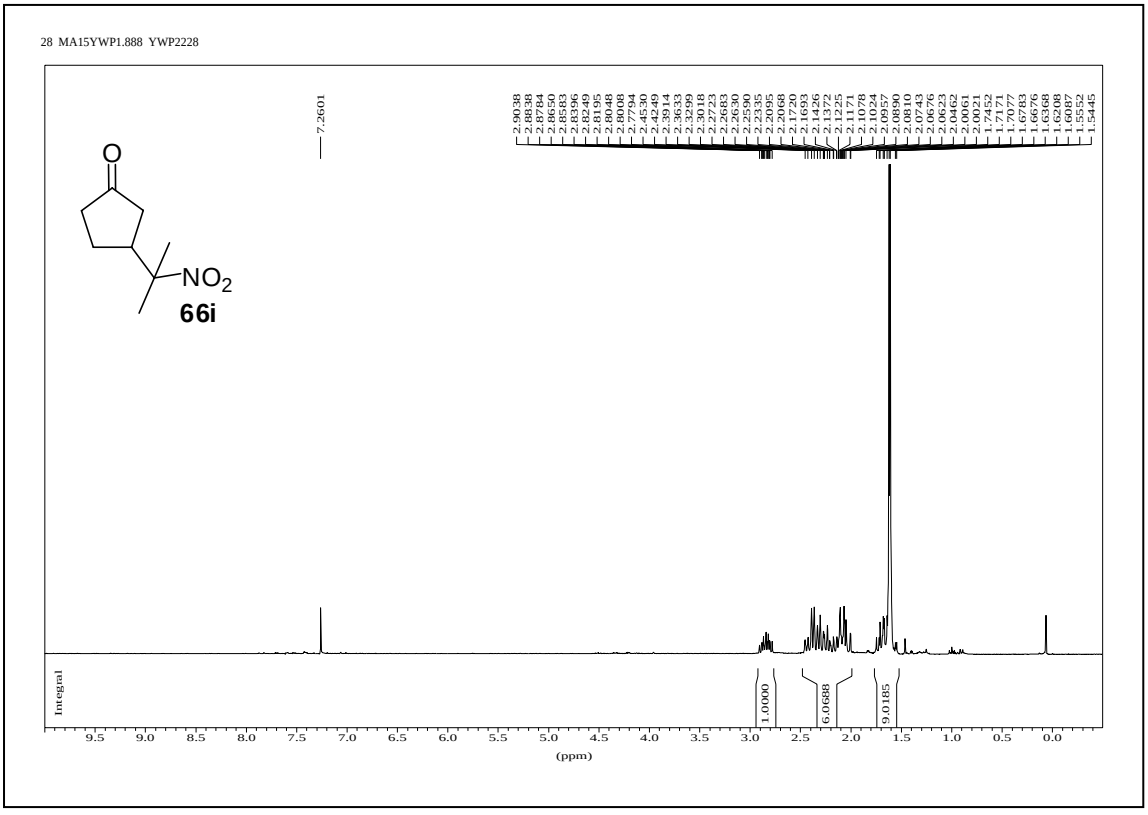
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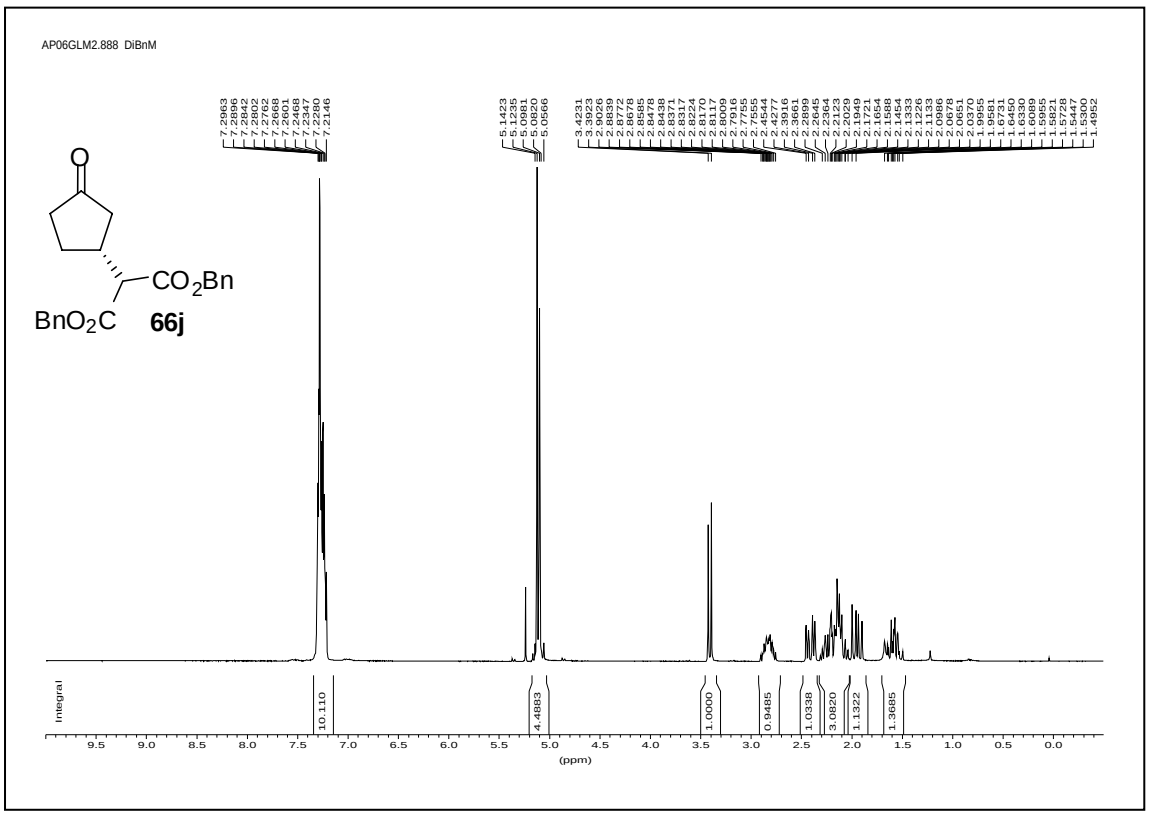
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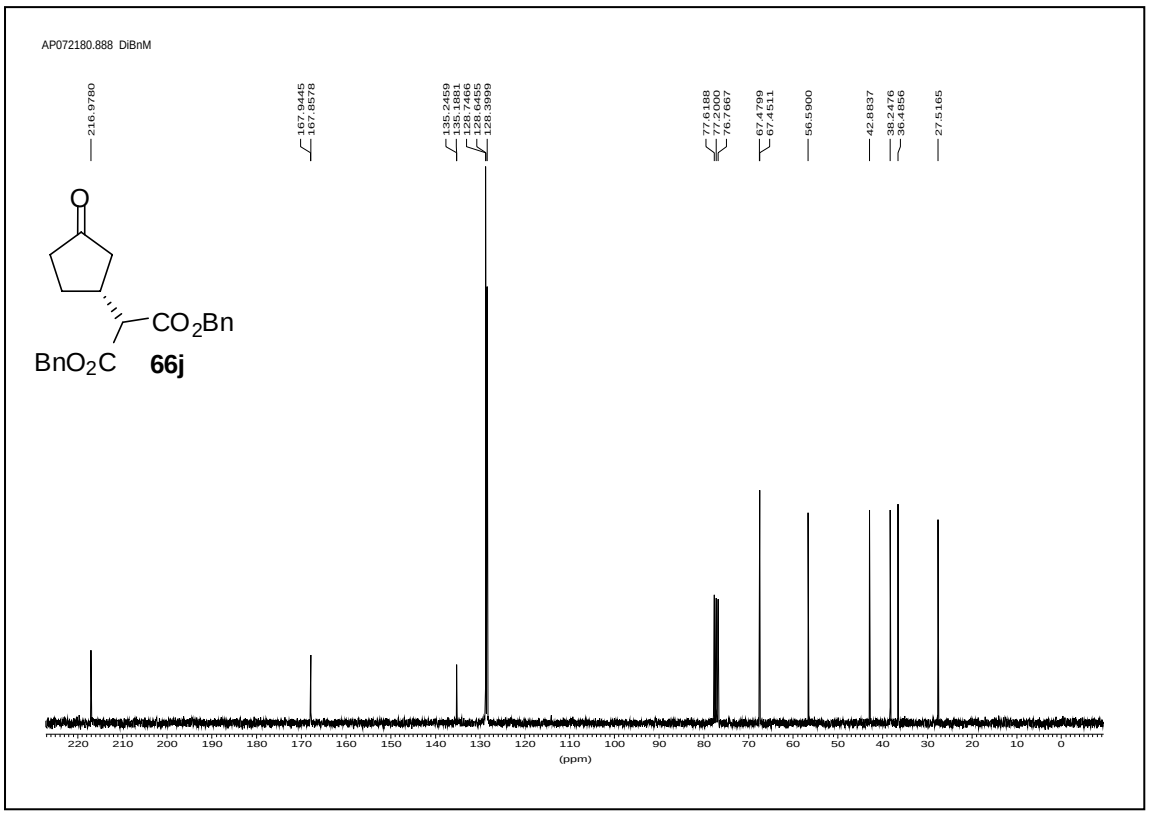
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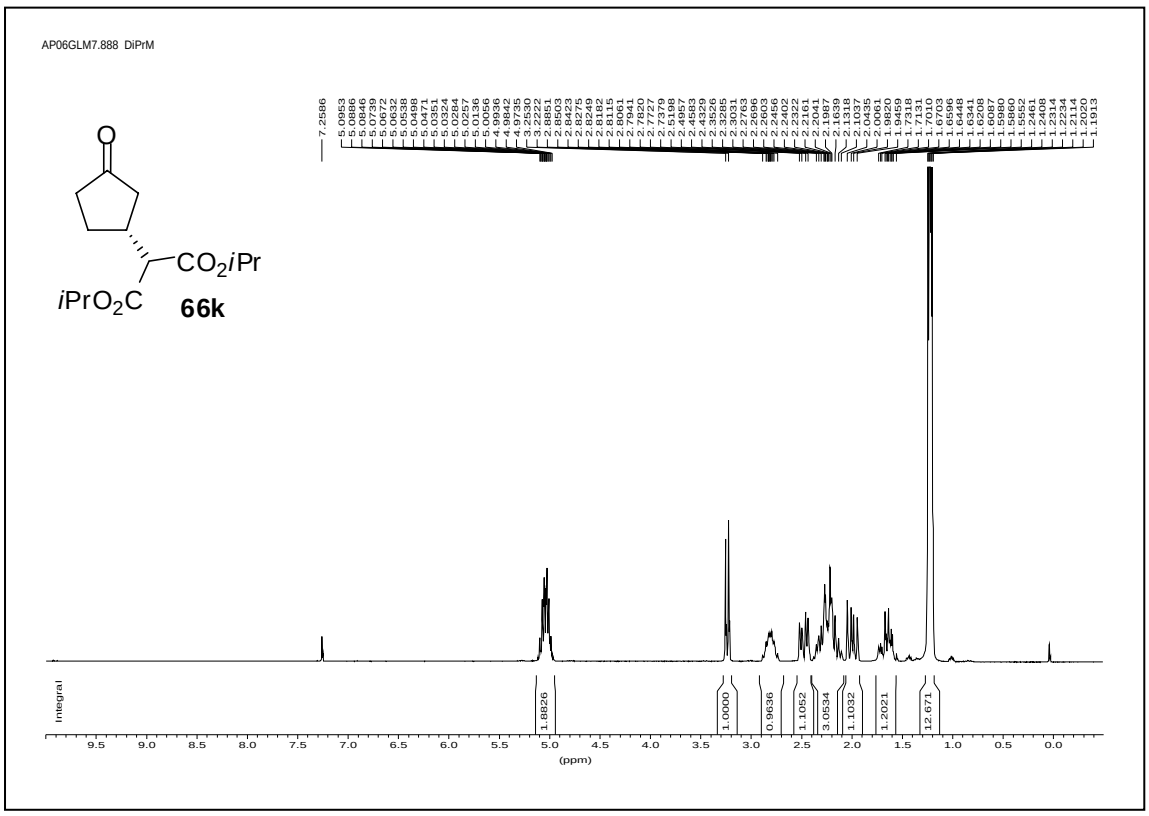
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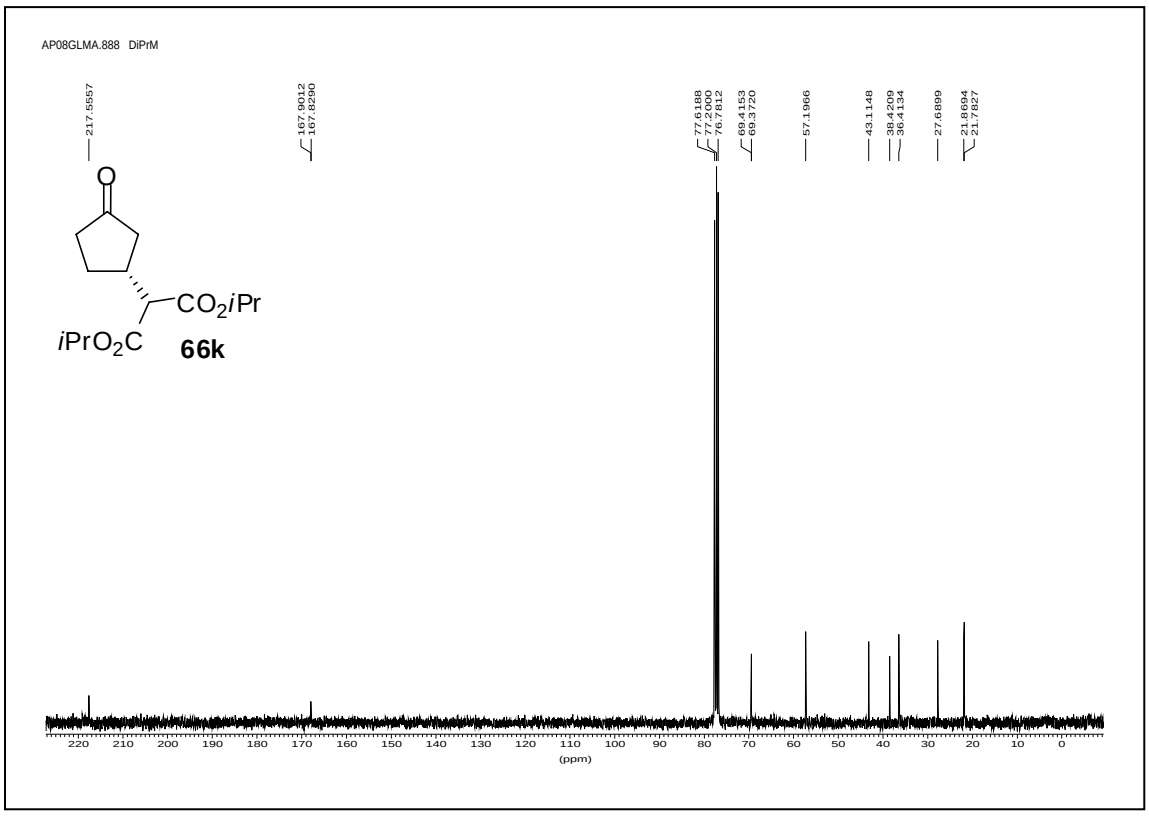
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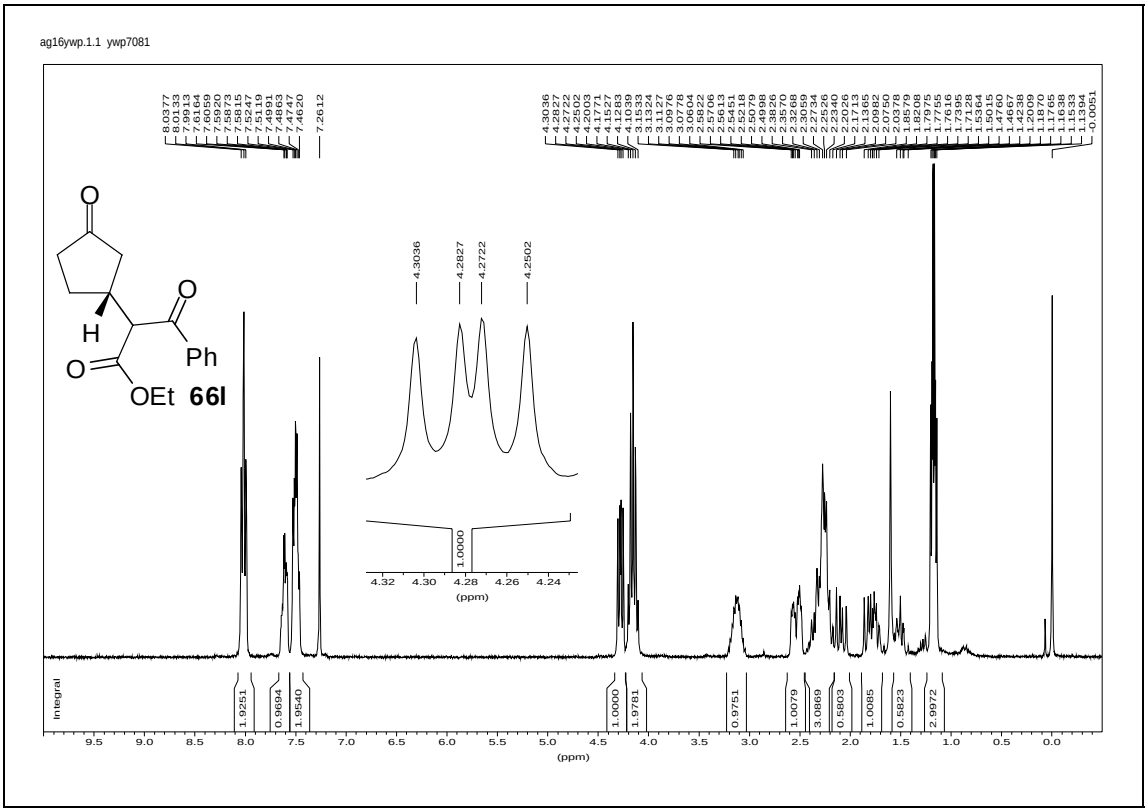
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O
Ph
O
OEt 66l
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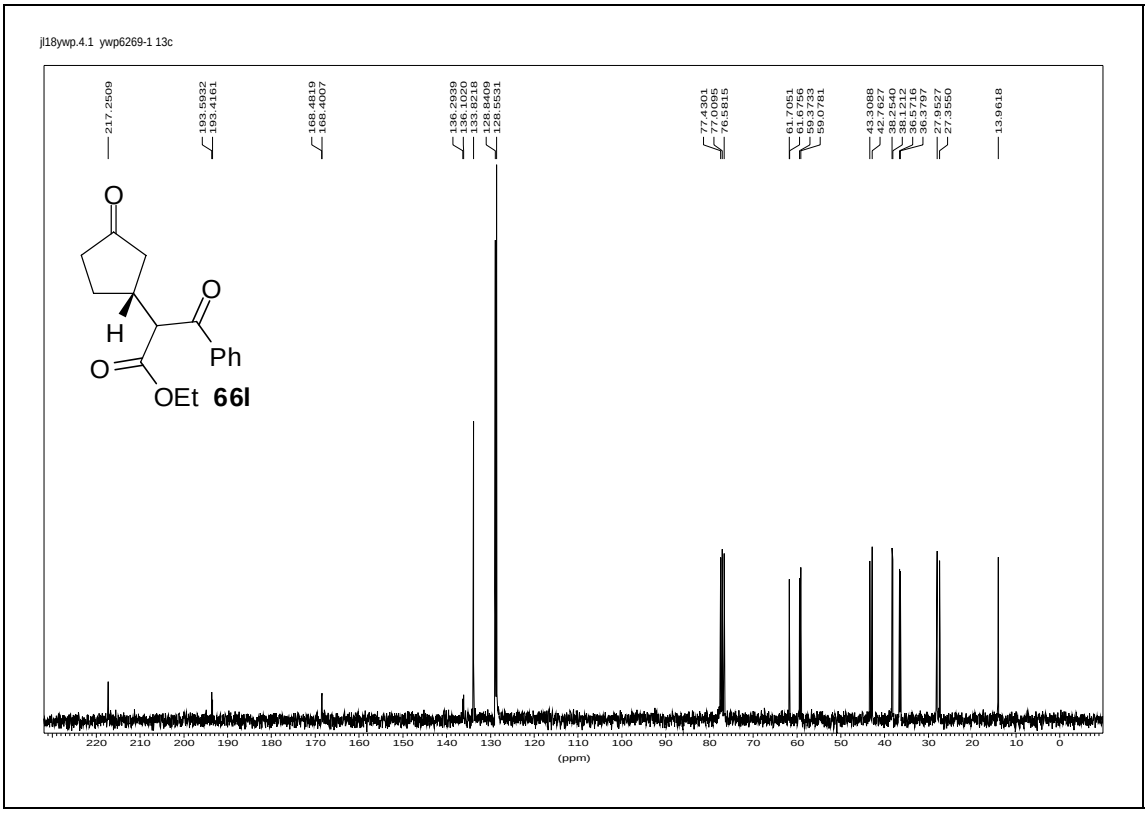
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O
Ph
O
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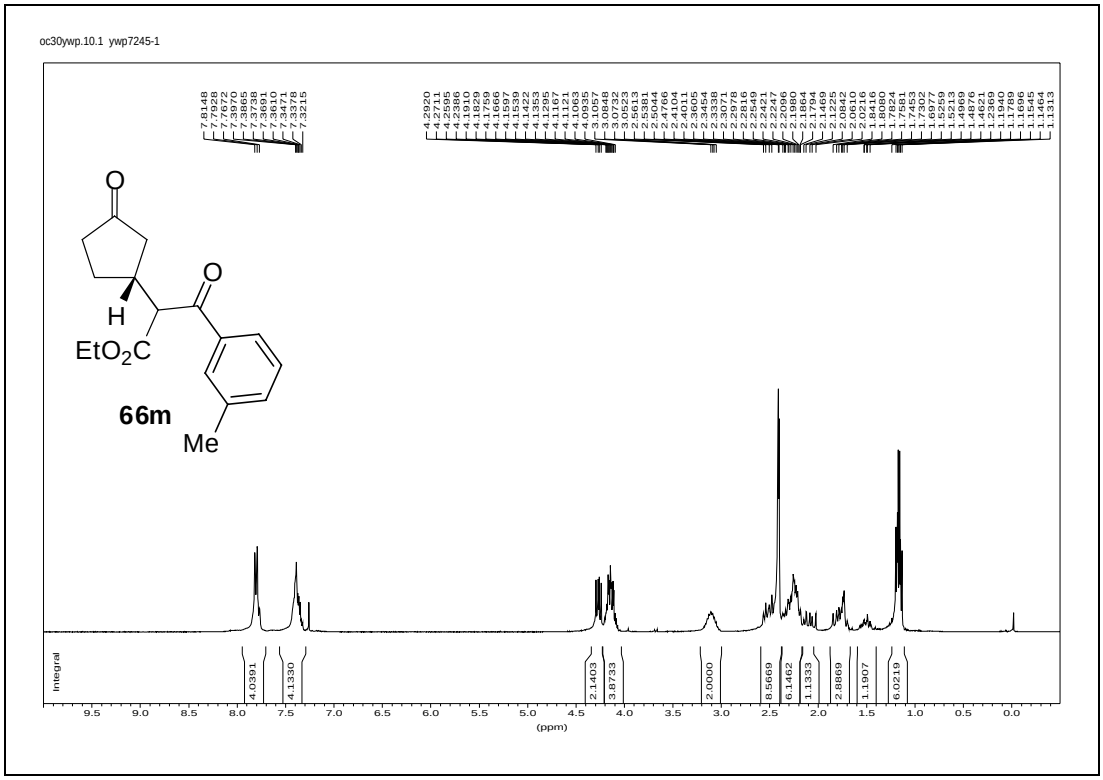
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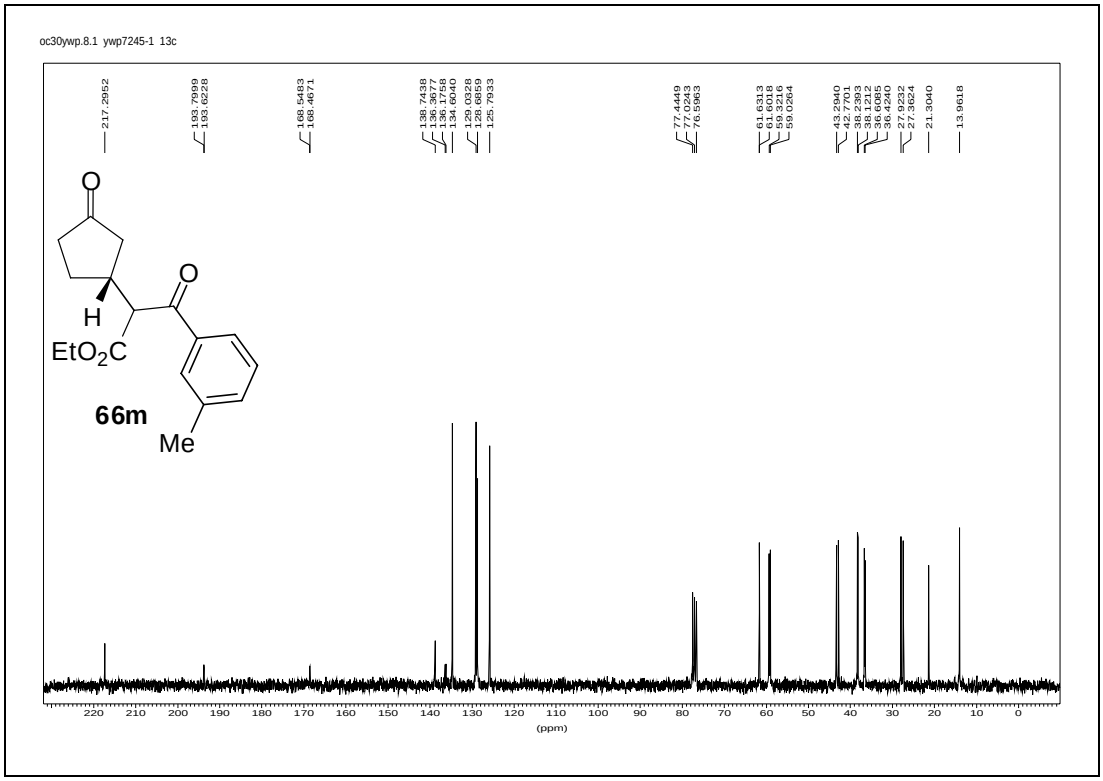
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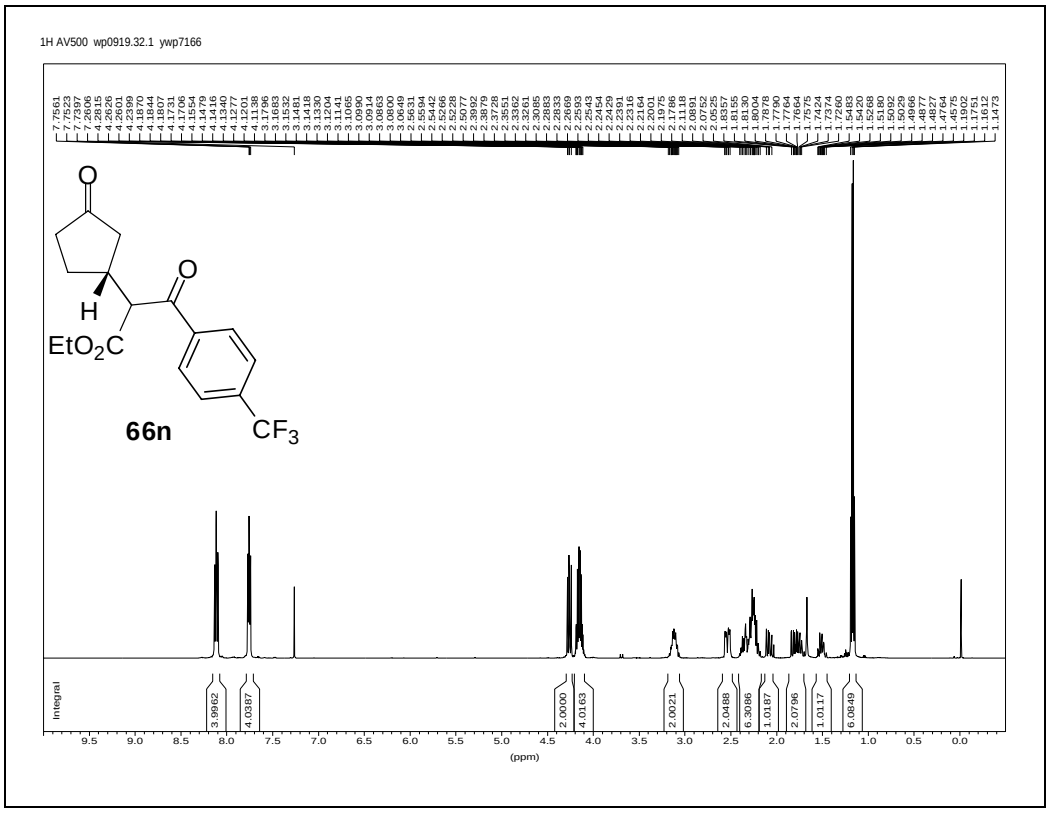
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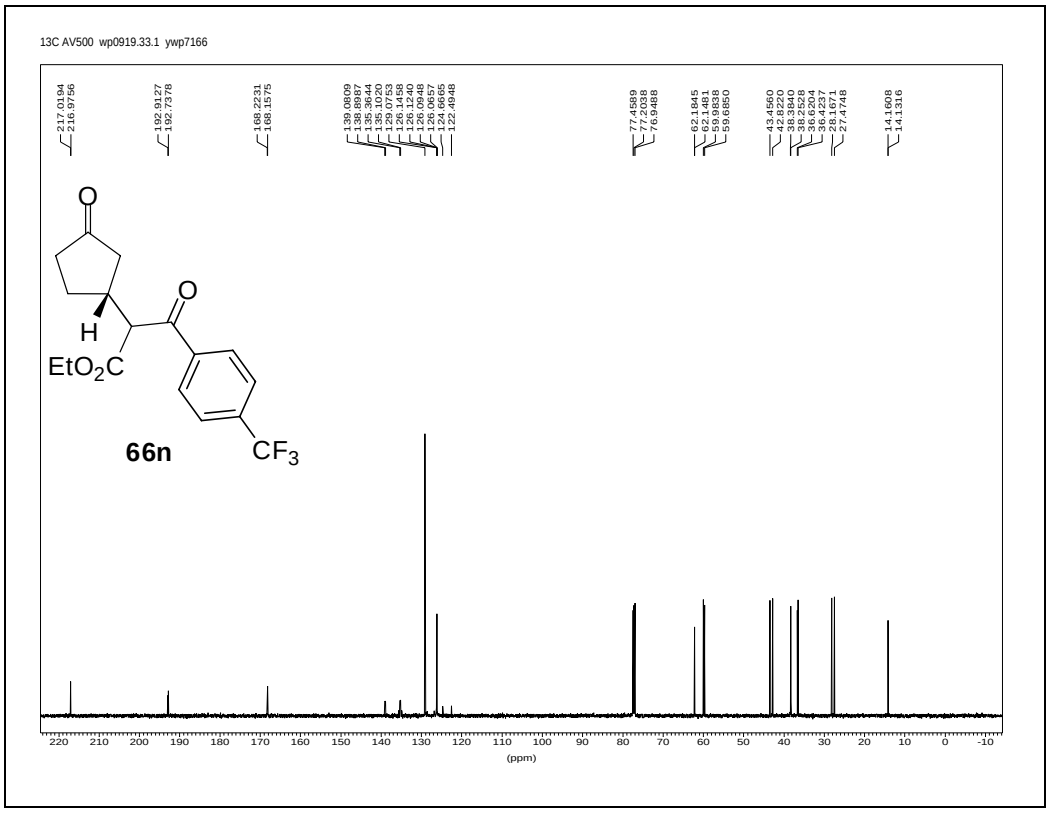
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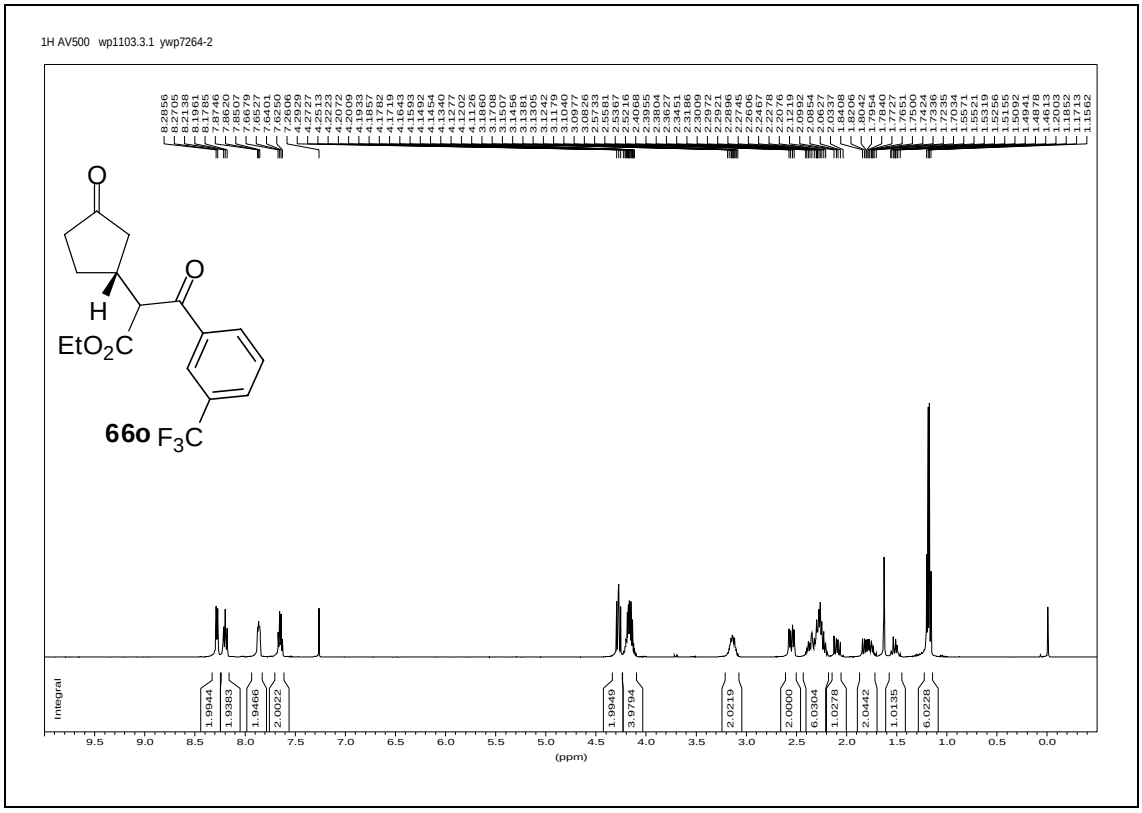
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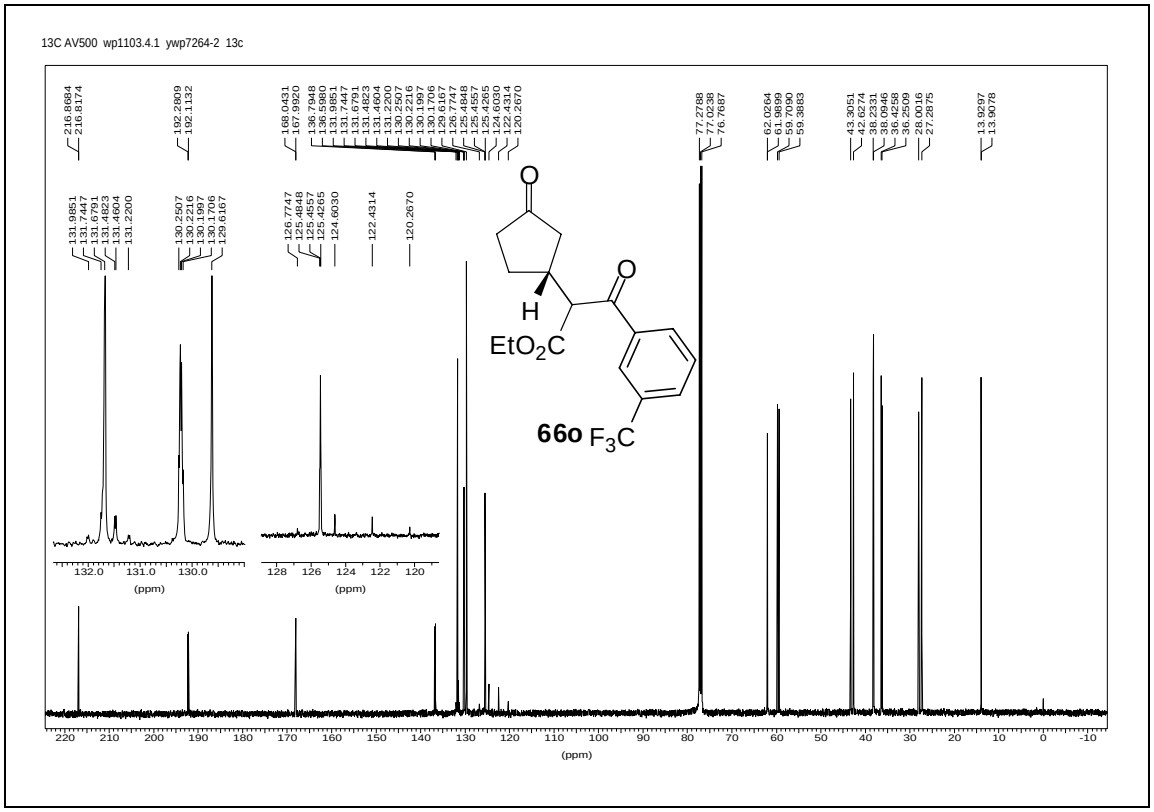
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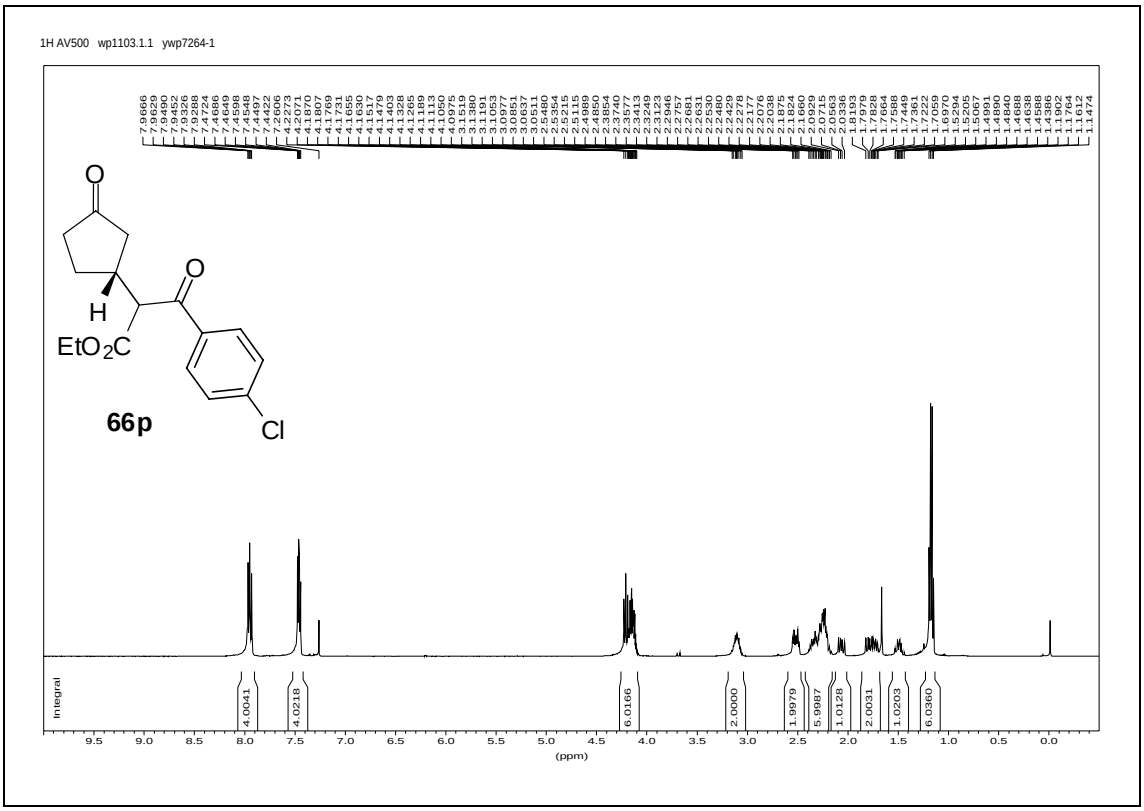
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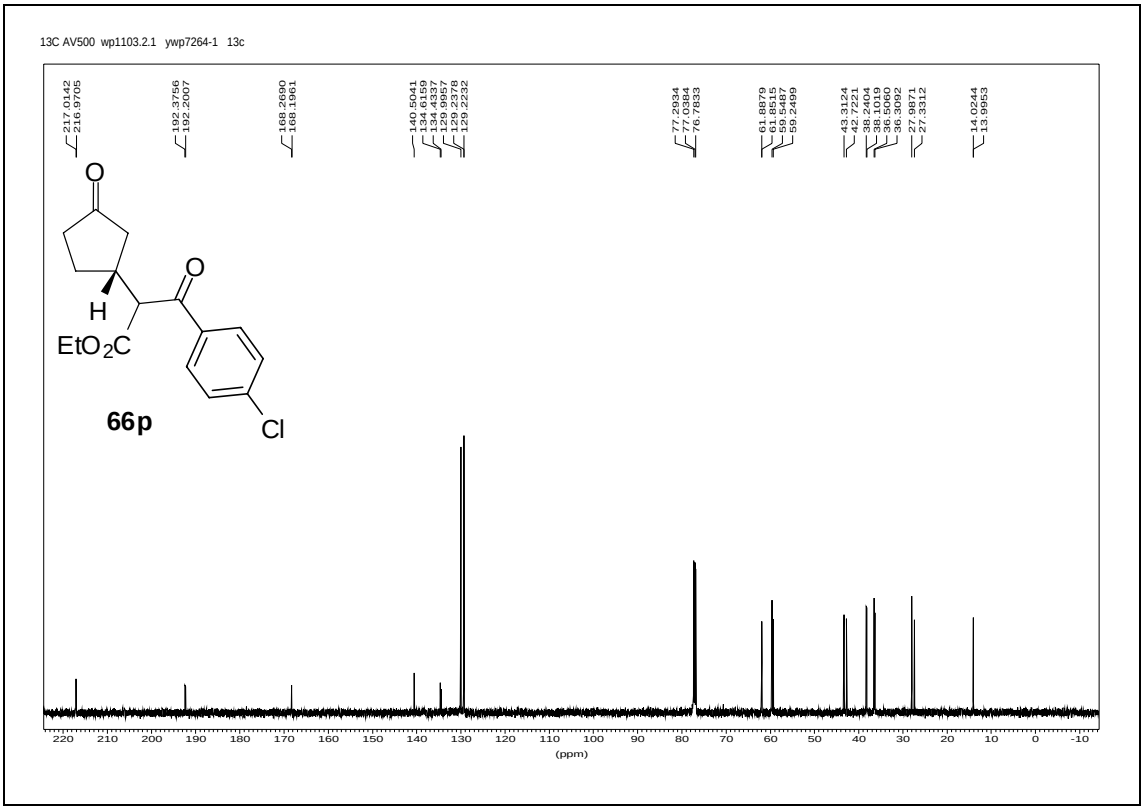
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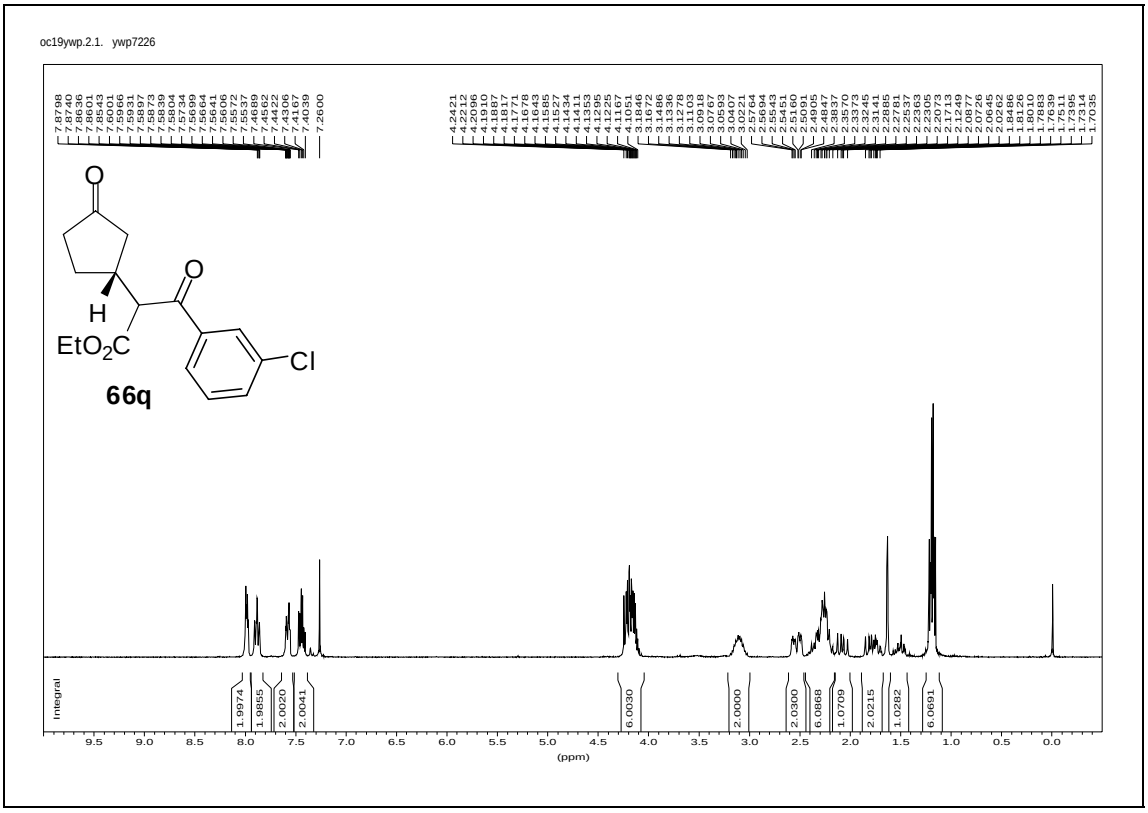
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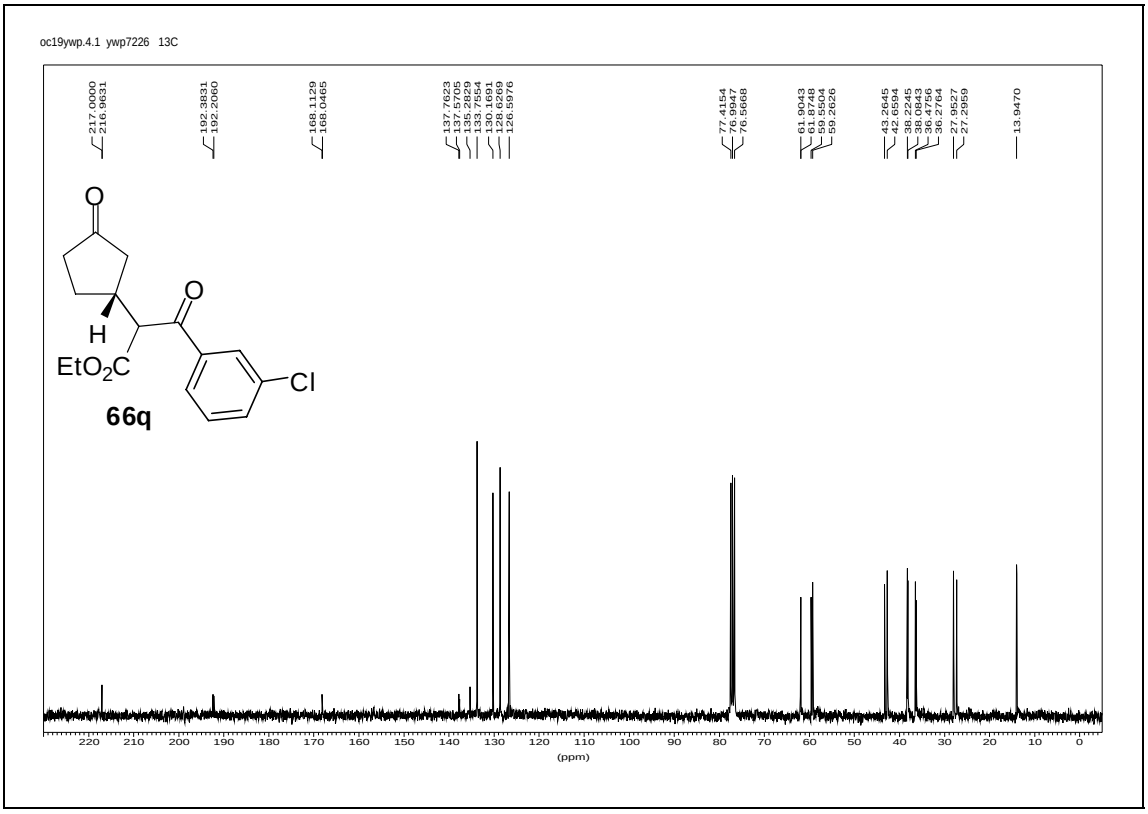
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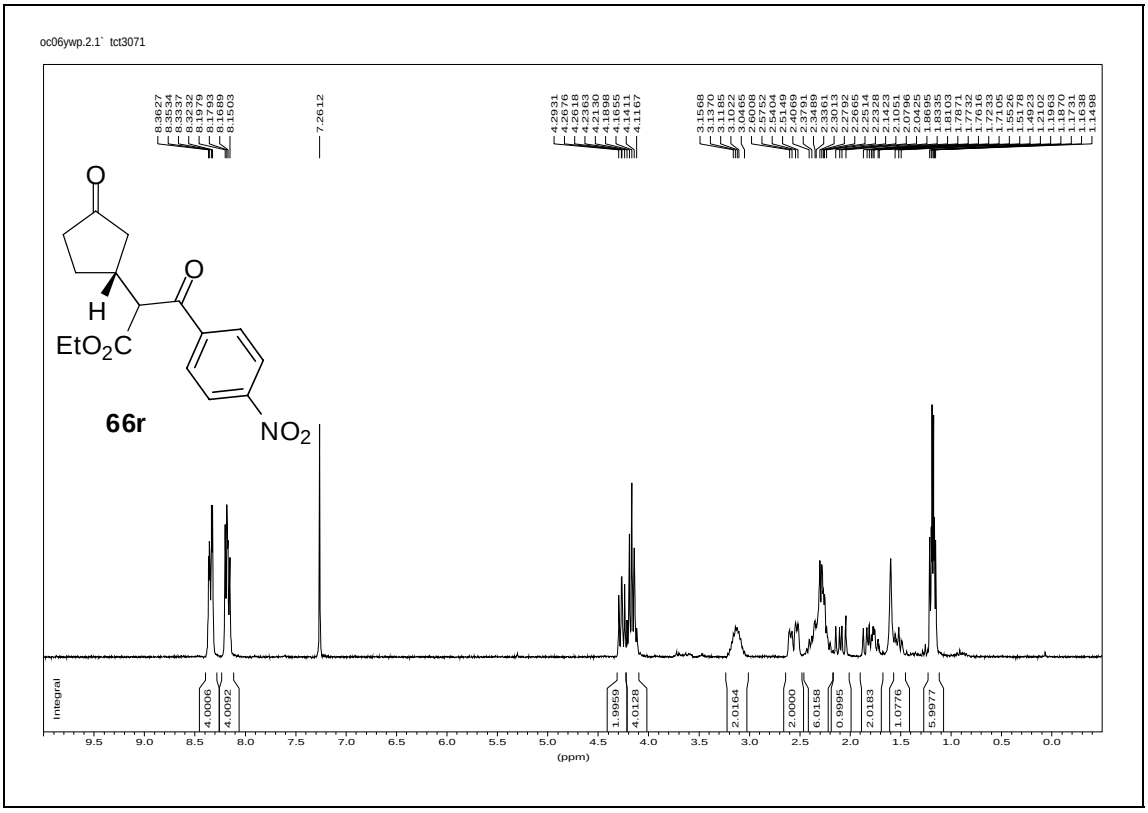
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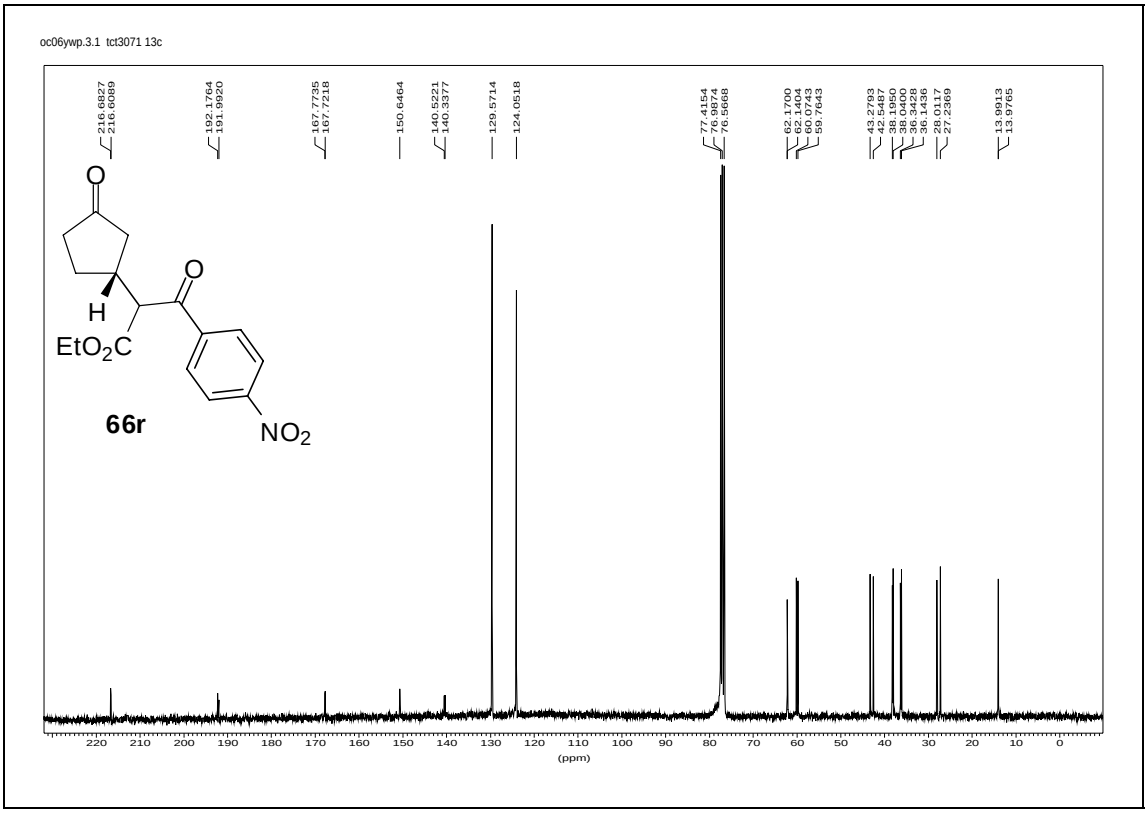
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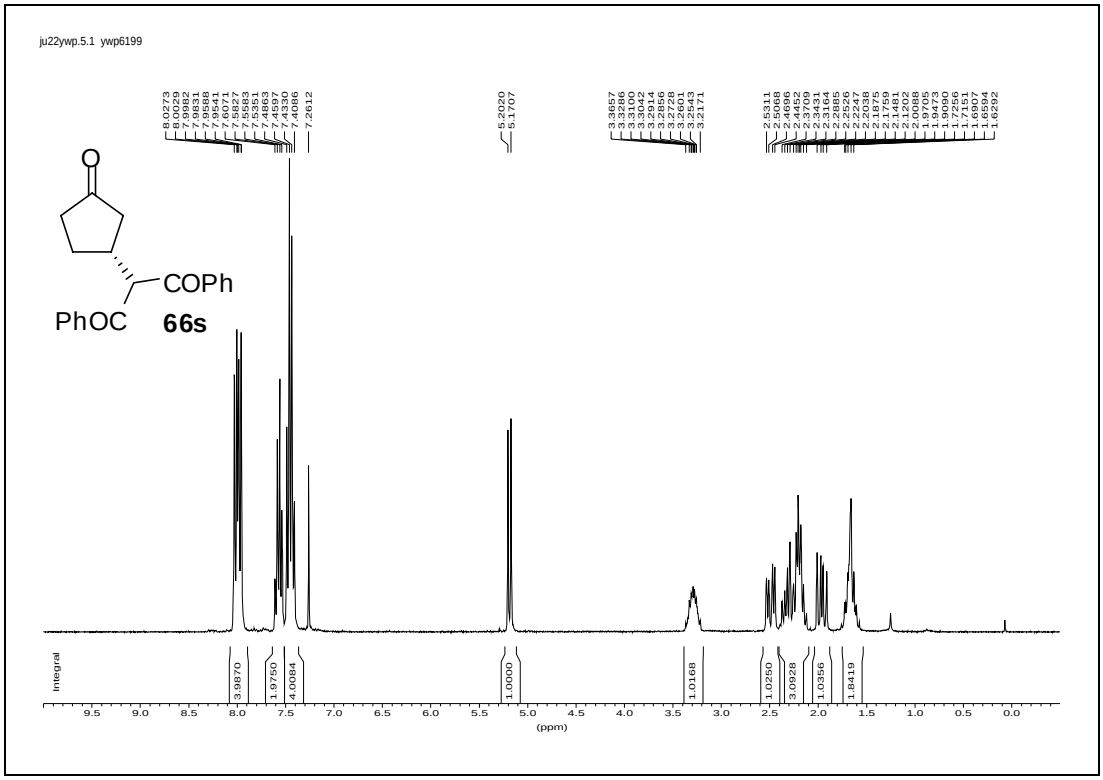
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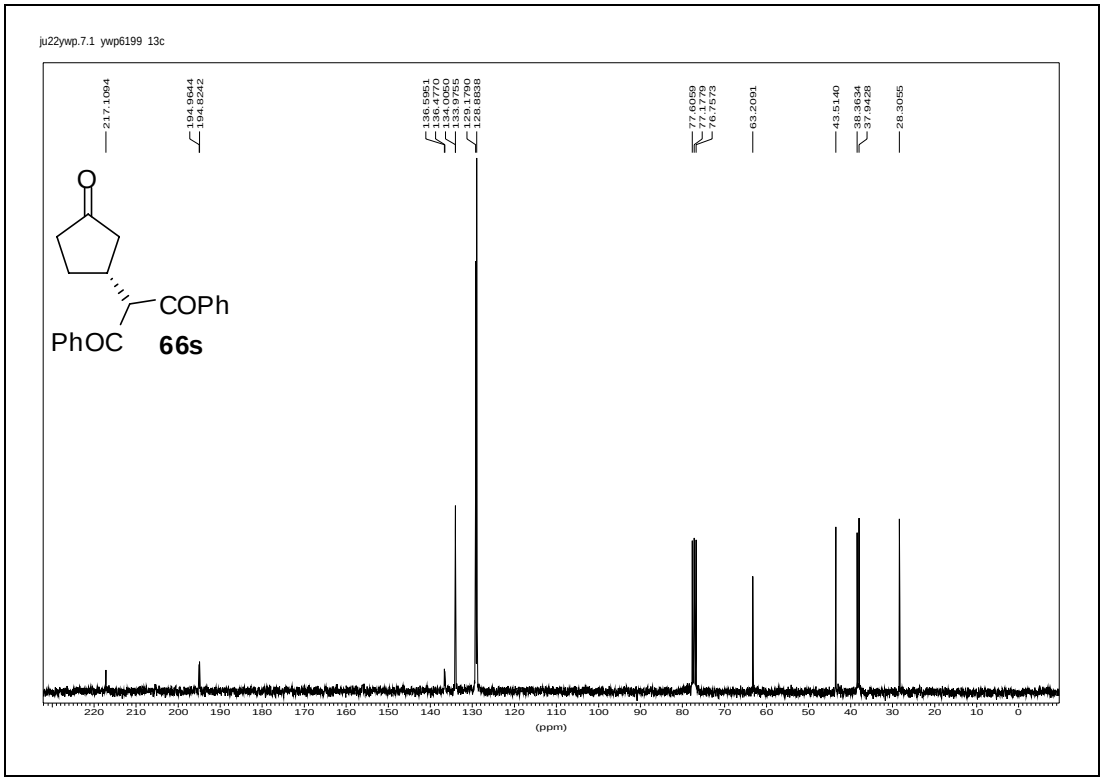
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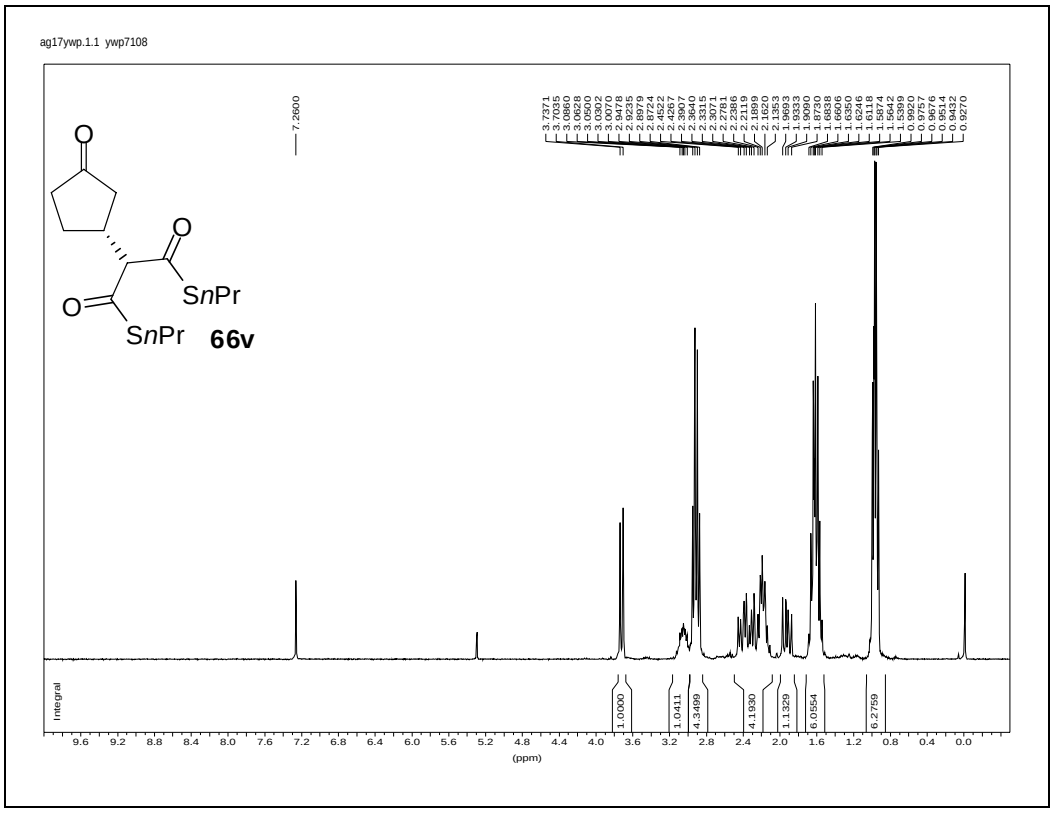
66s
(ppm)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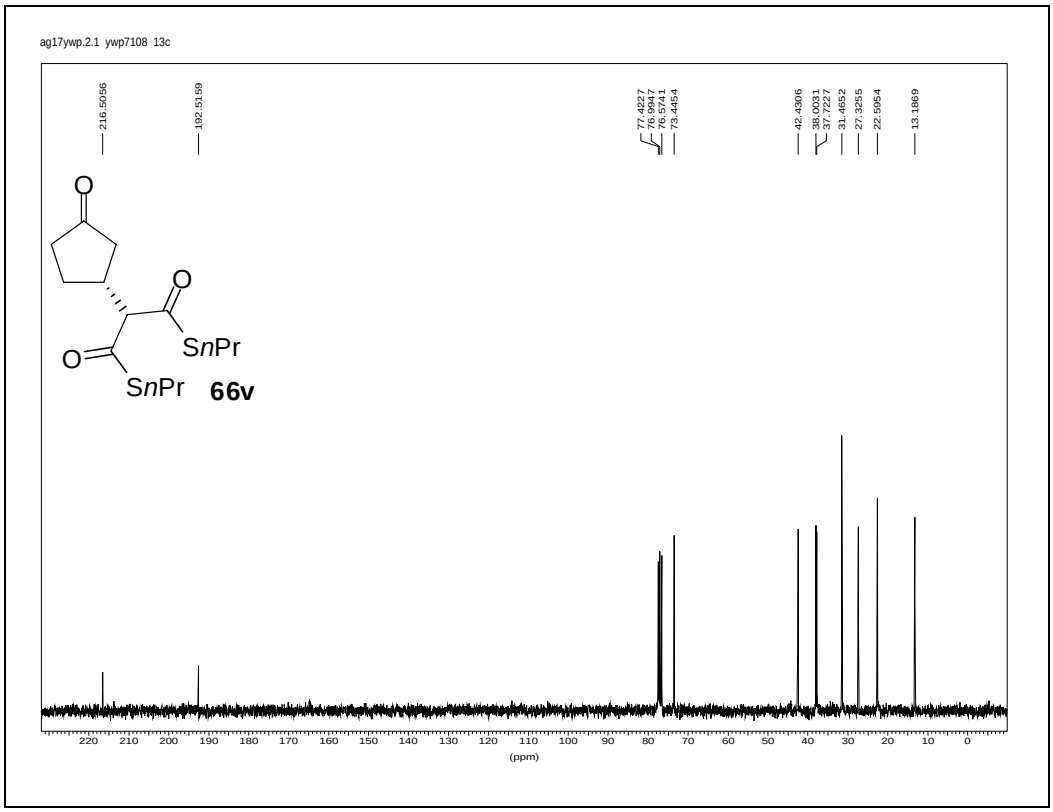
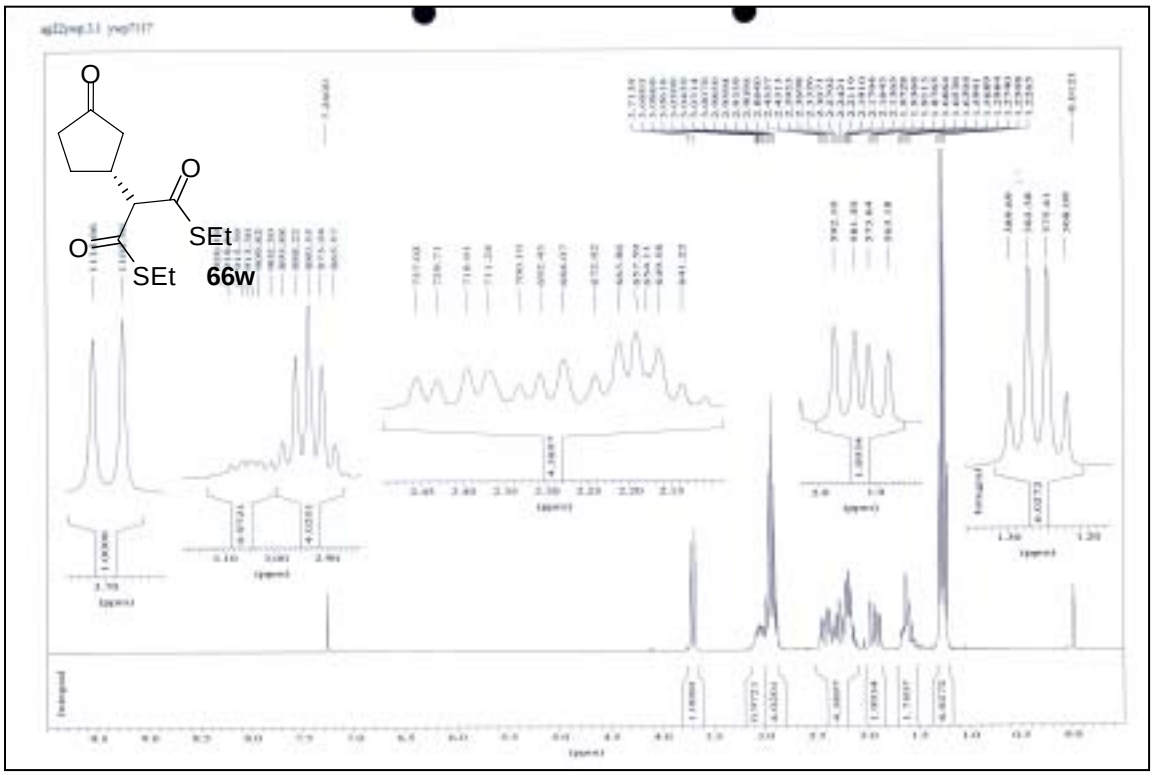
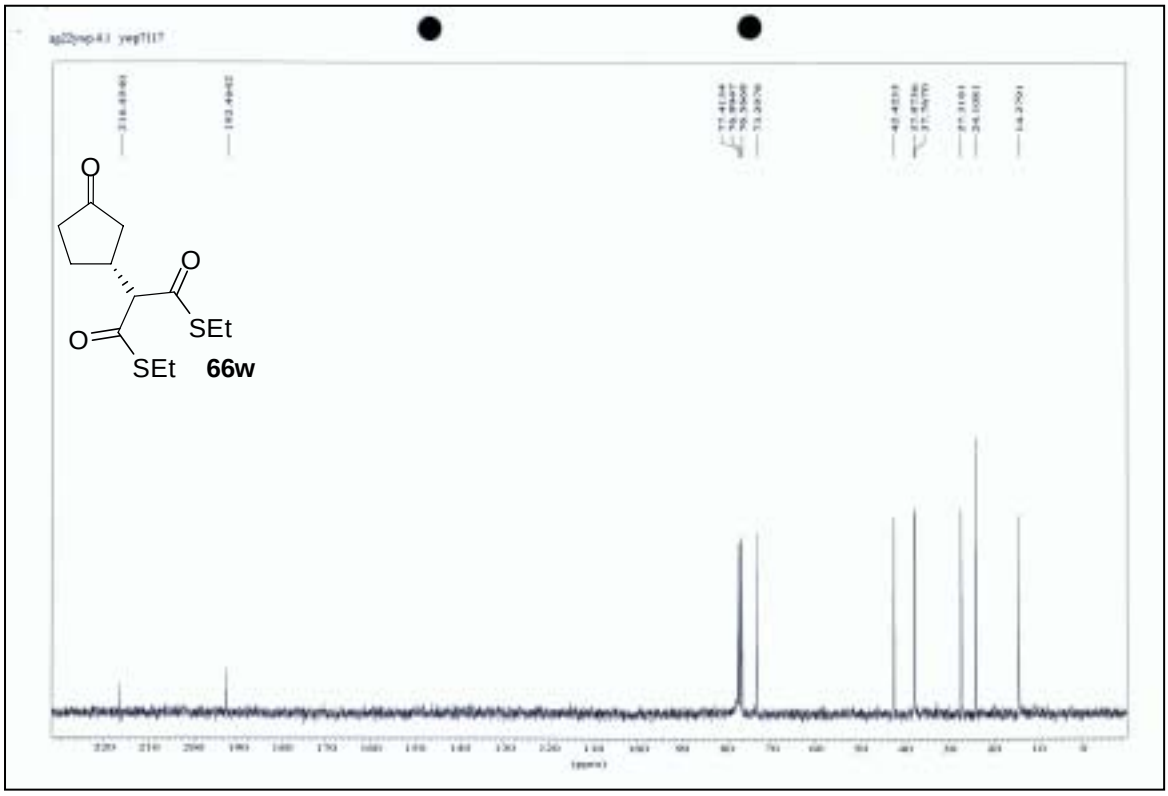
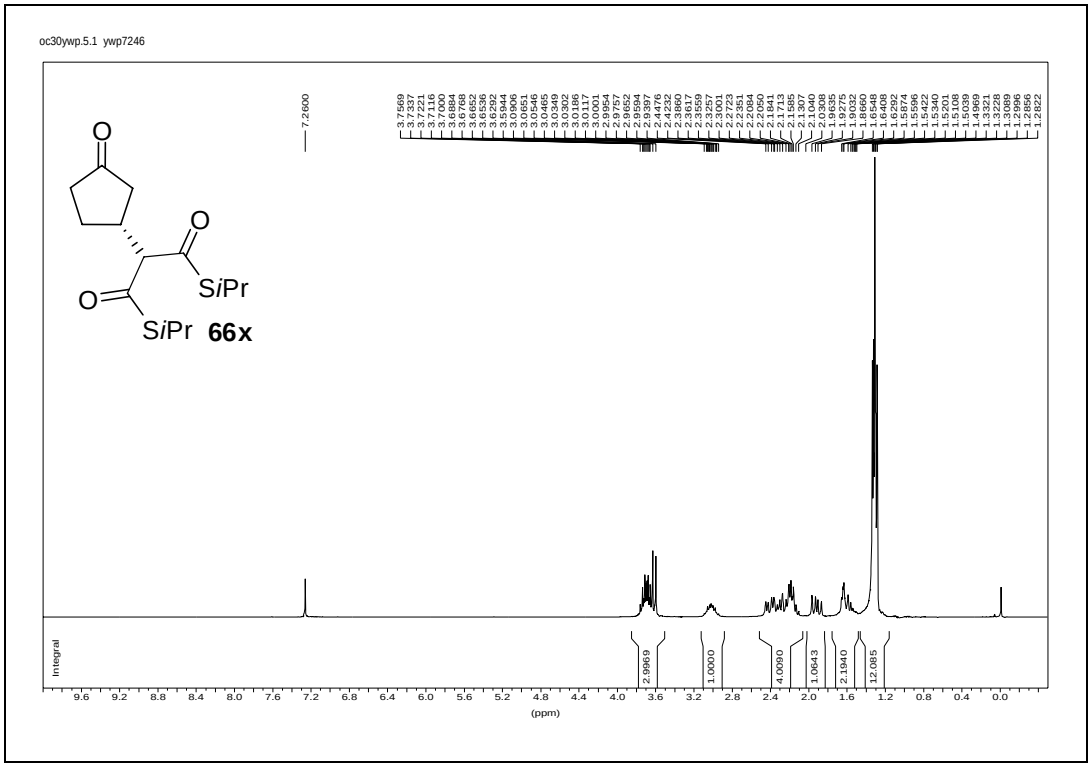
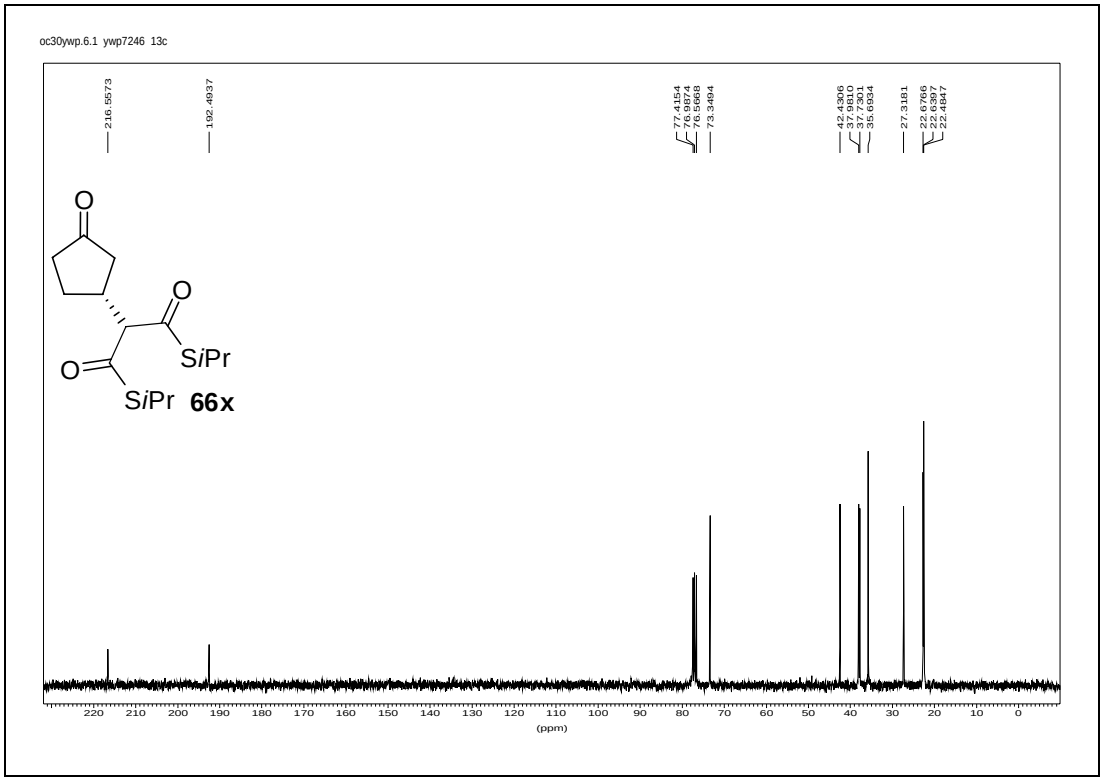
3.7371
3.7035
3.6960
3.0628
3.0500
3.0302
3.0070
2.9478
2.9235
2.8979
2.8774
2.4522
2.4267
2.3907
2.3640
2.3315
2.3071
2.2781
2.2586
2.2119
2.1889
2.1620
2.1353
1.9693
1.9333
1.8990
1.8750
1.8638
1.6606
1.6350
1.6046
1.6118
1.5874
1.5642
1.5398
0.9920
0.9757
0.9576
0.9514
0.9432
0.9270
O
O
O
SnPr
SnPr
66v
integral
1.0000
1.0411
4.3499
4.1930
1.1329
6.0554
6.2759
9.6 9.2 8.8 8.4 8.0 7.6 7.2 6.8 6.4 6.0 5.6 5.2 4.8 4.4 4.0 3.6 3.2 2.8 2.4 2.0 1.6 1.2 0.8 0.4 0.0
(ppm)


ag17ywp.2.1 ywp7108 13c
216.5056
192.5159
77.4227
77.0047
76.5741
73.4454
42.4306
38.0031
37.7227
31.4652
27.3255
22.5954
13.1869
O
O
O
SnPr
SnPr
66v
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)


O
O
SEt
O
SEt
66w


O
O
SEt
O
SEt
66w


oc30ywp.5.1 ywp7246
7.2600
Integral
2.9969
1.0000
4.0090
1.0643
2.1940
12.085
(ppm)
S*i*Pr
S*i*Pr
66x


oc30ywp.6.1 ywp7246 13c
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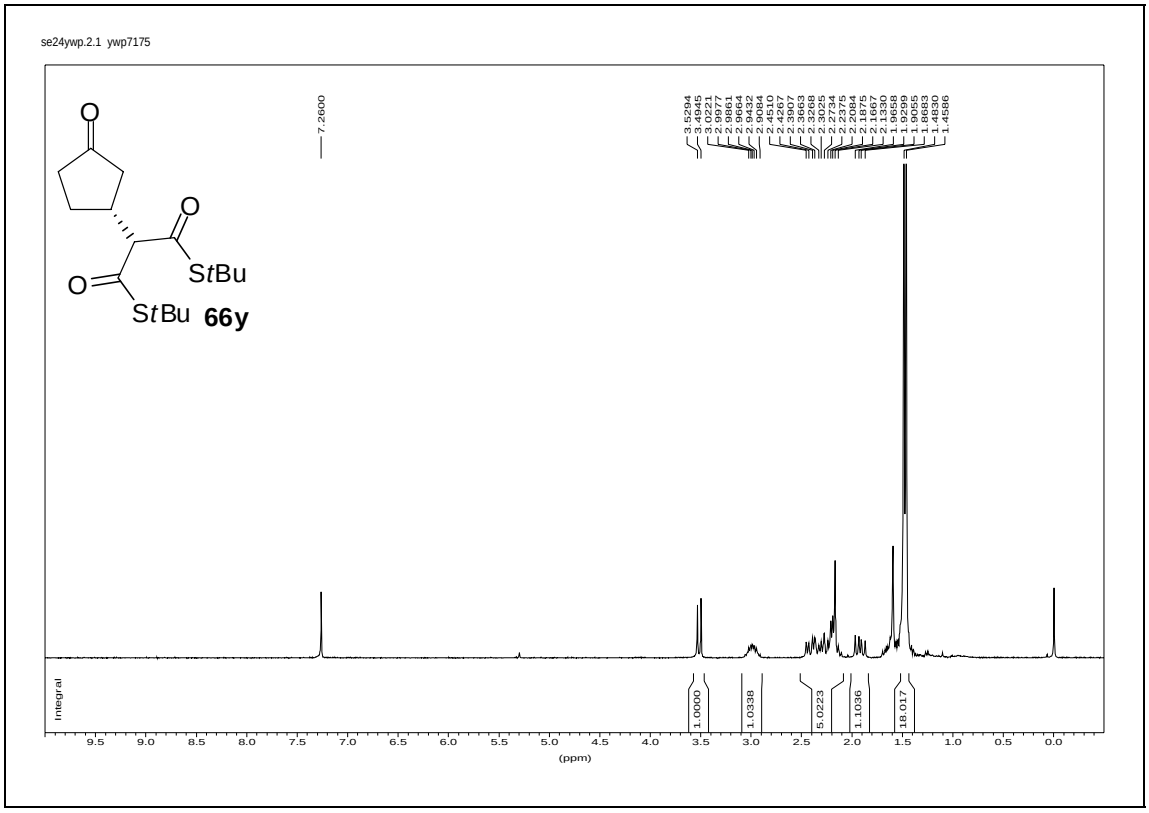
192.4937
77.4154
76.9874
76.5668
73.3494
42.4306
37.9810
37.7301
35.6934
27.3181
22.6766
22.6397
22.4847
(ppm)
S*i*Pr
S*i*Pr
66x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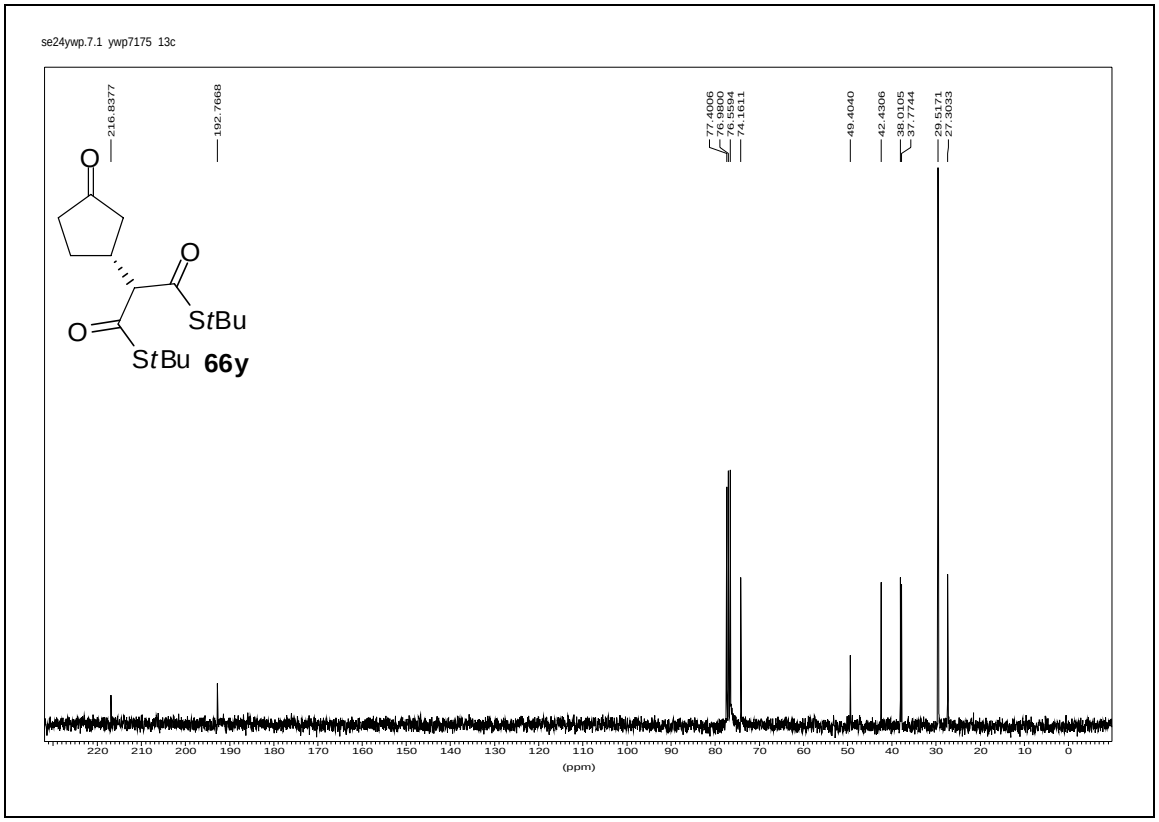
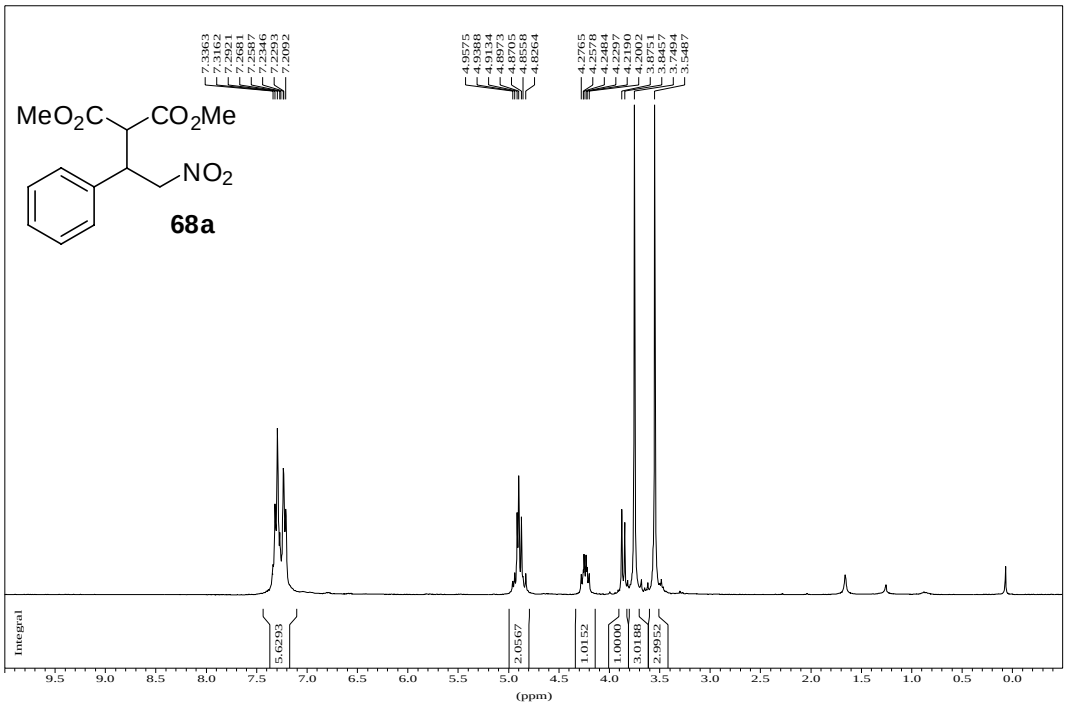
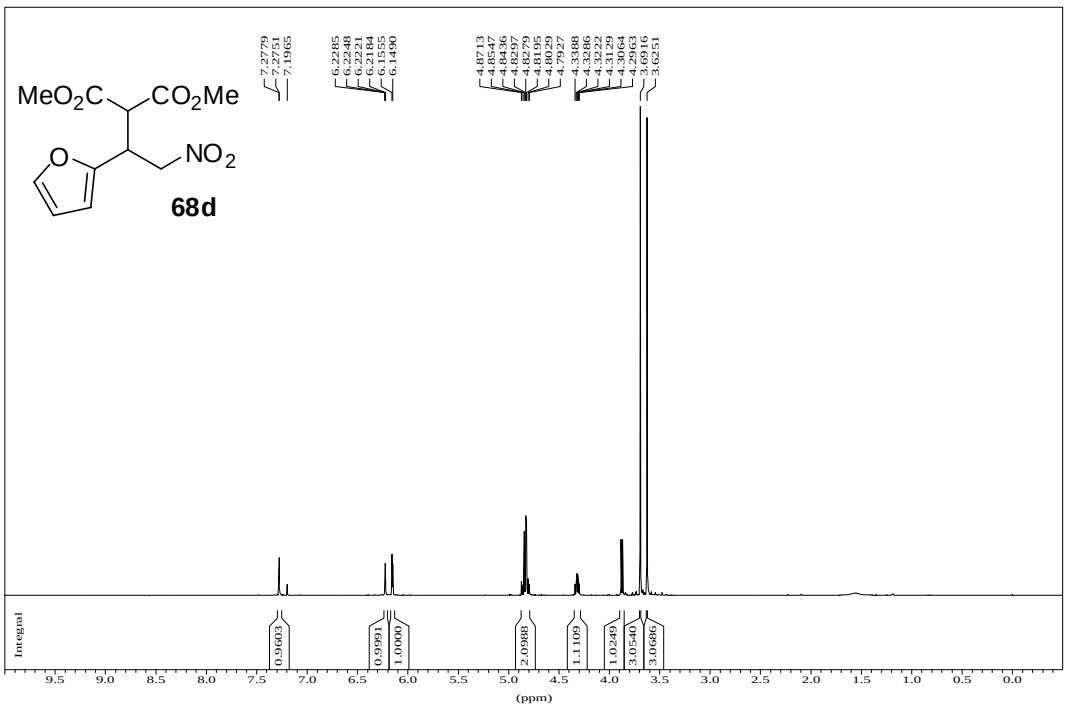
3.5294
3.4945
3.4721
2.9977
2.9861
2.9654
2.9454
2.9084
2.4510
2.4077
2.3907
2.3663
2.3268
2.3095
2.2734
2.2375
2.2084
2.1875
2.1667
2.1330
1.9658
1.9358
1.9055
1.8683
1.4490
1.4286
O
O
O
StBu
StBu
66y
integral
1.0000
1.0338
5.0223
1.1036
18.017
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)


se24ywp.7.1 ywp7175 13c
216.8377
192.7668
77.4006
76.9800
76.5594
74.1611
49.4040
42.4306
38.0105
37.7744
29.5171
27.3033
O
O
O
StBu
StBu
66y
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)

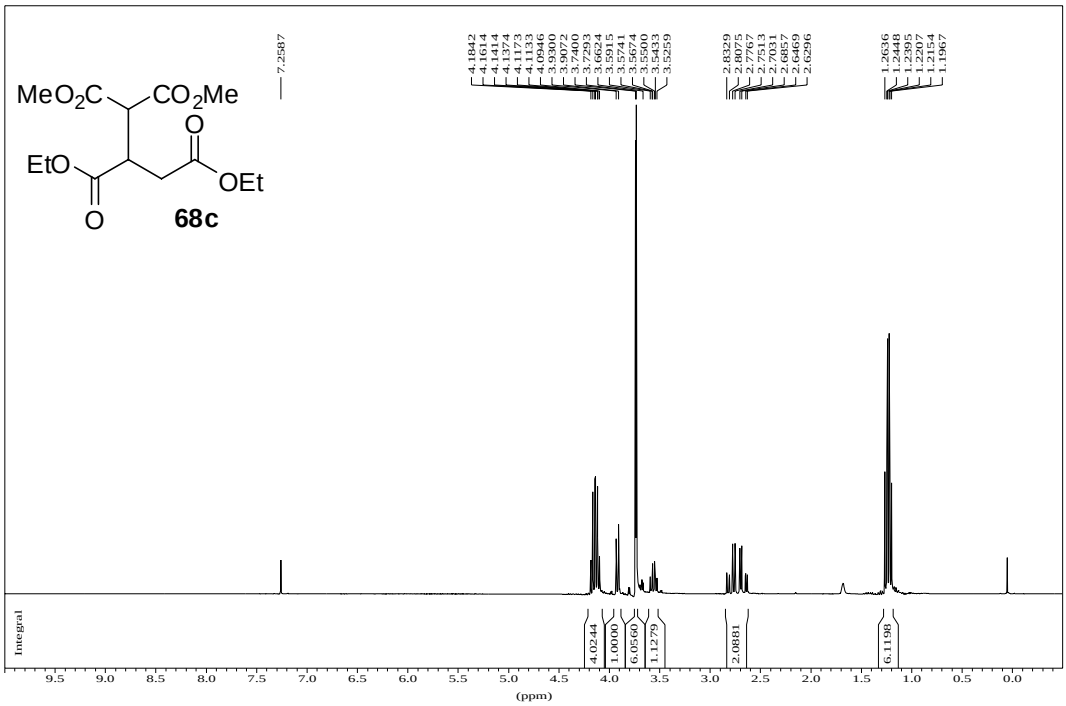
7 fe07ywp2.888 ywp2149



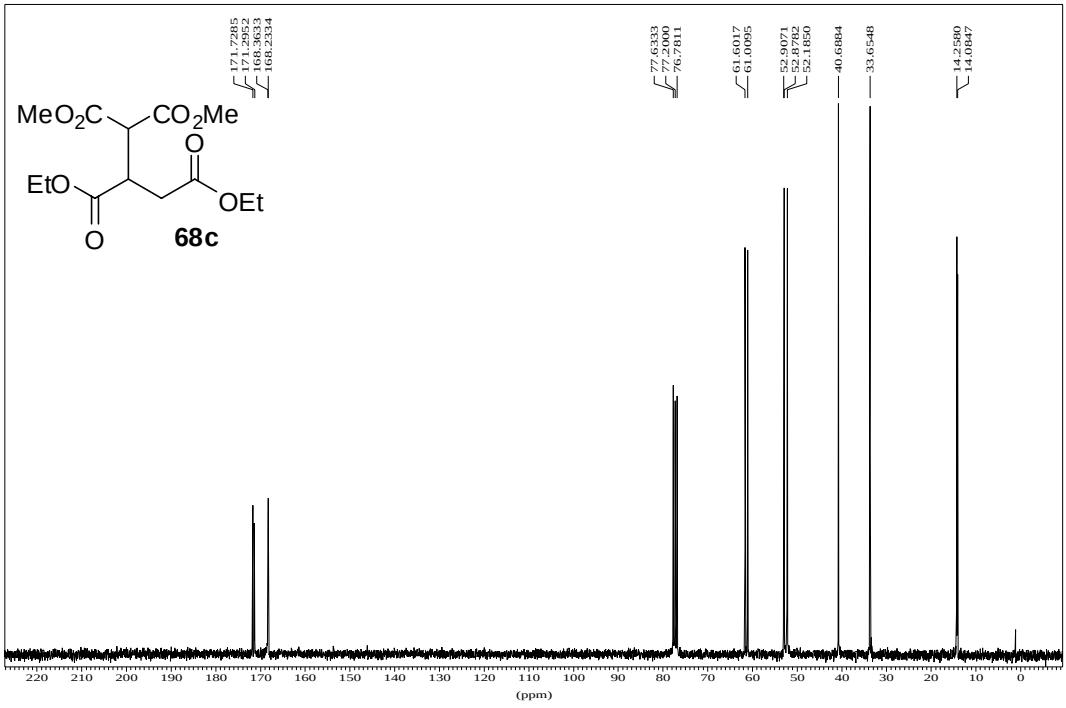
8 ywp2279-4 wp0329.81.1



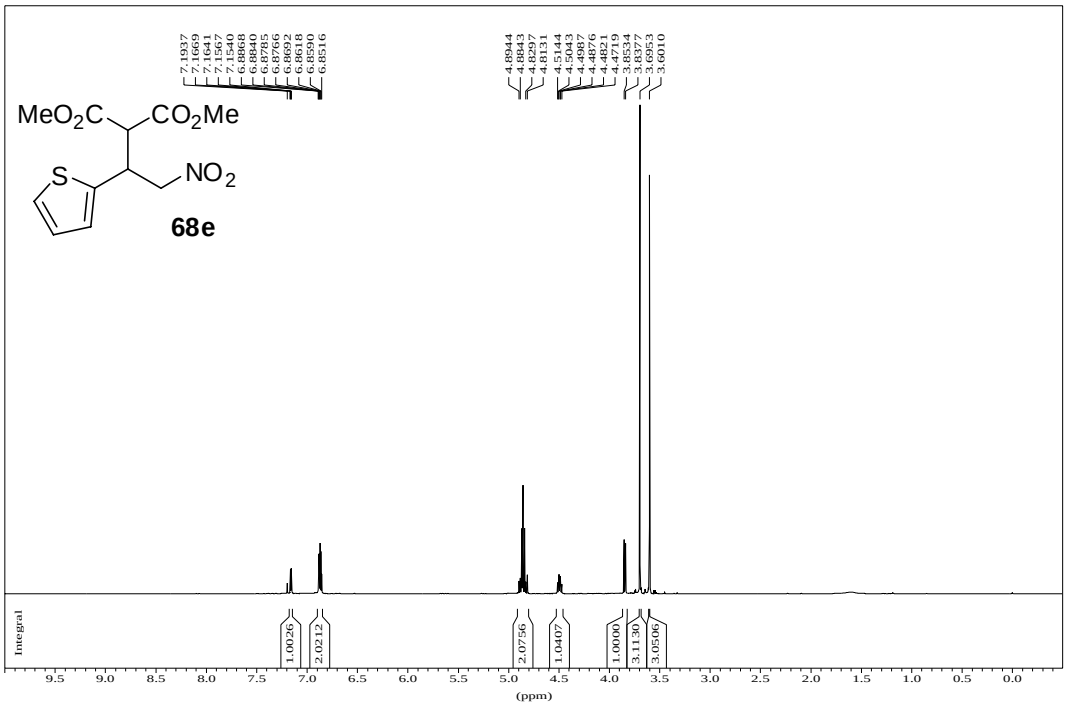
14H DC26YWP1.888 YWP2032-3



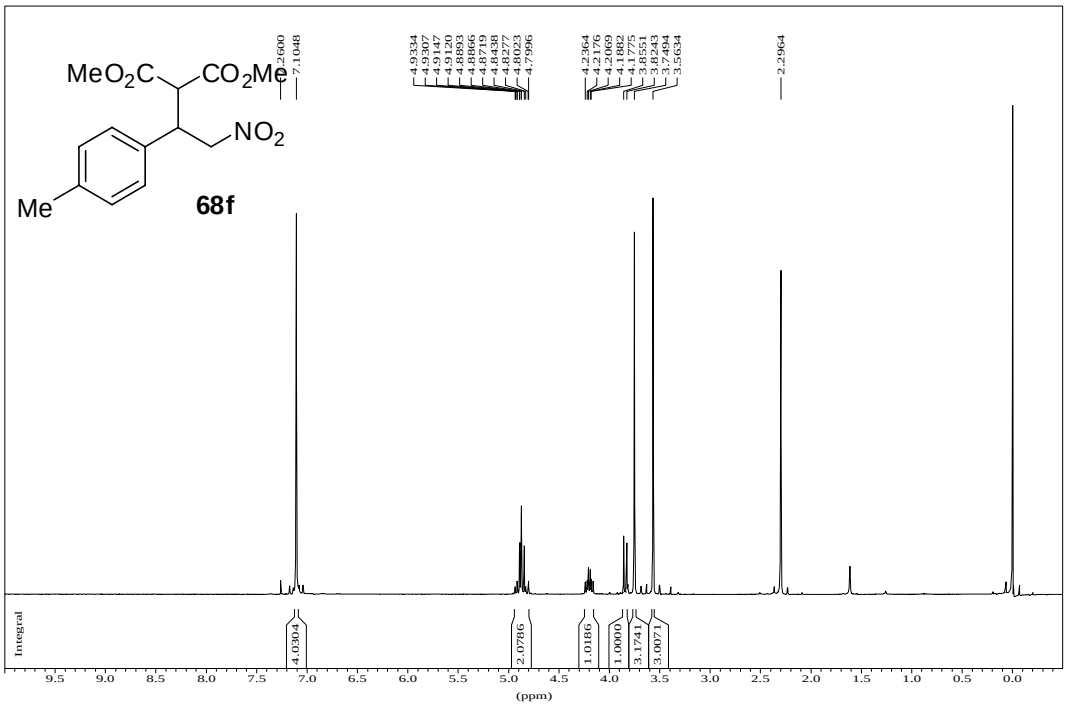
14c mja02ywp.888 ywp2032-3

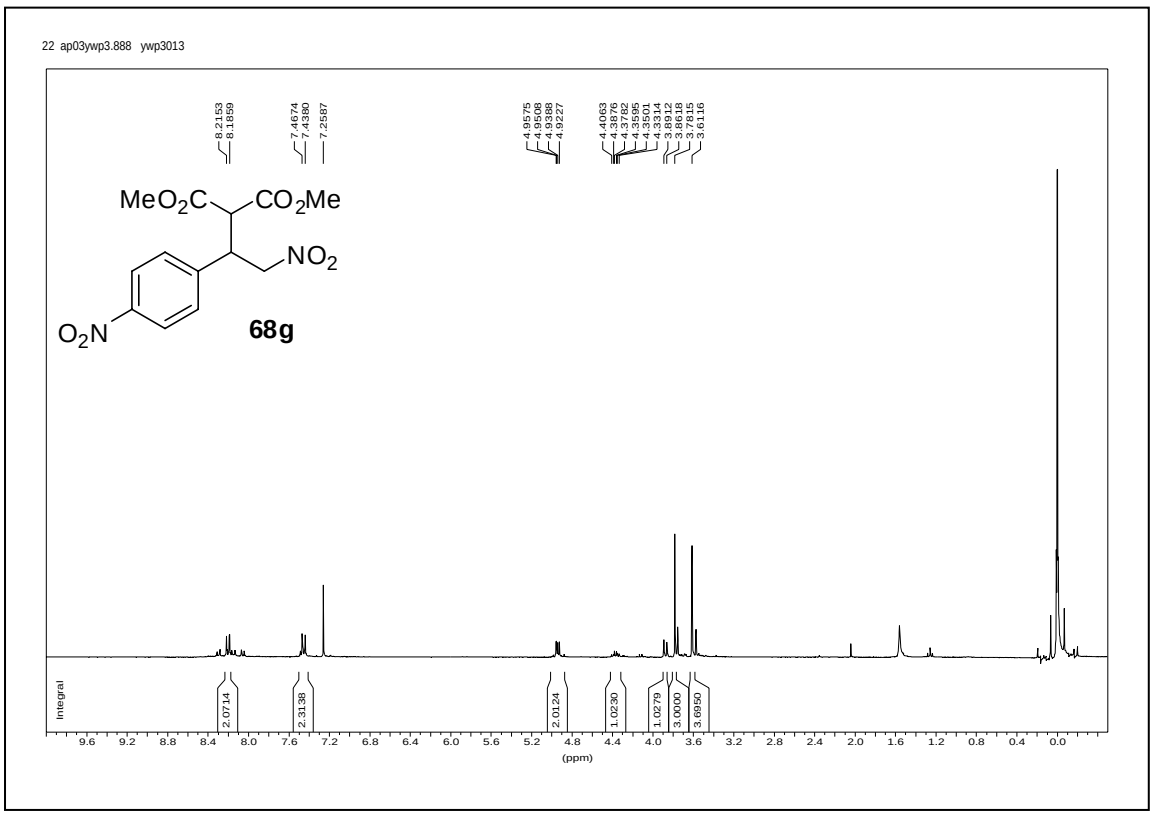


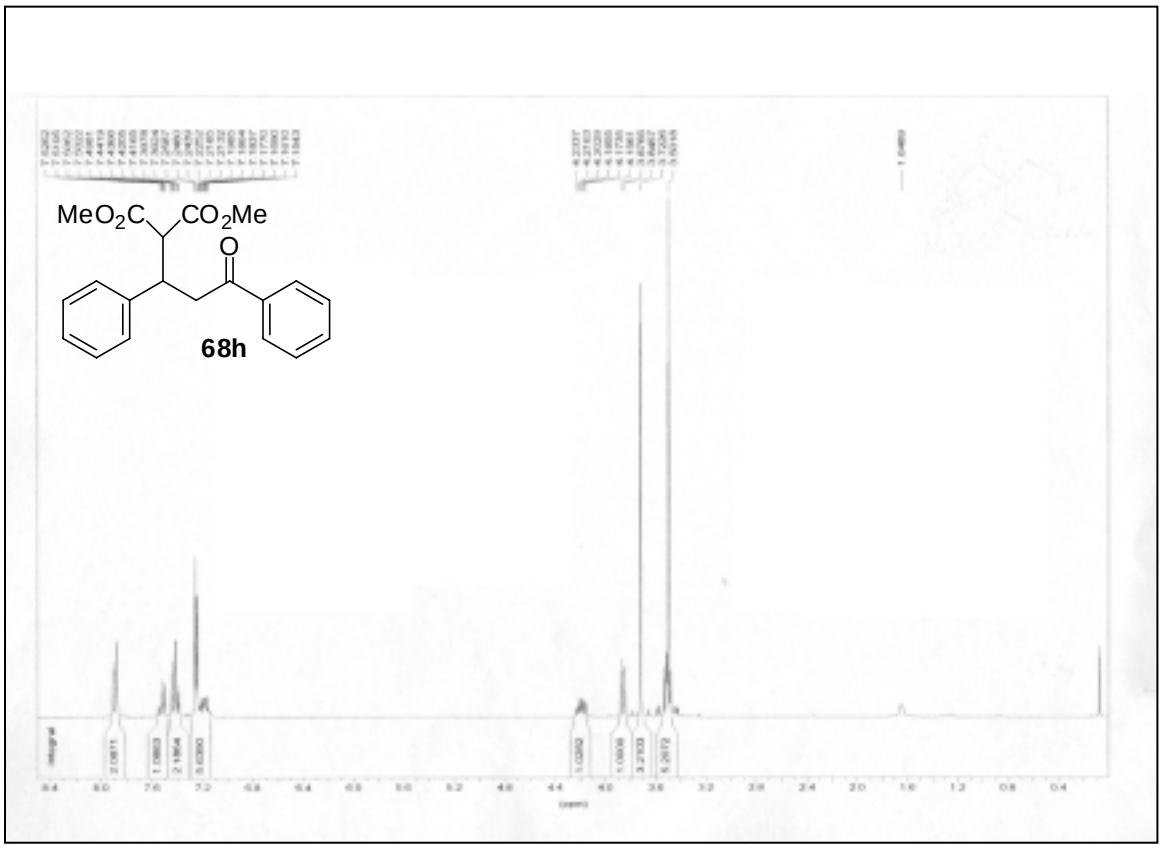
21 WP0329.71.1 Ywp2279-2

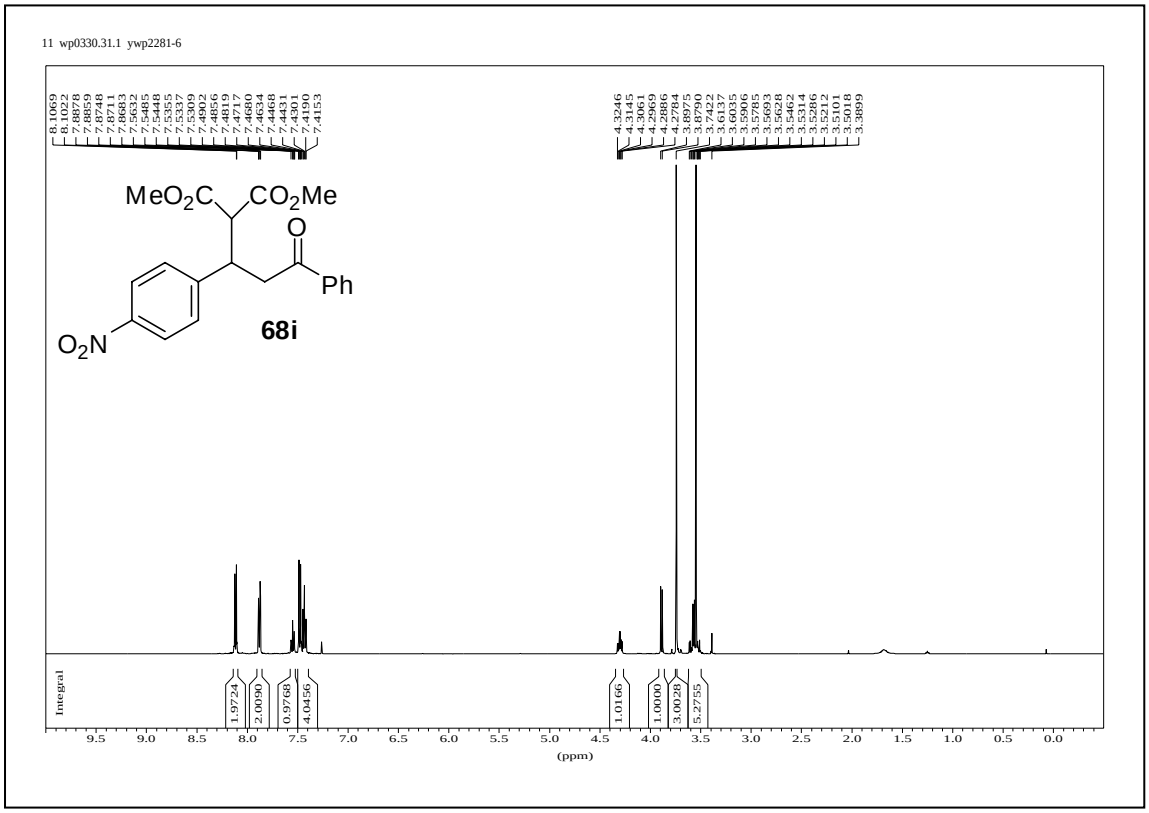


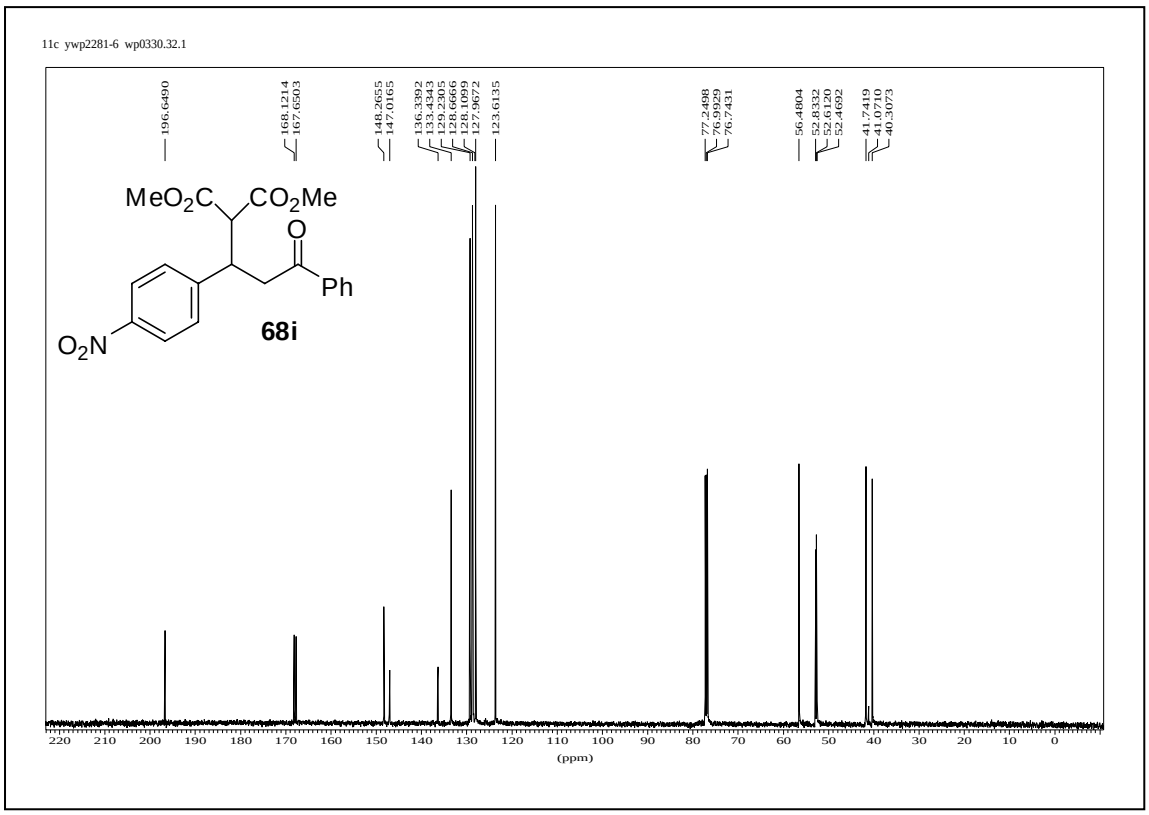
9 AP03YWP2.888 YWP2292-4

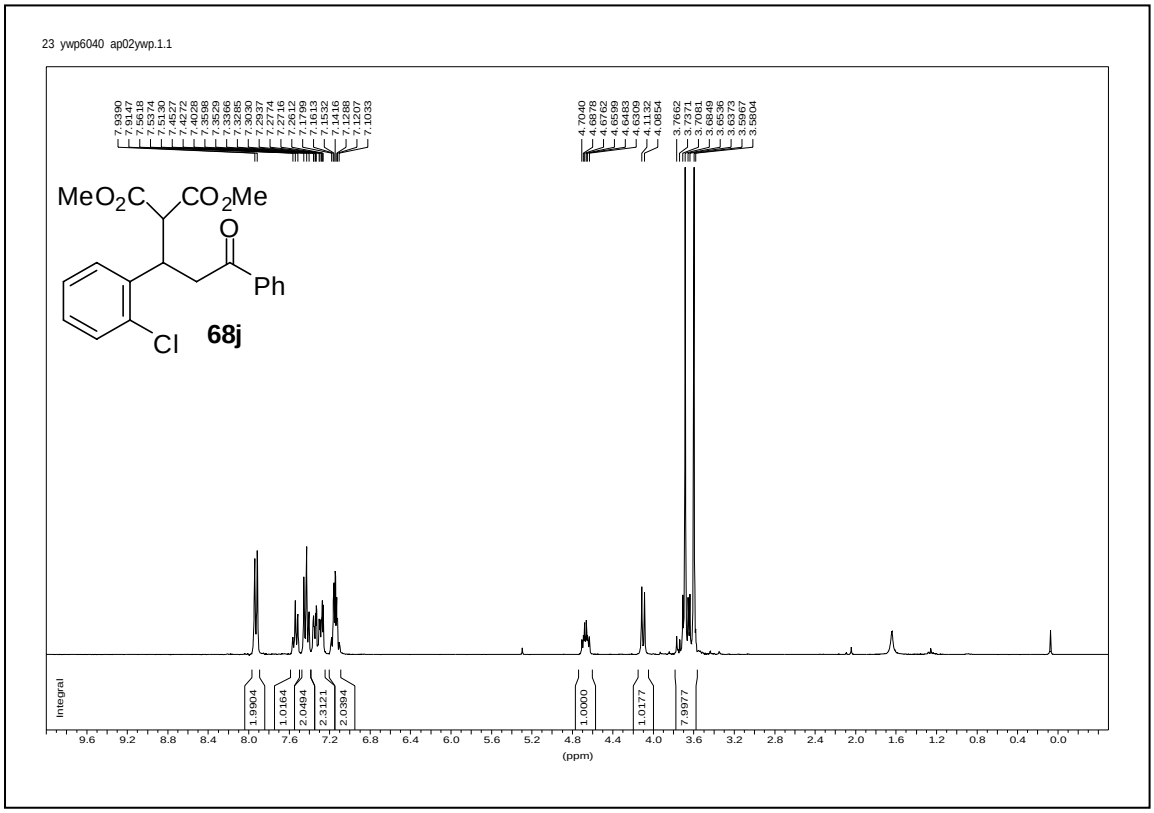


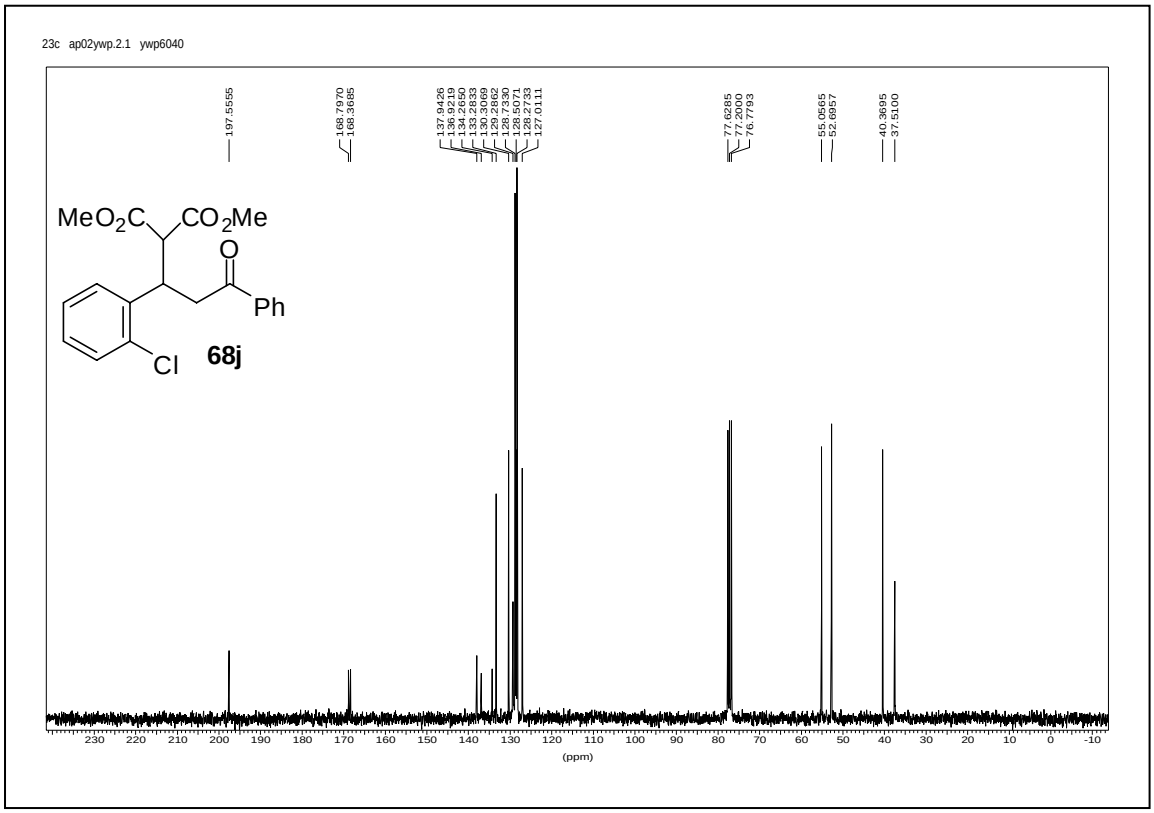

22 ap03ywp3.888 ywp3013
8.2153
8.1859
7.4674
7.4380
7.2587
4.9575
4.9508
4.9388
4.9227
4.4063
4.3876
4.3702
4.3595
4.3501
4.3314
3.8103
3.8018
3.7815
3.6116
MeO2C
CO2Me
NO2
O2N
68g
integral
2.0714
2.3138
2.0124
1.0230
1.0279
3.0000
3.6950
9.6 9.2 8.8 8.4 8.0 7.6 7.2 6.8 6.4 6.0 5.6 5.2 4.8 4.4 4.0 3.6 3.2 2.8 2.4 2.0 1.6 1.2 0.8 0.4 0.0
(ppm)


MeO2C
CO2Me
O
68h

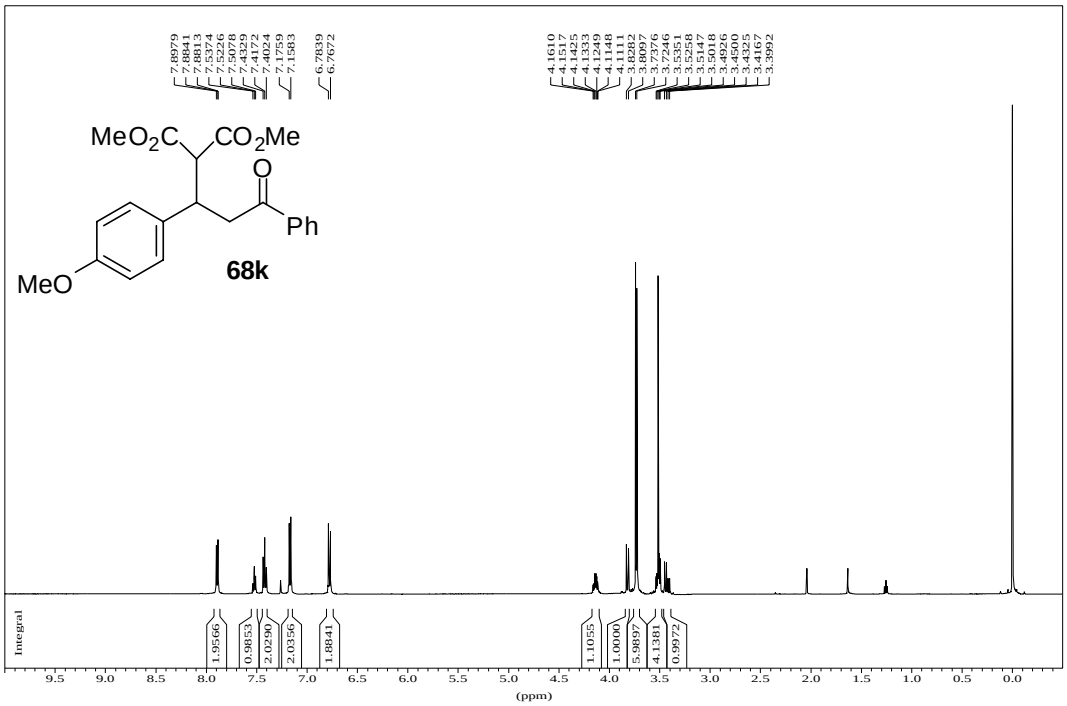

11 wp0330.31.1 ywp2281-6
MeO2C
CO2Me
O
Ph
O2N
68i
Integral
1.9724
2.0090
0.9768
4.0456
1.0166
1.0000
3.0928
5.2755
(ppm)


11c ywp2281-6 wp0330.32.1
MeO2C
CO2Me
O
Ph
O2N
68i
(ppm)

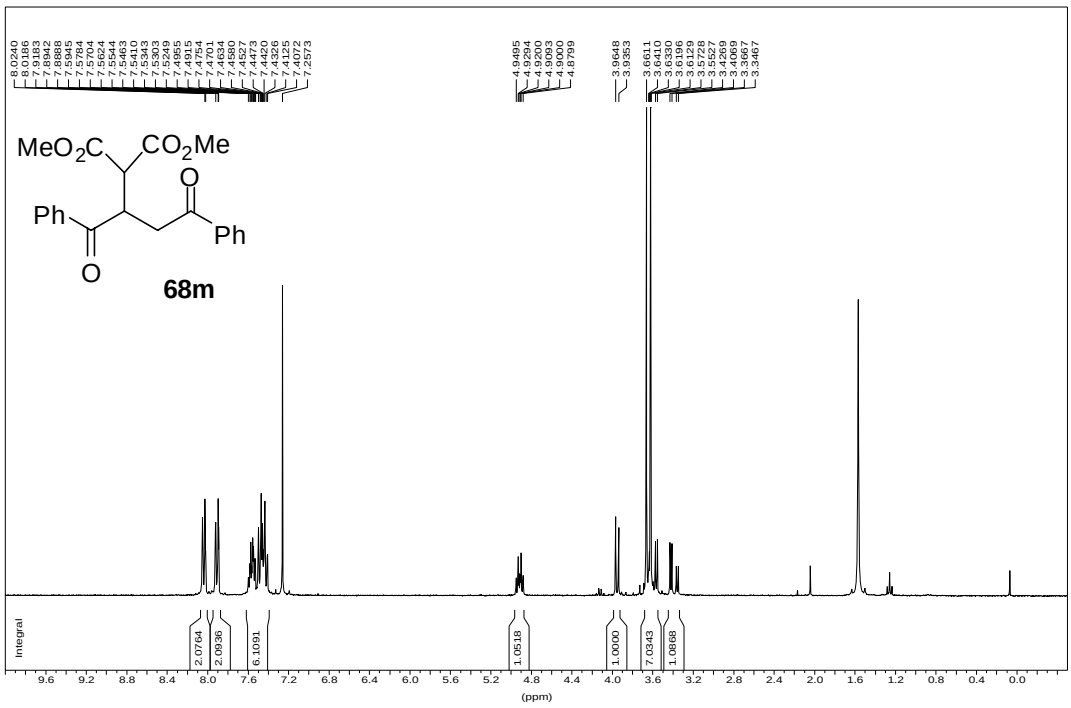

23 ywp6040 ap02ywp.1.1
MeO2C
CO2Me
O
Ph
Cl
68j
integral
1.9904
1.0164
2.0494
2.3121
2.0394
1.0000
1.0177
7.9977
(ppm)

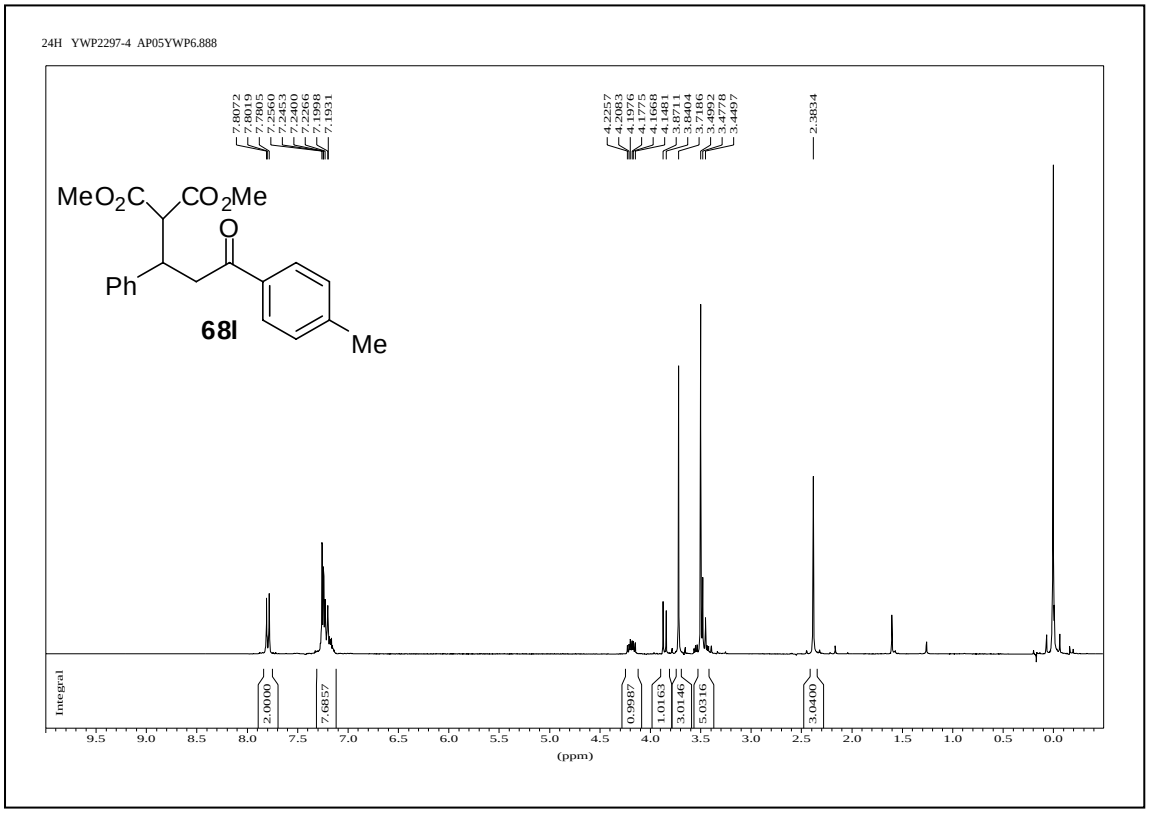

23c ap02ywp.2.1 ywp6040
MeO2C
CO2Me
O
Ph
Cl
68j
(ppm)

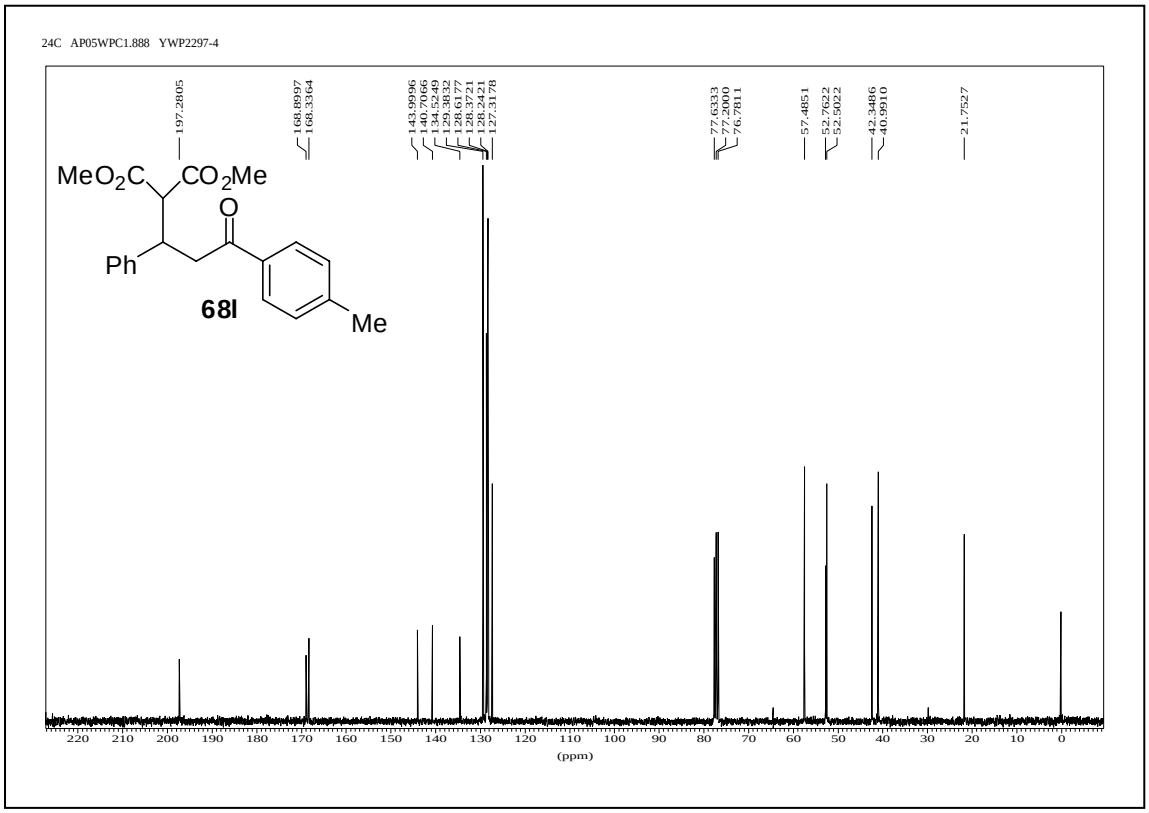
12 WP0416.21.1 ywp2297-2



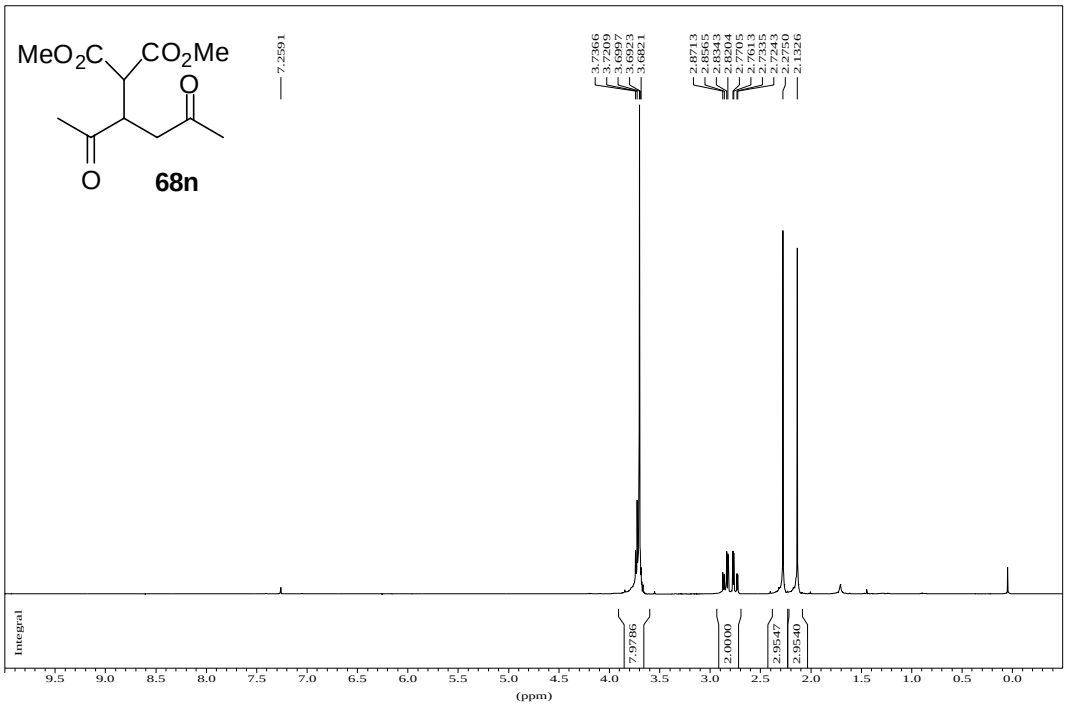
13 ja200723.888 ywp2072-3



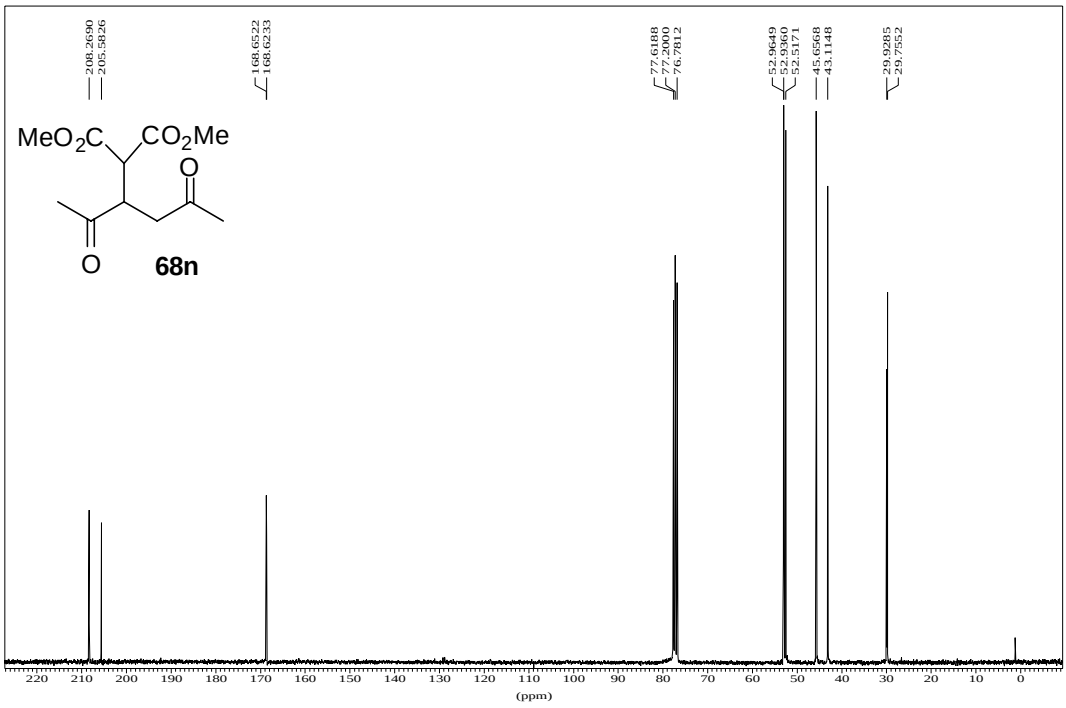

24H YWP2297-4 AP05YWP6.888
7.8072
7.8019
7.7805
7.2560
7.2453
7.2400
7.2266
7.1988
7.1931
4.2257
4.2083
4.1976
4.1775
4.1668
4.1481
3.8711
3.8404
3.7186
3.4992
3.4778
3.4497
2.3834
MeO2C
CO2Me
O
Ph
68l
Me
Integral
2.0000
7.6857
0.9987
1.0163
3.0146
5.0316
3.0400
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)


24C AP05WPC1.888 YWP2297-4
197.2805
168.8997
168.3364
143.9996
140.7066
134.5249
129.3832
128.6777
128.3721
128.2421
127.3178
77.6333
77.2000
76.7811
57.4851
52.7622
52.5022
42.3486
40.9910
21.7527
MeO2C
CO2Me
O
Ph
68l
Me
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)

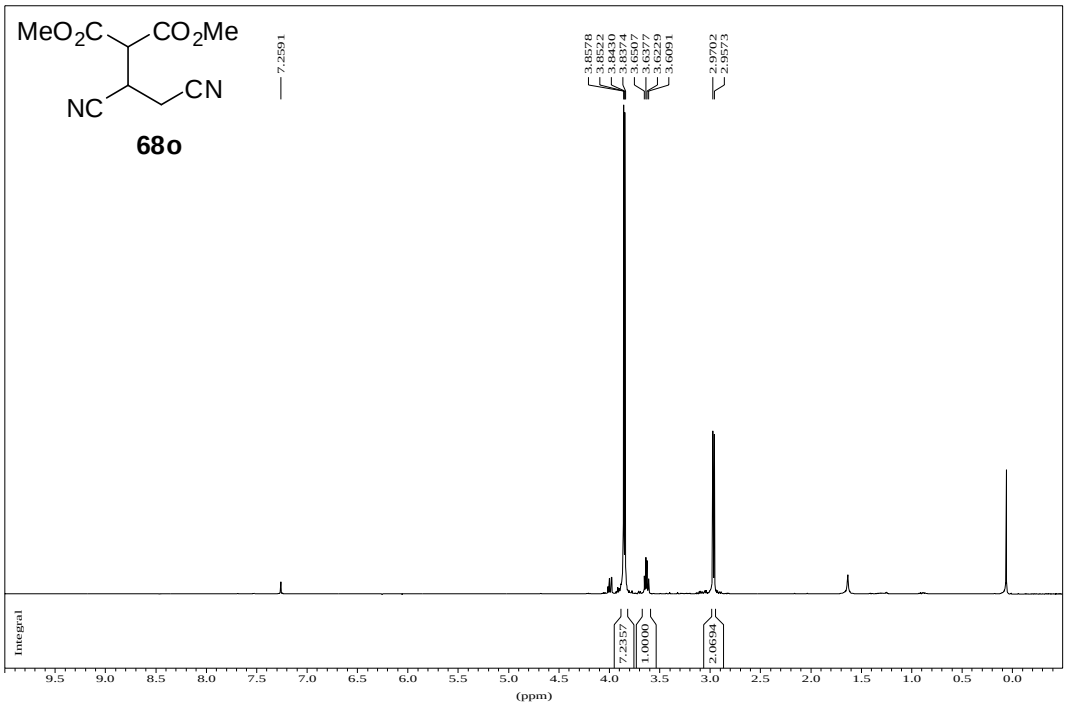
25H WP0311.41.1 ywp2213 1H



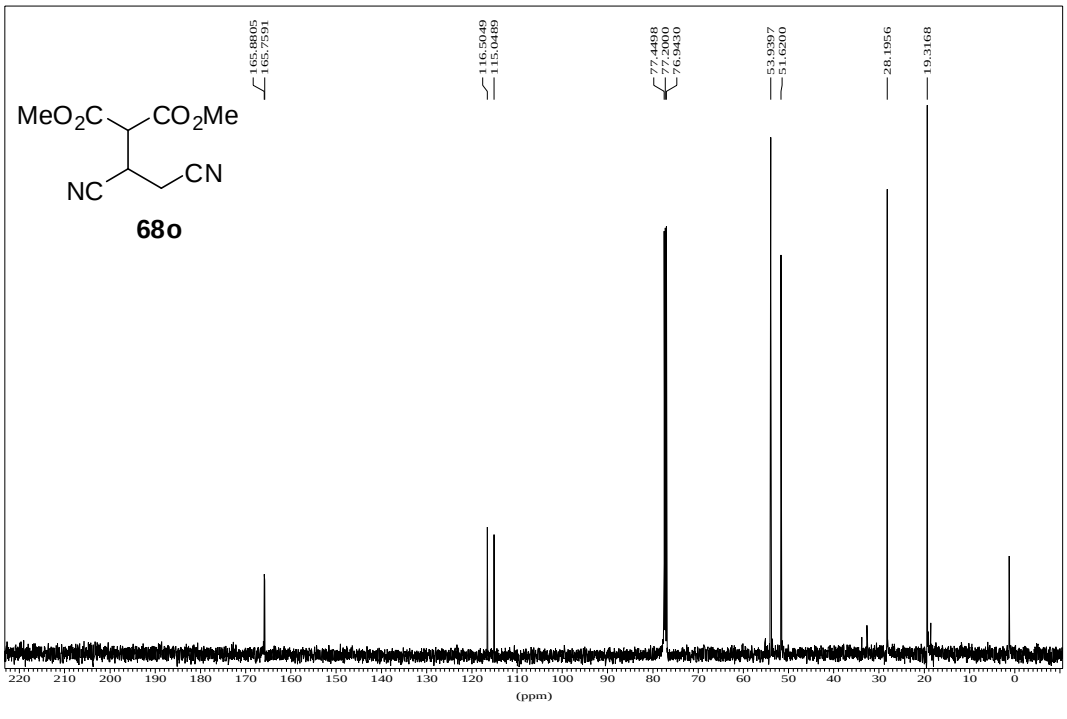
25C MA09WPC1.888 YWP2213



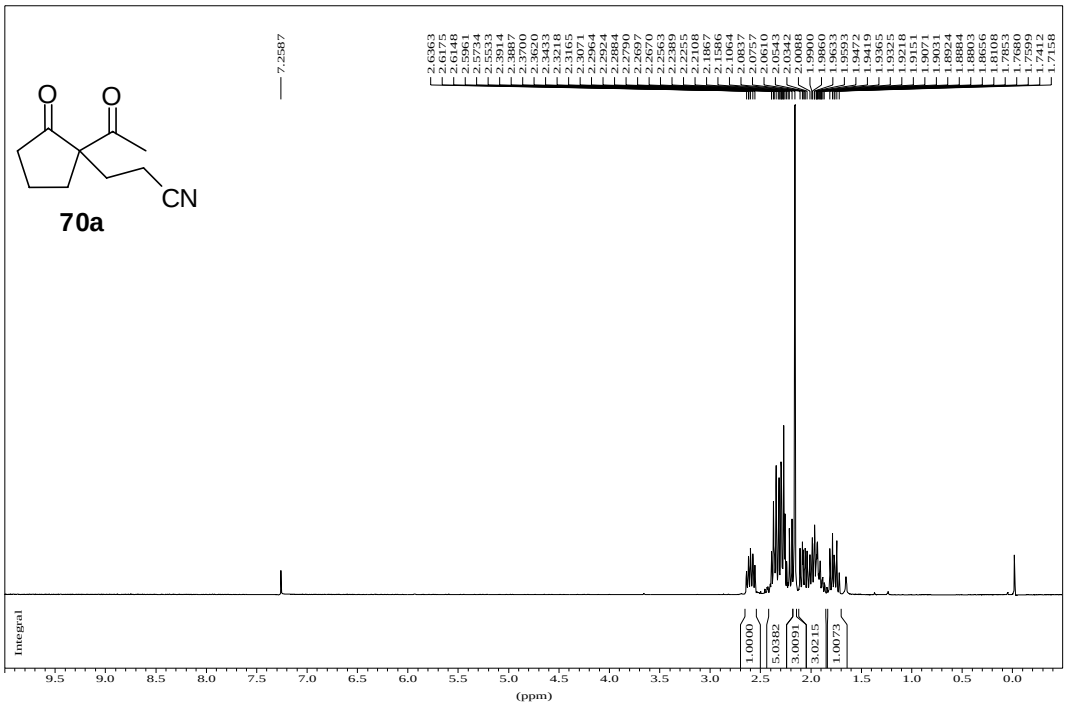
15h wp0309.11.1 ywp2212



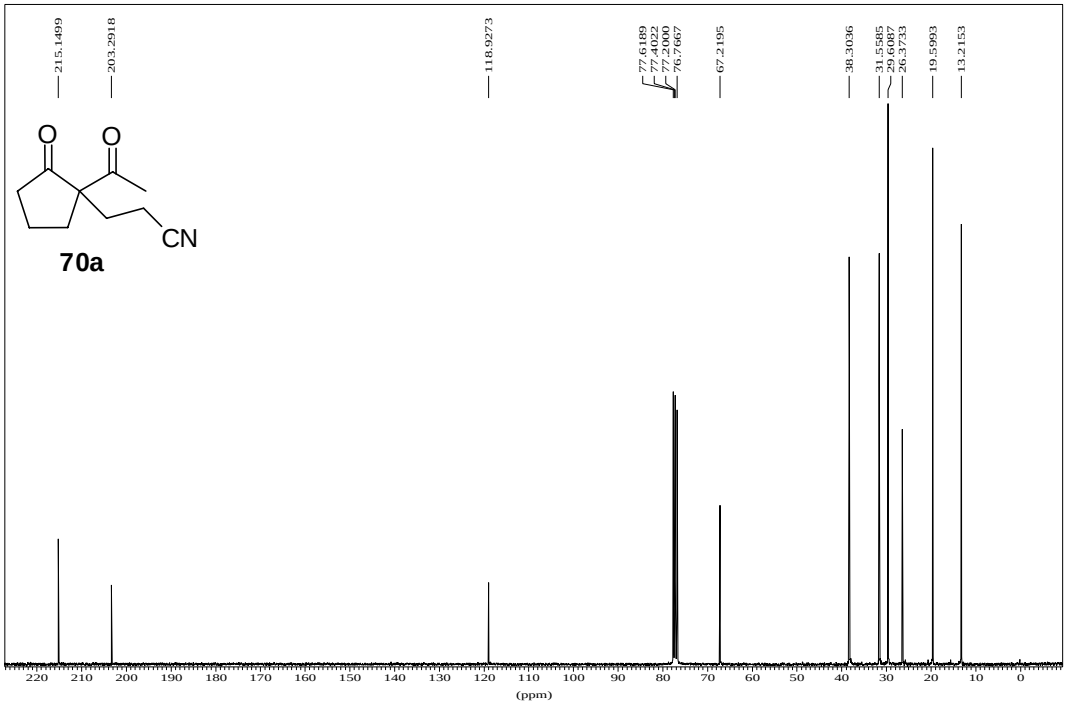
15c wp0309.12.1 ywp2212 13C

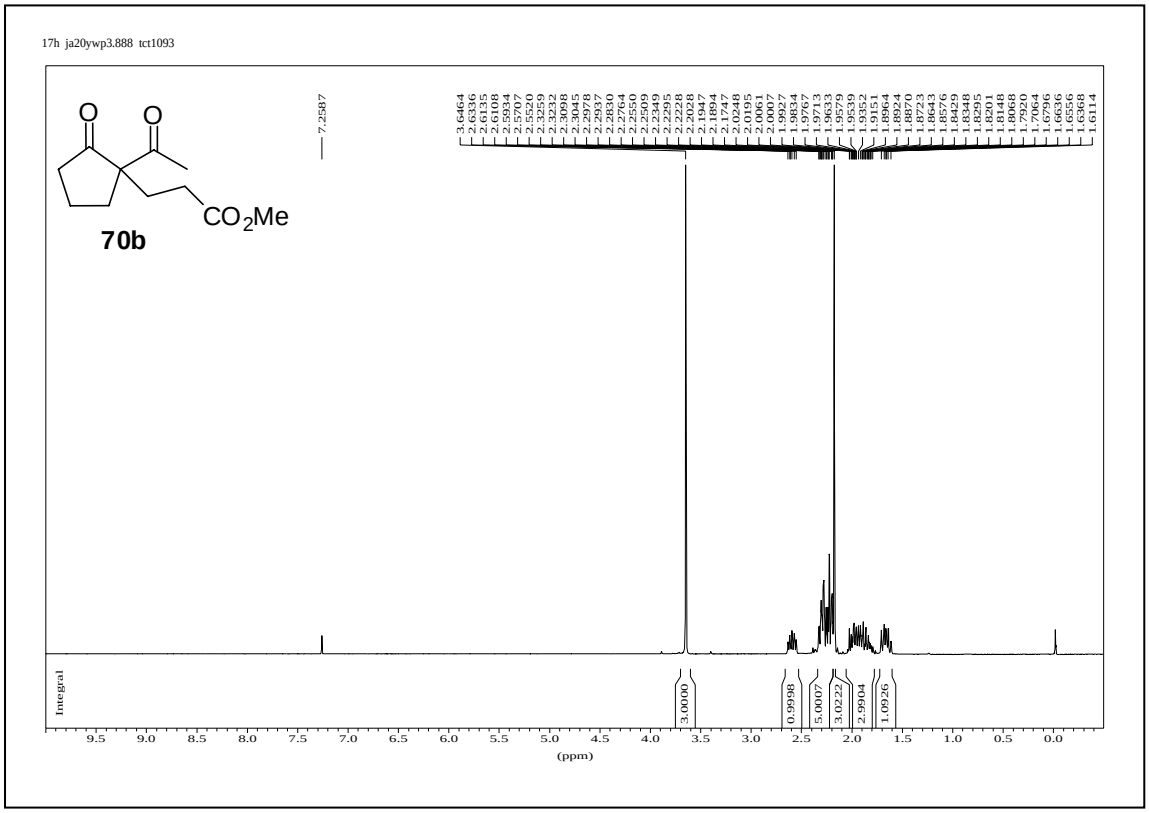


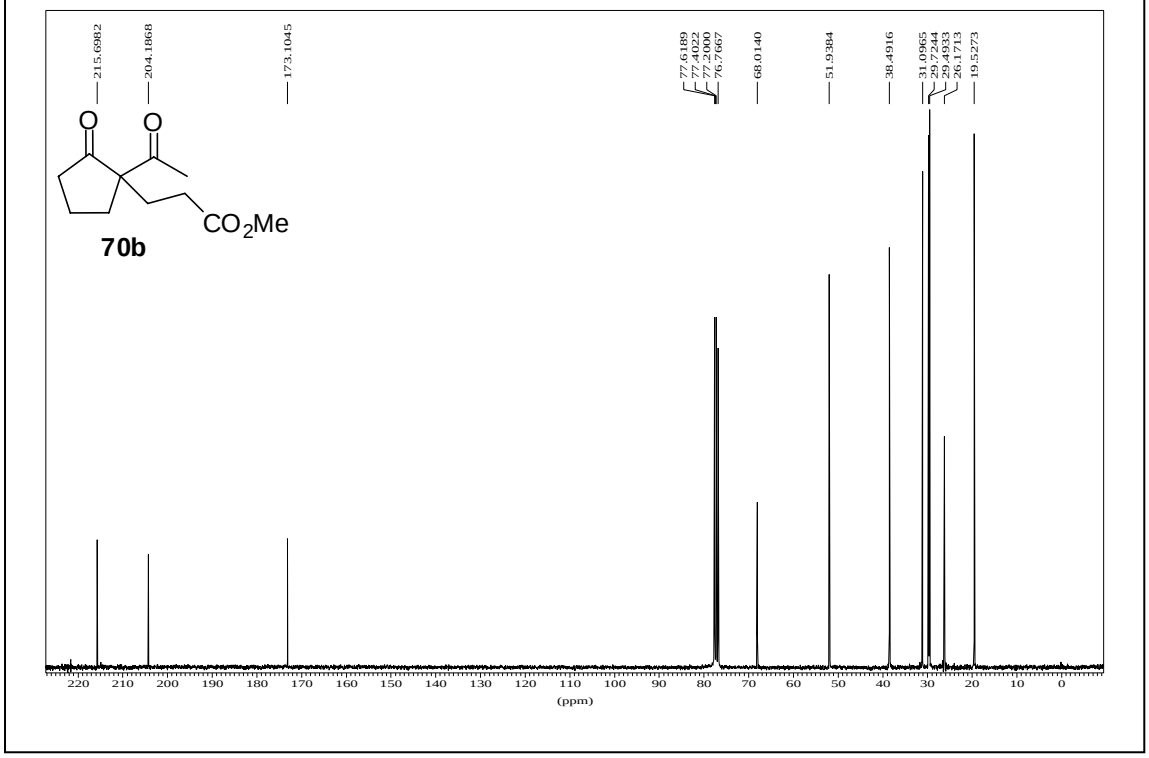
16H JA20YWP2.888 TCT1091

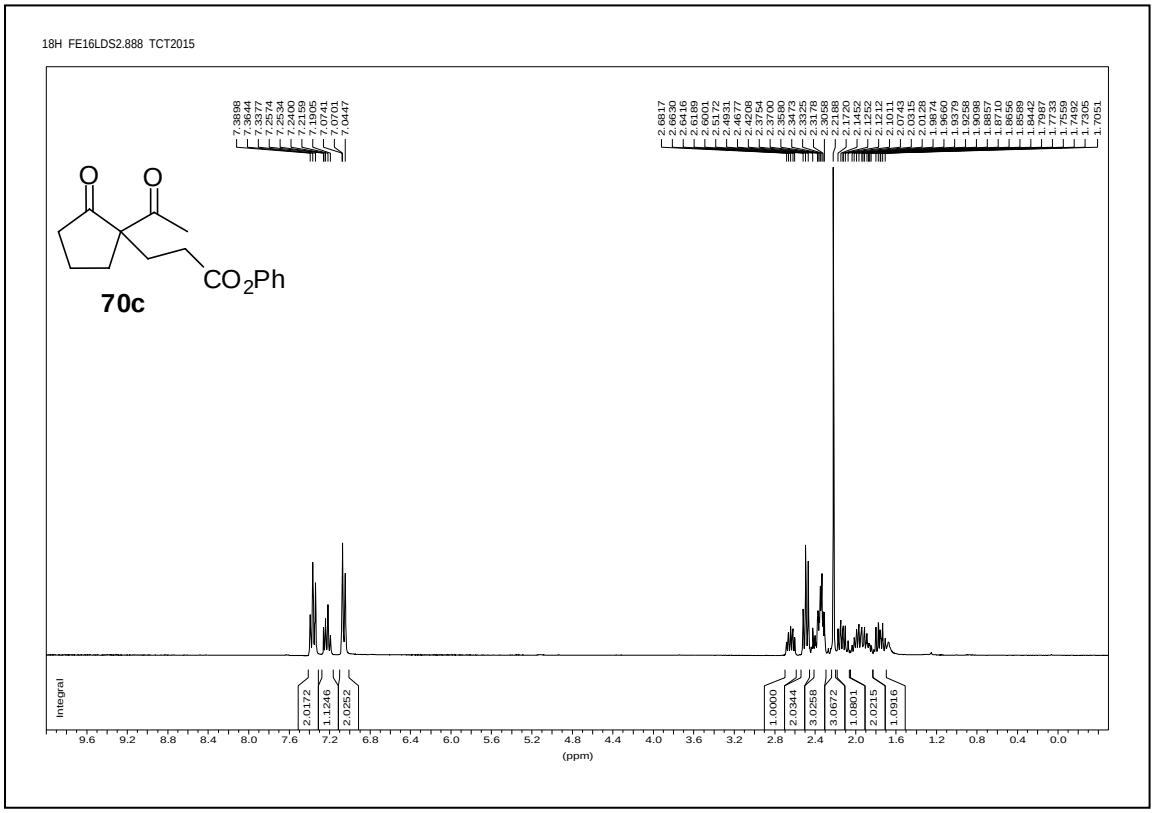


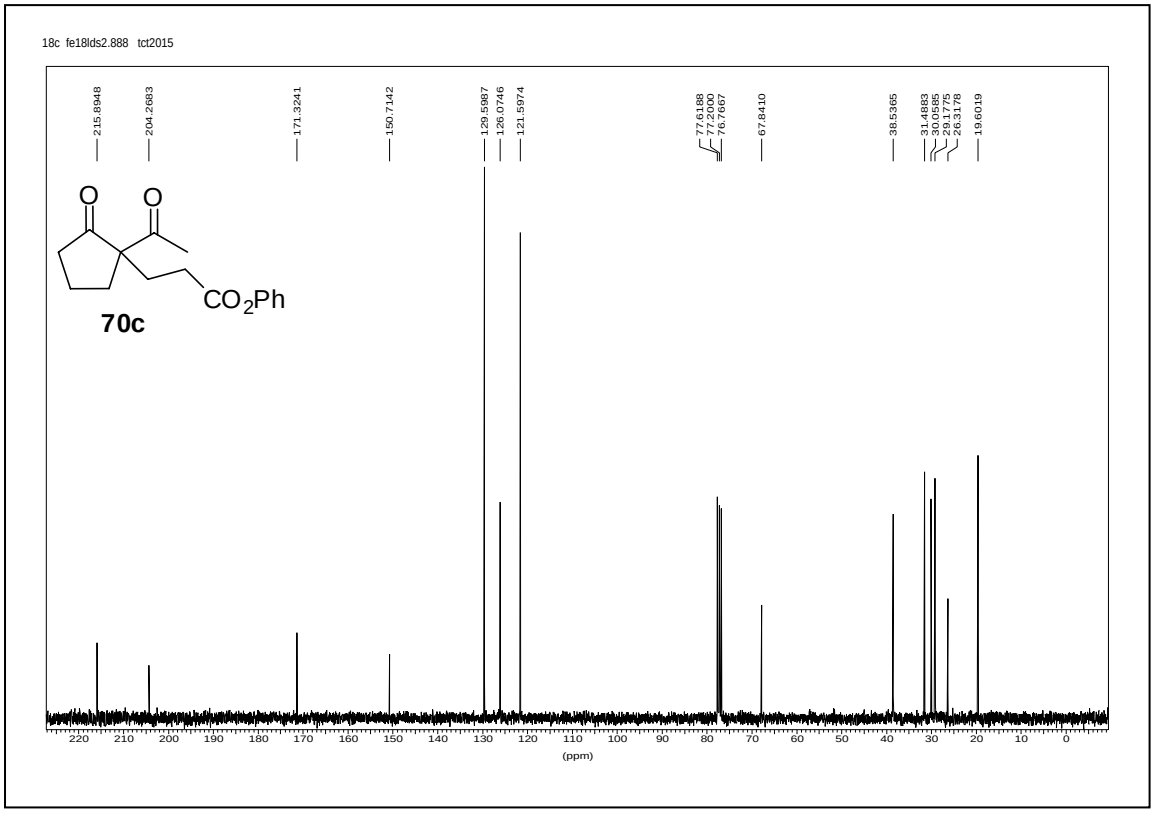
16C JA20YWP5.888 TCT1091

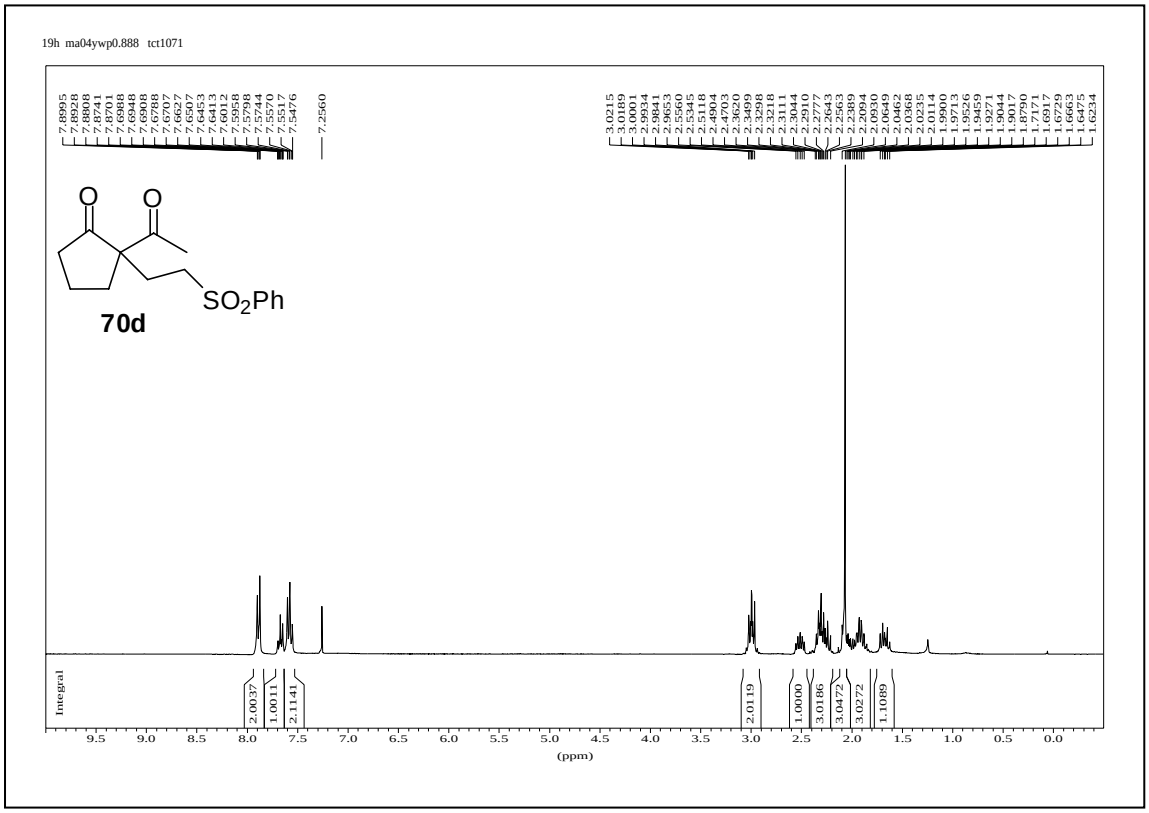



17h ja20ywp3.888 tct1093
O
O
CO2Me
70b
7.2587
3.6464
2.6176
2.6135
2.6108
2.5934
2.5707
2.3520
2.3239
2.3232
2.3098
2.3045
2.2978
2.2937
2.2830
2.2764
2.2550
2.2509
2.2349
2.2295
2.2228
2.2028
2.1947
2.1894
2.1747
2.1048
2.0195
2.0061
2.0007
1.9927
1.9884
1.9767
1.9713
1.9633
1.9579
1.9539
1.9382
1.9151
1.8964
1.8924
1.8870
1.8773
1.8643
1.8576
1.8429
1.8348
1.8295
1.8201
1.8148
1.8068
1.7920
1.7064
1.6736
1.6656
1.6556
1.6368
1.6114
Integral
3.0000
0.9998
5.0007
3.0222
2.9904
1.0926
9.5 9.0 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 0.0
(ppm)


17C JA21YWP7.888 TCT1093
O
O
CO2Me
70b
215.6982
204.1868
173.1045
77.6189
77.4022
77.2000
76.7667
68.0140
51.9384
38.4916
31.0965
29.9744
29.4933
26.1713
19.5273
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)


18H FE16LDS2.888 TCT2015
CO2Ph
70c
integral
(ppm)


18c fe18lds2.888 tct2015
CO2Ph
70c
(ppm)


19h ma04ywp0.888 tct1071
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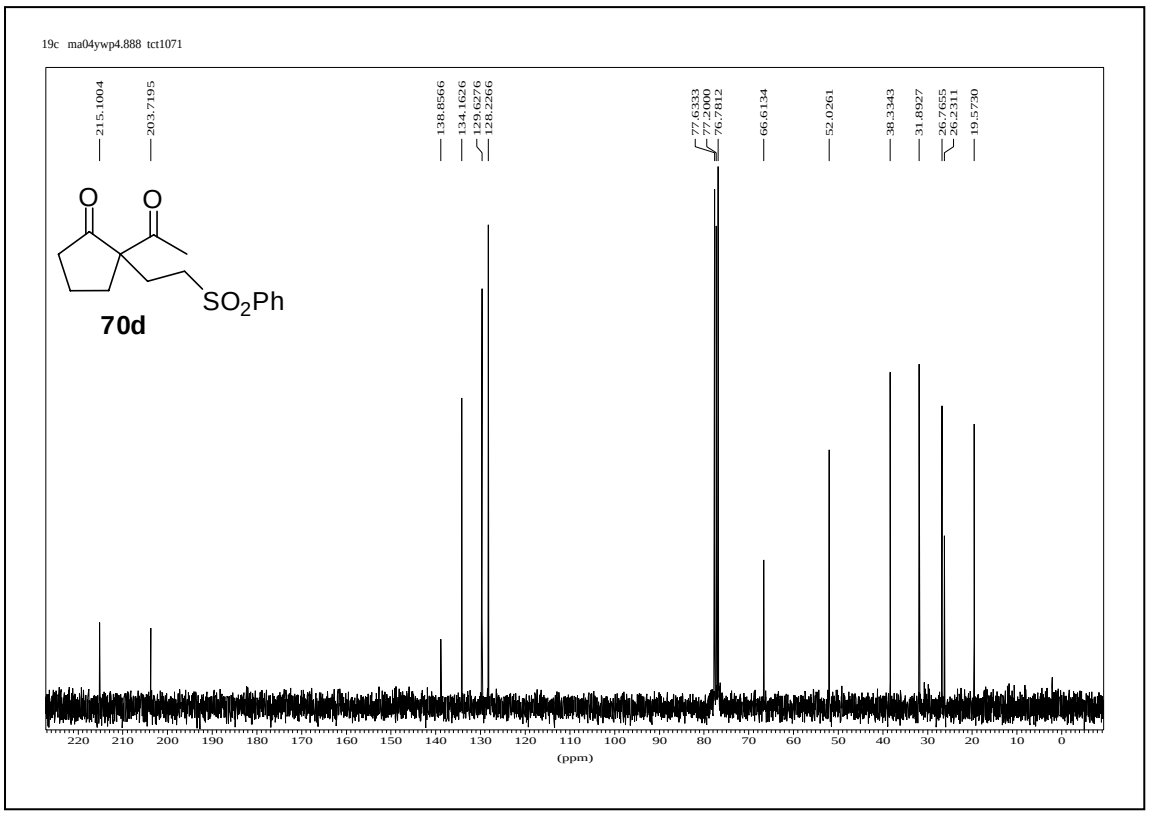
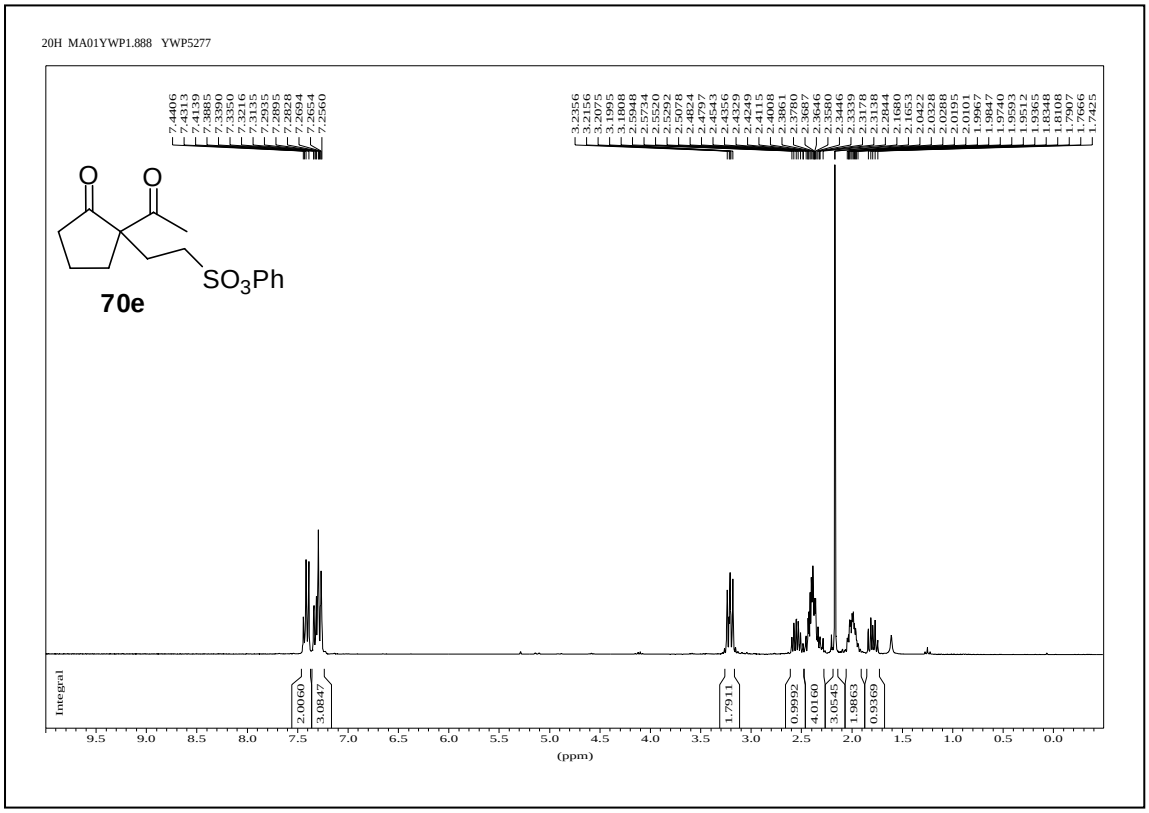
7.8928
7.8808
7.8741
7.8701
7.6988
7.6948
7.6908
7.6788
7.6707
7.6667
7.6507
7.6453
7.6413
7.6012
7.5958
7.5798
7.5744
7.5570
7.5517
7.5476
7.2560
3.0215
3.0189
3.0001
2.9934
2.9841
2.9663
2.5560
2.5345
2.5118
2.4904
2.4703
2.4620
2.3499
2.3298
2.3218
2.3111
2.3044
2.2910
2.2777
2.2643
2.2563
2.2389
2.2084
2.0930
2.0649
2.0462
2.0368
2.0215
2.0114
1.9900
1.9713
1.9526
1.9459
1.9271
1.9044
1.9017
1.8790
1.7171
1.6917
1.6729
1.6663
1.6475
1.6234
O
O
SO2Ph
70d
Integral
2.0037
1.0011
2.1141
2.0119
1.0000
3.0186
3.0472
3.0272
1.1089
9.5 9.0 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 0.0
(ppm)


19c ma04ywp4.888 tct1071
215.1004
203.7195
138.8566
134.1626
129.6276
128.2266
77.6333
77.2000
76.7812
66.6134
52.0261
38.3343
31.8927
26.7655
26.2311
19.5730
O
O
SO2Ph
70d
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)


20H MA01YWP1.888 YWP5277
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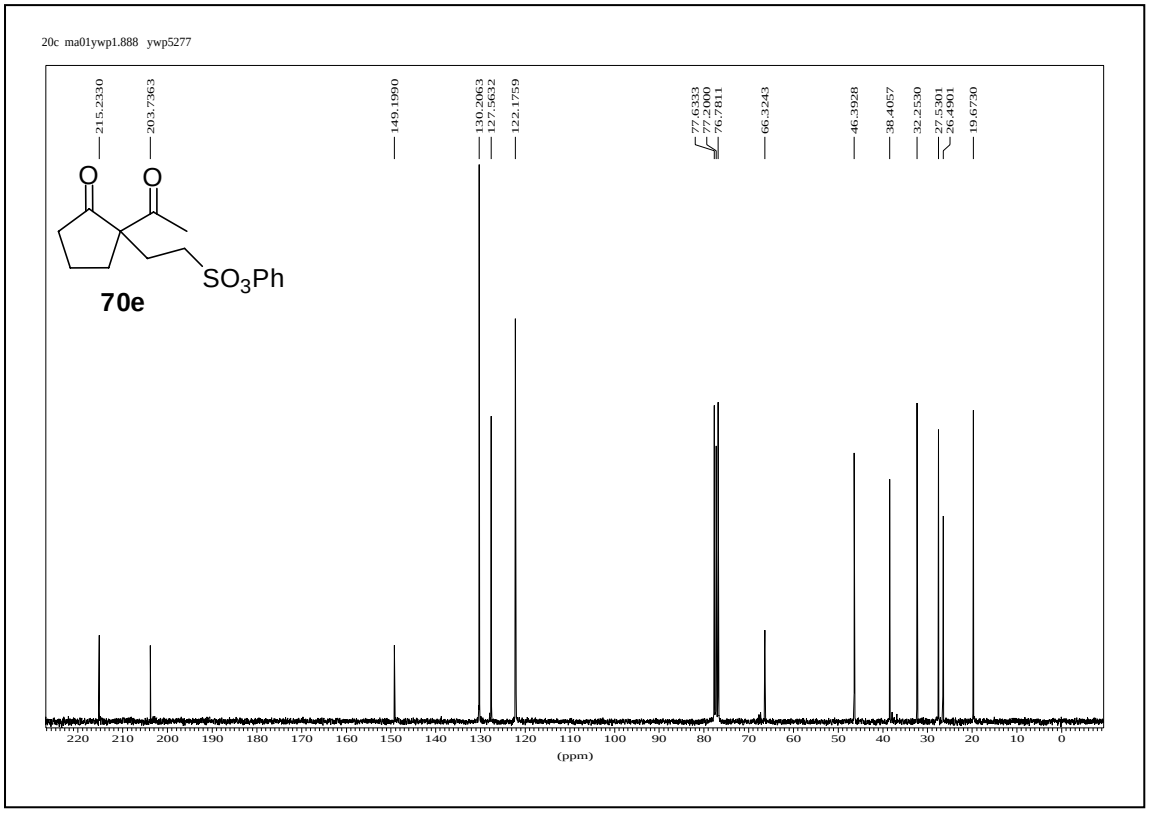
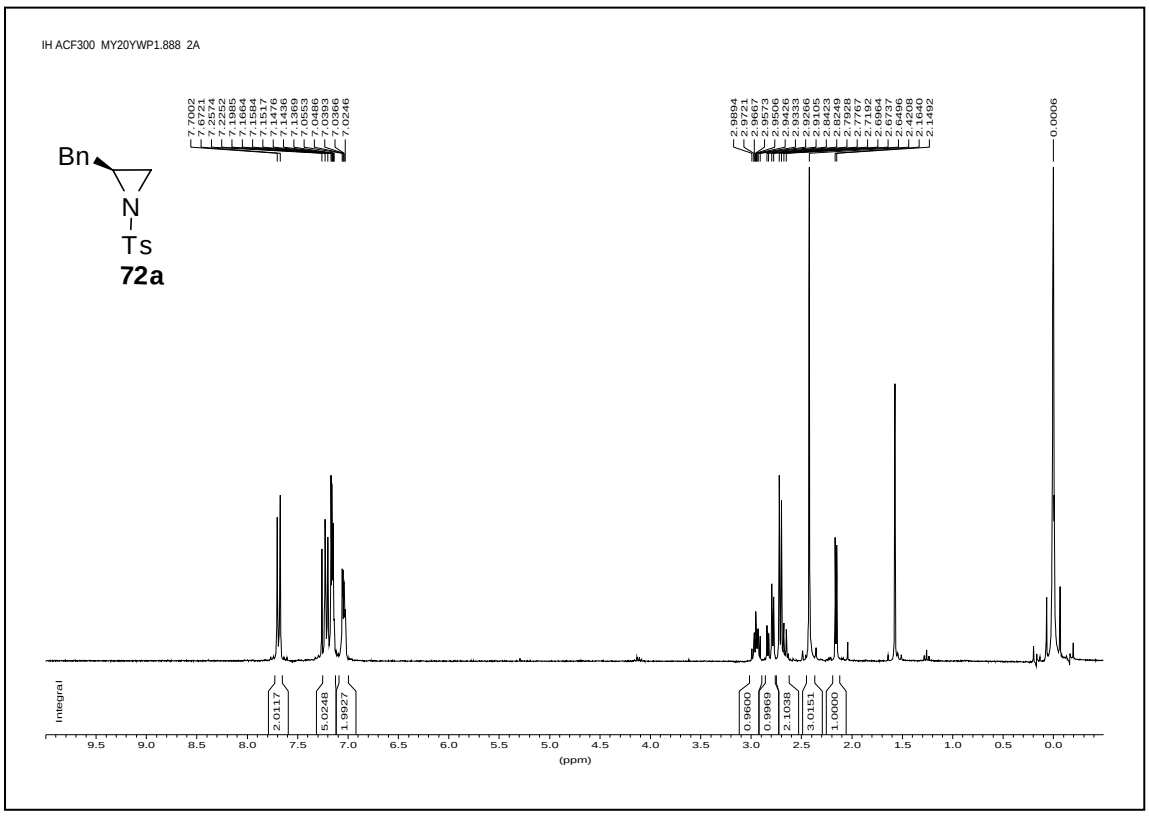
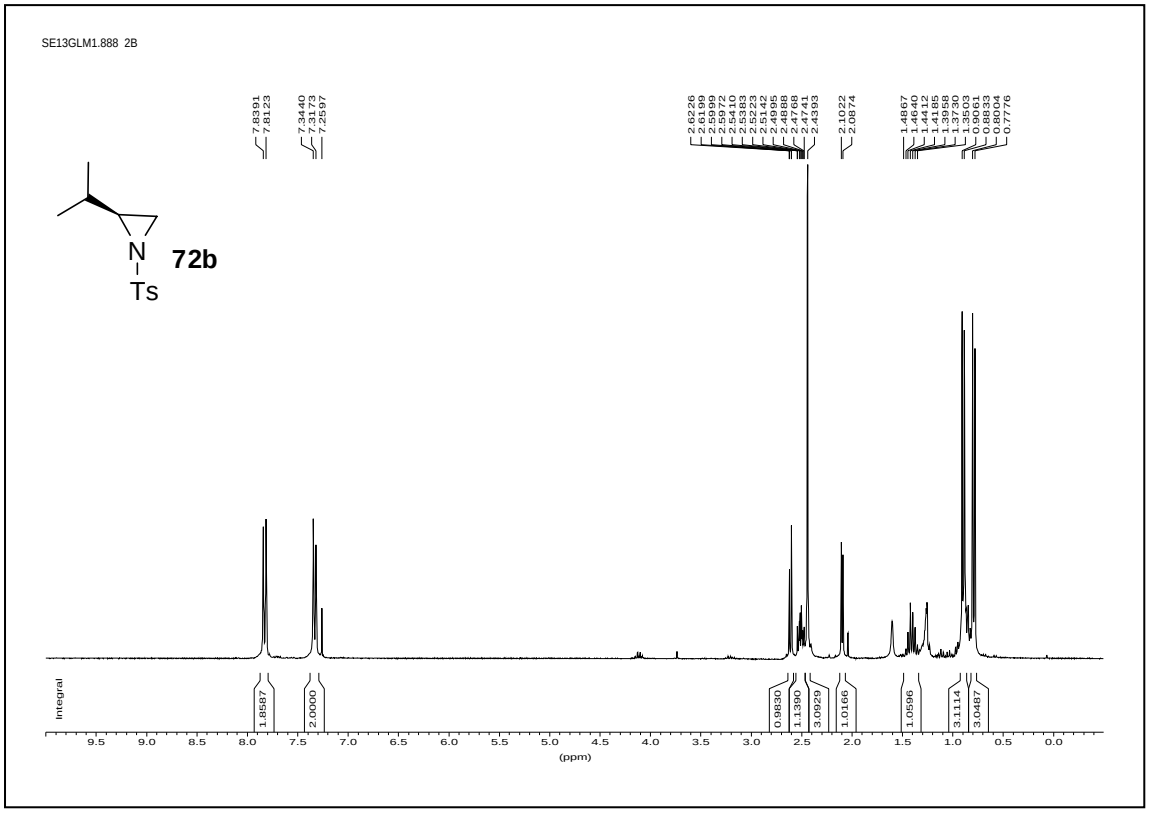
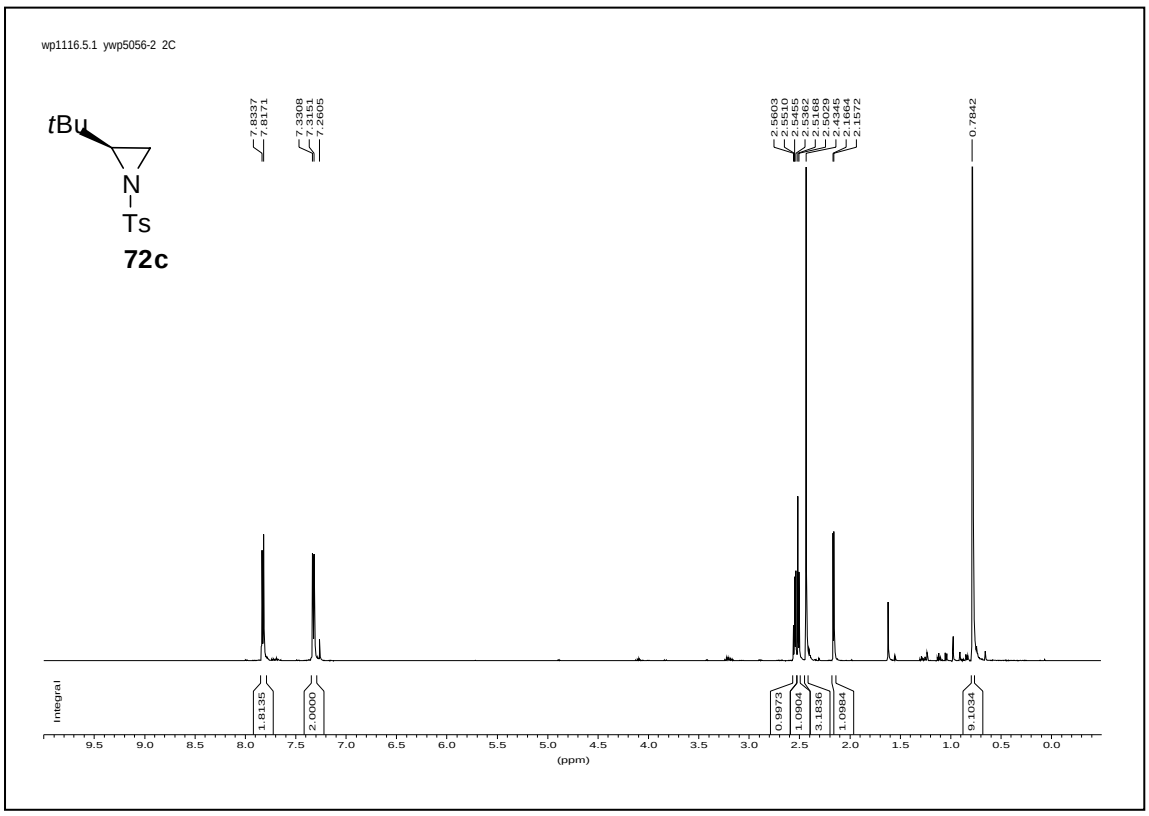
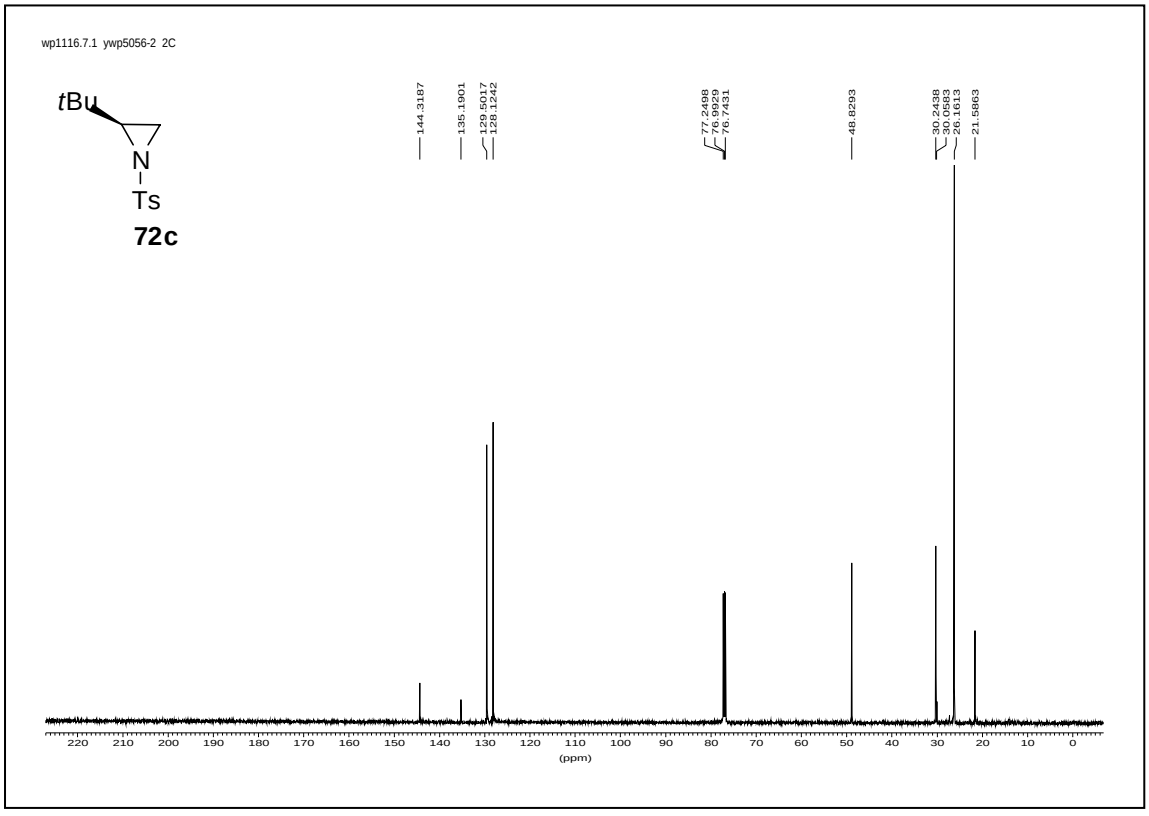
7.4313
7.4139
7.3885
7.3690
7.3350
7.3216
7.3135
7.2935
7.2885
7.2828
7.2694
7.2654
7.2560
3.2356
3.2156
3.1975
3.1995
3.1808
2.5948
2.5734
2.5520
2.5292
2.5078
2.4824
2.4797
2.4543
2.4356
2.4243
2.4249
2.4115
2.4008
2.3861
2.3700
2.3687
2.3646
2.3580
2.3446
2.3339
2.3178
2.3138
2.2844
2.1680
2.1653
2.0432
2.0328
2.0288
2.0195
2.0101
1.9967
1.9847
1.9740
1.9593
1.9512
1.9365
1.9248
1.8948
1.8108
1.7907
1.7666
1.7425
O
O
SO3Ph
70e
Integral
2.0060
3.0847
1.7911
0.9992
4.0160
3.0545
1.9863
0.9369
9.5 9.0 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 0.0
(ppm)

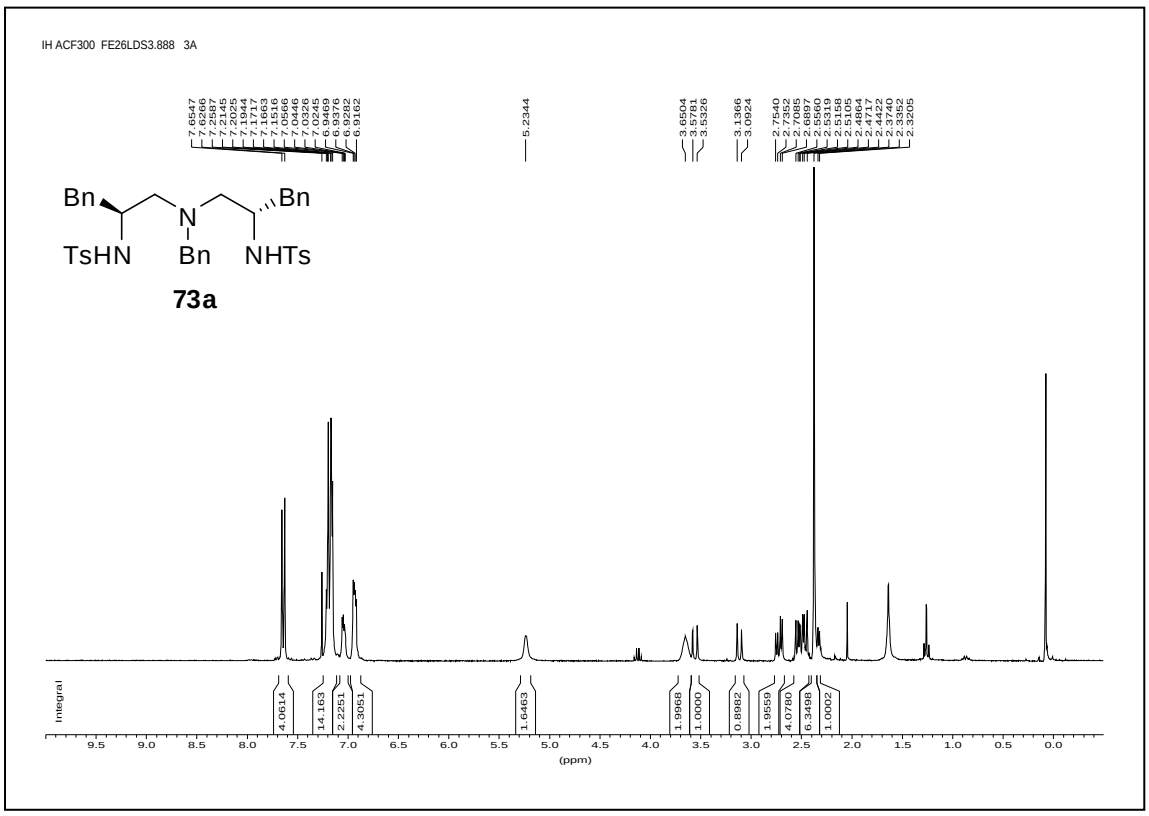

20c ma01ywp1.888 ywp5277
215.2330
203.7363
149.1990
130.2063
127.5632
122.1759
77.6333
77.2000
76.7811
66.3243
46.3928
38.4057
32.2530
27.5301
26.4901
19.6730
O
O
SO3Ph
70e
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)

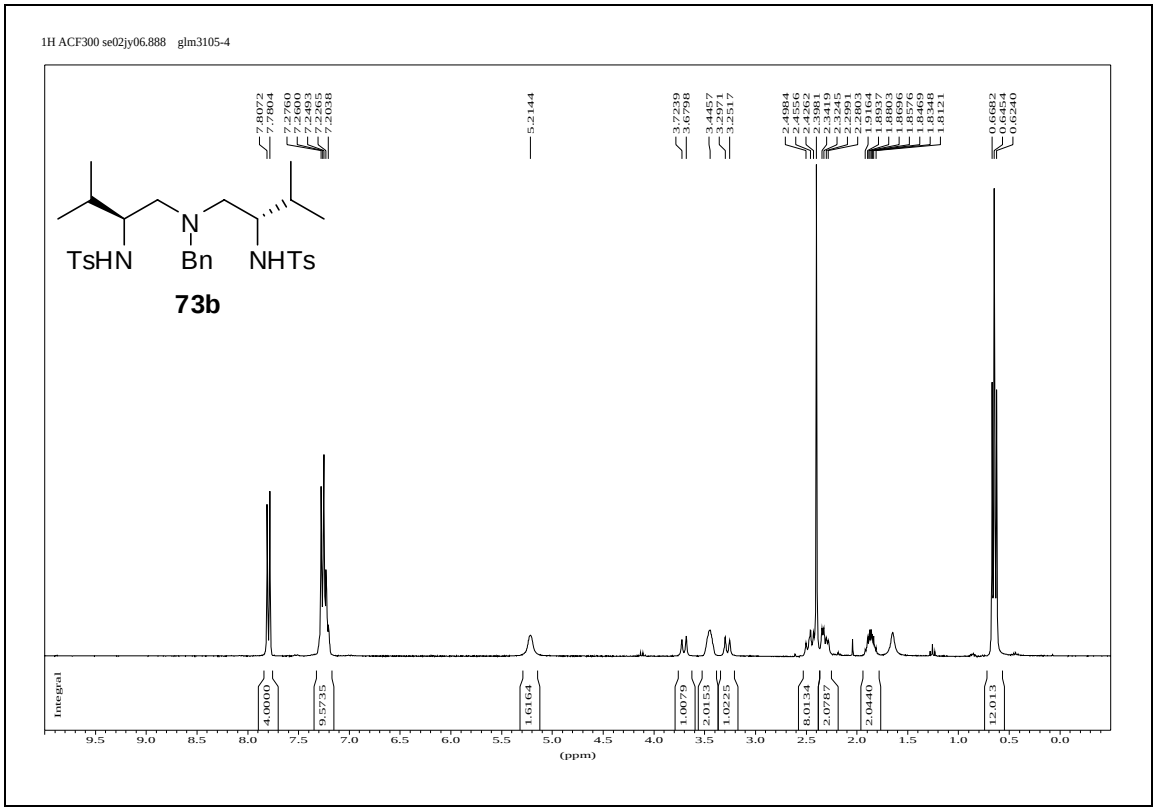

IH ACF300 MY20YWP1.888 2A
Bn
N
Ts
72a
7.7002
7.6721
7.2574
7.2252
7.1985
7.1664
7.1584
7.1517
7.1436
7.1369
7.0953
7.0486
7.0393
7.0366
7.0246
2.9894
2.9721
2.9667
2.9553
2.9506
2.9426
2.9333
2.9266
2.9105
2.8423
2.8229
2.7928
2.7767
2.7192
2.6994
2.6737
2.6496
2.4208
2.1640
2.1492
0.0006
Integral
2.0117
5.0248
1.9927
0.9600
0.9969
2.1038
3.0151
1.0000
(ppm)

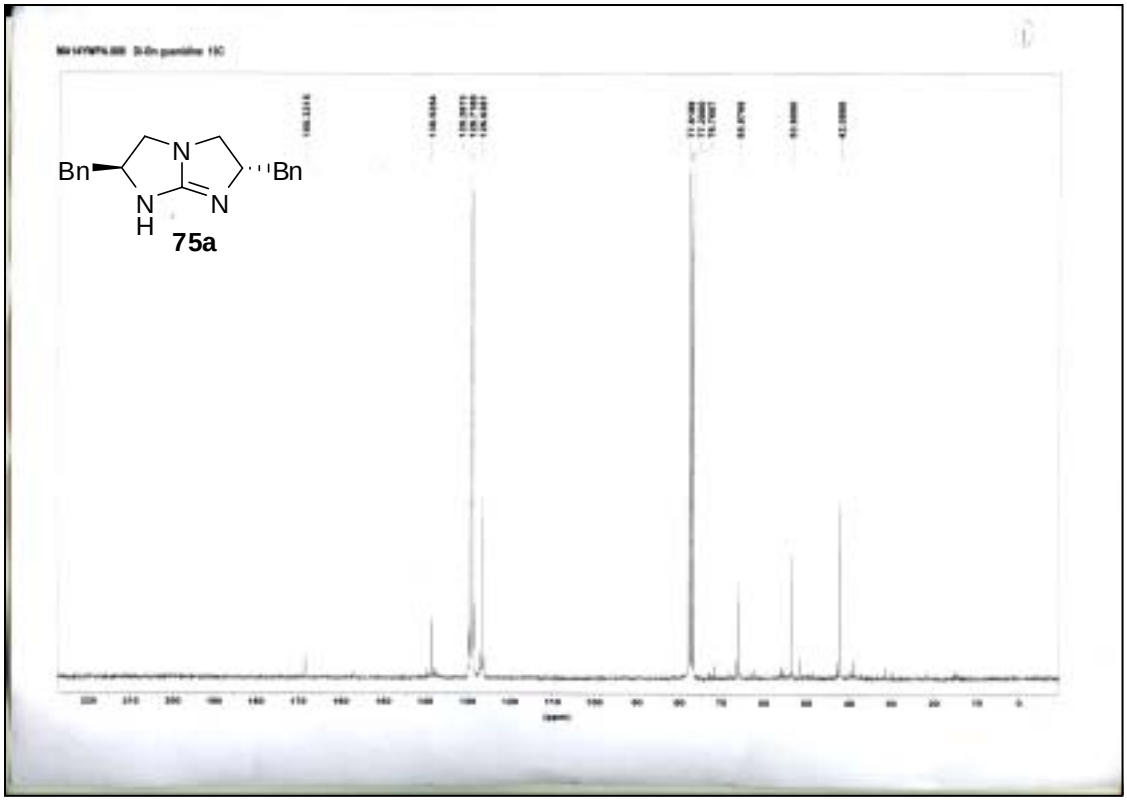

SE13GLM1.888 2B
N
Ts
72b
7.8391
7.8123
7.3440
7.3173
7.2597
2.6226
2.6199
2.5999
2.5827
2.5410
2.5383
2.5123
2.5042
2.4995
2.4888
2.4738
2.4741
2.4393
2.1022
2.0874
1.4867
1.4640
1.4412
1.4185
1.3958
1.3730
1.3503
1.0961
0.8833
0.8004
0.7776
Integral
1.8587
2.0000
0.9830
1.1390
3.0929
1.0166
1.0596
3.1114
3.0487
(ppm)

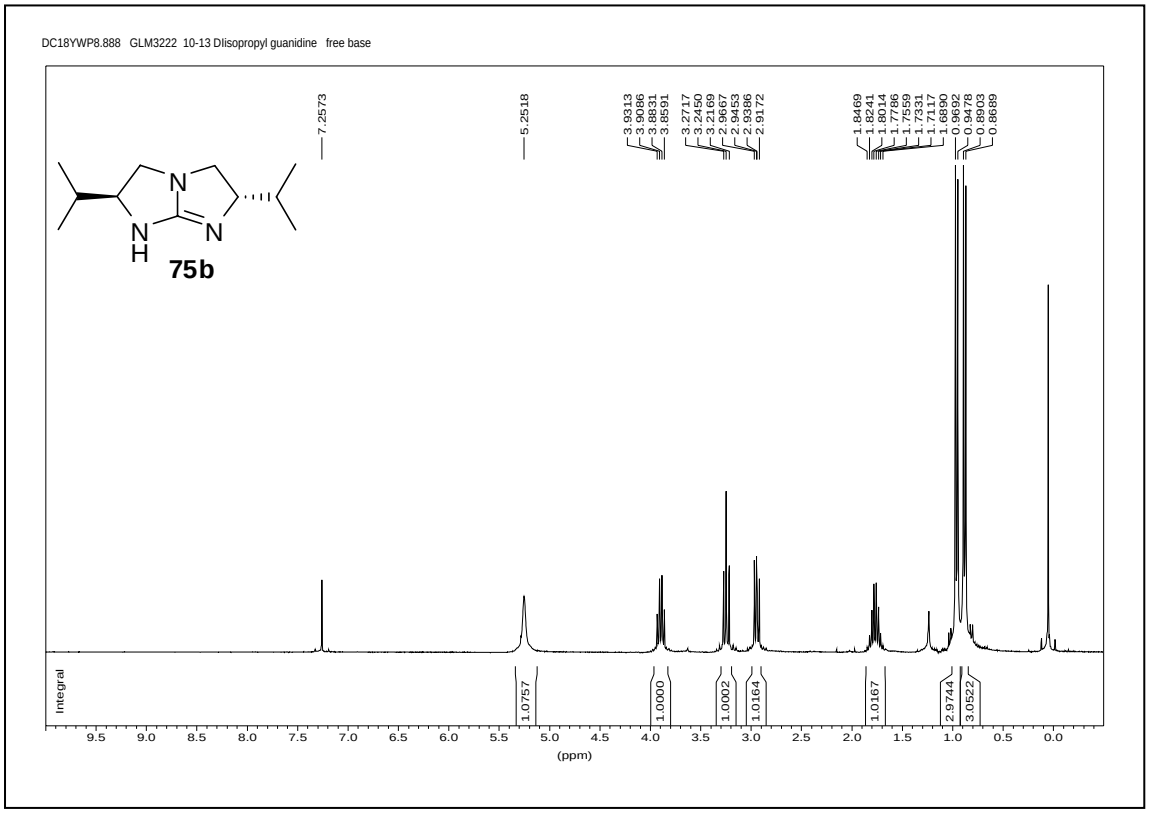

wp1116.5.1 ywp5056-2 2C
tBu
N
Ts
72c
7.8337
7.8171
7.3308
7.3151
7.2605
2.5603
2.5510
2.5455
2.5362
2.5168
2.5029
2.4845
2.1664
2.1572
0.7842
Integral
1.8135
2.0000
0.9973
1.0904
3.1836
1.0984
9.1034
(ppm)

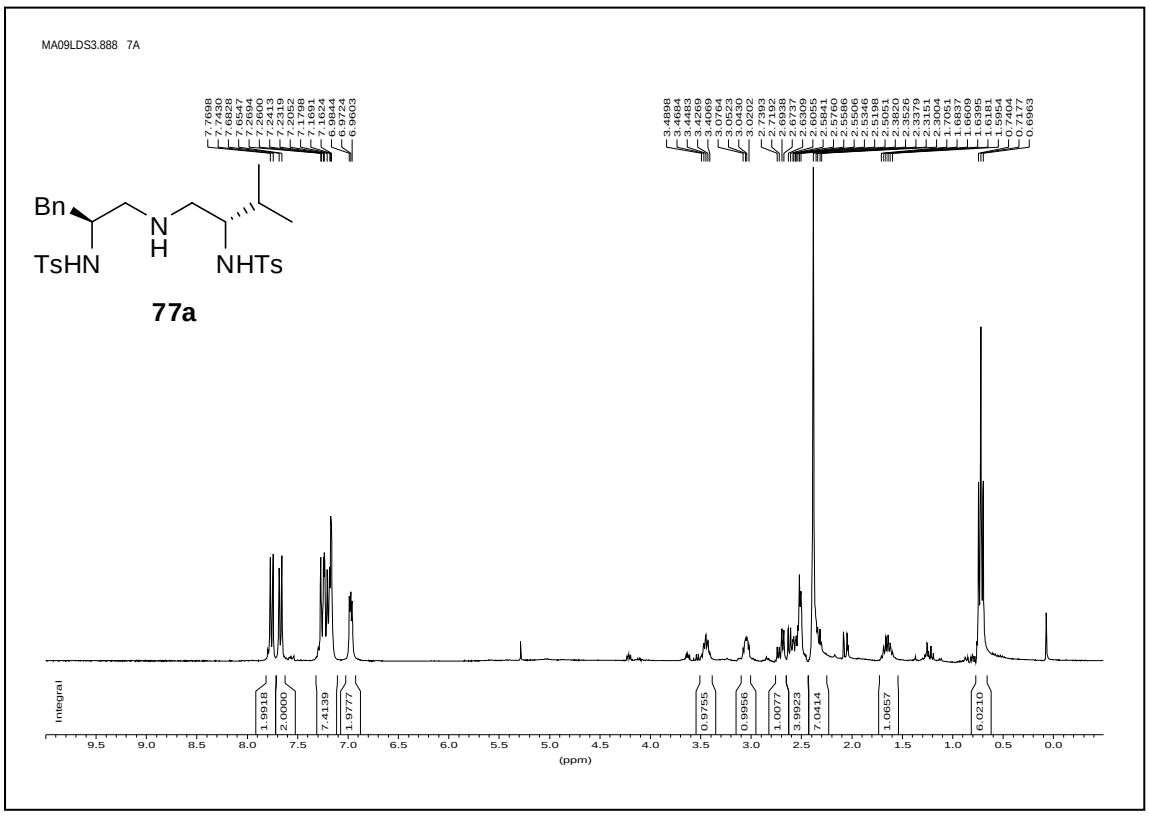

wp1116.7.1 ywp5056-2 2C
tBu
N
Ts
72c
144.3187
135.1901
129.5017
128.1242
77.2498
76.9929
76.7431
48.8293
30.2438
30.0653
26.1613
21.5863
(ppm)

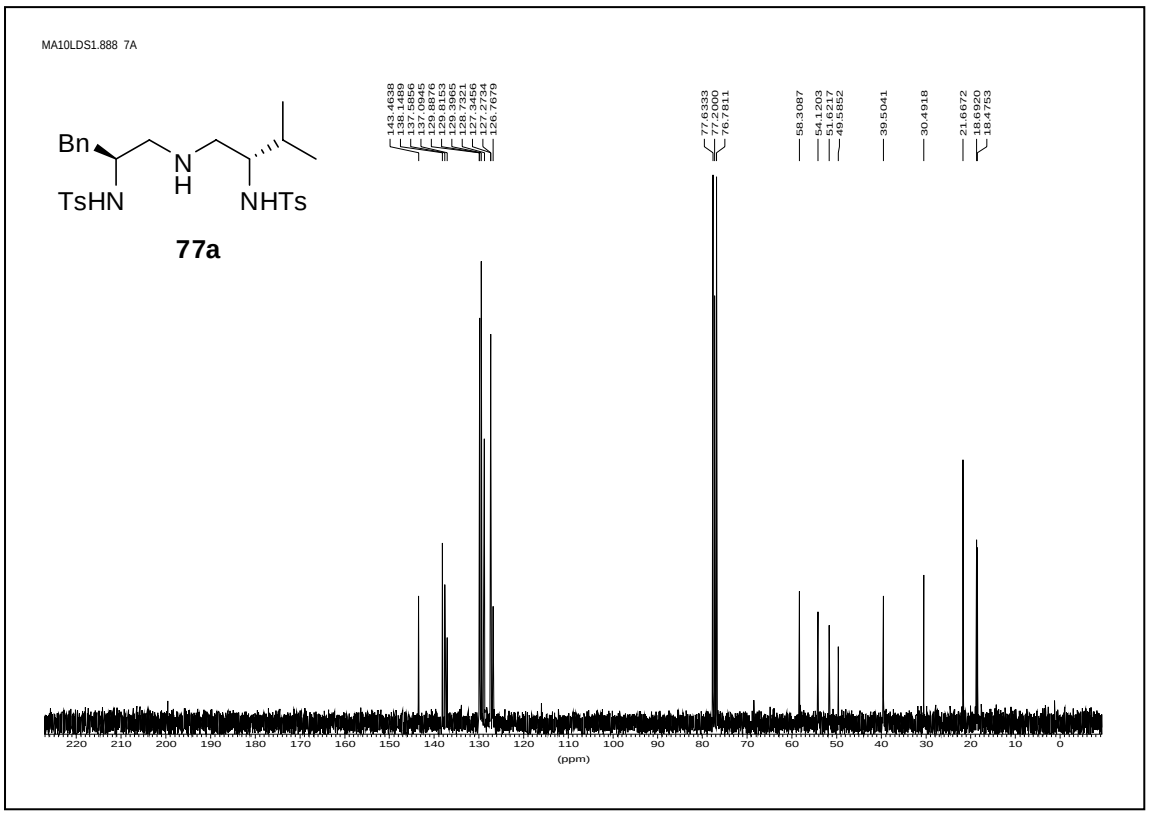

1H ACF300 FE26LDS3.888 3A
Bn
N
Bn
TsHN
Bn
NHTs
73a
integral
(ppm)

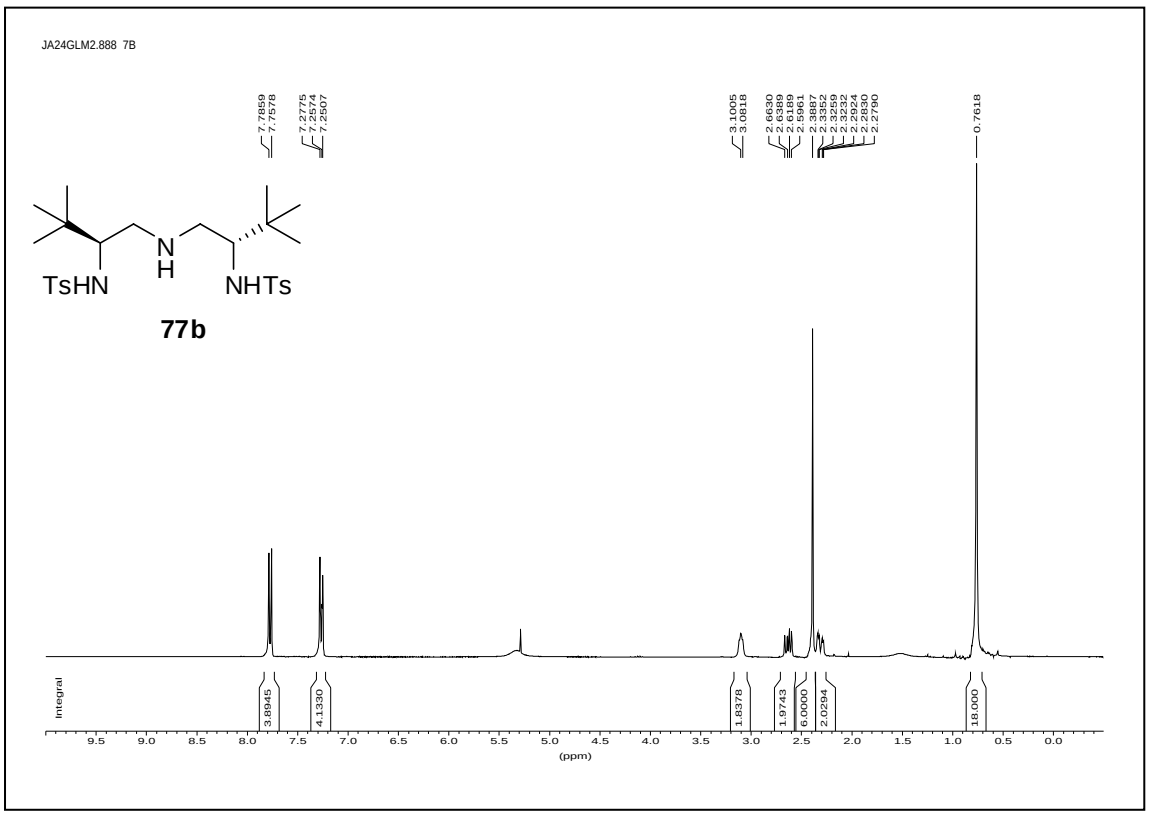

1H ACF300 se02jy06.888 glm3105-4
TsHN
N
Bn
NHTs
73b
Integral
(ppm)

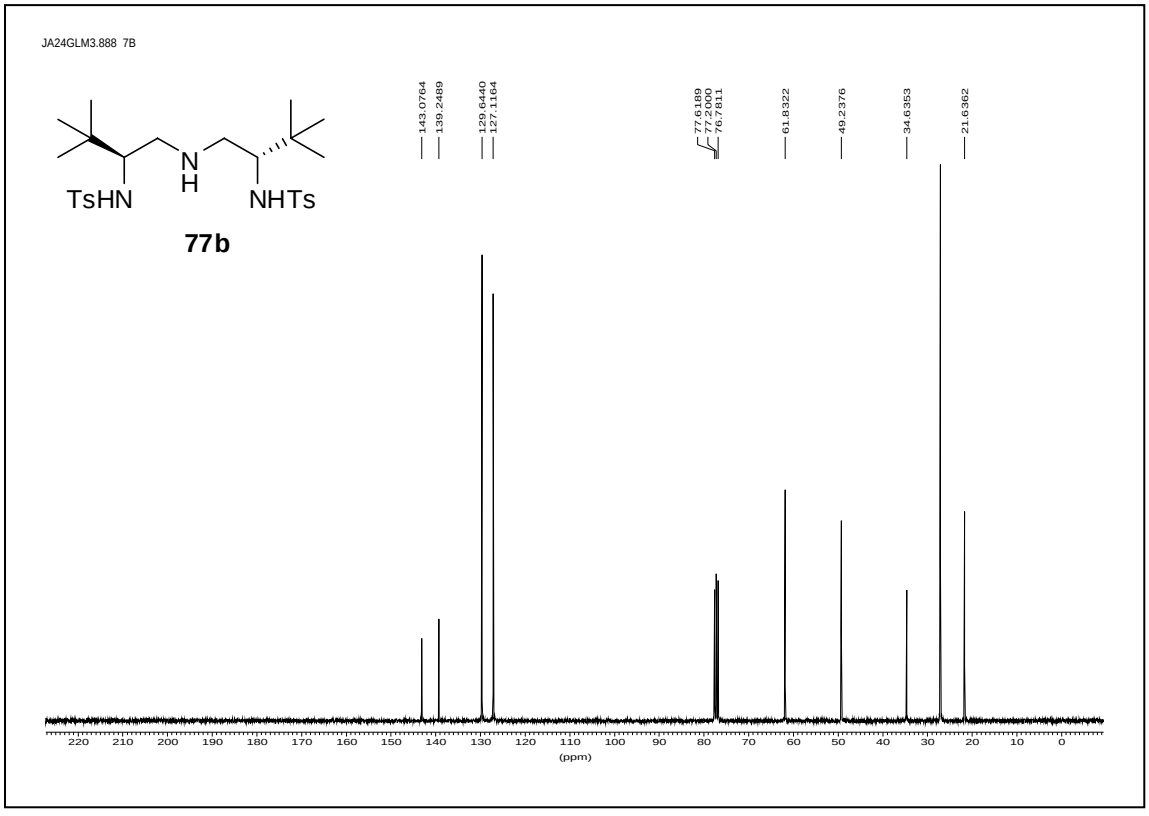

Bn
Bn
N
N
N
H
75a

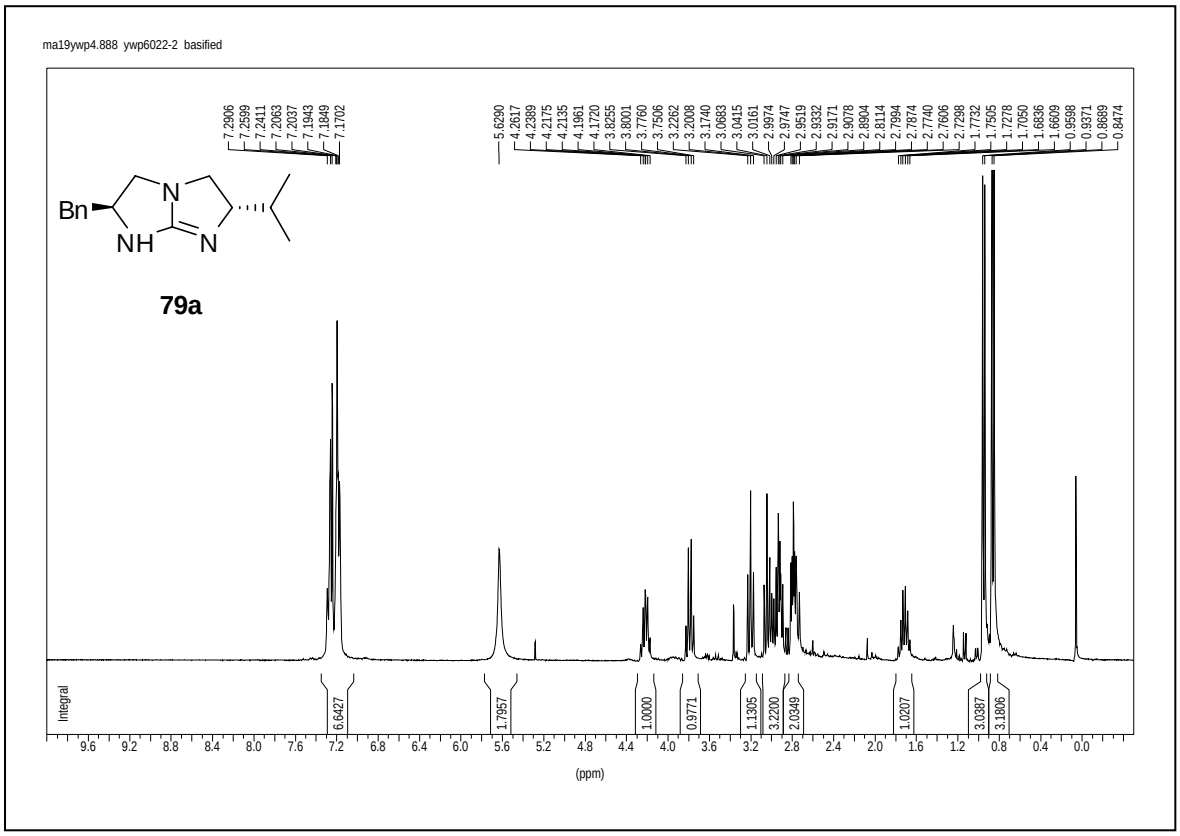

DC18YWP8.888 GLM3222 10-13 Diisopropyl guanidine free base
7.2573
5.2518
3.9313
3.9086
3.8931
3.8591
3.2717
3.2450
3.2169
3.1867
2.9453
2.9386
2.9172
1.8469
1.8241
1.8014
1.7786
1.7559
1.7331
1.7117
1.6890
0.9692
0.9478
0.8903
0.8689
N
N
N
H
75b
Integral
1.0757
1.0000
1.0002
1.0164
1.0167
2.9744
3.0522
9.5 9.0 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 0.0
(ppm)

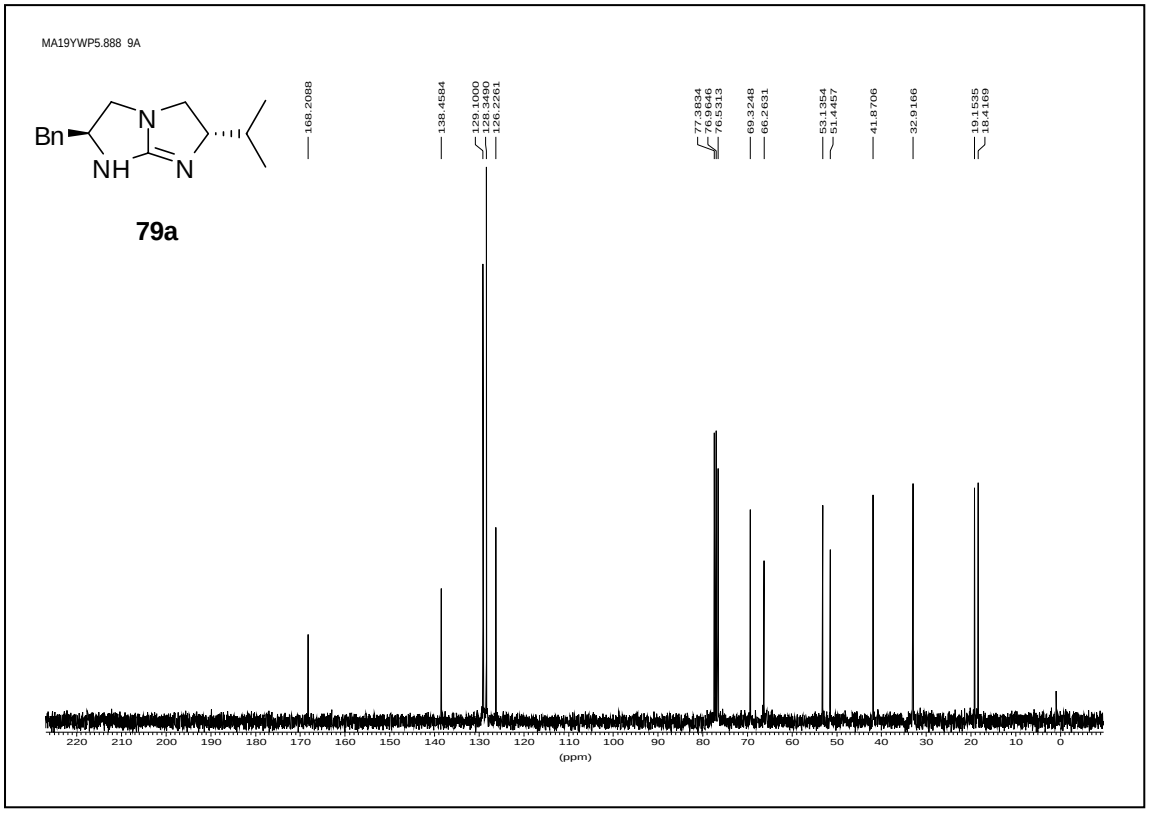

MA09LDS3.888 7A
Bn
N
H
TsHN
NHTs
77a
integral
(ppm)

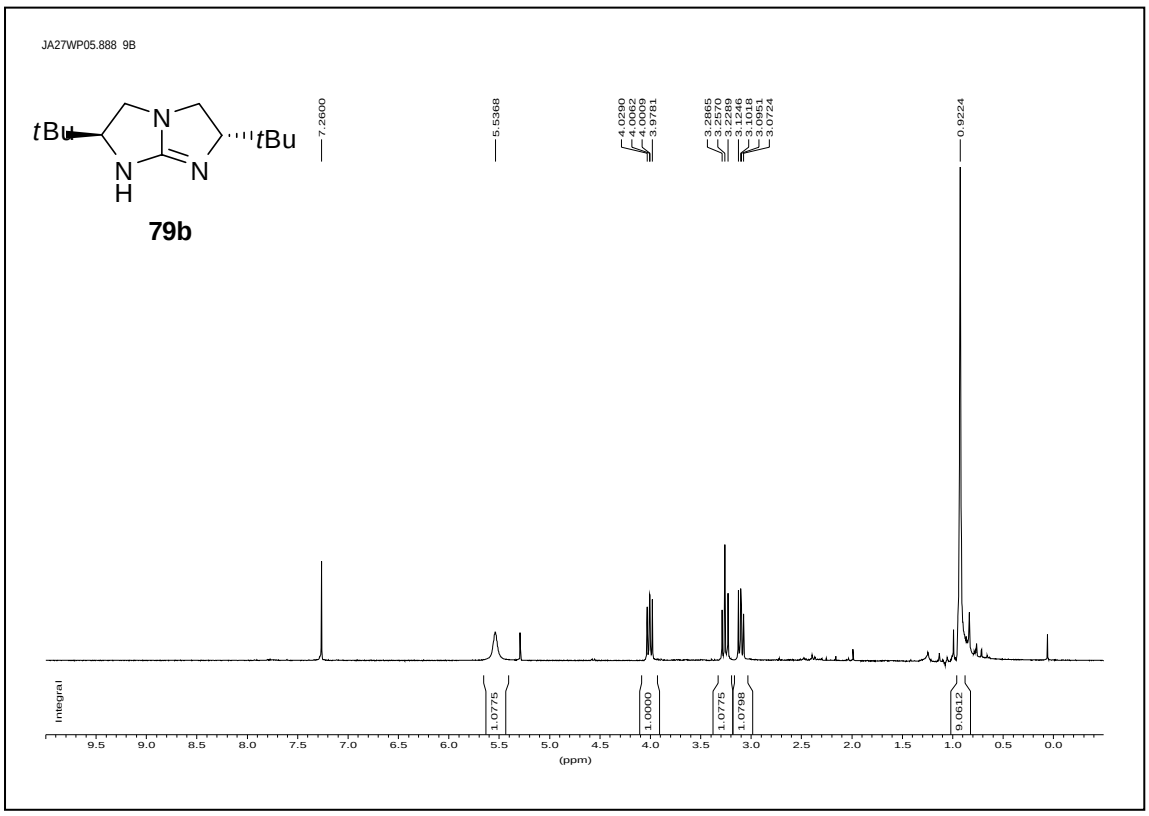

MA10LDS1.888 7A
Bn
N
H
TsHN
NHTs
77a
(ppm)

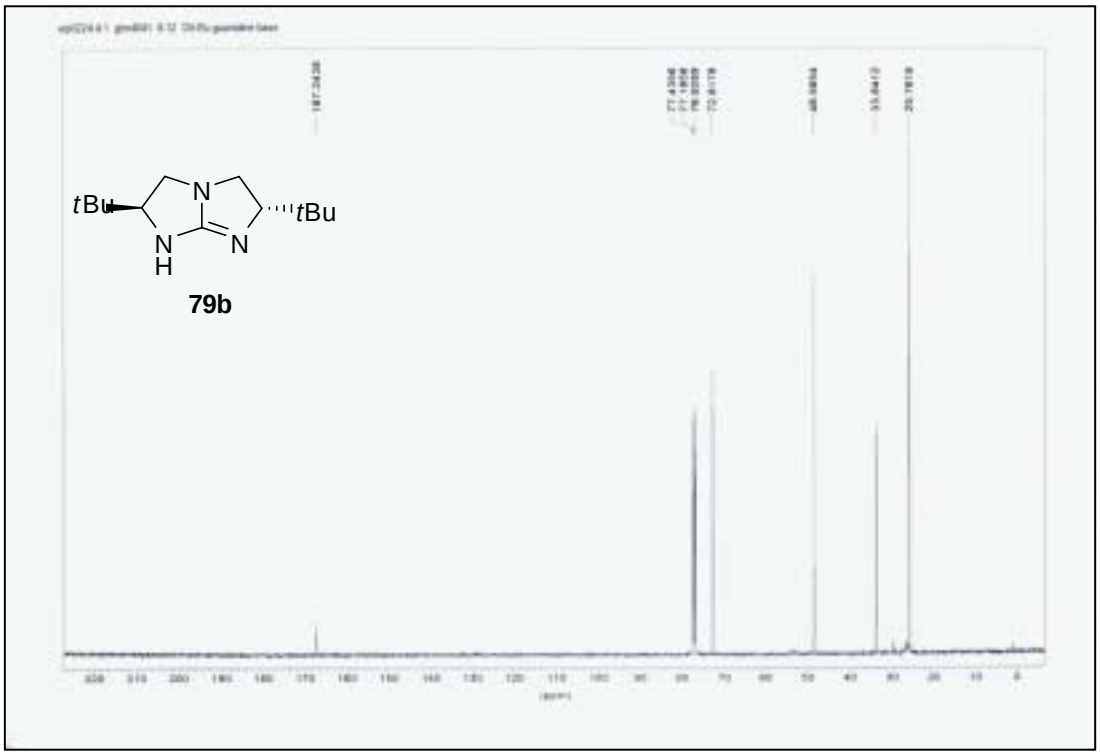

JA24GLM2.888 7B
7.7959
7.7578
7.2775
7.2574
7.2507
3.1005
3.0818
2.6630
2.6489
2.6189
2.5961
2.3887
2.3552
2.3350
2.3232
2.2924
2.2830
2.2790
0.7618
TsHN
NHTs
77b
Integral
3.8945
4.1330
1.8378
1.9743
6.0000
2.0294
18.000
(ppm)


JA24GLM3.888 7B
143.0764
139.2489
129.6440
127.1164
77.6189
77.2000
76.7811
61.8322
49.2376
34.6353
21.6362
TsHN
NHTs
77b
(ppm)

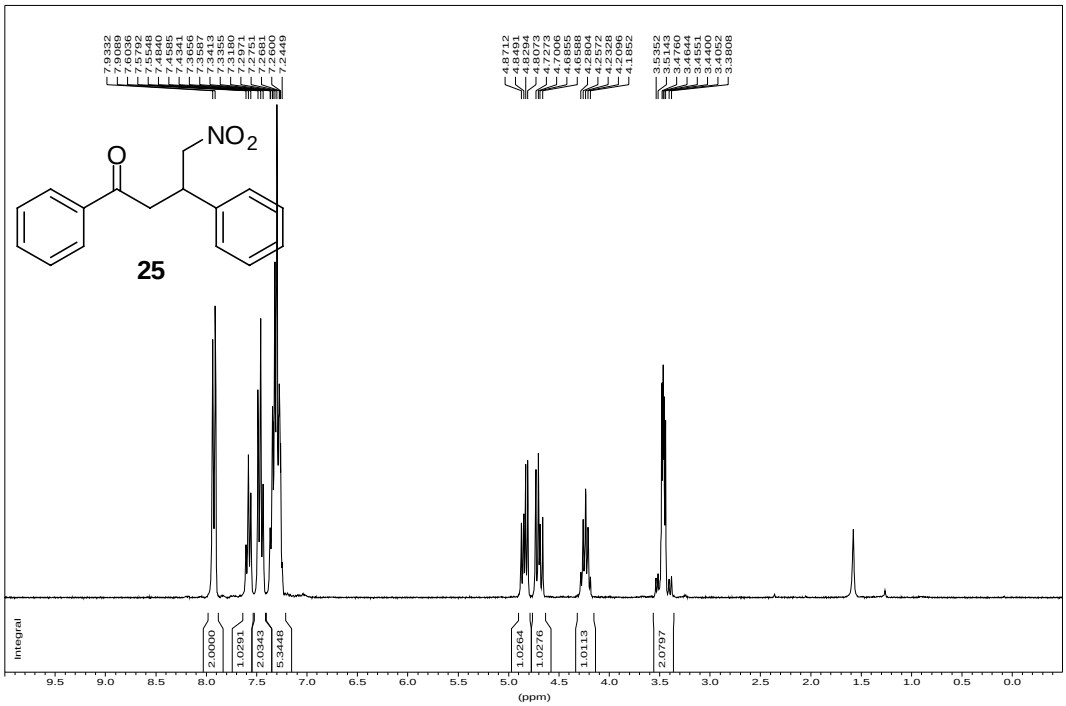

ma19ywp4.888 ywp6022-2 basified
Bn
NH
N
N
79a
Integral
(ppm)


MA19YWP5.888 9A
Bn
NH
N
N
79a
(ppm)

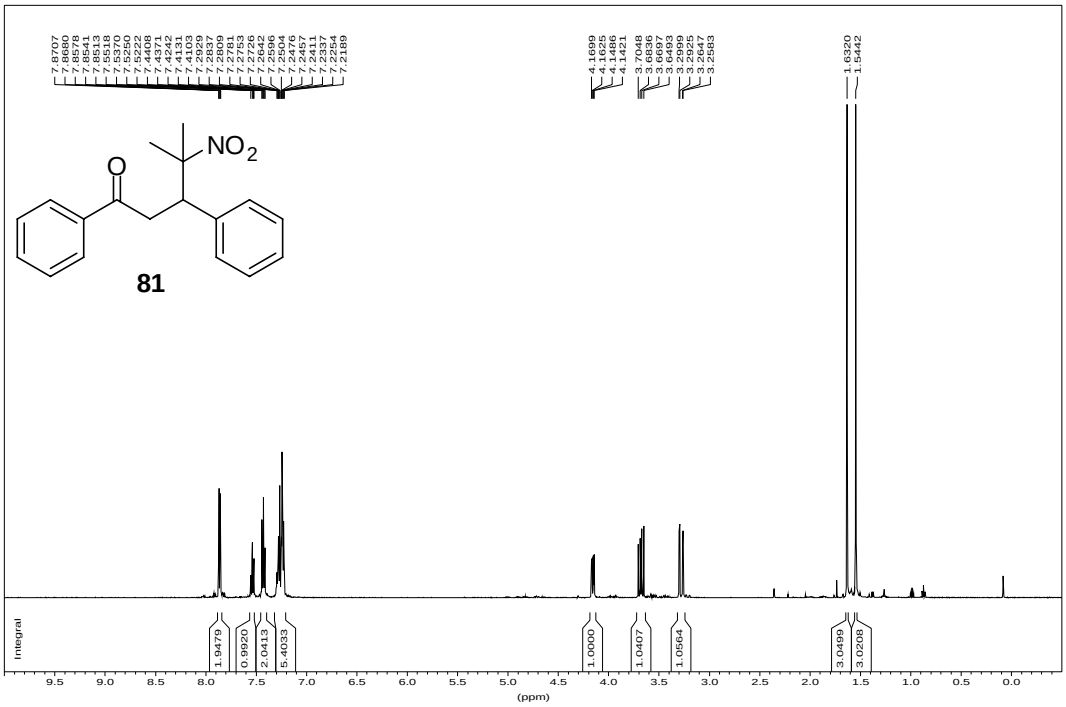

JA27WP05.888 9B
tBu
tBu
N
N
H
N
79b
7.2600
5.5368
4.0290
4.0062
4.0009
3.9701
3.2865
3.2570
3.2289
3.2046
3.1018
3.0951
3.0724
0.9224
Integral
1.0775
1.0000
1.0775
1.0798
9.0612
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)

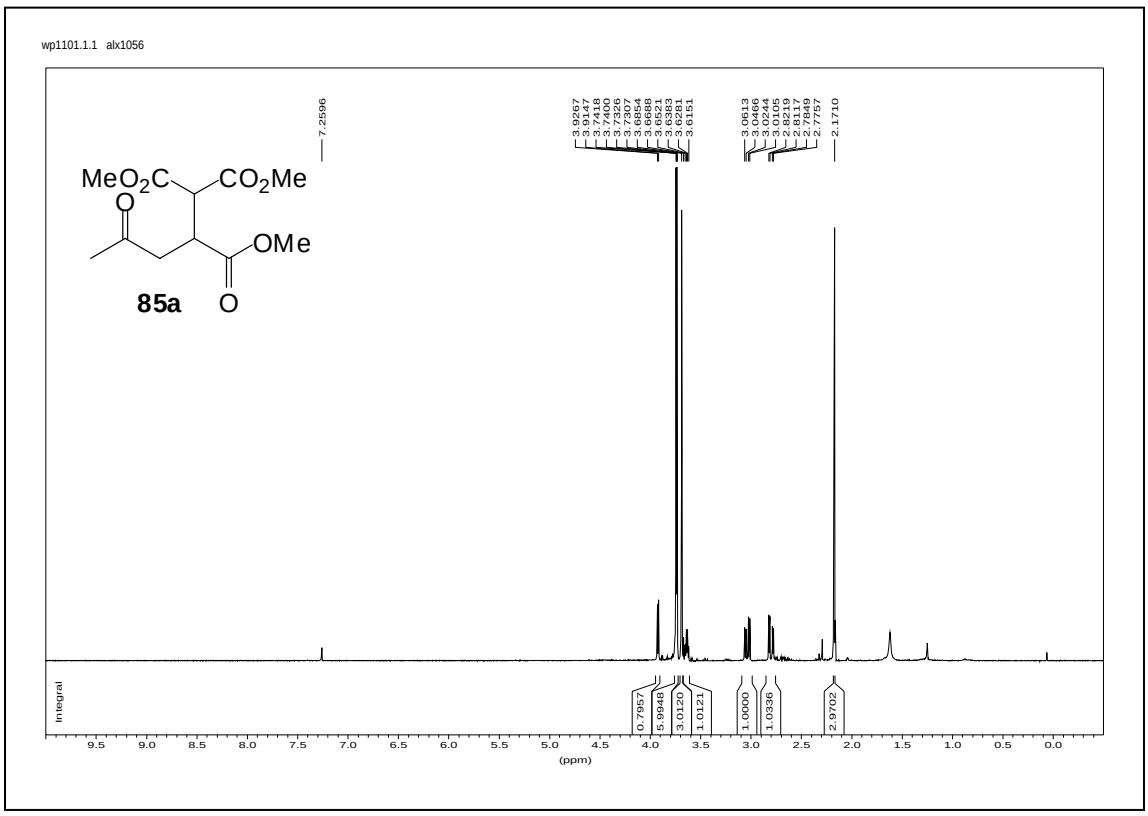

tBu
tBu
N
N
H
N
79b

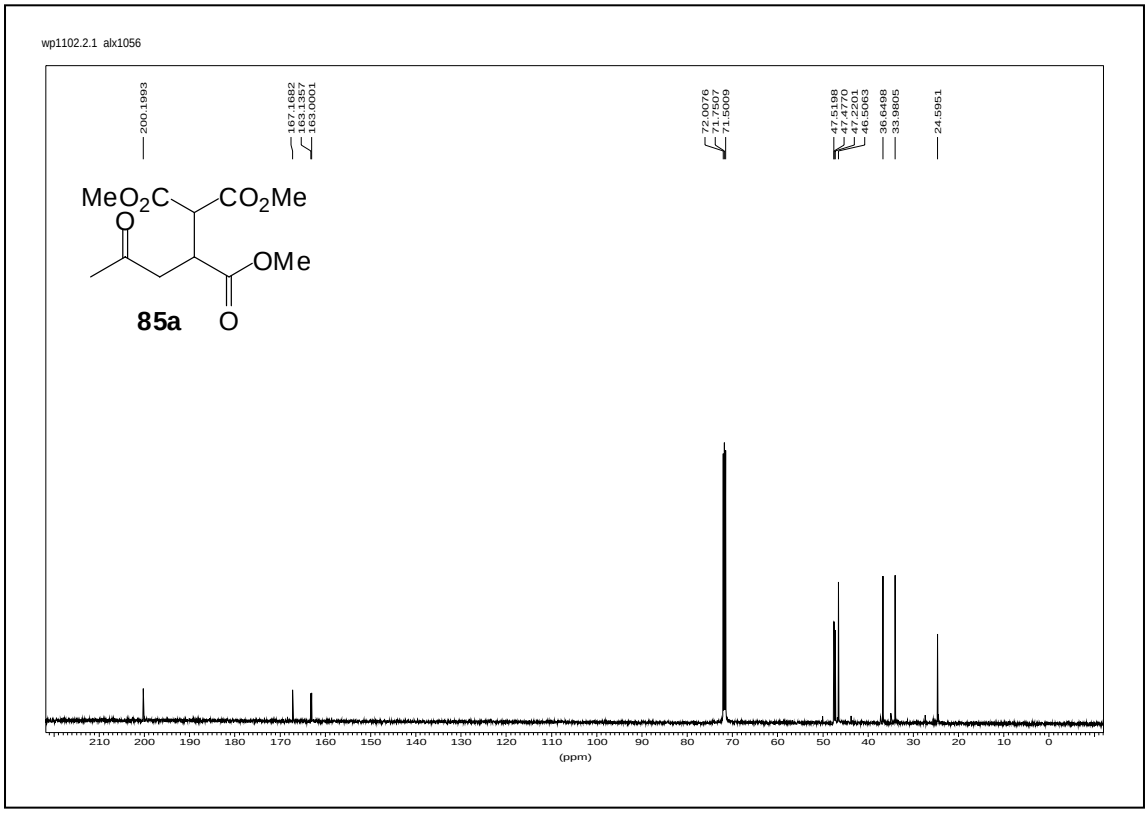
se16ywp.3.1 tct3049

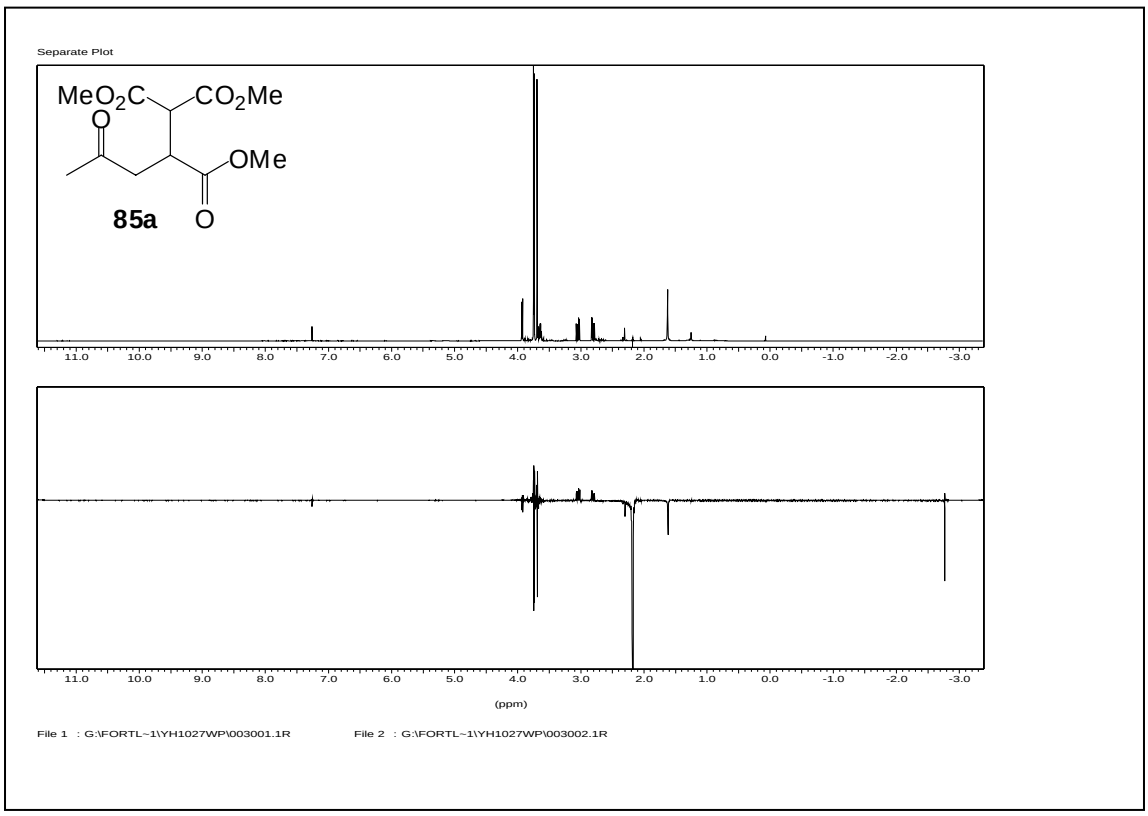


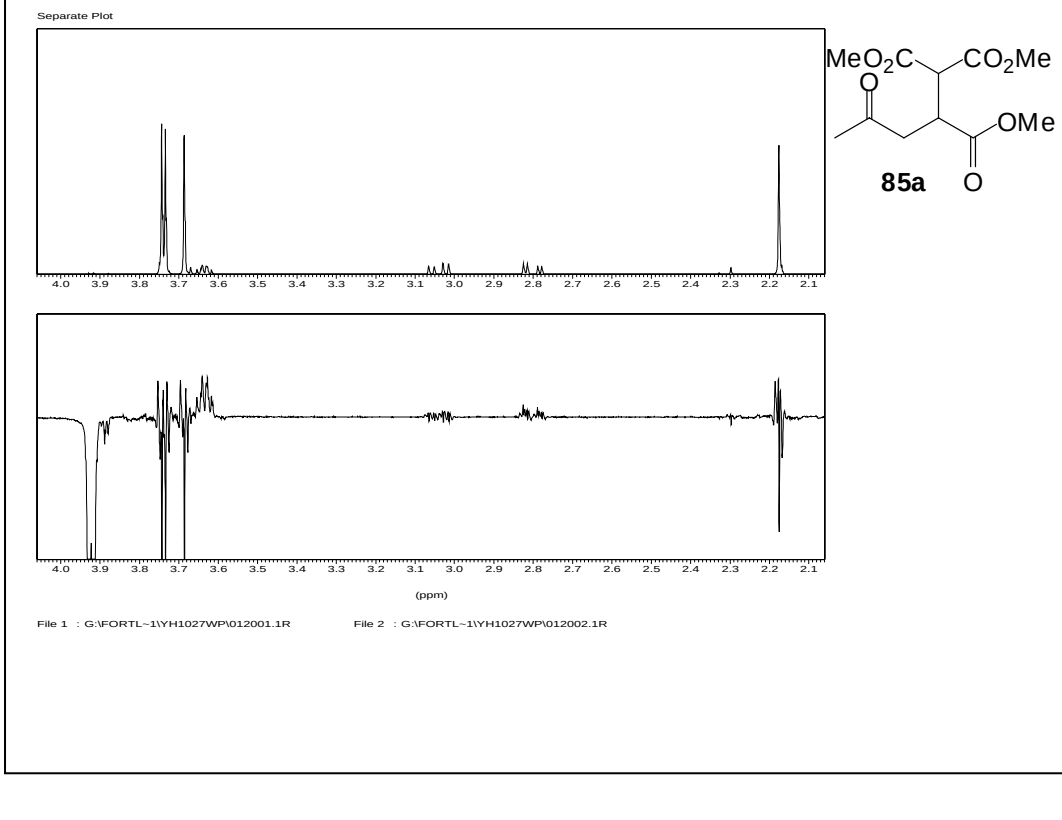
amx500 wp1122.1.1 ywp5071



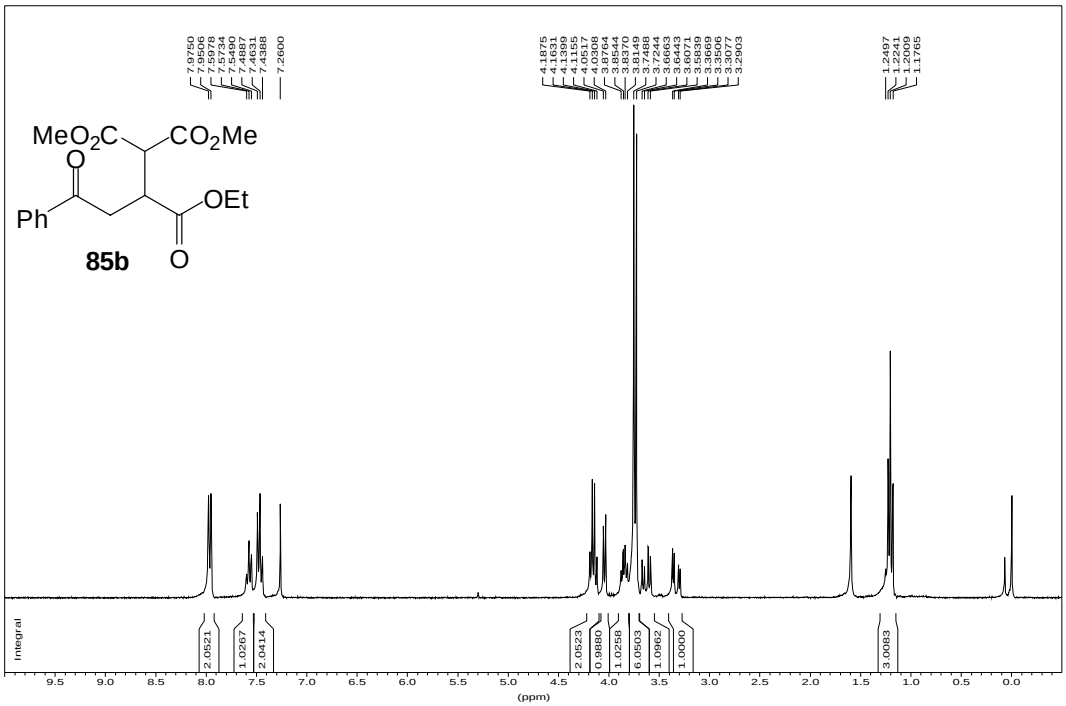

wp1101.1.1 alx1056
7.2596
3.9267
3.9147
3.7418
3.7400
3.7326
3.7307
3.6884
3.6688
3.6521
3.6283
3.6281
3.6151
3.0613
3.0466
3.0264
3.0105
2.8219
2.8117
2.7949
2.7757
2.1710
MeO2C
CO2Me
O
OMe
O
85a
integral
0.7957
5.9948
3.0120
1.0121
1.0000
1.0336
2.9702
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)


wp1102.2.1 alx1056
200.1993
167.1682
163.1357
163.0001
72.0076
71.7507
71.5009
47.5198
47.4770
47.2201
46.5063
36.6498
33.9805
24.5961
MeO2C
CO2Me
O
OMe
O
85a
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)

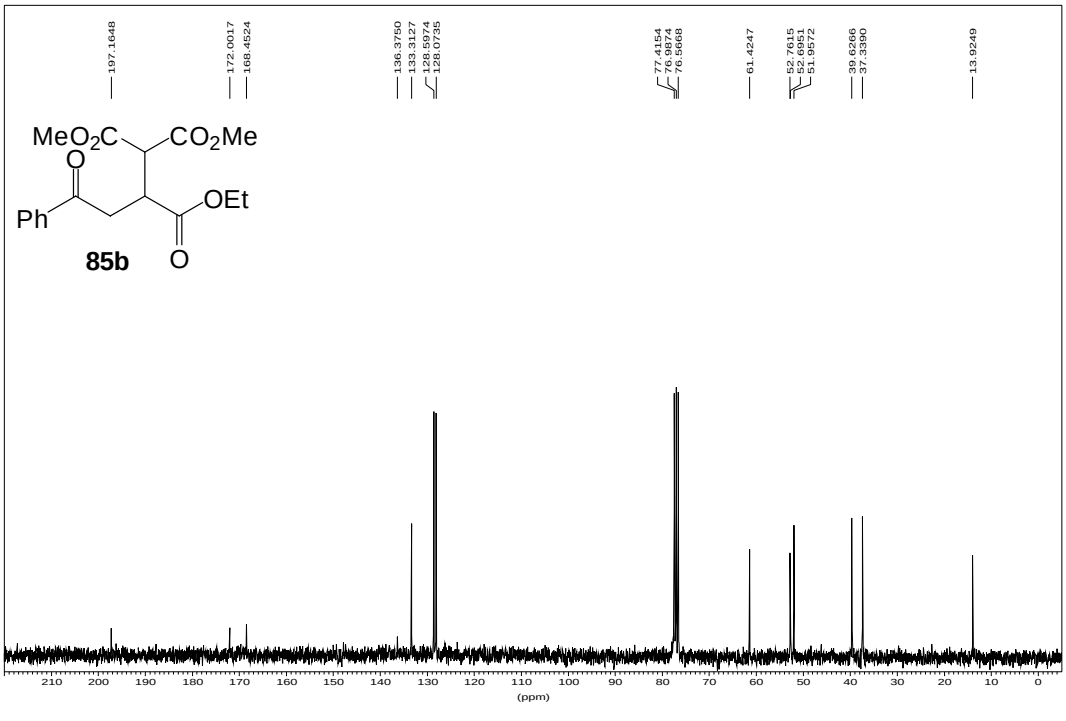

Separate Plot
MeO2C
CO2Me
O
OMe
85a
O
11.0 10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0 -1.0 -2.0 -3.0
11.0 10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0 -1.0 -2.0 -3.0
(ppm)
File 1 : G:\FORTL~1\YH1027WP\003001.1R
File 2 : G:\FORTL~1\YH1027WP\003002.1R

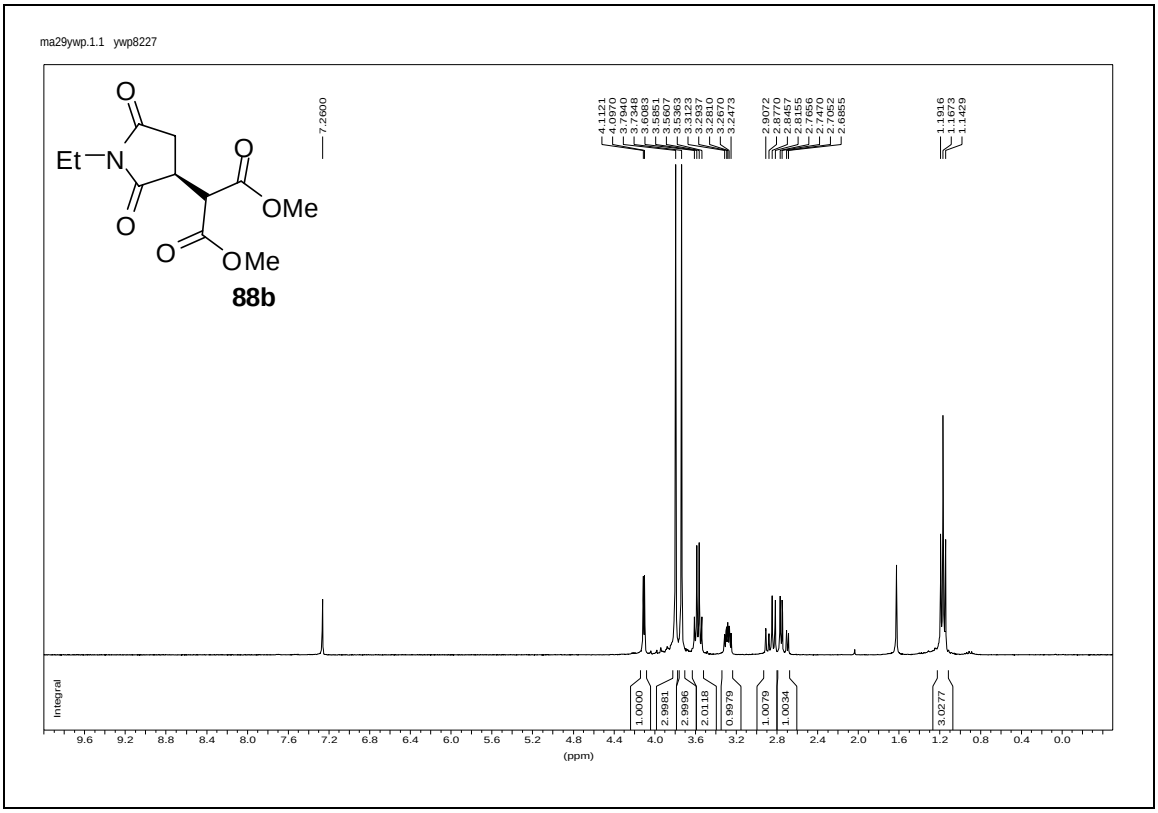

Separate Plot
MeO2C
CO2Me
O
OMe
85a
O
4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1
4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1
(ppm)
File 1 : G:\FORTL~1\YH1027WP\012001.1R
File 2 : G:\FORTL~1\YH1027WP\012002.1R

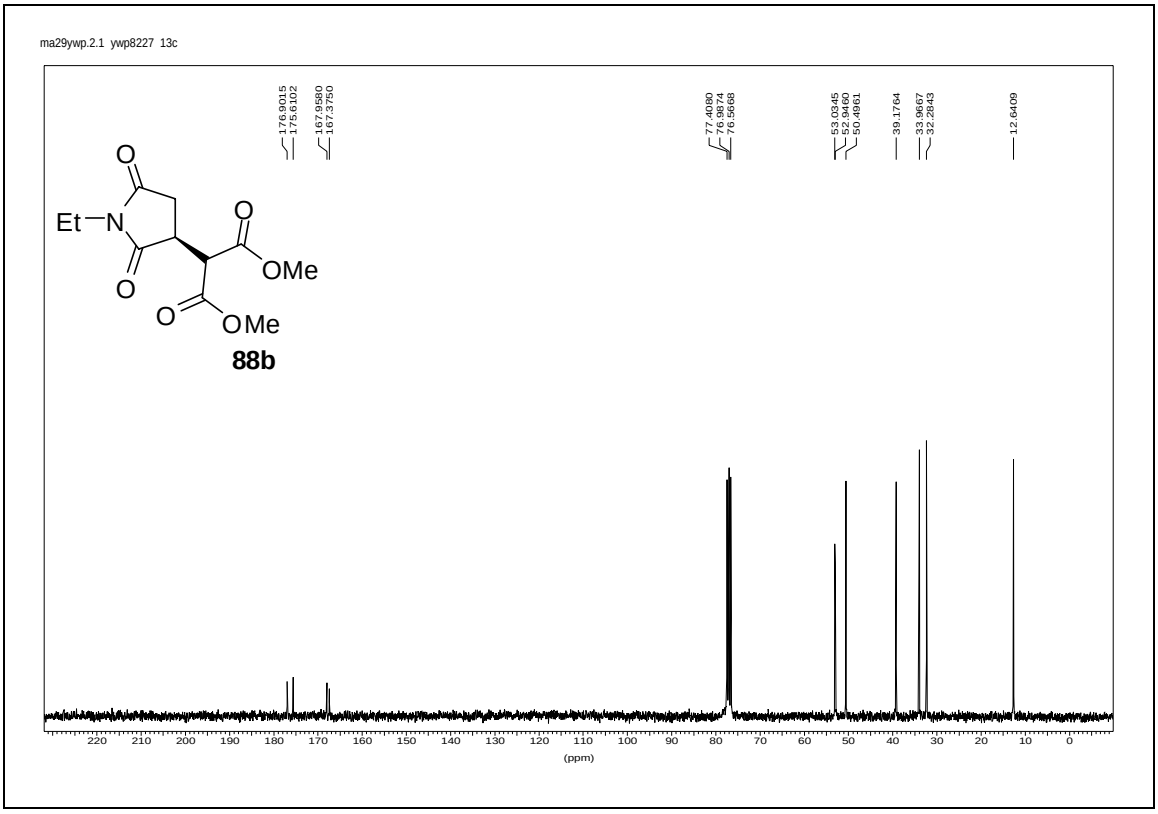
se14ywp.4.1 glm3275

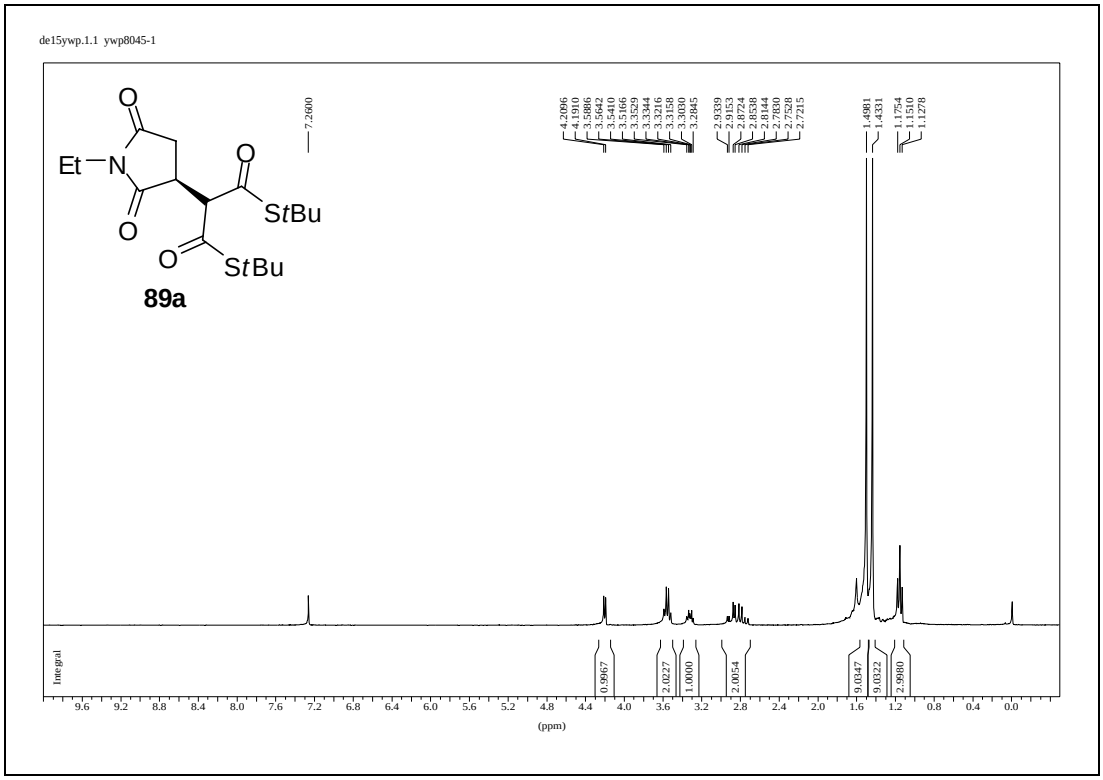


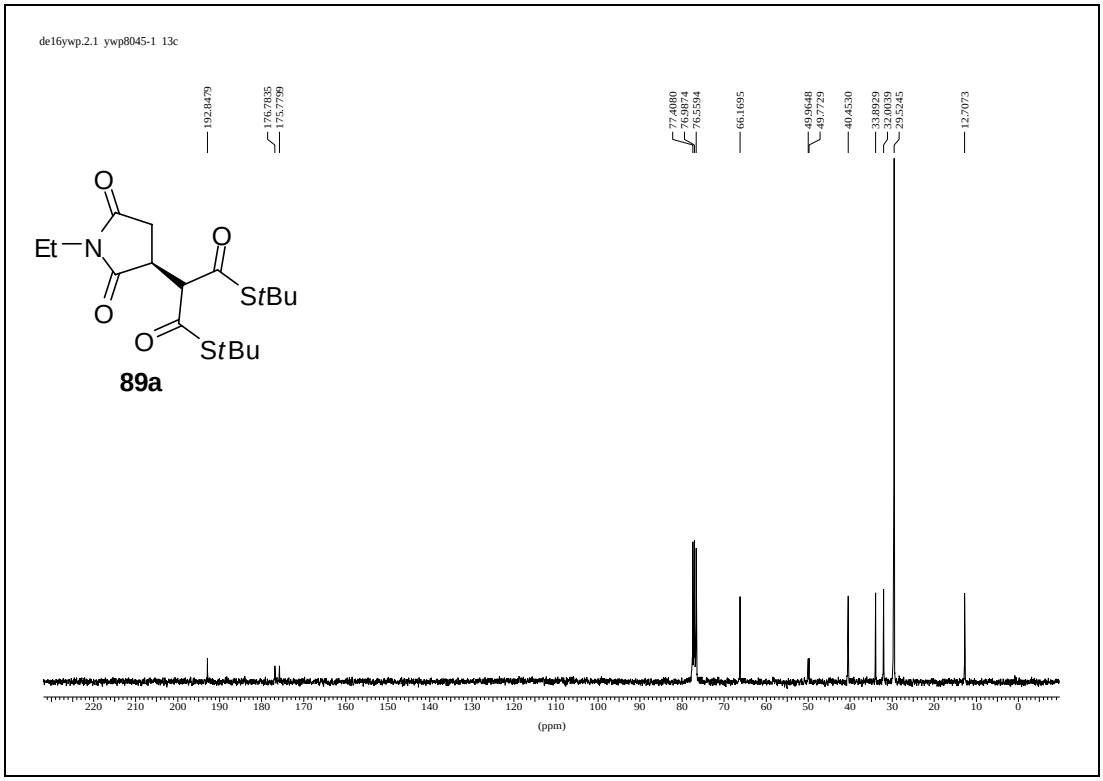
se14ywp.5.1 glm3275 13c

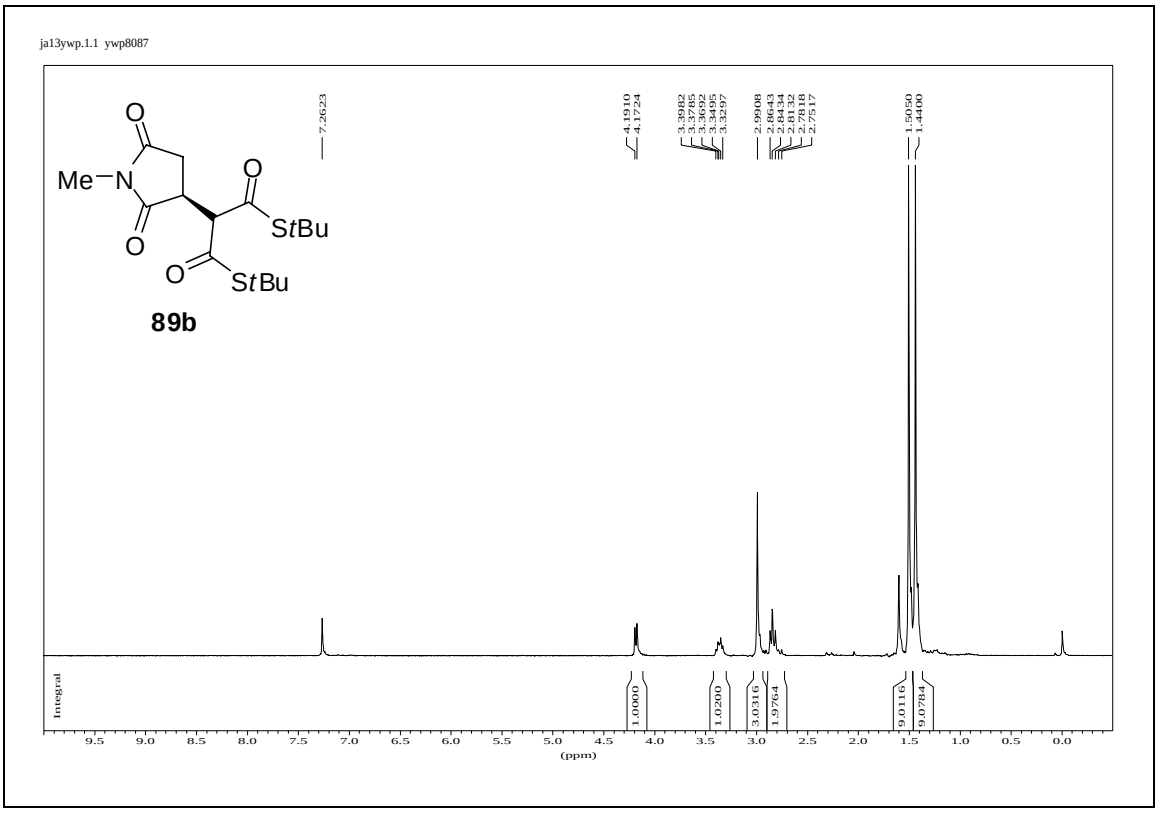


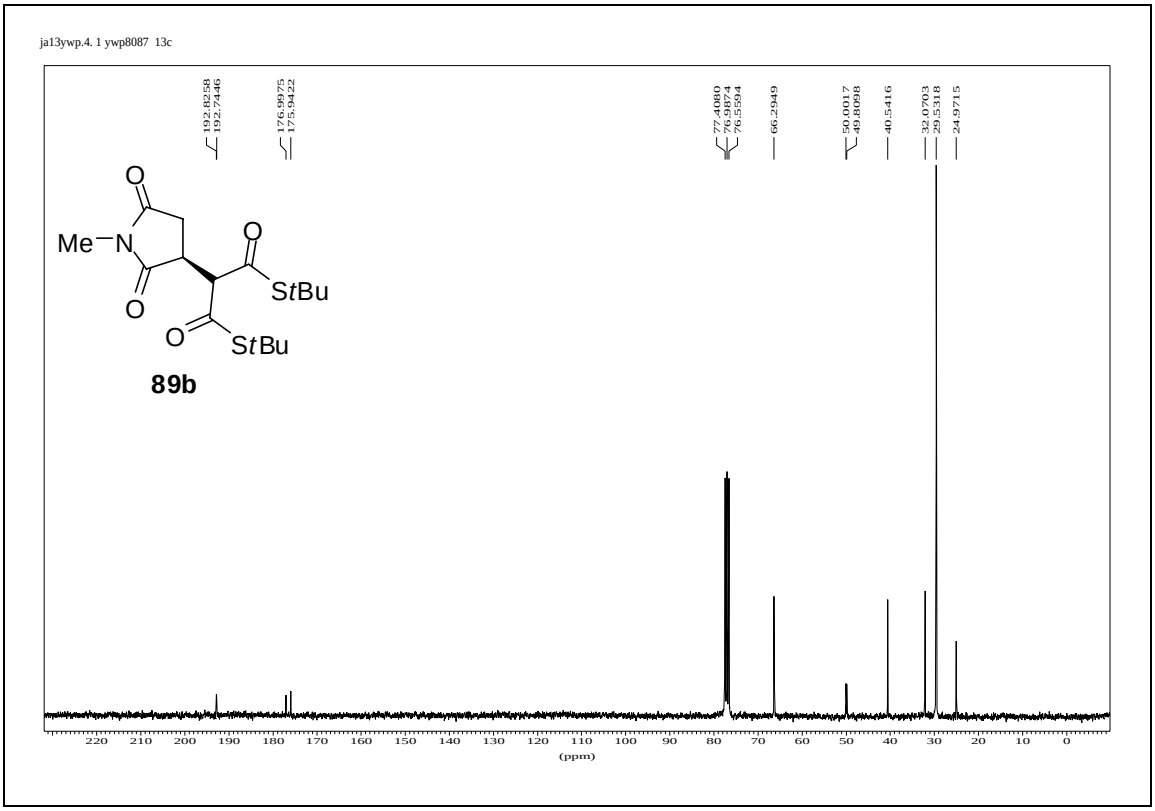

ma29ywp.1.1 ywp8227
Et
N
O
O
O
OMe
O
OMe
88b
7.2600
4.1121
4.0970
3.7940
3.7348
3.6083
3.5851
3.5697
3.5363
3.3123
3.2937
3.2810
3.2670
3.2473
2.9072
2.8770
2.8457
2.8155
2.7656
2.7470
2.7052
2.6855
1.1916
1.1673
1.1429
Integral
1.0000
2.9981
2.9996
2.0118
0.9979
1.0079
1.0034
3.0277
(ppm)

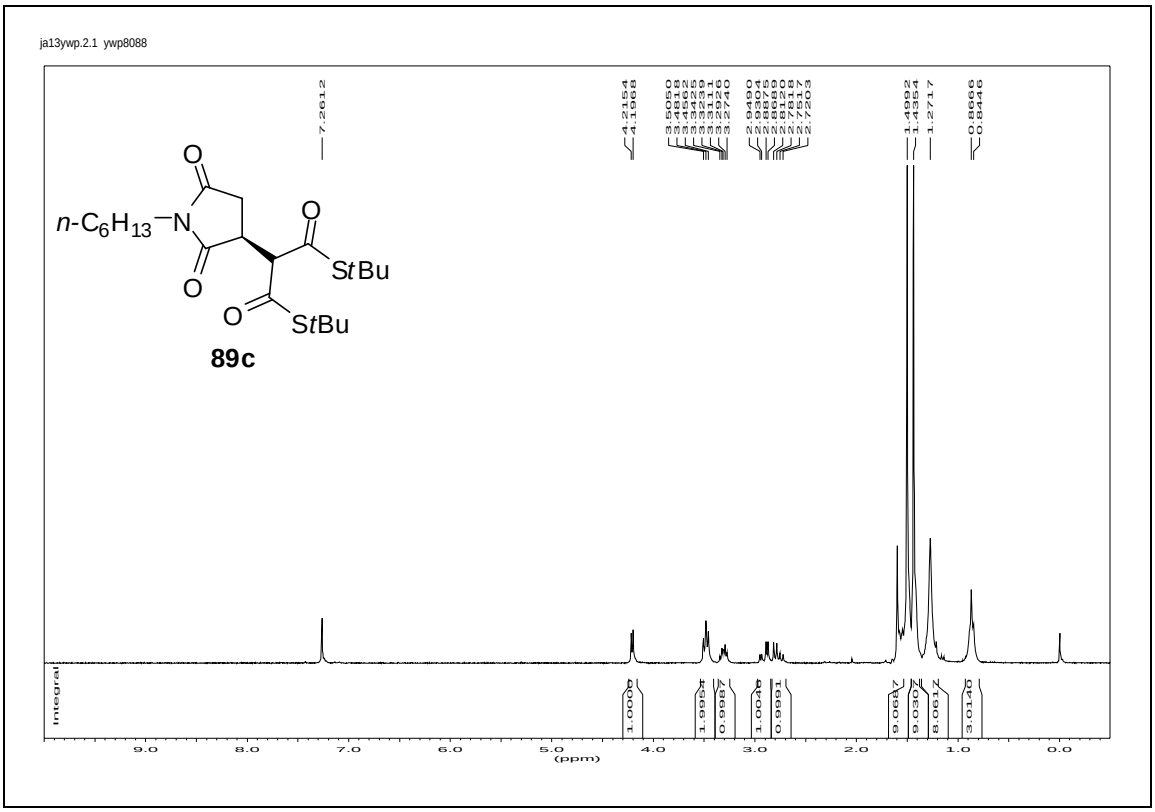

ma29ywp.2.1 ywp8227 13c
Et
N
O
O
O
OMe
O
OMe
88b
176.9015
175.6102
167.9580
167.3760
77.4080
76.9874
76.5668
53.0345
52.9460
50.4961
39.1764
33.9667
32.2943
12.6409
(ppm)

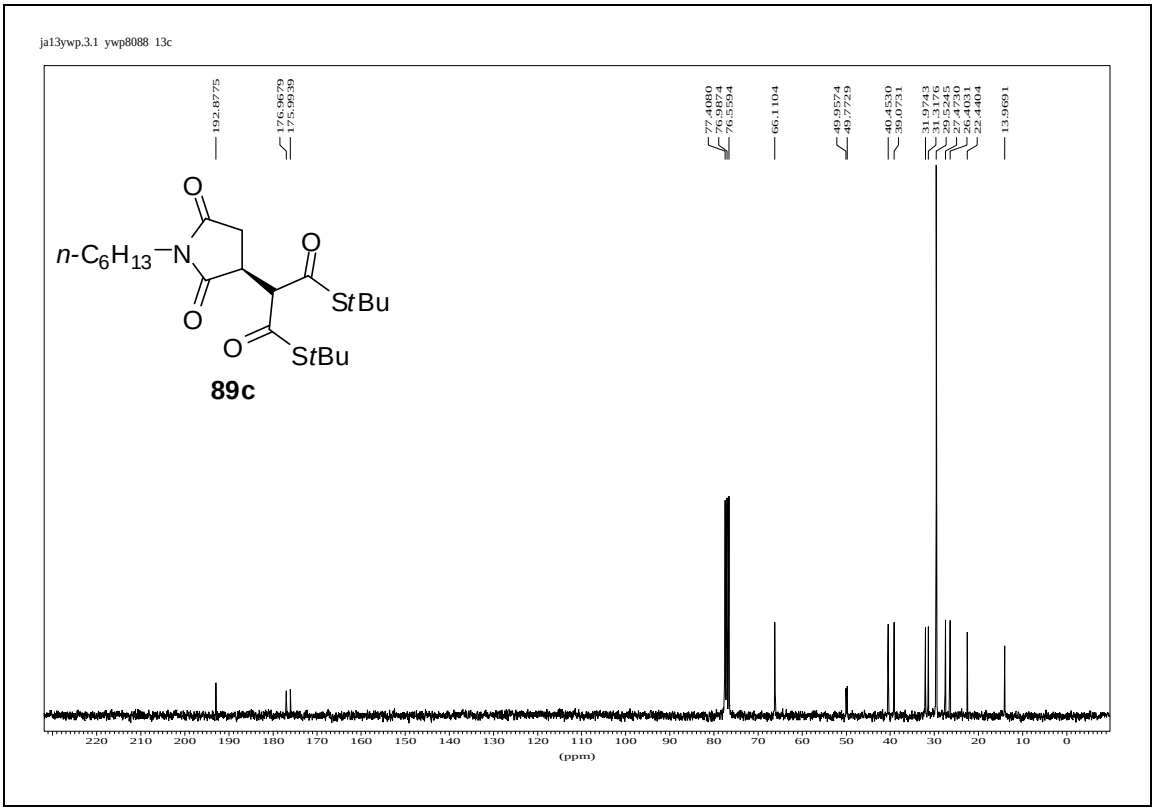

de15ywp.1.1 ywp8045-1
Et
N
O
O
O
O
O
StBu
StBu
89a
7.2600
4.2096
4.1910
3.5886
3.5642
3.5410
3.5166
3.3529
3.3344
3.3216
3.3158
3.3000
3.2845
2.9339
2.9153
2.8724
2.8538
2.8144
2.7830
2.7528
2.7215
1.4981
1.4331
1.1754
1.1510
1.1278
Integral
0.9967
2.0227
1.0000
2.0054
9.0347
9.0322
2.9980
9.6 9.2 8.8 8.4 8.0 7.6 7.2 6.8 6.4 6.0 5.6 5.2 4.8 4.4 4.0 3.6 3.2 2.8 2.4 2.0 1.6 1.2 0.8 0.4 0.0
(ppm)


de16ywp.2.1 ywp8045-1 13c
Et
N
O
O
O
O
O
StBu
StBu
89a
192.8479
176.7835
175.7799
77.4080
76.9874
76.5594
66.1695
49.9648
49.7729
40.4530
33.8929
32.0039
29.5245
12.7073
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)

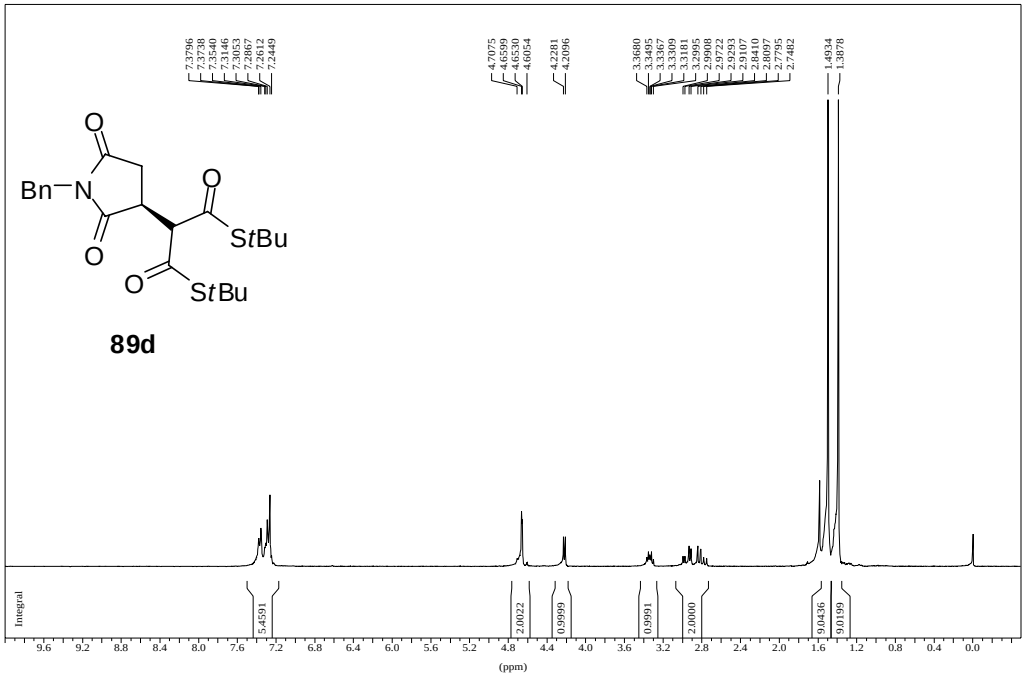

ja13ywp.1.1 ywp8087
Me−N
O
O
O
O
StBu
StBu
89b
7.2623
4.1910
4.1724
3.3982
3.3785
3.3692
3.3495
3.3297
2.9908
2.8643
2.8434
2.8132
2.7818
2.7517
1.5050
1.4400
Integral
1.0000
1.0200
3.0316
1.9764
9.0116
9.0784
(ppm)


ja13ywp.4. 1 ywp8087 13c
Me−N
O
O
O
O
StBu
StBu
89b
192.8238
192.7446
176.9975
175.9422
77.4080
76.9874
76.5594
66.2949
50.0017
49.8098
40.5416
32.0703
29.5318
24.9715
(ppm)


ja13ywp.2.1 ywp8088
7.2612
4.2154
4.1968
3.5650
3.4818
3.4562
3.3455
3.3239
3.3031
3.2926
3.2740
2.9490
2.9304
2.8875
2.8689
2.8120
2.7918
2.7517
2.7203
1.4992
1.4394
1.2717
0.8666
0.8446
n-C6H13−N
O
O
O
O
StBu
StBu
89c
Integral
1.0000
1.9954
0.9987
1.0042
0.9991
9.0687
9.0307
8.0617
3.0140
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

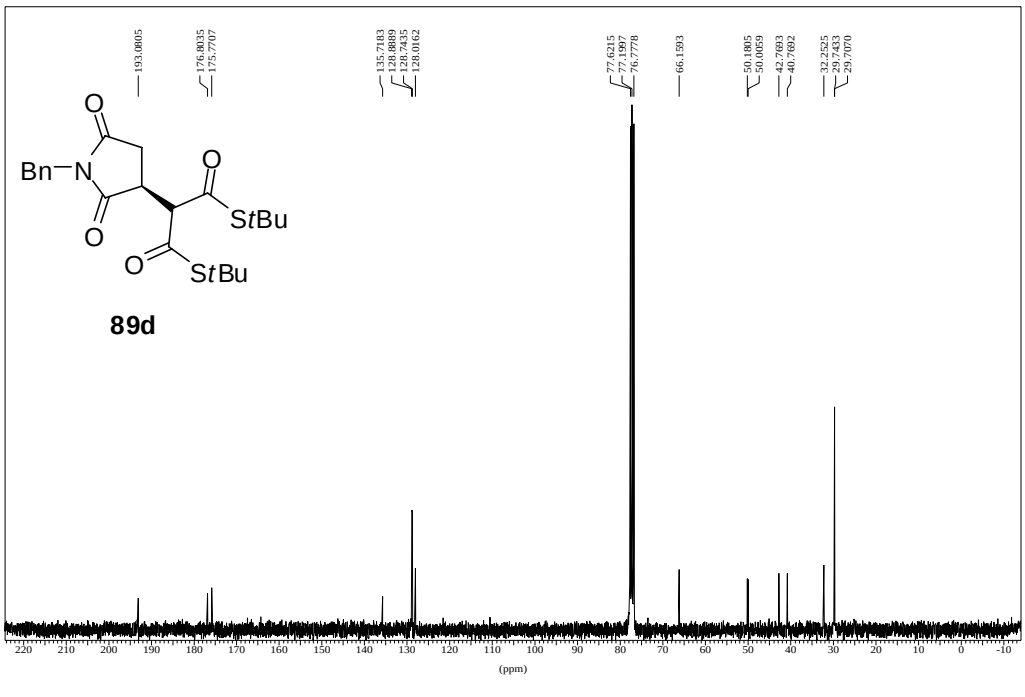

ja13ywp.3.1 ywp8088 13c
192.8775
176.9679
175.9939
77.4080
76.9874
76.5594
66.1104
49.9574
49.7729
40.4530
39.0731
31.9743
31.3176
29.2345
27.4730
26.4031
22.4404
13.9691
n-C6H13−N
O
O
O
O
StBu
StBu
89c
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)

de15ywp.2.1 ywp8045-2

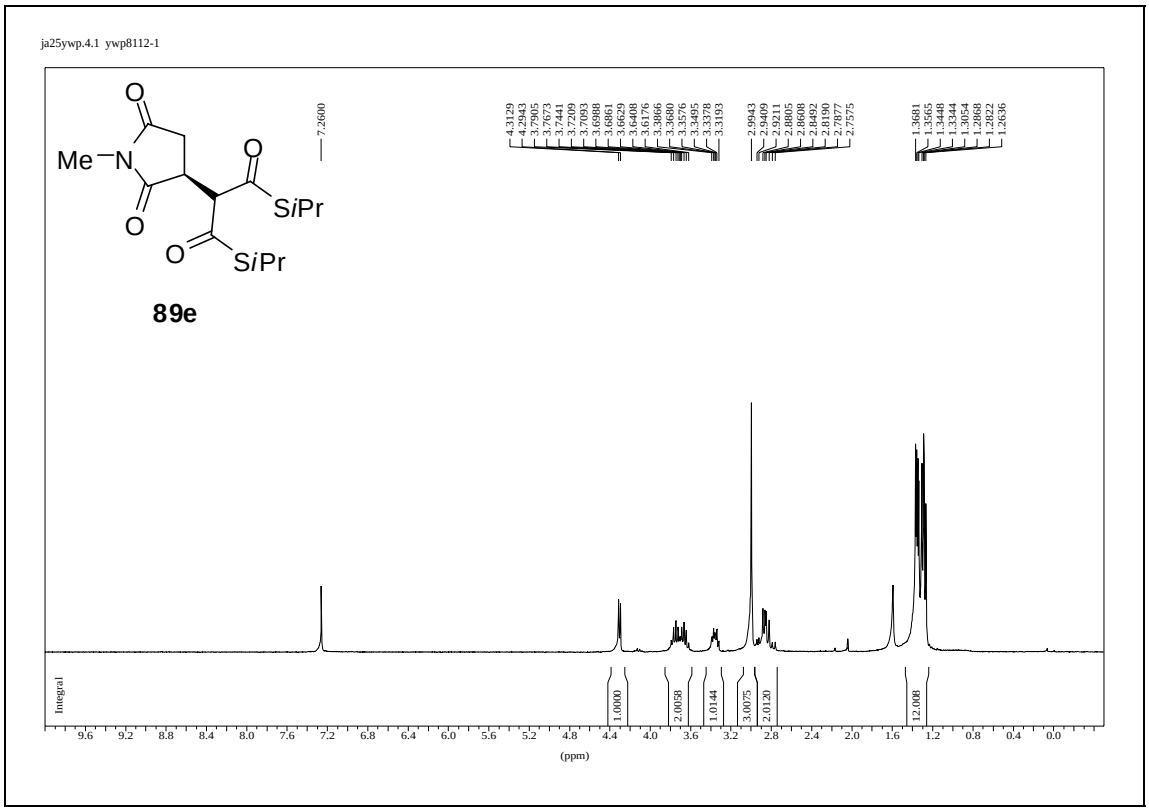


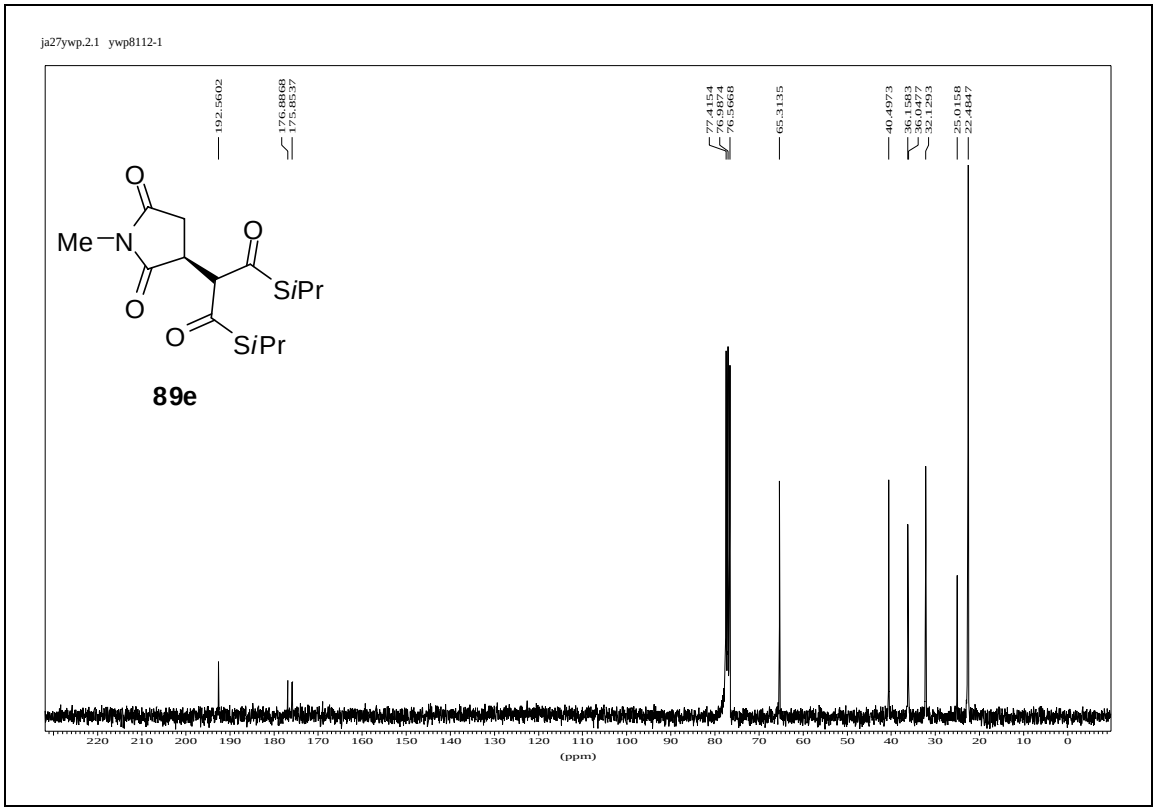
89d

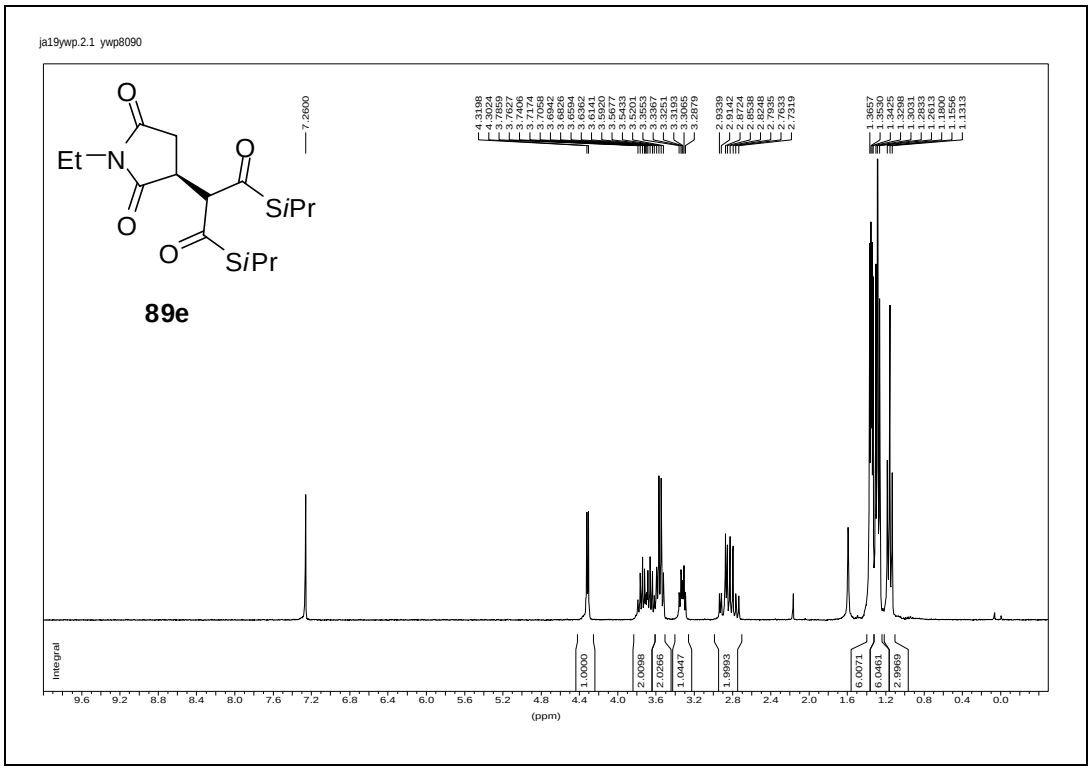
13C Standard AV300 de16ywp1.1.1 ywp8045-2

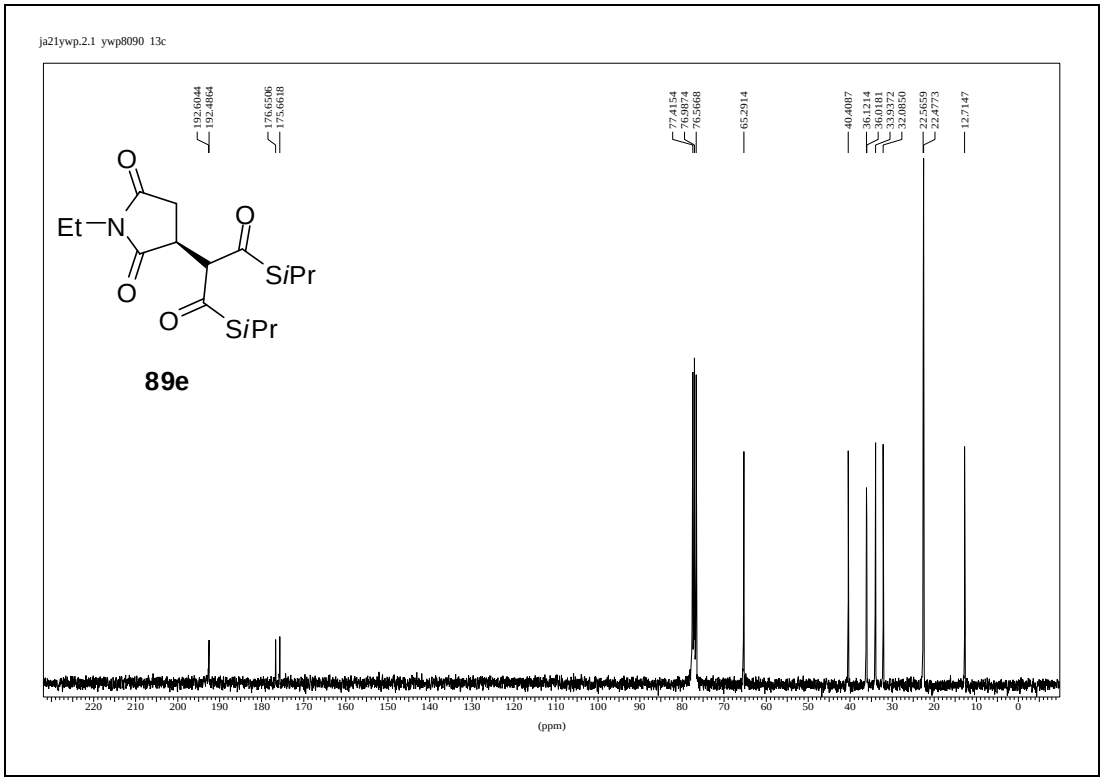


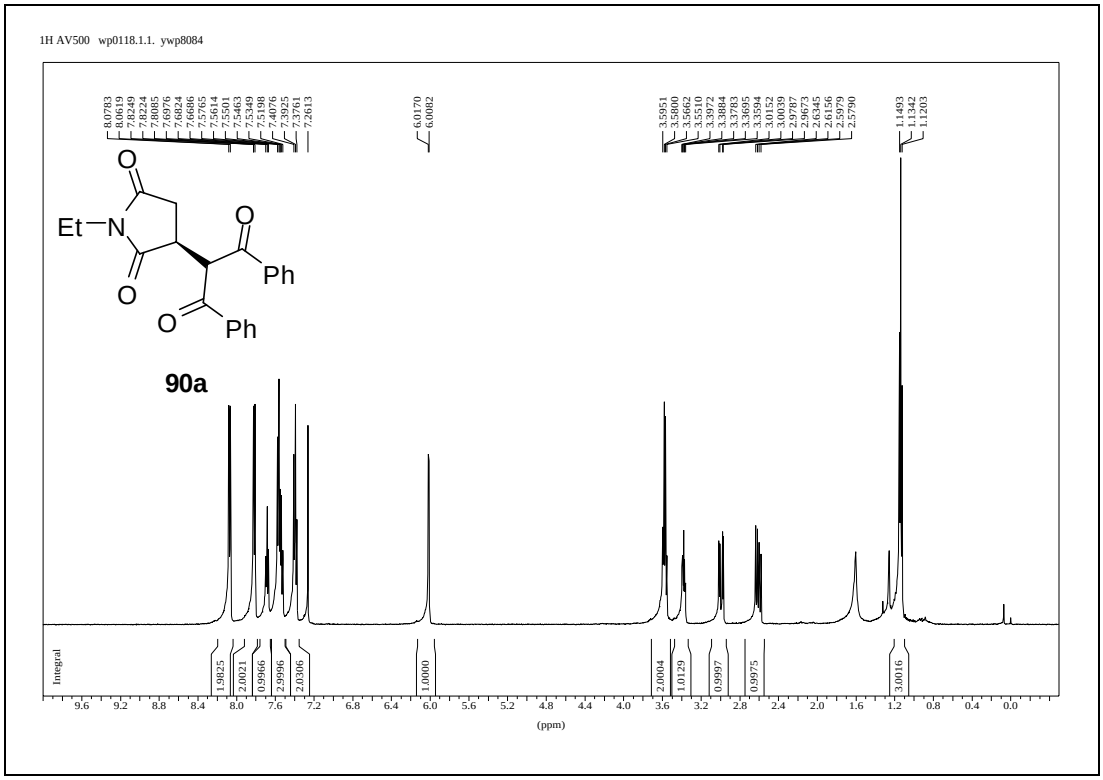
89d

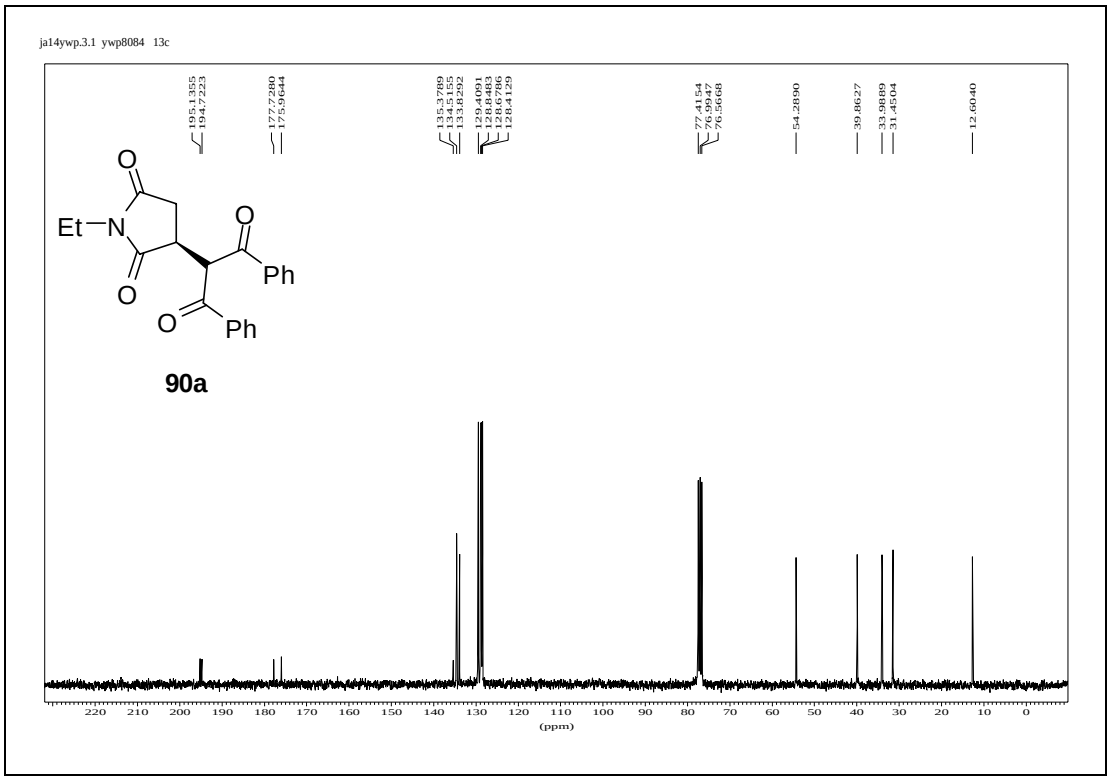

ja25ywp.4.1 ywp8112-1
Me
N
O
O
O
O
SiPr
SiPr
89e
7.2600
4.3129
4.2943
3.7905
3.7673
3.7441
3.7209
3.7093
3.6988
3.6861
3.6629
3.6408
3.6176
3.3866
3.3680
3.3576
3.3495
3.3378
3.3193
2.9943
2.9409
2.9211
2.8805
2.8608
2.8492
2.8190
2.7877
2.7575
1.3681
1.3565
1.3448
1.3344
1.3054
1.2868
1.2722
1.2636
Integral
1.0000
2.0058
1.0144
3.0075
2.0120
12.008
(ppm)


ja27ywp.2.1 ywp8112-1
Me
N
O
O
O
O
SiPr
SiPr
89e
192.5602
176.8868
175.8537
77.4154
76.9874
76.5668
65.3135
40.4973
36.1593
34.4477
32.1293
25.0158
22.4847
(ppm)

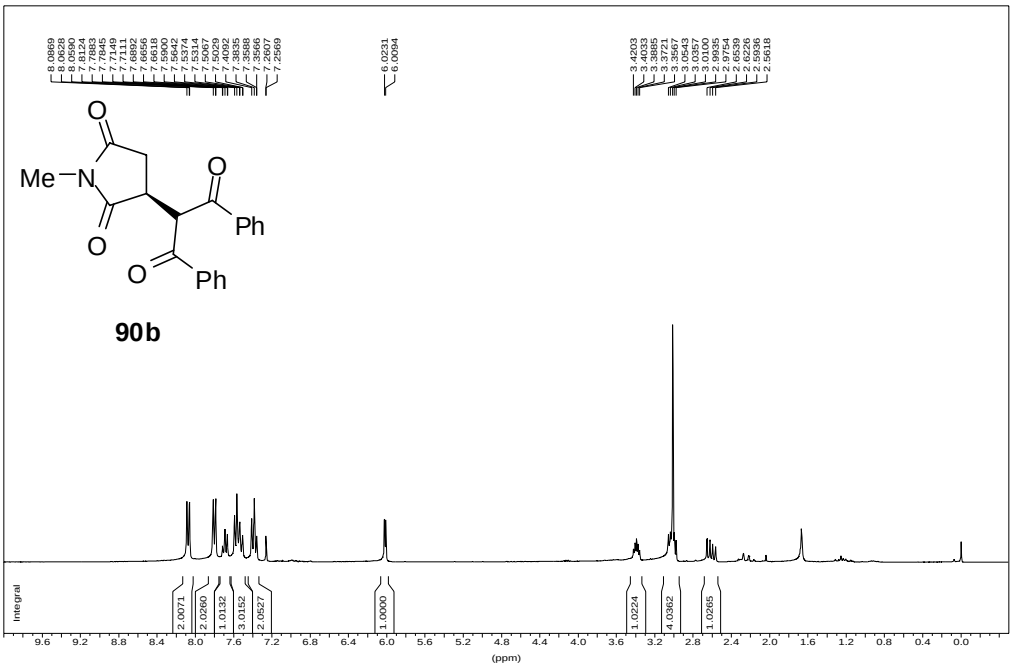

ja19ywp.2.1 ywp8090
Et
N
O
O
O
O
O
SiPr
SiPr
89e
7.2600
4.3198
4.3024
4.2869
3.7627
3.7406
3.7174
3.7006
3.6826
3.6584
3.6394
3.6141
3.5920
3.5677
3.5433
3.5201
3.3953
3.3657
3.3251
3.3193
3.3065
3.2870
2.9339
2.9142
2.8724
2.8538
2.8248
2.7935
2.7633
2.7319
1.3657
1.3530
1.3345
1.3298
1.3031
1.2833
1.2651
1.1800
1.1556
1.1313
Integral
1.0000
2.0098
2.0266
1.0447
1.9993
6.0071
6.0461
2.9969
9.6 9.2 8.8 8.4 8.0 7.6 7.2 6.8 6.4 6.0 5.6 5.2 4.8 4.4 4.0 3.6 3.2 2.8 2.4 2.0 1.6 1.2 0.8 0.4 0.0
(ppm)


ja21ywp.2.1 ywp8090 13c
Et
N
O
O
O
O
O
SiPr
SiPr
89e
192.6044
192.4864
176.6506
175.6618
77.4154
76.9874
76.5668
65.2914
40.4087
36.1214
33.0181
33.1372
32.0850
22.5659
22.4773
12.7147
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)


1H AV500 wp0118.1.1. ywp8084
8.0783
8.0619
7.8249
7.8224
7.8085
7.6976
7.6834
7.6686
7.5765
7.5614
7.5501
7.5463
7.5349
7.5198
7.4076
7.3925
7.3761
7.2613
6.0170
6.0082
3.5951
3.5800
3.5662
3.5510
3.3972
3.3884
3.3783
3.3695
3.3594
3.0152
3.0039
3.0007
2.9673
2.6345
2.6156
2.5979
2.5790
1.1493
1.1342
1.1203
Et
N
O
O
O
O
Ph
Ph
90a
Integral
1.9825
2.0021
0.9966
2.9996
2.0306
1.0000
2.0004
1.0129
0.9997
0.9975
3.0016
9.6 9.2 8.8 8.4 8.0 7.6 7.2 6.8 6.4 6.0 5.6 5.2 4.8 4.4 4.0 3.6 3.2 2.8 2.4 2.0 1.6 1.2 0.8 0.4 0.0
(ppm)

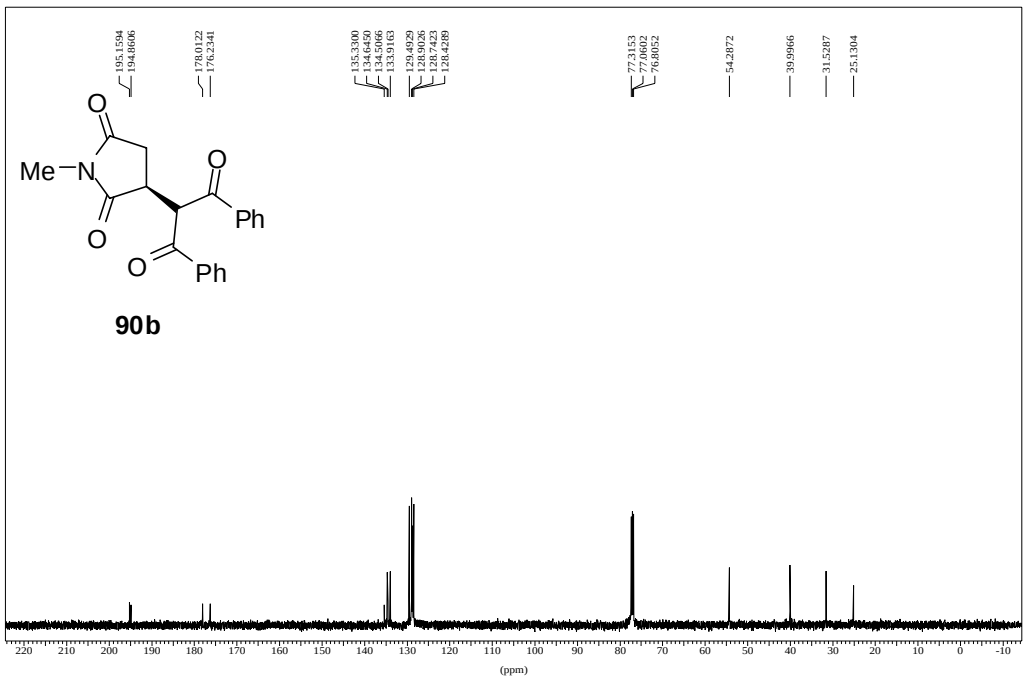

ja14ywp.3.1 ywp8084 13c
195.1355
194.7223
177.7280
175.9644
135.3789
134.5155
133.8292
129.4091
128.8483
128.6966
128.4129
77.4154
77.0947
76.5668
54.2890
39.8627
33.9889
31.4504
12.6040
Et
N
O
O
O
O
Ph
Ph
90a
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)

1H normal range AV300 de05ywp.1.1 ywp8036-1



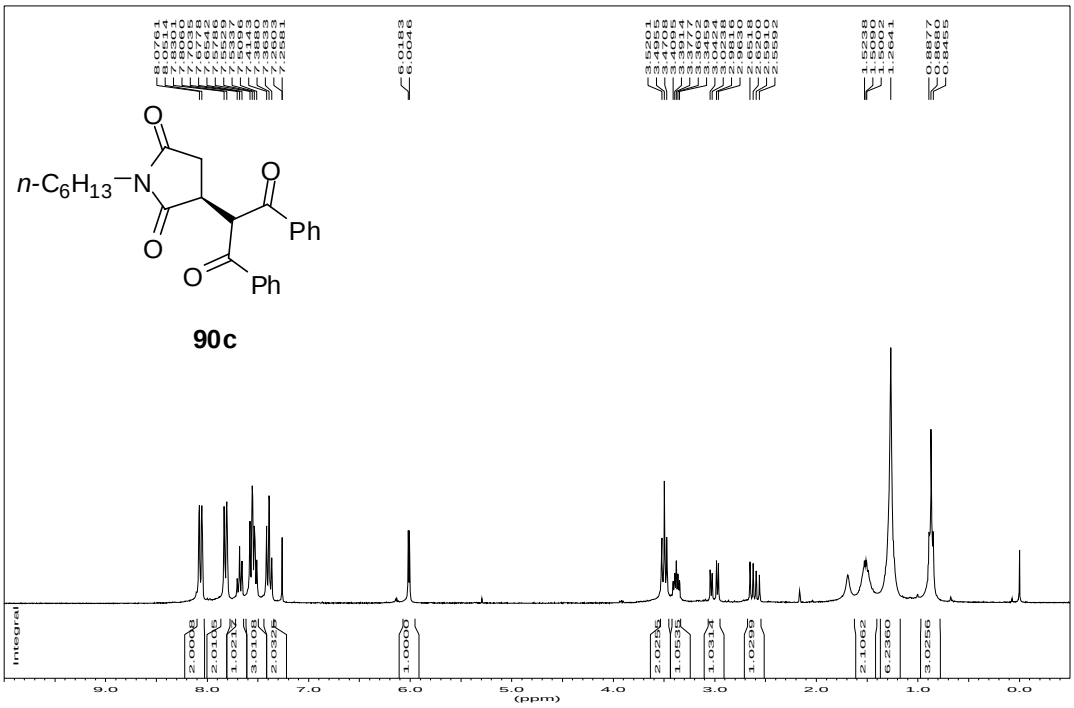
90b

13C AV500 wp1206.2.1 ywp8036-1 13c



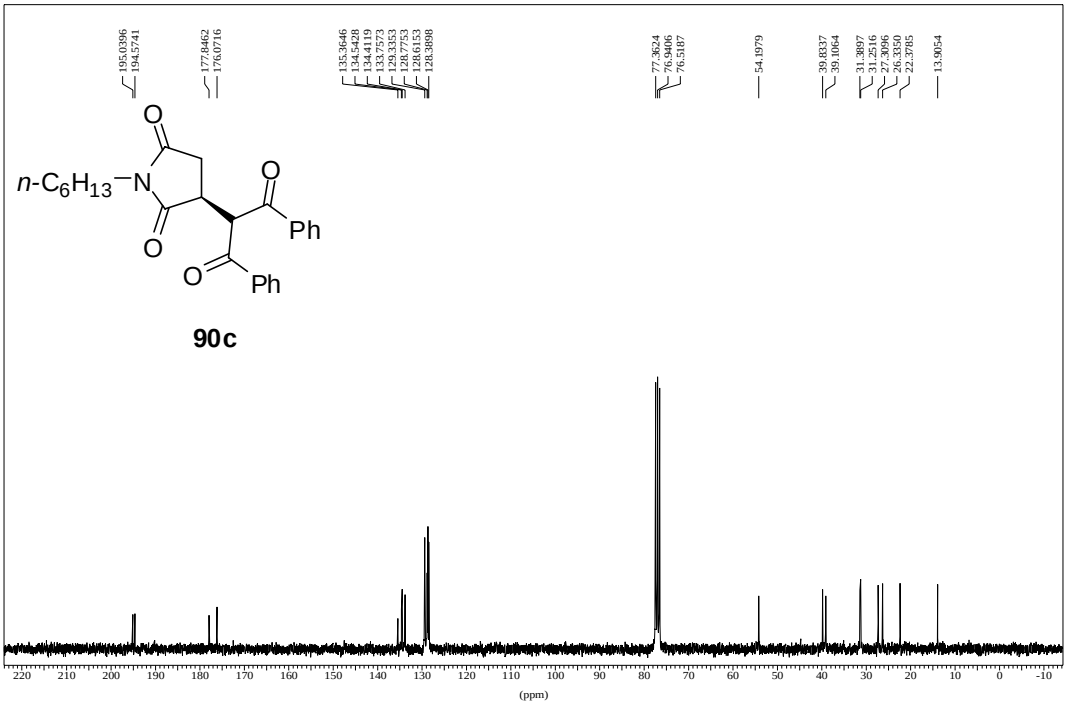
90b

1H normal range AV300 de05ywp.2.1 ywp8036-2

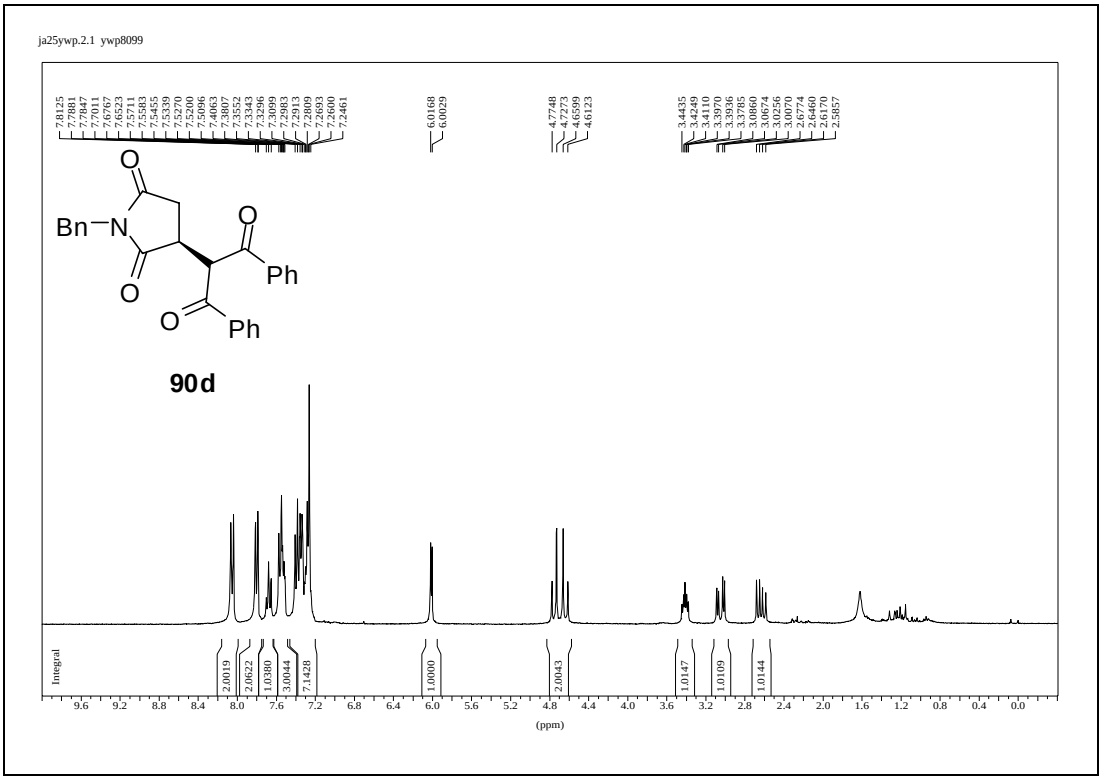


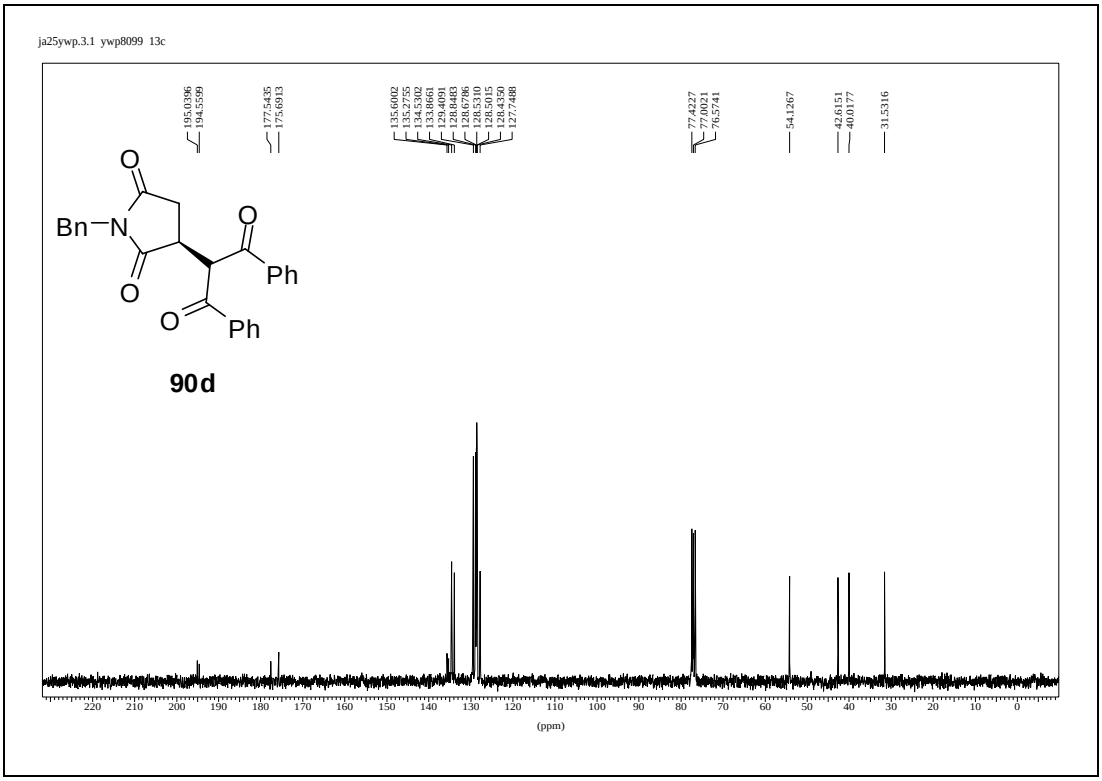
90c

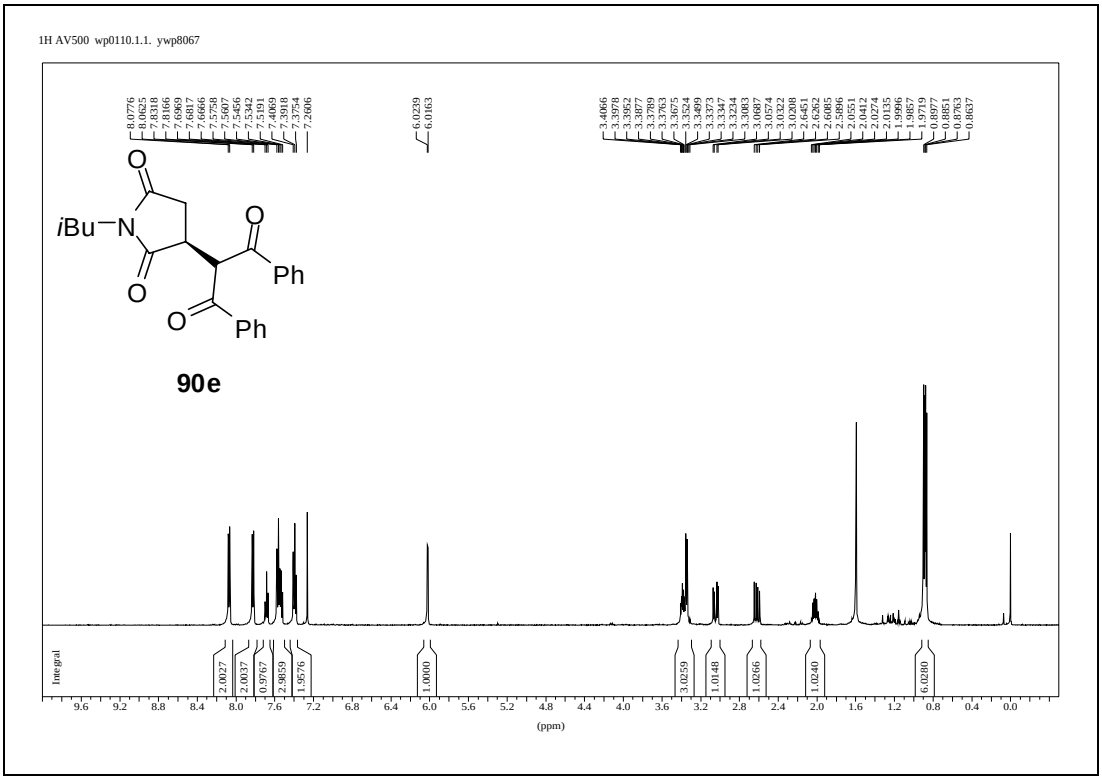
13C Standard AV300 de06ywp.2.1 ywp8036-2 13c

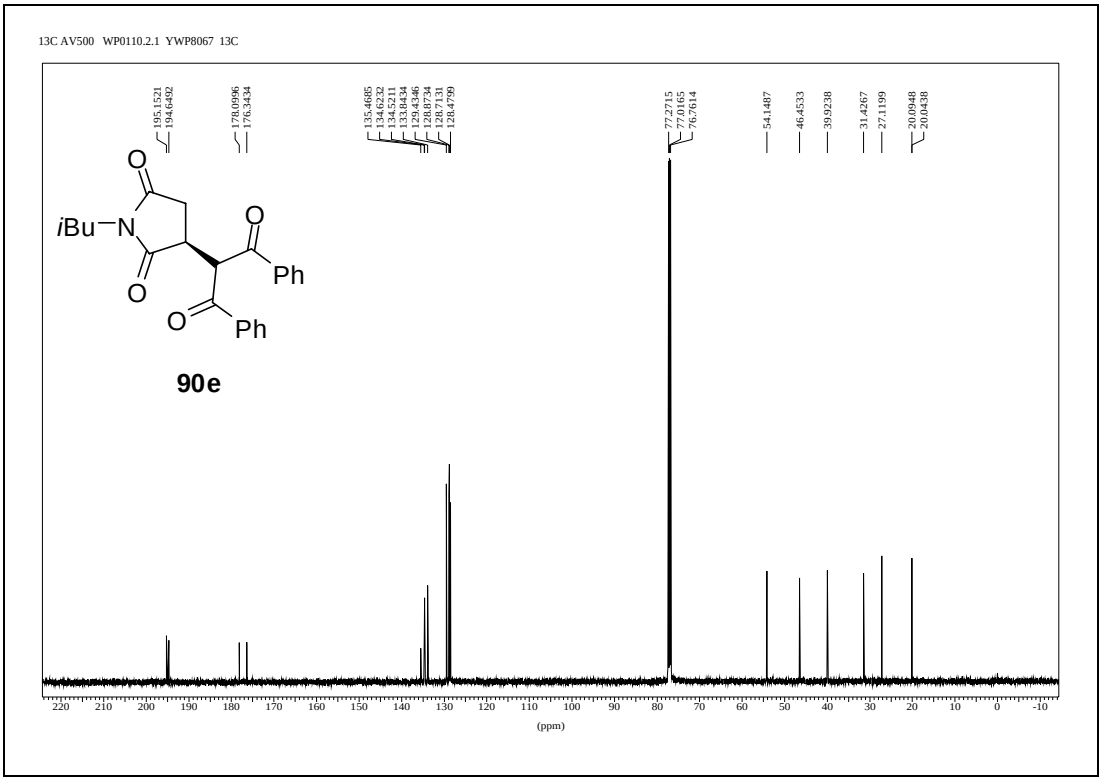


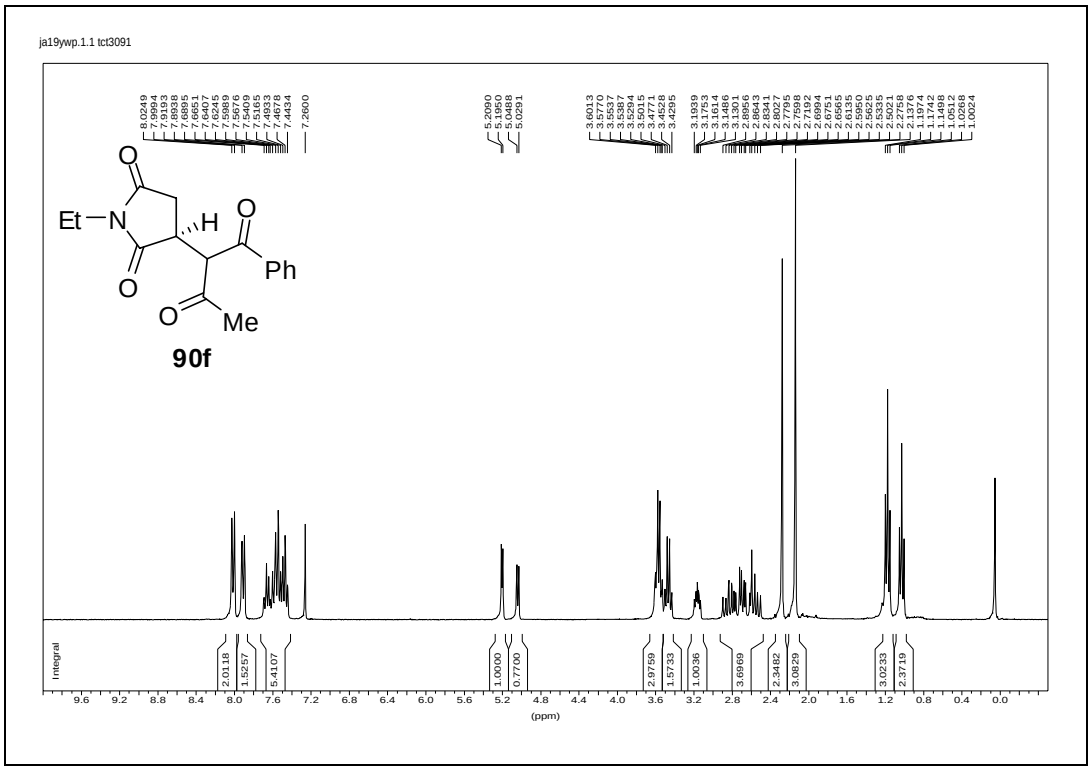
90c

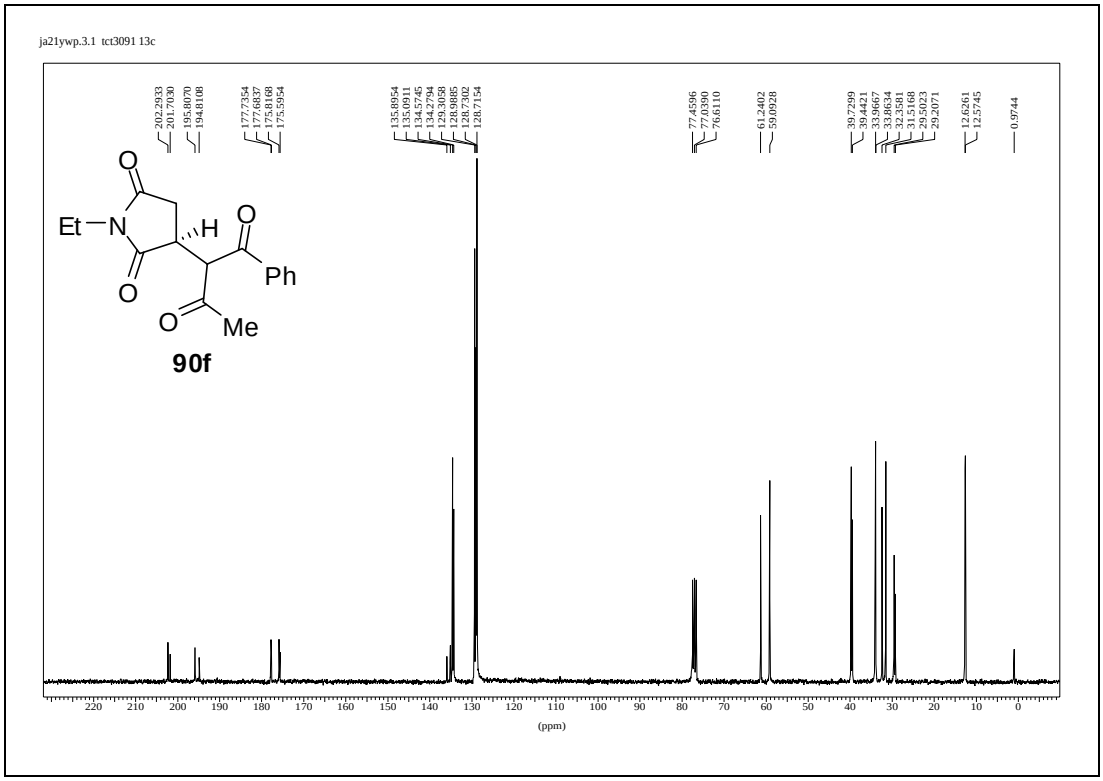

ja25ywp.2.1 ywp8099
Bn
N
O
Ph
90d
Integral
2.0019
2.0622
1.0380
3.0044
7.1428
1.0000
2.0043
1.0147
1.0109
1.0144
(ppm)


ja25ywp.3.1 ywp8099 13c
Bn
N
O
Ph
90d
(ppm)

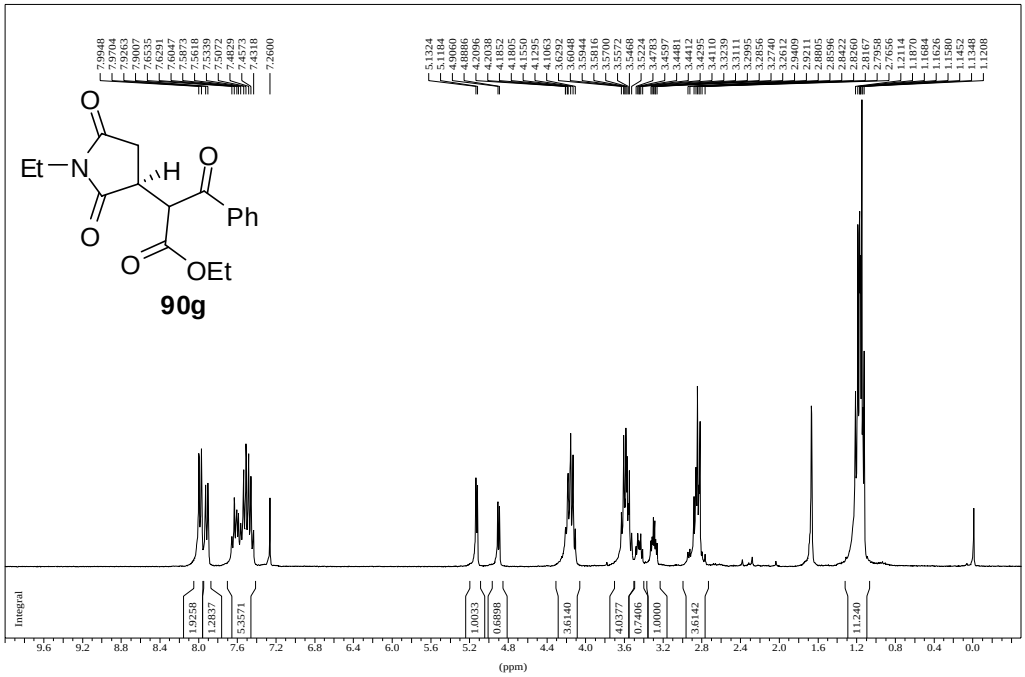

1H AV500 wp0110.1.1. ywp8067
8.0776
8.0625
7.8318
7.8166
7.6869
7.6717
7.6666
7.5758
7.5607
7.5456
7.5342
7.5191
7.4069
7.3918
7.3754
7.2606
6.0239
6.0163
3.4066
3.3978
3.3852
3.3727
3.3789
3.3763
3.3675
3.3524
3.3499
3.3373
3.3247
3.3234
3.3083
3.3087
3.0574
3.0322
3.0188
2.6451
2.6262
2.6085
2.5896
2.0551
2.0441
2.0274
2.0135
1.9996
1.9857
1.9719
0.8977
0.8851
0.8763
0.8637
iBu—N
O
O
O
Ph
O
Ph
90e
Integral
2.0027
2.0037
0.9767
2.9859
1.9576
1.0000
3.0259
1.0148
1.0266
1.0240
6.0280
9.6 9.2 8.8 8.4 8.0 7.6 7.2 6.8 6.4 6.0 5.6 5.2 4.8 4.4 4.0 3.6 3.2 2.8 2.4 2.0 1.6 1.2 0.8 0.4 0.0
(ppm)


13C AV500 WP0110.2.1 YWP8067 13C
195.1521
194.6492
178.0996
176.3434
135.4685
134.6232
134.5211
133.0434
130.4546
128.4234
128.7131
128.4799
77.2715
77.0155
76.7614
54.1487
46.4533
39.9238
31.4267
27.1199
20.0948
20.0438
iBu—N
O
O
O
Ph
O
Ph
90e
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)

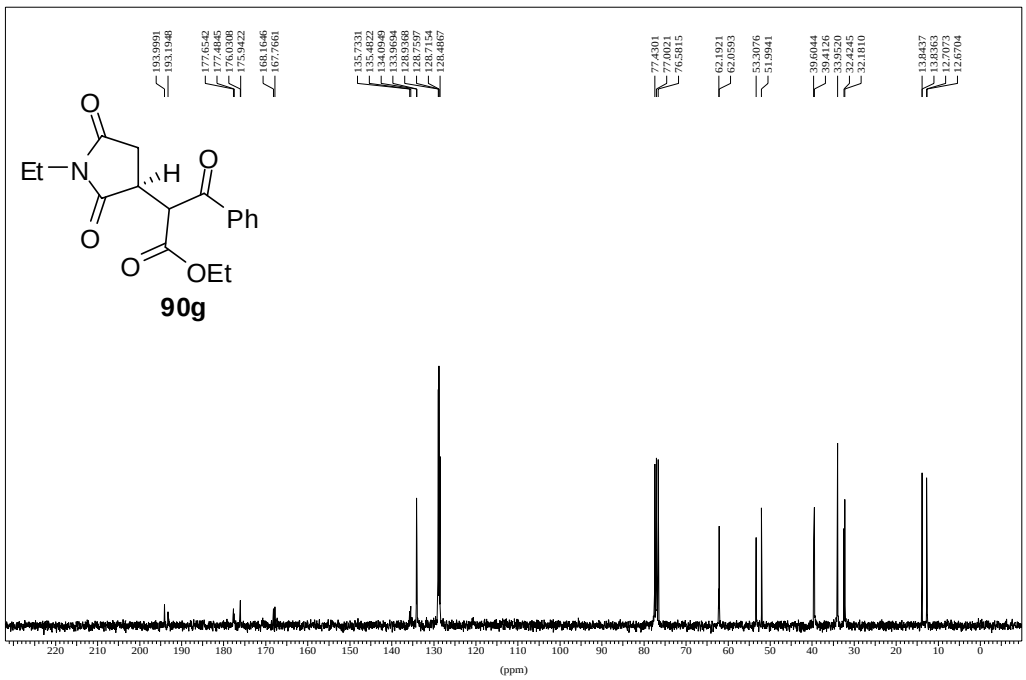

ja19ywp.1.1 tct3091
Et
N
H
O
Ph
Me
90f
Integral
2.0118
1.5257
5.4107
1.0000
0.7700
2.9759
1.5733
1.0036
3.6969
2.3482
3.0829
3.0233
2.3719
(ppm)

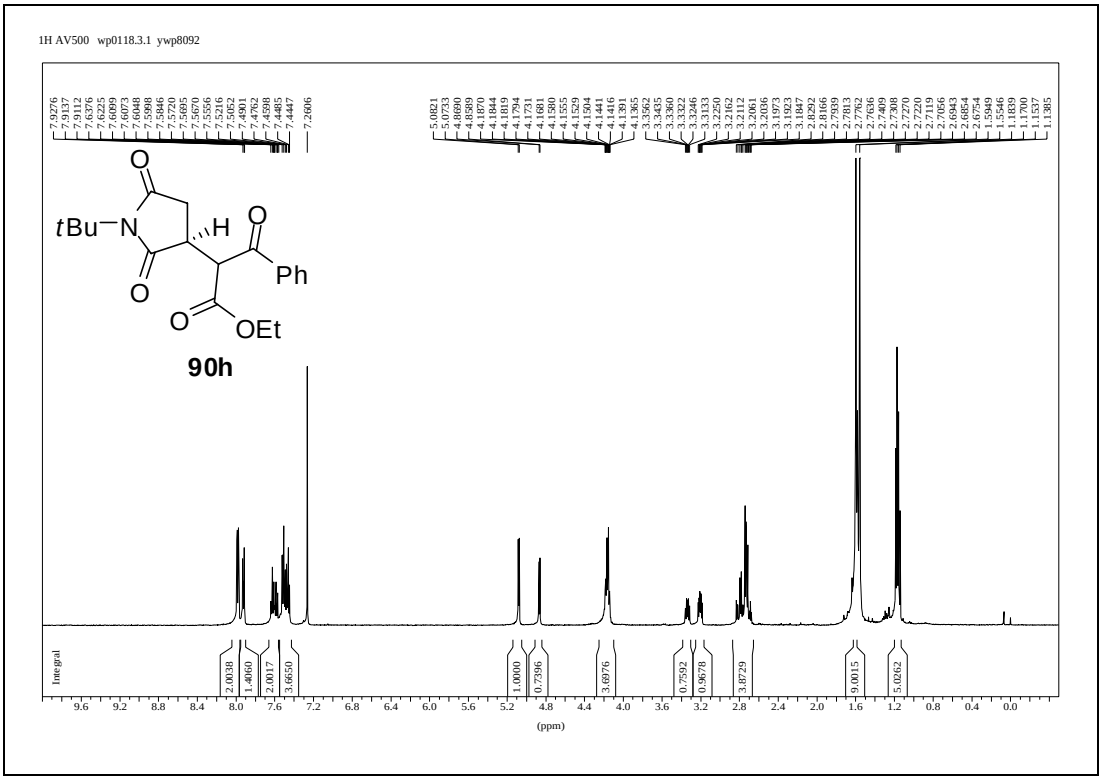

ja21ywp.3.1 tct3091 13c
Et
N
H
O
Ph
Me
90f
(ppm)

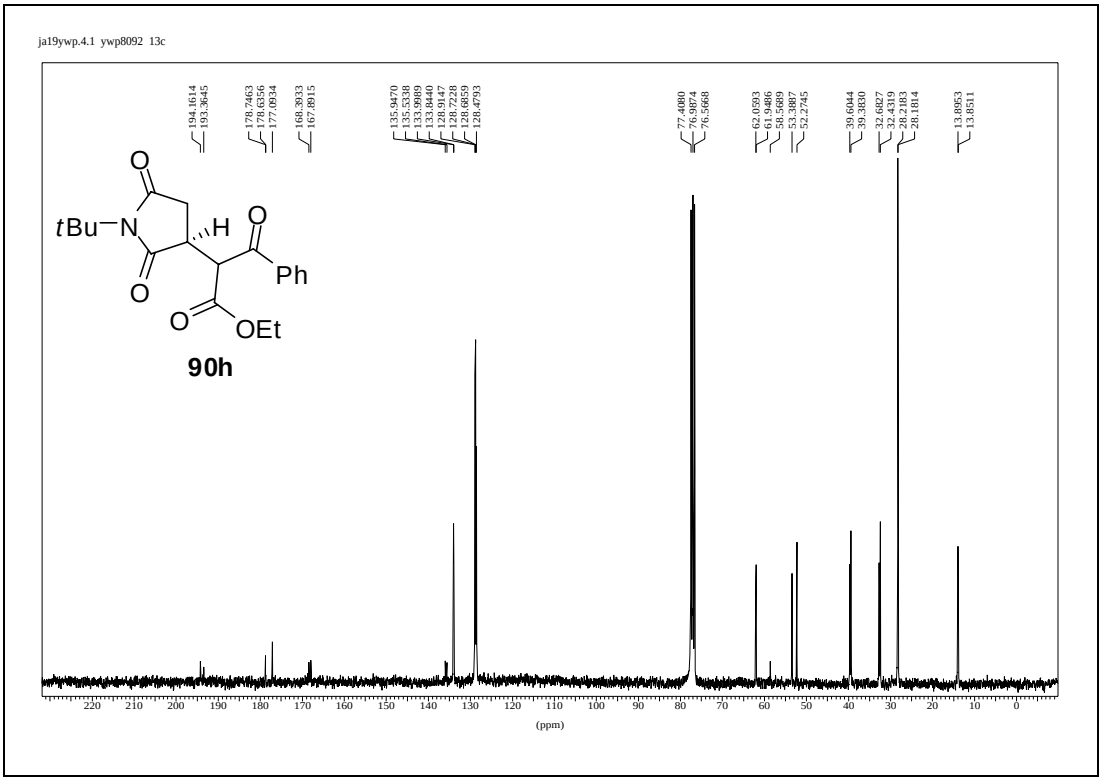
de15ywp.3.1 ywp8045-3

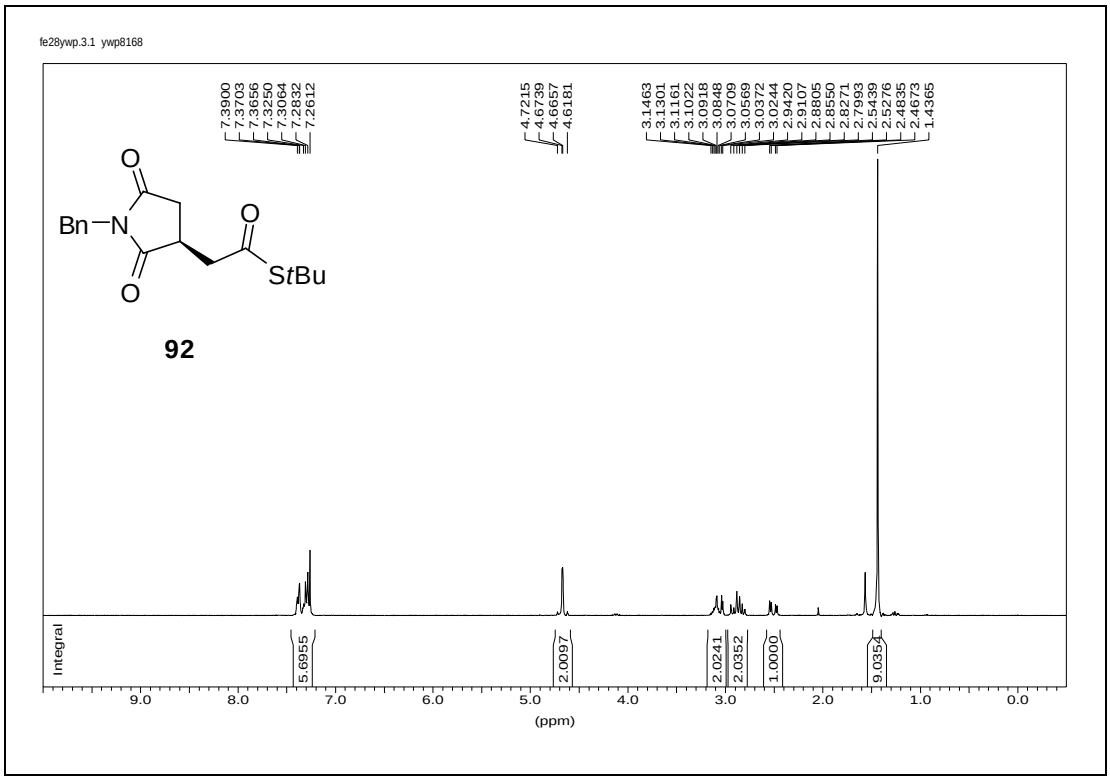


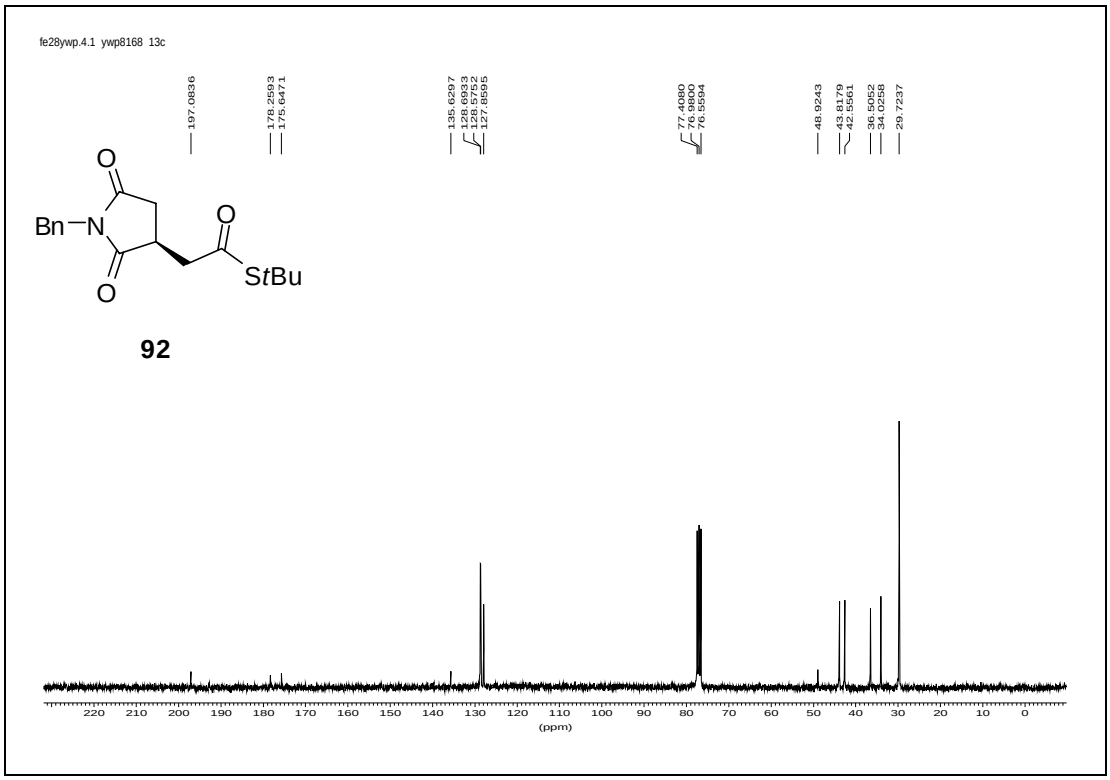
dpx300 de15ywp.4.1 ywp8045-3 13c

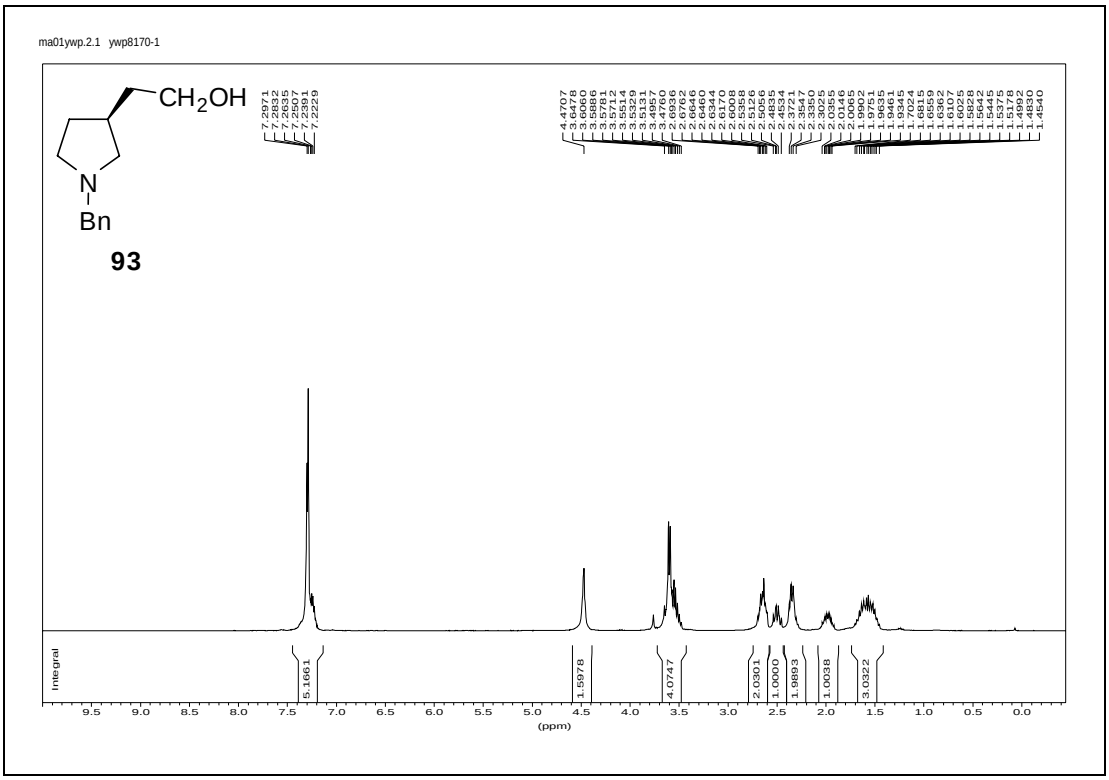


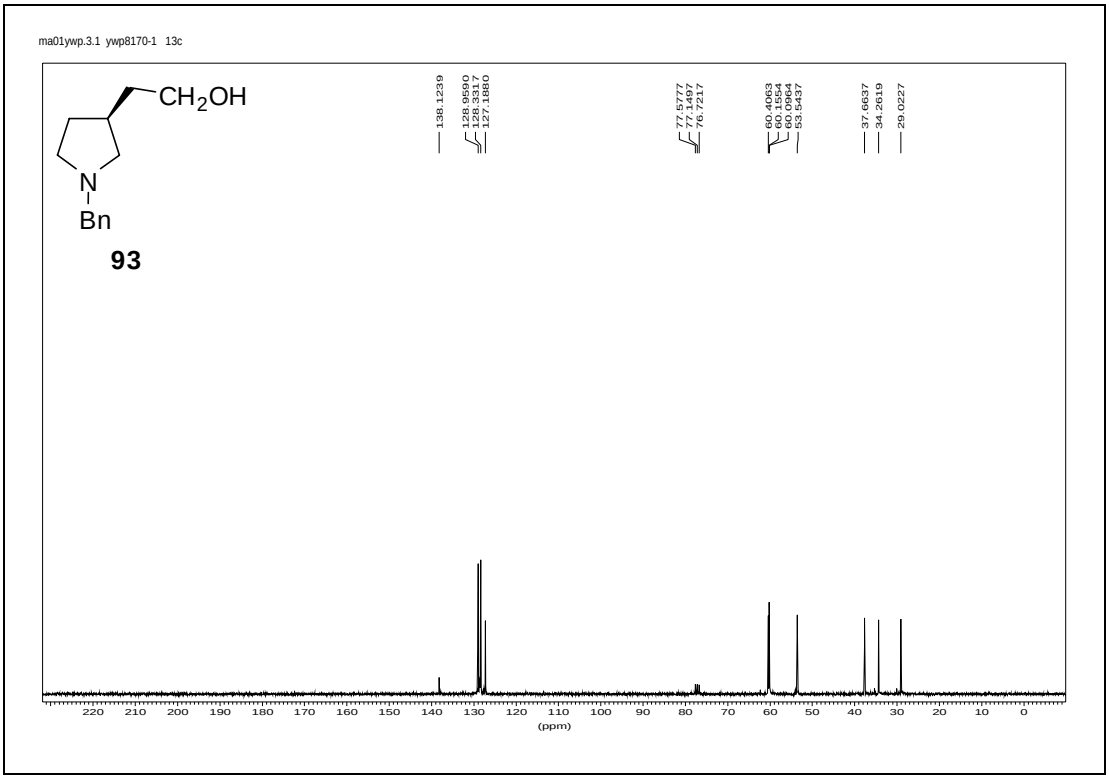

1H AV500 wp0118.3.1 ywp8092
tBu
N
H
O
Ph
OEt
90h
Integral
2.0038
1.4060
2.0017
3.6650
1.0000
0.7396
3.6976
0.7592
0.9678
3.8729
9.0015
5.0262
(ppm)

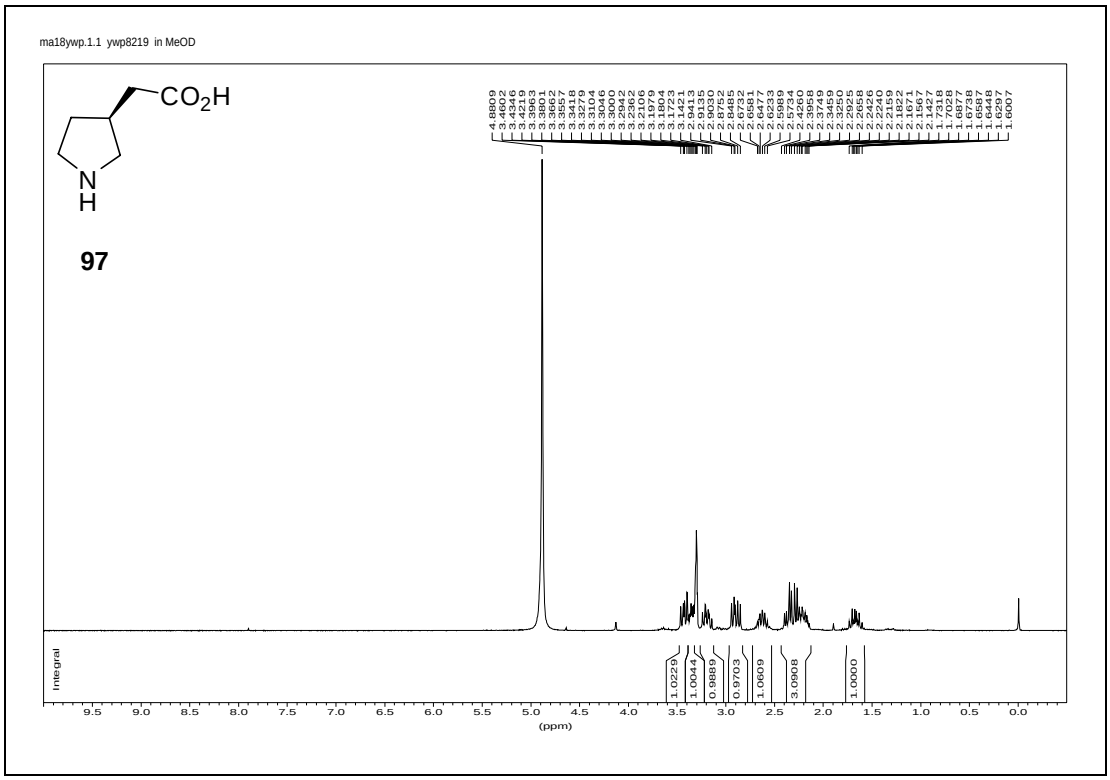

ja19ywp.4.1 ywp8092 13c
tBu
N
H
O
Ph
OEt
90h
(ppm)

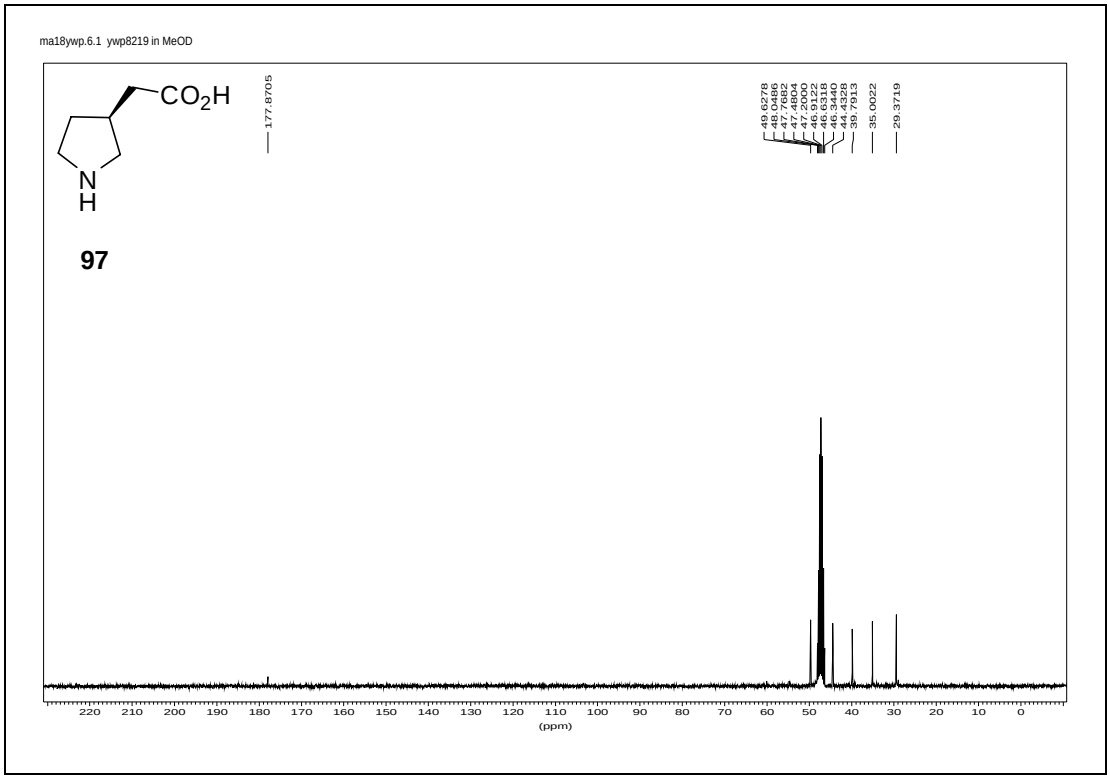

fe28ywp.3.1 ywp8168
7.3900
7.3703
7.3656
7.3250
7.3064
7.2832
7.2612
4.7215
4.6739
4.6657
4.6181
3.1463
3.1301
3.1161
3.1022
3.0918
3.0848
3.0709
3.0569
3.0372
3.0244
2.9420
2.9107
2.8805
2.8550
2.8271
2.7993
2.5439
2.5276
2.4835
2.4673
1.4365
Bn−N
O
O
O
StBu
92
Integral
5.6955
2.0097
2.0241
2.0352
1.0000
9.0351
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)


fe28ywp.4.1 ywp8168 13c
197.0836
178.2593
175.6471
135.6297
128.6933
128.5752
127.8995
77.4080
76.9800
76.5594
48.9243
43.8179
42.5561
36.5052
34.0258
29.7237
Bn−N
O
O
O
StBu
92
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)


ma01ywp.2.1 ywp8170-1
CH2OH
N
Bn
93
Integral
5.1661
1.5978
4.0747
2.0301
1.0000
1.9893
1.0038
3.0322
(ppm)


ma01ywp.3.1 ywp8170-1 13c
CH2OH
N
Bn
93
138.1239
128.9590
128.3317
127.1880
77.5777
77.1497
76.7217
60.4063
60.1554
60.0964
53.5437
37.6637
34.2619
29.0227
(ppm)


ma18ywp.1.1 ywp8219 in MeOD
CO2H
N
H
97
Integral
1.0229
1.0044
0.9889
0.9703
1.0609
3.0908
1.0000
(ppm)


ma18ywp.6.1 ywp8219 in MeOD
CO2H
N
H
97
177.8705
49.6278
49.0486
47.7682
47.4884
47.2000
46.9122
46.6318
46.3440
44.4328
39.7913
35.0022
29.3719
(ppm)

Publications

1 Ye, Weiping; Xu, Junye; Tan, Chin-Tong; Tan, Choon-Hong. 1,5,7-Triazabicyclo[4.4.0]- -dec-5-ene (TBD) Catalyzed Michael Reactions. *Tetrahedron Lett.* **2005**, *46*, 6875.

2 Ye, Weiping; Leow, Dasheng; Goh, Serena Li Min; Tan, Chin-Tong; Chian, Chee-Hoe; Tan, Choon-Hong. Chiral Bicyclic Guanidines: A Concise and Efficient Aziridine-Based Synthesis. *Tetrahedron Lett.* **2006**, *47*, 1007.

3 Ye, Weiping; Goh, Serena Li Min; Leow, Dasheng; Jiang, Zhiyong; Soh, Ying-Teck; Tan, Choon-Hong. Chiral Bicyclic Guanidine Catalyzed Michael Reaction; Application to the Enantioselective Synthesis of (*S*)-(+)-homo-β-Proline. *Submitted for publication.*

4 Ye, Weiping; Tan, Choon-Hong. Enantioselective Michael Reaction of 1,3-Dicarbonyl Compounds to Cyclopentenone Catalyzed by Chiral Bicyclic Guanidines. *Manuscript in preparation.*

5 Shen, Juan; Nguyen, Thanh Truc; Goh Yong-Peng; Ye, Weiping; Fu Xiao; Xu Junye; Tan Choon-Hong. Enantioselective Reactions of Anthrone Derivatives Catalyzed by Chiral Bicyclic Guanidine. *Manuscript in preparation.*