α- and β-Amino C–H Functionalization through Cooperative Catalysis

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When a catalytic reaction is carried out between two reactants, usually only one reactant is activated by a single catalyst while the other component is pre-activated so that the sluggish reactivity was compensated. In order to broaden the substrate scope, the development of cooperative catalysts that can generate both electrophilic and nucleophilic species in situ represents a compelling research objective. This thesis is focused on the development of cooperative catalyst systems and their applications to α- and β-amino C–H bond functionalization. In the first chapter of this thesis, a brief summary of the present cooperative catalysts will be discussed.

In the second chapter, the development of cooperative acid/acid catalysts for the α-alkynylation of *N*-alkylamines will be discussed. Typically, catalytic α-amino C–H alkynylation process is carried out under oxidative conditions, and enantioselective reactions are confined to tetrahydroisoquinoline derivatives. We disclose a strategy for the union of *N*-alkylamines and trimethylsilyl alkynes through cooperative actions of two Lewis acids, $B(C_6F_5)_3$ and a Cu-based complex without the use of oxidants. We proposed that various propargylamines can be synthesized through the reaction between a L_nCu–alkynyl complex and an iminium ion that are generated in situ. Furthermore, the utility of this protocol was demonstrated by applications in late stage α-alkynylation of bioactive amines and stereoselective synthesis of propargylamines.

In the third chapter of this thesis, catalytic and regioselective deuteration of β-amino C–H bonds in an array of *N*-alkylamine-based pharmaceutical compounds will be described. Isotopic labeling of β-amino C–H bond is promoted by the cooperative action of Lewis acidic $B(C_6F_5)_3$ and Brønsted basic *N*-alkylamine, converting a bioactive amine first into an iminium ion and then the corresponding enamine. Meanwhile, the acid/base catalysts can also promote the dedeuteration of acetone-d_6 to afford a deuterated ammonium ion and a boron enolate. Ensuing deuteration of the enamine by deuterated

ammonium ion followed by borohydride reduction leads to the formation of β-deuterated bioactive amines with up to 99% deuterium incorporation.

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List of Abbreviations

Ac	acyl
Asp	aspartic acid
Boc	*tert*-butoxycarbonyl
BOX	bisoxazoline
Bn	benzyl
Bu	butyl
Cbz	carboxybenzyl
CF_3	trifluoromethyl
CuAAC	Copper(I)-catalyzed Azide-Alkyne Cycloaddition
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DART	direct analysis in real time
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DMF	*N*, *N*-dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
dppe	1,2-bis(diphenylphosphino)ethane

dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
er	enatiomeric ratio
Et	ethyl
FLPs	frustrated Lewis pairs
HAT	hydrogen atom transfer
Hex	hexyl
HFIP	1,1,1,3,3,3-hexafluoroisopropanol
HIE	hydrogen isotope exchange
His	histidine
HPLC	high-performance liquid chromatography
LED	light-emitting diode
Me	methyl
MS	molecular sieve
NHC	*N*-heterocyclic carbene
NMI	*N*-methylimidazole
NMP	*N*-methyl piperidine
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
Ph	phenyl
PHOX	phosphinoxazoline

pK_a	negative base-10 logarithm of the acid dissociation constant of a solution
PMP	1,2,2,6,6-pentamethylpiperidine
ppm	parts per million
Pr	propyl
PyBOX	bis(oxazolinyl)pyridine
QUINAP	[1-(1-isoquinolinyl)-2-naphthyl]diphenylphosphine
SET	single electron transfer
TBAF	tetra-*n*-butylammonium fluoride
TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene
TBSCl	*tert*-butyldimethylsilyl chloride
TCYP	tricyclohexylphosphine
TET	ten-eleven translocation
Tf	trifluoromethanesulfonyl
TLC	thin-layer chromatography
TMS	trimethylsilyl
Tol	tolyl
TPP	triphenylphosphine
UV	ultraviolet
ZPE	zero-point energy

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Chapter 1

A Summary of Cooperative Catalysis

1.1 Introduction

Cooperative catalysis involves the combination of one or more catalysts to activate various substrates to generate reactive coupling partners to afford a single chemical transformation.[1] Cooperative acid/base catalysts have been utilized in transformations to simultaneously activate and generate both nucleophilic and electrophilic species in situ which circumvents the wasteful pre-activation step. However, many cooperative acid/base catalysts can only incorporate weak to moderately acidic and basic moieties in their scaffold[1] because the acidic and basic components of the catalyst can undergo acid-base complexation with the catalyst, substrate, and product, thus, deactivating the catalysts. A possible solution to this problem is to avoid utilizing the combination of catalysts that may have a strong affinity to interact with each other (i.e., hard-hard or soft-soft combinations).[1,2] Thus, it is highly desired to achieve an efficient and stereoselective transformation that is atom-[3] and step-economical,[4] which has been important criteria in the field of synthetic organic chemistry.

Cooperative catalysis has been successfully applied to a variety of transformations (aldol, Mannich, Henry, and alkynylation reactions, among others)[1] to afford the desired

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[1] (a) 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. (g) Romiti, F.; del Pozo, J.; Paioti, P. H. S.; Gonsales, S. A.; Li, X.; Hartrammpf, F. W. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2019**, *141*, 17952–17961.

[2] (a) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656–5682. (b) Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 4222–4266. (c) Adair, G.; Mukherjee, S.; List, B. *Aldrichimica Acta* **2008**, *41*, 31–39. (d) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.,* **2009**, *38*, 1187–1198. (e) Phipps, R. J.; Hamilton, G. L.; Toste, F. D. *Nat. Chem.* **2012**, *4*, 603–614. (f) Brak, K.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2013**, *52*, 534–561. (g) Neel, A. J.; Hilton, M. J.; Sigman, M. S.; Toste, F. D. *Nature* **2017**, *543*, 637–646.

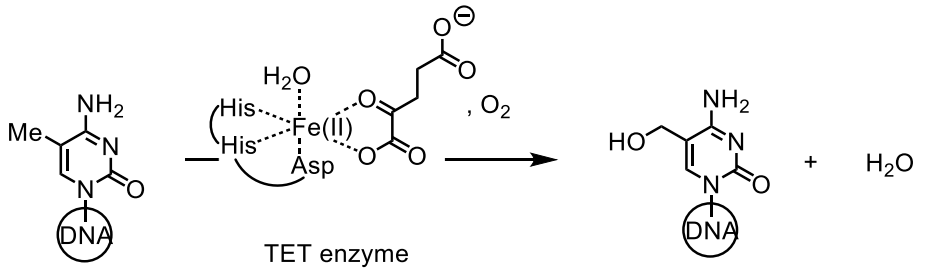
[3] Trost, B. M. *Science* **1991**, *254*, 1471–1477.

[4] Wender, P. A.; Miller, B. L. *Nature* **2009**, *460*, 197–201.

product in an efficient and stereoselective manner. This chapter will serve as a brief summary of cooperative acid/acid and acid/base catalyst systems.

1.2 Cooperative Catalysis

Nature utilizes enzymes as catalysts to promote biosystematic processes. Enzymatic reactions typically do not rely on a single acidic or basic unit. Instead, they work cooperatively with other small molecules or enzymes to let the biosystem run properly.[5] For instance, in the presence of Fe-based ten-eleven translocation (TET) enzyme and oxygen, 5-methylcytosine residue of DNA is oxidized and results in 5-hydroxymethylcytosine (Scheme 1.1).[6] Inspired by enzymatic systems, chemists have developed catalyst systems to achieve the activation of both coupling partners for various transformations to avoid a wasteful pre-activation step.[7]



Scheme 1.1 Fe-Based TET Enzyme-Catalyzed Oxidation of 5-Methylcytosine Residue

1.2.1 Cooperative Acid/Acid Catalysis

[5] (a) Brown, K. A.; Kraut, J. *Faraday Discuss*., **1992**, *93*, 217–224. (b) Polshakov, V. I. *Russ. Chem. Bull*., **2001**, *50*, 1733–1751. (c) Weckbecker, A.; Gröger, H., Hummel, W. *Adv. Biochem. Eng./Biotechnol*., **2010**, *120*, 195–242. (d) Wu, H., Tian, C.; Song, X.; Liu, C.; Yang, D.; Jiang, Z. *Green Chem*., **2013**, *15*, 1773–1789. (e) Strater, N.; Lipscomb, W. N.; Klabunde, T.; Krebs, B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2024–2055.

[6] Kohli, R. M.; Zhang, Y. *Nature* **2013**, *502,* 472–479.

[7] Shibasaki, M.; Kumagai, N.; Moberg, C.; Trincado, M.; Grützmacher, H.; Wang, H.; Deng, Y; Lu, X.; Li, D.; Wu, H.; He, Y.; Gong, L.; Waser, M.; Novacek, J.; Gratzer, K.; Weiss, M.; Peters, R.; Paradies, J.; Mancin, F.; Prins, L. J.; Scrimin, P.; Gröger, H.; Nigra, M. M.; Katz, A.; Winnacker, M.; Vagin, S.; Rieger, B. *Cooperative Catalysis: Designing Efficient Catalysts for Synthesis*. Peters, R. (ed.). Wiley-VCH: New York, 2015.

Enantioselective transformations promoted by two metal-based complexes,[8] as well as Brønsted acid and organometallic complexes[9] or hydrogen-bond donors,[10] have been reported in the literature (Figure 1.1).

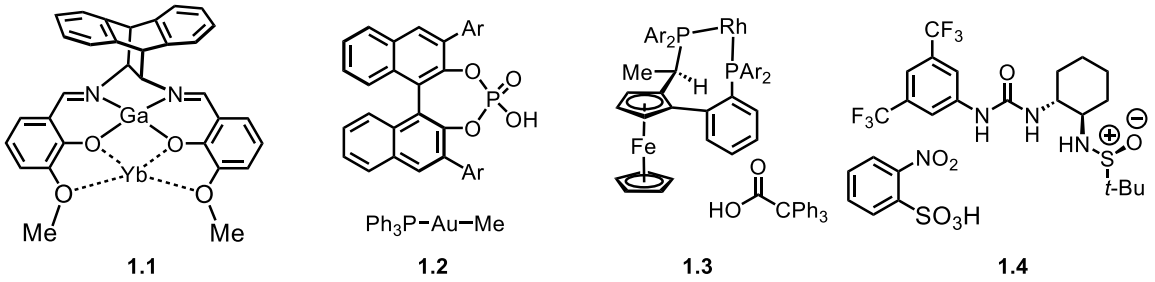
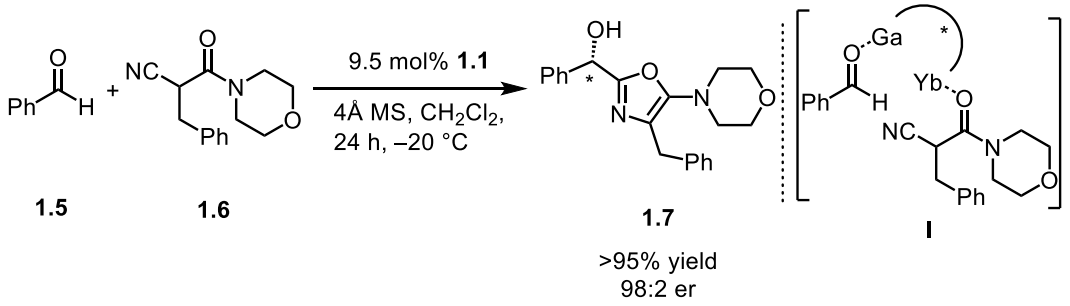


Figure 1.1 Structure of Cooperative Acid/Acid Catalysts

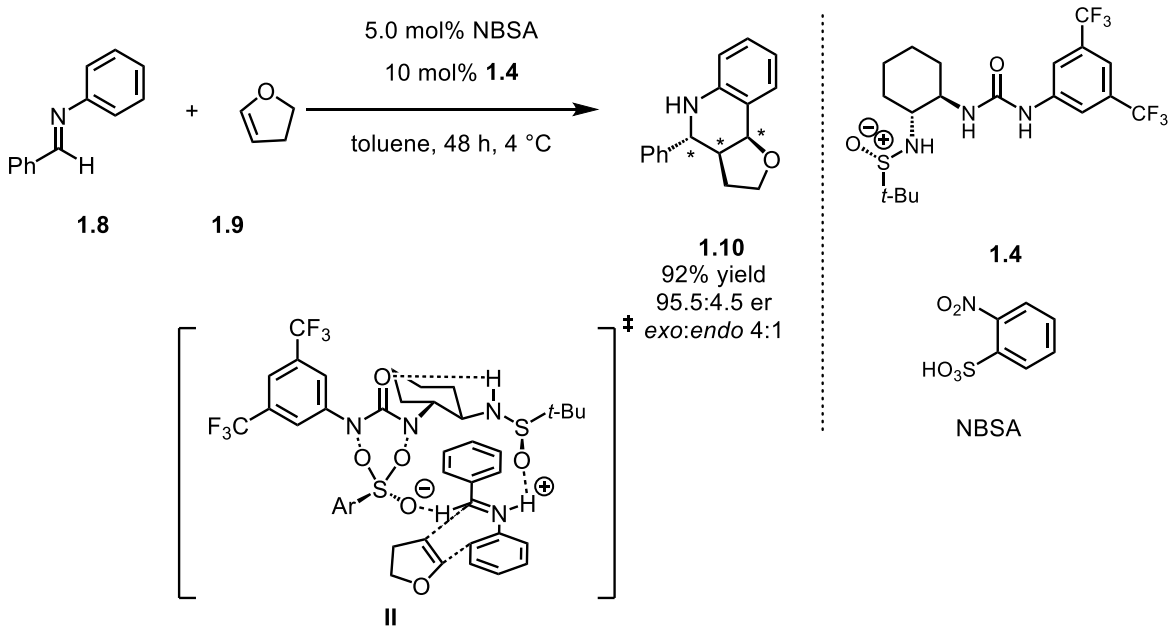
The Shibasaki group has reported the *α*-addition of isocyanides to aldehydes using a heterobimetallic Ga/Yb–Schiff base complex (Scheme 1.2).[8] The bimetallic catalyst is not only responsible for the activation of benzaldehyde **1.5** but could interact with 2-benzyl-3-morpholino-3-oxopropanenitrile **1.6** to effectively control the orientation of the two substrates in enantio-determining step (**I**). Following cyclization gives (*S*)-(4-benzyl-5-morpholinooxazol-2-yl)(phenyl)methanol **1.7** in quantitative yield with 98:2 er. This work has demonstrated that two metal-based Lewis acids could work cooperatively to promote chemical reactions.



Scheme 1.2 Enantioselective *α*-Addition of Isocyanides to Aldehydes

[8] Mihara, H.; Xu, Y.; Shepherd, N. E.; Matsunaga, S.; Shibasaki, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 8384–8385.
[9] Kong, J.-R.; Ngai, M.-Y.; Krische, M. J. J. *J. Am. Chem. Soc*. **2006**, *128*, 718–719.
[10] Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. *Science* **2010**, *327*, 986–990.

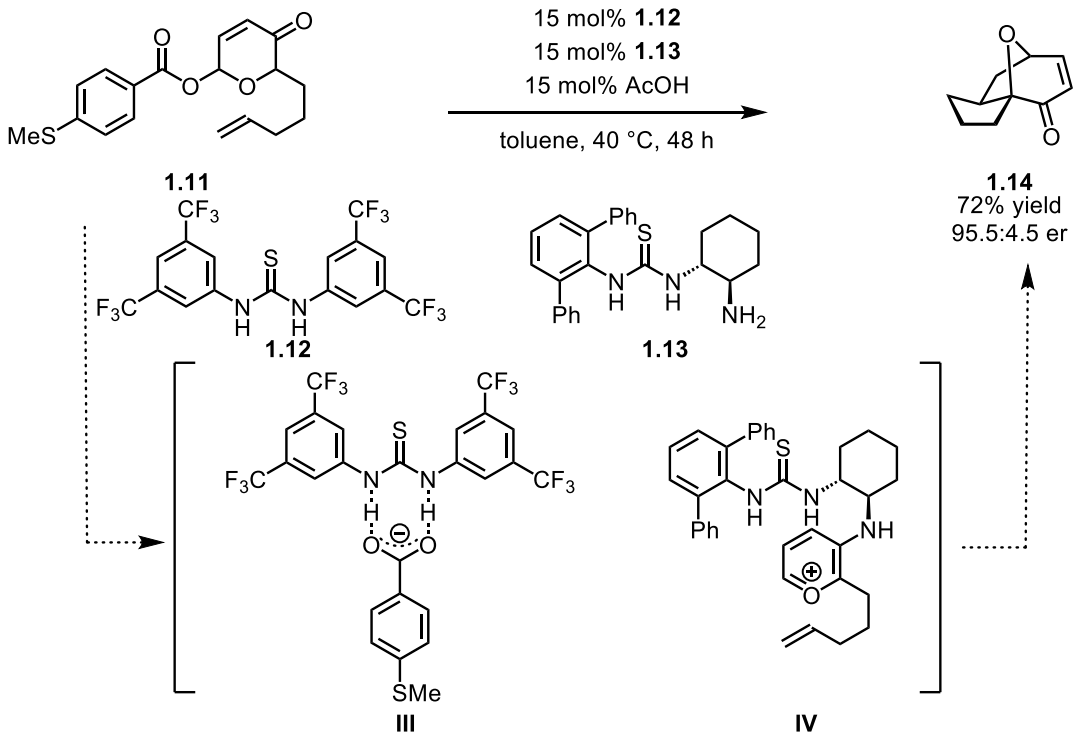
Hydrogen bond donors are able to interact with anionic species or bind to the Lewis basic site of an electrophile through hydrogen bonding interactions.[11] Jacobson and coworkers carried out a Brønsted acid-promoted enantioselective Povarov reaction[12] using a chiral urea catalyst (Scheme 1.3).[10] They found that the combination of bifunctional sulfinamido urea derivative **1.4** and *o*-nitrobenzenesulfonic acid (NBSA) were able to catalyze the reaction between (*E*)-*N*,1-diphenylmethanimine **1.8** and 2,3-dihydrofuran **1.9**. NBSA was first activated by urea **1.4**, which then protonated aldimine **1.8**. A rigid structure was formed to control enantioselectivity through hydrogen bonding interactions (**II**). As a result, tetrahydroquinoline derivative **1.10**, which has three contiguous stereogenic centers, was obtained in 92% yield with 95.5:4.5 er. The nature of the interactions between substrates and catalysts and the likely basis for enantioinduction were revealed based on detailed experimental and computational analysis of this catalyst system.



Scheme 1.3 Cooperative Acid/Acid-catalyzed Enantioselective Povarov Reaction

[11] Doyle, A. G.; Jacobsen, E, N. *Chem. Rev.* **2007**, *107*, 5713–5743.
[12] Kouznetsov, V. V. *Tetrahedron*, **2009**, *65*, 2721–2750.

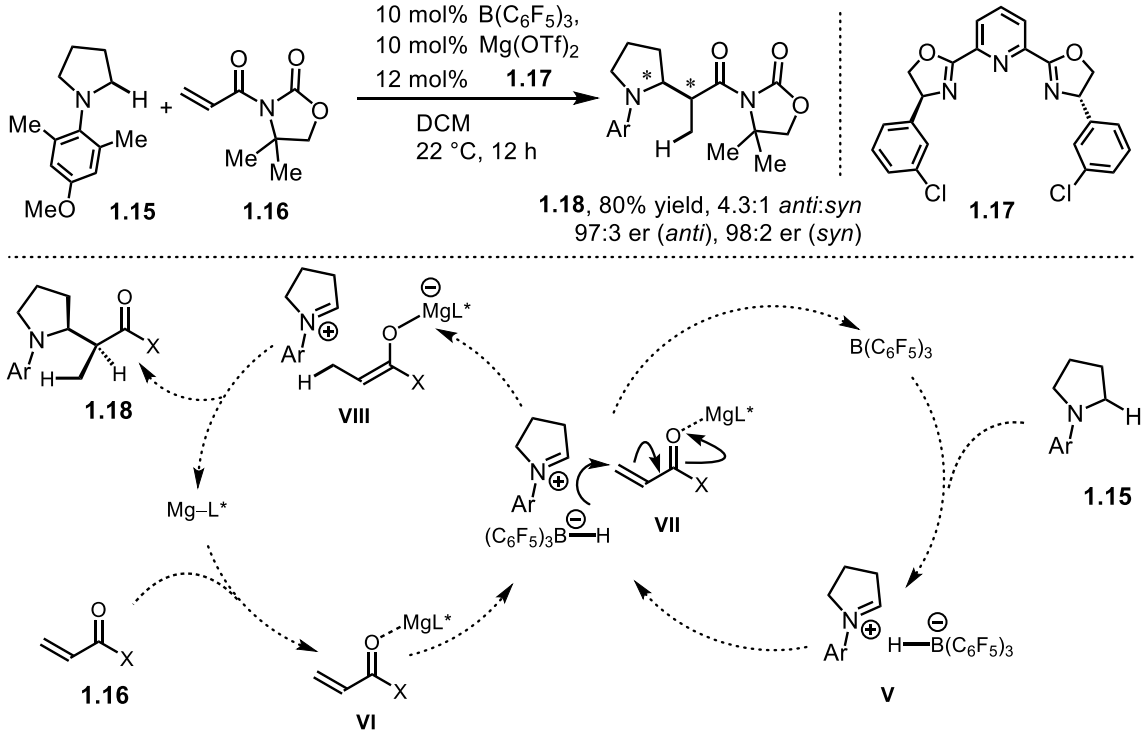
The same group also reported the dual thiourea catalyst system (**1.12** and **1.13**) for intramolecular oxidopyrylium [5+2] cycloaddition reactions (Scheme 1.4). [13] Acetoxypyranone **1.11** can be converted to enantioenriched 8-oxabicyclo[3.2.1]octane **1.14** in 72% yield with 94.5:5.5 er by using thiourea catalysts **1.12** and **1.13**, as well as catalytic amount of acetic acid. Control reactions demonstrated that with only chiral thiourea **1.13**, the desired product can be obtained in 32% yield with 86:14 er. By using thiourea cocatalyst **1.12**, which is responsible for the ionization of substrate **1.11**, the reaction efficiency and enantioselectivity were improved. Substituents on the thiourea catalysts with different electronic properties were evaluated. Electron-deficient thiourea catalyst **1.12** helps rupture the C–O bond of acetoxypyranone **1.11** and stabilizes anion **III**, while the primary amine of chiral thiourea catalyst **1.13** was converted to aminopyrylium **IV** to promote enantioselective C–C bond formation.



Scheme 1.4 [5+2] Cycloaddition through Two Hydrogen Bond Donors Catalysis

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

Recently, our group developed α-amino C–H bond functionalization through hydride abstraction to synthesize enantioenriched α-amino acid derivatives.[14] We reported the $B(C_6F_5)_3$ and Mg–PyBOX complex-catalyzed α-alkylation reaction between 1-(4-methoxy-2,6-dimethylphenyl)pyrrolidine **1.15** and acryloyloxazolidinone **1.16** to afford enantioenriched product **1.18** in 88% yield with 98:2 er (Scheme 1.5). This transformation was proposed to proceed through $B(C_6F_5)_3$-catalyzed hydride abstraction of amine **1.15** to generate an ion pair consisting of an iminium ion and borohydride **V**. At the same time, α, β-unsaturated compound **1.16** is activated by Mg–PyBOX complex (**VI**), which can be reduced by in situ generated borohydride to give enantioenriched enolate **VIII**. The enolate can then attack the in situ generated iminium ion in a stereoselective manner to afford the enantioenriched α-amino carbonyl compound **1.18** in 80% yield with up to 98:2 er.



Scheme 1.5 α-Amino C–H Bond Functionalization through Hydride Abstraction

[14] (a) 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. (b) Chan, J. Z.; Chang, Y.; Wasa, M. *Org. Lett.* **2019**, *21*, 984–988.

1.2.2 Cooperative Acid/Base Catalysis

There have been reports on cooperative acid/base catalysts including proline,[15] cinchona alkaloid,[16] aminothiourea,[17] chiral phosphoric acid,[18] ZnProPhenol complex,[19] and Cu–bisphosphine/Barton's base,[20] that can promote various enantioselective transformations (Figure 1.2).

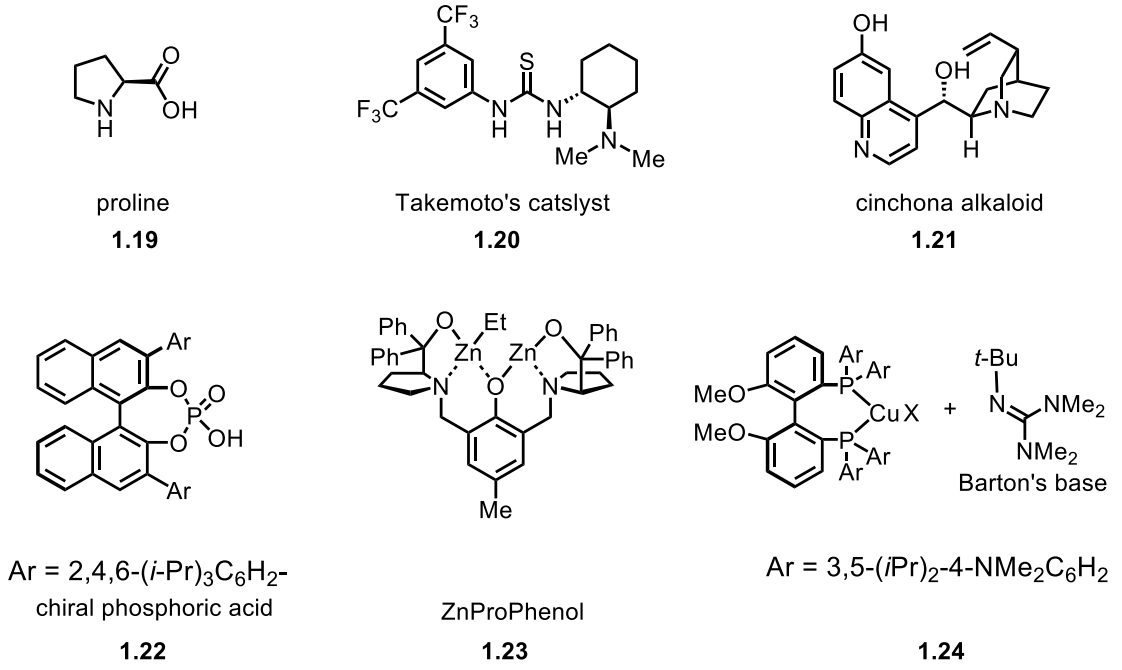
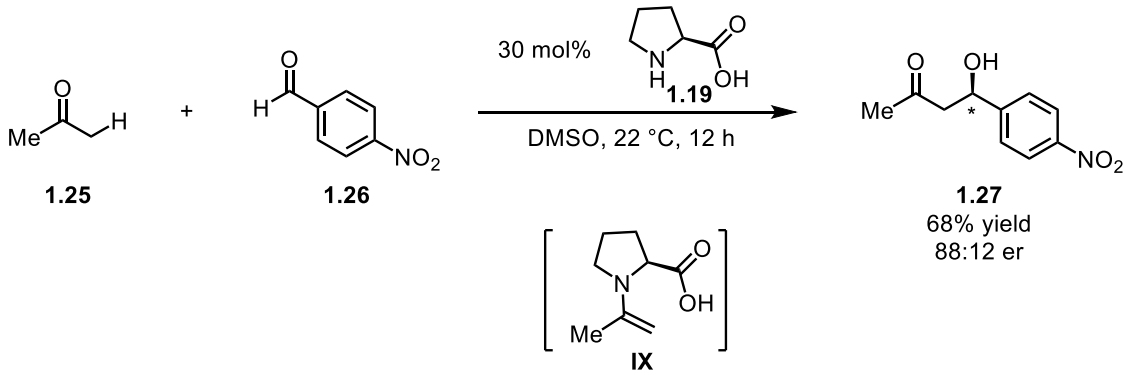


Figure 1.2 Structure of Cooperative Acid/Base Catalysts

In 2000, List and Barbas reported that proline **1.19** catalyzed enantioselective aldol reaction between acetone **1.25** and *p*-nitrobenzaldehyde **1.26** to afford (*R*)-4-hydroxy-4-(4-nitrophenyl)butan-2-one **1.27** in 68% yield with 88:12 er (Scheme 1.6).[15] In this transformation, they proposed that the secondary amine generates enamine intermediate **IX** upon reaction with the ketone after carboxylic acid-assisted dehydration. This seminal

[15] List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.
[16] Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.
[17] Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906–9907.
[18] Terada, M.; Tanaka, H.; Sorimachi, K. *J. Am. Chem. Soc.* **2009**, *131*, 3430–3431.
[19] Trost, B. M.; Bartlett, M. J. *Acc. Chem. Res.* **2015**, *48*, 688–701.
[20] Shibasaki, M.; Kumagai, N. in *Cooperative Catalysis: Designing Efficient Catalysts for Synthesis*, Peters, R. (ed.). Wiley-VCH: New York, 2015; Chapter 1.

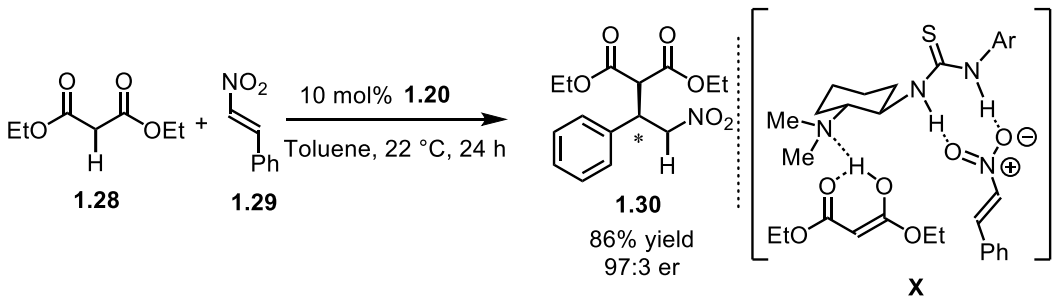
report of utilizing proline as a cooperative acid/base catalyst served as an inspiration for the development of various enantioselective transformations catalyzed by enantiomerically-enriched secondary amines.[21]



Scheme 1.6 Proline-Catalyzed Aldol Reaction

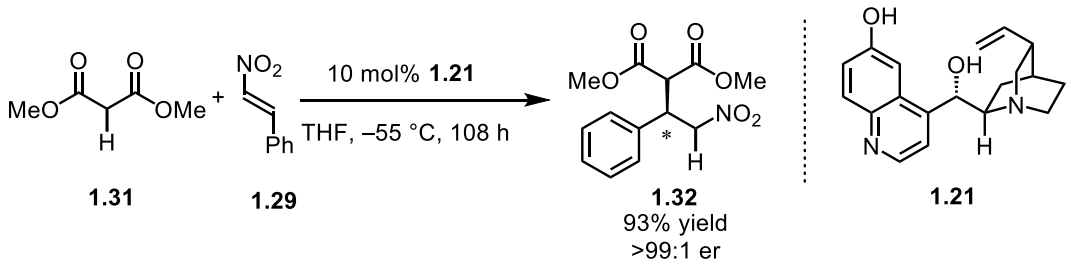
Takemoto and coworkers reported the enantioselective Michael addition catalyzed by chiral aminothiourea catalyst **1.20**.[16] In this transformation, thiourea catalyst **1.20** promotes the coupling of ethyl malonate **1.28** and (*E*)-(2-nitrovinyl)benzene **1.29** to afford the desired product **1.30** in 86% yield with 97:3 er (Scheme 1.7). Malonate **1.28** is deprotonated by an amine moiety of aminothiourea **1.20**, and the enolate formed in situ can interact with the catalyst through hydrogen bonding interactions. Nitroalkene can also interact with aminothiourea **1.20** through hydrogen bonding interactions, which gives a rigid structure (**X**) for enantioselective C–C bond formation. Although this bifunctional catalyst can facilitate the enantioselective Michael reaction, this method requires the use of highly acid-sensitive pronucleophiles and electrophiles as substrates.

[21] (a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244. (b) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423–2425. (c) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051–15053. (d) Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D. W. C. *Science*, **2007**, *316*, 582–585.



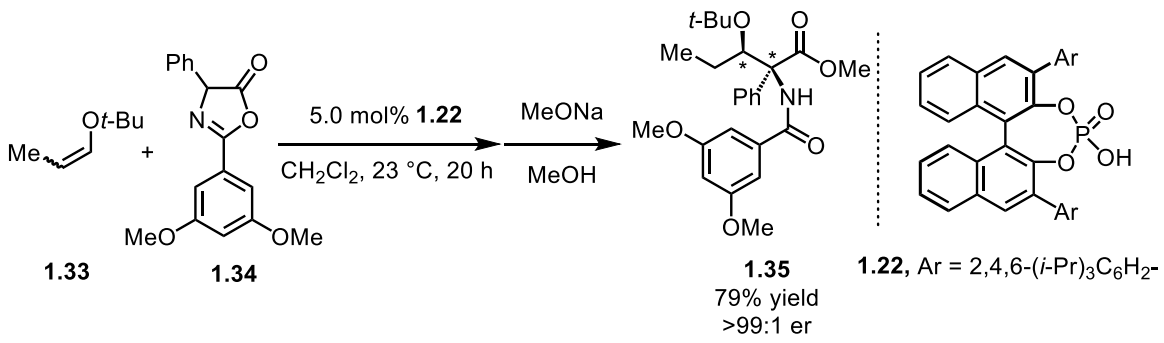
Scheme 1.7 Enantioselective Conjugate Addition Promoted by the Takemoto's Catalyst

The Deng group utilized a cinchona alkaloid derivative to catalyze the Michael reaction between malonate **1.31** and (*E*)-(2-nitrovinyl)benzene **1.29** to afford the product **1.32** in 93% yield with over 99:1 er (Scheme 1.8).[17] The acidic phenolic-OH and basic quinuclidine moieties in this bifunctional catalyst are responsible for stabilizing and organizing the transition state assembly of the enantioselective 1,4-addition.



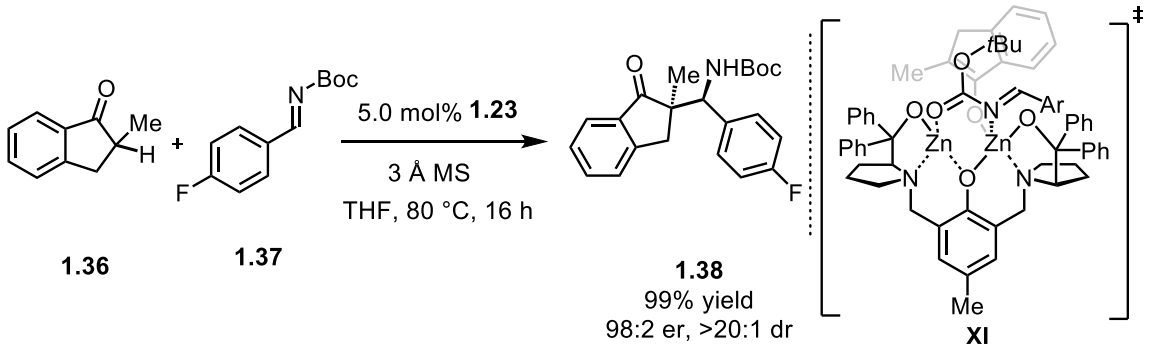
Scheme 1.8 Enantioselective Conjugate Addition Promoted by Cinchona Alkaloids

The Terada group reported the use of chiral phosphoric acid **1.22** to promote the enantioselective reaction between vinyl ether **1.33** and oxazol-5(4*H*)-one derivative **1.34** to afford the desired product **1.35** in 79% yield with >99:1 er after methanolysis (Scheme 1.9).[18] Chiral phosphoric acid **1.22** was responsible for the protonation of vinyl ether **1.33** and control the stereoselectivity through hydrogen bonding interactions.



Scheme 1.9 Enantioselective Direct Aldol-Type Reaction of Azlactone

Trost has reported that ZnProPhenol catalyst **1.23** can promote the enantioselective direct Mannich-type reaction between methyl indanone **1.36** and *N*-Boc-substituted aldimine **1.37**.[19,22] *β*-Amino carbonyl compound **1.38** was obtained in 99% yield with 98:2 er and >20:1 dr (Scheme 1.10). Indanone **1.36** was deprotonated by ZnProPhenol catalyst **1.23** to form zinc enolate which then undergoes transition state (**XI**) with *N*-Boc-substituted aldimine **1.37** through two-point binding with the dinuclear catalyst to control enantioselectivity. Although various *α*-substituted carbonyl compounds can be converted into corresponding *α*-amino carbonyl compounds using the bifunctional catalyst **1.23**, the scope of the pronucleophiles is limited to ketones.

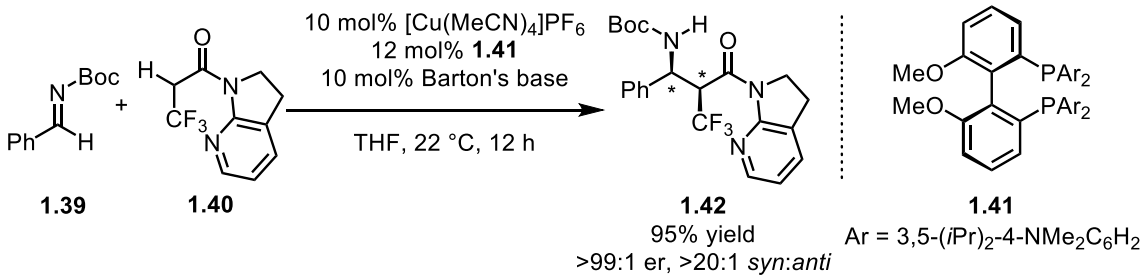


Scheme 1.10 ZnProPhenol-Catalyzed Mannich-Type Reaction

In 2014, the Shibasaki group reported the chiral Cu(I)/bisphosphine and Barton's base-catalyzed Mannich-type reaction of *N*-Boc-benzaldimine **1.39** and 7-

[22] Trost, B. M.; Saget, T.; Hung, C.-I. *J. Am. Chem. Soc.* **2016**, *138*, 3659–3662.

azaindolinylamide **1.40** (Scheme 1.11).[23] In this transformation, they obtained the □-amino carbonyl compound **1.42** in 95% yield with >99:1 er. The combination of soft Lewis acid and hard Brønsted base can overcome acid-base complexation and promote the formation of the nucleophile from amide substrate **1.39**. However, the electron-withdrawing trifluoromethyl substituent of **1.40** is necessary, which lowers the pK_a of the α-C–H bond of the amide substrate.

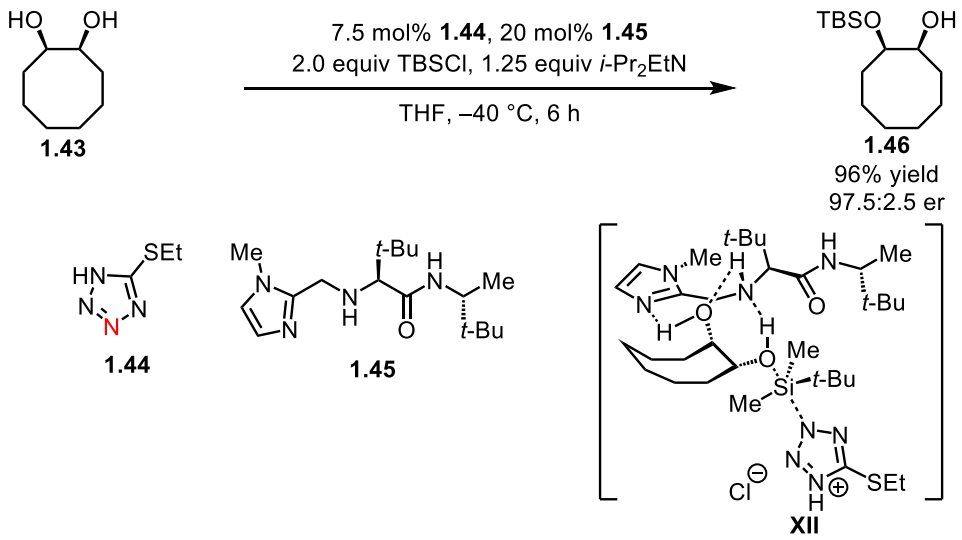


Scheme 1.11 Enantioselective Mannich-Type Reaction of α-CF_3 Amides

1.2.3 Selected Examples for Other Variations of Cooperative Catalysis

The catalytic enantioselective monosilyl protection of diols providing valuable alcohol-containing molecules was reported using cooperative Lewis base and Brønsted base catalysis (Scheme 1.12).[24] Amino acid-derived catalyst **1.45** could be readily associated with cyclooctanediol **1.43** through hydrogen bonding interaction (**XII**). Diol **1.43** could undergo stereoselective silyl protection using the combination of tetrazole **1.44** and amino acid-derived **1.45** to give the desired product **1.46** in 96% yield with 97.5:2.5 er.

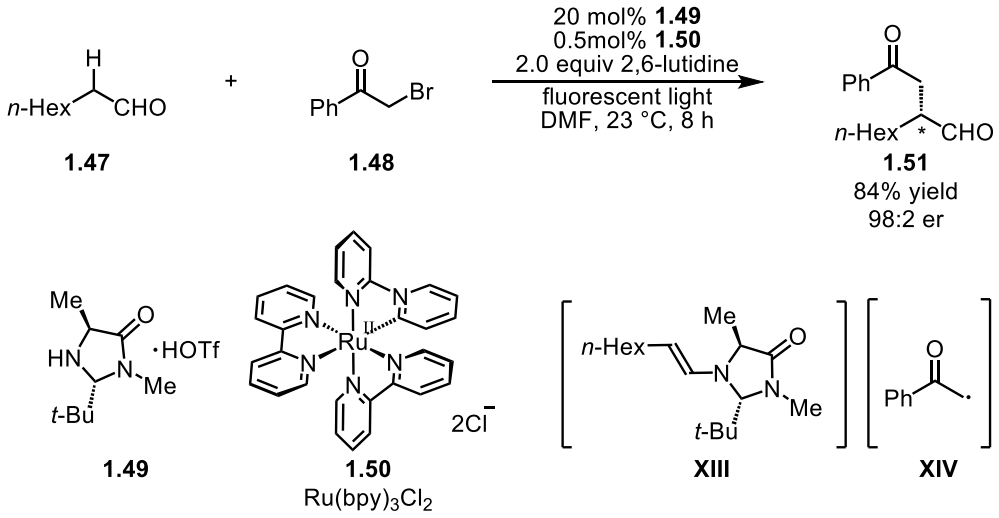
[23] Yin, L.; Brewitz. L.; Kumagai, N.; Shibasakl, M. *J. Am. Chem. Soc*. **2014**, *136*, 17958–17961.
[24] a) Zhao, Y.; Rodrigo, J.; Hoveyda, A. H.; Snapper, M. L. *Nature* **2006**, *443*, 67–70. (b) You, Z.; Hoveyda, A. H.; Snapper, M. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 547–550. (c) Sun, X.; Worthy, A. D.; Tan, K. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8167–8171. (d) Manville, N.; Alite, H.; Haeffner, F.; Hoveyda, A. H.; Snapper, M. L. *Nat. Chem.* **2013**, *5*, 768–774.



Scheme 1.12 Silyl Protection by Cooperative Lewis Base and Brønsted Base Catalysis

Secondary amine[25] and photoredox catalysis[26] are two powerful systems that have found applications in organic synthesis. The combination of secondary amine and photoredox catalyst systems was reported by MacMillan for the α-alkylation reaction of **1.47** by 2-bromo-1-phenylethan-1-one **1.48** (Scheme 1.13).[27] The use of secondary amine catalyst **1.49** and Ru-based photoredox catalyst **1.50** delivers enantiomerically enriched product **1.51** in 84% yield and 98:2 er. Chiral secondary amine catalyst **1.49** is responsible for generating an enamine intermediate **XIII** from aldehyde **1.47**. Meanwhile, electron-deficient alkyl radical **XIV** can be generated through the reaction between the alkyl bromide and Ru(I) complex. This transformation can be carried out under mild conditions, and diastereoselective α-alkylation was demonstrated to be practical.

[25] (a) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev*. **2007**, *107*, 5416–5470. (b) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev*. **2007**, *107*, 5471–5569.
[26] Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, *116*, 10075–10166.
[27] Nicewicz, D. A.; MacMillan, D. W. C. *Science*, **2008**, *322*, 77–80.



Scheme 1.13 Cooperative Secondary Amine and Photoredox Catalysis

Another significant mode of substrate activation is using frustrated Lewis pairs (FLPs) which make use of the earth-abundant main group elements. A pair of Lewis acid and Lewis base, such as $B(C_6F_5)_3$ and $P(t\text{-}Bu)_3$, can overcome mutual quenching due to steric repulsion (Figure 1.3).[28] The Stephan group demonstrated that this pair of Lewis acid and Lewis base can promote the reversible activation of dihydrogen.[29]

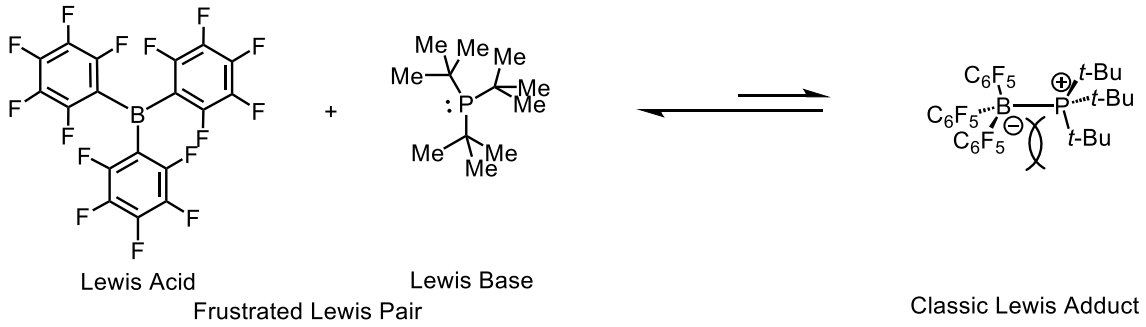
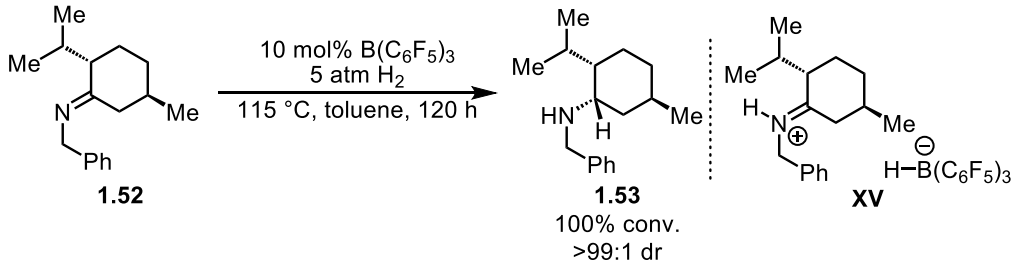


Figure 1.3 Frustrated Lewis Pair

[28] (a) Welch, G. C.; Juan, R. R. S.; Masuda, J. D.; Stephan, D. W. *Science* **2006**, *314*, 1124-1126. (b) *Frustrated Lewis Pairs I*; Stephan, D. W.; Erker, G. (eds.). Springer Press: New York, 2013; Vol. 332. (c) *Frustrated Lewis Pairs II: Expanding the Scope*; Erker, G.; Stephan, D. W. (eds.). Springer: Berlin, 2013; Vol. 334. (d) Stephan, D. W.; Erker, G. *Angew. Chem., Int. Ed.* **2015**, *54*, 6400-6441. (e) Stephan, D. W. *J. Am. Chem. Soc.* **2015**, *137*, 10018-10032.

[29] Stephan, D. W. *Org. Biomol. Chem.* **2008**, *6*, 1535-1539.

The Stephan group has reported that $B(C_6F_5)_3$ catalyzed hydrogenation of imine **1.52** (Scheme 1.14).[30] In this transformation, they disclosed that $B(C_6F_5)_3$ in pair with Lewis basic imine **1.52** can activate and split dihydrogen to generate an iminium ion and a borohydride (**XV**). Upon reduction of the iminium ion by the in situ generated borohydride, amine **1.53** can be obtained with >99:1 dr.



Scheme 1.14 Hydrogenation through Frustrated Lewis Pair Catalysis

Other than dihydrogen, a number of small molecules, such as CO_2, SO_2, and NO, among others, are known to be activated by FLPs.[28] Although FLPs have been demonstrated to promote the catalytic hydrogenation of unsaturated compounds,[29] the application of FLPs as catalysts for C–C bond formation to generate useful products has not been well developed. The unique capability of FLPs to overcome mutual quenching with various functional groups demonstrates the potential for them to be used as cooperative catalysts. The utilization of FLPs has been an area of research that our group has been interested in over the past few years.

1.3 Conclusion and Outlook

The development of cooperative catalysis has provided various modes of activation for substrates, which may circumvent the use of pre-activated coupling partners. Although new disconnections have been achieved, many of the reported methods are highly dependent on the use of precious transition metal-based catalysts and often have poor functional group tolerance. It represents a compelling research objective to develop cooperative catalyst systems that are based on main group element-derived catalysts to

[30] (a) Chase, P. A.; Jurca, T.; Stephan, D. W. *Chem. Commun*., **2008**, 1701–1703. (b) Heiden, M. Z.; Stephan, D. W. *Chem. Commun*., **2011**, 5729–5731.

promote chemical transformations under redox-neutral conditions with broad functional group compatibility.

Development of *α*-Amino C–H Alkynylation through Cooperative Actions of $B(C_6F_5)_3$ and Organocopper Complex

2.1 Introduction

Propargylamines are prevalent in pharmaceuticals[31] and are useful synthetic building blocks for the manufacturing of various organic substrates, natural products, and drugs.[32] Drugs derived from propargylamine such as rasagiline,[33] selegiline,[31a] and DPC 961,[34] have been directly applied to the treatment of neurodegenerative diseases (Figure 2.1). Since propargylamine contains an alkyne unit, it is also amenable to synthesize triazole under classic click reaction conditions: Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC).[35] In addition, the amine moiety of propargylamines could also undergo nucleophilic reactions (Scheme 2.1),[36] thus, highlighting the importance of this class of molecule.

[31] (a) Birks, J.; Flicker, L. *Cochrane Database of Systematic Reviews*; John Wiley & Sons, Ltd: Chichester, UK, 2003; Vol. 1. (b) Boulton, A. A.; Davis, B. A.; Durden, D. A.; Dyck, L. E.; Juorio, A. V.; Li, X.-M.; Paterson, I. A.; Yu, P. H. *Drug Dev. Res.* **1997**, *42*, 150–156. (c) Chen, J. J.; Swope, D. M. *J. Clin. Pharmacol*. **2005**, *45*, 878–894.

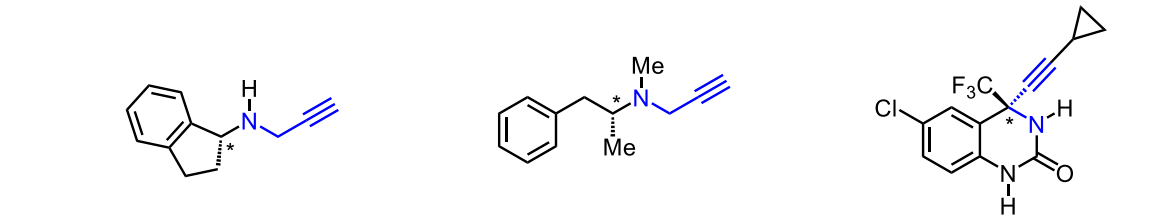
[32] (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599. (b) Coqueron, P.-Y.; Didier, C.; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1411–1414. (c) Ermolat'ev, D. S.; Bariwal, J. B.; Steenackers, H. P. L.; De Keersmaecker, S. C. J.; Van der Eycken, E. V. *Angew. Chem., Int. Ed.* **2010**, *49*, 9465–9468. (d) Gainer, M. J.; Bennett, N. R.; Takahashi, Y.; Looper, R. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 684–687. (e) Arshadi, S.; Vessally, E.; Edjlali, L.; Hosseinzadeh-Khanmiri, R.; Ghorbani-Kalhor, R. *Beilstein J. Org. Chem.* **2017**, *13*, 625–638. (f) Zhao, X.-B.; Ha, W.; Jiang, K.; Chen, J.; Yang, J.-L.; Shi, Y.-P. *Green Chem.* **2017**, *19*, 1399–1406. (g) Lauder, K.; Toscani, A.; Scalacci, N.; Castagnolo, D. *Chem. Rev.* **2017**, *117*, 14091–14200.

[33] Chen, J. J.; Swope, D. M. *J. Clin. Pharmacol.* **2005**, *45*, 878–894.

[34] Cox, P. M.; Bumpus, N. N. *ChemMedChem* **2016**, *11*, 2630–2637.

[35] (a) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem*. **2002**, *67*, 3057–3064. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, B.K. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599. (c) Kolb, H.C.; Sharpless, B.K. *Drug Discov Today*. **2003**, *8*, 1128–1137.

[36] Mali, J. K.; Takale, B. S.; Telvekar, V. N. *RSC Adv*. **2017**, *7*, 2231–2235.

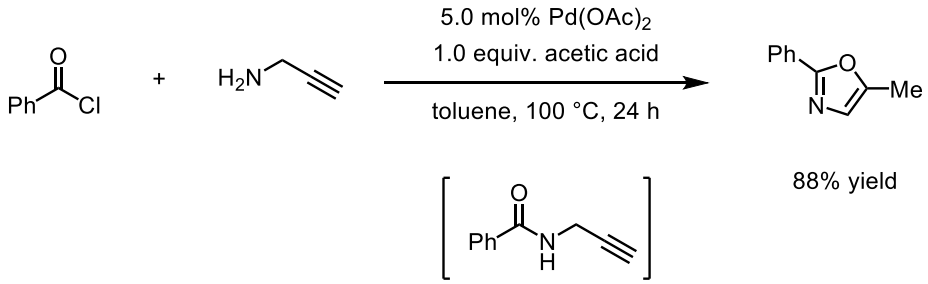


Rasagiline
(treatment for Parkinson's disease)

Selegiline
(antidepressant, treatment for Parkinson's disease)

DPC 961
(reverse transcriptase inhibitor)

Figure 2.1 Pharmaceuticals that Contain a Propargylamine Unit



Scheme 2.1 Nucleophilic Reaction of Propargylamine to Synthesize Oxazoline

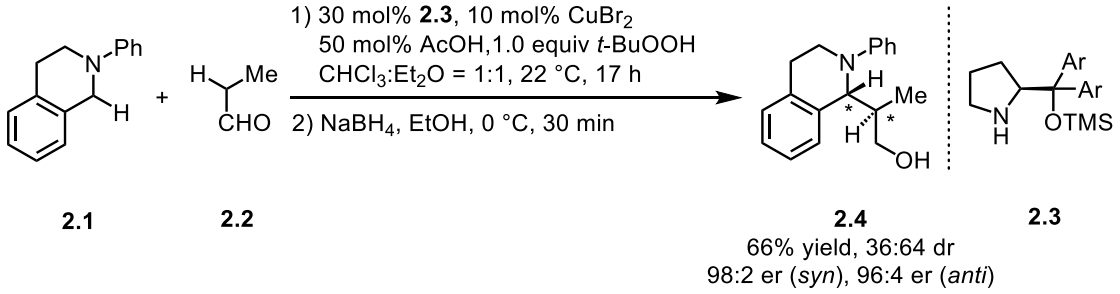
2.2 *α*-Amino C–H Activation and Synthesis of Propargylamines

2.2.1 *α*-Amino C–H Activation

Amines and amides are among the most abundant structural motifs in nature.[37] An attractive method to synthesize amines is to directly achieve catalytic regioselective C–H bond activation without using any pre-activating step or reagents to couple an undecorated amine with organic molecules of interest. This field has been extensively studied by many groups, leading to the development of various strategies for the goal of amino C–H activation over the last decade.[38] One example is the work reported by Chi group where they demonstrated the combination of secondary amine **2.3** and $CuBr_2$-catalyzed alkylation of *N*-phenyltetrahydroisoquinoline **2.1** and propionaldehyde **2.2**

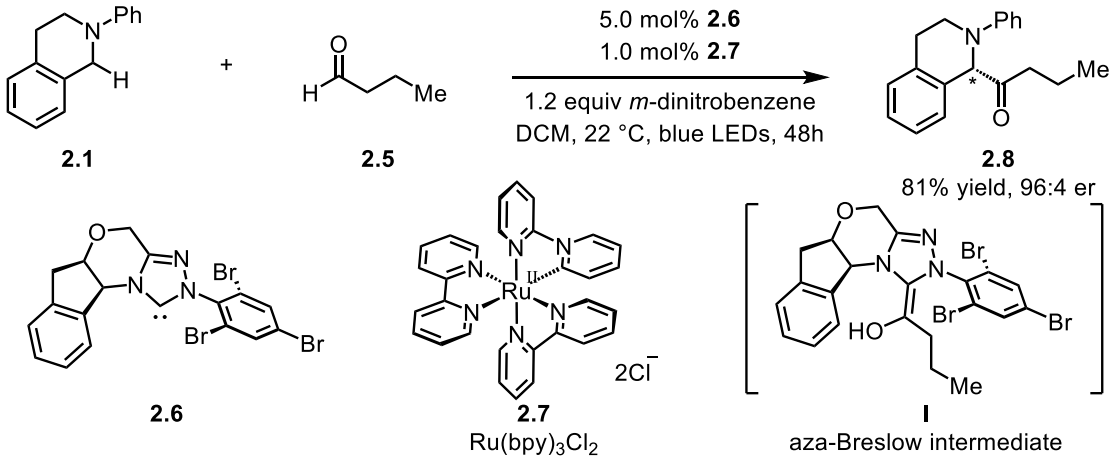
[37] Blunt, J. W.; Copp, B. R.; Keyzers, R. A.; Munro, M. H. G.; Prinsep, M. R. *Nat. Prod. Rep.*, **2017**, *34*, 235–294.
[38] (a) Sud, A.; Sureshkumar, D.; Klussmann, M. *Chem. Commun.* **2009**, 3169–3171. (b) Zhang, J.; Tiwari, B.; Xing, C.; Chen, X.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 3649–3652.

under oxidative conditions (Scheme 2.2).[38b] A subsequent reduction provided reduced Mannich product **2.4** in 66% yield with 98:2 (*syn*) and 96:4 (*anti*) er.



Scheme 2.2 Enantioselective Alkylation of *N*-Phenyltetrahydroisoquinoline

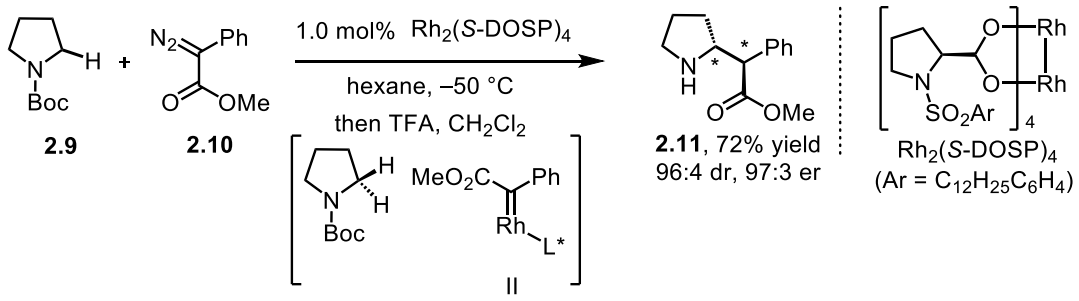
In the same year, Rovis achieved *α*-amino C–H acylation by cooperative *N*-heterocyclic carbene (NHC) and photoredox catalysis (Scheme 2.3).[39] The authors proposed that *N*-phenyltetrahydroisoquinoline **2.1** can be oxidized into an iminium ion by a Ru-based photoredox catalyst in the presence of dinitrobenzene as the oxidant, and butyraldehyde **2.5** can be converted into Breslow intermediate **I**. Desired product **2.8** can be obtained in 81% yield with 96:4 er. Enantioselective C–C bond formation was achieved by the cooperative action of *N*-heterocyclic carbene and photoredox catalysts. However, the amine substrate scope of this transformation is contrived with *N*-aryltetrahydroisoquinoline derivatives to generate a stabilized iminium ion in situ.



Scheme 2.3 *α*-Acylation of Tetrahydroisoquinoline via NHC and Photoredox Catalysis

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

In 2003, Davis carried out a unique way for α-alkylation of *N*-Boc-pyrrolidine **2.9** through rhodium-carbenoid insertion (Scheme 2.4).[40] Methyl 2-diazo-2-phenylacetate **2.10** was converted into the corresponding rhodium-carbenoid **II**, which was subsequently inserted into the α-amino C–H bond of *N*-Boc-pyrrolidine **2.9**. β-Amino acid derivative **2.11** was obtained with 72% yield and 97:3 er. This strategy is suitable for several cyclic *N*-Boc amines. However, they have a very narrow scope of both coupling partners.



Scheme 2.4 α-Amino C–H functionalization through Carbene Insertion

Inspired by Beak's discovery on deprotonation of *N*-Boc-pyrrolidine by *s*-BuLi,[41] Campos [42] and O'Brien [43] developed an enantioselective Negishi coupling reaction between *N*-Boc-pyrrolidine and aryl halide. Later, Fu reported the same type of cross-coupling between *N*-Boc-pyrrolidine and alkyl halide instead of aryl halide promoted by a Ni-based catalyst (Scheme 2.5).[44] *N*-Boc-pyrrolidine **2.9** can undergo directed lithiation in the presence of stoichiometric amounts of *s*-BuLi and (-)-sparteine to form enantioenriched alkyl lithium species that can be trapped by ZnI_2. Subsequently, in situ generated chiral organozinc species can be directly used for Negishi cross-coupling with cyclohexyliodide to afford corresponding product **2.13** in 86% yield with 96.5:3.5 er.

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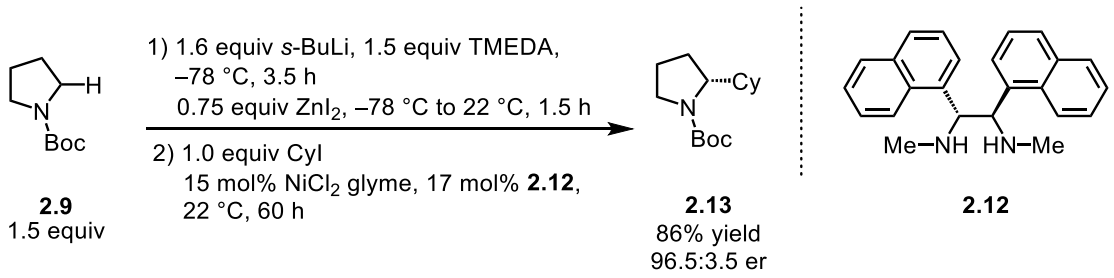
[40] Davies, H. M. L.; Venkataramani, C.; Hansen, T.; Hopper, D. W. *J. Am. Chem. Soc.* **2003**, *125*, 6462–6468.
[41] Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231–3239.
[42] Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C.-Y. *J. Am. Chem. Soc*. **2006**, *128*, 3538–3539.
[43] Barker, G.; McGrath, J. L.; Klapars, A.; Stead, D.; Zhou, G.; Campos, K. R.; O'Brien, P. *J. Org. Chem.* **2011**, *76*, 5936–5953.
[44] Cordier, C. J.; Lundgren, R. J.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 10946–10949.



2.9
1.5 equiv

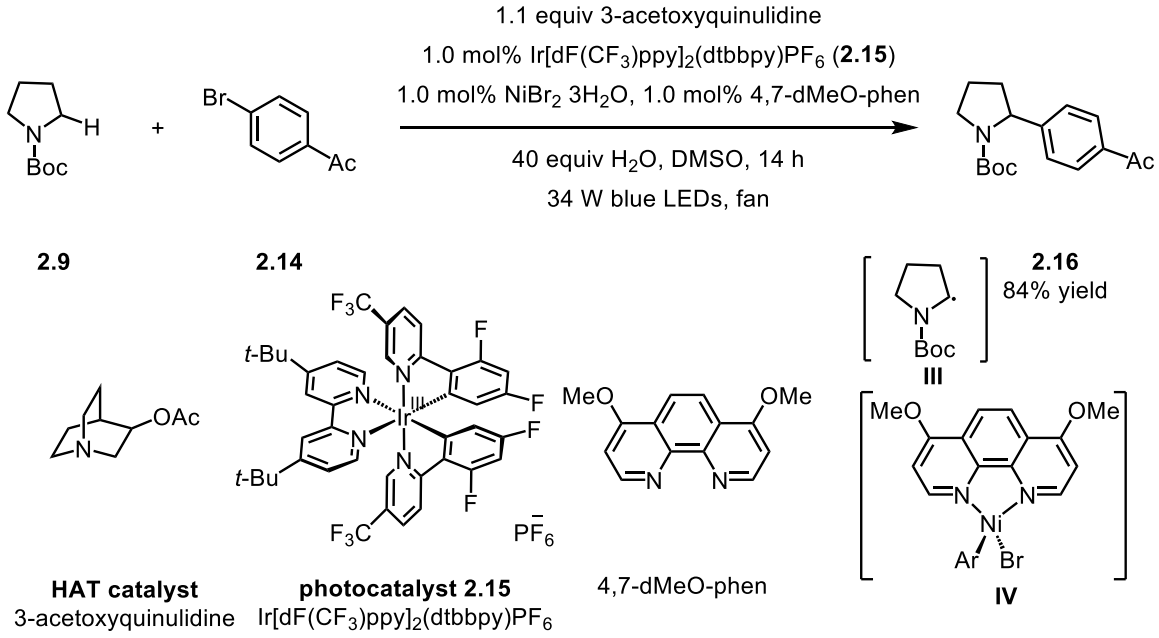
2.13
86% yield
96.5:3.5 er

2.12

Scheme 2.5 Enantioselective Negishi *α*-Alkylation of *N*-Boc-Pyrrolidine

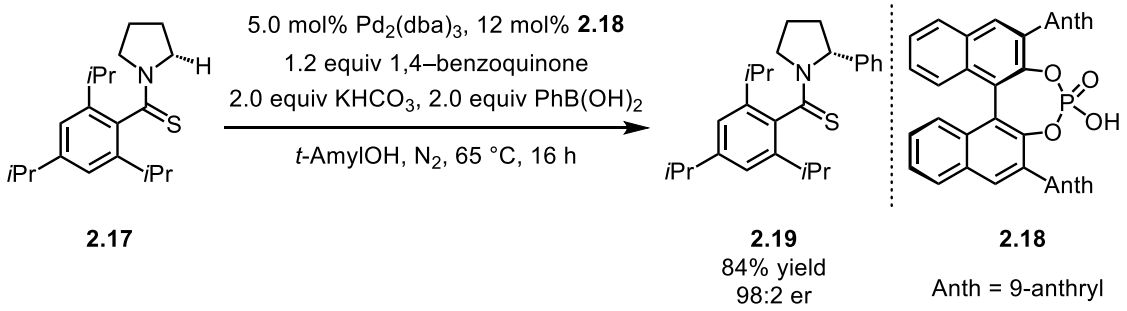
Photoredox catalysis was demonstrated to achieve *α*-amino C–H activation as early as 1988 to access synthetically useful products.[45] Recently, a number of protocols for direct *α*-amino C–H activation through photoredox catalysis have been reported.[46] *α*-Arylation of *N*-Boc-pyrrolidine **2.9** through the use of a photoredox catalyst was demonstrated by MacMillan.[47] The same substrate as Fu[44] used, *N*-Boc-pyrrolidine **2.9** was subjected to photoredox conditions with the help of Ir-based photoredox and HAT (hydrogen atom transfer) catalysts generating *α*-amino radical **III** as the reactive intermediate. Meanwhile, oxidative addition took place between **2.14** and the nickel complex to form aryl nickel species **IV**. A further reaction between **III** and aryl nickel, followed by reductive elimination, afforded the desired product in 84% yield (Scheme 2.6). The coupling did not have any bias on aryl group with different electronic natures and was applied to *α*-oxy, as well as benzylic C–H arylation. However, this work still relies on the use of an Ir-based catalyst.

[45] Pandey, G.; Kumaraswamy, G. *Tetrahedron Lett*. **1988**, *29*, 4153–4156.
[46] (a) Zhu, S.; Das, A.; Bui, L.; Zhou, H.; Curran, D. P.; Rueping, M. *J. Am. Chem. Soc.* **2013**, *135*, 1823–1829. (b) Le, C.; Liang, Y.; Evans, R. W.; Li, X.; MacMillan, D. W. C. *Nature* **2017**, *547*, 79–83. (c) McManus, J. B.; Onuska, J. B.; Nicholas. P. R.; Nicewicz, D. A. *J. Am. Chem. Soc*. **2018**, *140*, 9056–9060.
[47] Shaw, M. H.; Shurtleff, V. W.; Terrett, J. A.; Cuthbertson, J. D.; MacMillan, D. W. C. *Science* **2016**, *352*, 1304–1308.



Scheme 2.6 Cross-Coupling in Combination with Photoredox Catalysis

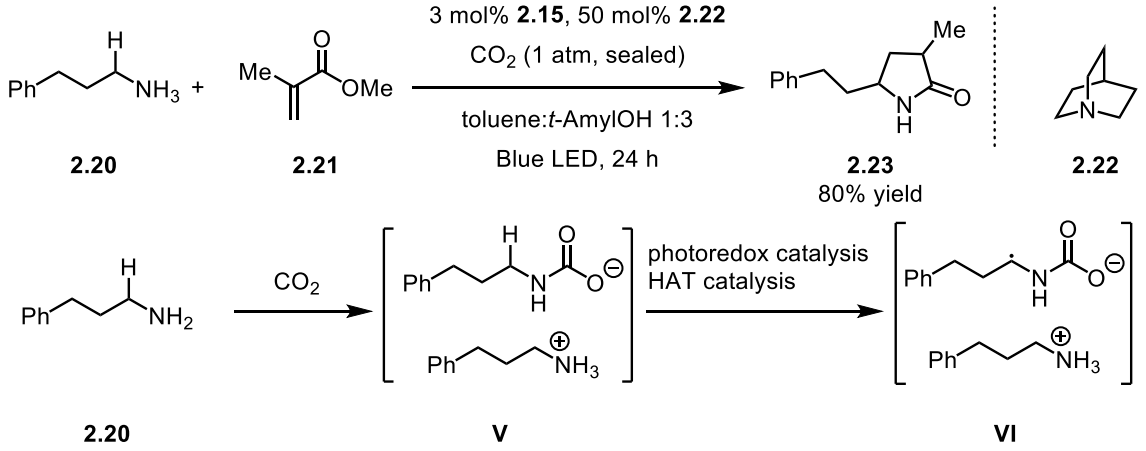
In 2017, Yu reported the Pd-catalyzed directed enantioselective *α*-arylation of thioamide **2.17** (Scheme 2.7).[48] The authors proposed that the sulfur atom of the thionyl group is responsible for promoting directed C–H activation due to soft acid and base interactions between the sulfur atom and Pd-based catalyst. Thioamide **2.17** was converted to *α*-arylthioamide **2.19** in the presence of chiral phosphoric acid **2.18** (Scheme 2.5). Cyclic and acyclic thioamides were suitable substrates for this reaction, and a high er was obtained using phenylboronic acid as the coupling partner.



Scheme 2.7 Directed *α*-Amino C–H Activation by Pd-based Catalyst

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

In 2018, Rovis disclosed the direct α-amino C–H bond activation of primary alkyl amines through a combination of photoredox catalyst **2.15** and HAT catalyst using carbon dioxide as an activating agent.[49] 3-Phenylpropylamine **2.20** was converted into lactam **2.23** after reacting with methyl methacrylate **2.21** (Scheme 2.8). Primary amine **2.20** was activated by carbon dioxide to afford ammonium carbamate **V**. Subsequently, α-amino radical was generated through photoredox and HAT catalysis (**VI**) and reacted with **2.21** to afford lactam **2.23** in 80% yield.



Scheme 2.8 α-Amino C–H Bond Activation of Primary Amines

α-Amino C–H bond activation is an important topic of study for synthetic organic chemists and has been extensively explored. However, the reported methods are highly dependent on the use of stoichiometric oxidants, precious transition metal-based (Ru, Ir and Pd) catalysts and the use of directing groups. Therefore, it is desirable to develop a general catalytic strategy for the functionalization of amino C–H bonds to overcome these problems.

2.2.2 Synthesis of Propargylamines by Copper Salt Catalyzed Alkynylation

There are two common strategies to synthesize enantioenriched propargylamines. The first is the addition of organometallic-alkynyl species to imines that are either pre-formed

[49] Ye, J.; Kalvet, I.; Schoenebeck, F.; Rovis, T. *Nat. Chem.* **2018**, *10*, 1037–1041.

or in situ generated.[50] Another method is through the alkynylation of in situ generated iminium ions that are generated under oxidative conditions.[51] However, these methods are often limited to aryl-substituted amine substrates to stabilize the imine or iminium ion that is generated. Additionally, under oxidative conditions, these methods have poor tolerance for various functional groups. Therefore, it is important to develop a general method for highly enantioselective alkynylation of *α*-amino C–H bonds of *N*-alkylamines that may contain acid- or base-sensitive functional groups, under redox neutral conditions.

In 2002, Knochel reported the CuBr/QUINAP-catalyzed enantioselective alkynylation of enamine **2.24** with phenylacetylene **2.25** (Scheme 2.9).[52] Enamine **2.24** and alkyne **2.25** were converted into enantioenriched propargylamine **2.27** in 83% yield with 95:5 er in the presence of copper bromide and (*R*)-QUINAP **2.26**. Although enamines can undergo *α*-alkynylation to generate enantioenriched propargylamines, the functional group tolerance of this transformation is poor, and the requirement of pre-formed enamines prevents this method from being applied to the late-stage functionalization of bioactive amines.

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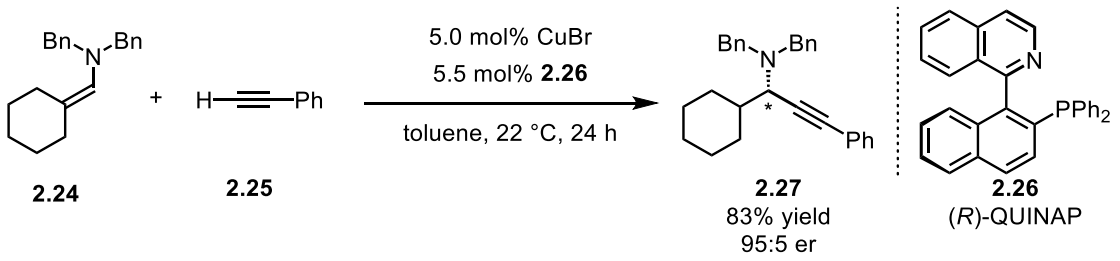
[50] (a) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5638–5639. (b) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763–5766. (c) Knöpfel, T. F.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5971–5973. (d) Bisai, A.; Singh, V. K. *Org. Lett.* **2006**, *8*, 2405–2408. (e) Zani, L.; Bolm, C. *Chem. Commun.* **2006**, *41*, 4263–4275. (f) Hatano, M.; Asai, T.; Ishihara, K. *Tetrahedron Lett.* **2008**, *49*, 379–382. (g) Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963–983. (h) Yin, L.; Otsuka, Y.; Takada, H.; Mouri, S.; Yazaki, R.; Kumagai, N.; Shibasaki, M. *Org. Lett.* **2013**, *15*, 698–701. (i) Lin, W.; Cao, T.; Fan, W.; Han, Y.; Kuang, J.; Luo, H.; Miao, B.; Tang, X.; Yu, Q.; Yuan, W.; Zhang, J.; Zhu, C.; Ma, S. *Angew. Chem., Int. Ed.* **2014**, *53*, 277–281. (j) Zhao, C.; Seidel, D. *J. Am. Chem. Soc.* **2015**, *137*, 4650–4653. (k) Takada, H.; Kumagai, N.; Shibasaki, M. *Org. Lett.* **2015**, *17*, 4762–4765.

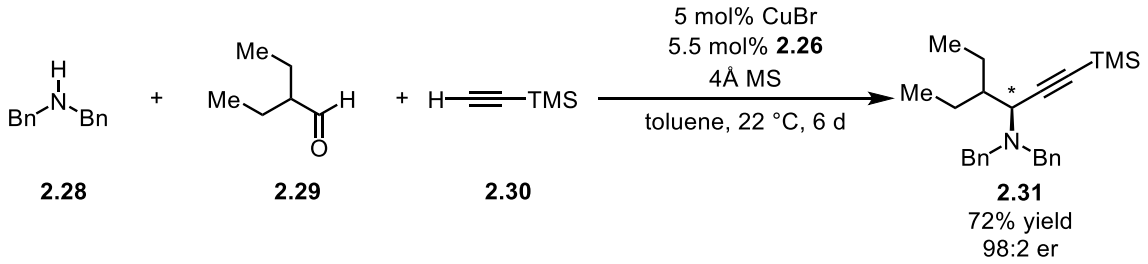
[51] (a) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004***, 126*, 11810–11811. (b) Li, Z.; Li, C.-J. *Org. Lett.* **2004**, *6*, 4997–4999. (c) Li, Z.; MacLeod, P. D.; Li, C.-J. *Tetrahedron: Asymmetry* **2006**, *17*, 590–597. (d) Sun, S.; Li, C.; Floreancig, P. E.; Lou, H.; Liu, L. *Org. Lett.* **2015**, *17*, 1684–1687. (e) Xie, Z.; Liu, X.; Liu, L. *Org. Lett.* **2016**, *18*, 2982–2985.

[52] Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2535–2538.



Scheme 2.9 Enantioselective Alkynylation of Enamines

Another method to synthesize propargylamines is the A^3 reaction, which couples aldehydes, alkynes, and amines.[53] Knochel achieved the enantioselective A^3 reaction by treating dibenzylamine **2.28**, 2-ethylbutanal **2.29**, and trimethylsilylacetylene **2.30** with a catalytic amount of copper bromide and (*R*)-QUINAP **2.26** to obtain enantioenriched propargylamine **2.31** in 72% yield with 98:2 er (Scheme 2.10).[54] High diastereoselectivity was obtained when enantioenriched amines were used without ligands.

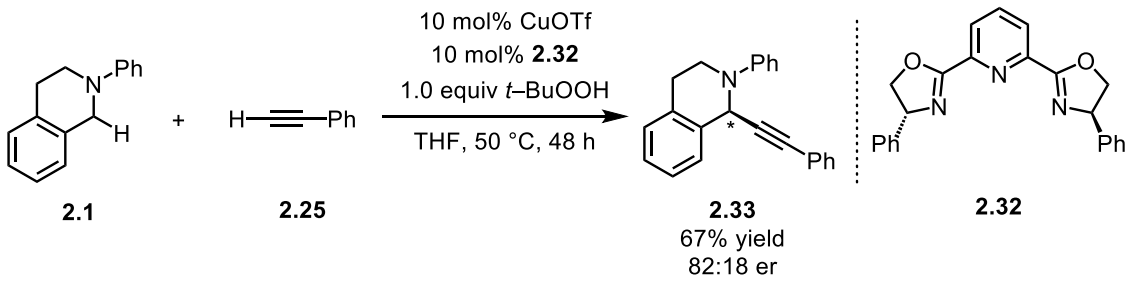


Scheme 2.10 Enantioselective A^3 Reaction

A notable method carried out by Li is direct *α*-amino C–H bond activation under oxidative conditions.[51a] The enantioselective Cu(I)–PyBOX complex-catalyzed alkynylation of benzylic *α*-amino C–H bonds of *N*-phenyltetrahydroisoquinoline **2.1** was reported (Scheme 2.11).[51b] Propargylamine **2.33** was obtained in 67% yield with 82:18 er. Although this method does not require the use of a pre-formed imine, the substrate scope was limited to tetrahydroisoquinolines to generate a stabilized iminium ion in situ.

[53] (a) Wei, C.; Li, Z.; Li, C.-J. *Synlett* **2004**, 1472–1483. (b) Zani, L.; Bolm, C. *Chem. Commun.* **2006**, 4263–4275. (c) Li, C.-J. *Acc. Chem. Res*. **2010**, *43*, 581–590. (d) Peshkov, V. A.; Pereshivko, O. P.; Van der Eycken, E. V. *Chem. Soc. Rev*., **2012**, *41*, 3790–3807.
[54] Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed*. **2003**, *42*, 5763–5766.

Furthermore, the use of stoichiometric oxidant limited the substrate scope due to poor functional group tolerance.



2.1 **2.25** **2.33** 67% yield 82:18 er **2.32**

Scheme 2.11 Enantioselective Alkynylation of *N*-Phenyltetrahydroisoquinoline

2.3 Development of α-Amino C–H Alkynylation

2.3.1 Optimized Conditions for α-Amino C–H Alkynylation

Stereoselective α-amino alkynylation is still highly dependent on the use of pre-activated substrates and external oxidants.[51] It is important to develop a general method for α-amino C–H alkynylation of non-pre-activated amines, including N-based pharmaceuticals. α-Alkynylated derivatives of these amine-containing drug molecules could serve as versatile intermediates for late-stage diversification.[32]

We envisioned that the use of $B(C_6F_5)_3$ and the chiral copper complex would be a suitable catalyst combination for alkynylation of amines (Figure 2.2). In the proposed mechanism, $B(C_6F_5)_3$ receives a hydroxide to form hydroxyl borate **VIII**. Upon reaction with trimethylsilylacetylene **2.35**, alkynyl boron complex **IX** is formed, which is then transmetalated to form L_nCu–alkynyl complex **X**.[55] $B(C_6F_5)_3$ receives a hydride from amine **2.34** to generate an iminium ion and a borohydride (**VIII**). Subsequently, C–C bond formation between the in situ generated iminium ion and L_nCu–alkynyl complex affords the desired propargylamine product **2.36**. Hydroxyl borate anion **VIII** is regenerated after borohydride reacts with alcohol additive **2.37**, thus, close the catalytic cycle.

[55] (a) Herron, J. R.; Ball, Z. T. *J. Am. Chem. Soc.* **2008**, *130*, 16486–16487. (b) Lee, K.-S.; Hoveyda, A. H. *J. Org. Chem.* **2009**, *74*, 4455–4462. (c) Gurung, S. K.; Thapa, S.; Vangala, A. S.; Giri, R. *Org. Lett.* **2013**, *15*, 5378–5381.

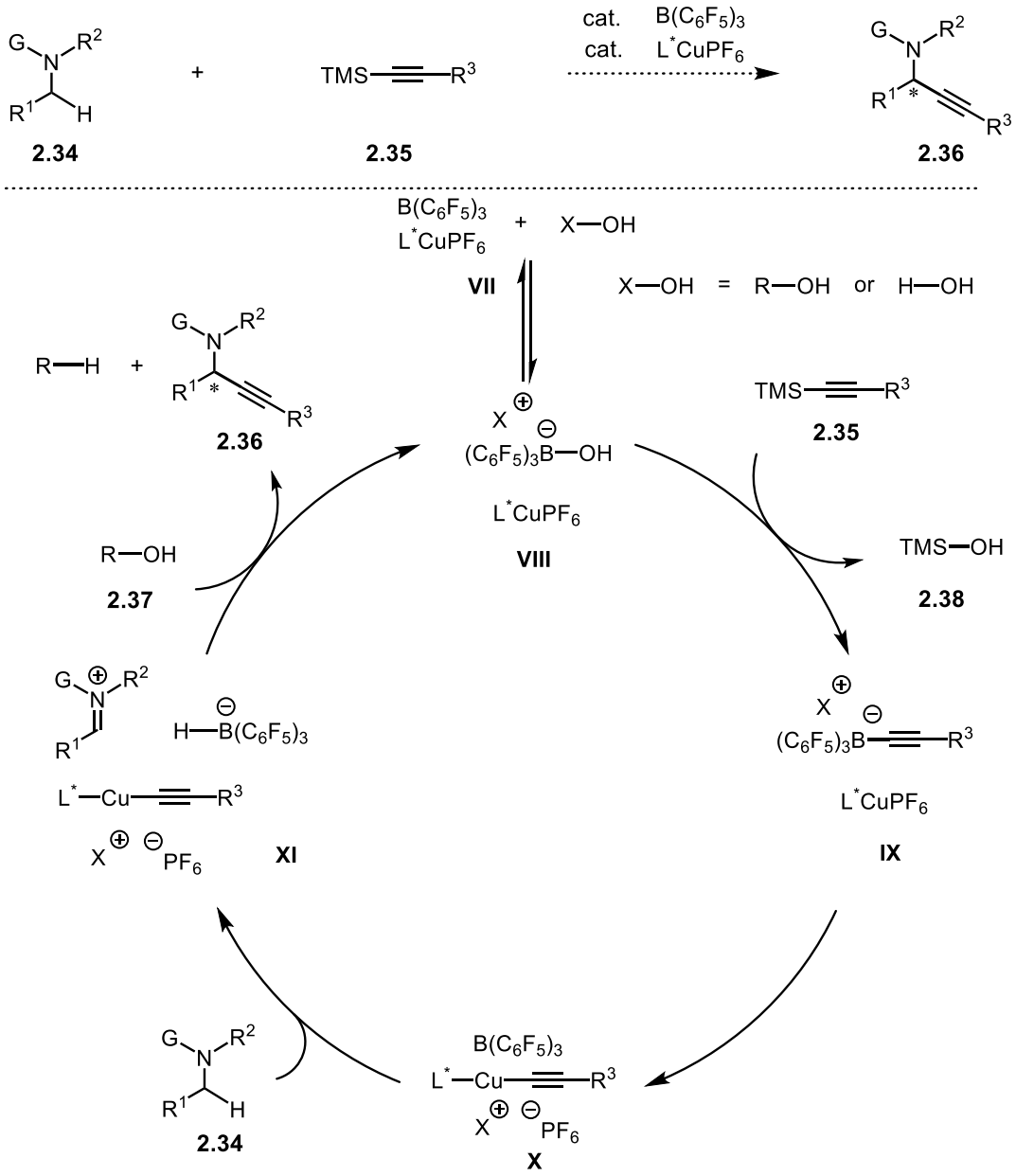
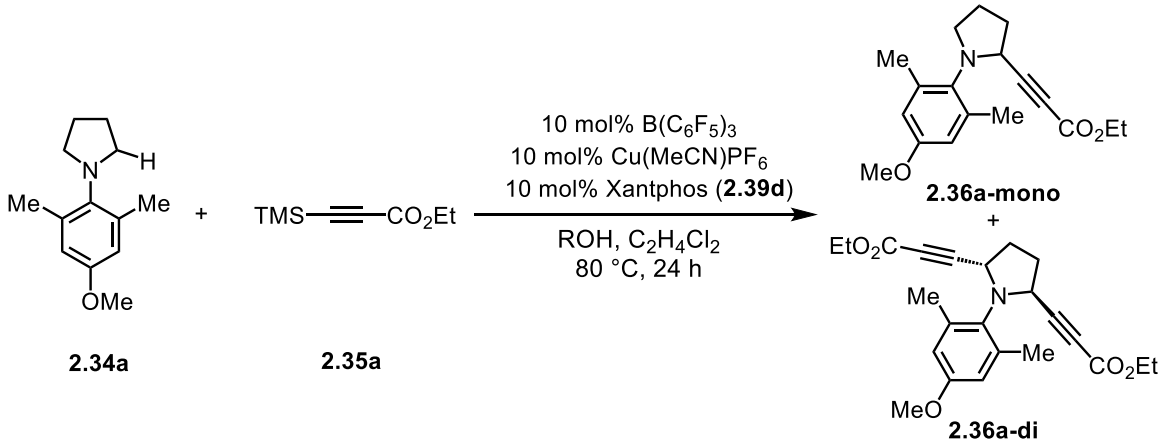


Figure 2.2 Proposed Catalytic Cycle

We first set out to look for a suitable reaction system for *α*-amino C–H alkynylation (Table 2.1). When **2.34a** and **2.35a** were treated with 10 mol% of $B(C_6F_5)_3$ and 10 mol% of Cu–Xantphos complex at 80 °C, **2.36a-mono** was obtained in 15% yield (entry 1). Using *i*-PrOH as the additive could enhance the yield of **2.36a-mono** to 26% (entry 2).

Moreover, we started to observe the formation of **2.36a-di** when *t*-BuOH was used (entry 3). We hypothesized that the reaction efficiency could increase when the alcohol additive generates a more stabilized carbocation**.** In line with our hypothesis, the use of triphenylmethanol resulted in the highest conversion affording **2.36a-mono** in 52% yield as well as di-alkynylated product **2.36a-di** in 34% yield (entry 5). To suppress the formation of **2.36a-di** and improve the selectivity towards the formation of **2.36a-mono**, several strategies were applied. A lower reaction temperature decreased the yield of **2.36a-di** (entry 6). Reduced equivalence of alcohol and shorter reaction time further minimized the formation of **2.36a-di** and afforded **2.36a-mono** selectively in 90% yield (entry 8).



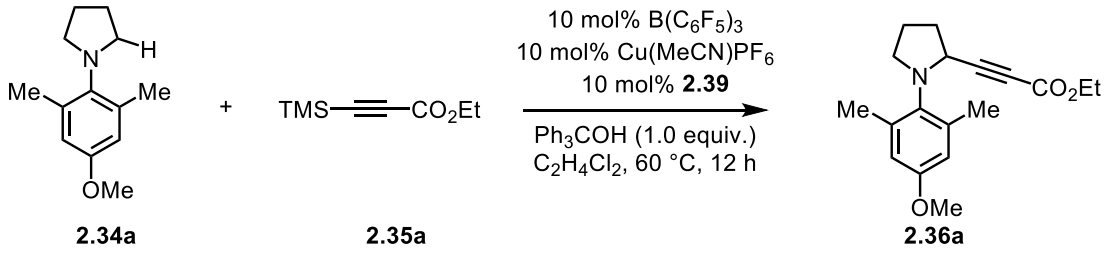
2.34a **2.35a**

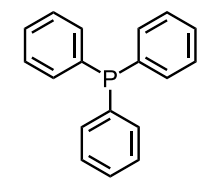
none	2.0 equiv. *i*-PrOH	2.0 equiv.*t*-BuOH	2.0 equiv. BnOH
2.36a-mono 15%	**2.36a-mono** 26%	**2.36a-mono** 64%	**2.36a-mono** 34%
2.36a-di 0%	**2.36a-di** 0%	**2.36a-di** 5%	**2.36a-di** 0%
1	2	3	4
2.0 equiv. Ph_3COH	2.0 equiv. Ph_3COH 60 °C	1.0 equiv.Ph_3COH 60 °C	1.0 equiv. Ph_3COH 60 °C, 12 h
2.36a-mono 52%	**2.36a-mono** 79%	**2.36a-mono** 83%	**2.36a-mono** 90%
2.36a-di 34%	**2.36a-di** 19%	**2.36a-di** 15%	**2.36a-di** <5%
5	6	7	8

Conditions: *N*-arylpyrrolidine (**2.34a**, 0.1 mmol), 3-(trimethylsilyl)propiolate (**2.35a**, 0.2 mmol), $B(C_6F_5)_3$ (10 mol%), $Cu(MeCN)_4PF_6$ (10 mol%), Xantphos (10 mol%), alcohol (0.2 or 0.1 mmol), $C_2H_4Cl_2$ (0.4 mL), under N_2. Yield values were determined by ^1H NMR analysis of unpurified reaction mixtures using mesitylene as the internal standard.

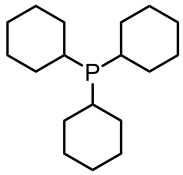
Table 2.1 Evaluation of Reaction Conditions

Given that the steric and electronic properties of ligands play important roles in organometallic transformations, ligands were also evaluated (Table 2.2). When monodentate phosphine ligands **2.39a** and **2.39b** were utilized, the yields of the desired product were lower (≤13%) compared to the bidentate ligand **2.39c**, which gave a slightly higher yield (43%). Structurally more rigid and sterically more hindered ligand **2.39d** afforded product in 90% yield while **2.39e** and non-phosphine ligand **2.39f** did not provide the desired product.

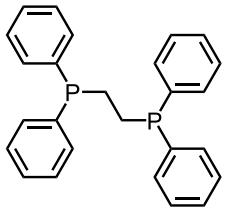




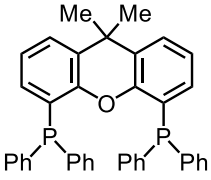
2.39a (TPP)
2.36a, 0% yield[a]



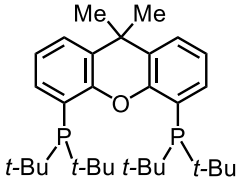
2.39b (TCHP)
2.36a, 13% yield[a]



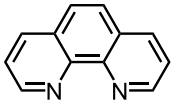
2.39c (dppe)
2.36a, 43% yield



2.39d (Xantphos)
2.36a, 90% yield



2.39e (*t*-Bu-Xantphos)
2.36a, 0% yield



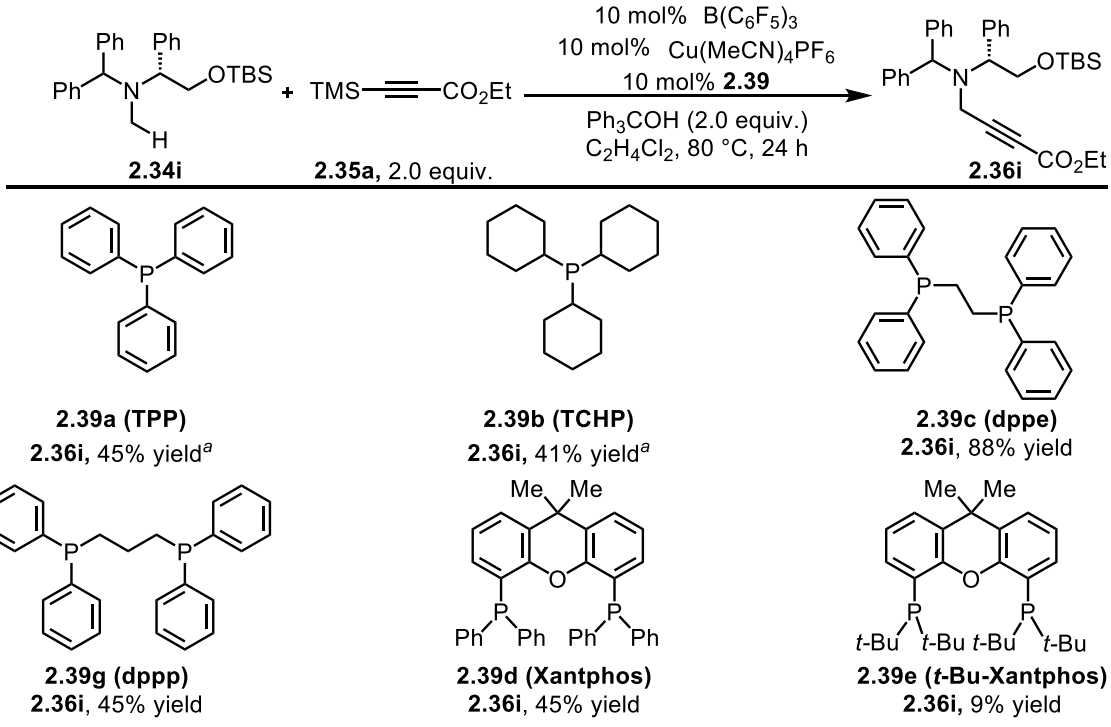
2.39f
2.36a, 0% yield

Conditions: *N*-arylpyrrolidine (**2.34a**, 0.1 mmol), 3-(trimethylsilyl)propiolate (**2.35a**, 0.2 mmol), $B(C_6F_5)_3$ (10 mol%), $Cu(MeCN)_4PF_6$ (10 mol%), ligand (10 mol%), triphenylmethanol (0.1 mmol), $C_2H_4Cl_2$ (0.4 mL), under N_2, 60 °C, 12 h. Yield values were determined by ^1H NMR analysis of unpurified reaction mixtures using mesitylene as the internal standard. [a]20 mol% ligand was used.

Table 2.2 Evaluation of Ligands for Cyclic Amine[a]

Having explored the optimal conditions for α-alkynylation of cyclic amine, we set out to exam a scope of ligands for α-alkynylation of acyclic trialkyl amine. To prevent the substrate from undergoing di-alkynylation, we selected (*R*)-*N*-benzhydryl-2-((tert-butyldimethylsilyl)oxy)-*N*-methyl-1-phenylethan-1-amine (**2.34i**) as the model substrate

because of its steric nature (Table 2.3). We next tuned the conditions to two equivalents of triphenylmethanol at 80 °C for 24 hours since the second alkynylation is less likely to occur on the sterically more hindered benzyl or benzhydryl position. Under this condition, monodentate ligands **2.39a** and **2.39b** gave moderate yield while bidentate ligand 1,2-bis(diphenylphosphino)ethane (dppe) **2.39c** provided the desired product in 88% yield. However, using ligand 1,3-bis(diphenylphosphaneyl)propane (dppp) **2.39g** resulted in the formation of **2.36i** in a lower yield (45%). Sterically hindered ligands **2.39d** and **2.39e** with less flexibility were likely to have steric repulsion with substrate **2.34i** and, therefore, had lower yields.

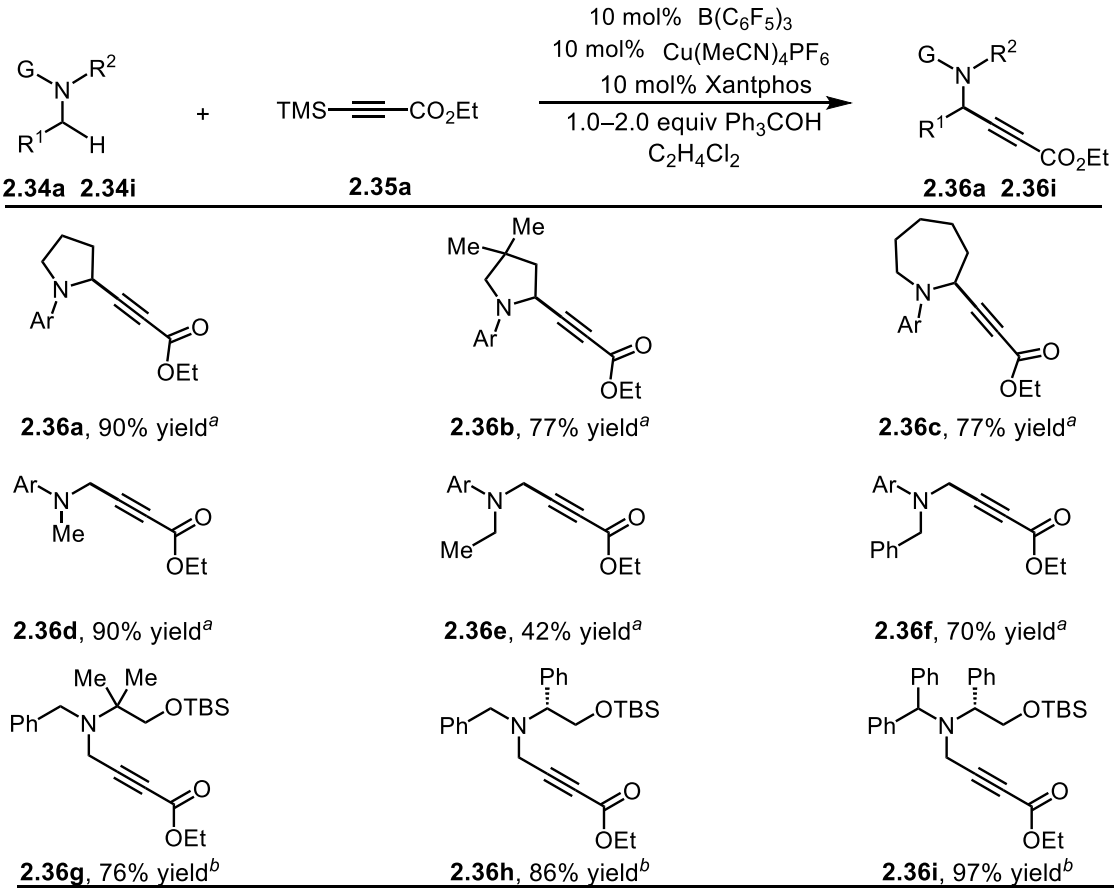


Conditions: Trialkylamine (**2.34i**, 0.1 mmol), 3-(trimethylsilyl)propiolate (**2.35a**, 0.2 mmol), $B(C_6F_5)_3$ (10 mol%), $Cu(MeCN)_4PF_6$ (10 mol%), ligand (10 mol%), triphenylmethanol (0.2 mmol), $C_2H_4Cl_2$ (0.4 mL), under N_2, 80 °C, 24 h. Yield values were determined by ^1H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard. [a]20 mol% ligand was used.

Table 2.3 Evaluation of Ligands for Acyclic Trialkyl Amine[a]

2.3.2 Evaluation of Substrate Scope and Application to Late-Stage Functionalization of Drug Molecules

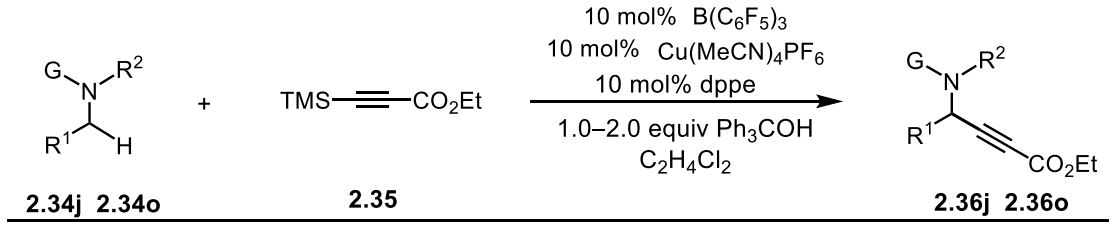
With optimized reaction conditions, we evaluated the scope of cyclic and acyclic amines (Table 2.4). Cyclic amines such as *N*-arylpyrrolidines and *N*-arylazepanen (**2.34a**–**2.34c**) gave corresponding products **2.36a**–**2.36c** in 77-90% yield. Acyclic amines **2.34d**–**2.34f** were selectively alkynylated at the *N*-methyl site to afford the desired products **2.36d**–**2.36f** in 42–90% yield. Trialkyl amines (**2.34g**–**2.34i**) without fused aromatic rings provided corresponding products in 76-97% yield (**2.36g**–**2.36i**, dppe as ligand). As steric hindrance increased from **2.34g** to **2.34i**, products were obtained with higher yields. With benzhydryl group protected amine **2.34h**, the product was obtained in 97% yield while benzyl protected amine **2.34i** provided the product in a relatively lower yield (86%), showing that the benzhydryl group was a superior nitrogen protecting group.



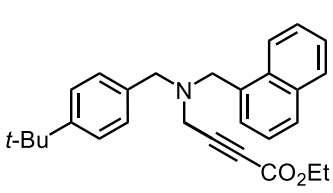
[a]Conditions: *N*-alkylamine (**2.34**, 0.2 mmol), 3-(trimethylsilyl)propiolate (**2.35a**, 0.3 mmol), $B(C_6F_5)_3$ (10 mol%), $(MeCN)_4CuPF_6$ (10 mol%), Xantphos (10 mol%), triphenylmethanol (0.2 mmol), $C_2H_4Cl_2$ (0.8 mL), under N_2, 60 °C, 12 h. [b]1,2-bis(diphenylphosphino)ethane (dppe) was used as a ligand using triphenylmethanol (0.2 mmol) at 80 °C for 24 h. [c]Yield of isolated and purified product.

Table 2.4 Amine Scope of α-Amino C–H Alkynylation[a,b,c]

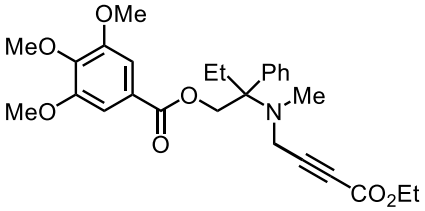
This protocol was applicable to the late-stage functionalization of bioactive amines that contain various Lewis acid-sensitive functional groups such as ether (**2.34k**, **2.34l**, **2.34n**), ester (**2.34k**) and thiophene (**2.34n**) (Table 2.5). Drug molecules containing an *N*-methyl unit (**2.34j**–**2.34k**) were readily converted to corresponding propargylamines (**2.36j**–**2.36k**) in 56-76% yield. *N*-Methyl secondary amine moieties of drugs were protected by a benzhydryl group (**2.34l**–**2.34o**) and afforded **2.36l**–**2.36o** in 56-74% yield after alkynylation.



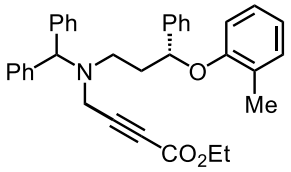
2.34j 2.34o **2.35** **2.36j 2.36o**



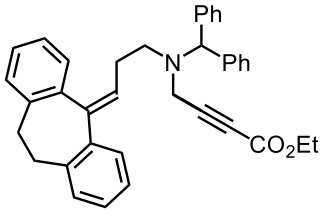
2.36j, 76% yield
butenafine derivative



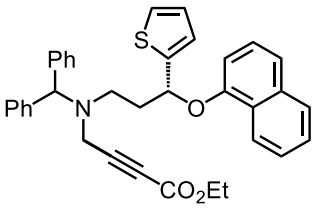
2.36k, 71% yield
trimebutine derivative



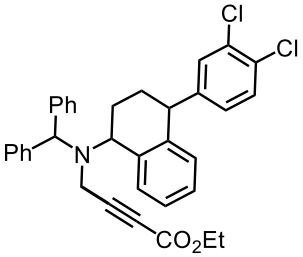
2.36l, 56% yield
atomoxetine derivative



2.36m, 74% yield
nortriptyline derivative



2.36n, 68% yield
duloxetine derivative

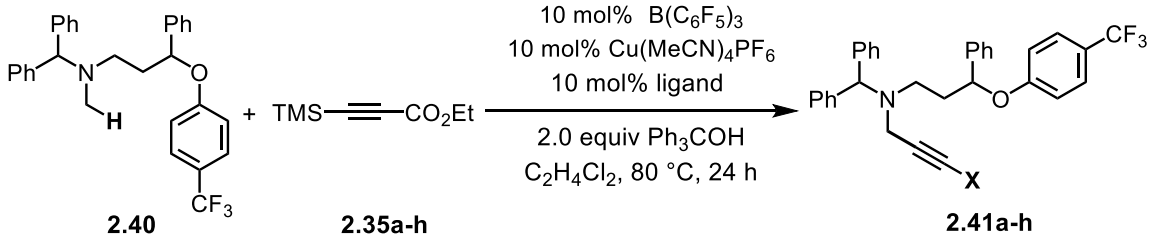


2.36o, 67% yield
sertraline derivative

[a]Conditions: *N*-alkylamine (**2.34**, 0.2 mmol), 3-(trimethylsilyl)propiolate (**2.35a**, 0.3 mmol), $B(C_6F_5)_3$ (10 mol%), $(MeCN)_4CuPF_6$ (10 mol%), 1,2-bis(diphenylphosphino)ethane (10 mol%), triphenylmethanol (0.2 mmol), $C_2H_4Cl_2$ (0.8 mL), under N_2, 80 °C, 24 h. [b]Yield of isolated and purified product.

Table 2.5 Late-Stage Functionalization of Drug Derivatives[a,b]

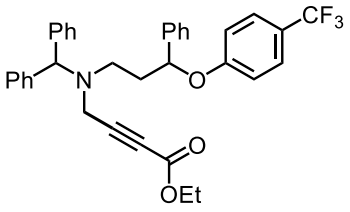
When *N*-benzhydryl fluoxetine **2.40** was subjected to identical conditions, we were able to obtain **2.41a** in 82% yield. Having demonstrated the amine scope of alkynylation, we set out to study the scope of trimethylsilyl acetylene derivatives using *N*-benzhydryl fluoxetine **2.40** as the standard substrate (Table 2.6). Esters and amide **2.35a**–**2.35c** were tolerated in the alkynylation protocol giving **2.41a**–**2.41c** in 76–82% yield. Aryl acetylenes **2.35d**–**2.35g** were efficiently coupled with **2.40** (74–82% yield). Notably, thiophene **2.35g,** which contains a sulfur atom that has high affinity to many transition metals, was well tolerated and did not hamper reactivity. 1,2-Bis(trimethylsilyl)ethyne **2.35h** underwent selective mono alkynylation in 87% yield.



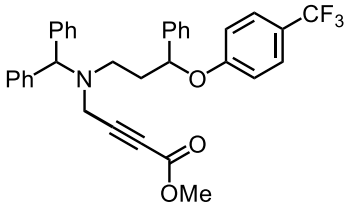
2.40
***N*-Bzh fluoxetine**
(antidepressant)

2.35a-h

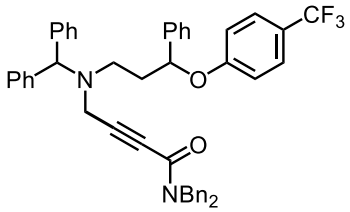
2.41a-h



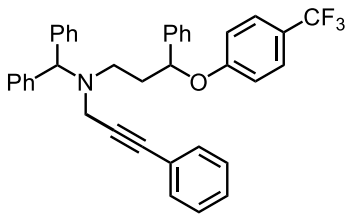
2.41a, 82% yield[a]



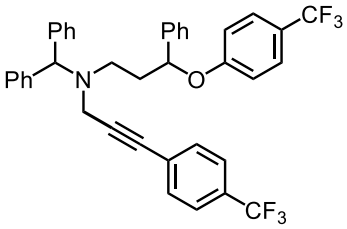
2.41b, 76% yield[a]



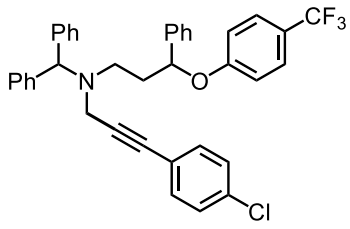
2.41c, 80% yield[b]



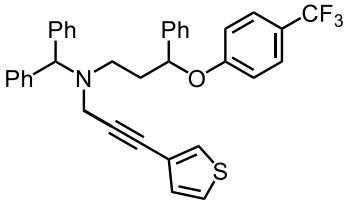
2.41d, 75% yield[b]



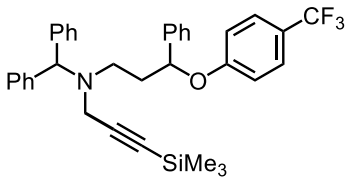
2.41e, 82% yield[b]



2.41f, 80% yield[b]



2.41g, 74% yield[b]



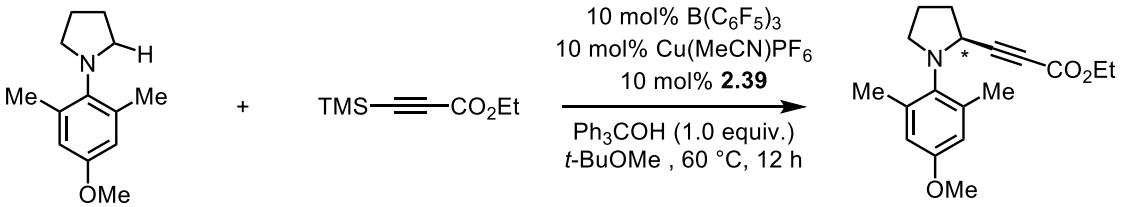
2.41h, 87% yield[b]

[a] Conditions: *N*-Bzh fluoxetine (**2.40**, 0.2 mmol), 3-(trimethylsilyl)acetylene (**2.35**, 0.4 mmol), $B(C_6F_5)_3$ (10 mol%), $(MeCN)_4CuPF_6$ (10 mol%), 1,2-bis(diphenylphosphino)ethane (10 mol%), triphenylmethanol (0.4 mmol), $C_2H_4Cl_2$ (0.8 mL), under N_2, 80 °C, 24 h. [b] (S)-Ph-PyBOX was used as a ligand. [c] Yield of isolated and purified product. d Blue color indicates protecting groups.

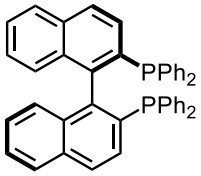
Table 2.6 Scope of Trimethyl Acetylene Derivatives[a,b,c]

2.4 Enantioselective *α*-Amino C–H Alkynylation of Amines

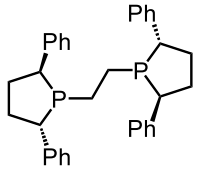
The enantioselective version of this transformation was developed by using the cooperative borane/chiral copper complex (Table 2.7). When bisphosphine ligands **2.39h** and **2.39j** were tested, racemic products were obtained. Phosphinooxazoline (PHOX) ligand **2.39k** also gave a racemic product but with much lower yield (15%). Both bisoxazoline (BOX) ligands **2.39i** and **2.39l** resulted in a racemic product. However, when BOX ligand **2.39m** was used, we obtained the desired product in 29% yield and 66:34 er. We subsequently tested the scope of BOX ligands. Ligand **2.39n** gave the product with higher enantioselectivity (72:28 er) but in lower yield (6%). Structural analog (*S*)-Ph-PyBOX (**2.32**) enhanced the desired product yield to 84% and enantioselectivity to 82:18 er. Based on this encouraging finding, we tuned the ligand properties by installing substituents on the phenyl ring to improve enantioselectivity. By incorporating *meta*-methyl group ligand 2,6-bis((*S*)-4-(*m*-tolyl)-4,5-dihydrooxazol-2-yl)pyridine **2.39o,** the desired product had 90:10 er. Since the aryl substituent on oxazoline may rotate to give a different conformer and lose the chance to give rigid control of the transition state, we hypothesized that additional *meta*-methyl substituents on the aryl group could have better control and further increase enantioselectivity. Moreover, when **2.39p** was utilized, the product was obtained with a higher enantioselectivity of 95:5 er. Sterically more hindered *meta*, *meta*-diethylphenyl-, or dimethoxyphenyl-substituted ligand **2.39q** and **2.39r** were not able to give products with higher enantioselectivity or efficiency.



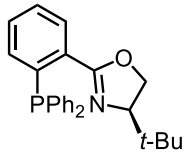
2.34a **2.35a** **2.36a**



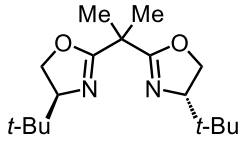
2.39h
2.36a, 61% yield
49:51 er



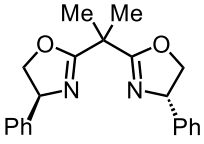
2.39j
2.36a, 70% yield
45:55 er



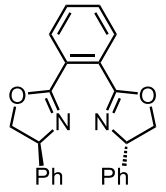
2.39k
2.36a, 15% yield
41:59 er



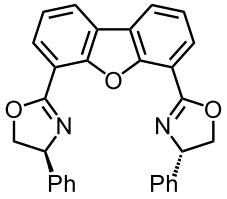
2.39i
2.36a, 81% yield
52:48 er



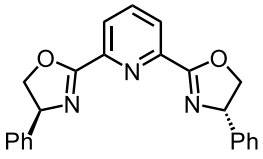
2.39l
2.36a, 53% yield
48:52 er



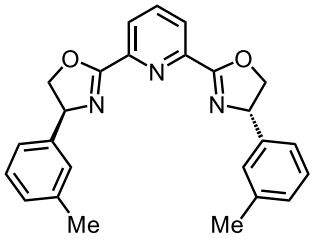
2.39m
2.36a, 29% yield
66:34 er



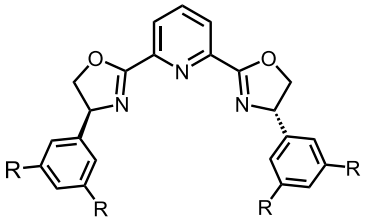
2.39n
2.36a, 6% yield
72:28 er



2.32
2.36a, 84% yield
82:18 er



2.39o
2.36a, 53% yield
90:10 er



2.39p, **R = Me**
2.36a, 75% yield
95:5 er

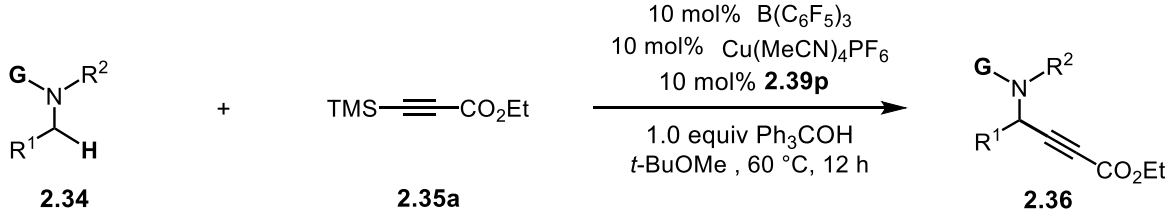
2.39q, **R = Et**
2.36a, 36% yield
82:18 er

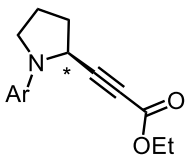
2.39r, **R = OMe**
2.36a, 29% yield
94:6 er

Conditions: *N*-arylpyrrolidine (**2.34a**, 0.1 mmol), 3-(trimethylsilyl)propiolate (**2.36a**, 0.15 mmol), $B(C_6F_5)_3$ (10 mol%), $Cu(MeCN)_4PF_6$ (10 mol%), Ligand (10 mol%), triphenylmethanol (0.1 mmol), *t*-BuOMe (0.4 mL), under N_2, 60 °C, 12 h. Yield values were determined by ^1H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard. Enantiomeric ratio (er) was determined by HPLC of the purified product.

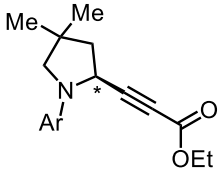
Table 2.7 Evaluation of Chiral Copper-Ligand Complexes

Having explored the enantioselective α-amino alkynylation of **2.34a**, an array of amines were tested under the optimized conditions (Table 2.8). Aniline **2.34a**-**2.34c** were alkynylated in 64% to 75% yield with 93:7 to 95:5 er. **2.34b** was selectively alkynylated on the less hindered site. The α-benzylic C–H bond of acyclic (*E*)-*N*,*N*-dibenzyl-4,4,4-trifluorobut-2-en-1-amine **2.34p** could also be alkynylated to provide **2.36p** in 45% yield and 84:16 er. Racemic **2.34q** was alkynylated with high diastereoselectivity to afford **2.36q** (6.3:1 *trans*:*cis*) with 83:17 er (*trans*). Enantioenriched **2.34r** was transformed into **2.36r** with 11.8:1 dr (*trans*:*cis*) and 97:3 er (*trans*).

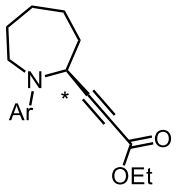




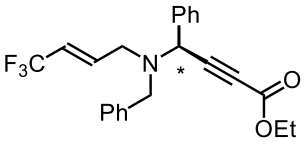
2.36a-(*S*), 75% yield
95:5 er



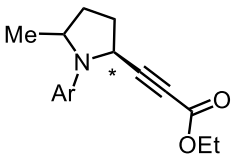
2.36b, 69% yield
93:7 er



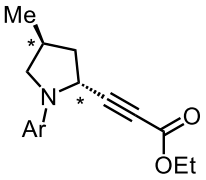
2.36c, 64% yield
95:5 er



2.36p, 45% yield
84:16 er



2.36q, 66% yield
6.3:1 *trans*:*cis*
83:17 er (*trans* isomer)



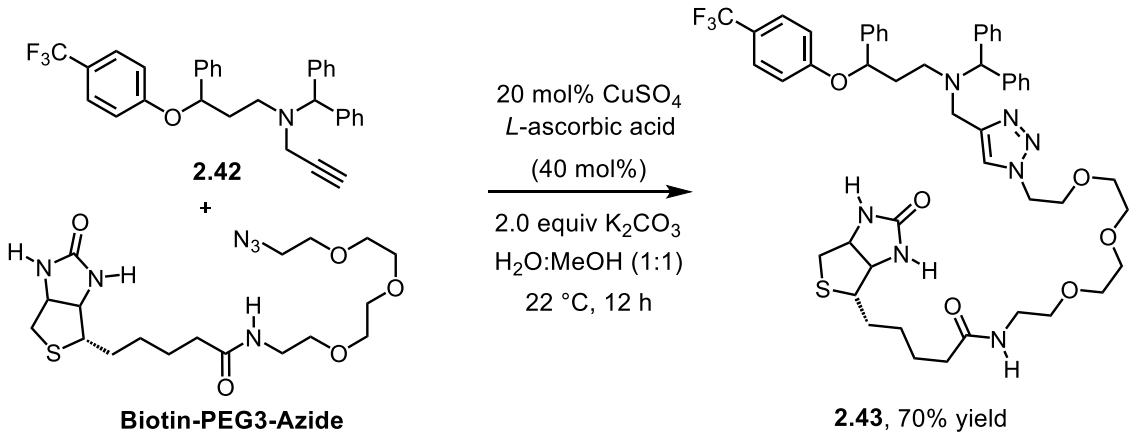
2.36r, 64% yield
11.8:1 *trans*:*cis*
97:3 er (*trans* isomer)

[a] Conditions: *N*-alkylamine (**2.34**, 0.1 mmol), 3-(trimethylsilyl)propiolate (**2.35a**, 0.15 mmol), $B(C_6F_5)_3$ (10 mol%), $Cu(MeCN)_4PF_6$ (10 mol%), ligand **2.39p** (10 mol%), triphenylmethanol (0.1 mmol), *t*-BuOMe (0.4 mL), under N_2, 60 °C, 12 h. [b] Yield of isolated and purified product. Enantiomeric ratio (er) was determined by HPLC of the purified product. The ratio of trans:cis was determined by the 1H NMR analysis of the unpurified reaction mixtures. [c] The absolute configuration of **2.36a** was determined as (*S*) by X-ray crystallographic analysis. The relative configuration of **2.36q** and **2.36r** were determined by 2D NMR experiments.

Table 2.8 Amine Scope for Enantioselective α-Amino C–H Alkynylation[a,b,c]

2.5 Derivatization of Product

Removal of the TMS group from fluoxetine derivative **2.41h** could be readily achieved through its treatment with tetra-*n*-butylammonium fluoride (TBAF) to produce **2.42** containing a terminal alkyne moiety in >95% yield. Treatment of **2.42** with Biotin-PEG3-Azide in the presence of $CuSO_4$/*L*-ascorbic acid and K_2CO_3 afforded the Click product **2.43** in 70% yield (Scheme 2.12).[56]



Scheme 2.12 Derivatization of Propargylamine Product

2.6 Conclusion

An efficient enantioselective *α*-amino C–H alkynylation protocol was developed using cooperative organoborane and copper complex catalysis. Pre-activated or pre-formed substrates are not required in the transformation since both electrophile and nucleophile are generated in situ. This work demonstrated that $B(C_6F_5)_3$ and an enantioenriched copper complex can cooperatively catalyze a stereoselective *α*-alkynylation of amines while tolerating a variety of Lewis acid-sensitive functional groups such as ethers, esters, and amides, enabling late-stage derivatization of drug molecules. The utility of the propargylamine product was demonstrated by its derivatization in the bioconjugation system.

2.7 Experimental Data

[56] (a) Gevorgyan, C.; Liu, J.-X., Rubin M.; Benson, S.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 8919–8922. (b) Parks, D. J.; Blackwell, J. M.; Piers, W. E. *J. Org. Chem.* **2000**, *65*, 3090–3098. (c) Seo, Y.; Lowe, J. M.; Gagné, M. R. *ACS Catal.* **2019**, *9*, 6648–6652.

2.7.1 General Information

This work is in collaboration with Jessica Chan, Ahmet Yesilcimen, Min Cao and Yuyang Zhang. My work was focused on expanding the scope of trialkylamines for racemic α-amino C–H alkynylation as well as the synthesis of amine substrates and ligand **2.39p**.

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.[57] 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 **2.30** and **2.39i**–**2.39r** were prepared according to the literature procedures.[58]

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

[57] (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.

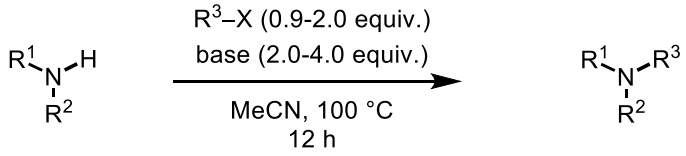
[58] (a) Tse, M. D.; Bhor, S.; Klawonn, M.; Anilkumar, G.; Jiao, H.; Döbler, C.; Spannenberg, A.; Mägerlein, W.; Hugl, H.; Beller, M. *Chem*. *Eur*. *J*. **2006**, *12*, 1855-1874. (b) Eno, M. S.; Lu, A.; Morken, J. P. *J. Am. Chem. Soc*. **2016**, *138*, 7824-7827. (c) Lovinger, G. J., Morken, J. P. *J. Am. Chem. Soc.* **2017**, *139*, 17293-17296. (d) Yoon, T.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 2911-2912.

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 $CDCl_3$. 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 Data

General Procedure for Preparation of Tertiary or Secondary Amines

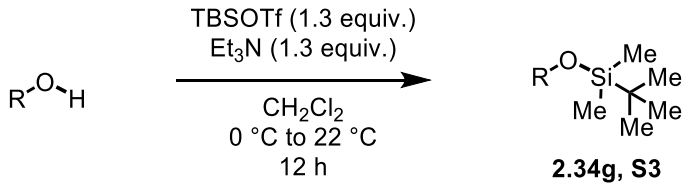


S1, **S6**, **2.34l–2.34p**, **2.34s–2.34t**

Amines **S1**, **S6**, **2.34l**–**2.34p** and **2.34s**–**2.34t** 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.

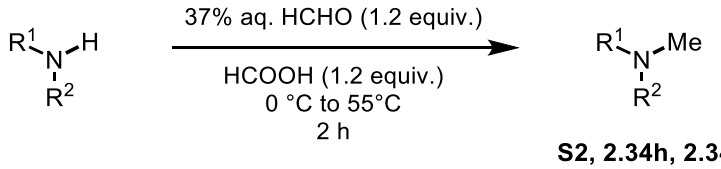
General Procedure for TBS Protection of Alcohols



2.34g, S3

Substrates **2.34g** 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.

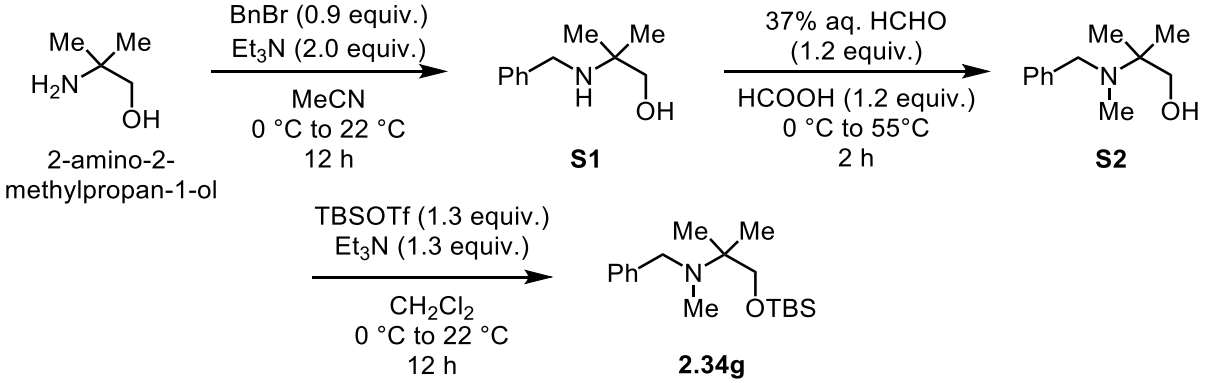
General Procedure for *N*-Methylation of Secondary Amines



S2, 2.34h, 2.34i

Substrates **S2**, **2.34h**, and **2.34i** 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 (2.34g)



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).

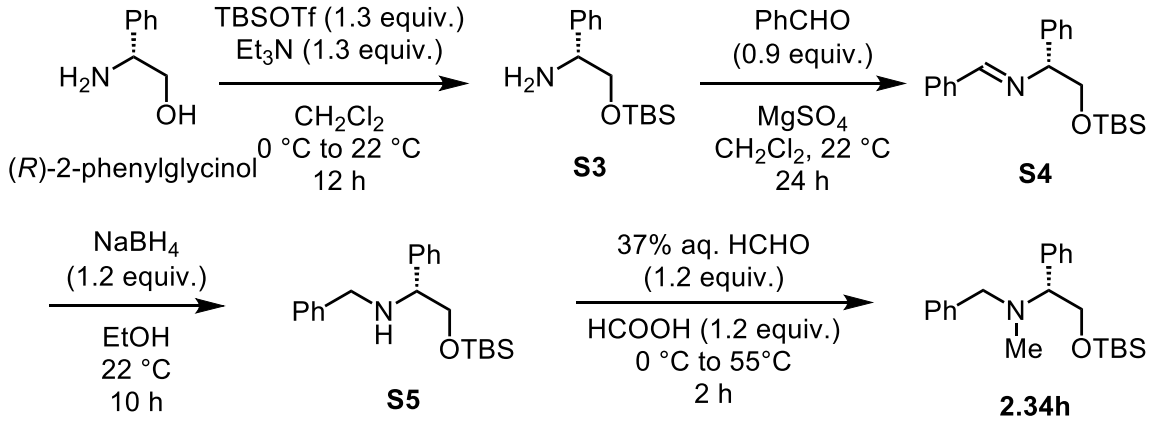
***N*-Benzyl-1-((*tert*-butyldimethylsilyl)oxy)-*N*,2-dimethylpropan-2-amine (2.34g)**

N-Benzyl-1-((*tert*-butyldimethylsilyl)oxy)-*N*,2-dimethylpropan-2-amine **2.34g** was prepared following **General Procedure for TBS Protection of Alcohols** using 2-(benzyl(methyl)amino)-2-methylpropan-1-ol (10 mmol). The amine product **2.34g** 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 (2.34h)



(*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*,*E*)-*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).

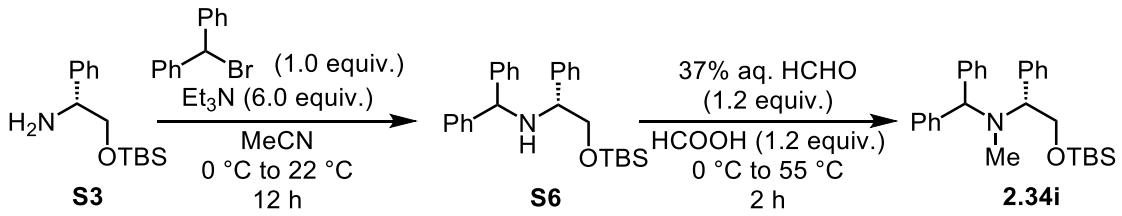
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 - 7.27 (m, 2H), 7.24 (ddd, *J* = 7.9, 6.7, 1.6 Hz, 2H), 7.22 - 7.15 (m, 5H), 7.13 (td, *J* = 6.9, 1.7 Hz, 1H), 3.71 (dd, *J* = 9.2, 4.0 Hz, 1H), 3.65 (d, *J* = 13.5 Hz, 1H), 3.56 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.51 - 3.42 (m, 2H), 0.78 (d, *J* = 1.8 Hz, 9H), -0.06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

(*R*)-*N*-Benzyl-2-((*tert*-butyldimethylsilyl)oxy)-*N*-methyl-1-phenylethan-1-amine (2.34h)

(*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 **2.34h** 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 (2.34i)



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

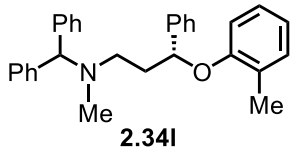
(*R*)-*N*-Benzhydryl-2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethan-1-amine was prepared using **General Procedure for Preparation of Secondary Amines** using (*R*)-2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethan-1-amine (46 mmol). The amine product **S6** was obtained after purification by flash 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 (2.34i)

(*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 **2.34i** 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).

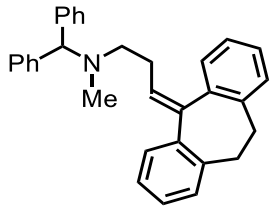
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (ddd, J = 11.6, 8.2, 1.3 Hz, 4H), 7.34 -7.29 (m, 6H), 7.25 - 7.19 (m, 4H), 7.17 - 7.12 (m, 1H), 4.80 (s, 1H), 4.06 (dd, J = 9.7, 5.9 Hz, 1H), 3.98 - 3.89 (m, 2H), 2.13 (s, 3H), 0.85 (s, 9H), -0.03 (d, J = 6.5 Hz, 6H).



(*R*)-*N*-Benzhydryl-*N*-methyl-3-phenyl-3-(*o*-tolyloxy)propan-1-amine (2.34l)

(*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 **2.34l** 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).

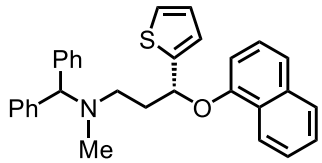


2.34m

***N*-Benzhydryl-3-(10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-ylidene)-*N*-methylpropan-1-amine (2.34m) CAS:2378471-89-5**

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 **2.34m** 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 (d, *J* = 8.7 Hz, 2H), 2.32 (dd, *J* = 15.7, 8.4 Hz, 2H), 2.07 (s, 3H).

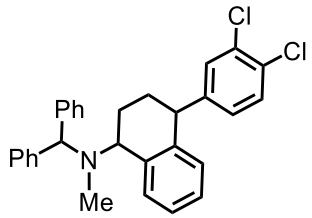


2.34n

(*R*)-*N*-Benzhydryl-*N*-methyl-3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propan-1-amine (2.34n)

(*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 **2.34n** 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).



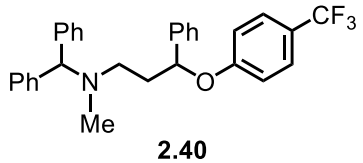
2.34o

***N*-Benzhydryl-4-(3,4-dichlorophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine (2.34o)**

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 **2.34o** 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).



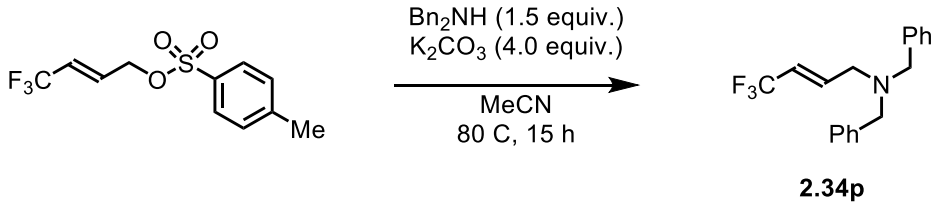
2.40

_N_-Benzhydryl-_N_-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine (2.40)

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 **2.40** 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 (2.34p)

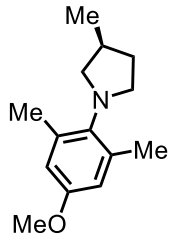


2.34p

(*E*)-*N,N*-Dibenzyl-4,4,4-trifluorobut-2-en-1-amine (2.34p)

(*E*)-*N,N*-Dibenzyl-4,4,4-trifluorobut-2-en-1-amine was prepared following the literature previously reported.[57a] 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 **2.34p** 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).



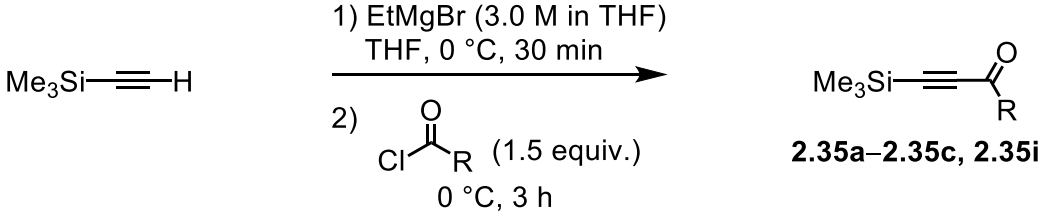
(*S*)-2.34r

(*S*)-1-(4-Methoxy-2,6-dimethylphenyl)-3-methylpyrrolidine ((*S*)-2.34r)

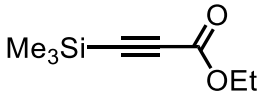
(*S*)-1-(4-Methoxy-2,6-dimethylphenyl)-3-methylpyrrolidine was prepared following **General Procedure for Preparation of Tertiary Amines** using 4-methoxy-2,6-dimethylaniline (1.65 g, 10.9 mmol), (*S*)-1,4-dibromo-2-methylbutane (0.9 equiv.) and K_2CO_3 (2.0 equiv.). The amine product **(*S*)-2.34r** 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



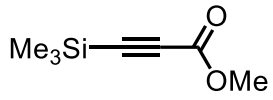
3-(Trimethylsilyl)propiolates **2.35a**-**2.35c**, **2.35i** were prepared according to the literature procedure.[57c] To a solution of ethynyltrimethylsilane (20 mmol) in THF (20 mL) was added ethylmagnesium bromide (3.0 M solution in THF) in a dropwise manner at 0 °C. The reaction mixture was allowed 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.



2.35a

Ethyl 3-(trimethylsilyl)propiolate (**2.35a**) was prepared according to **General Procedure for Preparation of 3-(Trimethylsilyl)propiolates** using ethyl chloroformate. The propiolate **2.35a** 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).

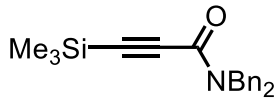


2.35b

Methyl 3-(trimethylsilyl)propiolate (2.35b)

Methyl 3-(trimethylsilyl)propiolate was prepared according to **General Procedure for Preparation of 3-(Trimethylsilyl)propiolates** using methyl chloroformate. The propiolate **2.35b** 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).



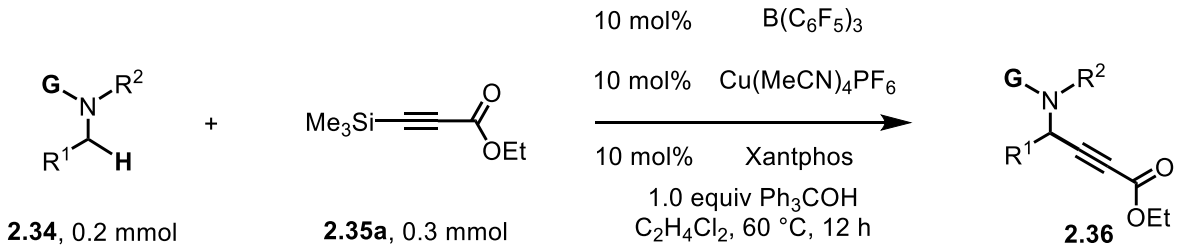
2.35c

***N,N*-Dibenzyl-3-(trimethylsilyl)propiolamide (2.35c)**

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 **2.35c** was obtained after purification by flash silica gel column chromatography (Et_2O:hexanes = 1:99) as a colorless oil (3.3 g, 51%).

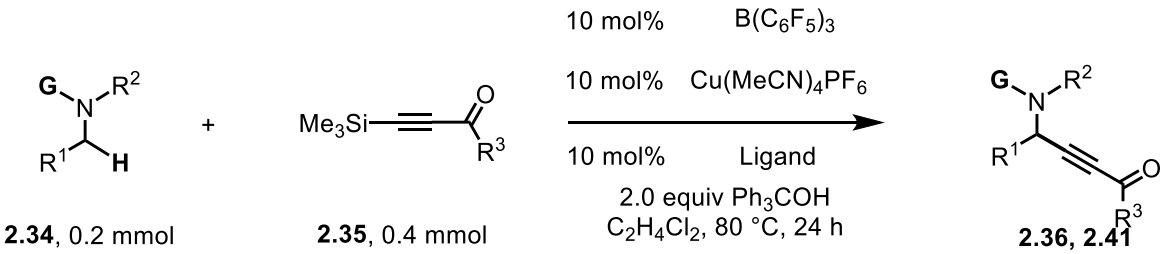
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 - 7.19 (m, 10H), 4.67 (s, 2H), 4.50 (s, 2H), 0.21 (s, 9H).

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



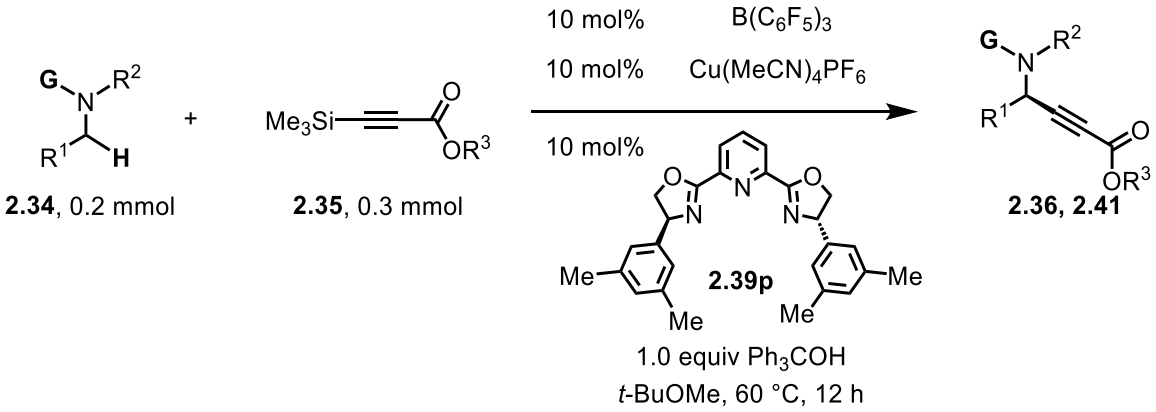
An oven-dried sealed tube equipped with a magnetic stir bar was used. To the sealed tube were added $Cu(MeCN)_4PF_6$ (0.02 mmol), Xantphos (0.02 mmol), and $C_2H_4Cl_2$ (0.4 mL) under nitrogen atmosphere. The mixture was allowed to stir for 20 minutes at 22 °C, then ethyl 3-(trimethylsilyl)propiolate **2.35a** (0.3 mmol), triphenylmethanol (0.2 mmol), amine **2.34** (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



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 **2.35** (0.4 mmol), triphenylmethanol (0.4 mmol), amine **2.34** (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.

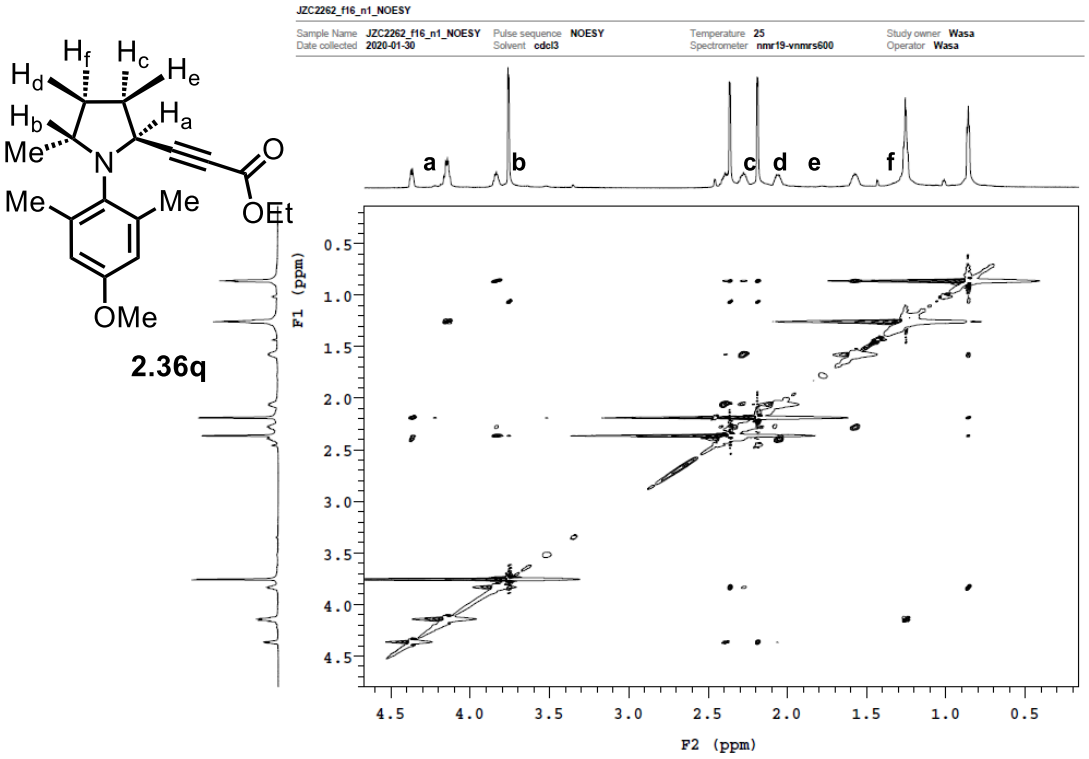
General Procedure C for Stereoselective *α*-C–H Alkynylation of *N*-Alkylamines Catalyzed by $B(C_6F_5)_3$ and Organocopper Complex



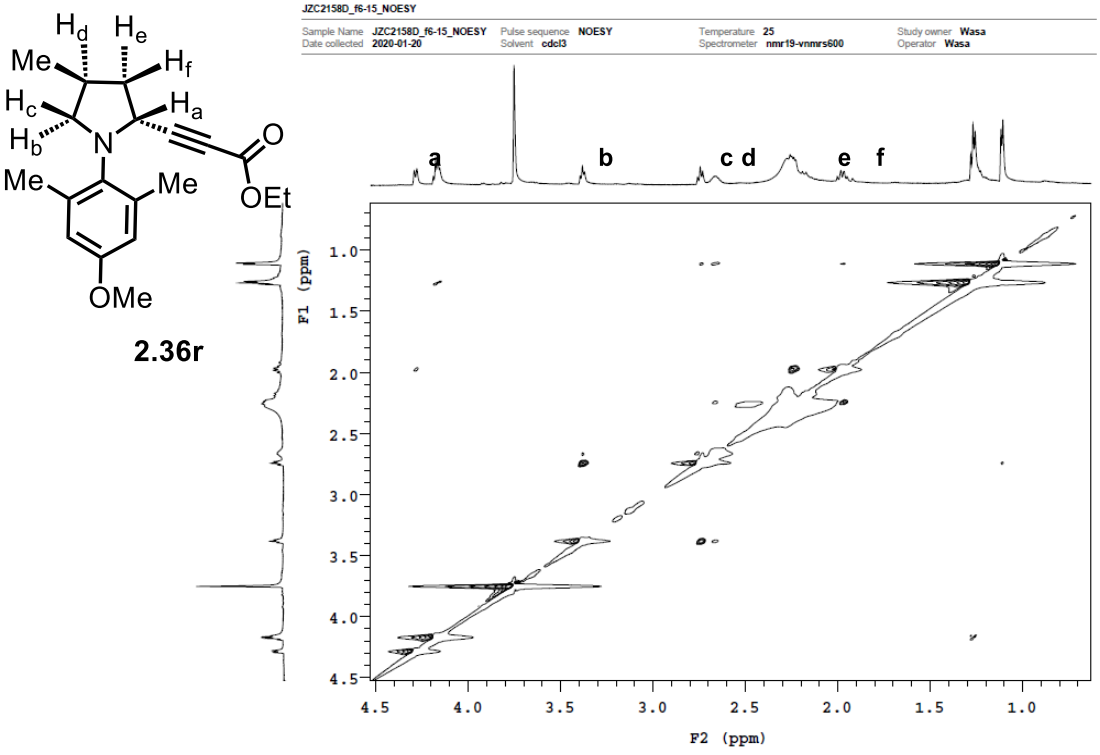
An oven-dried sealed tube equipped with a magnetic stir bar was used. To the sealed tube were added $Cu(MeCN)_4PF_6$ (0.02 mmol), (*S*)-(3,5-dimethylphenyl)PyBOX **2.39p** (0.02 mmol), and *t*-BuOMe (0.4 mL) under nitrogen atmosphere. The mixture was allowed to stir for 20 minutes at 22 °C, then (trimethylsilyl)propiolate **2.35** (0.3 mmol), triphenylmethanol (0.2 mmol), amine **2.34** (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

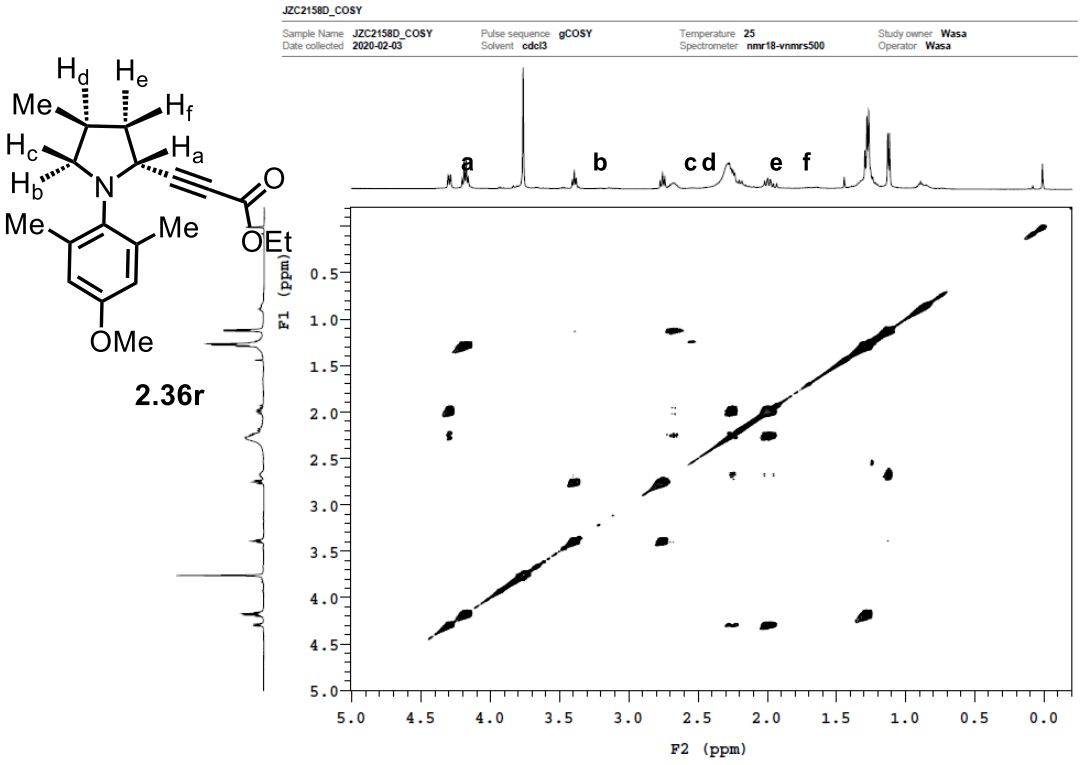
We carried out the following 2D NMR studies in order to determine relative configuration of enantioenriched products **2.36q, 2.36r**.



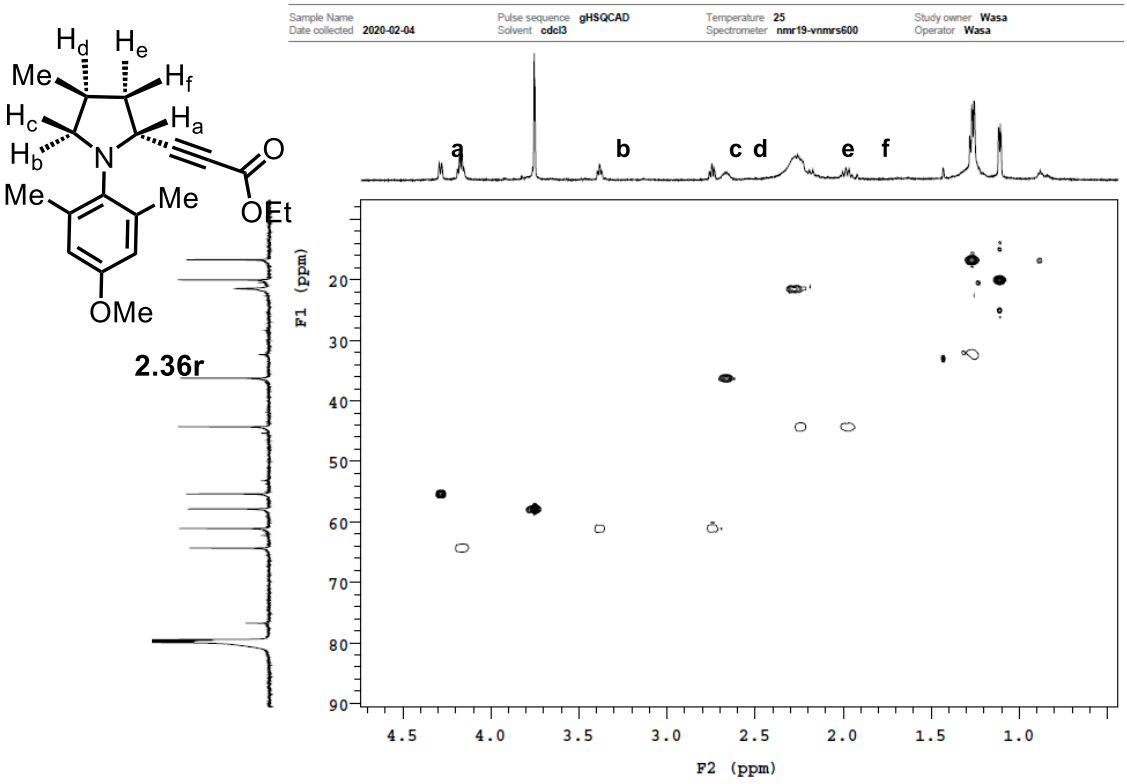
The relative configuration of the major diastereomer of **2.36q** was assigned to be *trans*.


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

2.36r

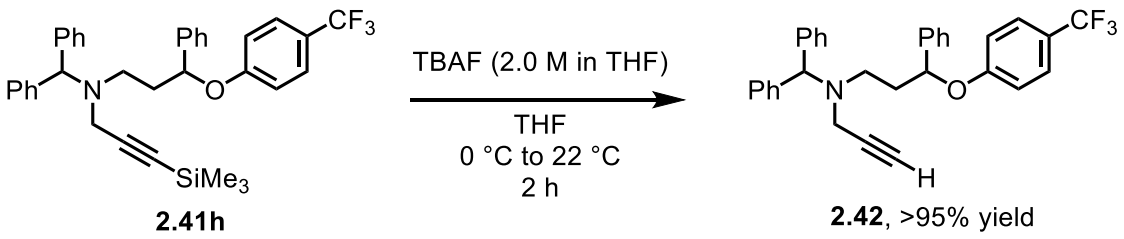

JZC2158D_COSY
Sample Name JZC2158D_COSY
Date collected 2020-02-03
Pulse sequence gCOSY
Solvent cdcl3
Temperature 25
Spectrometer nmr18-vnmrs500
Study owner Wasa
Operator Wasa
Me
Hd
He
Hf
Hc
Ha
Hb
N
O
OEt
Me
Me
OMe
a
b
c d
e
f
F1 (ppm)
F2 (ppm)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
0.0

2.36r



The relative configuration of the major diastereomer of **2.36r** was assigned as *trans*.

Procedure for Removal of Trimethylsilyl Group



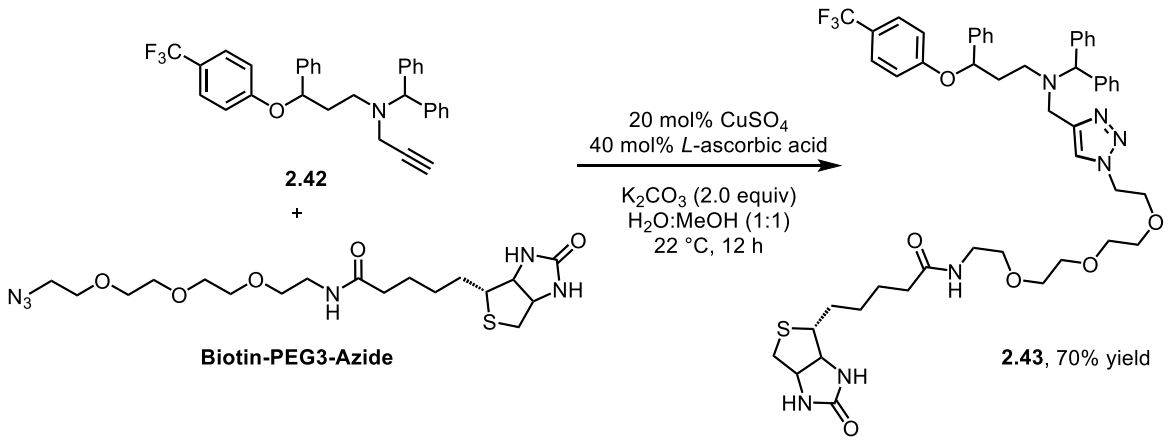
***N*-Benzhydryl-*N*-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)prop-2-yn-1-amine (2.42)**

To a solution of **2.41h** (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 **2.42** 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, 3H), 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 160.61, 143.89, 142.63, 142.53, 141.38, 130.03, 129.44, 128.73, 128.57, 128.52, 128.48, 128.44, 128.38, 128.28, 128.25, 128.00, 127.96, 127.93, 127.92, 127.83, 127.80, 127.71, 127.41, 127.24, 127.15, 127.09, 126.96, 126.92, 126.68, 126.65, 126.63, 126.60, 126.28, 125.80, 125.64, 125.51, 125.35, 123.55, 122.59 (q, *J* = 32.7 Hz), 121.75, 115.70, 78.16, 77.75, 73.51, 72.24, 56.83, 46.35, 39.13, 36.84; **^{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 (2.43)**

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.[59]

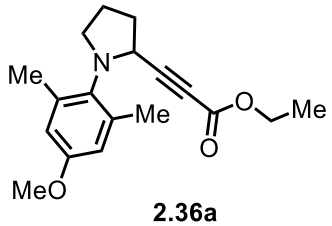
To a solution of alkyne **2.42** (100 mg, 0.2 mmol) in MeOH (2.0 mL) was added K_2CO_3 (55 mg, 0.4 mmol), $CuSO_4$ (6.4 mg, 0.04 mmol), Biotin-PEG3-azide (98 mg, 0.22 mmol), *L*-ascorbic acid (14.1 mg, 0.08 mmol), and H_2O (2.0 mL). The reaction mixture was then allowed to stir for 12 h. Upon completion (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 **2.43** 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 173.21, 163.98, 160.52, 144.77, 142.18, 141.59, 141.29, 128.64, 128.54, 128.44, 128.34, 128.31, 128.26, 128.13, 127.60, 127.07, 127.00, 126.96, 126.62, 126.60, 126.57, 126.55, 125.67, 125.46, 125.28, 123.47, 122.42 (q, *J* = 32.5 Hz), 121.68, 115.64, 77.83, 77.21, 77.00, 76.94, 76.79, 70.60, 70.48, 70.41, 70.30, 69.95, 69.90, 69.82, 69.50, 65.79, 61.69, 60.12, 55.55, 50.01, 46.07, 44.88, 40.43, 39.05, 36.05, 35.93, 35.88, 30.27, 29.64, 29.59, 28.15, 28.04, 25.52, 15.22, -0.06; **^{19}F NMR** (564 MHz, $CDCl_3$) δ -61.44; **IR** (neat) 3287, 2921, 2863, 1698, 1612, 1451,

[59] Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599.

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

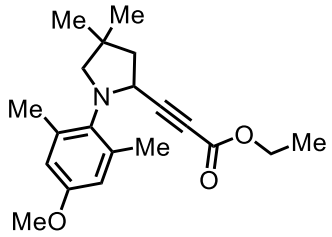


2.36a

Ethyl 3-(1-(4-methoxy-2,6-dimethylphenyl)pyrrolidin-2-yl)propiolate (2.36a)

1-(4-Methoxy-2,6-dimethylphenyl)pyrrolidine **2.34a** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.35a** following **General Procedure A**. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.36a** 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 157.2, 153.3, 136.6, 136.6, 113.2, 91.5, 73.9, 63.3, 55.9, 52.3, 51.0, 35.8, 26.7, 18.4, 15.1; **IR** (neat) n 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.



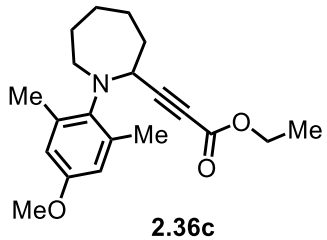
2.36b

1-(4-Methoxy-2,6-dimethylphenyl)-3,3-dimethylpyrrolidine (2.36b)

1-(4-Methoxy-2,6-dimethylphenyl)-3,3-dimethylpyrrolidine **2.34b** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.35a** following **General Procedure A**. After purification by

column chromatography (Et_2O:hexanes = 1:19), **2.36b** 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 157.2, 153.8, 135.4, 135.4, 113.7, 91.0, 74.3, 64.5, 61.6, 55.2, 51.9, 47.0, 39.1, 27.8, 27.2, 19.0, 14.0; **IR** (neat) n 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.

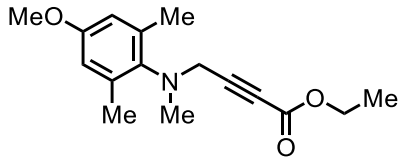


2.36c

Ethyl 3-(1-(4-methoxy-2,6-dimethylphenyl)azepan-2-yl)propiolate (2.36c)

1-(4-Methoxy-2,6-dimethylphenyl)azepane **2.34c** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.35a** following **General Procedure A**. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.36c** 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 (m, 2H), 1.28 (t, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.4, 153.8, 140.9, 139.7, 137.9, 114.1, 113.6, 90.3, 75.6, 59.4, 55.6, 53.0, 51.3, 34.8, 31.4, 28.9, 25.2, 20.1, 19.6, 14.0; **IR** (neat) n 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.

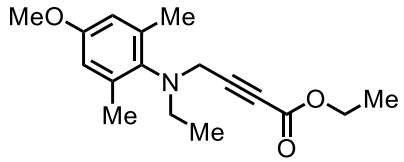


2.36d

Ethyl 4-((4-methoxy-2,6-dimethylphenyl)(methyl)amino)but-2-ynoate (2.36d)

4-Methoxy-*N,N*,2,6-tetramethylaniline **2.34d** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.35a** following **General Procedure A**. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.36d** 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 156.3, 153.6, 140.9, 138.7, 112.8, 86.1, 75.6, 61.8, 55.2, 44.8, 40.1, 19.4, 13.9; **IR** (neat) n 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.

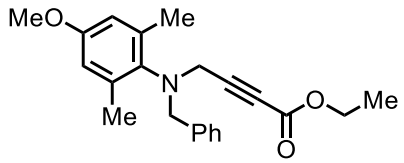


2.36e

Ethyl 4-(ethyl(4-methoxy-2,6-dimethylphenyl)amino)but-2-ynoate (2.36e)

N-Ethyl-4-methoxy-*N*,2,6-trimethylaniline **2.34e** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.35a** following **General Procedure A**. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.36e** 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 156.8, 153.7, 139.5, 139.3, 113.6, 86.7, 75.5, 61.8, 55.2, 47.2, 42.9, 19.6, 14.3, 14.0; **IR** (neat) n 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.

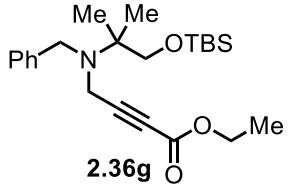


2.36f

Ethyl 4-(benzyl(4-methoxy-2,6-dimethylphenyl)amino)but-2-ynoate (2.36f)

N-Benzyl-4-methoxy-*N*,2,6-trimethylaniline **2.34f** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.35a** following **General Procedure A**. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.36f** 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 156.8, 153.5, 140.6, 139.0, 138.5, 128.9, 128.4, 127.2, 113.4, 85.4, 75.3, 61.8, 58.5, 55.2, 41.5, 19.9, 13.2; **IR** (neat) n 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.



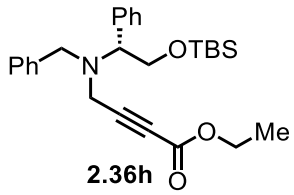
2.36g

Ethyl 4-(benzyl(1-((*tert*-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)amino)but-2-ynoate (2.36g)

N-Benzyl-1-((*tert*-butyldimethylsilyl)oxy)-*N*,2-dimethylpropan-2-amine **2.34g** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.35a** following **General Procedure B** using 1,2-bis(diphenylphosphino)ethane as the ligand. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.36g** 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 153.6, 140.3, 128.4, 128.2, 126.9, 87.6, 76.7, 69.7, 61.8, 58.6, 51.4, 36.7, 25.9, 22.9, 18.2, 14.1, -5.6; **IR** (neat) n 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.

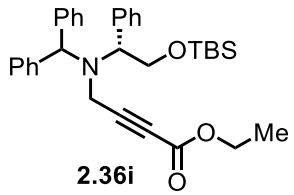


2.36h

Ethyl (*R*)-4-(benzyl(2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethyl)amino)but-2-ynoate (2.36h)

(*R*)-*N*-Benzyl-2-((*tert*-butyldimethylsilyl)oxy)-*N*-methyl-1-phenylethan-1-amine **2.34h** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.35a** following **General Procedure B** using 1,2-bis(diphenylphosphino)ethane as the ligand. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.36h** 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 153.6, 141.1, 138.8, 128.9, 128.5, 128.30, 128.26, 127.4, 127.1, 84.5, 77.84, 67.6, 65.9, 61.9, 55.1, 39.1, 25.8, 18.2, 14.1, -5.67, -5.69; **IR** (neat) n 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).

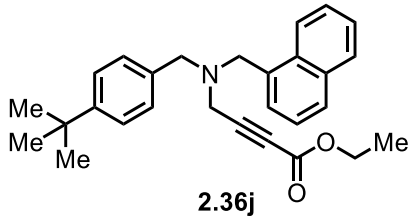


2.36i

Ethyl (*R*)-4-(benzhydryl(2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethyl)amino)but-2-ynoate (2.36i)

(*R*)-*N*-Benzhydryl-2-((*tert*-butyldimethylsilyl)oxy)-*N*-methyl-1-phenylethan-1-amine **2.34i** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.35a** following **General Procedure B** using 1,2-bis(diphenylphosphino)ethane as the ligand. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.36i** 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 153.4, 142.0, 141.9, 139.8, 128.7, 128.6, 128.49, 128.47, 128.39, 128.1, 127.24, 127.15, 86.5, 76.6, 69.2, 63.1, 62.9, 61.6, 36.6, 25.9, 18.2, 14.1, -5.55, -5.57; **IR** (neat) n 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).



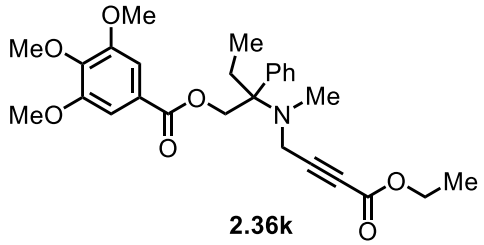
2.36j

Ethyl 4-((4-(*tert*-butyl)phenyl)(naphthalen-1-ylmethyl)amino)but-2-ynoate (2.36j)

4-(*tert*-Butyl)-*N*-methyl-*N*-(naphthalen-1-ylmethyl)aniline **2.34j** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.35a** following **General Procedure B** using 1,2-bis(diphenylphosphino)ethane as the ligand. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.36j** 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, 3H), 1.30 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.6, 150.3, 135.1, 133.9, 133.7, 132.5,

128.9, 128.4, 128.3, 127.8, 125.8, 125.7, 125.3, 125.2, 124.9, 83.6, 78.3, 62.0, 57.7, 56.2, 40.9, 34.5, 31.4, 14.1; **IR** (neat) n 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.

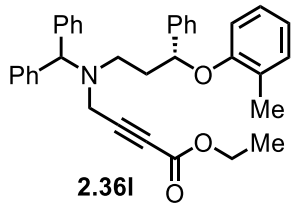


2.36k

2-((4-Ethoxy-4-oxobut-2-yn-1-yl)(methyl)amino)-2-phenylbutyl-3,4,5-trimethoxybenzoate (2.36k)

2-(Dimethylamino)-2-phenylbutyl 3,4,5-trimethoxybenzoate **2.34k** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.35a** following **General Procedure B** using 1,2-bis(diphenylphosphino)ethane as the ligand. After purification by column chromatography (Et_2O:hexanes = 1:2), **2.36k** 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, 3H), 0.69 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.8, 153.5, 152.9, 142.3, 141.7, 128.2, 127.3, 126.9, 124.8, 106.8, 86.2, 75.5, 65.7, 64.8, 61.8, 60.8, 56.1, 42.1, 35.8, 30.1, 13.9, 8.5; **IR** (neat) n 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.

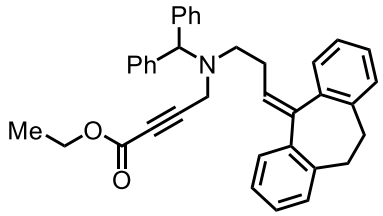


2.36l

Ethyl (*R*)-4-(benzhydryl(3-phenyl-3-(*o*-tolyloxy)propyl)amino)but-2-ynoate (2.36l)

(*R*)-*N*-Benzhydryl-*N*-methyl-3-phenyl-3-(*o*-tolyloxy)propan-1-amine **2.34l** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.35a** following **General Procedure B** using 1,2-bis(diphenylphosphino)ethane as the ligand. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.36l** 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, 153.4, 142.33, 142.26, 142.2, 130.5, 128.7, 128.6, 128.5, 127.91, 127.88, 127.7, 127.4, 127.20, 127.15, 127.1, 126.4, 125.6, 120.0, 112.3, 83.5, 77.9, 76.9, 72.6, 61.9, 47.3, 39.5, 37.2, 16.3, 14.1; **IR** (neat) n 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.



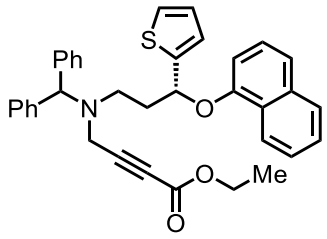
2.36m

Ethyl4-(benzhydryl(3-(10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-ylidene)propyl)amino)but-2-ynoate (2.36m)

N-Benzhydryl-3-(10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-ylidene)-*N*-methylpropan-1-amine **2.34m** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.35a** following **General Procedure B** using 1,2-bis(diphenylphosphino)ethane as the ligand. After purification by column chromatography (Et_2O:hexanes = 1:4), **2.36m** 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 153.4, 143.8, 142.4, 141.2, 139.9, 139.3, 137.0, 130.0, 129.0, 128.6, 128.50, 128.48, 128.2, 128.0, 127.9, 127.4, 127.1, 127.0, 123.0, 125.8, 83.7, 77.8, 72.3, 61.9, 50.3, 39.3, 33.8, 32.0, 27.6; **IR** (neat) n 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.

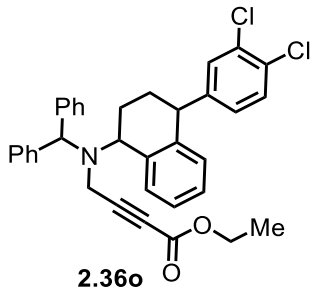


2.36n

Ethyl (*R*)-4-(benzhydryl(3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propyl)amino)but-2-ynoate (2.36n)

(*R*)-*N*-Benzhydryl-*N*-methyl-3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propan-1-amine **2.34n** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.35a** following **General Procedure B** using 1,2-bis(diphenylphosphino)ethane as the ligand. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.36n** 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 153.4, 153.3, 145.3, 142.3, 141.9, 134.5, 128.7, 128.5, 127.9, 127.7, 127.3, 127.2, 126.9, 126.5, 126.2, 126.1, 125.6, 125.1, 124.6, 124.5, 122.2, 120.5, 106.4, 83.4, 78.1, 73.9, 72.5, 61.9, 47.1, 39.7, 37.2, 14.0; **IR** (neat) n 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.

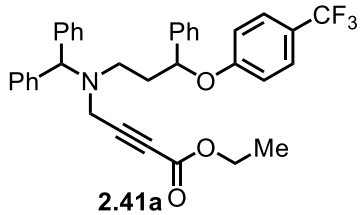


2.36o

Ethyl 4-(benzhydryl(4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-yl)amino)but-2-ynoate (2.36o)

N-Benzhydryl-4-(3,4-dichlorophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine **2.34o** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.35a** following **General Procedure B** using 1,2-bis(diphenylphosphino)ethane as the ligand. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.36o** 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 153.3, 147.2, 142.24, 142.18, 139.1, 138.6, 132.2, 130.7, 130.04, 129.99, 129.87, 128.8, 128.74, 128.70, 128.5, 128.3, 128.2, 128.1, 127.93, 127.91, 127.58, 127.56, 127.45, 127.38, 127.3, 127.2, 127.0, 86.3, 77.5, 69.1, 61.7, 57.8, 43.4, 36.2, 30.3, 17.5, 13.9; **IR** (neat) n 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.

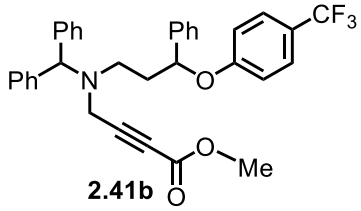


2.41a

Ethyl 4-(benzhydryl(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)amino)but-2-ynoate (2.41a)

N-Benzhydryl-*N*-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine **2.40** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.35a** following **General Procedure B** using 1,2-bis(diphenylphosphino)ethane as the ligand. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.41a** 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, 9H), 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, $CDCl_3$) δ 160.5, 153.4, 142.13, 142.08, 141.2, 128.8, 128.6, 128.5, 128.0, 127.8, 127.3, 127.1, 126.7 (d, J_{CF} = 3.3 Hz), 125.6, 124.4 (d, J_{CF} = 271.1 Hz), 122.7 (q, J_{CF} = 32.7 Hz), 122.3, 115.7, 83.3, 78.0, 77.7, 72.5, 62.0, 46.9, 39.5, 36.8, 14.0; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -61.53; **IR** (neat) n 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.



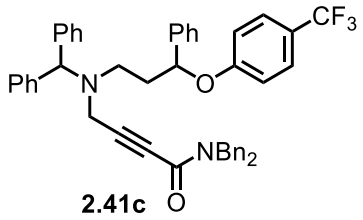
2.41b

Methyl 4-(benzhydryl(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)amino)but-2-ynoate (2.41b)

N-Benzhydryl-*N*-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine **2.40** was reacted with methyl 3-(trimethylsilyl)propiolate **2.35b** following **General Procedure B** using 1,2-bis(diphenylphosphino)ethane as the ligand. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.41b** 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 160.5, 153.8, 142.11, 142.05, 141.2, 128.8, 128.7, 128.6, 127.9, 127.79, 127.75, 127.3, 127.2, 126.7 (d, J_{CF} = 3.8 Hz), 125.6, 124.4 (d, J_{CF} = 271.3 Hz), 122.7 (q, J_{CF} = 32.5 Hz), 115.7, 83.7, 77.7, 72.5, 53.4, 52.7, 46.9, 39.5, 36.8; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -61.50; **IR** (neat) n 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.



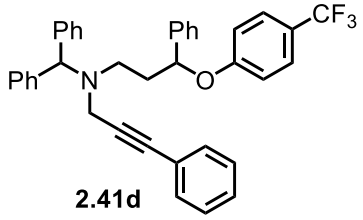
2.41c

4-(Benzhydryl(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)amino)-*N*,*N*-dibenzylbut-2-ynamide (2.41c)

N-Benzhydryl-*N*-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine **2.40** was reacted with *N,N*-dibenzyl-3-(trimethylsilyl)propiolamide **2.35c** following **General Procedure B** using (*S*)-PhPyBOX as the ligand. After purification by column chromatography (Et_2O:hexanes = 1:4), **2.41c** 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 160.5, 154.7, 142.13, 142.06, 141.1, 136.2, 136.0, 129.0, 128.8, 128.7, 128.6, 128.5, 128.0, 127.8, 127.7, 127.6, 127.24, 127.20, 127.0, 126.6 (d, J_{CF} = 3.0 Hz), 125.6, 125.3, 123.5 (d, J_{CF} = 271.1 Hz), 122.7 (q, J_{CF} = 32.7 Hz), 115.7, 87.7, 78.90, 77.7, 72.6, 51.3, 46.9, 46.5, 39.6, 36.8; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -61.48; **IR** (neat)

n 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.

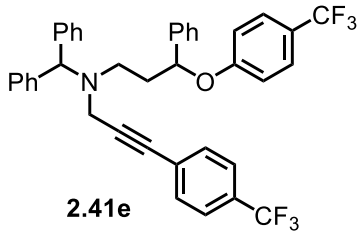


2.41d

***N*-Benzhydryl-3-phenyl-*N*-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)prop-2-yn-1-amine (2.41d)**

N-Benzhydryl-*N*-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine **2.40** was reacted with trimethyl(phenylethynyl)silane **2.35d** following **General Procedure B** using (*S*)-PhPyBOX as the ligand. After purification by column chromatography (Et_2O:hexanes = 1:49), **2.41d** 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 160.6, 142.8, 142.7, 141.4, 131.7, 128.7, 128.5, 128.4, 128.3, 128.1, 127.9, 127.7, 127.1, 127.0, 126.6 (d, J_{CF} = 3.1 Hz), 125.7, 125.5, 124.5 (d, J_{CF} = 271.5 Hz), 123.3, 122.6 (q, J_{CF} = 32.6 Hz), 115.7, 85.9, 84.2, 77.9, 72.6, 46.7, 40.0, 36.9; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -61.49; **IR** (neat) n 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.

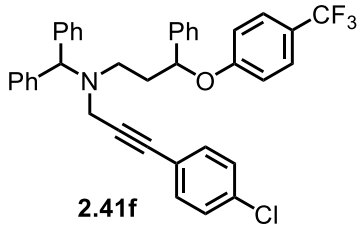


2.41e

***N*-Benzhydryl-*N*-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)-3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-amine (2.41e)**

N-Benzhydryl-*N*-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine **2.40** was reacted with trimethyl((4-(trifluoromethyl)phenyl)ethynyl)silane **2.35e** following **General Procedure B** using (*S*)-PhPyBOX as the ligand. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.41e** 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 160.6, 142.6, 142.5, 141.3, 132.4, 132.0 (d, J_{CF} = 293.4 Hz), 129.8 (q, J_{CF} = 32.6 Hz), 129.4, 128.8, 128.6, 128.5, 128.0, 127.9, 127.8, 127.2, 127.1, 126.7 (d, J_{CF} = 2.9 Hz), 125.7, 125.2 (d, J_{CF} = 2.8 Hz), 124.2 (d, J_{CF} = 211.0 Hz), 122.7 (q, J_{CF} = 32.5 Hz), 115.7, 87.1, 84.6, 77.9, 72.6, 46.8, 40.0, 36.9; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -61.45, -62.75; **IR** (neat) n 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.

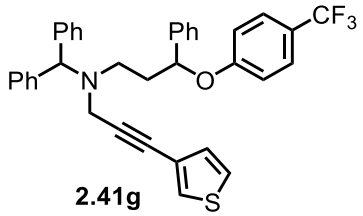


2.41f

***N*-Benzhydryl-3-(4-chlorophenyl)-*N*-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)prop-2-yn-1-amine (2.41f)**

N-Benzhydryl-*N*-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine **2.40** was reacted with ((4-chlorophenyl)ethynyl)trimethylsilane **2.35f** following **General Procedure B** using (*S*)-PhPyBOX as the ligand. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.41f** 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 160.6, 142.7, 142.5, 141.4, 134.0, 132.9, 128.7, 128.6, 128.53, 128.45, 128.0, 127.9, 127.7, 127.1, 127.0, 126.7 (d, J_{CF} = 2.6 Hz), 125.7, 124.4 (d, J_{CF} = 271.1 Hz), 122.6 (q, J_{CF} = 32.8 Hz), 121.8, 115.7, 85.3, 84.7, 77.9, 72.6, 46.7, 40.0, 36.9; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -61.50; **IR** (neat) n 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.



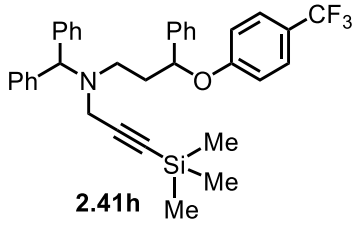
2.41g

***N*-Benzhydryl-*N*-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)-3-(thiophen-3-yl)prop-2-yn-1-amine (2.41g)**

N-Benzhydryl-*N*-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine **2.40** was reacted with trimethyl(thiophen-3-ylethynyl)silane **2.35g** following **General Procedure B** using (*S*)-PhPyBOX as the ligand. After purification by column chromatography (Et_2O:hexanes = 1:49), **2.41g** 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 160.6, 142.7, 142.6, 141.4, 130.0, 128.7, 128.5, 128.4, 128.3, 128.0, 127.9, 127.7, 127.1, 127.0, 126.7 (d, *J* = 3.6 Hz), 125.7, 125.3, 124.7 (d, *J* = 267.9 Hz), 122.6 (d, *J* = 32.9 Hz), 122.3, 115.7, 83.8, 80.8, 77.8, 72.5, 46.6, 40.0, 36.9; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -

61.41; **IR** (neat) n 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.

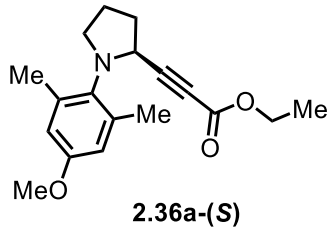


2.41h

***N*-Benzhydryl-*N*-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)-3-(trimethylsilyl)prop-2-yn-1-amine (2.41h)**

N-Benzhydryl-*N*-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine **2.40** was reacted with 1,2-bis(trimethylsilyl)ethyne **2.35h** following **General Procedure B** using (*S*)-PhPyBOX as the ligand. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.41h** 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) n 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.



2.36a-(*S*)

Ethyl (*S*)-3-(1-(4-methoxy-2,6-dimethylphenyl)pyrrolidin-2-yl)propiolate (2.36a-(*S*))

1-(4-Methoxy-2,6-dimethylphenyl)pyrrolidine **2.34a** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.35a** following **General Procedure C**. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.36a-(*S*)** was obtained as a colorless liquid (45 mg, 75%). The absolute configuration of **2.36a-(*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 157.2, 153.3, 136.6, 136.6, 113.2, 91.5, 73.9, 63.3, 55.9, 52.3, 51.0, 35.8, 26.7, 18.4, 15.1; **IR** (neat) n 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; **2.36a-(*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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                  0mL.M (Sequence Method)
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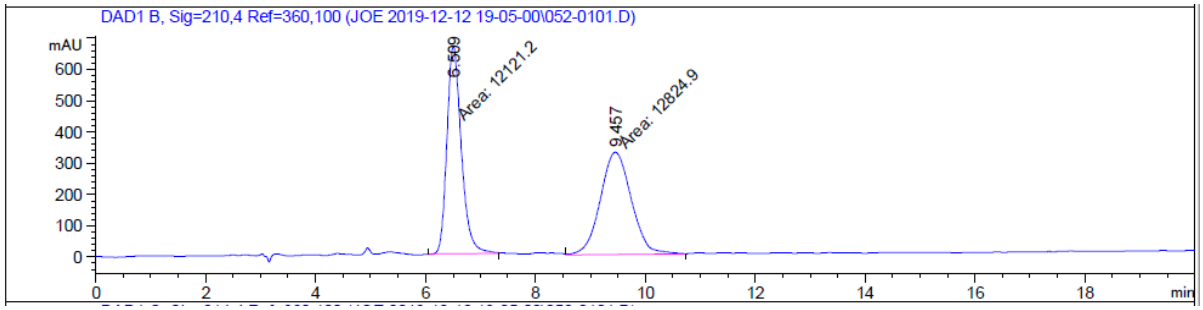


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Signal 2: DAD1 B, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
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----|-------|----|-------|----------|----------|--------|
   1   6.509 MM    0.3045 1.21212e4   663.55304  48.5896
   2   9.457 MM    0.6531 1.28249e4   327.28235  51.4104
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                                               Inj Volume : 4.000 µl
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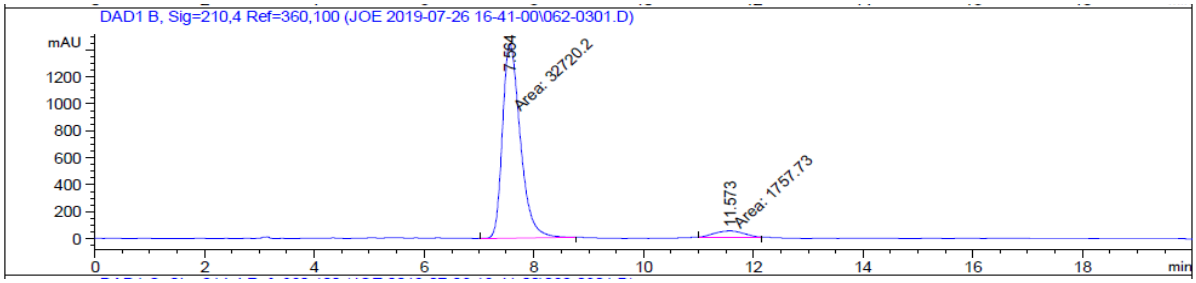

Signal 2: DAD1 B, Sig=210,4 Ref=360,100

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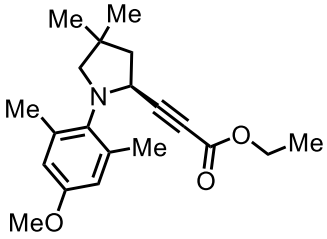
2	11.573	MM	0.6270	1757.73438	46.72317	5.0981



2.36b-(*S*)

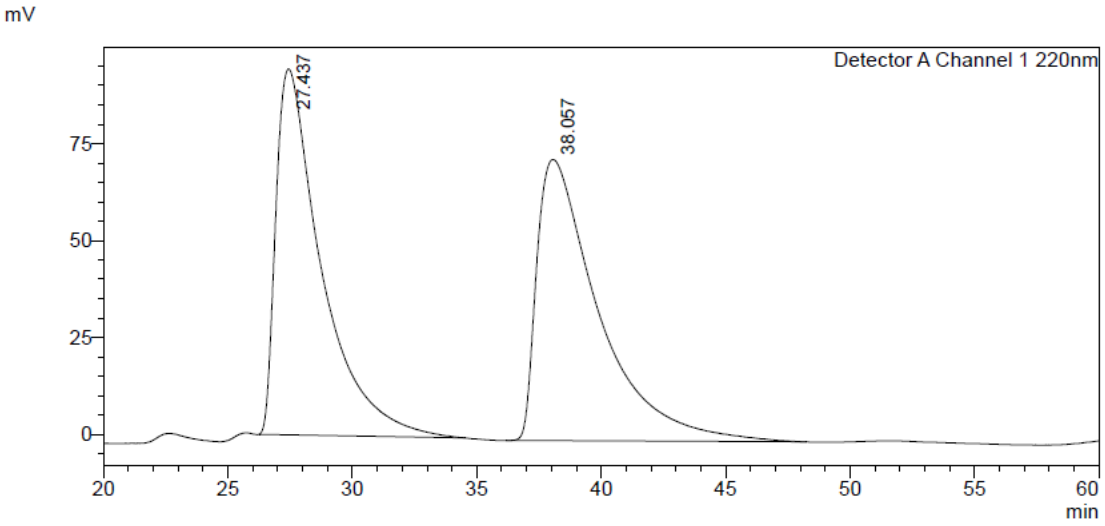
Ethyl (*S*)-3-(1-(4-methoxy-2,6-dimethylphenyl)-4,4-dimethylpyrrolidin-2-yl)propiolate (2.36b-(S))

1-(4-Methoxy-2,6-dimethylphenyl)-3,3-dimethylpyrrolidine **2.34b** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.35a** following **General Procedure C**. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.36b** was obtained as a yellow oil (45 mg, 69%). The absolute configuration of **2.36b** was assigned in analogy to **2.36a-(*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 (s, J = 1.0 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.2, 153.8, 135.4, 135.4, 113.7, 91.0, 74.3, 64.5, 61.6, 55.2, 51.9, 47.0, 39.1, 27.8, 27.2, 19.0, 14.0; **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; **2.36b:** tr = 27.4 min (major), 38.1 min (minor); 93:7 er.

Sample Name	: 8c_rac5_JZC2152A_n2n1_AY-3_2-10		
Sample ID	: 8c_rac5_JZC2152A_n2n1_AY-3_2-10		
Data Filename	: 8c_rac5_JZC2152A_n2n1_AY-3_2-10.lcd		
Method Filename	: 99.9_0.1_60min_0.3mL.lcm		
Batch Filename	: batch8.lcb		
Vial #	: 1-24	Sample Type	: Unknown
Injection Volume	: 10 uL		
Date Acquired	: 2/11/2020 2:39:47 AM	Acquired by	: System Administrator
Date Processed	: 2/11/2020 10:17:04 AM	Processed by	: System Administrator



Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%
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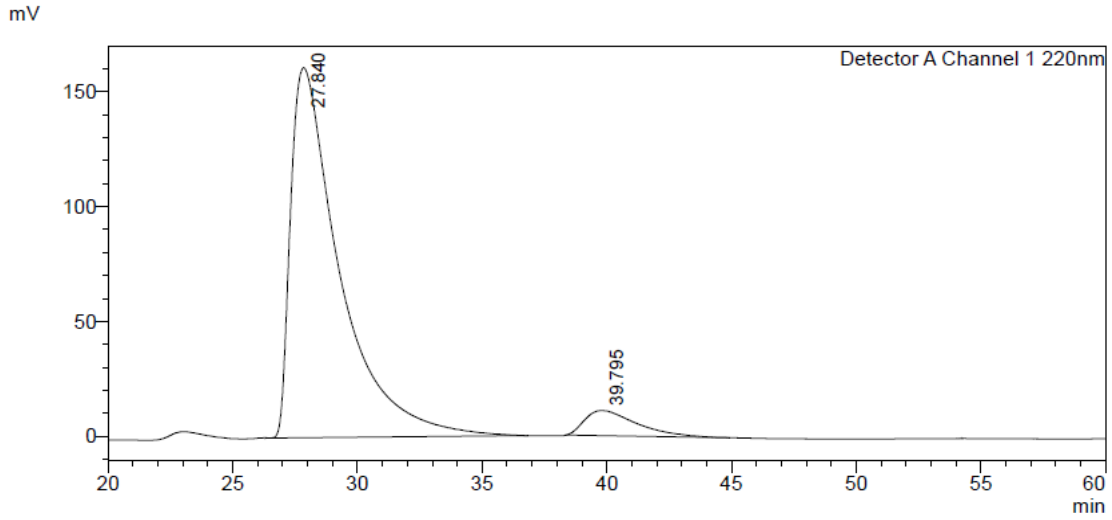
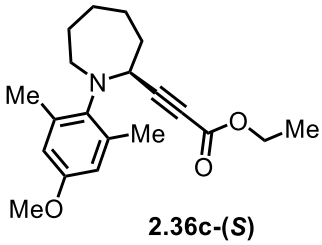
2	38.057	12512111	51.047
Total		24511111	100.000

Sample Name	: 8c_ee4_JZC2101A_AY-3_2-10		
Sample ID	: 8c_ee4_JZC2101A_AY-3_2-10		
Data Filename	: 8c_ee4_JZC2101A_AY-3_2-10.lcd		
Method Filename	: 99.9_0.1_60min_0.3mL.lcm		
Batch Filename	: batch8.lcb		
Vial #	: 1-25	Sample Type	: Unknown
Injection Volume	: 4 uL		
Date Acquired	: 2/11/2020 3:40:02 AM	Acquired by	: System Administrator
Date Processed	: 2/12/2020 4:33:05 PM	Processed by	: System Administrator



Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%
1	27.840	22004548	93.243
2	39.795	1594617	6.757
Total		23599165	100.000



2.36c-(*S*)

Ethyl (*S*)-3-(1-(4-methoxy-2,6-dimethylphenyl)azepan-2-yl)propiolate (2.36c-(S))

1-(4-Methoxy-2,6-dimethylphenyl)azepane **2.34c** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.35a** following **General Procedure C**. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.36c** was obtained as a colorless liquid (42 mg, 64%). The absolute configuration of **2.36c** was assigned in analogy to **2.36a-(*S*)**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.57 (d, *J* = 13.4 Hz, 2H), 4.18 (q, *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 (m, 2H), 1.28 (t, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.4, 153.8, 140.9, 139.7, 137.9, 114.1, 113.6, 90.3, 75.6, 59.4, 55.6, 53.0, 51.3, 34.8, 31.4, 28.9, 25.2, 20.1, 19.6, 14.0; **IR** (neat) n 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; **2.36c:** tr = 14.8 min (major), 17.4 min (minor); 95:5 er.

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Acq. Instrument : Wasa_LC1                          Location :   41
Injection Date   : 6/6/2019 11:37:23 AM                  Inj :   1
                                                  Inj Volume : 4.000 µl
Acq. Method      : C:\Chem32\1\Data\JOE 2019-06-06 11-04-24\column4 1.5%IPA 98.5% hexane 60min
                   -0.5mL.M
Last changed     : 6/6/2019 11:04:28 AM by SYSTEM
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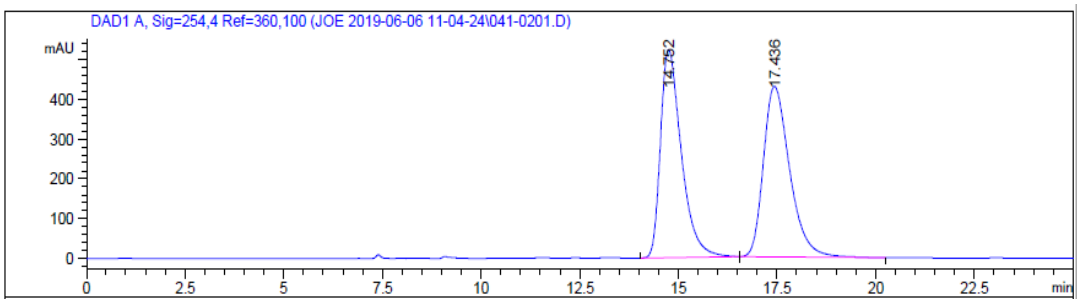


```
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   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
Last changed    : 8/7/2019 3:42:08 PM by SYSTEM
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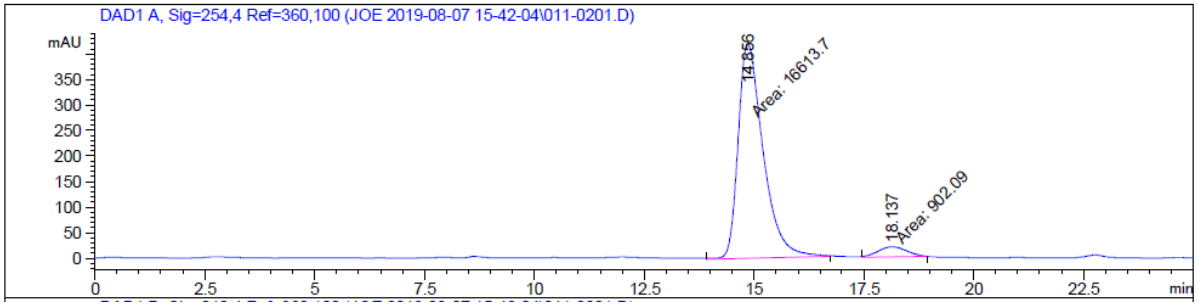
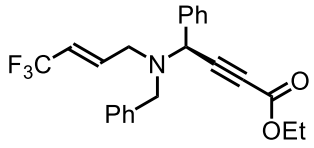



```
Signal 2: DAD1 B, Sig=210,4 Ref=360,100

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



2.36p

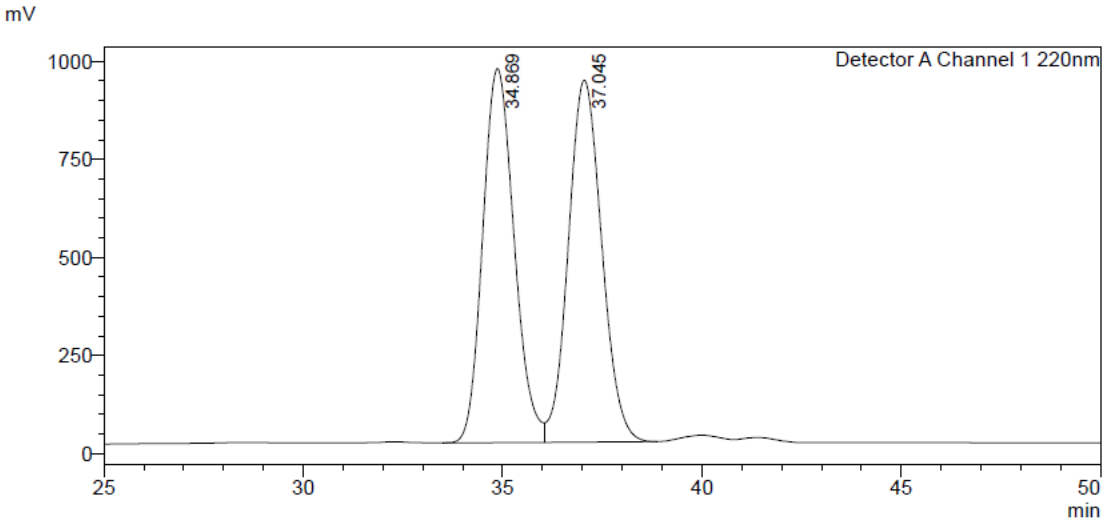
Ethyl (*S*,*E*)-4-(benzyl(4,4,4-trifluorobut-2-en-1-yl)amino)-4-phenylbut-2-ynoate (2.36p)

(*E*)-*N*,*N*-Dibenzyl-4,4,4-trifluorobut-2-en-1-amine **2.34p** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.35a** following **General Procedure C** using (*S*)-PhPyBOX as the ligand. After purification by column chromatography (Et_2O:hexanes = 1:19), **2.36p** 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 153.4, 138.1, 138.03, 137.99, 137.95, 137.93, 136.5, 128.84, 128.81, 128.68, 128.65, 128.60, 128.57, 128.5, 128.42, 128.36, 128.3, 128.2, 128.0, 127.9, 127.6, 127.21, 127.16, 123.7, 121.9, 120.7, 120.5, 120.3, 120.0, 82.8, 80.5, 62.3, 58.3, 56.3, 55.4, 53.5, 50.6, 14.1; **^{19}F NMR** (564 MHz, $CDCl_3$) δ -64.09 (m); **IR** (neat) n 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; **2.36p:** tr = 34.9 min (minor), 37.0 min (major); 84:16 er.

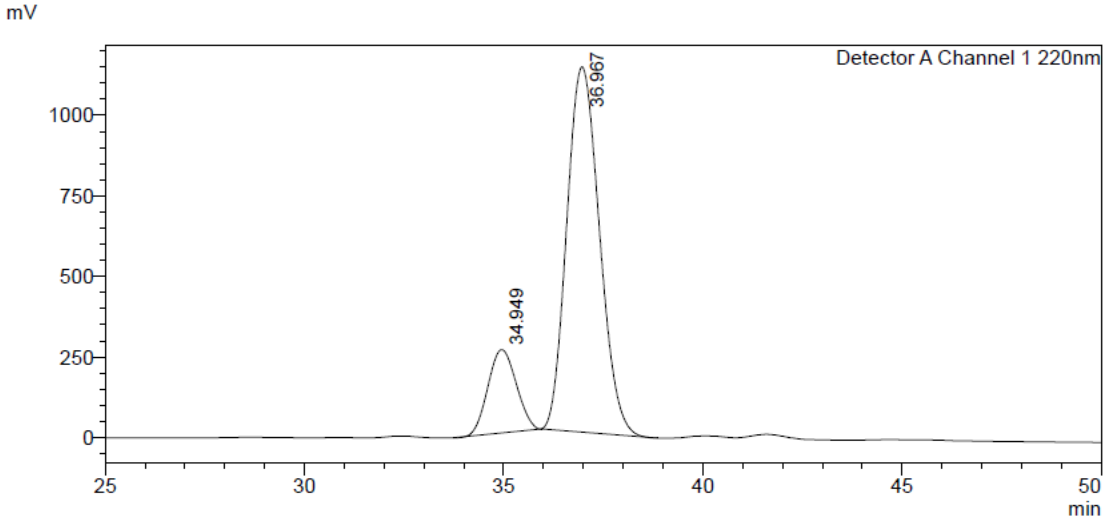
Sample Name	: 8e_rac3_JZC2017H2_AD-H_0.3mL		
Sample ID	: 8e_rac3_JZC2017H2_AD-H_0.3mL		
Data Filename	: 8e_rac3_JZC2017H2_AD-H_0.3mL.lcd		
Method Filename	: 995_05_60min_03mL.lcm		
Batch Filename	: batch9.lcb		
Vial #	: 1-4	Sample Type	: Unknown
Injection Volume	: 4 uL		
Date Acquired	: 2/9/2020 5:43:00 PM	Acquired by	: System Administrator
Date Processed	: 2/10/2020 9:51:53 AM	Processed by	: System Administrator



Detector A Channel 1 220nm

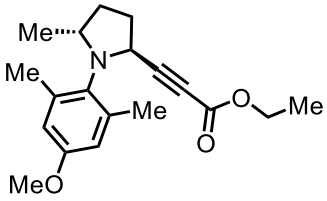
Peak#	Ret. Time	Area	Area%
1	34.869	52257747	49.272
2	37.045	53800949	50.728
Total		106058696	100.000

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		
Date Acquired	: 2/9/2020 6:43:34 PM	Acquired by	: System Administrator
Date Processed	: 2/10/2020 9:40:28 AM	Processed by	: System Administrator



Detector A Channel 1 220nm

Peak#	Ret. Time	Area	Area%
1	34.949	12756097	16.485
2	36.967	64623088	83.515
Total		77379185	100.000



2.36q

Ethyl 3-((2*S*,5*R*)-1-(4-methoxy-2,6-dimethylphenyl)-5-methylpyrrolidin-2-yl)propiolate (2.36q)

1-(4-Methoxy-2,6-dimethylphenyl)-2-methylpyrrolidine ***rac*-2.34q** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.35a** 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), **2.36q** was obtained

as a yellow oil (42 mg, 66%). The relative configuration of **2.36q** 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 (t, *J* = 0.9 Hz, 3H), 0.86 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 156.8, 153.8, 140.2, 139.7, 133.6, 113.9, 113.2, 91.0, 74.6, 61.7, 55.2, 55.1, 52.2, 33.2, 31.4, 20.3, 19.9, 19.0, 14.0; **IR** (neat) n 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; **2.36q:** 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		
Vial #	: 1-20	Sample Type	: Unknown
Injection Volume	: 30 uL		
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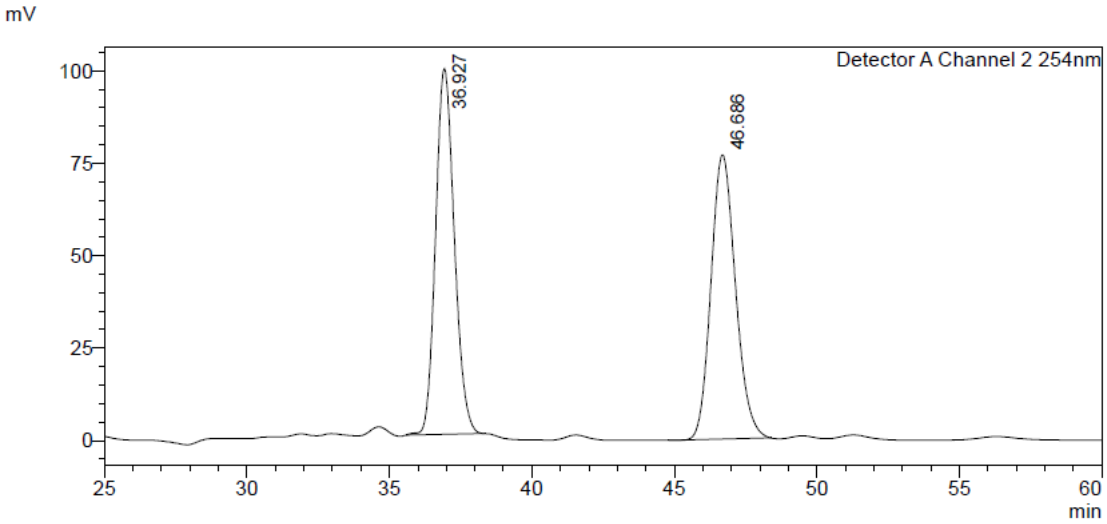
Date Processed	: 2/13/2020 11:43:41 PM	Processed by	: System Administrator



Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Area%
1	36.927	4524255	49.641
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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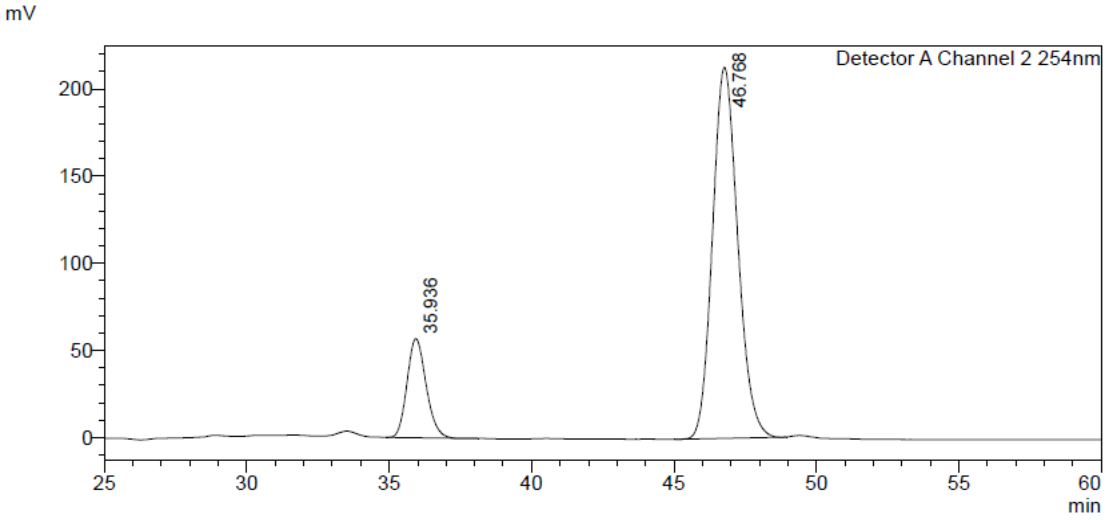
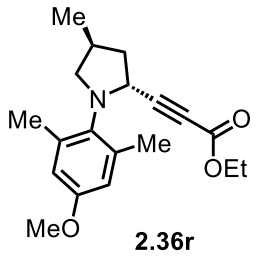
Date Processed	: 2/13/2020 8:34:17 PM	Processed by	: System Administrator



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



2.36r

Ethyl 3-((2*R*,4*S*)-1-(4-methoxy-2,6-dimethylphenyl)-4-methylpyrrolidin-2-yl)propiolate (2.36r)

(*S*)-1-(4-Methoxy-2,6-dimethylphenyl)-3-methylpyrrolidine **(*S*)-2.34r** was reacted with ethyl 3-(trimethylsilyl)propiolate **2.35a** 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), **2.36r** was obtained as a colorless liquid (40 mg, 64%). The relative configuration of **2.36r** 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 157.1, 153.9, 135.8, 135.8, 113.6, 91.2, 74.1, 61.7, 58.4, 55.2, 52.7, 41.6, 33.6, 18.8, 17.3, 14.0; **IR** (neat) n 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; **2.36r:** tr = 23.0 min (major), 24.0 min (minor); 97:3 er.

```
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Acq. Instrument  : Wasa_LC1                         Location :   61
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                                                  Inj Volume : 4.000 µl
Acq. Method      : C:\Chem32\1\Data\JOE 2020-02-13 17-34-27\column6 2.5%IPA 97.5% hexane 40min
                   -0.2mL.M
Last changed     : 2/13/2020 5:34:32 PM by SYSTEM
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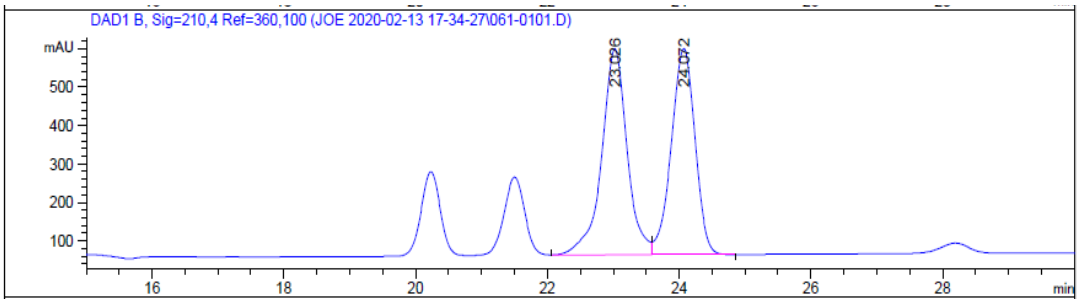


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Signal 2: DAD1 B, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  23.026 VV    0.4035 1.44252e4   536.82739  51.7382
   2  24.072 VB    0.3885 1.34559e4   536.65869  48.2618
```

```
Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : Wasa_LC1                         Location :   62
Injection Date  : 2/13/2020 6:16:42 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2020-02-13 17-34-27\column6 2.5%IPA 97.5% hexane 40min
                  -0.2mL.M
Last changed    : 2/13/2020 5:34:32 PM by SYSTEM
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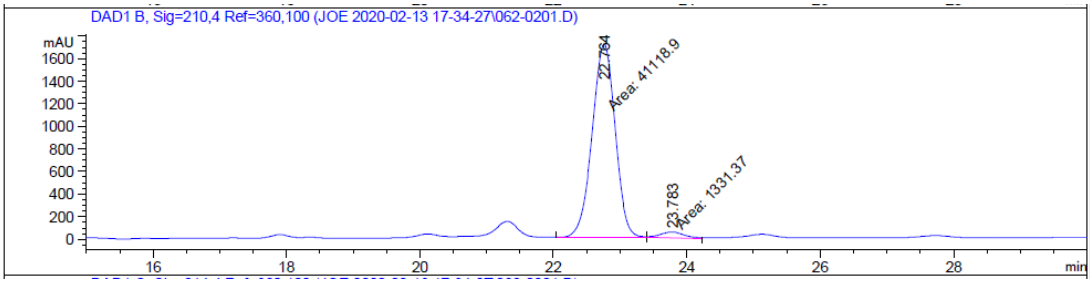


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Signal 2: DAD1 B, Sig=210,4 Ref=360,100
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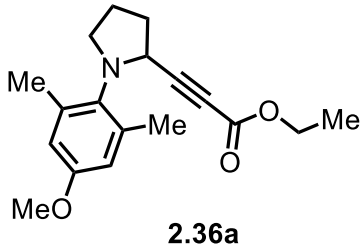
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.764	MM	0.3995	4.11189e4	1715.43152	96.8637
2	23.783	MM	0.4273	1331.37109	51.93531	3.1363

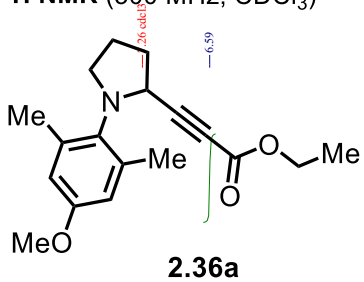
2.7.3 NMR Spectral Data

^{1}H NMR (500 MHz, $CDCl_3$)



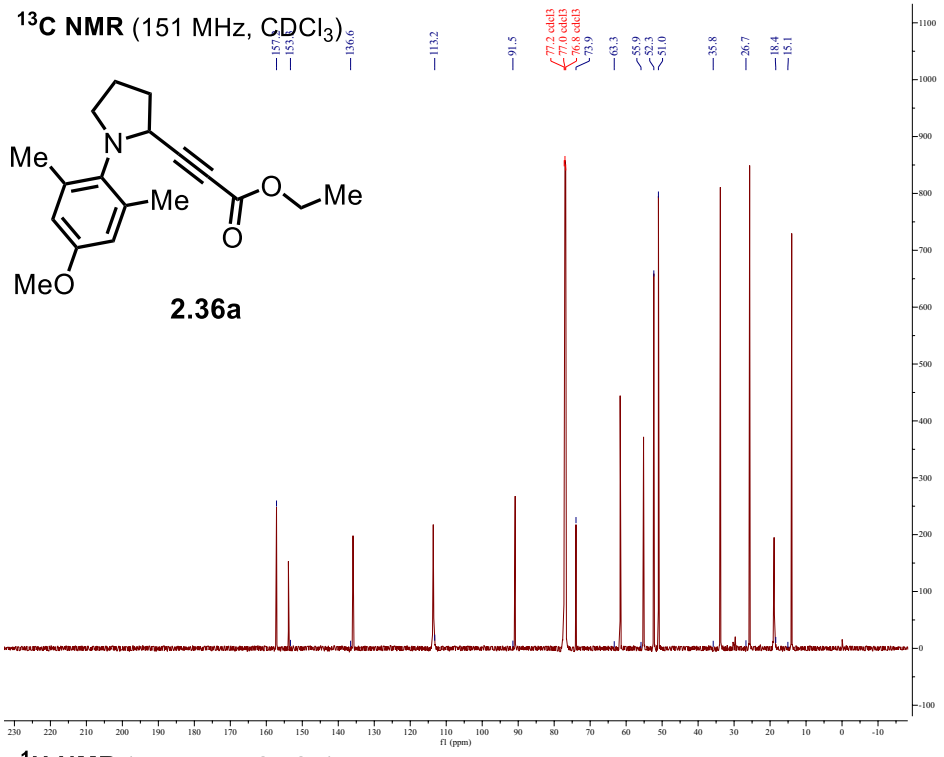
2.36a

^{1}H NMR (500 MHz, $CDCl_3$)



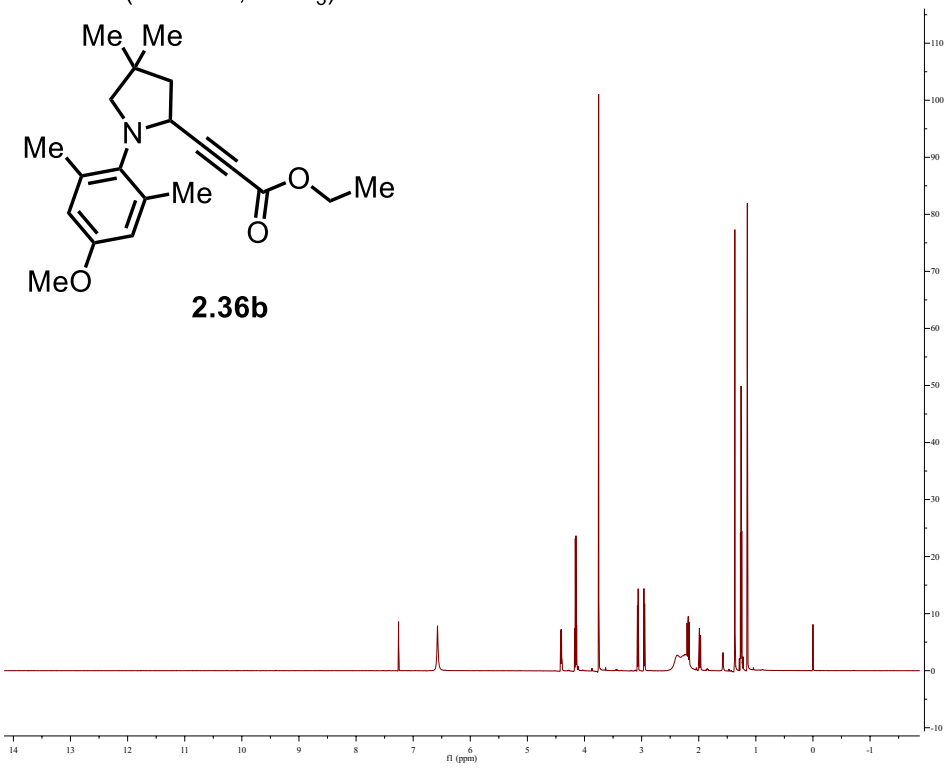
2.36a

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

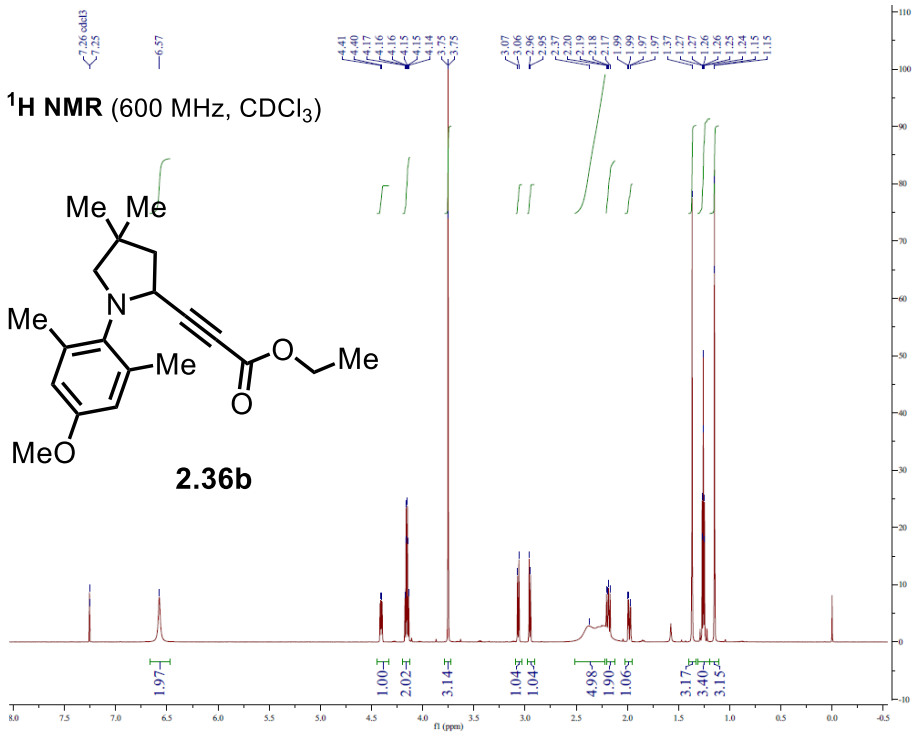


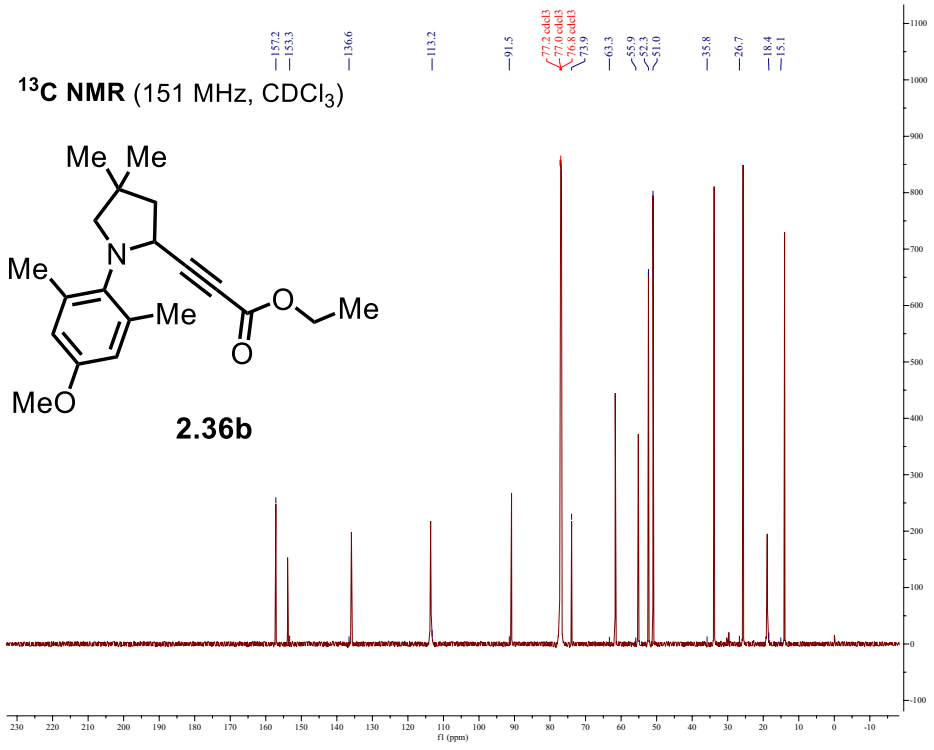
2.36a

^{1}H NMR (600 MHz, $CDCl_3$)

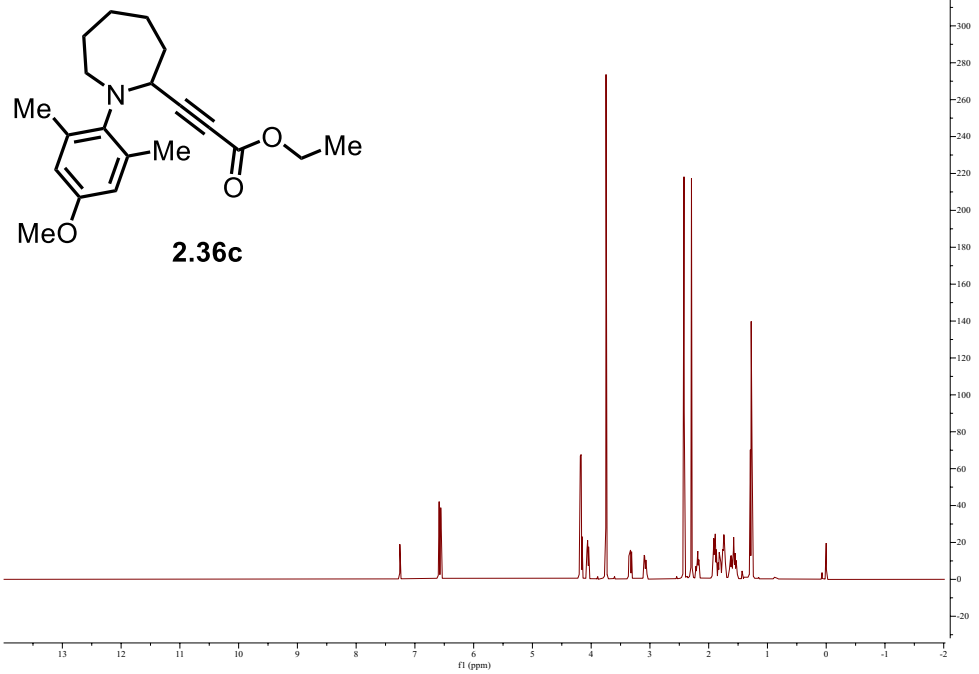


2.36b


1H NMR (600 MHz, CDCl3)
Me
Me
N
Me
Me
O
O
Me
MeO
2.36b

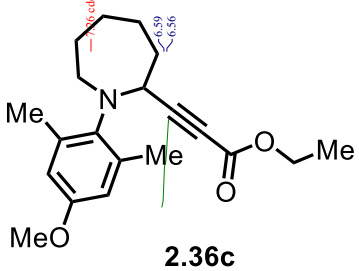

13C NMR (151 MHz, CDCl3)
Me
Me
N
Me
Me
O
O
Me
MeO
2.36b

^{1}H NMR (500 MHz, $CDCl_3$)



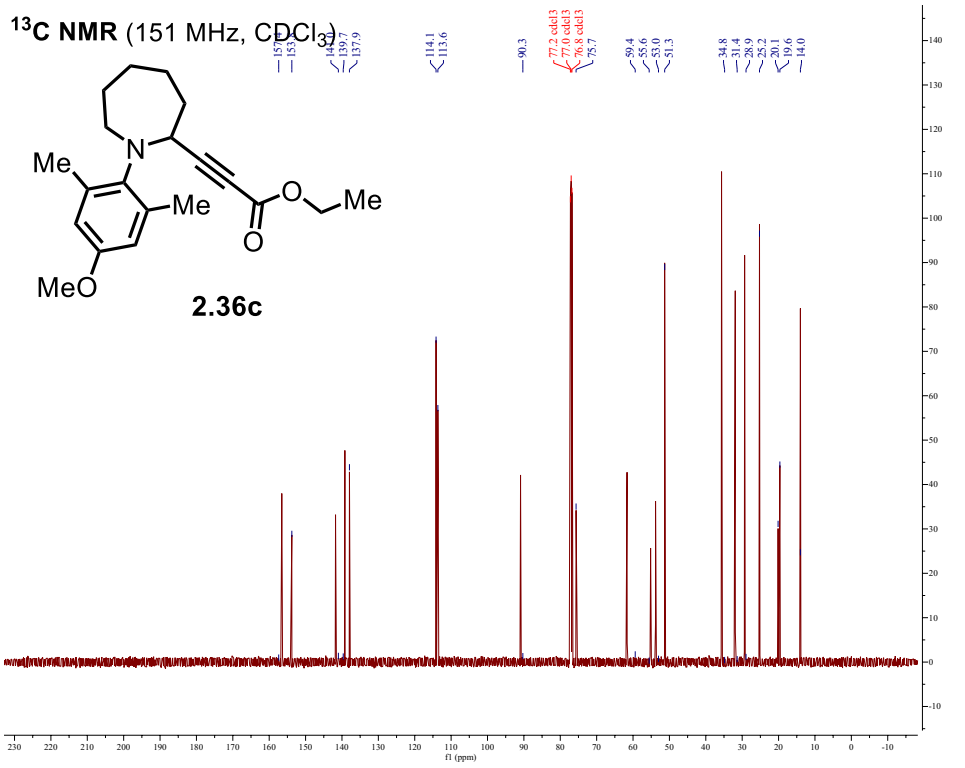
2.36c

^{1}H NMR (500 MHz, $CDCl_3$)



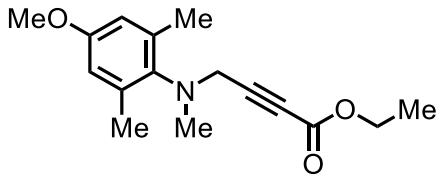
2.36c

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



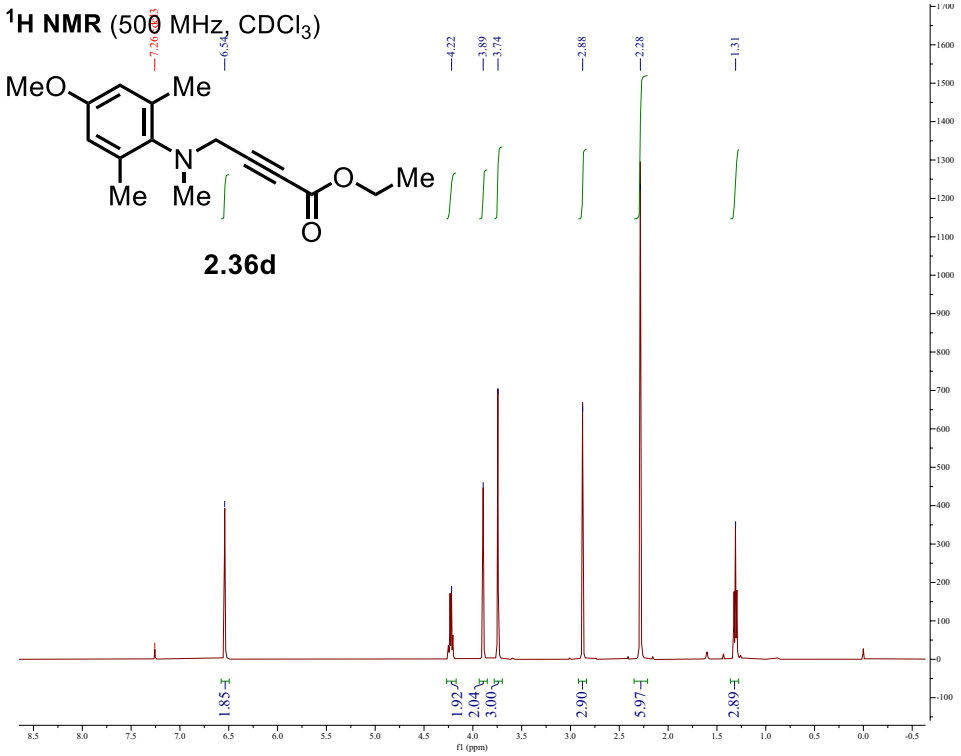
2.36c

^{1}H NMR (500 MHz, $CDCl_3$)



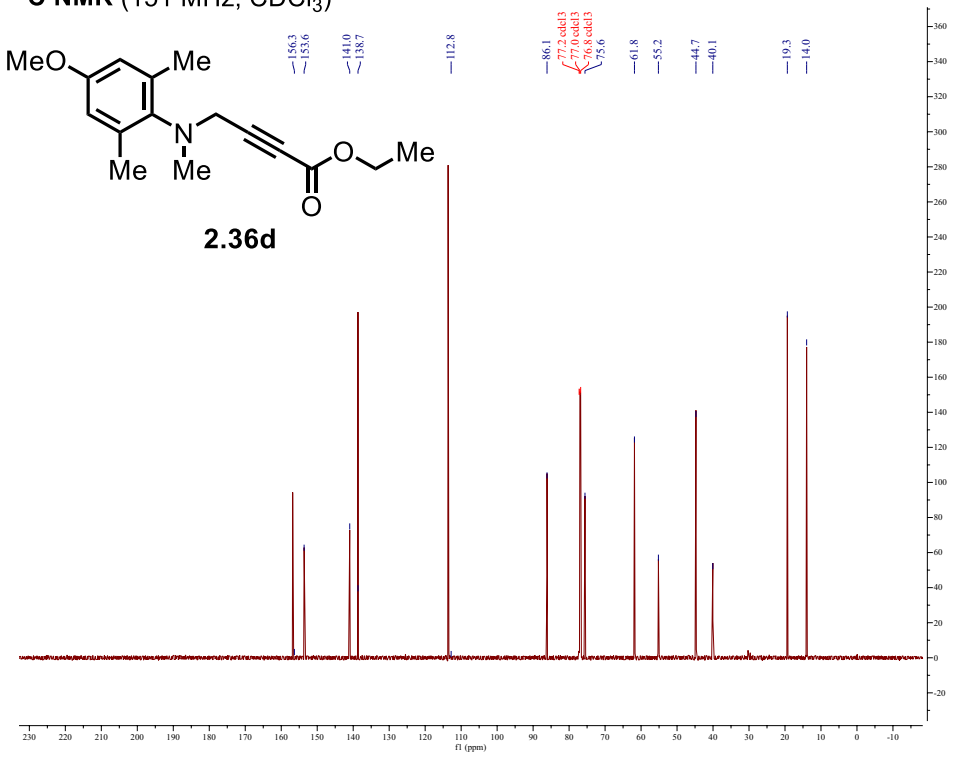
2.36d

^{1}H NMR (500 MHz, $CDCl_3$)



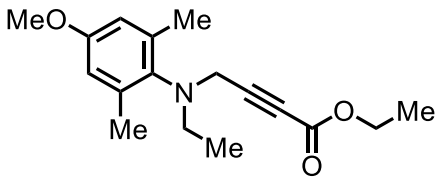
2.36d

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



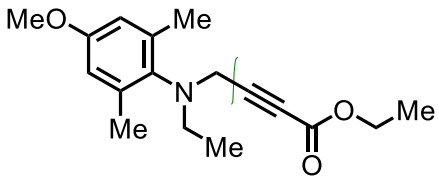
2.36d

^{1}H NMR (500 MHz, $CDCl_3$)



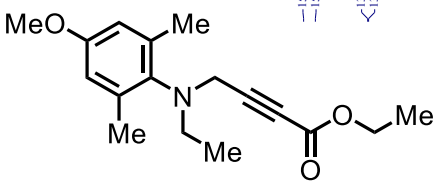
2.36e

^{1}H NMR (500 MHz, $CDCl_3$)



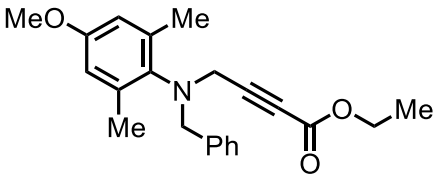
2.36e

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



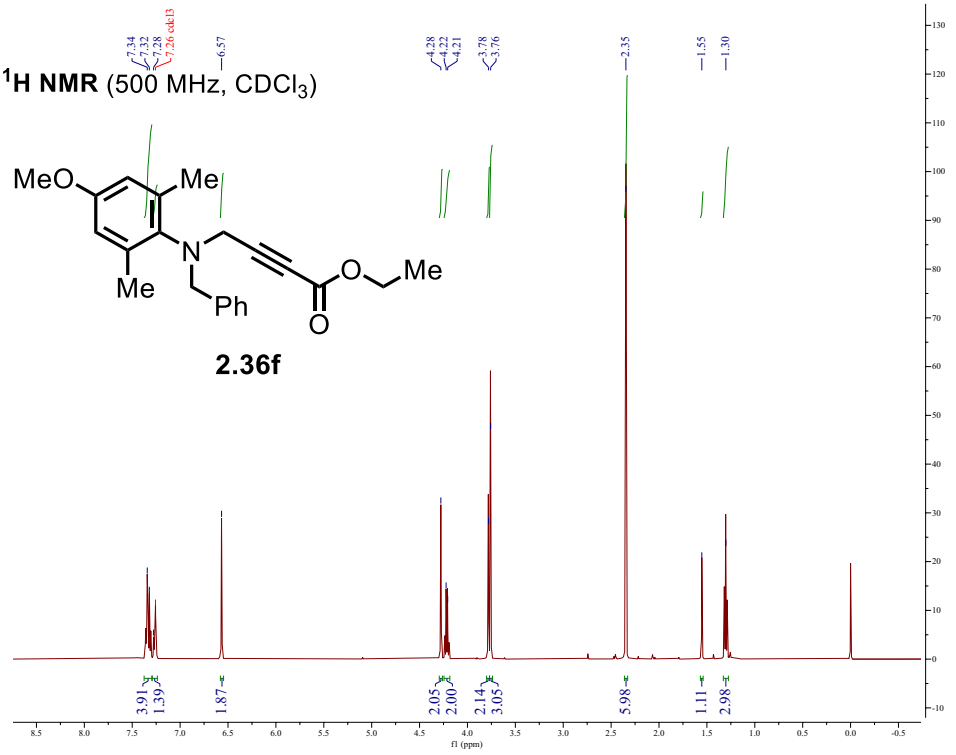
2.36e

^{1}H NMR (500 MHz, $CDCl_3$)



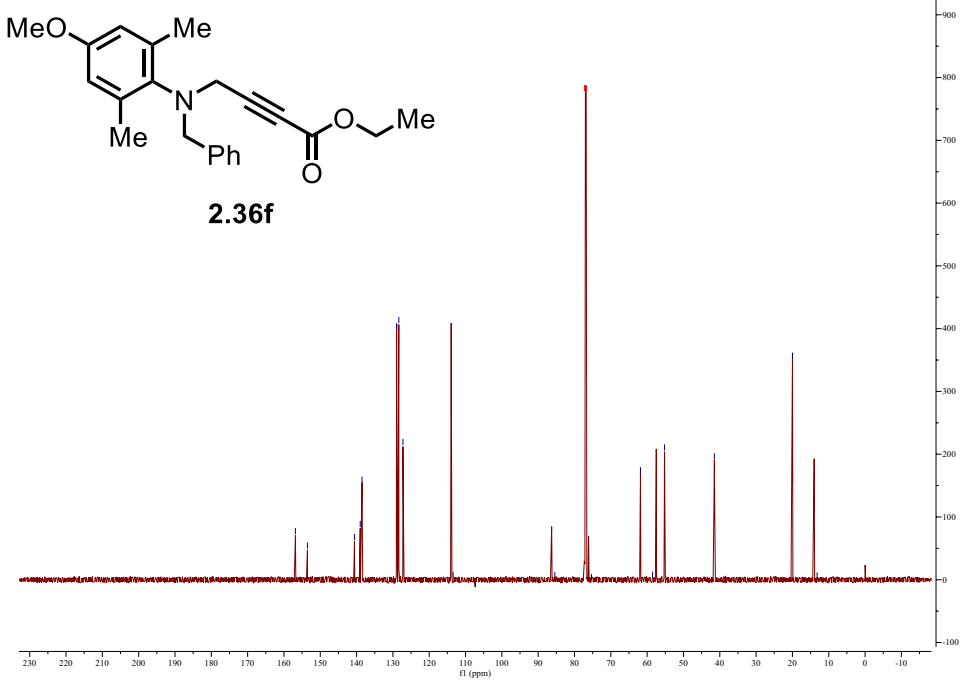
2.36f

^{1}H NMR (500 MHz, $CDCl_3$)



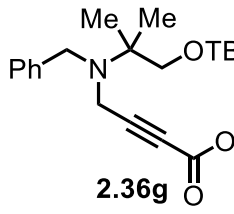
2.36f

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



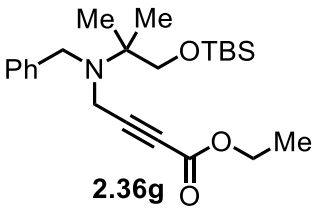
2.36f

^{1}H NMR (500 MHz, $CDCl_3$)



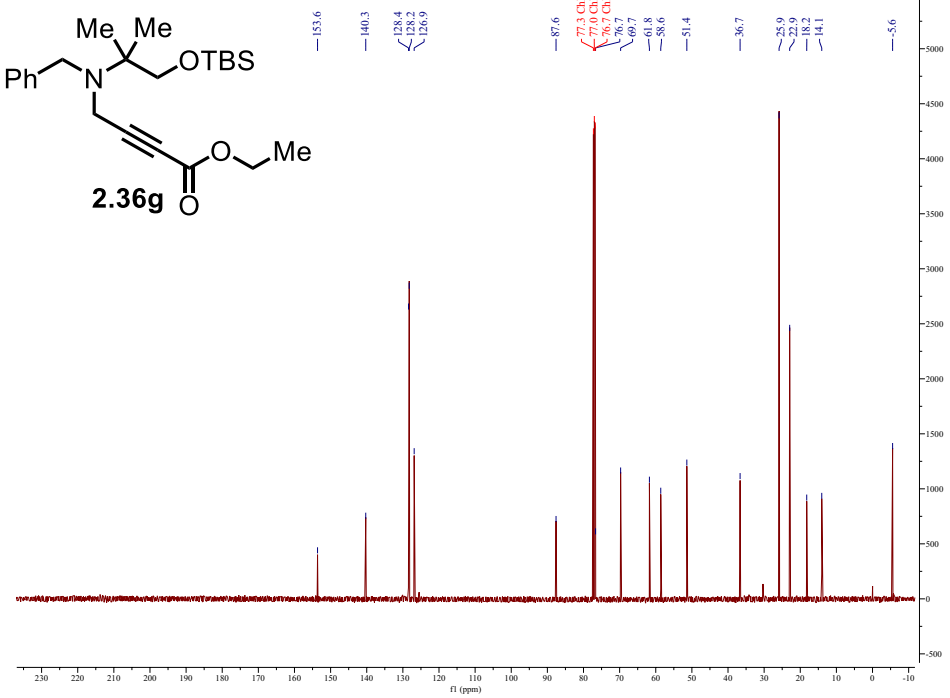
2.36g

^{1}H NMR (500 MHz, $CDCl_3$)

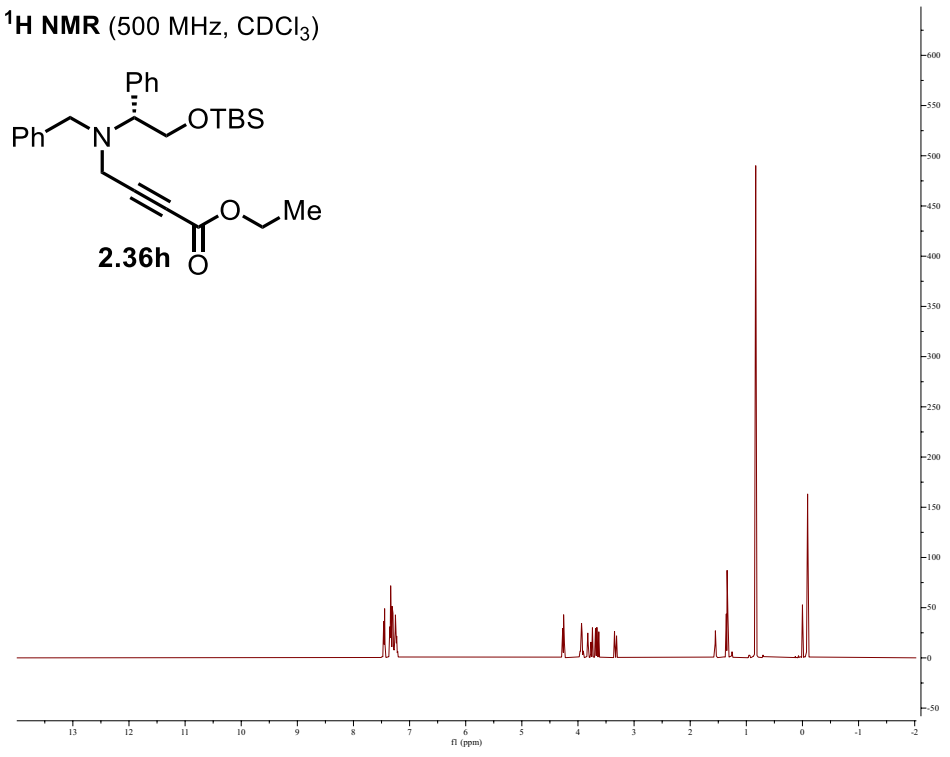


2.36g

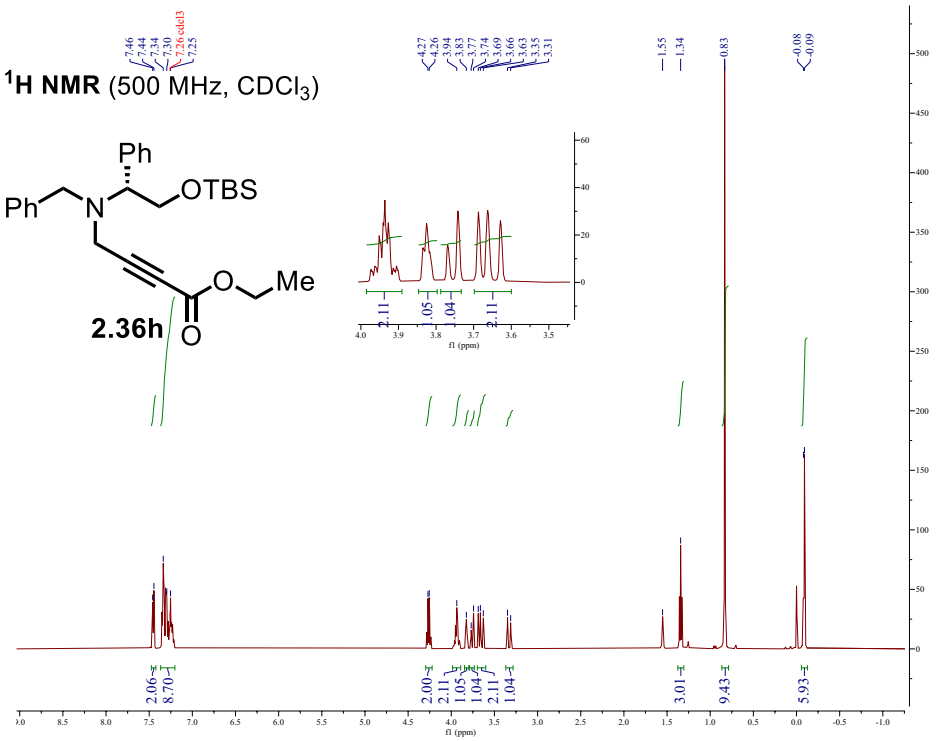
^{13}C NMR (126 MHz, $CDCl_3$)



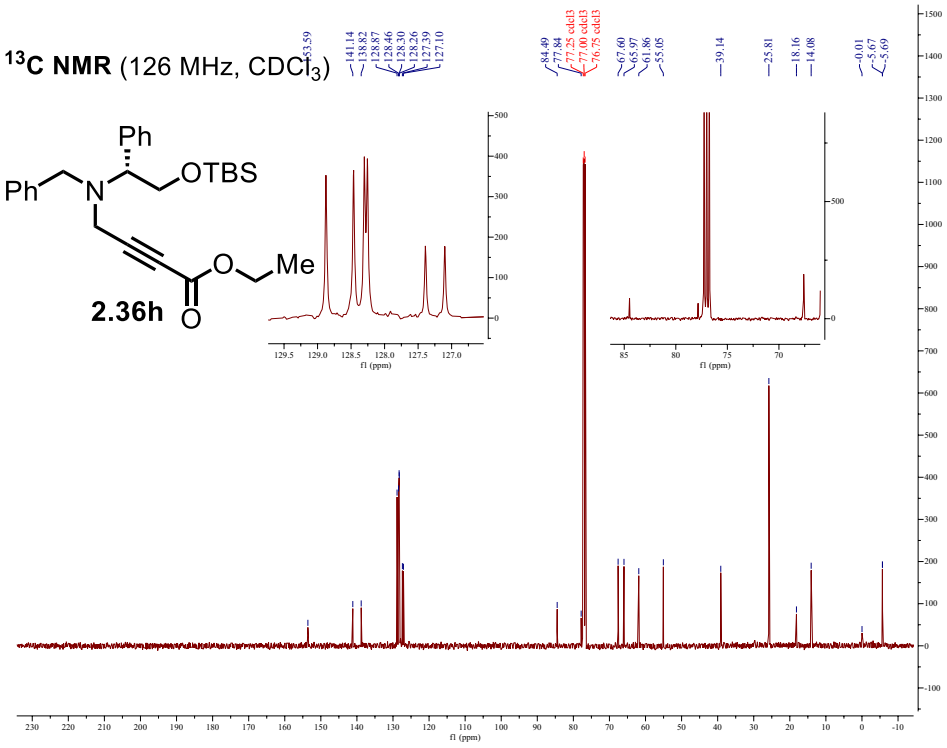
^{1}H NMR (500 MHz, $CDCl_3$)



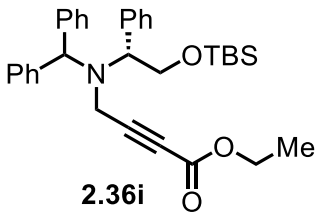
^{1}H NMR (500 MHz, $CDCl_3$)



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

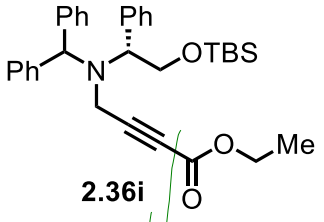


^{1}H NMR (600 MHz, $CDCl_3$)



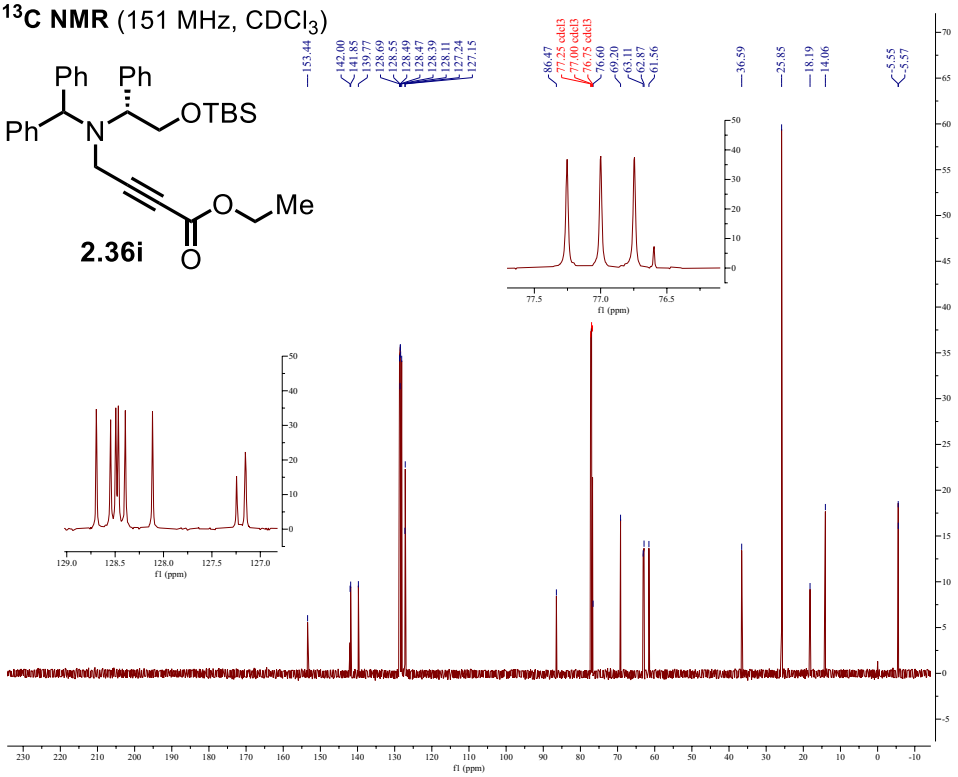
2.36i

^{1}H NMR (600 MHz, $CDCl_3$)

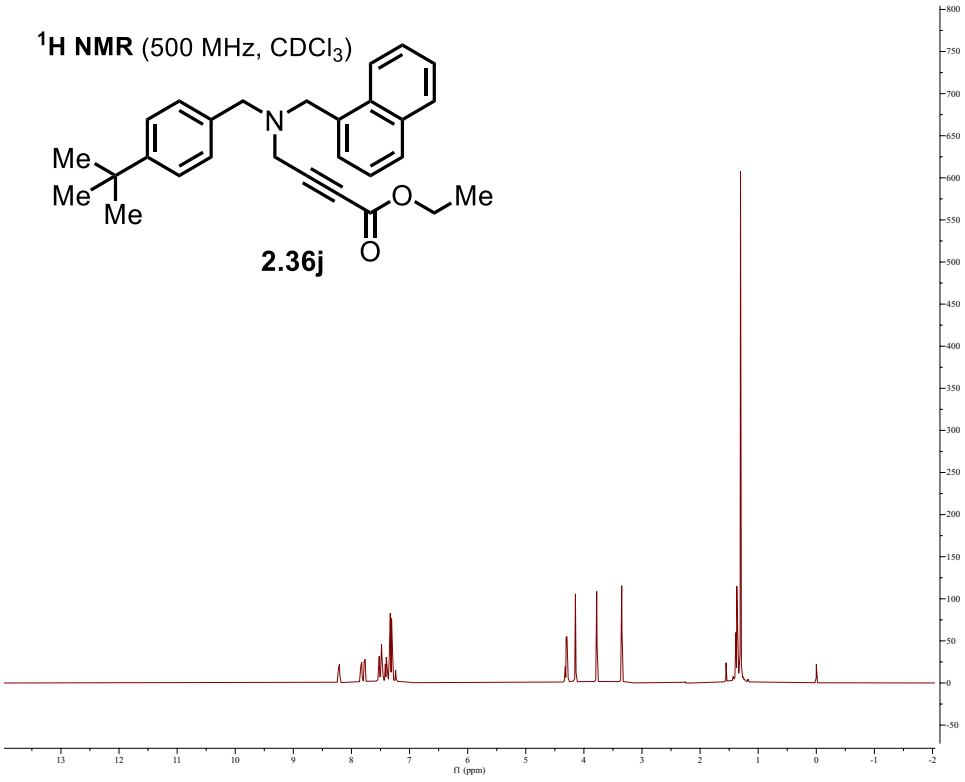


2.36i

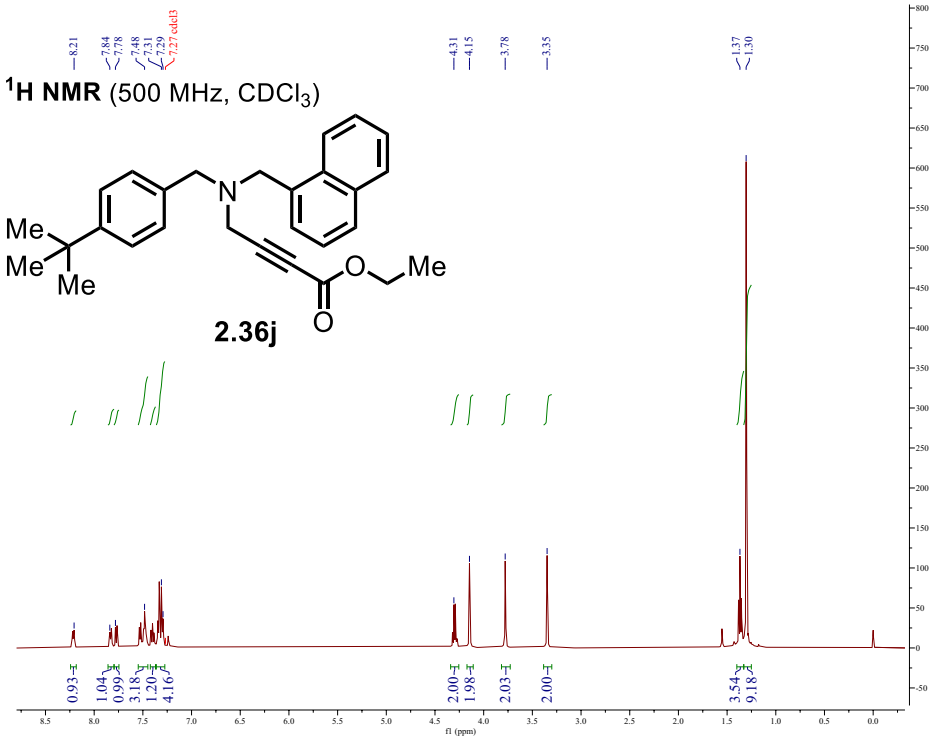
^{13}C NMR (151 MHz, $CDCl_3$)



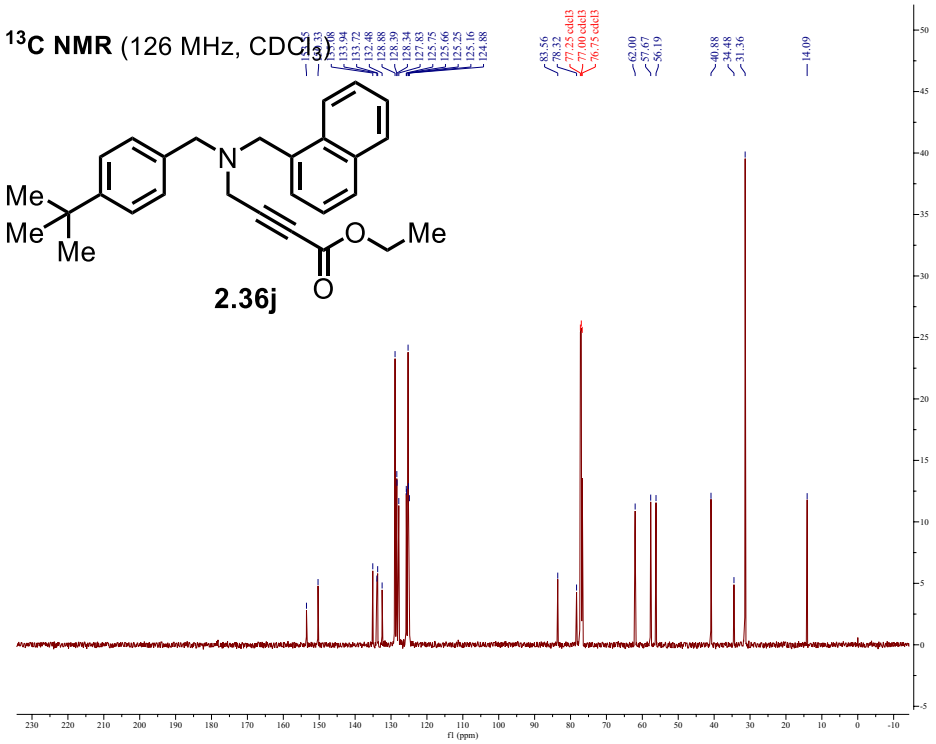
^{1}H NMR (500 MHz, $CDCl_3$)



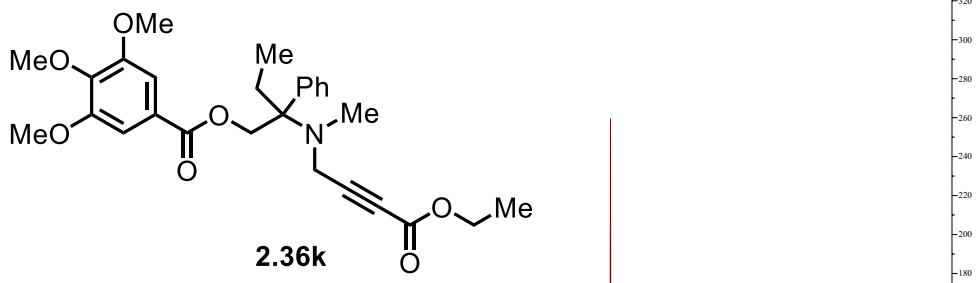
^{1}H NMR (500 MHz, $CDCl_3$)



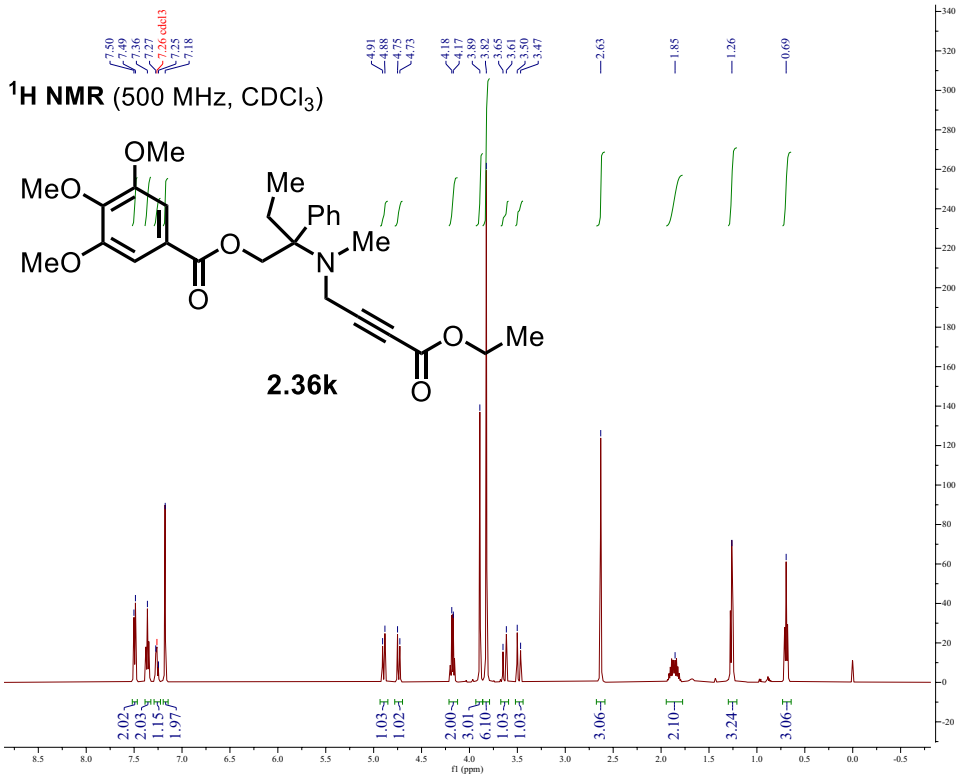
^{13}C NMR (126 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)



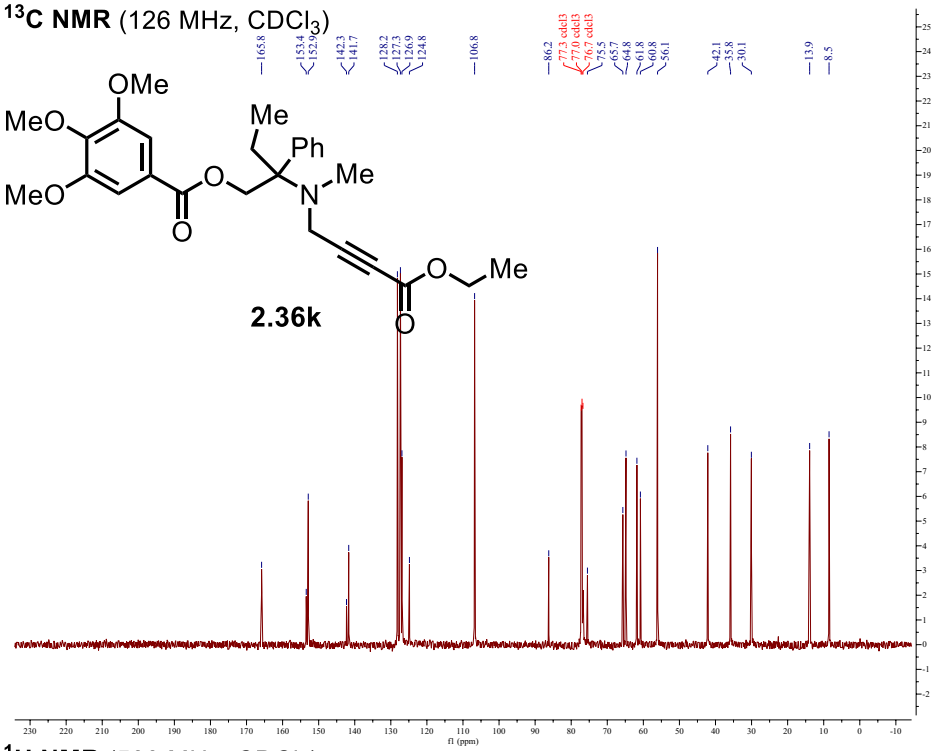
2.36k



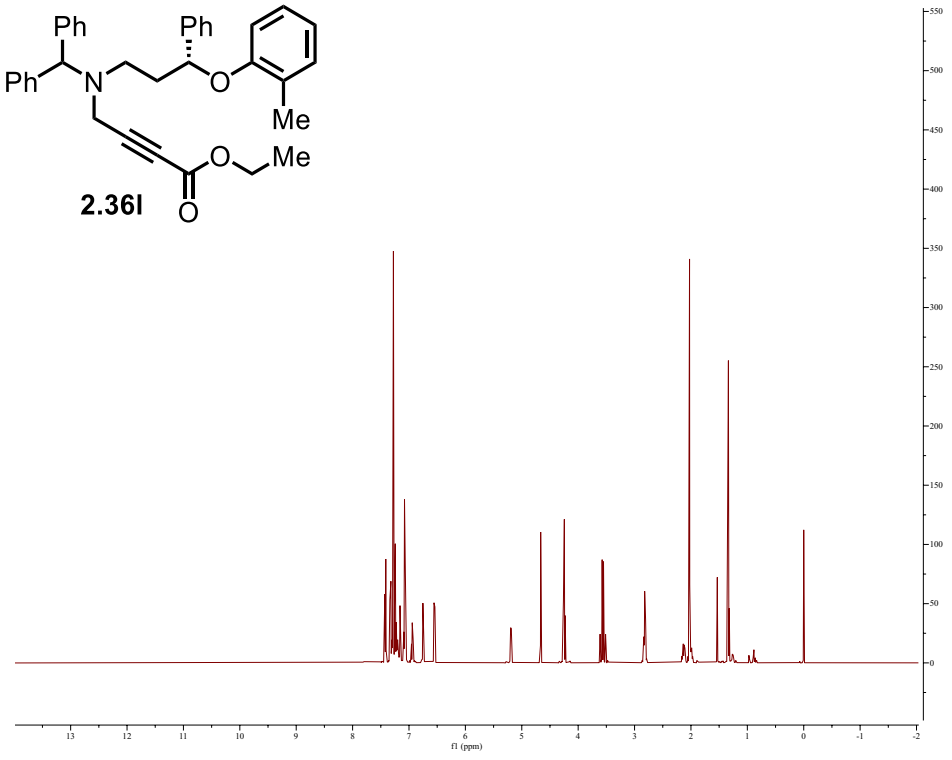
^{1}H NMR (500 MHz, $CDCl_3$)

2.36k

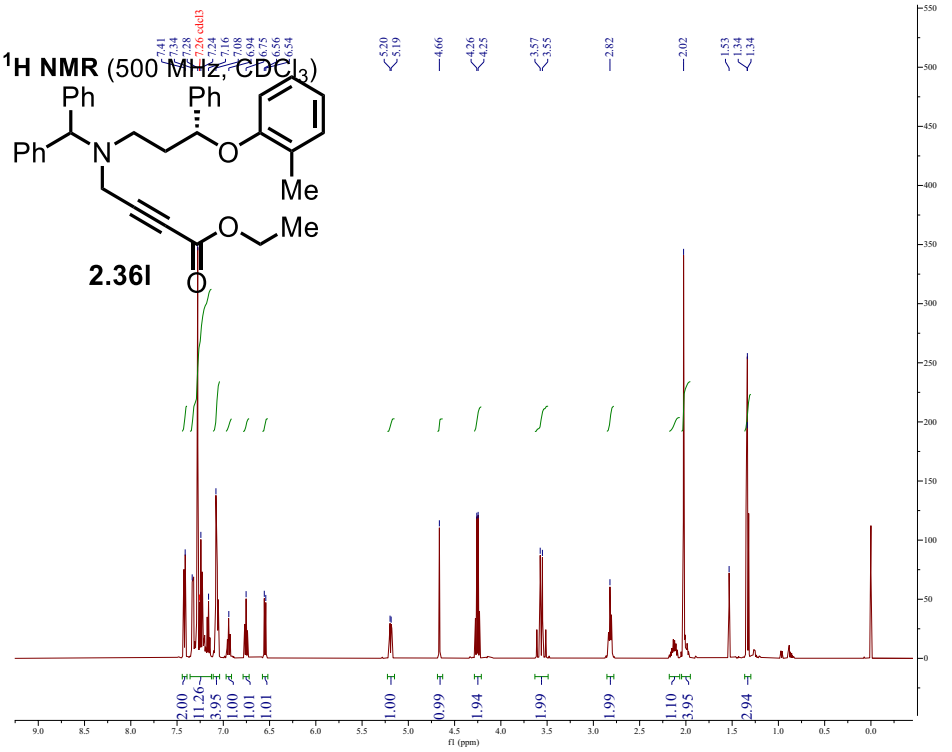
^{13}C NMR (126 MHz, $CDCl_3$)



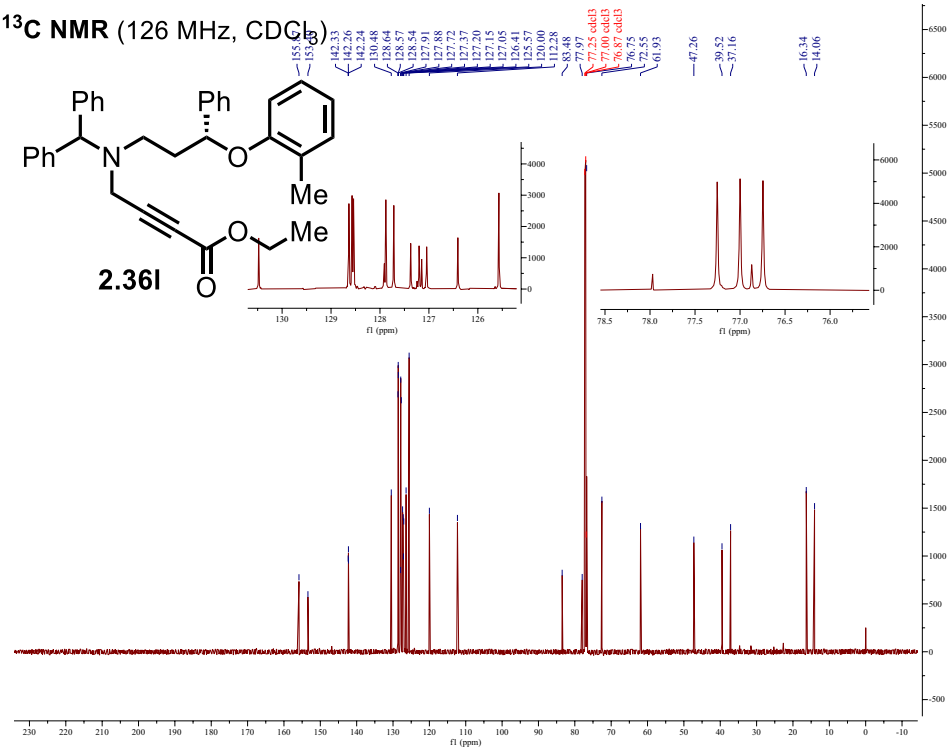
^{1}H NMR (500 MHz, $CDCl_3$)



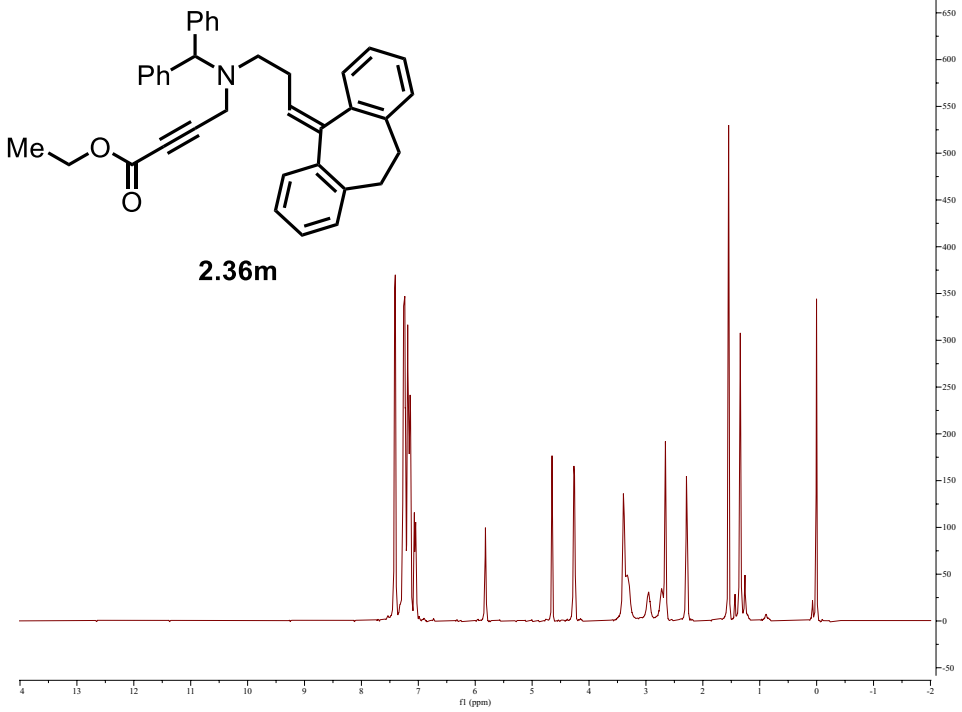
^{1}H NMR (500 MHz, $CDCl_3$)



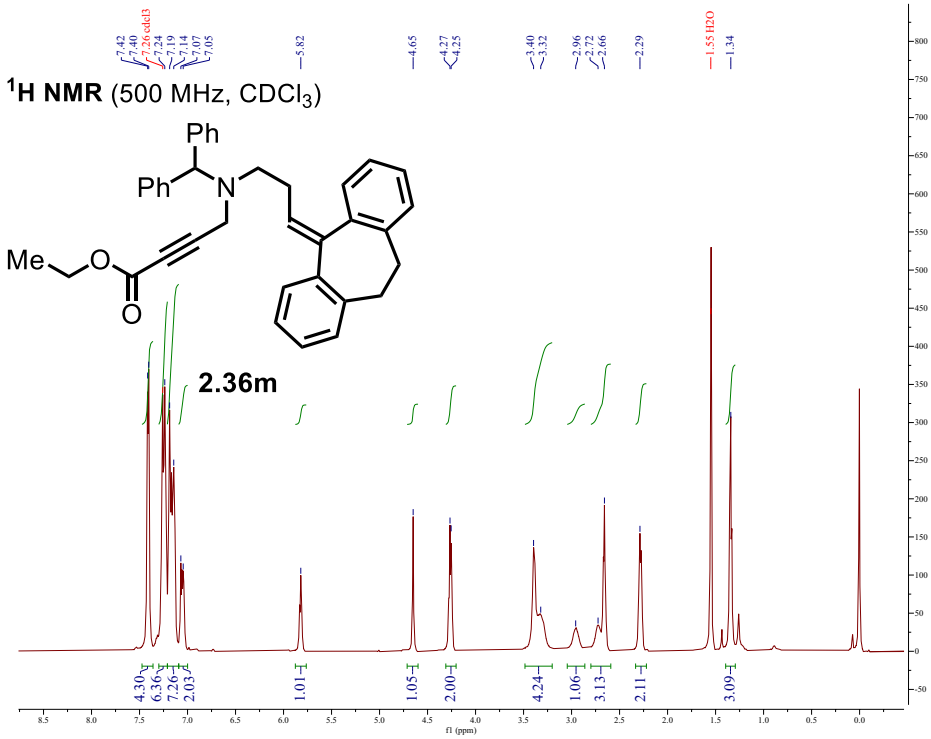
^{13}C NMR (126 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)



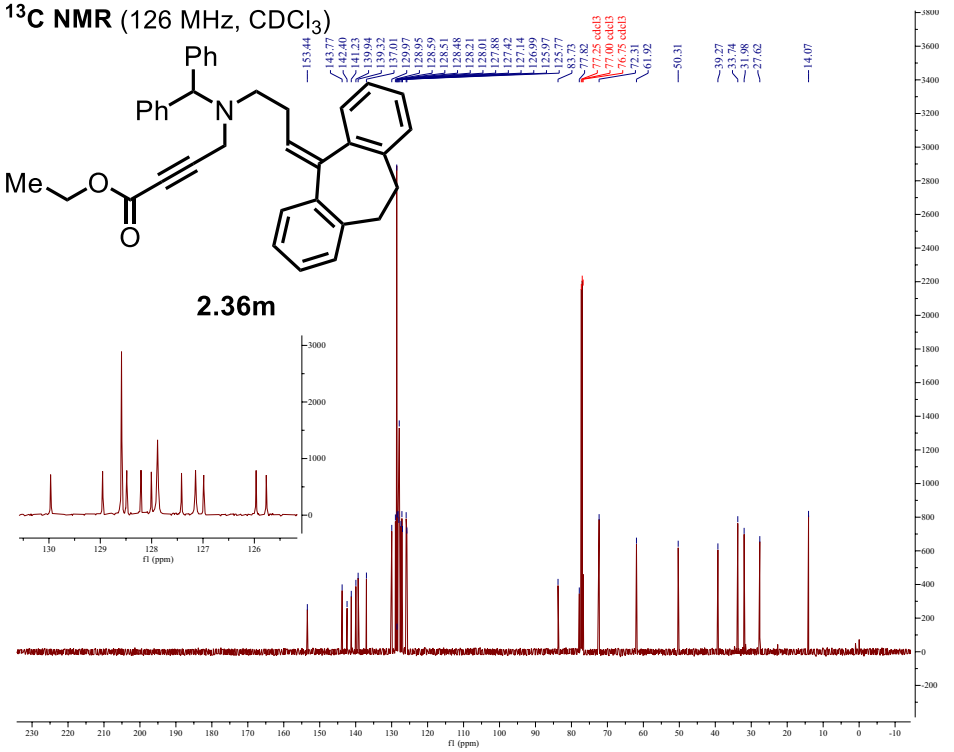
2.36m



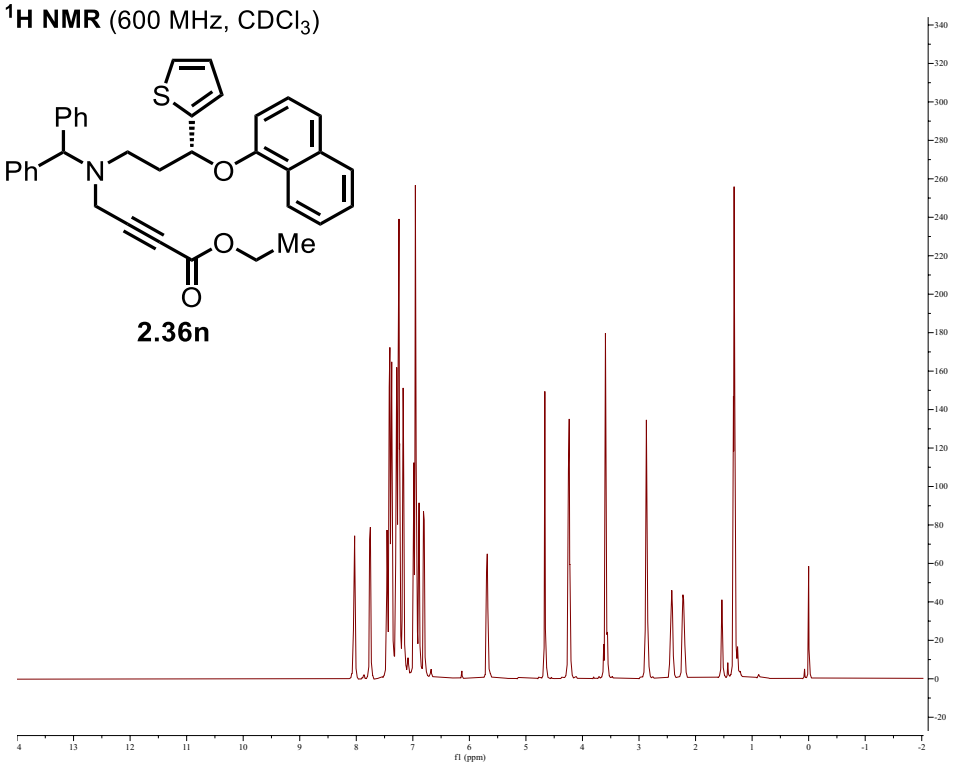
^{1}H NMR (500 MHz, $CDCl_3$)

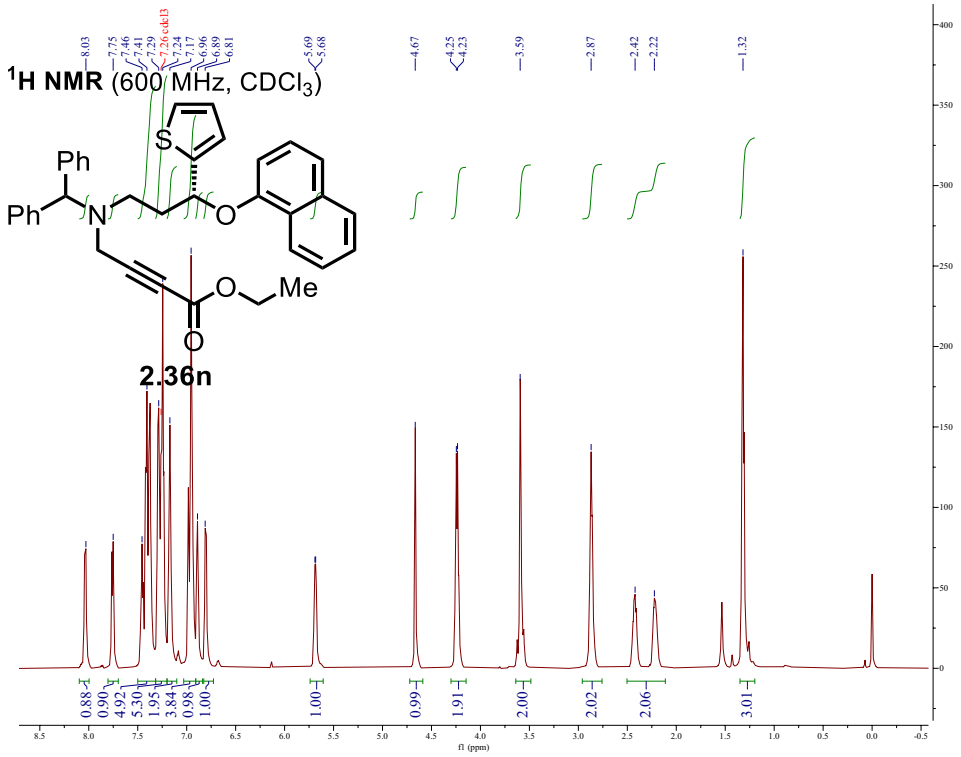
2.36m

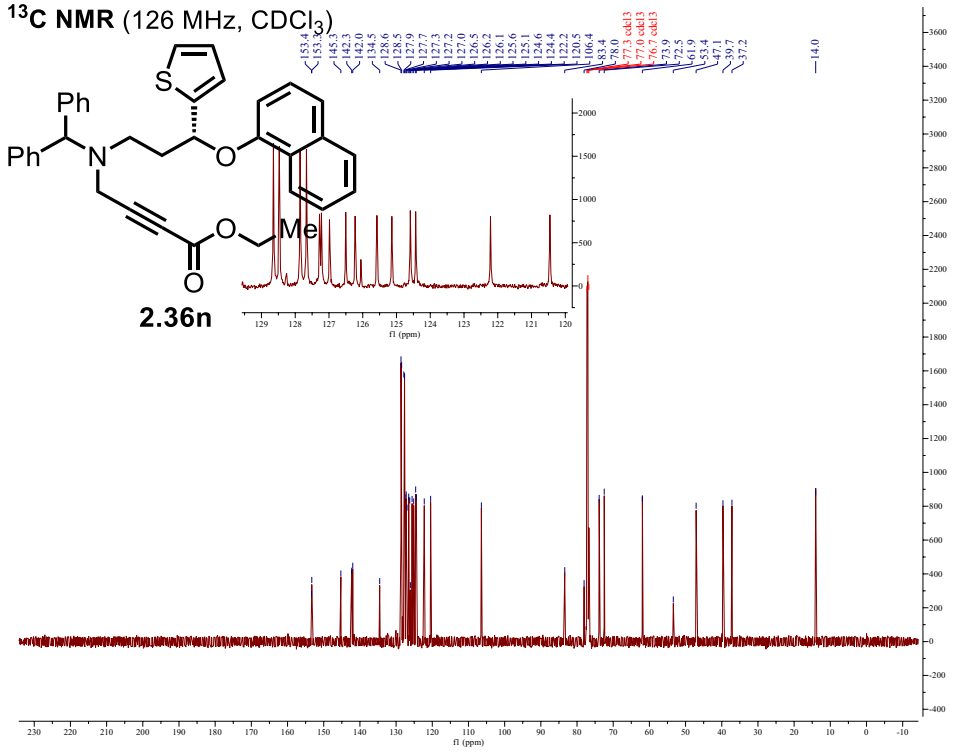
^{13}C NMR (126 MHz, $CDCl_3$)



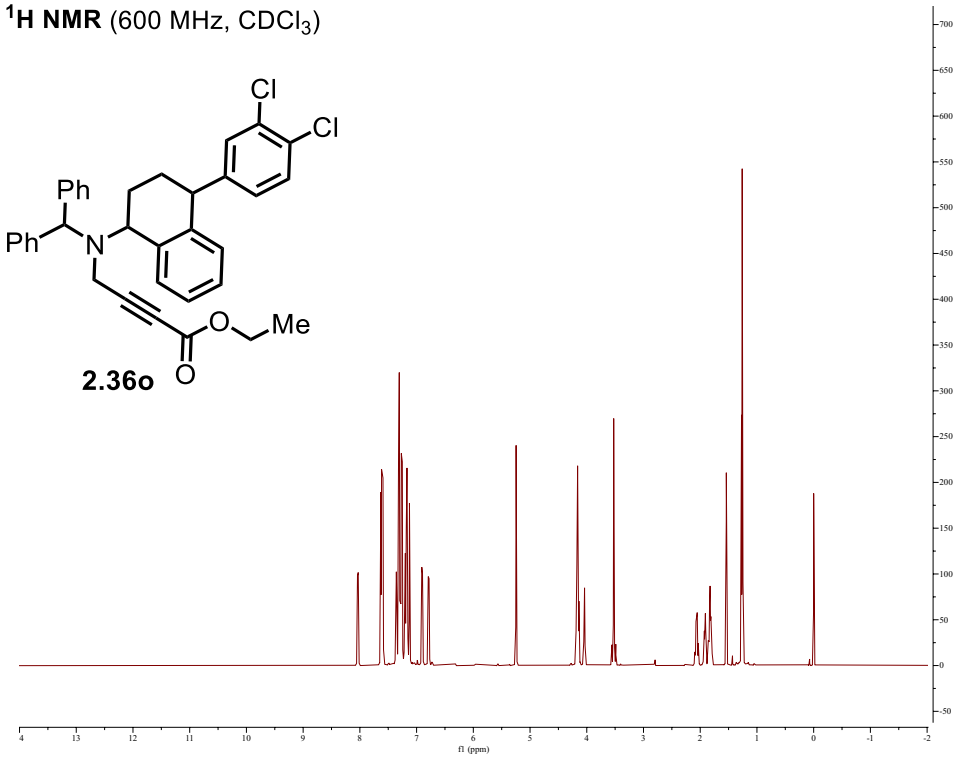
^{1}H NMR (600 MHz, $CDCl_3$)



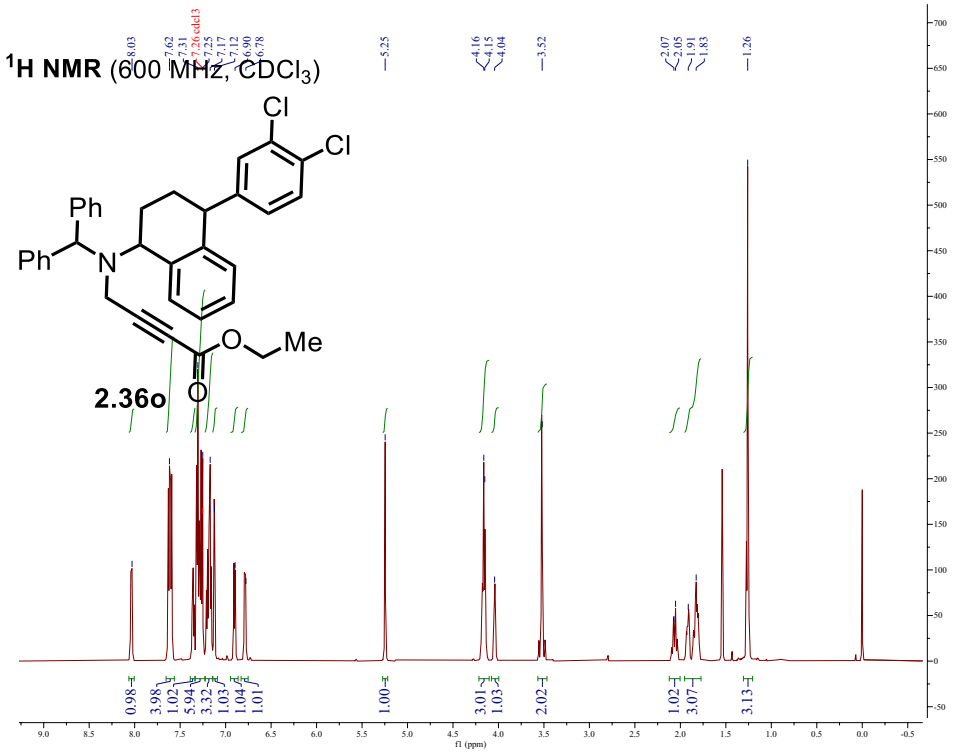

1H NMR (600 MHz, CDCl3)
Ph
Ph
N
S
O
O
O
Me
O
2.36n


13C NMR (126 MHz, CDCl3)
Ph
Ph
N
S
O
O
O
Me
O
2.36n

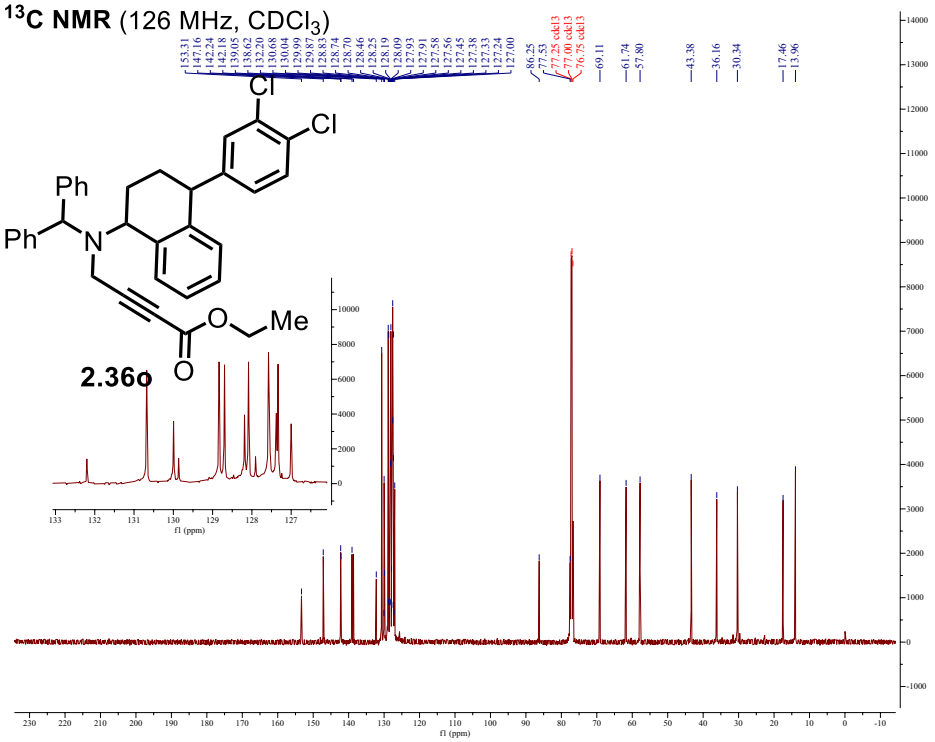
^{1}H NMR (600 MHz, $CDCl_3$)



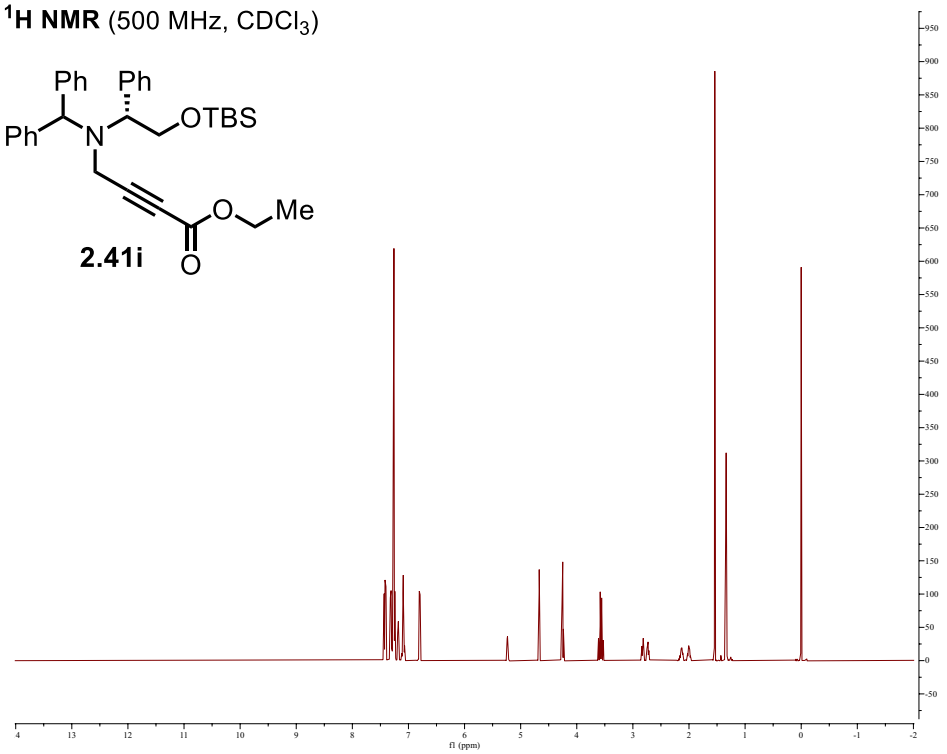
^{1}H NMR (600 MHz, $CDCl_3$)



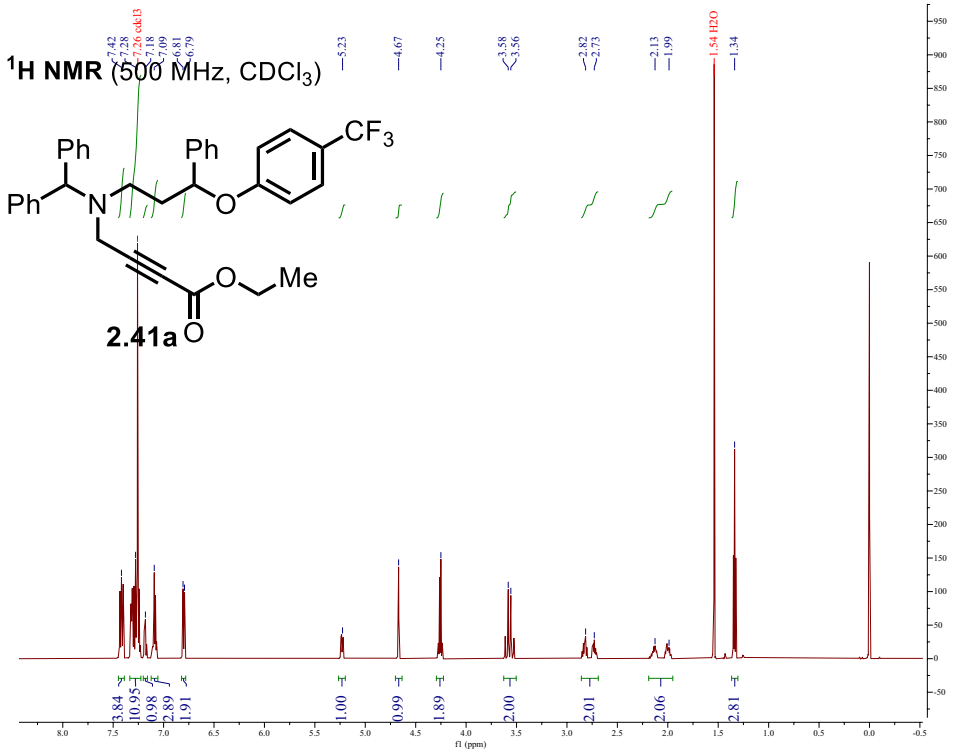
^{13}C NMR (126 MHz, $CDCl_3$)



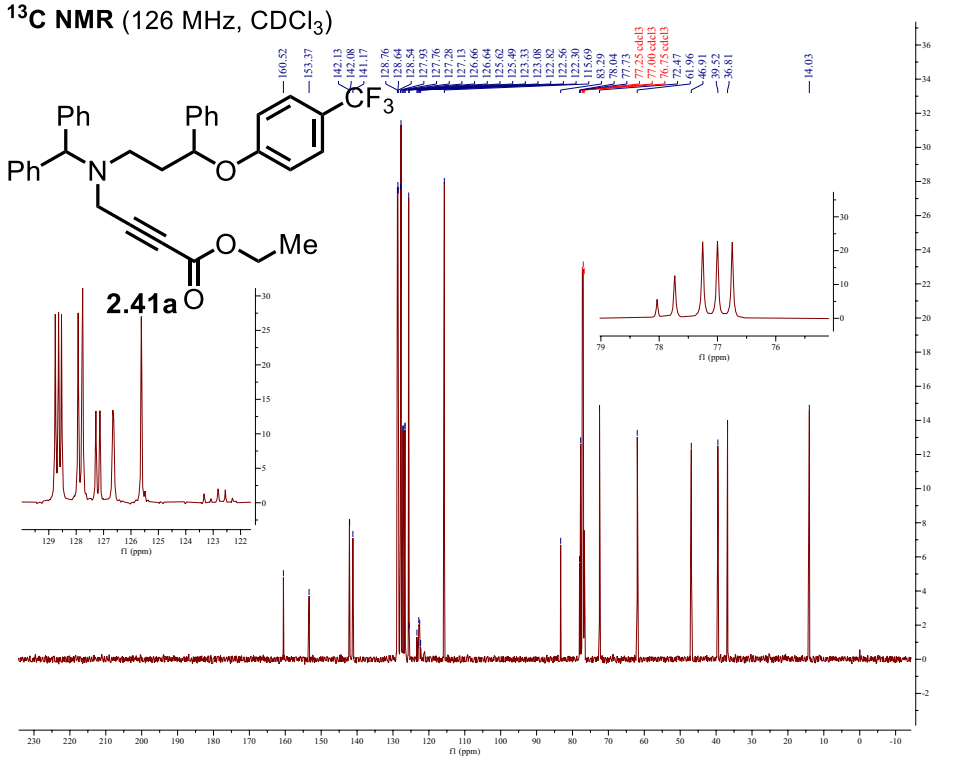
^{1}H NMR (500 MHz, $CDCl_3$)



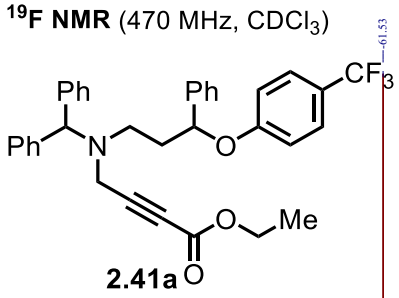
^{1}H NMR (500 MHz, $CDCl_3$)



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

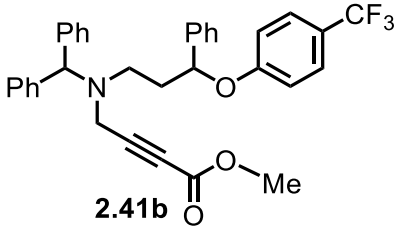


^{19}F NMR (470 MHz, $CDCl_3$)

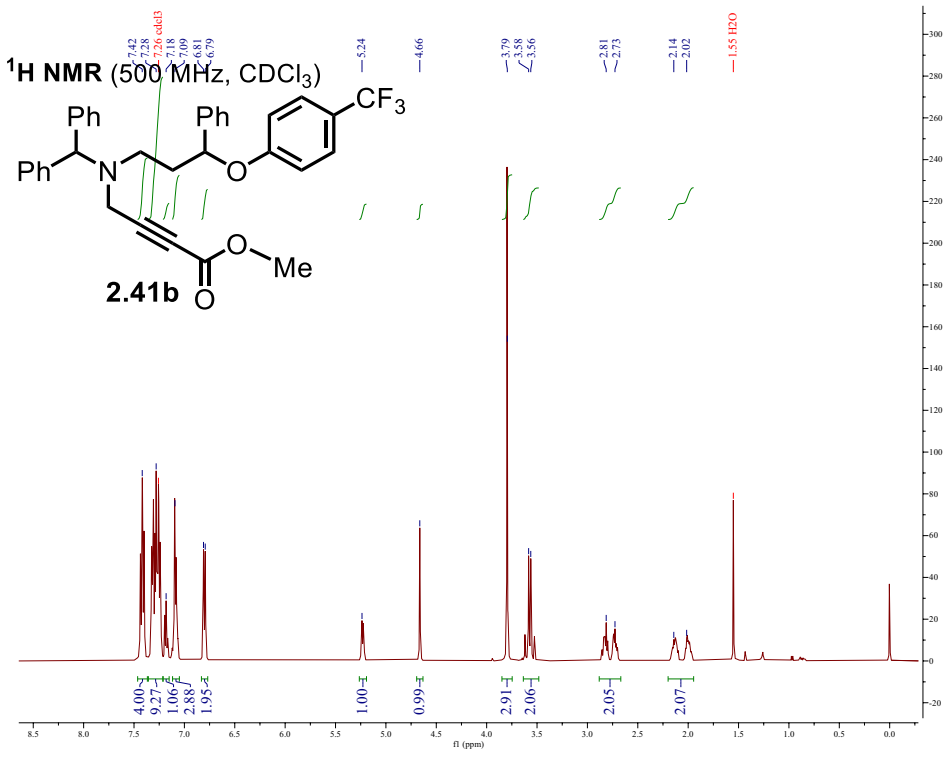


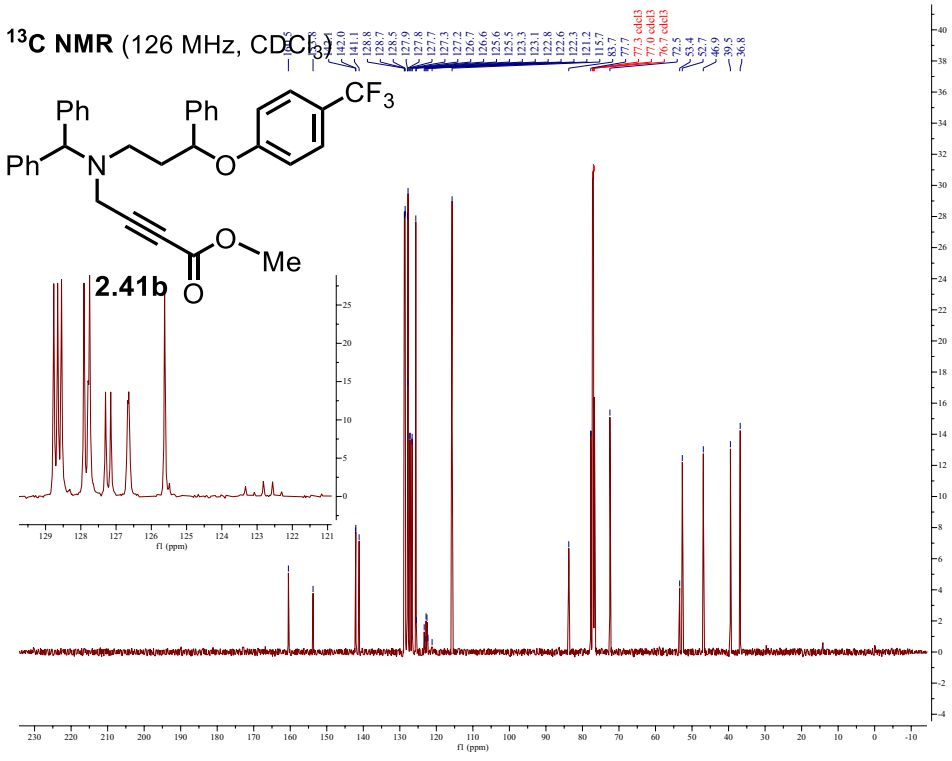
2.41a

^{1}H NMR (500 MHz, $CDCl_3$)

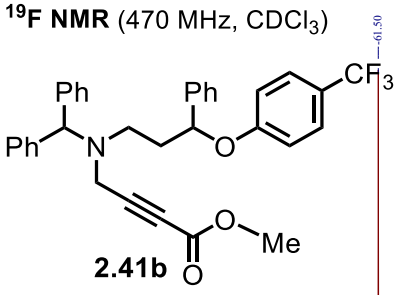


2.41b


1H NMR (500 MHz, CDCl3)
Ph
Ph
Ph
N
O
CF3
O
Me
O
2.41b
7.42
7.28
7.26 cdcl3
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
1.55 H2O
4.00
9.27
1.06
2.88
1.95
1.00
0.99
2.91
2.06
2.05
2.07
f1 (ppm)

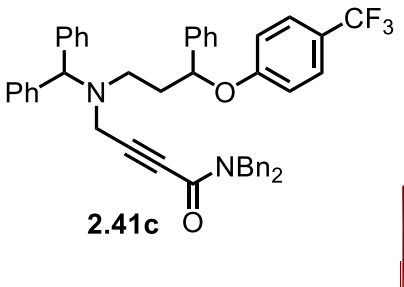

13C NMR (126 MHz, CDCl3)
Ph
Ph
Ph
N
O
CF3
O
Me
O
2.41b
142.0
141.1
128.8
128.7
128.5
127.9
127.8
127.7
127.3
127.2
126.7
126.6
125.6
125.5
123.3
123.1
122.8
122.6
122.3
121.2
115.7
83.7
77.7
77.3 cdcl3
77.0 cdcl3
76.7 cdcl3
72.5
53.4
52.7
46.9
39.5
36.8
f1 (ppm)

^{19}F NMR (470 MHz, $CDCl_3$)



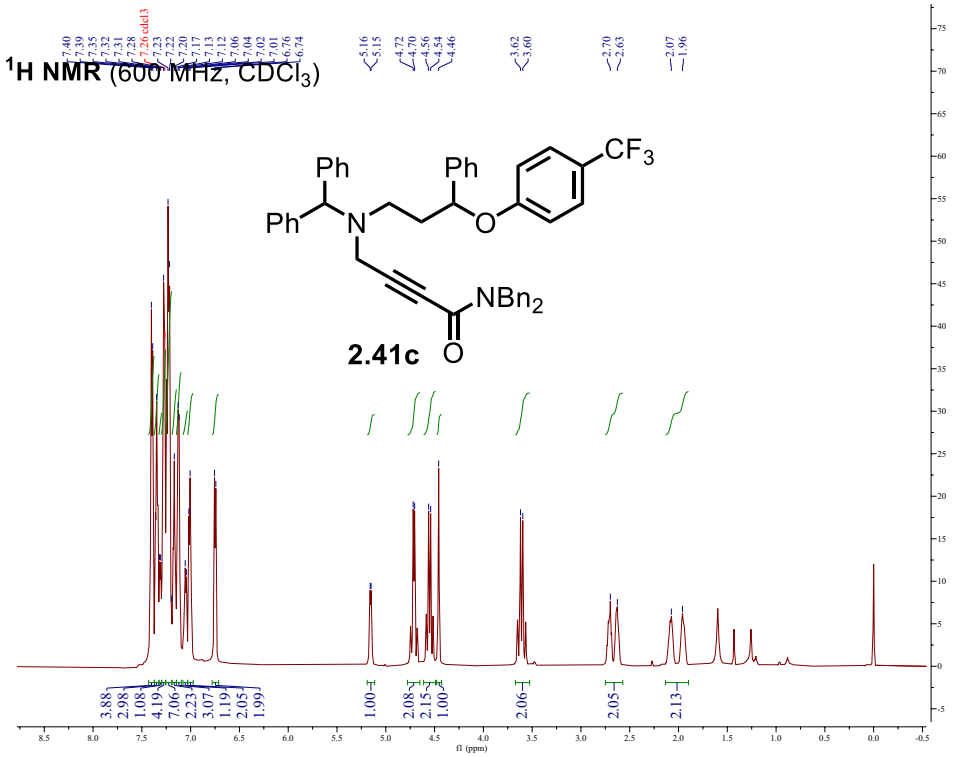
2.41b

^{1}H NMR (600 MHz, $CDCl_3$)

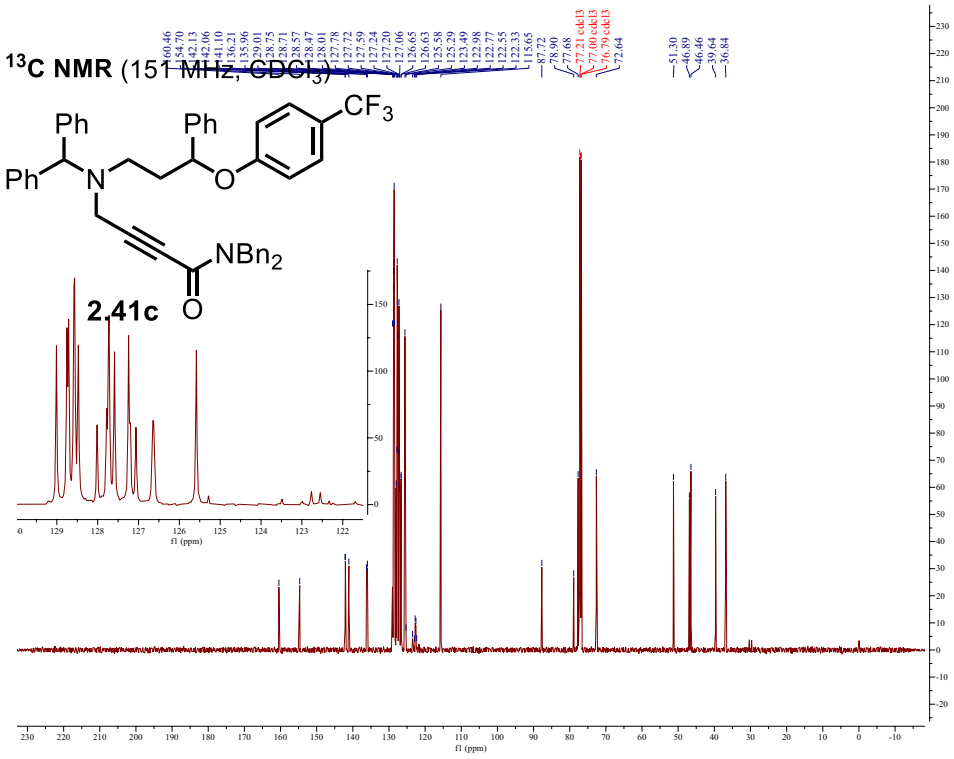


2.41c

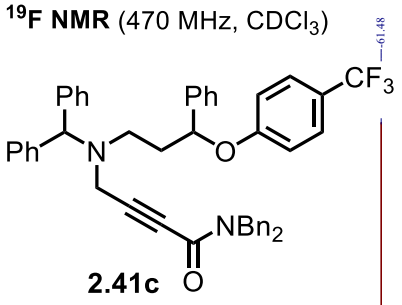
^{1}H NMR (600 MHz, $CDCl_3$)



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

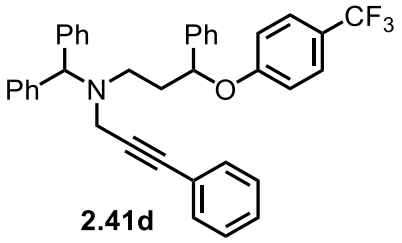


^{19}F NMR (470 MHz, $CDCl_3$)



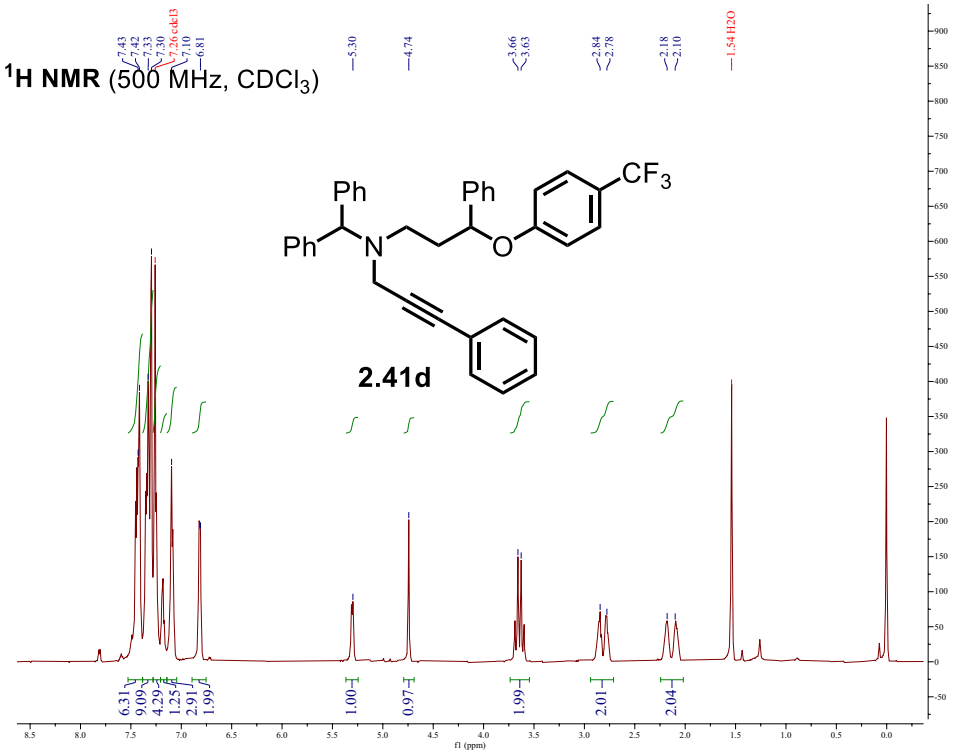
2.41c

^{1}H NMR (500 MHz, $CDCl_3$)



2.41d

^{1}H NMR (500 MHz, $CDCl_3$)



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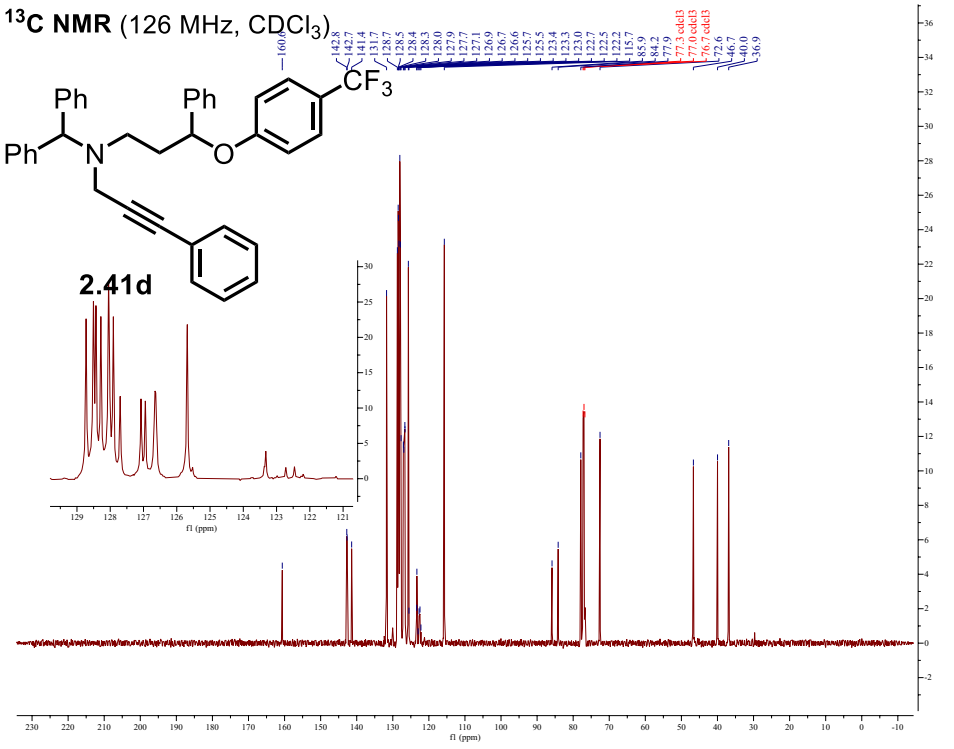
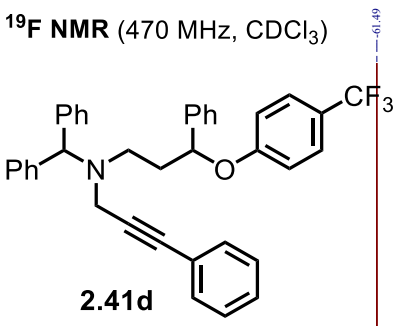
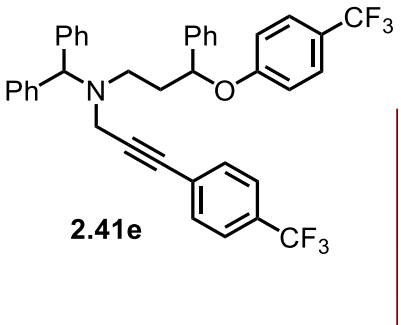


^{19}F NMR (470 MHz, $CDCl_3$)



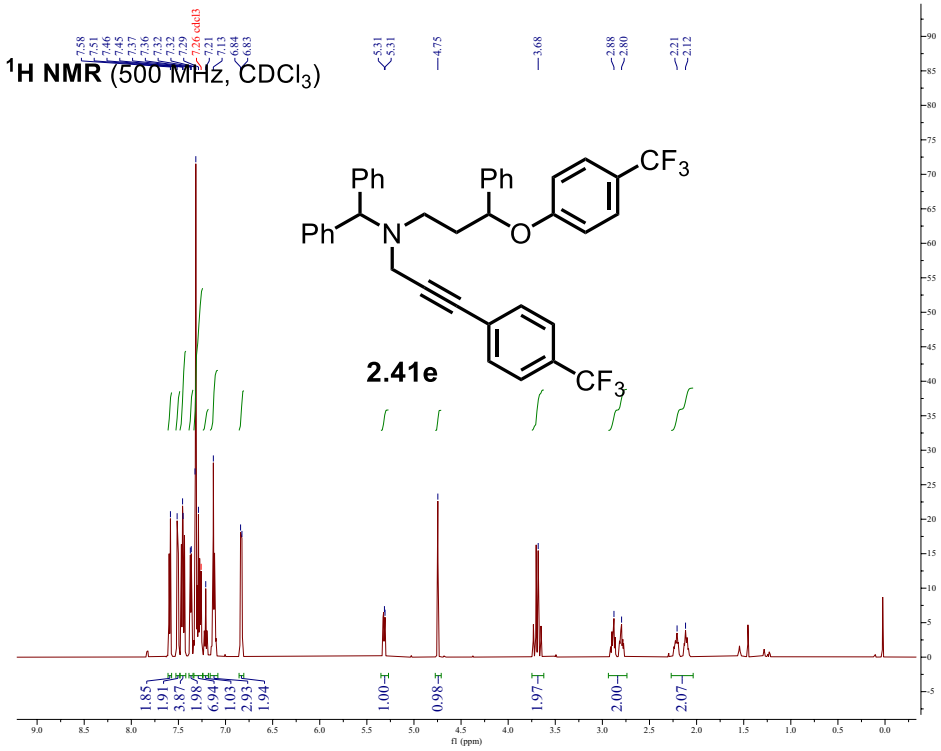
2.41d

^{1}H NMR (500 MHz, $CDCl_3$)

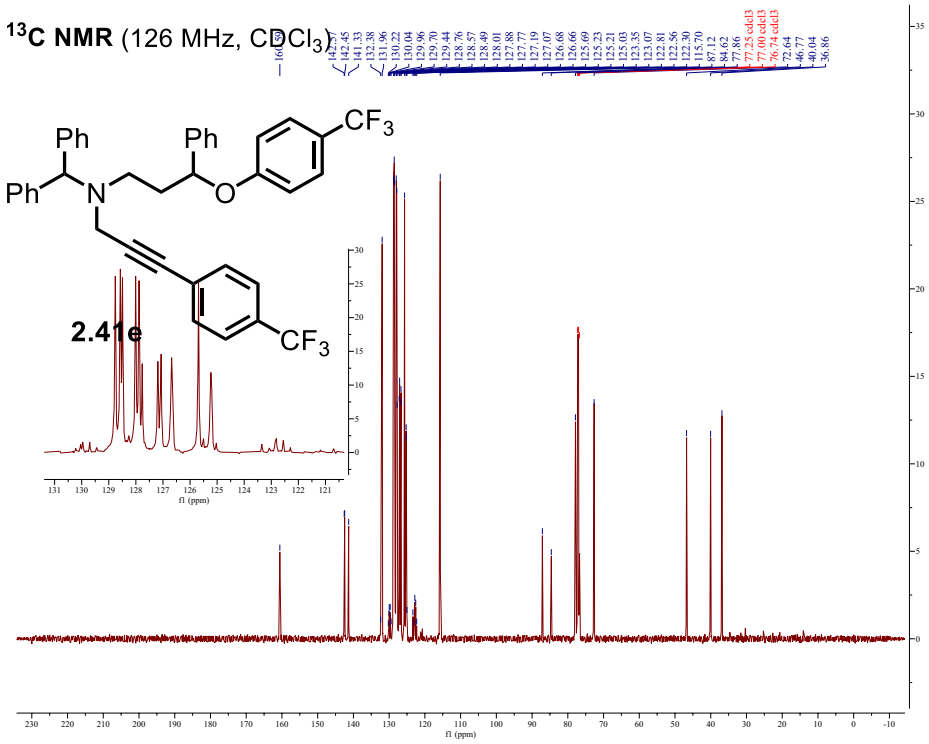


2.41e

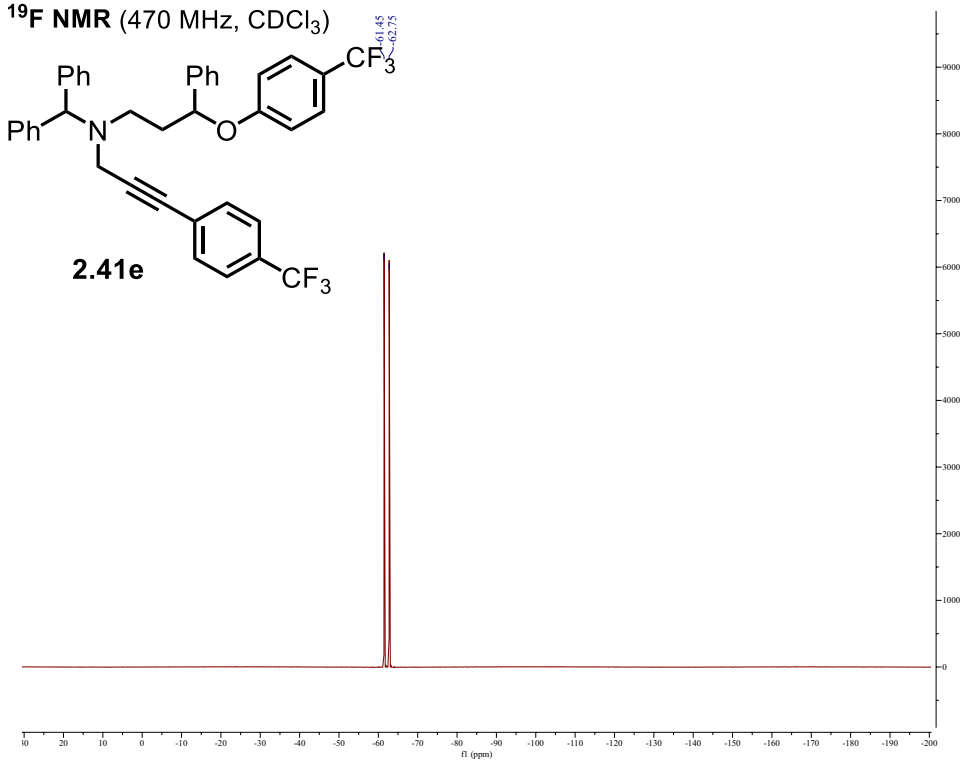
^{1}H NMR (500 MHz, $CDCl_3$)



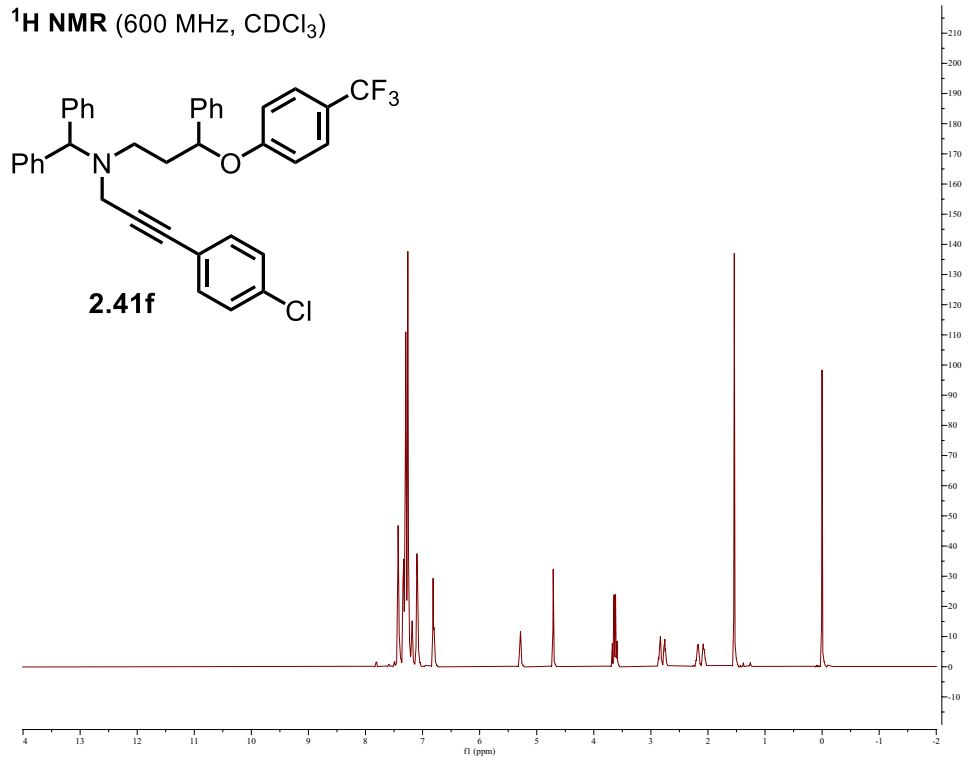
^{13}C NMR (126 MHz, $CDCl_3$)

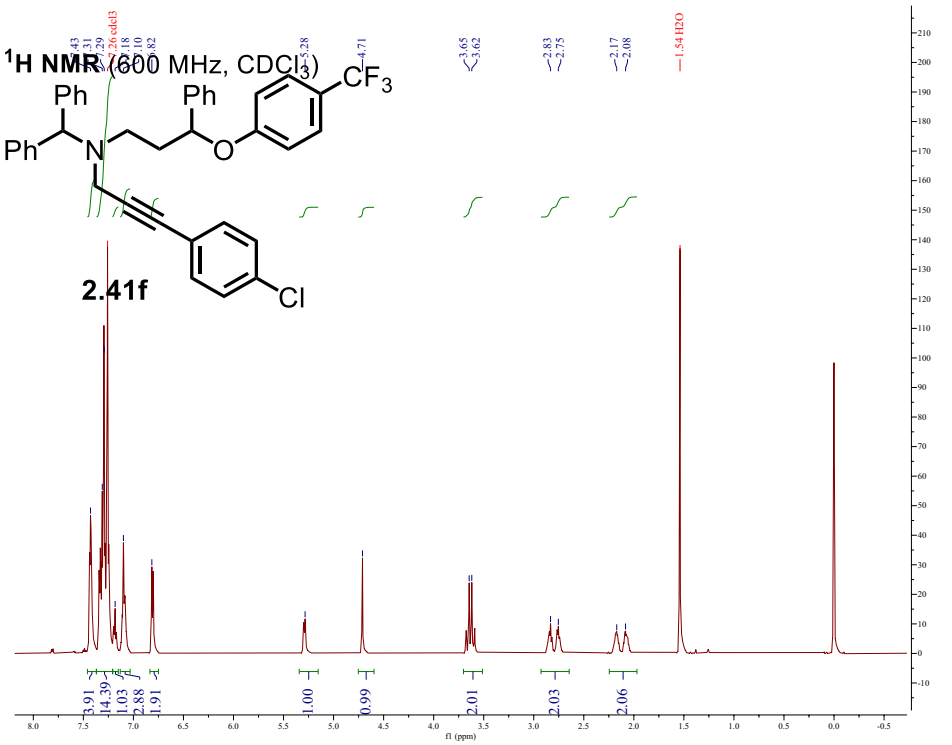


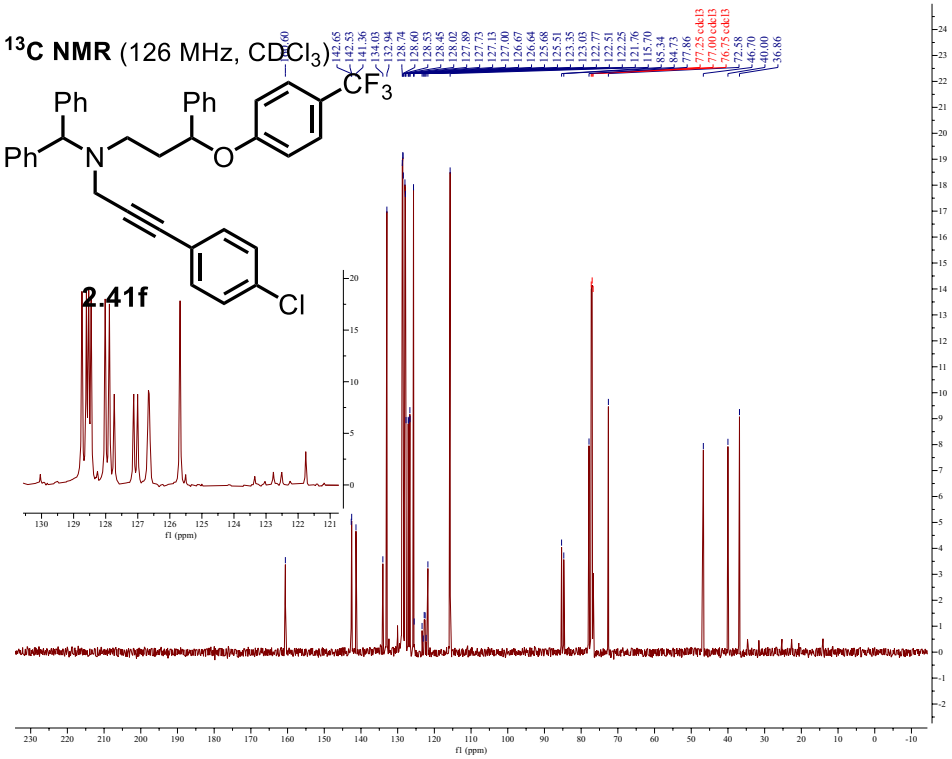
^{19}F NMR (470 MHz, $CDCl_3$)



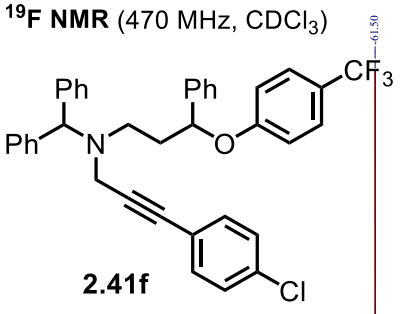
^{1}H NMR (600 MHz, $CDCl_3$)




1H NMR (600 MHz, CDCl3)
Ph
Ph
Ph
N
O
CF3
Cl
2.41f
7.43
7.31
7.29
7.26 cdcl3
7.18
7.10
7.02
5.28
4.71
3.65
3.62
2.83
2.75
2.17
2.08
1.54 H2O
3.91
4.39
1.03
2.88
1.91
1.00
0.99
2.01
2.03
2.06
f1 (ppm)

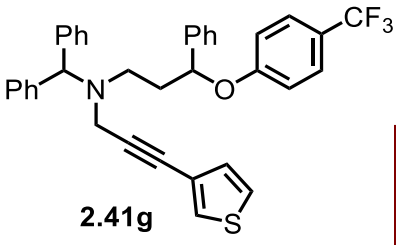

13C NMR (126 MHz, CDCl3)
Ph
Ph
Ph
N
O
CF3
Cl
2.41f
142.65
142.53
141.36
134.03
132.94
128.74
128.66
128.53
128.45
128.02
127.89
127.73
127.13
127.00
126.67
126.64
125.68
125.51
123.35
123.05
122.77
122.51
122.25
121.76
115.70
85.34
84.73
77.86
77.25 cdcl3
77.00 cdcl3
76.75 cdcl3
72.58
46.70
40.00
36.86
f1 (ppm)

^{19}F NMR (470 MHz, $CDCl_3$)



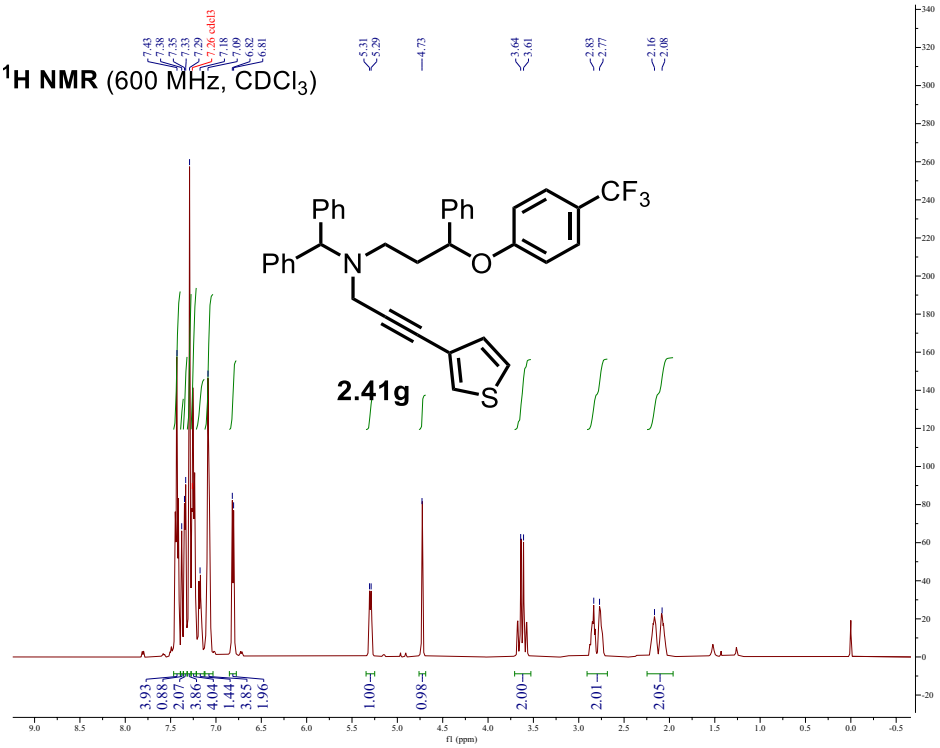
2.41f

^{1}H NMR (600 MHz, $CDCl_3$)

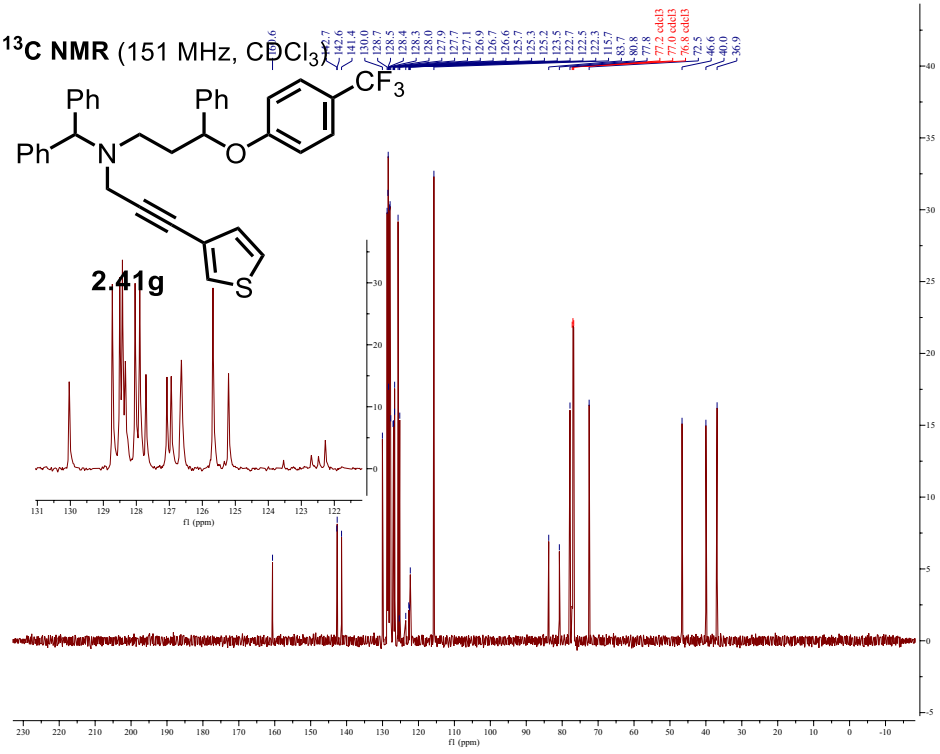


2.41g

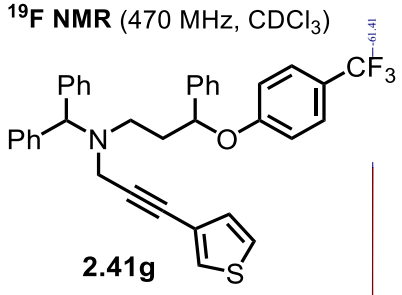
^{1}H NMR (600 MHz, $CDCl_3$)



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

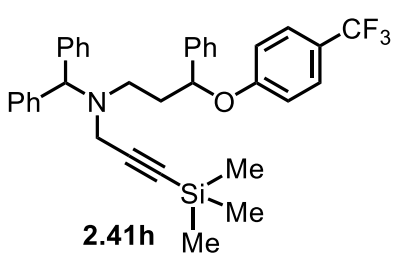


^{19}F NMR (470 MHz, $CDCl_3$)



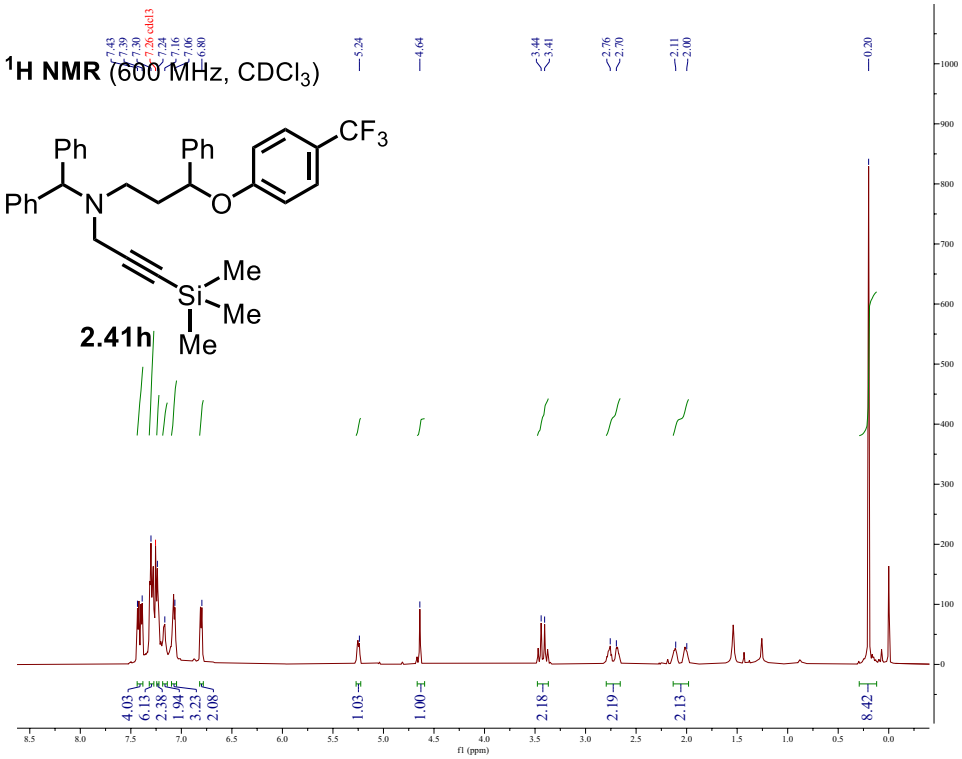
2.41g

^{1}H NMR (600 MHz, $CDCl_3$)

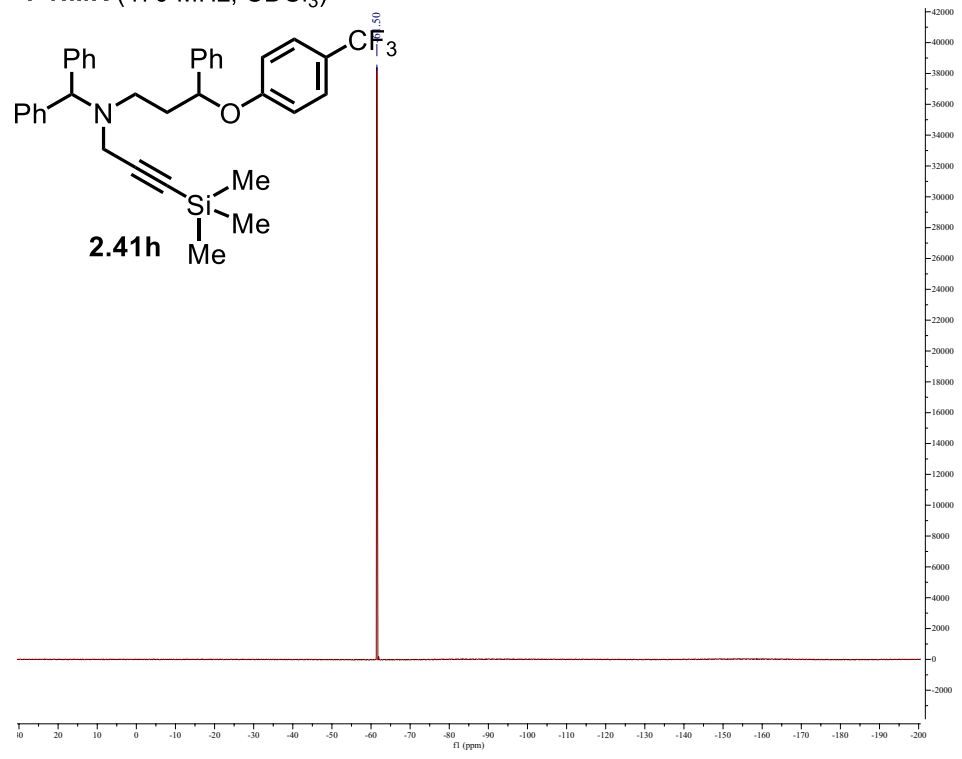


2.41h

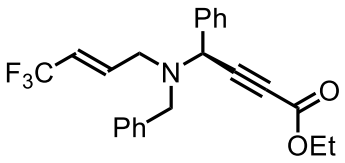
^{1}H NMR (600 MHz, $CDCl_3$)



^{19}F NMR (470 MHz, $CDCl_3$)

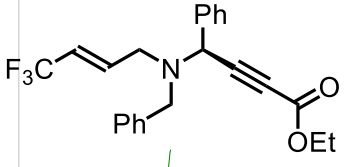


^{1}H NMR (600 MHz, $CDCl_3$)



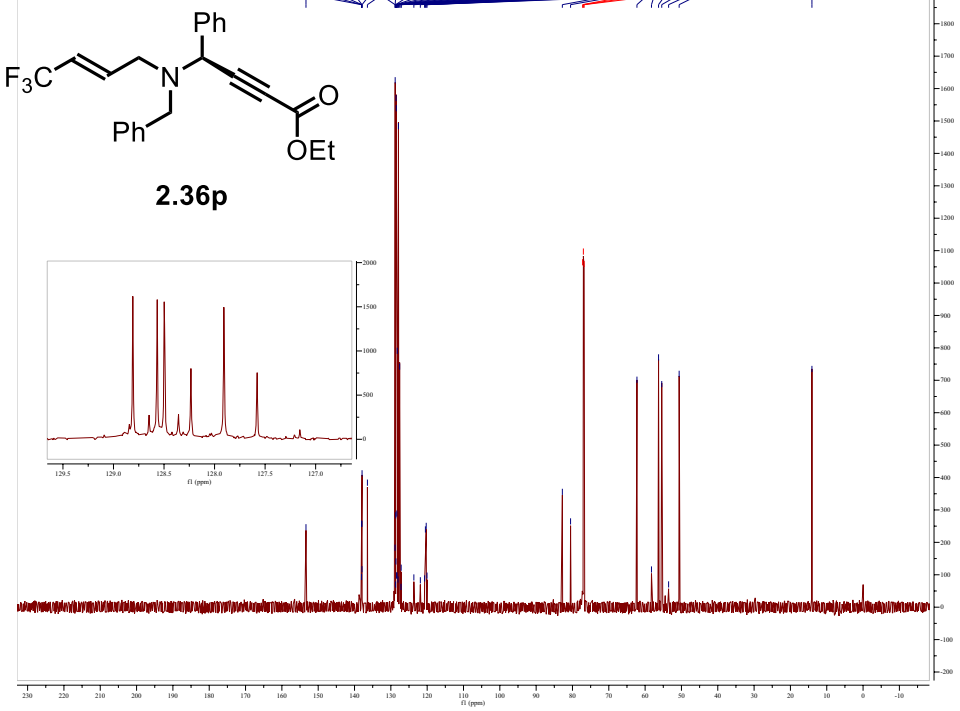
2.36p

^{1}H NMR (600 MHz, $CDCl_3$)



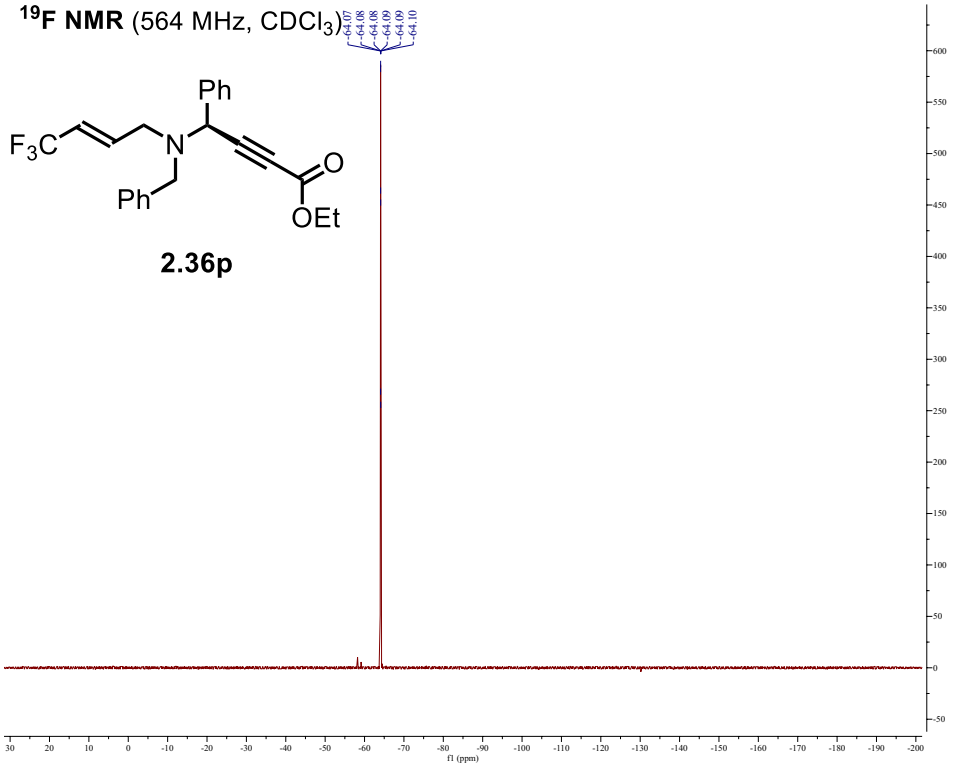
2.36p

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



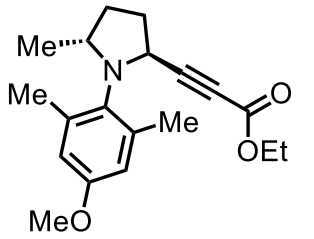
2.36p

^{19}F NMR (564 MHz, $CDCl_3$)

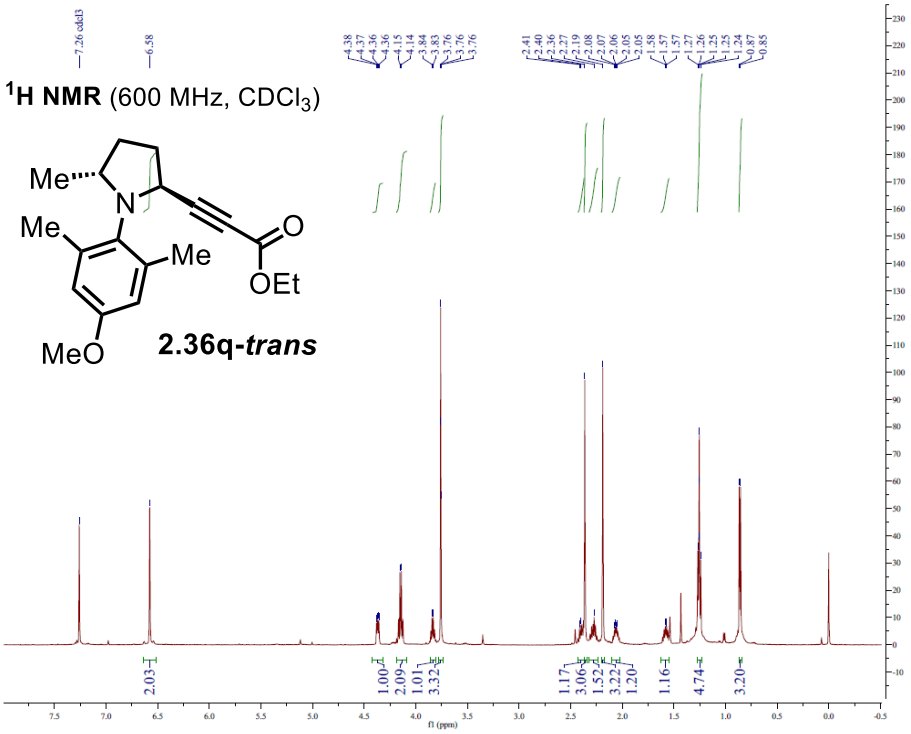


2.36p

^{1}H NMR (600 MHz, $CDCl_3$)



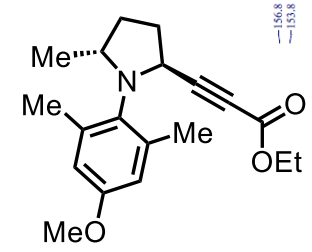
2.36q-*trans*



^{1}H NMR (600 MHz, $CDCl_3$)

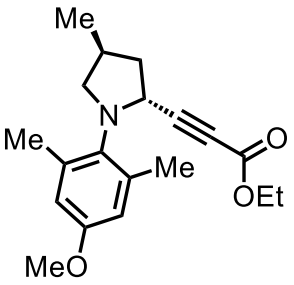
2.36q-*trans*

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



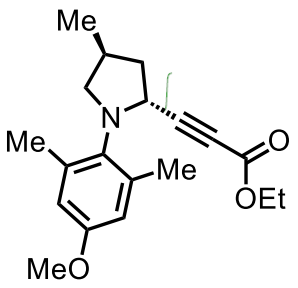
2.36q-*trans*

^{1}H NMR (600 MHz, $CDCl_3$)



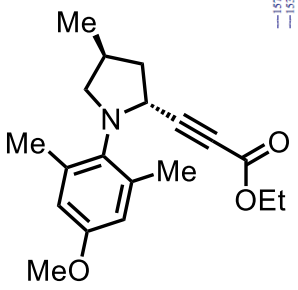
2.36r-*trans*

^{1}H NMR (600 MHz, $CDCl_3$)

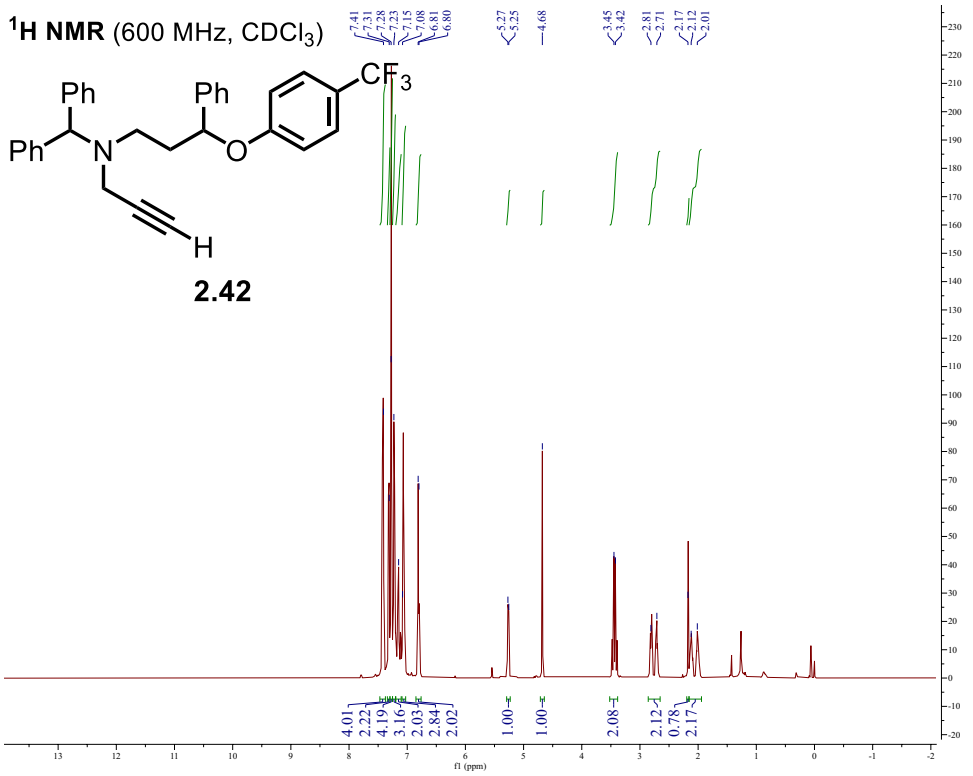


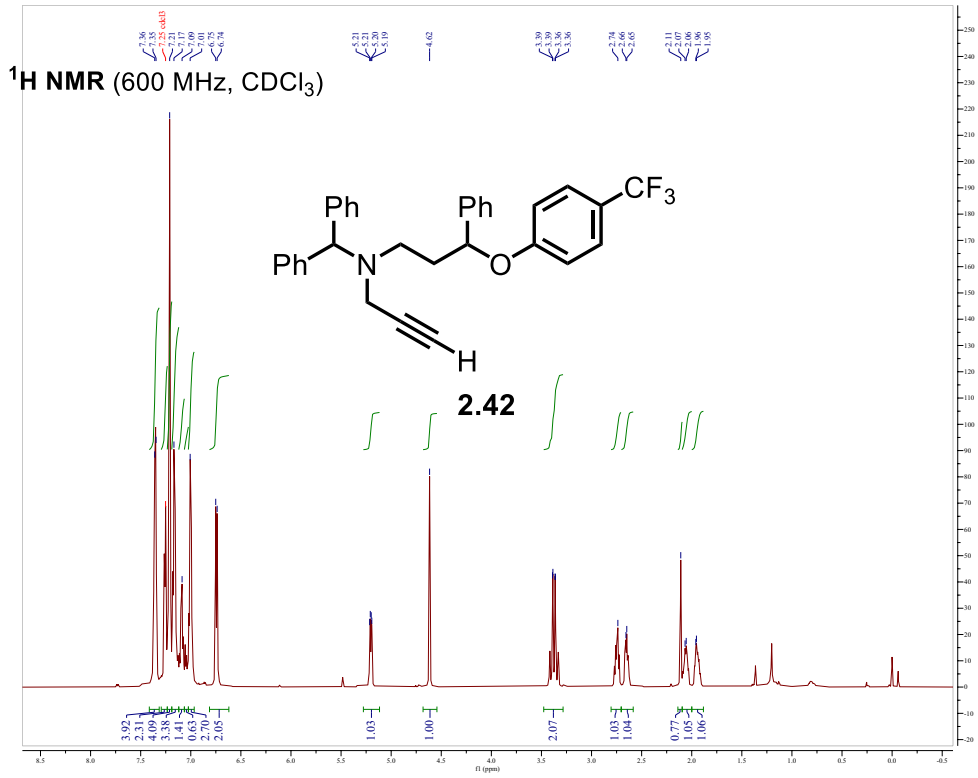
2.36r-*trans*

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

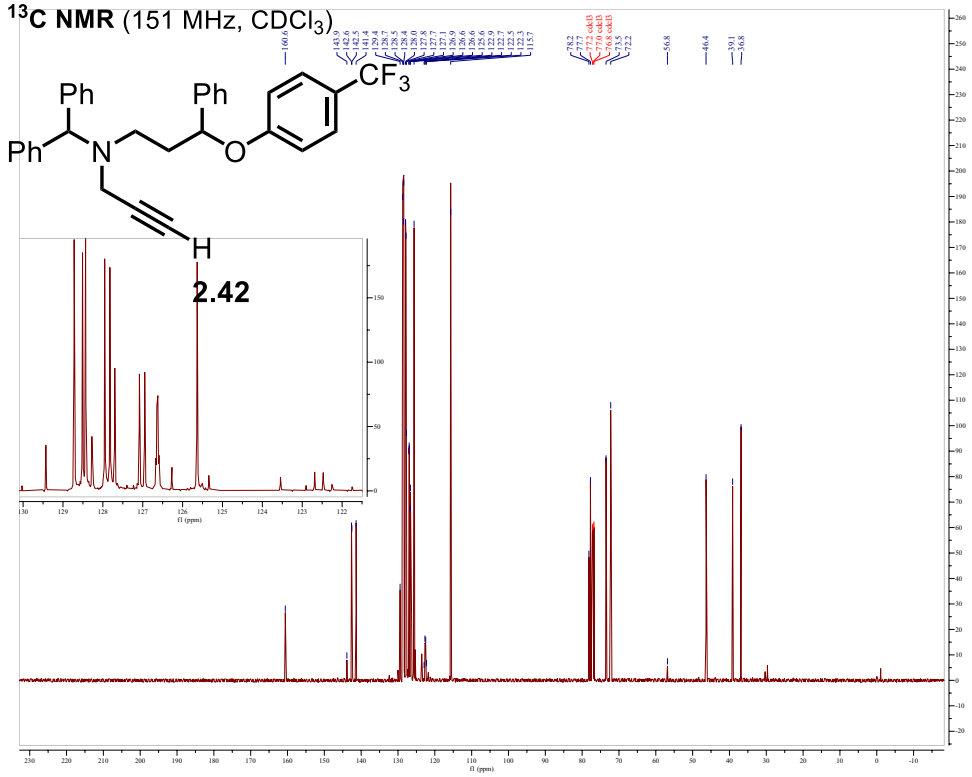


2.36r-*trans*

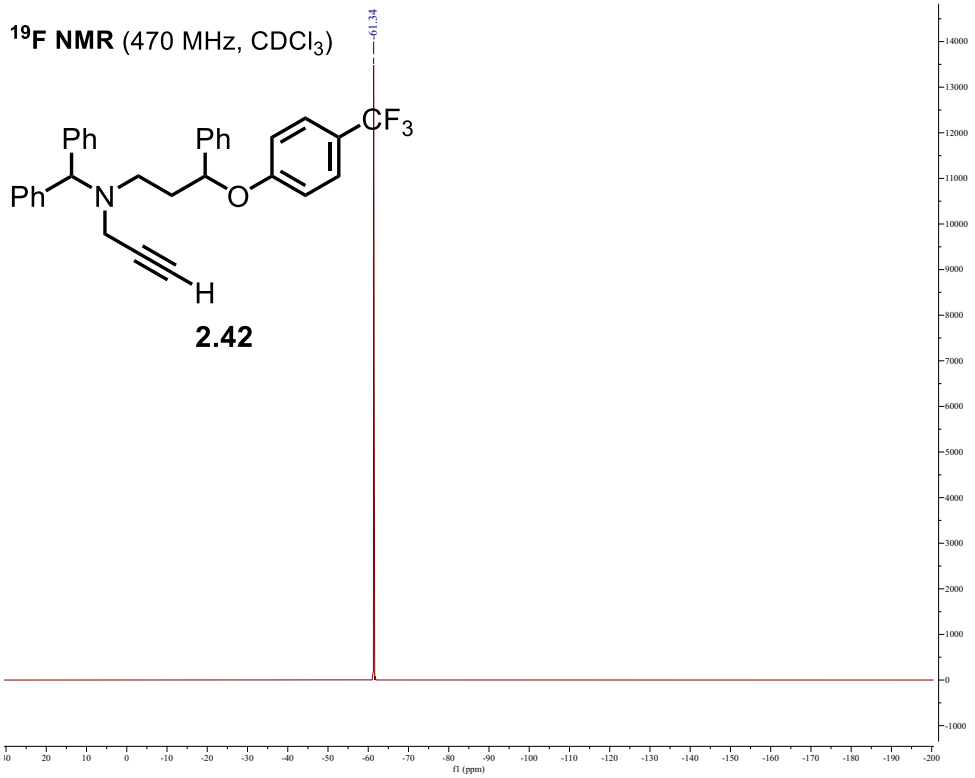

1H NMR (600 MHz, CDCl3)
Ph
Ph
Ph
N
O
CF3
H
2.42


1H NMR (600 MHz, CDCl3)
Ph
Ph
Ph
N
O
CF3
H
2.42

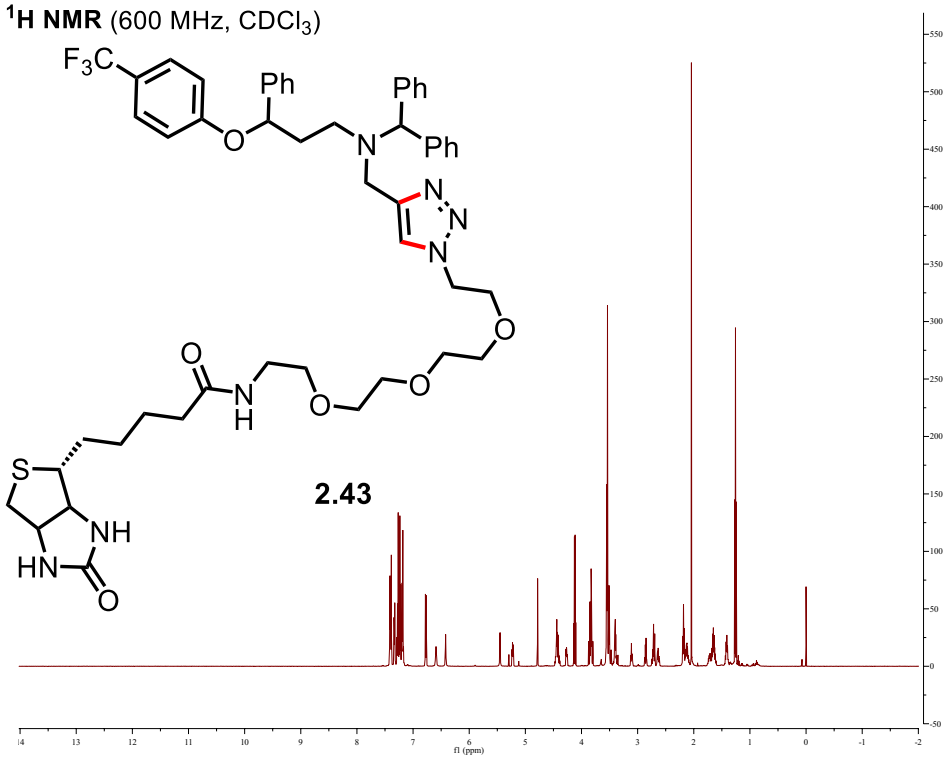
^{13}C NMR (151 MHz, $CDCl_3$)



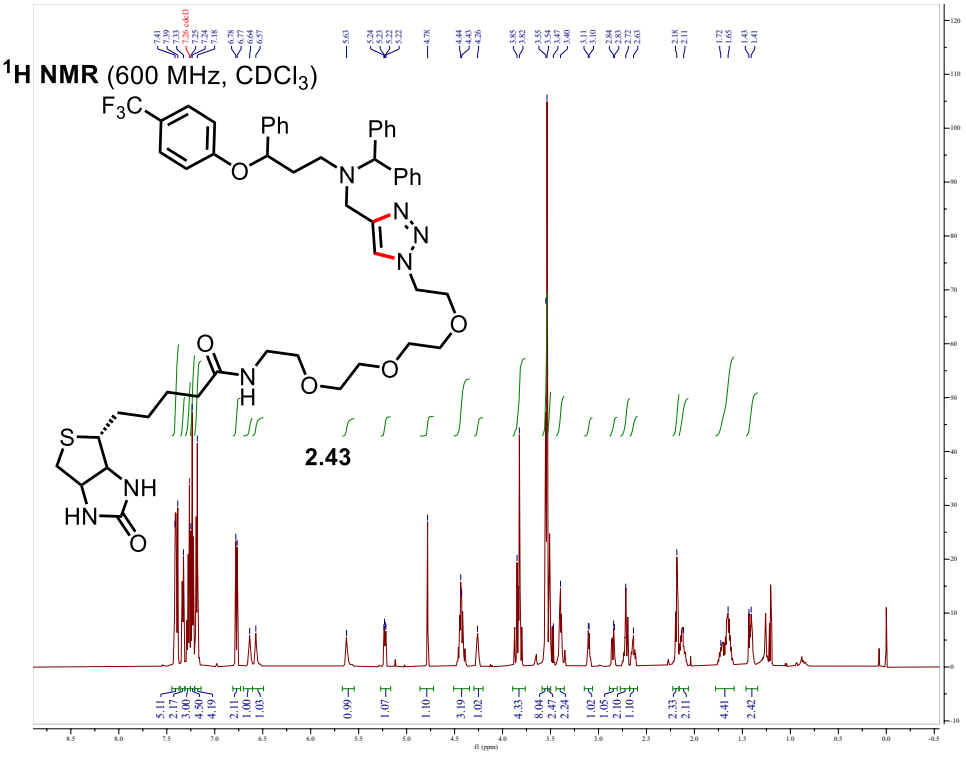
^{19}F NMR (470 MHz, $CDCl_3$)

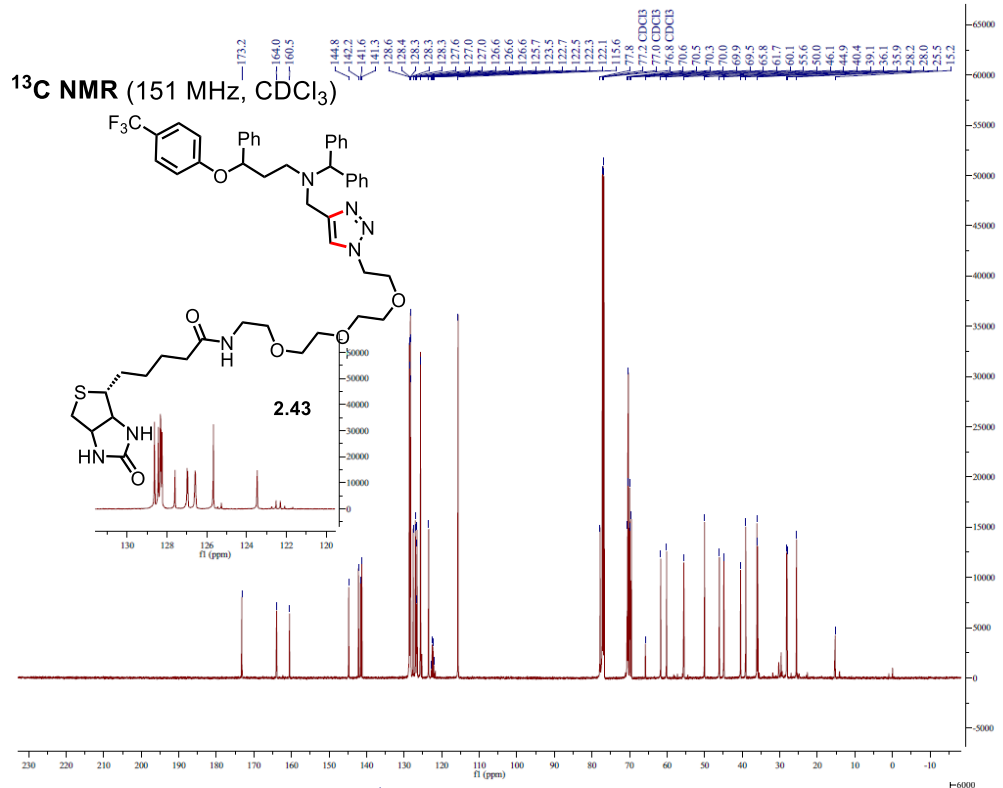


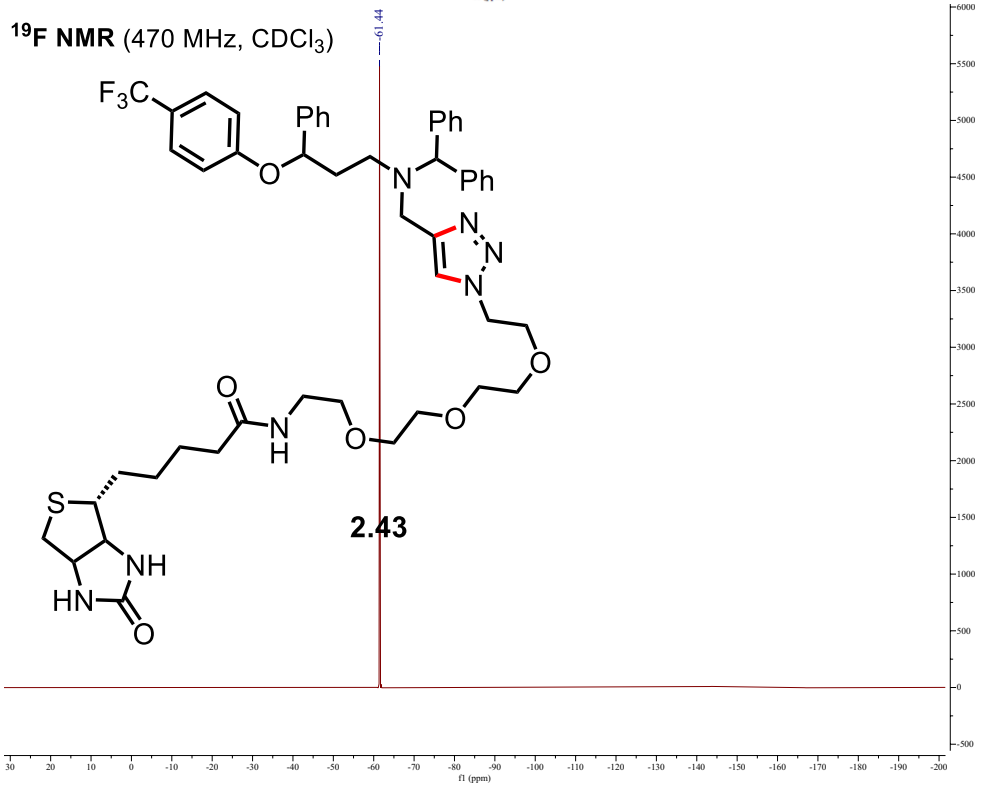
^{1}H NMR (600 MHz, $CDCl_3$)



^{1}H NMR (600 MHz, $CDCl_3$)




13C NMR (151 MHz, CDCl3)
2.43


19F NMR (470 MHz, CDCl3)
2.43

Chapter 3

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

3.1 Introduction

The discovery of deuterium can be dated back to 1932.[60] Natural abundance of deuterium is about 15 ppm and is generally in the form of D_2O in ocean water. Therefore, D_2O is a commonly used *d*-source along with D_2. Deuterium is a stable non-radioactive element that resembles hydrogen, a lighter isotope, in almost every aspect, including physical and chemical properties. However, deuterium has greater mass compared to hydrogen and, thus, has lower zero-point energy (ZPE) with a C–D bond.[61] The incorporation of deuterium has been widely used by chemists for mechanistic studies,[62] and as an internal standard for mass spectrometry for drug candidate absorption, distribution, metabolism and excretion (ADME) studies.[63] The development of high-performance mass spectrometry has led to a revolution of deuterium labeling to be utilized in the quantification of bioactive compounds and their metabolites in biological systems which promotes drug discovery.[64]

There are generally two ways to synthesize deuterated bioactive compounds: either through multi-step synthesis or late-stage hydrogen isotope exchange (HIE). Time-efficient direct HIE has been preferable to synthesize drug isotopologues compared to multi-step synthesis starting from isotopically labeled building blocks or reduction of halogenated or unsaturated drug precursors. In recent years, transition metal-catalyzed C–H activation has provided a way to directly incorporate deuterium into small molecules

[60] Urey, H. C.; Brickwedde, F. G.; Murphy, G. M. *Phys. Rev.* **1932**, *39*, 164–165.
[61] Wiberg, K. B. *Chem. Rev.* **1955**, *55*, 713–743.
[62] Gómez-Gallego, M.; Sierra, M. A. *Chem. Rev.* **2011**, *111*, 4857–4963.
[63] Scheiner, S.; Čuma, M. *J. Am. Chem. Soc.* **1996**, *118*, 1511–1521.
[64] (a) Elmore, C. S.; Bragg, R. A. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 167–171. (b) Uhl, P.; Fricker, G.; Haberkorn, U.; Mier, W. *Drug Discovery Today* **2015**, *20*, 198–208. (c) Filer, C. N. *J. Labelled Compd. Radiopharm*. **2017**, *60*, 96–109.

through HIE.[65] However, positions that are deuterated through HIE using metal-based catalysis could undergo enzymatic degradation and are likely to lose isotope labels.[66] This is caused by enzymes involved in biological systems, such as the cytochrome P450 family, that commence metabolism by oxidizing the most activated C–H bonds or even N–H bonds.[67] In order to use deuterium-labeled compounds as internal standards to compensate for the matrix effect[68] and increase the accuracy of quantitation, it is important to minimize the loss of isotopic labeling.

Since amines take part in over 50% of top-selling commercial drugs,[69] there have been efforts to incorporate hydrogen isotopes onto amine-containing pharmaceuticals.[70] If deuteration of β-amino C–H bond can be achieved, the loss of isotopes could be minimized since the β-amino C–H bond is metabolically stable. However, there are few literature precedents for β-amino C–H activation compared to well-precedented α- or γ-amino C–H activation protocols because the β-amino C–H bond is neither acidic nor hydridic.[71] Reported methods of activating β-amino C–H bonds are generally through the formation of iminium ions, which can lower the pK_a of the α-amino C–H bond. The α-iminium C–H bond will then be easily deprotonated by a suitable base to generate an

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[65] (a) Pieters, G.; Taglang, C.; Bonnefille, E.; Gutmann, T.; Puente, C.; Berthet, J. -C.; Dugave, C.; Chaudret, B.; Rousseau, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 230–234. (b) Hale, L. V. A.; Szymczak, N. K. *J. Am. Chem. Soc.* **2016**, *138*, 13489–13492. (c) Chatterjee, B.; Krishnakumar, V.; Gunanathan, C. *Org. Lett.* **2016**, *18*, 5892–5895.

[66] (a) Nelson, S. D.; Trager, W. F. *Drug Metab. Dispos*. **2003**, *31*, 1481–1497. (b) Swann, P. F.; Mace, R.; Angeles, R. M.; Keefer, L. K. *Carcinogenesis* **1983**, *4*, 821–825. (c) Bell, L. C.; Guengerich, F. P. *J. Biol. Chem.* **1997**, *272*, 29643–29651.

[67] (a) Sono, M.; Roach, M. P.; Coulter, E. D.; Dawson, J. H. *Chem. Rev.* **1996**, *96*, 2841–2887. (b) Loew, G. H.; Harris, D. L. *Chem. Rev.* **2000**, *100*, 407–419. (c) Ortiz de Montellano, P. R.; De Voss, J. J. *Nat. Prod. Rep.* **2002**, *19*, 477–493. (d) Groves, J. T. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 3569–3574. (e) Meunier, B.; de Visser, S. P.; Shaik, S. *Chem. Rev.* **2004**, *104*, 3947–3980. (f) Shaik, S.; Kumar, D.; de Visser, S. P.; Altun, A.; Thiel, W. *Chem. Rev.* **2005**, *105*, 2279–2328. (g) Denisov, I. G.; Makris, T. M.; Sligar, S. G.; Schlichting, I. *Chem. Rev.* **2005**, *105*, 2253–2278. (h) Kim, D.; Guengerich, F. P. *Ann. Rev. Pharmacol. Toxicol.* **2005**, *45*, 27–49. (i) Groves, J. T. *J. Inorg. Biochem.* **2006**, *100*, 434–447.

[68] Fifield, F. W.; Haines, P. J. *Environmental Analytical Chemistry*. Blackwell Publishing, **2000**, 4–5.

[69] McGrath, N. A.; Brichacek, M.; Njardarson, J. T. *J. Chem. Educ*. **2010**, *87*, 1348–1349.

[70] (a) 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. (b) 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.

[71] (a) Yu, P.; Zheng, S.-C.; Yang, N.-Y.; Tan, B.; Liu, X.-Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 4041–4045. (b) Ma, L.; Paul, A.; Breugst, M.; Seidel, D. *Chem. - Eur. J.* **2016**, *22*, 18179–18189.

enamine as a reactive intermediate (Figure 3.1).[71b] In this chapter, recent advances on HIE of bioactive amines will be summarized and regioselective deuteration of metabolically stable *β*-amino C−H bonds of N-containing drug molecules will be discussed.

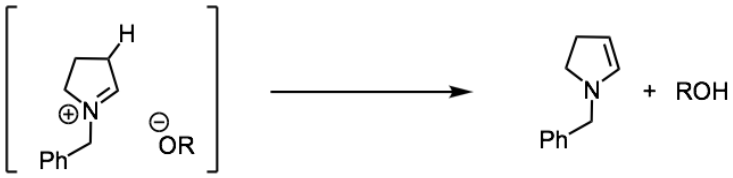

Figure 3. *β*-Amino C–H Activation

3.2 Catalytic HIE Reactions of Amines

Over the years, catalytic HIE reactions on aromatic and hetero aromatic,[72] vinylic,[73] allylic,[74] and aliphatic[75] C–H bonds, as well as those adjacent to O- and N-based functional groups[76] have been extensively studied. Despite the considerable progress in organic synthesis and mechanistic studies, the remaining drawbacks of these methods are the use of precious transition metal-based catalysts (e.g., Pd, Ir, Ru, Pt), global deuteration without chemoselectivity, and harsh reaction conditions such as high temperature as well as high pressure.

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[72] (a) Emmert, M. H.; Gary, J.; Villalobos, J.; Sanford, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 5884–5886. (b) Prechtl, M. H. G.; Hölscher, M.; Ben-David, Y.; Theyssen, N.; Milstein, D.; Leitner, W. *Eur. J. Inorg. Chem.* **2008**, 3493–3500. (c) Kloek Hanson, S.; Heinekey, D. M.; Goldberg, K. I. *Organometallics* **2008**, *27*, 1454–1463. (d) Prechtl, M. H. G.; Hölscher, M.; Ben-David, Y.; Theyssen, N.; Loschen, R.; Milstein, D.; Leitner, W. *Angew. Chem., Int. Ed.* **2007**, *46*, 2269–2272. (e) Lockley, W. J. S. *J. Labelled Compd. Radiopharm.* **2007**, *50*, 779–788. (f) Ito, N.; Watahiki, T.; Maesawa, T.; Maegawa, T.; Sajiki, H. *Adv. Synth. Catal.* **2006**, *348*, 1025–1028. (g) Feng, Y.; Lail, M.; Barakat, K. A.; Cundari, T. R.; Gunnoe, T. B.; Petersen, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 14174–14175. (h) Sajiki, H.; Ito, N.; Esaki, H.; Maesawa, T.; Maegawa, T.; Hirota, H. *Tetrahedron Lett.* **2005**, *46*, 6995–6998.

[73] (a) Di Giuseppe, A.; Castarlenas, R.; Perez-Torrente, J. J.; Lahoz, F. J.; Polo, V.; Oro, L. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 3938–3942. (b) Tse, S. K. S.; Xue, P.; Lin, Z.; Jia, G. *Adv. Synth. Catal.* **2010**, *352*, 1512–1522. (c) Zhou, R. J.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 5783–5787. (d) Rybtchinski, B.; Cohen, R.; Ben-David, Y.; Martin, J. M. L.; Milstein, D. *J. Am. Chem. Soc.* **2003**, *125*, 11041–11050.

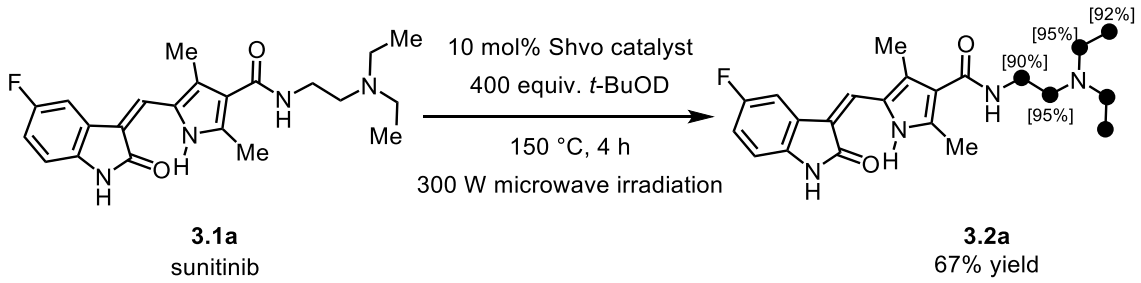
[74] Erdogan, G.; Grotjahn, D. B. *J. Am. Chem. Soc.* **2009**, *131*, 10354–10355.

[75] (a) Maegawa, T.; Fujiwara, Y.; Inagaki, Y.; Esaki, H.; Monguchi, Y.; Sajiki, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 5394–5397. (b) Hirano, M.; Sakaguchi, Y.; Yajima, T.; Kurata, N.; Komine, N.; Komiya, S. *Organometallics* **2005**, *24*, 47994–809.

[76] (a) Maegawa, T.; Fujiwara, Y.; Inagaki, Y.; Monguchi, Y.; Sajiki, H. *Adv. Synth. Catal.* **2008**, *350*, 2215–2219. (b) Takahashi, M.; Oshima, K.; Matsubara, S. *Chem. Lett.* **2005**, *34*, 192–193 (c) Ishibashi, K.; Takahashi, M.; Yokota, Y.; Oshima, K.; Matsubara, S. *Chem. Lett.* **2005**, *34*, 664–665.

Since amines are common in pharmaceuticals,[77] it is important to develop suitable methods to incorporate deuterium into these molecules. As early as 2005, chemists have been trying to incorporate deuterium into amino acids,[78] secondary amine[79] and trialkyl amine-containing drug molecules.[80] However, these methods only have very contrived substrate structures, and some do not have a clear mechanistic rationale.

In 2012, the Beller group reported a selective *α, β*-deuteration of bioactive amines by a Ru-based catalyst (Scheme 3.1).[70a] When sunitinib **3.1a** was treated with Shvo catalyst, *t*-BuOD at 150 °C under 300 W microwave irradiation for 4 hours, deuterated sunitinib **3.2a** was obtained in 67% yield, where up to 95% of *α*-amino C–H bonds were converted to C–D bonds and over 90% *β*-amino C–H bonds were converted to C–D bonds.



3.1a
sunitinib

3.2a
67% yield

Scheme 3.1 *α, β*-Deuteration of Bioactive Amines by Ru-Based Catalyst

The mechanism was proposed based on a redox mechanism by Ru-based catalyst (Figure 3.2).[81] There is an equilibrium between the Shvo catalyst and its monomer (**I** and **II**), where **I** is the active catalyst to start the catalytic cycle. Trialkylamine substrate **3.1** coordinates with active catalyst **I** to form **III**, which undergoes *α*-H atom abstraction by the cyclopentadienyl alkoxide moiety of **III** to generate intermediate **IV**. After *β*-hydride elimination, enamine **3.3** was released, while in situ generated counter monomer **II** underwent deuterium exchange with the *d*-source to form deuterated intermediate **V**.

[77] Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451–3479.
[78] Maegawa, T.; Akashi, A.; Esaki, H.; Aoki, F.; Sajiki, H.; Hirota, K. *Synlett* **2005**, 845–847.
[79] Alexakis, E.; Hickey, M. J.; Jones, J. R.; Kingston, L. P.; Lockley, W. J. S.; Mather, A. N.; Smith, T.; Wilkinson, D. J. *Tetrahedron Lett.* **2005**, *46*, 4291–4293.
[80] Derdau, V.; Atzrodt, J. *Synlett* **2006**, 1918–1922.
[81] (a) Warner, M. C.; Casey, C. P.; Backvall, J.-E. *Top. Organonomet. Chem.* **2011**, *37*, 85–125. (b) Fabrello, A.; Bachelier, A.; Urrutigoity, M.; Kalck, P. *Coord. Chem. Rev*. **2010**, *254*, 273–284.

Subsequently, migratory insertion followed by deuteration gave deuterated product **3.2** and regenerated active catalyst intermediate **I**.

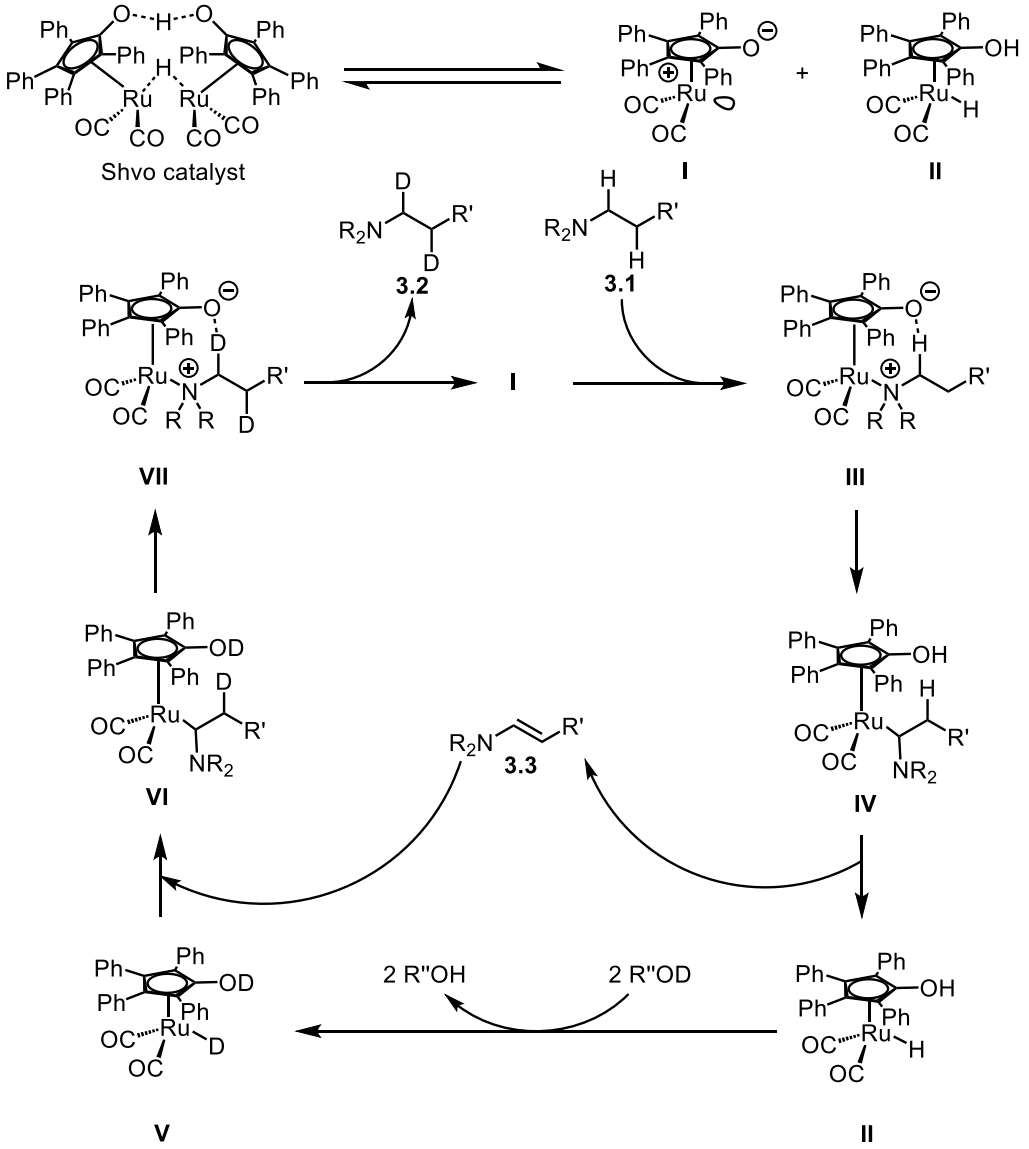


Figure 3.2 Proposed Mechanism for *α, β*-Deuteration of Bioactive Amines

With the success of *α, β*-deuteration of **3.1a**, other trialkylamine-containing molecules were tested as well (Table 3.1). Lidocaine **3.1b** did not generate the deuterated product with high efficiency (44-72%) even when the temperature was raised to 170 °C. Yet, metoclopramide **3.1c** underwent almost quantitative deuteration at the desired position

but at the C–H next to the amide moiety. On top of α- and β-amino C–H deuteration, volinanserin **3.1d** underwent α-hydroxyl C–H deuteration through an oxidation and reduction process catalyzed by the Shvo catalyst.[82] *N*-Methyl substituent (**3.2e**, **3.2f**) was hardly deuterated (7% and 3%). With **3.2g**, other than α- and β-amino C–H, scrambling occurs also at the aromatic C–H bond.

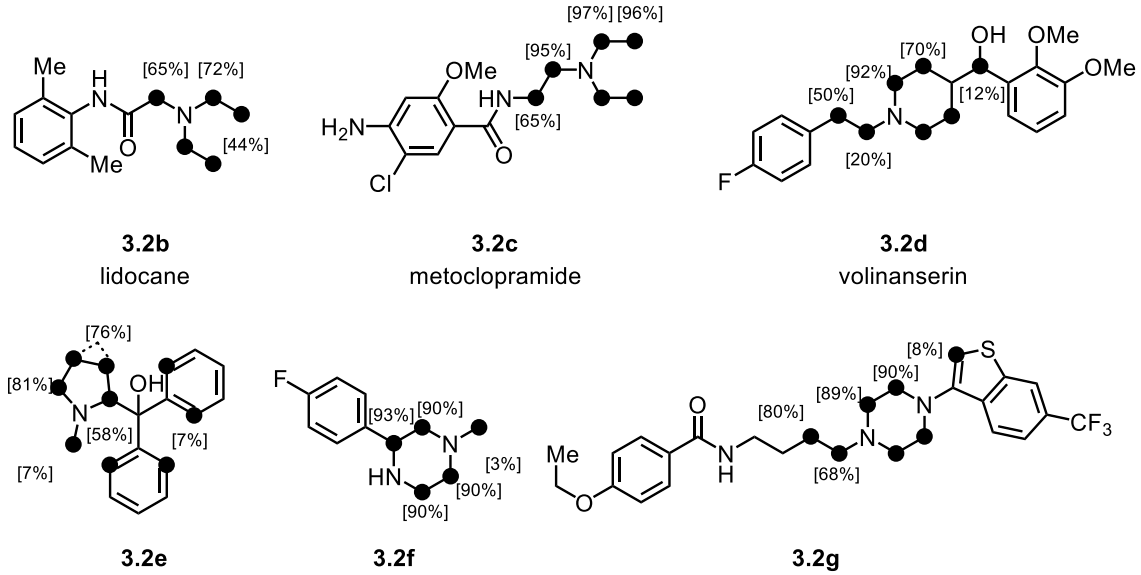
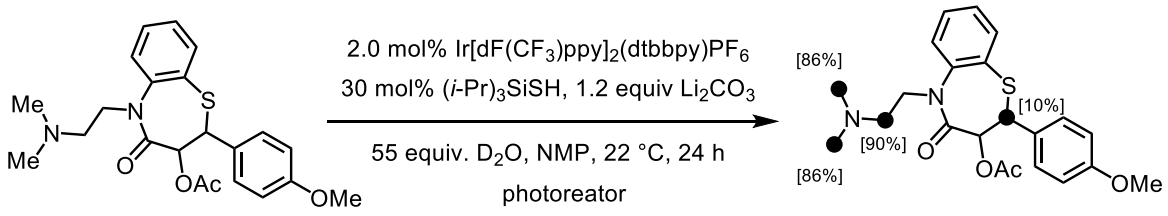


Table 3.1 Substrate Scope for α, β-Deuteration of Bioactive Amines

The achievement of highly deuterated products from bioactive molecules is remarkable, but traditional transition metal-catalyzed HIE reactions only work for structurally simple substrates. Furthermore, there are several limitations related to the method, such as the requirements of precious Ru-based catalysts; additionally, carbonyl groups of ketones and olefinic double bonds are prone to undergo hydrogenation under these reaction conditions. These methods also require the use of a large excess of deuterating agents.

[82] (a) Wang, G. -Z.; Andreasson, U.; Bäckvall, J.-E. *Chem. Commun*. **1994**, 1037–1038. (b) Persson, B.; Larsson, A. L. E.; Ray, M. L.; Bäckvall, J.-E. *J. Am. Chem. Soc*. **1999**, *121*, 1645–1650. (c) Csjernyik, G.; Éll, A. H.; Fadini, L.; Pugin, B.; Bäckvall, J.-E. *J. Org. Chem.* **2002**, *67*, 1657–1662. (d) Éll, A. H.; Samec, J. S. M.; Brasse, C.; Bäckvall, J.-E. *Chem. Commun.* **2002**, 1144–1145. (e) Johnson, J. B.; Bäckvall, J.-E. *J. Org. Chem.* **2003**, *68*, 7681–7684.

In 2017, MacMillan reported photoredox-catalyzed deuteration of N-containing pharmaceutical compounds.[70b] Since photoredox has been demonstrated to access transformation through SET events by trapping α-amino radicals,[83] the authors exploited the generation of α-amino radicals to obtain α-deuterated and α-tritiated bioactive amines. When diltiazem **3.4c** was treated with an iridium-based photocatalyst and HAT catalyst ((*i*-Pr)$_3$SiSH) using D_2O as a deuterium source, α-amino C–H deuteration was achieved in up to 90% (Scheme 3.2). Labile benzylic C–H bonds were also deuterated as a result (10%).

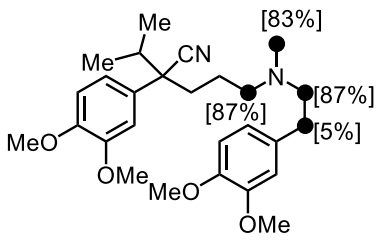


3.4c → **3.5c** 85% yield

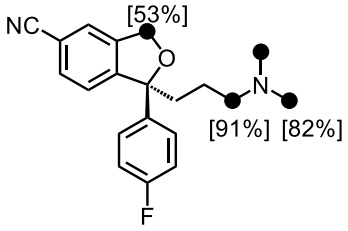
Scheme 3.2 Photoredox-Catalyzed Deuteration of Pharmaceutical Compounds

They tested the scope of drug molecules bearing various functional groups. Deuterium incorporation generally gave moderate to good levels of HIE products of acyclic amines, piperidines, piperazines and macrolides (Table 3.2). Nitrile (**3.4a**, **3.4b**), amide (**3.4c**, **3.4f**), ether (**3.4d**, **3.4f**), carboxylic acid (**3.4e**) and even free hydroxyl groups (**3.4h**) were compatible under the photoredox conditions. In chiral molecules, stereogenic centers that are not adjacent to the reaction site were undisturbed while labile benzylic C–H bonds were deuterated (**3.5c**, **3.5d**, **3.5f**).

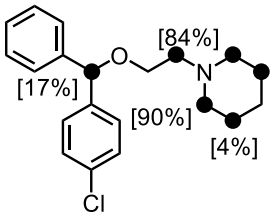
[83] (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322–5363. (b) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. *J. Org. Chem.* **2016**, *81*, 6898–6926. (c) Kärkäs, M. D.; Porco Jr., J. A.; Stephenson, C. R. J. *Chem. Rev.* **2016**, *116*, 9683–9747.



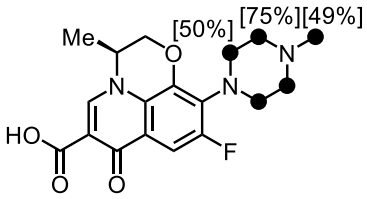
3.5a
verapamil
84% yield



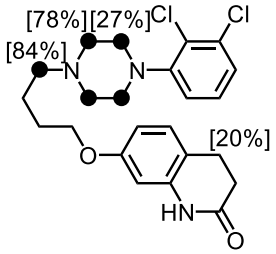
3.5b
escitalopram
71% yield



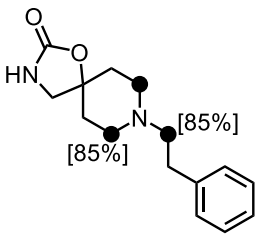
3.5d
cloperastine
78% yield



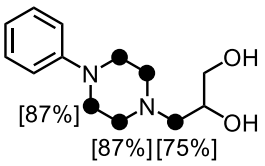
3.5e
levofloxacin
75% yield



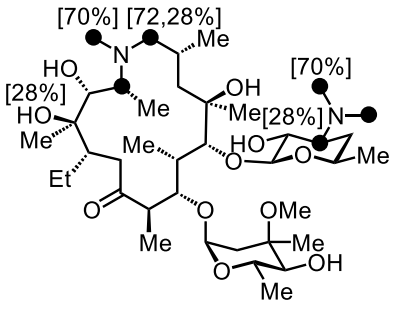
3.5f
aripiprazole
80% yield



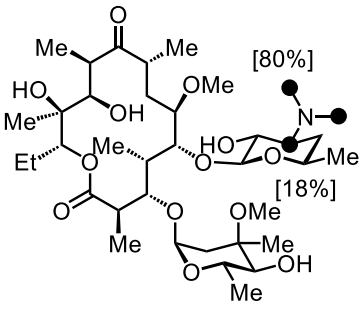
3.5g
fenspiride
71% yield



3.5h
dropropizine
80% yield



3.5i
azithromycin
85% yield



3.5j
clarithromycin
70% yield

Table 3.2 Scope of Photoredox-Catalyzed Deuteration of Pharmaceutical Compounds

Despite the notable achievements of the reported protocols, amino C–H deuteration methods still require the use of a large excess of deuterium sources as well as precious metal-based catalysts. It is important to develop a more general method to realize regioselective deuteration of metabolically more stable *β*-amino C–H bonds.

3.3 Development of *β*-Amino C–H Bonds Deuteration of Drug Molecules

We set out to design a possible way to achieve regioselective *β*-amino deuteration of biologically active compounds that contain *N*-alkylamine units. In the proposed catalytic cycle, $B(C_6F_5)_3$ could receive a hydride from amine **3.6** to generate a borohydride and an iminium ion (**VIII)**. Brønsted basic *N*-alkylamine-mediated deprotonation of the iminium ion would give the corresponding enamine with borohydride and ammonium ion pair (**IX**, Figure 3.3).[84] At the same time, acetone-d_6 **3.7** is activated by $B(C_6F_5)_3$, which could be easily dedeuterated by *N*-alkylamine, generating boron enolate and deuterated ammonium ion pair (**X)**. [85] Subsequent deuteration of the enamine followed by borohydride reduction would afford *β*-deuterated amine products **3.8**.

[84] (a) Focante, F.; Mercandelli, P.; Sironi, A.; Resconi, L. *Coord. Chem. Rev*. **2006**, *250*, 170–188. (b) Zhang, J.; Park, S.; Chang, S. *J. Am. Chem. Soc.* **2018**, *140*, 13209–13213. (c) Li, R.; Chen, Y.; Jiang, K.; Wang, F.; Lu, C.; Nie, J.; Chen, Z.; Yang, G.; Chen, Y. -C.; Zhao, Y.; Ma, C. *Chem. Commun.* **2019**, 55, 1217–1220. (d) Maier, A. F. G.; Tussing, S.; Schneider, T.; Flörke, U.; Qu, Z.-W.; Grimme, S.; Paradies, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 12219–12223. (e) Kojima, M.; Kanai, M. *Angew. Chem., Int. Ed.* **2016**, *55*, 12224–12227.

[85] Cao, M.; Yesilcimen, A.; Wasa, M. *J. Am. Chem. Soc.* **2019**, *141*, 4199–4203.

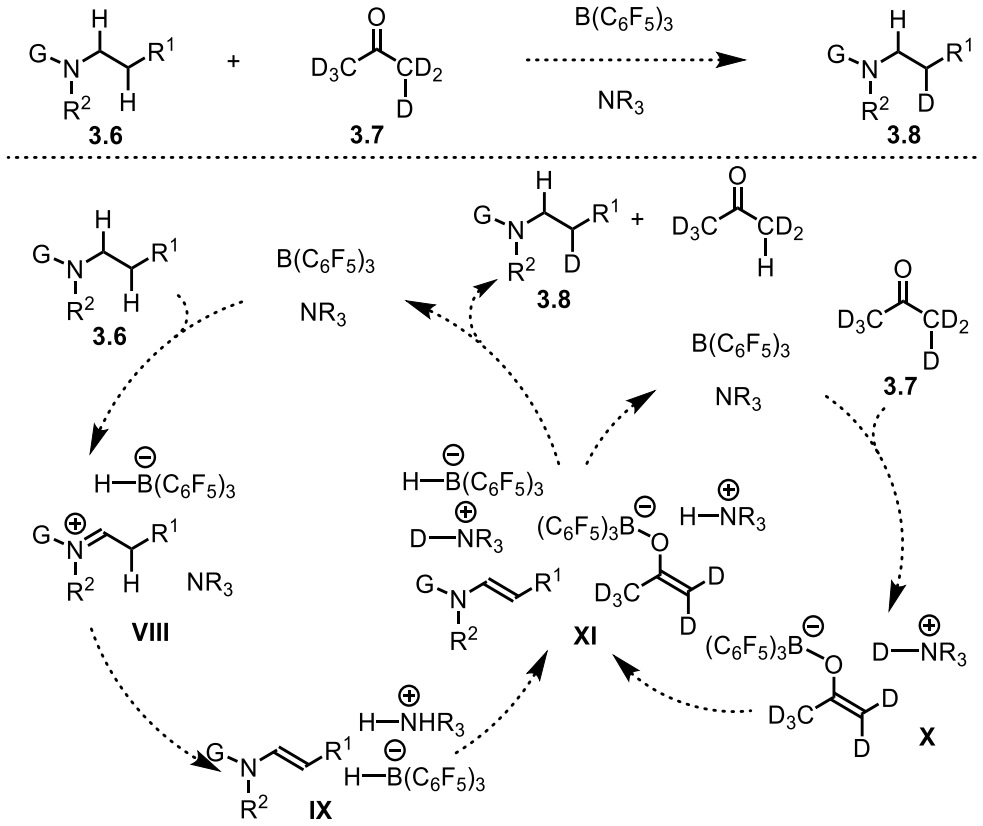
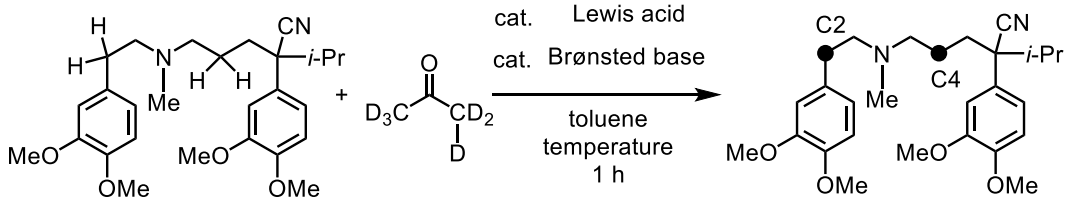


Figure 3.3 Proposed Catalytic Cycle

3.3.1 Optimization of Reaction Conditions

We first set out to determine a suitable combination of Lewis acid and Brønsted base catalysts to achieve *β*-amino C–H deuteration (Table 3.3). When trialkylamine NEt_3, NBn_3, and 1,2,2,6,6-pentamethylpiperidine (PMP) were used as Brønsted base cocatalysts, the *β*-amino C–H bond of verapamil **3.6a** was deuterated by 16–26% (entries 1-3). More Brønsted basic 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) did not generate any deuterated product (entry 4). However, in the absence of Brønsted base cocatalysts, we observed 21 and 35% deuterium incorporation (entry 5), indicating that **3.6a** and/or **3.8a** could serve as Brønsted bases to promote deprotonation of the iminium ion. Conducting the reaction at 100°C gave poor results for deuteration (entry 6), while heating the system to 150°C resulted in >80% deuterium incorporation (entry 7). Increasing $B(C_6F_5)_3$ loading to 10 mol% improved the labeling rate up to 92% (entry 8).

Moreover, we were able to obtain **3.8a** with over 95% *β*-amino C–H deuterated after treating **3.6a** with two batches of 5.0 mol% $B(C_6F_5)_3$ (entry 9). $B(C_6F_5)_3$ is necessary for the deuteration process since there was no deuterium incorporated in **3.6a** without using $B(C_6F_5)_3$ (entry 10). Deuteration did not occur when less hindered BF_3 or less Lewis acidic BPh_3 was used (entries 11-12).



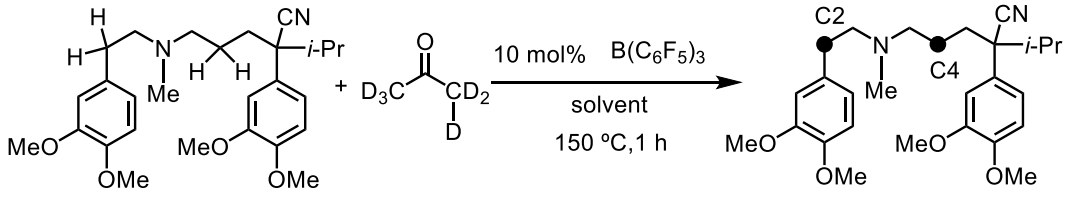
3.6a, verapamil | **3.7**, acetone-d_6 | **3.8a**, verapamil-*d* >90% yield

5.0 mol% $B(C_6F_5)_3$ 10 mol% NEt_3 125 °C [C2] 17% [C4] 26% 1	5.0 mol% $B(C_6F_5)_3$ 10 mol% NBn_3 125 °C [C2] 20% [C4] 34% 2	5.0 mol% $B(C_6F_5)_3$ 10 mol% PMP 125 °C [C2] 16% [C4] 26% 3
5.0 mol% $B(C_6F_5)_3$ 10 mol% DBU 125 °C [C2] 0% [C4] 0% 4	5.0 mol% $B(C_6F_5)_3$ 125 °C [C2] 21% [C4] 35% 5	5.0 mol% $B(C_6F_5)_3$ 100 °C [C2] <5% [C4] 7% 6
5.0 mol% $B(C_6F_5)_3$ 150 °C [C2] 80% [C4] 85% 7	10 mol% $B(C_6F_5)_3$ 150 °C [C2] 88% [C4] 92% 8	2 x 5.0 mol% $B(C_6F_5)_3$ 150 °C [C2] 95% [C4] >98% 9
150 °C [C2] 0% [C4] 0% 10	5.0 mol% BF_3•OEt_2 150 °C [C2] 0% [C4] 0% 11	5.0 mol% BPh_3 150 °C [C2] 0% [C4] 0% 12

[a]Conditions: verapamil (**3.6a**, 0.1 mmol), acetone-d_6 (**3.7**, 0.68 mmol), organoborane, Brønsted base, toluene (0.4 mL), under N_2, 1 h. [b]Yield and deuterium incorporation level was determined by ^1H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard. [c]Conditions: verapamil (**3.6a**, 0.2 mmol), acetone-d_6 (**3.7**, 1.36 mmol), $B(C_6F_5)_3$ (5.0 mol%), toluene (0.8 mL), under N_2, 150 °C, 1 h. Isolated and purified **3.8a** was reacted with acetone-d_6 (**3.7**, 1.36 mmol), $B(C_6F_5)_3$ (5.0 mol%), toluene (0.8 mL), under N_2, 150 °C, 1 h.

Table 3.3 Evaluation of Reaction Parameters[a,b,c,d]

Using verapamil **3.6a** as the model substrate, additional variants were modified. Evaluation of solvents (Table 3.4) revealed that in less polar solvents, the product had over 80% deuterium incorporation (entries 1–2). Halogenated solvents still gave a high level of deuteration in the product (entries 3–4). Ether type solvents caused a drastic reduction in HIE efficiency; in Et_2O and THF, we observed less than 25% deuterium incorporation (entries 5–6). Among the solvents tested, toluene was found to be the optimal solvent.



3.6a, verapamil **3.7**, acetone-d_6 **3.8a**, verapamil-*d*

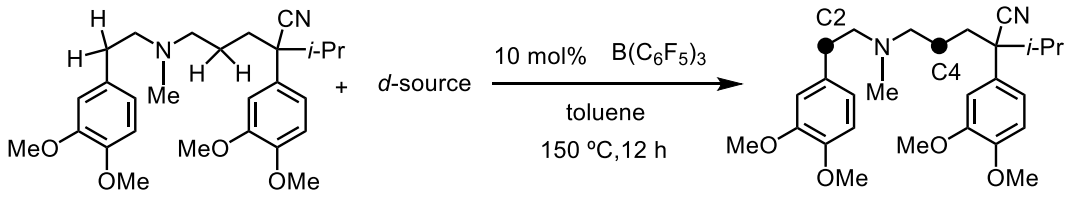
toluene	benzene	$ClCH_2CH_2Cl$
[C2] 90% [C4]92%	[C2] 84% [C4]91%	[C2] 78% [C4]90%
1	2	3
$CHCl_3$	Et_2O	THF
[C2] 71% [C4]85%	[C2] 14% [C4]24%	[C2] <5% [C4]<5%
4	5	6

Conditions: verapamil (**3.6a**, 0.1 mmol), $B(C_6F_5)_3$ (10 mol%), solvent (0.4 mL), acetone-d_6 (**3.7**, 0.68 mmol) under N_2, 150 ºC. Yield and deuterium incorporation rate was determined by ^1H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard.

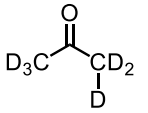
Table 3.4 Evaluation of Solvent

Various deuterium sources were also evaluated (Table 3.5). Acyclic deuterated ketone had a higher deuterium incorporation ratio of product, while *α*-deuterated cyclohexanone afforded the product with a lower deuterium incorporation level (entries 1–3). Deuterated alcohols could also be a deuterium source but showed much lower reaction efficiency.

Primary and secondary deuterated alcohols showed poor efficiency, yet sterically hindered *t*-BuOD had a relatively higher level of deuterium incorporation (entries 4–6). Among the deuterium sources tested, acetone-d_6 **3.7** was the most efficient deuterating agent. With acetone-d_6 as the most effective agent, the equivalence of **3.7** was also tested (Table 3.6). 6.8 Equivalent of acetone-d_6 was found to be the most effective (entry 3).

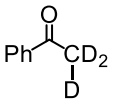


3.8a, verapamil **3.7** (6.8equiv.) **3.8a**



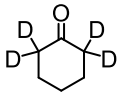
[C2] 90% [C4] 92%

1



[C2] 79% [C4] 92%

2



[C2] 90% [C4] 92%

3

CH_3OD

[C2] 14% [C4] 20%

4

$(CD_3)_2CDOD$

[C2] 17% [C4] 21%

5

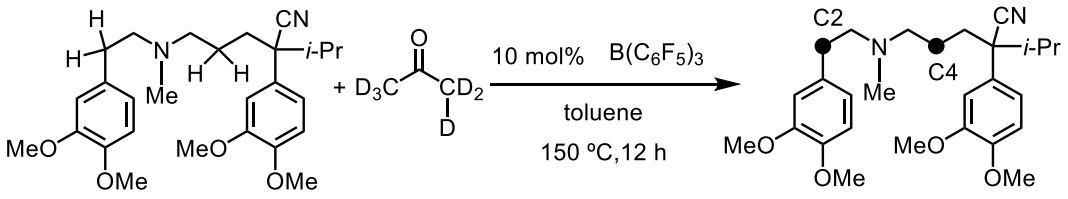
t-BuOD

[C2] 63% [C4] 58%

6

Conditions: verapamil (**3.6a**, 0.1 mmol), $B(C_6F_5)_3$ (10 mol%), toluene (0.4 mL), *d*-source (**3.7**) under N_2, 150 ºC. Yield and deuterium incorporation rate was determined by ^1H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard.

Table 3.5 Evaluation of Deuterium Source



3.6a, verapamil **3.7** **3.8a**, verapamil-*d*

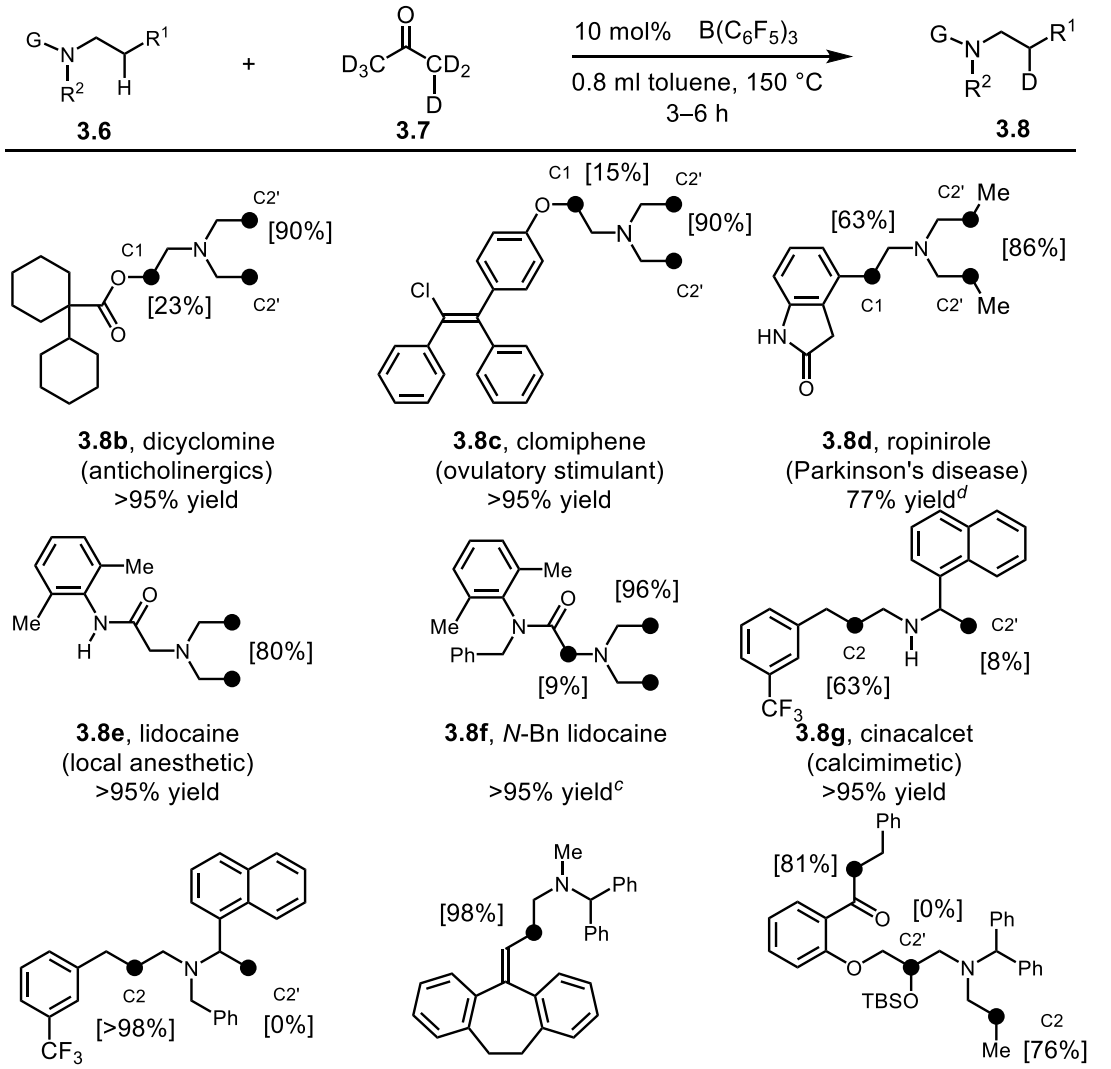
2.0 equiv. of **3.7** [C2] 47% [C4] 60% 1	4.0 equiv. of **3.7** [C2] 72% [C4] 82% 2
6.8 equiv. of **3.7** [C2] 80% [C4] 86% 3	10 equiv. of **3.7** [C2] 70% [C4] 85% 4

Conditions: verapamil (**3.6a**, 0.3 mmol), $B(C_6F_5)_3$ (2.5 mol%), toluene (1.2 mL), acetone-d_6 (**3.7**) under N_2, 150 °C. Yield and deuterium incorporation rate were determined by ^1H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard.

Table 3.6 Evaluation of Equivalence of Acetone-d_6

3.3.2 Evaluation of Substrate Scope

After determining the optimal conditions, we evaluated a scope of acyclic amine-containing drug molecules and drug derivatives (Table 3.7). Functionalities, such as ether (**3.6c**, **3.6j**), ester (**3.6b**), amide (**3.6d**–**3.6f**), ketone (**3.6j**), and halogen (**3.6c**, **3.6h**) were well tolerated under the deuteration conditions. *β*-Amino C–H bonds adjacent to oxygen-containing functional groups was found to be deuterated less efficiently (**3.8b**–**3.8c**) presumably due to instability of their in situ generated enamine. Amine and amide with a N-protecting group had higher levels of deuterium incorporation (**3.8f** vs **3.8e**, **3.8h** [C2] vs **3.8g** [C2]). Deuteration did not occur to the *β*-amino C–H bond of the amine substituent with excessive steric hindrance (**3.8h** [C2]', **3.8j** [C2]'). Secondary amine-containing molecule cinacalcet **3.6g** was compatible under these conditions. Sterically less hindered secondary amines were able to get 76-98% *β*-amino C–H deuteration after installing benzhydryl groups (**3.8i**–**3.8j**). In addition, we also observed deuteration of acidic *α*-carbonyl C–H (**3.8f**, **3.8j**).



3.8b, dicyclomine (anticholinergics) >95% yield

3.8c, clomiphene (ovulatory stimulant) >95% yield

3.8d, ropinirole (Parkinson's disease) 77% yield[d]

3.8e, lidocaine (local anesthetic) >95% yield

3.8f, *N*-Bn lidocaine >95% yield[c]

3.8g, cinacalcet (calcimimetic) >95% yield

3.8h, *N*-Bn cinacalcet >95% yield[c]

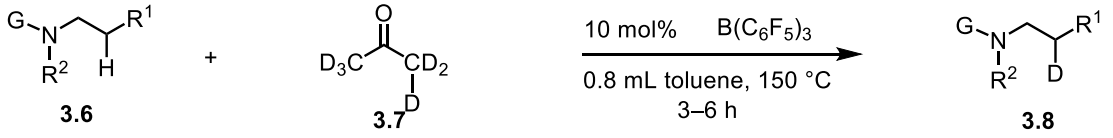
3.8i, *N*-Bzh nortriptyline >95% yield[c]

3.8j, *N*-Bzh, *O*-TBS propafenone 92% yield

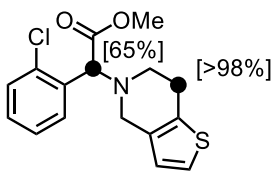
[a]Conditions: *N*-alkylamine (**3.6**, 0.2 mmol), acetone-d_6 (**3.7**, 1.36 mmol), $B(C_6F_5)_3$ (10 mol%), toluene (0.8 mL), under N_2, 150 °C, 3 h. [b]Yield of isolated and purified products. Deuterium incorporation level was determined by 1H NMR analysis of the isolated and purified product. [c]Conditions: *N*-alkylamine (**3.6**, 0.2 mmol), acetone-d_6 (**3.7**, 1.36 mmol), $B(C_6F_5)_3$ (5.0 mol%), toluene (0.8 mL), under N_2, 150 °C, 3 h. After filtration of the crude reaction mixture through a pad of silica gel and removal of volatiles, acetone-d_6 (**3.7**, 1.36 mmol), $B(C_6F_5)_3$ (5.0 mol%), and toluene (1.0 mL) were added under N_2, and then heated at 150 °C, 3 h. [d]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 3.7 Deuteration of Acyclic *β*-Amino C–H Bonds[a,b,c,d]

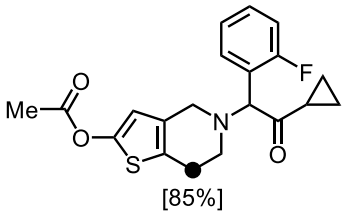
Thereafter, we applied the reaction system to cyclic amine-containing pharmaceuticals and their derivatives (Table 3.8). A wide range of functional groups were compatible under the deuteration conditions, including ester (**3.6k**–**3.6l**), ether (**3.6m**, **3.6o**–**3.6s**), ketone (**3.6m**, **3.6q**), amide (**3.6n**), halide (**3.6k**–**3.6l**, **3.6o**–**3.6p**), thiophene (**3.6k**–**3.6l**, **3.6q**), piperidine (**3.6k**–**3.6q**), diazepane (**3.6r**), guanidine (**3.6r**), and piperazine (**3.6s**). The acidic *α*-carbonyl C–H bond of **3.6k**–**3.6m** were deuterated (*α*-carbonyl C–H of **3.8l** lost labeling after purification). In bupivacaine **3.8n**, the cyclic *β*-amino C–H bond had a higher deuteration rate compared to the acyclic *β*-amino C–H bond (90% at [C5] vs 14% at [C2]'). No deuteration at [C3] of **3.8n** was observed since the formation of the corresponding iminium ion was not favored. With paroxetine derivative **3.6o** and **3.6p**, deuteration did not take place at [C3]. Meanwhile, *N*-Bzh paroxetine **3.8p** had higher deuteration efficiency at [C5] than *N*-Bn paroxetine **3.8o** (92% vs 76%), showing that a more hindered benzhydryl group is a better N-protecting group for paroxetine. *β*-Amino C–H bond of *O*-TBS raloxifene **3.6q** was deuterated by 29% and 97%. With emedastine **3.6r**, *β*-amino C–H bonds of tertiary amine were deuterated by 33% and 61%. The piperazine ring of *O*-TBS dropropizine **3.6s** underwent C–H and C–D bond exchange and resulted in 86% and 93% deuterium incorporation. The sterically more hindered site of *O*-TBS dropropizine **3.6s** was not labeled (0% at [C2]').



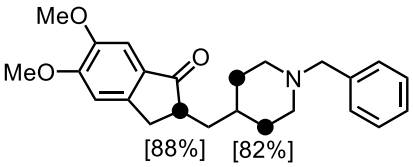
3.6 + **3.7** → **3.8**



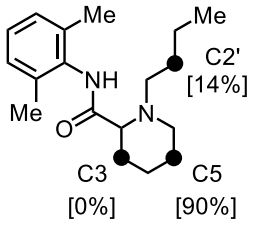
3.8k, clopidogrel (antiaggregant)
94% yield[c]



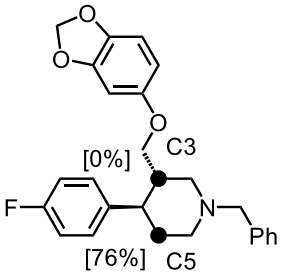
3.8l, prasugrel (antiaggregant)
85% yield[d]



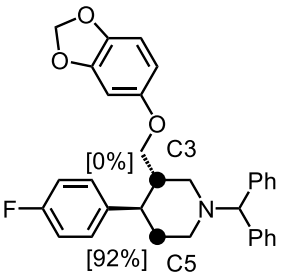
3.8m, donepezil (anti-Alzheimer)
>95% yield



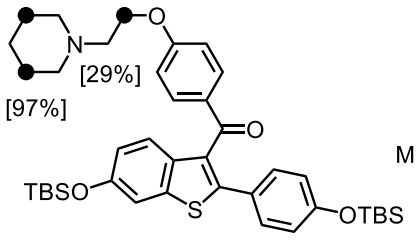
3.8n, bupivacaine (local anesthetic)
>95% yield



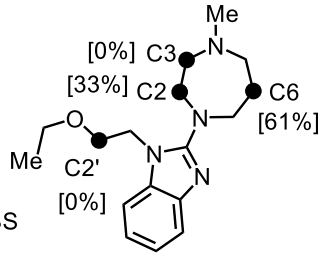
3.8o, *N*-Bn paroxetine
>95% yield



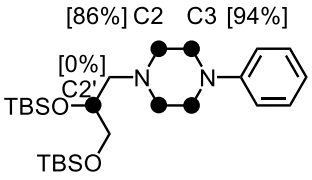
3.8p, *N*-Bzh paroxetine
95% yield



3.8q, *O*-TBS raloxifene
>95% yield



3.8r, emedastine (antihistamine)
88% yield

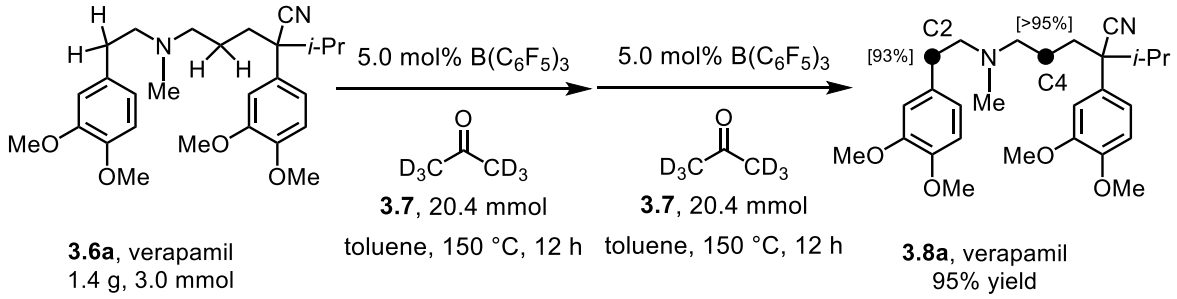


3.8s, *O*-TBS dropropizine
94% yield[c]

[a]Conditions: *N*-alkylamine (**3.6**, 0.2 mmol), acetone-d_6 (**3.7**, 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 products. Deuterium incorporation level was determined by 1H NMR analysis of the isolated and purified product. [c]Conditions: *N*-alkylamine (**3.6**, 0.2 mmol), acetone-d_6 (**3.7**, 1.36 mmol), $B(C_6F_5)_3$ (5.0 mol%), toluene (0.8 mL), under N_2, 150 °C, 3 h. After filtration of the crude reaction mixture through a pad of silica gel and removal of volatiles, acetone-d_6 (2, 1.36 mmol), $B(C_6F_5)_3$ (5.0 mol%), and toluene (1.0 mL) were added under N_2, and then heated at 150 °C, 3 h. [d]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 Cyclic *β*-Amino C–H Bonds [a,b,c,d]

We also found that the method for *β*-amino C–H bonds deuteration is readily scalable. When 1.4 g (3.0 mmol) of verapamil **3.6a** was treated with two batches of 5.0 mol% $B(C_6F_5)_3$, 20.4 mmol acetone-d_6, **3.8a** was obtained in 95% yield with >93% deuterium incorporation (Scheme 3.3).



Scheme 3.3 Gram-Scale *β*-Amino C–H Deuteration

3.4 Conclusion

We have achieved regioselective deuterium labeling of metabolically stable *β*-amino C–H bonds in bioactive amines and their derivatives without using precious transition metal-based catalyst. It is feasible to achieve both conversion of N-containing pharmaceuticals into corresponding enamines and the generation of a deuterating agent in situ from acetone-d_6 through the cooperative Lewis acidic $B(C_6F_5)_3$ and Brønsted basic *N*-alkylamine catalysts system. The generation of an enamine from its corresponding *N*-alkylamine, and the reaction between the enamine and in situ generated electrophile provides a method for late-stage functionalization of *N*-alkylamine containing bioactive molecules.

3.5 Experimental Data

3.5.1 General Information

This work was in cooperation with Yejin Chang, Ahmet Yesilcimen, Min Cao, Yuyang Zhang and Jessica Chan. My work was focused on the preparation of amine substrates when the protecting group was necessary and isolation as well as characterization of some deuterated product.

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.[86] 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.

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[86] (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.

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 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 ^{1}H 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

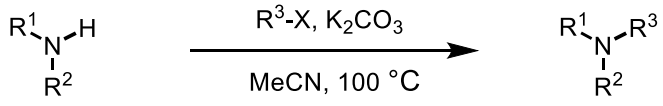
calculated as the sum of the relative signal intensities of a given isotopologue multiplied with the corresponding m/z values derived from the mass spectrum.

3.5.2 Experimental Procedures and Characterization Data

General Procedure for the Free-Basing Amine Salts[86a]

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.

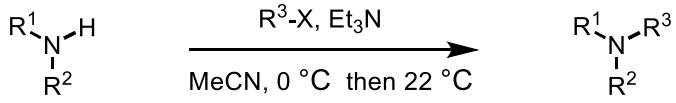
General Procedure A for the Alkylation of Amines[86c]



amine **3.6h**–3.**6i**, **3.6o**

Amines **3.6h**, **3.6i** and **3.6o** 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.

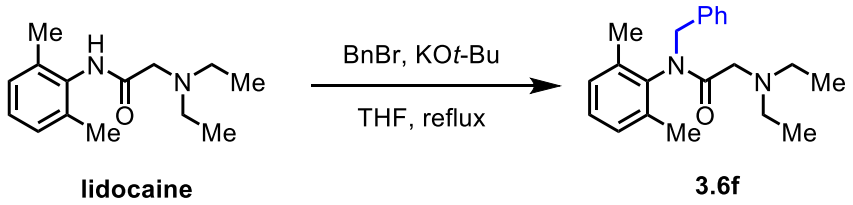
General Procedure B for the Alkylation of Amines[86d]



amine **3.6j**, **3.6p**

Amines **3.6j** and **3.6p** 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.

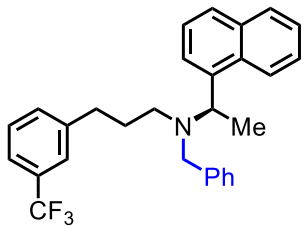


lidocaine **3.6f**

***N*-Bn lidocaine (3.6f)**

N-Bn lidocaine was prepared following a known procedure.[86b] 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 **3.6f** as a yellow liquid (2.5 g, 60%).

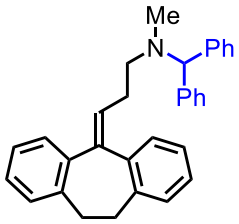
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 – 7.16 (m, 5H), 7.12 (d, J = 7.5 Hz, 1H), 7.04 (d, J = 7.5 Hz, 2H), 4.73 (s, 2H), 2.80 (s, 2H), 2.57 (q, J = 7.1 Hz, 4H), 1.87 (s, 6H), 0.91 (t, J = 7.1 Hz, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 170.64, 138.99, 137.10, 136.31, 130.16, 128.92, 128.18, 127.97, 127.49, 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 (3.6h)**

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 **3.6h** 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 (t, 2H), 2.33 (d, *J* = 14.0 Hz, 1H), 2.26 (d, *J* = 13.9 Hz, 1H), 1.66 – 1.57 (m, 2H), 1.53 (d, *J* = 6.8 Hz, 3H); **^{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, 123.19, 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}.

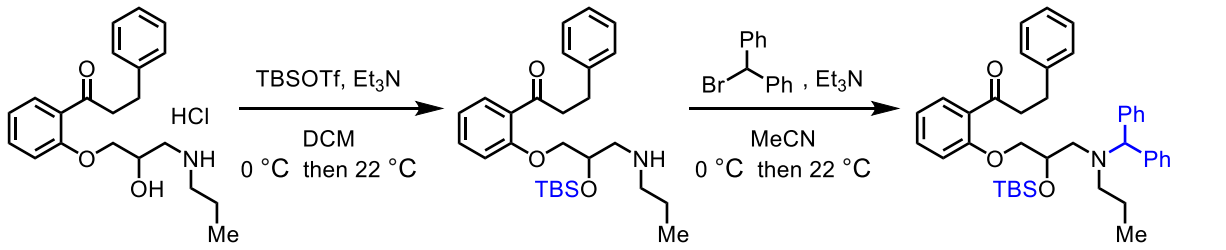


_N_-Bzh nortriptyline (3.6i)

N-Bzh nortriptyline 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 **3.6i** 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,

137.93, 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}.



propafenone HCl ***O*-TBS propafenone** **3.6j**, *N*-Bzh, *O*-TBS propafenone

***O*-TBS propafenone**

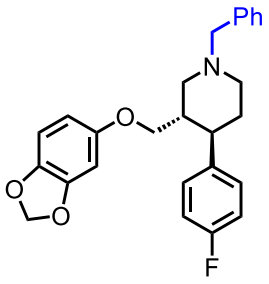
O-TBS propafenone was prepared following the known procedure[86e]. To a solution of propafenone HCl (2.0 g, 5.29 mmol) in DCM at 0 °C, imidazole (5.0 equiv.) was added, followed by the dropwise addition of TBSCl (1.3 equiv.). After the addition, the reaction mixture was allowed to warm to 22 °C and stirred 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 (3.6j)**

N-Bzh, *O*-TBS 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 **3.6j** 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 (dd, *J* = 25.5, 8.1 Hz, 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 (m, *J* = 6.0 Hz, 2H), 1.43 (m, *J* = 7.4 Hz, 2H),

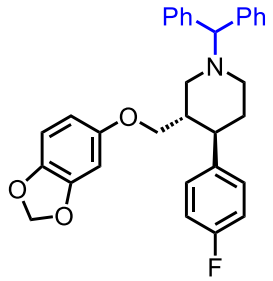
0.79 (s, 9H), 0.71 (t, J = 7.3 Hz, 3H), -0.06 (s, 3H), -0.09 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 201.22, 158.19, 142.06, 141.67, 141.51, 133.30, 130.45, 128.78, 128.68, 128.44, 128.26, 128.21, 128.15, 128.12, 126.91, 126.88, 125.68, 120.47, 112.33, 71.18, 70.47, 69.93, 54.23, 54.02, 45.40, 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 (3.6o)

_N_-Bn paroxetine 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 **3.6o** as a white solid (2.9 g, 84%).

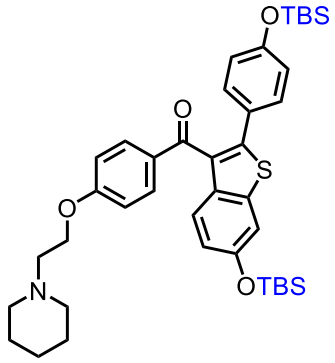
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 4H), 7.25 (s, 1H), 7.16 (dd, J = 8.6, 5.5 Hz, 2H), 6.96 (t, J = 8.7 Hz, 2H), 6.61 (d, J = 8.4 Hz, 1H), 6.31 (d, J = 2.5 Hz, 1H), 6.10 (dd, J = 8.5, 2.5 Hz, 1H), 5.87 (s, 2H), 3.64 (d, J = 13.1 Hz, 1H), 3.59 – 3.50 (m, 2H), 3.44 (d, J = 6.9 Hz, 1H), 3.25 – 3.22 (m, 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 (3.6p)

_N_-Bzh paroxetine 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 **3.6p** as a white solid (3.5 g, 86%).

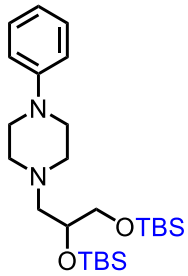
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.35 (m, 4H), 7.28 (t, J = 7.5 Hz, 4H), 7.17 (dt, J = 8.5, 6.4 Hz, 4H), 6.96 (t, J = 8.6 Hz, 2H), 6.57 (d, J = 8.5 Hz, 1H), 6.21 (d, J = 2.5 Hz, 1H), 6.01 (dd, J = 8.5, 2.5 Hz, 1H), 5.85 (d, J = 0.9 Hz, 2H), 4.37 (s, 1H), 3.50 (dd, J = 9.5, 2.9 Hz, 1H), 3.38 (dd, 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 (3.6q)

O-TBS raloxifene was prepared following the known procedure[86e]. 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 **3.6q** 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}.



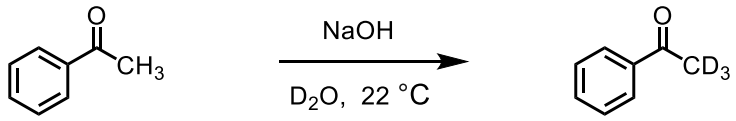
_O_-TBS dropropizine (3.6s)

O-TBS dropropizine was prepared following the known procedure.[86f] 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 **3.6s** 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 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.06 (s, 3H); **^{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

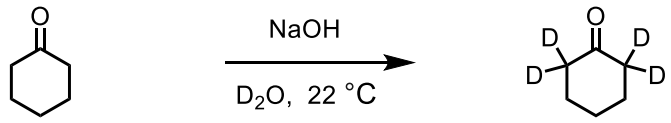


acetophenone **acetophenone-d_3**

Acetophenone-d_3

Acetophenone-d_3 was synthesized following the known procedure.[87] 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[87].

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

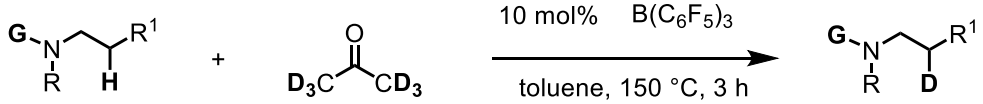


cyclohexanone **cyclohexa-1-one-2,2,6,6,-d_4**

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

Cyclohexan-1-one-2,2,6,6-d_4 was synthesized following the known procedure.[87] 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.[88]

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

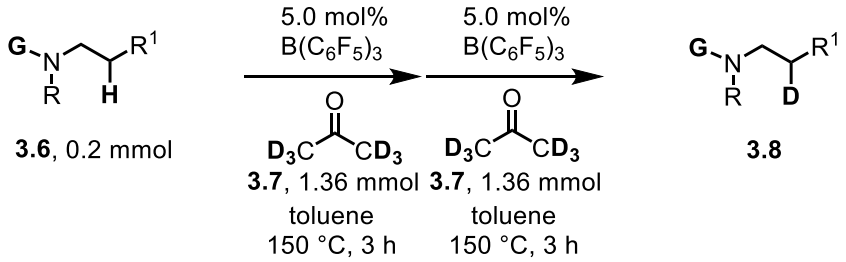


3.6, 0.2 mmol **3.7**, 1.36 mmol **3.8**

To a 15 mL oven-dried pressure vessel was added amine **3.6** (0.2 mmol), $B(C_6F_5)_3$ (10 mol%), toluene (0.8 mL), and acetone-d_6 92 (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.

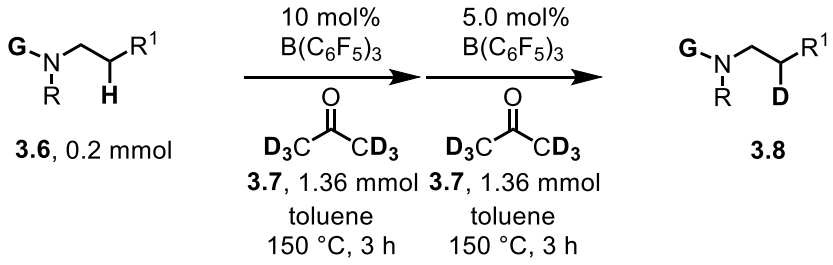
General Procedure B for the *β*-Deuteration of *N*-Alkylamines

[88] 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.



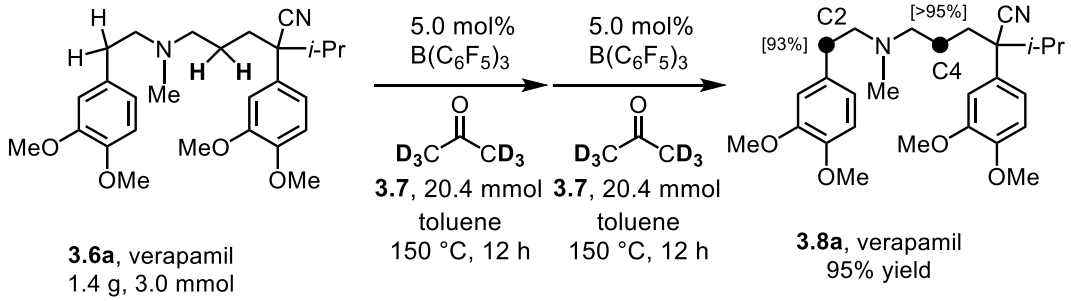
To a 15 mL oven-dried pressure vessel was added amine **3.6** (0.2 mmol), $B(C_6F_5)_3$ (5.0 mol%), toluene (0.8 mL), and acetone-d_6 **3.7** (1.36 mmol, 6.8 equiv.) under a nitrogen atmosphere. The reaction mixture was allowed to stir for 3 hours at 150 °C. After the purification by silica gel column chromatography and removal of volatiles, $B(C_6F_5)_3$ (5.0 mol%), toluene (0.8 mL), and acetone-d_6 **3.7** (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



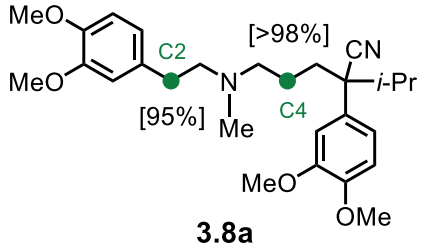
To a 15 mL oven-dried pressure vessel was added amine **3.6** (0.2 mmol), $B(C_6F_5)_3$ (10 mol%), toluene (0.8 mL), and acetone-d_6 **3.7** (1.36 mmol, 6.8 equiv.) under a nitrogen atmosphere. The reaction mixture was allowed to stir for 3 hours at 150 °C. After the purification by silica gel column chromatography and removal of volatiles, $B(C_6F_5)_3$ (5.0 mol%), toluene (0.8 mL), and acetone-d_6 **3.7** (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 **3.6** (3.0 mmol), $B(C_6F_5)_3$ (5.0 mol%), toluene (12 mL), and acetone-d_6 **3.7** (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 **7** (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 **3.8a** as a yellow liquid (1.29 g, 95%).

3.5.3 Analytical Data and NMR Spectral Data



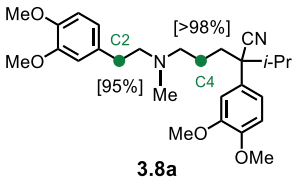
3.8a

Verapamil, 3.8a

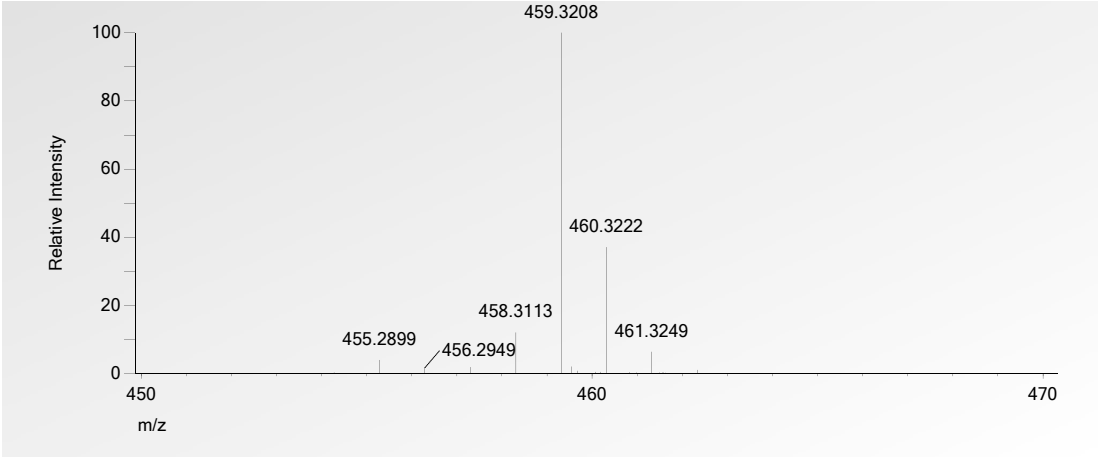
Verapamil **3.6a** was reacted with acetone-d_6 **3.7** following the General Procedure B. After purification by column chromatography (MeOH:DCM = 1:49), **3.8a** was obtained as a yellow liquid (84 mg, 92%).

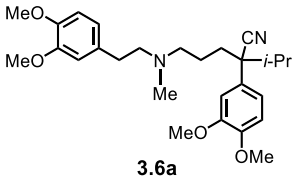
Deuterium incorporation: 3.86 D/molecule (^{1}H NMR), 4.11 D/molecule [HRMS (DART)]

^{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}.

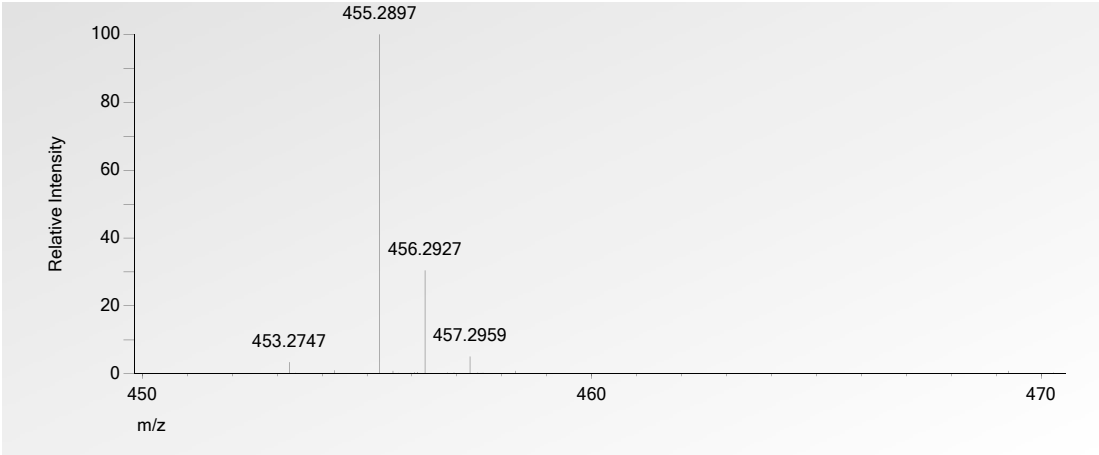

MeO
MeO
C2
[95%]
N
Me
[>98%]
C4
CN
i-Pr
MeO
OMe

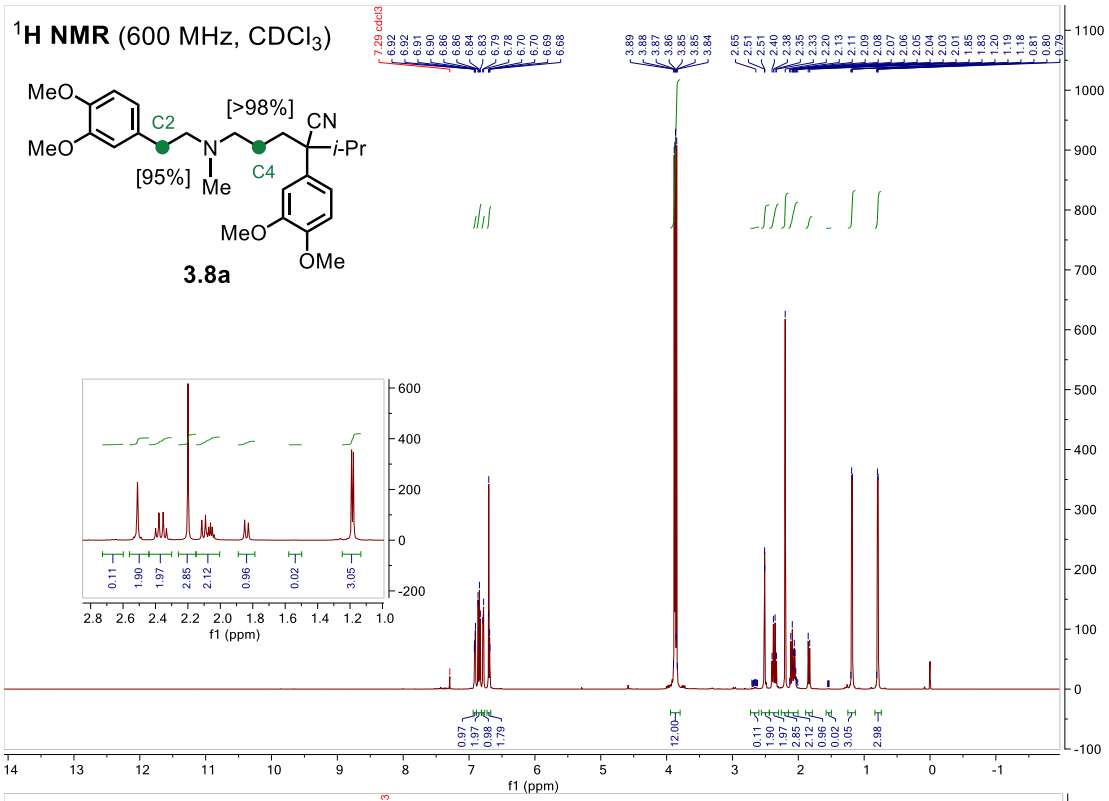
3.8a

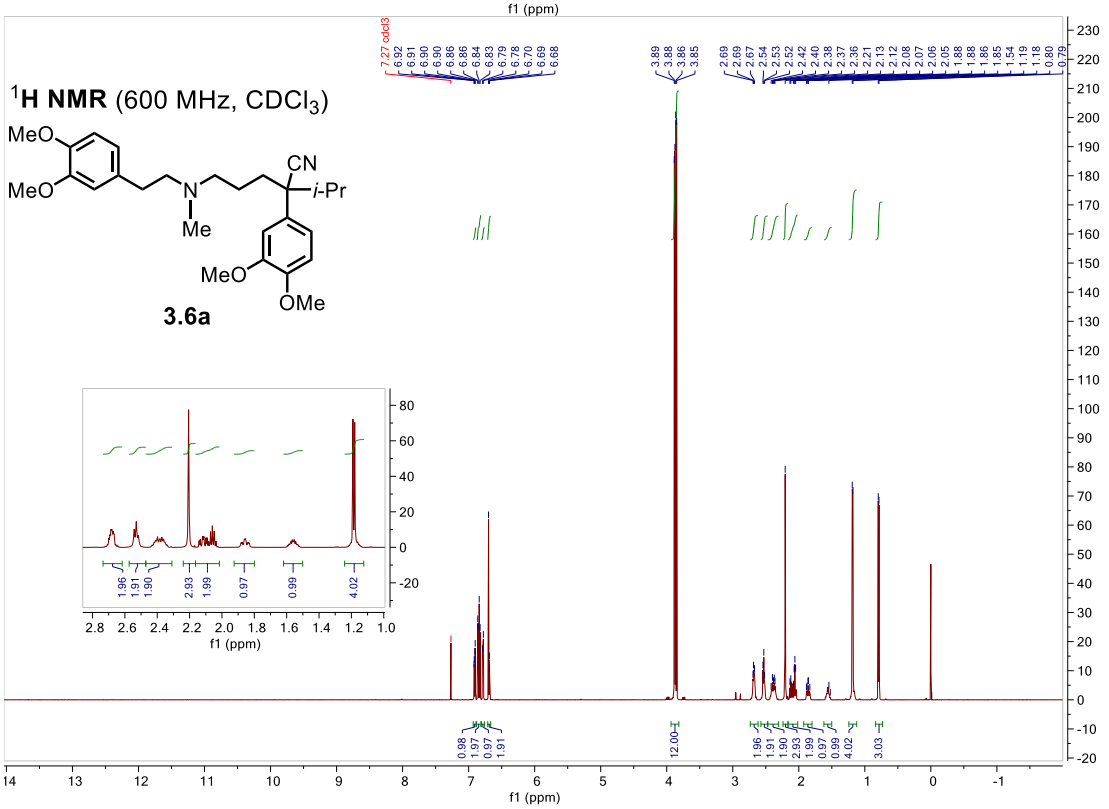

459.3208
100
80
60
40
20
0
Relative Intensity
460.3222
458.3113
461.3249
455.2899
456.2949
450
460
470
m/z

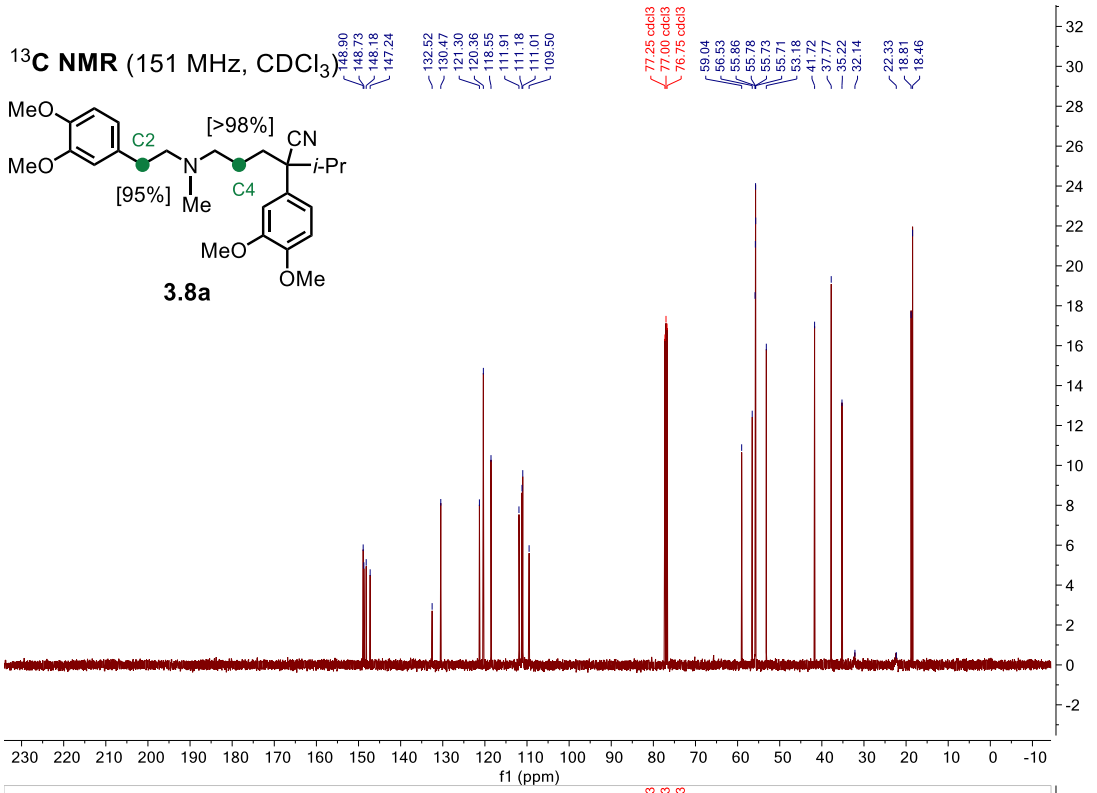

MeO
MeO
N
Me
CN
i-Pr
MeO
OMe

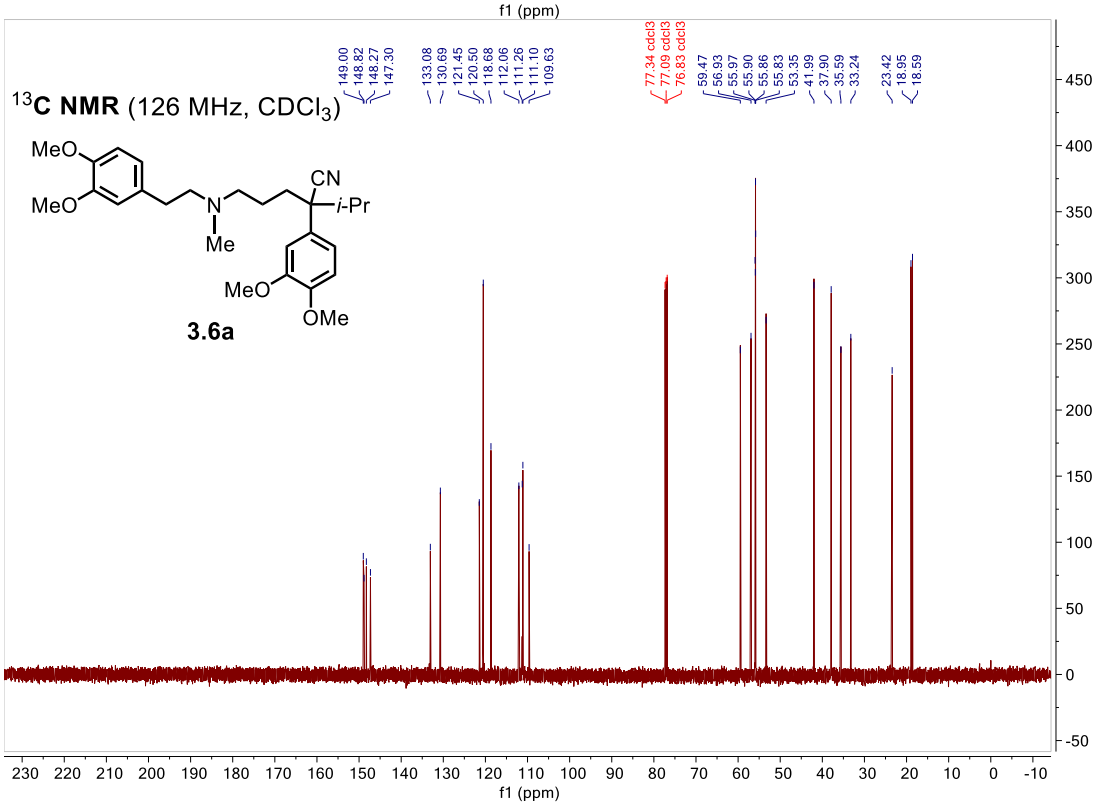
3.6a

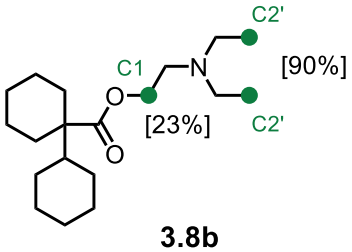

455.2897
100
80
60
40
20
0
Relative Intensity
456.2927
453.2747
457.2959
450
460
470
m/z


^{1}H NMR (600 MHz, $CDCl_3$)
MeO
MeO
C2
[95%]
N
Me
[>98%]
CN
i-Pr
C4
MeO
OMe
3.8a
f1 (ppm)


^{1}H NMR (600 MHz, $CDCl_3$)
MeO
MeO
N
Me
CN
i-Pr
MeO
OMe
3.6a
f1 (ppm)


13C NMR (151 MHz, CDCl3)
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
MeO
MeO
C2
[95%]
N
Me
[>98%]
C4
CN
i-Pr
MeO
OMe
3.8a
f1 (ppm)


13C NMR (126 MHz, CDCl3)
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
55.90
55.86
55.83
53.35
41.99
37.90
35.59
33.24
23.42
18.95
18.59
MeO
MeO
N
Me
CN
i-Pr
MeO
OMe
3.6a
f1 (ppm)



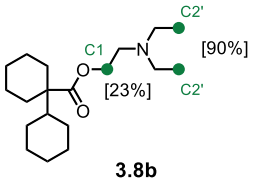
3.8b

Dicyclomine, 3.8b

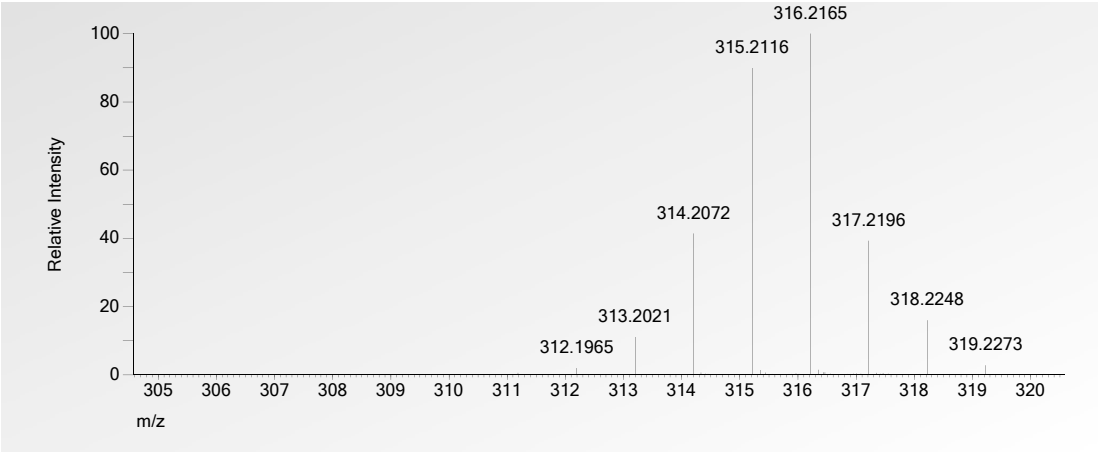
Dicyclomine **3.6b** was reacted with acetone-d_6 **3.7** following the General Procedure A. After purification by column chromatography (MeOH:DCM = 1:49), **3.8b** was obtained as a colorless liquid (60 mg, 97%).

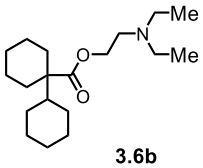
Deuterium incorporation: 5.86 D/molecule (^{1}H NMR), 5.50 D/molecule [HRMS (DART)]

^{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, 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}.

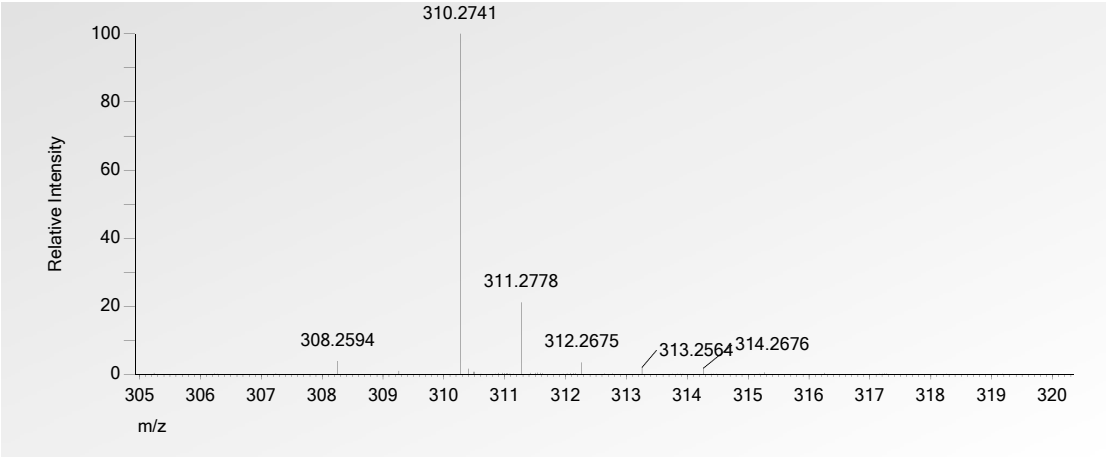

C2'
C1
N
[90%]
O
[23%]
C2'
O

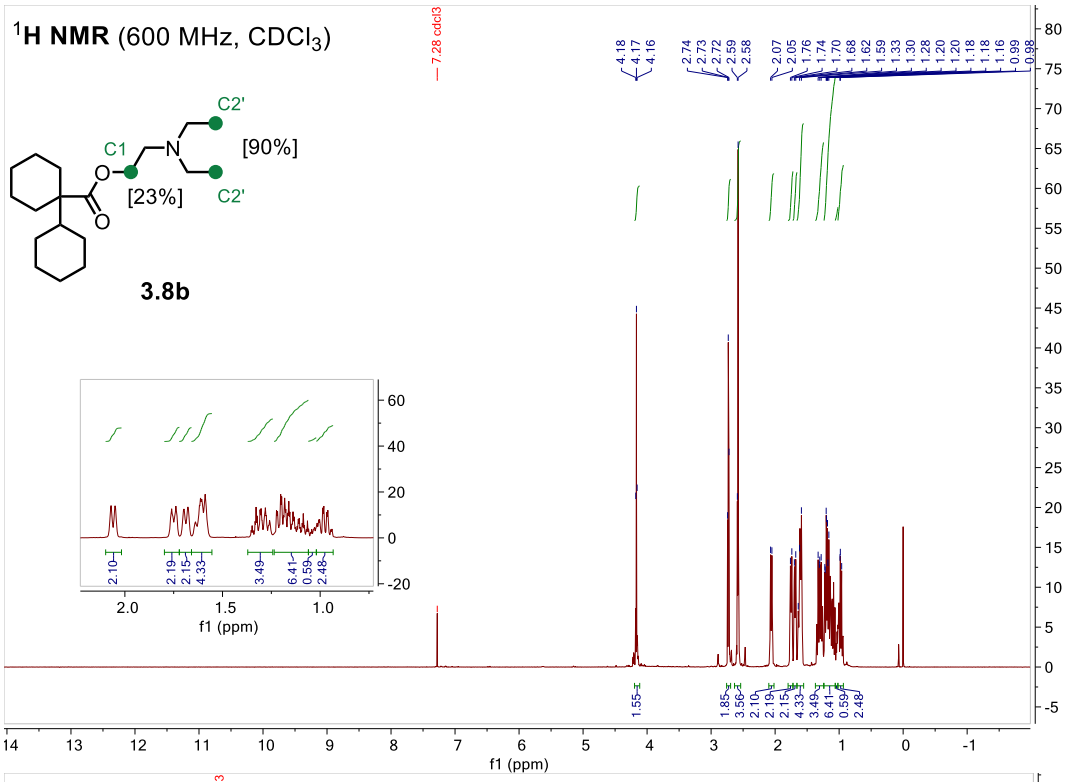
3.8b

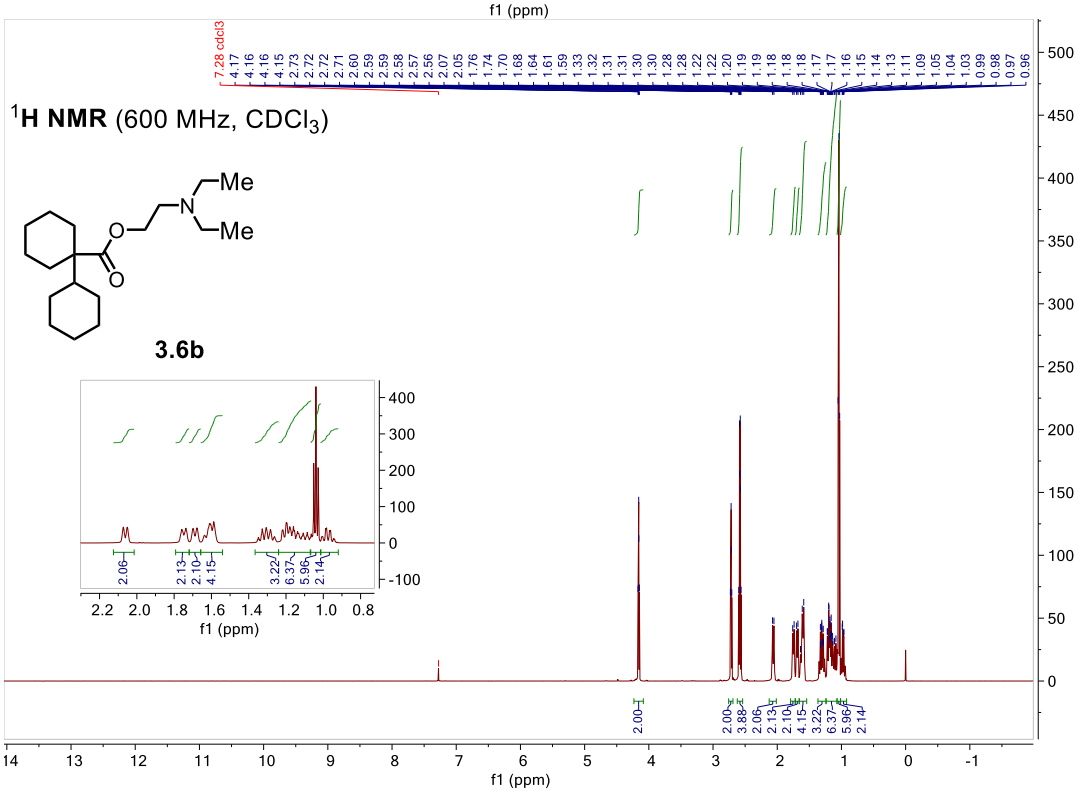

316.2165
315.2116
314.2072
317.2196
318.2248
313.2021
312.1965
319.2273
Relative Intensity
m/z

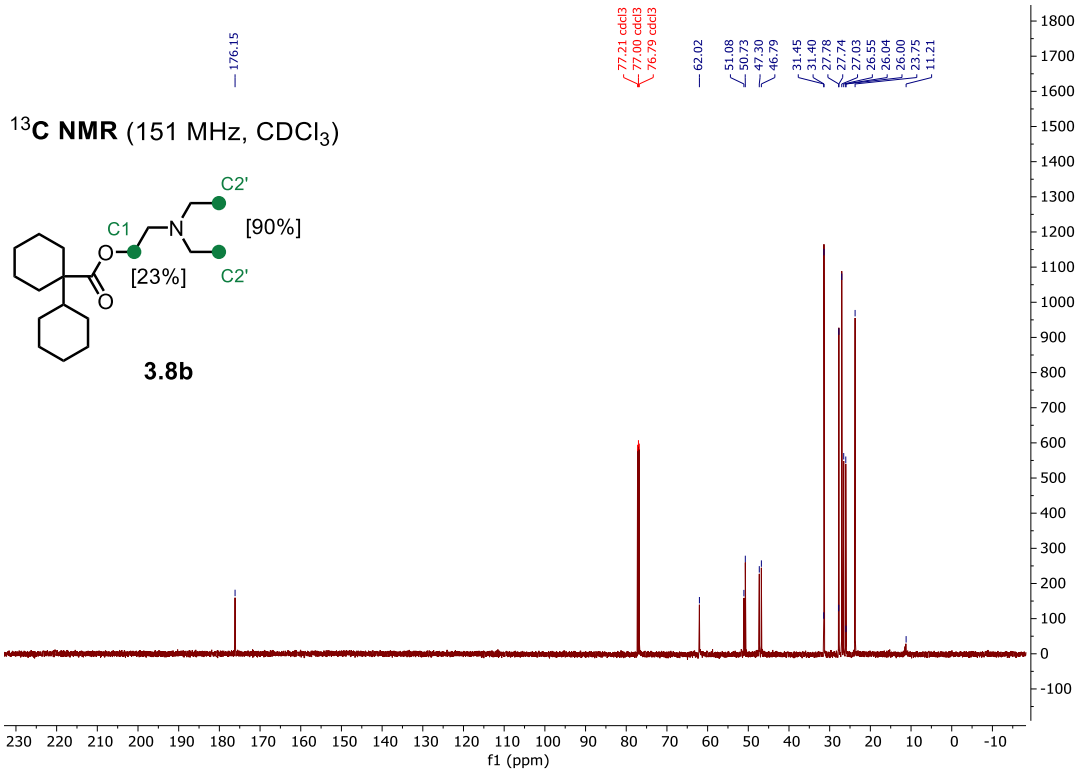

Me
N
Me
O
O

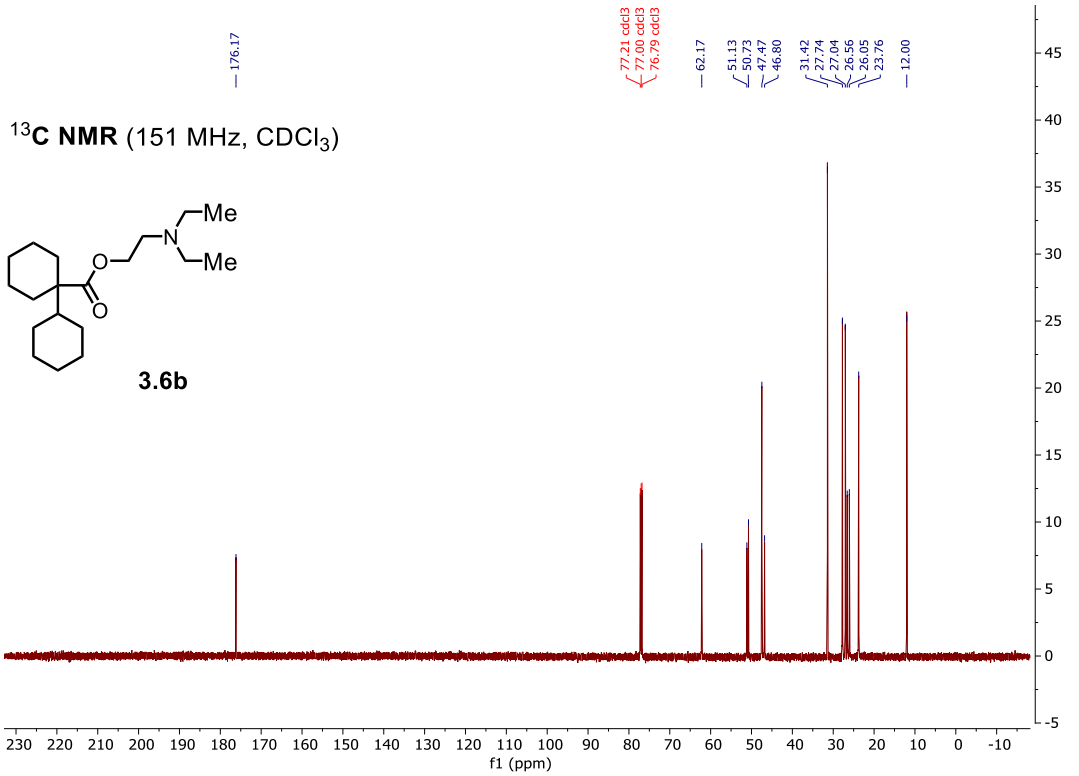
3.6b

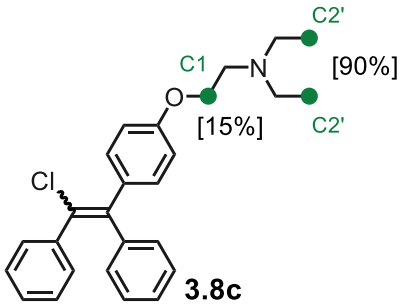

310.2741
311.2778
308.2594
312.2675
313.2564
314.2676
Relative Intensity
m/z


^{1}H NMR (600 MHz, $CDCl_3$)
C2'
C1
N
[90%]
O
[23%]
C2'
O
3.8b
f1 (ppm)


^{1}H NMR (600 MHz, $CDCl_3$)
Me
N
Me
O
O
3.6b
f1 (ppm)


176.15
77.21 cdcl3
77.00 cdcl3
76.79 cdcl3
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
13C NMR (151 MHz, CDCl3)
C2'
C1
N
[90%]
O
[23%]
C2'
O
3.8b
f1 (ppm)


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
13C NMR (151 MHz, CDCl3)
Me
N
Me
O
O
3.6b
f1 (ppm)



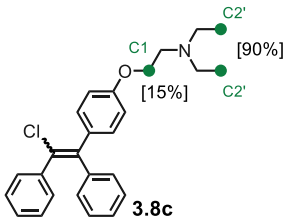
3.8c

Clomiphene, 3.8c

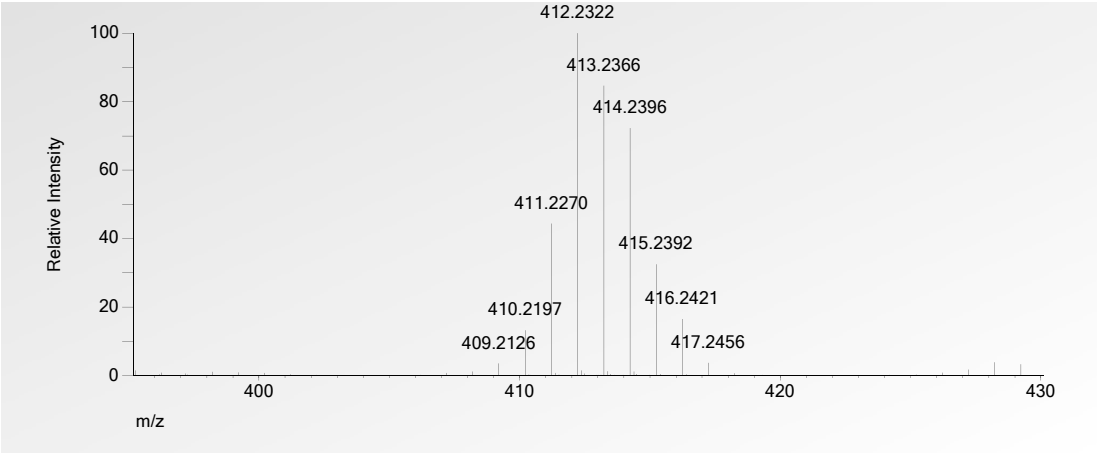
Clomiphene **3.6c** was reacted with acetone-d_6 **3.7** following the General Procedure A. After purification by column chromatography (MeOH:DCM = 1:19), **3.8c** was obtained as a colorless liquid (78 mg, 96%).

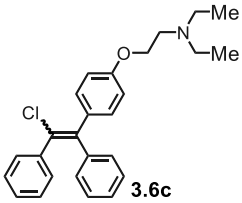
Deuterium incorporation: 5.70 D/molecule (^{1}H NMR), 6.89 D/molecule [HRMS (DART)]

^{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}.

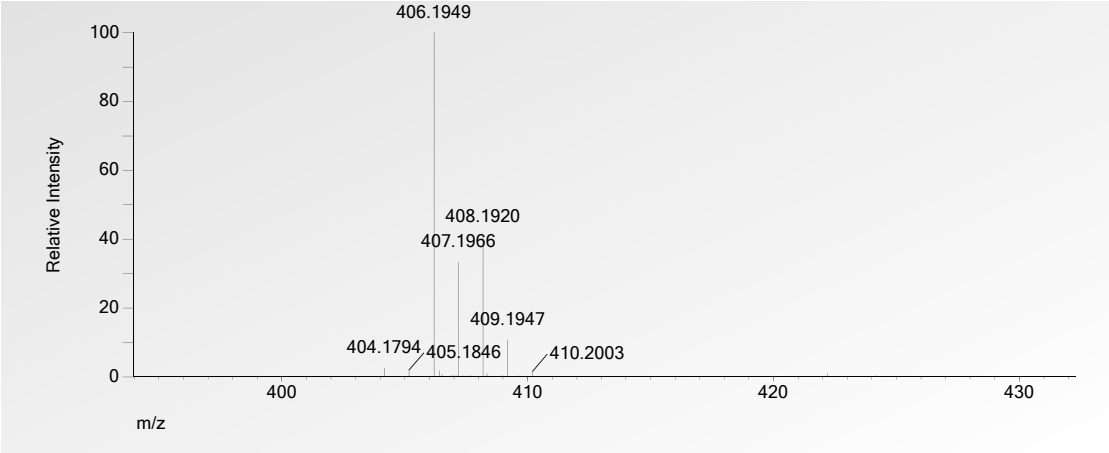

C2'
C1
N
[90%]
O
[15%]
C2'
Cl

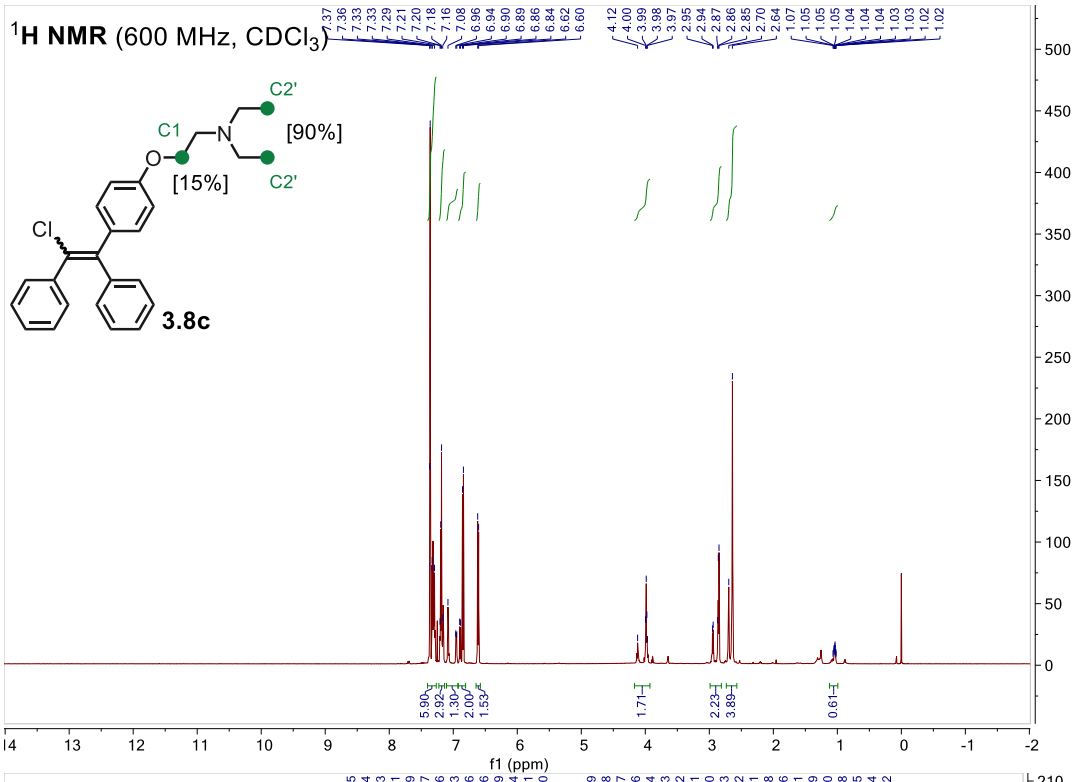
3.8c

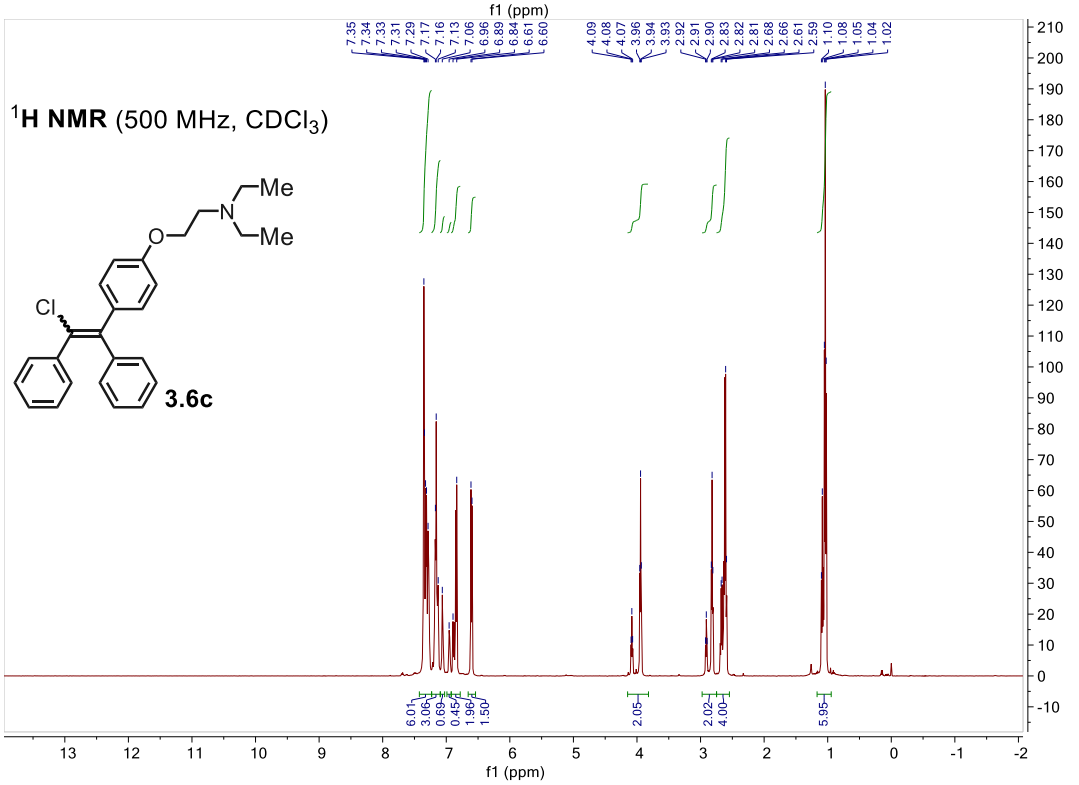

412.2322
413.2366
414.2396
411.2270
415.2392
416.2421
410.2197
409.2126
417.2456
100
80
60
40
20
0
Relative Intensity
400
410
420
430
m/z

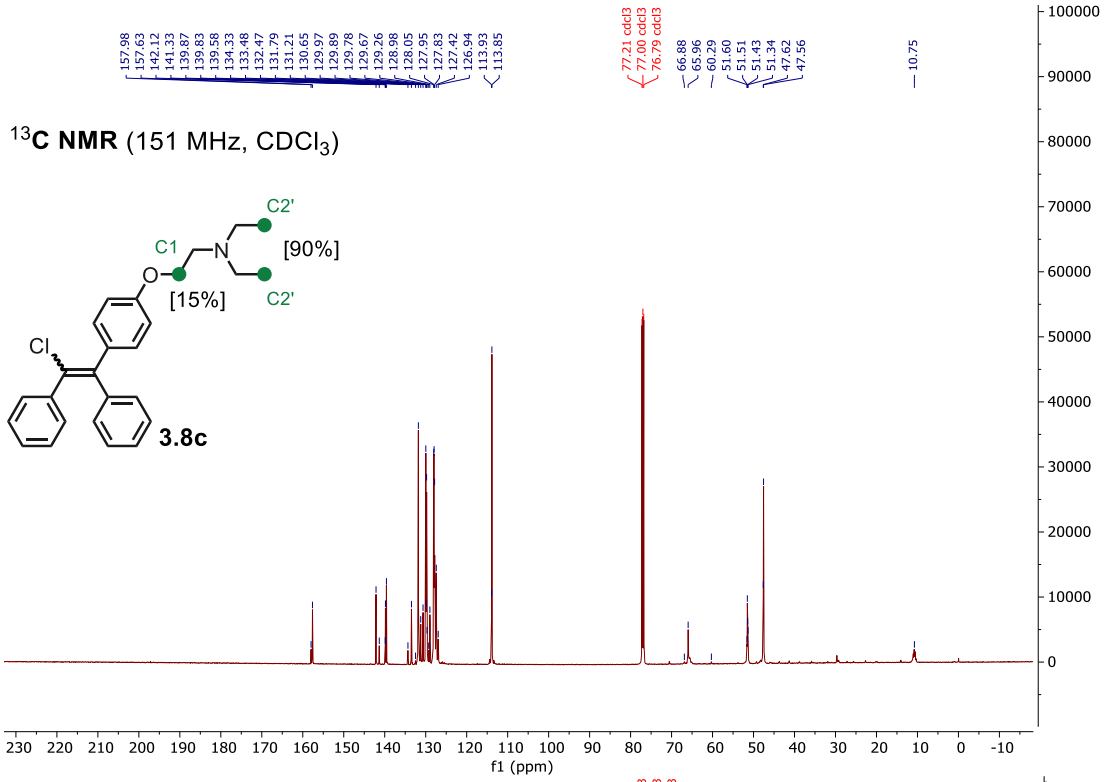

Me
N
Me
O
Cl

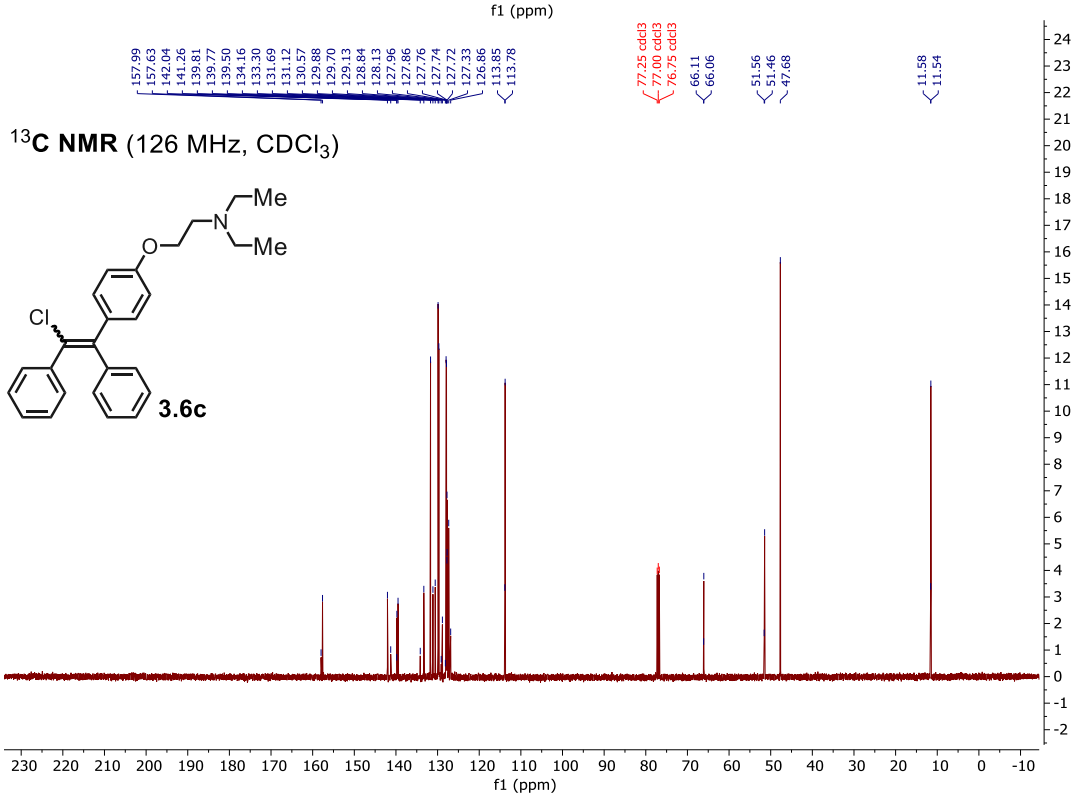
3.6c

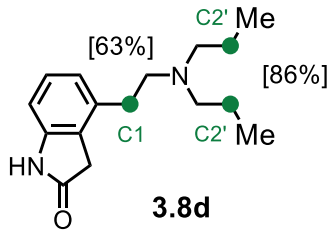

406.1949
408.1920
407.1966
409.1947
404.1794
405.1846
410.2003
100
80
60
40
20
0
Relative Intensity
400
410
420
430
m/z


1H NMR (600 MHz, CDCl3)
C2'
C1
N
[90%]
O
[15%]
C2'
Cl
3.8c
f1 (ppm)


1H NMR (500 MHz, CDCl3)
Me
N
Me
O
Cl
3.6c
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'
C1
N
[90%]
O
[15%]
C2'
Cl
3.8c
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
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
Cl
3.6c
24
23
22
21
20
19
18
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



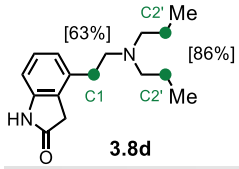
3.8d

Ropinirole, 3.8d

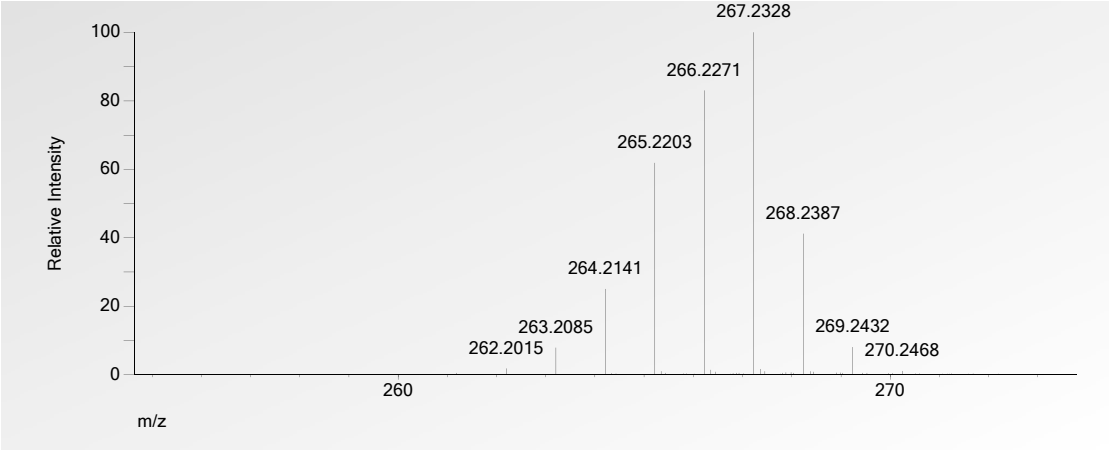
Ropinirole **3.6d** was reacted with acetone-d_6 **3.7** following the General Procedure C. After purification by column chromatography (MeOH:DCM = 1:24), **3.8d** was obtained as a white solid (40 mg, 77%).

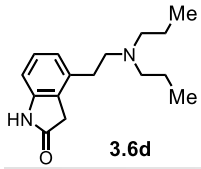
Deuterium incorporation: 4.70 D/molecule (^{1}H NMR), 5.24 D/molecule [HRMS (DART)]

^{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}.

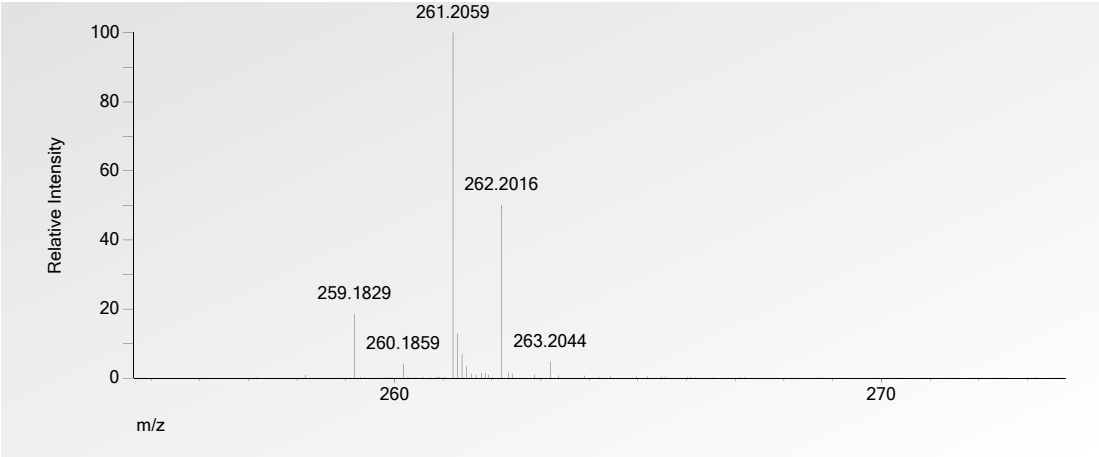

[63%]
C2' Me
N
[86%]
C1
C2' Me
HN
O

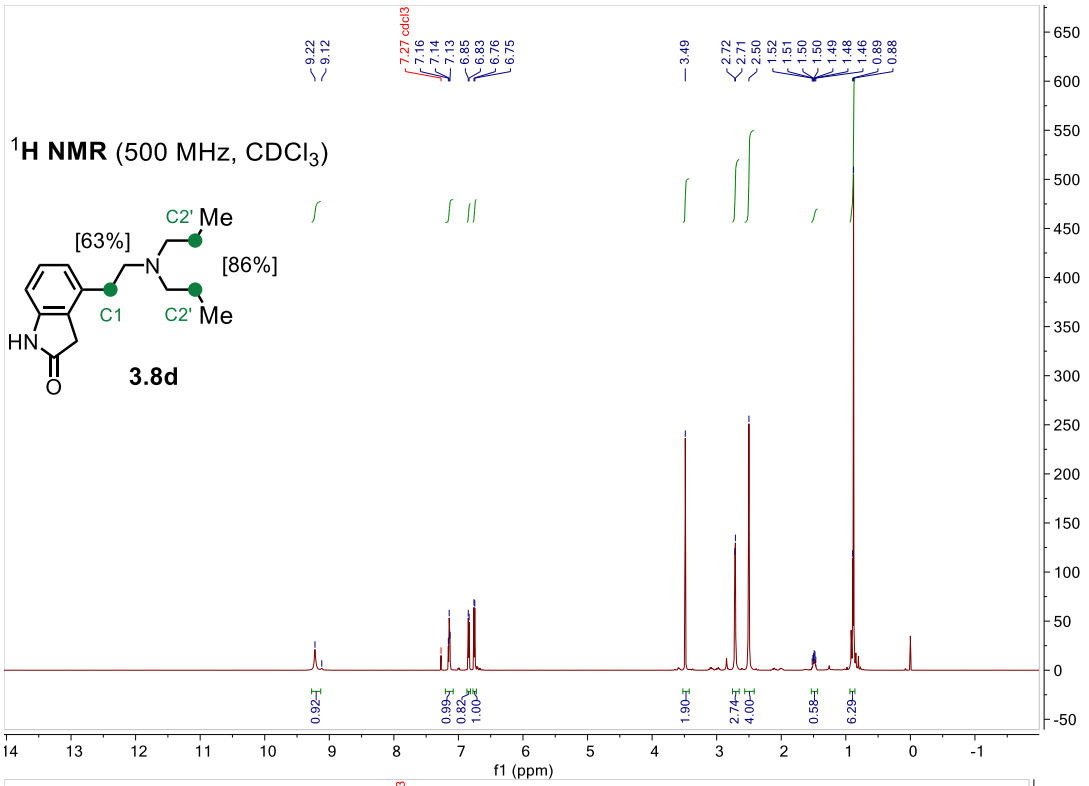
3.8d

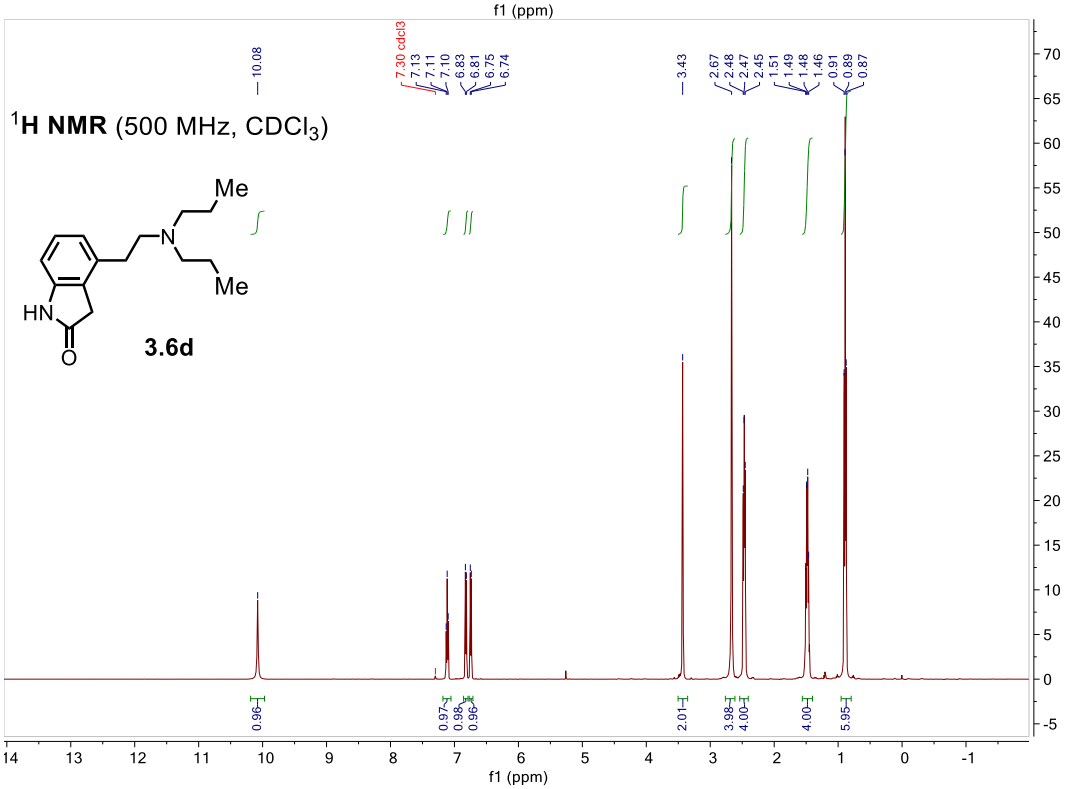

267.2328
266.2271
265.2203
268.2387
264.2141
263.2085
262.2015
269.2432
270.2468
100
80
60
40
20
0
Relative Intensity
260
270
m/z

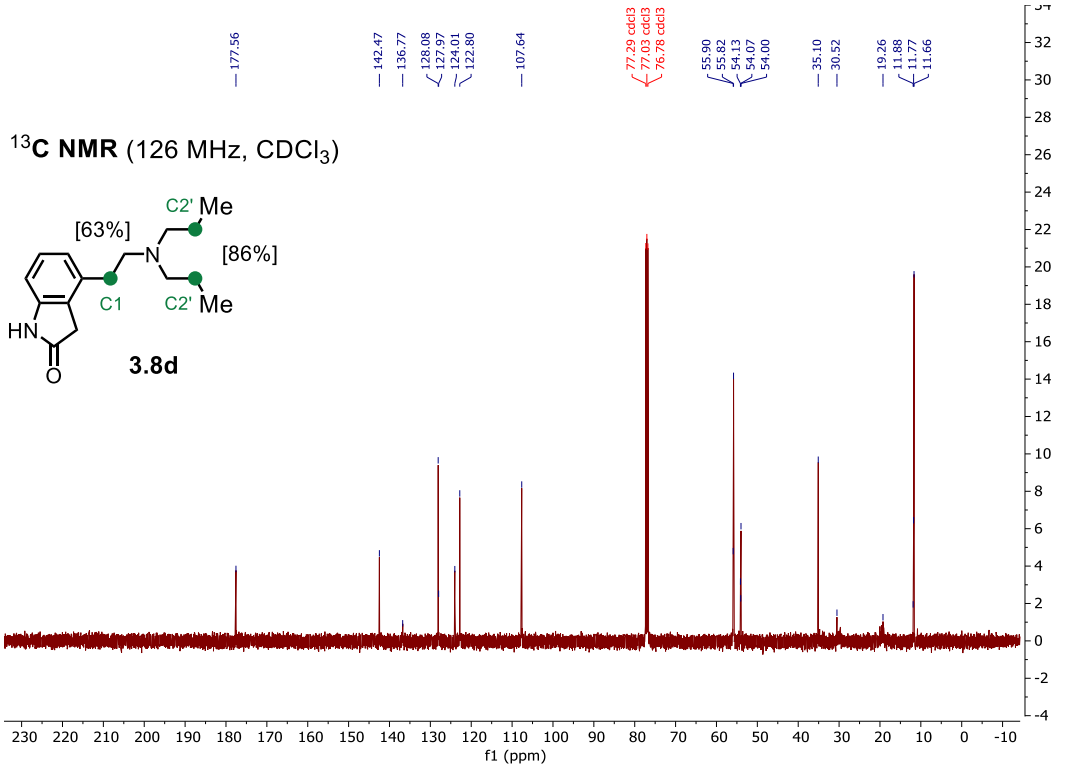

Me
N
Me
HN
O

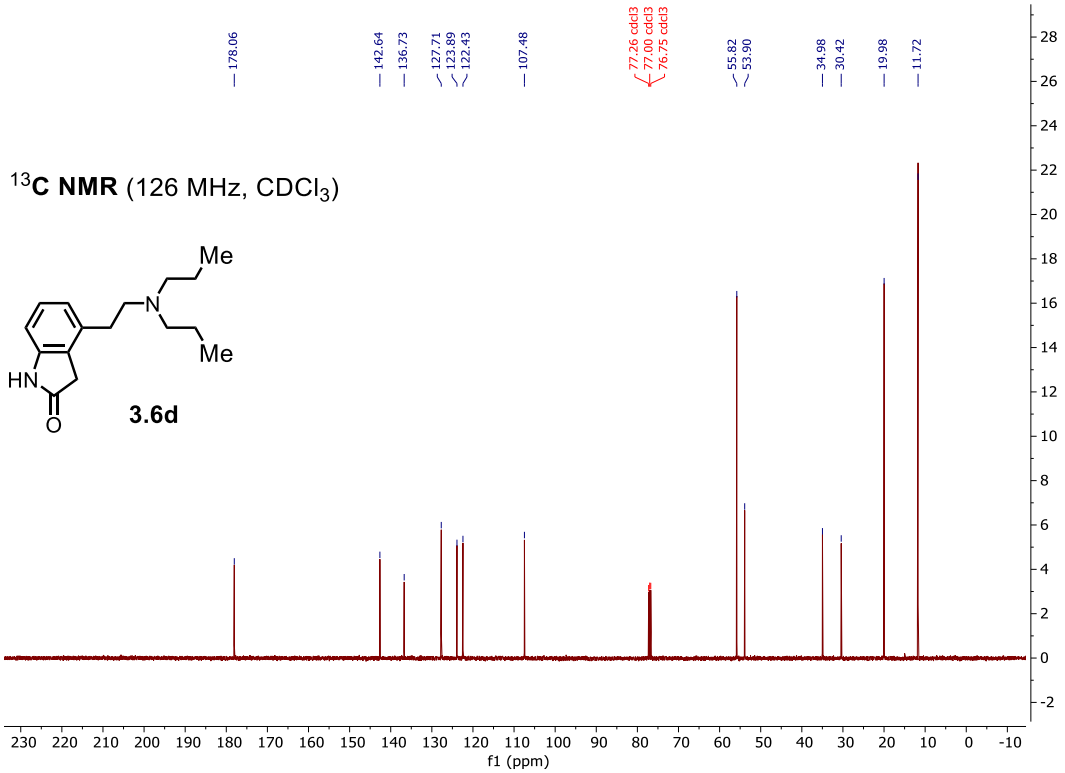
3.6d

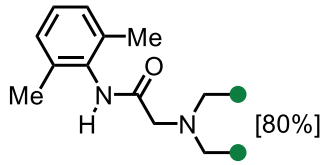

261.2059
262.2016
259.1829
260.1859
263.2044
100
80
60
40
20
0
Relative Intensity
260
270
m/z


^{1}H NMR (500 MHz, $CDCl_3$)
[63%]
[86%]
C1
C2' Me
C2' Me
HN
O
3.8d
f1 (ppm)


^{1}H NMR (500 MHz, $CDCl_3$)
Me
Me
HN
O
3.6d
f1 (ppm)


177.56
142.47
136.77
128.08
127.97
124.01
122.80
107.64
77.29 cdcl3
77.03 cdcl3
76.78 cdcl3
55.90
55.82
54.13
54.07
54.00
35.10
30.52
19.26
11.88
11.77
11.66
13C NMR (126 MHz, CDCl3)
[63%]
C2' Me
N
[86%]
C1
C2' Me
HN
O
3.8d
f1 (ppm)


178.06
142.64
136.73
127.71
123.89
122.43
107.48
77.26 cdcl3
77.00 cdcl3
76.75 cdcl3
55.82
53.90
34.98
30.42
19.98
11.72
13C NMR (126 MHz, CDCl3)
Me
N
Me
HN
O
3.6d
f1 (ppm)

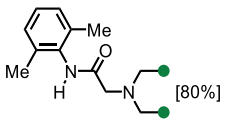


3.8e

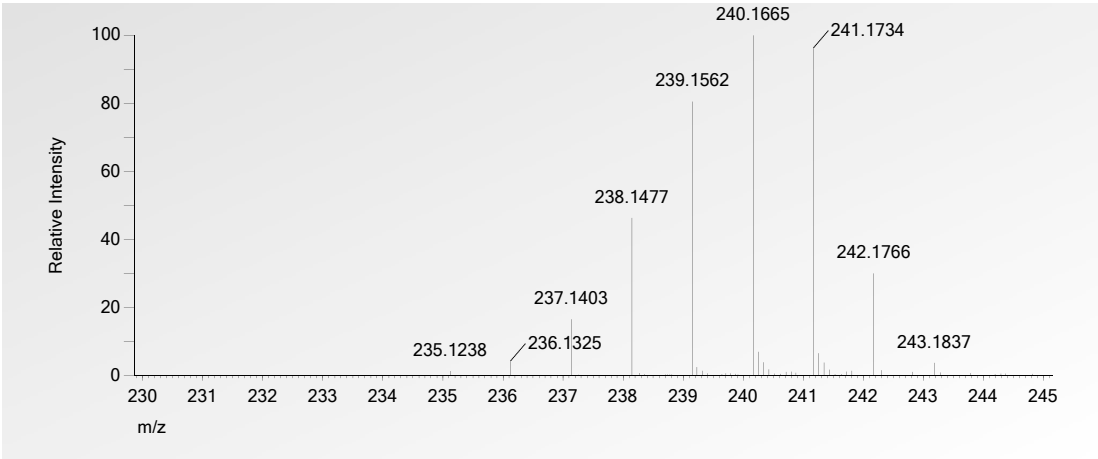
Lidocaine, 3.8e

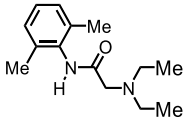
Lidocaine **3.6e** was reacted with acetone-d_6 **3.7** following the General Procedure A. After purification by column chromatography (MeOH:DCM = 1:49), **3.8e** was obtained as a white solid (46 mg, 99%).

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}.

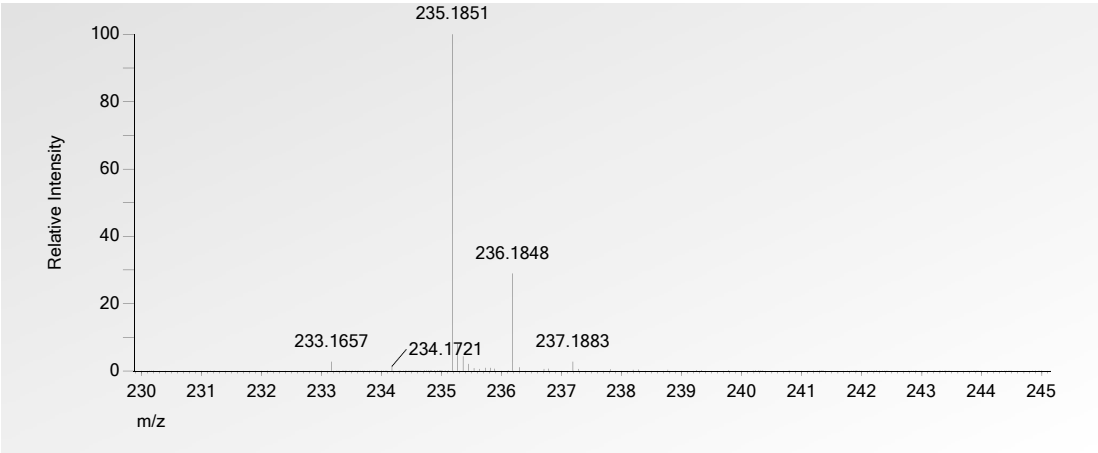

Me
Me
O
N
H
N
[80%]

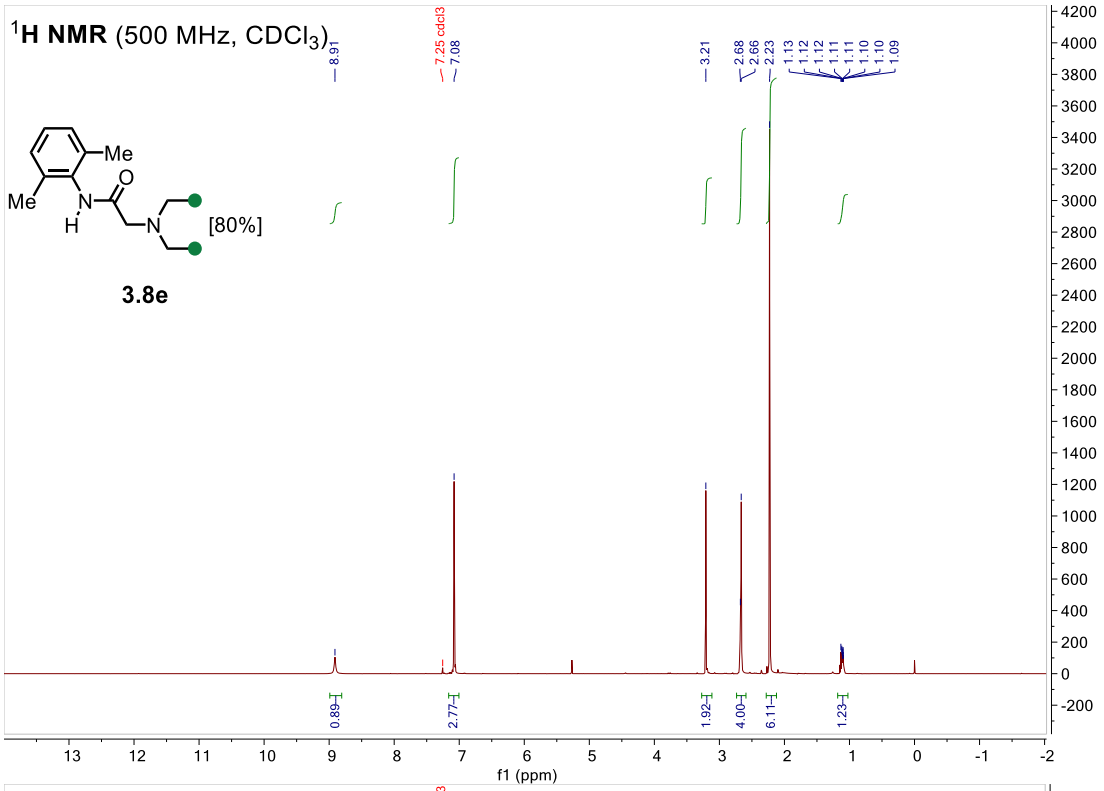
3.8e

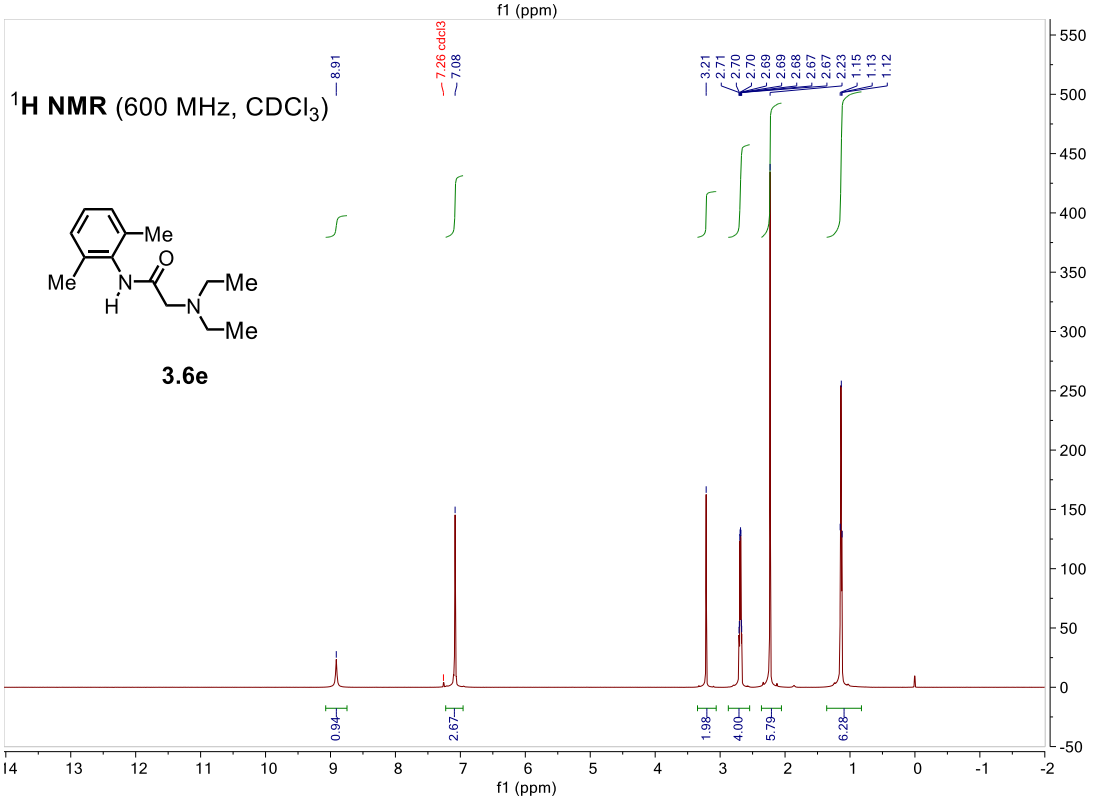

240.1665
241.1734
239.1562
238.1477
242.1766
237.1403
235.1238
236.1325
243.1837
100
80
60
40
20
0
Relative Intensity
230
231
232
233
234
235
236
237
238
239
240
241
242
243
244
245
m/z

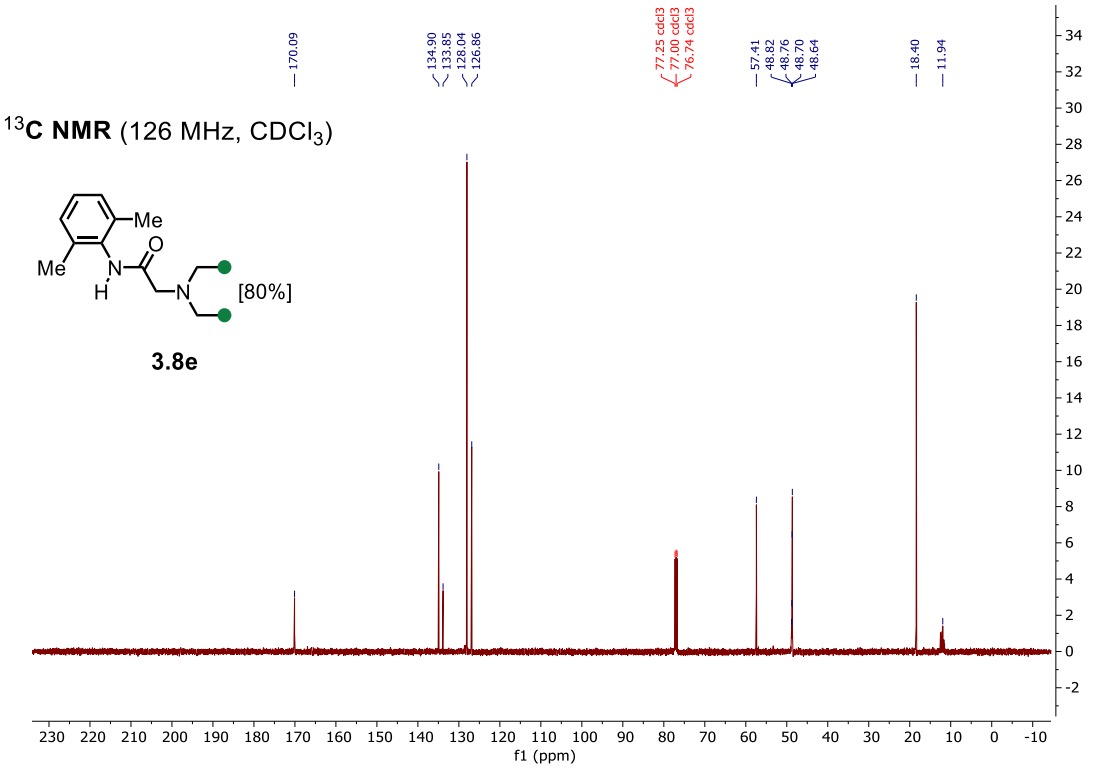

Me
Me
O
N
H
N
Me
Me

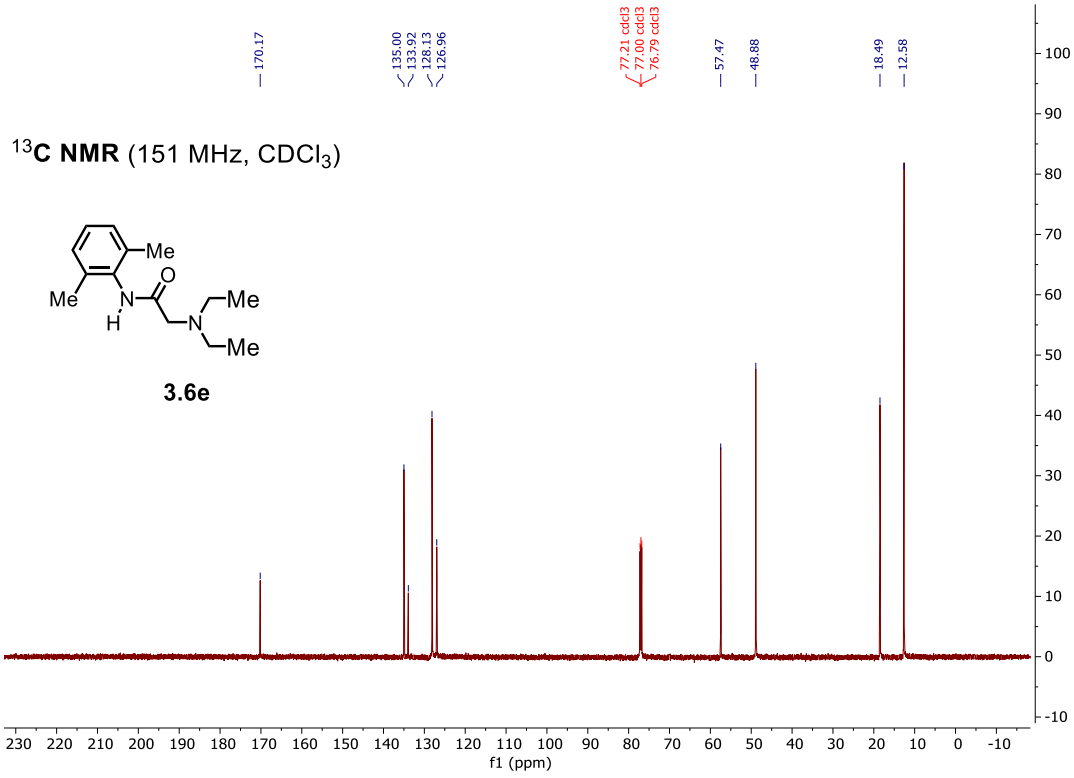
3.6e

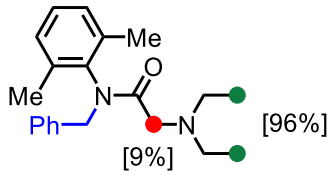

235.1851
236.1848
233.1657
234.1721
237.1883
100
80
60
40
20
0
Relative Intensity
230
231
232
233
234
235
236
237
238
239
240
241
242
243
244
245
m/z


1H NMR (500 MHz, CDCl3)
Me
Me
N
H
O
N
[80%]
3.8e
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)


1H NMR (600 MHz, CDCl3)
Me
Me
N
H
O
N
Me
Me
3.6e
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)


170.09
134.90
133.85
128.04
126.86
77.25 cdcl3
77.00 cdcl3
76.74 cdcl3
57.41
48.82
48.76
48.70
48.64
18.40
11.94
13C NMR (126 MHz, CDCl3)
Me
Me
O
N
H
N
[80%]
3.8e
f1 (ppm)


170.17
135.00
133.92
128.13
126.96
77.21 cdcl3
77.00 cdcl3
76.79 cdcl3
57.47
48.88
18.49
12.58
13C NMR (151 MHz, CDCl3)
Me
Me
O
N
H
N
Me
Me
3.6e
f1 (ppm)



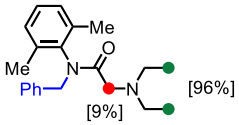
3.8f

***N*-Bn lidocaine, 3.8f**

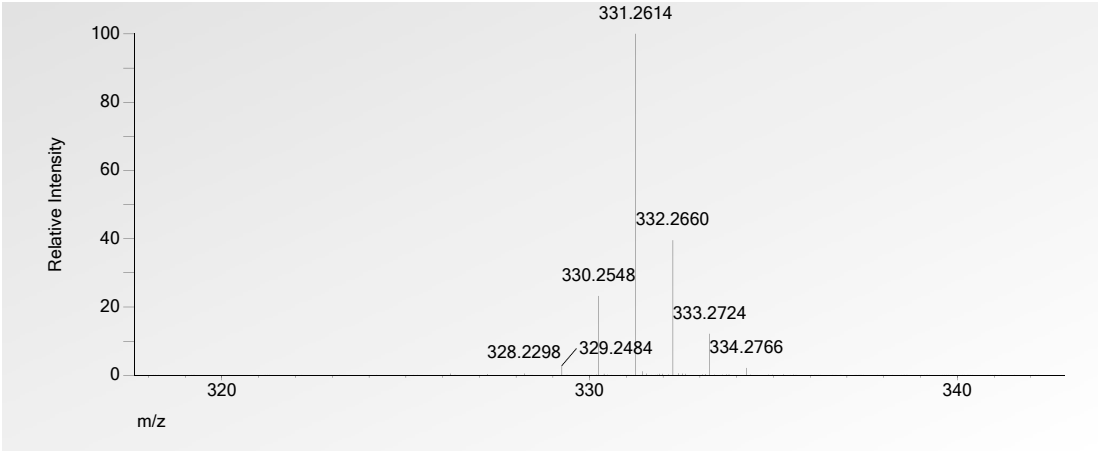
N-Bn lidocaine **3.6f** was reacted with acetone-d_6 **3.7** following the General Procedure B. After purification by column chromatography (MeOH:DCM = 1:49), **3.8f** was obtained as a yellow liquid (62 mg, 96%).

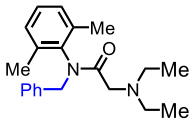
Deuterium incorporation: 6.18 D/molecule (^{1}H NMR), 6.26 D/molecule [HRMS (DART)]

^{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}.

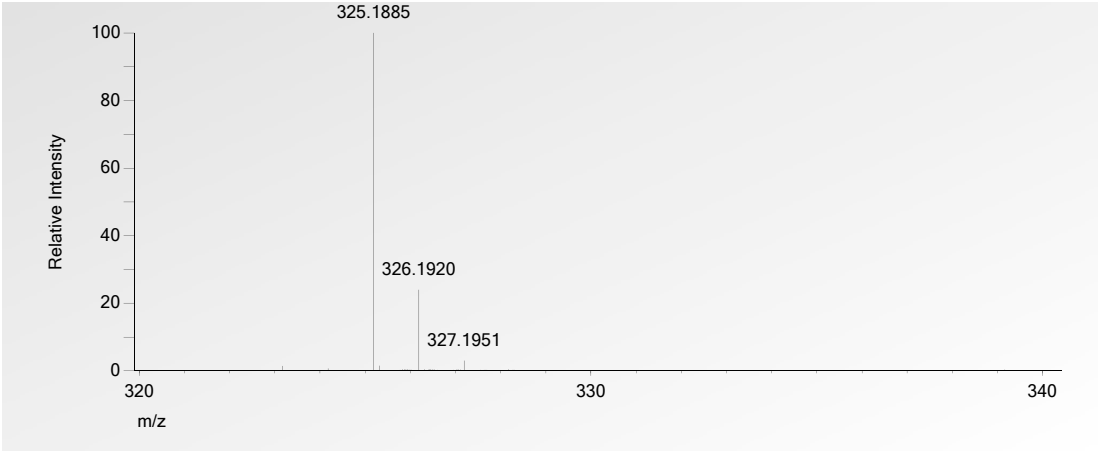

Me
Me
O
N
Ph
N
[96%]
[9%]

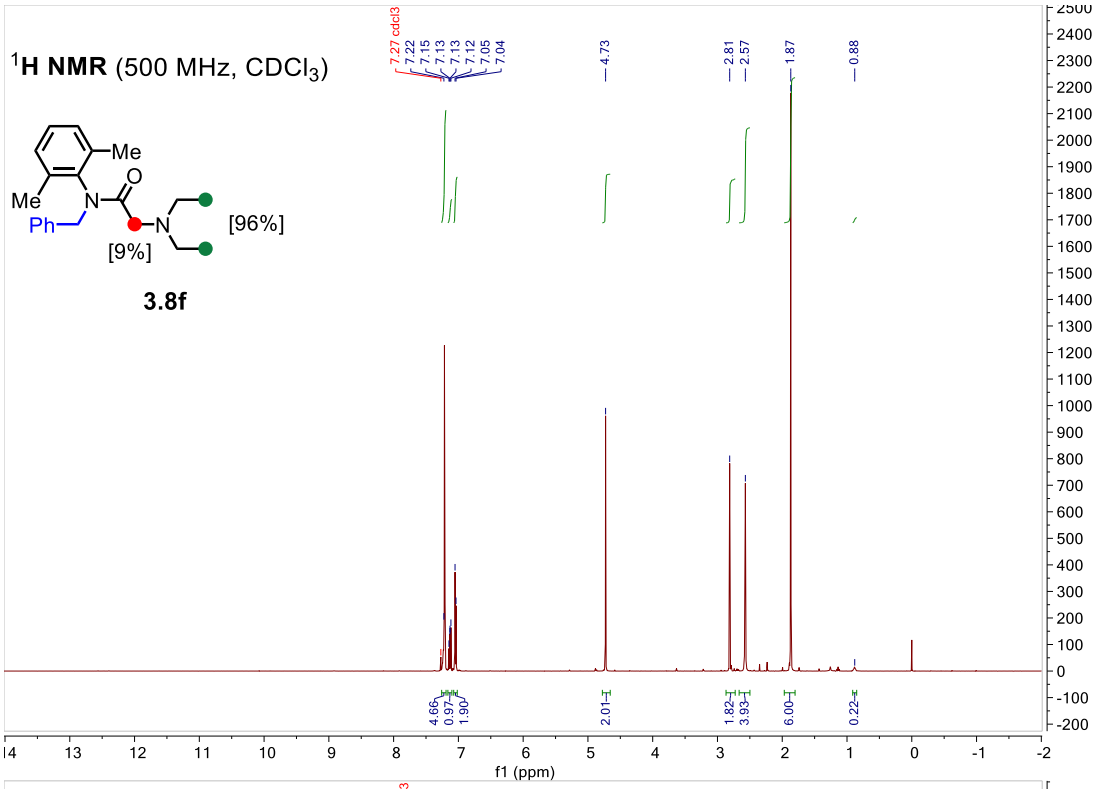
3.8f

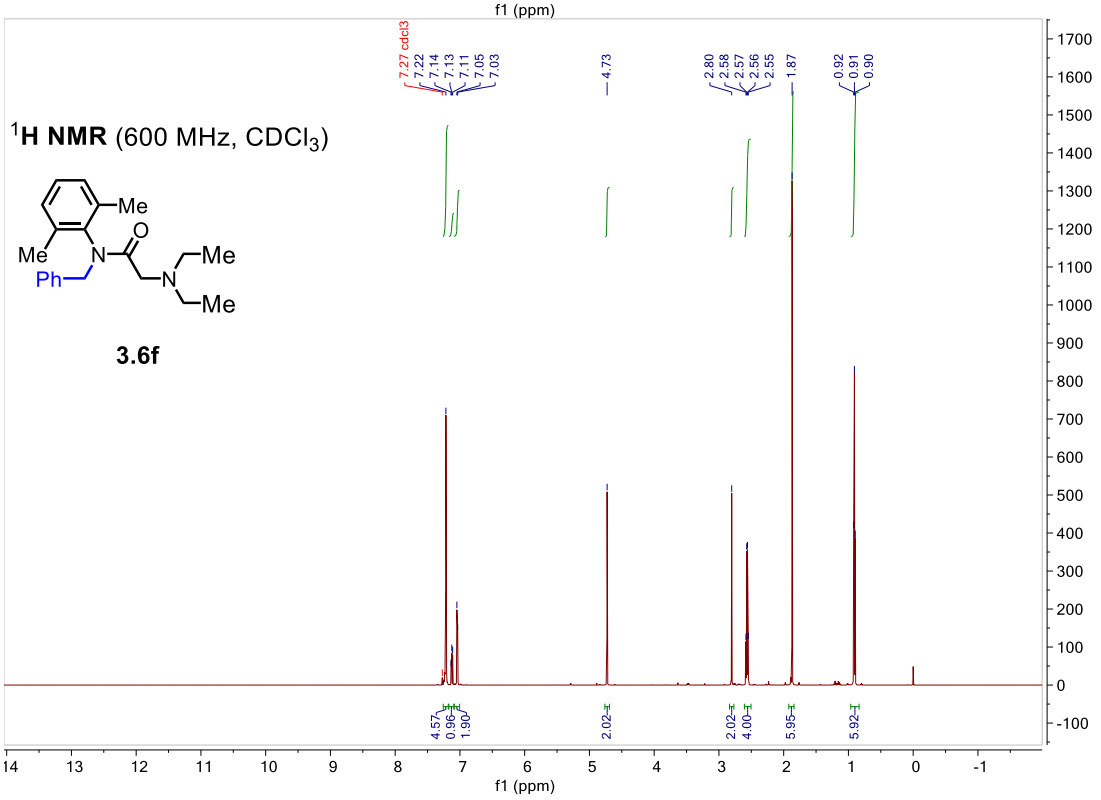

331.2614
100
80
60
40
20
0
Relative Intensity
332.2660
330.2548
333.2724
328.2298
329.2484
334.2766
320
330
340
m/z

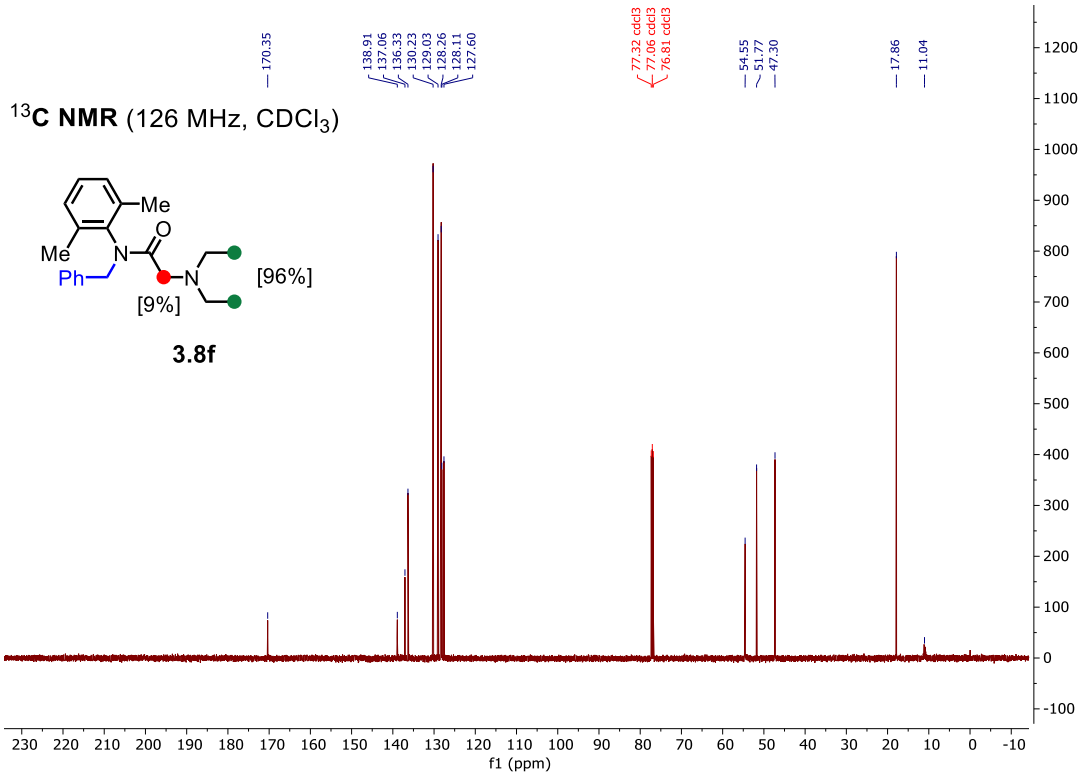

Me
Me
O
N
Ph
N
Me
Me

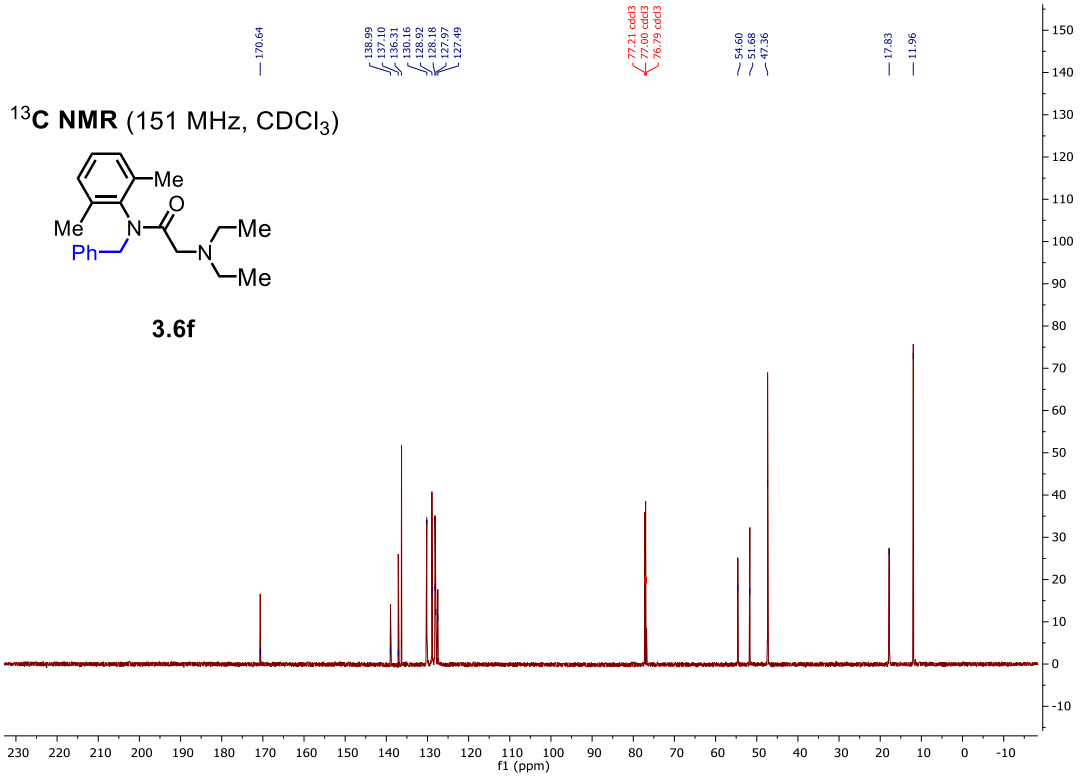
3.6f

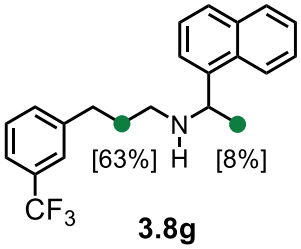

325.1885
100
80
60
40
20
0
Relative Intensity
326.1920
327.1951
320
330
340
m/z


1H NMR (500 MHz, CDCl3)
Me
Me
N
O
Ph
N
[96%]
[9%]
3.8f
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
Ph
N
Me
Me
3.6f
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
Ph
N
[96%]
[9%]
3.8f
f1 (ppm)


170.64
138.99
137.10
136.31
130.16
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
Ph
N
Me
Me
3.6f
f1 (ppm)

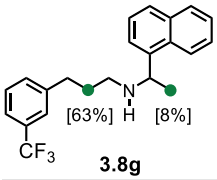


3.8g

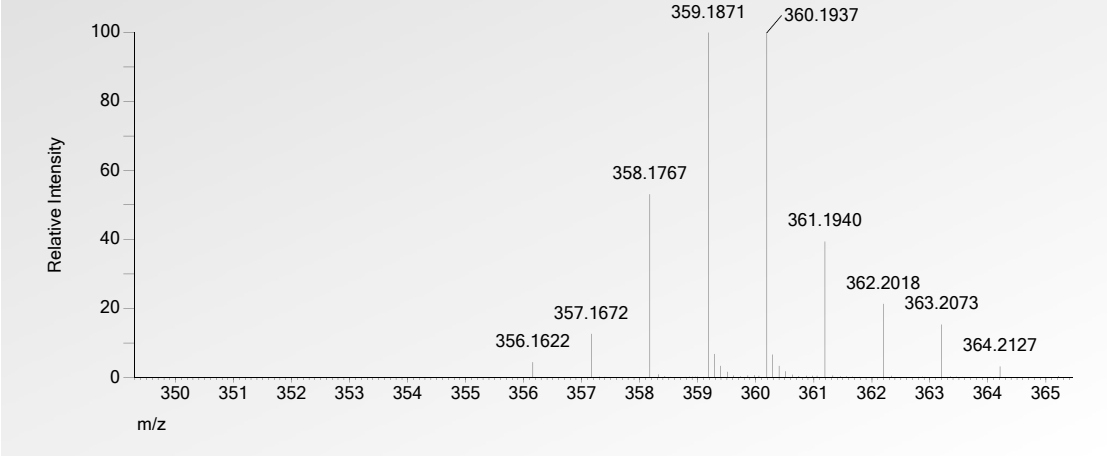
Cinacalcet, 3.8g

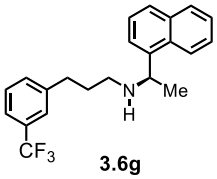
Cinacalcet **3.6g** was reacted with acetone-d_6 **3.7** following the General Procedure A. After purification by column chromatography (MeOH:DCM = 1:19), **3.8g** was obtained as a yellow liquid (69 mg, 97%).

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).

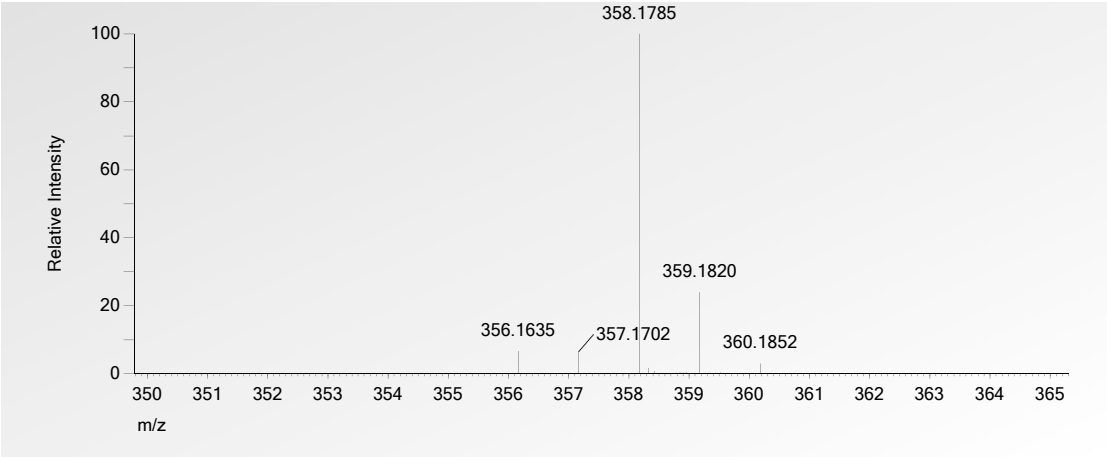

[63%]
H
[8%]
CF3

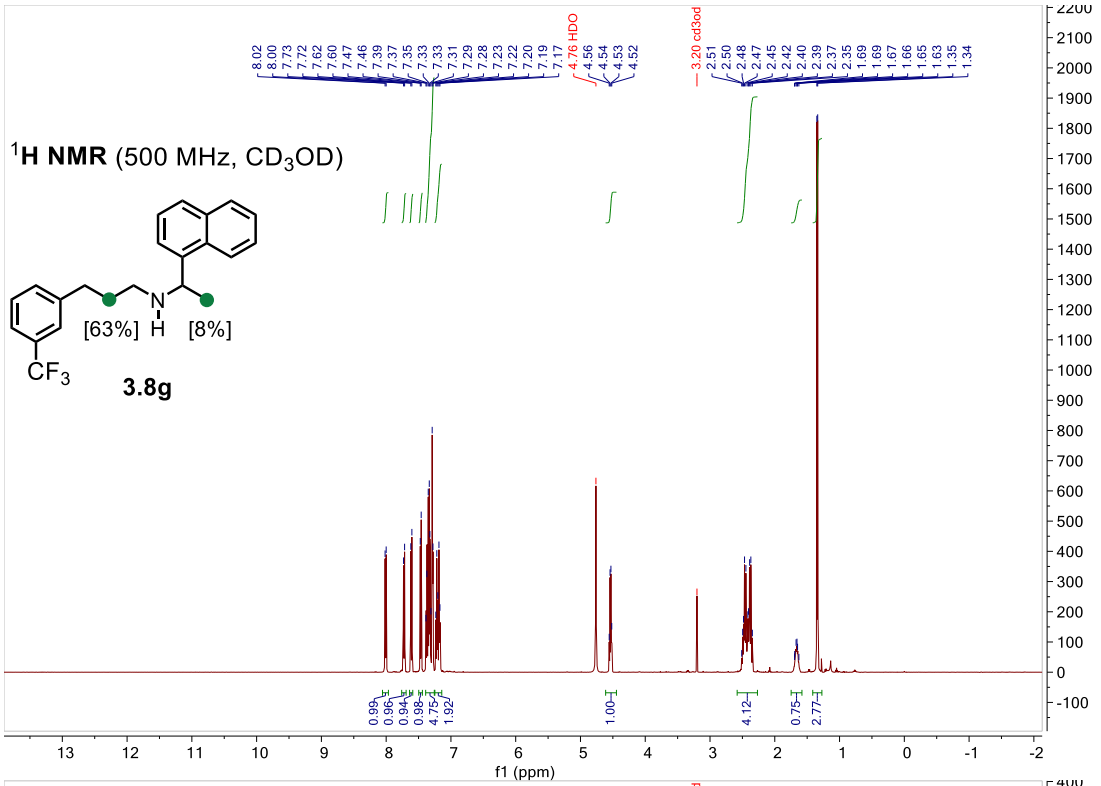
3.8g

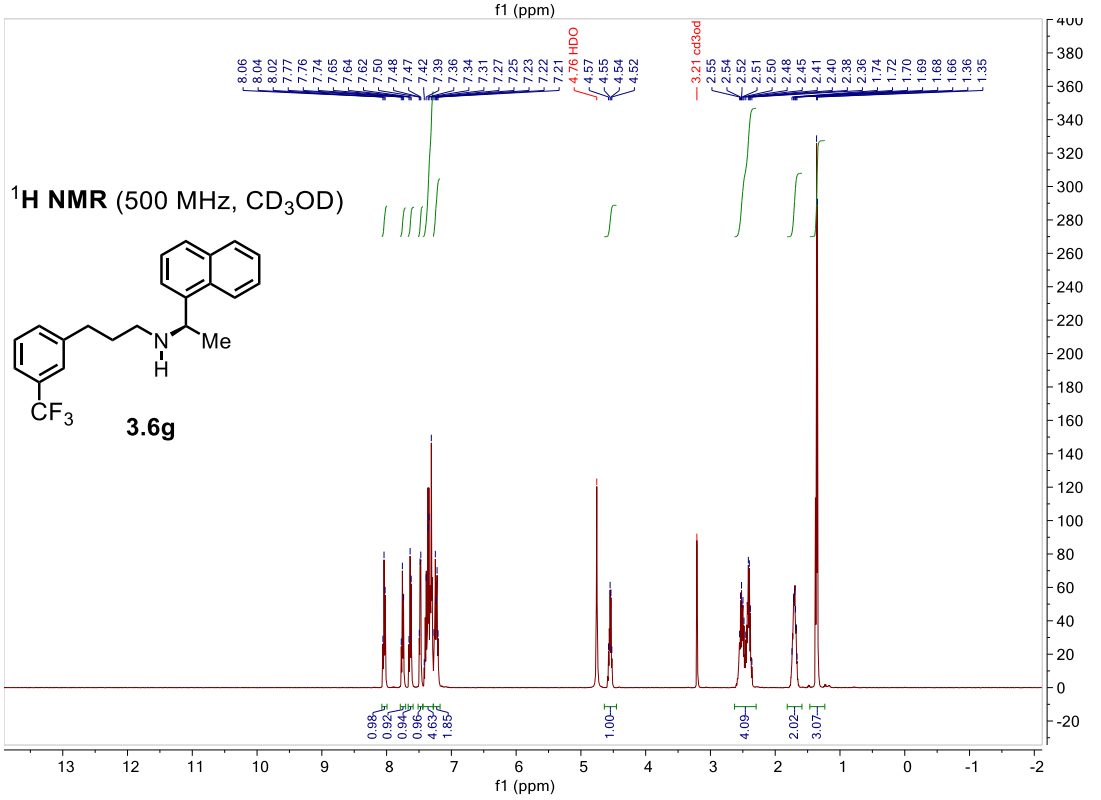

359.1871
360.1937
358.1767
361.1940
362.2018
363.2073
357.1672
356.1622
364.2127
Relative Intensity
m/z

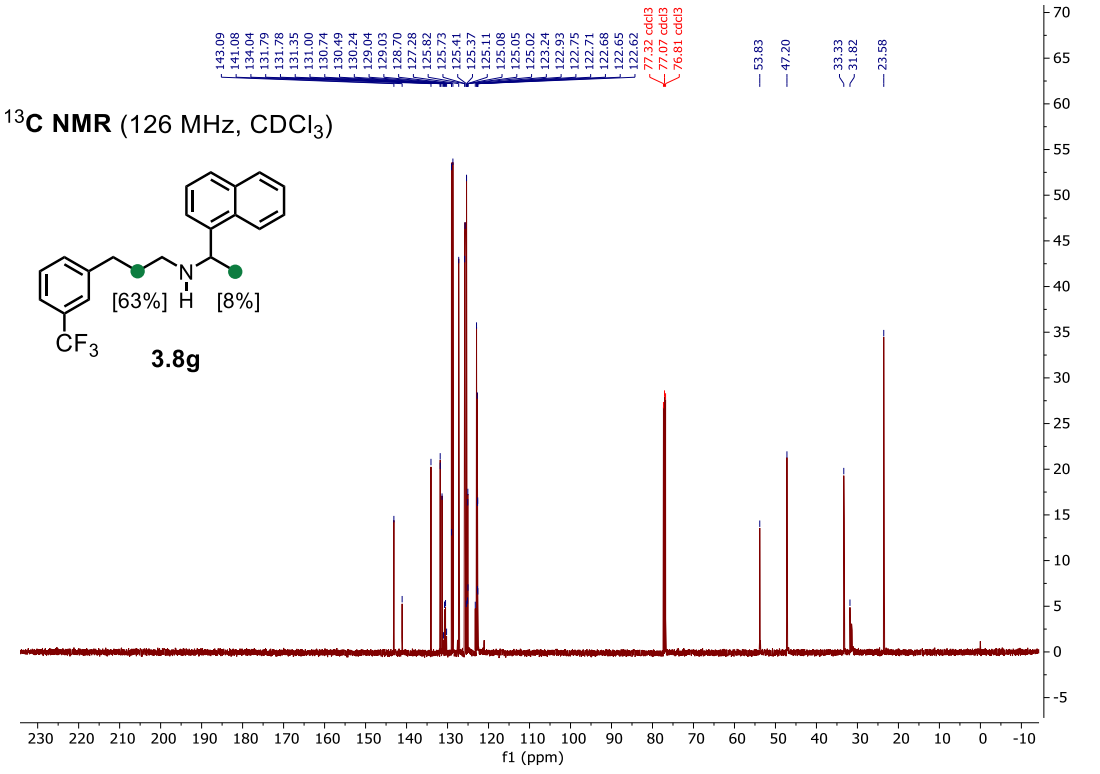

Me
H
CF3

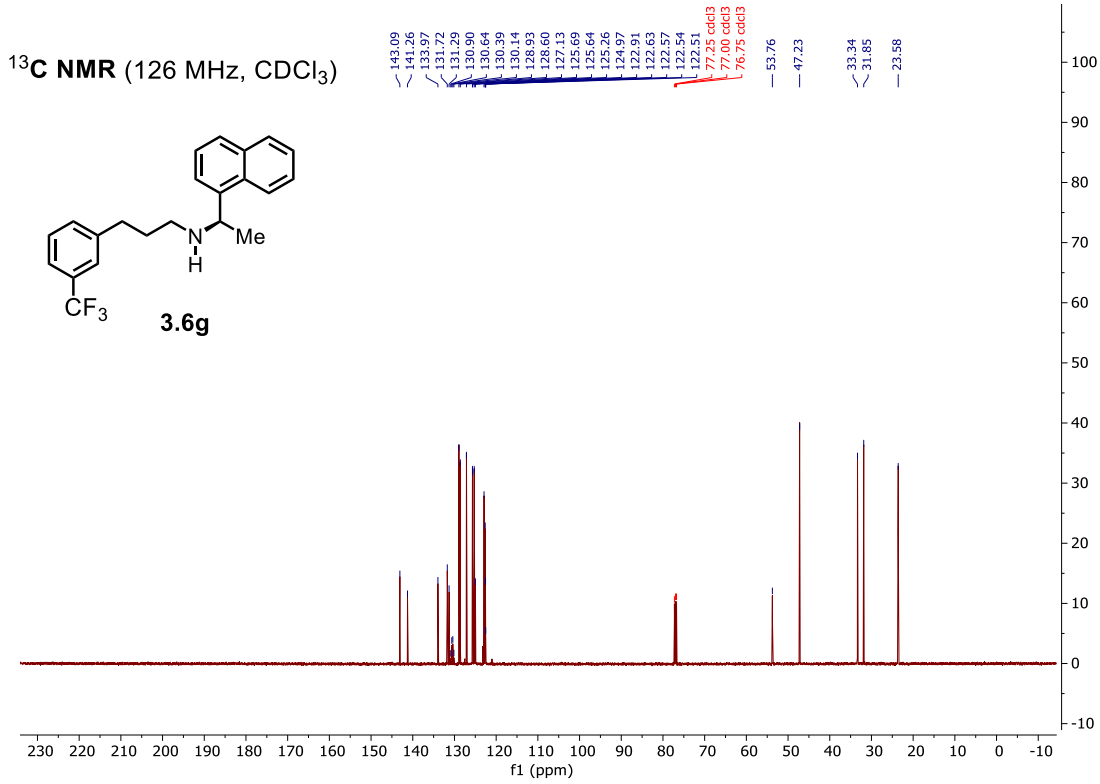
3.6g

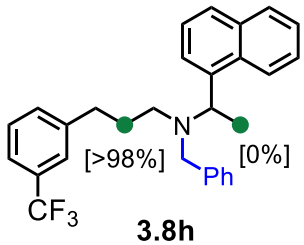

358.1785
359.1820
356.1635
357.1702
360.1852
Relative Intensity
m/z


1H NMR (500 MHz, CD3OD)
[63%] H [8%]
CF3
3.8g
f1 (ppm)


1H NMR (500 MHz, CD3OD)
Me
CF3
3.6g
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)
[63%] H [8%]
CF3
3.8g
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)
Me
H
CF3
3.6g
f1 (ppm)



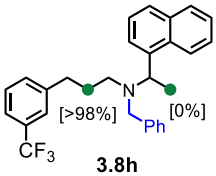
3.8h

***N*-Bn cinacalcet, 3.8h**

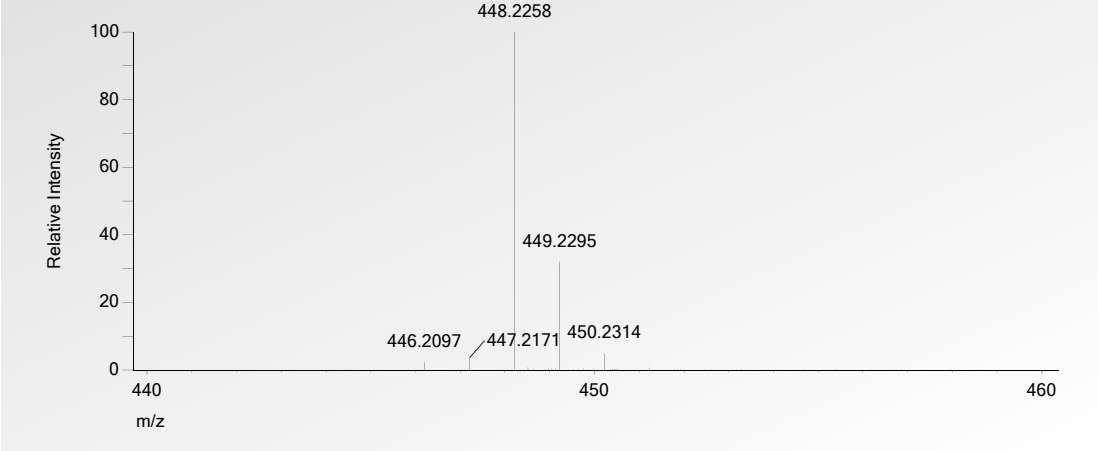
N-Bn cinacalcet **3.6h** was reacted with acetone-d_6 **3.7** following the General Procedure B. After purification by column chromatography (Et_2O:hexanes = 1:9), **3.8h** was obtained as a yellow liquid (88 mg, 98%).

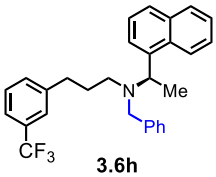
Deuterium incorporation: 1.99 D/molecule (^{1}H NMR), 2.28 D/molecule [HRMS (DART)]

^{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).

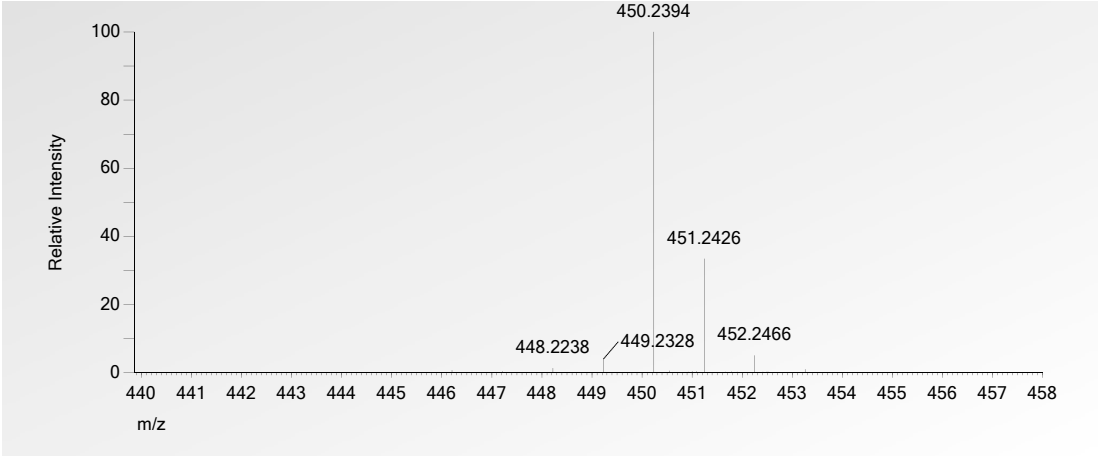

[>98%]
N
[0%]
Ph
CF3

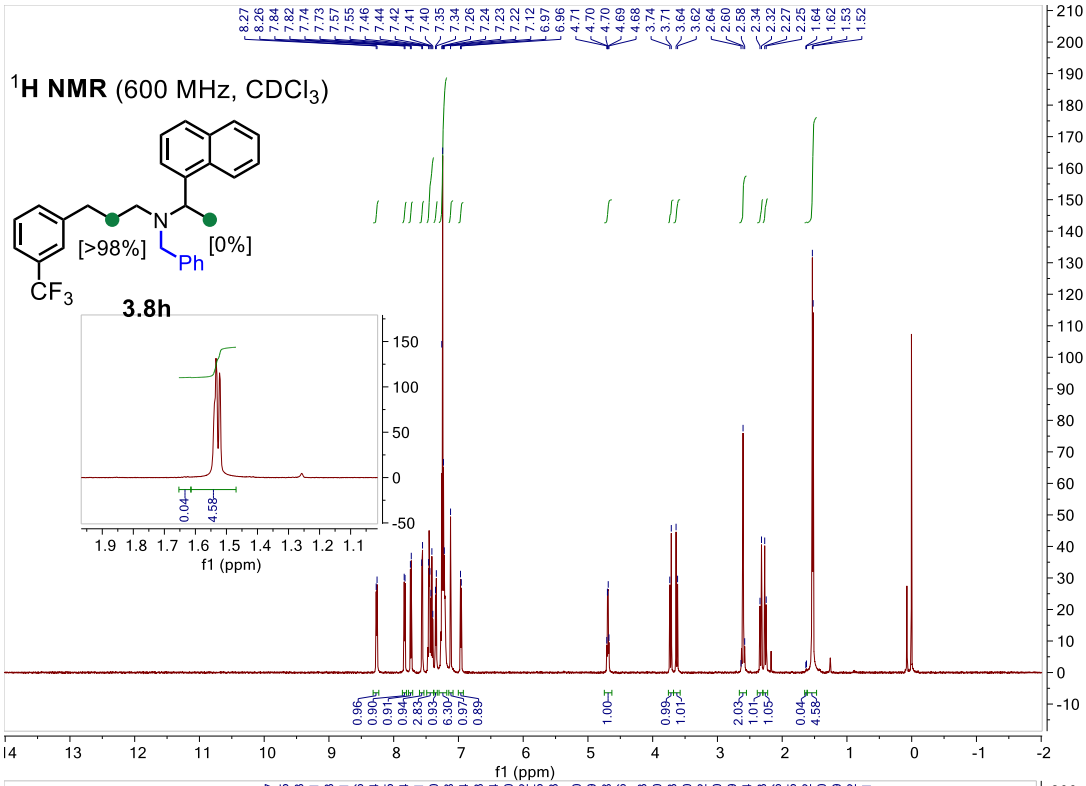
3.8h

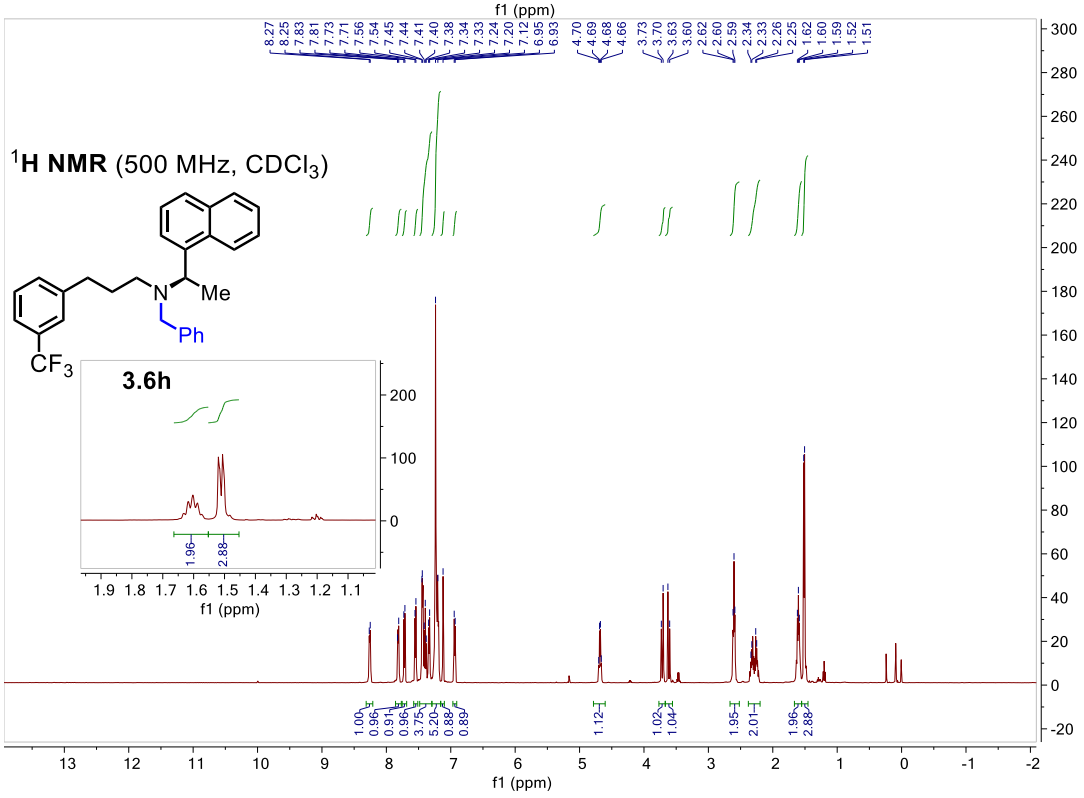

448.2258
100
80
60
40
20
0
Relative Intensity
449.2295
446.2097
447.2171
450.2314
440
450
460
m/z

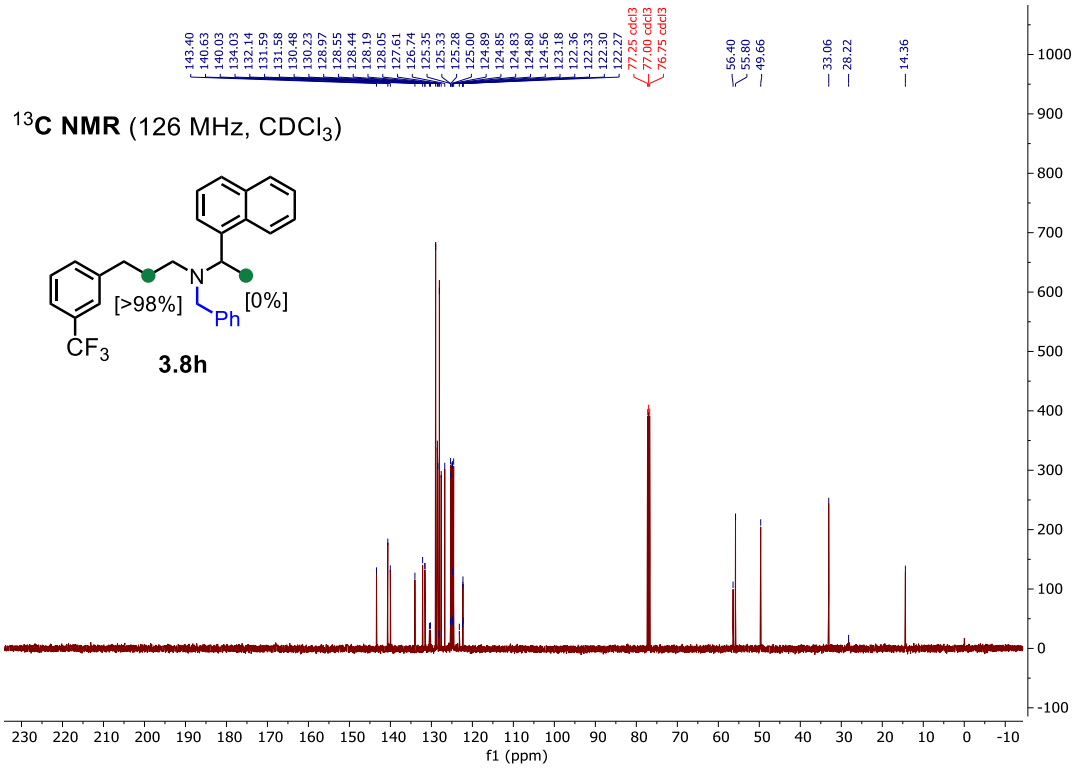

N
Me
Ph
CF3

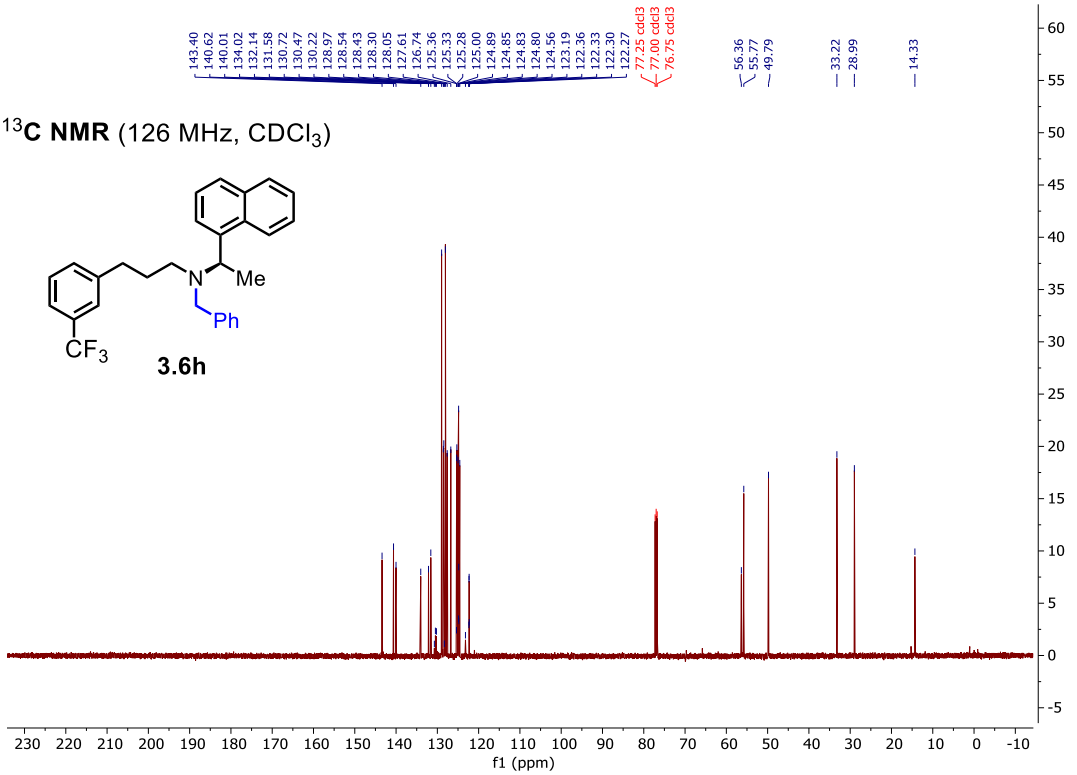
3.6h

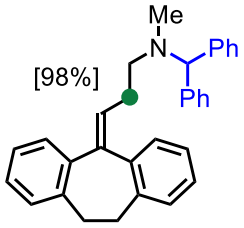

450.2394
100
80
60
40
20
0
Relative Intensity
451.2426
448.2238
449.2328
452.2466
440
441
442
443
444
445
446
447
448
449
450
451
452
453
454
455
456
457
458
m/z


1H NMR (600 MHz, CDCl3)
[>98%]
[0%]
Ph
CF3
3.8h
f1 (ppm)


1H NMR (500 MHz, CDCl3)
N
Me
Ph
CF3
3.6h
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)
[>98%]
[0%]
Ph
CF3
3.8h
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)
N
Me
Ph
CF3
3.6h
f1 (ppm)



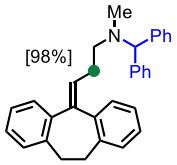
3.8i

***N*-Bzh nortriptyline, 3.8i**

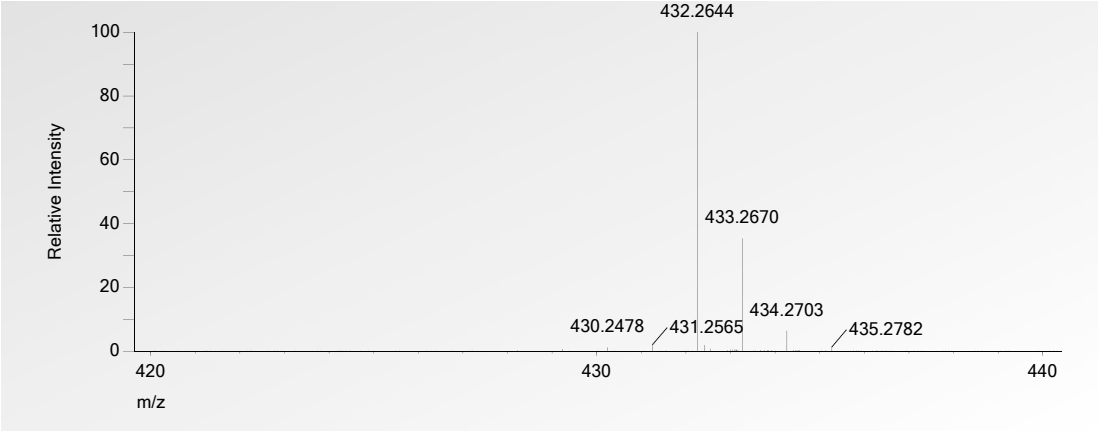
N-Bzh nortriptyline **3.6i** was reacted with acetone-d_6 **3.7** following the General Procedure B. After purification by column chromatography (Et_2O:hexanes = 1:9), **3.8i** was obtained as a yellow liquid (83 mg, 96%).

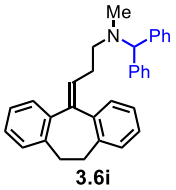
Deuterium incorporation: 1.96 D/molecule (^{1}H NMR), 2.34 D/molecule [HRMS (DART)]

^{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}.

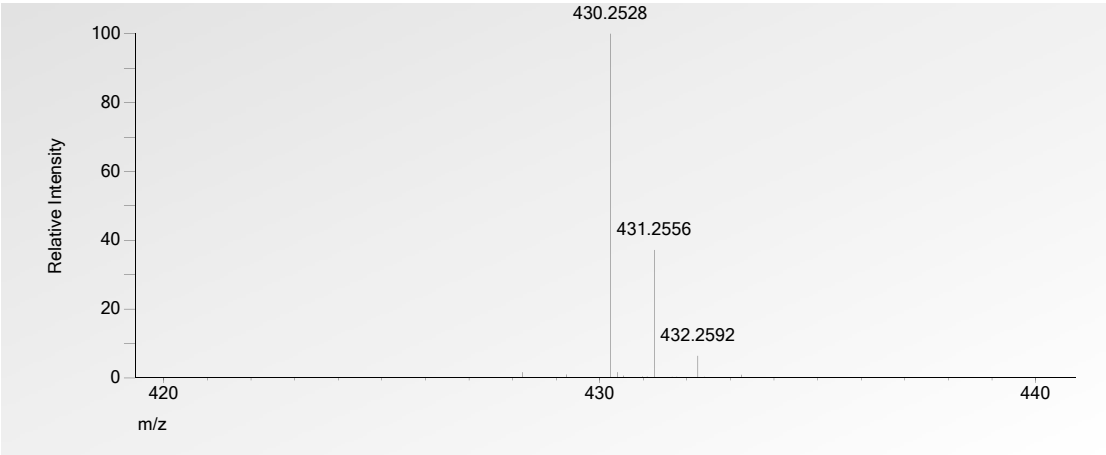

Me
N
Ph
Ph
[98%]

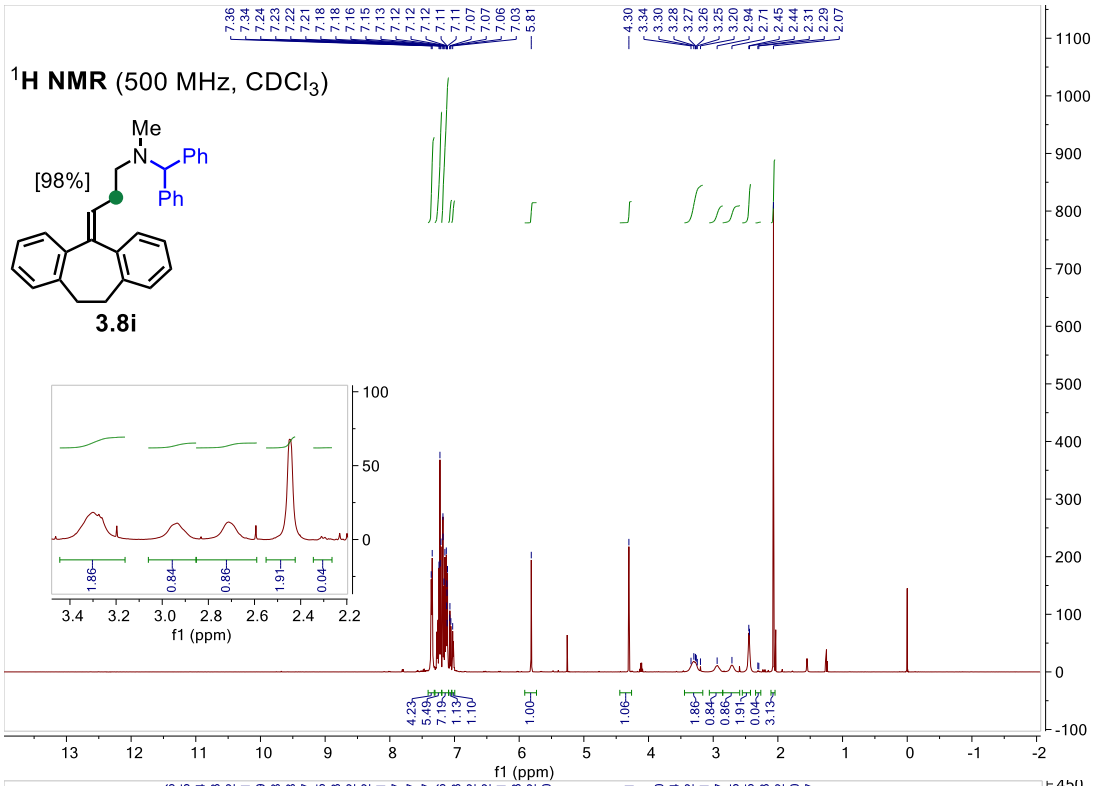
3.8i

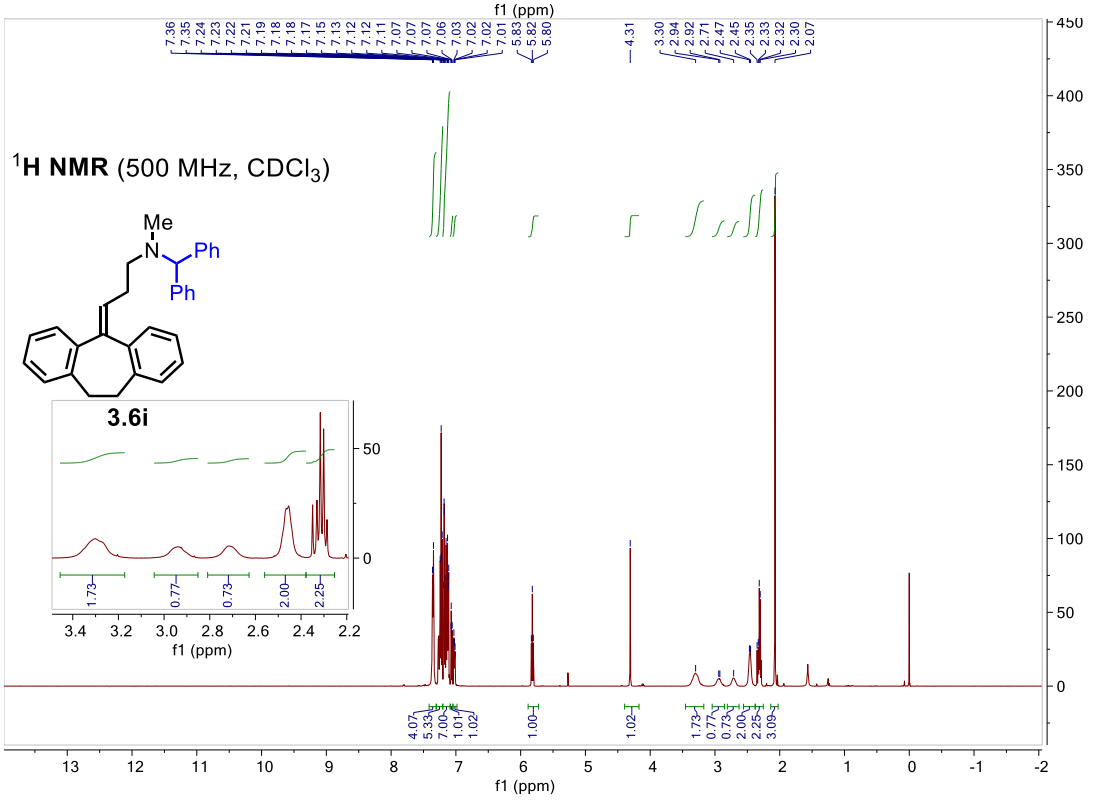

432.2644
433.2670
434.2703
430.2478
431.2565
435.2782
Relative Intensity
m/z
100
80
60
40
20
0
420
430
440

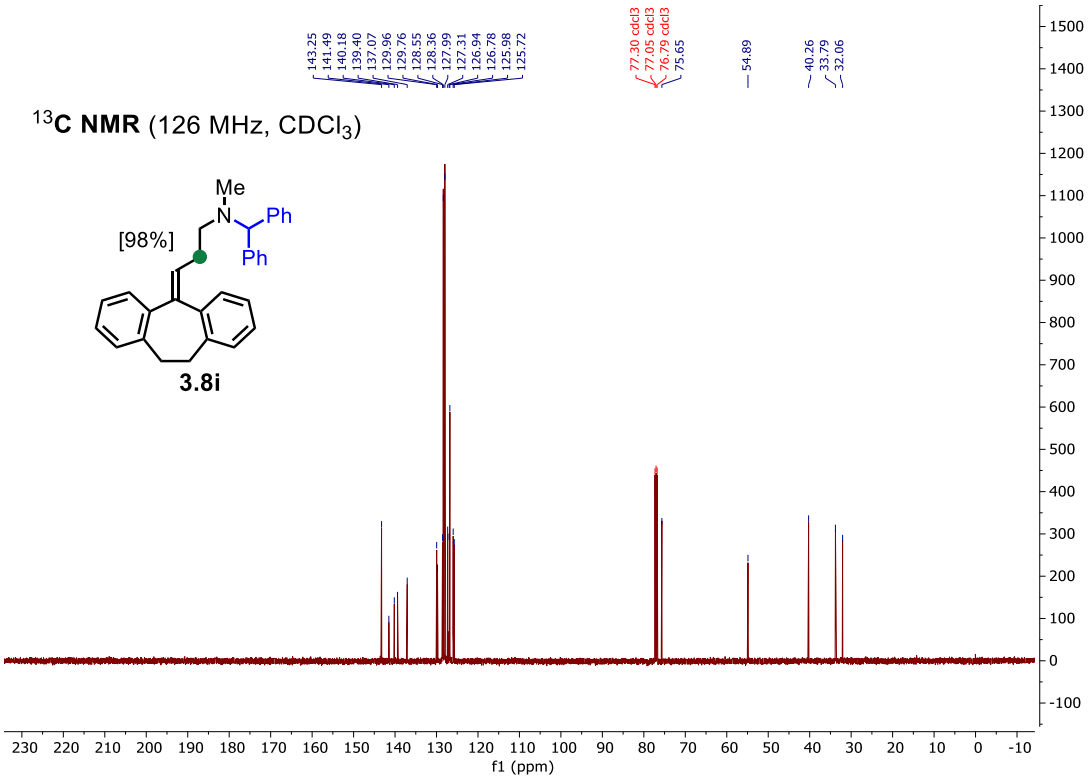

Me
N
Ph
Ph

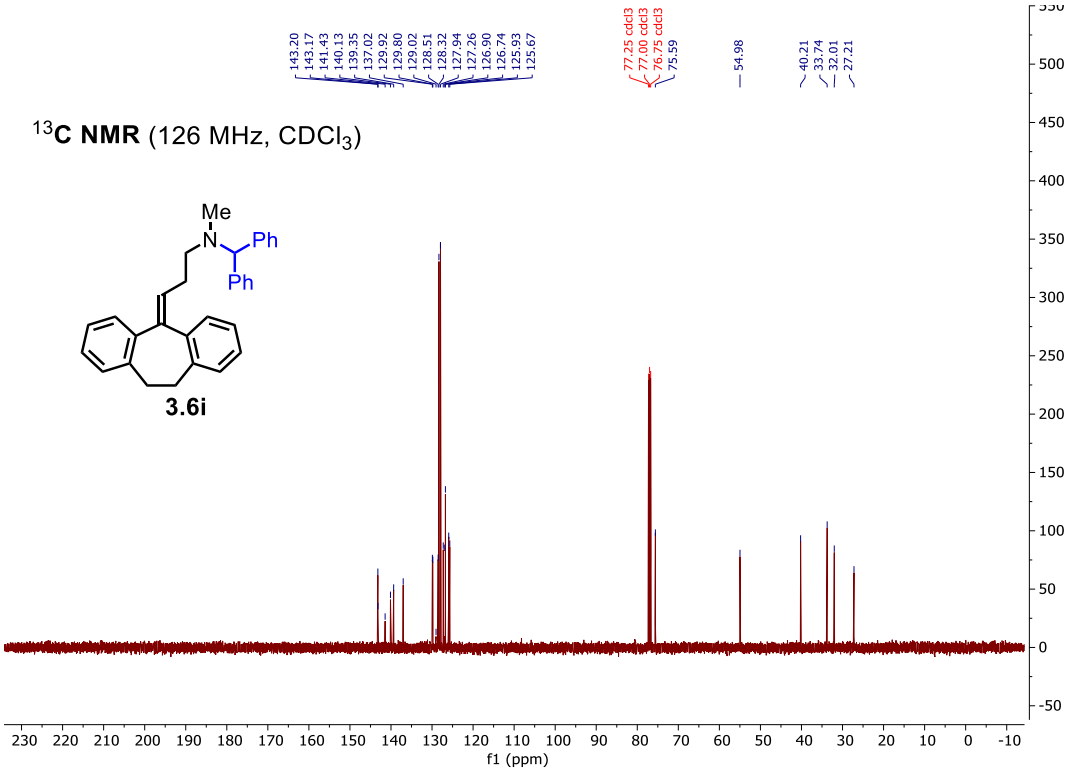
3.6i

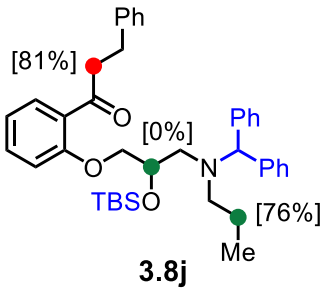

430.2528
431.2556
432.2592
Relative Intensity
m/z
100
80
60
40
20
0
420
430
440


1H NMR (500 MHz, CDCl3)
Me
N
Ph
Ph
[98%]
3.8i
f1 (ppm)


1H NMR (500 MHz, CDCl3)
Me
N
Ph
Ph
3.6i
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%]
3.8i
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
3.6i
f1 (ppm)



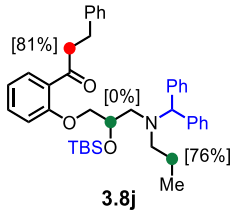
3.8j

***N*-Bzh, *O*-TBS propafenone, 3.8j**

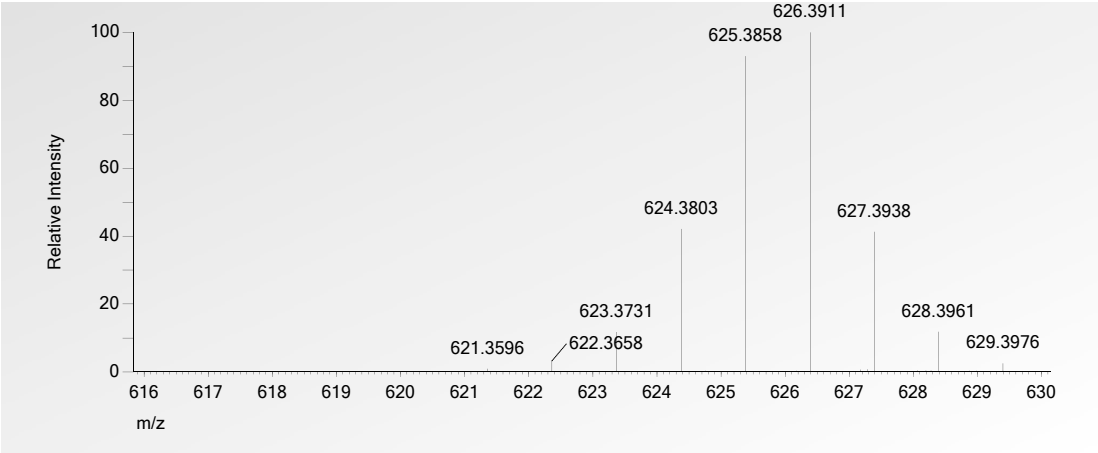
N-Bzh, *O*-TBS propafenone **3.6j** was reacted with acetone-d_6 **3.7** following the General Procedure A. After purification by column chromatography (Et_2O:hexanes = 1:9), **3.8j** was obtained as a yellow liquid (114 mg, 92%).

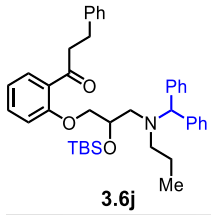
Deuterium incorporation: 3.14 D/molecule (^{1}H NMR), 3.51 D/molecule [HRMS (DART)]

^{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}.

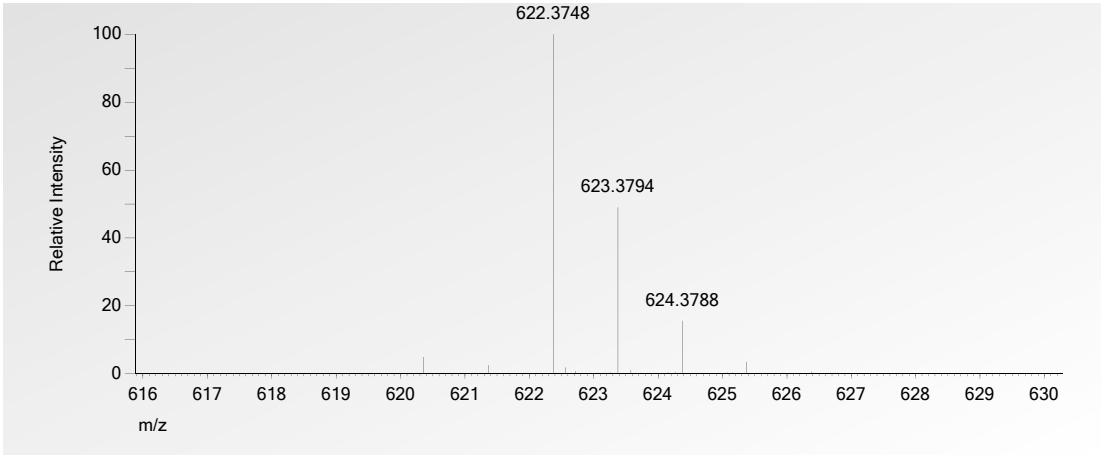

Ph
[81%]
O
[0%]
Ph
Ph
N
O
TBSO
[76%]
Me

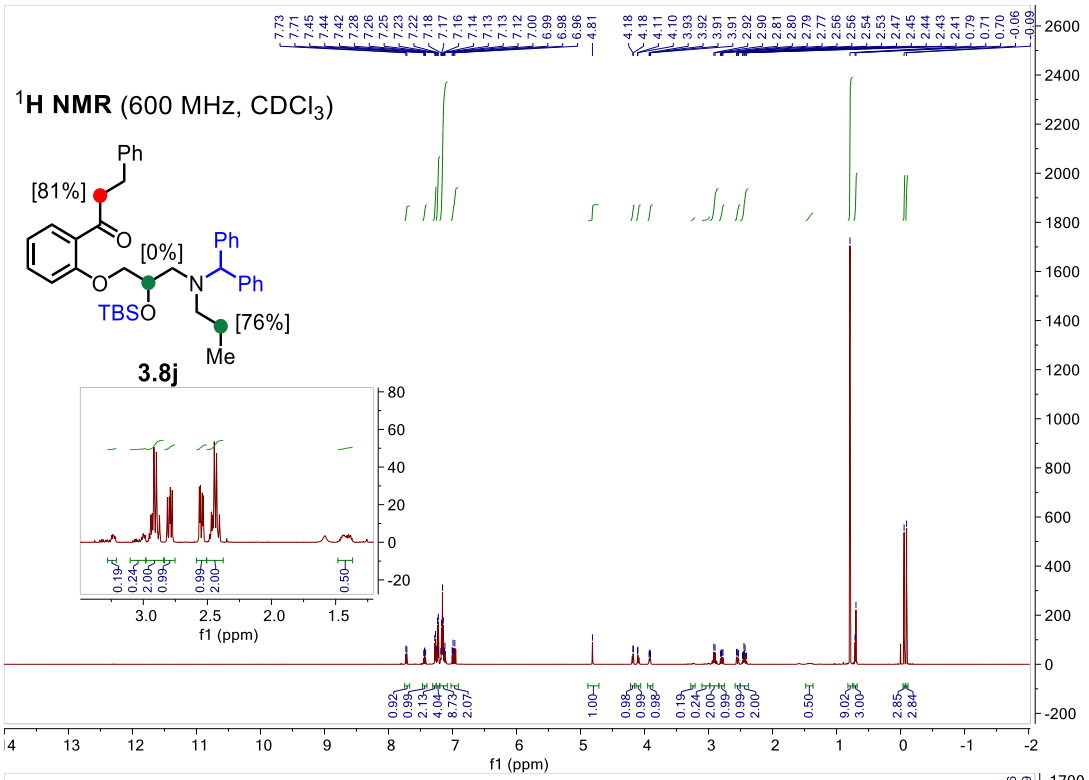
3.8j

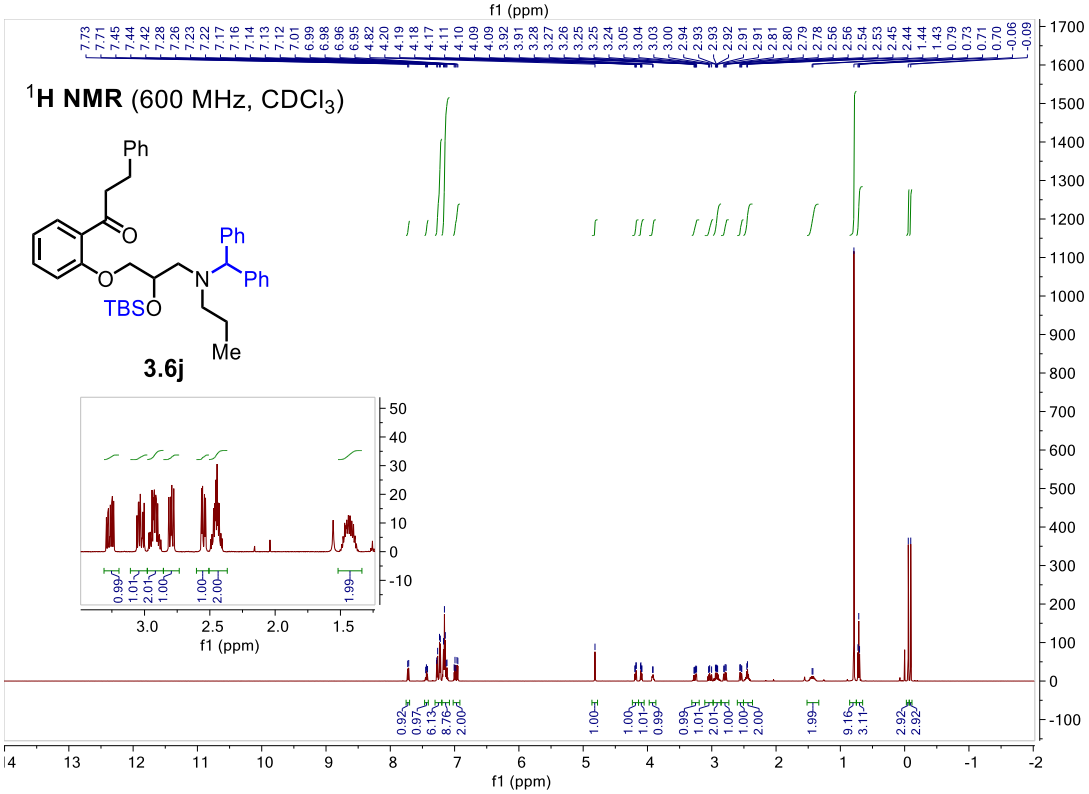

626.3911
625.3858
624.3803
627.3938
623.3731
628.3961
629.3976
622.3658
621.3596
Relative Intensity
m/z
100
80
60
40
20
0
616
617
618
619
620
621
622
623
624
625
626
627
628
629
630

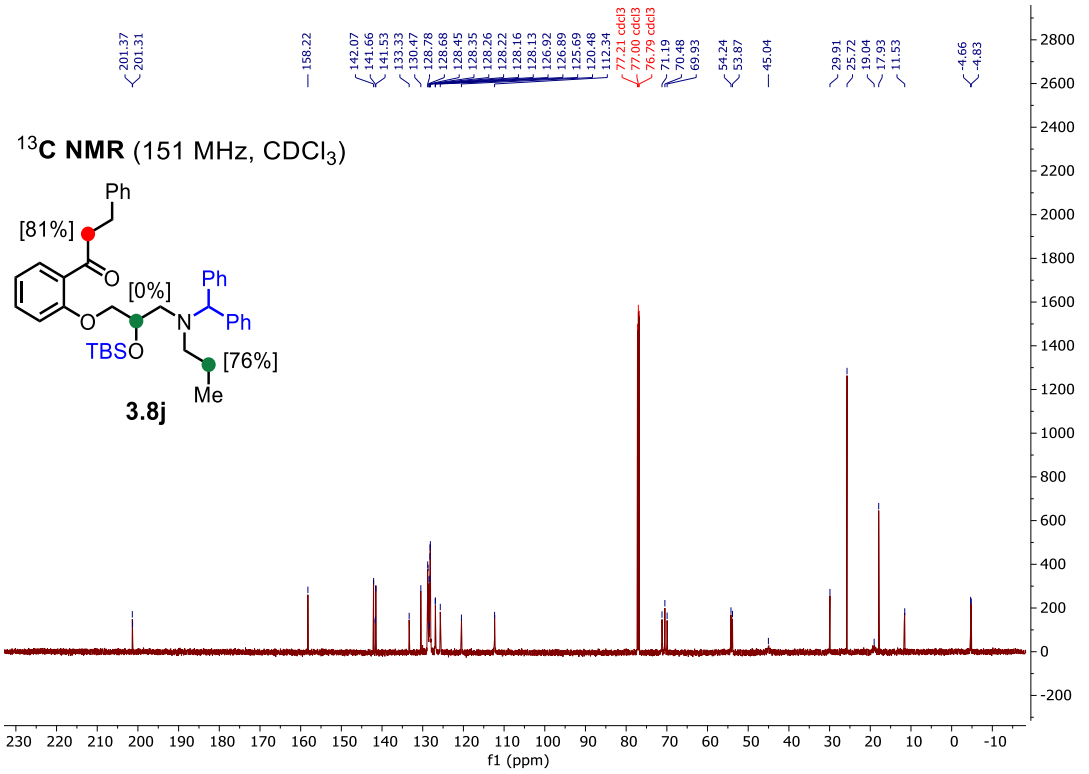

Ph
O
Ph
Ph
N
O
TBSO
Me

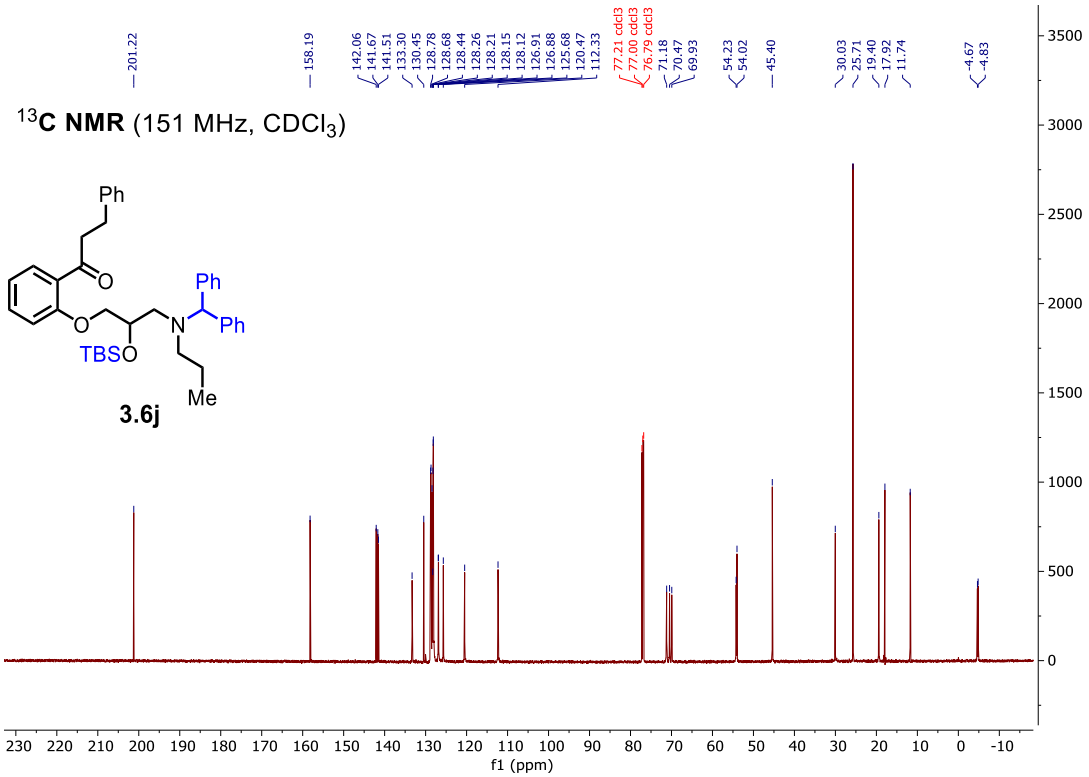
3.6j

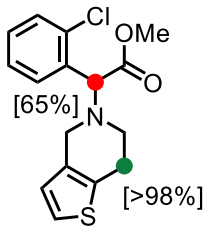

622.3748
623.3794
624.3788
Relative Intensity
m/z
100
80
60
40
20
0
616
617
618
619
620
621
622
623
624
625
626
627
628
629
630


1H NMR (600 MHz, CDCl3)
Ph
[81%]
O
[0%]
Ph
N
Ph
O
TBSO
[76%]
Me
3.8j
f1 (ppm)


1H NMR (600 MHz, CDCl3)
Ph
O
Ph
N
Ph
O
TBSO
Me
3.6j
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%]
Ph
N
Ph
O
TBSO
[76%]
Me
3.8j
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
O
N
Ph
TBSO
Me
3.6j
f1 (ppm)

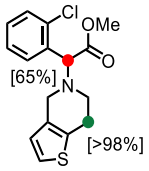


3.8k

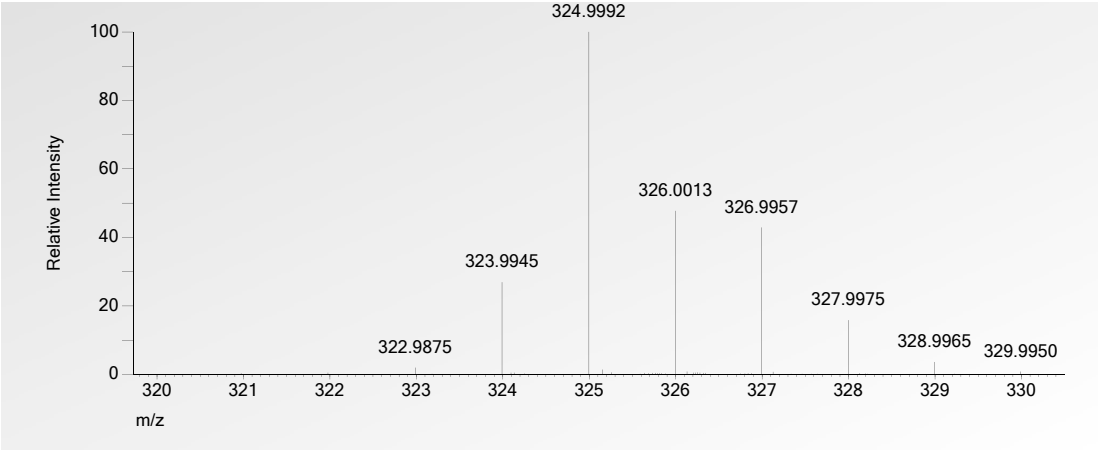
Clopidogrel, 3.8k

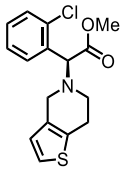
Clopidogrel **3.6k** was reacted with acetone-d_6 **3.7** following the General Procedure B. After purification by column chromatography (Et_2O:hexanes = 1:9), **3.8k** was obtained as a colorless liquid (61 mg, 94%).

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).

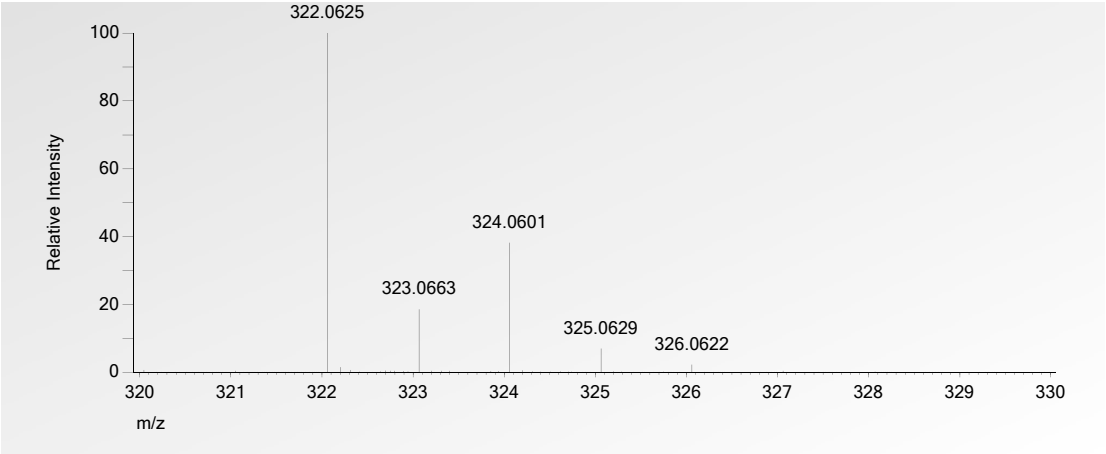

Cl
OMe
O
[65%]
N
S
[>98%]

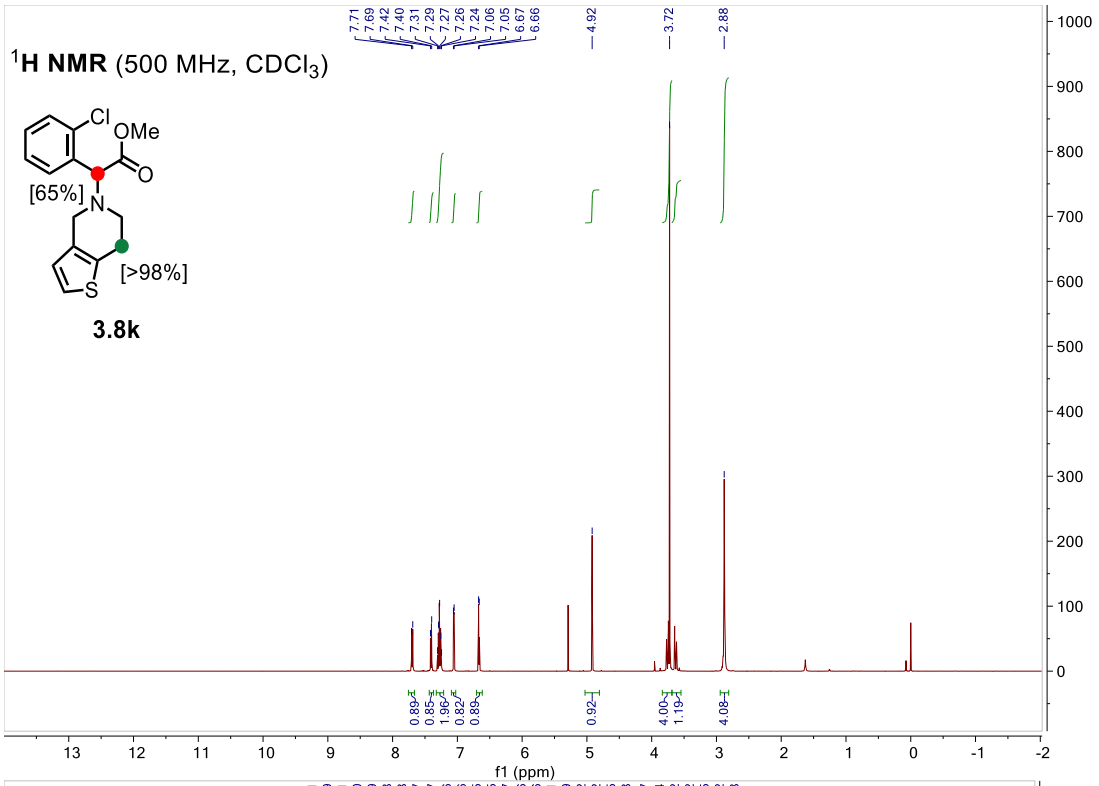
3.8k

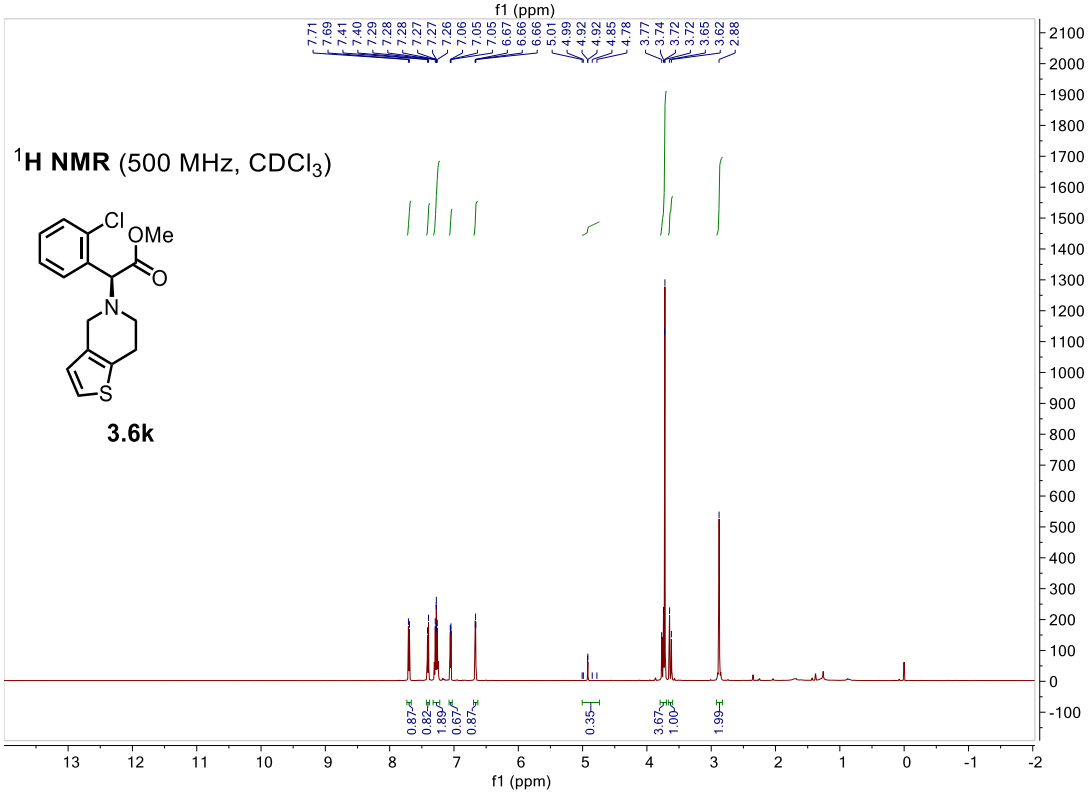

324.9992
326.0013
326.9957
323.9945
327.9975
322.9875
328.9965
329.9950
Relative Intensity
m/z

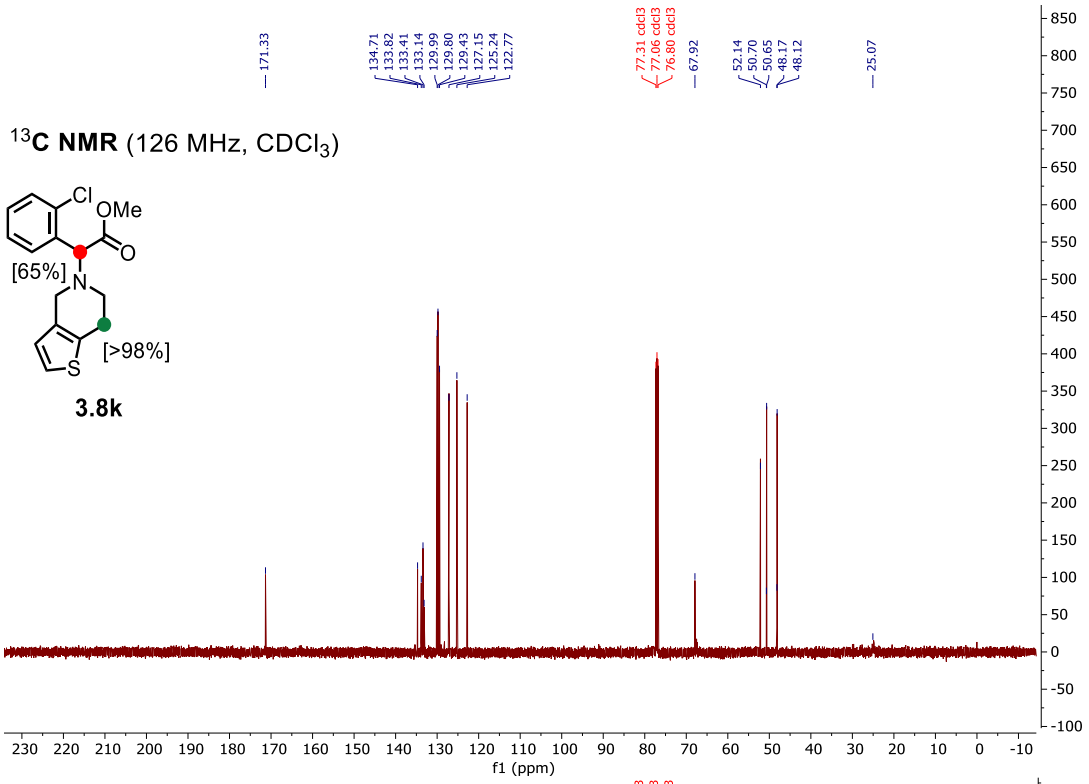

Cl
OMe
O
N
S

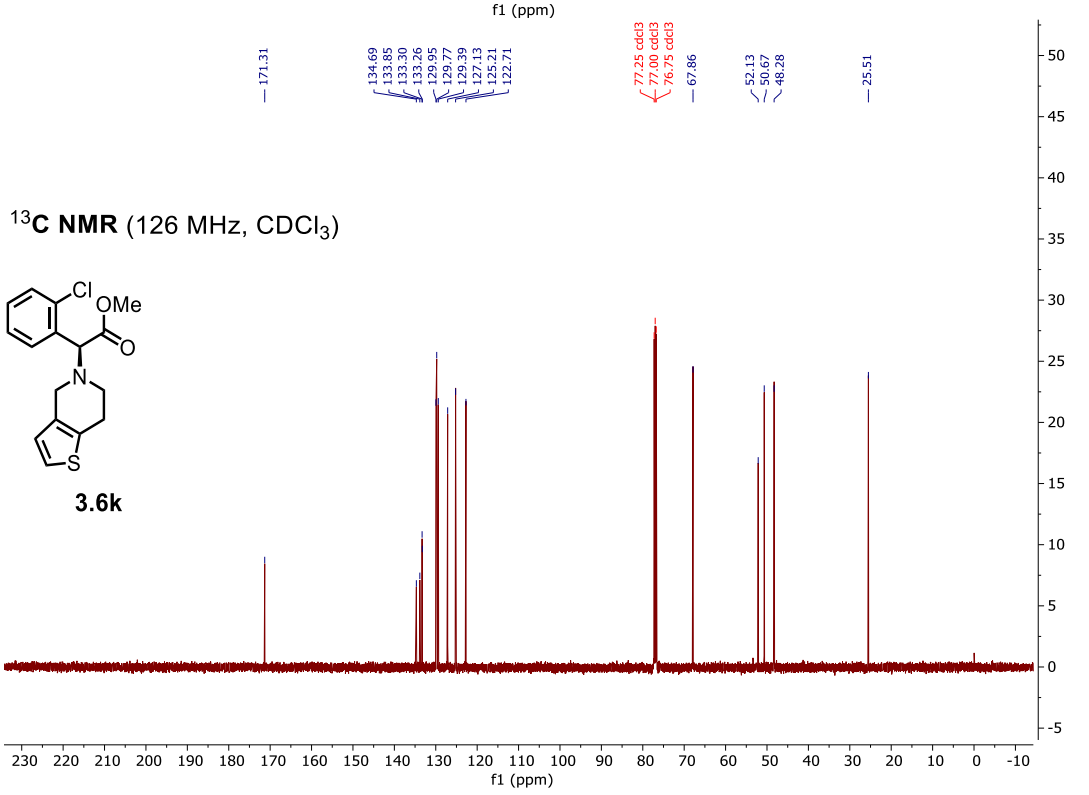
3.6k

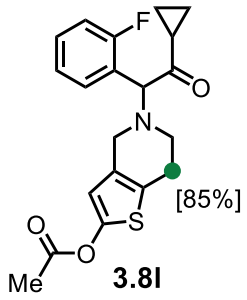

322.0625
324.0601
323.0663
325.0629
326.0622
Relative Intensity
m/z


1H NMR (500 MHz, CDCl3)
Cl
OMe
O
[65%]
N
[>98%]
S
3.8k
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
OMe
O
N
S
3.6k
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
OMe
O
[65%]
N
[>98%]
S
3.8k
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
OMe
O
N
S
3.6k
f1 (ppm)



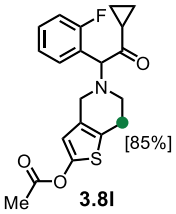
3.8l

Prasugrel, 3.8l

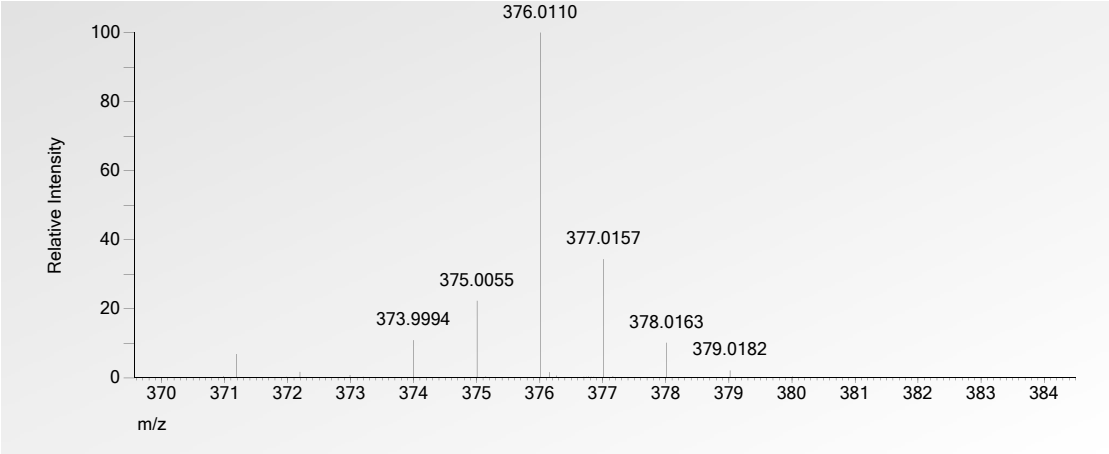
Prasugrel **3.6l** was reacted with acetone-d_6 **3.7** following the General Procedure C. After purification by column chromatography (Et_2O:hexanes = 1:19), **3.8l** was obtained as a white solid (64 mg, 85%).

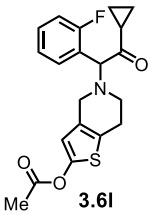
Deuterium incorporation: 1.70 D/molecule (^{1}H NMR), 1.99 D/molecule [HRMS (DART)]

^{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}.

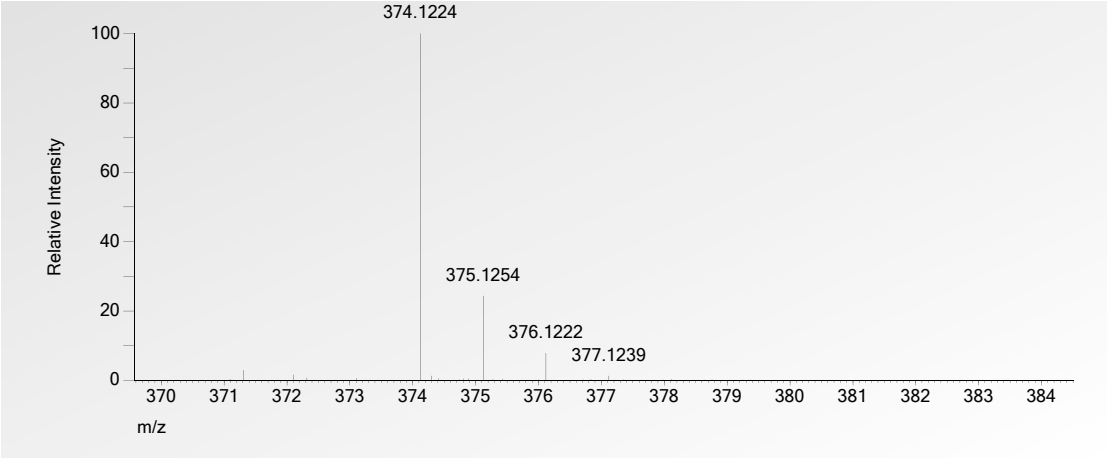

F
O
N
[85%]
S
O
O
Me

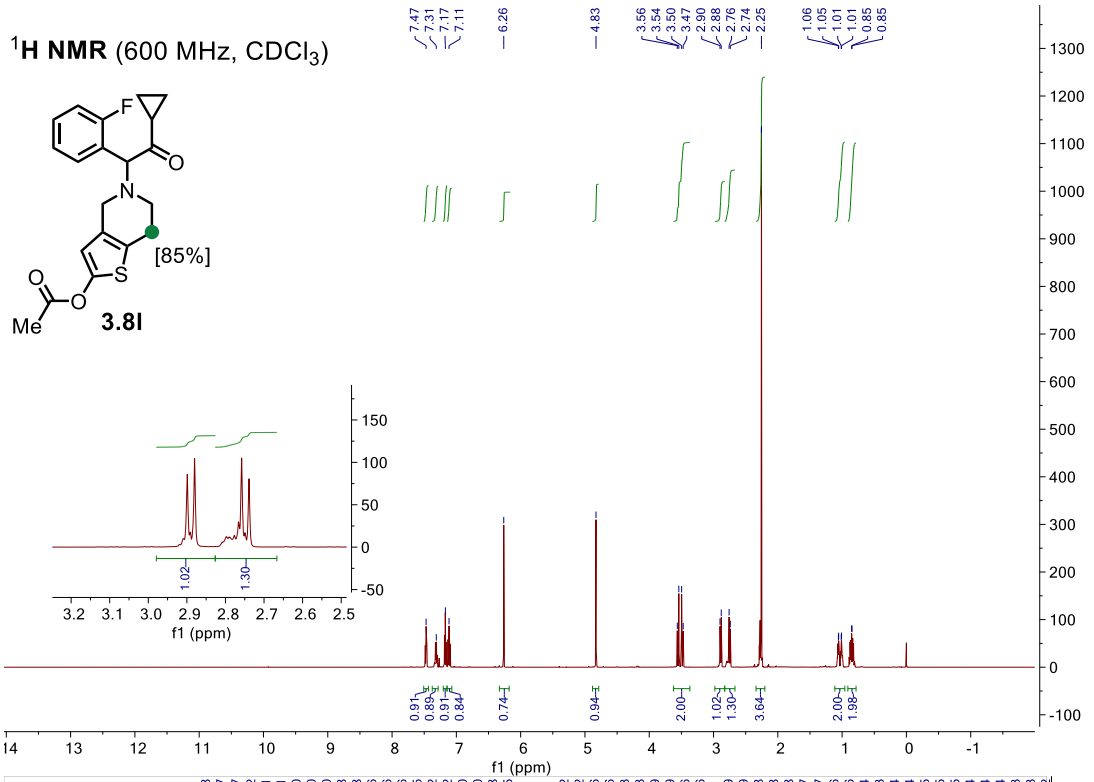
3.8l

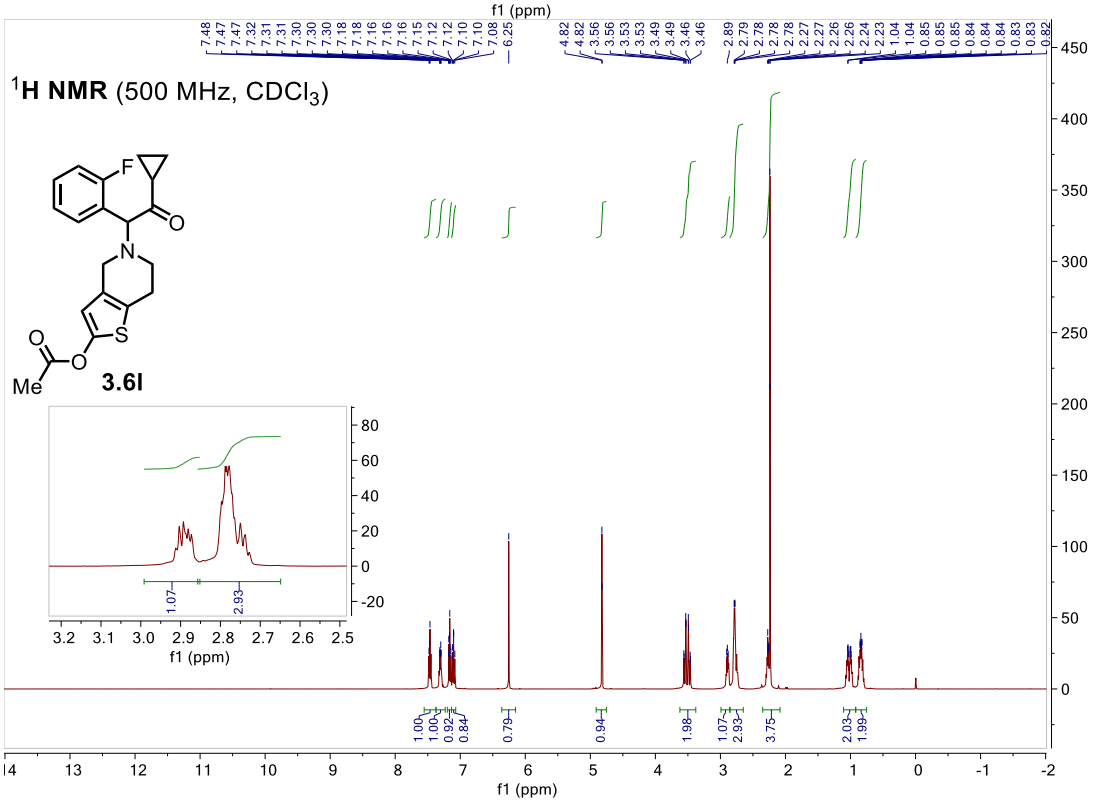

376.0110
377.0157
375.0055
373.9994
378.0163
379.0182
Relative Intensity
m/z

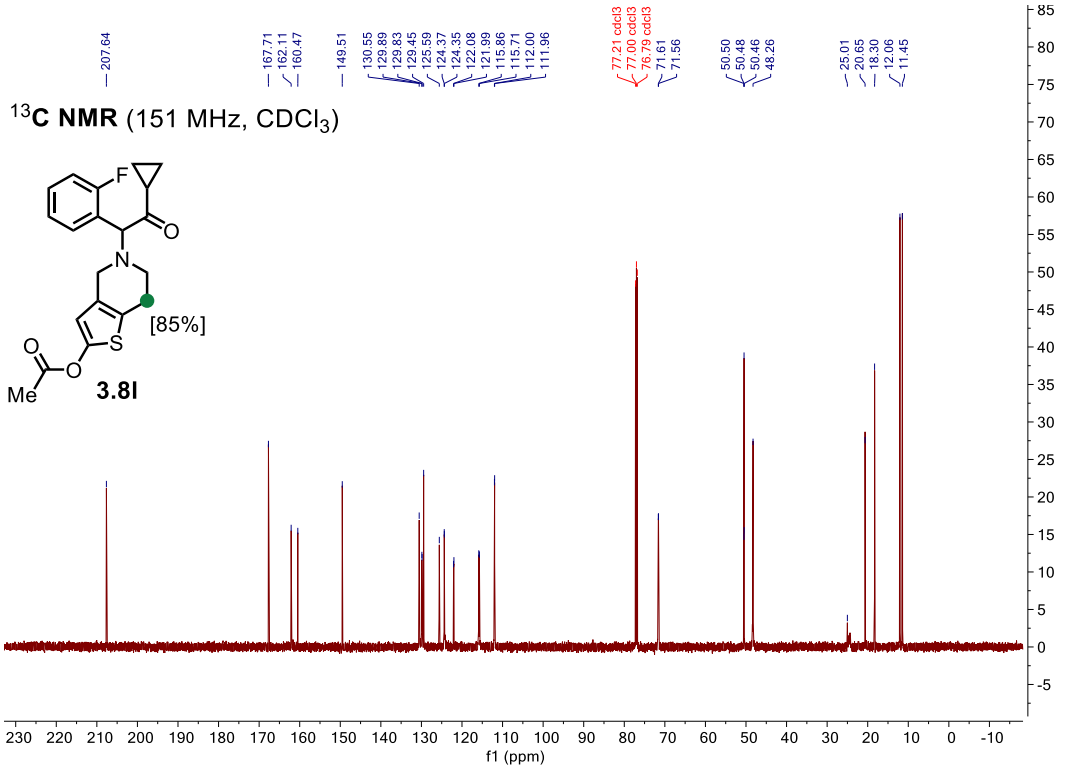

F
O
N
S
O
O
Me

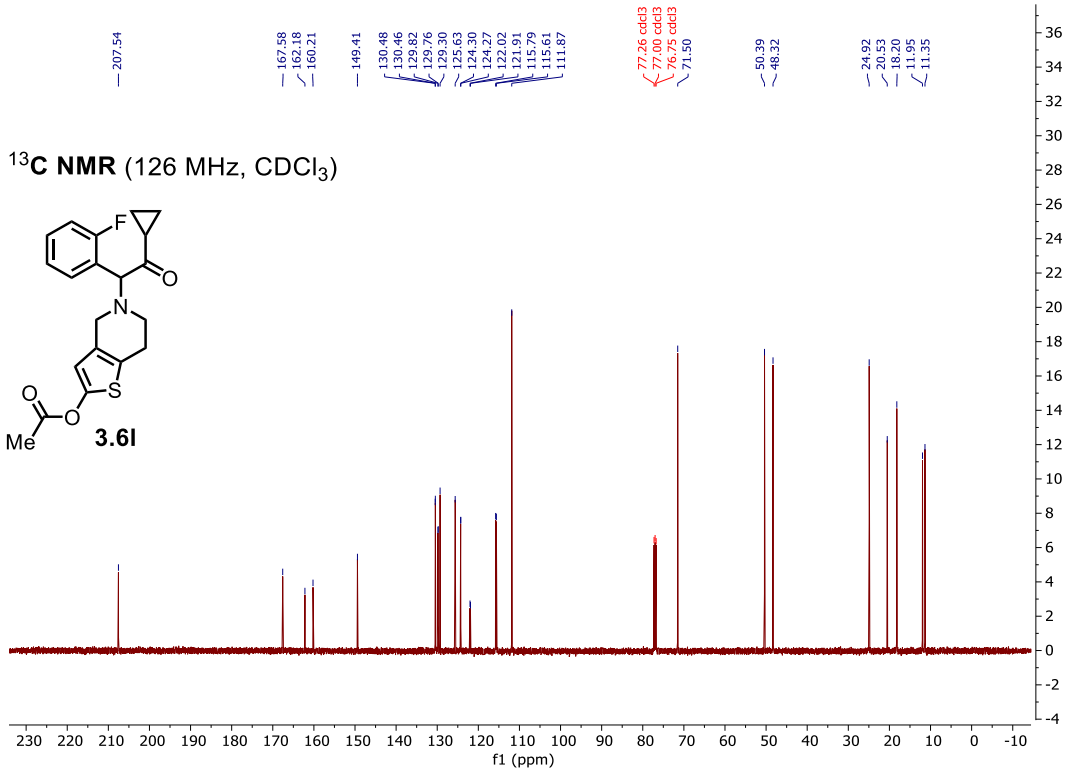
3.6l

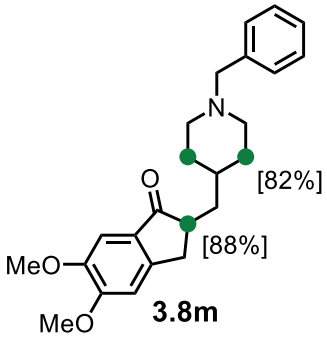

374.1224
375.1254
376.1222
377.1239
Relative Intensity
m/z


^{1}H NMR (600 MHz, CDCl$_3$)
F
O
N
S
O
O
Me
[85%]
3.8l
f1 (ppm)


^{1}H NMR (500 MHz, CDCl$_3$)
F
O
N
S
O
O
Me
3.6l
f1 (ppm)


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
77.21 cdcl3
77.00 cdcl3
76.79 cdcl3
71.61
71.56
50.50
50.48
50.46
48.26
25.01
20.65
18.30
12.06
11.45
13C NMR (151 MHz, CDCl3)
F
O
N
S
O
O
Me
[85%]
3.8l
f1 (ppm)


207.54
167.58
162.18
160.21
149.41
130.48
130.46
129.82
129.76
129.30
125.63
124.30
124.27
122.02
121.91
115.79
115.61
111.87
77.26 cdcl3
77.00 cdcl3
76.75 cdcl3
71.50
50.39
48.32
24.92
20.53
18.20
11.95
11.35
13C NMR (126 MHz, CDCl3)
F
O
N
S
O
O
Me
3.6l
f1 (ppm)

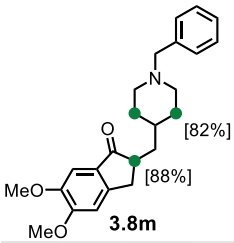


Donepezil, 3.8m

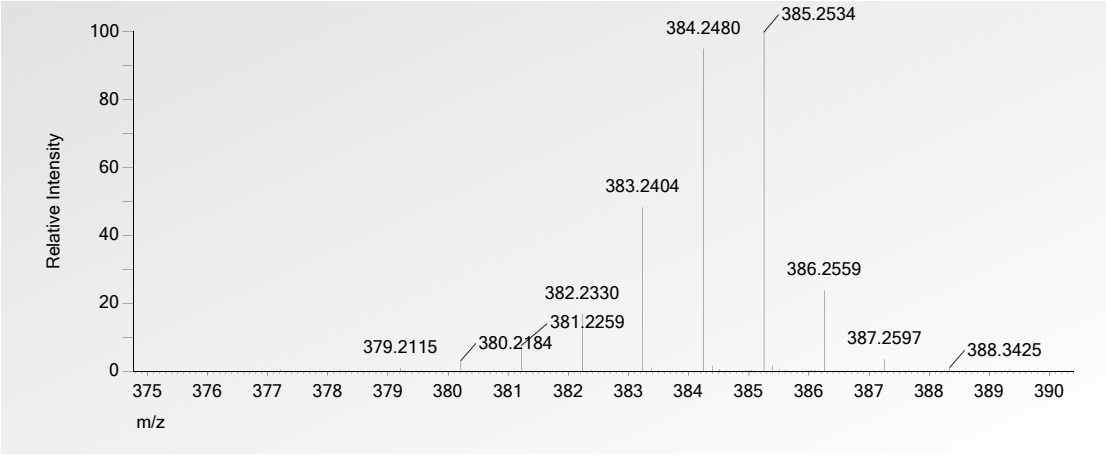
Donepezil **3.6m** was reacted with acetone-d_6 **3.7** following the General Procedure A. After purification by column chromatography (MeOH:DCM = 1:49), **3.8m** was obtained as a white solid (74 mg, 98%).

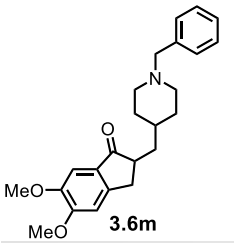
Deuterium incorporation: 5.04 D/molecule (^{1}H NMR), 4.17 D/molecule [HRMS (DART)]

^{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}.

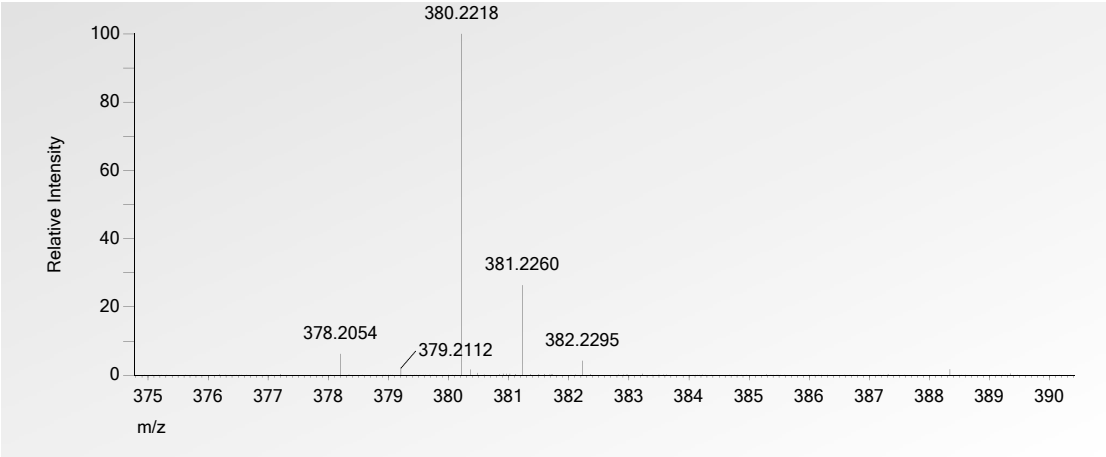

N
O
[82%]
[88%]
MeO
MeO

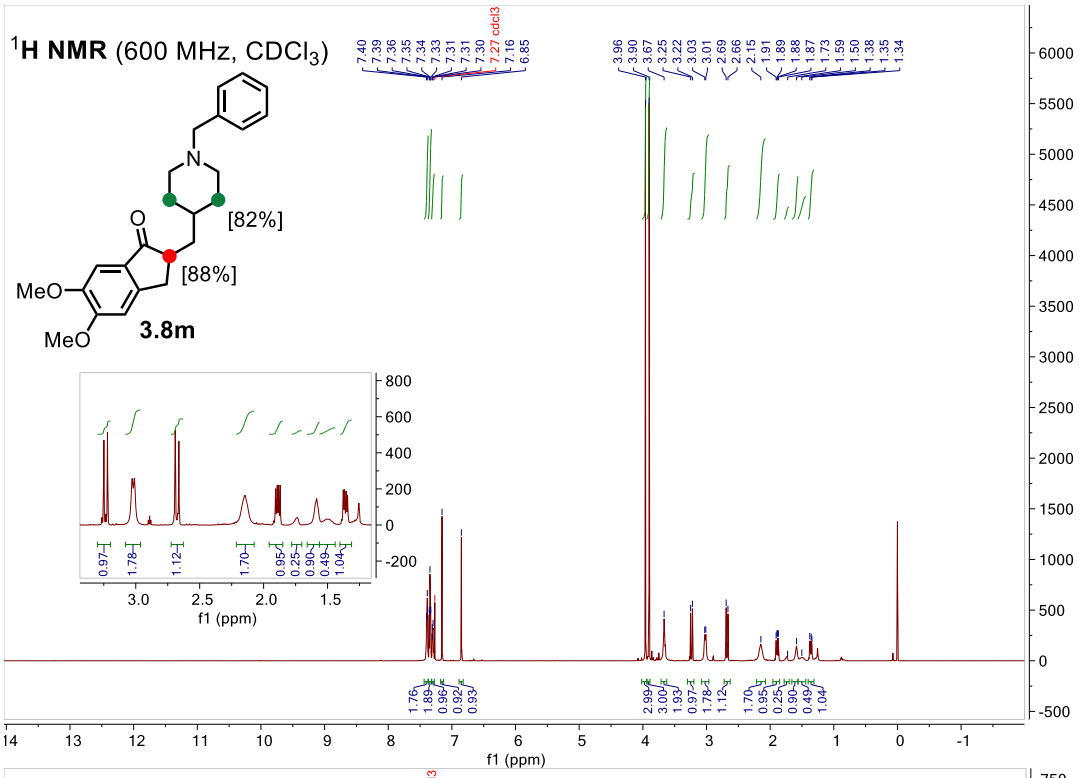
3.8m

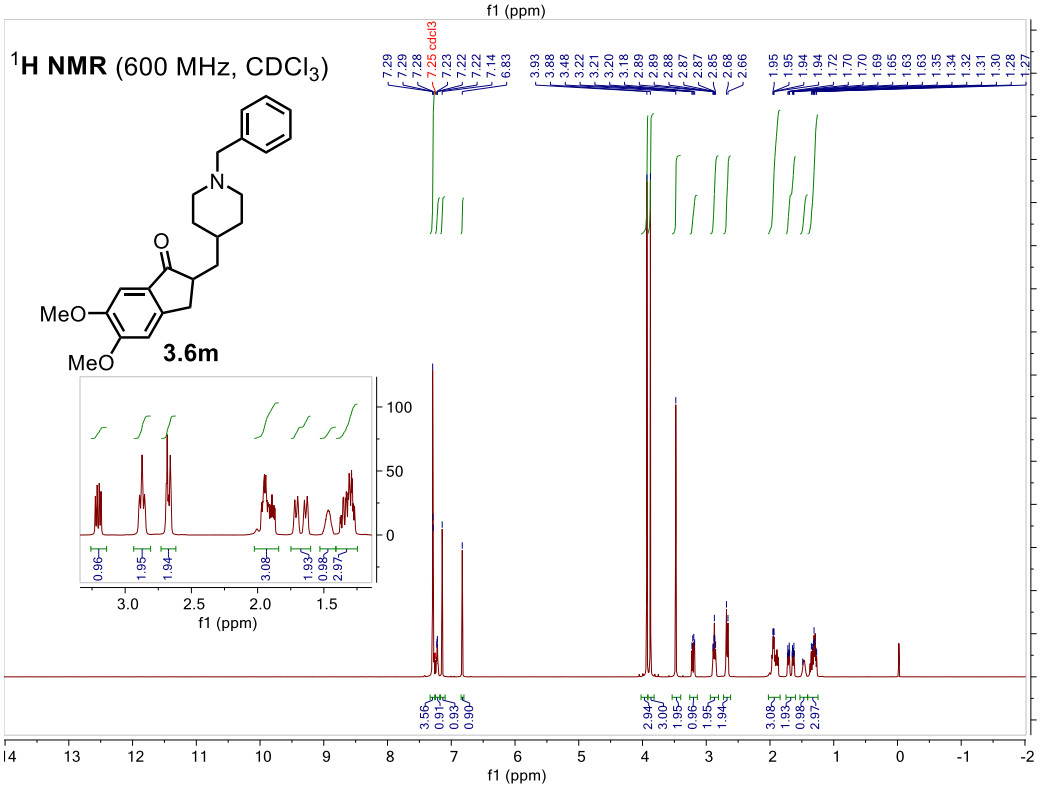

Relative Intensity
m/z
384.2480
385.2534
383.2404
386.2559
382.2330
381.2259
379.2115
380.2184
387.2597
388.3425

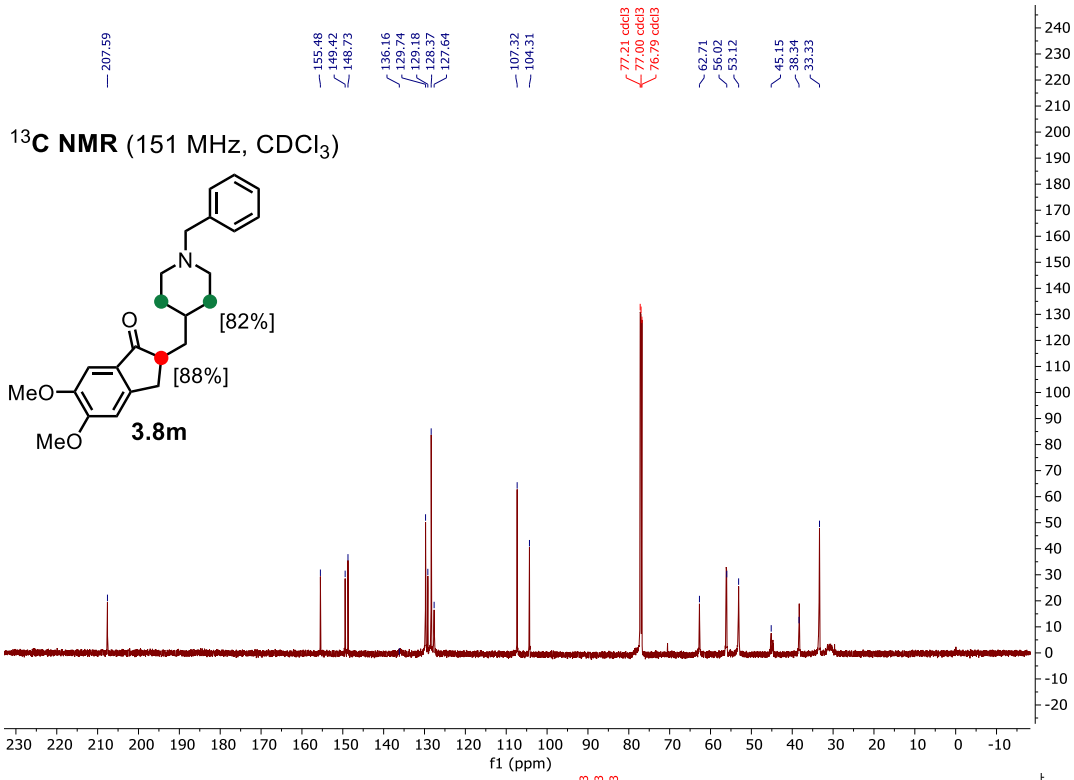

N
O
MeO
MeO

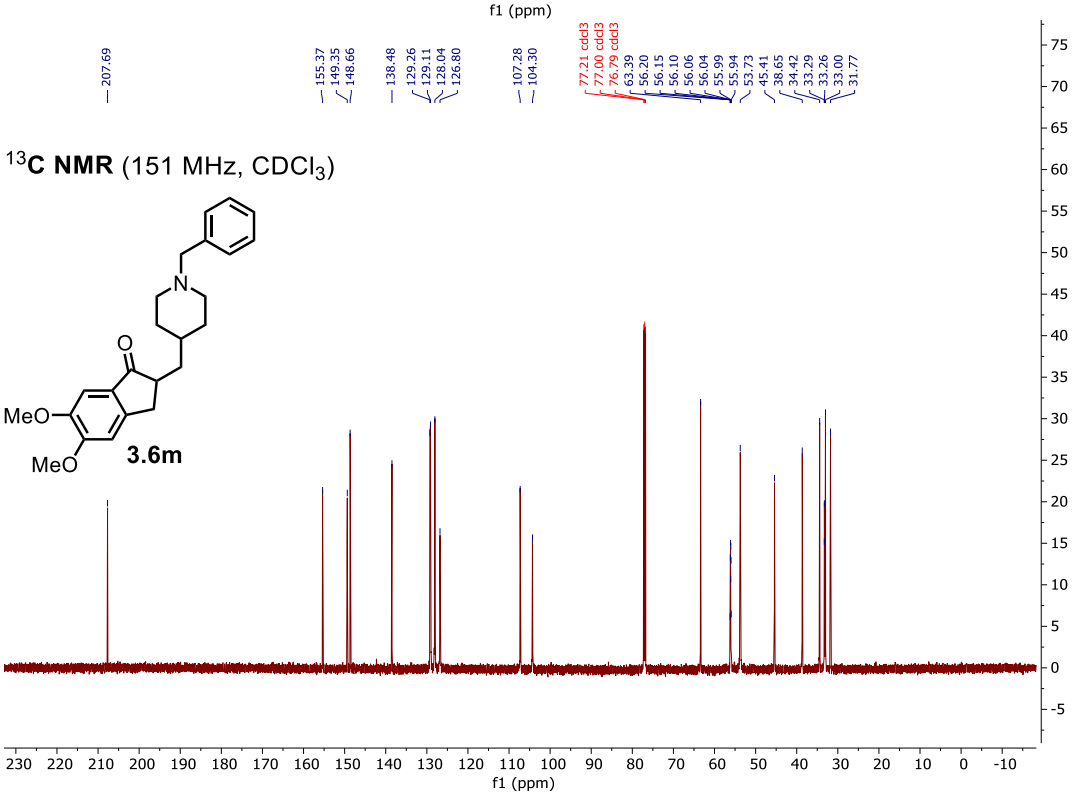
3.6m

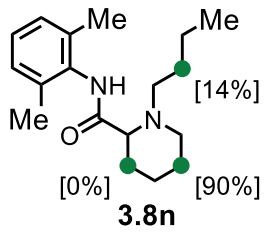

Relative Intensity
m/z
380.2218
381.2260
378.2054
379.2112
382.2295


1H NMR (600 MHz, CDCl3)
[82%]
[88%]
MeO
MeO
3.8m
f1 (ppm)


1H NMR (600 MHz, CDCl3)
MeO
MeO
3.6m
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
3.8m
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
3.6m
f1 (ppm)



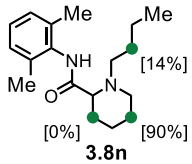
3.8n

Bupivacaine, 3.8n

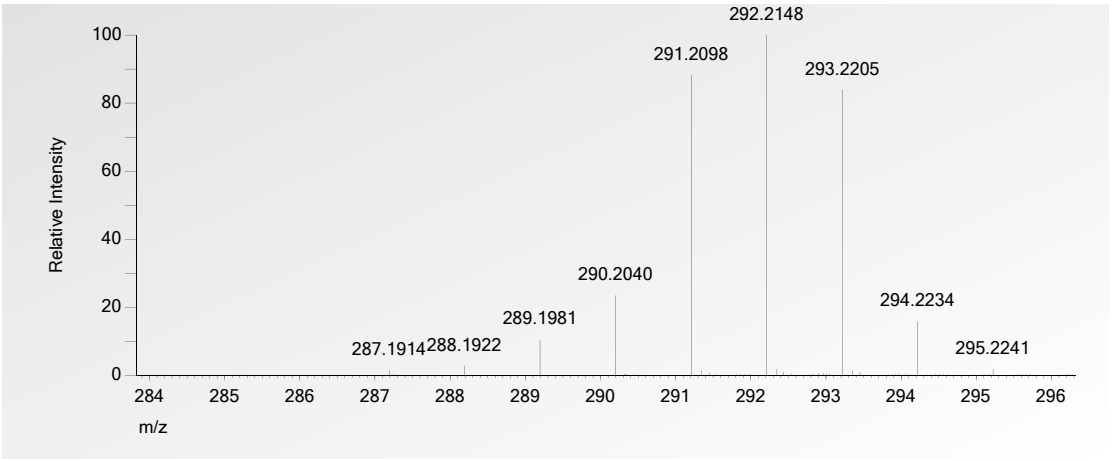
Bupivacaine **3.6n** was reacted with acetone-d_6 **3.7** following the General Procedure A. After purification by column chromatography (MeOH:DCM = 1:49), **3.8n** was obtained as a white solid (55 mg, 96%).

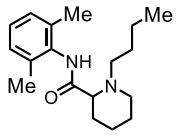
Deuterium incorporation: 2.08 D/molecule (^{1}H NMR), 2.83 D/molecule [HRMS (DART)]

^{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}.

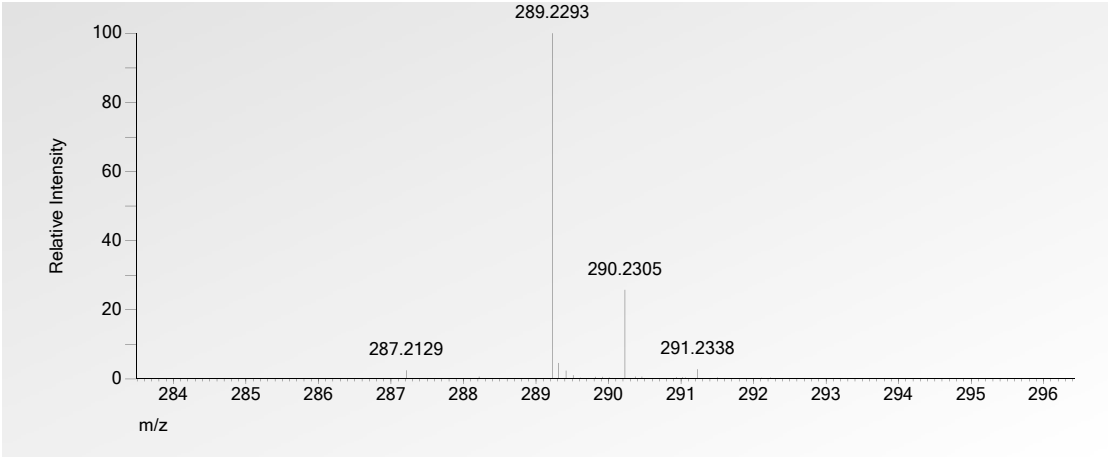

Me
Me
NH
[14%]
Me
O
N
[0%]
[90%]

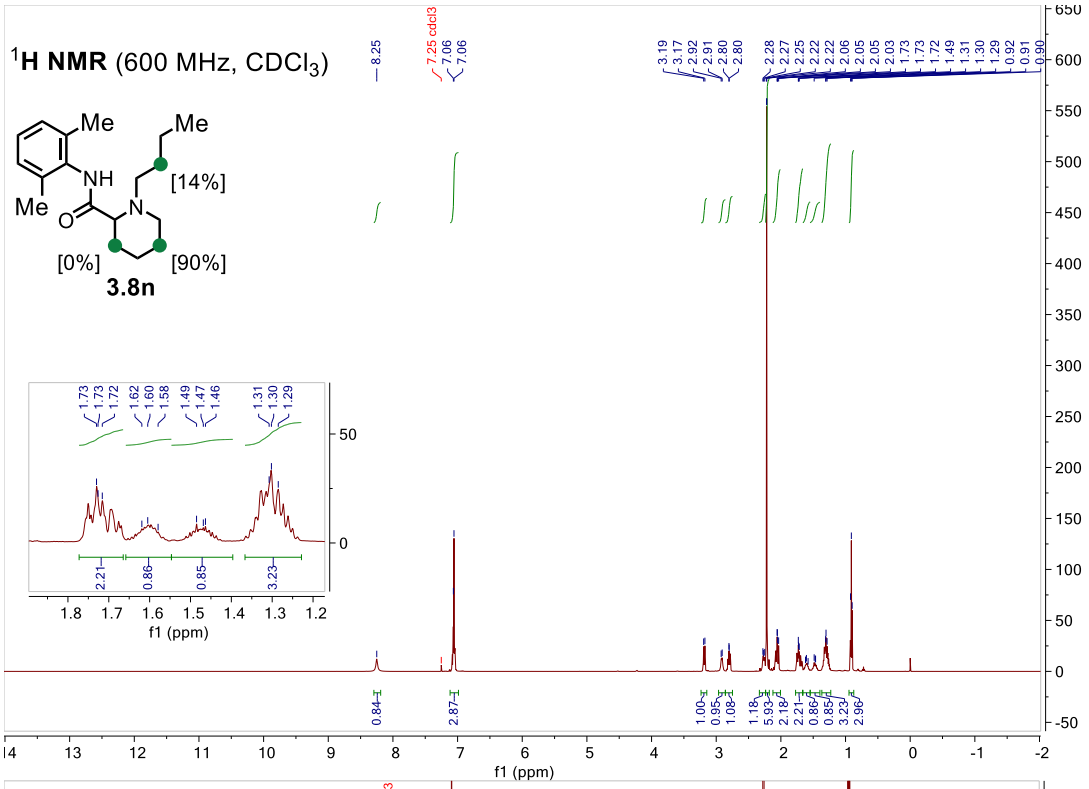
3.8n

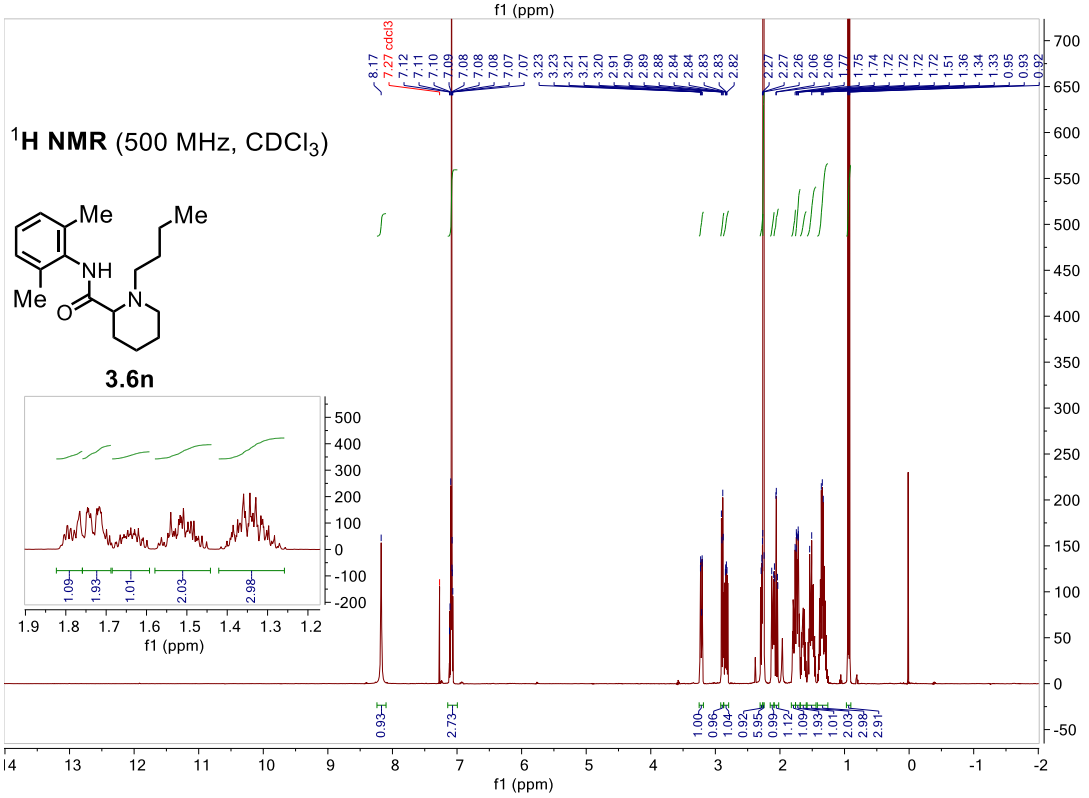

292.2148
291.2098
293.2205
290.2040
294.2234
289.1981
287.1914
288.1922
295.2241
Relative Intensity
m/z

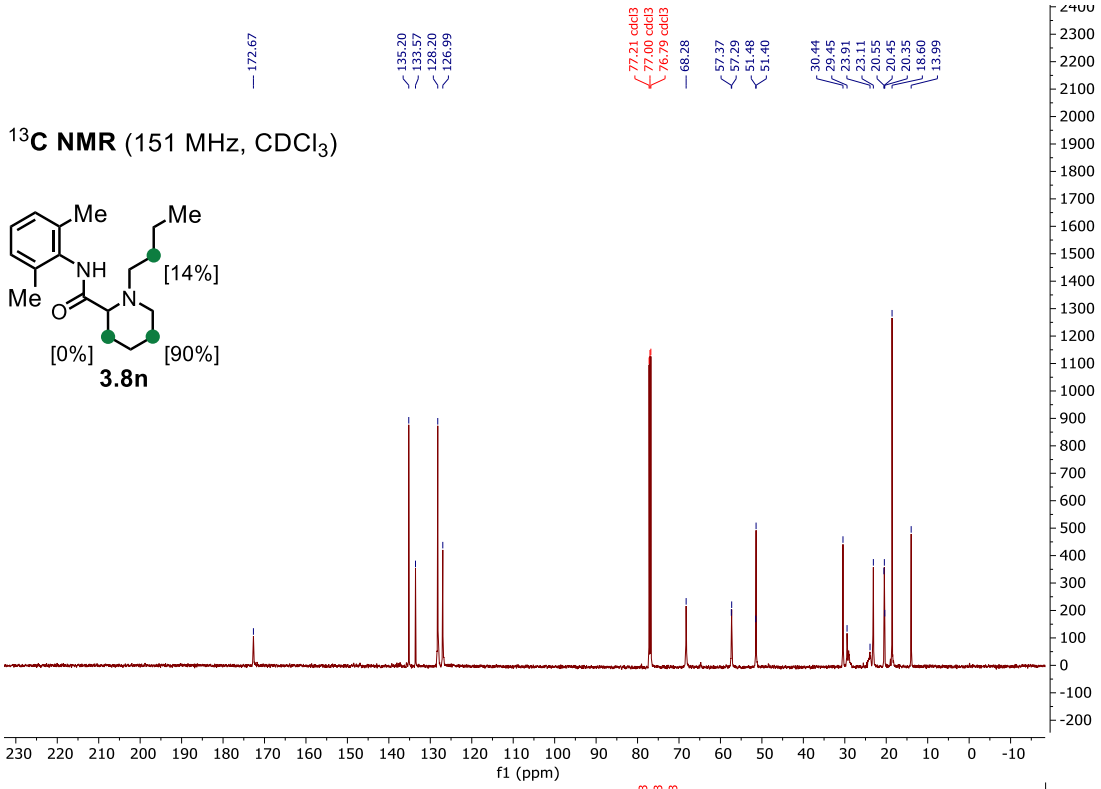

Me
Me
NH
Me
O
N

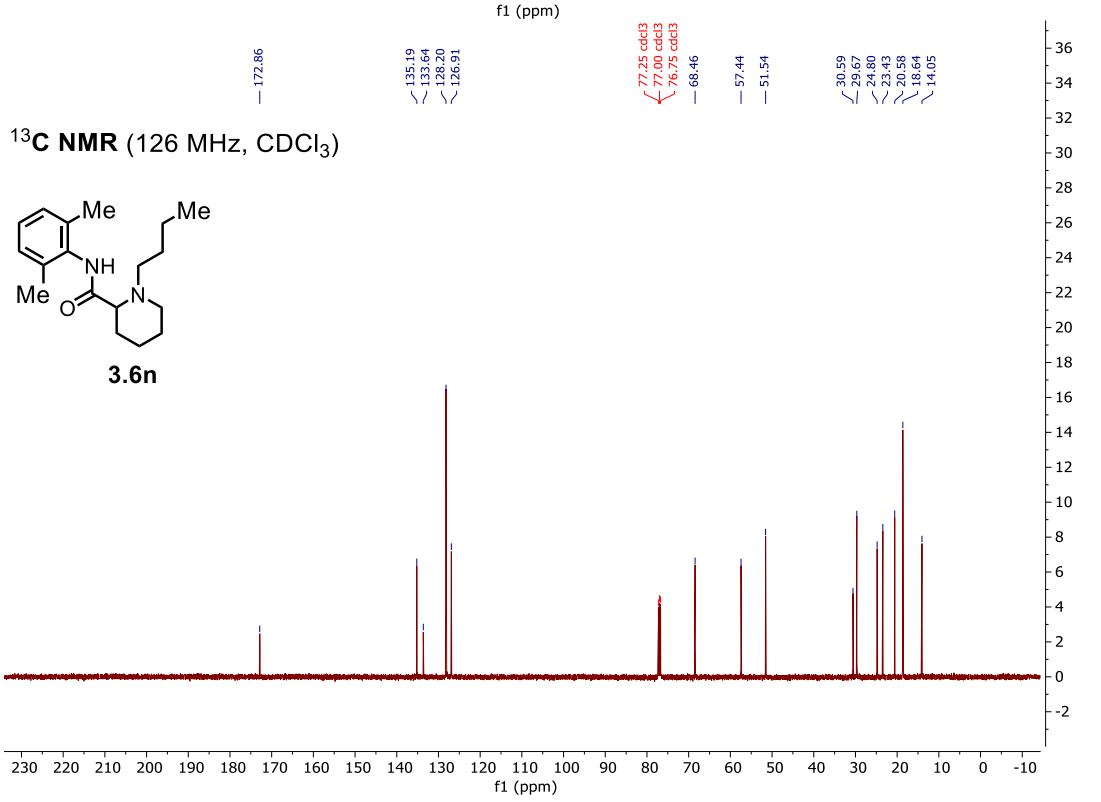
3.6n

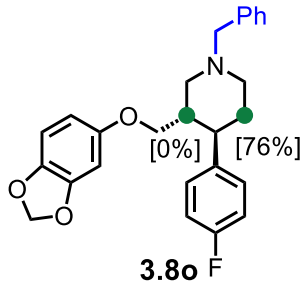

289.2293
290.2305
287.2129
291.2338
Relative Intensity
m/z


^{1}H NMR (600 MHz, CDCl$_3$)
Me
Me
NH
Me
O
N
[14%]
[0%]
[90%]
3.8n
f1 (ppm)


^{1}H NMR (500 MHz, CDCl$_3$)
Me
Me
NH
Me
O
N
3.6n
f1 (ppm)


172.67
135.20
133.57
128.20
126.99
77.21 cdcl3
77.00 cdcl3
76.79 cdcl3
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
13C NMR (151 MHz, CDCl3)
Me
Me
NH
Me
O
N
[14%]
[0%]
[90%]
3.8n
f1 (ppm)


172.86
135.19
133.64
128.20
126.91
77.25 cdcl3
77.00 cdcl3
76.75 cdcl3
68.46
57.44
51.54
30.59
29.67
24.80
23.43
20.58
18.64
14.05
13C NMR (126 MHz, CDCl3)
Me
Me
NH
Me
O
N
3.6n
f1 (ppm)



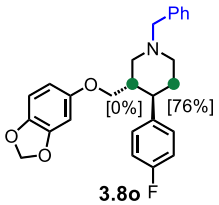
3.8o

***N*-Bn paroxetine, 3.8o**

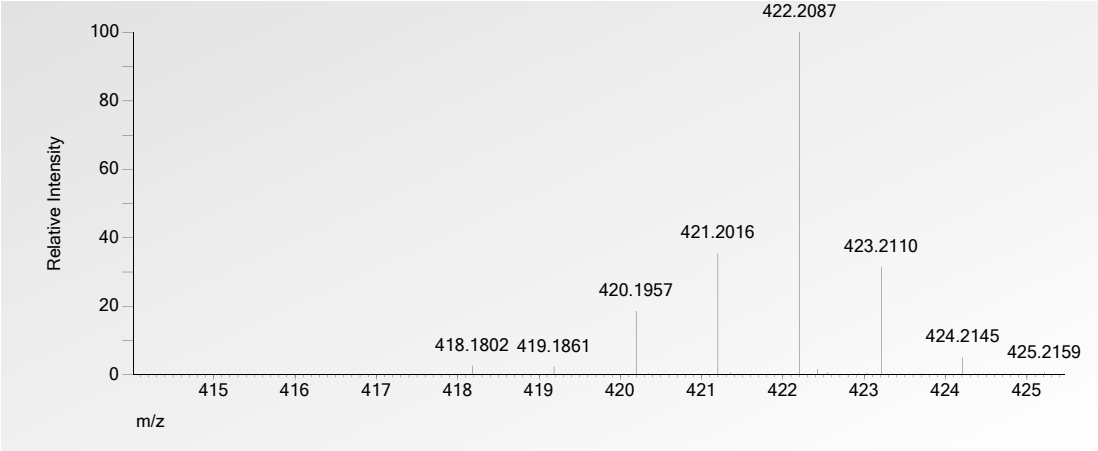
N-Bn paroxetine **3.6o** was reacted with acetone-d_6 **3.7** following the General Procedure A. After purification by column chromatography (Et_2O:hexanes = 1:9), **3.8o** was obtained as a white solid (82 mg, 98%).

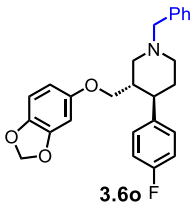
Deuterium incorporation: 1.52 D/molecule (^{1}H NMR), 1.85 D/molecule [HRMS (DART)]

^{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).

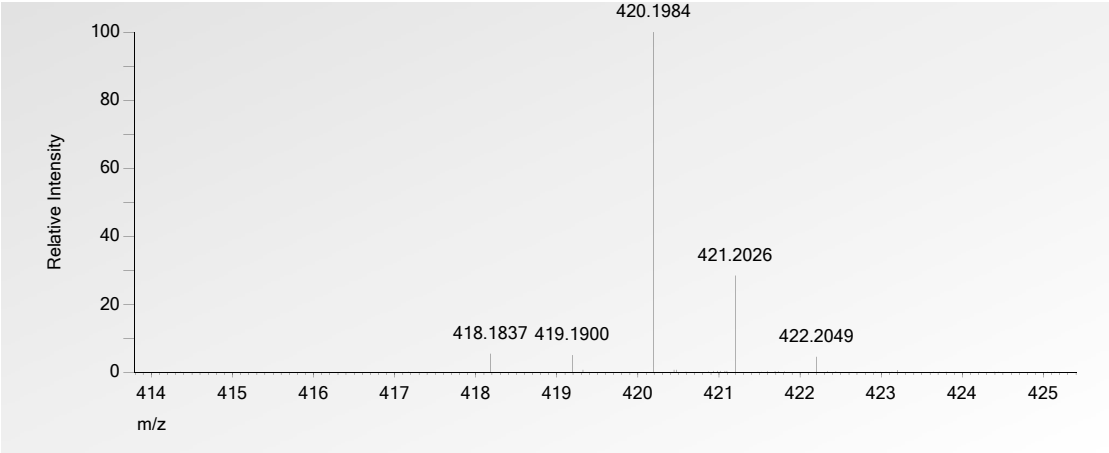

Ph
N
O
[0%]
[76%]
O
O
F

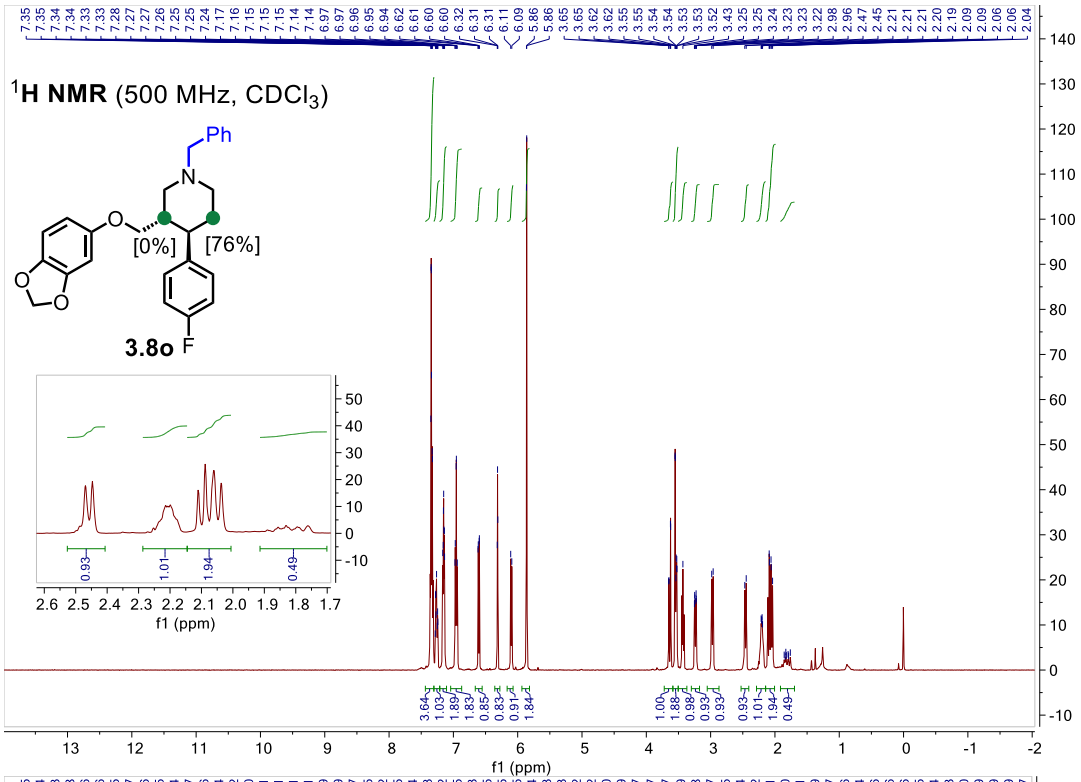
3.8o

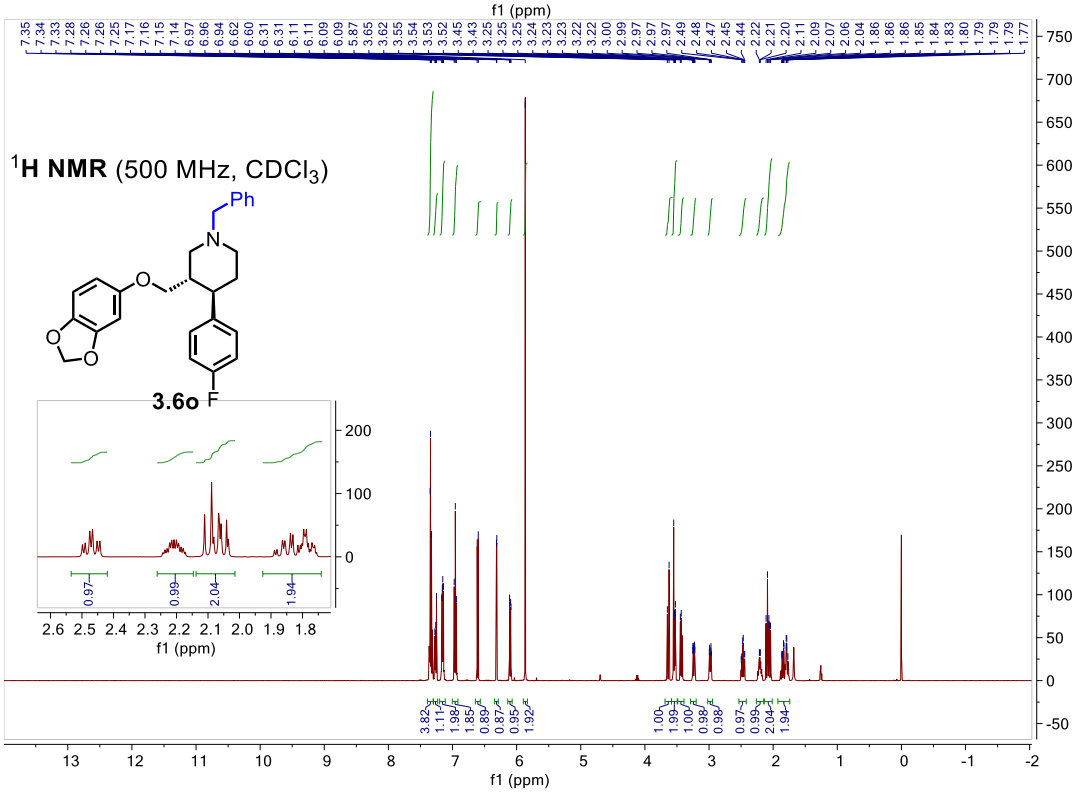

422.2087
100
80
60
40
20
0
Relative Intensity
421.2016
423.2110
420.1957
424.2145
418.1802
419.1861
425.2159
415
416
417
418
419
420
421
422
423
424
425
m/z

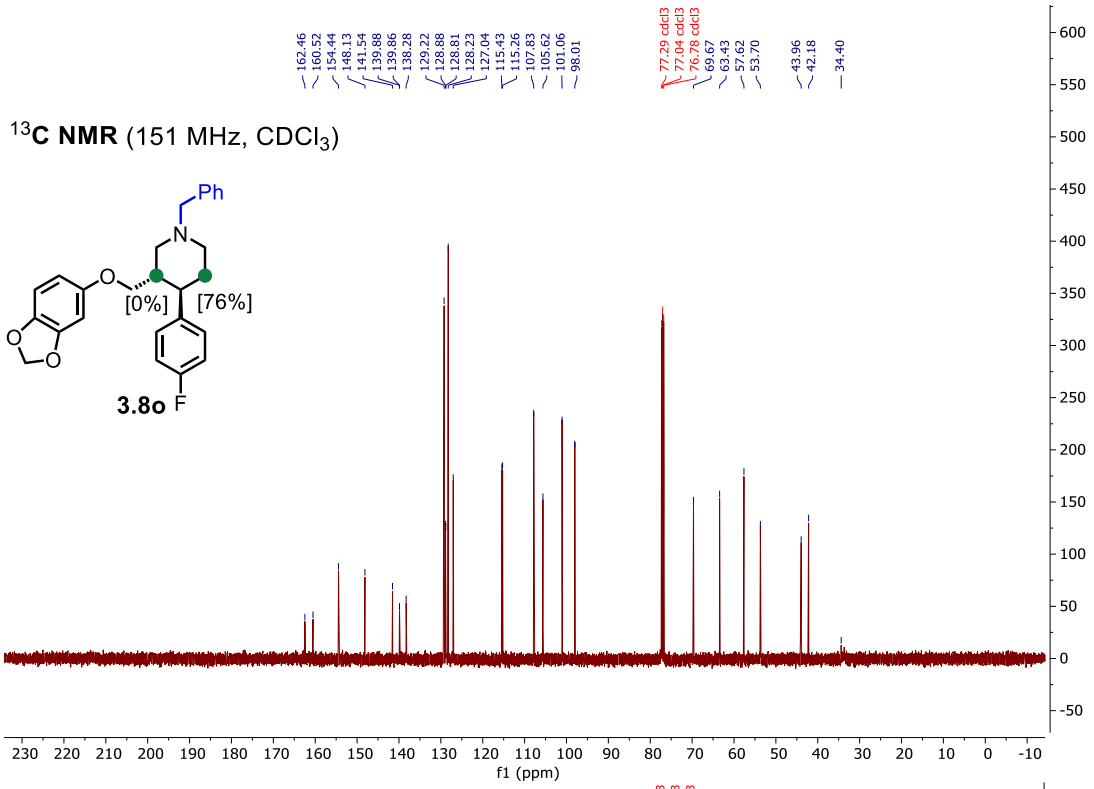

Ph
N
O
O
O
F

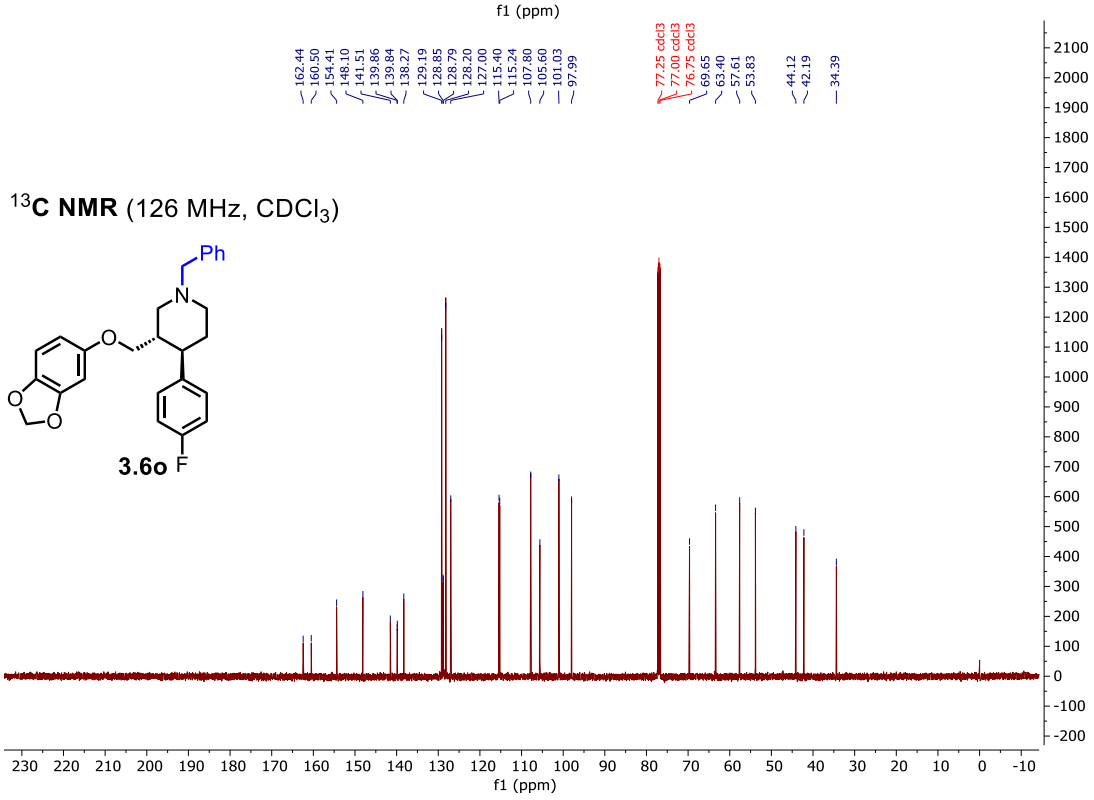
3.6o

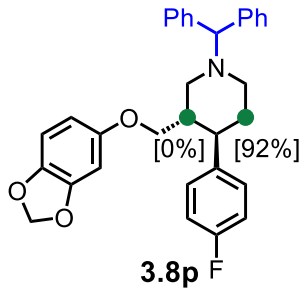

420.1984
100
80
60
40
20
0
Relative Intensity
421.2026
418.1837
419.1900
422.2049
414
415
416
417
418
419
420
421
422
423
424
425
m/z


1H NMR (500 MHz, CDCl3)
Ph
N
O
[0%]
[76%]
O
O
F
3.8o
f1 (ppm)


1H NMR (500 MHz, CDCl3)
Ph
N
O
O
O
F
3.6o
f1 (ppm)


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
77.29 cdcl3
77.04 cdcl3
76.78 cdcl3
69.67
63.43
57.62
53.70
43.96
42.18
34.40
^{13}C NMR (151 MHz, CDCl$_3$)
Ph
N
O
[0%]
[76%]
O
O
F
3.8o
f1 (ppm)


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
^{13}C NMR (126 MHz, CDCl$_3$)
Ph
N
O
O
O
F
3.6o
f1 (ppm)



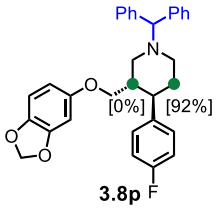
3.8p

***N*-Bzh Paroxetine, 3.8p**

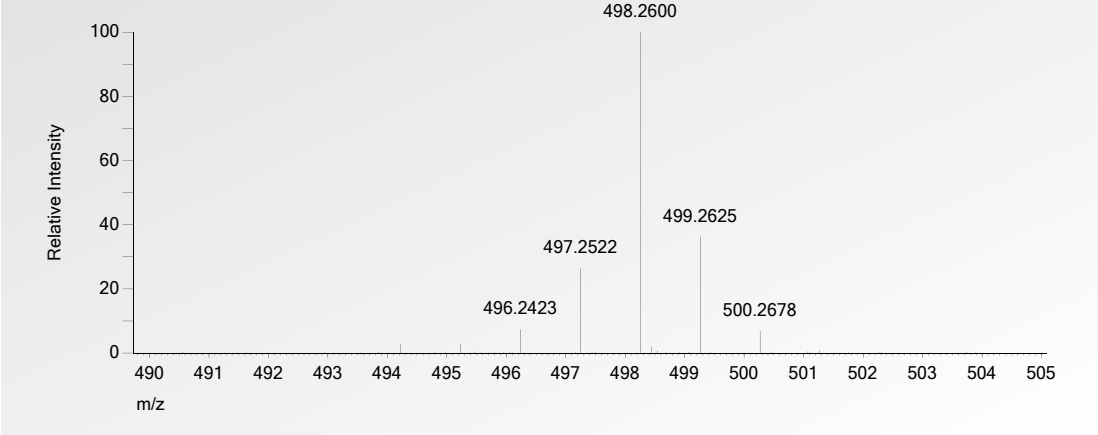
N-Bzh paroxetine **3.6p** was reacted with acetone-d_6 **3.7** following the General Procedure A. After purification by column chromatography (Et_2O:hexanes = 1:9), **3.8p** was obtained as a colorless liquid (94 mg, 95%).

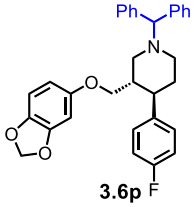
Deuterium incorporation: 1.88 D/molecule (^{1}H NMR), 2.09 D/molecule [HRMS (DART)]

^{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).

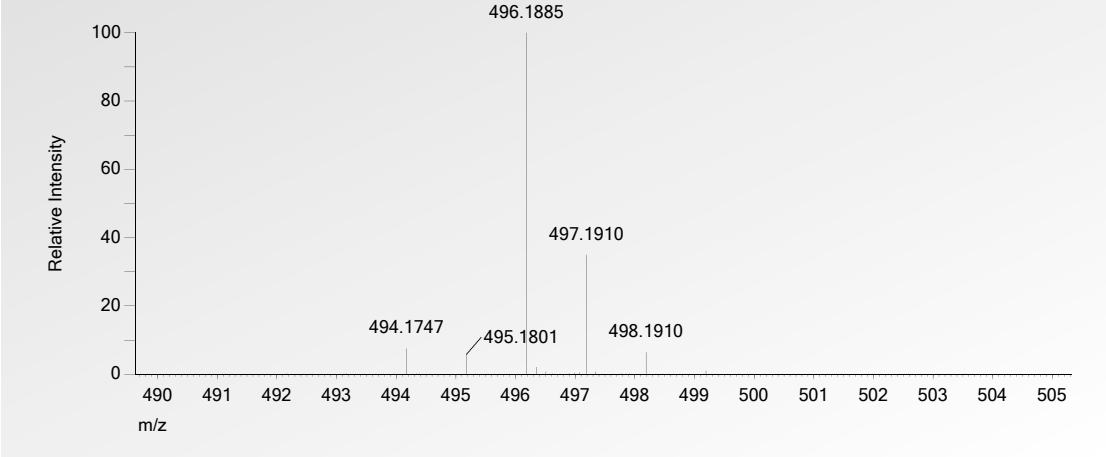

Ph
Ph
N
O
[0%]
[92%]
O
O
F

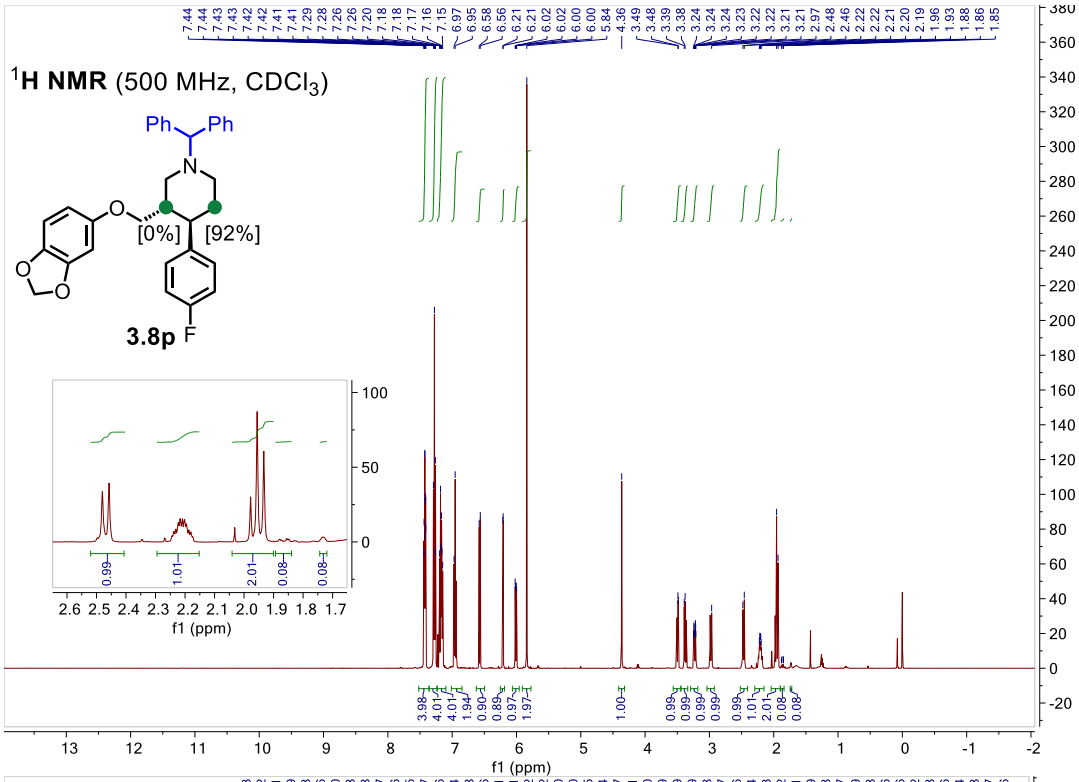
3.8p

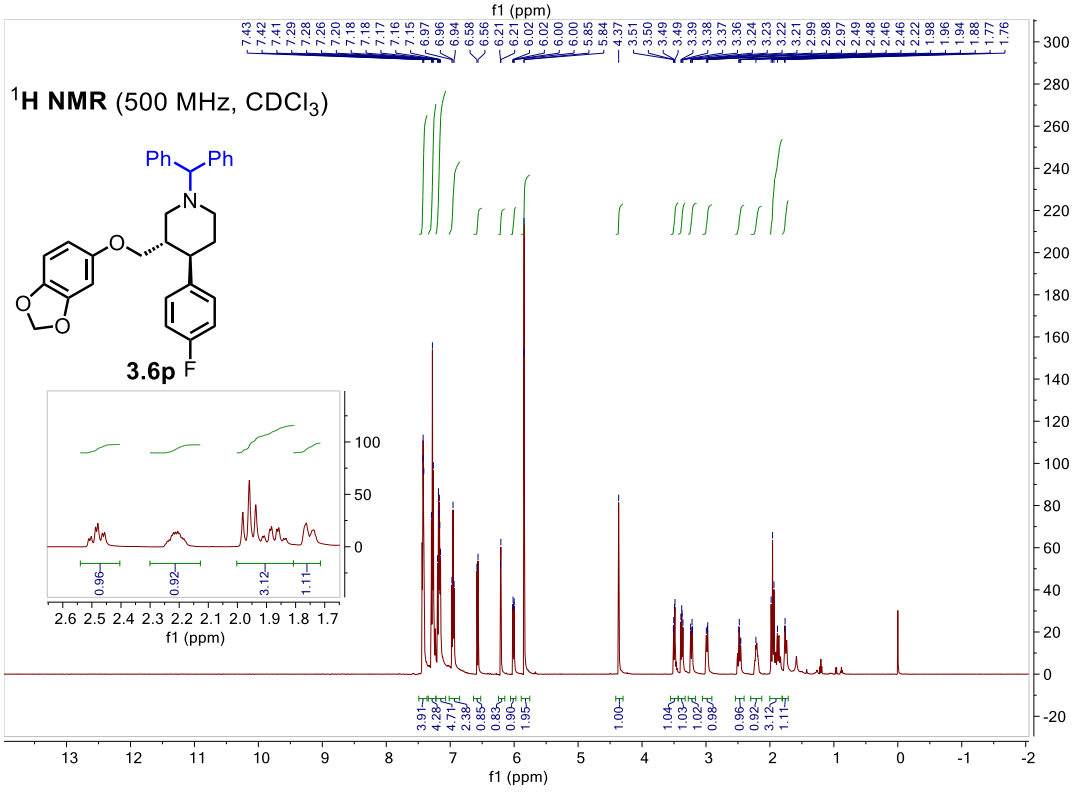

498.2600
499.2625
497.2522
496.2423
500.2678
Relative Intensity
m/z
100
80
60
40
20
0
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505

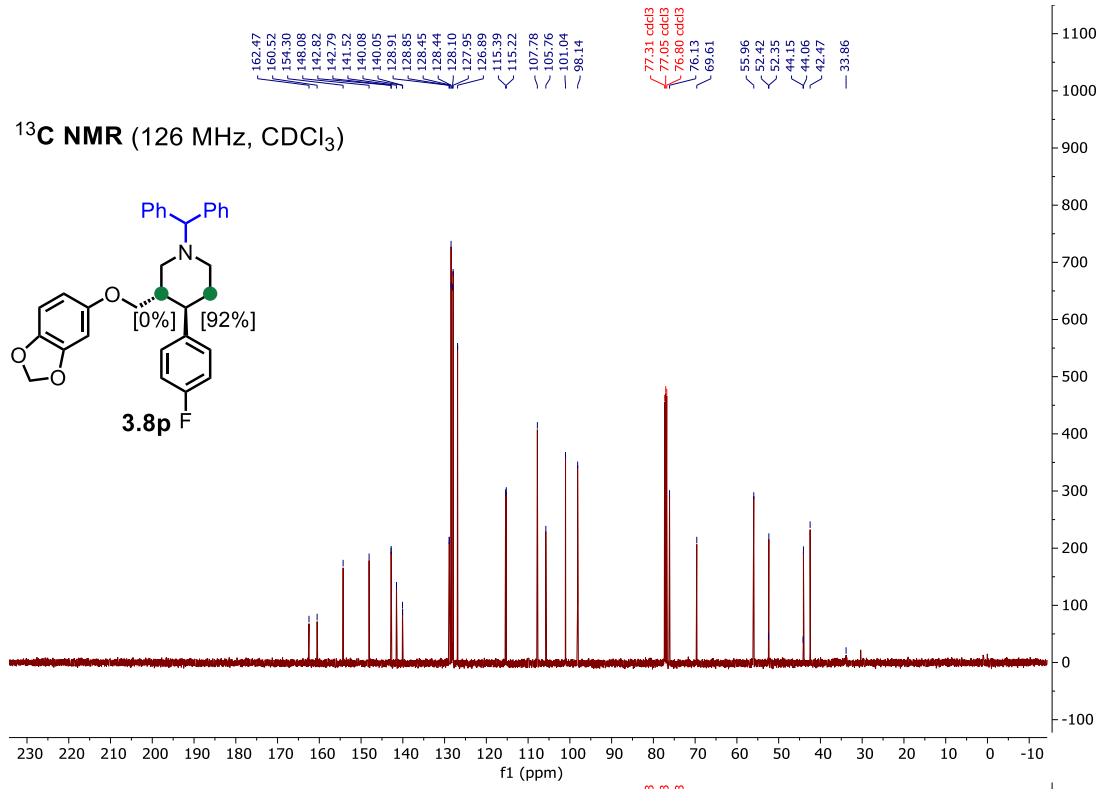

Ph
Ph
N
O
O
O
F

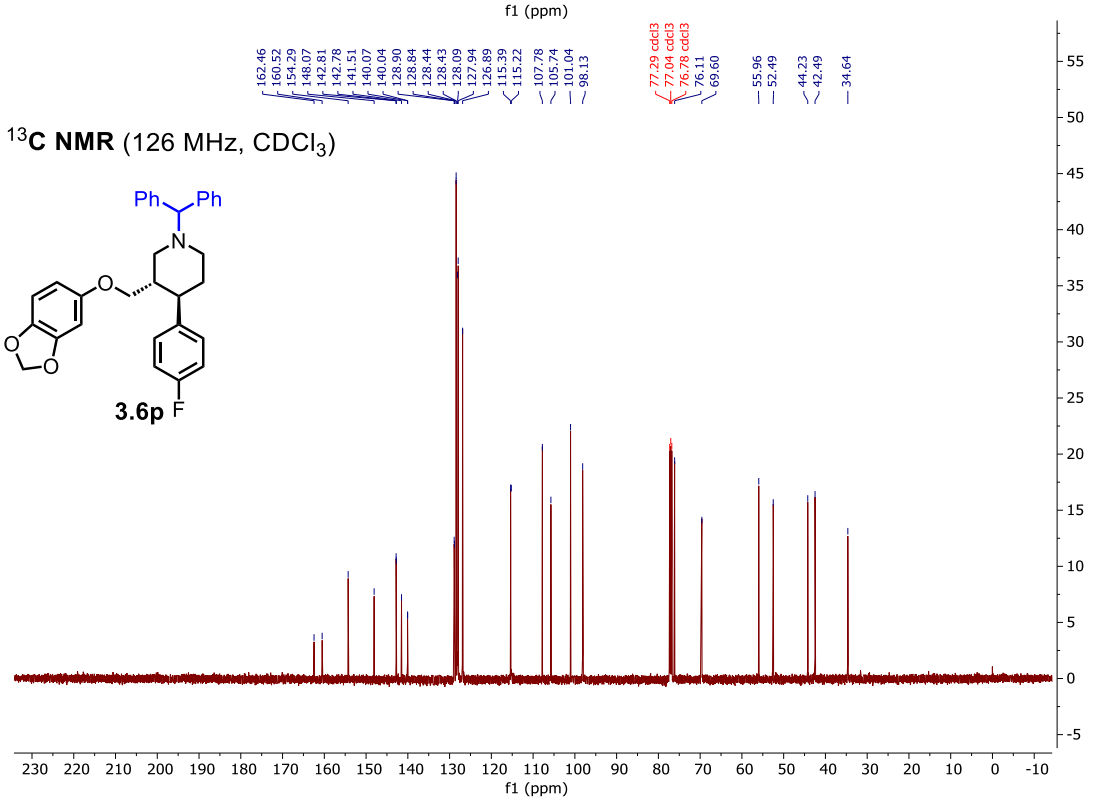
3.6p

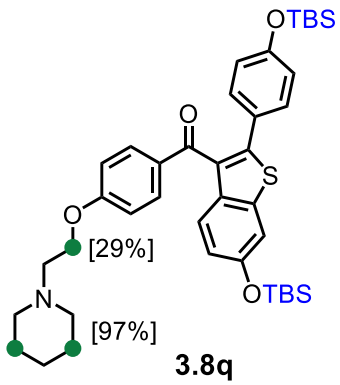

496.1885
497.1910
494.1747
495.1801
498.1910
Relative Intensity
m/z
100
80
60
40
20
0
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505


1H NMR (500 MHz, CDCl3)
Ph
Ph
N
O
[0%]
[92%]
O
O
3.8p
F
f1 (ppm)


1H NMR (500 MHz, CDCl3)
Ph
Ph
N
O
O
O
3.6p
F
f1 (ppm)


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
13C NMR (126 MHz, CDCl3)
Ph
Ph
N
O
[0%]
[92%]
O
O
3.8p
F
f1 (ppm)


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
13C NMR (126 MHz, CDCl3)
Ph
Ph
N
O
O
O
3.6p
F
f1 (ppm)



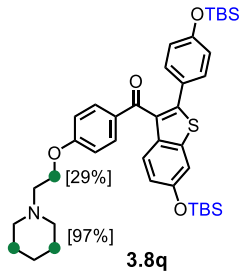
3.8q

***O*-TBS raloxifene, 3.8q**

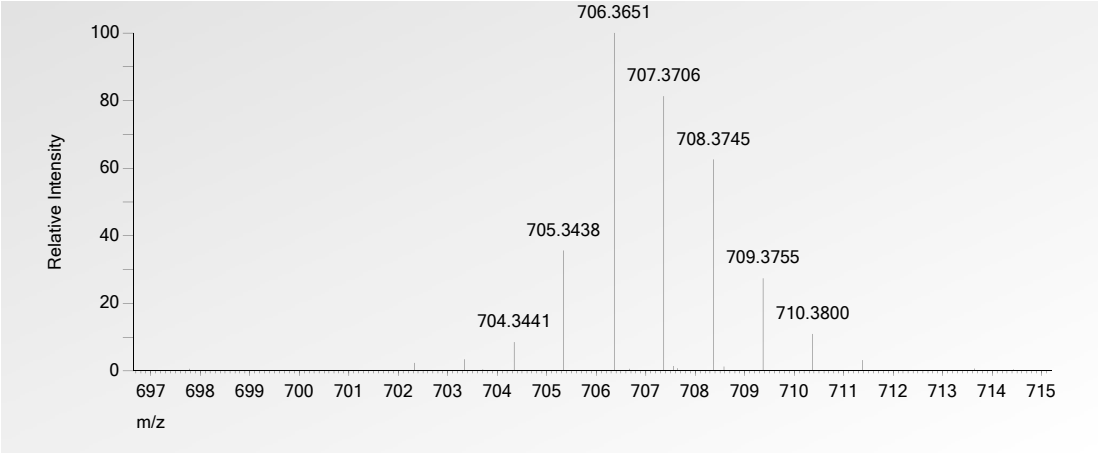
O-TBS raloxifene **3.6q** was reacted with acetone-d_6 **3.7** following the General Procedure A. After purification by column chromatography (MeOH:DCM = 1:49), **3.8q** was obtained as a yellow liquid (136 mg, 97%).

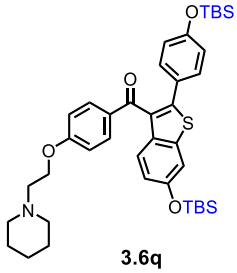
Deuterium incorporation: 4.46 D/molecule (^{1}H NMR), 5.08 D/molecule [HRMS (DART)]

^{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}.

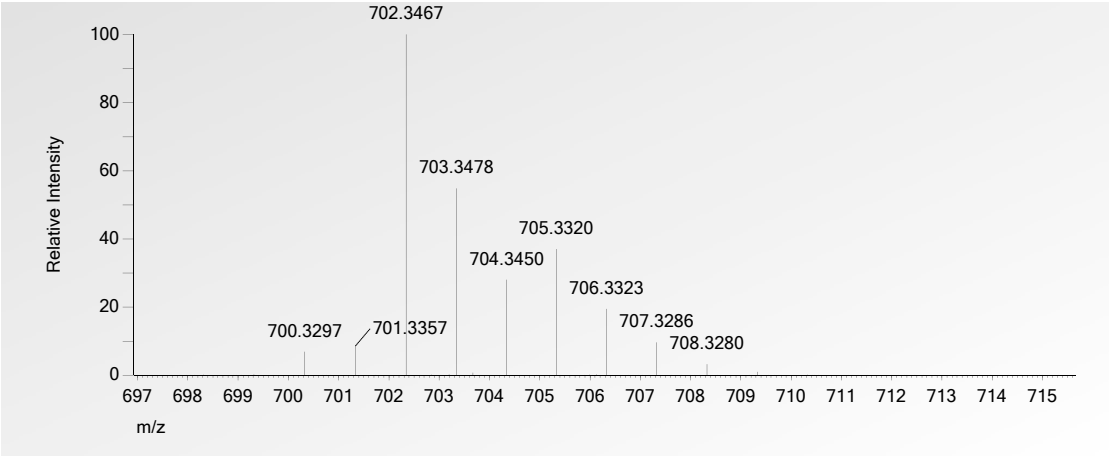

OTBS
O
S
O
[29%]
N
[97%]
OTBS

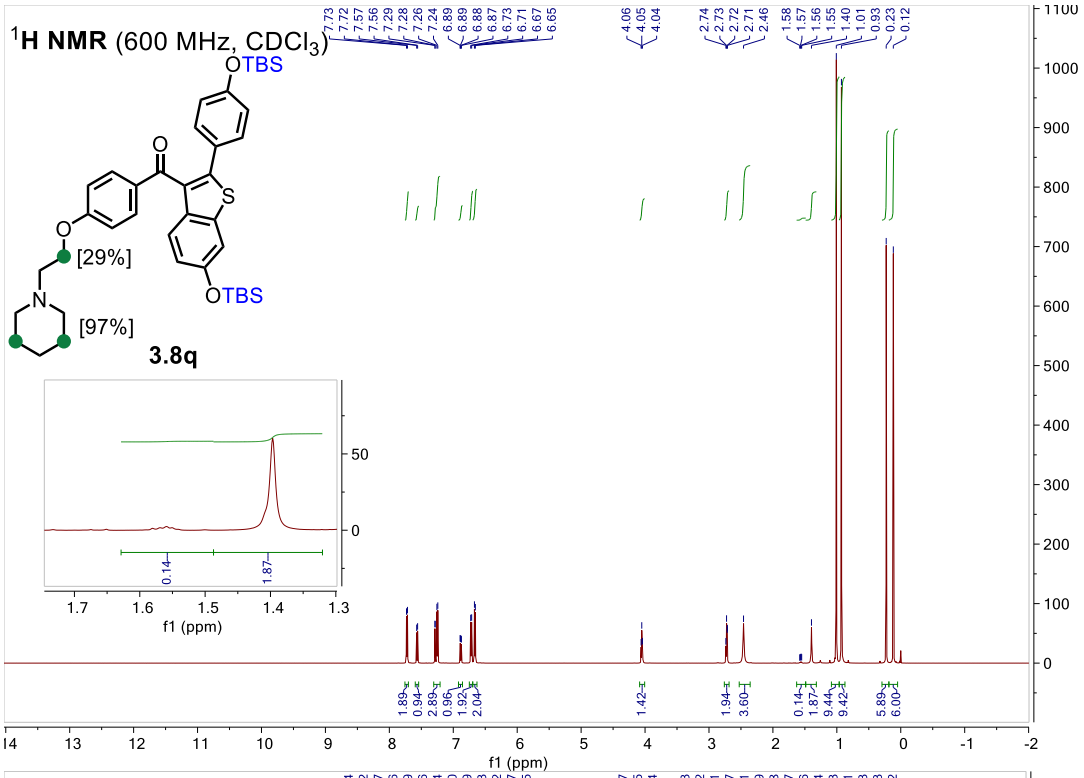
3.8q

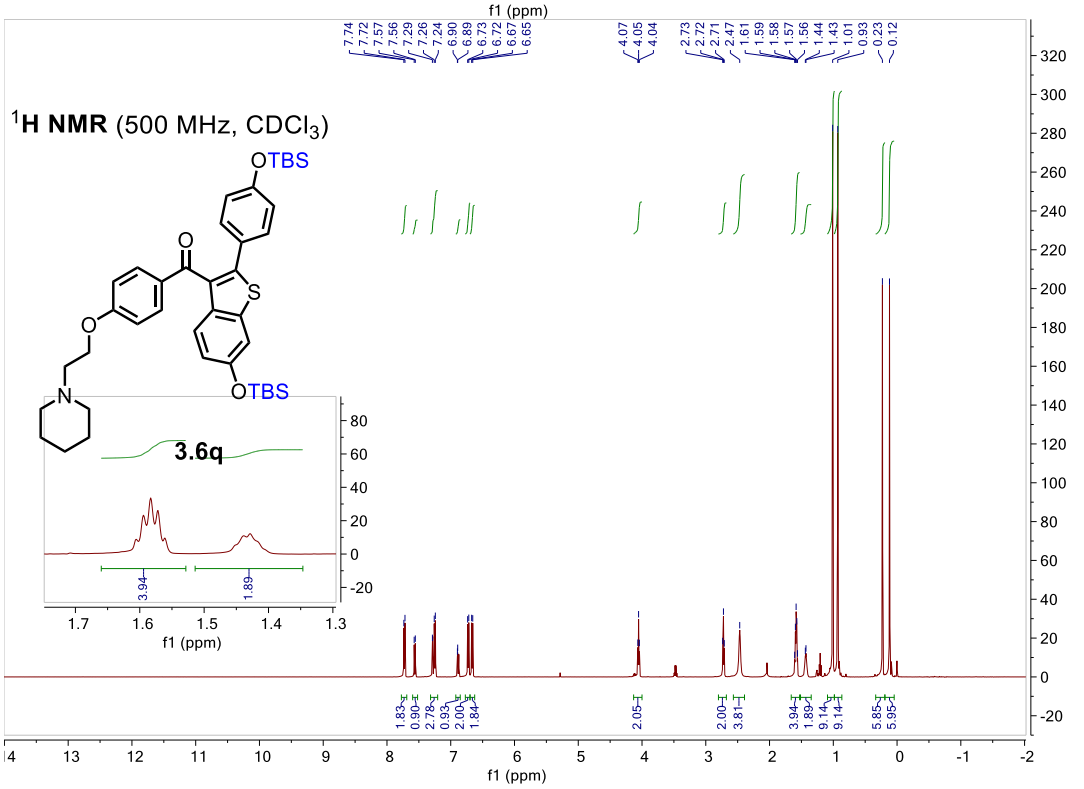

706.3651
707.3706
708.3745
705.3438
709.3755
710.3800
704.3441
100
80
60
40
20
0
Relative Intensity
697 698 699 700 701 702 703 704 705 706 707 708 709 710 711 712 713 714 715
m/z

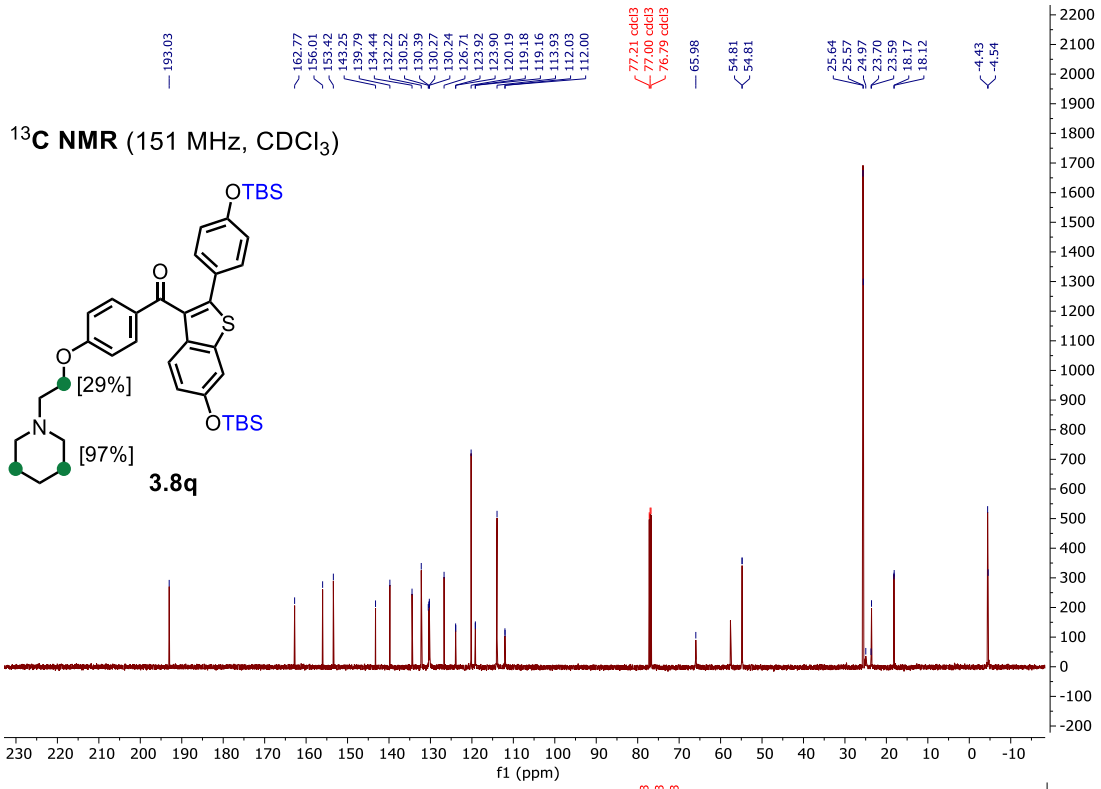

OTBS
O
S
O
N
OTBS

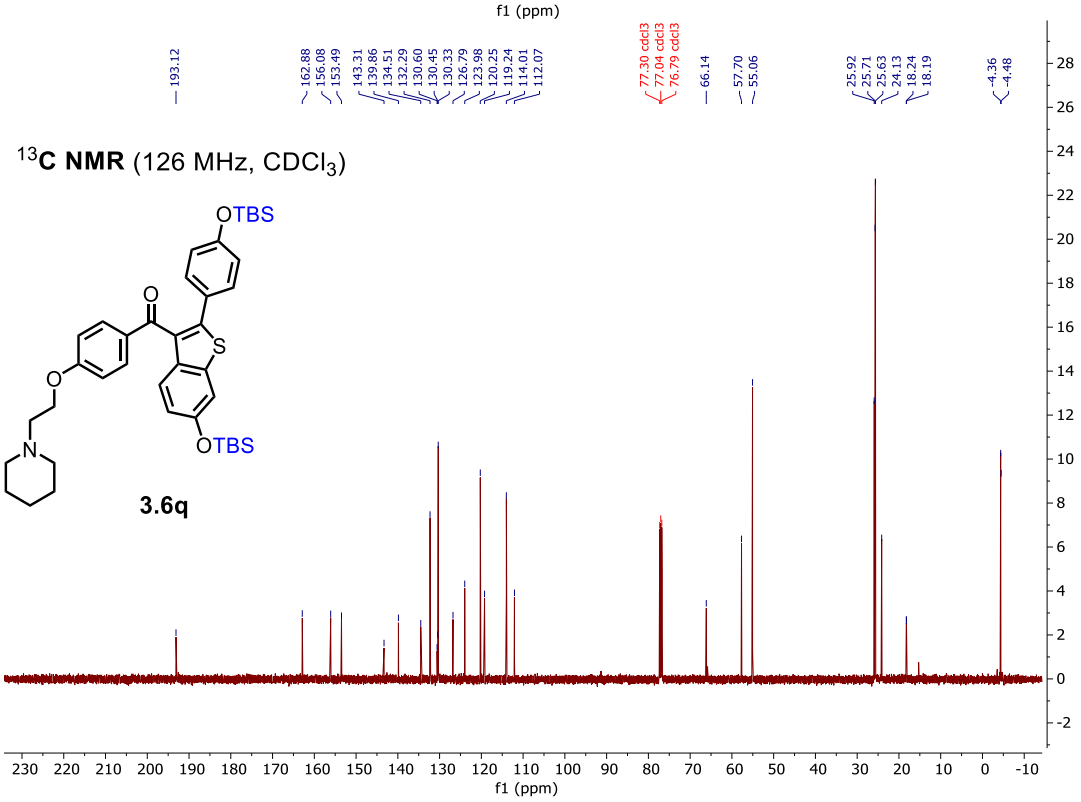
3.6q

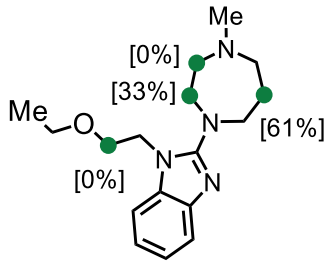

702.3467
703.3478
705.3320
704.3450
706.3323
707.3286
708.3280
700.3297
701.3357
100
80
60
40
20
0
Relative Intensity
697 698 699 700 701 702 703 704 705 706 707 708 709 710 711 712 713 714 715
m/z


1H NMR (600 MHz, CDCl3)
OTBS
O
S
O
[29%]
N
[97%]
OTBS
3.8q
f1 (ppm)


1H NMR (500 MHz, CDCl3)
OTBS
O
S
O
N
OTBS
3.6q
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
3.8q
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 (126 MHz, CDCl3)
OTBS
O
S
O
N
OTBS
3.6q
f1 (ppm)



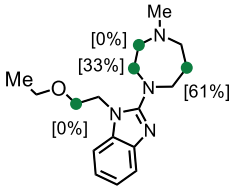
3.8r

Emedastine, 3.8r

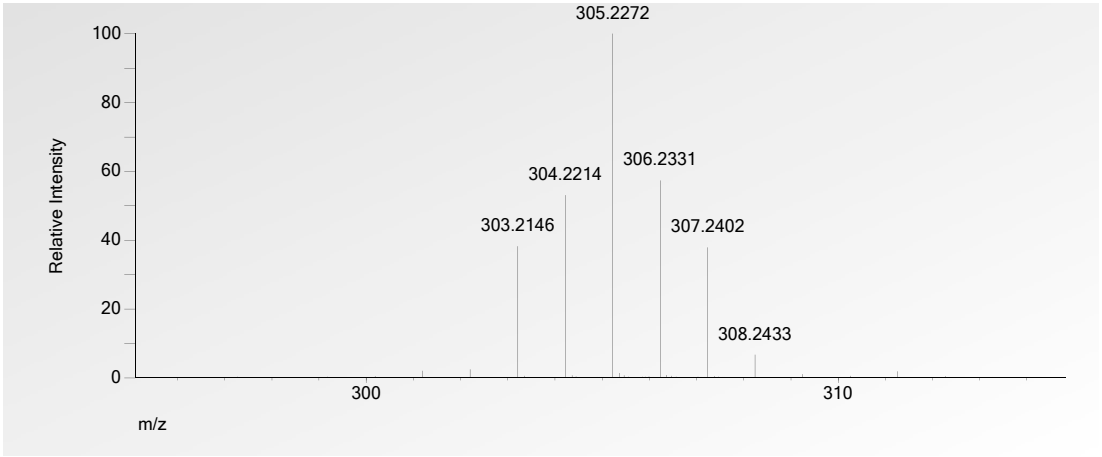
Emedastine **3.6r** was reacted with acetone-d_6 **3.7** following the General Procedure A. After purification by column chromatography (MeOH:DCM = 1:15), **3.8r** was obtained as a colorless liquid (53 mg, 88%).

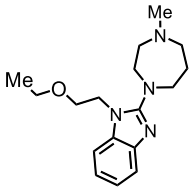
Deuterium incorporation: 1.88 D/molecule (^{1}H NMR), 2.03 D/molecule [HRMS (DART)]

^{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}.

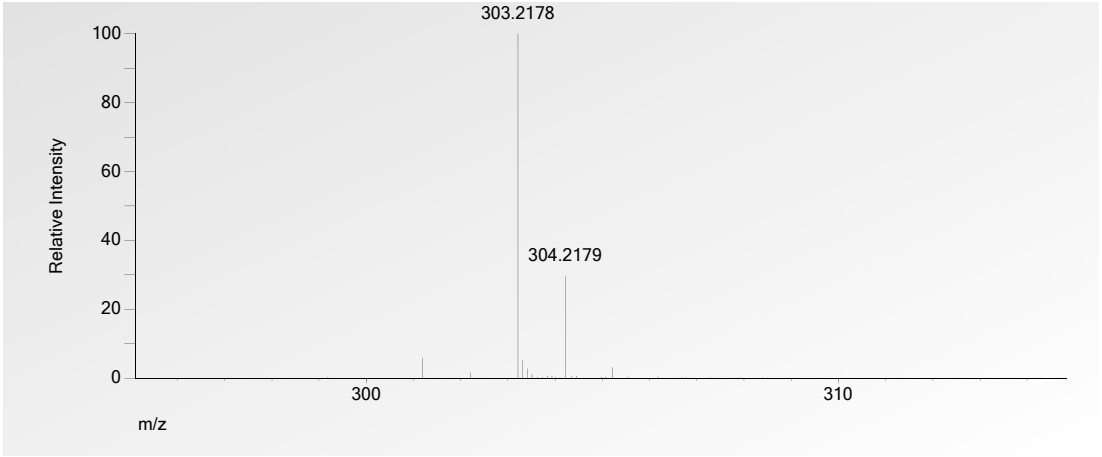

Me
[0%]
[33%]
Me
O
[61%]
[0%]
N
N

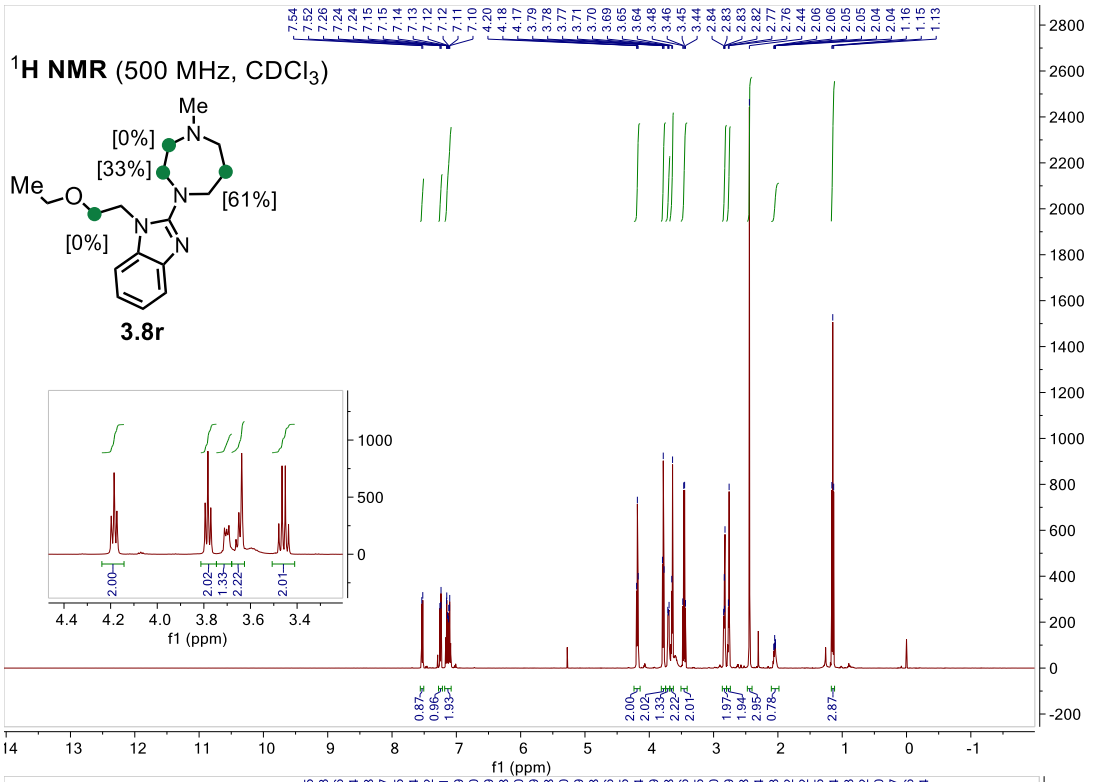
3.8r

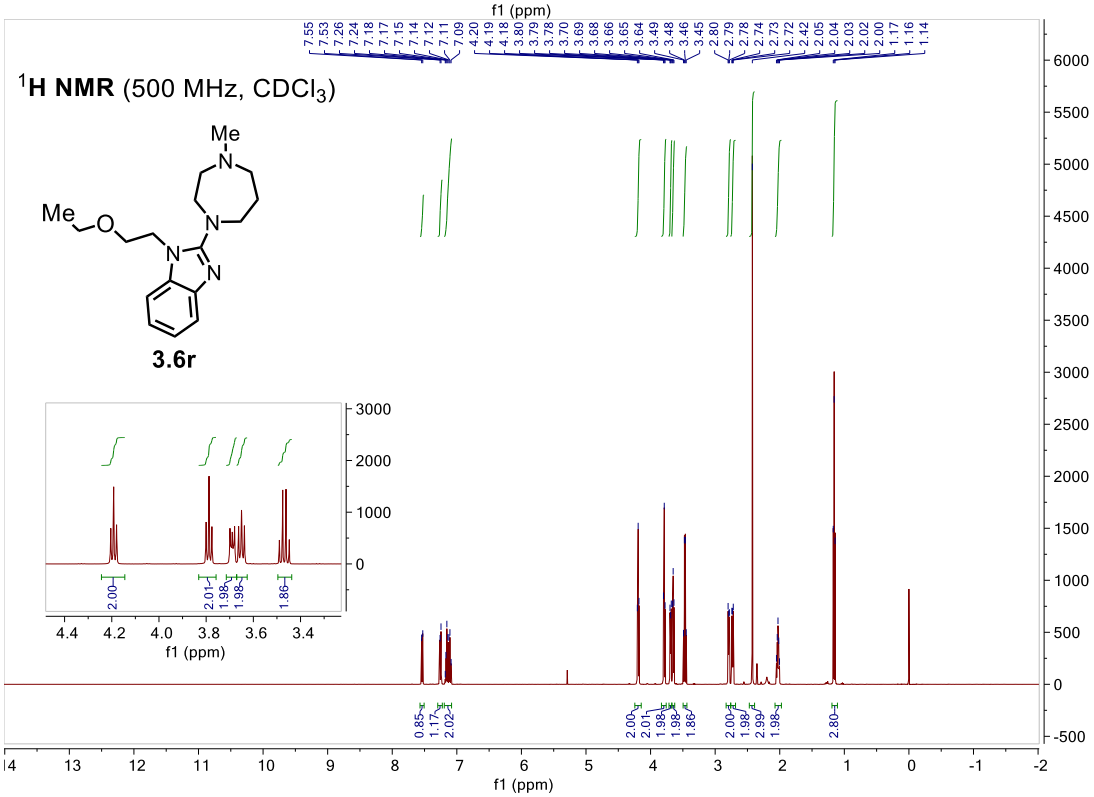

305.2272
304.2214
306.2331
303.2146
307.2402
308.2433
Relative Intensity
100
80
60
40
20
0
300
310
m/z

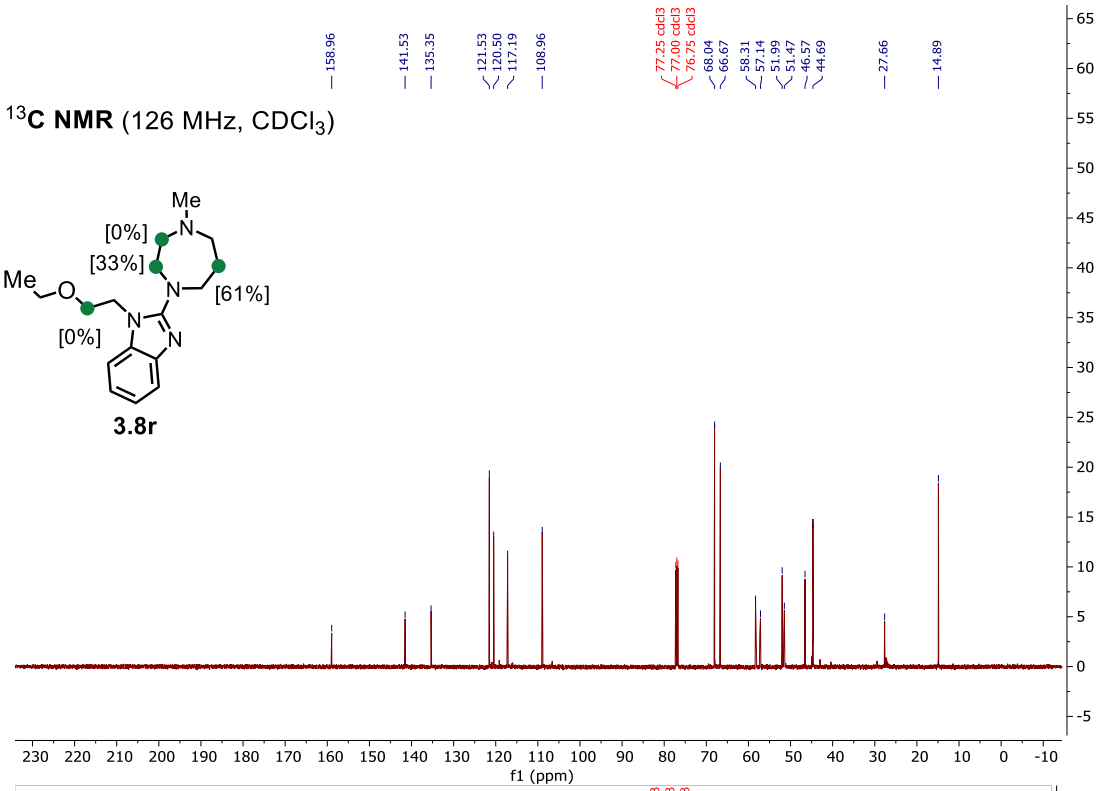

Me
Me
O
N
N

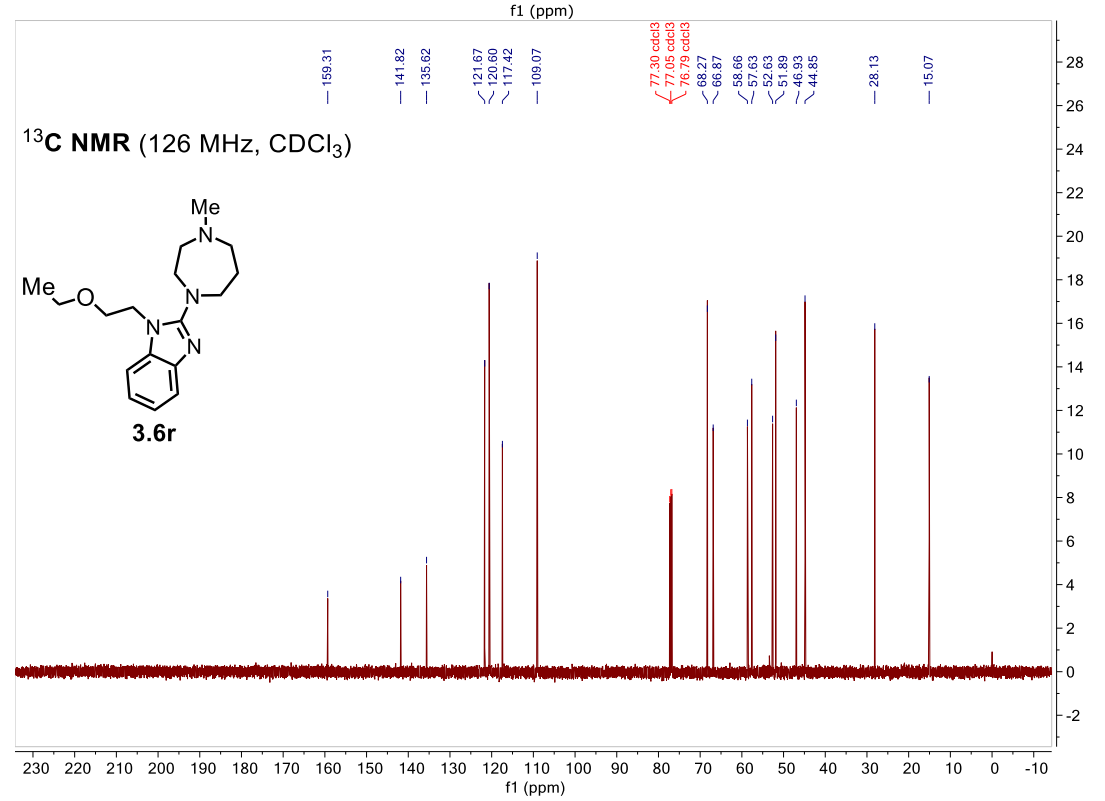
3.6r

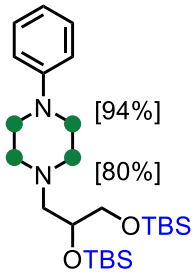

303.2178
304.2179
Relative Intensity
100
80
60
40
20
0
300
310
m/z


^{1}H NMR (500 MHz, CDCl$_3$)
Me
[0%]
[33%]
[61%]
Me
[0%]
3.8r
f1 (ppm)


^{1}H NMR (500 MHz, CDCl$_3$)
Me
Me
3.6r
f1 (ppm)


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
13C NMR (126 MHz, CDCl3)
Me
[0%]
[33%]
[61%]
Me
O
[0%]
N
N
N
N
3.8r
f1 (ppm)


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
13C NMR (126 MHz, CDCl3)
Me
Me
O
N
N
N
N
3.6r
f1 (ppm)



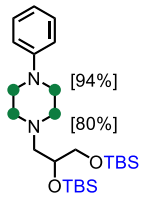
3.8s

***O*-TBS dropropizine, 3.8s**

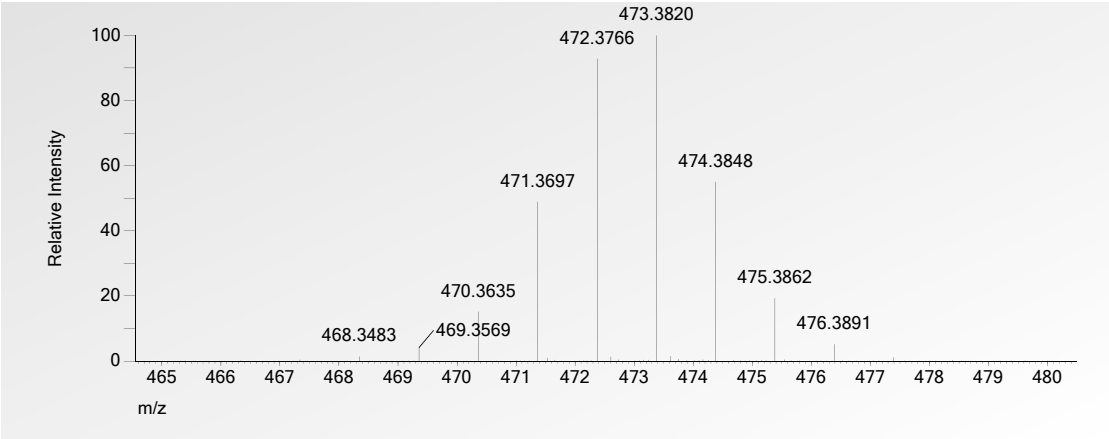
O-TBS dropropizin*e* **3.6s** was reacted with acetone-d_6 **3.7** following the General Procedure B. After purification by column chromatography (MeOH:DCM = 1:99), **3.8s** was obtained as a yellow liquid (87 mg, 94%).

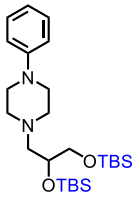
Deuterium incorporation: 6.96 D/molecule (^{1}H NMR), 7.61 D/molecule [HRMS (DART)]

^{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}.

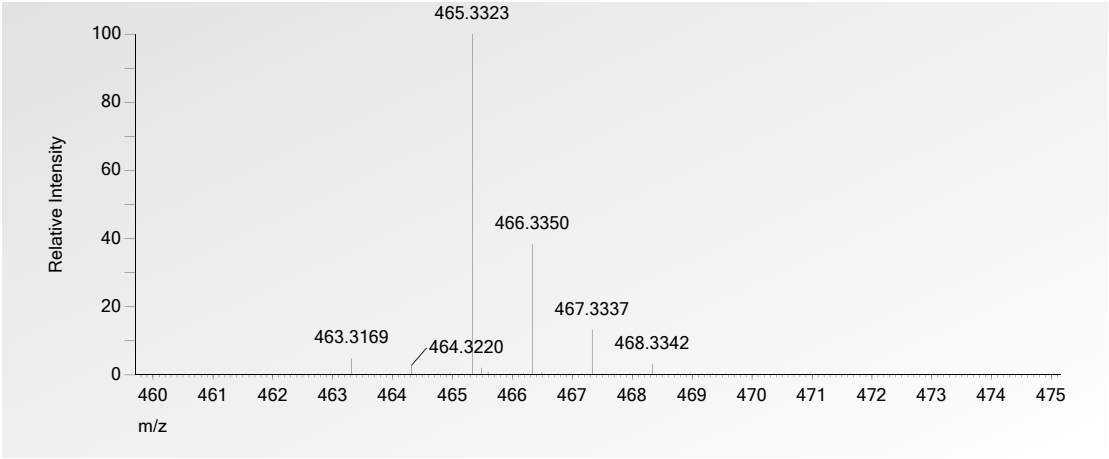

[94%]
[80%]
OTBS
OTBS

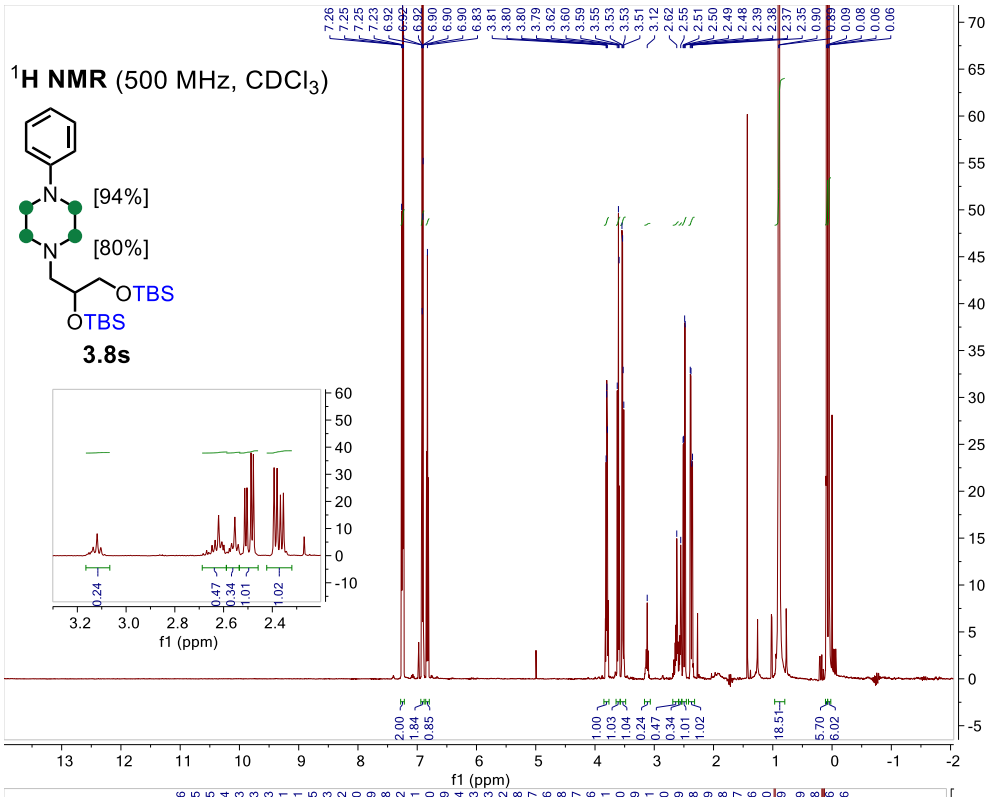
3.8s

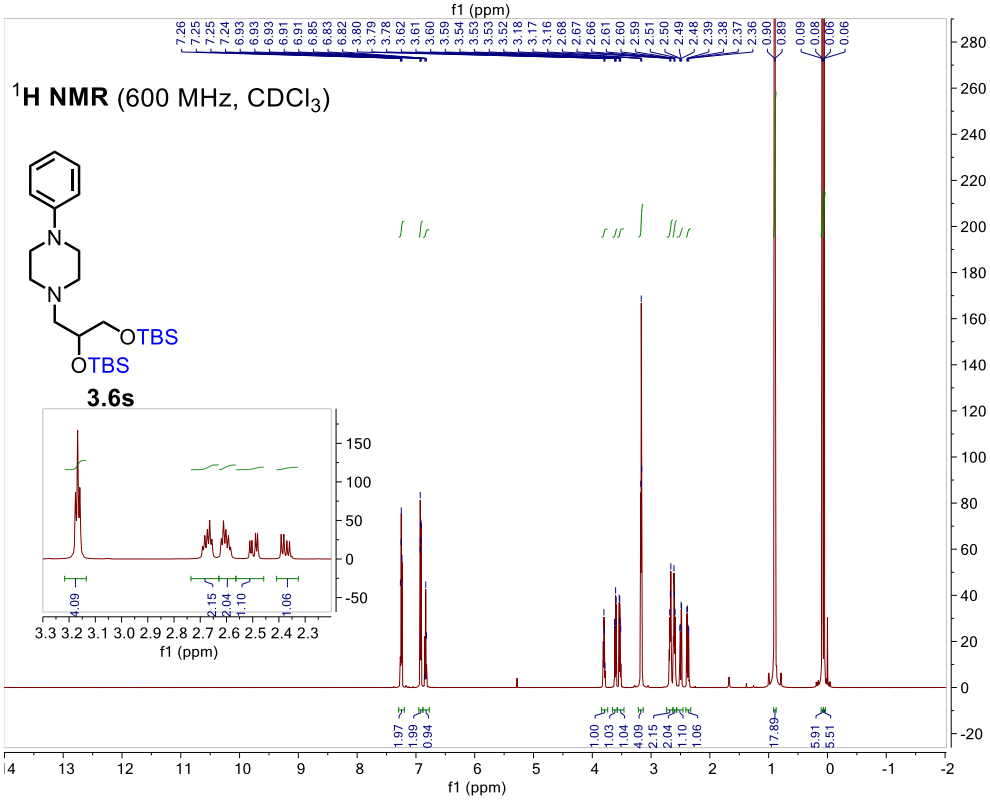

473.3820
472.3766
474.3848
471.3697
475.3862
470.3635
476.3891
468.3483
469.3569
Relative Intensity
m/z

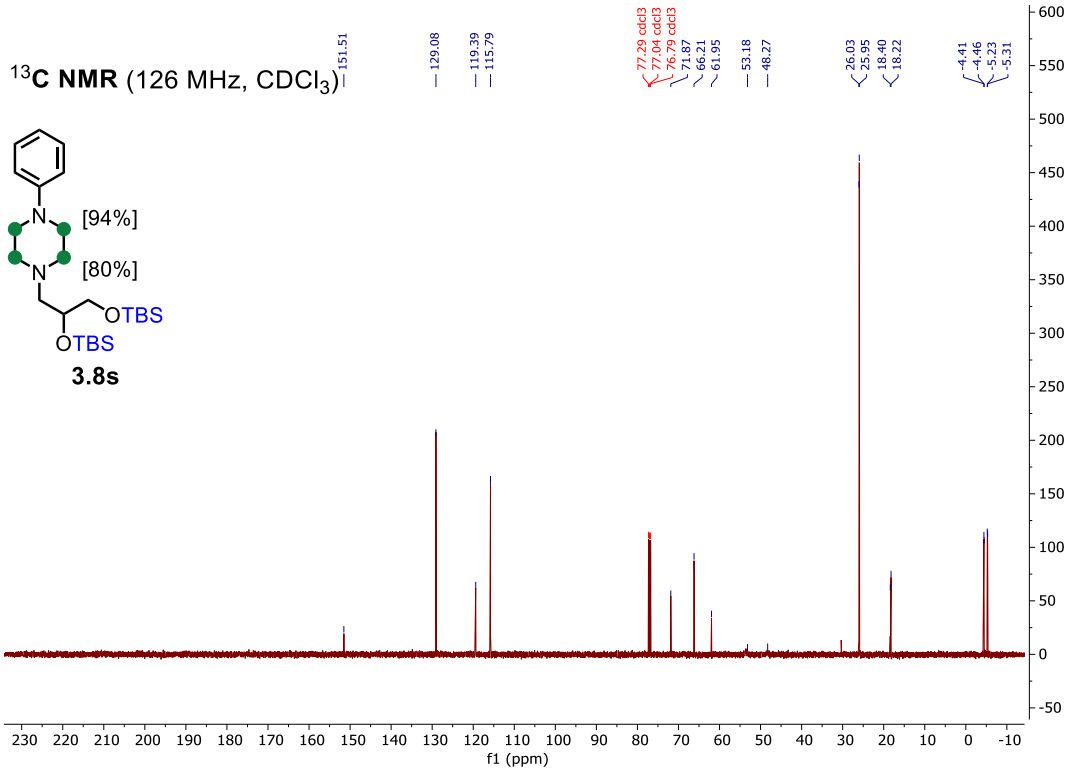

OTBS
OTBS

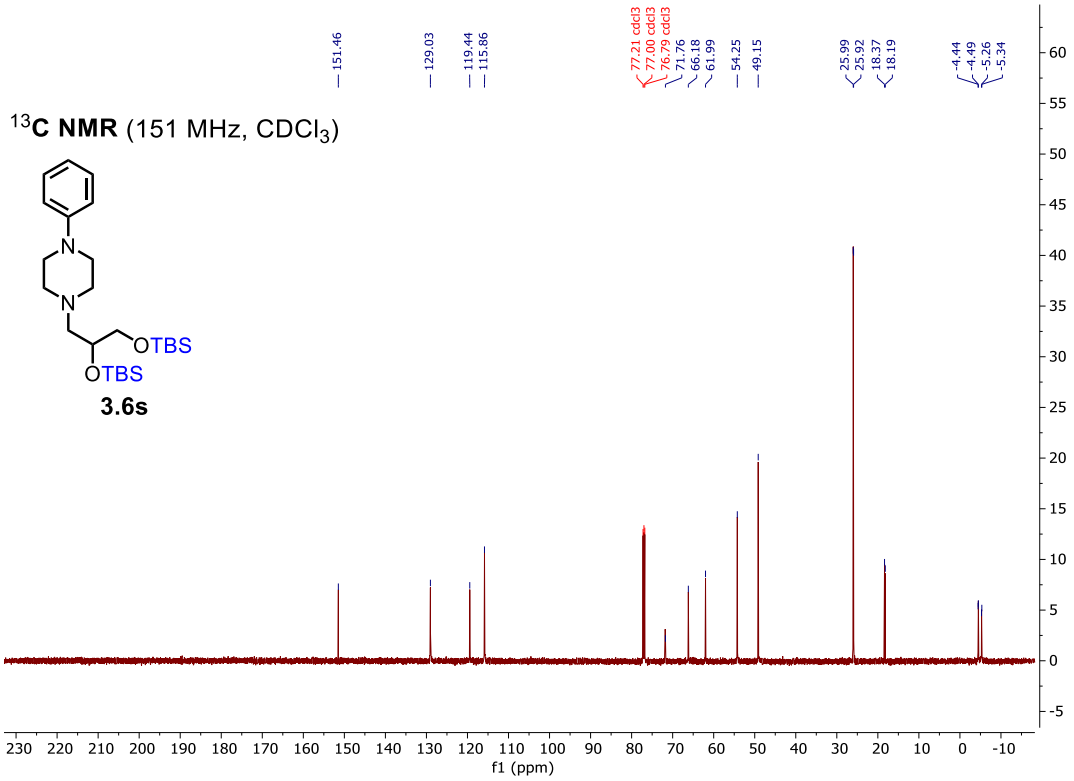
3.6s


465.3323
466.3350
467.3337
463.3169
464.3220
468.3342
Relative Intensity
m/z


1H NMR (500 MHz, CDCl3)
[94%]
[80%]
OTBS
OTBS
3.8s
f1 (ppm)


1H NMR (600 MHz, CDCl3)
OTBS
OTBS
3.6s
f1 (ppm)


13C NMR (126 MHz, CDCl3)
151.51
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
[94%]
[80%]
OTBS
OTBS
3.8s
f1 (ppm)


13C NMR (151 MHz, CDCl3)
151.46
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
OTBS
OTBS
3.6s
f1 (ppm)