Functionalization of α- and β-Amino C–H Bonds using Cooperative Catalysis

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Abstract

Cooperative catalysis has been developed for transformations where at least two reactants are activated in situ by acid or base sensitive catalysts to form the reactive species and subsequent bond formation leads to desired product. This thesis focuses on the development of α-amino C–H alkynylation and β-amino C–H deuteration through the use of cooperative catalysts. In the alkynylation reaction, *N*-alkylamines and trimethylsilyl substituted alkynes were used to synthesize propargylamines by the cooperative actions of Lewis acid catalysts, $B(C_6F_5)_3$ and copper complex. The reaction between in situ generated iminium ion and copper alkyne complex afforded the product. The method is applicable to the late-stage functionalization of bioactive amine drug molecules and has been shown to tolerate different functional groups on trimethylsilyl-substituted alkynes. In addition, an enantioselective and diastereoselective version of the method was also developed through the use of chiral copper complex. In the second part, selective deuteration of β-amino C–H bonds of various acylic and cyclic alkyl amines will be introduced. $B(C_6F_5)_3$ and Brønsted base work cooperatively to afford enamine and deuterated ammonium ion as reactive intermediate. Deuteration of enamine at the β-position and hydride reduction at the α-position gave the selectively deuterated products. Acetone-d_6 was the found to be the optimal source of deuterium. This method was able to incorporate deuterium atoms up to 99% and can be applied in a gram scale reaction without compromising the yield or *d*-incorporation level.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF SCHEMES

LIST OF ABBREVIATIONS

Å angstrom

Ac acyl

acac acetylacetonate

ADHD attention-deficit/hyperactivity disorder

Anth anthracene

aq. aqueous

Boc *tert*-butoxycarbonyl

BOX bisoxazoline

Bn benzyl

bpy bipyridine

Bu butyl

Cbz carboxybenzyl

CFL compact fluorescent light

cod cyclooctyldiene

Ci Curie

Cp cyclopentyl

Cy cyclohexyl

DART direct analysis in real time

dba dibenzylideneacetone

DBU 1,8-diazabicyclo[5.4.0]undec-7-ene

DCE 1,2-dichloroethane

DCM dichloromethane

DIPEA *N*,*N*-diisopropylethylamine

DMAP 4-dimethylaminopyridine

DMF dimethylformamide

DMSO dimethylsulfoxide

DPEphos bis[(2-diphenylphosphino)phenyl]ether

dppe 1,2-bis(diphenylphosphino)ethane

dr diastereomeric ratio

ee enantiomeric excess

equiv equivalence

er enatiomeric ratio

Et ethyl

FLPs frustrated Lewis pairs

glyme dimethoxyethane

h hour

HAT hydrogen atom transfer

Hex hexyl

HPLC high-performance liquid chromatography

i-Bu isobutyl

i-Pr isopropyl

LC/MS liquic chromatography/mass spectrometry

LED light-emitting diode

m- meta

Me methyl

Mes mesityl

M.S. molecular sieve

NHC *N*-heterocyclic carbene

NMP *N*-methyl piperidine

NMR nuclear magnetic resonance

NOESY nuclear Overhauser effect spectroscopy

n-Pent *n*-pentyl

p- para

Ph phenyl

pK_a negative base-10 logarithm of the acid dissociation constant (K_a) of a solution

PMP 1,2,2,6,6-pentamethylpiperidine

Pr propyl

PyBOX bis(oxazolinyl)pyridine

QUINAP [1-(1-isoquinolinyl)-2-naphthyl]diphenylphosphine

SET single electron transfer

t-Bu tert-butyl

TBAF tetrabutylammonium fluoride

TBME *tert*-butylmethyl ether

TBS *tert*-butyldimethylsilyl

Tf trifluoromethanesulfonyl

TFA trifluoroacetic acid

THF tetrahydrofuran

TMEDA tetramethylethylenediamine

TMS trimethylsilyl

s-Bu sec-butyl

Xantphos 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

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I would like to thank Prof. Masayuki Wasa for giving me the opportunity to study in his group. I would also like to thank Prof. James Morken and Prof. Marc Snapper for being on my committee and reviewing my thesis.

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Lastly, special thanks go to my parents for the strongest support that one could ever get.

CHAPTER ONE: Introduction to Cooperative Catalysis

Cooperative catalysis describes a catalyst system where there can be two distinct catalysts that activate both the nucleophile and electrophile independently and synergistically;[1] this is also known as "dual catalysis"[2] or "synergistic catalysis"[3] (Fig 1.1A). Cooperative catalysis can be found in nature, where enzymes work with co-catalysts to facilitate the synthesis of small molecules.

Cooperative catalysis should be distinguished from bifunctional catalysis, cascade catalysis and double activation catalysis (Fig 1). In a general bifunctional catalyst system, a single catalyst contains both acidic and basic functional groups, which can activate different substrates independently and bring the nucleophile and electrophile into proximity to promote the bond formation (Fig 1.1B). A cascade catalyst system often times describes a sequential activation of substrate by two or more catalysts (Fig 1.1C). A starting material first undergoes reaction with a catalyst to form an intermediate, which then undergoes a following reaction with another catalyst to form a second intermediate and regenerate the first catalyst. The second intermediate will react with the other coupling partner to form the desired compound and release the latter catalyst. Double activation catalysis describes a system where two different catalysts activate the same substrate simultaneously to form the reactive intermediates, which then leads to subsequent bond forming reactions (Fig 1.1C).[3]

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[1] Schindler, C.; Jacobsen, E. N. *Science* **2013**, *340*, 1052–1052.
[2] Sammis, G. M.; Danjo, H.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2004**, *126*, 32, 9928–9929.
[3] Allen, A. E.; MacMillan D. W. C. *Chem. Sci.* **2012**, *3*, 633–658.

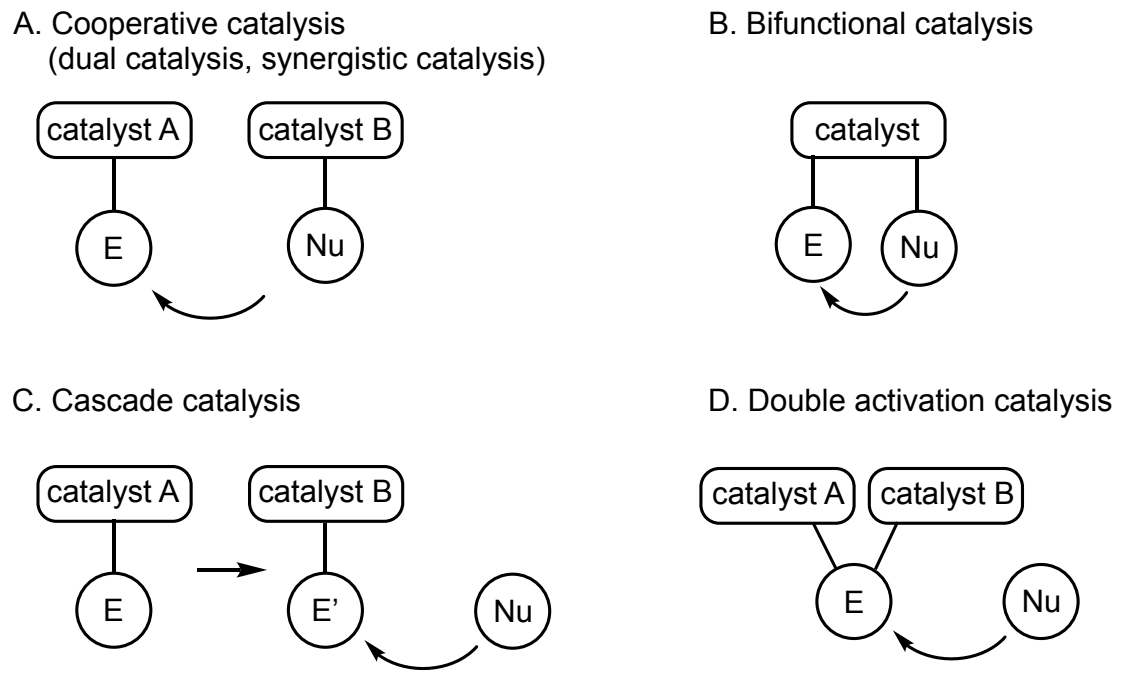


Fig 1.1 Classification of catalytic systems involving two catalysts

For the catalysts and substrates to work cooperatively, there are three major points to overcome. First, the catalysts must not quench each other, such as forming tight acid and base ion pairs, or cannot undergo ligand exchange, which could deactivate the catalysts. Second, the catalyst cannot have overlapping functions so that they can react with the according substrates independently to deliver the respective intermediates that will produce the desired product. Lastly, the substrates cannot be so reactive that they react with each other without activation by the catalyst and may lose stereoselectivity.[4]

Some additional underlying challenges include turning over the catalysts efficiently. Since both substrates require activation independently, the concentration of the intermediates is low in the reaction mixture. Furthermore, when performing stereoselective reactions using cooperative catalyst systems, it is important that the non-stereoselective processes or epimerization can be suppressed so that enantioselectivity is not affected.

Some selected examples using cooperative acid/acid, acid/base, and base/base catalyst systems will be introduced. In addition, reactions that incorporate hydrogen bonding

[4] Romiti, F.; del Pozo, J.; Paioti, P. H. S.; Gonsales, S. H.; Li, X.; Hartrampf, F. W. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2019**, *141*, 17952–17961

catalysis and photoredox catalysis in a cooperative catalyst system will also be briefly discussed.

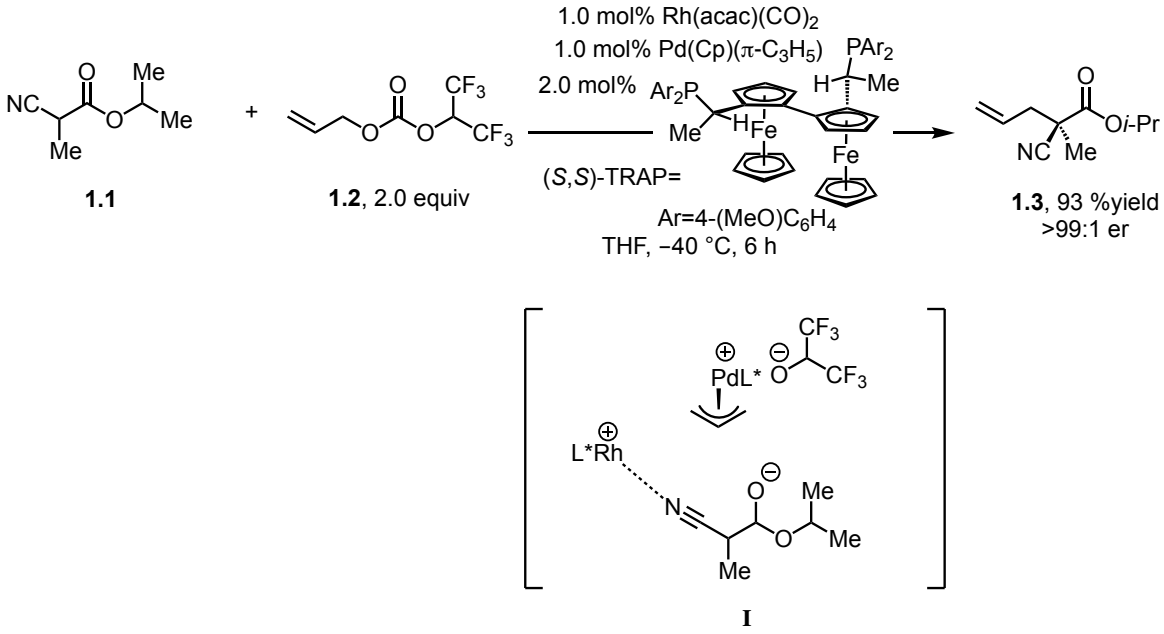
1.1 Cooperative acid/acid catalysis

Lewis acids and Brønsted acids can be combined to achieve more efficient reactions with higher reactivity, selectivity, and/or broader substrate scope through the design of catalyst systems.[5] One of the common activation modes of Lewis acid activation is coordination to carbonyl groups, which enhances the acidity of the α-proton and leads to various transformations.

The Ito group reported an enantioselective allylic alkylation of activated nitriles catalyzed by Rh-/Pd-complexes (Scheme 1.1).[6] Ester **1.1** and allyl carbamate **1.2** with 1.0 mol% of $Rh(acac)(CO)_2$, 1.0 mol% of $Pd(Cp)(\pi\text{-}C_3H_5)$, and (*S*,*S*)-TRAP ligand in THF at –40 °C gave allyl ester **1.3** in 93% yield and >99:1 er. This reaction is an example where both the metal ligand complexes are chiral, but only one controls enantioselectivity. The Rh-TRAP ligand complex activates cyanopropionate **1.1**, forming enolate intermediate **I** as the electrons from ester are delocalized onto the complex while coordinating with rhodium. The palladium catalyst forms π-allyl species with allyl carbonate **1.2** through decarboxylative oxidative addition while releasing CO_2 and alkoxide. The Pd-allyl complex is then attacked by the enolate intermediate to form the C–C bond. Through mechanistic studies, it was found that the Pd-TRAP complex promotes the reaction but has no influence on the enantioselectivity, as no product formed when only Rh-catalyst was used but only racemic product was observed when only palladium catalyst was used. This can be easily explained that the nucleophile attacks the allyl complex anti to palladium. Another interesting note is that $(CF_3)_2CH$ carbonate **1.2** was used because if an ethoxide was released from the allyl carbonate, it is basic enough to deprotonate the ester **1.1**, which influenced enantioselectivity, while the released $(CF_3)_2CHO^-$ is less basic because of

[5] Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924−1942.
[6] Sawamura, M.; Sudoh, M.; Ito, Y. *J. Am. Chem. Soc.* **1996**, *118*, 3309−3310.

electron withdrawing effect from CF_3 groups and has more affinity to rhodium atom because of its soft character.

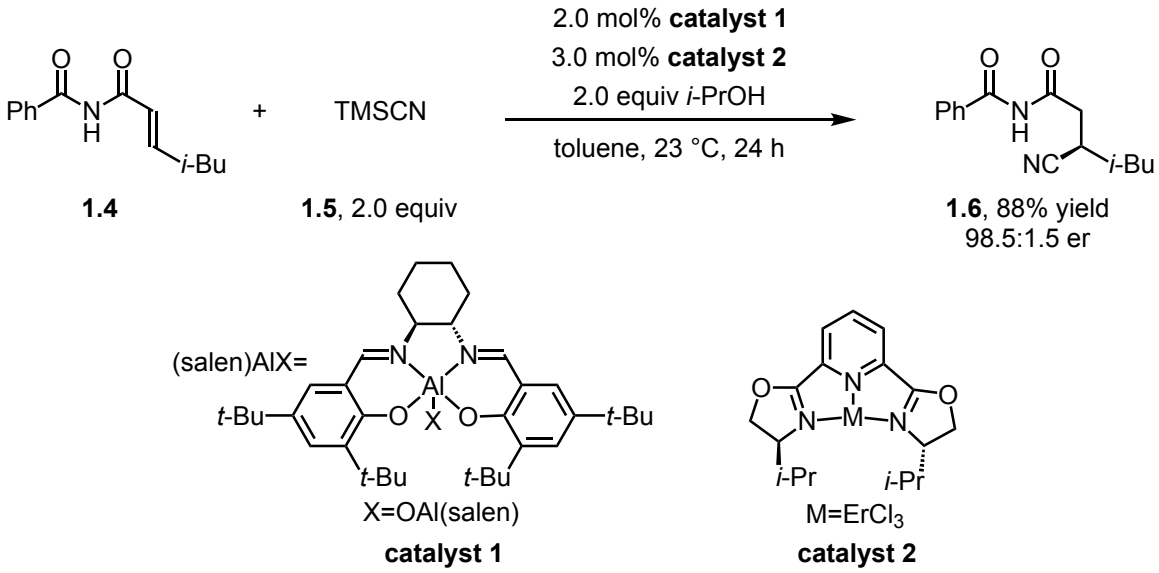


Scheme 1.1 Enantioselective Rh-/Pd- catalyzed allylic alkylation by Ito

The Jacobsen group reported a highly enantioselective conjugate cyanation of unsaturated imides, where both metal complexes are required for high efficiency and enantioselectivity (Scheme 1.2).[7] Unsaturated imide **1.4** and TMSCN **1.5** undergoes cyanation to form enantioenriched cyanide product **1.6** with 2.0 mol% of aluminum based **catalyst 1** and 3.0 mol% of erbium based **catalyst 2**, 2.0 equiv of isopropanol in toluene at 23 °C. From previous method of cyanation addition to saturated imide, it was found that the reactive species involves a homobimetallic pathway, in which the catalyst activates both cyanide and the saturated imide. **Catalyst 1** alone could not catalyze the reaction, since it cannot activate cyanide. An additional chiral catalyst, **catalyst 2**, was therefore designed and found to be more efficient for activation of cyanide. With the two catalysts activating each substrate independently and cooperatively, the reaction time was reduced from 26-48 h to 8-14, loading of TMSCN was lowered from 2.5-4.0 equiv to 2.0 equiv, and total

[7] Sammis, G.M.; Danjo, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 9928–9929.

catalyst amount decreased from 15 mol% to 7.0 mol%. From mechanistic studies, initial rate of reaction has first order dependence on both catalysts, indicating that both catalysts are involved in the rate-determining step. Changing either ligand on each metal from chiral to achiral gives product with lowered er, which suggests that both catalysts are also involved in asymmetric induction.



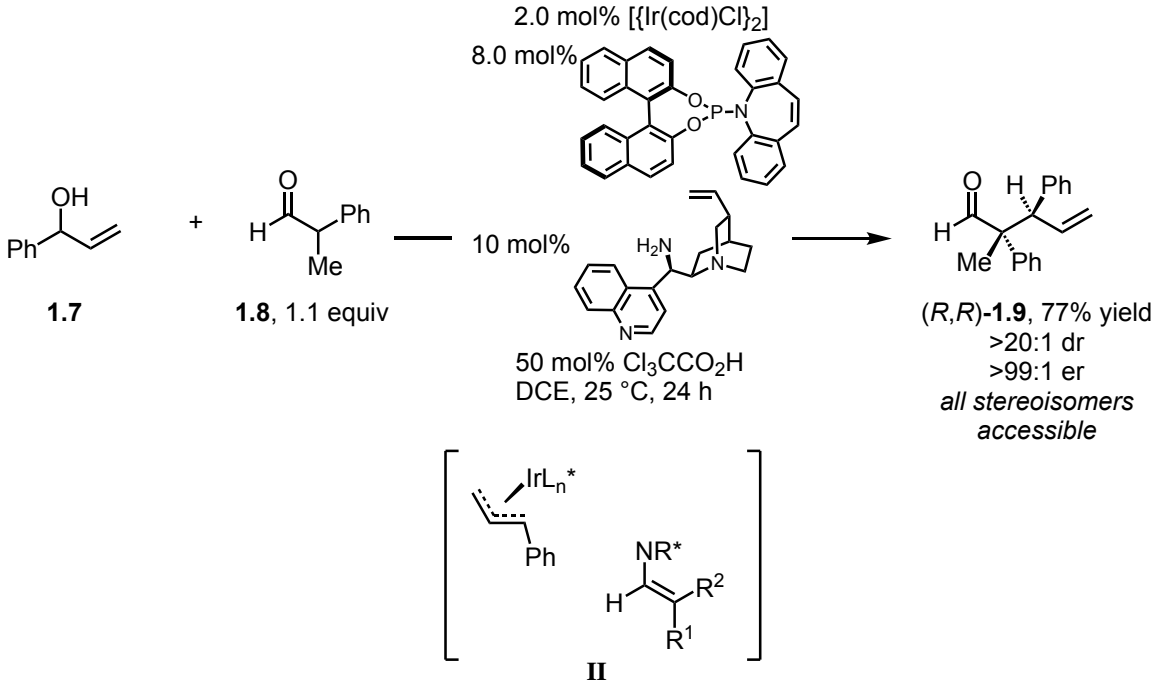
Scheme 1.2 Enantioselective conjugate cyanation by Jacobsen

1.2 Cooperative acid/base catalysis

The Carreira group reported an enantio- and diastereodivergent α-allylation of α-substituted aliphatic aldehydes with the use of Ir-phosphoramidite complex and cinchona-alkaloid derived primary chiral amine, forming χ,δ-unsaturated aldehyde **1.9**.[8] Allyl alcohol **1.7** and 1.1 equiv of aldehyde **1.8** with 2.0 mol% of Iridium salt and 8.0% of chiral (P, olefin) ligand, 10 mol% of cinchona alkaloid-derived chiral primary amine, 50 mol% of trichloroacetic acid in DCE at 25 °C obtained product (*R*,*R*)-**1.9** in 77% yield with >20:1 dr and >99:1 er. Each chiral catalyst is responsible for activation of one substrate and controls enantioselectivity at different position independently. Without one of the catalysts, the reaction would not proceed. The iridium catalyzed reaction forms the branched product by having the nucleophile attack the more substituted side of the allyl complex. During the

[8] Krautwald, S.; Sarlah, D.; Schafroth, M.A.; Carreira, E.M. *Science* **2013**, *340*, 1065–1068.

C–C bond forming step, the π-allyl Ir complex from a secondary allylic alcohol and enamine intermediate from aldehyde condense onto primary amine are both planar (**II**), which minimizes the match and mismatch effect. By changing the combination of chiral and achiral (P, olefin) ligand on iridium and the primary amine, it was found that the amine controls stereochemistry at the α- position and the iridium complex controls the β-position. By switching to the pseudo enantiomer of primary amine, the opposite enantiomer at α-position was observed. Using the opposite enantiomer of P/olefin ligand, the opposite enantiomer at β-position was observed. In each case, high enantioselectivity and high diastereoselectivity were obtained.

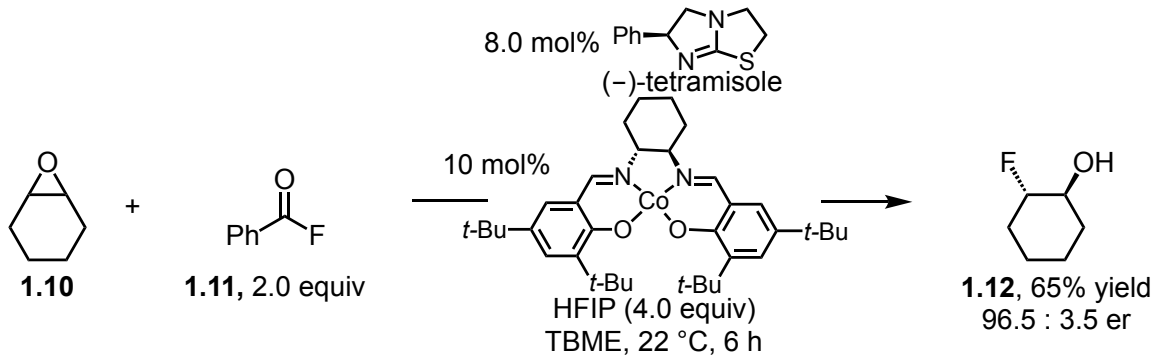


Scheme 1.3 Enantio- and diastereodivergent α-allylation of α-substituted aliphatic aldehydes by Carreira

Doyle and coworkers reported an enantioselective ring opening of epoxides by fluoride anion with chiral (salen)-Co complex and chiral amine (–)-tetramisole co-catalysts (Scheme 1.4).[9] Epoxide **1.10** and 2.0 equiv of benzoyl fluoride **1.11** with 8.0 mol% of (–)-tetramisole and 10 mol% of cobalt-salen complex and 4.0 equiv of HFIP in TBME at 22 °C

[9] Kalow, J. A.; Doyle, A. G. *J. Am. Chem. Soc.* **2010**, *132*, 3268–3269.

afforded fluoro-alcohol in 65% yield and 96.5:3.5 er. The amine generates HF from benzoyl fluoride **1.11** and HFIP. Reactions with only amine or only cobalt Lewis acid catalyst gave low conversion and low enantioselectivity. When both catalysts are used, the enantiomeric excess increased from <5 to 54%. A matched/mismatched effect was observed for chiral amine and chiral (salen)-Co complex. Only when using the right enantiomers of both catalysts, the optimal ee was observed.

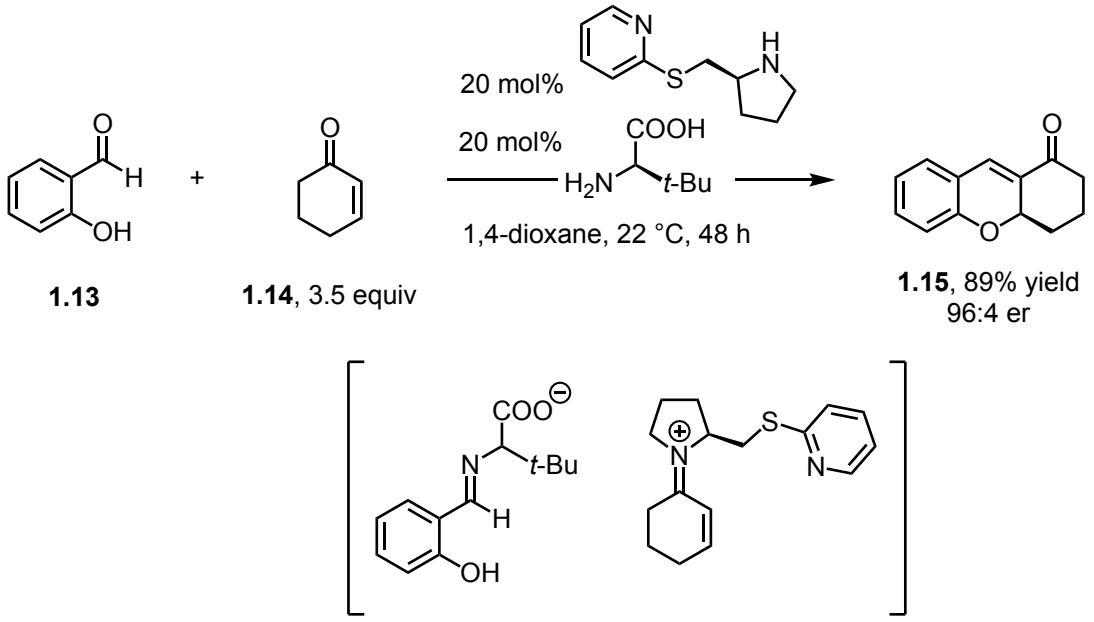


Scheme 1.4 Enantioselective ring opening of epoxides by fluoride anion by Doyle

1.3 Cooperative base/base catalysis

Reactions catalyzed by two bases are less common. In 2009, the Xu group reported an oxa-Michael-Mannich reaction to access tetrahydroxanthenones by the use of catalytic pyrrolidine and *tert*-Leucine (Scheme 1.5).[10] Salicylic aldehyde **1.13** and α,β-unsaturated cyclohexanone **1.14** with 20 mol% of (*S*)-2-((pyrrolidin-2-ylmethyl)thio)pyridine and 20 mol% of *tert*-Leucine in 1,4-dioxane at 22 °C gave tetrahydroxanthenones in 89% yield and 96:4 er. Salicylic aldehyde **1.13** forms imine through condensation with tert-Leucine; cyclohexanone **1.14** condenses onto pyrrolidine to form iminium ion. Imine and iminium form the ion pair, intermediate **III**, then undergoes the enantioselective oxa-Michael addition and intramolecular Mannich reaction. After hydrolysis to afford the product. Without either amine, the reaction did not proceed, only trace amount of products were obtained and enantioselectivities were not obtained. Unfortunately, the authors did not demonstrate the specificity for amine activation.

[10] Xia, A. −B.; Xu, D. −Q.; Luo, S. −P.; Jiang, J. −R.; Tang, J.; Wang, Y. −F.; Xu, Z. −Y. *Chem. Eur. J.* **2010**, *16*, 801−804.

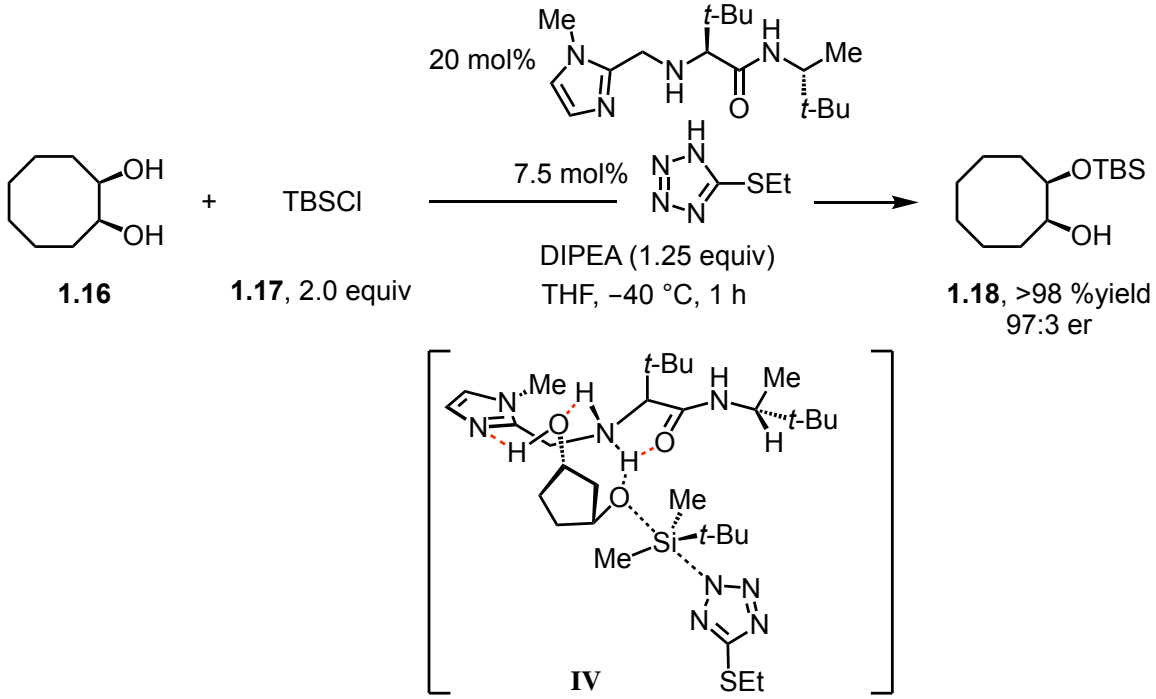


Scheme 1.5 oxa-Michael-Mannich reaction by Xu

In 2013, the Hoveyda and Snapper group reported a catalytic enantioselective mono silyl protection of diols and triols promoted by two heterocyclic Lewis base catalysts. Diol **1.16** was treated with 2.0 equiv of TBSCl **1.17** with 20 mol% of an amino acid derived polypeptide catalyst, 7.5% of 5-ethylthiotetrazole, and 1.25 equiv of DIPEA in THF at –40 °C in 1 h to give mono-protected alcohol **1.18** in >98% yield and 97:3 er (Scheme 1.6).[11] In this transformation, although two catalysts are structurally similar, they have different functions and are both required for it to proceed with high efficiency and enantioselectivity. The polypeptide catalyst serves as a chiral base to induce enantioselectivity through hydrogen bonding interactions with the diol substrate (**IV**). To avoid steric repulsion and less effective action of the diol, the smaller side on diol is proposed to position closer to the polypeptide catalyst to reveal one of the enantiotopic alcohol groups. Deprotonated 5-ethylthiotetrazole, generated by DIPEA, acts as the nucleophilic co-catalyst (**IV**). The high-energy highest occupied molecular orbital caused by neighboring heteroatoms and a sterically accessible site for displacement of a chloride make it reactive towards silyl chlorides. Less basic DIPEA does not interact with alcohol

[11] Manville, N.; Alite, H.; Haeffner, F.; Hoveyda, A. H.; Snapper, M. L. *Nat. Chem.* **2013**, *5*, 768–774.

substrates. Instead, it can help to quench the HCl generated from the silylation to regenerate the polypeptide catalyst.



Scheme 1.6 Enantioselective silyl protection of alcohols by Hoveyda and Snapper

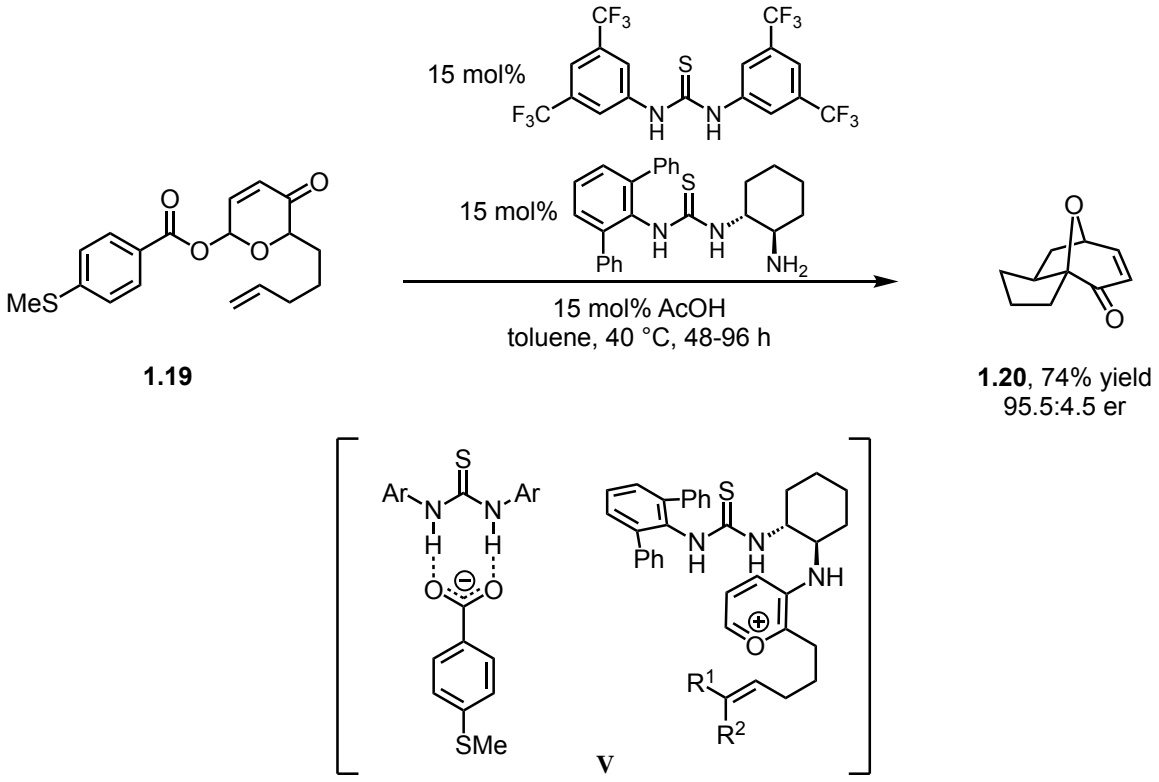
1.4 Cooperative catalysis and hydrogen bonding catalysis

There are many examples of cooperative catalysis where one of the substrates is activated by hydrogen bonding interactions. Some well-known hydrogen bonding catalysts include thiourea, squaramide, phosphoric acid, etc. are combined with other catalyst to achieve various transformations.

The Jacobsen group reported an enantioselective oxidopyrylium-based [5+2] dipolar cycloaddition reaction in 2011 (Scheme 1.7).[12] *p*-Thiomethylbenzoyl substrate **1.19** with 15 mol% of achiral thiourea and 15 mol% of primary aminothiourea and 15 mol% of acetic acid in toluene at 40 °C affords the cyclized product **1.20** in 74% yield and 95.5:4.5 er. This is an example where an additional co-catalyst improves both the yield and enantioselectivity of product. The achiral thiourea serves as anion abstractor, which abstracts the aryl carboxylate leaving group from **1.19** to afford pyrylium intermediate **V**.

[12] Burns, N. Z.; Witten, M. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 14578–14581.

Subsequent intramolecular [5+2] cycloaddition affords the desired product **1.20**. Initially, when a chiral thiourea catalyst and stoichiometric triethylamine were used, no stereoselectivity was observed. When a bifunctional thiourea containing a primary amine was used, low enantioselectivity was observed (37% yield, 60.5:39.5 er). Through systematic screening, it was found that addition of achiral thiourea improve both the yield and enantioselectivity and acetic acid as co-catalysts also help to enhance the yield. Mechanistic investigation showed that either aminocarbazole, or diamine or tertiary aminothiourea catalysts could not generate the product with high yield and enantioselectivity.

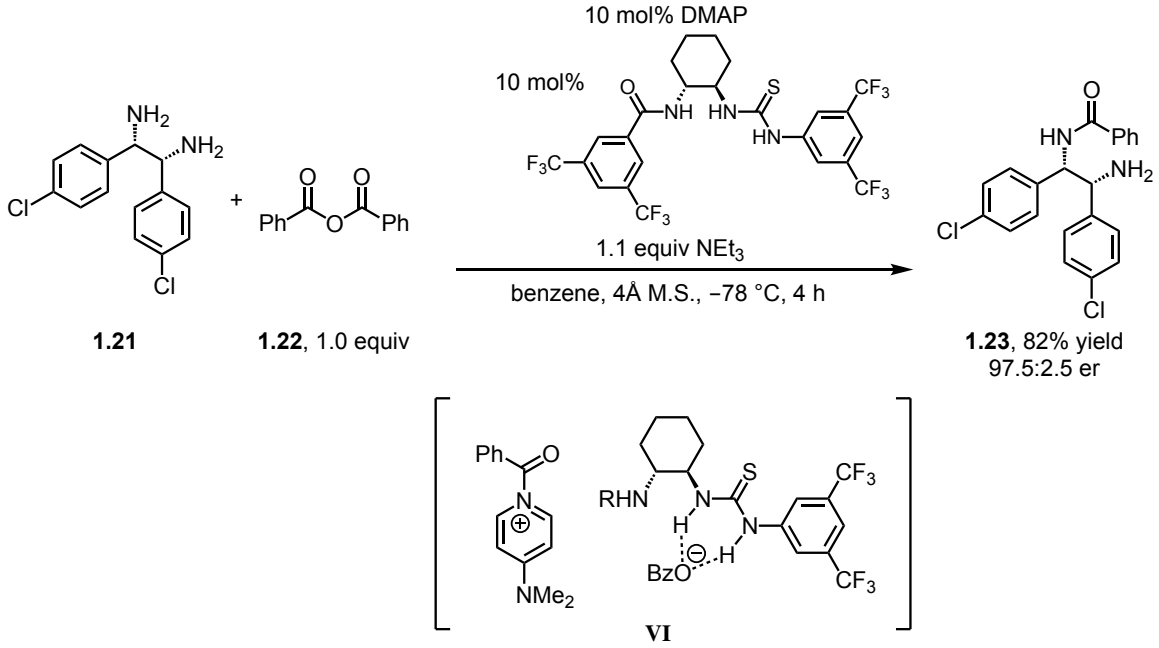


Scheme 1.7 Enantioselective oxidopyrylium-based [5+2] cycloaddition by Jacobsen

Another example of involving hydrogen bonding catalysis was demonstrated by Seidel in 2011 (Scheme 1.8).[13] A catalytic desymmetrization of *meso*-diamines was shown through enantioselective monobenzoylation of diamine **1.21** by using anhydride **1.22** and catalyst combination of 10 mol% of DMAP and 10 mol% of a thiourea based chiral anion

[13] De, C. K.; Seidel, D. *J. Am. Chem. Soc.* **2011**, *133*, 14538–14541.

receptor with 1.1 equiv of triethylamine in benzene at −78 °C to afford product **1.23** in 82% yield and 97.5:2.5 er. Both catalysts are required for the reaction to take place with high yield, without either catalyst, the product was obtained with diminished yield and enantioselectivity. The two catalysts have to work cooperatively to form a tight ion pair **VI**, from which the benzoyl anion is delivered enantioselectively to the amine.



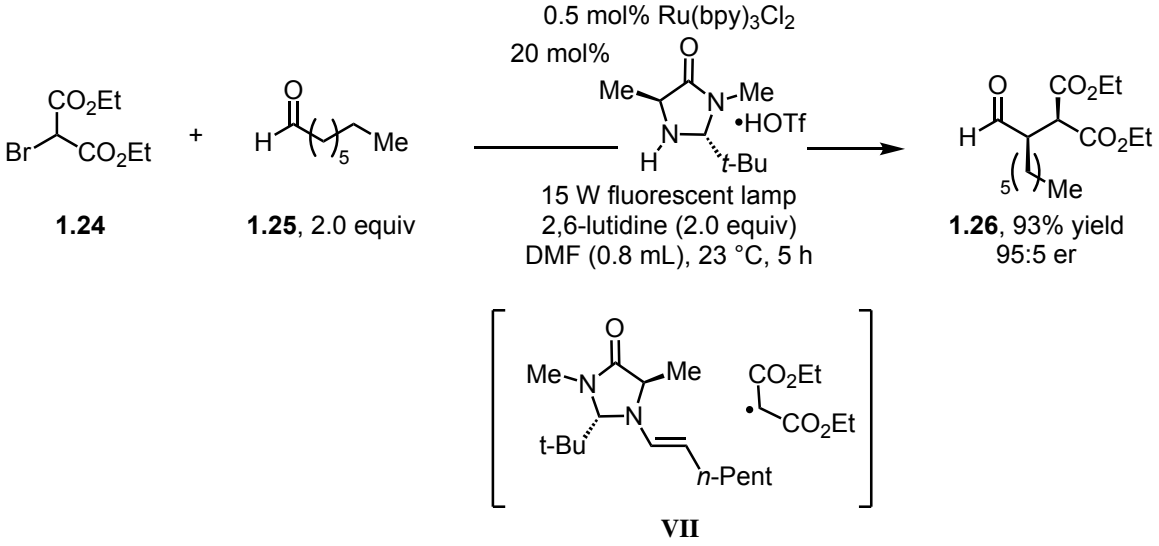
Scheme 1.8 Desymmetrization of *meso*-diamines by Seidel

1.5 Cooperative catalysis and photoredox catalysis

Photoredox catalysis provides radical intermediates, which can also be useful intermediates in cooperative catalysis. The MacMillan group reported an enantioselective intermolecular α-alkylation of aldehydes with alkyl bromides using photoredox catalyst $Ru(bpy)_3Cl_2$ and secondary amine catalyst (Scheme 1.9).[14] Alkyl halide **1.24** and 2.0 equiv of aldehyde **1.25** with 0.5 mol% of ruthenium-based catalyst and 20 mol% of secondary amine catalyst 2.0 equiv of 2,6-lutidine under 15 W fluorescent lamp in DMF at 23 °C gave product **1.26** in 93% yield and 95:5 er. The Ru-based catalyst, through SET, reduces alkyl bromide to form an electron deficient alkyl radical (**VII**). At the same time, secondary amine catalyst and the aldehyde forms a reactive enamine intermediate (**VII**). Subsequently,

[14] Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77–80.

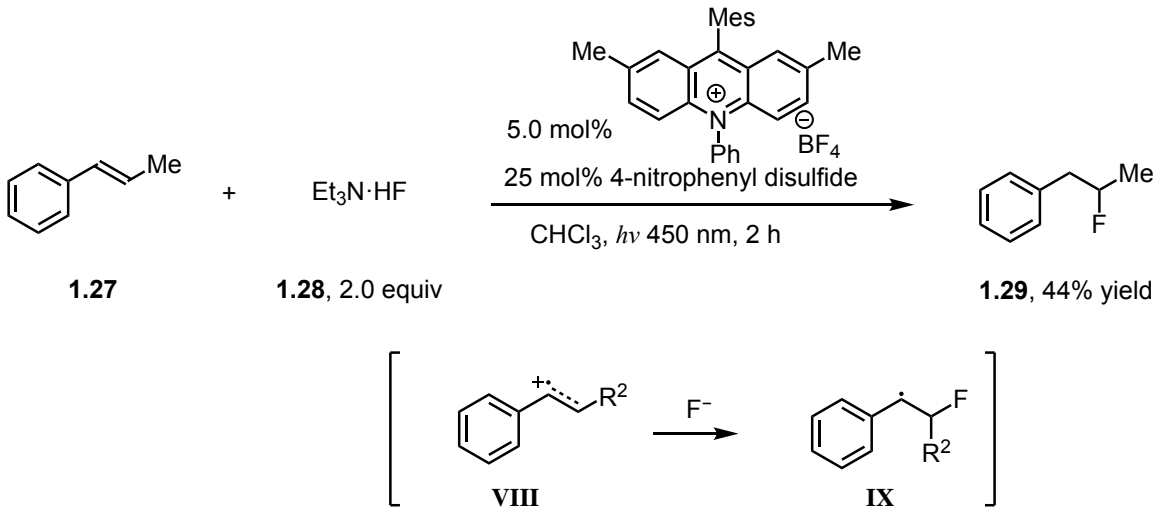
the SOMOphilic enamine adds to alkyl radical to furnish the product **1.26**. The two catalysts do not have overlapping functions and generate individual reactive species to allow C–C bond formation.



Scheme 1.9 Enantioselective intermolecular α-alkylation of aldehydes by MacMillan

An *anti*-Markovnikov addition of Brønsted acidic nucleophiles of chorides, fluorides, phosphoric acid and sulfonic acid to styrene derivatives was reported by Nicewicz using an acridinium based organo-photoredox catalyst and hydrogen atom donor catalyst (Scheme 1.10).[15] Styrene **1.27** and $Et_3N{\cdot}HF$ **1.28** undergoes fluorination with 5.0 mol% of photoredox catalyst, 9-mesityl-10-methylacridinium, and 25 mol% of 4-nitrophenyl disulfide under 450 nm radiation in chloroform. The excited photoredox catalysts, through photoinduced electron transfer, generates alkene radical cation **VIII**. Nucleophilic fluorides from $Et_3N{\cdot}HF$ **1.28**, in this case, attacks the *anti*-Markovnikov position to afford benzylic radical **IX**. Thiophenol, from consecutive steps of homolytic cleavage of disulfide, reduction and protonation, transfers hydrogen radical to afford the final product. Both catalysts contribute to the regioselectivity observed here. If both catalysts are excluded from the reaction, halogenation was observed only at the α-position. No other side products in this reaction was obtained. Without the use of disulfide, the reaction did not proceed.

[15] Wilger, D. J.; Grandjean, J-M. M.; Lammert, T. R.; Nicewicz, D. A. *Nat. Chem.* **2014**, *6*, 720–726.



Scheme 1.10 *Anti*-Markovnikov fluorination by Nicewicz

Many other transformations using the concept of photoredox catalysis in combination with other catalysts have also been developed.[16]

1.6 Conclusion

In this short overview of cooperative catalysis, various reactions using different acid/acid, acid/base, and or base/base cooperative catalyst combination have been briefly introduced. As the field of cooperative catalysis develops, hydrogen bonding catalysis as well as photoredox catalysis are incorporated to provide different mode of activation. Cooperative catalyst system gives more access to otherwise less reactive intermediates and thus opened more possible reaction pathways. Yet, the inherent challenge of mutual quenching among catalysts and substrates still prevents the discovery of general methods and subsequently apply in synthesis of useful compounds.

[16] a) Twilton, J.; Le, C.; Zhang, P.; Shaw, M. H.; Evans, R. W.; MacMillan, D. W. C. *Nat. Rev. Chem.* **2017**, *1*, 0052; b) Prier, C. K.; Rankic, D. A.; MacMilan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322–5363; c) Milligan, J. A.; Phelan, J. P.; Badir, S. O.; Molander, G. A. *Angew. Chem., Int. Ed.* **2019**, *58*, 6152–6163.

CHAPTER TWO α-C–H Alkynylation of *N*-Alkylamines by Cooperative Actions of $B(C_6F_5)_3$ and Organocopper Complex: Applications in Late-Stage Functionalization and Stereoselective Synthesis

2.1 Introduction

Development of efficient and selective C–C bond forming reactions is important in organic synthesis.[1] Substitution reactions, nucleophilic additions and Friedel-Crafts reactions represent some of the traditional methods to build complexity through the formation of C–C bonds.[2] Over the years, scientists have developed transition metal catalyzed reactions for C–C bond formation, one of which being cross coupling reactions. However, it sometimes requires prefunctionalization or preactivation of the starting materials, which will need at least one step synthesis before using and generates stoichiometric amount of metal salt byproduct. Therefore, the route involving direct C–H bond activation and subsequent C–C bond formation is more attractive.[3]

Various methods of α-amino C(sp^3)–H bond activation by transition metal complexes have been reported by different groups.[4] Here are some selected examples by different activation modes.

The Davies reported an enantioselective C–H activation by the use of Rh-based catalyst (Scheme 2.1).[5] *N*-Boc protected cyclic amine **2.1** and methyl phenyldiazoacetate **2.2** with the use of 1.0 mol% of Rh prolinate catalyst through rhodium-carbenoid insertion intermediate **I** afford the alkylated product **2.3** in 72% yield, 96:4 dr and 97:3 er. Even though high diastereoselectivity and enantioselectivity were achieved, the reaction required a Rh dimer catalyst and a diazo compound for the generation of carbene.

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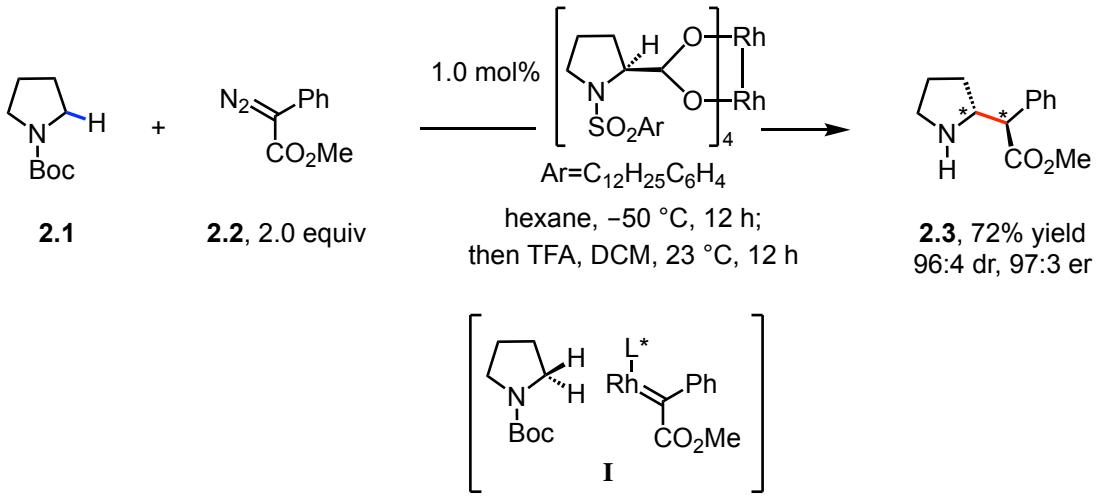
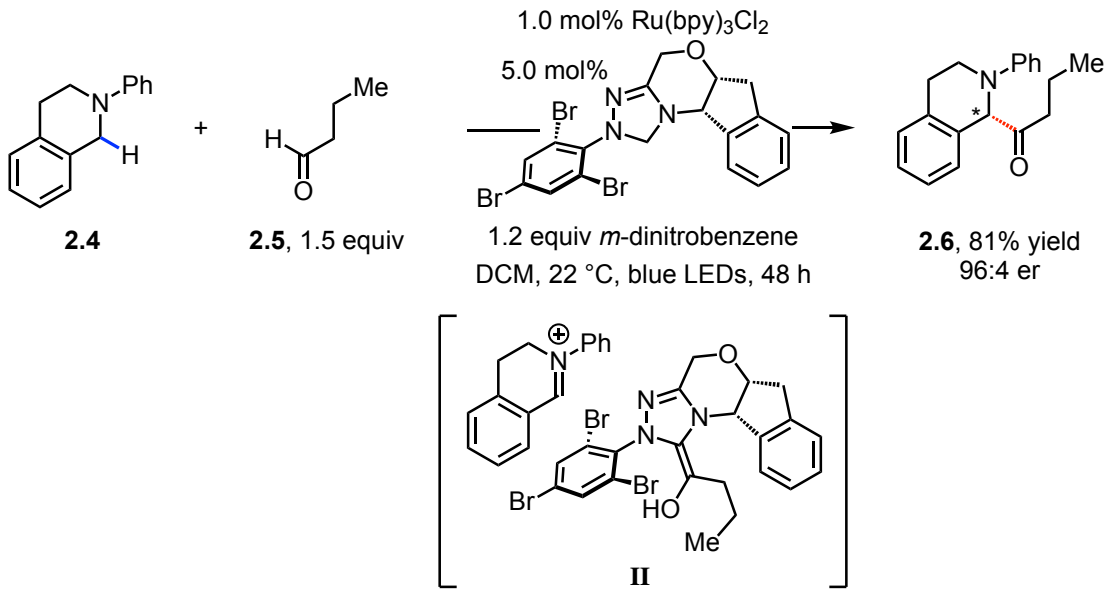
[1] Corey, E.J.; Cheng, X.M. *The Logic of Chemical Synthesis;* John Wiley & Sons: New York, **1989**; pp 1–91.
[2] Fleming, I. *Pericyclic Reactions*; Oxford University Press: New York, **1999**; pp 1–89.
[3] Li, C-J. *Acc. Chem. Res.* **2009**, *42*, 335–344.
[4] a) Shaw, M. H.; Shurtleff, V. W.; Terrett, J. A.; Cuthbertson, J. D.; MacMillan, D. W. C. *Science* **2016**, *352*, 1304–1308; b) McQuaid, K. M.; Sames, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 402–403; c) Murarka, S.; Deb, I.; Zhang, C.; Seidel, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 13226–13227; d) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069–1084; e) Osberger, T. J.; Rogness, D. C.; Kohrt, J. T.; Stepan, A. F.; White, M. C. *Nature* **2016**, *537*, 214–219; f) Chen, W.; Ma, L.; Paul, A.; Seidel, D. *Nat. Chem.* **2018**, *10*, 165–169; g) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417–424.
[5] Davies, H. M. L.; Venkataramani, C.; Hansen, T.; Hopper, D. W. *J. Am. Chem. Soc.* **2003**, *125*, 6462–6468.



Scheme 2.1 Enantioselective α-amino C–H activation by Rh-prolinate catalyst by Davies

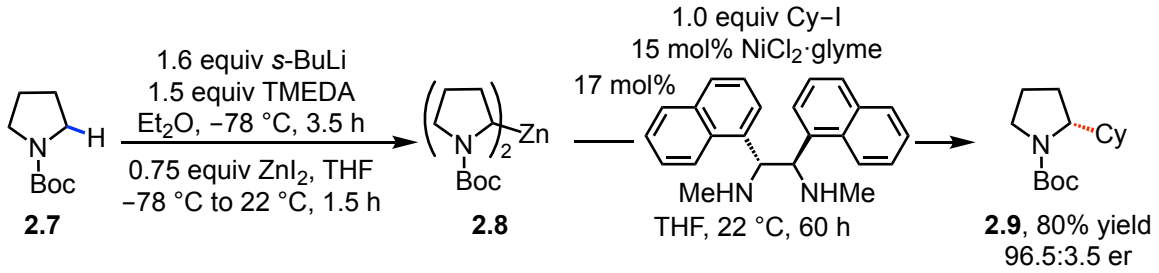
In 2006, Rovis reported an enantioselective α-acylation of tertiary amines facilitated by the combination of photoredox catalysis and NHC catalysis (Scheme 2.2).[6] *N*-Phenyl tetrahydroisoquinoline **2.4** and butanal **2.5** gave acylated product **2.6** in 81% yield and 96:4 er with the use of 1.0 mol% of $Ru(bpy)_3Cl_2$, 5.0 mol% of an aminoindanol-derived NHC, and 1.2 equiv of weak organic oxidant *m*-dinitrobenzene under blue LED in 48 h. Single electron oxidation by $[Ru(bpy)]^{3+}$, from excited $[Ru(bpy)]^{2+}$, followed by hydrogen atom abstraction generates iminium ion (**II**). Interactions between the NHC catalyst and the aldehyde substrate result in a Breslow intermediate (**II**), which can undergo subsequent nucleophilic attack to the iminium ion to afford the product. The scope of the reaction is limited to *N*-aryl tetrahydroisoquinolines and alkyl aldehydes. In addition, the reaction takes 48 h to only give moderate yield.

[6] DiRocco, D. A.; Rovis, T. J. *J. Am. Chem. Soc.* **2012**, *134*, 8094–8097.



Scheme 2.2 Enantioselective *a*-amino acylation by Rovis

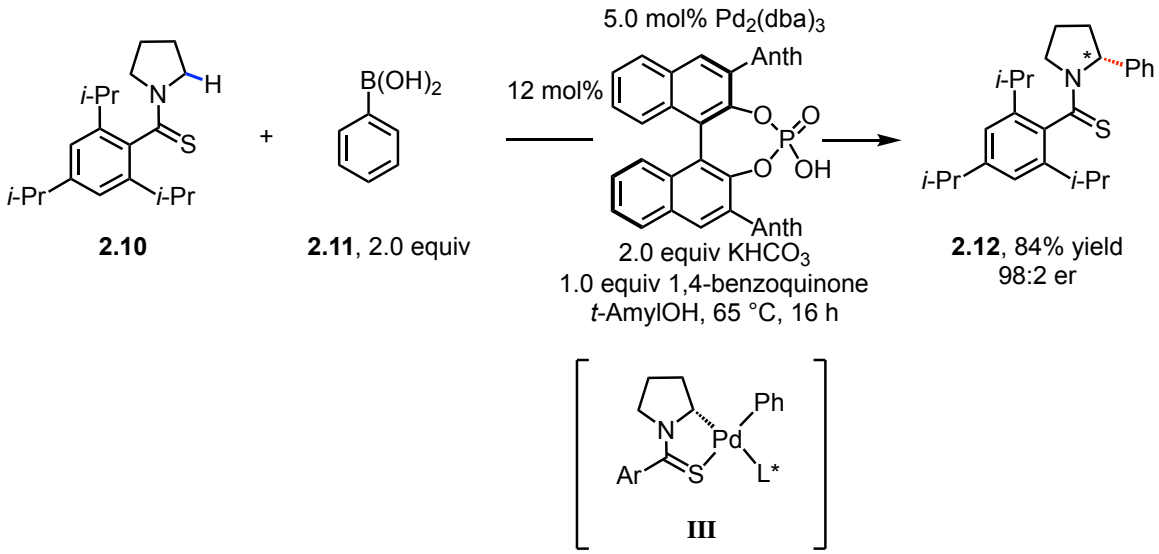
Fu reported a catalytic enantioselective Negishi cross-coupling of α-zincated *N*-Boc pyrrolidine with secondary halides in 2013.[7] The organozinc reagent **2.8** is first prepared by lithiation of *N*-Boc pyrrolidine **2.7** with 1.6 equiv of *s*-BuLi and 1.5 equiv of donor ligand TMEDA and then followed by addition of 0.75 equiv of ZnI_2 at –78 °C. It is then subjected to 1.0 equiv of cyclohexyl iodide with 15 mol% of $NiCl_2$·glyme and 17 mol% of chiral diamine ligand in one pot to form alkylated product **2.9** in 80% yield and 96.5:3.5 er. Although the reaction can be performed in one pot, it needs preparation of organozinc reagent by the use of volatile dangerous lithium reagent in cryogenic conditions to only give 0.75 equiv of the desired compound. Furthermore, the Nigeishi cross-coupling step needs high catalyst loading and long reaction time.



Scheme 2.3 Enantioselective Negishi cross-coupling by Fu

[7] Cordier, C. J.; Lundgren, R. J.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 10946–10949.

Yu reported an enantioselective thioamide directed α-amino C–H arylation by the use of Pd-based catalyst and chiral phosphoric acid in 2017 (Scheme 2.4).[8] Thioamide **2.10** and 2.0 equiv of phenyl boronic acid **2.11** were treated with 5.0 mol% $Pd(dba)_3$, 12 mol% of chiral phosphoric acid, 2.0 equiv of $KHCO_3$, and 1.0 equiv of 1,4-benzoquinone to afford arylated product **2.12** in 84% yield and 98:2 er. The palladium ligand complex forms a five-membered palladacycle with thioamide **2.10** (**III**). Although high regioselectivity is achieved by directing group, the starting material requires an additional step to synthesize and the removal of directing group needs two steps, reduction of S=C to CH_2 and debenzylation, to reveal the amine.



Scheme 2.4 Enantioselective thioamide directed α-amino C–H arylation by Yu

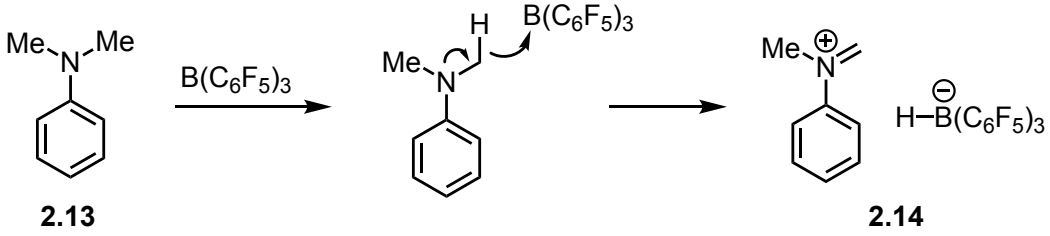
These transformations, although provide α-functionalized amines, either require the use of precious transition metal-based catalysts, such as (Rh, Ru, or Pd), or need stoichiometric amount of dangerous lithium reagent. In addition, they often require long reaction time, as shown in the case of Rovis and Fu, 48 and 60 h respectively.

There were no good general methodd for the functionalization of α-amino C–H bonds. We wanted to develop a new catalyst system, where we could achieve catalytic α-amino C–H functionalization with the use of more economical catalyst and mild condition.

[8] Jain, P.; Verma, P.; Xia, G.; Yu, J.-Q. *Nat. Chem.* **2017**, *9*, 140–144.

Cooperative catalyst systems have been developed over the years, which circumvents pre-activation from using stoichiometric transition metals.[9] These catalysts are capable of activating the nucleophile and electrophile precursors independently and simultaneously as discussed in Chapter One. Through covalent and non-covalent interactions, the catalyst brings the two substrates in close proximity and thus enhances the rate of reaction. However, self-quenching of the acidic and basic functional groups in from the catalyst and substrates is one of its major limitations. The use of weak acid or base catalyst can only activate highly base or acid sensitive substrates, which further limits the scope of transformation. The approach of incorporating the concept of Frustrated Lewis pairs (FLP) into cooperative catalysts, which consists of a Lewis acid and Lewis base pair, can help to overcome mutual quenching due to steric hindrance.

FLP has been demonstrated that it can activate unreactive small molecules, such as H_2, CO, and CO_2.[10] Furthermore, in 2002, the group of Basset has shown that $B(C_6F_5)_3$ can abstract hydride from α-amino position on dimethylaniline **2.13** to give an ion pair of iminium and borohydride **2.14** (Scheme 2.5).[11]



2.13 **2.14**

Scheme 2.5 Formation of FLP consisting of iminium ion and borohydride

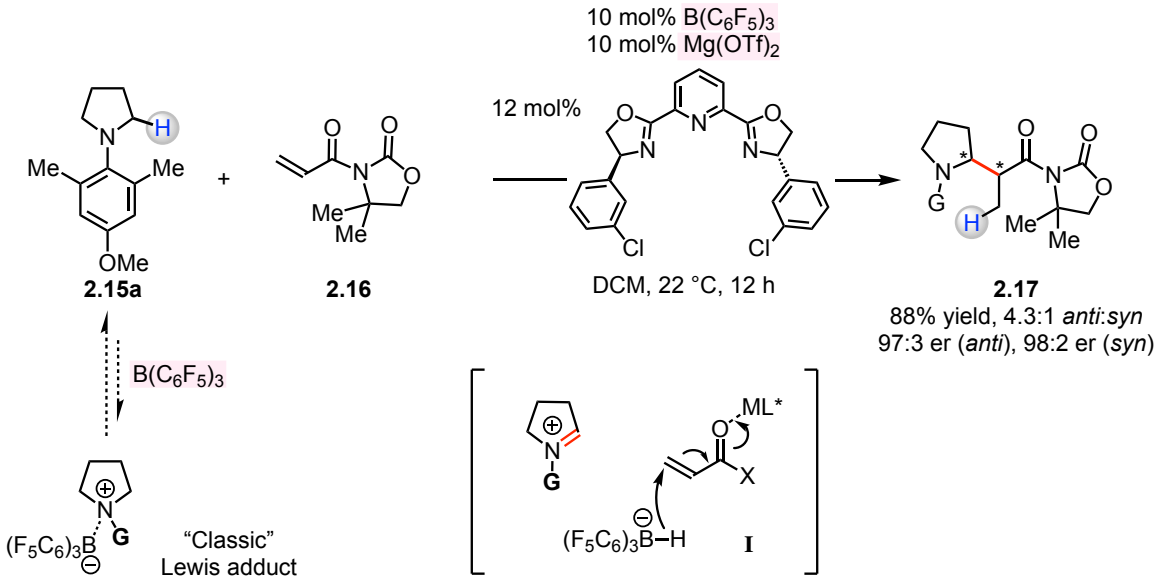
Our group was inspired by this chemistry and developed an α-amino alkylation reaction by the use of achiral and chiral Lewis acid catalysts, which function cooperatively

[9] a) Cooperative Catalysis: Designing Efficient Catalysts for Synthesis; Peters, R., Ed.; Wiley-VCH: New York, **2015**. b) van den Beuken, E. K.; Feringa, B. L. *Tetrahedron* **1998**, *54*, 12985–13011. c) Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924–1942. d) Matsunaga, S.; Shibasaki, M. *Chem Commun.* **2014**, *50*, 1044–1057. e) Trost, B. M.; Bartlett, M. J. *Acc. Chem. Res*. **2015**, *48*, 688–701. f) Wang, M. H.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2016**, *55*, 14912–14922.

[10] a) Stephan, D. W. *J. Am. Chem. Soc*. **2015**, *137*, 10018–10032. b) Stephan, D. W.; Erker, G. *Angew. Chem., Int. Ed.* **2015**, *54*, 6400–6441. c) Stephan, D. W. *Science* **2016**, *354*, aaf7229. d) Ashely, A. E.; O'Hare, D. *Top. Curr. Chem.* **2012**, *334*, 191–218.

[11] Millot, N.; Santini C.C.; Fenet, B.; Basset, J. M. *Eur. J. Inorg. Chem.* **2002**, 3328–3335.

(Scheme 2.6).[12] *N*-aryl pyrrolidine **2.15a** and α,β-unsaturated compound **2.16** with 10 mol% mold of $B(C_6F_5)_3$, 10 mol% of $Mg(OTf)_2$ and 12 mol% of chiral PyBOX ligand generate alkylated product **2.17** in 88% yield, 4.3:1 *anti*:*syn*, 97:3 er (*anti*), and 98:2 er (*syn*). The catalyst combination can avoid formation of "classic" Lewis acid adduct with a sterically hindered amine and generate iminium ion and borohydride by $B(C_6F_5)_3$-catalyzed hydride abstraction at the α-amino position. The iminium ion is then coupled with an in situ generated boron enolate from α,β-unsaturated compound to afford the α-alkylated amine in an enantioselective manner.



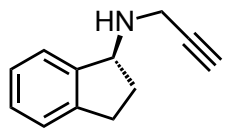
Scheme 2.6 $B(C_6F_5)_3$ and magnesium complex catalyzed alkylation through α-amino C–H activation

Since it has been shown that an iminium intermediate can be generated efficiently and $B(C_6F_5)_3$ can work cooperatively with a Lewis acid metal complex, we envisioned the development of various transformations with different nucleophilic coupling partners.

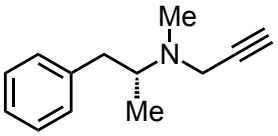
[12] Shang, M.; Chan, J. Z.; Cao, M.; Chang, Y.; Wang, Q.; Cook, B.; Torker, S.; Wasa, M. *J. Am. Chem. Soc.* **2018**, *140*, 10593–10601.

2.2 Background

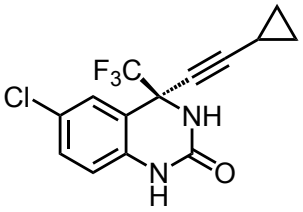
Propargylamines are one of the commonly found moieties in pharmaceuticals such as these molecules shown in Fig. 2.1.[13] Intermediates containing propargyl amines are as well useful for the synthesis of bioactive molecules.[14]



Rasagiline
(treatment for Parkinson's disease)



Selegiline
(antidepressant)



DPC 961
(reverse transcriptase inhibitor)

Fig 2.1 Examples of propargyl amines in bioactive molecules

Enantio-enriched propargylamines are commonly synthesized through addition of organometallic alkyne complexes to preformed imines or by a three-compounent coupling reactions.[15] However, because of poor electrophilicity of imines comparing to aldehydes, aryl or other electron rich protecting groups, such as *p*-methoxyphenyl, tosyl, or diphenylphosphinoyl, among others, are installed to activate imines. Furthermore, strongly basic, stoichiometric nucleophilic metal alkynyl species generated from organolithium, Grignard reagent, or LDA, are used, which are incompatible with base sensitive substrates and difficult to control enantioselectivity.

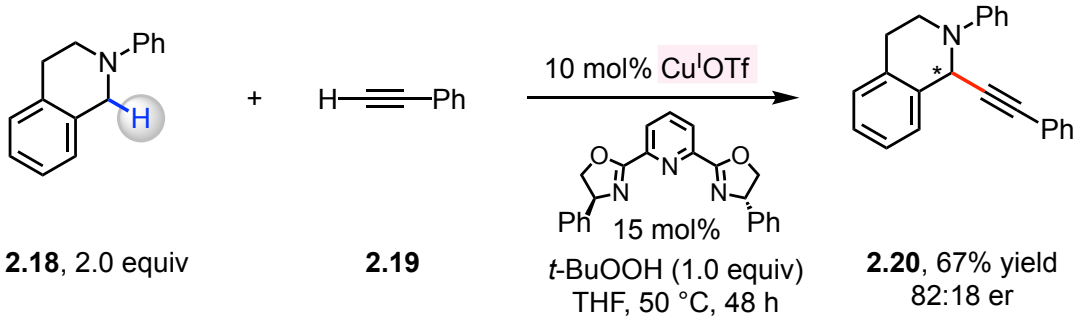
A solution to a more general method with broader scope of substrate would be incorporating more reactive iminium intermediate and generation of nucleophilic metal alkynyl species in situ from suitable metal precursors. In 2004, the Li group reported an enantioselective alkynylation to the benzylic α-amino C–H of *N*-phenyl

[13] a) Chen, J.J.; Swope, D. M. *J. Clin. Pharmacol.* **2005**, *45*, 878–894. b) Birks. J.; Flicker, L. *Cochrane Database of Systematic Reviews* **2003**, Issue 1. Art. No.: CD000442. DOI: 10.1002/14651858.CD000442. c) Li, S.; Ma, J. A. *Chem Soc Rev.* **2015,** *44*, 7439-48.

[14] a) Ermolat'ev, D. S.; Bariwal, J. B.; Steenackers, H. P. L.; De Keersmaecker, S. C. J.; Van der Eycken, E. V. *Angew. Chem., Int. Ed*., **2010**, *49*, 9465–9468. b) Arshadi, S.; Vessally, E.l Edjlali, L.; Hosseinzadeh-Khanmiri, R.; Ghorbani-Kalhor, R. Beilstein *J. Org. Chem.* **2017**, *13*, 625–638.

[15] a) Friestad, G.K.; Mathies, A.K. *Tetrahedron* **2006**, *63*, 2541–2569. b) Yamada, K.; Tomioka, K. *Chem. Rev*. **2008**, *108*, 2874–2886. c) Zani, L.; Bolm, C. *Chem. Commun.* **2006**, 4263–4275. d) Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963–983. e) Lauder, K.; Toscani, A.; Scalacci, N.; Castagnolo, D. *Chem. Rev.* **2017**, *117*, 14091–14200.

tetrahydroisoquinolines **2.18** with phenylacetylene **2.19** by the use of Cu^{I}-PyBOX complex with stoichiometric external oxidant *t*-BuOOH (Scheme 2.4).[16] However, this method and other similar strategies are confined to the use of activated tetrahydroisoquinoline structure and phenylacetylenes, producing moderate yield and enantioselectivity in long reaction hours.



Scheme 2.4 Enantioselective *α*-amino C–H alkynylation of tetrahydroisoquinolines

Given these limitations, we envision a more general method that does not require the use of external oxidant and targets *α*-amino C–H bonds from trialkyl amines to synthesize propargyl amines. Since *α*-amino C–H bonds of bioactive *N*-alkylamines constitute over 50% of the top selling commercial drugs, and estimated that 26% of all drugs and agrochemicals contains trialkyl amine moieties,[17] we would like our method to be applicable to such existing well streamlined molecules. The alkyne unit on bioactive molecules can serve as a handle for late-stage diversification.[9e] Catalytic coupling of *α*-amino C(sp^3)–H bonds and alkyne is an attractive strategy to provide propargylamines.

2.3 Development of Alkynylation Reaction

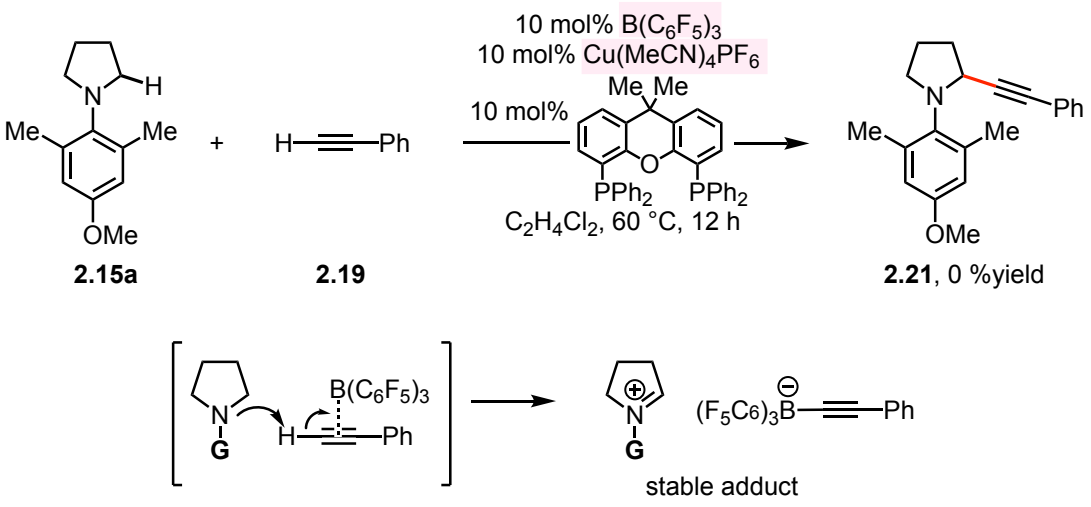
2.3.1 Discovery

From our previously discussed section 2.1 (Scheme 2.6), iminium ion can be generated in situ through cooperative actions of sterically hindered amine and $B(C_6F_5)_3$, which affords an electrophile. On the other hand, copper ligand complex is known to form nucleophilic copper alkynyl species with terminal alkyne. We hypothesized that if we were

[16] Li, Z.; Li, C.-J. *Org. Lett.* **2004**, *18*, 2982–2985.
[17] a) Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451–3479. b) Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W. *Chem. Soc. Rev.* **2016**, *45*, 546–576.

to make the two catalytic systems compatible, they might work cooperatively, and a C–C bond forming reaction might occur to afford propargyl amines.

The initial reaction was carried out with *N*-aryl pyrrolidine **2.15a**, which is known to generate iminium ion efficiently, and phenylacetylene **2.19**, known to form copper alkynyl species was reacted with 10 mol% of $B(C_6F_5)_3$, 10 mol% of $Cu(MeCN)_4PF_6$ and 10 mol% of Xantphos at 60 °C in $C_2H_4Cl_2$ (Scheme 2.8). After 12 hours, the reaction did not give the desired product. We reasoned that terminal alkyne can also interact with the sterically hindered amine and $B(C_6F_5)_3$ to form a stable adduct (Scheme 2.8), previously shown by Stephan, preventing the desired alkynylation reaction to proceed.[18] The iminium ion generated in situ is much shorter lived than the ones generated from tetrahydroisoquinolines, which is stabilized by the extended conjugated aromatic system. The shorter-lived iminium ion therefore has less probability to interact with the nucleophile that requires longer formation time.



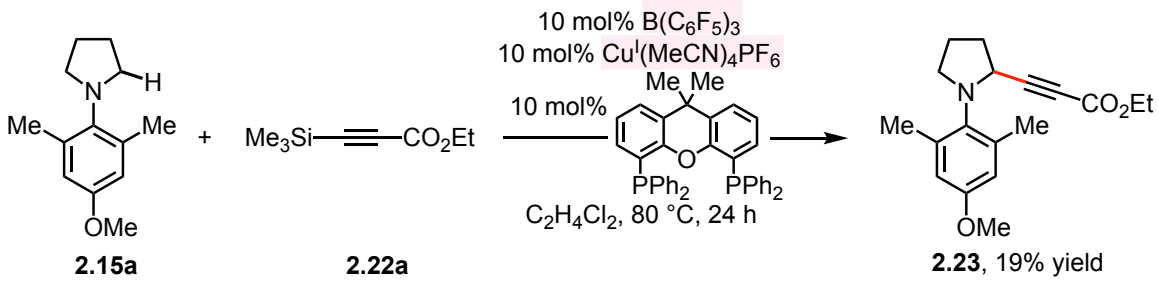
Scheme 2.8 Initial alkynylation reaction

2.3.2 Optimization

Next, we hypothesized that if we were to use a disubstituted alkyne that could transmetalate with copper, the desired copper alkynyl complex could also be afforded. From Hiyama-Denmark cross coupling, it is known that silicon transmetalates with copper efficiently. We found that with trimethylsilyl substituted alkyne **2.15a** under similar

[18] Dureen, M. A.; Stephan, D. W. *J. Am. Chem. Soc.* **2009**, *131*, 24, 8396–8397.

reaction conditions, the desired C–C bond forming product was generated in 19% yield. (Scheme 2.9)



Scheme 2.9 Reaction with silicon substituted alkyne

Potentially, similar to cross coupling reactions in general, homocoupling or desilylation reaction is happening faster than the C–C bond formation, leading to low yield of the desired compound. We hypothesized that $B(C_6F_5)_3$ could be interacting with silane from the reaction mixture. If $B(C_6F_5)_3$ is released faster, giving copper species less time to react with itself, the side reactions could be minimized.

In 2000, the Yamamoto group reported that catalytic $B(C_6F_5)_3$ and stoichiometric amount of silane can reduce alcohols to alkanes and form silanols as byproducts.[19] This could be a potential method to decompose silane generated byproducts and release $B(C_6F_5)_3$. The proposed catalytic cycle to turnover $B(C_6F_5)_3$ and trimethylsilane is shown in Fig 2.2. $B(C_6F_5)_3$ and trimethylsilane form intermediate **I**. Addition of alcohol gives intermediate **II** and then after release of trimethylsilanol, it affords carbocation and borohydride intermediate **III**. Lastly, alkane is produced as the product and $B(C_6F_5)_3$ is released to turn over the catalytic cycle.

[19] Gevogyan, V.; Rubin, M.; Benson, S.; Liu, J-X.; Yamamoto, Y. *J. Org. Chem.* **2000**, 65, 6179–6186.

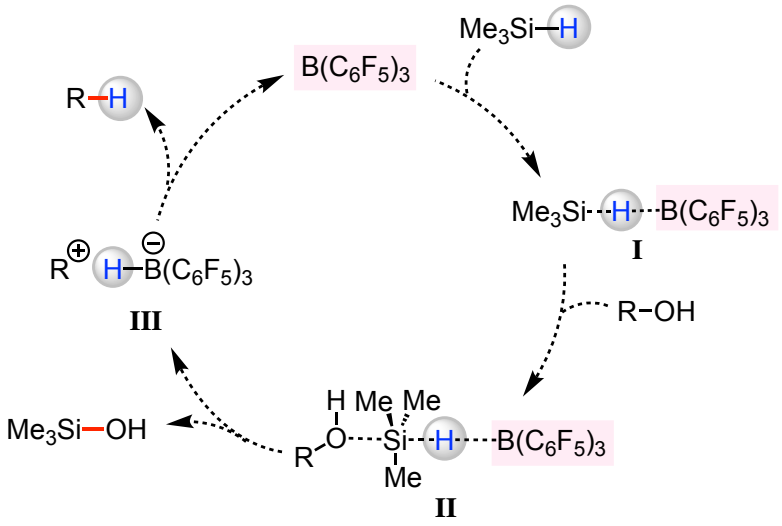
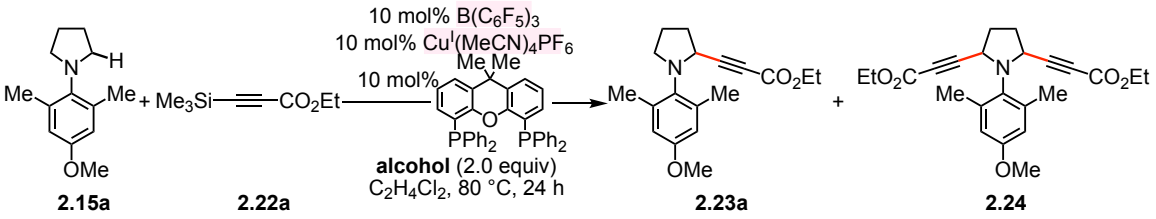


Figure 2.2 $B(C_6F_5)_3$-Catalyzed reduction of alcohols and cleavage of aryl and alkyl ethers with hydrosilanes

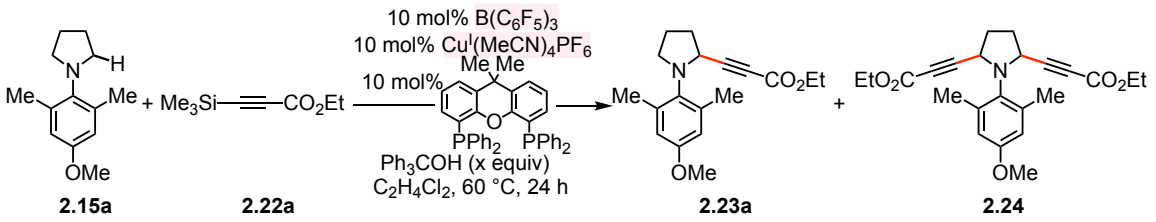
Different alcohols were evaluated to see if it would influence the yield of product. As the sterics increased from isopropanol **A1** to *t*-BuOH **A3**, the yield of mono product **2.23a** increased from 26% to 64%. Higher yield from *t*-BuOH than isopropanol could be explained by the generation of a more stable carbocation from *t*-BuOH. Benzylic carbocations are more stabilized than alkyl carbocations through delocalization through phenyl rings. Phenyl substituted alcohols were then tested: benzyl alcohol **A4** afforded 34%, benzhydrol **A5** 28% and triphenylmethanol **A6** gave 52% yield of **2.23a** and 34% yield of **2.24**. Adamantol **A7** produced 93% of **2.23a** and <5% yield of **2.24** (Table 2.1).



none **2.23a**, 19% yield **2.24**, 0% yield	**A1** **2.23a**, 26% yield **2.24**, 0% yield	**A2** **2.23a**, 50% yield **2.24**, 8% yield	**A3** **2.23a**, 64% yield **2.24**, 5% yield
A4 **2.23a**, 34% yield **2.24**, 0% yield	**A5** **2.23a**, 28% yield **2.24**, 0% yield	**A6** **2.23a**, 52% yield **2.24**, 34% yield	**A7** **2.23a**, 93% yield **2.24**, <5% yield

Table 2.1 Evaluation of alcohols

When temperature is lowered to 60 °C, triphenylmethanol **A6** gave higher yield than adamantol **A7**, with 52% of **2.23a** and 34% of **2.24** (Table 2.2, entry 1). Lowering the loading of triphenylmethanol to 1.0 equivalent reduces the amount of di-addition product and reducing the reaction time further reduced the formation of **2.24** (<5%), giving **2.23a** in 90% yield (Table 2.2, entry 2 and 3). Reducing the amount of catalyst loading gave lower yields of the product (Table 2.2, entry 4). No product was observed without catalyst, or when less hindered BF_3 or less Lewis acidic BPh_3 were used (Table 2.2, entries 5-7).



entry	Lewis acid (mol%)	equiv of Ph_3COH	yield (%)	
			2.23a	**2.24**
1	$B(C_6F_5)_3$ (10)	2	52	34
2	$B(C_6F_5)_3$ (10)	1	83	15
3*	$B(C_6F_5)_3$ (10)	1	90	<5
4	$B(C_6F_5)_3$ (5)	1	81	<5
5	none	1	0	0
6	$BF_3{\cdot}OEt_2$ (10)	1	0	0
7	BPh_3 (10)	1	0	0

* Reaction mixture was stirred for 12 h

Table 2.2 Optimization table

2.3.3 Proposed catalytic cycle

From the above results, our proposed catalytic cycle is presented in Fig 2.3. $B(C_6F_5)_3$ could receive a hydride from *N*-alkylamine **2.15**, giving iminium and borohydride ion pair (**I**). Cu(I)-complex could coordinate with trimethyl substituted alkyne **2.22**. Transmetalation between copper and silicon affords copper alkynyl species and release of trimethylsilane, which is then quenched by triphenylmethanol to give trimethylsilanol and triphenylmethane following cycle proposed in Fig 2.2. Subsequently, C–C bond formation between iminium and copper alkynyl complex (**III**) affords product **2.14** and regenerate the catalysts to close the catalytic cycle.

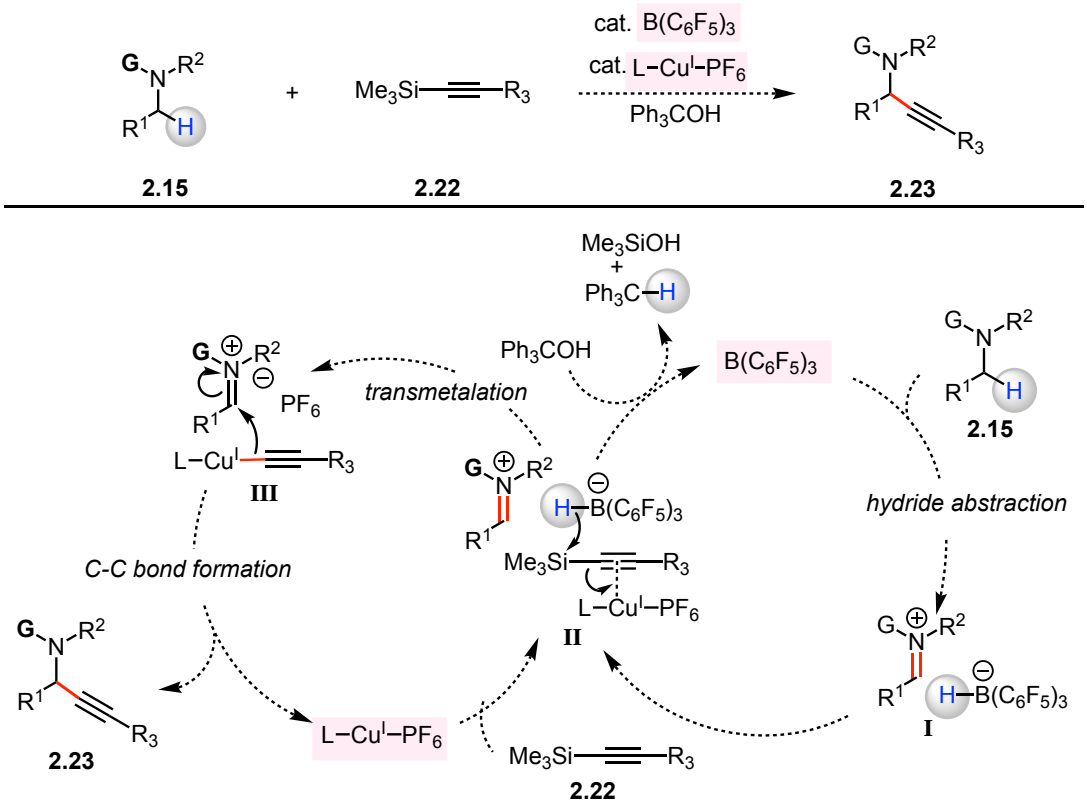
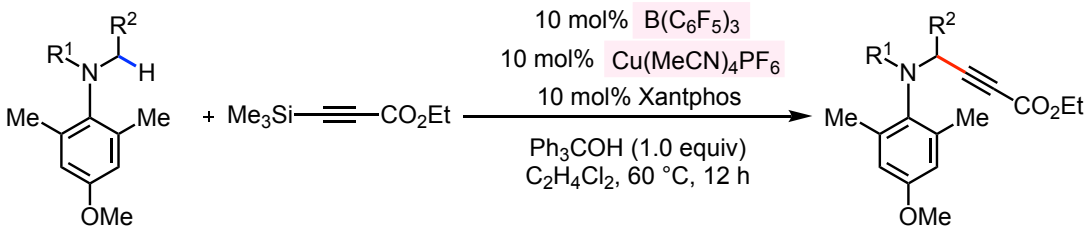


Fig 2.3 Proposed catalytic cycle

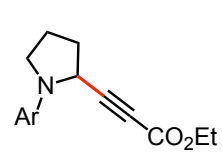
2.4 Evaluation of Substrates

2.4.1 *N*-aryl substituted amines

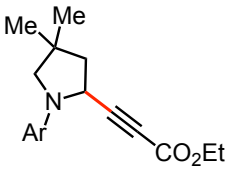
Different cyclic and acyclic *N*-aryl substituted substrates were subjected under the same reaction conditions (Table 2.3). *N*-aryl pyrrolidines derivatives afforded products **2.23a** and **2.23b** in 90% yield and 77% yield respectively, and *N*-aryl azepane **2.15c** gave 77% yield of isolated product. Acyclic *N*-aryl substrate **2.15d** generated the mono-addition product **2.23d** in 90% yield, with less than 5% yield of di-addition product. For *N*-ethyl and *N*-benzyl substituted *N,N*-arylmethyl substrates, alkyne predominantly adds to *N*-methyl site, giving **2.23e** in 42% yield and **2.23f** in 70% yield.



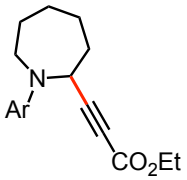
2.15, 0.2 mmol **2.22a,** 0.3 mmol **2.23**



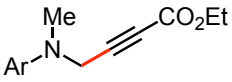
2.23a, 90% yield



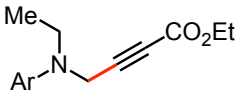
2.23b, 77% yield



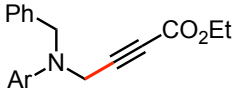
2.23c, 77% yield



2.23d, 90% yield



2.23e, 42% yield

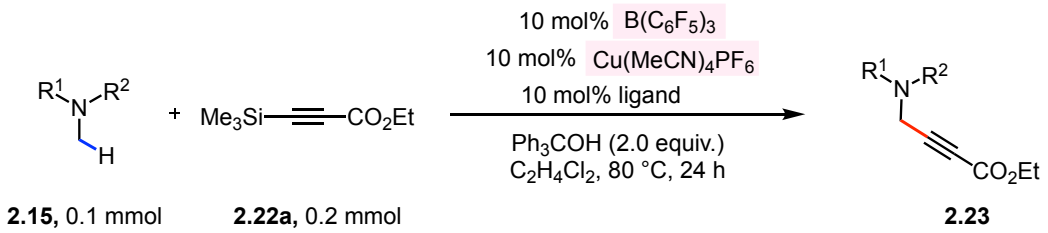


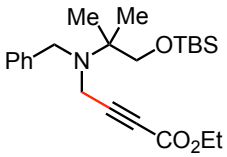
2.23f, 70% yield

Table 2.3 Alkynylation of *N*-aryl amines

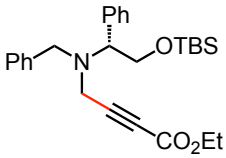
2.4.2 Trialkylamines

We wanted to perform alkynylation on trialkylamines, because eventually we would like to apply our methods to N-containing drug molecules. When Xantphos was used as the ligand for trialkylamines, it gave 11-28% yield of propargylamines (Table 2.4). Dppe was identified to be the optimal ligand after evaluation. We reasoned that since these trialkylamines are more sterically hindered than *N*-aryl amines, a more flexible ligand dppe is required than the more structurally more rigid ligand Xantphos. With dppe, **2.23g** is obtained in 76% yield. Noticeably, larger groups around the amine gives higher yield of product, **2.23h** with benzyl substituent (86% yield) and **2.23i** with benzhydryl substituent (97% yield) (Table 2.4).

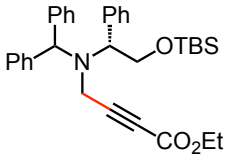




with Xantphos: **2.23g,** 28% yield
with dppe: **2.23g**, 76% yield



with Xantphos: **2.23h,** 11% yield
with dppe: **2.23h**, 86% yield

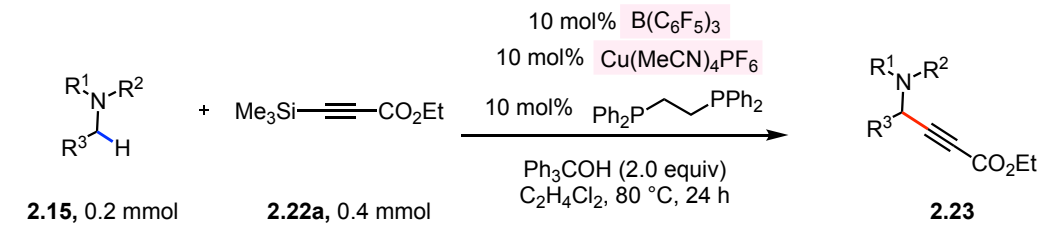


with Xantphos: **2.23i,** 24% yield
with dppe: **2.23i**, 97% yield

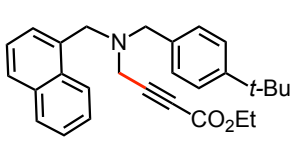
Table 2.4 Alkynylation of trialkylamines

2.4.3 Functionalization of N-containing drug molecules

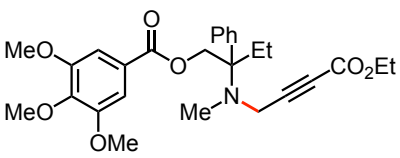
Butenafine **2.15j** and trimebutine **2.15k** can be alkynylated in 76% yield and 71% yield respectively. Secondary amine drug molecules are protected with benzhydryl groups, derivatives of atomoxetine **2.15l**, nortriptyline **2.15m**, duloxetine **2.15n**, and sertraline **2.15o** to give the desired product in 56% to 74% yield (Table 2.5). Ether, ester, thiophene, and chlorides are tolerated in this reaction condition.



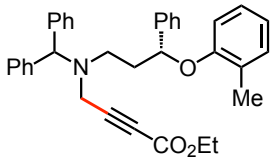
2.15, 0.2 mmol **2.22a,** 0.4 mmol **2.23**



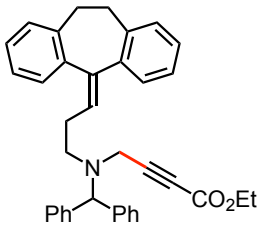
2.23j, 76% yield
butenafine
(antifungal)



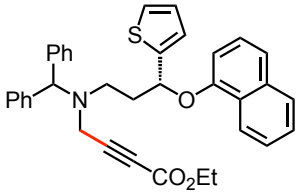
2.23k, 71% yield
trimebutine
(spasmolytic agent)



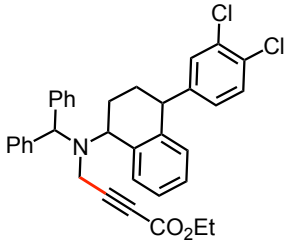
2.23l, 56% yield
atomoxetine derivative
(treatment for ADHD)



2.23m, 74% yield
nortriptyline derivative
(antidepressant)



2.23n, 68% yield
duloxetine derivative
(antidepressant)

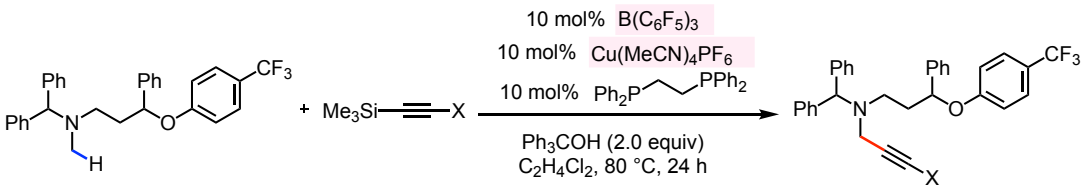


2.23o, 67% yield
sertraline derivative
(antidepressant)

Table 2.5 Alkynylation of N-containing drug molecules

2.4.4 Scope of alkynes

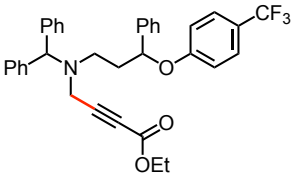
Using benzhydryl protected fluoxetine **2.15p**, we explored the scope of alkynes (Table 2.6). Ethyl ester, methyl ester, and amide are all tolerated and gave up to 80% yield (**2.25a**, **2.25b**, **2.25c**). The reaction of **2.15p** with ethyl ester alkyne **2.22a** could be scaled up to 1.0 g, giving alkynylated product **2.25a** in 93% yield after 48 h. Phenyl substituted (**2.25d**), as well as, electron rich chloro- (**2.25e**) and electron deficient trifluoromethyl groups (**2.25f**) are compatible with the system, generating the corresponding product with 75-82% yield. 2-Thiophene alkyne and trimethylsilyl substituted alkyne generated **2.25g** in 74% and **2.25h** 87% yield.



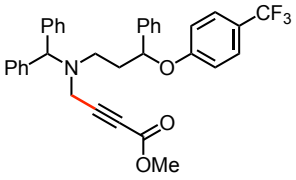
2.15p, 0.1 mmol
***N*-benzhydryl fluoxetine**
(antidepressant)

2.22, 0.2 mmol

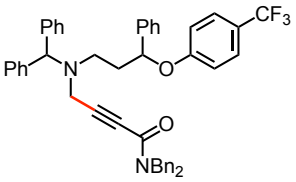
2.25



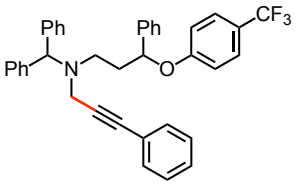
2.25a, 82% yield



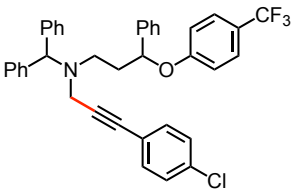
2.25b, 76% yield



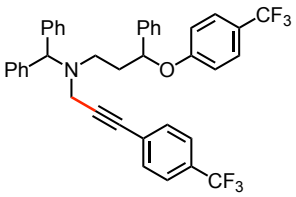
2.25c, 80% yield[a]



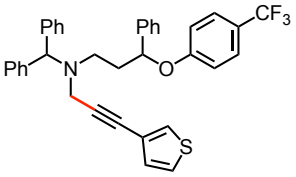
2.25d, 75% yield[a]



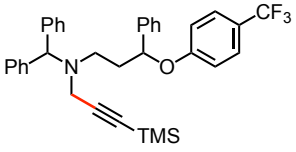
2.25e, 82% yield[a]



2.25f, 80% yield[a]



2.25g, 74% yield[a]



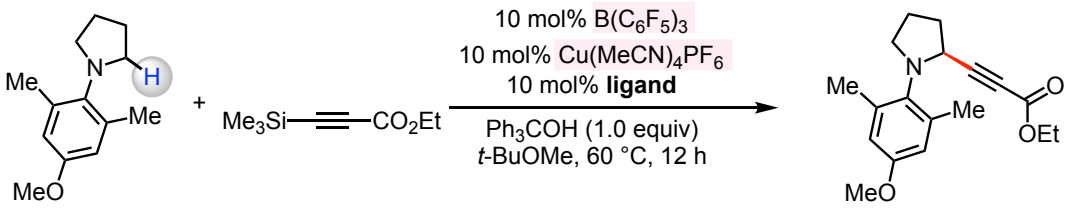
2.25h, 87% yield[a]

[a] (*S*)-Ph-PyBOX was used as the ligand

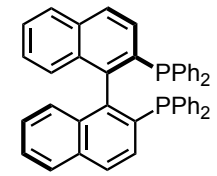
Table 2.6 Scope of alkynes with benzhydryl fluoxetine derivative

2.4.5 Application towards enantioselective transformation

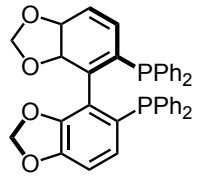
Chiral ligands of different scaffolds were screened (Table 2.7). Bis-phosphine ligands (**L1**-**L3**) gave **(*S*)-2.23a** in 61-89% yield, but the enantioselectivity is low, with the highest 45:55 er. Bis-oxazoline ligands of different backbones (**L4**-**L6**) were then tested. PyBOX ligand **L6** gave the highest yield, 84% and highest er, 82:18.



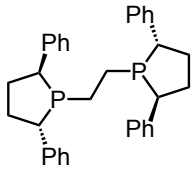
2.15a, 0.1 mmol **2.22a**, 1.5 equiv (*S*)-**2.23a**



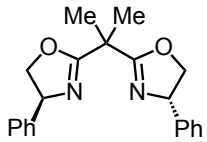
L1
(*S*)-**2.23a**, 61% yield
49:51 er



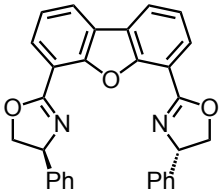
L2
(*S*)-**2.23a**, 89% yield
49:51 er



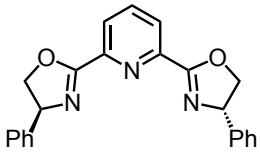
L3
(*S*)-**2.23a**, 70% yield
45:55 er



L4
(*S*)-**2.23a**, 53% yield
48:52 er



L5
(*S*)-**2.23a**, 6% yield
72:28 er



L6
(*S*)-**2.23a**, 84% yield
82:18 er

Table 2.7 Evaluation of chiral organocopper complexes

Since Ph-PyBox gave promising enantioselectivity, different substituents on the aromatic ring were then explored to see if it would influence the selectivity (Table 2.8). *meta*-Dimethyl substituted ligand **L7** gave **(*S*)-2.23a** in 89% yield and 90:10 er. *meta*-Substituted electron withdrawing trifluoromethyl ligand **L8** gave lowered yield (54%) and er (80:20). The yield and er improved significantly when more sterically more hindered 2,6-bis((*S*)-4- (3,5-dimethylphenyl)-4,5-dihydrooxazol-2-yl)pyridine (**L9**) was used, 75%

yield and 95:5 er. However, with more sterically hindered *meta*,*meta*-diethylphenyl- (**L10**) or more electron donating *meta*,*meta*-dimethoxyphenyl- (**L11**) substituted ligands showed diminished yield and enantioselectivity.

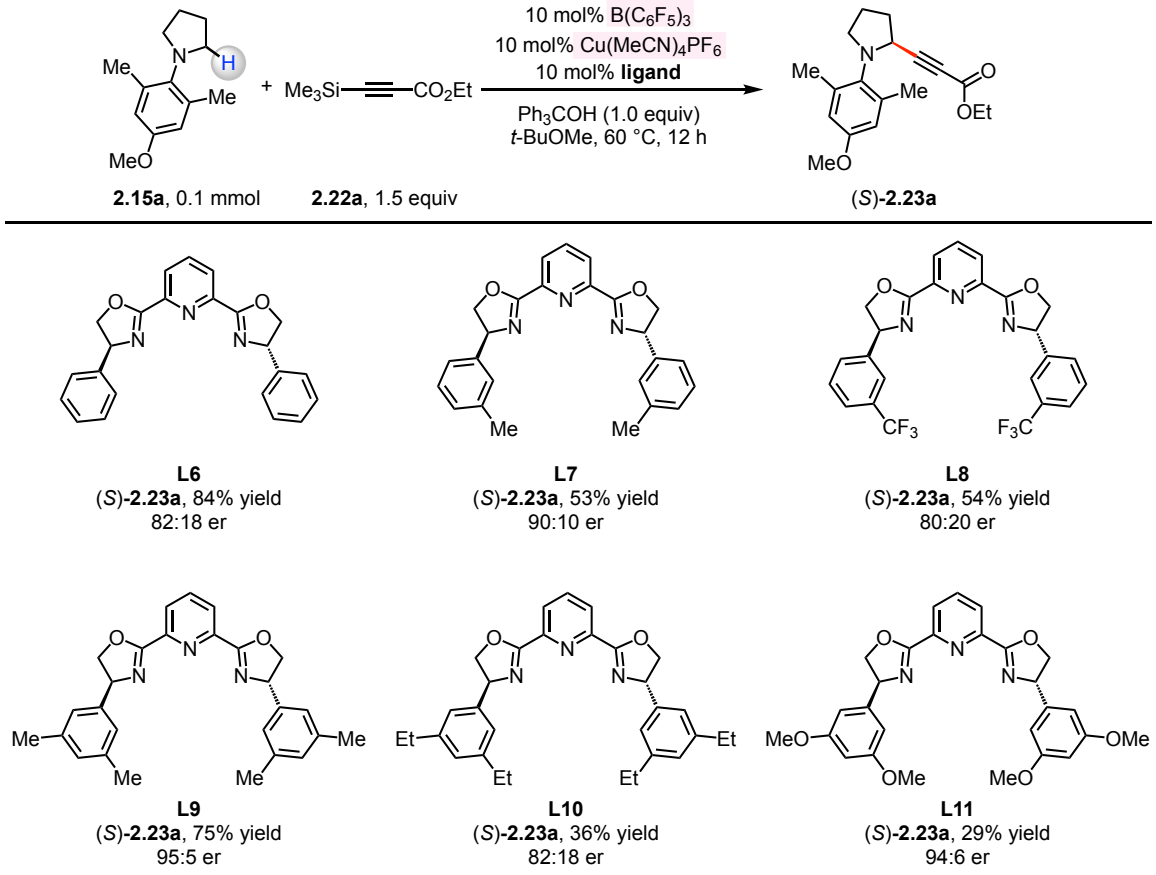
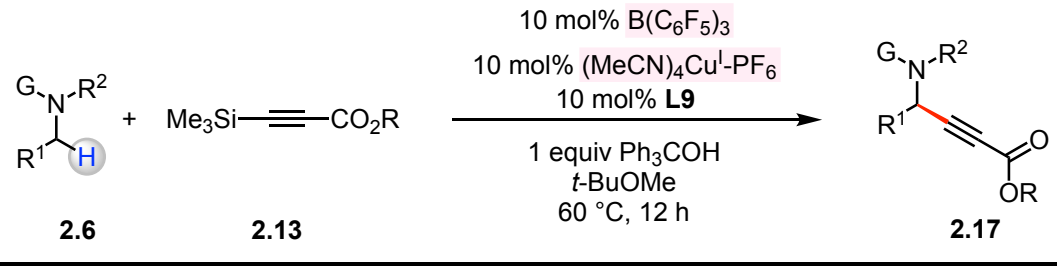
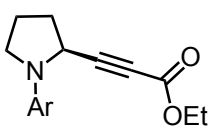


Table 2.8 Ph-PyBOX ligand evaluation

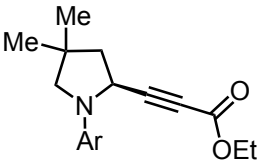
Using the optimal chiral ligand in combination with our conditions, various *N*-alkyl amines were tested for stereoselective alkynylation (Table 2.9). *N*-aryl pyrrolidines (**2.17a** and **2.17b**) and *N*-aryl azepane (**2.17c**) generated products in 64-75% yield and 95:5 to 93:7 er, while giving less than 5% di-alkynylated products. Only one regioisomer was observed for **2.17b**. The reaction of **2.6a** and **2.13a** could be scaled up to 1.0 mmol, with catalyst combination of 5.0 mol% of $B(C_6F_5)_3$, 5.0 mol% of $Cu(MeCN)_4PF_6$ and 5.0 mol% of **L9** in 72 h, affording **2.17a** in 95% yield and 95:5 er. α-Benzylic C–H bond could also be activated, giving product **2.17d** in 45% yield and 84:16 er. Alkynylation occurs at less

sterically hindered position for pyrrolidine with subsituents, giving **2.17e** and **2.17f** in 66% yield and 6.3:1 *trans*:*cis* and 64% yield and 11.8:1 *trans*:*cis*.

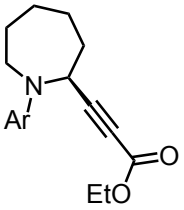




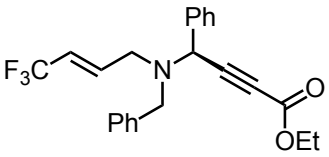
2.17a, 75% yield
95:5 er



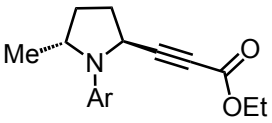
2.17b, 69% yield
7:93 er



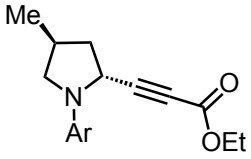
2.17c, 64% yield
95:5 er



2.17d, 45% yield
84:16 er



2.17e, 66% yield
6.3:1
83:17 er (trans isomer)

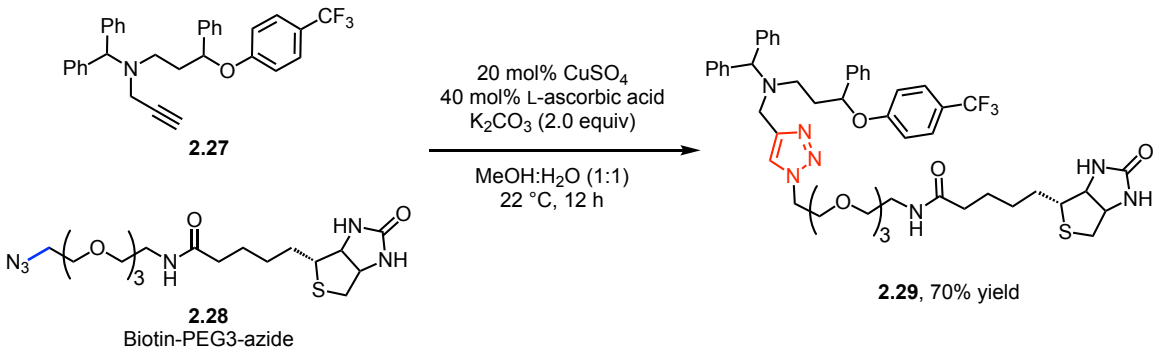


2.17f, 64% yield
11.8:1
97:3 er (trans isomer)

Table 2.9 Enantio- and diastereo-selective alkynylation of amines

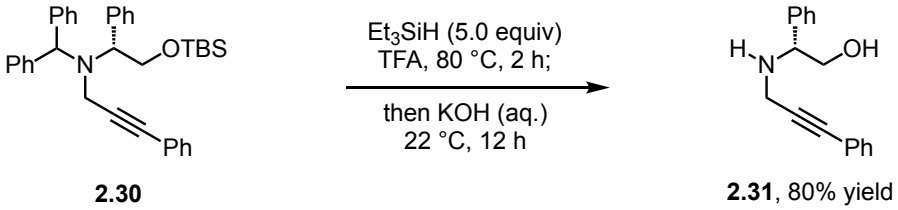
2.5 Further derivatization

Alkynylated product **2.25h** was treated with TBAF to remove trimethylsilyl group to expose the terminal alkyne **2.27**. It could be then subjected to Click reaction with biotin-PEG3-azide **2.28** to afford the triazole product **2.29** in 70% yield (Scheme 2.10).



Scheme 2.10 CuAAC reaction with fluoxetine derivative

Removal of benzhydryl group is demonstrated with propargyl amine **2.30** (Scheme 2.11). It is removed by using triethylsilane under acidic conditions, followed by basic work up. Under acidic conditions, TBS is also removed to afford the amino alcohol **2.31** in 80% yield.



Scheme 2.11 Removal of benzhydryl group

2.6 Conclusion

In summary, we have achieved alkynylation of α-amino C–H bonds by developing a cooperative catalyst system that avoids the use of stoichiometric, strong basic metal reagents or precious metal catalyst. We further applied our methods to late-stage functionalization of a range of N-containing drug molecules. The enantioselective variation of this transformation was also pursued. With our optimal ligand, we were able to achieve moderate to high enantioselectivity and high diastereoselectivity while not compromising the yield of reaction. Our cooperative catalyst system shows functional group tolerance of alkenes, esters, amides, ethers, as well as halogens, which are Lewis acids sensitive. Potentially, this catalyst system will provide the framework for future development in the late-stage stereoselective α-funcitonalization of bioactive amines.

2.7 Experimental data

2.7.1 General information

General experimental procedures. All reactions were performed in standard, dry glassware fitted with rubber septa under an inert atmosphere of nitrogen unless otherwise described. Stainless steel syringes or cannulae were used to transfer air- and moisture-sensitive liquids. Reported concentrations refer to solution volumes at room temperature. Evaporation and concentration *in vacuo* were performed using house vacuum (ca. 40 mm Hg). Column chromatography was performed with SiliaFlash® 60 (40–63 micron) silica gel from Silicycle. Thin layer chromatography (TLC) was used for reaction monitoring and product detection using pre-coated glass plates covered with 0.25 mm silica gel with fluorescent indicator; visualization by UV light (λ_{ex} = 254 nm) or $KMnO_4$ stain.

Materials. Reagents were purchased in reagent grade from commercial suppliers and used without further purification, unless otherwise described. Amines and trimethylsilyl propiolate compounds were prepared according to the procedures reported previously.[1] H_2O, in synthetic procedures, refers to distilled water. Tris(pentafluorophenyl)borane, $Cu(MeCN)_4PF_6$, Xantphos, and 1,2-bis(diphenylphosphino)ethane were purchased from TCI and used without further purification. Chiral ligands **L4-7**, **L10**, and **L14-19** were prepared according to the literature procedures.[5-8]

Instrumentation. Proton nuclear magnetic resonance (^{1}H NMR) spectra and proton-decoupled carbon nuclear magnetic resonance (^{13}C {^{1}H} NMR) spectra were recorded at 25 °C (unless stated otherwise) on Inova 600 (600 MHz), Varian Unity/Inova 500 (500 MHz) or Oxford AS400 (400 MHz) spectrometers at the Boston College nuclear magnetic resonance facility. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to 0 ppm. Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent. The peak positions are quoted to one decimal place unless they are indistinguishable. The solvent peak was referenced to 77.0 ppm for ^{13}C for $CDCl_3$.

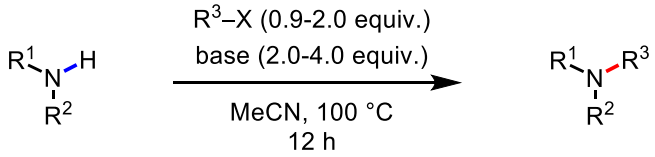
[1] (a) Chang, Y.; Yesilcimen, A.; Cao, M.; Zhang, Y.; Zhang. B.; Chan, J. Z.; Wasa, M. *J. Am. Chem. Soc.* **2019**, *141*, 14570–14575. (b) Kojima, R.; Akiyama, S.; Ito, H. *Angew. Chem., Int. Ed.* **2018**, *57*, 7196–7199. (c) Kraihanzel, C. S.; Losee, M. L. *J. Org. Chem.* **1968**, *33*, 1983–1986.

Benzotrifluoride was used as an external standard for ^{19}F NMR and referenced to 63.7 ppm. Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz). Infrared spectra were recorded on a Bruker FT-IR Alpha (ATR mode) spectrophotometer. Data are represented as follows: frequency of absorption (cm^{-1}).

High-resolution mass spectrometry was performed on a JEOL AccuTOF-DART (positive mode) at the Mass Spectrometry Facility, Boston College. Chiral HPLC analyses were carried using Agilent 1200 series instruments and Shimadzu chromatograph with Daicel CHIRALPAK® columns or Daicel CHIRALCEL® columns (internal diameter 4.6 mm, column length 250 mm, particle size 5 μm).

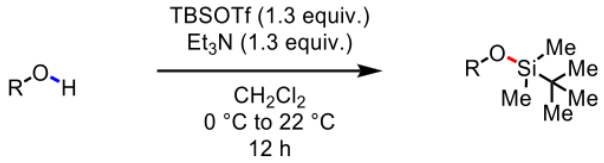
2.7.2 Experimental Procedures and Characterization of Substrates and Products

General Procedure for Preparation of Tertiary or Secondary Amines



Amines **S1**, **2.15l-p** and **2.15s-t** were prepared by alkylation of the corresponding primary or secondary amines. To a solution of amine (1.0 equiv) and K_2CO_3 or Et_3N (2.0–4.0 equiv) in MeCN was added alkyl halide (R^3–X; 0.9–2.0 equiv). The reaction mixture was allowed to stir at 100 °C for 12 h. Upon completion (determined by TLC), H_2O was added and the organic material was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The desired amine products were obtained after purification by flash silica gel column chromatography.

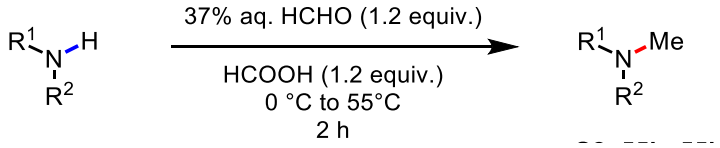
General Procedure for TBS Protection of Alcohols



Substrates **2.23g** and **S3** were prepared by TBS protection of alcohols. To a solution of alcohol in CH_2Cl_2 at 0 ° C, Et_3N (1.3 equiv) and TBSOTf (1.3 equiv) were added in a

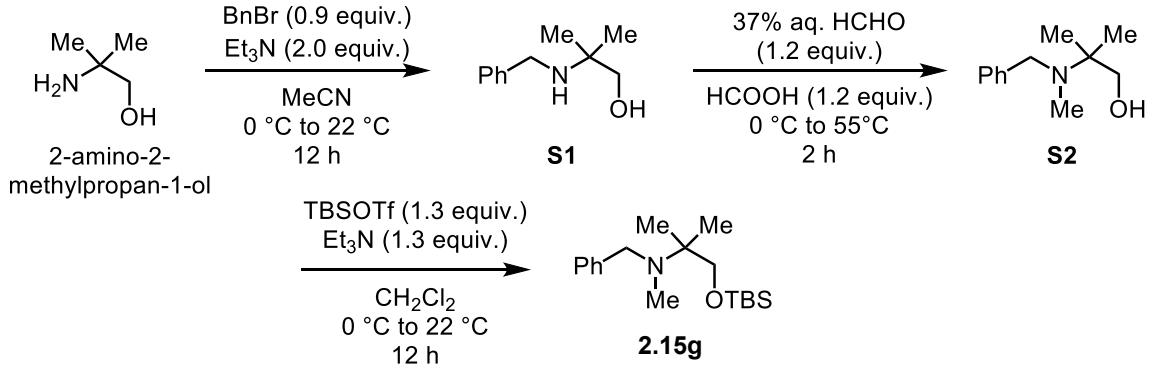
dropwise manner. After the addition, the reaction mixture was allowed to warm to 22 ° C and stirred for 12 h. Upon completion (determined by TLC), H_2O was added and the organic material was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The desired silyl ether products were obtained after purification by flash silica gel column chromatography.

General Procedure for *N*-Methylation of Secondary Amines



Substrates **S2**, **2.15h**, and **2.15i** were prepared by *N*-methylation of secondary amines. A solution of amine and formaldehyde (37% aq. solution, 1.2 equiv) was cooled to 0 °C. To the reaction mixture was added formic acid (1.2 equiv) in a dropwise manner. The reaction mixture was allowed to warm to 55 °C and stirred for 2 h. Upon completion (determined by TLC), the reaction mixture was cooled to 0 °C, NaOH (1.0 M aq. solution) was added until the aqueous layer was alkaline. The organic material was extracted with Et_2O (3 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The desired amine products were obtained after flash silica gel column chromatography.

Procedure for Preparation of *N*-Benzyl-1-((*tert*-butyldimethylsilyl)oxy)-*N*,2-dimethyl-propan-2-amine (2.15g)



2-(Benzylamino)-2-methylpropan-1-ol (S1)

2-(Benzylamino)-2-methylpropan-1-ol was prepared following **General Procedure for Preparation of Secondary Amines** using 2-amino-2-methylpropan-1-ol (69 mmol). The amine product **S1** was obtained after purification by flash silica gel column chromatography (EtOAc:hexanes = 1:1) as a colorless oil (9.0 g, 73% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 - 7.30 (m, 3H), 7.26 (d, *J* = 1.0 Hz, 2H), 3.69 (s, 2H), 3.35 (s, 2H), 1.15 (d, *J* = 1.0 Hz, 6H).

2-(Benzyl(methyl)amino)-2-methylpropan-1-ol (S2)

2-(Benzyl(methyl)amino)-2-methylpropan-1-ol was prepared following **General Procedure for *N*-Methylation of Secondary Amines** using 2-(benzylamino)-2-methylpropan-1-ol (20 mmol). The amine product **S2** was obtained after purification by flash silica gel column chromatography (EtOAc:Et_3N:hexanes = 20:1:79) as a colorless oil (2.0 g, 50% yield).

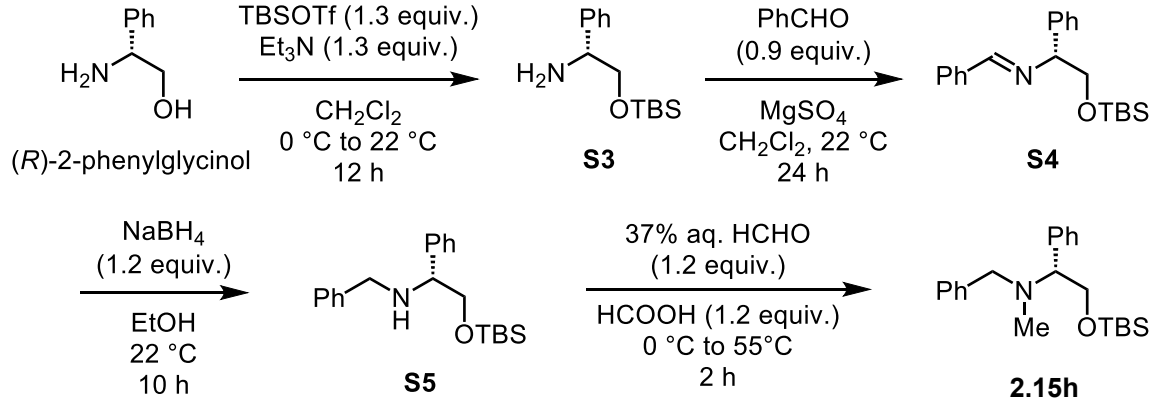
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 1.8 Hz, 1H), 7.26 - 7.20 (m, 4H), 3.52 (s, 2H), 3.44 (s, 2H), 2.09 (s, 3H), 1.13 (s, 6H).

***N*-Benzyl-1-((*tert*-butyldimethylsilyl)oxy)-*N*,2-dimethylpropan-2-amine (2.15g)**

N-Benzyl-1-((*tert*-butyldimethylsilyl)oxy)-*N*,2-dimethylpropan-2-amine **2.15g** was prepared following **General Procedure for TBS Protection of Alcohols** using 2-(benzyl(methyl)amino)-2-methylpropan-1-ol (10 mmol). The amine product **2.15g** was obtained after purification by flash silica gel column chromatography (Et_2O:hexanes = 1:9) as a colorless oil (3.0 g, 95% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 - 7.24 (m, 4H), 7.24 - 7.17 (m, 1H), 3.63 (s, 2H), 3.56 (s, 2H), 2.15 (s, 3H), 1.11 (s, 6H), 0.91 (s, 9H), 0.06 (s, 6H).

Procedure for Preparation of (*R*)-*N*-Benzyl-2-((*tert*-butyldimethylsilyl)oxy)-*N*-methyl-1-phenylethan-1-amine (2.15h)



(*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-1-phenylethan-1-amine (S3)

(*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-1-phenylethan-1-amine was prepared following **General Procedure for TBS Protection of Alcohols** using (*R*)-2-amino-2-phenylethan-1-ol (60 mmol). The amine product **S3** was obtained after purification by flash silica gel column chromatography (Et_3N:hexanes = 1:19) as a colorless oil (14.0 g, 93% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 - 7.21 (m, 4H), 7.19 - 7.13 (m, 1H), 3.98 (dd, *J* = 8.4, 3.9 Hz, 1H), 3.63 (dd, *J* = 9.8, 3.9 Hz, 1H), 3.43 (dd, *J* = 9.8, 8.3 Hz, 1H), 0.81 (s, 9H), -0.07 (d, *J* = 1.6 Hz, 6H).

(*R,R*)-*N*-(2-((*tert*-Butyldimethylsilyl)oxy)-1-phenylethyl)-1-phenylmethanimine (S4)

To a solution of amine **S1** (33 mmol, 1.1 equiv.) and benzaldehyde (30 mmol, 1.0 equiv.) in CH_2Cl_2, was added $MgSO_4$. The reaction mixture was allowed to stir for 24 h at 22 °C. Upon completion (determined by TLC), the unpurified mixture was filtered over a pad of Celite and rinsed with CH_2Cl_2. The organic layer was concentrated *in vacuo*, and the product obtained was directly used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.76 - 7.65 (m, 2H), 7.49 - 7.37 (m, 2H), 7.37 - 7.28 (m, 3H), 7.28 - 7.21 (m, 2H), 7.20 - 7.12 (m, 1H), 4.33 (dd, *J* = 8.6, 4.4 Hz, 1H), 3.86 - 3.68 (m, 2H), 0.73 (s, 9H), -0.10 (s, 3H), -0.16 (s, 3H).

(*R*)-*N*-Benzyl-2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethan-1-amine (S5)

To a solution of imine **S4** (30 mmol, 1.0 equiv.) in EtOH, was added $NaBH_4$ (36 mmol, 1.2 equiv.) at 0 °C. The reaction mixture was allowed to stir for 10 h. Upon completion (monitored by TLC), the reaction mixture was diluted with H_2O, and extracted with EtOAc (3 x 20 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The amine product **S5** was obtained after purification by flash silica gel column chromatography (Et_3N:hexanes = 1:50) as a colorless oil (10 g, 98% yield).

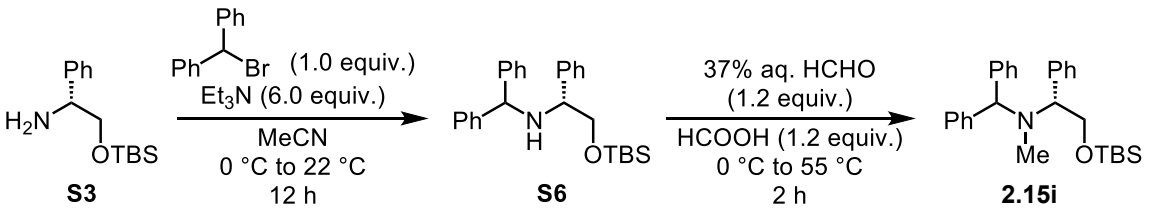
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 - 7.27 (m, 2H), 7.24 (ddd, *J* = 7.9, 6.7, 1.6 Hz, 2H), 7.22 - 7.15 (m, 5H), 7.13 (td, *J* = 6.9, 1.7 Hz, 1H), 3.71 (dd, *J* = 9.2, 4.0 Hz, 1H), 3.65 (d, *J* = 13.5 Hz, 1H), 3.56 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.51 - 3.42 (m, 2H), 0.78 (d, *J* = 1.8 Hz, 9H), -0.06 - -0.12 (m, 6H).

(*R*)-*N*-Benzyl-2-((*tert*-butyldimethylsilyl)oxy)-*N*-methyl-1-phenylethan-1-amine (2.15h)

(*R*)-*N*-Benzyl-2-((*tert*-butyldimethylsilyl)oxy)-*N*-methyl-1-phenylethan-1-amine was prepared using **General Procedure for *N*-Methylation of Secondary Amines** using (*R*)-*N*-benzyl-2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethan-1-amine (21 mmol). The amine product **2.15h** was obtained after purification by flash silica gel column chromatography (EtOAc: Et_3N: hexanes 20:1:79) as a colorless oil (6.8 g, 93% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 - 7.34 (m, 3H), 7.34 - 7.28 (m, 5H), 7.28 - 7.24 (m, 1H), 7.24 - 7.18 (m, 1H), 4.07 (dd, *J* = 10.4, 6.1 Hz, 1H), 3.94 - 3.85 (m, 1H), 3.70 - 3.56 (m, 2H), 3.45 (d, *J* = 13.5 Hz, 1H), 2.19 (s, 3H), 0.83 (s, 9H), -0.06 (d, *J* = 7.9 Hz, 6H); $[\alpha]^{25}_D$ = 1.6° (*c* 1.0, CH_2Cl_2).

Procedure for Preparation of (*R*)-*N*-Benzyl-2-((*tert*-butyldimethylsilyl)oxy)-*N*-methyl-1-phenylethan-1-amine (2.15i)



(*R*)-*N*-Benzhydryl-2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethan-1-amine (S6)

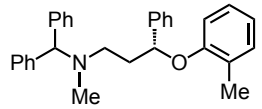
(*R*)-*N*-Benzhydryl-2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethan-1-amine was prepared using **General Procedure for Preparation of Secondary Amines** using (*R*)-2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethan-1-amine (46 mmol). The amine product **S6** was obtained after purification by flash silica gel column chromatography (Et_3N:hexanes = 1:19) as a colorless oil (9.5 g, 49% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 - 7.25 (m, 7H), 7.22 (t, *J* = 6.7 Hz, 6H), 7.19 - 7.10 (m, 2H), 4.62 (s, 1H), 3.68 (dd, *J* = 8.5, 3.7 Hz, 1H), 3.61 (dd, *J* = 9.2, 2.3 Hz, 2H), 0.85 (s, 9H), -0.05 (d, *J* = 11.4 Hz, 6H); $[\alpha]^{25}_D$ = 6.8° (*c* 1.0, CH_2Cl_2).

(*R*)-*N*-Benzyl-2-((*tert*-butyldimethylsilyl)oxy)-*N*-methyl-1-phenylethan-1-amine (2.15i)

(*R*)-*N*-Benzyl-2-((*tert*-butyldimethylsilyl)oxy)-*N*-methyl-1-phenylethan-1-amine was prepared using **General Procedure for *N*-Methylation of Secondary Amines** using (*R*)-*N*-benzhydryl-2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethan-1-amine (24 mmol). The amine product **2.15i** was obtained after purification by flash silica gel column chromatography (EtOAc:Et_3N: hexanes 20:1:79) as a colorless oil (10.1 g, 98% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (ddd, *J* = 11.6, 8.2, 1.3 Hz, 4H), 7.34 - 7.29 (m, 6H), 7.25 - 7.19 (m, 4H), 7.17 - 7.12 (m, 1H), 4.80 (s, 1H), 4.06 (dd, *J* = 9.7, 5.9 Hz, 1H), 3.98 - 3.89 (m, 2H), 2.13 (s, 3H), 0.85 (s, 9H), -0.03 (d, *J* = 6.5 Hz, 6H).

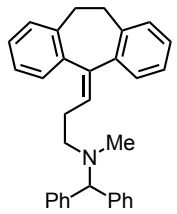


2.15l

(*R*)-*N*-Benzhydryl-*N*-methyl-3-phenyl-3-(*o*-tolyloxy)propan-1-amine (2.15l)

(*R*)-*N*-Benzhydryl-*N*-methyl-3-phenyl-3-(*o*-tolyloxy)propan-1-amine was prepared following **General Procedure for Preparation of Tertiary Amines** using (*R*)-*N*-methyl-3-phenyl-3-(o-tolyloxy)propan-1-amine (1.5 g, 5.9 mmol), (2-bromoethyl)benzene (1.2 equiv.) and K_2CO_3 (1.2 equiv.). The amine product **2.15l** was obtained after purification by flash silica gel column chromatography (EtOAc:hexanes = 1:19) as a colorless oil (2.0 g, 82%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.6 Hz, 2H), 7.29 (d, *J* = 4.4 Hz, 6H), 7.23 (t, *J* = 7.3 Hz, 3H), 7.15 (t, *J* = 6.7 Hz, 1H), 7.10 - 7.05 (m, 4H), 6.95 (t, *J* = 7.8 Hz, 1H), 6.75 (t, *J* = 7.5 Hz, 1H), 6.58 (d, *J* = 8.2 Hz, 1H), 5.25 (dd, *J* = 8.9, 3.7 Hz, 1H), 4.33 (s, 1H), 2.72 - 2.65 (m, 1H), 2.48 (ddd, *J* = 12.6, 8.1, 4.5 Hz, 1H), 2.18 (s, 3H), 2.17 - 2.11 (m, 1H), 2.08 - 2.00 (m, 4H).

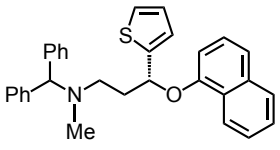


2.15m

***N*-Benzhydryl-3-(10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-ylidene)-*N*-methylpropan-1-amine (2.15m)**

N-Benzhydryl-3-(10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-ylidene)-*N*-methylpropan-1-amine was prepared following **General Procedure for Preparation of Tertiary Amines** using 3-(10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-ylidene)-*N*-methylpropan-1-amine (4.3 g, 16 mmol), (bromomethylene)dibenzene (1.2 equiv.) and K_2CO_3 (2.0 equiv.). The amine product **2.15m** was obtained after purification by flash silica gel column chromatography (Et_2O:hexanes = 1:19) as a colorless oil (6.5 g, 91%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.5 Hz, 5H), 7.23 (s, 4H), 7.19 (d, *J* = 1.0 Hz, 2H), 7.17 – 7.10 (m, 5H), 7.07 (d, *J* = 7.4 Hz, 1H), 7.03 (d, *J* = 4.1 Hz, 1H), 5.82 (t, *J* = 7.5 Hz, 1H), 4.31 (s, 1H), 3.30 (s, 2H), 2.94 (s, 1H), 2.72 (s, 1H), 2.46 (s, 2H), 2.31 (d, *J* = 7.4 Hz, 2H), 2.07 (s, 3H).

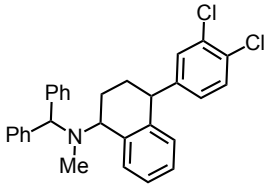


2.15n

(*R*)-*N*-Benzhydryl-*N*-methyl-3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propan-1-amine (2.15n)

(*R*)-*N*-Benzhydryl-*N*-methyl-3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propan-1-amine was prepared following **General Procedure for Preparation of Tertiary Amines** using (*R*)-*N*-methyl-3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propan-1-amine (0.9 g, 2.9 mmol), (bromomethylene)dibenzene (1.2 equiv.) and K_2CO_3 (2.0 equiv.). The amine product **2.15n** was obtained after purification by flash silica gel column chromatography (Et_2O:hexanes = 1:4) as a colorless oil (1.2 g, 90%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.76 (d, *J* = 7.9 Hz, 1H), 7.51 – 7.42 (m, 1H), 7.42 – 7.30 (m, 4H), 7.30 – 7.09 (m, 7H), 7.04 – 6.94 (m, 4H), 6.94 – 6.88 (m, 1H), 6.88 – 6.81 (m, 1H), 5.75 (s, 1H), 4.35 (s, 1H), 2.76 – 2.65 (m, 1H), 2.61 – 2.51 (m, 1H), 2.51 – 2.38 (m, 1H), 2.32 – 2.16 (m, 4H).

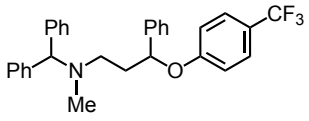


2.15o

***N*-Benzhydryl-4-(3,4-dichlorophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine (2.15o)**

N-Benzhydryl-4-(3,4-dichlorophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine was prepared following **General Procedure for Preparation of Tertiary Amines** using 4-(3,4-dichlorophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine (2.9 g, 6.0 mmol), (bromomethylene)dibenzene (1.2 equiv.) and K_2CO_3 (2.0 equiv.). The amine product **2.15o** was obtained after purification by flash silica gel column chromatography (Et_2O:hexanes = 1:4) as a colorless oil (1.4 g, 49%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 – 8.13 (m, 1H), 7.56 (td, *J* = 7.1, 6.3, 1.5 Hz, 4H), 7.38 – 7.33 (m, 1H), 7.29 (ddt, *J* = 7.9, 4.3, 2.0 Hz, 3H), 7.26 – 7.23 (m, 2H), 7.16 (dtd, *J* = 17.5, 7.2, 1.4 Hz, 3H), 7.08 (d, *J* = 1.9 Hz, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 6.79 (dt, *J* = 8.2, 1.9 Hz, 1H), 4.73 (d, *J* = 1.6 Hz, 1H), 4.08 – 3.99 (m, 2H), 2.04 (d, *J* = 1.7 Hz, 3H), 1.91 (q, *J* = 5.0, 4.5 Hz, 2H), 1.76 – 1.65 (m, 1H), 1.65 – 1.58 (m, 1H).



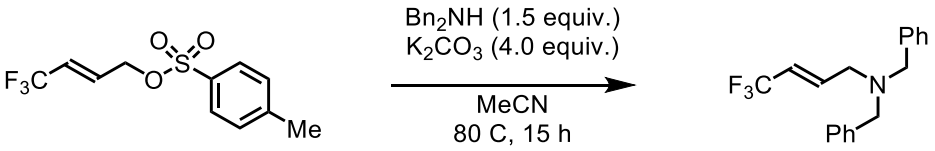
2.15p

_N_-Benzhydryl-_N_-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine (2.15p)

_N_-Benzhydryl-_N_-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine was prepared following **General Procedure for Preparation of Tertiary Amines** using _N_-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine (2.8 g, 9.0 mmol), (bromomethylene)dibenzene (1.2 equiv.) and K_2CO_3 (2.0 equiv.). The amine product **2.15p** was obtained after purification by flash silica gel column chromatography (Et_2O:hexanes = 1:9) as a colorless oil (3.0 g, 70%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, _J_ = 8.4 Hz, 2H), 7.38 – 7.33 (m, 2H), 7.29 (dtd, _J_ = 7.3, 5.7, 4.7, 1.6 Hz, 6H), 7.23 (td, _J_ = 7.5, 1.7 Hz, 3H), 7.19 – 7.14 (m, 1H), 7.12 – 7.07 (m, 3H), 6.84 – 6.79 (m, 2H), 5.34 – 5.29 (m, 1H), 4.35 (s, 1H), 2.71 (dt, _J_ = 13.9, 7.5 Hz, 1H), 2.39 (dt, _J_ = 12.2, 5.9 Hz, 1H), 2.18 (d, _J_ = 1.6 Hz, 3H), 2.13 (dd, _J_ = 13.8, 7.2 Hz, 1H), 2.08 – 1.99 (m, 1H); **^{19}F NMR** (564 MHz, $CDCl_3$) δ -61.51.

Procedure for Preparation of (_E_)-_N,N_-Dibenzyl-4,4,4-trifluorobut-2-en-1-amine (2.15q)

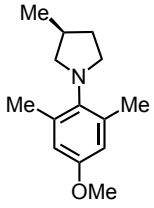


(_E_)-_N,N_-Dibenzyl-4,4,4-trifluorobut-2-en-1-amine (2.15q)

(_E_)-_N,N_-Dibenzyl-4,4,4-trifluorobut-2-en-1-amine was prepared following the literature previously reported.[2] To a solution of (_E_)-4,4,4-trifluorobut-2-en-1-yl 4-methylbenzenesulfonate (7.0 g, 25 mmol) and K_2CO_3 (13.8 g, 100 mmol) in MeCN (100 mL) was added dibenzylamine (7.4 g, 37.5 mmol). The reaction mixture was then allowed to stir at 80 °C for 15 hours. Upon completion (determined by TLC), the reaction mixture was filtered and concentrated _in vacuo_. The amine product **2.15q** was obtained after

purification by flash silica gel column chromatography (EtOAc:hexanes = 1:20) as a colorless oil (5.9 g, 77%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.29 (m, 8H), 7.28 – 7.22 (m, 2H), 6.51 – 6.30 (m, 1H), 5.85 (ddt, *J* = 15.8, 6.5, 1.7 Hz, 1H), 3.59 (s, 4H), 3.26 – 3.03 (m, 2H); **^{19}F NMR** (470 MHz, $CDCl_3$) δ -63.97 (d, *J* = 6.1 Hz).



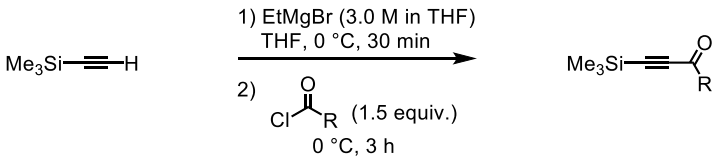
(*S*)-2.15r

(*S*)-1-(4-Methoxy-2,6-dimethylphenyl)-3-methylpyrrolidine ((*S*)-2.15r)

(*S*)-1-(4-Methoxy-2,6-dimethylphenyl)-3-methylpyrrolidine was prepared following **General Procedure for Preparation of Tertiary Amines** using 4-methoxy-2,6-dimethylaniline (1.65 g, 10.9 mmol), (*S*)-1,4-dibromo-2-methylbutane (0.9 equiv.) and K_2CO_3 (2.0 equiv.). The amine product **(*S*)-2.15r** was obtained after purification by flash silica gel column chromatography (Et_2O:hexanes = 1:19) as a colorless oil (1.8 g, 82%).

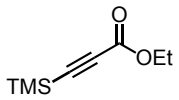
^{1}H NMR (600 MHz, $CDCl_3$) δ 6.57 (s, 2H), 3.75 (s, 3H), 3.26 – 3.21 (m, 1H), 3.21 – 3.17 (m, 2H), 2.79 (t, *J* = 7.5 Hz, 1H), 2.39 (dt, *J* = 8.5, 6.8 Hz, 1H), 2.23 (s, 6H), 2.12 – 2.02 (m, 1H), 1.59 (dd, *J* = 11.9, 8.1 Hz, 1H), 1.11 (d, *J* = 6.7 Hz, 3H); $[\alpha]^{25}_D$ = 19.5° (*c* 0.25, CH_2Cl_2).

General Procedure for Preparation of 3-(Trimethylsilyl)propiolates



3-(Trimethylsilyl)propiolates **2.22a-c**, **2.22i** were prepared according to the literature procedure.[4] To a solution of ethynyltrimethylsilane (20 mmol) in THF (20 mL) was added ethylmagnesium bromide (3.0 M solution in THF) in a dropwise manner at 0 °C. The reaction mixture was allowed to stir for 30 min. The corresponding chloroformate (30 mmol) in THF (30 mL) was added dropwise and the reaction mixture was allowed to stir at 0 °C for 3 h. Upon completion (determined by TLC), H_2O (50 mL) was added and the

organic material was extracted using Et_2O (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The desired alkyne products were obtained after purification by flash silica gel column chromatography.

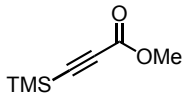


2.22a

Ethyl 3-(trimethylsilyl)propiolate (2.22a)

Ethyl 3-(trimethylsilyl)propiolate was prepared according to **General Procedure for Preparation of 3-(Trimethylsilyl)propiolates** using ethyl chloroformate. The propiolate **2.22a** was obtained after purification by flash silica gel column chromatography (Et_2O:hexanes = 1:99) as a colorless oil (2.7 g, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (q, *J* = 7.2 Hz, 2H), 1.31 (td, *J* = 7.1, 0.9 Hz, 3H), 0.25 (s, 9H).

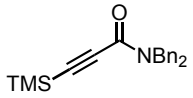


2.22b

Methyl 3-(trimethylsilyl)propiolate (2.22b)

Methyl 3-(trimethylsilyl)propiolate was prepared according to **General Procedure for Preparation of 3-(Trimethylsilyl)propiolates** using methyl chloroformate. The propiolate **2.22b** was obtained after purification by flash silica gel column chromatography (Et_2O:hexanes = 1:99) as a colorless oil (2.6 g, 83%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.77 (s, 3H), 0.25 (s, 9H).



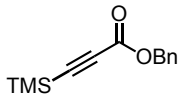
2.22a

***N,N*-Dibenzyl-3-(trimethylsilyl)propiolamide 2.22c)**

N,N-Dibenzyl-3-(trimethylsilyl)propiolamide was prepared according to **General Procedure for Preparation of 3-(Trimethylsilyl)propiolates** using *N,N*-

dibenzylcarbamoyl chloride. The propiolate **2.22c** was obtained after purification by flash silica gel column chromatography (Et_2O:hexanes = 1:99) as a colorless oil (3.3 g, 51%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 - 7.19 (m, 10H), 4.67 (s, 2H), 4.50 (s, 2H), 0.21 (s, 9H).



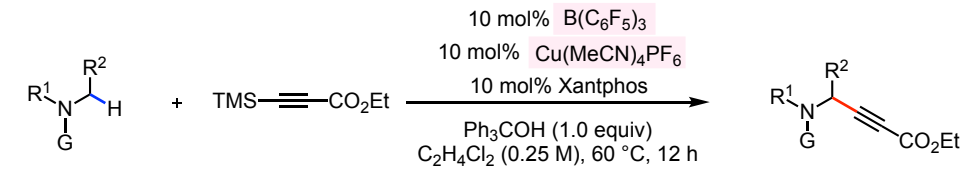
2.22i

Benzyl 3-(trimethylsilyl)propiolate (2.22i)

Benzyl 3-(trimethylsilyl)propiolate was prepared according to **General Procedure for Preparation of 3-(Trimethylsilyl)propiolates** using benzyl chloroformate. The propiolate **2.22i** was obtained after purification by flash silica gel column chromatography (Et_2O:hexanes = 1:99) as a colorless oil (3.9 g, 84%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (s, 2H), 5.11 (hept, J = 6.2 Hz, 2H), 1.29 (d, J = 6.3 Hz, 12H).

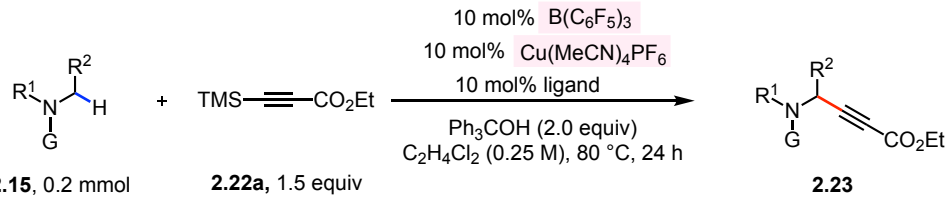
General Procedure A for *α*-C-H Alkynylation of *N*-Alkylamines Catalyzed by $B(C_6F_5)_3$ and Organocopper Complex



2.15, 0.2 mmol **2.22a,** 1.5 equiv **2.23**

An oven-dried sealed tube equipped with a magnetic stir bar was used. To the sealed tube were added $Cu(MeCN)_4PF_6$ (0.02 mmol), Xantphos (0.02 mmol), and $C_2H_4Cl_2$ (0.4 mL) under nitrogen atmosphere. The mixture was allowed to stir for 20 minutes at 22 °C, then ethyl 3-(trimethylsilyl)propiolate **2.22a** (0.3 mmol), triphenylmethanol (0.2 mmol), amine **2.15** (0.2 mmol), $B(C_6F_5)_3$ (0.02 mmol, 10 mol%), and $C_2H_4Cl_2$ (0.4 mL) were added to the vessel. The reaction mixture was allowed to stir at 60 °C for 12 h. Upon completion, the unpurified reaction mixture was filtered through a short plug of Celite and rinsed with CH_2Cl_2. The combined organic material was then concentrated *in vacuo*. The propargylamine product was purified and isolated by silica gel column chromatography.

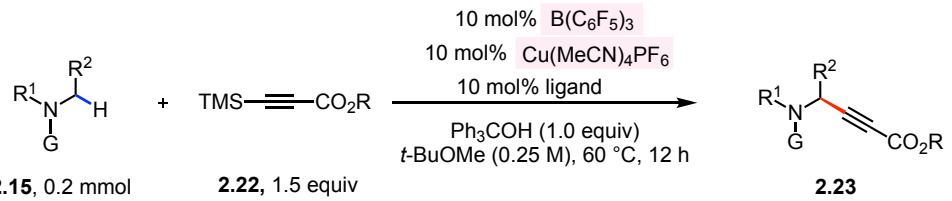
General Procedure B for *α*-C-H Alkynylation of *N*-Alkylamines Catalyzed by $B(C_6F_5)_3$ and Organocopper Complex



2.15, 0.2 mmol **2.22a,** 1.5 equiv **2.23**

An oven-dried sealed tube equipped with a magnetic stir bar was used. To the sealed tube were added $Cu(MeCN)_4PF_6$ (0.02 mmol), ligand (1,2-bis(diphenylphosphino)ethane or (*S*)-PhPyBOX, 0.02 mmol), and $C_2H_4Cl_2$ (0.4 mL) under nitrogen atmosphere. The mixture was allowed to stir for 20 minutes at 22 °C, then (trimethylsilyl)propiolate **2.22** (0.4 mmol), triphenylmethanol (0.4 mmol), amine **2.15** (0.2 mmol), $B(C_6F_5)_3$ (0.02, 10 mol%), and $C_2H_4Cl_2$ (0.4 mL) were added to the vessel. The reaction mixture was allowed to stir at 80 °C for 24 h. Upon completion, the unpurified reaction mixture was filtered through a short plug of Celite and rinsed with CH_2Cl_2. The combined organic material was then concentrated *in vacuo*. The propargylamine product was purified and isolated by silica gel column chromatography.

General Procedure C for Stereoselective *α*-C-H Alkynylation of *N*-Alkylamines Catalyzed by $B(C_6F_5)_3$ and Organocopper Complex



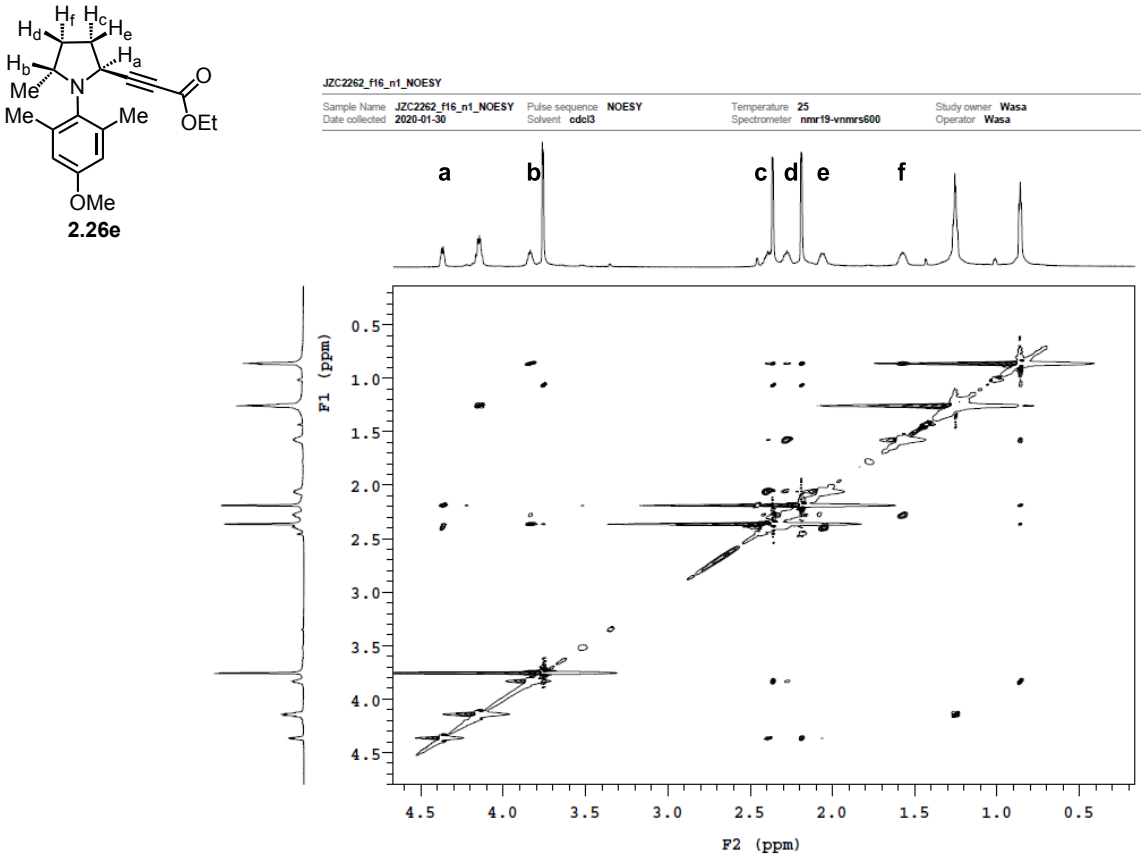
2.15, 0.2 mmol **2.22,** 1.5 equiv **2.23**

An oven-dried sealed tube equipped with a magnetic stir bar was used. To the sealed tube were added $Cu(MeCN)_4PF_6$ (0.02 mmol), (*S*)-(3,5-dimethylphenyl)PyBOX (0.02 mmol), and *t*-BuOMe (0.4 mL) under nitrogen atmosphere. The mixture was allowed to stir for 20 minutes at 22 °C, then (trimethylsilyl)propiolate **2.22** (0.3 mmol), triphenylmethanol (0.2 mmol), amine **2.15** (0.2 mmol), $B(C_6F_5)_3$ (0.02 mmol, 10 mol%), and solvent (0.4 mL) were added to the vessel. The reaction mixture was allowed to stir at 60 °C for 12 h. Upon completion, the unpurified reaction mixture was filtered through a short plug of Celite and rinsed with Et_2O. The combined organic material was then concentrated *in vacuo*. The

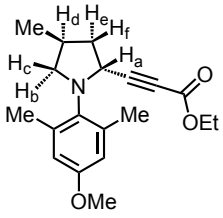
propargylamine product was purified isolated by silica gel column chromatography. The er values were determined by HPLC analysis of the isolated product.

Determination of Relative Configuration

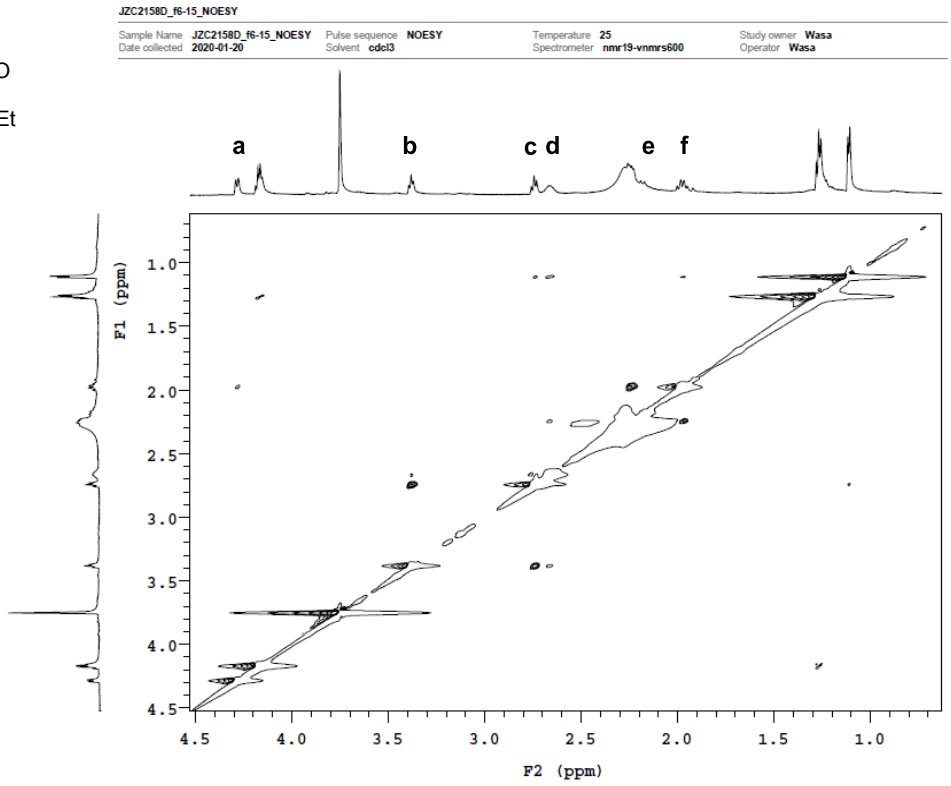
We carried out the following 2D NMR studies in order to determine relative configuration of enantioenriched products **2.26e, 2.26f**.

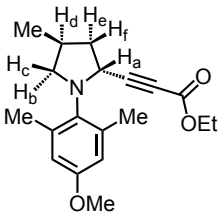


The relative configuration of the major diastereomer of **2.26e** was assigned to be *trans*.

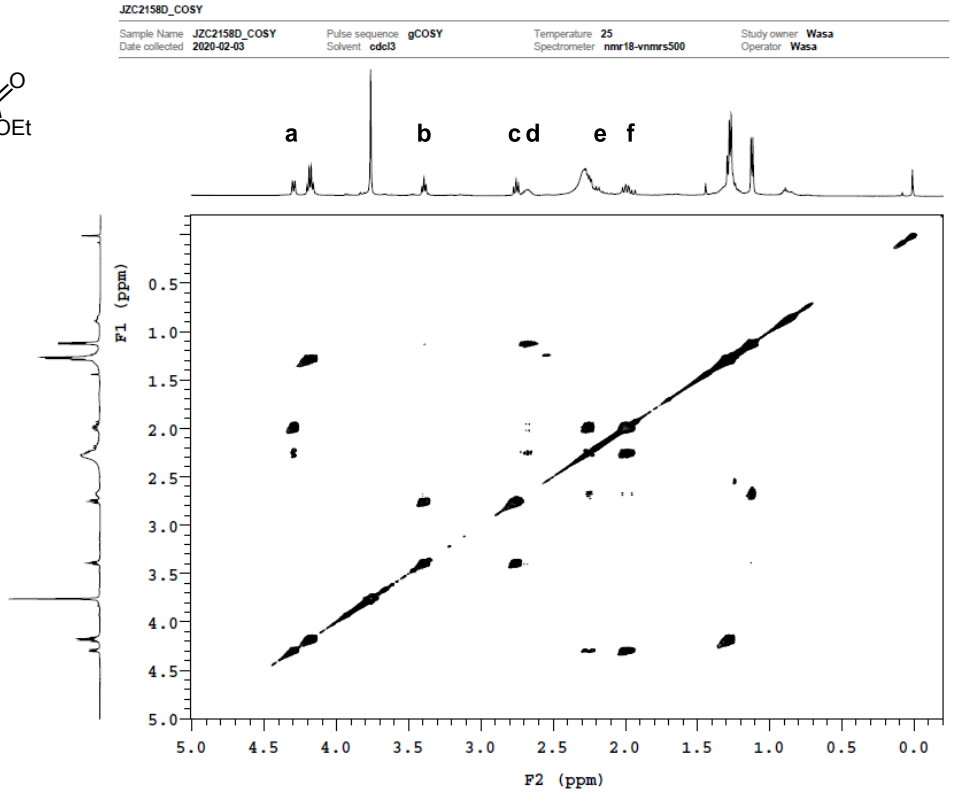

Me
Hd He Hf
Ha
Hc
Hb
N
Me
Me
O
OEt
OMe

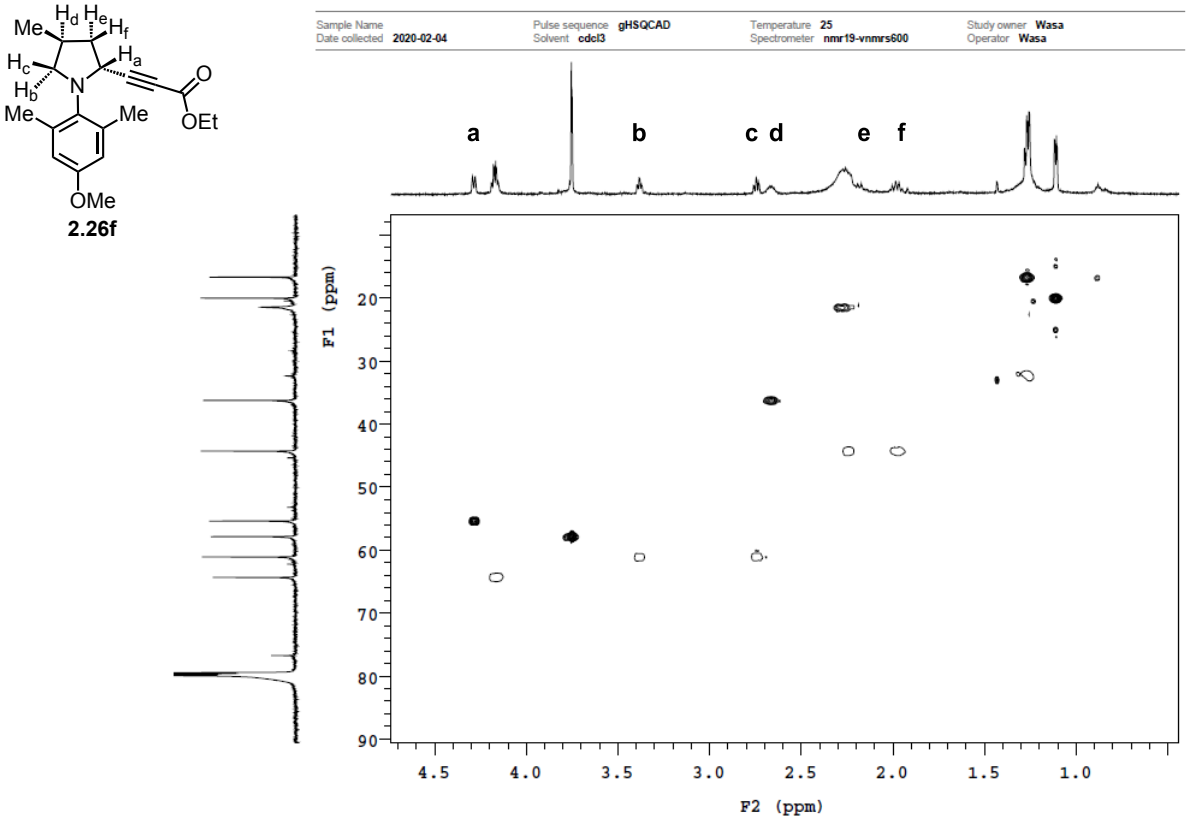
2.26f


JZC2158D_f6-15_NOESY
Sample Name JZC2158D_f6-15_NOESY
Date collected 2020-01-20
Pulse sequence NOESY
Solvent cdcl3
Temperature 25
Spectrometer nmr19-vnmrs600
Study owner Wasa
Operator Wasa
a
b
c d
e
f
F1 (ppm)
F2 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5


Me
Hd He Hf
Ha
Hc
Hb
N
O
OEt
Me
Me
OMe

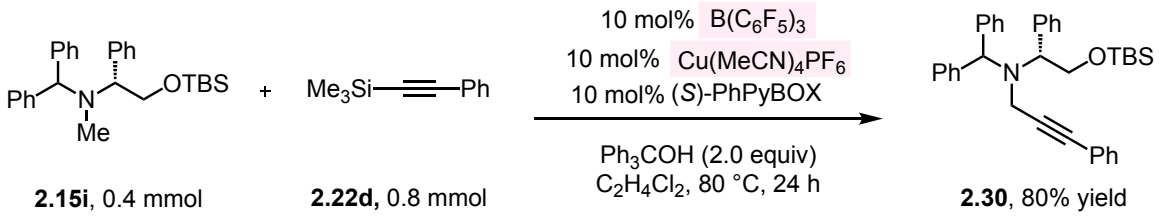
2.26f


JZC2158D_COSY
Sample Name JZC2158D_COSY
Date collected 2020-02-03
Pulse sequence gCOSY
Solvent cdcl3
Temperature 25
Spectrometer nmr18-vnmrs500
Study owner Wasa
Operator Wasa
a
b
c d
e
f
F1 (ppm)
F2 (ppm)



The relative configuration of the major diastereomer of **2.23r** was assigned as *trans*.

Procedure for Preparation of Propargylamine 2.30



2.15i, 0.4 mmol **2.22d,** 0.8 mmol **2.30**, 80% yield

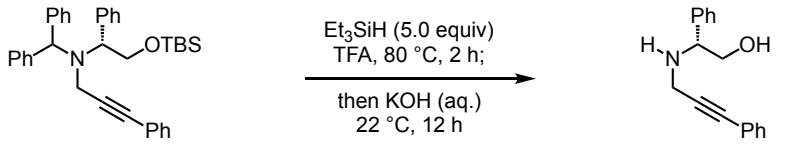
(*R*)-*N*-Benzhydryl-*N*-(2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethyl)-3-phenylprop-2-yn-1-amine (2.30)

An oven-dried sealed tube equipped with a magnetic stir bar was used. To the sealed tube were added $Cu(MeCN)_4PF_6$ (0.04 mmol), (*S*)-PhPyBOX, 0.04 mmol), and $C_2H_4Cl_2$ (0.4 mL) under nitrogen atmosphere. The mixture was allowed to stir for 20 minutes at 22 °C, then (trimethylsilyl)propiolate **2.22d** (0.8 mmol), triphenylmethanol (0.8 mmol), amine **2.15i** (0.4 mmol), $B(C_6F_5)_3$ (0.04 mmol, 10 mol%), and $C_2H_4Cl_2$ (0.4 mL) were added to

the vessel. The reaction mixture was allowed to stir at 80 °C for 24 h. Upon completion, the unpurified reaction mixture was filtered through a short plug of Celite and rinsed with CH_2Cl_2. The combined organic material was then concentrated *in vacuo*. The propargylamine product was purified and isolated by silica gel column chromatography (1:9 CH_2Cl_2:hexane) to afford **2.30** as a colorless oil (170.2 mg, 80% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 – 7.58 (m, 6H), 7.47 – 7.33 (m, 12H), 7.33 – 7.24 (m, 2H), 5.40 (s, 1H), 4.38 (dd, J = 10.2, 5.1 Hz, 1H), 4.34 (dd, J = 10.2, 7.3 Hz, 1H), 4.30 (dd, J = 7.2, 5.1 Hz, 1H), 3.75 (d, J = 1.4 Hz, 2H), 0.92 (s, 9H), 0.08 (s, 3H), 0.02 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 142.6, 142.4, 140.5, 131.5, 128.9, 128.6, 128.5, 128.38, 128.35, 128.07, 128.06, 127.9, 127.7, 127.03, 126.95, 126.9, 123.7, 87.7, 84.4, 69.2, 63.4, 62.8, 37.0, 25.9, 18.2, -5.45, -5.47; **IR** (neat) 3057, 3025, 2924, 2852, 1597, 1488, 1451, 1251, 1095, 835, 813, 744, 699 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{36}H_{42}NOSi$ (MH^+): 532.3030; found: 532.3023; $[\alpha]25_D$ = –25.1° (*c* 1.0, CH_2Cl_2).

Procedure for Deprotection of *N*-Benzhydryl Group



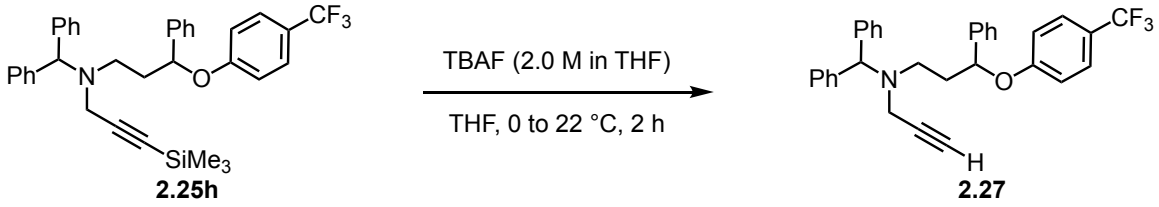
2.30 **2.31**, 80% yield

(*R*)-2-Phenyl-2-((3-phenylprop-2-yn-1-yl)amino)ethan-1-ol (2.31)

(*R*)-2-Phenyl-2-((3-phenylprop-2-yn-1-yl)amino)ethan-1-ol was prepared according to the literature procedure.[11] To a solution of **2.30** (100 mg, 0.2 mmol) in TFA (1.5 mL) was added triethylsilane (0.14 mL, 0.9 mmol). The mixture was allowed to stir at 80 °C for 2 h. The mixture was cooled to 22 °C and KOH (1.0 M, aq.) was added in a dropwise manner until the solution was alkaline. The reaction mixture was allowed to stir at 22 °C for 12 h. CH_2Cl_2 (5 mL) was added and the organic material was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The amine product **2.31** was obtained after purification by flash silica gel column chromatography (EtOAc:hexanes = 8:2) as a colorless solid (36.2 mg, 80%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 – 7.38 (m, 2H), 7.38 – 7.33 (m, 4H), 7.32 – 7.26 (m, 4H), 4.06 (dd, J = 8.3, 4.4 Hz, 1H), 3.78 (dd, J = 10.9, 4.4 Hz, 1H), 3.68 – 3.60 (m, 2H), 3.45 (d, J = 17.0 Hz, 1H), 2.42 – 2.12 (m, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 139.70, 131.63, 128.66, 128.21, 128.03, 127.81, 127.57, 123.09, 87.29, 83.71, 66.79, 63.22, 36.72; **IR** (neat) 3288, 3056, 2914, 2847, 1488, 1451, 1329, 1026, 754, 690, 526 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{17}H_{18}NO$ (MH^+): 252.1383; found: 252.1379; $[\alpha]25_D$ = 199.1° (*c* 1.0, CH_2Cl_2).

Procedure for Removal of Trimethylsilyl Group

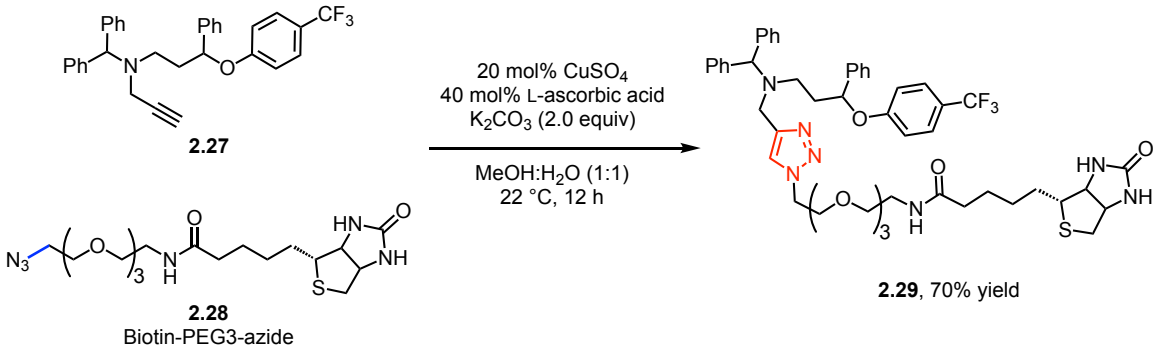


***N*-Benzhydryl-*N*-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)prop-2-yn-1-amine (2.27)**

To a solution of **2.25h** (228 mg, 0.4 mmol) in THF (10 mL) was added TBAF (1.0 mL, 2.0 M in THF) at 0 °C. The reaction mixture was allowed to stir for 2 h at 22 °C. Upon completion (determined by TLC), the reaction mixture was concentrated *in vacuo*. The amine product **2.27** was obtained after purification by flash silica gel column chromatography (Et_2O:hexane = 1:99) as a colorless solid (200 mg, 99% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 8.4, 3.5 Hz, 4H), 7.34 – 7.30 (m, 2H), 7.28 (d, *J* = 5.9 Hz, 4H), 7.23 (t, *J* = 7.7 Hz, 3H), 7.20 – 7.10 (m, 2H), 7.06 (q, *J* = 7.0, 6.4 Hz, 3H), 6.80 (d, *J* = 8.4 Hz, 2H), 5.26 (d, *J* = 3.8 Hz, 1H), 4.68 (s, 1H), 3.44 (qd, *J* = 17.7, 2.4 Hz, 2H), 2.86 – 2.65 (m, 2H), 2.17 (s, 1H), 2.16 – 1.94 (m, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 160.6, 143.9, 142.6, 142.5, 141.4, 130.0, 129.4, 128.7, 128.6, 128.52, 128.48, 128.44, 128.38, 128.28, 128.25, 128.00, 127.96, 127.93, 127.92, 127.83, 127.80, 127.7, 127.4, 127.24, 127.15, 127.1, 126.96, 126.92, 126.68, 126.65, 126.63, 126.60, 126.3, 125.8, 125.6, 125.5, 125.4, 123.6, 122.6 (q, *J* = 32.7 Hz), 121.8, 115.7, 78.2, 77.8, 73.5, 72.2, 56.8, 46.4, 39.1, 36.8; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -61.34; **IR** (neat)□□ 3298, 3060, 3025, 2924, 2831, 1700, 1612, 1515, 1491, 1326, 1250, 1110, 1066, 834, 700 cm^{-1}; **HRMS** (DART) Calcd for $C_{32}H_{29}NOF_3$ (MH^+): 500.2196; found: 500.2183.

Procedure for Organocopper-Catalyzed Alkyne Azide Click Reaction



***N*-(2-(2-(2-(2-(4-((Benzhydryl(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)amino)methyl)-1*H*-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)ethyl)-5-((4*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanamide (2.29)**

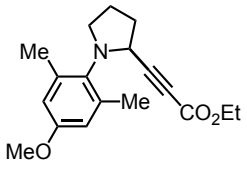
N-(2-(2-(2-(2-(4-((Benzhydryl(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)amino)methyl)-1*H*-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)ethyl)-5-((4*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanamide was prepared according to the literature procedure.[12]

To a solution of alkyne **2.27** (100 mg, 0.2 mmol) in MeOH (2.0 mL) was added K_2CO_3 (55 mg, 0.4 mmol), $CuSO_4$ (6.4 mg, 0.04 mmol), Biotin-PEG3-azide (98 mg, 0.22 mmol), *L*-ascorbic acid (14.1 mg, 0.08 mmol), and H_2O (2.0 mL). The reaction mixture was then allowed to stir for 12 h. Upon completion (determined by TLC), the reaction mixture was concentrated *in vacuo* to remove the organic solvent. EtOAc (3 x 5 mL) was used to extract the organic material. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The amine product **2.29** was obtained after purification by flash silica gel column chromatography (MeOH:CH_2Cl_2 = 1:99) as a colorless solid (132 mg, 70%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 – 7.36 (m, 4H), 7.36 – 7.30 (m, 2H), 7.30 – 7.26 (m, 3H), 7.24 (t, *J* = 7.8 Hz, 4H), 7.19 (q, *J* = 7.2, 6.1 Hz, 4H), 6.77 (d, *J* = 8.5 Hz, 2H), 6.64 (s, 1H), 6.57 (s, 1H), 5.63 (s, 1H), 5.23 (dd, *J* = 8.5, 4.2 Hz, 1H), 4.78 (s, 1H), 4.42 (dtt, *J*

= 14.3, 10.5, 5.2 Hz, 3H), 4.26 (dd, *J* = 7.8, 4.7 Hz, 1H), 3.94 – 3.74 (m, 4H), 3.54 (d, *J* = 7.2 Hz, 8H), 3.51 (t, *J* = 5.2 Hz, 2H), 3.40 (t, *J* = 5.2 Hz, 2H), 3.10 (td, *J* = 7.3, 4.5 Hz, 1H), 2.85 (dd, *J* = 12.7, 4.9 Hz, 1H), 2.77 – 2.68 (m, 2H), 2.63 (ddd, *J* = 12.9, 7.7, 4.6 Hz, 1H), 2.18 (t, *J* = 7.5 Hz, 2H), 2.12 (dtd, *J* = 14.5, 7.6, 7.0, 3.8 Hz, 2H), 1.78 – 1.56 (m, 4H), 1.46 – 1.34 (m, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.2, 164.0, 160.5, 144.8, 142.2, 141.6, 141.30, 128.6, 128.5, 128.4, 128.34, 128.31, 128.26, 128.1, 127.6, 127.07, 127.00, 126.96, 126.62, 126.60, 126.57, 126.55, 125.7, 125.5, 125.3, 123.5, 122.4 (q, *J* = 32.5 Hz), 121.9, 115.6, 77.8, 77.2, 77.0, 76.9, 76.8, 70.6, 70.5, 70.4, 70.3, 70.0, 69.9, 69.8, 69.5, 65.8, 61.7, 60.1, 55.6, 50.0, 46.1, 44.9, 40.4, 39.1, 36.1, 35.9, 35.9, 30.3, 29.6, 29.6, 28.2, 28.0, 25.5, 15.2; **^{19}F NMR** (564 MHz, $CDCl_3$) δ -61.44; **IR** (neat) 3287, 2921, 2863, 1698, 1612, 1451, 1325, 1250, 1109, 1066, 835, 734, 701 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{50}H_{61}F_3N_7O_6S$ (MH^+): 944.4278; found: 944.4342.

Experimental Data for Products

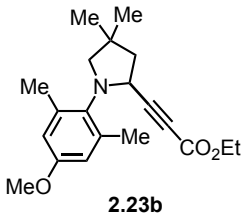


2.23a

Ethyl 3-(1-(4-methoxy-2,6-dimethylphenyl)pyrrolidin-2-yl)propiolate (2.23a)

1-(4-Methoxy-2,6-dimethylphenyl)pyrrolidine **2.23a** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.22a** following **General Procedure A**. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.23a** was obtained as a colorless liquid (54 mg, 90%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.58 (s, 2H), 4.27 (ddd, *J* = 7.8, 3.5, 1.3 Hz, 1H), 4.17 (qd, *J* = 7.2, 1.3 Hz, 2H), 3.75 (s, 3H), 3.43 – 3.31 (m, 1H), 3.09 (q, *J* = 6.9 Hz, 1H), 2.47 – 2.22 (m, 6H), 2.22 – 2.10 (m, 3H), 2.09 – 1.94 (m, 1H), 1.27 (td, *J* = 7.2, 1.4 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.15, 153.86, 135.89, 113.60, 90.83, 73.94, 61.66, 55.16, 52.31, 51.03, 33.83, 25.68, 18.89, 13.99; **IR** (neat) ν 2967, 2837, 2224, 1707, 1599, 1476, 1366,1244, 1153, 1067, cm^{-1}; **HRMS** (DART) Calcd for $C_{18}H_{24}NO_3$ (MH^+): 302.1751; found: 302.1755.

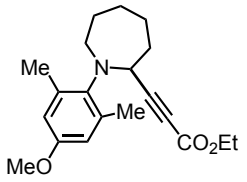


2.23b

1-(4-Methoxy-2,6-dimethylphenyl)-3,3-dimethylpyrrolidine (2.23b)

1-(4-Methoxy-2,6-dimethylphenyl)-3,3-dimethylpyrrolidine **2.23b** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.22a** following **General Procedure A**. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.23b** was obtained as a colorless liquid (51 mg, 77%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.57 (s, 2H), 4.41 (dd, *J* = 9.0, 3.8 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.75 (s, 3H), 3.07 (d, *J* = 7.9 Hz, 1H), 2.95 (d, *J* = 7.8 Hz, 1H), 2.37 (s, 5H), 2.19 (dd, *J* = 12.5, 9.0 Hz, 2H), 1.98 (dd, *J* = 12.5, 3.9 Hz, 1H), 1.37 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.15 (d, *J* = 1.0 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.17, 153.83, 135.35, 113.68, 90.96, 74.30, 64.52, 61.63, 55.15, 51.92, 47.01, 39.12, 27.77, 27.24, 13.98; **IR** (neat) ν 2954, 2864, 2228, 1707, 1601, 1465, 1243, 1094, 1023, 751 cm^{-1}; **HRMS** (DART) Calcd for $C_{20}H_{28}NO_3$ (MH^+): 330.2063; found: 330.2069.



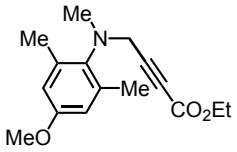
2.23c

Ethyl 3-(1-(4-methoxy-2,6-dimethylphenyl)azepan-2-yl)propiolate (2.23c)

1-(4-Methoxy-2,6-dimethylphenyl)azepane **2.23c** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.22a** following **General Procedure A**. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.23c** was obtained as a colorless liquid (51 mg, 77%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.57 (d, *J* = 13.4 Hz, 2H), 4.18 (d, *J* = 7.1 Hz, 2H), 4.06 (d, *J* = 2.7 Hz, 1H), 3.75 (s, 3H), 3.32 (d, *J* = 9.1 Hz, 1H), 3.08 (d, *J* = 11.1 Hz, 1H), 2.42 (s, 3H), 2.29 (s, 3H), 2.19 (d, *J* = 1.5 Hz, 1H), 1.95 – 1.85 (m, 2H), 1.85 – 1.79 (m, 1H), 1.79 – 1.70 (m, 2H), 1.57 (s, 2H), 1.28 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 156.53, 153.77, 141.76, 139.19, 137.94, 114.13, 113.64, 90.92, 75.66, 61.65, 55.17, 53.81, 51.31, 35.68,

31.91, 29.33, 25.25, 20.14, 19.65, 14.01; **IR** (neat) ν 2926, 2845, 2221, 1707, 1598, 1474, 1309, 1240, 1065, 853 cm^{-1}; **HRMS** (DART) Calcd for $C_{20}H_{28}NO_3$ (MH^+): 330.2063; found: 330.2061.

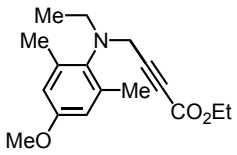


2.23d

Ethyl 4-((4-methoxy-2,6-dimethylphenyl)(methyl)amino)but-2-ynoate (2.23d)

4-Methoxy-*N,N*,2,6-tetramethylaniline **2.23d** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.22a** following **General Procedure A**. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.23d** was obtained as a colorless liquid (50 mg, 90%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.54 (s, 2H), 4.23 (q, *J* = 7.1, 1.5 Hz, 2H), 3.89 (s, 2H), 3.74 (s, 3H), 2.88 (s, 3H), 2.29 (s, 6H), 1.31 (t, *J* = 7.1, 1.5 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 156.81, 153.63, 140.96, 138.67, 113.62, 86.13, 75.59, 61.84, 55.18, 44.75, 40.06, 19.36, 14.00; **IR** (neat) ν 2933, 2228, 1707, 1598, 1480, 1309, 1244, 1155, 1060, 855 cm^{-1}; **HRMS** (DART) Calcd for $C_{16}H_{22}NO_3$ (MH^+): 276.1594; found: 276.1609.



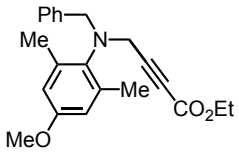
2.23e

Ethyl 4-(ethyl(4-methoxy-2,6-dimethylphenyl)amino)but-2-ynoate (2.23e)

N-Ethyl-4-methoxy-*N*,2,6-trimethylaniline **2.23e** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.22a** following **General Procedure A**. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.23e** was obtained as a colorless liquid (24 mg, 42%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.56 (s, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.92 (s, 2H), 3.76 (s, 3H), 3.21 (q, *J* = 7.2 Hz, 2H), 2.30 (s, 6H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.04 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.84, 153.66, 139.52, 139.27, 113.62, 86.75, 77.25,

77.00, 76.75, 75.51, 61.80, 55.17, 47.18, 42.98, 19.62, 14.28, 14.01; **IR** (neat) ν 2933, 2230, 1707, 1598, 1490, 1309, 1254, 1120, 1060, 840 cm^{-1}; **HRMS** (DART) Calcd for $C_{17}H_{24}NO_3$ (MH^+): 290.1751; found: 290.1755.

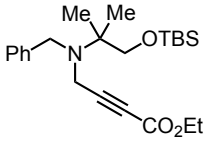


2.23f

Ethyl 4-(benzyl(4-methoxy-2,6-dimethylphenyl)amino)but-2-ynoate (2.23f)

N-Benzyl-4-methoxy-*N*,2,6-trimethylaniline **2.23f** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.22a** following **General Procedure A**. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.23f** was obtained as a colorless liquid (51 mg, 72%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 4H), 7.28 – 7.23 (m, 1H), 6.57 (s, 2H), 4.28 (s, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 2H), 3.76 (s, 3H), 2.34 (s, 6H), 1.30 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 156.81, 153.51, 140.56, 138.98, 138.48, 128.96, 128.35, 127.22, 113.94, 86.27, 76.12, 61.83, 57.48, 55.20, 41.47, 19.98, 14.01; **IR** (neat) ν 2927, 2841, 2230, 1708, 1598, 1479, 1312, 1245, 1065, 855 cm^{-1}; **HRMS** (DART) Calcd for $C_{22}H_{26}NO_3$ (MH^+): 352.1907; found: 352.1895.



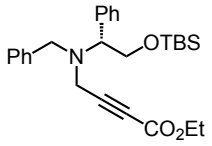
2.23g

Ethyl 4-(benzyl(1-((*tert*-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)amino)but-2-ynoate (2.23g)

N-Benzyl-1-((*tert*-butyldimethylsilyl)oxy)-*N*,2-dimethylpropan-2-amine **2.23g** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.22a** following **General Procedure B** using 1,2-bis(diphenylphosphino)ethane as the ligand. After purification by column

chromatography (Et_2O:hexanes = 1:19), **2.23g** was obtained as a colorless liquid (61 mg, 76%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (dt, *J* = 6.6, 1.1 Hz, 2H), 7.32 – 7.27 (m, 2H), 7.24 – 7.20 (m, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 3.91 (s, 2H), 3.60 (s, 2H), 3.51 (s, 2H), 1.31 (t, *J* = 7.1, 0.8 Hz, 3H), 1.23 (s, 6H), 0.91 (s, 9H), 0.06 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.61, 140.27, 128.43, 128.23, 126.86, 87.60, 76.67, 69.73, 61.76, 58.62, 58.61, 51.40, 36.66, 30.33, 25.87, 22.94, 18.22, 14.06; **IR** (neat) ν 2949, 2855, 2221, 1708, 1463, 1364, 1237, 1092, 840, 774 cm^{-1}; **HRMS** (DART) Calcd for $C_{23}H_{38}NO_3Si$ (MH^+): 404.2615; found: 404.2610.

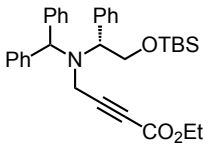


2.23h

Ethyl (*R*)-4-(benzyl(2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethyl)amino)but-2-ynoate (2.23h)

(*R*)-*N*-Benzyl-2-((*tert*-butyldimethylsilyl)oxy)-*N*-methyl-1-phenylethan-1-amine **2.23h** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.22a** following **General Procedure B** using 1,2-bis(diphenylphosphino)ethane as the ligand. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.23h** was obtained as a colorless liquid (78 mg, 86%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.5 Hz, 2H), 7.37 – 7.20 (m, 8H), 4.26 (q, *J* = 7.1, 2.1 Hz, 2H), 3.94 (dd, *J* = 7.3, 4.9 Hz, 2H), 3.82 (d, *J* = 2.0 Hz, 1H), 3.74 (d, *J* = 2.1 Hz, 1H), 3.70 – 3.60 (m, 2H), 3.37 – 3.28 (m, 1H), 1.34 (t, *J* = 2.0 Hz, 3H), 0.83 (s, 9H), -0.09 (d, *J* = 5.7, 2.1 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.58, 141.14, 138.81, 128.87, 128.46, 128.30, 128.25, 127.39, 127.10, 84.49, 77.84, 67.60, 65.97, 61.87, 55.06, 39.14, 25.81, 18.16, 15.27, 14.09, -5.66; **IR** (neat) ν 2923, 2853, 2222, 1709, 1458, 1365, 1239, 1095, 870, 698 cm^{-1}; **HRMS** (DART) Calcd for $C_{27}H_{38}NO_3Si$ (MH^+): 452.2615; found: 452.2612; $[\alpha]^{25}_D$ = 36.7° (*c* 0.2, CH_2Cl_2).

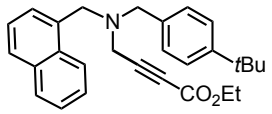


2.23i

Ethyl (*R*)-4-(benzhydryl(2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethyl)amino)but-2-ynoate (2.23i)

(*R*)-*N*-Benzhydryl-2-((*tert*-butyldimethylsilyl)oxy)-*N*-methyl-1-phenylethan-1-amine **2.23i** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.22a** following **General Procedure B** using 1,2-bis(diphenylphosphino)ethane as the ligand. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.23i** was obtained as a colorless liquid (102 mg, 97%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52 – 7.46 (m, 4H), 7.42 (dt, *J* = 8.1, 1.1 Hz, 2H), 7.35 – 7.14 (m, 9H), 5.23 (s, 1H), 4.24 – 4.06 (m, 5H), 3.55 (s, 2H), 1.31 (t, *J* = 7.1, 3H), 0.82 (s, 9H), -0.04 (d, *J* = 20.0, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 153.41, 141.98, 139.74, 128.67, 128.53, 128.47, 128.44, 128.37, 128.09, 127.22, 127.13, 86.44, 76.59, 69.17, 63.09, 62.85, 61.54, 36.57, 25.84, 18.18, 14.04; **IR** (neat) ν 3026, 2930, 2855, 2224, 1708, 1456, 1362, 1243,1095, 837 cm^{-1}; **HRMS** (DART) Calcd for $C_{33}H_{42}NO_3Si$ (MH^+): 528.2928; found: 528.2922; $[\alpha]^{25}_D = -16.2°$ (*c* 0.8, CH_2Cl_2).



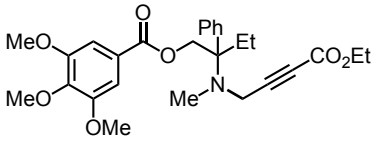
2.23j

Ethyl 4-((4-(*tert*-butyl)phenyl)(naphthalen-1-ylmethyl)amino)but-2-ynoate (2.23j)

4-(*tert*-Butyl)-*N*-methyl-*N*-(naphthalen-1-ylmethyl)aniline **2.23j** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.22a** following **General Procedure B** using 1,2-bis(diphenylphosphino)ethane as the ligand. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.23j** was obtained as a colorless liquid (63 mg, 76%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 7.4 Hz, 1H), 7.86 – 7.80 (m, 1H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.55 – 7.45 (m, 3H), 7.40 (dd, *J* = 8.6, 6.6 Hz, 1H), 7.36 – 7.27 (m, 4H), 4.30 (q, *J* = 7.2 Hz, 2H), 4.15 (s, 2H), 3.78 (s, 2H), 3.35 (s, 2H), 1.37 (t, *J* = 7.1 Hz, 4H), 1.30 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.55, 150.33, 135.08, 133.94, 133.72, 132.48,

128.88, 128.39, 128.34, 127.83, 125.75, 125.66, 125.25, 125.16, 124.88, 83.56, 78.32, 62.00, 57.67, 56.19, 40.88, 34.48, 31.36, 14.09; **IR** (neat) ν 2957, 2825, 2220, 1707, 1597, 1509, 1239, 1107, 1050, 791 cm^{-1}; **HRMS** (DART) Calcd for $C_{28}H_{32}NO_2$ (MH^+): 414.2428; found: 414.2429.

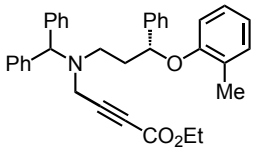


2.23k

2-((4-Ethoxy-4-oxobut-2-yn-1-yl)(methyl)amino)-2-phenylbutyl 3,4,5-trimethoxybenzoate (2.23k)

2-(Dimethylamino)-2-phenylbutyl 3,4,5-trimethoxybenzoate **2.23k** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.22a** following **General Procedure B** using 1,2-bis(diphenylphosphino)ethane as the ligand. After purification by column chromatography (Et_2O:hexanes = 1:2), **2.23k** was obtained as a colorless liquid (69 mg, 71%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.46 (m, 2H), 7.40 – 7.33 (m, 2H), 7.29 – 7.22 (m, 1H), 7.18 (d, *J* = 1.4 Hz, 2H), 4.89 (dd, *J* = 12.1, 1.3 Hz, 1H), 4.74 (dd, *J* = 12.0, 1.3 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 3H), 3.82 (s, 6H), 3.63 (d, *J* = 17.6 Hz, 1H), 3.48 (d, *J* = 17.6 Hz, 1H), 2.63 (s, 3H), 1.95 – 1.78 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 2H), 0.69 (t, *J* = 7.3 Hz, 4H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.82, 153.45, 152.89, 142.29, 141.67, 128.17, 127.34, 126.92, 124.84, 106.78, 86.22, 75.49, 65.68, 64.81, 61.78, 60.82, 56.06, 42.13, 35.82, 30.05, 13.90, 8.52; **IR** (neat) ν 2939, 2231, 1709, 1586, 1498, 1331, 1239, 1123, 1006, 756 cm^{-1}; **HRMS** (DART) Calcd for $C_{27}H_{34}NO_7$ (MH^+): 484.2330; found: 484.2322.

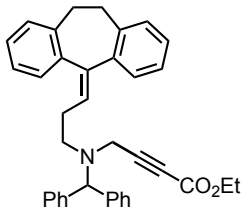


2.23l

Ethyl (R)-4-(benzhydryl(3-phenyl-3-(o-tolyloxy)propyl)amino)but-2-ynoate (2.23l)

(*R*)-*N*-Benzhydryl-*N*-methyl-3-phenyl-3-(*o*-tolyloxy)propan-1-amine **2.23l** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.13a** following **General Procedure B** using 1,2-bis(diphenylphosphino)ethane as the ligand. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.23l** was obtained as a colorless liquid (58 mg, 56%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.40 (m, 2H), 7.35 – 7.13 (m, 10H), 7.07 (qt, *J* = 5.7, 1.3 Hz, 4H), 6.94 (td, *J* = 7.8, 1.8 Hz, 1H), 6.75 (td, *J* = 7.4, 1.1 Hz, 1H), 6.57 – 6.52 (m, 1H), 5.19 (dd, *J* = 9.2, 3.4 Hz, 1H), 4.66 (s, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.63 – 3.50 (m, 2H), 2.86 – 2.77 (m, 2H), 2.13 (dddd, *J* = 19.3, 9.2, 7.5, 5.6 Hz, 1H), 2.02 (s, 3H), 2.02 – 1.95 (m, 1H), 1.34 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.87, 155.86, 153.40, 142.33, 142.26, 142.24, 130.48, 128.64, 128.57, 128.54, 127.91, 127.88, 127.72, 127.37, 127.20, 127.15, 127.05, 126.41, 125.57, 120.00, 112.28, 77.97, 76.87, 72.55, 61.93, 47.26, 39.52, 37.16, 16.34, 14.06; **IR** (neat) ν 3025, 2933, 2831, 2220, 1707, 1594, 1490, 1240, 1049, 749 cm^{-1}; **HRMS** (DART) Calcd for $C_{35}H_{36}NO_3$ (MH^+): 518.2689; found: 518.2691.



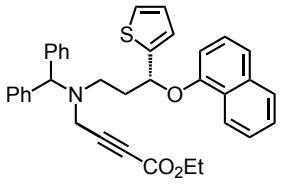
2.23m

Ethy l4-(benzhydryl(3-(10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-ylidene)propyl)amino)but-2-ynoate (2.23m)

N-Benzhydryl-3-(10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-ylidene)-*N*-methylpropan-1-amine **2.23m** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.22a** following **General Procedure B** using 1,2-bis(diphenylphosphino)ethane as the ligand. After purification by column chromatography (Et_2O:hexanes = 1:4), **2.23m** was obtained as a colorless liquid (79 mg, 74%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 4H), 7.30 – 7.22 (m, 5H), 7.22 – 7.12 (m, 7H), 7.10 – 7.02 (m, 2H), 5.84 (t, *J* = 7.5, 1.5 Hz, 1H), 4.67 (s, 1H), 4.27 (q, *J* = 7.1, 1.5 Hz, 2H), 3.47 – 3.19 (m, 4H), 2.97 (s, 1H), 2.67 (t, *J* = 7.2 Hz, 3H), 2.30 (q, *J* = 7.2 Hz, 2H), 1.36 (t, *J* = 7.1, 1.4 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.44, 143.77, 142.40,

141.22, 139.94, 139.32, 137.01, 129.96, 128.95, 128.58, 128.50, 128.48, 128.20, 128.00, 127.88, 127.41, 127.14, 126.98, 125.96, 125.76, 83.73, 77.82, 72.31, 61.92, 50.32, 39.28, 33.75, 31.98, 27.63; **IR** (neat) ν 3020, 2922, 2836, 2224, 1707, 1484, 1448, 1365, 11243, 751 cm^{-1}; **HRMS** (DART) Calcd for $C_{37}H_{36}NO_2$ (MH^+): 526.2740; found: 526.2751.

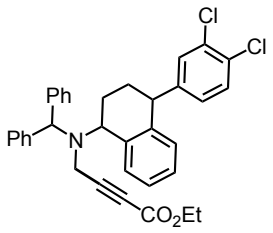


2.23n

Ethyl (*R*)-4-(benzhydryl(3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propyl)amino)but-2-ynoate (2.23n)

(*R*)-*N*-Benzhydryl-*N*-methyl-3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propan-1-amine **2.23n** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.22a** following **General Procedure B** using 1,2-bis(diphenylphosphino)ethane as the ligand. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.23n** was obtained as a colorless liquid (76 mg, 68%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.3 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 7.3 Hz, 1H), 7.40 (dd, *J* = 19.1, 7.8 Hz, 4H), 7.27 (dt, *J* = 25.2, 7.3 Hz, 5H), 7.17 (q, *J* = 5.5 Hz, 2H), 7.01 – 6.91 (m, 4H), 6.89 (t, *J* = 4.4 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 5.69 (dd, *J* = 8.5, 4.3 Hz, 1H), 4.67 (s, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.59 (d, *J* = 4.6 Hz, 2H), 2.86 (d, *J* = 7.7 Hz, 2H), 2.49 – 2.11 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.30, 145.27, 142.27, 141.98, 134.53, 128.65, 128.47, 127.86, 127.67, 127.28, 127.22, 126.98, 126.51, 126.23, 125.58, 125.14, 124.59, 124.44, 122.22, 120.46, 106.43, 83.39, 78.05, 73.88, 72.48, 61.94, 53.39, 47.09, 39.67, 37.18, 14.04; **IR** (neat) ν 3055, 2926, 2837, 2220, 1707, 1579, 1453, 1243, 1092, 702 cm^{-1}; **HRMS** (DART) Calcd for $C_{36}H_{34}NO_3S$ (MH^+): 560.2254; found: 560.2239.

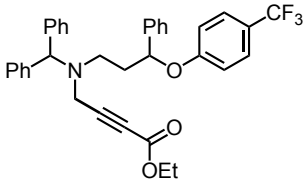


2.23o

Ethyl 4-(benzhydryl(4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-yl)amino)but-2-ynoate (2.23o)

N-Benzhydryl-4-(3,4-dichlorophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine **2.23o** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.22a** following **General Procedure B** using 1,2-bis(diphenylphosphino)ethane as the ligand. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.23o** was obtained as a colorless liquid (76 mg, 67%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.1 Hz, 1H), 7.72 – 7.56 (m, 4H), 7.42 – 7.07 (m, 10H), 6.85 (dd, *J* = 69.9, 8.1 Hz, 2H), 5.31 – 5.17 (m, 1H), 4.28 – 4.11 (m, 3H), 4.05 (s, 1H), 3.53 (s, 2H), 2.06 (t, *J* = 12.1 Hz, 1H), 2.00 – 1.75 (m, 3H), 1.27 (t, *J* = 7.1, 3.2 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.30, 147.15, 142.24, 139.04, 138.62, 132.19, 130.67, 129.99, 129.86, 128.83, 128.69, 128.18, 128.08, 127.90, 127.57, 127.37, 127.33, 126.99, 86.25, 77.53, 69.11, 61.74, 57.80, 43.38, 36.16, 30.34, 17.46, 13.97; **IR** (neat) ν 3023, 2931, 2860, 2221, 1706, 1592, 1459, 1241, 1117, 1052 cm^{-1}; **HRMS** (DART) Calcd for $C_{35}H_{32}NO_2Cl_2$ (MH^+): 568.1805; found: 568.1799.



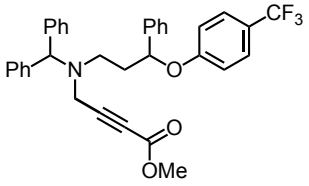
2.25a

Ethyl 4-(benzhydryl(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)amino)but-2-ynoate (2.25a)

N-Benzhydryl-*N*-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine **2.15p** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.22a** following **General Procedure B** using 1,2-bis(diphenylphosphino)ethane as the ligand. After purification by column

chromatography (Et_2O:hexanes = 1:19), **2.25a** was obtained as a colorless liquid (94 mg, 82%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.39 (m, 4H), 7.35 – 7.22 (m, 10H), 7.18 (tt, *J* = 7.4, 1.5 Hz, 1H), 7.14 – 7.04 (m, 3H), 6.83 – 6.77 (m, 2H), 5.28 – 5.19 (m, 1H), 4.67 (s, 1H), 4.26 (q, *J* = 7.2, 2.4 Hz, 2H), 3.64 – 3.50 (m, 2H), 2.88 – 2.78 (m, 1H), 2.78 – 2.68 (m, 1H), 2.19 – 2.08 (m, 1H), 2.04 – 1.94 (m, 1H), 1.34 (t, *J* = 7.2, 2.4 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ160.52, 153.37, 142.13, 142.08, 141.17, 128.76, 128.64, 128.54, 127.93, 127.76, 127.28, 127.13, 126.65 (d, J_{CF} = 3.3 Hz), 125.62, 124.41 (d, J_{CF} = 271.1 Hz), 122.69 (q, J_{CF} = 32.7 Hz), 115.69, 83.29, 78.04, 77.73, 72.47, 61.96, 46.91, 39.52, 36.81, 14.03; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -61.53; **IR** (neat) ν 3028, 2930, 2834, 2221, 1708, 1612, 1513, 1451, 1324, 1246, 1114 cm^{-1}; **HRMS** (DART) Calcd for $C_{35}H_{33}NO_3F_3(MH^+)$: 572.2407; found: 572.2402.



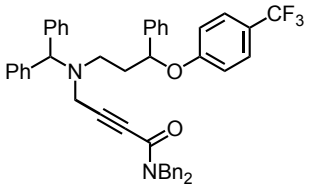
2.25b

Methyl 4-(benzhydryl(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)amino)but-2-ynoate (2.25b)

N-Benzhydryl-*N*-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine **2.15p** was reacted with methyl 3-(trimethylsilyl)propiolate **2.22b** following **General Procedure B** using 1,2-bis(diphenylphosphino)ethane as the ligand. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.25b** was obtained as a colorless liquid (76 mg, 68%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.37 (m, 4H), 7.36 – 7.21 (m, 9H), 7.18 (tt, *J* = 7.1, 1.5 Hz, 1H), 7.12 – 7.05 (m, 3H), 6.80 (d, *J* = 8.4 Hz, 2H), 5.23 (dd, *J* = 9.1, 3.6 Hz, 1H), 4.66 (s, 1H), 3.80 (s, 3H), 3.57 (d, *J* = 10.6 Hz, 2H), 2.88 – 2.67 (m, 2H), 2.20 – 1.95 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.51, 153.76, 142.11, 142.05, 141.15, 128.77, 128.66, 128.55, 127.91, 127.79, 127.75, 127.30, 127.15, 126.65 (d, J_{CF} = 3.8 Hz), 125.62, 124.41 (d, J_{CF} = 271.3 Hz), 122.69 (q, J_{CF} = 32.5 Hz), 115.69, 83.74, 77.72, 72.49, 53.39,

52.66, 46.91, 39.49, 36.81; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -61.50; **IR** (neat) ν 3028, 2946, 2832, 2226, 1713, 1513, 1445, 1324, 1249, 1114 cm^{-1}; **HRMS** (DART) Calcd for $C_{34}H_{31}NO_3F_3$ (MH^+): 558.2251; found: 558.2246.

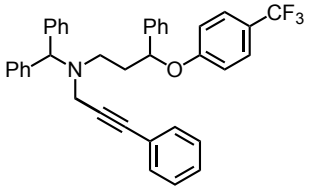


2.25c

4-(Benzhydryl(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)amino)-*N*,*N*-dibenzylbut-2-ynamide (2.25c)

N-Benzhydryl-*N*-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine **2.15p** was reacted with *N,N*-dibenzyl-3-(trimethylsilyl)propiolamide **2.22c** following **General Procedure B** using (*S*)-PhPyBOX as the ligand. After purification by column chromatography (Et_2O:hexanes = 1:4), **2.25c** was obtained as a colorless liquid (116 mg, 80%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.0 Hz, 4H), 7.35 (t, *J* = 7.5 Hz, 3H), 7.31 (d, *J* = 6.8 Hz, 1H), 7.27 (d, *J* = 7.4 Hz, 4H), 7.23 (t, *J* = 9.3 Hz, 7H), 7.17 (t, *J* = 7.5 Hz, 2H), 7.15 – 7.10 (m, 3H), 7.06 (t, *J* = 7.3 Hz, 1H), 7.01 (t, *J* = 7.4 Hz, 2H), 6.75 (d, *J* = 8.4 Hz, 2H), 5.16 (dd, *J* = 9.0, 3.7 Hz, 1H), 4.78 – 4.65 (m, 2H), 4.55 (q, *J* = 14.8 Hz, 2H), 4.46 (s, 1H), 3.61 (q, *J* = 18.3 Hz, 2H), 2.75 – 2.57 (m, 2H), 2.13 – 1.90 (m, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 160.46, 154.70, 142.13, 142.06, 141.10, 136.21, 135.96, 129.01, 128.75, 128.71, 128.57, 128.47, 128.01, 127.78, 127.72, 127.59, 127.24, 127.20, 127.06, 126.64 (d, J_{CF} = 3.0 Hz), 125.58, 124.39 (d, J_{CF} = 271.1 Hz), 122.66 (q, J_{CF} = 32.7 Hz), 115.65, 87.72, 78.90, 77.68, 72.64, 51.30, 46.89, 46.46, 39.64, 36.84; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -61.48; **IR** (neat) ν 3028, 2925, 2830, 2221, 1628, 1324, 1245, 1162, 1113, 700 cm^{-1}; **HRMS** (DART) Calcd for $C_{47}H_{42}N_2O_2F_3$ (MH^+): 723.3193; found: 723.3167.

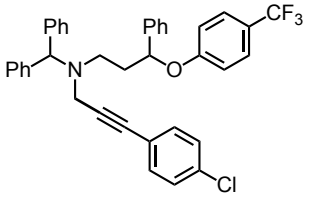


2.25d

***N*-Benzhydryl-3-phenyl-*N*-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)prop-2-yn-1-amine (2.25d)**

N-Benzhydryl-*N*-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine **2.15p** was reacted with trimethyl(phenylethynyl)silane **2.22d** following **General Procedure B** using (*S*)-PhPyBOX as the ligand. After purification by column chromatography (Et_2O:hexanes = 1:49), **2.25d** was obtained as a colorless liquid (86 mg, 75%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.38 (m, 6H), 7.37 – 7.14 (m, 13H), 7.08 (d, J = 6.6 Hz, 3H), 6.81 (d, J = 8.4 Hz, 2H), 5.30 (dd, J = 9.0, 3.8 Hz, 1H), 4.74 (s, 1H), 3.72 – 3.56 (m, 2H), 2.91 – 2.70 (m, 2H), 2.24 – 2.00 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.63, 142.75, 142.66, 141.41, 131.73, 128.72, 128.50, 128.43, 128.28, 128.05, 127.91, 127.70, 127.07, 126.95, 126.64 (d, J_{CF} = 3.1 Hz), 125.68, 124.45 (d, J_{CF} = 271.5 Hz), 123.32, 122.59 (q, J_{CF} = 32.6 Hz), 115.72, 85.86, 84.16, 77.88, 72.55, 46.67, 39.98, 36.89; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -61.49; **IR** (neat) ν 3060, 2927, 2829, 2096, 1513, 1491, 1324, 1249, 1162, 1114, 698 cm^{-1}; **HRMS** (DART) Calcd for $C_{38}H_{33}NOF_3$ (MH^+): 576.2509; found: 576.2504.

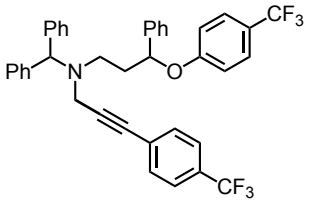


2.25e

***N*-Benzhydryl-*N*-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)-3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-amine (2.25e)**

N-Benzhydryl-*N*-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine **2.15p** was reacted with trimethyl((4-(trifluoromethyl)phenyl)ethynyl)silane **2.22e** following **General Procedure B** using (*S*)-PhPyBOX as the ligand. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.25e** was obtained as a colorless liquid (106 mg, 82%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 8.4, 4.1 Hz, 2H), 7.48 (dd, *J* = 8.1, 4.1 Hz, 2H), 7.43 (ddd, *J* = 13.0, 8.0, 4.1 Hz, 4H), 7.35 (tt, *J* = 4.9, 2.2 Hz, 2H), 7.29 (d, *J* = 4.8 Hz, 4H), 7.28 – 7.22 (m, 3H), 7.19 (td, *J* = 7.1, 4.4 Hz, 1H), 7.10 (p, *J* = 5.2 Hz, 3H), 6.81 (dd, *J* = 9.0, 4.0 Hz, 2H), 5.30 (dt, *J* = 8.5, 4.0 Hz, 1H), 4.73 (d, *J* = 4.2 Hz, 1H), 3.73 – 3.60 (m, 2H), 2.97 – 2.70 (m, 2H), 2.25 – 2.00 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.59, 142.57, 142.45, 141.33, 132.38, 132.17 (d, J_{CF} = 293.4 Hz), 129.83 (q, J_{CF} = 32.6 Hz), 128.76, 128.57, 128.49, 128.01, 127.88, 127.77, 127.19, 127.07, 126.67 (d, J_{CF} = 2.9 Hz), 125.69, 125.22 (d, J_{CF} = 2.8 Hz), 124.19 (d, J_{CF} = 211.0 Hz), 122.68 (q, J_{CF} = 32.5 Hz), 115.70, 87.12, 84.62, 77.86, 72.64, 46.77, 40.04, 36.86; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -61.45, -62.75; **IR** (neat) ν 3027, 2931, 2829, 1612, 1513, 1450, 1322, 1249, 1116, 701 cm^{-1}; **HRMS** (DART) Calcd for $C_{39}H_{32}NOF_6$ (MH^+): 644.2383; found: 644.2365.



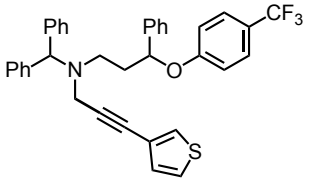
2.25f

***N*-Benzhydryl-3-(4-chlorophenyl)-*N*-(3-phenyl-3-(4(trifluoromethyl)phenoxy) propyl)prop-2-yn-1-amine (2.25f)**

N-Benzhydryl-*N*-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine **2.15p** was reacted with ((4-chlorophenyl)ethynyl)trimethylsilane **2.22f** following **General Procedure B** using (*S*)-PhPyBOX as the ligand. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.25f** was obtained as a colorless liquid (98 mg, 80%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 – 7.37 (m, 4H), 7.29 (dddd, *J* = 22.3, 20.6, 9.1, 7.4 Hz, 13H), 7.18 (ddd, *J* = 7.4, 6.1, 1.4 Hz, 1H), 7.13 – 7.03 (m, 3H), 6.81 (d, *J* = 8.4 Hz, 2H), 5.29 (dd, *J* = 9.0, 3.8 Hz, 1H), 4.71 (s, 1H), 3.63 (q, *J* = 17.7 Hz, 2H), 2.93 – 2.65 (m, 2H), 2.25 – 1.97 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.60, 142.65, 142.53, 141.36, 134.03, 132.94, 128.74, 128.60, 128.53, 128.45, 128.02, 127.89, 127.73, 127.13, 127.00, 126.65 (d, J_{CF} = 2.6 Hz), 125.68, 124.43 (d, J_{CF} = 271.1 Hz), 122.64 (q, J_{CF} = 32.8 Hz), 121.76, 115.70, 85.34, 84.73, 77.86, 72.58, 46.70, 40.00, 36.86; **^{19}F NMR** (470 MHz,

$CDCl_3$) δ -61.50; **IR** (neat) ν 3055, 2928, 2832, 2223, 1707, 1608, 1488, 1245, 1113, 701 cm^{-1}; **HRMS** (DART) Calcd for $C_{38}H_{32}NOF_3Cl$ (MH^+): 610.2119; found: 610.2125.

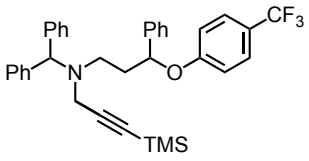


2.25g

***N*-Benzhydryl-*N*-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)-3-(thiophen-3-yl)prop-2-yn-1-amine (2.25g)**

N-Benzhydryl-*N*-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine **2.15p** was reacted with trimethyl(thiophen-3-ylethynyl)silane **2.22g** following **General Procedure B** using (*S*)-PhPyBOX as the ligand. After purification by column chromatography (Et_2O:hexanes = 1:49), **2.25g** was obtained as a colorless liquid (86 mg, 74%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (dt, *J* = 8.9, 5.0 Hz, 4H), 7.38 (d, *J* = 2.9 Hz, 1H), 7.34 (dd, *J* = 6.2, 3.4 Hz, 2H), 7.29 (t, *J* = 3.4 Hz, 4H), 7.25 (ddq, *J* = 9.9, 7.1, 4.3, 3.5 Hz, 4H), 7.18 (dt, *J* = 7.8, 3.8 Hz, 1H), 7.08 (dt, *J* = 8.8, 4.2 Hz, 4H), 6.81 (dd, *J* = 8.8, 2.5 Hz, 2H), 5.30 (dd, *J* = 9.1, 3.9 Hz, 1H), 4.72 (s, 1H), 3.62 (q, *J* = 17.8 Hz, 2H), 2.80 (ddt, *J* = 50.2, 12.0, 6.5 Hz, 2H), 2.12 (dt, *J* = 55.1, 12.1 Hz, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 160.62, 142.73, 142.62, 141.41, 130.03, 128.73, 128.50, 128.42, 128.33, 128.04, 127.90, 127.71, 127.07, 126.94, 125.68, 126.65 (d, *J* = 3.6 Hz), 124.69 (d, *J* = 267.9 Hz), 122.59 (d, *J* = 32.9 Hz), 122.27, 115.70, 83.75, 80.78, 77.83, 72.49, 46.64, 39.99, 36.88; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -61.41; **IR** (neat) ν 3026, 2929, 2829, 2166, 1514, 1450, 1324,1249, 1114, 700 cm^{-1}; **HRMS** (DART) Calcd for $C_{36}H_{31}NOF_3S$ (MH^+): 582.2073; found: 582.2074.

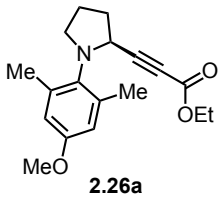


2.25h

***N*-Benzhydryl-*N*-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)-3-(trimethylsilyl) prop-2-yn-1-amine (2.25h)**

N-Benzhydryl-*N*-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine **2.15p** was reacted with 1,2-bis(trimethylsilyl)ethyne **2.22h** following **General Procedure B** using (*S*)-PhPyBOX as the ligand. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.25h** was obtained as a colorless liquid (99 mg, 87%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 20.0, 8.2 Hz, 4H), 7.32 – 7.27 (m, 6H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 7.5 Hz, 2H), 7.10 – 7.05 (m, 3H), 6.80 (d, *J* = 8.4 Hz, 2H), 5.25 (dd, *J* = 9.2, 3.4 Hz, 1H), 4.64 (s, 1H), 3.42 (q, *J* = 17.9 Hz, 2H), 2.80 – 2.66 (m, 2H), 2.13 – 1.98 (m, 2H), 0.20 (s, 9H); **^{19}F NMR** (470 MHz, $CDCl_3$) δ -61.50; **IR** (neat) ν 3059, 2951, 2848, 2160, 1612, 1324, 1250, 1116, 840, 700 cm^{-1}; **HRMS** (DART) Calcd for $C_{35}H_{37}NOF_3Si(MH^+)$: 572.2591; found: 572.2579.



2.26a

Ethyl (*S*)-3-(1-(4-methoxy-2,6-dimethylphenyl)pyrrolidin-2-yl)propiolate (2.26a)

1-(4-Methoxy-2,6-dimethylphenyl)pyrrolidine **2.15a** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.22a** following **General Procedure C**. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.26a-(*S*)** was obtained as a colorless liquid (45 mg, 75%). The absolute configuration of **2.26a-(*S*)** was assigned as (*S*).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.58 (s, 2H), 4.27 (ddd, *J* = 7.8, 3.5, 1.3 Hz, 1H), 4.17 (qd, *J* = 7.2, 1.3 Hz, 2H), 3.75 (s, 3H), 3.43 – 3.31 (m, 1H), 3.09 (q, *J* = 6.9 Hz, 1H), 2.47 – 2.22 (m, 6H), 2.22 – 2.10 (m, 3H), 2.09 – 1.94 (m, 1H), 1.27 (td, *J* = 7.2, 1.4 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.15, 153.86, 135.89, 113.60, 90.83, 73.94, 61.66, 55.16, 52.31, 51.03, 33.83, 25.68, 18.89, 13.99; **IR** (neat) ν 2967, 2837, 2224, 1707, 1599, 1476, 1366,1244, 1153, 1067, cm^{-1}; **HRMS** (DART) Calcd for $C_{18}H_{24}NO_3$ (MH^+): 302.1751; found: 302.1755; $[\alpha]^{25}_D$ = 76.2° (*c* 1.0, CH_2Cl_2); **HPLC** (Chiralcel OJ-H; 95:5 hexane:isopropanol, 1.0 mL/min; **2.26a-(*S*):** tr = 6.5 min (major), 9.5 min (minor); 95:5 er.

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                                                 Inj Volume : 4.000 µl
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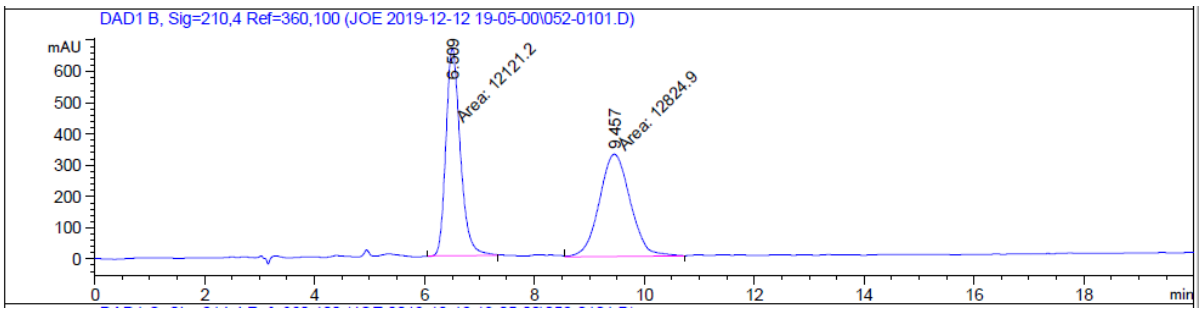

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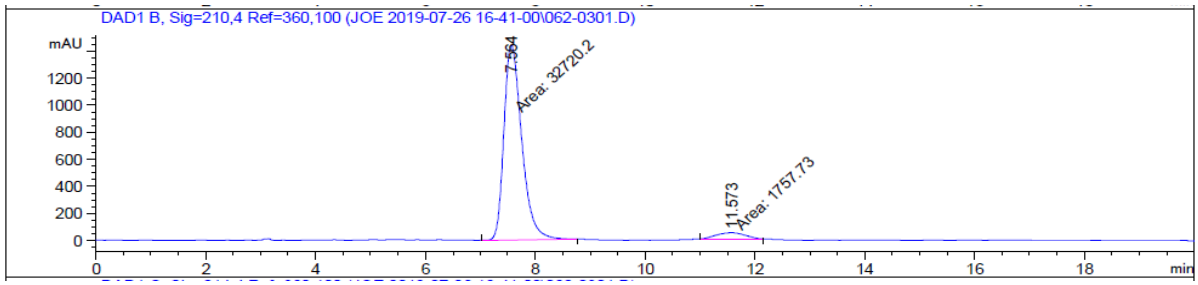

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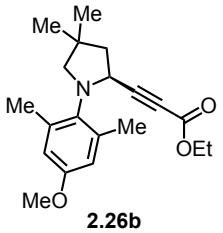

2.26b

Ethyl (*S*)-3-(1-(4-methoxy-2,6-dimethylphenyl)-4,4-dimethylpyrrolidin-2-yl)propiolate (2.26b)

1-(4-Methoxy-2,6-dimethylphenyl)-3,3-dimethylpyrrolidine **2.15b** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.22a** following **General Procedure C**. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.26b** was obtained as a yellow oil (45 mg, 69%). The absolute configuration of **2.26b** was assigned in analogy to **2.26a-(*S*)**.

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.57 (s, 2H), 4.41 (dd, *J* = 9.0, 3.8 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.75 (s, 3H), 3.07 (d, *J* = 7.9 Hz, 1H), 2.95 (d, *J* = 7.8 Hz, 1H), 2.37 (s, 5H), 2.19 (dd, *J* = 12.5, 9.0 Hz, 2H), 1.98 (dd, *J* = 12.5, 3.9 Hz, 1H), 1.37 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.15 (d, *J* = 1.0 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.17, 153.83, 135.35, 113.68, 90.96, 74.30, 64.52, 61.63, 55.15, 51.92, 47.01, 39.12, 27.77, 27.24, 13.98; **IR** (neat) 2954, 2864, 2228, 1707, 1601, 1465, 1243, 1094, 1-23, 751 cm^{-1}; **HRMS** (DART) Calcd for $C_{20}H_{28}NO_3$ (MH^+): 330.2063; found: 330.2069; $[\alpha]^{25}_D$ = 20.5° (*c* 0.3, CH_2Cl_2); **HPLC** (Chiralpak AY-3; 99.9:0.1 hexane:isopropanol, 0.3 mL/min; **2.26b:** tr = 27.4 min (major), 38.1 min (minor); 93:7 er.

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Method Filename	: 99.9_0.1_60min_0.3mL.lcm		
Batch Filename	: batch8.lcb		
Vial #	: 1-24	Sample Type	: Unknown
Injection Volume	: 10 uL		
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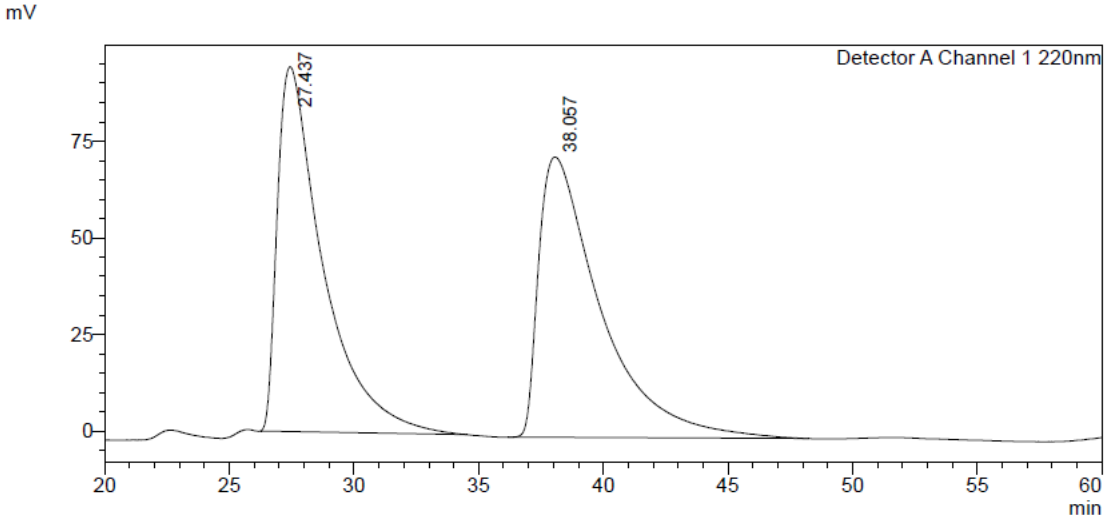
Date Processed	: 2/11/2020 10:17:04 AM	Processed by	: System Administrator



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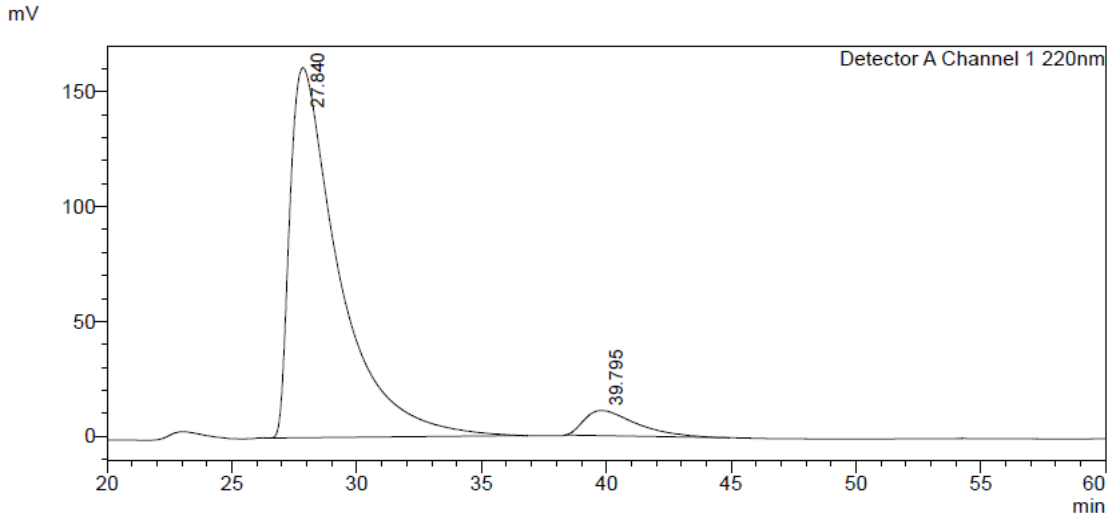

Detector A Channel 1 220nm

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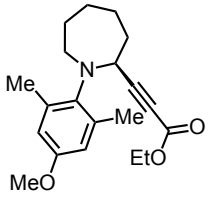

2.26c

Ethyl (*S*)-3-(1-(4-methoxy-2,6-dimethylphenyl)azepan-2-yl)propiolate (2.26c)

1-(4-Methoxy-2,6-dimethylphenyl)azepane **2.15c** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.22a** following **General Procedure C**. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.26c** was obtained as a colorless liquid (42 mg, 64%). The absolute configuration of **2.26c** was assigned in analogy to **2.26a-(*S*)**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.57 (d, *J* = 13.4 Hz, 2H), 4.18 (d, *J* = 7.1 Hz, 2H), 4.06 (d, *J* = 2.7 Hz, 1H), 3.75 (s, 3H), 3.32 (d, *J* = 9.1 Hz, 1H), 3.08 (d, *J* = 11.1 Hz, 1H), 2.42 (s, 3H), 2.29 (s, 3H), 2.19 (d, *J* = 1.5 Hz, 1H), 1.95 – 1.85 (m, 2H), 1.85 – 1.79 (m, 1H), 1.79 – 1.70 (m, 2H), 1.57 (s, 2H), 1.28 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 156.53, 153.77, 141.76, 139.19, 137.94, 114.13, 113.64, 90.92, 75.66, 61.65, 55.17, 53.81, 51.31, 35.68, 31.91, 29.33, 25.25, 20.14, 19.65, 14.01; **IR** (neat) ν 2926, 2845, 2221, 1707, 1598, 1474, 1309, 1240, 1065, 853 cm^{-1}; **HRMS** (DART) Calcd for $C_{20}H_{28}NO_3$ (MH^+): 330.2063;

found: 330.2061; $[\alpha]^{25}_{D}$ = 30.1° (c 1.0, CH_2Cl_2); **HPLC** (Chiralcel OJ-H; 98.5:1.5 hexane:isopropanol, 0.5 mL/min; **2.26c:** tr = 14.8 min (major), 17.4 min (minor); 95:5 er.

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                                                  Inj Volume : 4.000 µl
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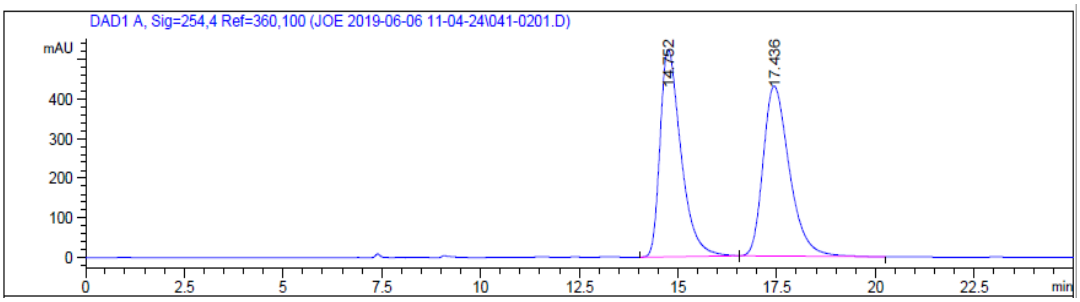


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Signal 1: DAD1 A, Sig=254,4 Ref=360,100
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1	14.752	BB	0.5570	1.92070e4	522.36609	49.2058
2	17.436	BB	0.7122	1.98270e4	428.21890	50.7942

```
Acq. Operator    : SYSTEM                          Seq. Line :   2
Acq. Instrument : Wasa_LC1                          Location :   11
Injection Date   : 8/7/2019 4:14:59 PM                  Inj :   1
                                                  Inj Volume : 4.000 µl
Acq. Method      : C:\Chem32\1\Data\JOE 2019-08-07 15-42-04\column4 1.5%IPA 98.5% hexane 30min
                   -0.5mL.M
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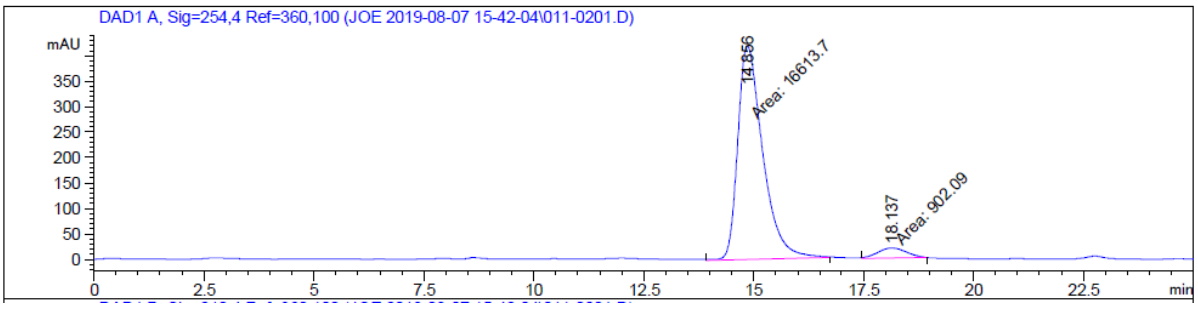
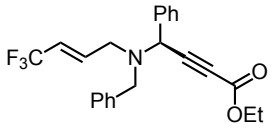


Signal 2: DAD1 B, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.856	MM	0.6745	9.39466e4	2321.40063	95.4662
2	18.137	MM	0.6770	4461.63379	109.84474	4.5338



2.26d

Ethyl (*S,E*)-4-(benzyl(4,4,4-trifluorobut-2-en-1-yl)amino)-4-phenylbut-2-ynoate (2.26d)

(*E*)-*N,N*-Dibenzyl-4,4,4-trifluorobut-2-en-1-amine was reacted with ethyl 3-(trimethylsilyl)propiolate **2.22a** following **General Procedure C** using (*S*)-PhPyBOX as the ligand. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.26d** was obtained as a colorless liquid (36 mg, 45%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 (dt, *J* = 8.1, 1.1 Hz, 2H), 7.40 – 7.31 (m, 7H), 7.31 – 7.25 (m, 1H), 6.33 (dddd, *J* = 15.8, 7.5, 4.2, 2.1 Hz, 1H), 5.94 – 5.84 (m, 1H), 4.87 (s, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.83 (d, *J* = 13.5 Hz, 1H), 3.54 (d, *J* = 13.5 Hz, 1H), 3.28 (dq, *J* = 15.6, 3.2 Hz, 1H), 3.21 – 3.14 (m, 1H), 1.38 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 153.38, 137.94, 136.46, 128.85, 128.82, 128.66, 128.58, 128.51, 128.37, 128.24, 127.92, 127.59, 127.16, 123.67, 121.89, 120.38 (q, *J* = 33.9 Hz), 82.79, 80.53, 62.25, 58.25, 56.30, 55.43, 52.91, 50.63, 14.08; **^{19}F NMR** (564 MHz, $CDCl_3$) δ -64.07, -64.08, -64.08, -64.09, -64.09, -64.10; **IR** (neat) ν 2925, 2222, 1711, 1492, 1450, 1242, 1119, 749, 698 cm^{-1}; **HRMS** (DART) Calcd for $C_{23}H_{23}NO_2F_3$ (MH^+): 402.1675; found: 402.1667; $[\alpha]^{25}_D$ = –45.3° (*c* 1.0, CH_2Cl_2); **HPLC** (Chiralcel AD-H; 99.5:0.5 hexane:isopropanol, 0.3 mL/min; **2.26p:** tr = 34.9 min (minor), 37.0 min (major); 2.17:16 er.

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Sample ID	: 8e_rac3_JZC2017H2_AD-H_0.3mL		
Data Filename	: 8e_rac3_JZC2017H2_AD-H_0.3mL.lcd		
Method Filename	: 995_05_60min_03mL.lcm		
Batch Filename	: batch9.lcb		
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Injection Volume	: 4 uL		
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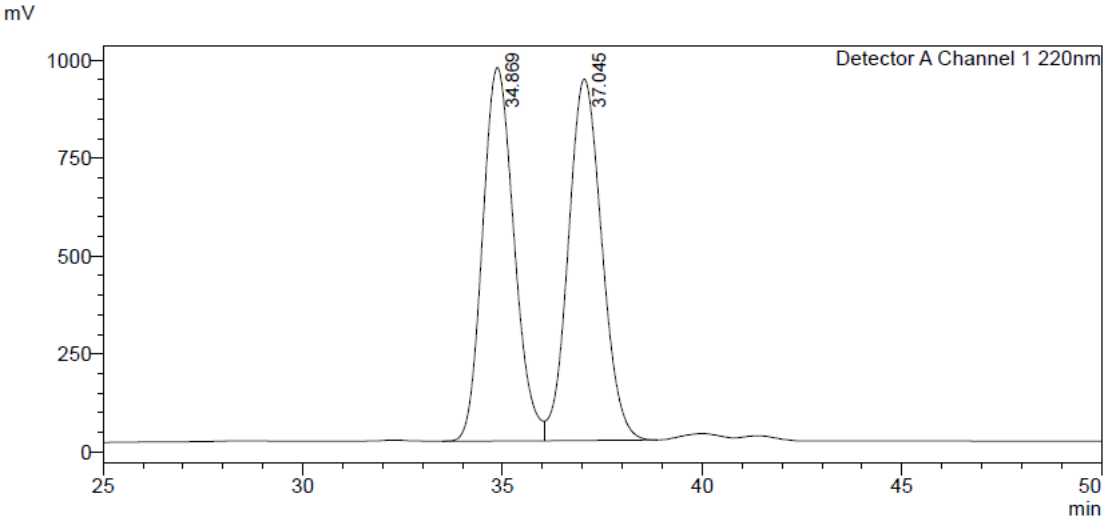
Date Processed	: 2/10/2020 9:51:53 AM	Processed by	: System Administrator



Detector A Channel 1 220nm

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2	37.045	53800949	50.728
Total		106058696	100.000

Sample Name	: 8e_ee3_JZC2187BC_n1n1_AD-H_0.3mL		
Sample ID	: 8e_ee3_JZC2187BC_n1n1_AD-H_0.3m		
Data Filename	: 8e_ee3_JZC2187BC_n1n1_AD-H_0.3mL.lcd		
Method Filename	: 995_05_60min_03mL.lcm		
Batch Filename	: batch9.lcb		
Vial #	: 1-5	Sample Type	: Unknown
Injection Volume	: 4 uL		
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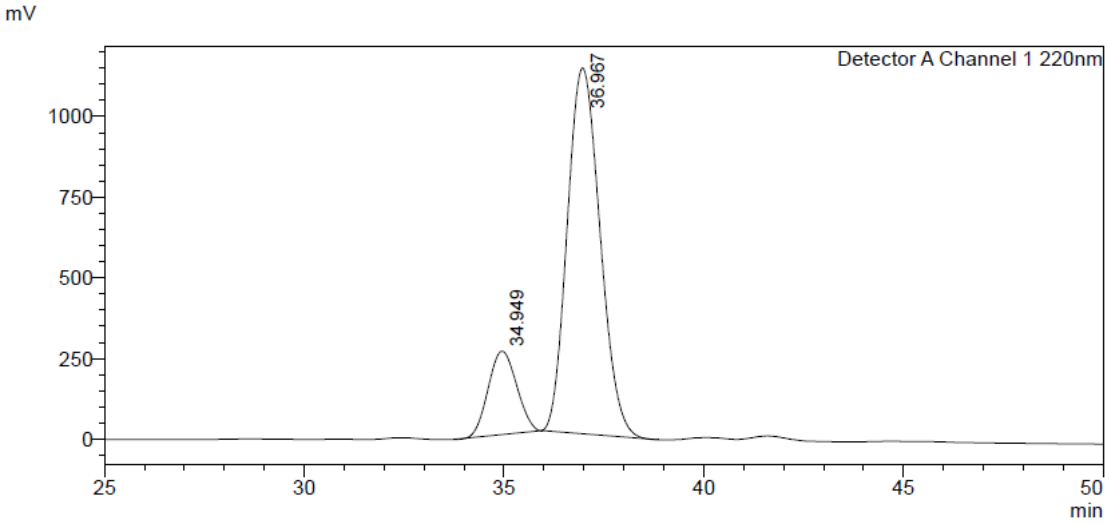
Date Processed	: 2/10/2020 9:40:28 AM	Processed by	: System Administrator



Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%
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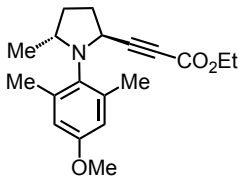
2	36.967	64623088	83.515
Total		77379185	100.000



2.26e

Ethyl 3-((2*S*,5*R*)-1-(4-methoxy-2,6-dimethylphenyl)-5-methylpyrrolidin-2-yl)propiolate (2.26e)

1-(4-Methoxy-2,6-dimethylphenyl)-2-methylpyrrolidine was reacted with ethyl 3-(trimethylsilyl)propiolate **2.22a** following **General Procedure C**. The *trans*:*cis* ratio was determined to be 6.3:1 by ^{1}H NMR analysis of the unpurified reaction mixtures. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.26e** was obtained as a yellow oil (42 mg, 66%). The relative configuration of **2.26e** was assigned by NOESY analysis as described in SI Section 3.

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.58 (d, *J* = 1.2 Hz, 2H), 4.37 (dd, *J* = 7.7, 4.1 Hz, 1H), 4.15 (qd, *J* = 7.1, 0.8 Hz, 2H), 3.84 (q, *J* = 6.1 Hz, 1H), 3.76 (s, 3H), 2.43 – 2.37 (m, 1H), 2.36 (s, 3H), 2.32 – 2.25 (m, 1H), 2.19 (s, 3H), 2.09 – 2.02 (m, 1H), 1.61 – 1.55 (m, 1H), 1.25 (d, *J* = 0.9 Hz, 3H), 0.86 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 156.76, 153.75, 140.20, 139.66, 133.55, 113.85, 113.17, 90.98, 74.59, 61.65, 55.20, 55.11, 52.16,

33.15, 31.40, 20.31, 19.89, 19.04, 13.99; **IR** (neat) ν 2956, 2222, 1705, 1597, 1471, 1368, 1234, 1152, 1065, 852 cm^{-1}; **HRMS** (DART) Calcd for $C_{19}H_{26}NO_3$ (MH^+): 316.1907; found: 316.1905; $[\alpha]^{25}_D$ = 12.1° (*c* 0.3, CH_2Cl_2); **HPLC** (Chiralpak AD-H; 99.7:0.3 hexane:isopropanol, 0.3 mL/min; **2.26e:** tr = 36.9 min (minor), 46.7 min (major); 83:17 er.

Sample Name	: 8b_rac1_aMe_f6_AD-H_inst4_0.3mL_3		
Sample ID	: 8b_rac1_aMe_f6_AD-H_inst4_0.3mL		
Data Filename	: 8b_rac1_aMe_f6_AD-H_inst4_0.3mL_3.lcd		
Method Filename	: 99.7_0.3_60min_0.3mL.lcm		
Batch Filename	: batch9.lcb		
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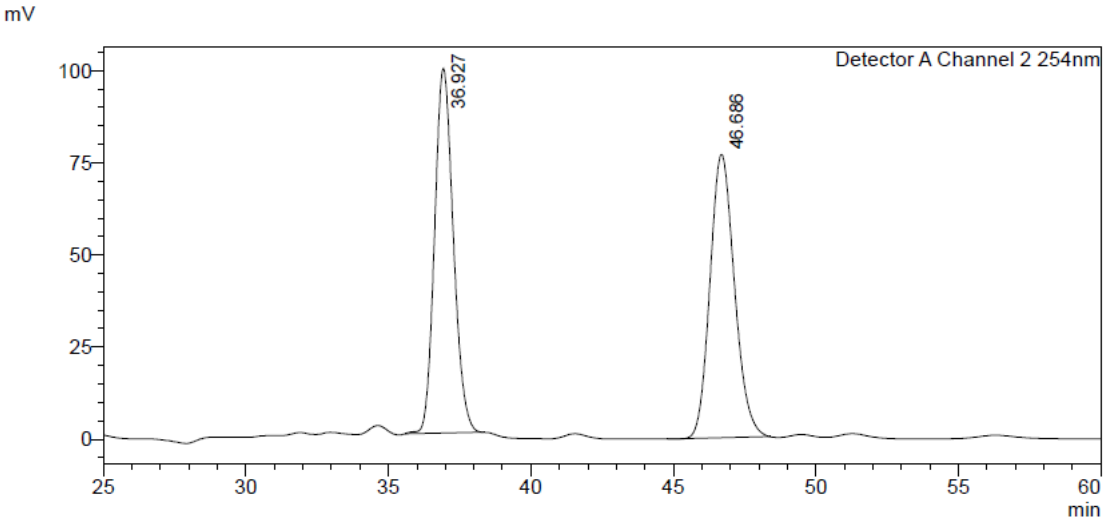

Detector A Channel 2 254nm

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2	46.686	4589671	50.359
Total		9113925	100.000

Sample Name	: 8b_ee2_JZC2264_f9_AD-H_inst4_0.3mL		
Sample ID	: 8b_ee2_JZC2264_f9_AD-H_inst4_0.		
Data Filename	: 8b_ee2_JZC2264_f9_AD-H_inst4_0.3mL.lcd		
Method Filename	: 99.7_0.3_60min_0.3mL.lcm		
Batch Filename	: batch9.lcb		
Vial #	: 1-21	Sample Type	: Unknown
Injection Volume	: 20 uL		
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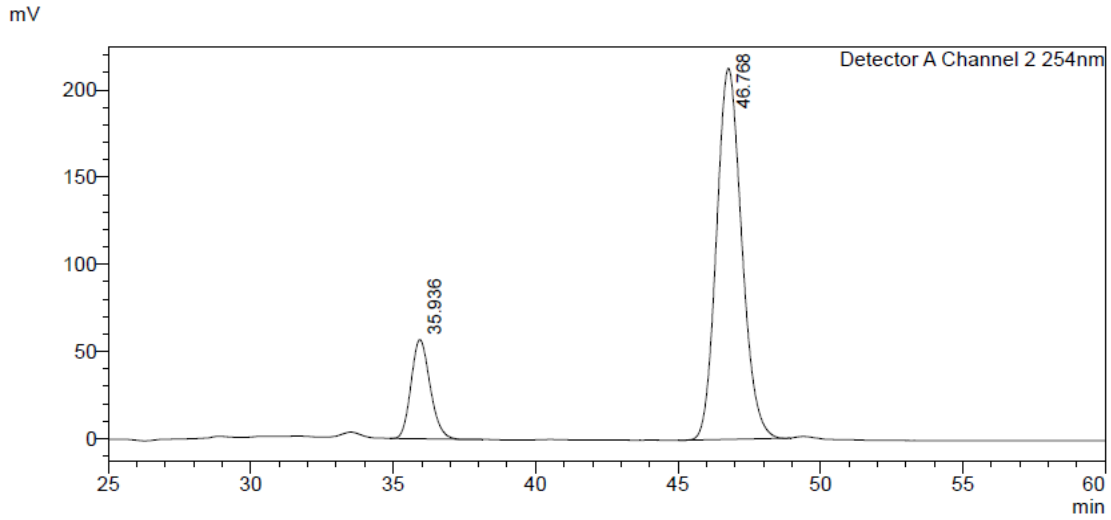
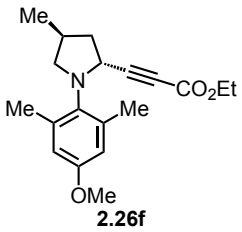


Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Area%
1	35.936	2651131	16.814
2	46.768	13116228	83.186
Total		15767359	100.000



2.26f

Ethyl 3-((2*R*,4*S*)-1-(4-methoxy-2,6-dimethylphenyl)-4-methylpyrrolidin-2-yl)propiolate (2.26f)

(*S*)-1-(4-Methoxy-2,6-dimethylphenyl)-3-methylpyrrolidine was reacted with ethyl 3-(trimethylsilyl)propiolate **2.22a** following **General Procedure C**. The *trans*:*cis* ratio was determined to be 11.8:1 by ^{1}H NMR analysis of the unpurified reaction mixtures. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.26f** was obtained as a colorless liquid (40 mg, 64%). The relative configuration of **2.26f** was assigned by NOESY, COSY, and HSQC analysis (see SI Section 3).

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.58 (s, 2H), 4.29 (dd, *J* = 8.6, 1.8 Hz, 1H), 4.17 (qd, *J* = 7.1, 1.0 Hz, 2H), 3.75 (d, *J* = 1.0 Hz, 3H), 3.38 (t, *J* = 7.2 Hz, 1H), 2.74 (dd, *J* = 8.8, 7.8 Hz, 1H), 2.71 – 2.62 (m, 1H), 2.42 – 2.18 (m, 7H), 2.03 – 1.94 (m, 1H), 1.27 (td, *J* = 7.1, 0.9 Hz, 3H), 1.11 (dd, *J* = 6.5, 0.9 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.14, 153.93, 135.78, 113.60, 91.17, 74.06, 61.66, 58.42, 55.19, 52.71, 41.62, 33.57, 18.79, 17.34, 14.01;

IR (neat) ν 2954, 2924, 1708, 1601, 1484, 1465, 1244, 1154, 1066 cm^{-1}; **HRMS** (DART) Calcd for $C_{19}H_{26}NO_3$ (MH^+): 316.1907; found: 316.1904; $[\alpha]^{25}_D$ = 63.0° (*c* 0.2, CH_2Cl_2); **HPLC** (Chiralpak IA; 97.5:2.5 hexane:isopropanol, 0.2 mL/min; **2.26f:** tr = 23.0 min (major), 24.0 min (minor); 97:3 er.

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                                                  Inj Volume : 4.000 µl
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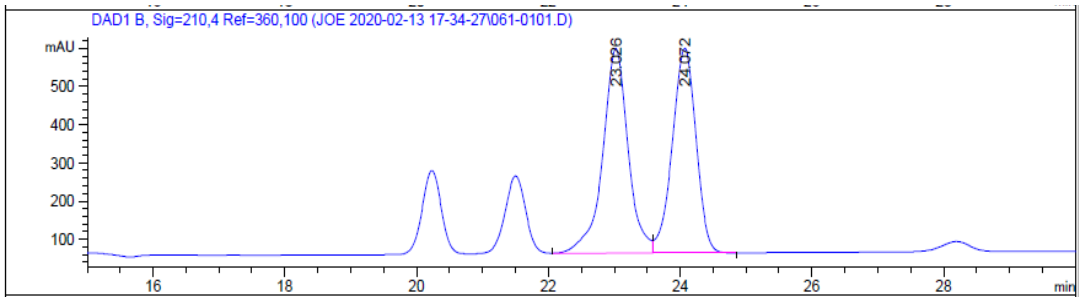


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Signal 2: DAD1 B, Sig=210,4 Ref=360,100

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----|-------|----|-------|----------|----------|--------|
   1  23.026 VV    0.4035 1.44252e4   536.82739  51.7382
   2  24.072 VB    0.3885 1.34559e4   536.65869  48.2618
```

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                                                  Inj Volume : 4.000 µl
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                   -0.2mL.M
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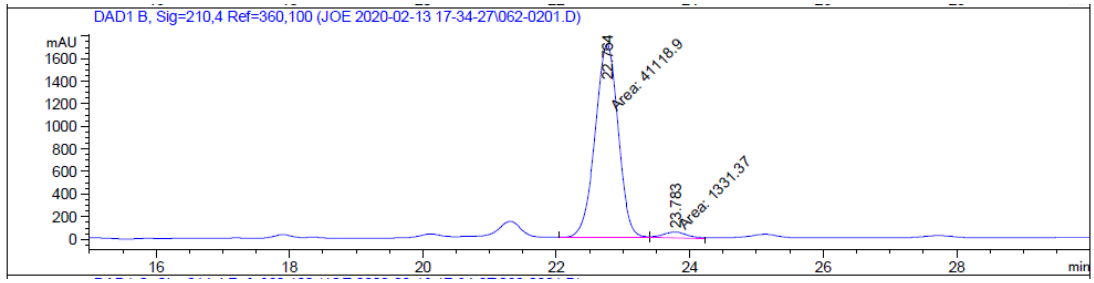

Signal 2: DAD1 B, Sig=210,4 Ref=360,100

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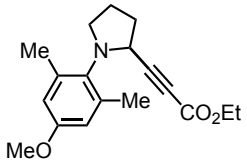
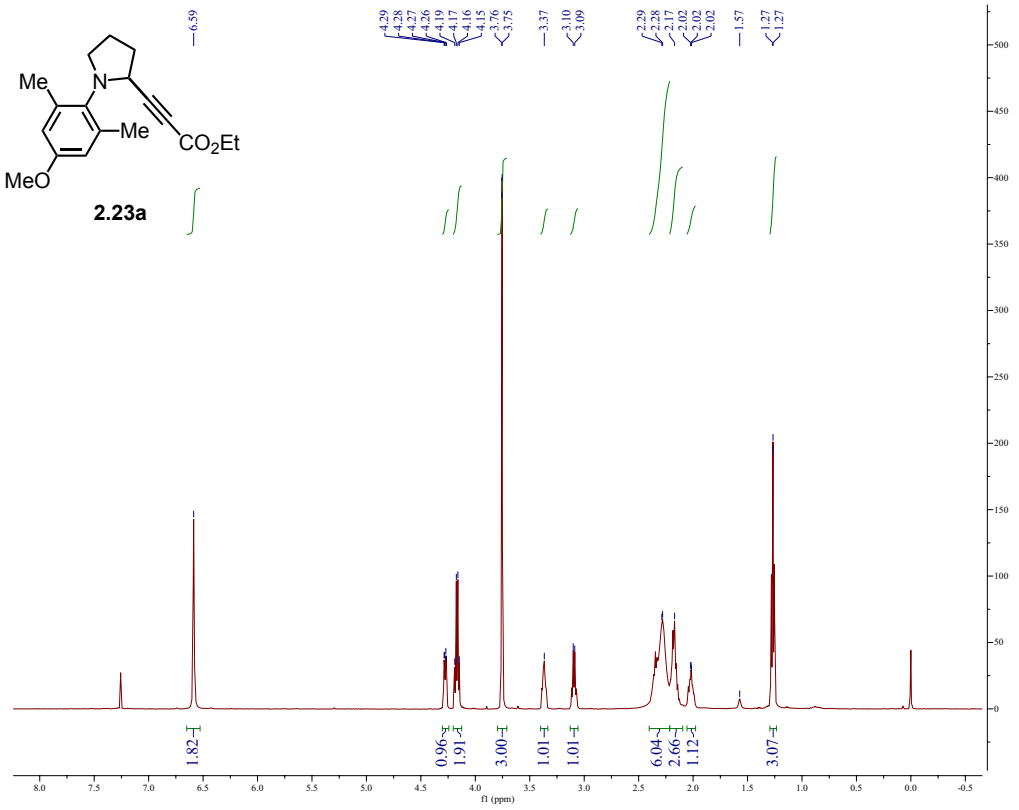
2	23.783	MM	0.4273	1331.37109	51.93531	3.1363

2.7.3 NMR Spectral Data

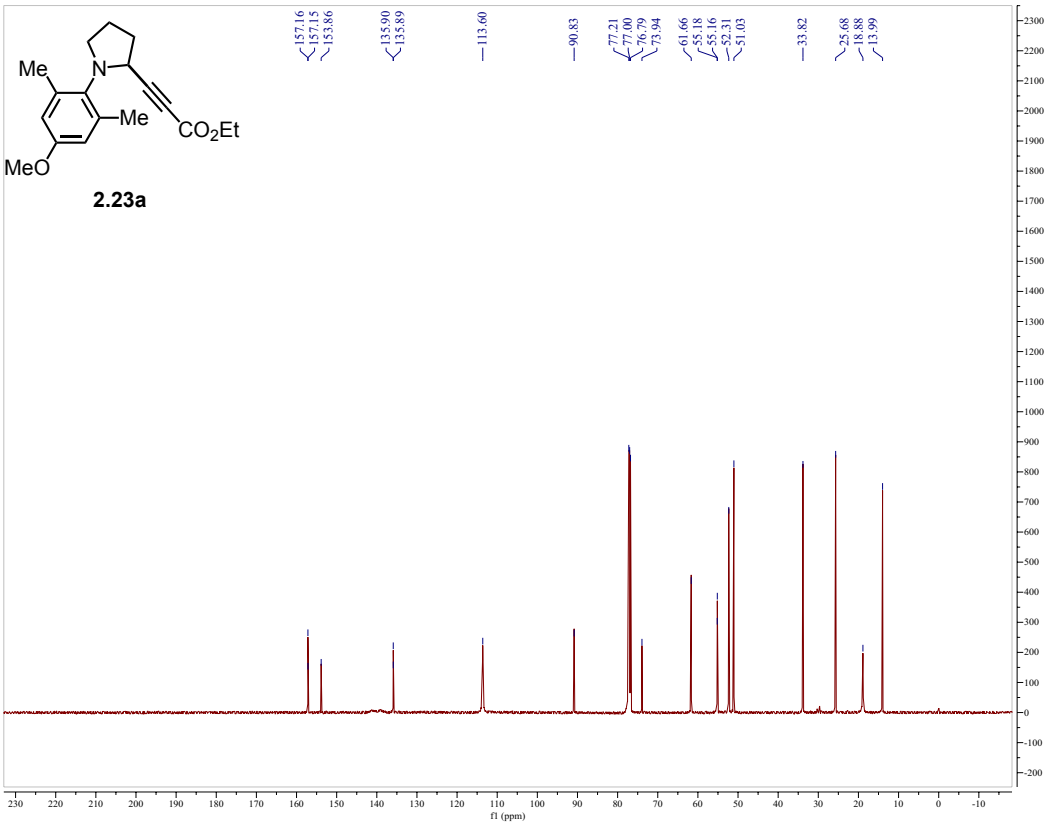


2.23a

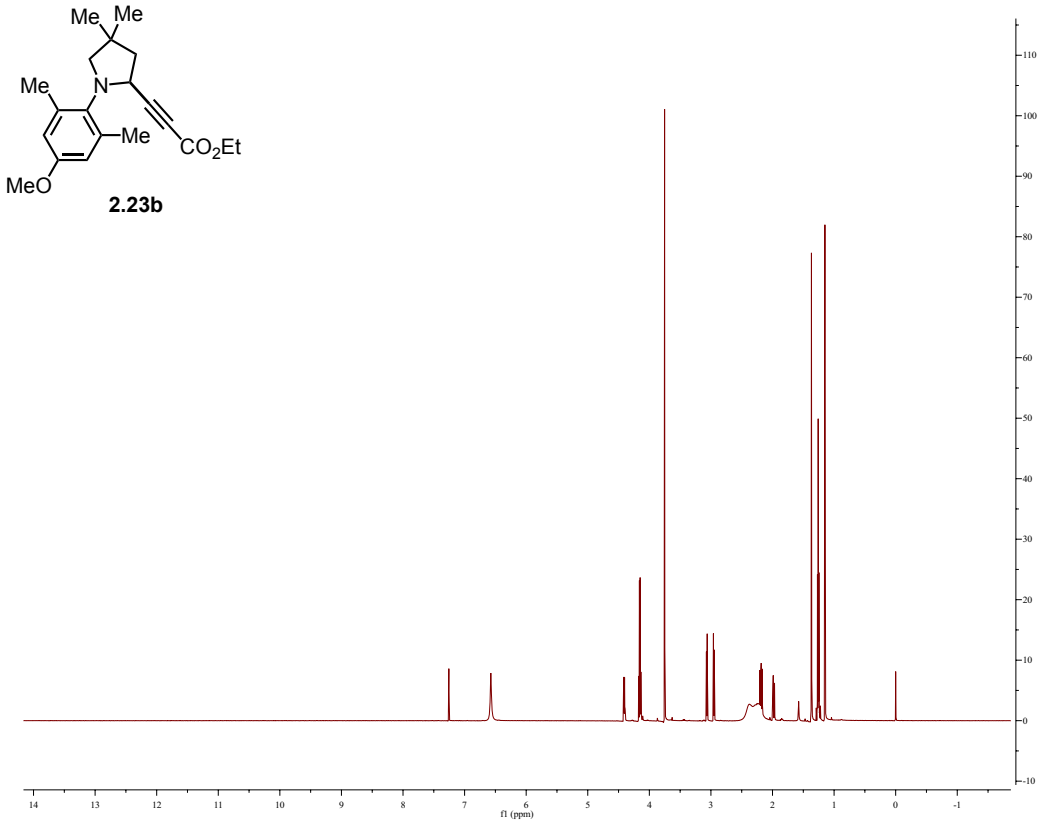


Me
N
Me
CO2Et
MeO

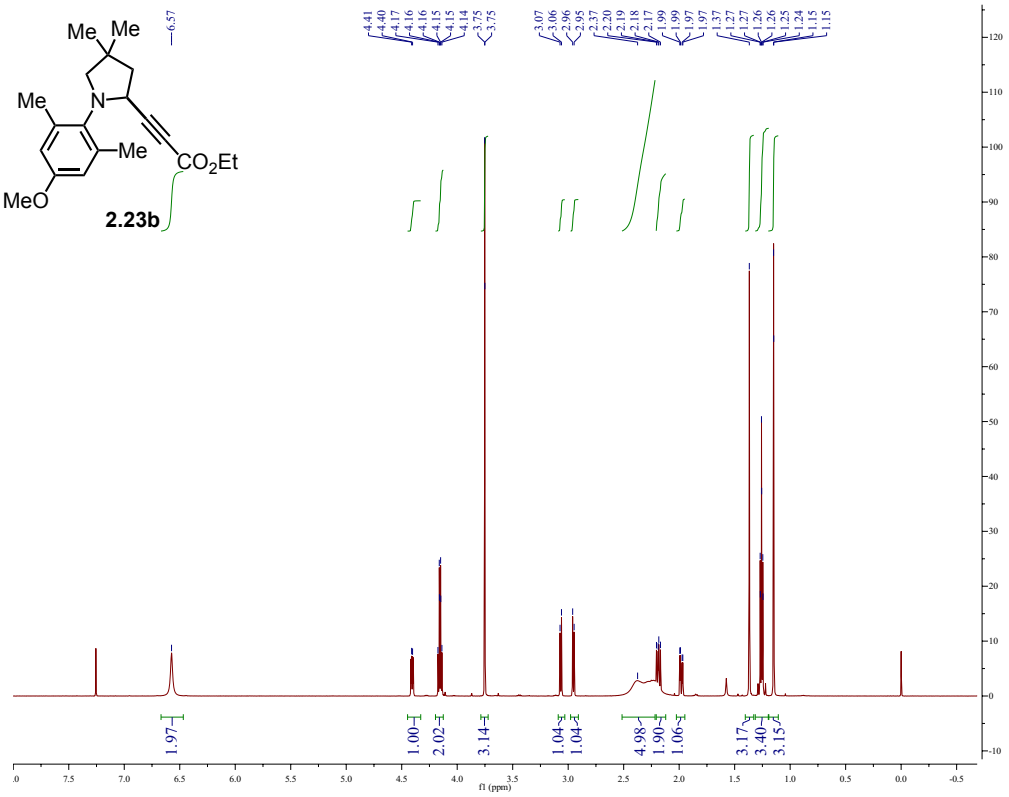
2.23a


Me
N
Me
CO2Et
MeO
157.16
157.15
153.86
135.90
135.89
113.60
90.83
77.21
77.00
76.79
73.94
61.66
55.18
55.16
52.31
51.03
33.82
25.68
18.88
13.99
f1 (ppm)

2.23a


Me
Me
N
Me
CO2Et
MeO
f1 (ppm)

2.23b


Me
Me
Me
N
Me
MeO
CO2Et
2.23b
6.57
4.41
4.40
4.17
4.16
4.16
4.15
4.15
4.14
3.75
3.75
3.07
3.06
2.96
2.95
2.37
2.20
2.19
2.18
2.17
1.99
1.99
1.97
1.97
1.37
1.27
1.27
1.26
1.26
1.25
1.24
1.15
1.15
1.97
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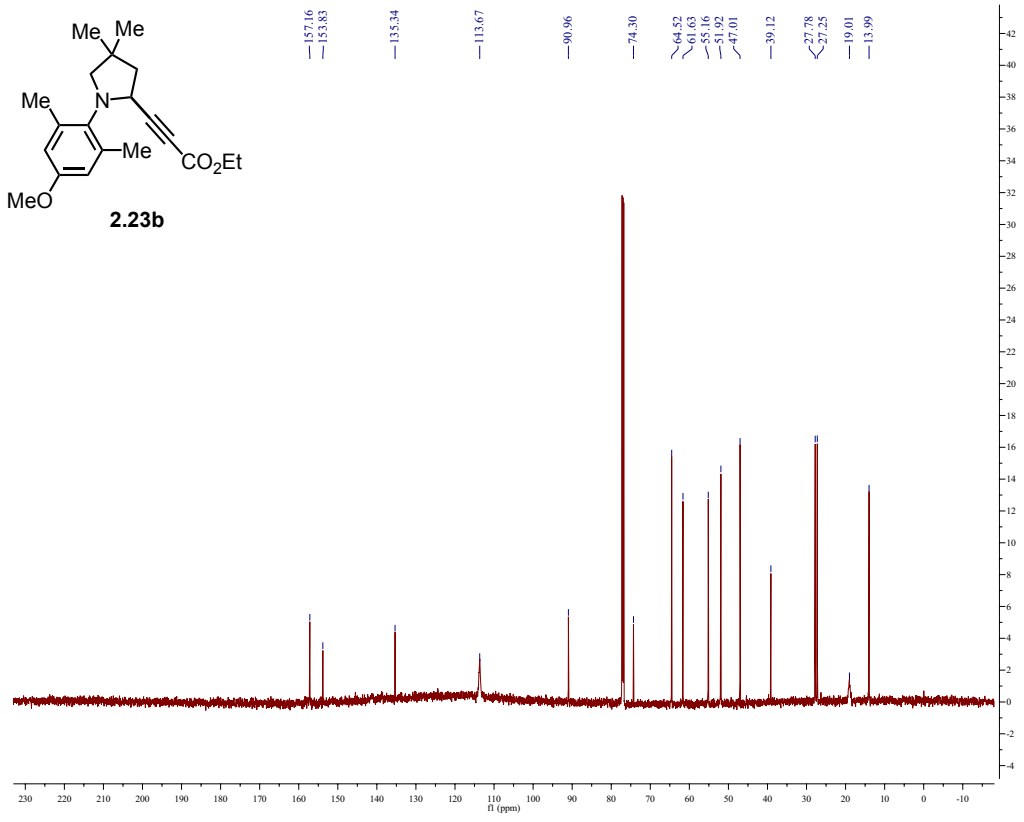
1.06
3.17
3.40
3.15
f1 (ppm)


Me
Me
Me
N
Me
MeO
CO2Et
2.23b
157.16
153.83
135.34
113.67
90.96
74.30
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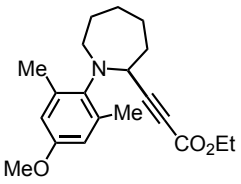
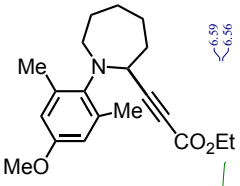
27.78
27.25
19.01
13.99
f1 (ppm)


Me
N
Me
CO2Et
MeO

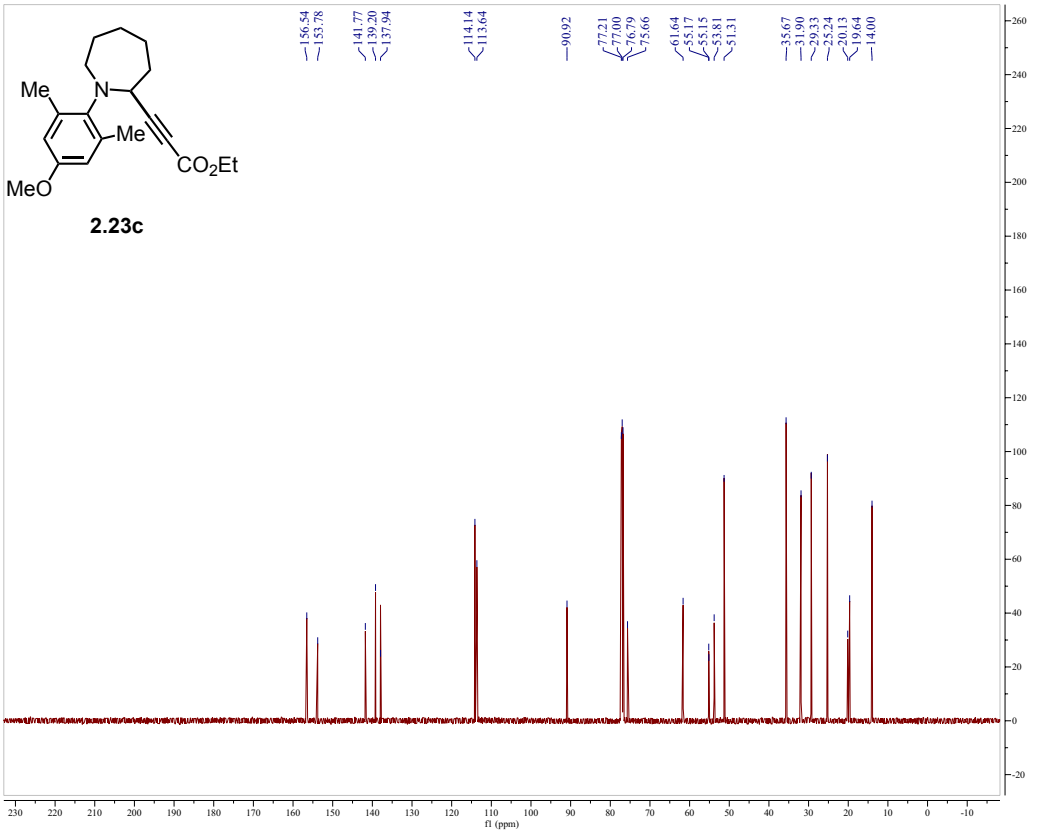
2.23c

f1 (ppm)

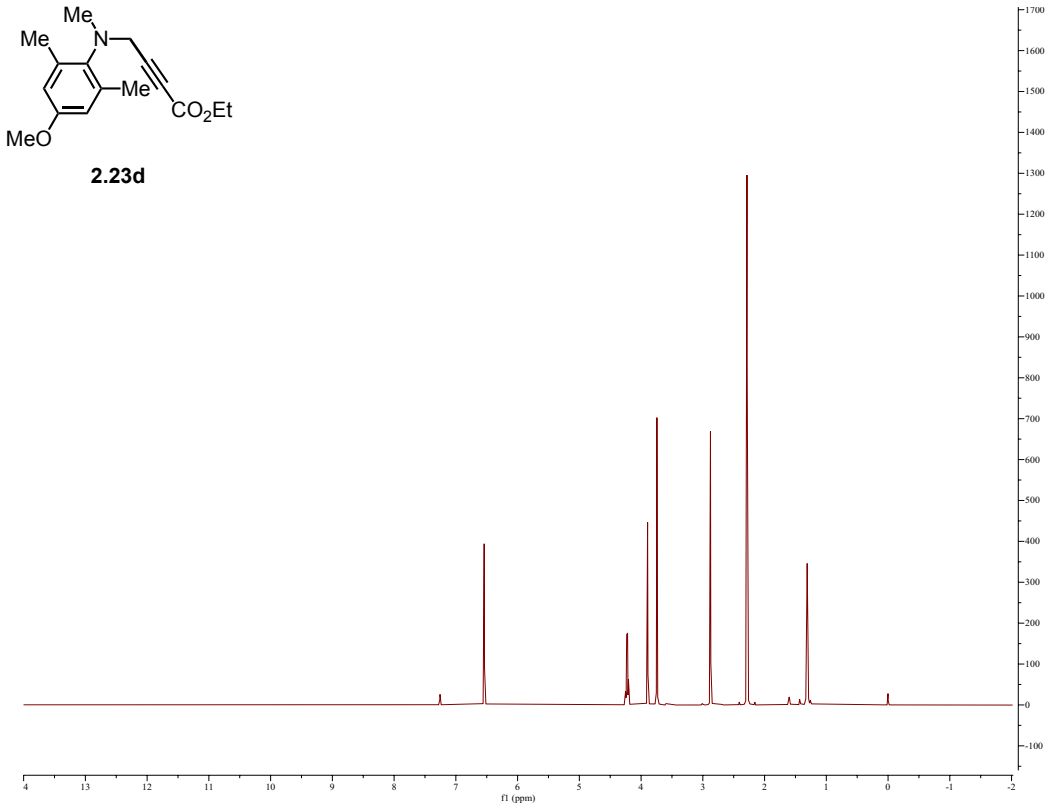

Me
N
Me
CO2Et
MeO

2.23c

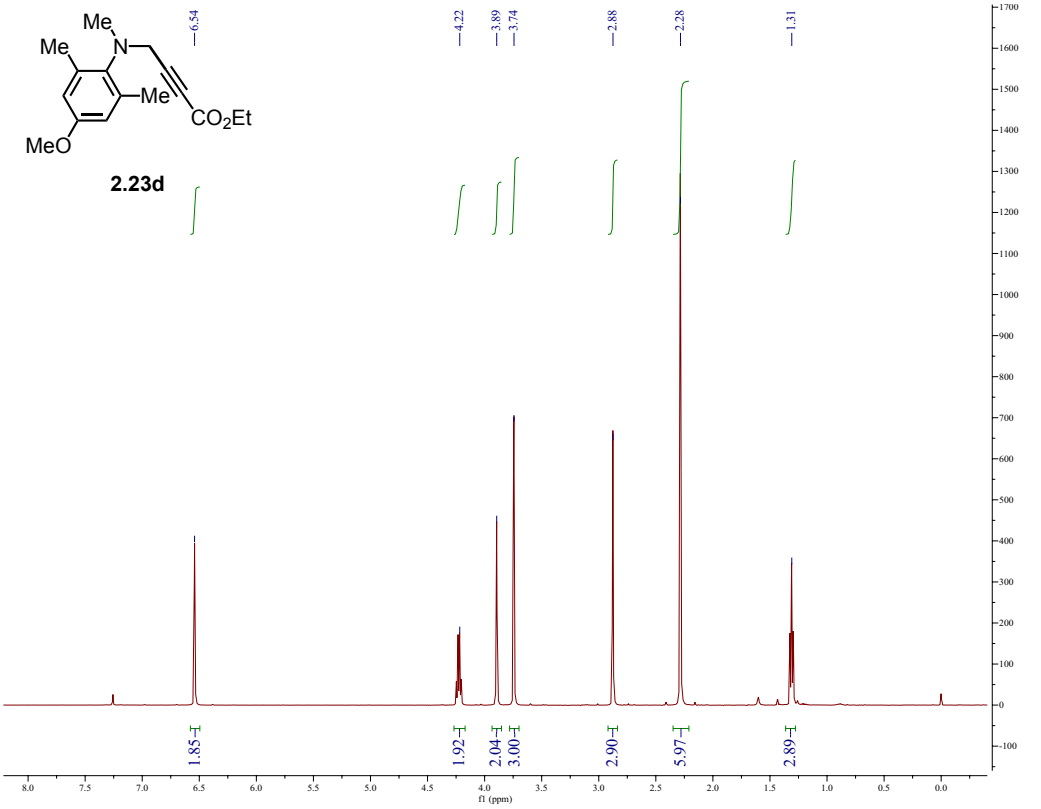
6.59
6.56
4.18
4.17
4.06
4.05
3.75
3.33
3.31
3.09
3.07
2.42
2.29
2.19
2.19
1.90
1.82
1.74
1.74
1.61
1.57
1.57
1.53
1.28
1.81
1.90
0.97
3.00
1.01
1.00
3.00
3.06
1.06
2.09
0.97
2.20
2.48
3.07
f1 (ppm)

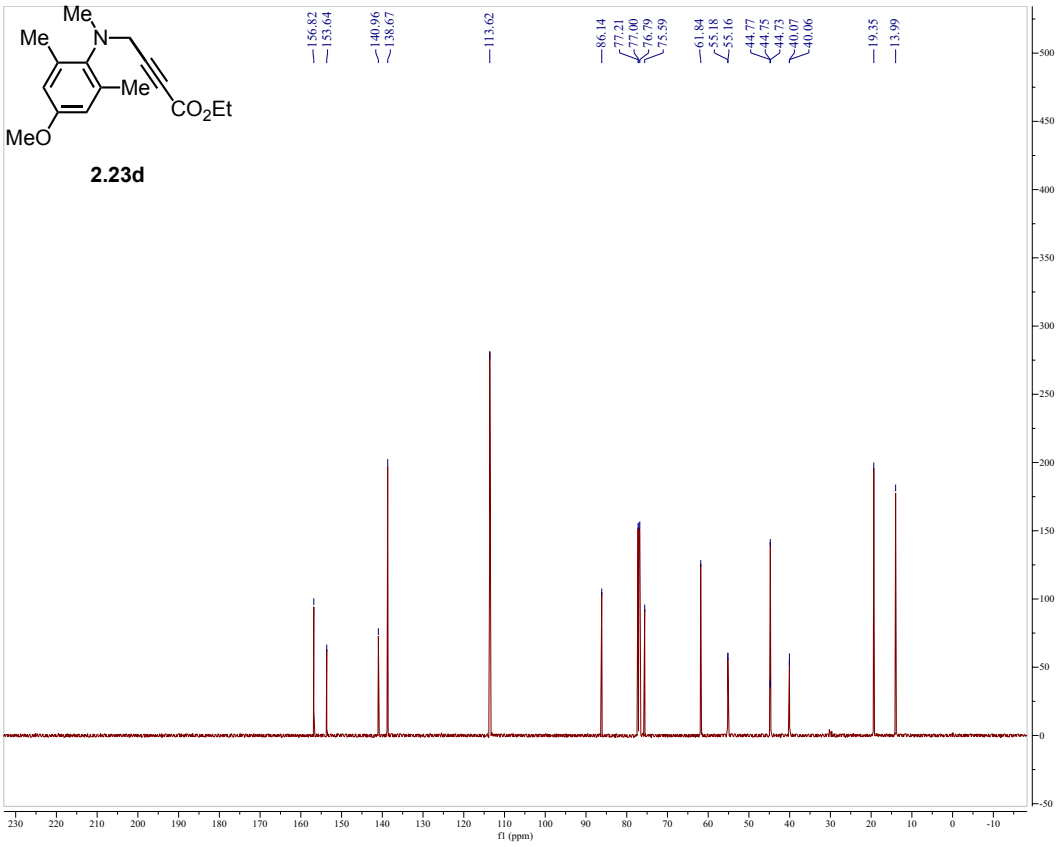

Me
N
Me
MeO
CO2Et
156.54
153.78
141.77
139.20
137.94
114.14
113.64
90.92
77.21
77.00
76.79
75.66
61.64
55.17
55.15
53.81
51.31
35.67
31.90
29.33
25.24
20.13
19.64
14.00
f1 (ppm)

2.23c


Me
Me
N
Me
MeO
CO2Et
f1 (ppm)

2.23d


Me
N
Me
Me
MeO
CO2Et
2.23d
6.54
4.22
3.89
3.74
2.88
2.28
1.31
1.85
1.92
2.04
3.00
2.90
5.97
2.89
f1 (ppm)


Me
N
Me
Me
MeO
CO2Et
2.23d
156.82
153.64
140.96
138.67
113.62
86.14
77.21
77.00
76.79
75.59
61.84
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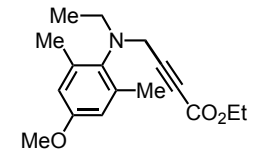
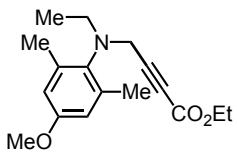
55.16
44.77
44.75
44.73
40.07
40.06
19.35
13.99
f1 (ppm)


Me
Me
N
Me
CO2Et
MeO

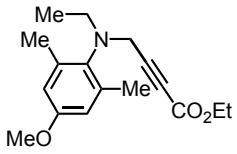
2.23e

f1 (ppm)


Me
Me
N
Me
CO2Et
MeO

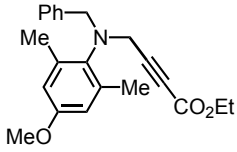
2.23e

6.56
4.25
4.25
4.25
4.23
4.23
4.22
4.22
4.21
4.20
3.92
3.92
3.76
3.76
3.76
3.23
3.23
3.21
3.21
3.20
3.20
3.19
3.18
2.86
2.85
2.30
1.33
1.33
1.31
1.31
1.30
1.30
1.05
1.05
1.04
1.04
1.03
1.02
2.00
2.00
1.84
3.00
1.82
0.30
6.19
3.05
2.73
f1 (ppm)


Me
Me
N
Me
CO2Et
MeO

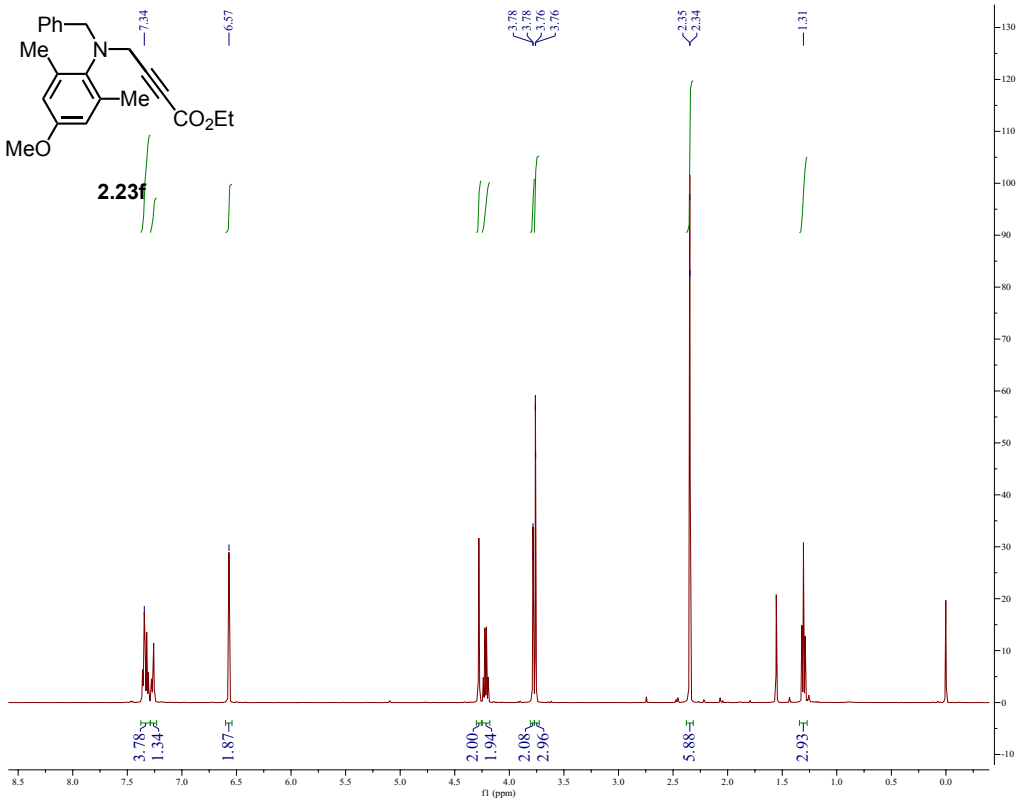
2.23e

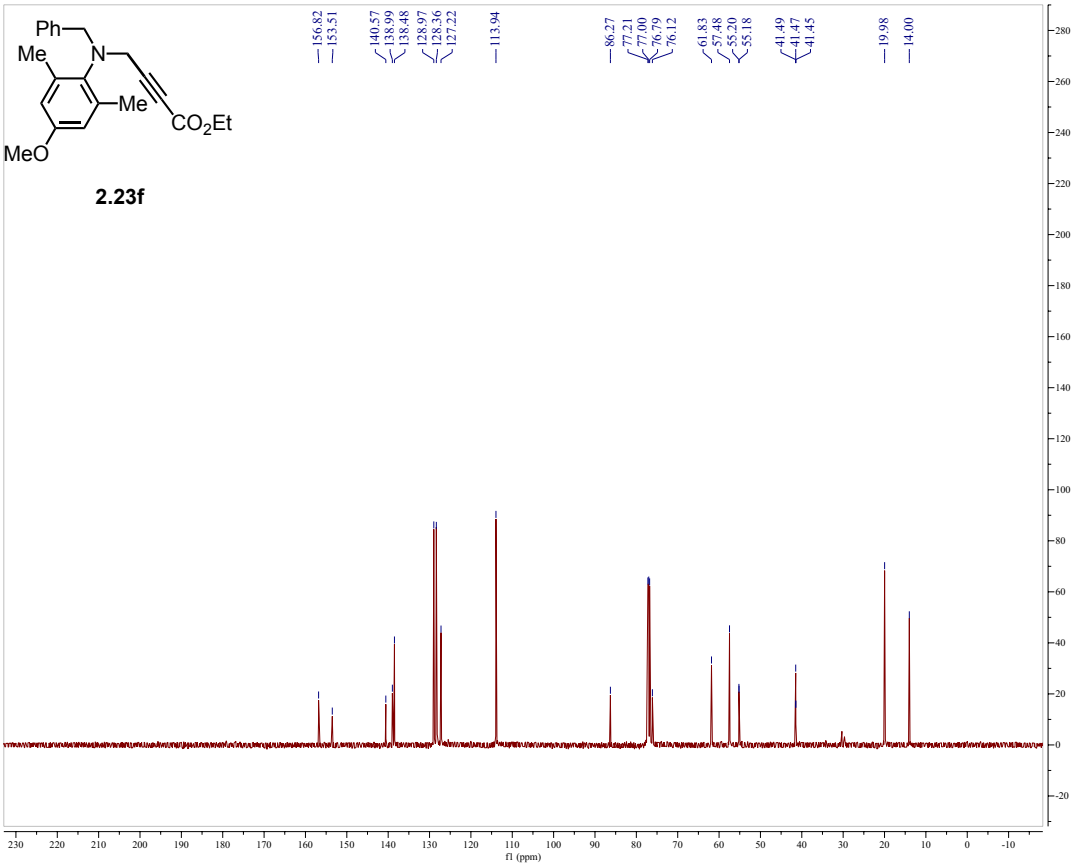
156.84
153.66
139.52
139.27
113.62
86.75
77.25
77.00
76.75
75.51
61.80
55.17
47.18
42.98
19.62
14.28
14.01
f1 (ppm)

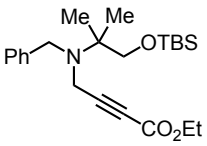

Ph
Me
N
Me
CO2Et
MeO

2.23f

f1 (ppm)

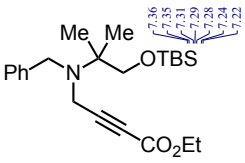

Ph
Me
N
Me
CO2Et
MeO
2.23f
7.34
6.57
3.78
3.78
3.76
3.76
2.35
2.34
1.31
3.78
1.34
1.87
2.00
1.94
2.08
2.96
5.88
2.93
f1 (ppm)


Ph
Me
N
Me
CO2Et
MeO
2.23f
156.82
153.51
140.57
138.99
138.48
128.97
128.36
127.22
113.94
86.27
77.21
77.00
76.79
76.12
61.83
57.48
55.20
55.18
41.49
41.47
41.45
19.98
14.00
f1 (ppm)


Me
Me
OTBS
Ph
N
CO2Et

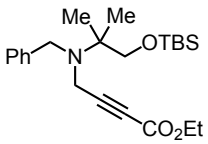
2.23g

f1 (ppm)


Me
Me
OTBS
Ph
N
CO2Et

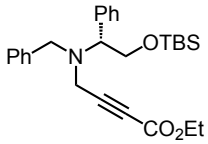
2.23g

7.36
7.35
7.31
7.29
7.28
7.24
7.22
4.25
4.24
4.22
4.21
3.91
3.60
3.51
1.33
1.31
1.30
1.23
0.91
0.06
1.83
1.88
1.01
1.99
2.00
2.05
1.98
2.88
5.74
8.73
5.69
f1 (ppm)


Me
Me
Ph
N
OTBS
CO2Et

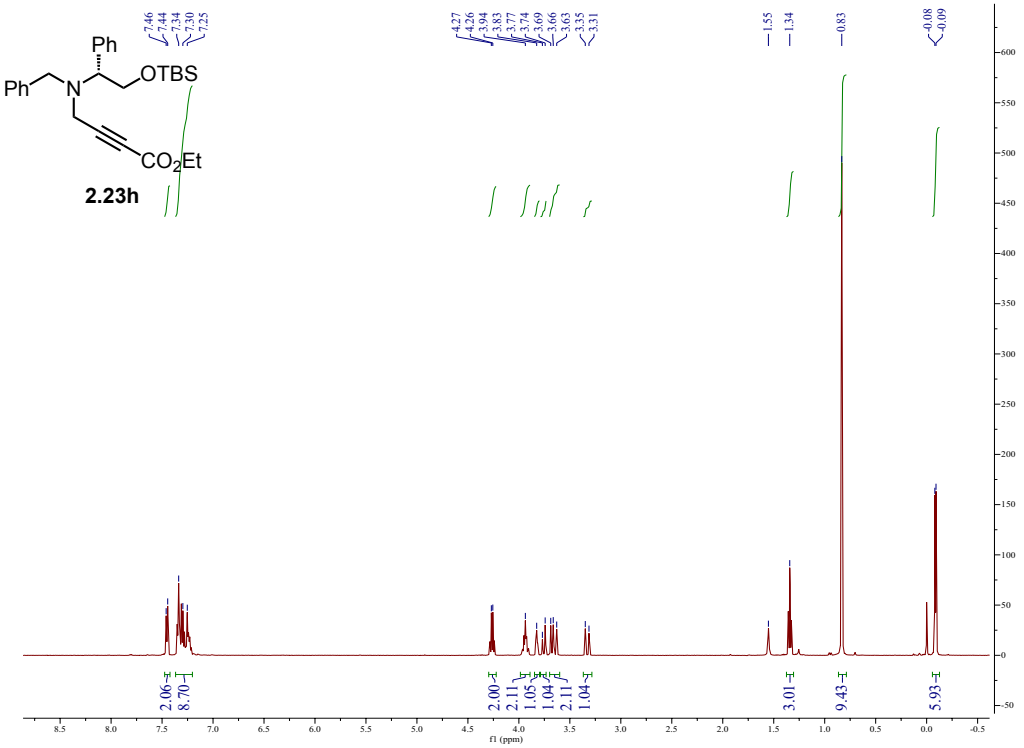
2.23g

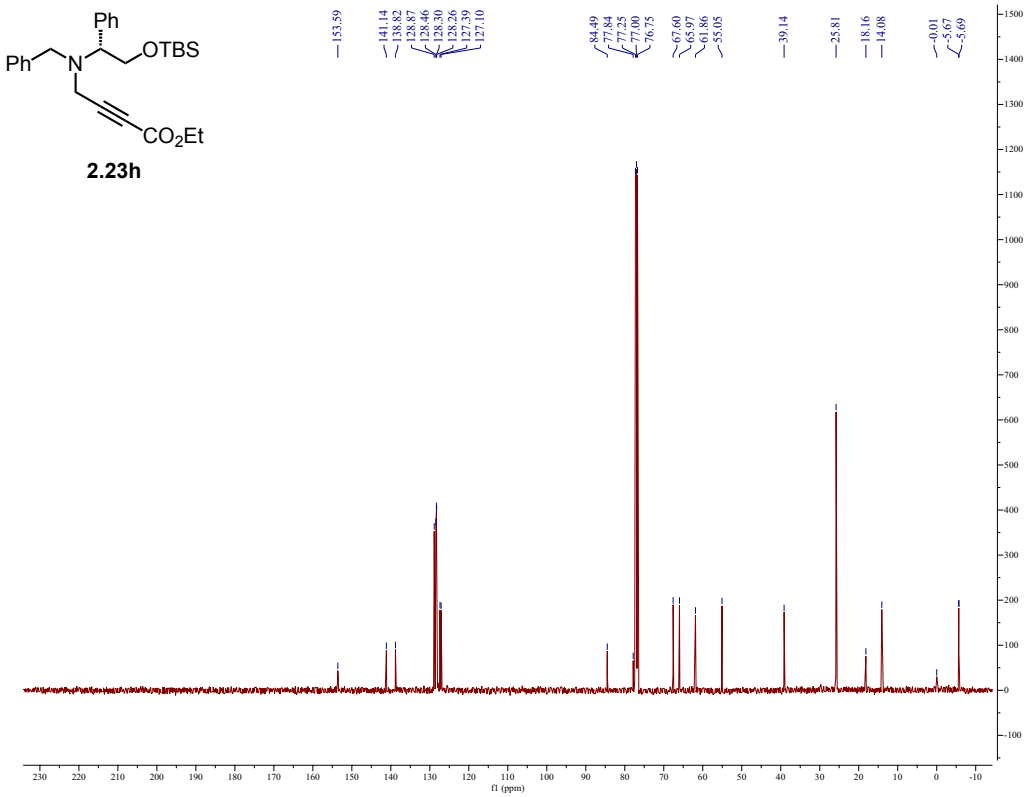
153.62
140.28
128.43
128.23
126.87
87.60
77.25
77.00
76.75
76.67
69.72
61.76
58.62
51.40
36.66
25.86
22.93
18.21
14.05
-5.56
f1 (ppm)

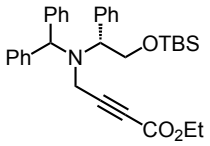

Ph
Ph
N
OTBS
CO2Et

2.23h

f1 (ppm)

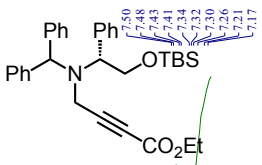

Ph
Ph
N
OTBS
CO2Et
2.23h
7.46
7.44
7.34
7.30
7.25
4.27
4.26
3.94
3.83
3.77
3.74
3.69
3.66
3.63
3.35
3.31
1.55
1.34
0.83
0.08
0.09
2.06
8.70
2.00
2.11
1.05
1.04
2.11
1.04
3.01
9.43
5.93
f1 (ppm)


Ph
Ph
N
OTBS
CO2Et
2.23h
153.59
141.14
138.82
128.87
128.46
128.30
128.26
127.39
127.10
84.49
77.84
77.25
77.00
76.75
67.60
65.97
61.86
55.05
39.14
25.81
18.16
14.08
-0.01
-5.67
-5.69
f1 (ppm)


Ph
Ph
Ph
N
OTBS
CO2Et

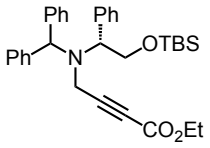
2.23i

f1 (ppm)


Ph
Ph
Ph
N
OTBS
CO2Et

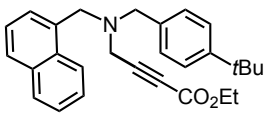
2.23i

7.50
7.48
7.43
7.41
7.34
7.32
7.30
7.26
7.21
7.17
5.23
4.18
4.14
3.55
1.30
0.82
0.82
-0.02
-0.07
4.02
1.97
9.40
0.98
5.12
2.00
3.01
9.05
5.86
f1 (ppm)


Ph
Ph
Ph
N
OTBS
CO2Et

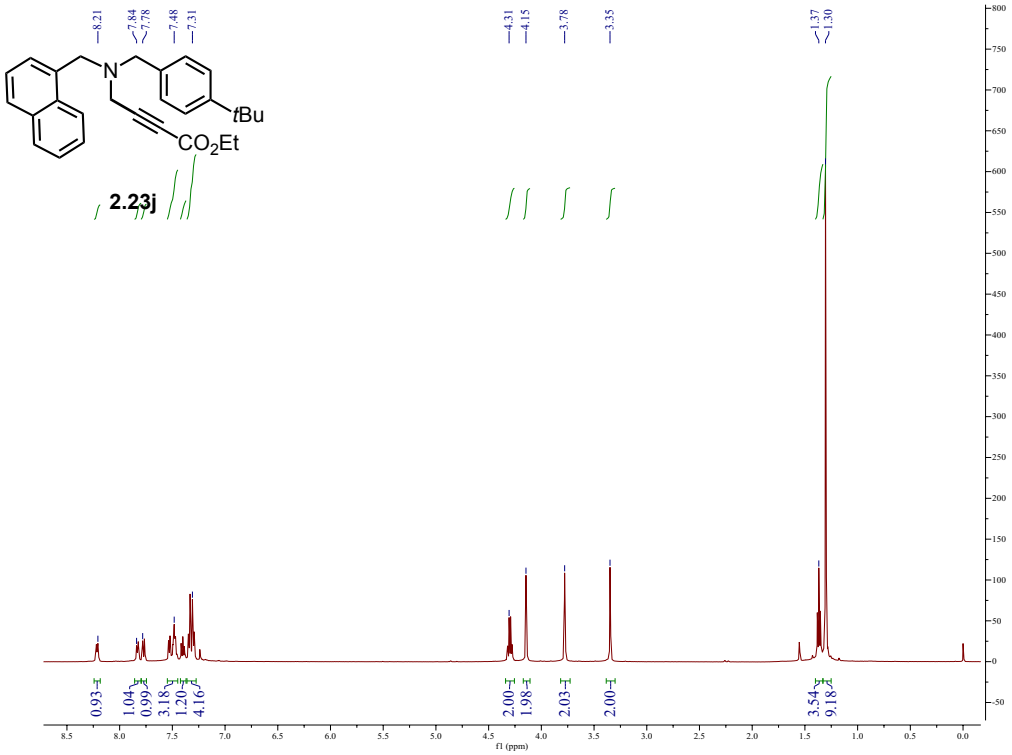
2.23i

153.44
142.00
141.85
139.77
128.69
128.55
128.49
128.47
128.39
128.11
127.24
127.15
86.47
77.25
77.00
76.75
76.60
69.20
63.11
62.87
61.56
36.59
25.85
18.19
14.06
-5.55
-5.57
f1 (ppm)

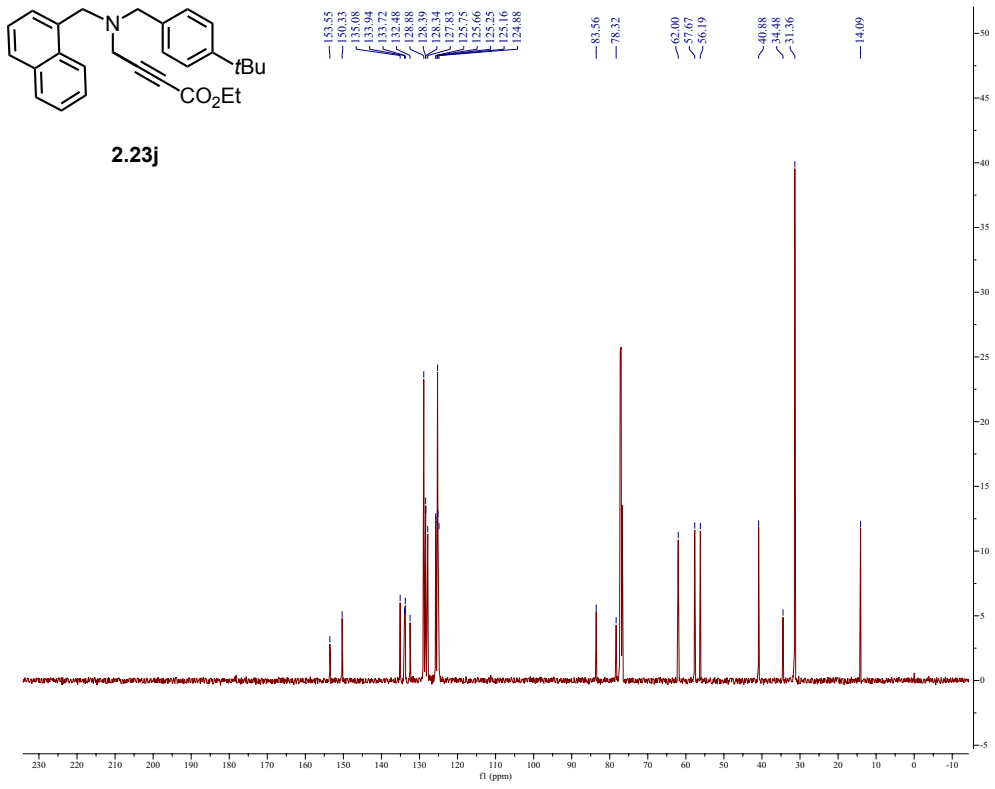

N
tBu
CO2Et

2.23j

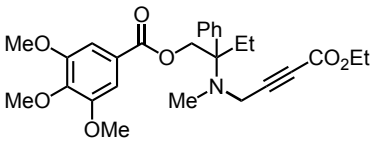
f1 (ppm)


8.21
7.84
7.78
7.48
7.31
4.31
4.15
3.78
3.35
1.37
1.30
tBu
CO2Et
0.93
1.04
0.99
3.18
1.20
4.16
2.00
1.98
2.03
2.00
3.54
9.18
f1 (ppm)

2.23j

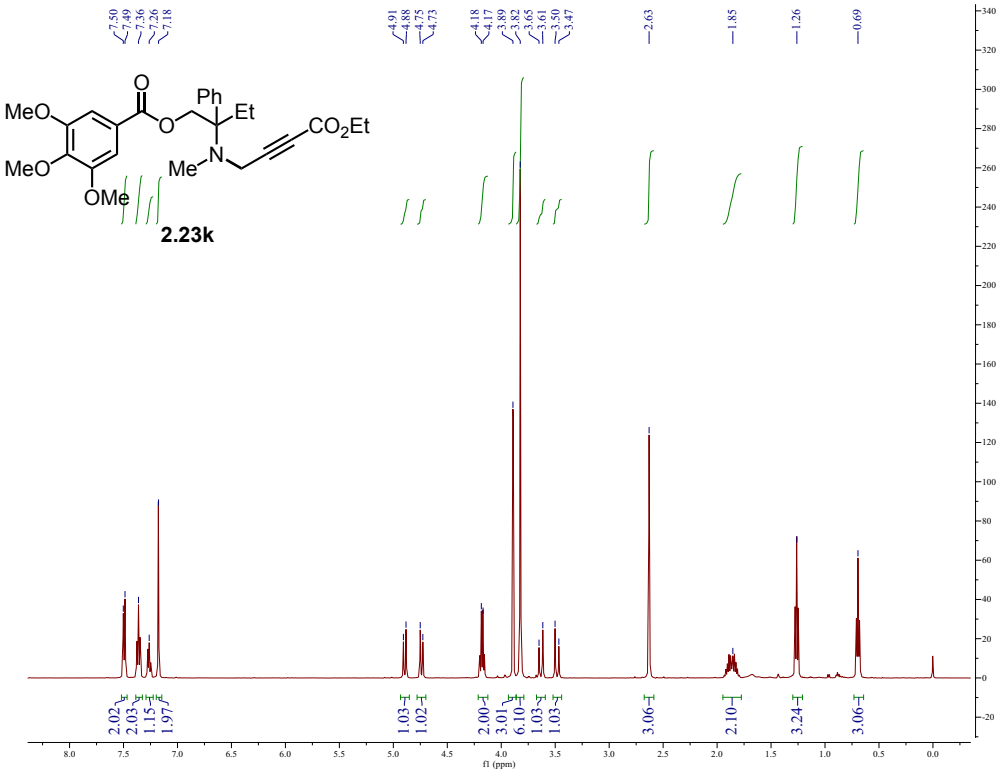

153.55
150.33
135.08
133.94
133.72
132.48
128.88
128.39
128.34
127.83
125.75
125.66
125.25
125.16
124.88
83.56
78.32
62.00
57.67
56.19
40.88
34.48
31.36
14.09
tBu
CO2Et
f1 (ppm)

2.23j

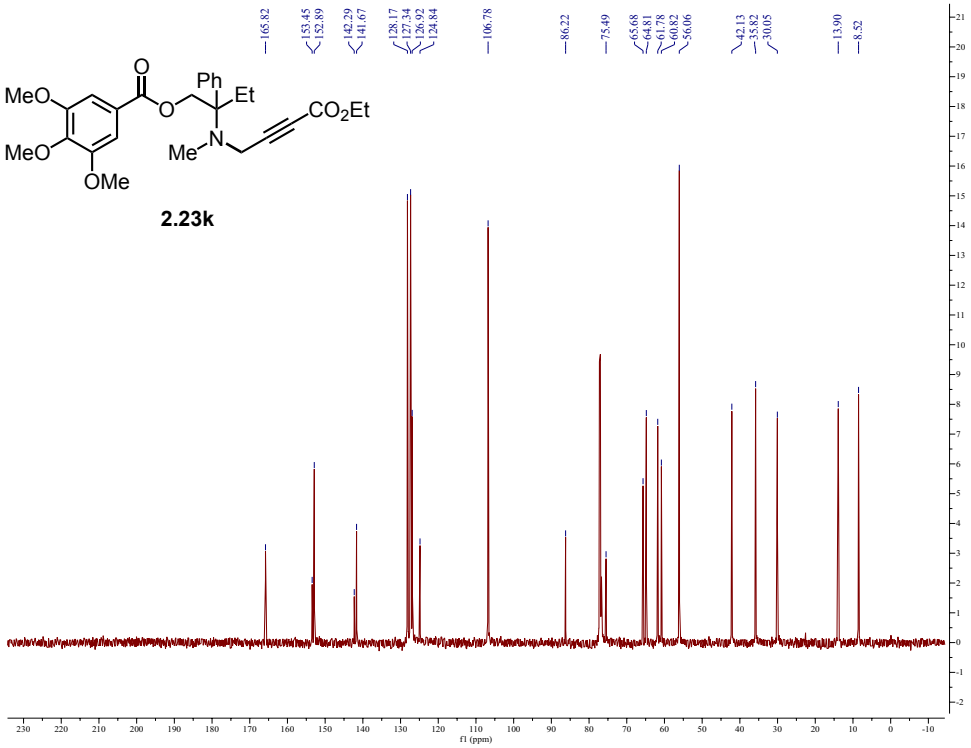

MeO
MeO
OMe
O
O
Ph
Et
N
Me
CO2Et

2.23k

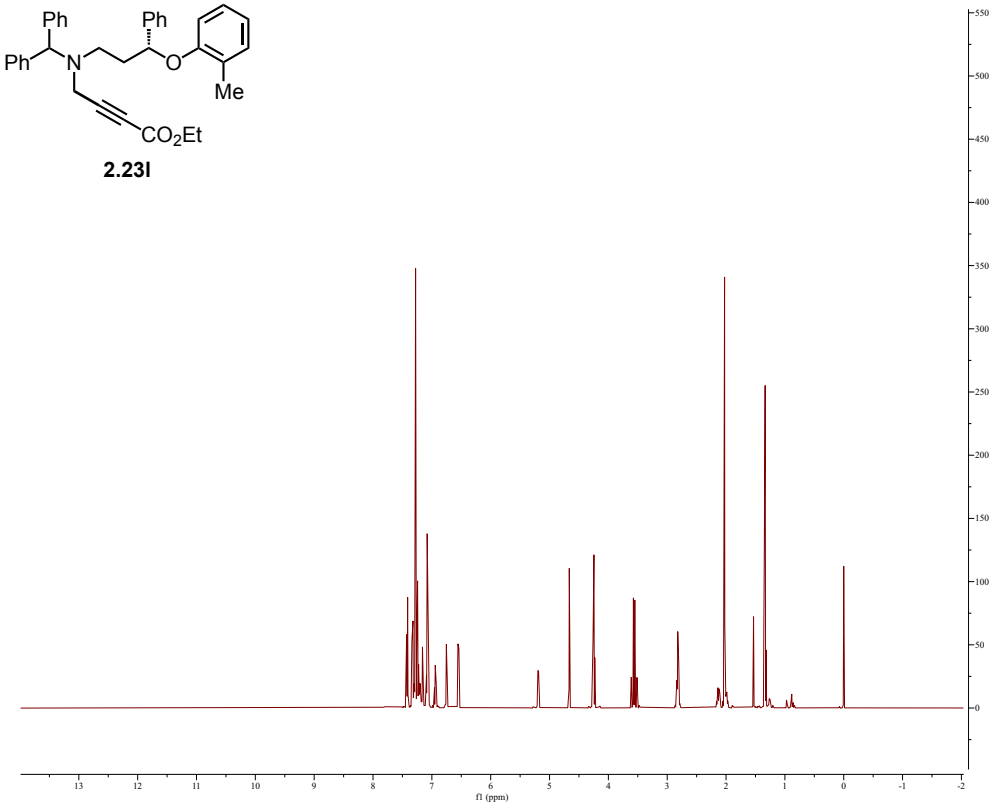
f1 (ppm)


7.50
7.49
7.36
7.26
7.18
4.91
4.88
4.75
4.73
4.18
4.17
3.89
3.82
3.65
3.61
3.50
3.47
2.63
1.85
1.26
0.69
2.02
2.03
1.15
1.97
1.03
1.02
2.00
3.01
6.10
1.03
1.03
3.06
2.10
3.24
3.06
f1 (ppm)

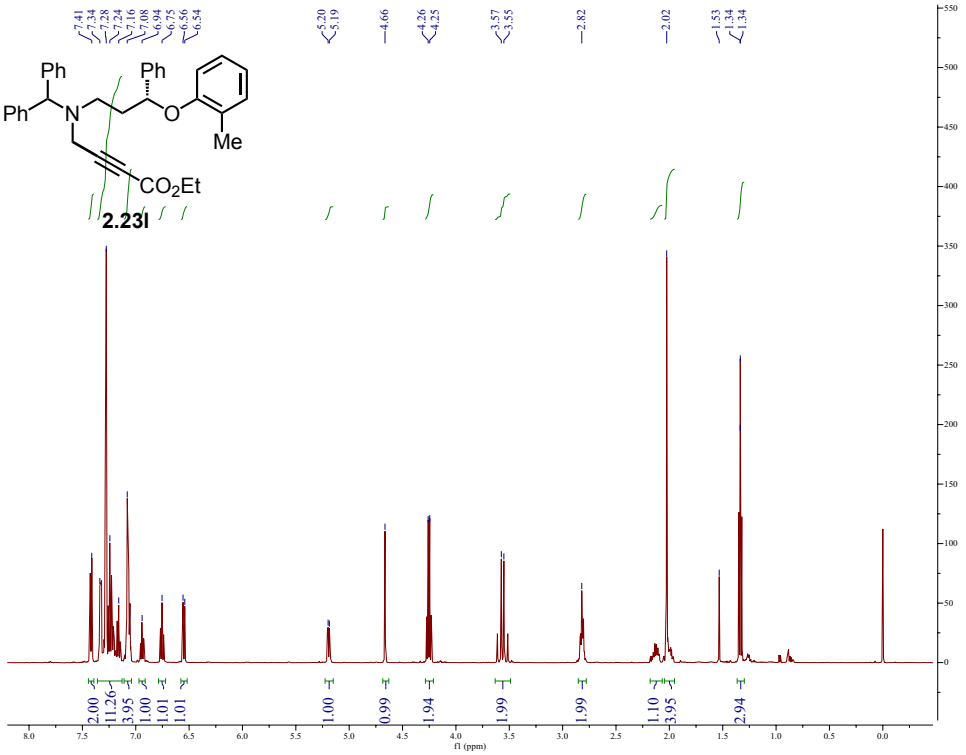
2.23k

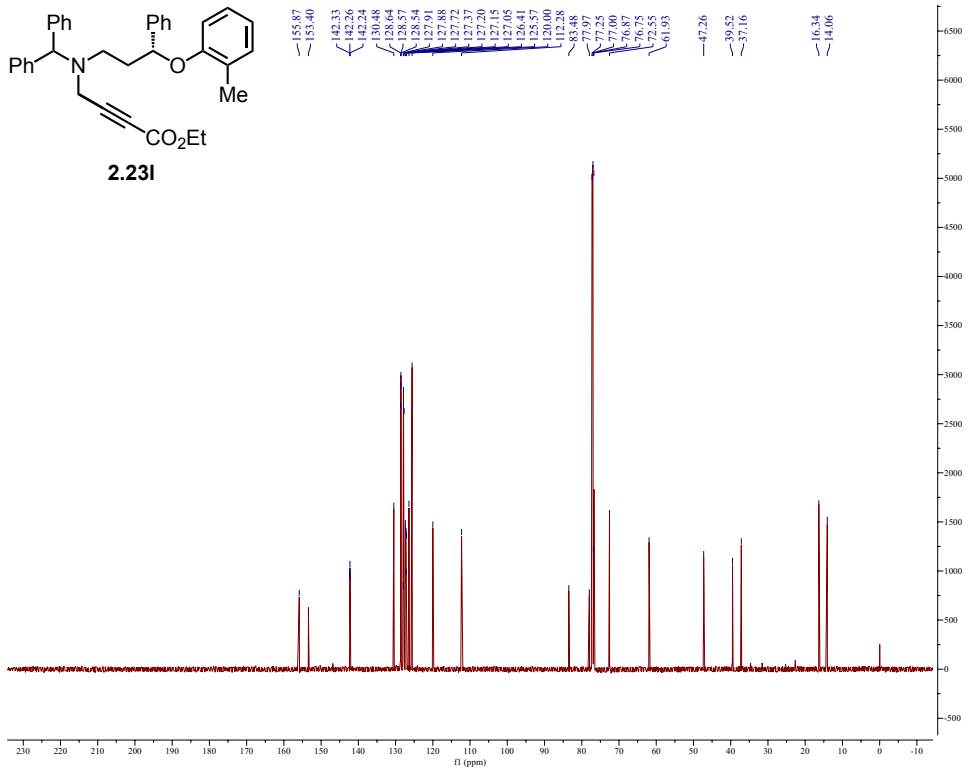

MeO
MeO
OMe
O
O
Ph
Et
N
Me
CO2Et
165.82
153.45
152.89
142.29
141.67
128.17
127.34
126.92
124.84
106.78
86.22
75.49
65.68
64.81
61.78
60.82
56.06
42.13
35.82
30.05
13.90
8.52
f1 (ppm)

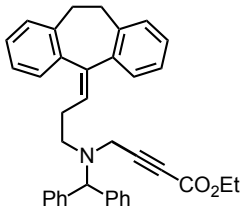
2.23k


Ph
Ph
Ph
N
O
Me
CO2Et
f1 (ppm)

2.23l

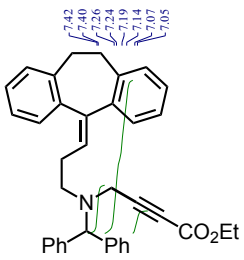

Ph
Ph
N
Ph
O
Me
CO2Et
2.23l


Ph
Ph
N
Ph
O
Me
CO2Et
2.23l

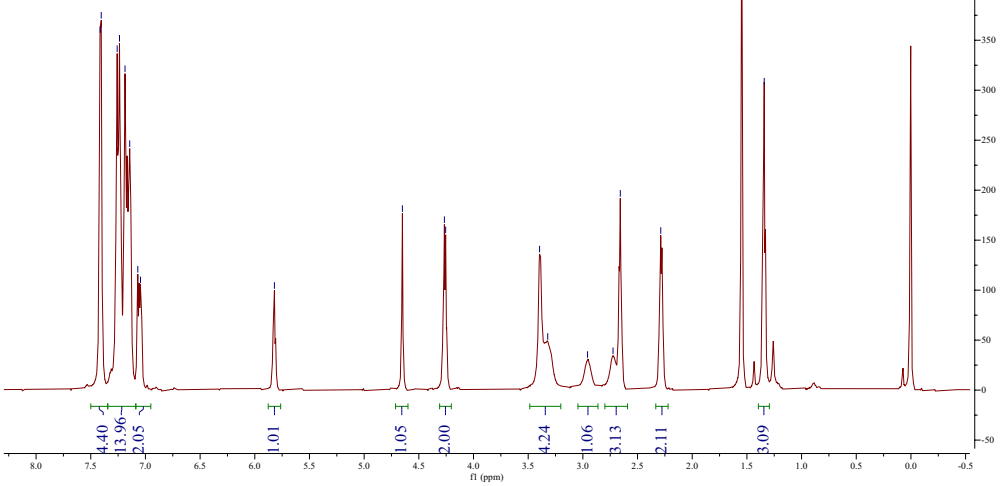

N
Ph
Ph
CO2Et

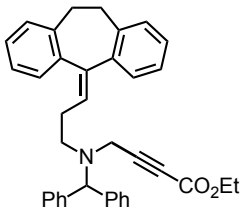
2.23m

f1 (ppm)


7.42
7.40
7.26
7.24
7.19
7.14
7.07
7.05
5.82
4.65
4.27
4.25
3.40
3.32
2.96
2.72
2.66
2.29
1.34
N
Ph
Ph
CO2Et

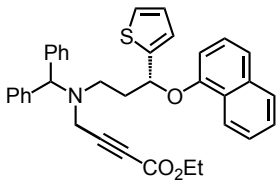
2.23m


4.40
13.96
2.05
1.01
1.05
2.00
4.24
1.06
3.13
2.11
3.09
f1 (ppm)


N
Ph
Ph
CO2Et

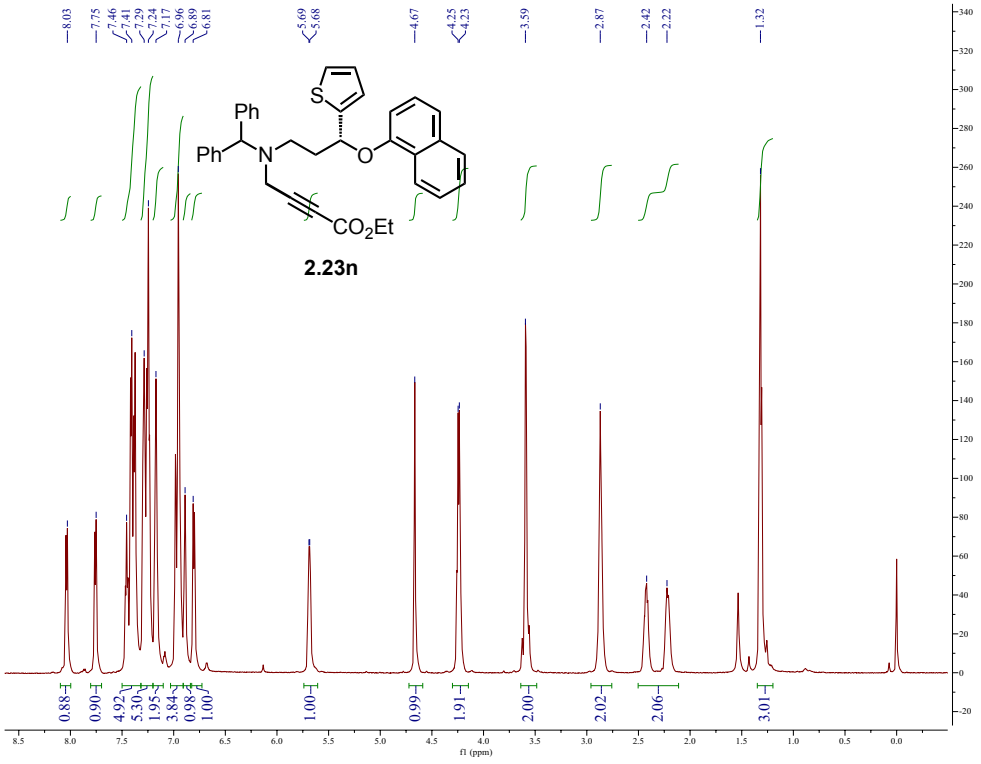
2.23m

153.44
143.77
142.40
141.23
139.94
139.32
137.01
129.97
128.95
128.59
128.51
128.48
128.21
128.01
127.88
127.42
127.14
126.99
125.97
125.77
83.73
77.82
77.25
77.00
76.75
72.31
61.92
50.31
39.27
33.74
31.98
27.62
14.07
f1 (ppm)

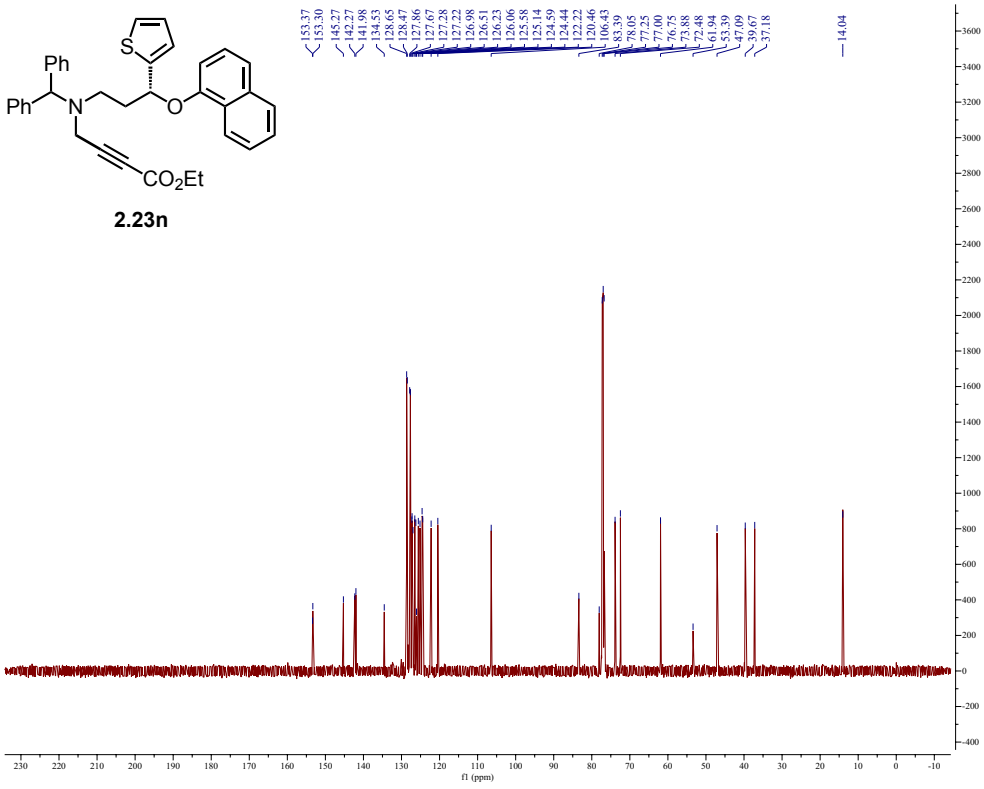

S
Ph
Ph
N
O
CO2Et

2.23n

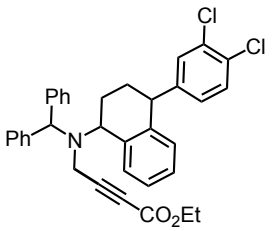
f1 (ppm)


8.03
7.75
7.46
7.41
7.29
7.24
7.17
6.96
6.89
6.81
5.69
5.68
4.67
4.25
4.23
3.59
2.87
2.42
2.22
1.32
Ph
Ph
N
S
O
CO2Et
0.88
0.90
4.92
5.30
1.95
3.84
0.98
1.00
1.00
0.99
1.91
2.00
2.02
2.06
3.01
f1 (ppm)

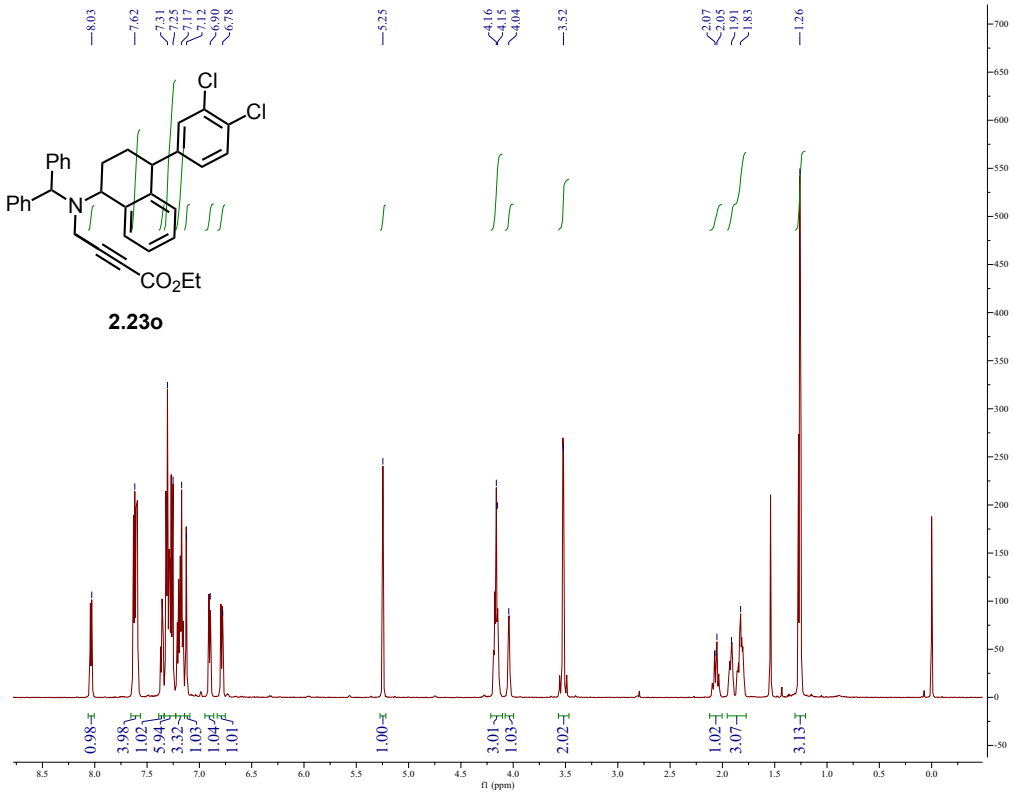
2.23n


153.37
153.30
145.27
142.27
141.98
134.53
128.65
128.47
127.86
127.67
127.28
127.22
126.98
126.51
126.23
126.06
125.58
125.14
124.59
124.44
122.22
120.46
106.43
83.39
78.05
77.25
77.00
76.75
73.88
72.48
61.84
61.39
47.09
39.67
37.18
14.04
Ph
Ph
N
S
O
CO2Et
f1 (ppm)

2.23n

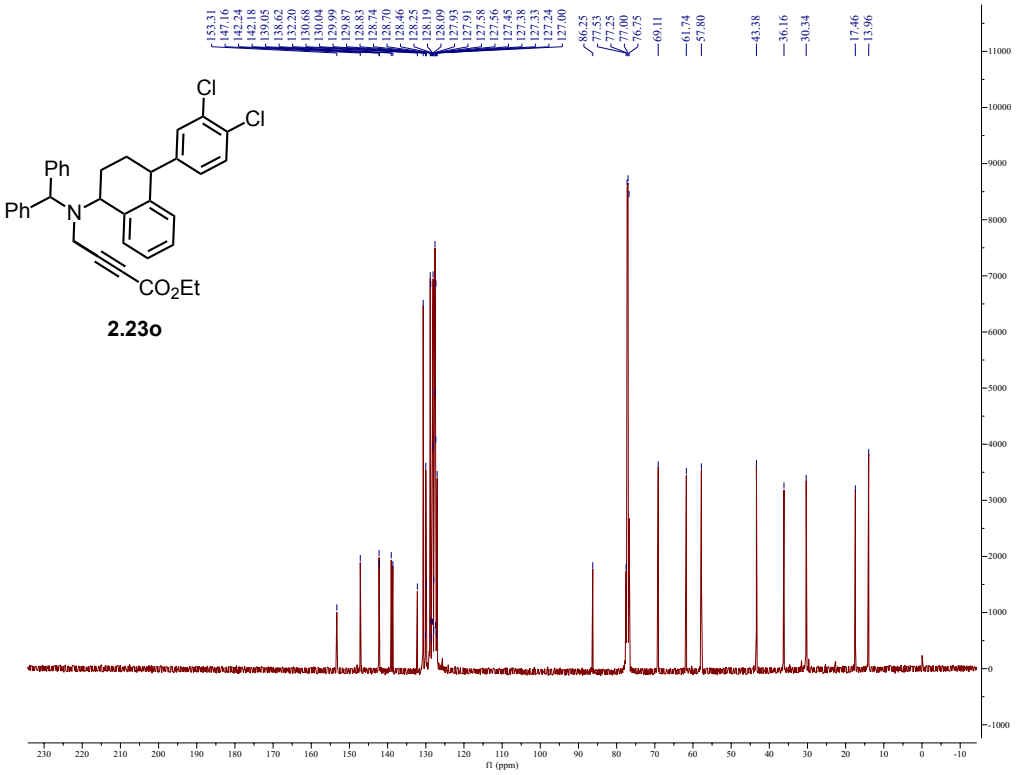


2.23o

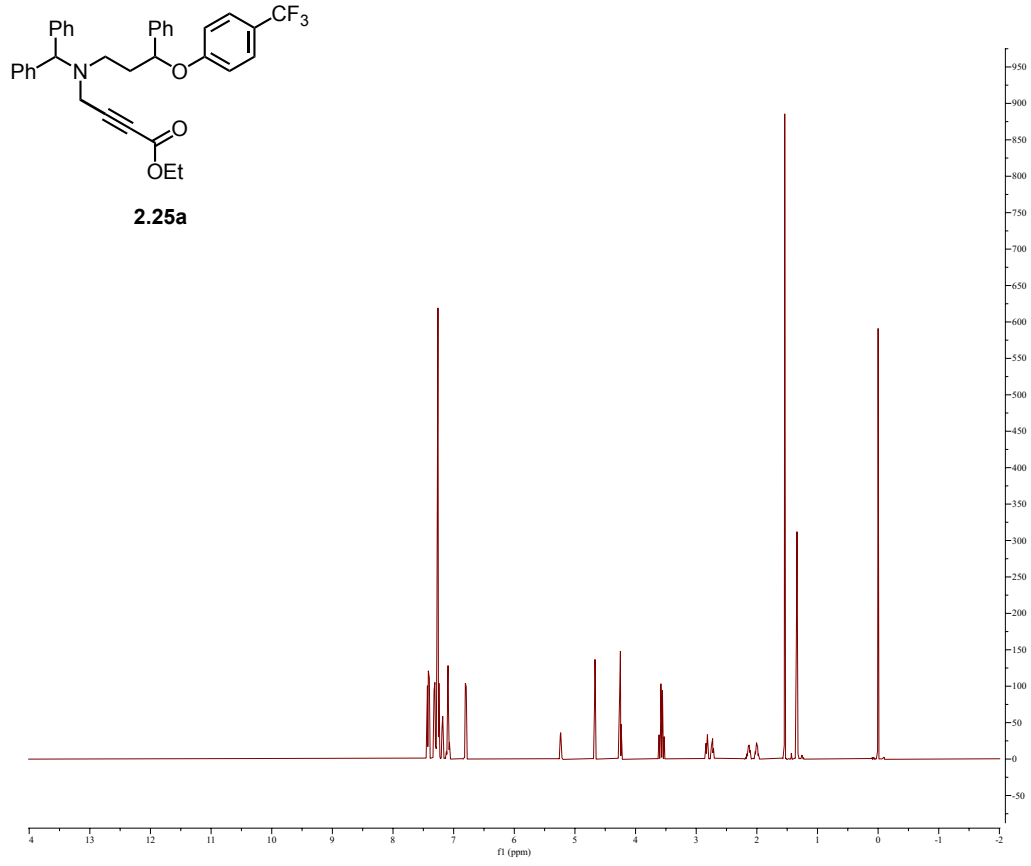


Cl
Cl
Ph
Ph
N
CO2Et

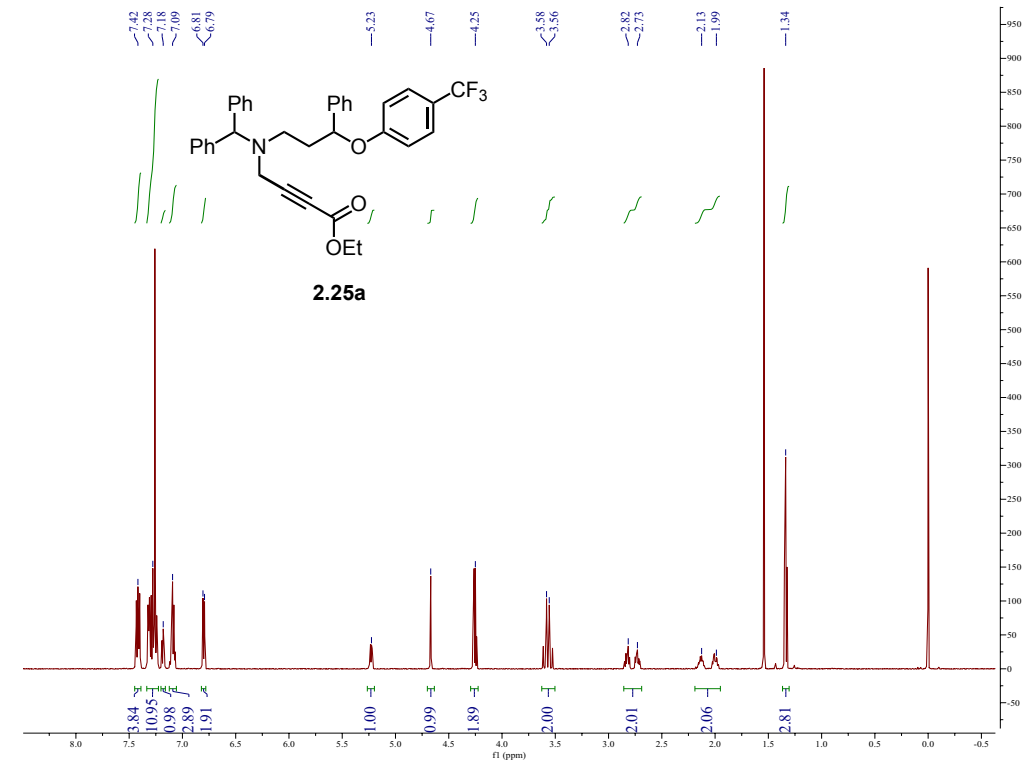
2.23o


Cl
Cl
Ph
Ph
N
CO2Et
153.31
147.16
142.24
142.18
139.05
138.62
132.20
130.68
130.04
129.99
129.87
128.83
128.74
128.70
128.46
128.25
128.19
128.09
127.93
127.91
127.58
127.56
127.45
127.38
127.33
127.24
127.00
86.25
77.53
77.25
77.00
76.75
69.11
61.74
57.80
43.38
36.16
30.34
17.46
13.96
f1 (ppm)

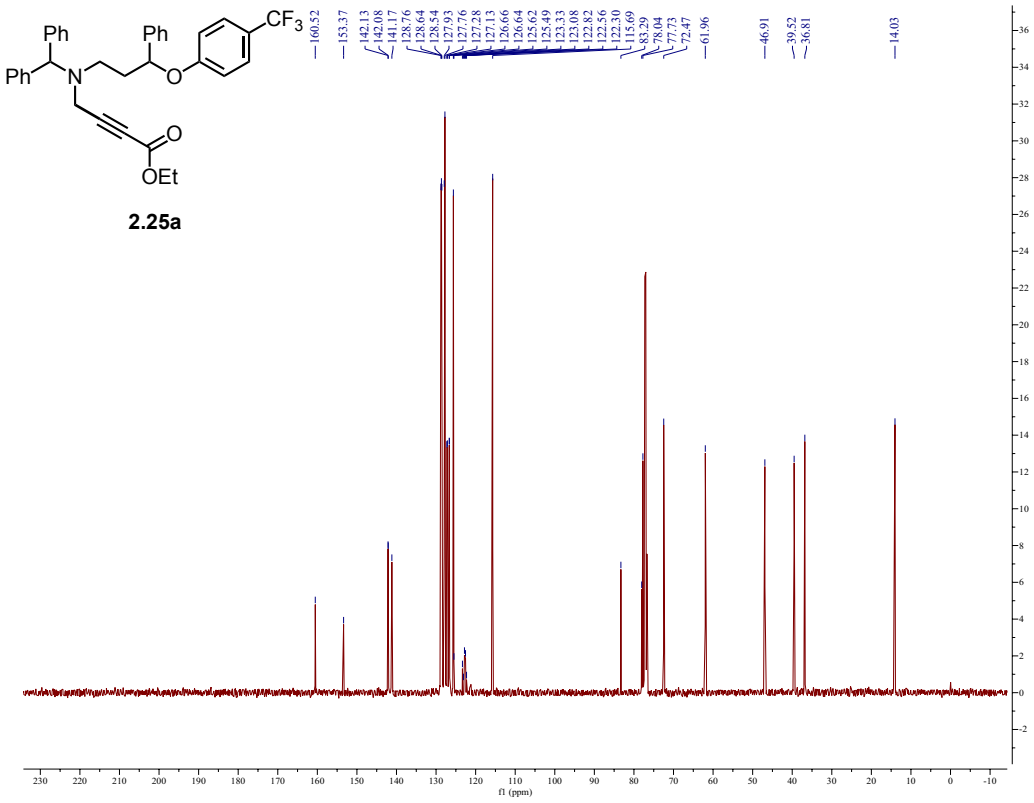
2.23o


Ph
Ph
N
Ph
O
CF3
O
OEt
f1 (ppm)

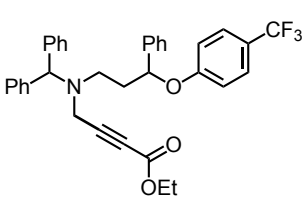
2.25a


7.42
7.28
7.18
7.09
6.81
6.79
5.23
4.67
4.25
3.58
3.56
2.82
2.73
2.13
1.99
1.34
Ph
Ph
Ph
N
O
CF3
O
OEt
3.84
10.95
0.98
2.89
1.91
1.00
0.99
1.89
2.00
2.01
2.06
2.81
f1 (ppm)

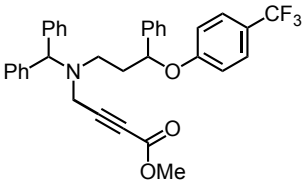
2.25a


160.52
153.37
142.13
142.08
141.17
128.76
128.64
128.54
127.93
127.76
127.28
127.13
126.66
126.64
125.62
125.49
123.33
123.08
122.82
122.56
122.30
115.69
83.29
78.04
77.73
72.47
61.96
46.91
39.52
36.81
14.03
Ph
Ph
Ph
N
O
CF3
O
OEt
f1 (ppm)

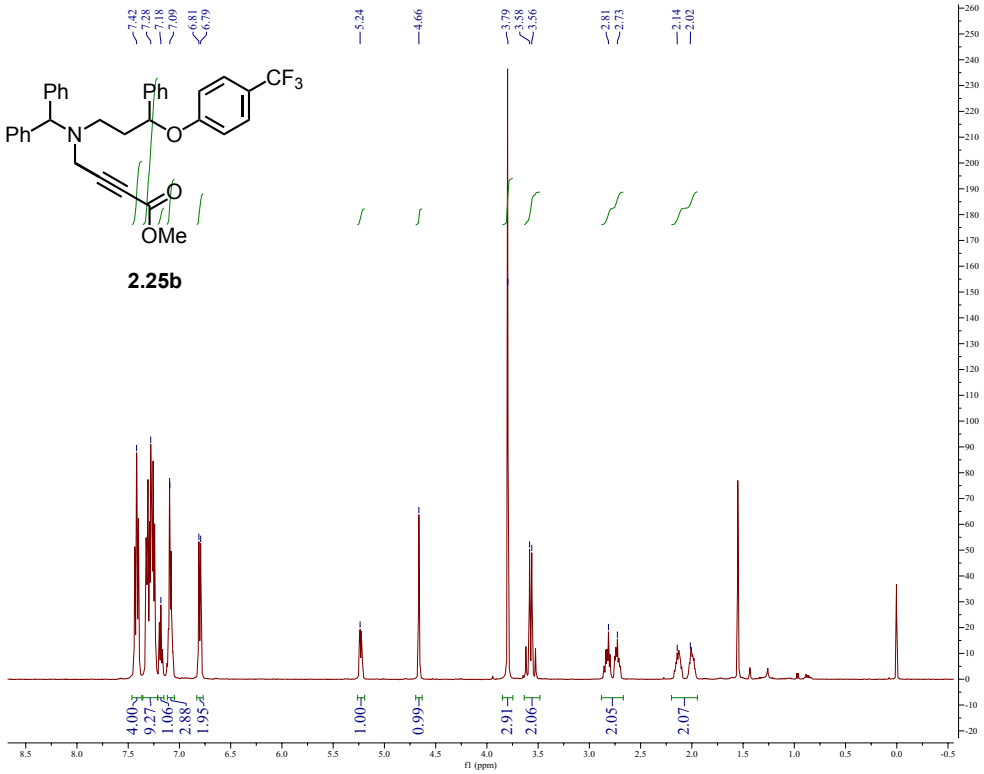
2.25a



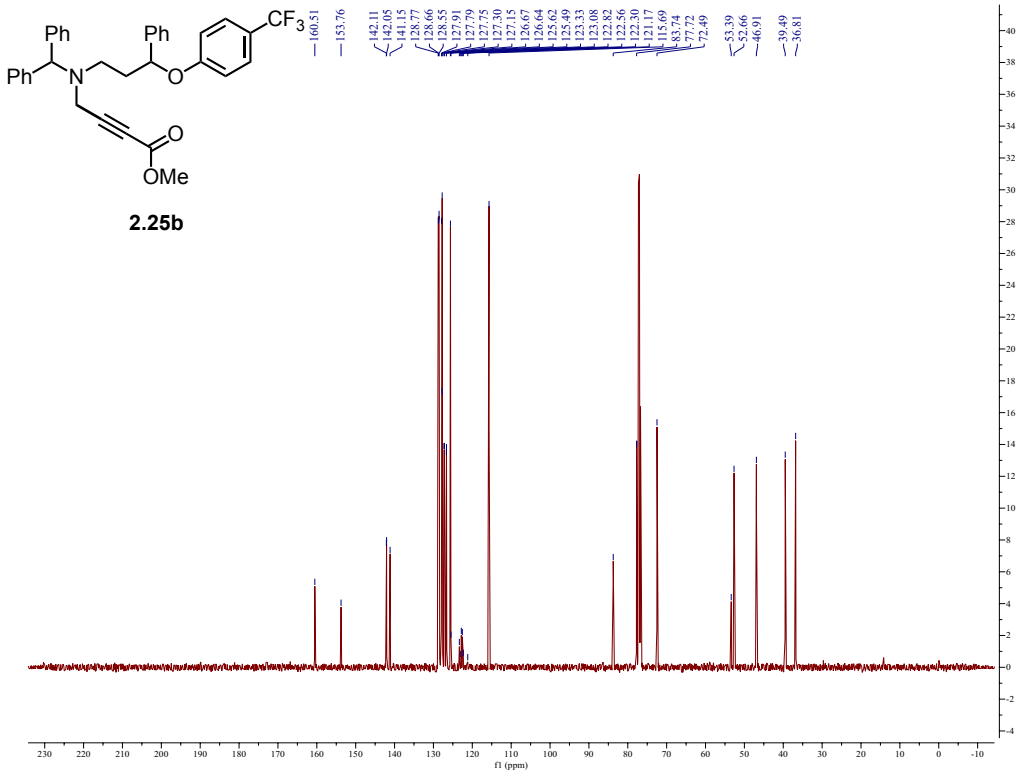
2.25a



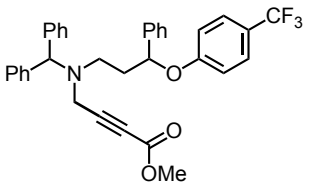
2.25b


7.42
7.28
7.18
7.09
6.81
6.79
5.24
4.66
3.79
3.58
3.56
2.81
2.73
2.14
2.02
Ph
Ph
Ph
N
O
CF3
O
OMe
4.00
9.27
1.06
2.88
1.95
1.00
0.99
2.91
2.06
2.05
2.07
f1 (ppm)

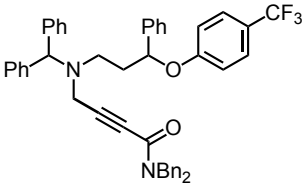
2.25b


160.51
153.76
142.11
142.05
141.15
128.77
128.66
128.55
127.91
127.79
127.75
127.30
127.15
126.67
126.64
126.62
125.49
123.33
123.08
122.82
122.56
122.30
121.17
115.69
83.74
77.72
72.49
53.39
52.66
46.91
39.49
36.81
Ph
Ph
Ph
N
O
CF3
O
OMe
f1 (ppm)

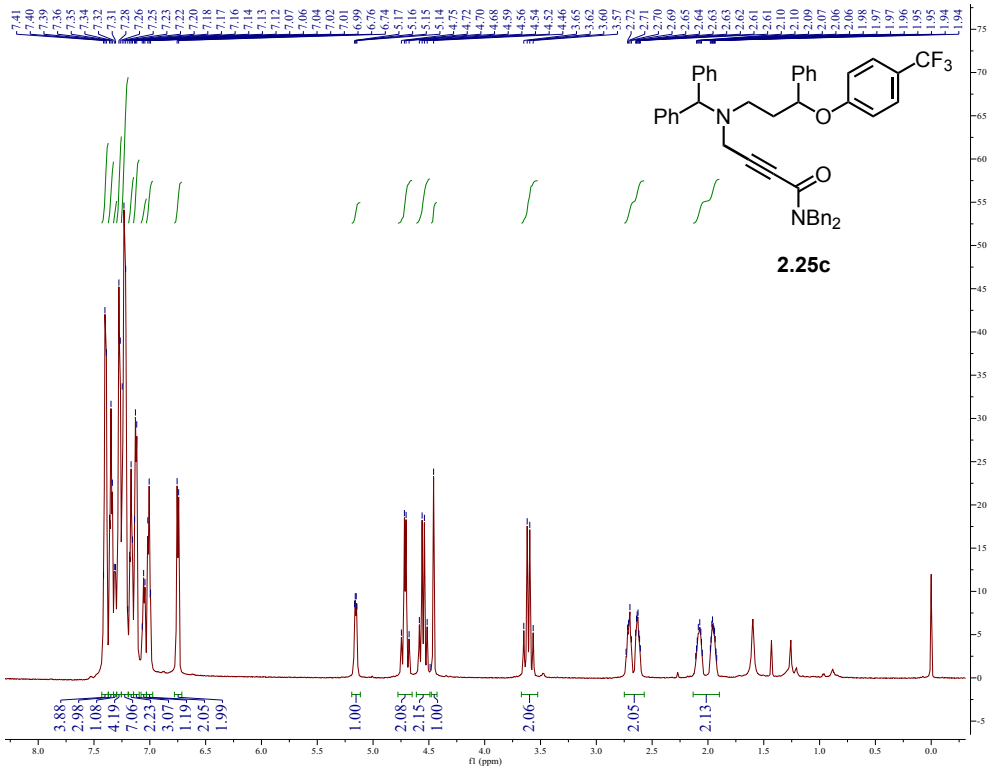
2.25b



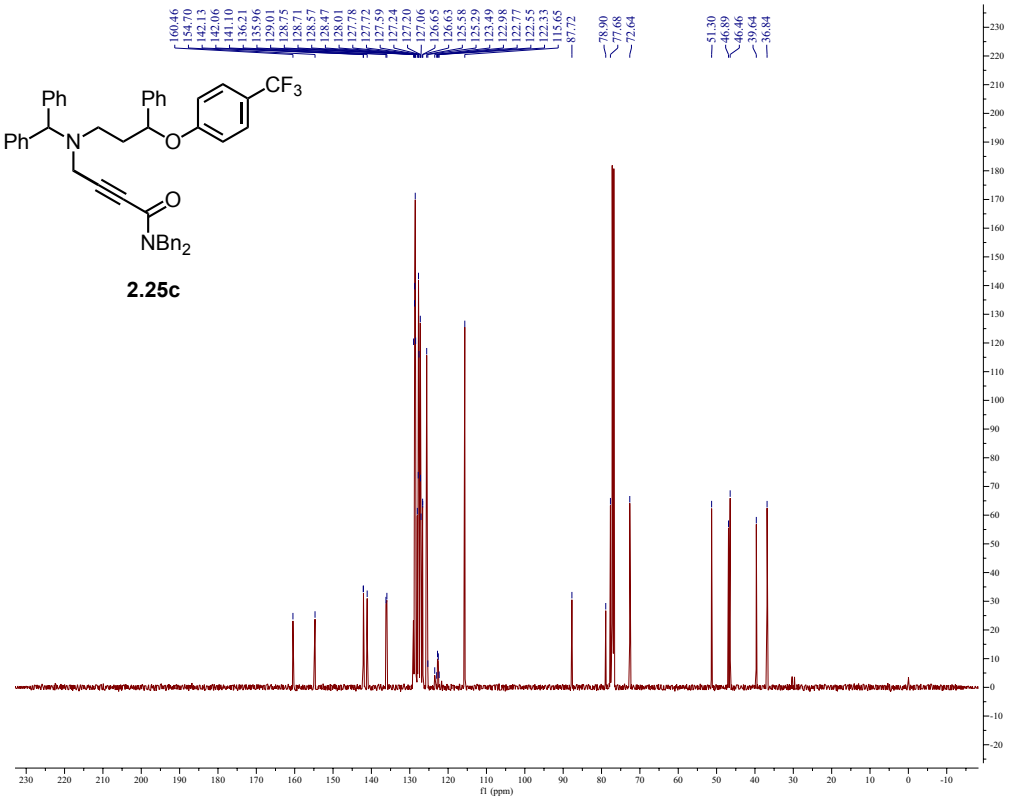
2.25b



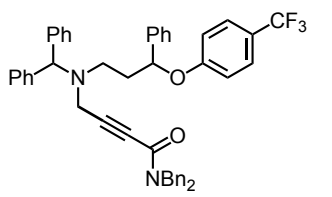
2.25c



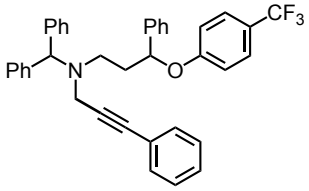
2.25c



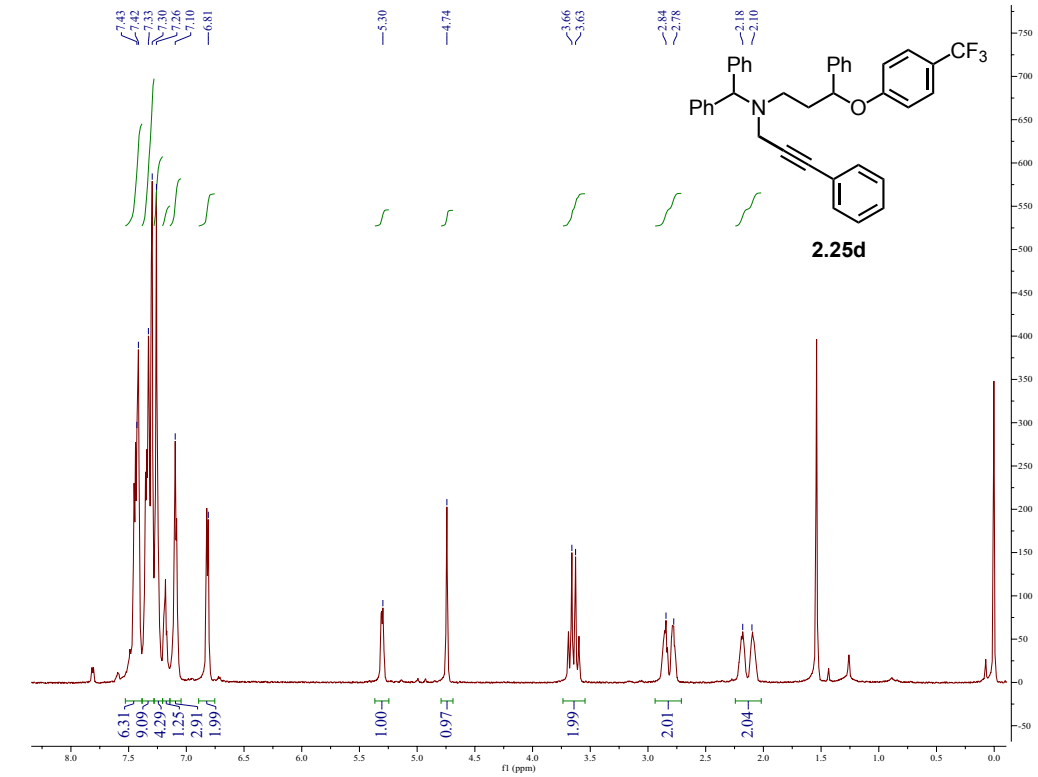
2.25c



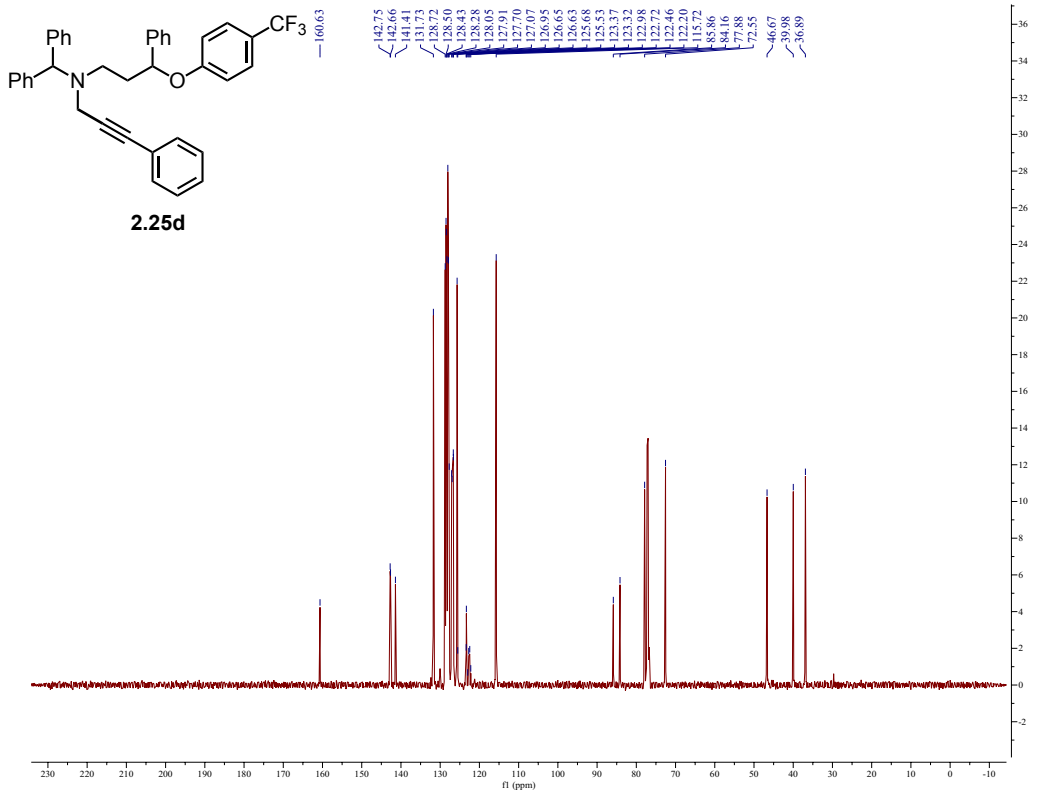
2.25c



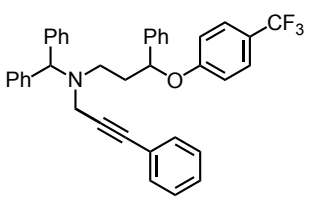
2.25d


7.43
7.42
7.33
7.30
7.26
7.10
6.81
5.30
4.74
3.66
3.63
2.84
2.78
2.18
2.10
Ph
Ph
Ph
N
O
CF3
6.31
9.09
4.29
1.25
2.91
1.99
1.00
0.97
1.99
2.01
2.04
f1 (ppm)

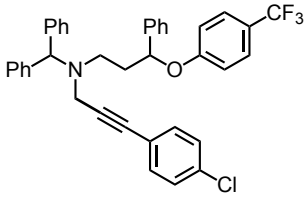
2.25d


Ph
Ph
Ph
N
O
CF3
160.63
142.75
142.66
141.41
131.73
128.72
128.50
128.43
128.28
128.05
127.91
127.70
127.07
126.95
126.65
126.63
125.68
125.53
123.37
123.32
122.98
122.72
122.46
122.20
115.72
85.86
84.16
77.88
72.55
46.67
39.98
36.89
f1 (ppm)

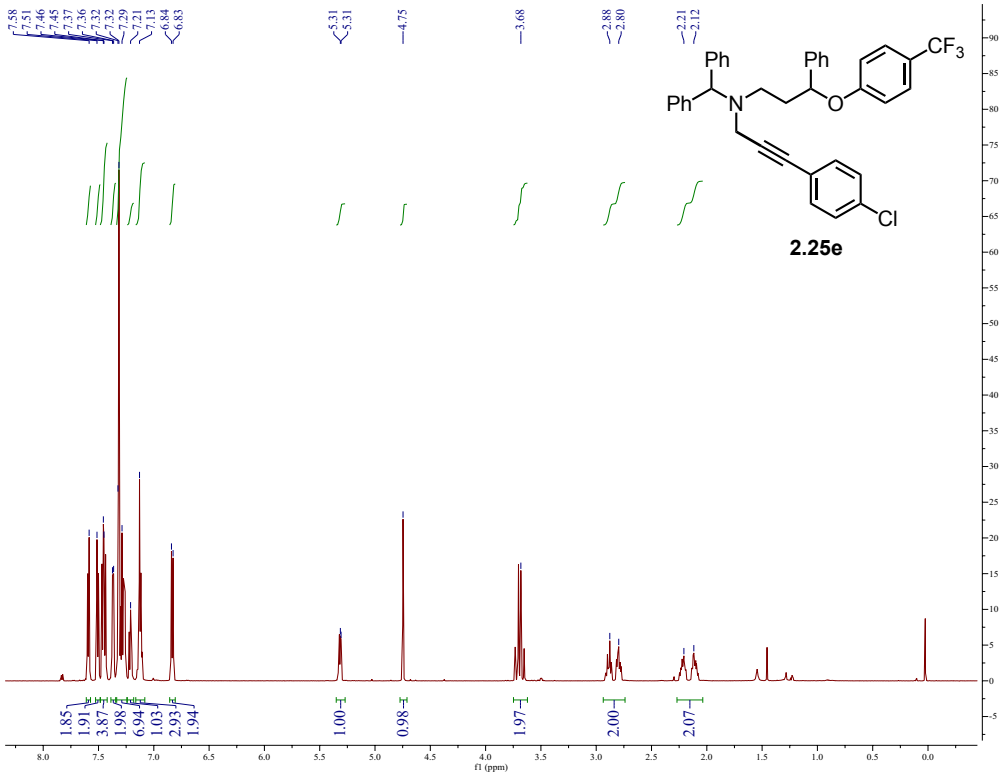
2.25d

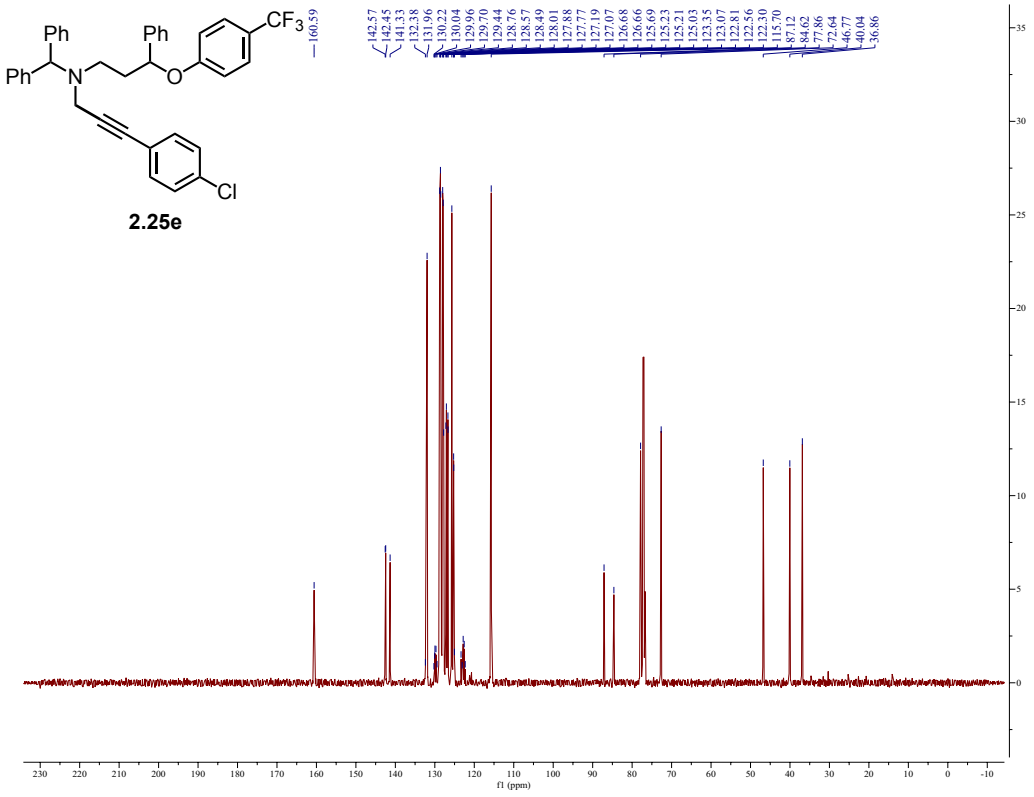


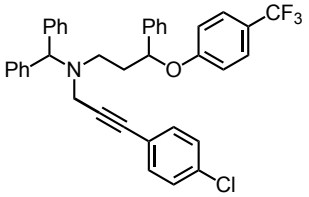
2.25d



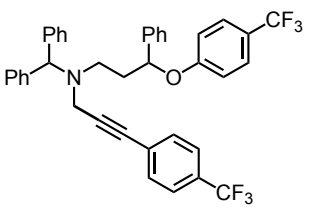
2.25e


7.58
7.51
7.46
7.45
7.37
7.36
7.32
7.29
7.21
7.13
6.84
6.83
5.31
5.31
4.75
3.68
2.88
2.80
2.21
2.12
Ph
Ph
Ph
N
O
CF3
Cl
2.25e
1.85
1.91
3.87
1.98
6.94
1.03
2.93
1.94
1.00
0.98
1.97
2.00
2.07
f1 (ppm)

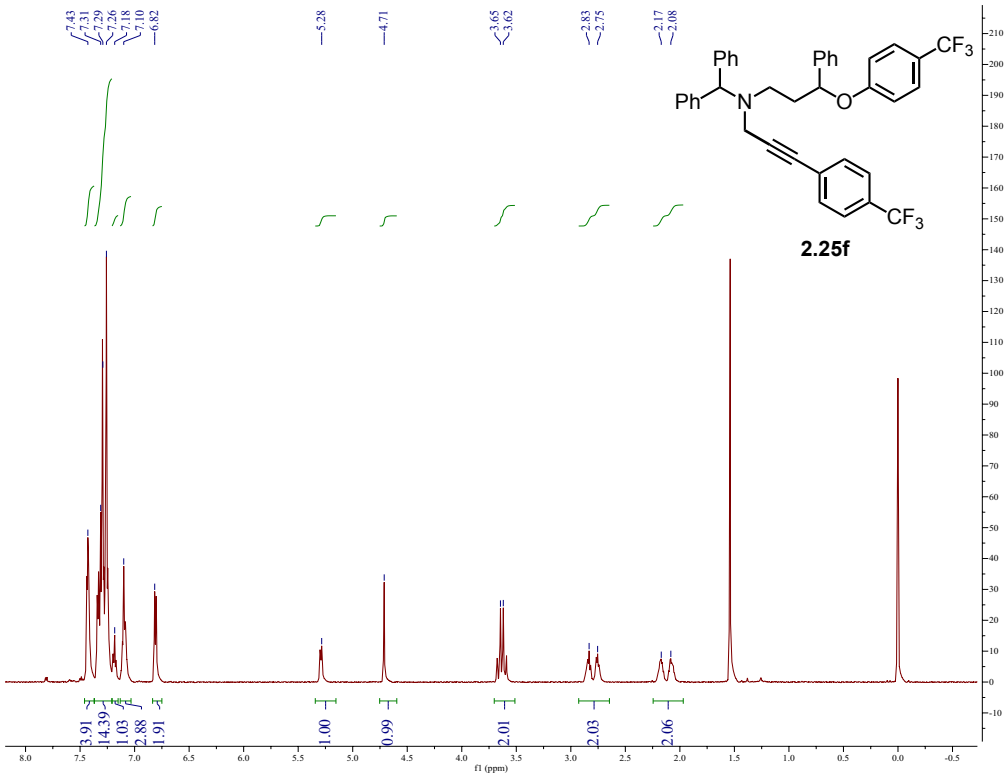

Ph
Ph
Ph
N
O
CF3
Cl
2.25e
160.59
142.57
142.45
141.33
132.38
131.96
130.22
130.04
129.96
129.70
129.44
128.76
128.57
128.49
128.01
127.88
127.77
127.19
127.07
126.68
126.66
125.69
125.23
125.21
125.03
123.35
123.07
122.81
122.56
122.30
115.70
97.12
84.62
77.86
72.64
46.77
40.04
36.86
f1 (ppm)

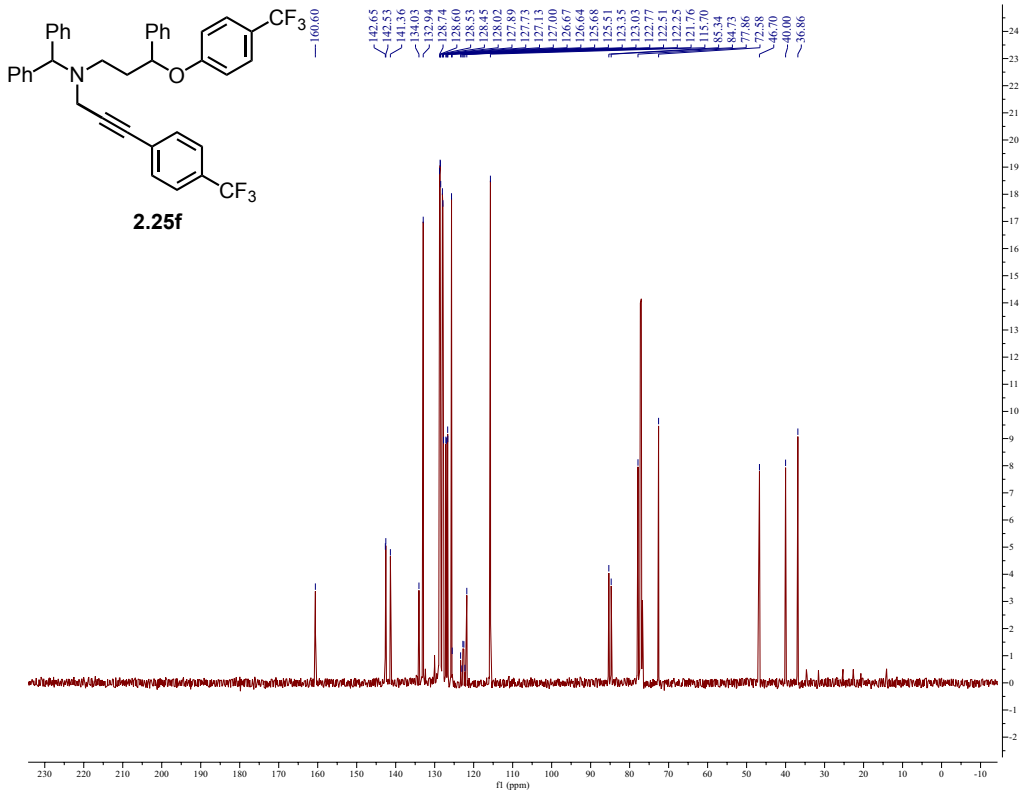


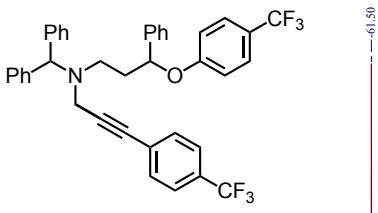
2.25e



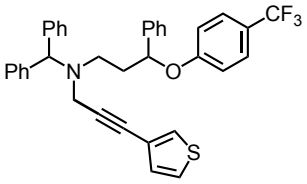
2.25f


7.43
7.31
7.29
7.26
7.18
7.10
6.82
5.28
4.71
3.65
3.62
2.83
2.75
2.17
2.08
Ph
Ph
Ph
N
O
CF3
CF3
2.25f
3.91
14.39
1.03
2.88
1.91
1.00
0.99
2.01
2.03
2.06
f1 (ppm)

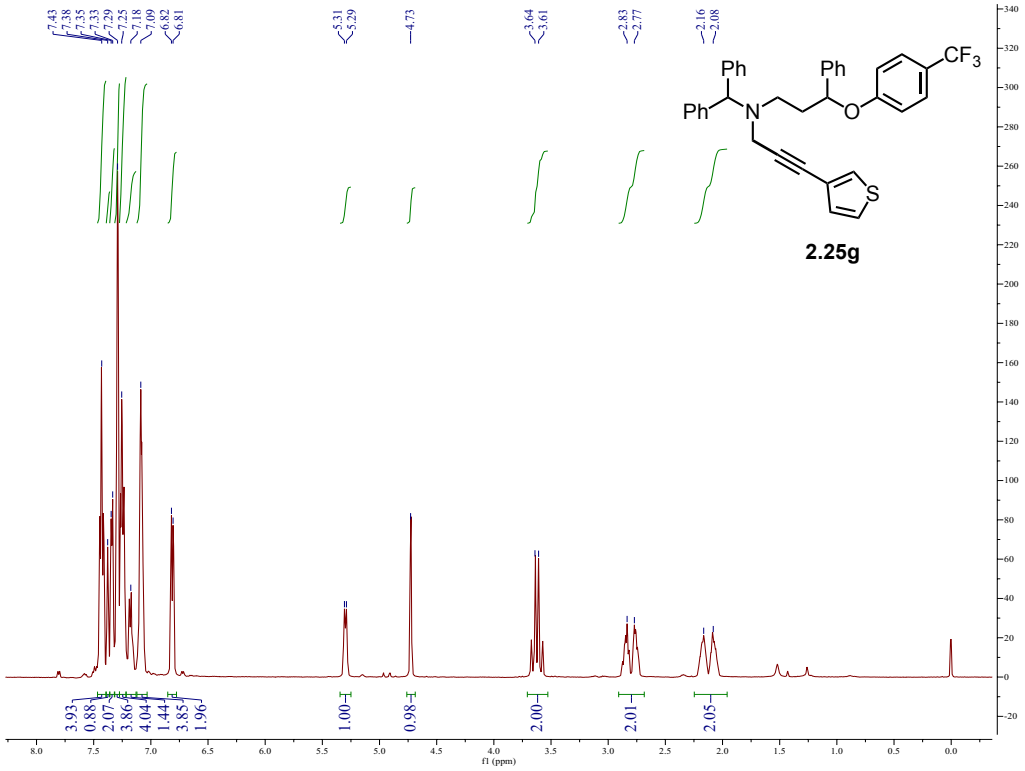

160.60
142.65
142.53
141.36
134.03
132.94
128.74
128.60
128.53
128.45
128.02
127.89
127.73
127.13
127.00
126.67
126.64
125.68
125.51
123.35
123.03
122.77
122.51
122.25
121.76
115.70
85.34
84.73
77.86
72.58
46.70
40.00
36.86
Ph
Ph
Ph
N
O
CF3
CF3
2.25f
f1 (ppm)

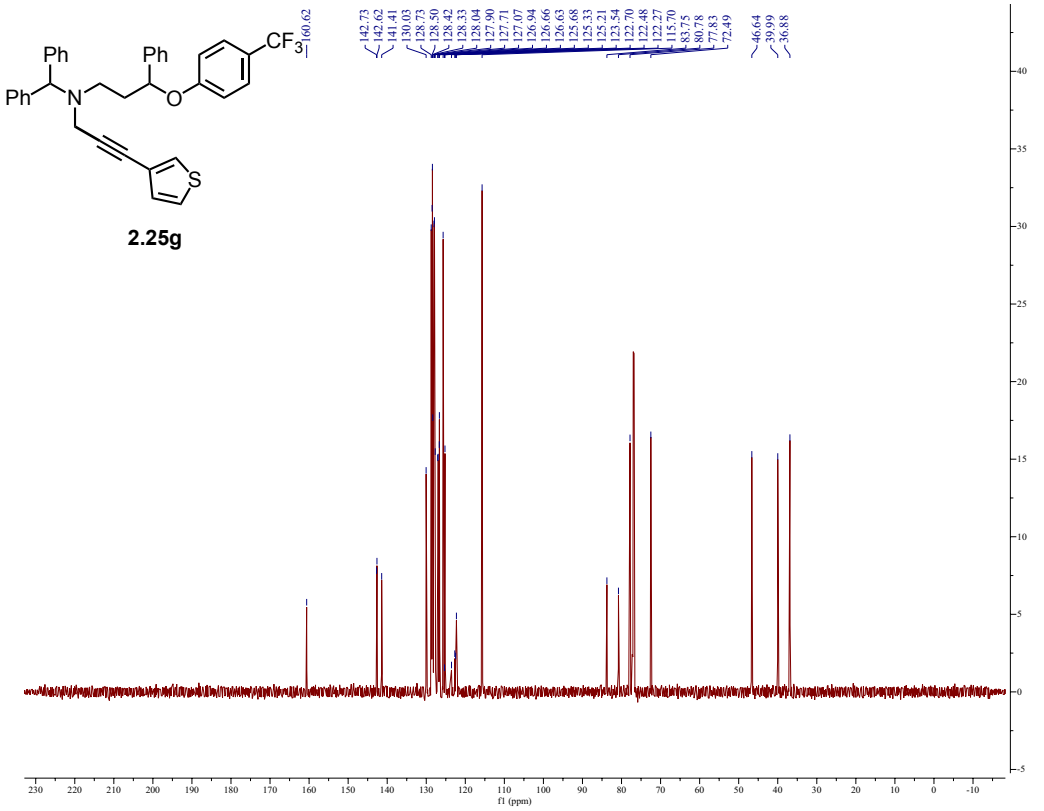


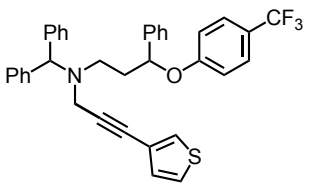
2.25f



2.25g


7.43
7.38
7.35
7.33
7.29
7.25
7.18
7.09
6.82
6.81
5.31
5.29
4.73
3.64
3.61
2.83
2.77
2.16
2.08
Ph
Ph
Ph
N
O
CF3
S
2.25g
3.93
0.88
2.07
3.86
4.04
1.44
3.85
1.96
1.00
0.98
2.00
2.01
2.05
f1 (ppm)


Ph
Ph
Ph
N
O
CF3
S
2.25g
142.73
142.62
141.41
130.03
128.73
128.50
128.42
128.33
128.04
127.90
127.71
127.07
126.94
126.66
126.63
125.68
125.33
125.21
123.54
122.70
122.48
122.27
115.70
83.75
80.78
77.83
72.49
46.64
39.99
36.88
f1 (ppm)



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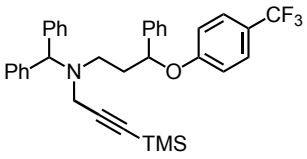

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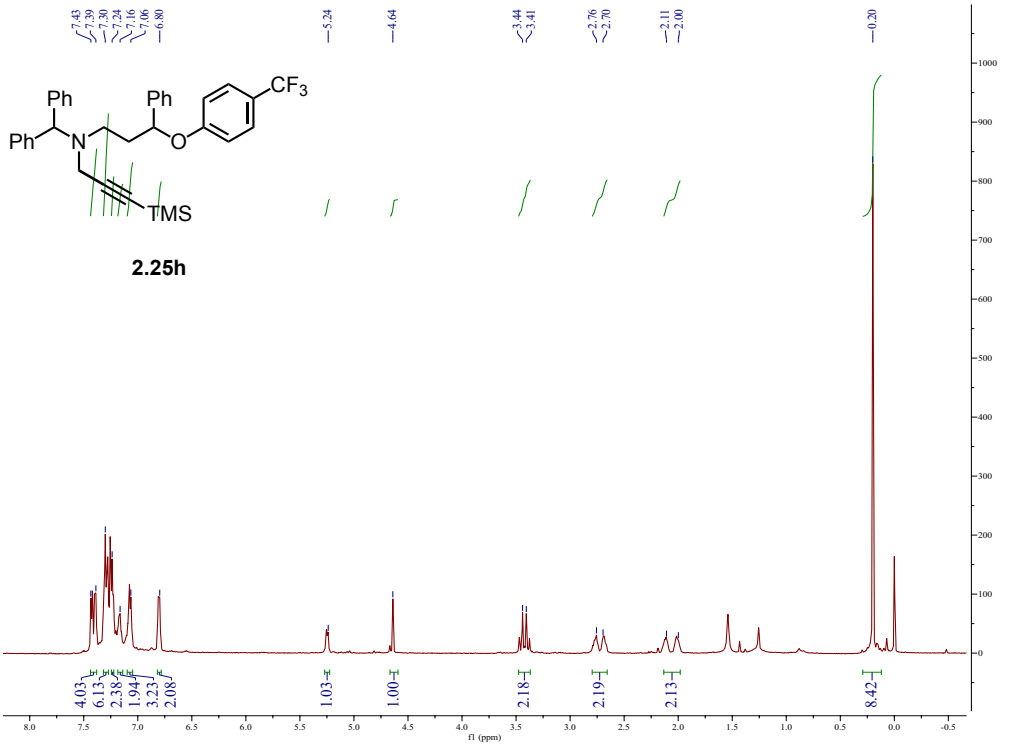
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2.11
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Ph
Ph
N
O
CF3
TMS
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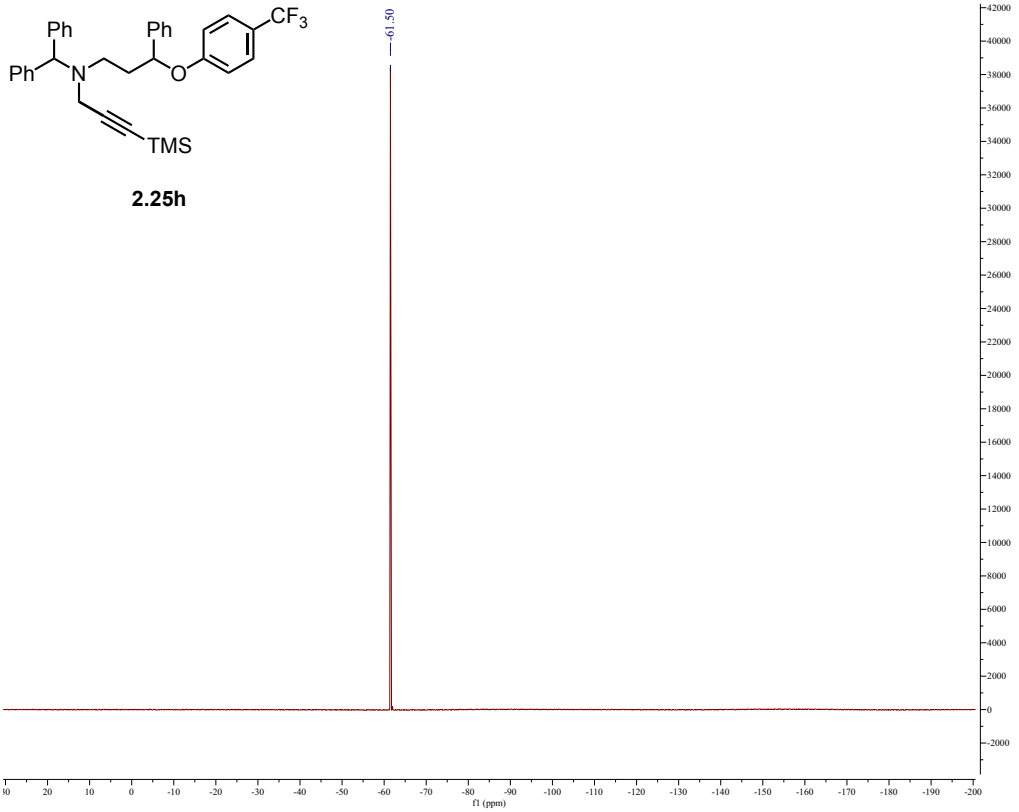
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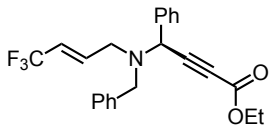
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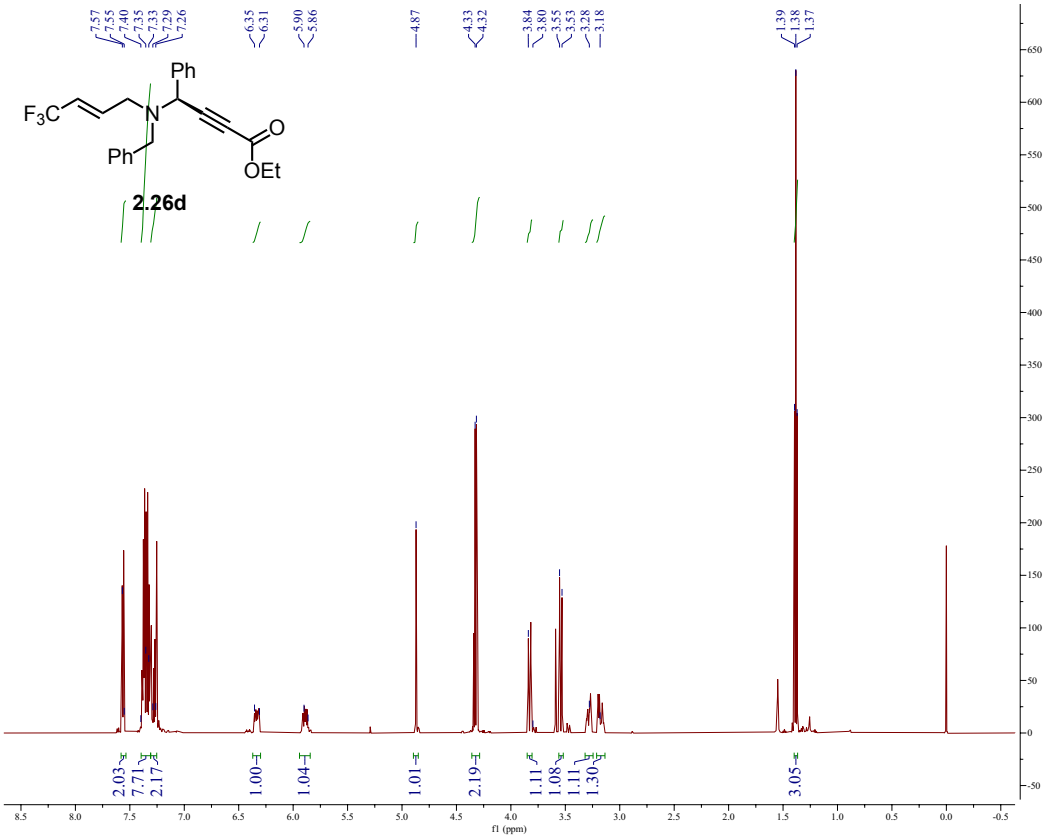
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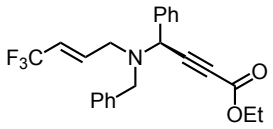
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2.26d

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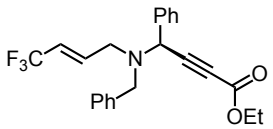
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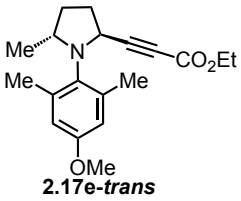

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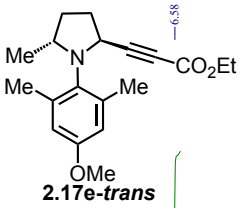

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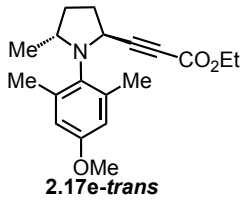

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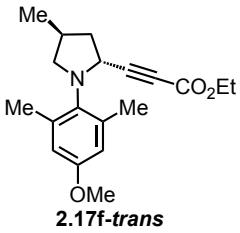

2.17f-*trans*

CHAPTER THREE Catalytic Deuterium Incorporation within Metabolically Stable β-Amino C–H Bonds of Drug Molecules

3.1 Introduction

Deuterium, the isotope of hydrogen, was discovered by Harold Urey and was awarded the Nobel Prize in 1934 "for his discovery of heavy hydrogen".[1] It has natural abundance of 0.0156% on Earth, which makes it a rare resource.[2] Deuterium has a smaller molar volume by 0.140 cm^3/mol per atom compared to hydrogen, which makes it less lipophilic ($\Delta \log P_{oct} = -0.006$), and potentially shows a slightly different pK_a.[3] C–D bonds are shorter than C–H bonds by 0.005 Å given that deuterium is heavier than hydrogen atom. The ground state vibrational energy of deuterium is lower than that of hydrogen and so does the ground state energy. Therefore, deuterium is more stable in oxidative processes, because the energy required from ground state to transition state will also be larger for C–D bonds than that of C–H bonds.[4]

There has been an increasing demand of deuterated bioactive molecules for their importance in determining the outcome of bioactive molecules and metabolites, including fields such as drug discovery and development, toxicology, pharmacology, food science, etc.[5] It is mainly used for three purposes. The first one is application in LC/MS. When the mass difference between the internal standard and the material tested is larger than 4 m/z, the separation between the corresponding peaks is obvious, and so it can give quantitative determination. Secondly, it could be used in kinetic isotope studies to establish reaction order and clarify the mechanism of a transformation. Lastly, molecules tagged with deuterium could act as a tracer. The intermediates and product could be identified after isolation.

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[1] O'Leary, D. *Nat. Chem*. **2012**, 4, 236.
[2] Established by the internationally accepted Vienna Standard Mean Ocean Water (VSMOW). Rosman, K. J. R.; Taylor, P. D. P. *Pure Appl. Chem.* **1998**, 70, 217−235.
[3] Meanwell, N. A. *J. Med. Chem*. **2011**, 54, 2529−2591.
[4] Pirali, T.; Serafini, M.; Cargnin, S.; Genazzani, A. A. *J. Med. Chem.* **2019**, 62, 5276−5297.
[5] Atzrodt, J.; Derdau, V.; Fey, T.; Zimmermann, J. *Angew. Chem., Int. Ed.* **2007**, 46, 7744−7765.

In particular, deuterated molecules have been widely used in examining absorption, distribution, metabolism and excretion (ADME) properties of drug candidates. They have the unique benefits of retaining the pharmacologic profile of physiologically active compounds.[6] In some cases, it was discovered that deuterated drugs give better performance than its hydrogenated version for less prone to epimerization or decomposition.[3]

3.2 Background

Since C–D bonds have higher stabilization that C–H bonds, researchers have been investigating on methods to incorporate deuteriums into bioactive compounds. Preparation of deuterium/tritium incorporated molecules generally is classified into two types: conventional multistep synthesis starting with deuterated materials or hydrogen isotope exchange (HIE).[7] The classical approach usually starts with deuterium sources, such as D_2O or D_2. It can be time and resources consuming as it requires multiple steps of synthesis and purification.[7] The second method, HIE, direct exchange of hydrogen with deuterium, is more efficient and effective.[5] HIE reaction targeting $C(sp^3)$–H bonds on bioactive amines is an interesting topic of study, given that *N*-alkylamine units can be found in over 50% of the top selling commercial drugs.[8]

Regioselectivity in deuterium incorporation is important, depending on the purpose of the tag. Putting deuteriums at a labile position could invalidate a study focused on tracing a bioactive molecule, as heavy water is generated as the byproduct through metabolic systems and excreted as waste, causing mass imbalance.[9] The β-position of amines, on the other hand, is more inert compared with α-C–H bond. Therefore, it will be less affected during the metabolic processes, which will leave the starting molecule with the tag intact. The β-C–H bond of *N*-alkylamines is also versatile, presenting in many bioactive molecules and enantioselective catalysts.

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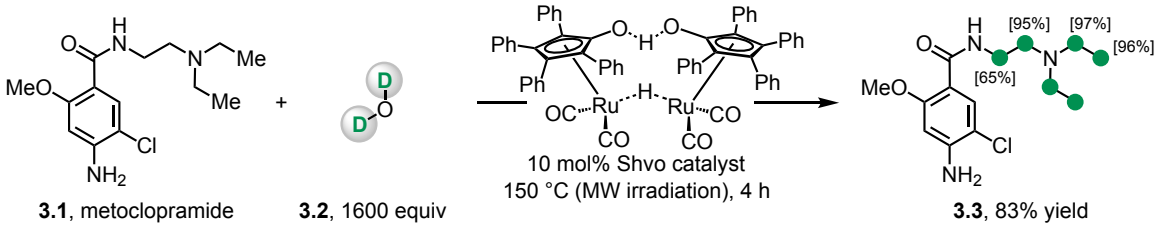
[6] Harbeson, S. L.; Tung, R. D. *MedChem. News* **2014**, 2, 8–22.
[7] Atzrodt, J.; Derdau, V.; Kerr, W. J.; Reid, M. *Angew. Chem., Int. Ed.* **2018**, 57, 3022–3047.
[8] McGrath, N. A.; Brichacek, M.; Njardarson, J. T. *J. Chem. Educ.* **2010**, *87*, 1348−1349.
[9] Penner, N.; Klunk, L. J.; Prakash, C. *Biopharm. Drug Dispos.* **2009**, 30, 185–203.

Current state of the art catalytic amine deuteration method involves the use of transition metal catalysts. The Beller group reported an α- and β-amino C–H deuteration of metoclopramide and two other structurally related drug molecules promoted by the use of Ru-based Shvo catalyst with high level of incorporation and high yield (Scheme 3.1).[10] Metoclopramide **3.1** was treated with 1600 equiv of D_2O with 10 mol% of Shvo catalyst under microwave irradiation at 150 °C to give deuterated product with 83% yield and from 65-97% of *d*-incorporation at α- or β- amino C–H bonds. However, the catalyst loading is high, and the method has contrived substrate scope. Functional groups, such as ketones and olefinic double bonds, are at risk of hydrogenation under their standard reaction conditions. Furthermore, primary and secondary aliphatic amines lead to dimerization side reactions.



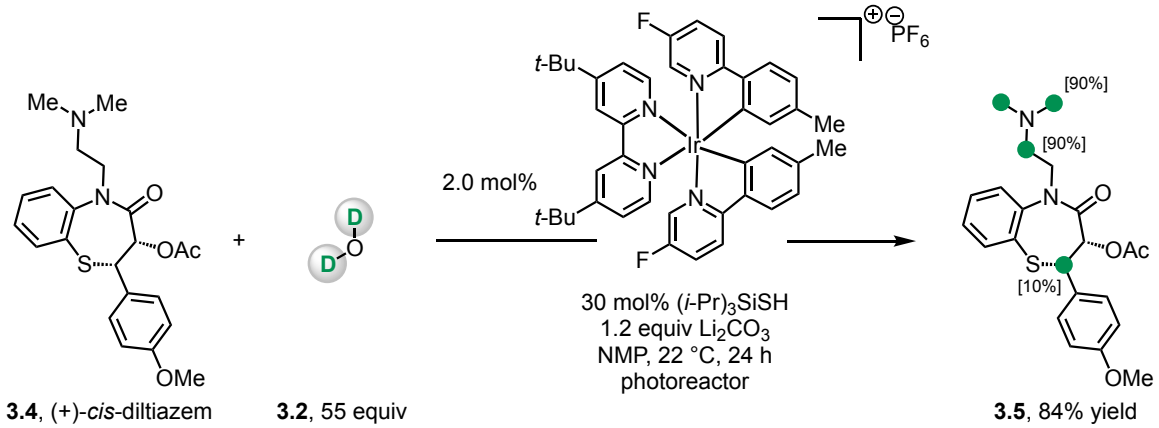
3.1, metoclopramide **3.2**, 1600 equiv **3.3**, 83% yield

Scheme 3.1 α- and β- Deuteration of amines using Ru-based catalyst

Another example reported by the MacMillan group involves the use of photoredox catalyst.[11] (+)-*Cis*-diltiazem **3.4** and 55 equiv of D_2O reacted with 2.0 mol% of Ir-based catalyst, 30 mol% of $(i\text{-Pr})_3SiSH$, and 1.2 equiv of Li_2CO_3 in NMP in a photoreactor at 22 °C to afford deuterated product with 84% yield and 90% deuterium incorporation at α-amino C–H bonds and 10% at C–H adjacent to sulfur. Their method can incorporate deuterium or tritium onto cyclic and acylic *N*-alkylamine containing drug molecules using Ir-based photoredox catalyst with moderate to high level of incorporation and yield. However, at labile positions other than α-amino C–H bonds, such as C–H adjacent to oxygen or sulfur atoms, low level of deuterium incorporation was also observed.

[10] Neubert, L.; Michalik, D.; Bahn, S.; Imm, S.; Neumann, H.; Atzrodt, J.; Derdau, V.; Holla, W.; Beller, M. *J. Am. Chem. Soc.* **2012**, *134*, 12239−12244.

[11] Loh, Y. Y.; Nagao, K.; Hoover, A. J.; Hesk, D.; Rivera, N. R.; Colletti, S. L.; Davies, I. W.; MacMillan, D. W. C. *Science* **2017**, *358*, 1182−1187.



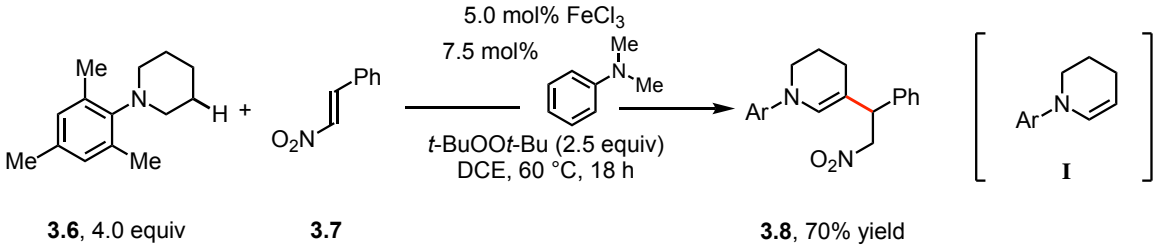
3.4, (+)-*cis*-diltiazem **3.2**, 55 equiv **3.5**, 84% yield

Scheme 3.2 Deuteration of amines by photoredox catalysts

In these methods, they use readily accessible deuterium source, D_2O and can be applicable to commercial amine drug molecules with high level of *d*-incorporation and high yield. However, the development for regioselective *β*-deuteration of amines is still lacking. Activation of the inert *β*-position of *N*-alkyl amines is also difficult, as the *β*-amino C–H bond is less hydridic comparing to the *α*-amino C–H bond. A transformation that could target poorly activated *β*-position of amines, which contain acid and base sensitive functional groups, without the use of precious metal-based catalysts and using readily accessible deuterium sources, is challenging. Synthesis of functionalized *β*-amino C–H bond requires multiple steps and direct functionalization has only a few examples.

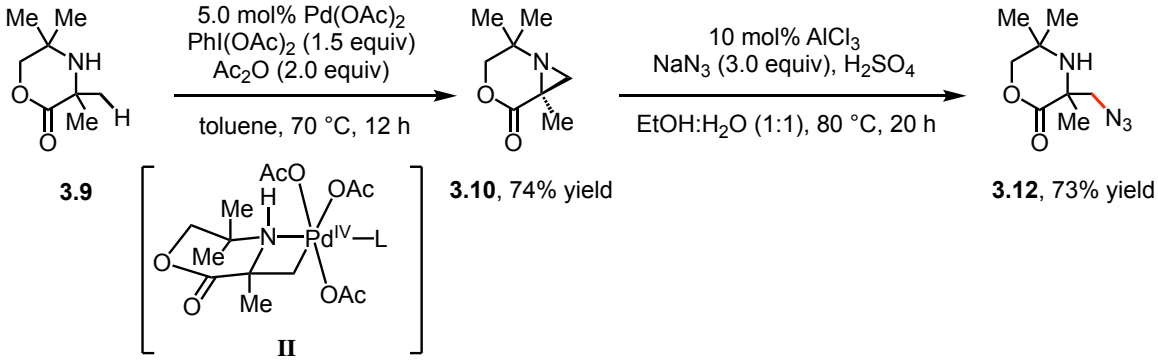
In 2013, the Kanai group reported an oxidative *β*-amino C–H alkylation catalyzed by $FeCl_3$ (Scheme 3.3).[12] Mesityl protected amine **3.6** and alkene **3.7** gave 70% of alkylated enamine product **3.8** with 5.0 mol% of $FeCl_3$, 7.5% of DMAP, and 2.5 equiv of *tert*-butyl peroxide in DCE at 60 °C. $FeCl_3$ and *tert*-butyl peroxide generates amino radical, which is then transformed to iminium ion by the loss of hydrogen radical to form *tert*-butanol. Another tert-butoxide deprotonates at the *β*-position to afford the reactive enamine intermediate **I**. This method is applicable to cyclic amines of different ring sizes and with oxygen or sulfur containing heterocylces with 44-91% yield. Only three examples of acyclic amines were reported with 32-64% yield.

[12] Takasu, N., Oisaki, K., Kanai, M. *Org. Lett.* **2013**, *15*, 1918–1921.



Scheme 3.3 Oxidative *β*-amino C–H alkylation by Kanai

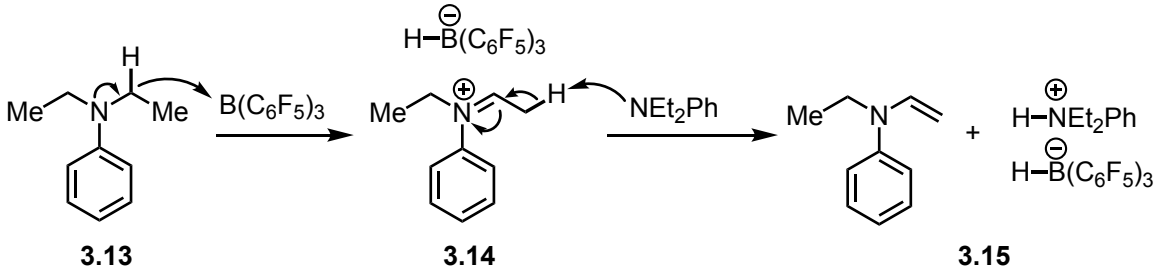
In 2014, the Gaunt group reported a C–H activation of aliphatic amines by the use of palladium-based catalysts (Scheme 3.4).[13] Amino lactone **3.9** with 5.0 mol% of $Pd(OAc)_2$, 1.5 equiv of phenyliodine diacetate, and 2.0 equiv of acetic anhydride in toluene at 70 °C afforded aziridine product **3.10** in 74% yield. The aziridine product 3.10 could be subjected to ring opening reactions. With 10 mol% of $AlCl_3$ and 3.0 equiv of NaN_3 and H_2SO_4 in EtOH:H_2O (1:1) at 80 °C gave azide **3.12** in 73% yield. Palladium activates the *β*-amino C–H bond and forms a four membered palldium(IV) cycle (**II**). The ring opening reaction can tolerate different heteroatom nucleophiles. However, this transformation has limited substrate scope where most substrates are lactones and contain the geminal dimethyl group and only achieved moderate yield in long reaction times. It is also wasteful to perform a two-step reaction that uses transition metal-based catalyst and stoichiometric amount of oxidizing agent.



Scheme 3.4 C–H activation of aliphatic amines by Gaunt

[13] Gaunt, M. J. *et al*. *Nature* **2014**, *510*, 129–133.

Our group has studied various transformations involving the concept of FLP. Based on our previous studies, we wanted to develop a selective *β*-amino C–H deuteration method without the use of precious metal-based catalysts. As discussed in Chapter I introduction, $B(C_6F_5)_3$ is able to generate iminium intermediate in situ. The iminium ion can be deprotonated by a Brønsted base at the *β*-position to afford an enamine intermediate. The Basset group reported that $B(C_6F_5)_3$ abstracts hydride first from diethyl aniline **3.13** to generate iminium and borohydride intermediate **3.14**.[14] Then, another molecule of diethylaniline **3.13** can act as a base to deprotonate the *β*-position of iminium to afford enamine and an ion pair of ammonium and borohydride **3.15**.



Scheme 3.5 Generation of enamine, and borohydride and ammonium ion

The reactive enamine could serve as a nucleophile to react with different electrophilic deuterium sources. Here, we report a catalytic method using the concept of FLP that selectively deuterates *β*-amino C–H bond of acyclic and cyclic bioactive amines.

3.3 Proposed catalytic cycle and optimization

In this transformation, $B(C_6F_5)_3$ and amine work cooperatively. NR_3 could be an amine additive, the amine starting material **3.16**, and/or the amine product **3.18**. $B(C_6F_5)_3$ receives a hydride from amine **3.16** first to form iminium and borohydride (**I**). An amine can subsequently deprotonate the iminium at the *β*-position to form an enamine, a borohydride and an ammonium (**II**). At the same time, $B(C_6F_5)_3$ and amine can dedeuterate acetone-d_6 **3.17a** to form deuterated ammonium ion and boroenolate (**III**). After ion pair exchange,

[14] Millot, N.; Santini C.C.; Fenet, B.; Basset, J. M. *Eur. J. Inorg. Chem.* **2002**, 3328–3335.

deuteration at β-position and hydride reduction at α-position could take place to give the β-deuterated amine product and regenerate the catalyst.

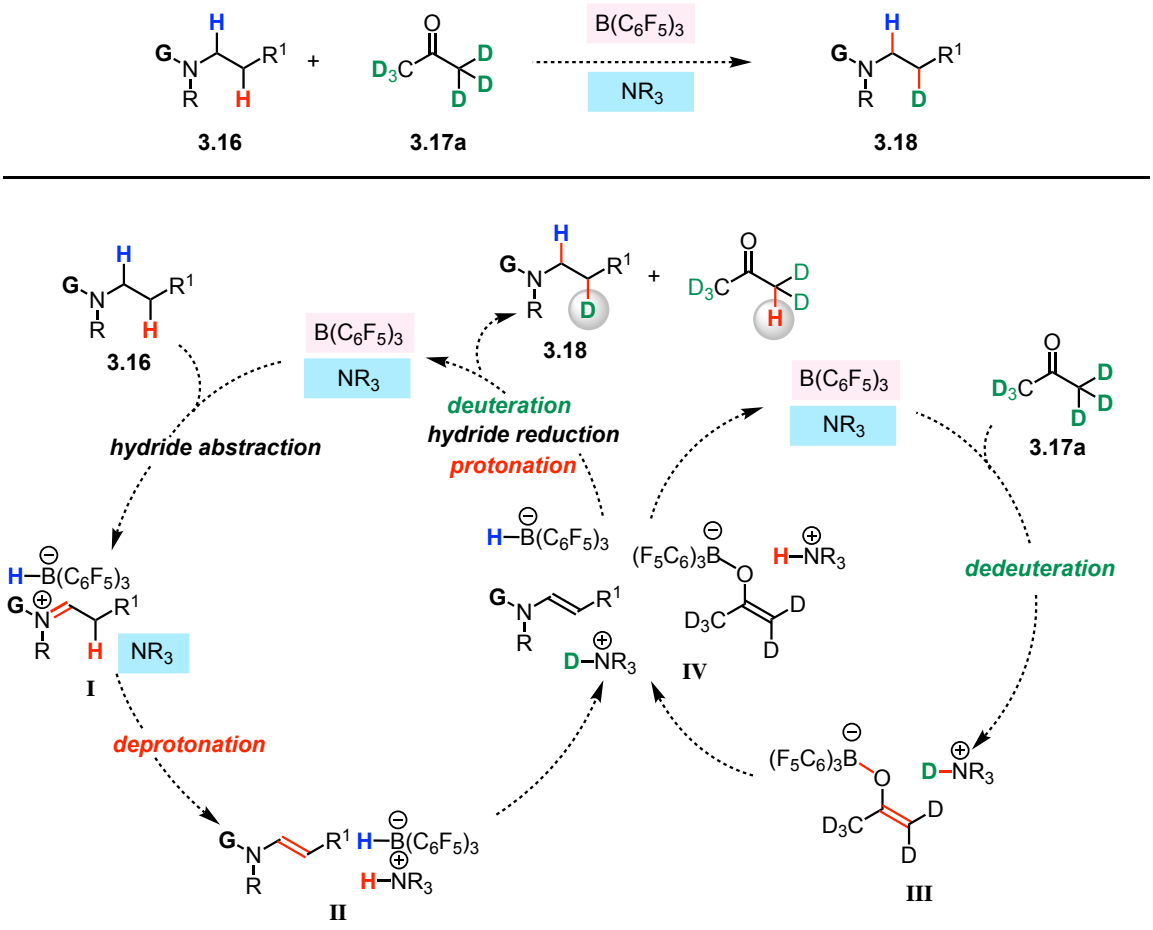
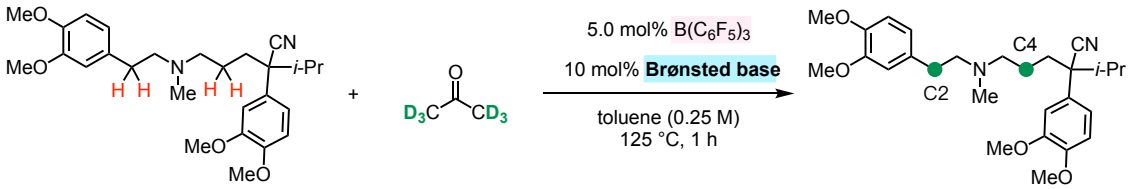


Figure 3.1 Proposed catalytic cycle for deuteration

3.3.1 Evaluation of catalyst combination

First, the catalyst combination of a suitable Brønsted base and $B(C_6F_5)_3$ was explored for reaction between 0.1 mmol of verapamil **3.16a** and acetone-d_6 (6.8 equiv) **3.17a** to generate **3.18a**. Amine additives with different basicity were tested as a Brønsted base co-catalyst. Trialkyl amines, including NEt_3, NBn_3, and PMP, gave **3.18a** in >90% yield with 17-34% of deuterium incorporation at β-amino position (Table 3.1, entries 1-3). However, when more basic DBU was used, no deuteriums were incorporated (Table 3.1, entry 4). When the reaction was performed without base, we observed 21% deuterium incorporation at C2 and 35% at C4 (Table 3.1, entry 5). This result led us to the conclusion that **3.16a**

and/or **3.18a** can act as a Brønsted base in the reaction mixture. An external base catalyst, therefore, is not required.



3.16a, 0.1 mmol verapamil

3.17a, 0.68 mmol

3.18a

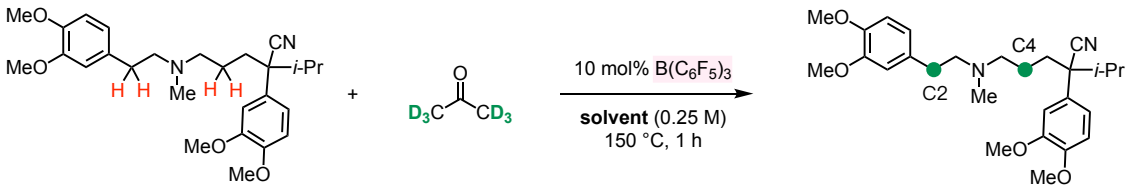
entry	Brønsted base	*d*-incorporation (%)[a]	
		[C2]	[C4]
1	NEt_3	17	26
2	NBn_3	20	34
3	PMP	16	26
4	DBU	0	0
5	none	21	35

[a] *d*-incorporation rate was determined by ^{1}H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard

Table 3.1 Evaluation of Brønsted bases

3.3.2 Evaluation of solvents

Non-polar solvents in general give higher *d*-incorporation, 90% and 92% with toluene and 84% and 91% with benzene (Table 3.2, entries 1 and 2). When halogenated solvents, dichloroethane (78% and 90%) and chloroform (71% and 85%), the reaction was slightly less efficient (Table 3.2, entries 3 and 4). Ether solvents resulted in low level of deuterium incorporation (Table 3.2, entries 5 and 6). Diethyl ether gave 14% and 24% *d*-incorporation at C2 and C4 respectively, and THF with less than 5% at both positions. Toluene was chosen as the optimal solvent.



3.16a, 0.1 mmol verapamil

3.17a, 0.68 mmol

3.18a

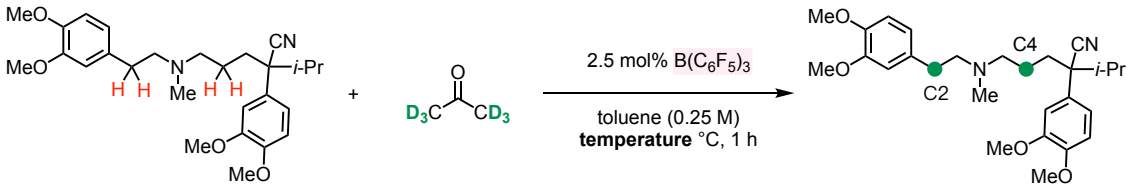
entry	solvent	*d*-incorporation (%)[a]	
		[C2]	[C4]
1	toluene	90	92
2	benzene	84	91
3	$ClCH_2CH_2Cl$	78	90
4	$CHCl_3$	71	85
5	Et_2O	14	24
6	THF	<5	<5

[a]*d*-incorporation rate was determined by ^1H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard

Table 3.2 Evaluation of solvents

3.3.3 Evaluation of temperature

As the reaction temperature was increased, the level of deuterium incorporation increased. At 100 °C, less than 7% of deuteriums were incorporated at both C2 and C4 (Table 3.3, entry 1). At 150 °C, 80-85% *d*-incorporation was reached (Table 3.3, entry 3). At the reaction temperature of above 150 °C, the change in the level of deuterium incorporation did not increase any higher. To minimize the energy input and to avoid decomposition of molecules at elevated temperature, 150 °C was chosen as the optimal reaction temperature.



3.16a, 0.1 mmol verapamil | **3.17a**, 0.68 mmol | **3.18a**

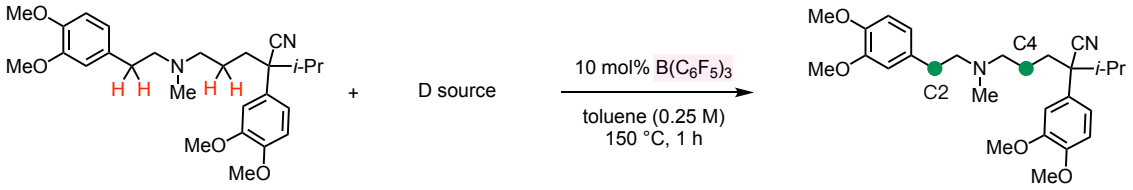
entry	temperature	*d*-incorporation (%)[a]	
		[C2]	[C4]
1	100	<5	7
2	125	21	35
3	150	80	85

[a]*d*-incorporation rate was determined by ^{1}H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard

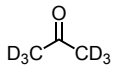
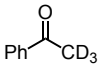
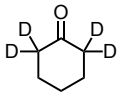
Table 3.3 Evaluation of reaction temperature

3.3.4 Evaluation of deuterium source

Different sources of deuteriums were tested using the same catalyst system. When using the same equivalence of deuterium sources, acetone-d_6 **3.17a** provided the greatest number of deuteriums per molecule, and it was found to be the most efficient source of deuteriums. Acetophenone-d_3 **3.17b**, although it can potentially form a more stabilized intermediate **IV** (see Fig. 3.1) comparing to acetone-d_6 **3.17a**, generated product with lower level of deuterium incorporation (Table 3.4, entry 2). Cyclohexanone-d_4 **3.17c** was also found to be less efficient, giving 45% and 50% at C2 and C4 respectively (Table 3.4, entry 3). Deuterated alcohol (MeOD **3.17d**, isopropanol-d_8 **3.17e**, *t*-BuOD **3.17f**) could also serve as deuterium source in this reaction, but they show inferior level of *d*-incorporation of the product (Table 3.4, entries 4-6). *t*-BuOD **3.17f** gave the highest level of incorporation at the same equivalence among the alcohol sources. We wondered if the same number of deuteriums were added as acetone-d_6, it would affect the level of incorporation. However, we found that the reaction did not proceed as we increased the amount of *t*-BuOD (Table 3.4, entry 7). One of the potential reasons could be excess alcohol coordinating with borane Lewis acid and preventing it to undergo hydride abstraction to form intermediate **I** (see Fig. 3.1).



3.16a, 0.1 mmol verapamil | **3.17** | **3.18a**

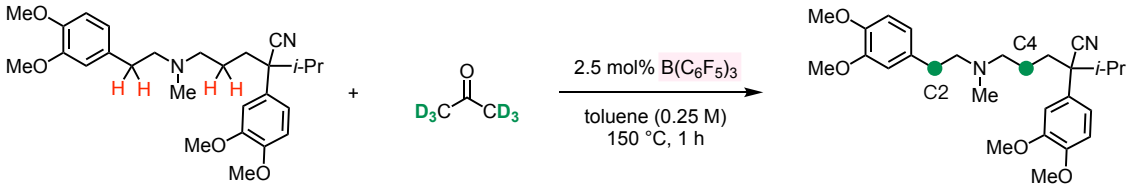
entry	D source	equiv of **2** (D/molecule)	*d*-incorporation (%)[a] [C2]	[C4]
1	 **3.17a**	6.8 (40.8)	90	92
2	 **3.17b**	6.8 (20.4)	79	71
3	 **3.17c**	6.8 (27.2)	45	50
4	CH_3OD **3.17d**	6.8 (6.8)	14	20
5	$(CD_3)_2CDOD$ **3.17e**	6.8 (6.8)	17	21
6	*t*-BuOD **3.17f**	6.8 (6.8)	63	58
7	*t*-BuOD **3.17f**	40.8 (40.8)	0	0

[a] *d*-incorporation rate was determined by ^{1}H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard

Table 3.4 Evaluation of deuterium sources

3.3.5 Evaluation of equivalence of acetone-d_6

With 2.5 mol% of Lewis acid catalyst, the reaction showed that as the equivalence of acetone-d_6 increases from 2.0 to 6.8, the level of incorporation increased (Table 3.5, entries 1-3). However, with 10 equiv of acetone-d_6, the level of incorporation was slightly lowered at C2 position (Table 3.5, entry 4). Excess amount of acetone may favor the formation of boron enolate intermediate and slowing down the formation of iminium ion through hydride abstraction.



3.16a, 0.3 mmol verapamil | **3.17a** | **3.18a**

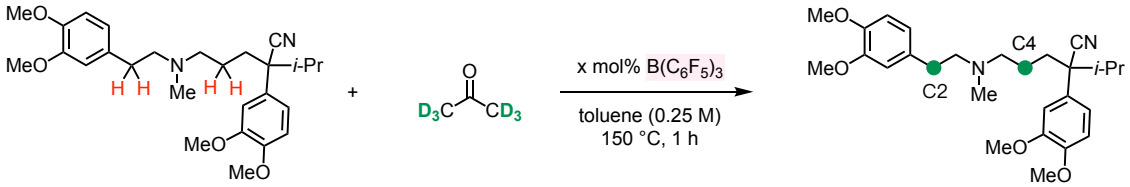
entry	equiv of **3.17a**	*d*-incorporation (%)[a]	
		[C2]	[C4]
1	2.0	47	60
2	4.0	72	82
3	6.8	80	86
4	10	70	85

[a]*d*-incorporation rate was determined by ^{1}H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard

Table 3.5 Evaluation of equivalence of acetone-d$_6$

3.3.6 Evaluation of catalyst loading

We attempted to lower the catalyst loading of $B(C_6F_5)_3$. With 2.5 mol% or 5 mol% the level of incorporation decreased to 80-86% (Table 3.6, entries 1-2). 10 mol% of $B(C_6F_5)_3$ was found to be the most efficient, showing 88-92% of deuterium incorporation (Table 3.6, entry 3). Furthermore, an alternative method was found that subjecting the reaction to 5 mol% of $B(C_6F_5)_3$ and resujecting to the same reaction condition after isolation of deuterated product gave higher level of *d*-incorportion, 95% at C2 and >98% at C4 (Table 3.6, entry 4).



3.16a, 0.1 mmol
verapamil

3.17a, 0.68 mmol

3.18a

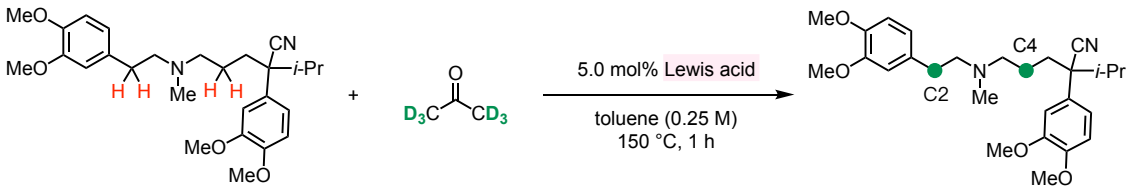
entry	loading of $B(C_6F_5)_3$ (mol%)	*d*-incorporation (%)[a] [C2]	[C4]
1	2.5	80	86
2	5.0	80	85
3	10	88	92
4[b]	5.0 × 2	95	>98

[a]*d*-incorporation rate was determined by ^{1}H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard; [b]Condition: verapamil(1, 0.2 mmol), acetone-d_6 (2, 1.36 mmol), $B(C_6F_5)_3$ (5 mol%), toluene (0.8 mL), under N_2, 150 °C, 1 h. Isolated and purified 3 was reacted with acetone-d_6(2, 1.36 mmol), $B(C_6F_5)_3$ (5 mol%), toluene (0.8 mL), under N_2, 150 °C, 1 h.

Table 3.6 Evaluation of loading of Lewis acid catalyst

3.3.7 Control experiments

Without any Lewis acid, the reaction did not proceed (Table 3.7, entry 1). No deuterium incorporation was observed when less hindered BF_3 or less Lewis acidic BPh_3 were used (Table 3.7, entries 2 and 3).



3.16a, 0.1 mmol verapamil

3.17a, 0.68 mmol

3.18a

entry	Lewis acid	*d*-incorporation (%)[a] [C2]	[C4]
1	none	0	0
2	$BF_3{\cdot}OEt_2$	0	0
3	BPh_3	0	0
4	$B(C_6F_5)_3$	88	92

[a]*d*-incorporation rate was determined by ^{1}H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard

Table 3.7 Control experiments with Lewis acids

3.4 Scope of Amine Substrates

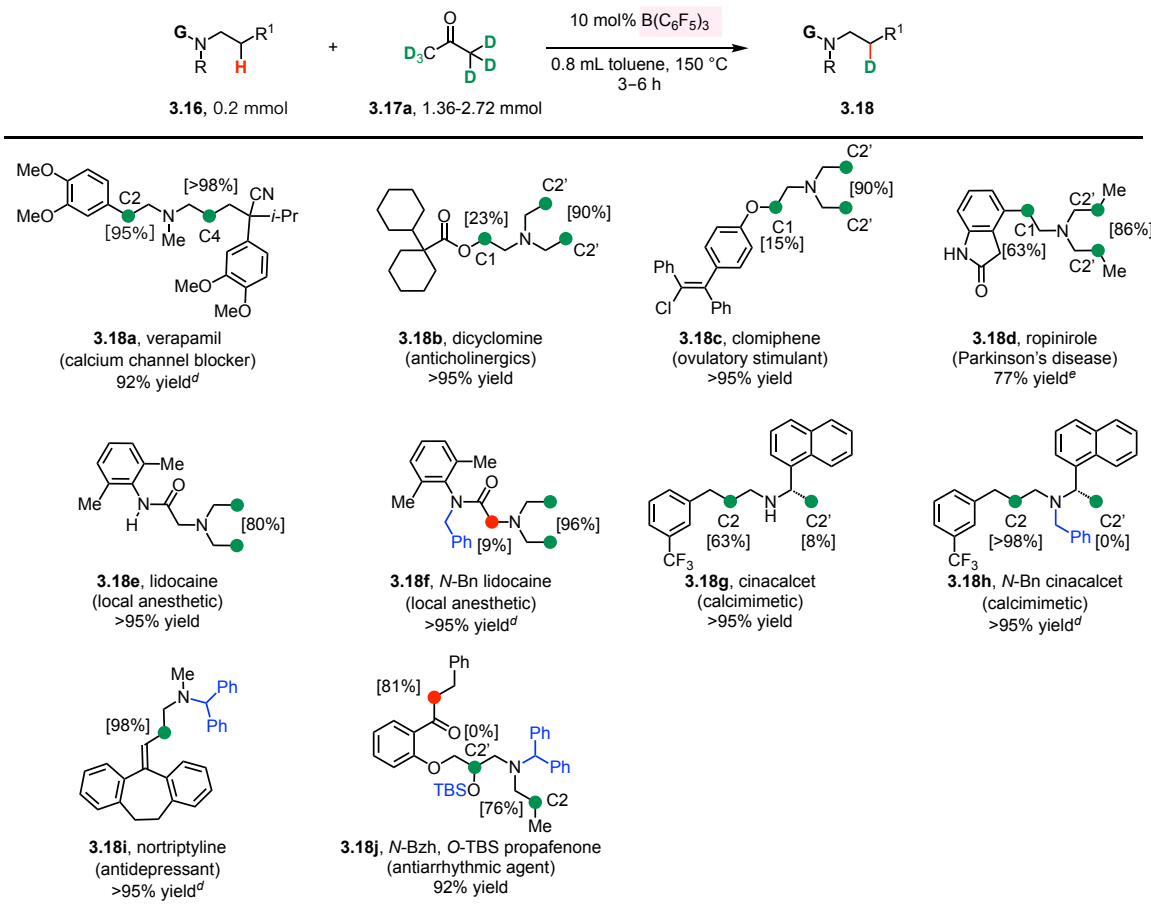
3.4.1 Acyclic amines

Deuteration of various acyclic bioactive amines was shown to be effective. Some Lewis acid sensitive functional groups were found to be intact while selective deuteration took place at *β*-position of amines. Cyano (**3.16a**), ester (**3.16b**), amide (**3.16d-3.16f**) and ketone (**3.16j**) were tolerated under the reaction conditions and gave corresponding products **3.18a-3.18j** in 77 to >95% yield and with high regioselectivity of labeling. Deuteration also occurred at acidic *α*-carbonyl C–H bonds for ropinirole **3.16d** and propafenone derivative **3.16j** based on analysis of ^{1}H NMR of crude reaction mixture. Yet, during purification, the *α*-carbonyl C–D of **3.18d** underwent hydrogen deuterium exchange.

Different electronics and steric hindrance around *β*-amino C–H affected the level of deuterium incorporation. Verapamil, **3.16a**, showed higher level of deuterium incorporation at non-benzylic site C4 (>98%) than benzylic position C2 (95%). This observation could be explained by that the substrate or the product is acting as the Brønsted base, which is very bulky, it has less steric hindrance when approaching C4 where the

adjacent unit is methylene versus from the C2 side with an adjacent aryl ring. The effect is more prominent when temperature is lowered (see Table 3.3, entries 1 and 2). For dicyclomine **3.16b**, 90% at C2' was deuterated, while at C1, adjacent to ester, only 23% was observed. Similar trend of decreased *d*-incorporation was noted for clomiphene **3.16c** with 90% at C2' but 15% at α-aryloxy C1. On ropinirole **3.16d**, benzylic position (C2', 86%) and β-position of *N*-propyl group (C1, 63%) showed different level of *d*-incorporation.

Protecting groups of amines and alcohols could help to achieve higher level of incorporation. Lidocaine, **3.16e**, underwent 80% of deuterium incorporation. If the acidic amide N–H were to be protected by benzyl group, **3.16f** was deuterated more efficiently with 96% *d*-incorporation and deuteration of α-carbonyl was observed (9%) due to increased acidity of α-proton from benzyl group. The secondary amine containing cinacalcet **3.16g**, without protecting group gave **3.18g** with 63% at C2 and 8% at C2', but if protected with benzyl group, deuterium is exclusively installed at C2 with >98%. Lowered deuterium incorporation level at C2' than C2 could be because hydride abstraction from a tertiary C–H is more difficult from secondary C–H at C2. Deuteration of less sterically hindered secondary amines, nortriptyline **3.16i** and propafenone **3.16j**, without protecting groups was inhibited. With *N*-benzhydryl protected **3.16i** and **3.16j**, the corresponding products were obtained. *O*-TBS protection of alcohol on propafenone **3.16j** was effective, giving 76% at less hindered C2 and 0% at more sterically hindered C2' position.



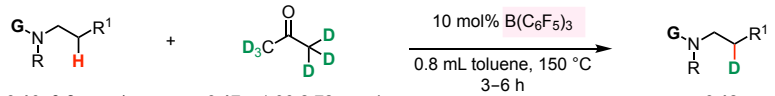
[a]Conditions:*N*-alkylamine (**3.4**, 0.2 mmol), acetone-d_6 (**3.5a**, 1.36 mmol), $B(C_6F_5)_3$ (10 mol%), toluene (0.8 mL), under N_2, 150 °C, 3 h. [b]Yield of isolated and purified product. Deuterium incorporation level was determined by 1H NMR analysis of the isolated and purified product. [c]Green label indicates sites that are beta to N. Red label is used for any other sites that undergo deuteration. Blue color indicates protecting groups. [d]Conditions:*N*-alkylamine (**3.4**, 0.2 mmol), acetone-d_6 (**3.5a**, 1.36 mmol), $B(C_6F_5)_3$ (5.0 mol%), toluene (0.8 mL), under N_2, 150 °C, 3 h. After the filtration of the crude reaction mixture through a pad of silica gel and removal of volatiles, acetone-d_6 (**3.5a**, 1.36 mmol), $B(C_6F_5)_3$ (5.0 mol%), toluene (0.8 mL) were added under N_2, and then heated at 150 °C, 3 h. The reaction was carried out in two batches, using 10 mol% of $B(C_6F_5)_3$ in the first batch and 5.0 mol% in the second.

Table 3.8 Deuteration of acyclic *β*-amino C–H bonds[a,b,c]

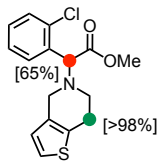
3.4.2 Cyclic amines

A wide variety of cyclic amine drug molecules were then tested (Table 3.9). Heterocycles, such as peperidine (**3.16k-q**), 1,4-diazepane (**3.16r**), piperazine (**3.16s**), thiophene (**3.16k** and **3.16l**), indanone (**3.16m**), benzodioxole (**3.16o** and **3.16p**), benzothiophene (**3.16q**), and benzoimidazole (**3.16r**) were tolerated, affording the corresponding products in 85-95% yield. Both *β*-amino C–H bonds and enolizable *α*-carbonyl C–H bonds from clopidogrel **3.16k**, prasugrel **3.16l**, and donepezil **3.16m** were deuterated. However, during purification, *α*-keto C–D was converted back to C–H on **3.18l**.

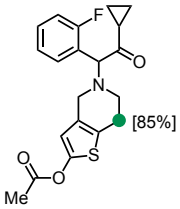
The α-amide C–H on bupivacaine **3.16n** is less acidic, and therefore was untouched. Labelling of β-amino C–H is more efficient on cyclic amines than non-cyclic ones as shown with bupivacaine **3.18n** (90% at C3 and 14% at C2') and raloxifene **3.28q** (97% vs 29%). Steric hindrance of protecting groups affected *d*-incorporation. *N*-benzyl protected paroxetine **3.18o** showed 76% *d*-incorporation at C5, while with more hindered *N*-benzhydryl group **3.18p**, 92% deuterium was incorporated at C5. In addition, C5 was exclusively deuterated while tertiary C3–H remained untouched, because hydride abstraction from tertiary hindered C–H at C3 is more difficult than from less hindered secondary C–H at C5. Only C2 (33%) and C6 (61%) on emedastine **3.16r** were found to be labelled. The guanidine type structure in the molecule could potentially make the adjacent α-amino C–H less electron rich, making hydride abstraction more difficult. *O*-TBS protected dropropizine **3.16s** was deuterated for all eight possible hydrogens, with 94% and 86% *d*-incorporation.



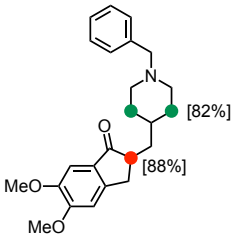
3.16, 0.2 mmol + **3.17a**, 1.36-2.72 mmol → **3.18**



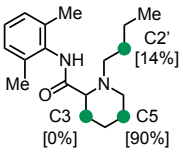
3.18k, clopidogrel
(antiaggregant)
94% yield[d]



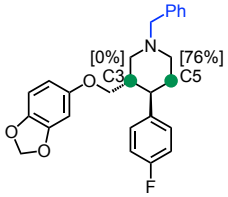
3.18l, prasugrel
(antiaggregant)
85% yield



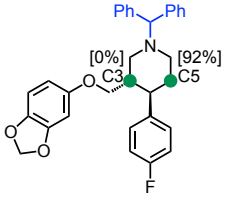
3.18m, donepezil
(anti-Alzheimer)
>95% yield



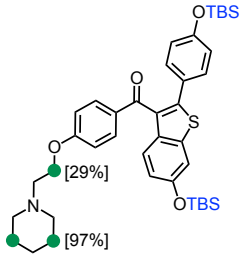
3.18n, bupivacaine
(local anesthetic)
>95% yield



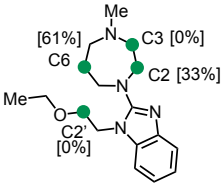
3.18o, *N*-Bn paroxetine
(antidepressant)
>95% yield[e]



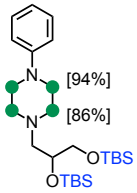
3.18p, *N*-Bzh paroxetine
(antidepressant)
95% yield



3.18q, *O*-TBS raloxifene
(treats osteoporosis)
>95% yield



3.18r, emedastine
(antihistamine)
88% yield



3.18s, *O*-TBS dropropizine
(cough suppressant)
94% yield[d]

[a]Conditions:*N*-alkylamine (**3.4**, 0.2 mmol), acetone-d_6 (**3.5a**, 1.36 mmol), $B(C_6F_5)_3$ (10 mol%), toluene (0.8 mL), under N_2, 150 °C, 3 h. [b]Yield of isolated and purified product. Deuterium incorporation level was determined by 1H NMR analysis of the isolated and purified product. [c]Green label indicates sites that are beta to N. Red label is used for any other sites that undergo deuteration. Blue color indicates protecting groups. [d]Conditions:*N*-alkylamine (**3.4**, 0.2 mmol), acetone-d_6 (**3.5a**, 1.36 mmol), $B(C_6F_5)_3$ (5.0 mol%), toluene (0.8 mL), under N_2, 150 °C, 3 h. After the filtration of the crude reaction mixture through a pad of silica gel and removal of volatiles, acetone-d_6 (**3.5a**, 1.36 mmol), $B(C_6F_5)_3$ (5.0 mol%), toluene (0.8 mL) were added under N_2, and then heated at 150 °C, 3 h. The reaction was carried out in two batches, using 10 mol% of $B(C_6F_5)_3$ in the first batch and 5.0 mol% in the second.

Table 3.9 Deuteration of cyclic *β*-amino C–H bonds[a,b,c]

3.5 Conclusion

In summary, we developed an efficient catalytic method for regioselective deuterium labeling of *β*-amino C–H bonds. The method is applicable to a broad scope of acyclic and cyclic amines, demonstrated through the deuteration of various commercially available amine drug molecules. Lewis acid sensitive functional groups, such as cyano, ester, amide, and ketone, were tolerated under the reaction condition. Protection of amines and alcohols resulted in improved *d*-incorporation level.

3.6 Experimental

3.6.1 General Information

General Experimental Procedures. All reactions were performed in standard, oven-dried glassware fitted with rubber septa under an inert atmosphere of nitrogen unless otherwise described. Stainless steel syringes or cannulas were used to transfer air- and moisture-sensitive liquids. Reported concentrations refer to solution volumes at room temperature. Evaporation and concentration *in vacuo* were performed using house vacuum (ca. 40 mm Hg). Column chromatography was performed with SiliaFlash® 60 (40-63 micron) silica gel from Silicycle. Thin layer chromatography (TLC) was used for reaction monitoring and product detection using pre-coated glass plates covered with 0.25 mm silica gel with fluorescent indicator; visualization by UV light (λ_{ex} = 254 nm) or $KMnO_4$ stain.

Materials. Reagents were purchased in reagent grade from commercial suppliers and used without further purification, unless otherwise described. Amines were prepared according to the procedures reported previously.[1]. Tris(pentafluorophenyl)borane was purchased from TCI and used without further purification. Acetone-d_6 was purchased from Cambridge Isotope Laboratory and used without further purification. H_2O, in synthetic procedures, refers to distilled water.

Instrumentation. Proton nuclear magnetic resonance (^{1}H NMR) spectra and proton-decoupled carbon nuclear magnetic resonance (^{13}C {^{1}H} NMR) spectra were recorded at 25 °C (unless stated otherwise) on Inova 600 (600 MHz) or Varian Unity/Inova 500 (500 MHz) or Oxford AS400 (400 MHz) spectrometers at the Boston College nuclear magnetic resonance facility. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to 0 ppm. Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon

[1] (a) Heinz, C.; Lutz, J. P.; Simmons, E. M.; Miller, M. M.; Ewing, W. R.; Doyle, A. G. *J. Am. Chem. Soc*. **2018**, *140*, 2292−2300. (b) Sun, Y-H.; Sun, T-Y.; Wu, Y-D.; Zhang, X.; Rao, Y. *Chem. Sci.* **2016,** *7*, 2229–2238. (c) Banwell, M. G.; Coster, M. J.; Harvey, M. J.; Moraes, J. *J. Org. Chem.* **2003**, *68*, 613–616. (d) Park, C. M.; Kim, S. Y.; Park, W. K.; Choi, J. H.; Seong, C. M. *Bioorg. Med. Chem. Lett*. **2010**, *20*, 5221–5224. (e) Liu, L-L.; Yeung, K-S.; Yu, J-Q. *Chem. Eur. J*. **2019**, *25*, 2199–2202. (f) Nicolaou, K. C.; Claiborne, C. F.; Nantermet, P. G.; Couladouros, E. A.; Sorensen, E. J. *J. Am. Chem. Soc.***1994**, *116*, 4, 1591–1592.

resonances of the solvent. The peak positions are quoted to one decimal place unless they are indistinguishable. The solvent peak was referenced to 77.0 ppm for ^{13}C for $CDCl_3$. Benzotrifluoride was used as an external standard for ^{19}F NMR and referenced to -63.7 ppm. Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz).

Infrared spectra were recorded on a Bruker FT-IR Alpha (ATR mode) spectrophotometer. Data are represented as follows: frequency of absorption (cm^{-1}).

Optical rotations were measured using a 1 mL cell with a 5 cm path length on a Rudolph Research Analytical Autopol IV Polarimeter. Infrared spectra were recorded on a Bruker FT-IR Alpha (ATR mode) spectrophotometer. Data are represented as follows: frequency of absorption (cm^{-1}). High-resolution mass spectrometry was performed on a JEOL AccuTOF-DART (positive mode) at the Mass Spectrometry Facility, Boston College.

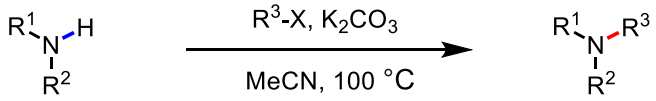
Determination of Deuterium Content. The amount of incorporated deuterium in a sample was quantified by mass spectrometry and by the decrease of ^1H NMR integral intensities at the specified positions compared to the starting material. Integral intensities were calibrated against hydrogen signals that do not undergo H/D-exchange. Mass spectrometry quantification was performed by subtraction of the mean molecular masses of the product and substrate isotopologue clusters in order to eliminate the contribution of the natural isotope abundance to the total mass. The mean molecular masses were calculated as the sum of the relative signal intensities of a given isotopologue multiplied with the corresponding m/z values derived from the mass spectrum.

3.6.2 Experimental Procedures and Characterization Data

General Procedure for the Free-Basing Amine Salts

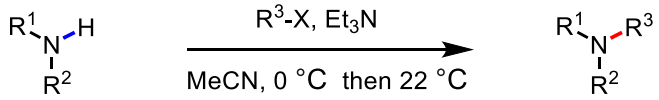
To a 250-mL Erlenmeyer flask was added amine salt and DCM. 2 M NaOH (*aq*.) was added dropwise to the stirred solution until pH paper indicated that the aqueous layer is basic. The aqueous layer was extracted with DCM and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting amine was used without further purification.

General Procedure A for the Alkylation of Amines[1c]

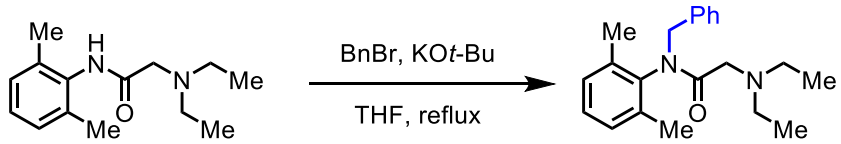


Amines **3.16h**, **3.16i** and **3.16o** were prepared by the alkylation of secondary amines. To a solution of amine (1.0 equiv.) and K_2CO_3 (5.0 equiv.) in MeCN was added alkyl halide (1.5 equiv.). The reaction mixture was then allowed heated to 100 °C for 12 hours. Upon completion (monitored by TLC), H_2O was added and the organic material was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The unpurified product mixture was subjected to silica gel chromatography.

General Procedure B for the Alkylation of Amines[1d]



Amines **3.16j** and **3.16p** were prepared by the alkylation of secondary amines. To a solution of amine (1.0 equiv.) and alkyl halide (1.1 equiv.) in MeCN, Et_3N (3.0 equiv.) was added at 0 °C. The reaction mixture was then warmed up to 22 °C and allowed to stir for 12 hours. Upon completion (monitored by TLC), H_2O was added and the organic material was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The unpurified product mixture was subjected to silica gel chromatography.

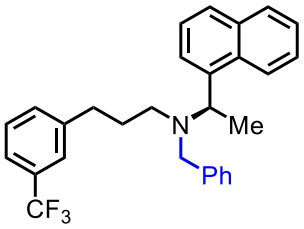


***N*-Bn lidocaine (3.16f)**

N-Bn lidocaine was prepared following a known procedure.[1b] To a solution of lidocaine (3.0 g, 12.8 mmol) in THF (45 mL) was added benzyl bromide (1.8 mL, 15.4 mmol). To the reaction mixture, KO*t*-Bu (2.9 g, 25.6 mmol) was then added portionwise and the reaction mixture was allowed to stir at reflux for 48 hours. The reaction mixture was then

cooled and concentrated *in vacuo* to remove THF. To the mixture was added H_2O and was extracted with EtOAc. The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The unpurified product mixture was then subjected to silica gel column chromatography (MeOH:DCM = 1:99) to afford **3.16f** as a yellow liquid (2.5 g, 60%).

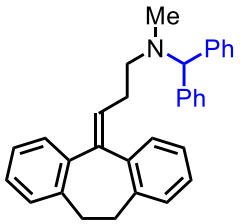
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 – 7.16 (m, 5H), 7.12 (d, *J* = 7.5 Hz, 1H), 7.04 (d, *J* = 7.5 Hz, 2H), 4.73 (s, 2H), 2.80 (s, 2H), 2.57 (q, *J* = 7.1 Hz, 4H), 1.87 (s, 6H), 0.91 (t, *J* = 7.1 Hz, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 170.64, 138.99, 137.10, 136.31, 128.92, 128.18, 127.97, 127.49, 54.60, 51.68, 47.36, 17.83, 11.96; **IR** (neat) 2964, 2926, 1653, 1466, 1453, 1400, 1385, 1258, 1242, 1195, 1078, 773, 743, 699 cm^{-1}.



***N*-Bn cinacalcet (3.16h)**

N-Bn cinacalcet was prepared following a General Procedure A for the Alkylation of Amines using cinacalcet hydrochloride (1.0 g, 2.5 mmol) and benzyl bromide. The unpurified product mixture was then subjected to silica gel column chromatography (EtOAc:hexanes = 1:4) to afford **3.16h** as a colorless liquid (0.9 g, 82%).

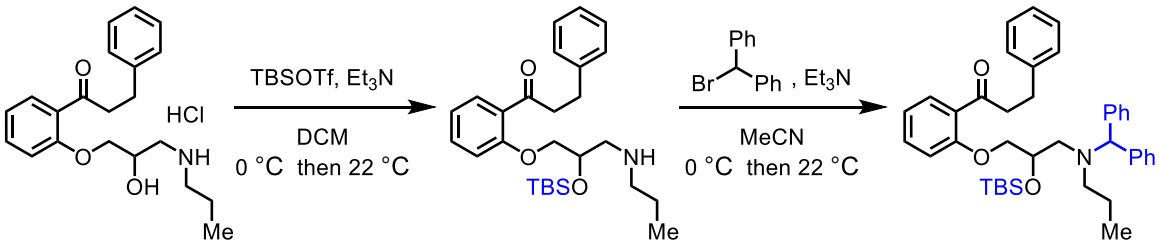
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.56 (d, *J* = 7.1 Hz, 1H), 7.50 – 7.38 (m, 3H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.24 (t, *J* = 7.8 Hz, 6H), 7.12 (s, 1H), 6.96 (d, *J* = 7.4 Hz, 1H), 4.75 – 4.62 (m, 1H), 3.72 (d, *J* = 13.8 Hz, 1H), 3.63 (d, *J* = 13.8 Hz, 1H), 2.60 (s, 2H), 2.33 (d, *J* = 14.0 Hz, 1H), 2.26 (d, *J* = 13.9 Hz, 1H), 1.53 (d, *J* = 6.8 Hz, 5H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.40, 140.62, 140.01, 134.02, 132.14, 131.58, 130.47, 130.22, 128.97, 128.54, 128.43, 128.05, 127.61, 126.74, 125.33, 125.28, 125.00, 124.85, 124.56, 122.30, 56.36, 55.77, 49.79, 33.22, 28.99, 14.33; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -62.40 (d, *J* = 3.0 Hz); **IR** (neat) 2968, 2939, 1492, 1327, 1160, 1120, 1072, 797, 778, 699 cm^{-1}.



_N_-Bzh nortriptyline (3.16i)

N-Bzh nortriptyline **3.16i** was prepared following a General Procedure A for the Alkylation of Amines using nortriptyline hydrochloride (2.0 g, 6.7 mmol) and (bromomethylene)dibenzene. The unpurified product mixture was then subjected to silica gel column chromatography (Et_2O:hexanes = 1:49) to afford **3.16i** as a yellow liquid (2.2 g, 77%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, J = 7.6 Hz, 4H), 7.23 (dd, J = 8.3, 6.9 Hz, 5H), 7.20 – 7.09 (m, 7H), 7.09 – 7.05 (m, 1H), 7.02 (dd, J = 5.3, 3.8 Hz, 1H), 5.82 (t, J = 7.5 Hz, 1H), 4.31 (s, 1H), 3.30 (s, 2H), 2.94 (s, 1H), 2.71 (s, 1H), 2.46 (d, J = 8.7 Hz, 2H), 2.32 (dd, J = 15.7, 8.4 Hz, 2H), 2.07 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.20, 143.17, 141.43, 140.13, 139.35, 137.02, 129.92, 129.80, 129.02, 128.51, 128.32, 127.94, 127.26, 126.90, 126.74, 125.93, 125.67, 75.59, 54.98, 40.21, 33.74, 32.01, 27.21; **IR** (neat) 3061, 3020, 1485, 1451, 1278, 1079, 756, 743, 704 cm^{-1}.



_O_-TBS propafenone

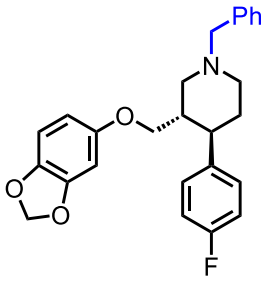
O-TBS propafenone was prepared following the known procedure.[1e] To a solution of propafenone HCl (2.0 g, 5.29 mmol) in DCM at 0 °C, imidazole (5.0 equiv.) was added, followed by the dropwise addition of TBSCl (1.3 equiv.). After the addition, the reaction mixture was allowed to warm to 22 °C and stirred for 12 hours. Upon completion (monitored by TLC), H_2O was added and the organic material was then extracted with DCM. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in*

vacuo. The unpurified product mixture was subjected to silica gel column chromatography (MeOH:DCM = 1:19) to afford *O*-TBS propafenone as a colorless liquid (2.0 g, 83%).

_N_-Bzh, _O_-TBS propafenone (3.16j)

N-Bzh, *O*-TBS **3.16j** propafenone was prepared following the General Procedure B for the Alkylation of Amines using *O*-TBS propafenone (2.0 g, 4.4 mmol) and (bromomethylene)dibenzene. The unpurified product mixture was subjected to silica gel column chromatography (Et_2O:hexanes = 1:19) to afford **3.16j** as a colorless liquid (2.2 g, 81%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 9.5 Hz, 1H), 7.47 – 7.40 (m, 1H), 7.25 (m, 6H), 7.14 (dt, *J* = 15.4, 7.7 Hz, 9H), 7.03 – 6.92 (m, 2H), 4.82 (s, 1H), 4.18 (dd, *J* = 9.5, 3.8 Hz, 1H), 4.10 (dd, *J* = 9.5, 3.3 Hz, 1H), 3.92 (d, *J* = 4.3 Hz, 1H), 3.36 – 3.16 (m, 1H), 3.08 – 2.99 (m, 1H), 2.98 – 2.84 (m, 2H), 2.79 (dd, *J* = 13.5, 9.0 Hz, 1H), 2.55 (dd, *J* = 13.5, 4.7 Hz, 1H), 2.45 (d, *J* = 6.0 Hz, 2H), 1.43 (d, *J* = 7.4 Hz, 2H), 0.79 (s, 9H), 0.71 (t, *J* = 7.3 Hz, 3H), -0.06 (s, 3H), -0.09 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 201.22, 158.19, 142.06, 141.67, 141.51, 133.30, 130.45, 128.78, 128.68, 128.44, 128.26, 128.21, 128.15, 128.12, 126.91, 126.88, 125.68, 120.47, 112.33, 71.18, 70.47, 69.93, 54.23, 54.02, 45.40, 30.03, 25.71, 19.40, 17.92, 11.74, -4.67, -4.83; **IR** (neat) 2953, 2926, 1671, 1595, 1578, 1469, 1248, 1110, 838, 752, 698 cm^{-1}.

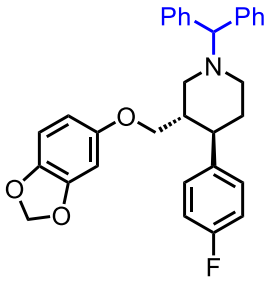


_N_-Bn paroxetine (3.16o)

N-Bn paroxetine **3.16o** was prepared following the General Procedure A for the Alkylation of Amines using paroxetine hydrochloride (3.0 g, 8.2 mmol) and benzyl bromide. The unpurified product was subjected to silica gel column chromatography (EtOAc:hexanes = 1:9) to afford **3.16o** as a white solid (2.9 g, 84%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 4H), 7.25 (s, 1H), 7.16 (dd, *J* = 8.6, 5.5 Hz, 2H), 6.96 (t, *J* = 8.7 Hz, 2H), 6.61 (d, *J* = 8.4 Hz, 1H), 6.31 (d, *J* = 2.5 Hz, 1H), 6.10

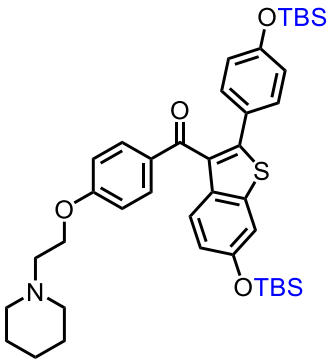
(dd, J = 8.5, 2.5 Hz, 1H), 5.87 (s, 2H), 3.64 (d, J = 13.1 Hz, 1H), 3.59 – 3.50 (m, 2H), 3.44 (d, J = 6.9 Hz, 1H), 3.04 – 2.96 (m, 1H), 2.55 – 2.42 (m, 1H), 2.27 – 2.14 (m, 1H), 2.12 – 2.01 (m, 2H), 1.90 – 1.73 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.44, 160.50, 154.41, 148.10, 141.51, 139.86, 139.84, 138.27, 129.19, 128.85, 128.79, 128.20, 127.00, 115.40, 115.24, 107.80, 105.60, 101.03, 97.99, 69.65, 63.40, 57.61, 53.83, 44.12, 42.19, 34.39; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -116.71 (d, J = 7.5 Hz); **IR** (neat) 2912, 1602, 1506, 1485, 1221, 1181, 1132, 1036, 933, 831, 781, 738 cm^{-1}.



***N*-Bzh paroxetine (3.16p)**

N-Bzh paroxetine **3.16p** was prepared following the General Procedure B for the Alkylation of Amines using paroxetine hydrochloride (3.0 g, 8.2 mmol), (bromomethylene)dibenzene. The unpurified product was subjected to silica gel column chromatography (Et_2O:hexanes = 1:9) to afford **3.16p** as a white solid (3.5 g, 86%).

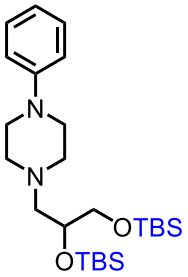
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.35 (m, 4H), 7.28 (t, J = 7.5 Hz, 4H), 7.17 (dt, J = 8.5, 6.4 Hz, 5H), 6.96 (t, J = 8.6 Hz, 2H), 6.57 (d, J = 8.5 Hz, 1H), 6.21 (d, J = 2.5 Hz, 1H), 6.01 (dd, J = 8.5, 2.5 Hz, 1H), 5.85 (d, J = 0.9 Hz, 2H), 4.37 (s, 1H), 3.50 (dd, J = 9.5, 2.9 Hz, 1H), 3.38 (dd, J = 9.5, 6.7 Hz, 1H), 3.23 (dd, J = 11.4, 2.9 Hz, 1H), 3.08 – 2.89 (m, 1H), 2.47 (dd, J = 11.6, 4.2 Hz, 1H), 2.22 (s, 1H), 2.06 – 1.81 (m, 3H), 1.77 (d, J = 3.6 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.46, 160.52, 154.29, 148.07, 142.81, 142.78, 141.51, 140.07, 140.04, 128.90, 128.84, 128.44, 128.43, 128.09, 127.94, 126.89, 115.39, 115.22, 107.78, 105.74, 101.04, 98.13, 76.11, 69.60, 55.96, 52.49, 44.23, 42.49, 34.64; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -116.74 (ddd, J = 14.0, 8.9, 5.3 Hz); **IR** (neat) 2912, 1506, 1485, 1466, 1336, 1268, 1222, 1037, 815, 705 cm^{-1}.



***O*-TBS raloxifene (3.16q)**

O-TBS raloxifene **3.16q** was prepared following the known procedure.[1e] To a solution of raloxifene HCl (2.0 g, 3.9 mmol) in DCM at 0 °C, imidazole (5.0 equiv.) was added, followed by the dropwise addition of TBSCl (2.6 equiv.). After the addition, the reaction mixture was allowed to warm to 22 °C and stirred for 12 hours. Upon completion (monitored by TLC), H_2O was added and the organic material was then extracted with DCM. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The unpurified product mixture was then subjected to silica gel column chromatography (MeOH:DCM = 1:49) to afford **3.16q** as a colorless liquid (2.0 g, 73%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.8 Hz, 2H), 7.56 (s, 1H), 7.32 – 7.22 (m, 3H), 6.89 (s, 1H), 6.73 (d, *J* = 8.9 Hz, 2H), 6.66 (d, *J* = 8.6 Hz, 2H), 4.05 (t, *J* = 6.0 Hz, 2H), 2.72 (t, *J* = 6.0 Hz, 2H), 2.47 (s, 4H), 1.58 (p, *J* = 5.6 Hz, 4H), 1.46 – 1.39 (m, 2H), 1.01 (s, 9H), 0.93 (s, 9H), 0.23 (s, 6H), 0.12 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 193.12, 162.88, 156.08, 153.49, 143.31, 139.86, 134.51, 132.29, 130.60, 130.45, 130.33, 126.79, 123.98, 120.25, 119.24, 114.01, 112.07, 66.14, 57.70, 55.06, 25.92, 25.71, 25.63, 24.13, 18.24, 18.19, -4.36, -4.48; **IR** (neat) 2927, 2891, 1596, 1464, 1255, 1164, 943, 909, 837, 780 cm^{-1}.

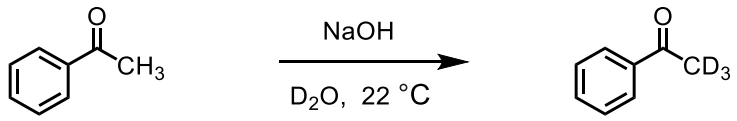


_O_-TBS dropropizine (3.16s)

O-TBS dropropizine **3.16s** was prepared following the known procedure.[1e] To a solution of dropropizine (1.2 g, 5.0 mmol) in DCM at 0 °C, Et_3N (2.6 equiv.) was added, followed by the dropwise addition of TBSOTf (2.6 equiv.). After the addition, the reaction mixture was allowed to warm to 22 °C and stirred for 12 hours. Upon completion (monitored by TLC), H_2O was added and the organic material was then extracted with DCM. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The unpurified product mixture was then subjected to silica gel column chromatography (MeOH:DCM = 1:99) to afford **3.16s** as a colorless liquid (1.6 g, 69%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 8.8, 7.2 Hz, 2H), 6.95 – 6.88 (m, 2H), 6.83 (d, *J* = 7.3 Hz, 1H), 3.80 (d, *J* = 5.1 Hz, 1H), 3.61 (dd, *J* = 10.0, 5.7 Hz, 1H), 3.53 (dd, *J* = 10.0, 5.6 Hz, 1H), 3.17 (t, *J* = 5.0 Hz, 4H), 2.72 – 2.64 (m, 2H), 2.64 – 2.57 (m, 2H), 2.50 (dd, *J* = 13.0, 4.8 Hz, 1H), 2.38 (dd, *J* = 13.0, 6.1 Hz, 1H), 0.90 (d, *J* = 5.1 Hz, 18H), 0.09 (d, *J* = 7.5 Hz, 6H), 0.06 (d, *J* = 1.8 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 151.46, 129.03, 119.44, 115.86, 71.76, 66.18, 61.99, 54.25, 49.15, 25.99, 25.92, 18.37, 18.19, -4.44, -4.49, -5.26, -5.34; **IR** (neat) 2925, 2853, 1598, 1500, 1460, 1229, 1107, 1082, 989, 829, 772 cm^{-1}.

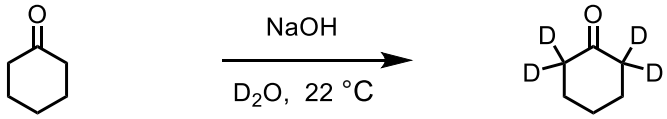
Preparation of α-Deuterated Ketone Substrates



acetophenone **acetophenone-d_3**

Acetophenone-d_3

Acetophenone-d_3 **3.17b** was synthesized following the known procedure [2]. Acetophenone (5.8 g, 48 mmol), NaOH (0.16 g, 4.0 mmol) and D_2O (32 mL) was allowed to stir at 22 °C for 24 hours under nitrogen. The reaction mixture was diluted with diethyl ether. The aqueous layer was extracted with diethyl ether. The combined organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The unpurified product mixture was subjected to silica gel column chromatography using hexanes as elute to afford the acetophenone-d_3 as colorless liquid (4.9 g, 97%D, 84% yield). The spectroscopic data matched those reported by Zhou.[2]



cyclohexanone **cyclohexa-1-one-2,2,6,6,-d_4**

Cyclohexan-1-one-2,2,6,6-d_4

Cyclohexan-1-one-2,2,6,6-d_4 **3.17c** was synthesized following the known procedure[98]. Cyclohexanone (5.2 mL, 50 mmol), NaOH (0.16 g, 1.0 mmol) and D_2O (32 mL) was allowed to stir at 22 °C for 24 hours under nitrogen. The reaction mixture was diluted with diethyl ether. The aqueous layer was extracted with diethyl ether. The combined organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The unpurified product mixture was distilled (40 mmHg, 40 °C) to afford the cyclohexan-1-one-2,2,6,6-d_4 as colorless liquid (4.0 g, 95%D, 78% yield). The spectroscopic data matched those reported by Chang[3].

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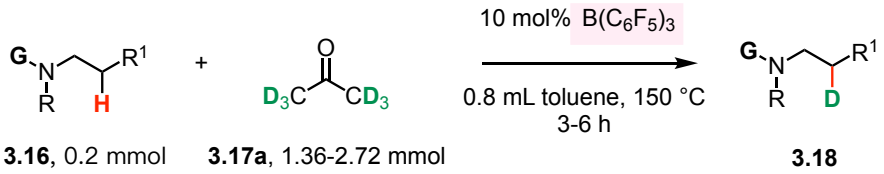
[2] Lei, C.; Yip, Y. J.; Zhou, J. S. *J. Am. Chem. Soc*. **2017**, *139*, 6086–6089.

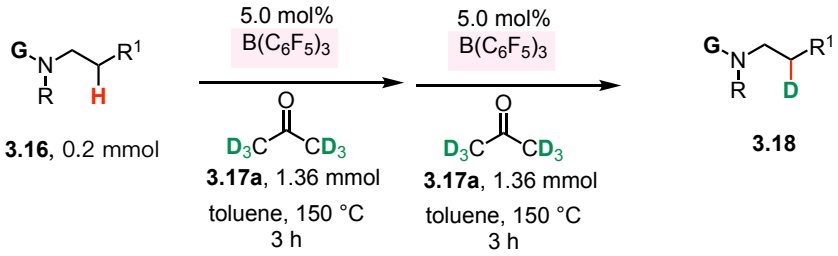
[3] Chang, D.; Li, T.; Li, L.; Jakowski, J.; Huang, J.; Keum, J. K.; Lee, B.; Bonnesen, P. V.; Zhou, M.; Garashchuk, S.; Sumpter, B. G.; Hong, K. *Macromolecules* **2018,** *51*, 9393–9404.

General Procedure A for the β-Deuteration of *N*-Alkylamines



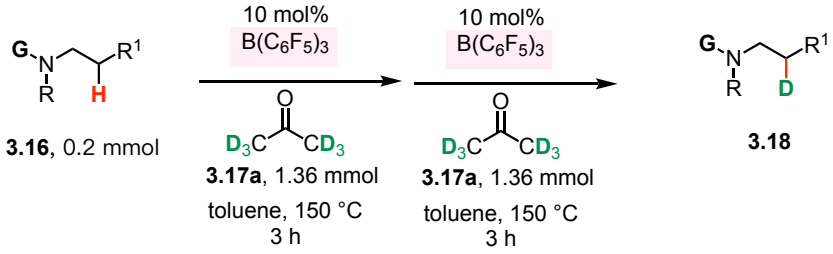
To a 15 mL oven-dried pressure vessel was added amine **3.16** (0.2 mmol), $B(C_6F_5)_3$ (10 mol%), toluene (0.8 mL), and acetone-d_6 **3.17a** (1.36 mmol, 6.8 equiv.) under a nitrogen atmosphere. The reaction mixture was allowed to stir for 3 hours at 150 °C. Upon completion, the reaction mixture was concentrated *in vacuo* and purified by silica gel column chromatography.

General Procedure B for the β-Deuteration of *N*-Alkylamines



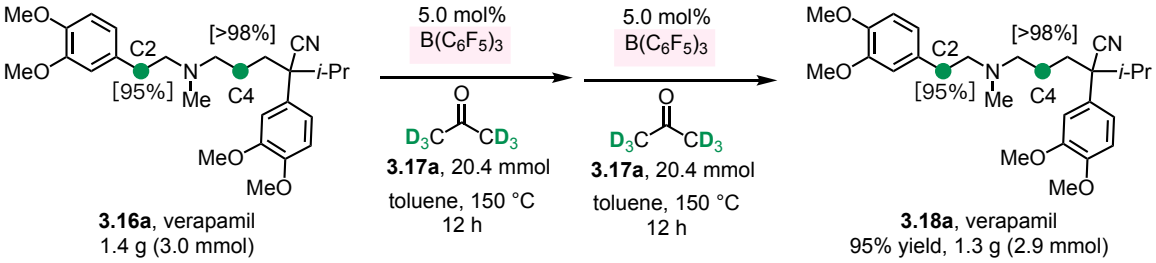
To a 15 mL oven-dried pressure vessel was added amine **3.16** (0.2 mmol), $B(C_6F_5)_3$ (5.0 mol%), toluene (0.8 mL), and acetone-d_6 **3.17a** (1.36 mmol, 6.8 equiv.) under a nitrogen atmosphere. The reaction mixture was allowed to stir for 3 hours at 150 °C. After the purification by silica gel column chromatography and removal of volatiles, $B(C_6F_5)_3$ (5.0 mol%), toluene (0.8 mL), and acetone-d_6 **3.17a** (1.36 mmol, 6.8 equiv.) were added under a nitrogen atmosphere and was allowed to stir for 3 hours at 150 °C. Upon completion, the reaction mixture was concentrated *in vacuo* and purified by silica gel column chromatography.

General Procedure C for the β-Deuteration of *N*-Alkylamines



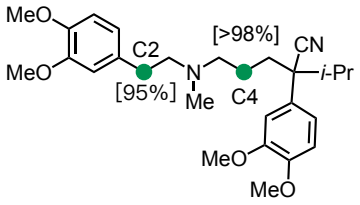
To a 15 mL oven-dried pressure vessel was added amine **3.16** (0.2 mmol), $B(C_6F_5)_3$ (10 mol%), toluene (0.8 mL), and acetone-d_6 **3.17a** (1.36 mmol, 6.8 equiv.) under a nitrogen atmosphere. The reaction mixture was allowed to stir for 3 hours at 150 °C. After the purification by silica gel column chromatography and removal of volatiles, $B(C_6F_5)_3$ (5.0 mol%), toluene (0.8 mL), and acetone-d_6 **3.17a** (1.36 mmol, 6.8 equiv.) were added under a nitrogen atmosphere and was allowed to stir for 3 hours at 150 °C. Upon completion, the reaction mixture was concentrated *in vacuo* and purified by silica gel column chromatography.

Procedure for Scale-Up Reaction



To a 100 mL oven-dried Schlenk flask was added amine **3.16a** (3.0 mmol), $B(C_6F_5)_3$ (5.0 mol%), toluene (12 mL), and acetone-d_6 **3.17a** (20.4 mmol, 6.8 equiv.) under a nitrogen atmosphere. The reaction mixture was allowed to stir for 12 hours at 150 °C. After the purification by silica gel column chromatography and removal of volatiles, $B(C_6F_5)_3$ (5.0 mol%), toluene (12 mL), and acetone-d_6 **3.17a** (20.4 mmol, 6.8 equiv.) were added under a nitrogen atmosphere and was allowed to stir for 12 hours at 150 °C. Upon completion, the reaction mixture was concentrated *in vacuo* and purified by silica gel column chromatography (MeOH:DCM = 1:49) to afford **3.18a** as a yellow liquid (1.29 g, 95%).

3.6.3 Analytical Data and NMR Spectral Data



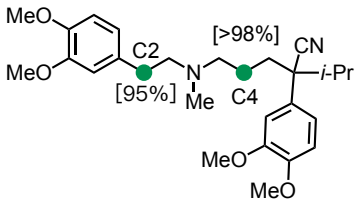
3.18a

Verapamil, 3.18a

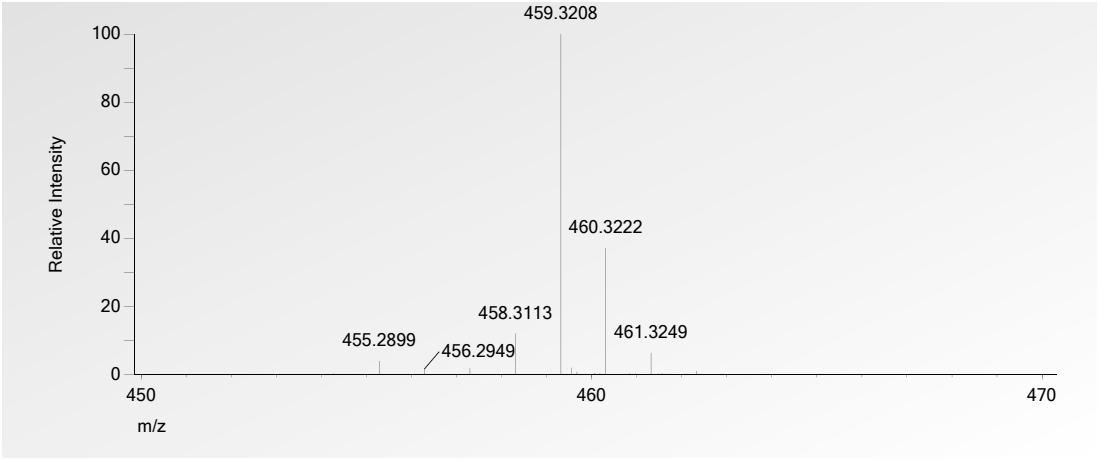
Verapamil **3.16a** was reacted with acetone-d_6 **3.17a** following the General Procedure B. After purification by column chromatography (MeOH:DCM = 1:49), **3.18a** was obtained as a yellow liquid (84 mg, 92%).

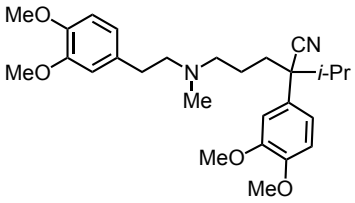
Deuterium incorporation: 3.86 D/molecule (^{1}H NMR), 4.11 D/molecule [HRMS (DART)]

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.91 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.88 – 6.81 (m, 2H), 6.79 (d, *J* = 7.9 Hz, 1H), 6.69 (d, *J* = 7.8 Hz, 2H), 3.94 – 3.76 (m, 12H), 2.73 – 2.60 (m, 0.11H, 95%D), 2.56 – 2.46 (m, 2H), 2.44 – 2.29 (m, 2H), 2.20 (s, 3H), 2.15 – 1.99 (m, 2H), 1.84 (d, *J* = 13.7 Hz, 1H), 1.58 – 1.49 (m, 0.02H, 99%D), 0.79 (d, *J* = 6.7 Hz, 3.05H, 98%D); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 148.90, 148.73, 148.18, 147.24, 132.52, 130.47, 121.30, 120.36, 118.55, 111.91, 111.18, 111.01, 109.50, 59.04, 56.53, 55.86, 55.78, 55.73, 55.71, 53.18, 41.72, 37.77, 35.22, 32.14, 22.33, 18.81, 18.46; **IR** (neat) 2933, 1512, 1460, 1411, 1258, 1237, 1162, 1141, 1024, 804, 764 cm^{-1}.

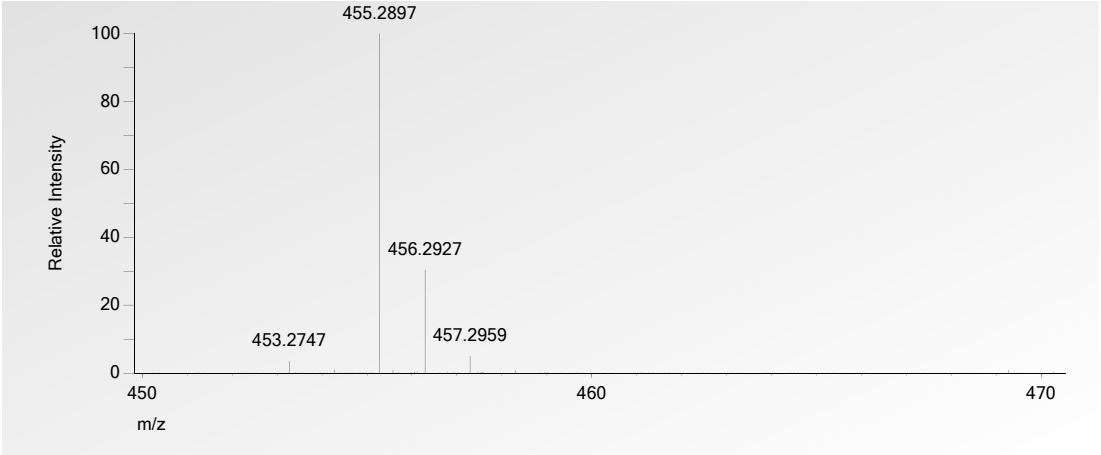

MeO
MeO
C2
[95%]
N
Me
[>98%]
C4
CN
i-Pr
MeO
MeO

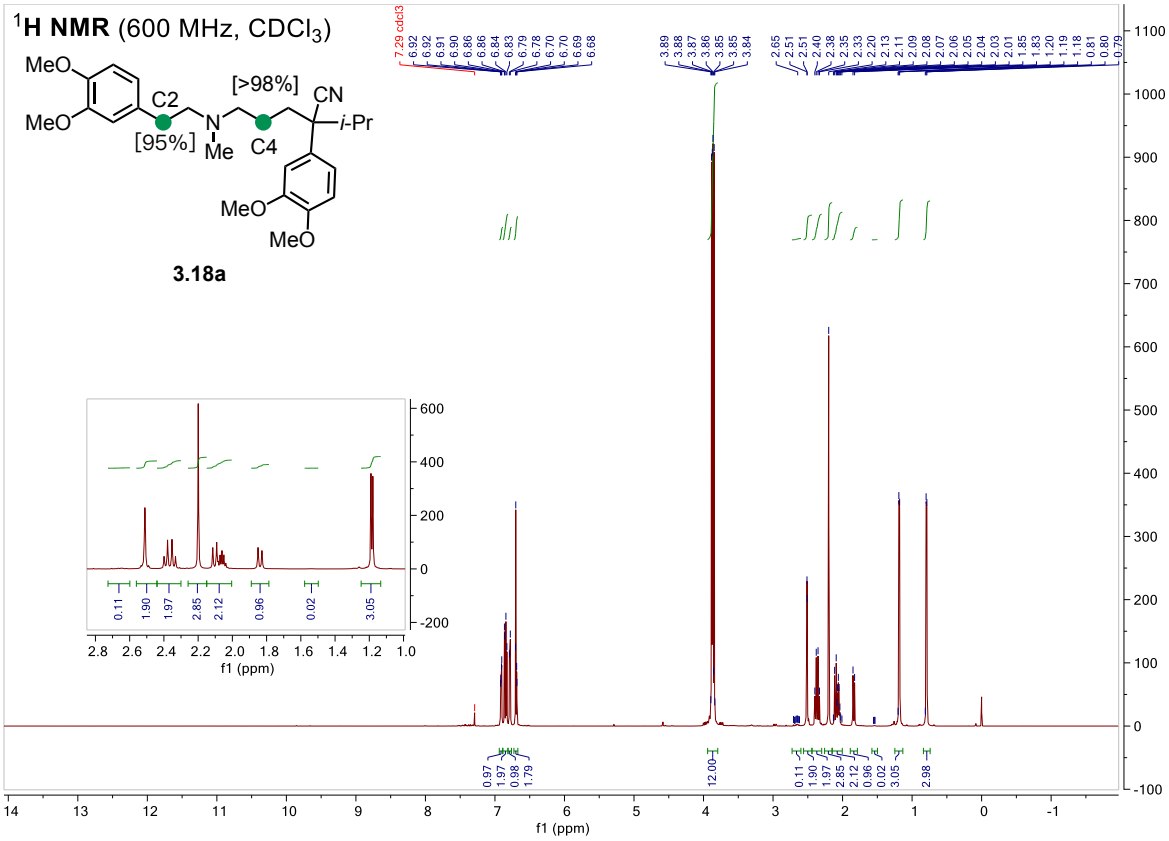
3.18a

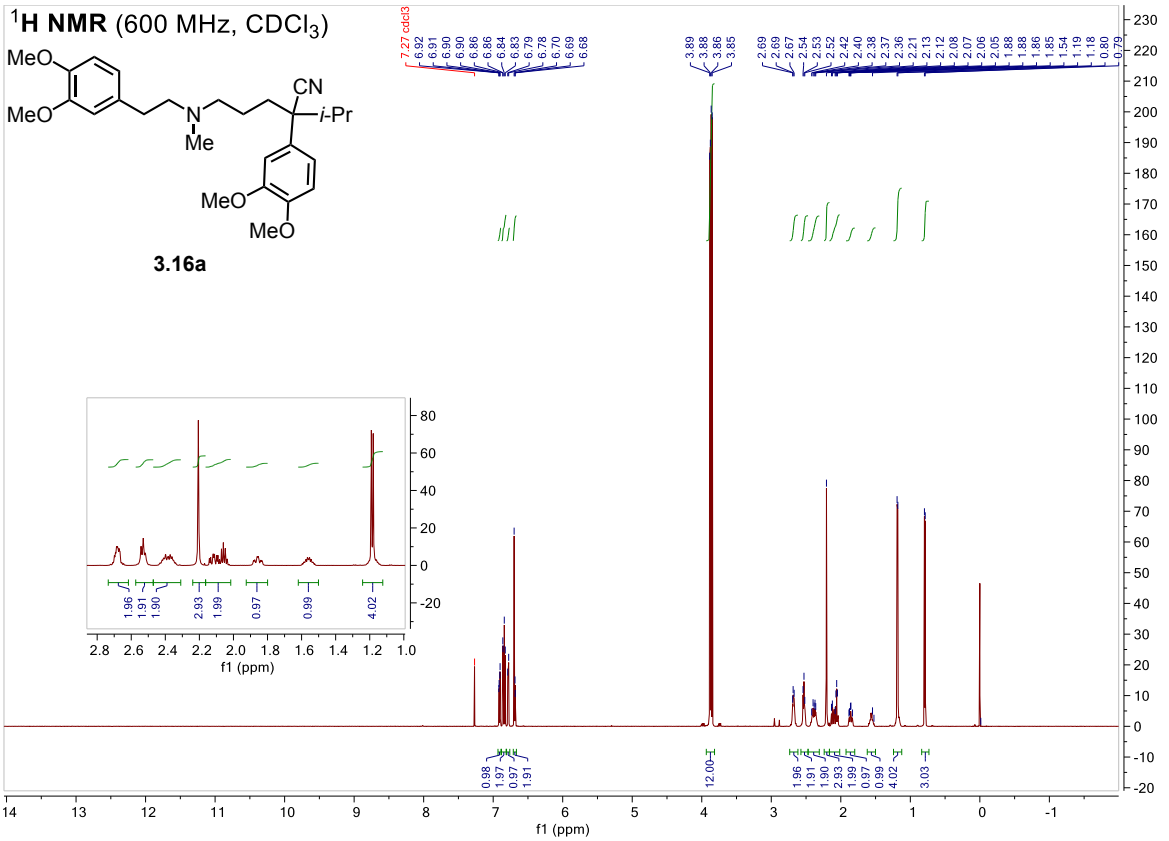

459.3208
100
80
60
40
20
0
Relative Intensity
460.3222
458.3113
461.3249
455.2899
456.2949
450
460
470
m/z

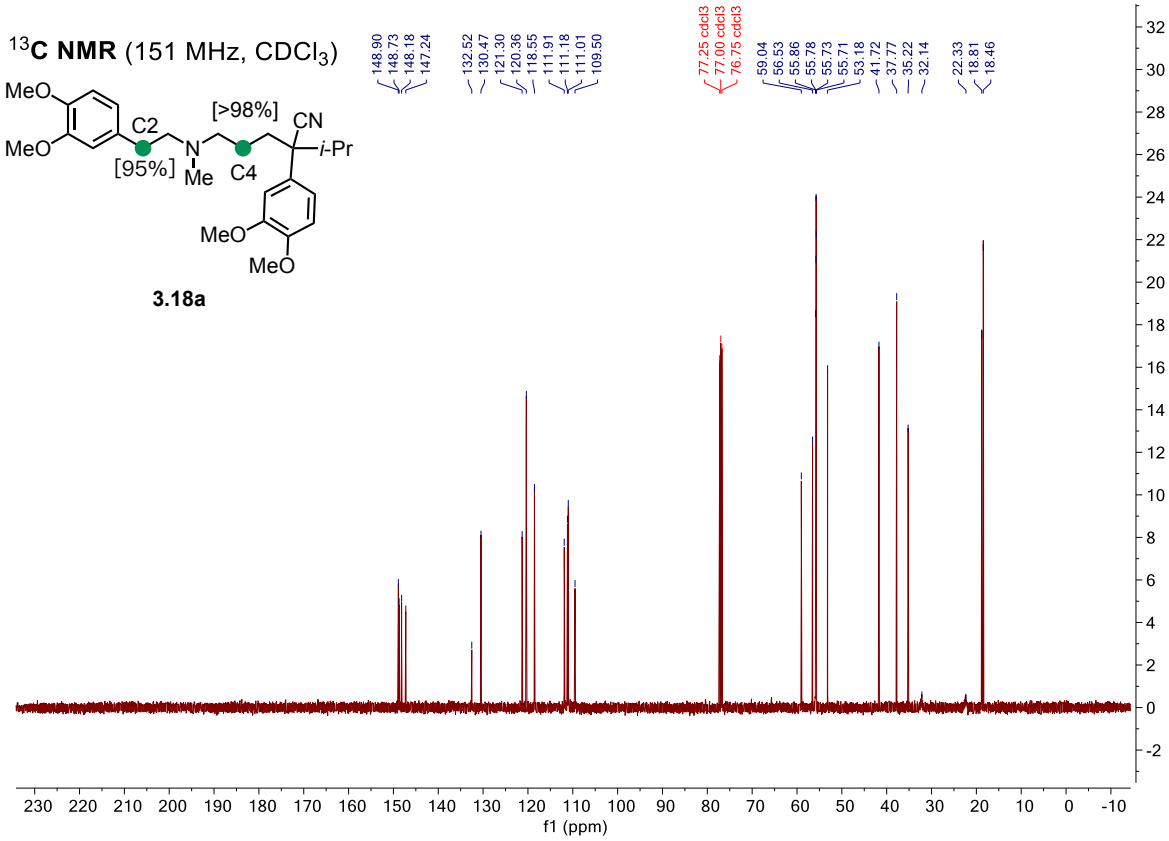

MeO
MeO
N
Me
CN
i-Pr
MeO
MeO

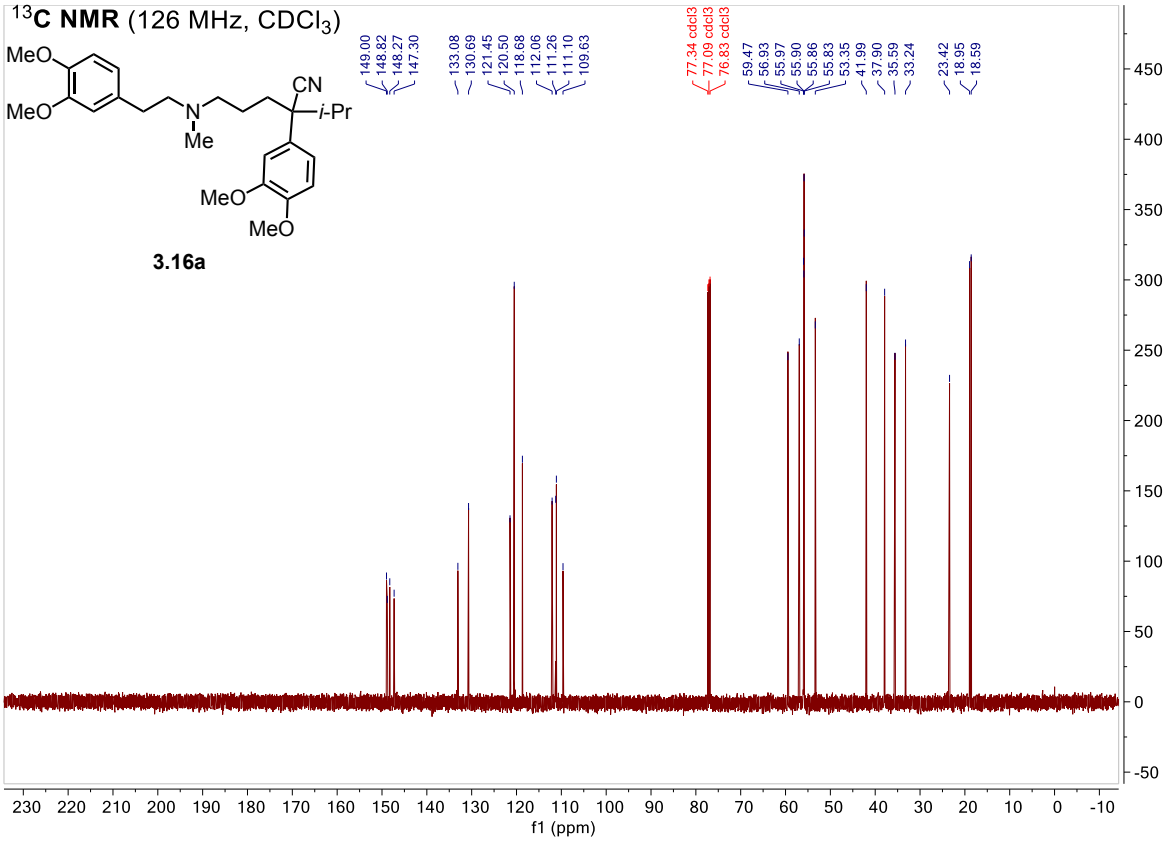
3.16a

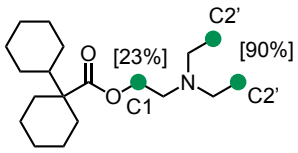

455.2897
100
80
60
40
20
0
Relative Intensity
456.2927
453.2747
457.2959
450
460
470
m/z


1H NMR (600 MHz, CDCl3)
MeO
MeO
C2
[95%]
N
Me
[>98%]
C4
CN
i-Pr
MeO
MeO
3.18a
f1 (ppm)


1H NMR (600 MHz, CDCl3)
MeO
MeO
N
Me
CN
i-Pr
MeO
MeO
3.16a
f1 (ppm)


13C NMR (151 MHz, CDCl3)
MeO
MeO
C2
[95%]
N
Me
[>98%]
C4
CN
i-Pr
MeO
MeO
3.18a
148.90
148.73
148.18
147.24
132.52
130.47
121.30
120.36
118.55
111.91
111.18
111.01
109.50
77.25 cdcl3
77.00 cdcl3
76.75 cdcl3
59.04
56.53
55.86
55.78
55.73
55.71
53.18
41.72
37.77
35.22
32.14
22.33
18.81
18.46
f1 (ppm)


13C NMR (126 MHz, CDCl3)
MeO
MeO
N
Me
CN
i-Pr
MeO
MeO
3.16a
149.00
148.82
148.27
147.30
133.08
130.69
121.45
120.50
118.68
112.06
111.26
111.10
109.63
77.34 cdcl3
77.09 cdcl3
76.83 cdcl3
59.47
56.93
55.97
55.97
55.90
55.86
55.83
53.35
41.99
37.90
35.59
33.24
23.42
18.95
18.59
f1 (ppm)



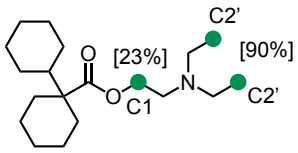
3.18b

Dicyclomine, 3.18b

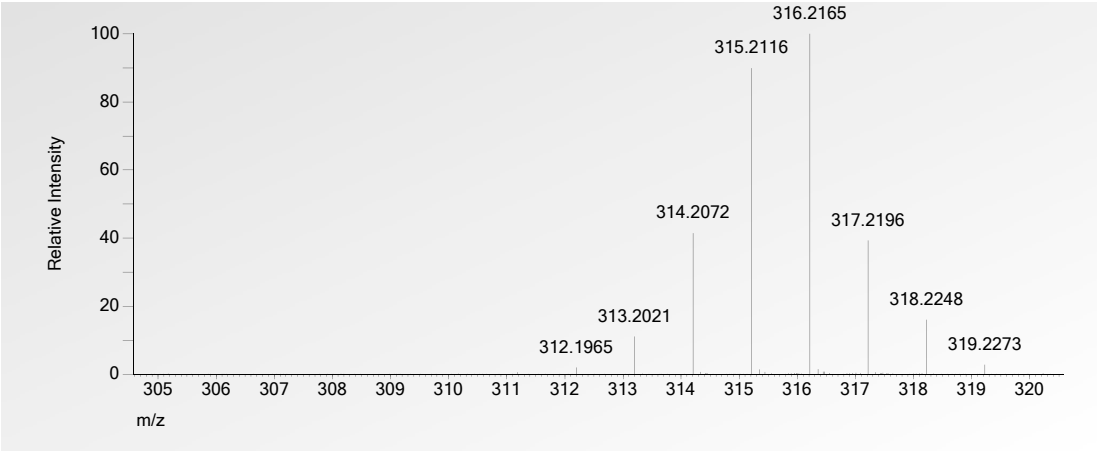
Dicyclomine **3.16b** was reacted with acetone-d_6 **3.17a** following the General Procedure A. After purification by column chromatography (MeOH:DCM = 1:49), **3.18b** was obtained as a colorless liquid (60 mg, 97%).

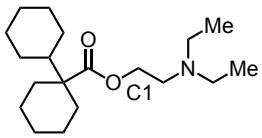
Deuterium incorporation: 5.86 D/molecule (^{1}H NMR), 5.50 D/molecule [HRMS (DART)]

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.17 (t, J = 6.3 Hz, 1.55H, 23%D), 2.73 (t, J = 6.5 Hz, 2H), 2.58 (d, J = 7.0 Hz, 4H), 2.06 (d, J = 12.4 Hz, 2H), 1.75 (m, 2H), 1.69 (d, J = 12.9 Hz, 2H), 1.66 – 1.54 (m, 4H), 1.37 – 1.24 (m, 3H), 1.23 – 1.06 (m, 6H), 1.06 – 1.02(m, 0.59H, 90%D), 1.02 – 0.93 (m, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 176.15, 77.21, 77.00, 76.79, 62.02, 51.08, 50.73, 47.30, 46.79, 31.45, 31.40, 27.78, 27.74, 27.03, 26.55, 26.04, 26.00, 23.75, 11.21; **IR** (neat) 2923, 2850, 1720, 1449, 1207, 1194, 1171, 1156, 1125, 1101, 1049 cm^{-1}.

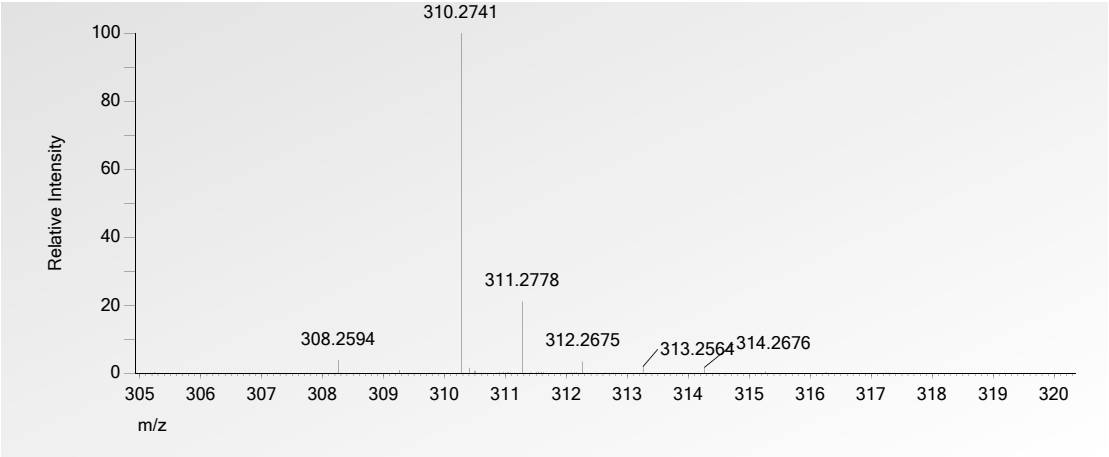

C2'
O
[23%]
[90%]
O
C1
N
C2'

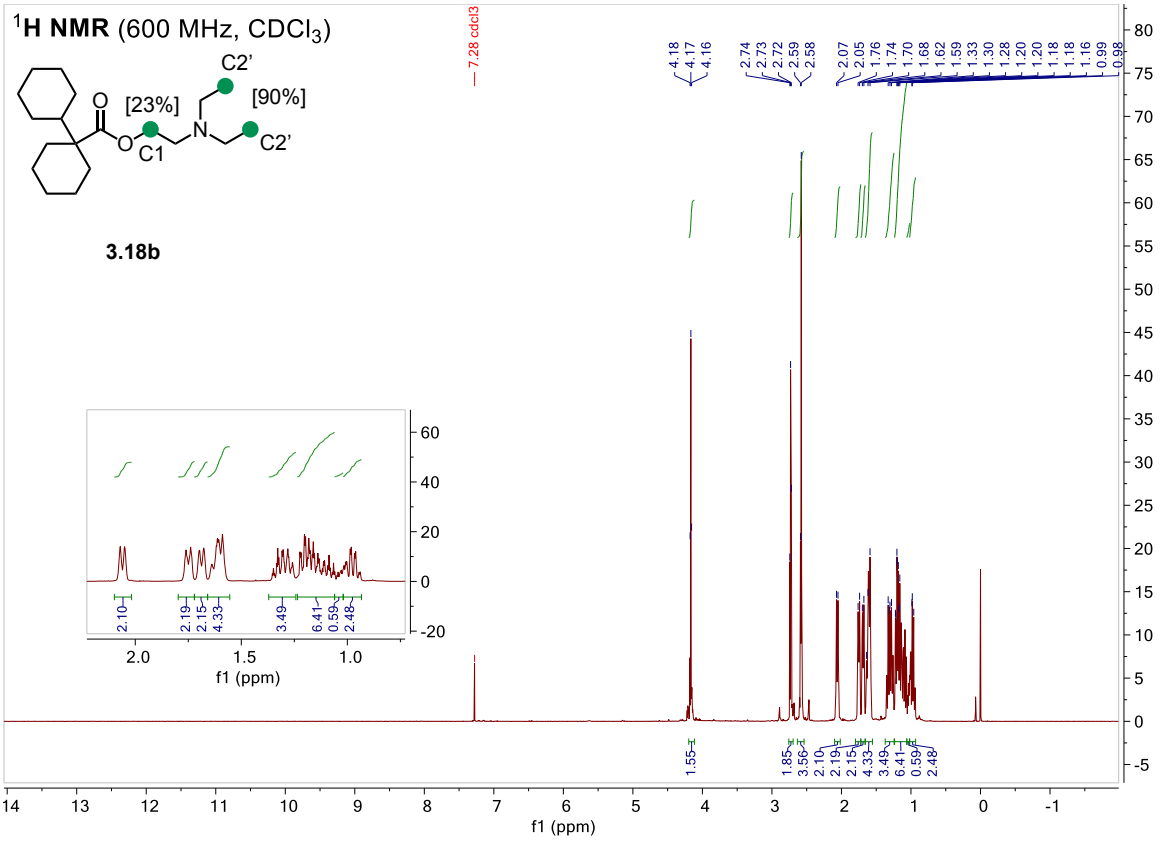
3.18b

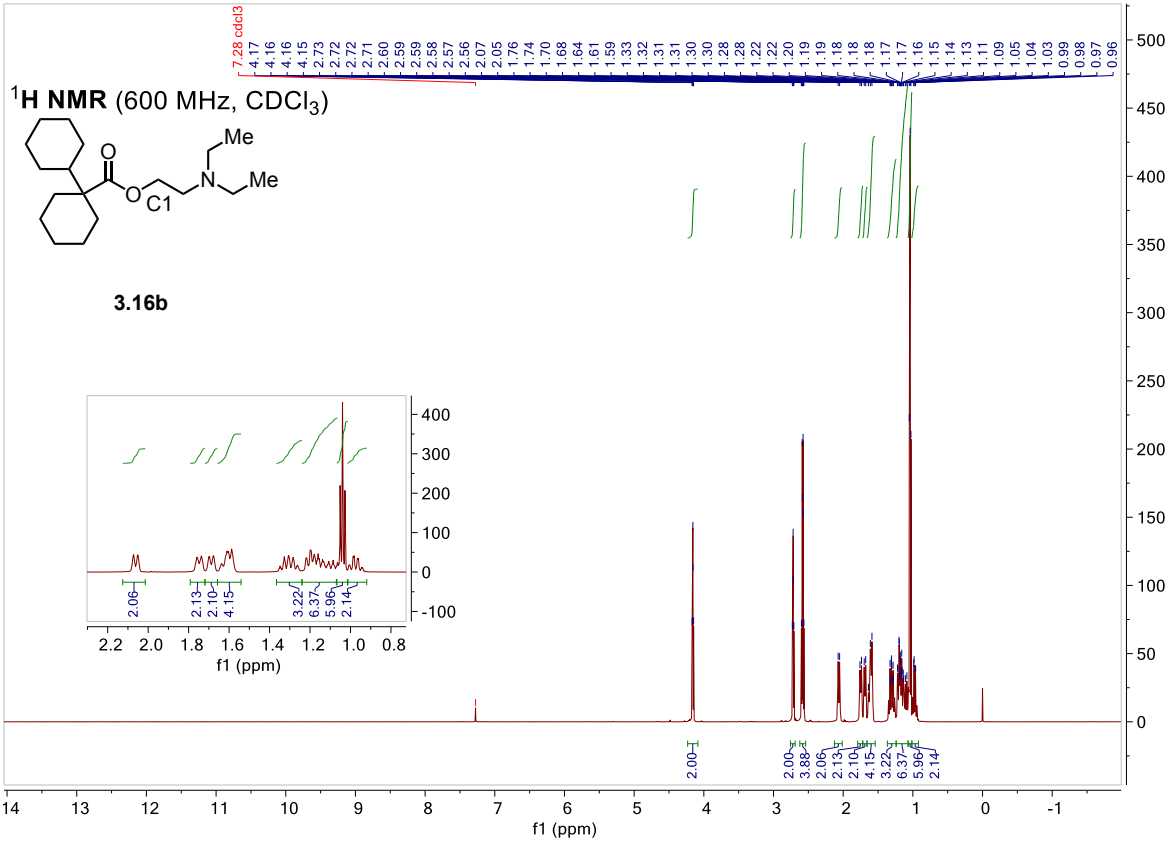

316.2165
315.2116
314.2072
317.2196
318.2248
313.2021
312.1965
319.2273
Relative Intensity
m/z

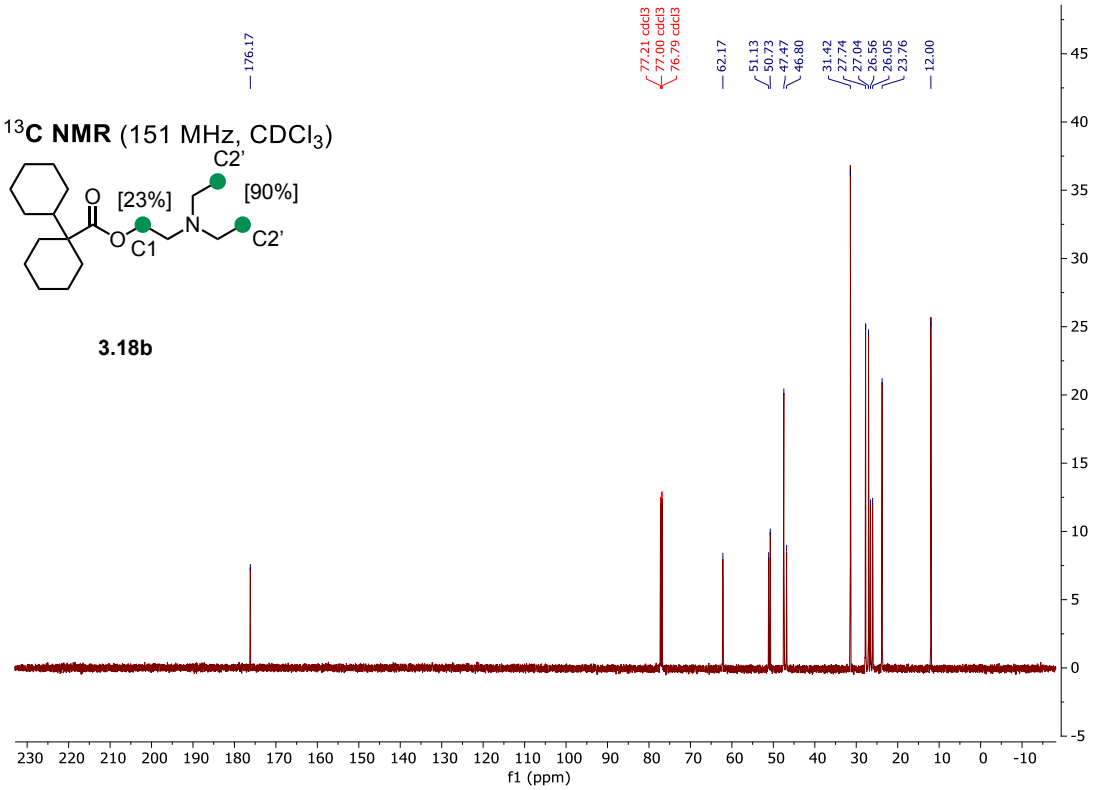

Me
O
N
Me
O
C1

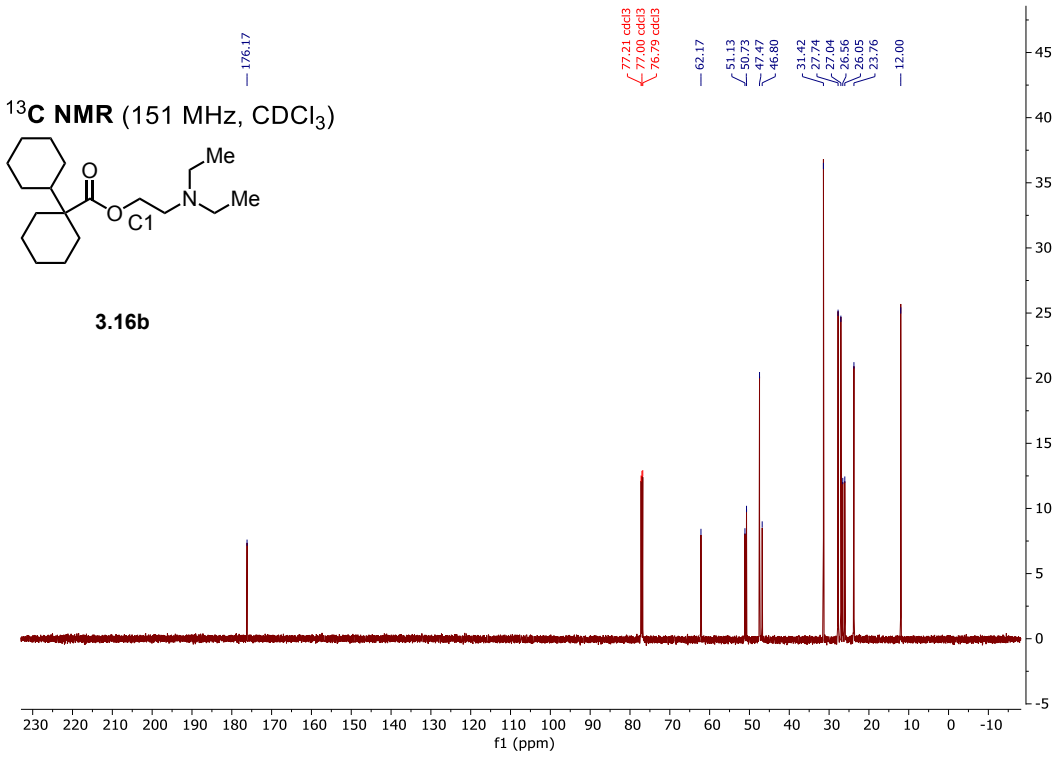
3.16b

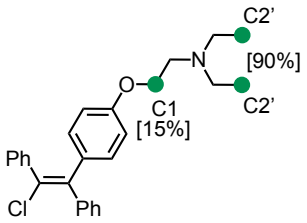

310.2741
311.2778
308.2594
312.2675
313.2564
314.2676
Relative Intensity
m/z


^{1}H NMR (600 MHz, CDCl$_3$)
C2'
[23%]
[90%]
O
O
C1
N
C2'
3.18b
7.28 cdcl3
f1 (ppm)


^{1}H NMR (600 MHz, CDCl$_3$)
Me
O
O
C1
N
Me
3.16b
7.28 cdcl3
f1 (ppm)


13C NMR (151 MHz, CDCl3)
C2'
O
[23%]
[90%]
N
O
C1
C2'
3.18b
176.17
77.21 cdcl3
77.00 cdcl3
76.79 cdcl3
62.17
51.13
50.73
47.47
46.80
31.42
27.74
27.04
26.56
26.05
23.76
12.00
f1 (ppm)


13C NMR (151 MHz, CDCl3)
Me
O
N
Me
O
C1
3.16b
176.17
77.21 cdcl3
77.00 cdcl3
76.79 cdcl3
62.17
51.13
50.73
47.47
46.80
31.42
27.74
27.04
26.56
26.05
23.76
12.00
f1 (ppm)



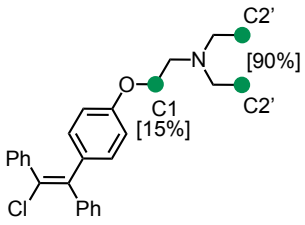
3.18c

Clomiphene, 3.18c

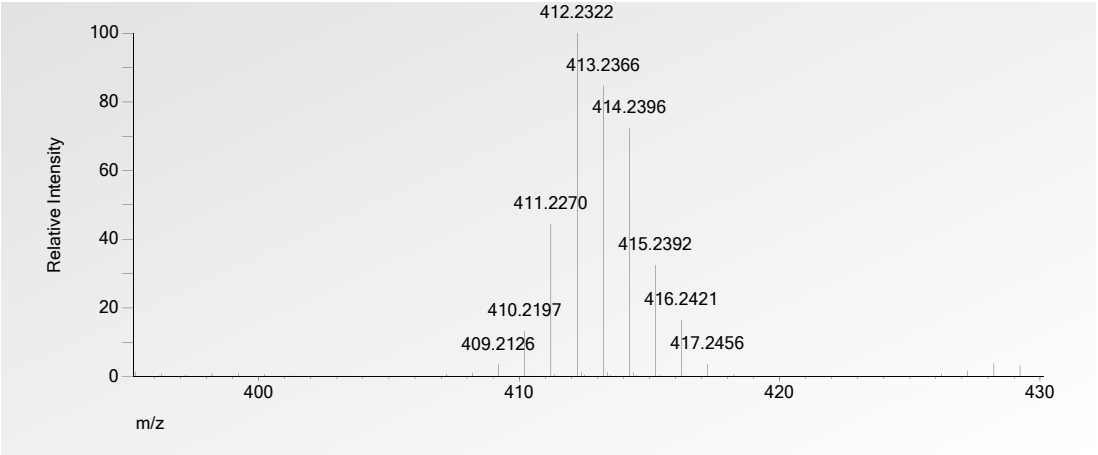
Clomiphene **3.16c** was reacted with acetone-d_6 **3.17a** following the General Procedure A. After purification by column chromatography (MeOH:DCM = 1:19), **3.18c** was obtained as a colorless liquid (78 mg, 96%).

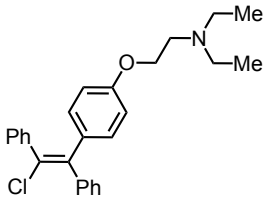
Deuterium incorporation: 5.70 D/molecule (^{1}H NMR), 6.89 D/molecule [HRMS (DART)]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 – 7.26 (m, 6H), 7.22 – 7.13 (m, 3H), 7.11 – 6.93 (m, 1H), 6.87 (dd, J = 26.9, 8.7 Hz, 2H), 6.61 (d, J = 8.8 Hz, 2H), 4.16 – 3.93 (m, 1.71H, 15%D), 3.00 – 2.81 (m, 2H), 2.67 (d, J = 34.3 Hz, 4H), 1.13 – 0.98 (m, 0.61H, 90%D); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.98, 157.63, 142.12, 141.33, 139.87, 139.83, 139.58, 134.33, 133.48, 132.47, 131.79, 131.21, 130.65, 129.97, 129.89, 129.78, 129.67, 129.26, 128.98, 128.05, 127.95, 127.83, 127.42, 126.94, 113.93, 113.85, 66.88, 65.96, 60.29, 51.60, 51.51, 51.43, 51.34, 47.62, 47.56, 10.75; **IR** (neat) 2940, 2806, 1603, 1505, 1244, 1174, 1153, 1029, 758, 745, 695 cm^{-1}.

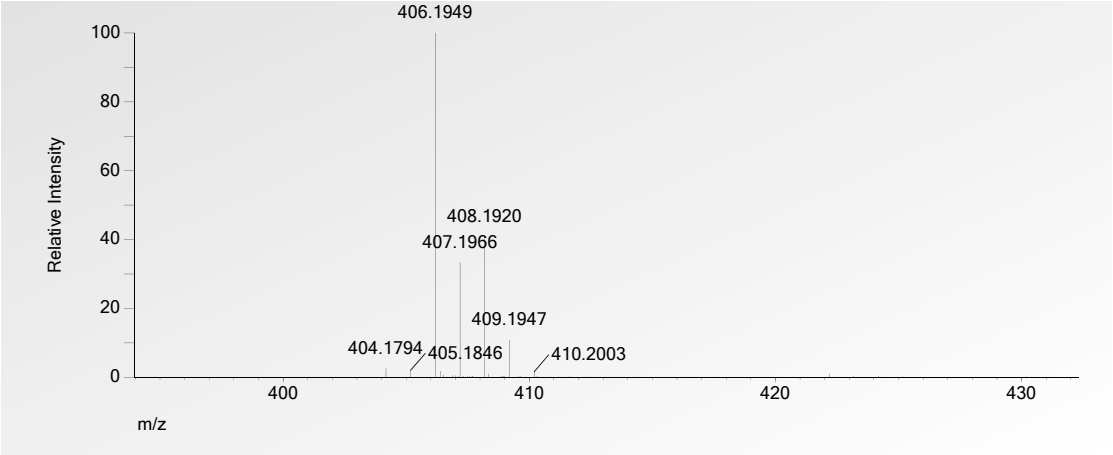

C2'
N
[90%]
O
C1
[15%]
C2'
Ph
Cl
Ph

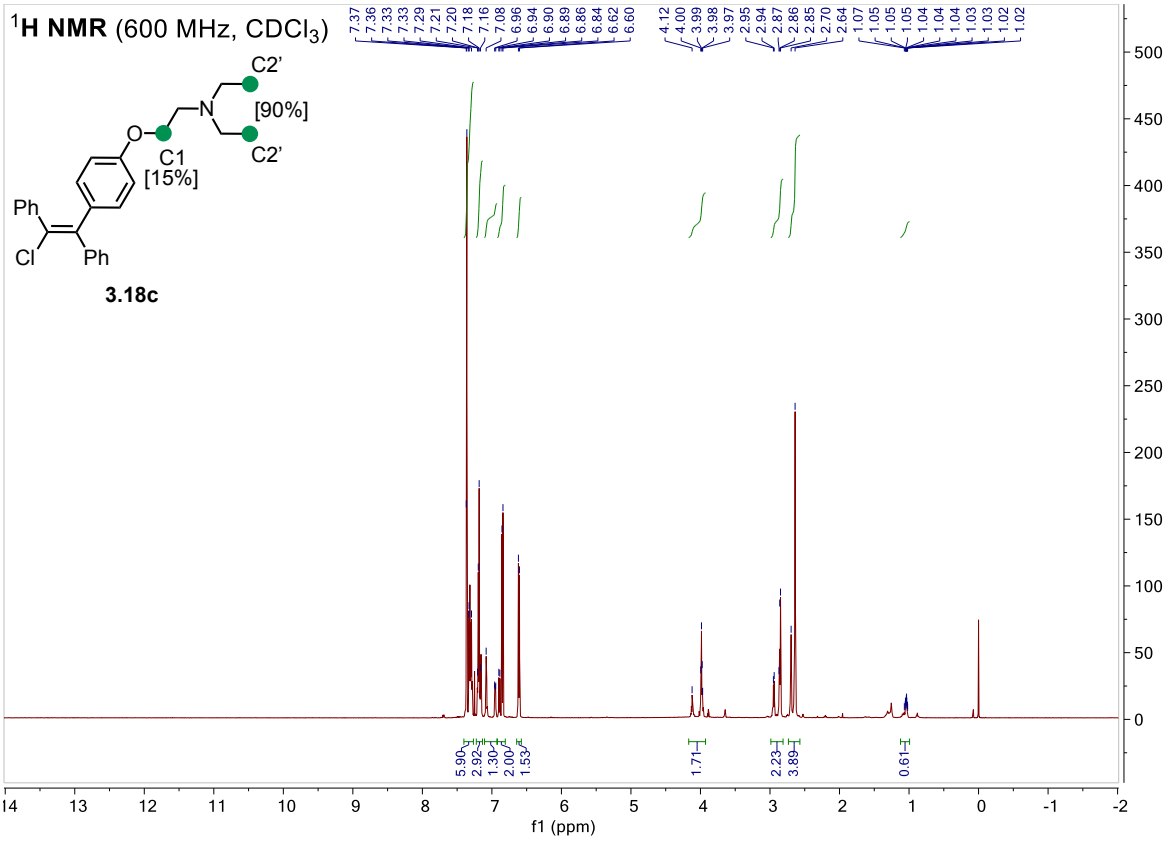
3.18c

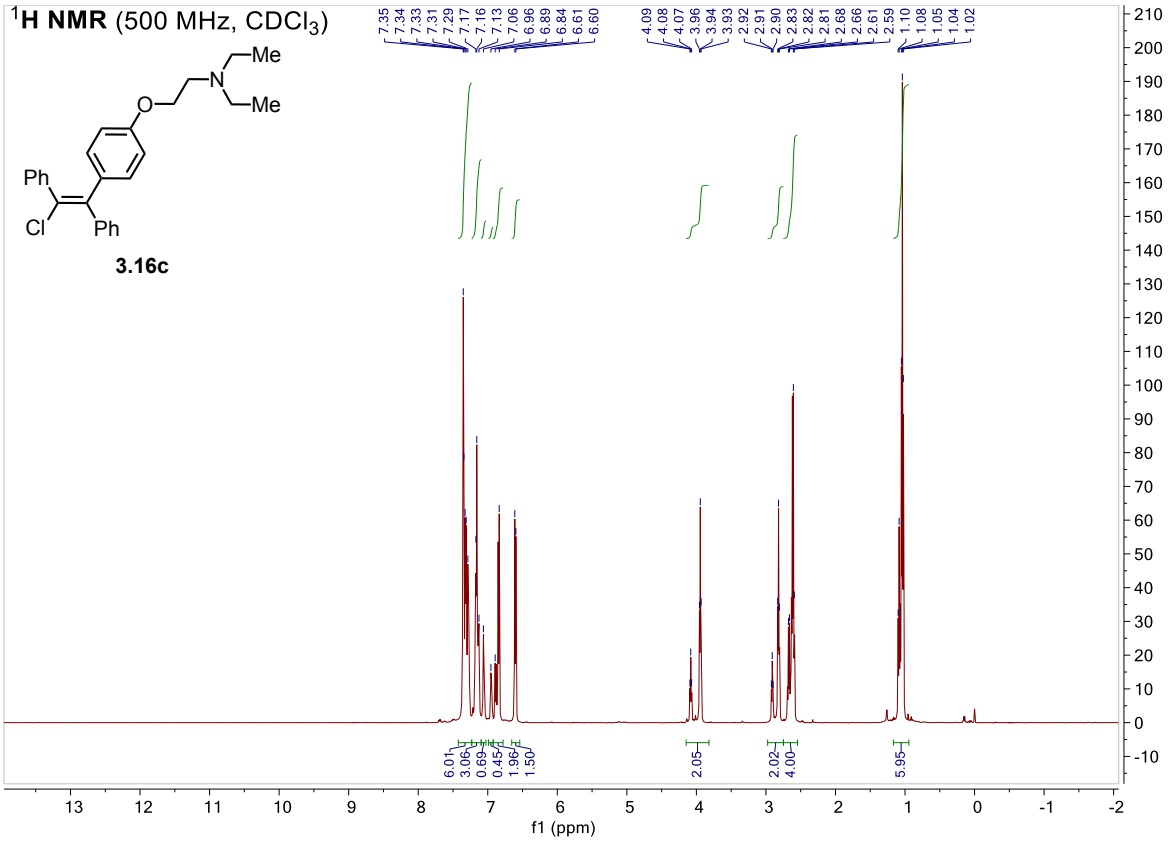

412.2322
413.2366
414.2396
411.2270
415.2392
416.2421
410.2197
409.2126
417.2456
Relative Intensity
m/z
100
80
60
40
20
0
400
410
420
430

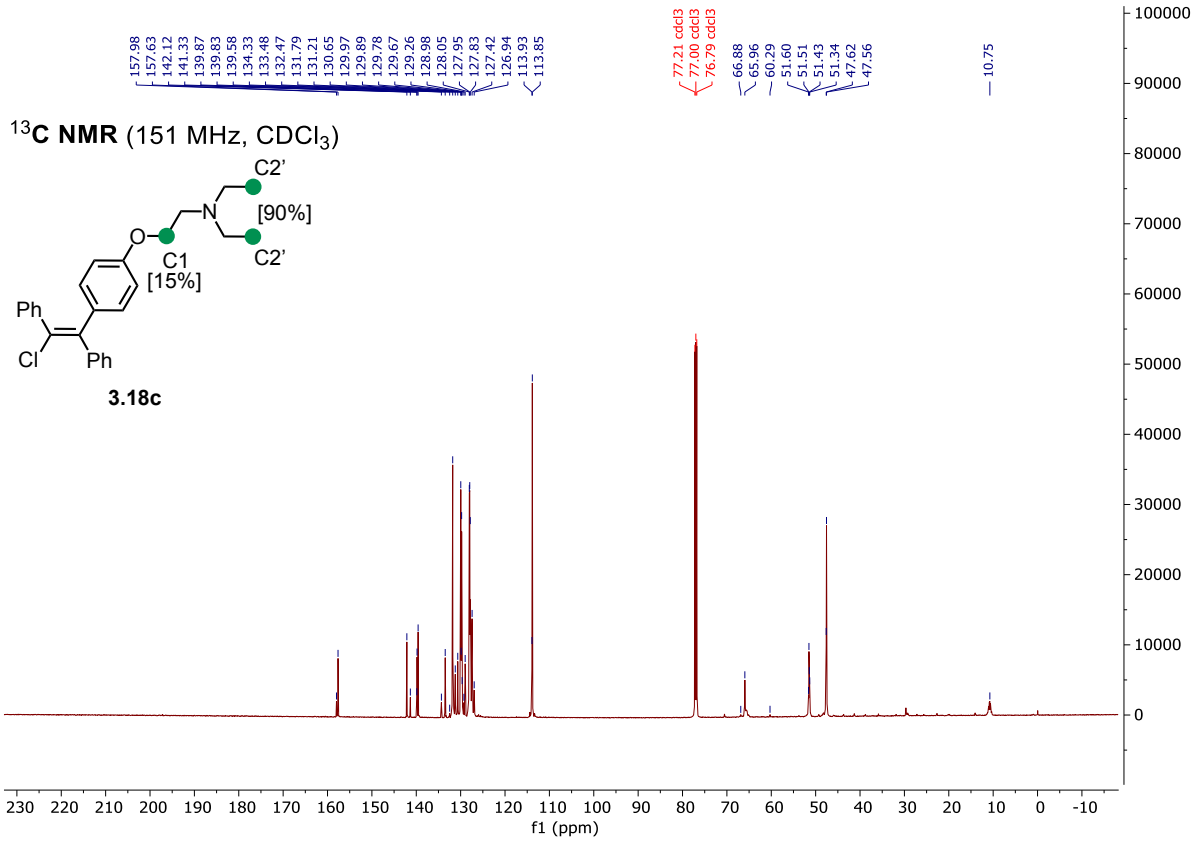

Me
N
Me
O
Ph
Cl
Ph

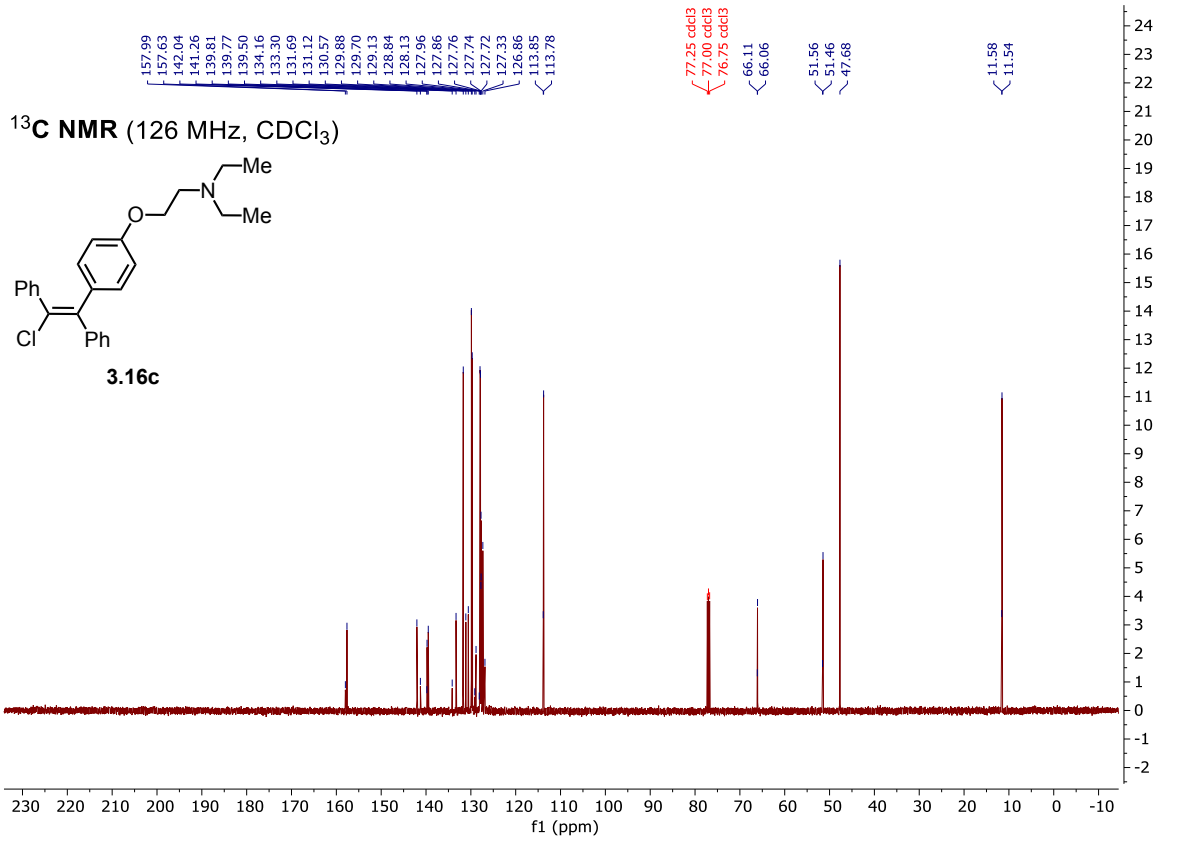
3.16c

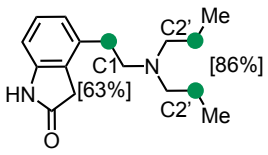

406.1949
408.1920
407.1966
409.1947
404.1794
405.1846
410.2003
Relative Intensity
m/z
100
80
60
40
20
0
400
410
420
430


1H NMR (600 MHz, CDCl3)
C2'
[90%]
N
O
C1
[15%]
C2'
Ph
Cl
Ph
3.18c
f1 (ppm)


1H NMR (500 MHz, CDCl3)
Me
N
Me
O
Ph
Cl
Ph
3.16c
f1 (ppm)


157.98
157.63
142.12
141.33
139.87
139.83
139.58
134.33
133.48
132.47
131.79
131.21
130.65
129.97
129.89
129.78
129.67
129.26
128.98
128.05
127.95
127.83
127.42
126.94
113.93
113.85
77.21 cdcl3
77.00 cdcl3
76.79 cdcl3
66.88
65.96
60.29
51.60
51.51
51.43
51.34
47.62
47.56
10.75
13C NMR (151 MHz, CDCl3)
C2'
N
[90%]
O
C1
[15%]
C2'
Ph
Cl
Ph
3.18c
f1 (ppm)


157.99
157.63
142.04
141.26
139.81
139.77
139.50
134.16
133.30
131.69
131.12
130.57
129.88
129.70
129.13
128.84
128.13
127.96
127.86
127.76
127.74
127.72
127.33
126.86
113.85
113.78
77.25 cdcl3
77.00 cdcl3
76.75 cdcl3
66.11
66.06
51.56
51.46
47.68
11.58
11.54
13C NMR (126 MHz, CDCl3)
Me
N
Me
O
Ph
Cl
Ph
3.16c
f1 (ppm)



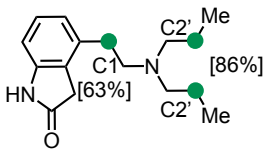
3.18d

Ropinirole, 3.18d

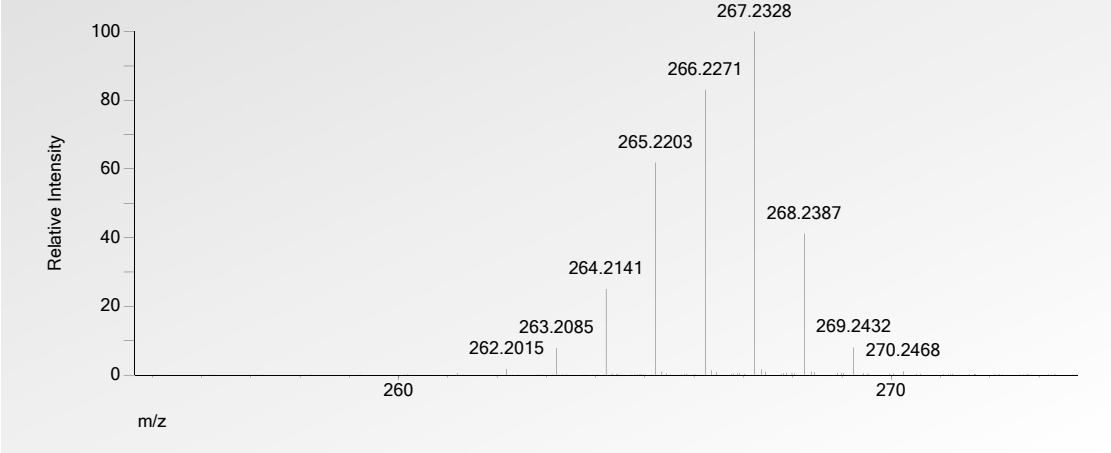
Ropinirole **3.16d** was reacted with acetone-d_6 **3.17a** following the General Procedure C. After purification by column chromatography (MeOH:DCM = 1:24), **3.18d** was obtained as a white solid (40 mg, 77%).

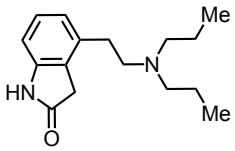
Deuterium incorporation: 4.70 D/molecule (^{1}H NMR), 5.24 D/molecule [HRMS (DART)]

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.22 (s, 1H), 7.14 (t, *J* = 7.7 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 6.75 (d, *J* = 7.7 Hz, 1H), 3.49 (s, 2H), 2.71 (d, *J* = 5.1 Hz, 2.74H, 63%D), 2.50 (s, 4H), 1.55 – 1.44 (m, 0.58H, 86%D), 0.89 (d, *J* = 8.5 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 177.56, 142.47, 136.77, 128.08, 127.97, 124.01, 122.80, 107.64, 55.90, 55.82, 54.13, 54.07, 54.00, 35.10, 30.52, 19.26, 11.88, 11.77, 11.66; **IR** (neat) 2952, 2928, 2799, 1701, 1615, 1601, 1453, 1254, 762, 719 cm^{-1}.

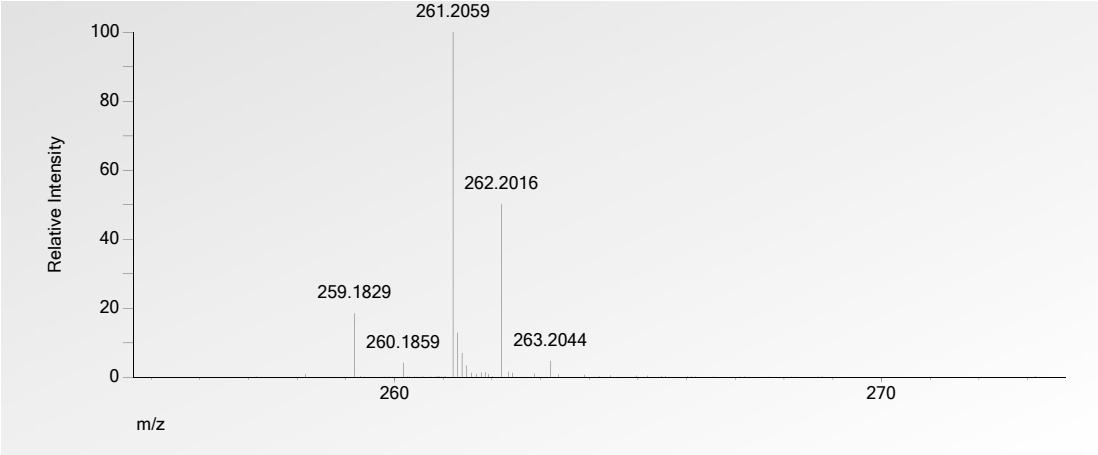

C2'
Me
C1
N
[86%]
HN
[63%]
C2'
Me
O

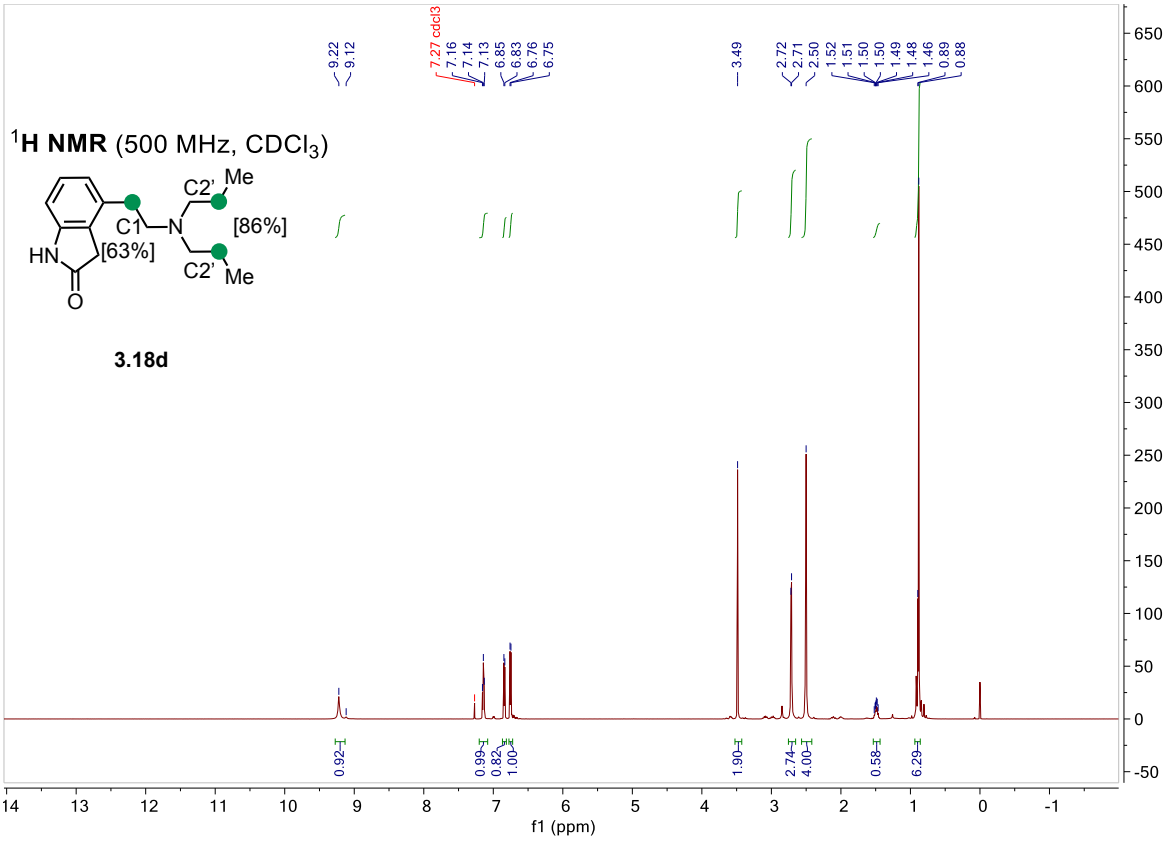
3.18d

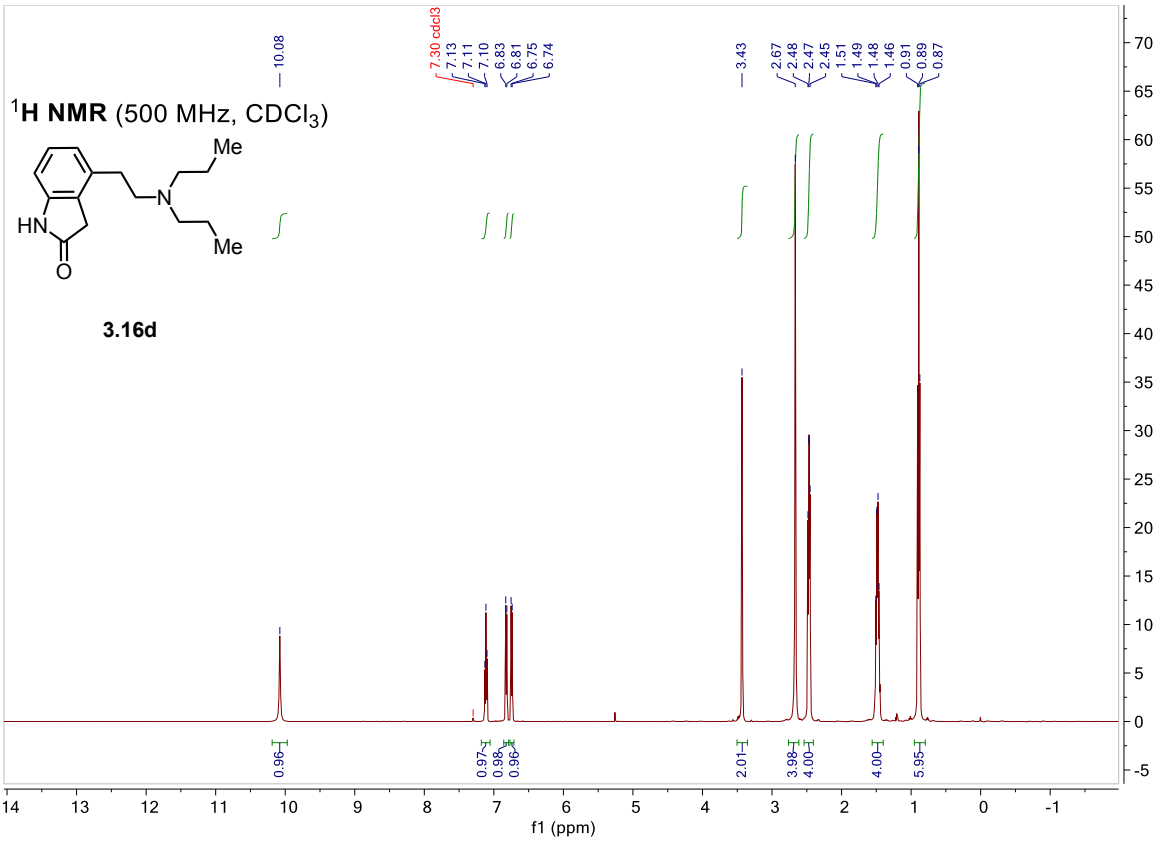

267.2328
266.2271
265.2203
268.2387
264.2141
263.2085
262.2015
269.2432
270.2468
100
80
60
40
20
0
Relative Intensity
260
270
m/z

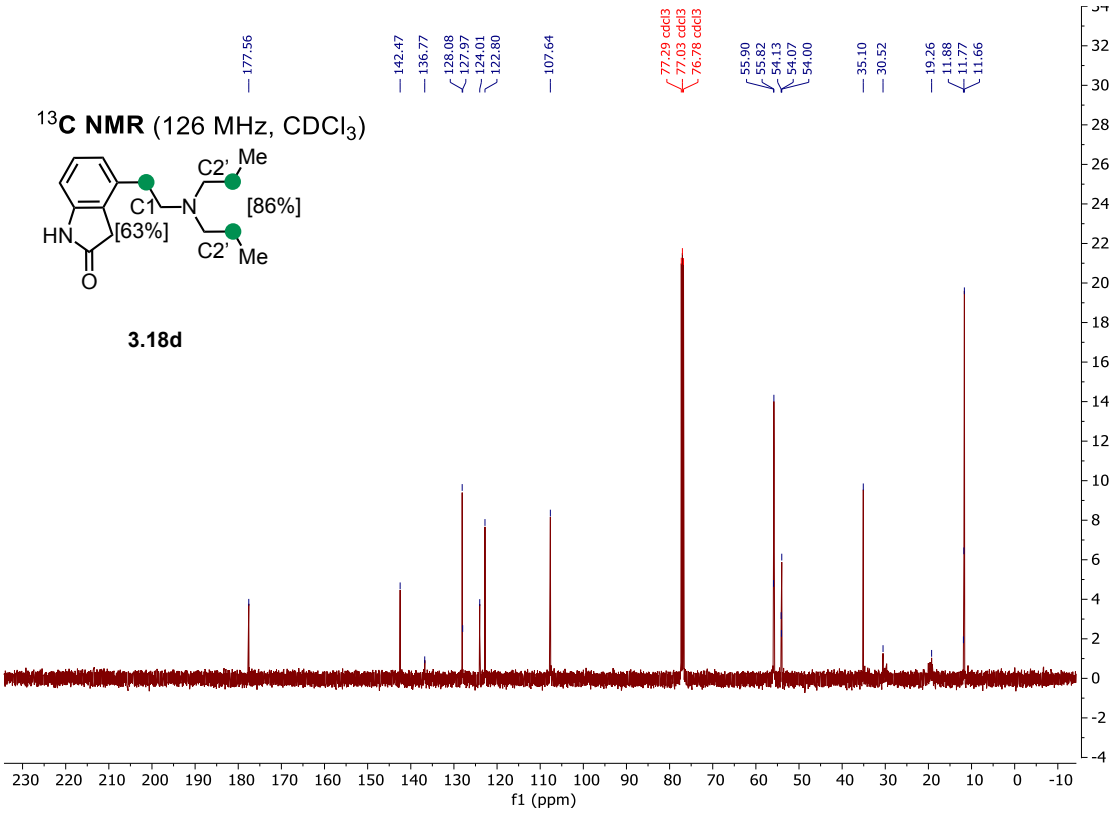

Me
N
HN
Me
O

3.16d


261.2059
262.2016
259.1829
260.1859
263.2044
100
80
60
40
20
0
Relative Intensity
260
270
m/z

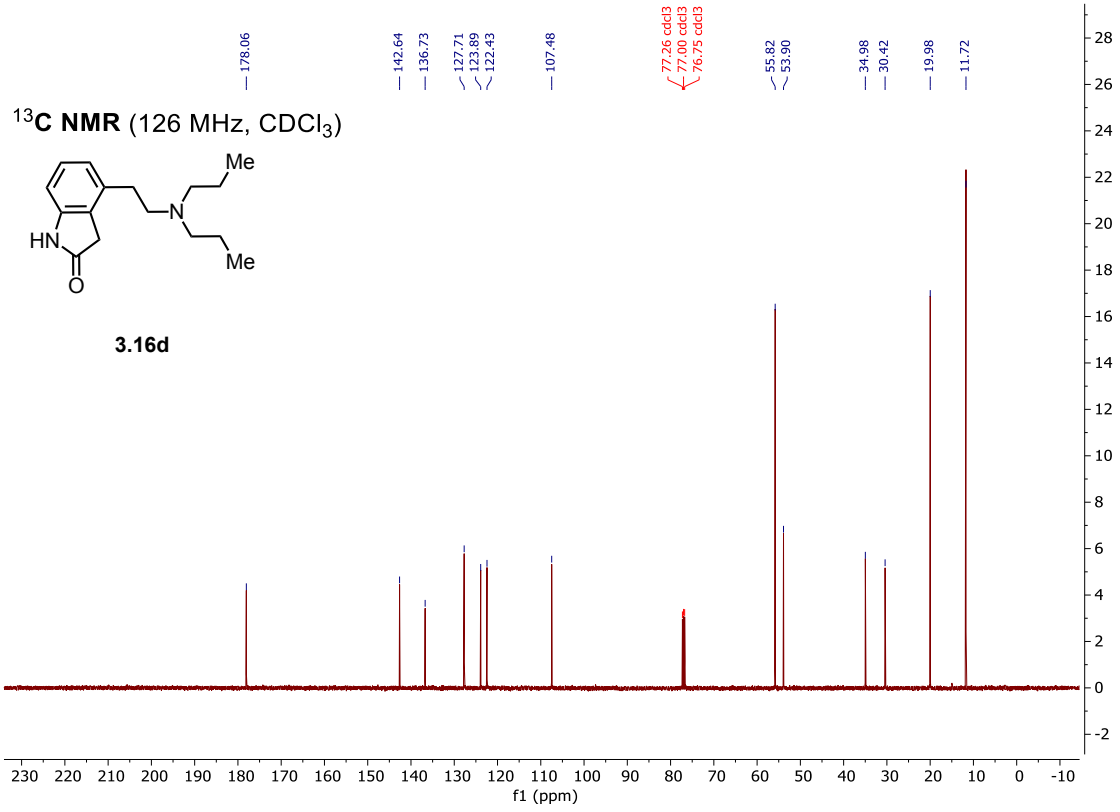

1H NMR (500 MHz, CDCl3)
C2'
Me
C1
N
[86%]
HN
[63%]
C2'
Me
O
3.18d
f1 (ppm)


1H NMR (500 MHz, CDCl3)
Me
N
HN
Me
O
3.16d
f1 (ppm)



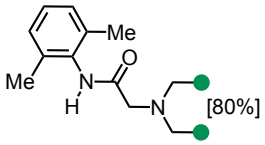
^{13}**C NMR** (126 MHz, $CDCl_3$)

3.18d



^{13}**C NMR** (126 MHz, $CDCl_3$)

3.16d



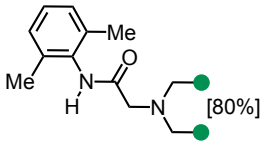
3.18e

Lidocaine, 3.18e

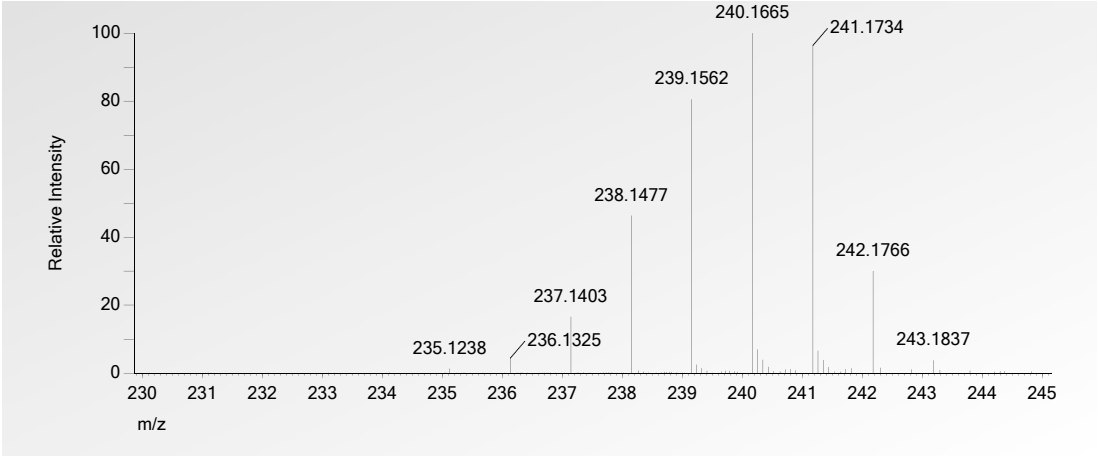
Lidocaine **3.16e** was reacted with acetone-d_6 **3.17a** following the General Procedure A. After purification by column chromatography (MeOH:DCM = 1:49), **3.18e** was obtained as a white solid (46 mg, 99%).

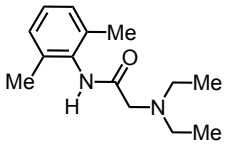
Deuterium incorporation: 4.80 D/molecule (^{1}H NMR), 4.78 D/molecule [HRMS (DART)]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.91 (s, 1H), 7.08 (s, 3H), 3.21 (s, 2H), 2.77 – 2.54 (m, 4H), 2.23 (s, 6H), 1.23 – 1.01 (m, 1.23H, 80%D); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.09, 134.90, 133.85, 128.04, 126.86, 57.41, 48.82, 48.76, 48.70, 48.64, 18.40, 11.94; **IR** (neat) 3265, 2936, 2818, 2219, 1684, 1491, 1284, 1163, 1051, 767 cm^{-1}.

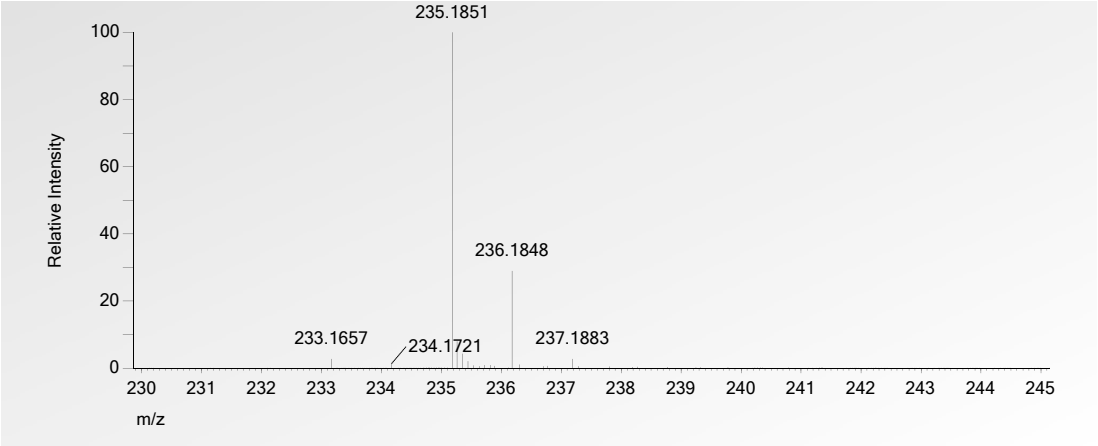

Me
Me
O
N
H
N
[80%]

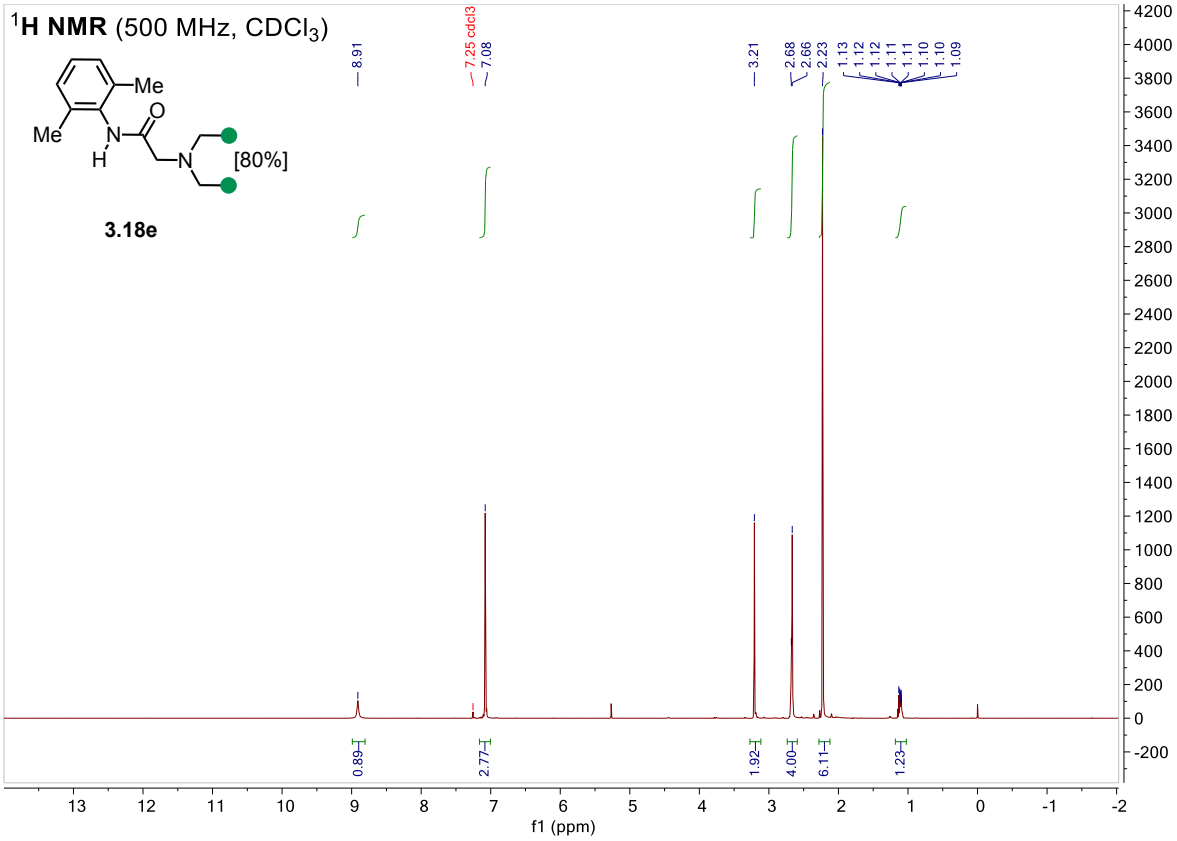
3.18e

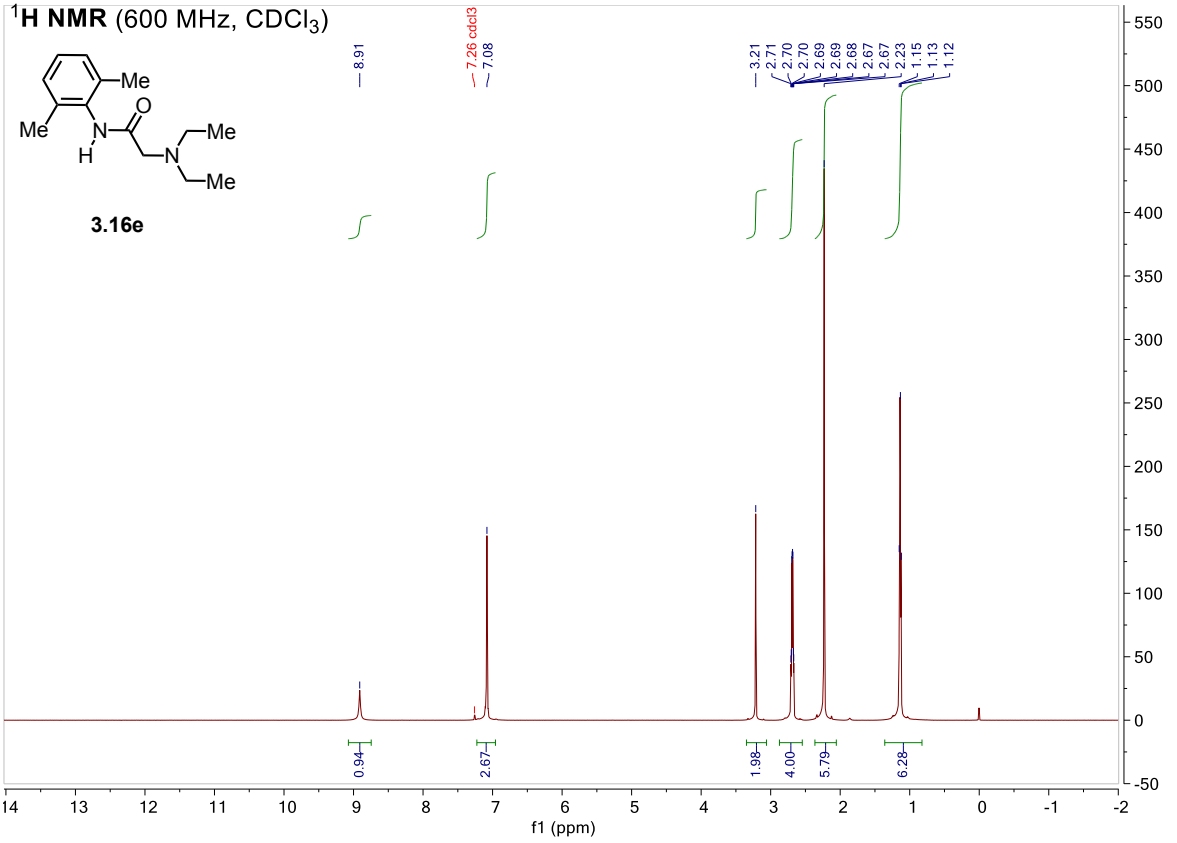

240.1665
241.1734
239.1562
238.1477
242.1766
237.1403
235.1238
236.1325
243.1837
100
80
60
40
20
0
Relative Intensity
230
231
232
233
234
235
236
237
238
239
240
241
242
243
244
245
m/z


Me
Me
O
N
H
Me
N
Me

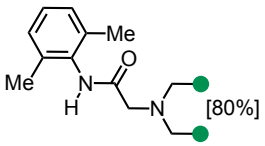
3.16e


235.1851
236.1848
233.1657
234.1721
237.1883
100
80
60
40
20
0
Relative Intensity
230
231
232
233
234
235
236
237
238
239
240
241
242
243
244
245
m/z


^{1}H NMR (500 MHz, CDCl$_3$)
Me
Me
N
H
O
N
[80%]
3.18e
8.91
7.25 cdcl3
7.08
3.21
2.68
2.66
2.23
1.13
1.12
1.12
1.11
1.11
1.10
1.10
1.09
0.89
2.77
1.92
4.00
6.11
1.23
f1 (ppm)

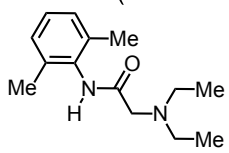

^{1}H NMR (600 MHz, CDCl$_3$)
Me
Me
N
H
O
N
Me
Me
3.16e
8.91
7.26 cdcl3
7.08
3.21
2.71
2.70
2.70
2.69
2.69
2.68
2.67
2.67
2.23
1.15
1.13
1.12
0.94
2.67
1.98
4.00
5.79
6.28
f1 (ppm)

^{13}**C NMR** (126 MHz, $CDCl_3$)

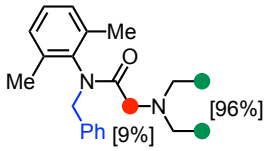


3.18e

^{13}**C NMR** (151 MHz, $CDCl_3$)



3.16e



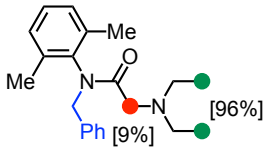
3.18f

_N_-Bn lidocaine, 3.18f

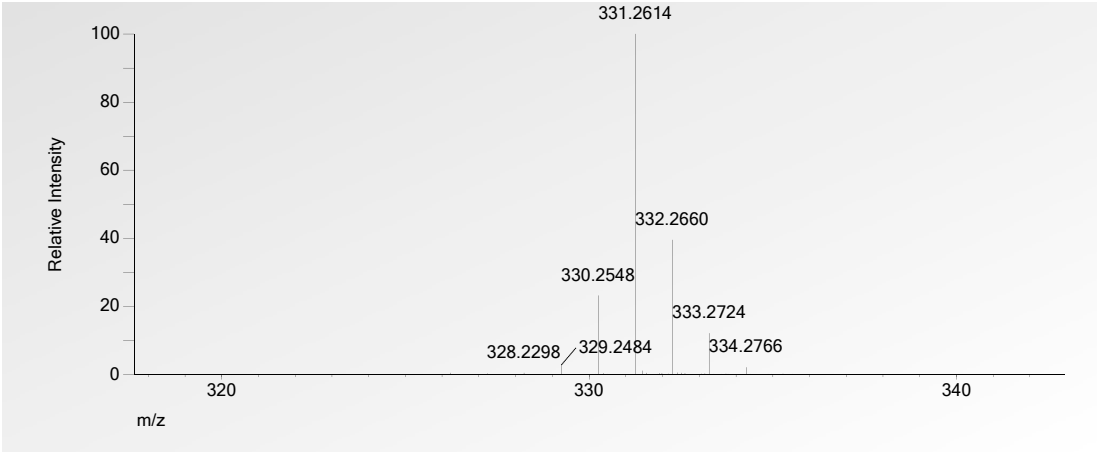
_N_-Bn lidocaine **3.16f** was reacted with acetone-d_6 **3.17a** following the General Procedure B. After purification by column chromatography (MeOH:DCM = 1:49), **3.18f** was obtained as a yellow liquid (62 mg, 96%).

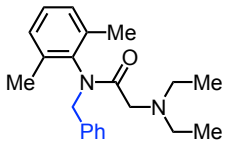
Deuterium incorporation: 6.18 D/molecule (^{1}H NMR), 6.26 D/molecule [HRMS (DART)]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (s, 5H), 7.13 (dd, J = 8.0, 7.0 Hz, 1H), 7.04 (d, J = 7.6 Hz, 2H), 4.73 (s, 1.82H, 9%D), 2.81 (s, 2H), 2.57 (s, 4H), 1.87 (s, 6H), 0.88 (s, 0.22H, 96%D); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.35, 138.91, 137.06, 136.33, 130.23, 129.03, 128.26, 128.11, 127.60, 54.55, 51.77, 47.30, 17.86, 11.04; **IR** (neat) 2926, 1650, 1460, 1400, 1242, 1141, 1078, 773, 743, 700 cm^{-1}.

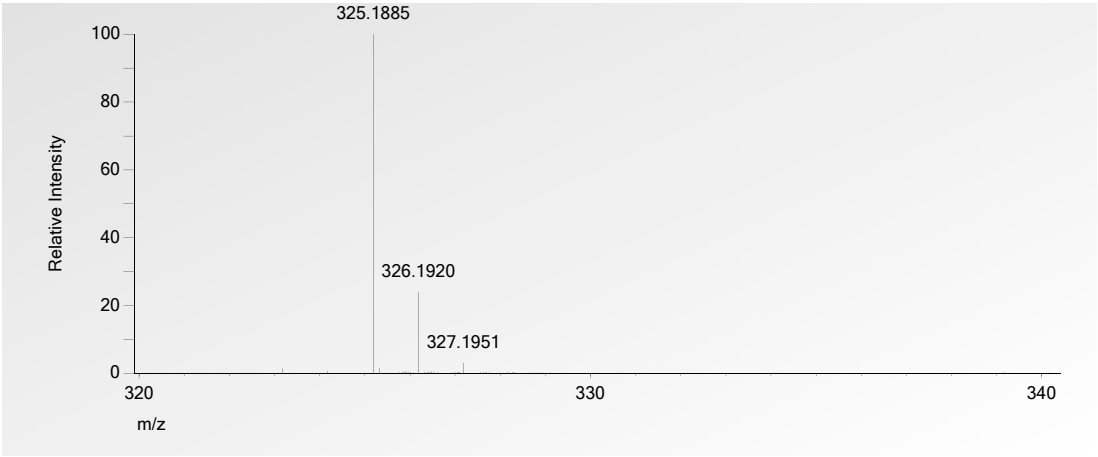

Me
Me
O
N
N
[96%]
Ph [9%]

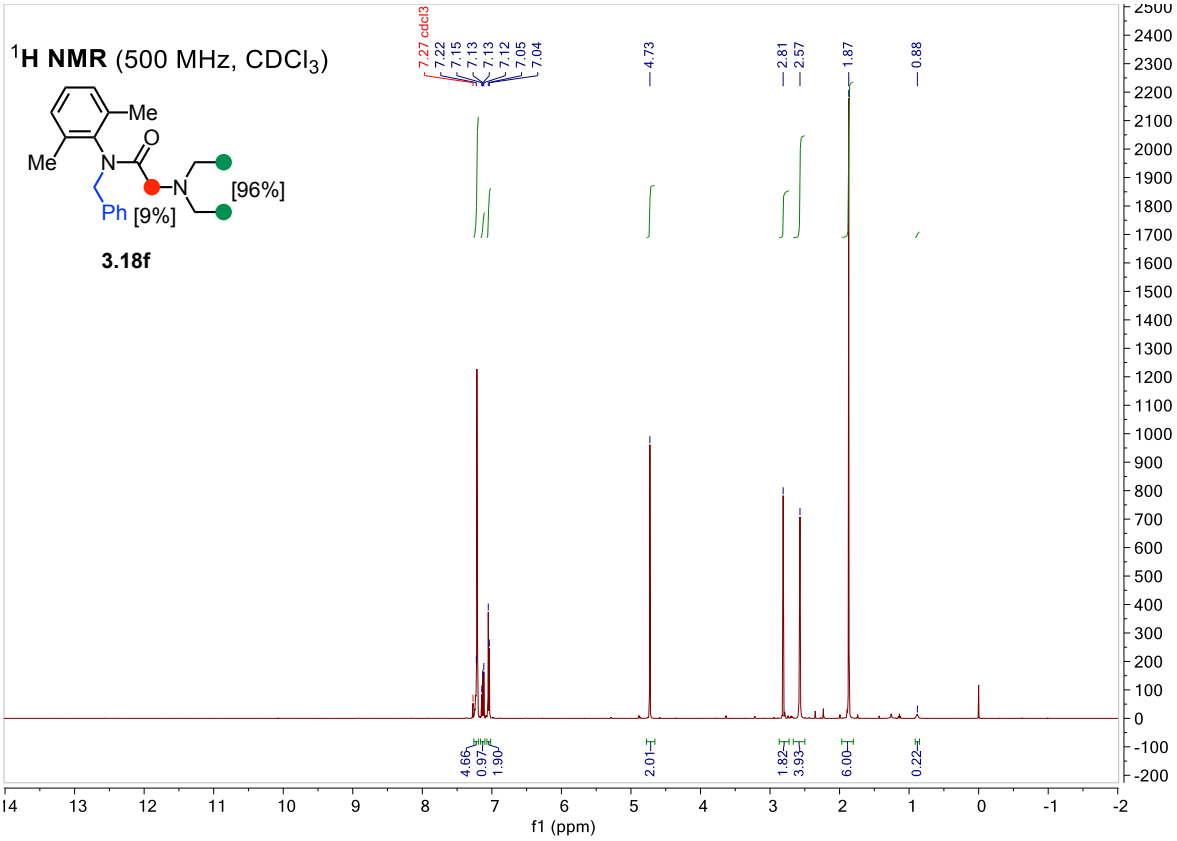
3.18f

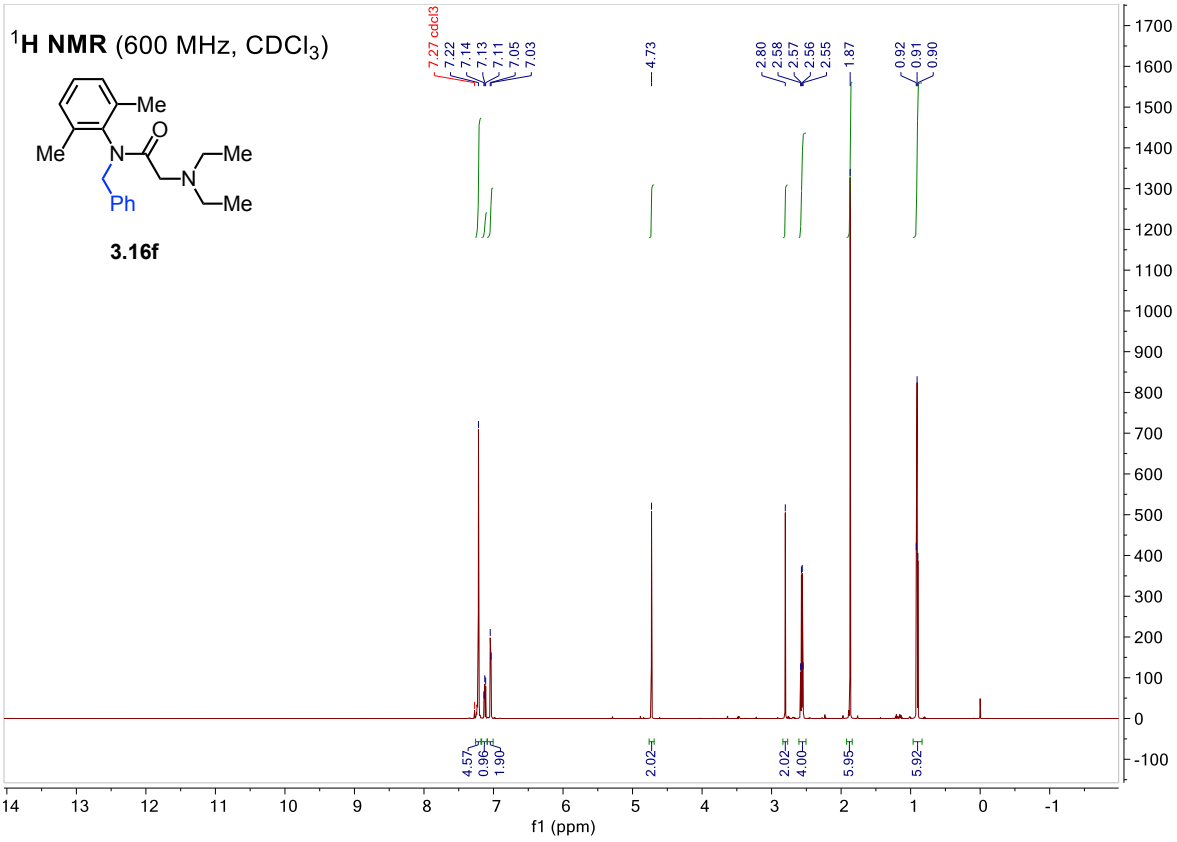

331.2614
100
80
60
40
20
0
Relative Intensity
332.2660
330.2548
333.2724
328.2298
329.2484
334.2766
320
330
340
m/z

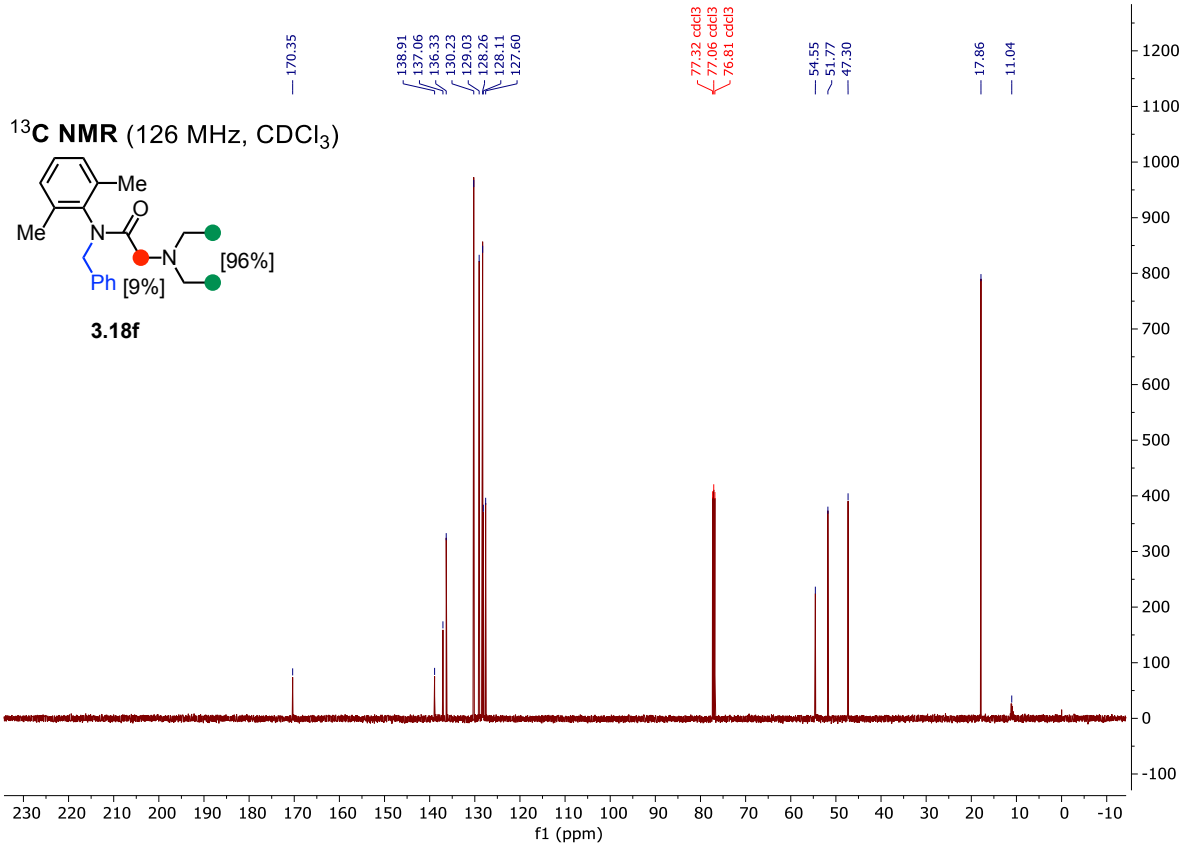

Me
Me
O
N
N
Me
Me
Ph

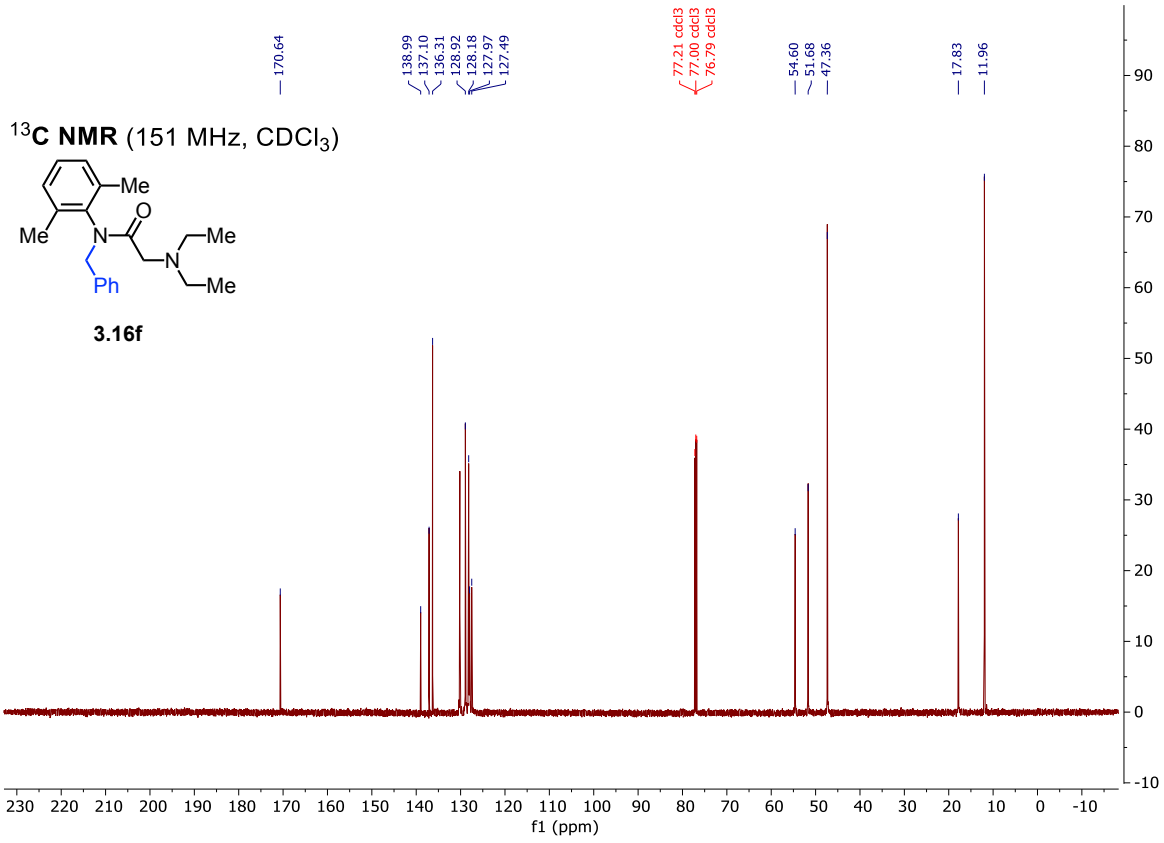
3.16f

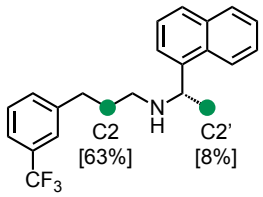

325.1885
100
80
60
40
20
0
Relative Intensity
326.1920
327.1951
320
330
340
m/z


1H NMR (500 MHz, CDCl3)
Me
Me
N
O
N
[96%]
Ph [9%]
3.18f
7.27 cdcl3
7.22
7.15
7.13
7.13
7.12
7.05
7.04
4.73
2.81
2.57
1.87
0.88
4.66
0.97
1.90
2.01
1.82
3.93
6.00
0.22
f1 (ppm)


1H NMR (600 MHz, CDCl3)
Me
Me
N
O
N
Me
Me
Ph
3.16f
7.27 cdcl3
7.22
7.14
7.13
7.11
7.05
7.03
4.73
2.80
2.58
2.57
2.56
2.55
1.87
0.92
0.91
0.90
4.57
0.96
1.90
2.02
2.02
4.00
5.95
5.92
f1 (ppm)


170.35
138.91
137.06
136.33
130.23
129.03
128.26
128.11
127.60
77.32 cdcl3
77.06 cdcl3
76.81 cdcl3
54.55
51.77
47.30
17.86
11.04
13C NMR (126 MHz, CDCl3)
Me
Me
N
O
N
[96%]
Ph [9%]
3.18f
f1 (ppm)


170.64
138.99
137.10
136.31
128.92
128.18
127.97
127.49
77.21 cdcl3
77.00 cdcl3
76.79 cdcl3
54.60
51.68
47.36
17.83
11.96
13C NMR (151 MHz, CDCl3)
Me
Me
N
O
N
Me
Me
Ph
3.16f
f1 (ppm)



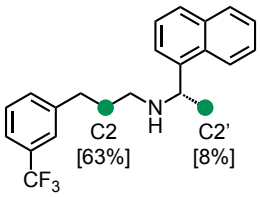
3.18g

Cinacalcet, 3.18g

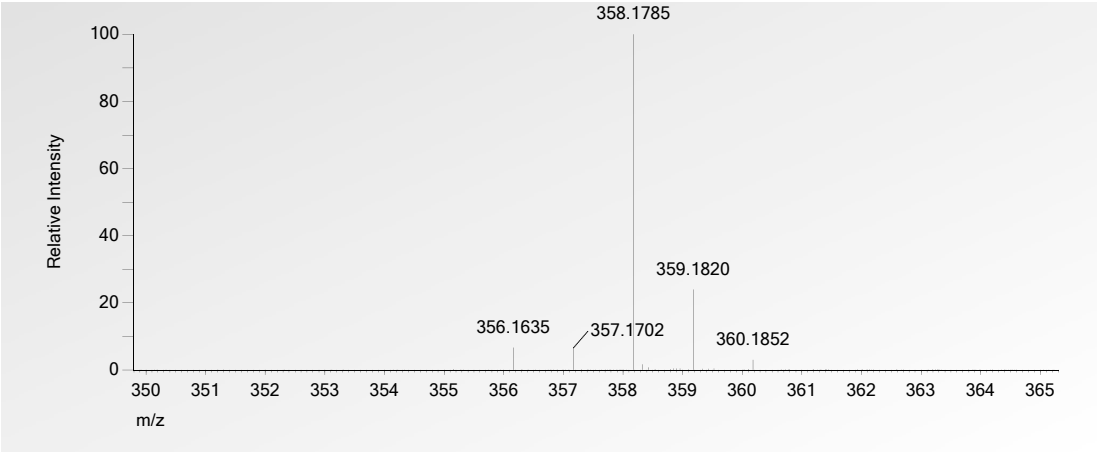
Cinacalcet **3.16g** was reacted with acetone-d_6 **3.17a** following the General Procedure A. After purification by column chromatography (MeOH:DCM = 1:19), **3.18g** was obtained as a yellow liquid (69 mg, 97%).

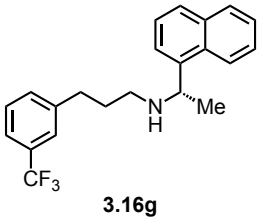
Deuterium incorporation: 1.50 D/molecule (^{1}H NMR), 1.52 D/molecule [HRMS (DART)]

^{1}H NMR (500 MHz, CD_3OD) δ 8.01 (d, *J* = 8.5 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.61 (d, *J* = 8.2 Hz, 1H), 7.47 (d, *J* = 7.2 Hz, 1H), 7.40 – 7.26 (m, 5H), 7.20 (dt, *J* = 16.2, 7.6 Hz, 2H), 4.54 (q, *J* = 6.5 Hz, 1H), 2.43 (ddd, *J* = 38.2, 16.0, 8.0 Hz, 4H), 1.75 – 1.57 (m, 0.75H, 63%D), 1.34 (d, *J* = 6.7 Hz, 2.72H, 8%D); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.09, 141.08, 134.04, 131.79, 131.78, 131.35, 131.00, 130.74, 130.49, 130.24, 129.04, 129.03, 128.70, 127.28, 125.82, 125.73, 125.41, 125.37, 125.11, 125.08, 125.05, 125.02, 123.24, 122.93, 122.75, 122.71, 122.68, 122.65, 122.62, 53.83, 47.20, 33.33, 31.82, 23.58; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -62.47; **IR** (neat) 2923, 1448, 1326, 1198, 1160, 1119, 1072, 798, 777, 701, 659 cm^{-1}; $[\alpha]^{25}_{D}$ = +19.1° (c = 1.0, CH_2Cl_2 labeled), $[\alpha]^{25}_{D}$ = +28.3° (c = 1.0, CH_2Cl_2 unlabeled).

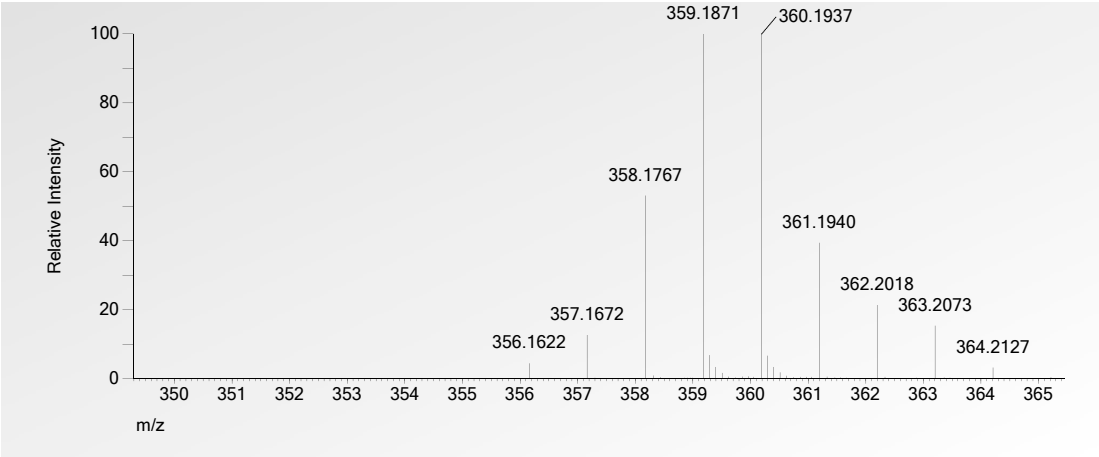

N
H
C2
[63%]
C2'
[8%]
CF3

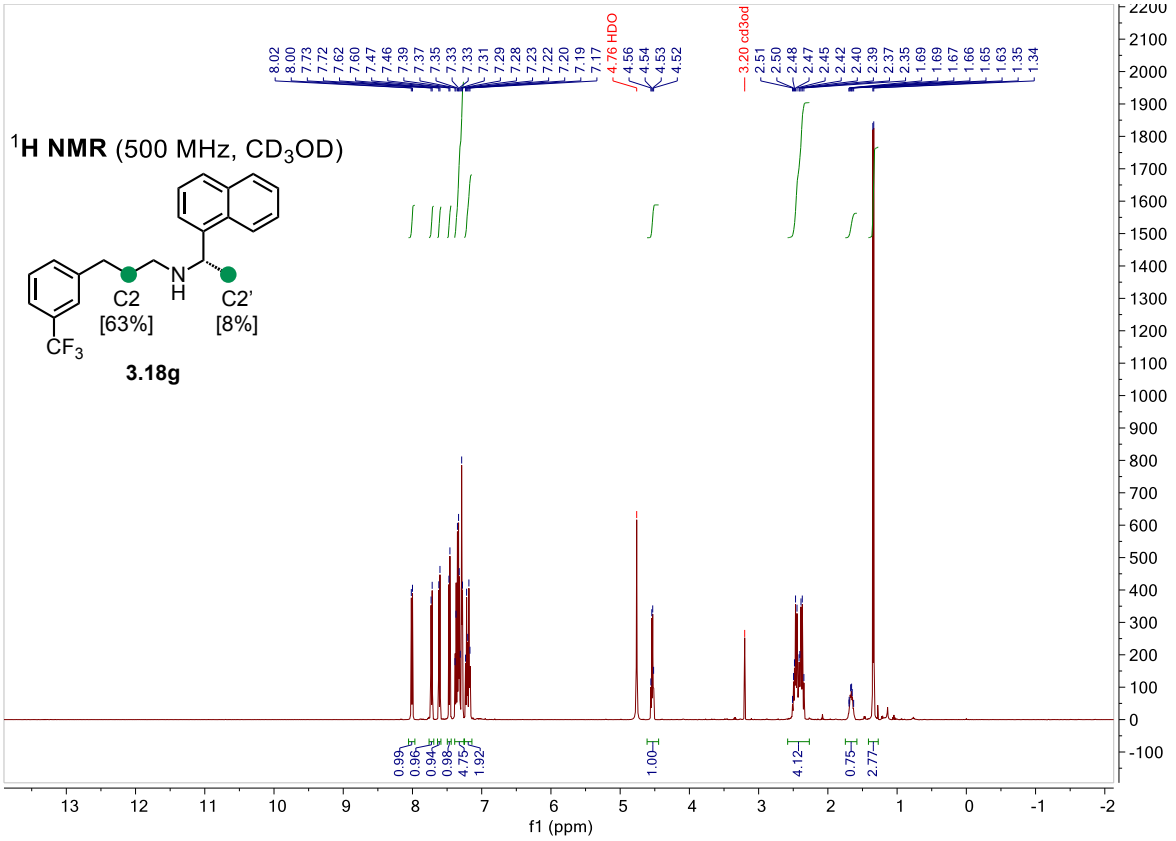
3.18g

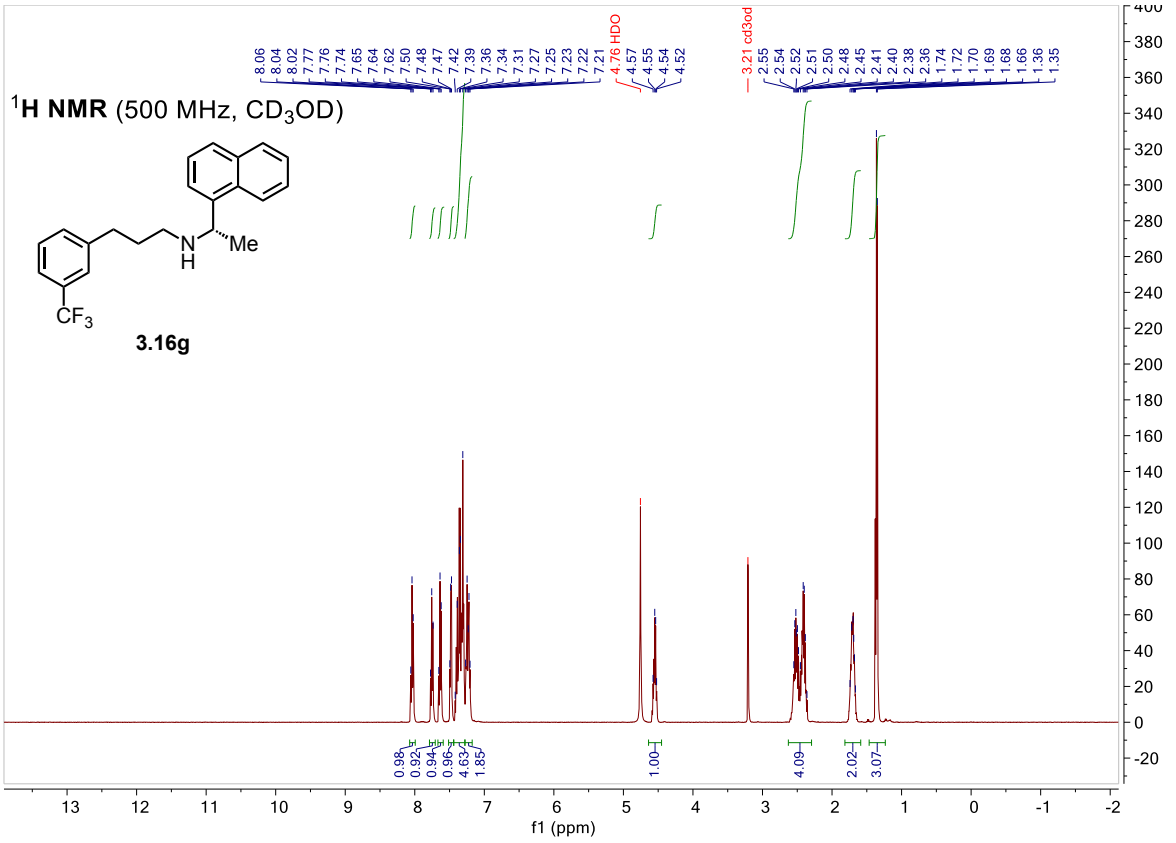

358.1785
359.1820
356.1635
357.1702
360.1852
Relative Intensity
m/z

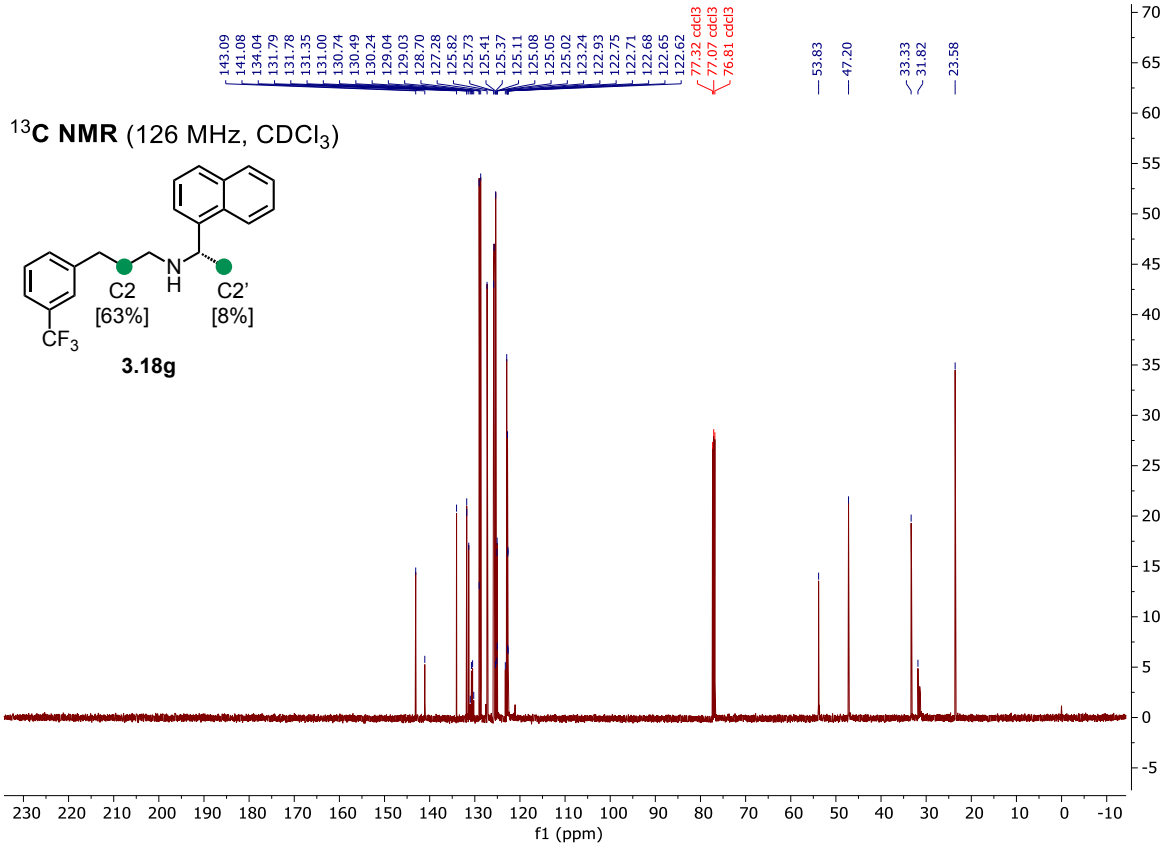

N
H
Me
CF3

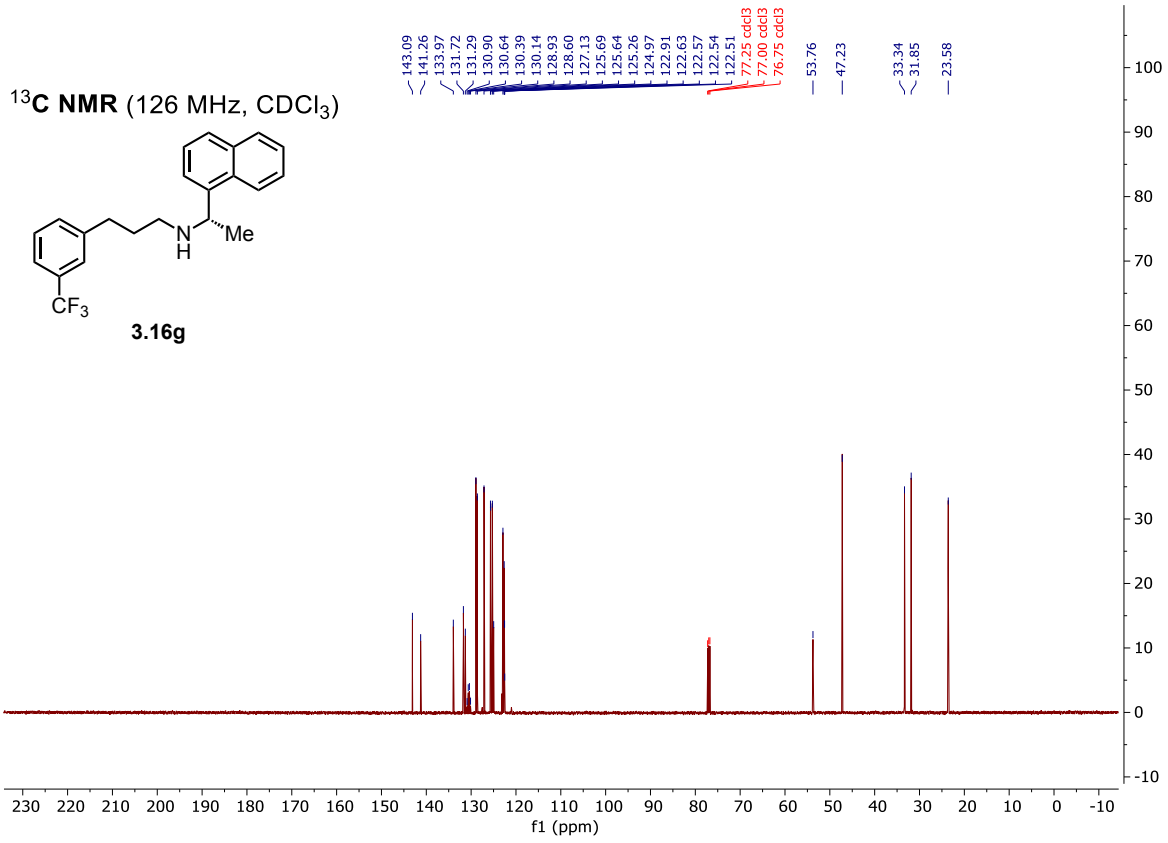
3.16g

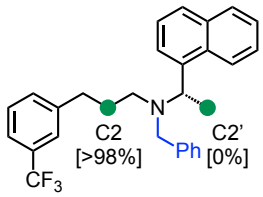

359.1871
360.1937
358.1767
361.1940
362.2018
363.2073
357.1672
356.1622
364.2127
Relative Intensity
m/z


1H NMR (500 MHz, CD3OD)
C2
[63%]
C2'
[8%]
CF3
3.18g
f1 (ppm)


1H NMR (500 MHz, CD3OD)
Me
CF3
3.16g
f1 (ppm)


143.09
141.08
134.04
131.79
131.78
131.35
131.00
130.74
130.49
130.24
129.04
129.03
128.70
127.28
125.82
125.73
125.41
125.37
125.11
125.08
125.05
125.02
123.24
122.93
122.75
122.71
122.68
122.65
122.62
77.32 cdcl3
77.07 cdcl3
76.81 cdcl3
53.83
47.20
33.33
31.82
23.58
13C NMR (126 MHz, CDCl3)
C2
[63%]
C2'
[8%]
N
H
CF3
3.18g
f1 (ppm)


143.09
141.26
133.97
131.72
131.29
130.90
130.64
130.39
130.14
128.93
128.60
127.13
125.69
125.64
125.26
124.97
122.91
122.63
122.57
122.54
122.51
77.25 cdcl3
77.00 cdcl3
76.75 cdcl3
53.76
47.23
33.34
31.85
23.58
13C NMR (126 MHz, CDCl3)
N
H
Me
CF3
3.16g
f1 (ppm)



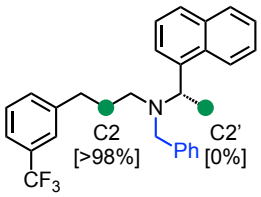
3.18h

***N*-Bn cinacalcet, 3.18h**

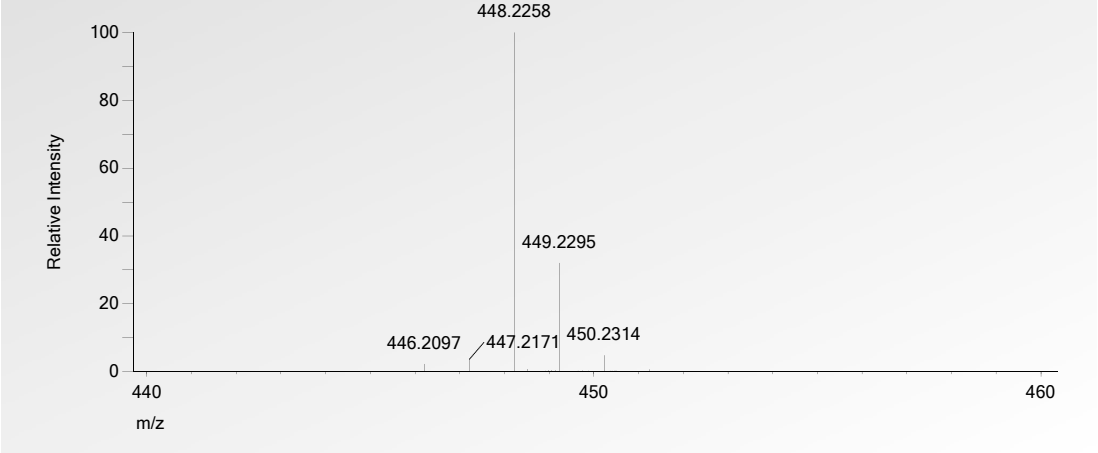
N-Bn cinacalcet **3.16h** was reacted with acetone-d_6 **3.17a** following the General Procedure B. After purification by column chromatography (Et_2O:hexanes = 1:9), **3.18h** was obtained as a yellow liquid (88 mg, 98%).

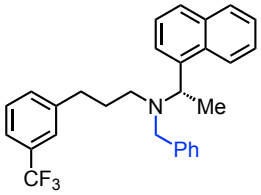
Deuterium incorporation: 1.99 D/molecule (^{1}H NMR), 2.28 D/molecule [HRMS (DART)]

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.56 (d, *J* = 7.1 Hz, 1H), 7.50 – 7.38 (m, 3H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.24 (t, *J* = 7.8 Hz, 6H), 7.12 (s, 1H), 6.96 (d, *J* = 7.4 Hz, 1H), 4.75 – 4.62 (m, 1H), 3.72 (d, *J* = 13.8 Hz, 1H), 3.63 (d, *J* = 13.8 Hz, 1H), 2.60 (s, 2H), 2.33 (d, *J* = 14.0 Hz, 1H), 2.26 (d, *J* = 13.9 Hz, 1H), 1.63 (d, *J* = 6.3 Hz, 0.02H, >98%D), 1.53 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.40, 140.63, 140.03, 134.03, 132.14, 131.59, 131.58, 130.48, 130.23, 128.97, 128.55, 128.44, 128.19, 128.05, 127.61, 126.74, 125.35, 125.33, 125.28, 125.00, 124.89, 124.85, 124.83, 124.80, 124.56, 123.18, 122.36, 122.33, 122.30, 122.27, 56.40, 55.80, 49.66, 33.06, 28.22, 14.36; **^{19}F NMR** (564 MHz, $CDCl_3$) δ -62.49; **IR** (neat) 2858, 1449, 1331, 1197, 1159, 1118, 1097, 797, 778, 733, 699 cm^{-1}; $[\alpha]^{25}_{D}$ = -28.5° (c = 1.0, CH_2Cl_2 labeled), $[\alpha]^{25}_{D}$ = -39.2° (c = 1.0, CH_2Cl_2 unlabeled).

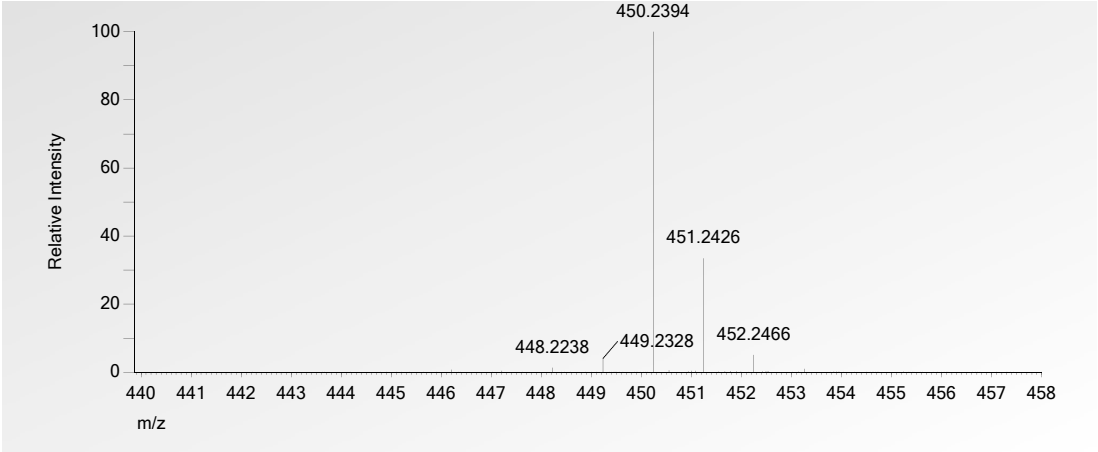

N
C2
[>98%]
Ph
C2'
[0%]
CF3

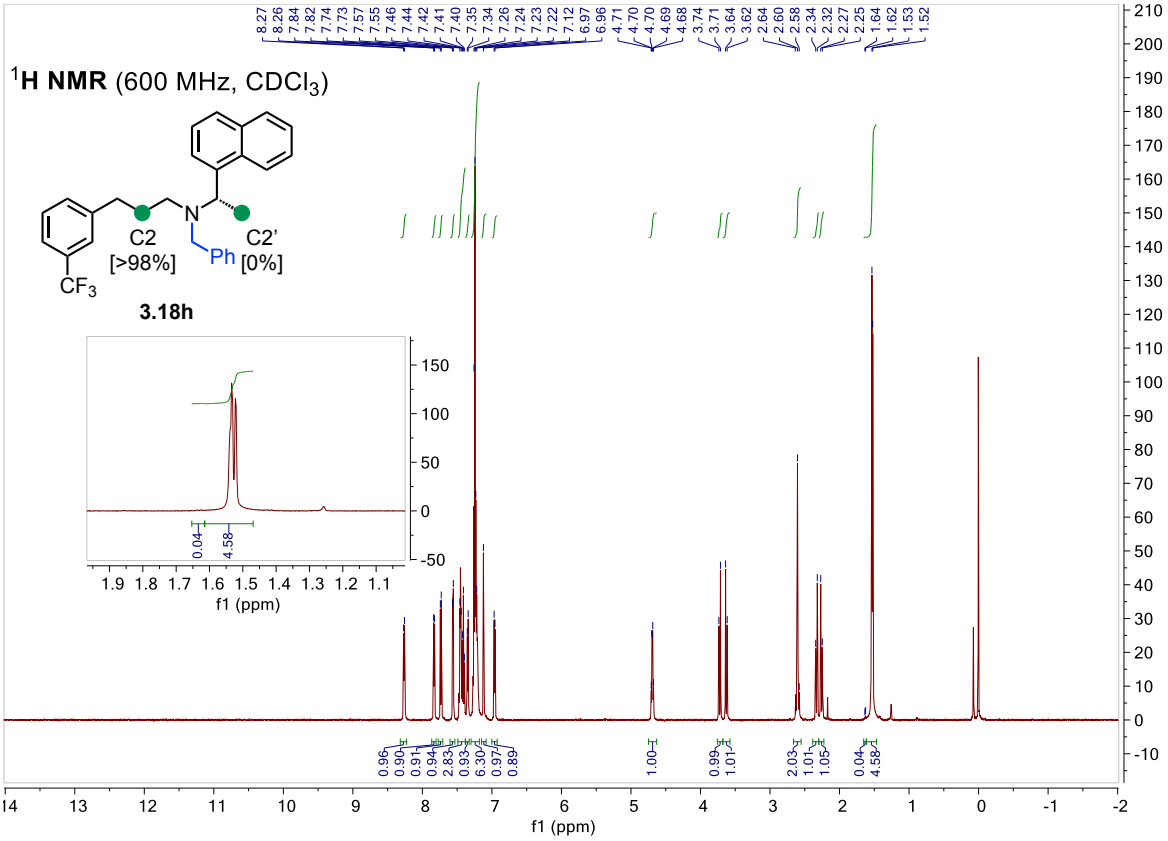
3.18h

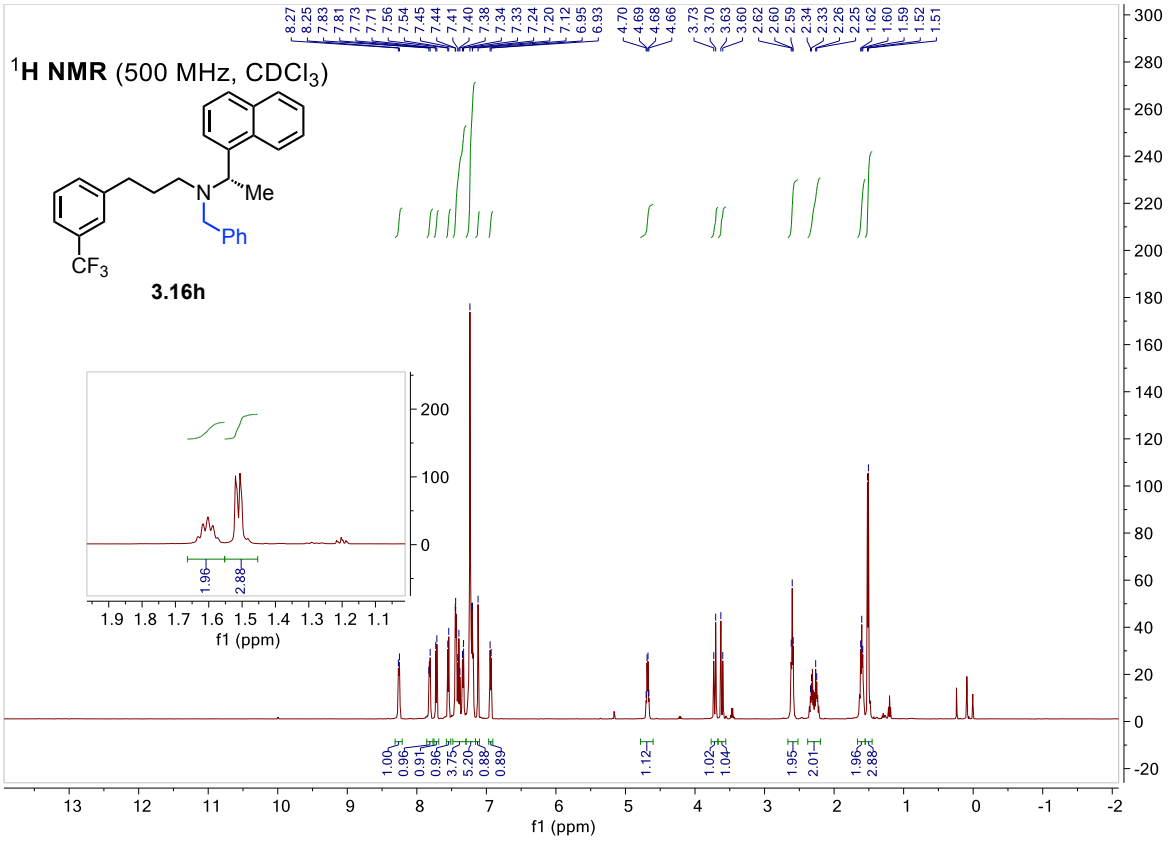

448.2258
449.2295
446.2097
447.2171
450.2314
Relative Intensity
m/z
100
80
60
40
20
0
440
450
460

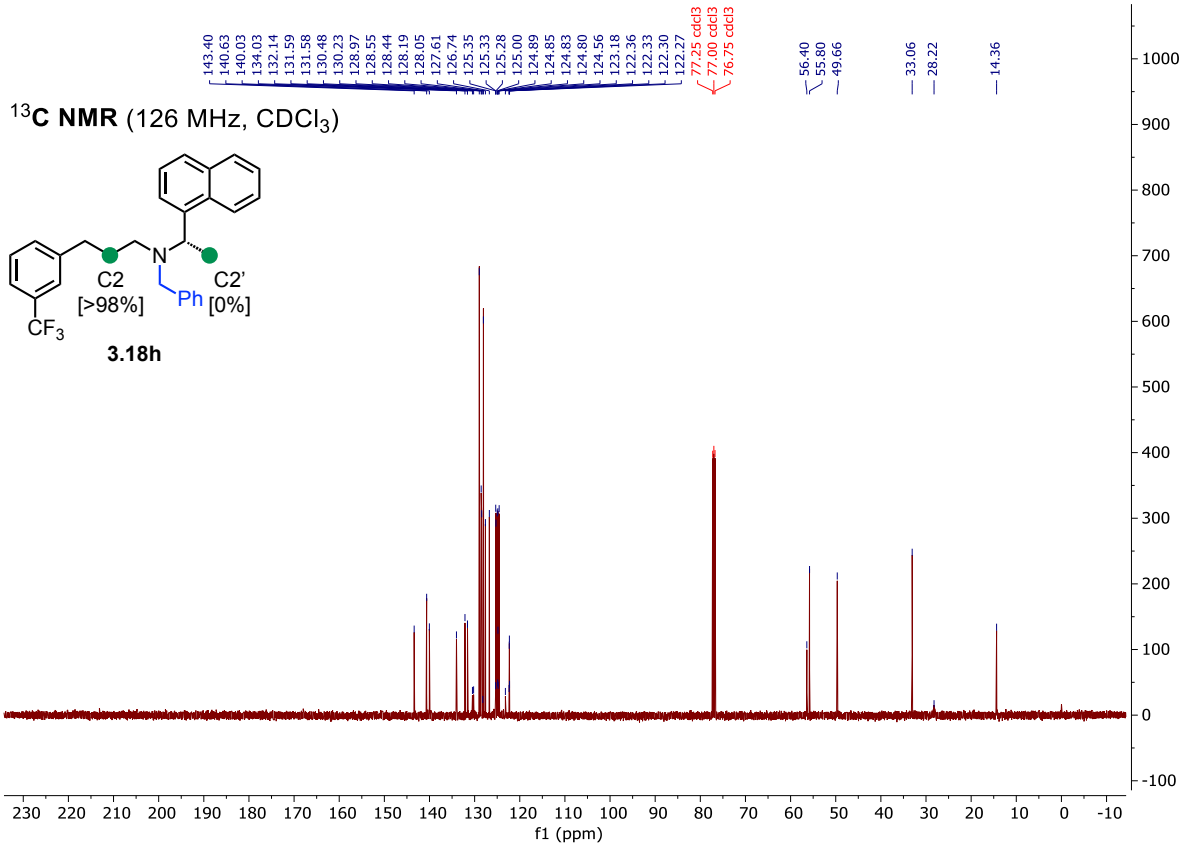

N
Me
Ph
CF3

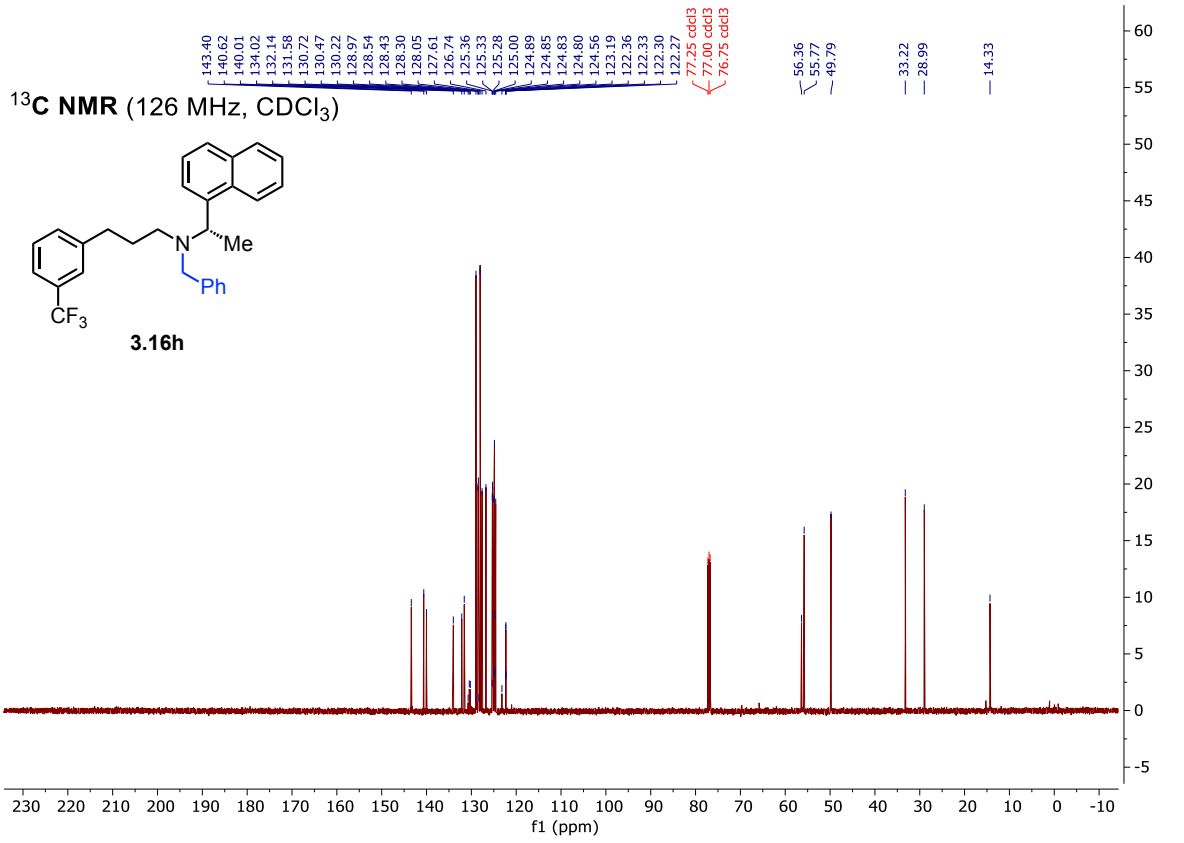
3.16h

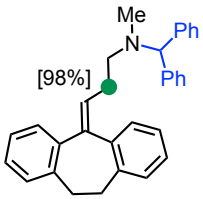

450.2394
451.2426
448.2238
449.2328
452.2466
Relative Intensity
m/z
100
80
60
40
20
0
440
441
442
443
444
445
446
447
448
449
450
451
452
453
454
455
456
457
458


1H NMR (600 MHz, CDCl3)
C2
[>98%]
C2'
[0%]
Ph
CF3
3.18h
f1 (ppm)


1H NMR (500 MHz, CDCl3)
N
Me
Ph
CF3
3.16h
f1 (ppm)


143.40
140.63
140.03
134.03
132.14
131.59
131.58
130.48
130.23
128.97
128.55
128.44
128.19
128.05
127.61
126.74
125.35
125.33
125.28
125.00
124.89
124.85
124.83
124.80
124.56
123.18
122.36
122.33
122.30
122.27
77.25 cdcl3
77.00 cdcl3
76.75 cdcl3
56.40
55.80
49.66
33.06
28.22
14.36
13C NMR (126 MHz, CDCl3)
C2
[>98%]
C2'
[0%]
Ph
CF3
3.18h
f1 (ppm)


143.40
140.62
140.01
134.02
132.14
131.58
130.72
130.47
130.22
128.97
128.54
128.43
128.30
128.05
127.61
126.74
125.36
125.33
125.28
125.00
124.89
124.85
124.83
124.80
124.56
123.19
122.36
122.33
122.30
122.27
77.25 cdcl3
77.00 cdcl3
76.75 cdcl3
56.36
55.77
49.79
33.22
28.99
14.33
13C NMR (126 MHz, CDCl3)
Me
Ph
CF3
3.16h
f1 (ppm)



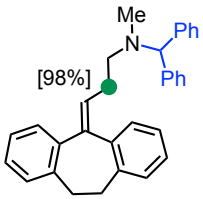
3.18i

***N*-Bzh nortriptyline, 3.18i**

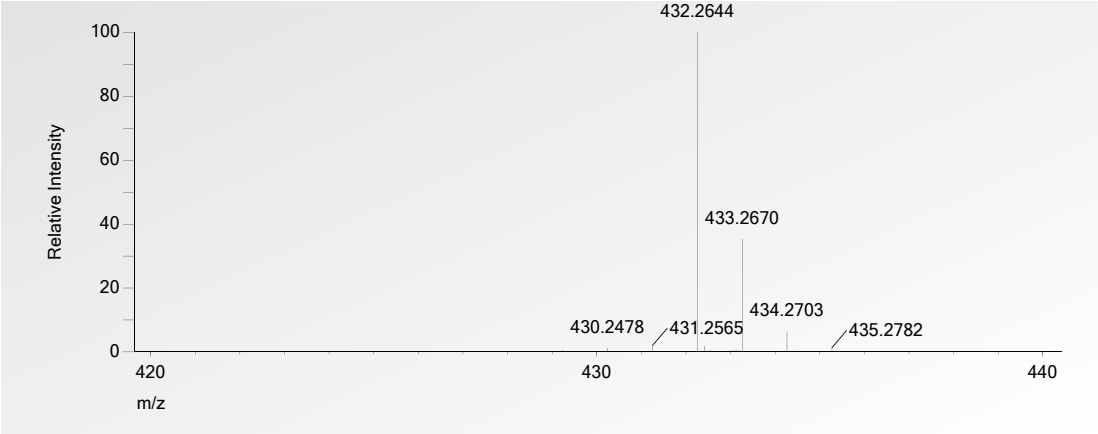
N-Bzh nortriptyline **3.16i** was reacted with acetone-d_6 **3.17a** following the General Procedure B. After purification by column chromatography (Et_2O:hexanes = 1:9), **3.18i** was obtained as a yellow liquid (83 mg, 96%).

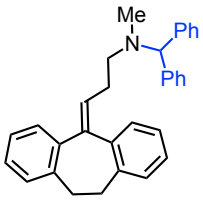
Deuterium incorporation: 1.96 D/molecule (^{1}H NMR), 2.34 D/molecule [HRMS (DART)]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, J = 7.6 Hz, 4H), 7.22 (dd, J = 8.4, 6.8 Hz, 5H), 7.20 – 7.09 (m, 7H), 7.09 – 7.04 (m, 1H), 7.03 (s, 1H), 5.81 (s, 1H), 4.30 (s, 1H), 3.27 (dt, J = 32.1, 23.1 Hz, 2H), 2.94 (s, 1H), 2.71 (s, 1H), 2.44 (d, J = 5.3 Hz, 2H), 2.30 (d, J = 7.5 Hz, 0.04H, 98%D), 2.07 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.25, 141.49, 140.18, 139.40, 137.07, 129.96, 129.76, 128.55, 128.36, 127.99, 127.31, 126.94, 126.78, 125.98, 125.72, 75.65, 54.89, 40.26, 33.79, 32.06; **IR** (neat) 3020, 2784, 1485, 1451, 1265, 1028, 1012, 924, 756, 742, 704 cm^{-1}.

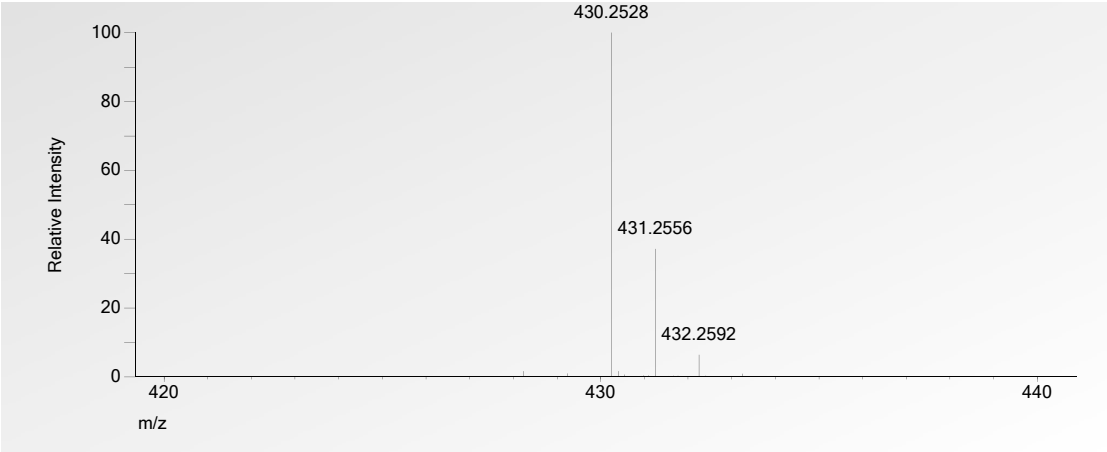

Me
N
Ph
Ph
[98%]

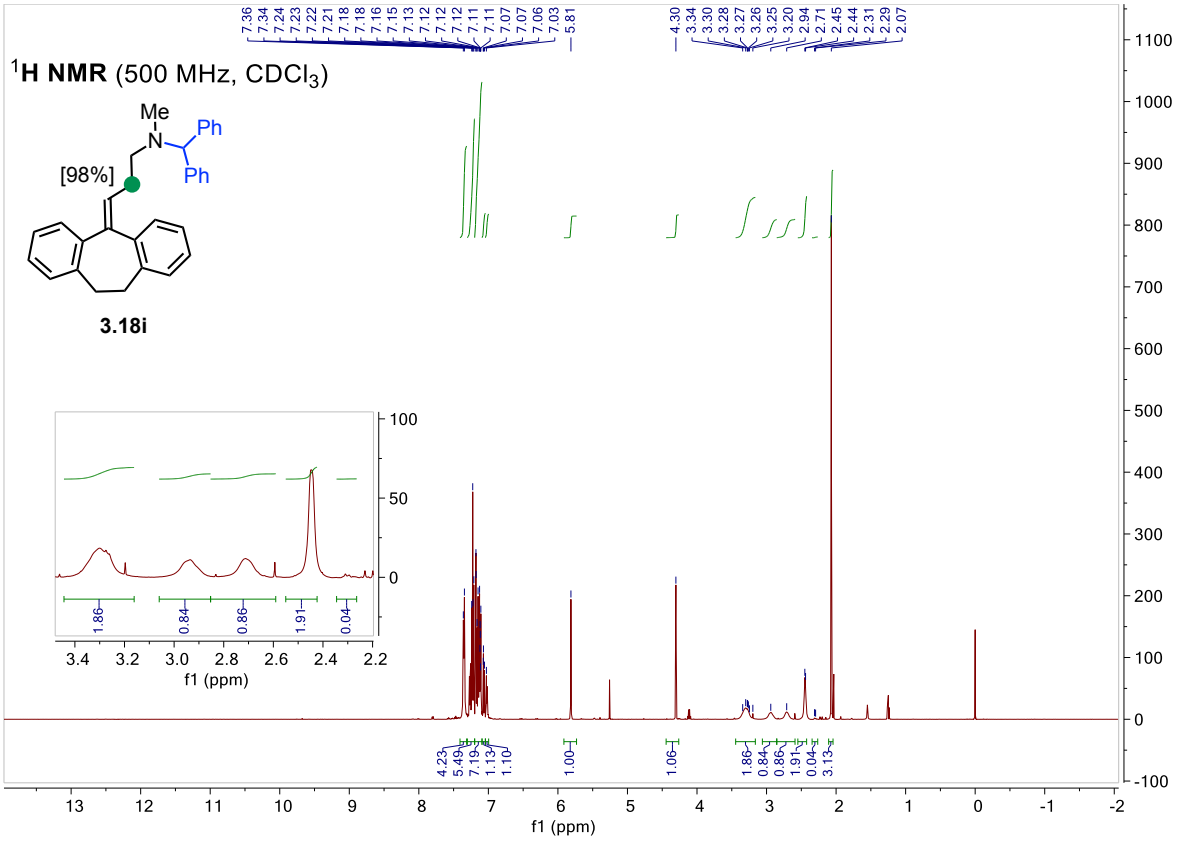
3.18i

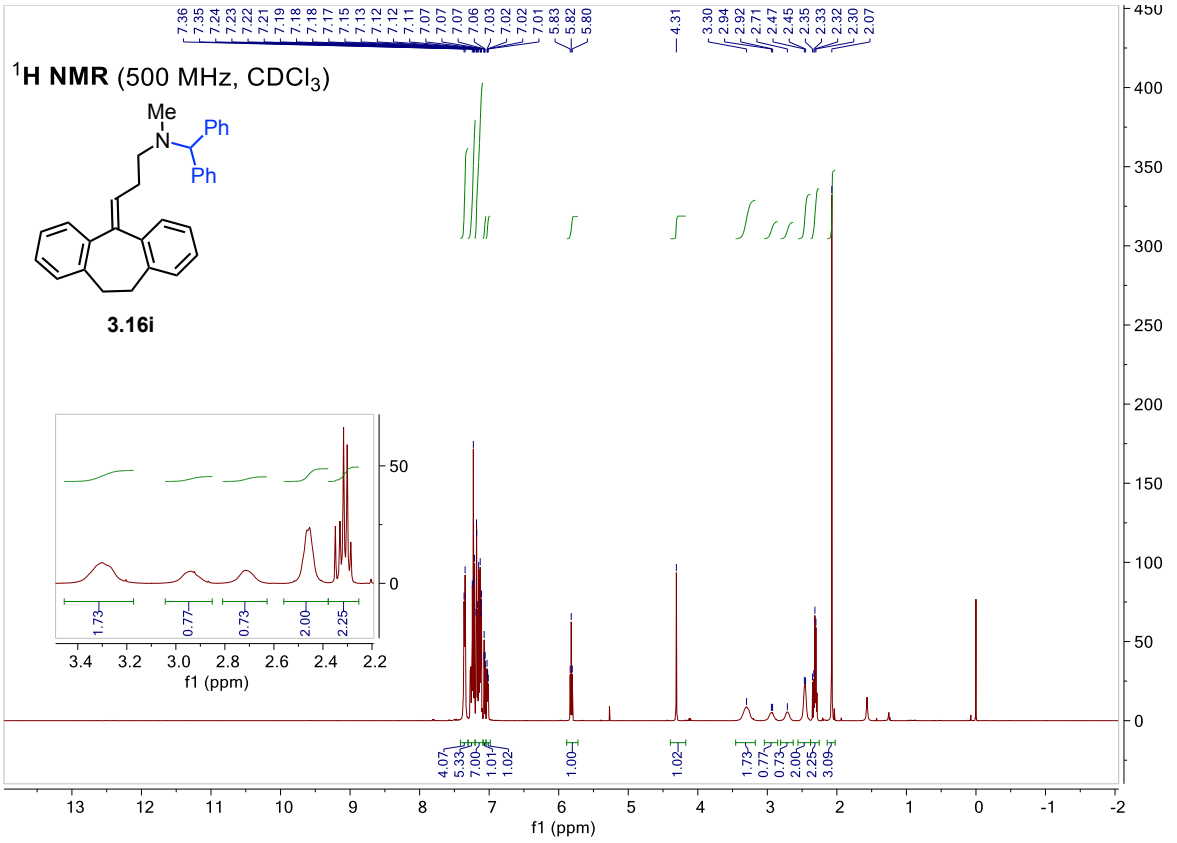

432.2644
433.2670
434.2703
430.2478
431.2565
435.2782
Relative Intensity
100
80
60
40
20
0
420
430
440
m/z

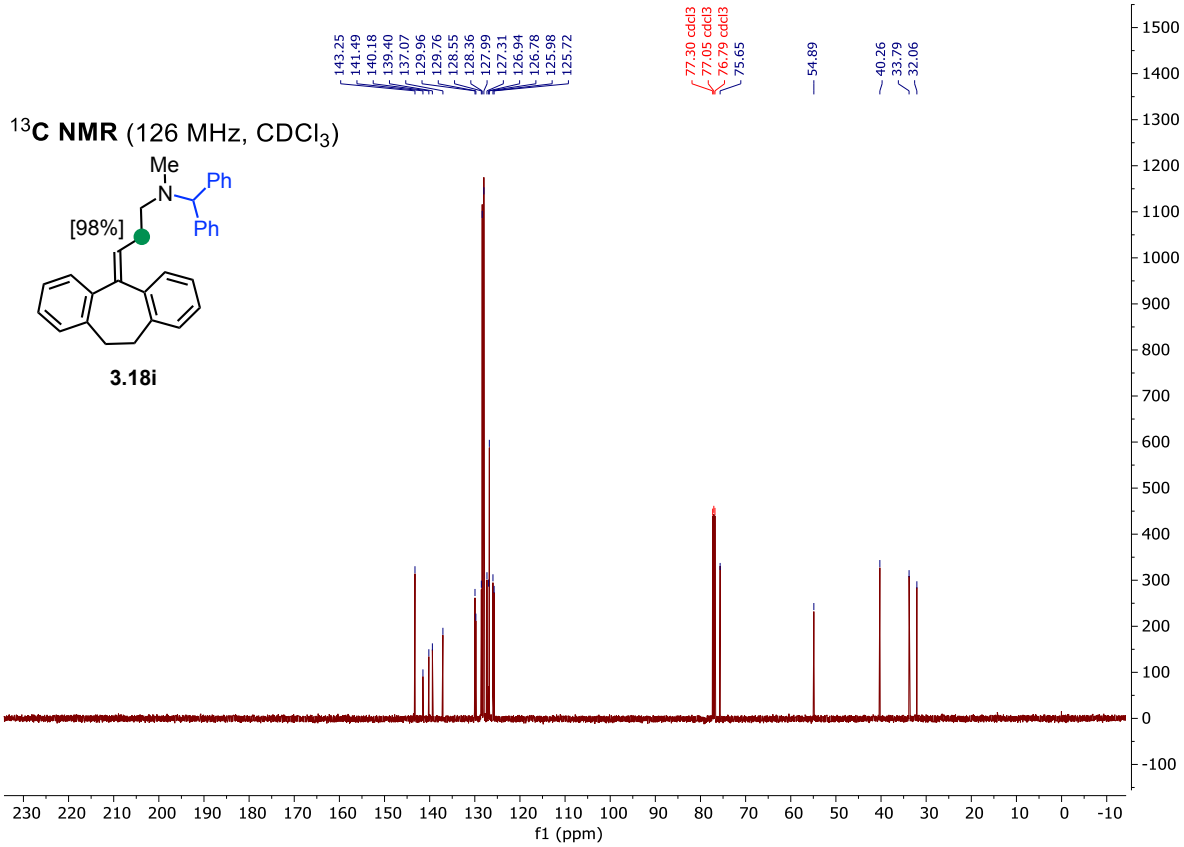

Me
N
Ph
Ph

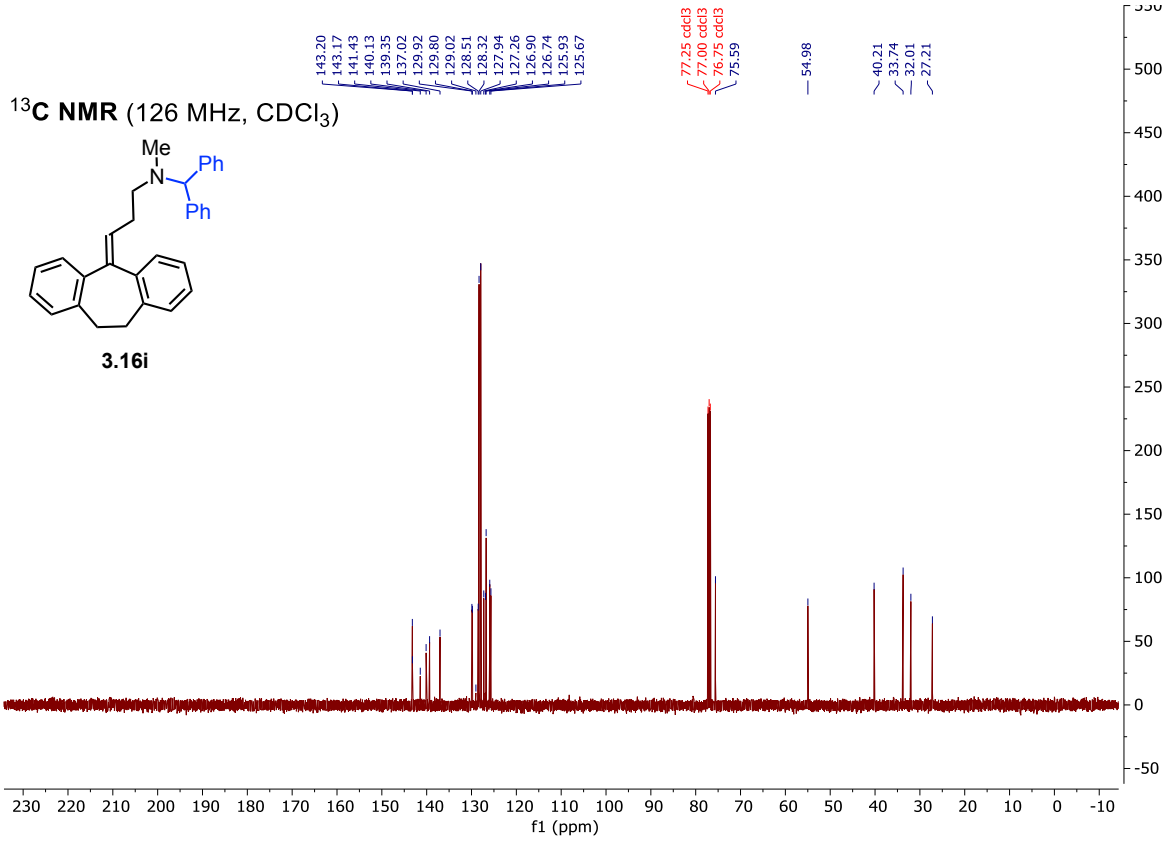
3.16i

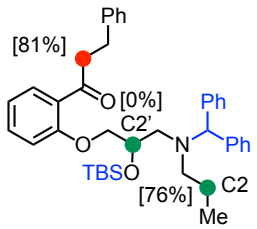

430.2528
431.2556
432.2592
Relative Intensity
100
80
60
40
20
0
420
430
440
m/z


1H NMR (500 MHz, CDCl3)
Me
N
Ph
Ph
[98%]
3.18i
f1 (ppm)


1H NMR (500 MHz, CDCl3)
Me
N
Ph
Ph
3.16i
f1 (ppm)


143.25
141.49
140.18
139.40
137.07
129.96
129.76
128.55
128.36
127.99
127.31
126.94
126.78
125.98
125.72
77.30 cdcl3
77.05 cdcl3
76.79 cdcl3
75.65
54.89
40.26
33.79
32.06
13C NMR (126 MHz, CDCl3)
Me
N
Ph
Ph
[98%]
3.18i
f1 (ppm)


143.20
143.17
141.43
140.13
139.35
137.02
129.92
129.80
129.02
128.51
128.32
127.94
127.26
126.90
126.74
125.93
125.67
77.25 cdcl3
77.00 cdcl3
76.75 cdcl3
75.59
54.98
40.21
33.74
32.01
27.21
13C NMR (126 MHz, CDCl3)
Me
N
Ph
Ph
3.16i
f1 (ppm)



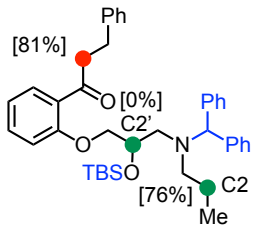
3.18j

***N*-Bzh, *O*-TBS propafenone, 3.18j**

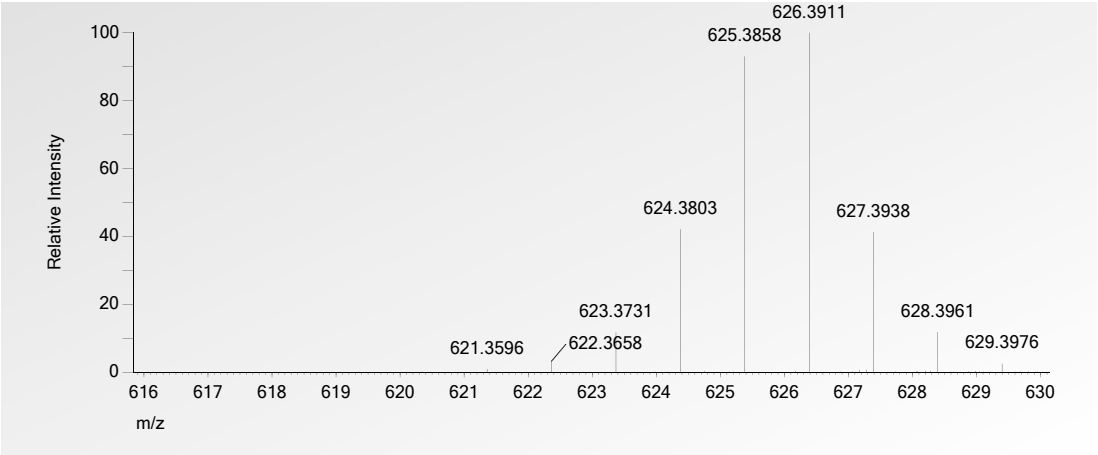
N-Bzh, *O*-TBS propafenone**3.16j** was reacted with acetone-d_6 **3.17a** following the General Procedure A. After purification by column chromatography (Et_2O:hexanes = 1:9), **3.18j** was obtained as a yellow liquid (114 mg, 92%).

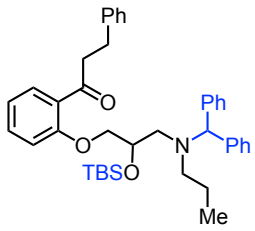
Deuterium incorporation: 3.14 D/molecule (^{1}H NMR), 3.51 D/molecule [HRMS (DART)]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 9.4 Hz, 1H), 7.47 – 7.40 (m, 1H), 7.27 (d, *J* = 7.1 Hz, 2H), 7.23 (d, *J* = 7.6 Hz, 4H), 7.20 – 7.08 (m, 9H), 6.99 (dd, *J* = 15.9, 8.8 Hz, 2H), 4.81 (s, 1H), 4.18 (d, *J* = 3.8 Hz, 1H), 4.11 (d, *J* = 3.3 Hz, 1H), 3.92 (dd, *J* = 8.7, 4.3 Hz, 1H), 3.35 – 3.18 (m, 0.19H, 81%D), 3.11 – 2.97 (m, 0.24H, 76%D), 2.91 (d, *J* = 11.4 Hz, 2H), 2.79 (dd, *J* = 13.5, 8.9 Hz, 1H), 2.55 (dd, *J* = 13.5, 4.6 Hz, 1H), 2.51 – 2.38 (m, 2H), 1.50 – 1.35 (m, 0.50H, 76%D), 0.79 (s, 9H), 0.75 – 0.66 (m, 3H), -0.06 (s, 3H), -0.09 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 201.37, 201.31, 158.22, 142.07, 141.66, 141.53, 133.33, 130.47, 128.78, 128.68, 128.45, 128.35, 128.26, 128.22, 128.16, 128.13, 126.92, 126.89, 125.69, 120.48, 112.34, 71.19, 70.48, 69.93, 54.24, 53.87, 45.04, 29.91, 25.72, 19.04, 17.93, 11.53, -4.66, -4.83; **IR** (neat) 2950, 2926, 1669, 1595, 1470, 1293, 1248, 1113, 833, 747, 699 cm^{-1}.

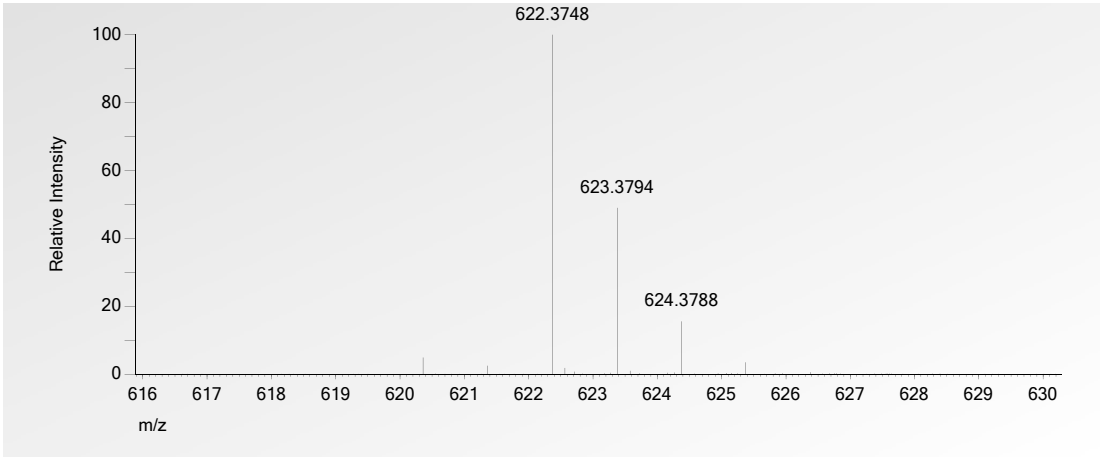

Ph
[81%]
O
[0%]
C2'
Ph
N
Ph
O
TBSO
[76%]
C2
Me

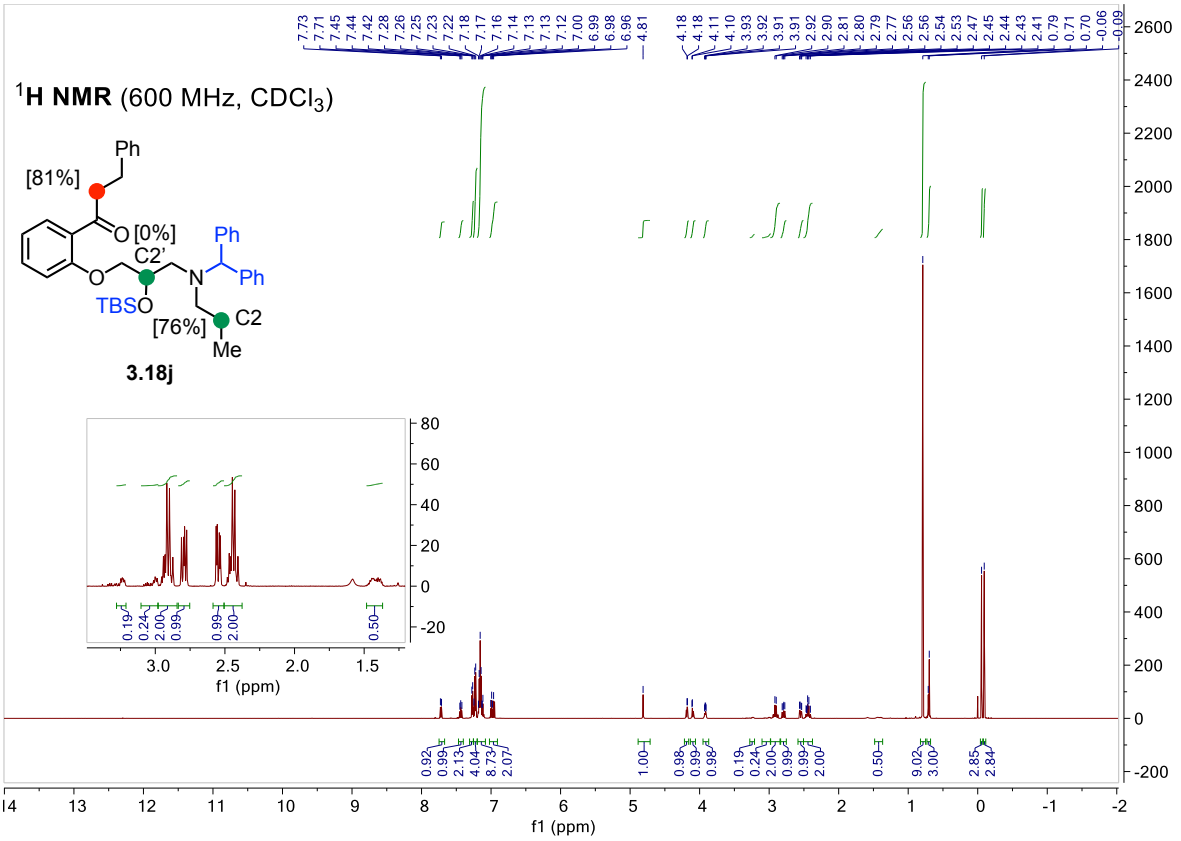
3.18j

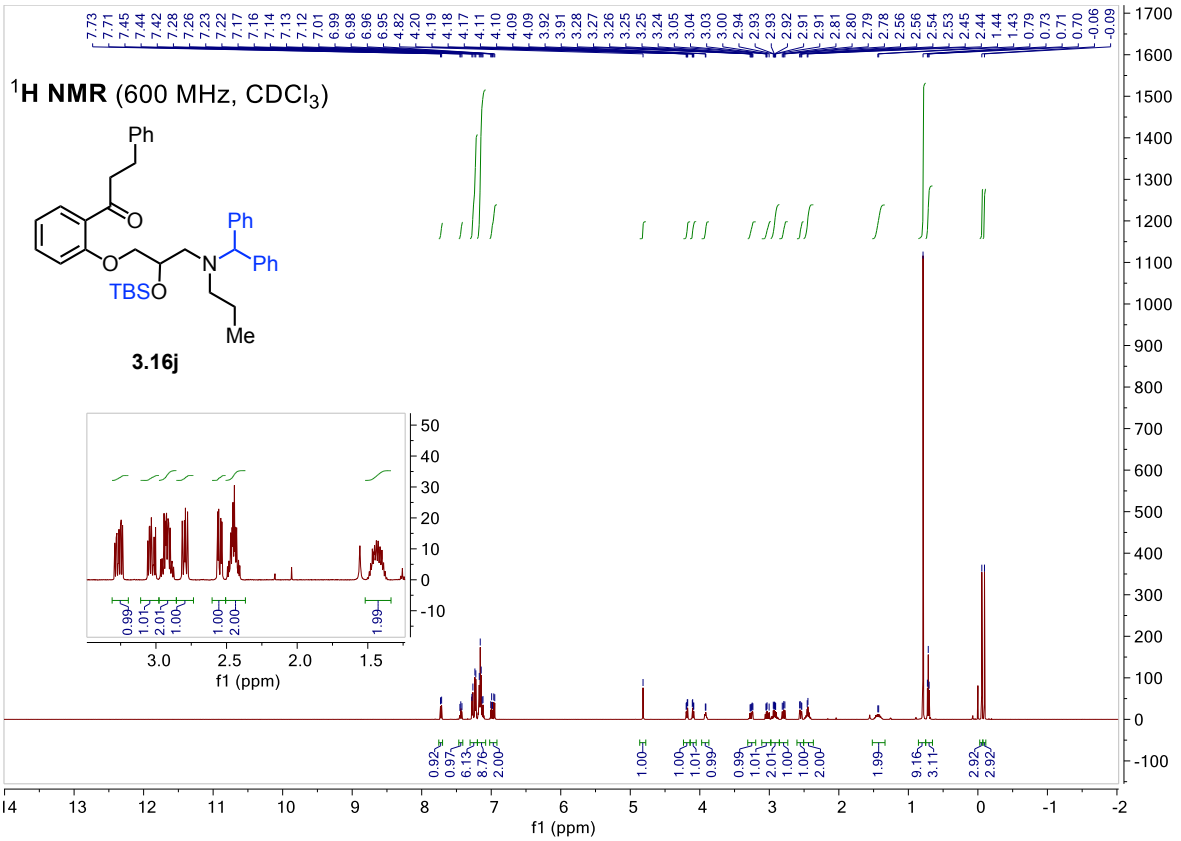

626.3911
625.3858
624.3803
627.3938
623.3731
628.3961
621.3596
622.3658
629.3976
Relative Intensity
m/z

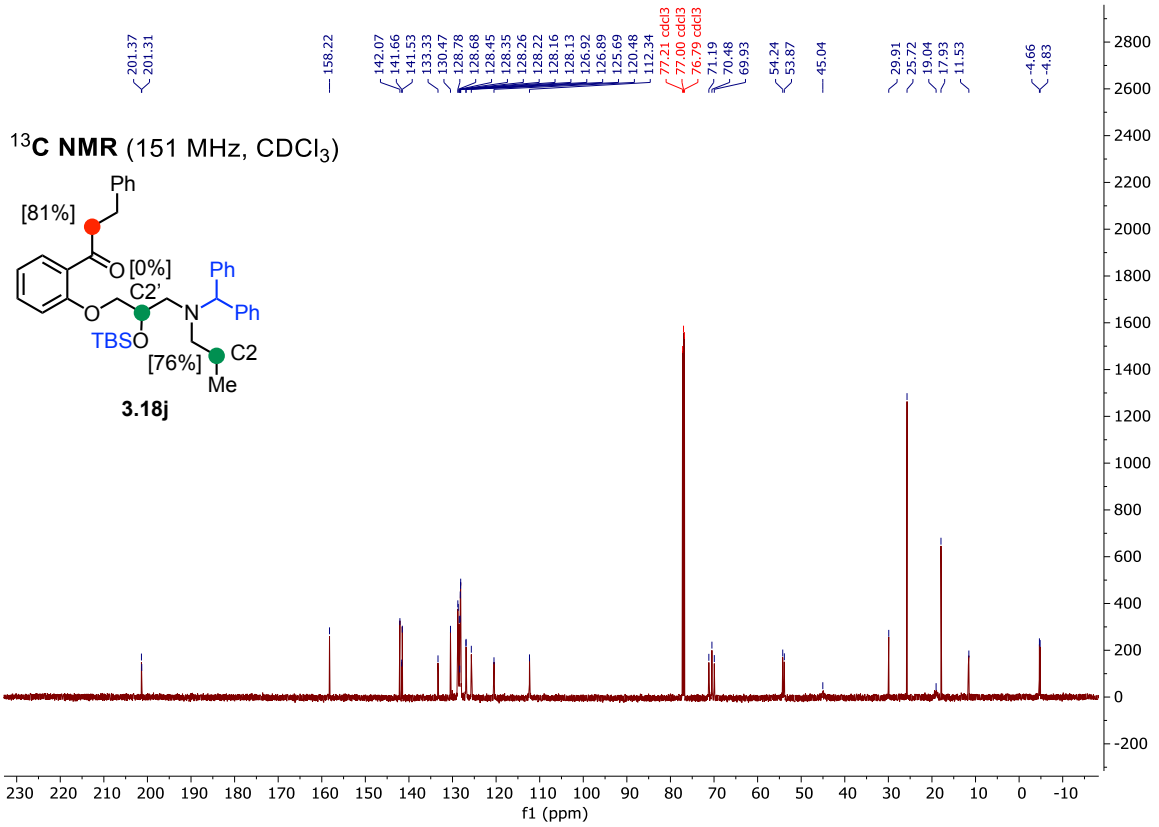

Ph
O
Ph
N
Ph
O
TBSO
Me

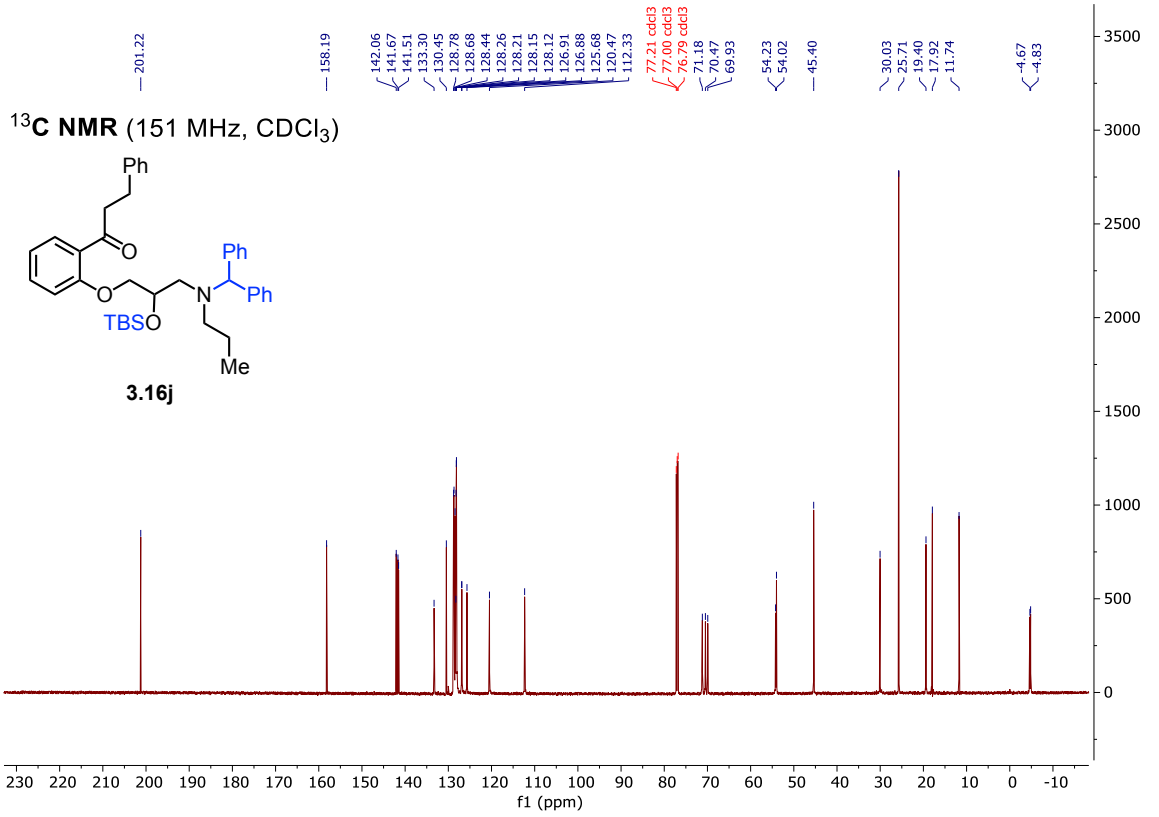
3.16j

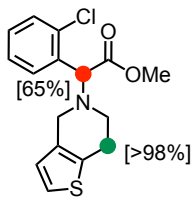

622.3748
623.3794
624.3788
Relative Intensity
m/z


^{1}H NMR (600 MHz, $CDCl_3$)
Ph
[81%]
O
[0%]
C2'
Ph
N
Ph
TBSO
[76%]
C2
Me
3.18j
f1 (ppm)


^{1}H NMR (600 MHz, $CDCl_3$)
Ph
O
Ph
N
Ph
TBSO
Me
3.16j
f1 (ppm)


201.37
201.31
158.22
142.07
141.66
141.53
133.33
130.47
128.78
128.68
128.45
128.35
128.26
128.22
128.16
128.13
126.92
126.89
125.69
120.48
112.34
77.21 cdcl3
77.00 cdcl3
76.79 cdcl3
71.19
70.48
69.93
54.24
53.87
45.04
29.91
25.72
19.04
17.93
11.53
-4.66
-4.83
13C NMR (151 MHz, CDCl3)
Ph
[81%]
O
[0%]
C2'
Ph
N
Ph
TBSO
[76%]
C2
Me
3.18j
f1 (ppm)


201.22
158.19
142.06
141.67
141.51
133.30
130.45
128.78
128.68
128.44
128.26
128.21
128.15
128.12
126.91
126.88
125.68
120.47
112.33
77.21 cdcl3
77.00 cdcl3
76.79 cdcl3
71.18
70.47
69.93
54.23
54.02
45.40
30.03
25.71
19.40
17.92
11.74
-4.67
-4.83
13C NMR (151 MHz, CDCl3)
Ph
O
Ph
N
Ph
TBSO
Me
3.16j
f1 (ppm)



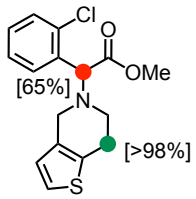
3.18k

Clopidogrel, 3.18k

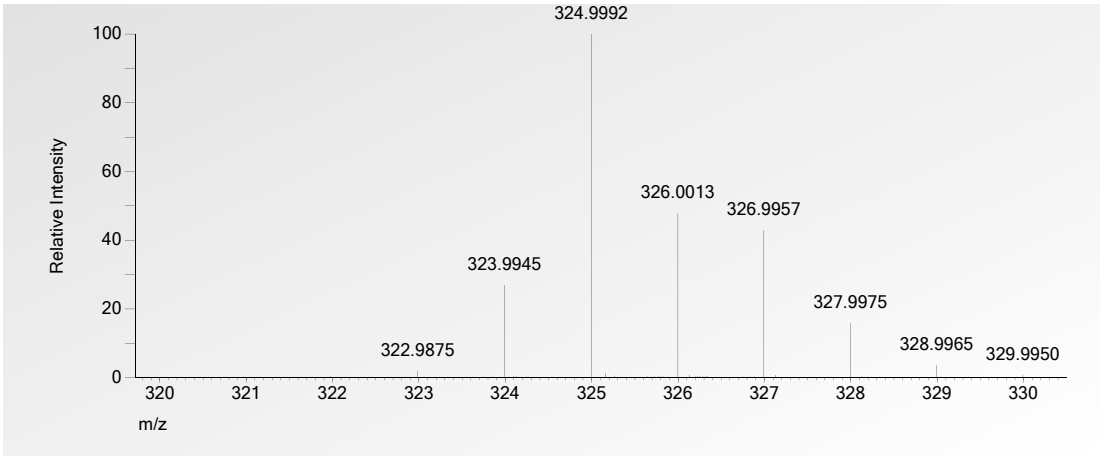
Clopidogrel **3.16k** was reacted with acetone-d_6 **3.17a** following the General Procedure B. After purification by column chromatography (Et_2O:hexanes = 1:9), **3.18k** was obtained as a colorless liquid (61 mg, 94%).

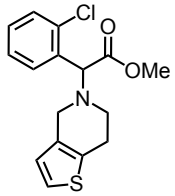
Deuterium incorporation: 2.65 D/molecule (^{1}H NMR), 2.88 D/molecule [HRMS (DART)]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J = 7.4 Hz, 1H), 7.40 (d, J = 7.5 Hz, 1H), 7.36 – 7.18 (m, 2H), 7.11 – 7.00 (m, 1H), 6.75 – 6.59 (m, 1H), 4.92 (d, J = 2.0 Hz, 0.35H, 65%D), 3.79 – 3.70 (m, 4H), 3.63 (d, J = 14.2 Hz, 1H), 2.88 (s, 2.00H, >98%D); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.33, 134.71, 133.82, 133.41, 133.14, 129.99, 129.80, 129.43, 127.15, 125.24, 122.77, 67.92, 52.14, 50.70, 50.65, 48.17, 48.12, 25.07; **IR** (neat) 2947, 1735, 1469, 1431, 1245, 1140, 1105, 1064, 752, 704 cm^{-1}; $[\alpha]^{25}_D$ = 0.7° (c = 1.0, CH_2Cl_2 labeled), $[\alpha]^{25}_D$ = 15.0° (c = 1.0, CH_2Cl_2 unlabeled).

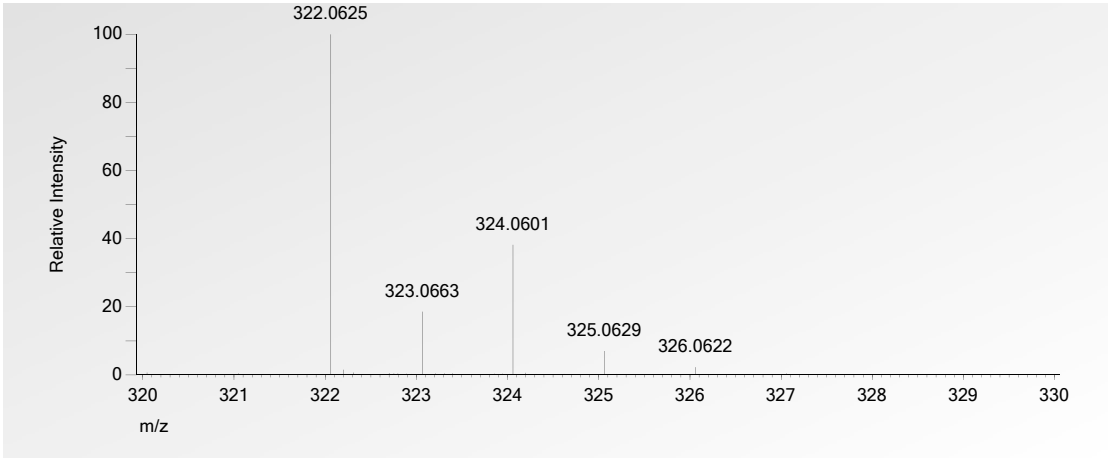

Cl
O
OMe
[65%]
N
[>98%]
S

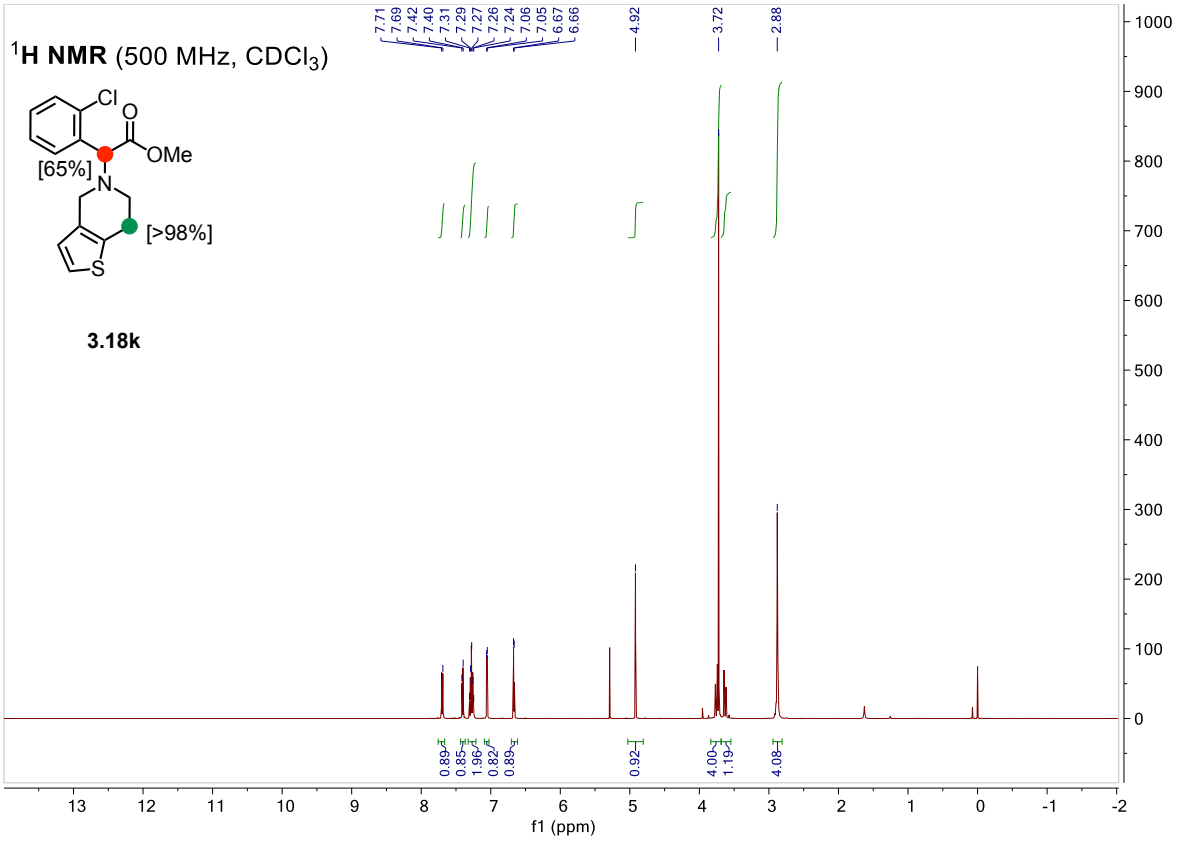
3.18k

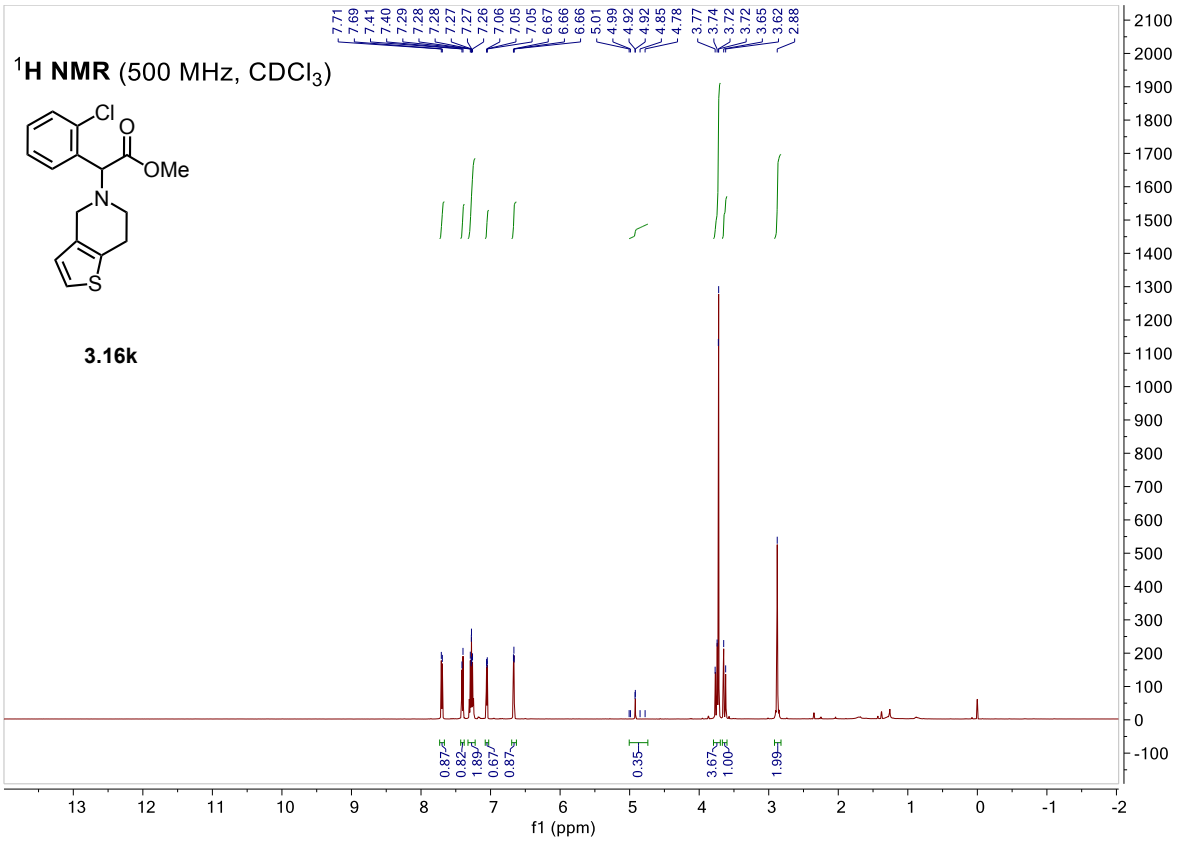

324.9992
100
80
60
40
20
0
Relative Intensity
326.0013
326.9957
323.9945
327.9975
322.9875
328.9965
329.9950
320
321
322
323
324
325
326
327
328
329
330
m/z

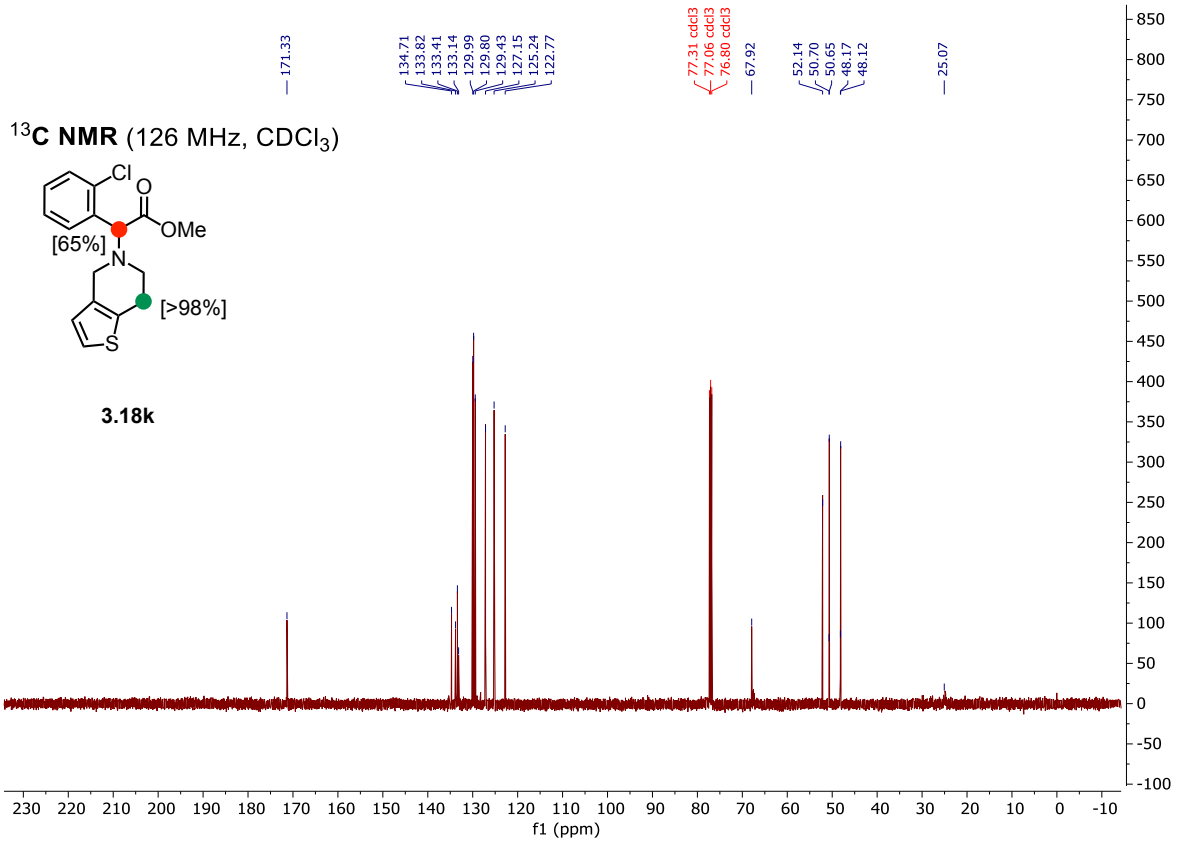

Cl
O
OMe
N
S

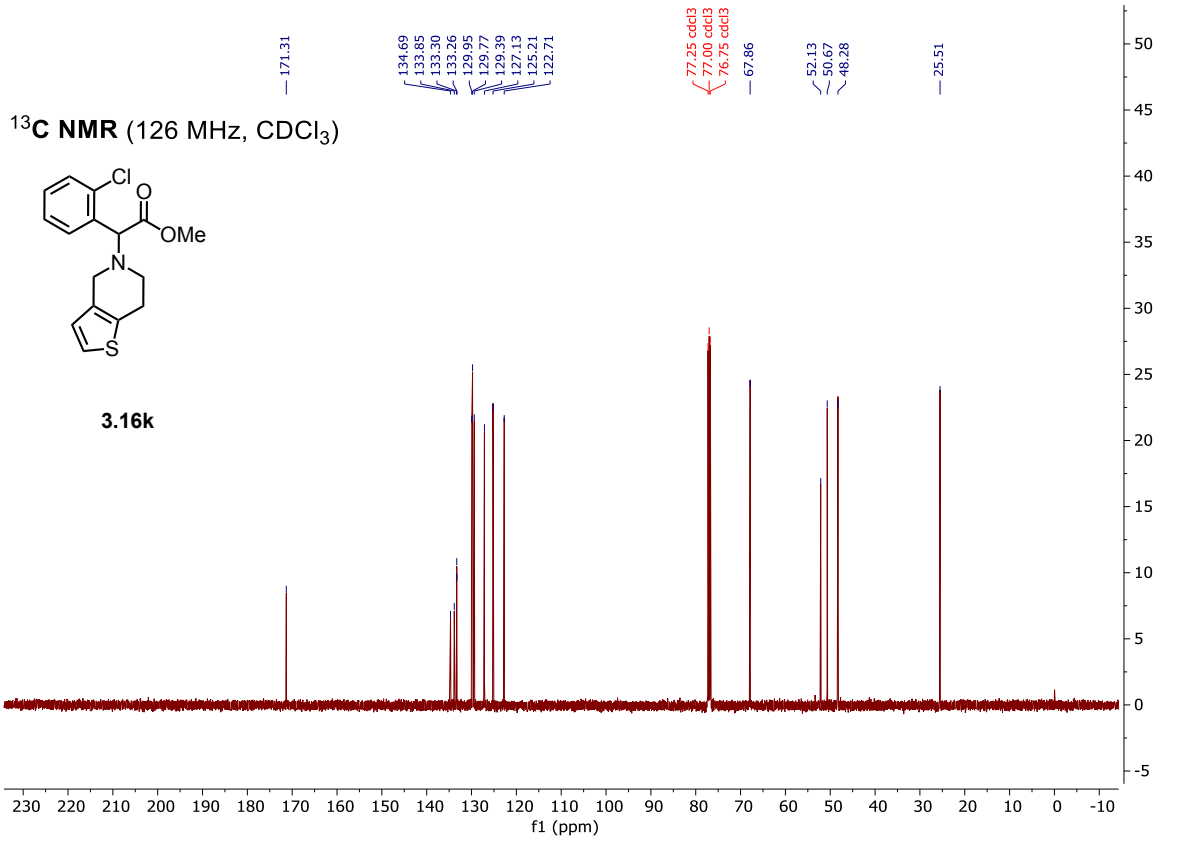
3.16k

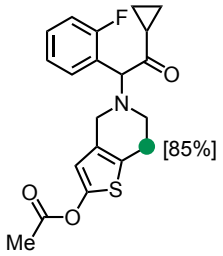

322.0625
100
80
60
40
20
0
Relative Intensity
324.0601
323.0663
325.0629
326.0622
320
321
322
323
324
325
326
327
328
329
330
m/z


1H NMR (500 MHz, CDCl3)
Cl
O
OMe
[65%]
N
[>98%]
S
3.18k
7.71
7.69
7.42
7.40
7.31
7.29
7.27
7.26
7.24
7.06
7.05
6.67
6.66
4.92
3.72
2.88
0.89
0.85
1.96
0.82
0.89
0.92
4.00
1.19
4.08
f1 (ppm)


1H NMR (500 MHz, CDCl3)
Cl
O
OMe
N
S
3.16k
7.71
7.69
7.41
7.40
7.29
7.28
7.28
7.27
7.27
7.26
7.06
7.05
7.05
6.67
6.66
6.66
5.01
4.99
4.92
4.92
4.85
4.78
3.77
3.74
3.72
3.72
3.65
3.62
2.88
0.87
0.82
1.89
0.67
0.87
0.35
3.67
1.00
1.99
f1 (ppm)


171.33
134.71
133.82
133.41
133.14
129.99
129.80
129.43
127.15
125.24
122.77
77.31 cdcl3
77.06 cdcl3
76.80 cdcl3
67.92
52.14
50.70
50.65
48.17
48.12
25.07
13C NMR (126 MHz, CDCl3)
Cl
O
OMe
[65%]
N
[>98%]
S
3.18k
f1 (ppm)


171.31
134.69
133.85
133.30
133.26
129.95
129.77
129.39
127.13
125.21
122.71
77.25 cdcl3
77.00 cdcl3
76.75 cdcl3
67.86
52.13
50.67
48.28
25.51
13C NMR (126 MHz, CDCl3)
Cl
O
OMe
N
S
3.16k
f1 (ppm)



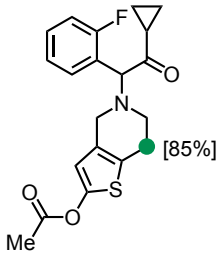
3.18l

Prasugrel, 3.18l

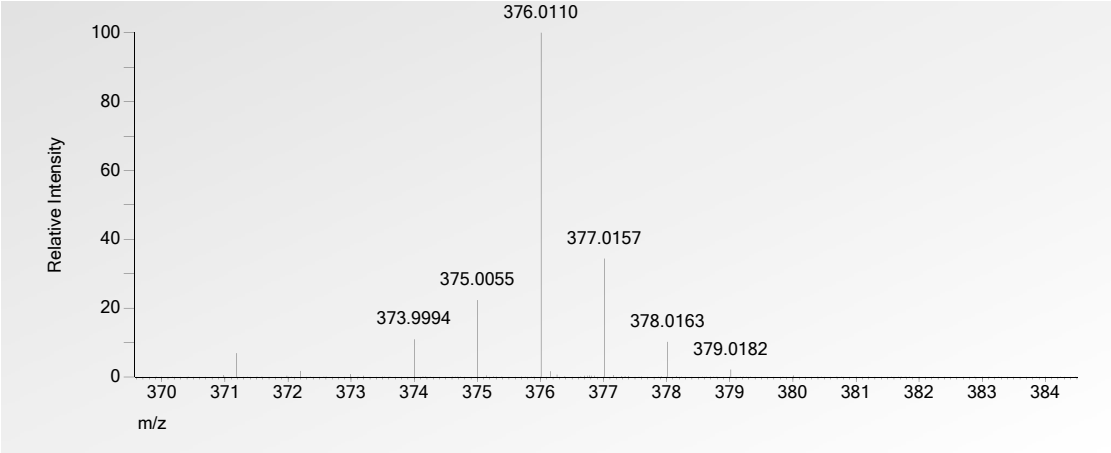
Prasugrel **3.16l** was reacted with acetone-d_6 **3.17a** following the General Procedure C. After purification by column chromatography (Et_2O:hexanes = 1:19), **3.18l** was obtained as a white solid (64 mg, 85%).

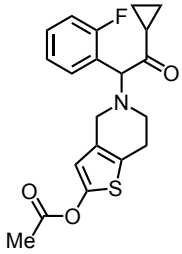
Deuterium incorporation: 1.70 D/molecule (^{1}H NMR), 1.99 D/molecule [HRMS (DART)]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.31 (s, 1H), 7.17 (s, 1H), 7.11 (s, 1H), 6.26 (s, 1H), 4.83 (s, 1H), 3.63 – 3.43 (m, 2H), 2.89 (d, *J* = 11.5 Hz, 1H), 2.75 (d, *J* = 11.4 Hz, 1.30H, 85%D), 2.25 (s, 4H), 1.03 (dd, *J* = 26.7, 2.8 Hz, 2H), 0.85 (d, *J* = 2.7 Hz, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 207.64, 167.71, 162.11, 160.47, 149.51, 130.55, 129.89, 129.83, 129.45, 125.59, 124.37, 124.35, 122.08, 121.99, 115.86, 115.71, 112.00, 111.96, 71.61, 71.56, 50.50, 50.48, 50.46, 48.26, 25.01, 20.65, 18.30, 12.06, 11.45; **^{19}F NMR** (564 MHz, $CDCl_3$) δ -114.68 – -118.69 (m); **IR** (neat) 1776, 1758, 1698, 1486, 1454, 1369, 1191, 1086, 1037, 1008, 903, 759 cm^{-1}.

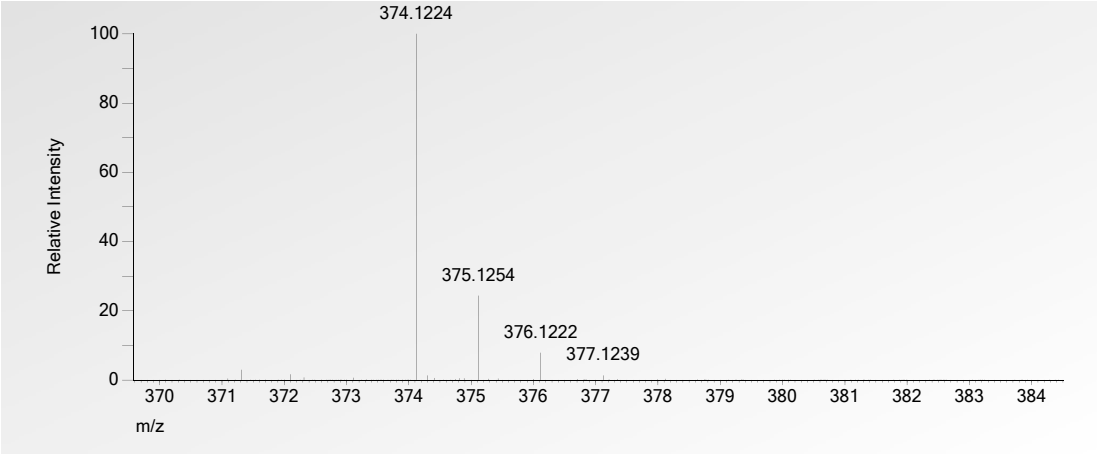

F
O
N
[85%]
S
O
O
Me

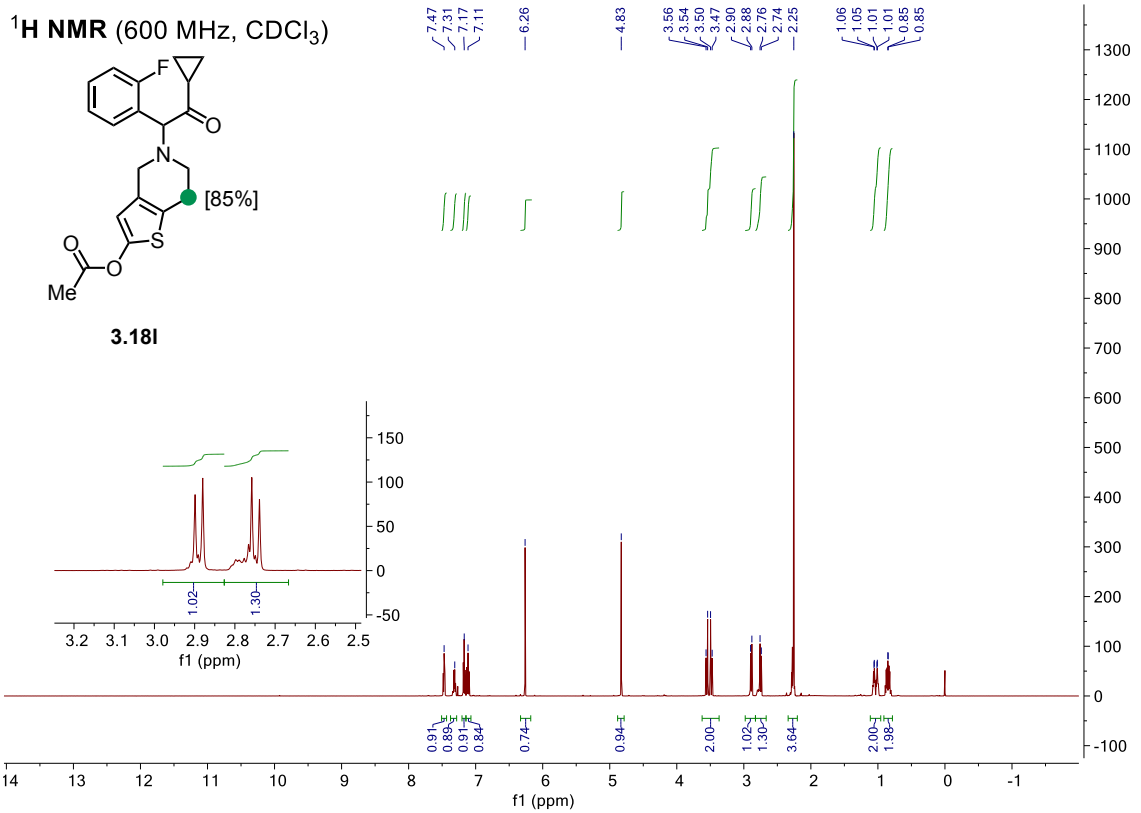
3.18l

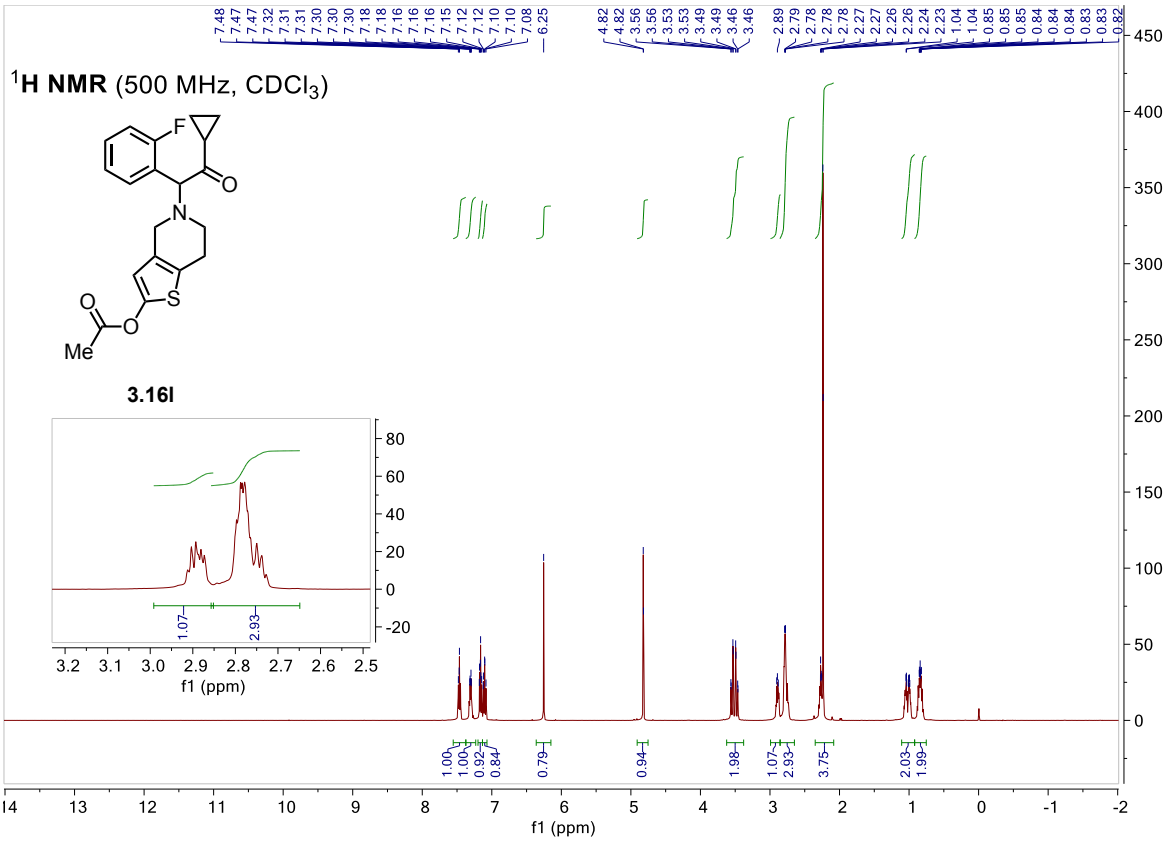

376.0110
100
80
60
40
20
0
Relative Intensity
377.0157
375.0055
373.9994
378.0163
379.0182
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
m/z

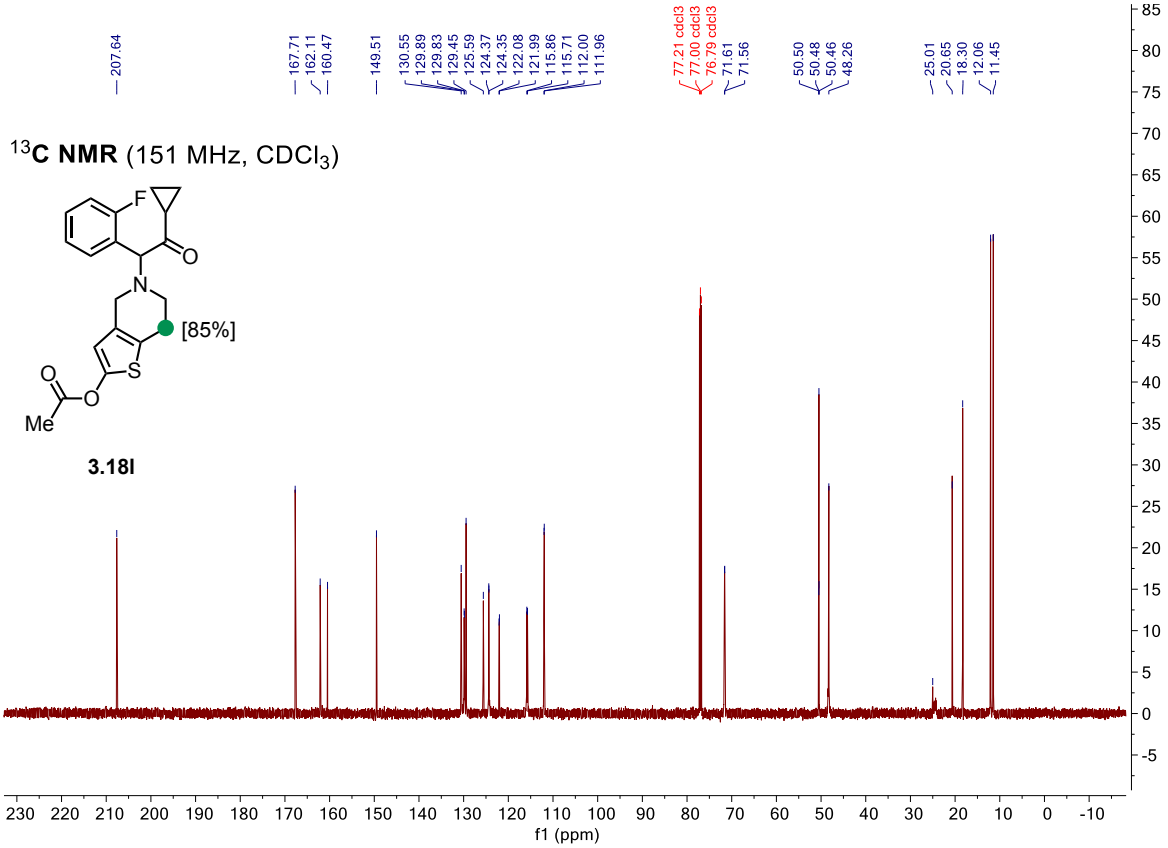

F
O
N
S
O
O
Me

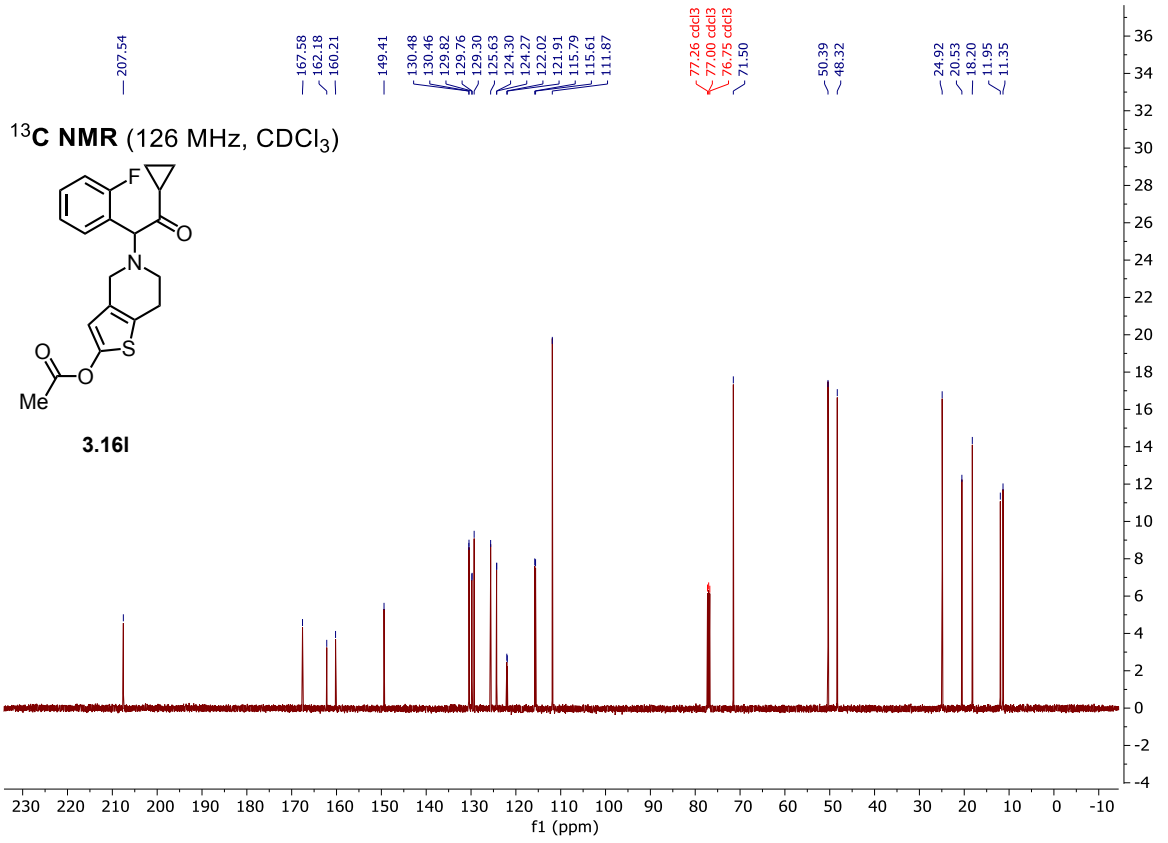
3.16l

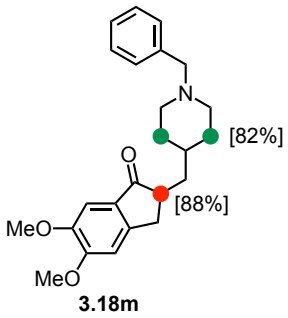

374.1224
100
80
60
40
20
0
Relative Intensity
375.1254
376.1222
377.1239
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
m/z


1H NMR (600 MHz, CDCl3)
F
O
N
[85%]
S
O
O
Me
3.18l
f1 (ppm)


1H NMR (500 MHz, CDCl3)
F
O
N
S
O
O
Me
3.16l
f1 (ppm)


13C NMR (151 MHz, CDCl3)
[85%]
3.18l
f1 (ppm)


13C NMR (126 MHz, CDCl3)
3.16l
f1 (ppm)



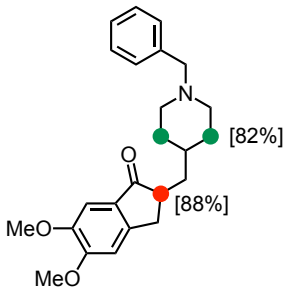
3.18m

Donepezil, 3.18m

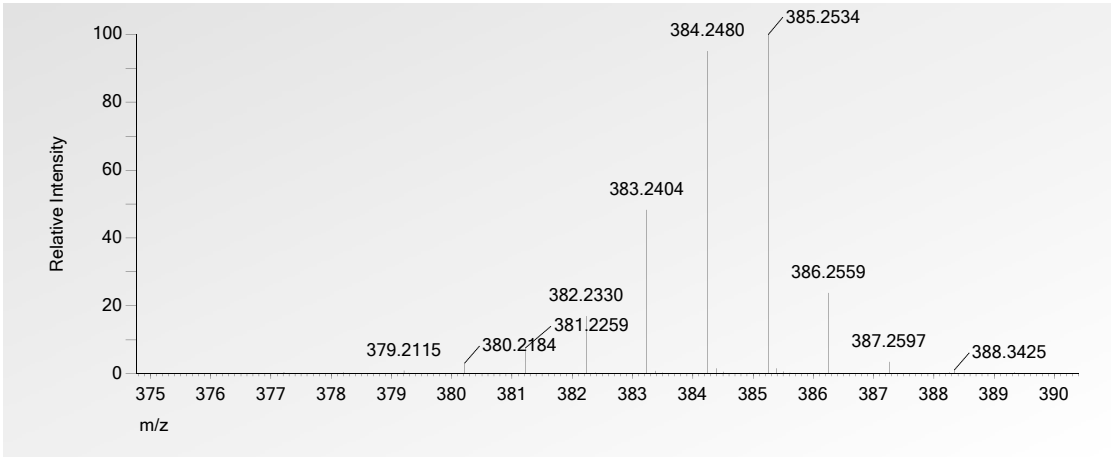
Donepezil **3.16m** was reacted with acetone-d_6 **3.17a** following the General Procedure A. After purification by column chromatography (MeOH:DCM = 1:49), **3.18m** was obtained as a white solid (74 mg, 98%).

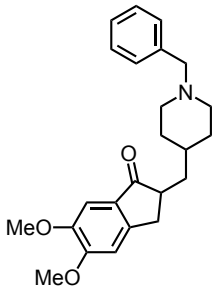
Deuterium incorporation: 5.04 D/molecule (^{1}H NMR), 4.17 D/molecule [HRMS (DART)]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 (d, J = 7.5 Hz, 2H), 7.34 (t, J = 7.4 Hz, 2H), 7.30 (d, J = 7.1 Hz, 1H), 7.16 (s, 1H), 6.85 (s, 1H), 3.96 (s, 3H), 3.90 (s, 3H), 3.67 (s, 2H), 3.24 (d, J = 16.9 Hz, 1H), 3.02 (d, J = 10.6 Hz, 2H), 2.68 (d, J = 16.9 Hz, 1.12H, 88%D), 2.15 (s, 2H), 1.89 (dd, J = 13.8, 7.6 Hz, 1H), 1.78–1.70 (m, 0.25H, 88%D), 1.59 (s, 1H), 1.56–1.44 (m, 0.49H, 75%D), 1.43 – 1.32 (m, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 207.59, 155.48, 149.42, 148.73, 136.16, 129.74, 129.18, 128.37, 127.64, 107.32, 104.31, 62.71, 56.02, 53.12, 45.15, 38.34, 33.33; **IR** (neat) 2913, 1691, 1590, 1499, 1454, 1310, 1269, 1247, 1218, 1114, 727 cm^{-1}.

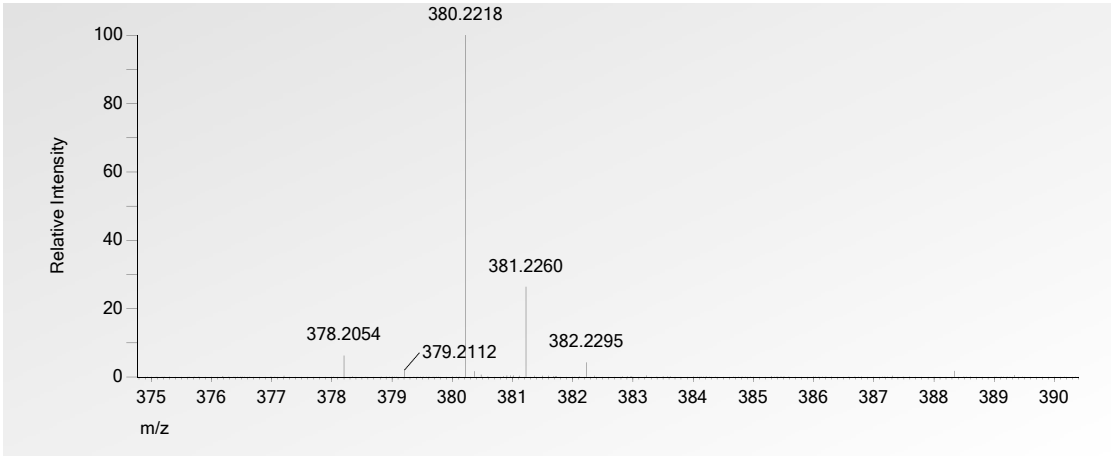

N
[82%]
O
[88%]
MeO
MeO

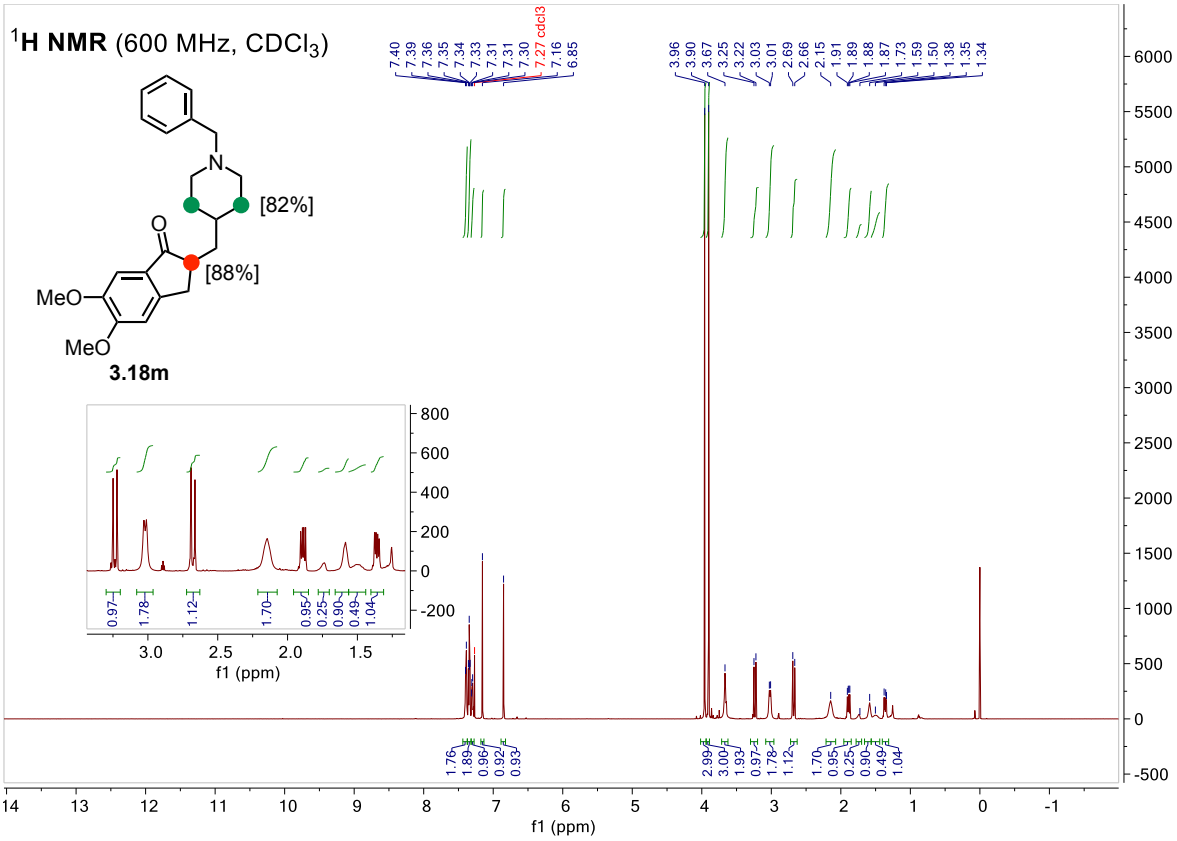
3.18m

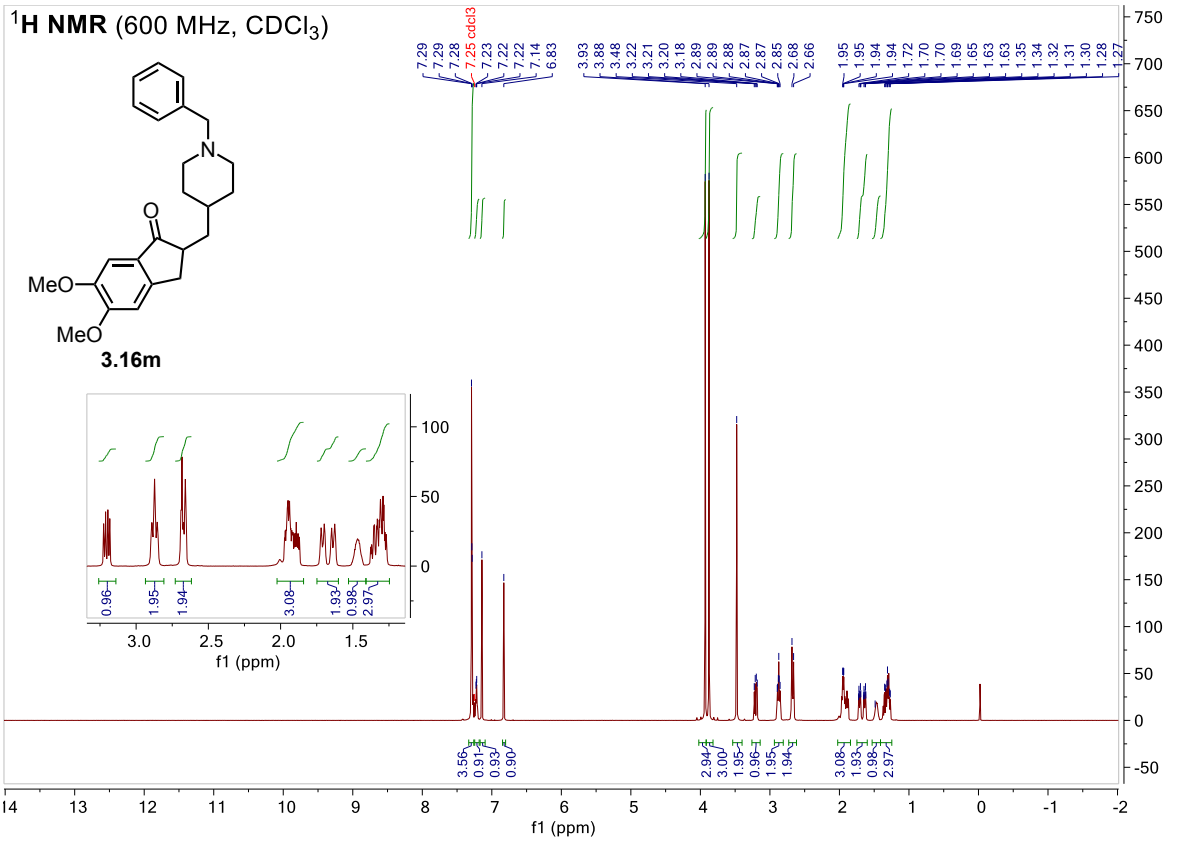

Relative Intensity
m/z
384.2480
385.2534
383.2404
386.2559
382.2330
381.2259
379.2115
380.2184
387.2597
388.3425

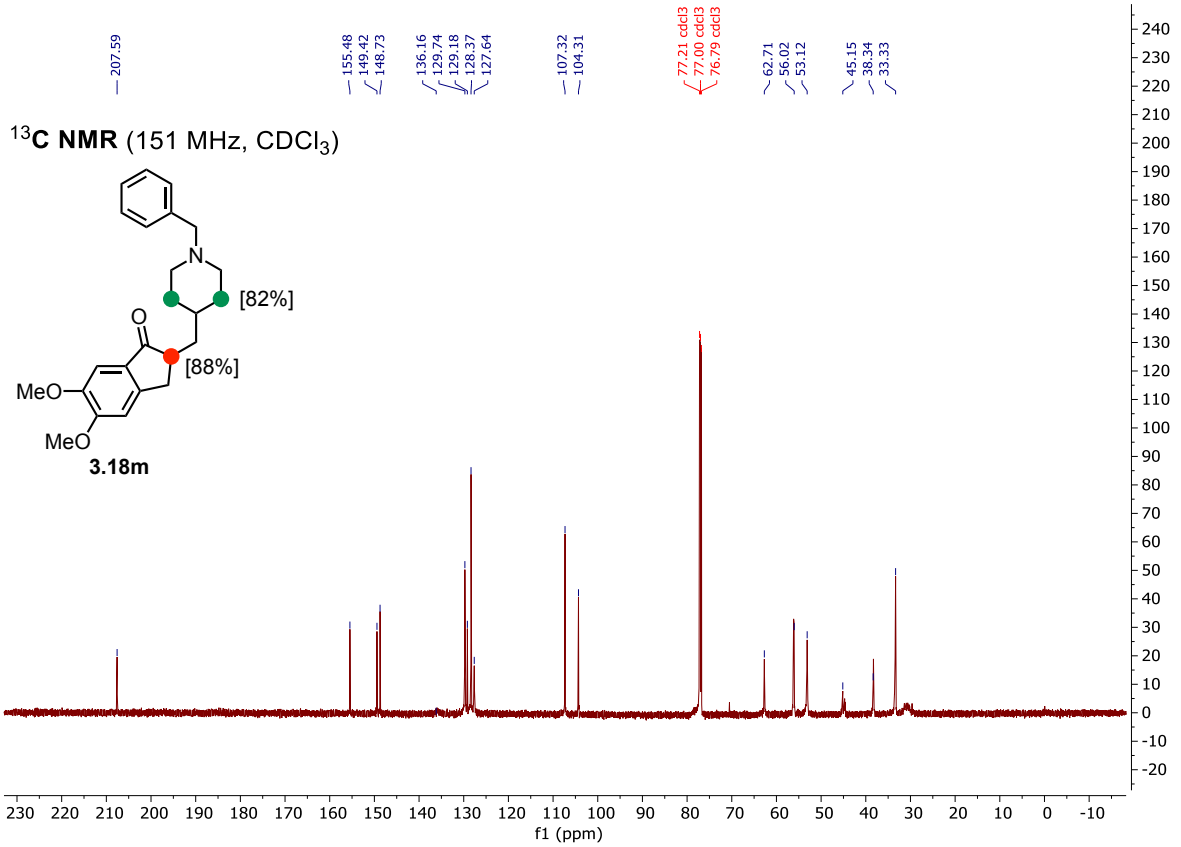

N
O
MeO
MeO

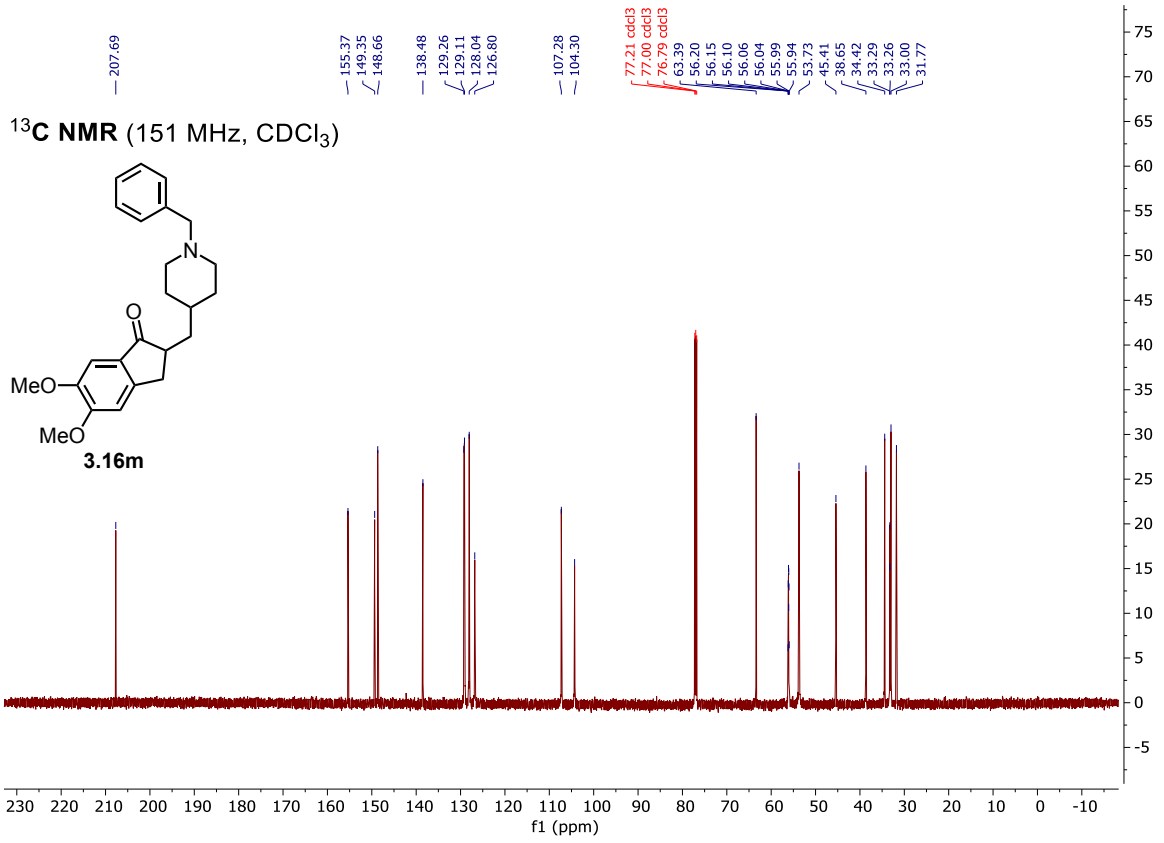
3.16m

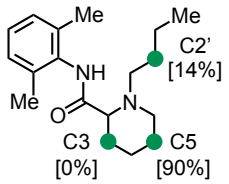

Relative Intensity
m/z
380.2218
381.2260
378.2054
379.2112
382.2295


1H NMR (600 MHz, CDCl3)
[82%]
[88%]
MeO
MeO
3.18m
f1 (ppm)


1H NMR (600 MHz, CDCl3)
MeO
MeO
3.16m
f1 (ppm)


207.59
155.48
149.42
148.73
136.16
129.74
129.18
128.37
127.64
107.32
104.31
77.21 cdcl3
77.00 cdcl3
76.79 cdcl3
62.71
56.02
53.12
45.15
38.34
33.33
13C NMR (151 MHz, CDCl3)
[82%]
[88%]
MeO
MeO
3.18m
f1 (ppm)


207.69
155.37
149.35
148.66
138.48
129.26
129.11
128.04
126.80
107.28
104.30
77.21 cdcl3
77.00 cdcl3
76.79 cdcl3
63.39
56.20
56.15
56.10
56.06
56.04
55.99
55.94
53.73
45.41
38.65
34.42
33.29
33.26
33.00
31.77
13C NMR (151 MHz, CDCl3)
MeO
MeO
3.16m
f1 (ppm)



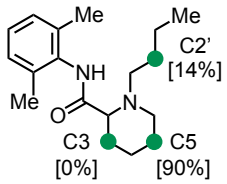
3.18n

Bupivacaine, 3.18n

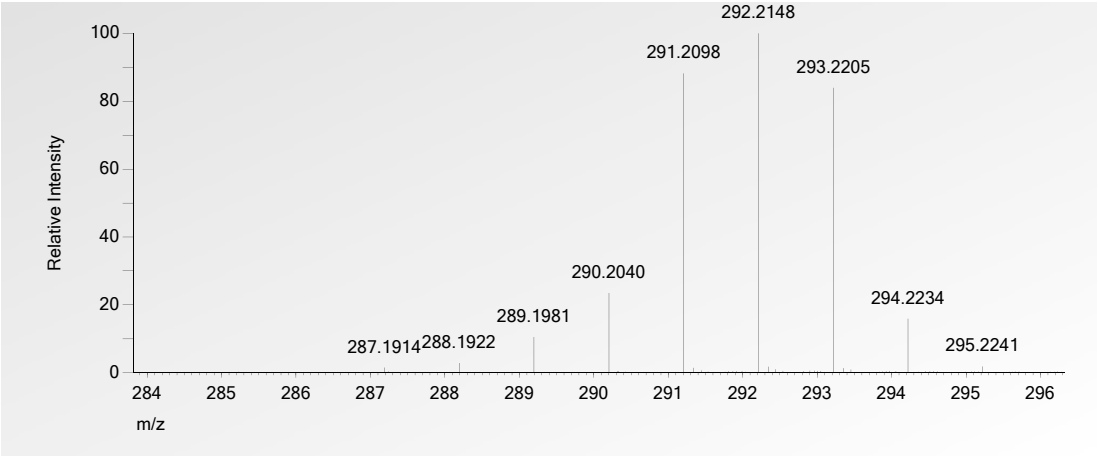
Bupivacaine **3.16n** was reacted with acetone-d_6 **3.17a** following the General Procedure A. After purification by column chromatography (MeOH:DCM = 1:49), **3.18n** was obtained as a white solid (55 mg, 96%).

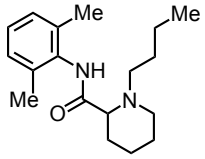
Deuterium incorporation: 2.08 D/molecule (^{1}H NMR), 2.83 D/molecule [HRMS (DART)]

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.06 (d, J = 5.5 Hz, 3H), 3.18 (d, J = 11.6 Hz, 1H), 2.92 (d, J = 9.3 Hz, 1H), 2.86 – 2.74 (m, 1H), 2.31 – 2.17 (m, 7H), 2.11 – 2.01 (m, 2H), 1.77 – 1.66 (m, 2.2H, 80%D), 1.65 – 1.54 (m, 0.86H, 14%D), 1.54 – 1.39 (m, 0.85H, 15%D and >98%D), 1.41 – 1.24 (m, 3H), 0.91 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.67, 135.20, 133.57, 128.20, 126.99, 68.28, 57.37, 57.29, 51.48, 51.40, 30.44, 29.45, 23.91, 23.11, 20.55, 20.45, 20.35, 18.60, 13.99; **IR** (neat) 3224, 2952, 2927, 2855, 1650, 1513, 1463, 1228, 1097, 764 cm^{-1}.

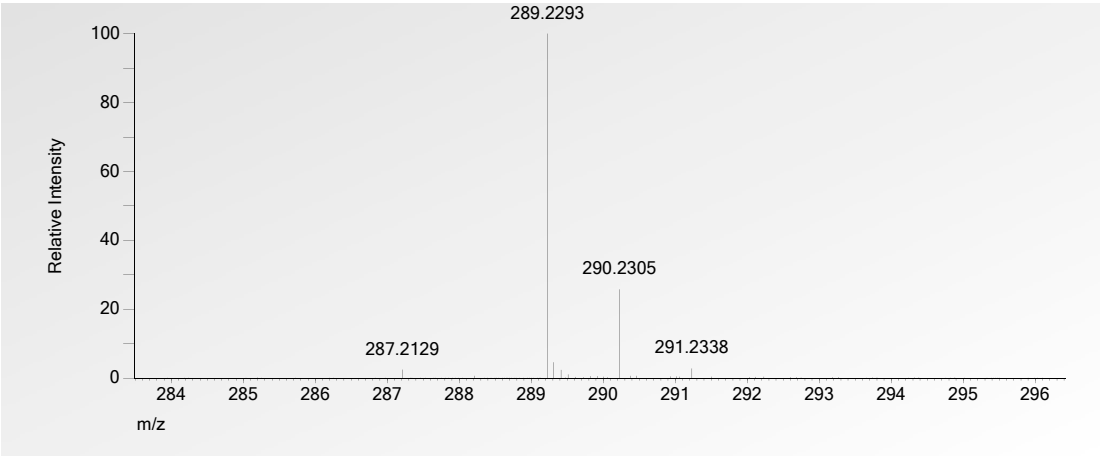

Me
Me
C2'
[14%]
NH
Me
O
N
C3
[0%]
C5
[90%]

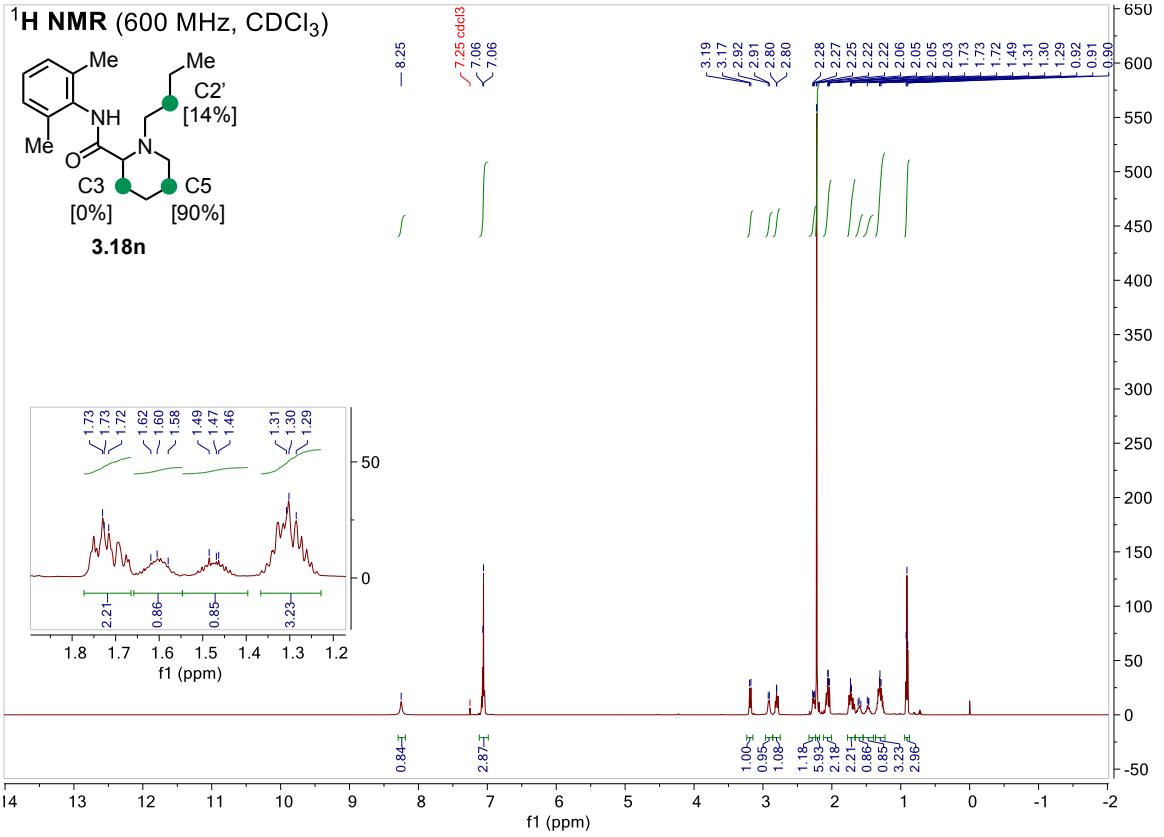
3.18n

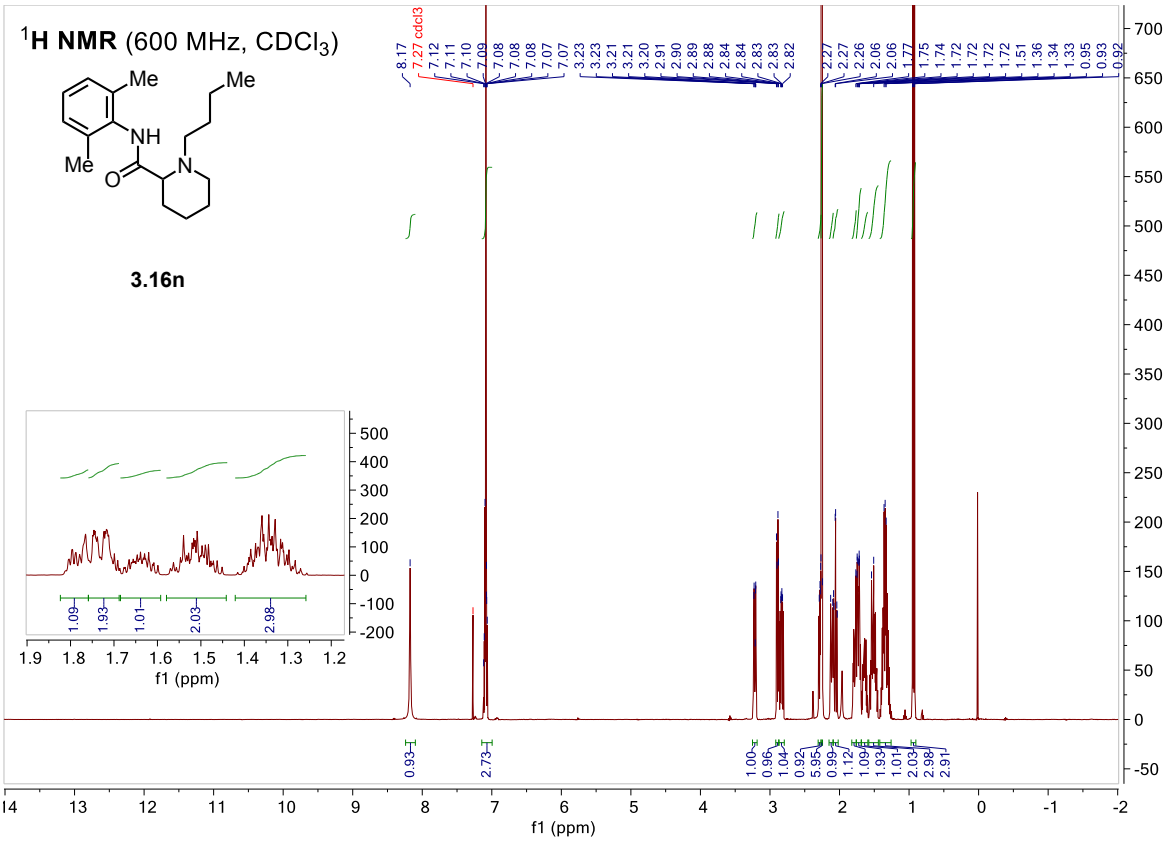

292.2148
291.2098
293.2205
290.2040
294.2234
289.1981
287.1914
288.1922
295.2241
Relative Intensity
m/z


Me
Me
NH
Me
O
N

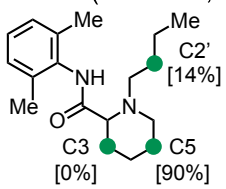
3.16n


289.2293
290.2305
287.2129
291.2338
Relative Intensity
m/z


^{1}H NMR (600 MHz, CDCl$_3$)
Me
Me
C2'
[14%]
NH
Me
O
N
C3
[0%]
C5
[90%]
3.18n
f1 (ppm)

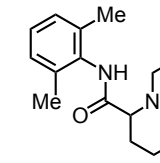

^{1}H NMR (600 MHz, CDCl$_3$)
Me
Me
NH
Me
O
N
3.16n
f1 (ppm)

^{13}C NMR (151 MHz, $CDCl_3$)

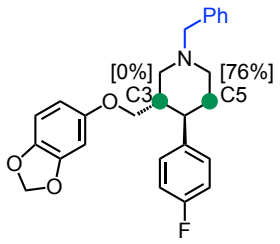


3.18n

^{13}C NMR (151 MHz, $CDCl_3$)



3.16n



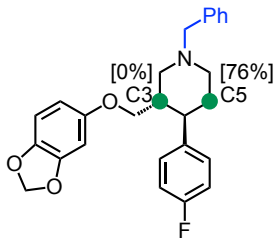
3.18o

_N_-Bn paroxetine, 3.18o

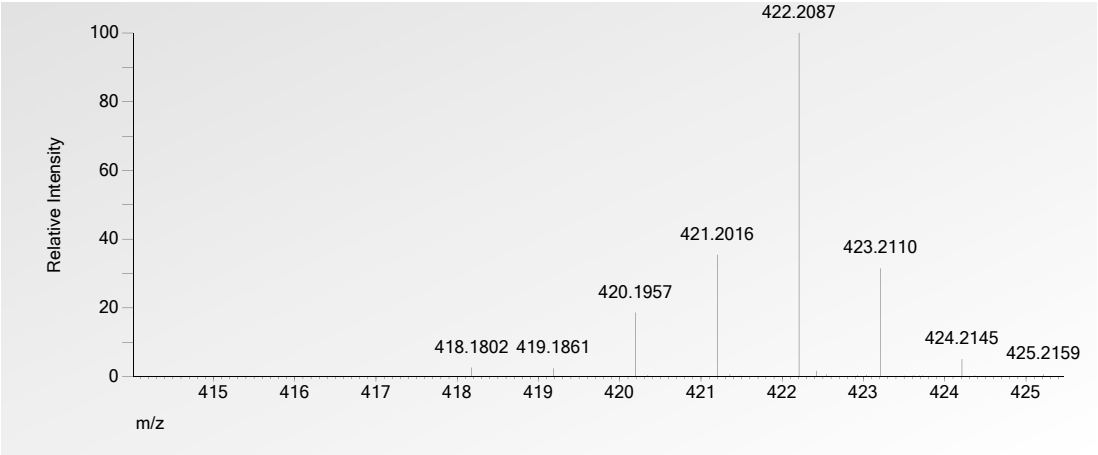
_N_-Bn paroxetine **3.16o** was reacted with acetone-d_6 **3.17a** following the General Procedure A. After purification by column chromatography (Et_2O:hexanes = 1:9), **3.18o** was obtained as a white solid (82 mg, 98%).

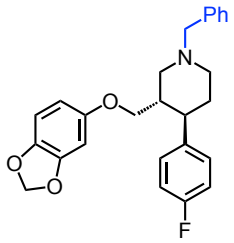
Deuterium incorporation: 1.52 D/molecule (^{1}H NMR), 1.85 D/molecule [HRMS (DART)]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.30 (m, 4H), 7.30 – 7.21 (m, 1H), 7.15 (ddd, J = 7.1, 5.3, 2.7 Hz, 2H), 7.04 – 6.87 (m, 2H), 6.61 (dd, J = 8.5, 1.6 Hz, 1H), 6.31 (t, J = 2.1 Hz, 1H), 6.10 (d, J = 8.5 Hz, 1H), 5.86 (d, J = 1.7 Hz, 2H), 3.64 (dd, J = 13.2, 1.6 Hz, 1H), 3.59 – 3.49 (m, 2H), 3.43 (s, 1H), 3.31 – 3.17 (m, 1H), 2.97 (d, J = 11.2 Hz, 1H), 2.46 (d, J = 11.1 Hz, 1H), 2.20 (dd, J = 7.5, 3.3 Hz, 1H), 2.14 – 2.00 (m, 2H), 1.92 – 1.73 (m, 0.49H, 76%D); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 162.46, 160.52, 154.44, 148.13, 141.54, 139.88, 139.86, 138.28, 129.22, 128.88, 128.81, 128.23, 127.04, 115.43, 115.26, 107.83, 105.62, 101.06, 98.01, 69.67, 63.43, 57.62, 53.70, 43.96, 42.18, 34.40; **^{19}F NMR** (564 MHz, $CDCl_3$) δ -116.68 (td, J = 8.8, 4.5 Hz); **IR** (neat) 2895, 2799, 1506, 1486, 1466, 1451, 1222, 1181, 1090, 1037, 830, 744, 705 cm^{-1}; $[\alpha]^{25}_D$ = -27.3° (c = 1.0, CH_2Cl_2 labeled), $[\alpha]^{25}_D$ = -44.9° (c = 1.0, CH_2Cl_2 unlabeled).

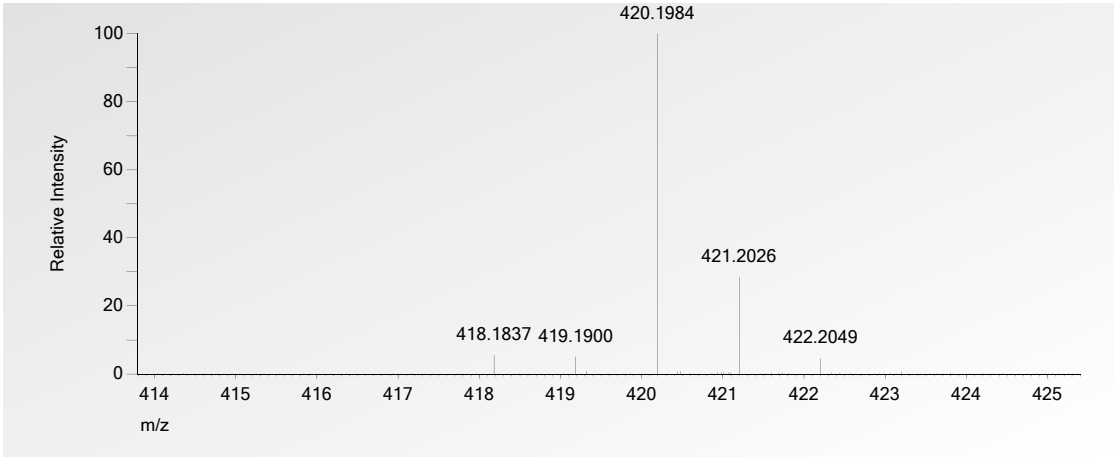

Ph
N
[0%]
C3
[76%]
C5
O
O
O
F

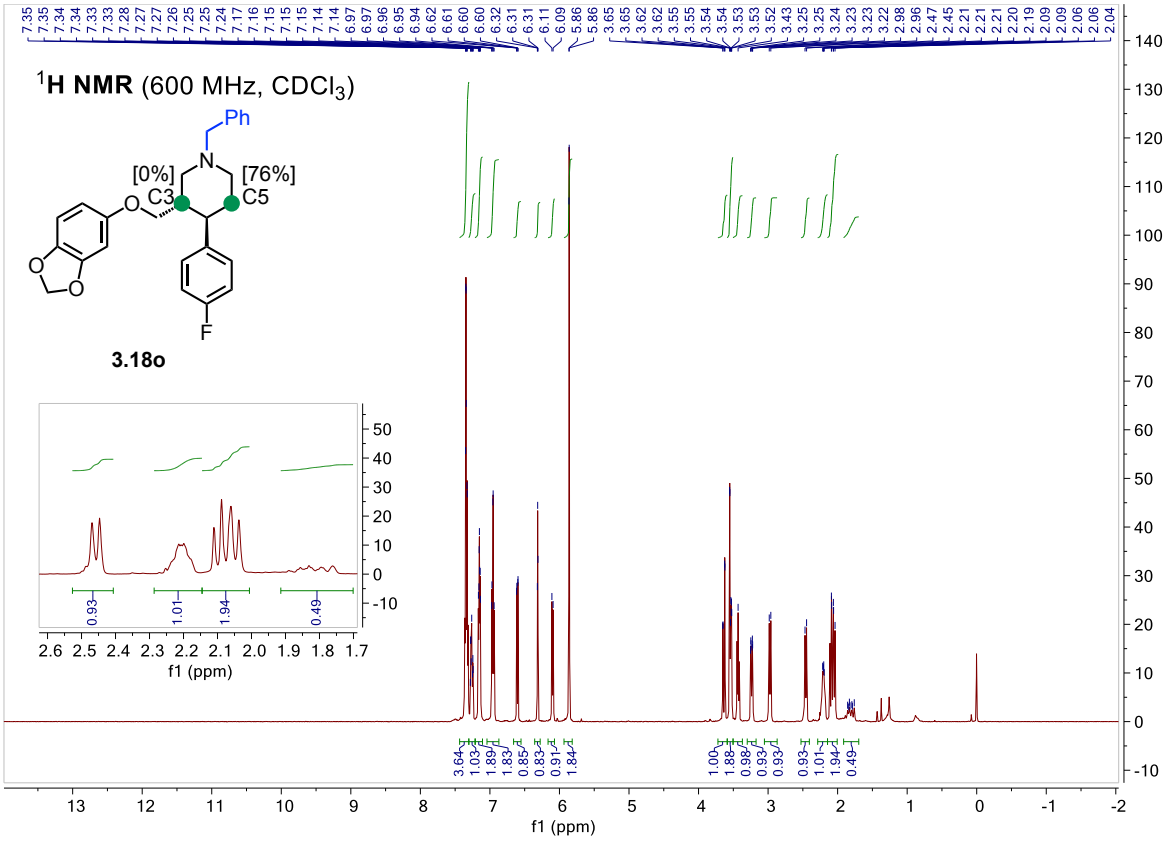
3.18o

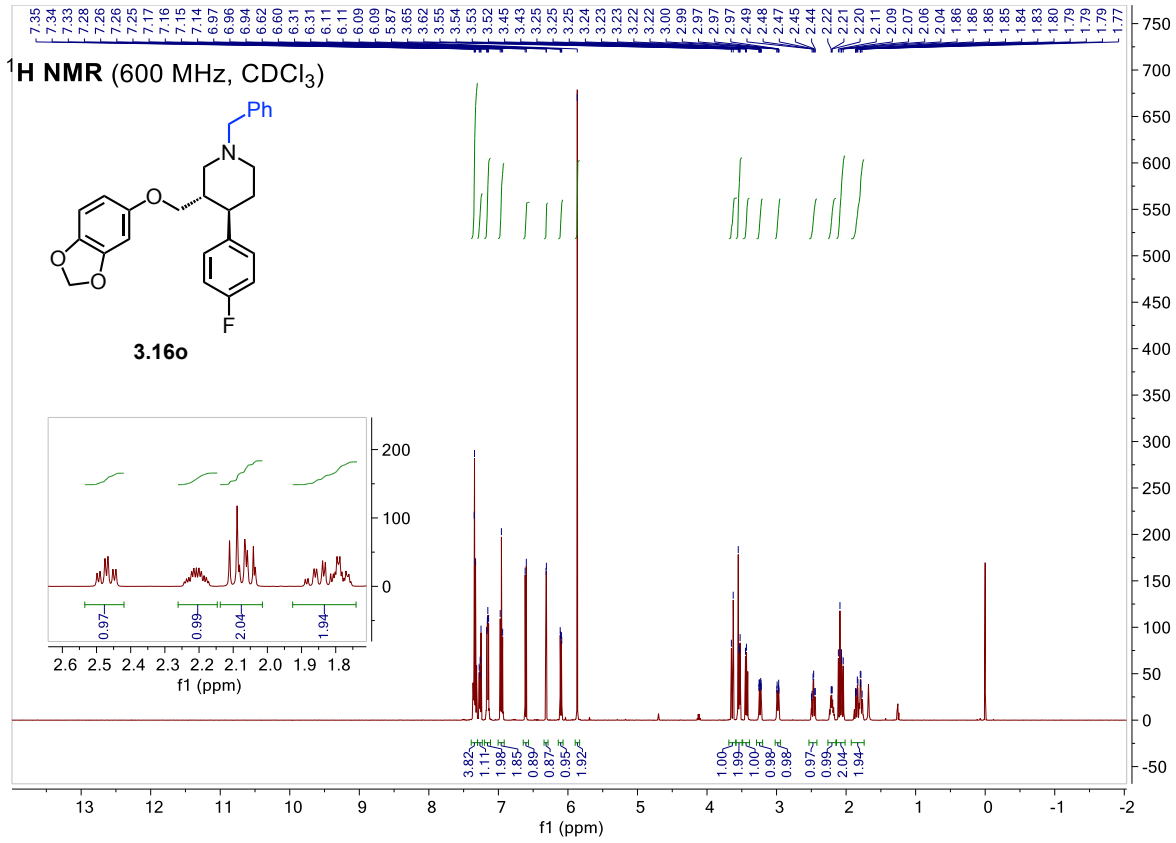

422.2087
100
80
60
40
20
0
Relative Intensity
421.2016
423.2110
420.1957
424.2145
418.1802
419.1861
425.2159
415
416
417
418
419
420
421
422
423
424
425
m/z

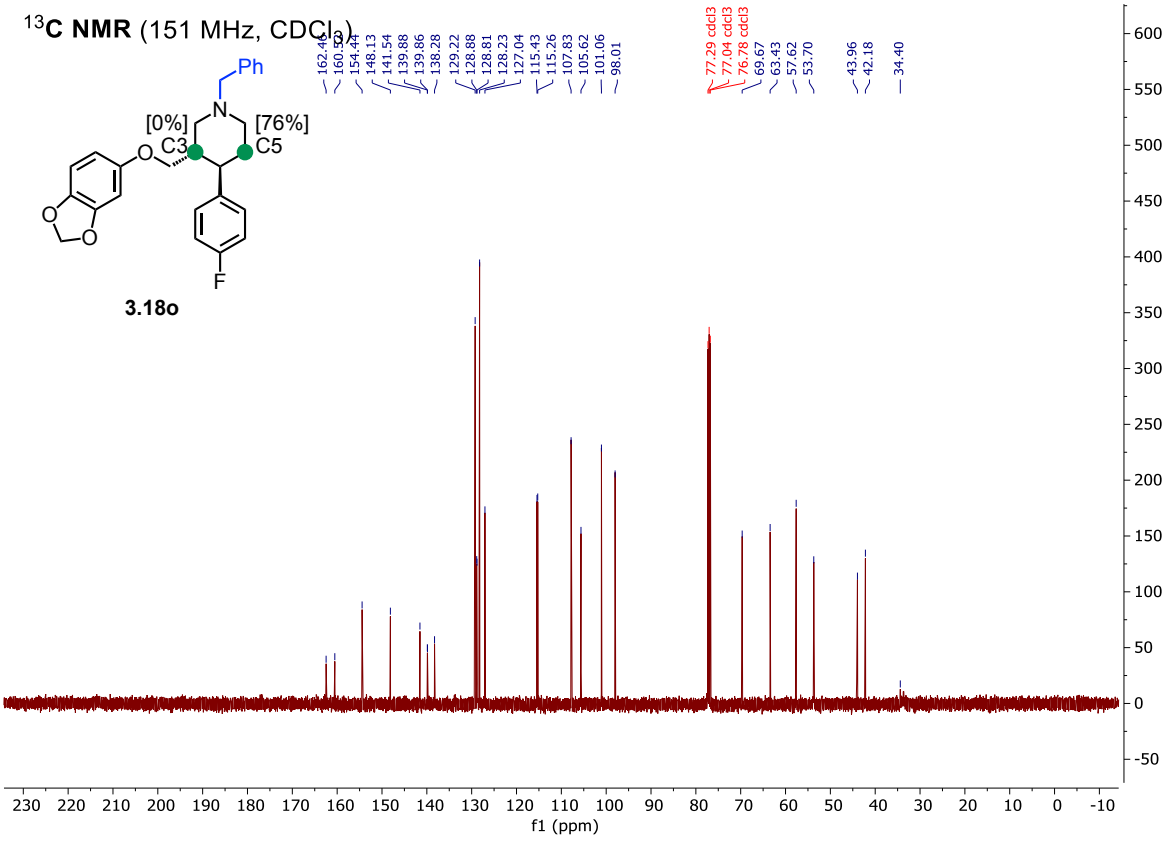

Ph
N
O
O
O
F

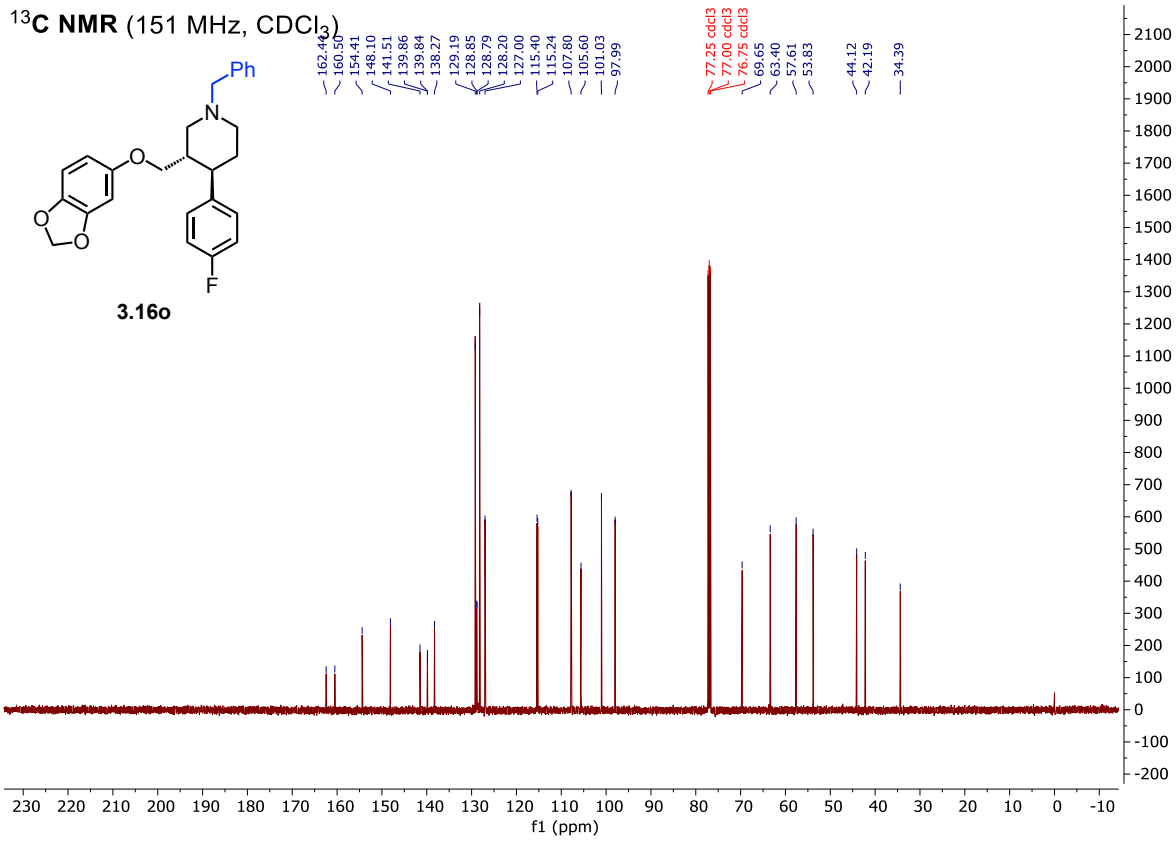
3.16o

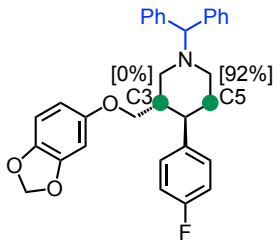

420.1984
100
80
60
40
20
0
Relative Intensity
421.2026
418.1837
419.1900
422.2049
414
415
416
417
418
419
420
421
422
423
424
425
m/z


1H NMR (600 MHz, CDCl3)
Ph
N
[0%]
C3
[76%]
C5
O
O
O
F
3.18o
f1 (ppm)


1H NMR (600 MHz, CDCl3)
Ph
N
O
O
O
F
3.16o
f1 (ppm)


13C NMR (151 MHz, CDCl3)
Ph
N
[0%]
C3
[76%]
C5
O
O
O
F
3.18o
162.44
160.53
154.44
148.13
141.54
139.88
139.86
138.28
129.22
128.88
128.81
128.23
127.04
115.43
115.26
107.83
105.62
101.06
98.01
77.29 cdcl3
77.04 cdcl3
76.78 cdcl3
69.67
63.43
57.62
53.70
43.96
42.18
34.40
f1 (ppm)


13C NMR (151 MHz, CDCl3)
Ph
N
O
O
O
F
3.16o
162.44
160.50
154.41
148.10
141.51
139.86
139.84
138.27
129.19
128.85
128.79
128.20
127.00
115.40
115.24
107.80
105.60
101.03
97.99
77.25 cdcl3
77.00 cdcl3
76.75 cdcl3
69.65
63.40
57.61
53.83
44.12
42.19
34.39
f1 (ppm)



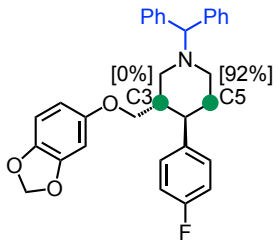
3.18p

***N*-Bzh Paroxetine, 3.18p**

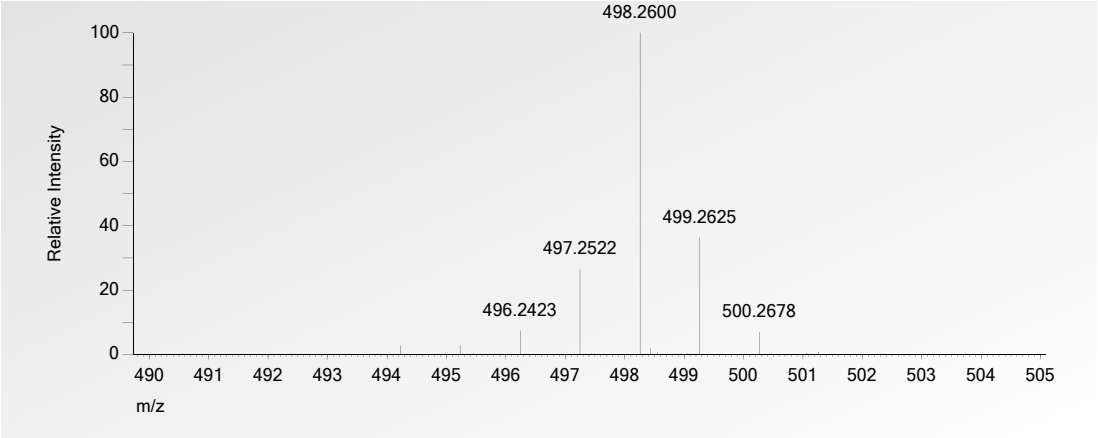
N-Bzh paroxetine **3.16p** was reacted with acetone-d_6 **3.17a** following the General Procedure A. After purification by column chromatography (Et_2O:hexanes = 1:9), **3.18p** was obtained as a colorless liquid (94 mg, 95%).

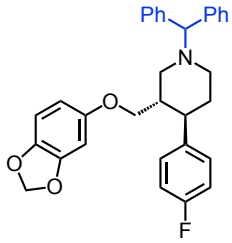
Deuterium incorporation: 1.88 D/molecule (^{1}H NMR), 2.09 D/molecule [HRMS (DART)]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.37 (m, 4H), 7.28 (t, *J* = 7.7 Hz, 4H), 7.23 – 7.08 (m, 4H), 6.96 (d, *J* = 8.7 Hz, 2H), 6.57 (d, *J* = 8.4 Hz, 1H), 6.21 (d, *J* = 2.4 Hz, 1H), 6.01 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.84 (s, 2H), 4.36 (s, 1H), 3.49 (d, *J* = 2.9 Hz, 1H), 3.39 (d, *J* = 6.8 Hz, 1H), 3.23 (ddd, *J* = 11.4, 3.6, 2.1 Hz, 1H), 2.97 (s, 1H), 2.47 (d, *J* = 11.2 Hz, 1H), 2.21 (dt, *J* = 7.2, 3.5 Hz, 1H), 1.94 (d, *J* = 11.3 Hz, 2H), 1.89 – 1.84 (m, 0.08H, 92%D), 1.75 – 1.71 (m, 0.08H, 92%D); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.47, 160.52, 154.30, 148.08, 142.82, 142.79, 141.52, 140.08, 140.05, 128.91, 128.85, 128.45, 128.44, 128.10, 127.95, 126.89, 115.39, 115.22, 107.78, 105.76, 101.04, 98.14, 76.13, 69.61, 55.96, 52.42, 52.35, 44.15, 44.06, 42.47, 33.86; **^{19}F NMR** (564 MHz, $CDCl_3$) δ -116.80 (tt, J = 8.8, 5.2 Hz); **IR** (neat) 2895, 2799, 1506, 1486, 1466, 1222, 1182, 1037, 830, 705 cm^{-1}; $[\alpha]^{25}_{D}$ = -36.5 ° (c = 1.0, CH_2Cl_2 labeled), $[\alpha]^{25}_{D}$ = -43.4° (c = 1.0, CH_2Cl_2 unlabeled).

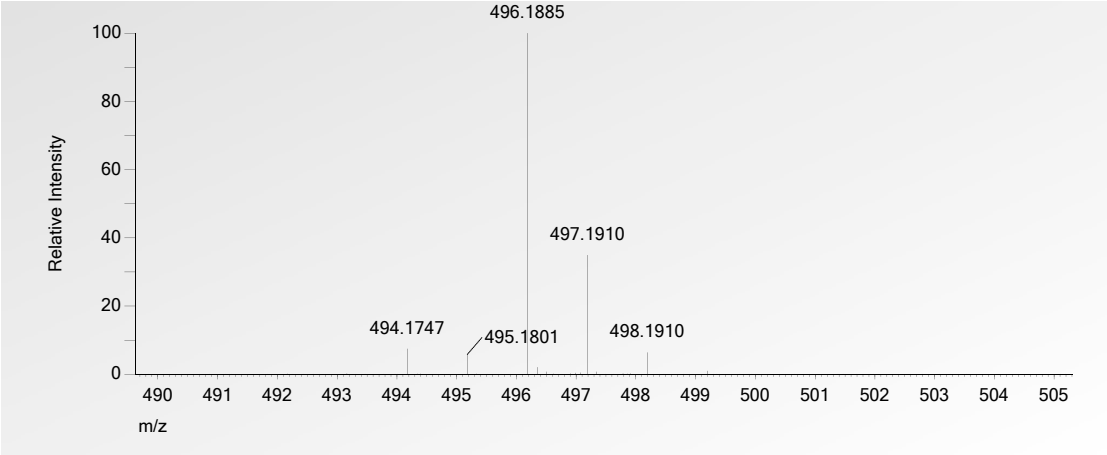

Ph
Ph
N
[0%]
C3
[92%]
C5
O
O
O
F

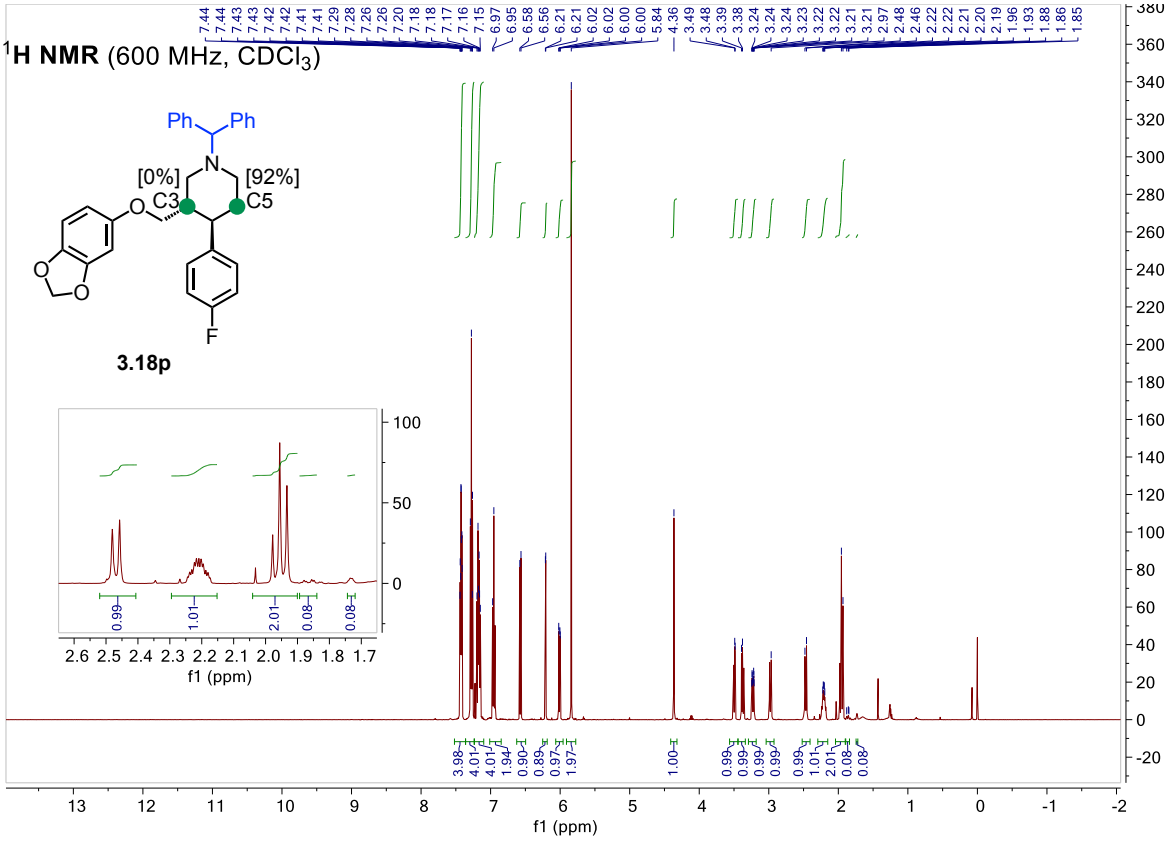
3.18p

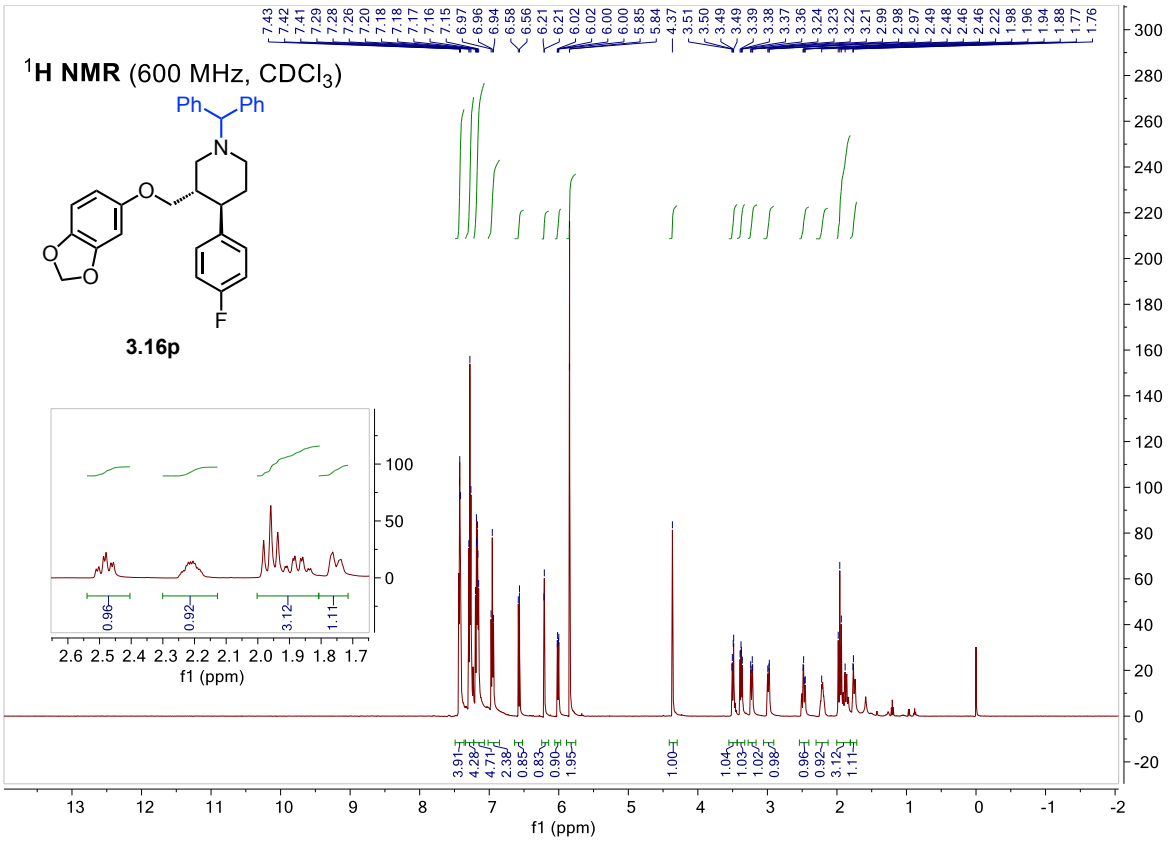

498.2600
499.2625
497.2522
496.2423
500.2678
Relative Intensity
m/z
100
80
60
40
20
0
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505

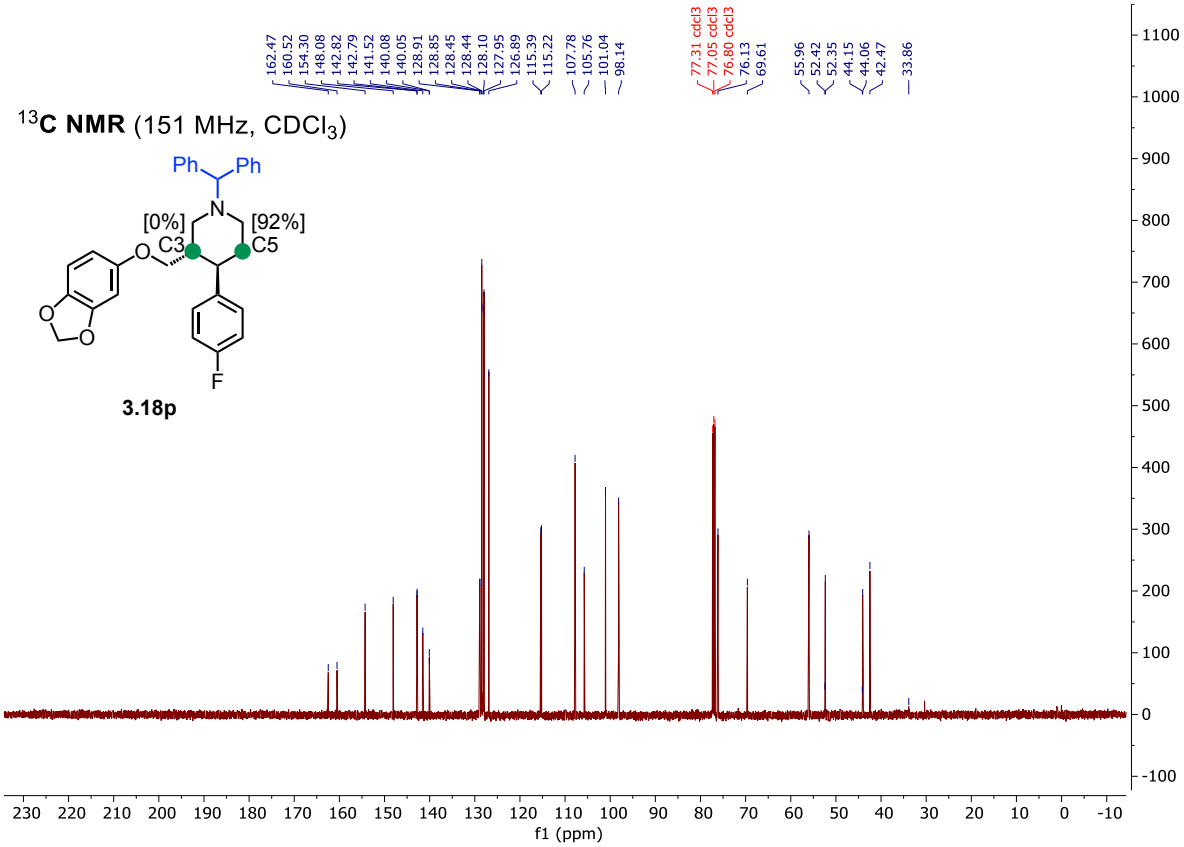

Ph
Ph
N
O
O
O
F

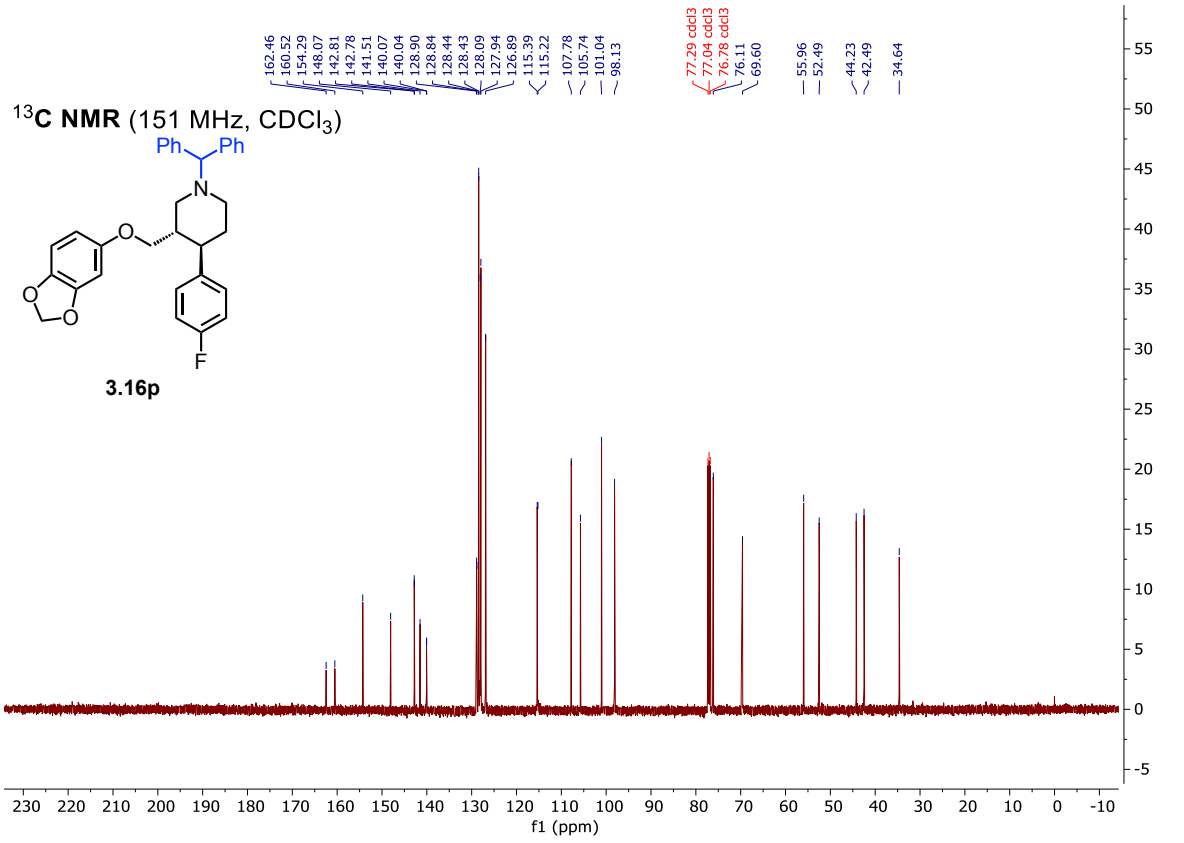
3.16p

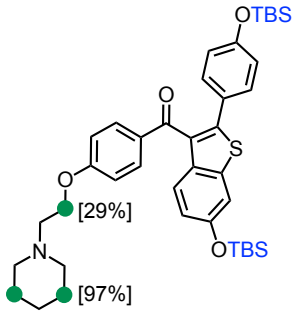

496.1885
497.1910
494.1747
495.1801
498.1910
Relative Intensity
m/z
100
80
60
40
20
0
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505


^{1}H NMR (600 MHz, $CDCl_3$)
Ph
Ph
N
[0%]
[92%]
C3
C5
O
O
O
F
3.18p
f1 (ppm)


^{1}H NMR (600 MHz, $CDCl_3$)
Ph
Ph
N
O
O
O
F
3.16p
f1 (ppm)


13C NMR (151 MHz, CDCl3)
Ph
Ph
N
[0%]
C3
[92%]
C5
O
O
O
F
3.18p
162.47
160.52
154.30
148.08
142.82
142.79
141.52
140.08
140.05
128.91
128.85
128.45
128.44
128.10
127.95
126.89
115.39
115.22
107.78
105.76
101.04
98.14
77.31 cdcl3
77.05 cdcl3
76.80 cdcl3
76.13
69.61
55.96
52.42
52.35
44.15
44.06
42.47
33.86
f1 (ppm)


13C NMR (151 MHz, CDCl3)
Ph
Ph
N
O
O
O
F
3.16p
162.46
160.52
154.29
148.07
142.81
142.78
141.51
140.07
140.04
128.90
128.84
128.44
128.43
128.09
127.94
126.89
115.39
115.22
107.78
105.74
101.04
98.13
77.29 cdcl3
77.04 cdcl3
76.78 cdcl3
76.11
69.60
55.96
52.49
44.23
42.49
34.64
f1 (ppm)



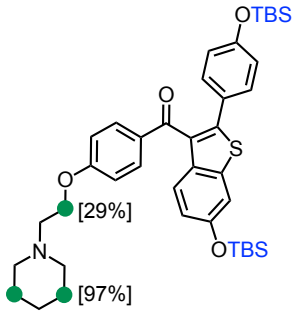
3.18q

***O*-TBS raloxifene, 3.18q**

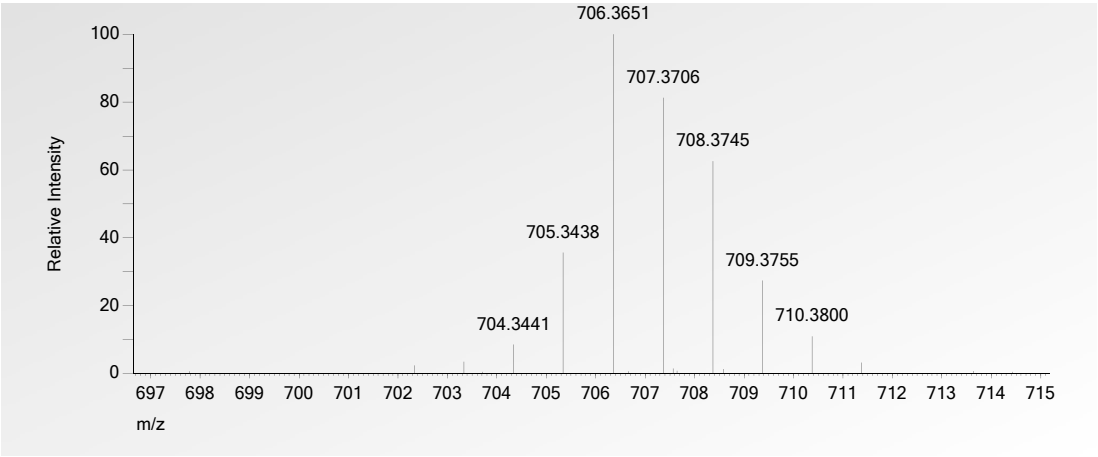
O-TBS raloxifene **3.16q** was reacted with acetone-d_6 **3.17a** following the General Procedure A. After purification by column chromatography (MeOH:DCM = 1:49), **3.18q** was obtained as a yellow liquid (136 mg, 97%).

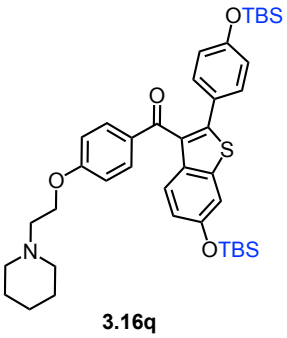
Deuterium incorporation: 4.46 D/molecule (^{1}H NMR), 5.08 D/molecule [HRMS (DART)]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, J = 8.9 Hz, 2H), 7.57 (d, J = 8.7 Hz, 1H), 7.33 – 7.22 (m, 3H), 6.88 (dd, J = 8.8, 2.2 Hz, 1H), 6.72 (d, J = 9.0 Hz, 2H), 6.66 (d, J = 8.6 Hz, 2H), 4.05 (s, 1.42H, 29%D), 2.77 – 2.70 (m, 2H), 2.46 (s, 4H), 1.62 – 1.51 (m, 0.14H, 97%D), 1.40 (s, 2H), 1.01 (s, 9H), 0.93 (s, 9H), 0.23 (s, 6H), 0.12 (s, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 193.03, 162.77, 156.01, 153.42, 143.25, 139.79, 134.44, 132.22, 130.52, 130.39, 130.27, 130.24, 126.71, 123.92, 123.90, 120.19, 119.18, 119.16, 113.93, 112.03, 112.00, 65.98, 54.81, 54.81, 25.64, 25.57, 24.97, 23.70, 23.59, 18.17, 18.12, -4.43, -4.54; **IR** (neat) 2927, 1595, 1463, 1252, 1164, 939, 907, 827, 779, 734 cm^{-1}.

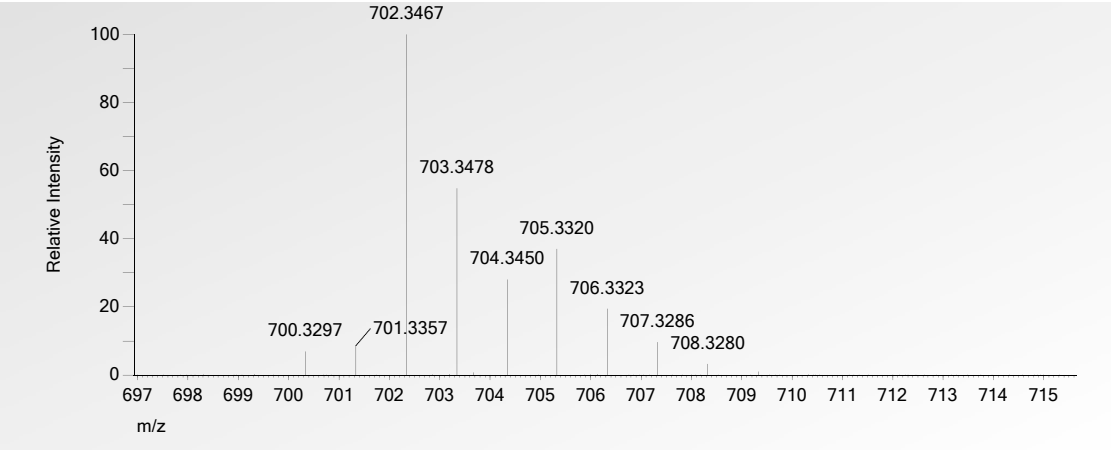

OTBS
O
S
O
[29%]
OTBS
N
[97%]

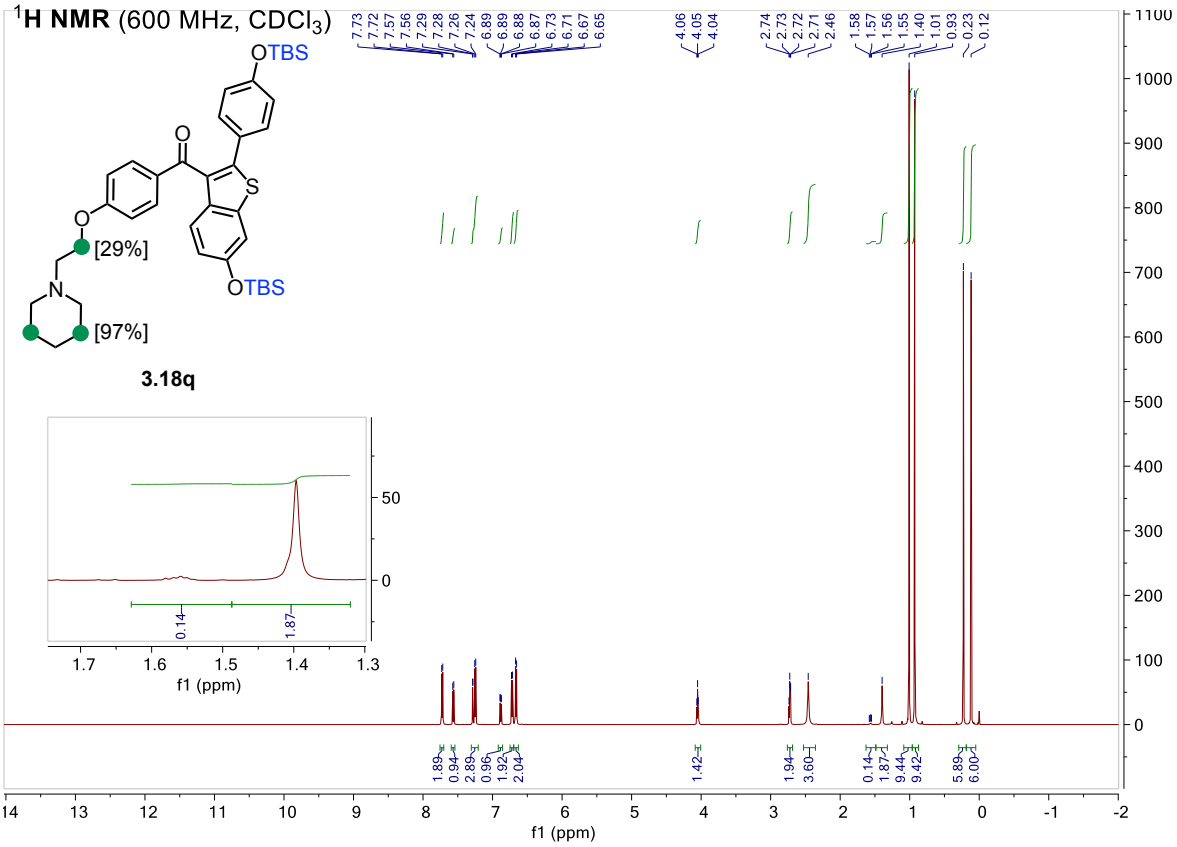
3.18q

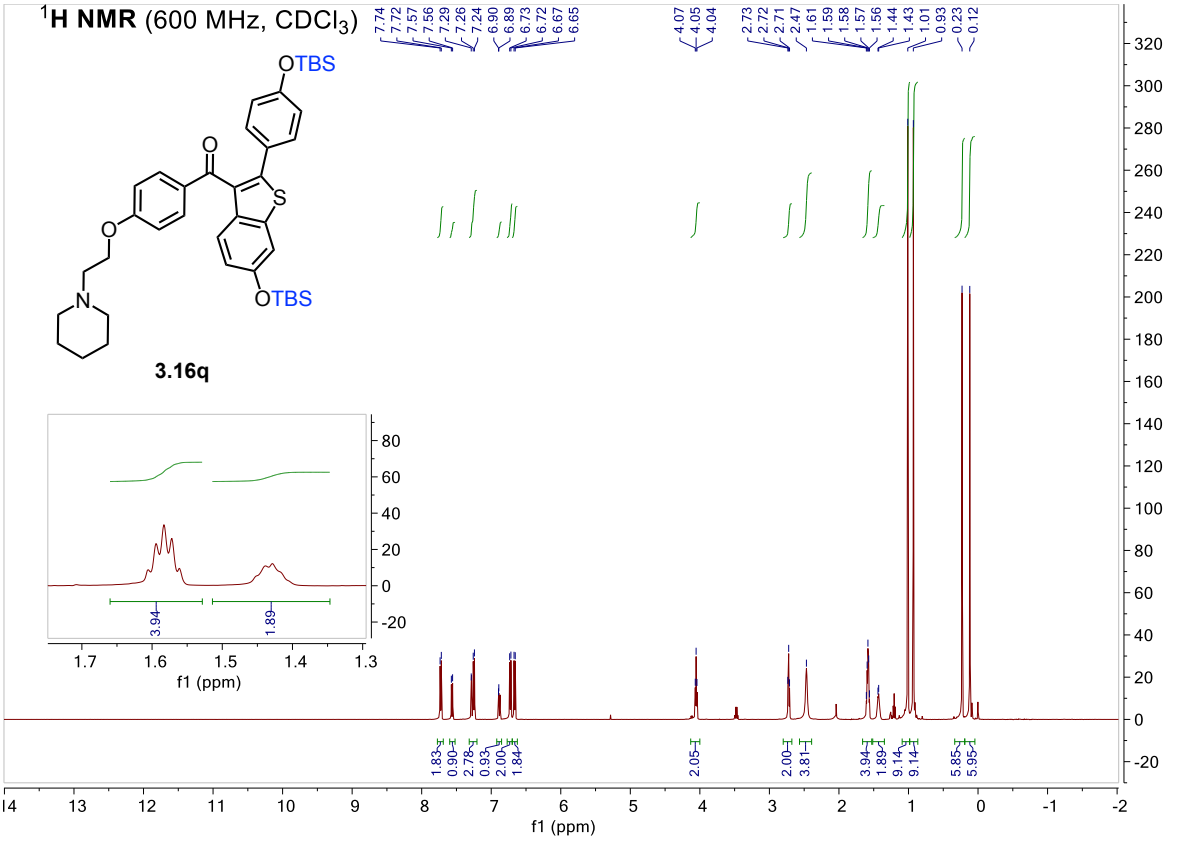

706.3651
707.3706
708.3745
705.3438
709.3755
710.3800
704.3441
100
80
60
40
20
0
Relative Intensity
697 698 699 700 701 702 703 704 705 706 707 708 709 710 711 712 713 714 715
m/z

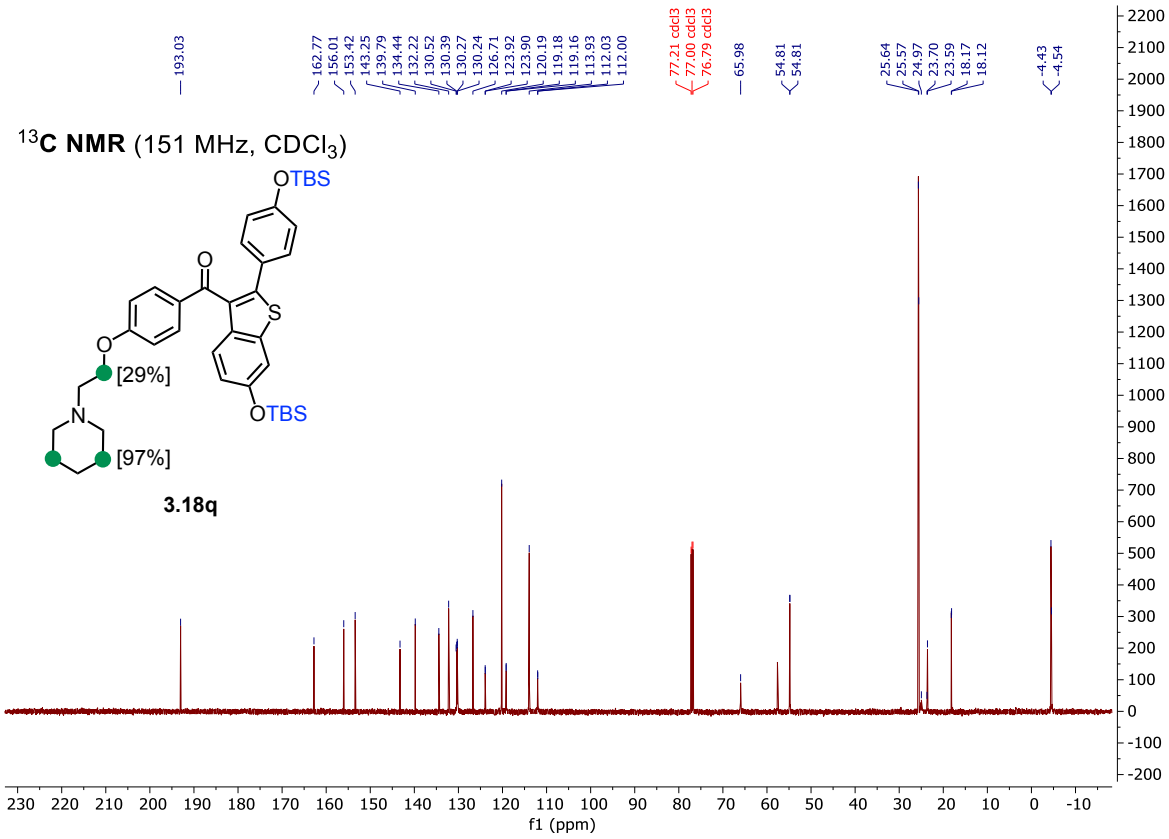

OTBS
O
S
O
N
OTBS

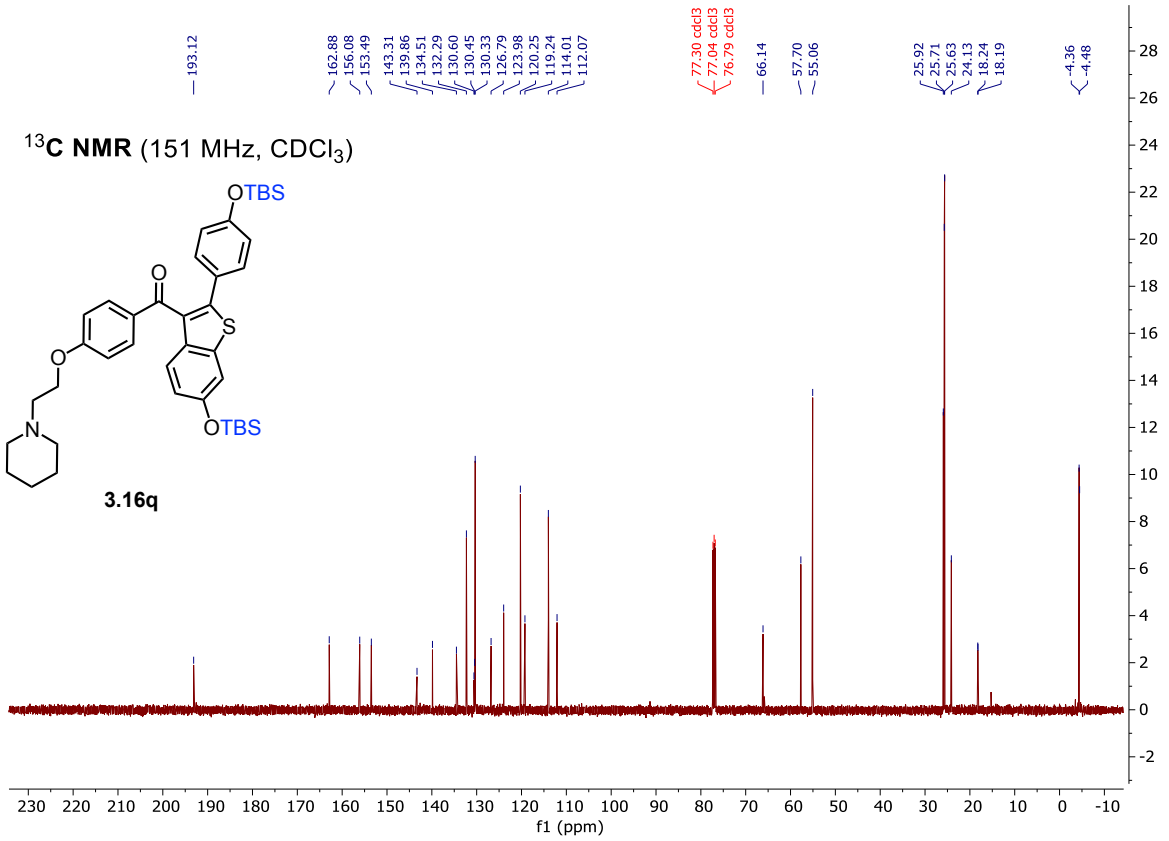
3.16q

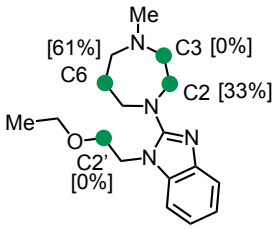

702.3467
703.3478
705.3320
704.3450
706.3323
707.3286
708.3280
700.3297
701.3357
100
80
60
40
20
0
Relative Intensity
697 698 699 700 701 702 703 704 705 706 707 708 709 710 711 712 713 714 715
m/z


1H NMR (600 MHz, CDCl3)
OTBS
O
S
O
[29%]
N
[97%]
OTBS
3.18q
f1 (ppm)


1H NMR (600 MHz, CDCl3)
OTBS
O
S
O
N
OTBS
3.16q
f1 (ppm)


193.03
162.77
156.01
153.42
143.25
139.79
134.44
132.22
130.52
130.39
130.27
130.24
126.71
123.92
123.90
120.19
119.18
119.16
113.93
112.03
112.00
77.21 cdcl3
77.00 cdcl3
76.79 cdcl3
65.98
54.81
54.81
25.64
25.57
24.97
23.70
23.59
18.17
18.12
-4.43
-4.54
13C NMR (151 MHz, CDCl3)
OTBS
O
S
O
[29%]
N
[97%]
OTBS
3.18q
f1 (ppm)


193.12
162.88
156.08
153.49
143.31
139.86
134.51
132.29
130.60
130.45
130.33
126.79
123.98
120.25
119.24
114.01
112.07
77.30 cdcl3
77.04 cdcl3
76.79 cdcl3
66.14
57.70
55.06
25.92
25.71
25.63
24.13
18.24
18.19
-4.36
-4.48
13C NMR (151 MHz, CDCl3)
OTBS
O
S
O
N
OTBS
3.16q
f1 (ppm)



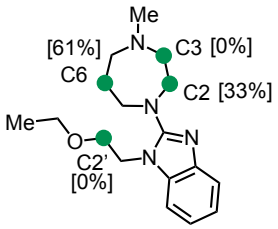
3.18r

Emedastine, 3.18r

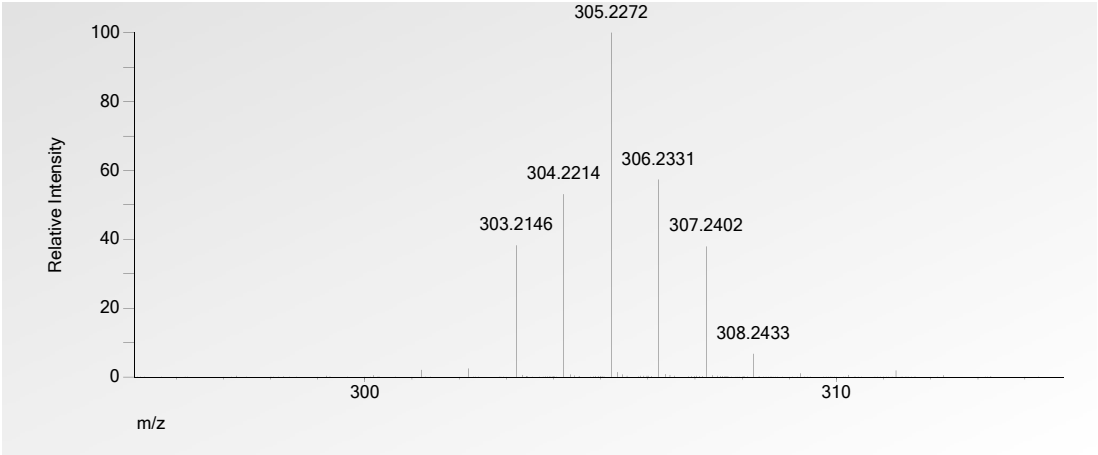
Emedastine **3.16r** was reacted with acetone-d_6 **3.17a** following the General Procedure A. After purification by column chromatography (MeOH:DCM = 1:15), **3.18r** was obtained as a colorless liquid (53 mg, 88%).

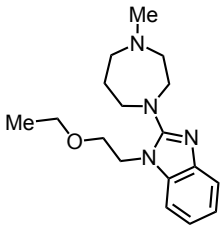
Deuterium incorporation: 1.88 D/molecule (^{1}H NMR), 2.03 D/molecule [HRMS (DART)]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, J = 7.4 Hz, 1H), 7.28 – 7.21 (m, 1H), 7.13 (ddd, J = 15.5, 7.6, 1.4 Hz, 2H), 4.19 (t, J = 6.0 Hz, 2H), 3.78 (t, J = 6.0 Hz, 2H), 3.74 – 3.68 (m, 1.33H, 33%D), 3.64 (d, J = 6.1 Hz, 2H), 3.46 (q, J = 7.0 Hz, 2H), 2.86 – 2.80 (m, 2H), 2.76 (d, J = 5.6 Hz, 2H), 2.44 (s, 3H), 2.10 – 1.98 (m, 0.78H, 61%D), 1.15 (t, J = 7.0 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.11, 141.68, 135.51, 121.69, 120.66, 117.34, 109.12, 68.20, 66.83, 58.47, 57.30, 52.15, 51.62, 46.73, 44.84, 27.81, 15.05; **IR** (neat) 1522, 1460, 1405, 1375, 1349, 1283, 1115, 1045, 1009, 761, 741cm^{-1}.

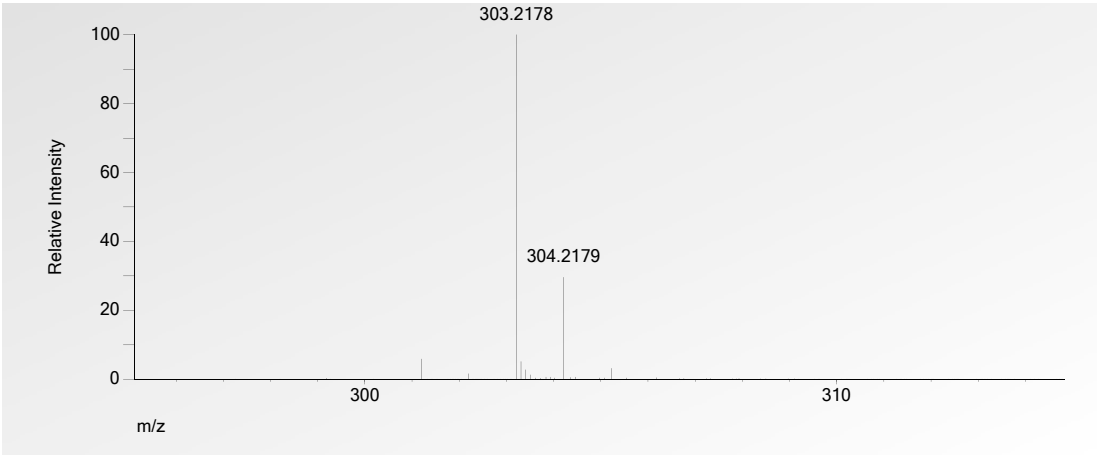

Me
[61%]
N
C3 [0%]
C6
C2 [33%]
N
Me
O
N
N
C2'
[0%]

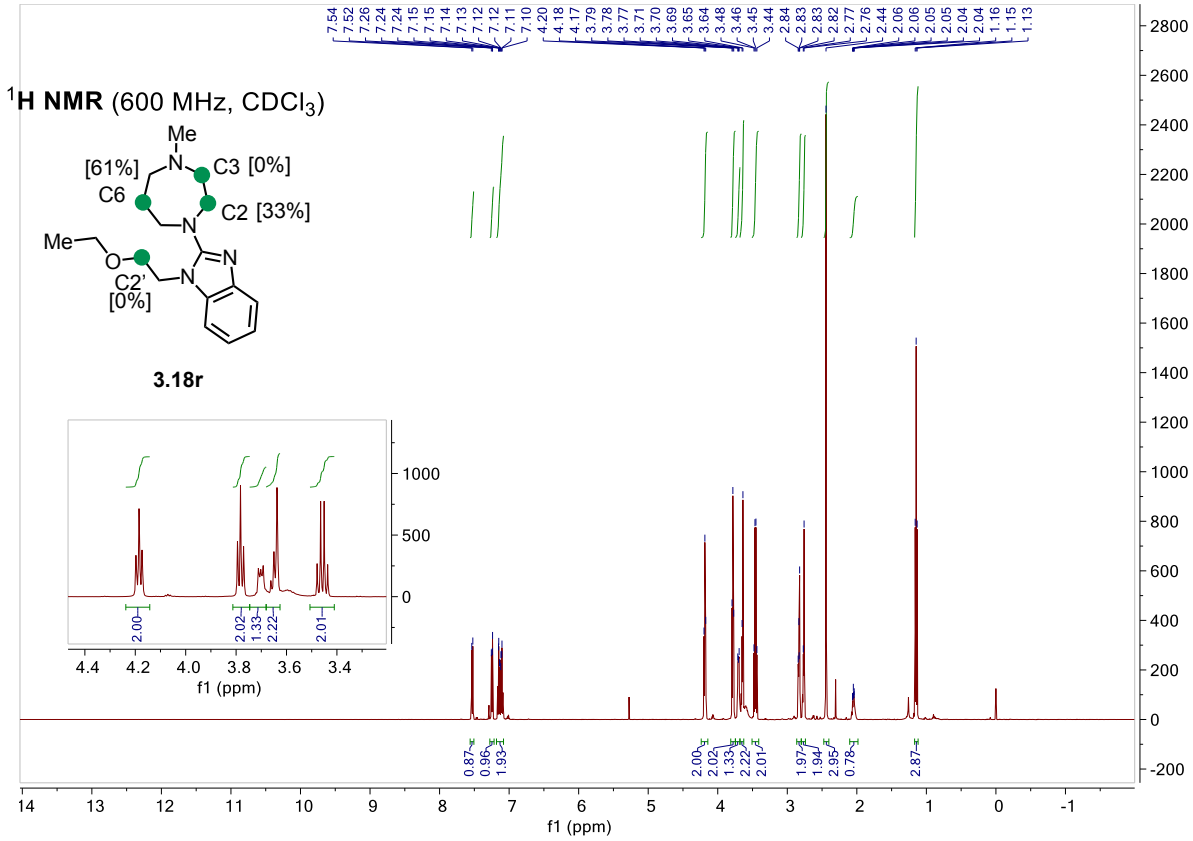
3.18r

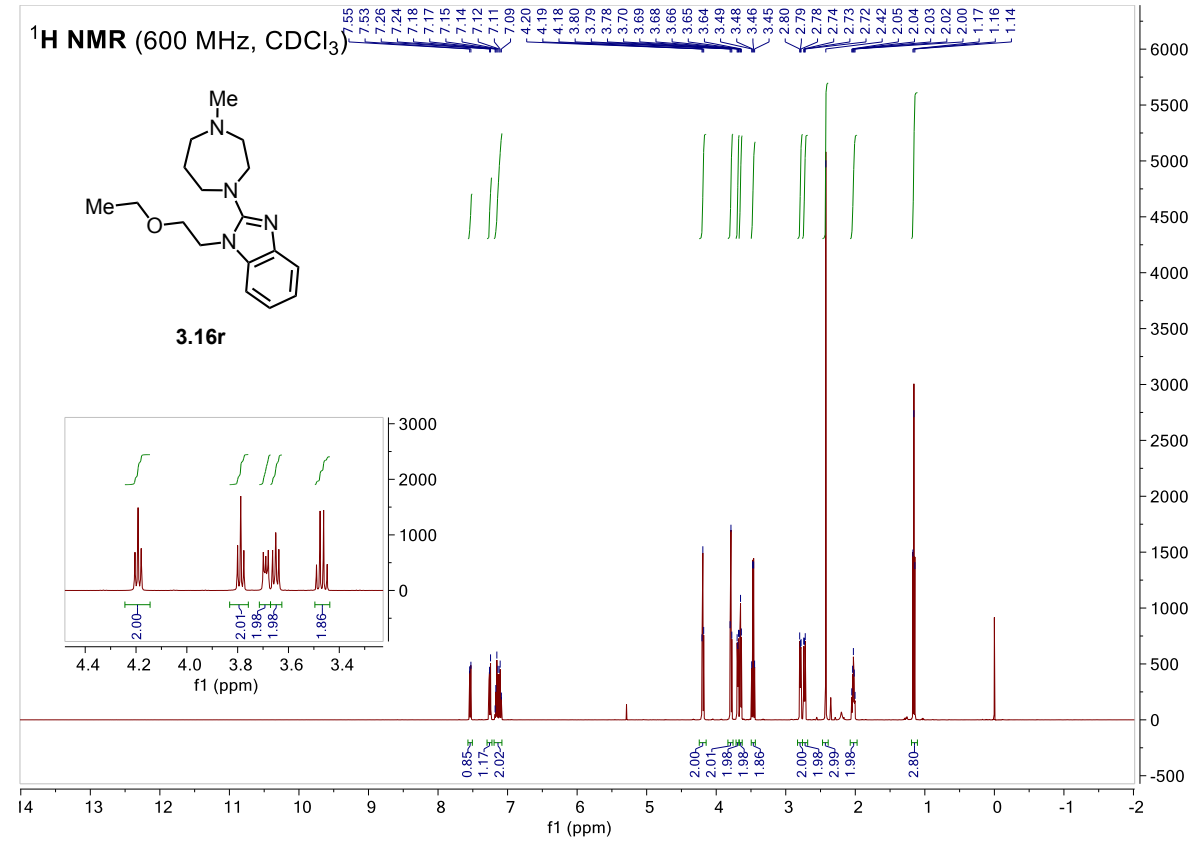

305.2272
100
80
60
40
20
0
Relative Intensity
304.2214
306.2331
303.2146
307.2402
308.2433
300
310
m/z

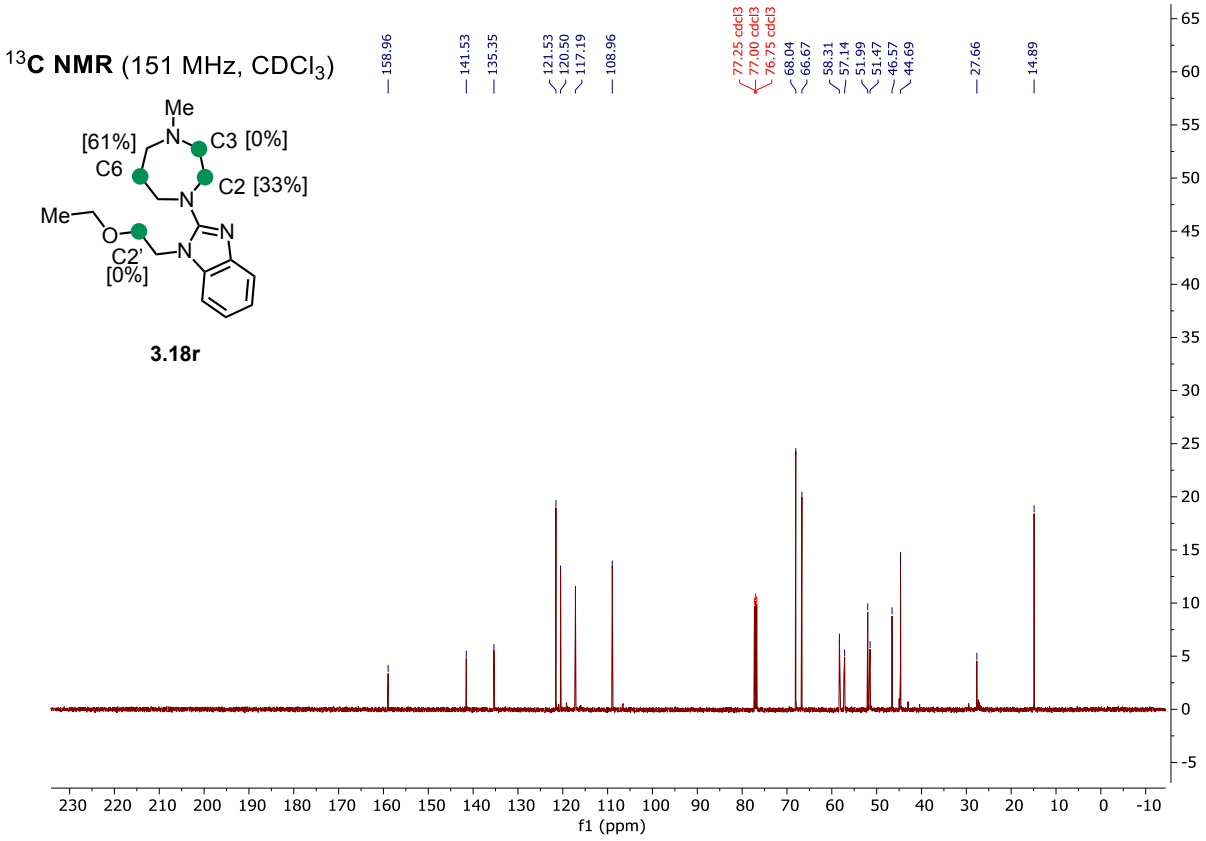

Me
N
N
Me
O
N
N

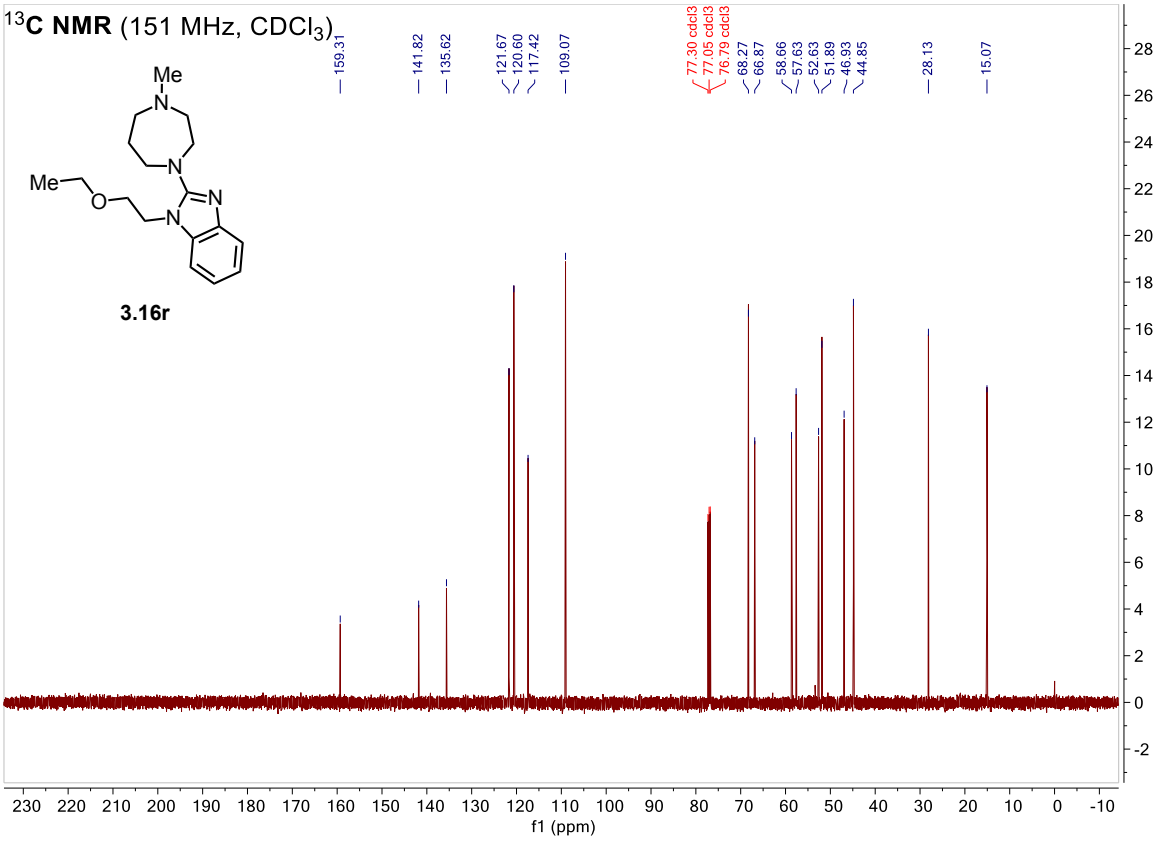
3.16r

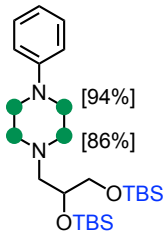

303.2178
100
80
60
40
20
0
Relative Intensity
304.2179
300
310
m/z


1H NMR (600 MHz, CDCl3)
Me
[61%]
C6
N
C3 [0%]
C2 [33%]
Me
O
C2'
[0%]
3.18r
f1 (ppm)


1H NMR (600 MHz, CDCl3)
Me
Me
O
3.16r
f1 (ppm)


13C NMR (151 MHz, CDCl3)
Me
[61%]
C6
N
C3 [0%]
C2 [33%]
Me
O
C2'
[0%]
3.18r
158.96
141.53
135.35
121.53
120.50
117.19
108.96
77.25 cdcl3
77.00 cdcl3
76.75 cdcl3
68.04
66.67
58.31
57.14
51.99
51.47
46.57
44.69
27.66
14.89
f1 (ppm)


13C NMR (151 MHz, CDCl3)
Me
N
Me
O
3.16r
159.31
141.82
135.62
121.67
120.60
117.42
109.07
77.30 cdcl3
77.05 cdcl3
76.79 cdcl3
68.27
66.87
58.66
57.63
52.63
51.89
46.93
44.85
28.13
15.07
f1 (ppm)



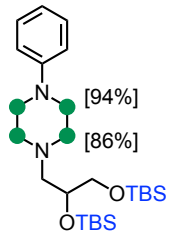
3.18s

O-TBS dropropizine, 3.18s

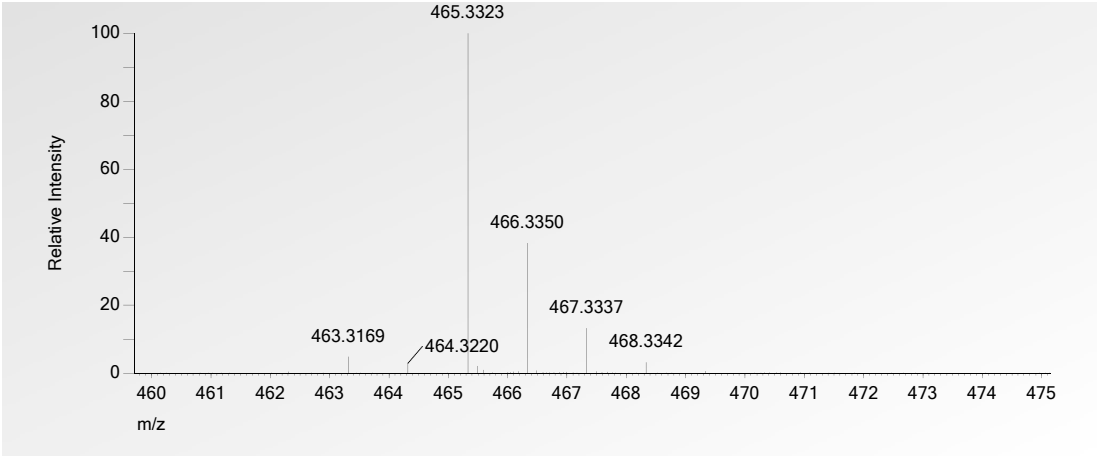
O-TBS dropropizin*e* **3.16s** was reacted with acetone-d_6 **3.17a** following the General Procedure B. After purification by column chromatography (MeOH:DCM = 1:99), **3.18s** was obtained as a yellow liquid (87 mg, 94%).

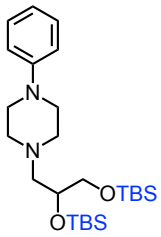
Deuterium incorporation: 6.96 D/molecule (^{1}H NMR), 7.61 D/molecule [HRMS (DART)]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 8.8, 7.3 Hz, 2H), 6.91 (dt, *J* = 7.8, 1.0 Hz, 2H), 6.83 (s, 1H), 3.80 (dd, *J* = 6.0, 4.9 Hz, 1H), 3.66 – 3.57 (m, 1H), 3.53 (dd, *J* = 10.0, 5.6 Hz, 1H), 3.12 (s, 0.24H, 94%D), 2.62 (s, 0.47H, 77%D), 2.55 (s, 0.34H, 83%D), 2.50 (dd, *J* = 13.0, 4.7 Hz, 1H), 2.37 (dd, *J* = 13.0, 6.1 Hz, 1H), 0.90 (d, *J* = 4.3 Hz, 18H), 0.09 (d, *J* = 6.1 Hz, 6H), 0.06 (d, *J* = 1.6 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 151.51, 129.08, 119.39, 115.79, 71.87, 66.21, 61.95, 53.18, 48.27, 26.03, 25.95, 18.40, 18.22, -4.41, -4.46, -5.23, -5.31; **IR** (neat) 2925, 2853, 1598, 1499, 1250, 1091, 1003, 830, 810, 773, 753, 689 cm^{-1}.

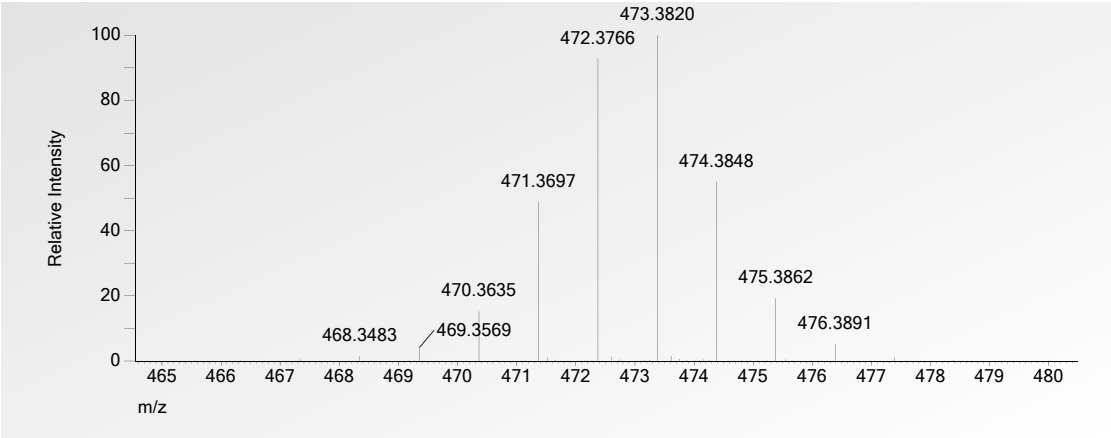

[94%]
[86%]
OTBS
OTBS

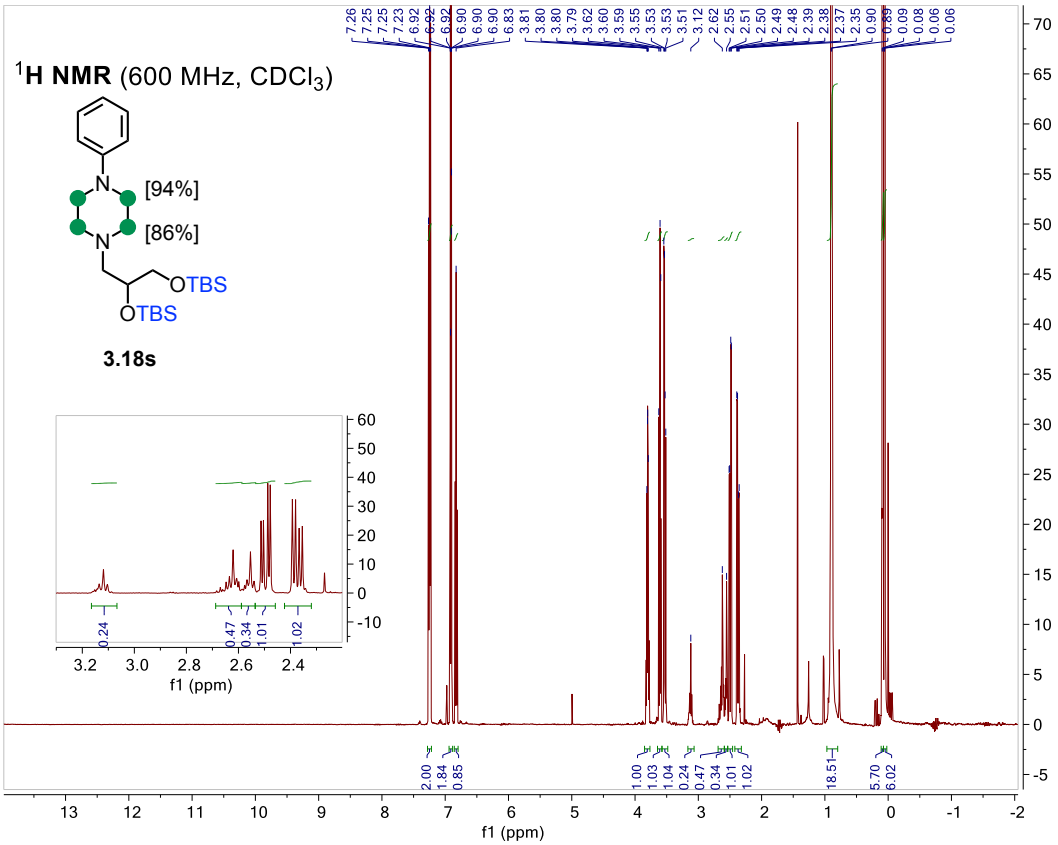
3.18s

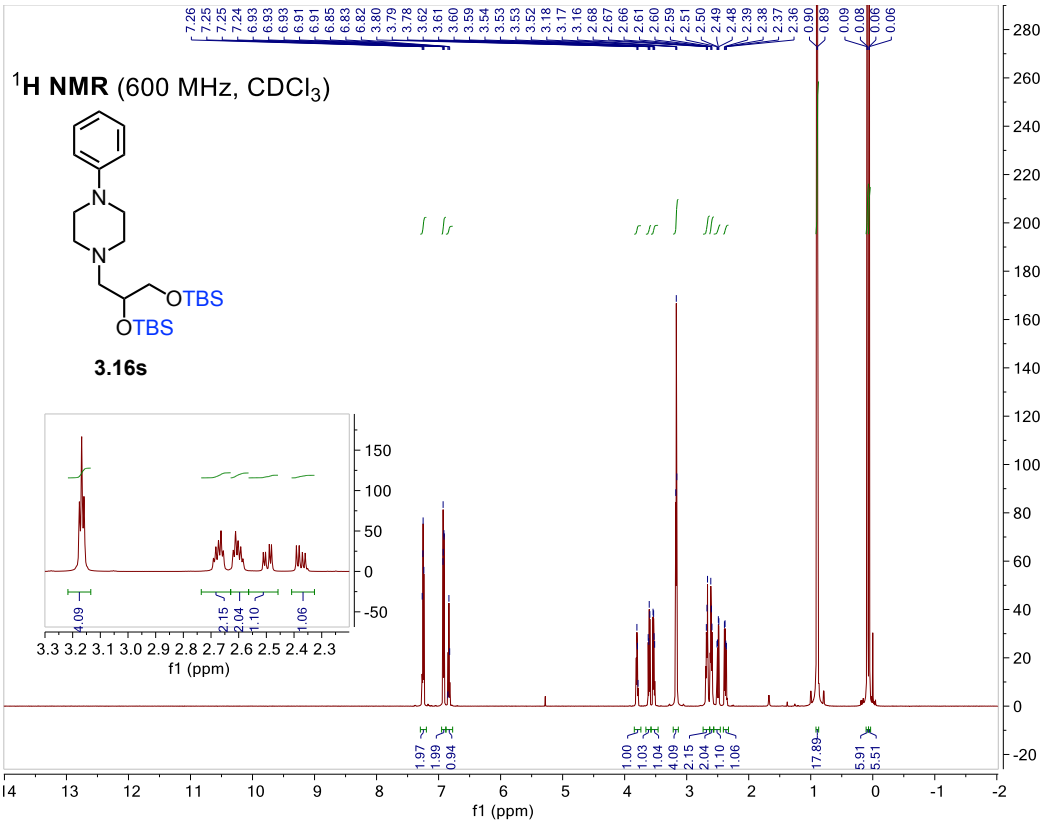

465.3323
466.3350
467.3337
463.3169
464.3220
468.3342
Relative Intensity
m/z

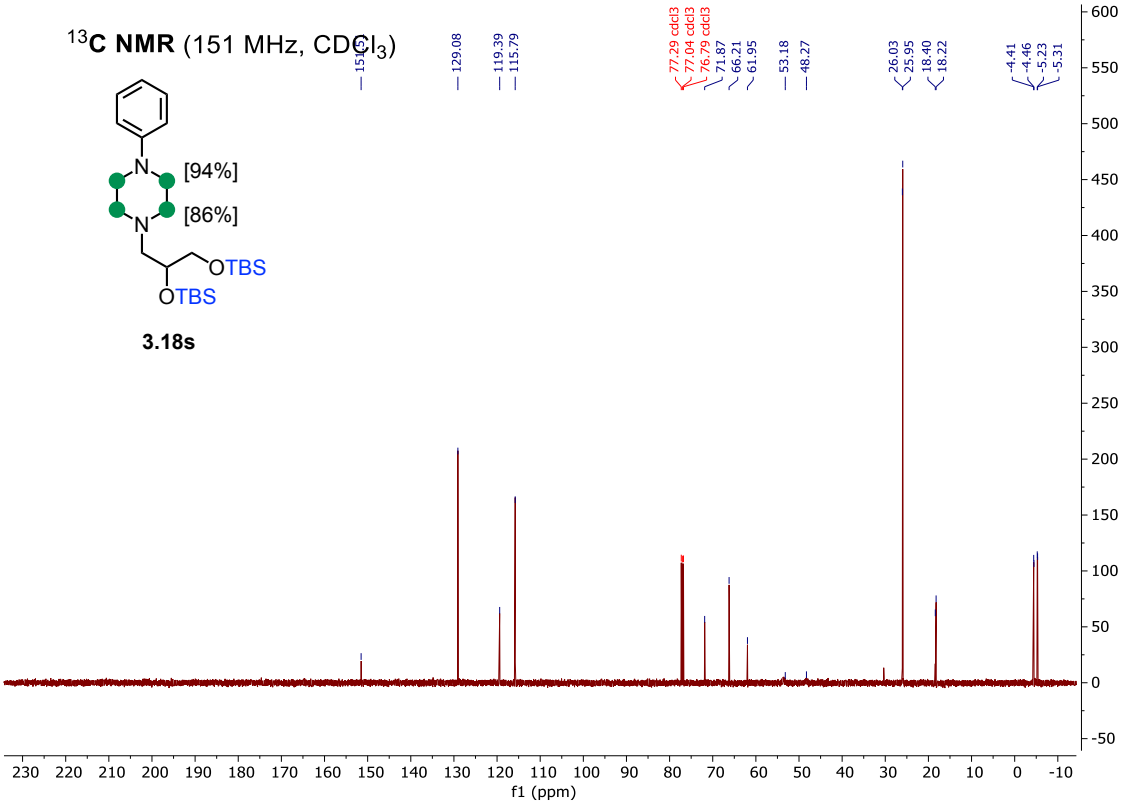

OTBS
OTBS

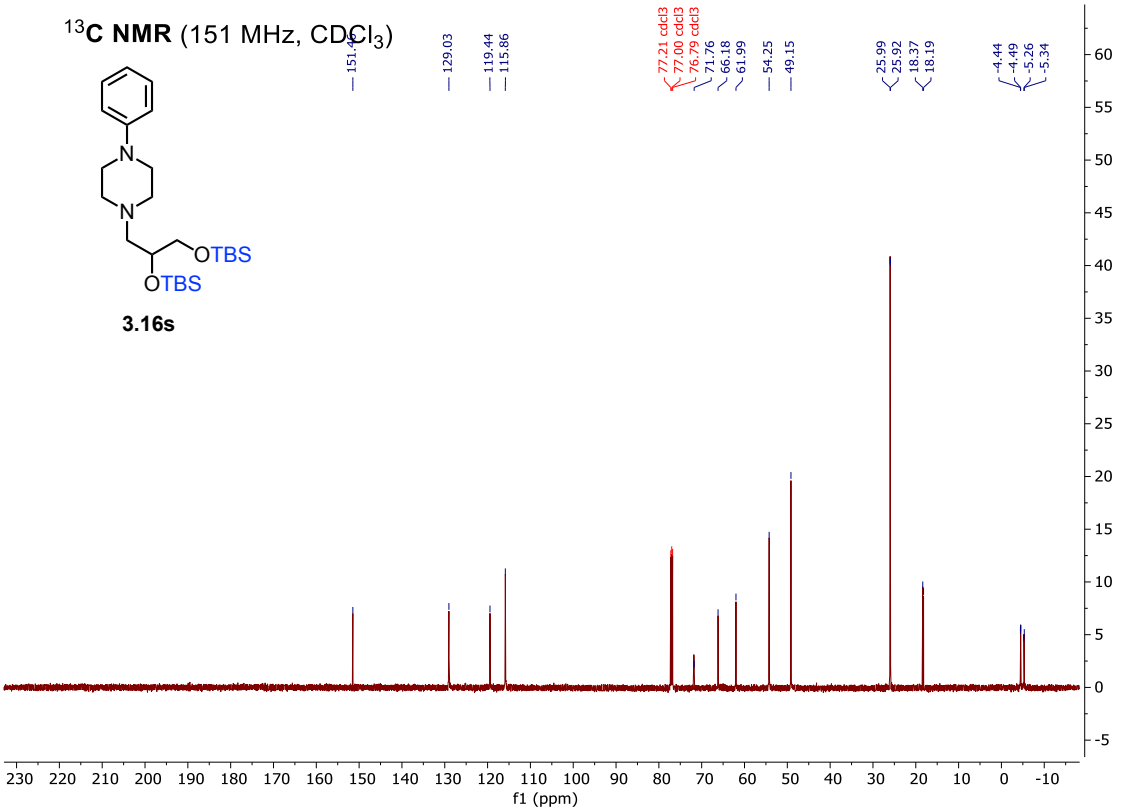
3.16s


473.3820
472.3766
474.3848
471.3697
475.3862
470.3635
476.3891
468.3483
469.3569
Relative Intensity
m/z


1H NMR (600 MHz, CDCl3)
[94%]
[86%]
OTBS
OTBS
3.18s
f1 (ppm)


1H NMR (600 MHz, CDCl3)
OTBS
OTBS
3.16s
f1 (ppm)


13C NMR (151 MHz, CDCl3)
[94%]
[86%]
OTBS
OTBS
3.18s
151.47
129.08
119.39
115.79
77.29 cdcl3
77.04 cdcl3
76.79 cdcl3
71.87
66.21
61.95
53.18
48.27
26.03
25.95
18.40
18.22
-4.41
-4.46
-5.23
-5.31
f1 (ppm)


13C NMR (151 MHz, CDCl3)
OTBS
OTBS
3.16s
151.44
129.03
119.44
115.86
77.21 cdcl3
77.00 cdcl3
76.79 cdcl3
71.76
66.18
61.99
54.25
49.15
25.99
25.92
18.37
18.19
-4.44
-4.49
-5.26
-5.34
f1 (ppm)