N-Heterocycle Synthesis via Pd(0)-Catalysed C–H Activation: Kinetic Resolution and Pd Shift

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Abstract

Transition-metal-catalysed C–H bond functionalisation has exponentially developed as an efficient strategy for valuable molecules since the turn of the 21st century. Our group's research focuses on the activation and functionalisation of naturally abundant C–H bonds in organic molecules, which can develop new methodologies and applications, including asymmetric catalysis, mechanistic studies and total synthesis of natural products. However, it remains challenging and limited despite numerous C–H bond functionalisation methodologies developed until today when it comes to kinetic resolution via Pd(0)-catalysed C–H activation. This topic is underdeveloped despite great synthetic potential.

In this thesis, we aimed to develop a novel methodology on Pd(0)/Pd(II) catalysed C–H activation to achieve the total synthesis of a natural product and synthesis of the biologically valuable moiety.

This thesis is divided into kinetic resolution and remote construction of *N*-heterocycles.

In the first project, we identified that specific substrates showed the behaviour of parallel kinetic resolution in excellent enantioselectivity by C(sp^3)–H arylation. Then, that efficiency was envisioned to translate into the asymmetric framework construction of polycyclic natural alkaloid cryptowolinol.

In the second project, we developed remote construction of isoindolines. Interestingly, during the course of investigations on kinetic resolution, an isoindoline product was serendipitously identified arising from a novel 1,4-Pd shift and subsequent C(sp^3)–C(sp^2) bond formation. This new reactivity was exemplified in the synthesis of biologically exciting isoindolines. In addition, mechanistic studies were implemented to clarify the nature of this transformation. *N*-heterocyclic carbene ligands showed superior product selectivity compared to previously used phosphine-type ligands and proved to be critical to its success.

Keywords: C–C coupling, C–H activation, kinetic resolution, *N*-heterocycles, palladium, total synthesis, cryptowolinol, 1,4-Pd shift, isoindoline

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Published works during the PhD

- **Remote Construction of N-Heterocycles via 1,4-Palladium Shift-Mediated Double C–H Activation**
  T. Miyakoshi, N. E. Niggli, O. Baudoin, *Angew. Chem. Int. Ed.* **2022**, *61*, e202116101; *Angew. Chem.* **2022**, *134*, e202116101.

- **C(sp^3)–H Arylation Promoted by a Heterogeneous Palladium-N-Heterocyclic Carbene Complex in Batch and Continuous Flow**
  F. Francesco, I. Anastasiou, N. Salameh, T. Miyakoshi, O. Baudoin, L. Vaccaro, *ChemSusChem*. **2022**, *15*, e202102736.

- **Chiral Catalysts for Pd^0-Catalyzed Enantioselective C–H Activation**
  O. Vyhivskyi, A. Kudashev, T. Miyakoshi, O. Baudoin, *Chem. Eur. J*. **2021**, *27*, 1231-1257.

Abbreviations

Ac: Acetyl

Ad: Adamantyl

Ar: Aryl

BCB: Benzocyclobutene

Bn: benzyl

Cat.: catalyst

CDC: cross dehydrogenative coupling

CMD: Concerted metalation deprotonation

CPME: Cyclopentyl methyl ether

Cy: Cyclohexyl

d.r.: Diastereoisomeric ratio

dba: Dibenzylideneacetone

DBAD: Di-*tert*-butyl azodicarboxylate

DCE: 1,2-dichloroethane

DCM: Dichloromethane

DFT: Density Functional Theory

DIAD: Diisopropyl azodicarboxylate

DKR: Dynamic kinetic resolution

DMAP: *N*,*N*-dimethylaminopyridine

DMF: Dimethylformamide

DMSO: Dimethylsulfoxide

e.r.: Enantiomeric ratio

equiv.: Equivalent

Et: Ethyl

FG: Functional Group

HPLC: High-performance liquid chromatography

Imid.: Imidazole

KIE: Kinetic Isotope Effect

KR: Kinetic resolution

L: Ligand

MS: Molecular sieves

MOM: Methoxymethyl

MPAA: Mono-protected amino acid

NBS: *N*-bromosuccinimide

n-Bu: 1-Butyl

NCI: Non-covalent interactions

NHC: *N*-heterocyclic carbene

NMR: Nuclear magnetic resonance

PEt_3: Triethylphosphine

Ph: Phenyl

PIDA: Iodobenzene diacetate

PMB: *p*-Methoxybenzyl

Piv: Pivalic

PKR: Parallel kinetic resolution

PPTS: Pyridinium *p*-toluenesulfonate

*p*TSA: *p*-Toluenesulfonic acid

Py: Pyridine

r.t.: Room temperature

SM: Starting material

Temp: Temperature

TADDOL: α,α,α',α'-Tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol

TBDPS: *tert*-Butyldiphenylsilyl

TBS: *tert*-Butyldimethylsilyl

TES: Triethylsilyl

TIPS: Triisopropylsilyl

Tf: Triflyl

TFA: Trifluoroacetic acid

TFAA: Trifluoroacetic anhydride

TFE: 2,2,2-trifluoroethanol

THF: Tetrahydrofuran

TM: Transition metal

TMB: Trimethoxybenzyle

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1. General Introduction

1.1 Generality

Even if you are not a synthetic organic chemist, you are already a highly skilled organic chemist. For instance, you are using retinal with your eyes to read this sentence by converting visible light into a nerve impulse. In addition, every anatomical motion inside and outside your body utilises organic compounds even without conscious thinking.[1] Indeed, even before the birth of organic chemistry, humans used various organic materials, food and perfumes such as musk, camphor, soap, and alcohol. In the 1780s, Karl Wilhelm Scheele succeeded in extracting organic compounds from biological materials, and organic chemistry gradually developed after that, as represented by Friedrich Wöhler's synthesis of urea in 1828.

Starting with William Perkin's synthesis of the purple dye mauve in 1857, organic chemistry was applied to meeting the requirements of various industries.[2] In the latter half of the 19th century, applications spread to the pharmaceutical industry. Since then, countless other applications of organic synthesis have had a transformative effect on the modern world.

As synthetic organic chemistry flourished, the construction and/or functionalisation of valuable organic compounds has been enabled by transforming pre-existing functional groups (Figure 1). These classical approaches are reliable and widely applicable, allowing us to reach molecules of varying levels of complexity. On the other hand, when synthesising complex molecules, these often produce too many unwanted by-products and tend to lose time economy, resulting from the multiple steps required toward the desired compound and/or transformation.[3]

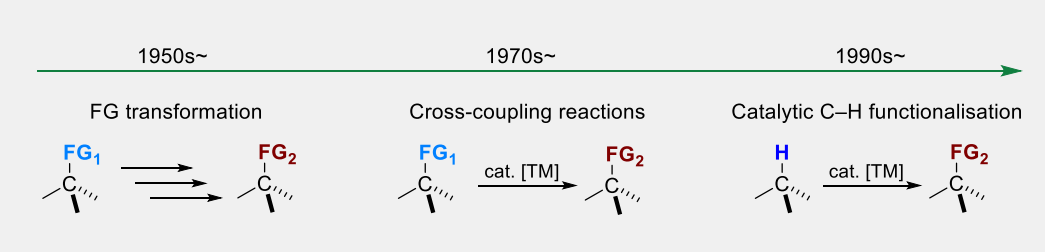


Figure 1. Schematic diagram of different approaches for functionalisation

Transition-metal catalysis has been developed over the past decades, providing some of the most convenient and powerful transformations to make new carbon–carbon and carbon–heteroatom bonds.[4] Undoubtingly, such cross-coupling reactions are the gold standard of research for bond formations up to the present.[5] Notably, Pd-catalysed cross-coupling reactions have emerged as a powerful and sophisticated tool, and consequently, the Royal Swedish Academy of Sciences recognised them when awarding the Nobel prize in 2010 to Heck, Negishi and Suzuki for palladium-catalysed cross-couplings in organic synthesis.[6–8] Palladium-catalysed cross-coupling reactions solved the aforementioned problems and have been used worldwide in research and commercial production.[9–14]

The general mechanisms for these palladium-catalysed cross-coupling reactions are depicted in Figure 2.[14] Both coupling reactions start from the oxidative addition of the aryl halide (or pseudohalide) to the

Pd(0) species, which initiates the catalytic cycle. In the Mizoroki–Heck coupling,[8] the reaction proceeds by coordination of an alkene to the Pd(II) species, followed by its *syn* migratory insertion. The regioselectivity of this insertion depends on the nature of the alkene, the catalyst, and the reaction conditions employed. The organopalladium species undergo C–C bond rotation and *syn* β-H elimination to form the alkenyl product. Subsequently, reductive elimination of H–X from Pd(II) species regenerate the Pd(0) catalyst. Alternatively, in the Negishi and Suzuki–Miyaura reactions, the oxidative addition is followed by transmetalation of an organometallic species (Zinc or Boron) to generate a Pd(II) intermediates. Subsequent reductive elimination results in C–C bond formation with the regeneration of Pd(0) species to reenter into the catalytic cycle.

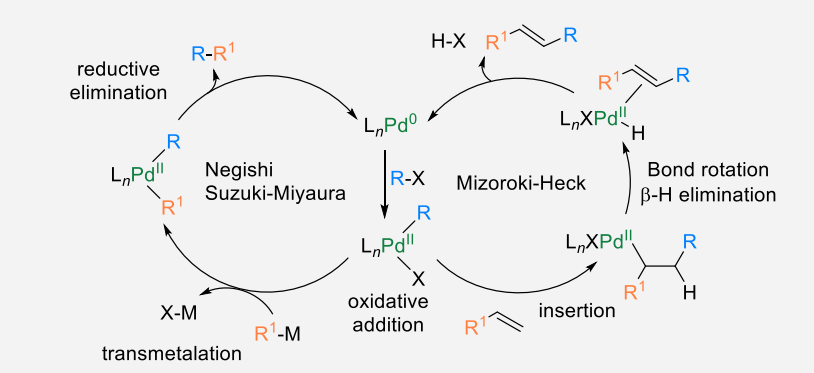


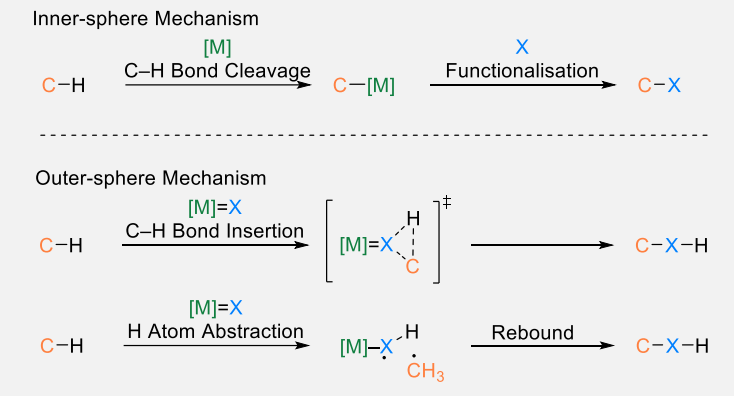
Figure 2. General catalytic cycles for Mizoroki-Heck, Negishi and Suzuki-Miyaura reactions

These reactions are most likely impeccable in terms of carbon-carbon bond formations, although, especially from an industrial point of view, at least one of the coupling partners requires prefunctionalisations; thus, multistep preparative sequences are often necessary. In addition, many organometallic reactants (including their by-products) are highly toxic and air and moisture sensitive. Indeed, this fact triggered chemists to accelerate the development of direct C–H functionalisation, which can take advantage of the ubiquity of C–H bonds in organic molecules. However, the ubiquitous nature of this bond means that significant challenges remain regarding reactivity and selectivity for these transformations.

1.1.2 C–H activation

As previously mentioned, these transition-metal-catalysed cross-coupling reaction classes still face limitations despite their use in academic and industrial settings. From this background, the direct activation of carbon−hydrogen (C−H) conceptually represents an elegant, atom- and step-economic solution.[15–17]

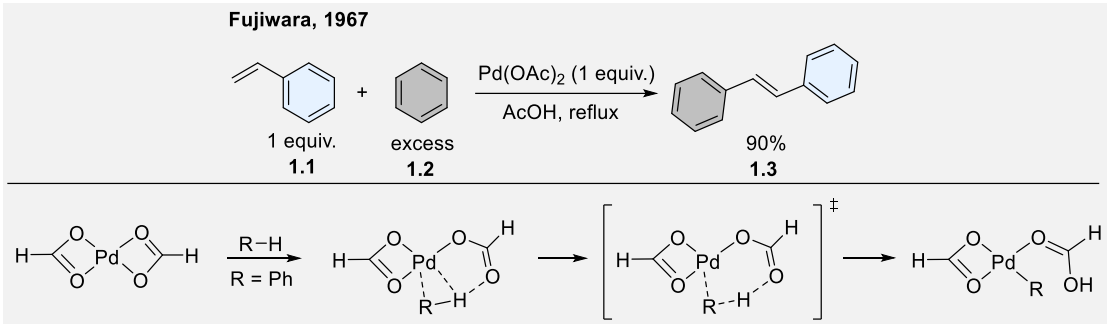
C–H activation can operate within two mechanistic manifolds: inner-sphere and outer-sphere mechanisms (Scheme 1). The inner-sphere C–H activation mechanism consists of cleavage of C–H bond to afford a transition metal alkyl/aryl species, then functionalisation by reaction with either an external reagent or at the metal centre. This mechanism can be discriminated by the formation of a discrete organometallic intermediate. In contrast, the outer-sphere mechanism mimics biological oxidation reactions catalysed by enzymes such as cytochrome P450 and methane mono-oxygenase. These reactions do not include direct interaction with the C–H bond and the metal centre. These processes can proceed via either a concerted insertion process, such as in the case of metal–carbenoid and –nitrenoid species, or via an H atom abstraction/rebound sequence. In general, inner-sphere processes are particularly sensitive to the steric environment of the C−H bond. In contrast, outer-sphere reactions are usually selective for the weakest C−H bonds.[18]



Scheme 1. Mechanistic classification of transition-metal-catalysed C–H functionalisation

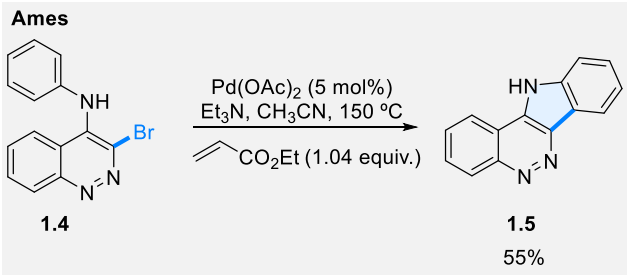
1.1.3 Pd-catalysed C(sp^2)–H activation

Palladium is one of the most commonly employed transition metals for inner-sphere C–H activation reactions. A ground-breaking achievement was disclosed by Fujiwara and Moritani in 1967 when the Pd(II) mediated arene vinylation to afford product **1.3** was reported (Scheme 2).[19] From a mechanistic point of view, previously, experimental studies provided evidence for the electrophilic character of $Pd(OAc)_2$ in the reaction of simple arenes, and a kinetic isotope effect (KIE) of $k_H/k_D = 5.1$ was observed for these palladation reactions.[20] Sakaki and co-workers found computationally that benzene's C–H bond activation is significantly more facile with $Pd(\kappa^2\text{-}O_2CH)_2$ than with $Pd(PH_3)_2$.[21] Thus, the palladation with $Pd(\kappa^2\text{-}O_2CH)_2$ was determined to proceed through κ^1,π-complex (R = Ph) as intermediate, followed by the formation of a six-membered transition state (Scheme 2). The exothermic nature of this process was attributed to the formation of the strong O–H bond through the assistance of the coordinated formate ligand. Following this, they developed a catalytic hydrogenative coupling in the presence of $Cu(OAc)_2/O_2$ as the oxidising reagent.[22] This reaction has been successfully extended to rhodium and ruthenium catalysts.[23,24]



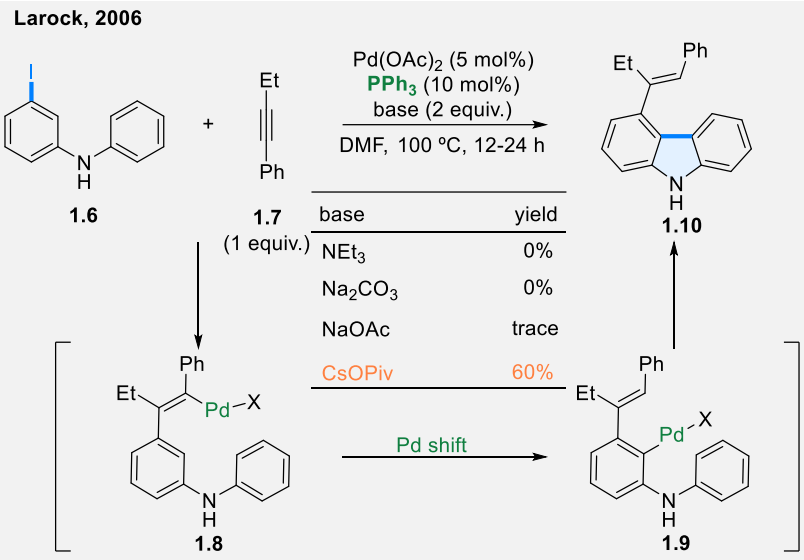
Scheme 2. Fujiwara-Moritani reaction and the calculated intermolecular palladation

In the 1980s, the research groups of Tajima[25] and Ames[26–28] independently reported the first palladium-catalysed direct arylations of (hetero)arenes (Scheme 3). Contrary to oxidative direct arylations, these redox-neutral processes do not require stoichiometric metal salts as the terminal oxidants and can ensure regioselectivity through easily accessible yet ecologically benign halides as leaving groups.[29] These reactions involve the cleavage of the C–H bond by a divalent base bound to an electrophilic transition-metal.



Scheme 3. First palladium-catalysed direct arylations

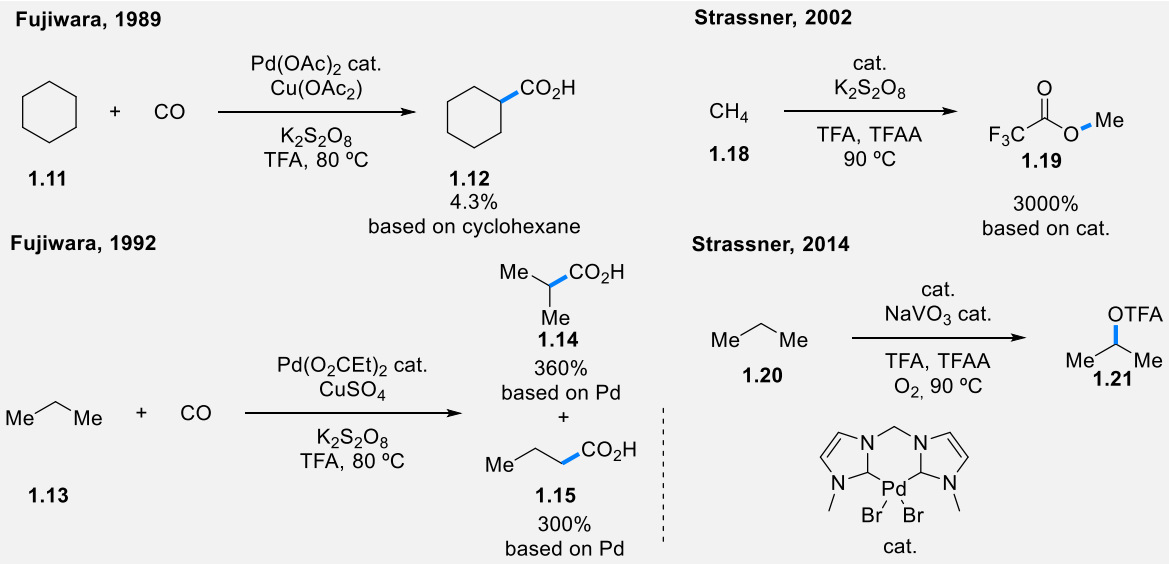
In the early 2000s, Larock and co-workers observed that the nature of stoichiometrically used carboxylate bases executed a significant effect on palladium-catalysed C–H activation,[30–32] which resulted in the observation of a palladium shift process when CsOPiv was used as the base (Scheme 4).[33] Palladium(II) has proven particularly efficient and versatile in intramolecular C−H activation, leading to overall catalytic inter- or intramolecular functionalisation. Two main sets of methods have been developed in the past decade: those initiated by coordinating a Pd(II) complex to a Lewis-basic hetero-atom[34–36] and oxidative addition of a carbon−leaving group bond to a Pd(0) complex. The second category has been the main focus of this thesis.



Scheme 4. Effect of bases on palladium-migration mediated direct arylation

1.1.4 Pd-catalysed C(sp^3)–H activation

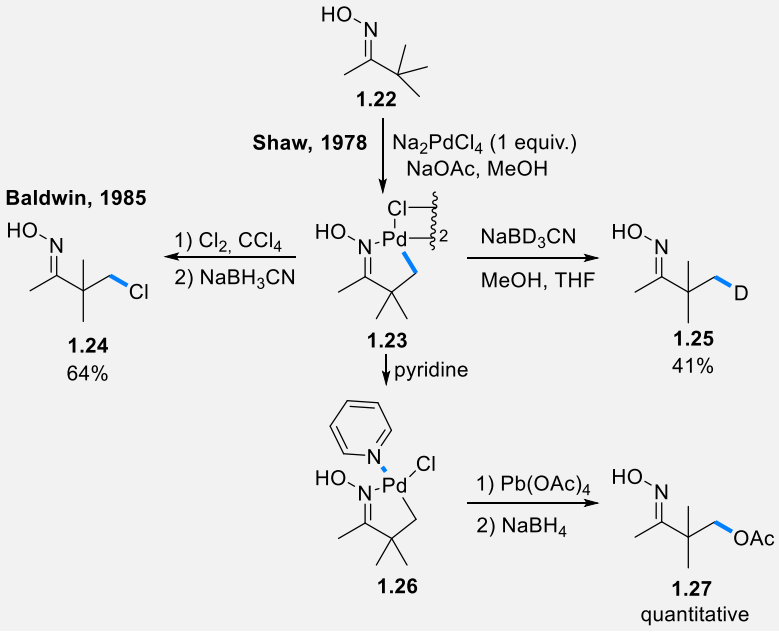
Among all categories of C−H bonds, C(sp^3)−H bonds of alkyl groups have been recognised as particularly challenging to activate and functionalise since they do not benefit from the precoordination of the transition metal to neighbouring π or π* orbitals. Seminal work by Fujiwara and co-workers described carbonylation of the unactivated C(sp^3)–H bond of cyclohexane **1.11** with a Pd(II)/Cu(II) catalytic system in the presence of high-pressure CO to afford cyclohexane carboxylic acid **1.12** in 4.3% based on cyclohexane **1.11** (Scheme 5).[37] Subsequently, they reported C(sp^3)−H carboxylation reactions of gaseous acyclic alkanes **1.13** to give the corresponding aliphatic acids **1.14**, **1.15**.[38] Mechanistically, the initial generation of cationic [Pd(TFA)]$^+$ species in TFA is attached by C(sp^3)–H bonds to give [alkyl–Pd(II)–TFA] species.[39] The use of chelating bis(*N*-heterocyclic carbene) ligands to promote Pd(II)-catalysed C(sp^3)−H activation of methane **1.18** was first reported by Strassner and co-workers.[40] The same bis(NHC) palladium catalyst was also employed for the oxidation of propane **1.20**.[41] The mechanism is believed to proceed through C(sp^3)–H bond cleavage by Pd(II), followed by oxidation of Pd(II) to Pd(IV) by bromine.[42] The weak affinity of alkanes to the catalyst requires the use of excessive amounts of solvents. Additionally, controlling the regioselectivity and chemoselectivity of the reaction to avoid over-functionalisation has been difficult. In order to overcome these difficulties, methodologies with pre-existing functional groups to coordinate Pd have emerged since the 1960s.



Scheme 5. Seminal work of C(sp^3)–H activation of "paraffin" alkanes

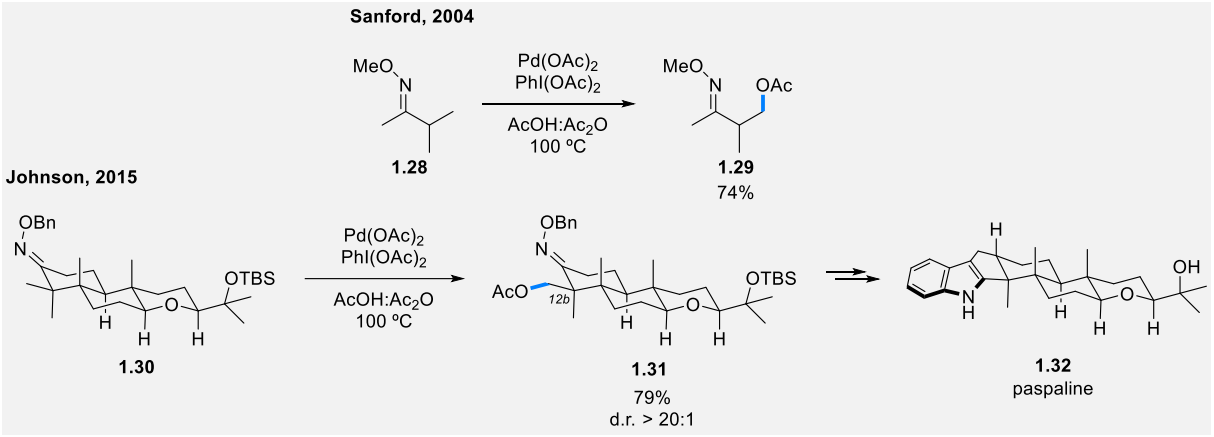
1.1.5 Directed Pd-catalysed C(sp^3)–H activation

By introducing pre-existing functional groups, C–H activation can take advantage of precoordination to overcome the abovementioned issues on the unreactive nature of C–H bonds. Traditionally strong σ-donors and/or π-acceptors have been utilised as auxiliaries such as nitrogen-, sulfur-, or phosphorus-containing moieties. Substantial efforts have been put into understanding the mechanism and making this behaviour synthetically useful since the 1960s. In 1978, Shaw and co-workers described a pioneering example of the directed palladation of oximes **1.22** (Scheme 6).[43] A stoichiometric amount of Na_2PdCl_4 and NaOAc induced cleavage of the C(sp^3)–H bond of the *tert*-butyl group to give the chloro-bridged dimerised palladacycle **1.23**. In 1985, Baldwin and co-workers achieved functionalisation of the C(sp^3)–Pd bond in Shaw`s oxime-derived palladacycle **1.23**.[44] Chlorination of the complex with chloride and subsequent reduction with sodium cyanoborohydride led to the β-chlorinated oxime derivative **1.24**. Direct reduction of the complex with sodium cyanoborodeuteride afforded β-deuterated product **1.25**. Furthermore, monomeric pyridine complex **1.26** reacted with lead tetraacetate, followed by reduction with sodium borohydride, leading to the formation of acetoxylated product **1.27** in quantitative yield.



Scheme 6. Cyclometallaiton with directing groups and their corresponding functionalisation

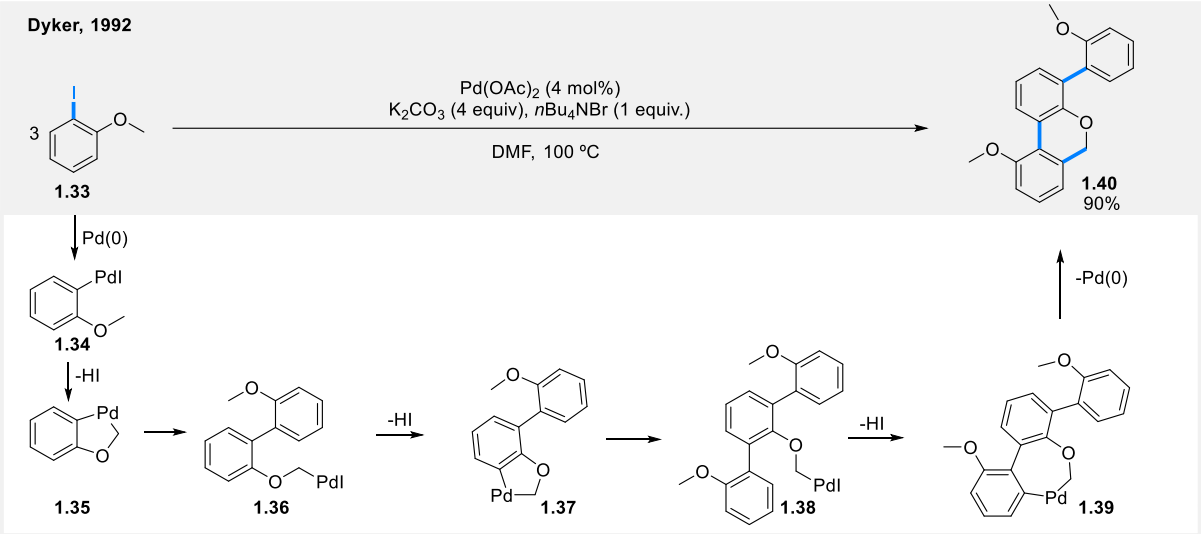
By taking advantage of these precedents, Sanford and co-workers disclosed Pd(II)/Pd(IV) catalysis with directing groups in the presence of iodobenzene diacetate as a stoichiometric oxidant, which could circumvent the previous problem that strongly chelating substrates give rise to thermodynamically stable and less reactive cyclometalated intermediates (Scheme 7).[45] The Johnson group later reported the total synthesis of the indole diterpenoid paspaline **1.32** by using this method to construct the C12b quaternary centre with high levels of diastereoselectivity.[46] Since then, a variety of directed Pd-catalysed C(sp^3)–H activation reactions via Pd(II)/Pd(IV) with a stoichiometric oxidant have been accomplished up to date.[39]



Scheme 7. C(sp^3)–H activation via Pd(II)/Pd(IV) catalysis and the application

1.1.6 Oxidative addition-induced Pd-catalysed C(sp^3)–H activation

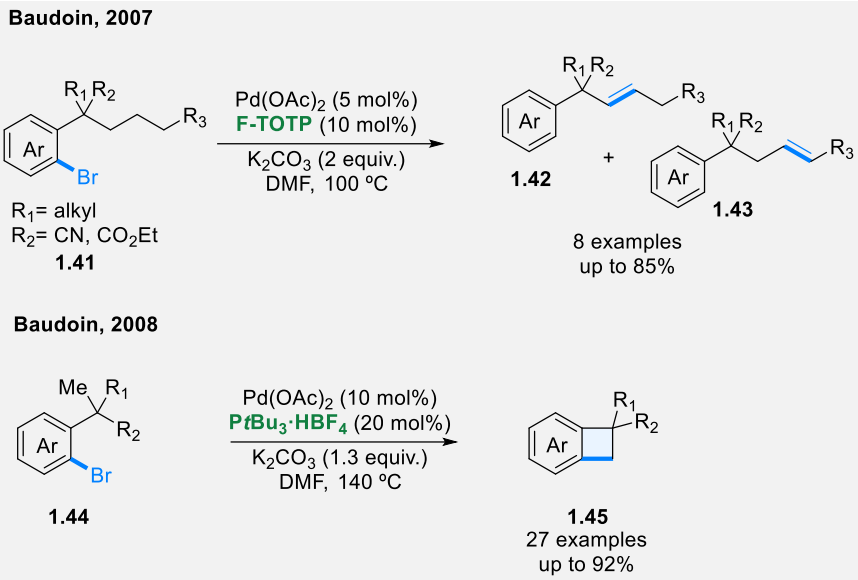
In contrast to the addition of an external oxidant, Dyker reported the first oxidative addition mediated C(sp^3)–H activation in 1992 (Scheme 8).[47] The polycyclic compound **1.40** was obtained under Heck-type conditions by the self-condensation of three molecules of aryl halide **1.33**. The mechanism is initiated by oxidative addition of C–I to Pd(0), followed by intramolecular C(sp^3)–H activation of the methoxy group to generate palladacyle **1.35**, which undergoes second oxidative addition to generate Pd(IV) species, followed by reductive elimination towards **1.36**. Complex **1.36** undergoes C(sp^2)–H activation to form palladacycle **1.37**. Subsequent oxidative addition and reductive elimination provide **1.38**. Finally, 7-membered palladacycle **1.39** is formed by another C(sp^2)–H activation, followed by reductive elimination to generate **1.40** and Pd(0) species. After this initial work, Dyker reported a series of articles indicating the feasibility of the translation of Pd(0)-catalysed C(sp^2)–H arylation to C(sp^3)–H arylation.[48–50]



Scheme 8. First oxidative addition induced C(sp^3)–H activation

In 2003, the Baudoin group reported that phosphine ligands could suppress aryl halide self-condensation.[51] In this study, two different products were observed depending on the benzylic alkyl substitutions on substrates, olefination and benzocyclobutene (BCB), with tri-*o*-tolyphosphine (**TOTP**) as the best ligand, arising from C(sp^3)–H activation and either β-H elimination or reductive elimination. Four years later, the Baudoin group disclosed that more electron-deficient tri-(5-fluoro-2-methyl phenyl)phosphine (**F-TOTP**) could yield the olefin **1.42**/**1.43** selectively at relatively low temperatures (Scheme 9).[52] A computational study revealed that the olefination occurs via 1,4-Pd shift upon methylene position to give alkyl palladium species, which gives rise to olefins by β-H elimination.[53] Later, the formation of BCB ring **1.45** was further investigated by the Baudoin group, showing that the combination of a bulky trialkyl phosphine ligand, **P*t*Bu$_3$**, with potassium carbonate in a polar solvent (DMF) gave rise to the products in good yields.[54] Fascinated by these early studies, the Baudoin group

primarily focuses on oxidative addition-induced Pd(0)-catalysed C(sp^3)–H activation and its application to natural product synthesis up to date.[55–57]



Scheme 9. Synthesis of olefins and BCBs by the Baudoin group

1.1.7 Intramolecular Pd(0)-catalysed C(sp^3)–H activation towards valuable scaffolds

There have been several key advances in the Pd(0)-catalysed C(sp^3)–H activation since the turn of the century. The key developments are depicted in Figure 3. After the reports mentioned above on β-H elimination **1.42**/**1.43**, five-membered ring systems such as indanes **1.46**,[58] dihydrobenzofurans **1.47**,[59] indolines **1.48a**,[60] hexahydroindoles **1.48b**,[61] oxindoles **1.49**[62] and γ-lactams **1.53**[63] were accomplished. The formation of larger rings **1.51**, **1.52** proceeding through less favourable larger palladacycles has also been reported.[64,65] Furthermore, biologically interesting four-membered cycles were accessible such as β-lactams **1.50**, **1.54**.[66,67] The most common types of activated C–H bonds are methyl groups and cyclopropanes, which align with selectivities observed in directed Pd(II)-catalysed reactions.[57]

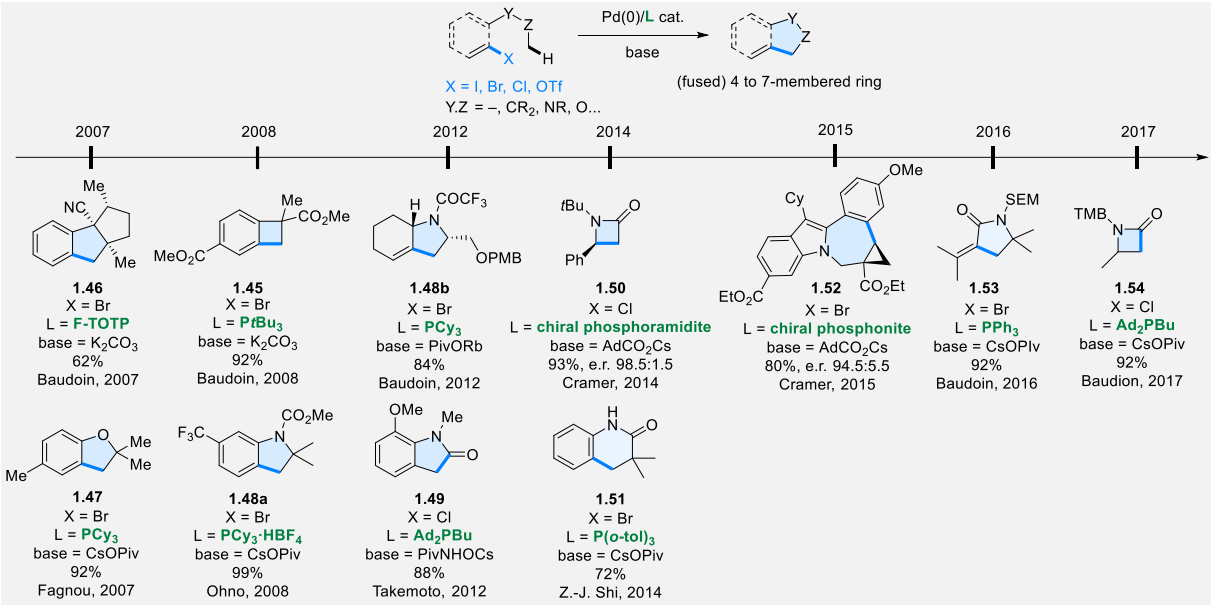


Figure 3. Representative ring construction via Pd(0)-catalysed C–H activation

1.1.8 Mechanism

After initial direct arylation reactions with palladium catalysts were reported,[26] it was believed that the direct arylation occurs via an electrophilic aromatic substitution (S_EAr) pathway, in which the nucleophilic arene would interact with palladium (II) species via a Wheland-like intermediate followed by reductive elimination to afford the cross-coupled product. However, mechanistic studies on palladium-catalysed direct arylation as representative by Davies and Macgregor,[68] Maseras and Echavarren,[69,70] Fagnou and Gorelsky[71] led to the postulation of a second mode of C–H cleavage that does not involve a Wheland-like intermediate, which they termed concerted metalation-deprotonation (CMD) mechanism. This mechanism is less dependent on nucleophilicity and has a broad scope with electron-deficient and electron-neutral arenes.[72] Experimentally, the effect of a *meta*-substituent (OMe, Me, CO_2Me, Cl *etc*) on regioselectivity towards *ortho*-position was evaluated, wherein a more sterically accessible *para*-position was reacted in most cases.[73] In contrast, direct *ortho*-arylation resulted when a fluorine substituent was present at the *meta*-position rather than the remote *para*-arylation. Such selectivity was reasoned due to the more acidity of the *ortho*-C–H bonds than those at *para*-positions. This so-called *ortho*-fluorine effect has been studied by Lynam, Fairlamb and their co-workers in 2022.[74] To rationalise this reactivity, Echavarren and Maseras implemented the first theoretical support with DFT calculations,[69] which displayed anionic ligand exchange could occur to form a palladium carbonate species with significantly low energy barriers to undergo the CMD process. In 2007, Fagnou and co-workers, in 2008, Baudoin, Clot and their co-workers independently reported a DFT computational study on the mechanism involved in the synthesis of dihydrobenzofurans **1.47** and BCBs **1.45** via C(sp^3)–H activation showing that the CMD process also takes place as C(sp^2)–H activation.[53,54,59] Interestingly, when computing with different reaction conditions (ligands/bases), the energy profile trends were significantly altered, leading to the conclusion that the transition state geometry is affected depending on the substrate and reaction conditions. Pd(0)-catalysed C(sp^3)–H activation occurs as below (Figure 4). Initial oxidative addition of C–(pseudo)halide bond into Pd(0) species generates Pd(II) species **II**. Ligand exchange of the (pseudo)halide with a carbonate or carboxylate, followed by C–H activation via the CMD mechanism **IV**, **V**, leads to palladacycle **VI**, **VII**. Subsequent pathways are either carbonate or carboxylate dissociation, followed by reductive elimination furnishing polycyclic products **VIII**, **IX** or proton transfer from the protonated carbonate or carboxylate into the aryl to undergo either β-H elimination forming olefin **XI** via the σ-alkylpalladium species **X** or another C–H activation to regenerate palladacycle. If no β-H elimination occurs, the alkylpalladium species **X** can undergo further functionalisation reaction, which is named Pd shift/migrating.[75]

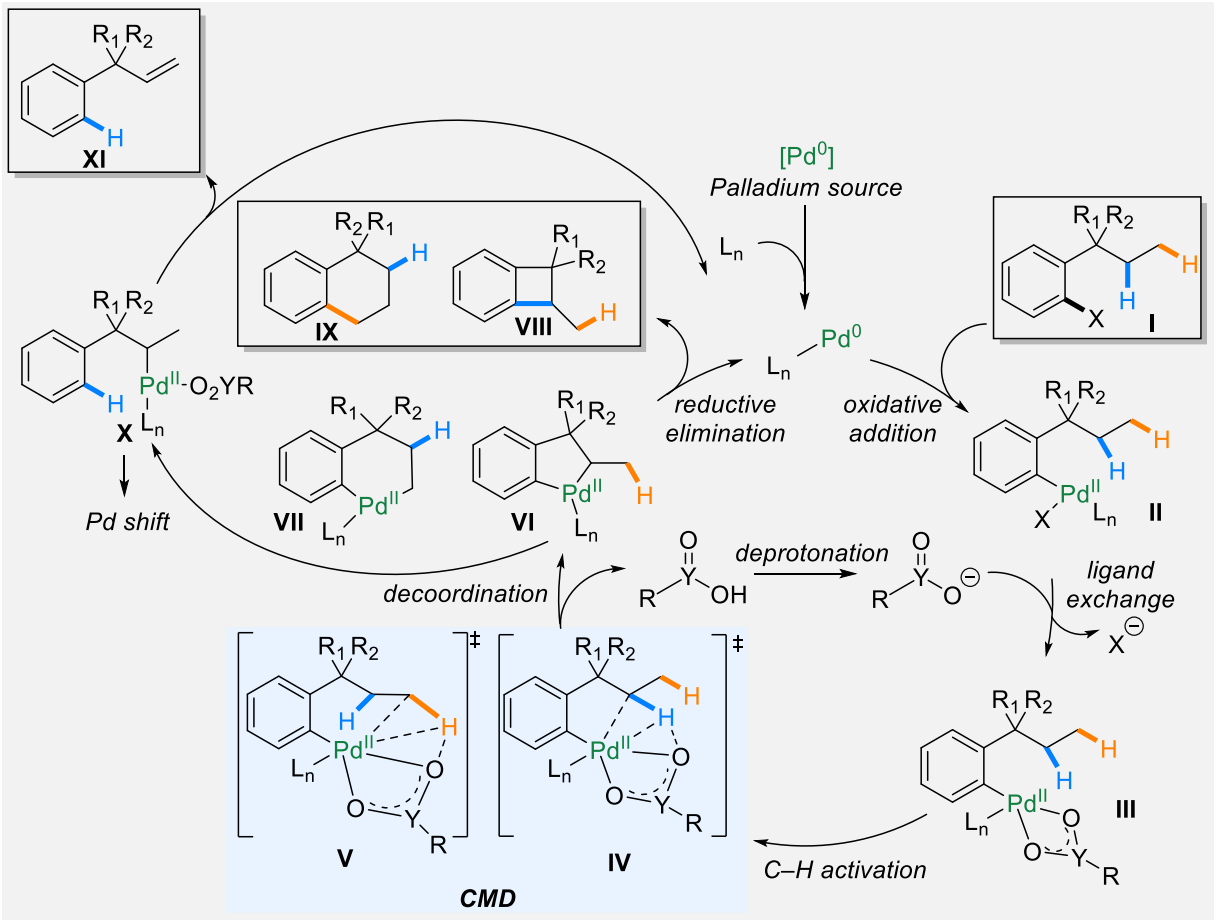


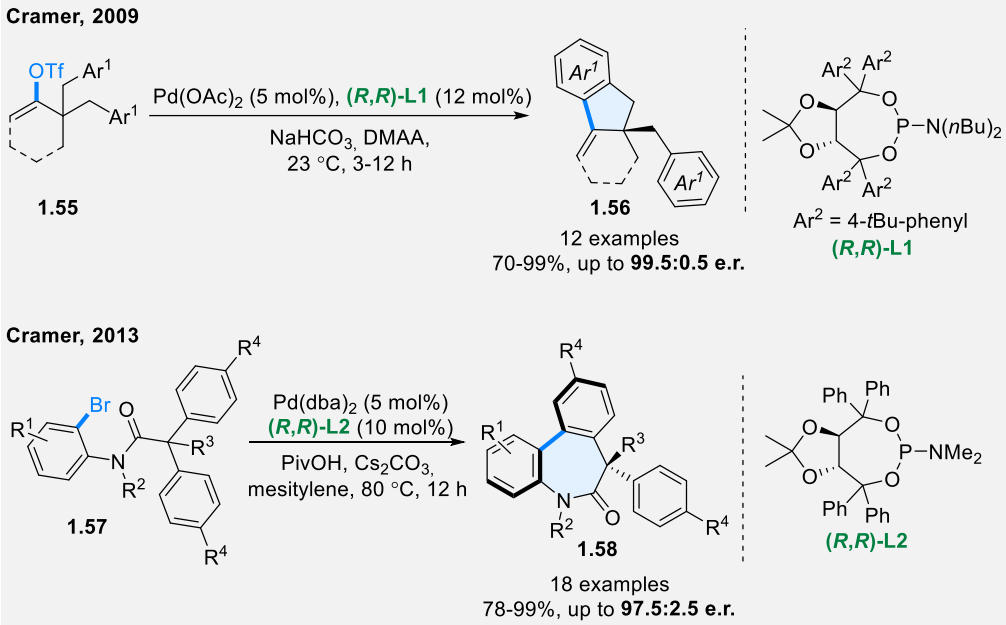
Figure 4. Mechanism of the Pd(0)-catalysed C(sp^3)–H activation reaction

1.2 Enantioselective intramolecular C–H arylation

Constant progress in the transition metal catalysed C–H activation has led to the discovery of enantioselective methods to generate and control various types of stereogenic elements to furnish scalemic molecules. Enantioselectivity is accessible either by using a chiral ligand or a chiral active base that controls the orientation of substituents and the directionality of palladium–carbon bond formation in the catalytic cycle. This chapter will describe essential milestones in Pd(0)-catalysed enantioselective C–H activation.

1.2.1 Enantioselective intramolecular C(sp^2)–H arylation

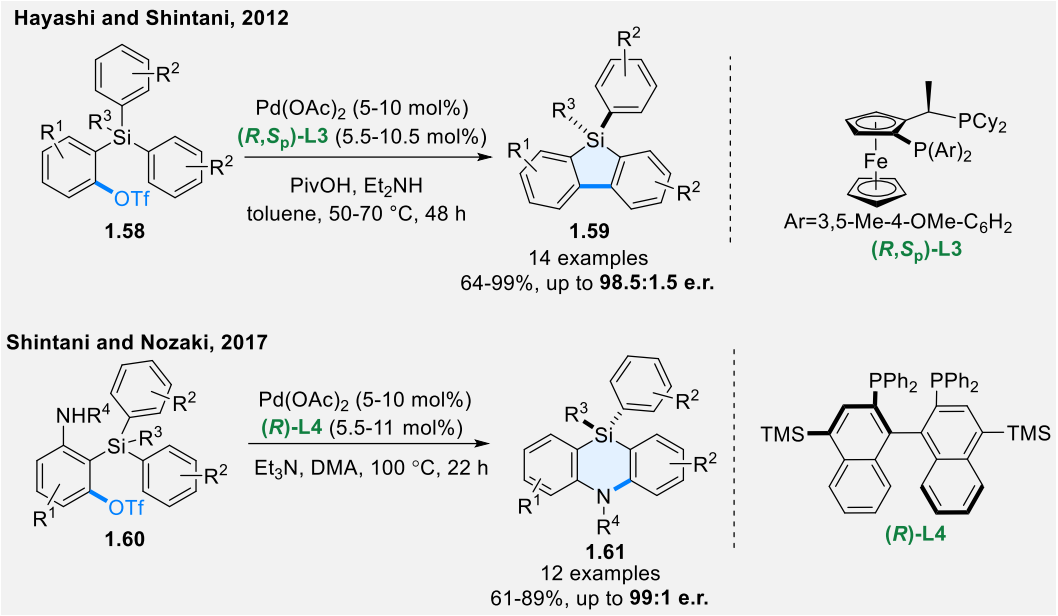
The first successful example of enantioselective Pd(0)-catalysed C(sp^2)–H activation was reported by Cramer in 2009, employing a TADDOL-phosphoramidite ligand **L1** at ambient temperature to achieve indanes synthesis **1.56** from bis-benzylated vinyl triflates **1.55** (Scheme 10).[76] Interestingly, the optimisation study showed that polar, aprotic dimethylacetamide (DMA) was the most efficient solvent. Four years later, similar TADDOL-phosphoramidite ligand **L2** was successfully employed to obtain dibenzazepinones **1.58** with excellent enantioselectivity from the reductive elimination of larger eight-membered palladacycles.[77]



Scheme 10. First desymmetrisation of C(sp^2)–H bonds in the presence of phosphoramidite ligands

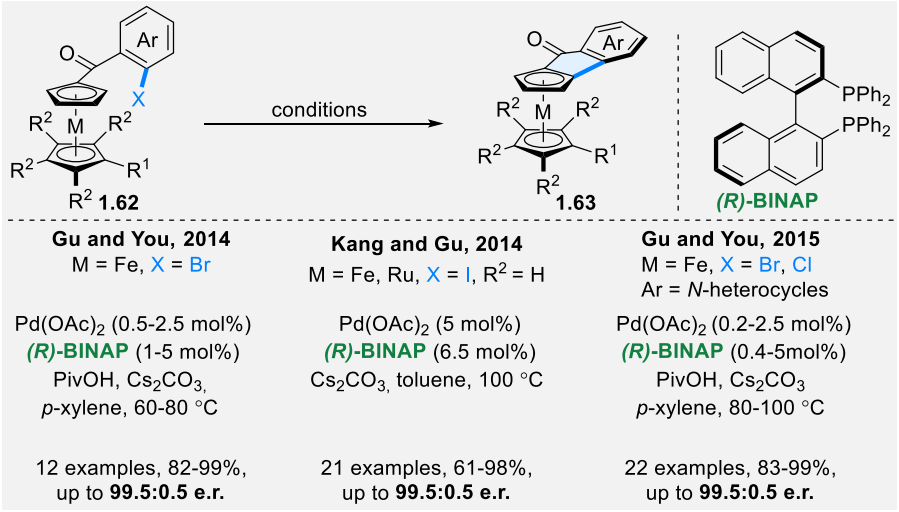
In 2012, Shintani and Hayashi reported an enantioselective approach for the formation of Si-stereogenic centres via C(sp^2)–H arylation/desymmetrisation of triarylsilanes with the electron-rich Josiphos-type ligand **L3** to yield dibenzosiloles **1.59** with high enantioselectivities.[78] In 2017, as a follow-up study, Nozaki, Shintani and co-workers reported the enantioselective synthesis of Si-stereogenic 5,10-

dihydrophenazasilines **1.61** via enantioselective 1,5-Pd migration and intramolecular C–N bond formation, employing TMS-substituted (*R*)-BINAP **L4** as the chiral ligand (Scheme 11).[79]



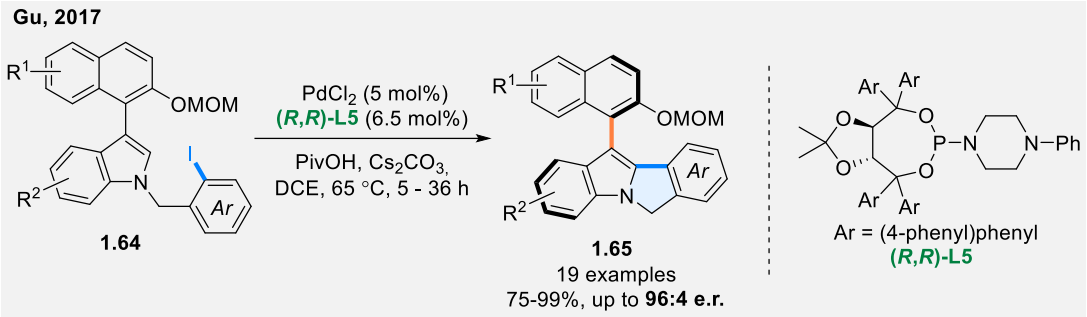
Scheme 11. Formation of Si-stereogenic centres by C(sp^2)–H arylation

In 2014, the use of chiral ligands for the generation of planar chiral metallocenes **1.63** was disclosed by the groups of Q. Gu and You[80] and Kang and Z. Gu[81] independently. The protocol developed by Kang and Gu allows for the derivatisation of ruthenocenes in addition to ferrocenes. The Gu–You group later extended this methodology towards *N*-heterocyclic derivatives at very low catalyst loadings (0.2 mol%) (Scheme 12).[82]



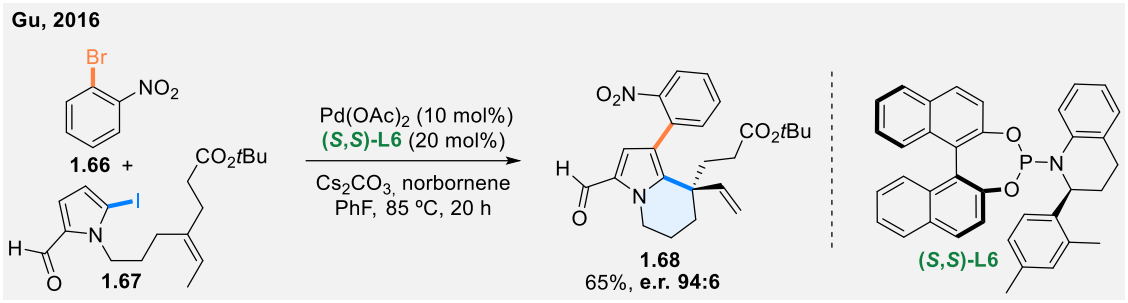
Scheme 12. Representative routes to metallocenes with planar chirality

The success of atroposelective processes heavily relies on the stability of the formed stereogenic axis. In 2017, Gu and co-workers efficiently controlled the biaryl axes **1.65** through chiral phosphoramidite ligand **L5**, containing biphenyl substituents at the TADDOL backbone and a piperazine moiety on phosphorus (Scheme 13).[83]



Scheme 13. Atroposelective C–H arylation

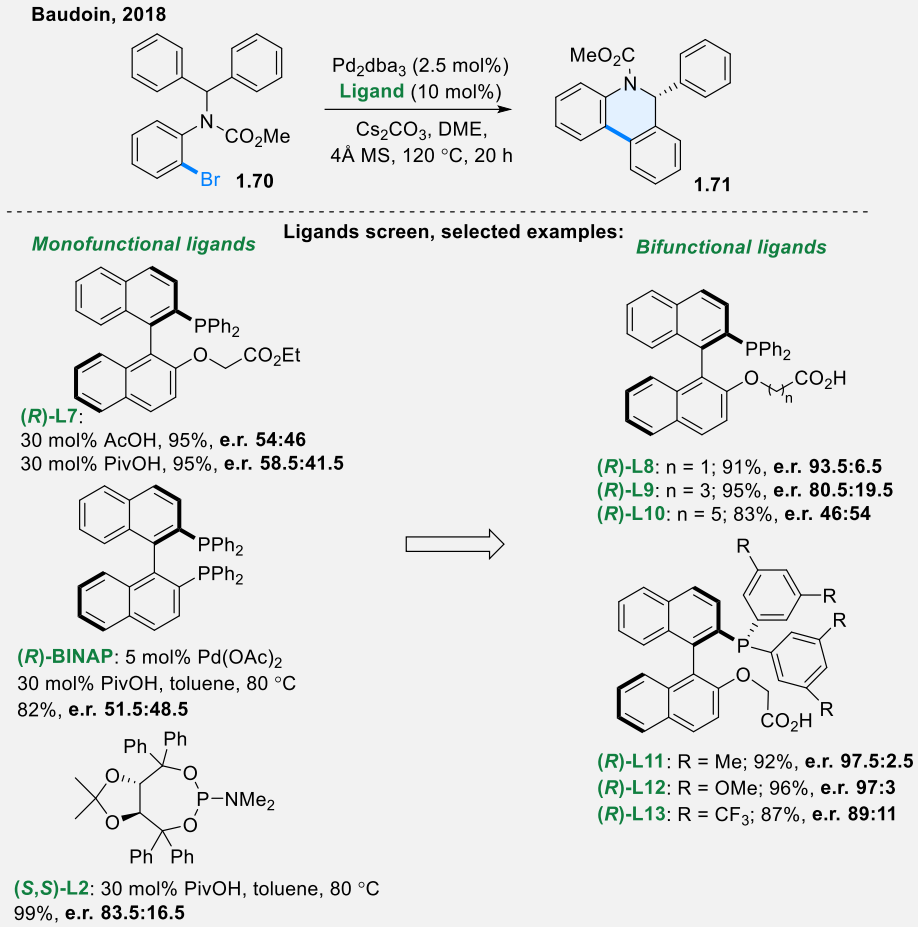
The Catellani reaction is a powerful multi-component process including a C(sp^2)–H activation step, which allows for the rapid construction of polysubstituted aromatic rings.[84] In 2016, Gu and co-workers reported the first enantioselective version of this reaction with phosphoramidite ligand **L6** bearing an α-stereogenic tetrahydroquinoline ring in the context of the total synthesis of the rhazinilam family of natural products (Scheme 14).[85] In this case, the intramolecular alkene carbopalladation, occurring after C–H arylation with aryl bromide **1.66**, is the enantiodetermining step of the reaction. This key intermediate was then converted to rhazinilam and several congeners efficiently.



Scheme 14. Enantioselective Catellani reaction

Chiral ancillary ligand/achiral base and chiral base/achiral ligand approaches in enantioselective intramolecular reactions are well-known procedures in which the C–H activation step is enantiodetermining and occurs through the CMD mechanism.[56] The designing of bifunctional ligands combining these two elements in a single chiral catalyst constitutes an alternative approach pioneered by the Yu group. Employing mono-protected amino acids as chiral ligands for enantioselective Pd(II)-catalysed reactions led to high levels of enantioselectivities.[86,87]

In 2018, the Baudoin group reported the first example of Pd(0)-catalysed intramolecular C–H arylation using bifunctional ligands **L8-L13** (Scheme 15),[88] based on MOP-type ligands[89] bearing a chiral binaphthyl scaffold substituted on one side with phosphine and on the other with a carboxylic acid. Interestingly, monofunctional ligands such as MOP and classic chiral ligands such as TADDOL-based phosphoramidite **L2**, **BINAP** and NHCs provided lower enantioselectivities in combination with an external carboxylic acid. In 2021, the Baudoin group successfully translated this theory into the synthesis of chiral fluoradenes and other warped molecules, and some of them were found to have a strong ellipticity and an emission band located in the visible region.[90]



Scheme 15. Bifunctional ligands in desymmetrising enantioselective C–H arylation

Recent years have seen the emergence of an array of enantioselective C–H functionalisation reactions, among which there have been several Pd(0)-catalysed reactions. Despite these advances, a number of significant challenges remain to be addressed. For instance, intramolecular enantioselective C–H arylations are limited to the formation of five- to seven-membered rings, and both smaller and larger rings are lacking in the reaction portfolio.[56]

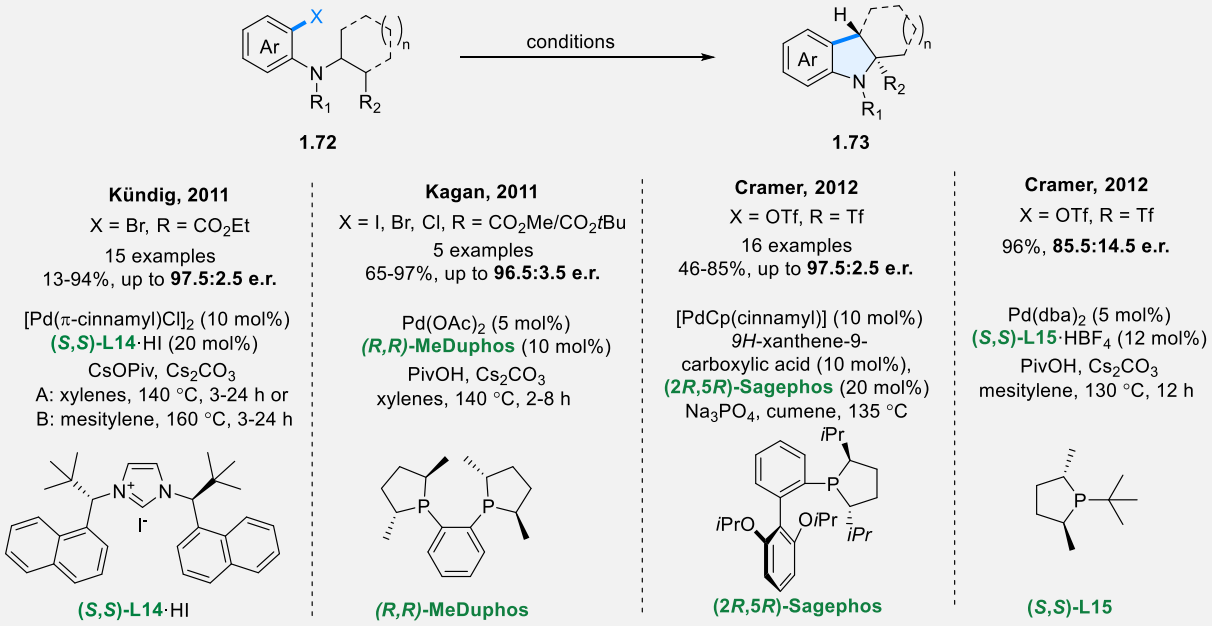
1.2.2 Enantioselective intramolecular C(sp^3)–H arylation

Alkyl C–H bonds are generally less reactive than C(sp^2)–H bonds toward the activation by palladium complexes.[57] Therefore their enantioselective functionalisation is particularly challenging. To this end, Kündig and co-workers disclosed in 2011 the first enantioselective protocol for the desymmetrisation of methylene C(sp^3)–H bonds. Employing NHC-based chiral ligand **L14**, fused indolines **1.73** were accessed in high yields and enantioselectivities and in a *trans*-diastereoselective fashion, despite the employed high temperature (Scheme 16).[91]

Concurrently, Kagan and co-workers reported the enantioselective synthesis of indolines by intramolecular C(sp^3)–H arylation.[92] They employed commercially available **(*R*,*R*)-MeDuphos** for the desymmetrisation of methyl and methylene on cyclohexyl groups.

In 2012, another example of an enantioselective synthesis of indolines was disclosed by Cramer and co-workers. They examined the effect of carboxylic acids of various bulk and found that 9*H*-xanthene-9-carboxylic acid provided the best enantioselectivity in combination with **Sagephos**, a chiral ligand.[93]

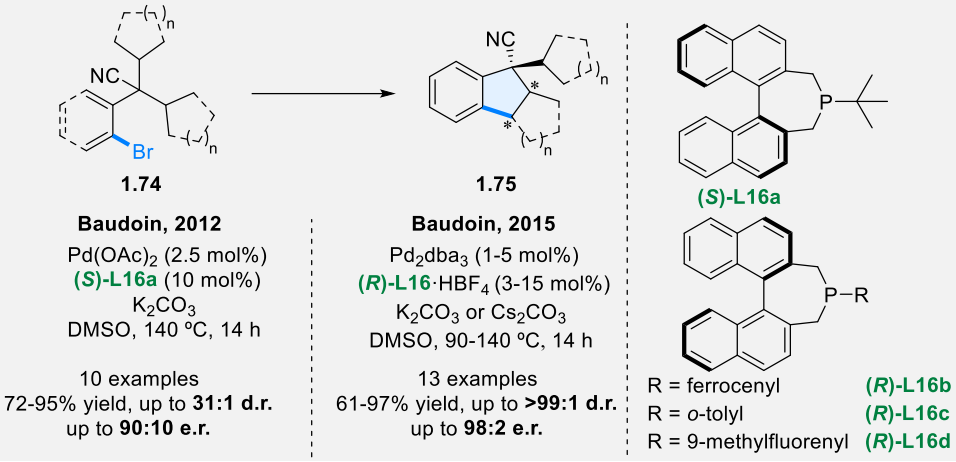
In the same year, as a chiral version of widely-used electron-rich, monodentate phosphines such as PCy_3 and $P(tBu)_3$, Cramer and co-workers reported that **L15** could give rise to target indoline with an e.r. of 85.5:15.5 and an excellent yield.[94]



Scheme 16. Enantioselective synthesis of indolines by C(sp^3)–H activation

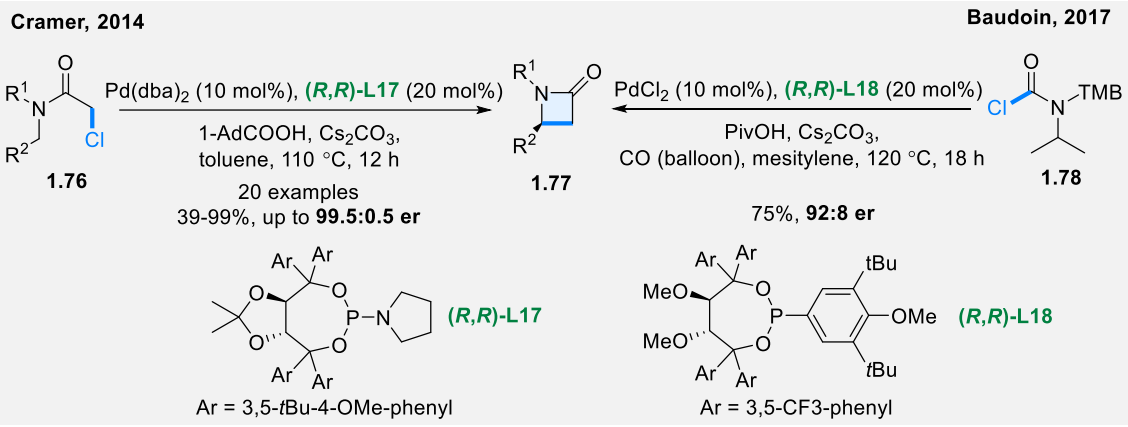
In 2012 and 2015, the Baudoin group used Binepines,[95] chiral monophosphines, for enantioselective intramolecular C(sp^3)–H arylations establishing scalemic indanes (Scheme 17). Initially, a combination of *tert*-butyl-substituted Binepine **L16a** as a chiral ligand and $Pd(OAc)_2$ as the palladium source in DMSO as the optimal solvent was employed, providing indanes **1.75** possessing two stereogenic centres with high yields and diastereoselectivities, but moderate enantioselectivities.[96] In 2015, an improved protocol was reported leading to higher enantioselectivities and compatibility with a broader scope of

structures.[97] Reaction optimisations revealed three Binepines **L16b-d** as optimal ligands, containing a bulky substituent such as ferrocene **L16b** for the arylation of primary C(sp^3)–H bonds, *o*-tolyl **L16c** for the methylene activation and 9-methylfluorenyl **L16d** for a pyridine-containing substrate.



Scheme 17. Pd(0)/Binepine-catalysed intramolecular C(sp^3)–H arylation for the synthesis of fused indanes

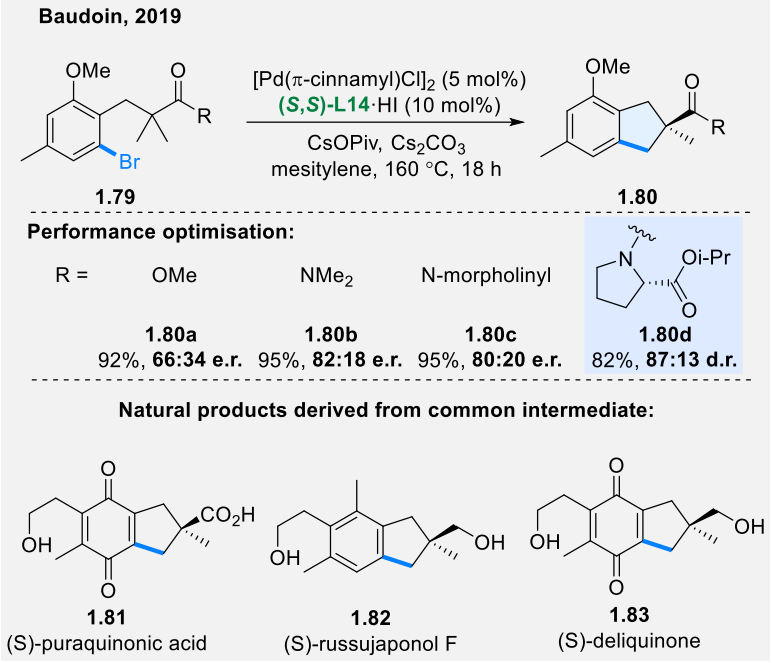
Biologically relevant β-lactams **1.77** were constructed with intramolecular C(sp^3)–H alkylation of benzylic secondary C–H bonds from corresponding α-chloroamides **1.76** by the Cramer group in 2014 (Scheme 18).[66] In this case, the chiral catalyst discriminates between the enantiotopic hydrogen atoms on the methylene position, and a stereogenic centre is created at the activated C–H bond. A careful adjustment of its steric properties revealed phosphoramidite **L17** to be the most efficient ligand for this transformation. Three years later, the Baudoin group reported synthesising β-lactams **1.77**, employing C(sp^3)–H carbamoylation (Scheme 18).[67] This challenging desymmetrisation of unactivated methyl groups was achieved by the TADDOL-derived phosphonite ligand **L18**.



Scheme 18. Enantioselective synthesis of β-lactam by intramolecular C(sp^3)–H activation

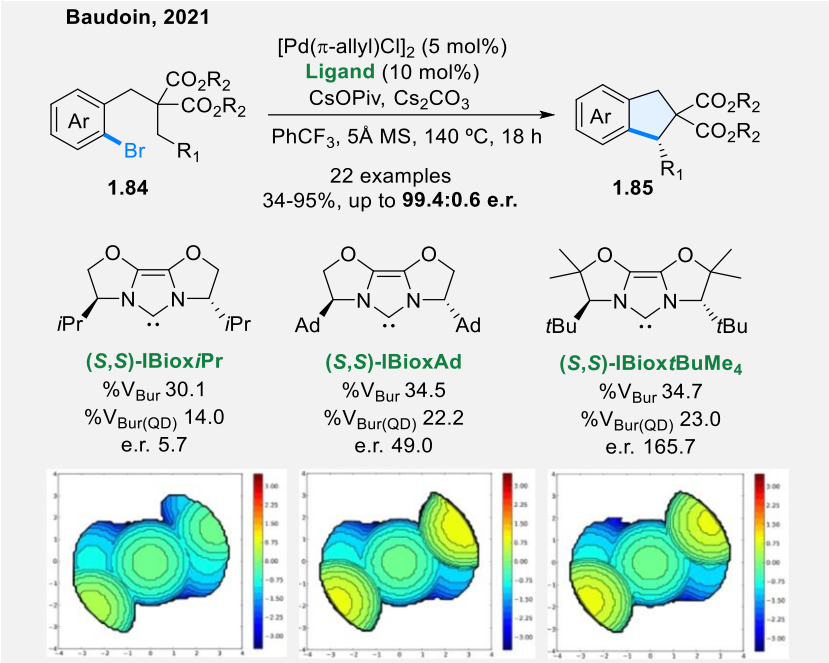
In 2019, the desymmetrisation of methyl groups by asymmetric C(sp^3)–H arylation was employed as the critical step in the enantioselective synthesis of (nor)illudalane sesquiterpenes **1.81-83** reported by the Baudoin group (Scheme 19).[98] (Nor)illudalane sesquiterpenes, such as puraquinonic acid **1.81**, russujaponol F **1.82** and deliquinone **1.83** are bioactive secondary metabolites isolated from various species of edible mushrooms which induce the differentiation of leukaemia HL-60 cells.[99] The key for

high levels of stereoselectivity was the use of a chiral amide group derived from (*S*)-proline ester compared with achiral precursors and **L14** as a chiral NHC ligand. After cleavage of the prolinamide group, the synthesis of the (*S*)-enantiomers of the aforementioned natural products were achieved.



Scheme 19. Total synthesis of (nor)illudalane families by desymmetrising C(sp^3)–H arylation

In contrast to the desymmetrisation of two enantiotopic alkyl groups, leading to the generation of a stereogenic centre remote to the activated C–H bond,[91,100,101] the desymmetrisation of enantiotopic hydrogen atoms on secondary carbons had remained elusive. This was mainly due to the lower reactivity of the secondary C–H bonds and competing β-H elimination, leading to the formation of olefins instead of reductive elimination products.[66] In 2021, the Baudoin group disclosed that IBiox-type chiral NHCs showed an exceptional reactivity for unbiased secondary C–H bonds, and high enantioselectivity was achieved by newly synthesised **IBioxAd** and **IBiox*t*BuMe$_4$** for the formation of scalemic indanes **1.85** (Scheme 20).[102] When they compared IBiox-type ligands with %V_{Bur} computed using the application developed by Cavallo and co-workers,[103] there was no correlation between the %V_{Bur} and the measured e.r. values. However, %$V_{Bur(QD)}$, the occupation difference between the two sets of opposite quadrans deduced from the %V_{Bur} calculated in each quadrant, was better correlated to the observed e.r. than the global buried volumes, with higher %$V_{Bur(QD)}$ values corresponding to higher enantioselectivities.



Steric maps and buried volumes of IBiox ligands (L) in [PdL(π-allyl)Cl] complexes.
The quadrant difference buried volume is defined as:
$\%V_{Bur(QD)}=[\%V_{Bur(NE\ quadrant)}+\%V_{Bur(SW\ quadrant)}-\%V_{Bur(NW\ quadrant)}-\%V_{Bur(SE\ quadrant)}]/2$.

Scheme 20. Enantioselective intramolecular arylation of enantiotopic secondary C–H bonds

1.3 Kinetic resolution

Kinetic resolution is a means of differentiating two enantiomers in a racemic mixture. In other words, enantiomers of a racemic substrate react at different reaction rates to form a product that may or may not be chiral. In a catalytic kinetic resolution, a chiral ligand or chiral catalyst is required to facilitate the transformation of one enantiomer over the other, giving the mixture of the enantioenriched product and unreacted enantiopure starting material. The relative reaction rate of each enantiomer in a racemic mixture is expressed as *s*-factor or $k_{rel} = k_{fast}/k_{slow}$, which is dictated by the magnitude of $\Delta\Delta G^{\ddagger}$ (Figure 5).[104] Whilst both enantiomers as starting materials have the same Gibbs free energy level by definition and the products also have equal levels, $\Delta G^{\ddagger}$ can be different.

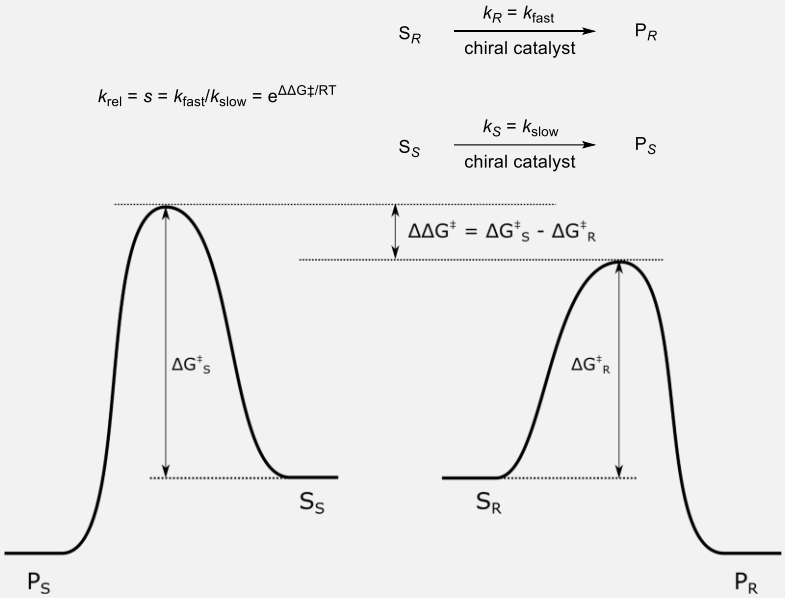


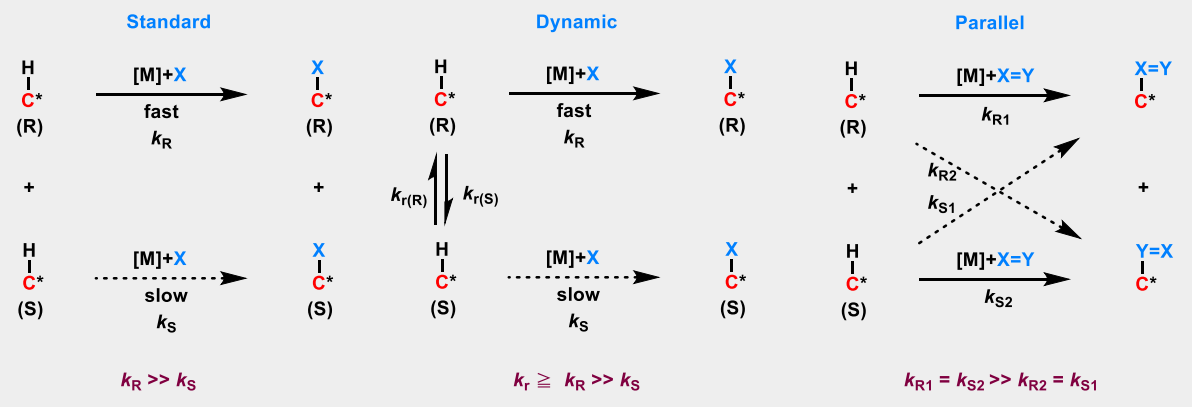
Figure 5. Relative rate constants in kinetic resolution

The former gives a product with constant *ee* in comparison between the enantioselective reactions and kinetic resolution. However, *ee* obtained in the latter changes as a function of conversion. In kinetic resolution, chiral molecules can be prepared in organic synthesis, even though kinetic resolution utilising chiral reagents and catalysts is less joint than enzymatic kinetic resolution.[105,106]

The first kinetic resolution was achieved by Pasteur in 1858, resolving the racemic ammonium tartrate reacting with a mould from *Penicillium glaucum*. From a synthetic point of view, Marckwald and McKenzie reported the resolution of mandelic acid via esterification with enantiopure (–)-menthol in 1899. They found that (+)-mandelic acid reacted quicker than the other enantiomer, forming the corresponding menthol ester.[107] After this significant finding, kinetic resolution has been divided into the following research areas such as acylative and deacylative resolutions,[108–110] oxidative resolutions,[111–116] reductive resolutions,[117–120] organometallic resolutions[121] and resolution of epoxides by nucleophilic ring opening.[122–124]

1.3.1 Kinetic resolution by transition-metal-catalysed C–H activation

Several resolutions involving a transition-metal-catalysed C–H activation have been reported. These methodologies can be classified based on the nature of the overall process (Scheme 21).[125]



Scheme 21. Classification of kinetic resolution, including transition-metal-catalysed C–H activation

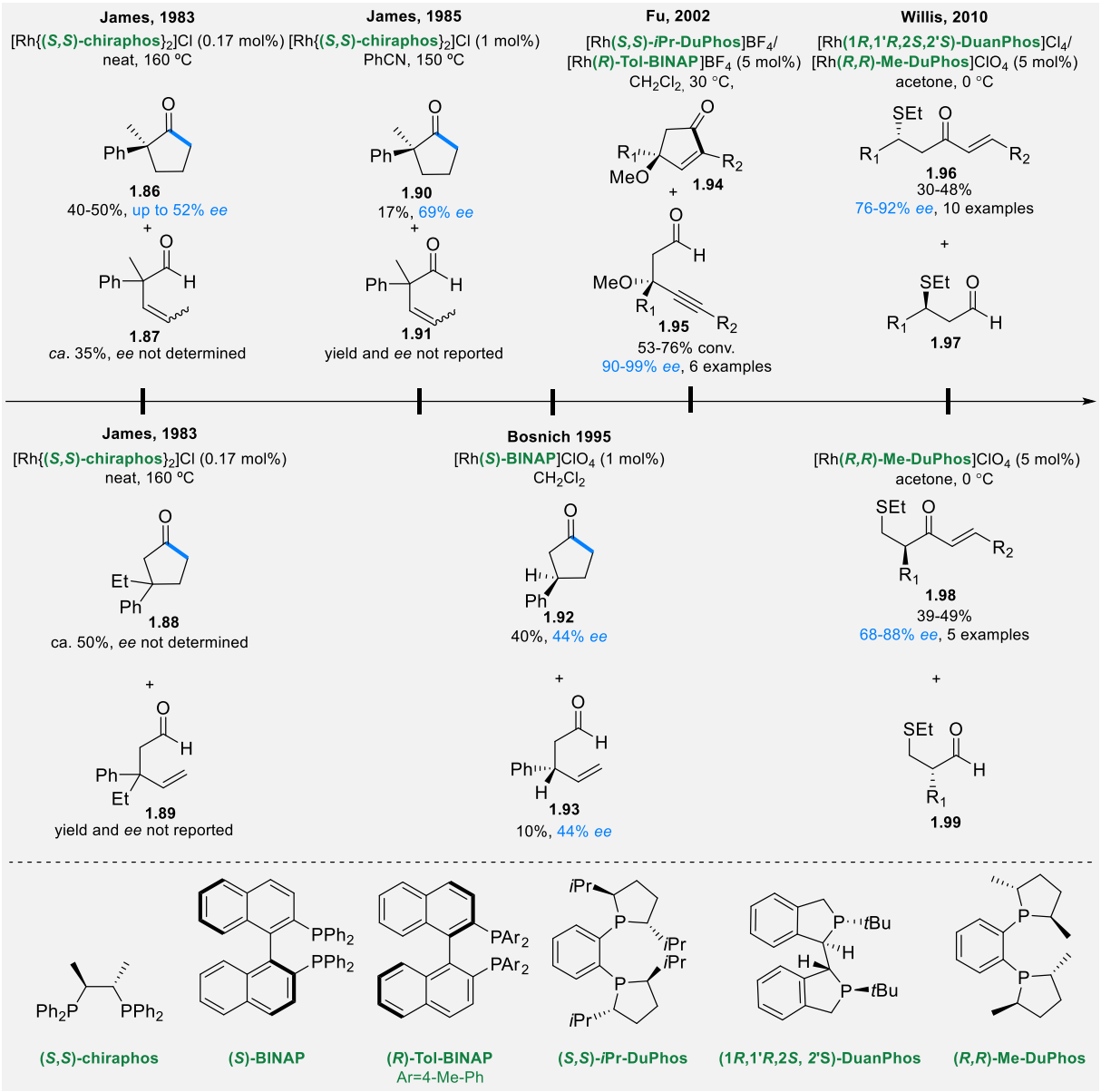
A standard kinetic resolution relies on different reaction rates of enantiomers in the same transformation. Ideally, a maximum 50% yield of unreacted enantiopure starting material and 50% yield of the enantiopure product are obtainable. Dynamic kinetic resolutions also rely on different reaction rates of enantiomers. However, reactions of this type incorporate a process whereby the two enantiomeric substrates can interconvert rapidly. If this process is sufficiently faster than the functionalisation step, a 100% yield of enantiopure material is theoretically obtainable. In contrast, parallel kinetic resolution takes advantage of differing regio, chemo, and stereoselectivity between enantiomers, producing two new products in up to 50% yield each.[125] In parallel kinetic resolution, two enantiomers react at similar rates but in different directions. In order to achieve parallel kinetic resolution, two reaction pathways with respective enantiomeric substrates should have similar reaction rates, ideally (k_{R1} = k_{S2}), and the other two competitive reactions (k_{R2} and k_{S1}) should occur at a substantially slower rate.

1.3.2 Standard kinetic resolution by transition-metal-catalysed C–H activation

In 1983, the first example of a standard kinetic resolution involving a transition-metal-catalysed C–H activation was reported by James and Young. They obtained enantioenriched cyclopentanone **1.86** in 40-50% yield and 52% *ee* along with 35% of the isomerised starting material **1.87**, employing chiral Rh catalyst, neat at 160 ºC (Scheme 22).[126]

Starting with this inspiring work, James and Young also demonstrated standard kinetic resolution by Rh-catalysed intramolecular hydroacylation in 1985.[127] A similar approach was also shown by Bosnich in 1995.[128] The latter reported moderate enantioselectivity (44% *ee*) on cyclised product **1.92** and starting material **1.93**.

Furthermore, two research groups have disclosed hydroacylation reactions incorporating an alkyne as a coupling partner. In the early 2000s, Tanaka and Fu demonstrated the intramolecular hydroacylation with terminal aldehyde and an internal alkyne to obtain enantioenriched starting material **1.95**.[129] In 2010, the Willis group disclosed an intermolecular alkyne hydroacylation, using racemic β-ethylthio substituted aldehydes **1.97**/**1.99** and terminal alkynes to obtain saturated ketones **1.96**/**1.98** in up to 49% yield and 92% *ee*.[130]

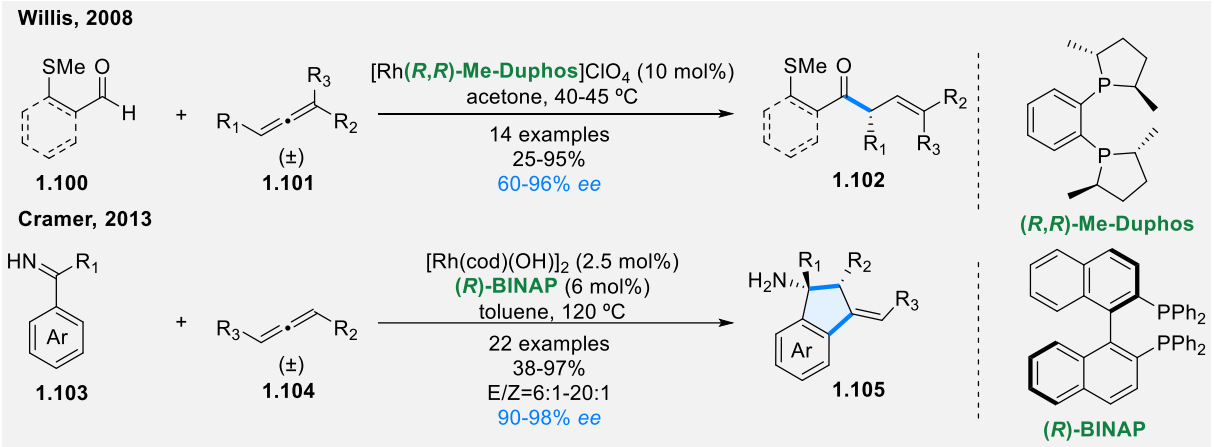


Scheme 22. Development of kinetic resolution involving transition-metal-catalysed C–H activation

1.3.3 Dynamic kinetic resolution by transition-metal-catalysed C–H activation

In 2008, Willis and co-workers discovered the first intermolecular asymmetric hydroacylation, presumably by dynamic kinetic resolution manner, employing an acyclic coupling partner (Scheme 23).[131] Aryl and alkyl aldehyde **1.100** smoothly reacted with racemic allenes **1.101** under Rh catalysis at mild temperatures. Mechanistic studies suggested the possibility that the allene isomerisation occurs under the reaction conditions, which is consistent with a dynamic kinetic resolution even though further analysis was not provided.

In 2013, Tran and Cramer reported the asymmetric transformation of racemic allenes **1.104** via [3+2]-annulation with aryl ketimines **1.103**, employing $[Rh(cod)(OH)]_2$ with **(*R*)-BINAP** to obtain highly functionalised indenylamines **1.105** with good to excellent e.r. (Scheme 23).[132]

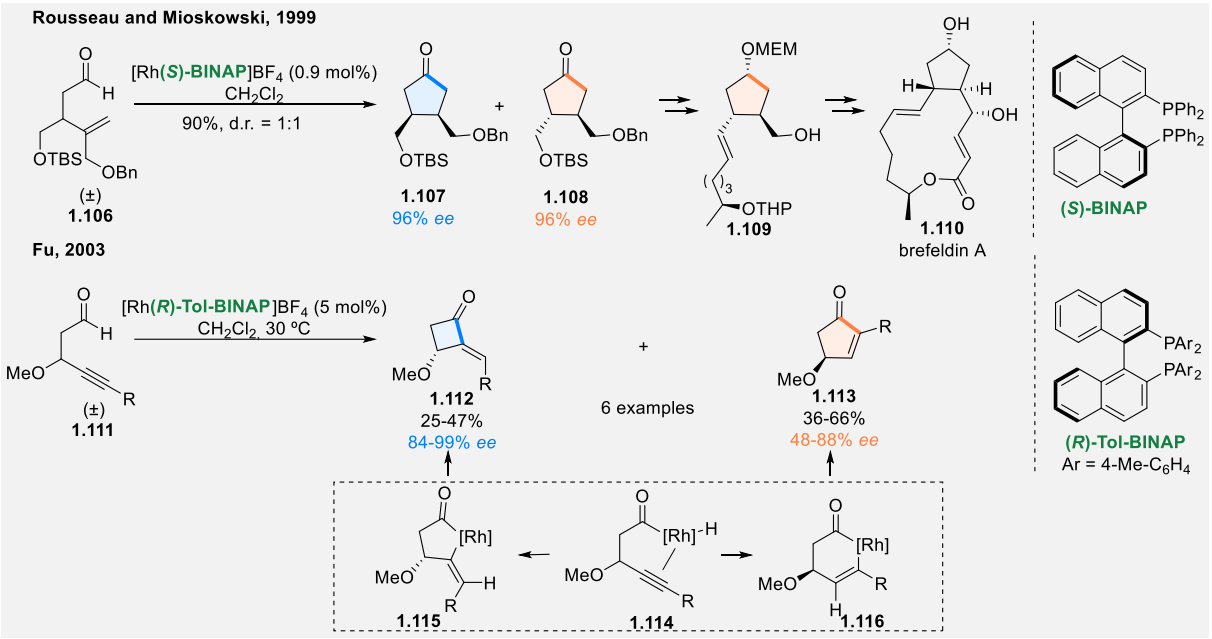


Scheme 23. Asymmetric transformation of racemic allenes via dynamic kinetic resolution

1.3.4 Parallel kinetic resolution by transition-metal-catalysed C–H activation

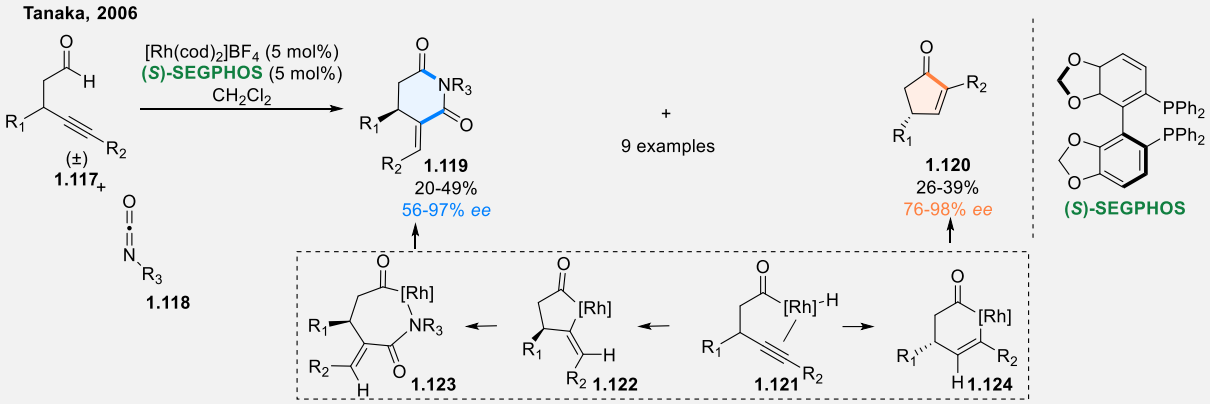
The two earliest parallel kinetic resolutions proceeded via an intramolecular hydroacylation reaction (Scheme 24). In 1999, Rousseau, Mioskowski and co-workers reported a parallel kinetic resolution for stereodivergent synthesis of bredfeldin A **1.110**.[133] The racemic starting material **1.106** was reacted with [Rh**(*S*)-BINAP**]BF_4 to give rise to cyclopentanones **1.107**, **1.108** as 1:1 d.r. and 96% *ee* for both compounds. The *cis*-compound **1.107** was transformed into a thermodynamically stable *trans*-configuration **1.108** and applied to natural product synthesis.

Second, in 2003, Fu and co-workers reported a follow-up study of their early work in 2002,[134] regiodivergent parallel kinetic resolution towards synthesising cyclobutanones **1.112** in 25-47% yield and up to 99% *ee*, cyclopentenones **1.113** in 36-66% yield and up to 88% *ee*. Mechanistic studies revealed that the insertion of Rh–hydride bond of the oxidative addition intermediate **1.114** to construct a six-membered rhodacycle **1.116** leads to cyclopentenones **1.113**. On the other hand, in the case of a five-membered rhodacycle **1.115**, cyclobutene **1.112** is formed, followed by direct reductive elimination.



Scheme 24. Regiodivergent hydroacylation via parallel kinetic resolution

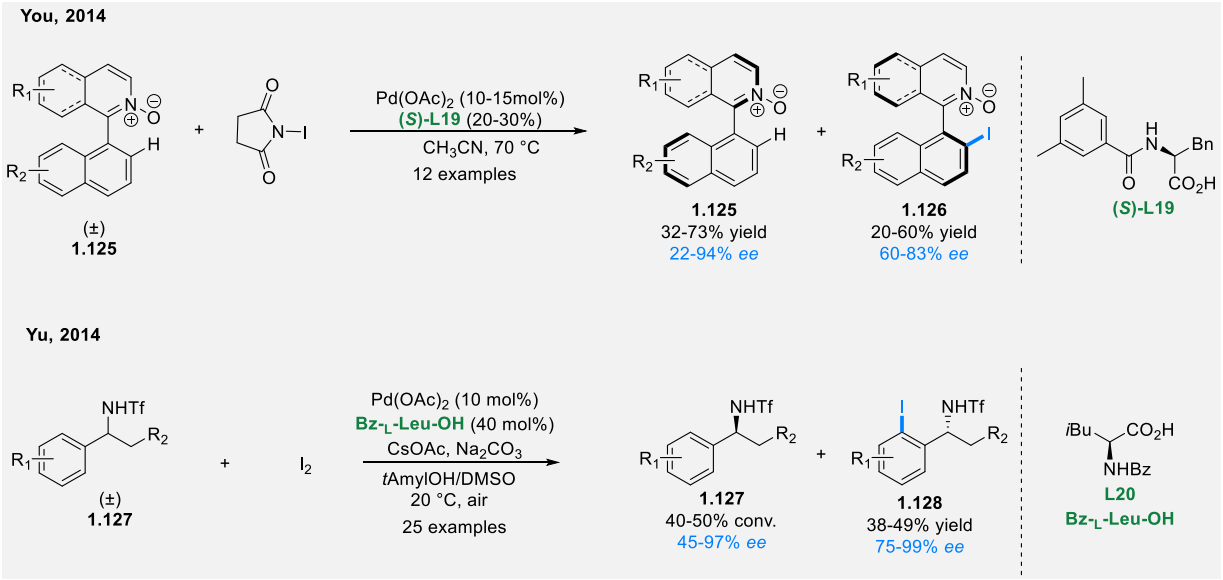
Tanaka and co-workers reported the parallel kinetic resolution of alkynals **1.117** with isocyanates **1.118** to generate enantioenriched glutarimides **1.119** and cyclopentenones **1.120** by Rh-catalysed C–H functionalisation in the presence of **(*S*)-SEGPHOS** as a chiral ligand (Scheme 25).[135] Mechanistically, the reaction proceeds via similar pathway to the one proposed by Fu (see above). After the migratory insertion of an alkyne into Rh–hydride, complexation and second migratory insertion of isocyanates **1.118** lead to enantioenriched glutarimides **1.119**. Whilst the six-membered rhodacycle intermediate **1.124** undergoes direct reductive elimination to form chiral cyclopentanones **1.120**.



Scheme 25. Parallel kinetic resolution of alkynals with isocyanates

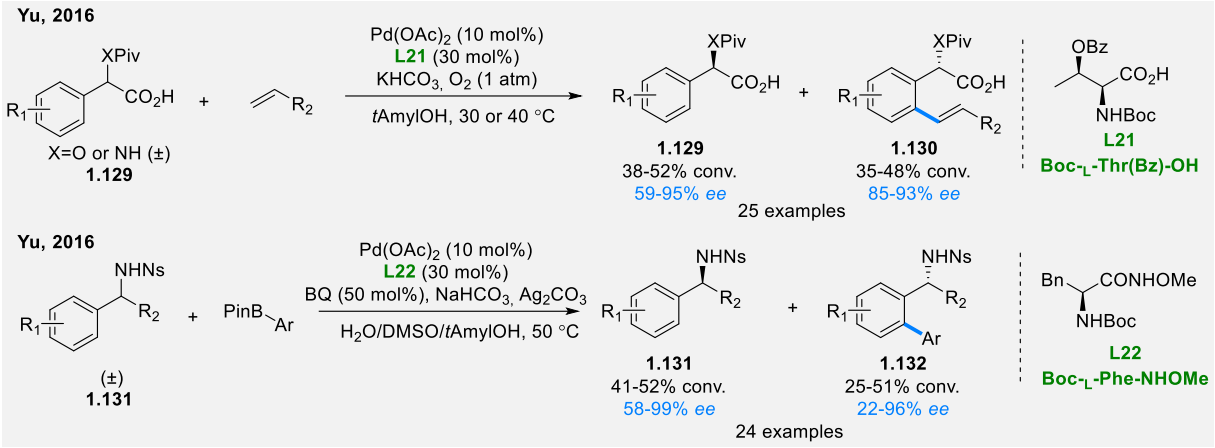
1.3.5 Kinetic resolution by Pd-catalysed C–H activation

Kinetic resolution by Pd-catalysed aryl C–H functionalisation has recently been achieved. In 2014, Gu, You and co-workers developed kinetic resolution of axially chiral aryl isoquinoline *N*-oxides **1.125** by a directed C–H iodination (Scheme 26).[136] They employed the mono-protected amino acid (MPAA) **L19** as a chiral ligand to provide selectivity with *s*-factor from 4.1-27. In the same year, Yu group reported the selective C–H iodination of benzylic amine derivatives **1.127** (*s*-factor up to 244) with relatively high loading of MPAA ligand **L20** (40 mol%).[137] They showed a variety of transformations of functionalised products, such as deprotection of triflyl groups and coupling reactions, without racemisation. From a mechanistic point of view, the computational study proposed that the reaction proceeds through the Pd(II)/Pd(IV) catalytic cycle.[138]



Scheme 26. Kinetic resolution via Pd(II)-catalysed C–H aryl iodination

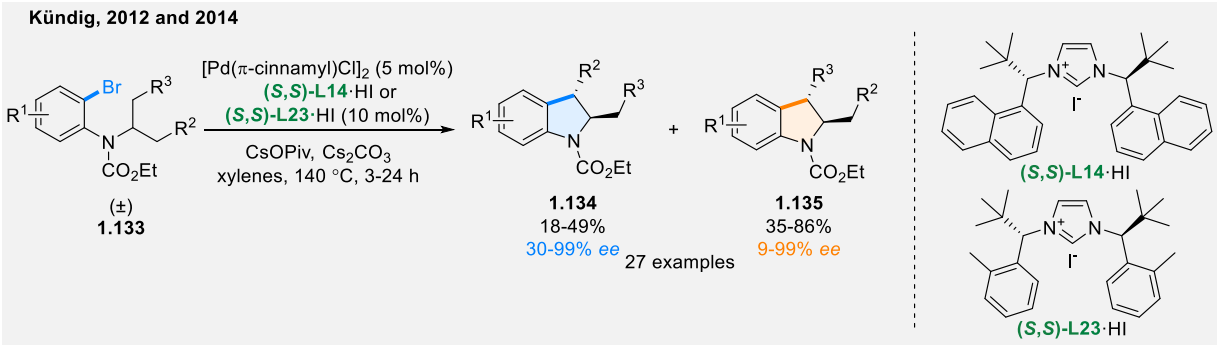
In 2016, the Yu group disclosed two reports on the directed functionalisation of aryl C–H bonds (Scheme 27). First, racemic mandelic and phenylglycine pivalate derivatives **1.129** were successfully olefinated to furnish a variety of enantioenriched α-hydroxy and α-amino phenylacetic acid derivatives.[139] The reaction used $Pd(OAc)_2$ as a palladium source in the weak basic condition in the presence of steric bulk-protected threonine **L21** as a chiral ligand with oxygen as a terminal oxidant. In that same year, they reported that kinetic resolution was feasible via cross-coupling with arylboronic acid pinacol ester of *N*-nosylbenzylamine derivatives **1.131** using a modified phenylalanine derivative **L22** as a chiral ligand.[140]



Scheme 27. Pd(II)/Pd(0)-catalysed kinetic resolution via aryl C–H functionalisation

Although Pd(II) catalysts have been employed widely for kinetic resolution by taking advantage of a variety of chiral ligands and directing groups, the use of Pd(0) species in terms of standard kinetic resolution has remained challenging and scarce.

In 2012 and 2014, Kündig and co-workers extended their enantioselective Pd(0)-catalysed C(sp^3)–H bond functionalisation to regiodivergent synthesis of indolines (Scheme 28).[100,141] In this optimised condition, racemic aryl bromide **1.133** provided approximately 1:1 mixtures of indoline regioisomers **1.134**/**1.135** in almost quantitative yield. **1.134**/**1.135** had excellent enantioselectivities upon differentiation of the two alkyl groups by the catalyst formed from NHCs **L14**/**L23**. This remarkably efficient parallel kinetic resolution displayed high enantioselectivities across the broad range of substrates, where both primary and secondary C–H bonds were reactive. The observed selectivities were rationalised with the help of DFT calculations. The DFT calculations showed that (*R*)-**1.133a** preferably undergoes CH_2 activation to afford **1.134a**, whereas (*S*)-**1.133a** undergoes CH_3 activation to provide **1.135a** in the presence of (*S*,*S*)-NHC **L23** (Figure 6).



Scheme 28. Regiodivergent synthesis of indolines from racemic carbamates

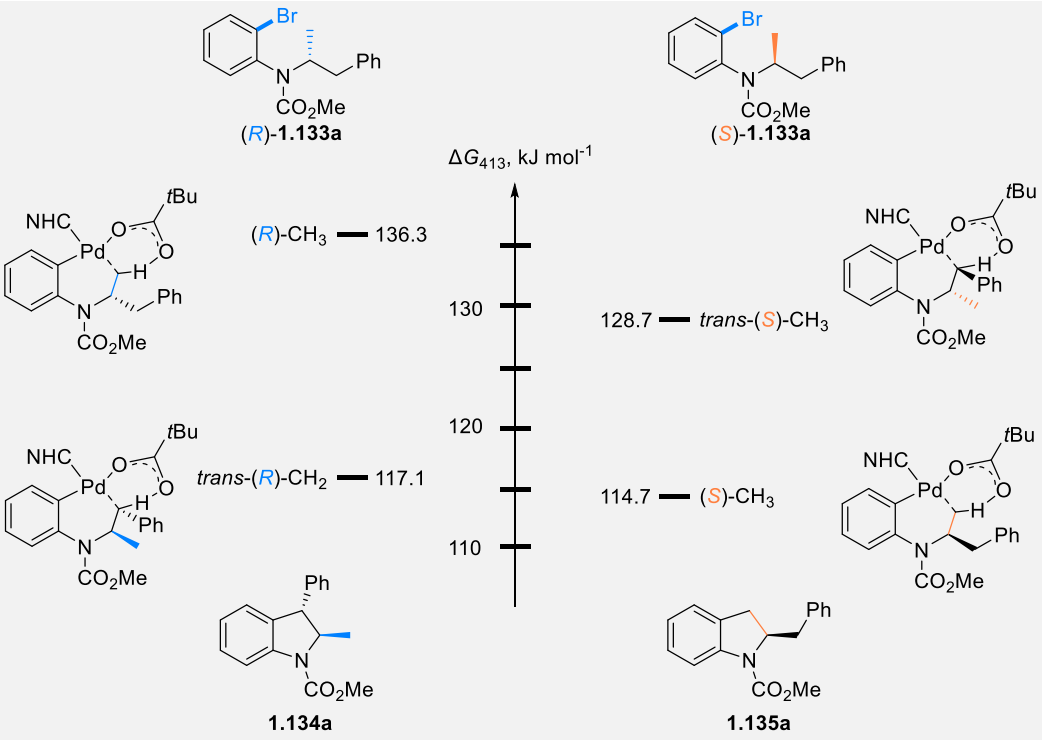
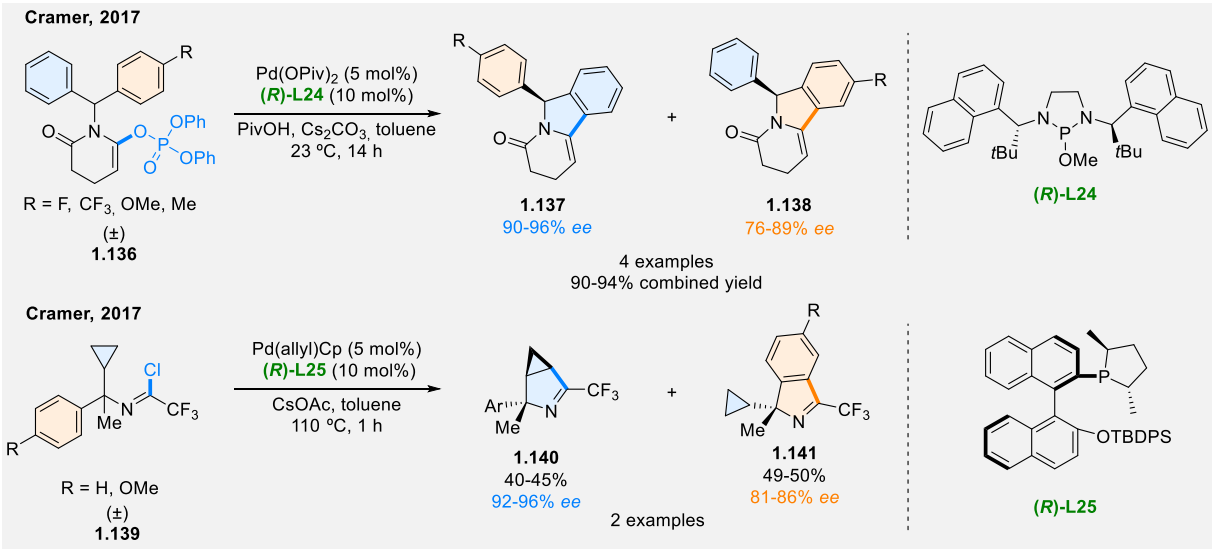


Figure 6. Activation barriers (ΔG_{413}, gas phase) for the CMD step with (*S*,*S*)-NHC L23 and substrate 1.133a

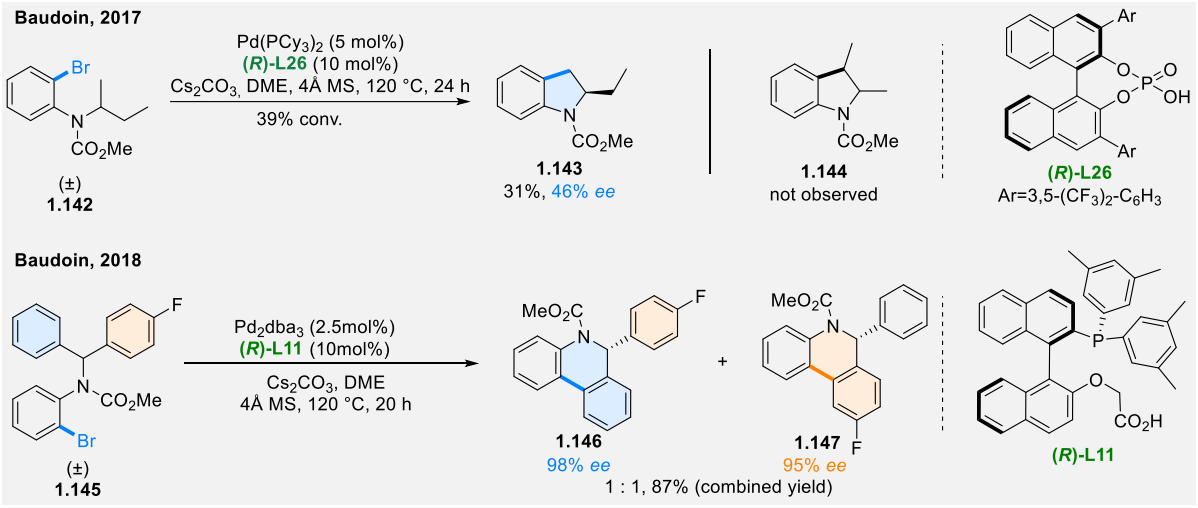
In 2017, Cramer and co-workers disclosed a parallel kinetic resolution via C–H alkenylation at ambient temperature (Scheme 29).[142] Regardless of the electronic bias (R = F, CF_3, OMe, Me) of the targeted aryl groups, the functionalisation proceeded in a regiodivergent manner to afford the products **1.137**/**1.138** with high enantioselectivities. They also distinguished the C–H bond between a cyclopropane C(sp^3)–H and aryl C(sp^2)–H in the study of the synthesis of densely substituted 3-azabicyclo[3.1.0]hexanes.[143] Phenyl substituted starting material **1.139** was efficiently resolved, affording constitutional isomers **1.140**/**1.141**.



Scheme 29. Parallel kinetic resolution with C(sp^2)–H vs C(sp^2)–H, C(sp^3)–H

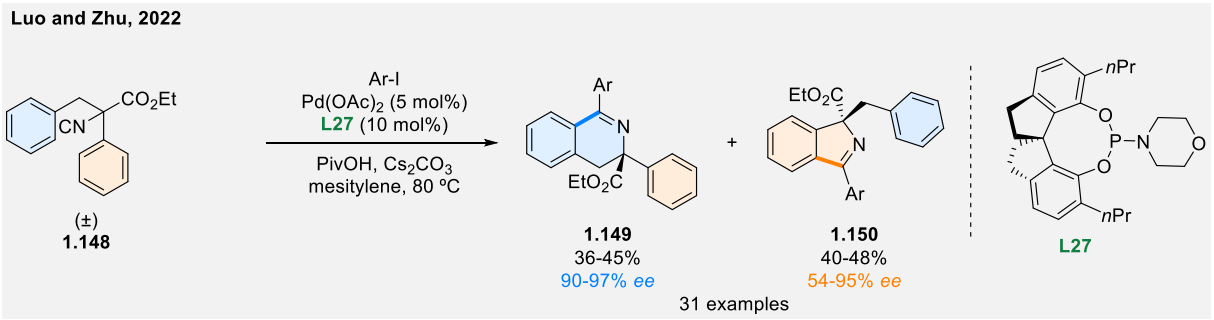
In 2017, Baudoin and co-workers optimised their conditions in the same parallel kinetic resolution process, employing binol-derived phosphoric acid **L26** as a chiral base (Scheme 30).[144] The product **1.143** was isolated in 31% yield and 46% *ee*, with no starting material **1.142** and constitutional isomer **1.144** observed, different to the parallel kinetic resolution reported by Kündig.[100,141]

The following year, the Baudoin group examined the parallel kinetic resolution of the racemic substrates **1.145**, using the optimal bifunctional phosphine-carboxylated ligand **L11** to provide approximately 1:1 mixtures of the highly enantioenriched isomers **1.146**/**1.147** in excellent yields.[88]



Scheme 30. Chiral base mediated Pd(0)-catalysed C–H activation towards parallel kinetic resolution

More recently, Luo and Zhu and their co-workers developed regiodivergent and stereospecific synthesis of dihydroisoquinolines **1.149** and 1*H*-isoindoles **1.150** by C(sp^2)–H imidoylative cyclisation in the presence of SPINOL-derived phosphoramidites **L27** (Scheme 31).[145] They provided broad substrate scope, including reductions of imine as further transformation. DFT calculations revealed similar energy barriers to the rate- and enantio-determining C–H activation for both enantiomers of the racemate, which led to the success of this parallel kinetic resolution. Furthermore, Non-covalent interactions (NCI) analysis of the transition states indicated that there is an apparent dispersion effect between the phenyl groups of the chiral ligand and substrates, which suggested that the chiral ligand can differentiate the phenyl rings and benzyl groups with each configuration of transition states of the C–H activation step.

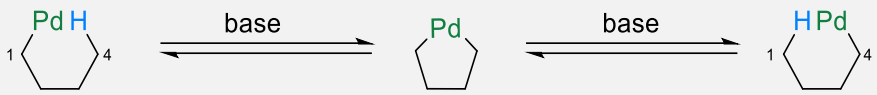


Scheme 31. Divergent enantioselective cycloimidoylation by Luo and Zhu

1.4 1,4-Pd shift

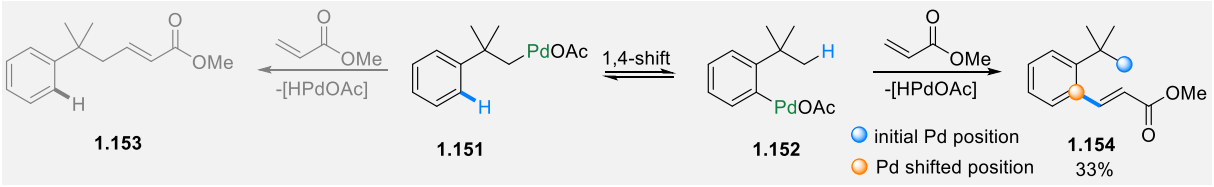
As previously mentioned, the traditional ways by inner-sphere mechanism to generate carbon–carbon or carbon–heteroatom bonds require carbon-metal species. Among other metals, palladium-catalysed C–H activation has advantages in terms of the number of subsequent transformations due to the utility of the resultant C–Pd bond.[72]

Palladium migration is a mechanistically exciting and synthetically valuable process, allowing access to challenging bonds/structures that cannot be readily prepared through classic methods. For example, the 1,4-shift is the most commonly seen among all palladium migrations because of the easily accessible but strained five-membered palladacycle. In this process, palladium shifts from one carbon to another carbon which is separated by two additional atoms (Scheme 32).[72]



Scheme 32. General outline of a 1,4-Pd shift

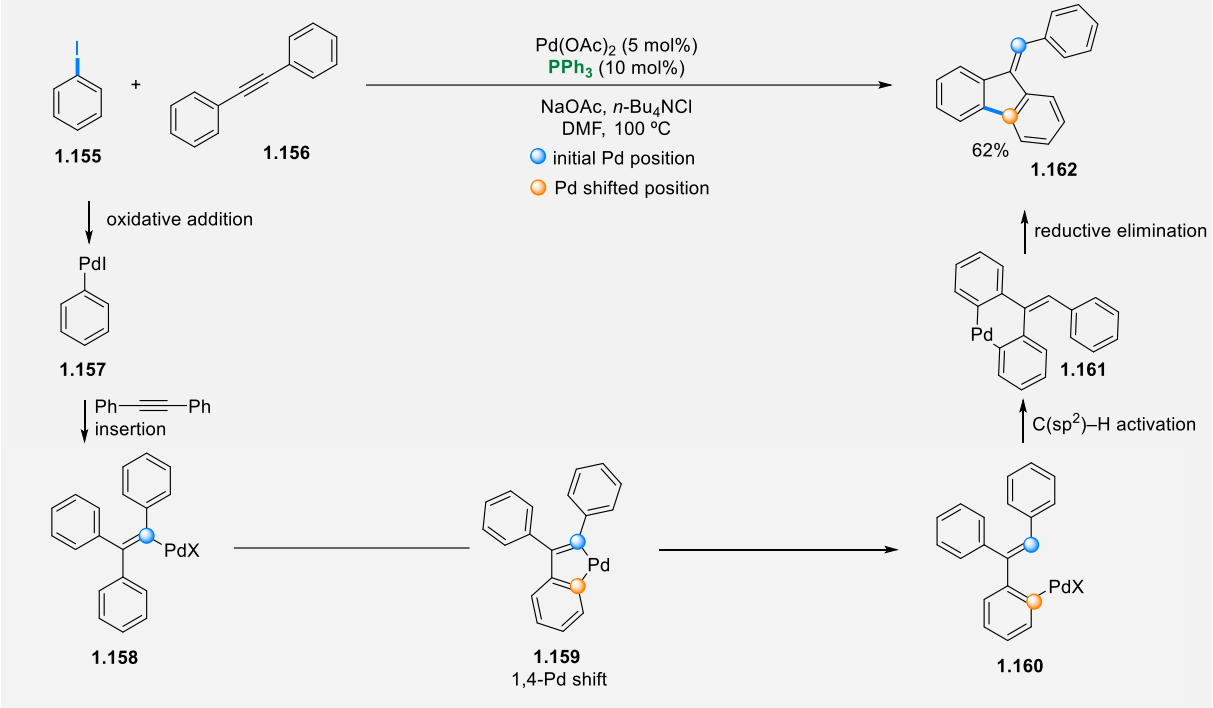
1,4-Pd Shift was pioneered by Heck in 1972 (Scheme 33).[146] Palladium acetate reacted with the corresponding mercury acetate to afford σ-alkyl palladium species **1.151**, which reacted with methyl acrylate to isolate the unexpected regioisomer, C(sp^2)–H coupled product **1.154** in 33% yield. This fact proved that cross-dehydrogenative coupling (CDC), the most promising process for generating carbon–carbon bonds, is possible due to the initial oxidative addition of carbon–halide bonds into Pd(0) species.



Scheme 33. Initial observation of 1,4-Pd shift by Heck

1.4.1 C(sp^2) to C(sp^2) shift

In 2000, a novel annulation reaction via 1,4-Pd shift to C(sp^2) from C(sp^2) was reported by the Larock group to afford 9-benzylidene-9*H*-fluorene **1.162** in 62% yield, employing iodobenzene **1.155** and diphenylacetylene **1.156** in the presence of $Pd(OAc)_2$ (Scheme 34).[147] The reaction initiated from the oxidative addition of the C–I bond into Pd(0), followed by migratory insertion of the alkyne **1.156** towards the intermediate **1.158**. Then, a 1,4-Pd shift occurs to C(sp^2) on the arene via a five-membered palladacycle **1.159** to form a second intermediate **1.160.** Single bond rotation, followed by a second C(sp^2)–H activation, gives palladacycle **1.161**. The reductive elimination of **1.161** furnishes the desired compound **1.162**. Extension of this vinylic to aryl palladium was subsequently reported, furnishing carbazoles, indoles and dibenzofurans starting from the appropriate substrates.[31,33]



Scheme 34. Novel annulation via 1,4-Pd shift by Larock

Aryl to aryl palladium migrations have also been studied. The first examples were reported by the Larock group[30] and the Gallagher group[148] in 2002, shifting between the *o* to *o*' position to afford biphenyl system. Both reports employed acrylate as a trapping reagent of aryl palladium species after the migration, competing direct Heck reaction. Indeed, another trapping reagent was also employed by the Larock group,[149] such as boronic acid (Suzuki-Miyaura coupling), even though the product distribution was not satisfying. These pioneering works contributed significantly to the further development of the 1,4-Pd migration reaction (Figure 7). In 2003, Larock and co-workers reported aryl to aryl Pd shift to afford the desired 4-phenyldibenzofuran **1.163** in 89% yield from the corresponding electron-rich iodinated starting material.[32] Feng and co-workers discovered the first example of the aryl to vinyl 1,4-Pd shift in 2016.[150] In this study, alkenyl palladium species were trapped by diboron reagents to

synthesise β,β-disubstituted vinylboronates **1.164**. Tuning the phosphine ligand was the key to controlling the vinyl vs aryl regioselectivity, which could achieve a ratio larger than 20:1. They also realised a stereoselective synthesis of 1,3-diene **1.165** via aryl to vinyl Pd shift by closing the catalytic cycle as Heck reaction with acrylates.[151] This strategy was successfully applied to alkyne insertion to obtain naphthalene derivatives **1.166**.[152] In 2019, the group of Baudoin disclosed 1,4-Pd shift from aryl to α-position of α,β-unsaturated carbonyls. Subsequent C(sp^3)–H activation to trap the Pd species granted access to deliver γ-lactams and indanones **1.167**.[153]

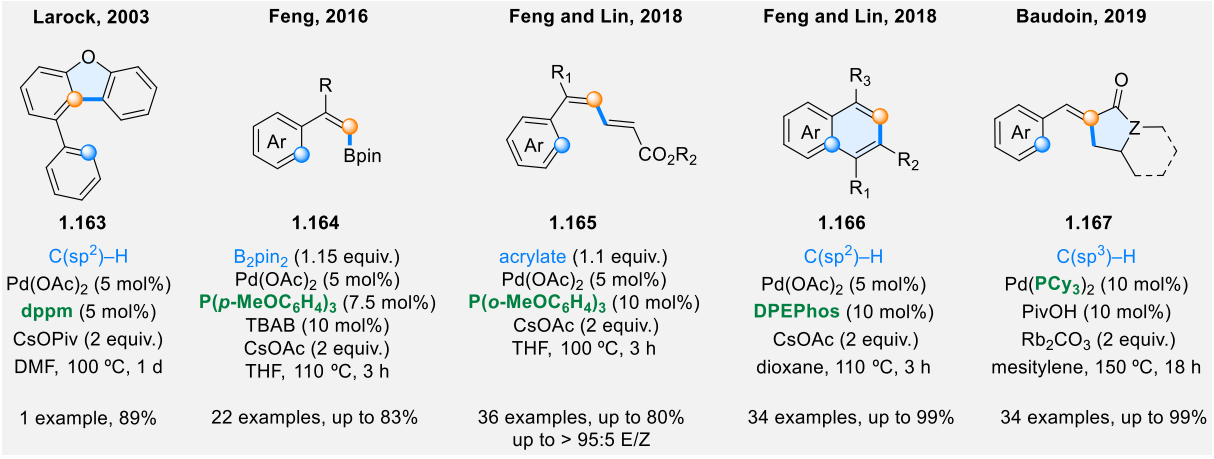
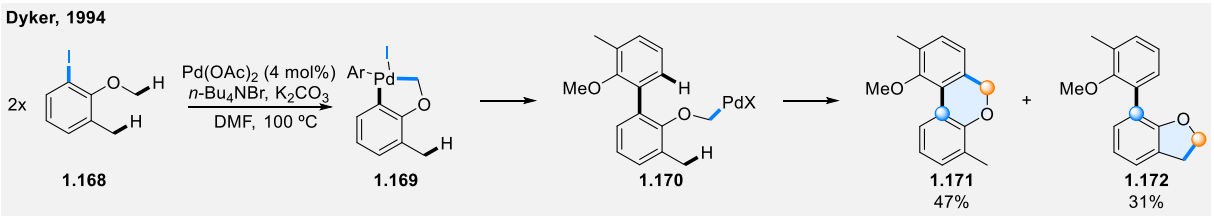


Figure 7. Representative 1,4-Pd shift from C(sp^2) to C(sp^2) and subsequent functionalisation

1.4.2 C(sp^2) to C(sp^3) shift

In comparison to the palladium shift from C(sp^2) to C(sp^2), migrating to C(sp^3)–H is arguably more challenging due to the propensity of σ-alkyl palladium species to undergo protodemetallation or β-H elimination, especially at high temperature.[154] Seminal works from Dyker in the 1990s showed that alkyl palladium intermediates **1.170** generated from palladium shift to C(sp^3)–H at the methoxy group are able to undergo subsequent C(sp^2)–H or C(sp^3)–H activation (Scheme 35). Significantly, iodoarene **1.168** transformed into dimeric products in the presence of $Pd(OAc)_2$ and stoichiometric carbonate in DMF. From a mechanistic point of view, a five-membered palladacycle **1.169** is formed by activating C(sp^3)–H at the *o*-methoxy group after the second oxidative addition of C–I bond. Reductive elimination forges the biaryl bond and generates alkyl palladium species **1.170**, which can undergo either C(sp^2)–H activation upon another phenyl ring towards dibenzopyran **1.171** or C(sp^3)–H activation upon the *o*-methyl group towards dihydrobenzofurane **1.172**, followed by reductive elimination. The dimeric compound was expected to be avoided by the proper tuning of an appropriate ancillary ligand in order to facilitate direct reductive elimination to obtain dihydrobenzofuranes **1.72**.



Scheme 35. C(sp^2) to C(sp^3) shift reported by Dyker

In 2003, the Baudoin group disclosed an olefination leading to products such as **1.173** via β-H elimination (Figure 8).[51] In this study, two different products were observed depending on the benzylic alkyl substitutions on substrates, olefination products **1.173** and benzocyclobutenes **1.174**, with tri-*o*-tolyphosphine (**TOTP**) as the best ligand, arising from C(sp^3)–H activation and either β-H elimination or reductive elimination. Four years later, the Baudoin group reported that more electron-deficient tri-(5-fluoro-2-methyl phenyl)phosphine (**F-TOTP**) could yield the olefin selectively at relatively low temperatures.[58] A computational study revealed that the olefination occurs via 1,4-Pd shift upon methylene position to give the alkyl palladium intermediate, which gives rise to the olefin by β-H elimination.[53] Another observation upon 1,4-Pd shift was reported in the synthesis of benzocyclobutane **1.174** by Clot and Baudoin and their co-workers in 2008.[54] In the presence of substitution (R_3) at the *para*-position relative to the halide on the arene partner, two inseparable products were obtained, including the Pd-shifted product. Increasing the steric bulk with substitution replacement (R_3) such as CF_3, Tf, and Ns promoted the formation of the standard C(sp^3)–H activation product. In 2019, the Baudoin group developed the intramolecular coupling of two C(sp^3)–H bonds via 1,4-Pd shift to furnish dihydrobenzofuranes **1.175**, indolines **1.175**, chromanones **1.176**, and benzofuranols **1.175** resulting from the attack to the ketone by the formed organo-palladium intermediates.[154] The use of *N*-protecting

groups, such as the trifluoroacetyl group on the *N*-methyl position, was necessary to suppress the demethylation under Pd(0) catalysis, which occurs after 1,4-Pd shift and iminium formation.[155] The kinetic isotope effect indicates that the first C(sp^3)–H bond cleavage is the turnover-limiting step.[156] This cross-dehydrogenative coupling (the so-called "cut and sew" strategy) is also applied to the cyclopropanation reaction.[157] After extensive screening reaction conditions, it was found that potassium carbonate as the CMD-promoting base in the intramolecular C–H arylation provided benzocyclobutane exclusively; however, replacing carbonate with pivalate led to an entirely different selectivity for cyclopropane **1.177**, rising from C(sp^3)–H activation of *gem*-methyl C–H bonds. Mechanistically, it transpired that reductive elimination from five-membered palladacycle is preferred with carbonate, but pivalate is not. This methodology was successfully utilised to synthesise Lemborexant, a dual antagonist of the orexin OX_1 and OX_2 receptors.

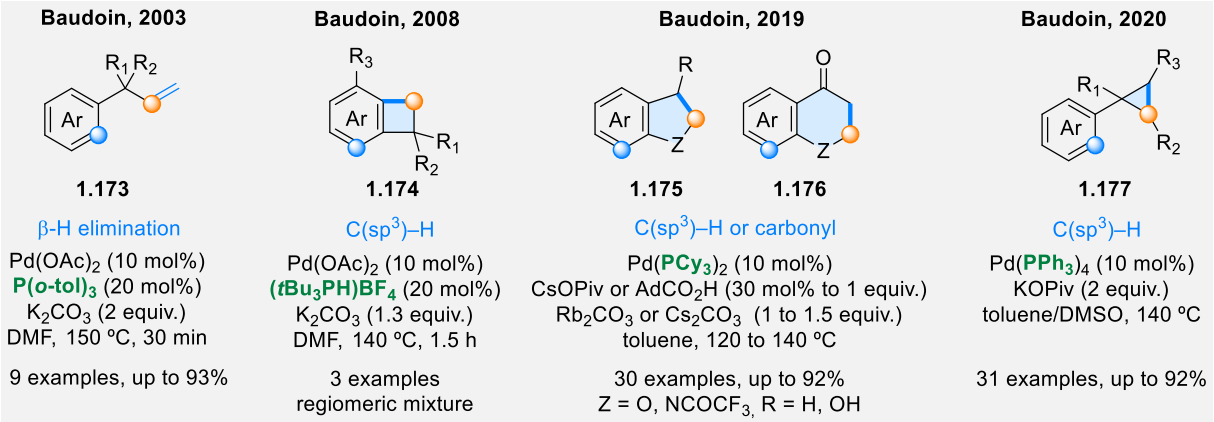


Figure 8. Representative 1,4-Pd shift from C(sp^2) to C(sp^3)

The 1,4-Pd shift process to C(sp^3) was also shown to be applicable towards intermolecular reactions, meaning that the alkyl palladium species reacts with a variety of nucleophiles (Figure 9). In 2005, Buchwald and co-workers disclosed tandem C–H functionalisation/Suzuki-Miyaura coupling, employing 2,4,6-tri-*tert*-butylbromobenzene with phenylboronic acid with **SPhos** as a ligand to afford the compound **1.178**.[158] The steric bulk of the substrates and boronic acid was vital for excellent reactivity and selectivity. Based on these results, in 2011, the Buchwald group postulated that a related transformation involving an intermolecular tandem C(sp^3)–H activation/C–N coupling might be feasible. Indeed, reaction optimisation allowed them to conduct C–H amination product **1.179** after the 1,4-Pd shift with **SIPr** as the optimal ligand.[159] Interestingly steric bulk at the *para* position to bromide seemed critical for minimising by-products such as olefination and benzocyclobutane. In 2020, the Baudoin group reported amino- or alkoxycarbonylation **1.180** at the terminal position in the presence of carbon monoxide and the corresponding amine or alcohol.[160] A careful mechanistic study indicated that the first C(sp^3)–H activation is the rate-limiting step. Also, the CO insertion and nucleophilic addition of amine or alcohol proceeded faster than the indanones formation from CO insertion and subsequent reductive elimination reported by the Wang group.[161]

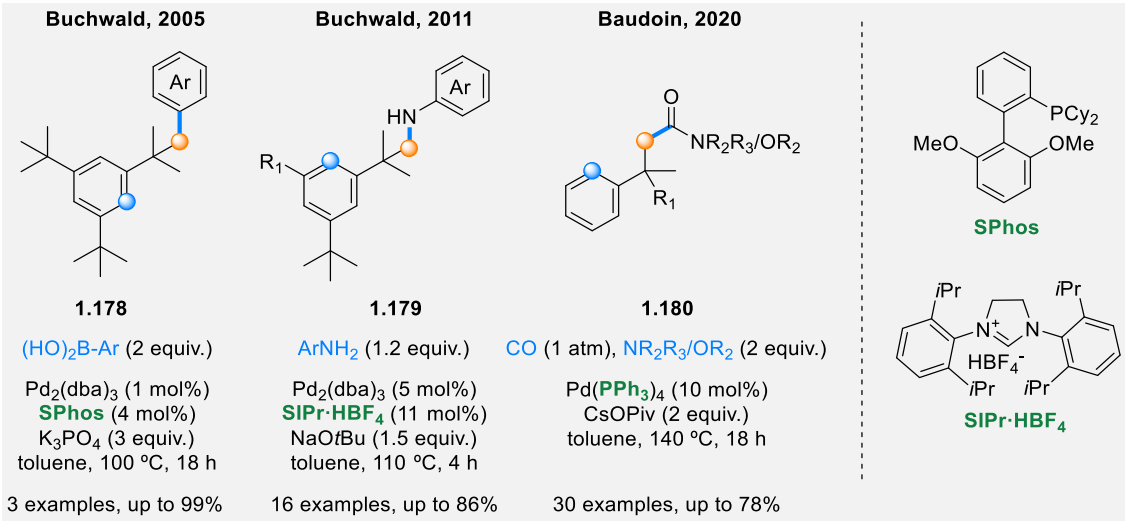
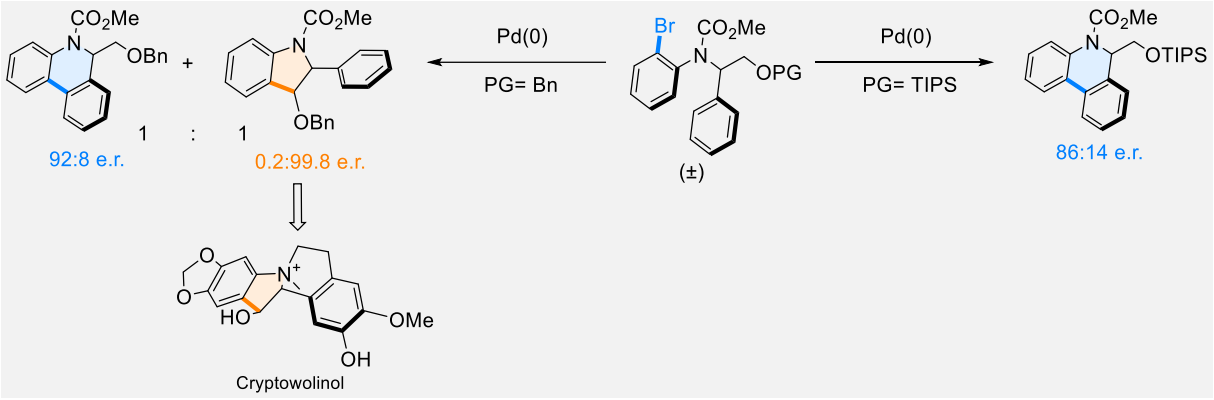


Figure 9. Representative intermolecular couplings via 1,4-Pd shift from C(sp^2) to C(sp^3)

1.5 Research aim and work described in this thesis

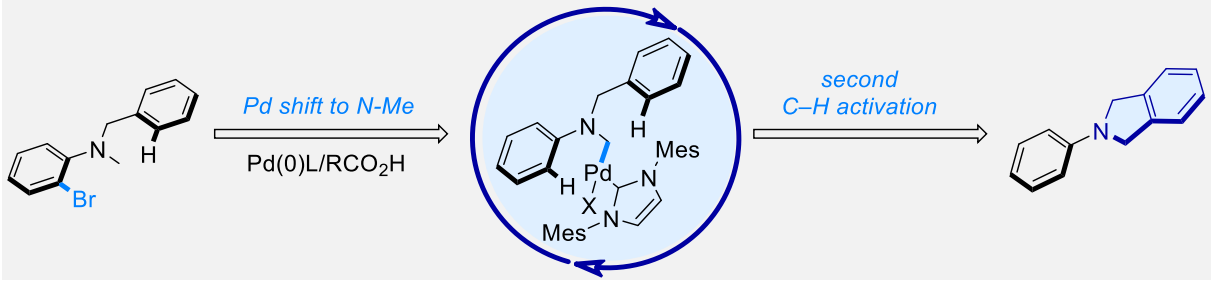
In the last two decades, Pd(0)-catalysed C–H activation has provided efficient and step/atom-economical methods to synthesise carbo- and heterocycles via direct C–C bond formation. In 2012 and 2014, Kündig and co-workers reported parallel kinetic resolution via Pd(0)-catalysed C(sp^3)–H arylation leading to two differently functionalised indolines in excellent enantioselectivity.[141] Subsequently, Cramer,[142,143] Baudoin,[88,144] and Luo and Zhu[145] independently disclosed parallel kinetic resolution procedures based on Pd(0)-catalysed C–H activation. However, standard kinetic resolution with Pd(0)-catalysed C–H activation has remained challenging.

Encouraged by those contexts, we first explored the possibility of a standard kinetic resolution with Pd(0)-catalysed C(sp^2)–H arylation to develop a robust methodology, which we would then apply to the synthesis of the complex polycyclic natural products. This study found interesting regiodivergent and stereospecific transformations by tuning the substrates and ligands (Scheme 36). Then, we commenced the substrate synthesis to translate this into a complex natural alkaloid, cryptowolinol.



Scheme 36. Kinetic resolution via Pd(0)-catalysed C–H activation

Finally, a highly efficient and novel synthesis of isoindolines by 1,4-Pd shift-mediated double C–H activation is described (Scheme 37). This method allows access to valuable isoindolines found in numerous biologically relevant molecules.

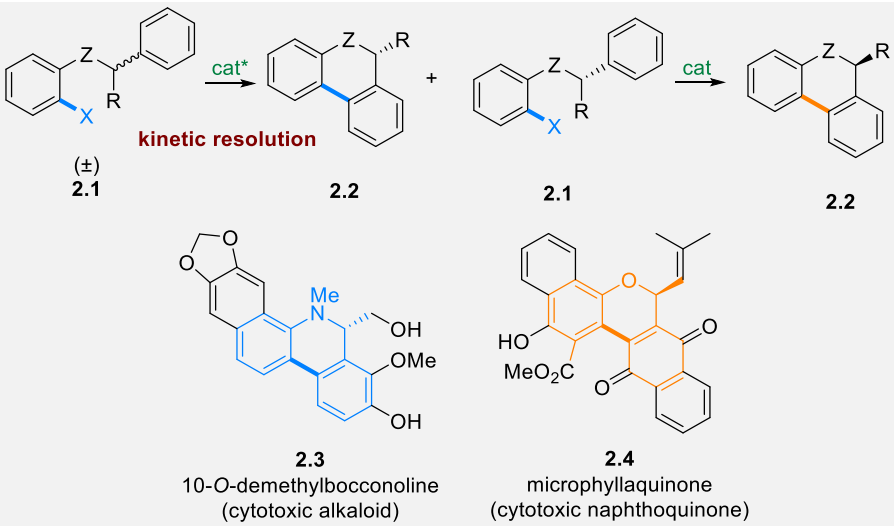


Scheme 37. Isoindolines synthesis via 1,4-Pd shift mediated double C–H activation

2. Kinetic resolution with Pd(0)-catalysed C–H activation

2.1 Introduction

The classic kinetic resolution with Pd(II)-catalysed C–H activation has been studied well,[125] taking advantage of directing groups and chiral ligands at relatively low reaction temperatures. In contrast, standard kinetic resolution with Pd(0)-catalysed C–H activation remains a uniquely challenging process, despite holding great synthetic potential.[162] Our plan was to investigate kinetic resolution based on the more facile C(sp^2)–H activation reactions, which are designed for application in natural product synthesis (Scheme 38). The kinetic resolution of prototypical substrates **2.1** via C(sp^2)–H arylation in the presence of a chiral catalyst would furnish an enantiomerically enriched product **2.2** together with the unreacted enantiomer **2.1**. In principle, after separation, the latter can react again in the presence of an achiral catalyst to give **2.2**. Hence this method would lead to both enantiomers of product **2.2** in a simple manner. Various substrates with Z= *N*-CO_2Me or *O* were investigated, as shown in Scheme 38. The corresponding products **2.2** contain the core structure of several natural products, such as 10-*O*-demethylbocconoline **2.3**, a cytotoxic dihydrobenzo[*c*]phenanthridine alkaloid and microphyllaquinone **2.4**, a cytotoxic naphthoquinone. In this context, three types of chiral catalysts developed in the Baudoin group, chiral ancillary ligand,[67,96,97] anion[144] and bifunctional ligand,[88,90] were attempted in the kinetic resolution, as well as different functional groups on substrates.

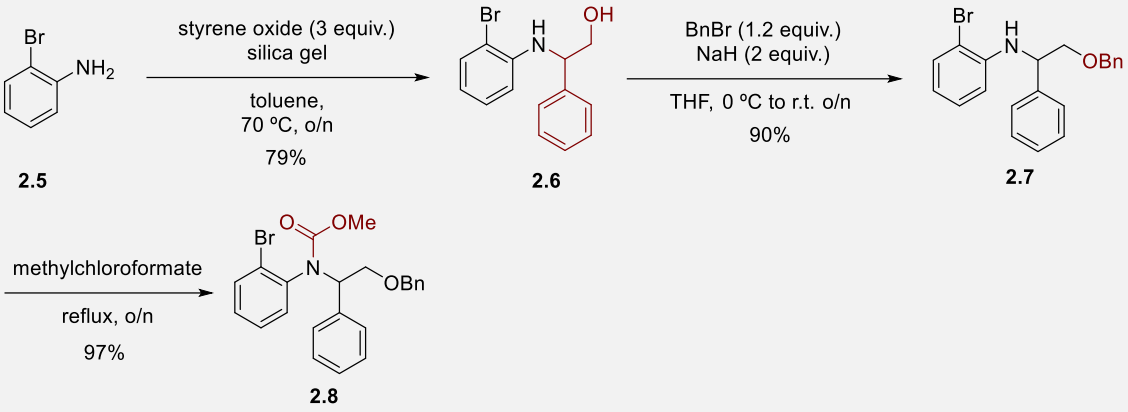


Scheme 38. Kinetic resolution via Pd(0)-catalysed C–H activation and natural products targets (The absolute configuration of 2.1/2.2 was chosen arbitrarily.)

2.2 Result and discussion

2.2.1 Substrate synthesis for model experiments

In order to optimise structural factors suitable for standard kinetic resolution, we synthesised several model substrates (Scheme 39) (for other model substrates, see experimental parts.). As a result, **2.8** was synthesised in 69% over three steps. First, the epoxide opening strategy was taken to obtain amino alcohol moiety **2.6**. In general, aniline possessing an electron-withdrawing group at *ortho*-position makes the regioselectivity ambiguous; therefore, we decided to optimise the epoxide opening. Various Lewis and Brønsted acids were attempted; however, acceptable regioselectivity was not observed. Interestingly, the product was found to be regioselectively generated on TLC that only spotted aniline **2.5** and styrene oxide, which inspired us to take this reaction with silica gel as a catalyst. Finally managed to produce the desired amino alcohol compound **2.6** in 79% isolated yield. Subsequent alcohol protection and carbamation were no issues to yield those compounds **2.7**, **2.8** in 90% and 97%, respectively.

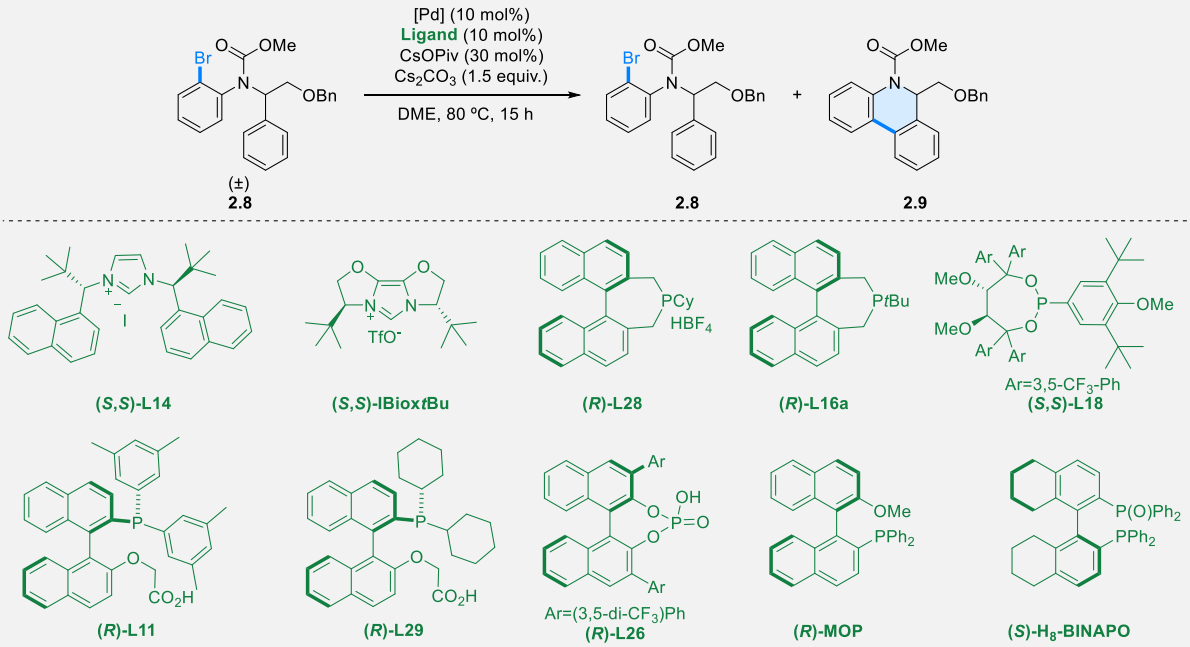


Scheme 39. Substrate synthesis with amino alcohol moiety

2.2.2 Screening of chiral ligands

We first tried to decrease the reaction temperature using model substrate **2.8**. In a preliminary study, we found that the C(sp^2)–H activation proceeded at 80 ºC with Pd_2dba_3 and **PCy_3·HBF_4** in DME as a solvent. Then different families of chiral ligands were engaged in C(sp^2)–H activation (Table 1). NHCs (**L14**, **IBiox*t*Bu**)[102,141] were attempted. However, no reaction proceeding was observed at 80 ºC on GC-MS analysis (entries 1-2). Two Binepines (**L16a**, **L28**) displayed reactivity, leading to the formation of the desired product **2.9**. The recovered starting material and obtained product were racemic mixtures by HPLC analysis (entries 3, 4). TADDOL-based phosphonite ligand **L18** did not display any reactivity (entry 5). One of the bifunctional ligands (**L11**)[88] and chiral binol phosphoric acid (**L26**)[144] gave intermediate conversion (entries 6-8), which resulted in the finding that **L11** produced moderate enantioinduction on the product (67:33 e.r., entry 6) with the racemic starting material. **MOP** ligand[89] led complete conversion at 80 ºC (entry 9). In contrast, **H_8-BINAPO** gave no product (entry 10). **MOP** ligand could successfully decrease the reaction temperature to 60 ºC to stop the reaction at around 30% conversion after two hours, and slight enantioenrichment was observed on both the unreacted starting material and the product (entry 11). Despite trying further reaction optimisation, such as stopping the reaction with less than 50% conversion on different conditions, an outstanding result was not achieved.

Table 1. Screening of various families of chiral ligands[a]



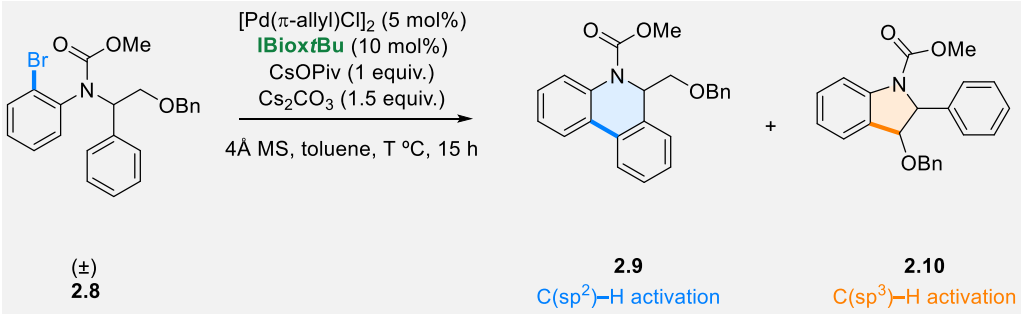
Entry	Ligand	GC-MS ratio 2.8/2.9	e.r. 2.8/2.9
1[b]	**L14**	N.R.	–
2[c]	**IBioxtBu**	N.R.	–
3[c]	**L28**	90:10	rac/rac
4[c]	**L16a**	38:62	rac/rac
5[c]	**L18**	N.R.	–
6[c]	**L11**	74:26	rac/67:33
7[c]	**L29**	90:10	–
8[c,d]	**L26**	62:38	rac/rac
9[c]	**MOP**	0:100	–
10[c,e]	**H_8-BINAPO**	N.R.	–
11[c,f,g]	**MOP**	73/27	55:45/65:35

[a]**2.8** (0.1 mmol) was engaged. [b][Pd(π-cinn)Cl]$_2$ as Pd source. [c]Pd_2dba_3 as Pd source. [d]$PCy_3 \cdot HBF_4$ as ligand. [e]CH_3CN as a solvent instead of DME. [f]Reaction at 60 ºC. [g]Reaction time is 2 h.

2.2.3 Observation of parallel kinetic resolution of C(sp^2)–H vs C(sp^3)–H

Since focusing on phosphine ligands could not get any promising starting point, we decided to consider another class of ligands, NHCs. In our previous ligand screening, two of the NHCs **L14**, **IBiox*t*Bu** displayed no reactivity. Thus, the temperature was increased to have conversion (Table 2). Interestingly, **IBiox*t*Bu** at 140 ºC produced two differently functionalised products, **2.9**, **2.10** resulting from C(sp^2)–H and C(sp^3)–H activation, the latter of which turned out to have excellent enantioselectivity (99.5:0.5 e.r., entry 1). The product ratio has not changed with increased temperature. This behaviour is similar to Kündig`s parallel kinetic resolution.[141] However, surprisingly, this is a parallel kinetic resolution by Pd(0)-catalysed C–H activation between facile C(sp^2)–H bond and challenging C(sp^3)–H bond. Other IBiox-type ligands, such as **IBioxPh** and **IBioxCy**, did not perform as well as **IBiox*t*Bu**. The serendipitous parallel kinetic resolution was successfully optimised later and envisioned to translate into a natural product synthesis (see chapter 4).

Table 2. Observation of parallel kinetic resolution between C(sp^2)–H and C(sp^3)–H[a]



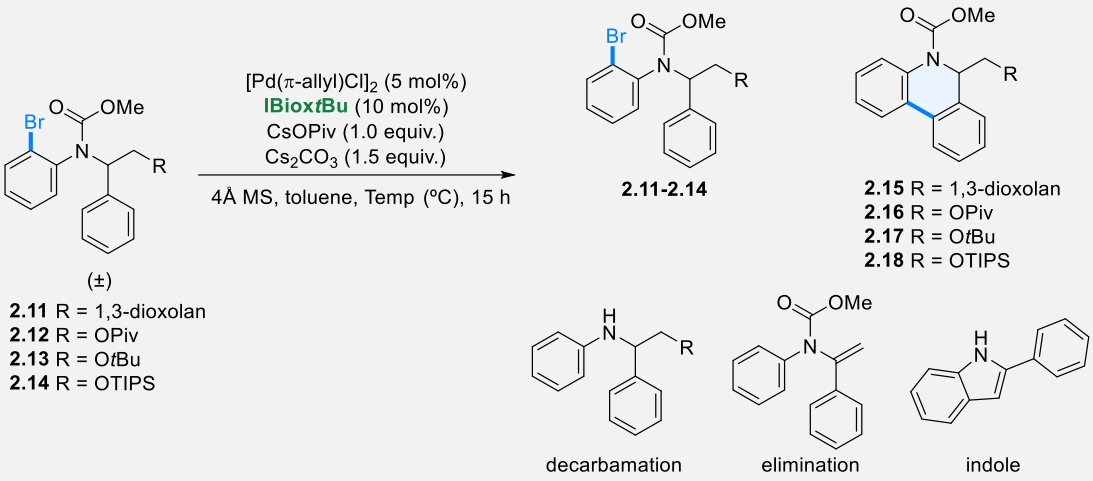
Entry	Temp.[ºC]	GC-MS ratio 2.9/2.10	e.r. of 2.9	e.r. of 2.10
1	140	74:21	31:69	99.5:0.5
2[b]	160	80:17	29:71	99.3:0.7

[a]**2.8** (0.1 mmol) was engaged. [b]xylenes as a solvent.

2.2.4 Protecting group modification

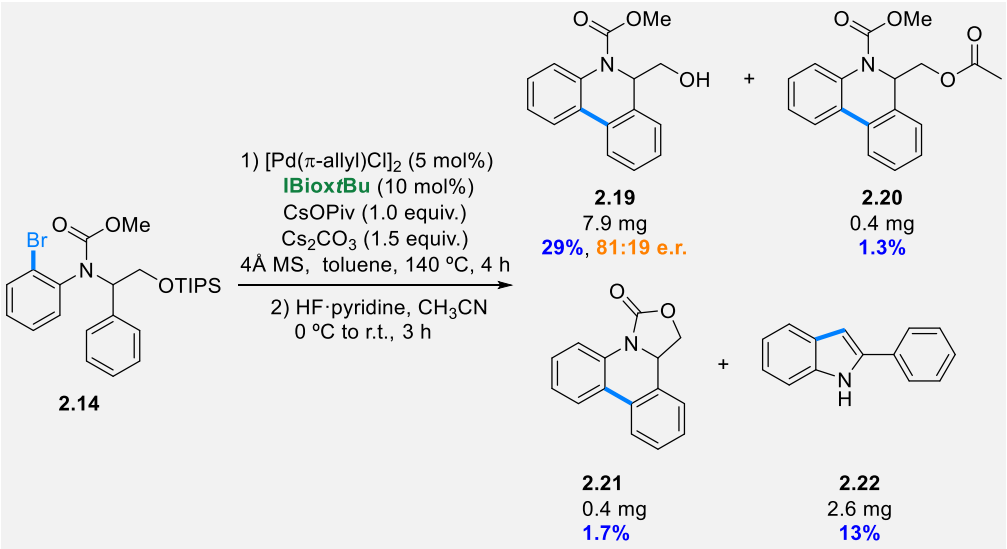
After finding two different C–H activation that could happen, we replaced the benzyl group at the hydroxyl group with other protecting groups to suppress C(sp^3)–H activation (Table 3). 1,3-Dioxolane **2.11** gave almost 50% conversion in the presence of **IBiox*t*Bu**. However, unreacted starting materials were racemic mixtures. **IBioxAd**, which possesses the similar %V_{Bur} value as **IBiox*t*Bu,** did not give promising results. (entries 1, 2). The Pivaloyl group **2.12** provided the complete conversion to furnish the product with a moderate e.r. alongside the olefinated product, presumably resulting from benzylic proton abstraction (entries 3, 4). The *t*Bu ether **2.13** produced four different compounds, C(sp^2)–H activation product **2.17** and unreacted starting material in moderate e.r., with C(sp^3)–H activation product and decarbamation product (entries 5, 6). When silyl protecting groups were used (TIPS) **2.14**, the obtained product was found to have good enantioselectivity (81:19 e.r.) after TIPS deprotection for easy purification, even though the unreacted starting material was a completely racemic mixture (entry 7). Four compounds **2.19**-**2.22** were isolated through exhaustive analysis of the crude material, indicating that this reaction behaves as a sort of parallel kinetic resolution, producing several compounds and decomposing (Scheme 40). Notably, a reasonable amount of indole was speculated to result from enantioselective benzyl proton abstraction during CMD and, subsequently, Heck reaction. In order to make the purification facile, preparative TLC was implemented to purify 43% of the desired product **2.18** with 86:14 e.r. (entry 8), which was slightly better than e.r. after the deprotection of TIPS. Considering the stereogenic centre is at the benzylic position, we also tested for racemisation by heating in the presence of additive and the external base and did not observe significant racemisation (Scheme 41).

Table 3. Effects of different protecting groups at the hydroxyl group on resolution[a]

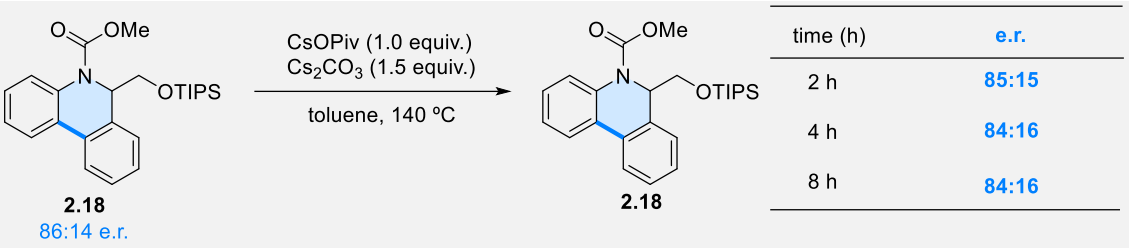


Entry	R	Temp. (°C)	GC-MS ratio[%] 2.11-14/2.15-18	e.r. 2.11-14/2.15-18
1[b]	1,3-dioxolan	140	56:41[d]	51:49/55.5:44.5
2[c]	1,3-dioxolan	140	39:61[d]	50:50/52:48
3	OPiv	120	0:75	–
4	OPiv	140	0:72:26(elimination):3(indole)	–/77:23
5	O*t*Bu	110	16:80:4(decarbamate):1(C(sp^3)–H)	57:43/69:31
6	O*t*Bu	140	0:88:6(decarbamate):5(C(sp^3)–H)	–/59:41
7[e]	OTIPS	130	76:19	50:50[g]/81:19[g]
8[f]	OTIPS	140	0:75:2(dehalo):7(decarbamate):16(indole)	–/86:14 (46)[h]

[a]**2.11-2.14** (0.1 mmol) was engaged. [b]Reaction time for 7 h. [c]Employed IBioxAd as a ligand. [d]Carbamate cleavaged product was obtained. [e]Reaction time for 3h. [f]Reaction time for 4 h. [g]e.r. after desilylation by HF·pyridine. [h]Isolated yield.



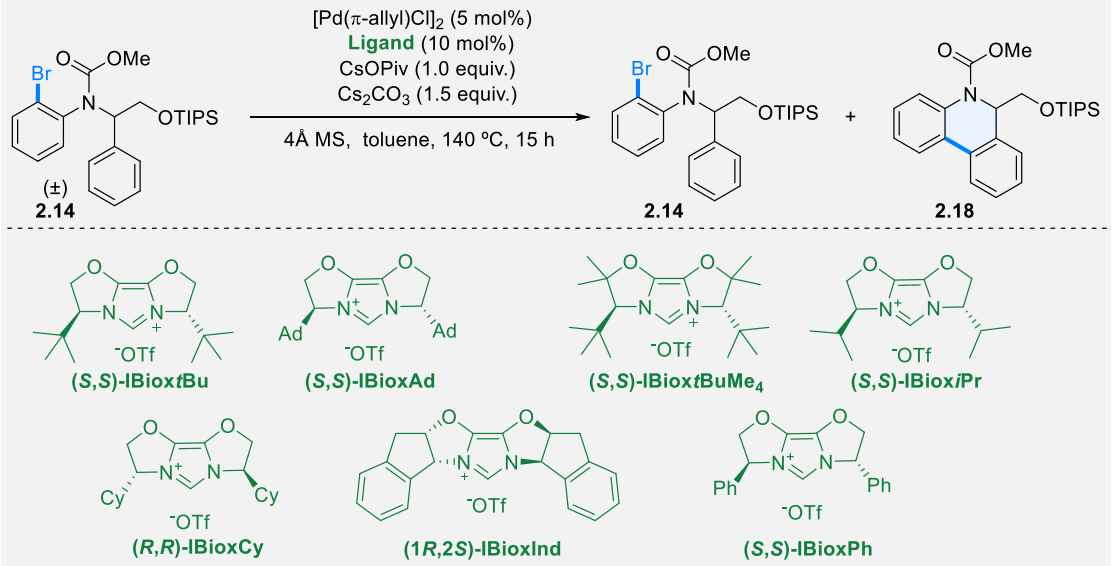
Scheme 40. Analysis of obtained compounds after deprotection of the TIPS group



Scheme 41. Racemisation test with the enantioenriched product

To take advantage of this parallel kinetic resolution, we screened chiral NHCs to get applicable enantioinduction for total synthesis. (Table 4). Unfortunately, the previously employed **IBiox*t*Bu** was the best in this transformation (entry 1). **IBioxAd** and **IBiox*t*BuMe$_4$** displayed similar trends but with decreased e.r. of product **2.18** (entries 2, 3). **IBiox(*i*Pr**, **Cy**, **Ind** and **Ph)** interestingly stopped the reaction around 50% conversion but gave neither the possibility of standard kinetic resolution nor parallel kinetic resolution (entries 4-7).

Table 4. Screening of NHC ligands for parallel kinetic resolution



Entry[a]	IBioxR	Isolated yield [%] 2.14/2.18	e.r. 2.14/2.18
1	***t*Bu**	0:46	–/86:14
2	**Ad**	0:47	–/74:26
3	***t*BuMe$_4$**	0:85	–/60:40
4	***i*Pr**	54:29	57.5:42.5/61.5:38.5
5	**Cy**	trace:19	56.5:43.5/66:34
6	**Ind**	12:30	57:43/64:36
7	**Ph**	33:62	55.5:44.5/52:48

[a]Conditions: **2.14** (0.1 mmol), [Pd(π-allyl)Cl]$_2$ (5 mol%), IBioxR (10 mol%), CsOPiv (1 equiv.), Cs_2CO_3 (1.5 equiv.), 4 Å MS, toluene, 140 °C, 15 h.

Moreover, other combinations of *N*- and *O*-protecting groups were also attempted (Figure 10). Ethyl carbamate **2.23** instead of methyl carbamate **2.14** showed similar trends but with decreased e.r.. The *N*-$COCF_3$ protected **2.24** did not give satisfactory results. Other *O*-protecting attempts found TIPS to get

the highest e.r. (**2.14**, **2.25**-**2.27**). Of note, in the case of MOM protected **2.28**, C(sp^3)–H activation occurred with over 99% *ee*. We stopped the reaction in several cases (**2.23**, **2.24**) to see whether the standard kinetic resolution could happen, which was unfortunately not the case. Despite many efforts, a kinetic resolution could not be optimised at this stage. Notably, interesting 1,4-Pd shift-mediated isoindoline synthesis was observed in the presence of the *N*-methyl group (see chapter 5).

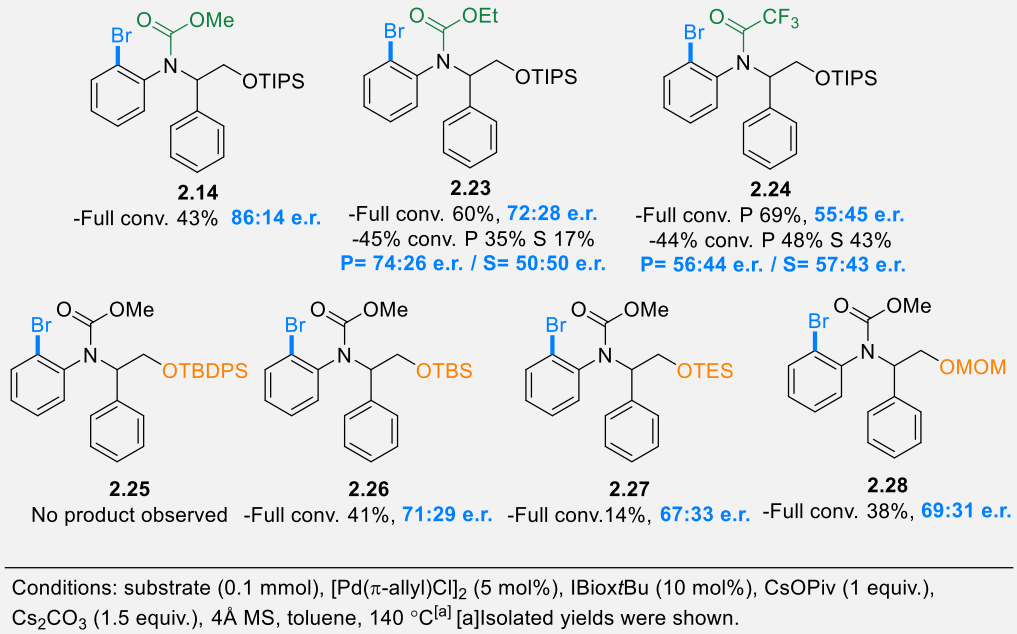
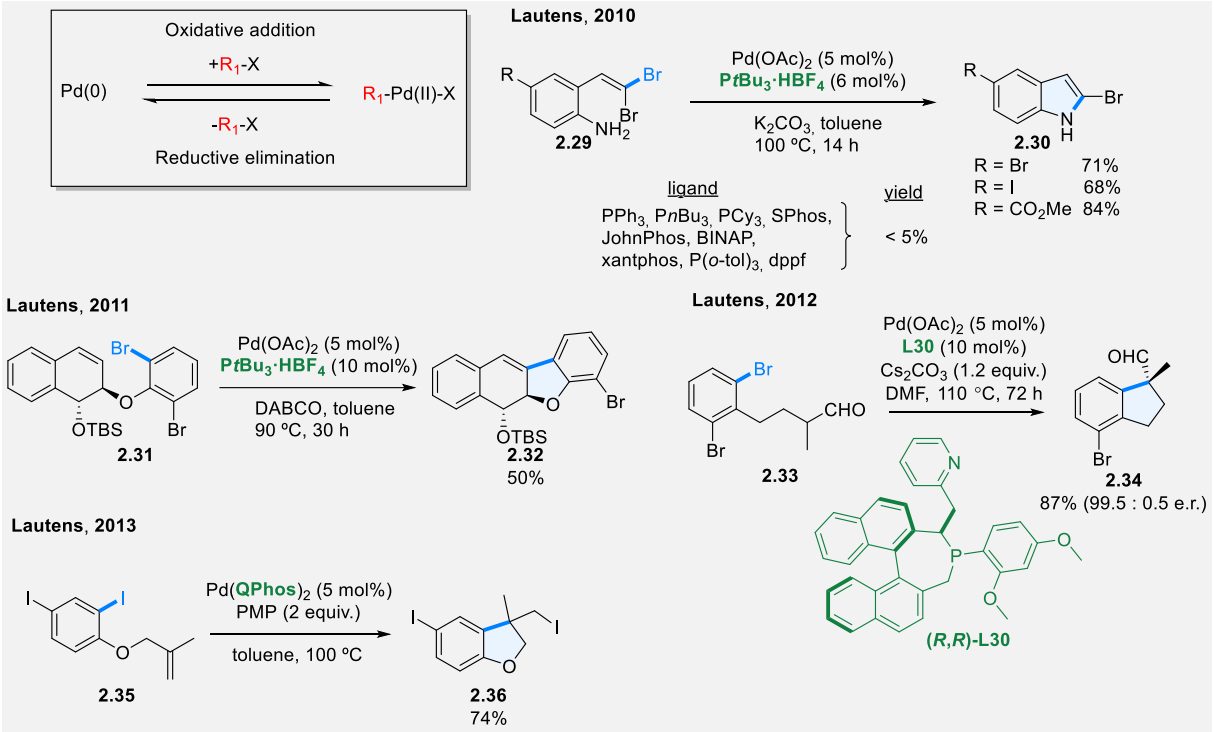


Figure 10. Effect of other *N*- and *O*- protecting groups[a]

2.2.5 Reversible oxidative addition

As another strategy for kinetic resolution, we came up with reversible oxidative addition. There are many precedents, some of which are shown in Scheme 42.[163–165] A Pd(0)/Pd(II) catalytic cycle will be terminated if Pd(0) initially undergoes oxidative addition at a non-productive site or after the turnover, as the resulting Pd(II) complex is catalytically inactive.[165] Otherwise, a suitable exogenous coupling partner is required to accomplish catalyst turnover. It is unfavourable to have multiple (pseudo)halides, especially when a halogenated product is coveted. In the early 2000s, Hartwig and co-workers reported the reductive elimination of Ar–X from ArPd(II)X complex.[166–168] Newman, Lautens and their co-workers successively disclosed a catalytic application of this process.[163] Notably, the mechanistic and practical study revealed bulky phosphorus-type ligands, such as **P*t*Bu$_3$**, **L30** and **QPhos**, gave suitable conditions for these transformations, which is in accordance with Roy and Hartwig`s finding that sterically hindered ligands facilitate reductive elimination of ArPd(II)X.[166]

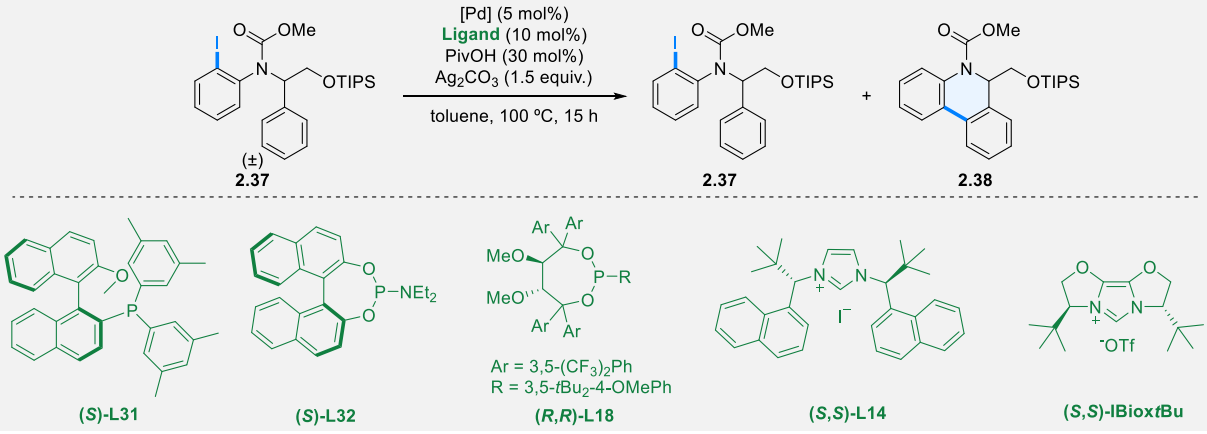


Scheme 42. Representative examples of reversible oxidative addition

We sought to apply this reversible oxidative addition for kinetic resolution, as one enantiomer undergoes C(sp^2)–H activation, and the other remains intact from reversibility. Different halides (Br, I) were attempted with several chiral ligands, and iodide was reactive enough to decrease the reaction temperature to 130 °C and obtain 43% conversion after three hours. In order to prevent iodine accumulation, Cs_2CO_3 was replaced by Ag_2CO_3[73] as an external base, which could further lower the temperature to 100 °C, as the product and starting material were cleanly obtained, differently from parallel kinetic resolution occurred with bromide. Following this, different families of ligands were tested (Table 5). **L32**, **L18** and **L14** displayed reactivity for almost complete conversion (entries 2-4).

Interestingly, **L31** and **IBiox*t*Bu** could stop the reaction at 50% conversion after 15 h; however, only the racemic mixture of products was obtained (entries 1, 5). Unfortunately, these results suggested that the oxidative addition seemed irreversible.

Table 5. Screening of chiral ligands for reversible oxidative addition aiming kinetic resolution

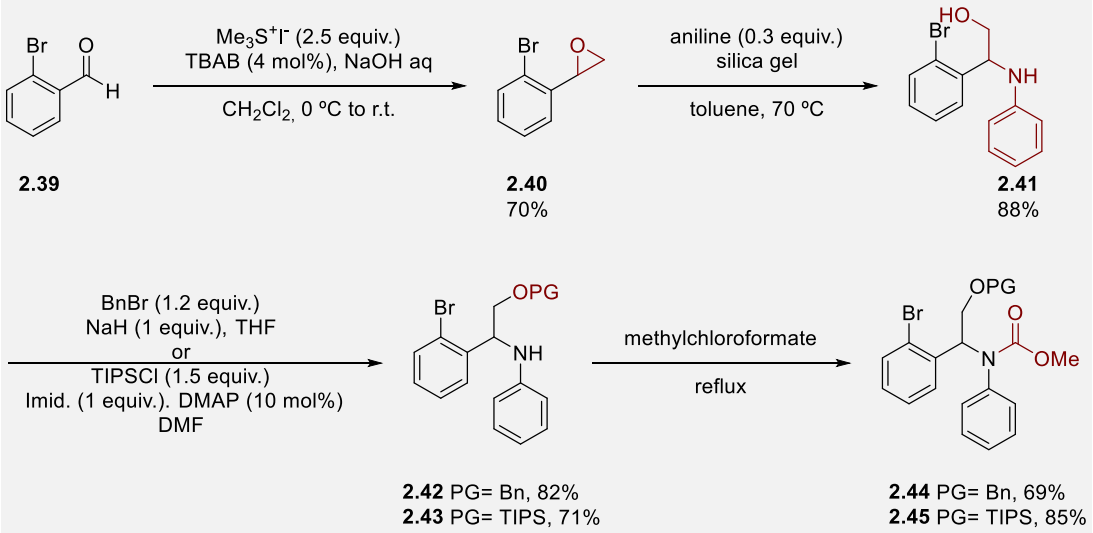


Entry[a]	[Pd]	Ligand	NMR yield [%][b] 2.37/2.38	e.r. 2.37/2.38
1	Pd_2dba_3	**L31**	36:61	–/51:49
2	Pd_2dba_3	**L32**	11:88	–
3	Pd_2dba_3	**L18**	0:69	–
4	$[Pd(\pi\text{-allyl})Cl]_2$	**L14**	0:95	–
5	$[Pd(\pi\text{-allyl})Cl]_2$	**IBiox*t*Bu**	42:53	–/52:48

[a]**2.37** (0.1 mmol) was engaged. [b]Determined by ^{1}H NMR using trichloroethylene as internal standard.

2.2.6 Changing position for oxidative addition

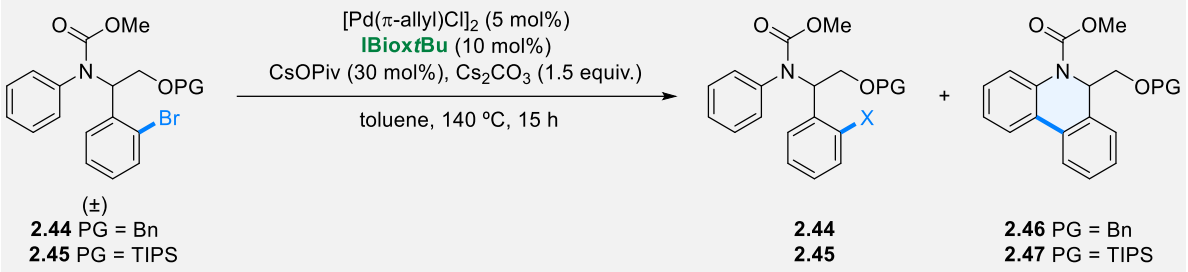
Traditionally in this field, the aniline bearing the halide unit is used as the coupling partner for these reactions. However, this is not a requirement, and the halide fragment can be attached to the other coupling partner. We, therefore, commenced the substrate synthesis from the desired epoxide **2.40** formation by the Corey-Chaykovsky reaction of *ortho*-bromo acetaldehyde **2.39** (Scheme 43). The regioselective reaction of aniline to the epoxide **2.40** readily produced the amino alcohol **2.41** in 88%. Following protection of the alcohol and secondary amine, the desired starting material of C–H activation was obtained over four steps in 35% for benzyl-protected substrate **2.44**, in 37% for TIPS-protected substrate **2.45**.



Scheme 43. Synthesis of substrates with halide on the phenyl ring

This starting material was subjected to a round of screening in order to test the feasibility of this process (Table 6). In contrast to previous substrates, the conversion was moderate even after 24 h at 140 ºC (entries 1, 2), which was promising from a kinetic resolution point of view. Even after 48 h, **2.45** was not fully converted into product **2.47** with moderate enantioselectivity (entry 3). **2.44** with benzyl group also displayed the similar reactivity to obtain moderate e.r. of product **2.46** with racemic starting material (entry 4). Reaction completion after 48 h gave the decreased e.r. of product **2.46** (entry 5). Unfortunately, promissing starting point of a standard kinetic resolution was not observed at this stage.

Table 6. Reaction attempts of substrates with halide at another phenyl ring



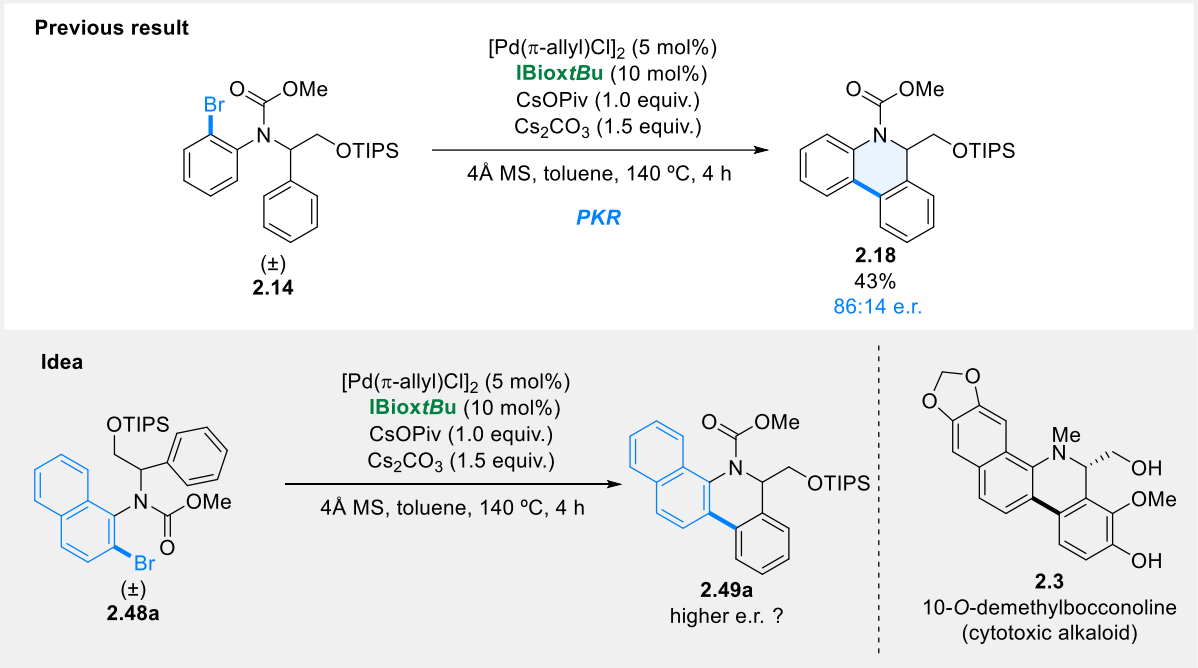
Entry	PG	NMR Yield[%][a] 2.44-45/2.46-47	e.r. 2.44-45/2.46-47
1	TIPS	68:18	–
2[b]	TIPS	39:29	46:54/35:65
3[c]	TIPS	13:46	–/38:62
4	Bn	18:35	42:58/24:76
5[c]	Bn	0:38[d]	–/39:61

[a]Determined by ^{1}H NMR using trichloroethylene as internal standard. [b]Reaction time for 24 h. [c]Reaction time for 48 h. [d]Isolated yield.

Furthermore, we decreased the amount of external base to 0.5 equivalent that deprotonates carboxylic acid to reenter the catalytic cycle and intentionally get less than 50% conversion. However, a promising result has never been obtained.

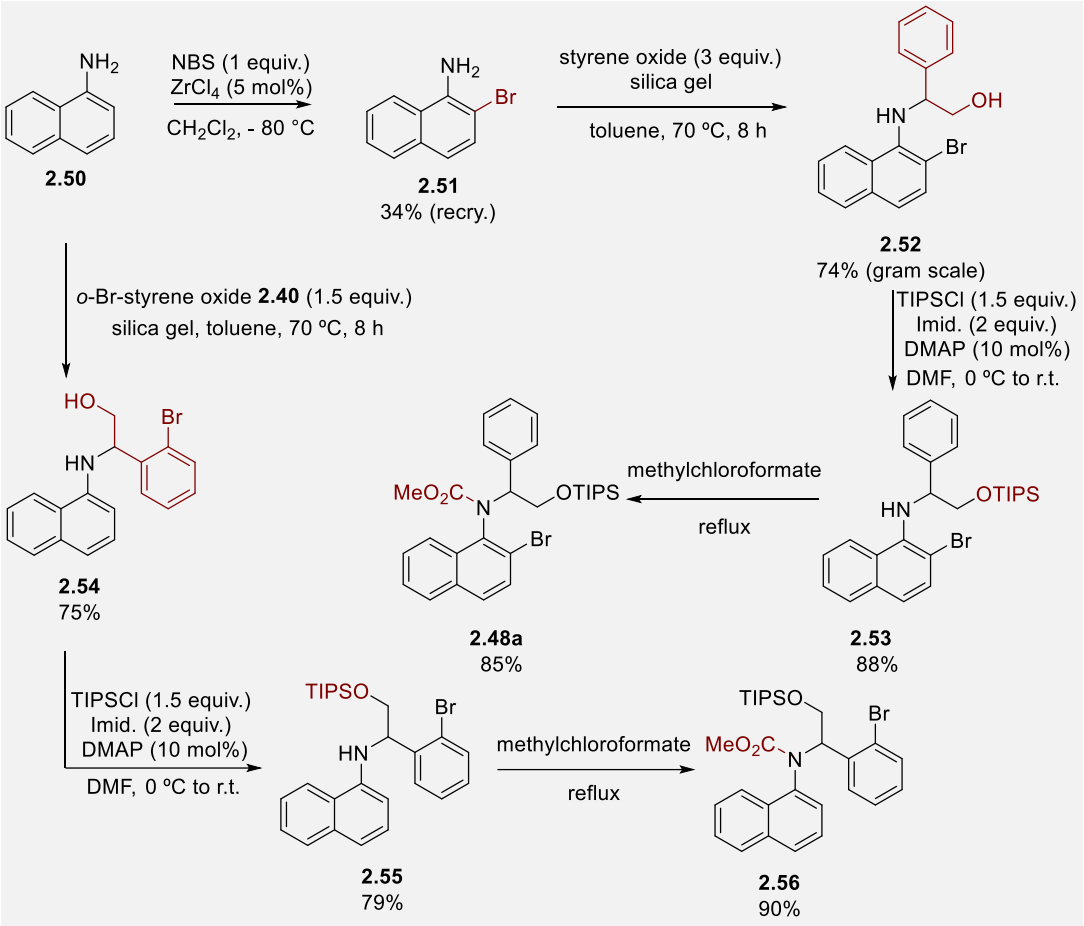
2.2.7 Replacement of aniline with naphthylamine

Our target molecule via kinetic resolution, 10-*O*-demethylbocconoline **2.3**, a cytotoxic dihydrobenzo[*c*]phenanthridine alkaloid, has a naphthylamine core instead of aniline core that we used for the model substrate. Therefore, we considered the effect of the steric bulk of the naphthalene core and whether this could lead to a parallel kinetic resolution with a higher e.r., taking advantage of more robust interactions between the substrate and ligands (Scheme 44).



Scheme 44. The closer model substrate to the actual system for parallel kinetic resolution

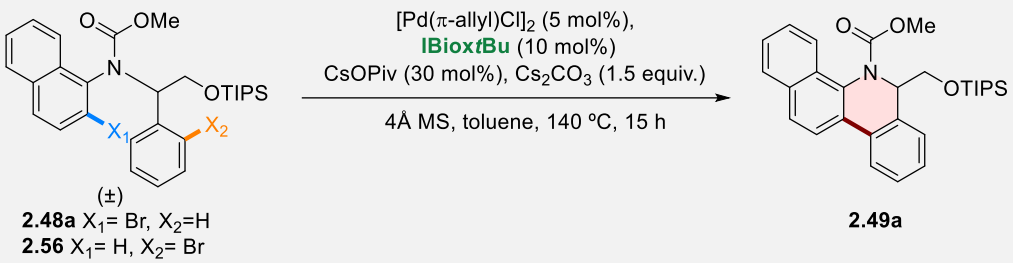
Two model substrates were synthesised that were more similar to the desired substrate for the total synthesis, one of which has a halide on the naphthylamine core and the other on the phenyl ring (Scheme 45). Naphthylamine **2.50** was successfully brominated selectively in the presence of NBS and $ZrCl_4$ by the reported procedure by Yamamoto and co-workers.[169] Epoxide opening worked well on a gram scale to afford **2.52** in 74%. The resulting alcohol was subsequently protected in excellent yield. Following this, secondary amine was protected to deliver the substrate **2.48a**. For access to a substrate with halide on another aromatic ring, we employed the same strategy as before, employing *ortho*-bromo styrene oxide **2.40** provided by the Corey-Chaykovsky reaction to obtain **2.54** in 75%. Then TIPS protection and carbamation led to the desired substrate **2.56**.



Scheme 45. Synthesis of new model substrates that are closer to the actual system

With the substrates in hand, we attempted to subject them to a reaction with catalytic palladium (Table 7). The standard reaction conditions with **IBiox*t*Bu** resulted in a complete conversion (entry 1). Notably, substrate **2.48a** did not display the behaviour of parallel kinetic resolution indicating the robustness of the substrate to transform into the product without producing the expected indole derivative. Therefore, 0.5 equivalent of the external base was used to stop the reaction at 50% conversion; however, no enantioinduction was observed (entry 2). The substrate with halide on the phenyl ring **2.56** had a similar low reactivity as before to show the moderately enantioenriched product (entry 3). The conversion to the product was not increased despite a prolonged reaction time of 60 h; in this case, a slightly decreased e.r. was observed (entry 4). In order to get around 50% conversion, an extra 10 mol% of the catalyst and ligand with stirring for 48 h resulted in 30:70 e.r. for the product (entry 5). We observed moderate enantioinduction in the last cases. However, despite many further attempts, no improvement was observed in the reactivity and enantioenrichment of the system. For instance, we also prepared substrate with Bn group instead of TIPS **2.48a**. This case surprisingly suppressed C(sp^3)–H activation product completely, giving C(sp^2)–H activation product in 72% NMR yield, unlike the previous result with aniline core **2.8**.

Table 7. Reaction screening with substrates, including naphthylamine moiety[a]

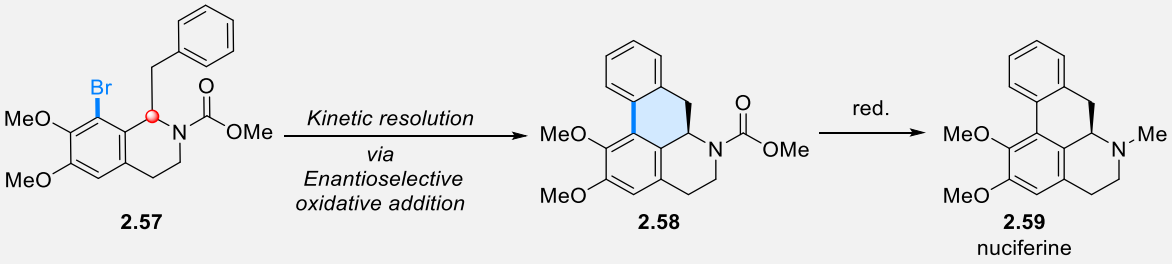


Entry	X_1	X_2	NMR yield[%][b] 2.48a, 2.56/2.49a	e.r. of 2.49a
1	Br	H	0:84	51:49
2[c]	Br	H	39:30	49:51
3	H	Br	69:21	32:68
4[d]	H	Br	56:19	35:65
5[e]	H	Br	41:49	30:70

[a]**2.48a**, **2.50** (0.1mmol) was engaged. [b]Determined by ^{1}H NMR using trichloroethylene as internal standard. [c]0.5 equivalent of Cs_2CO_3 was employed. [d]Reaction time for 60 h. [e][Pd(π-allyl)Cl]$_2$ (10 mol%), IBiox*t*Bu (20 mol%), 48 h.

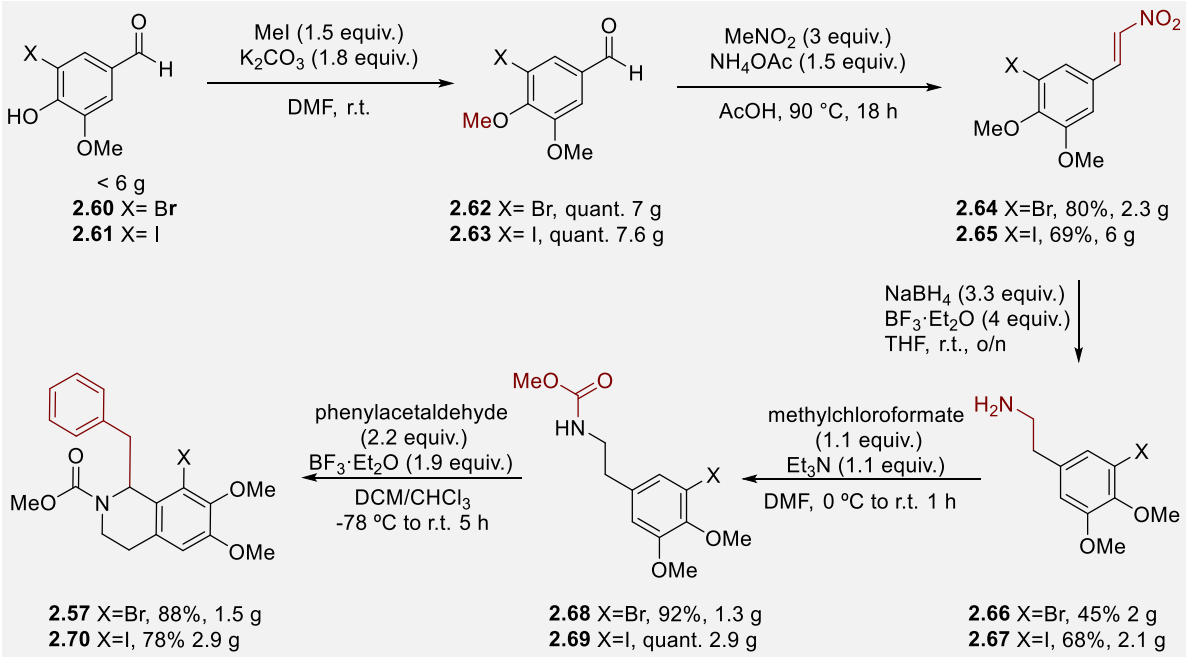
2.2.8 The different scaffold for reversible oxidative addition

Given the results obtained previously, it turned out that the scaffolds of previous starting materials could not give us favourable classic kinetic resolution. Furthermore, while using previous starting materials, we were unsure whether the oxidative addition was reversible. Therefore, in order to take full advantage of enantioselective reversible oxidative addition, we redesigned the scaffold of substrate **2.57**, in which the stereogenic centre is located on a fused ring system and only two carbons away from the oxidative addition site, meaning that the chiral ligands could potentially influence the configuration more easily and oxidative addition could be stereodetermining step (Scheme 46). This product **2.58** is a proposed intermediate of the total synthesis of nuciferine **2.59**.[170]



Scheme 46. Redesigned scaffold for reversible oxidative addition

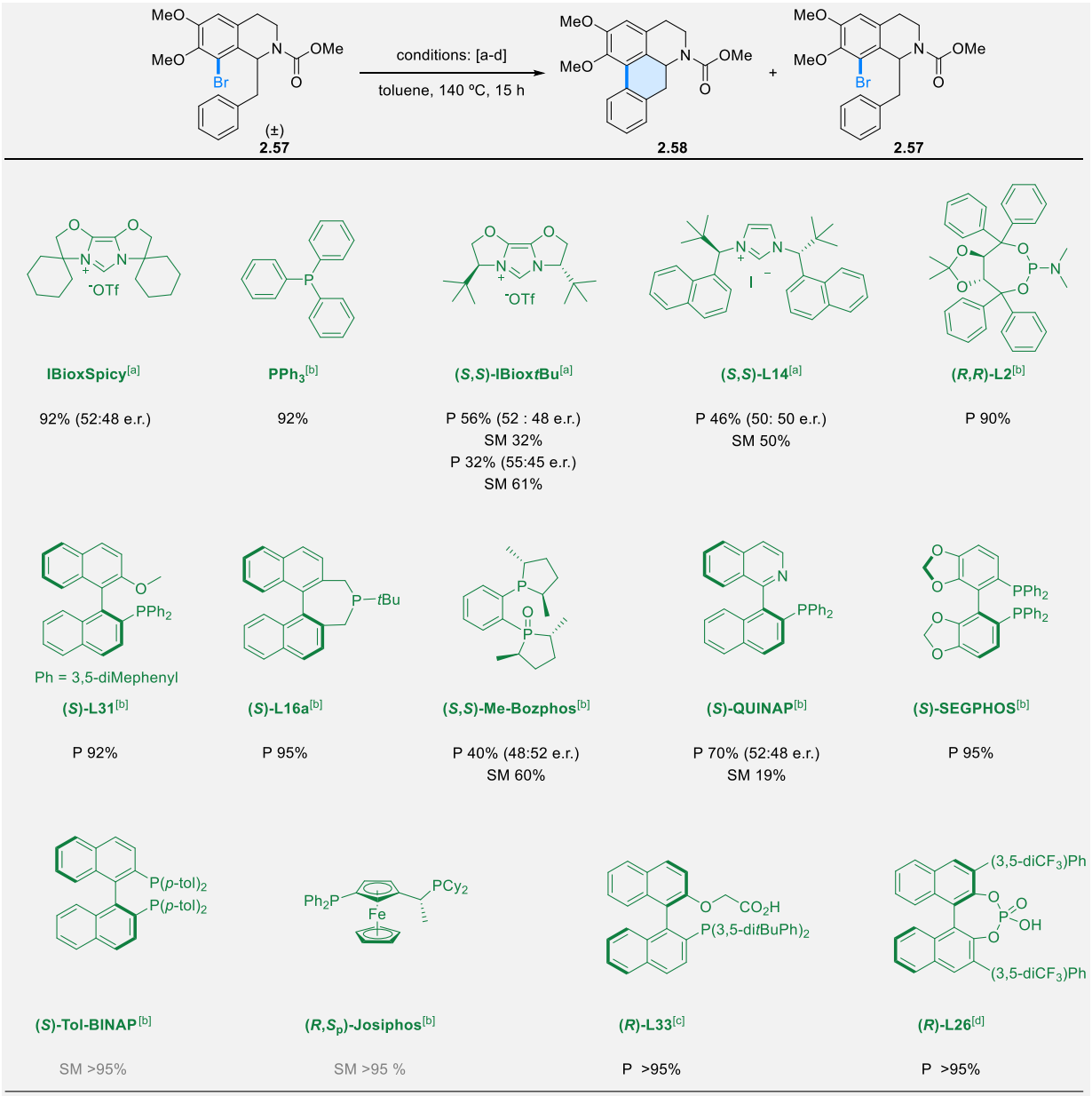
We synthesised the substrate **2.57**, **2.70** for C–H activation, as shown in Scheme 47. Methylation of vanillin derivatives possessing bromide or iodide proceeded well to obtain **2.62**, **2.63** in quantitative yield, which was engaged in the Henry reaction to afford nitro alkene **2.64**, **2.65** after dehydration in 80% and 69%, respectively. Double reduction of nitro group and alkene produced **2.66**, **2.67**, followed by carbamation. Finally, the Pictet-Spengler reaction could produce the C–H activation substrates **2.57**, **2.70** on gram scale.



Scheme 47. Gram-scale substrate synthesis for nuciferine synthesis

As shown in Table 8, various chiral ligands were screened with this newly synthesised substrate **2.57**. Several ligands (**L2**, **L16a**, **L26**, **L31**, **L33**, **SEGPHOS**) displayed high reactivity to convert the substrate fully to the product, meaning that these could potentially decrease the reaction temperature to make an enantioselective oxidative addition feasible. Other ligands, unfortunately, did not allow any stereoinduction, even though there were ligands that could stop the reaction at around 50% conversion (**IBiox*t*Bu**, **L14**, **Me-Bozphos**, **QUINAP**).

Table 8. Ligands screening for enantioselective oxidative addition

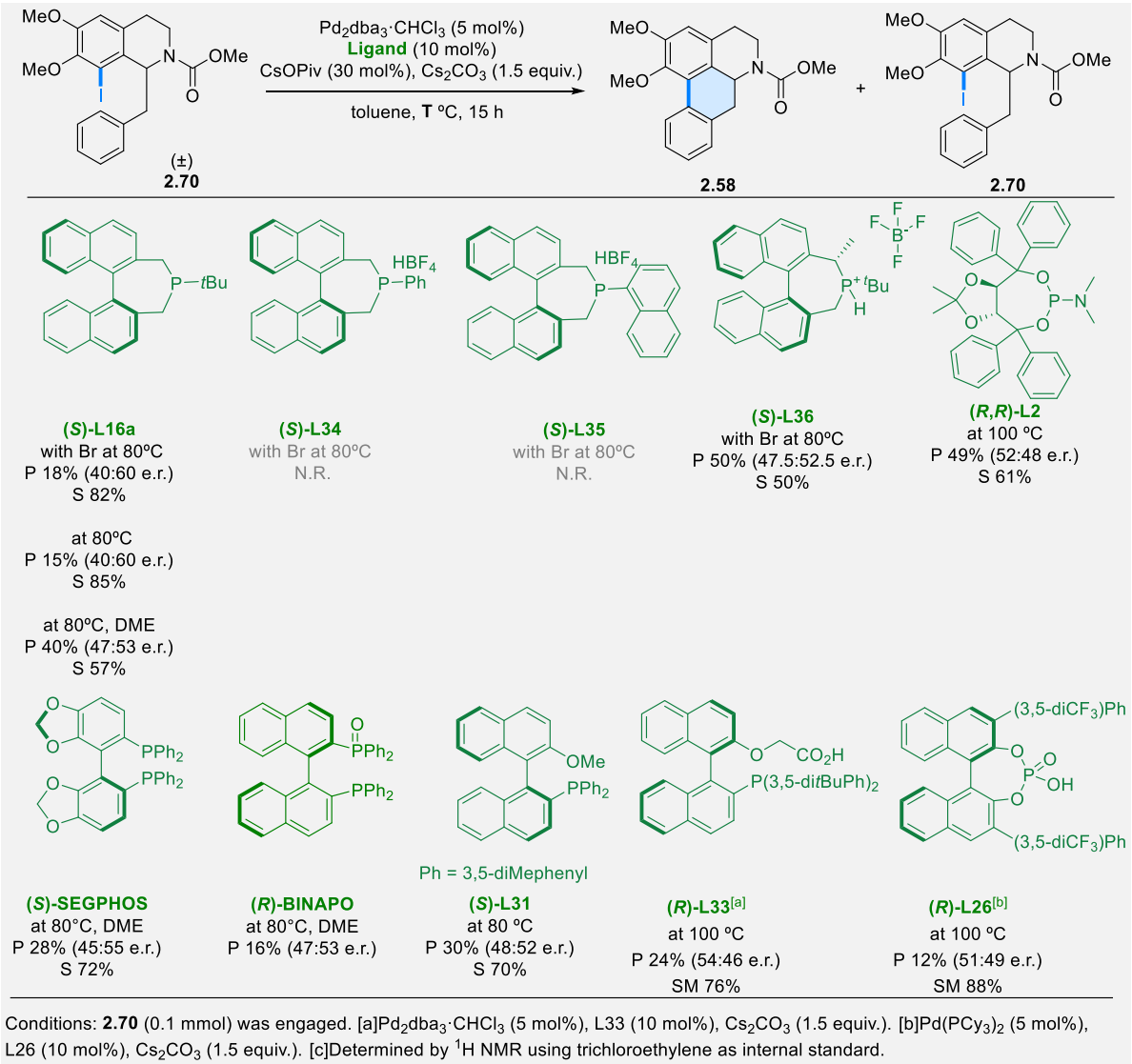


Conditions: **2.57** (0.1 mmol) was engaged. NMR yield was shown, determined by ^{1}H NMR using trichloroethylene as internal standard. [a][Pd(π-allyl)Cl]$_2$ (5 mol%), Ligand (10 mol%), CsOPiv (30 mol%), Cs_2CO_3 (1.5 equiv.). [b]Pd_2dba_3 (5 mol%), Ligand (10 mol%), CsOPiv (30 mol%), Cs_2CO_3 (1.5 equiv.). [c]Pd_2dba_3·$CHCl_3$ (5 mol%), Ligand (10 mol%), Cs_2CO_3 (1.5 equiv.). [d]$Pd(PCy_3)_2$ (5 mol%), Ligand (10 mol%), Cs_2CO_3 (1.5 equiv.).

For the second round of the ligand screening, we selected highly reactive ligands and their derivatives with substrate possessing iodide instead of bromide in order to take advantage of the relative ease of oxidative addition (Table 9). **L16a** of Binepines showed high reactivity enough to proceed with the

reaction at 80 ºC in toluene as a solvent. Thus polar solvent (DME) was employed to get roughly 50% conversion, which did not lead to an enantioenriched product as well as when employing **SEGPHOS**, **BINAPO**. In contrast, **L34** and **L35** did not proceed with the reaction, probably due to the electron deficiency of the aromatic ring next to phosphorus in a less efficient oxidative addition. Binepine **L36** and TADDOL-based phosphoramidite **L2** gave moderate conversion, but no scalemic product was obtained. Due to the low reactivity at 80 °C, increased temperatures with bifunctional ligand **L33** and chiral phosphoric acid **L26** were tested; however, this did not give promising results for enantioselective oxidative addition. Despite many attempts, classic kinetic resolution with Pd(0)-catalysed C–H activation has not been observed yet.

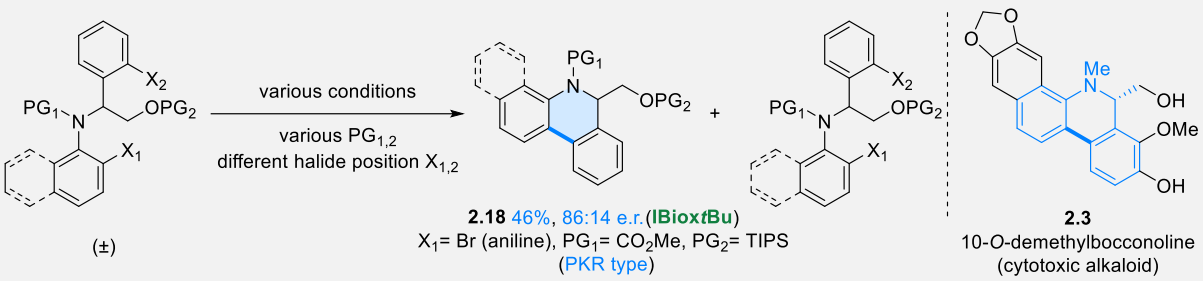
Table 9. Second ligand screening for enantioselective oxidative addition[a-c]



Conditions: **2.70** (0.1 mmol) was engaged. [a]$Pd_2dba_3{\cdot}CHCl_3$ (5 mol%), L33 (10 mol%), Cs_2CO_3 (1.5 equiv.). [b]$Pd(PCy_3)_2$ (5 mol%), L26 (10 mol%), Cs_2CO_3 (1.5 equiv.). [c]Determined by ^1H NMR using trichloroethylene as internal standard.

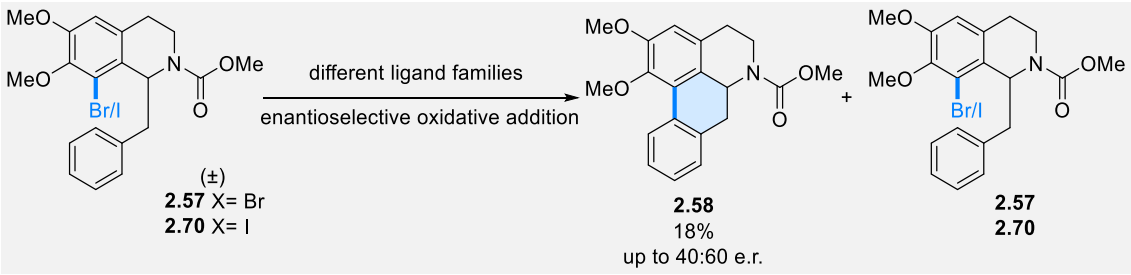
2.3 Conclusion and outlook

In chapter 2, we attempted to develop a classic kinetic resolution with Pd(0)-catalysed C–H activation for the total synthesis of 10-*O*-demethylbocconoline **2.3**. Various model substrates were synthesised and subjected to C–H activation reactions in the presence of a variety of chiral ligands. Nevertheless, we could not find a reasonable standard kinetic resolution except for a parallel kinetic resolution that produced C(sp^2)–H activation product and several by-products, including indoles. In order to take advantage of this reaction, we screened different protecting groups on *O*- and *N*- and chiral ligands, showing that TIPS and methylcarbamate were the best-protecting groups and **IBiox*t*Bu** as the chiral ligand (Scheme 48). However, as soon as the naphthylamine core, which is closer to the actual system, was introduced instead of aniline, the previously observed parallel kinetic resolution was not observed at all, producing an excellent yield of the C(sp^2)–H activation product as a racemate instead.



Scheme 48. Summary of condition optimisation for kinetic resolution

We attempted to modulate the reaction conditions to improve the result of the reaction focused on reversible oxidative addition. Different halide positions could stop the reaction around 50% conversion, which resulted in low enantioselectivity. Another scaffold, **2.57**, **2.70**, which have an oxidative addition site closer to the stereogenic centre located on a fused ring system, has never shown promising outcomes after attempting most of all the chiral ligand families we have in the group. We concluded that entirely different substrate systems or reaction conditions would be required to allow enantioselective oxidative addition to achieving a classic kinetic resolution.



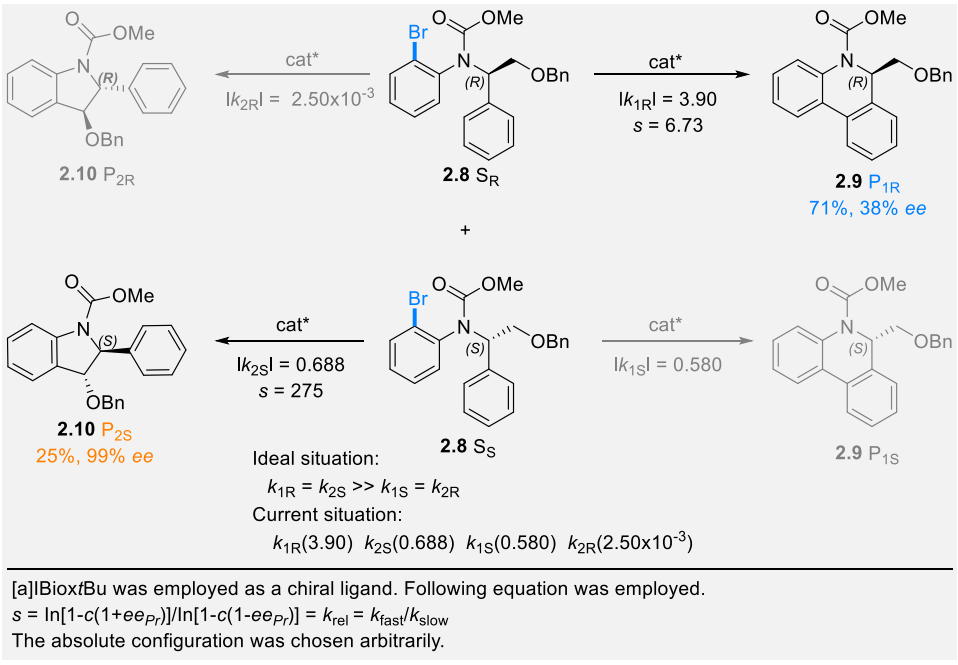
Scheme 49. Summary of study for enantioselective oxidative addition

Conversely, during this course of study, we could also find interesting parallel kinetic resolution between the C(sp^2)–H and C(sp^3)–H activation under **IBiox*t*Bu** conditions, which was later optimised in chapter 4. Furthermore, interesting 1,4-Pd shift-mediated isoindoline synthesis was observed in the presence of the *N*-methyl group, which was successfully optimised. (see chapter 5)

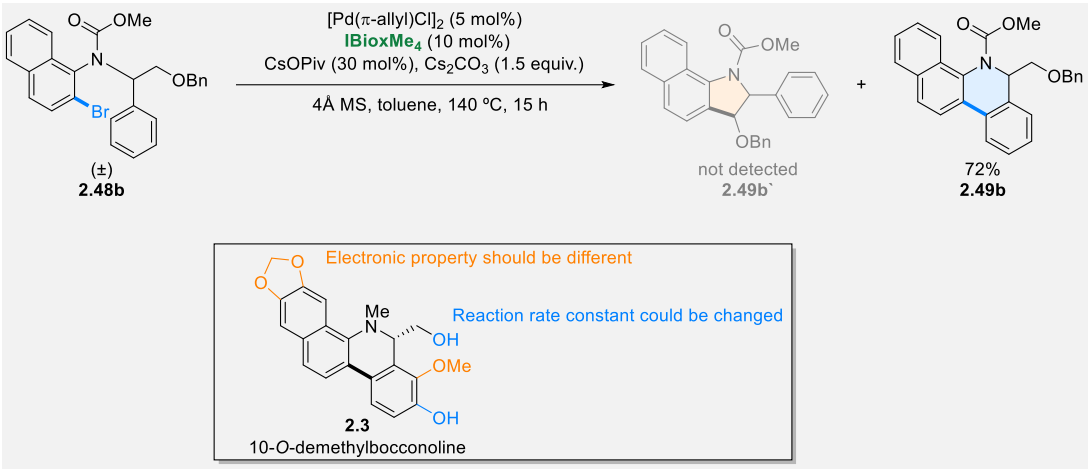
3. Parallel kinetic resolution towards the total synthesis of 10-*O*-demethylbocconoline

3.1 Introduction

Despite many efforts towards a classic kinetic resolution, no promising results have been observed. However, the early stage of this study displayed parallel kinetic resolution could happen in the mode of C(sp^2)–H vs C(sp^3)–H, with a moderate e.r. on the C(sp^2)–H activation product and excellent e.r. on the C(sp^3)–H activation product. We devised an idea to utilise this parallel kinetic resolution to synthesise 10-*O*-demethylbocconoline **2.3**. It was known that C(sp^3)–H activation could occur in the presence of an ether-type protection group at the hydroxy group. In order to clarify this reaction theoretically, the reaction profile was calculated (Scheme 50).[104,171–174] In fact, the current situation was far from the ideal situation of the parallel kinetic resolution as though the k_{2S} has an excellent number, the k_{1R} has a moderate number. Thus we aimed to control the reaction rate constants of C(sp^2)–H and C(sp^3)–H activation. As previously mentioned, in the presence of a naphthylamine core and Bn for protecting group **2.48b**, C(sp^3)–H activation **2.49b`** was completely suppressed, with 72% of the C(sp^2)–H activation product **2.49b** being observed by NMR (Scheme 51). However, in the actual system, one of the C(sp^2)–H is blocked by the methoxy group (in orange of **2.3**), and the electronic property of the naphthylamine ring is different due to the dioxole (in orange of **2.3**). Furthermore, the steric difference of protecting groups (in the blue of **2.3**) could play a role in facilitating C(sp^3)–H activation to balance the two reaction rate constants.



Scheme 50. Reaction profile of the observed regiodivergent enantioselective C–H activation[a]

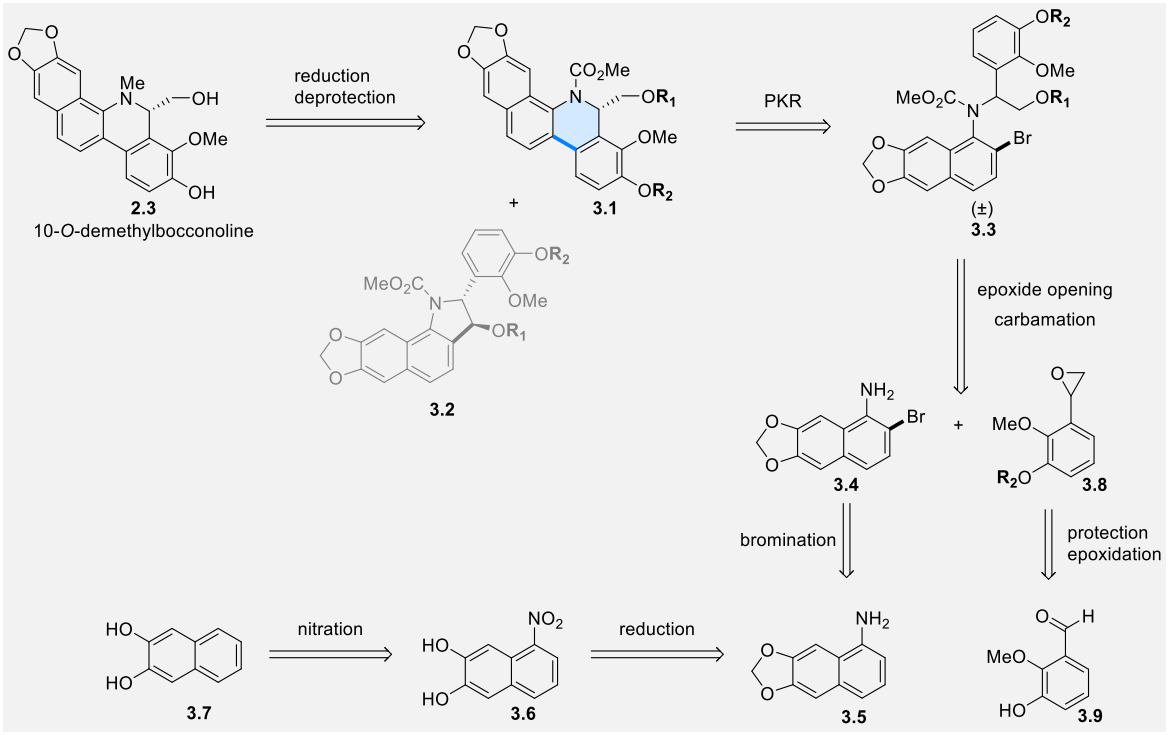


Scheme 51. Previous result with naphthylamine based substrate 2.48b with benzyl protecting group

3.2 Result and discussion

3.2.1 Synthetic plan for10-*O*-demthylbocconoline via parallel kinetic resolution

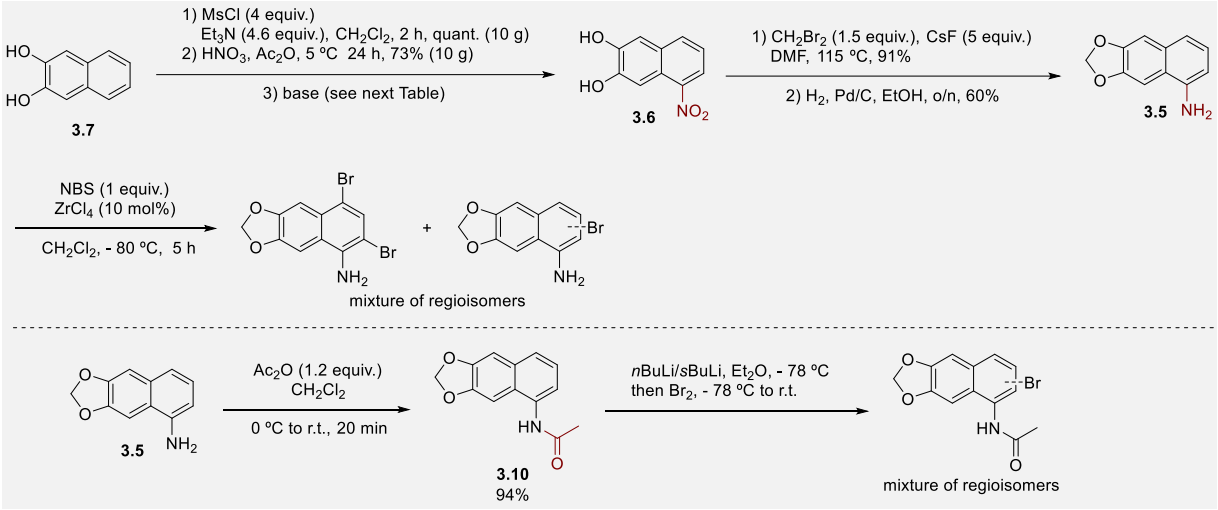
Our retrosynthetic scheme is shown in Scheme 52. First, the naphthylamine core will be synthesised from di-naphthol **3.7**, with selective nitration and acetal formation, followed by a reduction of nitro to amine **3.5**. Then, Yamamoto`s procedure for *ortho*-selective bromination,[169] will produce the desired *ortho*-bromo naphthylamine moiety **3.4**. The coupling partner will be epoxide **3.8**, which should be readily accessed from a protected aldehyde by epoxidation. These two compounds will be engaged in epoxide opening conditions in the presence of a catalytic amount of silica gel. Next, the generated alcohol will be protected, followed by carbamation, leading to substrate **3.3** for C–H activation in parallel kinetic resolution to obtain an enantioenriched C(sp^2)–H product **3.1**. Finally, reducing methyl amine and deprotection should provide the natural product **2.3**.



Scheme 52. Retrosynthetic scheme of 10-*O*-demthylbocconoline via parallel kinetic resolution

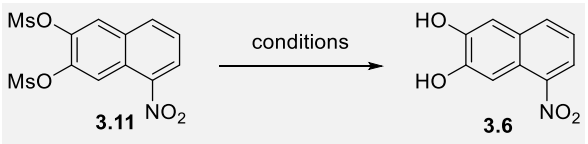
3.2.2 Synthesis of the *ortho*-bromo naphthylamine derivative

We began by synthesising naphthylamine derivative **3.5** (Scheme 53). First, naphthalene-diol **3.7** was employed as starting material, which was engaged in nitration after double mesylation. Then demesylation gave diol **3.6** under the basic conditions. The reference procedure by Shibaike and co-workers gave a quantitative yield on a small scale; however, issues arose when the procedure was attempted on a larger scale. As a result of a small screening of the conditions, TMSOK in CH_3CN produced the desired product **3.6** in 98%, which was scaled up without any issue (Table 10, entries 6, 7). Acetal formation by double S_N2 reaction in the presence of CsF as a base and subsequent hydrogenation led to the desired naphthylamine **3.5**. Yamamoto`s procedure for *ortho*-selective bromination was attempted,[169] however, a mixture of regioisomers and dibrominated compounds was unexpectedly detected by GC-MS analysis and NMR. The *ortho*-lithiation-bromination strategy was next tried after introducing anilide **3.10**, which did not give a clean result.



Scheme 53. Synthesis of *ortho*-bromo-naphthylamine derivative

Table 10. Conditions screening for demesylation

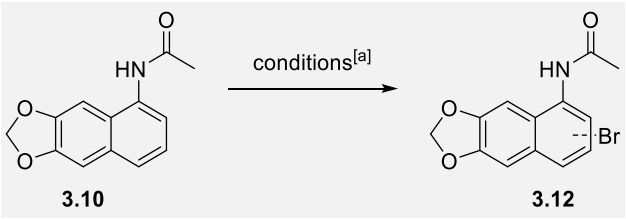


Entry	Conditions	Result
1	5% NaOH aq, 100 °C, overnight	quant.[c]
2	2% NaOH aq, 100 °C, overnight	SM remained
3	TBAF (6 equiv), THF, r.t. 2 h	unknowns with SM and P
4	TBAF (6 equiv), THF, 0 to r.t. 5 h	61% product[d]
5	TMSOK (10 equiv), CH_3CN, r.t., 4 h	SM remained
6[a]	TMSOK (20 equiv), CH_3CN, r.t., 4 h	98%[c]
7[b]	TMSOK (20 equiv), CH_3CN, r.t., 4 h	quant.[c]

[a]100 mg of starting material was engaged. [b]1 g of starting material was engaged. [c]Isolated yield. [d]NMR yield determined by ^1H NMR using trichloroethylene as internal standard.

Due to the failure of selective *ortho*-bromination in classical conditions, we relied on C–H bromination catalysed by transition metals (Table 11). Conditions of Pd (entries 1, 3),[175,176] Co (entry 2),[177] Ag (entry 4)[178] and Ni (entries 5, 6)[178] were screened, and all of the cases detected dibrominated, mono-brominated compounds and remaining starting material. 2 equivalents of NBS resulted in an increased ratio of the dibrominated compound, instead of converting remaining starting material into the mono brominated product. Also, it turned out that regioisomers of mono-brominated compounds were included in the crude mixture. Unfortunately, C–H bromination resulted in poor selectivity.

Table 11. Screening regioselective C–H bromination conditions[a]

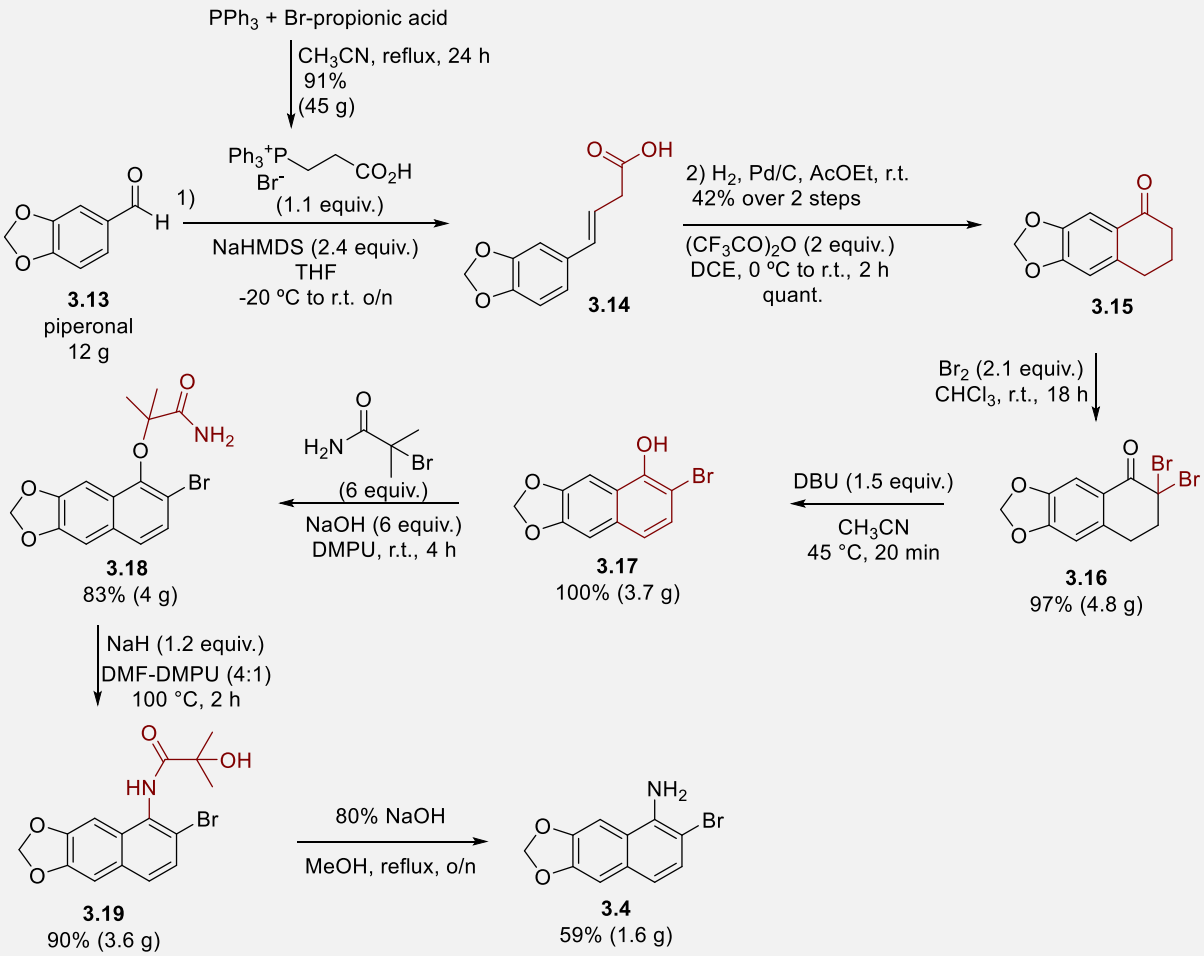


3.10 3.12

Entry	Conditions	GC-MS ratio[%] 3.10/Mono/Di
1	NBS (1.1 equiv., recrystallised), $Pd(OAc)_2$ (10 mol%), $Cu(OTf)_2$ (0.5 equiv.), DCE (0.2 M), 80 ºC, 6 h	7:47:31:15(DeAc+Br)
2	NBS (1.1 equiv., recrystallised), $Co(OAc)_2$ (10mol%), Ag_2O (20 mol%), TFA (25 mol%), DCE (0.2 M), 60 ºC, 16 h	7:67:15
3	NBS (1.1 equiv., recrystallised), $Pd(OAc)_2$ (5 mol%), *p*TSA (50 mol%), toluene (0.25 M), r.t. 4 h	9:53:38
4	NBS (1.1 equiv., recrystallised), Ag_2CO_3 (10 mol%), methanesulfonic acid (3 equiv.), toluene (0.25 M), 50°C, 8 h	47:45:8
5	NBS (1.1 equiv., recrystallised), $NiCl_2 \cdot H_2O$ (10 mol%), methanesulfonic acid (3 equiv.), H_2O (0.25 M), r.t 5 h	50:47:3
6	NBS (1.1 equiv., recrystallised), $NiCl_2 \cdot H_2O$ (10 mol%), methanesulfonic acid (3 equiv.), H_2O (0.25 M), r.t o/n	66:32:1

[a]0.1 mmol of starting material was employed.

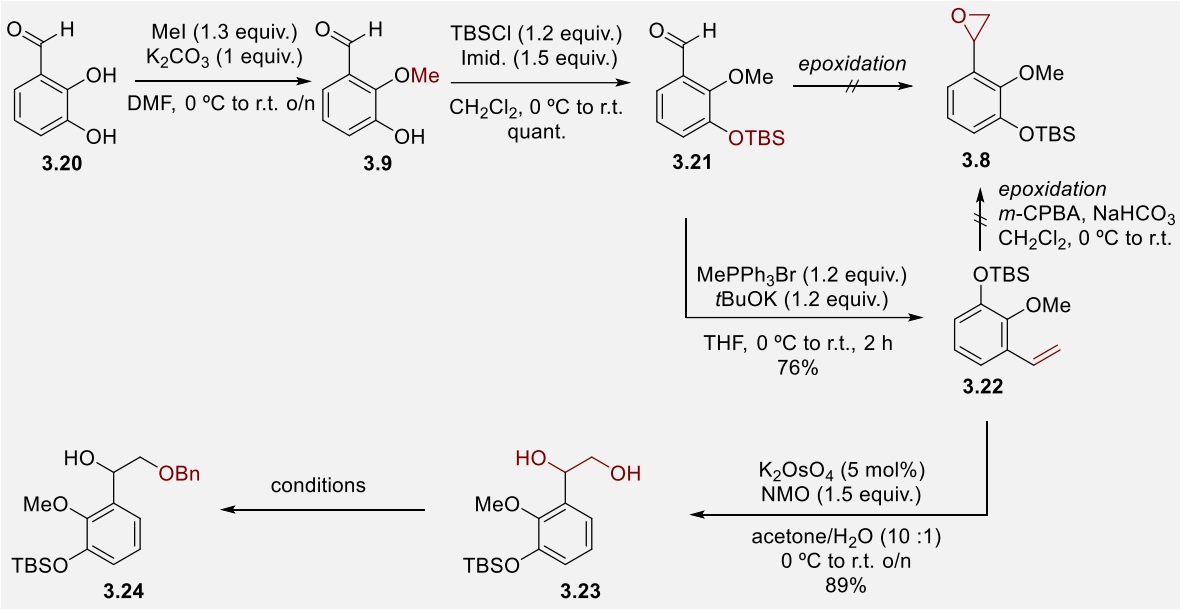
Alternatively, we attempted another synthetic pathway towards the *ortho*-bromo-naphthylamine derivative (Scheme 54), referring to the previous report by Geen and co-workers.[179] Piperonal **3.13** was used as starting material and subjected to a Wittig reaction to form **3.14**. Hydrogenation and subsequent intramolecular Friedel-Crafts acylation provided **3.15**. α-Bromination and aromatisation, followed by Smiles rearrangement, successfully introduced amine moiety **3.19**. Finally, basic conditions hydrolysed the amide to afford the desired compound **3.4**.



Scheme 54. Scalable synthesis of the *ortho*-bromo-naphthylamine derivative

3.2.3 Synthesis of the epoxide as coupling partner

We then started the synthesis of epoxide **3.8** (Scheme 55). The o*rtho*-hydroxy group of 2,3-dihydroxybenzaldehyde **3.20** was selectively methylated, followed by TBS protection at the *meta*-hydroxy group. Then, with this aldehyde **3.21**, epoxidation with the Corey-Chaykovsky reaction gave a complex mixture. This unexpected reactivity was also observed in the epoxidation of styrene derivative **3.22** with *m*-CPBA. In order to avoid epoxidations, Upjohn dihydroxylation was attempted and gave **3.23** in excellent yield. Following this, we sought to selectively protect the primary alcohol, which turned out to be unselective under standard conditions such as BnBr, NaH, THF, 0 ºC to r.t. (Table 12, entries 1, 2). Several reported conditions were attempted, and it found that borinic acid[180] and organotin[181] could coordinate these alcohols to protect primary alcohol selectively by increasing the effect of a steric hindrance (Table 12, entry 3, 4). However, the selectivity was not sufficient (up to 85:15 r.r., entry 4), leading to a purification issue due to the similar polarity of those compounds. Therefore, the following substitution reaction employed the mixture of regioisomers of protected alcohol.



Scheme 55. Synthesis of the coupling partner of naphthylamine derivative

Table 12. Condition screening for regioselective protection of diol compound

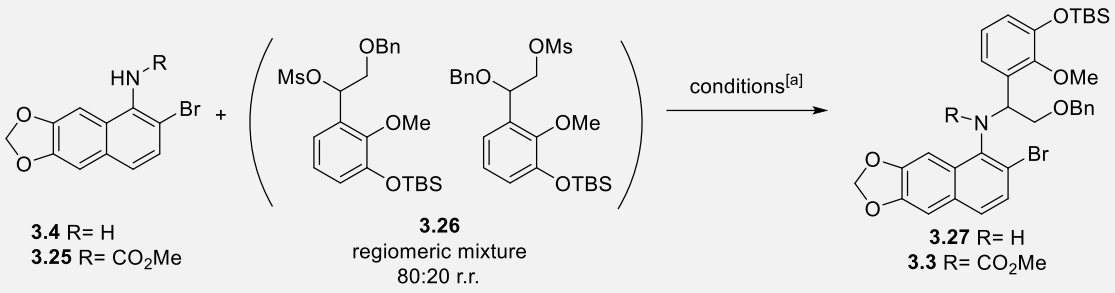
Entry	Conditions[a]	Result
1	BnBr (1.1 equiv.), NaH (2.2 equiv.), DMF, - 78 ºC to r.t.	63:37 r.r.
2	BnBr (1.1 equiv.), NaH (2.2 equiv.), THF, - 78 ºC to r.t.	50:50 r.r.
3	BnBr (1.5 equiv.), 2-aminoethyl dienyl borinate (10 mol%), KI (1 equiv.), K_2CO_3 (1.2 equiv.), CH_3CN, 60 ºC, 24 h	50%[b], 75:25 r.r.
4	Bu_2SnO (10 mol%), toluene, 100 ºC, 1 h then BnBr (2 equiv.), TBAB (10 mol%), K_2CO_3 (1.5 equiv.), CH_3CN/DMF (10:1), 80 ºC, 3 h	70%[b], 85:15 r.r.
5[c]	Bu_2SnO (10 mol%), toluene, 100 ºC, 1 h then BnBr (2 equiv.), TBAB (10 mol%), K_2CO_3 (1.5 equiv.), CH_3CN/DMF (10:1), 80 ºC, 3 h	53%[b], 80:20 r.r.

[a]**3.23** (0.1 mmol) was engaged. [b]Isolated yield. [c]600 mg of starting material was engaged.

3.2.4 Coupling of the naphthylamine and the epoxide

We explored the coupling conditions with synthesised compounds (Table 13). Due to issues with the synthesis of the required epoxide, we attempted a new synthetic route for the synthesis of the desired compound. Firstly, simple nucleophilic substitution with amine **3.4** was attempted in the presence of methanesulfonate **3.26** and weak to strong base to abstract the amine proton, which only gave the product that primary methanesulfonate was reacted (Table 13, entries 1-3).

Table 13. Nucleophilic substitution reaction with amine and methanesulfonate[a]

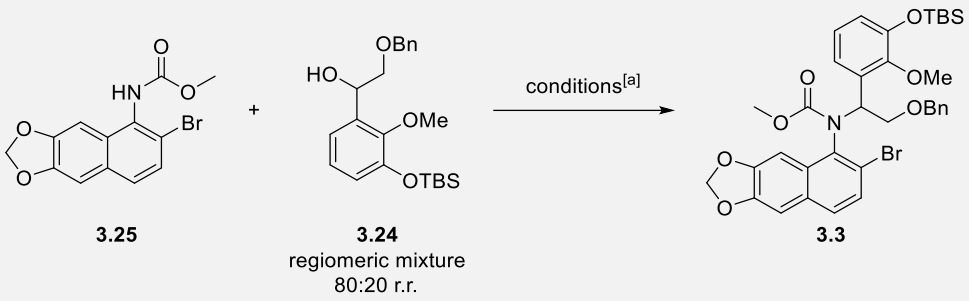


Entry	R	Conditions	Result
1	H	K_2CO_3, CH_3CN, 60 ºC	N.R.
2	H	NaH, THF, 0 to 60 ºC	Only minor isomer reacted
3	CO_2Me	LiHMDS, THF, -78 ºC to r.t. then 60 ºC	Only minor isomer reacted

[a]amine (0.05 mmol), methanesulfonate (0.065 mmol) and base (1.1 equiv) were used.

We then investigated the possibility of using the Mitsonobu reaction for the synthesis of **3.3**.[182] Firstly typical conditions for Mitsunobu displacement were attempted and observed direct coupling with DIAD and benzyl alcohol **3.24** (Table 14, entry 1). The desired product was not detected even if alkylphosphine and more bulky azo reagent DBAD were employed (entries 2, 3). We wondered what caused that low reactivity and changed each substrate into simpler ones, resulting in 85% NMR yield of the expected product using simple benzyl alcohol 1-phenylethan-1-ol (entry 4). This result clearly indicated that our benzyl alcohol derivative **3.24** is too hindered from proceeding. Other than these, further efforts, such as Barbier coupling and imine formation followed by nucleophilic addition, have been attempted; however, we could not get positive results.

Table 14. Conditions screening of Mitsunobu displacement



Entry	Conditions	Result
1	**3.25** (1 equiv.), **3.24** (1 equiv.), DIAD (1.5 equiv.), PPh_3 (1.5 equiv.) THF (0.3 M), 0 ºC to r.t., o/n	Direct coupling with DIAD
2	**3.25** (1 equiv.), **3.24** (1 equiv.), DIAD (1.5 equiv.), PEt_3 (1.5 equiv.) THF (0.3 M), 0 ºC to r.t., o/n	N.D.
3	**3.25** (1 equiv.), **3.24** (1 equiv.), DBAD (1.5 equiv.), PEt_3 (1.5 equiv.) THF (0.3 M), 0 ºC to r.t., o/n	N.D.
4	**3.25** (1 equiv.), 1-phenylethan-1-ol (1 equiv.), DIAD (1.5 equiv.) PPh_3 (1.5 equiv.), THF (0.3 M), 0 ºC to r.t., o/n	85%[b]

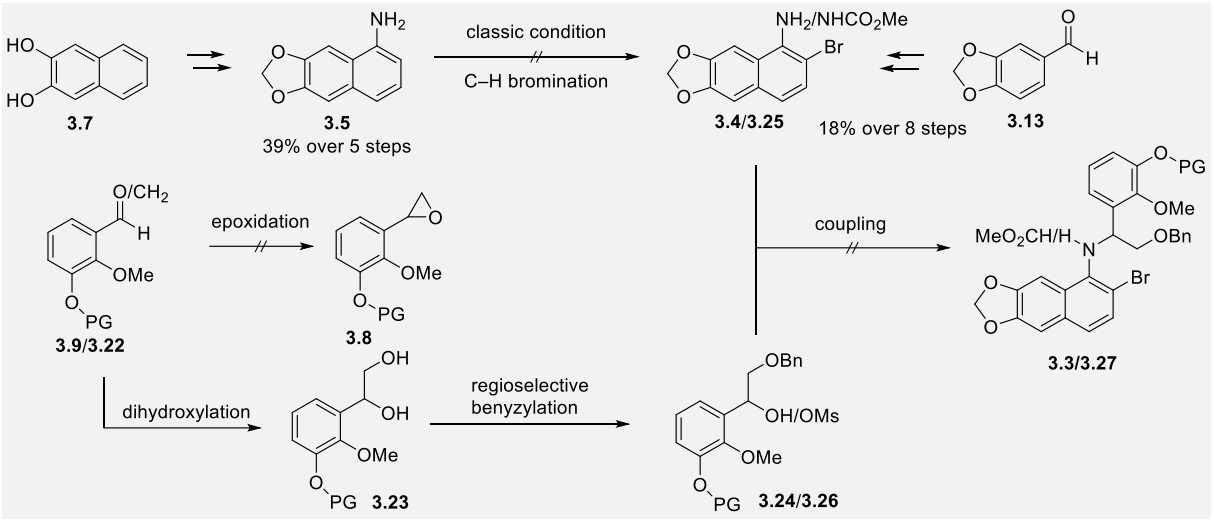
[a]**3.25** (0.05 mmol) was used. [b]Determined by ^{1}H NMR using trichloroethylene as internal standard.

3.3 Conclusion and outlook

In chapter 3, the total synthesis of complex natural product 10-*O*-demethylbocconoline **2.3** via parallel kinetic resolution with Pd(0)-catalysed C–H activation was attempted. Although the naphthyl ring could somehow prevent parallel kinetic resolution completely and calculation on the model substrate showed that the situation among reaction rate constants is not ideal, we commenced with the synthesis of the substrate for the actual system as it has fewer C(sp^2)–H bond to be activated, meaning that reaction rate constant should be different from the model case. From the retrosynthetic analysis, *ortho*-bromo naphthylamine derivative **3.4** and epoxide **3.8** as the coupling partner were required.

Firstly, the naphthylamine derivative was synthesised in five steps from naphthyl-diol **3.7**. However, the regioselective introduction of bromide was problematic. Secondly, we modified the reported procedure and could finally obtain the desired material **3.4** on a gram scale.

As the coupling partner, epoxide **3.8** was needed; however, epoxidation with typical conditions indicated that the product was unstable inside the reaction and thus could not be obtained. Alternatively, dihydroxylation and regioselective protection of primary alcohol were executed, and product **3.24**/**3.26** was engaged in numerous substitution conditions. However, these have never given the coupled product. This difficulty made us move to another natural product to utilise parallel kinetic resolution between C(sp^2)–H and C(sp^3)–H.



Scheme 56. Summary of attempts towards the total synthesis of 10-*O*-demethylbocconoline via parallel kinetic resolution

4. Total synthesis of cryptowolinol via parallel kinetic resolution by Pd(0)-catalysed C–H activation

4.1 Introduction

Cryptowolinol is a natural product isolated from *Cryptocarya phyllostemon*, including an *N*-containing fused ring system (Figure 11). Structurally there is an unusual presence of a hydroxy group at the benzylic position at one of the stereogenic centres.[183] However, since its isolation in 1989, no total synthesis has been reported, and its bioactivity has not been assessed.

Early in our kinetic resolution study, we observed parallel kinetic resolution between C(sp^2)–H and C(sp^3)–H bonds, which is the rare example excluding cyclopropyl C(sp^3)–H vs arenyl C(sp^2)–H activation by Cramer`s resolution.[143] Interestingly, our C(sp^3)–H activation product from parallel kinetic resolution has excellent enantioselectivity and is potentially applicable to the framework of cryptowolinol.

From these contexts, we sought to explore parallel kinetic resolution between C(sp^2)–H and C(sp^3)–H and apply for the first enantioselective total synthesis of cryptowolinol.

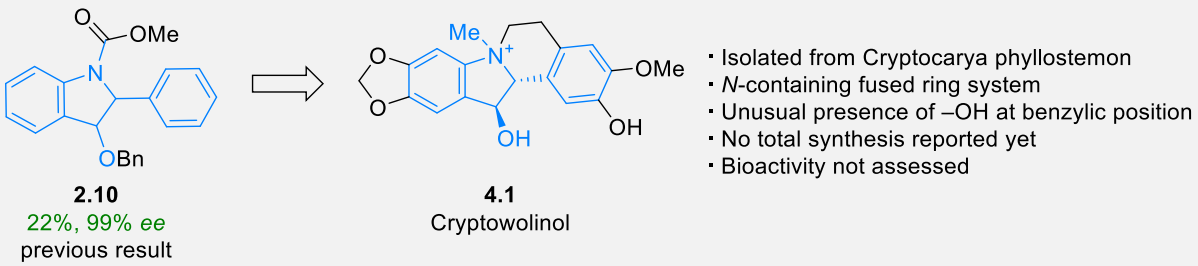
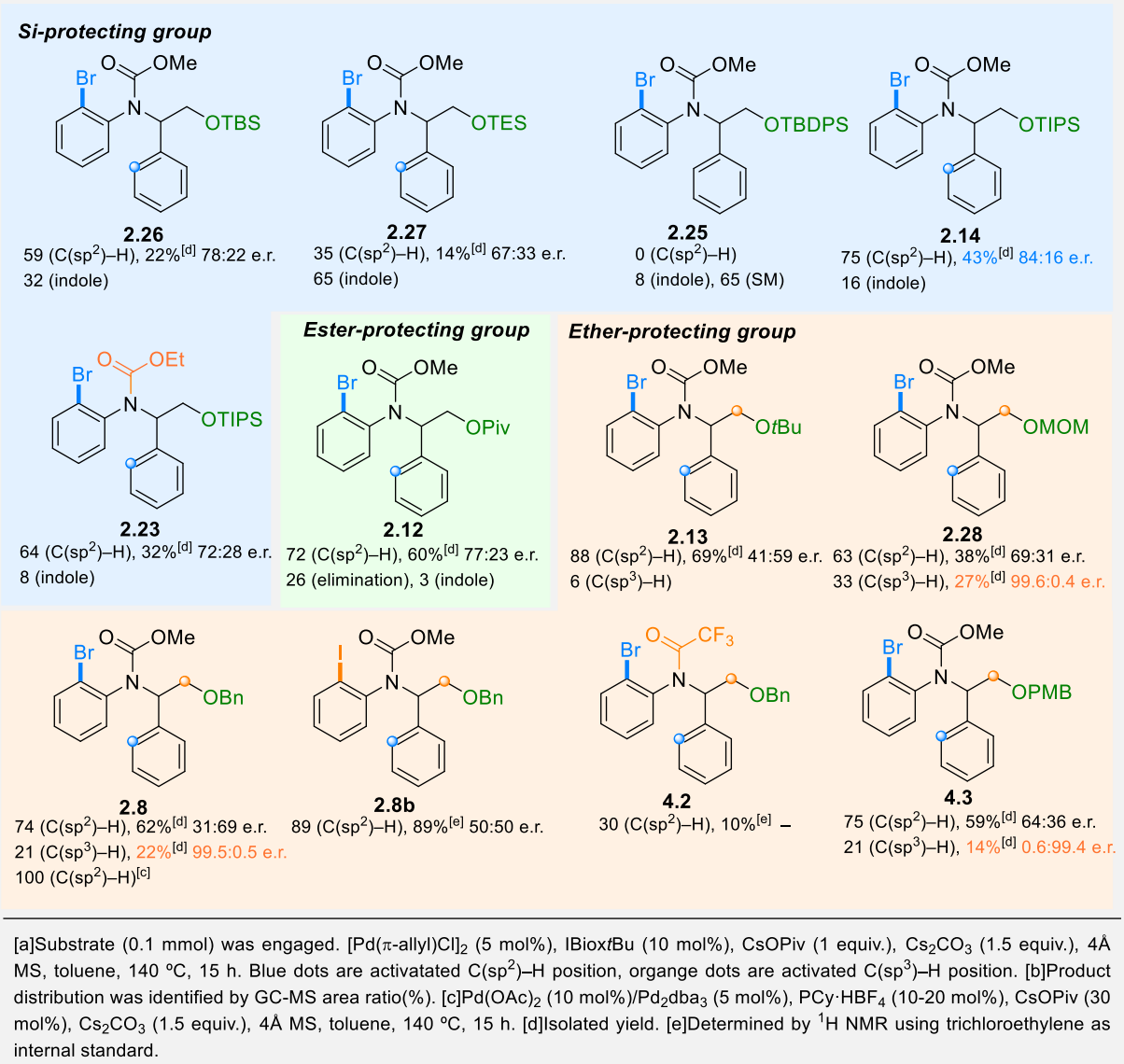


Figure 11. The idea of application of parallel kinetic resolution to the total synthesis of cryptowolinol

4.2 Result and discussion on the parallel kinetic resolution

4.2.1 Effect of protecting groups for parallel kinetic resolution

Firstly, we investigated the effect of protecting groups on the hydroxyl group on the perfect parallel kinetic resolution (Figure 12). Silyl-based protecting group resulted in a moderate to good parallel kinetic resolution, as discussed in chapter 2. As a trend, the bigger silyl protecting group tends to produce the higher e.r. of the C(sp^2)–H activation product. However, the TBDPS **2.25** group did not give the desired product, producing many unidentified compounds. Furthermore, the bulkier *N*-substituent **2.23** did not improve the selectivity. When chloride **2.14c** was used instead of bromide **2.14**, no reaction took place, even at elevated temperatures. Ester-type protecting group **2.12** was also introduced, which gave the C(sp^2)–H activation product in moderate e.r., presumably, resulting from parallel kinetic resolution as the silyl group did, producing the elimination product of the ester group. Surprisingly, C(sp^3)–H activation product alongside C(sp^2)–H activation product was only observed in the presence of the ether type-protecting group (**2.13**, **2.28**, **2.8**, **4.3**). It seems necessary to have at least one methylene next to oxygen not to increase the steric hindrance. MOM **2.28**, Bn **2.8** and PMB **4.3** could perform well to gain C(sp^3)–H activation products in moderate yield with excellent enantioselectivities. Aryl iodide **2.8b** showed high reactivity, but C(sp^2)–H arylation was dominant. When $COCF_3$ was used as a protecting group **4.2**, multiple compounds were observed in the reaction, with only 10% of the product observed by ^{1}H NMR.



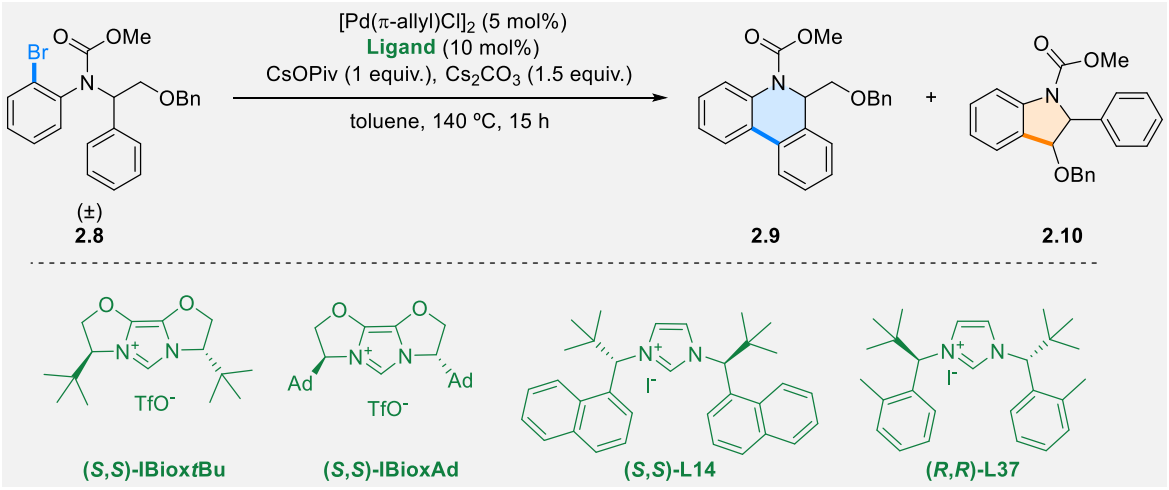
[a]Substrate (0.1 mmol) was engaged. $[Pd(\pi\text{-allyl})Cl]_2$ (5 mol%), IBiox*t*Bu (10 mol%), CsOPiv (1 equiv.), Cs_2CO_3 (1.5 equiv.), 4Å MS, toluene, 140 °C, 15 h. Blue dots are activatated C(sp^2)–H position, organge dots are activated C(sp^3)–H position. [b]Product distribution was identified by GC-MS area ratio(%). [c]$Pd(OAc)_2$ (10 mol%)/Pd_2dba_3 (5 mol%), PCy·HBF_4 (10-20 mol%), CsOPiv (30 mol%), Cs_2CO_3 (1.5 equiv.), 4Å MS, toluene, 140 °C, 15 h. [d]Isolated yield. [e]Determined by ^1H NMR using trichloroethylene as internal standard.

Figure 12. Effect of protecting groups for parallel kinetic resolution[a]

4.2.2 Ligand screening for parallel kinetic resolution

Ether-type protecting groups were shown to be superior for the parallel kinetic resolution to furnish C(sp^2)–H and C(sp^3)–H activation products during our screening. However, the yield and enantioselectivity of the parallel kinetic resolution remained poor. Therefore, in order to optimise chiral ligands towards parallel kinetic resolution discriminating C(sp^2)–H and C(sp^3)–H bonds by configurations of each enantiomer, a variety of ligands were screened (Table 15). **IBioxAd**, which gave better results on the desymmetrisation of enantiotopic C–H bonds,[102] produced a similar outcome in this reaction as **IBiox*t*Bu** gained (entries 1, 2). **L14** showed a slightly improved product distribution ratio of C(sp^2) vs C(sp^3), leading to a better e.r. on C(sp^2)–H activation product (entry 3). We found that **L37** could perform best, resulting in a nearly 1:1 mixture of two distinct products (entry 4). Those products were successfully isolated in 52% and 47% yields. HPLC analysis revealed the e.r. of each product to observe 92:8 e.r. for C(sp^2)–H and 0.2:99.8 e.r. for C(sp^3)–H activation product. The difference in yield and e.r. between **2.9** and **2.10** suggested that it was easier to perform C(sp^2)–H arylation compared to C(sp^3)–H arylation; thus, the formation of **2.9** was higher yield but slightly less enantioselectivity.

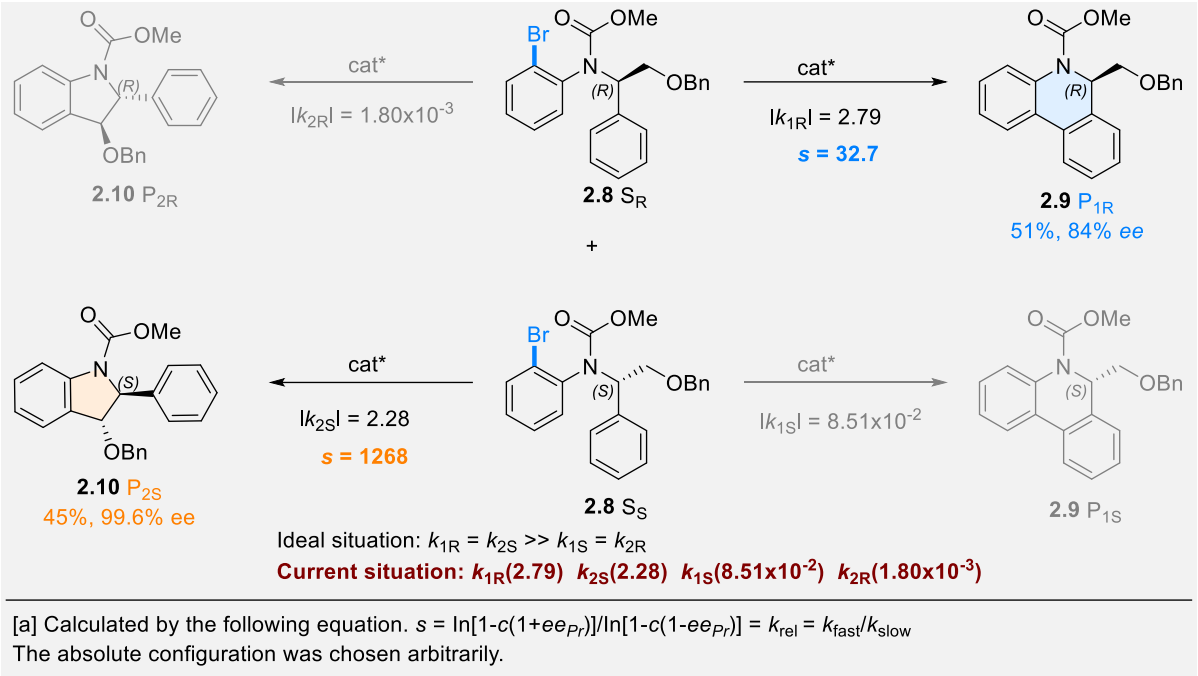
Table 15. NHCs screening for parallel kinetic resolution between C(sp^2)–H and C(sp^3)–H[a]



Entry	NHC	NMR yield of 2.9/2.10[b]	*ee* (%) of 2.9/*ee* (%) of 2.10
1	**IBiox*t*Bu**	71% (62%)[c]/ 25% (22%)[c]	38/99
2	**IBioxAd**	70% (60%)[c]/ 25% (21%)[c]	38/98
3	**L14**	56% (47%)[c]/ 42% (35%)[c]	68/99.6
4	**L37**	51% (52%)[c] 45% (47%)[c]	84/99.6

[a]**2.8** (0.1 mmol) was engaged. [b]Determined by ^{1}H NMR using trichloroethylene as internal standard. [c]Isolated yield.

The newly calculated reaction profile is shown below (Figure 13). Pleasingly, the *s* factors suggest a proper kinetic resolution, and relationships between the reaction rate constants turned into an almost ideal situation.

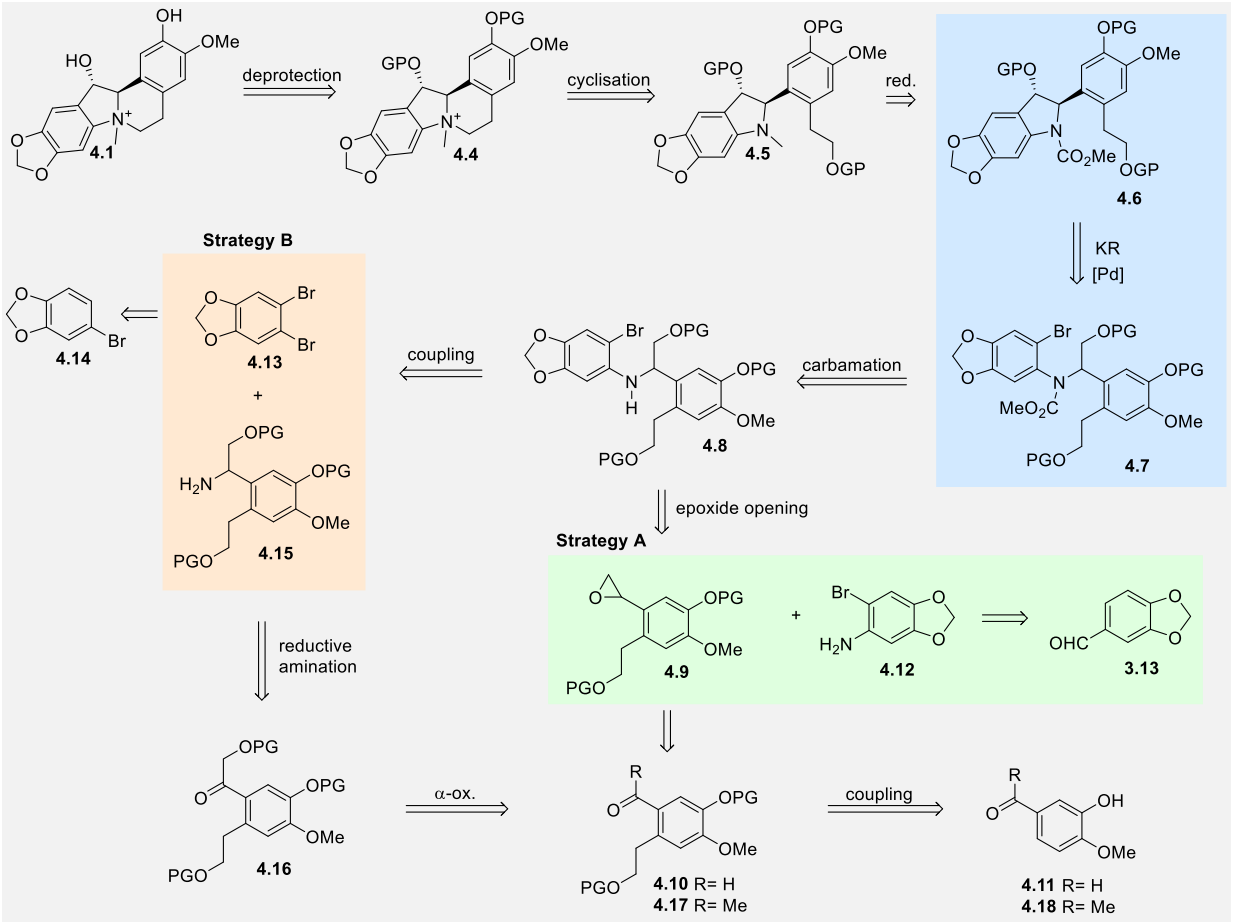


[a] Calculated by the following equation. $s = \ln[1-c(1+ee_{Pr})]/\ln[1-c(1-ee_{Pr})] = k_{rel} = k_{fast}/k_{slow}$
The absolute configuration was chosen arbitrarily.

Figure 13. Reaction profile with L37[a]

4.3 Synthetic plan for the total synthesis of cryptowolinol

In order to take advantage of optimised parallel kinetic resolution conditions, our synthetic plan was elaborated, as depicted in Scheme 57. The parallel kinetic resolution would generate two adjacent stereogenic centres of **4.6**, which will then be engaged in intramolecular cyclisation, followed by global deprotection towards yield **4.1**. Substrate **4.7** could be obtained either from strategy A or B. In strategy A, epoxide opening would provide amino alcohol moiety **4.8** from *ortho*-bromo aniline derivative **4.12** and epoxide **4.9**. The aniline bromide **4.12** will be readily prepared from piperonal **3.13** by bromination and the following nitration. In strategy B, C–N cross-coupling would synthesise the desired substrate **4.8**. In both strategies, epoxide **4.9** and amino alcohol with an alkyl chain **4.15** will be accessible from corresponding aryl ketone **4.18** or aldehyde **4.11**. The alkyl chain was considered to be introduced by cross-coupling or C–H alkylation.

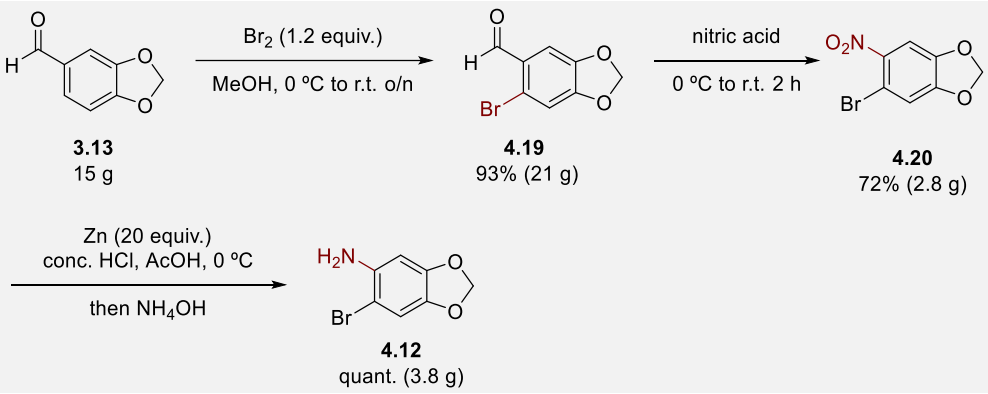


Scheme 57. Synthetic plan for the total synthesis of cryptowolinol

4.4 Result and discussion on strategy A

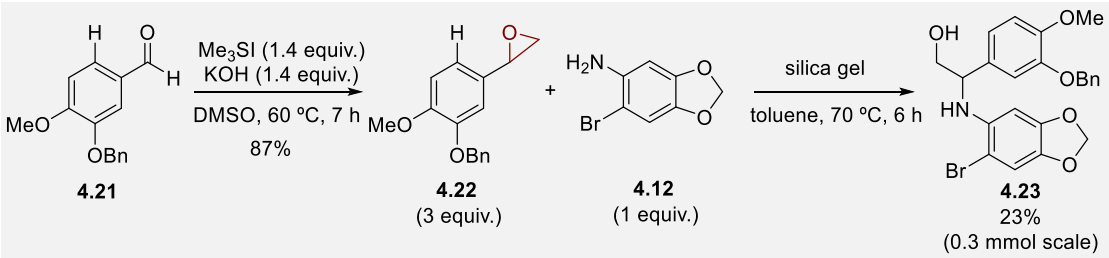
4.4.1 Towards the total synthesis of cryptowolinol: strategy A

In strategy A, we envisioned the epoxide opening with the *ortho*-bromo aniline derivative **4.12** to construct the amino alcohol moiety **4.8**. Firstly, we worked on synthesising the *ortho*-bromo aniline derivative **4.12** (Scheme 58). Piperonal **3.13** was brominated in 93%, and aldehyde **4.19** was transformed into a nitro group **4.20**. The reduction successfully occurred in the presence of zinc under acidic conditions to afford the desired aniline derivative **4.12** on the gram scale.



Scheme 58. Synthesis of *ortho*-bromo aniline derivative

Then we moved on to the synthesis of the epoxide, which proceeded smoothly to afford 87% of the desired epoxide as the model substrate **4.22** without an alkyl chain (Scheme 59). To understand the reactivity of epoxide opening, this model epoxide and *ortho*-bromo aniline derivative **4.12** were engaged and provided the desired compound **4.23** regioselectively but low yield. This result indicates that this strategy would be less promising in the actual system due to increased bulkiness on the *ortho*-position of the epoxide. Also, when considering the atom economy, this approach is less ideal. In addition to this low reactivity, various conditions to introduce an alkyl chain, such as Suzuki-Miyaura cross-coupling,[6] Murai reactions[184,185], and their modifications[29] did not give the desired *ortho*-functionalised aldehyde derivatives **4.10** for the actual system.



Scheme 59. Epoxidation and the opening as a model experiment

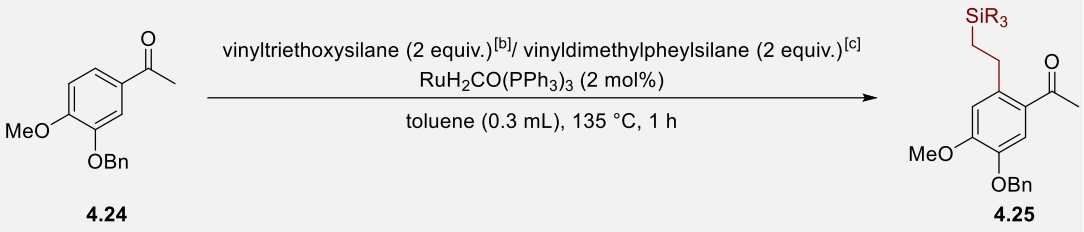
4.5. Result and discussion on strategy B

(with Sota Tamaki as visiting student from Osaka University for four months)

4.5.1 Murai reaction for alkyl chain introduction

In order to introduce the alkyl chain at the *ortho*-position to the aldehyde, many attempts, including Suzuki-Miyaura cross-coupling, Murai reaction and their modification, and changing protecting groups of the aldehyde, were made. However, the desired product has never been obtained. By changing the tactics, apocynin derivative **4.24** instead of vanillin derivative was chosen as starting material, which turned out to be a suitable substrate for the Murai reaction to introduce the alkyl chain. In a small screening of the reaction conditions, two different vinyl silanes were found to be compatible (Table 16, entries 1, 7), in which vinyldimethylpheylsilane gave better reactivity producing a di-functionalised product but lower selectivity. The excess of vinyltriethoxysilane did not change the efficiency (entry 2). Thus catalyst loading had to be increased to 6 mol% to obtain the product **4.25** (with vinyltriethoxysilane) in 75% isolated yield (entries 3-5) and scaled up to a 2 mmol scale for 96% isolated yield (entry 6). For introducing vinyldimethylphenylsilane, 3 mol% of Ru was required for complete conversion, and the vinylsilane was successfully decreased to 1.2 equivalents. Although the di-functionalised product was still observed by ^{1}H NMR and could not be avoided after several attempts, 4 mmol scales could give a 90% isolated yield (entry 8). Given the stability of these two different silyl groups against various conditions, we decided to take vinyldimethylpheylsilane as a coupling partner. Importantly catalysis tube could be replaced with a reflux condenser to obtain a comparable isolated yield (entry 9). Gratifyingly it could be scaled up to a decagram scale effectively (entry 10).

Table 16. Condition screening of Murai reaction[a]



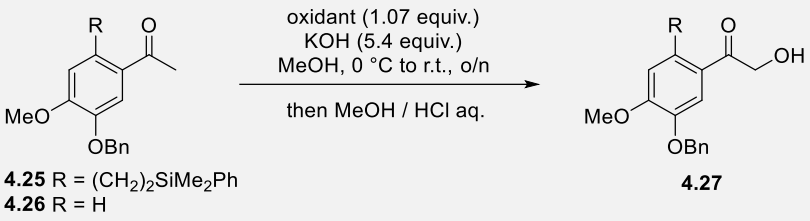
Entry	Deviation	GC-MS ratio [%] 4.24/4.25
1[b]	none	81:19
2	Vinyltriethoxysilane (4 equiv.)	82:18
3[b]	Ru (4 mol%)	28:75
4[b]	Ru (5 mol%)	8:92
5[b]	Ru (6 mol%)	0:100 (75)[d]
6[e]	Ru (6 mol%)	96[f]
7[c]	none	47:53[g]
8	Ru (3 mol%), vinyldimethylphenylsilane (1.2 equiv.)	90[h]
9	Ru (3 mol%), vinyldimethylphenylsilane (1.2 equiv.)	73[h][i]
10	Ru (3 mol%), vinyldimethylphenylsilane (1.2 equiv.)	74[j]

[a]**4.24** (0.2 mmol) was engaged with a catalysis tube. [b]Employed vinyltriethoxysilane. [c]Employed vinyldimethylphenysilane. [d]Determined by ^{1}H NMR using trimethoxybenzene internal standard. [e]2 mmol scales. [f]Isolated yield on 2 mmol scales. [g]Product ratios determined by ^{1}H NMR. [h]Isolated yield on 4 mmol scales. [i]Reflux condenser instead of catalysis tube. [j]Isolated yield on a decagram scale with a reflux condenser.

4.5.2 Synthesis of the amino alcohol moiety

In order to lead to the amino alcohol, we envisioned the sequence of α-oxidation and reductive amination. When employing substrate **4.26** without the alkyl silyl group, α-oxidation by PIDA worked better than PIFA (Table 17, entries 1, 2).[186] This condition was applied to 10 mmol scales to afford **4.27** in 53% isolated yield (entry 3). However, oxidation conditions in the presence of a silyl group turned out to be an issue, giving a complicated mixture (entry 4).

Table 17. Optimisation of α-oxidation with a model substrate

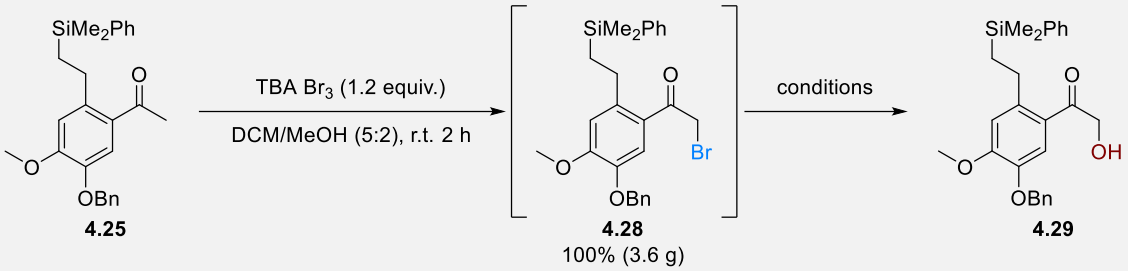


Entry	Oxidant	NMR yield of 4.27[b]
1	PIDA	60
2	PIFA	53
3	PIDA	53[c][d]
4[e]	PIDA	N.D.

[a]**4.26** (0.4 mmol) was engaged. [b]Determined by ^{1}H NMR using trimethoxybenzene as internal standard. [c]Isolated yield. [d]**4.26** (10 mmol) was engaged to obtain 1.45 g of **4.27**. [e]**4.25** (0.1 mmol) was enagaged.

Notably, Rubbotom oxidation with **4.25** gave unstable silyl enol ether, which ended up with a mixture of ketone and silyl enol ether after the extraction. A one pot strategy was also tested, but no oxidation could occur with *m*-CPBA. Then the Davis reagent was prepared and tested with **4.25**, but unfortunately, no product was detected. Considering these failures with the silyl alkyl chain, we took two steps to introduce the α-hydroxy group. α-Bromination worked well with tetrabutylammonium tribromide at room temperature in a quantitative yield of **4.28** (Table 18). **4.28** was engaged in an S_N2 reaction to possess a hydroxy group. Substitution of bromide needed optimisation, as shown in Table 18. We first tried cesium formate in methanol at reflux,[187] to obtain 62% NMR yield (entry 1). However, TLC shows several compounds, which makes purification difficult. Potassium formate created a more complicated TLC (entry 2). Sodium formate could give the cleanest TLC, as column chromatography was the easiest of the three conditions to obtain the product in 66% isolated yield of **4.29** on a 500 mg scale (entry 3). To increase the efficiency, different solvents were attempted and gave less yield (entries 4, 5). Finally, modification of the purification process allowed to produce **4.29** in 75% on gram scale (entry 6).

Table 18. Two steps strategy towards α-hydroxy group instead of one-step oxidation

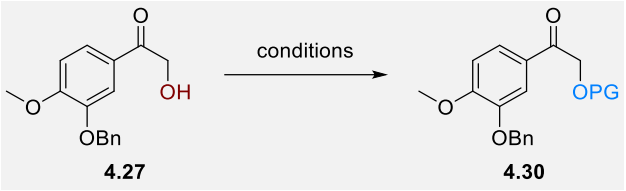


entry	conditions	NMR yield
1	Cesium formate (3 equiv), 70 ºC (reflux), 2 h	62
2	Potassium formate (3 equiv), 70 ºC (reflux), 12 h	52[a]
3	Sodium formate (3 equiv), 70 ºC (reflux), 12 h	66[a]
4	Sodium formate (3 equiv), EtOH/H_2O (85:15), 70 ºC, 12 h	39
5	Sodium formate (3 equiv), DMF, 70 ºC, 12 h	N.D.
6[c]	Sodium formate (3 equiv), 70 ºC (reflux), 12 h	75[b]

[a]Isolated yield on 500 mg scale. [b]Isolated yield on gram scale. [c]Directly purified by silica gel column chromatography after evaporation of the solvent.

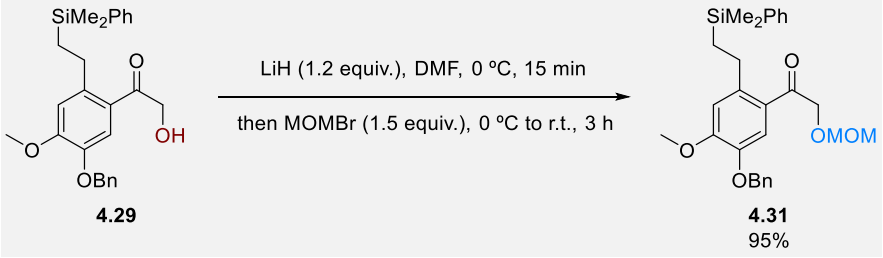
With α-hydroxy model compound in hand, we tried to protect this alcohol. We intended to introduce ether-protecting groups due to the result of early screening (Figure 12); thus, firstly benzyl group was selected from the point of view of easy deprotection at the late stage. However, there were issues for the reaction with this specific substrate **4.27** (Table 19). Benzyl 2,2,2-trichloroacetimidate in the presence of TfOH was not ideal (entry 1).[188] Different acids, such as PPTS, did not produce the desired product. Next, basis conditions were attempted. Strong base, NaO*t*Bu, produced α-functionalised product, leaving the alcohol intact (entry 2). A weak base, K_2CO_3, gave benzyl ester derived from C–C bond cleavage through the intramolecular oxygen atom rearrangement (entries 3, 4).[189] Although LiH as a base also did not work for benzyl protection, surprisingly, MOM was successfully introduced in 100% NMR yield of **4.30** after three hours. Then MOM protection was applied to substrate **4.29** to obtain the product **4.31** in 95% isolated yield (Scheme 60).

Table 19. Screening for protection of α-hydroxy group with the model substrate[a]



Entry	Conditions	Result
1[b]	Benzyl 2,2,2-trichloroacetimidate (1.2 equiv.) TfOH (10 mol%), dichloroethylene, 0 ºC to r.t. for 48 h	N.D.
2	BnBr (1 equiv.), NaO*t*Bu (1.5 equiv.), THF, 0 ºC, 1 h	α-C–H reacted
3	BnBr (1 equiv.), K_2CO_3 (1 equiv.), acetone, r.t., 18 h	N.D.
4	BnBr (1 equiv.), K_2CO_3 (1 equiv.), acetone, 50 ºC, 18 h	Benzyl ester obtained
5	BnBr (1.5 equiv.), LiH (1.2 equiv.), DMF, 0 ºC to r.t., 18 h	N.R.
6	MOMBr (1.5 equiv.), LiH (1.2 equiv.), DMF, 0 ºC to r.t., 3 h	100%

[a]**4.27** (0.1 mmol) was engaged. [b]**4.27** (0.2 mmol) was engaged.

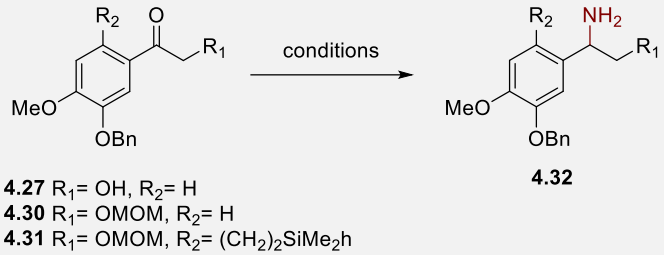


Scheme 60. MOM protection of α-hydroxy group

For the cross-coupling reaction towards the substrate for C–H activation, amine was sought to be introduced by reductive amination. Usually, reductive amination uses an excess of readily available primary/secondary amine as a nucleophile to form ketimine, aldimine or iminium that is subsequently reduced to a new C–N bond. Alternatively, an excess of commercially available aldehydes, such as formaldehyde or acetaldehyde, are employed. In the case of primary amine synthesis via reductive amination, we can employ hydrogen gas in the presence of Pd/C or Ni, which we want to avoid due to the benzyl group on the molecule. Given that MOM and benzyl have a similar outcome regarding enantioselectivity and yield of C(sp^3)–H activation product, the benzyl at the phenolic position might have been replaced by MOM. However, MOM-protected phenol turned out to be easily deprotected by a weak acid which meant that this strategy was not feasible. Therefore it was decided to keep the benzyl protection and undertake global deprotection at a late stage. Also, imine formed by ammonia should be a weak equilibrium heading to ketone, which sometimes makes reductive amination with ammonia impractical. Firstly, we tried reductive amination of model substrate **4.30** with ammonium acetate in methanol as a solvent, which led to poor reactivity (Table 20, entry 1)—harsher conditions with acetic acid as solvent led to conversion with **4.27**. However, the obtained product was found to be the directly reduced diol product (entry 2). Recently, Bhattacharyya and co-workers reported titanium complex-

mediated primary amine synthesis.[190] They proposed a titanium (IV) complex as a stable intermediate generated by the nucleophilic addition of ammonia to carbonyl, which is either reduced directly or via a transient imine species. Indeed, after temperature optimisation, where we found 60 ºC is required for our case, these conditions could give us desired amino alcohol moiety with MOM-protected substrate **4.30** in 94% NMR yield (entry 3) but did not work in the presence of free alcohol **4.27** (entry 4). Finally, the real substrate **4.31** with an alkyl chain was applied and transformed into the desired compound **4.32** in 67% NMR yield (entry 5).

Table 20. Condition screening of reductive amination[a]

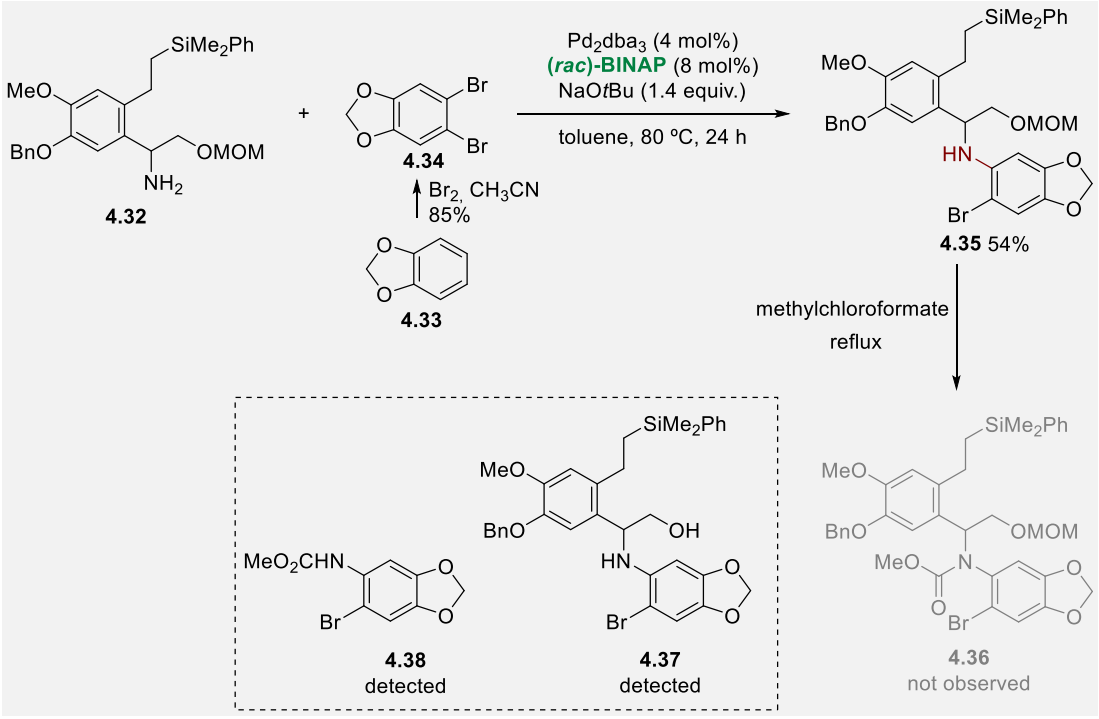


Entry	R_1/R_2	Conditions	Results[b]
1	OMOM/H	NH_4OAc (10 equiv.), $NaBH_3CN$ (3 equiv.), MeOH, r.t.	N.D.
2	OH/H	NH_4OAc (10 equiv.), $NaBH_3CN$ (3 equiv.) AcOH, r.t., 30 min	N.D.(96%)[c]
3	OMOM/H	$Ti(OiPr)_4$ (2 equiv.), NH_3 (5 equiv.), EtOH, 60 ºC, 6 h then $NaBH_4$ (2 equiv.), 0 ºC to r.t., 3 h	94%
4	OH/H	$Ti(OiPr)_4$ (2 equiv.), NH_3 (5 equiv.), EtOH, 60 ºC, 6 h then $NaBH_4$ (2 equiv.), 0 ºC to r.t., 3 h	N.D.
5[d]	OMOM/ $(CH_2)SiMe_2Ph$	$Ti(OiPr)_4$ (2 equiv.), NH_3 (5 equiv.), EtOH, 60 ºC., 6 h then $NaBH_4$ (2 equiv.), 0 ºC to r.t., 3 h	67%

[a]Substrate (0.2 mmol) was engaged. [b]NMR yield determined by ^1H NMR using trichloroethylene as internal standard. [c]Diol was generated via direct reduction of the ketone. [d]**4.32** (0.1 mmol) was employed.

4.5.3 C–N cross-coupling reaction and carbamation

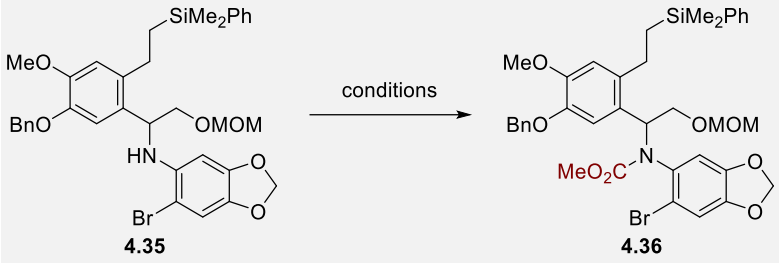
With the synthesised amino alcohol **4.32** in hand, we started a cross-coupling reaction with dibromo 5,6-dibromobenzo[*d*][1,3]dioxole **4.34**. Fortunately, **4.35** was produced in 54% isolated yield in the presence of Pd_2dba_3 as Pd source, **(*rac*)-BINAP** as ligand and NaO*t*Bu as a base (Scheme 61).[191] In contrast, copper-catalysed C–N coupling did not work for these substrates.[192]



Scheme 61. Buchwald-Hartwig cross-coupling and subsequent carbamation

Subsequently, carbamation was taken place. However, unexpectedly, carbamation gave a messy reaction mixture, in which we detected MOM deprotected compound **4.37** and C–N bond cleavage **4.38** occurred. This result indicated MOM group seemed vulnerable under neat carbamation conditions. Then other milder conditions were tested (Table 21). In order to activate methyl formate, triethylamine was employed to find no conversion (entry 1).[193] More reactive triphosgene with pyridine[194] and dimethyl carbonate with DBU was also investigated. However, unfortunately, nothing could provide the desired compound **4.36** (entries 2-4). Deprotonation by Grignard reagent and nucleophilic attack to dimethylcarbonate also did not give any conversion (entry 5).[195]

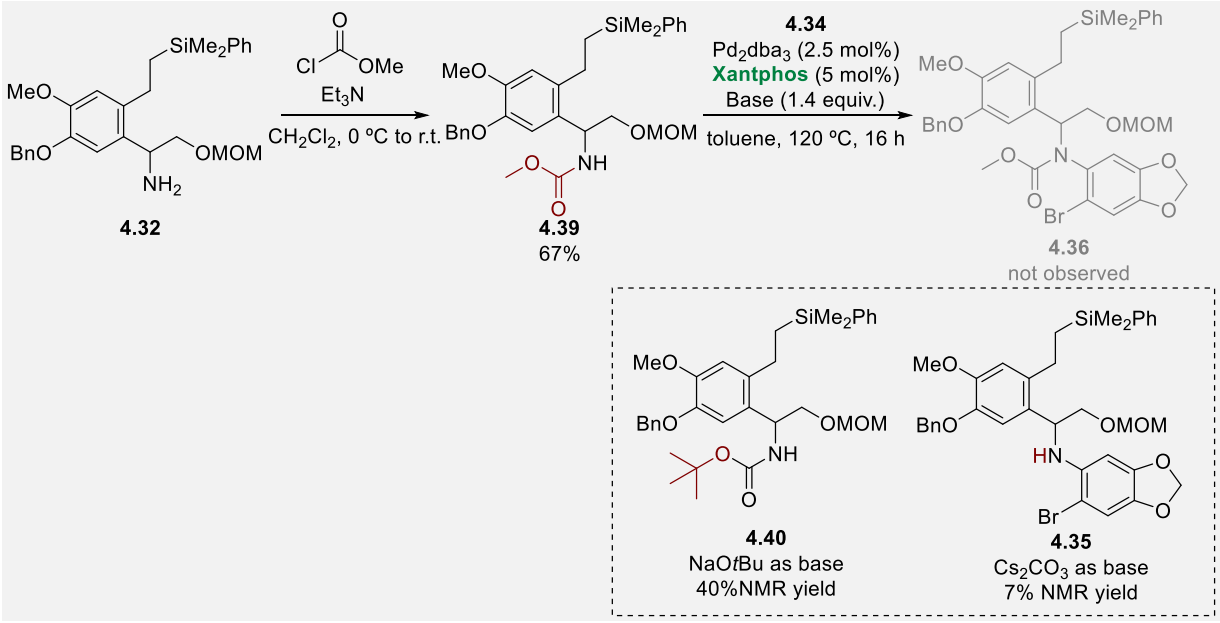
Table 21. Other conditions for carbamate introduction[a]



Entry	Conditions	Results
1	methyl chloroformate (5 equiv.), Et_3N (10 equiv.), CH_2Cl_2, r.t., o/n	N.R.
2	triphosgene (3 equiv.), pyridine (32 equiv.), CH_2Cl_2, 0 ºC to r.t., 4 h, then MeOH	MOM deprotected
3	Dimethyl carbonate, DBU (1.2 equiv.), 90 ºC, 24 h	N.R.
4	Dimethyl carbonate, DBU (1.2 equiv.), 100 ºC, 30 min, MW	N.R.
5	Dimethyl carbonate (17 equiv.), MeMgCl (17 equiv.) THF, reflux, o/n	N.R.

[a]**4.34** (0.02 mmol) was engaged.

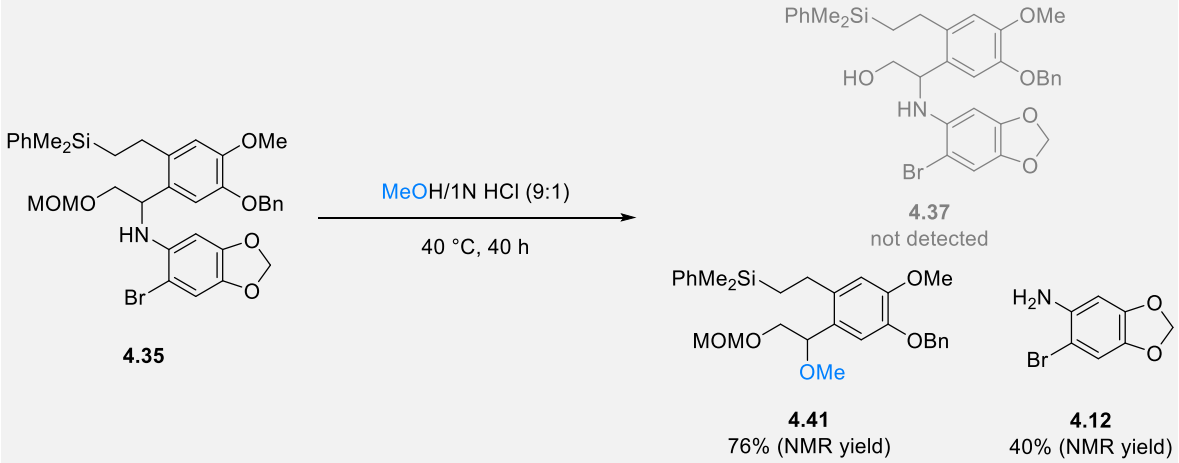
Since no reaction could introduce carbamate, the reaction order was changed; firstly, carbamation of primary amine, then cross-coupling was undertaken (Scheme 62). **4.39** was engaged in cross-coupling in the presence of NaO*t*Bu as a base, which provided carbamate exchange to the butoxy group in 40% NMR yield of **4.40**. Owing to this, Cs_2CO_3 was employed instead, and we detected hydrolysed product **4.35** in 7% NMR yield from almost no reaction crude mixture.



Scheme 62. Changing the reaction order, carbamation and cross-coupling

In order to get a substrate for C–H activation, we then tried to deprotect the MOM group in acidic conditions to do carbamation in the presence of free alcohol, then MOM protection again. As a typical condition of deprotection of MOM, we exposed **4.39** to a mixture of excess 1N HCl in MeOH (Scheme 63). Surprisingly no reaction was observed at room temperature, but at 40 ºC provided **4.12** and **4.41**

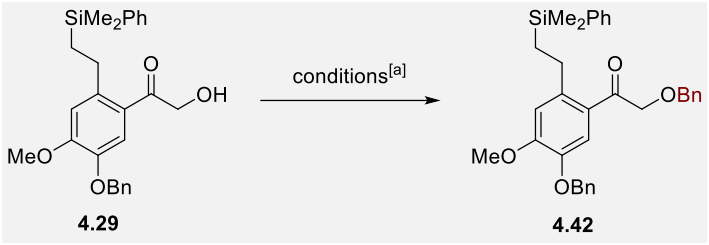
without **4.37** detected. Presumably, ammonium salt worked as a good leaving group to accept methoxide as a nucleophile in the S_N2 pathway. In order to avoid this substitution, the solvent was changed into THF and stirred at 40 ºC for 40 h, but this time conversion was not observed.



Scheme 63. Unexpected substitution with methoxide

In spite of unexpected complications with this seemingly simple process, we once again attempted to protect α-hydroxy group with the benzyl group. When we had previously attempted benzyl protection, we had to change the solvent from reported Et_2O to DCE due to the insolubility of the model substrate **4.27**, a solid without an alkyl chain, which could be the reason for our lack of observed reactivity. However, **4.29** displayed no such solubility issue in Et_2O. Thus, we again attempted an acid-catalysed benzylation process to protect this material **4.29** (Table 22). The first test showed reaction proceeded in 47% NMR yield, with unreacted starting material in 16% NMR yield (entry 1). Then we increased the loading of acetimidate (1.5 equiv. and 3 equiv., entries 2, 3), which resulted in a lower product yield. The reaction with weaker acid, PPTS, did not proceed (entry 4). When CPME was used as a solvent, the reaction was less efficient (entry 5). Neutral benzyl protection with the Dudley reagent[196,197] gave a full conversion, albeit with 20% NMR yield (entry 6). Mixed solvents such as CH_2Cl_2/hexane facilitated the decomposition of starting material as well as using CH_2Cl_2 as the sole solvent (entries 7, 8). TMSOTf was not a sufficient alternative to TfOH as a catalyst (entry 9). Furthermore, the direct substitution of bromide with benzylalkoxide was tried to detect product **4.42** in only 17% NMR yield and 10% of proto-dehalogenated product **4.25**.

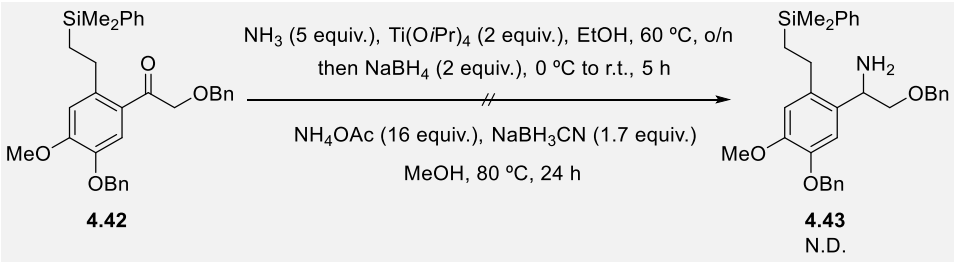
Table 22. Screening of benzyl protection condition[a]



Entry	Conditions	Result[b] 4.29/4.42
1	Benzyl 2,2,2-trichloroacetimidate (1.2 equiv.), TfOH (10 mol%), Et_2O, 0 ºC to r.t., 20 h	16/47
2	Benzyl 2,2,2-trichloroacetimidate (1.5 equiv.), TfOH (10 mol%), Et_2O, 0 ºC to r.t., 20 h	6/22
3	Benzyl 2,2,2-trichloroacetimidate (3 equiv.), TfOH (10 mol%), Et_2O, 0 ºC to r.t., 20 h	0/5
4	Benzyl 2,2,2-trichloroacetimidate (1.2 equiv.), PPTS (10 mol%), Et_2O, 0 ºC to r.t., 20 h	N.R.
5	Benzyl 2,2,2-trichloroacetimidate (1.2 equiv.), TfOH (10 mol%), CPME, 0 ºC to r.t., 48 h	27/24
6	Dudley reagent (2 equiv.), MgO (2 equiv.), CF_3Ph, 83 ºC, 24 h	0/21
7	Benzyl 2,2,2-trichloroacetimidate (1.2 equiv.), TfOH (10 mol%), CH_2Cl_2/hexane, 0 ºC to r.t., 20 h	Decomp.
8	Benzyl 2,2,2-trichloroacetimidate (1.2 equiv.), TfOH (10 mol%), CH_2Cl_2, 0 ºC to r.t., 20 h	Decomp.
9	Benzyl 2,2,2-trichloroacetimidate (1.5 equiv.), TMSOTf (10 mol%), Et_2O/hexane (2:1), 0 ºC to r.t., 20 h	24/17

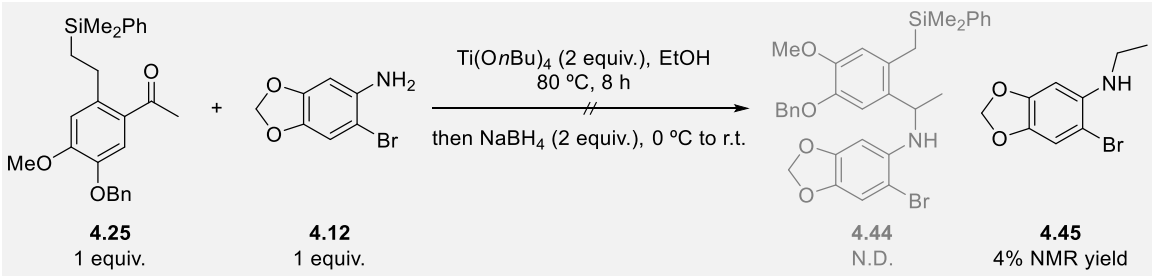
[a]Conditions: **4.29** (0.025 mmol) was engaged. [b]NMR yield determined by ^1H NMR using trichloroethylene as internal standard.

As the next step, we moved to reductive amination with benzyl-protected substrate **4.42**, employing the previously optimised condition (Scheme 64). However, unexpected reactivity was observed, and the desired primary amine derivative **4.43** was not detected. Furthermore, the other typical condition with NH_4OAc did not produce the desired product. Also, reductive amination with **4.29** in the presence of free alcohol was attempted under several conditions, which unfortunately gave unsatisfactory results.



Scheme 64. Attempts of reductive amination with α-benzyl-protected substrate

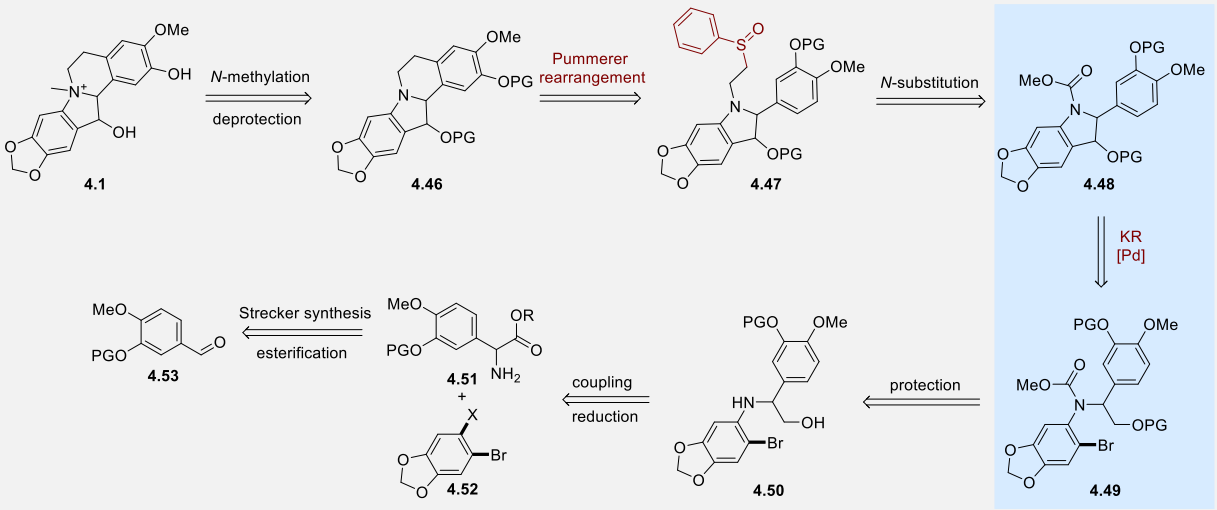
In order to shorten the sequence, reductive amination with *ortho*-bromo-aniline derivative **4.12** was attempted with **4.25** (Scheme 65). As a result, the ethanol-coupled product **4.45** was detected in 4% NMR yield, whilst most of the starting material was unreacted.



Scheme 65. Reductive amination with aryl ketone and *ortho*-bromo-aniline derivative in the presence of Ti(O*n*Bu)$_4$

4.5.4 New synthetic plan

In order to avoid reductive amination and to obtain modifiability of protecting group at the hydroxy group, the new synthetic plan was reconsidered, as shown in Scheme 66. In contrast to the previous scheme, the C2 unit is placed on the *N*-substituent, and the tetrahydroisoquinoline of **4.46** will be constructed by C–C bond formation enabled by the Pummerer rearrangement.[198] Substrate **4.49** for the parallel kinetic resolution is closer to model substrate **2.8**. The desired amino acid ester **4.51** for C–N coupling should be accessible from the corresponding isovaniline derivative **4.53** by a sequence of the Strecker amino nitrile synthesis and the Pinner reaction. This route is currently ongoing.



Scheme 66. New retrosynthetic scheme towards cryptowolinol

4.6 Outlook and conclusion

In chapter 4, we successfully optimised reaction conditions for parallel kinetic resolution, which can be applied to the total synthesis of cryptowolinol. Benzyl group at hydroxyl group and methyl carbamate at secondary amine (**2.8**) were found the best using chiral NHC as a ligand to afford a 1:1 mixture of C(sp^2)–H activation product **2.9** and C(sp^3)–H activation product **2.10** with excellent enantioselectivities (Figure 14). Calculated selectivity factors and reaction rate constants showed that proper resolution was achieved.

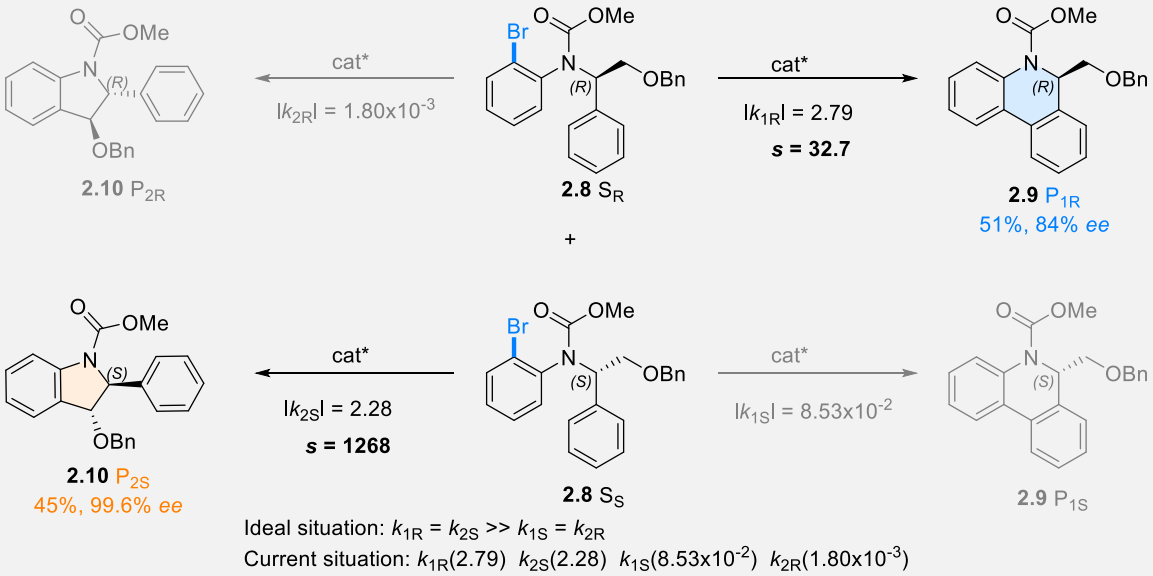
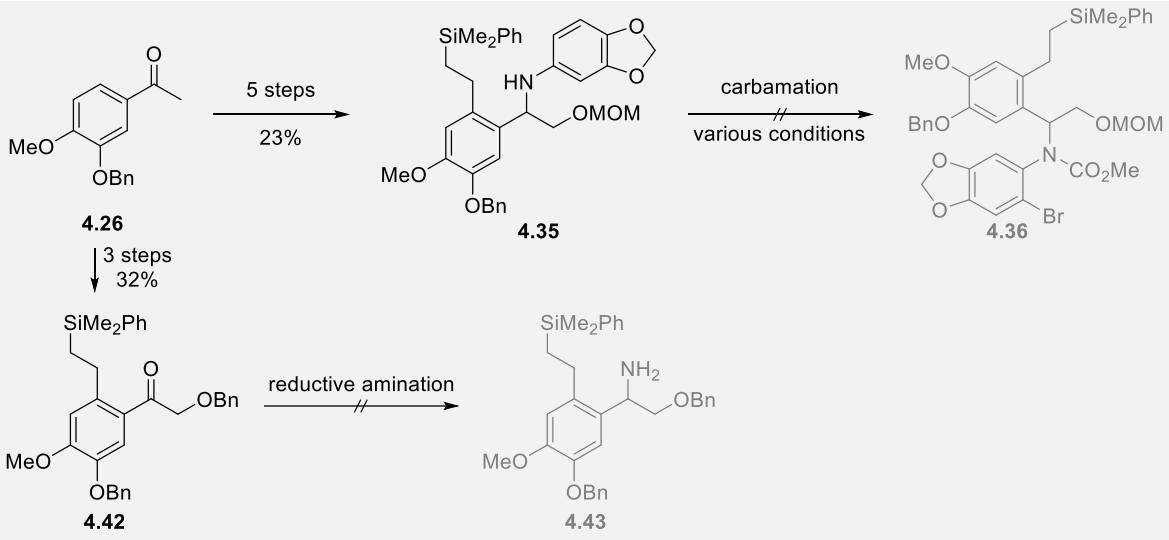


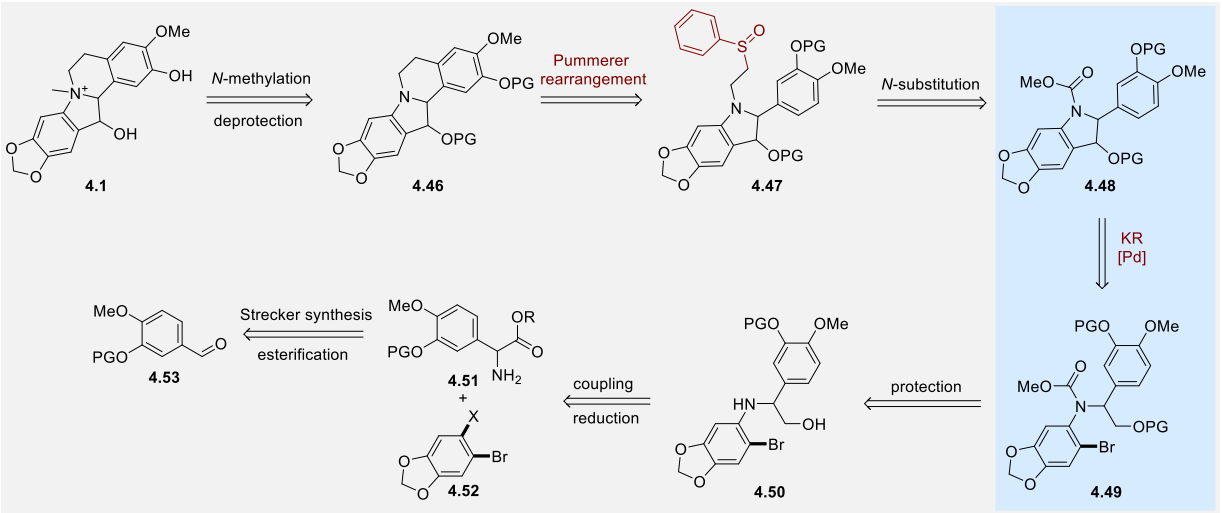
Figure 14. Parallel kinetic resolution between C(sp^2)–H and C(sp^3)–H bonds

To apply this methodology for the total synthesis, we commenced substrate synthesis for C–H activation (Scheme 67). First, epoxide opening with *ortho*-bromo aniline derivative and the corresponding styrene oxide displayed low efficiency. Then we moved on to C–N coupling strategy. However, a carbamation of **4.35** in the presence of the MOM group was found to be an issue. Furthermore, the benzyl group of **4.42** was problematic in the reductive amination to obtain the precursor **4.43** for the following coupling reaction.



Scheme 67. Attempts towards the substrate for C–H activation

Because of low protecting group modifiability and long steps towards the substrate for C–H activation, a new synthetic plan was made (Scheme 68). The introduction of the alkyl chain was placed after the C–H activation to employ a more similar substrate as model substrate **2.8**. Therefore we will start from the Strecker amino nitrile synthesis using isovanillin **4.53**, which will lead to the desired amino acid moiety **4.51**. After parallel kinetic resolution via Pd(0)-catalysed C–H activation employing **4.49**, the Pummerer rearrangement will take place to access the cyclised product **4.46**, followed by ammonium salt formation and global deprotection to obtain cryptowolinol **4.1**. This route is currently ongoing.



Scheme 68. New synthetic plan for the total synthesis of cryptowolinol

5. Synthesis of isoindolines via 1,4-Pd shift-mediated double C–H activation

It is adapted from T. Miyakoshi, N. E. Niggli, O. Baudoin, *Angew. Chem. Int. Ed.* **2022**, *61*, e202116101.[199]

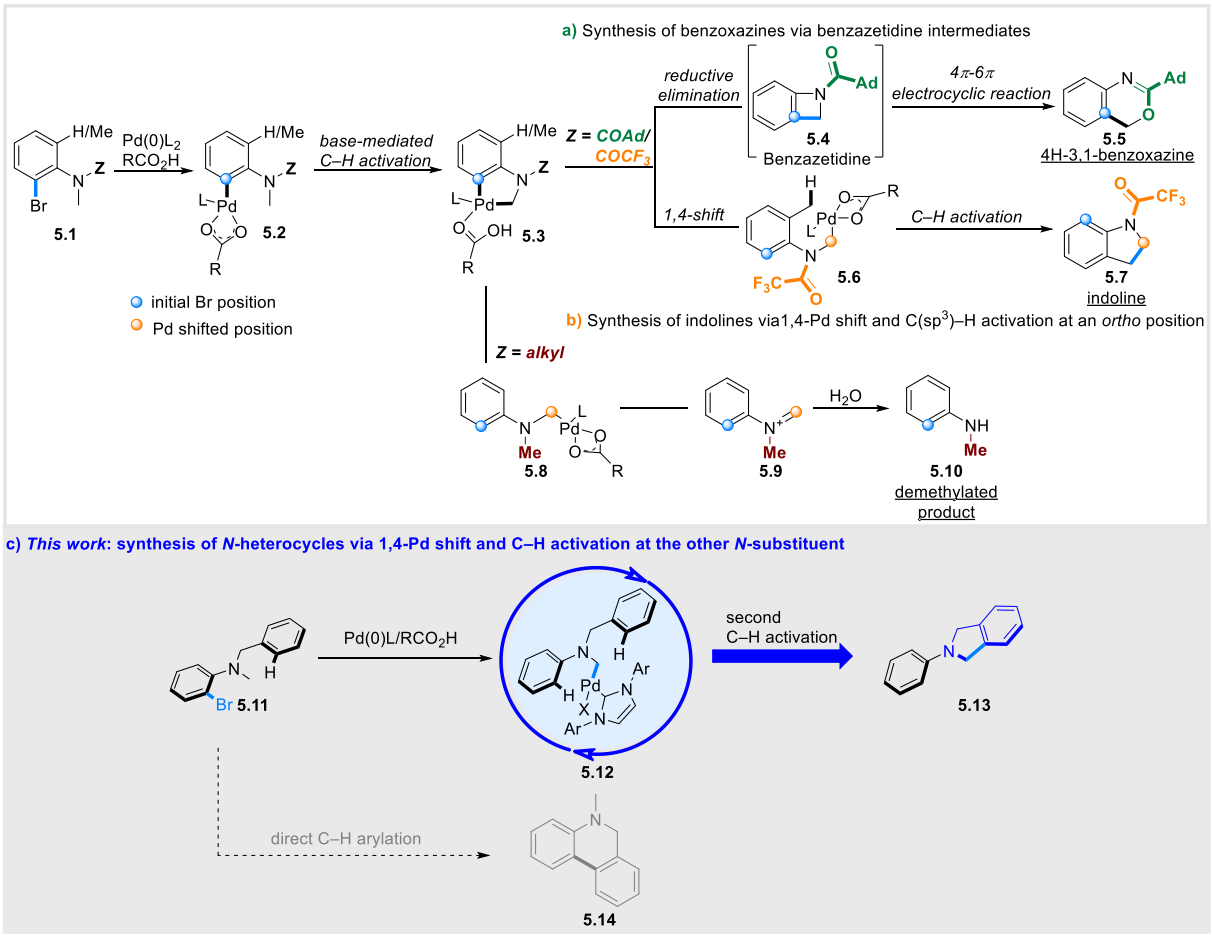
5.1 Introduction

Nitrogen-containing heterocycles are privileged motifs in synthetic organic chemistry due to their natural abundance and prevalence in agrochemicals, functionalised materials, and pharmaceuticals.[200] In particular, they account for over 60% of small-molecule drugs approved by the FDA. Thus, significant effort has been devoted to the development of new synthetic routes towards the synthesis of these essential building blocks. Over the last two decades, C–H activation-based methods have been established as powerful tools for the atom- and step-economical de novo construction of diverse azacycles.[201,202] In particular, Pd(0)-catalysed C(sp^3)–H activation allows the direct formation of C(sp^2)–C(sp^3) bonds and the generation of nitrogen heterocycles from easily accessible C(sp^2)–(pseudo)halides.[57] For instance, the reaction of 2-bromo-*N*-methyl anilines **5.1** equipped with a bulky carbonyl substituent on the nitrogen atom was shown to produce benzoxazines **5.5** via C(sp^3)–H activation at the *N*-methyl group (Scheme 69a), giving rise to 5-membered palladacycle **5.3**, which upon reductive elimination generates benzazetidine **5.4**. The latter is unstable under the reaction conditions and undergoes a 4π/6π electrocyclic cascade to furnish product **5.5**. In addition, *N*-demethylation **5.10** was observed when an *N*–alkyl substituent was present instead of the carbonyl group, which presumably occurs through reversible reprotonation of palladacycle **5.3** to furnish σ-alkyl palladium intermediate **5.8** and demetallation via formation of an iminium species **5.9**.[155,203,204] The formation of σ-alkyl palladium complex **5.6**/**5.8** from the oxidative addition complex arising from **5.1** and the active Pd(0) catalyst formally results in a 1,4-Pd shift. 1,4-Pd shifts were initially reported by Heck in 1972[146] and subsequently exploited to generate hard-to-reach C(sp^2)–C(sp^2) and C(sp^2)–C(sp^3) bonds remotely from C(sp^2)–halides.[72,75,205]

Inspired by seminal work by Dyker,[47–50] the Baudoin group showed that a 1,4-Pd shift onto an adjacent position to an oxygen or nitrogen atom gives rise to a σ-alkyl palladium complex which can effect further C(sp^3)–H activation on a substituent located at the next *ortho* position.[154] Accordingly, 2-bromo-*N*-methylanilines **5.1**, wherein the lone pair of the nitrogen atom was deactivated by a trifluoroacetyl group to avoid the abovementioned demethylation process, gave rise to indolines **5.7** via σ-alkyl palladium intermediate **5.6** (Scheme 69b), albeit with a modest reaction scope. This 1,4-Pd shift-based strategy allowing the remote construction of C(sp^3)–C(sp^3) bonds via twofold C(sp^3)–H bond cleavage was recently employed to synthesise cyclopropanes.[157] Of note, it was also shown that σ-alkyl palladium intermediates generated by 1,4-Pd shift could be trapped through various processes.[51,58,158–160]

Following up on those works, we sought to expand the scope of this 1,4-Pd shift-based strategy to access a valuable azacycle by installing a suitable *N*-substituent which would trap the transient σ-alkyl palladium intermediate **5.12** by C(sp^2)–H activation (Scheme 69c). Herein we report the strategy implementation for the synthesis of isoindolines **5.13**, which cannot be easily accessed by direct Pd(0)-catalysed C(sp^3)–H activation[57] and is a biologically relevant heterocycle.[206] At the onset of this work, we realised that developing such reactions would be challenging because 1. the desired migration

pathway would compete with the direct C–H arylation leading to 5,6-dihydrophenanthridines **5.14**[88] and 2. *N*-demethylation could occur without an electron-withdrawing group adjacent to the nitrogen atom. However, previous studies pointed at the effect of the base and the ligand to favour the 1,4-Pd shift pathway over the direct reaction[154,157] and suggested that the desired selectivity could be achieved by studying these factors.



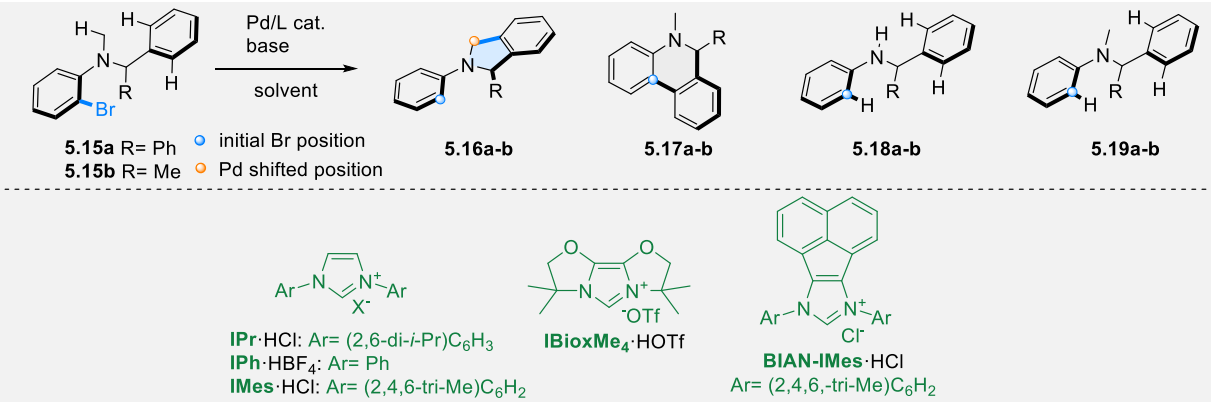
Scheme 69. Pd(0)-catalysed C(sp^3)–H activation of 2-bromo-*N*-methyl-anilines for nitrogen heterocycles

5.2 Result and discussion

5.2.1 Reaction optimisation

We set out to explore the reactivity of several *o*-bromoaniline substrates using three different catalytic systems, which proved successful in the previous Pd(0)-catalysed C(sp^3)–H activation reactions, i.e. $[Pd(\pi\text{-allyl})Cl]_2$/NHC,[91,102] Pd_2dba_3/PR_3[154,155] and $Pd(PPh_3)_4$[157] (Table 23, entries 1–5, see Table S1 for further details). As a result, **IBioxMe$_4$**[102,207] was identified as the optimal ligand to convert substrate **5.15a** to the desired isoindoline **5.16a** in 99% NMR yield and minimise the formation of the direct C(sp^2)–H arylation product **5.17a**, *N*-demethylated product **5.18a**, and proto-dehalogenated product **5.19a** (entry 1). Interestingly, the previously developed conditions for 1,4-Pd shift-mediated double C–H activation reactions employing phosphine ligands provided **5.17a** as the primary product (entries 3–5). In contrast, NHC ligands[208,209] seem to favour the 1,4-Pd shift on the *N*-methyl group (entries 1, 2). Motivated by these results, we turned our attention to the more challenging substrate **5.15b** bearing a methyl instead of the second phenyl group at the α position to the nitrogen atom. Indeed, in this case, the trapping of the σ-alkyl palladium intermediate arising from 1,4-Pd shift (see **5.12**, Scheme 69c) by C(sp^2)–H arylation is less favourable than in **5.15a** since fewer C(sp^2)–H bonds are accessible. In addition, the direct C(sp^3)–H arylation at the α-Me group[60] could potentially be an additional competitive reaction. With substrate **5.15b**, **IMes** was found to be superior to the bis-oxazoline-based IBiox NHC to reduce the amount of *N*-demethylated product **5.18b** and increase the yield of isoindoline **5.16b** (entries 6 and 7, see also Tables S2–S3). Further optimisations led to identifying *m*-xylene as the optimal solvent under slightly more diluted conditions, at 110°C and in the presence of 5Å MS (entry 8). Then, the effect of the ligand structure was further investigated (Table S12). No reaction occurred with **IPh**, bearing unsubstituted Ph groups (entry 9). The IMes analogue **BIAN-IMes**[210] also furnished isoindoline **5.16b**, but with a reduced yield (entry 10). Under the optimised conditions (entry 8), isoindoline **5.16b** was formed in a high yield (78% upon isolation) and selectivity.

Table 23. Optimisation of the isoindoline synthesis[a]

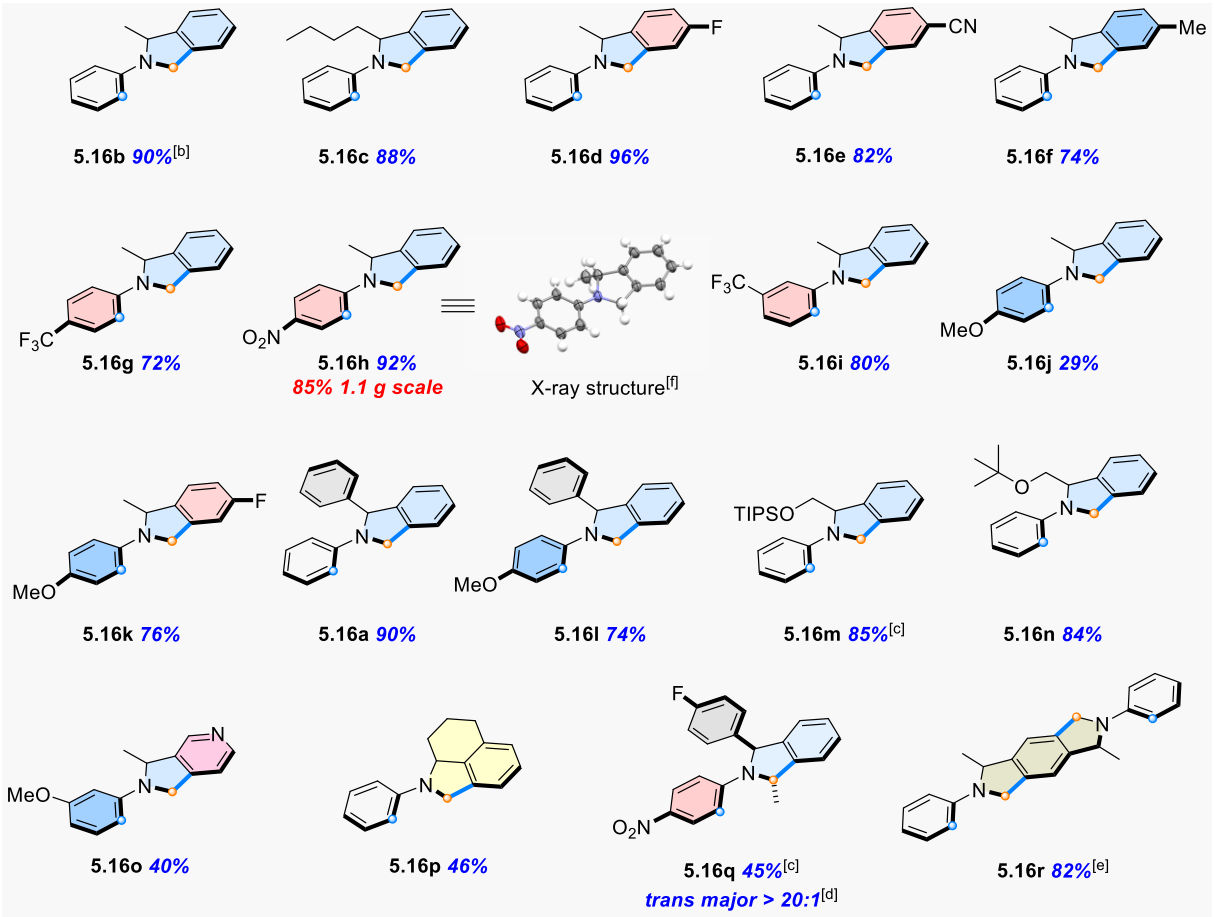


Entry	Substrate	Pd/L	Temp[°C]/Solvent	Yield[b] 5.16a,b/5.17a,b/5.18a,b/5.19a,b
1	a	[Pd(π-allyl)Cl]$_2$ /**IBioxMe$_4$**	140/toluene	99 : 0 : 0 : 0
2	a	[Pd(π-allyl)Cl]$_2$/**IPr**	140/toluene	73 : 0 : 26 : 0
3	a	Pd$_2$dba$_3$/**PCy$_3$**	140/toluene	10 : 61 : 11 : 2
4	a	Pd$_2$dba$_3$/**PPh$_3$**	140/toluene	0 : 61 : 30 : 9
5[c]	a	Pd(**PPh$_3$**)$_4$	140 toluene/DMSO	0 : 43 : 18 : 9
6	b	[Pd(π-allyl)Cl]$_2$ /**IBioxMe$_4$**	140/toluene	68 : 0 : 32 : 0
7	b	[Pd(π-allyl)Cl]$_2$/**IMes**	140/toluene	82 : 0 : 17 : 1
8	b	[Pd(π-allyl)Cl]$_2$/**IMes**	110/*m*-xylene[d,e]	94(78)[f] : 0 : 5 : 1
9	b	[Pd(π-allyl)Cl]$_2$/**IPh**	110/*m*-xylene[d,e]	2: 0 : trace : trace
10	b	[Pd(π-allyl)Cl]$_2$ /**BIAN-IMes**	110/*m*-xylene[d,e]	80 : 0 : 9 : 4

[a]Reactions were performed on a 0.1 mmol scale using 10 mol% [Pd] and ligand, Cs_2CO_3 (1.5 equiv.), CsOPiv (30 mol%), solvent (c 0.1 M) and 4Å MS for 15 h. [b]NMR yield determined using trichloroethylene as internal standard. [c]Using KOPiv (2 equiv.) instead of Cs_2CO_3/CsOPiv and toluene/DMSO 95:5. [d]c 0.067 M. [e]Using 5Å MS. [f]Yield of the isolated product.

5.2.3 Scope of the reaction

With the optimised conditions, the versatility of the 1,4-Pd shift-based isoindoline synthesis was investigated (Scheme 70). In addition to the aryl bromide precursor, the electron-rich **IMes** ligand allowed the use of the corresponding aryl chloride with similar efficiency (90%, **5.16b**). Furthermore, another alkyl group could be introduced at the α position to the nitrogen atom without detrimental effect on the yield (**5.16c**). Electron-withdrawing or -donating groups on the remote aryl ring were well tolerated, affording the corresponding isoindolines in good to excellent yields (**5.16d–f**). In addition, substrates bearing electron-withdrawing groups in the *meta* or *para* position of the *N*-aryl ring also reacted in good yields **(5.16g–i**, 72–92%). Of note, the reaction providing isoindoline **5.16h** was successfully conducted on a gram scale without significantly impacting the efficiency. However, a significant yield drop was observed upon introducing an electron-donating group on the *N*-aryl ring (**5.16j**). This effect was nevertheless counter-balanced by installing either an electron-withdrawing group on the remote aryl ring (**5.16k**) or employing a more reactive *gem*-diphenyl substrate (**5.16l**). In addition to an alkyl group, a protected primary alcohol was well tolerated at the α position to the nitrogen atom (**5.16m, n**). Notably, trapping by C(sp^2)–H activation at a pyridine ring could also be realised, albeit in a modest yield (**5.16o**). Interestingly, the strained hexahydrobenzoindole system (**5.16p**) could be constructed in moderate yield from the corresponding tetrahydronaphthalene precursor. To further increase the molecular complexity, the *N*-methyl group was replaced with a *para*-fluorobenzyl moiety, which enabled 1,4-Pd shift on a methylene position and afforded the trisubstituted isoindoline **5.16q** as a single trans diastereoisomer. Finally, using a symmetrical dibrominated substrate set the stage for a twofold reaction involving a quadruple C–H activation, which furnished hexahydropyrroloisoindole **5.16r** in 82% yield.

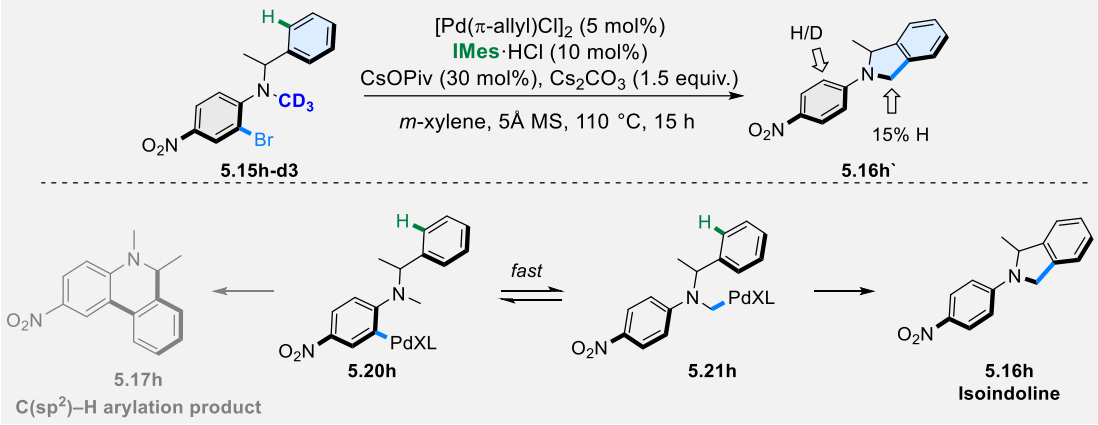


[a]Aryl bromide (0.2 mmol), $[Pd(\pi\text{-allyl})Cl]_2$ (5 mol%), IMes·HCl (10 mol%), Cs_2CO_3 (1.5 equiv.), CsOPiv (30 mol%), *m*-xylene, 5 Å MS, 110°C, 15 h. [b]Using the aryl chloride instead of the aryl bromide. [c]Performed at 140 °C. [d]Determined by ^1H NMR of the crude mixture. [e]Using 10 mol% $[Pd(\pi\text{-allyl})Cl]_2$ and 20 mol% IMes·HCl. [f]Thermal ellipsoids shown at 50% probability

Scheme 70. Scope of the isoindoline synthesis[a]

5.2.4 Mechanistic study

Preliminary mechanistic investigations were conducted with deuterated substrates **5.15h-d3** (Scheme 71). The reaction of **5.15h-d3** under standard conditions showed significant proton incorporation on the newly formed methylene position of isoindoline **5.16h`** by $^{1}$H NMR. Moreover, $^{2}$H NMR experiments revealed deuterium incorporation on the *N*-aryl ring of the C–H activation products **5.16h`**. These observations indicate that the 1,4-Pd shift between the *N*-aryl and *N*-methyl groups is fast and reversible. As illustrated with **5.20h**-**5.21h** (Scheme 71, bottom), a Curtin–Hammett scenario is likely at play in these reactions, whereby product selectivity is controlled by the trapping rate of the σ-aryl- and σ-alkyl palladium intermediates **5.20h** and **5.21h** by C–H functionalisation at the C(sp^2)–H of the benzyl ring.



Scheme 71. Deuterium-labelling experiments reveal H/D scrambling, indicating a reversible 1,4-Pd shift

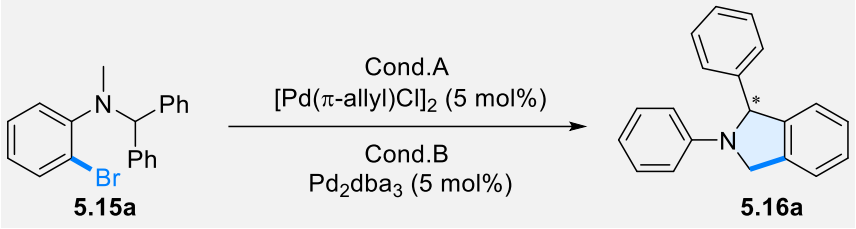
5.2.5 Expansion to enantioselective isoindoline synthesis via 1,4-Pd shift

At this point, we questioned if this isoindoline synthesis could apply to enantioselective synthesis taking advantage of NHCs, which have an extensive arsenal. To the best of our knowledge, enantioselective *N*-heterocycles synthesis via 1,4-Pd shift has never been reported up to date.

Various chiral NHCs were attempted with a relatively facile substrate **5.15a** employed in the racemic synthesis of isoindoline **5.16a** (Table 24). **IBiox-type** (***t*Bu**, **Ad**, **Menth** and **Ind**) ligand gave almost the same, moderate enantioselectivity (entries 3-6). From this series, **IBioxMenth** performed the best with an e.r. of 34:66 (entry 5). However, in this case, 53% of starting material **5.15a** and 12% of the demethylated product **5.18a** were observed along with the desired product on GC-MS analysis. Another NHC ligand **L14** gave a racemic mixture of the product (entry 8). Unfortunately, chiral SIMes derivative **L38** did not display efficient enantioinduction (entry 9). Next TADDOL-based phosphoramidites **L18**/ **L2**, **L31**, Binepine **L16a** and **Me-Bozphos** were investigated (entries 10-14). They showed lower reactivity for Pd migration, producing direct C(sp^2)–H activation product **5.17a** and demethylation **5.18a** as major products. Given the high reactivity for isoindoline synthesis and relatively high enantioinduction, **IBioxInd** was chosen for further optimisation. Then, the influence of decreased lower temperatures with **IBioxInd** was investigated. A lower temperature of 110 ºC led to a slight increase in e.r. (entry 6, 33.5:67.5 e.r.).

With this ligand and temperature in hand, solvent screening was performed, as depicted in Table 25. Other aromatic solvents gave slightly decreased enantioselectivity compared to toluene (Table 25, entries 1-6). Solvents such as DME, CH_3CN and DMA also provided compatible e.r., but with a low isolated yield of the desired product **5.16a** alongside the remaining starting material **5.15a** and proto-dehalogenated product **5.19a** (Table 25, entries 7-9). Finally, a mixture of toluene and DMSO gave the best e.r. (30:70, Table 25, entry 10). However, despite increased reaction time and many attempts, the conversion could not be improved. The targeted enantioselectivity (e.r. > 95:5) was not achieved within the limited research time. Nevertheless, it could be proved that the transformation can be performed in an enantioselective manner. To achieve the desired e.r., modifications of **IBioxInd** could be studied.

Table 24. Ligand optimisation for enantioselective isoindoline synthesis



Entry	Condition[a]	Ligand	Yield[b]	e.r.
1	A	**IBioxMe$_4$**	61	52:48
2	A	**IBioxIPr**	74	51:49
3	A	**IBiox*t*Bu**	60	40:60
4	A	**IBioxAd**	68	41:59
5	A	**IBioxMenth**	21[c]	34:66
6	A	**IBioxInd**	77(73)[d]	37:63 (33.5:67.5)[e]
7	A	**IBioxPh**	41	49:51
8	A	**L14**	67	48:52
9	A	**L38**	73[c]	47:53
10	B	**L18**	0	–
11	B	**L2**	0	–
12	B	**L31**	0	–
13	B	**L16a**	23	–
14	B	**Me-Bozphos**	10	–

[a]Reactions were performed on a 0.1 mmol scale using 10 mol% [Pd] and ligand, Cs_2CO_3 (1.5 equiv.), CsOPiv (30 mol%), toluene (c 0.1 M) and 4Å MS for 15 h. [b]NMR yield determined using trichloroethylene as internal standard. [c]Isolated yield. [d]Isolated yield after reaction at 110 ºC. [e]E.r. of obtained product at 110 ºC.

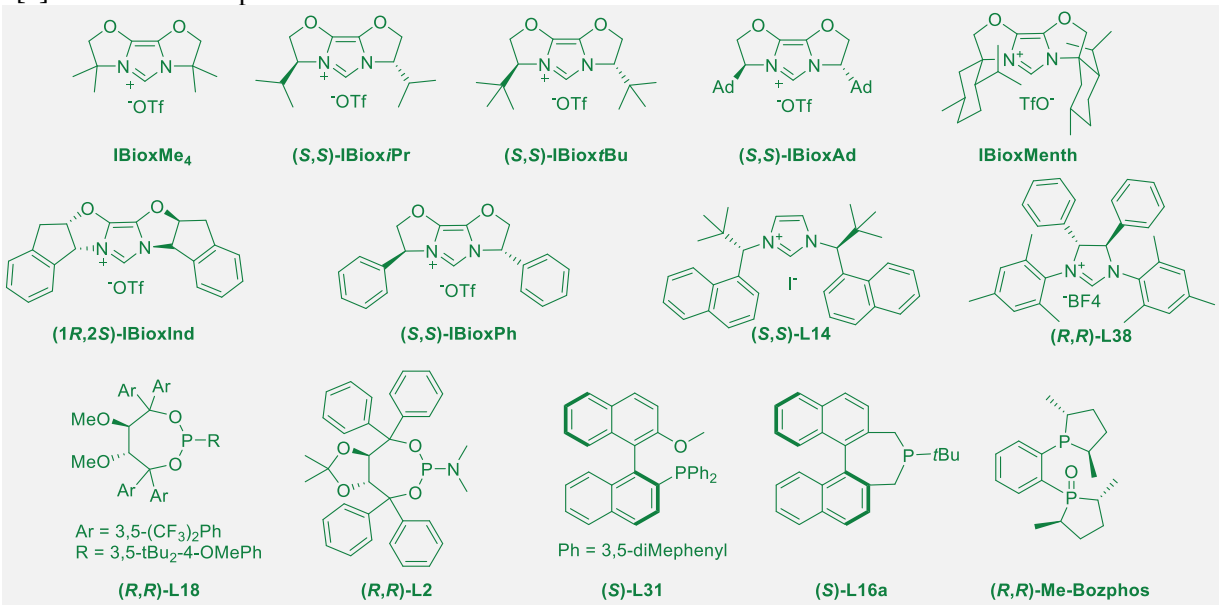
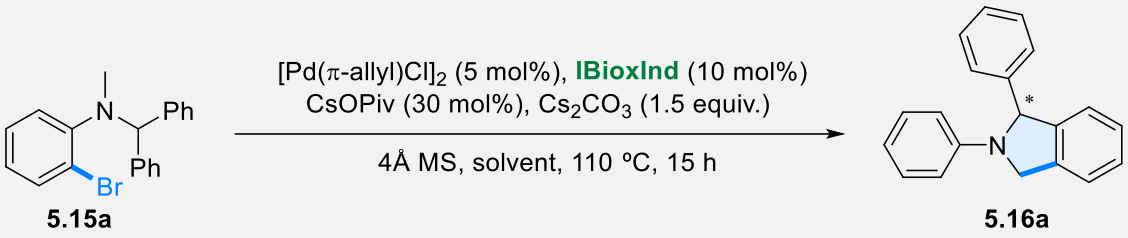


Table 25. Solvent screening for enantioselective isoindoline synthesis[a]



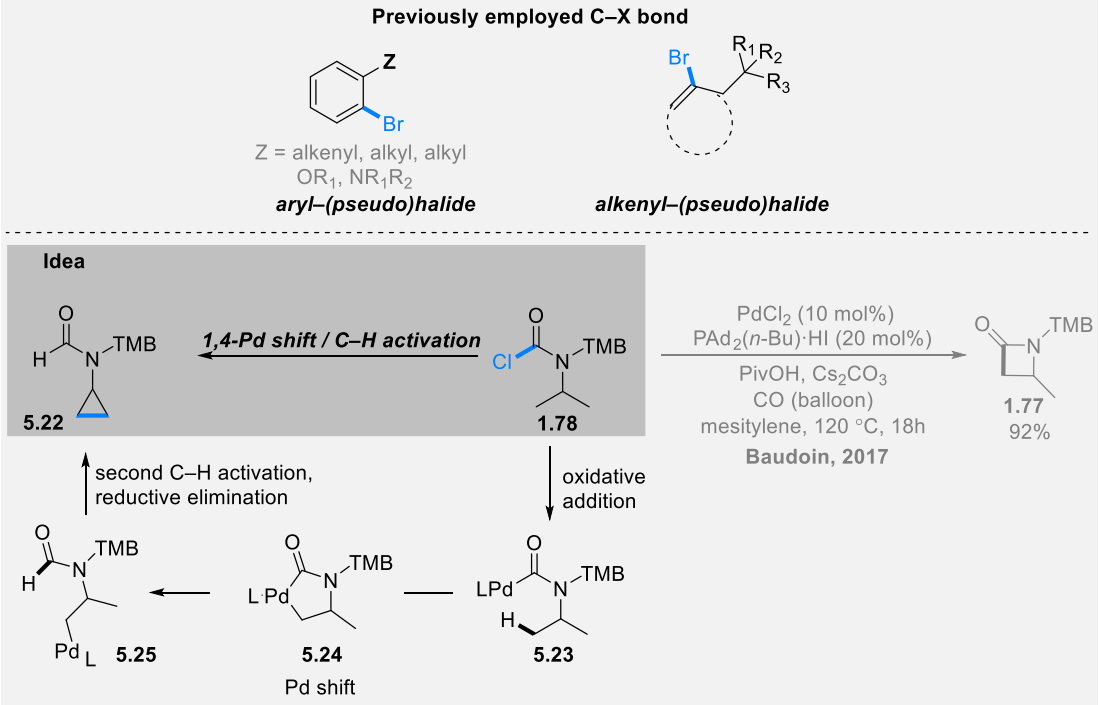
5.15a **5.16a**

Entry	Solvent	Yield[b]	e.r.
1	toluene	73	32.5:67.5
2	*m*-xylene	56	35:65
3	*o*-xylene	55	46:54
4	*p*-xylene	65	42:58
5	mesitylene	60	42:58
6	CF_3Ph	51(14)[c]	34:66
7	DME	29 (57)[c]	34:66
8	CH_3CN	6 (70)[c]	37:63
9	DMA	6 (59)[d]	38:62
10	toluene/DMSO	18 (31)[c]	30:70

[a]Reactions were performed on a 0.1 mmol scale using 10 mol% [Pd] and ligand, Cs_2CO_3 (1.5 equiv), CsOPiv (30 mol%), solvent (c 0.1 M) and 4Å MS for 15 h. [b]Isolated yield. [c]NMR yield of remained **5.15a** determined using trichloroethylene as internal standard. [d]Isolated yield of the proto-dehalogenated compound.

5.2.6 Expansion of 1,4-Pd shift to employ different oxidative addition site

The Baudoin group has put great effort into developing Pd(0)-catalysed C–H activation utilising 1,4-Pd shift since 2019.[153] Those reactions start from the oxidative addition of carbon–halide into Pd(0) species, followed by 1,4-Pd shift and subsequent C–H activation. As an oxidative addition site, we have been using aryl–(pseudo)halide[153,154,157,160,199] and alkenyl–(pseudo)halide (ongoing project), which inspired us to investigate different oxidative addition sites to access new scaffold via 1,4-Pd shift mediated double C–H activation. As a first attempt, we came up with carbamoyl halide, which the Baudoin group used in the study of β-lactam synthesis in 2017 (Scheme 18).[67] We envisioned obtaining structure **5.22** by cyclopropanation using the same substrate **1.78** instead of synthesising β-lactams **1.77** (Scheme 72). Oxidative addition of carbamoyl chloride into Pd(0) could generate Pd(II) complex **5.23**, which would then undergo 1,4-Pd shift via five-membered palladacycle **5.24**. A second C(sp^3)–H activation with **5.25** and following reductive elimination should provide cyclopropane **5.22**.

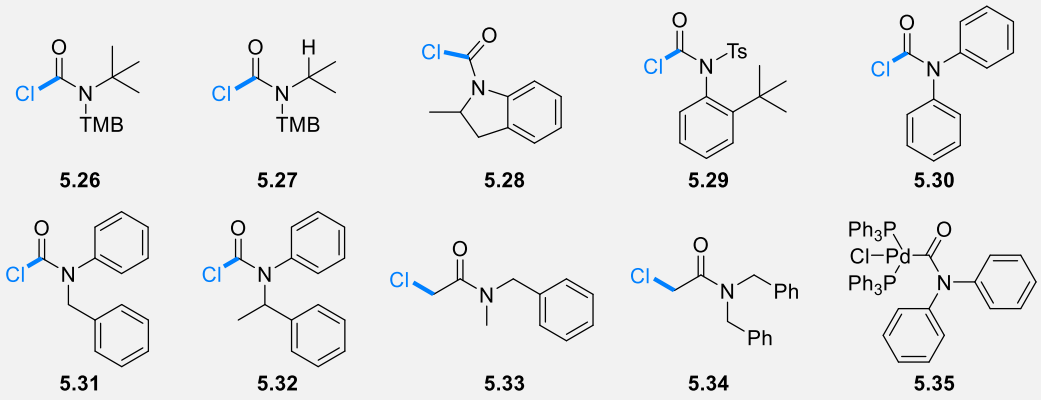


Scheme 72. Use of carbamoyl chloride as oxidative addition site for 1,4-Pd shift-mediated cyclopropanation

To test this idea, we synthesised a variety of carbamoyl chloride substrates **5.26**-**5.32** and α-chloroamides **5.33**, **5.34**. We attempted five conditions for the Pd shift reported by the Baudoin group.[153,154,157,199] **5.26** gave trimethoxytoluene as a primary product with all reaction conditions, which was interesting since it seemed that hydrogenation occurred for the deprotection of the trimethoxybenzyl group (entry 1). Unfortunately, from **5.27** to **5.32**, mainly decarbonylation was observed in all cases without traces of cyclopropanation product (entries 2-7). With α-chloroamide-based substrates **5.33**,

5.34, the nucleophilic substitution of the Cl atom with additives, as reported by Cramer and co-workers, was observed (entries 8, 9).[66] Although they could suppress S_N2 by taking bulky additives such as $AdCO_2H$, in our cases, the direct substitution occurred along with β-lactam in 33% NMR yield from **5.34** (entry 9). Finally, we prepared Pd complex **5.35** by oxidative addition of substrate **5.30** into $Pd(PPh_3)_4$ and subjected it to C–H activation conditions. Even in the presence of CO gas atmosphere (1 atm) gave only decarbonylation product (entry 10). So far, we have not observed any Pd shift with different oxidative addition sites.

Table 26. Substrates for different oxidative addition sites[a-e]

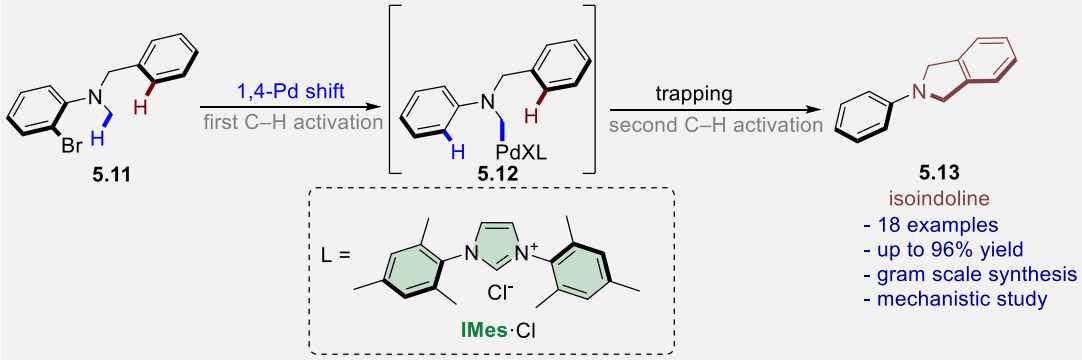


Entry	Substrate	Results
1	**5.26**	28-58%[f] of trimethoxytoluene
2	**5.27**	decarbonylation, dechlorination
3	**5.28**	deegradation[a,b,e], dimerization[c,d]
4	**5.29**	decarbonylation
5	**5.30**	decarbonylation
6	**5.31**	decarbonylation
7	**5.32**	decarbonylation
8	**5.33**	S_N2 by ^-OPiv [a,b,d,e], dehalogenation[c]
9	**5.34**	S_N2 by ^-OPiv and $AdCO_2^-$[a-e], β-lactam[c]
10	**5.35**	decarbonylation[a-c]

Conditions: substrate (0.1 mmol) was engaged for 15h. [a]$Pd(PPh_3)_4$ (10 mol%), KOPiv (2 equiv.), toluene, 110 ºC. [b]$Pd(PCy_3)_2$ (10 mol%), CsOPiv (2 equiv.), toluene, 110 ºC. [c]$Pd(PCy_3)_2$ (10 mol%), $AdCO_2H$ (30 mol%), Rb_2CO_3 (1.5 equiv.), toluene, 110 ºC. [d]$[Pd(\pi\text{-allyl})Cl]_2$ (5 mol%), IMes·Cl (10 mol%), CsOPiv (30 mol%), Cs_2CO_3 (1.5 equiv.), *m*-xylene, 110 ºC. [e]$[Pd(\pi\text{-cinnamyl})Cl]_2$ (5 mol%), IBiox·HOTf (10 mol%), CsOPiv (30 mol%), Cs_2CO_3 (1 equiv.), CPME, 110 ºC. [f]NMR yield determined by ^1H NMR using trichloroethylene as internal standard.

5.3 Conclusion and outlook

The synthesis of isoindolines from readily available *o*-bromo-*N*-methyl aniline precursors is reported (Scheme 73). These reactions proceed by a 1,4-Pd shift on the *N*-methyl group and intramolecular trapping via C(sp^2)–H at another nitrogen substituent and allow the construction of C–C bonds remotely to the initial C–Br bond. *N*-Heterocyclic carbene ligands were vital to controlling the selectivity in favour of the remote vs the direct C–H functionalisation products. This method allows access to isoindolines, a valuable nitrogen heterocycle found in numerous biologically relevant molecules. Furthermore, the desymmetrisation of *gem*-diphenyl was investigated by screening a variety of chiral ligands. Moderate enantioinduction was observed with **IBioxInd** as a chiral ligand.



Scheme 73. Summary of isoindoline synthesis via 1,4-Pd shift mediated double C–H activation

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C-H Activation | Hot Paper

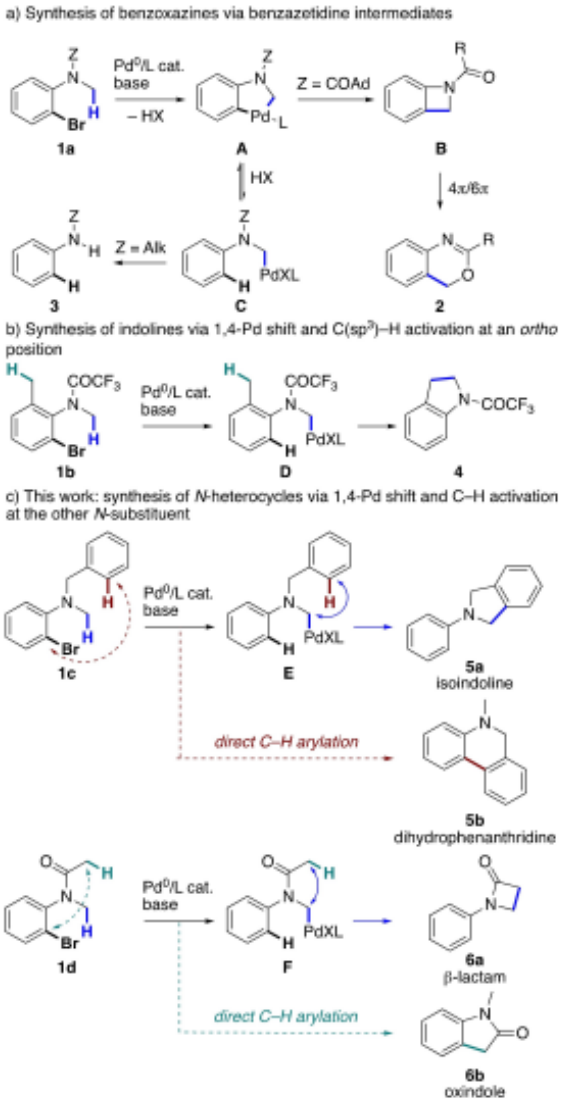
Remote Construction of N-Heterocycles via 1,4-Palladium Shift-Mediated Double C–H Activation

*Takeru Miyakoshi[+], Nadja E. Niggli[+], and Olivier Baudoin**

Abstract: In the past years, Pd^0-catalyzed $C(sp^3)$–H activation provided efficient and step-economical methods to synthesize carbo- and heterocycles via direct $C(sp^2)$–$C(sp^3)$ bond formation. We report herein that a 1,4-Pd shift allows access to N-heterocycles which are difficult to build via a direct reaction. It is shown that *o*-bromo-*N*-methylanilines undergo a 1,4-Pd shift at the *N*-methyl group, followed by intramolecular trapping by $C(sp^2)$–H or $C(sp^3)$–H activation at another nitrogen substituent and remote C–C bond formation to generate biologically relevant isoindolines and β-lactams. The product selectivity is influenced by the employed ligand, with NHCs favoring the product of remote C–C coupling against products arising from direct C–C coupling and N-demethylation.

Introduction

Nitrogen-containing heterocycles are privileged motifs in synthetic organic chemistry due to their abundance in nature and their prevalence in agrochemicals, functionalized materials, and pharmaceuticals.[1] In particular, they account for over 60% of small-molecule drugs approved by the FDA. Thus, many efforts have been devoted to the development of new synthetic routes towards the synthesis of these essential building blocks. Over the last two decades, C–H activation-based methods have been established as powerful tools for the atom- and step-economical de novo construction of diverse azacycles.[2] In particular, Pd^0-catalyzed $C(sp^3)$–H activation allows the direct formation of $C(sp^2)$–$C(sp^3)$ bonds and generation of nitrogen heterocycles from easily accessible $C(sp^2)$ (pseudo)-halides.[3] For instance, the reaction of 2-bromo-*N*-methyl anilines **1a** equipped with a bulky carbonyl substituent on the nitrogen atom was shown to produce benzoxazines **2** via $C(sp^3)$–H activation at the *N*-methyl group (Scheme 1a), giving rise to 5-membered palladacycle **A**, which upon reductive elimination generates



Scheme 1. Pd^0-catalyzed $C(sp^3)$–H activation of 2-bromo-*N*-methylanilines for the synthesis of nitrogen heterocycles.

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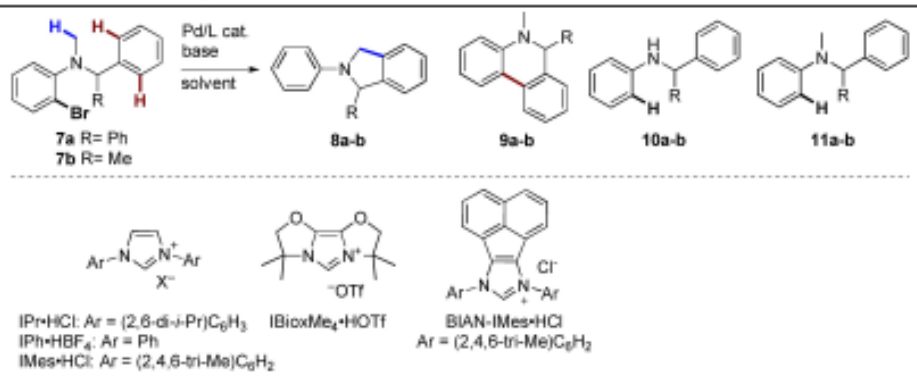
Table 1: Optimization of the isoindoline synthesis.[a]



Entry	Substrate	Pd/L	Temp [°C]/Solvent	Yield[b] 8a,b/9a,b/10a,b/11a,b
1	**7a**	[Pd(π-allyl)Cl]$_2$/IBioxMe$_4$	140/PhMe	99:0:0:0
2	**7a**	[Pd(π-allyl)Cl]$_2$/IPr	140/PhMe	73:0:26:0
3	**7a**	Pd$_2$dba$_3$/PCy$_3$	140/PhMe	10:61:11:2
4	**7a**	Pd$_2$dba$_3$/PPh$_3$	140/PhMe	0:61:30:9
5[c]	**7a**	Pd(PPh$_3$)$_4$	140/PhMe/DMSO	0:43:18:9
6	**7b**	[Pd(π-allyl)Cl]$_2$/IBioxMe$_4$	140/PhMe	68:0:32:0
7	**7b**	[Pd(π-allyl)Cl]$_2$/IMes	140/PhMe	82:0:17:1
8	**7b**	[Pd(π-allyl)Cl]$_2$/IMes	110/*m*-xylene[d,e]	94 (78)[f]:0:5:1
9	**7b**	[Pd(π-allyl)Cl]$_2$/IPh	110/*m*-xylene[d,e]	2:0:trace:trace
10	**7b**	[Pd(π-allyl)Cl]$_2$/BIAN-IMes	110/*m*-xylene[d,e]	80:0:9:4

[a] Reactions were performed on a 0.1 mmol scale using 10 mol% [Pd] and ligand, Cs_2CO_3 (1.5 equiv), CsOPiv (30 mol%), solvent (*c* 0.1 M) and 4 Å MS for 15 h. [b] NMR yield determined using trichloroethylene as internal standard. [c] Using KOPiv (2 equiv) instead of Cs_2CO_3/CsOPiv and toluene/DMSO 95:5. [d] *c* 0.067 M. [e] Using 5 Å MS. [f] Yield of the isolated product.

benzazetidine **B**. The latter is unstable under the reaction conditions and undergoes a 4π/6π electrocyclic cascade to furnish product **2**.[4] In addition, N-demethylation was observed when an *N*-alkyl substituent was present instead of the carbonyl group, which presumably occurs through reversible reprotonation of palladacycle **A** to furnish σ-alkylpalladium intermediate **C** and demetallation via formation of an iminium species.[4,5] The formation of σ-alkylpalladium complex **C** from the oxidative addition complex arising from **1a** and the active Pd^0 catalyst formally results in a 1,4-Pd shift. 1,4-Palladium shifts were initially reported by Heck in 1972[6] and subsequently exploited to generate hard-to-reach $C(sp^2)$–$C(sp^2)$ and $C(sp^2)$–$C(sp^3)$ bonds remotely from $C(sp^2)$ halides.[7]

Inspired from seminal work by Dyker,[8] we showed that a 1,4-Pd shift onto an adjacent position to an oxygen or nitrogen atom gives rise to a σ-alkylpalladium complex which can effect further $C(sp^3)$–H activation on a substituent located at the next *ortho* position.[9] Accordingly, 2-bromo-*N*-methylanilines **1b**, wherein the lone pair of the nitrogen atom was deactivated by a trifluoroacetyl group to avoid the abovementioned demethylation process, gave rise to indolines **4** via σ-alkylpalladium intermediate **D** (Scheme 1b), albeit with a modest reaction scope. This 1,4-Pd shift-based strategy allowing the remote construction of $C(sp^3)$–$C(sp^3)$ bonds via twofold $C(sp^3)$–H bond cleavage was recently employed to synthesize cyclopropanes.[10] Of note, it was also shown that σ-alkylpalladium intermediates generated by 1,4-Pd shift can be trapped through a range of other processes.[11]

Following up on this work, we sought to expand the scope of this 1,4-Pd shift-based strategy to access valuable azacycles by installing a suitable N-substituent which would trap the transient σ-alkylpalladium intermediate **E** or **F** by $C(sp^2)$–H or $C(sp^3)$–H activation, respectively (Scheme 1c). Herein, we report the implementation of this strategy for the synthesis of isoindolines **5a** and β-lactams **6a**, which cannot be easily accessed by direct Pd^0-catalyzed $C(sp^3)$–H activation,[3] and are biologically relevant heterocycles.[12,13] At the onset of this work, we realized that developing such reactions would be challenging because 1. the desired migration pathway would compete with the direct C–H arylation leading to 5,6-dihydrophenanthridines **5b**[14] and oxindoles **6b**,[15] respectively, and 2. N-demethylation could occur in the absence of an electron-withdrawing group adjacent to the nitrogen atom. However, previous studies pointed at the effect of the base and the ligand to favor the 1,4-Pd shift pathway over the direct reaction,[9,10] and thus gave us confidence that the desired selectivity could be achieved by playing on these factors.

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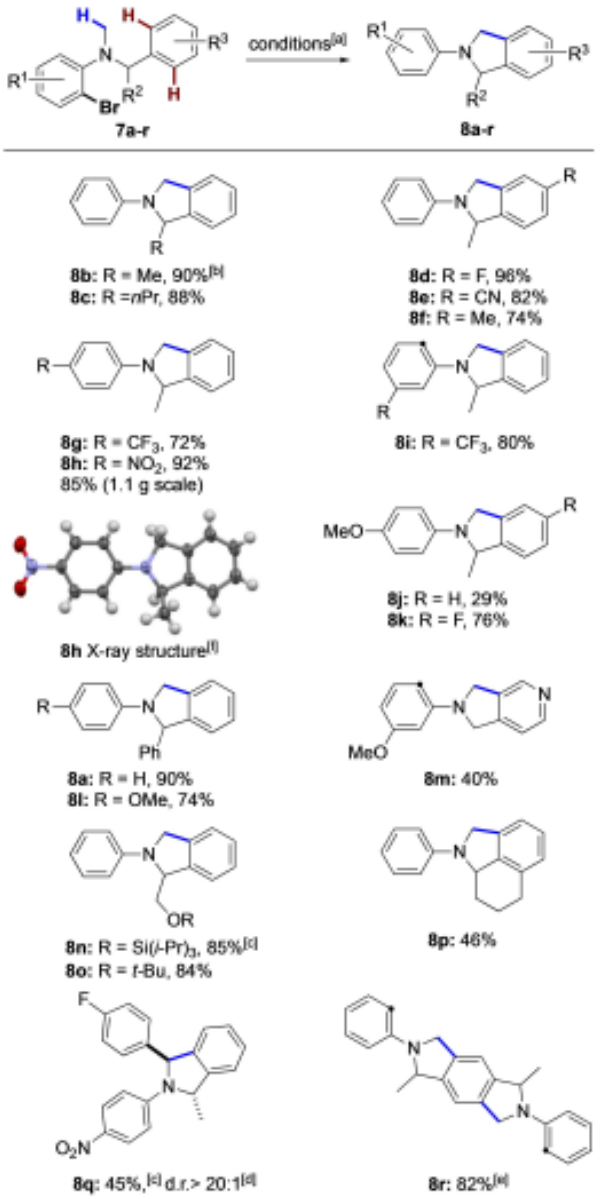
Results and Discussion

We set out to explore the reactivity of several *o*-bromoaniline substrates using three different catalytic systems, which proved successful in previous Pd^0-catalyzed $C(sp^3)$–H activation reactions, i.e. $[Pd(\pi\text{-allyl})Cl]_2$/NHC (NHC = N-heterocyclic carbene),[16] Pd_2dba_3/PR_3[4,9] and $Pd(PPh_3)_4$[10] (Table 1, entries 1–5, see Table S1 for details). As a result, $IBioxMe_4$[16b,17] was identified as the optimal ligand to convert substrate **7a** to the desired indoline **8a** in 99% NMR yield, and minimize the formation of the direct $C(sp^2)$–H arylation product **9a**, N-demethylated product **10a**, and proto-dehalogenated product **11a** (entry 1). Interestingly, the previously developed conditions for 1,4-Pd shift-mediated double C–H activation reactions employing phosphine ligands provided **9a** as the major product (entries 3–5). In contrast, NHC ligands[18] seem to favor the 1,4-Pd shift on the *N*-Me group (entries 1 and 2). Motivated by these results, we turned to the more challenging substrate **7b** bearing a methyl instead of the second phenyl group at the α position to the nitrogen atom. Indeed, in this case, the trapping of the σ-alkylpalladium intermediate arising from 1,4-Pd shift (see **E**, Scheme 1c) by $C(sp^2)$–H arylation is less favorable than in **7a** since less $C(sp^2)$–H bonds are accessible. In addition, the direct $C(sp^3)$–H arylation at the α-Me group[19] could potentially be an additional competitive reaction. With substrate **7b**, IMes was found to be superior to the bis-oxazoline-based IBiox NHC to reduce the amount of N-demethylated product **10b** and increase the yield of isoindoline **8b** (entries 6 and 7, see also Tables S2–S3). Further optimizations led to identify *m*-xylene as the optimal solvent under slightly more diluted conditions, at 110 °C and in the presence of 5 Å MS (entry 8). Then, the effect of the ligand structure was further investigated (Table S12). No reaction occurred with IPh, bearing unsubstituted Ph groups (entry 9). The IMes analogue BIAN-IMes[20] also furnished isoindoline **8b**, but with a reduced yield (entry 10). Under the optimized conditions (entry 8), isoindoline **8b** was formed with a high yield (78% upon isolation) and selectivity.

With these optimized conditions in hand, the versatility of this 1,4-Pd shift-based isoindoline synthesis was investigated (Scheme 2). In addition to the aryl bromide precursor, the use of the electron-rich IMes ligand allowed the use of the corresponding aryl chloride with a similar efficiency (90%, **8b**). Another alkyl group could be introduced at the α position to the nitrogen atom without detrimental effect on the yield (**8c**). Electron-withdrawing or -donating groups on the remote aryl ring were well tolerated, affording the corresponding isoindolines in good to excellent yields (**8d–f**). In addition, substrates bearing electron-withdrawing groups in the *meta* or *para* position of the *N*-aryl ring also reacted in good yields (**8g–i**, 72–92%). Of note, the reaction providing isoindoline **8h** was successfully conducted on gram scale without significant impact on the efficiency. However, a significant drop of yield was observed upon introduction of an electron-donating group on the *N*-aryl ring (**8j**). This effect was nevertheless counterbalanced by installing either an electron-withdrawing group on the remote aryl ring (**8k**) or by employing a more reactive *gem*-diphenyl substrate (**8l**). Interestingly, trapping by $C(sp^2)$–H activation at a pyridine ring could be also realized, albeit in modest yield (**8m**). In addition to an alkyl group, a protected primary alcohol was well tolerated at the α position to the nitrogen atom (**8n**, **8o**). Interestingly, the



Scheme 2. Scope of the isoindoline synthesis. [a] Aryl bromide (0.2 mmol), $[Pd(\pi\text{-allyl})Cl]_2$ (5 mol%), IMes·HCl (10 mol%), Cs_2CO_3 (1.5 equiv), CsOPiv (30 mol%), *m*-xylene, 5 Å MS, 110 °C, 15 h. Yields refer to the isolated isoindoline product. Dots indicate the initial position of the bromine atom, when ambiguous. [b] Using the aryl chloride instead of the aryl bromide. [c] Performed at 140 °C. [d] Determined by ^1H NMR of the crude mixture. [e] Using 10 mol% $[Pd(\pi\text{-allyl})Cl]_2$ and 20 mol% IMes·HCl. [f] Thermal ellipsoids shown at 50% probability.[23]

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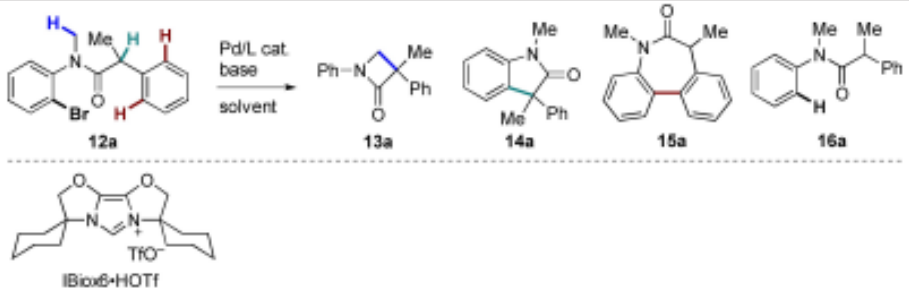
strained hexahydrobenzoindole system (**8p**) could be constructed in moderate yield from the corresponding tetrahydronaphthalene precursor. To further increase the molecular complexity, the *N*-methyl group was replaced with a *para*-fluorobenzyl moiety, which enabled 1,4-Pd shift on a methylene position and afforded the trisubstituted isoindoline **8q** as a single *trans* diastereoisomer. Finally, the use of a symmetrical dibrominated substrate set the stage for a twofold reaction involving a fourfold C–H activation, which furnished hexahydropyrroloisoindole **8r** in 82 % yield.

After the implementation of the 1,4-Pd shift-based strategy for the selective synthesis of isoindolines, we endeavored to further expand this methodology to build other N-heterocycles. The tertiary amide **12a**, which contains multiple C–H functionalization sites, was already employed in the direct α-arylation resulting in oxindole **14a** (Table 2).[15] Alternatively, β-lactam **13a** would arise from 1,4-Pd shift onto the *N*-methyl substituent and trapping by C(sp^3)–H alkylation. Finally, dibenzazepinone **15a** might arise from direct C(sp^2)–H arylation.[21] Since we expected a strong influence of the ligand on the reaction selectivity similar to the above isoindoline synthesis, we set out to explore the influence of different classes of ligands on the reaction of the model amide **12a** (entries 1–3, see also Table S13). Interestingly, a different product distribution was again observed with the three displayed ligands. The common phosphine ligand PCy_3 resulted in the preferential formation of dibenzazepinone **15a** (entry 1), with only traces of β-lactam **13a** being formed. In contrast, IPr clearly favored the oxindole product **14a** (entry 2). These results are rather unsurprising in light of literature precedents.[15c,21] In contrast, we were pleased to discover that IBiox-type ligands, and in particular the spirocyclic IBiox6,[17,22] provided the β-lactam product **13a** in 30 % NMR yield, along with oxindole **14a** (31 %), dibenzazepinone **15a** (23 %), and the proto-dehalogenated product **16a** (26 %, entry 3). Building on this result, the reaction conditions were optimized. In the first round, trifluorotoluene ($PhCF_3$) was found to be the best solvent, improving the yield of the β-lactam to 37 % and completely suppressing the formation of the dibenzazepinone product (entry 4). Moreover, stoichiometric Cs_2CO_3 and catalytic CsOPiv were found to be the best basic system for this transformation (Tables S15, S17–S20). Expectedly, employing stronger bases such as LiHMDS or NaO*t*-Bu resulted in the selective formation of the oxindole, presumably via an enolate arylation mechanism (entry 5).[15] Replacing IBiox6 with the smaller $IBioxMe_4$ ligand (see structure in Table 1) further improved the yield of the β-lactam product to 44 % (entry 6). A second optimization round with additional solvents revealed cyclopentyl methyl ether (CPME) as the optimal reaction medium, yielding 50 % of the desired product **13a**, along with 35 % of oxindole **14a** and 12 % of proto-dehalogenated product **16a** (entry 7). While cesium salts provided the best results, the amount of Cs_2CO_3 could be reduced to 1 equivalent (entry 8). Interestingly, omitting CsOPiv only resulted in a small decrease of efficiency (Table S20). Despite extensive efforts, the reaction could not be further optimized.

Repeating the reaction on a 0.3 mmol scale furnished a separable 3:2 mixture of remote and direct C(sp^3)–H functionalization products **13a** and **14a**, from which β-lactam **13a** could be isolated in 51 % yield (Scheme 3). Then, we explored the scope of this reaction. Various electron-donating substituents in *meta* and *para* position to the *N*-aryl

Table 2: Optimization of the β-lactam synthesis.[a]



Entry	Pd/L	Solvent	Base	Yield[b] 13a/14a/15a/16a
1	$Pd(PCy_3)_2$	mesitylene	Cs_2CO_3	6:0:66:0
2	[Pd(π-cinnamyl)Cl]$_2$/IPr[c]	mesitylene	Cs_2CO_3	2:84:0:8
3	[Pd(π-cinnamyl)Cl]$_2$/IBiox6[d]	mesitylene	Cs_2CO_3	30:31:23:26
4	[Pd(π-cinnamyl)Cl]$_2$/IBiox6[d]	$PhCF_3$	Cs_2CO_3	37:18:0:10
5	[Pd(π-cinnamyl)Cl]$_2$/IBiox6[d]	$PhCF_3$	NaOt-Bu	0:95:0:0
6	[[Pd(π-cinnamyl)Cl]$_2$/$IBioxMe_4$[d]	$PhCF_3$	Cs_2CO_3	44:25:0:19
7	[Pd(π-cinnamyl)Cl]$_2$/$IBioxMe_4$[d]	CPME	Cs_2CO_3	50:35:0:12
8	[Pd(π-cinnamyl)Cl]$_2$/$IBioxMe_4$[d]	CPME	Cs_2CO_3[e]	53:34:0:13

[a] Reactions were performed on a 0.1 mmol scale using 10 mol% [Pd] and ligand, base (1.5 equiv), CsOPiv (30 mol%), 160 °C, 18 h. [b] NMR yield determined using trichloroethylene as internal standard. [c] Using IPr·HCl (10 mol%). [d] Using IBiox·HOTf (10 mol%). [e] Using 1.0 equiv Cs_2CO_3.

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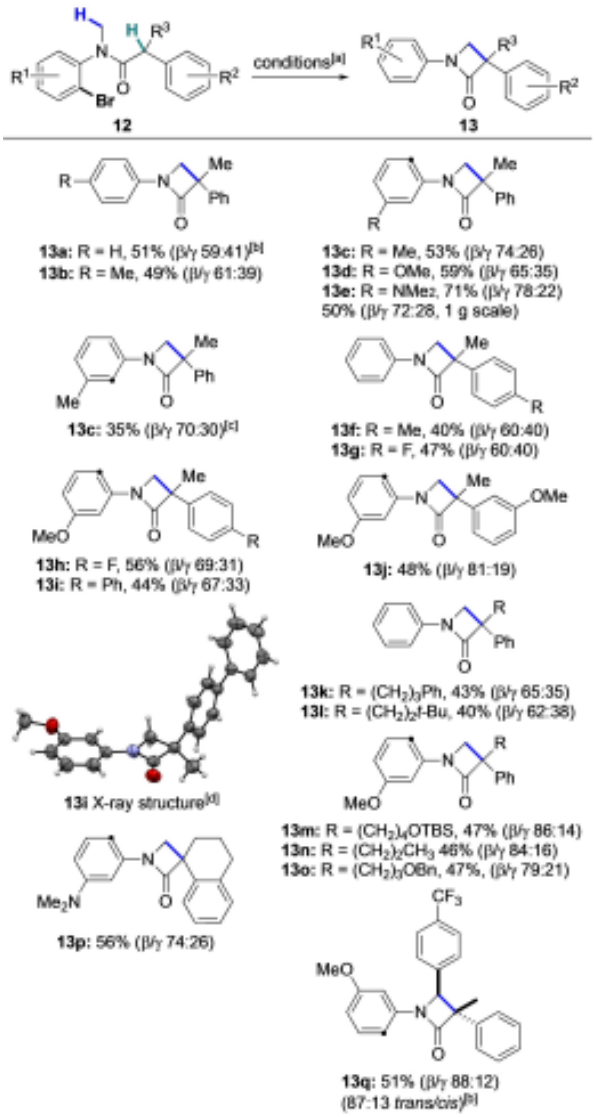
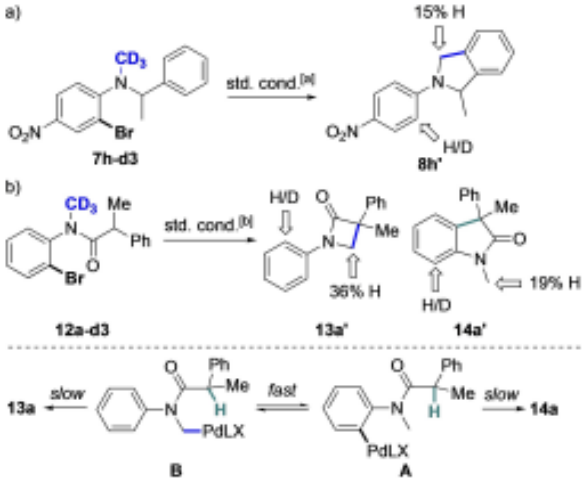


Scheme 3. Scope of the β-lactam synthesis. [a] Reaction conditions: **12** (0.3 mmol), [Pd(π-cinnamyl)Cl]$_2$ (5 mol%), IBioxMe$_4$·HOTf (10 mol%), Cs_2CO_3 (1 equiv), CsOPiv (30 mol%), CPME, 160 °C. Yields refer to the isolated β-lactam product. β/γ Ratios refer to the ratios of the β-lactam/oxindole products, as determined by GCMS, unless otherwise stated. Dots indicate the initial position of the bromine atom, when ambiguous. [b] Determined by ^{1}H NMR. [c] Starting from the 2-bromo-3-methylaniline derivative. [d] Thermal ellipsoids shown at 50% probability.[33]

ring were well tolerated, affording the corresponding β-lactams **13b**–**13e** in moderate to good yields. In particular, starting from the 2-bromo-5-methylaniline derivative (**12c**), **13c** was isolated in moderate yield (53%). However, when the 2-bromo-3-methylaniline isomer was engaged a lower yield of **13c** was observed (35%), probably due to a sterically challenging oxidative addition. A significant yield improvement was obtained by installing a strong electron-donating group (OMe, NMe$_2$) on the *N*-aryl ring (**13d**, **13e**). This result stands in contrast to the isoindoline case, for which electron-withdrawing substituents on the *N*-aryl ring provided a better yield. Electron-donating (**13f**, **13j**) and -withdrawing groups (**13g**, **13h**), as well as a phenyl substituent (**13i**) on the other aryl ring at the α position to the amide group were well tolerated, and provided yields in the range of 40–56%. Unfortunately, replacing this aryl group with an ester, amide, benzyl or alkyl substituent resulted in unproductive reactions. Moreover, different alkyl chains at the α position to the amide group were also compatible (**13k**–**13o**), and the corresponding products were isolated in 40–47% yield. Interestingly, a spirocyclic β-lactams (**13p**) was obtained in 56% yield from the corresponding tetrahydronaphthoic acid derivative. Gratifyingly, and similar to the isoindoline case, replacing the *N*-methyl with an *N*-(*p*-trifluoromethylbenzyl) substituent allowed the formation of highly substituted β-lactam **13q** in 51% yield and as the major *trans* diastereoisomer. This example further demonstrates the feasibility of 1,4-Pd shift onto an activated methylene position adjacent to a nitrogen atom. Finally, we successfully performed the reaction producing β-lactam **13e** on a gram scale.

Preliminary mechanistic investigations were conducted with deuterated substrates **7h-d3** and **12a-d3** (Scheme 4). The reaction of **7h-d3** under standard conditions showed significant proton incorporation on the newly formed methylene position of isoindoline **8h′** by ^{1}H NMR (Scheme 4a). Likewise, the methylene position of β-lactam **13a′** and the *N*-methyl group of oxindole **14a′** showed significant proton incorporation (Scheme 4b). Moreover, ^{2}H NMR experiments revealed deuterium incorporation on the *N*-aryl ring of the three C–H activation products **8h′**, **13a′** and **14a′**. These observations clearly indicate that the 1,4-Pd shift between the *N*-aryl and *N*-methyl groups is fast and reversible. As illustrated with **12a** (Scheme 4, bottom), a



Scheme 4. Deuterium-labeling experiments reveal H/D scrambling, indicating a reversible 1,4-Pd shift. [a] Standard conditions: see Scheme 2. [b] Standard conditions: see Scheme 3.

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Curtin–Hammett scenario is likely at play in these reactions, whereby product selectivity is controlled by the trapping rate of the σ-aryl- and σ-alkylpalladium intermediates **A** and **B** by C–H functionalization at the α position to the amide.

Conclusion

The synthesis of two types of nitrogen heterocycles from readily available *o*-bromo-*N*-methylaniline precursors is reported. These reactions proceed by a 1,4-Pd shift on the *N*-methyl group and intramolecular trapping via $C(sp^2)$–H or $C(sp^3)$–H activation at another nitrogen substituent, and allow the construction of C–C bonds remotely to the initial C–Br bond. N-Heterocyclic carbene ligands were found to be key to control the selectivity in favor of the remote vs. the direct C–H functionalization products. This method allows access to isoindolines and β-lactams, which are valuable nitrogen heterocycles found in numerous biologically relevant molecules.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: C–H Activation · Isoindolines · N-Heterocycles · Palladium · β-Lactams

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[23] Deposition Numbers 2124336 (for **8h**), and 2124341 (for **13i**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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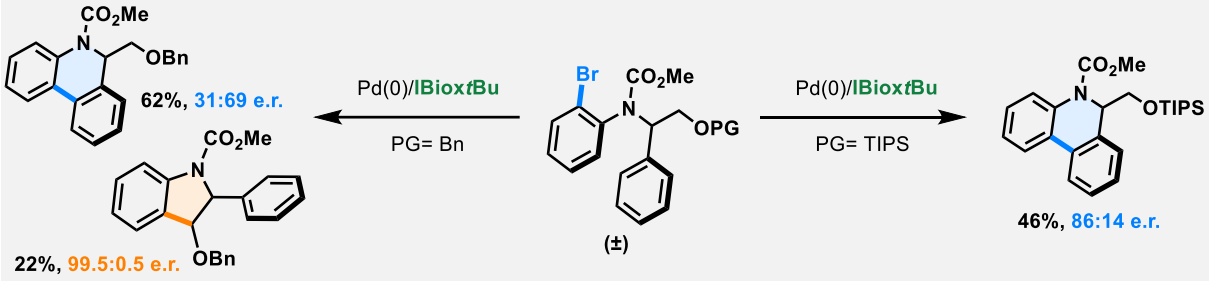
6. General conclusion

In the development of kinetic resolution by Pd(0)-catalysed C–H activation, various model substrates were successfully synthesised and engaged in numerous different reaction conditions. We first tried to decrease the reaction temperature as kinetic control could play a role. However, promising results have not been obtained. Interestingly, parallel kinetic resolution behaviour was observed by employing the chiral *N*-heterocyclic carbene ligand at high temperatures. As a result of differentiating protecting groups, a racemic substrate with TIPS-protected hydroxyl group gave the corresponding C(sp^2)–H activation product in moderate enantioselectivity (86:14 e.r.) with chiral **IBiox*t*Bu**. Furthermore, a benzyl-protected substrate was regiodivergent and stereospecifically transformed to afford the C(sp^2)–H activation product in 62% yield with moderate enantioselectivity (31:69 e.r.) and the scalemic C(sp^3)–H activation product as sole diastereomer in 22% yield (99.5:0.5 e.r.) (Scheme 74).

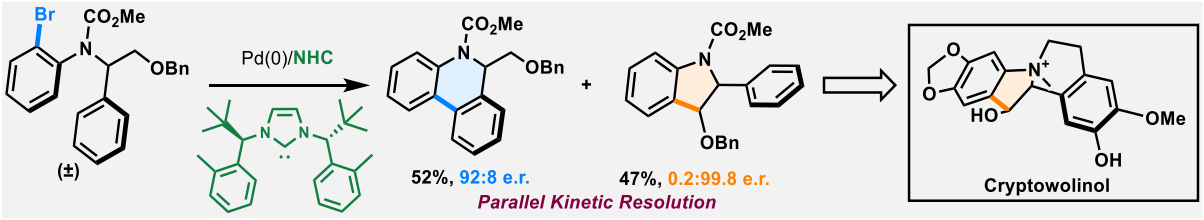


Scheme 74. Outlook of achieved kinetic resolution with different protecting groups

Based on these promising results, we explored the total synthesis of 10-*O*-demethylboccoline via parallel kinetic resolution. However, despite many efforts, a substrate for the key C–H activation could not be obtained successfully. Also, a model substrate closer to the natural product did not show parallel kinetic resolution.

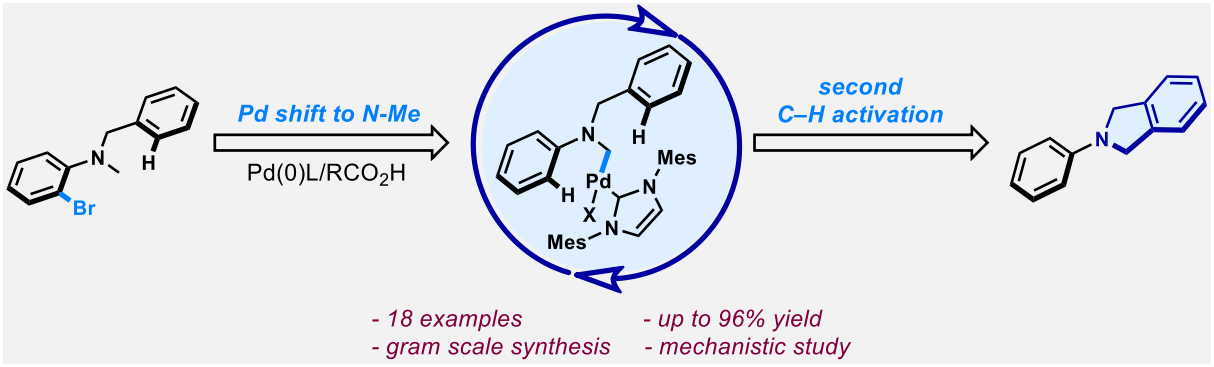
Next, the application of regiodivergent and stereospecific C–H activation in the total synthesis of cryptowolinol was attempted. Interestingly, this natural product has not been synthetically accessed and biologically assessed. With the model substrate, ligand screening revealed a suitable NHC ligand producing a nearly 1:1 mixture of two distinct products. These products were successfully isolated in 47% and 52% yields. HPLC analysis on a chiral stationary phase gave an e.r. of 0.2:99.8 for C(sp^3)–H and 92:8 for C(sp^2)–H activation product (Scheme 75). Relationships between the calculated reaction constants showed ideal parallel kinetic resolution. Notably, this is the rare example of resolution between facile C(sp^2)–H activation and challenging C(sp^3)–H activation as regiodivergent reactions. In order to take advantage of this result, we started synthesising the substrate for C–H activation towards the total

synthesis of cryptowolinol, which is currently undergoing.



Scheme 75. Development of parallel kinetic resolution between C(sp^2)–H and C(sp^3)–H

In the second part of this thesis, we elaborated the synthesis of *N*-heterocycle via 1,4-Pd shift mediated double Pd(0)-catalysed C–H activation (Scheme 76). This transformation proceeds by a 1,4-Pd shift on the *N*-methyl group and intramolecular trapping via C(sp^2)–H at another nitrogen substituent and therefore allows the construction of C–C bonds remotely to the initial C–Br bond. *N*-Heterocyclic carbene ligand **IMes** was vital to controlling the selectivity in favour of the remote vs the direct C–H functionalisation products. This method allowed access to a wide range of isoindoline derivatives, a valuable nitrogen heterocycle found in numerous biologically relevant molecules. Furthermore, the first enantioselective *N*-heterocycle synthesis via 1,4-Pd shift was observed as a proof of concept for future work.



Scheme 76. Synthesis of isoindolines with 1,4-Pd shift-mediated double C–H activation

7. Experimental part

7.1 General information

Experimental Procedures, Reagents, and Glassware: All reactions involving air-sensitive materials were carried out in pre-dried glassware under an argon atmosphere by using Schlenk techniques employing double-line argon-vacuum lines and working in an argon-filled glove box. Chemicals were used as obtained from the suppliers (Sigma Aldrich, Acros Organics, and Fluorochem) unless otherwise stated. Anhydrous CPME with inhibitor, THF, DMF, and DCM were purchased from Acros Organics or Sigma Aldrich. The solvents were degassed with a flow of argon for 20 minutes.

Chromatography: Analytical thin-layer chromatography (TLC) was performed using pre-coated Merck silica gel 60 F254 plates (0.25 mm). Visualization of the developed chromatogram was performed by UV absorbance (254 nm) or TLC stains ($KMnO_4$ and Phosphomolybdic acid). Flash chromatography was performed using Silicycle SiliaFlash P60 (230 – 400 mesh) with the indicated eluent system.

NMR Spectroscopy: Proton nuclear magnetic resonance (^{1}H NMR) data were acquired at 400 MHz on a Bruker Advance 400 spectrometer or at 500 MHz on a Bruker Advance 500 spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual chloroform (s, 7.26 ppm). Proton decoupled Carbon-13 nuclear magnetic resonance (^{13}C{^{1}H} NMR) data were acquired at 101 MHz on a Bruker Advance 400 spectrometer or at 126 MHz on a Bruker Advance 500 spectrometer. Chemical shifts are reported in ppm relative to residual chloroform (77.16 ppm). Proton decoupled Fluorine-19 nuclear magnetic resonance (^{19}F{^{1}H} NMR) were acquired at 376 MHz on a Bruker Advance 400 spectrometer. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; hept, heptet; dd, doublet of doublets; dt, doublet of triplets; ddd, doublet of doublets of doublets; tt, triplet of triplets; tq, triplet of quartets; qt, quartet of triplets; m, multiplet. All NMR data were recorded at 298 K. Infrared Spectroscopy Infrared (IR) data were recorded on an ATR Varian Scimitar 800. Absorbance frequencies are reported in reciprocal centimetres (cm^{-1}).

Mass Spectrometry: HRMS measurements were performed on a Bruker maXis 4G QTOF ESI. High-resolution mass are given in m/z.

HPLC: Performed using a Shimadzu Prominence system with SIL-20A auto sampler, CTO-20AC column oven, LC-20AD pump system, DGU-20A3 degasser and SPD-M20A Diode Array or UV/VIS detector. The following chiral columns from Daicel Chemical Industries were used: OD-H (Chiralcel®), OJ-H (Chiralcel®), IA (Chiralpak®) and IC (Chiralpak®), in 4.6 x 250 mm size.

Melting points: were measured on a Büchi B-565 and are uncorrected.

7.2 Kinetic resolution

7.2.1 General procedures

Synthesis of Secondary amines (general procedure A)

A mixture of primary amine (1 equiv.), styrene oxide (3 equiv.), and silica gel (10% w/w) in toluene (0.3 M) was heated to 70º C overnight. The solvent was evaporated *in vacuo*. The residue was purified by chromatography on silica gel using cyclohexane/AcOEt as a solvent to afford the pure compounds.

Carbamation of Secondary amines (general procedure B)

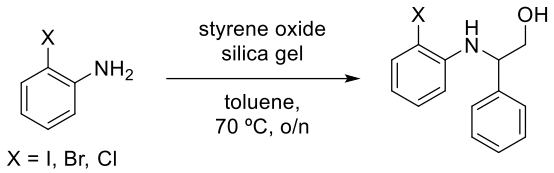
A mixture of *N*-alkyl-o-bromoarylamine in chloroformate (2-3 mL/mmol) was heated under reflux overnight. The mixture was concentrated *in vacuo*. The crude material was purified by flash column chromatography using cyclohexane/AcOEt mixture as an eluent.

C–H activation with NHCs (general procedure C)

Substrate (0.1 mmol, 1 equiv.) was weighed in a 10 mL tube. $[Pd(\pi\text{-allyl})Cl)]_2$ (1.88 mg, 0.005 mmol, 5 mol%), NHCs (0.01 mmol, 10 mol%), Cs_2CO_3 (48.9 mg, 0.15 mmol, 1.5 equiv.), CsOPiv (23.4 mg, 0.1 mmol, 1 equiv.) and 4Å MS (25 mg) were weighted in a glovebox. The tube was closed with a septum, removed from the glovebox, and added solvent (1 mL). The reaction was stirred in a heating block preheated at 140 °C for 15 h. The reaction was cooled to room temperature, filtered through a pad of *Celite*, washed with EtOAc and concentrated *in vacuo*. The crude mixture was analysed by GC-MS and purified by chromatography on silica gel or preparative thin-layer chromatography, providing the desired product.

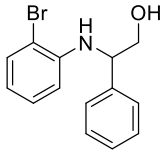
Racemic materials were obtained following the same procedure, using $IBioxMe_4 \cdot HOTf$ as a ligand.

7.2.2 Synthesis of model substrates for C–H activation



X = I, Br, Cl

2-((2-bromophenyl)amino)-2-phenylethan-1-ol (2.6):



Following general procedure A, a mixture of 2-bromoaniline (2.58 g, 15 mmol, 1 equiv.), styrene oxide (5.2 mL, 45 mmol, 3 equiv.), silica gel (10% w/w) in toluene (45 mL, 0.3 M) was heated to 70 ºC overnight. The solvent was evaporated *in vacuo,* and the residue was purified by chromatography on silica gel using cyclohexane/AcOEt as a solvent to afford 2-((2-bromophenyl)amino)-2-phenylethan-1-ol as a yellow solid (3.48 g, 11.9 mmol, 79%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.39 – 7.34 (m, 4H), 7.32 – 7.27 (m, 1H), 7.00 (ddd, *J* = 8.5, 7.3, 1.5 Hz, 1H), 6.54 ("t"d, *J* = 7.6, 1.5 Hz, 1H), 6.42 (dd, *J* = 8.2, 1.5 Hz, 1H), 5.18 (s, 1H), 4.57 (dd, *J* = 6.8, 4.2 Hz, 1H), 4.06 – 3.92 (m, 1H), 3.84 (dd, *J* = 11.3, 6.7 Hz, 1H), 1.72 (s, 1H).

^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 144.12, 139.57, 132.53, 129.07, 128.47, 127.94, 126.79, 118.51, 113.07, 110.50, 67.51, 59.95.

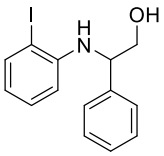
HRMS (ESI): Calcd for $C_{14}H_{15}BrNO$ $[M+H]^+$: 292.0332, found: 292.0331.

IR (neat): ν (cm^{-1}) 3317, 2934, 1595, 1505, 1452, 1323, 1176, 1063, 1012, 933, 854, 740, 698, 673.

Rf 0.18 (Cyclohexane:AcOEt = 7:1)

Melting point: 75 ºC

2-((2-iodophenyl)amino)-2-phenylethan-1-ol (2.6b):



Chemical Formula: $C_{14}H_{14}INO$
Molecular Weight: 339.18

Following general procedure A, a mixture of 2-iodoaniline (2.63 g, 12 mmol, 1 equiv.), styrene oxide (4.1 mL, 36 mmol, 3 equiv.), silica gel (10% w/w) in toluene (40 mL, 0.3 M) was heated to 70 ºC overnight. The solvent was evaporated *in vacuo,* and the residue was purified by chromatography on silica gel using cyclohexane/AcOEt as a solvent to afford 2-((2-iodophenyl)amino)-2-phenylethan-1-ol as a dark solid (2.98 g, 8.73 mmol, 73%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.67 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.35 (d, *J* = 3.8 Hz, 4H), 7.32 – 7.26 (m, 1H), 7.03 (ddd, *J* = 8.3, 7.3, 1.5 Hz, 1H), 6.42 ("t"d, *J* = 7.5, 1.5 Hz, 1H), 6.36 (dd, *J* = 8.2, 1.5 Hz, 1H), 5.07 (s, 1H), 4.57 (dd, *J* = 6.6, 4.2 Hz, 1H), 4.00 (dd, *J* = 11.1, 4.2 Hz, 1H), 3.84 (dd, *J* = 11.1, 6.6 Hz, 1H), 1.73 (s, 1H).

$^{13}C\{^{1}H\}$ NMR (126 MHz, Chloroform-*d*) δ 146.34, 139.50, 139.14, 129.41, 129.06, 127.93, 126.83, 119.37, 112.43, 86.26, 67.52, 60.30.

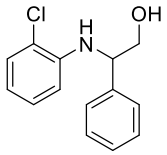
HRMS (ESI): Calcd for $C_{14}H_{15}INO$ $[M+H]^+$: 340.0193, found: 340.0197.

IR (neat): ν (cm^{-1}) 3360, 1584, 1503, 1448, 1304, 1172, 1058, 1006, 740, 643.

Rf 0.22 (Cyclohexane:AcOEt = 7:1)

Melting point: 69 ºC

2-((2-chlorophenyl)amino)-2-phenylethan-1-ol (2.6c):



Chemical Formula: $C_{14}H_{14}ClNO$
Molecular Weight: 247.72

Following general procedure A, a mixture of 2-chloroaniline (510 mg, 4 mmol, 1 equiv.), styrene oxide (1.37 mL, 12 mmol, 3 equiv.), silica gel (10% w/w) in toluene (13 mL, 0.3 M) was heated to 70 ºC overnight. The solvent was evaporated *in vacuo* and the residue was purified by chromatography on silica gel using cyclohexane/AcOEt as a solvent to afford 2-((2-chlorophenyl)amino)-2-phenylethan-1-ol as a yellow solid (874 mg, 3.53 mmol, 88%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.31 (m, 4H), 7.30 – 7.22 (m, 2H), 7.00 – 6.90 (m, 1H), 6.59 ("t"d, *J* = 7.6, 1.5 Hz, 1H), 6.42 (dd, *J* = 8.2, 1.5 Hz, 1H), 5.15 (s, 1H), 4.54 (dd, *J* = 6.8, 4.2 Hz, 1H), 3.96 (dd, *J* = 11.2, 4.3 Hz, 1H), 3.80 (dd, *J* = 11.2, 6.8 Hz, 1H), 1.82 (s, 1H).

$^{13}C\{^{1}H\}$ NMR (126 MHz, Chloroform-*d*) δ 143.16, 139.63, 129.24, 129.05, 127.92, 127.77, 126.77, 119.88, 117.96, 112.97, 67.48j, 59.78.

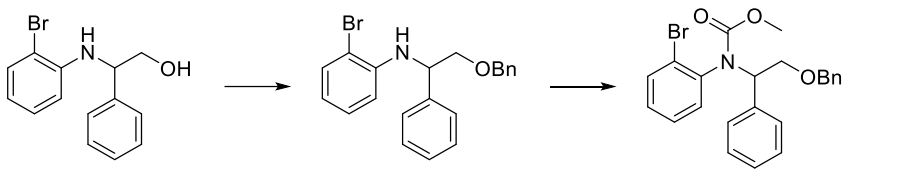
HRMS (ESI): Calcd for $C_{14}H_{15}ClNO$ $[M+H]^+$: 248.0837, found: 248.0839.

IR (neat): ν (cm^{-1}) 3401, 3330, 2936, 1597, 1507, 1451, 1323, 1117, 1031, 933, 858, 740, 698.

Rf 0.25 (Cyclohexane:AcOEt = 7:1)

Melting point: 66.6 ºC

Methyl (2-(benzyloxy)-1-phenylethyl)(2-bromophenyl)carbamate (2.8):



2.6

2.7
Chemical Formula: $C_{21}H_{20}BrNO$
Molecular Weight: 382.30

2.8
Chemical Formula: $C_{23}H_{22}BrNO_3$
Molecular Weight: 440.34

To a solution of 2-((2-bromophenyl)amino)-2-phenylethan-1-ol **2.6** (438 mg, 1.5 mmol, 1 equiv.) in THF (5 mL, 0.3 M) was added NaH (120 mg, 3 mmol, 2 equiv.) and BnBr (215 μL, 1.8 mmol, 1.2 equiv.) at 0 ºC and stirred at room temperature for three hours. NH_4Cl aq was added and extracted with AcOEt, washed with brine, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/ AcOEt (99:1, Rf= 0.25) as solvent to afford the pure compound *N*-(2-(benzyloxy)-1-phenylethyl)-2-bromoaniline **2.7** as a yellow oil (514 mg, 1.34 mmol, 90%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.40 – 7.35 (m, 2H), 7.36 – 7.24 (m, 8H), 6.98 – 6.92 (m, 1H), 6.52 ("t"d, *J* = 7.6, 1.5 Hz, 1H), 6.32 (dd, *J* = 8.2, 1.5 Hz, 1H), 5.32 (d, *J* = 3.7 Hz, 1H), 4.65 – 4.52 (m, 3H), 3.78 (dd, *J* = 9.9, 4.1 Hz, 1H), 3.65 (dd, *J* = 9.9, 8.2 Hz, 1H).

Following general procedure B, a mixture of *N*-(2-(benzyloxy)-1-phenylethyl)-2-bromoaniline **2.7** (514 mg, 1.34 mmol, 1 equiv.) in methyl chloroformate (6 mL) was heated under reflux overnight. The mixture was concentrated *in vacuo*. The crude material was purified by flash column chromatography using cyclohexane/AcOEt as a solvent to afford the pure compound Methyl (2-(benzyloxy)-1-phenylethyl)(2-bromophenyl)carbamate **2.8** as a colourless oil (570 mg, 1.29 mmol, 97%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.58 (dd, *J* = 6.0, 3.5 Hz, 0.4H), 7.45 (dd, *J* = 8.0, 1.5 Hz, 0.6H), 7.40 – 7.00 (m, 12.6H**),** 6.81 – 6.72 (m, 0.4H), 5.74 (br, 0.6H), 5.59 ("t", *J* = 7.1 Hz, 0.4H), 4.72 (d, *J* = 12.0 Hz, 0.6H), 4.66 (d, *J* =12.0Hz, 0.6H), 4.50 (d, *J* = 12.1 Hz, 0.4H), 4.45 (d, J = 12.1 Hz, 0.4H), 4.22 – 4.11 (br, 0.4H), 4.07 (dd, *J* = 10.6, 8.8 Hz, 0.6H), 3.85 (dd, *J* = 10.6, 5.8 Hz, 0.6H), 3.79 (dd, *J* = 9.9, 7.1 Hz, 0.4H), 3.75 – 3.53 (brs, 3H).

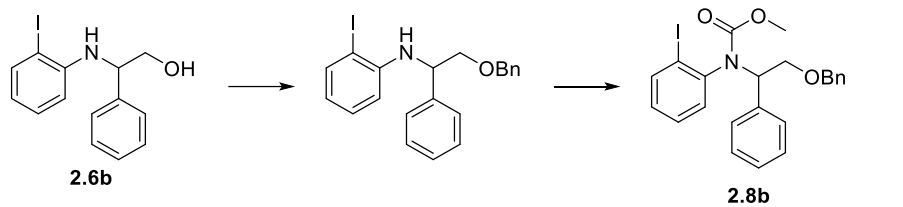
^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 156.10, 155.75, 139.31, 138.55, 138.11, 137.76, 136.25, 133.33, 133.26, 131.25, 129.11, 128.82, 128.51, 128.38, 128.36, 128.25, 128.21, 128.00, 127.96, 127.90, 127.81, 127.69, 127.68, 127.61, 126.64, 125.76, 73.16, 72.96, 69.91, 69.31, 62.36, 60.94, 53.29, 53.28.

HRMS (ESI): Calcd for $C_{23}H_{23}BrNO_3$ $[M+H]^+$: 440.0856, found: 440.0850.

IR (neat): ν (cm^{-1}) 2941, 2861, 1706, 1585, 1441, 1331, 1091, 1029.

Rf 0.3 (Cyclohexane:AcOEt = 10:1)

Methyl (2-(benzyloxy)-1-phenylethyl)(2-iodophenyl)carbamate (2.8b):

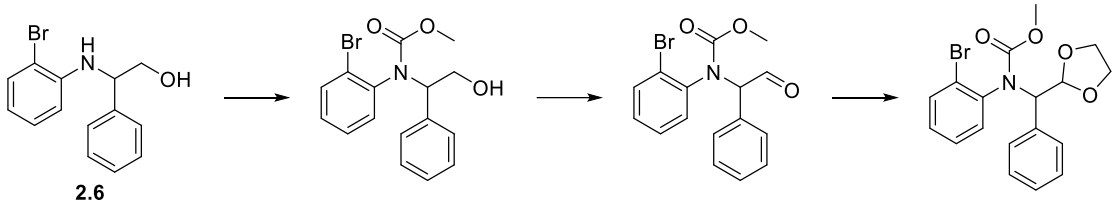


Chemical Formula: $C_{23}H_{22}INO_3$
Molecular Weight: 487.34

To a solution of 2-((2-iodophenyl)amino)-2-phenylethan-1-ol (2.78 g, 8.2 mmol, 1 equiv.) in THF (27 mL, 0.3 M) was added NaH (394 mg, 16.4 mmol, 2 equiv.) and BnBr (1.3 mL, 10.7 mmol, 1.3 equiv.) at 0 ºC and stirred at room temperature for three hours. NH_4Cl aq was added and extracted with AcOEt, washed with brine, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/AcOEt as solvent to afford the pure compound *N*-(2-(benzyloxy)-1-phenylethyl)-2-iodoaniline as a yellow oil (2.99 g, 6.96 mmol, 85%). Following general procedure B, a mixture of *N*-(2-(benzyloxy)-1-phenylethyl)-2-iodoaniline (1.50 g, 3.48 mmol, 1 equiv.) in methyl chloroformate (12 mL) was heated under reflux overnight. The mixture was concentrated *in vacuo*. The crude material was purified by flash column chromatography using cyclohexane/AcOEt as a solvent to afford the pure compound Methyl (2-(benzyloxy)-1-phenylethyl)(2-iodophenyl)carbamate **2.8b** as a colourless oil (1.1 g, 2.28 mmol, 65%).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.85 (dd, *J* = 7.9, 1.5 Hz, 0.4H), 7.74 (dd, *J* = 7.9, 1.5 Hz, 0.6H), 7.43 – 7.23 (m, 8H), 7.22 – 7.15 (m, 2.4H), 7.06 – 7.01 (m, 1.2H), 6.99 – 6.93 (m, 1H), 6.85 (dd, *J* = 7.9, 1.6 Hz, 0.4H), 5.71 (br, 0.6H), 5.53 (“t”, *J* = 7.1 Hz, 0.4H), 4.73 (d, *J* = 12.1 Hz, 0.6H), 4.61 (d, *J* = 12.0 Hz, 0.6H), 4.49 (d, *J* = 12.1 Hz, 0.4H), 4.41 (d, *J* = 12.1 Hz, 0.4H), 4.19 (br, 0.4H), 4.09 (dd, *J* = 10.6, 8.8 Hz, 0.6H), 3.84 (dd, *J* = 10.6, 5.8 Hz, 0.6H), 3.76 (dd, *J* = 9.9, 7.0 Hz, 0.4H), 3.68 (s, 3H).
^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 155.87, 155.47, 143.02, 141.09, 139.80, 139.73, 138.70, 138.13, 138.10, 136.19, 130.60, 130.39, 129.89, 129.86, 129.67, 129.48, 129.13, 128.84, 128.67, 128.51, 128.40, 128.37, 128.34, 128.32, 128.01, 127.98, 127.80, 127.74, 127.63, 103.95, 102.79, 73.15, 72.95, 70.23, 69.57, 62.82, 61.19, 53.32, 53.27.
HRMS (ESI): Calcd for $C_{23}H_{23}INO_3$ $[M+H]^+$: 488.0717, found: 488.0709.
IR (neat): ν (cm^{-1}) 3031, 2951, 2862, 1704, 1441, 1313, 1194, 1093, 1020.
Rf 0.28 (Cyclohexane:AcOEt = 10:1)

methyl ((1,3-dioxolan-2-yl)(phenyl)methyl)(2-bromophenyl)carbamate (2.11):



2.6

2.11

Chemical Formula: $C_{18}H_{20}BrNO_4$

Molecular Weight: 394.27

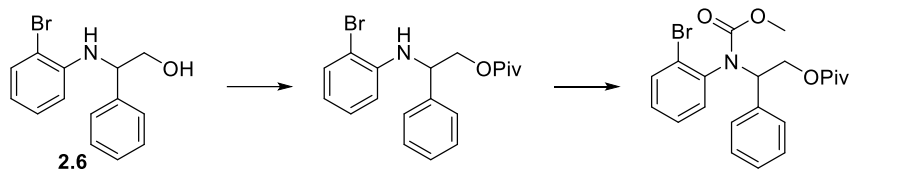
Following general procedure B, a mixture of 2-((2-bromophenyl)amino)-2-phenylethan-1-ol **2.6** (1.75 g, 6 mmol, 1 equiv.) in methyl chloroformate (18 mL) was heated under reflux overnight. The mixture was concentrated *in vacuo*. The crude material was purified by flash column chromatography using cyclohexane/AcOEt (2:1, Rf= 0.25) as a solvent to afford the pure compound methyl (2-bromophenyl)(2-hydroxy-1-phenylethyl)carbamate as a white solid (1.94 g, 5.54 mmol, 92%).

To a solution of methyl (2-bromophenyl)(2-hydroxy-1-phenylethyl)carbamate (502 mg, 1.43 mmol, 1 equiv.) in dichloromethane was added Dess-Martin Periodinan (1.82 g, 4.29 mmol, 3 equiv.) at 0 ºC, then warmed up to r.t. and stirred for 3 h. After reaction completion, diluted with AcOEt and added $NaHCO_3$ aq and Na_2SO_3 aq. extracted with AcOEt, dried over Na_2SO_4 and concentrated *in vacuo.* This material was used for the following reaction without further purification.

To a solution of the crude aldehyde (498 mg, 1.43 mmol, 1 equiv.) in toluene (5 mL) was added ethylene glycol (146 µL, 2.86 mmol, 2 equiv.) and *p*TSA (27 mg, 10 mol%) and stirred at reflux with dean stark apparatus overnight. After cooling to r.t., $NaHCO_3$ aq. was added and extracted by AcOEt, washed with brine, dried over Na_2SO_4 and concentrated i*n vacuo*. The crude material was purified by flash column chromatography using cyclohexane/AcOEt (4:1) as a solvent to afford the pure compound methyl ((1,3-dioxolan-2-yl)(phenyl)methyl)(2-bromophenyl)carbamate **2.11** as a colourless oil (296 mg, 0.76 mmol, 53%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.58 (dd, *J* = 8.0, 1.6 Hz, 0.3H), 7.54 (dd, *J* = 7.9, 1.6 Hz, 0.7H), 7.42 (ddd, *J* = 11.4, 7.7, 2.4 Hz, 1.2H), 7.35 (“t”d, *J* = 7.6, 1.5 Hz, 0.8H), 7.33 – 7.28 (m, 0.8H), 7.26 – 7.19 (m, 1H), 7.19 – 7.09 (m, 2.6H), 7.05 – 6.98 (m, 1.6H), 5.78 (s, 0.25H), 5.65 – 5.48 (m, 1.5H), 5.00 (d, *J* = 6.2 Hz, 0.25H), 4.12 (qt, *J* = 8.1, 4.4 Hz, 1H), 4.07 – 3.76 (m, 3H), 3.66 (d, *J* = 2.7 Hz, 3H).

2-((2-bromophenyl)(methoxycarbonyl)amino)-2-phenylethyl pivalate (2.12):

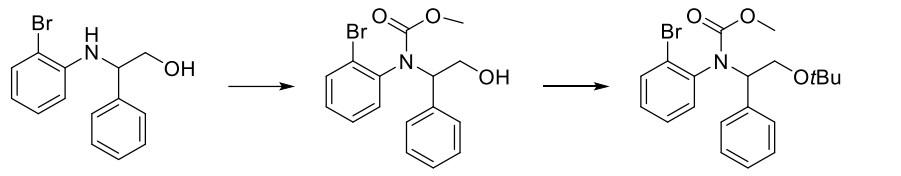


To a solution of 2-((2-bromophenyl)amino)-2-phenylethan-1-ol (250 mg, 0.856 mmol, 1 equiv.) in THF (3 mL, 0.3 M) was added DIPEA (598 μL, 3.42 mmol, 4 equiv.)and PivCl (211 μL, 1.71 mmol, 2 equiv.) at 0 ºC. After 30 min at that temperature, DMAP (10.5 mg, 0.0856 mmol, 10 mol%) was added and stirred at room temperature overnight. NH_4Cl aq was added and extracted with AcOEt, washed with brine, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/AcOEt as solvent to afford the pure compound 2-((2-bromophenyl)amino)-2-phenylethyl pivalate (322 mg, 0.856 mmol, 100%).

Following general procedure B, a mixture of 2-((2-bromophenyl)amino)-2-phenylethyl pivalate (322 mg, 0.856 mmol, 1 equiv.) in methyl chloroformate (3 mL) was heated under reflux overnight. The mixture was concentrated *in vacuo*. The crude material was purified by flash column chromatography using cyclohexane/AcOEt as a solvent to afford the pure compound 2-((2-bromophenyl)(methoxycarbonyl)amino)-2-phenylethyl pivalate **2.12** as a white solid (331 mg, 0.762 mmol, 89%).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.61 (dd, *J* = 7.9, 1.6 Hz, 0.4H), 7.44 (dd, *J* = 8.0, 1.5 Hz, 0.6H), 7.38 – 7.33 (m, 0.6H), 7.31 – 7.21 (m, 3.6H), 7.19 – 7.14 (m, 1.8H), 7.11 ("t"d, *J* = 7.7, 1.8 Hz, 0.4H), 7.06 ("t"d, *J* = 7.6, 1.6 Hz, 0.4H), 7.02 – 6.96 (m, 1.2H), 6.53 (dd, *J* = 7.8, 1.7 Hz, 0.4H), 5.81 (br, 1H), 4.67 – 4.52 (m, 1.6H), 4.53 – 4.39 (m, 0.4H), 3.80 – 3.52 (m, 3H), 1.17 (s, 5.4H), 1.03 (s, 3.6H).
^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 178.29, 178.12, 138.12, 137.53, 134.78, 133.56, 133.52, 130.90, 129.40, 129.35, 129.24, 128.88, 128.53, 128.47, 128.30, 128.25, 128.16, 127.70, 126.89, 125.87, 63.54, 62.77, 60.58, 60.19, 53.49, 53.40, 38.92, 38.73, 27.19, 27.10.
HRMS (ESI): Calcd for $C_{21}H_{24}BrNNaO_4$ $[M+Na]^+$: 456.0781, found: 456.0789.
IR (neat): ν (cm^{-1}) 2969, 0703, 1442, 1388, 1282, 1138, 1033.
Rf 0.33 (Cyclohexane:AcOEt = 10:1)
Melting point: 74 ºC

Methyl (2-bromophenyl)(2-(tert-butoxy)-1-phenylethyl)carbamate (2.13):



2.6 **2.13**

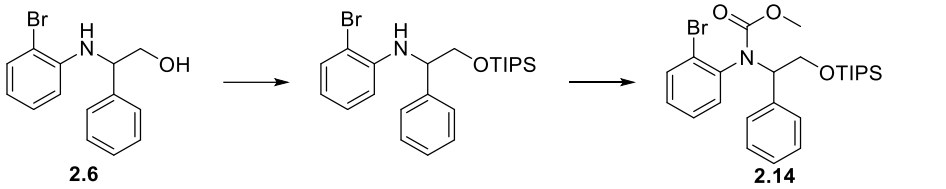
Chemical Formula: $C_{20}H_{24}BrNO_3$
Molecular Weight: 406.32

Following general procedure B, a mixture of 2-((2-bromophenyl)amino)-2-phenylethan-1-ol (1.75 g, 6 mmol, 1 equiv.) in methyl chloroformate (18 mL) was heated under reflux overnight. The mixture was concentrated *in vacuo*. The crude material was purified by flash column chromatography using cyclohexane/AcOEt (2:1, Rf= 0.25) as a solvent to afford the pure compound methyl (2-bromophenyl)(2-hydroxy-1-phenylethyl)carbamate as a white solid (1.94 g, 5.54 mmol, 92%).

In a two-necked flask equipped with a magnetic stirring bar and a condenser coil, $Mg(ClO_4)_2$ (47.5 mg, 0.197 mmol, 10 mol%) and methyl (2-bromophenyl)(2-hydroxy-1-phenylethyl)carbamate (689 mg, 1.97 mmol, 1 equiv.) were dissolved in CH_2Cl_2 (6 mL, 0.3 M). Then Boc_2O (989 mg, 4.53 mmol, 2.3 equiv.) was added, and bubbling was immediately observed. The mixture was stirred at reflux overnight. The crude mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was separated, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography using cyclohexane/AcOEt as a solvent to afford the pure compound Methyl (2-bromophenyl)(2-(*tert*-butoxy)-1-phenylethyl)carbamate **2.13** as a colourless oil (562 mg, 1.38 mmol, 70%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.58 (dd, *J* = 7.9, 1.6 Hz, 0.5H), 7.50 – 7.37 (m, 2H), 7.30 (m, 2H), 7.25 – 7.03 (m, 4.5H), 5.38 ("t", *J* = 6.8 Hz, 0.5H), 5.26 ("t", *J* = 7.1 Hz, 0.5H), 4.11 (br, 0.5H), 3.98 – 3.79 (m, 1H), 3.65 (s, 3H), 3.59 (dd, *J* = 9.4, 6.4 Hz, 0.5H), 1.22 (s, 4.5H), 1.08 (s, 4.5H).
^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 155.93, 155.44, 140.13, 139.06, 138.50, 137.26, 133.15, 133.02, 131.19, 130.82, 129.06, 128.84, 128.55, 128.48, 128.11, 127.97, 127.79, 127.63, 127.62, 127.54, 126.22, 125.73, 73.40, 73.19, 64.26, 62.98, 62.32, 61.17, 53.07, 53.03, 27.63, 27.33.
HRMS (ESI): Calcd for $C_{20}H_{25}BrNO_3$ $[M+H]^+$: 406.1012, found: 406.1004.
IR (neat): ν (cm^{-1}) 2973, 1709, 1586, 1441, 1364, 1308, 1192, 1083, 1028.
Rf 0.25 (Cyclohexane:AcOEt = 20:1)

Methyl (2-bromophenyl)(1-phenyl-2-((triisopropylsilyl)oxy)ethyl)carbamate (2.14):



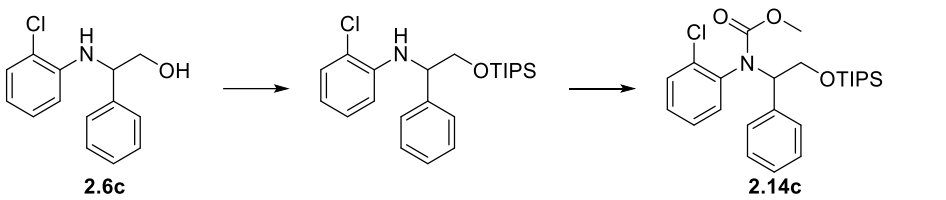
Chemical Formula: $C_{25}H_{36}BrNO_3Si$
Molecular Weight: 506.56

To a solution of 2-((2-bromophenyl)amino)-2-phenylethan-1-ol **2.6** (934 mg, 3.2 mmol, 1 equiv.) in DMF (11 mL, 0.3 M) was added imidazole (327 mg, 4.8 mmol, 1.5 equiv.), DMAP (39 mg, 0.32 mmol, 10 mol%) and TIPSCl (324 μL, 4.8 mmol, 1.3 equiv.) at 0 ºC and stirred at room temperature overnight. H_2O was added and extracted with Et_2O, washed with brine, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/ CH_2Cl_2 (94:6, Rf= 0.35) as a solvent to afford the pure compound 2-bromo-*N*-(1-phenyl-2-((triisopropylsilyl)oxy)ethyl)aniline as a yellow oil (1.03 g, 2.3 mmol, 72%).

Following general procedure B, a mixture of 2-bromo-*N*-(1-phenyl-2-((triisopropylsilyl)oxy)ethyl)aniline (1.31 g, 2.92 mmol, 1 equiv.) in methyl chloroformate (9 mL) was heated under reflux overnight. The mixture was concentrated *in vacuo*. The crude material was purified by flash column chromatography using cyclohexane/AcOEt as a solvent to afford the pure compound Methyl (2-bromophenyl)(1-phenyl-2-((triisopropylsilyl)oxy)ethyl)carbamate **2.14** as a colourless oil (1.26 g, 2.5 mmol, 86%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.58 (dd, *J* = 7.7, 1.8 Hz, 0.4H), 7.51 (ddd, *J* = 8.1, 4.0, 1.6 Hz, 0.6H), 7.46 (dd, *J* = 8.0, 1.5 Hz, 0.6H), 7.41 – 7.27 (m, 2.4H), 7.25 – 6.88 (m, 5H), 5.54 ("t", *J* = 7.4 Hz, 0.6H), 5.28 ("t", *J* = 7.3 Hz, 0.4H), 4.50 (br, 0.4H), 4.20 (dd, *J* = 10.7, 8.8 Hz, 0.6H), 4.11 ("t", *J* = 8.9 Hz, 0.6H), 3.91 (dd, *J* = 10.1, 7.7 Hz, 0.4H), 3.63 (s, 3H), 1.25 – 1.01 (m, 14H), 0.98 (m, 7H).
^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 156.13, 155.51, 140.00, 138.65, 137.94, 136.55, 133.26, 133.16, 131.32, 129.14, 129.00, 128.71, 128.42, 128.13, 128.11, 128.05, 127.85, 127.76, 127.68, 126.76, 125.51, 65.73, 63.67, 63.44, 62.69, 53.15, 53.12, 18.09, 18.08, 18.01, 17.99, 12.10, 12.03.
HRMS (ESI): Calcd for $C_{25}H_{37}BrNO_3Si$ $[M+H]^+$: 506.1721, found: 506.1717.
IR (neat): ν (cm^{-1}) 2944, 2866, 1712, 1586, 1442, 1315, 1194, 1114.
Rf 0.4 (Cyclohexane:AcOEt = 96:4)

Methyl (2-chlorophenyl)(1-phenyl-2-((triisopropylsilyl)oxy)ethyl)carbamate (2.14c):



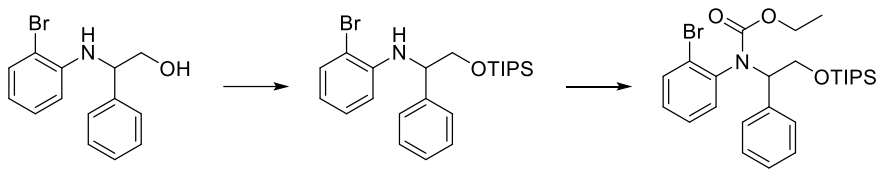
Chemical Formula: $C_{25}H_{36}ClNO_3Si$
Molecular Weight: 462.10

To a solution of 2-((2-chlorophenyl)amino)-2-phenylethan-1-ol (2.04 g, 8.23 mmol, 1 equiv.) in DMF (27 mL, 0.3 M) was added imidazole (840 mg, 12.3 mmol, 1.5 equiv.), DMAP (101 mg, 0.823 mmol, 10 mol%) and TIPSCl (2.3 mL, 12.3 mmol, 1.5 equiv.) at 0 ºC and stirred at room temperature overnight. H_2O was added and extracted with Et_2O, washed with brine, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/ AcOEt (99:1, Rf= 0.63) as a solvent to afford the pure compound 2-chloro-*N*-(1-phenyl-2-((triisopropylsilyl)oxy)ethyl) aniline as a yellow oil (2.86 g, 7.08 mmol, 86%).

Following general procedure B, a mixture of 2-bromo-*N*-(1-phenyl-2-((triisopropylsilyl)oxy)ethyl)aniline (1.63 g, 4.03 mmol, 1 equiv.) in methyl chloroformate (12 mL) was heated under reflux overnight. The mixture was concentrated *in vacuo*. The crude material was purified by flash column chromatography using cyclohexane/AcOEt as a solvent to afford the pure compound Methyl (2-chlorophenyl)(1-phenyl-2-((triisopropylsilyl)oxy)ethyl)carbamate **2.14c** as a colourless oil (1.15 g, 2.48 mmol, 62%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.52 (dd, *J* = 7.6, 1.7 Hz, 0.6H), 7.40 (dd, *J* = 8.0, 1.5 Hz, 0.4H), 7.37 – 6.95 (m, 7.6H), 6.88 (d, *J* = 7.9 Hz, 0.4H), 5.57 (t, *J* = 7.4 Hz, 0.6H), 5.31 (t, *J* = 7.4 Hz, 0.4H), 4.46 (m, 0.4H), 4.19 (dd, *J* = 10.8, 8.9 Hz, 0.6H), 4.12 ("t", *J* = 6.7 Hz, 0.6H), 3.94 (dd, *J* = 10.2, 7.6 Hz, 0.4H), 3.63 (d, *J* = 5.4 Hz, 3H), 1.21 – 1.03 (m, 13H), 0.99 (dd, *J* = 6.5, 3.6 Hz, 8H).
^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 156.30, 155.67, 138.59, 138.34, 136.66, 136.40, 135.68, 134.65, 131.28, 130.02, 129.95, 128.95, 128.53, 128.14, 128.13, 128.04, 127.70, 127.15, 127.05, 65.58, 63.48, 63.25, 62.56, 53.17, 53.14, 18.11, 18.10, 18.03, 18.01, 12.13, 12.05.
HRMS (ESI): Calcd for $C_{25}H_{37}ClNO_3Si$ $[M+H]^+$: 462.2226, found: 462.2224.
IR (neat): ν (cm-1) 2944, 2866, 1714, 1442, 1388, 1312, 1195, 1116.
Rf 0.5 (Cyclohexane:AcOEt = 96:4)

Ethyl (2-bromophenyl)(1-phenyl-2-((triisopropylsilyl)oxy)ethyl)carbamate (2.23):



2.6 **2.23**

Chemical Formula: $C_{26}H_{38}BrNO_3Si$
Molecular Weight: 520.58

To a solution of 2-((2-bromophenyl)amino)-2-phenylethan-1-ol **2.6** (934 mg, 3.2 mmol, 1 equiv.) in DMF (11 mL, 0.3 M) was added imidazole (327 mg, 4.8 mmol, 1.5 equiv.), DMAP (39 mg, 0.32 mmol, 10 mol%) and TIPSCl (324 μL, 4.8 mmol, 1.3 equiv.) at 0 ºC and stirred at room temperature overnight. H_2O was added and extracted with Et_2O, washed with brine, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/ CH_2Cl_2 (94:6, Rf= 0.35) as a solvent to afford the pure compound 2-bromo-*N*-(1-phenyl-2-((triisopropylsilyl)oxy)ethyl) aniline as a yellow oil (1.03 g, 2.3 mmol, 72%).

Following general procedure B, a mixture of 2-bromo-*N*-(1-phenyl-2-((triisopropylsilyl)oxy)ethyl)aniline (686 mg, 1.53 mmol, 1 equiv.) in ethyl chloroformate (6 mL) was heated under reflux overnight. The mixture was concentrated *in vacuo*. The crude material was purified by flash column chromatography using cyclohexane/AcOEt as a solvent to afford the pure compound Ethyl (2-bromophenyl)(1-phenyl-2-((triisopropylsilyl)oxy)ethyl)carbamate **2.23** as a pale yellow oil (760 mg, 1.46 mmol, 95%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.61 – 7.54 (m, 0.4H), 7.51 (dd, *J* = 7.7, 1.6 Hz, 0.6H), 7.46 (dd, *J* = 8.0, 1.4 Hz, 0.6H), 7.40 – 6.99 (m, 7H), 6.92 (d, *J* = 7.0 Hz, 0.4H), 5.55 (br, 0.6H), 5.29 ("t", *J* = 7.4 Hz, 0.4H), 4.49 (br, 0.4H), 4.28 – 3.97 (m, 3.2H), 3.90 (dd, *J* = 10.1, 7.7 Hz, 0.4H), 1.21 – 1.02 (m, 17H), 0.97 (dd, *J* = 6.4, 3.3 Hz, 7H).

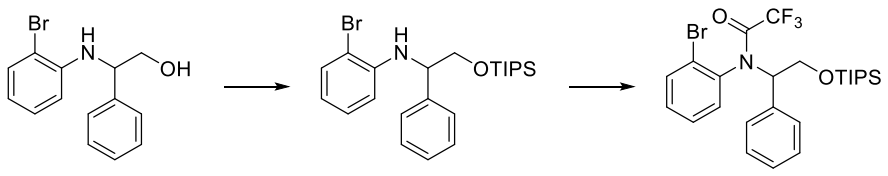
^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 155.51, 154.96, 140.18, 138.47, 137.97, 136.60, 133.08, 133.00, 131.28, 129.05, 128.90, 128.82, 128.56, 128.02, 127.99, 127.90, 127.69, 127.62, 127.52, 126.68, 125.44, 65.39, 63.39, 62.66, 61.7f8, 18.02, 18.01, 17.92, 17.91, 14.64, 14.56, 12.01, 11.93.

HRMS (ESI): Calcd for $C_{26}H_{39}BrNO_3Si$ $[M+H]^+$: 520.1877, found: 520.1877.

IR (neat): ν (cm^{-1}) 2943, 2866, 1708, 1856, 1484, 1404, 1295, 1113.

Rf 0.24 (cyclohexane:AcOEt = 98:2)

***N*-(2-bromophenyl)-2,2,2-trifluoro-*N*-(1-phenyl-2-((triisopropylsilyl)oxy)ethyl)acetamide (2.24)**:



2.6 **2.24**

Chemical Formula: $C_{25}H_{33}BrF_3NO_2Si$
Molecular Weight: 544.53

To a solution of 2-((2-bromophenyl)amino)-2-phenylethan-1-ol (934 mg, 3.2 mmol, 1 equiv.) in DMF (11 mL, 0.3 M) was added imidazole (327 mg, 4.8 mmol, 1.5 equiv.), DMAP (39 mg, 0.32 mmol, 10 mol%) and TIPSCl (324 μL, 4.8 mmol, 1.3 equiv.) at 0 ºC and stirred at room temperature overnight. H_2O was added and extracted with Et_2O, washed with brine, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/ CH_2Cl_2 (94:6, Rf= 0.35) as a solvent to afford the pure compound 2-bromo-*N*-(1-phenyl-2-((triisopropylsilyl)oxy)ethyl) aniline as a yellow oil (1.03 g, 2.3 mmol, 72%).

To a mixture of 2-bromo-*N*-(1-phenyl-2-((triisopropylsilyl)oxy)ethyl)aniline (1.35 g, 3.01 mmol, 1 equiv.) in CH_2Cl_2 (10 mL, 0.3 M) was added Et_3N (1.67 mL, 12 mmol, 4 equiv.), DMAP (37 mg, 0.301 mmol, 10 mol%) and TFAA (837 μL, 6.02 mmol, 2 equiv.) at 0 ºC and stirred at r.t. After the reaction completion, H_2O was added and extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography using cyclohexane/AcOEt as a solvent to afford the pure compound *N*-(2-bromophenyl)-2,2,2-trifluoro-*N*-(1-phenyl-2-((triisopropylsilyl)oxy)ethyl)acetamide **2.24** as a yellow oil (1.62 g, 2.97 mmol, 99%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.67 (ddd, *J* = 11.6, 7.7, 1.9 Hz, 1H), 7.56 (dd, *J* = 8.0, 1.5 Hz, 0.7H), 7.45 (“t”d, *J* = 7.7, 1.5 Hz, 0.7H), 7.41 – 7.30 (m, 2.9H), 7.30 – 7.22 (m, 2H), 7.11 – 7.02 (m, 1.7H), 5.96 (dd, *J* = 9.2, 5.5 Hz, 0.7H), 5.52 (“t”, *J* = 7.0 Hz, 0.3H), 4.60 (dd, *J* = 10.3, 6.5 Hz, 0.3H), 4.27 (dd, *J* = 11.0, 9.3 Hz, 0.7H), 4.17 (dd, *J* = 11.0, 5.5 Hz, 0.7H), 4.07 (dd, *J* = 10.2, 7.6 Hz, 0.3H), 1.28 – 1.11 (m, 16H), 1.10 – 0.92 (m, 5H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 157.72 (q, *J* = 35.7 Hz), 137.05, 136.59, 134.81, 134.80, 134.58, 133.55, 133.37, 133.12, 132.59 (q, *J* = 1.2 Hz), 130.81, 130.61, 129.77, 129.44, 128.89, 128.44, 128.34, 127.74, 127.73, 127.31 (q, *J* = 1.0 Hz), 125.71, 125.70, 116.25 (q, *J* = 289.2 Hz)., 67.65, 64.14, 62.58, 62.29, 18.06, 17.96, 12.06, 11.99.

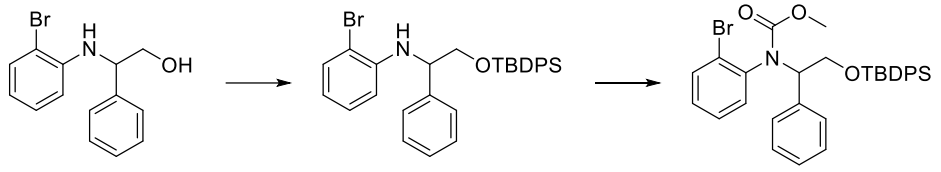
^{19}F{^{1}H} NMR (376 MHz, Chloroform-*d*) δ -68.67, -68.79.

HRMS (ESI): Calcd for $C_{25}H_{34}BrF_3NO_2Si$ $[M+H]^+$: 544.1489, found: 544.1492.

IR (neat): ν (cm^{-1}) 2944, 2867, 1701, 1474, 1205, 1154.

Rf 0.4 (Cyclohexane:AcOEt = 60:1)

Methyl (2-bromophenyl)(2-((tert-butyldiphenylsilyl)oxy)-1-phenylethyl)carbamate (2.25):



2.6 **2.25**

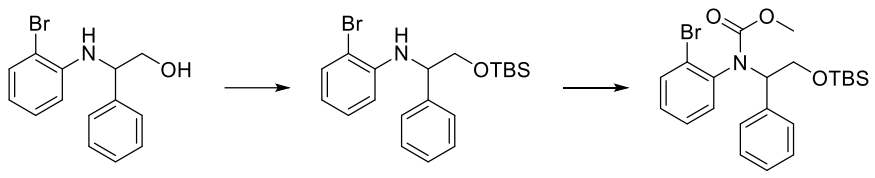
Chemical Formula: $C_{32}H_{34}BrNO_3Si$
Molecular Weight: 588.62

To a solution of 2-((2-bromophenyl)amino)-2-phenylethan-1-ol (584 mg, 2 mmol, 1 equiv.) in DMF (7 mL, 0.3 M) was added imidazole (272 mg, 4 mmol, 2 equiv.) and TBDPSCl (778 µL, 3 mmol, 1.5 equiv.) at 0 ºC and stirred at room temperature overnight. H_2O was added and extracted with Et_2O, washed with brine, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/CH_2Cl_2 as solvent to afford the pure compound 2-bromo-*N*-(2-((*tert*-butyldiphenylsilyl)oxy)-1-phenylethyl)aniline as a yellow oil (982 mg, 1.85 mmol, 93%).

Following general procedure B, a mixture of 2-bromo-*N*-(2-((tert-butyldiphenylsilyl)oxy)-1-phenylethyl)aniline (982 mg, 1.85 mmol, 1 equiv.) in methyl chloroformate (6 mL) was heated under reflux overnight. The mixture was concentrated *in vacuo*. The crude material was purified by flash column chromatography using cyclohexane/AcOEt as a solvent to afford the pure compound Methyl (2-bromophenyl)(2-((*tert*-butyldiphenylsilyl)oxy)-1-phenylethyl)carbamate **2.25** as a colourless oil (1.03 g, 1.75 mmol, 95%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.71 (d"t", *J* = 6.5, 1.6 Hz, 1.2H), 7.65 (d"t", *J* = 6.6, 1.6 Hz, 1.2H), 7.59 – 7.06 (m, 15H), 6.98 (d, *J* = 7.4 Hz, 0.4H), 6.91 (d, *J* = 7.5 Hz, 1.2H), 5.63 (br, 0.6H), 5.32 (t, *J* = 6.9 Hz, 0.4H), 4.34 (m, 0.4H), 4.18 (dd, *J* = 10.9, 9.1 Hz, 0.6H), 4.02 (dd, *J* = 10.4, 5.8 Hz, 0.6H), 3.88 (dd, *J* = 10.6, 7.1 Hz, 0.4H), 3.65 (s, 2H), 3.63 (s, 1H), 1.07 (s, 6H), 0.93 (s, 3H).
^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 156.00, 155.41, 139.72, 138.52, 137.77, 136.02, 135.69, 135.60, 135.57, 135.50, 133.51, 133.28, 133.15, 133.11, 133.01, 131.38, 131.05, 129.79, 129.66, 129.62, 129.05, 128.92, 128.78, 128.67, 128.05, 127.98, 127.80, 127.75, 127.71, 127.68, 127.64, 127.62, 127.60, 126.70, 125.54, 77.36, 65.31, 63.74, 63.21, 53.04, 52.99, 26.86, 26.74, 19.22, 19.10.
HRMS (ESI): Calcd for $C_{32}H_{35}BrNO_3Si$ $[M+H]^+$: 588.1564, found: 588.1556.
IR (neat): ν (cm^{-1}) 3069, 2953, 2858, 1710, 1441, 1315, 1109.
Rf 0.28 (Cyclohexane:AcOEt = 40:1)

Methyl (2-bromophenyl)(2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethyl)carbamate (2.26):



2.6 **2.26**

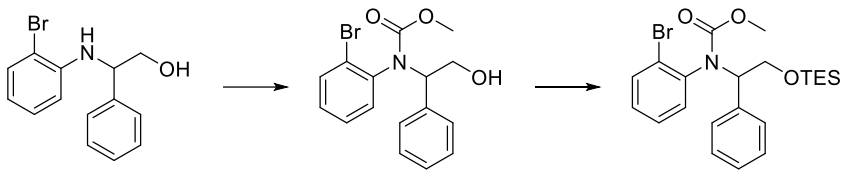
Chemical Formula: $C_{22}H_{30}BrNO_3Si$
Molecular Weight: 464.48

To a solution of 2-((2-bromophenyl)amino)-2-phenylethan-1-ol **2.6** (584 mg, 2 mmol, 1 equiv.) in DMF (7 mL, 0.3 M) was added imidazole (272 mg, 4 mmol, 2 equiv.), DMAP (24 mg, 0.2 mmol, 10 mol%) and TBSCl (520 μL, 3 mmol, 1.5 equiv.) at 0 ºC and stirred at room temperature overnight. H_2O was added and extracted with Et_2O, washed with brine, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/ CH_2Cl_2 (94:6, Rf= 0.35) as a solvent to afford the pure compound 2-bromo-*N*-(2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethyl)aniline as a yellow oil (1.31g, 2.89 mmol, 98%).

Following general procedure B, a mixture of 2-bromo-*N*-(2-((tert-butyldimethylsilyl)oxy)-1-phenylethyl)aniline (737 mg, 1.81 mmol, 1 equiv.) in methyl chloroformate (6 mL) was heated under reflux overnight. The mixture was concentrated *in vacuo*. The crude material was purified by flash column chromatography using cyclohexane/AcOEt as a solvent to afford the pure compound Methyl (2-bromophenyl)(2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethyl)carbamate **2.26** as a colourless oil (780 mg, 1.68 mmol, 93%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.58 (dd, *J* = 7.8, 1.6 Hz, 0.4H), 7.49 – 7.41 (m, 1.2H), 7.40 – 7.01 (m, 7H), 7.00 – 6.94 (m, 0.4H), 5.46 (“t”, *J* = 7.5 Hz, 0.6H), 5.23 (“t”, *J* = 7.1 Hz, 0.4H), 4.39 (br, 0.4H), 4.13 (dd, *J* = 10.9, 8.6 Hz, 0.6H), 4.03 (br, 0.6H), 3.85 (dd, *J* = 10.4, 7.2 Hz, 0.4H), 3.64 (s, 3H), 0.90 (s, 5.4H), 0.79 (s, 3.6H), 0.09 (s, 1.8H), 0.07 (s, 1.8H), -0.01 (s, 1.2H), -0.04 (s, 1.2H).
^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 156.14, 155.56, 140.24, 138.68, 138.07, 136.58, 133.27, 133.16, 131.26, 129.22, 129.05, 128.92, 128.69, 128.16, 128.13, 128.08, 127.87, 127.80, 127.71, 126.69, 125.54, 65.79, 63.67, 63.16, 62.49, 53.19, 53.15, 25.92, 25.91, 18.29, 18.26, -5.19, -5.28, -5.35, -5.43.
HRMS (ESI): Calcd for $C_{22}H_{31}BrNO_3Si$ $[M+H]^+$: 464.1251, found: 464.1244.
IR (neat): ν (cm^{-1}) 2953, 2856, 1711, 1442, 1391, 1314, 1256, 1193, 1108.
Rf 0.16 (Cyclohexane:AcOEt = 60:1)

Methyl (2-bromophenyl)(1-phenyl-2-((triethylsilyl)oxy)ethyl)carbamate (2.27):



2.6 **2.27**

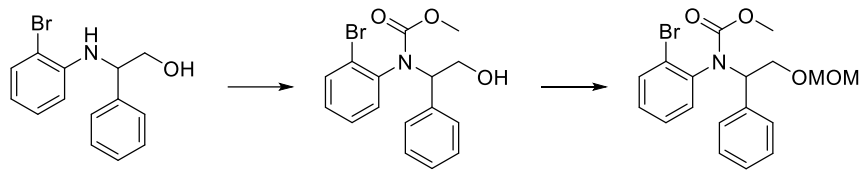
Chemical Formula: $C_{22}H_{30}BrNO_3Si$
Molecular Weight: 464.48

Following general procedure B, a mixture of 2-((2-bromophenyl)amino)-2-phenylethan-1-ol **2.6** (1.75 g, 6 mmol, 1 equiv.) in methyl chloroformate (18 mL) was heated under reflux overnight. The mixture was concentrated *in vacuo*. The crude material was purified by flash column chromatography using cyclohexane/AcOEt (2:1, Rf= 0.25) as a solvent to afford the pure compound methyl (2-bromophenyl)(2-hydroxy-1-phenylethyl)carbamate as a white solid (1.94 g, 5.54 mmol, 92%).

To a solution of methyl (2-bromophenyl)(2-hydroxy-1-phenylethyl)carbamate (350 mg, 1 mmol, 1 equiv.) in CH_2Cl_2 (3 mL) was added 2,6-lutidine (291 μL, 2.5 mmol, 2.5 equiv.) and TESOTf (452 μL, 2 mmol, 2 equiv.) at 0 ºC and stirred at room teperature overnight. NH_4Cl aq was added at 0ºC and extracted with CH_2Cl_2. The organic phases were washed with brine, dried, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography using cyclohexane/AcOEt as a solvent to afford the pure compound Methyl (2-bromophenyl)(1-phenyl-2-((triethylsilyl)oxy)ethyl)carbamate **2.27** as a colourless oil (435 mg, 0.94 mmol, 94%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.58 (dd, *J* = 7.8, 1.7 Hz, 0.4H), 7.50 – 7.40 (m, 1.2H), 7.41 – 7.01 (m, 7H), 6.99 – 6.91 (m, 0.4H), 5.43 (“t”, *J* = 7.3 Hz, 0.6H), 5.24 (“t”, *J* = 7.2 Hz, 0.4H), 4.39 (br, 0.4H), 4.15 (dd, *J* = 10.8, 8.2 Hz, 0.6H), 4.08 (br, 0.6H), 3.86 (dd, *J* = 10.4, 7.3 Hz, 0.4H), 3.65 (s, 3H), 0.95 (t, *J* = 7.9 Hz, 5H), 0.87 (t, *J* = 7.9 Hz, 4H), 0.63 (q, *J* = 8.1 Hz, 3.4H), 0.53 (q, *J* = 7.7 Hz, 2.6H).
^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 156.02, 155.44, 140.09, 138.56, 138.09, 136.63, 133.17, 133.05, 131.20, 131.19, 129.11, 128.92, 128.83, 128.58, 128.08, 128.04, 128.03, 127.97, 127.94, 127.75, 127.67, 127.64, 126.48, 125.49, 65.65, 63.82, 62.95, 62.05, 53.07, 53.03, 6.76, 6.69, 4.48, 4.30.
HRMS (ESI): Calcd for $C_{22}H_{31}BrNO_3Si$ $[M+H]^+$: 464.1251, found: 464.1250.
IR (neat): ν (cm^{-1}) 2953, 2877, 1711, 1586, 1442, 1391, 1314, 1193, 1108, 1009.
Rf 0.15 (Cyclohexane:AcOEt = 40:1)

Methyl (2-bromophenyl)(2-(methoxymethoxy)-1-phenylethyl)carbamate (2.28):



2.6 **2.28**

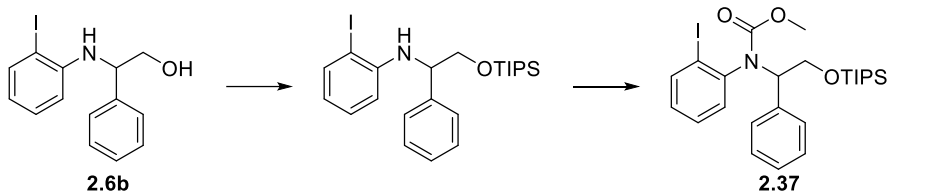
Chemical Formula: $C_{18}H_{20}BrNO_4$
Molecular Weight: 394.27

Following general procedure B, a mixture of 2-((2-bromophenyl)amino)-2-phenylethan-1-ol **2.6** (1.75 g, 6 mmol, 1 equiv.) in methyl chloroformate (18 mL) was heated under reflux overnight. The mixture was concentrated *in vacuo*. The crude material was purified by flash column chromatography using cyclohexane/AcOEt (2:1, R= 0.25) as a solvent to afford the pure compound methyl (2-bromophenyl)(2-hydroxy-1-phenylethyl)carbamate as a white solid (1.94 g, 5.54 mmol, 92%).

To a solution of Methyl (2-bromophenyl)(2-hydroxy-1-phenylethyl)carbamate (700 mg, 2 mmol, 1 equiv.) was added DIPEA (2.1 mL, 12 mmol, 6 equiv.) and MOMBr (653 µL, 8 mmol, 4 equiv.) at 0 ºC and stirred at room temperature for 4 h. After reaction completion, NH_4Cl aq was added and extracted with CH_2Cl_2. The organic layer was separated, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo.* The crude material was purified by flash column chromatography using cyclohexane/AcOEt as a solvent to afford the pure compound Methyl (2-bromophenyl)(2-(methoxymethoxy)-1-phenylethyl)carbamate **2.28** as a colourless oil (618 mg, 1.57 mmol, 78%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.66 – 7.57 (m, 0.4H), 7.53 – 7.42 (m, 0.6H), 7.38 – 7.27 (m, 3H), 7.25 – 7.01 (m, 4.6H), 6.74 – 6.61 (m, 0.4H), 5.63 (“t”, *J* = 7.2 Hz, 1H), 4.76 – 4.67 (m, 1.2H), 4.55 (m, 0.8H), 4.14 (dd, *J* = 10.5, 8.2 Hz, 0.8H), 4.03 (dd, *J* = 10.5, 6.7 Hz, 0.6H), 3.88 (dd, *J* = 10.1, 8.0 Hz, 0.6H), 3.66 (s, 3H), 3.35 (s, 1.8H), 3.23 (s, 1.2H).
^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ δ 155.93, 155.64, 138.72, 138.28, 137.81, 135.98, 133.34, 133.24, 131.14, 131.01, 129.10, 128.85, 128.75, 128.35, 128.15, 128.13, 127.99, 127.83, 127.57, 126.49, 125.68, 96.62, 96.43, 67.59, 66.56, 61.82, 61.22, 55.58, 55.46, 53.24, 53.21.
HRMS (ESI): Calcd for $C_{18}H_{20}BrNNaO_4$ $[M+Na]^+$: 416.0468, found: 416.0476.
IR (neat): ν (cm^{-1}) 2951, 2886, 1706, 1585, 1441, 1308, 1193, 1149, 1110, 1030.
Rf 0.5 (Cyclohexane:AcOEt = 3:1)

Methyl (2-iodophenyl)(1-phenyl-2-((triisopropylsilyl)oxy)ethyl)carbamate (2.37):



2.6b **2.37**

Chemical Formula: $C_{25}H_{36}INO_3Si$
Exact Mass: 553.15

The same procedure as **2.14** was applied to the synthesis of Methyl (2-iodophenyl)(1-phenyl-2-((triisopropylsilyl)oxy)ethyl)carbamate **2.37**.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.84 (dd, *J* = 7.9, 1.5 Hz, 0.3H), 7.75 (dd, *J* = 7.9, 1.5 Hz, 0.7H), 7.50 (dd, *J* = 7.9, 1.7 Hz, 0.7H), 7.44 – 7.32 (m, 1.3H), 7.33 – 7.27 (m, 1H), 7.24 (dd, *J* = 6.8, 1.9 Hz, 0.7H), 7.22 – 7.13 (m, 1.6H), 7.09 – 6.89 (m, 2.7H), 5.61 – 5.44 (m, 0.7H), 5.21 (t, *J* = 7.4 Hz, 0.3H), 4.57 (s, 0.3H), 4.20 (dd, *J* = 10.7, 8.9 Hz, 0.7H), 4.09 (d, *J* = 10.7 Hz, 0.7H), 3.87 (dd, *J* = 10.1, 7.6 Hz, 0.3H), 3.64 (s, 3H), 1.22 – 1.02 (m, 15H), 0.98 (dd, *J* = 6.6, 3.9 Hz, 6H).

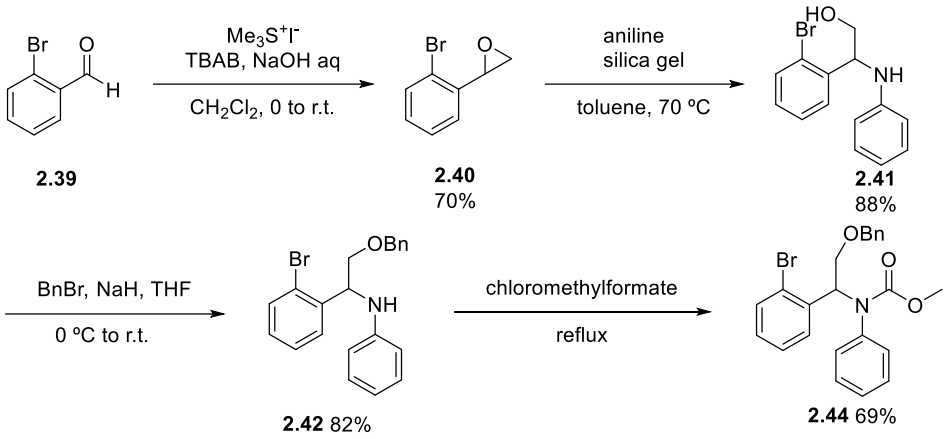
^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ 155.92, 155.23, 141.28, 139.72, 139.63, 138.78, 136.51, 130.71, 129.54, 129.16, 129.08, 128.84, 128.79, 128.25, 128.18, 128.15, 127.74, 104.23, 102.51, 63.90, 63.74, 53.21, 53.15, 18.13, 18.11, 18.05, 18.04, 12.12, 12.05.

HRMS (ESI): Calcd for $C_{25}H_{37}INO_3Si$ $[M+H]^+$: 554.1582, found: 554.1584.

IR (neat): ν (cm^{-1}) 2943, 2866, 1712, 1580, 1468, 1389, 1314, 1193, 1112, 1017.

Rf 0.5 (Cyclohexane:AcOEt = 96:4)

Methyl (2-(benzyloxy)-1-(2-bromophenyl)ethyl)(phenyl)carbamate (2.44):



To a solution of *ortho*-bromo-acetaldehyde **2.39** (5.35 g, 28.9 mmol, 1 equiv.) in CH_2Cl_2 (80 mL) was added Me_3SI (14.7 g, 72.3 mmol, 2.5 equiv.) and TBAB (373 mg, 116 mmol, 4 mol%), then 50% NaOH aq (40 mL) at 0 ºC. After 14 h at r.t., H_2O was added to the reaction mixture, and the resulting solution was extracted with CH_2Cl_2. After being concentrated *in vacuo*, MeOH was added, and $NaHSO_3$ aq as well. H_2O was added to dilute after shaking for 30 seconds and extracted with 10% AcOEt/cyclohexane. The organic layer was concentrated *in vacuo*, and this residue **2.40** was employed without further purification (4 g, 20.1 mmol, 70%).

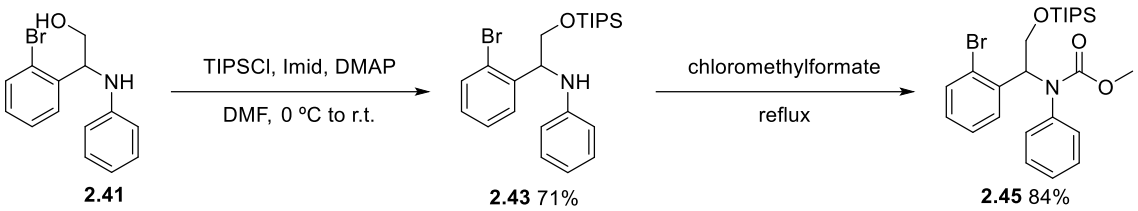
Following general procedure A, to a solution of **2.40** (3.58 g, 18 mmol, 3 equiv.) in toluene (15 mL) and *ortho*-bromoaniline (548 μL, 6 mmol, 1 equiv.) was added silica gel (10% w/w) and stirred for 8 h at 70 ºC. After reaction completion, the solvent was evaporated. Then, the residue was purified with silica gel column chromatography (cyclohexane:AcOEt = 4:1, Rf= 0.29) to obtain **2.41** (1.54 g, 5.28 mmol, 88%).

To a solution of **2.41** (960 mg, 3.29 mmol, 1 equiv.) in THF (11 mL, 0.3 M) was added NaH (263 mg, 6.58 mmol, 1 equiv.) at 0 ºC and stirred for 30 min. BnBr (472 μL, 3.95 mmol, 1.2 equiv.) was added at 0 ºC and stirred at room temperature overnight. NH_4Cl aq was added and extracted with AcOEt, washed with brine, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/AcOEt (15:1, Rf= 0.28) as solvent to afford the pure compound **2.42** as a yellow oil (1.04 g, 2.72 mmol, 83%).

Following general procedure B, a mixture of **2.42** (1.04 g, 2.72 mmol, 1 equiv.) in methyl chloroformate (9 mL) was heated under reflux overnight. The mixture was concentrated *in vacuo*. The crude material was purified by flash column chromatography using cyclohexane/AcOEt (10:1, Rf= 0.16) as a solvent to afford the pure compound **2.44** as a yellow oil (821 mg, 1.86 mmol, 69%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.58 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.38 – 7.25 (m, 5H), 7.21 – 7.13 (m, 3H), 7.05 (d"t"d, *J* = 16.1, 7.4, 1.7 Hz, 2H), 6.89 – 6.82 (m, 3H), 6.07 (dd, *J* = 8.0, 6.7 Hz, 1H), 4.74 – 4.53 (m, 2H), 4.07 (dd, *J* = 10.2, 8.0 Hz, 1H), 3.87 (dd, *J* = 10.2, 6.7 Hz, 1H), 3.69 (s, 3H).

Methyl (2-(benzyloxy)-1-(2-bromophenyl)ethyl)(phenyl)carbamate(2.45):



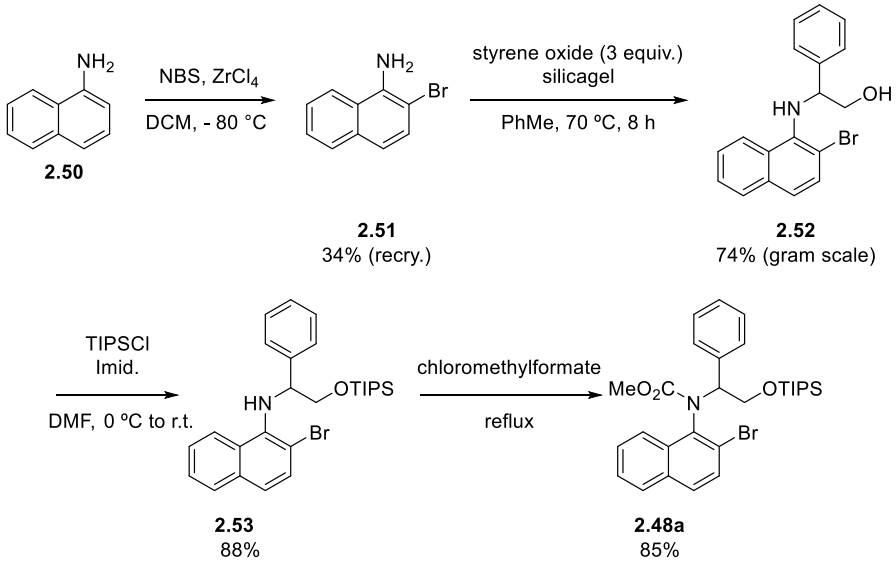
2.41 **2.43** 71% **2.45** 84%

To a solution of **2.41** (584 mg, 2 mmol, 1 equiv.) in DMF (7 mL, 0.3 M) was added imidazole (272 mg, 4 mmol, 1 equiv.), DMAP (24 mg, 0.2 mmol, 10 mol%) and TIPSCl (643 µL, 3 mmol, 1.5 equiv.) were added at 0 ºC and stirred at room temperature overnight. NH_4Cl aq was added and extracted with Et_2O, washed with brine, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/CH_2Cl_2 (98:2, Rf= 0.22) as a solvent to afford the pure compound **2.43** as a yellow oil (640 mg, 1.43 mmol, 71%).

Following general procedure B, a mixture of **2.43** (640 mg, 1.43 mmol, 1 equiv.) in methyl chloroformate (6 mL) was heated under reflux overnight. The mixture was concentrated *in vacuo*. The crude material was purified by flash column chromatography using cyclohexane/AcOEt (60:1) as a solvent to afford the pure compound **2.45** as a yellow oil (610 mg, 1.20 mmol, 84%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.61 – 7.53 (m, 1H), 7.23 – 7.16 (m, 3H), 7.09 – 7.03 (m, 2H), 7.01 – 6.90 (m, 3H), 5.84 (dd, *J* = 8.0, 6.8 Hz, 1H), 4.30 (dd, *J* = 10.3, 8.1 Hz, 1H), 4.09 (dd, *J* = 10.3, 6.8 Hz, 1H), 3.68 (s, 3H), 1.39 – 0.78 (m, 21H).

Methyl (2-bromonaphthalen-1-yl)(1-phenyl-2-((triisopropylsilyl)oxy)ethyl)carbamate (2.48a):



A solution of NBS (2.67 g, 15 mmol, 1 equiv.) in CH_2Cl_2 (120 mL) was cooled to -80 ºC, followed by an addition of $ZrCl_4$ (175 mg, 0.75 mmol, 5 mol%) and 1-aminonaphthalene **2.50** (2.15 g, 15 mmol, 1 equiv.) under argon atmosphere. The reaction mixture was stirred for 4 h and then quenched with $NaHCO_3$ aq. The reaction mixture was extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified with PE as white needles and then recrystallisation with pentane to obtain **2.51** as pale violet solid (11.3 g, 5.09 mmol, 34%).

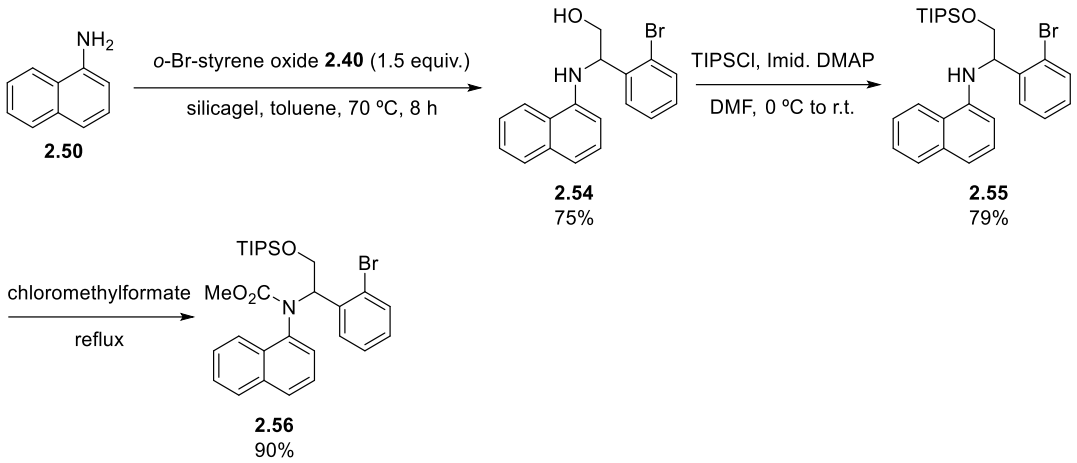
Following general procedure A, to a solution of **2.51** (1 g, 4.5 mmol, 1 equiv.) and styrene oxide (1.55 mL, 13.5 mmol, 3 equiv.) in toluene (13 mL) was added silica gel (10% w/w) and stirred for 8 h at 70 ºC. After reaction completion, the solvent was evaporated. The residue was purified with silica gel column chromatography cyclohexane/AcOEt (12:1, Rf= 0.26) to obtain **2.52** (1.14 g, 3.33 mmol, 74%). To a solution of **2.52** (1.14 g, 3.33 mmol, 1 equiv.) in DMF (10 mL) was added imidazole (453 mg, 6.66 mmol, 2 equiv.), DMAP (41 mg, 0.33 mmol, 10 mol%) and TIPSCl (1.1 mL, 5 mmol, 1.5 equiv.) were added at 0 ºC and stirred at room temperature overnight. NH_4Cl aq was added and extracted with Et_2O, washed with brine, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/CH_2Cl_2 (96:4, Rf= 0.18) as solvent to afford the pure compound **2.53** as a yellow oil (1.46 g, 2.93 mmol, 88%).

Following general procedure B, a mixture of **2.43** (1.46 g, 2.93 mmol, 1 equiv.) in methyl chloroformate (10 mL) was heated under reflux overnight. The mixture was concentrated *in vacuo*. The crude material was purified by flash column chromatography using cyclohexane/CH_2Cl_2 (80:20, Rf= 0.11) as a solvent to afford the pure compound **2.48a** as a yellow oil (1.39 g, 2.93 mmol, 85%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.30 (d, *J* = 8.0 Hz, 0.7H), 7.98 (d, *J* = 8.6 Hz, 0.3H), 7.79 (d, *J* = 19.6 Hz, 1H), 7.67 – 7.50 (m, 2H), 7.50 – 7.34 (m, 2H), 7.24 (d, *J* = 1.9 Hz, 1H), 7.21 – 6.91 (m, 4H),

5.25 (t, *J* = 6.9 Hz, 0.3H), 5.10 – 4.96 (m, 0.7H), 4.86 (t, *J* = 7.5 Hz, 0.7H), 4.52 – 4.40 (m, 0.3H), 4.40 – 4.31 (m, 0.3H), 4.17 (dd, *J* = 9.8, 7.3 Hz, 0.7H), 3.58 (s, 2.2H), 3.56 (s, 0.8H), 1.19 – 0.90 (m, 21H).

Methyl (1-(2-bromophenyl)-2-((triisopropylsilyl)oxy)ethyl)(naphthalen-1-yl)carbamate (2.56):



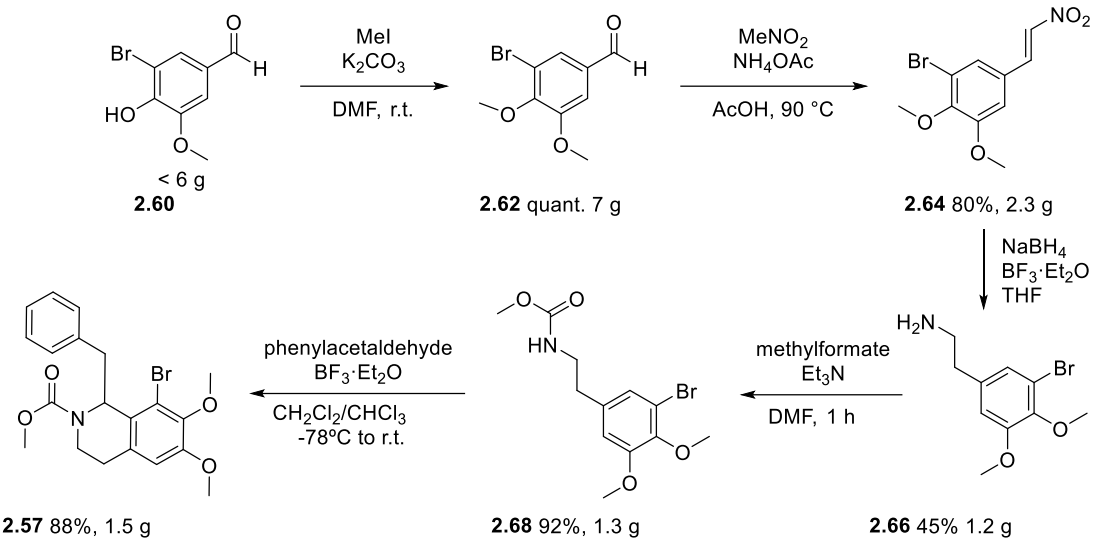
A solution of 1-aminonaphthalene **2.50** (645 µL, 5 mmol, 1 equiv.), **2.40** (1.5 g, 7.5 mmol, 1.5 equiv.) and silica gel (10% w/w) in toluene (15 mL) was stirred for 8 h at 60 ºC. After reaction completion, the solvent was evaporated *in vacuo*. The crude material was purified by flash column chromatography using cyclohexane/AcOEt (8:1, Rf= 0.25) as a solvent to afford the pure compound as a yellow oil **2.54** (1.29 g, 3.77 mmol, 75%).

To a solution of **2.54** (1.29 g, 3.77 mmol, 1 equiv.) in DMF (10 mL) was added imidazole (513 mg, 7.54 mmol, 2 equiv.), DMAP (41 mg, 0.33 mmol, 10 mol%) and TIPSCl (1.2 mL, 5.66 mmol, 1.5 equiv.) were added at 0 ºC and stirred at room temperature overnight. NH_4Cl aq was added and extracted with Et_2O, washed with brine, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/CH_2Cl_2 (96:4, Rf= 0.34) as a solvent to afford the pure compound **2.55** as a yellow oil (1.48 g, 2.96 mmol, 79%).

Following general procedure B, a mixture of **2.55** (738 mg, 1.48 mmol, 1 equiv.) in methyl chloroformate (6 mL) was heated under reflux overnight. The mixture was concentrated *in vacuo*. The crude material was purified by flash column chromatography using cyclohexane/AcOEt (60:1, Rf= 0.2) as a solvent to afford the pure compound **2.56** as a yellow oil (741 mg, 1.33 mmol, 90%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87 – 7.66 (m, 3H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.51 – 7.38 (m, 2H), 7.34 (s, 1H), 7.21 (s, 1H), 7.14 – 7.05 (m, 1H), 6.90 (m, 1H), 6.78 (m, 1H), 6.07 (m, 0.7H), 5.98 (m, 0.3H), 4.55 (m, 0.4H), 4.43 (m, 0.2H), 4.06 (d, *J* = 9.1 Hz, 0.8H), 3.93 (dd, *J* = 10.3, 6.2 Hz, 0.6H), 3.56 (s, 3H), 1.06 (m, 21H).

Methyl 1-benzyl-8-bromo-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (2.57):



Following the literature[211], **2.62** was synthesised successfully in quantitative yield.

2.62 (2.45 g, 10 mmol, 1 equiv.) was dissolved in AcOH (12 mL), and NH_4OAc (1.2 g, 15 mmol, 1.5 equiv.) and $MeNO_2$(1.62 mL, 30 mmol, 3 equiv.) were added successively. The resulting mixture was heated to 90 ºC for 18 h. After this time, the reaction mixture was cooled to r.t., quenched with H_2O and filtered. The filtrate was extracted with AcOEt, and the organic extracts combined with the filtrate, dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound **2.64,** which was used without further purification (2.3 g, 8 mmol, 80%).

A flame-dried, nitrogen-flushed, 100 ml flask equipped with a septum inlet, magnetic stirring bar and reflux condenser was cooled to 0 ºC. $NaBH_4$ (1.25 g, 33 mmol, 3.3 equiv.) was placed in the flask, followed by sequential addition of THF (40 ml) and BF_3-Et_2O (5 mL, 40 mmol, 4 equiv.) at 0 ºC. After the addition, the ice bath was removed, and the contents were stirred at room temperature for 20 min. The solution of **2.64** (2.88 g, 10 mmol, 1 equiv.) in THF (10 mL) was injected into the reaction flask via a syringe. The reaction was allowed to proceed at reflux overnight and quenched by the careful addition of ice. Most of the THF was removed on a rotary evaporator, and the reaction mixture was acidified by 1N HCl and then heated at 80-90 ºC (oil bath) for 2 h. After cooling to room temperature, The acidic layer was washed with ether (3x50 ml). Then, the aqueous phase was basified by adding 2M NaOH aq. Solid NaCl was added, and the product was extracted into ether. The combined ethereal extracts were dried over anhydrous Na_2SO_4., and the solvent was removed under reduced pressure to obtain **2.66** (1.17 g, 4.5 mmol, 45%).

To a solution of **2.66** (1.17 g, 4.5 mmol, 1 equiv.) and Et_3N (688 µL, 4.95 mmol, 1.1 equiv.) in DMF (14 mL) was added methyl chloroformate (383 µL, 4.95 mmol, 1.1 equiv.) at 0°C. The reaction mixture was stirred for 1 h at room temperature and diluted with Et_2O. The solution was washed three times with

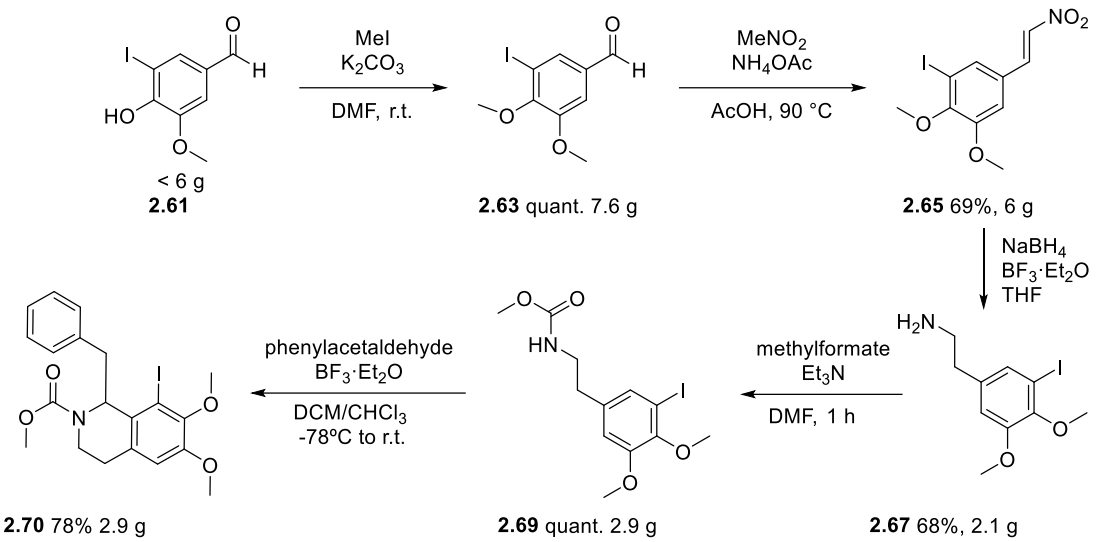
water. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to obtain **2.68** (1.31 g, 4.12 mmol, 92%). The residue was used for the following reaction without further purification.

A mixture of **2.68** (1.25 g, 3.92 mmol, 1 equiv.) and phenylacetaldehyde (1 mL, 8.62 mmol, 2.2 equiv.) in mixed solvents of CH_2Cl_2 and $CHCl_3$ (40:40 mL) was introduced by dropwise addition of BF_3-Et_2O (944 μL, 7.45 mmol, 1.9 equiv.) at -78 ºC. The resulting solution was stirred at room temperature, and TLC monitored the reaction. The reaction was quenched with $NaHCO_3$ aq, which was extracted with CH_2Cl_2. After the solvent removal, the residue was purified by silica gel column chromatography using cyclohexane/AcOEt (3:1, Rf= 0.25) to obtain **2.57** (1.45 g, 3.45 mmol, 88%) as a white solid.

^{1}H NMR is in good agreement with the literature.[212]
Major of rotamers (ratio of rotamers ≈ 70:30)
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 – 7.27 (m, 3H), 7.25 – 7.13 (m, 2H), 6.66 (s, 1H), 5.46 (dd, *J* = 10.3, 3.3 Hz, 1H), 4.23 – 4.15 (m, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.51 (ddd, *J* = 13.3, 10.2, 5.1 Hz, 1H), 3.30 (dd, *J* = 14.0, 3.4 Hz, 1H), 3.26 (s, 3H), 2.96 – 2.83 (m, 1H), 2.80 (dd, *J* = 13.9, 10.3 Hz, 1H), 2.68 (dt, *J* = 16.2, 4.5 Hz, 1H).

Minor of rotamers
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.28 (d, *J* = 6.2 Hz, 3H), 7.25 – 7.13 (m, 2H), 6.62 (s, 1H), 5.64 (dd, *J* = 9.0, 4.4 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.72 (dt, *J* = 12.7, 6.3 Hz, 1H), 3.60 (s, 3H), 3.54 (ddd, *J* = 13.2, 9.8, 5.4 Hz, 1H), 3.37 (dd, *J* = 14.2, 4.5 Hz, 1H), 2.96 – 2.80 (m, 1H), 2.70 (dt, *J* = 16.3, 5.1 Hz, 1H), 2.42 (dt, *J* = 16.0, 5.8 Hz, 1H).

Methyl 1-benzyl-8-iodo-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (2.70):



The same procedures were applied to the synthesis of **2.70** as **2.57**.

The crude was purified by silica gel column chromatography using cyclohexane/AcOEt (3:1, Rf= 0.26) to obtain **2.70** as orange oil.

Major of rotamers (ratio of rotamers ≈ 70:30)

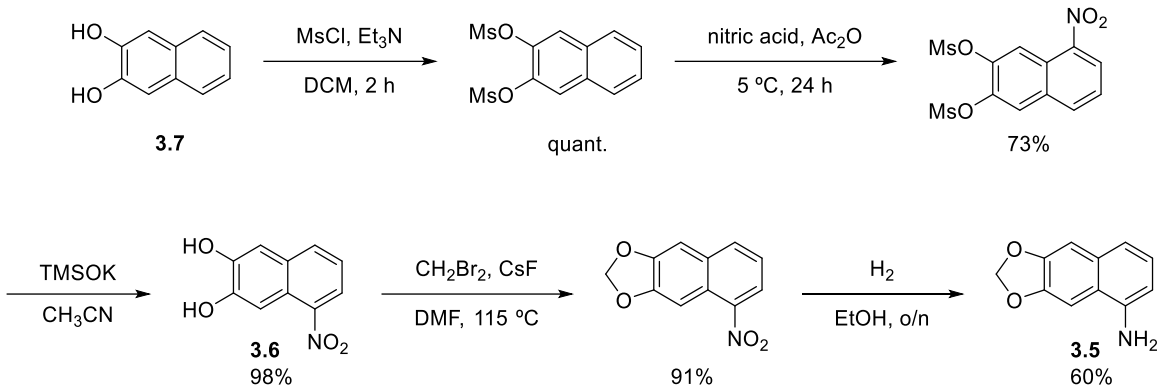
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.28 (d, *J* = 6.2 Hz, 3H), 7.26 – 7.13 (m, 2H), 6.68 (s, 1H), 5.41 (dd, *J* = 10.5, 3.4 Hz, 1H), 4.14 – 4.05 (m, 1H), 3.86 (s, 3H), 3.84 (s, 3jH), 3.54 (ddd, *J* = 13.2, 9.8, 5.4 Hz, 1H), 3.36 – 3.28 (m, 1H), 3.28 (s, 3H), 2.96 – 2.80 (m, 1H), 2.80 – 2.72 (m, 1H), 2.70 (dt, *J* = 16.3, 5.1 Hz, 1H).

Minor of rotamers

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 – 7.27 (m, 1H), 7.25 – 7.16 (m, 3H), 7.16 – 7.08 (m, 1H), 6.59 (s, 1H), 5.69 (dd, *J* = 8.8, 4.4 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.80 – 3.72 (m, 1H), 3.60 (s, 3H), 3.51 (ddd, *J* = 13.3, 10.2, 5.1 Hz, 1H), 3.37 (dd, *J* = 14.1, 4.3 Hz, 1H), 2.96 – 2.83 (m, 1H), 2.68 (dt, *J* = 16.2, 4.5 Hz, 1H), 2.41 (dt, *J* = 16.1, 5.4 Hz, 1H).

7.2.3 Synthesis of substrate for the total synthesis of 10-*O*-demethylbocconoline

Naphtho[2,3-*d*][1,3]dioxol-5-amine (3.5):



To a solution of 2,3-naphthalenediol (5 g, 31.2 mmol, 1 equiv.) in CH_2Cl_2 (50 mL) was added Et_3N (20 mL, 144 mmol, 4.6 equiv.) and then MsCl (14.3 g, 125 mmol, 4 equiv.) dropwise at 0 ºC. After 2 h at r.t., the white precipitate was collected by filtration and washed with ethanol to yield 2,3-dihydroxynaphthalene dimesitylate (15 g, 41.5 mmol, quant.) as a colourless solid.

To a solution of 2,3-dihydroxynaphthalene dimesitylate (5 g, 15.8 mmol, 1 equiv.) in acetic anhydride (51 mL), conc. HNO_3 (11.6 mL) was dropwise added while maintaining the reaction mixture at 35-40 °C. The mixture was then cooled to 5 °C, and stirred for 1 day. After the reaction mixture was poured into ice water, the resulting precipitates were collected and recrystallised from CH_3CN to give 5-nitronaphthalene-2,3-diyl dimethanesulfonate (4.17 g, 11.5 mmol, 73%) as orange solid.

To a solution of 5-nitronaphthalene-2,3-diyl dimethanesulfonate (1 g, 2.77 mmol, 1 equiv.) in CH_3CN was added potassium trimethylsilanolate (7.1 g, 55.4 mmol, 20 equiv.) at r.t. After 6 h, brine was added to quench, acidify the solution to pH 5 with conc. HCl, extracted with AcOEt. The organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford **3.6** (582 mg, 2.84 mmol, quant.)

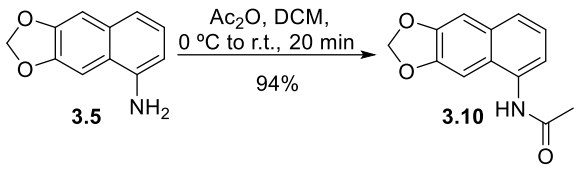
CsF (2.15 g, 14.2 mmol, 5 equiv.) was added to a solution of **3.6** (582 mg, 2.84 mmol, 1 equiv.) in DMF (6 mL), and then the mixture was stirred at rt for 1.5 h. To the mixture, CH_2Br_2 (300 μL, 4.26 mmol, 1.5 equiv.) was added, which was heated at 115 °C for 2.5 h. After the mixture was diluted with AcOEt and the insoluble material was removed by filtration, the mixture was washed with a 5% NaOH aqueous solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give 5-nitronaphtho[2,3-*d*][1,3]dioxole (563 mg, 2.59 mmol, 91%).

A solution of 5-nitronaphtho[2,3-*d*][1,3]dioxole (2.72 g, 12.5 mmol, 1 equiv.) and 10% Pd/C (20 mg, 0.188 mmol, 1.5 mol%) in EtOH (42 mL) was stirred under H_2 atmosphere overnight. After the reaction

completion, it was filtered over *Celite* and concentrated *in vacuo* to obtain naphtho[2,3-*d*][1,3]dioxol-5-amine **3.5** (1.41 g, 7.53 mmol, 60%) as pale violet fluffy solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.19 – 7.12 (m, 3H), 7.09 (s, 1H), 6.69 (dd, *J* = 6.4, 2.2 Hz, 1H), 6.03 (s, 2H), 3.92 (s, 3H).

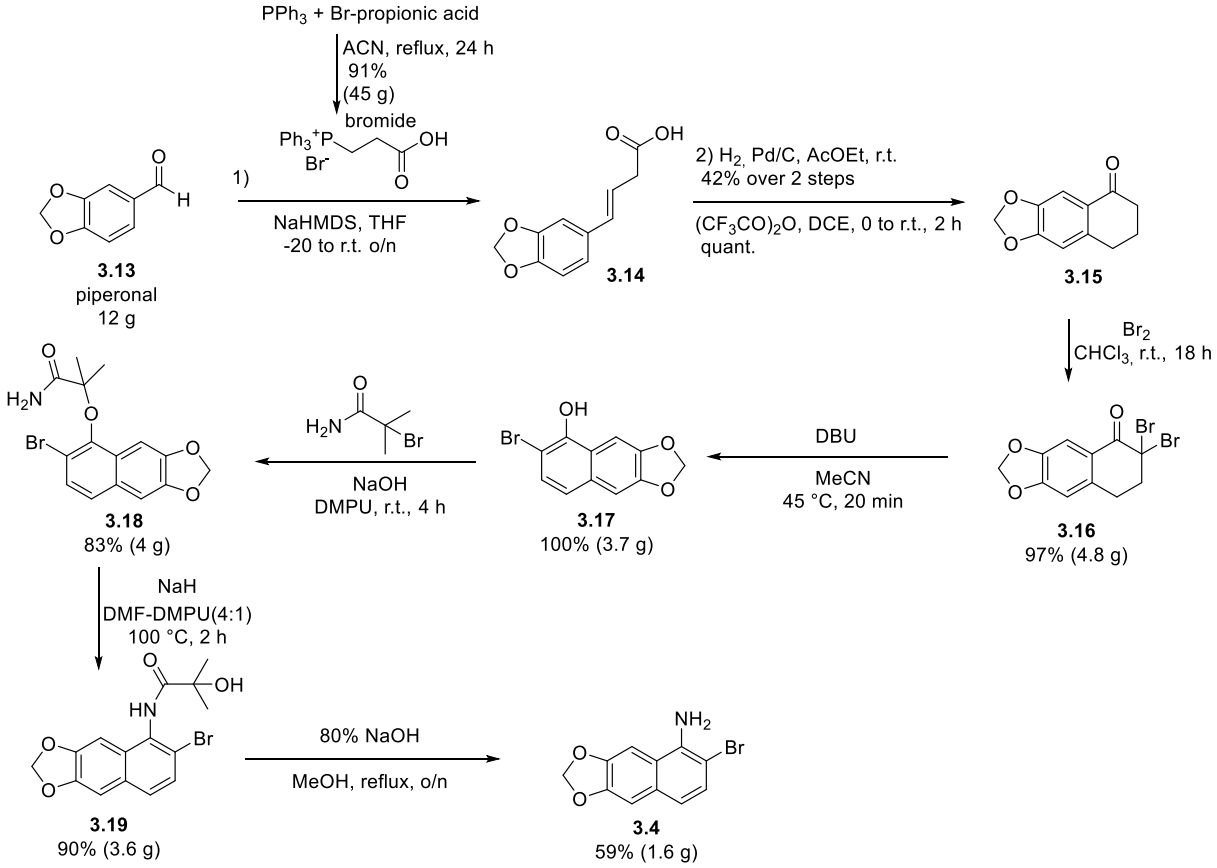
***N*-(naphtho[2,3-*d*][1,3]dioxol-5-yl)acetamide (3.10)**:



To a solution of naphtho[2,3-*d*][1,3]dioxol-5-amine **3.5** (187 mg, 1 mmol, 1 equiv.) in CH_2Cl_2 (4 mL) was added Ac_2O (113 mL, 1.2 mmol, 1.2 equiv.) at 0 ºC, and gradually warmed up to r.t. After reaction completion, H_2O was added and extracted with CH_2Cl_2, washed with brine, dried and concentrated in vacuo to obtain *N*-(naphtho[2,3-*d*][1,3]dioxol-5-yl)acetamide **3.10** (183 mg, 0.798 mmol, 80%) as white solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.67 (d, *J* = 8.2 Hz, 0.2H), 7.55 (dd, *J* = 7.8, 3.9 Hz, 1H), 7.32 ("t", *J* = 6.2 Hz, 1H), 7.23 (d, *J* = 6.3 Hz, 0.8H), 7.19 – 7.09 (m, 2H), 6.08 (s, 0.7H), 6.05 (s, 1.3H), 2.31 (s, 2.1H), 1.86 (s, 0.9H).

6-bromonaphtho[2,3-*d*][1,3]dioxol-5-amine (3.4):



(2-carboxyethyl)triphenylphosphonium was synthesized as below.

To an oven-dried 50 mL Schlenk flask equipped with a stir bar and reflux condenser was added PPh_3 (15.7 g, 60 mmol, 1 equiv.). The flask was then evacuated and backfilled with argon. Next, 3-bromo propionic acid (9.18 g, 60 mmol, 1 equiv.) in 60 mL anhydrous CH_3CN was added via a syringe. The homogeneous mixture was stirred at reflux for 36 h. The resulting colourless solution was cooled to room temperature, and then Et_2O was added. After keeping at -20 ºC for 4 h, the formed precipitate was filtered, washed with Et_2O, and dried *in vacuo* to afford the triphenylphosphonium bromide (22.6 g, 54.4 mmol, 91%) as a white solid.

Following the literature[179], successfully, **3.4** was synthesised as below.

A solution of (2-carboxyethyl)triphenylphosphonium bromide (18.3 g, 44 mmol, 1.1 equiv.) in THF (75 mL) was cooled to –20 °C. To the white suspension was added NaHMDS (96 mL, 96 mmol, 2.4 equiv.) dropwise via syringe. A solution of piperonal (6 g, 40 mmol, 1 equiv.) in 5 mL THF was added via a syringe at –20 °C. The resulting mixture was allowed to slowly warm to room temperature (23 ˚C) while stirring overnight. The heterogeneous reaction mixture was quenched with water (200 mL) and washed with ether. Then the aqueous layer was acidified to pH 1 by dropwise adding 50% sulfuric acid and extracted with AcOEt. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated i*n vacuo* to afford **3.14** (9.2 g, 44.6 mmol, quant.) of crude material that was directly used in the next step.

A solution of **3.14** (9.2 g, 44.6 mmol, 1 equiv.) and Pd/C (736 mg, 6.92 mmol, 15 mol%) in AcOEt (135 mL) was stirred under H_2 atmosphere overnight. After the reaction completion, it was filtered over *Celite* and concentrated *in vacuo.* The residue was purified by silica gel column chromatography using cyclohexane/AcOEt (3:1 with 1% formic acid, Rf= 0.2) to obtain 4-(benzo[*d*][1,3]dioxol-5-yl)butanoic acid (3.9 g, 18.7 mmol, 42% over 2 steps) as a white solid.

A solution of $(CF_3CO)_2O$ (3.81 mL, 27.4 mmol, 2 equiv.) in 1,2-dichloroethane (54 mL) was added dropwise to a solution of 4-(benzo[*d*][1,3]dioxol-5-yl)butanoic acid (2.86 g, 13.7 mmol, 1 equiv.) in dry 1,2-dichloroethane (27 mL) at 0·°C. The mixture was stirred at room temperature for 2 h. Then, the mixture was concentrated under reduced pressure on a rotary evaporator. The crude product was purified by silica gel column chromatography using cyclohexane/AcOEt (5:1, Rf= 0.35) to obtain **3.15** (2.68 g, 14.1 mmol, quant.) as a yellow solid.

A solution of bromine (272 mL, 5.31 mmol, 2.1 equiv.) in $CHCl_3$ (4 mL) was added dropwise to a stirred solution of **3.15** (481 mg, 2.53 mmol, 1 equiv.) in $CHCl_3$ (13 mL). The resulting mixture was stirred at ambient temperature overnight. Evaporation of the solvent gave the crude product of **3.16** (855 mg, 2.46 mmol, 97%) as a pink solid.

3.16 was stirred in CH_3CN (86 mL) at 40 ºC for 15 min. Next, DBU (3 mL, 200.6 mmol, 1.5 equiv.) was added, and the resulting mixture was stirred at 40-45 ºC for 20 min. After cooling to r.t., 1N HCl was added. The mixture was extracted with CH_2Cl_2, and the combined phases were washed with water, dried, and filtered. Finally, the solvent evaporated to give the crude product of **3.17** (3.67 g, 13.7 mmol, 100%).

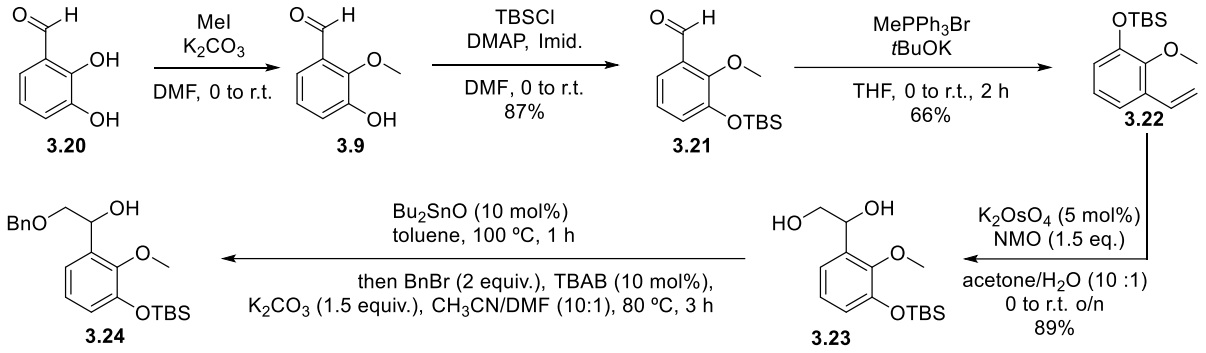
NaOH (3.30 g, 82.2 mmol, 6 equiv.) was added to a solution of the **3.17** in DMPU (32 mL) at r.t., and the resulting mixture was stirred for 15 min. 2-bromo-2-methylpropanamide (13.6 g, 82.2 mmol, 6 equiv.) was added and the mixture was stirred vigorously for 2-5h. Water was then added together with sufficient 5 M HCl to bring the mixture to pH 0. The resulting suspension was added to water and allowed to stand overnight. The product was filtered, washed with water and dried under vacuum at 60 ºC for 48 h to give an off-white solid of **3.18** (4 g, 11.4 mmol, 83%).

NaH (545 mg, 13.6 mmol, 1.2 equiv.) was added to a solution of the **3.18** in dry DMF (68 mL) and DMPU (18 mL). The resulting mixture was stirred at 100 ºC for 2 h under argon. The solution was then poured into water and extracted with AcOEt. The organic phase was washed with water, dried, filtered and evaporated to give the product an off-white solid of **3.19** (3.6 g, 10.2 mmol, 90%).

510 mL of NaOH (40 % aq) and 20-40 mesh beads (1.6 g, 408 mmol, 40 equiv.) were added to a solution of **3.19** in MeOH (40 mL), and the resulting mixture was stirred at reflux overnight. Further, NaOH (1.6 g, 408 mmol, 40 equiv.) was added, and reflux continued overnight. After cooling, water and AcOEt. The phases were separated, and the aqueous phase was extracted with AcOEt. The combined organic layers were washed with water, dried, filtered and evaporated to give dark brown glass, which was purified by silica gel column chromatography using cyclohexane/AcOEt (9:1, Rf= 0.2) to give **3.4** (1.6 g, 6 mmol, 59%) as white solid.

Obtained ^{1}H NMR showed good agreement with the reported spectra.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 (d, *J* = 8.6 Hz, 1H), 7.10 (s, 1H), 7.05 (s, 1H), 7.01 (d, *J* = 8.7 Hz, 1H), 6.05 (s, 2H), 4.40 (s, 2H).

2-(benzyloxy)-1-(3-((*tert*-butyldimethylsilyl)oxy)-2-methoxyphenyl)ethan-1-ol (3.24):



To a solution of 2,3-dihydroxybenzaldehyde (5.2 g, 37.7 mmol, 1 equiv.) in DMF (100 mL) was added K_2CO_3 (5.2 g, 37.7 mmol, 1 equiv.) and MeI (3.05 mL, 49 mmol, 1.3 equiv.) at 0 °C. The resulting mixture was warmed up to r.t. and stirred overnight. H_2O was added and extracted with Et_2O, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was recrystallisation from hexane to obtain **3.9** (3.46g, 22.7 mmol, 60%) as a white solid.

To a solution of **3.9** (913 mg, 6 mmol, 1 equiv.) in DMF (18 mL) was added imidazole (613 mg, 9 mmol, 1.5 equiv.) and TBSCl (1.09 g, 7.20 mmol, 1.2 equiv.) at 0 °C. The resulting mixture was warmed up to r.t. and stirred overnight. H_2O was added and extracted with Et_2O, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo.* The residue was purified by silica gel column chromatography using cyclohexane/AcOEt (98:2, Rf= 0.38) to obtain **3.21** (1.39 g, 5.22 mmol, 87%).

*t*BuOK (4.5 g, 40.5 mmol, 1.2 equiv.) was added portionwise to a solution of $MePPh_3Br$ (14.5 g, 405 mmol, 1.2 equiv.) in THF (80 mL) at 0 C. After 1 h, aldehyde **3.21** (9 g, 33.8 mmol, 1 equiv.) in THF (20 mL) was dropwised at 0 °C and stirred at r.t. After 1 h, NH_4Cl aq was added and extracted with AcOEt, brined, dried, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/CH_2Cl_2 (98:2, Rf= 0.35) to give **3.22** (810 mg, 3.06 mmol, 66%) as a colourless oil.

To a solution of **3.22** (700 mg, 2.65 mmol, 1 equiv.) and *N*-methylmorpholine *N*-oxide (466 mg, 3.98 mmol, 1.5 equiv.) in acetone (12 mL) and H_2O (1.3 mL) was added $K_2[OsO_2(OH)_4]$ (49 mg, 0.132 mmol, 5 mol%) at 0°C. After the reaction mixture was stirred for 18 h at r.t., it was quenched with saturated aq $Na_2S_2O_3$ and extracted with AcOEt. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/AcOEt (1:1, Rf= 0.3) to afford **3.23** (801 mg, 2.68 mmol, 101%).

3.23 (595 mg,1.99 mmol, 1 equiv.) and dibutyltin oxide (49.5 mg, 0.199 mmol, 10 mol%) were added in toluene (35 mL) and refluxed for 1 h. Then, after evaporation of the solvent under vacuum, the residue was dissolved in a mixture of CH_3CN (12 mL) and DMF (1.5 mL) in the presence of K_2CO_3(413 mg,

2.99 mmol, 1.5 equiv.), TBAB (64.2 mg, 0.199 mmol, 10 mol%) and BnBr (476 μL, 3.98 mmol, 2 equiv.) at 80 ºC for 3 h. The mixture was then transferred to a separatory funnel containing water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted two more times with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO4, filtered, and concentrated *in vacuo*. The resulting crude material was purified by silica gel column chromatography using cyclohexane/AcOEt (14% AcOEt, Rf= 0.25) to obtain **3.24** (407 mg, 1.05 mmol, 53%) with regioisomers (80:20 r.r.)

Major product (desired regioselectivity)

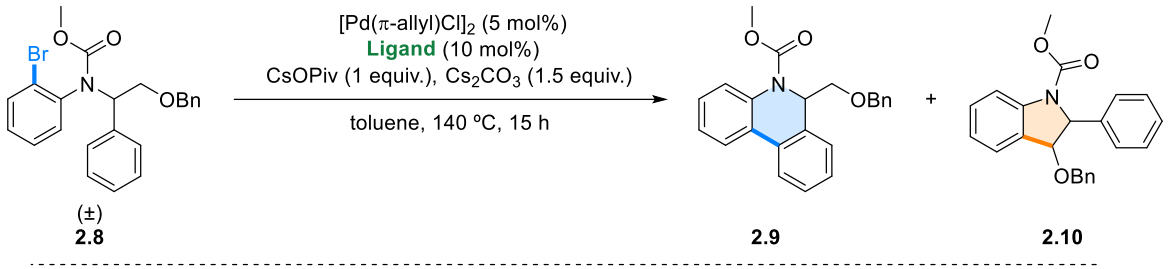
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 – 7.33 (m, 4H), 7.33 – 7.26 (m, 1H), 7.06 (ddd, *J* = 7.8, 1.7, 0.7 Hz, 1H), 6.96 (“t”, *J* = 7.9 Hz, 1H), 6.79 (dd, *J* = 8.0, 1.7 Hz, 1H), 5.22 (d”t”, *J* = 8.5, 3.2 Hz, 1H), 4.61 (s, 2H), 3.78 (s, 3H), 3.71 – 3.65 (m, 1H), 3.51 (dd, *J* = 9.7, 8.6 Hz, 1H), 2.88 (d, *J* = 3.3 Hz, 1H), 1.01 (s, 9H), 0.19 (s, 3H), 0.17 (s, 3H).

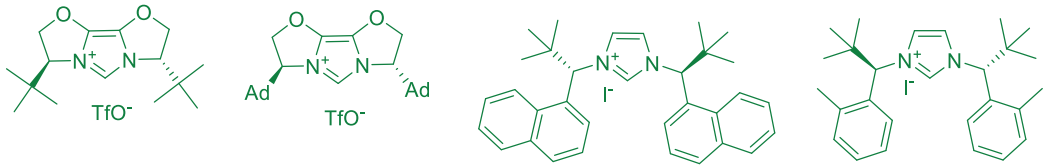
Minor product (undesired)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 – 7.33 (m, 4H), 7.33 – 7.26 (m, 1H), 7.06 (ddd, *J* = 7.8, 1.7, 0.7 Hz, 1H), 7.01 (t, *J* = 7.8 Hz, 1H), 6.83 (dd, *J* = 7.8, 1.8 Hz, 1H), 4.95 (dd, *J* = 7.3, 4.6 Hz, 1H), 4.61 (s, 2H), 4.54 (d, *J* = 11.3 Hz, 1H), 4.37 (d, *J* = 11.4 Hz, 1H), 3.78 (s, 3H), 2.32 – 2.25 (m, 1H), 1.02 (s, 9H), 0.21 (s, 3H), 0.20 (s, 3H).

7.3 Total synthesis of cryptowolinol via parallel kinetic resolution by Pd(0)-catalysed C–H activation

7.3.1 Optimisation of chiral ligands for parallel kinetic resolution





(*S*,*S*)-IBiox*t*Bu (*S*,*S*)-IBioxAd (*S*,*S*)-L14 (*R*,*R*)-L37

Entry	NHC	NMR yield of 2.9/2.10[b]	e.r. of 2.9/e.r. of 2.10
1	**IBiox*t*Bu**	71% (62%)[c]/ 25% (22%)[c]	31:69/99.5:0.5
2	**IBioxAd**	70% (60%)[c]/ 25% (21%)[c]	31:69/99:1
3	**L14**	56%(47%)[c]/ 42% (35%)[c]	16:84/99.8:0.2
4	**L37**	51% (52%)[c] 45% (47%)[c]	92:8/0.2:99.8

[a]**2.8** (0.1 mmol) was engaged. [b]Determined by ^{1}H NMR using trichloroethylene as internal standard. [c]Isolated yield.

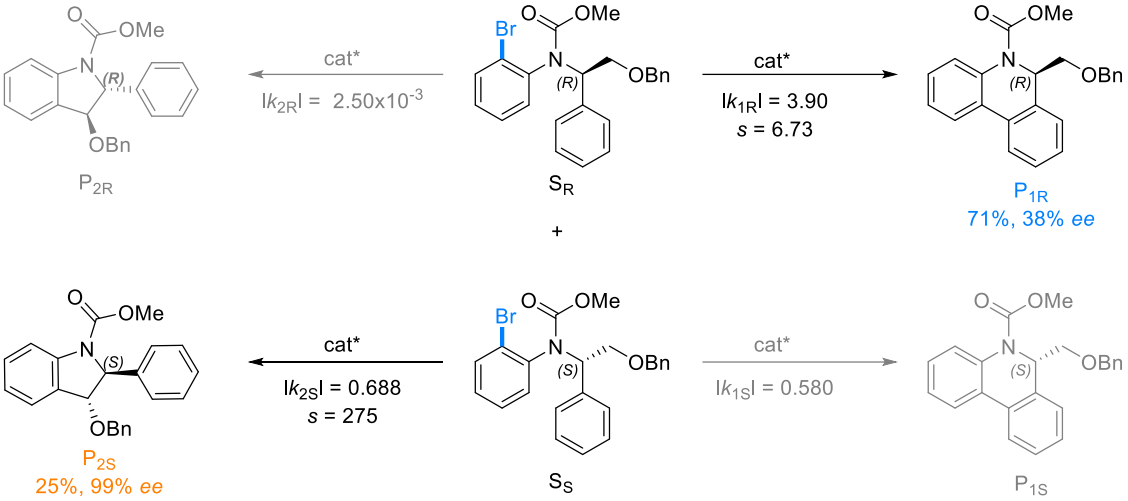
7.3.2 Calculated reaction profiles

The following equation was employed to obtain each number.

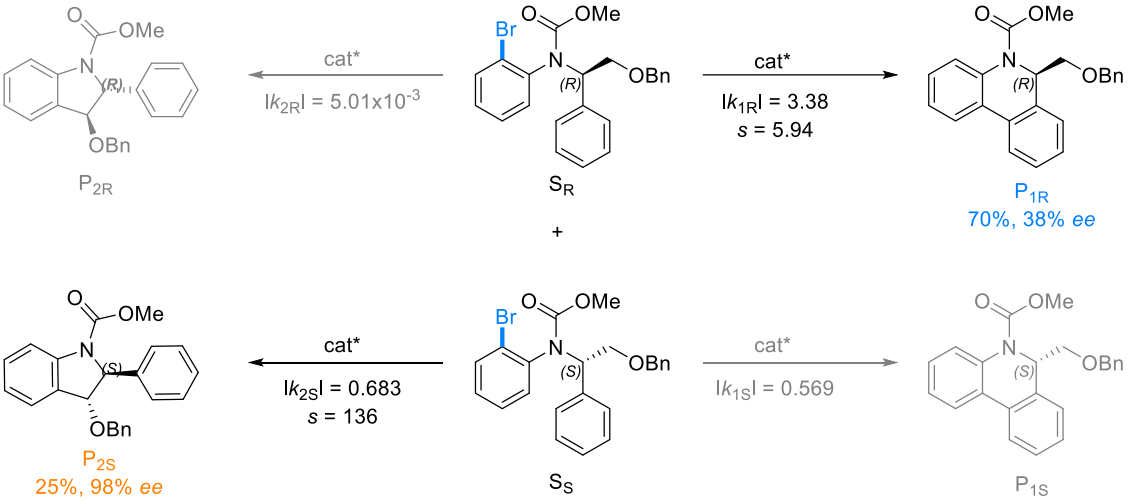
$$s = \ln[1-c(1+ee_{Pr})]/\ln[1-c(1-ee_{Pr})] = k_{rel} = k_{fast}/k_{slow}$$

The absolute configuration was chosen arbitrarily.

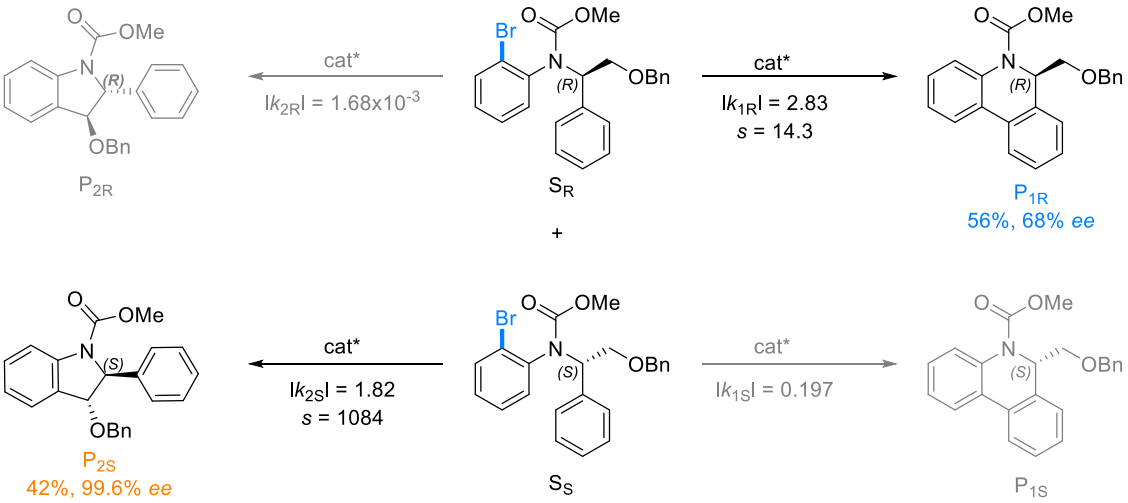
Entry 1 (IBiox*t*Bu)



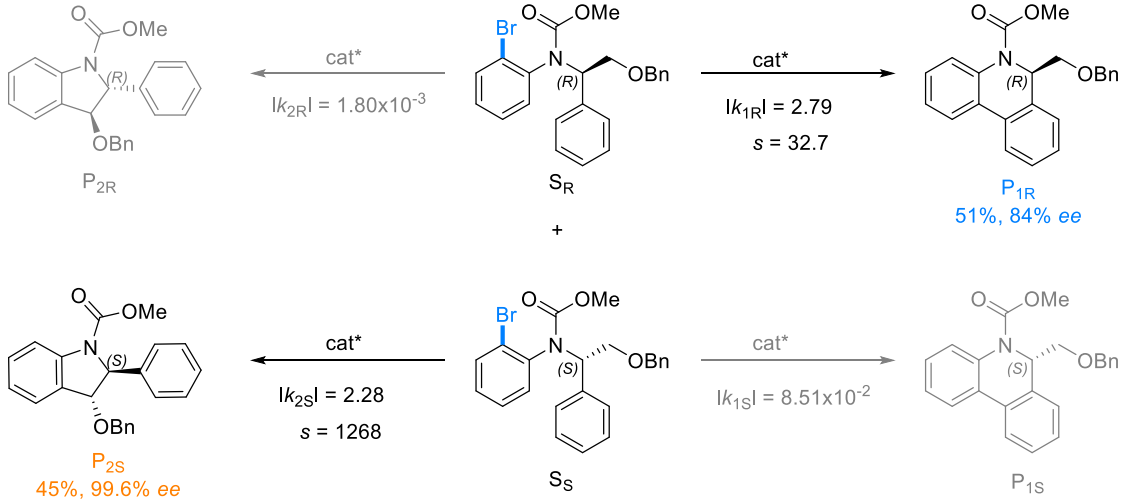
Entry 2 (IBioxIAd)



Entry 3 (L14)

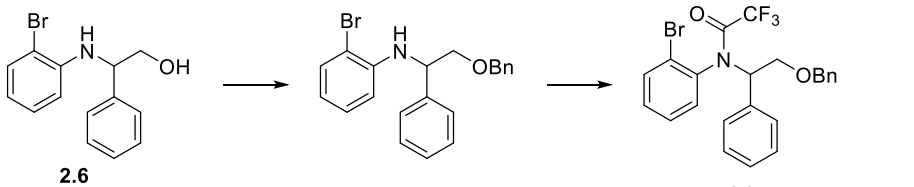


Entry 4 (L37)



7.3.3 Synthesis of model substrates for optimisation of parallel kinetic resolution

***N*-(2-(benzyloxy)-1-phenylethyl)-*N*-(2-bromophenyl)-2,2,2-trifluoroacetamide (4.2)**:



2.6 **4.2**

Chemical Formula: $C_{23}H_{19}BrF_3NO_2$
Molecular Weight: 478.31

To a solution of 2-((2-bromophenyl)amino)-2-phenylethan-1-ol **2.6** (438 mg, 1.5 mmol, 1 equiv.) in THF (5 mL, 0.3 M) was added NaH (120 mg, 3 mmol, 2 equiv.) and BnBr (215 μL, 1.8 mmol, 1.2 equiv.) at 0 ºC and stirred at room temperature for three hours. NH_4Cl aq was added and extracted with AcOEt, washed with brine, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/ AcOEt (99:1, Rf= 0.25) as a solvent to afford the pure compound *N*-(2-(benzyloxy)-1-phenylethyl)-2-bromoaniline as a yellow oil (514 mg, 1.34 mmol, 90%).

Following general procedure B, a mixture of *N*-(2-(benzyloxy)-1-phenylethyl)-2-bromoaniline (3.08 g, 8.05 mmol, 1 equiv.) in methyl chloroformate (26 mL) was heated under reflux overnight. The mixture was concentrated *in vacuo*. The crude material was purified by flash column chromatography using cyclohexane/AcOEt as a solvent to afford the pure compound *N*-(2-(benzyloxy)-1-phenylethyl)-*N*-(2-bromophenyl)-2,2,2-trifluoroacetamide **4.2** as a yellow oil (3.49 g, 7.3 mmol, 91%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.61 (dd, *J* = 7.9, 1.6 Hz, 0.3H), 7.52 – 7.45 (m, 0.7H), 7.41 – 7.08 (m, 11.3H), 7.05 – 6.98 (m, 1.4H), 6.85 (d, *J* = 8.1 Hz, 0.3H), 5.94 (dd, *J* = 8.7, 5.6 Hz, 0.7H), 5.71 ("t", *J* = 7.0 Hz, 0.3H), 4.71 (d, *J* = 12.0 Hz, 0.7H), 4.57 (d, *J* = 11.9 Hz, 0.7H), 4.51 (d, *J* = 12.0 Hz, 0.3H), 4.42 (d, *J* = 12.0 Hz, 0.3H), 4.25 (dd, *J* = 10.0, 6.8 Hz, 0.3H), 4.09 (dd, *J* = 10.7, 8.7 Hz, 0.7H), 3.92 (dd, *J* = 10.7, 5.6 Hz, 0.7H), 3.85 (dd, *J* = 10.0, 7.0 Hz, 0.3H).

^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 157.65 (q, *J* = 35.9 Hz), 137.84, 136.72, 136.38, 134.98, 134.41, 133.58, 133.43, 133.00, 132.47, 130.86, 130.64, 129.84, 129.33, 128.99, 128.60, 128.57, 128.49, 128.45, 127.98, 127.95, 127.78, 127.74, 127.64, 126.96, 125.82, 116.17 (q, *J* = 289.2 Hz), 73.28, 73.14, 69.17, 68.76, 64.77, 62.09.

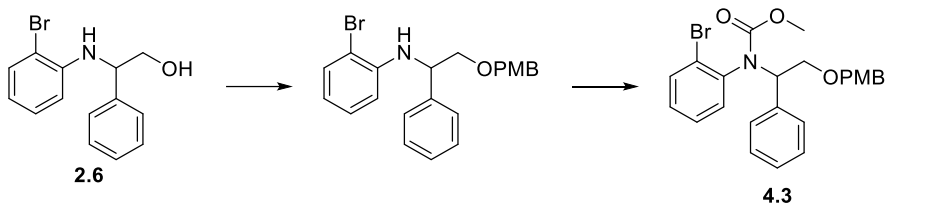
^{19}F{^{1}H} NMR (376 MHz, Chloroform-d) δ -68.71, -68.75.

HRMS (ESI): Calcd for $C_{23}H_{20}BrF_3NO_2$ $[M+H]^+$: 478.0624, found: 478.0619.

IR (neat): ν (cm^{-1}) 3034, 2866, 1696, 1585, 1475, 1410, 1365, 1181, 1121, 699, 632.

Rf 0.18 (Cyclohexane:AcOEt = 60:1)

Methyl (2-bromophenyl)(2-((4-methoxybenzyl)oxy)-1-phenylethyl)carbamate (4.3):



Chemical Formula: $C_{24}H_{24}BrNO_4$
Molecular Weight: 470.36

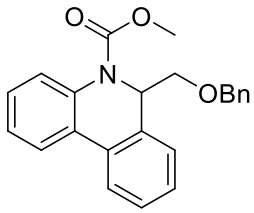
To a solution of 2-((2-bromophenyl)amino)-2-phenylethan-1-ol **2.6** (438 mg, 1.5 mmol, 1 equiv.) in THF (5 mL, 0.3 M) was added NaH (120 mg, 3 mmol, 2 equiv.) and PMBBr (245 μL, 1.8 mmol, 1.2 equiv.) at 0 ºC and stirred at room temperature for three hours. NH_4Cl aq was added and extracted with AcOEt, washed with brine, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/ AcOEt (94:6, Rf= 0.43) as a solvent to afford the pure compound 2-bromo-*N*-(2-((4-methoxybenzyl)oxy)-1-phenylethyl)aniline as a yellow oil (445 mg, 1.08mmol, 72%).

Following general procedure B, a mixture of 2-bromo-*N*-(2-((4-methoxybenzyl)oxy)-1-phenylethyl)aniline (445 mg, 1.08 mmol, 1 equiv.) in methyl chloroformate (3 mL) was heated under reflux overnight. The mixture was concentrated *in vacuo*. The crude material was purified by flash column chromatography using cyclohexane/AcOEt as a solvent to afford the pure compound Methyl (2-bromophenyl)(2-((4-methoxybenzyl)oxy)-1-phenylethyl)carbamate **4.3** as a colourless oil (468 mg, 0.995 mmol, 92%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.56 (d"t", *J* = 7.5, 3.7 Hz, 0.4H), 7.42 (dd, *J* = 8.0, 1.5 Hz, 0.6H), 7.37 – 6.97 (m, 9.8H), 6.91 – 6.84 (m, 1.2H), 6.84 – 6.78 (m, 0.6H), 6.78 – 6.69 (m, 0.4H), 5.72 (br, *J* = 9.7 Hz, 0.6H), 5.56 (t, *J* = 7.1 Hz, 0.4H), 4.64 (d, *J* = 11.7 Hz, 0.6H), 4.52 (d, *J* = 11.7 Hz, 0.6H), 4.41 (d, *J* = 11.7 Hz, 0.4H), 4.33 (d, *J* = 11.6 Hz, 0.4H), 4.09 (br, 0.4H), 4.01 (dd, *J* = 10.6, 8.9 Hz, 0.6H), 3.81-3.75 (br, 0.6H), 3.79 (s, 1.8H), 3.77 (s, 1.2H), 3.73 (dd, *J* = 9.9, 7.2 Hz, 0.4H), 3.70 – 3.56 (s, 3H).
^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 159.37, 159.21, 156.00, 155.74, 139.08, 138.58, 137.72, 136.29, 133.32, 133.25, 131.27, 130.19, 129.66, 129.35, 129.10, 128.81, 128.36, 128.24, 128.19, 127.94, 127.87, 127.67, 126.66, 125.76, 113.91, 113.77, 72.80, 72.58, 69.51, 69.15, 62.33, 60.86, 55.40, 55.36, 53.29, 53.28.
HRMS (ESI): Calcd for $C_{24}H_{25}BrNO_4$ $[M+H]^+$: 470.0961, found: 470.0953.
IR (neat): ν (cm-1) 2952, 2857, 1706, 1612, 1513, 1441, 1389, 1312, 1246, 1175, 1087, 1030.
Rf 0.13 (Cyclohexane:AcOEt = 91:9)

7.4 Characterisation data of Pd(0)-catalysed C–H activation products

Methyl 6-((benzyloxy)methyl)phenanthridine-5(6H)-carboxylate (2.9) / Methyl 3-(benzyloxy)-2-phenylindoline-1-carboxylate (2.10)



Chemical Formula: $C_{23}H_{21}NO_3$
Molecular Weight: 359.43

Following general procedure C ((with 1,3-bis((*R*)-2,2-dimethyl-1-(*o*-tolyl)propyl)-1H-imidazol-3-ium iodide as chiral ligand)), Methyl (2-(benzyloxy)-1-phenylethyl)(2-bromophenyl)carbamate was engaged. The crude was purified by preparative thin-layer chromatography.

Methyl 6-((benzyloxy)methyl)phenanthridine-5(6H)-carboxylate (2.9) (18.7 mg, 0.0520 mmol, 52%) as a pale yellow oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 7.8 Hz, 1H), 7.75 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.70-7.47 (m, 1H), 7.42 – 7.13 (m, 10H), 5.83 (br, 1H), 4.57 – 4.38 (m, 2H), 3.81 (s, 3H), 3.45 – 3.31 (m, 2H).

^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 154.80, 138.09, 134.58, 131.18, 128.46, 128.28, 128.06, 127.73, 127.62, 127.49, 127.37, 127.07, 125.06, 123.64, 123.47, 72.83, 70.00, 53.18, 29.72.

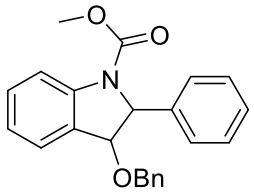
HRMS (ESI): Calcd for $C_{23}H_{22}NO_3$ $[M+H]^+$: 360.1594, found: 360.1590.

IR (neat): ν (cm^{-1}) 3030, 2952, 2856, 1703, 1604, 1439, 1388, 1328, 1253, 1193, 1106, 1075.

Rf 0.18 (Cyclohexane : AcOEt = 20 : 1)

$[\alpha]_D^{20}$: +154.5 º (c = 0.935, $CHCl_3$)

HPLC separation Chiralcel ® IC; 95:5 (*n*-heptane/*i*-PrOH), 1 $ml.min^{-1}$, 302 nm, t_R (major) = 14.2 min, t_R (minor) = 17.1 min, 92:8 e.r.



Chemical Formula: $C_{23}H_{21}NO_3$
Molecular Weight: 359.43

Methyl 3-(benzyloxy)-2-phenylindoline-1-carboxylate (**2.10)** (16.8 mg, 0.0467 mmol, 47%) as a pale yellow oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.20 – 7.52 (br, 1H), 7.42 ("t", *J* = 7.8 Hz, 1H), 7.35 (m, 5H), 7.32 – 7.20 (m, 4H), 7.16 – 7.04 (m, 3H), 5.41 (br, 1H), 4.76 – 4.71 (m, 1H), 4.69 (s, 2H), 3.75 (br, 3H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 153.41, 140.09, 137.72, 130.63, 128.84, 128.55, 127.91, 127.89, 127.66, 126.69, 125.45, 123.14, 115.41, 84.59, 70.11, 69.14, 52.72.

HRMS (ESI): Calcd for $C_{23}H_{21}NNaO_3$ $[M+Na]^+$: 382.1414, found: 382.1412.

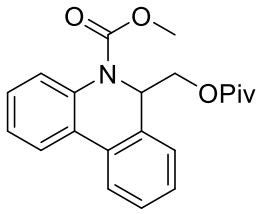
IR (neat): ν (cm^{-1}) 3031, 1708, 1604, 1441, 1383, 1342, 1263, 1140, 1053.

Rf 0.29 (Cyclohexane : AcOEt = 20 : 1)

$[\alpha]_D^{20}$: -91.4 º (c = 0.210, $CHCl_3$)

HPLC separation Chiralcel® IA; 97:3 (*n*-heptane/*i*-PrOH), 1 $ml.min^{-1}$, 255 nm, t_R (minor) = 11.1 min, t_R (major) = 13.2 min, 0.2:99.8 e.r.

Methyl 6-((pivaloyloxy)methyl)phenanthridine-5(6H)-carboxylate (2.16):



Chemical Formula: $C_{21}H_{23}NO_4$
Molecular Weight: 353.42

Following general procedure C (with IBiox*t*Bu as chiral ligand), 2-((2-bromophenyl)(methoxycarbonyl)amino)-2-phenylethyl pivalate (0.2 mmol) was engaged. The crude was purified by preparative thin-layer chromatography (42.5 mg, 0.12 mmol, 60%) as a pale yellow oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.96 – 7.48 (m, 3H), 7.41 (d"t", *J* = 7.8, 4.4 Hz, 1H), 7.38 – 7.28 (m, 3H), 7.28 – 7.20 (m, 1H), 5.98 – 5.74 (br, 1H), 4.11 (dd, *J* = 11.3, 5.0 Hz, 1H), 3.86 ("t", *J* = 10.4 Hz, 1H), 3.79 (s, 3H), 1.14 (s, 9H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 178.14, 154.65, 134.34, 133.26, 131.34, 128.90, 128.33, 127.97, 127.47, 127.13, 125.80, 125.33, 123.86, 123.65, 63.65, 55.03, 53.26, 38.87, 27.18.

HRMS (ESI): Calcd for $C_{21}H_{24}NO_4$ $[M+H]^+$: 354.1700, found: 354.1695.

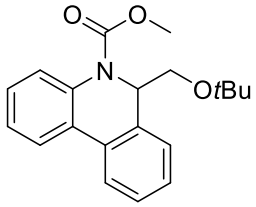
IR (neat): ν (cm^{-1}) 2782, 1708, 1605, 1440, 1394, 1328, 1257, 1194, 1144, 1060.

Rf 0.19 (Cyclohexane:AcOEt = 40:1)

$[\alpha]_D^{20}$: +129.7 º (c = 0.246, $CHCl_3$)

HPLC separation Chiralcel® AD-H; 99.5:0.5 (*n*-heptane/*i*-PrOH), 1 ml.min^{-1}, 270 nm, t_R (major) = 56.3 min, t_R (minor) = 62.4 min, 77:23 e.r.

Methyl 6-(*tert*-butoxymethyl)phenanthridine-5(6H)-carboxylate (2.17):



Chemical Formula: $C_{20}H_{23}NO_3$
Molecular Weight: 325.41

Following general procedure C (with IBiox*t*Bu as chiral ligand), Methyl (2-bromophenyl)(2-(*tert*-butoxy)-1-phenylethyl)carbamate (0.2 mmol) was engaged. The crude was purified by preparative thin-layer chromatography (45 mg, 0.138 mmol, 69%) as a white solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.02 – 7.47 (m, 3H), 7.38 (d"t", *J* = 7.8, 4.4 Hz, 1H), 7.35 – 7.27 (m, 3H), 7.22 ("t"d, *J* = 7.6, 1.3 Hz, 1H), 5.65 ("t", *J* = 7.4 Hz, 1H), 3.80 (s, 3H), 3.31 – 3.24 (m, 2H), 0.98 (s, 9H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 154.92, 134.91, 131.16, 128.79, 128.37, 127.96, 127.74, 127.60, 127.41, 125.90, 124.92, 123.62, 123.40, 73.31, 62.54, 56.79, 53.10, 27.39.

HRMS (ESI): Calcd for $C_{20}H_{23}NNaO_3$ $[M+Na]^+$: 348.1570, found: 348.1574.

IR (neat): ν (cm^{-1}) 3019, 1704, 1440, 1392, 1331, 1257, 1191, 1061.

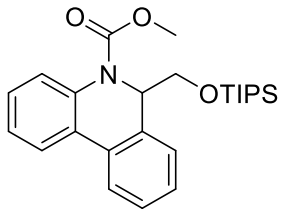
Rf 0.28 (Cyclohexane:AcOEt = 20:1)

$[\alpha]_D^{20}$: +15.3 º (c = 0.347, $CHCl_3$)

HPLC separation Chiralcel® IA; 99.5:0.5 (*n*-heptane/*i*-PrOH), 1 ml.min-[1], 270 nm, t_R (minor) = 19.4 min, t_R (major) = 20.6 min, 41:59 e.r.

Melting point: 99.6 ºC

Methyl 6-(((triisopropylsilyl)oxy)methyl)phenanthridine-5(6H)-carboxylate (2.18):



Chemical Formula: $C_{25}H_{35}NO_3Si$
Molecular Weight: 425.64

Following general procedure C (with IBiox*t*Bu as chiral ligand), Methyl (2-bromophenyl)(1-phenyl-2-((triisopropylsilyl)oxy)ethyl)carbamate was engaged. The crude was purified by preparative thin-layer chromatography (18.3 mg, 0.043 mmol, 43%) as a white solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.96 – 7.51 (m, 3H), 7.38 (ddd, *J* = 7.9, 5.2, 3.7 Hz, 1H), 7.35 – 7.27 (m, 3H), 7.21 ("t"d, *J* = 7.5, 1.3 Hz, 1H), 5.65 (br, 1H), 3.80 (s, 3H), 3.65 – 3.54 (m, 2H), 1.02 – 0.85 (m, 21H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 154.87, 134.93, 131.31, 128.43, 128.01, 127.58, 125.74, 124.90, 123.62, 123.40, 63.93, 58.25, 53.08, 17.95, 12.01.

HRMS (ESI): Calcd for $C_{25}H_{36}NO_3Si$ $[M+H]^+$: 426.2459, found: 426.2454.

IR (neat): ν (cm^{-1}) 2944, 2866, 1712, 1440, 1391, 1330, 1257, 1195, 1121, 1071.

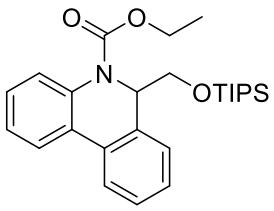
Rf 0.13 (Cyclohexane:CH_2Cl_2 = 85:15)

$[\alpha]_D^{20}$: -10.8 º (c = 0.176, $CHCl_3$)

HPLC separation Chiralcel® IC; 99:1 (*n*-heptane/*i*-PrOH), 1 ml.min^{-1}, 270 nm, t_R (major) = 13.1 min, t_R (minor) = 15.7 min, 84:16 e.r.

Melting point: 61.5 ºC

Ethyl 6-(((triisopropylsilyl)oxy)methyl)phenanthridine-5(6H)-carboxylate (2.23p):



Chemical Formula: $C_{26}H_{37}NO_3Si$
Molecular Weight: 439.67

Following general procedure C (with IBiox*t*Bu as chiral ligand), Ethyl (2-bromophenyl)(1-phenyl-2-((triisopropylsilyl)oxy)ethyl)carbamate was engaged. The crude was purified by preparative thin-layer chromatography (14 mg, 0.0318 mmol, 32 %) as a white solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.95 – 7.49 (m, 3H), 7.38 (ddd, *J* = 7.9, 5.8, 3.0 Hz, 1H), 7.34 – 7.26 (m, 3H), 7.25 – 7.17 (m, 1H), 5.65 (br, 1H), 4.45 – 4.13 (m, 2H), 3.67 – 3.45 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 3H), 0.93 (d, *J* = 3.9 Hz, 21H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 154.39, 135.06, 131.38, 130.12, 128.39, 128.31, 127.95, 127.64, 127.52, 125.83, 124.77, 123.61, 123.39, 63.91, 62.15, 58.01, 17.98, 14.66, 12.02.

HRMS (ESI): Calcd for $C_{26}H_{38}NO_3Si$ $[M+H]^+$: 440.2615, found: 440.2610.

IR (neat): ν (cm^{-1}) 2944, 2865, 1707, 1604, 1401, 1322, 1254, 1120, 1070.

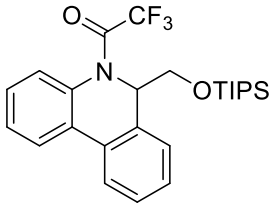
Rf 0.15 (Cyclohexane : CH_2Cl_2 = 85 : 15)

$[\alpha]_D^{20}$: -145.8 º (c = 0.166, $CHCl_3$)

HPLC separation Chiralcel® IC; 99:1 (*n*-heptane/*i*-PrOH), 1 $ml.min^{-1}$, 270 nm, t_R (major) = 13.9 min, t_R (minor) = 19.5 min, 72:28 e.r.

Melting point: 59.9 ºC

2,2,2-trifluoro-1-(6-(((triisopropylsilyl)oxy)methyl)phenanthridin-5(6H)-yl)ethan-1-one (2.24p):



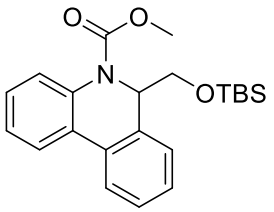
Chemical Formula: $C_{25}H_{32}F_3NO_2Si$
Molecular Weight: 463.62

Following general procedure C (with IBiox*t*Bu as chiral ligand), *N*-(2-bromophenyl)-2,2,2-trifluoro-*N*-(1-phenyl-2-((triisopropylsilyl)oxy)ethyl)acetamide was engaged and purified by preparative thin-layer chromatography (32.1mg, 0.0692 mmol, 69%) as a colorless oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.84 (m, 3H), 7.37 (m, 5H), 5.89 (br, 0.4H), 5.23 ("t", *J* = 7.3 Hz, 0.6H), 3.75 – 3.59 (m, 1H), 3.59 – 3.48 (m, 1H), 0.92 (d, *J* = 5.0 Hz, 21H).

^{19}F{^{1}H} NMR (376 MHz, Chloroform-*d*) δ- 65.54, -67.01.

Methyl 6-(((*tert*-butyldimethylsilyl)oxy)methyl)phenanthridine-5(6H)-carboxylate (2.26p):



Chemical Formula: $C_{22}H_{29}NO_3Si$
Molecular Weight: 383.56

Following general procedure C (with IBiox*t*Bu as chiral ligand), Methyl (2-bromophenyl)(2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethyl)carbamate (0.2 mmol) was engaged. The residue was purified by preparative thin-layer chromatography (17 mg, 0.0443 mmol, 22%) as a colourless oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.01 – 7.46 (m, 3H), 7.38 (ddd, *J* = 7.8, 5.9, 2.9 Hz, 1H), 7.36 – 7.25 (m, 3H), 7.22 ("t"d, *J* = 7.6, 1.3 Hz, 1H), 5.62 (br, 1H), 3.80 (s, 3H), 3.61 – 3.42 (m, 2H), 0.81 (s, 9H), -0.16 (s, 3H), -0.19 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 154.88, 134.88, 131.26, 128.47, 128.05, 127.61, 125.72, 124.94, 123.67, 123.42, 63.46, 58.07, 53.12, 25.85, 18.23, -5.50, -5.66.

HRMS (ESI): Calcd for $C_{22}H_{30}NO_3Si$ $[M+H]^+$: 384.1989, found: 384.1985.

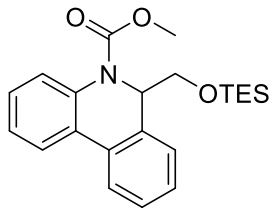
IR (neat): ν (cm^{-1}) 2954, 2857, 17120, 1605, 1440, 1392, 1330, 1255, 115, 1116, 1072.

Rf 0.28 (Cyclohexane:CH_2Cl_2 = 3:2)

$[\alpha]_D^{20}$: +17.6 º (c = 0.199, $CHCl_3$)

HPLC separation Chiralcel ® IC; 99:1 (*n*-heptane/*i*-PrOH), 1 ml.min^{-1}, 227 nm, t_R (major) = 21.7 min, t_R (minor) = 30.4 min, 78:22 e.r.

Methyl 6-(((triethylsilyl)oxy)methyl)phenanthridine-5(6H)-carboxylate (2.27p):



Chemical Formula: $C_{22}H_{29}NO_3Si$
Molecular Weight: 383.56

Following general procedure C (with IBiox*t*Bu as chiral ligand), Methyl (2-bromophenyl)(2-((triethylsilyl)oxy)-1-phenylethyl)carbamate was engaged. The crude was purified by preparative thin-layer chromatography (5.2 mg, 0.0136 mmol, 14%) as a colourless oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.95 – 7.50 (m, 3H), 7.38 (ddd, *J* = 7.8, 5.9, 2.9 Hz, 1H), 7.35 – 7.27 (m, 3jH), 7.22 ("t"d, *J* = 7.6, 1.3 Hz, 1H), 5.61 (br, 1H), 3.79 (s, 3H), 3.57 – 3.46 (m, 2H), 0.82 (t, *J* = 8.0 Hz, 9H), 0.43 (q, *J* = 8.0 Hz, 6H).

^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 154.91, 134.90, 131.22, 128.48, 128.05, 127.63, 125.79, 124.98, 123.67, 123.43, 63.34, 58.19, 53.15, 6.72, 4.41.

HRMS (ESI): Calcd for $C_{22}H_{30}NO_3Si$ $[M+H]^+$: 384.1989, found: 384.1988.

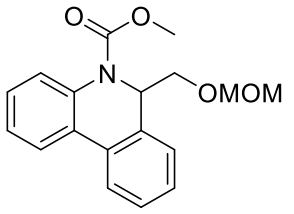
IR (neat): ν (cm^{-1}) 2955, 2910, 1711, 1605, 1441, 1391, 1330, 1258, 1195, 1156, 1072, 1013.

Rf 0.4 (Cyclohexane : CH_2Cl_2 = 3 : 2)

$[\alpha]_D^{20}$: -54.7 º (c = 0.167, $CHCl_3$)

HPLC separation Chiralcel® IC; 99:1 (*n*-heptane/*i*-PrOH), 1 ml.min^{-1}, 240 nm, t_R (major) = 14.6 min, t_R (minor) = 16.9 min, 67:33 e.r.

Methyl 6-((methoxymethoxy)methyl)phenanthridine-5(6H)-carboxylate (2.28p1) / Methyl 3-(methoxymethoxy)-2-phenylindoline-1-carboxylate (2.28p2)



Chemical Formula: $C_{18}H_{19}NO_4$
Molecular Weight: 313.35

Following general procedure C (with IBiox*t*Bu as chiral ligand), Methyl (2-bromophenyl)(2-((4-methoxybenzyl)oxy)-1-phenylethyl)carbamate was engaged. The crude was purified by preparative thin-layer chromatography.

Methyl 6-((methoxymethoxy)methyl)phenanthridine-5(6H)-carboxylate (2.28p1) (11.9 mg, 0.038 mmol, 38%) as white solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87 – 7.48 (m, 3H), 7.40 (ddd, *J* = 7.8, 5.5, 3.3 Hz, 1H), 7.36 – 7.28 (m, 3H), 7.23 (dd, *J* = 7.4, 1.3 Hz, 1H), 5.78 (br, 1H), 4.57 (d, *J* = 6.6 Hz, 1H), 4.49 (d, *J* = 6.6 Hz, 1H), 3.80 (s, 3H), 3.51 – 3.36 (m, 2H), 3.23 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 154.79, 134.41, 131.14, 128.52, 128.06, 127.77, 127.66, 127.05, 125.93, 125.20, 123.70, 123.52, 96.14, 67.17, 55.90, 55.17, 53.19.

HRMS (ESI): Calcd for $C_{18}H_{19}NNaO_4$ $[M+Na]^+$: 336.1206, found: 336.1212.

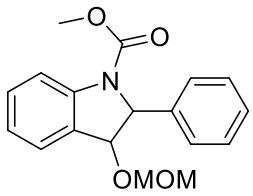
IR (neat): ν (cm^{-1}) 2955, 1701, 1442, 1328, 1265, 1112, 1028.

Rf 0.3 (Cyclohexane:AcOEt = 6:1)

$[\alpha]_D^{20}$: -109.8 º (c = 0.112, $CHCl_3$)

HPLC separation Chiralcel ® IC; 95:5 (*n*-heptane/*i*-PrOH), 1 ml.min^{-1}, 270 nm, t_R (major) = 21.5 min, t_R (minor) = 24.6 min, 69:31 e.r.

Melting point: 116.7 ºC



Chemical Formula: $C_{18}H_{19}NO_4$
Molecular Weight: 313.35

Methyl 3-(methoxymethoxy)-2-phenylindoline-1-carboxylate (2.28p2) (8.5 mg, 0.0271 mmol, 27%) as pale yellow oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.07 (br, 1H), 7.42 ("t", *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 7.4 Hz, 1H), 7.32 – 7.19 (m, 3H), 7.13 (d, *J* = 7.2 Hz, 2H), 7.09 ("t"d, *J* = 7.4, 1.0 Hz, 1H), 5.40 (br, 1H), 4.85 (s, 3H), 3.68 (br, 3H), 3.47 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 153.56, 140.04, 130.75, 128.97, 127.80, 126.85, 125.55, 123.37, 115.55, 95.23, 82.82, 69.73, 55.85, 52.85.

HRMS (ESI): Calcd for $C_{18}H_{19}NNaO_4$ $[M+Na]^+$: 336.1206, found: 336.1209.

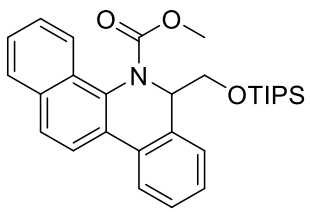
IR (neat): ν (cm^{-1}) 2954, 1413, 1605, 1484, 1443, 1387, 1148, 1026.

Rf 0.52 (Cyclohexane:AcOEt = 6:1)

$[\alpha]_D^{20}$: +3.67 º (c = 0.49, $CHCl_3$)

HPLC separation Chiralcel ® IA; 99:1 (*n*-heptane/*i*-PrOH), 0.5 ml.min^{-1}, 245 nm, t_R(major) = 43.9 min, t_R(minor) = 47.7 min 99.6:0.4 e.r.

Methyl 6-(((triisopropylsilyl)oxy)methyl)benzo[c]phenanthridine-5(6H)-carboxylate (2.49):

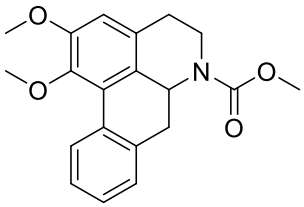


Chemical Formula: $C_{29}H_{37}NO_3Si$
Molecular Weight: 475.70

Following general procedure C (with IBiox*t*Bu as chiral ligand), methyl (2-bromonaphthalen-1-yl)(1-phenyl-2-((triisopropylsilyl)oxy)ethyl)carbamate was engaged. The crude was analysed by ^{1}H NMR using trichloroethylene as the internal standard (84% NMR yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.99 – 7.85 (m, 3H), 7.87 – 7.76 (m, 2H), 7.53 – 7.28 (m, 5H), 5.76 (s, 1H), 3.56 (m, 5H), 1.19 – 0.73 (m, 21H).

Methyl 1,2-dimethoxy-4,5,6a,7-tetrahydro-6H-dibenzo[de,g]quinoline-6-carboxylate (2.58):

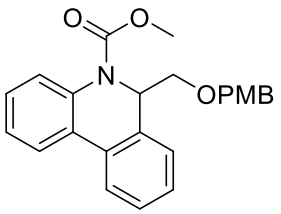


Chemical Formula: $C_{20}H_{21}NO_4$
Molecular Weight: 339.39

Following general procedure C (with IBioxSpicy), methyl 1-benzyl-8-bromo-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate was engaged. The crude was analysed by ^{1}H NMR using trichloroethylene as the internal standard (92% NMR yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.44 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.37 – 7.21 (m, 4H), 6.68 (s, 1H), 4.78 – 4.69 (m, 1H), 4.45 (d, *J* = 11.3 Hz, 1H), 3.90 (s, 3H), 3.76 (s, 3H), 3.66 (s, 3H), 3.06 – 2.92 (m, 2H), 2.93 – 2.78 (m, 2H), 2.66 (dt, *J* = 15.3, 2.3 Hz, 1H).

Methyl 6-(((4-methoxybenzyl)oxy)methyl)phenanthridine-5(6H)-carboxylate (4.3p1) / Methyl 3-((4-methoxybenzyl)oxy)-2-phenylindoline-1-carboxylate (4.3p2):



Chemical Formula: $C_{24}H_{23}NO_4$
Molecular Weight: 389.45

Following general procedure C (with IBiox*t*Bu as chiral ligand), Methyl (2-bromophenyl)(2-((4-methoxybenzyl)oxy)-1-phenylethyl)carbamate was engaged. The crude was purified by preparative thin-layer chromatography.

Methyl 6-(((4-methoxybenzyl)oxy)methyl)phenanthridine-5(6H)-carboxylate (4.3p1) (23.1 mg, 0.0593 mmol, 59%) as pale yellow oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.88 – 7.44 (m, 3H), 7.39 ("t"d, *J* = 7.5, 1.9 Hz, 1H), 7.35 – 7.26 (m, 3H), 7.23 ("t"d, *J* = 7.6, 1.3 Hz, 1H), 7.18 – 7.07 (m, 2H), 6.86 – 6.76 (m, 2H), 5.81 (br, 1H), 4.43 (d, *J* = 11.8 Hz, 1H), 4.37 (d, *J* = 11.7 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.43 – 3.28 (m, 2H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 159.21, 154.89, 134.64, 131.28, 130.27, 129.14, 128.54, 128.13, 127.82, 127.74, 127.17, 126.05, 125.15, 123.73, 123.58, 113.80, 72.59, 69.72, 56.02, 55.38, 53.28.

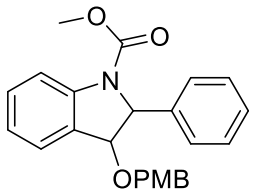
HRMS (ESI): Calcd for $C_{24}H_{24}NO_4$ $[M+H]^+$: 390.1700, found: 390.1694.

IR (neat): ν (cm^{-1}) 2954, 2862, 1705, 1611, 1513, 1441, 1331, 1251, 1104, 1037.

Rf 0.15 (Cyclohexane:AcOEt = 8:1)

$[\alpha]_D^{20}$: -16.6 º (c = 0.169, $CHCl_3$)

HPLC separation Chiralcel ® IC; 98:2 (*n*-heptane/*i*-PrOH), 1 ml.min^{-1}, 230 nm, t_R (major) = 51.3 min, t_R (minor) = 58.2 min, 64:36 e.r.



Chemical Formula: $C_{24}H_{23}NO_4$
Molecular Weight: 389.45

Methyl 3-((4-methoxybenzyl)oxy)-2-phenylindoline-1-carboxylate (4.3p2) (5.6 mg, 0.0144 mmol, 14%) as a pale yellow oil

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 (br, 1H), 7.41 ("t", *J* = 7.9 Hz, 1H), 7.33 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.30 – 7.22 (m, 5H), 7.15 – 7.04 (m, 3H), 6.91 – 6.84 (m, 2H), 5.39 (br, 1H), 4.71 (d, *J* = 1.0 Hz, 1H), 4.67 – 4.57 (m, 2H), 3.80 (s, 3H), 3.66 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 159.52, 140.27, 130.68, 129.89, 129.66, 128.94, 127.74, 126.76, 125.57, 123.23, 115.51, 114.08, 84.46, 69.94, 69.27, 55.45, 52.79.

HRMS (ESI): Calcd for $C_{24}H_{23}NNaO_4$ $[M+Na]^+$: 412.1519, found: 412.1519.

IR (neat): ν (cm^{-1}) 3030, 2950, 1708, 1609, 1442, 1386, 1247, 1177, 1031.

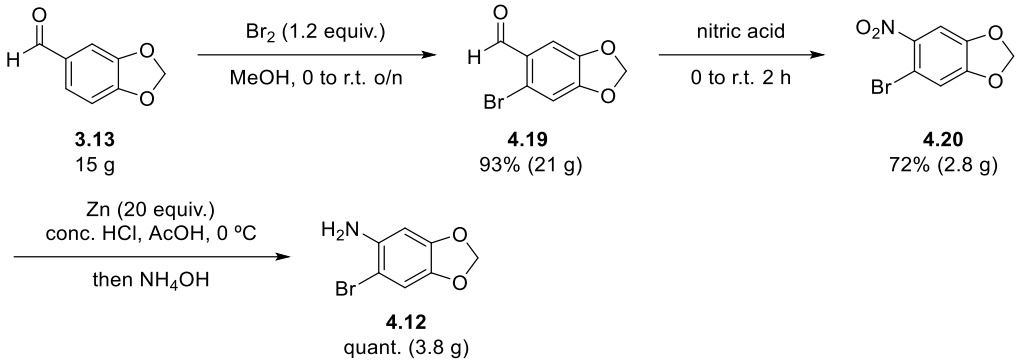
Rf 0.26 (Cyclohexane:AcOEt = 8:1)

$[\alpha]_D^{20}$: -89.6 º (c = 0.280, $CHCl_3$)

HPLC separation Chiralcel ® IA; 95:5 (*n*-heptane/*i*-PrOH), 1 $ml.min^{-1}$, 250 nm, t_R (minor) = 20.0 min, *t*R (major) = 22.0 min, 1:99 e.r.

7.5 Synthetic procedure for the total synthesis of crypotowolinol

6-bromobenzo[*d*][1,3]dioxol-5-amine (4.12):



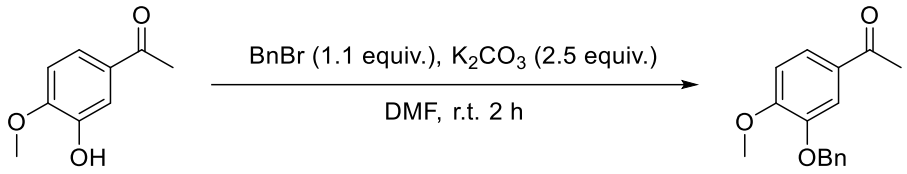
To a solution of piperonal **3.13**(15 g, 100 mmol, 1 equiv.) in MeOH (247 mL) was added bromine (6.2 mL, 120 mmol, 1.2 equiv.) in MeOH (20 mL) dropwise at 0 ºC. The reaction mixture was warmed up to r.t. and stirred overnight. The reaction mixture was concentrated *in vacuo*, and then taken up in H_2O. After stirring, the resulting solid is filtered and dried to obtain **4.19** (21.2 g, 92.6 mmol, 93%).

Concentrated nitric acid (119 mL) was cooled to 0 °C, and with stirring, **4.19** (3.55 g, 15.5 mmol, 1 equiv.) was added in small portions. After 2 h, the resulting yellow solution was poured onto ice water to precipitate a yellow solid. The solid was collected by filtration and washed well with water. Recrystallisation from ethanol afforded **4.20** (2.88 g, 11.7 mmol, 76%) as yellow needles.

4.20 (3.75 g, 15.2 mmol, 1 equiv.) was added to a mixture of 100 mL of conc. HCl and 100 mL of AcOH. With stirring at 0 °C, zinc powder (20 g, 304 mmol, 20 equiv.) was added in small portions over 1 h, after stirring an additional 15 min at 0 °C, conc. NH_4OH was added until the reaction mixture was slightly basic. After saturation with solid NaCl, the reaction mixture was extracted with CH_2Cl_2. After drying over Na_2SO_4, the organic layers were concentrated *in vacuo* to afford a solid. The solid was heated in EtOH, and insoluble material was filtered off. The mother liquid was concentrated *in vacuo* to give 6-bromobenzo[*d*][1,3]dioxol-5-amine **4.12** (3.8 gm 17.6 mmol, quant.) as a dark brown solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.88 (s, 1H), 6.37 (s, 1H), 5.87 (s, 2H), 3.82 (s, 2H).

1-(3-(benzyloxy)-4-methoxyphenyl)ethan-1-one (4.24):



4.24

Chemical Formula: $C_{16}H_{16}O_3$

Molecular Weight: 256.30

To a mixture of 1-(3-hydroxy-4-methoxyphenyl)ethan-1-one (4.15 g, 25.0 mmol, 1 equiv.) and K_2CO_3 (8.64 g, 62.5 mmol, 2.5 equiv.) in DMF (20 mL) was added benzyl bromide (3.29 mL, 27.5 mmol, 1.1 equiv.) dropwise at room temperature under air. After stirring for 2 h, the reaction mixture was poured into cold water (100 mL). The suspended solid was obtained by filtration, washed with water, and dried under air overnight. A pale brown solid (5.82 g, 22.7 mmol, 91%) was obtained without further purification.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.59 (d, *J* = 7.6 Hz, 2H), 7.50 – 7.41 (m, 2H), 7.41 – 7.34 (m, 2H), 7.32 (d, *J* = 7.2 Hz, 1H), 6.95 – 6.88 (m, 1H), 5.19 (s, 2H), 3.95 (s, 3H), 2.53 (s, 3H).

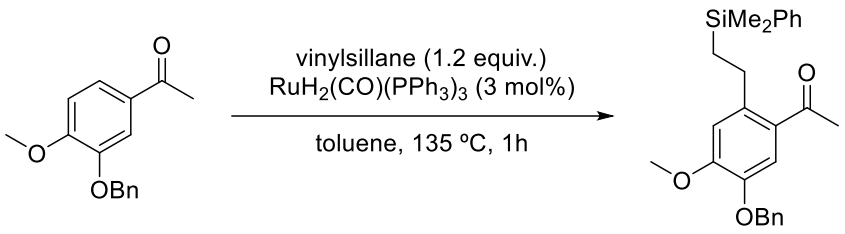
^{13}C NMR (101 MHz, Chloroform-*d*) δ 196.84, 154.04, 148.16, 136.68, 130.47, 128.73, 128.18, 127.66, 123.66, 112.81, 110.53, 71.07, 56.22, 26.35.

HRMS (ESI): Calcd for $C_{16}H_{16}NaO_3$ $[M+Na]^+$: 279.0097, found: 279.0992.

IR (neat): ν (cm^{-1}) 2933, 1666, 1583, 1508, 1423, 1380, 1257, 1143, 1005.

Melting point: 81.1 ºC

1-(5-(benzyloxy)-2-(2-(dimethyl(phenyl)silyl)ethyl)-4-methoxyphenyl)ethan-1-one (4.25):



4.24 **4.25**

Chemical Formula: $C_{26}H_{30}O_3Si$
Molecular Weight: 418.61

In a 10 mL tube, 1-(3-(benzyloxy)-4-methoxyphenyl)ethan-1-one **4.24** (1.03 g, 4 mmol, 1 equiv.) and $RuH_2(CO)(PPh_3)_3$ (110 mg, 0.12 mmol, 3 mol%) were weighted inside the glovebox and put the tube out of the glovebox after capping. A degassed pre-mixed solution of vinyldimethylphenylsilane (875 µl, 4.8 mmol, 1.2 equiv.) and toluene (6 mL, 0.66M) was added on a fumehood. The mixture was stirred at 135 ºC for 1 h. After filtration on the *Celite* pad, the solution was concentrated *in vacuo*. The residue was purified by silica gel column chromatography to obtain the pure title compound **4.25** (1.5 g, 3.58 mmol, 90%) as a right brown oil.

Decagram scale Murai reaction:

In a 250 mL two-neck flask, 1-(3-(benzyloxy)-4-methoxyphenyl)ethan-1-one **4.24** (11.3 g, 44.1 mmol, 1 equiv)and $RuH_2(CO)(PPh_3)_3$ (1.22 g, 1.32 mmol, 3 mol%) were weighted inside the glovebox and put the flack out of the glovebox. Vinyldimethylphenylsilane (9.65 mL, 52.9 mmol, 1.2 equiv.) and toluene (66 mL, 0.66M) were added on a fume hood. The mixture was stirred at 135 ºC for 1 h under Ar atmosphere with a bubbler equipped with a reflux condenser. After filtration on the *Celite* pad, the solution was concentrated *in vacuo*. The residue was purified by silica gel column chromatography to obtain the pure title compound **4.25** (13.6 g, 32.5 mmol, 74%) as a right brown oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.59 – 7.52 (m, 2H), 7.48 – 7.41 (m, 2H), 7.41 – 7.28 (m, 6H), 7.22 (s, 1H), 6.66 (s, 1H), 5.15 (s, 2H), 3.89 (s, 3H), 2.92 – 2.81 (m, 2H), 2.41 (s, 3H), 1.12 – 0.98 (m, 2H), 0.33 (s, 6H).

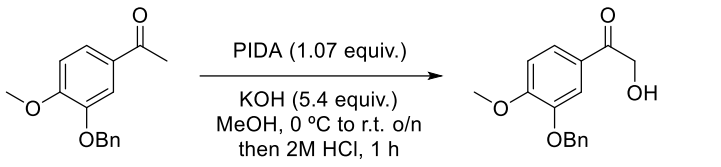
^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 199.56, 152.71, 145.14, 141.89, 139.48, 137.08, 133.80, 128.97, 128.76, 128.61, 128.18, 127.87, 127.59, 117.32, 113.69, 71.92, 56.06, 29.51, 28.80, 18.41, -2.98.

HRMS (ESI): Calcd for $C_{26}H_{30}NaO_3Si$ $[M+Na]^+$: 441.1856, found: 441.1854.

IR (neat): ν (cm^{-1}) 2955, 1675, 1565, 1514, 1358, 1260, 1150, 1057.

Rf 0.13 (Cyclohexane:AcOEt = 96:4)

1-(3-(benzyloxy)-4-methoxyphenyl)-2-hydroxyethan-1-one (4.27):



4.26 **4.27**

Chemical Formula: $C_{16}H_{16}O_4$
Exact Mass: 272.1049

KOH (3.39 g, 54.3 mmol, 5.4 equiv.) and PIDA (3.45 g, 10.7 mmol, 1.07 equiv.) were added to a stirred solution of the substrate **4.26** (2.56 g, 10 mmol, 1 equiv.) in MeOH (25 mL) at 0 ºC and the mixture was allowed to stir overnight at ambient temperature. The mixture was then extracted with CH_2Cl_2 and with ethyl acetate. The combined organic layers were dried Na_2SO_4, then filtered and concentrated. MeOH (0.25 mL) and aqueous 2M HCl (0.25 mL) were added to the residue, and the resulting mixture was stirred for 1 h. The solvent was removed under reduced pressure, and the residue was chromatographed on a silica gel column using cyclohexane/AcOEt to give the title compound **4.27** (1.45 g, 5.34 mmol, 53%) as white crystals.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.55 – 7.49 (m, 2H), 7.49 – 7.43 (m, 2H), 7.42 – 7.36 (m, 2H), 7.35 – 7.30 (m, 1H), 6.93 (d, *J* = 8.2 Hz, 1H), 5.20 (s, 2H), 4.78 (d, *J* = 4.6 Hz, 2H), 3.96 (s, 3H), 3.51 (t, *J* = 4.6 Hz, 1H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 196.86, 154.99, 148.50, 136.44, 128.82, 128.32, 127.63, 126.43, 122.73, 112.48, 110.89, 71.20, 65.07, 56.31.

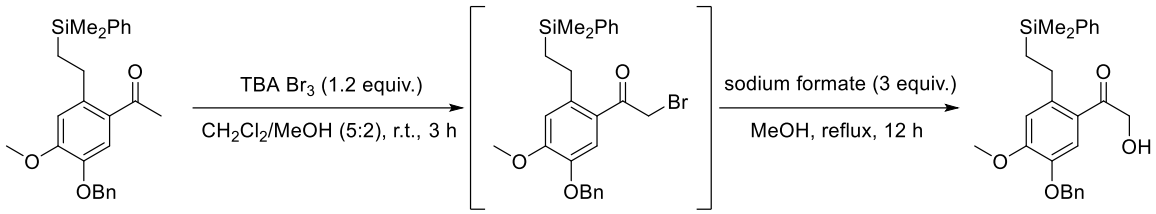
HRMS (ESI): Calcd for $C_{16}H_{16}NaO_4$ $[M+Na]^+$: 295.0941, found: 295.0939.

IR (neat): ν (cm-1) 3480, 2918, 1672, 1584, 1515, 1431, 1262, 1097, 1013.

Rf 0.33 (Cyclohexane:AcOEt = 2:1)

Melting point: 123 ºC

1-(5-(benzyloxy)-2-(2-(dimethyl(phenyl)silyl)ethyl)-4-methoxyphenyl)-2-hydroxyethan-1-ol (4.29):



4.25 **4.28** **4.29**

Chemical Formula: $C_{26}H_{30}O_4Si$
Molecular Weight: 434.61

To a solution of 1-(5-(benzyloxy)-2-(2-(dimethyl(phenyl)silyl)ethyl)-4-methoxyphenyl)ethan-1-one **4.25** (3 g, 7.17 mmol, 1 equiv.) in CH_2Cl_2/MeOH (5:2, 143 mL, 0.05 M) was added tetrabutylammonium tribromide (4.15 g, 3.48 mmol, 1.2 equiv.) portionwise in Ar atmosphere at room temperature, and stirred overnight. The solvent was evaporated *in vacuo*, and extracted with Et_2O, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to obtain the title product, 1-(5-(benzyloxy)-2-(2-(dimethyl(phenyl)silyl)ethyl)-4-methoxyphenyl)-2-bromoethan-1-one **4.28** as crude (3.58 g, 7.19 mmol, 100%). This crude material was used for the subsequent reaction directly without further purification.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.59 – 7.51 (m, 2H), 7.45 (m, 2H), 7.41 – 7.28 (m, 6H), 7.21 (s, 1H), 6.68 (s, 1H), 5.16 (s, 2H), 4.15 (s, 2H), 3.90 (s, 3H), 2.95 – 2.79 (m, 2H), 1.15 – 0.96 (m, 2H), 0.33 (s, 6H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 192.25, 153.46, 145.18, 143.59, 139.36, 136.89, 133.80, 129.02, 128.87, 128.85, 128.28, 127.92, 127.90, 127.56, 124.97, 116.99, 113.91, 71.92, 56.10, 33.19, 28.91, 18.21, -2.98.

A solution of 1-(5-(benzyloxy)-2-(2-(dimethyl(phenyl)silyl)ethyl)-4-methoxyphenyl)-2-bromoethan-1-one **4.28** (1.78 g, 3.58 mmol, 1 equiv.) and sodium formate (730 mg, 10.7 mmol, 3 equiv.)in dry MeOH (22 mL, 0.16 M) was refluxed overnight. Undissolved sodium formate was filtered off, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography to obtain the pure title compound (1.16 g, 2.68 mmol, 75%) as a yellow oil.

^{1}H NMR (400 MHz, Chloroform-*d*) 7.82 – 7.71 (m, 2H), 7.62 (ddd, *J* = 8.8, 7.3, 1.5 Hz, 3H), 7.60 – 7.49 (m, 5H), 7.26 (s, 1H), 6.90 (s, 1H), 5.35 (s, 2H), 4.71 (d, *J* = 4.6 Hz, 2H), 4.11 (s, 3H), 3.86 (t, *J* = 4.6 Hz, 1H), 3.20 – 3.08 (m, 2H), 1.32 – 1.18 (m, 2H), 0.55 (s, 6H).

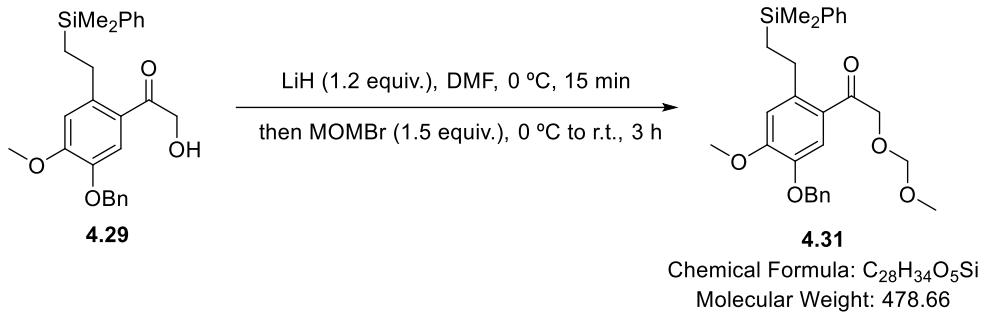
^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 198.06, 153.83, 145.42, 143.65, 139.30, 136.78, 133.79, 129.04, 128.87, 128.34, 127.90, 127.52, 123.67, 115.61, 113.91, 71.94, 66.03, 56.10, 29.00, 18.22, -2.98.

HRMS (ESI): Calcd for $C_{26}H_{30}NaO_4Si$ $[M+Na]^+$: 457.1806, found: 457.1804.

IR (neat): ν (cm^{-1}) 3421, 2945, 1673, 1604, 1519, 1453, 1350, 1264, 1141, 1085.

Rf 0.25 (Cyclohexane:AcOEt = 7:1)

1-(5-(benzyloxy)-2-(2-(dimethyl(phenyl)silyl)ethyl)-4-methoxyphenyl)-2-(methoxymethoxy)ethan-1-one (4.31):



To a solution of 1-(5-(benzyloxy)-2-(2-(dimethyl(phenyl)silyl)ethyl)-4-methoxyphenyl)-2-hydroxyethan-1-one **4.29** (799 mg, 1.84 mmol, 1 equiv.) in DMF (6 mL, 0.3M) was added LiH (17.6 mg, 2.21 mmol, 1.2 equiv.) at 0 ºC. The solution was stirred for 15 min at that temperature, followed by the addition of MOMBr (225 μL, 2.76 mmol, 1.5 equiv.) dropwise, then gradually warmed up to room temperature and stirred for 3 h. The reaction mixture was quenched by the addition of ice, then extracted with Et_2O, washed with brine, dried over Na_2SO_4, and then filtered and concentrated. The residue was purified by silica gel column chromatography to get the pure title compound **4.31** as a colourless oil (810 mg, 1.75 mmol, 95%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.54 (d"t"d, *J* = 6.3, 2.9, 1.4 Hz, 2H), 7.47 – 7.42 (m, 2H), 7.41 – 7.28 (m, 6H), 7.12 (s, 1H), 6.68 (s, 1H), 5.13 (s, 2H), 4.71 (s, 2H), 4.53 (s, 2H), 3.89 (s, 3H), 3.36 (s, 3H), 2.94 – 2.79 (m, 2H), 1.14 – 0.99 (m, 2H), 0.33 (s, 6H).

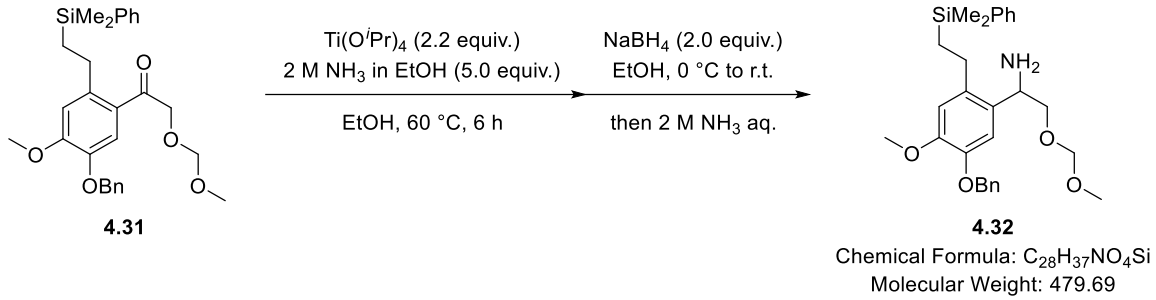
^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 196.79, 152.91, 145.09, 142.31, 139.32, 136.83, 133.67, 128.85, 128.65, 128.09, 127.74, 127.49, 125.80, 115.71, 113.64, 96.63, 71.81, 70.97, 55.92, 55.77, 28.48, 18.21, -3.10.

HRMS (ESI): Calcd for $C_{28}H_{35}O_5Si$ $[M+H]^+$: 479.2248, found: 479.2238.

IR (neat): ν (cm^{-1}) 2957, 1692, 1603, 1517, 1454, 1348, 1264, 1113, 1059.

Rf 0.26 (Cyclohexane:AcOEt = 7:1)

1-(5-(benzyloxy)-2-(2-(dimethyl(phenyl)silyl)ethyl)-4-methoxyphenyl)-2-(methoxymethoxy)ethan-1-amine (4.32):



4.31 **4.32**

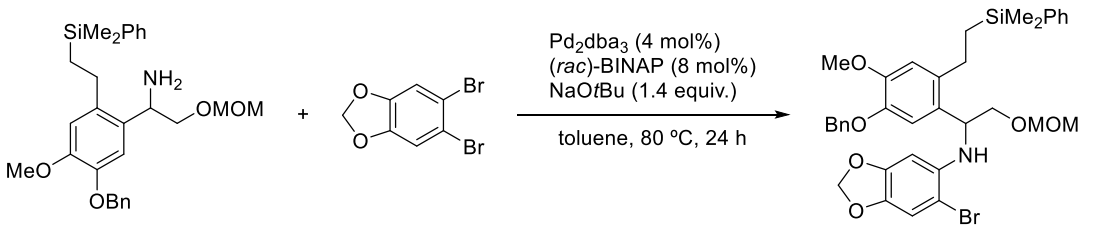
Chemical Formula: $C_{28}H_{37}NO_4Si$
Molecular Weight: 479.69

Titanium(IV) isopropoxide (0.527 mL, 1.76 mmol, 2.2 equiv.) was added to a mixture of 1-(5-(benzyloxy)-2-(2-(dimethyl(phenyl)silyl)ethyl)-4-methoxyphenyl)-2-(methoxymethoxy)ethan-1-one **4.31** (383 mg, 0.800 mmol, 1 equiv.) and ammonia in ethanol (2 M, 2.00 mL, 4.00 mmol, 5.0 equiv.) under Ar. The reaction mixture was stirred at 60 ºC for 6 h. Sodium borohydride (60.5 mg, 1.60 mmol, 2.0 equiv.) was added at 0 ºC, and the resulting mixture was stirred at room temperature overnight. The reaction was quenched by pouring into 2 M NH_3 solution. The resulting inorganic precipitate was filtered off by *Celite* and washed with ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was concentrated *in vacuo,* and the resulting residue was purified by silica gel column chromatography to get the pure title compound **4.32** as a yellow oil (175 mg, 0.365 mmol, 46%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.53 (ddd, *J* = 6.6, 3.0, 1.8 Hz, 2H), 7.46 – 7.40 (m, 2H), 7.41 – 7.27 (m, 6H), 7.09 (s, 1H), 6.63 (s, 1H), 5.11 (d, *J* = 2.4 Hz, 2H), 4.59 (s, 2H), 4.30 (dd, *J* = 8.9, 3.7 Hz, 1H), 3.83 (s, 3H), 3.50 (dd, *J* = 9.7, 3.7 Hz, 1H), 3.38 – 3.33 (m, 1H), 3.31 (s, 3H), 2.69 – 2.50 (m, 2H), 1.13 – 0.93 (m, 2H), 0.32 (s, 3H), 0.32 (s, 3H).

Rf 0.3 (Cyclohexane:AcOEt = 2:1 with 1% Et_3N)

***N*-(1-(5-(benzyloxy)-2-(2-(dimethyl(phenyl)silyl)ethyl)-4-methoxyphenyl)-2-(methoxymethoxy)ethyl)-6-bromobenzo[*d*][1,3]dioxol-5-amine (4.35)**:



4.32 **4.34** **4.35**

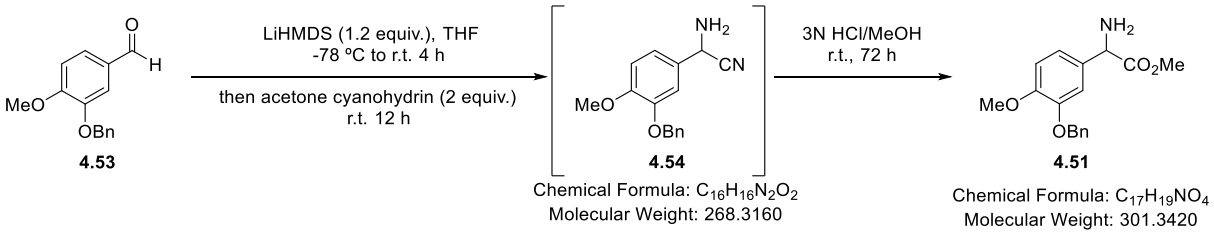
Chemical Formula: $C_{35}H_{40}BrNO_6Si$
Molecular Weight: 678.70

Into an oven-dried 10 mL catalysis tube equipped with a magnetic stir bar inside a glovebox was added Pd_2dba_3 (9.38 mg, 0.010 mmol, 4 mol %) and (*rac*)-BINAP (12.8 mg, 0.020 mmol, 8 mol %), **4.32** (123 mg, 0.256 mmol, 1 equiv.), **4.34** (72 mg, 0.256 mmol, 1 equiv.), NaO*t*Bu (36.9 mg, 0.384 mmol, 1.5 equiv.). Toluene (1.2 mL) was added via an oven-dried syringe, and the solution was heated in an oil bath at 80˚C for 24 h. The solution was allowed to cool to room temperature, filtered through a pad of *Celite* and concentrated *in vacuo* to give a crude dark brown oil. The residue was purified by silica gel column chromatography using cyclohexane/AcOEt to provide the title compound **4.35** (94.3 mg, 0.139 mmol, 54%) as a yellow oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.57 – 7.50 (m, 2H), 7.40 – 7.32 (m, 5H), 7.26 – 7.16 (m, 3H), 6.93 (s, 1H), 6.90 (s, 1H), 6.66 (s, 1H), 5.83 (s, 1H), 5.79 (dd, *J* = 7.7, 1.4 Hz, 2H), 5.05 (s, 2H), 4.81 (d, *J* = 3.4 Hz, 1H), 4.56 (d, *J* = 1.6 Hz, 2H), 4.51 (dt, *J* = 7.7, 3.6 Hz, 1H), 3.84 (s, 3H), 3.64 (dd, *J* = 10.5, 3.8 Hz, 1H), 3.46 (dd, *J* = 10.5, 8.4 Hz, 1H), 3.30 (s, 3H), 2.75 – 2.52 (m, 2H), 1.21 – 0.99 (m, 2H), 0.33 (s, 3H), 0.33 (s, 3H).

Rf 0.15 (Cyclohexane:AcOEt = 95:5)

methyl 2-amino-2-(3-(benzyloxy)-4-methoxyphenyl)acetate (4.51):



3-(benzyloxy)-4-methoxybenzaldehyde **4.53** (4 g, 16.5 mmol, 1 equiv.) was dissolved in anhydrous THF (48 mL) and cooled to -78 ºC under argon atmosphere. To this solution was added lithium bis(trimethylsilyl)amide (LiHMDS) (1.0 M solution in THF, 19.8 mL, 19.8 mmol, 1.2 equiv.) dropwise. The reaction mixture was warmed to r.t. and stirred for 4 h. Acetone cyanohydrin (3.02 mL, 33 mmol, 2 equiv.) was then added. The reaction mixture was stirred at r.t. for 12 h and then quenched with sat. $NaHCO_3$ and extracted with AcOEt, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to obtain the crude of title compound **4.54** as a pale yellow solid (4.58 g, 17.1 mmol, 103%).

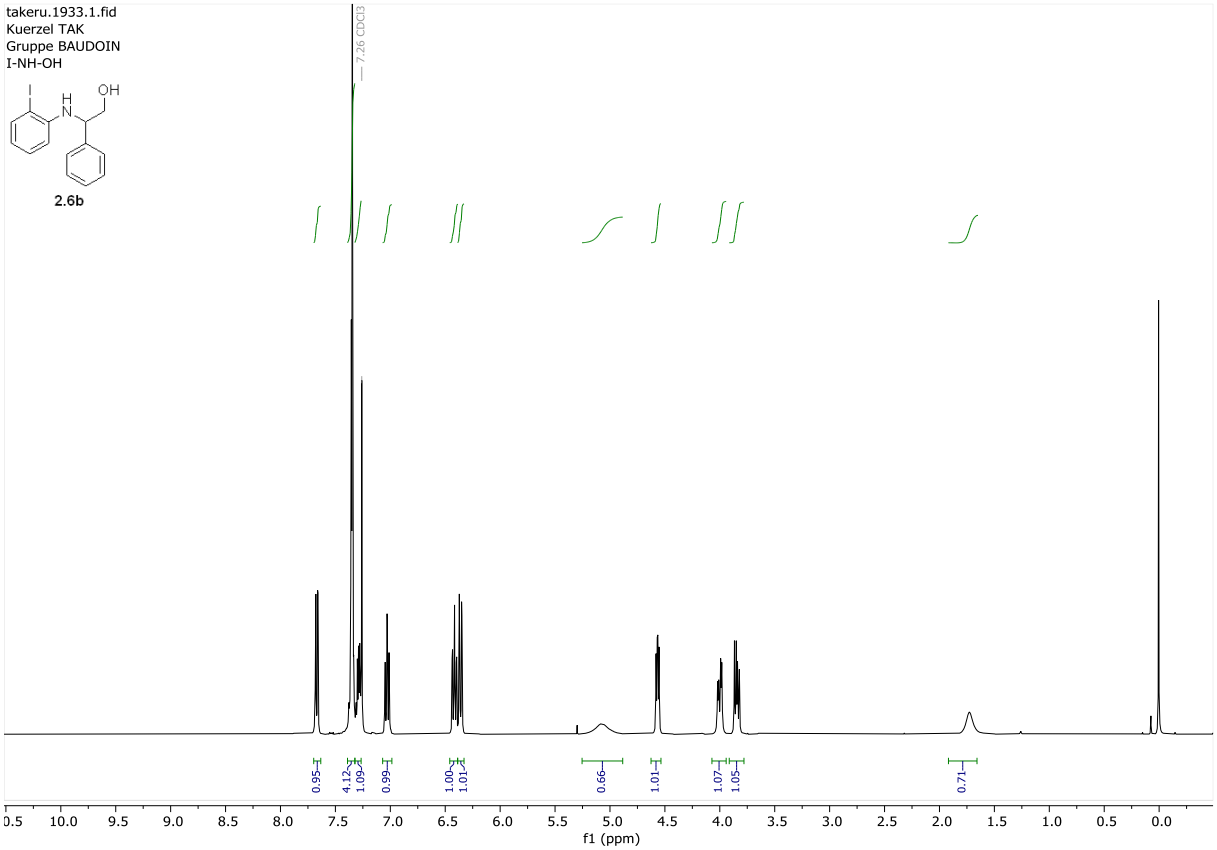
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.50 – 7.43 (m, 2H), 7.41 – 7.35 (m, 2H), 7.34 – 7.27 (m, 1H), 7.13 – 7.03 (m, 2H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.17 (s, 2H), 4.81 (s, 1H), 3.89 (s, 3H).
^{13}C NMR (126 MHz, Chloroform-*d*) δ 150.40, 148.67, 136.77, 128.74, 128.17, 127.63, 121.14, 119.69, 112.59, 111.94, 71.28, 56.24, 47.05.

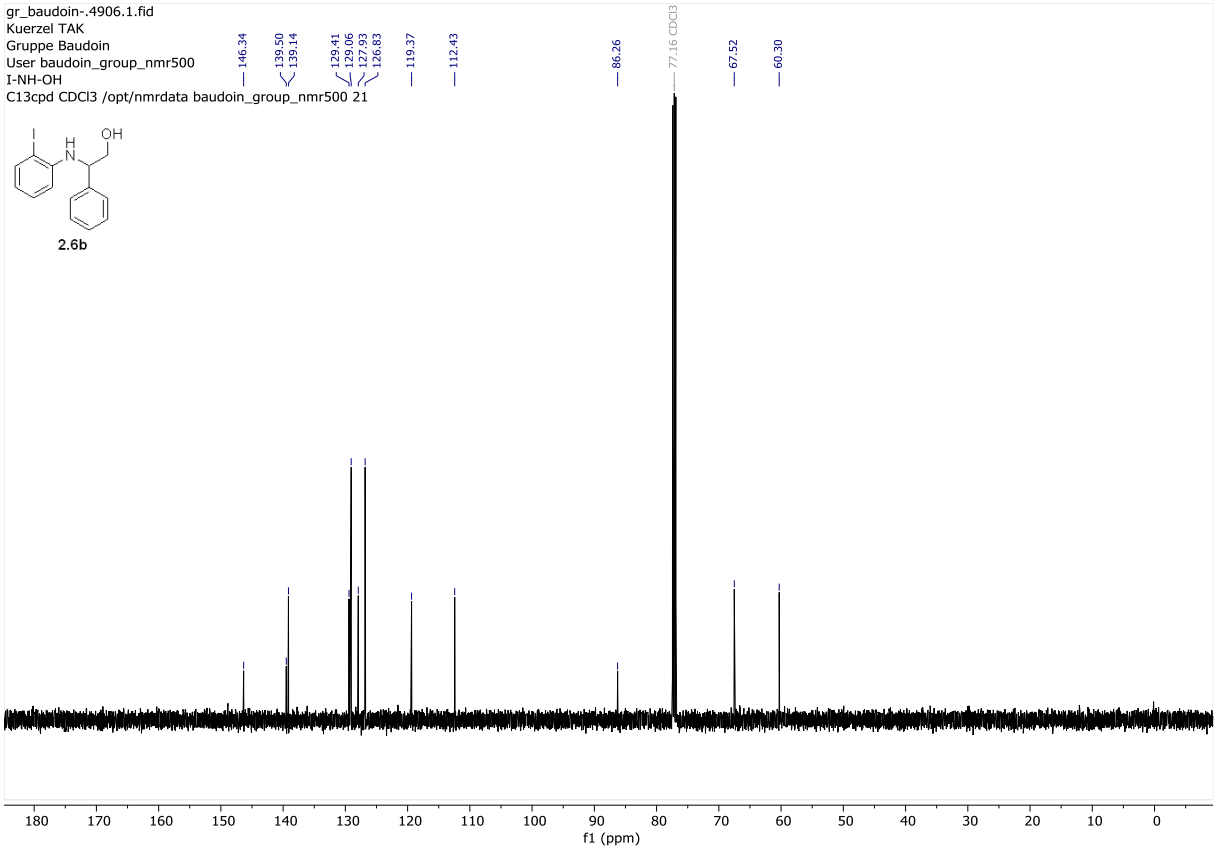
The crude of **4.54** (1 g, 3.73 mmol, 1 equiv.) was dissolved in methanolic 3N HCl (25 mL, 74.5 mmol, 20 equiv.) and stirred at r.t. for 72 h. The solvent was evaporated *in vacuo*, and the residue was treated with sat. $NaHCO_3$, extracted with AcOEt, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using CH_2Cl_2/AcOEt to provide the title compound **4.51** (421 mg, 1.40 mmol, 37% over 2 steps) as a pale yellow solid.

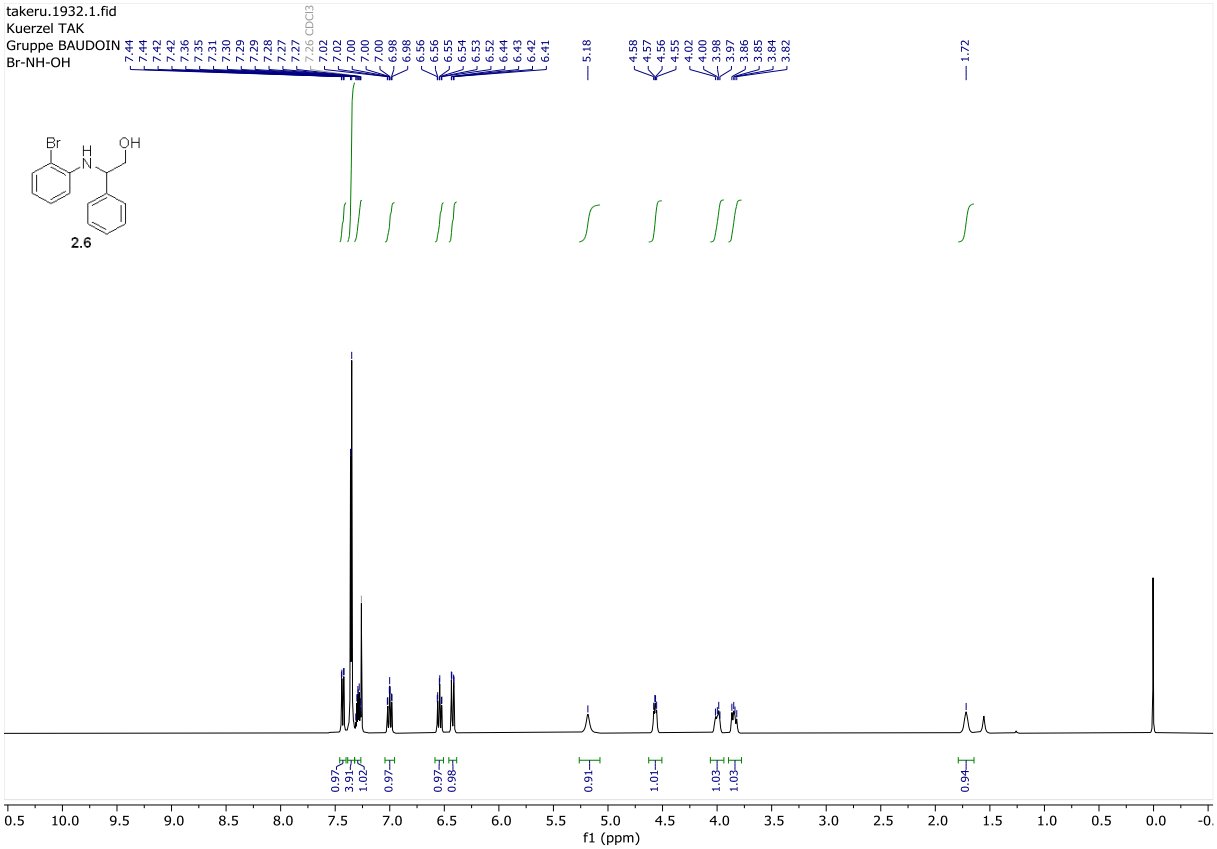
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.47 – 7.41 (m, 2H), 7.39 – 7.34 (m, 2H), 7.32 – 7.27 (m, 1H), 6.93 (dd, *J* = 6.2, 2.2 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 1H), 5.15 (s, 2H), 4.51 (s, 1H), 3.87 (s, 3H), 3.64 (s, 3H).
^{13}C NMR (126 MHz, Chloroform-*d*) δ 174.68, 149.71, 148.45, 137.09, 132.91, 128.67, 128.01, 127.58, 119.83, 112.79, 111.99, 71.17, 58.45, 56.21, 52.49.
Rf 0.18 (CH_2Cl_2:AcOEt = 1:5)

7.6 Experimental data in the study of kinetic resolution

7.6.1 NMR spectrum data of substrates



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Gruppe BAUDOIN
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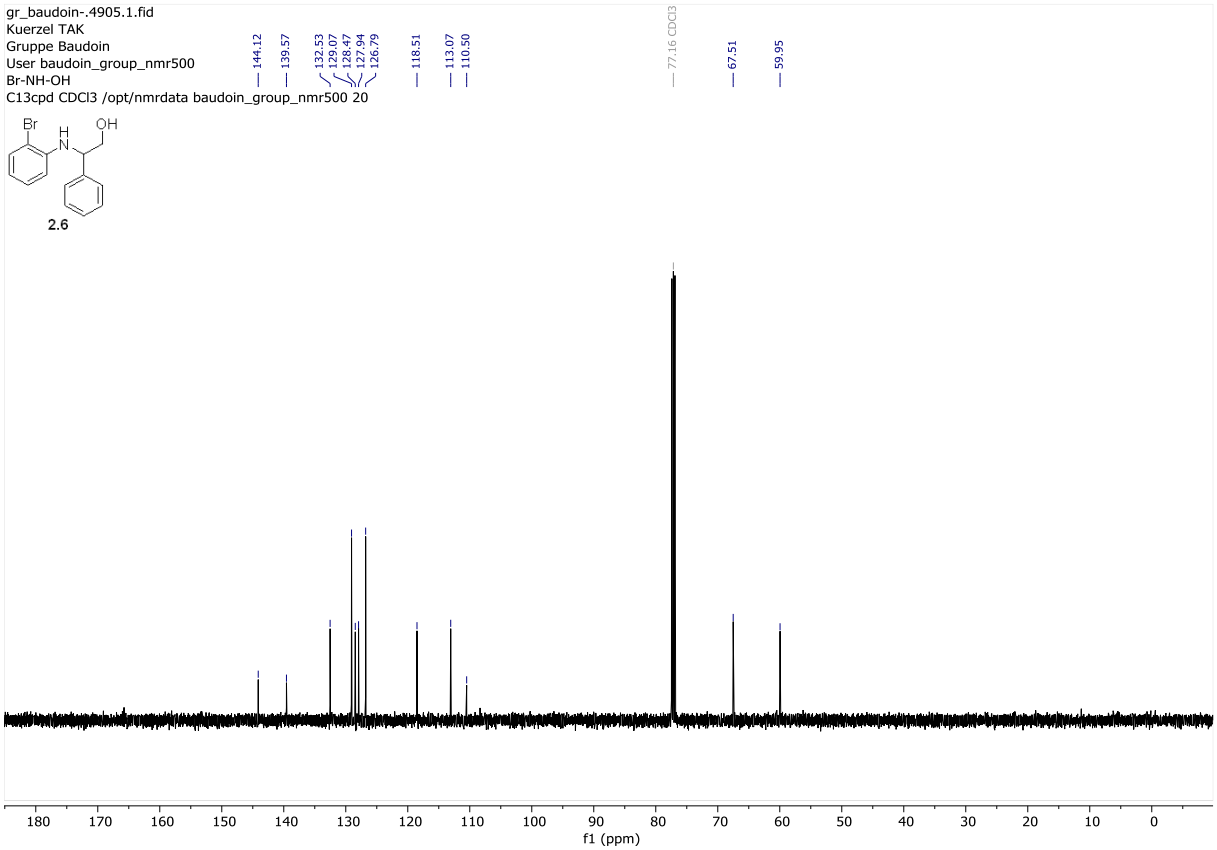
f1 (ppm)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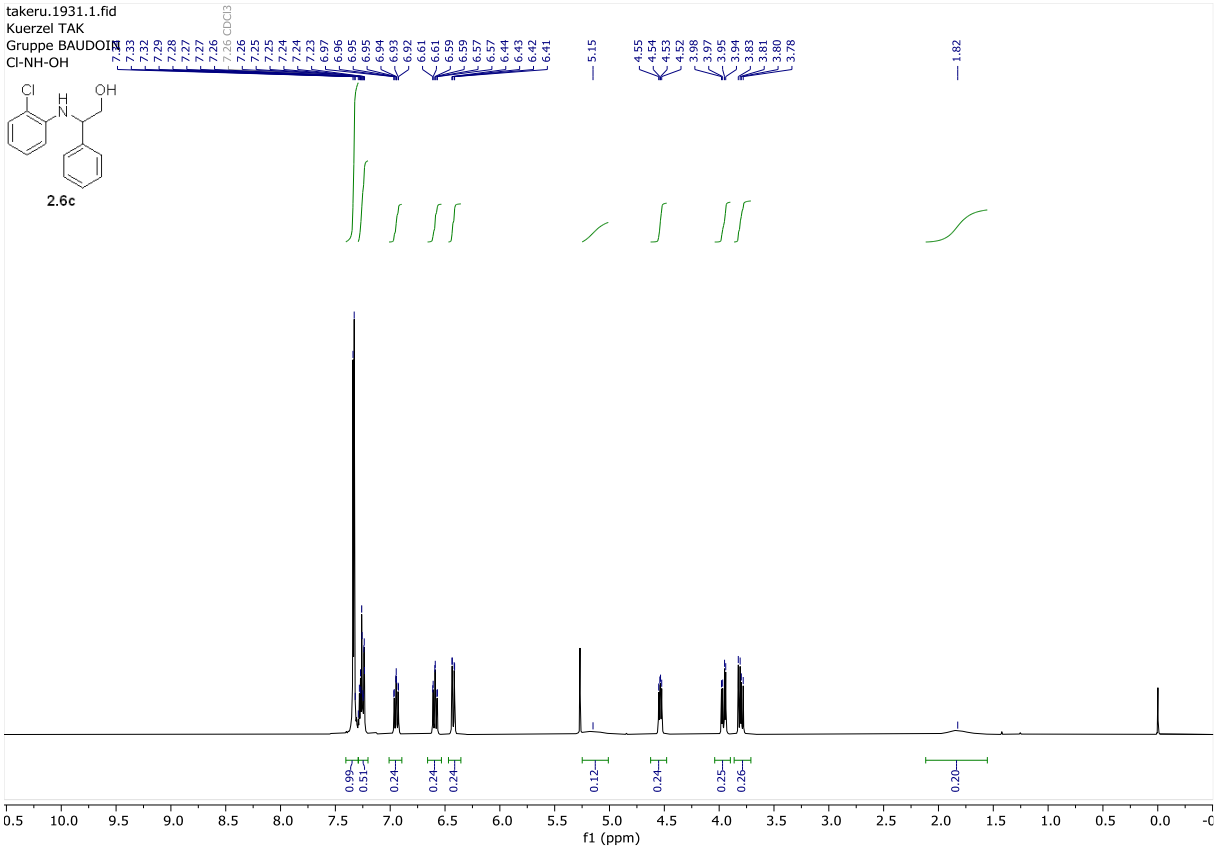
f1 (ppm)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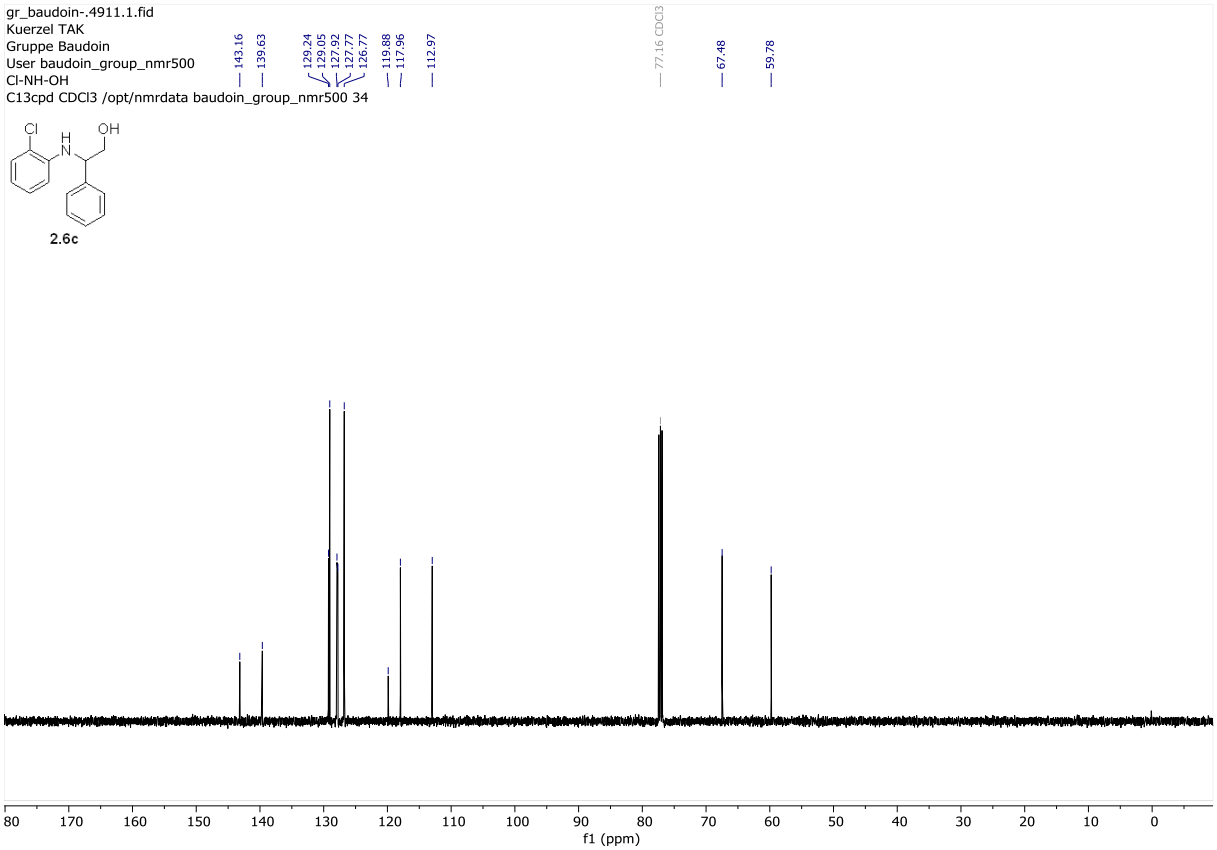
f1 (ppm)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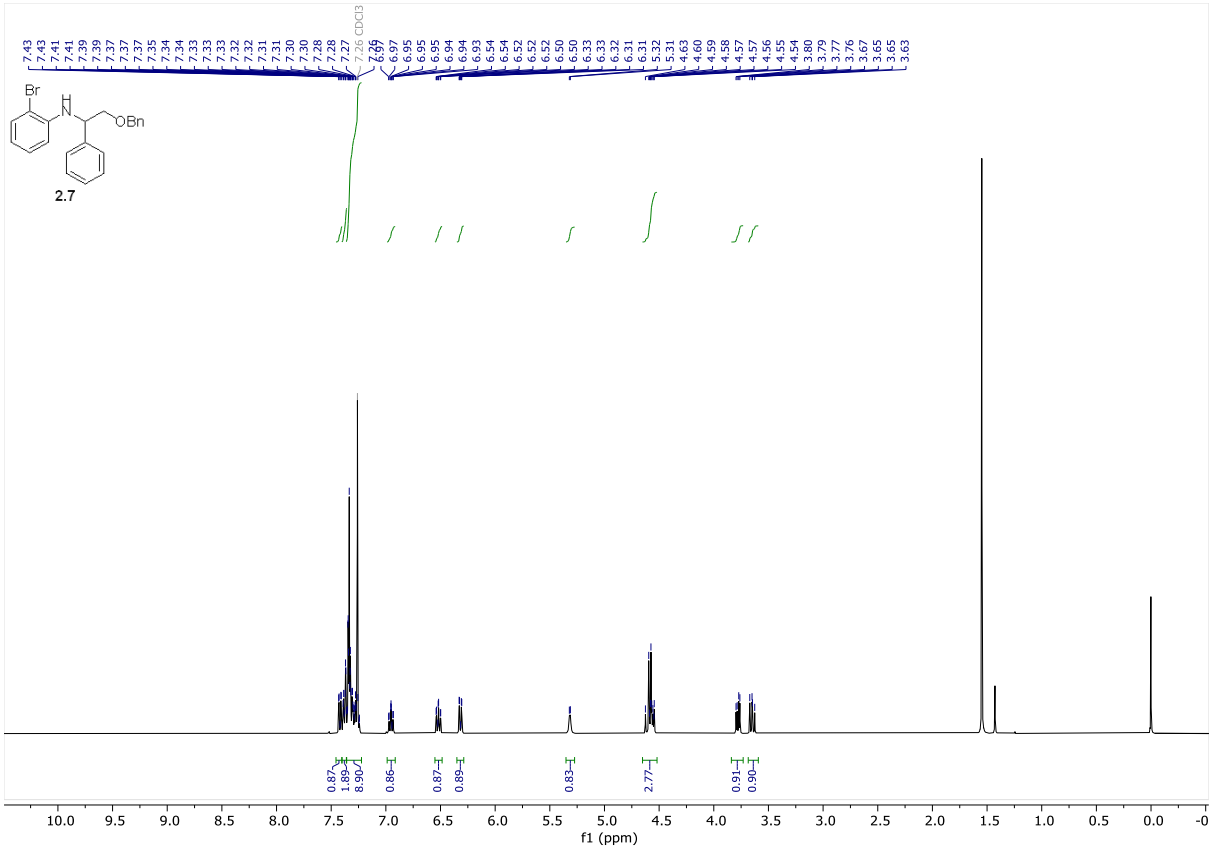
2.6c
f1 (ppm)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H
N
OBn
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CDCl3
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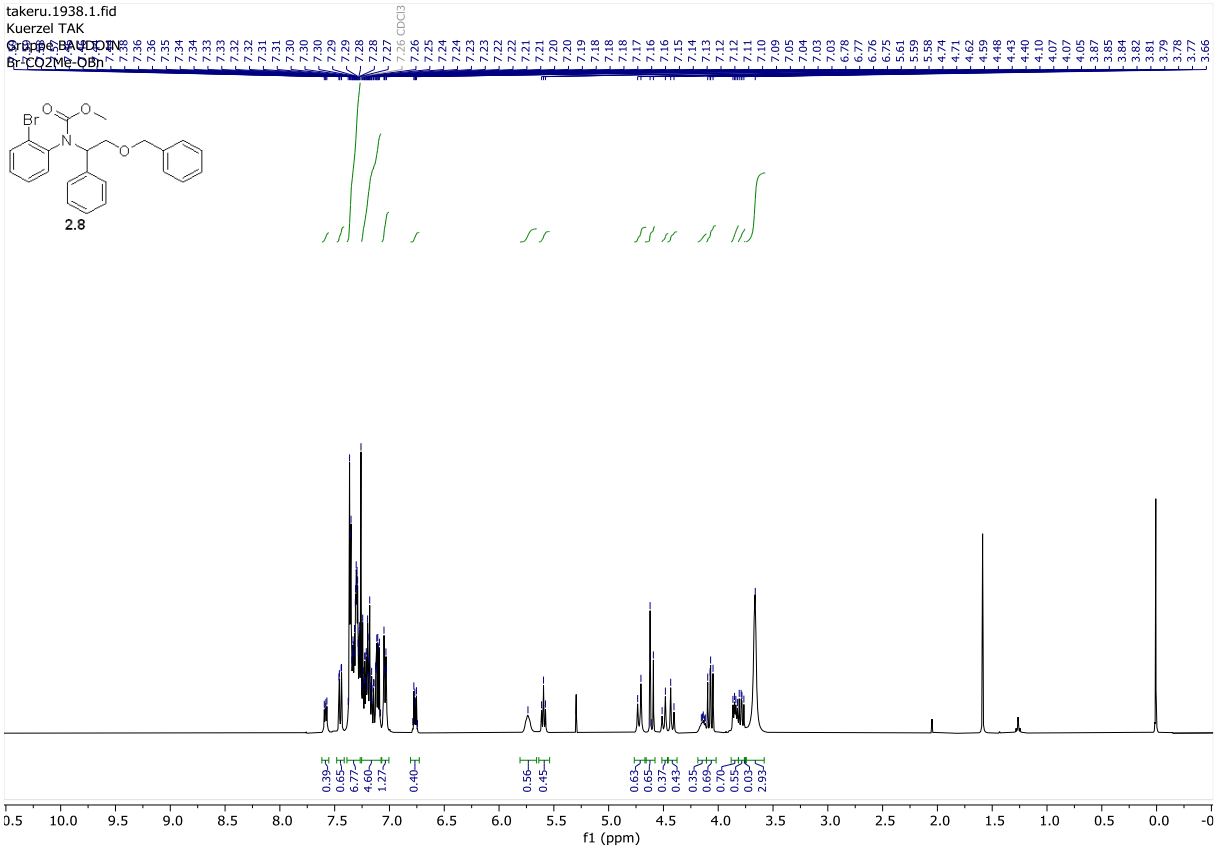
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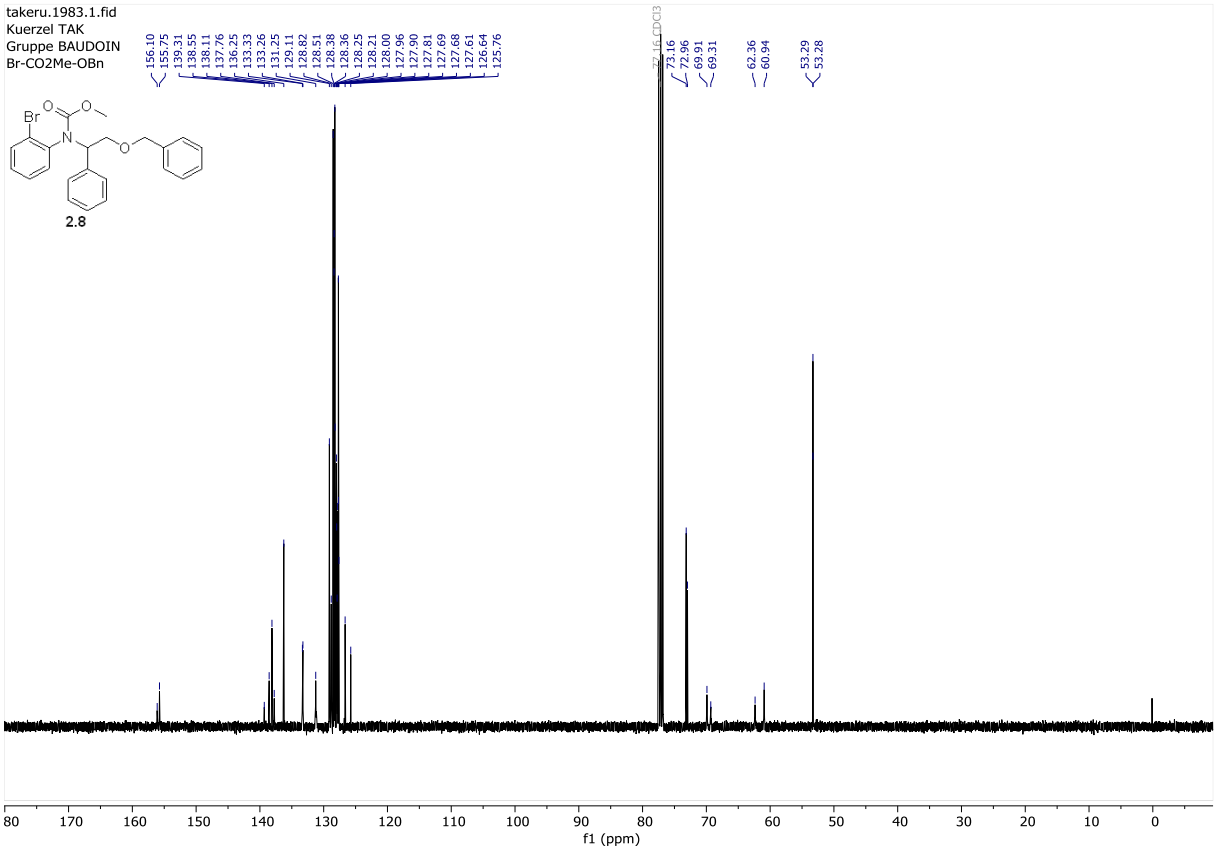
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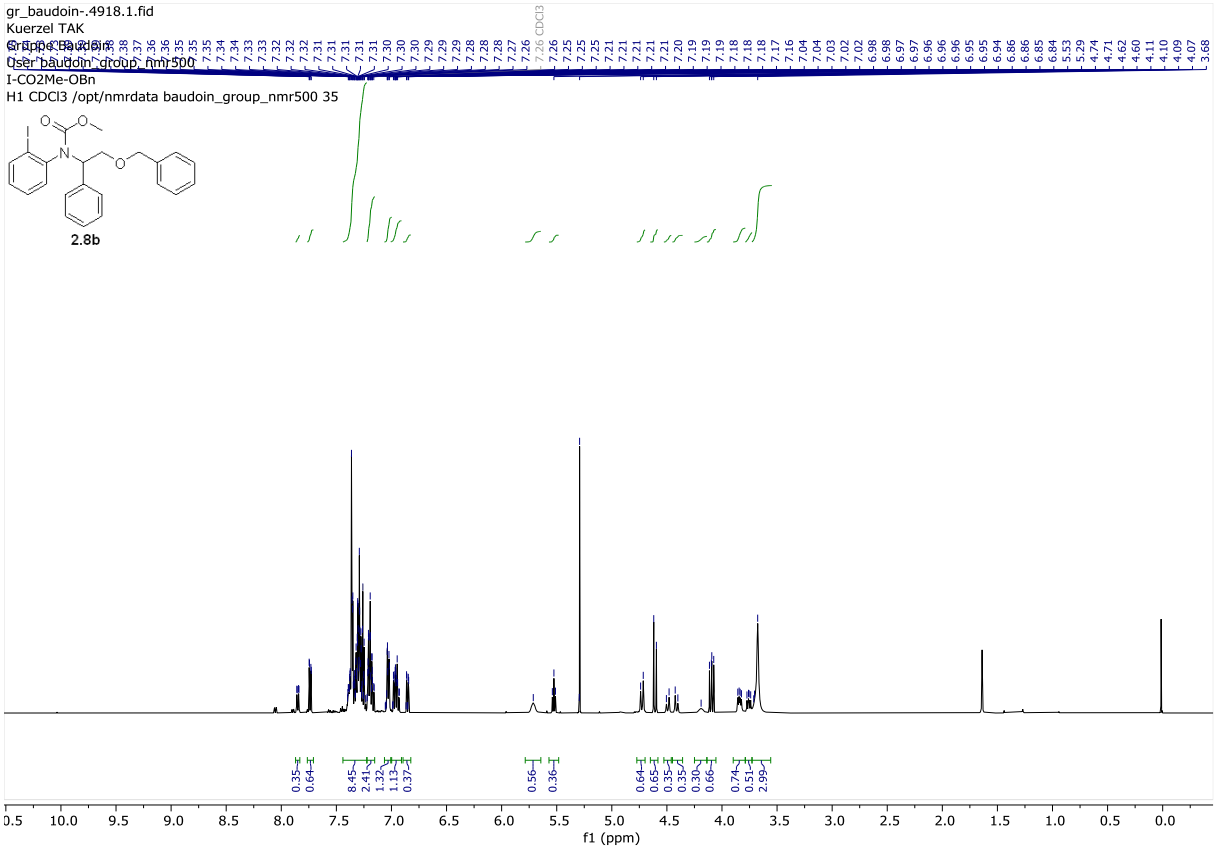
2.8
f1 (ppm)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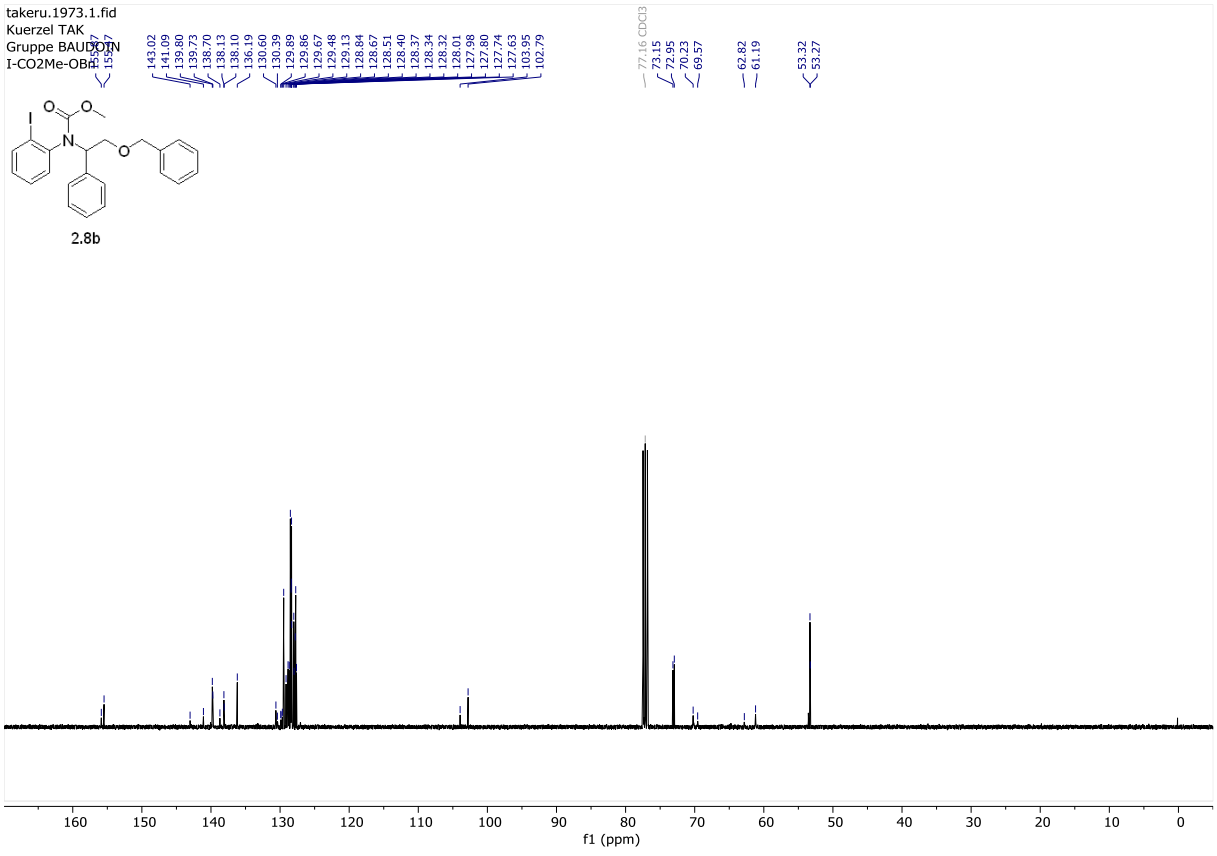
Kuerzel TAK
Gruppe Baudoin
User baudoin_group_nmr500
I-CO2Me-OBn
H1 CDCl3 /opt/nmrdata baudoin_group_nmr500 35
2.8b
f1 (ppm)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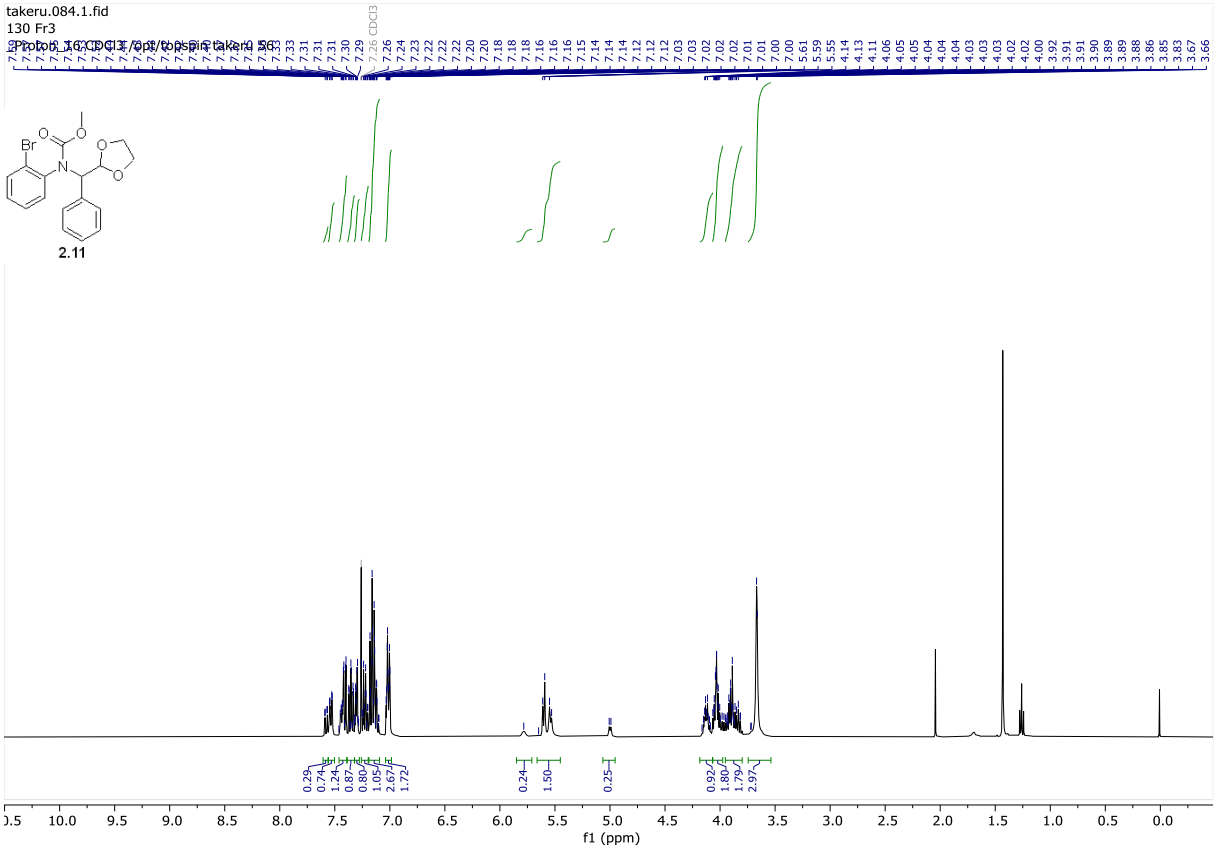
Gruppe BAUDOIN
I-CO2Me-OBn
2.8b
f1 (ppm)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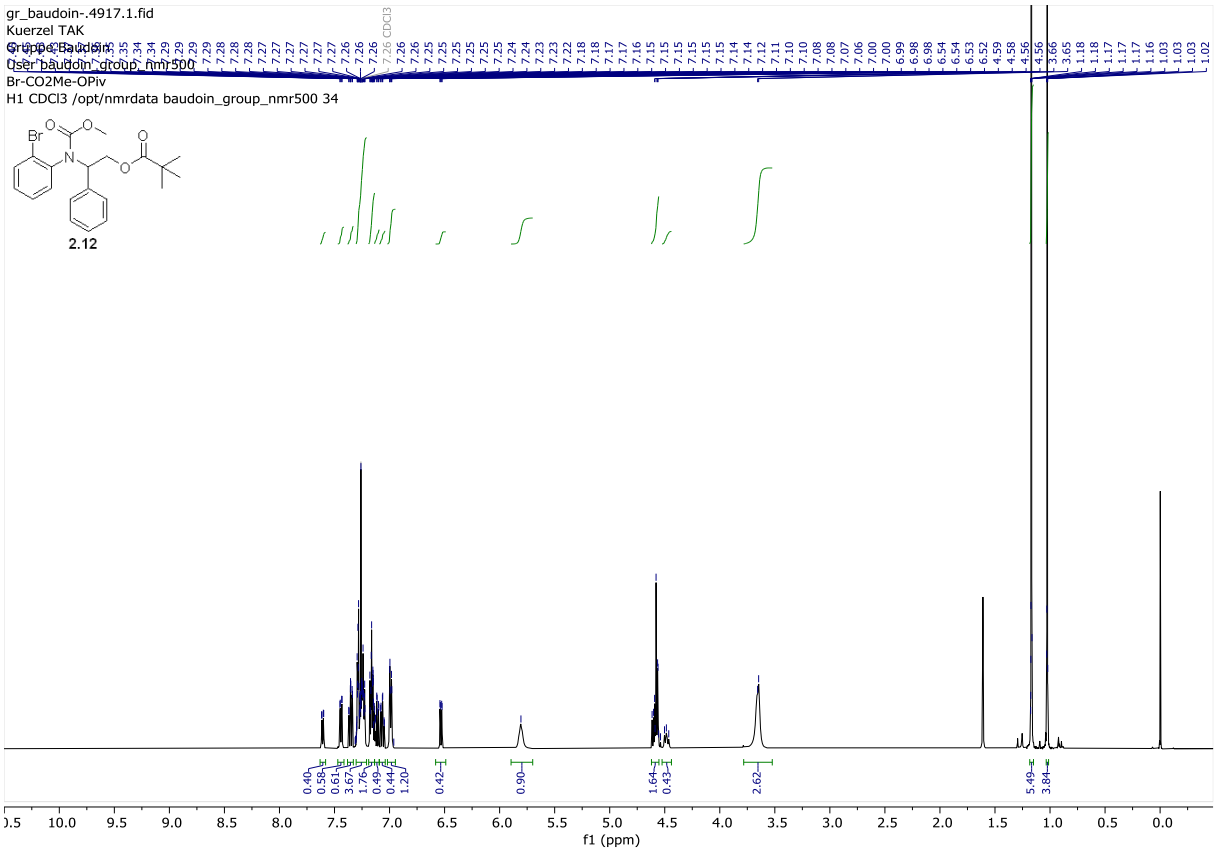
130 Fr3
Br
O
O
N
O
O
2.11
CDCl3
f1 (ppm)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Gruppe Baudoin
User baudoin_group_nmr500
Br-CO2Me-OPiv
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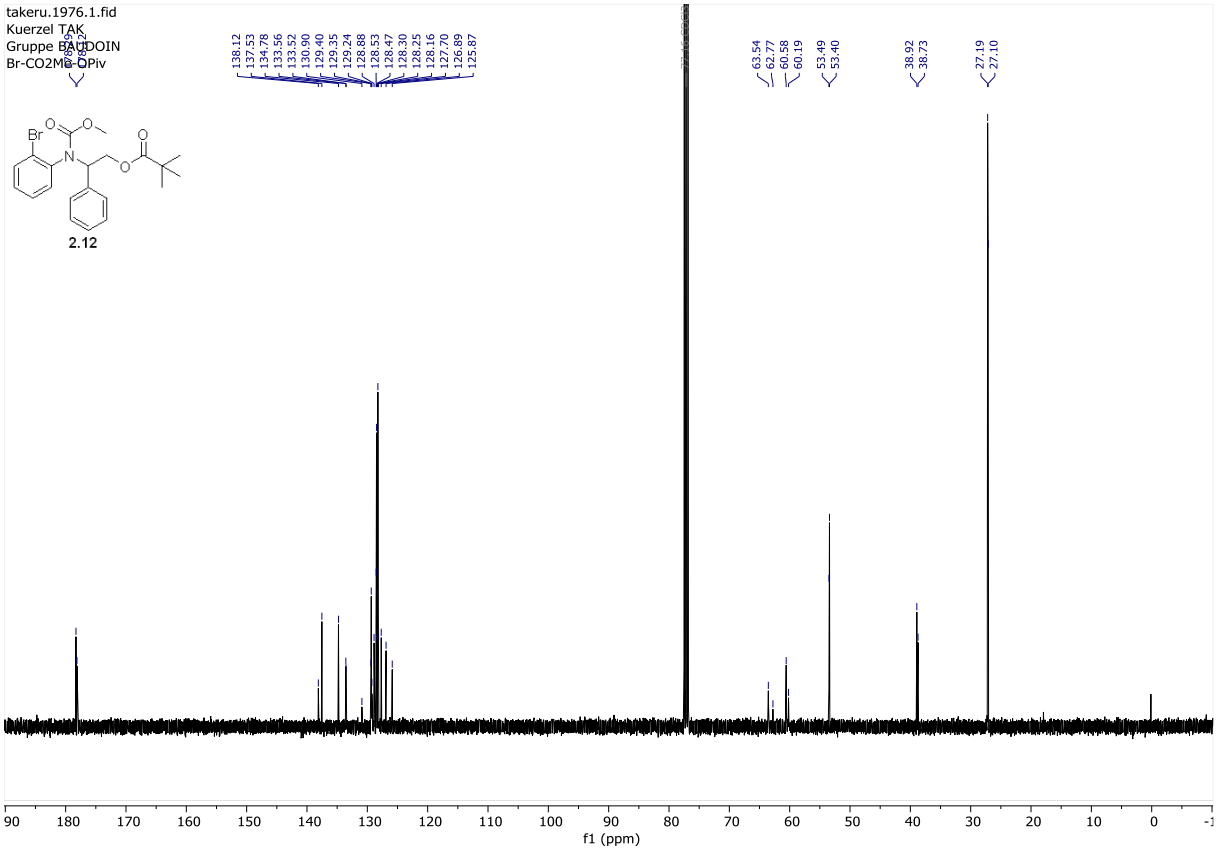
2.12
f1 (ppm)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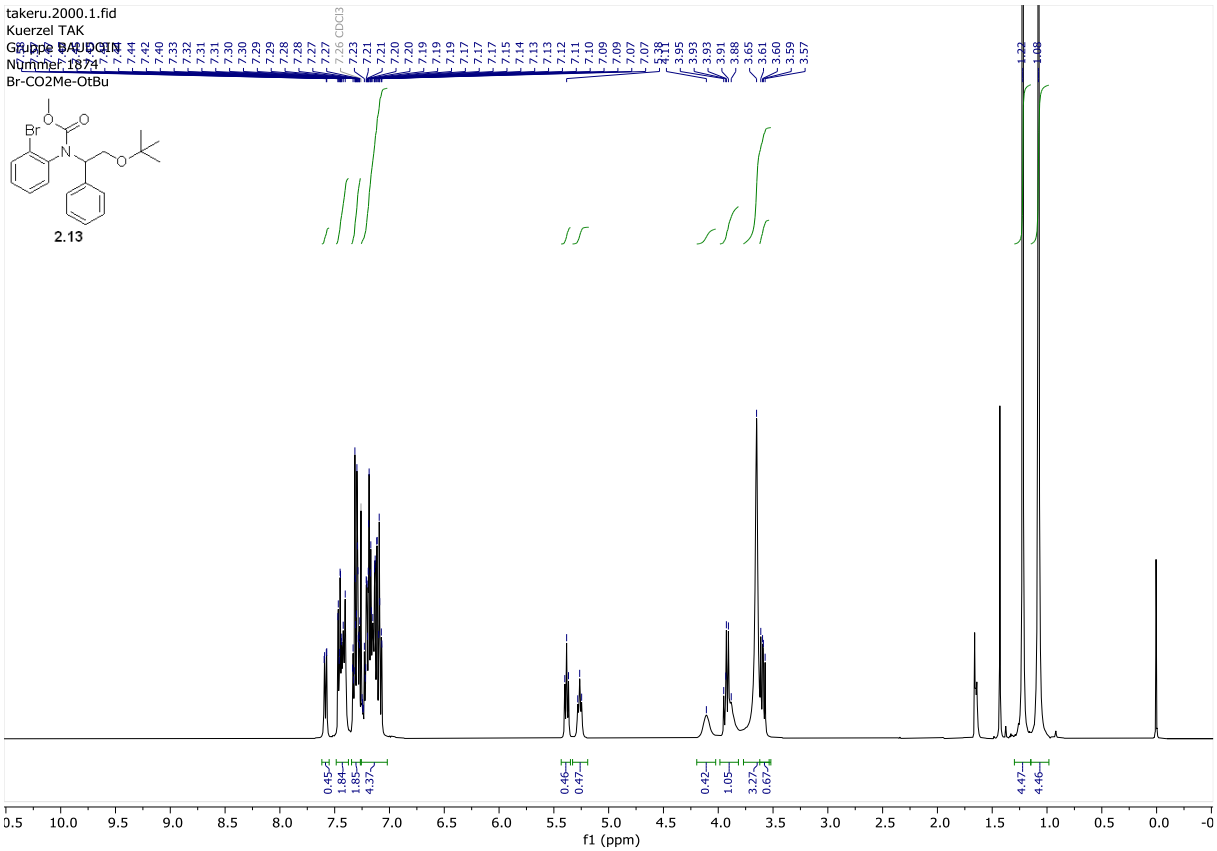
Gruppe BAUDOIN
Br-CO2Me-OPiv
2.12
f1 (ppm)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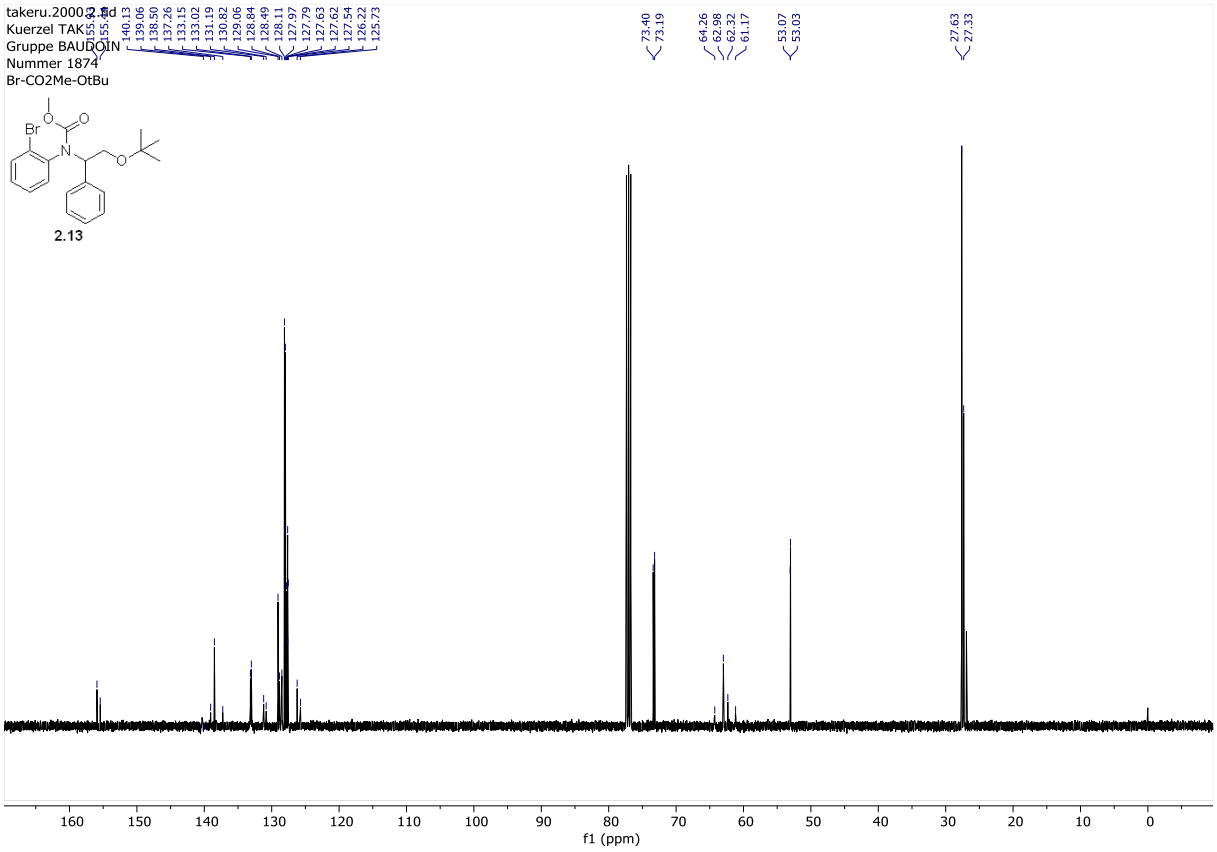
Nummer 1874
Br-CO2Me-OtBu
2.13
f1 (ppm)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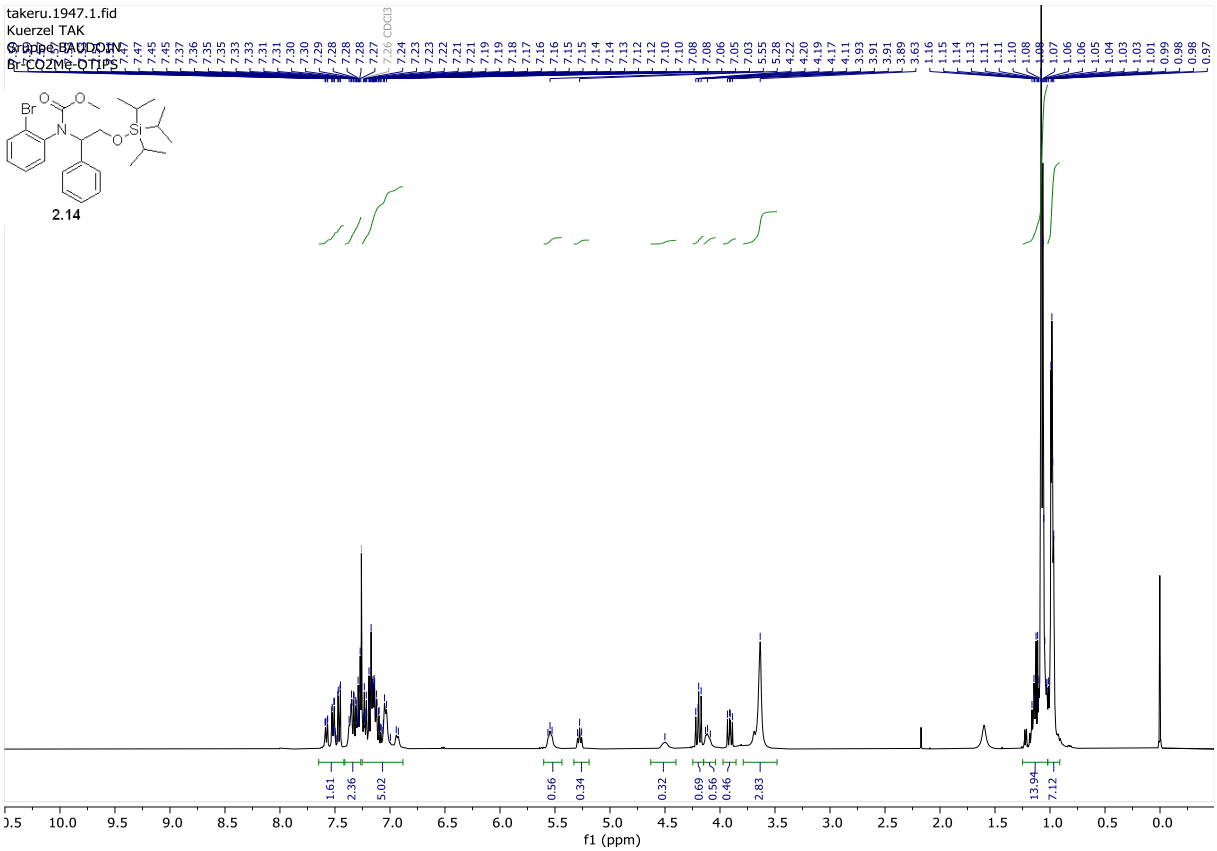
Gruppe BAUDOIN
Nummer 1874
Br-CO2Me-OtBu
2.13
f1 (ppm)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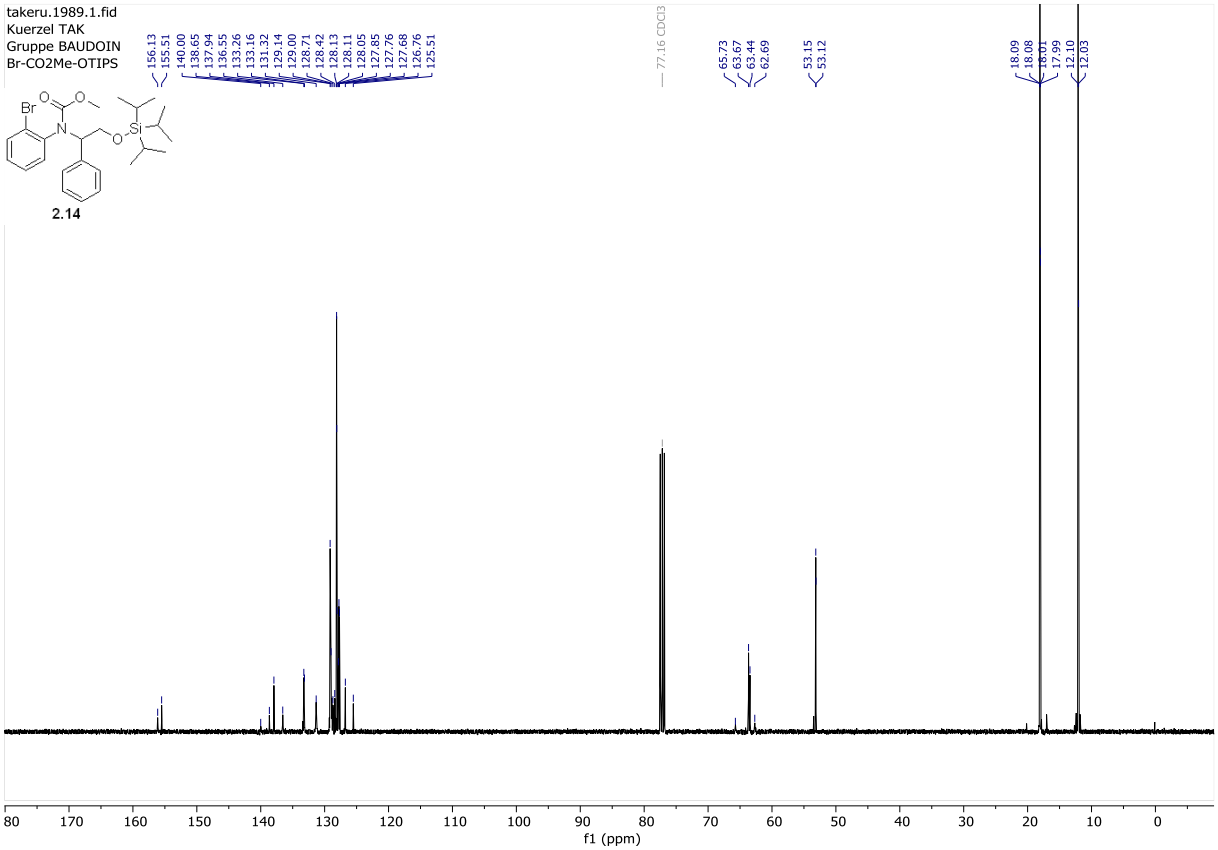
Gruppe BAUDOIN
Br-CO2Me-OTIPS
2.14
f1 (ppm)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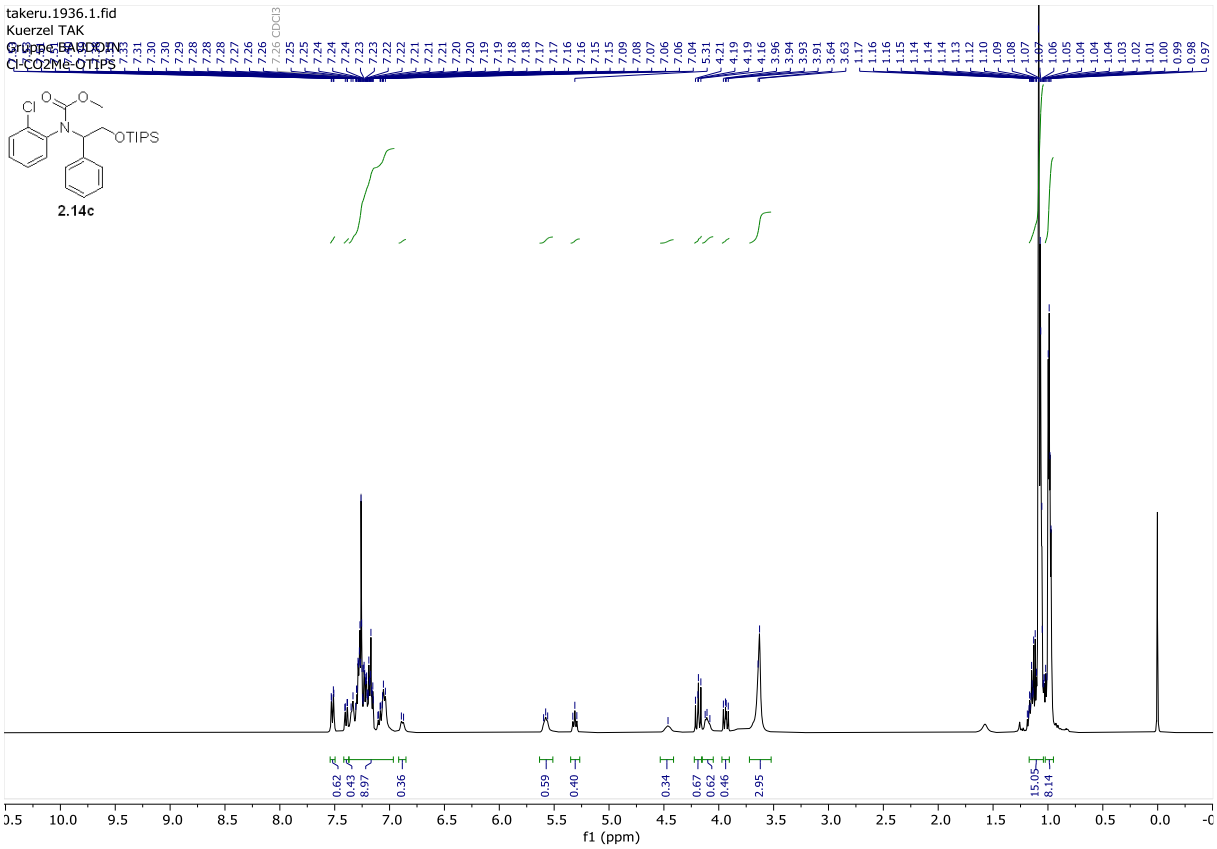
Gruppe BAUDOIN
Br-CO2Me-OTIPS
2.14
f1 (ppm)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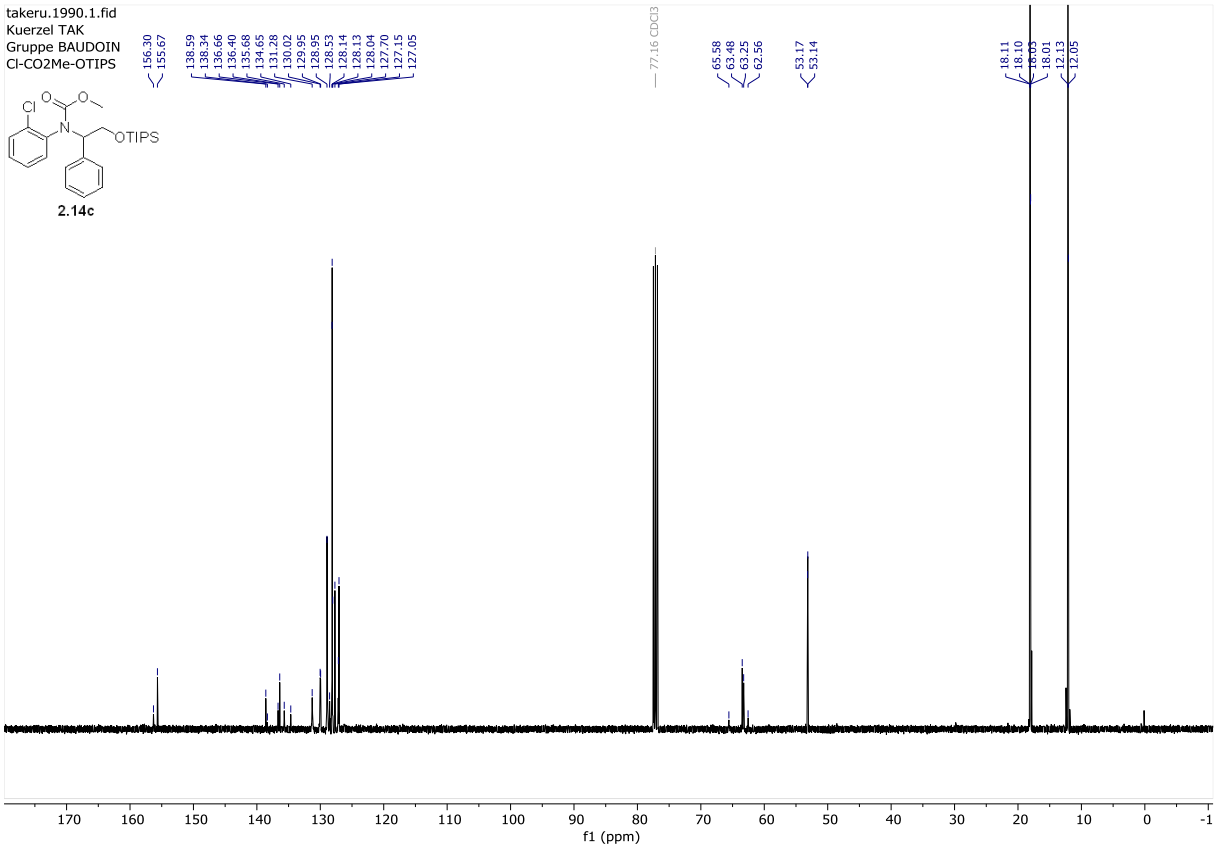
Gruppe BAUDOIN
Cl-CO2Me-OTIPS
OTIPS
2.14c
f1 (ppm)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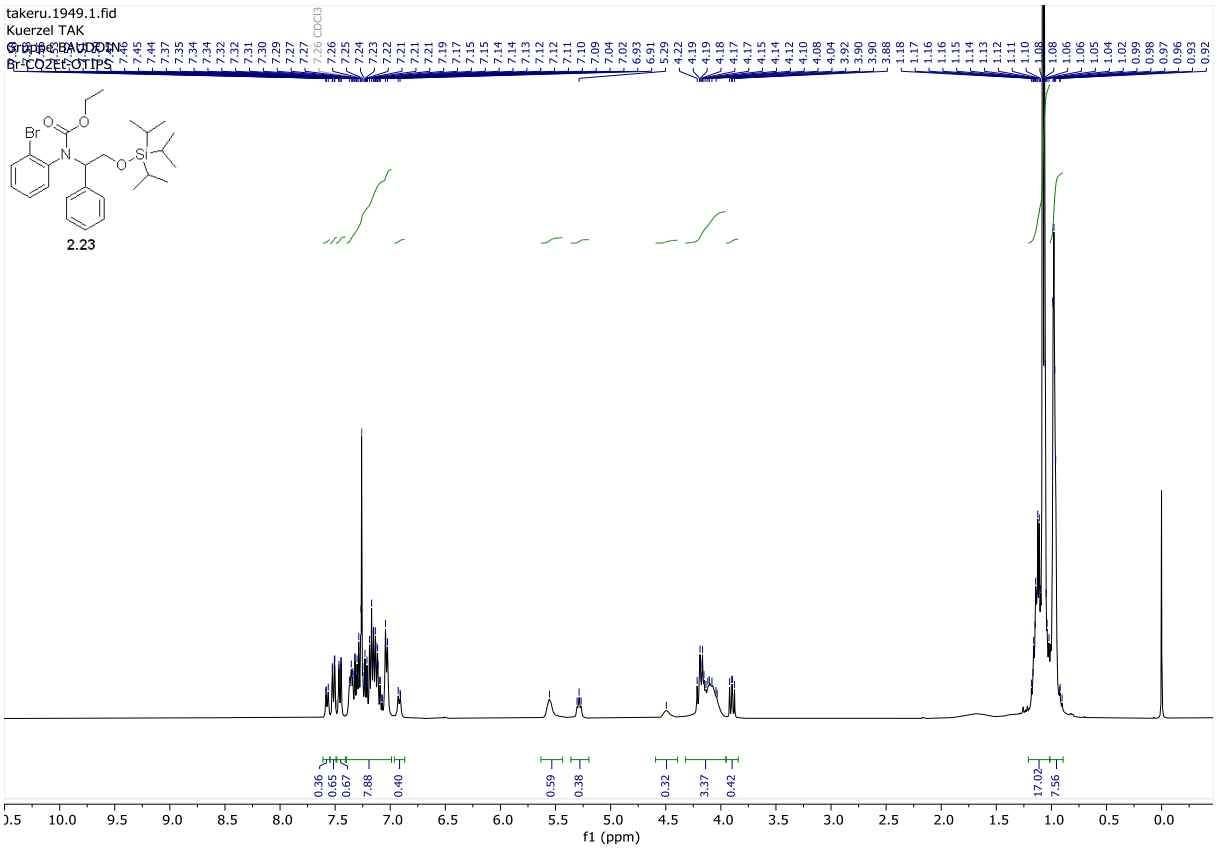
Gruppe BAUDOIN
Cl-CO2Me-OTIPS
OTIPS
2.14c
f1 (ppm)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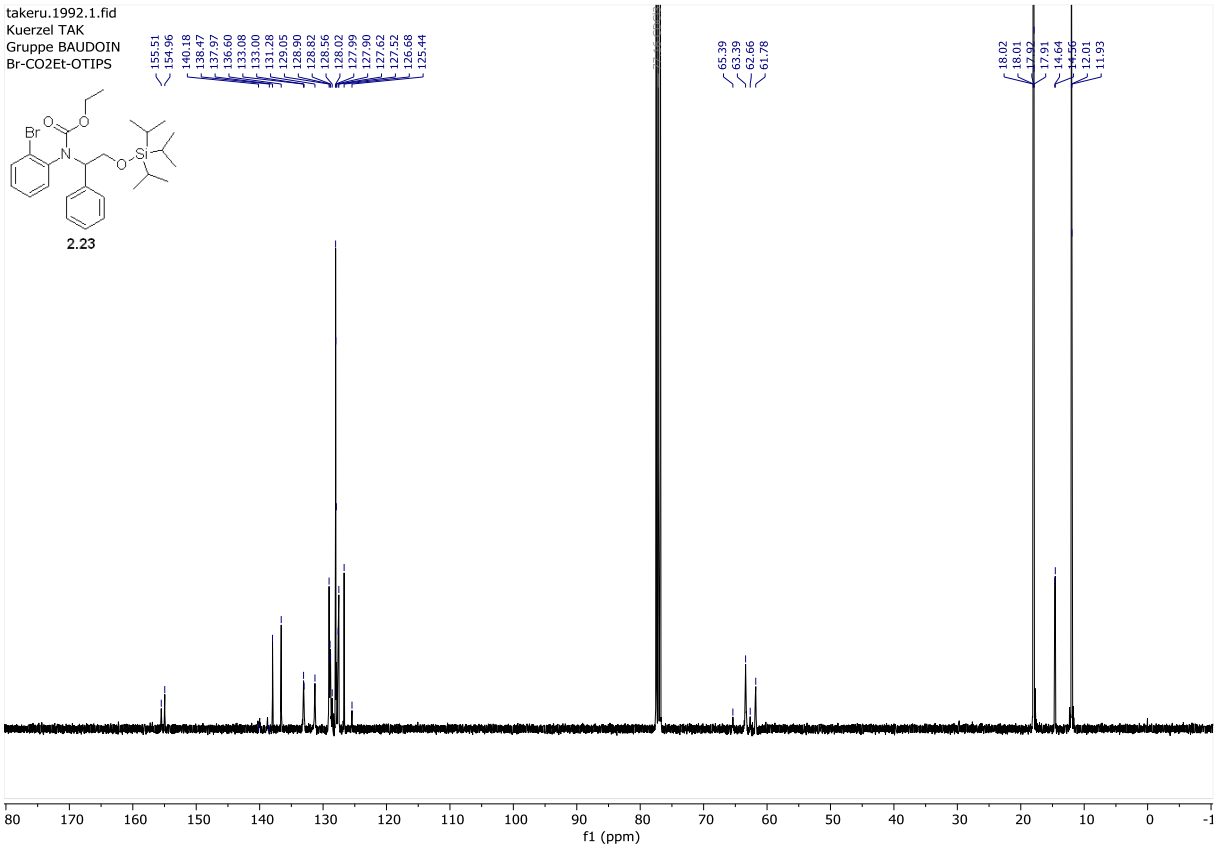
Kuerzel TAK
Gruppe BAUDOIN
Br-CO2Et-OTIPS
2.23
f1 (ppm)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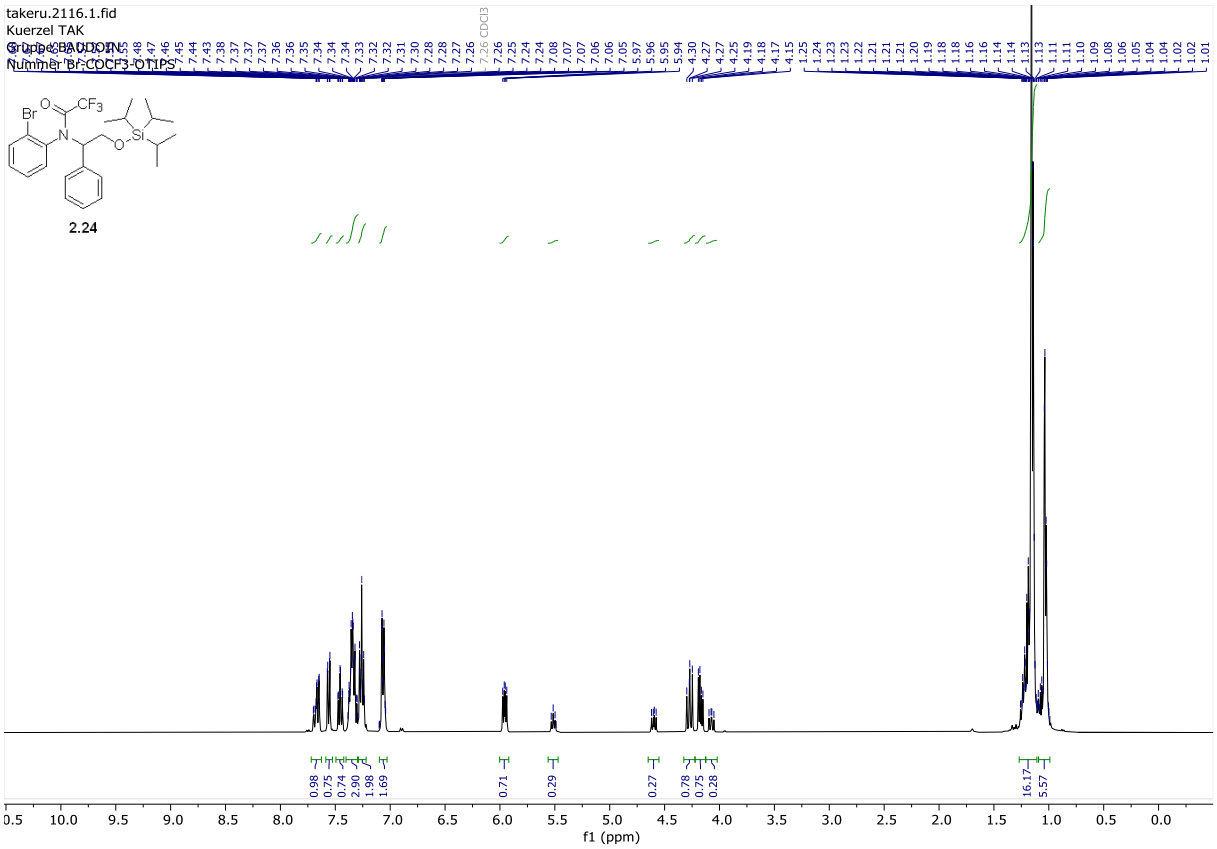
Gruppe BAUDOIN
Br-CO2Et-OTIPS
2.23
f1 (ppm)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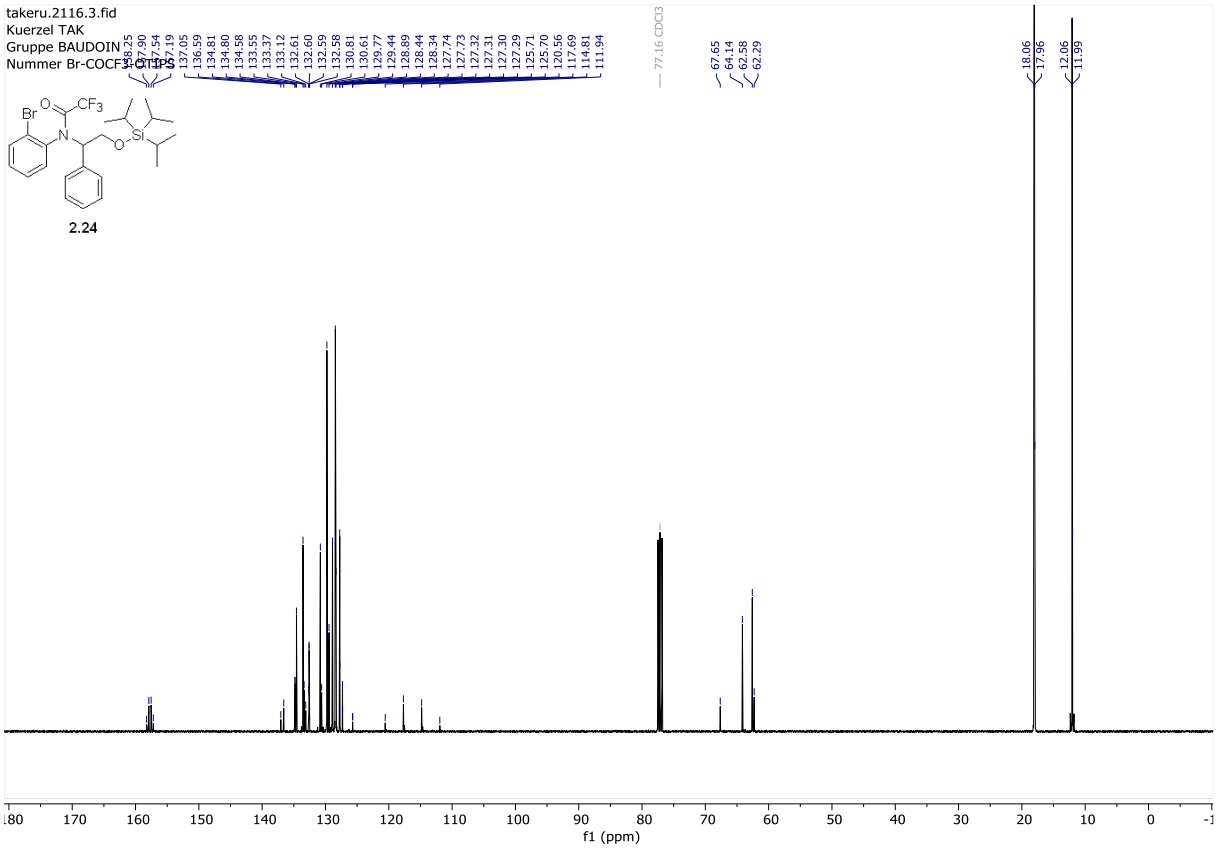
Gruppe BAUDOIN
Nummer Br-COCF3-OTIPS
2.24
f1 (ppm)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Kuerzel TAK
Gruppe BAUDOIN
Nummer Br-COCF3-OTIPS
2.24
f1 (ppm)

takeru.2116.2.fid
Kuerzel TAK
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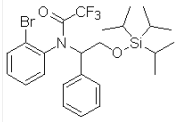
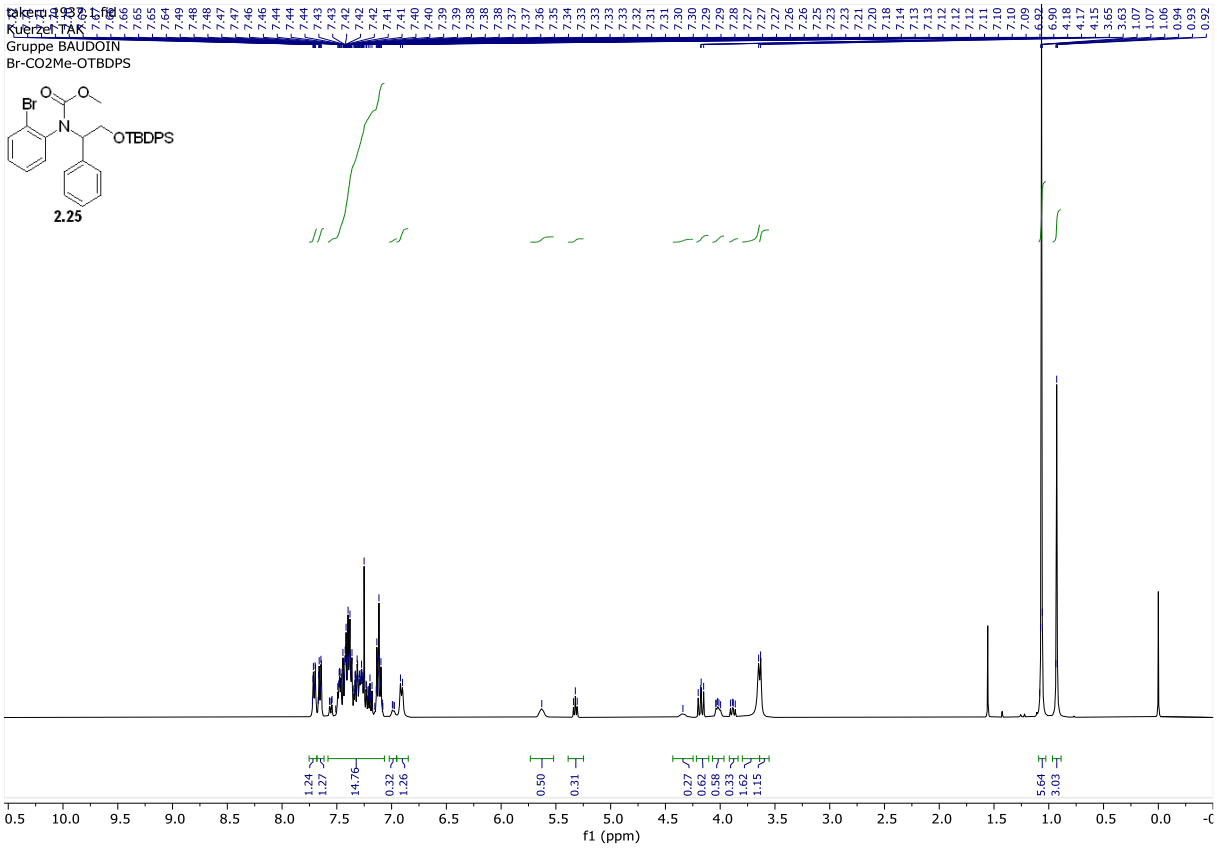
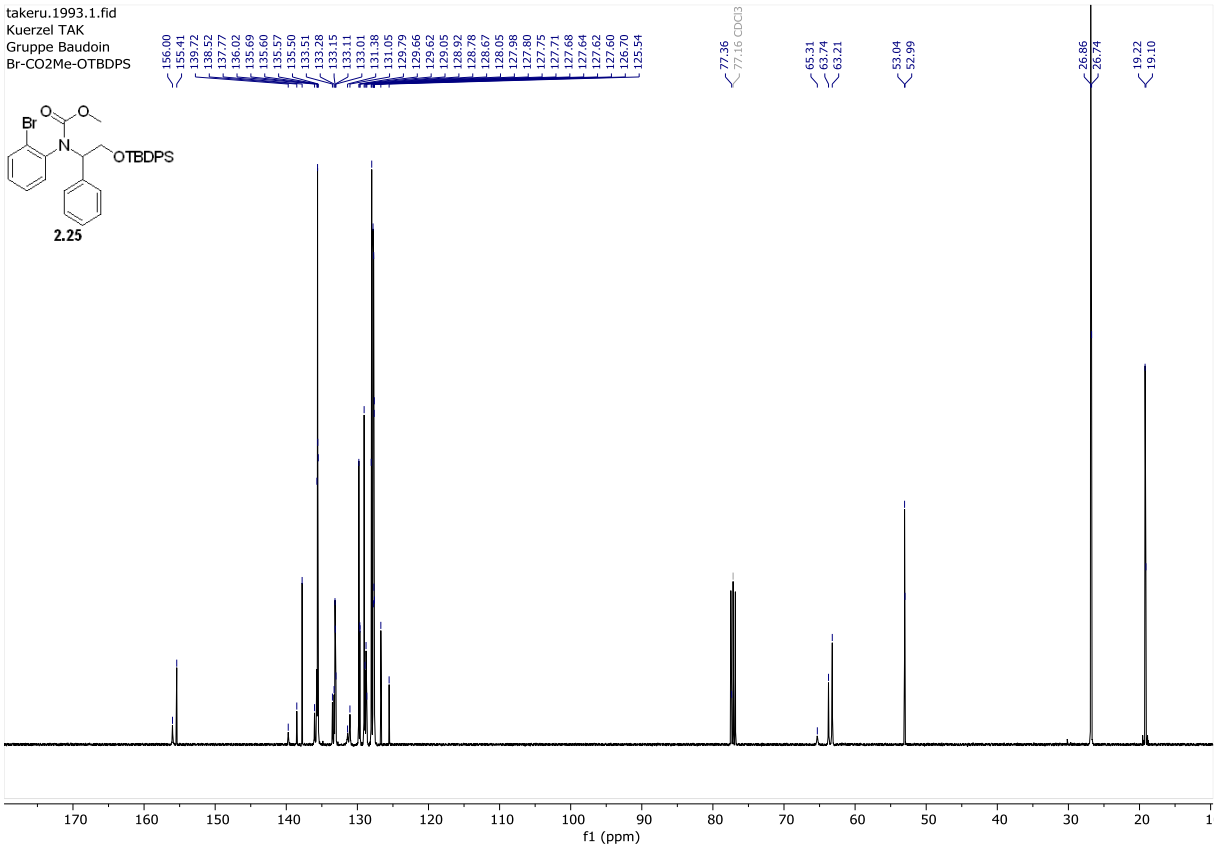
Nummer Br-COCF3-OTIPS



2.24


takeru.1993.1.fid
Kuerzel TAK
Gruppe BAUDOIN
Br-CO2Me-OTBDPS
Br
O
O
N
OTBDPS
2.25
1.24
1.27
14.76
0.32
1.26
0.50
0.31
0.27
0.62
0.58
0.33
1.62
1.15
5.64
3.03
f1 (ppm)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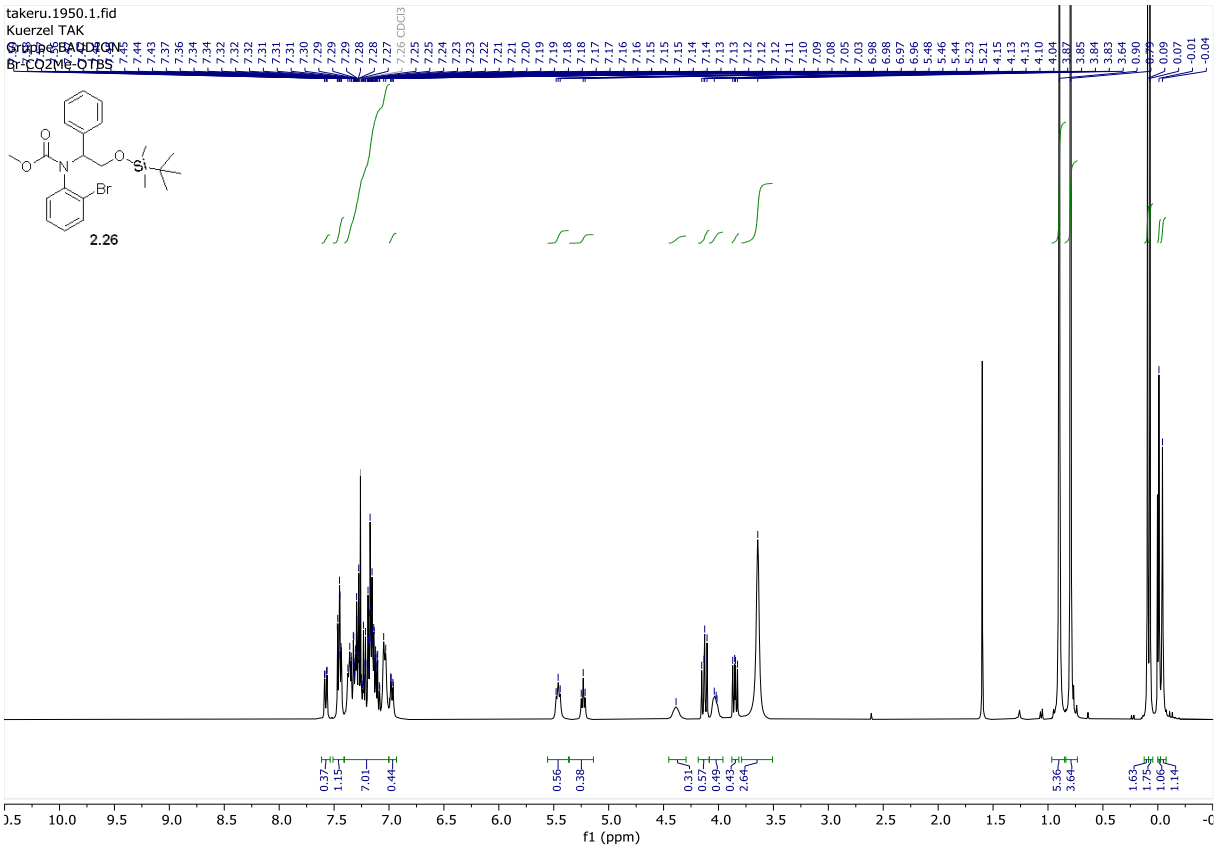
Kuerzel TAK
Gruppe Baudoin
Br-CO2Me-OTBDPS
156.00
155.41
139.72
138.52
137.77
136.02
135.69
135.60
135.57
135.50
133.51
133.28
133.15
133.11
133.01
131.38
131.05
129.79
129.66
129.62
129.05
128.92
128.78
128.67
128.05
127.98
127.80
127.75
127.71
127.68
127.64
127.62
127.60
126.70
125.54
77.36
77.16 CDCl3
65.31
63.74
63.21
53.04
52.99
26.86
26.74
19.22
19.10
Br
O
O
N
OTBDPS
2.25
f1 (ppm)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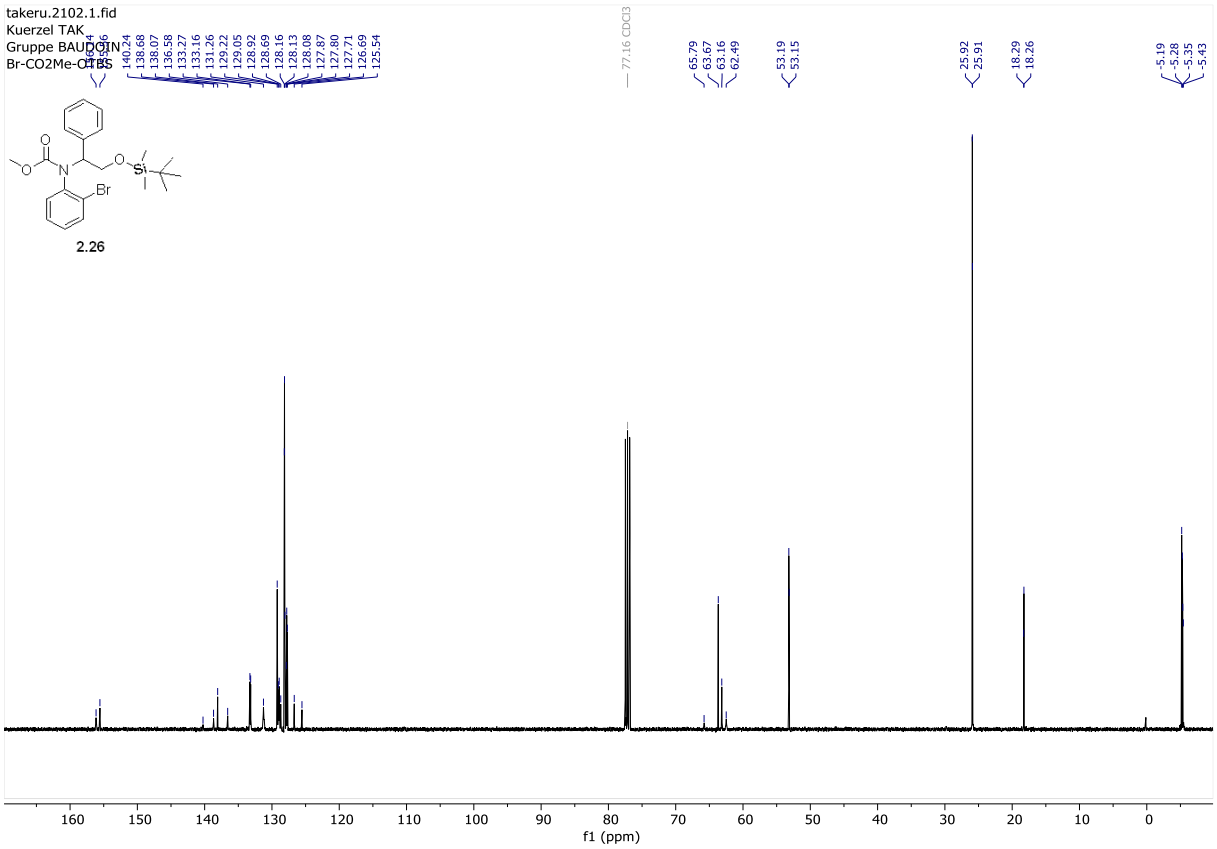
Gruppe BAUDOIN
Br-CO2Me-OTBS
2.26
f1 (ppm)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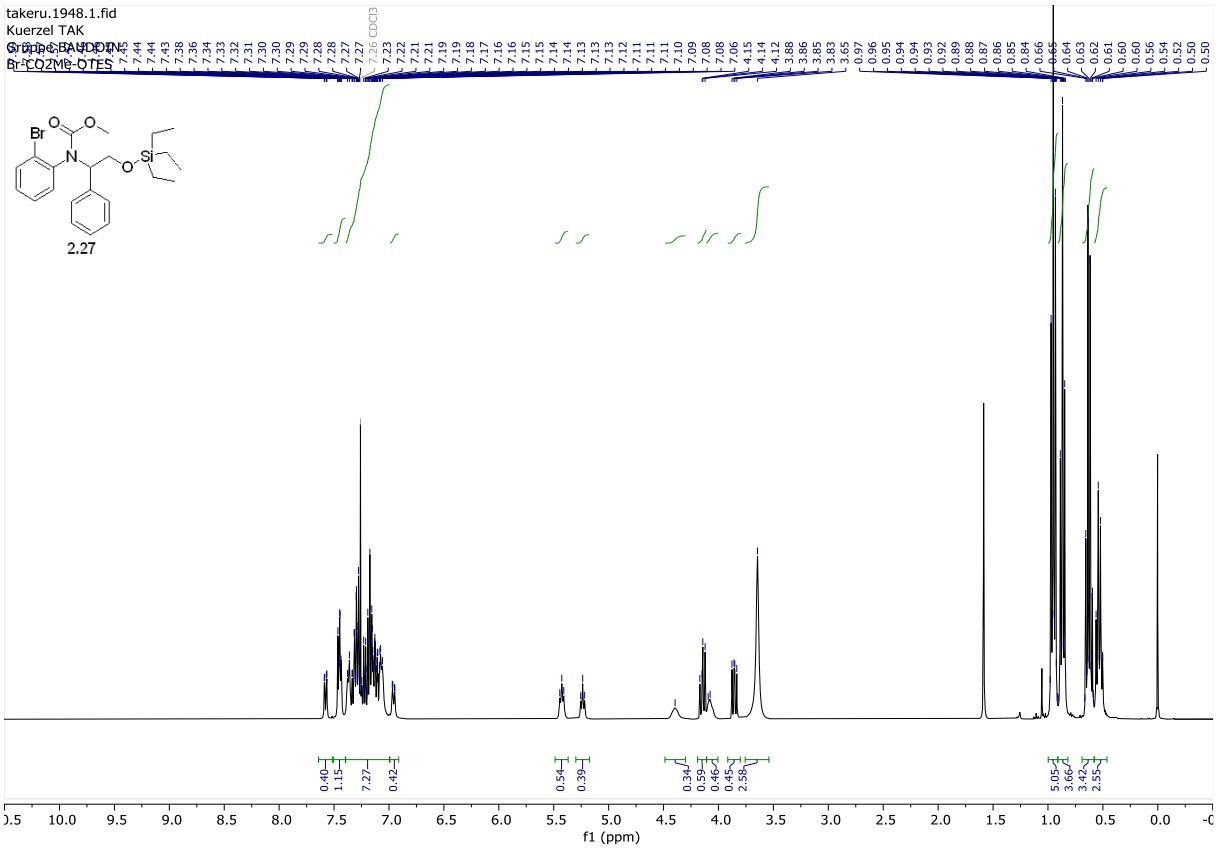
Br-CO2Me-OTBS
2.26
f1 (ppm)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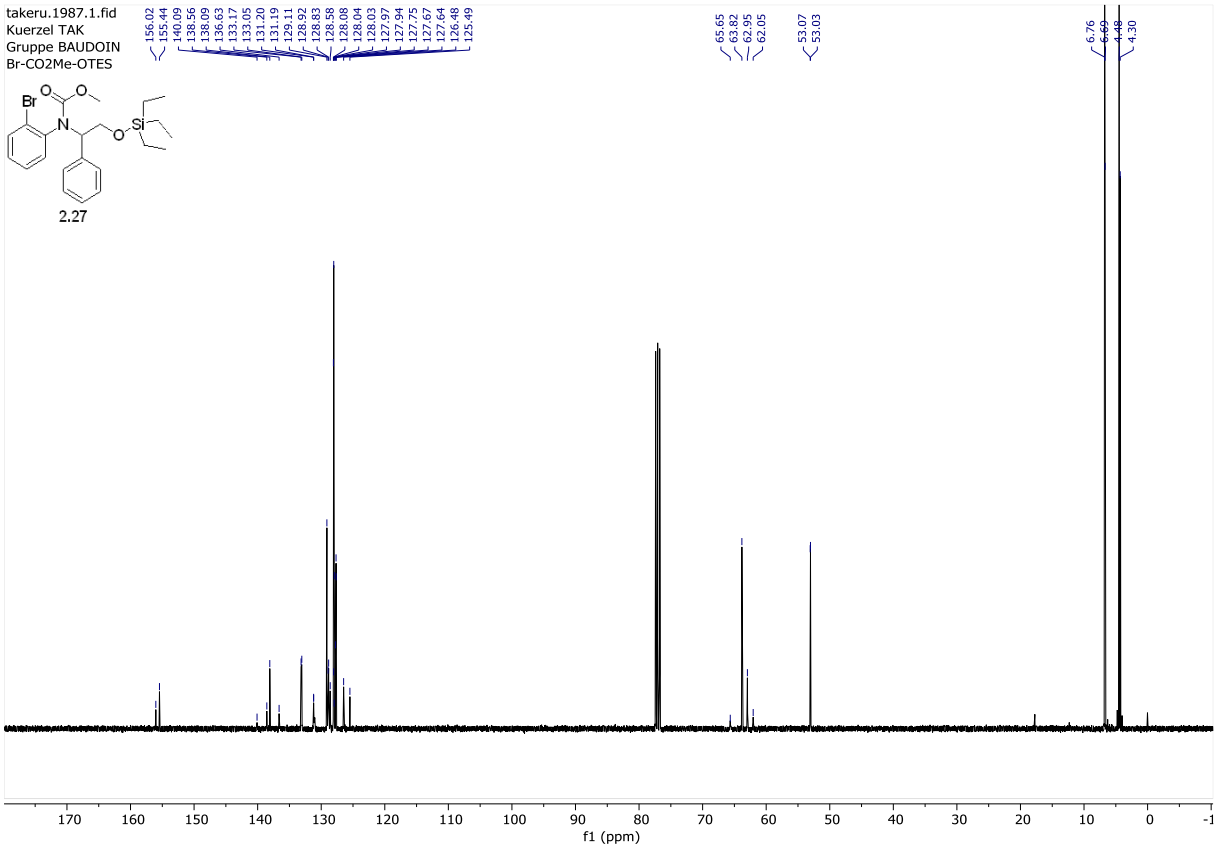
Gruppe BAUDOIN
Br-CO2Me-OTES
2.27
f1 (ppm)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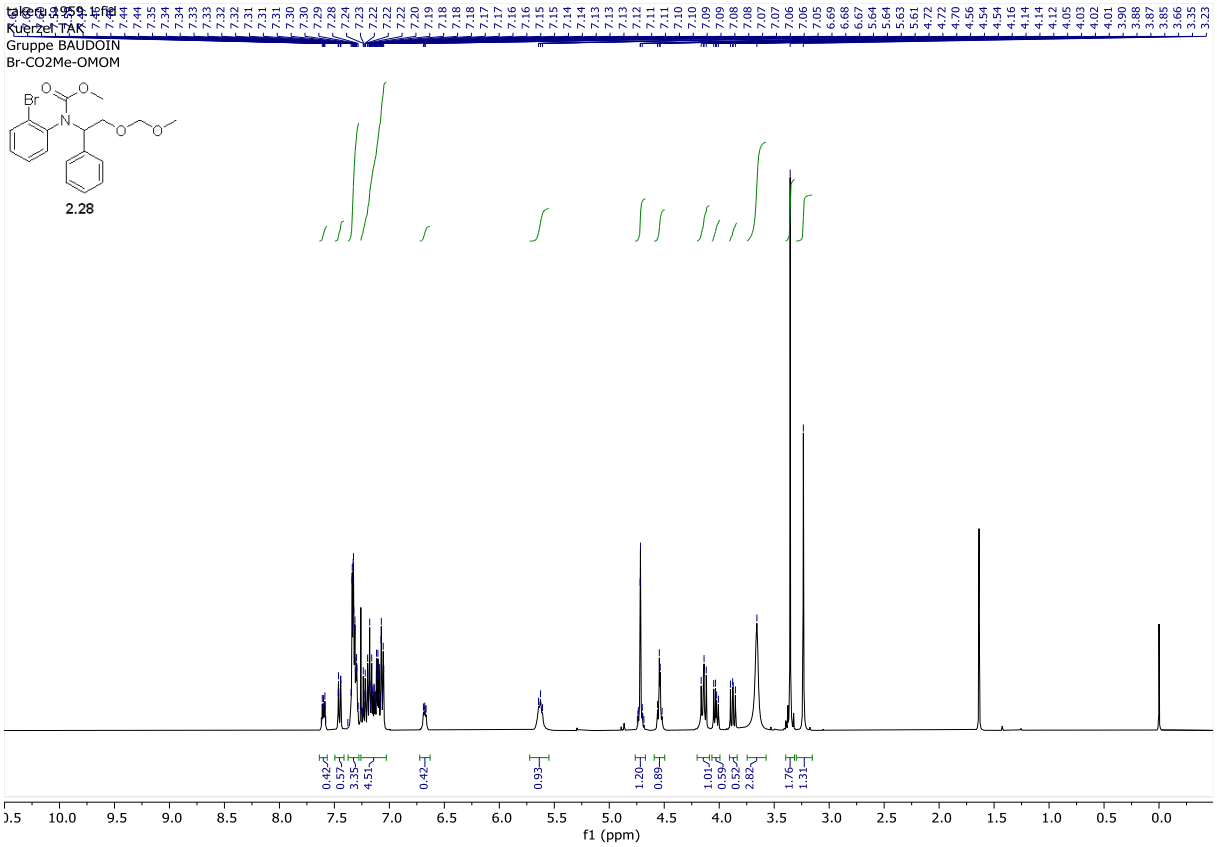
2.27
f1 (ppm)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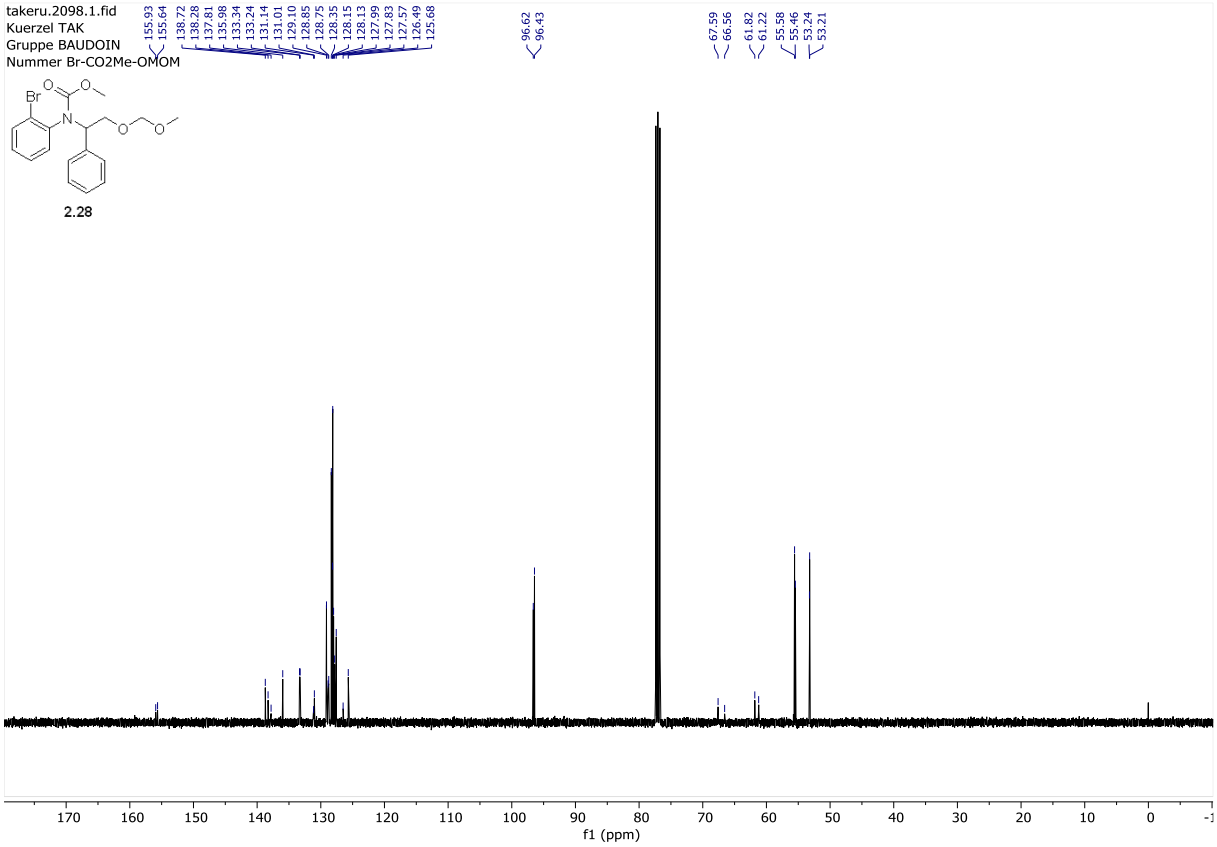
Gruppe BAUDOIN
Br-CO2Me-OMOM
2.28
f1 (ppm)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Nummer Br-CO2Me-OMOM
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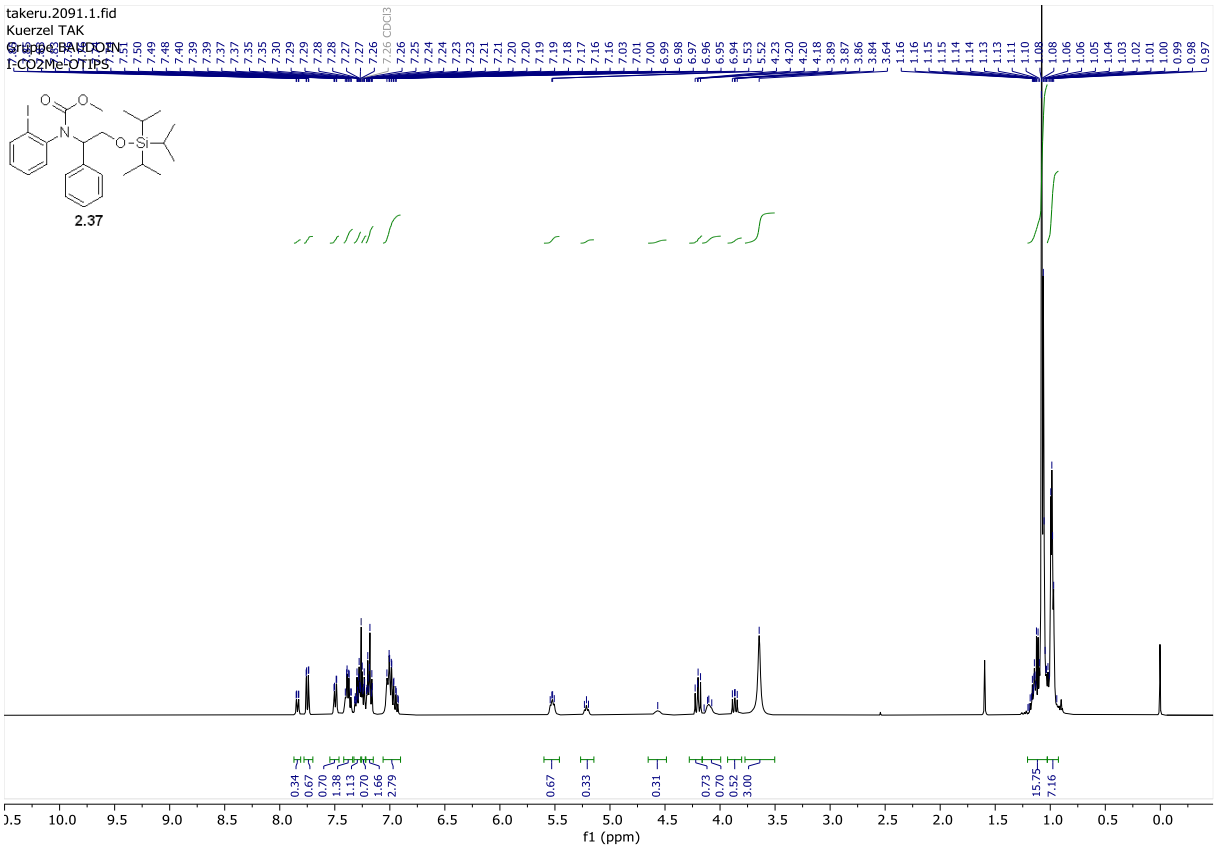
f1 (ppm)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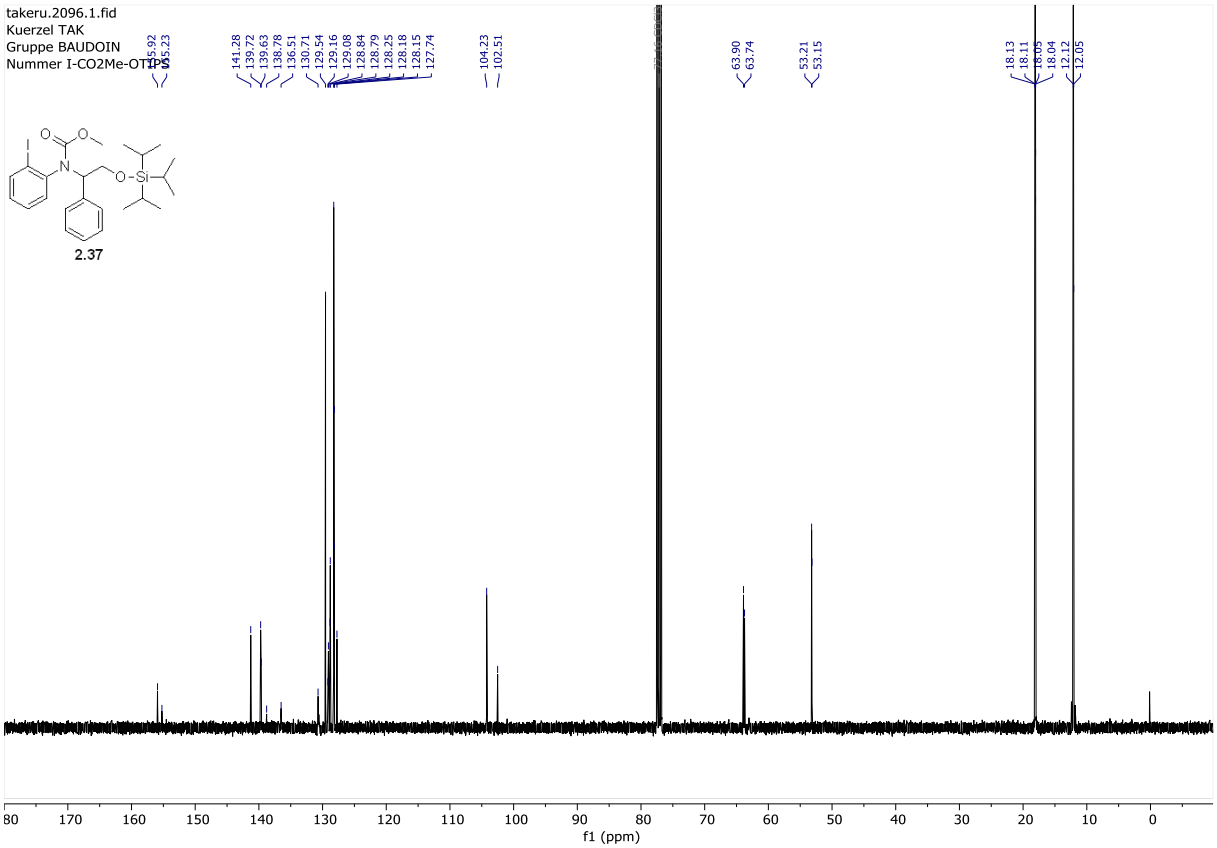
Gruppe BAUDOIN
I-CO2Me-OTIPS
2.37
f1 (ppm)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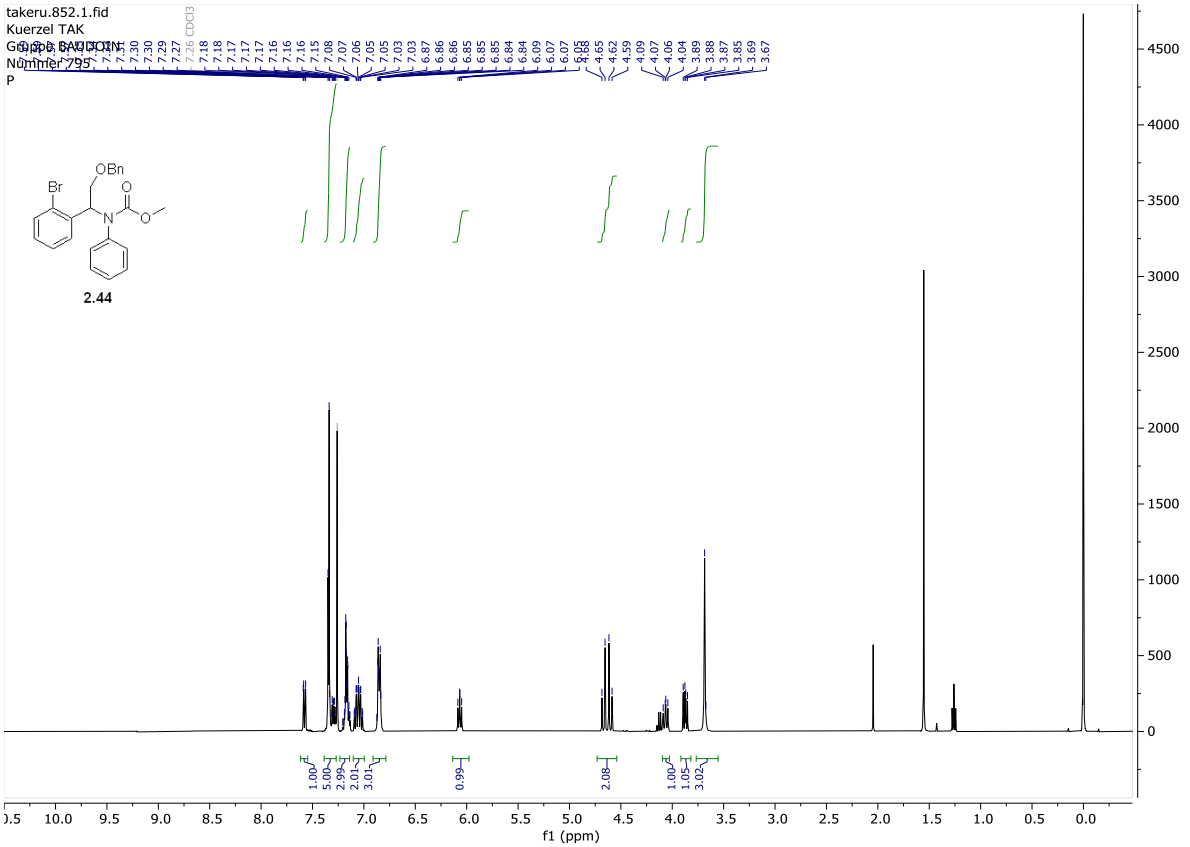
f1 (ppm)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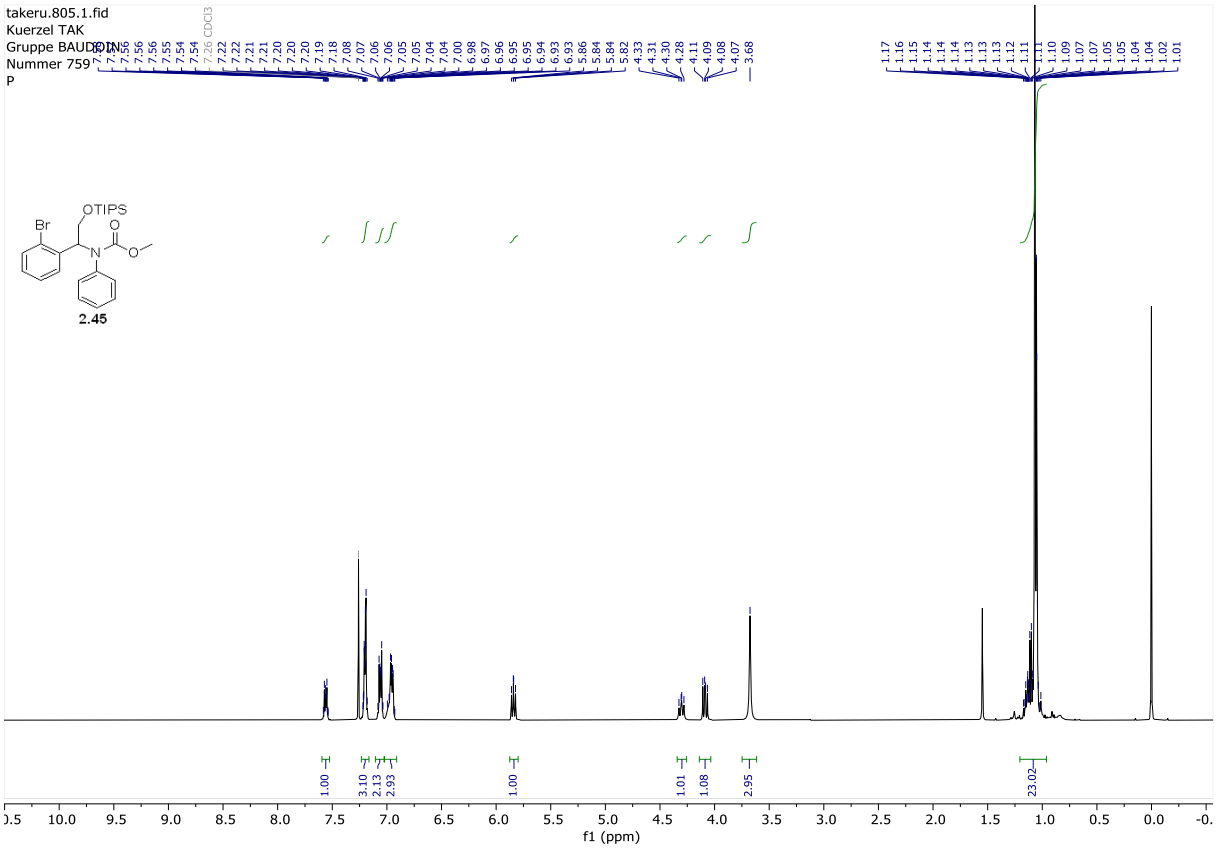
Nummer 795
P
OBn
Br
O
N
O
2.44
f1 (ppm)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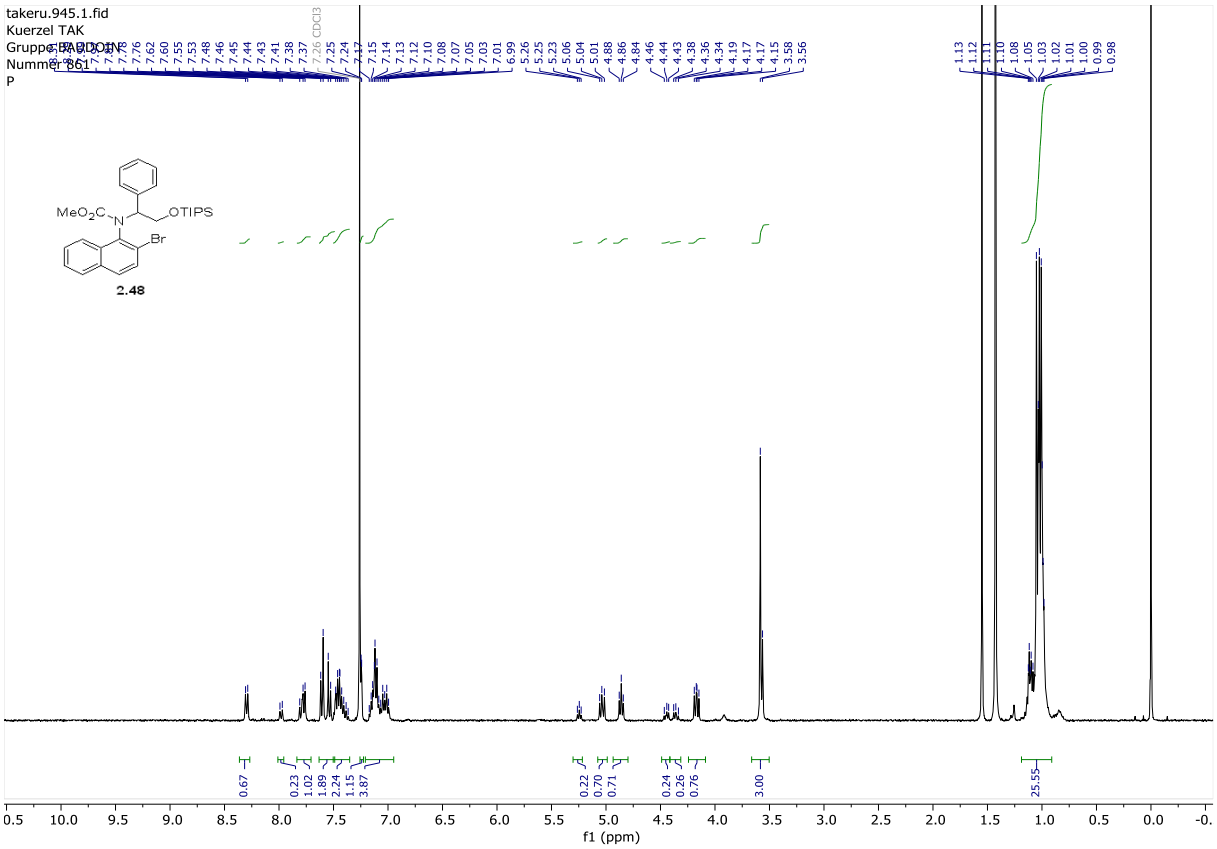
Nummer 759
P
OTIPS
Br
O
N
O
2.45
f1 (ppm)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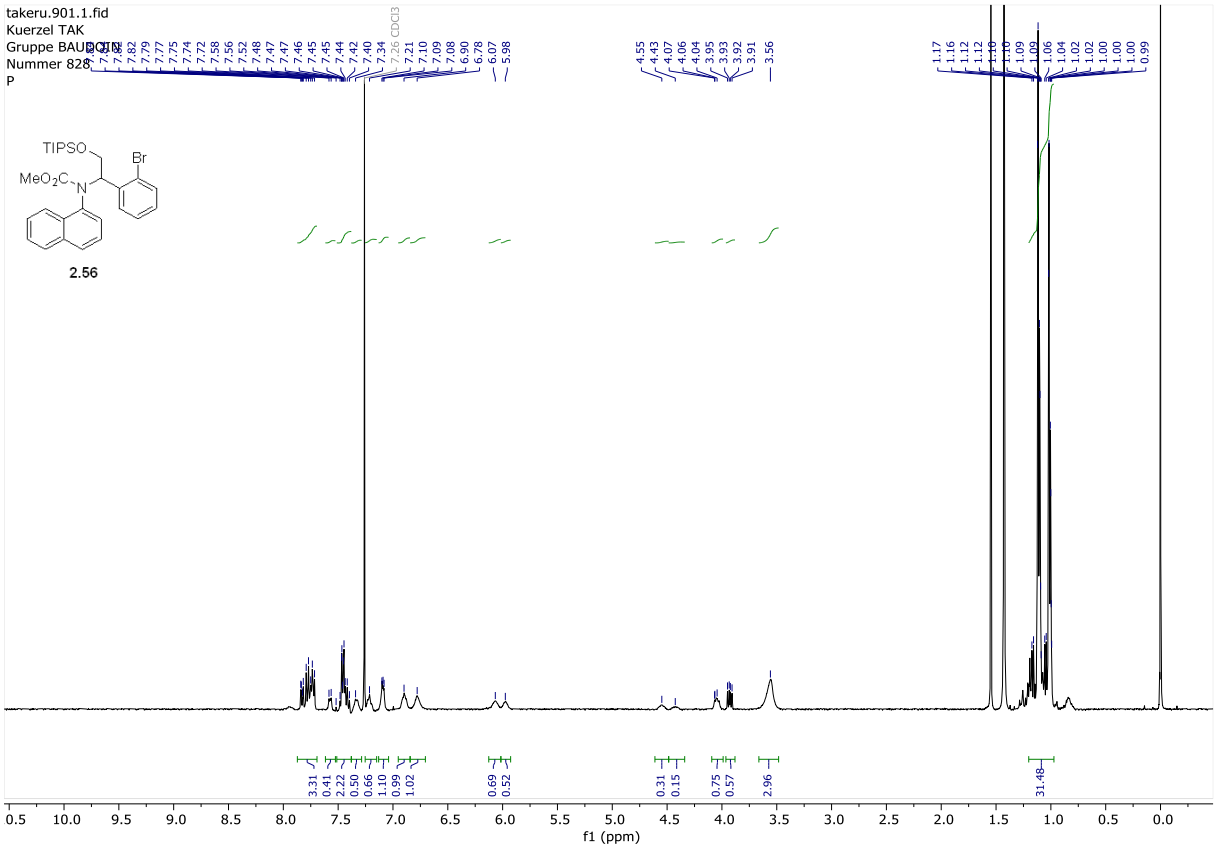
Nummer 861
P
MeO2C
N
OTIPS
Br
2.48
f1 (ppm)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Nummer 828
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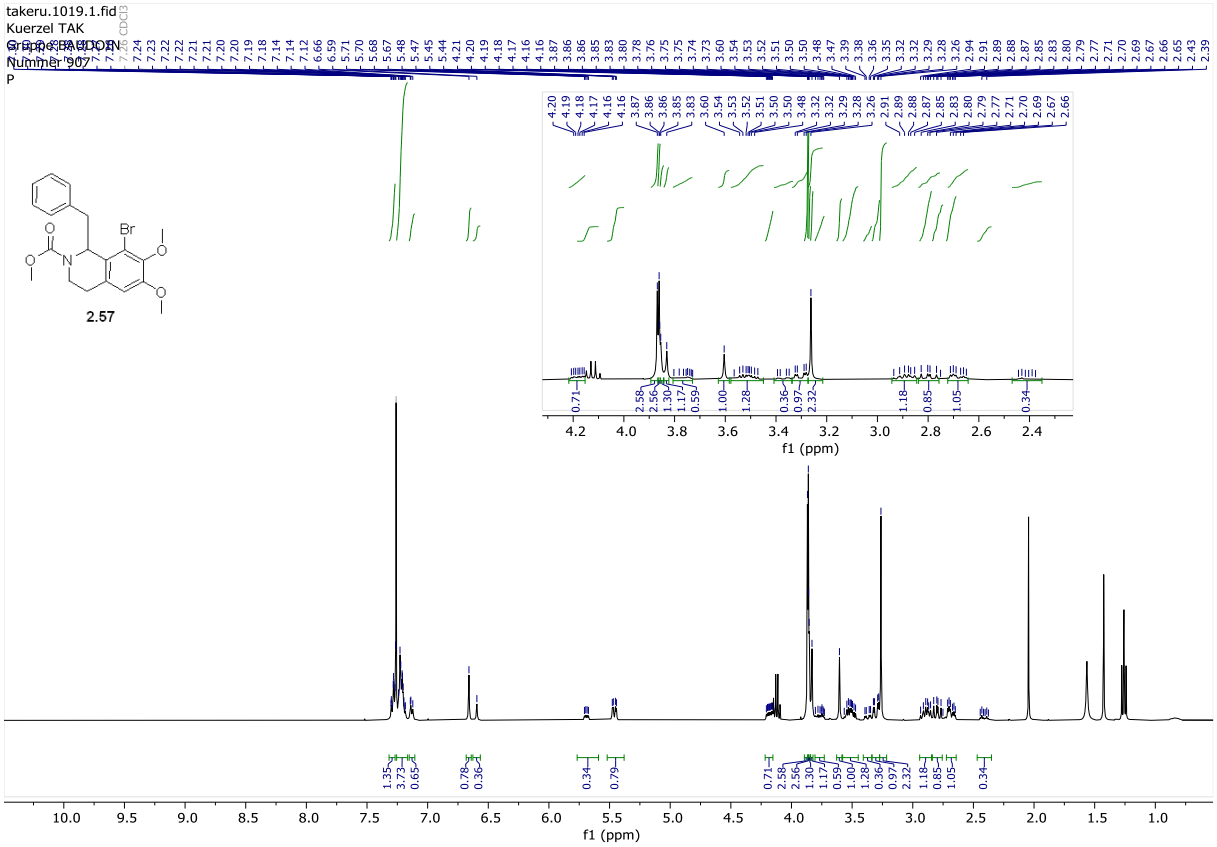
TIPSO
Br
MeO2C
N
2.56
f1 (ppm)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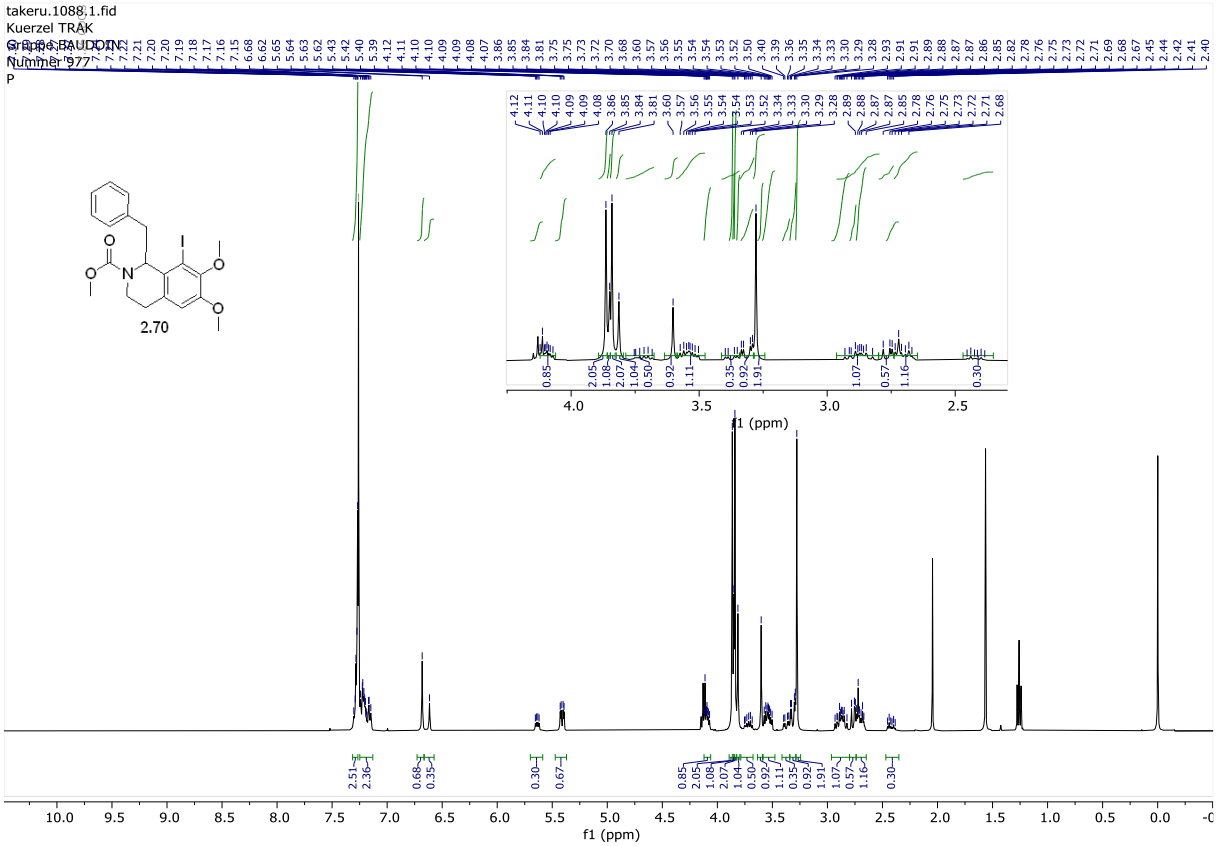
Gruppe BAUDOIN
Nummer 907
P
2.57
f1 (ppm)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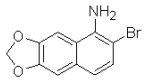
P
2.70
f1 (ppm)

takeru.1799.1.fid
Kuerzel TAK
Gruppe BAUDOIN
Nummer 1700
p



3.4

takeru.1697.1.fid
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Nummer 1569
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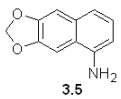
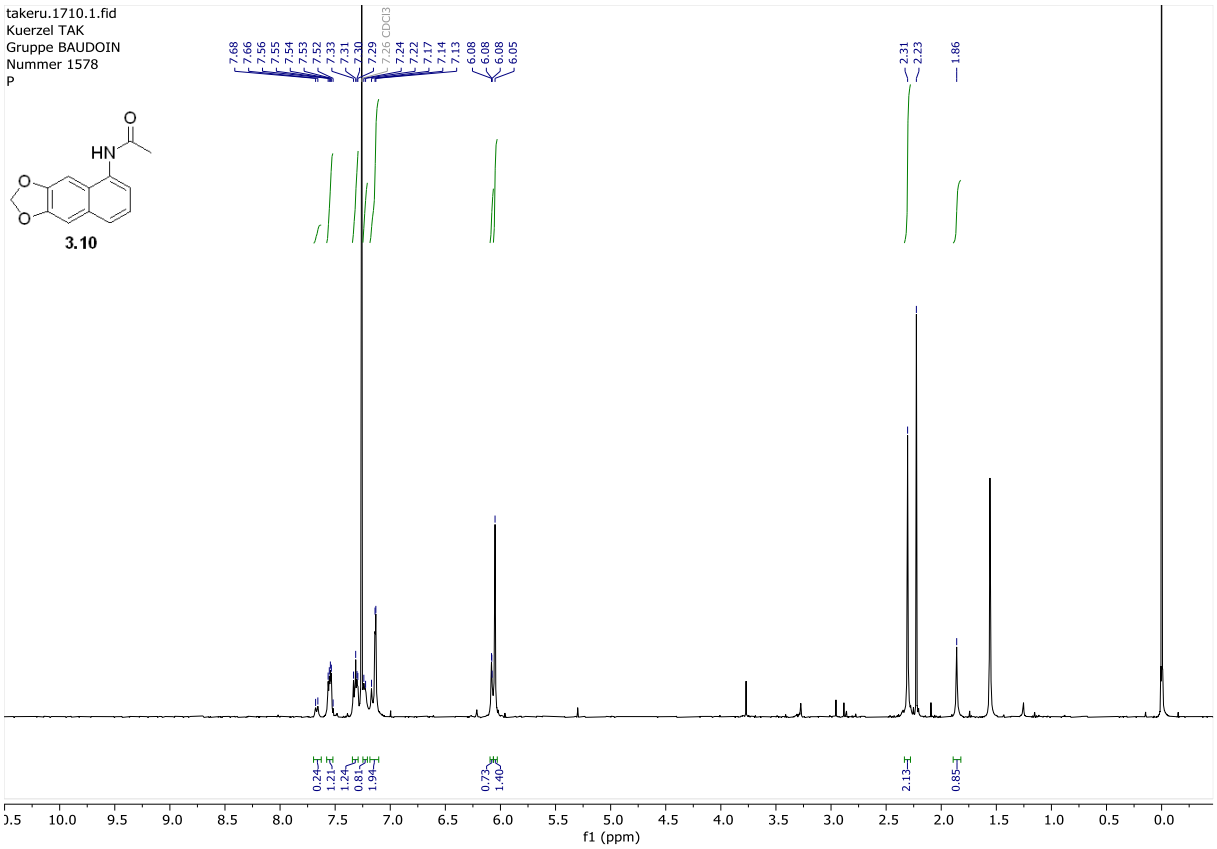


3.5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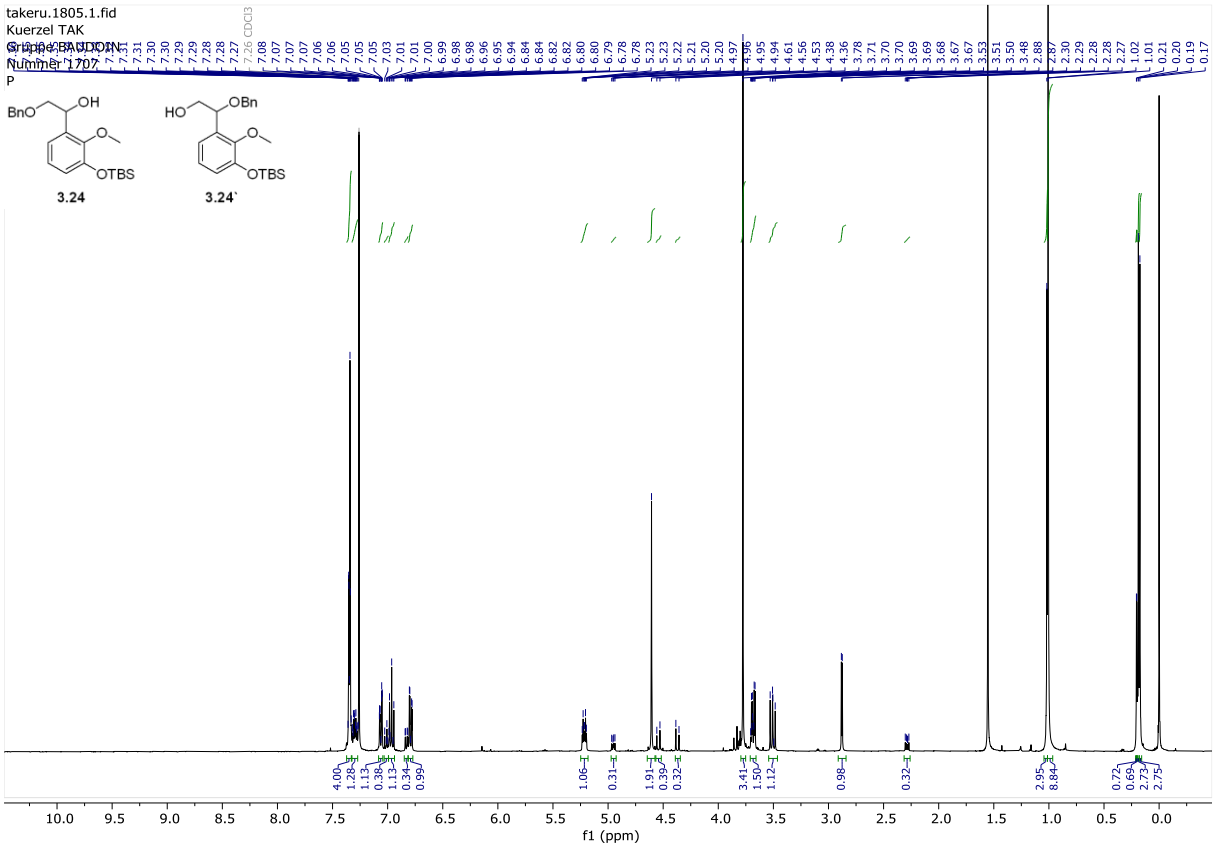
Gruppe BAUDOIN
Nummer 1578
P
3.10
f1 (ppm)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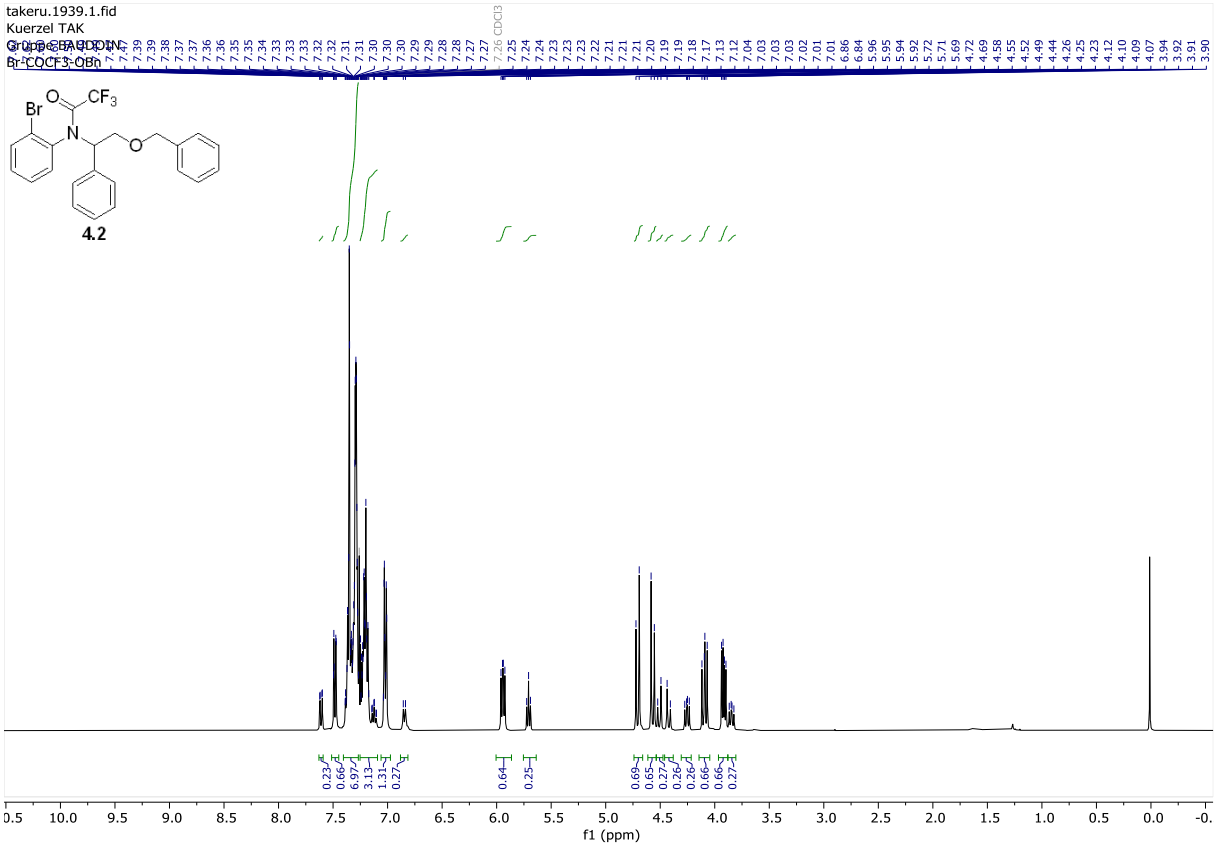
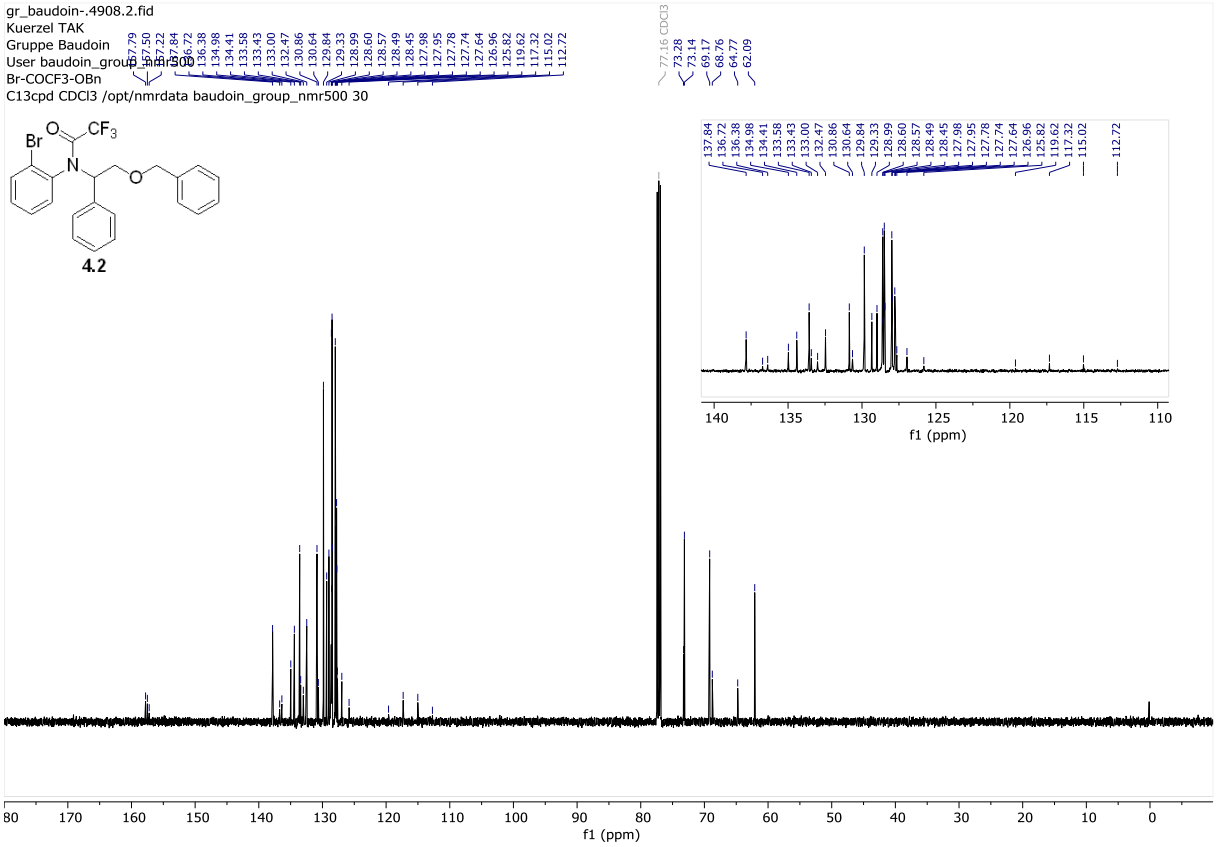
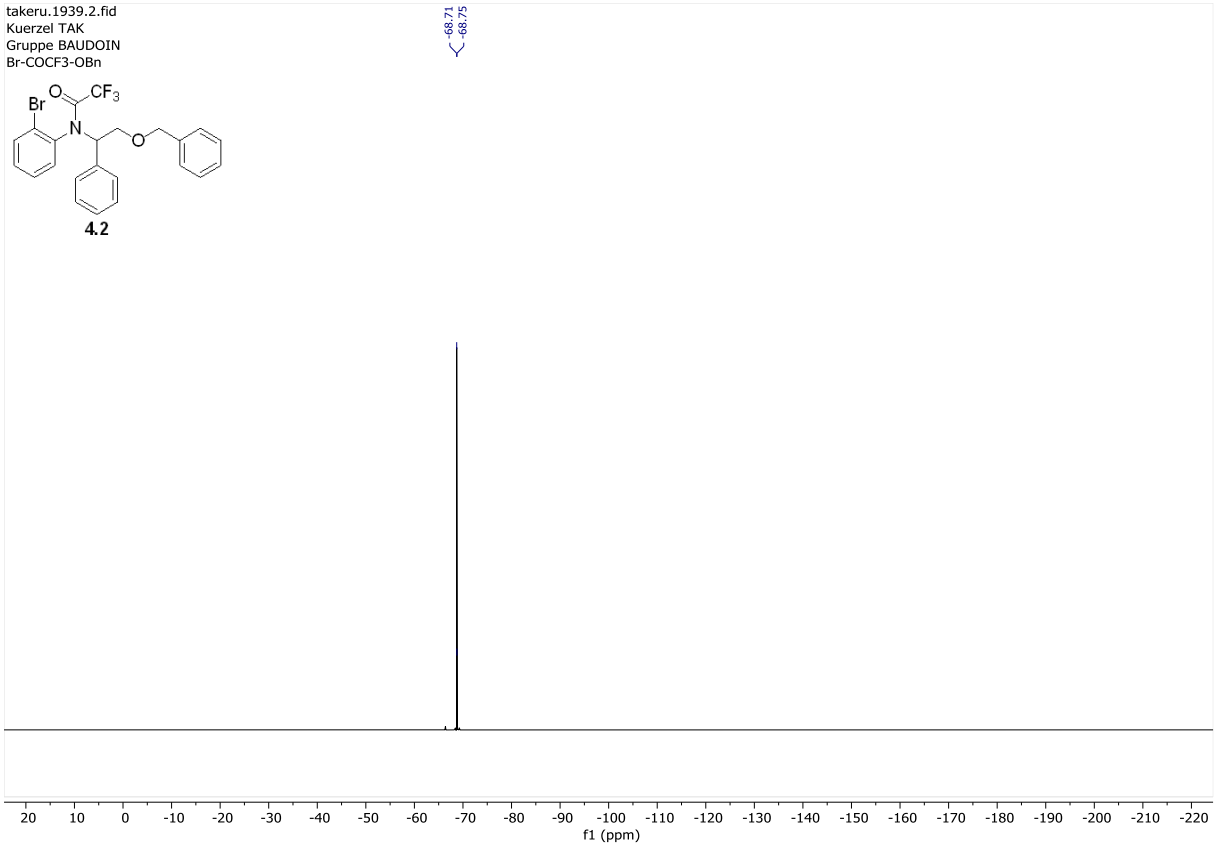
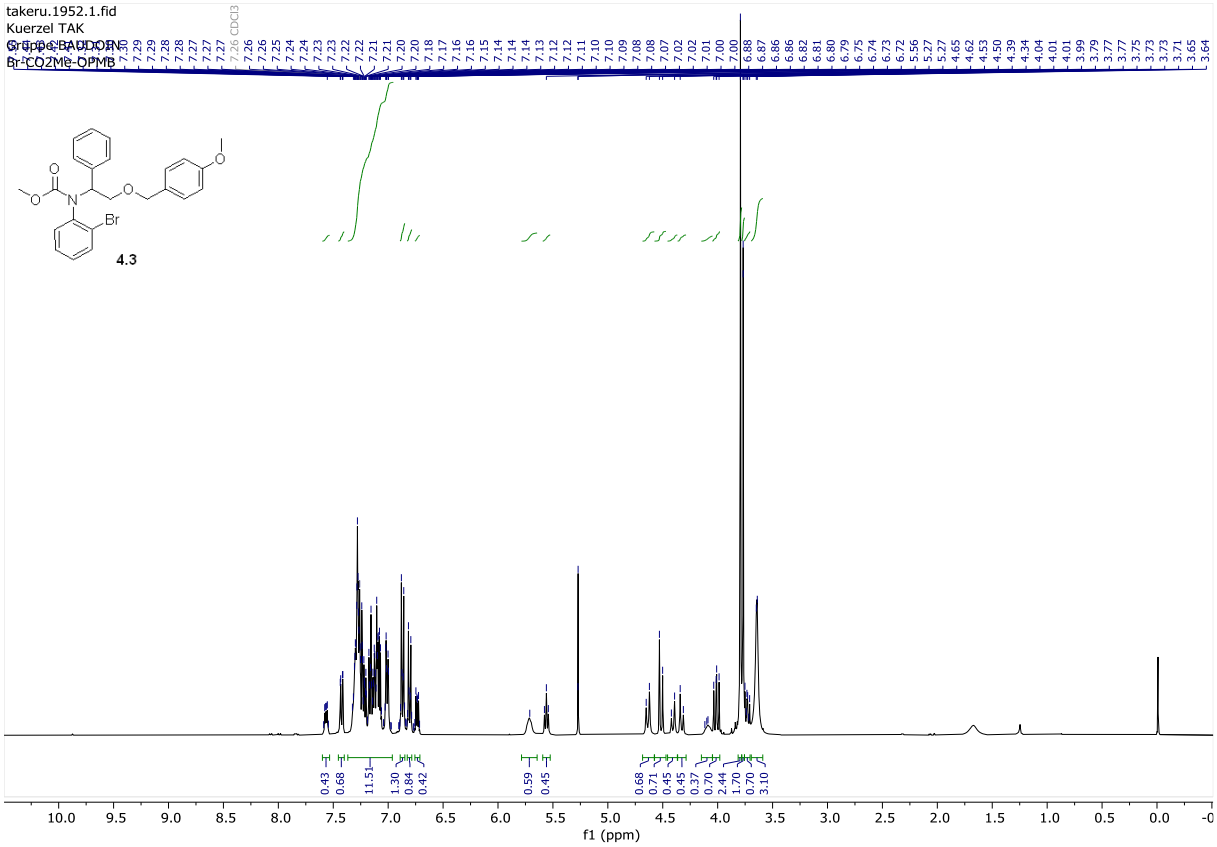
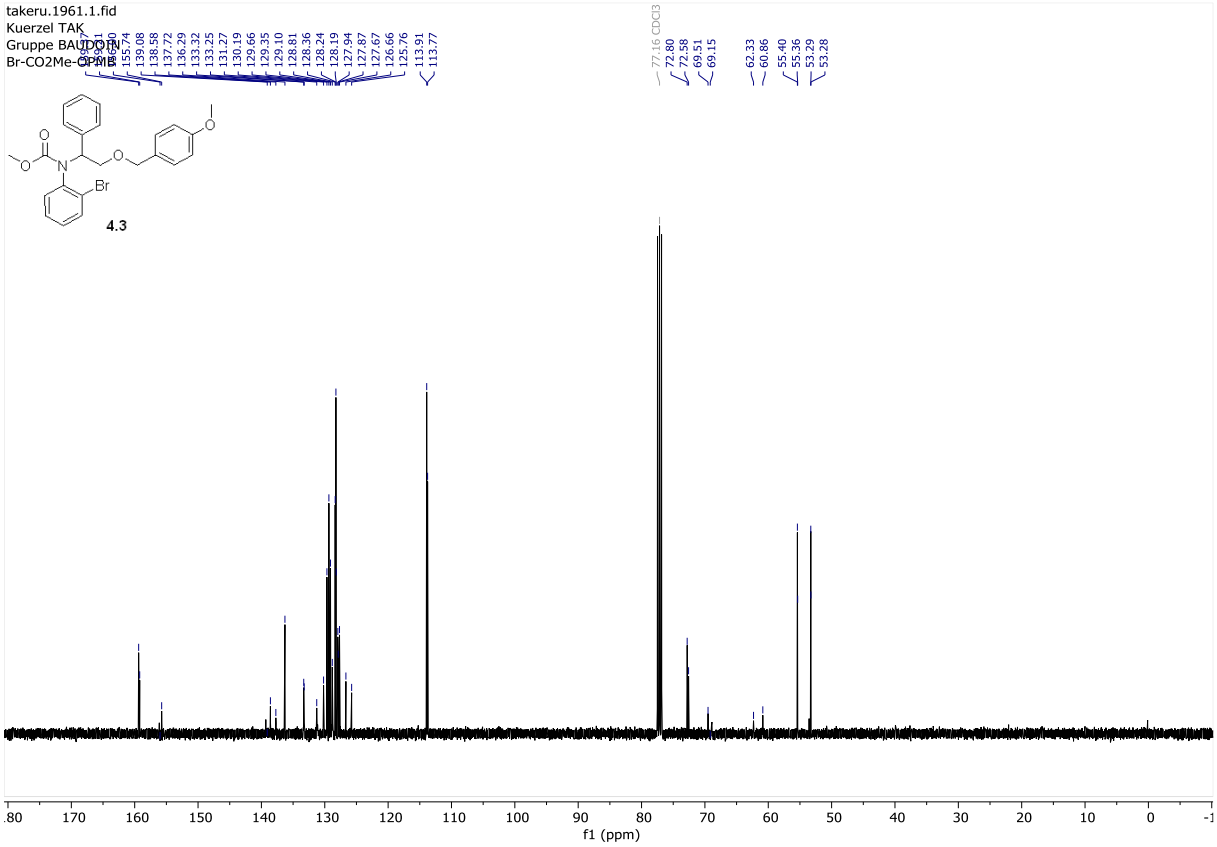
Kuerzel TAK
Gruppe BAUDOIN
Nummer 1707
P
3.24
3.24`
f1 (ppm)


takeru.1939.1.fid
Kuerzel TAK
Br-COCF3-OBn
4.2
f1 (ppm)

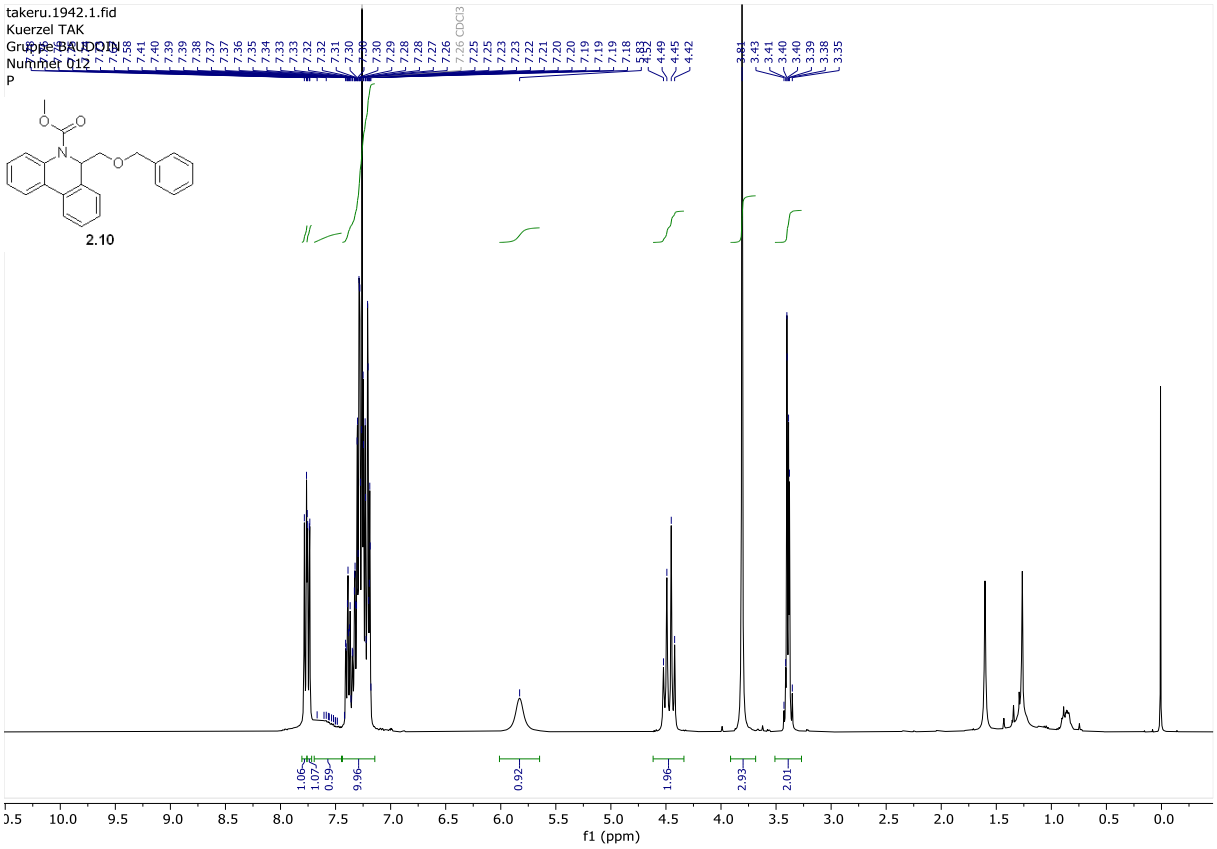

gr_baudoin-.4908.2.fid
Kuerzel TAK
Gruppe Baudoin
User baudoin_group_nmr500
Br-COCF3-OBn
C13cpd CDCl3 /opt/nmrdata baudoin_group_nmr500 30
4.2
f1 (ppm)

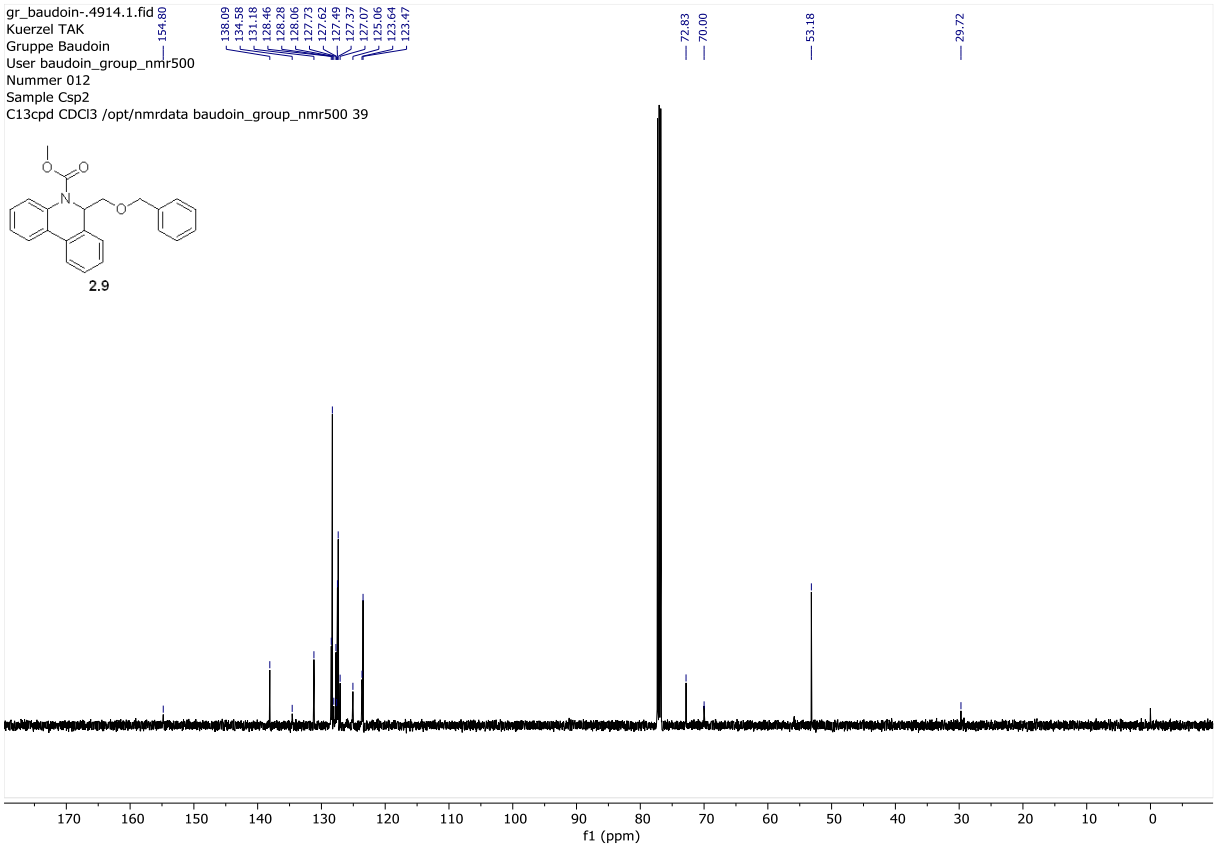

takeru.1939.2.fid
Kuerzel TAK
Gruppe BAUDOIN
Br-COCF3-OBn
68.71
68.75
Br
O
CF3
N
O
4.2
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)


takeru.1952.1.fid
Kuerzel TAK
Gruppe BAUDOIN
Br-CO2Me-OPMB
CDCl3
Br
4.3
f1 (ppm)


takeru.1961.1.fid
Kuerzel TAK
Gruppe BAUDOIN
Br-CO2Me-OPMB
CDCl3
Br
4.3
f1 (ppm)

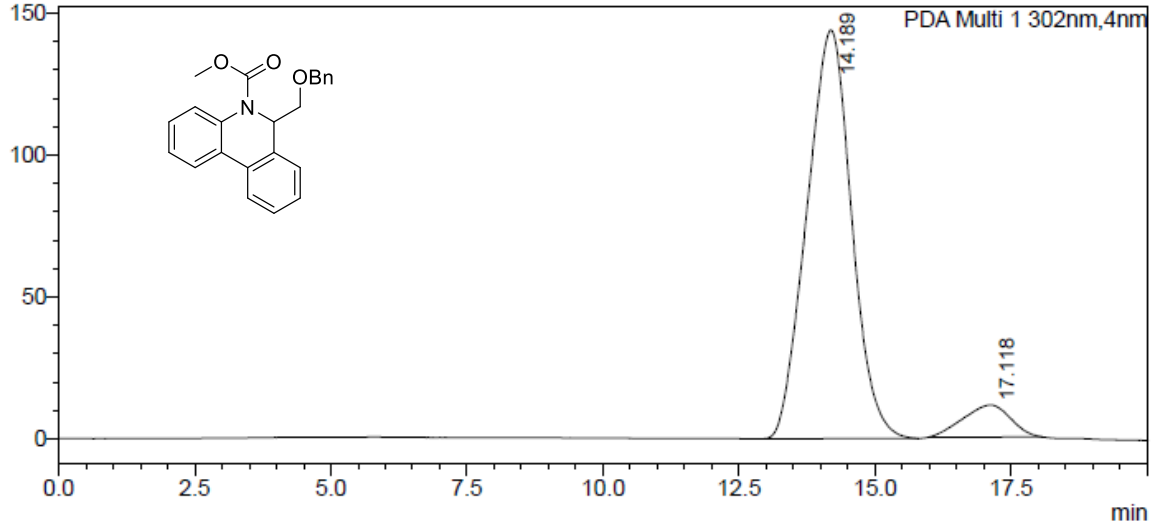
7.6.2 NMR and HPLC spectrum data of C–H products in kinetic resolution





<Chromatogram>

mAU



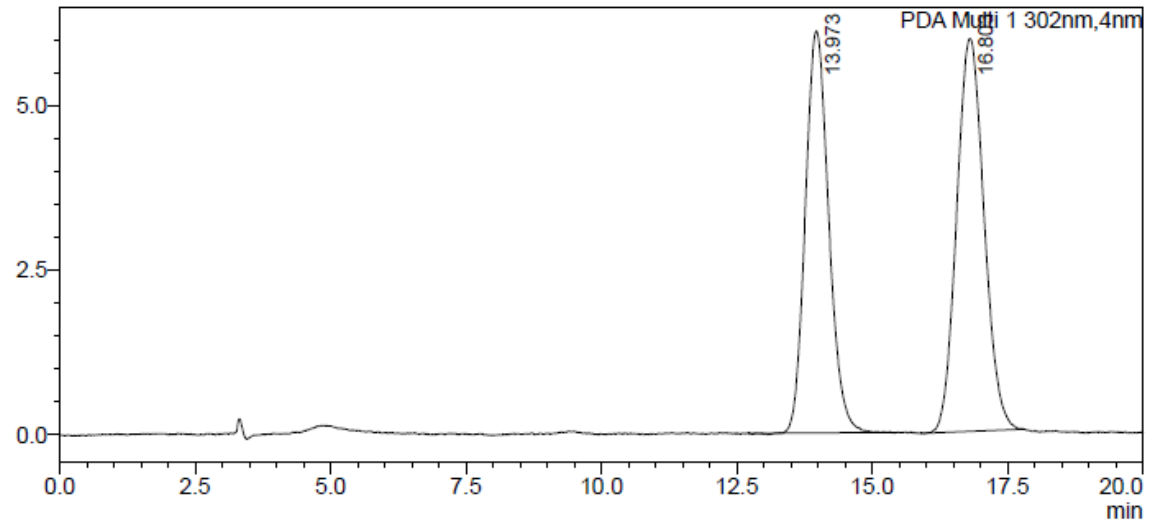
<Peak Table>

PDA Ch1 302nm

Peak#	Ret. Time	Area	Area%
1	14.189	8238696	92.254
2	17.118	691752	7.746
Total		8930448	100.000

<Chromatogram>

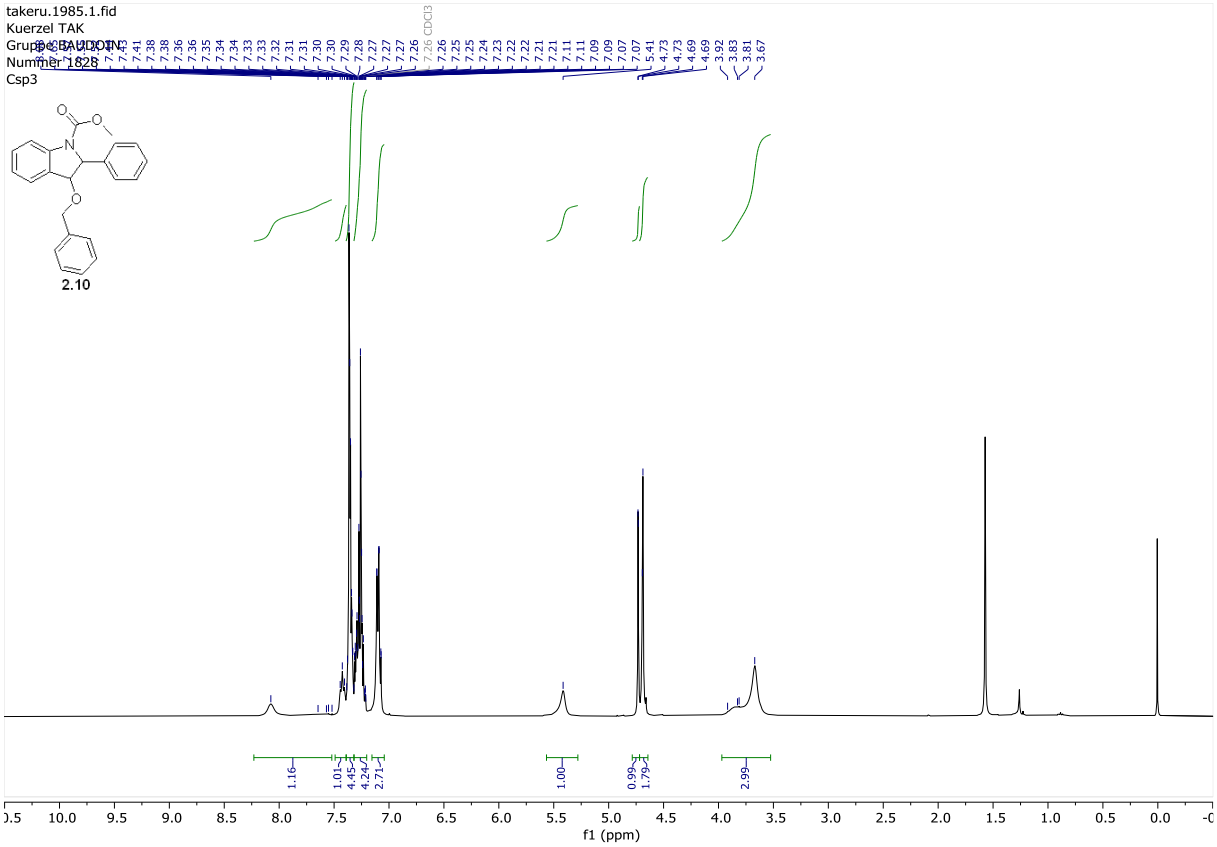
mAU

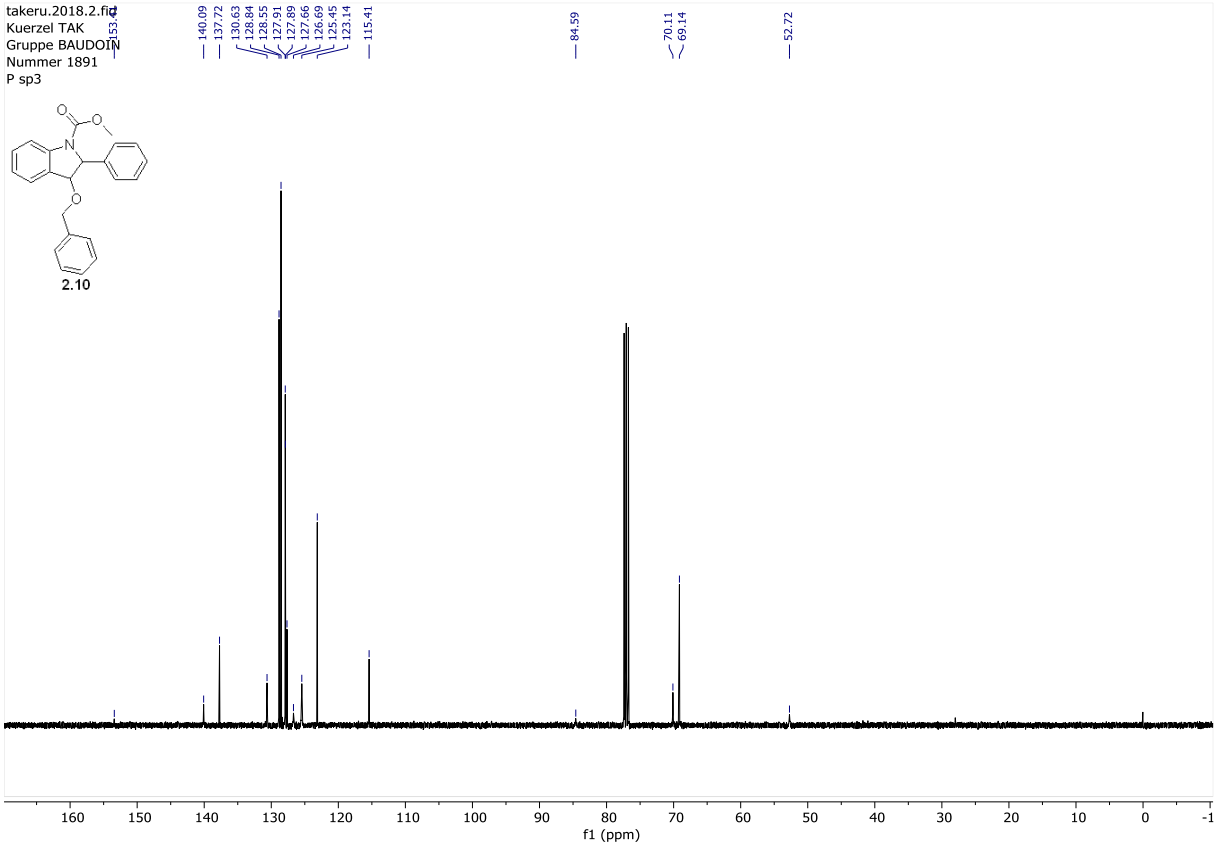


<Peak Table>

PDA Ch1 302nm

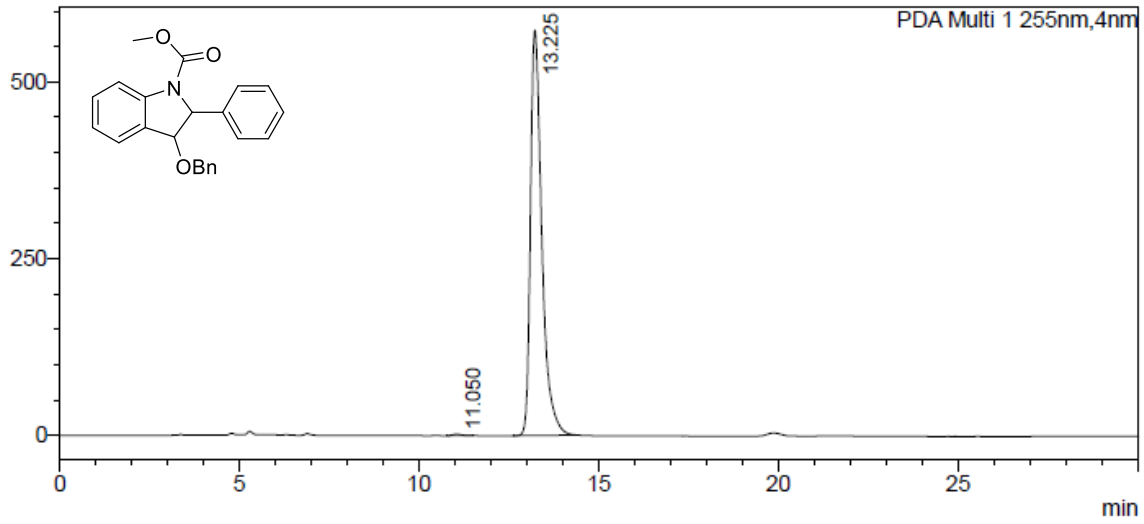
Peak#	Ret. Time	Area	Area%
1	13.973	183489	46.586
2	16.803	210384	53.414
Total		393873	100.000


takeru.1985.1.fid
Kuerzel TAK
Gruppe BAUDOIN
Nummer 1828
Csp3
2.10
CDCl3
1.16
1.01
4.45
4.24
2.71
1.00
0.99
1.79
2.99
f1 (ppm)


takeru.2018.2.fid
Kuerzel TAK
Gruppe BAUDOIN
Nummer 1891
P sp3
2.10
140.09
137.72
130.63
128.84
128.55
127.91
127.89
127.66
126.69
125.45
123.14
115.41
84.59
70.11
69.14
52.72
f1 (ppm)

<Chromatogram>

mAU



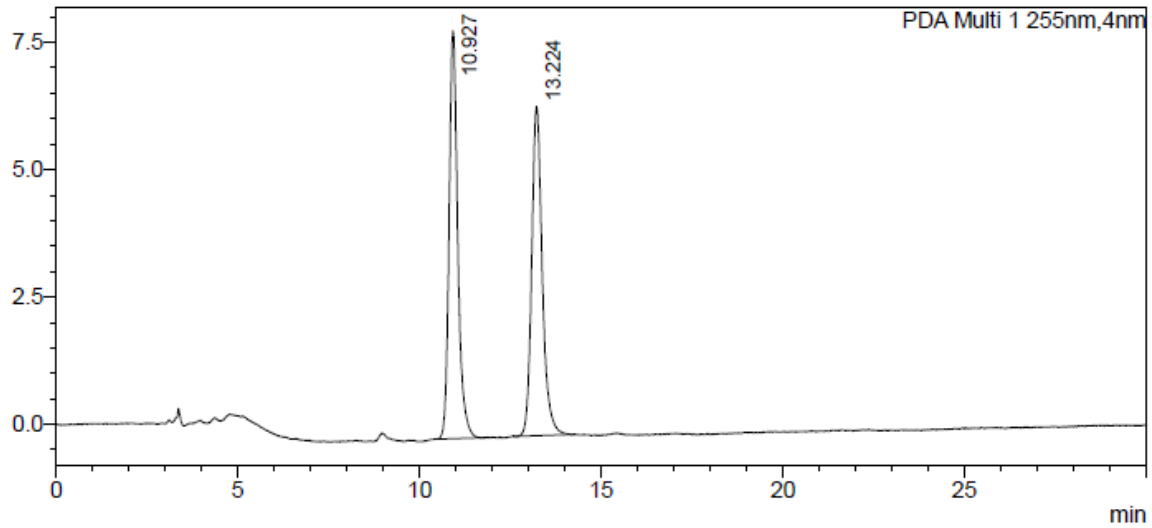
<Peak Table>

PDA Ch1 255nm

Peak#	Ret. Time	Area	Area%
1	11.050	30457	0.240
2	13.225	12635979	99.760
Total		12666436	100.000

<Chromatogram>

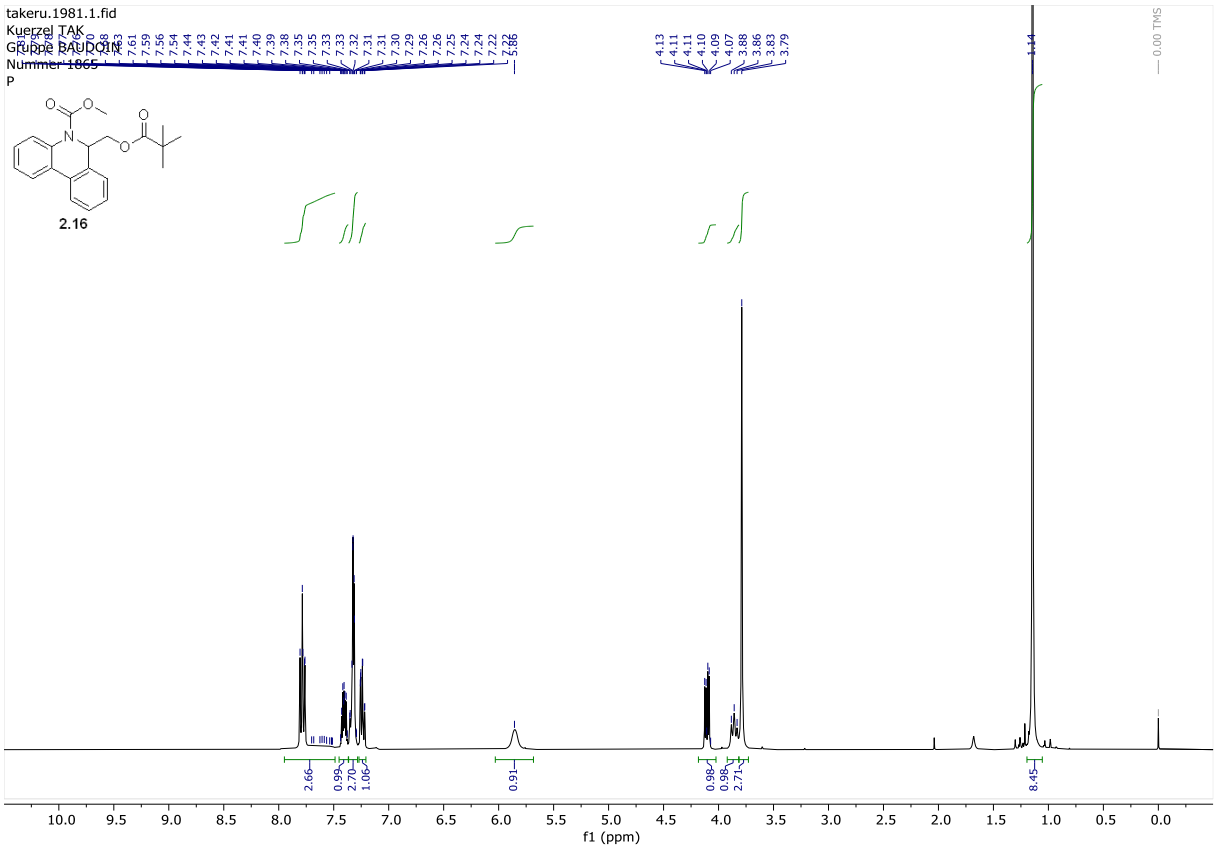
mAU

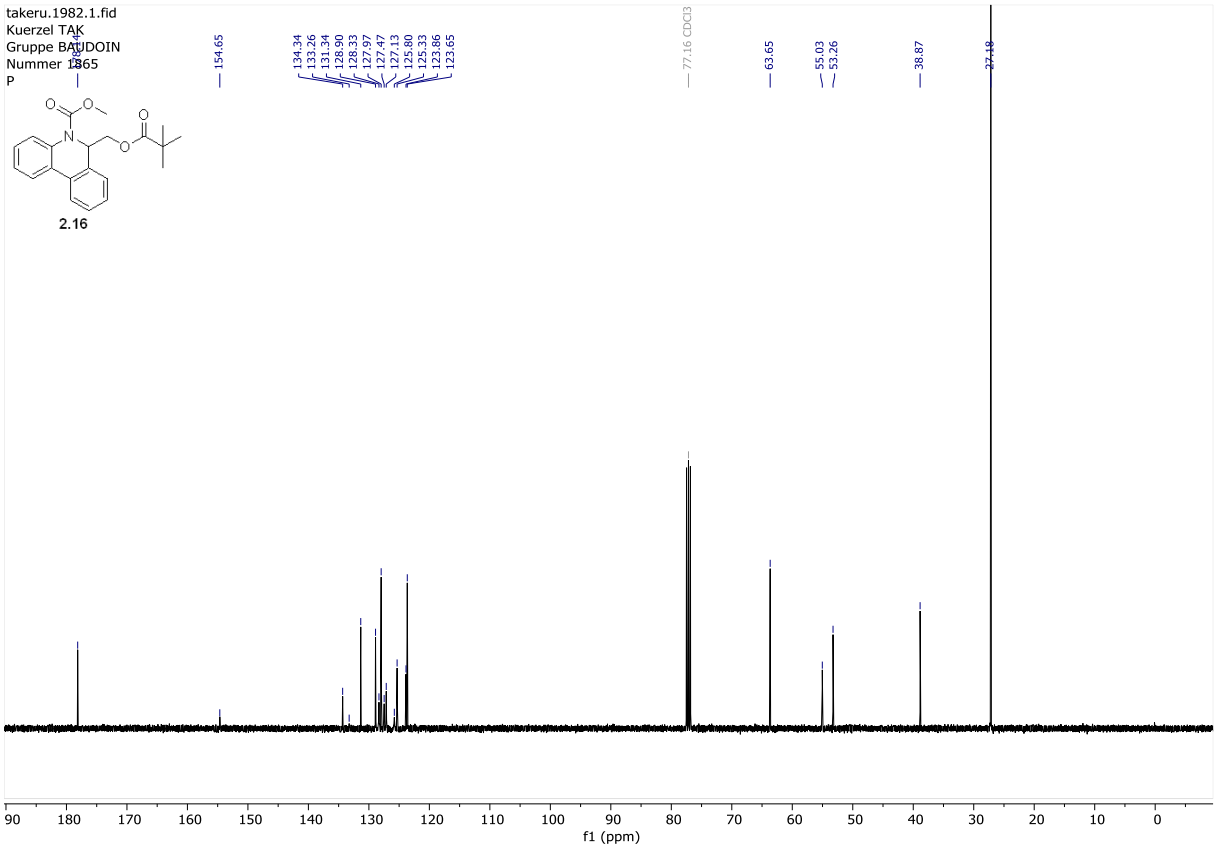


<Peak Table>

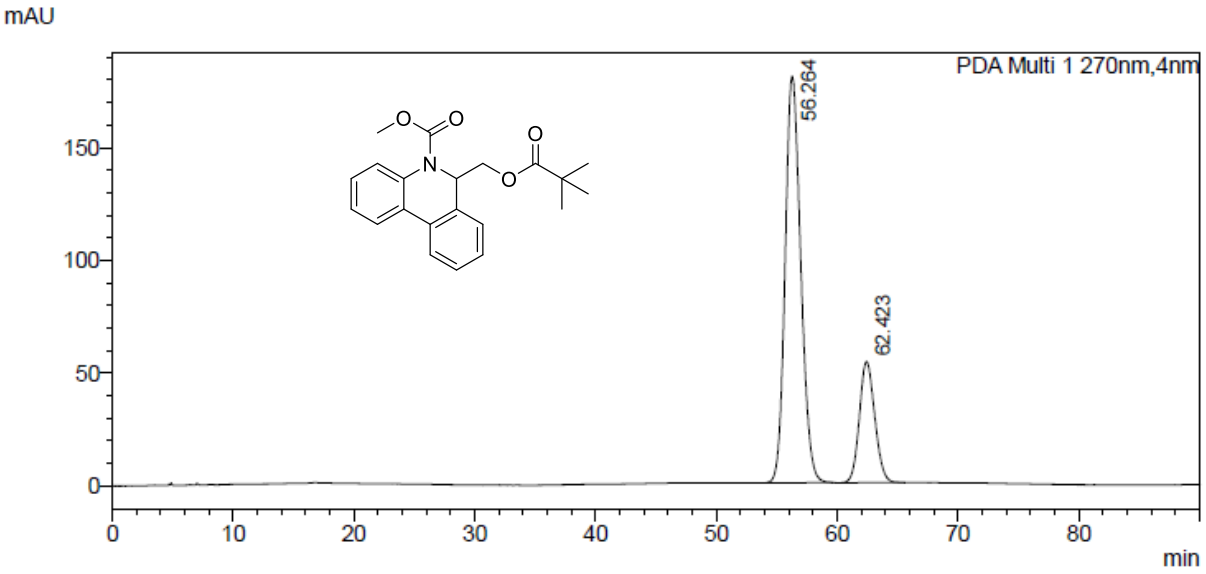
PDA Ch1 255nm

Peak#	Ret. Time	Area	Area%
1	10.927	133349	50.531
2	13.224	130544	49.469
Total		263893	100.000


takeru.1981.1.fid
Kuerzel TAK
Gruppe BAUDOIN
Nummer 1865
P
2.16
f1 (ppm)


takeru.1982.1.fid
Kuerzel TAK
Gruppe BAUDOIN
Nummer 1865
P
2.16
f1 (ppm)

<Chromatogram>

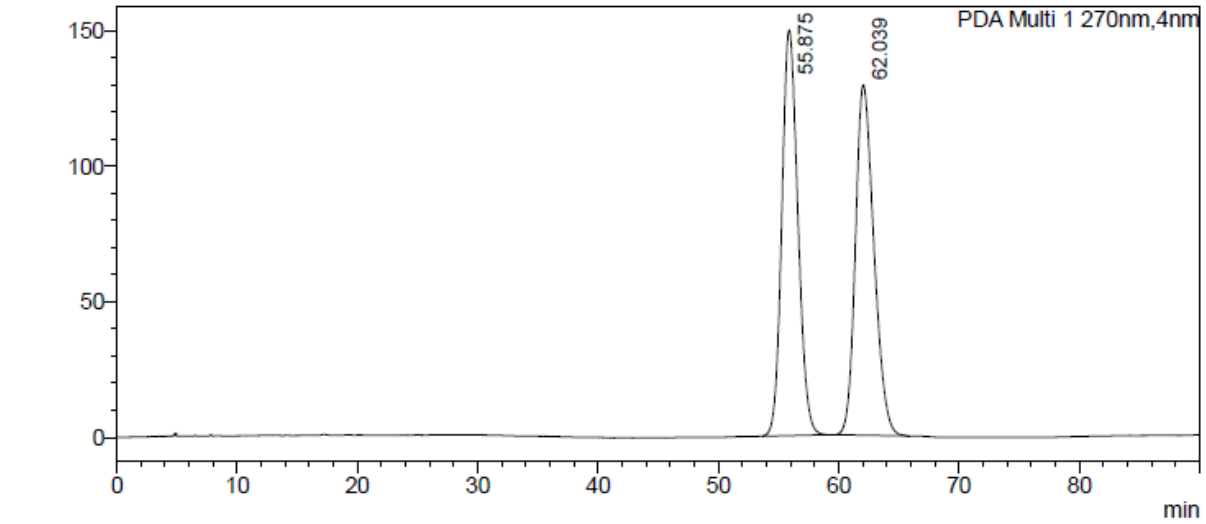


<Peak Table>

PDA Ch1 270nm

Peak#	Ret. Time	Area	Area%
1	56.264	16178273	77.273
2	62.423	4758351	22.727
Total		20936624	100.000

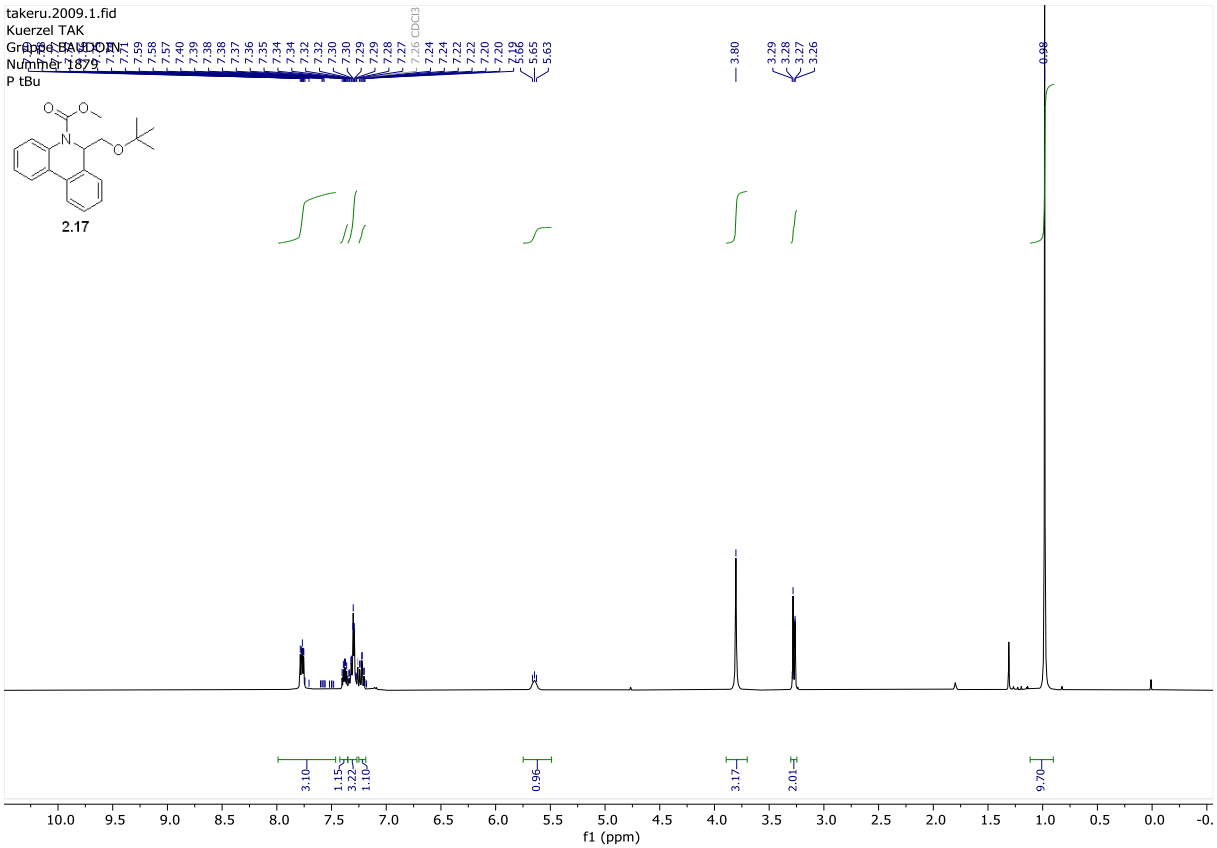
<Chromatogram>

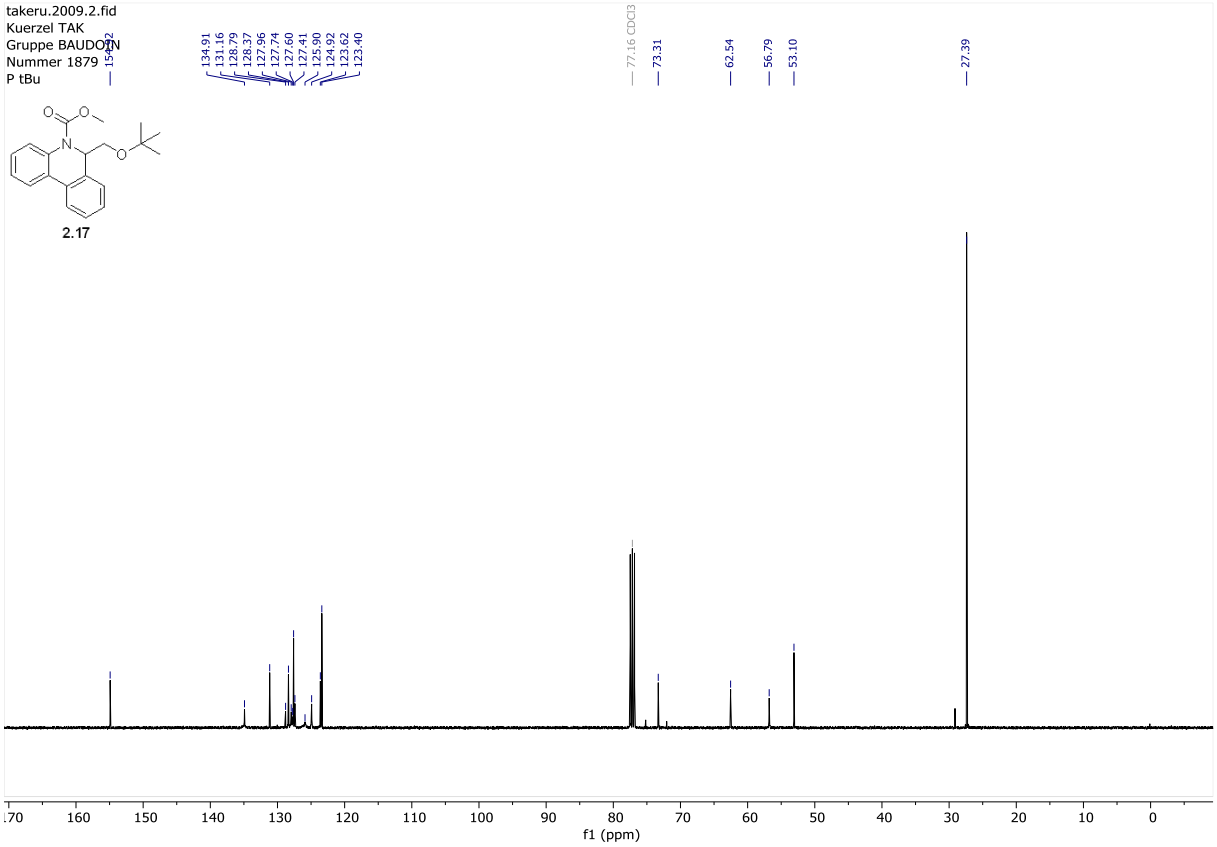


<Peak Table>

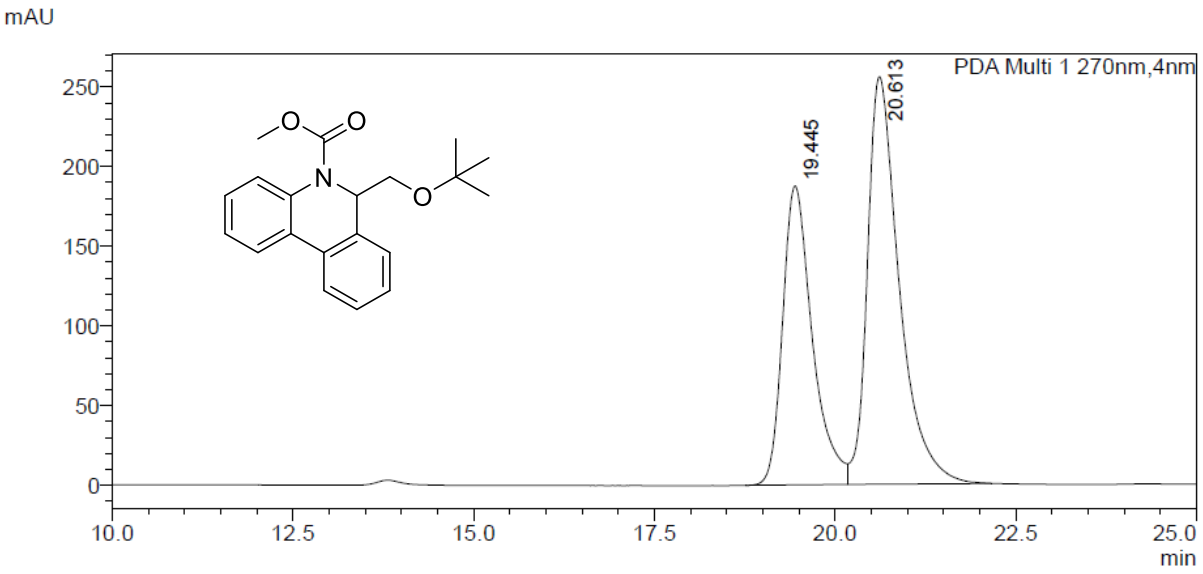
PDA Ch1 270nm

Peak#	Ret. Time	Area	Area%
1	55.875	13846718	50.038
2	62.039	13825594	49.962
Total		27672312	100.000


takeru.2009.1.fid
Kuerzel TAK
Gruppe BAUDOIN
Nummer 1879
P tBu
2.17
f1 (ppm)


takeru.2009.2.fid
Kuerzel TAK
Gruppe BAUDOIN
Nummer 1879
P tBu
2.17
f1 (ppm)

<Chromatogram>

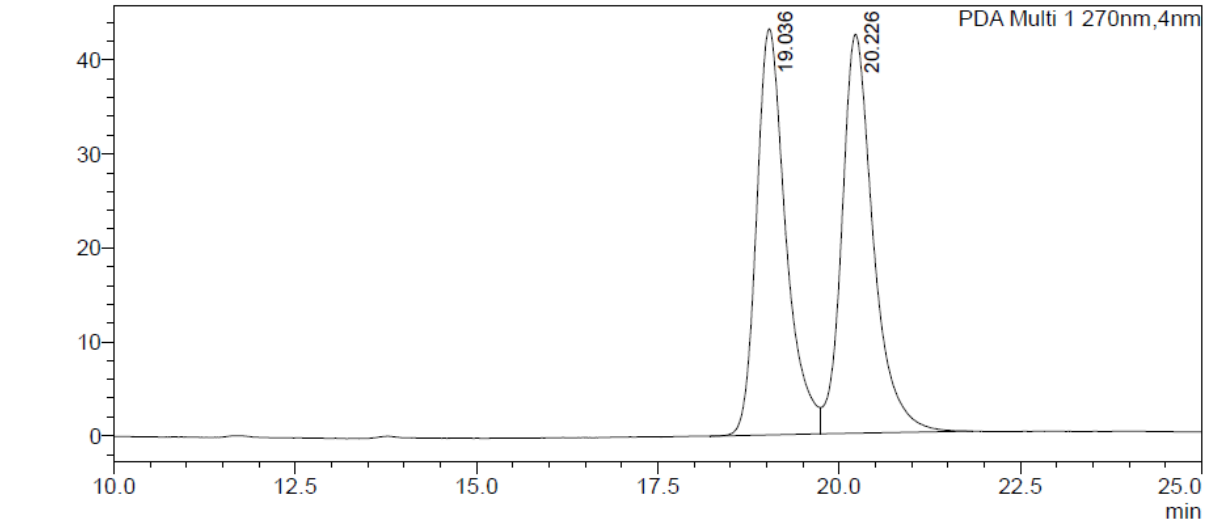


<Peak Table>

PDA Ch1 270nm

Peak#	Ret. Time	Area	Area%
1	19.445	5359271	40.606
2	20.613	7838992	59.394
Total		13198263	100.000

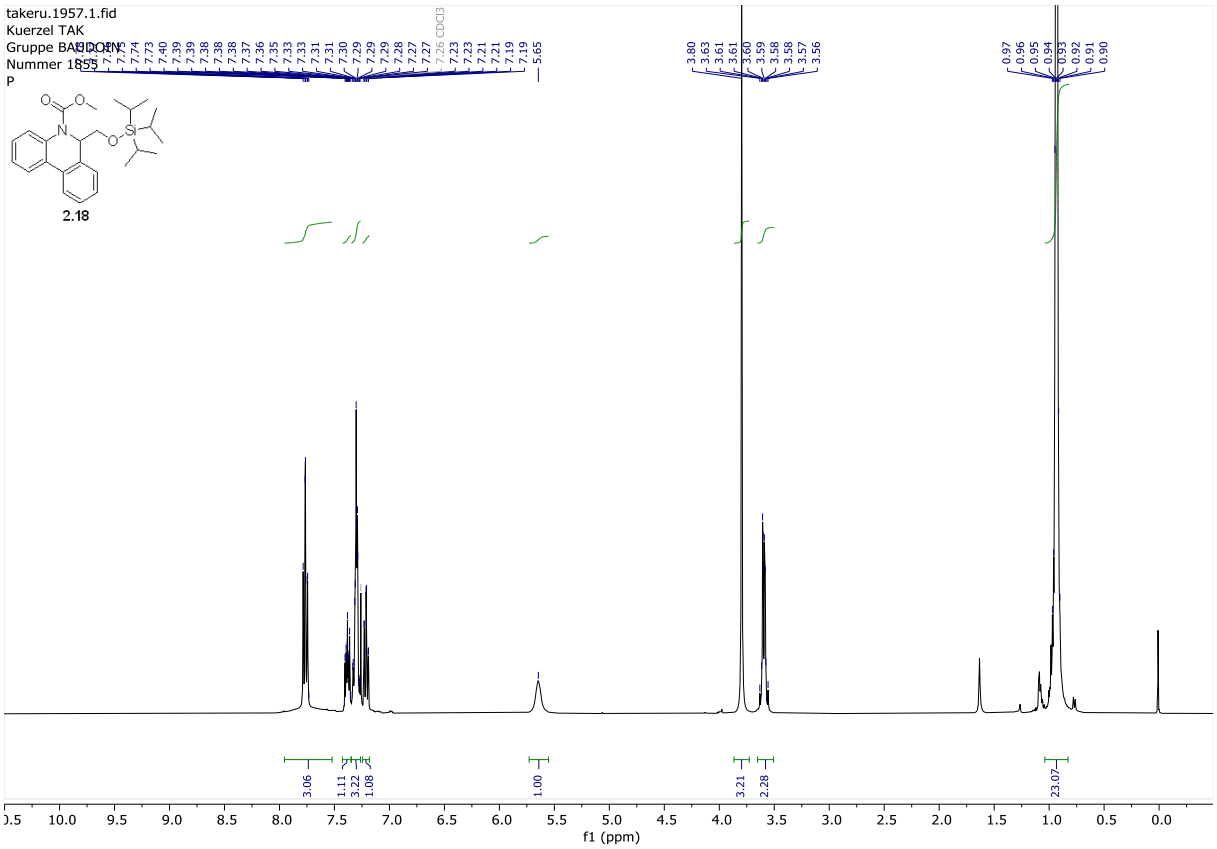
<Chromatogram>

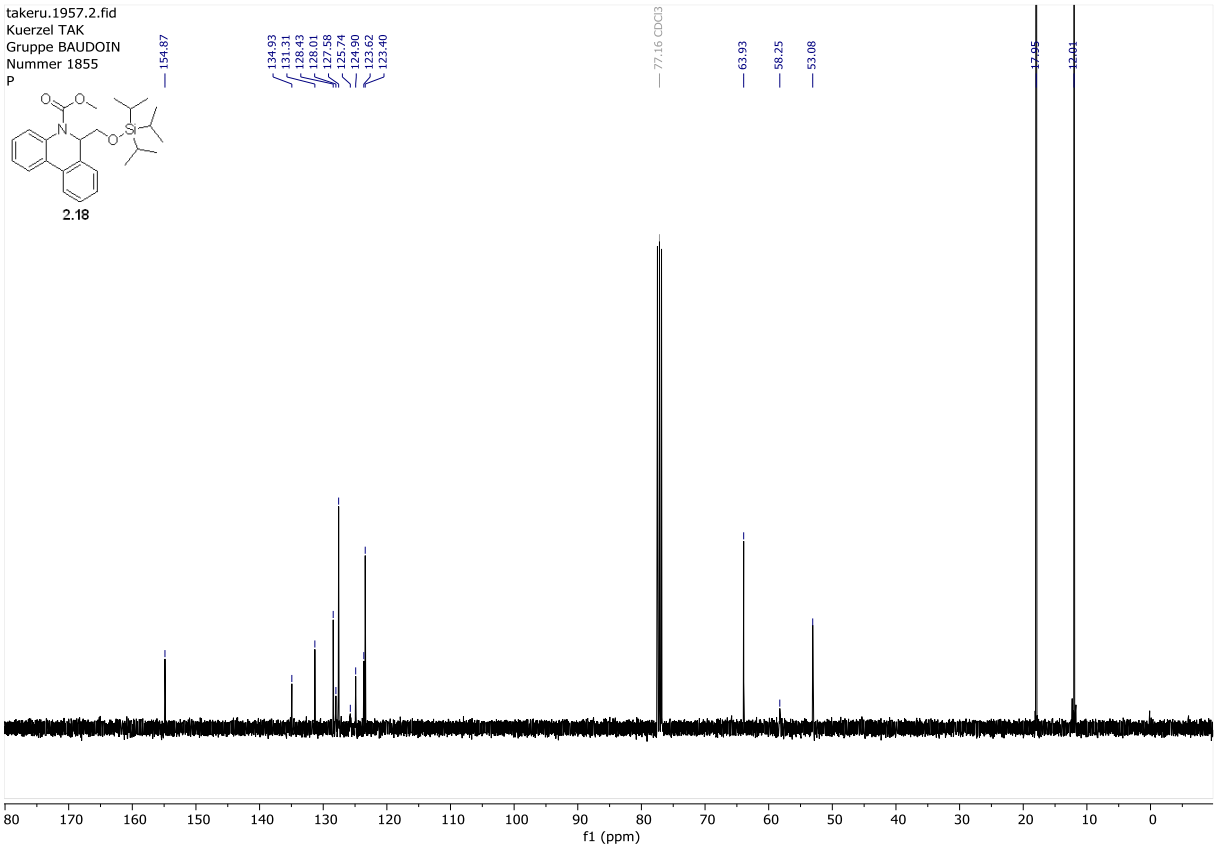


<Peak Table>

PDA Ch1 270nm

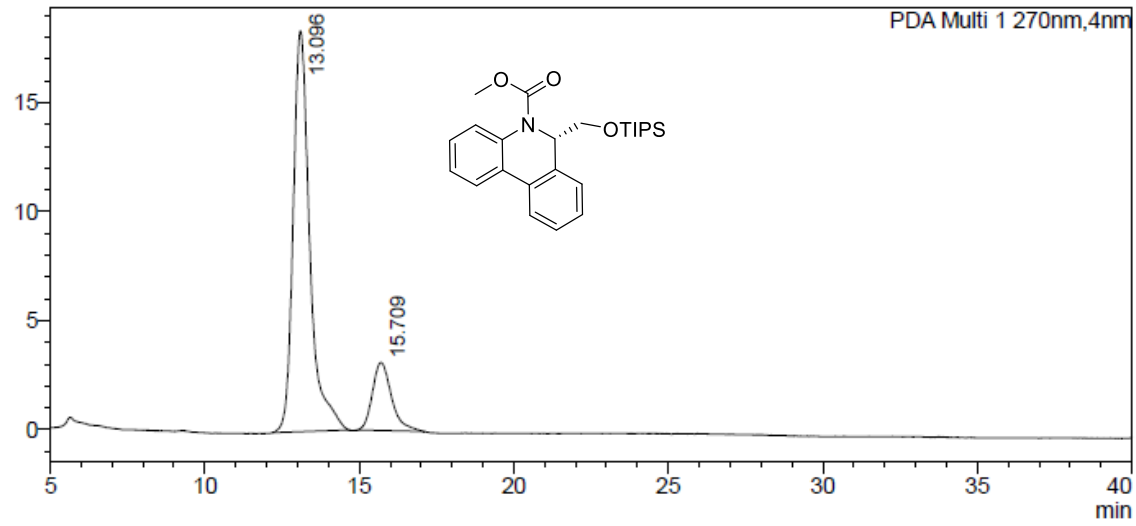
Peak#	Ret. Time	Area	Area%
1	19.036	1217764	48.728
2	20.226	1281322	51.272
Total		2499086	100.000


takeru.1957.1.fid
Kuerzel TAK
Gruppe BAUDOIN
Nummer 1855
P
2.18
7.26 CDCl3
3.06
1.11
3.22
1.08
1.00
3.21
2.28
23.07
f1 (ppm)


takeru.1957.2.fid
Kuerzel TAK
Gruppe BAUDOIN
Nummer 1855
P
2.18
154.87
134.93
131.31
128.43
128.01
127.58
125.74
124.90
123.62
123.40
77.16 CDCl3
63.93
58.25
53.08
17.95
13.01
f1 (ppm)

<Chromatogram>

mAU



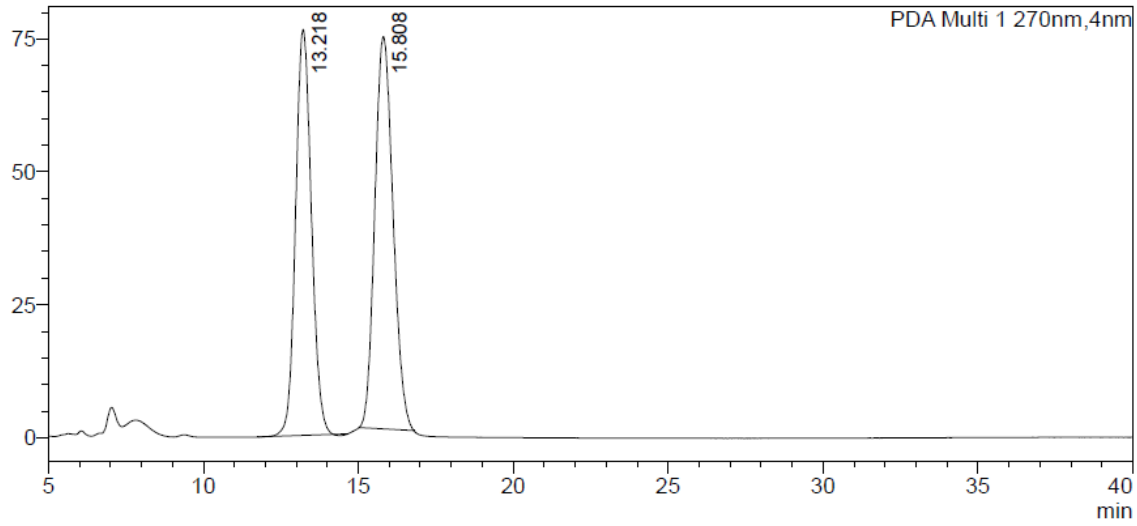
<Peak Table>

PDA Ch1 270nm

Peak#	Ret. Time	Area	Area%
1	13.096	687060	83.641
2	15.709	134379	16.359
Total		821439	100.000

<Chromatogram>

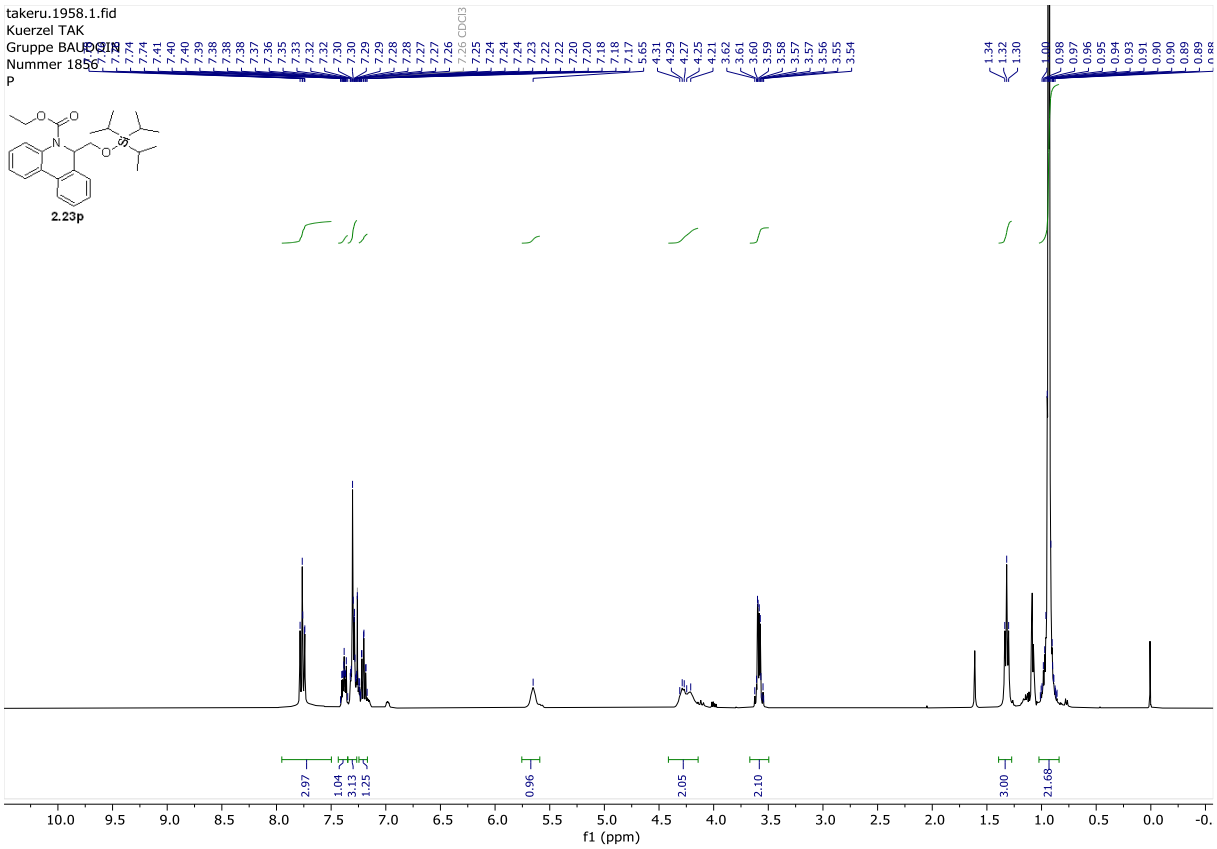
mAU



<Peak Table>

PDA Ch1 270nm

Peak#	Ret. Time	Area	Area%
1	13.218	2707157	47.343
2	15.808	3011047	52.657
Total		5718204	100.000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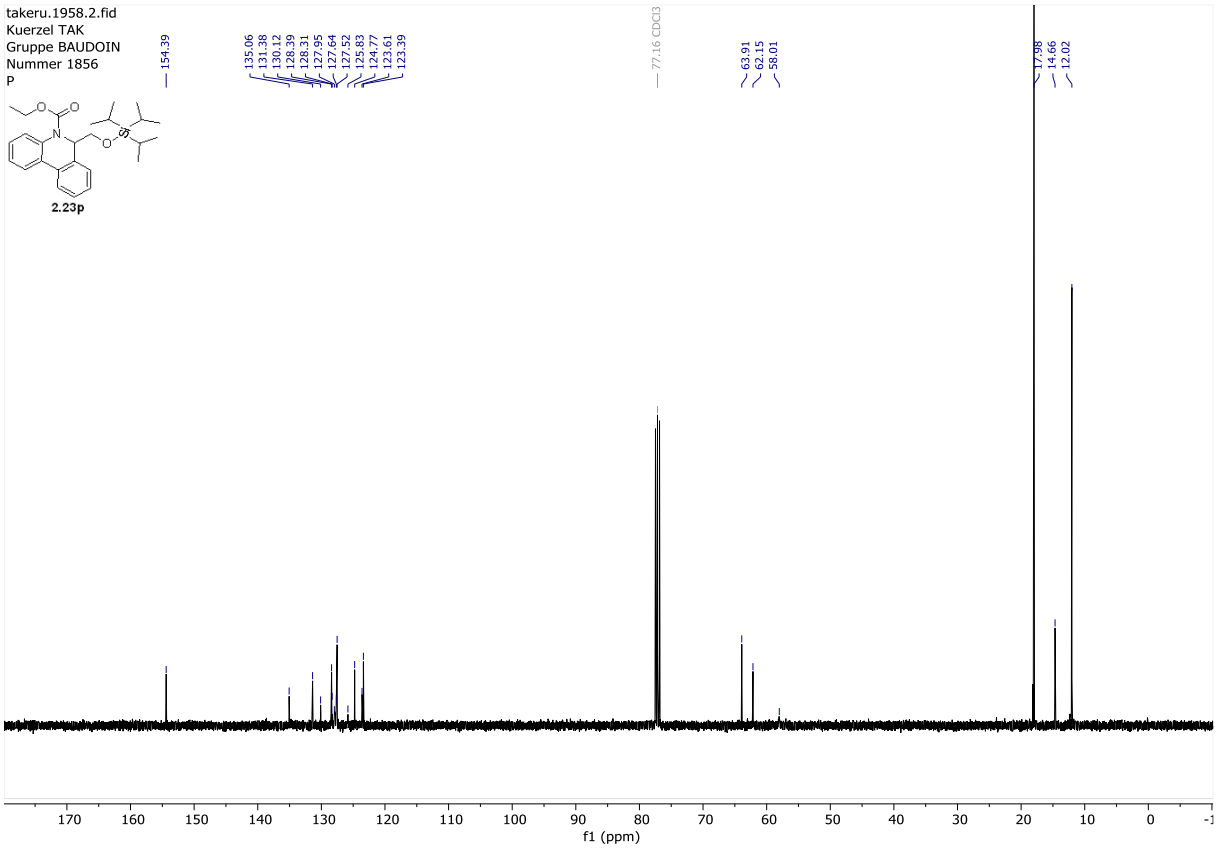
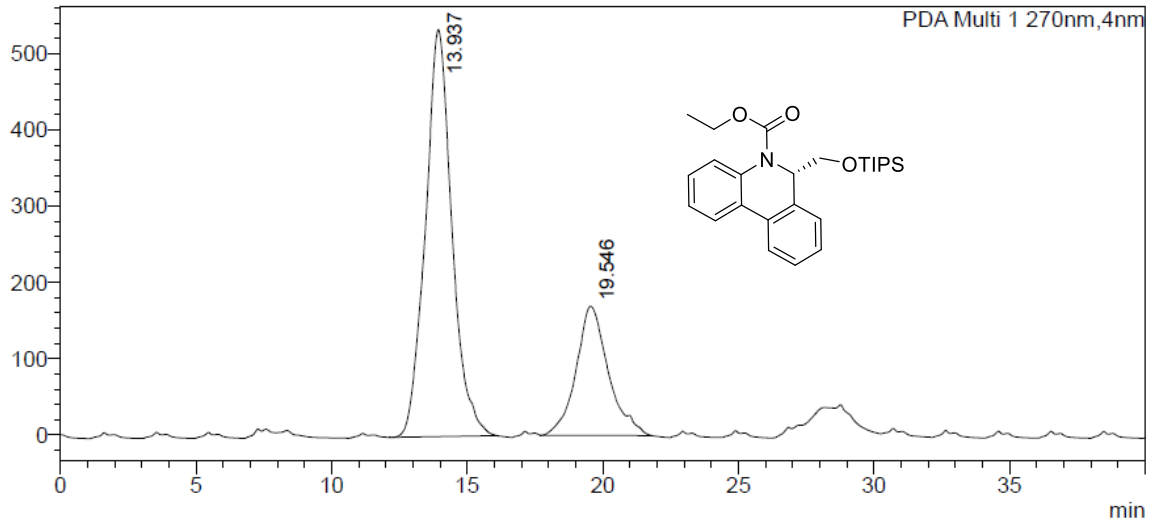
Kuerzel TAK
Gruppe BAUDOIN
Nummer 1856
P
2.23p
f1 (ppm)


takeru.1958.2.fid
Kuerzel TAK
Gruppe BAUDOIN
Nummer 1856
P
2.23p
f1 (ppm)

<Chromatogram>

mAU



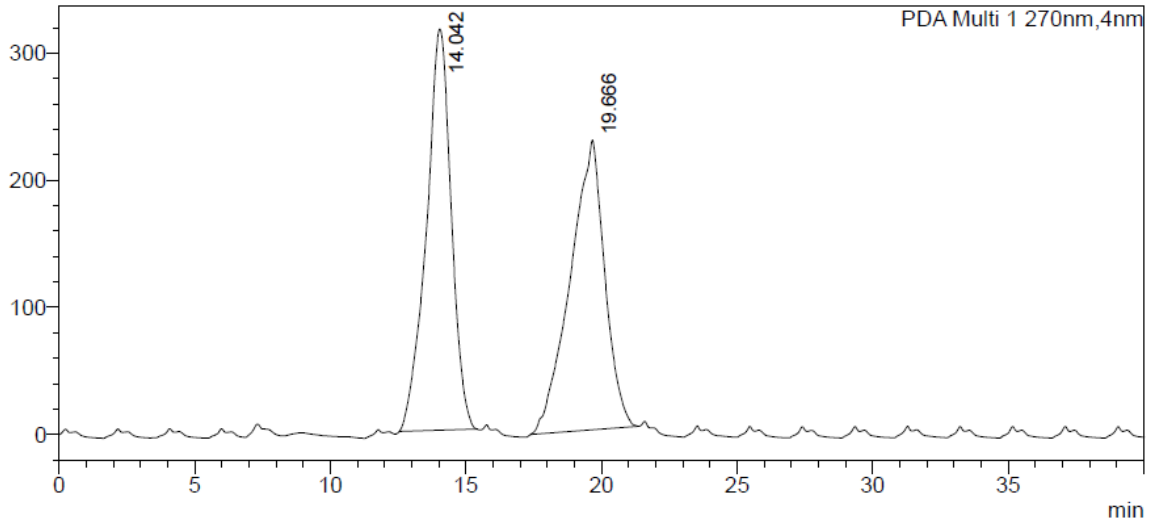
<Peak Table>

PDA Ch1 270nm

Peak#	Ret. Time	Area	Area%
1	13.937	36416725	72.147
2	19.546	14059347	27.853
Total		50476072	100.000

<Chromatogram>

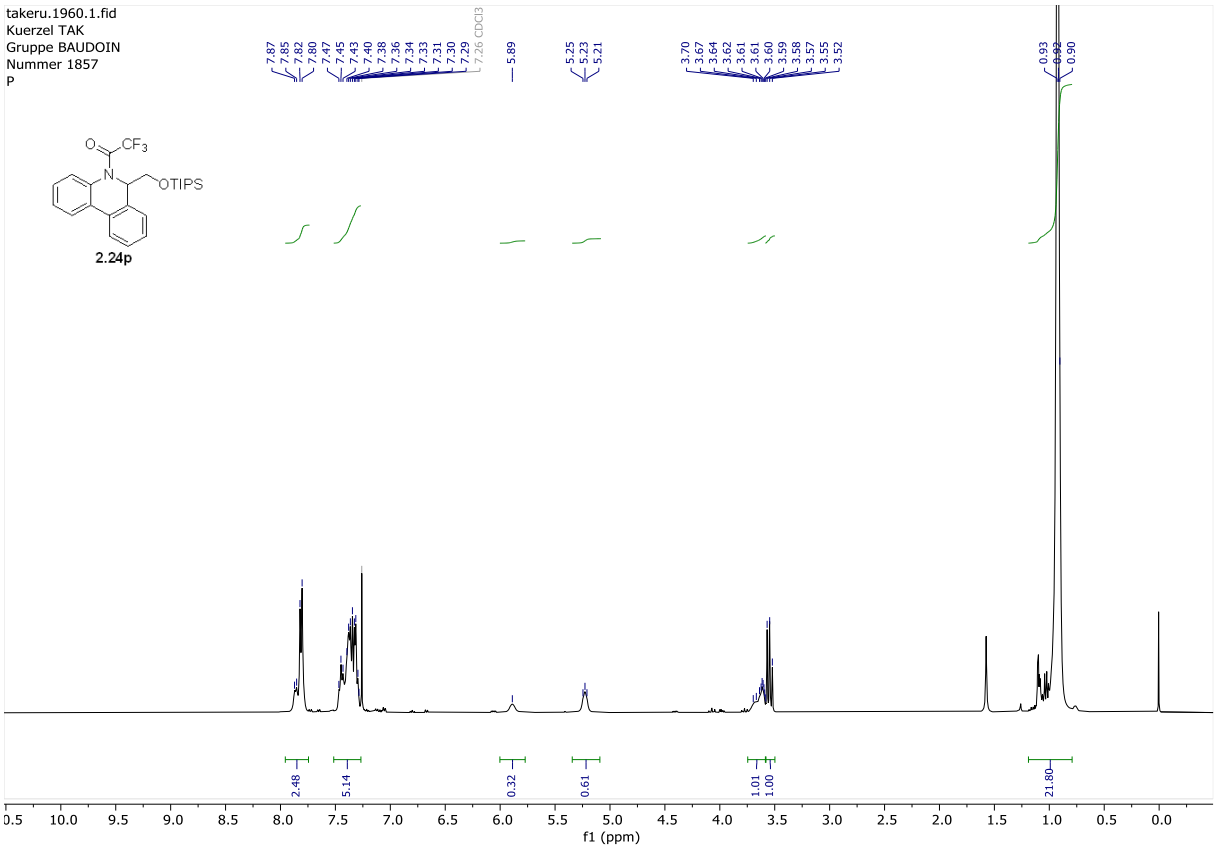
mAU

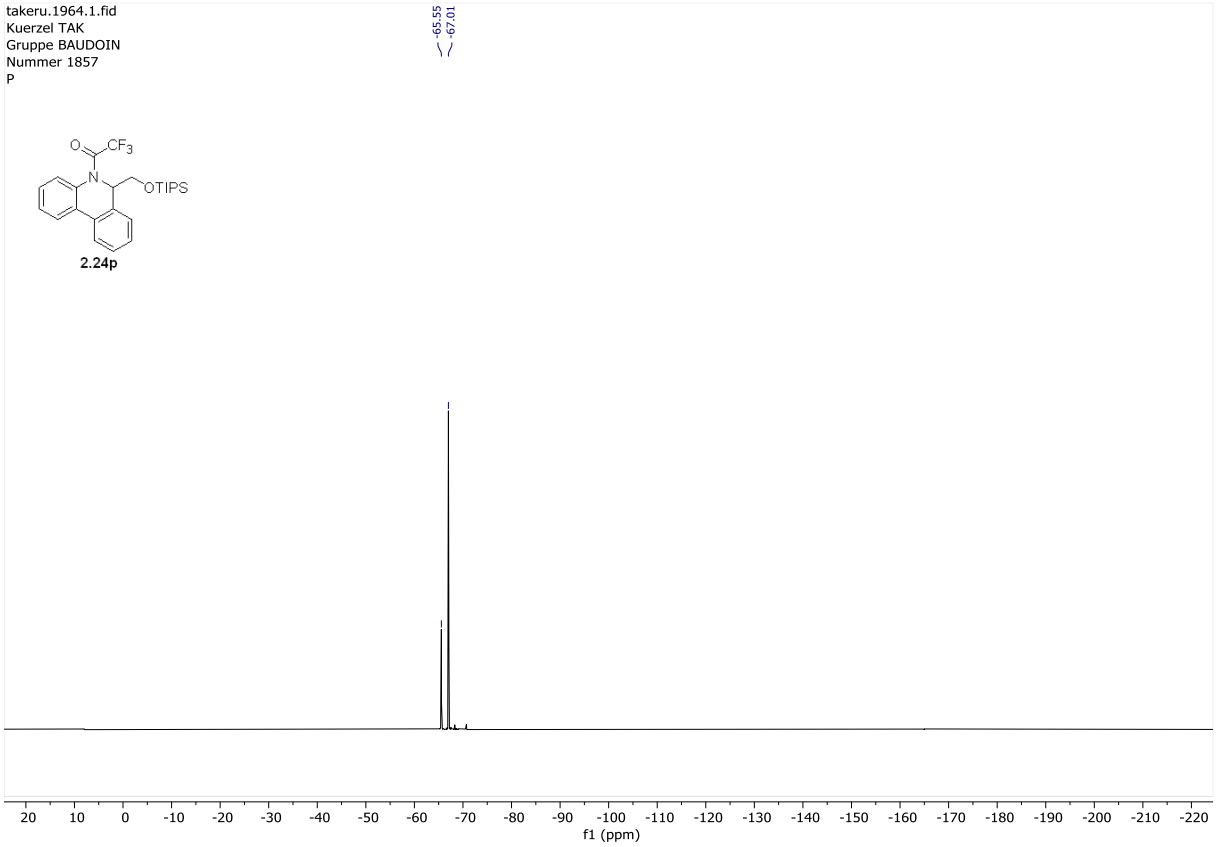


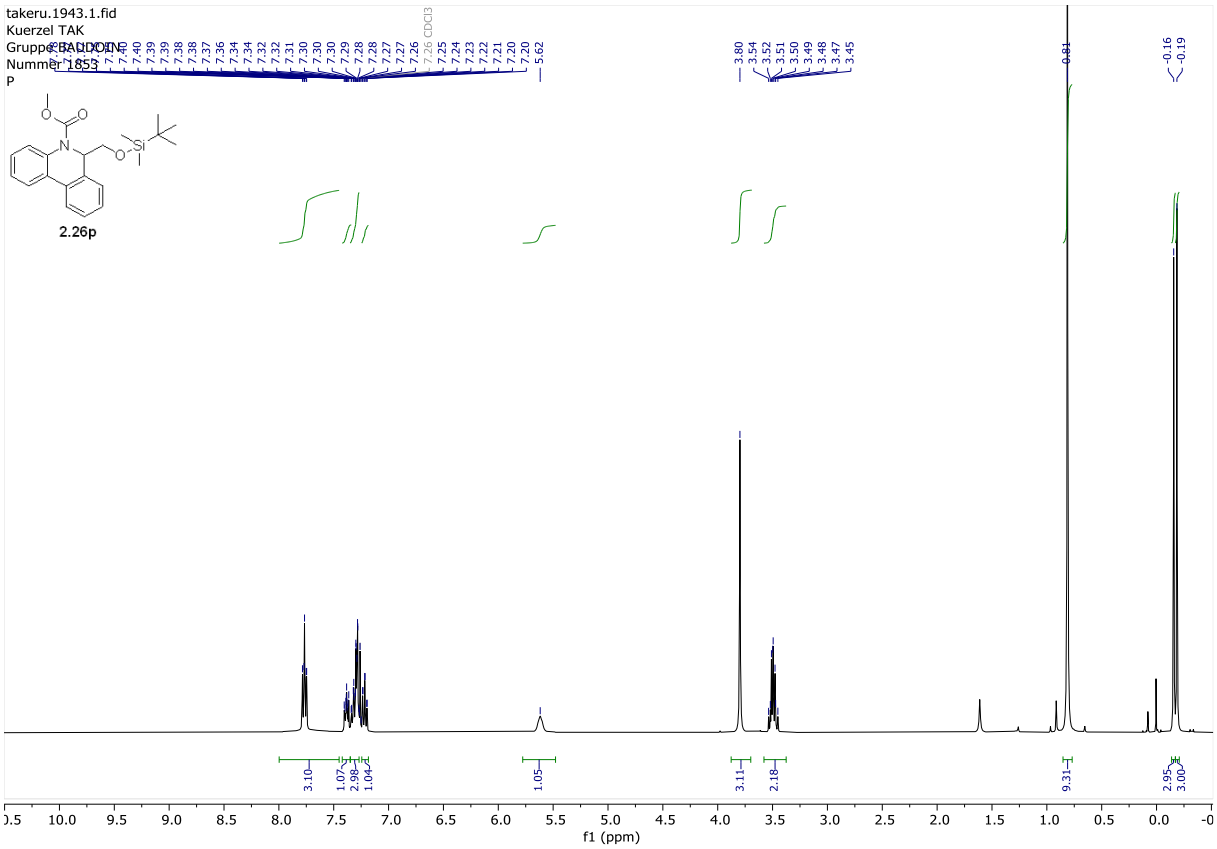
<Peak Table>

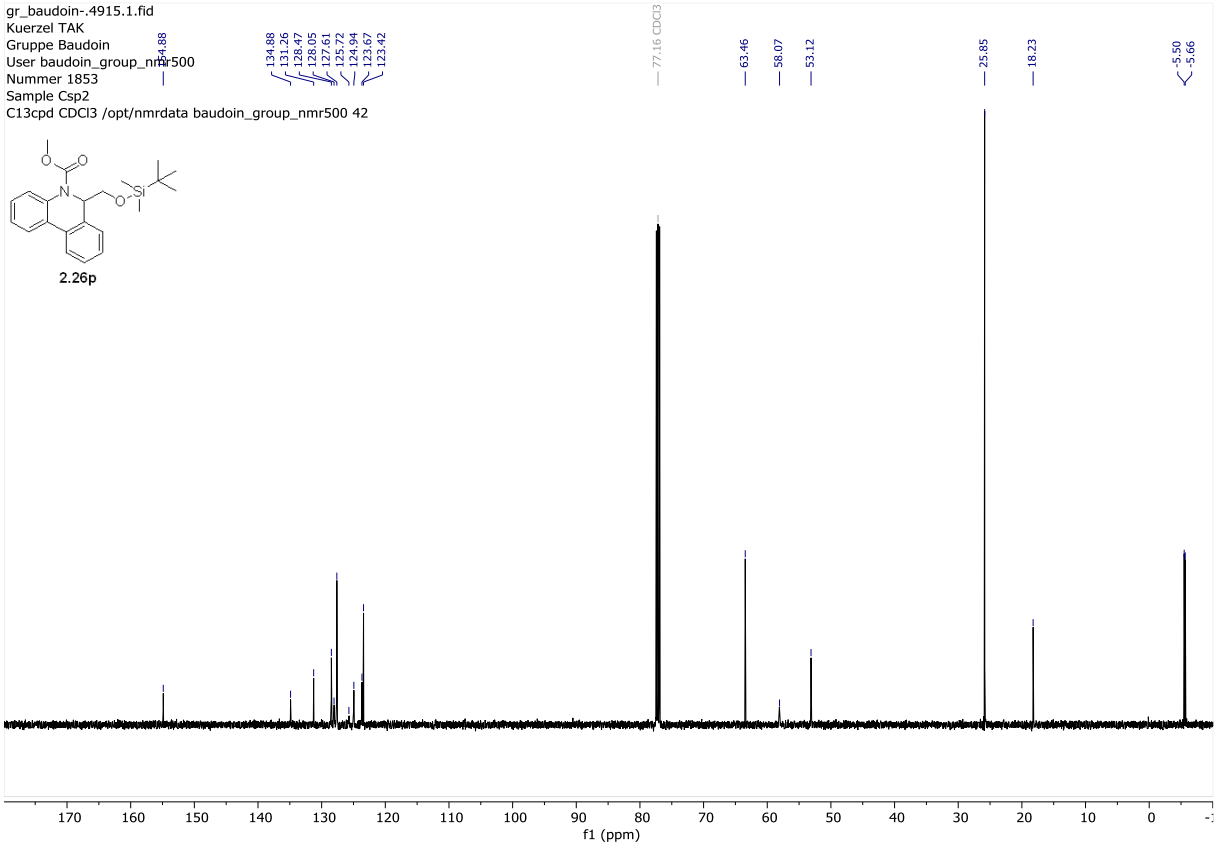
PDA Ch1 270nm

Peak#	Ret. Time	Area	Area%
1	14.042	20182017	50.030
2	19.666	20157928	49.970
Total		40339946	100.000

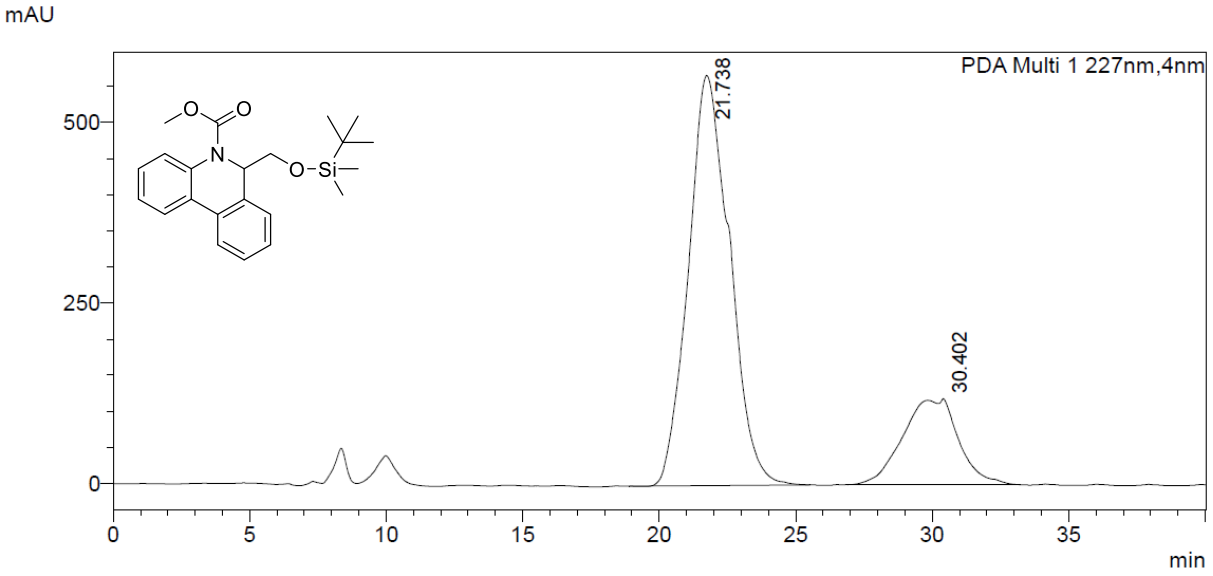

takeru.1960.1.fid
Kuerzel TAK
Gruppe BAUDOIN
Nummer 1857
P
7.87
7.85
7.82
7.80
7.47
7.45
7.43
7.40
7.38
7.36
7.34
7.33
7.31
7.30
7.29
7.26 CDCl3
5.89
5.25
5.23
5.21
3.70
3.67
3.64
3.62
3.61
3.61
3.60
3.59
3.58
3.57
3.55
3.52
0.93
0.92
0.90
O
CF3
N
OTIPS
2.24p
2.48
5.14
0.32
0.61
1.01
1.00
21.80
f1 (ppm)


takeru.1964.1.fid
Kuerzel TAK
Gruppe BAUDOIN
Nummer 1857
P
-65.55
-67.01
O
CF3
N
OTIPS
2.24p
f1 (ppm)


takeru.1943.1.fid
Kuerzel TAK
Gruppe BAUDOIN
Nummer 1853
P
2.26p
f1 (ppm)


gr_baudoin-.4915.1.fid
Kuerzel TAK
Gruppe Baudoin
User baudoin_group_nmr500
Nummer 1853
Sample Csp2
C13cpd CDCl3 /opt/nmrdata baudoin_group_nmr500 42
2.26p
f1 (ppm)

<Chromatogram>

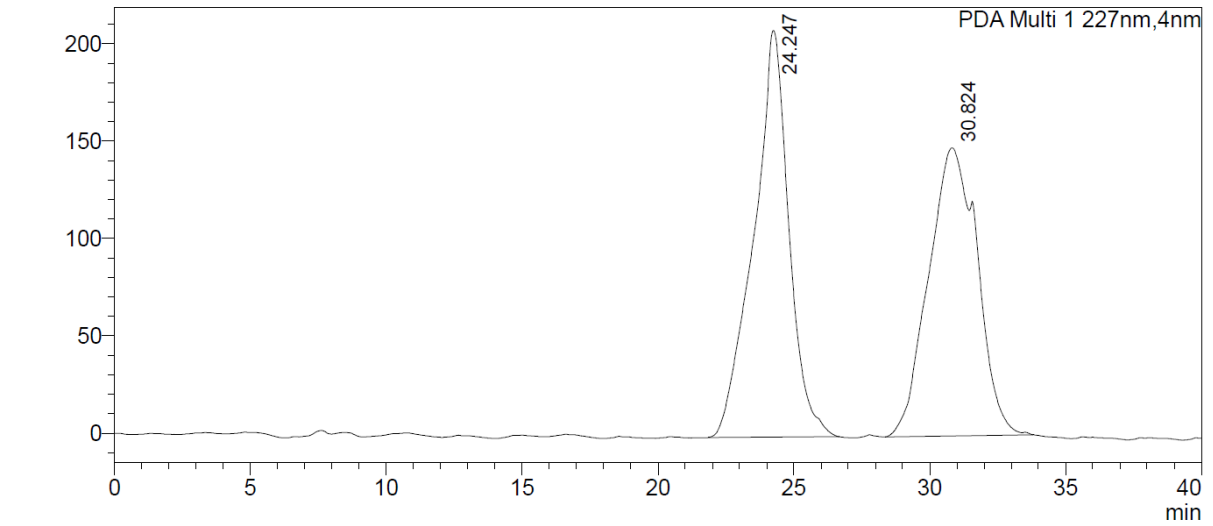


<Peak Table>

PDA Ch1 227nm

Peak#	Ret. Time	Area	Area%
1	21.738	59781836	77.961
2	30.402	16899985	22.039
Total		76681821	100.000

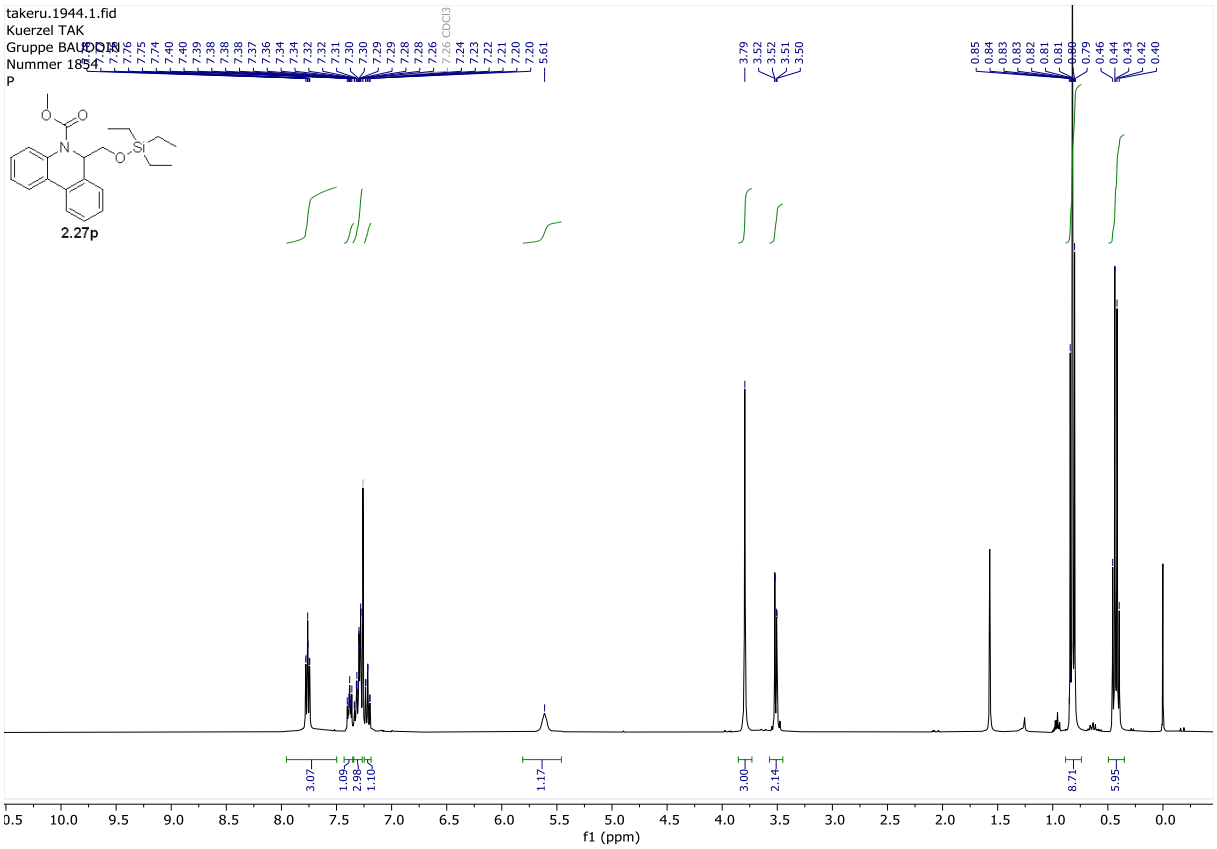
<Chromatogram>

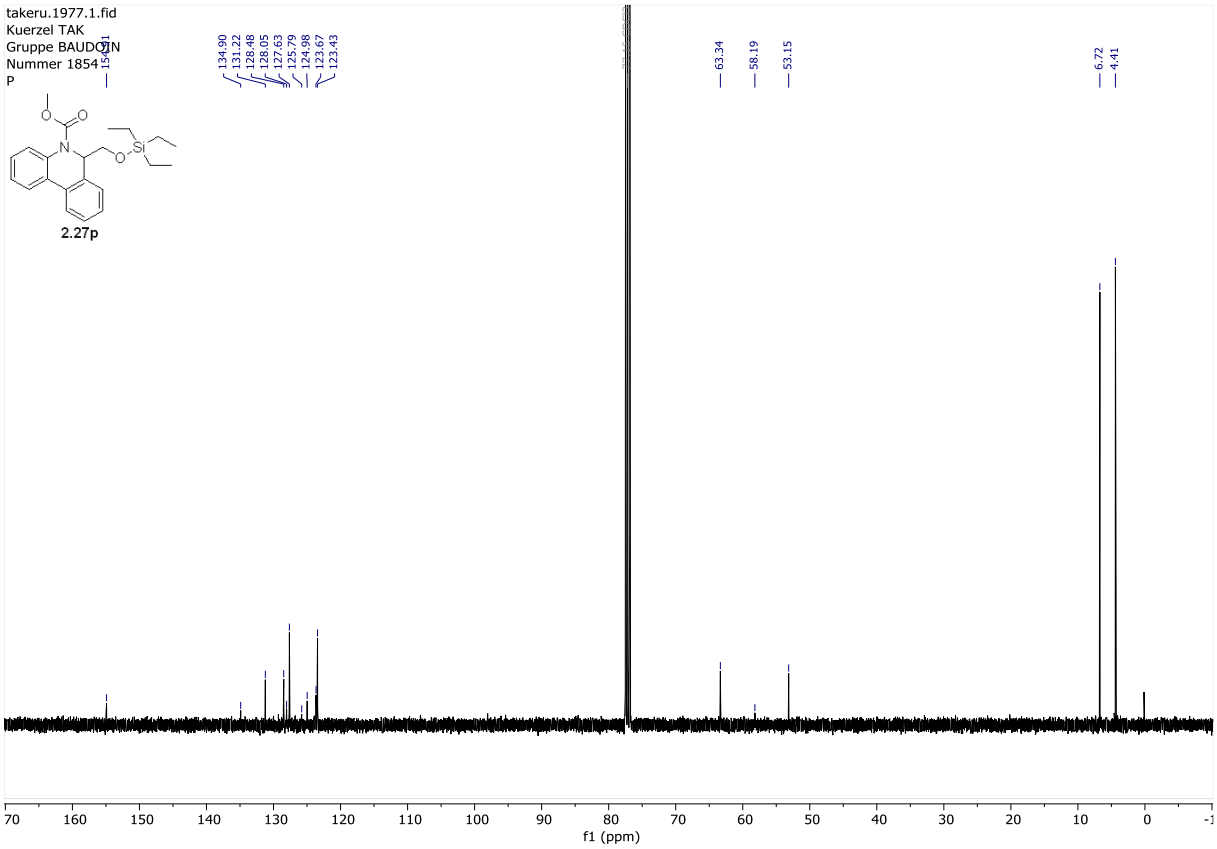


<Peak Table>

PDA Ch1 227nm

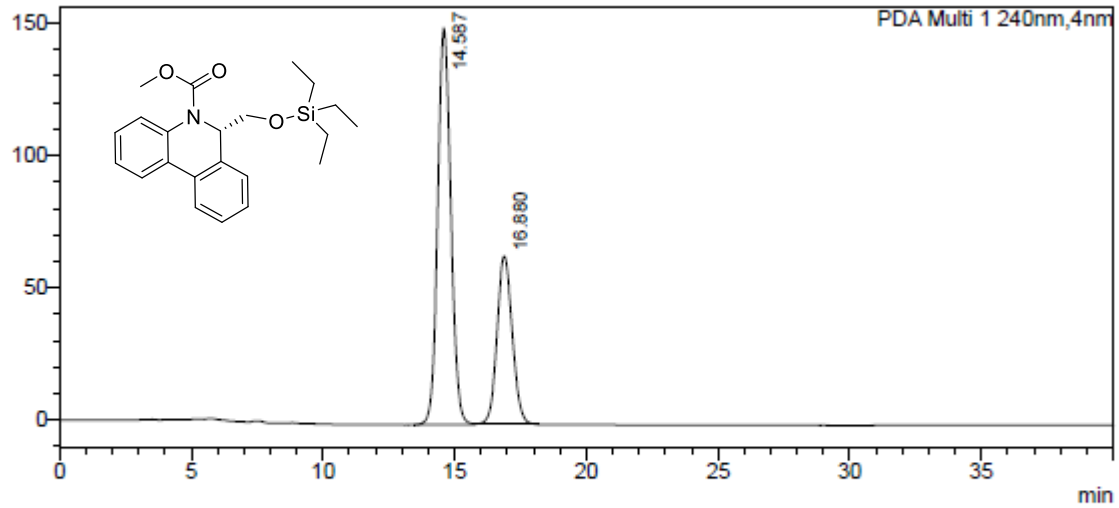
Peak#	Ret. Time	Area	Area%
1	24.247	18781771	50.426
2	30.824	18464140	49.574
Total		37245911	100.000


takeru.1944.1.fid
Kuerzel TAK
Gruppe BAUDOIN
Nummer 1854
P
2.27p
f1 (ppm)


takeru.1977.1.fid
Kuerzel TAK
Gruppe BAUDOIN
Nummer 1854
P
2.27p
f1 (ppm)

<Chromatogram>

mAU



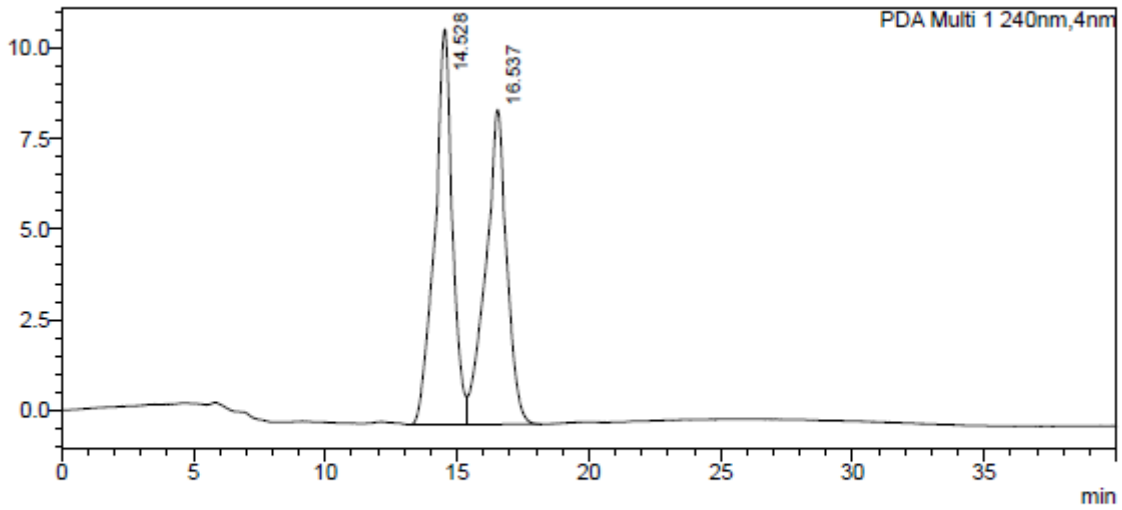
<Peak Table>

PDA Ch1 240nm

Peak#	Ret. Time	Area	Area%
1	14.587	5208190	67.021
2	16.880	2562771	32.979
Total		7770962	100.000

<Chromatogram>

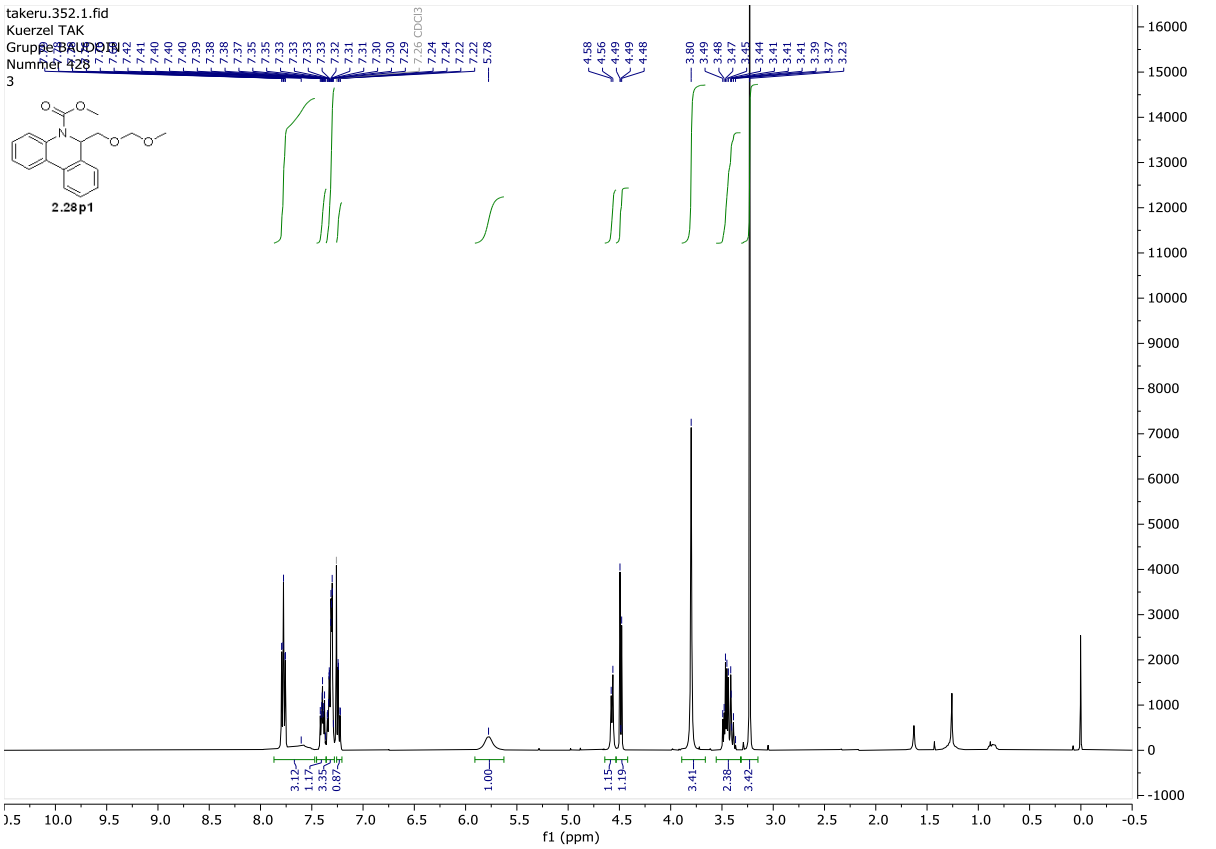
mAU

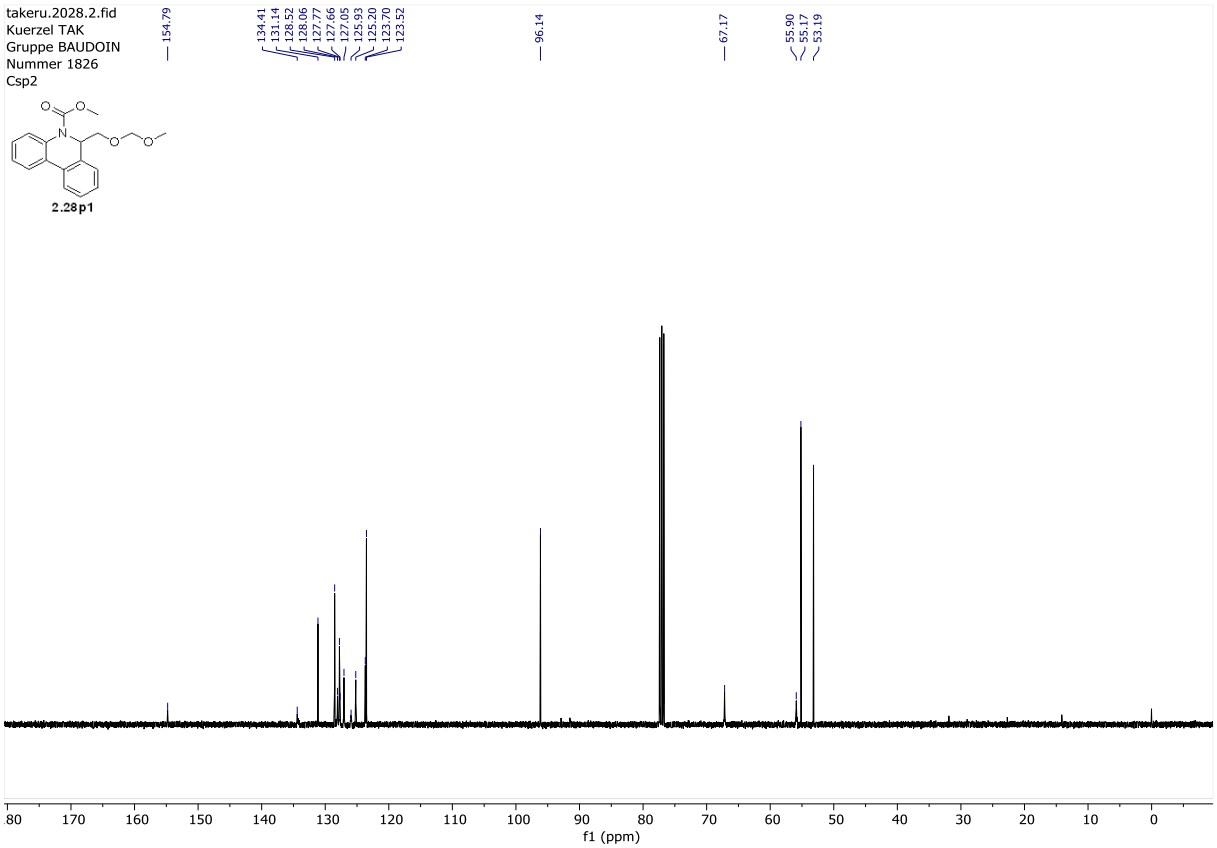


<Peak Table>

PDA Ch1 240nm

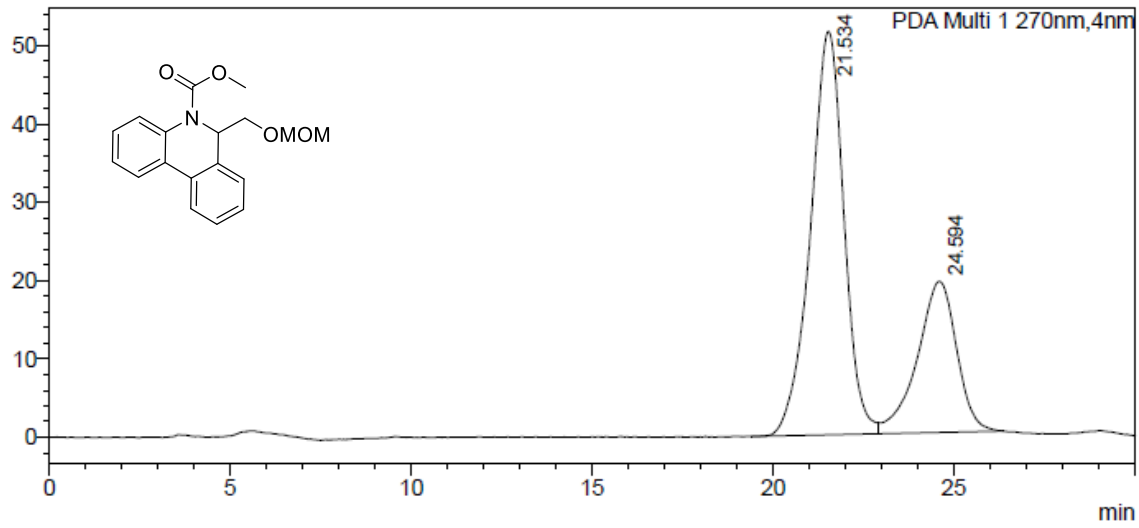
Peak#	Ret. Time	Area	Area%
1	14.528	511163	51.368
2	16.537	483930	48.632
Total		995093	100.000


takeru.352.1.fid
Kuerzel TAK
Gruppe BAUDOIN
Nummer 428
3
2.28p1
f1 (ppm)


takeru.2028.2.fid
Kuerzel TAK
Gruppe BAUDOIN
Nummer 1826
Csp2
2.28p1
f1 (ppm)

<Chromatogram>

mAU



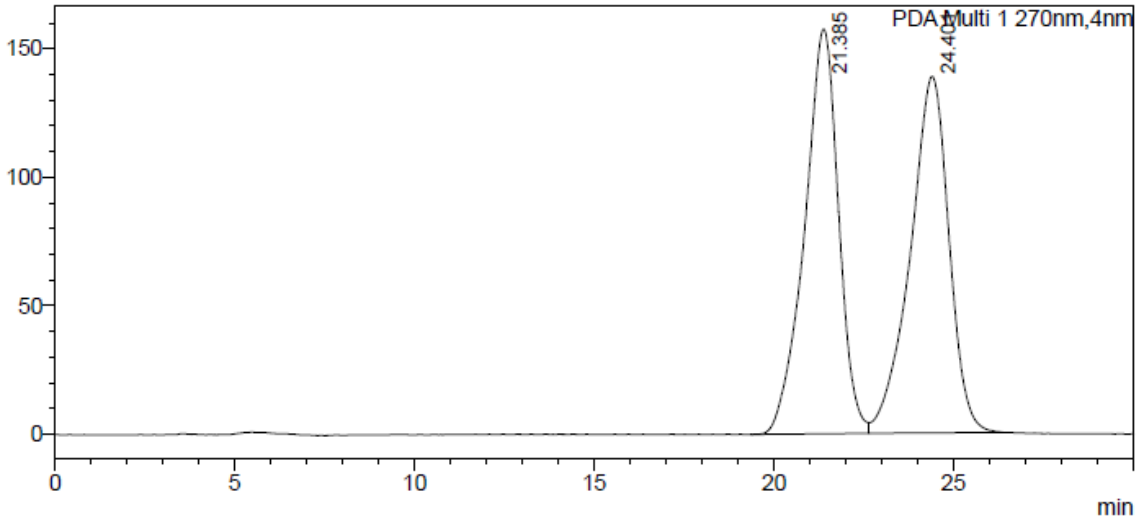
<Peak Table>

PDA Ch1 270nm

Peak#	Ret. Time	Area	Area%
1	21.534	3314975	69.357
2	24.594	1464638	30.643
Total		4779613	100.000

<Chromatogram>

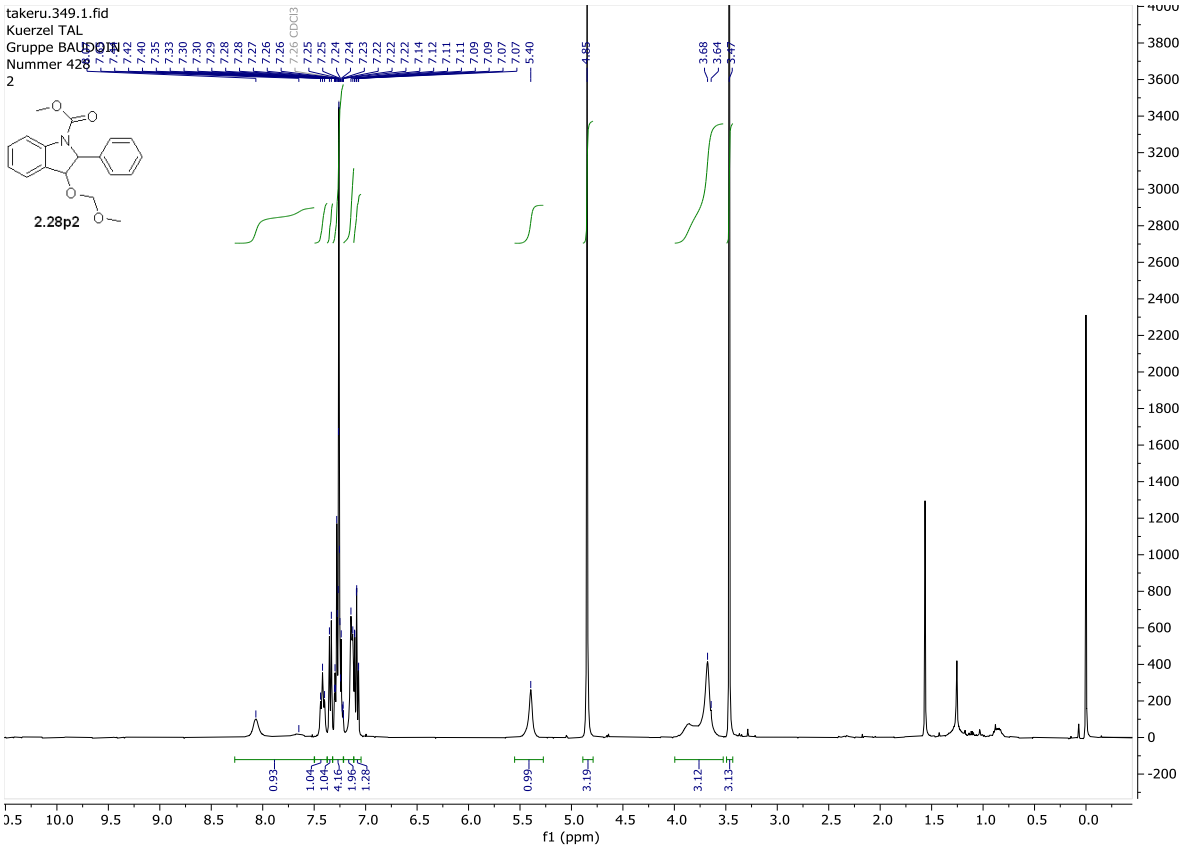
mAU

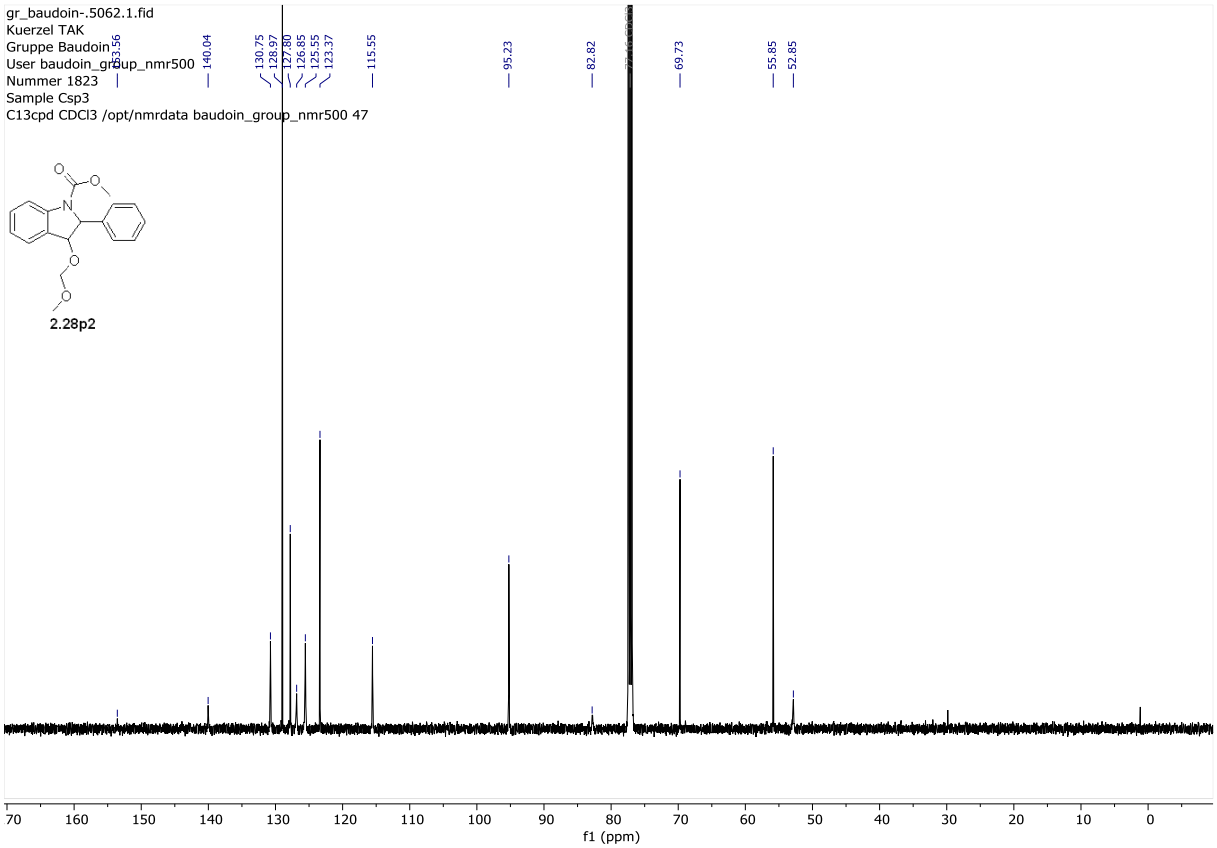


<Peak Table>

PDA Ch1 270nm

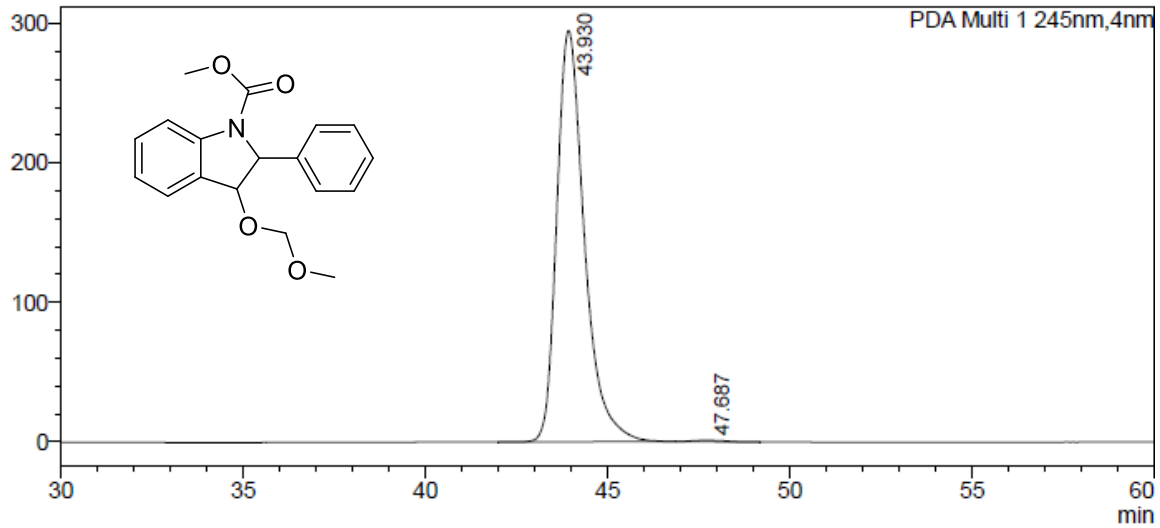
Peak#	Ret. Time	Area	Area%
1	21.385	10373093	49.910
2	24.401	10410461	50.090
Total		20783554	100.000


takeru.349.1.fid
Kuerzel TAL
Nummer 428
2
2.28p2
f1 (ppm)


gr_baudoin-.5062.1.fid
Kuerzel TAK
Gruppe Baudoin
User baudoin_group_nmr500
Nummer 1823
Sample Csp3
C13cpd CDCl3 /opt/nmrdata baudoin_group_nmr500 47
2.28p2
f1 (ppm)

<Chromatogram>

mAU



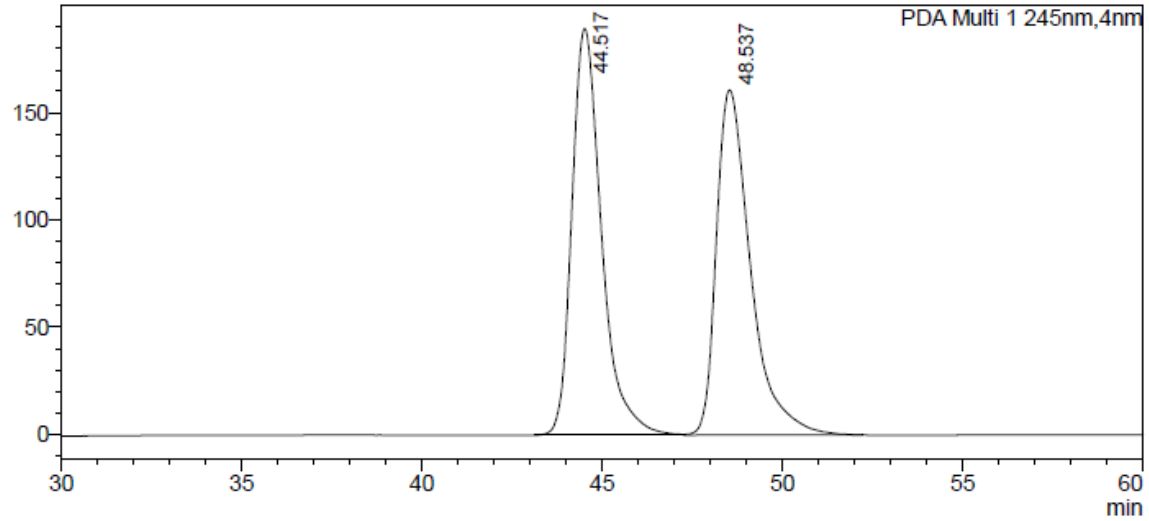
<Peak Table>

PDA Ch1 245nm

Peak#	Ret. Time	Area	Area%
1	43.930	15563110	99.616
2	47.687	60041	0.384
Total		15623151	100.000

<Chromatogram>

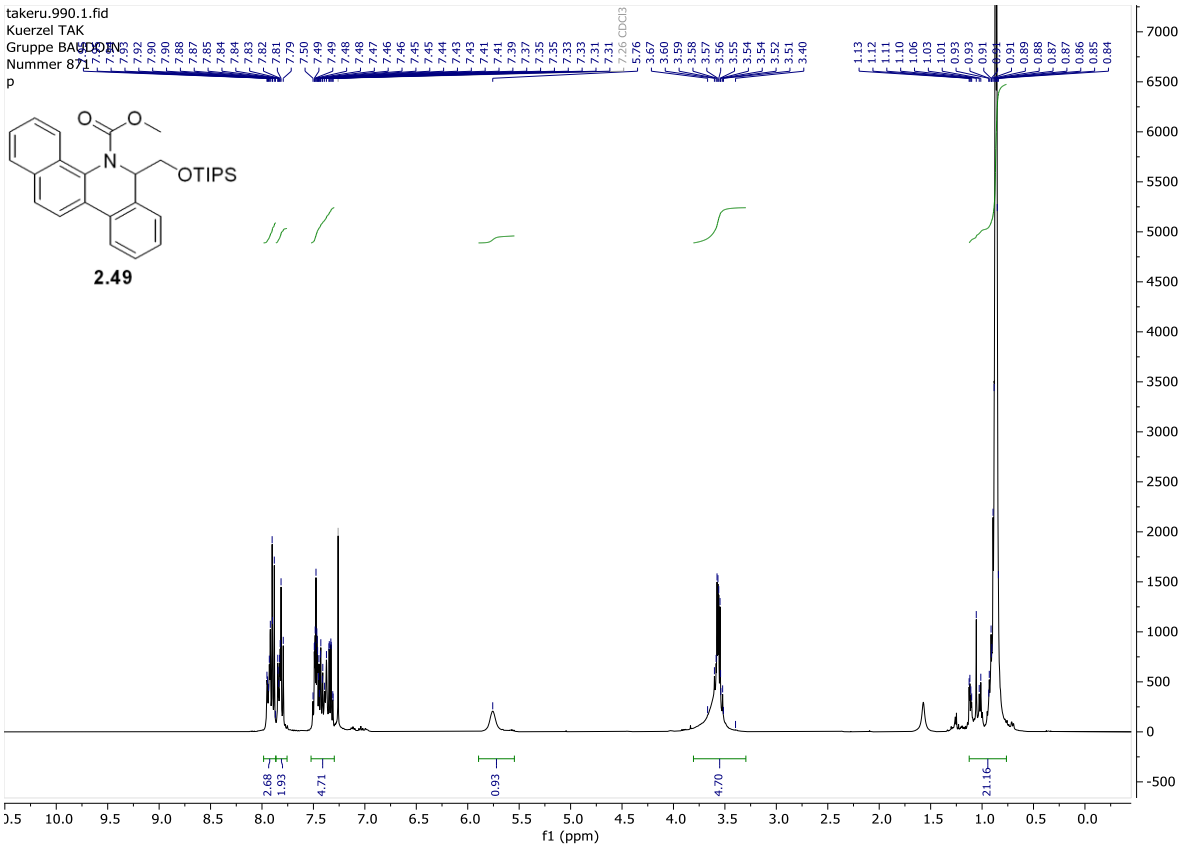
mAU

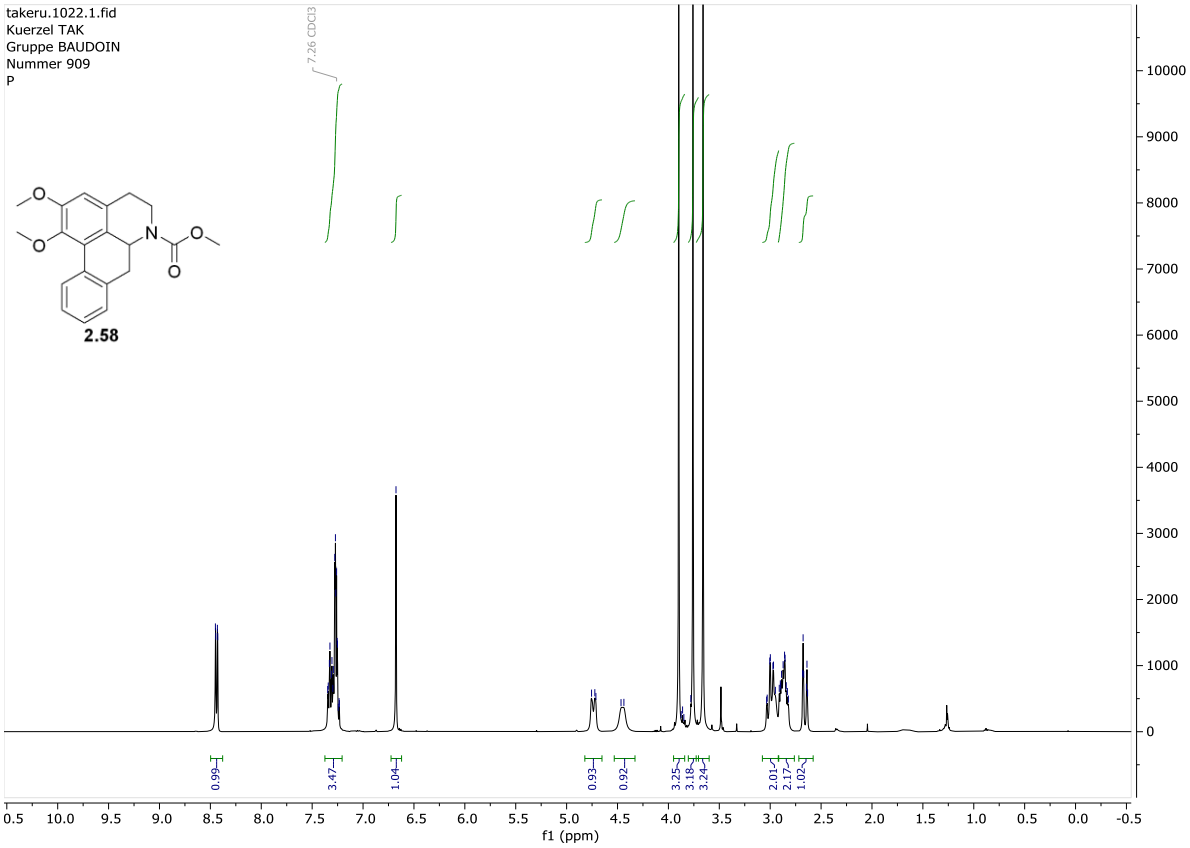


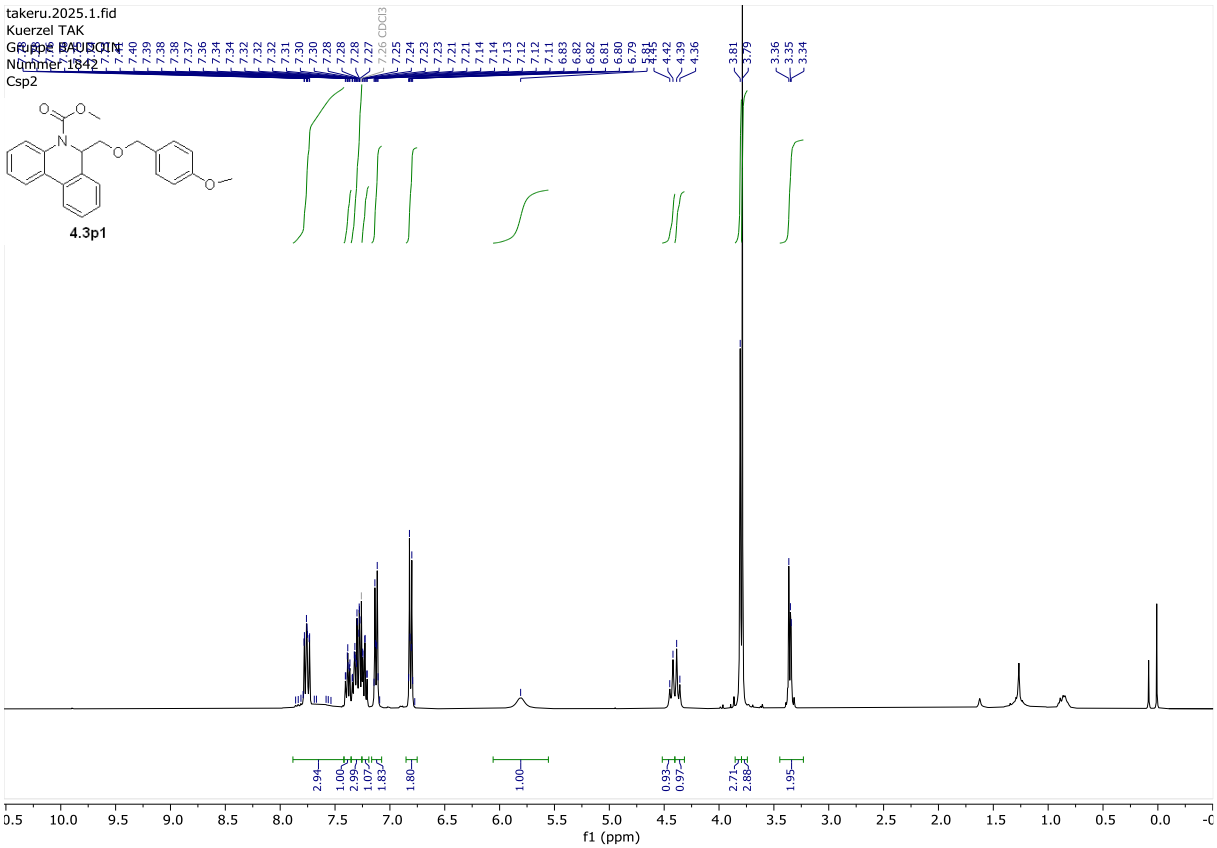
<Peak Table>

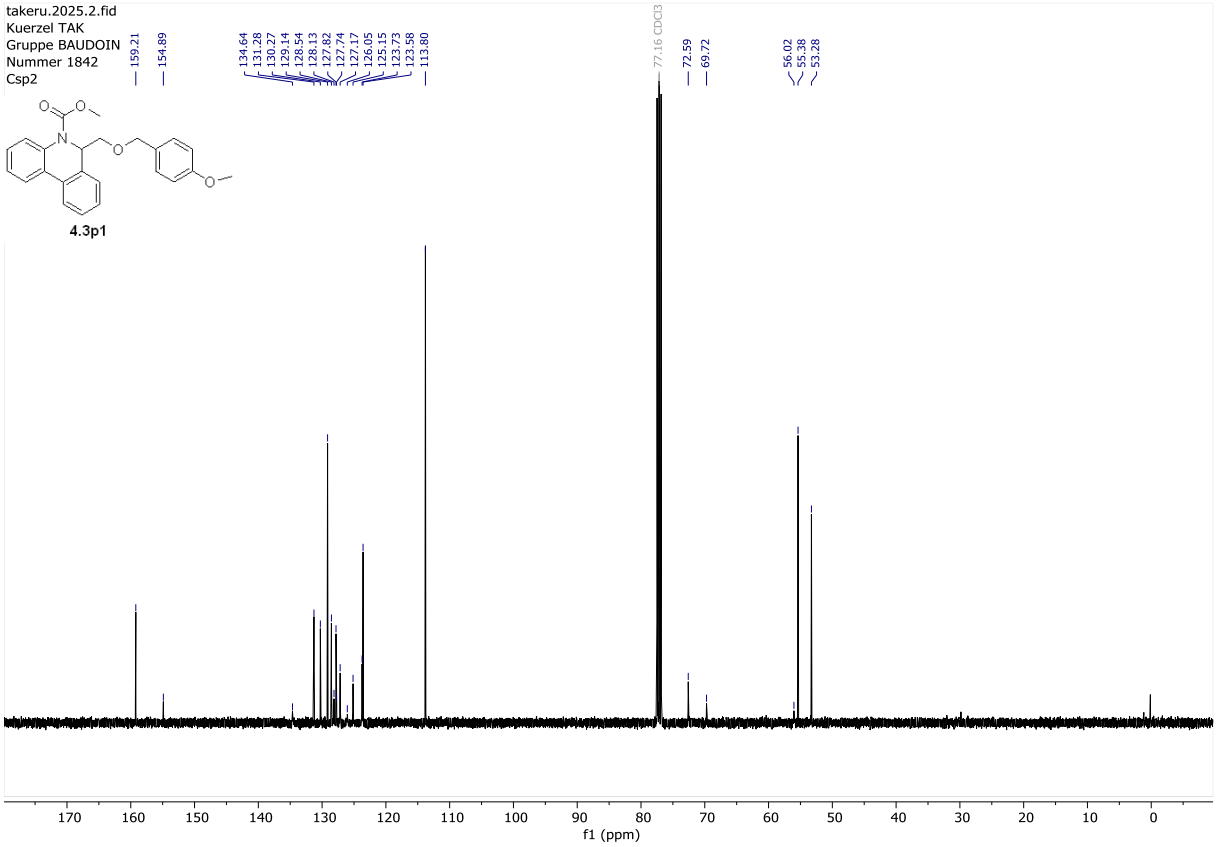
PDA Ch1 245nm

Peak#	Ret. Time	Area	Area%
1	44.517	10846819	50.528
2	48.537	10619972	49.472
Total		21466790	100.000


takeru.990.1.fid
Kuerzel TAK
Gruppe BAUDOIN
Nummer 871
p
OTIPS
2.49
7.26 CDCl3
2.68
1.93
4.71
0.93
4.70
21.16
f1 (ppm)

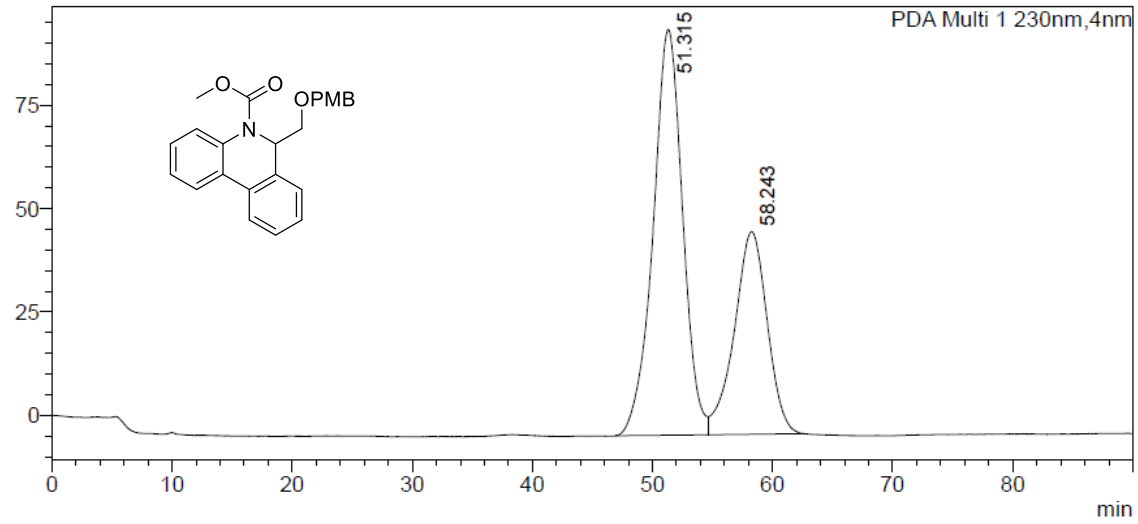

takeru.1022.1.fid
Kuerzel TAK
Gruppe BAUDOIN
Nummer 909
P
2.58
7.26 CDCl3
0.99
3.47
1.04
0.93
0.92
3.25
3.18
3.24
2.01
2.17
1.02
f1 (ppm)


takeru.2025.1.fid
Kuerzel TAK
Gruppe BAUDOIN
Nummer 1842
Csp2
4.3p1
f1 (ppm)


takeru.2025.2.fid
Kuerzel TAK
Gruppe BAUDOIN
Nummer 1842
Csp2
4.3p1
f1 (ppm)

<Chromatogram>

mAU



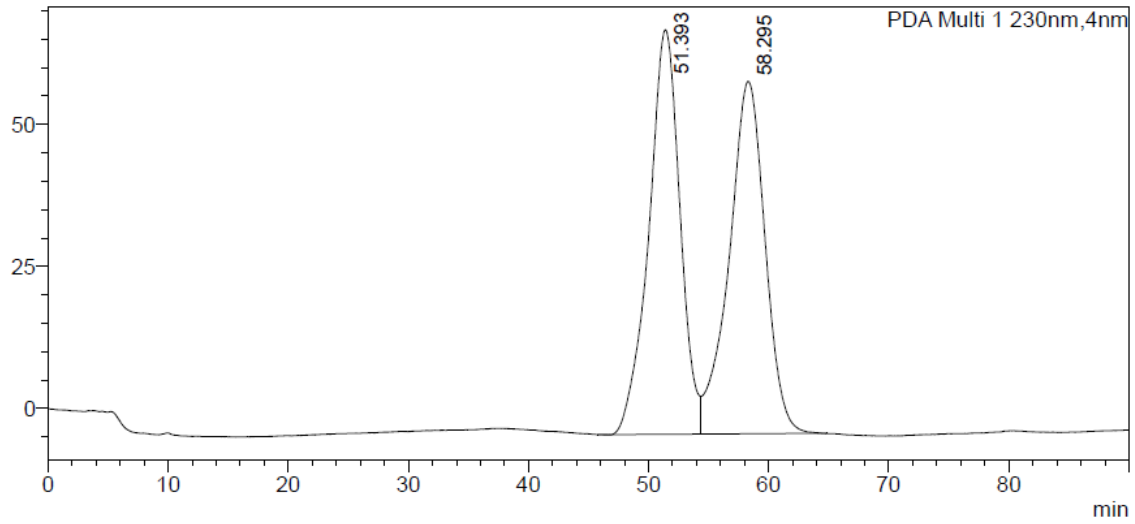
<Peak Table>

PDA Ch1 230nm

Peak#	Ret. Time	Area	Area%
1	51.315	16770515	64.137
2	58.243	9377643	35.863
Total		26148157	100.000

<Chromatogram>

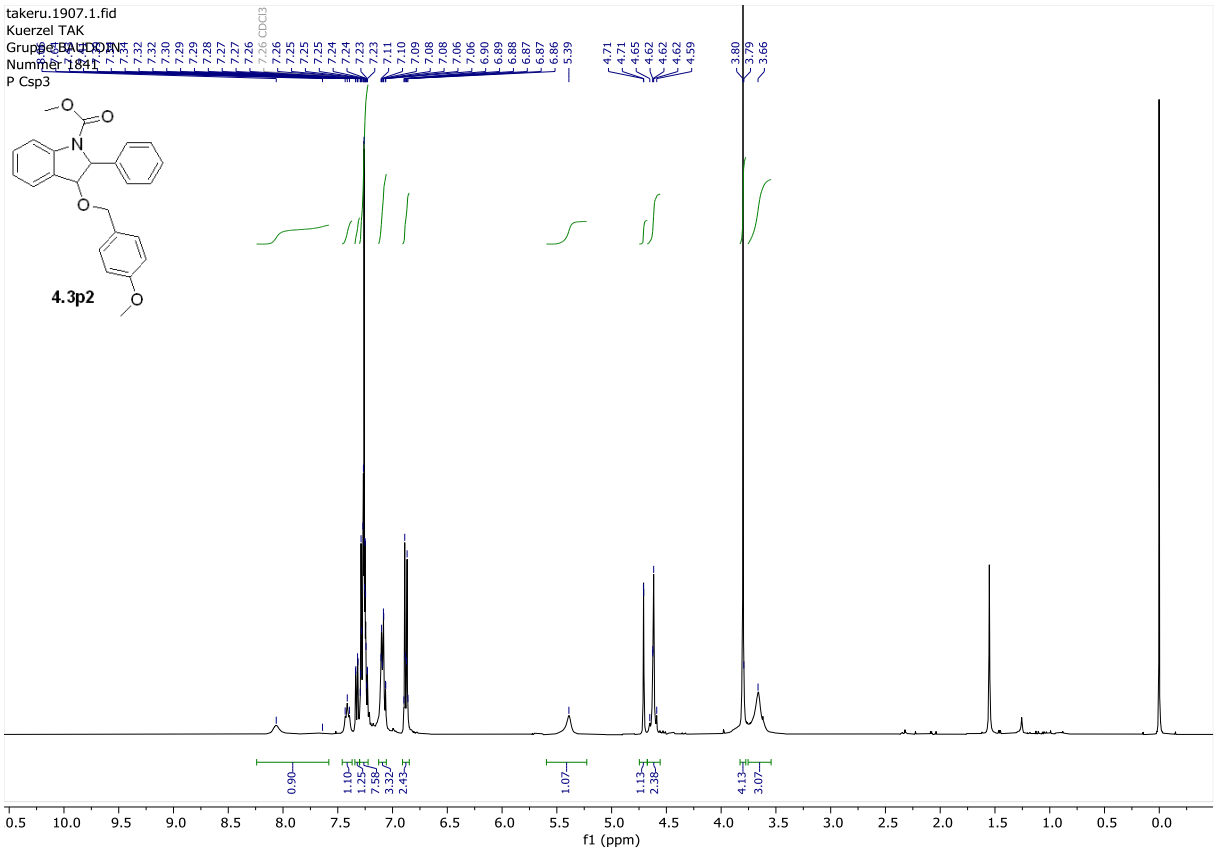
mAU

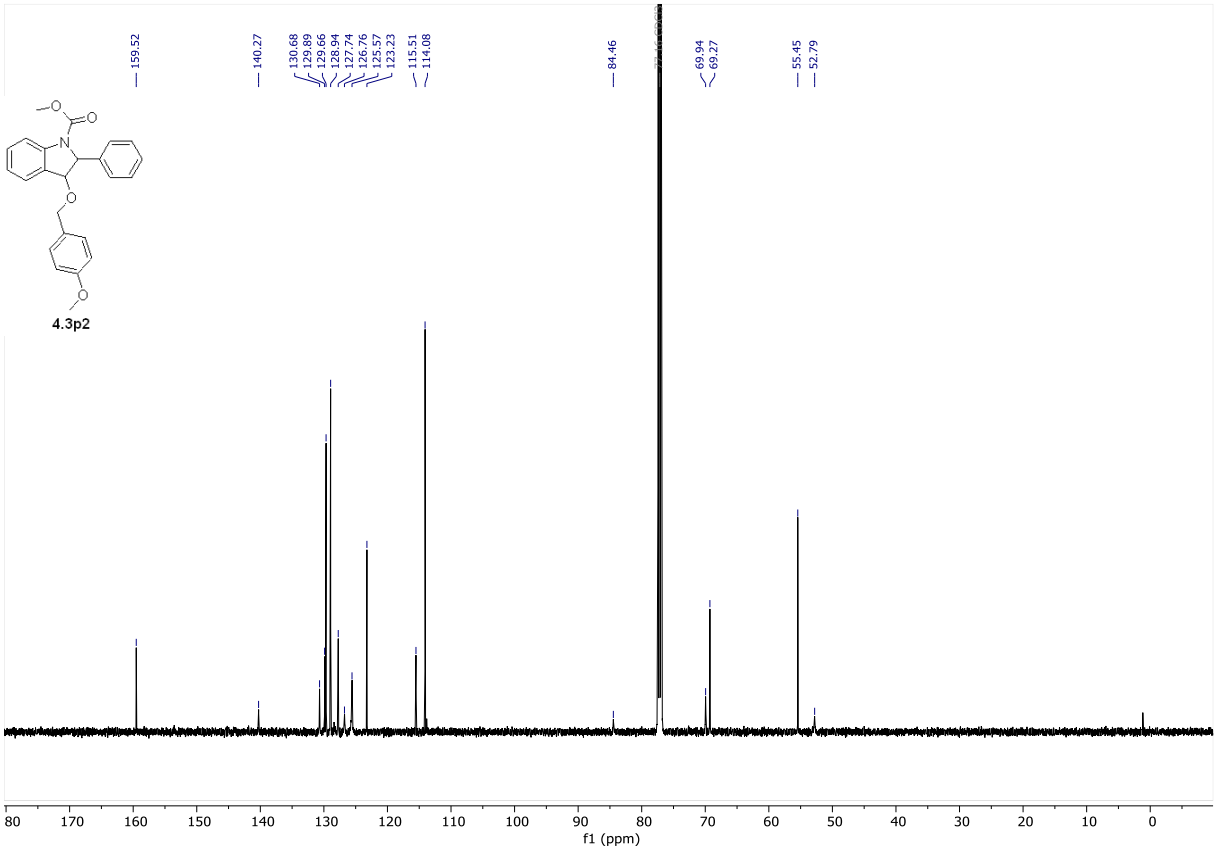


<Peak Table>

PDA Ch1 230nm

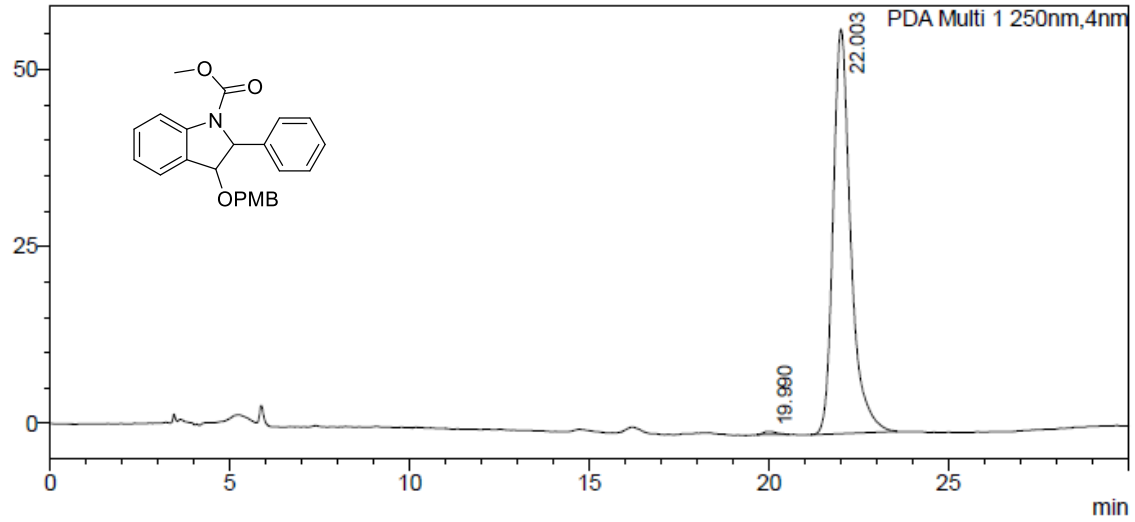
Peak#	Ret. Time	Area	Area%
1	51.393	12875934	49.884
2	58.295	12935588	50.116
Total		25811522	100.000


takeru.1907.1.fid
Kuerzel TAK
Gruppe BAUDORN
Nummer 1841
P Csp3
4.3p2
f1 (ppm)


4.3p2
f1 (ppm)

<Chromatogram>

mAU



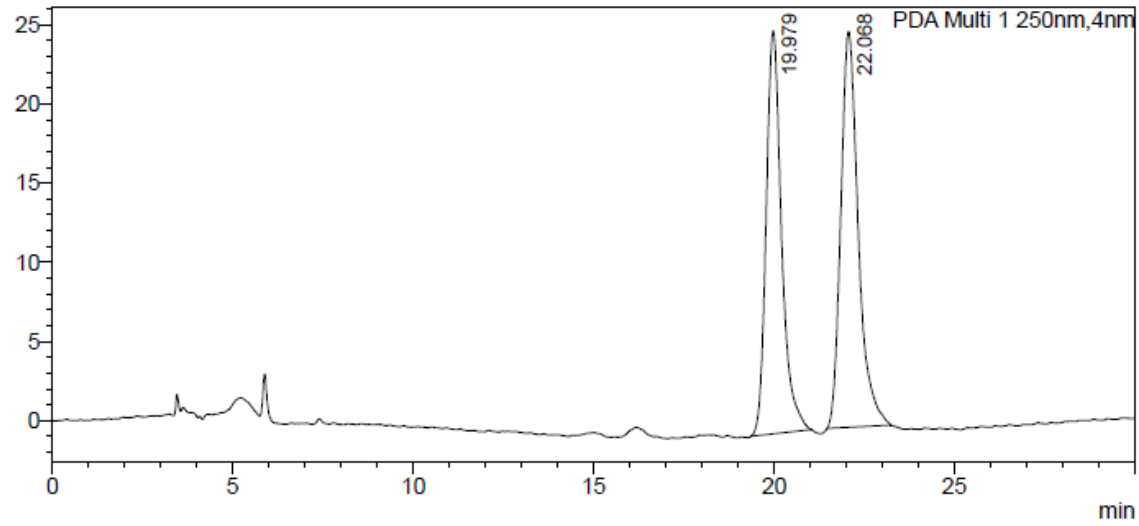
<Peak Table>

PDA Ch1 250nm

Peak#	Ret. Time	Area	Area%
1	19.990	11819	0.604
2	22.003	1944134	99.396
Total		1955953	100.000

<Chromatogram>

mAU

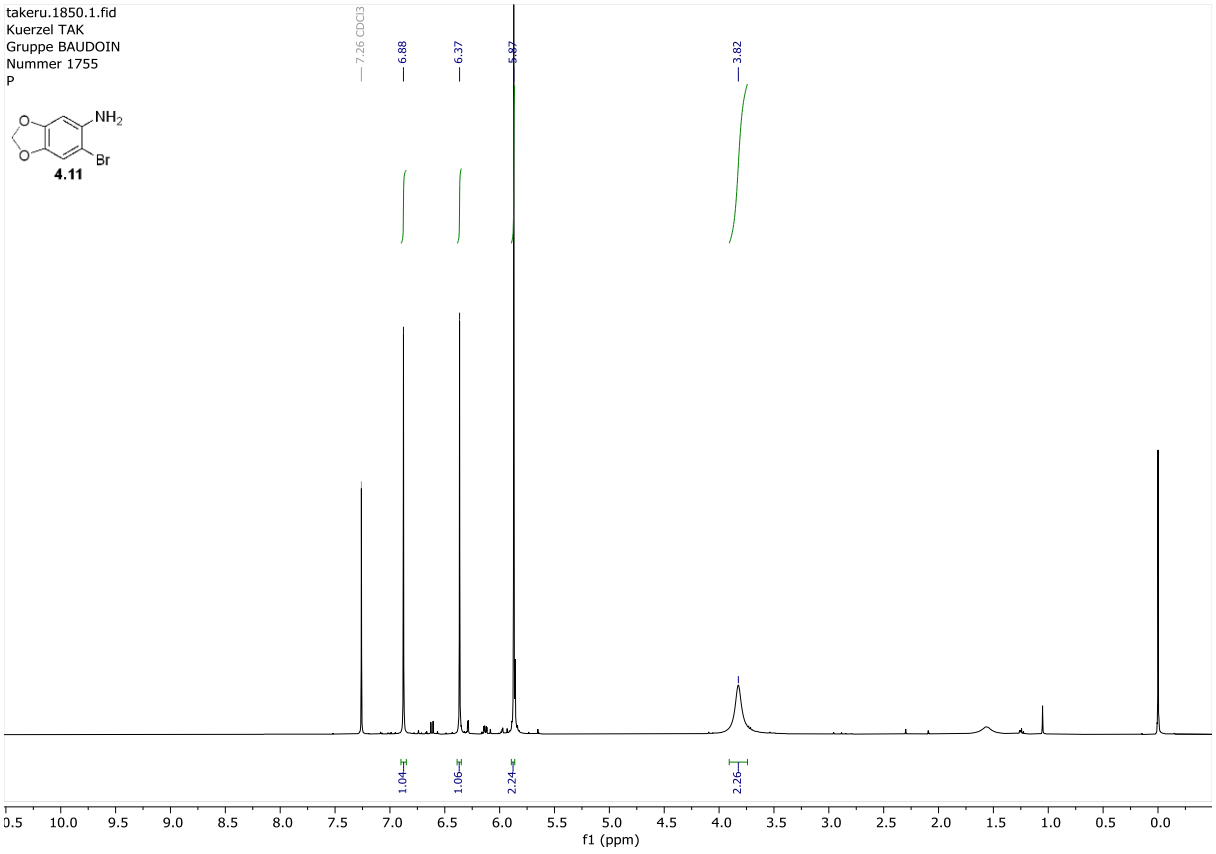


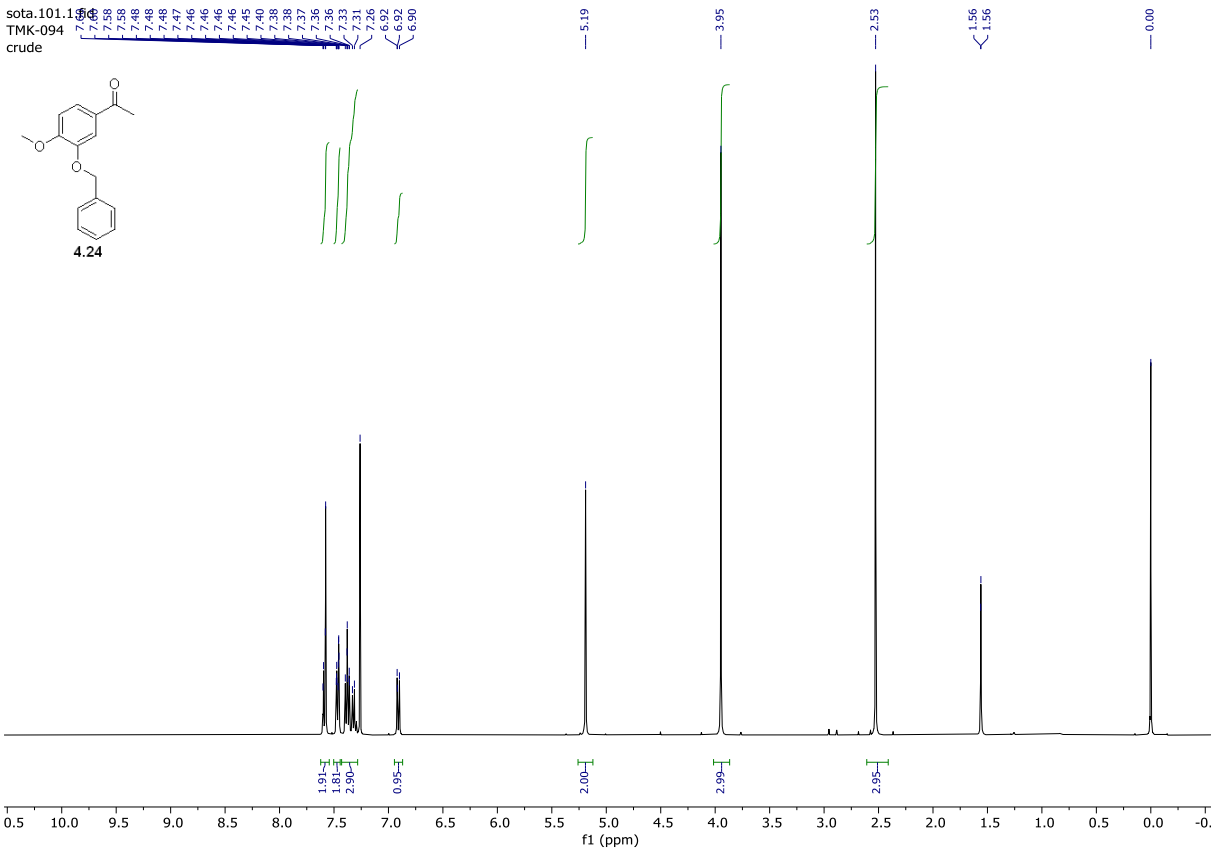
<Peak Table>

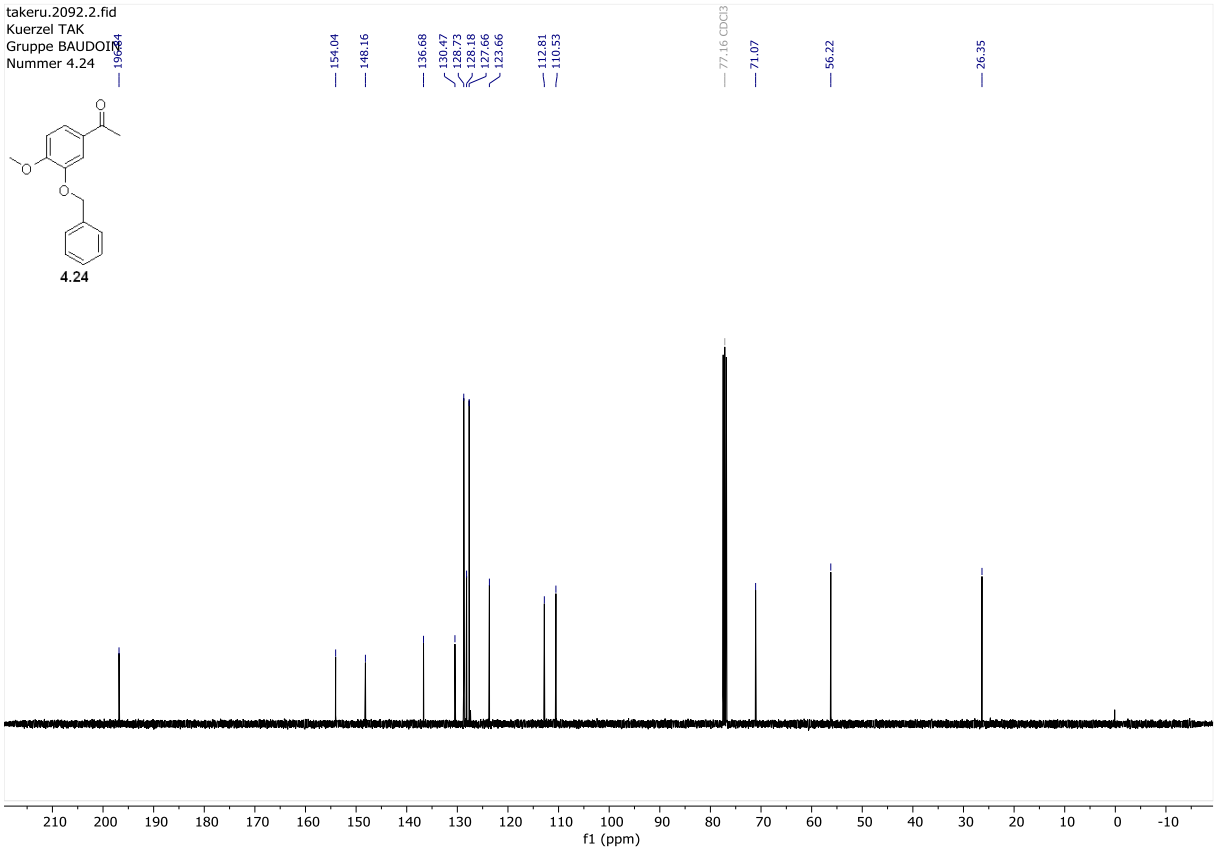
PDA Ch1 250nm

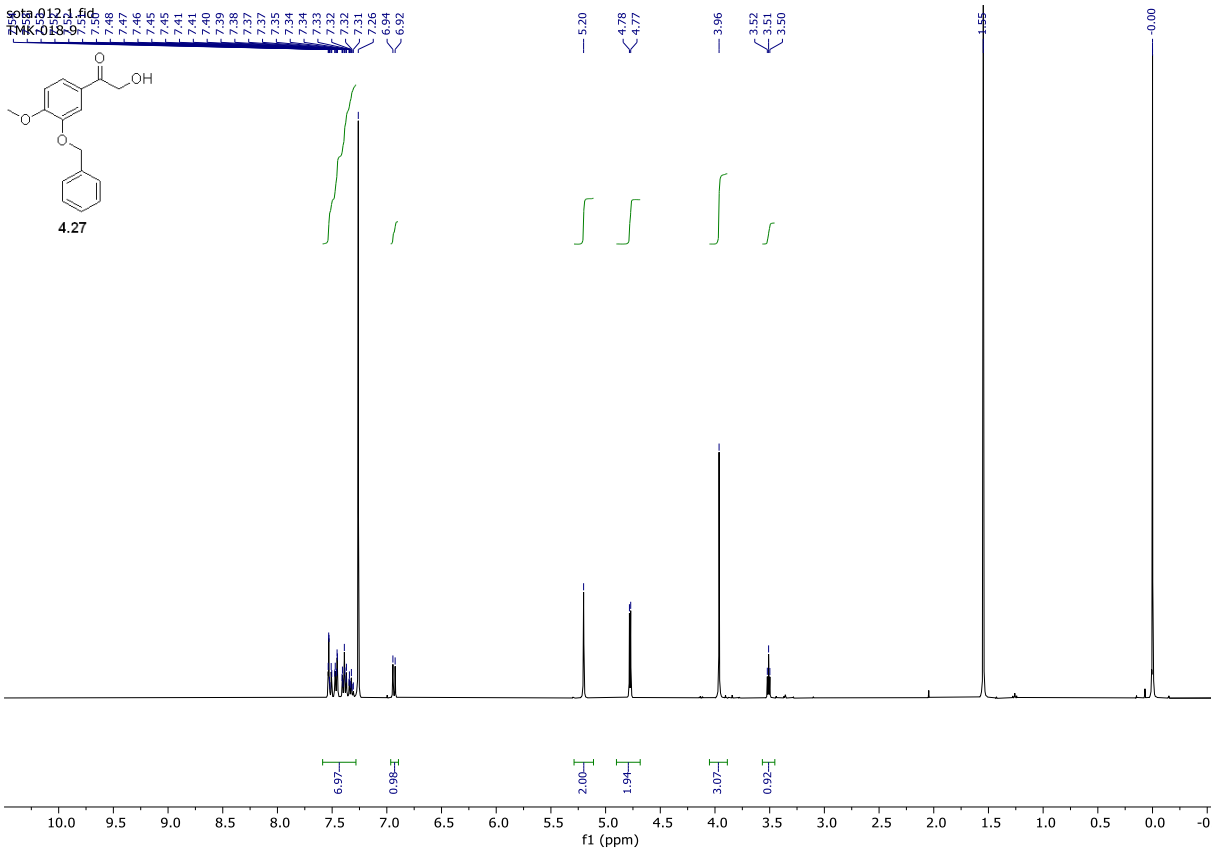
Peak#	Ret. Time	Area	Area%
1	19.979	754953	47.351
2	22.068	839425	52.649
Total		1594378	100.000

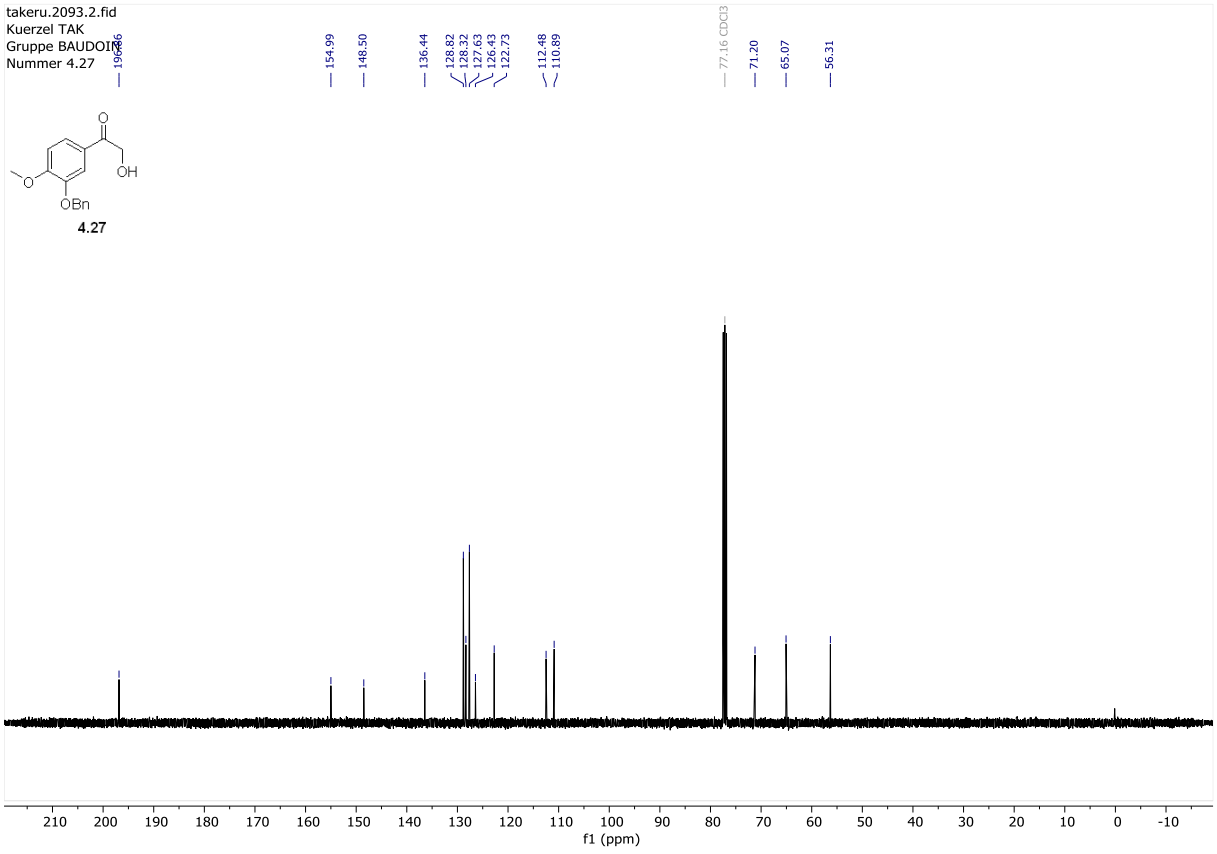
7.6.3 NMR and HPLC spectrum data in the total synthesis of cryptowolinol

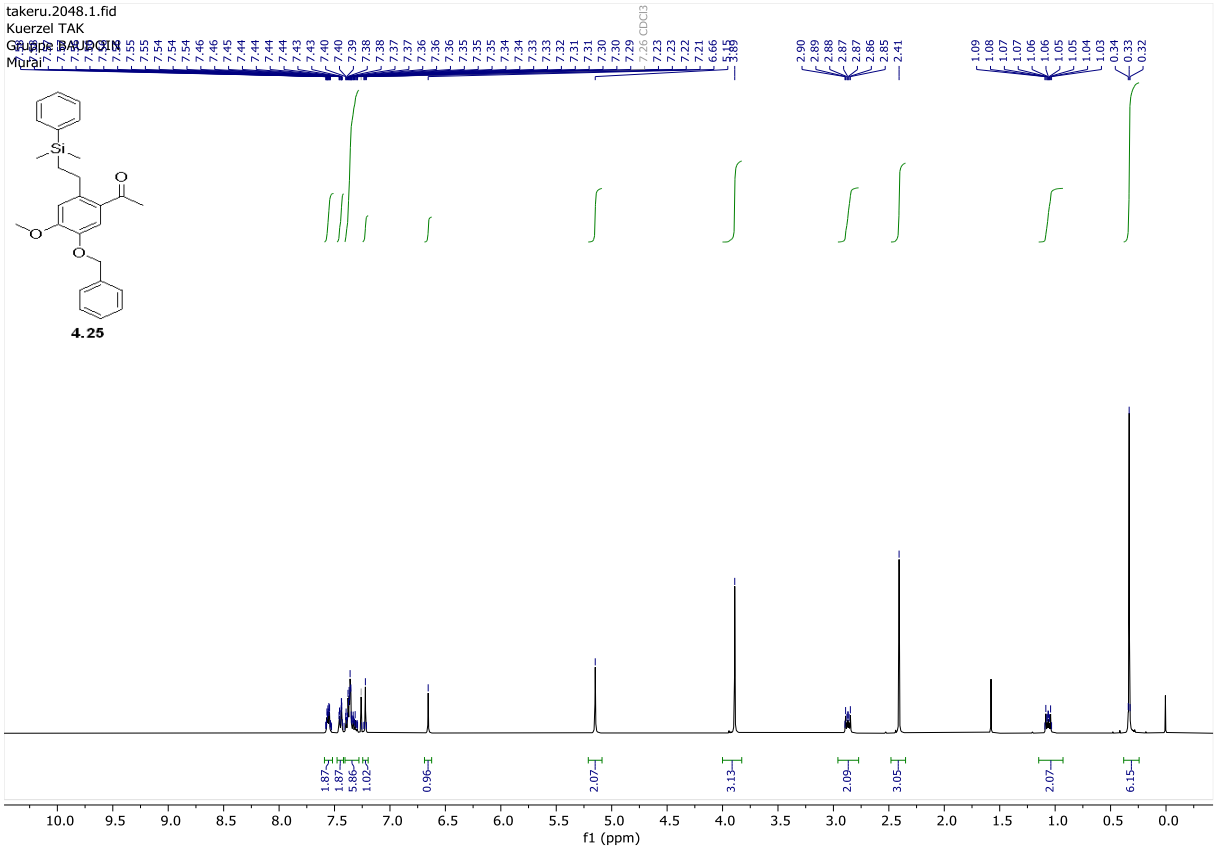


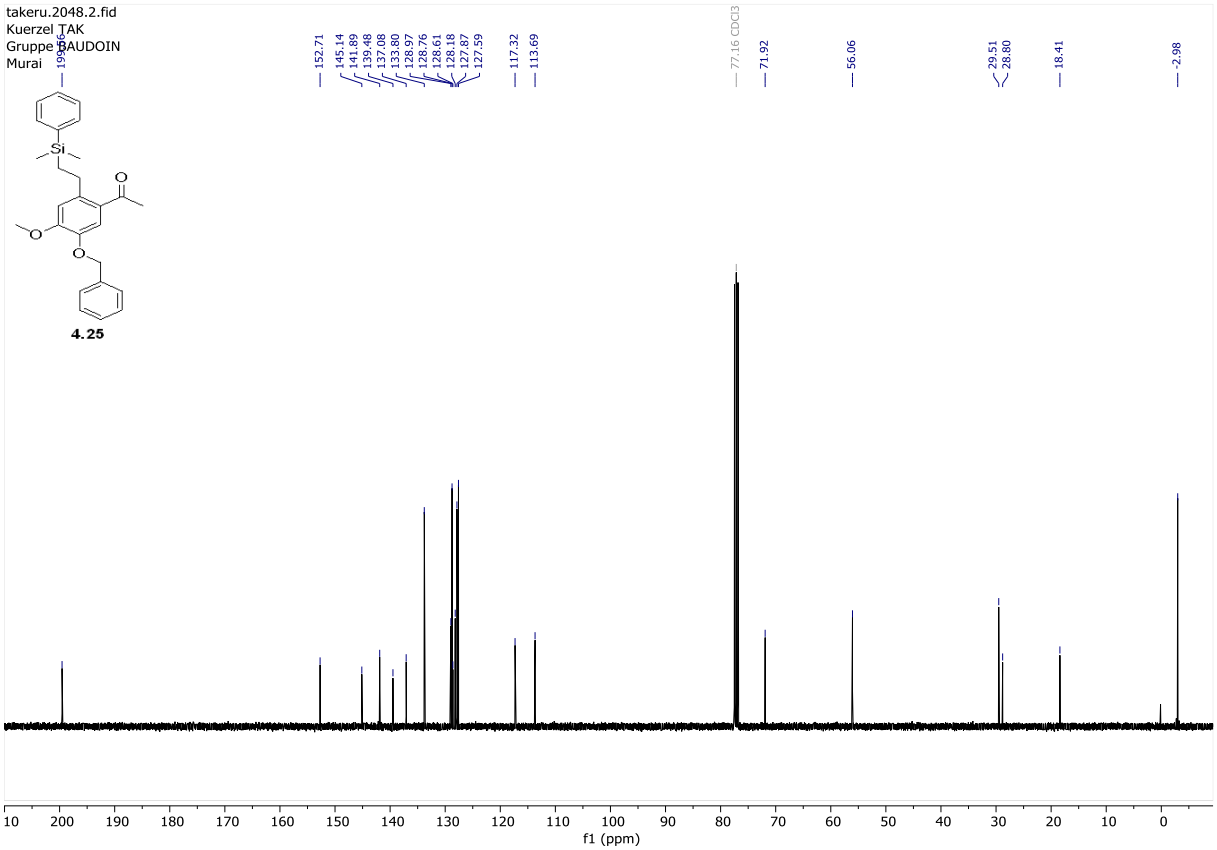

sota.101.1.fid
TMK-094
crude
4.24
f1 (ppm)


takeru.2092.2.fid
Kuerzel TAK
Gruppe BAUDOIN
Nummer 4.24
4.24
f1 (ppm)


sota.012.1.fid
TMK-018-9
OH
O
O
4.27
5.20
4.78
4.77
3.96
3.52
3.51
3.50
1.55
-0.00
6.97
0.98
2.00
1.94
3.07
0.92
f1 (ppm)


takeru.2093.2.fid
Kuerzel TAK
Gruppe BAUDOIN
Nummer 4.27
OH
OBn
4.27
154.99
148.50
136.44
128.82
128.32
127.63
126.43
122.73
112.48
110.89
77.16 CDCl3
71.20
65.07
56.31
f1 (ppm)


takeru.2048.1.fid
Kuerzel TAK
Gruppe BAUDOIN
Murai
4.25
f1 (ppm)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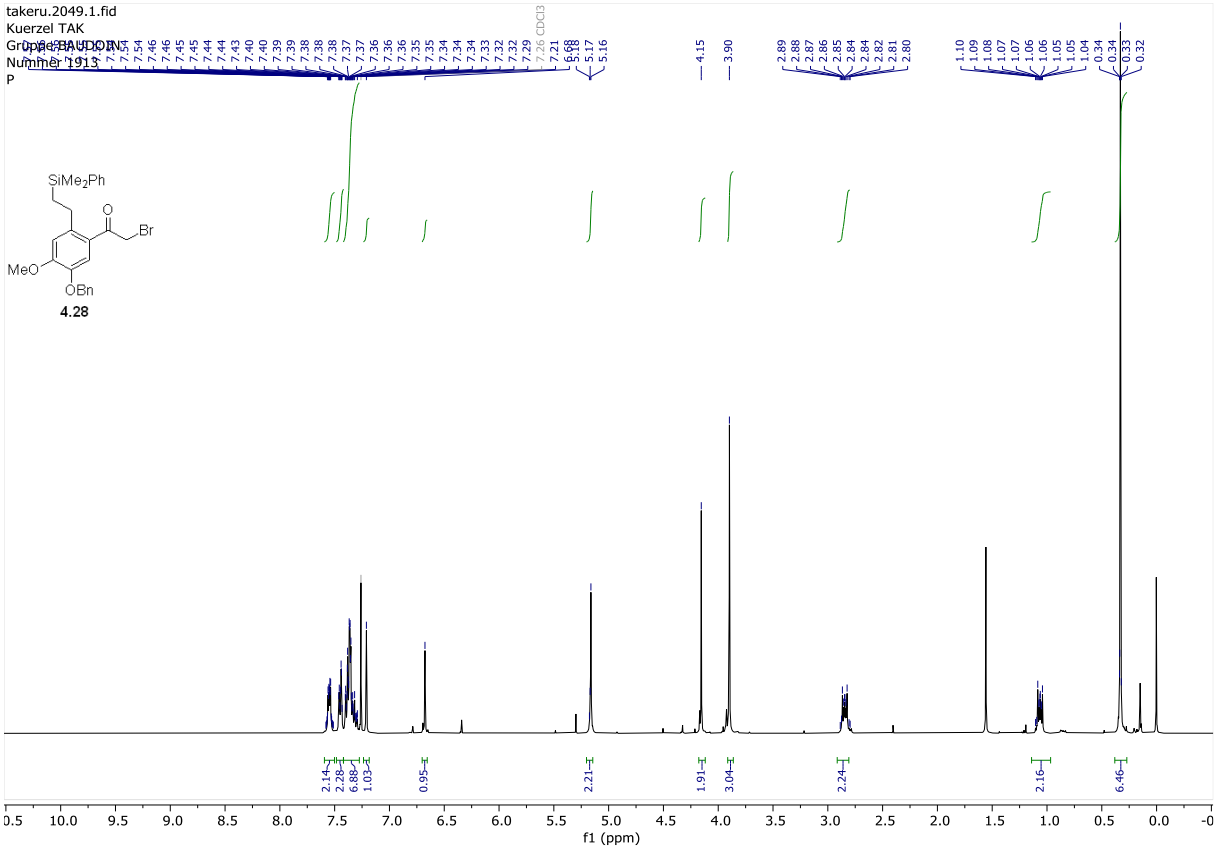
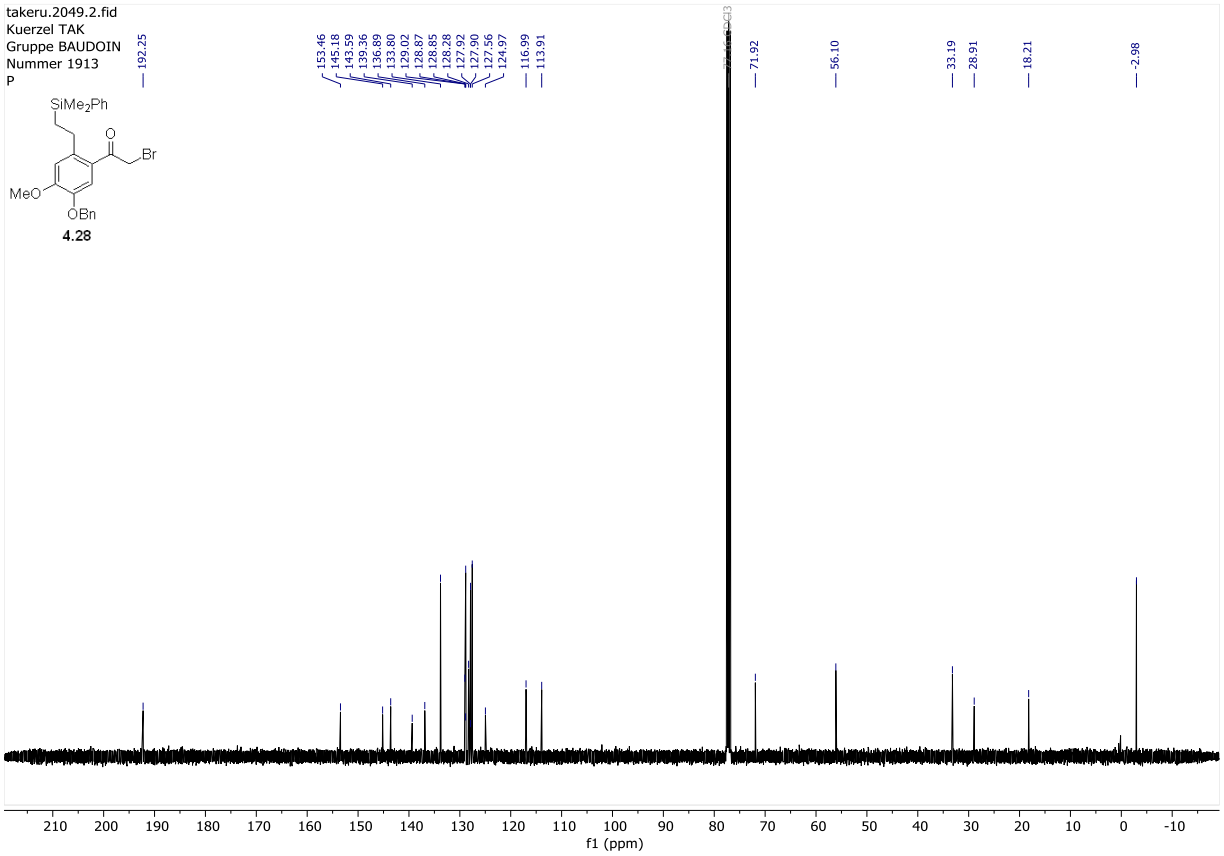
Kuerzel TAK
Gruppe BAUDOIN
Murai
4.25
f1 (ppm)


takeru.2049.1.fid
Kuerzel TAK
Gruppe BAUDOIN
Nummer 1913
P
SiMe2Ph
O
Br
MeO
OBn
4.28
f1 (ppm)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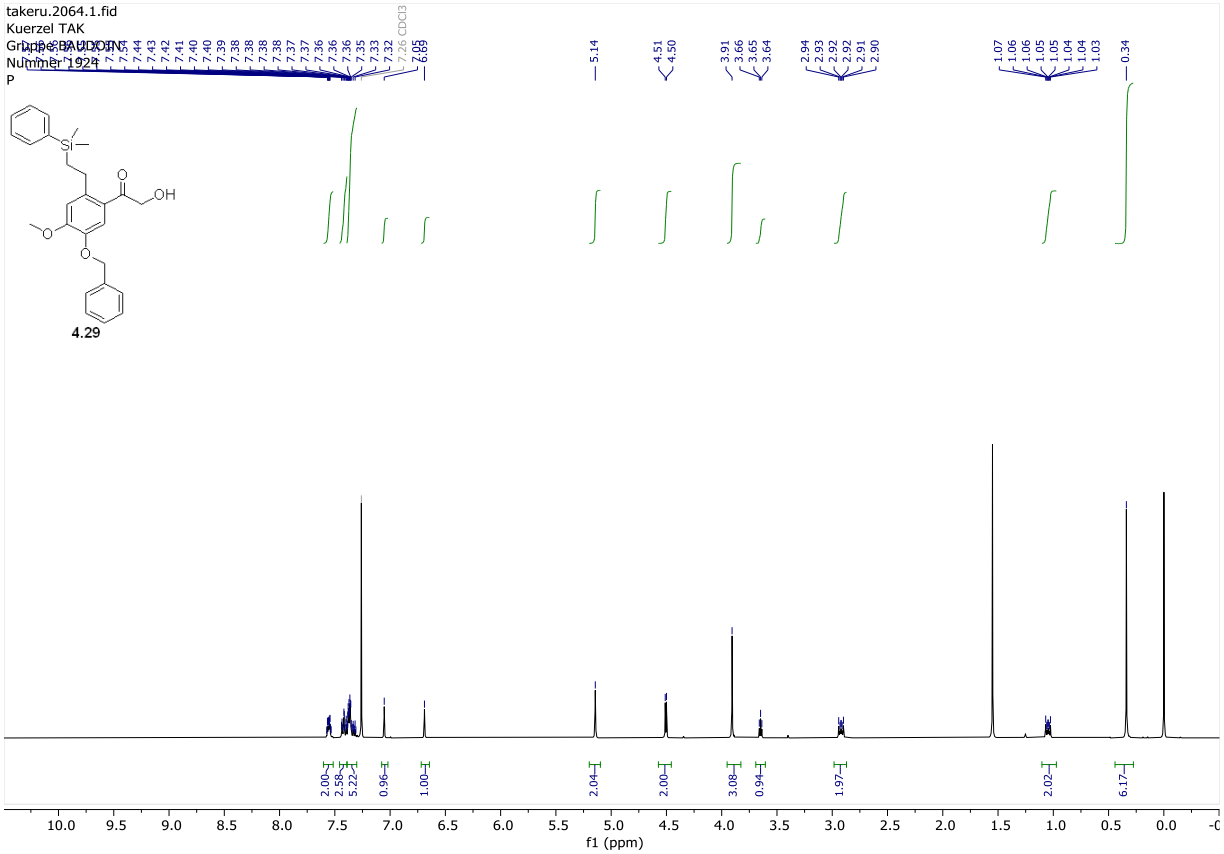
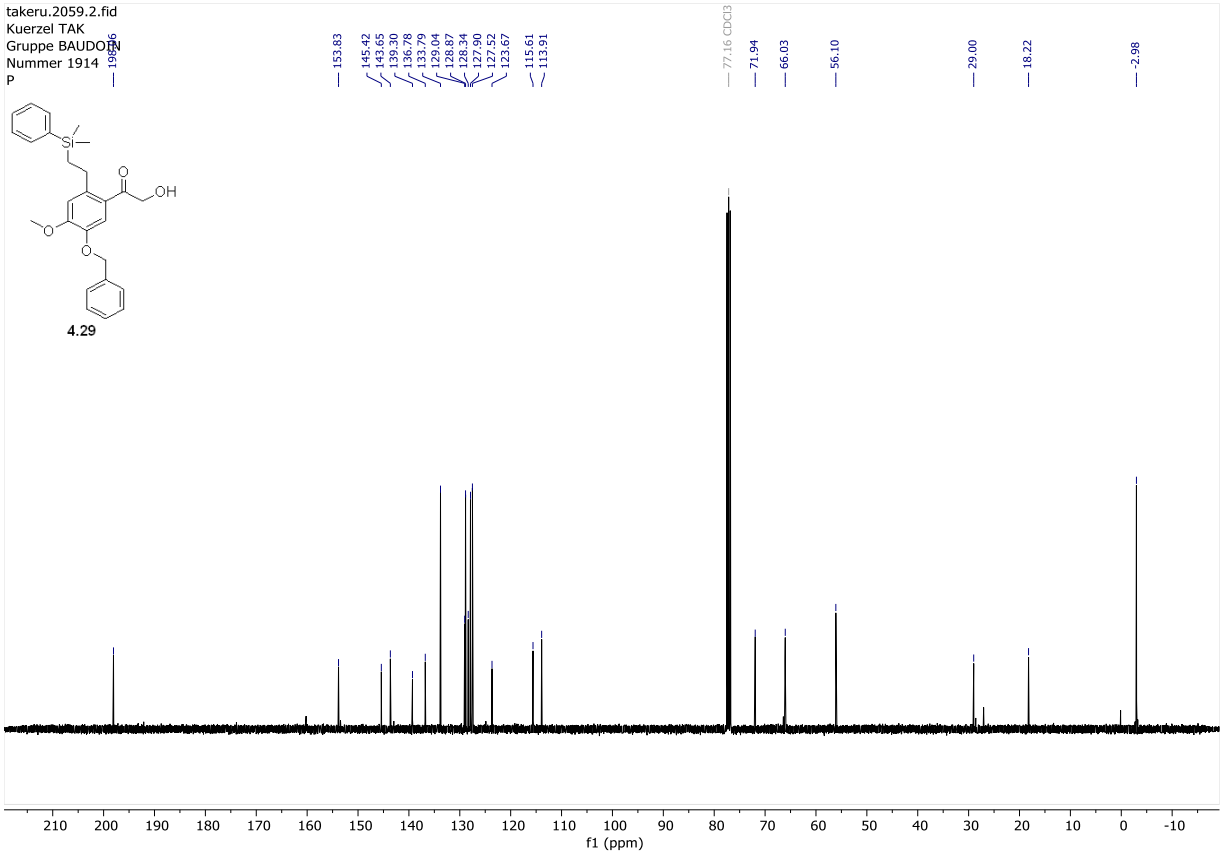
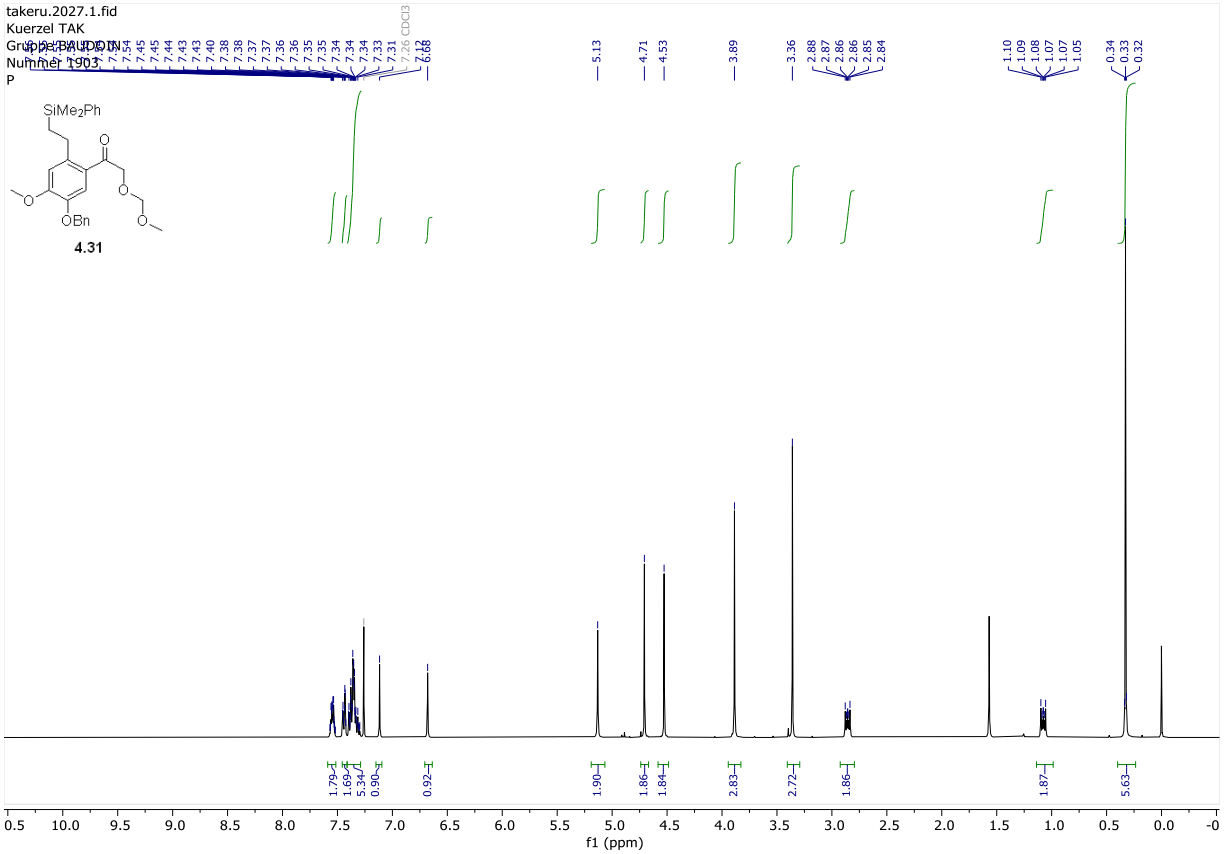
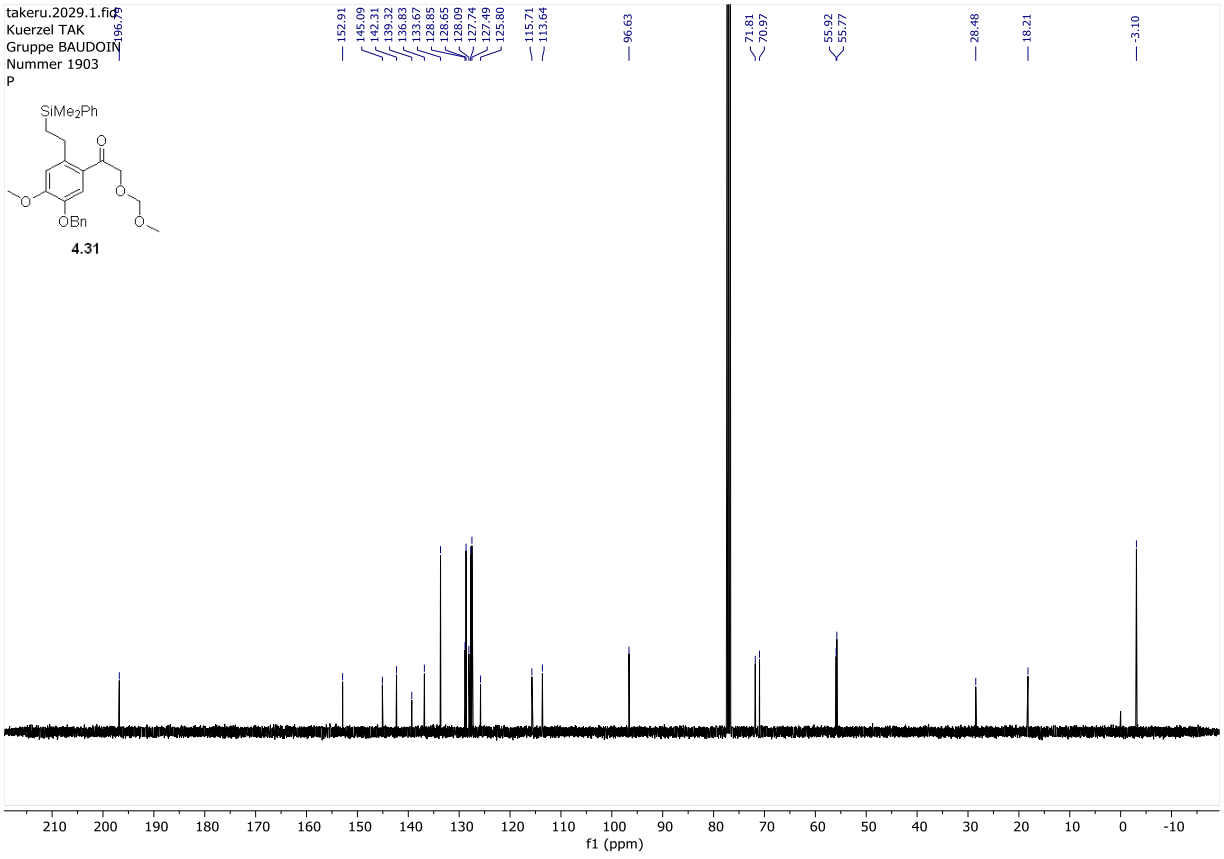
Kuerzel TAK
Gruppe BAUDOIN
Nummer 1913
P
SiMe2Ph
O
Br
MeO
OBn
4.28
f1 (ppm)


takeru.2064.1.fid
Kuerzel TAK
Gruppe BAUDOIN
Nummer 1924
P
4.29
f1 (ppm)


takeru.2059.2.fid
Kuerzel TAK
Gruppe BAUDOIN
Nummer 1914
P
4.29
f1 (ppm)


takeru.2027.1.fid
Kuerzel TAK
Gruppe BAUDOIN
Nummer 1903
P
SiMe2Ph
OBn
4.31
f1 (ppm)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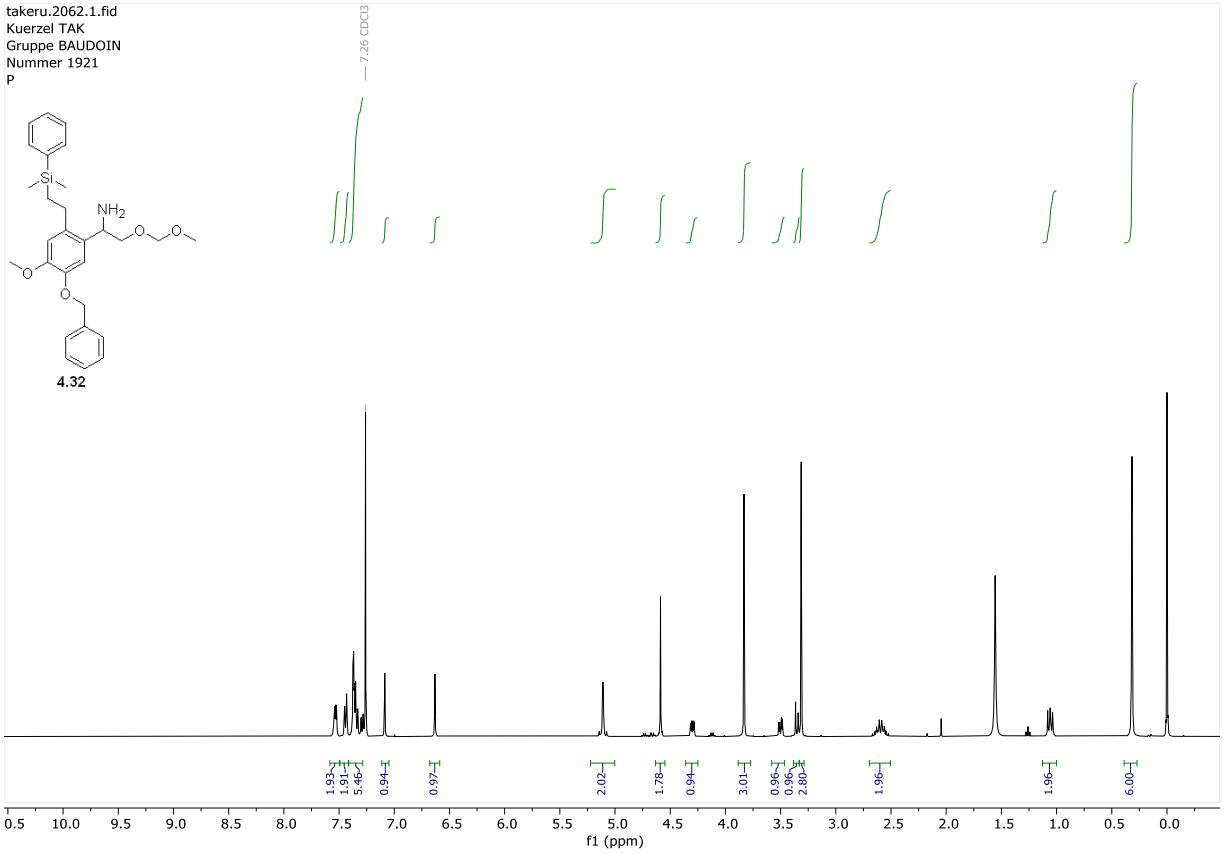
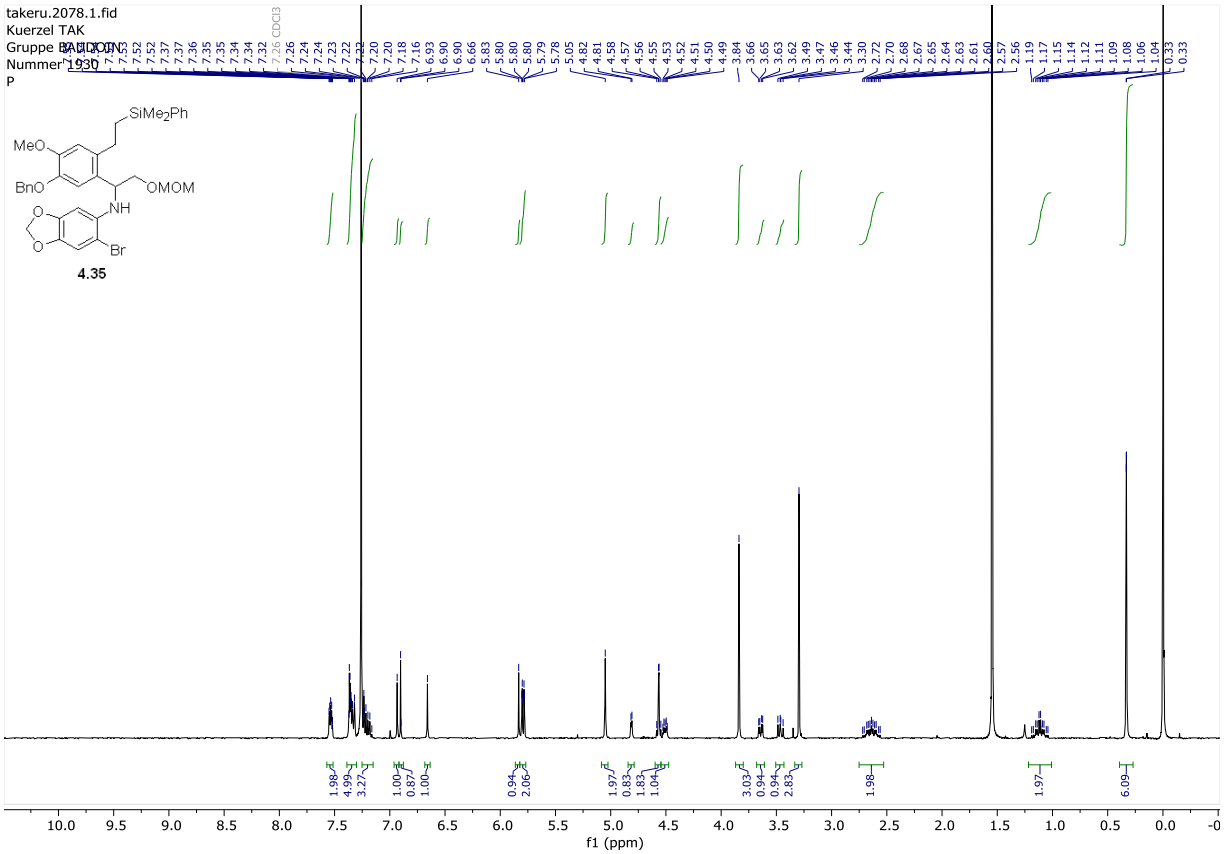
Kuerzel TAK
Gruppe BAUDOIN
Nummer 1903
P
SiMe2Ph
OBn
4.31
f1 (ppm)


takeru.2062.1.fid
Kuerzel TAK
Gruppe BAUDOIN
Nummer 1921
P
7.26 CDCl3
NH2
4.32
f1 (ppm)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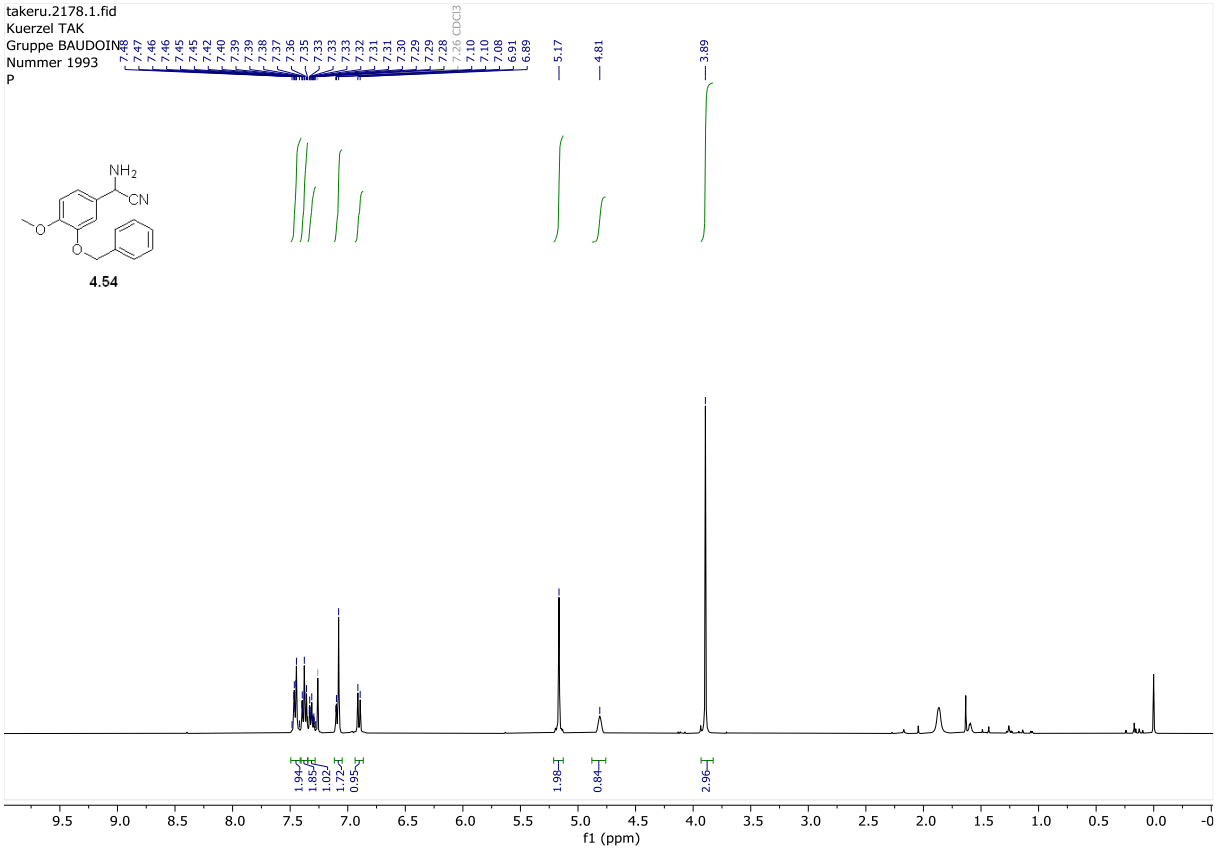
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6.89
5.17
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3.89
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CN
O
O
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1.85
1.02
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0.95
1.98
0.84
2.96
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9.0
8.5
8.0
7.5
7.0
6.5
6.0
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5.0
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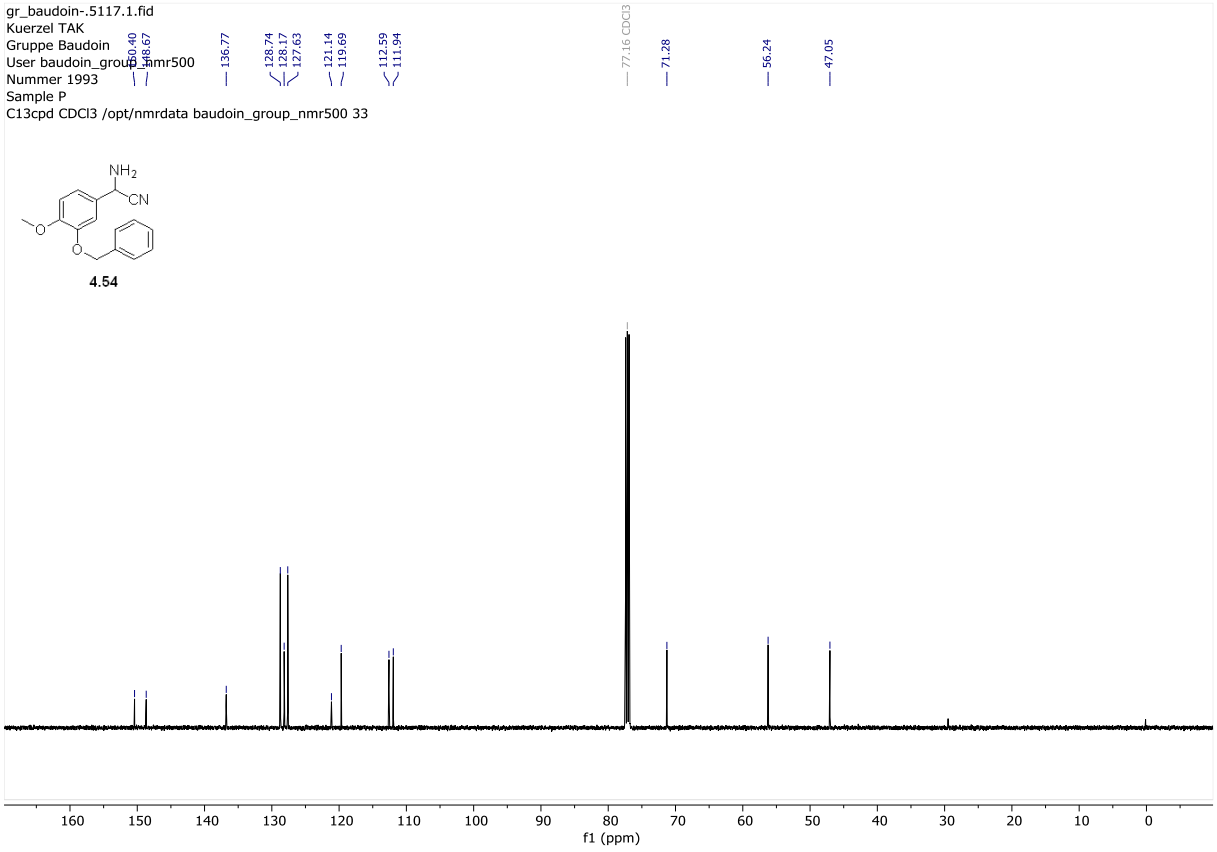
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47.05
NH2
CN
O
O
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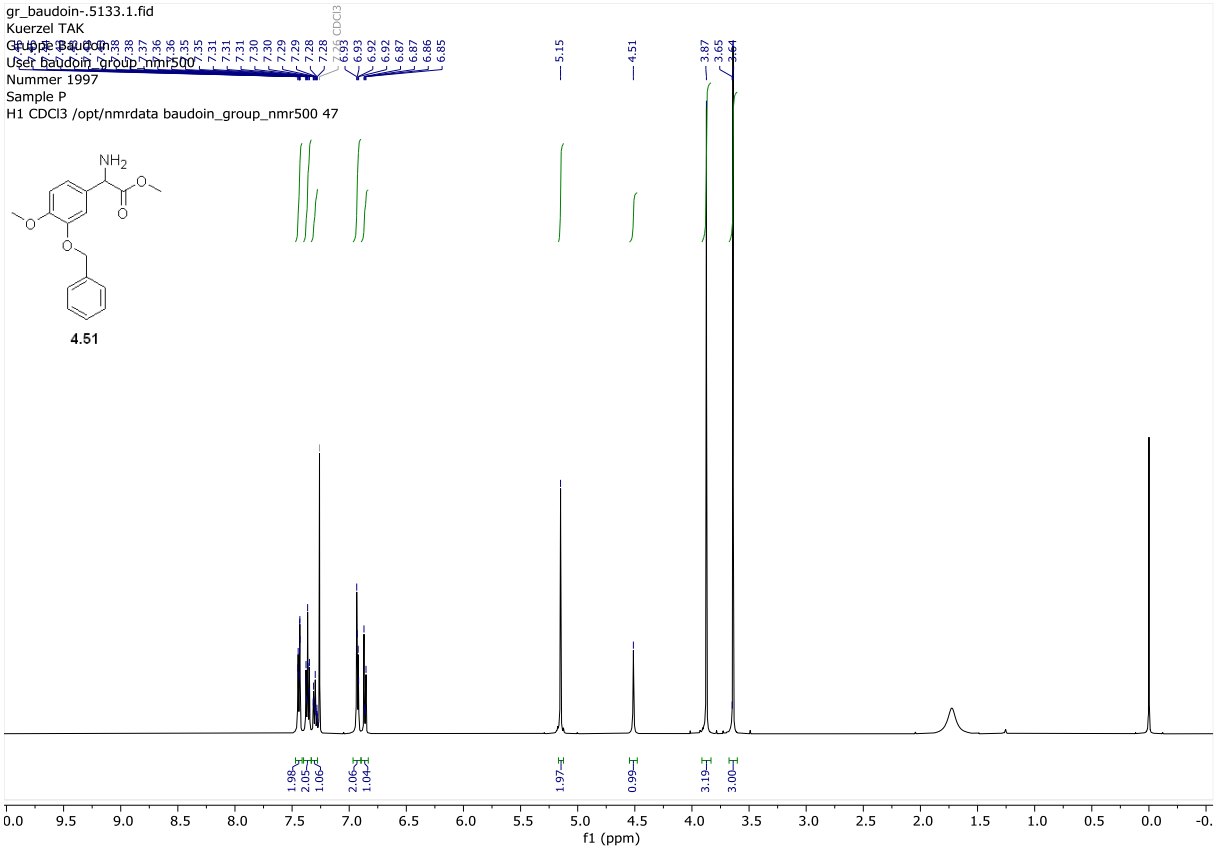
f1 (ppm)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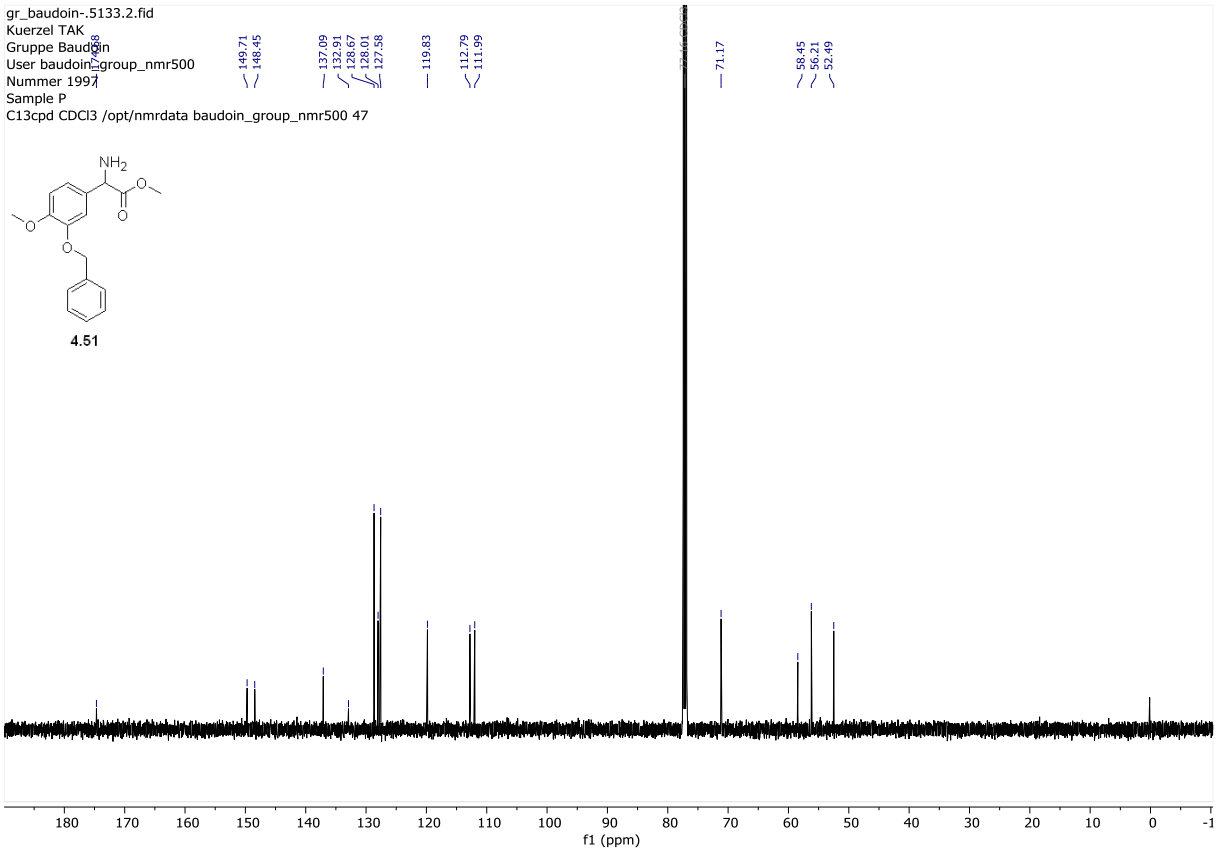
f1 (ppm)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4.51
f1 (ppm)

7.7 Synthesis of isoindolines via 1,4-Pd shift-mediated double C–H activation

7.7.1 General procedures

Synthesis of Secondary Amines *(general procedure A)* [213]

A solution of primary amine (1 equiv.), K_2CO_3 (1.5 eq.), KI (10 mol%) and alkyl bromide (1 equiv.) in CH_3CN was stirred at 60 ºC overnight. After cooling to room temperature, the reaction mixture was filtrated and evaporated *in vacuo*. The crude was purified by silica gel column chromatography using cyclohexane/ CH_2Cl_2 as a solvent to afford the desired products.

Synthesis of Secondary Amines *(general procedure B)* [214]

To an oven-dried 10 mL screw cap reaction tube was added $FeBr_2$ (5 mol%), $KHSO_4$ (1 equiv.), primary aniline derivatives (1 equiv.), benzyl alcohol derivatives (1.8 equiv.) and toluene (1 M). The reaction tube was capped, and the mixture was then heated to 120 ºC under air in a heating block for 24 h. The reaction mixture was allowed to cool, diluted with ethyl acetate, and filtered through a *Celite* pad. The crude was purified by silica gel column chromatography using cyclohexane/CH_2Cl_2 as a solvent to afford the desired products.

Synthesis of Secondary Amines *(general procedure C)*

A mixture of primary amine (1 equiv.), ketone and *p*TSA (10 mol%) in benzene (0.6 M) was refluxed overnight with the Dean-Stark apparatus. The reaction mixture was cooled to room temperature, and the solvent was evaporated *in vacuo*. The residue was dissolved in AcOH (0.3 M), and $NaBH_3CN$ (2 equiv.) was added and stirred for 2 h. The reaction was quenched with H_2O and extracted with CH_2Cl_2, and the combined organic layers were dried over sodium sulfate, filtered and evaporated under a vacuum. The crude was purified by chromatography on silica gel using cyclohexane/ CH_2Cl_2 as a solvent to afford the pure compounds.

Synthesis of Secondary Amines *(general procedure D)* [199]

A mixture of primary amine (1 equiv.), styrene oxide (3 equiv.), and silica gel (10% w/w) in toluene (0.3 M) was heated to 70º C overnight. The solvent was evaporated *in vacuo,* and the residue was purified by chromatography on silica gel using cyclohexane/AcOEt as a solvent to afford the pure compounds.

Methylation of Secondary Amines *(general procedure E)* [215]

To a solution of secondary amine (1 equiv.) in AcOH (0.3 M) was added aqueous formaldehyde solution (37 wt%, 10 equiv.) and stirred for 5 min and then $NaBH_3CN$ (2 equiv.). After the substrate completion, H_2O was added and extracted with CH_2Cl_2, dried over Na_2SO_4 anhydrous, filtered and concentrated in *vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/ CH_2Cl_2 as a solvent to afford the pure compounds.

Methylation of Secondary Amines *(general procedure F)* [216]

In a dry flask, NaH (60%, 1.2 equiv.) was weighed out, and anhydrous DMF (0.3 M) was added. The suspension thus obtained was stirred at room temperature, and the secondary amines (1 equiv.) was added. The colour of the reaction mixture immediately became deep red. This solution was stirred at rt for 30 min, and then MeI (2 equiv.) was added; the mixture was then stirred for an additional 2 h. during which time the colour changed to yellow. H_2O was added to the reaction mixture, and the resulting yellow turbid solution was stirred for 15 min. This was then extracted with Et_2O, and the organic layer was washed with H_2O. The combined organic layer was dried over sodium sulfate, and the solvent was evaporated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/ CH_2Cl_2 as a solvent to afford the pure compounds.

C–H Activation Synthesis of Isoindolines *(general procedure G)*

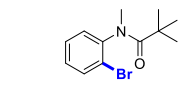
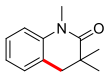
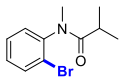
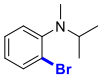
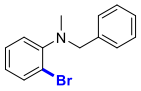
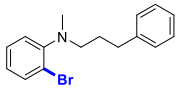
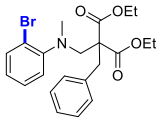
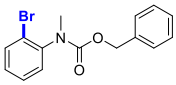
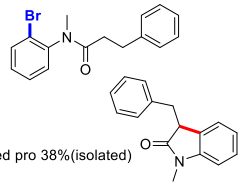
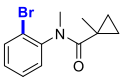
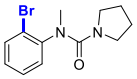
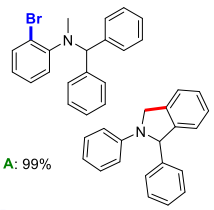
Substrate (0.2 mmol, 1 equiv.) was weighted in a 10 mL tube. $[Pd(\pi\text{-allyl})Cl)]_2$ (3.66 mg, 0.01 mmol, 5 mol%), IMes·Cl (6.82 mg, 0.02 mmol, 10 mol%), Cs_2CO_3 (97.7 mg, 0.3 mmol, 1.5 equiv.) and CsOPiv (14 mg, 0.06 mmol, 30 mol%) were weighted in a glovebox. The tube was closed with a septum, taken out of the glovebox, and *m*-xylene (3 mL, 0.067 M) was added. The reaction was stirred in a heating block preheated at 110 °C for 15 h. The reaction was cooled to room temperature, filtered through a pad of *Celite*, washed with EtOAc and concentrated *in vacuo*. The crude mixture was analyzed by ^1H NMR (using trichloroethylene as an internal standard) and purified by chromatography on silica gel or preparative thin-layer chromatography, providing the desired product.

Gram Scale Isoindoline Synthesis

A 100 mL pressure flask was charged with the corresponding amine (1.0 equiv.) and stirring bar. The flask was introduced into a glovebox and charged subsequently with Cs_2CO_3 (1.5 equiv.), CsOPiv (30 mol%), $[Pd(\pi\text{-allyl})Cl]_2$ (5 mol%), and IMes·Cl (10 mol%). Dried and degassed *m*-xylene (0.067 M) was added before the flask was sealed with the corresponding stopper and taken out of the glovebox. The content was stirred at rt for 5 min before it was inserted into a preheated oil bath at 110 °C. The reaction was stirred at this temperature for 15 h before it was allowed to cool down to rt and filtered through a pad of *Celite* (eluted with EtOAc). The filtrate was concentrated under reduced pressure. The crude was purified by silica gel column chromatography to afford the corresponding isoindoline.

7.7.2 Optimisation tables for the synthesis of isoindolines

Table S1. Preliminary substrates optimisation[a]

 **A:** SM 53%, DeBr 30%[b] **C**: 69%(Isolated) 	 **A**: SM 24%(NMR), DeBr 30%(NMR)[b]	 **A**: DeMe 75% (Isolated) **B**: DeMe 41-65%, DeBr 12-25% **C**:DeMe	 **A**: SM 7%, DeMe 8% **B**: DeMe 30-39%, DeBr 9-11% **C**:DeMe 41%, DeBr 5%
 **A**: DeMe 71% **B**: DeMe 48-60%, DeBr 16-27% **C**:DeMe 35%, DeBr 18%	 **A**: SM 69 (isolated), DeBr-mono-hydrolysis 18% (isolated) **B**: DeMe 9-14%, DeBr-mono-hydrolysis 27% SM 72%(with PPh_3) **C**:DeMe 31%(isolated), DeBr-mono-hydrolysis 23%(isolated)	 **A**: DeBr 64% **B**: DeBr 65-71%, Me-aniline 21-29% **C**: SM 44%, DeBr 27%
 **A**: α-activated pro 38%(isolated) **B**: α-activated pro 3-42%, SM 34-50%, DeX 20-23% **C**: α-activated pro 34%, SM 15%	 **A**: DeMe 8%, DeBr 9%, cyclopropane activated pro 9% (isolated) **B**:cyclopropane activated pro 80-96% **C**: cyclopropane activated 84%	 **A**: N.R. **B**:DeBr 11-12%, DeMe 19%, SM 52% **C**: DeMe 8%, DeBr 92%	 **A**: 99% **B**: DeMe 11-30%, DeBr 2-9%, Csp^2-H 61% (Isolated) **C**: DeMe 18%, DeBr 9%, Csp^2-H 43%(isolated)

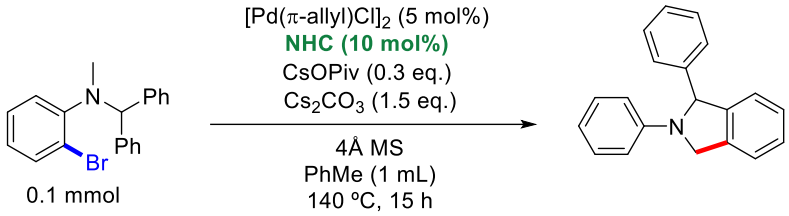
[a] ^{1}H NMR yield with trichloroethylene as internal standard unless mentioned [b] Employed NMP as solvent at 160ºC

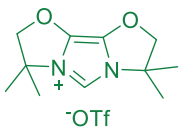
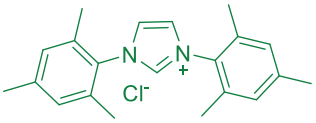
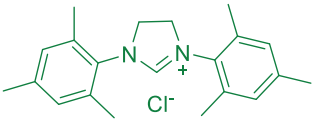
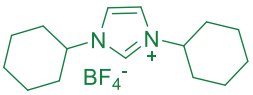
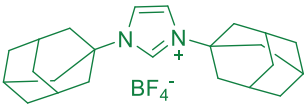
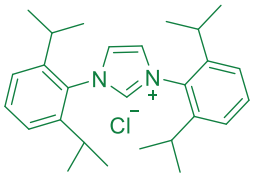
Condition A[207][91]: Aryl bromide (0.1 mmol), $[Pd(\pi\text{-allyl})Cl]_2$ (5 mol%), $IBioxMe_4$ (10 mol%), CsOPiv (30 mol%), Cs_2CO_3 (1.5 equiv.), 4Å MS, Toluene (1 mL), 140ºC

Condition B[154,155]: Aryl bromide (0.1 mmol), $Pd_2dba_3{\cdot}CHCl_3$ (5 mol%), PCy_3 or PPh_3 (10 mol%), CsOPiv (30 mol%), Cs_2CO_3 (1.5 equiv.), 4Å MS, Toluene (1 mL), 140ºC

Condition C[157]: Aryl bromide (0.1 mmol), $Pd(PPh_3)_4$ (10 mol%), KOPiv (2 equiv.), Toluene/DMSO (95:5, 2 mL), 140ºC

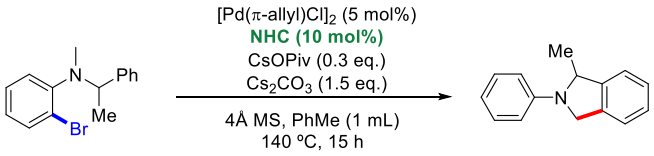
Table S2. Preliminary NHCs screening[a,b,c]

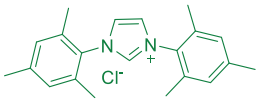


			
> 99%	> 99%	>99%	> 99%
			
> 99%	>99%	P 73%(NMR) DeMe 26%(NMR)	

[a] Reaction performed in 0.1 mmol scale [b] ^{1}H NMR yield unless mentioned
[c] trichloroethylene employed as internal standard

Table S3. NHCs Screening[a,b,c]





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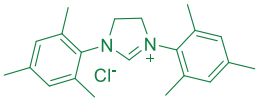
DeMe 17%



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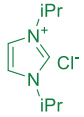
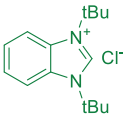
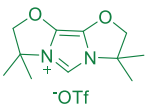
DeM 21%



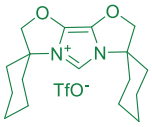
P 15%
DeMe 82%
DeBr 3%



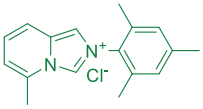
P 4%
SM 79%
DeMe 3%
DeBr 14%



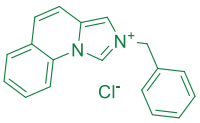
P 68%
DeMe 32%



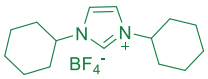
P 76%
DeMe 24%



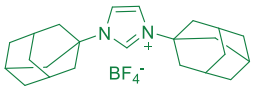
P 16%
SM 50%
DeMe 21%
DeBr 13%



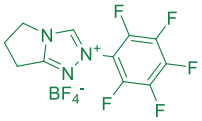
P 3%
SM 73%
DeMe 9%
DeBr 8%



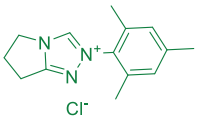
P 14%
DeMe 75%
DeBr 6%
SM 5%



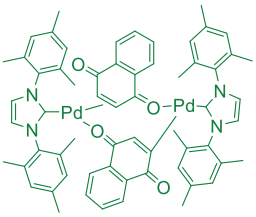
P 58%
SM 33%
DeMe 9%



P 0%
SM 80%
DeMe 20%
DeBr 4%



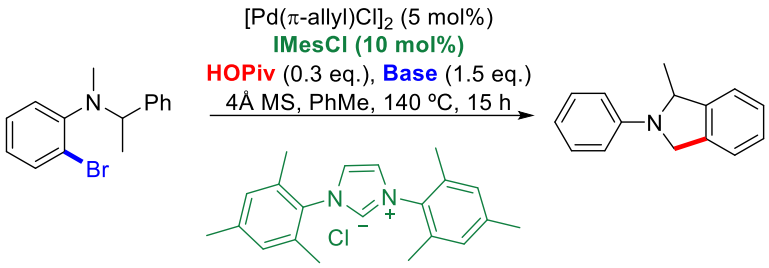
P 8%
SM 45%
DeMe 35%
DeBr 3%



P 10%
DeMe 81%
DeBr 9%

[a] Reaction performed in 0.1 mmol scale [b] ^{1}H NMR yield unless mentioned [c] trichloroethylene employed as internal standard

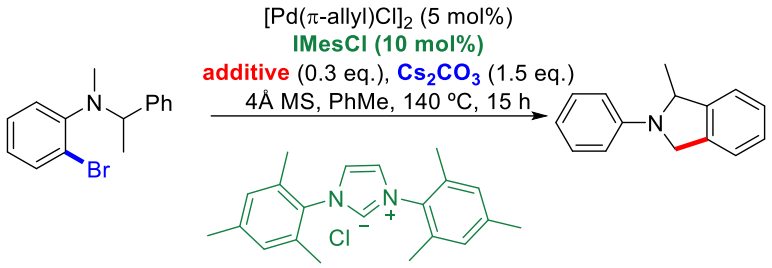
Table S4. External Bases Screening[a,b,c]



Base	Product	Demethylation	SM
Cs_2CO_3 with CsOPiv	**83**	**17**	-
Cs_2CO_3	77	23	-
Rb_2CO_3	72	28	-
K_2CO_3	68	36	-
Na_2CO_3	40	60	-
$PbCO_3$	-	16	84
$CaCO_3$	-	-	100
Guanidine carbonate	11	11	78

[a] Reaction performed in 0.1 mmol scale [b] ^{1}H NMR yield unless mentioned [c] trichloroethylene employed as internal standard.

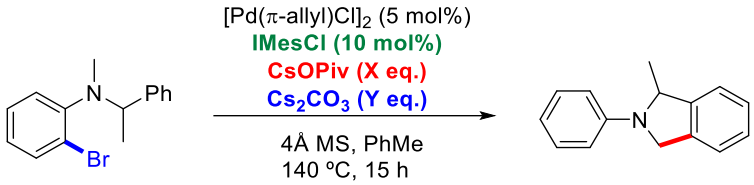
Table S5. Additives Screening[a,b,c]



Additive	Product	DeMe	DeX	SM
CsOPiv	**82**	**17**	**1**	
AcOH	78	16	6	-
CsOAc	73	8	19	-
TFA	7	58	6	-
$AdCO_2H$	73	27	-	-
Cesium decanoate	68	32	-	-
$(CH_2Cy)_3CCO_2H$	-	35	-	54
benzoic acid	40	60	-	-
2,2-diphenylpropionic acid	36	64	-	-
2,4,6-trimethylbenzoic acid	15	85	-	-
xanthene-9-carboxylic acid	24	69	6	-
2,4,6-trichlorobenzoic acid	54	46	-	-

[a] Reaction performed in 0.1 mmol scale [b] ^1H NMR yield unless mentioned [c] trichloroethylene employed as internal standard.

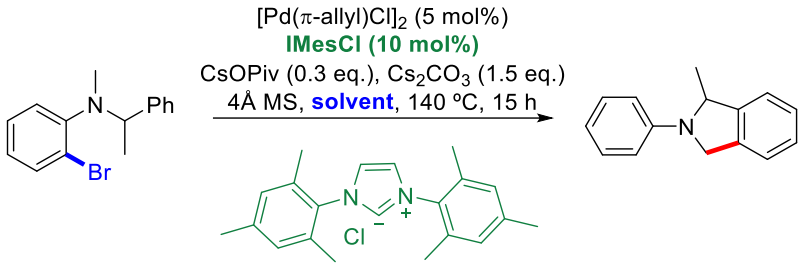
Table S6. Amount of Base and Additive[a,b,c]



CsOPiv(X eq.)	Cs_2CO_3(Y eq.)	Product	DeMe	DeBr	SM
0.3	**1.5**	**82**	**17**	**1**	**-**
1.5	-	4	90	-	-
-	1.5	33	13	<30	-
0.3	0.5	31	55	5	6
0.3	3	77	21	2	-
1.5	1.5	71	19	2	-

[a] Reaction performed in 0.1 mmol scales. [b] ^{1}H NMR yield unless mentioned. [c] trichloroethylene employed as internal standard.

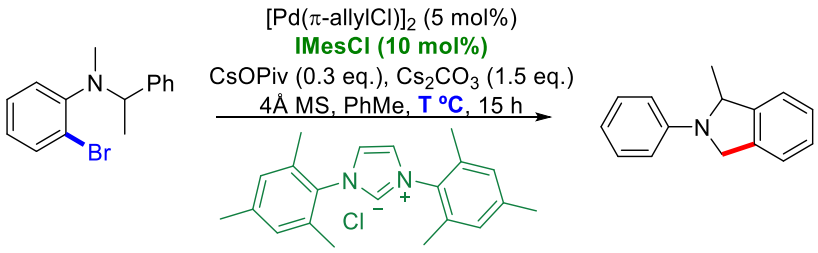
Table S7. Solvent Screening[a,b,c]



Solvent	Product	DeMe	DeX	SM
toluene	82	17	1	-
o-xylene	65	30	5	-
***m*-xylene**	**85**	**14**	**1**	**-**
p-xylene	78	19	3	-
mesitylene	67	27	6	-
CF_3Ph	71	26	3	-
PhMe/DMSO	61	39	1	-
CH_3CN	11	79	6	-
DMA	29	49	7	-
DMF	12	39	8	12
DME	78	17	5	-
1,4-dioxane	81	15	4	-
CPME	83	14	3	-
MeTHF	79	13	8	-
dibutyl ether	70	18	12	-
4-methyl anisole	62	32	6	-

[a] Reaction performed in 0.1 mmol scale [b] ^{1}H NMR yield unless mentioned [c] trichloroethylene employed as internal standard.

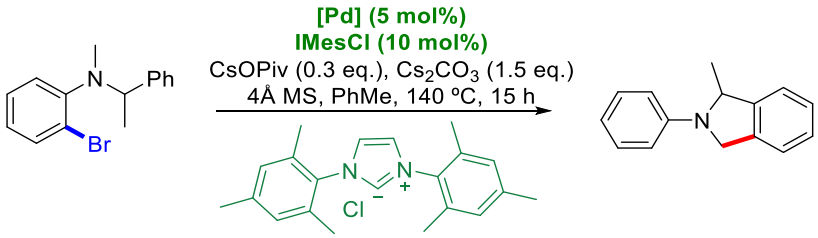
Table S8. Reaction Temperature Screening[a,b,c]



Temp.	Product	DeMe	DeBr	SM
160	74	24	2	-
140	82	17	1	-
130	74	23	3	-
120	84	13	3	-
110	**85**	**13**	**2**	**-**
105	75	9	3	13
100	40	-	-	60

[a] Reaction performed in 0.1 mmol scale [b] ^{1}H NMR yield unless mentioned [c] trichloroethylene employed as internal standard.

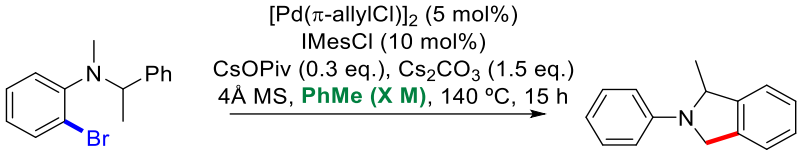
Table S9. Palladium Sources Screening[a,b,c]



[Pd]	Product	DeMe	DeBr	direct C(sp^2)-H
[Pd(π-allyl)Cl]$_2$ (homemade)	**82**	**17**	**1**	**-**
[Pd(π-allyl)Cl]$_2$ (commercial)	79	19	2	-
[Pd(π-cinn)Cl]$_2$ (commercial)	71	27	2	-
Pd_2·dba$_3$·$CHCl_3$	56	13	16	12
[Pd(π-indene)Cl]$_2$	73	16	6	4
[Pd(π-1-*t*Bu-indene)Cl]$_2$	<63	29	5	3
$Pd(OAc)_2$	<65	22	6	7
$PdCl_2$	<69	19	4	8

[a] Reaction performed in 0.1 mmol scale [b] ^{1}H NMR yield unless mentioned [c] trichloroethylene employed as internal standard

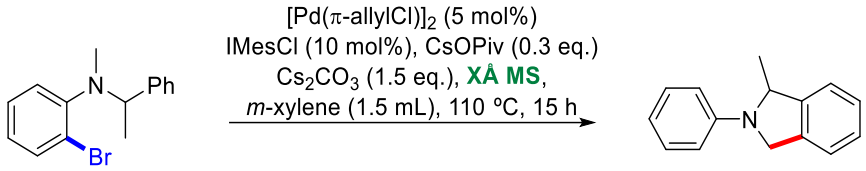
Table S10. Concentration Screening[a,b,c]



X (mol/L)	Product	DeMe	DeBr
0.05	80	18	2
0.067	**83**	**15**	**2**
0.1	82	17	1
0.134	80	18	2
0.2	80	19	1

[a] Reaction performed in 0.1 mmol scale [b] ^{1}H NMR yield unless mentioned [c] trichloroethylene employed as internal standard.

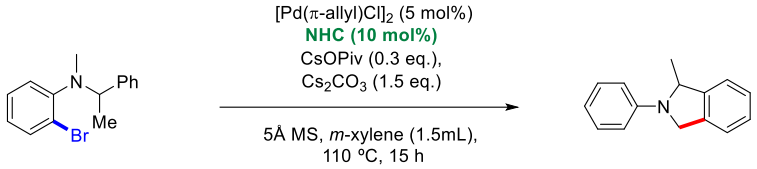
Table S11. Molecular Sieves Screening[a,b,c]

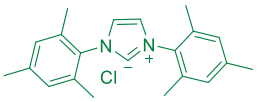
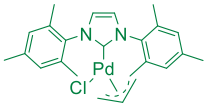
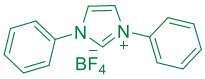
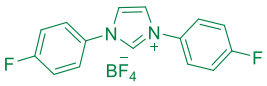
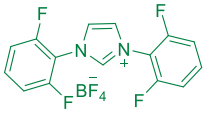
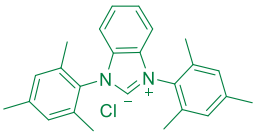
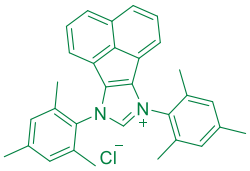


XÅ MS	Product	DeMe	DeBr
none	93	3	4
3	91	7	2
4	90	9	1
5	**94 [78]**[d]	**5**	**1**

[a] Reaction performed in 0.1 mmol scale [b] ^{1}H NMR yield unless mentioned [c] trichloroethylene employed as internal standard. [d] Isolated yield.

Table S12. Final NHCs Screening[a,b,c]

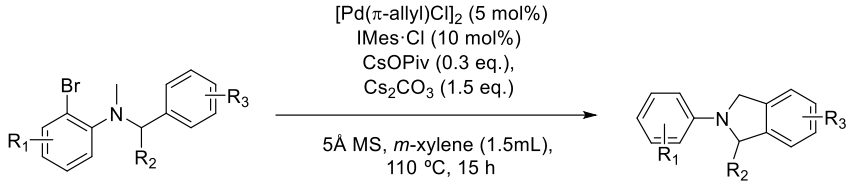


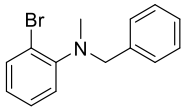
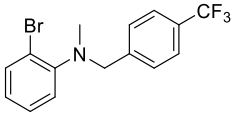
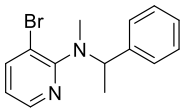
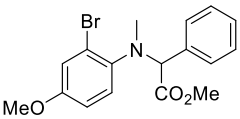
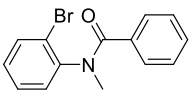
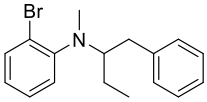
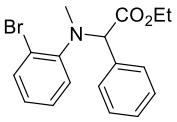
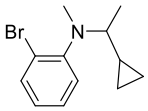
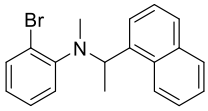
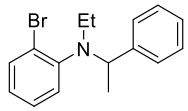
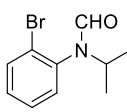
		
P 94% [78%][d] **DeMe 5%** **DeBr 1%**	P 91% DeMe 6% DeBr 3%	P 2% DeMe trace DeBr trace SM 98%
			
P 0% DeMe 3% DeBr trace SM 91%	P 0 % DeMe 0% DeBr 0 % SM 97%	P 71% DeMe 8% DeBr 4%	P 80% DeMe 9% DeBr 4%

[a] Reaction performed in 0.1 mmol scale [b] ^{1}H NMR yield unless mentioned [c] trichloroethylene employed as internal standard [d] Isolated yield

7.7.3 Other examples of isoindolines

Table S23. Synthesis of Isoindolines[a,b,c]

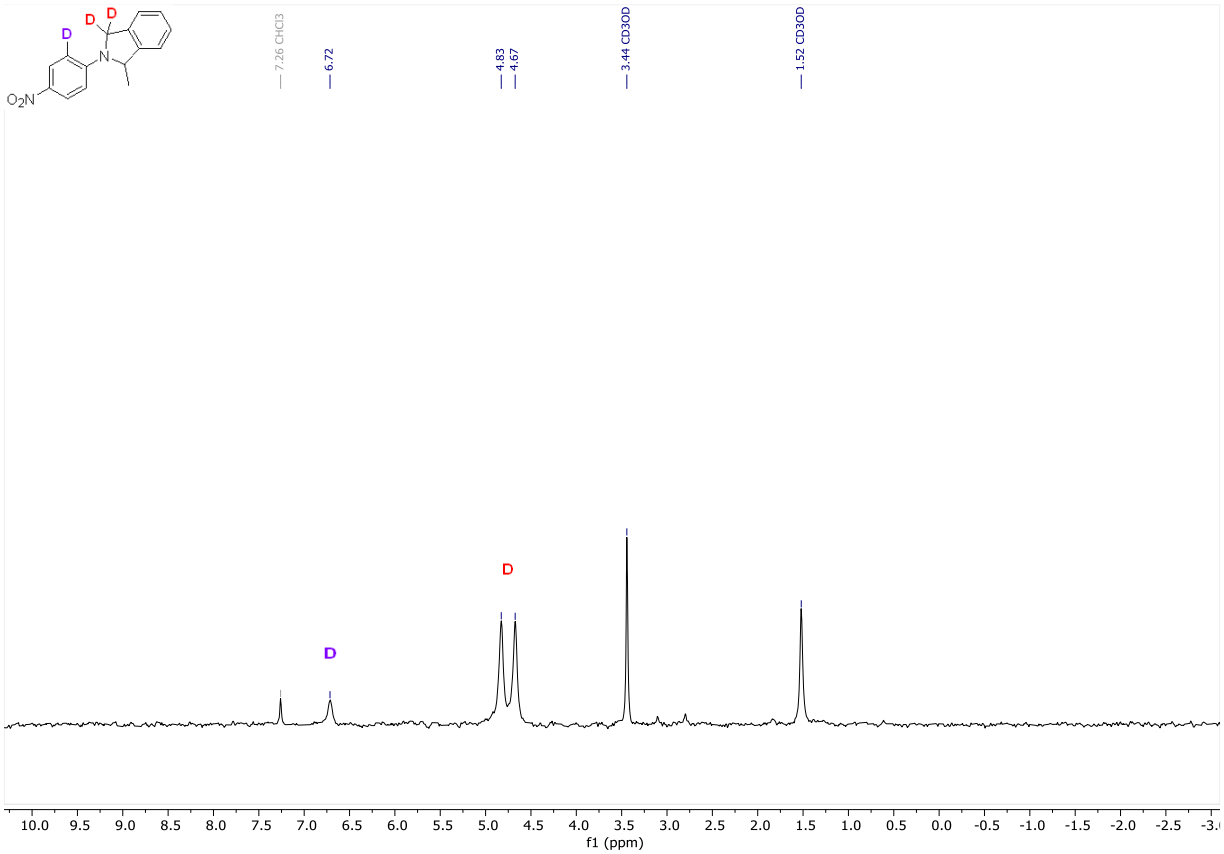


			
DeMe	P 10%, 71% DeMe[d]	N.R.	P 21% with SM, DeMe, DeBr, unknowns
			
P 15%, Csp2-H 85%	17%[d]	P 14%, DeMe 30%[d]	DeMe 89%[d]
			
P 35%, DeMe 45% P 14% DeMe 61%[d]	SM14%, 39% DeBr, <45% DeEt[d]	9%[e]	

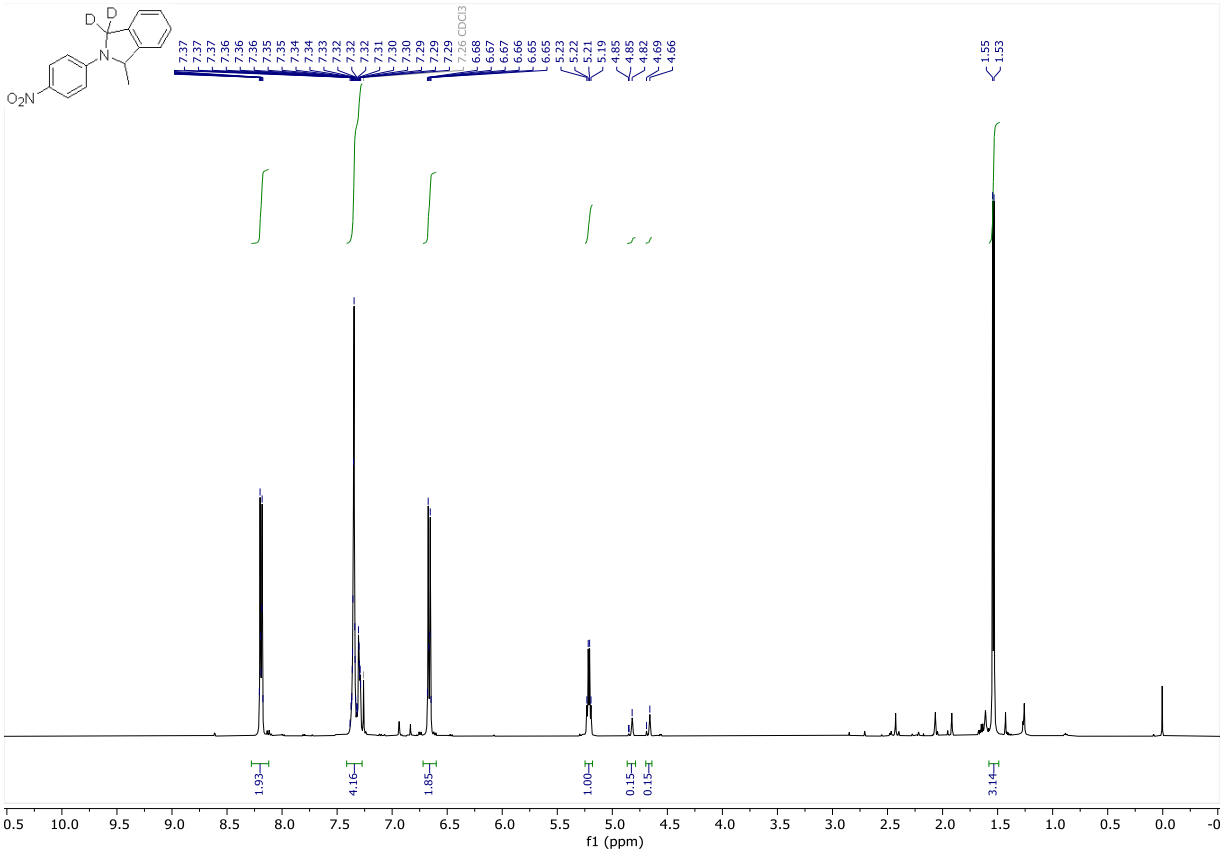
[a] Reaction performed in 0.1 mmol scale [b] ^{1}H NMR yield unless mentioned [c] trichloroethylene employed as internal standard
[d] Reaction performed at 140 °C [e] Isolated yield

7.7.4 NMR Studies with deuterium-labelled substrates

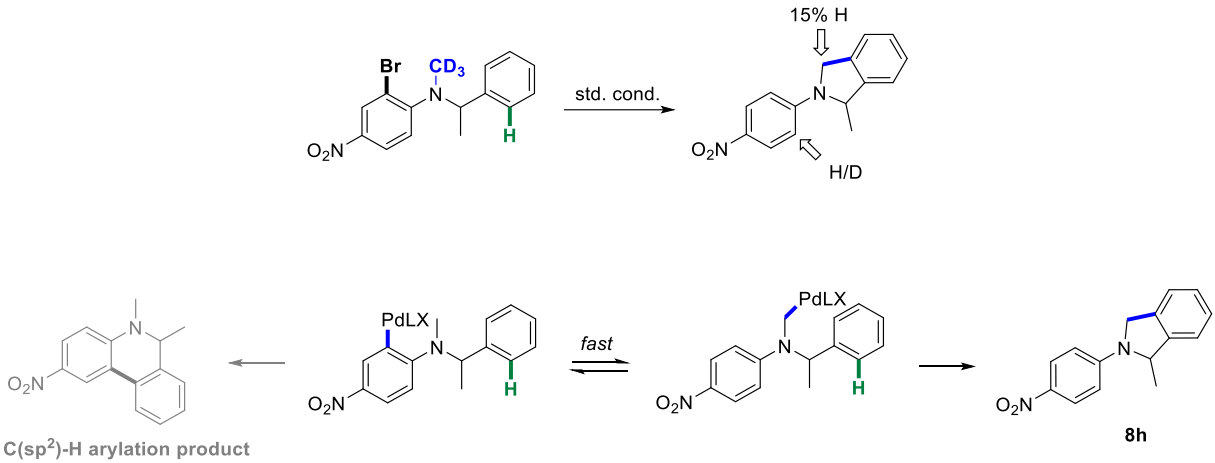
^{2}H NMR (92 MHz, Chloroform-*H*) with CD3OD as residual solvent



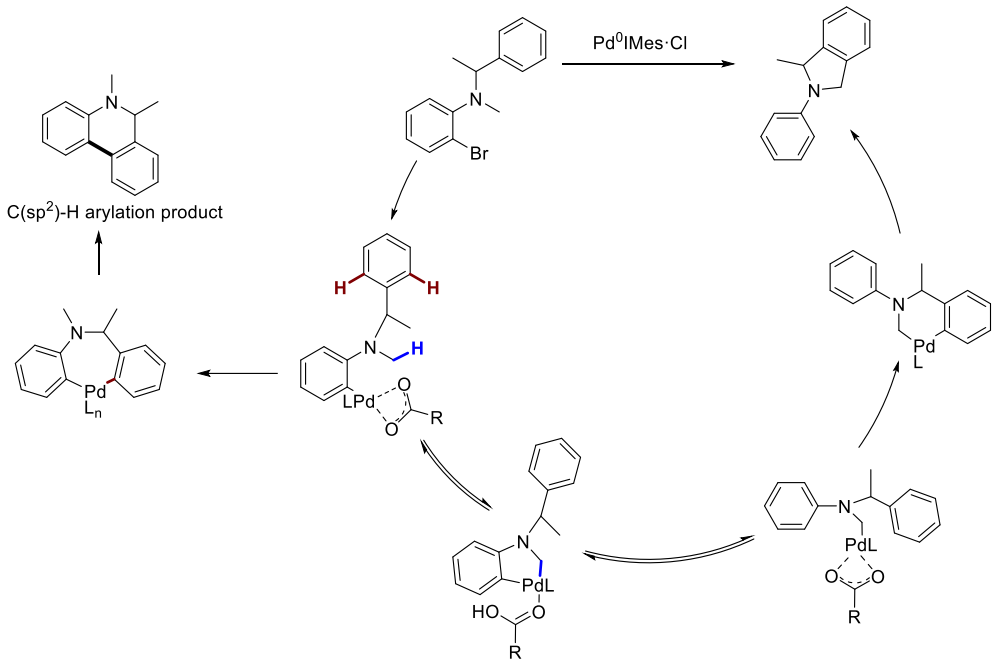
^{1}H NMR (500 MHz, Chloroform-*d)*



Experiments with Deuterium-Labelled Substrates



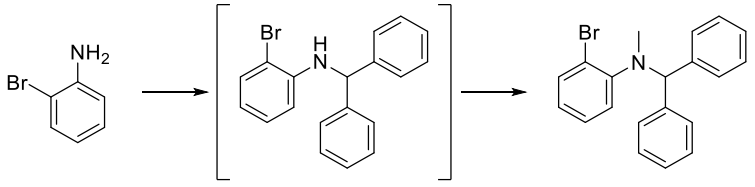
Scheme S1. Deuterium Experiments



Scheme S2. Proposed mechanism

7.7.5 Synthesis of isoindolines: synthesis of substsrates

***N*-benzhydryl-2-bromo-*N*-methylaniline (5.15a):**



5.15a
Chemical Formula: $C_{20}H_{18}BrN$
Molecular Weight: 352.28

Following general procedure A, a solution of 2-bromoaniline (860 mg, 5 mmol, 1 equiv.), K_2CO_3 (1.04 g, 7.5 mmol, 1.5 equiv.), KI (83 mg, 0.5 mmol, 10 mol%) and bromodiphenylmethane (1.24 g, 5 mmol, 1 equiv.) in CH_3CN was stirred at 60 ºC overnight. After cooling to room temperature, the reaction mixture was filtrated and evaporated *in vacuo*. The crude was purified by silica gel column chromatography using cyclohexane/ CH_2Cl_2 (98:2, Rf= 0.25) as a solvent to afford the desired product *N*-benzhydryl-2-bromoaniline as a yellow solid (1.37 g, 4.05 mmol, 81%).

Following general procedure E, to a solution of *N*-benzhydryl-2-bromoaniline (1 g, 2.96 mmol, 1 equiv.) in AcOH (9 mL, 0.3 M) was added aqueous formaldehyde solution (37wt%, 2.2 mL, 29.6 mmol, 10 equiv.) and stirred for 5 min and then $NaBH_3CN$ (744 mg, 11.8 mmol, 4 equiv.). After 2 h, H_2O was added and extracted with CH_2Cl_2, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/CH_2Cl_2 as solvent to afford the pure compound *N*-benzhydryl-2-bromo-*N*-methylaniline as a colourless oil (740 mg, 2.96 mmol, 71%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.56 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.44 – 7.38 (m, 4H), 7.24 (“t”, *J* = 7.6 Hz, 4H), 7.20 – 7.13 (m, 2H), 7.06 (“t”d, *J* = 7.7, 1.5 Hz, 1H), 6.88 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.84 (“t”d, *J* = 7.6, 1.6 Hz, 1H), 5.48 (s, 1H), 2.55 (s, 3H).

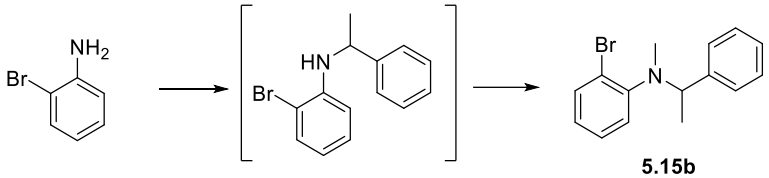
^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 150.5, 141.7, 133.6, 128.4, 128.3, 127.7, 127.0, 125.1, 125.0, 122.3, 72.4, 40.3.

HRMS (ESI): Calcd for $C_{20}H_{18}BrNNa$ $[M+Na]^+$: 374.0515, found: 374.0511.

IR (neat): ν (cm^{-1}) 3060, 1585, 1474, 1027.

Rf 0.32 (Cyclohexane:CH_2Cl_2 = 98:2)

2-bromo-*N*-methyl-*N*-(1-phenylethyl)aniline (5.15b):



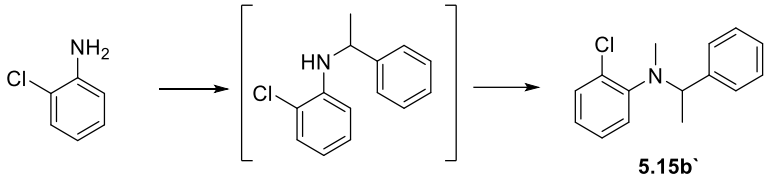
5.15b
Chemical Formula: $C_{15}H_{16}BrN$
Molecular Weight: 290.20

Following general procedure A, 2-bromoaniline (1.72 g, 10 mmol, 1 equiv.) was reacted with K_2CO_3 (1.66 g, 12 mmol, 1.2 equiv.), KI (166 mg, 1 mmol, 10 mol%) and α-methylbenzyl bromide (1.63 mL, 12 mmol, 1.2 equiv.). The crude was purified by chromatography on silica gel using cyclohexane/CH_2Cl_2 (94:6, Rf= 0.23) as a solvent to afford the desired product 2-bromo-*N*-(1-phenylethyl)aniline as a yellow oil (1.72g, 6.23 mmol, 62 %).

Following general procedure E, to a solution of 2-bromo-*N*-(1-phenylethyl)aniline (1.03 g, 3.73 mmol, 1 equiv.) in AcOH (12 mL, 0.3 M) was added aqueous formaldehyde solution (37 wt%, 1.03 mL, 37.3 mmol, 10 equiv.) and stirred for 5 min and then $NaBH_3CN$ (703 mg, 11.2 mmol, 3 equiv.). After 2 h, H_2O was added and extracted with CH_2Cl_2, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/CH_2Cl_2 as solvent to afford the pure compound 2-bromo-*N*-methyl-*N*-(1-phenylethyl)aniline as a colourless oil (1.04 g, 3.58 mmol, 96%).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.61 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.42 – 7.36 (m, 2H), 7.35 – 7.28 (m, 2H), 7.27 – 7.19 (m, 2H), 7.00 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.93 (ddd, *J* = 7.9, 7.2, 1.6 Hz, 1H), 4.57 (q, *J* = 6.8 Hz, 1H), 2.50 (s, 3H), 1.42 (d, *J* = 6.8 Hz, 3H).
^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 150.8, 142.4, 133.9, 128.2, 127.9, 127.8, 127.0, 124.7, 124.7, 121.8, 61.4, 36.5, 17.7.
HRMS (ESI): Calcd for $C_{15}H_{17}BrN$ $[M+H]^+$: 290.0539, found: 290.0537.
IR (neat): ν (cm^{-1}) 3058, 2976, 1581, 1472, 1026.
Rf 0.38 (Cyclohexane:CH_2Cl_2 = 94:6)

2-chloro-*N*-methyl-*N*-(1-phenylethyl)aniline (5.15b'):



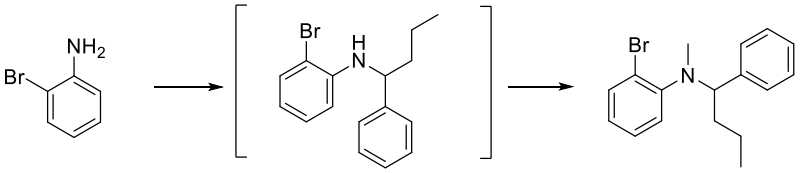
5.15b`
Chemical Formula: $C_{15}H_{16}ClN$
Molecular Weight: 245.75

Following general procedure A, 2-chloroaniline (1.28 g, 10 mmol, 1 equiv.) was reacted with K_2CO_3 (1.66 g, 12 mmol, 1.2 equiv.), KI (166 mg, 1 mmol, 10 mol%) and α-methylbenzyl bromide (1.63 mL, 12 mmol, 1.2 equiv.). The crude was purified by chromatography on silica gel using cyclohexane/CH_2Cl_2 (94:6, Rf= 0.4) as a solvent to afford the desired product, 2-chloro-*N*-(1-phenylethyl)aniline as a pale yellow oil (1.48 g, 6.39 mmol, 64 %).

Following general procedure E, to a solution of 2-chloro-*N*-(1-phenylethyl)aniline (1.96 g, 8.46 mmol, 1 equiv.) in AcOH (28 mL, 0.3 M) was added aqueous formaldehyde solution (37wt%, 6.3 mL, 84.6 mmol, 10 equiv.) and stirred for 5 min and then $NaBH_3CN$ (1.06 g, 16.9 mmol, 2 equiv.). After 2 h, H_2O was added and extracted with CH_2Cl_2, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/CH_2Cl_2 as a solvent to afford the pure compound, 2-chloro-*N*-methyl-*N*-(1-phenylethyl)aniline as a colourless oil (2.04 g, 8.30 mmol, 98%).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.40 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.41 – 7.35 (m, 2H), 7.35 – 7.28 (m, 2H), 7.27 – 7.23 (m, 1H), 7.21 – 7.14 (m, 1H), 7.01 – 6.94 (m, 2H), 4.66 (q, *J* = 6.8 Hz, 1H), 2.50 (s, 3H), 1.44 (d, *J* = 6.8 Hz, 3H).
^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 149.5, 142.2, 130.8, 130.2, 128.2, 127.8, 127.2, 127.0, 123.9, 123.8, 60.6, 35.2, 16.7.
HRMS (ESI): Calcd for $C_{15}H_{17}ClN$ $[M+H]^+$: 246.1044, found: 246.1042.
IR (neat): ν (cm^{-1}) 3061, 2976, 1478, 1116.
Rf 0.27 (Cyclohexane:CH_2Cl_2 = 94:6)

2-bromo-*N*-methyl-*N*-(1-phenylbutyl)aniline (5.15c):



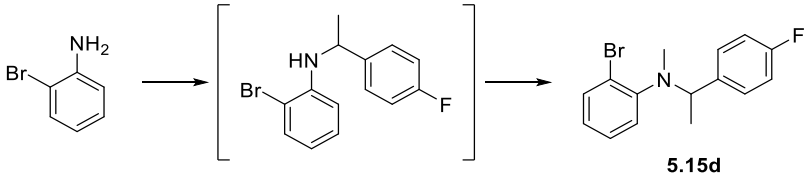
5.15c
Chemical Formula: $C_{17}H_{20}BrN$
Molecular Weight: 318.26

Following general procedure B, to an oven dried 10 mL screw cap reaction tube was added $FeBr_2$ (54 mg, 0.25 mmol, 5 mol%), $KHSO_4$ (681 mg, 5 mmol, 1 equiv.), 2-bromoaniline (860 mg, 5 mmol, 1 equiv.), 1-phenylbutan-1-ol (1.34 mL, 9 mmol, 1.8 equiv., prepared by reference[217]) and toluene (5 mL, 1 M). The reaction tube was capped, and the mixture was then heated to 120 ºC under air in a heating block for 24 h. The reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate, filtered through a *Celite* pad. The crude was purified by silica gel column chromatography using cyclohexane/ CH_2Cl_2 (98:2, Rf= 0.32) as a solvent to afford the desired product, 2-bromo-*N*-(1-phenylbutyl)aniline as an oil (400 mg, 1.32 mmol, 26%).

Following general procedure E, to a solution of 2-bromo-*N*-(1-phenylbutyl)aniline (400 mg, 1.31 mmol, 1 equiv.) in AcOH (4 mL, 0.3 M) was added aqueous formaldehyde solution (37wt%, 361 μL, 13.1 mmol, 10 equiv.) and stirred for 5 min and then $NaBH_3CN$ (247 mg, 3.93 mmol, 3 equiv.). After 2 h, H_2O was added and extracted with CH_2Cl_2, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/CH_2Cl_2 as a solvent to afford the pure compound, 2-bromo-*N*-methyl-*N*-(1-phenylbutyl)aniline as a colourless oil (390 mg, 1.23 mmol, 94%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.60 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.31 – 7.21 (m, 3H), 7.19 – 7.12 (m, 3H), 6.90 ("t"d, *J* = 7.6, 1.6 Hz, 1H), 6.80 (dd, *J* = 8.0, 1.6 Hz, 1H), 4.31 (dd, *J* = 9.4, 5.2 Hz, 1H), 2.49 (s, 3H), 1.99 – 1.76 (m, 2H), 1.29 – 1.11 (m, 2H), 0.85 (t, *J* = 7.4 Hz, 3H).
^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 150.9, 139.7, 133.8, 128.8, 128.0, 127.8, 127.1, 124.9, 124.7, 121.9, 66.7, 37.2, 34.6, 19.7, 14.3.
HRMS (ESI): Calcd for $C_{17}H_{21}BrN$ $[M+H]^+$:318.0852, found: 318.0852.
IR (neat): ν (cm^{-1}) 3060, 2956, 1473, 1585, 1027.
Rf 0.21 (Cyclohexane:CH_2Cl_2 = 98:2)

2-bromo-*N*-(1-(4-fluorophenyl)ethyl)-*N*-methylaniline (5.15d):



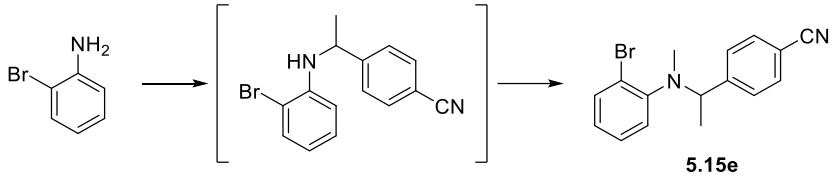
5.15d
Chemical Formula: $C_{15}H_{15}BrFN$
Molecular Weight: 308.19

Following general procedure C, a mixture of 2-Bromoaniline (1.72 g, 10 mmol, 1 equiv.), 4-Fluoro-acetophenon (1.21 mL, 10 mmol, 1 equiv.) and *p*TSA (190 mg, 1 mmol, 10 mol%) in toluene (17 mL, 0.6 M) was refluxed overnight with a Dean-Stark apparatus. The reaction mixture was cooled to room temperature, and the solvent was evaporated *in vacuo*. The residue was dissolved in AcOH (33 mL, 0.3 M), and $NaBH_3CN$ (1.26 g, 20 mmol, 2 equiv.) was added and stirred for 2h. The reaction was quenched with H_2O and extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude was purified by chromatography on silica gel using cyclohexane/ CH_2Cl_2 (94:6, Rf= 0.31) as a solvent to afford the pure compound, 2-bromo-*N*-(1-(4-fluorophenyl)ethyl)aniline as a colourless oil (960 mg, 3.26 mmol, 33%).

Following general procedure E, to a solution of 2-bromo-*N*-(1-(4-fluorophenyl)ethyl)aniline (960 mg, 3.26 mmol, 1 equiv.) in AcOH (10mL, 0.3 M) was added aqueous formaldehyde solution (37 wt%, 2.43mL, 32.6 mmol, 10 equiv.) and stirred for 5 min and then $NaBH_3CN$ (410 mg, 6.52 mmol, 2 equiv.). After the full consumption of the substrate, H_2O was added and extracted with CH_2Cl_2, dried over Na_2SO_4 anhydrous, filtered and concentrated in *vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/ CH_2Cl_2 as a solvent to afford the pure compound, 2-bromo-*N*-(1-(4-fluorophenyl)ethyl)-*N*-methylaniline as a pale yellow oil (930 mg, 3.02 mmol, 93%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.60 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.38 – 7.32 (m, 2H), 7.22 (ddd, *J* = 8.0, 7.2, 1.6 Hz, 1H), 7.04 – 6.96 (m, 3H), 6.93 (ddd, *J* = 8.0, 7.3, 1.6 Hz, 1H), 4.53 (q, *J* = 6.8 Hz, 1H), 2.47 (s, 3H), 1.38 (d, *J* = 6.8 Hz, 4H).
^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 162. (d, *J* = 244.7 Hz), 150.6, 138.2 (d, *J* = 3.2 Hz), 134.0, 129.3 (d, *J* = 7.8 Hz), 127.9, 124.8 (d, *J* = 24.9 Hz), 121.8, 114.9 (d, *J* = 21.0 Hz), 60.7, 36.4, 17.8.
^{19}F{^{1}H} NMR (376 MHz, Chloroform-*d*) δ -116.19.
HRMS (ESI): Calcd for $C_{15}H_{16}BrFN$ $[M+H]^+$: 308.0445, found: 308.0443.
IR (neat): ν (cm^{-1}) 3062, 2978, 1509, 1474, 1223.
Rf 0.36 (Cyclohexane:CH_2Cl_2 = 94:6)

4-(1-((2-bromophenyl)(methyl)amino)ethyl)benzonitrile (5.15e):



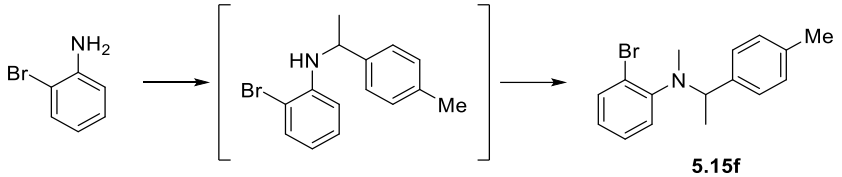
5.15e
Chemical Formula: $C_{16}H_{15}BrN_2$
Molecular Weight: 315.21

Following general procedure C, a mixture of 2-Bromoaniline (860 mg, 5 mmol, 1 equiv.), 4-acetylbenzonitrile (1.09 g, 7.5 mmol, 1.5 equiv.) and *p*TSA (95 mg, 0.5 mmol, 10 mol%) in benzene (8 mL, 0.6 M) was refluxed overnight with a Dean-Stark apparatus. The reaction mixture was cooled to room temperature, and the solvent was evaporated *in vacuo*. The residue was dissolved in AcOH (15 mL, 0.3 M), and $NaBH_3CN$ (723 mg, 11.5 mmol, 2.3 equiv.) was added and stirred for 2h. The reaction was quenched with H_2O and extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4, filtered and evaporated under a vacuum. The crude was purified by chromatography on silica gel using cyclohexane/ AcOEt (11:1, Rf= 0.25) as a solvent to afford the pure compound, 4-(1-((2-bromophenyl)amino)ethyl)benzonitrile as a colourless oil (1.28 g, 4.25 mmol, 85%)

Following general procedure E, to a solution of 4-(1-((2-bromophenyl)amino)ethyl)benzonitrile (600 mg, 1.99 mmol, 1 equiv.) in AcOH (6 mL, 0.3 M) was added aqueous formaldehyde solution (37 wt%, 548 μL, 19.9 mmol, 10 equiv.) and stirred for 5 min and then $NaBH_3CN$ (375 mg, 5.97 mmol, 3 equiv.). After the substrate was fully consumed, H_2O was added and extracted with CH_2Cl_2, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/ CH_2Cl_2 as a solvent to afford the pure compound 4-(1-((2-bromophenyl)(methyl)amino)ethyl)benzonitrile as a colourless oil (594 mg, 1.88 mmol, 95%).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.62 – 7.59 (m, 3H), 7.57 – 7.54 (m, 2H), 7.24 (ddd, *J* = 8.0, 7.4, 1.7 Hz, 1H), 7.03 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.96 (ddd, *J* = 7.9, 7.3, 1.6 Hz, 1H), 4.55 (q, *J* = 6.8 Hz, 1H), 2.49 (s, 3H), 1.38 (d, *J* = 6.7 Hz, 3H).
^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 150.1, 148.7, 134.0, 132.2, 128.4, 128.1, 125.4, 124.8, 122.1, 119.2, 110.9, 61.4, 37.2, 18.0.
HRMS (ESI): Calcd for $C_{16}H_{15}BrN_2Na$ $[M+Na]^+$: 337.0311, found: 337.0309.
IR (neat): ν (cm^{-1})3061, 2979, 2228, 1473, 1108.
Rf 0.44 (Cyclohexane:AcOEt = 10:1)

2-bromo-*N*-methyl-*N*-(1-(*p*-tolyl)ethyl)aniline (5.15f):



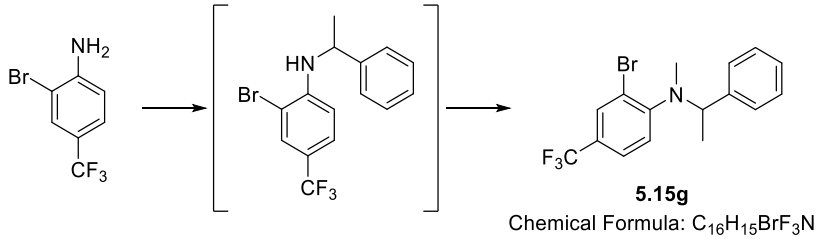
5.15f
Chemical Formula: $C_{16}H_{18}BrN$
Molecular Weight: 304.23

Following general procedure C, a mixture of 2-bromoaniline (2.06 g, 12 mmol, 1.2 equiv.), 4'-methylacetophenone (1.34 mL, 10 mmol, 1 equiv.) and *p*TSA (0.95 g, 5 mmol, 0.5 equiv.) in toluene (17 mL, 0.6 M) was refluxed overnight with a Dean-Stark apparatus. The reaction mixture was cooled to room temperature, and the solvent was evaporated *in vacuo*. The residue was dissolved in MeOH (33 mL, 0.3 M) and, AcOH (5.72 mL, 100 mmol, 10 equiv.) and $NaBH_3CN$ (943 mg, 15 mmol, 1.5 equiv.) added and stirred for 2h. The reaction was quenched with H_2O and extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4, filtered and evaporated under a vacuum. The crude was purified by chromatography on silica gel using cyclohexane/ CH_2Cl_2 (90:10, Rf= 0.31) as a solvent to afford the pure compound 2-bromo-*N*-(1-(p-tolyl)ethyl)aniline as a yellow oil (969 mg, 3.34 mmol, 33%).

Following general procedure E, to a solution of 2-bromo-*N*-(1-(p-tolyl)ethyl)aniline (961 mg, 3.34 mmol, 1 equiv.) in AcOH (11 mL, 0.3 M) was added aqueous formaldehyde solution (37wt%, 3.36 mL, 45.1 mmol, 13.5 equiv.) and stirred for 5 min and then $NaBH_3CN$ (850 mg, 13.5 mmol, 4 equiv.). After full conversion of the substrate, H_2O was added and extracted with CH_2Cl_2, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/ CH_2Cl_2 as a solvent to afford the pure compound 2-bromo-*N*-methyl-*N*-(1-(p-tolyl)ethyl)aniline as a colourless oil (280 mg, 0.92 mmol, 28%).

^{1}H NMR (500 MHz, Chloroform-d) δ 7.60 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.25 – 7.18 (m, 3H), 7.12 (d, *J* = 7.8 Hz, 2H), 6.97 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.92 ("t"d, *J* = 7.6, 1.6 Hz, 1H), 4.54 (q, *J* = 6.8 Hz, 1H), 2.48 (s, 3H), 2.34 (s, 3H), 1.40 (d, *J* = 6.8 Hz, 3H).
^{13}C{^{1}H} NMR (126 MHz, Chloroform-d) δ 150.9, 139.3, 136.6, 133.9, 128.9, 127.8, 127.8, 124.6, 121.7, 61.1, 36.3, 21.2, 17.7.
HRMS (ESI): Calcd for $C_{16}H_{19}BrN$ $[M+H]^+$: 304.0695, found: 304.0691.
IR (neat): ν (cm^{-1}) 3054, 2975, 1473, 1108, 1025.
Rf 0.25 (Cyclohexane:CH_2Cl_2 = 94:6)

2-bromo-*N*-methyl-*N*-(1-phenylethyl)-4-(trifluoromethyl)aniline (5.15g):



5.15g
Chemical Formula: $C_{16}H_{15}BrF_3N$
Molecular Weight: 358.20

Following general procedure A, 2-bromo-4-trifluoromethylaniline (1.2 g, 5 mmol, 1 equiv.) was reacted with K_2CO_3 (1.04 g, 7.5 mmol, 1.5 equiv.), KI (83 mg, 0.5 mmol, 10 mol%) and α-methylbenzyl bromide (0.68 mL, 5 mmol, 1 equiv.). The crude was purified by chromatography on silica gel using cyclohexane/CH_2Cl_2 (98:2, Rf= 0.26) as a solvent to afford the desired product, 2-bromo-*N*-(1-phenylethyl)-4-(trifluoromethyl) aniline as a yellow oil (510 mg, 1.48 mmol, 30 %).

Following general procedure E, to 2-bromo-*N*-(1-phenylethyl)-4-(trifluoromethyl) aniline (510 mg, 1.48 mmol, 1 equiv.) in AcOH (5 mL, 0.3 M) was added aqueous formaldehyde solution (37 wt%, 1.1 mL, 14.8 mmol, 10 equiv.) and stirred for 5 min and then $NaBH_3CN$ (186 mg, 2.96 mmol, 2 equiv.). After 2 h, H_2O was added and extracted with CH_2Cl_2, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo.* The residue was purified by silica gel column chromatography using cyclohexane/ CH_2Cl_2 as a solvent to afford the pure compound to get the pure product 2-bromo-*N*-methyl-*N*-(1-phenylethyl)-4-(trifluoromethyl)aniline as a colourless oil (372 mg, 1.04 mmol, 70%).

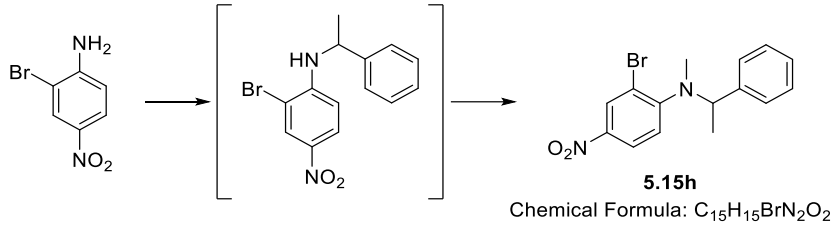
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 (dd, *J* = 2.1, 0.8 Hz, 1H), 7.47 – 7.43 (m, 1H), 7.34 – 7.29 (m, 4H), 7.28 – 7.23 (m, 1H), 6.96 (dd, *J* = 8.5, 0.9 Hz, 1H), 4.77 (q, *J* = 6.8 Hz, 1H), 2.52 (s, 3H), 1.50 (d, *J* = 6.9 Hz, 3H).

^{13}C{^{1}H} NMR (126 MHz, Chloroform-d) δ 154.1, 141.2, 131.3 (q, *J* = 3.8 Hz), 128.3, 127.7, 127.3, 125.8 (q, *J* = 33.1 Hz), 125.0 (q, *J* = 3.7 Hz), 123.7 (q, *J* = 271.9 Hz), 123.6, 120.1, 60.6, 35.2, 16.9.

^{19}F{^{1}H} NMR (376 MHz, Chloroform-d) δ -61.92.

HRMS (ESI): Calcd for $C_{16}H_{16}BrF_3N$ $[M+H]^+$: 358.0413, found: 358.0406.
IR (neat): ν (cm^{-1}) 3030. 2980, 1606, 1324, 1122.
Rf 0.17 (Cyclohexane:CH_2Cl_2 = 98:2)

2-bromo-*N*-methyl-4-nitro-*N*-(1-phenylethyl)aniline (5.15h):



5.15h
Chemical Formula: $C_{15}H_{15}BrN_2O_2$
Molecular Weight: 335.20

Following general procedure B, to an oven-dried 10 mL screw cap reaction tube was added $FeBr_2$ (54 mg, 0.25 mmol, 5 mol%), $KHSO_4$ (681 mg, 5 mmol, 1 equiv.), 2-Bromo-4-nitroaniline (1.09g, 5 mmol, 1 equiv.), 1-Phenyl-1-hydroxyethane (1.1 mL, 9 mmol, 1.8 equiv.) and toluene (5 mL, 1 M). The reaction tube was capped, and the mixture was then heated to 120 ºC under air in a heating block for 24 h. The reaction mixture was allowed to cool, diluted with ethyl acetate, filtered through a *Celite* pad. The crude was purified by silica gel column chromatography using cyclohexane/ AcOEt (94:6, Rf= 0.38) as a solvent to afford the desired product, 2-bromo-4-nitroso-*N*-(1-phenylethyl)aniline as an orange oil (840 mg, 2.62 mmol, 52%).

Following general procedure F, in a dry flask NaH (60%, 188 mg, 4.7 mmol, 2 equiv.) was weighed out, and to this anhydrous DMF (4 mL) was added. The suspension was stirred at room temperature, and 2-bromo-4-nitroso-*N*-(1-phenylethyl)aniline (756 mg, 2.35 mmol, 1 equiv.) was added. The color of the reaction mixture immediately became deep red. This solution was stirred at rt for 30 min and then MeI (731 μL, 11.8 mmol, 5 equiv.) was added; the mixture was then stirred for an additional 2 h. during which time the colour changed to yellow. H_2O was added to the reaction mixture and the resulting yellow turbid solution was stirred for 15 min. This was then extracted with Et_2O and the organic layer was washed with H_2O. The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/ AcOEt as a solvent to afford the pure compound, 2-bromo-*N*-methyl-4-nitro-*N*-(1-phenylethyl)aniline as an orange oil (680 mg, 2.35 mmol, 86%).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.50 (d, *J* = 2.7 Hz, 1H), 8.08 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.35 – 7.28 (m, 3H), 7.28 – 7.23 (m, 2H), 6.88 (d, *J* = 9.0 Hz, 1H), 5.03 (q, *J* = 6.9 Hz, 1H), 2.60 (s, 3H), 1.60 (d, *J* = 6.9 Hz, 3H).

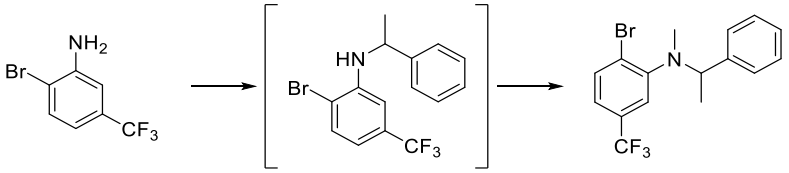
^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 156.9, 142.0, 140.2, 130.4, 128.5, 127.6, 127.5, 123.7, 121.7, 117.2, 60.4, 34.4, 16.6.

HRMS (ESI): Calcd for $C_{15}H_{15}BrN_2NaO_2$ $[M+Na]^+$: 357.0209, found: 357.0208.

IR (neat): ν (cm^{-1}) 3085, 2976, 1580, 1507, 1332, 1116.

Rf 0.37 (Cyclohexane:AcOEt = 96:4)

2-bromo-*N*,5-dimethyl-*N*-(1-phenylethyl)aniline (5.15i):



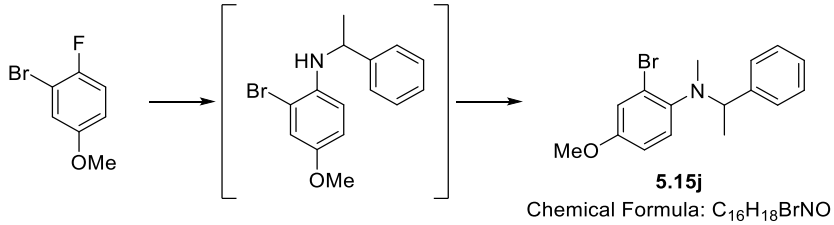
5.15i
Chemical Formula: $C_{16}H_{15}BrF_3N$
Molecular Weight: 358.20

Following general procedure A, 3-Amino-4-bromobenzotrifluoride (1.2 g, 5 mmol, 1 equiv.) was reacted with K_2CO_3 (1.04 g, 7.5 mmol, 1.5 equiv.), KI (83 mg, 0.5 mmol, 10 mol%) and α-methylbenzyl bromide (0.68 mL, 5 mmol, 1 equiv.). The crude was purified by chromatography on silica gel using cyclohexane/CH_2Cl_2 (98:2, Rf= 0.29) as a solvent to afford the desired product 2-bromo-*N*-(1-phenylethyl)-5-(trifluoromethyl)aniline as a yellow oil (720 mg, 2.09 mmol, 42 %).

Following general procedure E, to 2-bromo-*N*-(1-phenylethyl)-5-(trifluoromethyl) aniline (710 mg, 2.06 mmol, 1 equiv.) in AcOH (6 mL, 0.3 M) was added aqueous formaldehyde solution (37 wt%, 1.5 mL, 20.6 mmol, 10 equiv.) and stirred for 5 min and then $NaBH_3CN$ (186 mg, 2.96 mmol, 2 equiv.). After 2 h, H_2O was added and extracted with CH_2Cl_2, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo.* The residue was purified by silica gel column chromatography using cyclohexane/ CH_2Cl_2 as a solvent to afford the pure compound to get the pure product 2-bromo-*N*,5-dimethyl-*N*-(1-phenylethyl)aniline as a colourless oil (613 mg, 1.71 mmol, 83%).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.71 (dd, *J* = 8.7, 1.0 Hz, 1H), 7.37 – 7.29 (m, 4H), 7.29 – 7.22 (m, 1H), 7.18 – 7.13 (m, 2H), 4.63 (q, *J* = 6.8 Hz, 1H), 2.52 (s, 3H), 1.45 (d, *J* = 6.8 Hz, 3H).
^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 151.5, 141.6, 134.5, 130.4 (q, *J* = 32.5 Hz), 128.3, 127.7, 127.3, 125.2 (q, *J* = 1.6 Hz), 124.0 (q, *J* = 272.4 Hz), 121.1 (q, *J* = 3.7 Hz), 121.0 (q, *J* = 3.8 Hz), 61.1, 36.1, 17.4.
^{19}F{^{1}H} NMR (471 MHz, Chloroform-*d*) δ -62.67.
HRMS (ESI): Calcd for $C_{16}H_{16}BrF_3N$ $[M+H]^+$: 358.0413, found: 358.0408.
IR (neat): ν (cm^{-1}) 3088, 2984, 1403, 1328, 1169, 1127, 1081.
Rf 0.24 (Cyclohexane:CH_2Cl_2 = 98:2)

2-bromo-4-methoxy-*N*-methyl-*N*-(1-phenylethyl)aniline (5.15j):



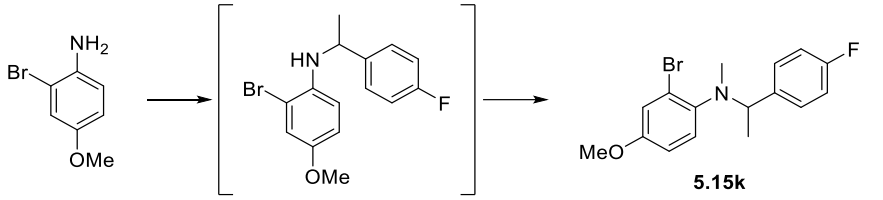
5.15j
Chemical Formula: $C_{16}H_{18}BrNO$
Molecular Weight: 320.23

To a 1 dram vial equipped with a stirring bar was added 9-Mesityl-2,7-dimethyl-10-phenylacridinium tetrafluoroborate (12.2 mg, 0.025 mmol, 5 mol%), DL(±)-α-Methylbenzylamine (193 μL, 1.5 mmol, 3 equiv.), and TFE (5 mL, 0.1 M). The vial was sealed with a PTFE lined screw cap and sparged with Ar for 5 minutes. After this time, the 2-bromo-1-fluoro-4-methoxy-benzene (67 μL, 1.5 mmol, 3 equiv.) was added via syringe. The cap was lined with Teflon tape and irradiated for 18 h, using a 456 nm blue LED lamp. After irradiation, the crude reaction mixture was filtered through a silica plug, eluting with DCM and EtOAc. The solvent was removed *in vacuo* and the crude was purified by chromatography on silica gel using cyclohexane/ CH_2Cl_2 (70:30, Rf= 0.27) as a solvent to afford the pure compound 2-bromo-4-methoxy-*N*-(1-phenylethyl)aniline as a colourless oil (42 mg, 0.137 mmol, 27%).[218]

Following general procedure E, to a solution of 2-bromo-4-methoxy-*N*-(1-phenylethyl)aniline (414 mg, 1.35 mmol, 1 equiv.) in AcOH (4.5 mL, 0.3 M) was added aqueous formaldehyde solution (37 wt%, 372 μL, 13.5 mmol, 10 equiv.) and stirred for 5 min and then $NaBH_3CN$ (255 mg, 4.05 mmol, 3 equiv.). After the substrate was fully consumed, H_2O was added and extracted with CH_2Cl_2, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/ CH_2Cl_2 as a solvent to afford the pure compound 2-bromo-4-methoxy-*N*-methyl-*N*-(1-phenylethyl)aniline as a pale yellow oil (412 mg, 1.29 mmol, 95%).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.44 – 7.38 (m, 2H), 7.35 – 7.28 (m, 2H), 7.27 – 7.20 (m, 1H), 7.17 (d, *J* = 2.9 Hz, 1H), 6.97 (d, *J* = 8.8 Hz, 1H), 6.80 (dd, *J* = 8.8, 2.9 Hz, 1H), 4.31 (q, *J* = 6.7 Hz, 1H), 3.78 (s, 3H), 2.44 (s, 3H), 1.32 (d, *J* = 6.7 Hz, 3H).
^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 156.5, 143.8, 143.4, 128.2, 127.8, 127.0, 125.6, 123.4, 118.5, 113.9, 62.5, 55.78, 38.4, 19.1.
HRMS (ESI): Calcd for $C_{16}H_{19}BrNO$ $[M+H]^+$: 320.0645, found: 320.0646.
IR (neat): ν (cm^{-1}) 3123, 2975, 1490, 1223, 1037.
Rf 0.26 (Cyclohexane:CH_2Cl_2 = 70:30)

2-bromo-*N*-(1-(4-fluorophenyl)ethyl)-4-methoxy-*N*-methylaniline (5.15k):



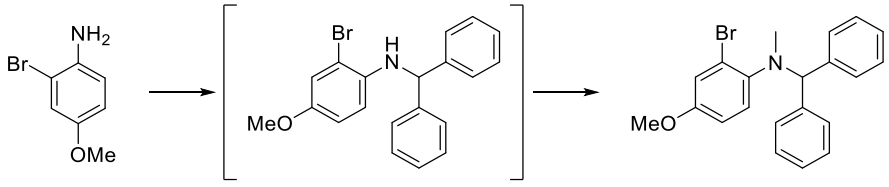
5.15k
Chemical Formula: $C_{16}H_{17}BrFNO$
Molecular Weight: 338.22

Following general procedure C, a mixture of 2-Bromo-4-methoxyaniline (10.1 g, 5 mmol, 1 equiv.), 4'-Fluoroacetophenone (829 mg, 6 mmol, 1.2 equiv.) and *p*TSA (95.1 mg, 0.5 mmol, 10 mol%) in benzene (8 mL, 0.6 M) was refluxed overnight with a Dean-Stark apparatus. The reaction mixture was cooled to room temperature and the solvent was evaporated *in vacuo*. The residue was dissolved in AcOH (17 mL, 0.3 M) and $NaBH_3CN$ (628 mg, 10 mmol, 2 equiv.) was added and stirred for 2 h. The reaction was quenched with H_2O and extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4, filtered and evaporated under vacuum. The crude was purified by chromatography on silica gel using cyclohexane/ CH_2Cl_2 (80:20, Rf= 0.42) as a solvent to afford the pure compound, 2-bromo-*N*-(1-(4-fluorophenyl)ethyl)-4-methoxyaniline as a colourless oil (780 mg, 2.41 mmol, 48%).

Following general procedure E, to a solution of 2-bromo-*N*-(1-(4-fluorophenyl)ethyl)-4-methoxyaniline (780 mg, 2.41 mmol, 1 equiv.) in AcOH (8 mL, 0.3 M) was added aqueous formaldehyde solution (37wt%, 664 μL, 24.1 mmol, 10 equiv.) and stirred for 5 min and then $NaBH_3CN$ (303 mg, 4.82 mmol, 2 equiv.). After the substrate was fully consumed, H_2O was added and extracted with CH_2Cl_2, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/ CH_2Cl_2 as a solvent to afford the pure compound 2-bromo-*N*-(1-(4-fluorophenyl)ethyl)-4-methoxy-*N*-methylaniline as a pale yellow oil (720 mg, 2.13 mmol, 88%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 – 7.33 (m, 2H), 7.16 (d, *J* = 2.9 Hz, 1H), 7.04 – 6.93 (m, 3H), 6.80 (dd, *J* = 8.8, 3.0 Hz, 1H), 4.29 (q, *J* = 6.7 Hz, 1H), 3.78 (s, 3H), 2.42 (s, 3H), 1.30 (d, *J* = 6.7 Hz, 3H).
^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 161.9 (d, *J* = 244.5 Hz), 156.6, 143.6, 139.1 (d, *J* = 3.1 Hz), 129.2 (d, *J* = 7.8 Hz), 125.5, 123.4, 118.5, 115.0 (d, *J* = 21.1 Hz), 113.9, 61.8, 55.8, 38.3, 19.2.
^{19}F{^{1}H} NMR (376 MHz, Chloroform-*d*) δ -116.28.
HRMS (ESI): Calcd for $C_{16}H_{18}BrFNO$ $[M+H]^+$: 338.0550, found: 338.0550.
IR (neat): ν (cm^{-1}) 2997, 2950, 1491, 1222, 1038.
Rf 0.38 (Cyclohexane:CH_2Cl_2 = 80:20)

***N*-benzhydryl-2-bromo-4-methoxy-*N*-methylaniline (5.15l):**



5.15l
Chemical Formula: $C_{21}H_{20}BrNO$
Molecular Weight: 382.30

Following general procedure A, 2-bromo-4methoxyaniline (3 g, 14.8 mmol, 1 equiv.) was reacted with K_2CO_3 (3.07 g, 22.2 mmol, 1.5 equiv.), KI (246 mg, 1.48 mmol, 10 mol%) and bromodiphenylmethyne (4.02 g, 16.3 mmol, 1.1 equiv.). The crude was purified by chromatography on silica gel using cyclohexane/CH_2Cl_2 (70:30, Rf= 0.35) as a solvent to afford the desired product *N*-benzhydryl-2-bromo-4-methoxyaniline as a yellow oil (5.37g, 14.6 mmol, 99 %).

Following general procedure E, to a solution of *N*-benzhydryl-2-bromo-4-methoxyaniline (570 mg, 1.55 mmol, 1 equiv.) in AcOH (6 mL, 0.3 M) was added aqueous formaldehyde solution (37 wt%, 1.2 mL, 15.5 mmol, 10 equiv.) and stirred for 5 min and then $NaBH_3CN$ (292 mg, 4.65 mmol, 3 equiv.). After 2 h, H_2O was added and extracted with CH_2Cl_2, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/ CH_2Cl_2 as a solvent to afford the pure compound *N*-benzhydryl-2-bromo-4-methoxy-*N*-methylaniline as a yellow oil (413 mg, 1.08 mmol, 70%).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.47 – 7.41 (m, 4H), 7.24 ("t", *J* = 7.6 Hz, 4H), 7.17 – 7.13 (m, 2H), 7.11 (d, *J* = 2.9 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 1H), 6.63 (dd, *J* = 8.8, 2.9 Hz, 1H), 5.32 (s, 1H), 3.71 (s, 3H), 2.52 (s, 3H).

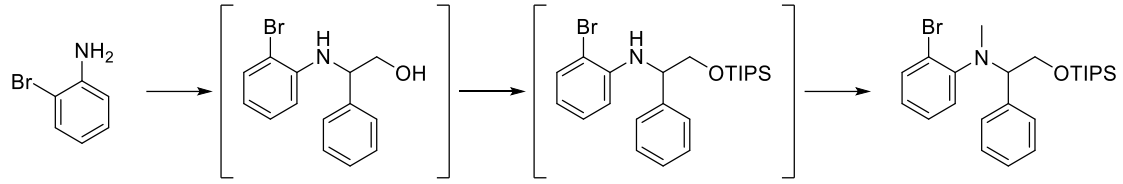
^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 156.3, 143.5, 142.2, 128.4, 128.3, 127.0, 125.5, 123.3, 118.4, 113.6, 73.1, 55.6, 41.4.

HRMS (ESI): Calcd for $C_{21}H_{21}BrNO$ $[M+H]^+$: 382.0801, found: 382.0793.

IR (neat): ν (cm^{-1}) 3027, 1492, 1223, 1034.

Rf 0.5 (Cyclohexane:CH_2Cl_2 = 70:30)

2-bromo-*N*-methyl-*N*-(1-phenyl-2-((triisopropylsilyl)oxy)ethyl)aniline (5.15m):



5.15m
Chemical Formula: $C_{24}H_{36}BrNOSi$
Molecular Weight: 462.55

Following general procedure D, a mixture of 2-bromoaniline (2.58 g, 15 mmol, 1 equiv.), styrene oxide (5.2 mL, 45 mmol, 3 equiv.), silica gel (10% w/w) in toluene (45 mL, 0.3 M) was heated to 70 ºC overnight. The solvent was evaporated *in vacuo* and the residue was purified by chromatography on silica gel using cyclohexane/AcOEt (7:1, Rf= 0.18) as a solvent to afford 2-((2-bromophenyl)amino)-2-phenylethan-1-ol as a yellow solid (3.48 g, 11.9 mmol, 79%).

To a solution of the amino alcohol, 2-((2-bromophenyl)amino)-2-phenylethan-1-ol (934 mg, 3.2 mmol, 1 equiv.) in DMF (24 mL, 0.3 M) was added imidazole (327 mg, 4.8 mmol, 1.5 equiv.), DMAP (39.1 mg, 0.32 mmol, 10 mol%) and TIPSCl (890 μL, 4.16 mmol, 1.3 equiv.) at 0 ºC and stirred at room temperature overnight. H_2O was added and extracted with Et_2O, washed with brine, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/ CH_2Cl_2 (94:6, Rf= 0.35) as a solvent to afford the pure compound 2-bromo-*N*-(1-phenyl-2-((triisopropylsilyl)oxy)ethyl)aniline as a yellow oil (1.03g, 2.3 mmol, 72%).

Following general procedure E, to a solution of 2-bromo-*N*-(1-phenyl-2-((triisopropylsilyl)oxy)ethyl)aniline (1.03 g, 2.3 mmol, 1 equiv.) in AcOH (6 mL, 0.3 M) was added aqueous formaldehyde solution (37 wt%, 0.6 mL, 23 mmol, 10 equiv.) and stirred for 5 min and then $NaBH_3CN$ (434 mg, 6.9 mmol, 3 equiv.). After 2 h, H_2O was added and extracted with CH_2Cl_2, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/ CH_2Cl_2 as a solvent to afford the pure compound, 2-bromo-*N*-methyl-*N*-(1-phenyl-2-((triisopropylsilyl)oxy)ethyl)aniline as a colourless oil (1020 mg, 2.21 mmol, 96%).

^{1}H NMR (400 MHz, Chloroform-d) δ 7.56 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.44 – 7.39 (m, 2H), 7.32 – 7.27 (m, 2H), 7.25 – 7.15 (m, 2H), 7.08 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.88 (td, *J* = 7.6, 1.6 Hz, 1H), 4.50 (dd, *J* = 7.0, 5.5 Hz, 1H), 4.15 – 4.05 (m, 2H), 2.63 (s, 3H), 0.98 – 0.88 (m, 21H).

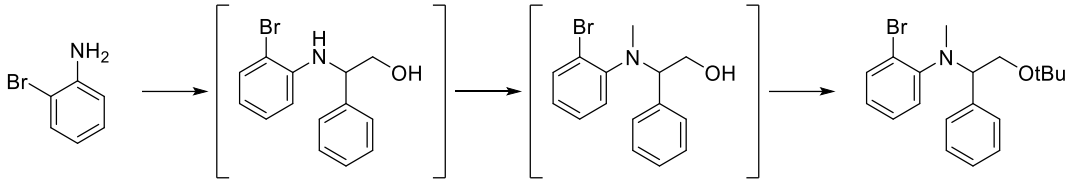
^{13}C{^{1}H} NMR (101 MHz, Chloroform-d) δ 151.1, 13876, 133.3, 128.2, 128.0, 127.8, 127.0, 124.7, 124.6, 121.3, 68.0, 64.8, 38.2, 18.1, 18.0, 12.0.

HRMS (ESI): Calcd for $C_{24}H_{37}BrNOSi$ $[M+H]^+$: 462.1822, found: 462.1824.

IR (neat): ν (cm^{-1}) 3062, 2866, 1473, 1116.

Rf 0.34 (Cyclohexane:CH_2Cl_2 = 96:4)

2-bromo-*N*-(2-(*tert*-butoxy)-1-phenylethyl)-*N*-methylaniline (5.15n):



5.15n
Chemical Formula: $C_{19}H_{24}BrNO$
Molecular Weight: 362.31

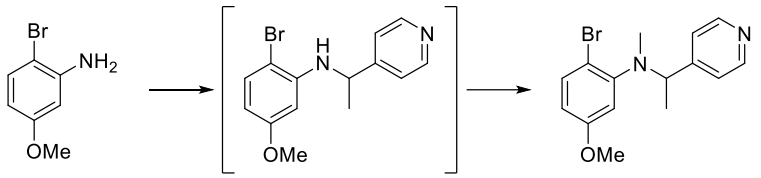
Following general procedure D, a mixture of 2-bromoaniline (2.58 g, 15 mmol, 1 equiv.), styrene oxide (5.2 mL, 45 mmol, 3 equiv.), silica gel (10% w/w) in toluene (45 mL, 0.3 M) was heated to 70 ºC overnight. The solvent was evaporated *in vacuo* and the residue was purified by chromatography on silica gel using cyclohexane/AcOEt (7:1, Rf= 0.18) as a solvent to afford 2-((2-bromophenyl)amino)-2-phenylethan-1-ol as a yellow solid (3.48 g, 11.9 mmol, 79%).

Following general procedure E, to 2-((2-bromophenyl)amino)-2-phenylethan-1-ol (2.22 g, 7.59 mmol, 1 equiv.) in AcOH (25 mL, 0.3 M) was added aqueous formaldehyde solution (37wt%, 2.1 mL, 76 mmol, 10 equiv.) and stirred for 5 min and then $NaBH_3CN$ (1.43 g, 22.8 mmol, 3 equiv.). After 2 h, H_2O was added and extracted with CH_2Cl_2, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo* to get the pure product 2-((2-bromophenyl)(methyl)amino)-2-phenylethan-1-ol (2.4 g, 7.84 mmol, quantitative) as a yellow oil.

Following the reported procedure,[219] to a solution of 2-((2-bromophenyl) (methyl)amino)-2-phenylethan-1-ol in CH_2Cl_2 was added $Mg(ClO_4)_2$ (60 mg, 0.25 mmol, 10 mol%) and Boc_2O (3.82 g, 18 mmol, 7 equiv.), then refluxed overnight. After cooling to room temperature, H_2O was added, and extracted with CH_2Cl_2, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/AcOEt as a solvent to afford the pure compound 2-bromo-*N*-(2-(*tert*-butoxy)-1-phenylethyl)-*N*-methylaniline as a yellow oil (526 mg, 1.45 mmol, 58%).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.56 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.47 – 7.39 (m, 2H), 7.33 – 7.27 (m, 2H), 7.26 – 7.16 (m, 2H), 7.11 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.89 (ddd, *J* = 7.9, 7.2, 1.6 Hz, 1H), 4.52 (dd, *J* = 6.2 Hz, 1H), 3.80 (dd, *J* = 9.3, 5.8 Hz, 1H), 3.71 (dd, *J* = 9.3, 6.7 Hz, 1H), 2.60 (s, 3H), 1.05 (s, 9H).
^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 151.2, 140.1, 133.7, 128.6, 128.0, 127.7, 127.0, 125.2, 124.6, 121.5, 73.1, 66.4, 63.4, 38.3, 27.5.
HRMS (ESI): Calcd for $C_{19}H_{25}BrNO$ $[M+H]^+$: 362.1114, found: 362.1113.
IR (neat): ν (cm^{-1}) 3061, 2973, 1474, 1362, 1194, 1080, 1026.
Rf 0.39 (Cyclohexane:AcOEt = 40:1)

2-bromo-5-methoxy-*N*-methyl-*N*-(1-(pyridin-4-yl)ethyl)aniline (5.15o):



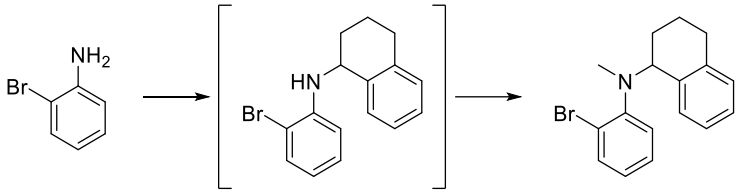
5.15o
Chemical Formula: $C_{15}H_{17}BrN_2O$
Molecular Weight: 321.22

Following general procedure C, a mixture of 2-Bromo-5-methoxyaniline (1.01 g, 5 mmol, 1 equiv.), 4-Acetylpyridine (667 μL, 6 mmol, 1.2 equiv.) and *p*TSA (95 mg, 0.5 mmol, 10 mol%) in benzene (17 mL, 0.6 M) was refluxed overnight with a Dean-Stark apparatus. The reaction mixture was cooled to room temperature and the solvent was evaporated *in vacuo*. The residue was dissolved in AcOH (17 mL, 0.3 M) and $NaBH_3CN$ (628 mg, 10 mmol, 2 equiv.) added and stirred for 2 h. The reaction was quenched with H_2O and extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4, filtered and evaporated under vacuum. The crude was purified by chromatography on silica gel using cyclohexane/ AcOEt (1:1, Rf= 0.24) as a solvent to afford the pure compound 2-bromo-5-methoxy-*N*-(1-(pyridin-4-yl)ethyl)aniline as a colourless oil (1.35 g, 4.40 mmol, 88%).

Following general procedure E, to a solution of 2-bromo-5-methoxy-*N*-(1-(pyridin-4-yl)ethyl)aniline (1.35 g, 4.39 mmol, 1 equiv.) in AcOH (15 mL, 0.3 M) was added an aqueous formaldehyde solution (37wt%, 3.27 mL, 43.9 mmol, 10 equiv.) and stirred for 5 min and then $NaBH_3CN$ (552 mg, 8.78 mmol, 2 equiv.). After the substrate was fully consumed, H_2O was added and extracted with CH_2Cl_2, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/CH_2Cl_2 as a solvent to afford the pure compound 2-bromo-5-methoxy-*N*-methyl-*N*-(1-(pyridin-4-yl)ethyl)aniline as a yellow oil (810 mg, 2.52 mmol, 57%).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.55 (d, *J* = 5.7 Hz, 2H), 7.47 (d, *J* = 8.7 Hz, 1H), 7.40 – 7.34 (m, 2H), 6.58 (d, *J* = 2.9 Hz, 1H), 6.52 (dd, *J* = 8.7, 2.9 Hz, 1H), 4.57 (q, *J* = 6.8 Hz, 1H), 3.76 (s, 3H), 2.49 (s, 3H), 1.40 (d, *J* = 6.8 Hz, 3H).
^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 159.6, 151.7, 151.0, 149.9, 134.1, 122.9, 111.8, 111.1, 109.8, 60.3, 55.6, 36.1, 16.6.
HRMS (ESI): Calcd for $C_{15}H_{18}BrN_2O$ $[M+H]^+$: 321.0597, found: 321.0602.
IR (neat): ν (cm^{-1}) 2981, 2833, 1591, 1470, 1221, 1109.
Rf 0.35 (Cyclohexane:AcOEt = 1:1)

***N*-(2-bromophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine (5.15p):**



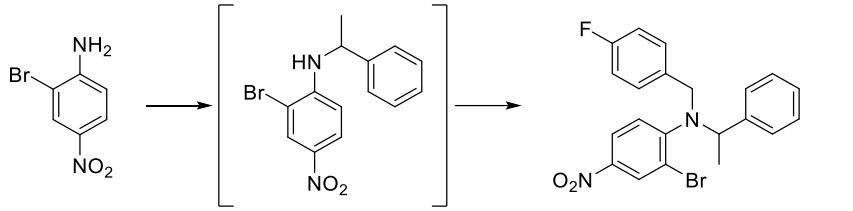
5.15p
Chemical Formula: $C_{17}H_{18}BrN$
Molecular Weight: 316.24

Following general procedure C, a mixture of 2-Bromoaniline (860 mg, 5 mmol, 1 equiv.), alpha-Tetralone (814 μL, 6 mmol, 1.2 equiv.) and *p*TSA (95 mg, 0.5 mmol, 10 mol%) in benzene (17 mL, 0.6 M) were refluxed overnight with a Dean-Stark apparatus. The reaction mixture was cooled to room temperature and the solvent was evaporated *in vacuo*. The residue was dissolved in AcOH (17 mL, 0.3 M) and $NaBH_3CN$ (628 mg, 10 mmol, 2 equiv.) added and stirred for 2 h. The reaction was quenched with H_2O and extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4, filtered and evaporated under vacuum. The crude was purified by chromatography on silica gel using cyclohexane/ CH_2Cl_2 (94:6, Rf= 0.43) as a solvent to afford the pure compound *N*-(2-bromophenyl)-1,2,3,4-tetrahydronaphthalen-1-amine as a colourless oil (1.3 g, 4.30 mmol, 86%).

Following general procedure E, to a solution of *N*-(2-bromophenyl)-1,2,3,4-tetrahydronaphthalen-1-amine (600 mg, 1.99 mmol, 1 equiv.) in AcOH (7 mL, 0.3 M) was added aqueous formaldehyde solution (37wt%, 548 μL, 19.9 mmol, 10 equiv.) and stirred for 5 min and then $NaBH_3CN$ (250 mg, 3.98 mmol, 2 equiv.). After the substrate was fully consumed, H_2O was added and extracted with CH_2Cl_2, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/CH_2Cl_2 as a solvent to afford the pure compound *N*-(2-bromophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine as a pale yellow oil (370 mg, 1.17 mmol, 59%).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.04 (d"t", *J* = 7.8, 1.4 Hz, 1H), 7.59 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.29 (ddd, *J* = 8.2, 7.2, 1.6 Hz, 1H), 7.25 – 7.16 (m, 3H), 7.11 (dd, *J* = 7.5, 1.6 Hz, 1H), 6.90 ("t"d, *J* = 7.6, 1.6 Hz, 1H), 4.78 (dd, *J* = 10.8, 5.6 Hz, 1H), 2.86 – 2.71 (m, 2H), 2.58 (s, 3H), 2.03 – 1.92 (m, 1H), 1.94 – 1.82 (m, 1H), 1.85 – 1.75 (m, 1H), 1.76 – 1.61 (m, 1H).
^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 150.7, 138.6, 137.5, 134.3, 129.0, 128.4, 127.9, 126.7, 126.0, 123.7, 123.7, 119.8, 61.1, 33.3, 30.0, 23.2, 22.3.
HRMS (ESI): Calcd for $C_{17}H_{19}BrN$ $[M+H]^+$: 316.0695, found: 316.0689.
IR (neat): ν (cm^{-1}) 3059, 2933, 1584, 1472, 1100.
Rf 0.35 (Cyclohexane:CH_2Cl_2 = 98:2)

2-bromo-*N*-(4-fluorobenzyl)-4-nitro-*N*-(1-phenylethyl)aniline (5.15q):



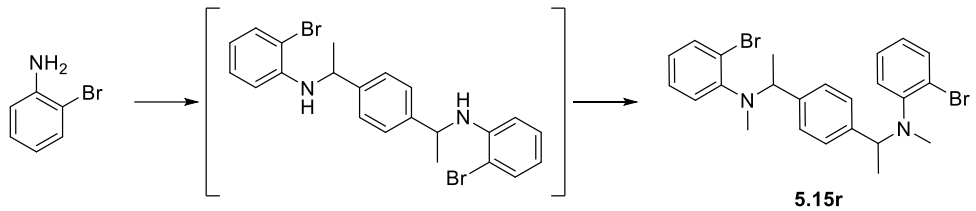
5.15q
Chemical Formula: $C_{21}H_{18}BrFN_2O_2$
Molecular Weight: 429.29

Following general procedure B, 2-bromo-4-nitroso-*N*-(1-phenylethyl)aniline was obtained as an orange oil (840 mg, 2.62 mmol, 52%).

Following general procedure F, in a dry flask NaH (60%, 199 mg, 4.98 mmol, 2 equiv.) was weighed out and to this anhydrous DMF (4 mL) was added. The suspension thus obtained was stirred at room temperature and 2-bromo-4-nitroso-*N*-(1-phenylethyl)aniline (800 mg, 2.49 mmol, 1 equiv.) was added. The color of the reaction mixture immediately became deep red. This solution was stirred at rt for 30 min and then 4-Fluorobenzyl bromide (1.24 mL, 9.96 mmol, 4 equiv.) was added; the mixture was then stirred for an additional 2 h. H_2O was added to the reaction mixture and then extracted with Et_2O and the organic layer was washed with H_2O. The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/CH_2Cl_2 as a solvent to afford the pure compound 2-bromo-*N*-(4-fluorobenzyl)-4-nitro-*N*-(1-phenylethyl)aniline as an orange solid (990 mg, 2.31 mmol, 93%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.48 (d, *J* = 2.7 Hz, 1H), 7.94 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.42 – 7.28 (m, 5H), 7.13 (dd, *J* = 8.5, 5.5 Hz, 2H), 6.93 – 6.79 (m, 3H), 4.93 (q, *J* = 6.9 Hz, 1H), 4.29 (d, *J* = 15.4 Hz, 1H), 3.89 (d, *J* = 15.4 Hz, 1H), 1.66 (d, *J* = 6.9 Hz, 3H).
^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 161.9 (d, *J* = 245.6 Hz), 154.3, 143.0, 140.5, 133.0 (d, *J* = 3.1 Hz), 130.1, 129.5 (d, *J* = 8.0 Hz), 128.6, 127.8, 127.6, 124.6, 122.8, 120.6, 115.4 (d, *J* = 21.4 Hz), 61.1, 48.9, 16.9.
^{19}F{^{1}H} NMR (376 MHz, Chloroform-*d*) δ -115.19.
HRMS (ESI): Calcd for $C_{21}H_{18}BrFN_2NaO_2$ $[M+Na]^+$: 451.0428, found: 451.0424.
IR (neat): ν (cm^{-1}) 3030, 2976, 1508, 1334, 1118.
Rf 0.25 (Cyclohexane:CH_2Cl_2 = 70:30)
Melting point: 92 ºC

***N,N'*-(1,4-phenylenebis(ethane-1,1-diyl))bis(2-bromo-*N*-methylaniline) (5.15r):**



5.15r
Chemical Formula: $C_{24}H_{26}Br_2N_2$
Molecular Weight: 502.29

Following general procedure B, to an oven-dried 10 mL screw cap reaction tube was added $FeBr_2$ (108 mg, 0.5 mmol, 10 mol%), $KHSO_4$ (2.45 g, 18 mmol, 1 equiv.), *o*-bromoaniline (3.10 g, 18 mmol, 3.6 equiv.), 1,1'-(1,4-phenylene)bis(ethan-1-ol) (831 mg, 5 mmol, 1 equiv., synthesized by reference[220]) and toluene (5 mL, 1 M). The reaction tube was capped and the mixture was then heated to 120 ºC under air in a heating block for 24 h. The reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate, and filtered through a *Celite* pad. The crude was purified by silica gel column chromatography using cyclohexane/CH_2Cl_2 (70:30, Rf= 0.25) as a solvent to afford the desired product *N,N'*-(1,4-phenylenebis(ethane-1,1-diyl))bis(2-bromoaniline) as a white solid (828 mg, 1.75 mmol, 35%).

Following general procedure E, to a solution of *N,N'*-(1,4-phenylenebis(ethane-1,1-diyl))bis(2-bromoaniline) (828 mg, 1.75 mmol, 1 equiv.) in AcOH (6 mL, 0.3 M) was added aqueous formaldehyde solution (964 μL, 35 mmol, 20 equiv.) and stirred for 5 min and then $NaBH_3CN$ (440 mg, 7 mmol, 4 equiv.). After the substrate was fully consumed, H_2O was added and extracted with CH_2Cl_2, dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/ CH_2Cl_2 as a solvent to afford the pure compound *N,N'*-(1,4-phenylenebis(ethane-1,1-diyl))bis(2-bromo-*N*-methylaniline) as a white solid (686 mg, 1.37 mmol, 78%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.60 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.31 (d, *J* = 3.6 Hz, 4H), 7.26 – 7.17 (m, 2H), 7.02 – 6.87 (m, 4H), 4.57 (qd, *J* = 6.8, 1.5 Hz, 2H), 2.47 (s, 6H), 1.41 (d, *J* = 6.8 Hz, 3H), 1.40 (d, *J* = 6.8 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 150.9, 140.8, 133.9, 127.8, 127.5, 124.6, 121.7, 61.0, 36.2, 17.3.

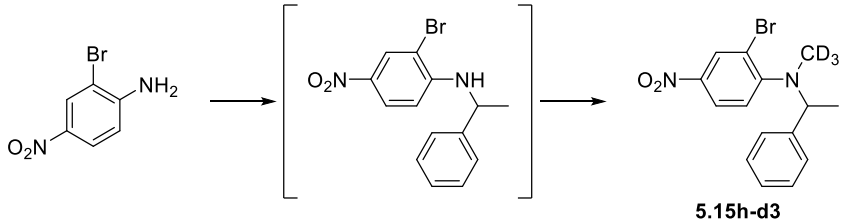
HRMS (ESI): Calcd for $C_{24}H_{27}Br_2N_2$ $[M+H]^+$: 501.0536, found: 501.0529.

IR (neat): ν (cm^{-1}) 2973, 1582, 1472, 1025.

Rf 0.19 (Cyclohexane:CH_2Cl_2 = 90:10)

Melting point: 112 ºC

2-bromo-*N*-(methyl-d_3)-4-nitro-*N*-(1-phenylethyl)aniline (5.15h-d3):



5.15h-d3
Chemical Formula: $C_{15}H_{12}D_3BrN_2O_2$
Molecular Weight: 338.22

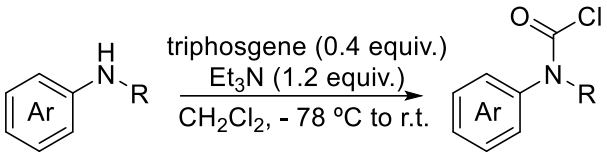
Following general procedure B, 2-bromo-4-nitroso-*N*-(1-phenylethyl)aniline was obtained as an orange oil (840 mg, 2.62 mmol, 52%).

Following general procedure F, in a dry flask NaH (60%, 398 mg, 10.0 mmol, 2 equiv.) was weighed out and to this anhydrous DMF (8 mL) was added. The suspension was stirred at room temperature and 2-bromo-4-nitroso-*N*-(1-phenylethyl)aniline (1.6 g, 4.98 mmol, 1 equiv.) was added. The colour of the reaction mixture immediately became deep red. This solution was stirred at rt for 30 min and then CD_3I (1.24 mL, 19.9 mmol, 4 equiv.) was added; the mixture was then stirred for an additional 2 h. H_2O was added to the reaction mixture and the resulting yellow turbid solution was stirred for 15 min. This was then extracted with Et_2O and the organic layer was washed with H_2O. The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. The residue was purified by silica gel column chromatography using cyclohexane/AcOEt as a solvent to afford the pure compound 2-bromo-*N*-(methyl-d_3)-4-nitro-*N*-(1-phenylethyl)aniline as an orange oil (1.54 g, 4.55 mmol, 91%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.50 (d, *J* = 2.7 Hz, 1H), 8.08 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.35 – 7.22 (m, 5H), 6.87 (d, *J* = 8.9 Hz, 1H), 5.04 (q, *J* = 6.9 Hz, 1H), 1.60 (d, *J* = 6.9 Hz, 3H).
^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 156.9, 142.0, 140.2, 130.4, 128.5, 127.6, 127.5, 123.7, 121.6, 117.1, 60.3, 24.8, 16.6.
HRMS (ESI): Calcd for $C_{15}H_{12}BrD_3N_2NaO_2$ $[M+Na]^+$: 360.0397, found: 360.0394.
IR (neat): ν (cm^{-1}) 3029, 2976, 1579, 1508, 1331, 1118.
Rf 0.28 (Cyclohexane:AcOEt = 96:4)

7.7.6 Synthesis of substrates for expansion of 1,4-Pd shift

Carbamoyl chloride (**5.26**-**5.30**):



To a solution of the corresponding secondary amine (1 equiv.) in CH_2Cl_2 was cooled to – 78 ºC under Ar atmosphere. Et_3N (1.2 equiv.) was added, and then triphosgene (1.2 equiv.) slowly at that temperature. The reaction mixture was warmed up to r.t. and stirred until reaction completion. The mixture was quenched with 1N HCl, extracted with CH_2Cl_2, and the organic layers were washed with $NaHCO_3$ aq, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting product was used for C–H activation without further purification.

***tert*-butyl(2,4,6-trimethoxybenzyl)carbamic chloride (5.26)** (339 mg, 1.07 mmol, 36%)
NMR spectra show good agreement with the literature.[67]

isopropyl(2,4,6-trimethoxybenzyl)carbamic chloride (5.27) (860 mg, 2.85 mmol, 95%)
NMR spectra show good agreement with the literature.[67]

2-methylindoline-1-carbonyl chloride (5.28)
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.92 – 7.82 (m, 0.7H), 7.54 – 7.42 (m, 0.1H), 7.31 – 7.16 (m, 1.9H), 7.15 – 6.83 (m, 1H), 7.01 – 6.82 (m, 0.3H), 4.85 – 4.71 (m, 0.4H), 4.70 – 4.55 (m, 0.6H), 3.46 (dd, *J* = 15.9, 9.0 Hz, 0.9H), 3.32 (ddd, *J* = 15.4, 12.0, 8.8 Hz, 0.1H), 2.79 – 2.62 (m, 1H), 1.46 – 1.34 (m, 3H).

(2-(*tert*-butyl)phenyl)(tosyl)carbamic chloride (5.29) (355 mg, 0..97 mmol, 97%)
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.01 – 7.86 (m, 2H), 7.67 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.45 (ddd, *J* = 8.3, 7.2, 1.5 Hz, 1H), 7.42 – 7.38 (m, 2H), 7.19 (ddd, *J* = 7.9, 7.2, 1.6 Hz, 1H), 6.71 (dd, *J* = 7.9, 1.5 Hz, 1H), 2.50 (s, 3H), 1.57 (s, 9H).

diphenylcarbamic chloride (5.30) (128 mg, 0.552 mmol, 18%)
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 – 7.26 (m, 10H).

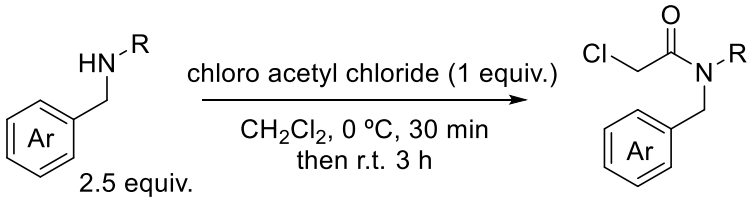
benzyl(phenyl)carbamic chloride (5.31) (520 mg, 2.12 mmol, 71%)
^{1}H NMR (250 MHz, Chloroform-*d*) δ 7.39 – 7.28 (m, 6H), 7.25 – 7.15 (m, 2H), 7.10 – 6.95 (m, 2H), 4.88 (s, 2H).

phenyl(1-phenylethyl)carbamic chloride (5.32) (582 mg, 2.24 mmol, 78%)

^{1}H NMR (250 MHz, Chloroform-*d*) δ 7.39 – 7.27 (m, 7H), 7.24 – 7.14 (m, 3H), 5.90 (q, *J* = 7.1 Hz, 1H), 1.54 (d, *J* = 7.2 Hz, 3H).

α-Chloroamide (5.33, 5.34)

They were synthesized by literature procedure.[66]



To a solution of the corresponding secondary amine (2.5 equiv.) in CH_2Cl_2 was cooled to 0 ºC under Ar atmosphere. Chloro acetyl chloride (1 equiv.) was added dropwise at that temperature and stirred for 30 min. Then the reaction mixture was warmed up to r.t. and stirred for 3 h. The mixture was quenched with 1N HCl, extracted with CH_2Cl_2, and the organic layers were washed with $NaHCO_3$ aq, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting product was used for C–H activation without further purification.

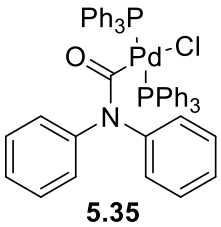
***N*-benzyl-2-chloro-*N*-methylacetamide (5.33)** (1.04 g, 5.26 mmol, 105 %)

^{1}H NMR (250 MHz, Chloroform-*d*) δ 7.45 – 7.15 (m, 5H), 4.61 (s, 2H), 4.15 (s, 1.2H), 4.11 (s, 0.8H), 3.00 (s, 1.8H), 2.98 (s, 1.2H).

***N,N*-dibenzyl-2-chloroacetamide (5.34)** (1.12 g, 4.09, 82%)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.44 – 7.27 (m, 6H), 7.25 – 7.19 (m, 2H), 7.17 (d, *J* = 7.4 Hz, 2H), 4.62 (s, 2H), 4.52 (s, 2H), 4.15 (s, 2H).

(diphenylcarbamoyl)palladium (II) ditriphenylphosphine chloride (5.35):



5.35

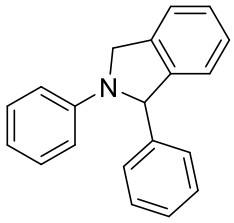
To a solution of tetrakistriphenylphosphine palladium(0) (1 g, 0.866 mmol, 1 equiv.) in toluene (18 mL) was added diphenylcarbamic chloride (**5.30**) (301 mg, 1.30 mmol, 1.5 equiv.) and stirred at 80°C overnight. The solution was cooled to ambient temperature and concentrated *in vacuo*. The residue was washed with diethyl ether and dried *in vacuo* to give the complex **5.35** a as a yellow powder (603mg,0.699 mmol, 81%).[67]

^{1}H NMR (250 MHz, Chloroform-*d*) δ 7.63 – 7.52 (m, 11H), 7.44 – 7.25 (m, 22H), 7.22 – 7.13 (m, 1H), 7.07 – 6.83 (m, 4H), 6.42 (d, *J* = 7.2 Hz, 2H).

^{31}P NMR (101 MHz, Chloroform-*d*) δ 19.01.

7.7.7 Synthesis of isoindolines: C–H activation products

1,2-diphenylisoindoline (5.16a)



Chemical Formula: $C_{20}H_{17}N$
Molecular Weight: 271.36

Following general procedure G, *N*-benzhydryl-2-bromo-*N*-methylaniline **5.15a** (705 mg, 0.2 mmol, 1 equiv.) was engaged. The crude was purified by preparative thin-layer chromatography (6% CH_2Cl_2 in *c*Hex) to afford the title compound **5.16a** (48.8 mg, 0.18 mmol, 90%) as a white solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.36 (m, 3H), 7.35 – 7.28 (m, 2H), 7.28 – 7.14 (m, 5H), 7.11 – 7.06 (m, 1H), 6.72 – 6.61 (m, 3H), 5.85 (d, *J* = 3.3 Hz, 1H), 5.09 (dd, *J* = 13.2, 3.5 Hz, 1H), 4.78 (dd, *J* = 13.2, 1.4 Hz, 1H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 146.6, 143.9, 142.7, 136.2, 129.3, 129.1, 127.6, 127.5, 127.5, 126.3, 123.4, 122.6, 116.7, 113.0, 69.1, 55.2.

HRMS (ESI): Calcd for $C_{20}H_{18}N$ $[M+H]^+$: 272.1434, found: 272.1428.

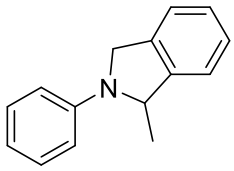
IR (neat): ν (cm^{-1}) 3039, 2827, 1597, 1501, 1360.

Rf 0.29 (Cyclohexane:CH_2Cl_2 = 94:6)

Melting point: 112 ºC

The analytical data are in full agreement with the reported ones.[221]

1-methyl-2-phenylisoindoline (5.16b)



Chemical Formula: $C_{15}H_{15}N$
Molecular Weight: 209.29

Following general procedure G, 2-chloro-*N*-methyl-*N*-(1-phenylethyl) aniline **5.15b`** (49.2 mg, 0.2 mmol, 1 equiv.) was engaged. The crude was purified by preparative thin-layer chromatography (6% CH_2Cl_2 in *c*Hex) to afford the title compound **5.16b** (37.6 mg, 0.18 mmol, 90%) as a white solid.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.39 – 7.26 (m, 6H), 6.79 – 6.71 (m, 3H), 5.12 (qd, *J* = 6.2, 3.0 Hz, 1H), 4.80 (ddd, *J* = 13.3, 3.1, 0.8 Hz, 1H), 4.56 (d, *J* = 12.8 Hz, 1H), 1.52 (d, *J* = 6.2 Hz, 3H).

^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 146.7, 143.8, 136.9, 129.5, 127.4, 127.3, 122.6, 122.3, 116.1, 112.4, 59.3, 54.2, 20.7.

HRMS (ESI): Calcd for $C_{15}H_{16}N$ $[M+H]^+$: 210.1277, found: 210.1281.

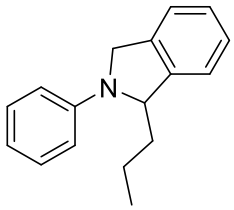
IR (neat): ν (cm^{-1}) 3041, 2928, 1595, 1501, 1362, 1156.

Rf 0.29 (Cyclohexane:CH_2Cl_2 = 94:6)

Melting point: 72 °C

The analytical data are in full agreement with the reported ones.[222]

2-phenyl-1-propylisoindoline (5.16c)



Chemical Formula: $C_{17}H_{19}N$
Molecular Weight: 237.35

Following general procedure G, 2-bromo-*N*-methyl-*N*-(1-phenylbutyl)aniline **5.15c** (63.7 mg, 0.2 mmol, 1 equiv.) was engaged. The crude was purified by preparative thin-layer chromatography (2% CH_2Cl_2 in *c*Hex) to afford the title compound **5.16c** (41.6 mg, 0.175 mmol, 88%) as a pale brown oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.27 (m, 6H), 6.81 – 6.69 (m, 3H), 5.17 (d"t", *J* = 5.9, 2.8 Hz, 1H), 4.75 (dd, *J* = 13.4, 3.1 Hz, 1H), 4.58 (d, *J* = 13.3 Hz, 1H), 2.10 (dddd, *J* = 13.8, 11.1, 6.0, 4.8 Hz, 1H), 1.85 (dddd, *J* = 14.0, 11.7, 4.9, 2.5 Hz, 1H), 1.35 – 1.17 (m, 1H), 1.13 – 0.95 (m, 1H), 0.82 (t, *J* = 7.3 Hz, 3H).

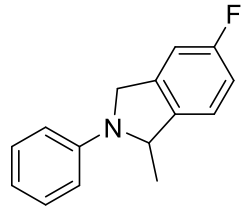
^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 146.5, 142.2, 137.8, 129.5, 127.2, 122.5, 122.4, 115.9, 112.1, 63.1, 54.7, 35.6, 16.9, 14.3.

HRMS (ESI): Calcd for $C_{17}H_{20}N$ $[M+H]^+$: 238.1590, found: 238.1586.

IR (neat): ν (cm^{-1}) 3060, 2960, 1598, 1499, 1379.

Rf 0.2 (Cyclohexane:CH_2Cl_2 = 98:2)

5-fluoro-1-methyl-2-phenylisoindoline (5.16d)



Chemical Formula: $C_{15}H_{14}FN$
Molecular Weight: 227.28

Following general procedure G, 2-bromo-*N*-(1-(4-fluorophenyl)ethyl)-*N*-methylaniline **5.15d** (61.6 mg, 0.2 mmol, 1 equiv.) was engaged. The crude was purified by preparative thin-layer chromatography (6% CH_2Cl_2 in *c*Hex) to afford the title compound **5.16d** (43.7 mg, 0.192 mmol, 96%) as a white solid.

^{1}H NMR (400 MHz, Chloroform-d) δ 7.37 – 7.28 (m, 2H), 7.21 (dd, *J* = 8.0, 5.0 Hz, 1H), 7.06 – 6.96 (m, 2H), 6.80 – 6.69 (m, 3H), 5.07 (dd, *J* = 6.5, 3.2 Hz, 1H), 4.77 (dd, *J* = 13.7, 3.1 Hz, 1H), 4.53 (d, *J* = 13.6 Hz, 1H), 1.50 (d, *J* = 6.1 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 162.6 (d, *J* = 243.9 Hz), 146.5, 139.4 (d, *J* = 2.5 Hz), 138.9 (d, *J* = 8.7 Hz), 129.5, 123.5 (d, *J* = 8.9 Hz), 116.4, 114.6 (d, *J* = 22.7 Hz), 112.4, 109.7 (d, *J* = 23.2 Hz), 58.8, 54.1 (d, *J* = 2.7 Hz), 20.8 (d, *J* = 1.0 Hz).

^{19}F{^{1}H} NMR (376 MHz, Chloroform-*d*) δ -115.87.

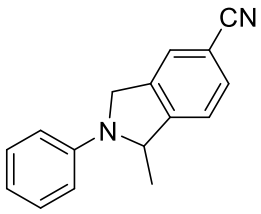
HRMS (ESI): Calcd for $C_{15}H_{15}FN$ $[M+H]^+$: 228.1183, found: 228.1186.

IR (neat): ν (cm^{-1}) 3069, 2923, 1597, 1490, 1362,

Rf 0.29 (Cyclohexane:CH_2Cl_2 = 94:6)

Melting point: 70 ºC

1-methyl-2-phenylisoindoline-5-carbonitrile (5.16e)



Chemical Formula: $C_{16}H_{14}N_2$
Molecular Weight: 234.30

Following general procedure G, 4-(1-((2-bromophenyl)(methyl)amino)ethyl)benzonitrile **5.15e** (63 mg, 0.2 mmol, 1 equiv.) was engaged. The crude was purified by preparative thin-layer chromatography (9% AcOEt in *c*Hex) to afford the title compound **5.16e** (38.3 mg, 0.163 mmol, 82%) as a pale yellow solid.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.64 – 7.59 (m, 2H), 7.38 (d, *J* = 7.7 Hz, 1H), 7.34 – 7.29 (m, 2H), 6.81 – 6.76 (m, 1H), 6.73 (d, *J* = 7.7 Hz, 2H), 5.17 (qd, *J* = 6.2, 3.1 Hz, 1H), 4.81 (dd, *J* = 13.8, 3.2 Hz, 1H), 4.58 (d, *J* = 13.8 Hz, 1H), 1.52 (d, *J* = 6.3 Hz, 3H).

^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 149.1, 146.0, 138.4, 131.7, 129.6, 126.5, 123.3, 119.1, 117.0, 112.5, 111.4, 59.4, 53.8, 20.4.

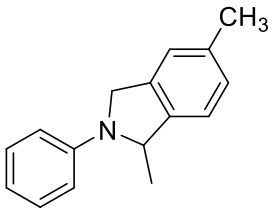
HRMS (ESI): Calcd for $C_{16}H_{15}N_2$ $[M+H]^+$: 235.1230, found: 235.1226.

IR (neat): ν (cm^{-1}) 3058, 2848, 2224, 1597, 1501, 1363.

Rf 0.37 (Cyclohexane:AcOEt = 10:1)

Melting point: 105 ºC

1,5-dimethyl-2-phenylisoindoline (5.16f)



Chemical Formula: $C_{16}H_{17}N$
Molecular Weight: 223.32

Following general procedure G, 2-bromo-*N*-methyl-*N*-(1-(p-tolyl)ethyl)aniline **5.15f** (60.8 mg, 0.2 mmol, 1 equiv.) was engaged. The crude was purified by preparative thin-layer chromatography (4% CH_2Cl_2 in *c*Hex) to afford the title compound **5.16f** (33 mg, 0.148 mmol, 74%) as a white solid.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.33 – 7.26 (m, 2H), 7.18 – 7.09 (m, 3H), 6.72 (dd, *J* = 8.2, 7.0 Hz, 3H), 5.06 (dt, *J* = 9.0, 4.5 Hz, 1H), 4.75 (dd, *J* = 13.3, 3.1 Hz, 1H), 4.51 (d, *J* = 13.3 Hz, 1H), 2.39 (d, *J* = 0.8 Hz, 3H), 1.49 (d, *J* = 6.2 Hz, 3H).

^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 146.8, 141.0, 137.0 (d, J = 2.7 Hz), 129.5, 128.2, 123.1, 122.1, 116.0, 112.4, 59.1, 54.2, 21.5, 20.8.

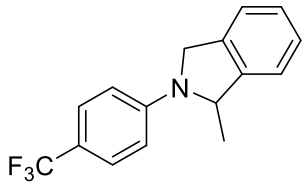
HRMS (ESI): Calcd for $C_{16}H_{18}N$ $[M+H]^+$: 224.1434, found: 224.1435.

IR (neat): ν (cm^{-1}) 3039, 2971, 1597, 1497, 1357.

Rf 0.2 (Cyclohexane:CH_2Cl_2 = 96:4)

Melting point: 102 ºC

1-methyl-2-(4-(trifluoromethyl)phenyl)isoindoline (5.16g)



Chemical Formula: $C_{16}H_{14}F_3N$
Molecular Weight: 277.29

Following general procedure G, 2-bromo-*N*-methyl-*N*-(1-phenylethyl)-4-(trifluoromethyl)aniline **5.15g** (71.6 mg, 0.2 mmol, 1 equiv.) was engaged. The crude was purified by preparative thin-layer chromatography (6% CH_2Cl_2 in *c*Hex) to afford the title compound **5.16g** (40.1 mg, 0.145 mmol, 72%) as a white solid.

^{1}H NMR (400 MHz, Chloroform-d) δ 7.56 – 7.48 (m, 2H), 7.39 – 7.24 (m, 4H), 6.78 – 6.69 (m, 2H), 5.16 (qd, *J* = 6.1, 2.7 Hz, 1H), 4.80 (dd, *J* = 13.5, 2.8 Hz, 1H), 4.60 (d, *J* = 13.5 Hz, 1H), 1.52 (d, *J* = 6.2 Hz, 3H).

^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 148.6, 143.1, 136.0, 127.5, 127.5, 126.6 (q, *J* = 3.8 Hz), 125.22(q, *J* = 269.0 Hz), 122.5, 122.2, 117.5 (q, *J* = 32.6 Hz), 111.5, 59.3, 53.8, 20.3.

^{19}F{^{1}H} NMR (376 MHz, Chloroform-d) δ -60.74.

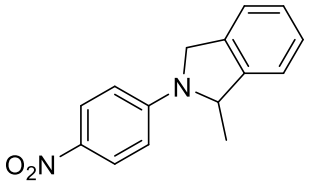
HRMS (ESI): Calcd for $C_{16}H_{15}F_3N$ $[M+H]^+$: 278.1151, found: 278.1146.

IR (neat): ν (cm^{-1}) 3057, 2985, 1611, 1375, 1320, 1104, 1066.

Rf 0.29 (Cyclohexane:CH_2Cl_2 = 94:6)

Melting point: 91 ºC

1-methyl-2-(4-nitrophenyl)isoindoline (5.16h)



Chemical Formula: $C_{15}H_{14}N_2O_2$
Molecular Weight: 254.29

Following general procedure G, 2-bromo-*N*-methyl-4-nitro-*N*-(1-phenylethyl)aniline **5.15h** (67 mg, 0.2 mmol, 1 equiv.) was engaged. The crude was purified by silica gel column chromatography (10% AcOEt in cHex) to afford the title compound **5.16h** (46.7 mg, 0.184 mmol, 92%) as a yellow solid. Suitable crystals for X-ray structure analysis were obtained by dissolving the sample in ethylformate and let stand at -26 ºC open to air.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.24 – 8.16 (m, 2H), 7.41 – 7.27 (m, 4H), 6.72 – 6.63 (m, 2H), 5.23 (qd, *J* = 6.2, 2.3 Hz, 1H), 4.85 (dd, *J* = 13.9, 2.3 Hz, 1H), 4.69 (d, *J* = 14.0 Hz, 1H), 1.54 (d, *J* = 6.3 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 151.0, 142.4, 137.4, 135.3, 128.0, 128.0, 126.5, 122.7, 122.4, 111.2, 60.0, 54.1, 20.6.

HRMS (ESI): Calcd for $C_{15}H_{14}N_2NaO_2$ $[M+Na]^+$: 277.0947, found: 277.0945.

IR (neat): ν (cm^{-1}) 3085, 2923, 1586, 1481, 1286, 1110.

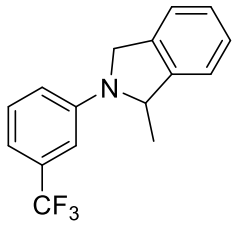
Rf 0.28 (Cyclohexane:AcOEt = 9:1)

Melting point: 154 ºC

Gram scale isoindoline synthesis

A 100 mL pressure flask was charged with the corresponding amine **5.15h** (1.1 g, 3.28 mmol, 1.0 equiv.) and a stirring bar. The flask was introduced into a glovebox and charged subsequently with Cs_2CO_3 (1.6 g, 4.92 mmol, 1.5 equiv.), CsOPiv (230 mg, 0.984 mmol, 30 mol%.), $[Pd(\pi\text{-allyl})Cl]_2$ (60 mg, 0.164 mmol, 5 mol%), and IMes·Cl (112 mg, 0.328 mmol, 10 mol%). Dried and degassed *m*-xylene (49 mL, 0.067 M) was added before the flask was sealed with the corresponding stopper and taken out of the glovebox. The content was stirred at rt for 5 min before it was inserted into a preheated oil bath at 110 °C. The reaction was stirred at this temperature for 15 h before it was allowed to cool down to rt and filtered through a pad of *Celite* (eluted with EtOAc). The filtrate was concentrated under reduced pressure. The crude was purified by silica gel column chromatography (*c*Hex/EtOAc = 9:1) to afford **5.16h** (708 mg, 2.78 mmol, 85%) as a yellow solid.

1-methyl-2-(3-(trifluoromethyl)phenyl)isoindoline (5.16i)



Chemical Formula: $C_{16}H_{14}F_3N$
Molecular Weight: 277.29

Following general procedure G, 2-bromo-*N*,5-dimethyl-*N*-(1-phenylethyl)aniline **5.15i** (71.6 mg, 0.2 mmol, 1 equiv.) was engaged. The crude was purified by preparative thin-layer chromatography (6% CH_2Cl_2 in *c*Hex) to afford the title compound **5.16i** (44.5 mg, 0.16 mmol, 80%) as a colourless oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 – 7.27 (m, 5H), 6.99 – 6.84 (m, 3H), 5.19 – 5.10 (m, 1H), 4.81 (dd, *J* = 13.3, 3.0 Hz, 1H), 4.58 (d, *J* = 13.2 Hz, 1H), 1.52 (d, *J* = 6.2 Hz, 3H).

^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 146.7, 143.3, 136.32, 131.8 (q, *J* = 31.4 Hz), 129.8, 127.6, 127.6, 124.7 (q, *J* = 272.4 Hz), 122.7, 122.4, 115.3 (q, *J* = 1.4 Hz), 112.5 (q, *J* = 3.9 Hz), 108.6 (q, *J* = 4.0 Hz), 59.4, 54.1, 20.5.

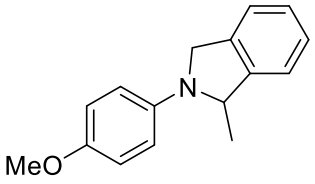
^{19}F{^{1}H} NMR (376 MHz, Chloroform-*d*) δ -62.68.

HRMS (ESI): Calcd for $C_{16}H_{15}F_3N$ $[M+H]^+$: 278.1151, found: 278.1145.

IR (neat): ν (cm^{-1}) 3053, 2981, 1455, 1372, 1324, 1117.

Rf 0.34 (Cyclohexane:CH_2Cl_2 = 94:6)

2-(4-methoxyphenyl)-1-methylisoindoline (5.16j)



Chemical Formula: $C_{16}H_{17}NO$
Molecular Weight: 239.32

Following general procedure G, 2-bromo-4-methoxy-*N*-methyl-*N*-(1-phenylethyl)aniline **5.15j** (64 mg, 0.2 mmol, 1 equiv.) was engaged. The crude was purified by preparative thin-layer chromatography (30% CH_2Cl_2 in *c*Hex) to afford the title compound **5.16j** (14 mg, 0.058 mmol, 29%) as a brown oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 – 7.25 (m, 4H), 6.96 – 6.87 (m, 2H), 6.75 – 6.66 (m, 2H), 5.04 (qd, *J* = 6.1, 2.9 Hz, 1H), 4.79 (dd, *J* = 13.1, 3.2 Hz, 1H), 4.49 (d, *J* = 13.0 Hz, 1H), 3.79 (s, 3H), 1.49 (d, *J* = 6.1 Hz, 3H).

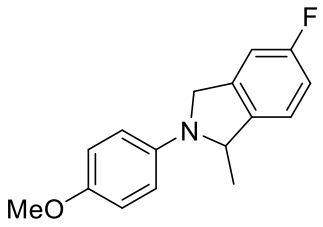
^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 151.2, 144.0, 141.6, 137.2, 127.3, 127.2, 122.5, 122.3, 115.3, 113.3, 59.6, 56.1, 54.9, 20.7.

HRMS (ESI): Calcd for $C_{16}H_{18}NO$ $[M+H]^+$: 240.1383, found: 240.1384.

IR (neat): ν (cm^{-1}) 3045, 2833, 1510, 1240, 1032.

Rf 0.18 (Cyclohexane:CH_2Cl_2 = 70:30)

5-fluoro-2-(4-methoxyphenyl)-1-methylisoindoline (5.16k)



Chemical Formula: $C_{16}H_{16}FNO$
Molecular Weight: 257.31

Following general procedure G, 2-bromo-*N*-(1-(4-fluorophenyl)ethyl)-4-methoxy-*N*-methylaniline **5.15k** (67.6 mg, 0.2 mmol, 1 equiv.) was engaged. The crude was purified by preparative thin-layer chromatography (20% CH_2Cl_2 in *c*Hex) to afford the title compound **5.16k** (39.2 mg, 0.152 mmol, 76%) as a pale yellow solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.19 (dd, *J* = 8.0, 5.0 Hz, 1H), 7.04 – 6.96 (m, 2H), 6.94 – 6.88 (m, 2H), 6.73 – 6.64 (m, 2H), 5.07 – 4.92 (m, 1H), 4.76 (dd, *J* = 13.5, 3.2 Hz, 1H), 4.46 (d, *J* = 13.4 Hz, 1H), 3.78 (s, 3H), 1.47 (d, *J* = 6.1 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 162.4 (d, *J* = 243.7 Hz), 151.3, 141.21, 139.4 (d, *J* = 2.4 Hz), 139.1 (d, *J* = 8.6 Hz), 123.4 (d, *J* = 8.8 Hz), 115.2, 114.30 (d, *J* = 22.7 Hz), 113.2, 109.5 (d, *J* = 23.1 Hz), 58.9, 55.9, 54.6 (d, *J* = 2.7 Hz), 20.6 (d, *J* = 1.0 Hz).

^{19}F{^{1}H} NMR (376 MHz, Chloroform-*d*) δ -116.05.

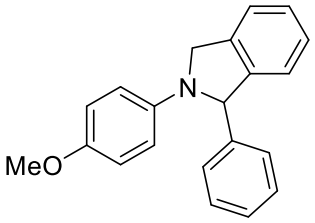
HRMS (ESI): Calcd for $C_{16}H_{17}FNO$ $[M+H]^+$: 258.1289, found: 258.1290.

IR (neat): ν (cm^{-1}) 3049, 2918, 1512, 1361, 1247, 1129, 1038.

Rf 0.13 (Cyclohexane:CH_2Cl_2 = 80:20)

Melting point: 100 ºC

2-(4-methoxyphenyl)-1-phenylisoindoline (5.16l)



Chemical Formula: $C_{21}H_{19}NO$
Molecular Weight: 301.39

Following general procedure G, *N*-benzhydryl-2-bromo-4-methoxy-*N*-methylaniline **5.15l** (76.5 mg, 0.2 mmol, 1 equiv.) was engaged. The crude was purified by preparative thin-layer chromatography (30% CH_2Cl_2 in *c*Hex) to afford the title compound **5.16l** (44.3 mg, 0.147 mmol, 74%) as a white solid.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.41 – 7.35 (m, 3H), 7.34 – 7.29 (m, 2H), 7.28 – 7.16 (m, 3H), 7.08 – 7.03 (m, 1H), 6.82 – 6.77 (m, 2H), 6.64 – 6.57 (m, 2H), 5.78 (dd, *J* = 3.4, 1.6 Hz, 1H), 5.07 (dd, *J* = 12.9, 3.5 Hz, 1H), 4.72 (d, *J* = 13.3 Hz, 1H), 3.72 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 151.5, 144.1, 142.9, 141.4, 136.6, 129.1, 127.5, 127.5, 127.4, 126.4, 123.4, 122.6, 115.1, 113.7, 69.6, 56.0, 55.7.

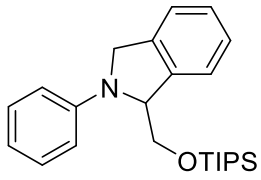
HRMS (ESI): Calcd for $C_{21}H_{20}NO$ $[M+H]^+$: 302.1539, found: 302.1542.

IR (neat): ν (cm^{-1}) 3049, 2799, 1511, 1460, 1254, 1239, 1039.

Rf 0.28 (Cyclohexane:CH_2Cl_2 = 70:30)

Melting point: 158 ºC

2-phenyl-1-(((triisopropylsilyl)oxy)methyl)isoindoline (5.16m)



Chemical Formula: $C_{24}H_{35}NOSi$
Molecular Weight: 381.64

Following general procedure G, 2-bromo-*N*-methyl-*N*-(1-phenyl-2-((triisopropylsilyl)oxy)ethyl)aniline **5.15m** (92.5 mg, 0.2 mmol, 1 equiv.) was engaged. The crude was purified by preparative thin-layer chromatography (2% CH_2Cl_2 in *c*Hex) to afford the title compound **5.16m** (64.5 mg, 0.169 mmol, 85%) as a pale brown oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.56 – 7.49 (m, 1H), 7.33 – 7.25 (m, 5H), 6.82 – 6.67 (m, 3H), 5.07 (d"t", *J* = 6.8, 3.2 Hz, 1H), 4.76 (dd, *J* = 13.1, 3.1 Hz, 1H), 4.54 (d, *J* = 13.1 Hz, 1H), 4.15 (dd, *J* = 9.6, 3.2 Hz, 1H), 3.74 (dd, *J* = 9.6, 7.2 Hz, 1H), 1.10 – 0.92 (m, 21H).

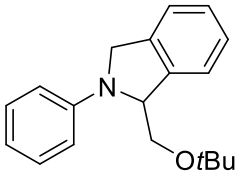
^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 146.8, 141.4, 137.7, 129.5, 127.4, 127.0, 123.7, 122.2, 116.3, 112.2, 65.1, 54.8, 18.1, 18.1, 12.3.

HRMS (ESI): Calcd for $C_{24}H_{36}NOSi$ $[M+H]^+$: 382.2561, found: 382.2560.

IR (neat): ν (cm^{-1}) 2940, 2865, 1682, 1465, 1380.

Rf 0.14 (Cyclohexane:CH_2Cl_2 = 98:2)

1-(*tert*-butoxymethyl)-2-phenylisoindoline (5.16n)



Chemical Formula: $C_{19}H_{23}NO$
Molecular Weight: 281.40

Following general procedure G, 2-bromo-*N*-(2-(*tert*-butoxy)-1-phenylethyl)-*N*-methylaniline **5.15n** (72.5 mg, 0.2 mmol, 1 equiv.) was engaged. The crude was purified by preparative thin-layer chromatography (20% CH_2Cl_2 in *c*Hex) to afford the title compound **5.16n** (47.1 mg, 0.167 mmol, 84%) as a white solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.60 – 7.52 (m, 1H), 7.35 – 7.27 (m, 5H), 6.81 – 6.77 (m, 2H), 6.77 – 6.71 (m, 1H), 5.04 (dt, *J* = 8.5, 3.2 Hz, 1H), 4.78 (dd, *J* = 13.2, 3.1 Hz, 1H), 4.55 (d, *J* = 13.2 Hz, 1H), 3.90 (dd, *J* = 8.6, 3.3 Hz, 1H), 3.24 (t, *J* = 8.5 Hz, 1H), 1.17 (s, 9H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-d) δ 147.0, 141.9, 137.3, 129.5, 127.4, 127.0, 124.0, 122.2, 116.4, 112.3, 73.3, 64.0, 63.6, 54.8, 27.7.

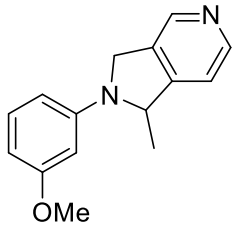
HRMS (ESI): Calcd for $C_{19}H_{24}NO$ $[M+H]^+$: 282.1852, found: 282.1851.

IR (neat): ν (cm^{-1}) 3061, 2973, 1699, 1500, 1371, 1094.

Rf 0.26 (Cyclohexane:CH_2Cl_2 = 80:20)

Melting point: 96 ºC

2-(3-methoxyphenyl)-1-methyl-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine (5.16o)



Chemical Formula: $C_{15}H_{16}N_2O$
Molecular Weight: 240.31

Following general procedure G, *N*-benzhydryl-2-bromo-4-methoxy-*N*-methylaniline **5.15o** (64.2 mg, 0.2 mmol, 1 equiv.) was engaged. The crude was purified by preparative HPLC (15% *i*PrOH in *n*Hex) to afford the title compound **5.16o** (19.4 mg, 0.081 mmol, 40%) as a colourless oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.68 – 8.64 (m, 1H), 8.59 (d, *J* = 5.1 Hz, 1H), 7.32 – 7.21 (m, 2H), 6.44 – 6.36 (m, 2H), 6.32 ("t", *J* = 2.4 Hz, 1H), 5.14 (qd, *J* = 6.3, 3.0 Hz, 1H), 4.84 (dd, *J* = 13.5, 3.2 Hz, 1H), 4.63 (d, *J* = 13.5 Hz, 1H), 3.87 (s, 3H), 1.55 (d, *J* = 6.3 Hz, 3H).

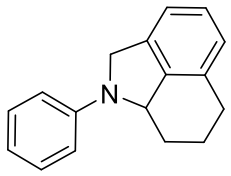
^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 161.1, 152.7, 148.5, 147.5, 144.5, 133.2, 130.3, 117.6, 105.7, 101.7, 99.2, 59.2, 55.3, 52.3, 20.1.

HRMS (ESI): Calcd for $C_{15}H_{17}N_2O$ $[M+H]^+$: 241.1335, found: 241.1335.

IR (neat): ν (cm^{-1}) 3194, 2969, 2835, 1607, 1496, 1363, 1212, 1167, 1050.

Rf 0.33 (Cyclohexane:*i*PrOH = 85:15)

1-phenyl-1,2,6,7,8,8a-hexahydrobenzo[cd]indole (5.16p)



Chemical Formula: $C_{17}H_{17}N$
Molecular Weight: 235.33

Following general procedure G, *N*-(2-bromophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine **5.15p** (63.2 mg, 0.2 mmol, 1 equiv.) was engaged. The crude was purified by preparative thin-layer chromatography (4% CH_2Cl_2 in cHex) to afford the title compound **5.16p** (21.8 mg, 0.093 mmol, 46%) as a colourless oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35 – 7.29 (m, 2H), 7.25 – 7.18 (m, 1H), 7.14 (d, *J* = 7.4 Hz, 1H), 7.06 (d, *J* = 7.5 Hz, 1H), 6.95 – 6.87 (m, 2H), 6.85 – 6.77 (m, 1H), 4.84 (dd, *J* = 13.4, 3.0 Hz, 1H), 4.57 – 4.39 (m, 2H), 2.94 (ddd, *J* = 17.4, 7.9, 2.7 Hz, 1H), 2.82 – 2.60 (m, 2H), 2.17 – 2.05 (m, 1H), 2.05 – 1.92 (m, 1H), 1.35 (tdd, *J* = 12.3, 10.6, 4.2 Hz, 1H).

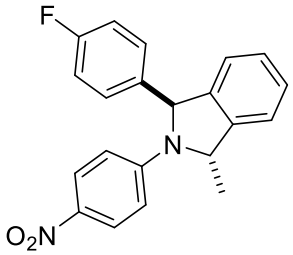
^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 149.4, 140.4, 136.2, 134.4, 129.4, 127.8, 126.2, 119.4, 114.1, 62.4, 57.1, 30.2, 25.8, 21.3.

HRMS (ESI): Calcd for $C_{17}H_{18}N$ $[M+H]^+$: 236.1434, found: 236.1433.

IR (neat): ν (cm^{-1}) 3040, 2935, 1598, 1500, 1361.

Rf 0.11 (Cyclohexane:CH_2Cl_2 = 96:4)

***trans*-1-(4-fluorophenyl)-3-methyl-2-(4-nitrophenyl)isoindoline (5.16q)**



Chemical Formula: $C_{21}H_{17}FN_2O_2$
Molecular Weight: 348.38

Following general procedure G, 2-bromo-*N*-(4-fluorobenzyl)-4-nitro-*N*-(1-phenylethyl)aniline **5.15q** (85.9 mg, 0.2 mmol, 1 equiv.) was engaged. The crude was purified by silica gel column chromatography (30% CH_2Cl_2 in *c*Hex) to afford the title compound **5.16p** (31.6 mg, 0.091 mmol, 45%) as a yellow solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.07 – 8.01 (m, 2H), 7.37 – 7.30 (m, 2H), 7.26 – 7.22 (m, 1H), 7.21 – 7.13 (m, 2H), 6.98 ("t"d, *J* = 8.3, 4.7 Hz, 3H), 6.72 – 6.60 (m, 2H), 6.08 (d, *J* = 2.6 Hz, 1H), 5.60 (qd, *J* = 6.6, 3.3 Hz, 1H), 1.60 (d, *J* = 6.1 Hz, 3H).

^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 162.3 (d, *J* = 246.8 Hz), 149.6, 140.6, 140.2, 137.8, 137.6 (d, *J* = 3.3 Hz), 128.3 (d, *J* = 3.3 Hz), 128.2 (d, *J* = 8.2 Hz), 125.7, 123.6, 122.4, 116.3 (d, *J* = 21.7 Hz), 114.3, 67.9, 60.5, 20.7.

^{19}F{^{1}H} NMR (376 MHz, Chloroform-*d*) δ -114.09.

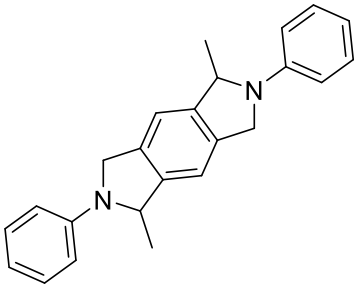
HRMS (ESI): Calcd for $C_{21}H_{17}FN_2NaO_2$ $[M+Na]^+$: 371.1166, found: 371.1167.

IR (neat): ν (cm^{-1}) 2974, 2922, 1591, 1504, 1292, 1110.

Rf 0.18 (Cyclohexane:CH_2Cl_2 = 70:30)

Melting point: 122 ºC

1,5-dimethyl-2,6-diphenyl-1,2,3,5,6,7-hexahydropyrrolo[3,4-*f*]isoindole (5.16r)



Chemical Formula: $C_{24}H_{24}N_2$
Molecular Weight: 340.47

Following general procedure G, *N*,*N*'-(1,4-phenylenebis(ethane-1,1-diyl))bis(2-bromo-*N*-methylaniline) **5.15r** (100 mg, 0.2 mmol, 1 equiv.) was weighted in a 30 mL tube. $(Pd(\pi\text{-allyl})Cl)_2$ (7.32 mg, 0.02 mmol, 10 mol%), IMesCl (13.6 mg, 0.04 mmol, 20 mol%), Cs_2CO_3 (195 mg, 0.6 mmol, 3 equiv.) and CsOPiv (28 mg, 0.12 mmol, 60 mol%) were weighted in a glovebox. The tube was closed with a sealed cap, taken out of the glovebox, and *m*-xylene (6 mL) was added. The reaction was stirred in a heating block preheated at 110 °C for 15 h. The reaction was cooled to room temperature, filtered through a pad of *Celite*, washed with EtOAc and concentrated *in vacuo*. The crude mixture was analyzed by ^{1}H NMR (using trichloroethylene as an internal standard) and purified by chromatography on silica gel (20% CH_2Cl_2 in *c*Hex), providing the desired product **5.16r** as a pale yellow solid (56.1 mg, 0.165 mmol, 82%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.28 (m, 4H), 7.25 – 7.18 (m, 2H), 6.82 – 6.70 (m, 6H), 5.14 (qd, *J* = 6.1, 2.7 Hz, 2H), 4.79 (dd, *J* = 13.3, 3.2 Hz, 2H), 4.59 – 4.49 (m, 2H), 1.54 (t, *J* = 6.5 Hz, 6H).

^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 146.6, 143.1, 131.2, 129.5, 121.4, 116.3, 112.4, 59.2, 53.0, 20.9.

HRMS (ESI): Calcd for $C_{24}H_{25}N_2$ $[M+H]^+$: 341.2018, found: 341.2012.

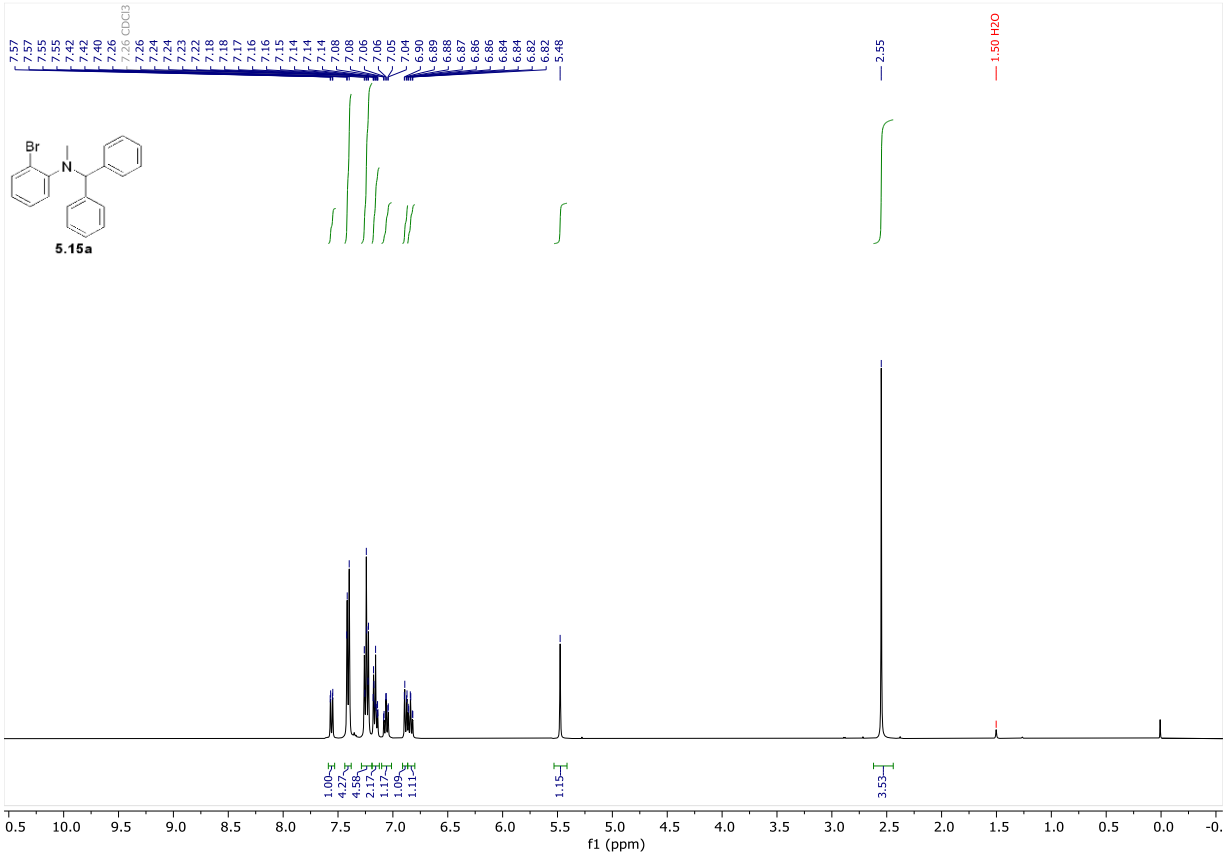
IR (neat): ν (cm^{-1}) 2922, 2853, 1703, 1496, 1367, 1149.

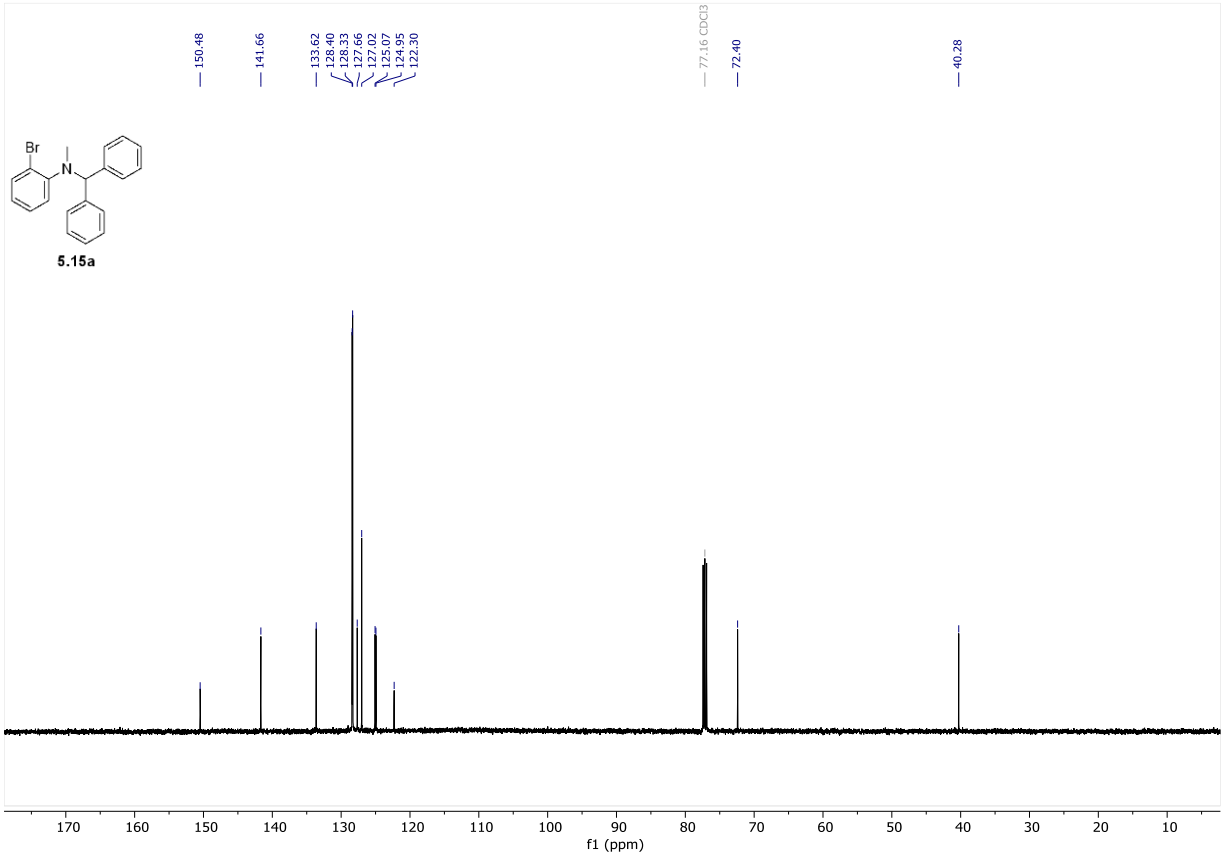
Rf 0.2 (Cyclohexane:CH_2Cl_2 = 80:20)

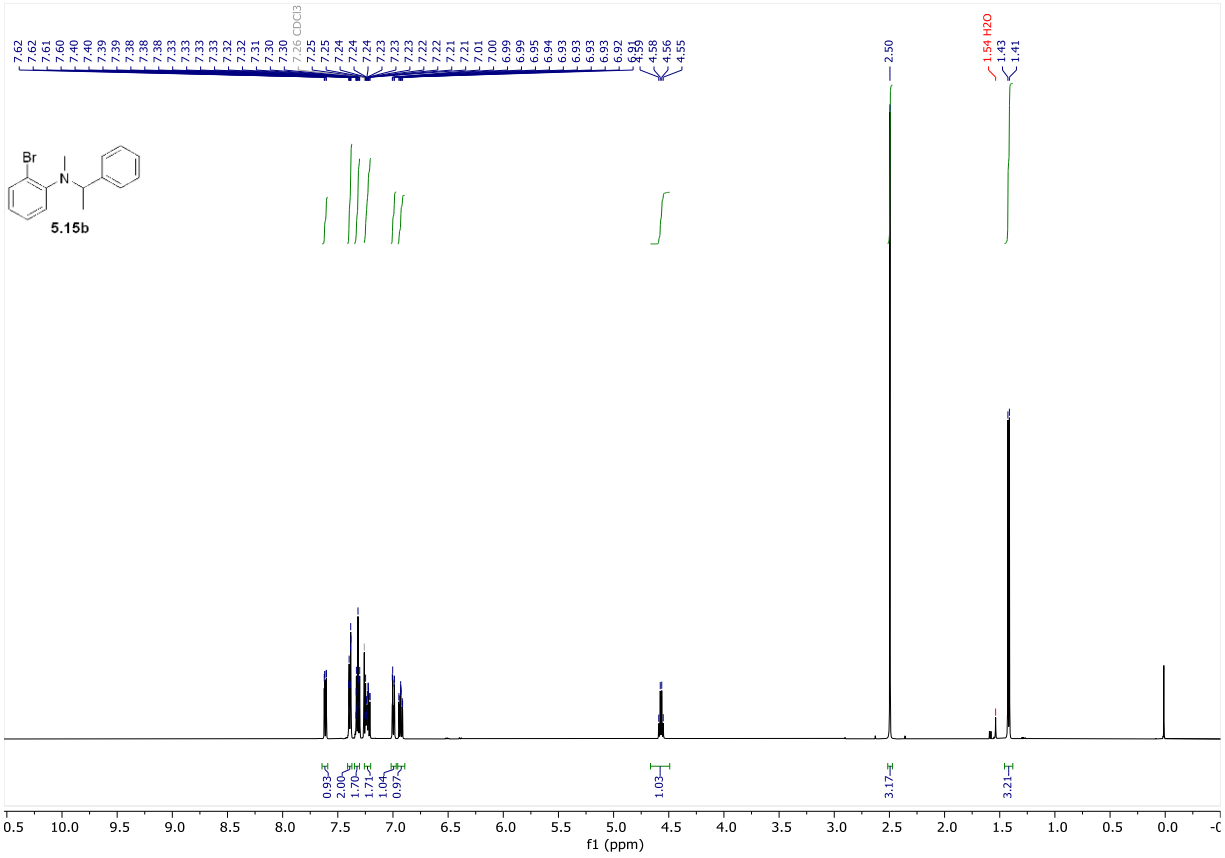
Melting point: 127 ºC

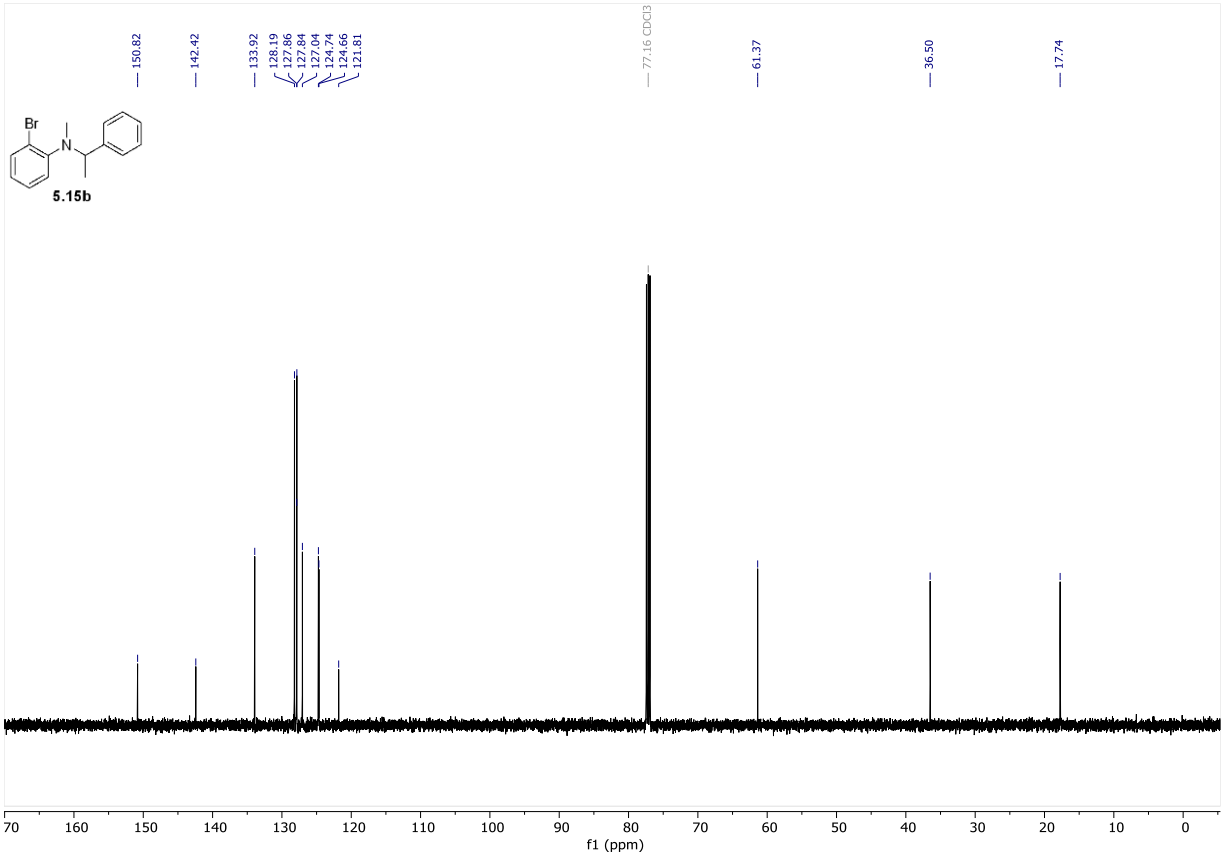
7.8 Experimental data in the study of Pd shift

7.8.1 NMR spectral data of substrates






7.62 7.62 7.61 7.60 7.40 7.40 7.39 7.39 7.38 7.38 7.38 7.33 7.33 7.33 7.32 7.32 7.31 7.30 7.30 7.26 CDCl3 7.25 7.25 7.24 7.24 7.24 7.23 7.23 7.23 7.22 7.22 7.21 7.21 7.01 7.00 6.99 6.99 6.95 6.94 6.93 6.93 6.93 6.93 6.92 4.58 4.56 4.55
2.50
1.54 H2O
1.43
1.41
Br
N
5.15b
0.93
2.00
1.70
1.71
1.04
0.97
1.03
3.17
3.21
f1 (ppm)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124.74
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121.81
77.16 CDCl3
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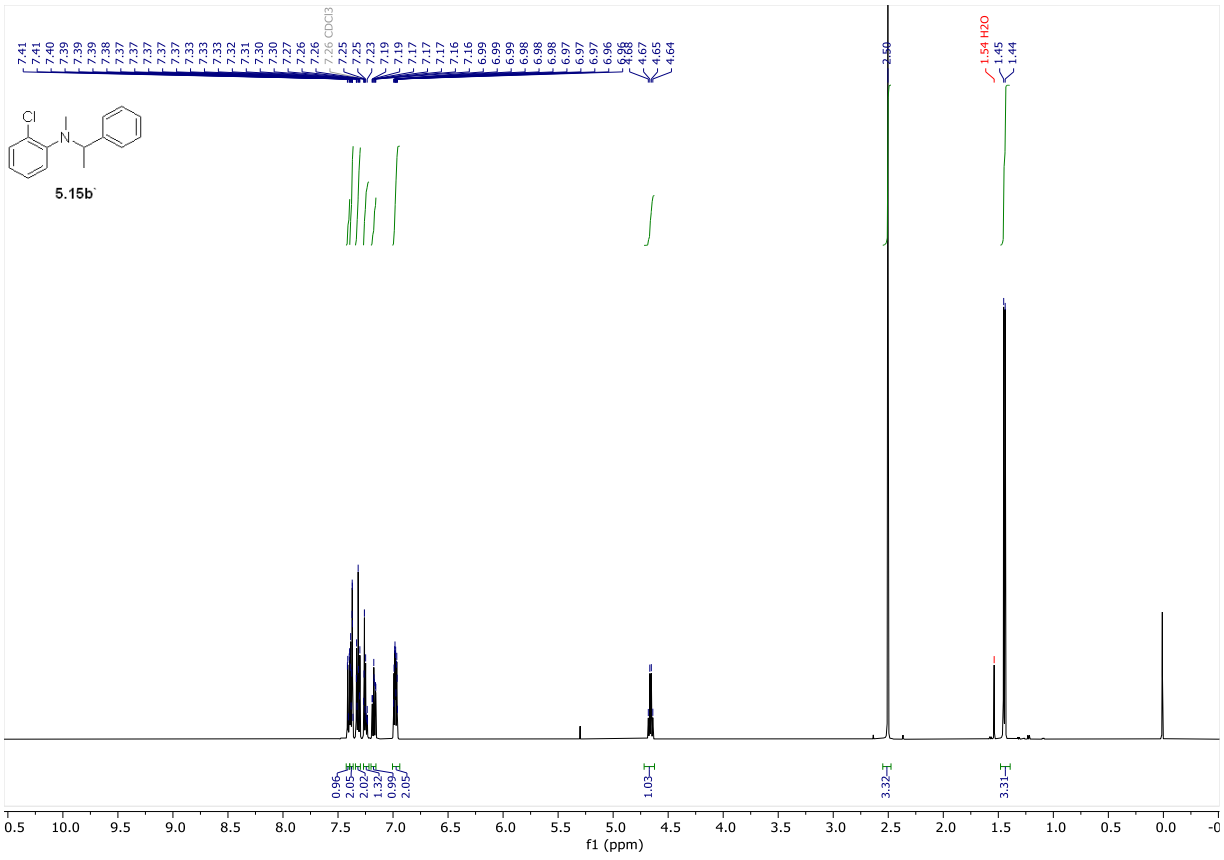
36.50
17.74
Br
N
5.15b
f1 (ppm)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7.25
7.23
7.19
7.17
7.16
6.99
6.98
6.97
6.96
4.68
4.67
4.65
4.64
2.50
1.54 H2O
1.45
1.44
Cl
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5.15b`
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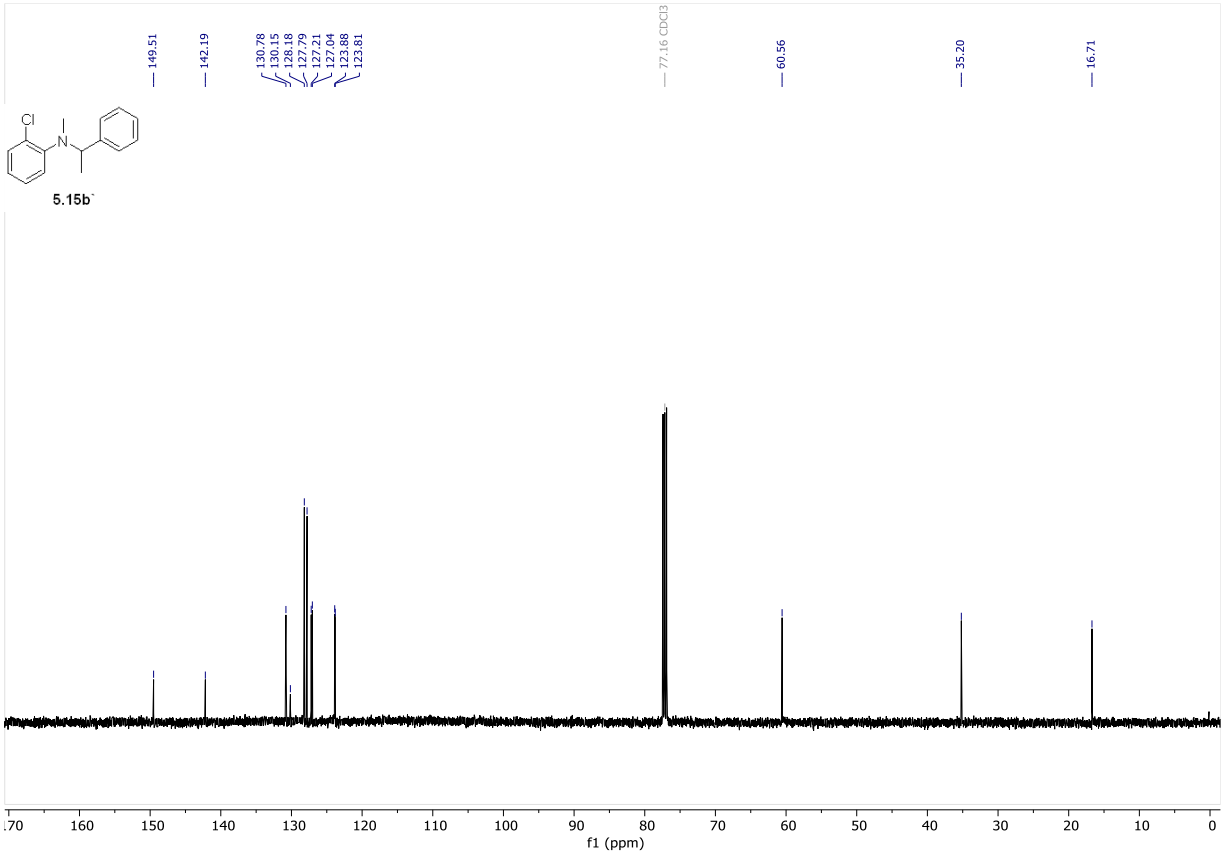
2.02
1.32
0.99
2.05
1.03
3.32
3.31
f1 (ppm)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123.81
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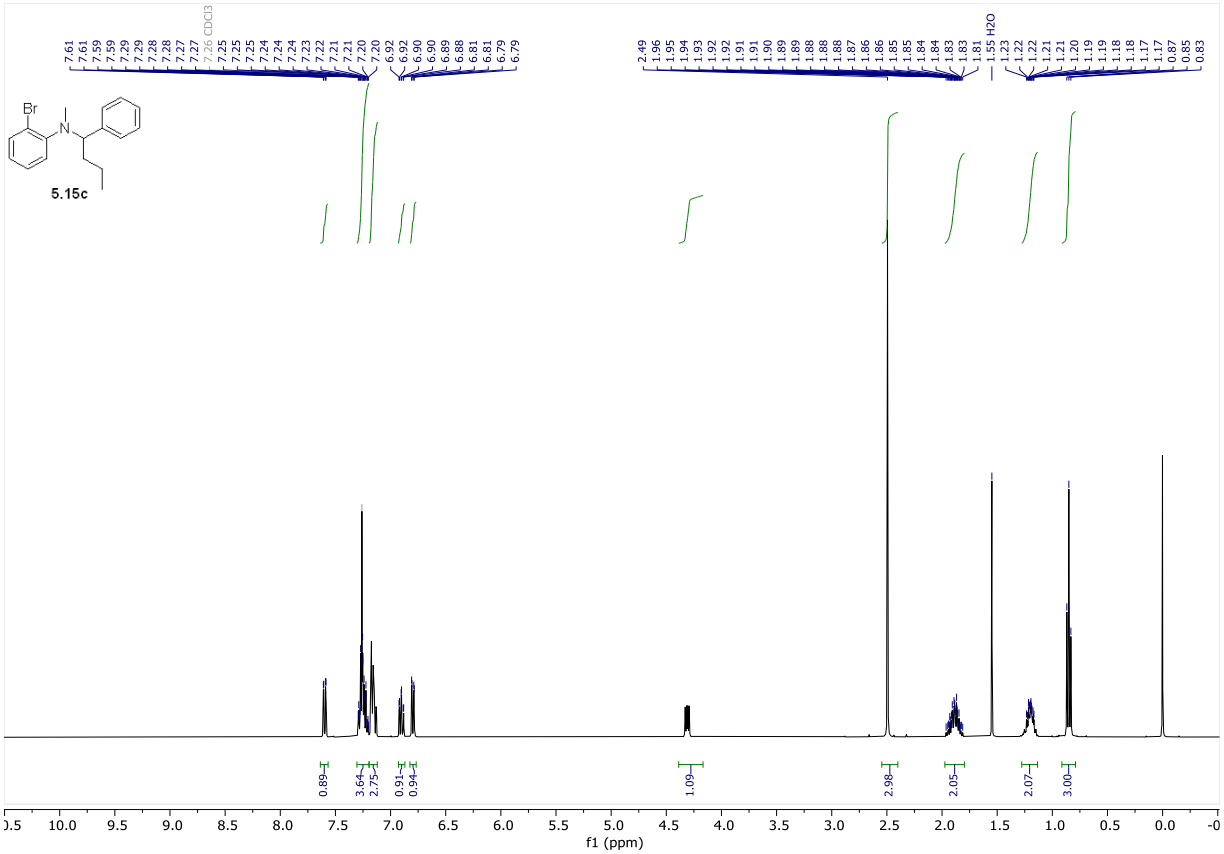
35.20
16.71
Cl
N
5.15b`
f1 (ppm)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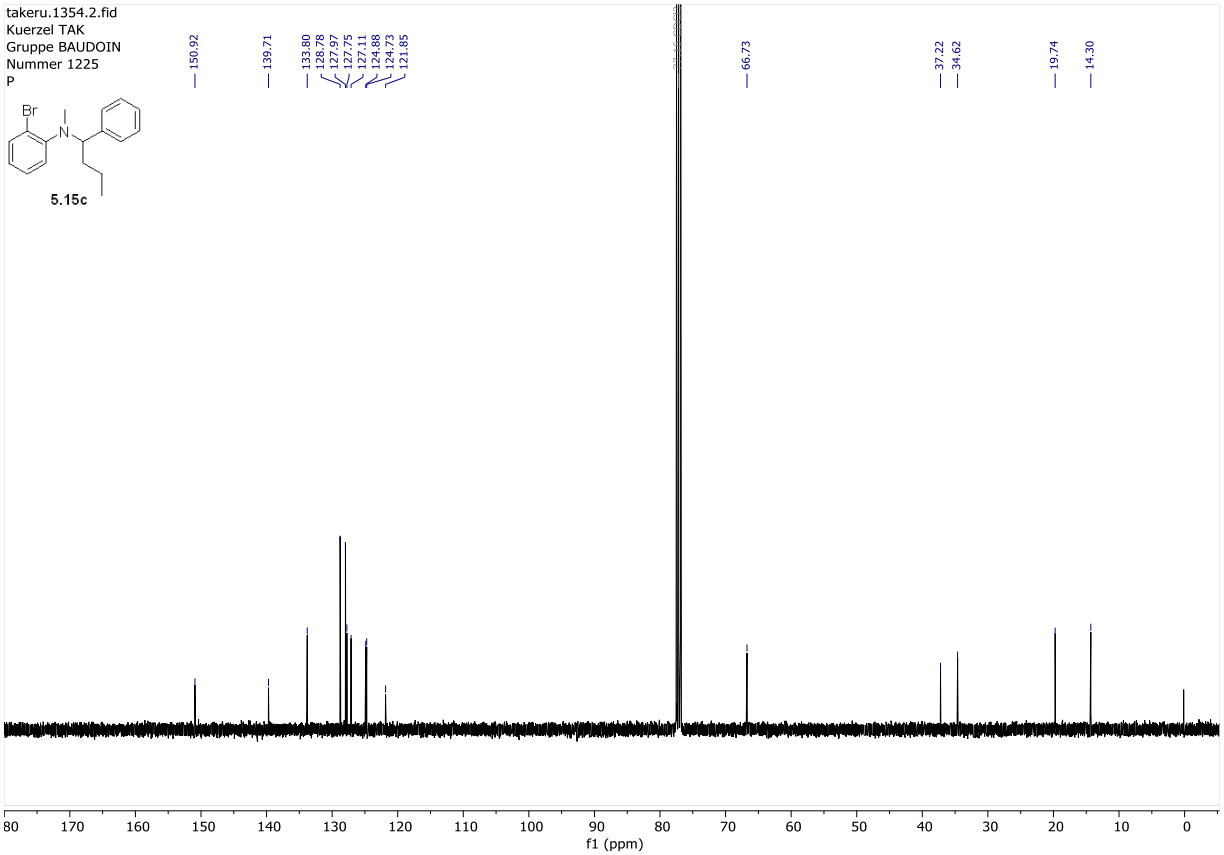
2.49 1.96 1.95 1.94 1.93 1.92 1.92 1.91 1.91 1.90 1.89 1.89 1.88 1.88 1.88 1.87 1.86 1.86 1.85 1.85 1.84 1.84 1.83 1.81 1.81 1.55 H2O 1.23 1.22 1.22 1.21 1.21 1.20 1.19 1.19 1.18 1.18 1.17 1.17 0.87 0.85 0.83
Br
N
5.15c
0.89 3.64 2.75 0.91 0.94 1.09 2.98 2.05 2.07 3.00
f1 (ppm)


takeru.1354.2.fid
Kuerzel TAK
Gruppe BAUDOIN
Nummer 1225
P
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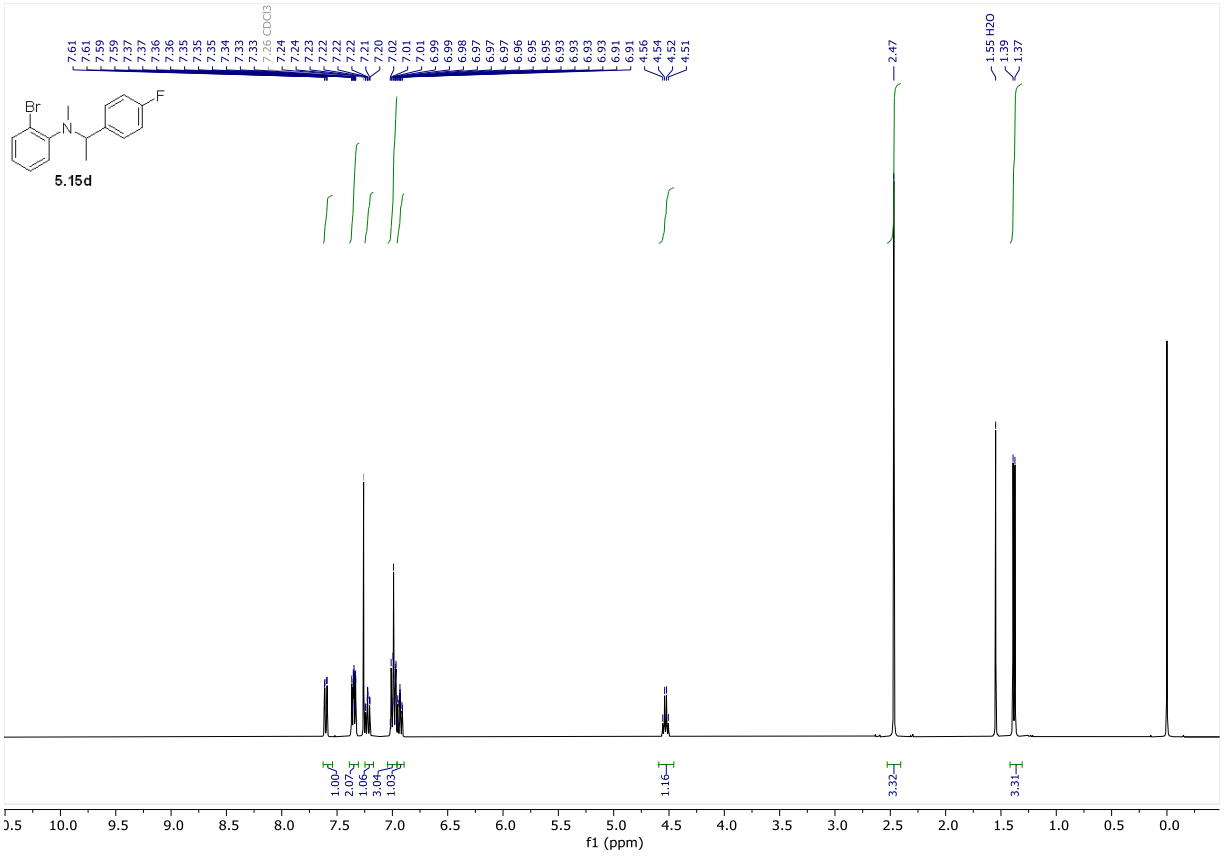
Br
N
5.15c
f1 (ppm)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7.35
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7.33
7.26 CDCl3
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7.23
7.22
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7.22
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7.20
7.02
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6.93
6.93
6.93
6.91
6.91
4.56
4.54
4.52
4.51
2.47
1.55 H2O
1.39
1.37
Br
N
F
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1.06
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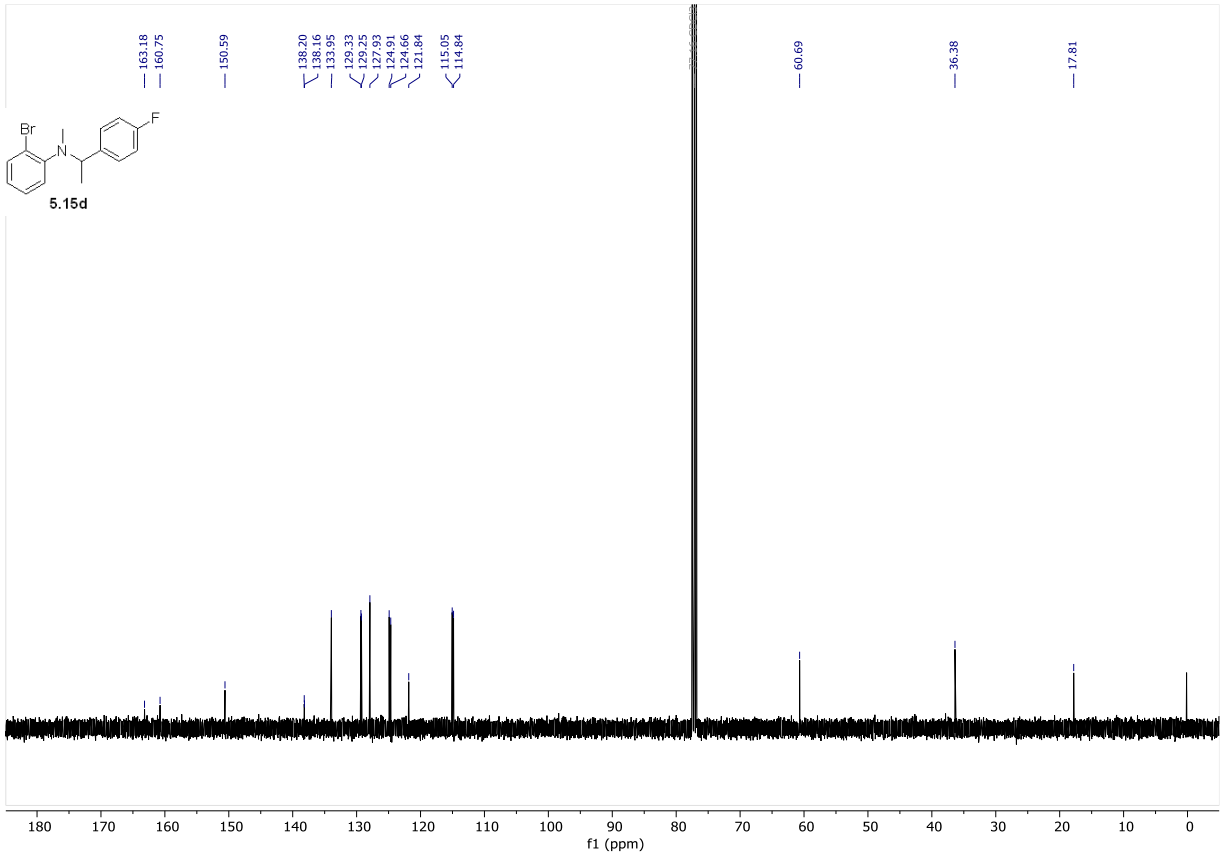
1.03
1.16
3.32
3.31
f1 (ppm)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138.16
133.95
129.33
129.25
127.93
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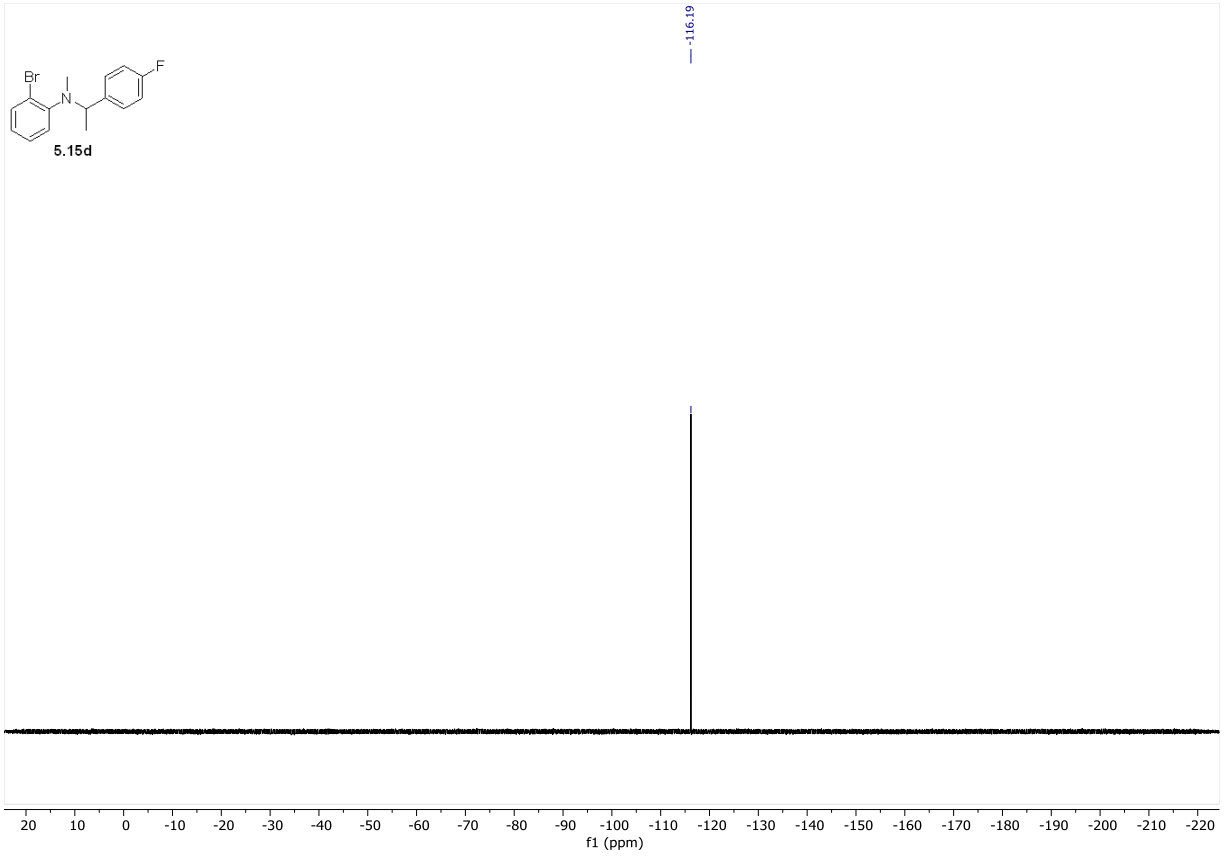
124.66
121.84
115.05
114.84
60.69
36.38
17.81
Br
N
F
5.15d
f1 (ppm)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Br
N
F
5.15d
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
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-140
-150
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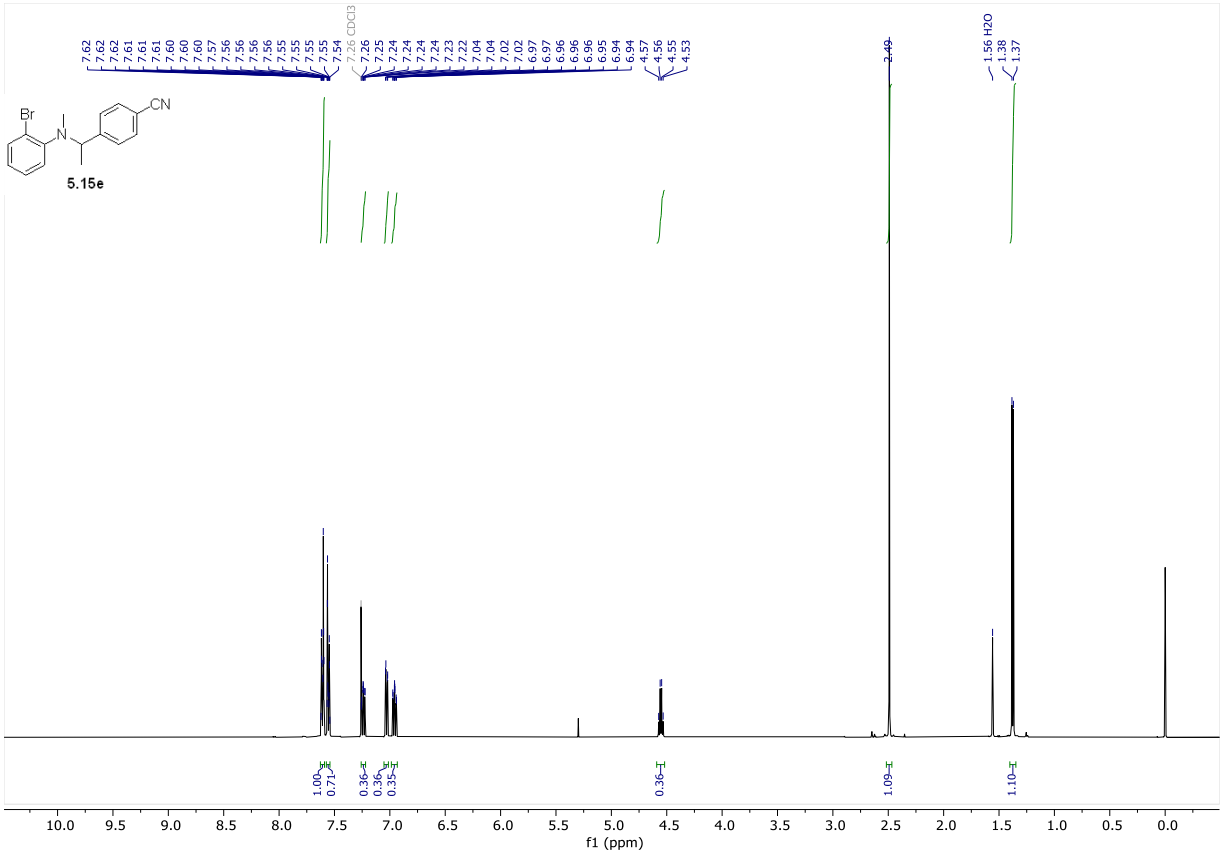
-180
-190
-200
-210
-220
f1 (ppm)


7.62
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6.96
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1.37
Br
N
CN
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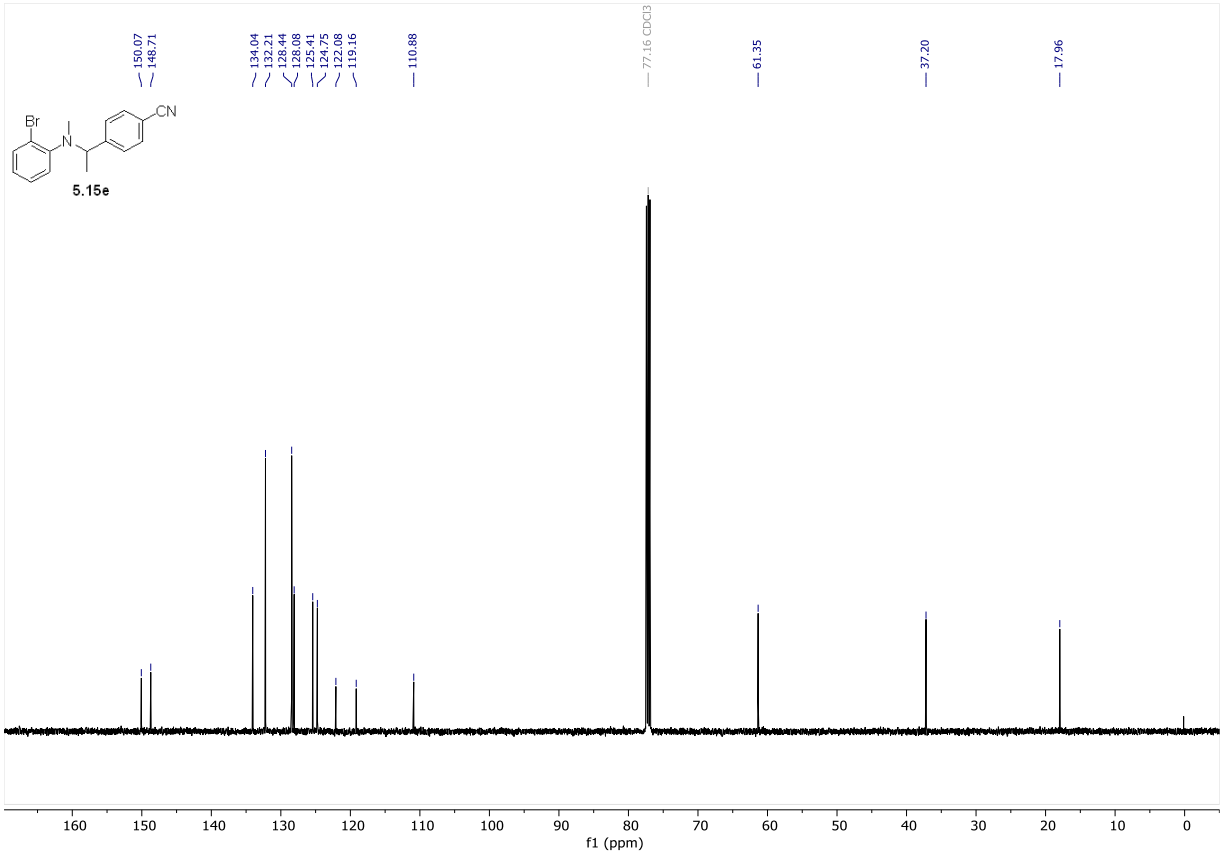
0.71
0.36
0.36
0.35
0.36
1.09
1.10
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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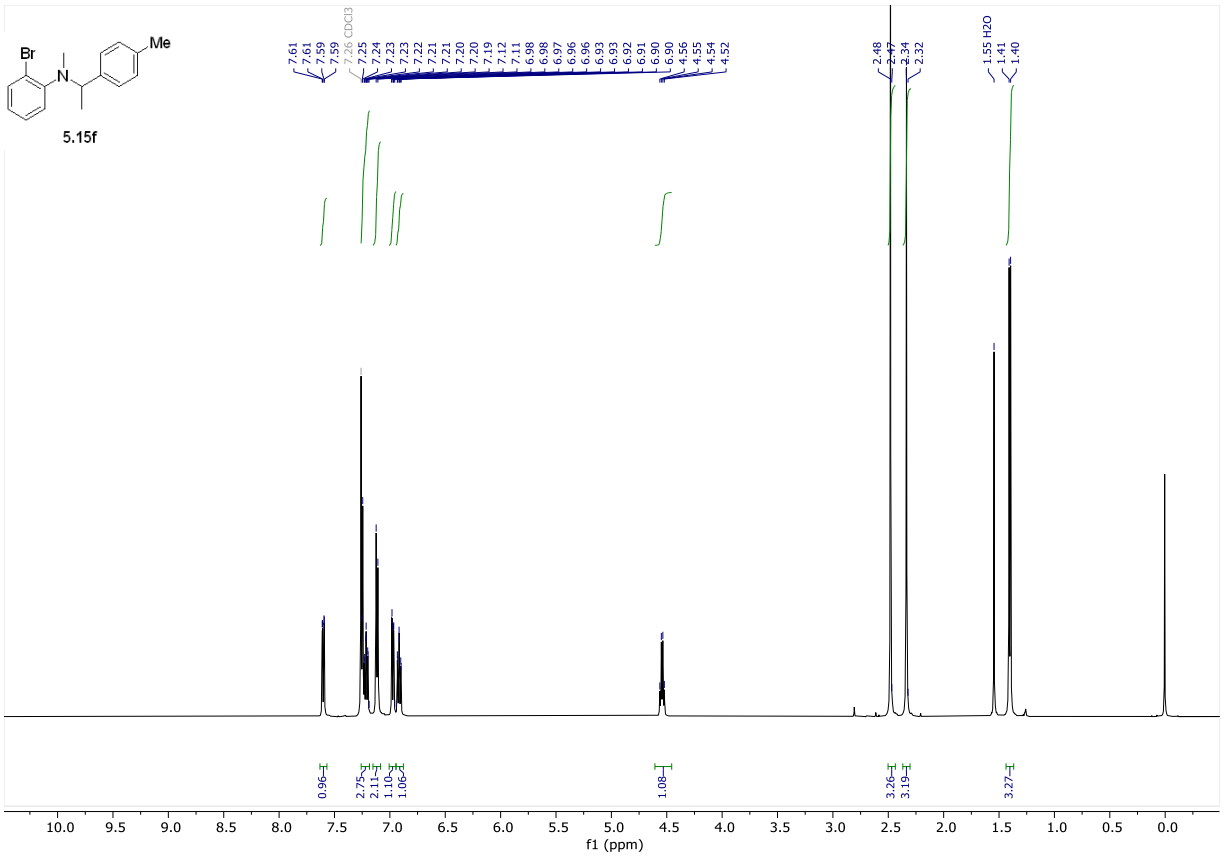
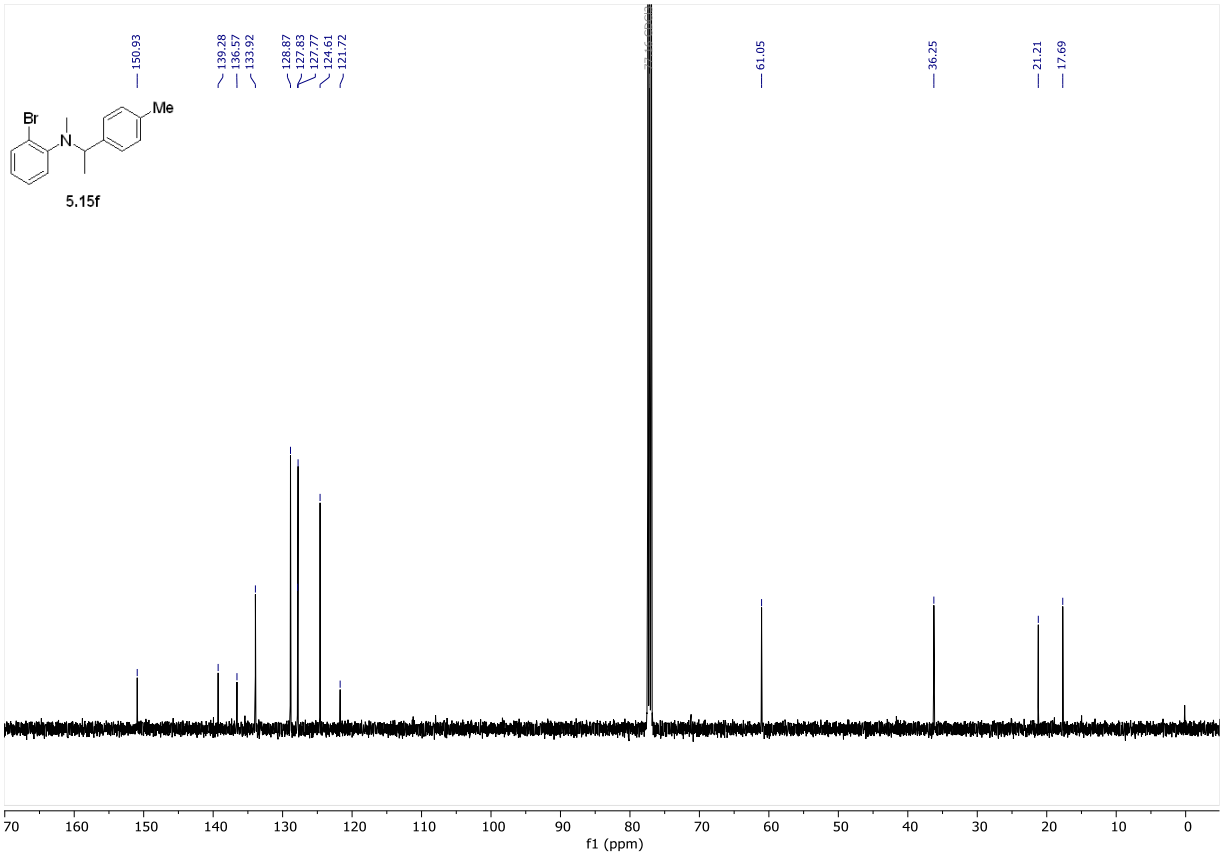
148.71
134.04
132.21
128.44
128.08
125.41
124.75
122.08
119.16
110.88
77.16 CDCl3
61.35
37.20
17.96
Br
N
CN
5.15e
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Br
N
Me
5.15f
7.61
7.61
7.59
7.59
7.26 CDCl3
7.25
7.24
7.23
7.23
7.22
7.21
7.21
7.20
7.20
7.19
7.12
7.11
6.98
6.98
6.97
6.96
6.96
6.93
6.93
6.92
6.91
6.90
6.90
4.56
4.55
4.54
4.52
2.48
2.47
2.34
2.32
1.55 H2O
1.41
1.40
0.96
2.75
2.11
1.10
1.06
1.08
3.26
3.19
3.27
10.0 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
f1 (ppm)


Br
N
Me
5.15f
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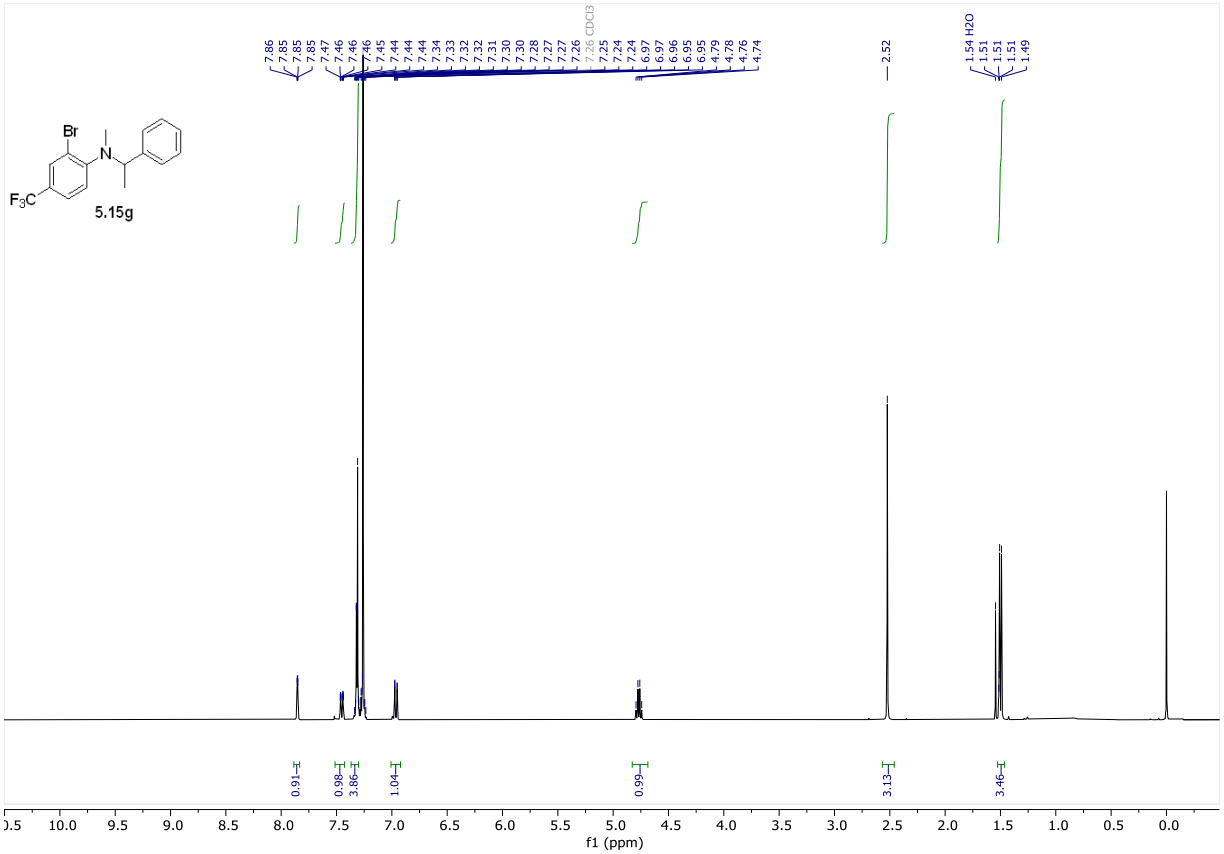
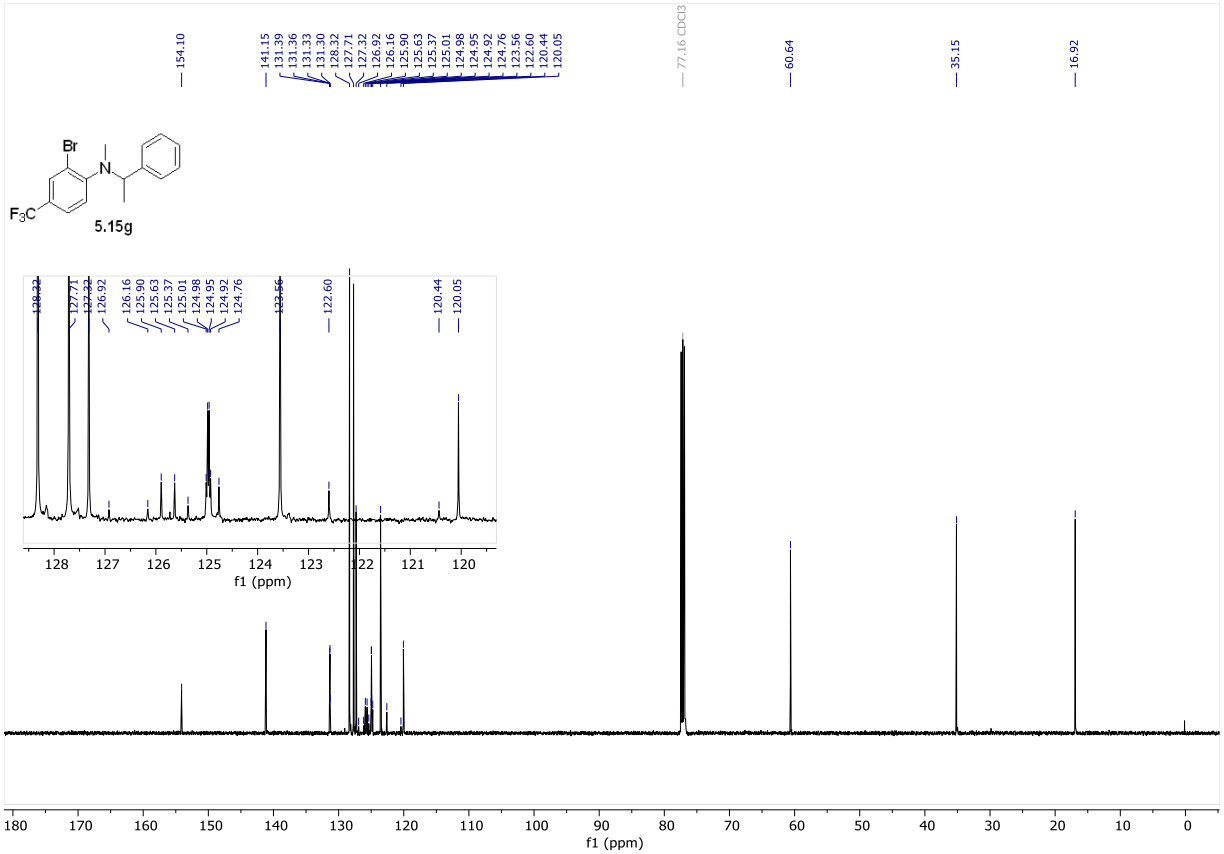
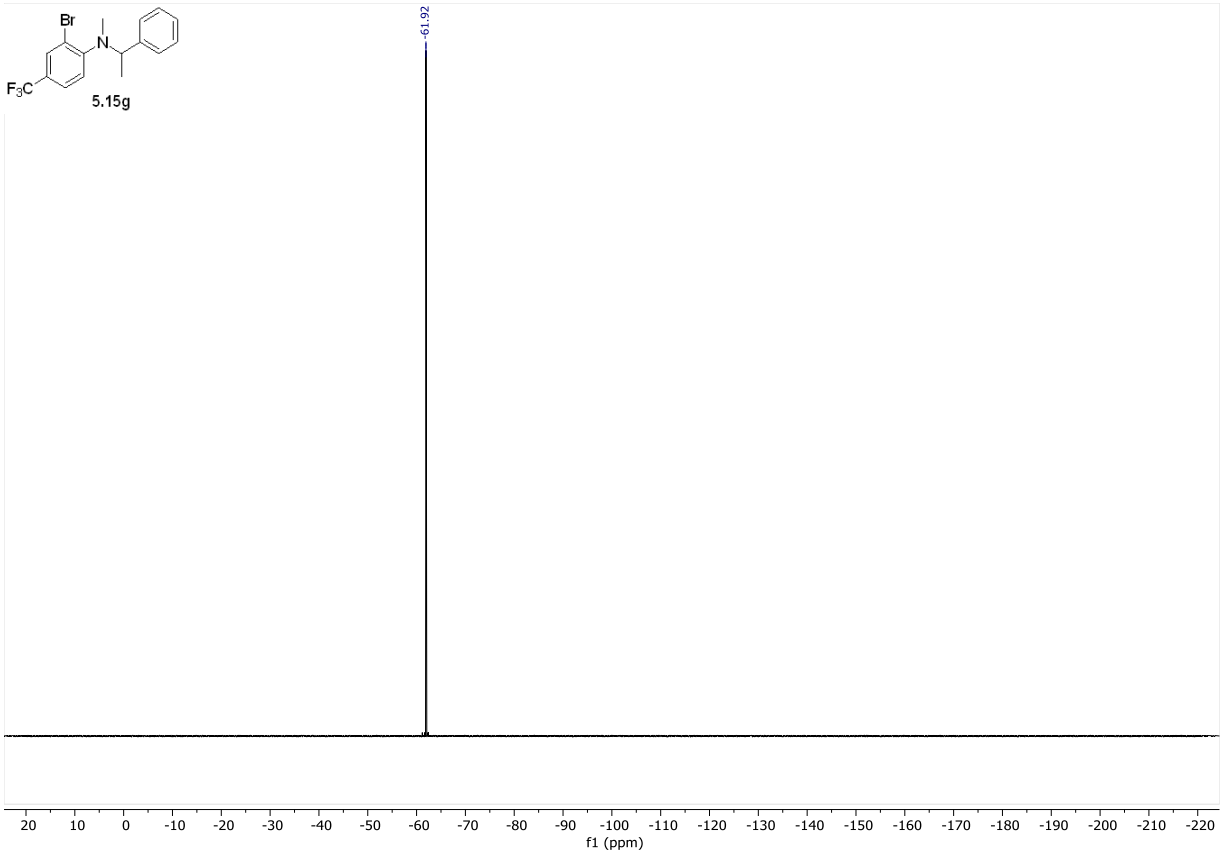
139.28
136.57
133.92
128.87
127.83
127.77
124.61
121.72
61.05
36.25
21.21
17.69
70 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Br
N
F3C
5.15g
7.86
7.85
7.85
7.85
7.47
7.46
7.46
7.46
7.45
7.44
7.44
7.44
7.34
7.33
7.32
7.32
7.31
7.30
7.30
7.28
7.27
7.27
7.26
7.26 CDCl3
7.25
7.24
7.24
6.97
6.97
6.96
6.95
6.95
4.79
4.78
4.76
4.74
2.52
1.54 H2O
1.51
1.51
1.51
1.49
0.91
0.98
3.86
1.04
0.99
3.13
3.46
f1 (ppm)


Br
N
F3C
5.15g
154.10
141.15
131.39
131.36
131.33
131.30
128.32
127.71
127.32
126.92
126.16
125.90
125.63
125.37
125.01
124.98
124.95
124.92
124.76
123.56
122.60
120.44
120.05
77.16 CDCl3
60.64
35.15
16.92
f1 (ppm)


Br
N
F3C
5.15g
-61.92
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
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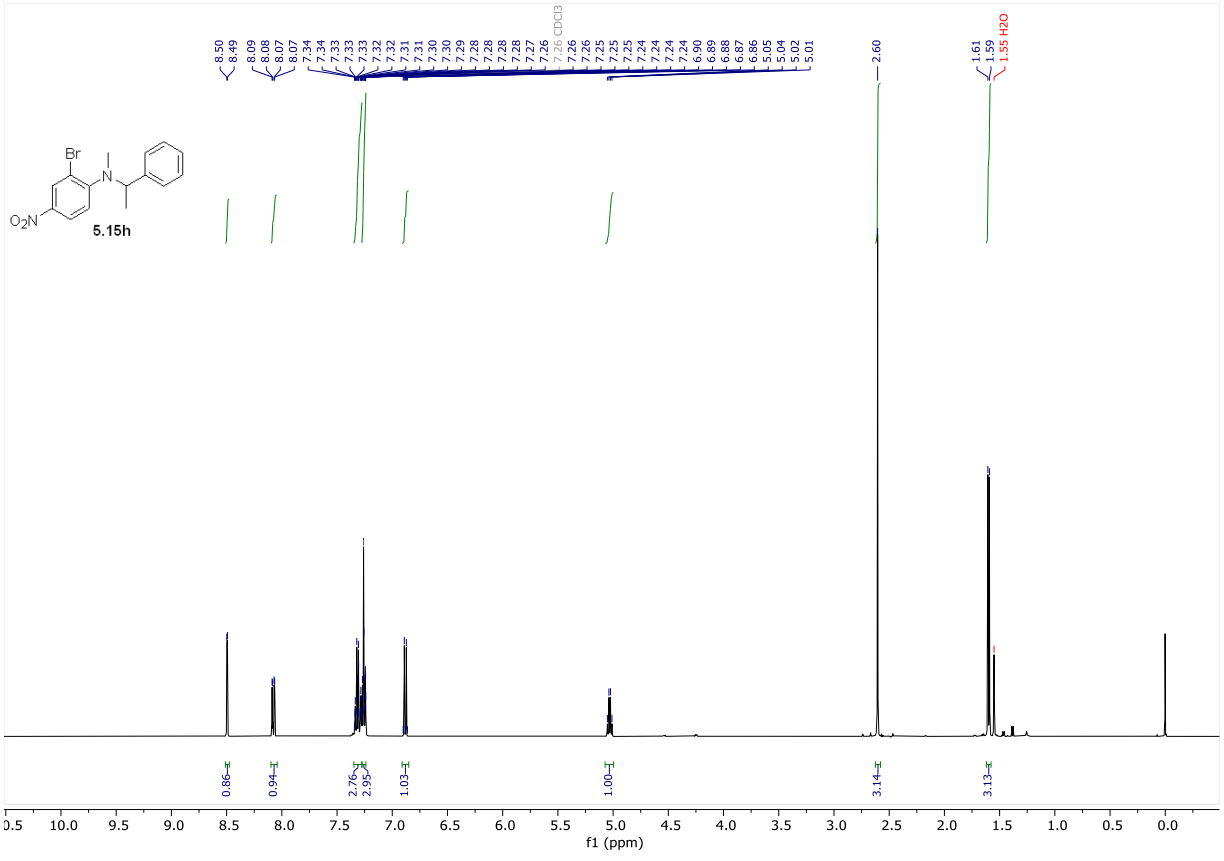
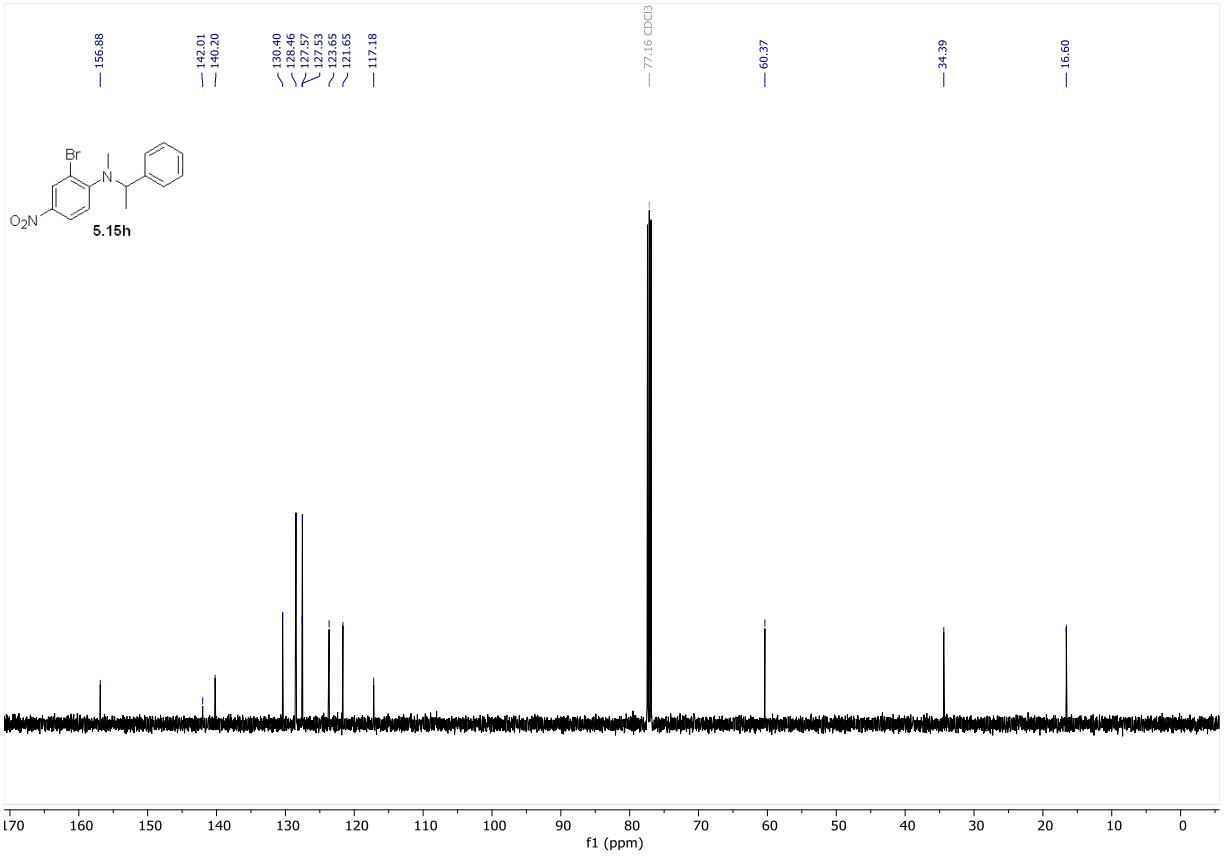
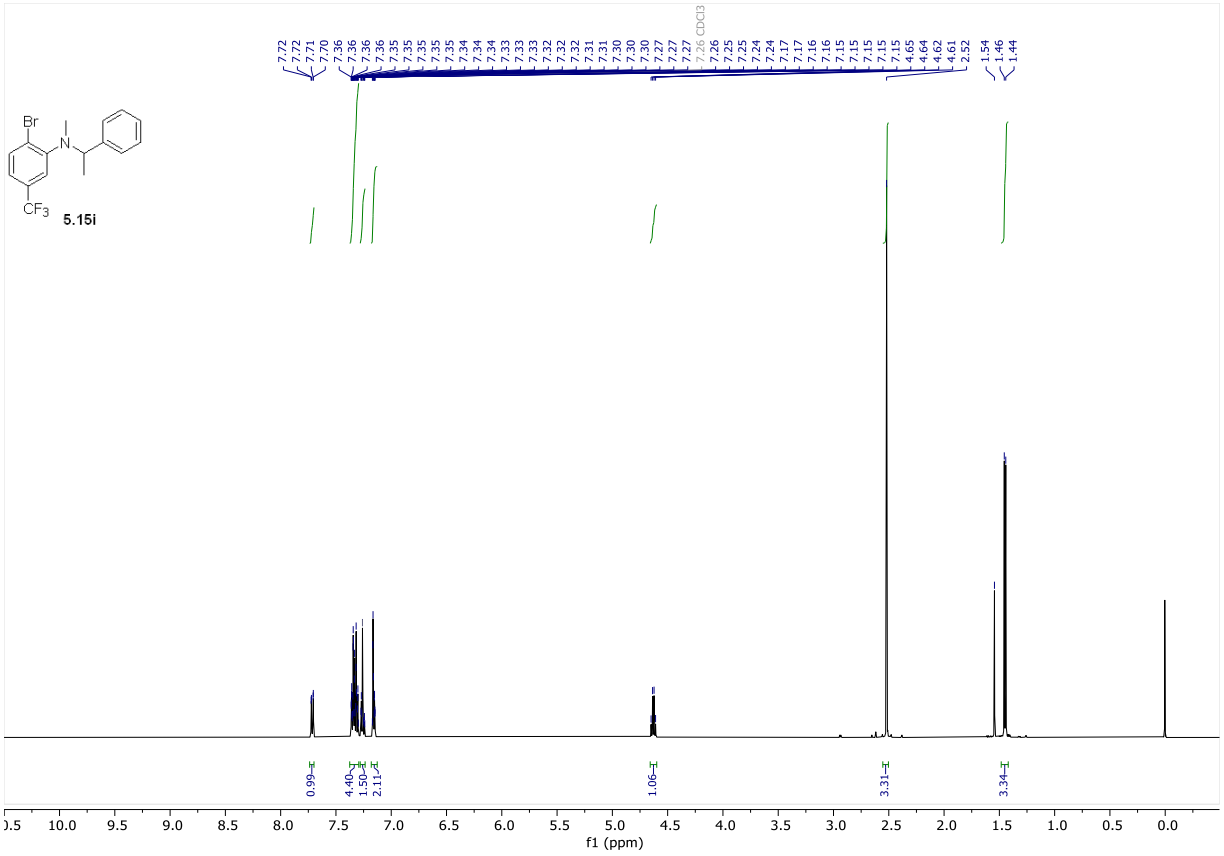
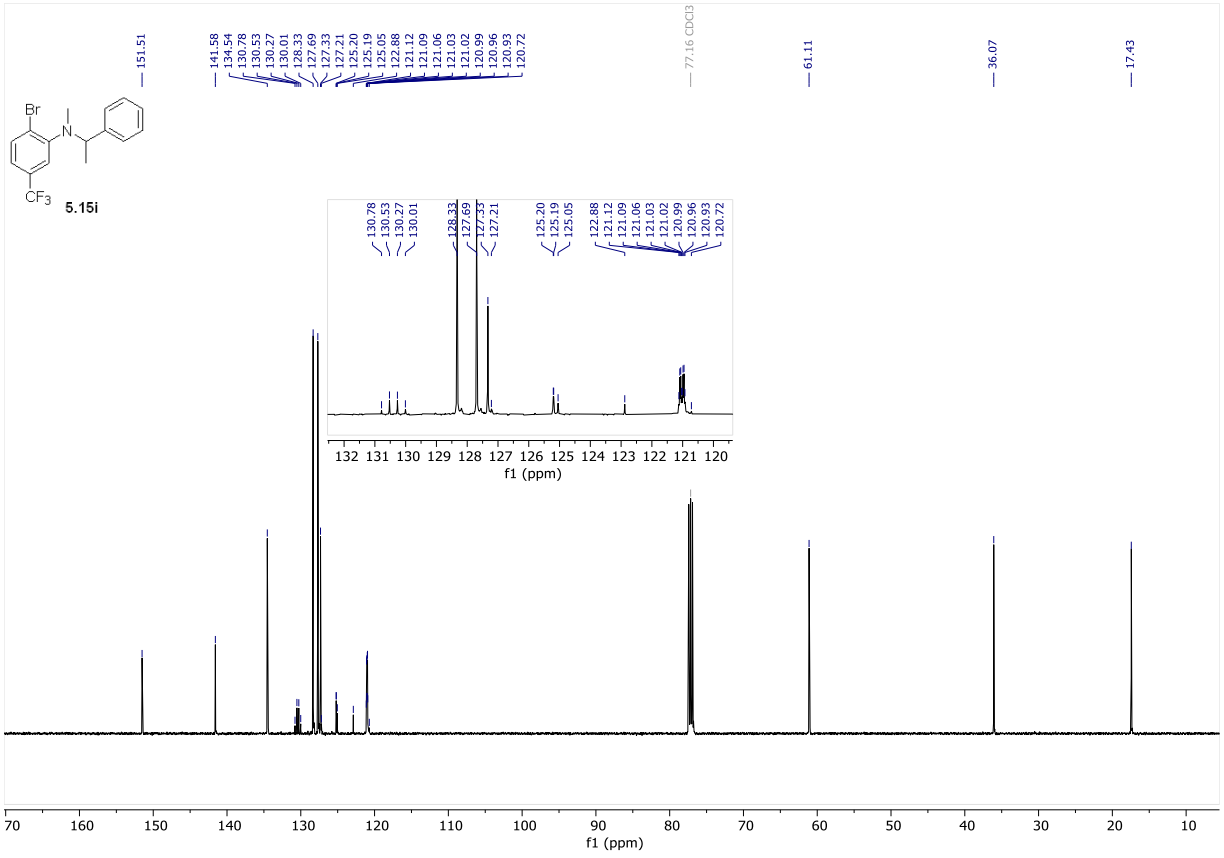
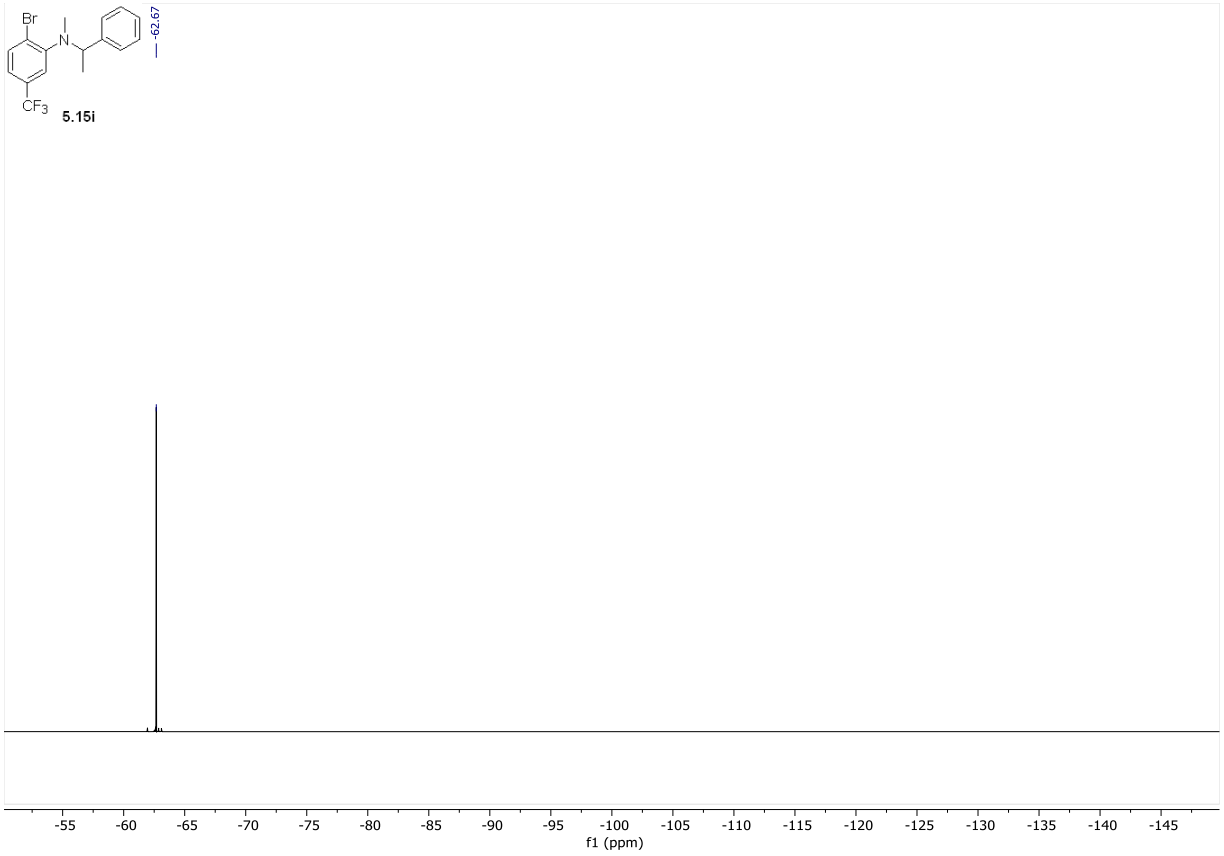
-180
-190
-200
-210
-220
f1 (ppm)

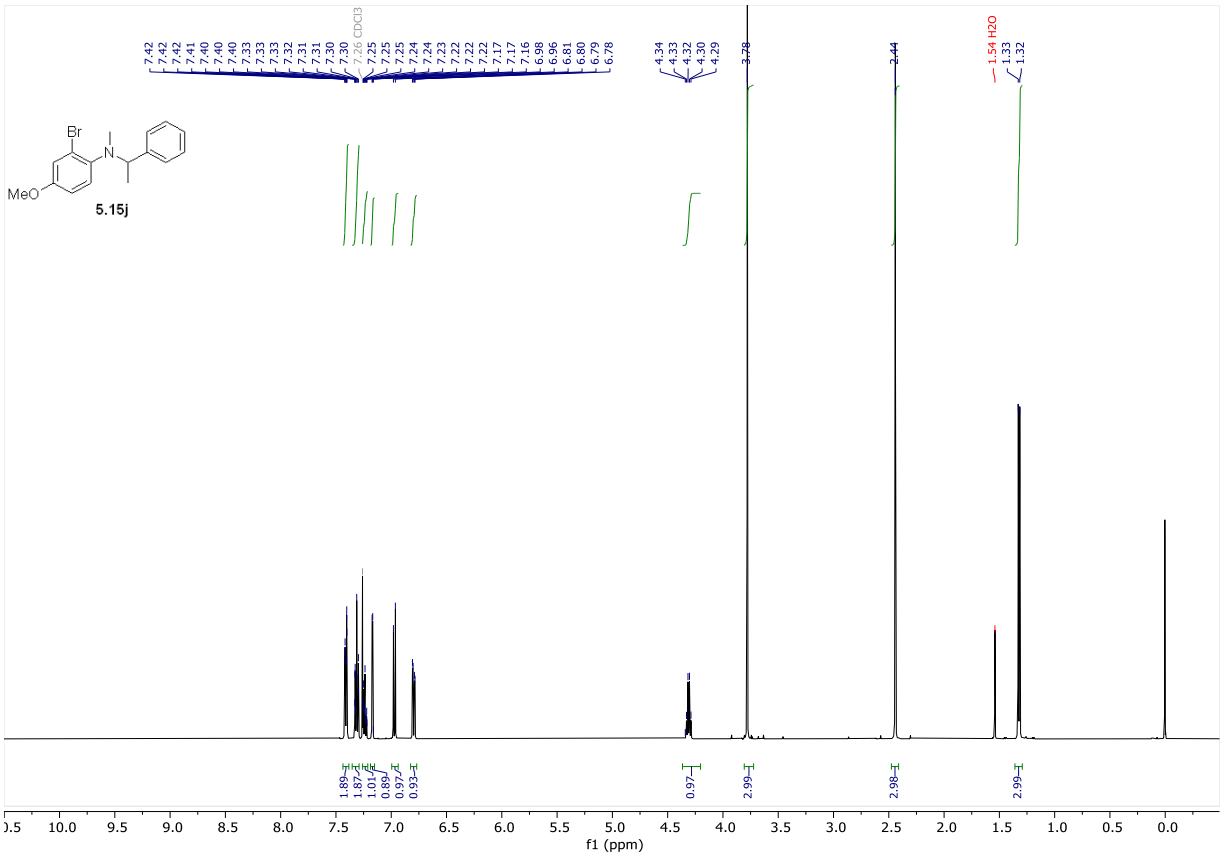

8.50
8.49
8.09
8.08
8.07
8.07
7.34
7.34
7.33
7.33
7.33
7.32
7.32
7.31
7.31
7.30
7.30
7.29
7.28
7.28
7.28
7.27
7.26
7.26 CDCl3
7.26
7.25
7.25
7.24
7.24
7.24
7.24
6.90
6.89
6.88
6.87
6.86
5.05
5.04
5.02
5.01
2.60
1.61
1.59
1.55 H2O
Br
N
O2N
5.15h
0.86
0.94
2.76
2.95
1.03
1.00
3.14
3.13
f1 (ppm)

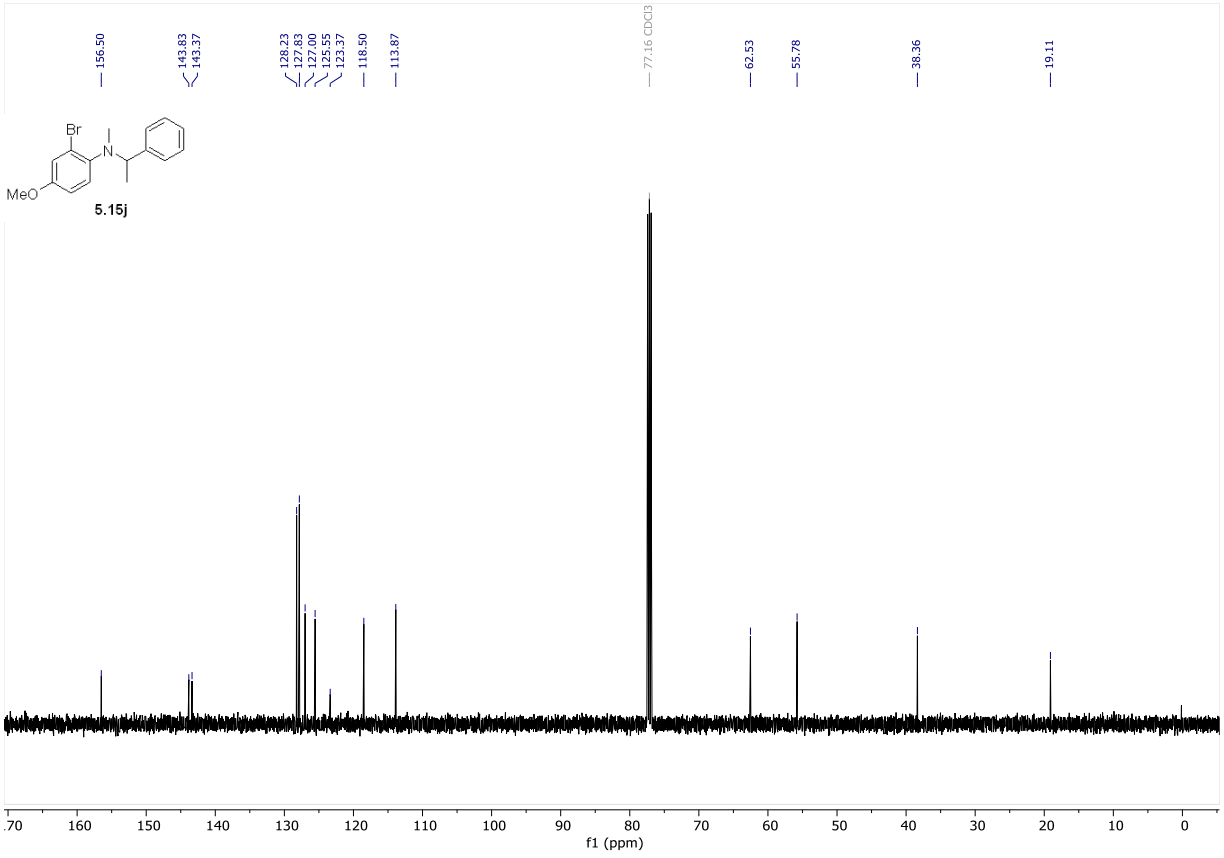

156.88
142.01
140.20
130.40
128.46
127.57
127.53
123.65
121.65
117.18
77.16 CDCl3
60.37
34.39
16.60
Br
N
O2N
5.15h
f1 (ppm)

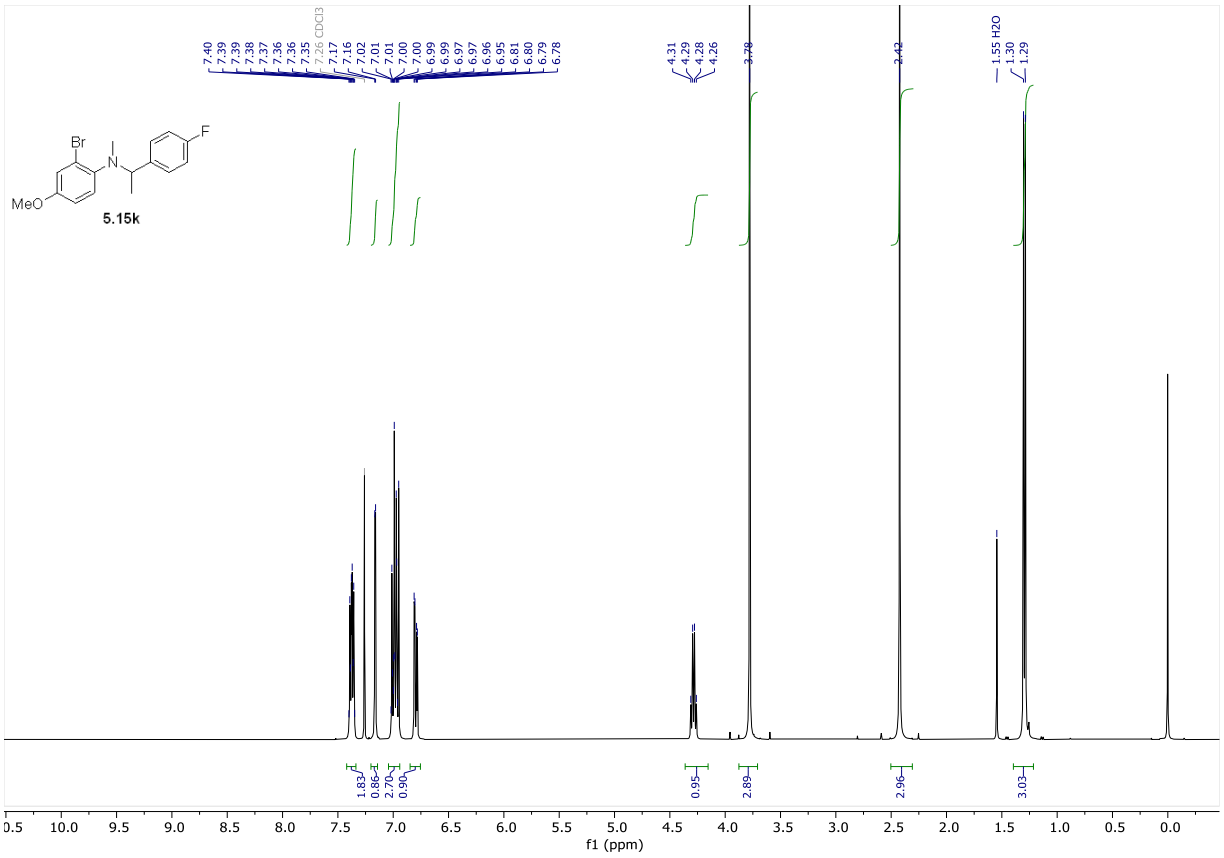

7.72 7.72 7.71 7.70 7.36 7.36 7.36 7.36 7.35 7.35 7.35 7.35 7.34 7.34 7.34 7.33 7.33 7.33 7.32 7.32 7.32 7.31 7.31 7.30 7.30 7.30 7.27 7.27 7.27 7.26 CDCl3 7.26 7.25 7.24 7.24 7.17 7.17 7.16 7.16 7.15 7.15 7.15 7.15 7.15 4.65 4.64 4.62 4.61 2.52 1.54 1.46 1.44
Br
N
CF3
5.15i
0.99 4.40 1.50 2.11 1.06 3.31 3.34
f1 (ppm)

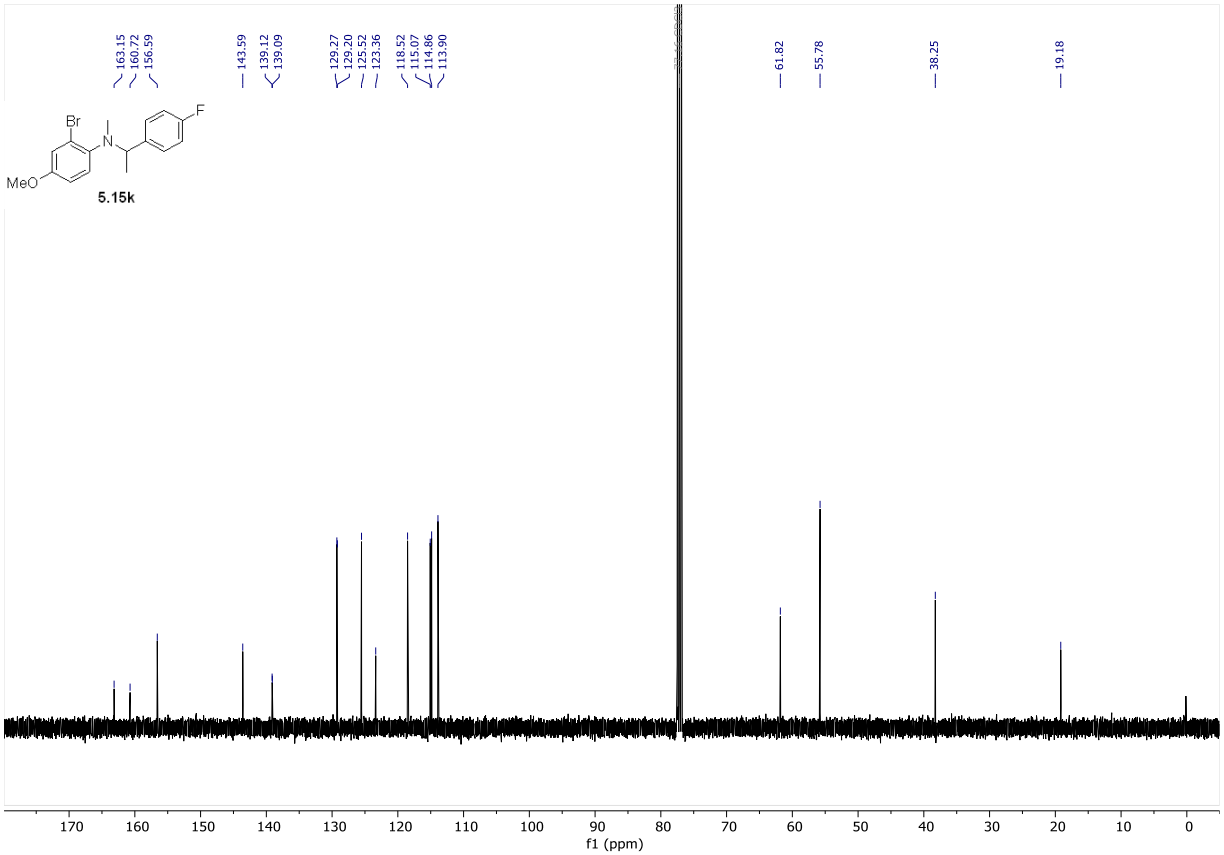

151.51 141.58 134.54 130.78 130.53 130.27 130.01 128.33 127.69 127.33 127.21 125.20 125.19 125.05 122.88 121.12 121.09 121.06 121.03 121.02 120.99 120.96 120.93 120.72 77.16 CDCl3 61.11 36.07 17.43
Br
N
CF3
5.15i
130.78 130.53 130.27 130.01 128.33 127.69 127.33 127.21 125.20 125.19 125.05 122.88 121.12 121.09 121.06 121.03 121.02 120.99 120.96 120.93 120.72
f1 (ppm)
f1 (ppm)

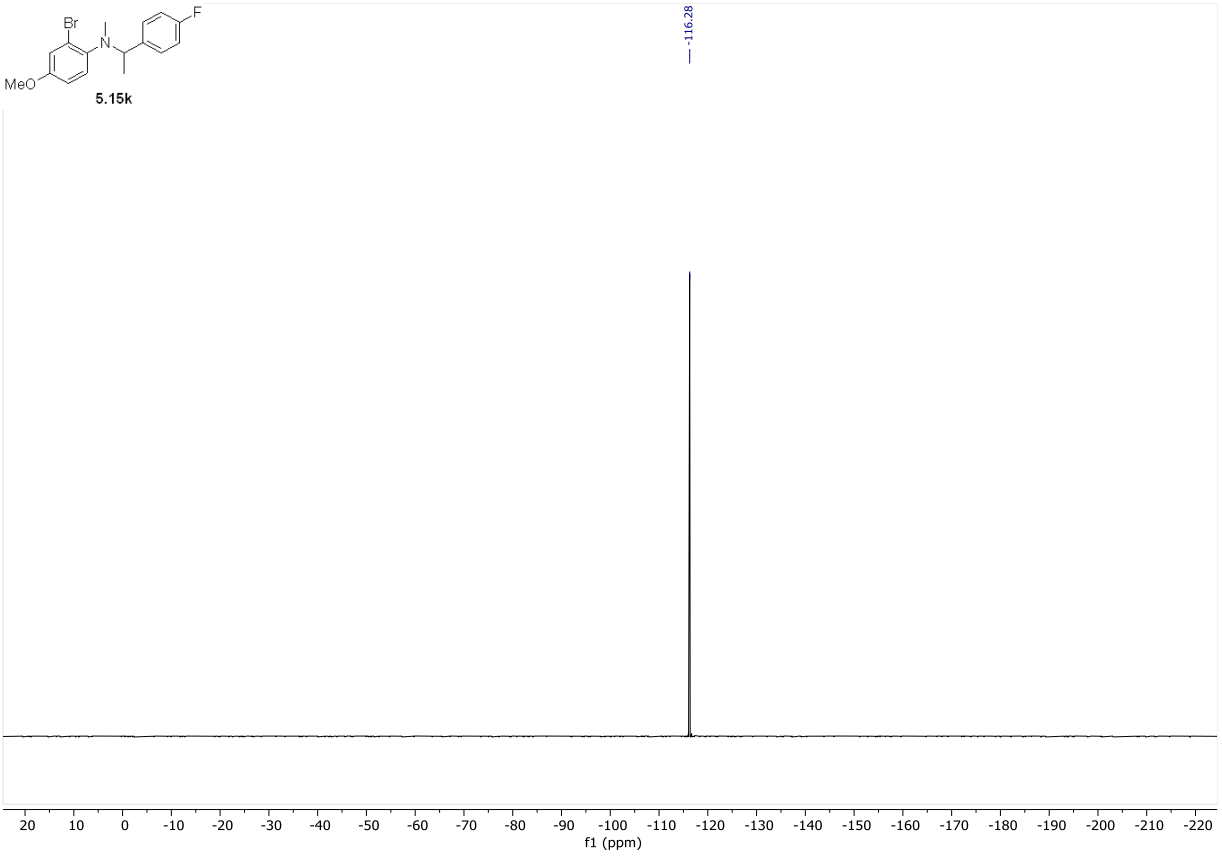

Br
N
CF3
-62.67
5.15i
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
f1 (ppm)

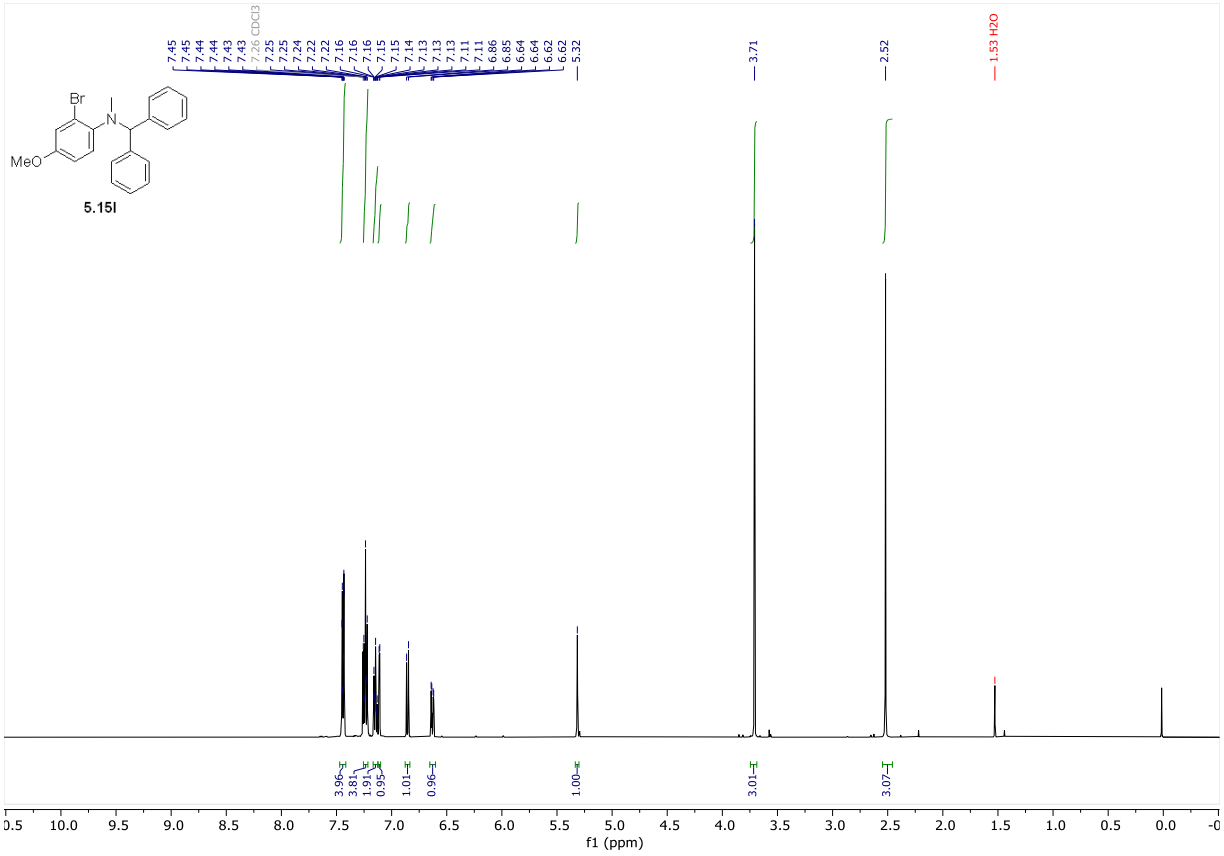

Br
N
MeO
5.15j
7.42 7.42 7.42 7.41 7.40 7.40 7.40 7.33 7.33 7.32 7.31 7.31 7.30 7.30 7.26 CDCl3 7.25 7.25 7.25 7.24 7.24 7.23 7.22 7.22 7.22 7.17 7.17 7.16 6.98 6.96 6.81 6.80 6.79 6.78
4.34 4.33 4.32 4.30 4.29
3.78
2.44
1.54 H2O
1.33
1.32
1.89
1.87
1.01
0.89
0.97
0.93
0.97
2.99
2.98
2.99
f1 (ppm)

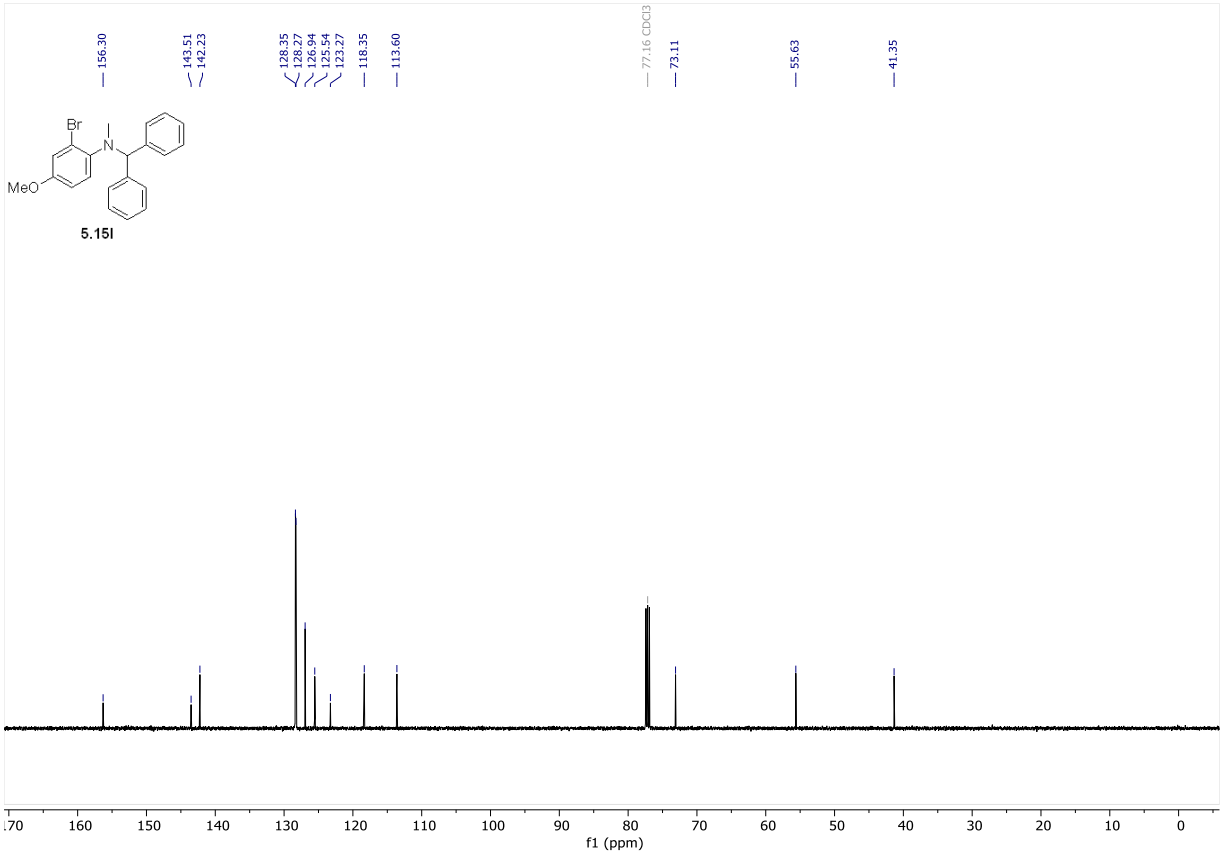

Br
N
MeO
5.15j
156.50
143.83
143.37
128.23
127.83
127.00
125.55
123.37
118.50
113.87
77.16 CDCl3
62.53
55.78
38.36
19.11
f1 (ppm)

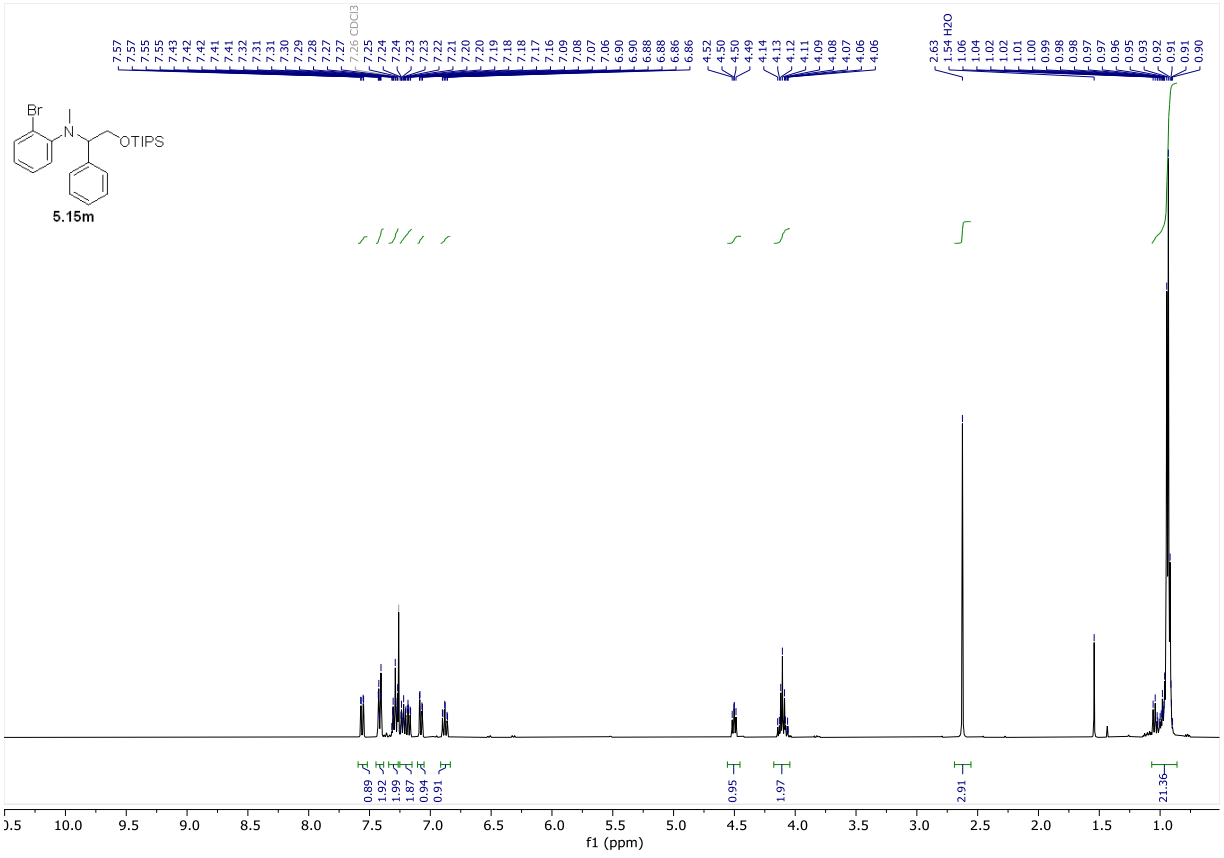

7.40
7.39
7.39
7.38
7.37
7.36
7.36
7.35
7.26 CDCl3
7.17
7.16
7.02
7.01
7.01
7.00
7.00
6.99
6.99
6.97
6.96
6.95
6.81
6.80
6.79
6.78
4.31
4.29
4.28
4.26
3.78
2.42
1.55 H2O
1.30
1.29
Br
F
N
MeO
5.15k
1.83
0.86
2.70
0.90
0.95
2.89
2.96
3.03
f1 (ppm)

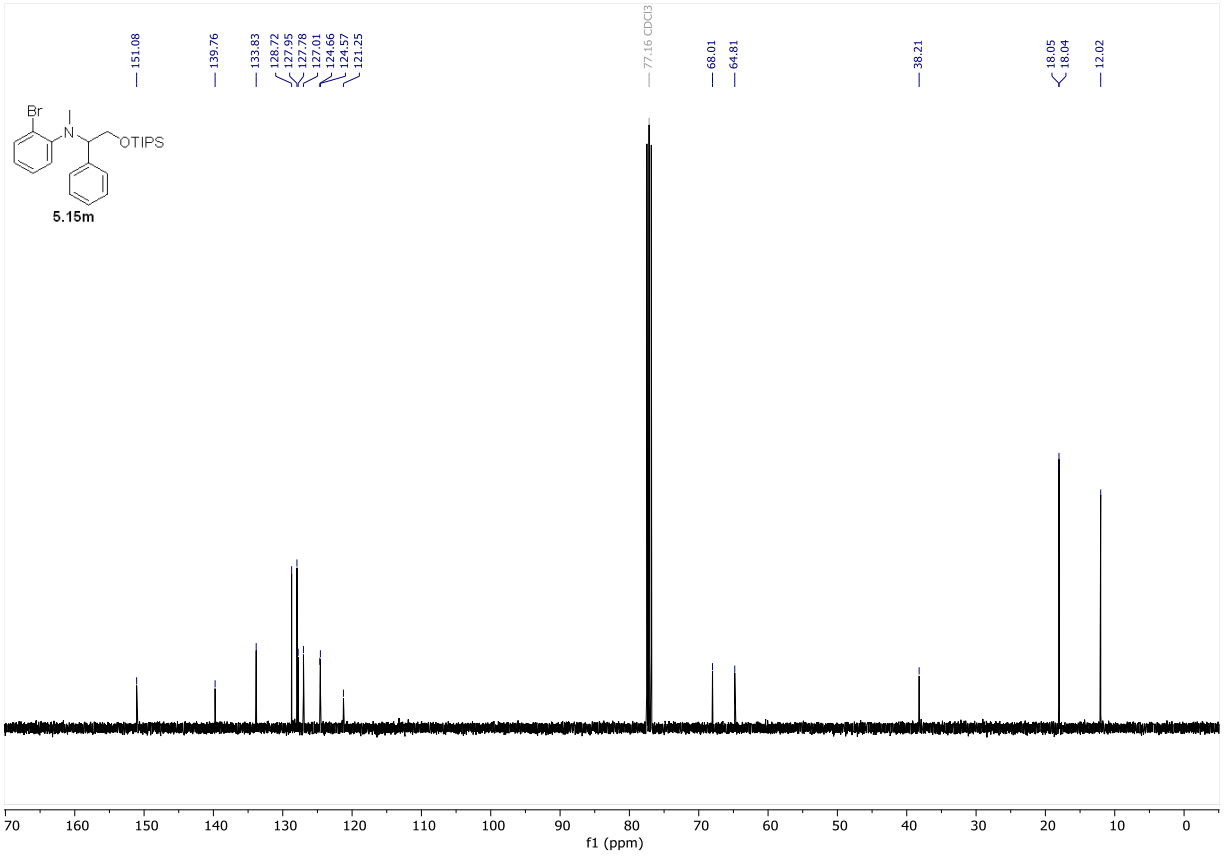

163.15
160.72
156.59
143.59
139.12
139.09
129.27
129.20
125.52
123.36
118.52
115.07
114.86
113.90
61.82
55.78
38.25
19.18
Br
F
N
MeO
5.15k
f1 (ppm)

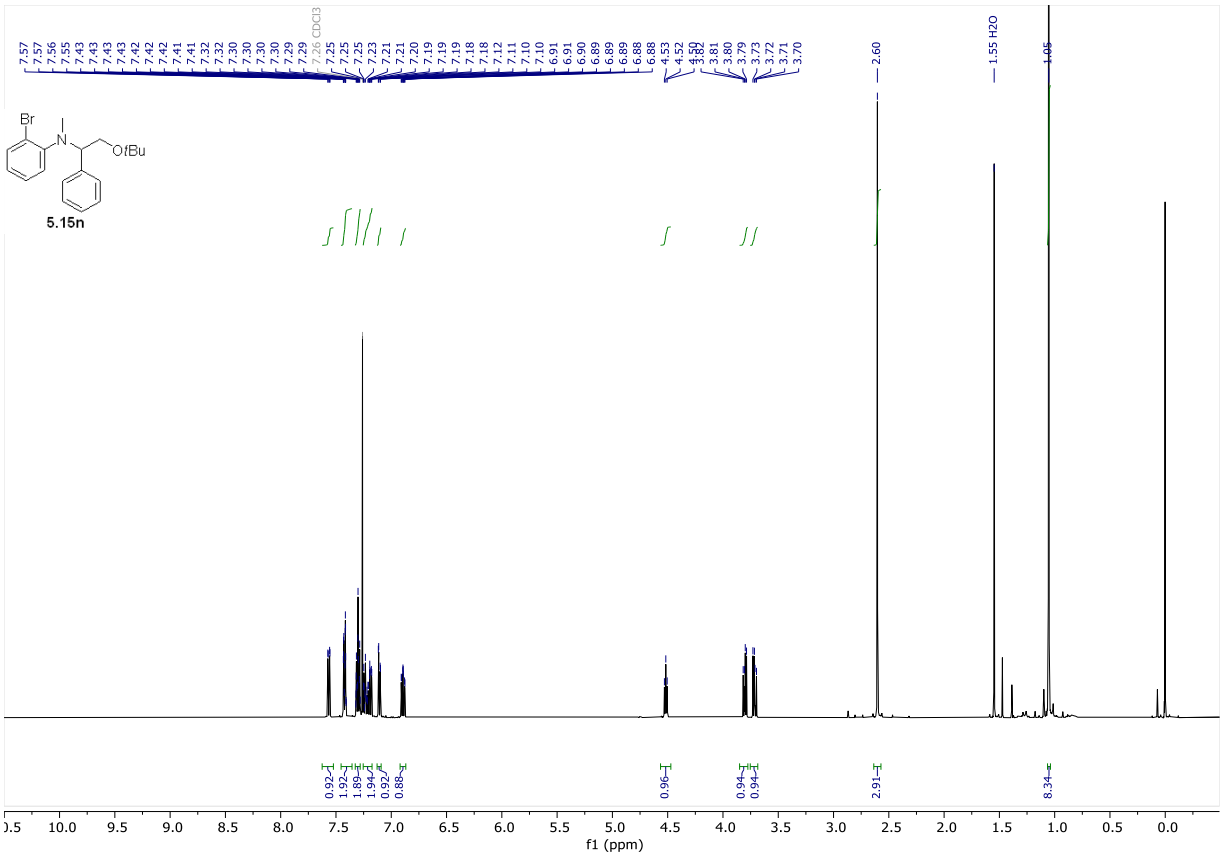

Br
N
F
MeO
5.15k
-116.28
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
f1 (ppm)

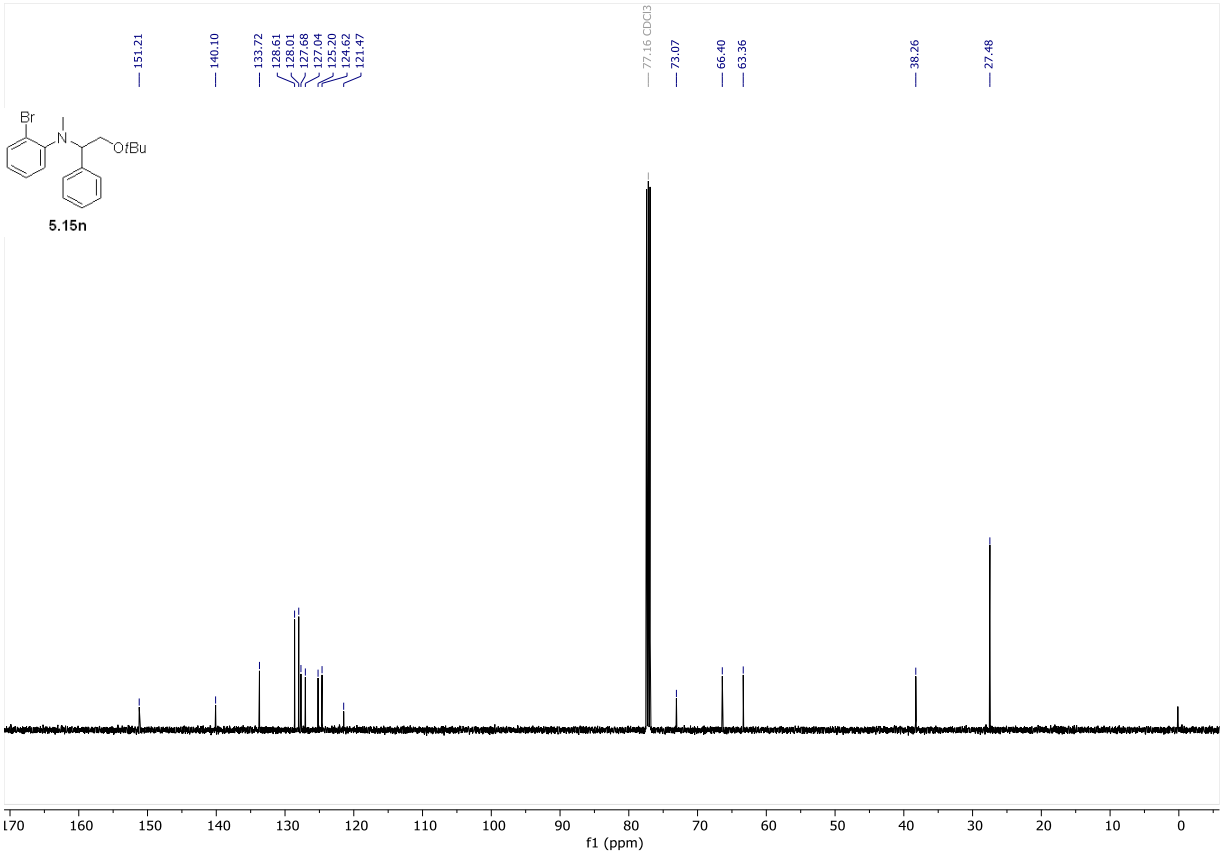

7.45
7.45
7.44
7.44
7.43
7.43
7.26 CDCl3
7.25
7.25
7.24
7.22
7.22
7.16
7.16
7.16
7.15
7.15
7.14
7.13
7.13
7.13
7.11
7.11
6.86
6.85
6.64
6.64
6.62
6.62
5.32
3.71
2.52
1.53 H2O
Br
N
MeO
5.15l
3.96
3.81
1.91
0.95
1.01
0.96
1.00
3.01
3.07
f1 (ppm)

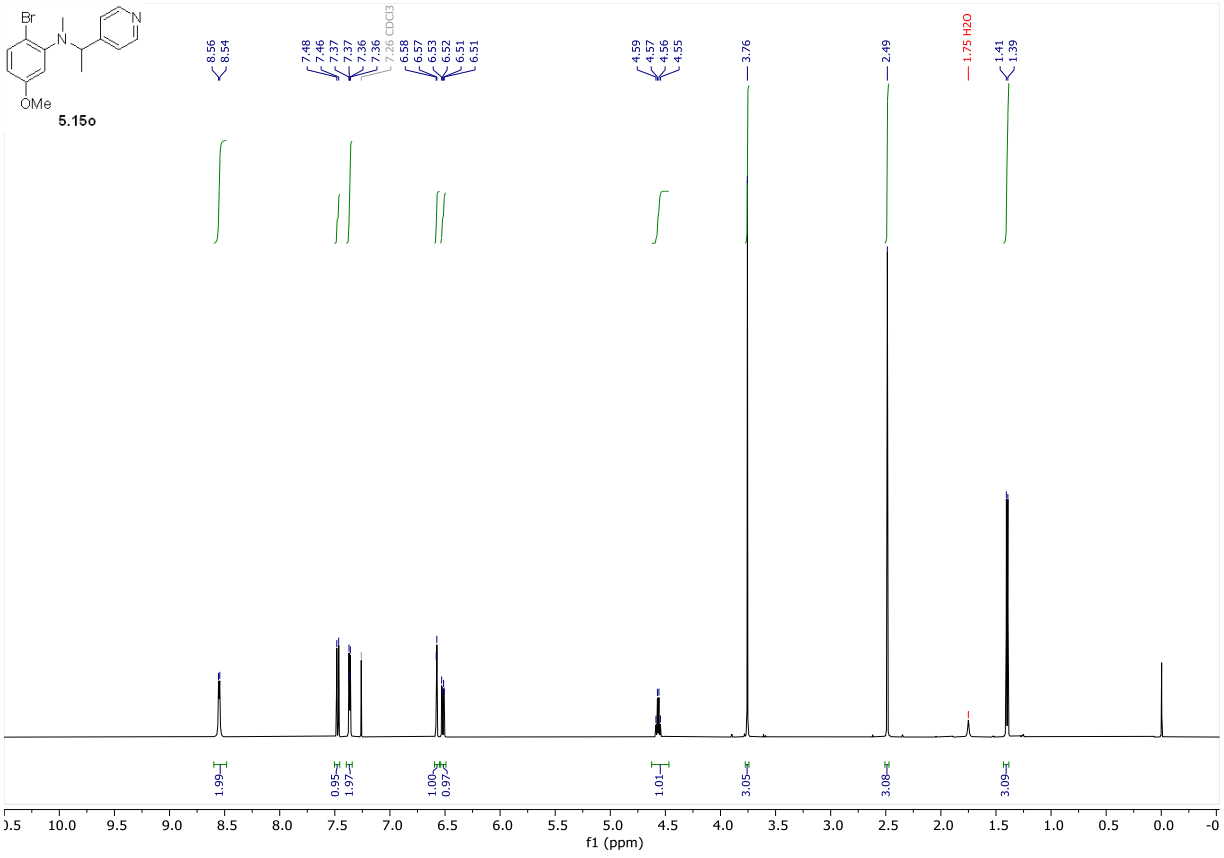

156.30
143.51
142.23
128.35
128.27
126.94
125.54
123.27
118.35
113.60
77.16 CDCl3
73.11
55.63
41.35
Br
N
MeO
5.15l
f1 (ppm)

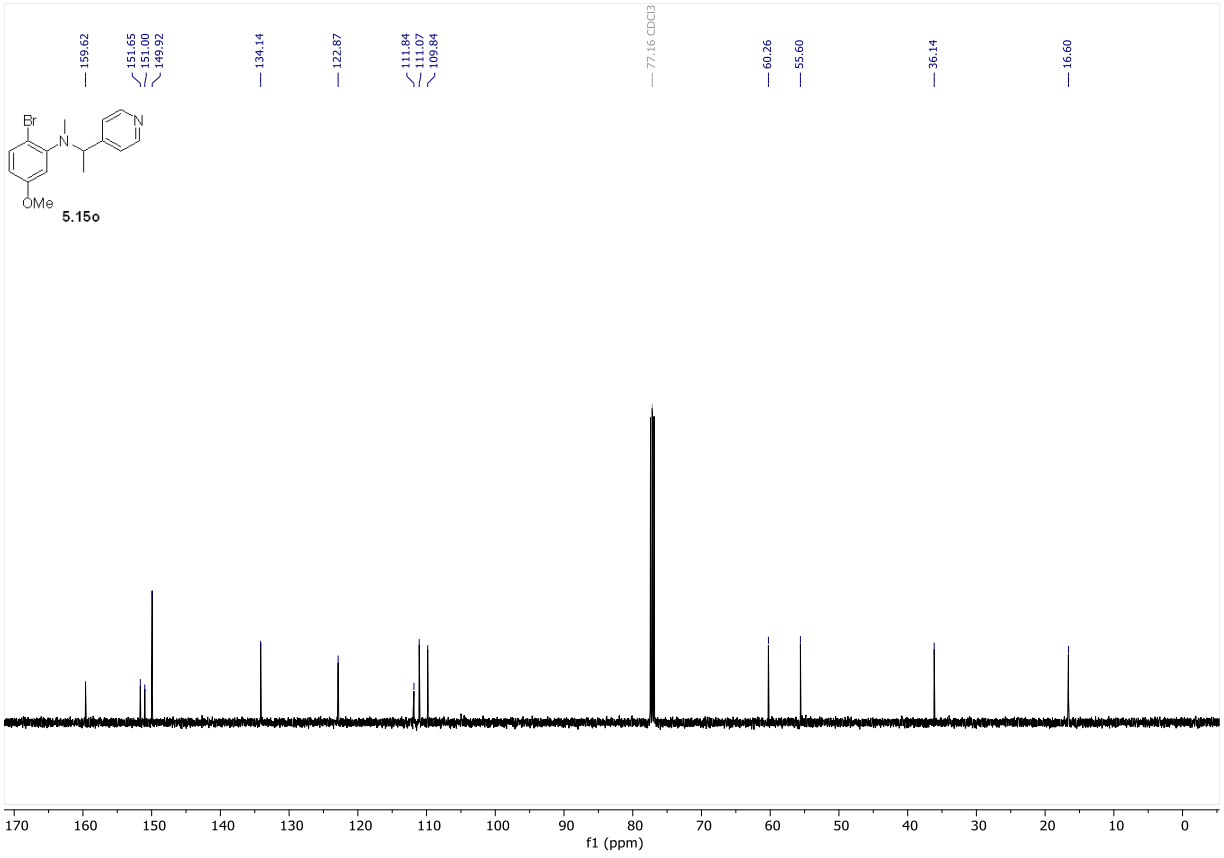

7.57 7.57 7.55 7.55 7.43 7.42 7.42 7.41 7.41 7.32 7.31 7.31 7.30 7.29 7.28 7.27 7.27 7.26 CDCl3 7.25 7.24 7.24 7.23 7.23 7.22 7.21 7.20 7.20 7.19 7.18 7.18 7.17 7.16 7.09 7.08 7.07 7.06 6.90 6.90 6.88 6.88 6.86 6.86
4.52 4.50 4.50 4.49 4.14 4.13 4.12 4.11 4.09 4.08 4.07 4.06 4.06
2.63 1.54 H2O 1.06 1.04 1.02 1.02 1.01 1.00 0.99 0.98 0.98 0.97 0.97 0.96 0.95 0.93 0.92 0.91 0.91 0.90
Br
N
OTIPS
5.15m
0.89 1.92 1.99 1.87 0.94 0.91
0.95
1.97
2.91
21.36
f1 (ppm)

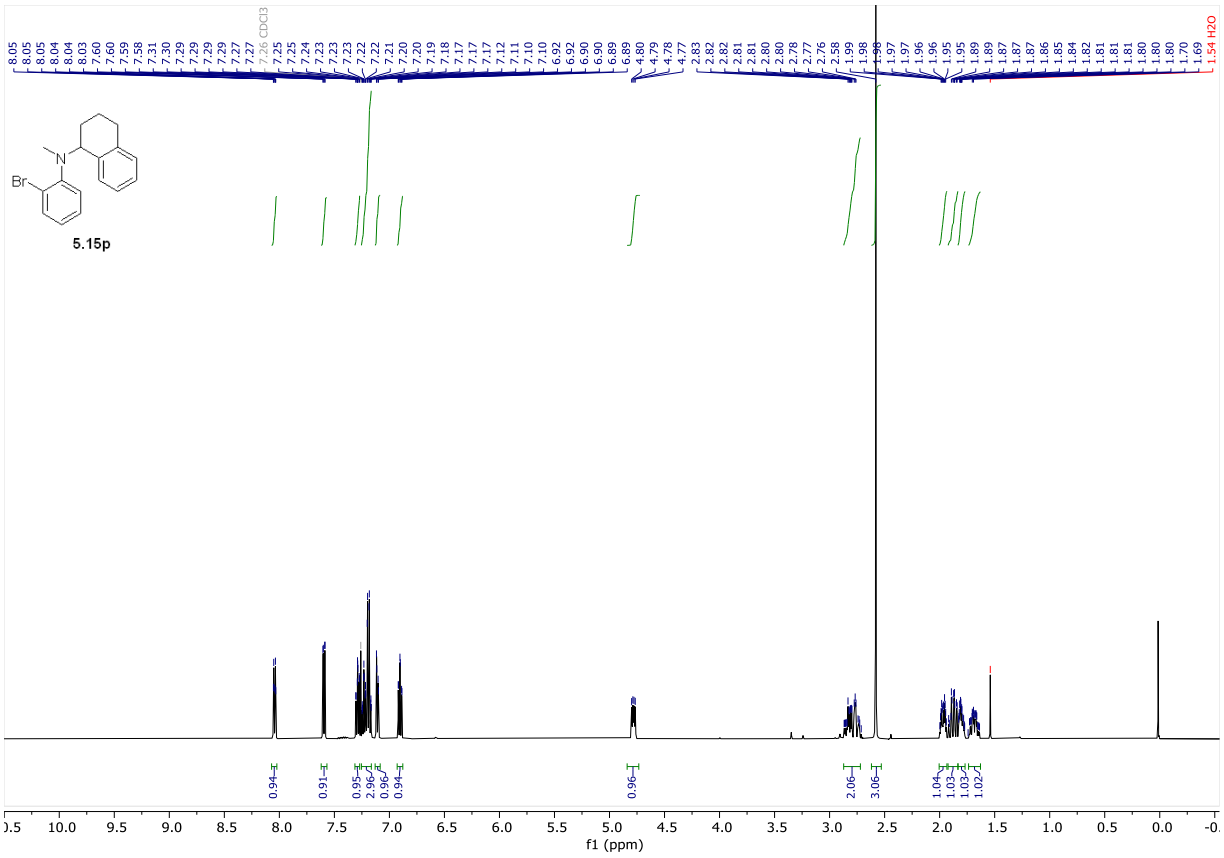

151.08
139.76
133.83
128.72
127.95
127.78
127.01
124.66
124.57
121.25
77.16 CDCl3
68.01
64.81
38.21
18.05
18.04
12.02
Br
N
OTIPS
5.15m
f1 (ppm)

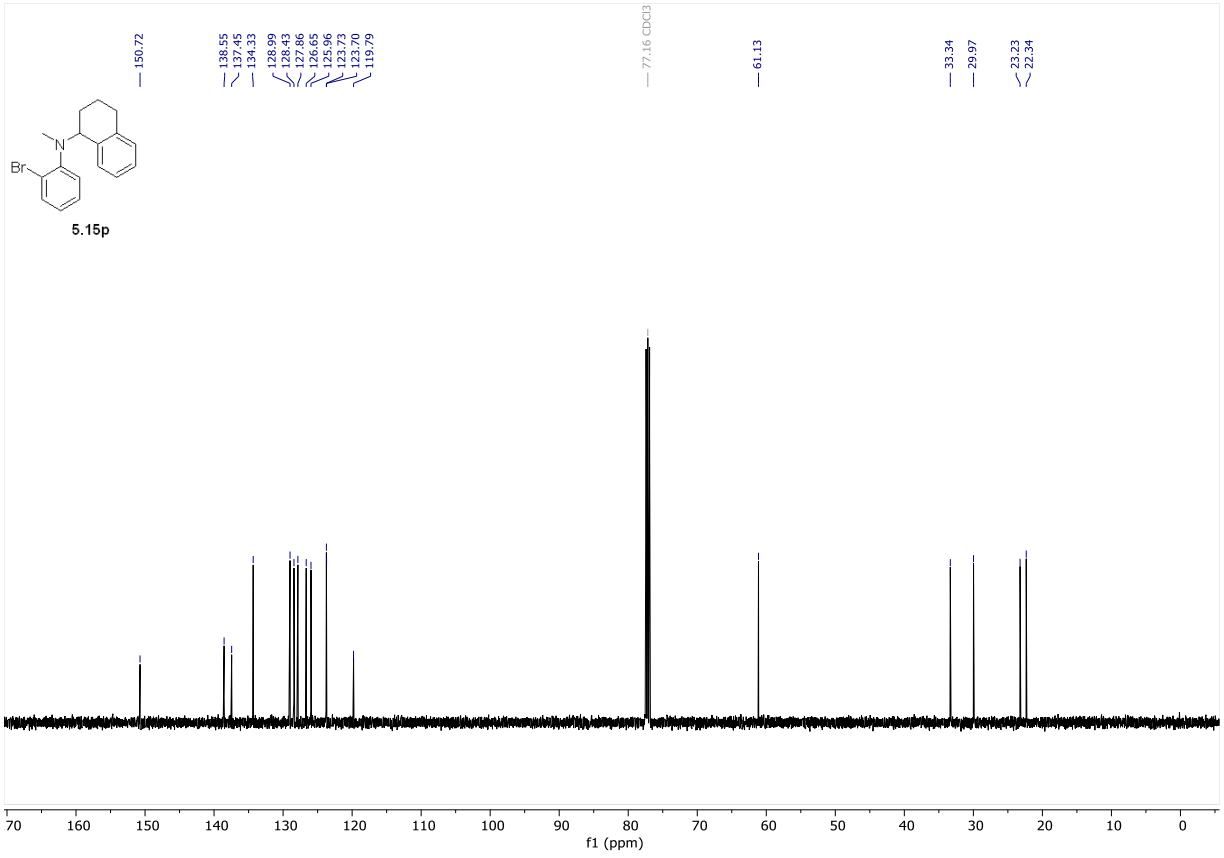

Br
N
OtBu
5.15n
7.57 7.57 7.56 7.55 7.43 7.43 7.43 7.42 7.42 7.42 7.41 7.41 7.32 7.30 7.30 7.30 7.29 7.29 7.26 CDCl3 7.25 7.25 7.25 7.23 7.21 7.21 7.20 7.19 7.19 7.19 7.18 7.18 7.12 7.11 7.10 7.10 6.91 6.91 6.90 6.89 6.89 6.89 6.88 6.88 4.53 4.52 4.50 3.82 3.81 3.80 3.79 3.73 3.72 3.71 3.70
2.60
1.55 H2O
1.05
0.92 1.92 1.89 1.94 0.92 0.88
0.96
0.94 0.94
2.91
8.34
f1 (ppm)

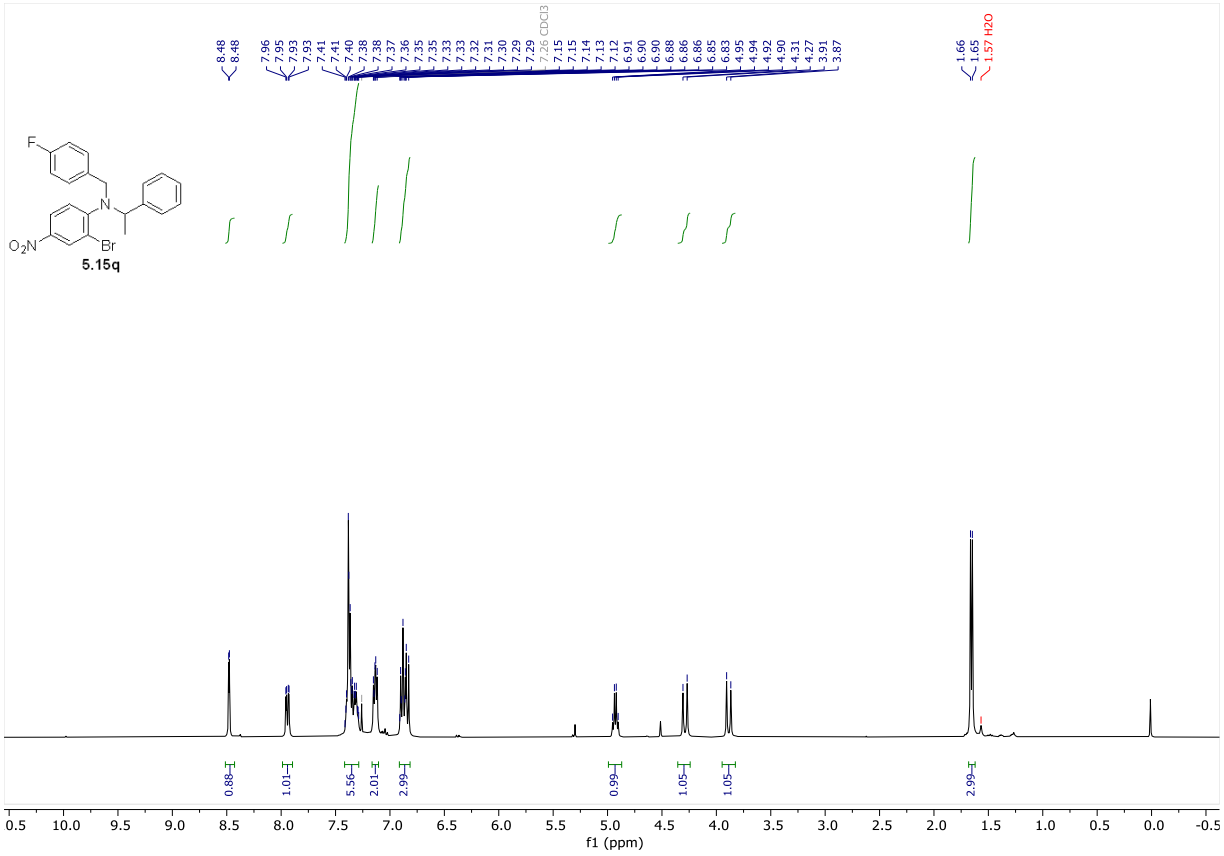

Br
N
OtBu
5.15n
151.21
140.10
133.72
128.61
128.01
127.68
127.04
125.20
124.62
121.47
77.16 CDCl3
73.07
66.40
63.36
38.26
27.48
f1 (ppm)

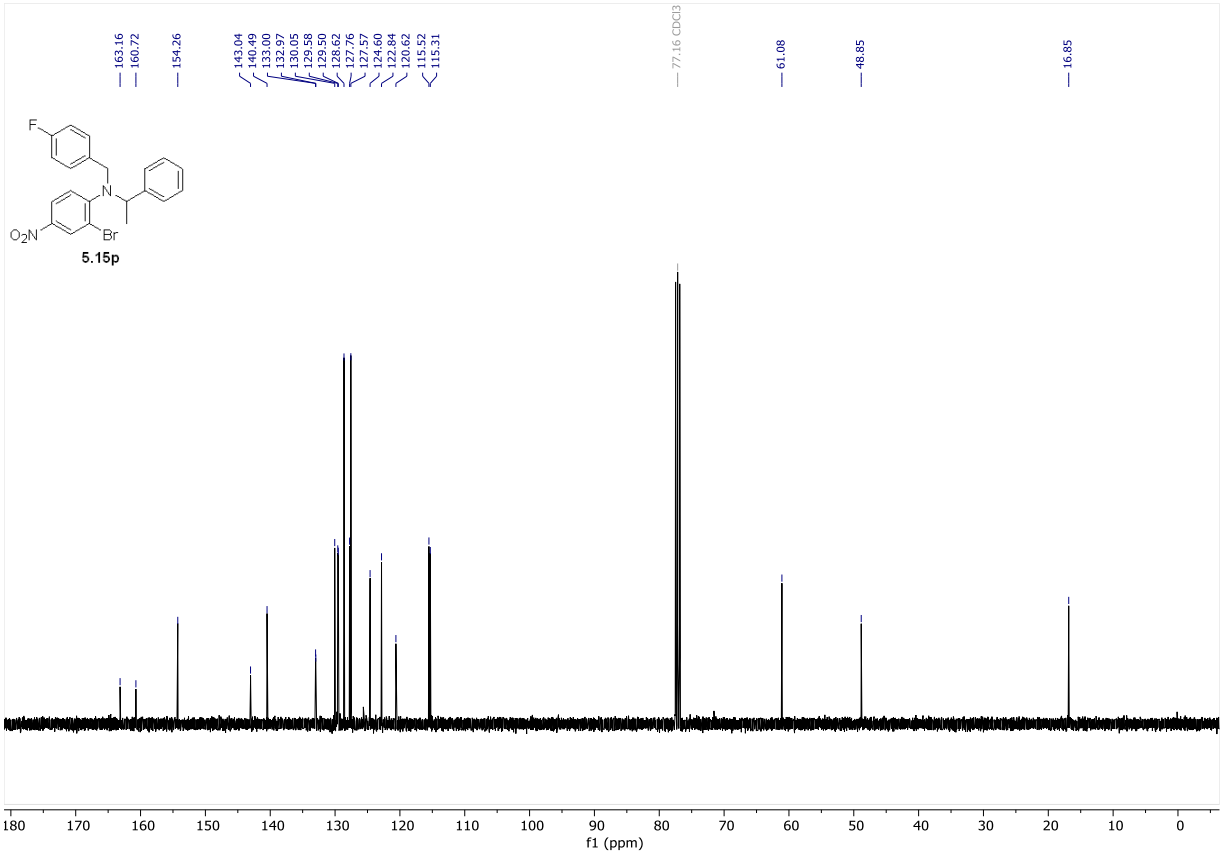

Br
N
OMe
5.15o
8.56
8.54
7.48
7.46
7.37
7.37
7.36
7.36
7.26 CDCl3
6.58
6.57
6.53
6.52
6.51
6.51
4.59
4.57
4.56
4.55
3.76
2.49
1.75 H2O
1.41
1.39
1.99
0.95
1.97
1.00
0.97
1.01
3.05
3.08
3.09
f1 (ppm)

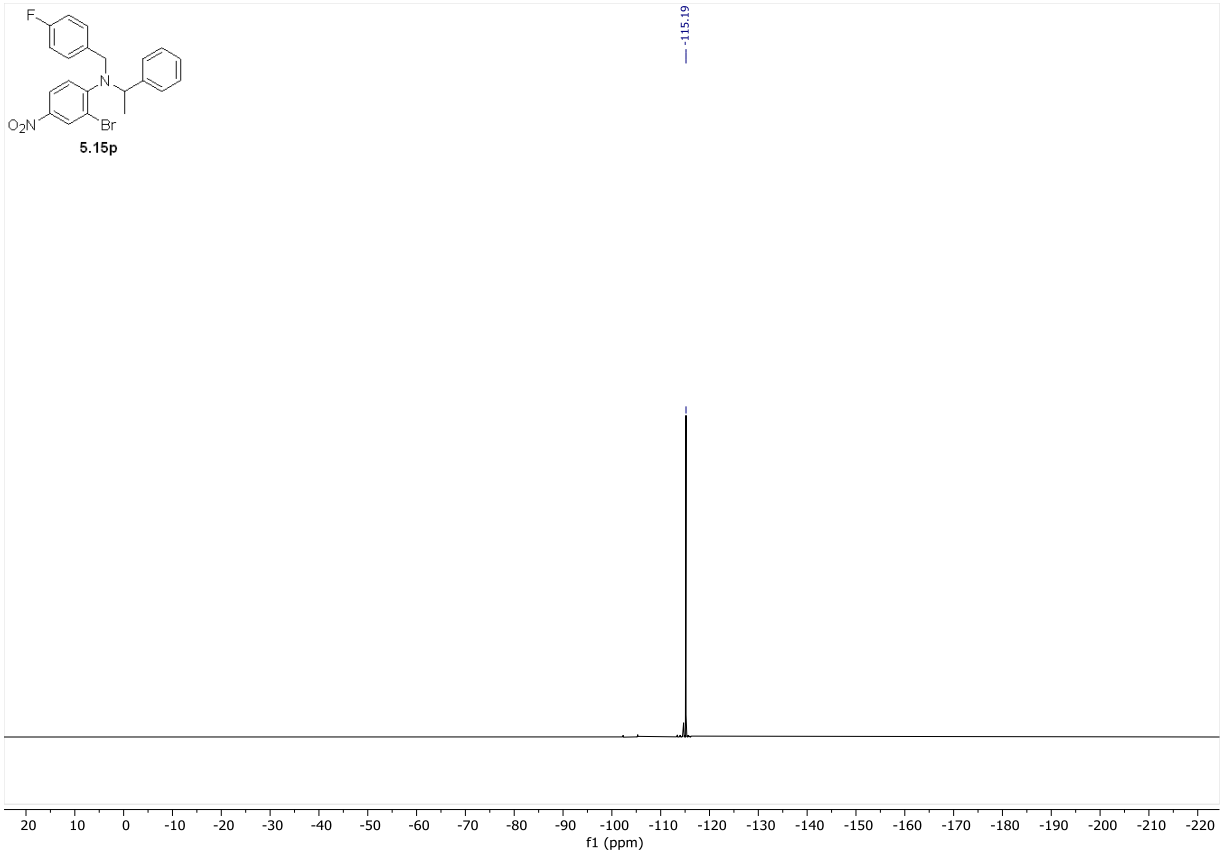

159.62
151.65
151.00
149.92
134.14
122.87
111.84
111.07
109.84
77.16 CDCl3
60.26
55.60
36.14
16.60
Br
N
OMe
5.15o
f1 (ppm)

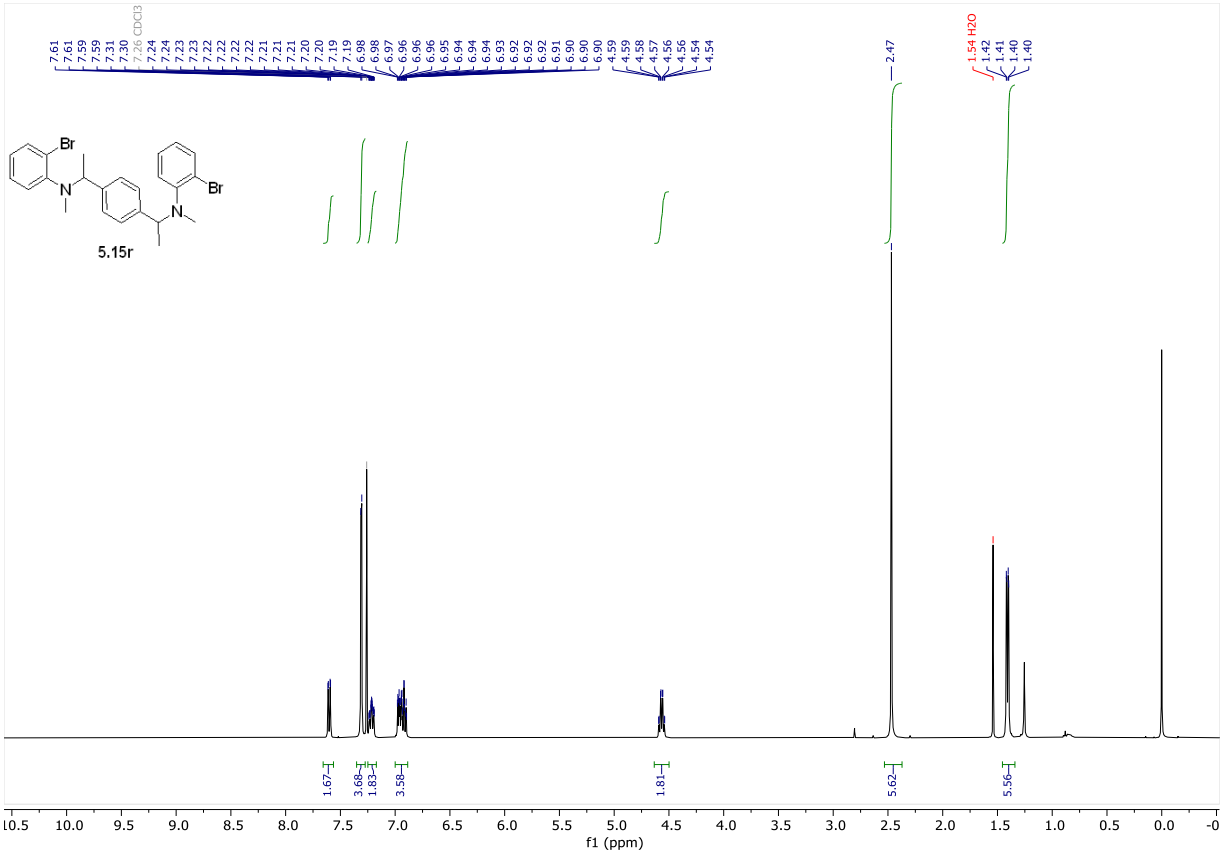

5.15p
f1 (ppm)

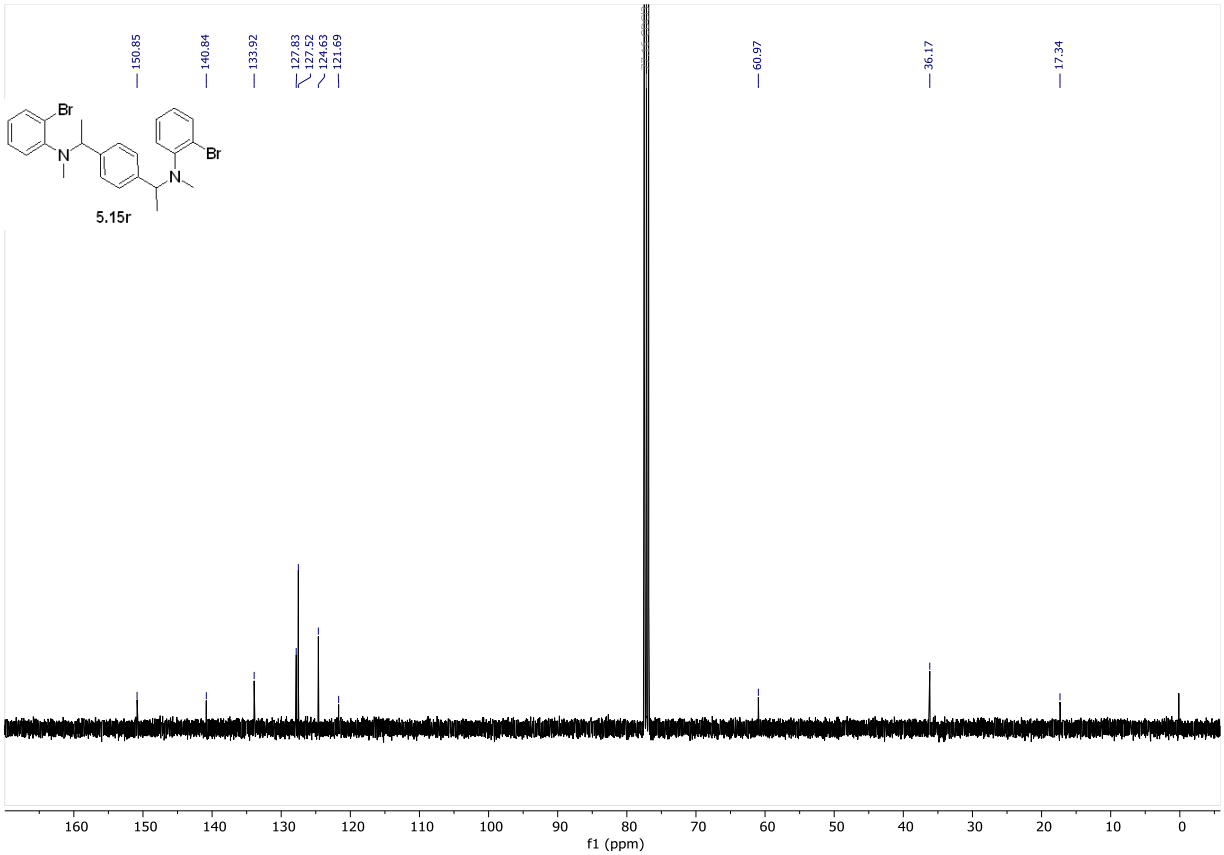

5.15p
f1 (ppm)

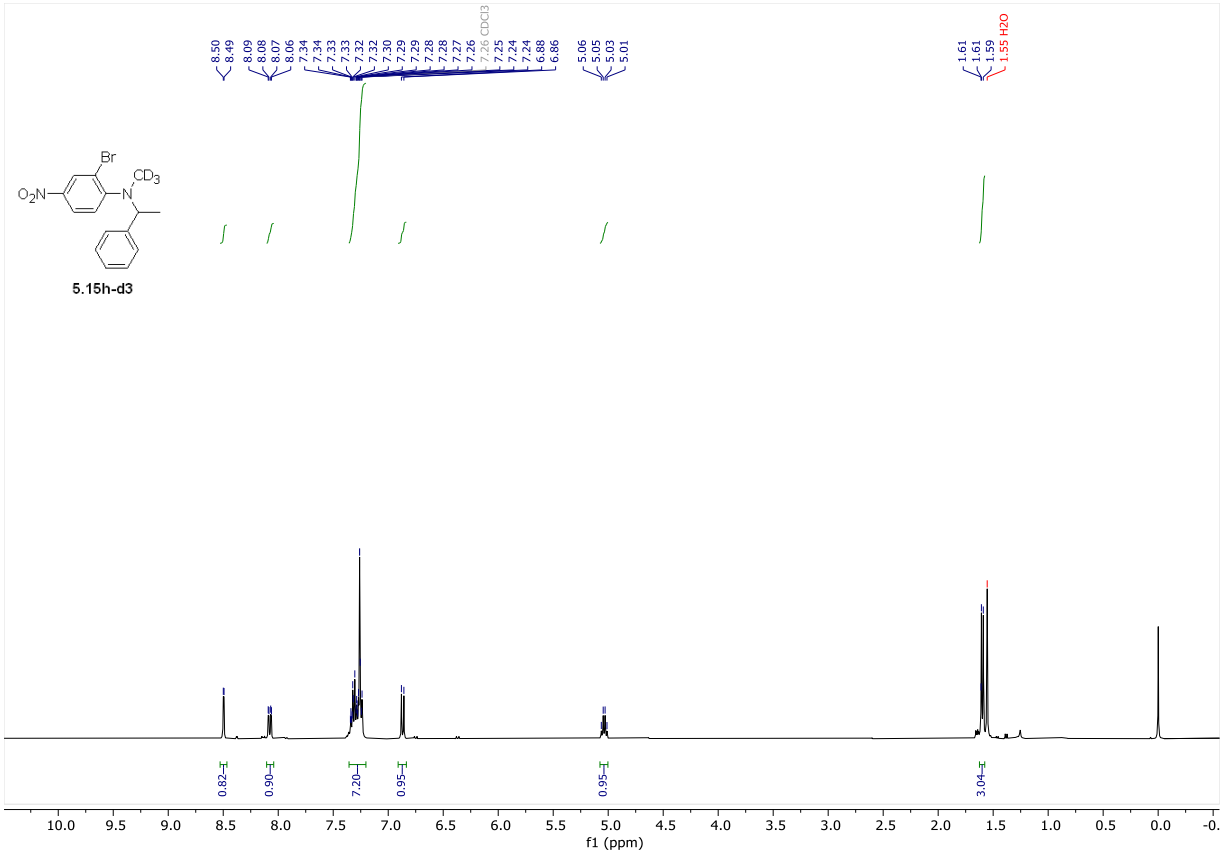

8.48
8.48
7.96
7.95
7.93
7.93
7.41
7.41
7.40
7.38
7.38
7.37
7.36
7.35
7.35
7.33
7.33
7.32
7.31
7.30
7.29
7.29
7.26 CDCl3
7.15
7.15
7.14
7.13
7.12
6.91
6.90
6.90
6.88
6.86
6.86
6.85
6.83
4.95
4.94
4.92
4.90
4.31
4.27
3.91
3.87
1.66
1.65
1.57 H2O
F
N
O2N
Br
5.15q
0.88
1.01
5.56
2.01
2.99
0.99
1.05
1.05
2.99
f1 (ppm)

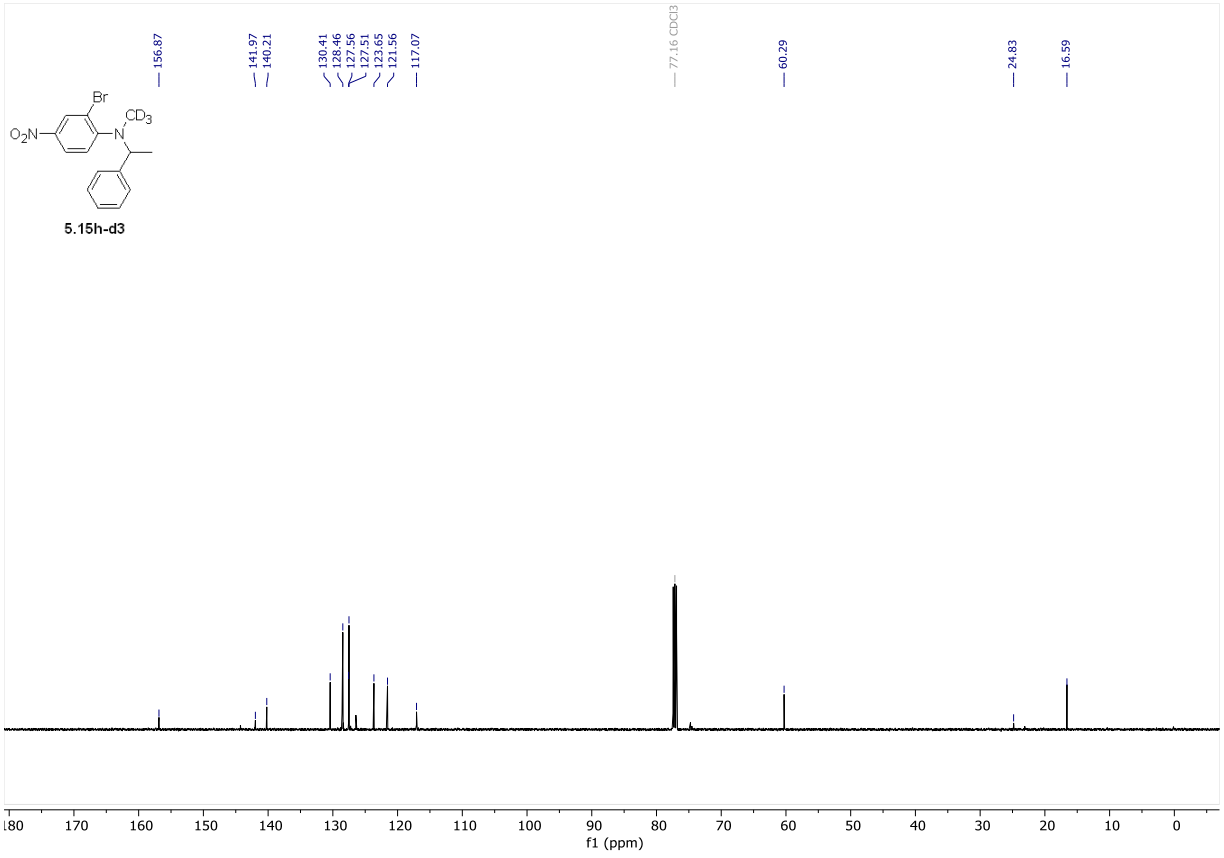

163.16
160.72
154.26
143.04
140.49
133.00
132.97
130.05
129.58
129.50
128.62
127.76
127.57
124.60
122.84
120.62
115.52
115.31
77.16 CDCl3
61.08
48.85
16.85
F
N
O2N
Br
5.15p
f1 (ppm)

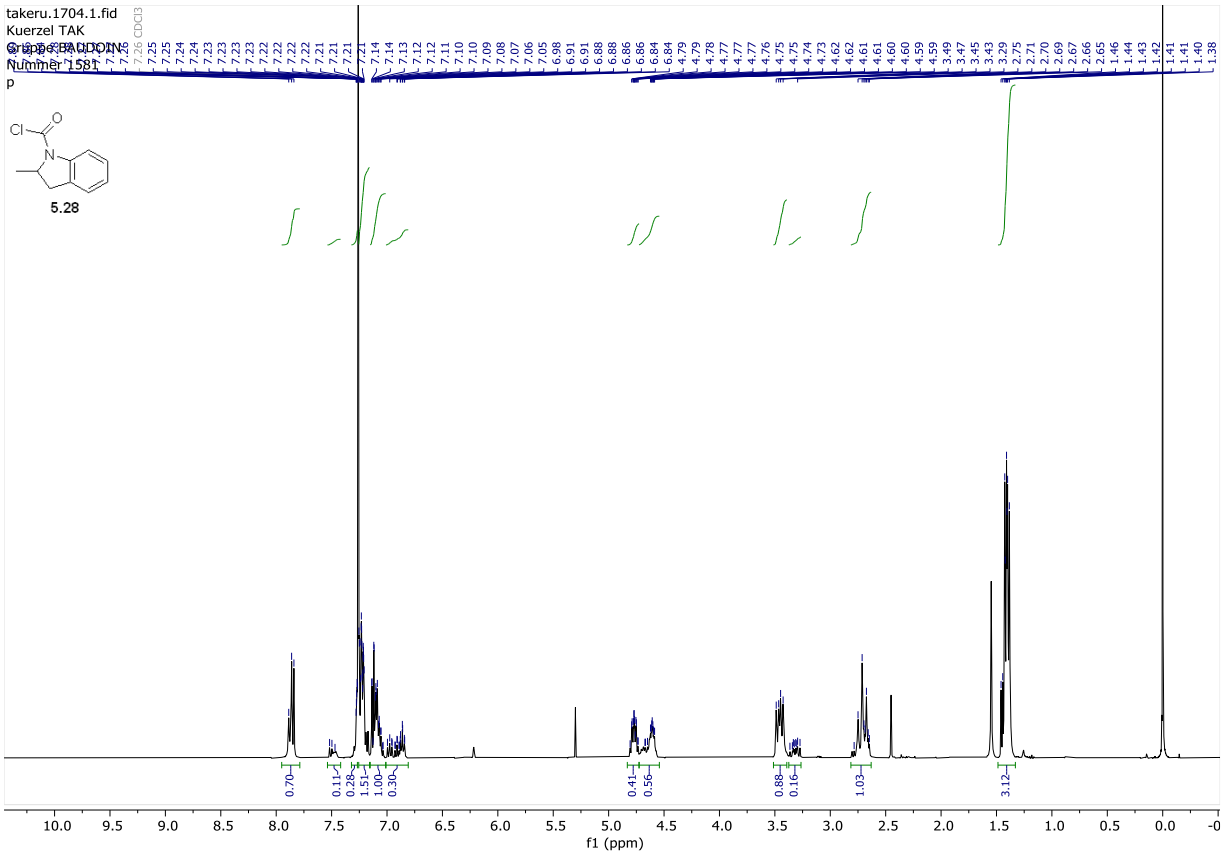

F
N
O2N
Br
5.15p
-115.19
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

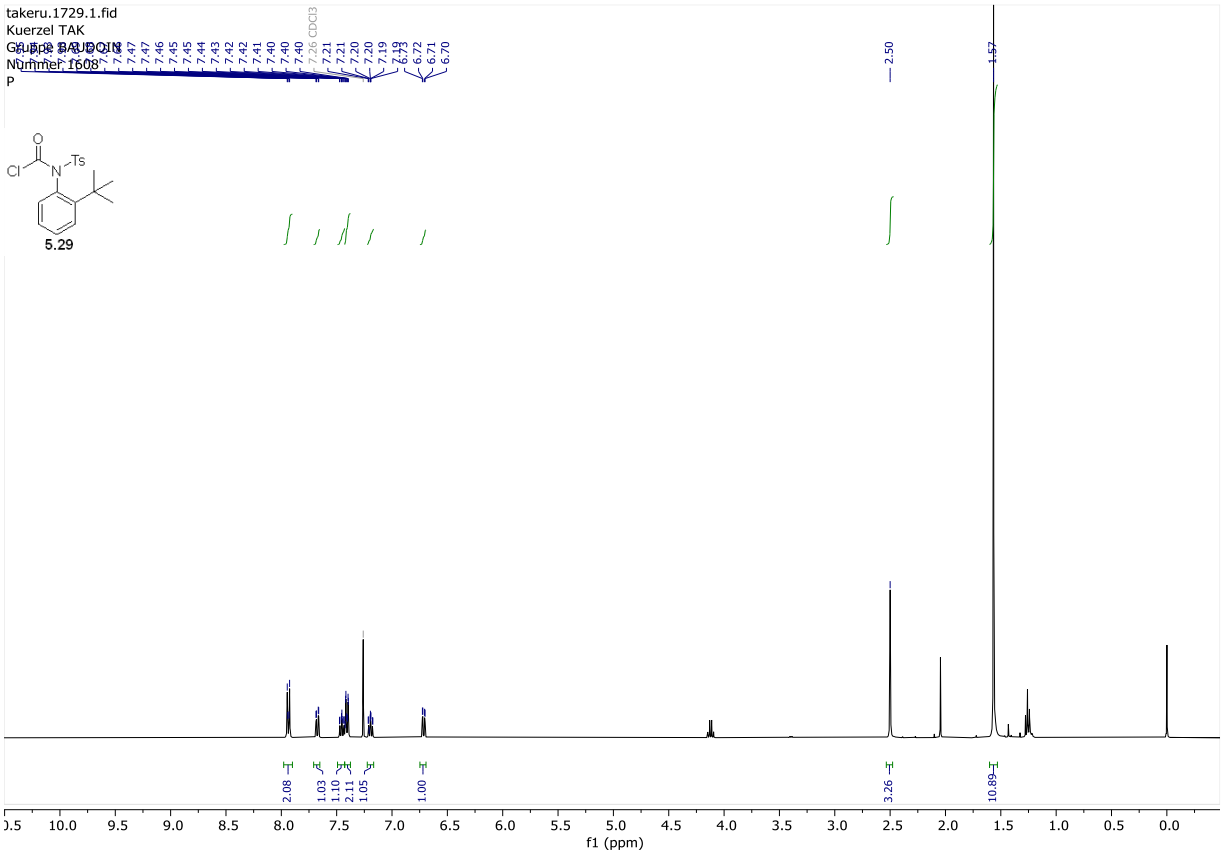

7.61
7.61
7.59
7.59
7.31
7.30
7.26 CDCl3
7.24
7.24
7.23
7.23
7.22
7.22
7.22
7.22
7.21
7.21
7.21
7.20
7.20
7.19
7.19
6.98
6.98
6.97
6.96
6.96
6.96
6.95
6.94
6.94
6.93
6.92
6.92
6.92
6.91
6.90
6.90
6.90
4.59
4.59
4.58
4.57
4.56
4.56
4.54
4.54
2.47
1.54 H2O
1.42
1.41
1.40
1.40
Br
N
Br
N
5.15r
1.67
3.68
1.83
3.58
1.81
5.62
5.56
f1 (ppm)


150.85
140.84
133.92
127.83
127.52
124.63
121.69
60.97
36.17
17.34
Br
N
Br
N
5.15r
f1 (ppm)

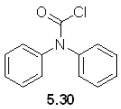

8.50
8.49
8.09
8.08
8.07
8.06
7.34
7.34
7.33
7.33
7.32
7.32
7.30
7.29
7.29
7.28
7.28
7.27
7.26
7.26 CDCl3
7.25
7.24
7.24
6.88
6.86
5.06
5.05
5.03
5.01
1.61
1.61
1.59
1.55 H2O
Br
O2N
N
CD3
5.15h-d3
0.82
0.90
7.20
0.95
0.95
3.04
f1 (ppm)


156.87
141.97
140.21
130.41
128.46
127.56
127.51
123.65
121.56
117.07
77.16 CDCl3
60.29
24.83
16.59
Br
O2N
N
CD3
5.15h-d3
f1 (ppm)


takeru.1704.1.fid
Kuerzel TAK
Gruppe BAUDOIN
Nummer 1581
p
5.28
f1 (ppm)

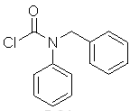

takeru.1729.1.fid
Kuerzel TAK
Gruppe BAUDOIN
Nummer 1608
P
5.29
f1 (ppm)

takeru.1755.1.fid
Kuerzel TAK
Gruppe BAUDOIN
Nummer 1641
P

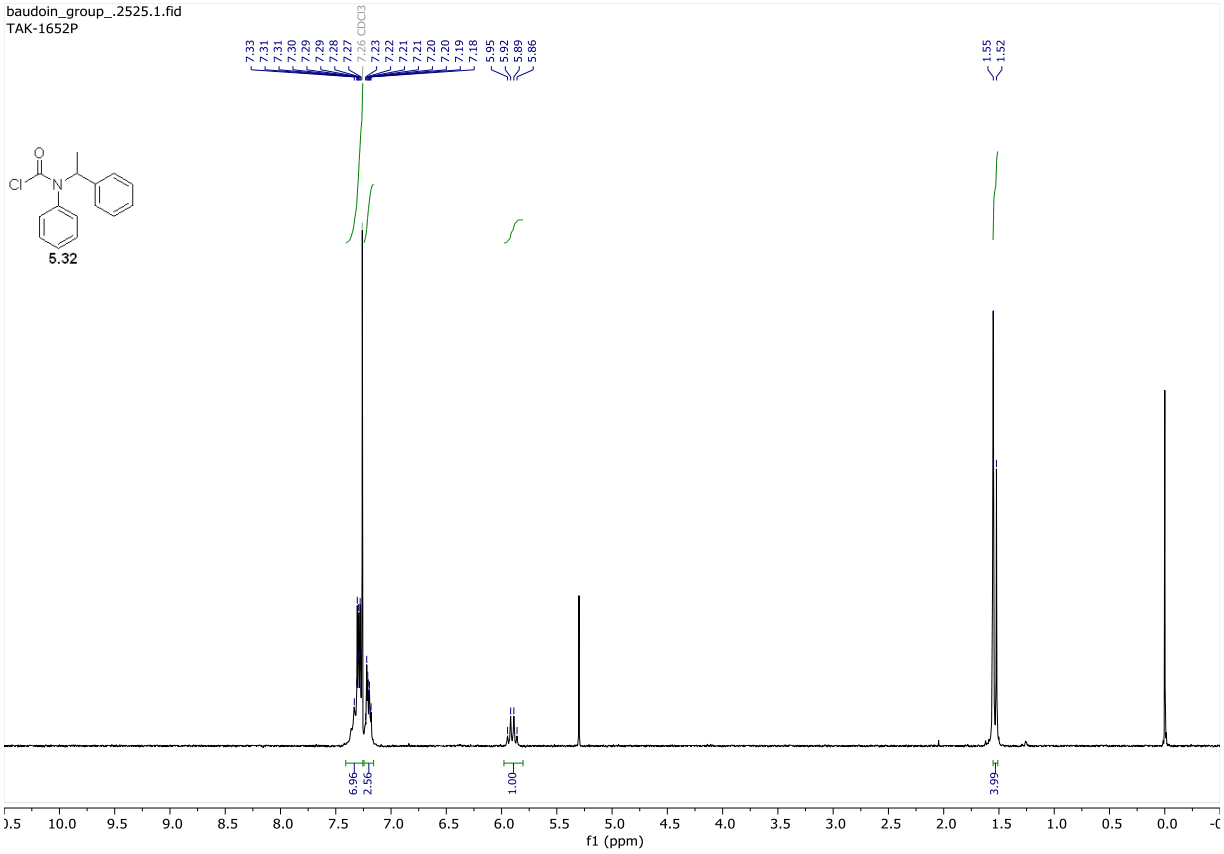


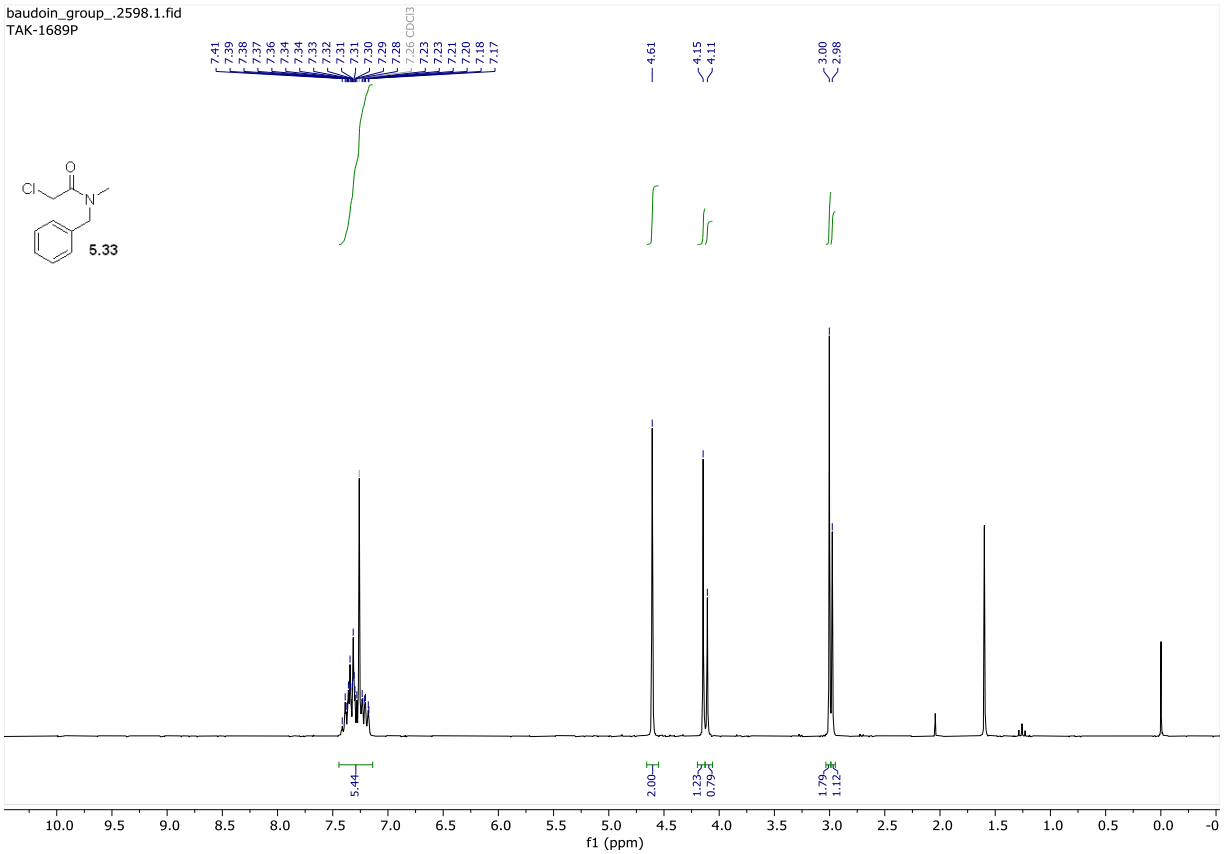
5.30

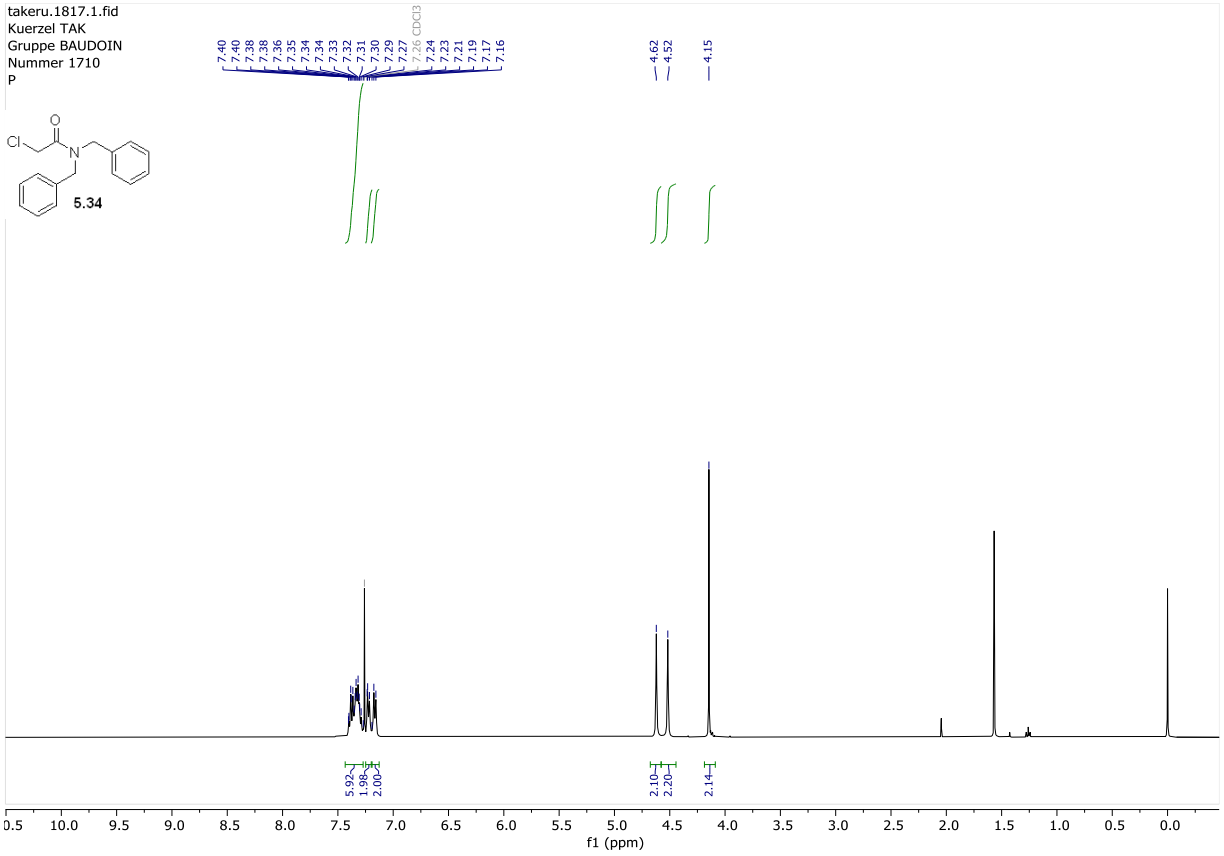
baudoin_group_.2515.1.fid
TAK-1632 P

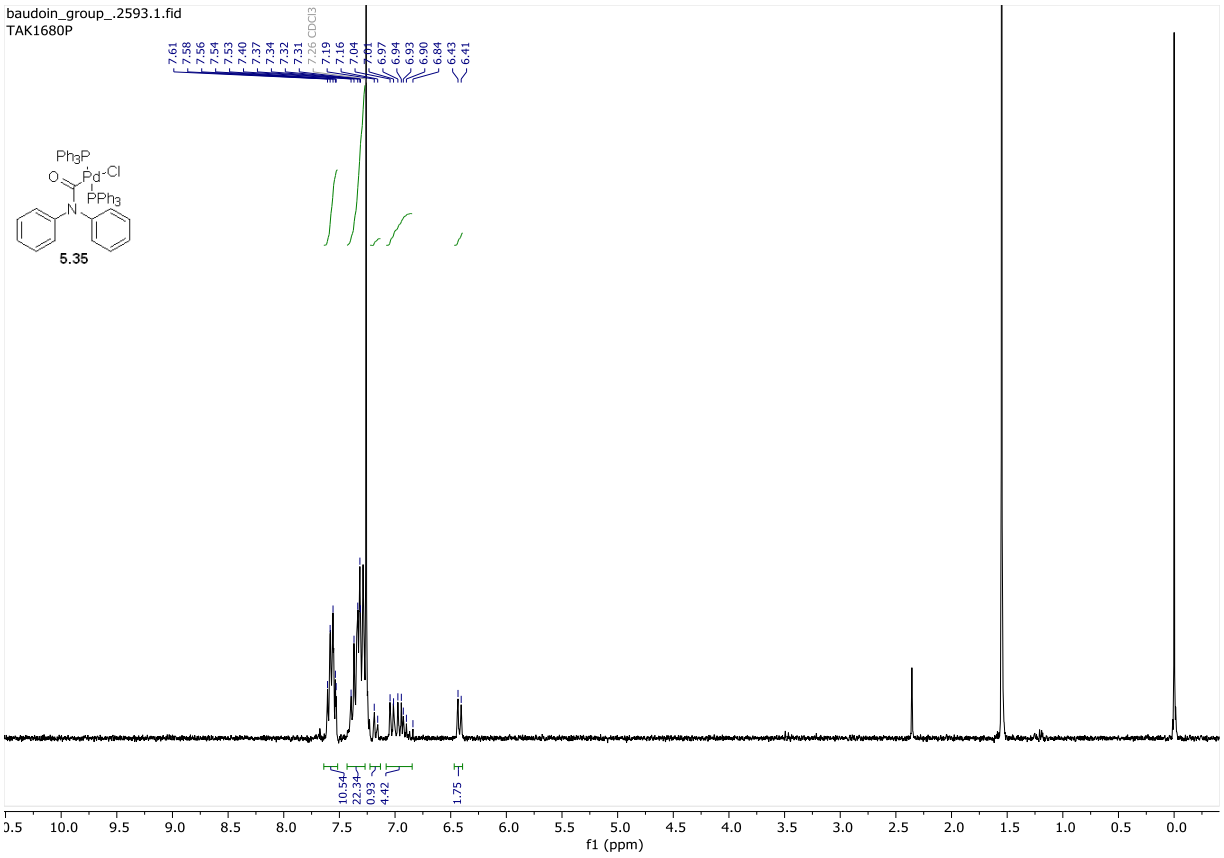


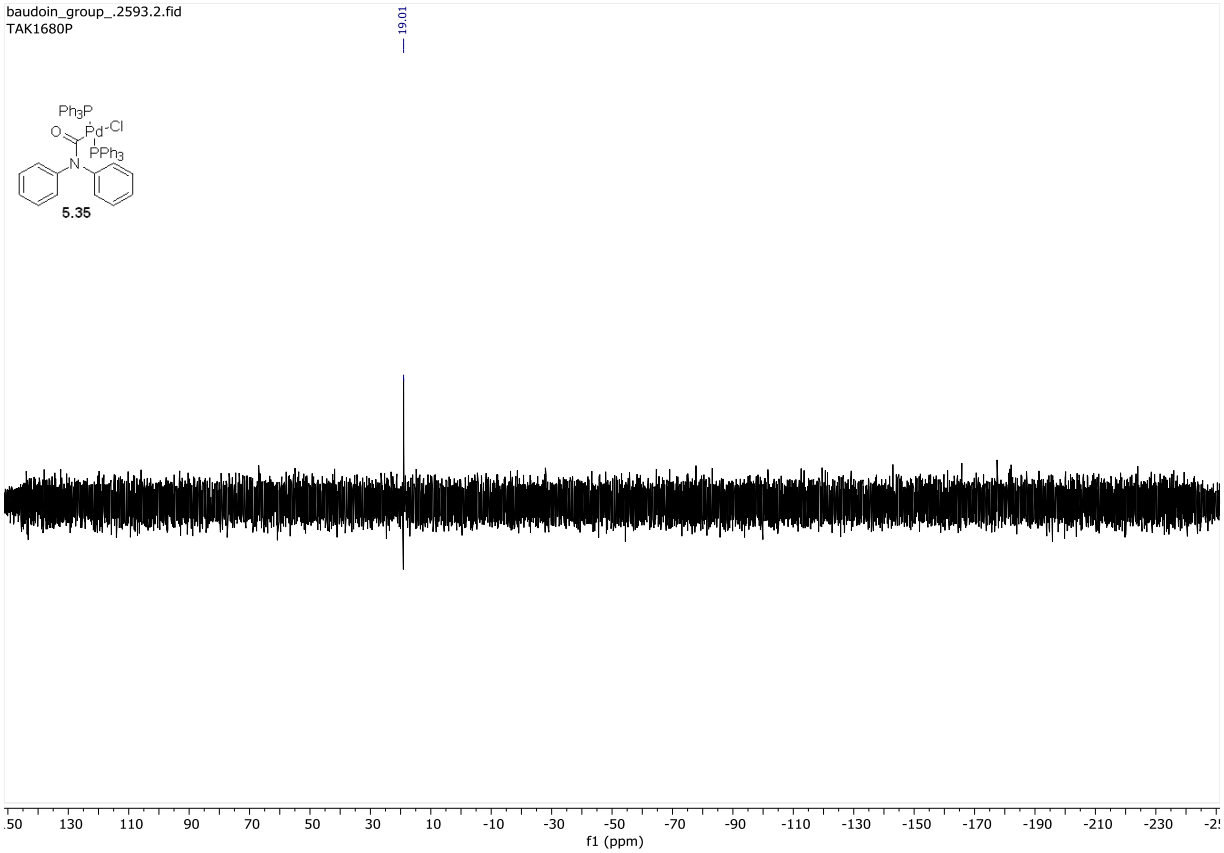
5.31


baudoin_group_.2525.1.fid
TAK-1652P
7.33
7.31
7.31
7.30
7.29
7.29
7.28
7.27
7.26 CDCl3
7.23
7.22
7.21
7.21
7.20
7.20
7.19
7.18
5.95
5.92
5.89
5.86
1.55
1.52
Cl
N
O
5.32
6.96
2.56
1.00
3.99
f1 (ppm)

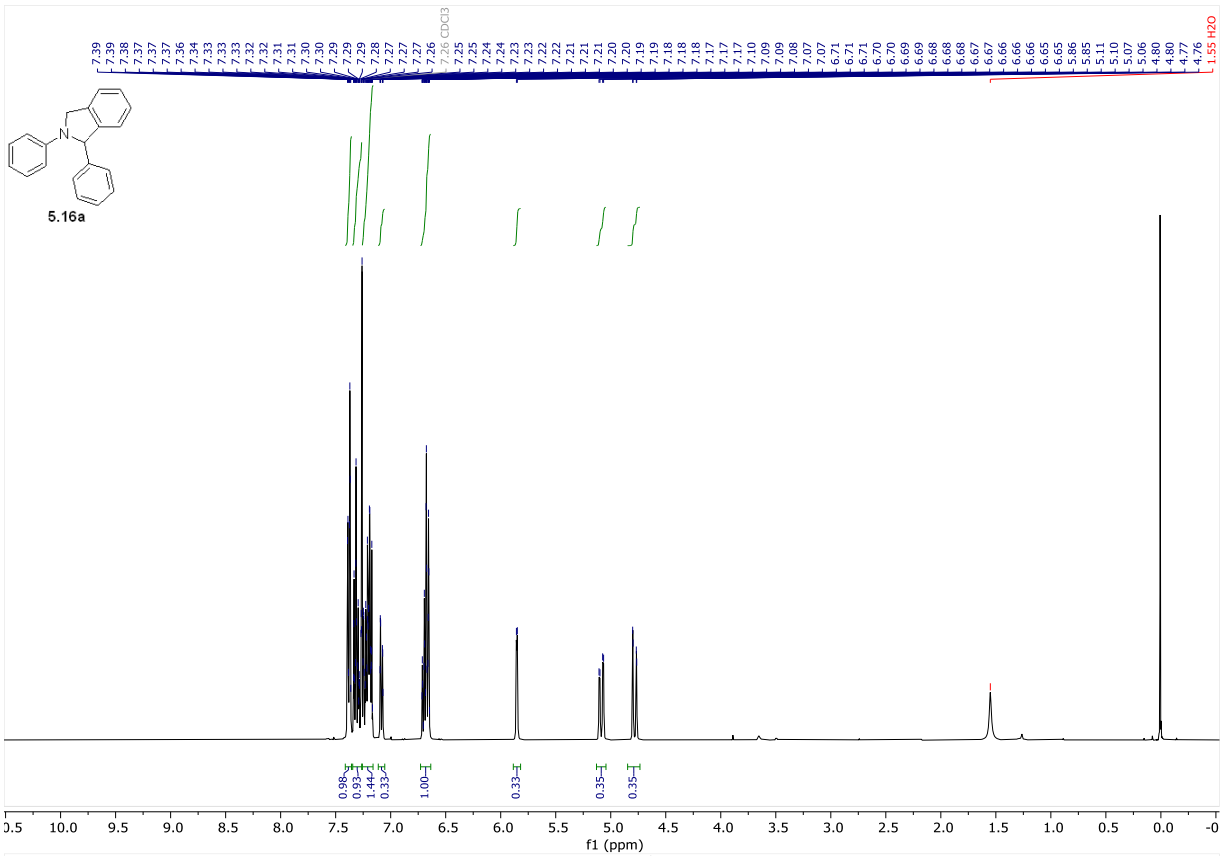

baudoin_group_.2598.1.fid
TAK-1689P
7.41
7.39
7.38
7.37
7.36
7.34
7.34
7.33
7.32
7.31
7.31
7.30
7.29
7.28
7.26 CDCl3
7.23
7.23
7.21
7.20
7.18
7.17
4.61
4.15
4.11
3.00
2.98
Cl
O
N
5.33
5.44
2.00
1.23
0.79
1.79
1.12
f1 (ppm)

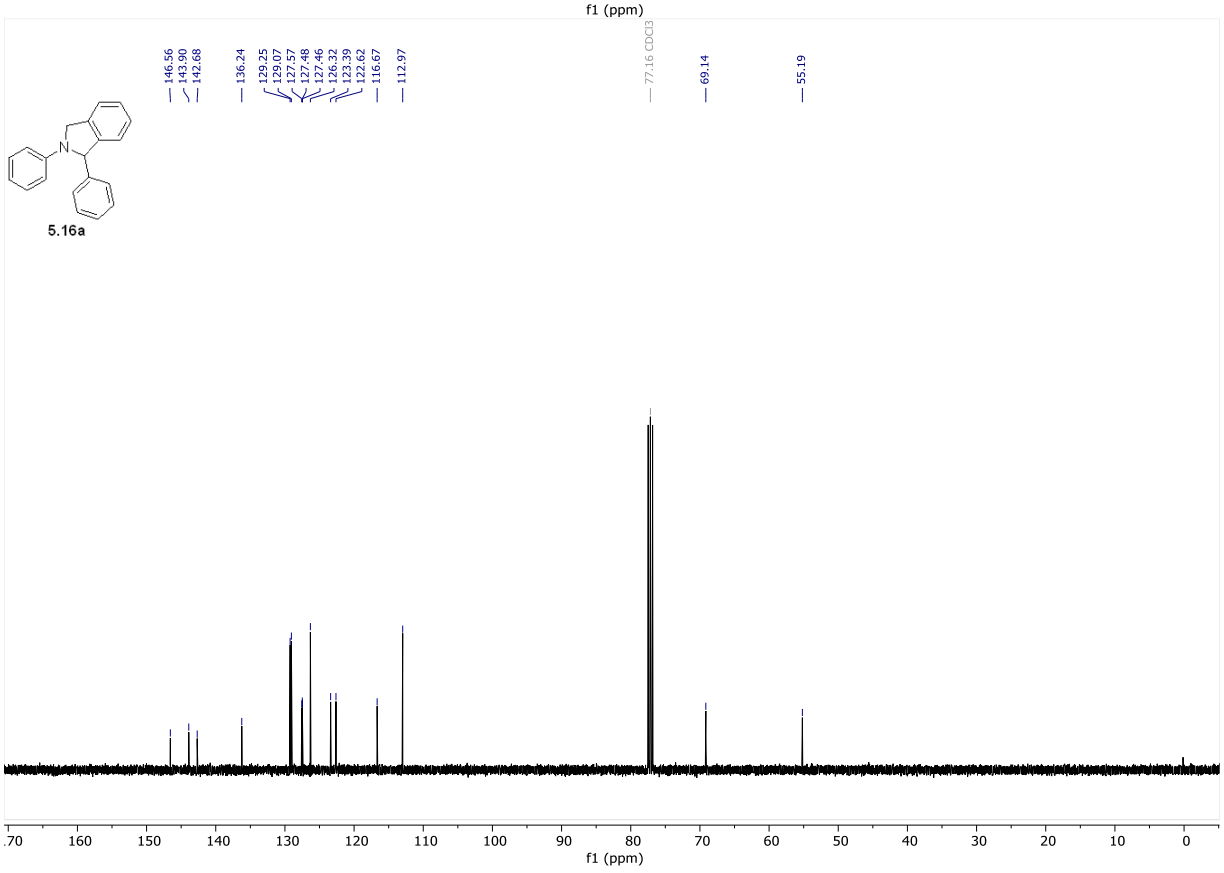

takeru.1817.1.fid
Kuerzel TAK
Gruppe BAUDOIN
Nummer 1710
P
5.34
7.40
7.40
7.38
7.38
7.36
7.35
7.34
7.34
7.33
7.32
7.31
7.30
7.29
7.27
CDCl3
7.26
7.24
7.23
7.21
7.19
7.17
7.16
4.62
4.52
4.15
5.92
1.98
2.00
2.10
2.20
2.14
f1 (ppm)

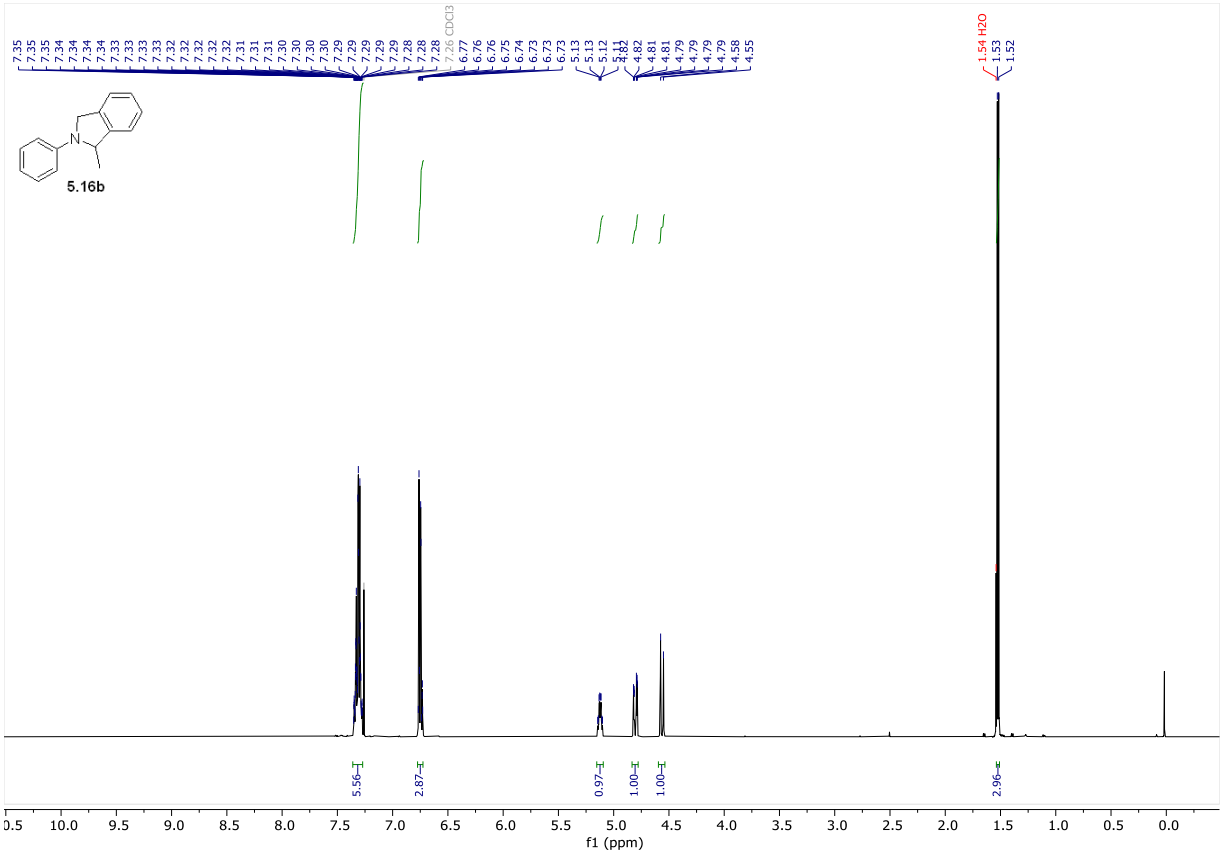

baudoin_group_.2593.1.fid
TAK1680P
7.61
7.58
7.56
7.54
7.53
7.40
7.37
7.34
7.32
7.31
7.26 CDCl3
7.19
7.16
7.04
7.01
6.97
6.94
6.93
6.90
6.84
6.43
6.41
Ph3P
O
Pd
Cl
PPh3
N
5.35
10.54
22.34
0.93
4.42
1.75
f1 (ppm)

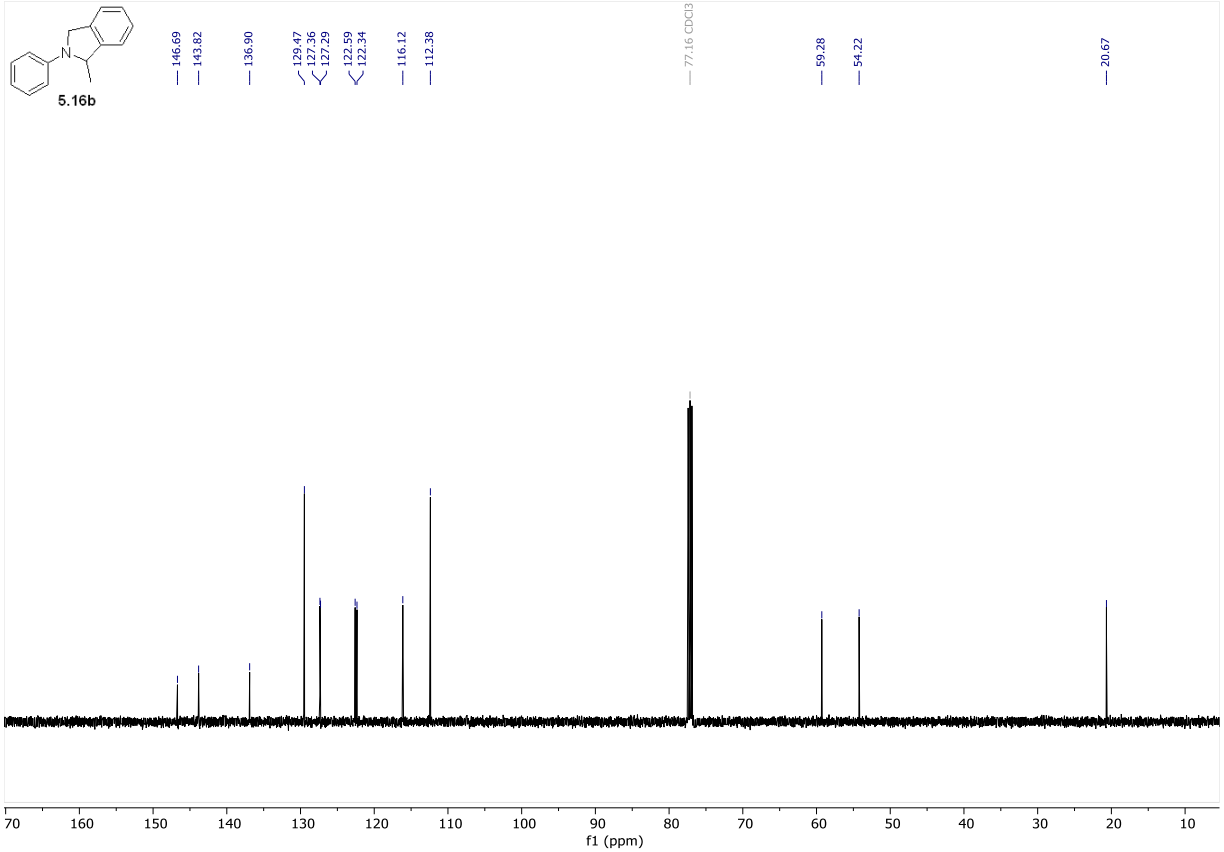

baudoin_group_.2593.2.fid
TAK1680P
19.01
Ph3P
O
Pd
Cl
PPh3
N
5.35
f1 (ppm)

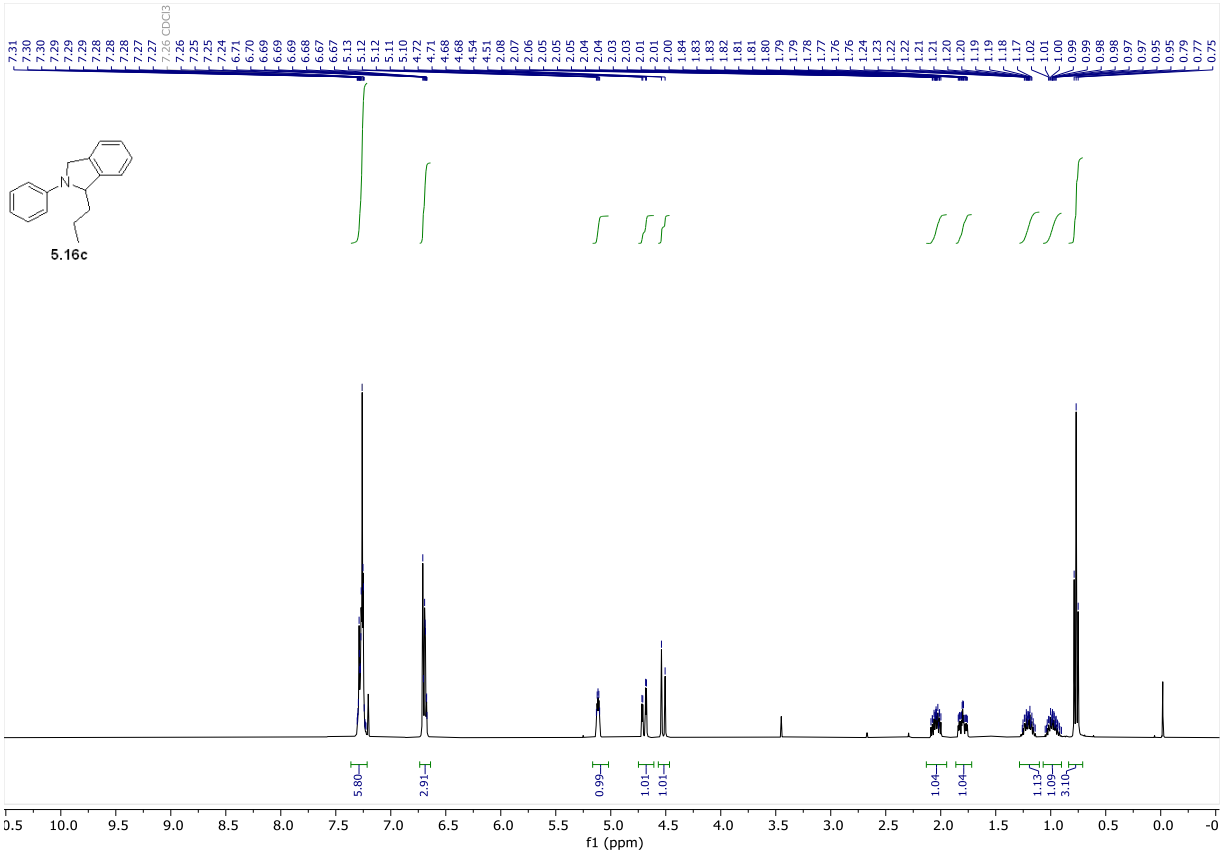
7.8.2 NMR spectral data of C–H activation products: isoindolines

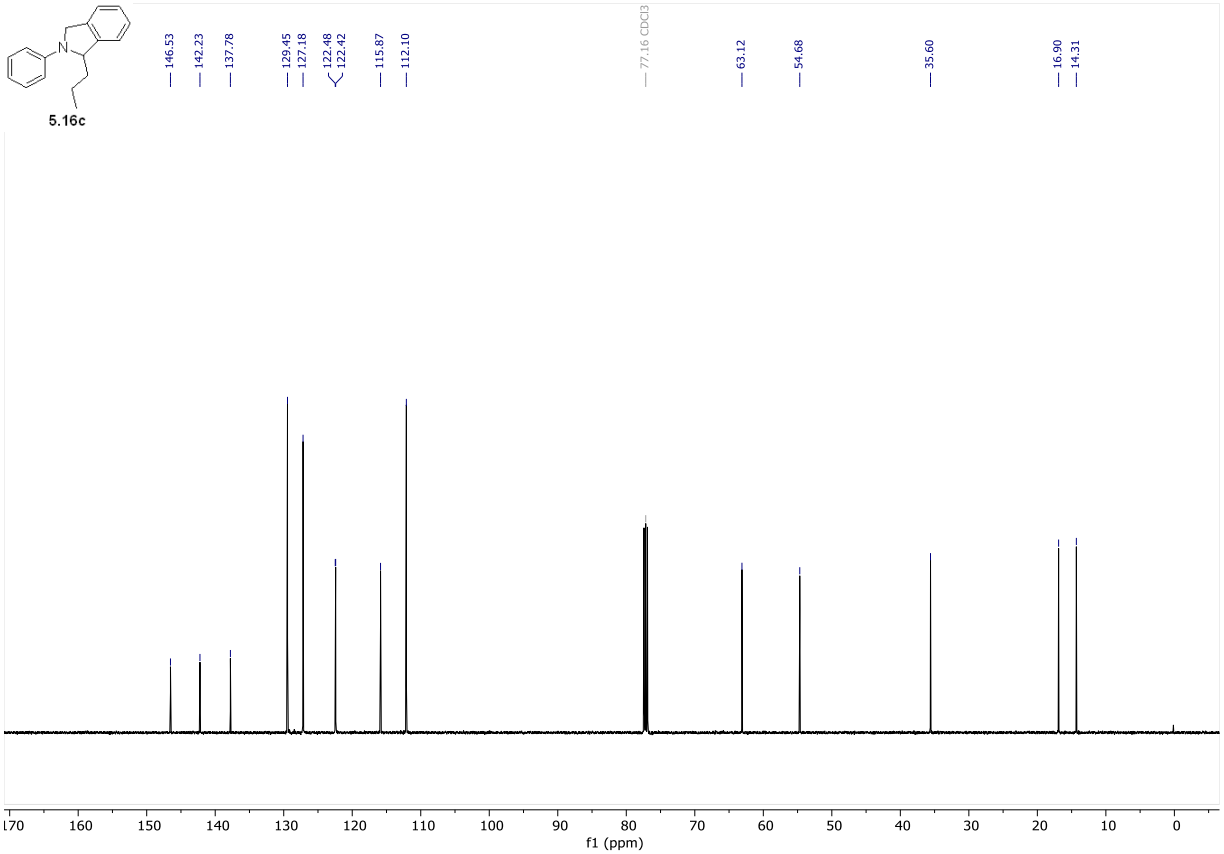


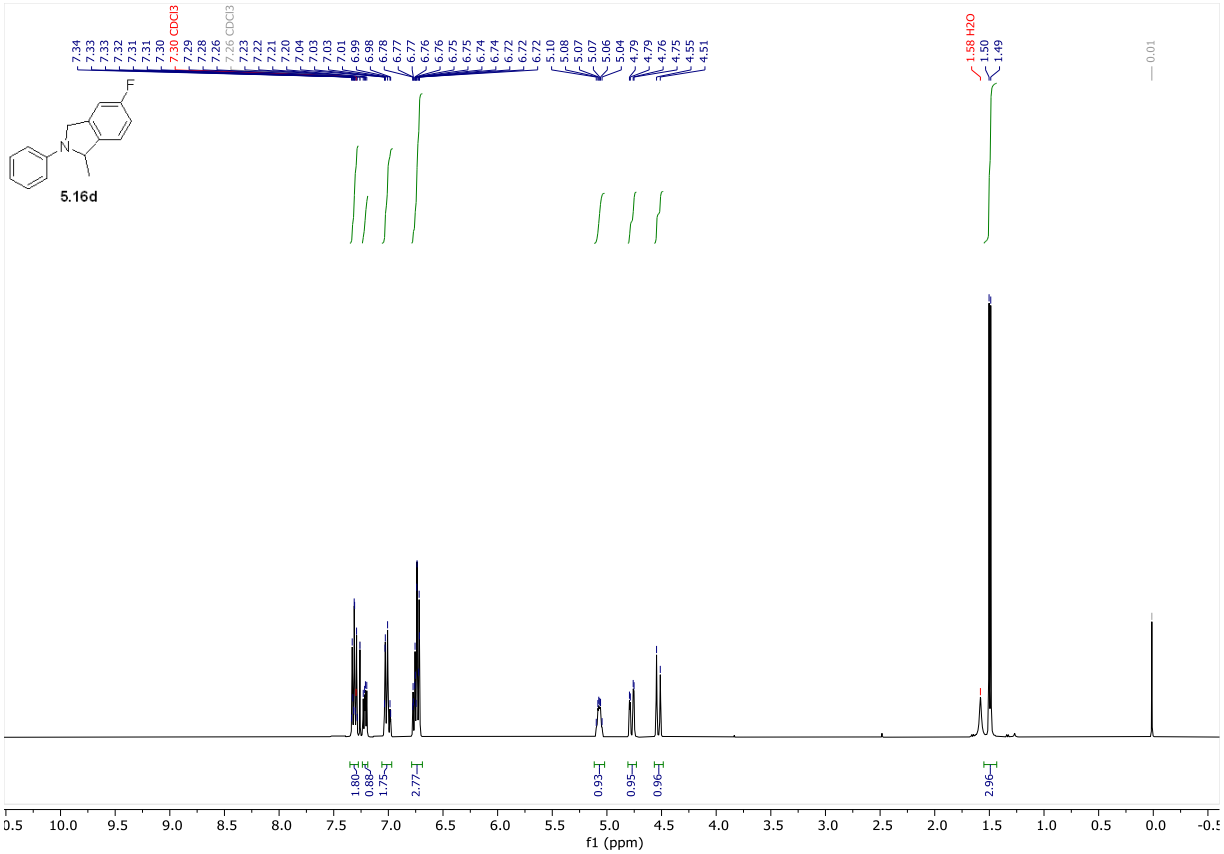


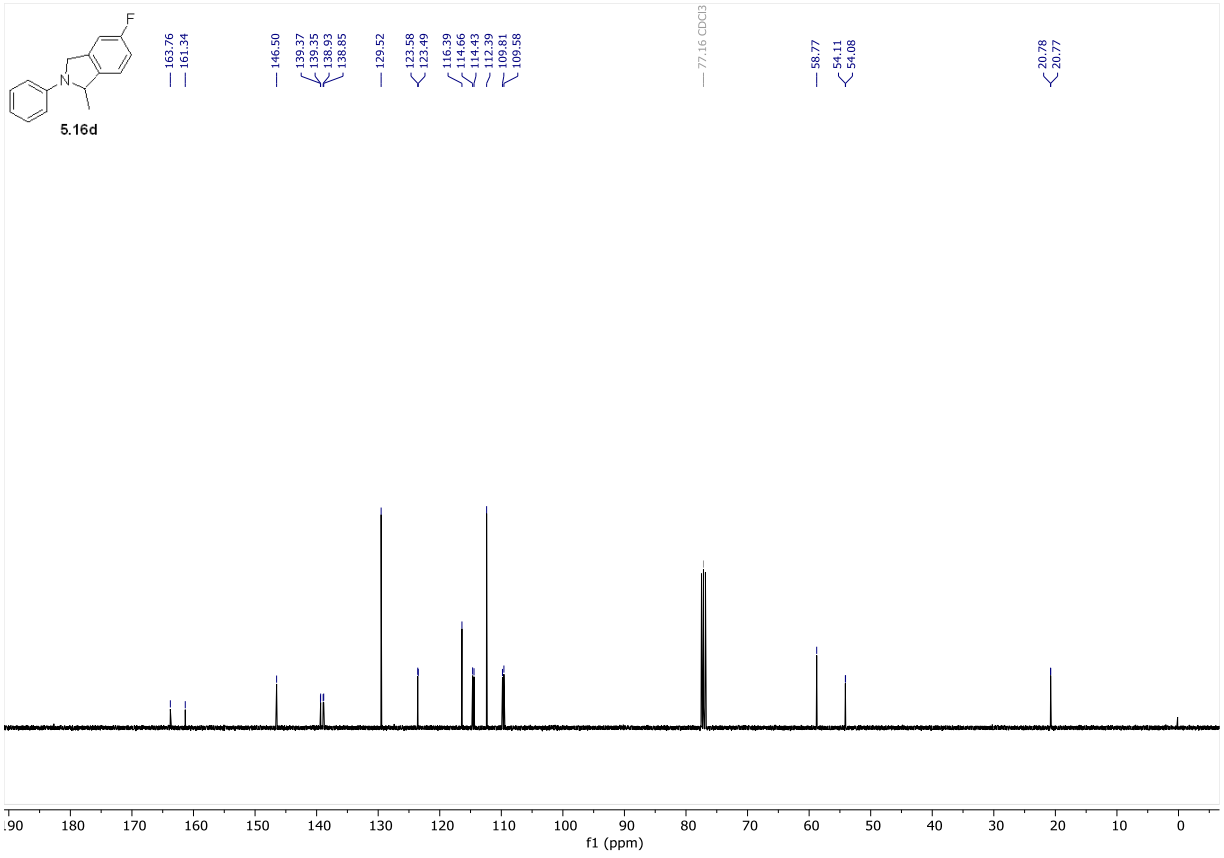

5.16b
7.35 7.35 7.35 7.34 7.34 7.34 7.34 7.33 7.33 7.33 7.32 7.32 7.32 7.32 7.32 7.31 7.31 7.31 7.30 7.30 7.30 7.30 7.29 7.29 7.29 7.29 7.29 7.28 7.28 7.28 7.26 CDCl3 6.77 6.76 6.76 6.75 6.74 6.73 6.73 6.73 5.13 5.13 5.12 4.82 4.82 4.81 4.81 4.79 4.79 4.79 4.79 4.58 4.55
1.54 H2O 1.53 1.52
5.56 2.87 0.97 1.00 1.00 2.96
f1 (ppm)

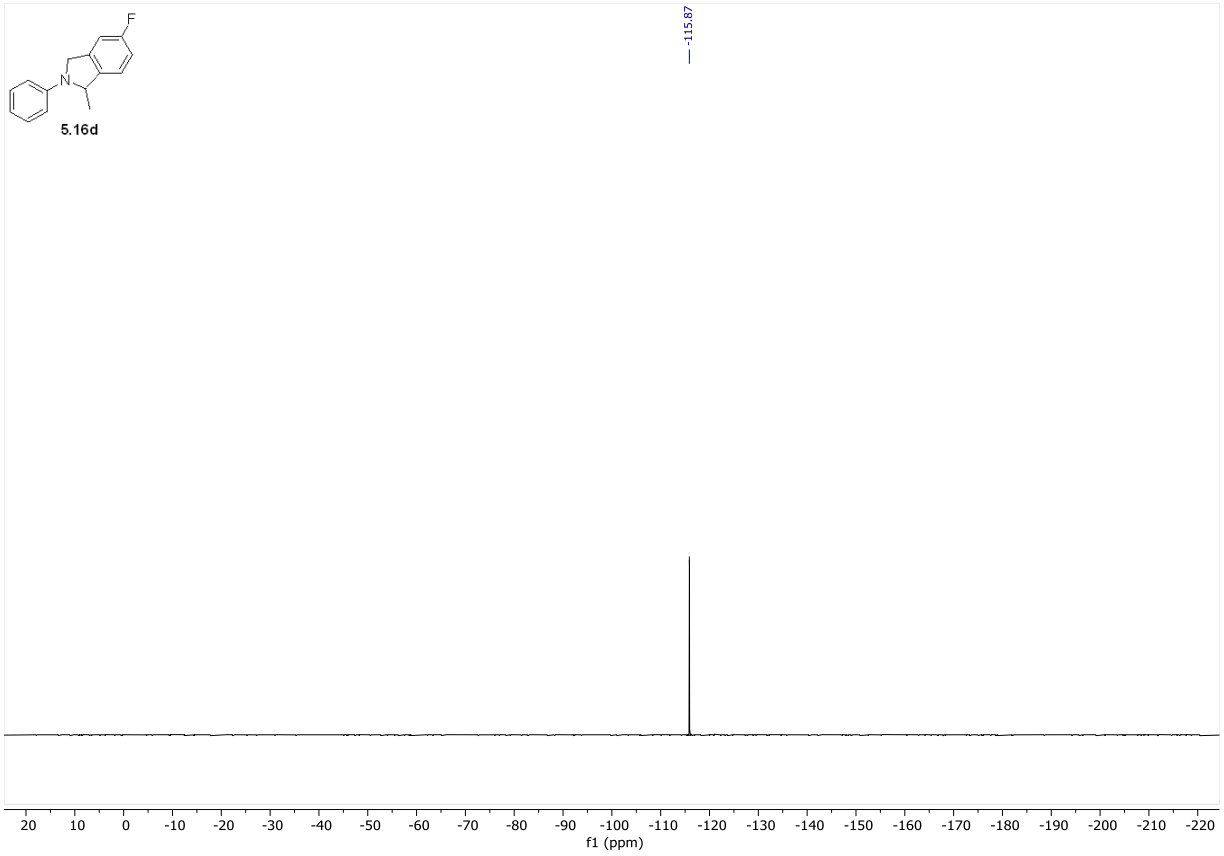

5.16b
146.69 143.82 136.90 129.47 127.36 127.29 122.59 122.34 116.12 112.38
77.16 CDCl3
59.28 54.22 20.67
f1 (ppm)


5.16c
f1 (ppm)


5.16c
f1 (ppm)


5.16d
7.34 7.33 7.33 7.32 7.31 7.31 7.30 7.30 CDCl3 7.29 7.28 7.26 7.26 CDCl3 7.23 7.22 7.21 7.20 7.04 7.03 7.03 7.01 6.99 6.98 6.78 6.77 6.77 6.76 6.76 6.75 6.74 6.72 6.72 6.72 5.10 5.08 5.07 5.07 5.06 5.04 4.79 4.79 4.76 4.75 4.55 4.51
1.58 H2O 1.50 1.49
0.01
1.80 0.88 1.75 2.77 0.93 0.95 0.96 2.96
f1 (ppm)


5.16d
163.76 161.34 146.50 139.37 139.35 138.93 138.85 129.52 123.58 123.49 116.39 114.66 114.43 112.39 109.81 109.58
77.16 CDCl3
58.77 54.11 54.08
20.78 20.77
f1 (ppm)


F
N
5.16d
-115.87
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
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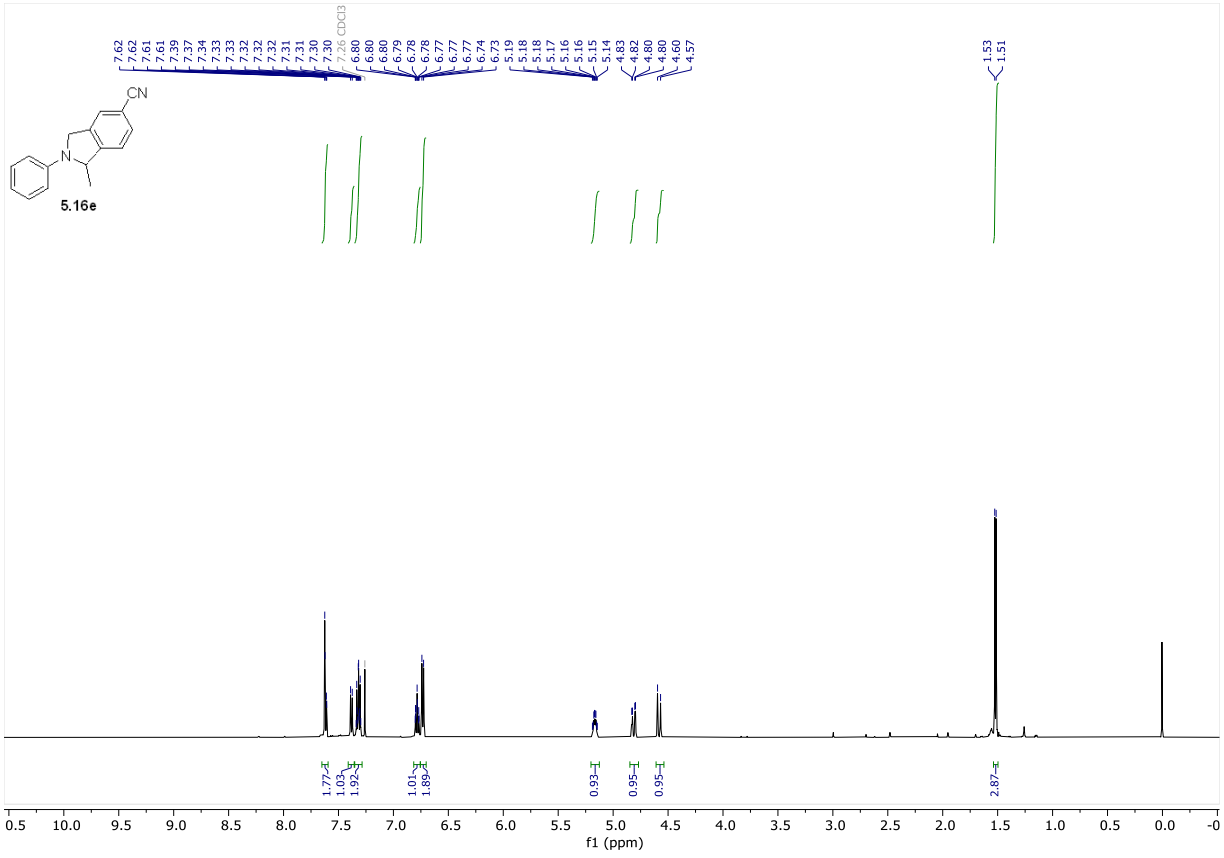
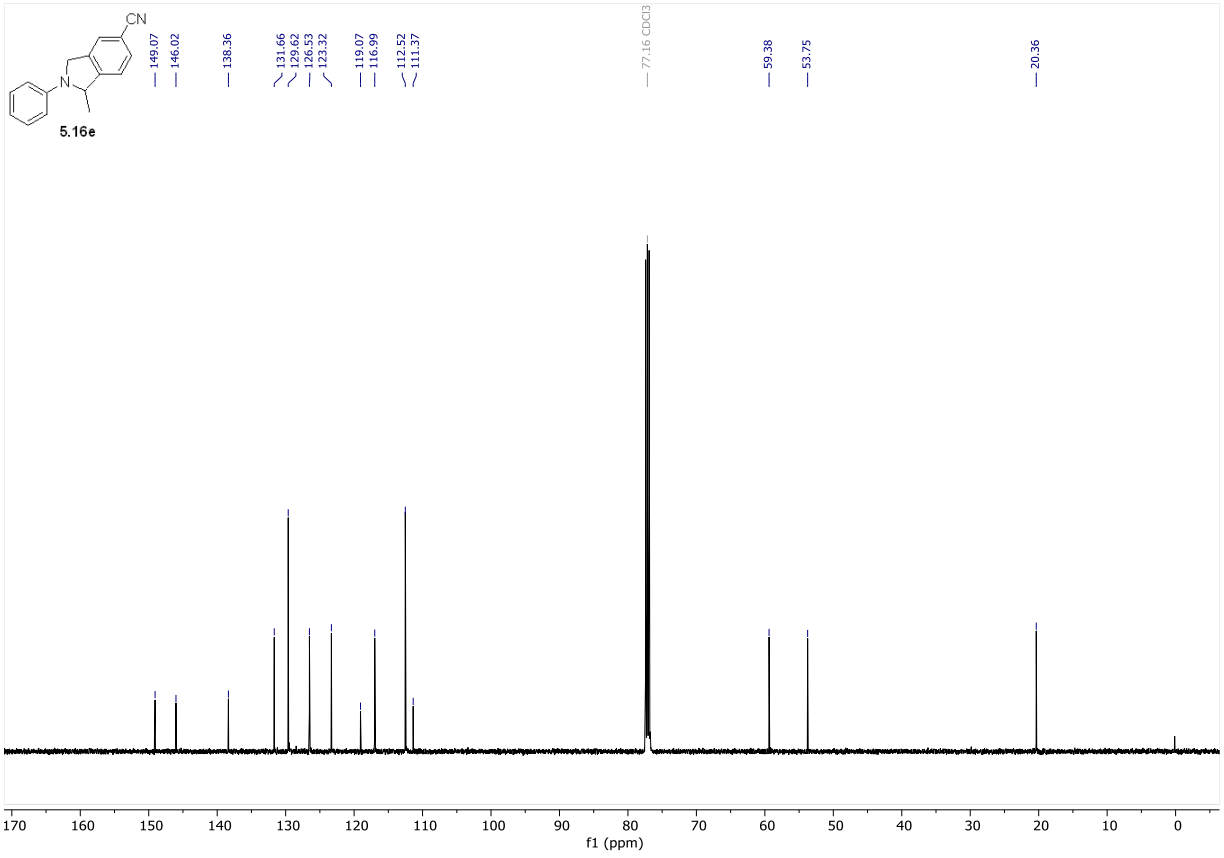
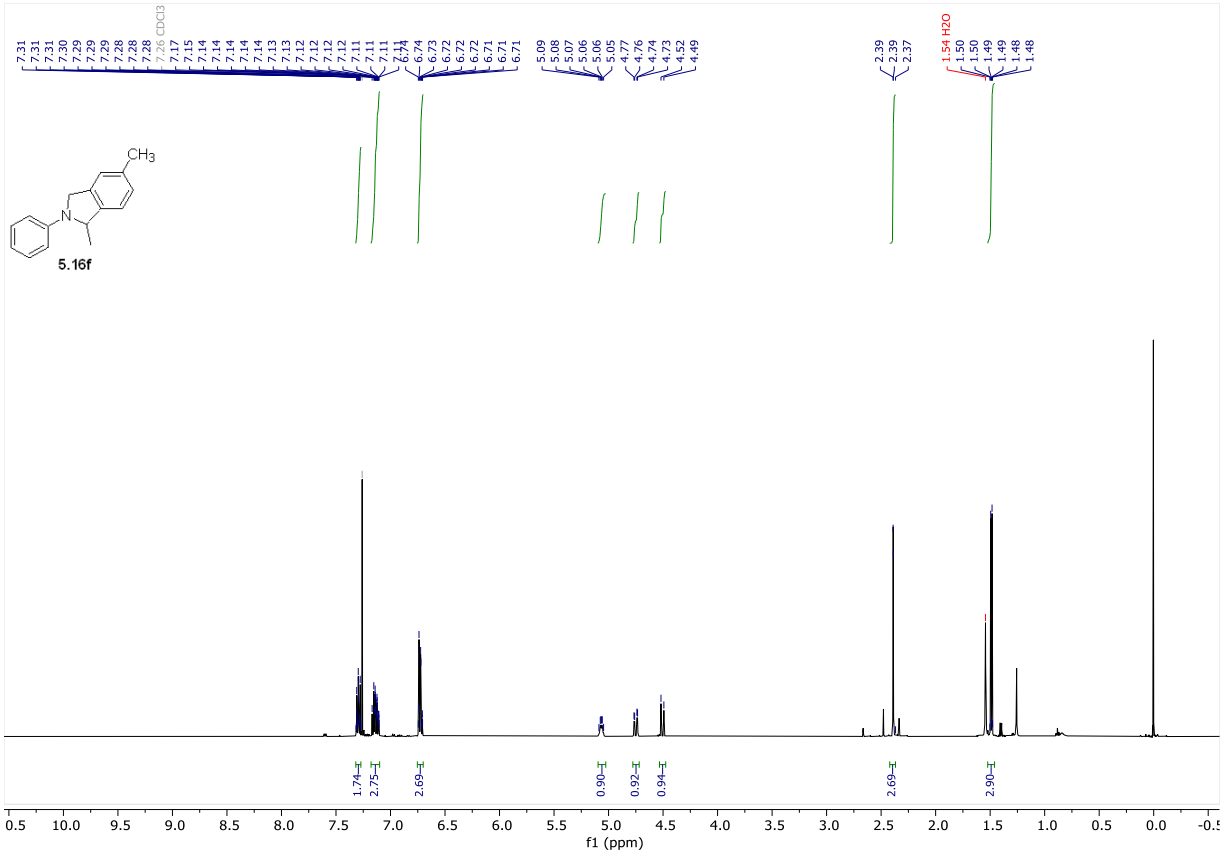
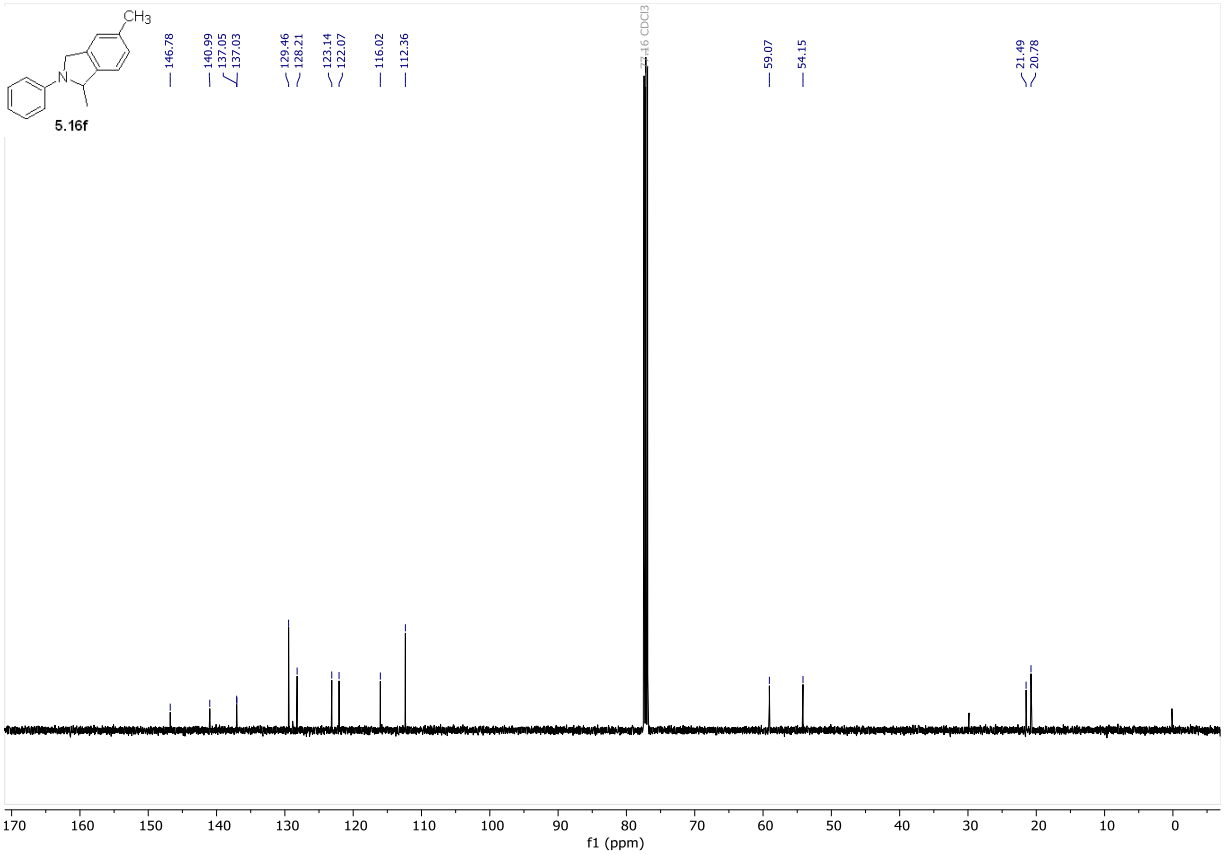
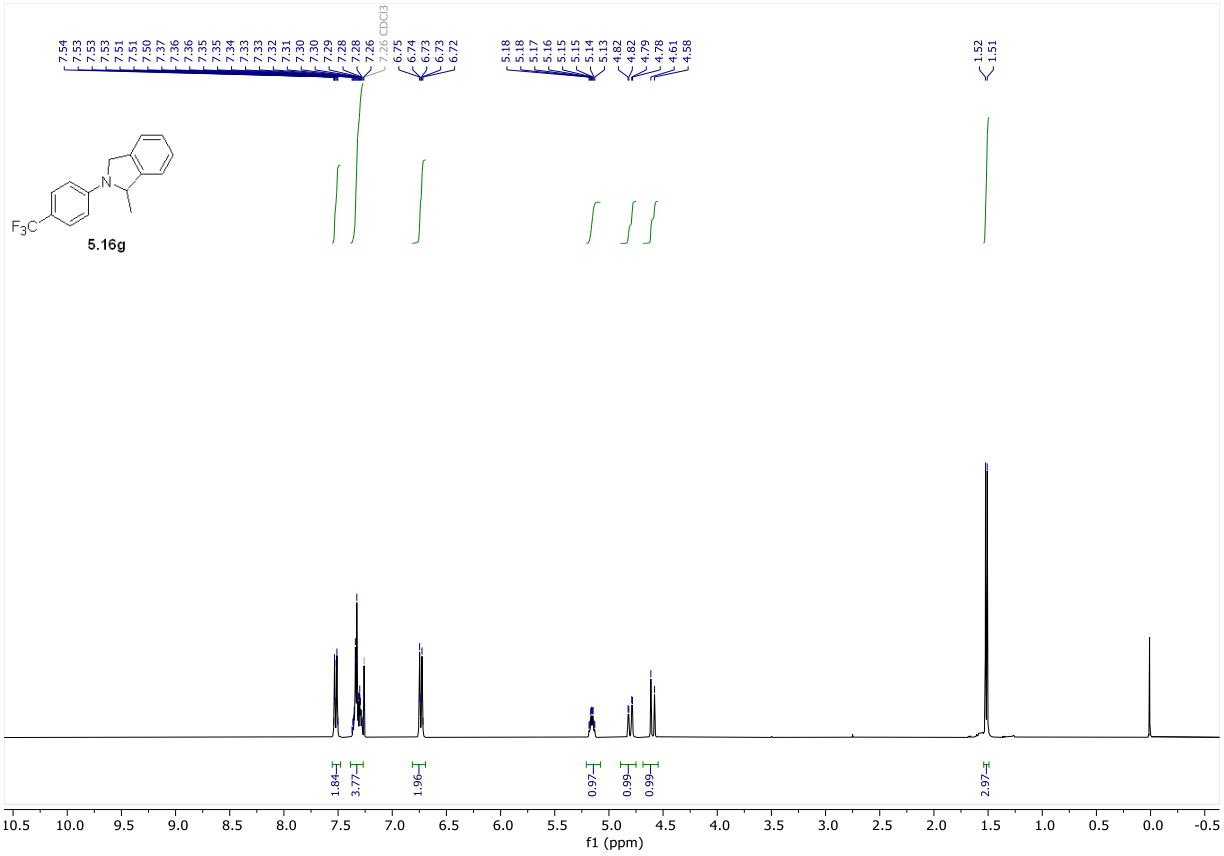
-170
-180
-190
-200
-210
-220
f1 (ppm)

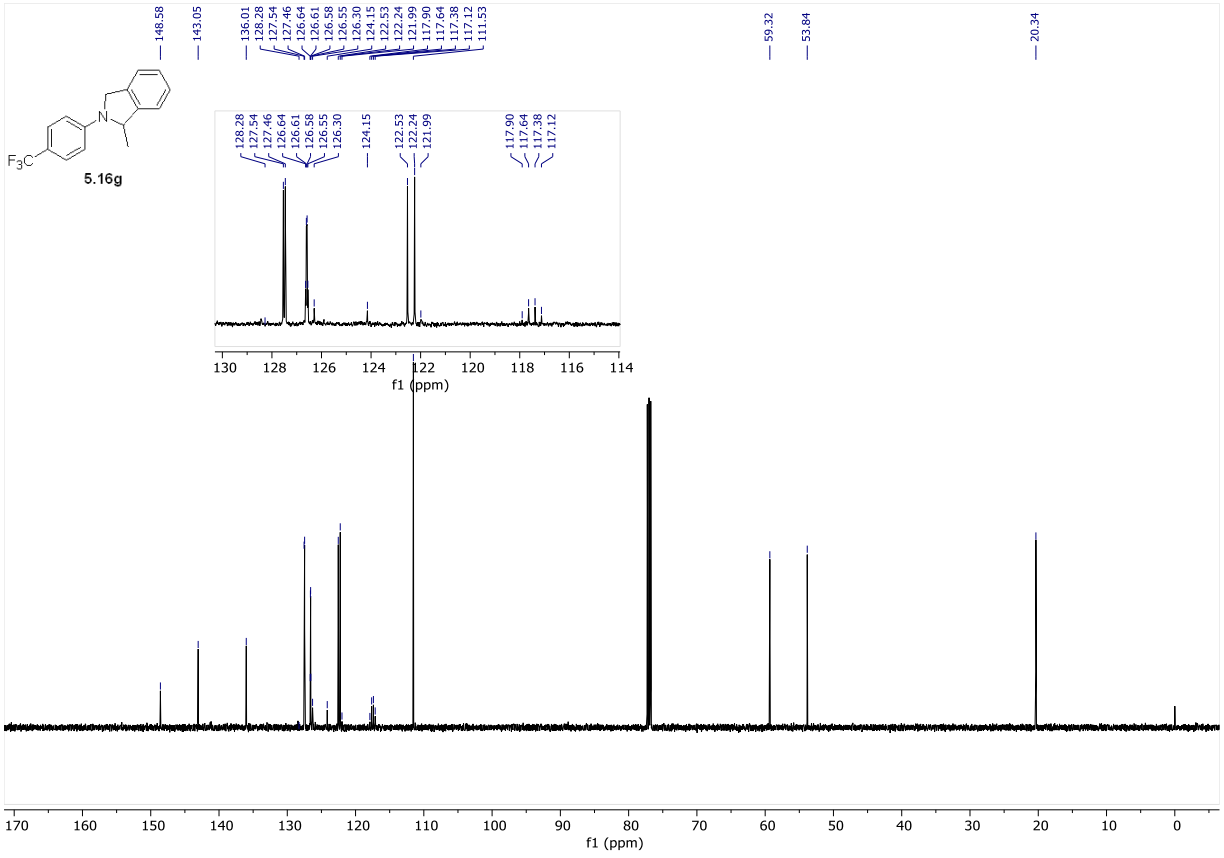

7.62
7.62
7.61
7.61
7.39
7.37
7.34
7.33
7.33
7.32
7.32
7.32
7.31
7.31
7.30
7.30
7.26 CDCl3
6.80
6.80
6.80
6.79
6.78
6.78
6.77
6.77
6.77
6.74
6.73
5.19
5.18
5.18
5.17
5.16
5.16
5.15
5.14
4.83
4.82
4.80
4.80
4.60
4.57
1.53
1.51
CN
N
5.16e
1.77
1.03
1.92
1.01
1.89
0.93
0.95
0.95
2.87
f1 (ppm)

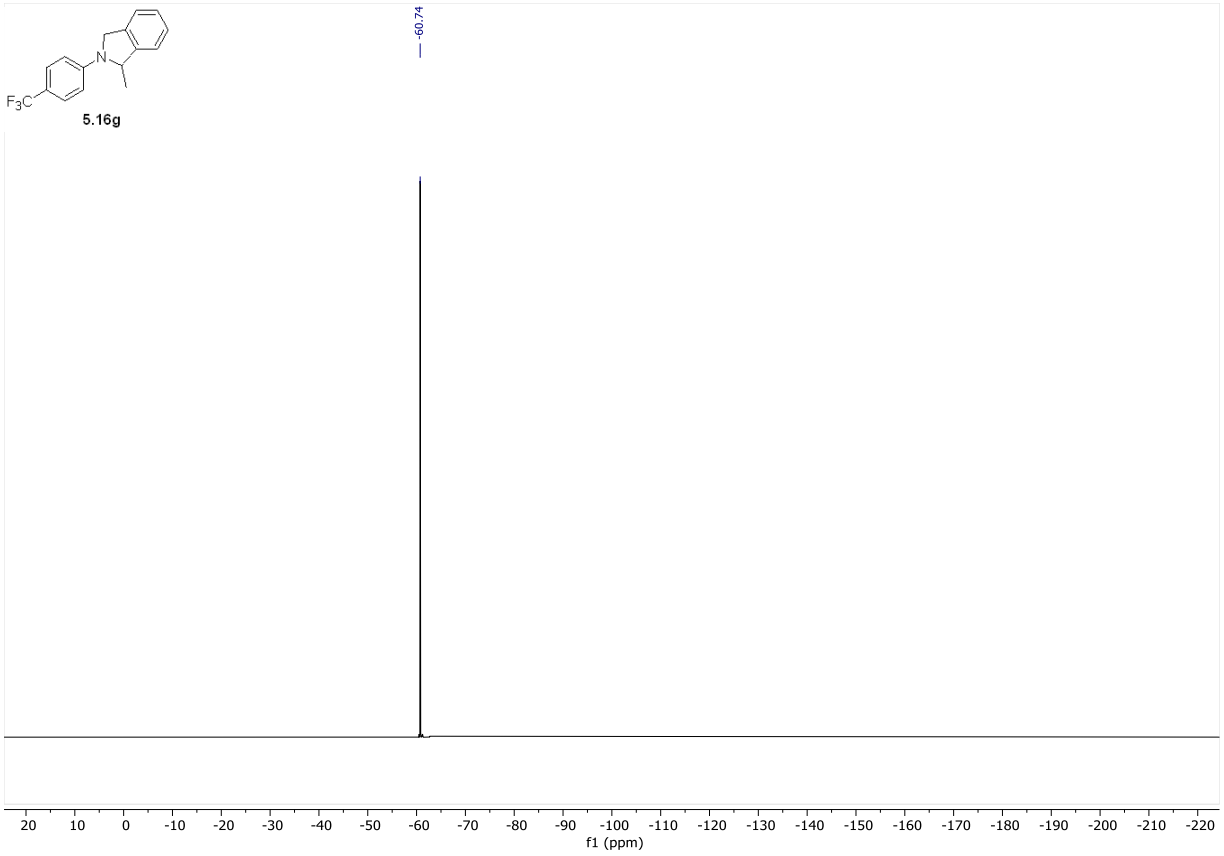

CN
N
5.16e
149.07
146.02
138.36
131.66
129.62
126.53
123.32
119.07
116.99
112.52
111.37
77.16 CDCl3
59.38
53.75
20.36
f1 (ppm)


7.31 7.31 7.31 7.30 7.29 7.29 7.28 7.28 7.28 7.26 CDCl3 7.17 7.15 7.14 7.14 7.14 7.14 7.13 7.12 7.12 7.12 7.12 7.11 7.11 7.11 6.74 6.74 6.73 6.72 6.72 6.72 6.71 6.71 6.71
5.09 5.08 5.07 5.06 5.06 5.05 4.77 4.76 4.74 4.73 4.52 4.49
2.39 2.39 2.37
1.54 H2O 1.50 1.50 1.49 1.49 1.48 1.48
CH3
5.16f
1.74 2.75 2.69 0.90 0.92 0.94 2.69 2.90
0.5 10.0 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 -0.5
f1 (ppm)


CH3
5.16f
146.78 140.99 137.05 137.03 129.46 128.21 123.14 122.07 116.02 112.36
77.46 CDCl3
59.07 54.15
21.49 20.78
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.54 7.53 7.53 7.53 7.51 7.51 7.50 7.37 7.36 7.36 7.35 7.35 7.34 7.33 7.33 7.32 7.31 7.30 7.30 7.29 7.28 7.28 7.26 7.26 CDCl3 6.75 6.74 6.73 6.73 6.72 5.18 5.18 5.17 5.16 5.15 5.15 5.14 5.13 4.82 4.82 4.79 4.78 4.61 4.58 1.52 1.51
F3C
5.16g
1.84 3.77 1.96 0.97 0.99 0.99 2.97
10.5 10.0 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 -0.5
f1 (ppm)


148.58 143.05 136.01 128.28 127.54 127.46 126.64 126.61 126.58 126.55 126.30 124.15 122.53 122.24 121.99 117.90 117.64 117.38 117.12 111.53 59.32 53.84 20.34
F3C
5.16g
128.28 127.54 127.46 126.64 126.61 126.58 126.55 126.30 124.15 122.53 122.24 121.99 117.90 117.64 117.38 117.12
130 128 126 124 122 120 118 116 114
f1 (ppm)
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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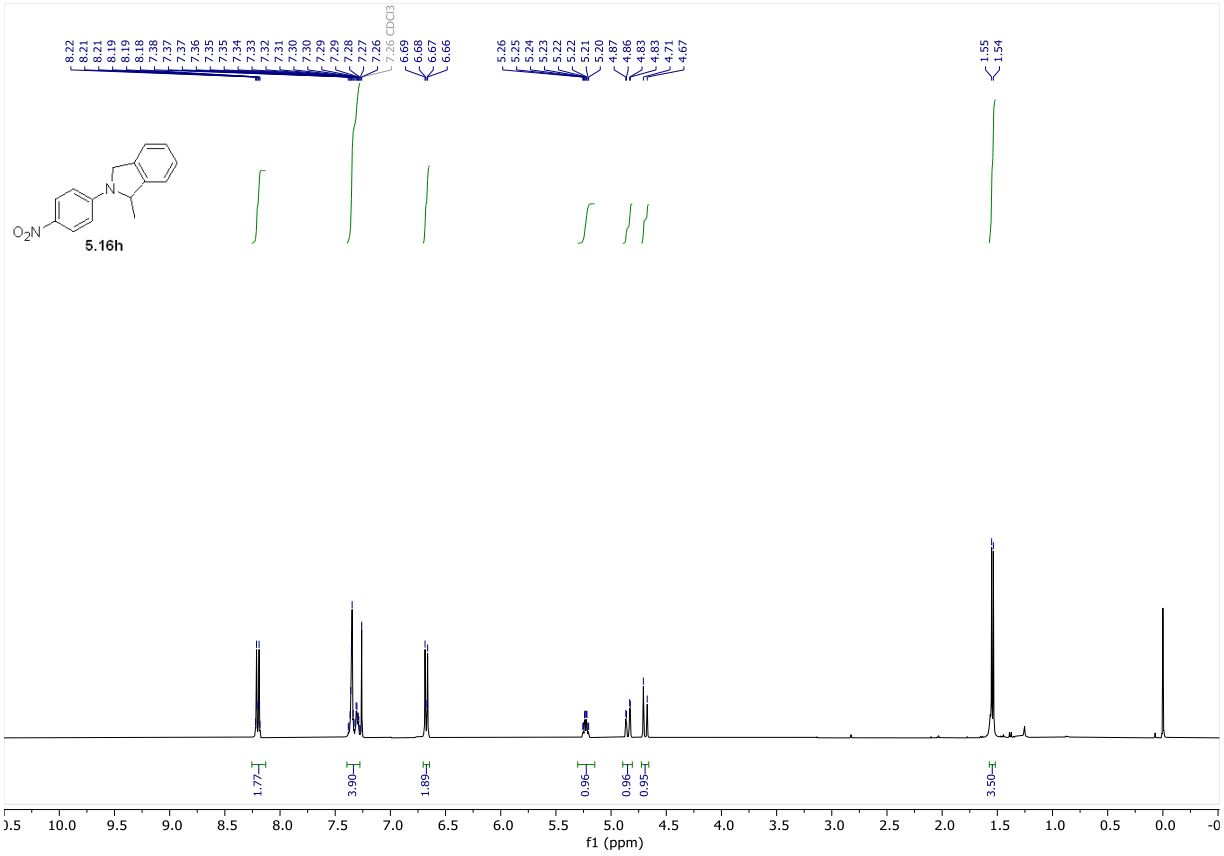
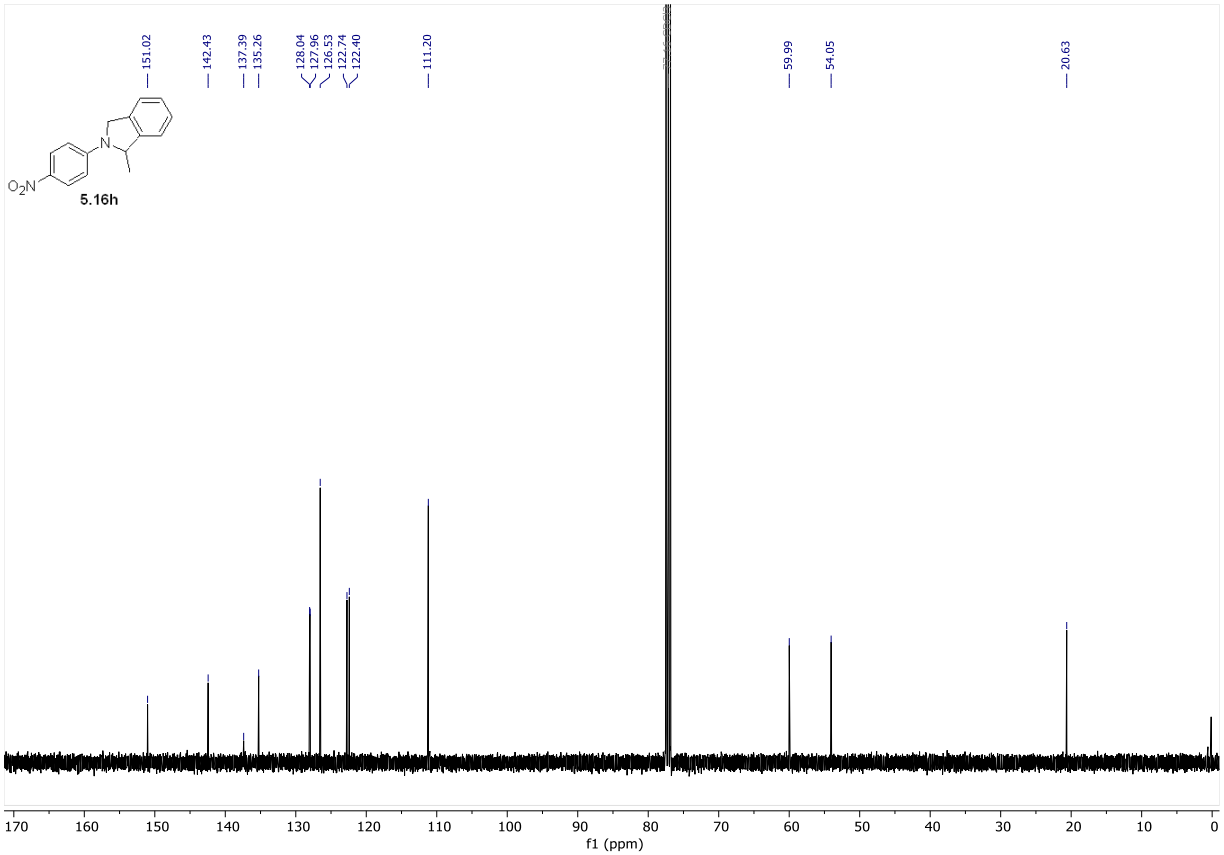
F3C
5.16g
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
f1 (ppm)


8.22
8.21
8.21
8.19
8.19
8.18
7.38
7.37
7.37
7.36
7.35
7.35
7.34
7.33
7.32
7.31
7.30
7.30
7.29
7.29
7.28
7.27
7.26
CDCl3
6.69
6.68
6.67
6.66
5.26
5.25
5.24
5.23
5.22
5.22
5.21
5.20
4.87
4.86
4.83
4.83
4.71
4.67
1.55
1.54
O2N
5.16h
1.77
3.90
1.89
0.96
0.96
0.95
3.50
f1 (ppm)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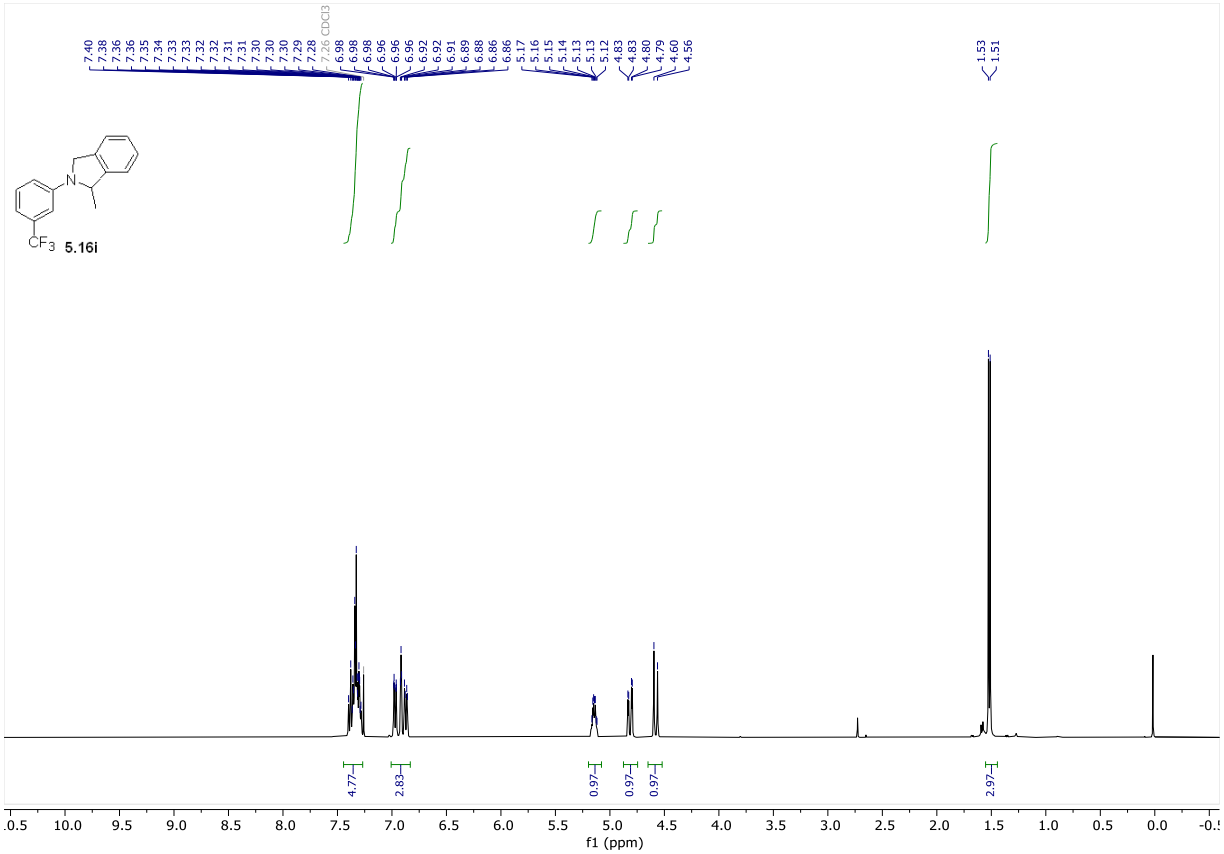
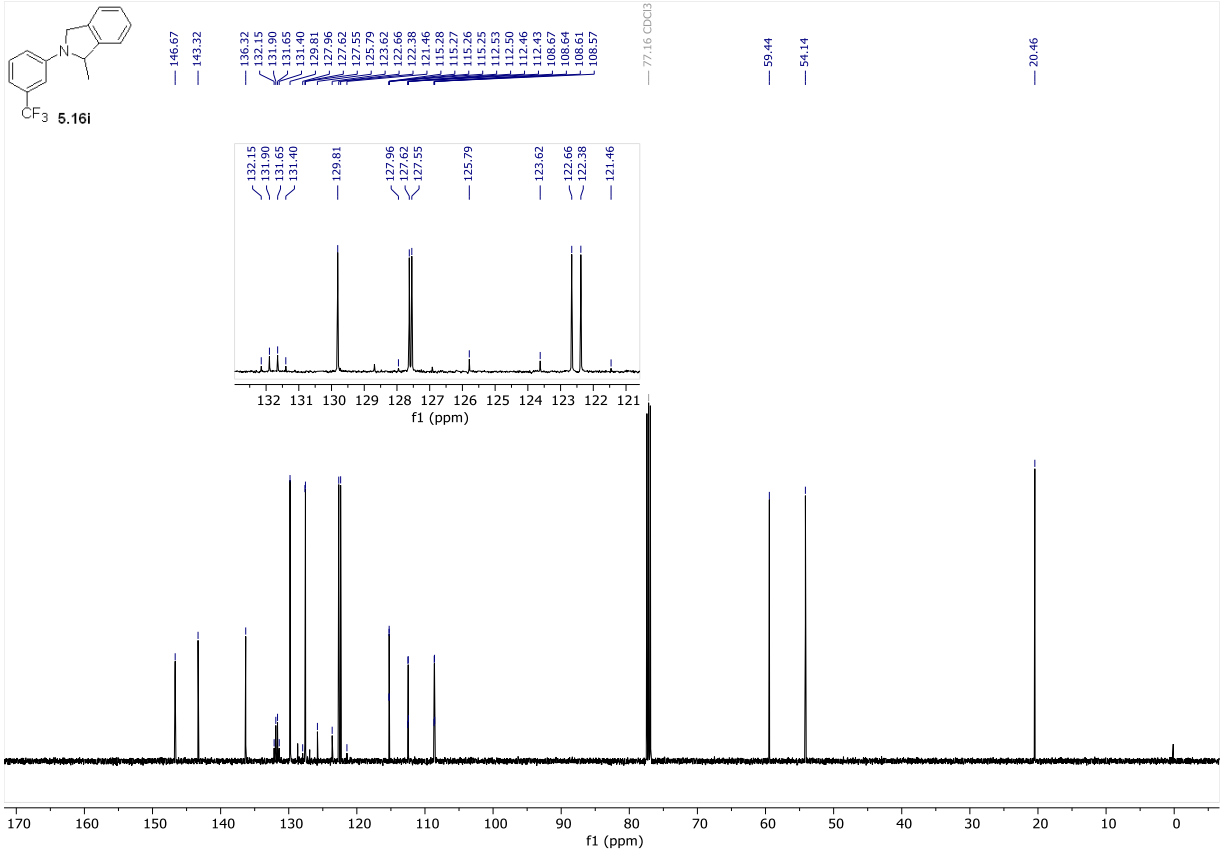
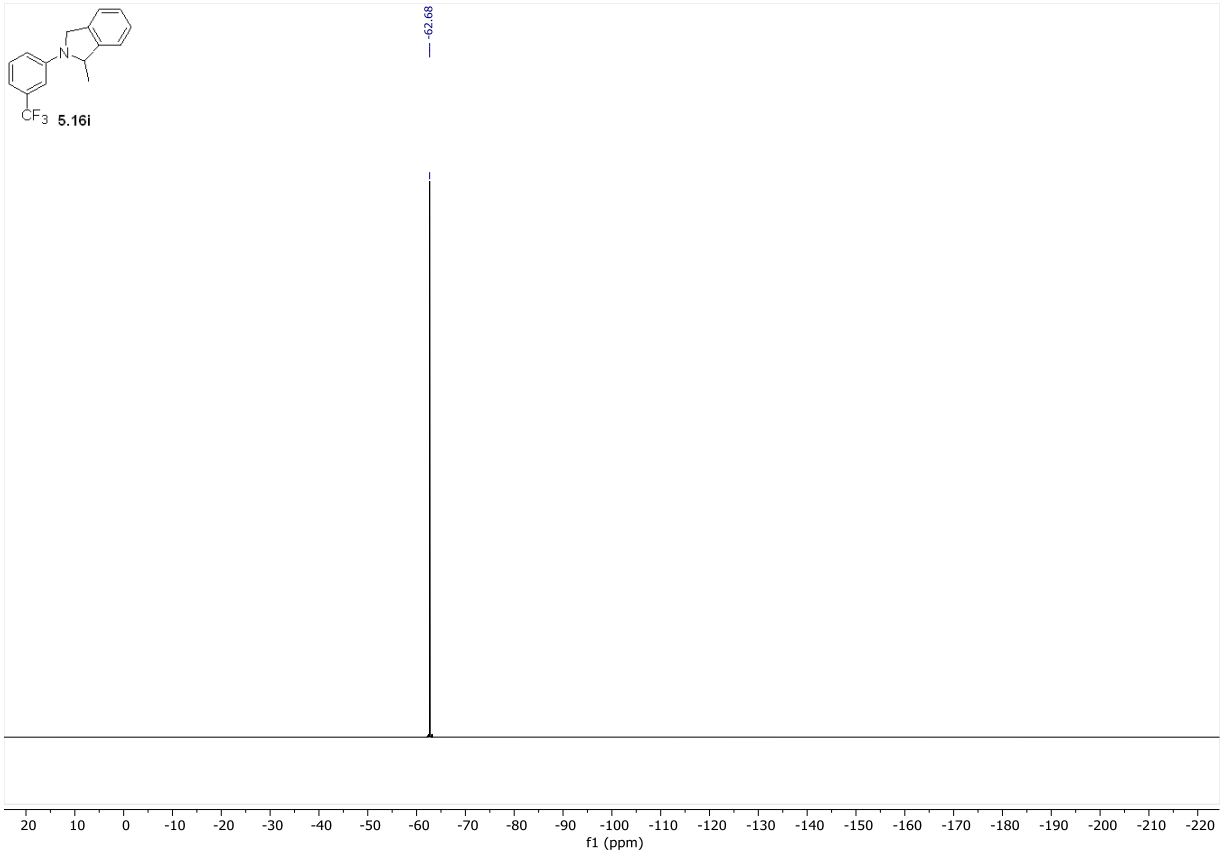
142.43
137.39
135.26
128.04
127.96
126.53
122.74
122.40
111.20
59.99
54.05
20.63
O2N
5.16h
f1 (ppm)


5.16i
f1 (ppm)


5.16i
f1 (ppm)
f1 (ppm)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CF3
5.16i
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
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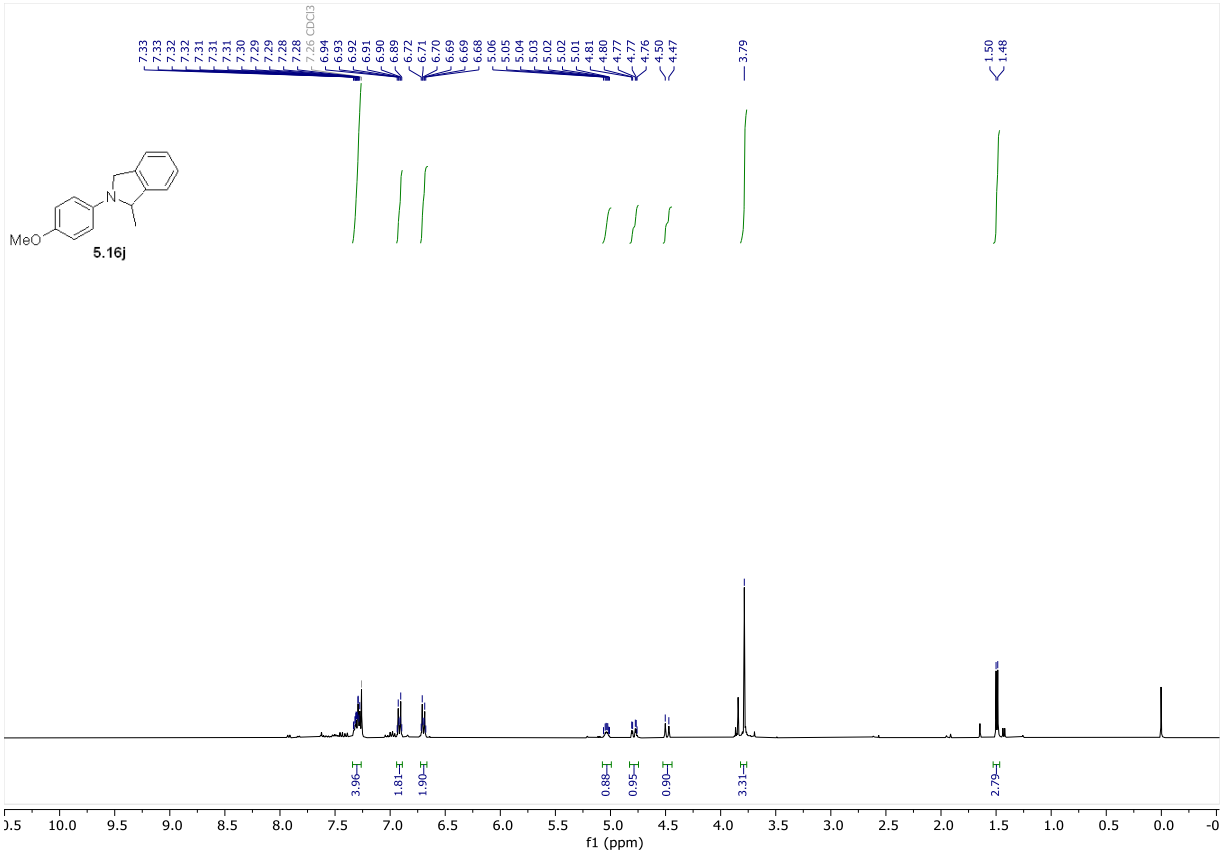
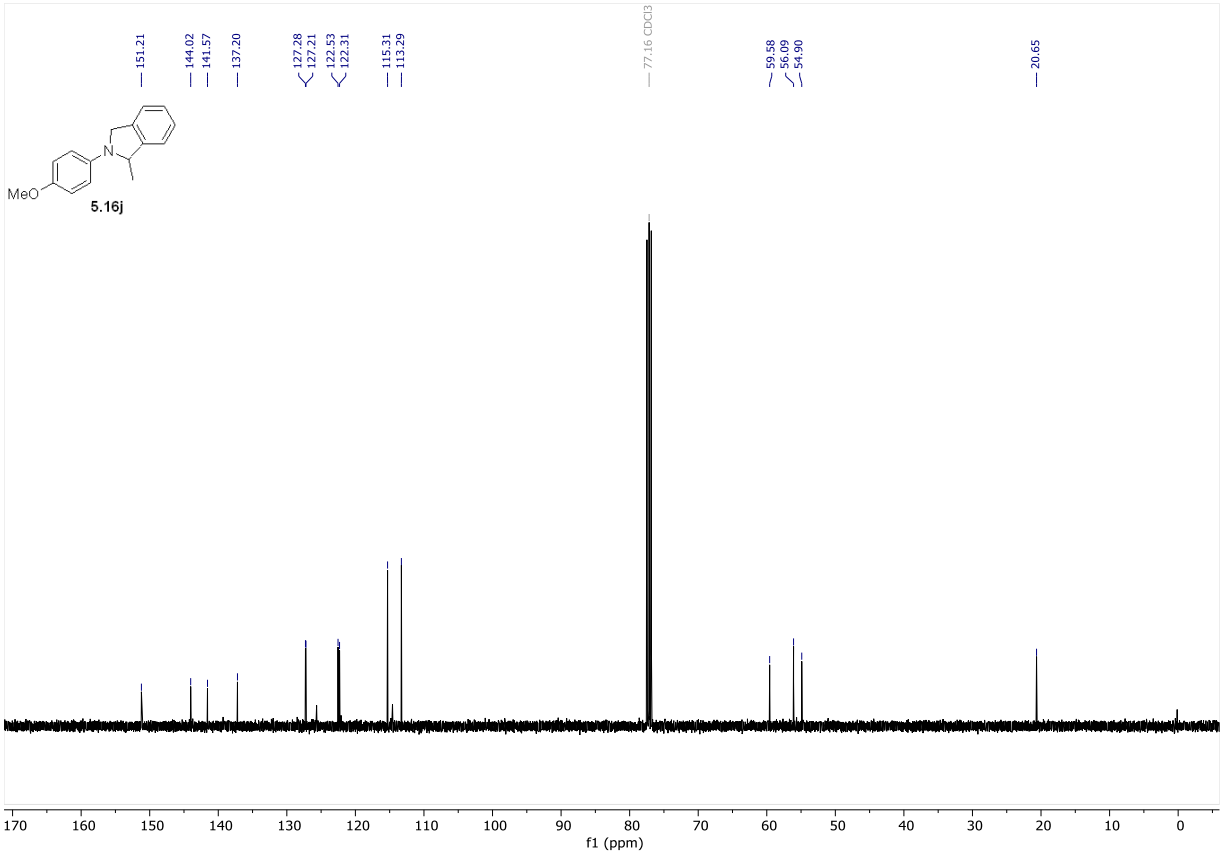
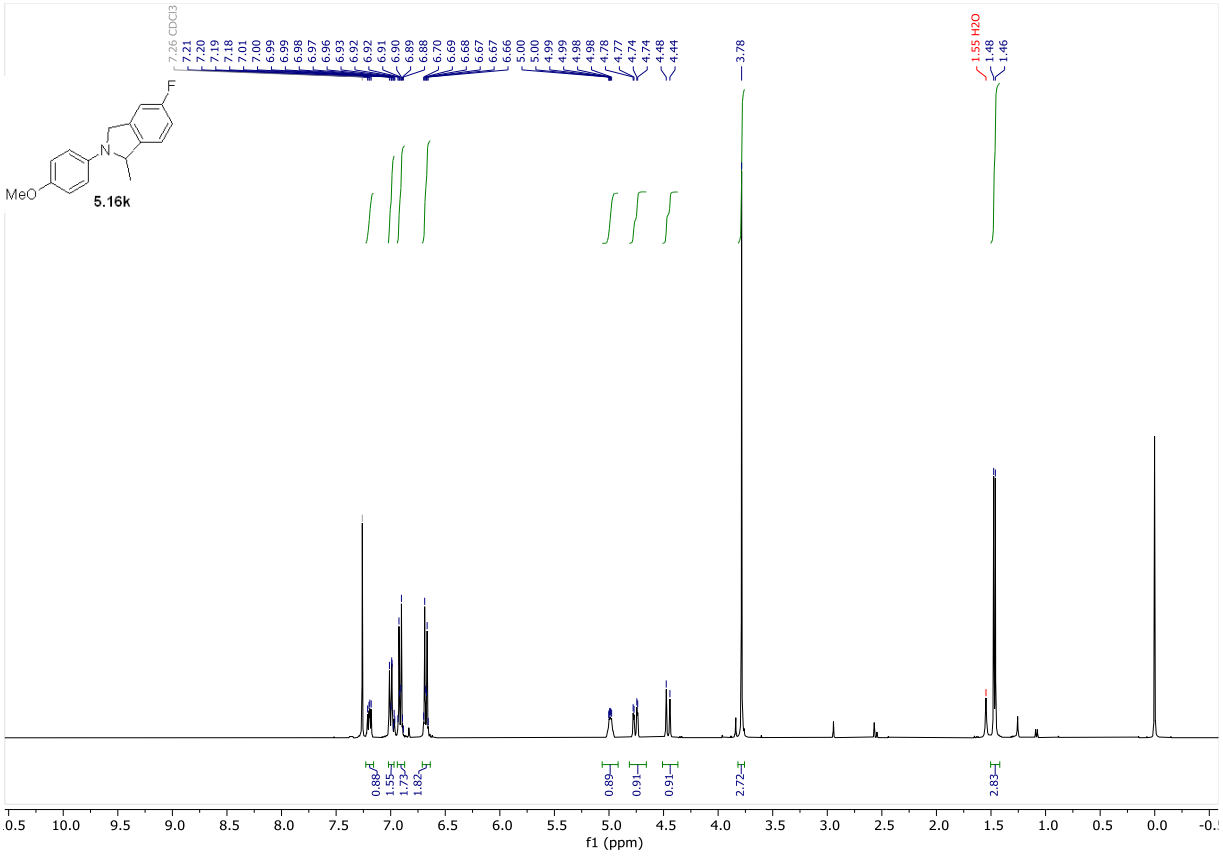
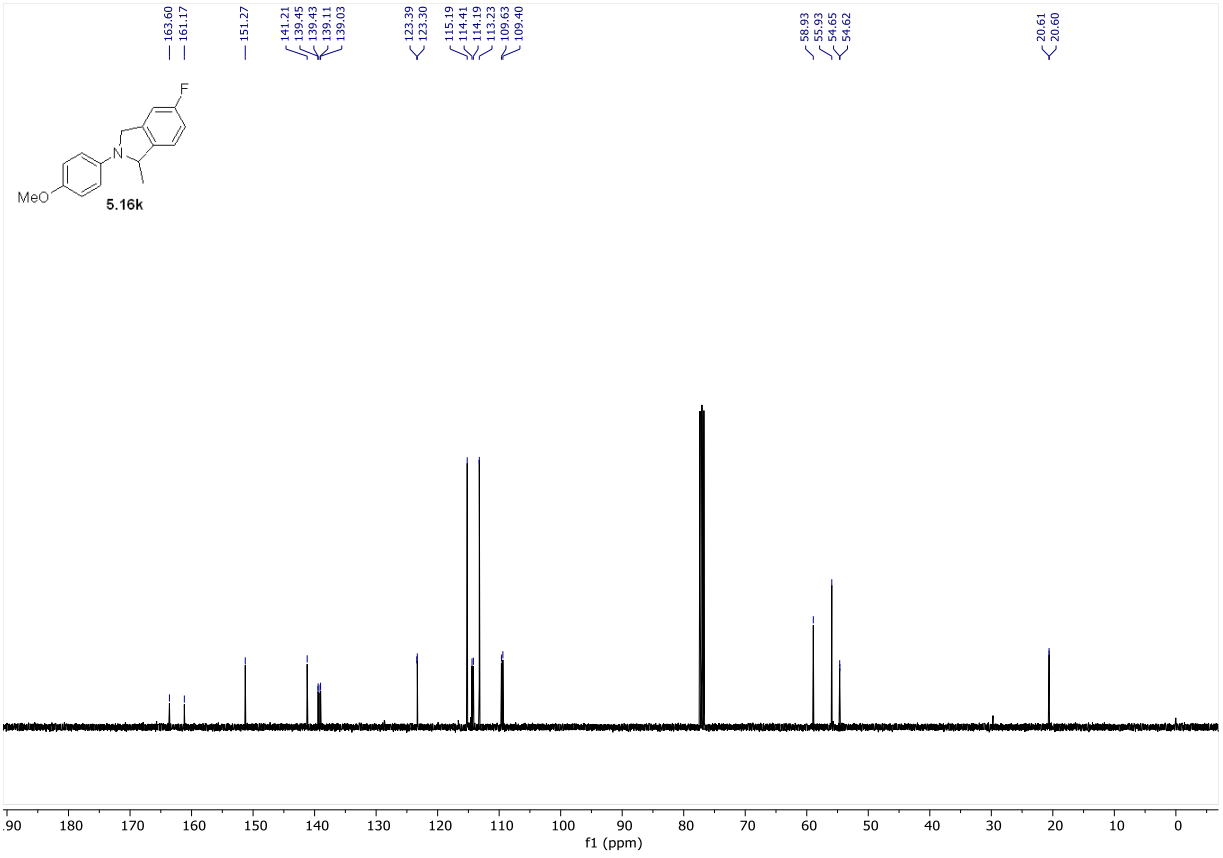
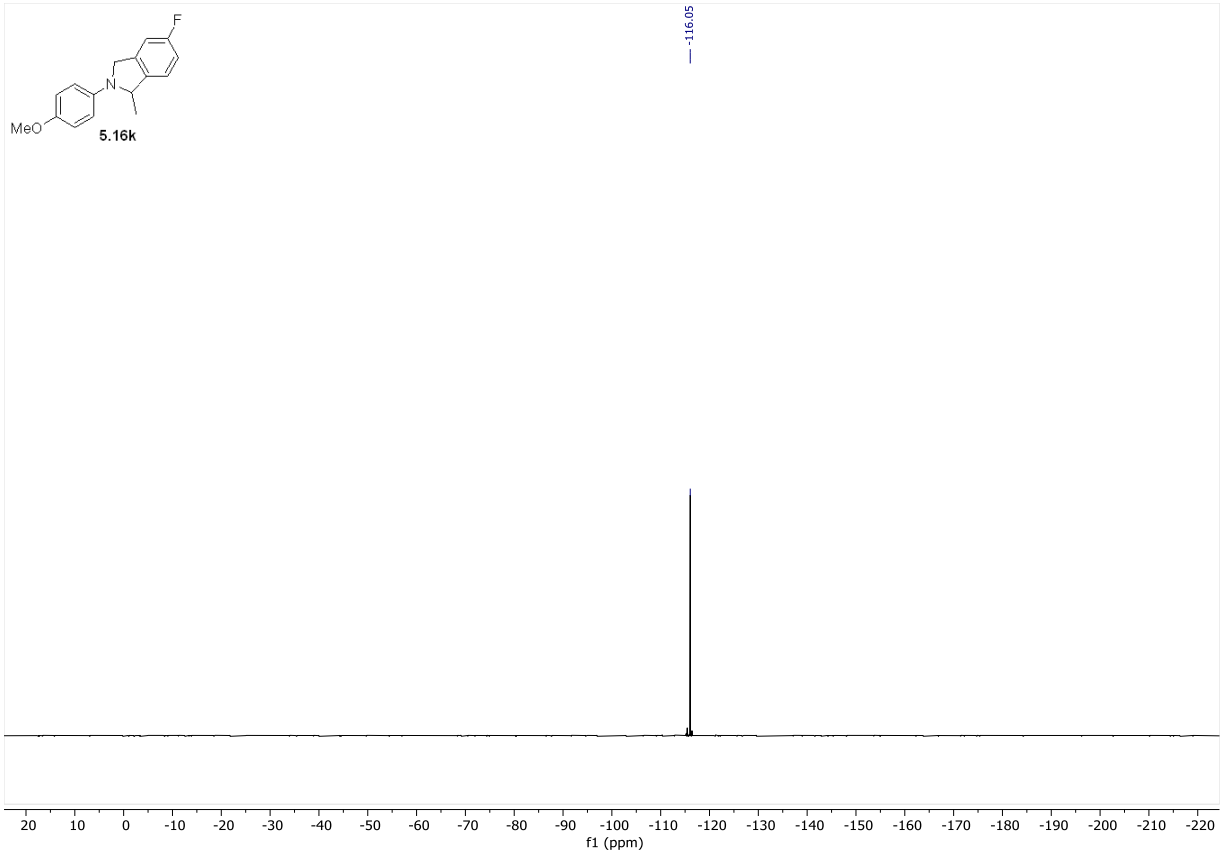
-180
-190
-200
-210
-220
f1 (ppm)


7.33
7.33
7.32
7.32
7.31
7.31
7.31
7.30
7.29
7.29
7.28
7.28
7.26 CDCl3
6.94
6.93
6.92
6.91
6.90
6.89
6.72
6.71
6.70
6.69
6.69
6.68
5.06
5.05
5.04
5.03
5.02
5.02
5.01
4.81
4.80
4.77
4.77
4.76
4.50
4.47
3.79
1.50
1.48
MeO
5.16j
3.96
1.81
1.90
0.88
0.95
0.90
3.31
2.79
f1 (ppm)


151.21
144.02
141.57
137.20
127.28
127.21
122.53
122.31
115.31
113.29
77.16 CDCl3
59.58
56.09
54.90
20.65
MeO
5.16j
f1 (ppm)


7.26 CDCl3
7.21
7.20
7.19
7.18
7.01
7.00
6.99
6.99
6.98
6.97
6.96
6.93
6.92
6.92
6.92
6.91
6.90
6.89
6.88
6.70
6.69
6.68
6.67
6.67
6.66
5.00
5.00
4.99
4.99
4.98
4.98
4.78
4.77
4.74
4.74
4.48
4.44
3.78
1.55 H2O
1.48
1.46
F
N
MeO
5.16k
0.88
1.55
1.73
1.82
0.89
0.91
0.91
2.72
2.83
f1 (ppm)


163.60
161.17
151.27
141.21
139.45
139.43
139.11
139.03
123.39
123.30
115.19
114.41
114.19
113.23
109.63
109.40
58.93
55.93
54.65
54.62
20.61
20.60
F
N
MeO
5.16k
f1 (ppm)


F
N
MeO
5.16k
-116.05
20
10
0
-10
-20
-30
-40
-50
-60
-70
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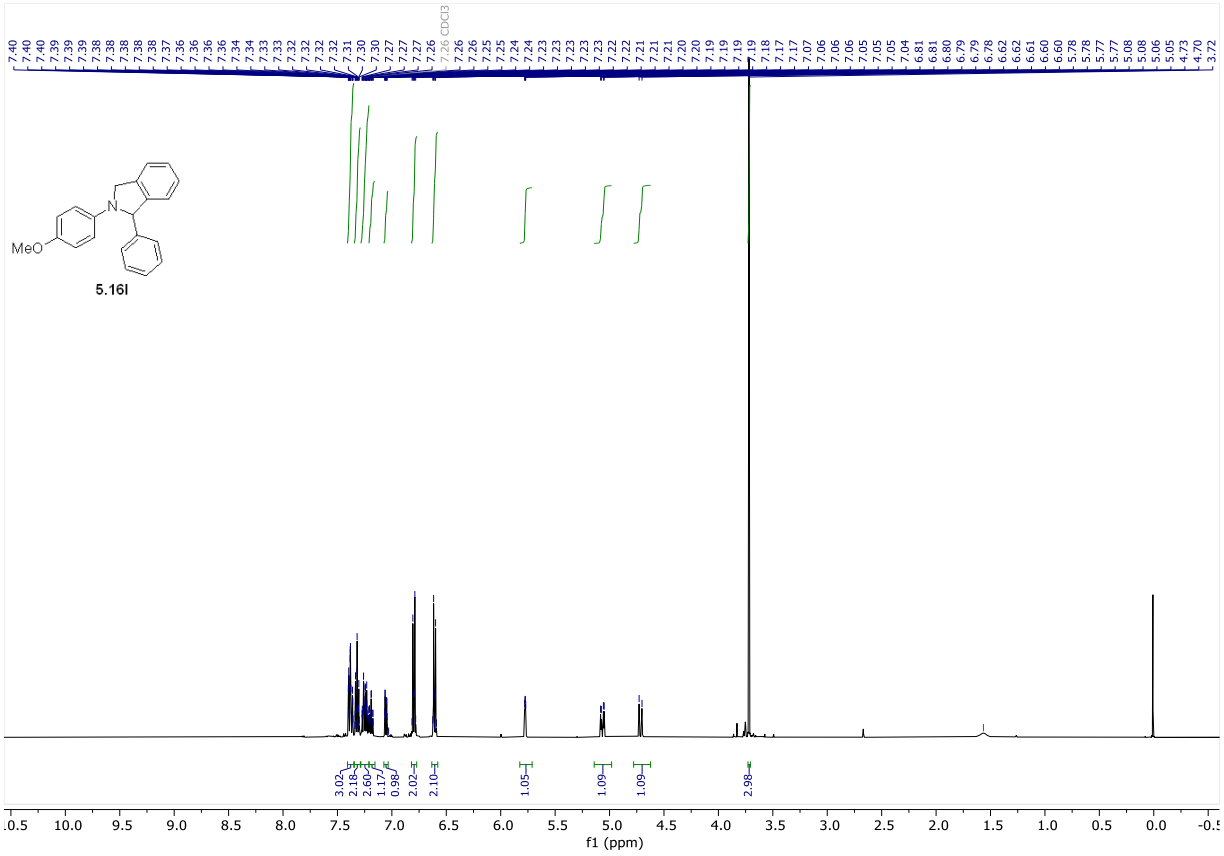
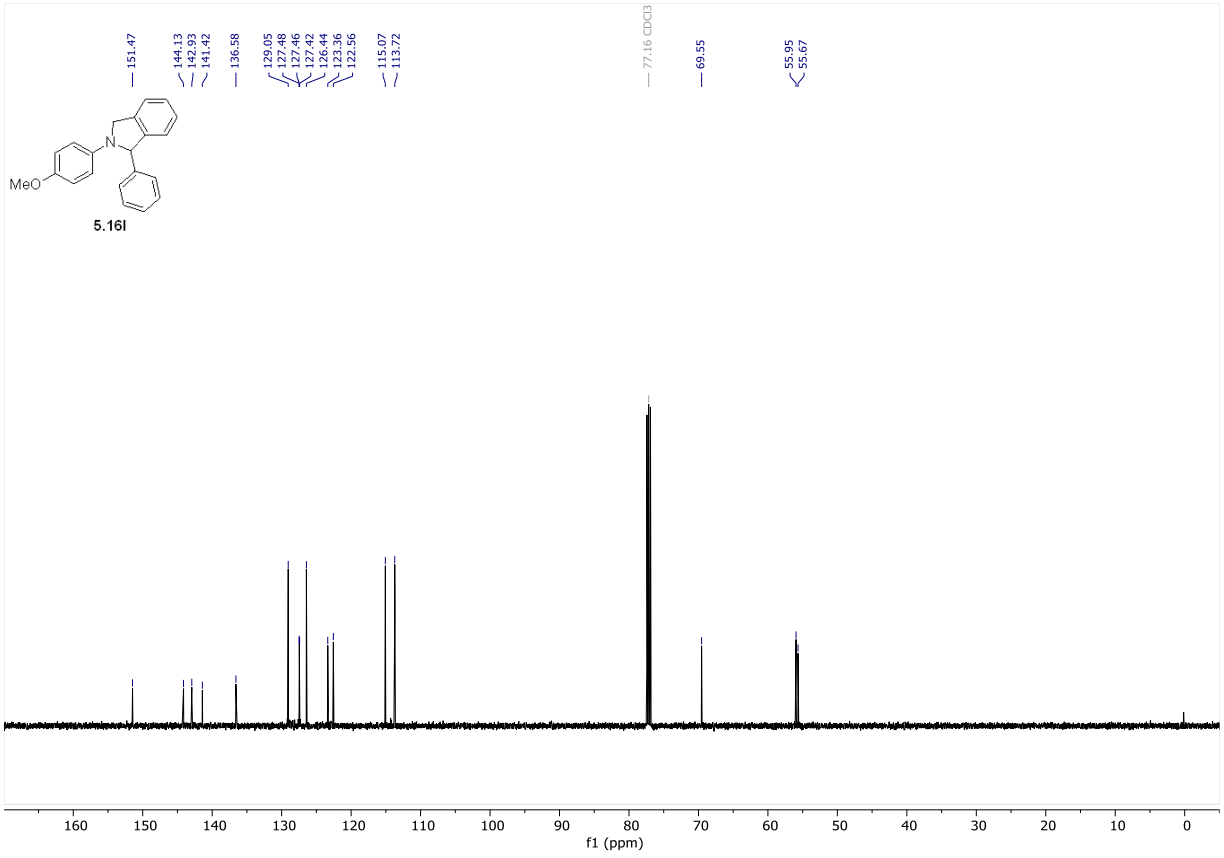
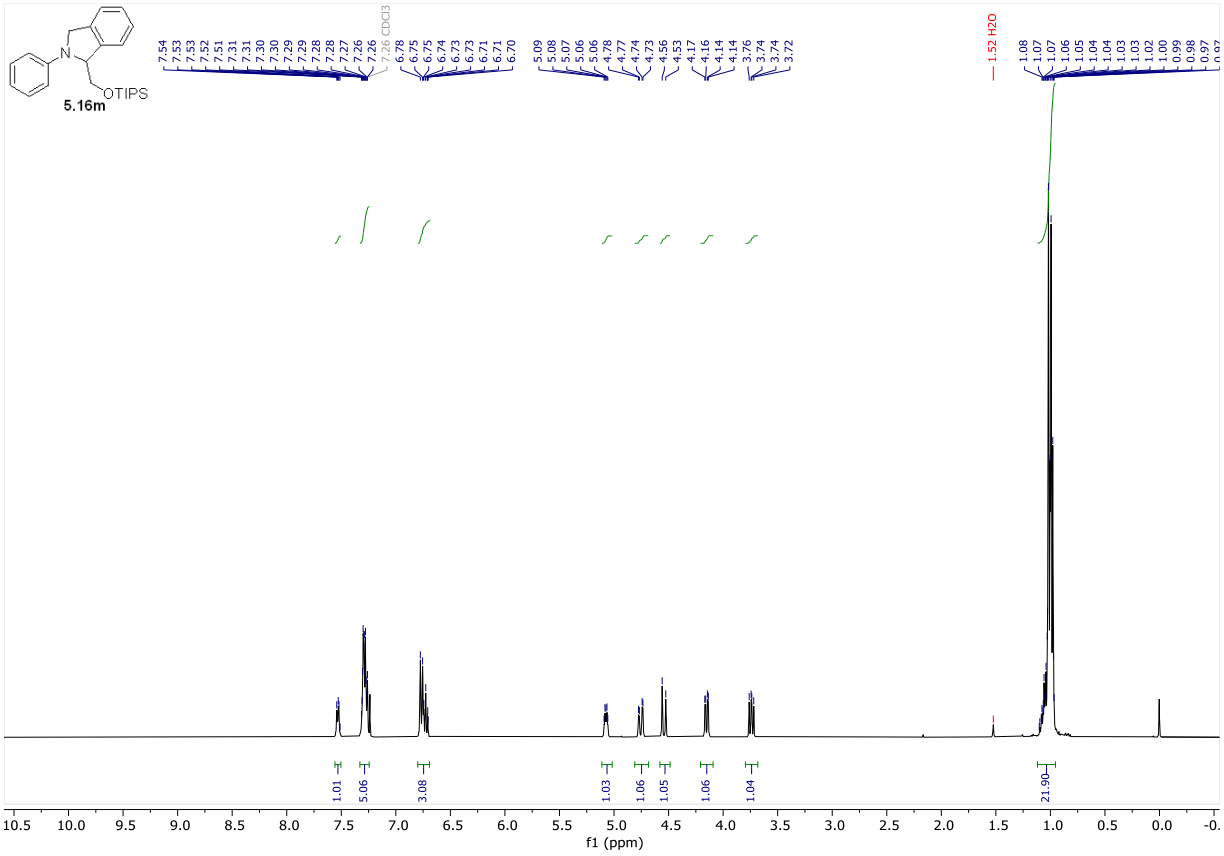
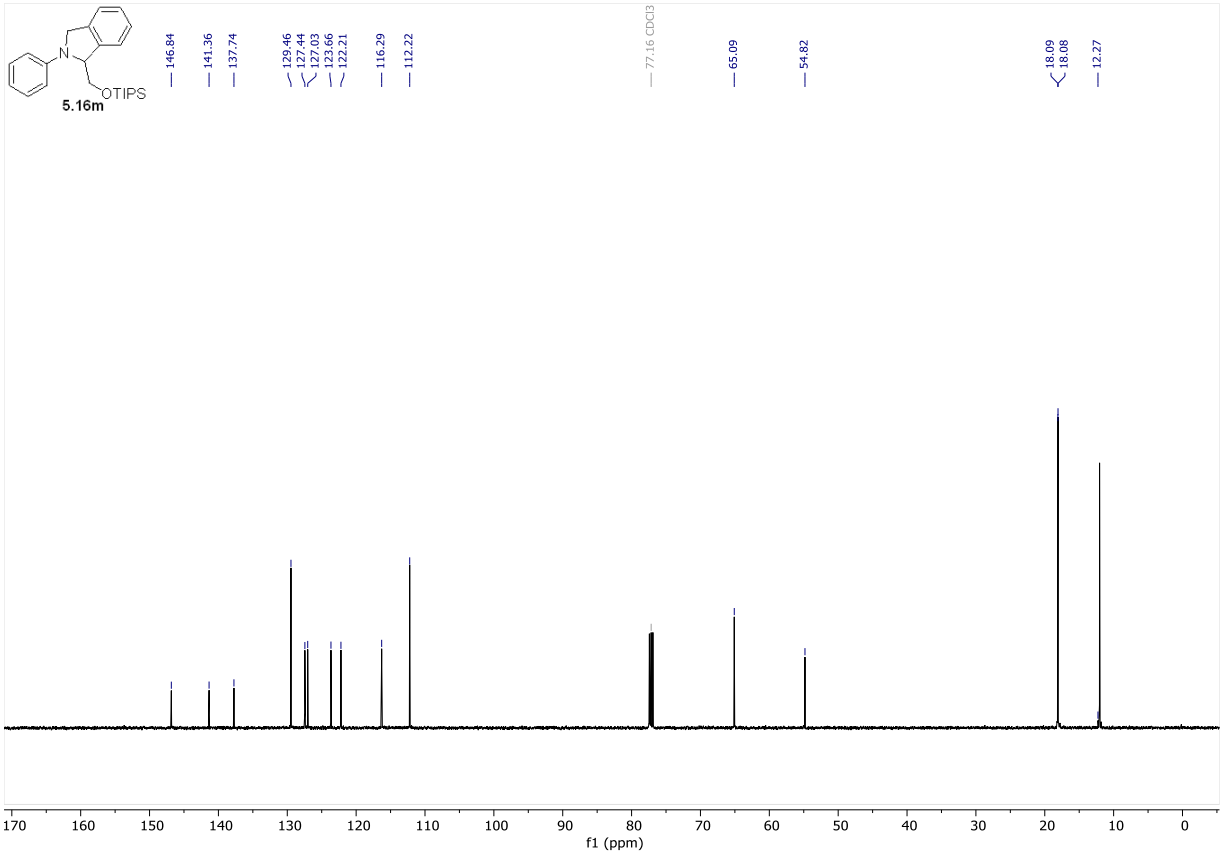
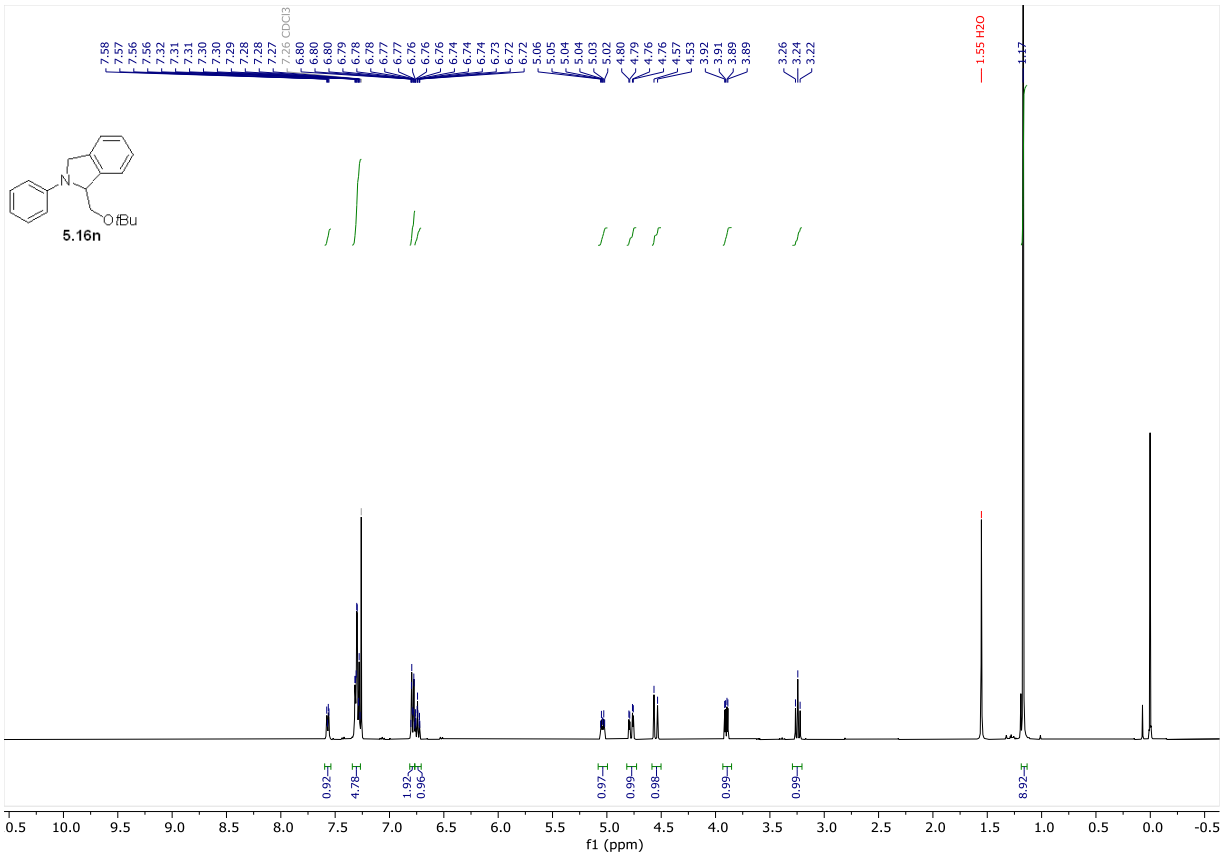
-180
-190
-200
-210
-220
f1 (ppm)

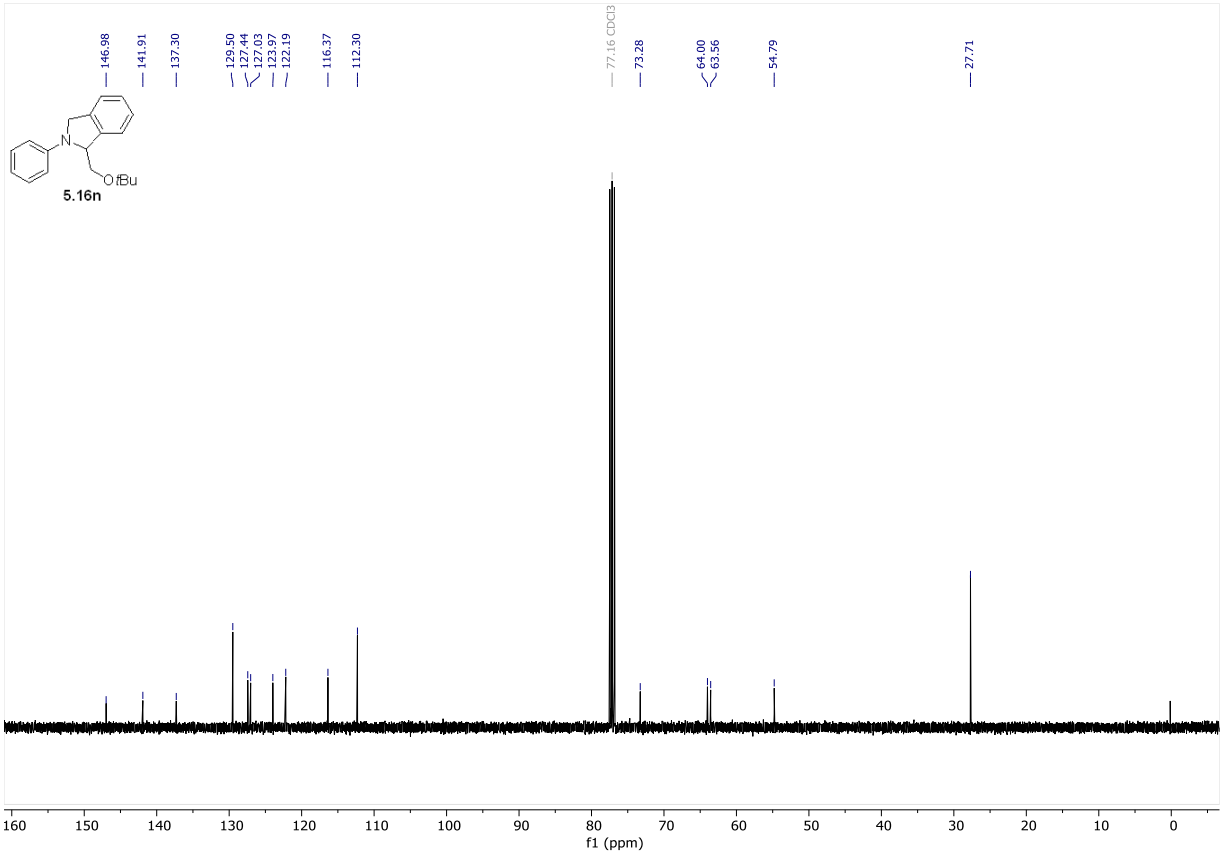

MeO
5.16l
f1 (ppm)

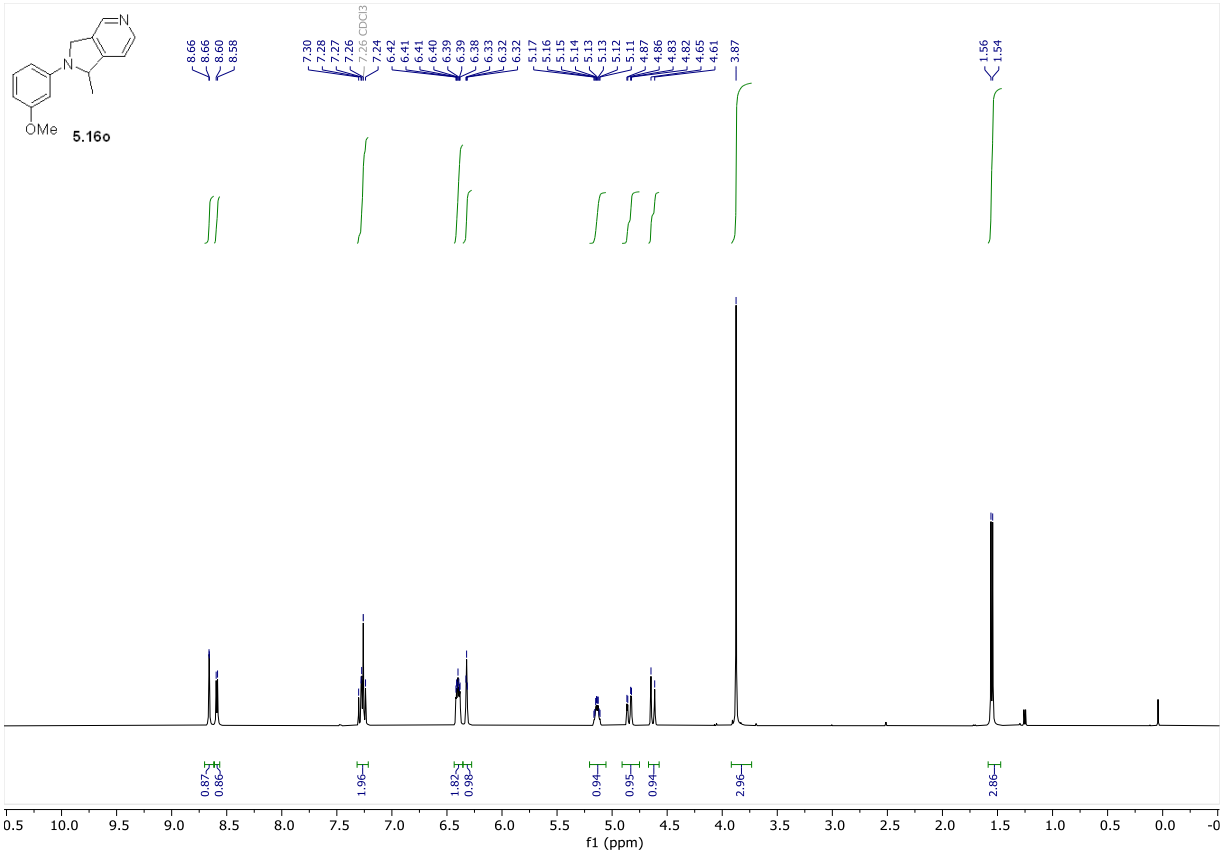

MeO
5.16l
f1 (ppm)


OTIPS
5.16m
7.54 7.53 7.53 7.52 7.51 7.31 7.31 7.30 7.30 7.29 7.29 7.28 7.28 7.27 7.26 7.26 7.26 CDCl3 6.78 6.75 6.75 6.74 6.73 6.73 6.71 6.71 6.70
5.09 5.08 5.07 5.06 5.06 4.78 4.77 4.74 4.73 4.56 4.53 4.17 4.16 4.14 4.14 3.76 3.74 3.74 3.72
1.52 H2O
1.08 1.07 1.07 1.06 1.05 1.04 1.04 1.03 1.03 1.02 1.00 0.99 0.98 0.97
1.01 5.06 3.08 1.03 1.06 1.05 1.06 1.04 21.90
10.5 10.0 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
f1 (ppm)


OTIPS
5.16m
146.84 141.36 137.74 129.46 127.44 127.03 123.66 122.21 116.29 112.22
77.16 CDCl3
65.09 54.82
18.09 18.08 12.27
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.58 7.57 7.56 7.56 7.32 7.31 7.30 7.30 7.29 7.28 7.28 7.27 7.26 CDCl3 6.80 6.80 6.80 6.79 6.78 6.78 6.77 6.77 6.76 6.76 6.76 6.74 6.74 6.74 6.73 6.72 6.72 5.06 5.05 5.04 5.04 5.03 5.02 4.80 4.79 4.76 4.76 4.57 4.53 3.92 3.91 3.89 3.89 3.26 3.24 3.22 1.55 H2O 1.17
OtBu
5.16n
0.92 4.78 1.92 0.96 0.97 0.99 0.98 0.99 0.99 8.92
f1 (ppm)


146.98 141.91 137.30 129.50 127.44 127.03 123.97 122.19 116.37 112.30 77.16 CDCl3 73.28 64.00 63.56 54.79 27.71
OtBu
5.16n
f1 (ppm)


OMe
5.16o
8.66
8.66
8.60
8.58
7.30
7.28
7.27
7.26
7.26 CDCl3
7.24
6.42
6.41
6.41
6.40
6.39
6.39
6.38
6.33
6.32
6.32
5.17
5.16
5.15
5.14
5.13
5.13
5.12
5.11
4.87
4.86
4.83
4.82
4.65
4.61
3.87
1.56
1.54
0.87
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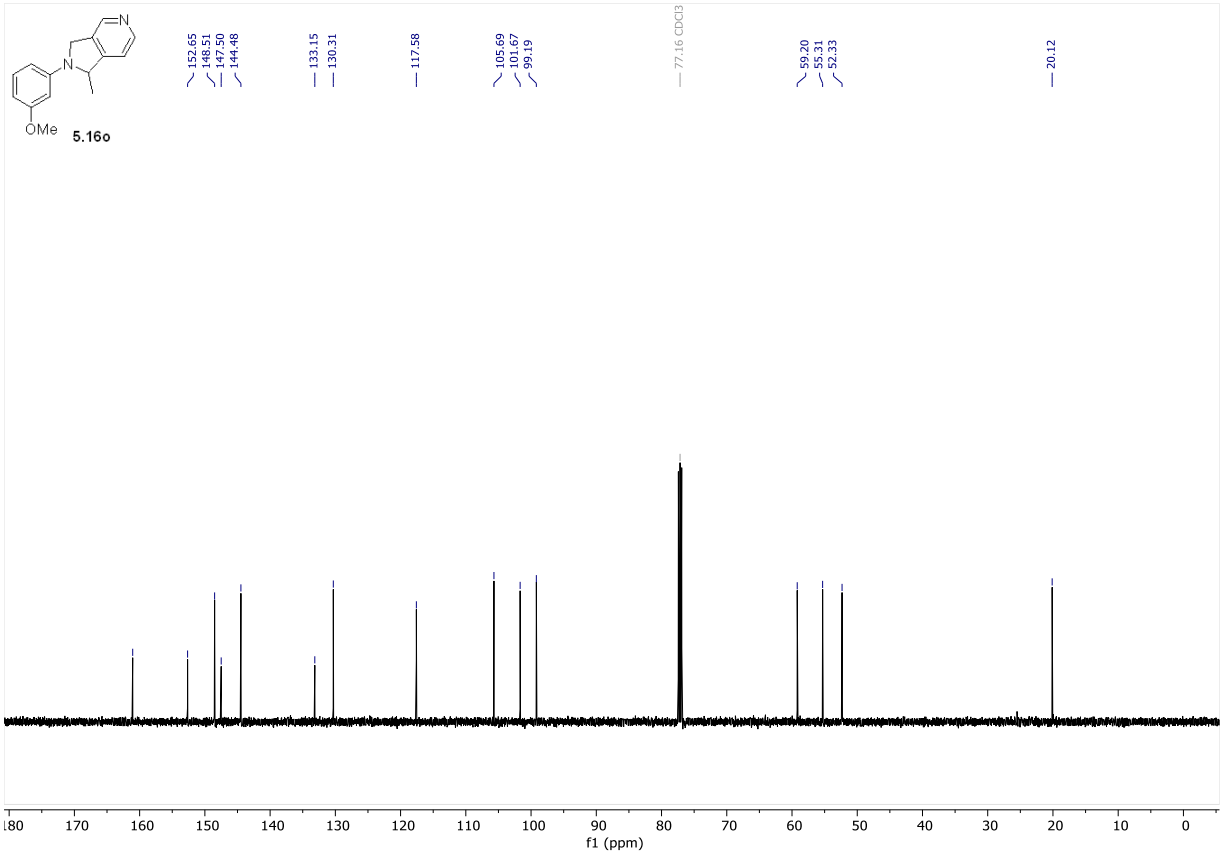
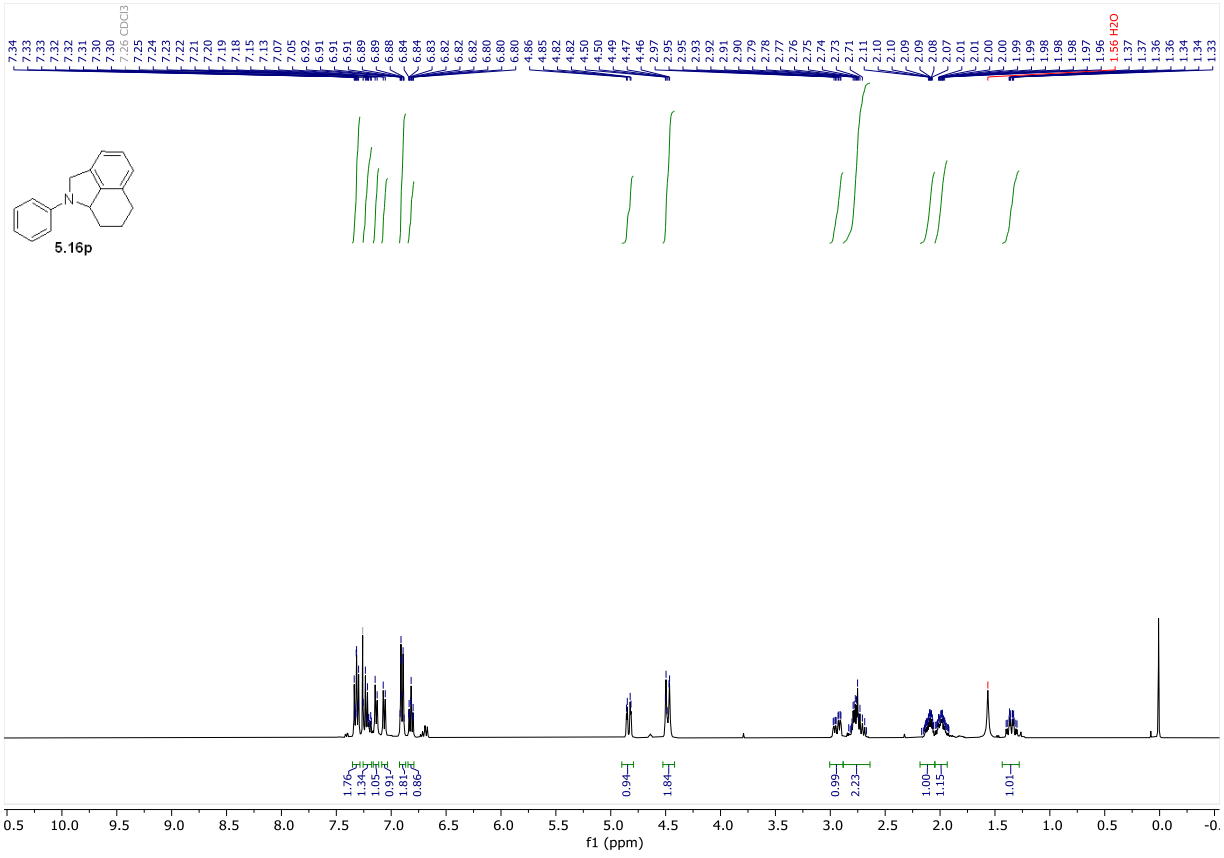
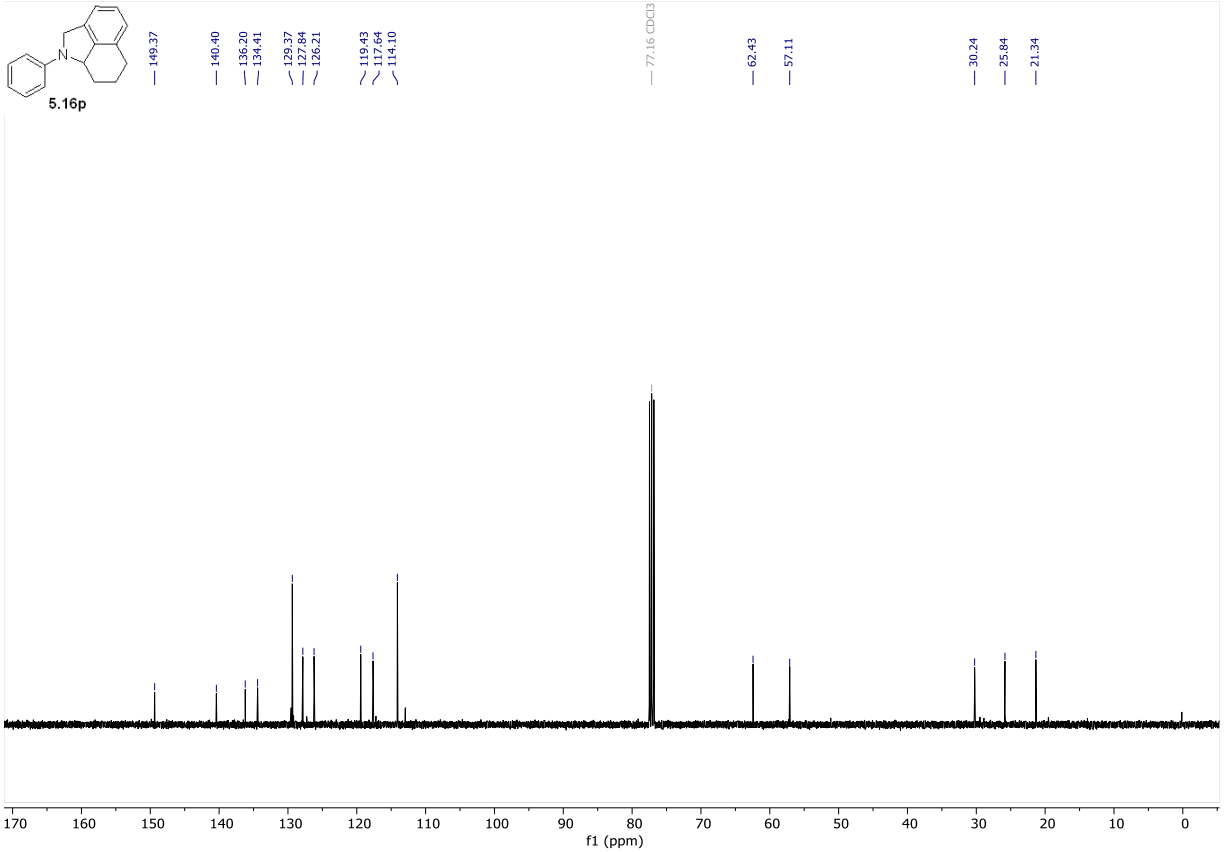
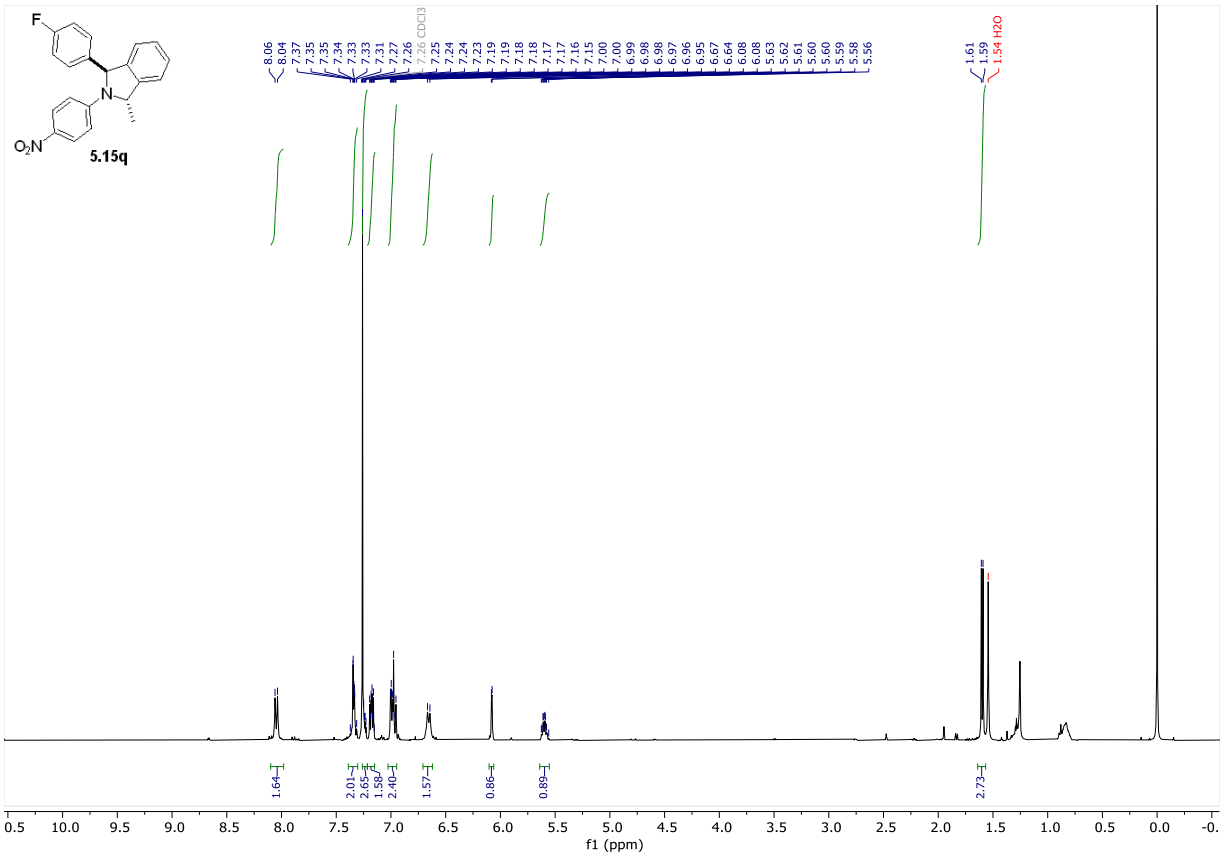
1.96
1.82
0.98
0.94
0.95
0.94
2.96
2.86
f1 (ppm)


OMe
5.16o
152.65
148.51
147.50
144.48
133.15
130.31
117.58
105.69
101.67
99.19
77.16 CDCl3
59.20
55.31
52.33
20.12
f1 (ppm)


7.34 7.33 7.33 7.32 7.32 7.31 7.30 7.30 7.26 CDCl3 7.25 7.24 7.23 7.22 7.21 7.20 7.19 7.18 7.15 7.13 7.07 7.05 6.92 6.91 6.91 6.91 6.89 6.89 6.88 6.84 6.84 6.83 6.82 6.82 6.82 6.80 6.80 6.80 4.86 4.85 4.82 4.82 4.50 4.50 4.49 4.47 4.46 2.97 2.95 2.95 2.93 2.92 2.91 2.90 2.79 2.78 2.77 2.76 2.75 2.74 2.73 2.71 2.11 2.10 2.10 2.09 2.09 2.08 2.07 2.01 2.01 2.00 2.00 1.99 1.99 1.98 1.98 1.98 1.97 1.96 1.56 H2O 1.37 1.37 1.36 1.36 1.34 1.34 1.33
5.16p
1.76 1.34 1.05 0.91 1.81 0.86 0.94 1.84 0.99 2.23 1.00 1.15 1.01
f1 (ppm)


5.16p
149.37 140.40 136.20 134.41 129.37 127.84 126.21 119.43 117.64 114.10 77.16 CDCl3 62.43 57.11 30.24 25.84 21.34
f1 (ppm)


F
N
O2N
5.15q
8.06
8.04
7.37
7.35
7.35
7.34
7.33
7.33
7.31
7.27
7.26 CDCl3
7.25
7.24
7.24
7.23
7.19
7.18
7.18
7.17
7.17
7.16
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6.08
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5.62
5.61
5.60
5.60
5.59
5.58
5.56
1.61
1.59
1.54 H2O
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2.40
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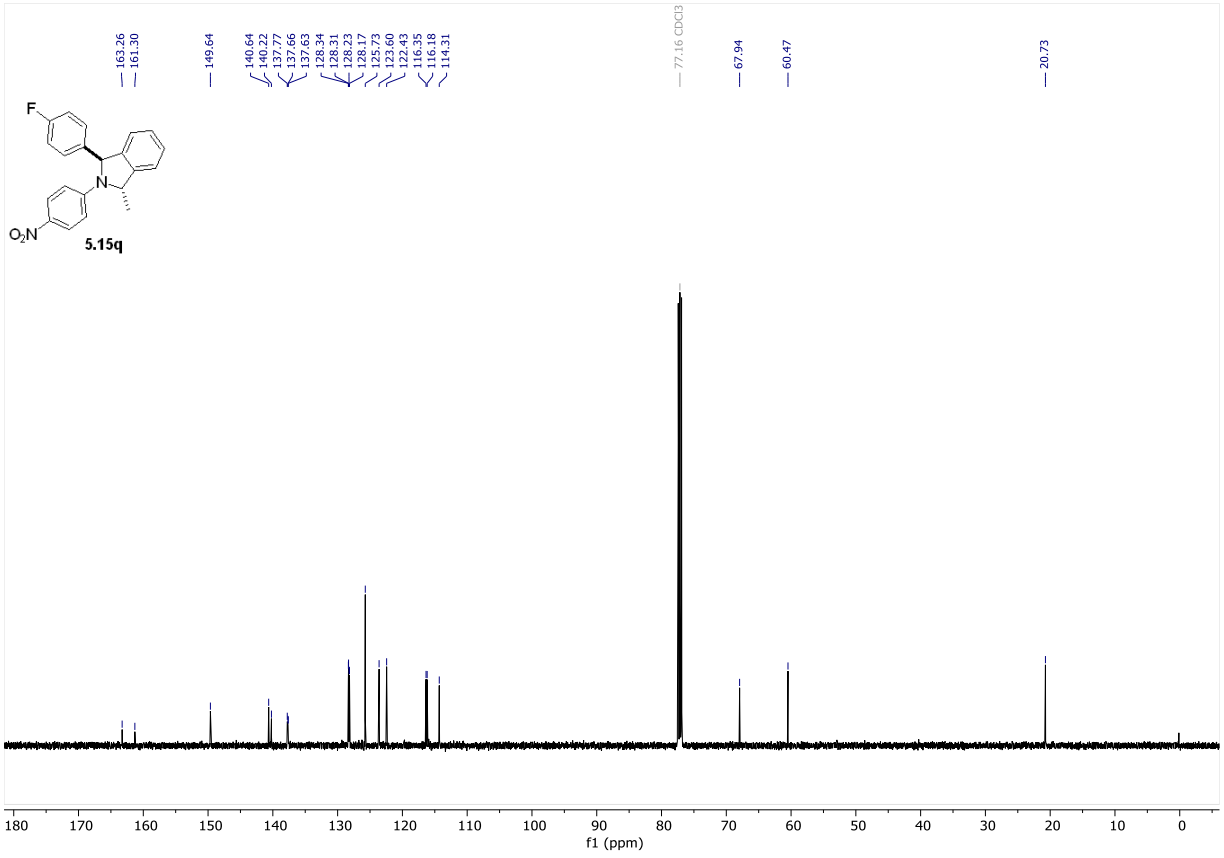
0.86
0.89
2.73
f1 (ppm)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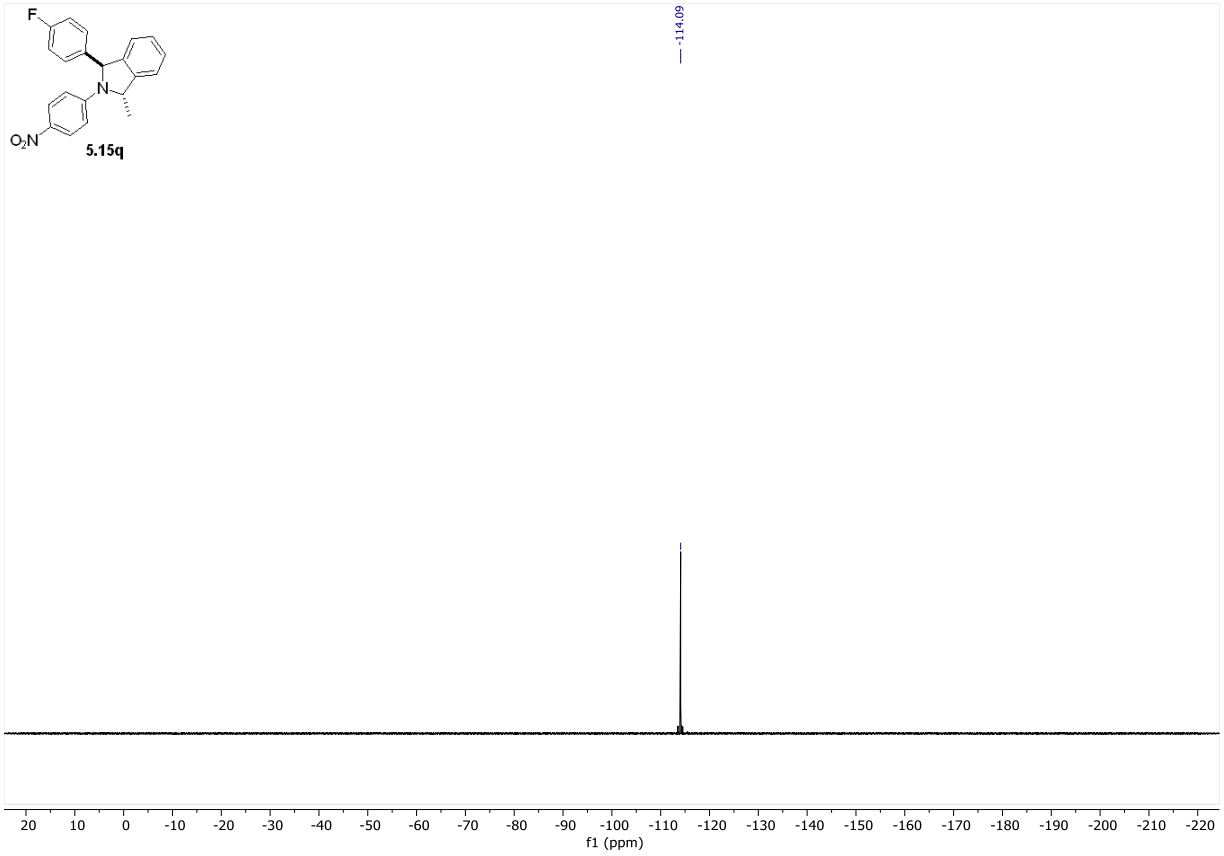
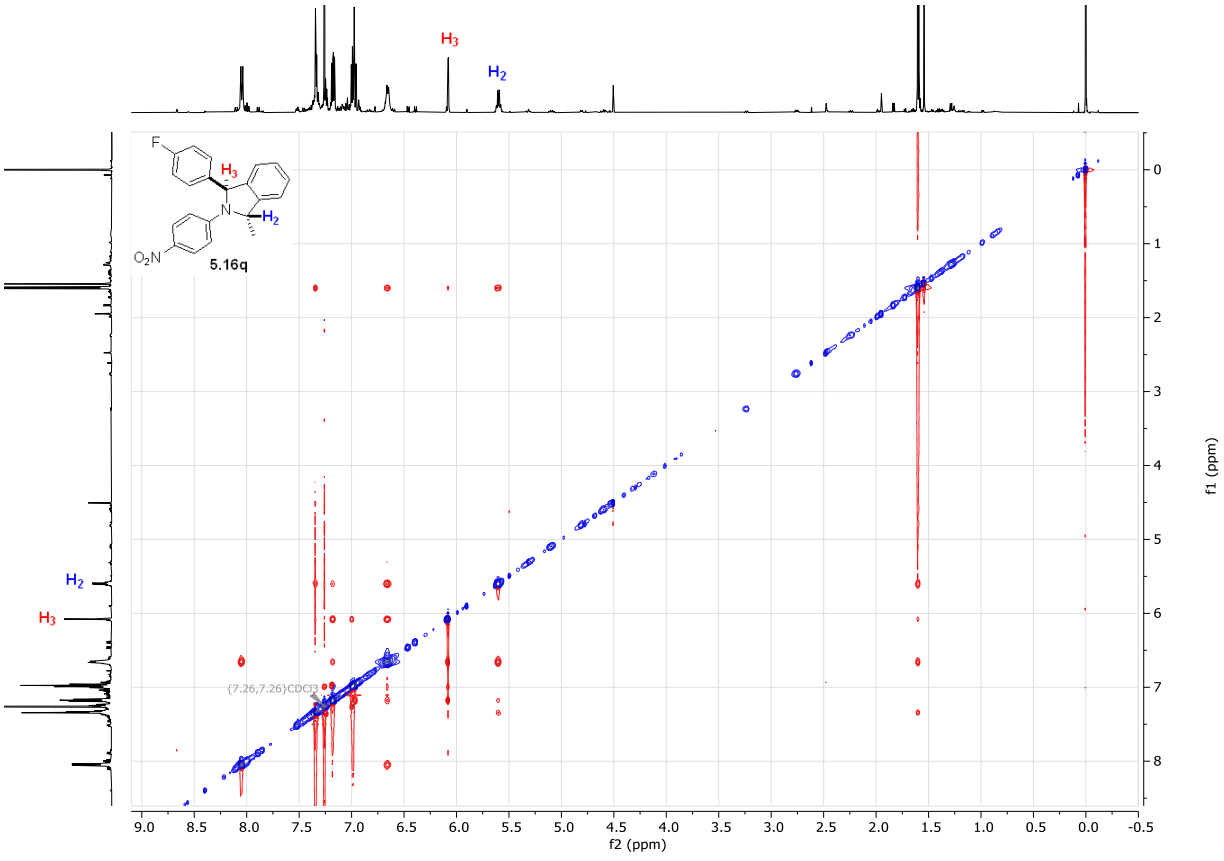
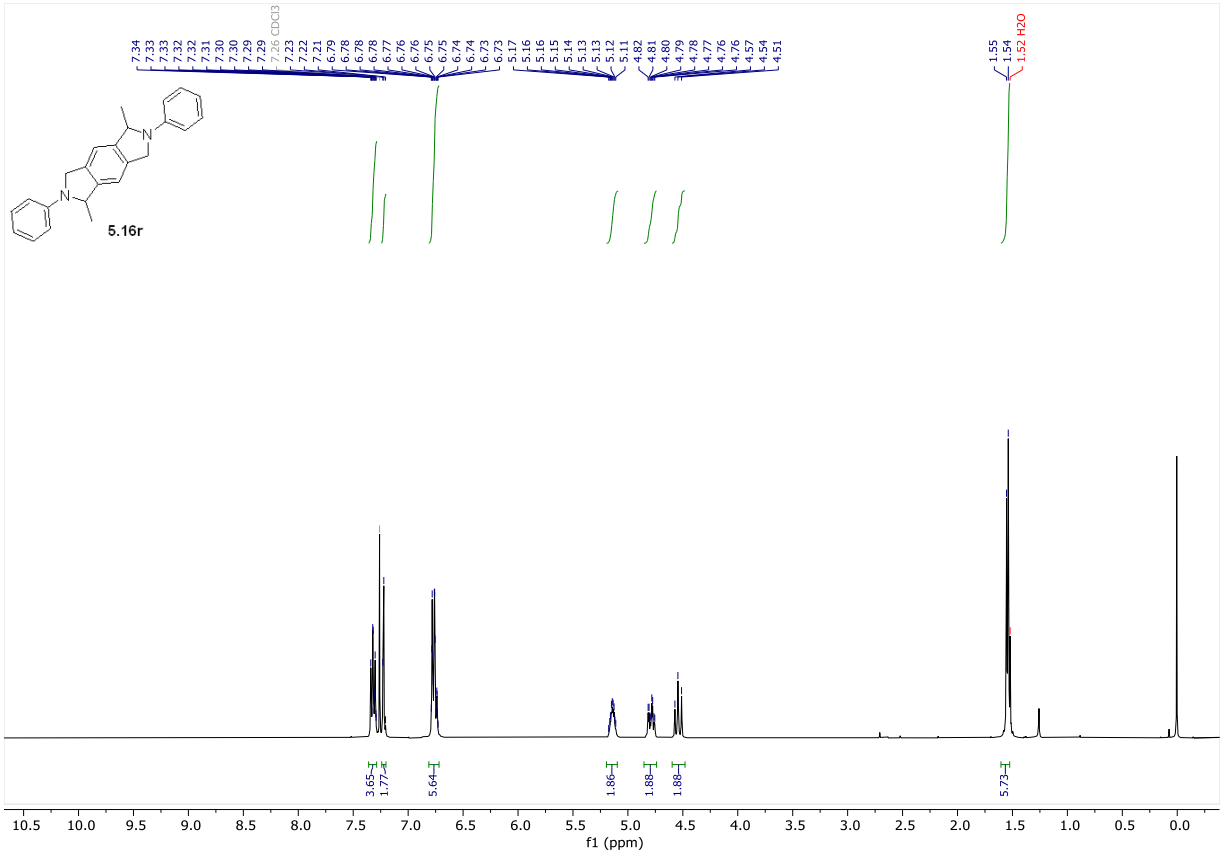
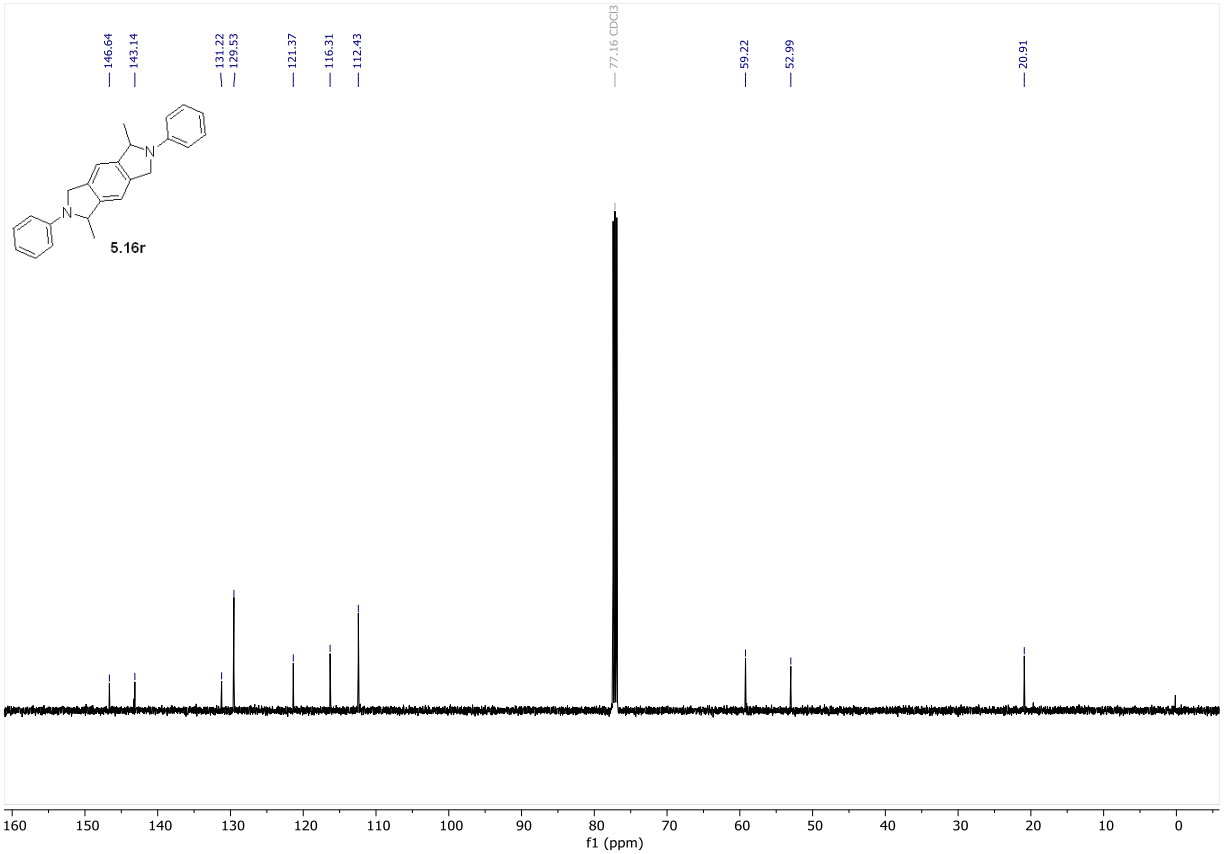
161.30
149.64
140.64
140.22
137.77
137.66
137.63
128.34
128.31
128.23
128.17
125.73
123.60
122.43
116.35
116.18
114.31
77.16 CDCl3
67.94
60.47
20.73
F
N
O2N
5.15q
f1 (ppm)


F
N
O2N
5.15q
-114.09
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

NOESY (crude)

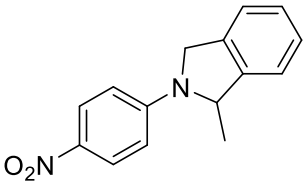

H3
H2
F
N
O2N
5.16q
{7.26,7.26}CDCl3
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f2 (ppm)
0 1 2 3 4 5 6 7 8
f1 (ppm)


7.34
7.33
7.33
7.32
7.32
7.31
7.30
7.30
7.29
7.29
7.26 CDCl3
7.23
7.22
7.21
6.79
6.78
6.78
6.78
6.77
6.76
6.76
6.75
6.75
6.74
6.74
6.73
6.73
5.17
5.16
5.16
5.15
5.14
5.13
5.13
5.12
5.11
4.82
4.81
4.80
4.79
4.78
4.77
4.76
4.76
4.57
4.54
4.51
1.55
1.54
1.52 H2O
5.16r
3.65
1.77
5.64
1.86
1.88
1.88
5.73
10.5 10.0 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
f1 (ppm)


146.64
143.14
131.22
129.53
121.37
116.31
112.43
77.16 CDCl3
59.22
52.99
20.91
5.16r
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

7.8.3 Crystallographic data

Crystallographic data of 5.16h



Chemical Formula: $C_{15}H_{14}N_2O_2$
Molecular Weight: 254.29

checkCIF/PLATON report

Structure factors have been supplied for datablock(s) tak1421p_150k

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: tak1421p_150k

```
Bond precision:   C-C = 0.0082 A          Wavelength=1.54186

Cell:           a=9.5912(5)       b=10.0859(6)      c=14.1454(8)
                alpha=72.574(4)   beta=77.141(4)    gamma=72.759(4)
Temperature:    150 K

                Calculated                  Reported
Volume          1233.39(13)                 1233.39(13)
Space group     P -1                        P -1
Hall group      -P 1                        -P 1
Moiety formula  C15 H14 N2 O2               C15 H14 N2 O2
Sum formula     C15 H14 N2 O2               C15 H14 N2 O2
Mr              254.28                      254.28
Dx,g cm-3       1.369                       1.369
Z               4                           4
Mu (mm-1)       0.750                       0.750
F000            536.0                       536.0
F000'           537.63
h,k,lmax        11,12,17                    11,12,17
Nref            4743                        4510
Tmin,Tmax       0.811,0.861                 0.469,0.709
Tmin'           0.811

Correction method= # Reported T Limits: Tmin=0.469 Tmax=0.709
AbsCorr = MULTI-SCAN

Data completeness= 0.951          Theta(max)= 70.730

R(reflections)= 0.1113( 3820)                wR2(reflections)=
                                             0.3079( 4510)
S = 0.943                 Npar= 345
```

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level B

```
PLAT930_ALERT_2_B FCF-based   Twin Law ( 0 0 1)         Est.d BASF       0.24 Check
```

Author Response: yes, the sample is indeed affected by twinning, however a twinned data processing has been attempted but, besides a better completeness, all the other statistics were considerably worse than those accomplished in this model as single domain.

Alert level C

```
PLAT029_ALERT_3_C _diffrn_measured_fraction_theta_full value Low .      0.969 Why?
PLAT082_ALERT_2_C High R1 Value ..................................       0.11 Report
PLAT084_ALERT_3_C High wR2 Value (i.e. > 0.25) ...................       0.31 Report
PLAT340_ALERT_3_C Low Bond Precision on  C-C Bonds ...............    0.00823 Ang.
PLAT790_ALERT_4_C Centre of Gravity not Within Unit Cell: Resd.  #          1 Note
            C15 H14 N2 O2
PLAT906_ALERT_3_C Large K Value in the Analysis of Variance ......     16.759 Check
PLAT906_ALERT_3_C Large K Value in the Analysis of Variance ......      3.086 Check
PLAT906_ALERT_3_C Large K Value in the Analysis of Variance ......      2.008 Check
PLAT911_ALERT_3_C Missing FCF Refl Between Thmin & STh/L=    0.600        137 Report
PLAT918_ALERT_3_C Reflection(s) with I(obs) much Smaller I(calc) .        10 Check
PLAT939_ALERT_3_C Large Value of Not (SHELXL) Weight Optimized S .      19.28 Check
```

Alert level G

```
PLAT083_ALERT_2_G SHELXL Second Parameter in WGHT  Unusually Large       8.00 Why ?
PLAT154_ALERT_1_G The s.u.'s on the Cell Angles are Equal ..(Note)      0.004 Degree
PLAT790_ALERT_4_G Centre of Gravity not Within Unit Cell: Resd.  #          2 Note
            C15 H14 N2 O2
PLAT793_ALERT_4_G Model has Chirality at C7          (Centro SPGR)          S Verify
PLAT793_ALERT_4_G Model has Chirality at C22         (Centro SPGR)          R Verify
PLAT870_ALERT_4_G ALERTS Related to Twinning Effects Suppressed ..          ! Info
PLAT912_ALERT_4_G Missing # of FCF Reflections Above STh/L=  0.600         97 Note
PLAT931_ALERT_5_G CIFcalcFCF  Twin Law ( 0 0 1)         Est.d BASF       0.24 Check
PLAT933_ALERT_2_G Number of OMIT Records in Embedded .res File ...         11 Note
PLAT941_ALERT_3_G Average HKL Measurement Multiplicity ...........        3.8 Low
PLAT992_ALERT_5_G Repd & Actual _reflns_number_gt Values Differ by          2 Check
```

```
   0 ALERT level A = Most likely a serious problem - resolve or explain
   1 ALERT level B = A potentially serious problem, consider carefully
  11 ALERT level C = Check. Ensure it is not caused by an omission or oversight
  11 ALERT level G = General information/check it is not something unexpected

   1 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
```

```
   4 ALERT type 2 Indicator that the structure model may be wrong or deficient
  10 ALERT type 3 Indicator that the structure quality may be low
   6 ALERT type 4 Improvement, methodology, query or suggestion
   2 ALERT type 5 Informative message, check
```

Validation response form

Please find below a validation response form (VRF) that can be filled in and pasted into your CIF.

```
# start Validation Reply Form
_vrf_PLAT029_tak1421p_150k
;
PROBLEM: _diffrn_measured_fraction_theta_full value Low .      0.969 Why?
RESPONSE: ...
;
_vrf_PLAT082_tak1421p_150k
;
PROBLEM: High R1 Value ..................................       0.11 Report
RESPONSE: ...
;
_vrf_PLAT084_tak1421p_150k
;
PROBLEM: High wR2 Value (i.e. > 0.25) ...................       0.31 Report
RESPONSE: ...
;
_vrf_PLAT340_tak1421p_150k
;
PROBLEM: Low Bond Precision on  C-C Bonds ...............    0.00823 Ang.
RESPONSE: ...
;
_vrf_PLAT790_tak1421p_150k
;
PROBLEM: Centre of Gravity not Within Unit Cell: Resd.  #          1 Note
RESPONSE: ...
;
_vrf_PLAT906_tak1421p_150k
;
PROBLEM: Large K Value in the Analysis of Variance ......     16.759 Check
RESPONSE: ...
;
_vrf_PLAT911_tak1421p_150k
;
PROBLEM: Missing FCF Refl Between Thmin & STh/L=    0.600        137 Report
RESPONSE: ...
;
_vrf_PLAT918_tak1421p_150k
;
PROBLEM: Reflection(s) with I(obs) much Smaller I(calc) .         10 Check
RESPONSE: ...
;
_vrf_PLAT939_tak1421p_150k
;
```

```
PROBLEM: Large Value of Not (SHELXL) Weight Optimized S .      19.28 Check
RESPONSE: ...
;
# end Validation Reply Form
```

It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the purpose of your study may justify the reported deviations and the more serious of these should normally be commented upon in the discussion or experimental section of a paper or in the "special_details" fields of the CIF. checkCIF was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

Publication of your CIF in IUCr journals

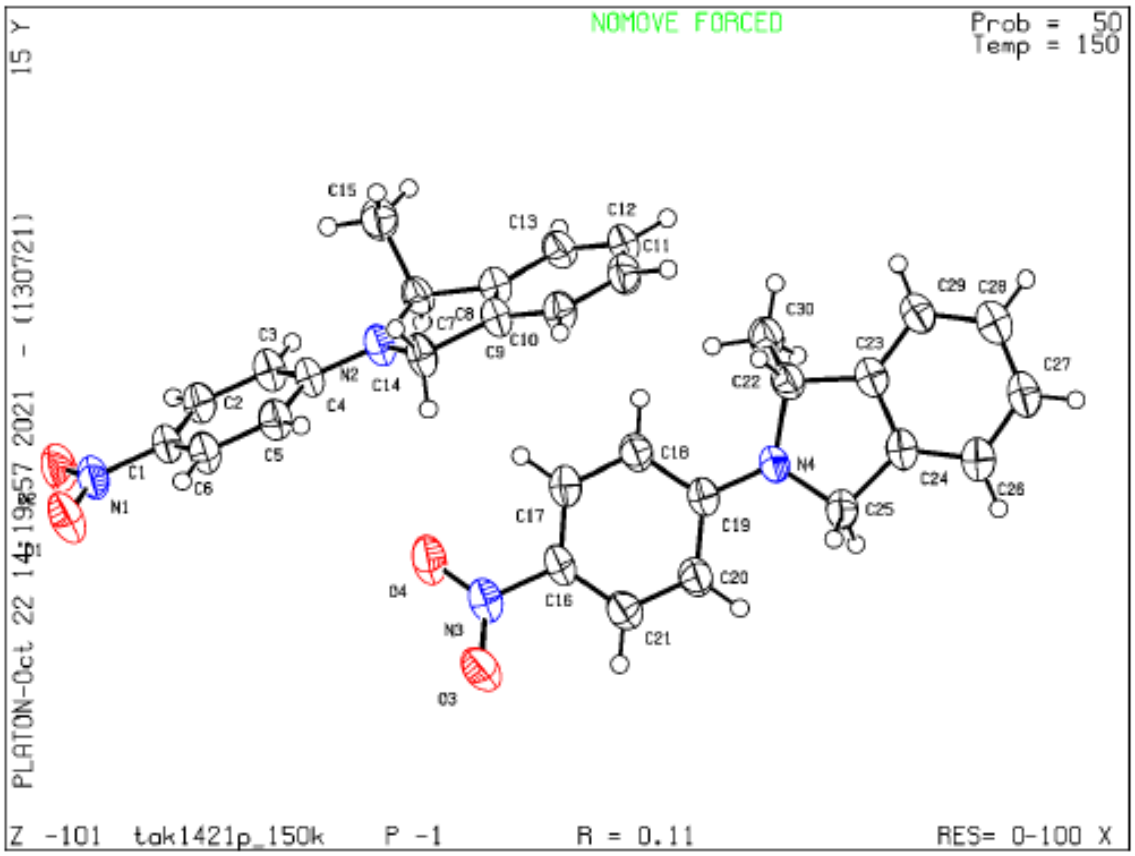
A basic structural check has been run on your CIF. These basic checks will be run on all CIFs submitted for publication in IUCr journals (*Acta Crystallographica*, *Journal of Applied Crystallography*, *Journal of Synchrotron Radiation*); however, if you intend to submit to *Acta Crystallographica Section C* or *E* or *IUCrData*, you should make sure that full publication checks are run on the final version of your CIF prior to submission.

Publication of your CIF in other journals

Please refer to the *Notes for Authors* of the relevant journal for any special instructions relating to CIF submission.

PLATON version of 13/07/2021; check.def file version of 13/07/2021

Datablock tak1421p_150k - ellipsoid plot



TAK1421P_150K

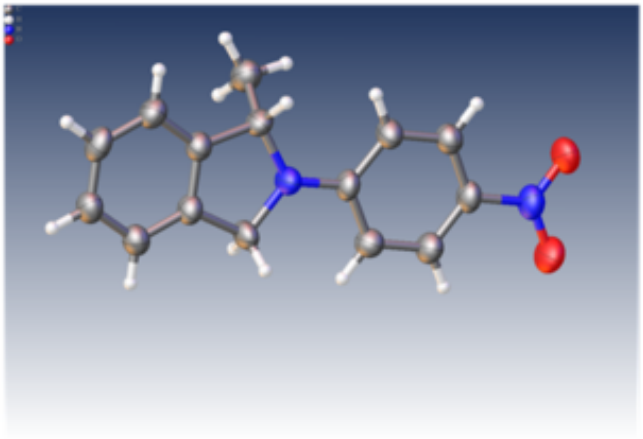
Submitted by: **Takeru Miyakoshi**

Solved by: **Alessandro Prescimone**

Sample ID: **TAK1421P**

R_1=11.13%

Crystal Data and Experimental



Experimental. Single yellow block-shaped crystals of **TAK1421P_150K** were used as supplied. A suitable crystal with dimensions 0.28 × 0.23 × 0.20 mm^3 was selected and The crystal was mounted on a mylar loop in perfluoroether oil on a STOE STADIVARI Cu diffractometer. The crystal was kept at a steady T = 150 K during data collection. The structure was solved with the **ShelXT** (Sheldrick, 2015) solution program using dual methods and by using **Olex2** 1.5 (Dolomanov et al., 2009) as the graphical interface. The model was refined with **ShelXL** 2018/3 (Sheldrick, 2015) using full matrix least squares minimisation on F^2.

Crystal Data. $C_{15}H_{14}N_2O_2$, M_r = 254.28, triclinic, P-1 (No. 2), a = 9.5912(5) Å, b = 10.0859(6) Å, c = 14.1454(8) Å, α = 72.574(4)°, β = 77.141(4)°, γ = 72.759(4)°, V = 1233.39(13) Å^3, T = 150 K, Z = 4, Z' = 2, μ(Cu K$_\alpha$) = 0.750, 17073 reflections measured, 4510 unique (R_{int} = 0.0534) which were used in all calculations. The final wR_2 was 0.3079 (all data) and R_1 was 0.1113 (I≥2 σ(I)).

Compound	**TAK1421P_150K**
Formula	$C_{15}H_{14}N_2O_2$
$D_{calc.}$/ g cm^{-3}	1.369
μ/mm^{-1}	0.750
Formula Weight	254.28
Colour	yellow
Shape	block-shaped
Size/mm^3	0.28×0.23×0.20
T/K	150
Crystal System	triclinic
Space Group	P-1
a/Å	9.5912(5)
b/Å	10.0859(6)
c/Å	14.1454(8)
α/°	72.574(4)
β/°	77.141(4)
γ/°	72.759(4)
V/Å^3	1233.39(13)
Z	4
Z'	2
Wavelength/Å	1.54186
Radiation type	Cu K$_\alpha$
Θ_{min}/°	3.311
Θ_{max}/°	70.730
Measured Refl's.	17073
Indep't Refl's	4510
Refl's I≥2 σ(I)	3820
R_{int}	0.0534
Parameters	345
Restraints	0
Largest Peak	0.451
Deepest Hole	-0.492
GooF	0.943
wR_2 (all data)	0.3079
wR_2	0.3005
R_1 (all data)	0.1236
R_1	0.1113

Structure Quality Indicators

Reflections:	d min (Cu\a) 2Θ=141.5°	0.82	I/σ(I)	31.0	Rint	5.34%	Full 135.4° 95% to 141.5°	96.9
Refinement:	Shift	0.000	Max Peak	0.5	Min Peak	-0.5	GooF	0.943

A yellow block-shaped-shaped crystal with dimensions 0.28 × 0.23 × 0.20 mm^3 was mounted on a mylar loop in perfluoroether oil. Data were collected using a STOE STADIVARI Cu diffractometer operating at T = 150 K.

Data were measured using rotation method, ω scans with Cu K_α radiation. The diffraction pattern was indexed and the total number of runs and images was based on the strategy calculation from the program X-Area Pilatus3_SV 1.31.170.0 (STOE, 2020). The maximum resolution that was achieved was Θ = 70.730° (0.82 Å).

The unit cell was refined using X-Area Integrate 1.78.3.0 (STOE, 2020)X-Area LANA 1.83.8.0 (STOE, 2020) on 32082 reflections, 188% of the observed reflections.

Data reduction, scaling and absorption corrections were performed using X-Area Integrate 1.78.3.0 (STOE, 2020)X-Area LANA 1.83.8.0 (STOE, 2020). The final completeness is 96.90 % out to 70.730° in Θ. A multi-scan absorption correction was performed using STOE X-Red32, absorption correction by Gaussian integration, analogous to P. Coppens in: F. R. Ahmed (Editor), "Crystallographic Computing", Munksgaard, Copenhagen (1970), 255 - 270. Afterwards scaling of reflection intensities was performed within STOE LANA. J. Koziskova, F. Hahn, J. Richter, J. Kozisek, Acta Chimica Slovaca, vol. 9, no. 2, 2016, pp. 136 - 140. Finally a spherical absorption correction was done within STOE LANA.. The absorption coefficient μ of this material is 0.750 mm^{-1} at this wavelength (λ = 1.54186Å) and the minimum and maximum transmissions are 0.469 and 0.709.

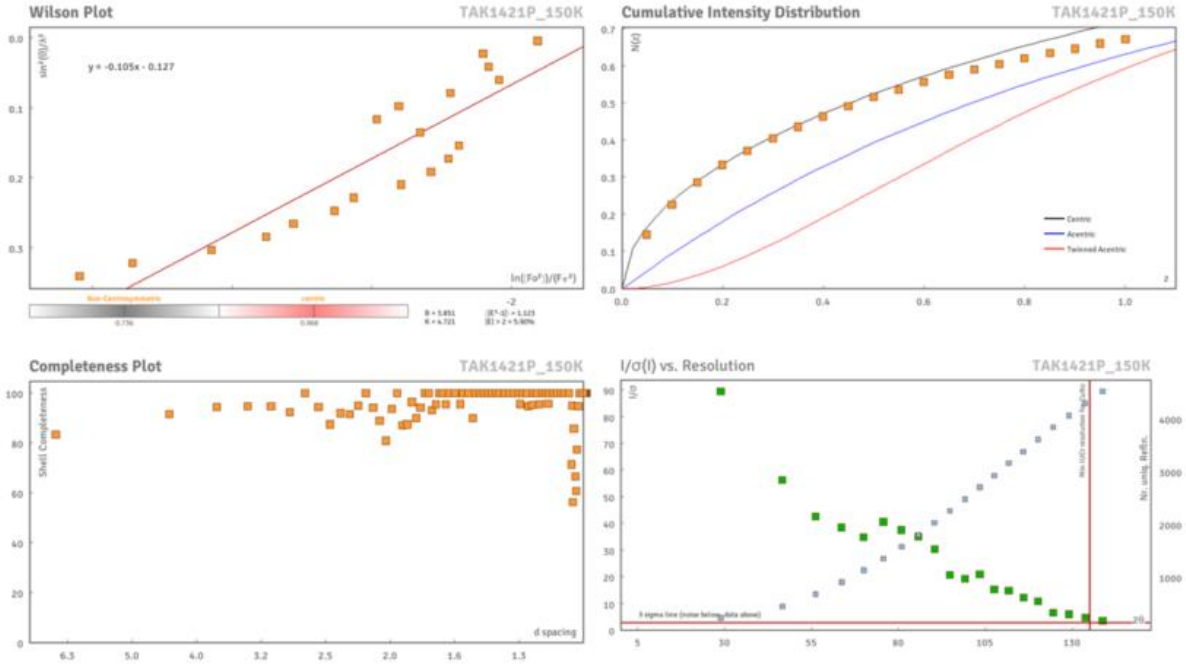
The structure was solved and the space group P-1 (# 2) determined by the ShelXT (Sheldrick, 2015) structure solution program using using dual methods and refined by full matrix least squares minimisation on F^2 using version 2018/3 of **ShelXL** 2018/3 (Sheldrick, 2015). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model. Hydrogen atom positions were calculated geometrically and refined using the riding model.

_refine_special_details: the sample is twinned and this is probably the reason for thebit-higher-than-usual R_1.Data processing as twinned was attempted but the resulting refined model hadworse statistics than the one presented that has been treated as single domain.

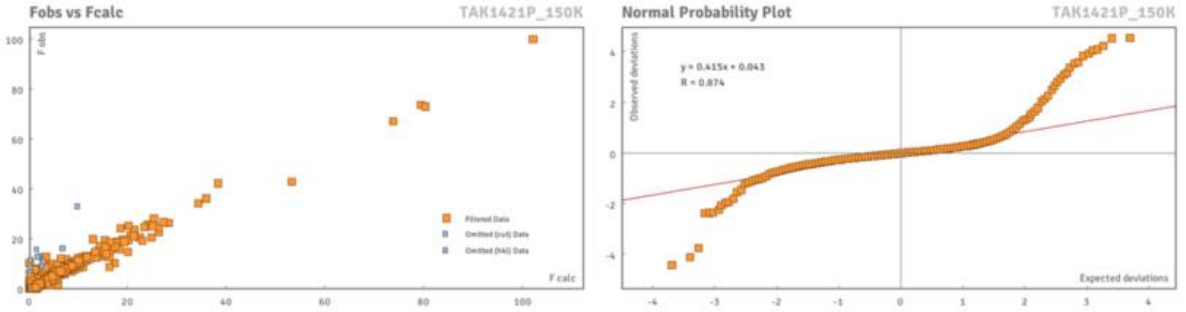
_exptl_absorpt_process_details: STOE X-Red32, absorption correction by Gaussian integration, analogous toP. Coppens in: F. R. Ahmed (Editor), "Crystallographic Computing", Munksgaard,Copenhagen (1970), 255 - 270. Afterwards scaling of reflection intensities wasperformed within STOE LANA. J. Koziskova, F. Hahn, J. Richter, J. Kozisek, ActaChimica Slovaca, vol. 9, no. 2, 2016, pp. 136 - 140.Finally a spherical absorption correction was done within STOE LANA.

The value of Z' is 2. This means that there are two independent molecules in the asymmetric unit.

Data Plots: Diffraction Data



Data Plots: Refinement and Data



Reflection Statistics

Total reflections (after filtering)	17118	Unique reflections	4510
Completeness	0.951	Mean I/σ	27.32
hkl_{max} collected	(11, 12, 17)	hkl_{min} collected	(-11, -8, -15)
hkl_{max} used	(11, 12, 17)	hkl_{min} used	(-11, -11, 0)
Lim d_{max} collected	100.0	Lim d_{min} collected	0.77
d_{max} used	13.35	d_{min} used	0.82
Friedel pairs	652	Friedel pairs merged	1
Inconsistent equivalents	501	R_{int}	0.0534
R_{sigma}	0.0323	Intensity transformed	0
Omitted reflections	0	Omitted by user (OMIT hkl)	45
Multiplicity	(966, 1334, 865, 723, 488, 370, 219, 125, 41, 29, 11, 2)	Maximum multiplicity	12
Removed systematic absences	0	Filtered off (Shel/OMIT)	0

Table 1: Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for **TAK1421P_150K**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij}.

Atom	x	y	z	U_{eq}
O4	8327(5)	2930(4)	7256(3)	59.3(11)
O3	5978(5)	3928(5)	7523(3)	58.8(11)

Atom	x	y	z	U_{eq}
O2	12697(5)	1700(5)	2977(3)	61.8(12)
N4	7515(5)	2154(5)	11912(3)	40.9(10)
N3	7187(5)	3302(5)	7822(3)	47.0(11)
O1	11733(5)	3998(5)	2682(3)	65.7(12)
N2	12532(5)	2688(5)	7189(3)	42.8(10)
N1	12259(5)	2823(5)	3253(3)	49.9(11)
C10	11811(6)	4193(6)	9358(4)	45.2(12)
C24	6841(6)	2546(6)	13506(4)	42.4(11)
C3	12900(6)	1433(6)	5893(4)	44.1(12)
C8	12741(6)	1965(6)	8871(4)	40.6(11)
C19	7448(6)	2403(5)	10913(4)	40.3(11)
C7	13149(6)	1412(5)	7937(4)	40.9(11)
C1	12323(6)	2787(6)	4265(4)	43.2(12)
C17	8641(6)	2515(6)	9197(4)	43.9(12)
C9	12172(6)	3446(6)	8634(4)	41.6(11)
C13	12940(6)	1217(6)	9850(4)	45.7(12)
C16	7267(6)	2998(6)	8880(4)	43.0(12)
C20	6062(6)	2880(6)	10565(4)	44.8(12)
C21	5988(6)	3173(6)	9555(4)	45.4(12)
C11	12013(6)	3460(6)	10341(4)	47.2(13)
C18	8736(6)	2226(6)	10201(4)	42.9(12)
C2	12832(6)	1465(6)	4928(4)	44.6(12)
C23	8357(6)	1999(6)	13363(4)	41.4(11)
C4	12472(6)	2698(6)	6228(3)	41.4(11)
C25	6205(6)	2694(6)	12589(4)	45.1(12)
C5	11957(6)	4015(6)	5539(4)	44.4(12)
C6	11887(6)	4039(6)	4574(4)	46.8(12)
C29	9165(6)	1728(6)	14135(4)	46.6(12)
C22	8904(6)	1765(6)	12331(4)	41.1(11)
C12	12574(6)	1977(7)	10579(4)	48.8(13)
C26	6102(7)	2890(6)	14396(4)	49.3(13)
C14	12046(7)	4006(6)	7536(4)	44.8(12)
C30	9851(6)	245(6)	12344(4)	46.8(12)
C28	8439(7)	2067(6)	15027(4)	49.9(13)
C27	6924(7)	2659(7)	15158(4)	52.6(14)
C15	14808(6)	854(7)	7707(4)	53.8(14)

Table 2: Anisotropic Displacement Parameters ($\times 10^4$) for **TAK1421P_150K**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2} \times U_{11} + \ldots + 2hka^* \times b^* \times U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O4	78(3)	55(2)	35(2)	-13.2(18)	-7.2(19)	-1(2)
O3	72(3)	62(3)	43(2)	-11.2(19)	-22(2)	-9(2)
O2	76(3)	70(3)	43(2)	-30(2)	-10(2)	-6(2)
N4	44(2)	50(2)	27.0(19)	-10.9(17)	-5.5(17)	-8.2(19)
N3	64(3)	43(2)	34(2)	-10.1(19)	-9(2)	-11(2)
O1	95(3)	65(3)	35(2)	-8(2)	-20(2)	-13(2)
N2	59(3)	40(2)	27(2)	-9.0(17)	-8.3(18)	-6(2)
N1	61(3)	61(3)	31(2)	-15(2)	-5(2)	-17(2)
C10	52(3)	48(3)	37(3)	-15(2)	-5(2)	-11(2)
C24	54(3)	41(3)	32(2)	-11(2)	-3(2)	-13(2)
C3	60(3)	42(3)	31(2)	-8(2)	-7(2)	-14(2)
C8	48(3)	43(3)	31(2)	-9(2)	-6(2)	-12(2)
C19	50(3)	41(3)	32(2)	-12(2)	-5(2)	-11(2)
C7	52(3)	37(3)	30(2)	-3(2)	-10(2)	-8(2)
C1	50(3)	54(3)	27(2)	-13(2)	-4(2)	-12(2)
C17	54(3)	45(3)	35(3)	-14(2)	-2(2)	-14(2)
C9	52(3)	45(3)	28(2)	-8(2)	-7(2)	-13(2)
C13	51(3)	48(3)	35(3)	-6(2)	-11(2)	-11(2)
C16	59(3)	43(3)	28(2)	-9(2)	-11(2)	-10(2)
C20	50(3)	49(3)	34(3)	-9(2)	-7(2)	-11(2)
C21	51(3)	48(3)	39(3)	-12(2)	-11(2)	-10(2)
C11	53(3)	55(3)	35(3)	-18(2)	-5(2)	-10(3)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C18	48(3)	47(3)	33(2)	-11(2)	-7(2)	-10(2)
C2	53(3)	46(3)	36(3)	-14(2)	-6(2)	-12(2)
C23	52(3)	42(3)	33(2)	-9(2)	-7(2)	-15(2)
C4	52(3)	49(3)	25(2)	-9(2)	-7(2)	-13(2)
C25	48(3)	53(3)	33(2)	-14(2)	-2(2)	-9(2)
C5	53(3)	42(3)	34(3)	-8(2)	-5(2)	-10(2)
C6	58(3)	49(3)	31(2)	-10(2)	-7(2)	-10(2)
C29	56(3)	51(3)	36(3)	-10(2)	-11(2)	-17(3)
C22	46(3)	43(3)	32(2)	-6(2)	-8(2)	-10(2)
C12	50(3)	66(4)	27(2)	-8(2)	-7(2)	-13(3)
C26	58(3)	52(3)	37(3)	-14(2)	-1(2)	-14(3)
C14	66(3)	40(3)	29(2)	-14(2)	-7(2)	-9(2)
C30	54(3)	43(3)	39(3)	-9(2)	-8(2)	-6(2)
C28	64(4)	51(3)	37(3)	-9(2)	-11(2)	-16(3)
C27	70(4)	58(3)	34(3)	-14(2)	-4(2)	-23(3)
C15	57(3)	59(4)	42(3)	-16(3)	-8(2)	-5(3)

Table 3: Bond Lengths in Å for **TAK1421P_150K**.

Atom	Atom	Length/Å
O4	N3	1.235(6)
O3	N3	1.243(6)
O2	N1	1.233(6)
N4	C19	1.373(6)
N4	C25	1.471(6)
N4	C22	1.478(6)
N3	C16	1.450(6)
O1	N1	1.251(6)
N2	C7	1.462(6)
N2	C4	1.371(6)
N2	C14	1.464(6)
N1	C1	1.435(6)
C10	C9	1.373(7)
C10	C11	1.392(7)
C24	C23	1.386(7)
C24	C25	1.502(7)
C24	C26	1.388(7)
C3	C2	1.371(7)
C3	C4	1.410(7)
C8	C7	1.514(7)
C8	C9	1.393(7)
C8	C13	1.389(7)
C19	C20	1.418(7)
C19	C18	1.413(7)
C7	C15	1.518(8)
C1	C2	1.402(8)
C1	C6	1.377(8)
C17	C16	1.388(7)
C17	C18	1.379(7)
C9	C14	1.505(7)
C13	C12	1.388(8)
C16	C21	1.378(8)
C20	C21	1.383(7)
C11	C12	1.394(8)
C23	C29	1.392(7)
C23	C22	1.501(7)
C4	C5	1.417(7)
C5	C6	1.375(7)
C29	C28	1.386(8)
C22	C30	1.530(7)
C26	C27	1.399(8)
C28	C27	1.390(8)

Table 4: Bond Angles in ° for **TAK1421P_150K**.

Atom	Atom	Atom	Angle/°
C19	N4	C25	120.3(4)
C19	N4	C22	124.0(4)
C25	N4	C22	113.2(4)
O4	N3	O3	122.8(4)
O4	N3	C16	118.4(5)
O3	N3	C16	118.7(5)
C7	N2	C14	114.0(4)
C4	N2	C7	124.2(4)
C4	N2	C14	121.7(4)
O2	N1	O1	122.0(4)
O2	N1	C1	119.5(5)
O1	N1	C1	118.5(5)
C9	C10	C11	119.6(5)
C23	C24	C25	110.6(4)
C23	C24	C26	121.3(5)
C26	C24	C25	128.1(5)
C2	C3	C4	121.3(5)
C9	C8	C7	110.7(4)
C13	C8	C7	128.9(5)
C13	C8	C9	120.3(5)
N4	C19	C20	120.2(5)
N4	C19	C18	121.7(5)
C18	C19	C20	118.1(4)
N2	C7	C8	101.6(4)
N2	C7	C15	113.8(4)
C8	C7	C15	110.9(4)
C2	C1	N1	119.1(5)
C6	C1	N1	120.1(5)
C6	C1	C2	120.8(5)
C18	C17	C16	119.8(5)
C10	C9	C8	120.8(5)
C10	C9	C14	128.8(5)

Atom	Atom	Atom	Angle/°
C8	C9	C14	110.4(4)
C12	C13	C8	118.7(5)
C17	C16	N3	119.1(5)
C21	C16	N3	119.9(5)
C21	C16	C17	121.0(5)
C21	C20	C19	120.4(5)
C16	C21	C20	120.0(5)
C10	C11	C12	119.6(5)
C17	C18	C19	120.7(5)
C3	C2	C1	119.1(5)
C24	C23	C29	120.1(5)
C24	C23	C22	111.4(4)
C29	C23	C22	128.5(5)
N2	C4	C3	122.2(5)

Atom	Atom	Atom	Angle/°
N2	C4	C5	119.6(5)
C3	C4	C5	118.1(4)
N4	C25	C24	102.7(4)
C6	C5	C4	120.2(5)
C5	C6	C1	120.5(5)
C28	C29	C23	119.0(5)
N4	C22	C23	102.0(4)
N4	C22	C30	115.2(4)
C23	C22	C30	112.7(4)
C13	C12	C11	121.0(5)
C24	C26	C27	118.4(6)
N2	C14	C9	102.3(4)
C29	C28	C27	120.8(5)
C28	C27	C26	120.3(5)

Table 5: Torsion Angles in ° for **TAK1421P_150K**.

Atom	Atom	Atom	Atom	Angle/°
O4	N3	C16	C17	10.2(7)
O4	N3	C16	C21	-169.0(5)
O3	N3	C16	C17	-169.6(5)
O3	N3	C16	C21	11.2(8)
O2	N1	C1	C2	-2.3(8)
O2	N1	C1	C6	177.7(5)
N4	C19	C20	C21	178.0(5)
N4	C19	C18	C17	-178.4(5)
N3	C16	C21	C20	179.8(5)
O1	N1	C1	C2	176.4(5)
O1	N1	C1	C6	-3.6(8)
N2	C4	C5	C6	-179.8(5)
N1	C1	C2	C3	179.7(5)
N1	C1	C6	C5	-179.4(5)
C10	C9	C14	N2	-177.4(5)
C10	C11	C12	C13	0.3(9)
C24	C23	C29	C28	-2.6(8)
C24	C23	C22	N4	-3.4(6)
C24	C23	C22	C30	-127.5(5)
C24	C26	C27	C28	-1.4(9)
C3	C4	C5	C6	-0.1(8)
C8	C9	C14	N2	2.6(6)
C8	C13	C12	C11	0.1(8)
C19	N4	C25	C24	-165.6(5)
C19	N4	C22	C23	165.8(5)
C19	N4	C22	C30	-71.8(6)
C19	C20	C21	C16	0.2(8)
C7	N2	C4	C3	5.3(8)
C7	N2	C4	C5	-175.0(5)
C7	N2	C14	C9	-8.8(6)
C7	C8	C9	C10	-176.0(5)
C7	C8	C9	C14	4.0(6)
C7	C8	C13	C12	175.3(5)
C17	C16	C21	C20	0.6(8)
C9	C10	C11	C12	-0.3(8)
C9	C8	C7	N2	-8.8(6)
C9	C8	C7	C15	112.5(5)
C9	C8	C13	C12	-0.6(8)
C13	C8	C7	N2	175.1(5)
C13	C8	C7	C15	-63.7(7)
C13	C8	C9	C10	0.6(8)
C13	C8	C9	C14	-179.5(5)
C16	C17	C18	C19	0.6(8)
C20	C19	C18	C17	0.2(8)
C11	C10	C9	C8	-0.1(8)

Atom	Atom	Atom	Atom	Angle/°
C11	C10	C9	C14	179.9(5)
C18	C19	C20	C21	-0.6(8)
C18	C17	C16	N3	179.8(5)
C18	C17	C16	C21	-1.0(8)
C2	C3	C4	N2	-180.0(5)
C2	C3	C4	C5	0.4(8)
C2	C1	C6	C5	0.6(9)
C23	C24	C25	N4	0.8(6)
C23	C24	C26	C27	-0.7(8)
C23	C29	C28	C27	0.5(8)
C4	N2	C7	C8	-172.5(5)
C4	N2	C7	C15	68.3(7)
C4	N2	C14	C9	174.5(5)
C4	C3	C2	C1	-0.1(8)
C4	C5	C6	C1	-0.4(9)
C25	N4	C19	C20	-14.5(7)
C25	N4	C19	C18	164.1(5)
C25	N4	C22	C23	4.0(6)
C25	N4	C22	C30	126.4(5)
C25	C24	C23	C29	-177.8(5)
C25	C24	C23	C22	1.7(6)
C25	C24	C26	C27	179.9(5)
C6	C1	C2	C3	-0.4(8)
C29	C23	C22	N4	176.0(5)
C29	C23	C22	C30	51.9(7)
C29	C28	C27	C26	1.5(9)
C22	N4	C19	C20	-175.1(5)
C22	N4	C19	C18	3.5(8)
C22	N4	C25	C24	-3.1(6)
C22	C23	C29	C28	178.0(5)
C26	C24	C23	C29	2.7(8)
C26	C24	C23	C22	-177.8(5)
C26	C24	C25	N4	-179.7(5)
C14	N2	C7	C8	10.9(6)
C14	N2	C7	C15	-108.3(5)
C14	N2	C4	C3	-178.3(5)
C14	N2	C4	C5	1.3(8)

Table 6: Hydrogen Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for **TAK1421P_150K**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij}.

Atom	x	y	z	U_{eq}
H10	11425.4	5202.99	9188.67	54
H3	13242.65	538.75	6345.43	53
H7	12646.05	636.95	8021.38	49
H17	9513.3	2385.01	8724.72	53
H13	13319.32	205.78	10016.77	55
H20	5178.1	2998.99	11028.69	54
H21	5056.33	3495.17	9326.64	55
H11	11771.47	3968.34	10846.09	57
H18	9677.1	1904.4	10415.39	51
H2	13125.04	604.23	4712.04	54
H25A	5479.15	2107.76	12744.19	54
H25B	5723.96	3706.66	12297.02	54
H5	11658.64	4884.55	5745.39	53
H6	11535.51	4924.53	4116.63	56
H29	10199.16	1317.49	14050.59	56
H22	9503.91	2465.97	11942.96	49
H12	12706.55	1477.45	11251.04	59
H26	5063.78	3274.13	14484.86	59
H14A	11016.69	4511.87	7428.32	54
H14B	12696.59	4661.66	7192.04	54
H30A	9301.63	-452.6	12770.45	70
H30B	10762.11	95.39	12609.46	70
H30C	10096.79	117.66	11661.27	70
H28	8982.38	1892.8	15555.39	60
H27	6445.85	2906.57	15767.82	63
H15A	15051.91	566.18	7074.9	81
H15B	15151.86	25.43	8248.72	81
H15C	15292.46	1611.23	7648.15	81

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9. Curriculum vitae

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EXPERIENCE

-Studying abroad for language (2013, Vancouver, Canada)
-Studying abroad for language (2014, Taiwan)
-Teaching Japanese and the culture (2015, Latvia)
-Seminar on the state of higher education in Japan and Finland (2016, Yamagata uni.)
-TA in bioorganic chemistry (2017)
-TA in organic chemistry (2019-2021)
-“Swiss Science Concentrates” columns of Chimia from March 2020 to March 2021

AWARD

-Valuable presentation award (Yamagata uni, 2017)
-The most valuable undergraduate student award (First place, Yamagata uni, 2017)
-Poster award (The International Symposium of YU-COE(C) AFTEC and HECT, 2017)
-SCS Chemistry Travel Award winner (2022)

SCHOLARSHIP

-Swiss Government Excellence Scholarship (Sep, 2019- March, 2023)

QUALIFICATION

-Class A Dangerous Goods Handler
-Dispensing Office Manager
-Regular driver's license

SKILLS

Proficient in Microsoft Office packages (Word, PowerPoint etc), using many chemistry software packages for drawing and spectral manipulation in Chemdraw, DELTA, MestReNova and in use of scientific database packages such as SciFinder, Reaxys and PDB.
GC, GCMS and Glovebox (including maintenance and troubleshooting)

CONFERENCE PRESENTATION

2017

-Miyakoshi, T.; Konno, H.; Novel metal-free pyridine synthesis: Application of Anibamine synthesis.(Short oral presentation and Poster, poster award) The International Symposium of YU-COE(C) AFTEC and HECT (November 30, 2017, Yonezawa, Yamagata, Japan)

2018

-Miyakoshi, T.; Konno, H.; Metal-free Pyridine Synthesis via Oxime Intermediate: Synthetic Study of Anibamine (Oral presentation)
Japan Society of Bioscience, Biotechnology and Agrochemistry annual conference (March 16-19, 2018, Meijo University, Nagoya, Japan)

-Miyakoshi, T.; Konno, H.; New pyridine synthesis with ketal protected 1,5-diketone: Application to Anibamine synthesis (Poster presentation)
19th Tetrahedron Symposium (June 26-29, 2018, Riva del garda, Italy)

-Miyakoshi, T.; Konno, H.; Total synthesis of Anibamine with acid-promoted pyridine synthesis (Poster presentation) 35th The Society of Synthetic Organic Chemistry, Japan seminar (September 18-20, 2018, Tendo, Yamagata, Japan)

2019

-Mihara, H.; Miyakoshi, T.; Konno, H.; Development of metal-free pyridine synthesis under acidic condition and total synthesis of Anibamine
(Oral presentation) Japan Society of Bioscience, Biotechnology and Agrochemistry annual conference (March 24-27, 2019, Tokyo University of Agriculture, Tokyo, Japan)

-Fujii, J.; Kobayashi, S.; Tokairin, T.; Miyakoshi, T.; Saito, T.; Nagaoka, K.; Ikeda, Y.; Konno, H. Quantitative analysis of γ-glutamylpeptides by LC-MS and application for studying liver injury and γ-glutamyltransferase assay. The 9th biennial Meeting of Society for Free Radical Research-Asia (SFRR-Asia 2019), 2019 (April 4-7, 2019, Kyoto, Japan)

-Konno, H.; Miyakoshi, T.; Mihara, H.; Total synthesis of Anibamine, pyridinium natural product. Organic Synthesis Symposium (June 6, 2019, Sendai, Japan)

-Miyakoshi, T; Baudoin, O.; Development of kinetic resolution with Pd^0 catalyzed C-H activation. (Oral presentation) 7th Cross disciplinary meeting of Japanese young scientists in Europe (August 3-4, 2019, Bonn, Germany)

2020

-Mihara, H.; Miyakoshi, T.; Konno, H.; Development of novel metal-free pyridine synthesis and application to total synthesis of natural products. Joint Meeting of the Tohoku Area Chemistry Societies (Sep. 26th, 2020, Hachinohe, Japan)

2022

-T. Miyakoshi, N. E. Niggli, and O. Baudoin, Remote Construction of N-Heterocycles via 1,4-Palladium Shift-Mediated Double C-H Activation (Poster presentation) (BOSS XVII, 17th Belgian Organic Synthesis Symposium, Namur, Belgium, July 3-8, 2022)

-T. Miyakoshi, N. E. Niggli, and O. Baudoin, Remote Construction of N-Heterocycles via 1,4-Palladium Shift-Mediated Double C-H Activation (Oral presentation) (40th REGIO-Symposium, Liestal, Switzerland, August 29-31, 2022)

INVITED LECTURTE

2021

-Miyakoshi, T; PhD study in Switzerland~From Yonezawa to Basel (Oct. 9th, 2021, online, Japan Society of Bioscience, Biotechnology and Agrochemistry, Tohoku branch)

SOCIETY

-JSBBA (Japan Society of Bioscience, Biotechnology and Agrochemistry)
-Swiss Chemical Society (2019-2022)

EDUCATION BACKGROUND HISTORY

2017

-Bachelor of Engineering, Laboratory of Bioorganic Chemistry, Yamagata University, 4-31-6, Jonan, Yonezawa, Yamagata, 992-8510, JAPAN.

2019

-Master of Engineering, Laboratory of Bioorganic Chemistry, Yamagata University, 4-31-6, Jonan, Yonezawa, Yamagata, 992-8510, JAPAN.
-Admitted to Department of Chemistry in University of Basel, St. Johanns-Ring 19, CH-4056, Basel, Switzerland, April 2019.

2023

-Expected to obtain PhD degree from University of Basel, as of April.
-Expected to work for Spiber Inc., as of June 1st.

LIST OF ACADEMIC PUBLICATION

1. Miyakoshi, T.; Konno, H.
Improved synthesis of 2,4,6-trialkylpyridines from 1,5-diketoalkanes: total synthesis of Anibamine. *Org. Biomol. Chem.*, **2019**, *17*, 2896–2905. (Highlighted in Organic Chemistry Portal, https://www.organic-chemistry.org/Highlights/2019/21October.shtm)

2. Kobayashi, S.; Tokairin, Y.; Miyakoshi, T.; Saito, T.; Nagaoka, K.; Ikeda, Y.; Fujii, J.; Konno, H. Quantitative analysis of g-glutamylpeptides by liquid chromarography-mass spectrometry and application for studying liver injury and g-glutamyltransferase assay. *Anal. Biochem.* **2019**, *578*, 13-22.

3. Mihara, H.; Miyakoshi, T.; Kikuchi, Y.; Konno, H. The one-pot synthesis of pyridine derivatives from the corresponding 1,5-dicarbonyl compounds. *Heterocycles*, **2019**, *98*, 1375-1383.

4. O. Vyhivskyi; A. Kudashev; T. Miyakoshi; O. Baudoin. Chiral Catalysts for Pd^0-Catalyzed Enantioselective C–H Activation. *Chem. Eur. J.* **2021**, *27*, 1231-1257.

5. F. Ferlin; I. Anastasiou; N. Salameh; T. Miyakoshi; O. Baudoin; L. Vaccaro. $C(sp^3)$–H Arylation Promoted by a Heterogeneous Palladium-N-Heterocyclic Carbene Complex in Batch and Continuous Flow. *ChemSusChem*, **2022**, e202102736.

6. T. Miyakoshi, N. E. Niggli, O. Baudoin. Remote Construction of N-Heterocycles via 1,4-Palladium Shift-Mediated Double C–H Activation. *Angew. Chem. Int. Ed.* **2022**, e202116101. (Selected as Hot paper, Highlighted in Synfacts, **2022**, 632, https://www.thieme-connect.de/products/ejournals/pdf/10.1055/s-0041-1738321.pdf)

REFERENCE

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