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< Regio- and Enantioselective C-C and C-N Bond Formations Catalyzed by Amphiphilic π-Allyliridium *C,O*-Benzoate Complexes>

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by

Woo-Ok Jung

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Abstract

< Regio- and Enantioselective C-C and C-N Bond Formations Catalyzed by Amphiphilic π-Allyliridium *C,O*-Benzoate Complexes>

Woo-Ok Jung, Ph.D.

The University of Texas at Austin, 2022

Supervisor: Michael J. Krische

Enantioselective nucleophilic and electrophilic allylations mediated by racemic branched allylic acetates and catalyzed by π-allyliridium *C,O*-benzoate complexes are described. The π-allyliridium *C,O*-benzoate-catalyzed reductive coupling of the commodity chemical allyl acetate with acetylenic ketones mediated by 2-propanol to form enantiomerically enriched tertiary propargyl alcohols was developed. The same π-allyliridium *C,O*-benzoate complexes were found to be competent catalysts for the enantioselective electrophilic allylations of secondary amines and α, α-disubstituted nitronates, delivering tertiary allylic amines and (after zinc-mediated reduction of the nitroalkane) β-stereogenic α-quaternary primary amines, respectively. These processes form hindered C-C and C-N bonds with complete levels of branched regioselectivity. Attempted use of linear allyl acetates in the aforesaid processes provided products hydroamination instead of the expected products of Tsuji-Trost-type allylation. As revealed by deuterium labelling studies, chelation of the iridium catalyst to the internal olefin and the acetate carbonyl played a key role in partitioning the hydroamination vs allylation pathways and directing the regioselectivity of hydroamination.

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Chapter 1: Catalytic Enantioselective Allylation of Nitronates

1.1 INTRODUCTION

Nitroalkanes are useful building blocks in organic synthesis[1] and serve as useful synthetic precursors to hydroxylamines, oximes, nitroso compounds, and amines, including α-tertiary amines, which are synthetically challenging motifs (Figure 1.1).[2] Furthermore, nitroalkanes are valuable precursors for C-C bond forming reactions, including Henry reactions,[3] Michael additions,[4] and Mannich (aza-Henry) reactions.[5] Nef oxidation of nitro compounds delivers ketones and aldehydes which can be subsquently reduced to provide the corresponding alkane. Alternatively, these ketones and aldehydes can be oxidized to the corresponding carboxylic acid.[6]

The nitro group is unique due to its strong electron-withdrawing ability and its hydrogen bonding capability in the pharmaceutical fields. Historically, nitro group containing pharmaceutical compounds were limited to aromatic systems, but recently, a significant number of nitroalkanes have been discovered in biologically active compounds and natural products (Figure 1.2).

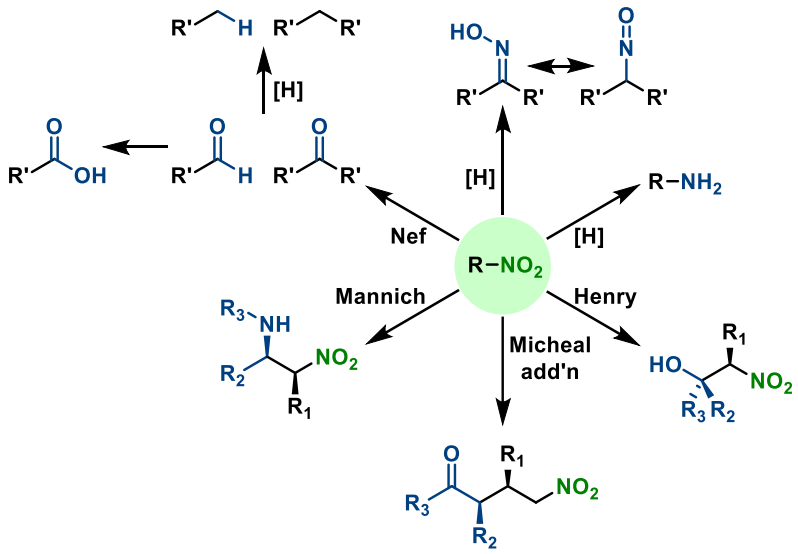


Figure 1. 1. Applications of nitro-compounds.

In this review, transition metal-catalyzed asymmetric allylic alkylation (AAA) of nitroalkanes will be discussed. Notwithstanding the advantages of nitro compounds to organic and medicinal chemistry, the use of nitroalkanes as pronucleophiles in transition-metal catalyzed C-C bond forming reactions remain a challenge for the following reasons: 1) *chemoselectivity* of *O*- vs *C*-alkylation products; 2) *stereoselectivity* issue because nitronate nucleophiles possess a planar geometry, which diminishes steric interactions with catalysts and electrophiles; and 3) *regioselectivity*, i.e. linear vs. branched products, that depend on the thermodynamic vs. kinetic selectivity and steric effects when the nucleophile attacks the π-allyl ligand on the catalyst.

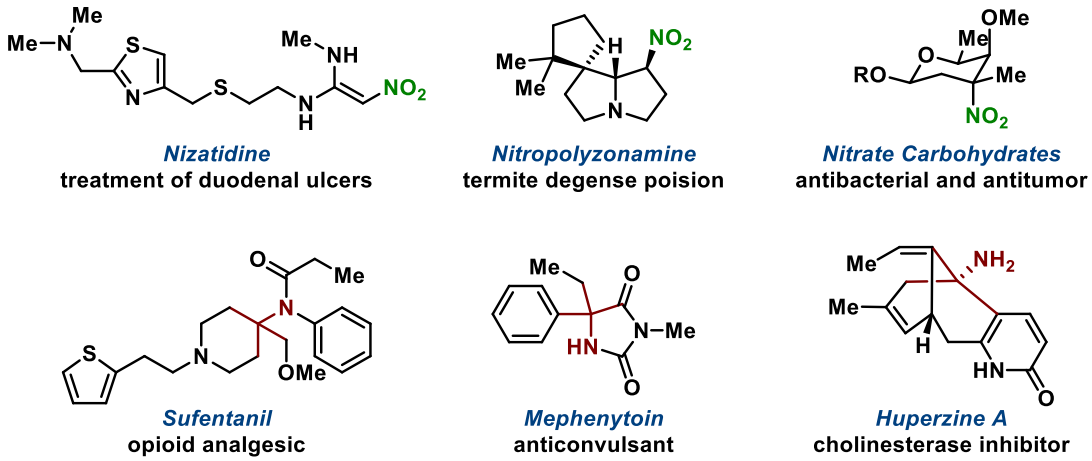
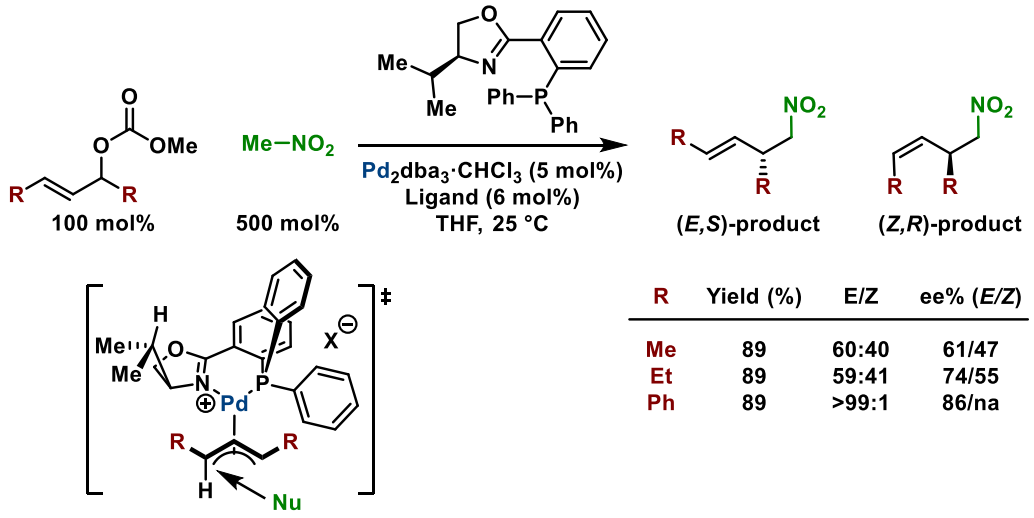


Figure 1. 2 Selected biologically active nitroalkanes and α-tertiary amines.

1.2 Formation of Linear Products: C1 Substitution

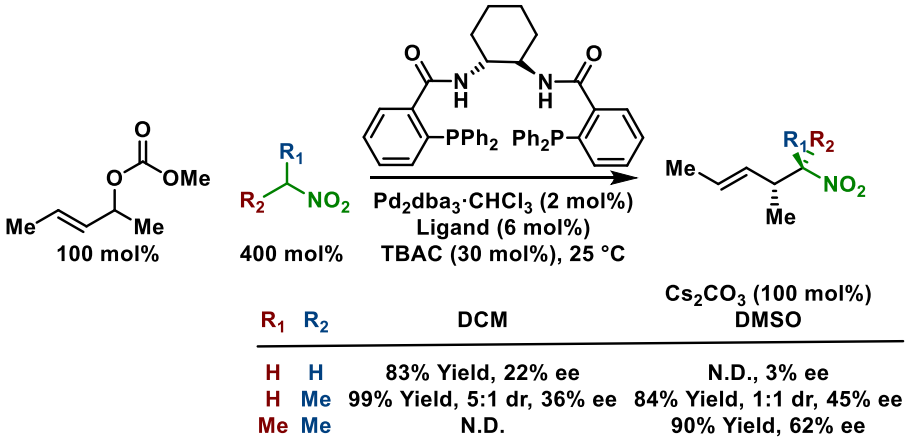


R	Yield (%)	E/Z	ee% (*E*/*Z*)
Me	89	60:40	61/47
Et	89	59:41	74/55
Ph	89	>99:1	86/na

Scheme 1. 1 The first enantioselective allylic alkylation of nitronate catalyzed by a palladium complex.

In 1995, Helmchen and co-workers reported the first enantioselective allylation of nitronates catalyzed by palladium dihydrooxazole complexes (Scheme 1.1).[7] With

symmetric aryl-substituted allyl carbonates, a palladium(0) precursor formed a stable electrophilic palladium π-allyl complex. Methoxide ions were produced as a byproduct and served as the base to deprotonate nitromethane. Since the allyl ligand is symmetric, there is no regioselectivity issue regarding the site at which the nucleophile attacks the allyl ligand. Enantioselectivity is controlled by steric effects and the stronger trans effect of phosphorous versus nitrogen on the dihydrooxazole ligand. Three different substituents on allyl carbonates were described to deliver the desired products with good yields, *E/Z* selectivities, and enantioselectivities. Interestingly, as the loading of nitroalkanes decreased, a higher yield of *di*-allylation product was observed. Furthermore, without the palladium catalyst, *O*-allylation product was formed predominantly. This work expands the scope of *C*-nucleophiles in enantioselective allylation reactions mediated by palladium π-allyl complexes. Nevertheless, no reaction with higher nitroalkanes was reported under the same reaction conditions.



Scheme 1. 2 The first palladium-catalyzed enantio- and diastereoselective allylic alkylations with higher nitroalkanes.

In 2000, Trost and co-workers reported the first palladium-catalyzed enantio- and diastereoselective allylic alkylations with higher nitroalkanes (Scheme 1.2).[8] The initial attempt at asymmetric allylic alkylations (AAA) with nitromethane, symmetric allyl carbonate, chiral Pd(0) complex, and tetra-*N*-butylammonium chloride (TBAC) in DCM delivered only the (*E*)-product in good yield but with poor enantioselectivity. Under the same reaction conditions, nitroethane gave a moderate diastereoselectivity in good yield but still with poor enantioselectivity. Using a more polar solvent (e.g. DMSO) and one equivalent of cesium carbonate helped to improve the enantioselectivity slightly but lowered the diastereoselectivity due to epimerization. 2-Nitropropane showed great reactivity and selectivity in a polar medium.

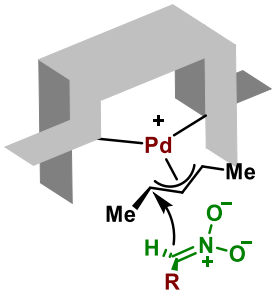
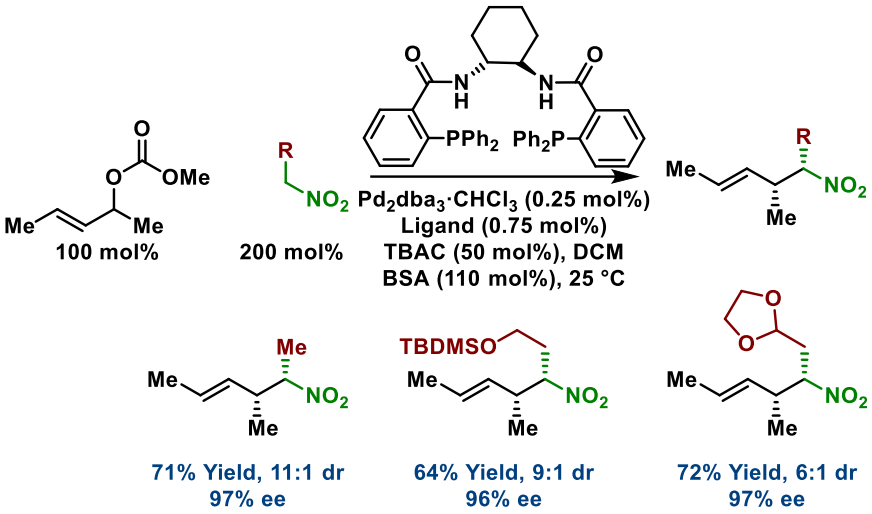


Figure 1. 3 π-Allylpalladium ion pair intermediate.

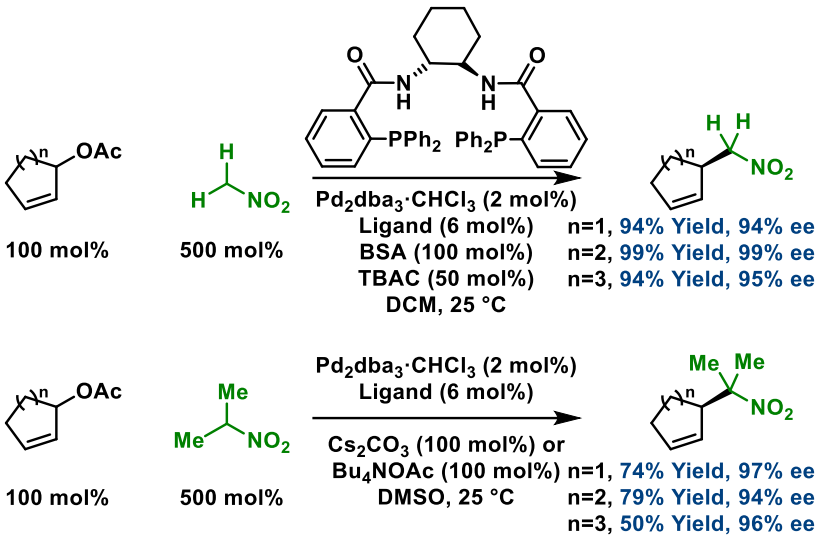
After base screening to improve the diastereoselectivities of AAA with nitroethane, bis(trimethylsilyl)acetamide (BSA) produced the product in 96% yield, 6:1 dr, 53% ee using DCM as solvent. Decreasing the loading of both catalyst and pronucleophile, increased diastereo- and enantioselectivities. The low concentration of the Pd-π-allyl complex and the nitronate slowed down nucleophilic attack, which allowed the π-allylpalladium ion pair to equilibrate completely before the C-C bond formation event

(Figure 1.3). Furthermore, the TBAC additive was found to assist this equilibrium by acting as an additional ligand on palladium complexes, and to improve enantioselectivity.[9]

Finally, with optimal conditions in hand, 0.25 mol% of palladium(0) dimer, 0.75 mol% of chiral ligand, a stoichiometric amount of BSA and sub-stoichiometric amount of TBAC in DCM, the authors were able to expand the nitroalkane substrate scope from a simple methyl group to five different alkyl groups with at least one methylene-bridge from the functional groups to the stereogenic center (Scheme 1.3).



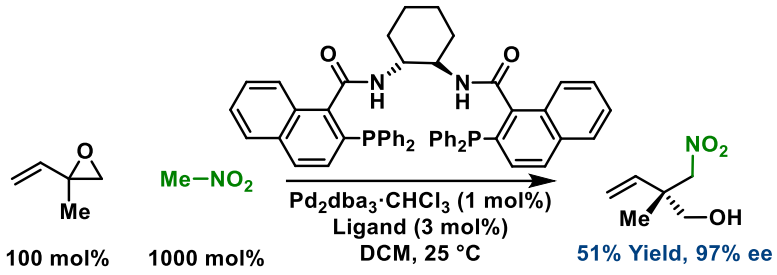
Scheme 1. 3 Selected examples of mono-substituted nitroalkanes in Pd-catalyzed AAA.



Scheme 1. 4 Allylic alkylation of nitroalkanes with cyclic allyl acetates: (top) Nitromethane was used as a pronucleophile.; (bottom) 2-Nitropropane was used as a pronucleophile.

Soon after, Trost and co-workers reported a palladium-catalyzed allylic alkylation of nitromethane and 2-nitropropane with cyclic allyl acetates (Scheme 1.4).[10] This transformation utilized the same catalytic system as previously reported work (Scheme 1.2).[8] The reaction with nitromethane worked better with a nonpolar solvent (e.g. DCM) and with BSA as base (Scheme 1.4, top). TBAC is a chloride source which acts as an additional ligand and prevents catalyst deactivation from the nitronate. Five, six and seven-membered allyl acetate delivered the desired products successfully with great yields and enantioselectivities. There were no regio- or *E*/*Z* isomers due to the symmetry of the cyclic proelectrophiles. Interestingly, utilizing 2-nitropropane showed better reactivity in a Lewis basic polar solvent (e.g. DMSO) with cesium carbonate as base (Scheme 1.4, bottom), but there was no reaction in the presence of BSA in DCM. 2-Nitropropane is a better pronucleophile because it forms a tertiary carbanion which is less stable than a primary carbanion. Five and seven-membered allyl acetates installed the C-C bond via palladium-

catalyzed allylic alkylation with cesium carbonate in good yields and great enantioselectivities. Cyclohexenyl acetate delivered the desired product in good yield and enantioselectivity with tetra-*N*-butylammonium acetate as an additive. This work highlights that the choice of nitroalkane significantly influences catalyst reactivity, since nitromethane and 2-nitropropane showed notably different reactivities.



Scheme 1. 5 Asymmetric creation of quaternary carbon: regio- and enantioselective reactions of vinyl epoxides with nitromethane.

In 2001, Trost and co-workers reported palladium-catalyzed regio- and enantioselective reactions of vinyl epoxides with nitromethane to construct all-carbon-quaternary centers (Scheme 1.5).[11] A 1,2-addition product was delivered exclusively with nitromethane and vinyl epoxide, catalyzed by a π-allylpalladium complex in DCM. Interestingly, a bulkier ligand showed better regioselectivity according to their optimization with β-ketoesters (not shown) due to the steric repulsion between the ligand and substituents on π-allyl (Figure 1.4). The π-allylpalladium intermediates had a higher preference to form **Pd-I** over **Pd-II** intermediate because of the strong kinetic discrimination in the initial ionization step with racemic epoxide, which favors an addition at the more substituted allyl terminus to deliver the 1,2-addition product. This kinetic preference is plausible due to the rapid interconversion of diastereomeric π-allylpalladium

complexes which would increase the regioselectivity and maintain the enantiomeric excess.[8]

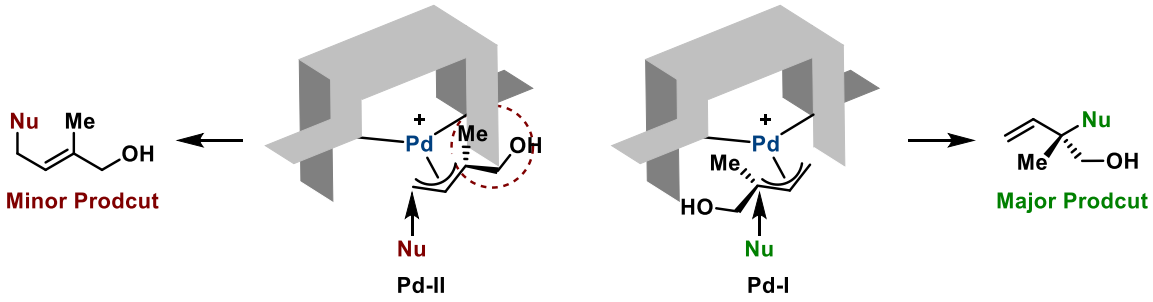
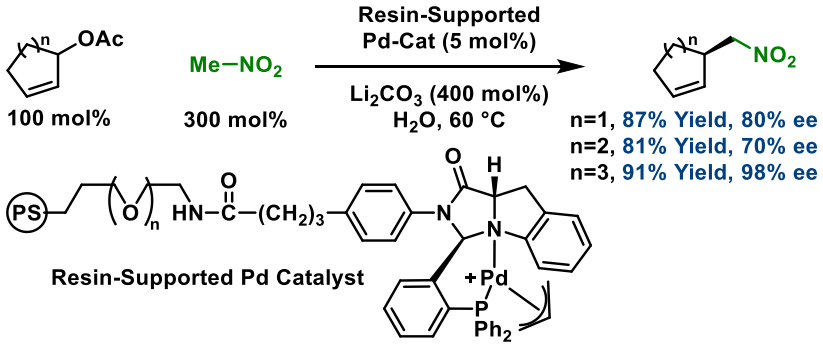


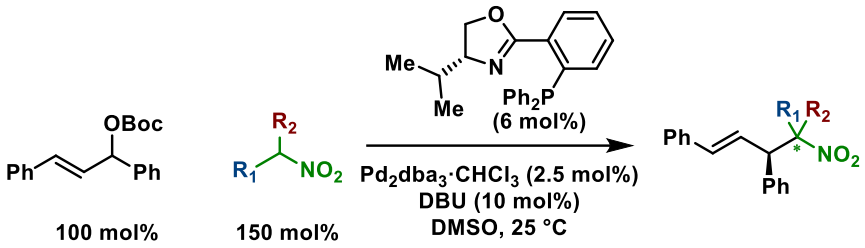
Figure 1. 4 Steric repulsion leads to high levels of regioselectivity.



Scheme 1. 6 π-Allylic C1-substitution in water with nitromethane using amphiphilic resin-supported palladium complexes.

In 2006, the Uozumi group reported allylic alkylations of cycloalkenyl esters with nitromethane using a resin-supported palladium complex in water (Scheme 1.6).[12] The authors claimed that previously reported reaction conditions for this transformation (Scheme 1.4)[10] exploded at 40 °C. To develop more reliable reaction conditions, a resin-supported Pd-catalyst, which was previously used in π-allylic alkylation and amination of cycloalkenyl esters,[13] was used. Under heterogeneous reaction conditions, the desired

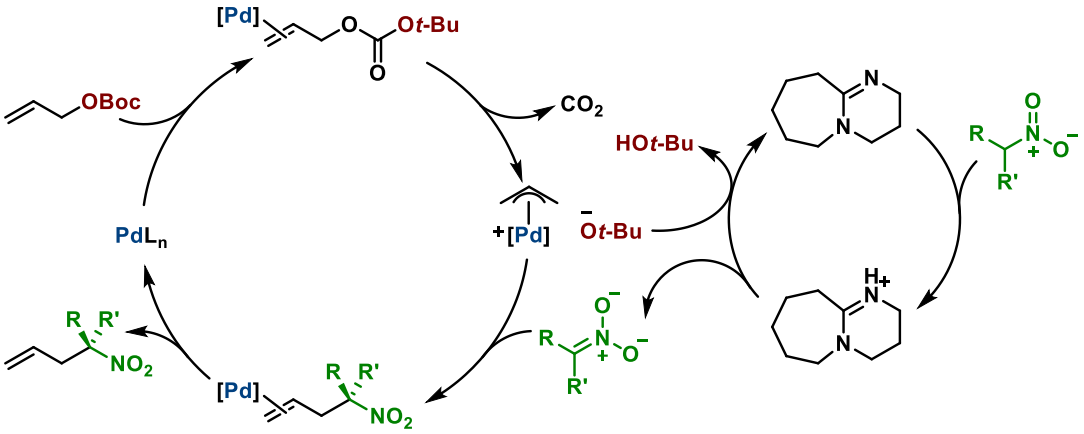
allylation products of nitromethane were delivered in great yields and enantioselectivities with five, six, and seven membered proelectrophiles. In organic solvents such as THF or DCM, the catalyst showed poor reactivity, resulting in no observed product formation. Furthermore, linear allyl acetates showed poor regioselectivity between linear and branched products.



R_1	R_2	Yield (%)	dr	ee (%)
Me	Me	100	-	94
c-Hex	-	78	-	82
c-Pent	-	100	-	5
Me	CO_2Et	83	1.6:1	93/94
Me	Bn	100	1.1:1	93/94

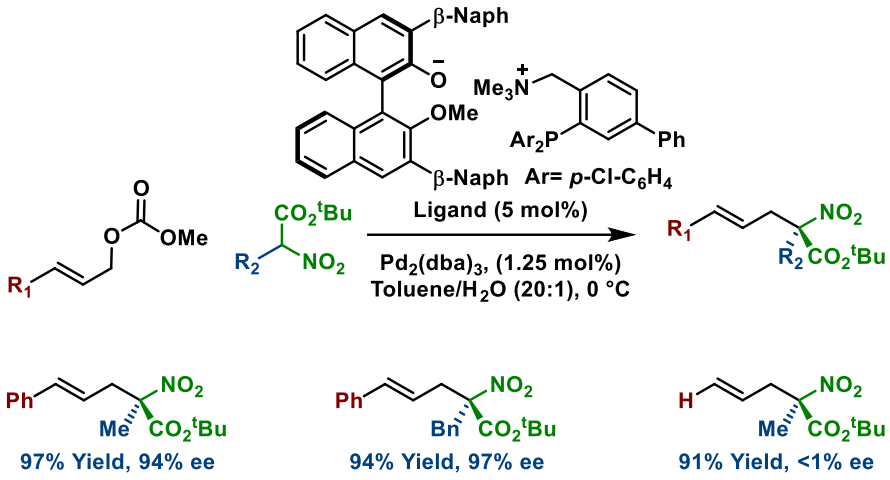
Scheme 1. 7 Palladium-catalyzed allylic alkylation of secondary nitroalkanes.

Shibasaki and co-workers reported palladium-catalyzed allylic alkylation of secondary nitroalkanes (Scheme 1.7)[14] under similar reaction conditions to those previously reported by Helmchen (Scheme 1.1).[7] With phenyl substituted symmetric allyl carbonate, 2-nitropropane and nitrocyclohexane delivered the desired products in great yields and with high levels of enantioselectivity when catalyzed by a Pd-PHOX complex. However, nitrocyclopentane gave low enantioselectivity. The authors' attempts with non-symmetric secondary nitroalkanes delivered the desired products in excellent yields and enantioselectivities but with low diastereoselectivities due to lack of differentiation between the two substituents on the nitronate nucleophiles ultimately leading to low π-facial selectivity.



Scheme 1. 8 Proposed mechanism.

The authors proposed a mechanism involving two separate deprotonation steps (Scheme 1.8). Catalytic amounts of DBU as the base are regenerated by *tert*-butoxide, which is a byproduct from the formation of the palladium π-allyl complex. Due to the steric bulkiness of *tert*-butoxide, deprotonation of the nitroalkane is slow.



Scheme 1. 9 Ion-paired chiral ligands for asymmetric palladium-catalyzed allylic alkylation of α-nitrocarboxylates.

In 2012, Ooi and co-workers reported palladium-catalyzed allylation of α-nitrocarboxylates mediated by ion-paired chiral ligands (Scheme 1.9).[15] The ion-paired chiral ligand is a complex of an achiral cationic ammonium–phosphine ligand with a chiral binaphtholate anion that are associated by electrostatic interaction (Figure 1.5). This non-bonding interaction allows the construction of complex chiral ligands by exploiting the possible combinations of achiral oniums with suitable coordinative functionalities and readily available chiral acids.

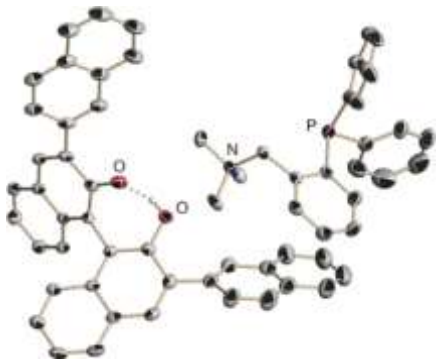


Figure 1. 5 ORTEP diagram of ion-paired chiral ligand — calculated hydrogen atoms are omitted for clarity.

This ion-paired chiral Pd-complex showed exceptional stereoselectivity in enantioselective allylic alkylation reactions with α-nitrocarboxylate pronucleophiles (Scheme 1.9). Aryl substituted linear allyl carbonates delivered the desired products in great yields and enantioselectivities with alkyl-substituted α-nitrocarboxylate. When a non-substituted allyl proelectrophile was applied to the reaction, there was no enantioselectivity, presumably due to low steric discrimination of π-facial selectivity of the π-allyl ligand.

The authors performed kinetic experiments to elucidate the detailed reaction profiles, which revealed a zero-order dependence on allyl carbonate, first-order dependence on α-nitrocarboxylate, and second-order dependence on ligands. However, the reactive palladium (II) complex was not detected by ^{1}H and ^{31}P NMR, but the existence of the non-reactive palladium (0) complex was confirmed with NMR. These data indicate that the C-C bond-forming event is the rate-determining step of the reaction, and the reactive palladium (II) species is generated in low concentrations in the reaction mixture *in situ*. Based on the kinetic studies, the proposed mechanism was described in the paper (not shown). The nitronate nucleophile forms a hydrogen bonding interaction with one of the phenolic protons and this chiral nucleophile attacks the π-allyl ligand at the less hindered site (Figure 1.6). This non-bonding interaction was confirmed by the fact that the use of protected phenol ligand gave racemic products under the same reaction conditions.

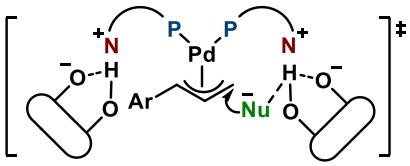
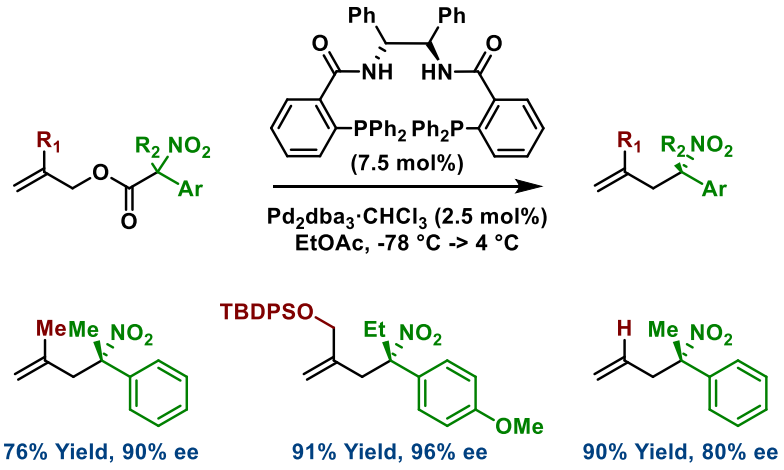


Figure 1. 6 The intermediate through nonbonded interactions in the transition state.



Scheme 1. 10 Chemo- and enantioselective Pd-catalyzed decarboxylative allylic alkylation of α-nitroesters.

In 2019, Trost and co-workers reported the intramolecular enantioselective allylic alkylation of α-nitroesters mediated by palladium catalysts in a decarboxylative pathway (Scheme 1.10).[16] Asymmetric *C*-allylation of secondary benzylic nitronates was an unsolved problem due to the propensity of nucleophilic nitronates to undergo *O*-allylation.[17] Also, previously reported allylic alkylation with benzylic potassium nitronate salts showed low chemoselectivities of *C*- vs. *O*-allylation, and mono- vs. dialkylation products.[18] To address these limitations, an ester group was installed on the nitroalkane pronucleophiles which could stabilize anionic nucleophiles. Once palladium (0) coordinates to the terminal olefin, it forms both the Pd(II)-π-allyl complex and the nitronate spontaneously through a decarboxylative pathway. The resulting Pd(II) cationic complex and nitronate anion form an ion-pair which stabilizes both coupling partners and improve the π-facial selectivities, and chemoselectivities of the reaction. Alkyl-substituted benzylic nitroesters deliver the desired products in good yields and enantioselectivities (Scheme

1.10). However, a significant amount of *O*-allylation product was formed along with the corresponding oxime with sterically bulky α-nitroesters (Figure 1.7).

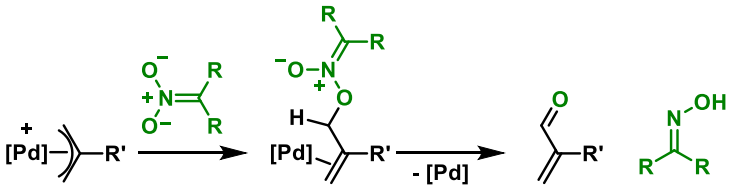
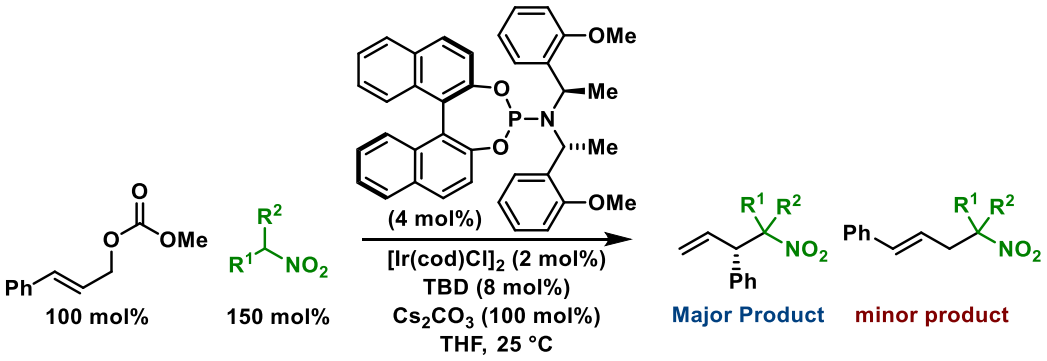
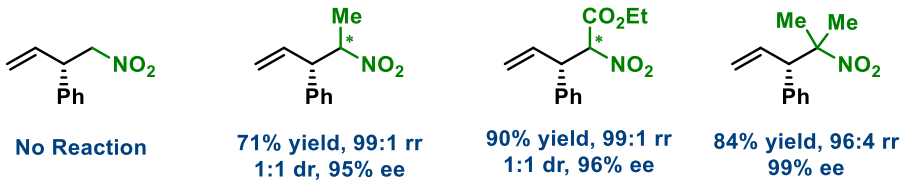


Figure 1. 7 The formation of O-allylation products and corresponding oximes.

1.3 Formation of Branched Products: C3 Substitution

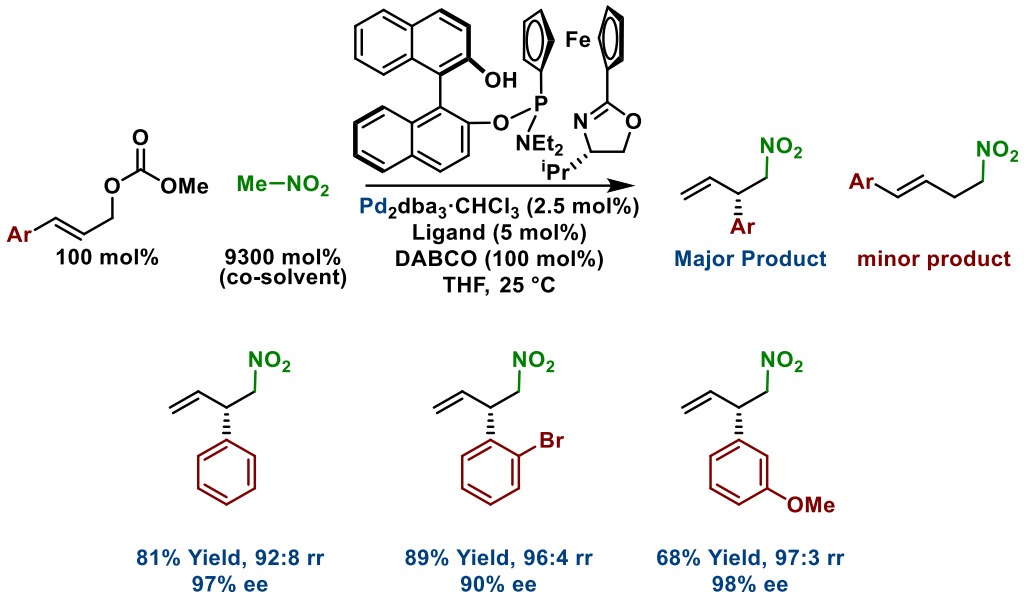




Scheme 1. 11 The first iridium-catalyzed enantioselective allylic substitutions with aliphatic nitro compounds.

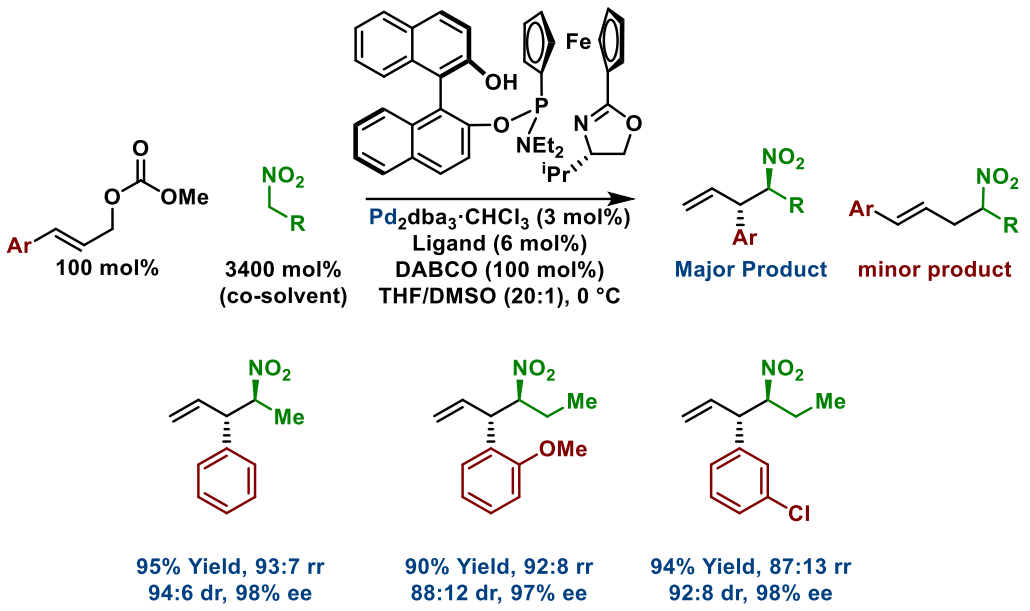
In transition metal-catalyzed asymmetric allylations, achieving complete levels of branched-regioselectivity is challenging because the steric repulsion between the

substituents on the allyl ligand and nucleophile diminishes the kinetic selectivity of nucleophilic attack on the more substituted site. As previously discussed, palladium-catalyzed allylations typically display linear regioselectivity. However, iridium-catalyzed allylations often show branched regioselectivity. In 2006, Helmchen and co-workers reported the first enantioselective allylations of nitroalkanes catalyzed by iridium-phosphoramidite complexes (Scheme 1.11).[19] Although only three examples were reported in the study, nitroethane, nitroester, and 2-nitropropane delivered the desired products in great yields and enantioselectivities. The products from nitroethane and nitroester showed no diastereoselectivity due to the presence of an epimerizable stereogenic center under relatively basic reaction conditions. Furthermore, the allylation product with 2-nitropropane displayed an incomplete level of regioselectivity because of the steric hinderance between the substitution on the allyl ligand and disubstituted nitronate nucleophile. Interestingly, nitromethane did not deliver the allylation product but only a trace amount of *di*-allylation product.



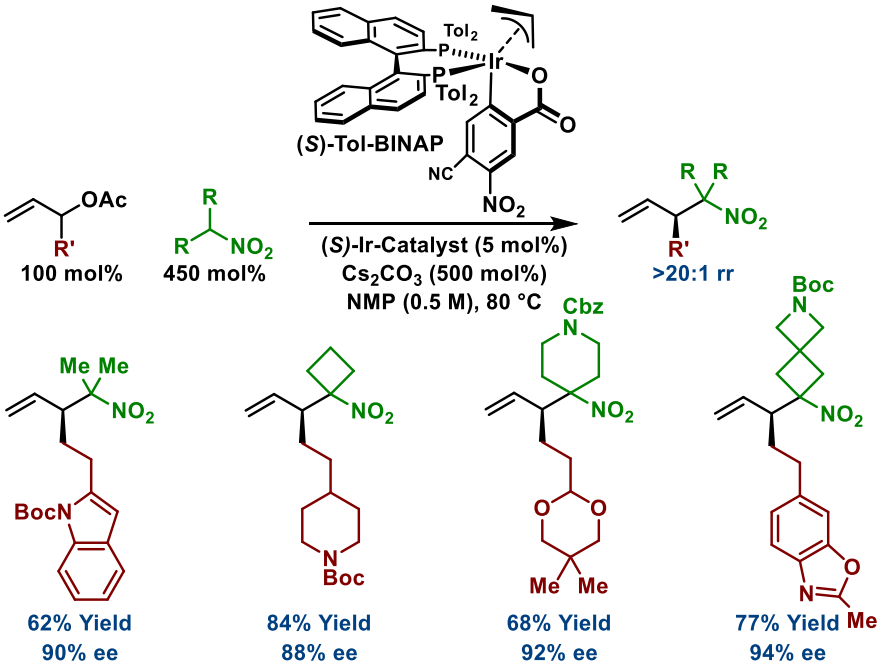
Scheme 1. 12 Regio- and enantioselective palladium-catalyzed allylic alkylation of nitromethane with monosubstituted allyl substrates.

In 2012, Wang and co-workers reported the first palladium-catalyzed allylic alkylation of nitromethane with branched regioselectivity using ferrocene-based chiral ligands, SIOCPhox (Scheme 1.12).[20] Both electron-deficient and rich aryl-substituted allyl proelectrophiles delivered the desired branched product in good yields, regio- and enantioselectivities with nitromethane as the co-solvent and pronucleophile. The developed protocol was applied to enantioselective syntheses of (*R*)-baclofen and (*R*)-rolipram (not shown). Alkyl substituted allyl carbonates were not explored under the palladium-catalyzed allylic alkylation reactions with nitromethane in this study.



Scheme 1. 13 Palladium-catalyzed regio-, diastereo-, and enantioselective allylation of nitroalkanes with mono-substituted allylic substrates.

The next year, Wang and co-workers reported the palladium-catalyzed allylic alkylation of nitroalkanes to construct two adjacent chiral centers with excellent regio-, diastereo-, and enantioselectivities (Scheme 1.13).[21] Similarly to their previous study, the nitroalkanes were used as a co-solvent with THF. In this study, epimerization was suppressed by lowering the reaction temperature, and this afforded high stereoselectivities. Lewis basic DMSO, improved the yields by increasing the reactivity of the anionic nucleophiles. Overall, the reaction tolerates both electron-withdrawing and donating groups on the aryl substituents. However, the reaction is limited to the aryl-substituted allyl carbonates with nitroethane and nitropropane. Furthermore, this work showed incomplete regioselectivity in all cases.



Scheme 1. 14 The first systematic study of nitronate nucleophiles in iridium-catalyzed allylic alkylation.

In 2021, Krische and co-workers reported the first systematic study of secondary nitroalkanes in iridium-catalyzed allylic alkylation using a tol-BINAP-modified π-allyliridium *C,O*-benzoate catalyst (Scheme 14).[22] This work will be discussed in a later chapter of this dissertation (see Chapter 4).

1.4 CONCLUSION

The use of nitro compounds in catalytic enantioselective allylic alkylations is a useful way to synthesize valuable building blocks in organic and medicinal chemistry. However, utilizing nitroalkanes as pronucleophiles in C-C bond forming reactions is still a challenge due to concerns about chemoselectivity, stereoselectivity and regioselectiviy. Furthermore, most of the previously reported work is limited to aryl substituted symmetric allyl carbonates with nitromethane, which is the least sterically hindered pronucleophile. To address these limitations, future developments will be expected to provide a wide range of reaction scope for both proelectrophiles and pronucleophiles with high levels of reactivities and selectivities.

Chapter 2: Hydroamination versus Allylic Amination in Iridium Catalyzed Reactions of Allylic Acetates with Amines: 1,3-Aminoalcohols via Ester-Directed

2.1 INTRODUCTION

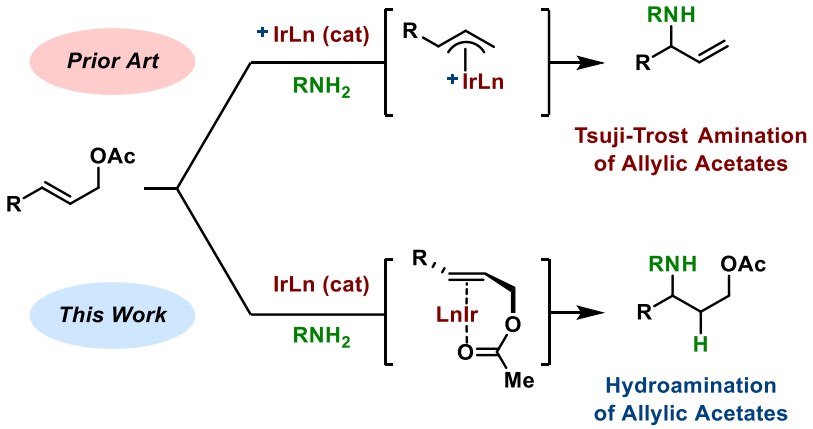


Figure 2. 1 Cationic *vs* neutral iridium catalysts promote Tsuji-Trost allylic amination and hydroamination, respectively.

The importance of nitrogen-containing compounds in pharmaceutical and agrichemical fields continues to develop transition metal-catlyzed hydroamination.[1,2] Among late transition metal catalysts,[1g] those based on rhodium[3,4] and iridium[5,6] have shown great promise, however, despite decades of research, many of the previous works are limited to intramolecular processes.[4,6] Intermolecular variants often require highly activated alkenes,[3b,5a-d] are accompanied by oxidative amination side-products[3c-i,5f] or exploit specialized directing groups to control regioselectivity.[3j,k] Further, the mechanisms

*This chapter is based on the previously published works: Kim, S. W.; Wurm, T.; Brito, G. A.; Jung, W.-O.; Zbieg, J. R.; Stivala, C. E.; Krische, M. J. *J. Am. Chem. Soc.* **2018**, *140*, 9087.
W. J. contributed to reaction optimization (Table 2.1), substrate scope (Tables 2.2), and preparation of manuscript and supporting information.

of these processes still under uncertain by the fact that simple Brønsted acids – even ammonium salts[7b,f] – catalyze hydroamination.[7,8] Here, we report the first hydroaminations of allylic acetates. Specifically, using a dppf-modified iridium catalyst in the presence of Cs_2CO_3, linear allylic acetates react with primary amines to form hydroamination products with complete 1,3-regioselectivity. These results are remarkable, as cationic iridium complexes are well-known to catalyze the substitution of allylic acetates with amines to form products of allylic amination (Figure 2.1).[9]

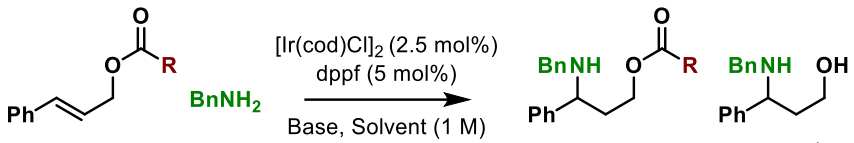
2.2 Reaction Development and Scope

Recently, in a collaborative endeavor, we reported that commercially available π-allyliridium *C,O*-benzoates catalyze highly enantioselective substitutions of branched allylic acetates with primary amines.[10] In the course of developing this process, significant quantities of hydroamination product were formed as single a regioisomer in attempted substitutions of linear allylic acetates. Since chiral ligands did not induce asymmetry of the products, 1,1'-bis(diphenylphosphino)ferrocene (dppf) was found to be most effective during the a survey of achiral phosphine ligands. Hydroamination products were not observed in the absence of metal, phosphine ligand or upon use of monophosphine ligands.

At this point, the effect of base was systematically investigated (Table 2.1, entries 1-5). In the presence of $[Ir(cod)Cl]_2$ (2.5 mol%), dppf (5 mol%) and Cs_2CO_3 (200 mol%) at 90 °C in THF (1.0 M), cinnamyl acetate **2.1a** (100 mol%) and benzyl amine **2.2a** (200 mol%) were converted the hydroamination products **2.3a** and the deactylated compound **2.3a′** in 66% yield with 2:1 ratio. In an attempt to minimize formation of **2.3a**, lower loadings of Cs_2CO_3 were explored (entries 1-3), however, the combined yield

hydroamination products **2.3a** and **2.3a′** declined.[11] Other bases were explored (Entries 4,5), but Cs_2CO_3 provided superior results. The use of cinnamic esters that are less prone to saponification were explored (Entries 6-10), but this also led to a decrease in the combined yield of hydroamination products **2.3a** and **2.3a′**. In all experiments, products of acyl transfer to benzyl amine were not observed.

Table 2. 1 Selected optimization experiments in the reaction of cinnamyl acetate **2.1a** with benzyl amine **2.2a** to form hydroamination product **2.3a**.[a]



2.1a **2.2a** **2.3a** **2.3a'**

Entry	**2.1a / 2.2a** (mol %)	**R**	Base (mol%)	Solvent	**2.3a /2.3a'** Yield (%)
1	100 / 200	Me	**Cs_2CO_3 (200 mol%)**	THF	45 / 21
2	100 / 200	Me	**Cs_2CO_3 (50 mol%)**	THF	15 / 6
3	100 / 200	Me	**Cs_2CO_3 (20 mol%)**	THF	trace
4	100 / 200	Me	**K_2CO_3 (200 mol%)**	THF	trace
5	100 / 200	Me	**K_3PO_4 (200 mol%)**	THF	22 / 8
6	100 / 200	**Et**	Cs_2CO_3 (200 mol%)	THF	28 / 9
7	100 / 200	**^{i}Pr**	Cs_2CO_3 (200 mol%)	THF	12 / trace
8	100 / 200	**^{t}Bu**	Cs_2CO_3 (200 mol%)	THF	NR
9	100 / 200	**OMe**	Cs_2CO_3 (200 mol%)	THF	NR
10	100 / 200	**NMe_2**	Cs_2CO_3 (200 mol%)	THF	NR
11	**100 / 100**	Me	Cs_2CO_3 (200 mol%)	THF	36 / trace
12	**200 / 100**	Me	Cs_2CO_3 (200 mol%)	THF	65 / trace
13	**300 / 100**	Me	Cs_2CO_3 (200 mol%)	THF	76 / trace
14	300 / 100	Me	Cs_2CO_3 (200 mol%)	**DME**	77 / trace

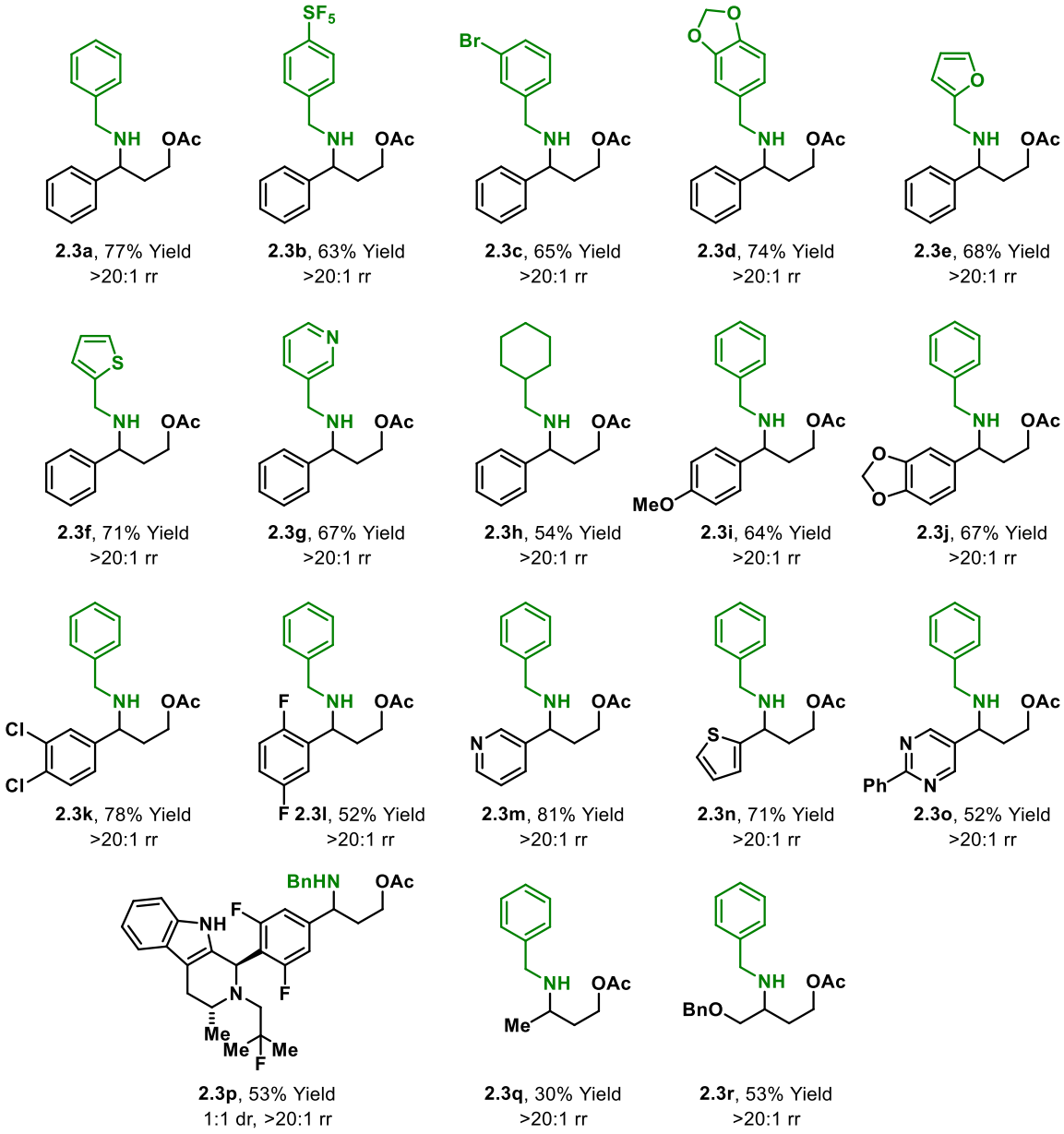
[a]All reactions were performed on 0.2 mmol scale. All yields are of material isolated by silica gel chromatography.

Acute sensitivity to the steric features of the esters (cf. Entries 1 and 7) along with the regioselectivity of hydroamination suggested a chelation of iridium between the acetate carbonyl and olefin moieties play a significant role. To enhance the chelating ability of iridium the stoichiometry of cinnamyl acetate **2.1a** and benzyl amine **2.2a** was altered

(Entries 11-13). Using cinnamyl acetate **2.1a** (300 mol%) and benzyl amine **2.2a** (100 mol%), the hydroamination product **2.3a** was obtained in 76% yield accompanied by only trace quantities of the **2.3a′** (Entry 13). To mitigate solvent evaporation, a number of higher boiling solvents were evaluated and it was found that 1,2-dimethoxyethane (DME) provided **2.3a** with equivalent efficiencies (Entry 14).

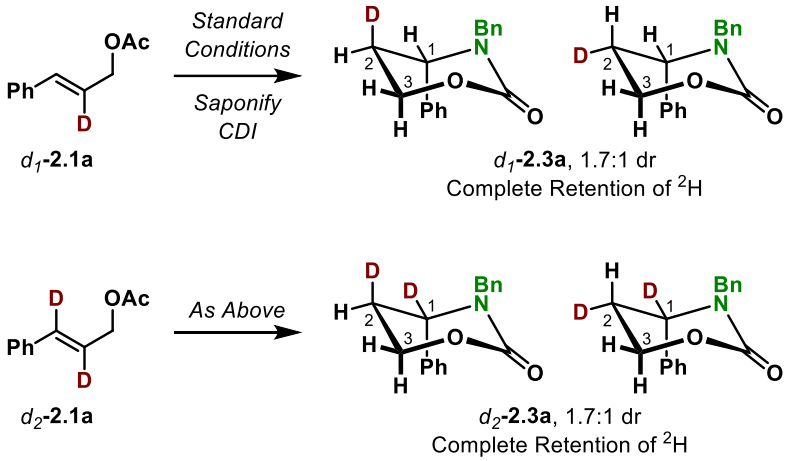
To illustrate scope, optimal conditions for hydroamination were applied to various linear allyl acetates and primary amines (Table 2.2). As demonstrated by the formation of hydroamination products **2.3a-2.3g**, primary benzylic amines are effective partners for hydroamination. Saturated primary amines provide moderate yields of hydroamination product (**2.3h**). A range of aryl-substituted linear allylic acetates also were evaluated (**2.3i-2.3p**). These experiments reveal that both electron rich and electron deficient aryl groups, as well as heteroaryl groups, are tolerated. The formation of adduct **2.3p**, derived from AZD-9496 (a non-steroidal oral estrogen receptor inhibitor),[12] which incorporates an unprotected indole moiety, highlights the functional group tolerance of the present hydroamination method. As illustrated by formation of **2.3q** and **2.3r**, alkyl-substituted allylic acetates provide modest yields of hydroamination product as single regioisomers. The regioselective formation **2.3r** is noteworthy, as it provides strong evidence of the directing influence of the acetate moiety. Indeed, as cinnamyl methyl ether, *trans*-β-methyl styrene and 1-octene do engage in hydroamination under these conditions, the acetate moiety not only directs regioselectivity but is required for the reactivities.

Table 2. 2 Regioselective iridium-catalyzed hydroamination of linear allylic acetates.[a]



[a]Yields of material isolated by silica gel chromatography. Standard conditions: $[Ir(cod)Cl]_2$ (2.5 mol%), dppf (5 mol%), Cs_2CO_3 (200 mol%), amine (100 mol%), DME (1 M), 90 °C All yields are of material isolated by silica gel chromatography.

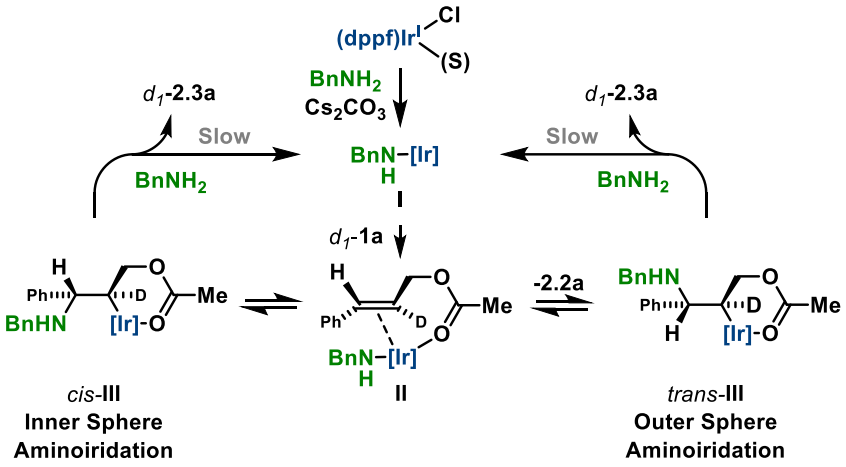
2.3 DISCUSSION



Scheme 2. 1 Deuterium labelling experiments.

To gain insight into the reaction mechanism, *mono*- and *di*-deuterated cinnamyl acetates *d*$_1$-**2.1a** and *d*$_2$-**2.1a** were subjected to the standard hydroamination conditions (Scheme 2.1). To clarify assignment of relative stereochemistry, the reaction products were converted to the cyclic carbamates *d*$_1$-**2.3a** and *d*$_2$-**2.3a**. Axial disposition of the phenyl moiety was corroborated by NOE experiments. As determined by ^{1}H NMR, ^{2}H NMR and HRMS, both compounds *d*$_1$-**2.3a**, *d*$_2$-**2.3a** and *cis*-*d*$_2$-**2.3a**, completely retain deuterium and were generated as 1.7:1 mixture of diastereomers. These deuterium labeling studies suggest a mechanism, involving rapid and reversible inner- or outer-sphere addition of amine species to alkenes (Scheme 2.2). The catalytic cycle starts with a base-mediated formation of amidoiridium species **I**.[11] Association of *d*$_1$-**2.1a** provides the chelated olefin complex **II**, which undergoes either inner- or outer-sphere alkene aminoiridation to form the σ-alkyliridium species *cis*-**III** and *trans*-**III**, respectively. Equilibrium between *cis*-**III** and *trans*-**III** occurs in advance of turn-over limiting proto-demetalation mediated by benzyl amine to release the product *d*$_1$-**2.3a** and regenerate amidoiridium species **I** to close the

catalytic cycle. Consistent with this mechanistic interpretation, chiral iridium complexes do not deliver enantiomerically enriched hydroamination product. Additionally, using *cis*-cinnamyl acetate, low conversion to hydroamination product is observed (15% yield) and recovered cinnamyl acetate is partially isomerized to the *trans*-isomer (8:1, *cis*:*trans*). These data suggest the small quantity of hydroamination product observed in reactions of *cis*-cinnamyl acetate are likely formed from the *trans*-isomer and, for *cis*-cinnamyl acetate, allylic strain may prevent acetate-mediated chelation of the olefin by iridium. Based on these data, mechanisms involving alkene isomerization appear less plausible.



Scheme 2. 2 General catalytic mechanism for iridium catalyzed hydroamination of linear allylic acetates, as corroborated by deuterium labeling.

2.4 CONCLUSION

To summarize, allylic acetates are well-known to undergo Tsuji-Trost amination upon exposure to *cationic* iridium catalysts and amines. Here, using *neutral* iridium

catalysts under basic conditions, we report the first examples of allylic acetates hydroamination. The collective data, including deuterium labeling studies, corroborate a catalytic mechanism involving rapid, reversible acetate-directed aminoiridation with inner sphere-outer/sphere cross-over in advance of turn-over limiting amine-mediated protodemetalation. The present studies establish a new mechanistic pathway for alkene hydroamination under basic conditions, broadening access to 1,3-aminoalcohols and related *N*-containing compounds.[13]

2.5 Experimental Details

2.5.1 General Information

All reactions were carried out under inert gas atmosphere (nitrogen or argon) unless otherwise indicated. Resealable pressure tubes (13x100 mm) were purchased from Fischer Scientific (catalog number 14-959-35C) and were flame dried followed by cooling in a desiccator or under a stream of inter gas prior to use. All commercial reagents and anhydrous solvents were used as received from vendors (Fischer Scientific, Sigma Aldrich and Combi Blocks) without further purification. $[Ir(cod)Cl]_2$ and dppf were used as received from Strem Chemicals Inc. Cs_2CO_3 was used as received from Rockwell Lithium. The compounds (4-(pentafluoro-λ^6-sulfaneyl)phenyl)methanamine[23] was prepared according to literature procedures. Preparative column chromatography employing Silicycle silica gel (40-63 μm) was performed according to the method of Still[24] or on a Teledyne Isco Combiflash Rf utilizing Silicycle HP columns using a mobile phase composed of either heptane/isopropyl acetate, hexanes/ethyl acetate or

dichloromethane/methanol. Reactions were monitored by a Shimadzu LCMS/UV system with LC-30AD solvent pump, 2020 MS, Sil-30AC autosampler, SPD-M30A UV detector, CTO-20A column oven, using a 2-98% acetonitrile/0.1% formic acid (or 0.001% ammonia) gradient over 2.5 minutes. Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates (Dynamic Absorbents F). Visualization was accomplished with UV light followed by dipping in CAM, *p*-Anisaldehyde (PAA), or $KMnO_4$ stain solution followed by heating. Specific optical rotations were recorded on an Atago AP-300 automatic polarimeter at the sodium line (589.3 nm) in $CHCl_3$ Solution concentrations are given in the units of 10^{-2} g ml $^{-1}$.

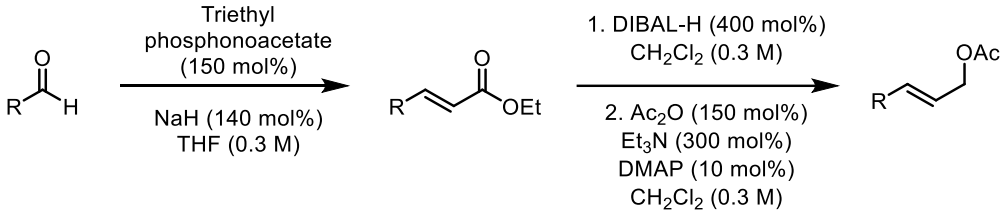
2.5.2 Spectroscopy, Spectrometry and Data Collection

Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M+H, M+Na), or a suitable fragment ion. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a Bruker BioSpin GmbG, Varian Gemini (400 MHz) or Varian INOVA (500 MHz) spectrometer equipped with a Bruker cryoprobe. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from tetramethylsilane or ppm relative to the center of the singlet at 7.26 ppm for deuteriochloroform. Data reported as multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Integration and coupling constants were reported in Hertz (Hz). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a Bruker BioSpin GmbG, Varian Gemini (100 MHz) or Varian INOVA (125 MHz) spectrometer and were routinely run with broadband decoupling.

Chemical shifts are reported in delta (δ) units, ppm relative to the center of the triplet at 77.16 ppm for deuteriochloroform. Fluorine-19 nuclear magnetic resonance (^{19}F NMR) spectra were recorded with a Varian Gemini (376 MHz) spectrometer.

2.5.3 Synthesis of Allylic Acetates 2.1i-2.1r

General procedure for the synthesis of allylic acetates. The allylic acetate **2.1i**, **2.1j**, **2.1k,** and **2.1o** were prepared by the Horner–Wadsworth–Emmons reaction, DIBAL reduction, and acetylation of the corresponding aldehyde as shown below. The allylic acetate **2.1l**, and **2.1r** were prepared by the acetylation of the corresponding allylic alcohol as shown below. The allylic acetates **2.1m**,[25] **2.1n**,[26] and **2.1q**,[27] were prepared according to the published procedures and were identical in all respects to the reported materials.

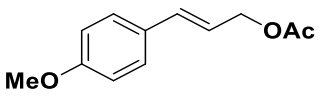


To a round-bottomed flask charged with sodium hydride (140 mol%, 60% in mineral oil) under an argon atmosphere was added THF (0.3 M), followed by triethyl phosphonoacetate (150 mol%). After 10 minutes, the corresponding aldehyde was added, and the mixture was stirred at room temperature overnight. After water was added, the mixture was transferred to a separatory funnel. The organic layer was extracted with ethyl acetate and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting oily residue was subjected to the next step without further purification.

To a round-bottomed flask charged with the crude substrate under an argon atmosphere was added CH_2Cl_2 (0.3 M). The reaction flask was placed an ice batch. After 10 minutes, diisobutylaluminum hydride (400 mol%, 1.0 M in hexanes) was added slowly and the mixture was stirred at room temperature for 1 hour, at which point saturated aqueous Rochelle salts were added and the reaction was stirred vigorously overnight. After water was added, the mixture was transferred to a separatory funnel. The organic layer was extracted with ethyl acetate and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting oily residue was subjected to the next step without further purification.

To a round-bottomed flask charged with the crude substrate and 4-dimethylaminopyridine (5 mol%) under an argon atmosphere was added CH_2Cl_2 (0.3 M), followed by acetic anhydride (150 mol%) and triethylamine (300 mol%). After 1 hour, saturated aqueous sodium bicarbonate was added and the mixture was transferred to a separatory funnel. The organic layer was extracted with CH_2Cl_2 and the combined organic layers were washed with 1 N HCl, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting oily residue was subjected to flash column chromatography give the corresponding allylic acetate over 3 steps.

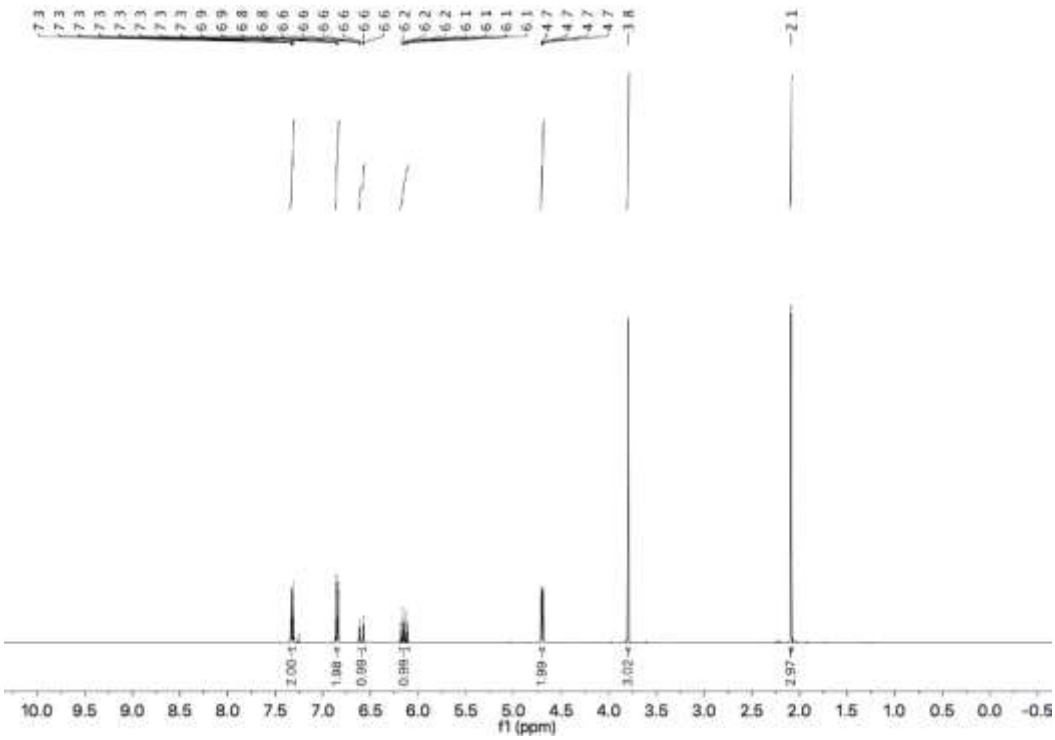
(*E*)-3-(4-Methoxyphenyl)allyl acetate (2.1i)



The title compound was prepared by the general procedure (Horner–Wadsworth–Emmons reaction, DIBAL reduction, and acetylation of the corresponding aldehyde). The spectral data were consistent with those reported.[27]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 – 7.29 (m, 2H), 6.88 – 6.83 (m, 2H), 6.60 (dd, *J* = 16.0, 1.4 Hz, 1H), 6.15 (dt, *J* = 15.8, 6.6 Hz, 1H), 4.70 (dd, *J* = 6.6, 1.3 Hz, 2H), 3.80 (s, 3H), 2.08 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 159.6, 134.0, 128.9, 127.9, 120.8, 114.0, 65.3, 55.3, 21.0.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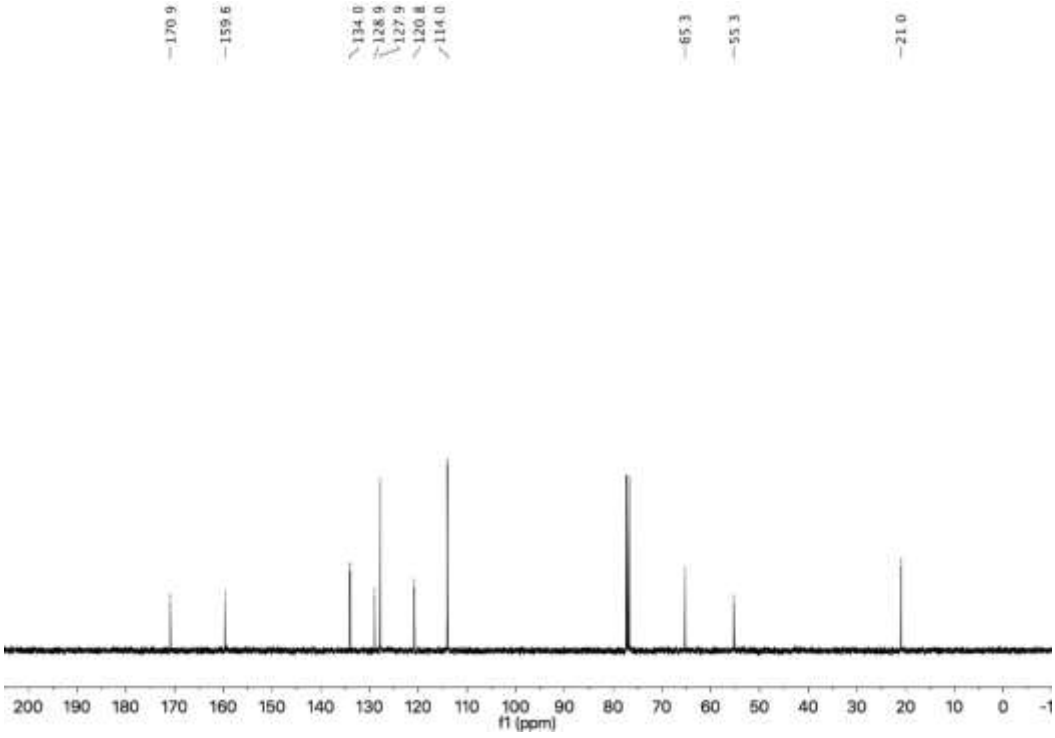
f1 (ppm)


170.9
159.6
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128.9
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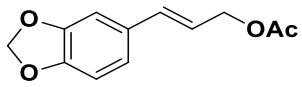
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

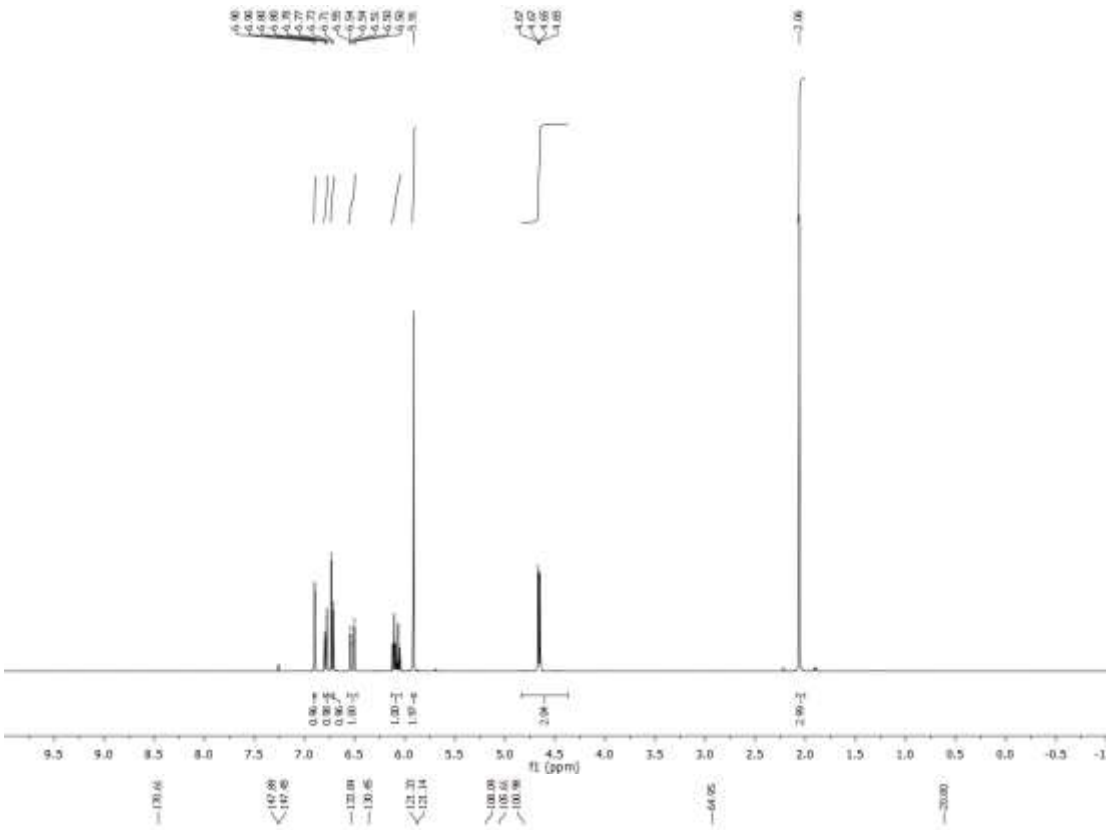
(*E*)-3-(Benzo[d][1,3]dioxol-5-yl)allyl acetate (2.1j)

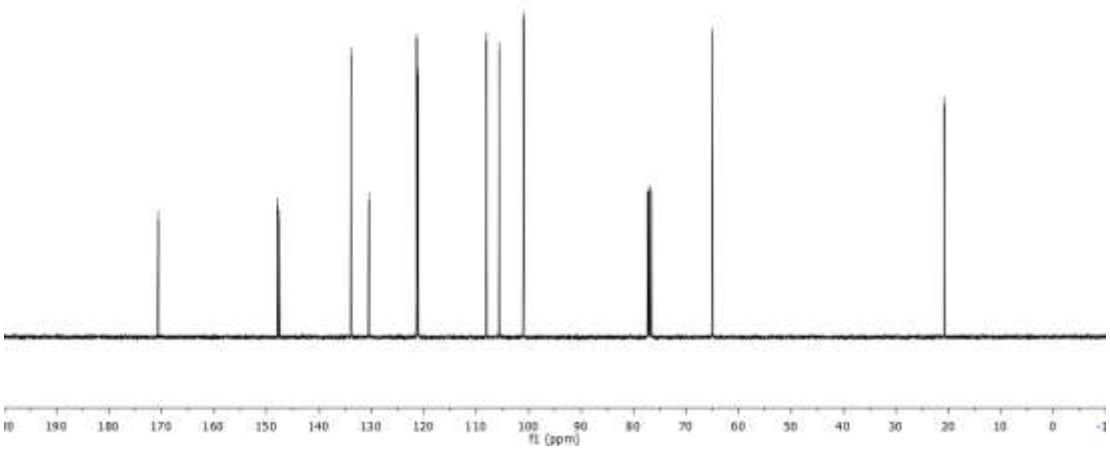


The title compound was prepared by the general procedure (Horner–Wadsworth–Emmons reaction, DIBAL reduction, and acetylation of the corresponding aldehyde). The spectral data were consistent with those reported.[29]

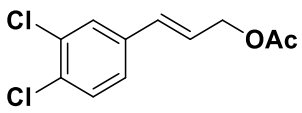
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.90 (d, *J* = 1.7 Hz, 1H), 6.79 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 6.52 (dt, *J* = 15.8, 1.4 Hz, 1H), 6.08 (dt, *J* = 15.8, 6.6 Hz, 1H), 5.91 (s, 2H), 4.66 (dd, *J* = 6.6, 1.4 Hz, 2H), 2.06 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 147.9, 147.5, 133.8, 130.5, 121.3, 121.1, 108.1, 105.6, 101.0, 65.0, 20.8.





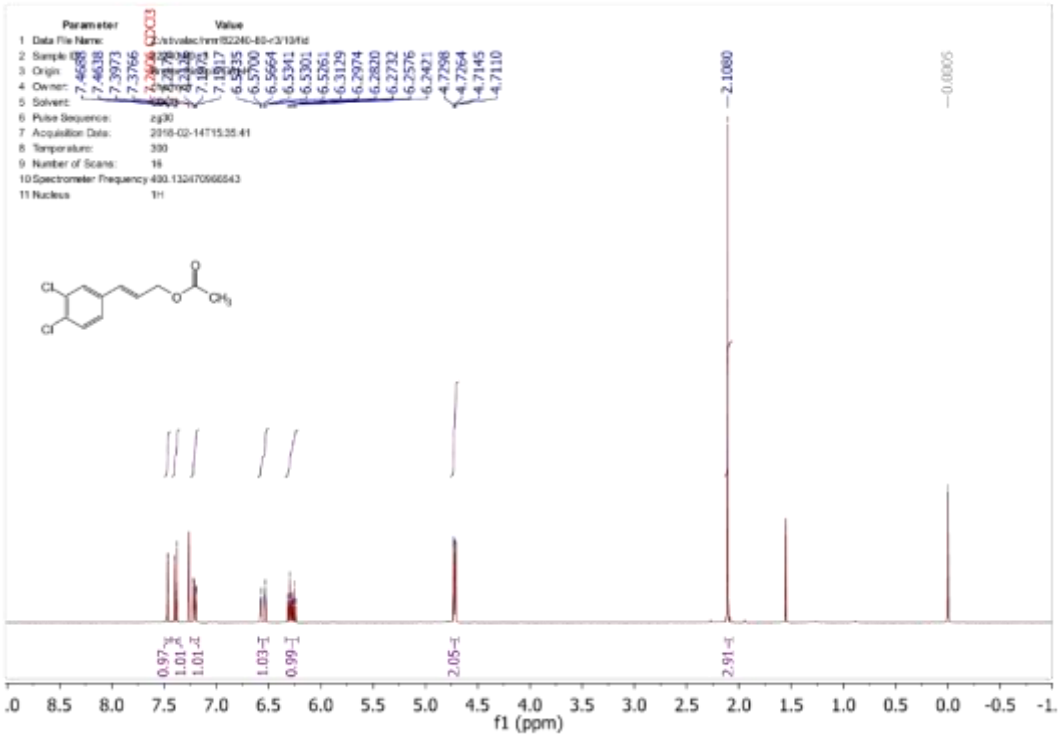
(*E*)-3-(3,4-Dichlorophenyl)allyl acetate (2.1k)

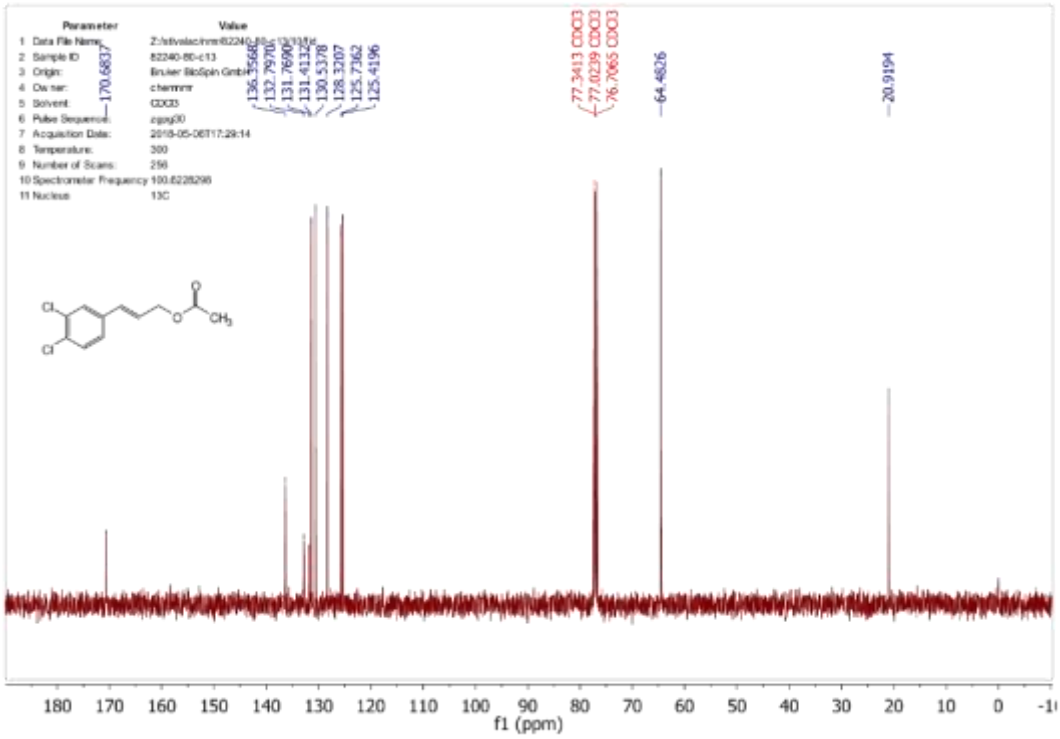


The title compound was prepared by the general procedure (Horner–Wadsworth–Emmons reaction, DIBAL reduction, and acetylation of the corresponding aldehyde). The spectral data were consistent with those reported.[30]

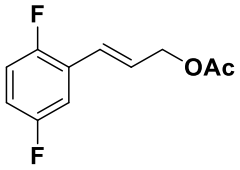
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 2.0 Hz, 1H), 7.39 (d, *J* = 8.3 Hz, 1H), 7.20 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.55 (dt, *J* = 16.1, 1.5 Hz, 1H), 6.28 (dt, *J* = 16.0, 6.2 Hz, 1H), 4.72 (dd, *J* = 6.2, 1.4 Hz, 2H), 2.11 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 136.4, 132.8, 131.8, 131.4, 130.5, 128.3, 125.7, 125.4, 64.5, 20.9.


Parameter
Value
f1 (ppm)


Parameter
Value
f1 (ppm)

(*E*)-3-(2,5-Difluorophenyl)allyl acetate (2.1l)

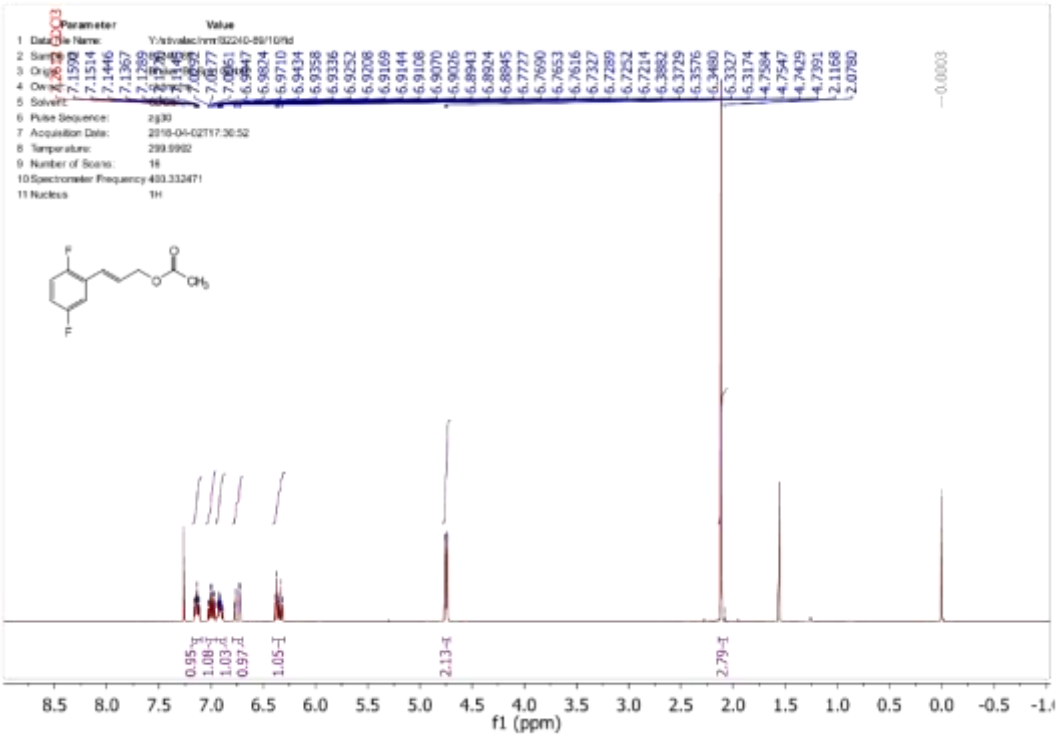


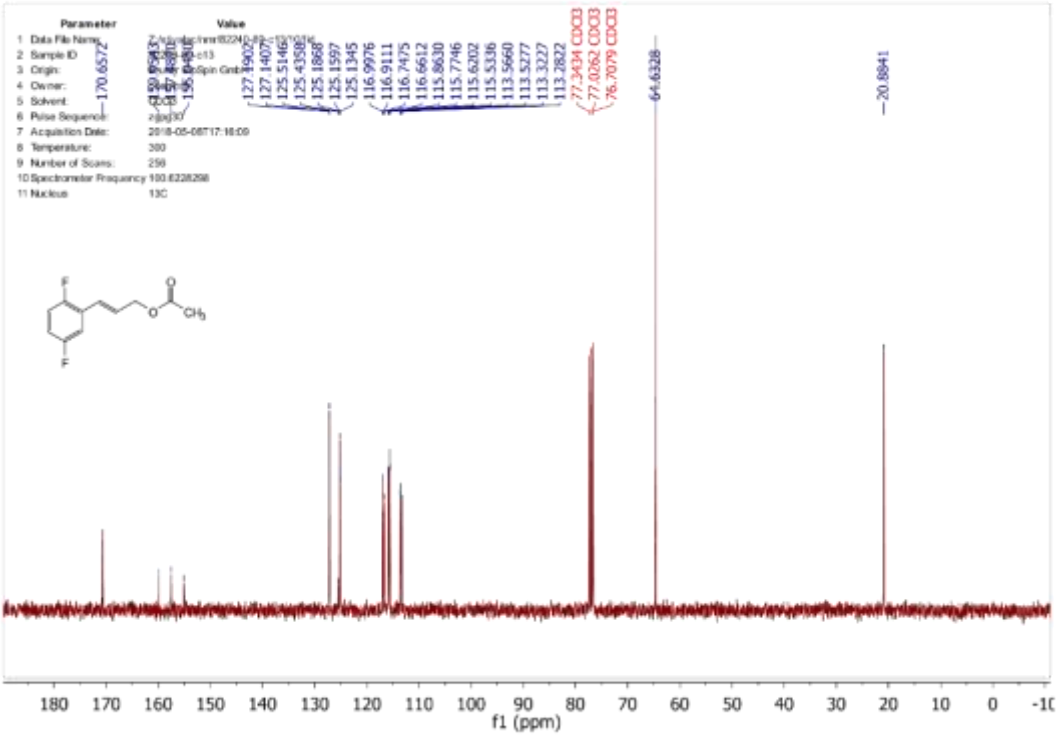
The title compound was prepared by the general procedure (acetylation of the corresponding allylic alcohol). The spectral data were consistent with those reported.[31]

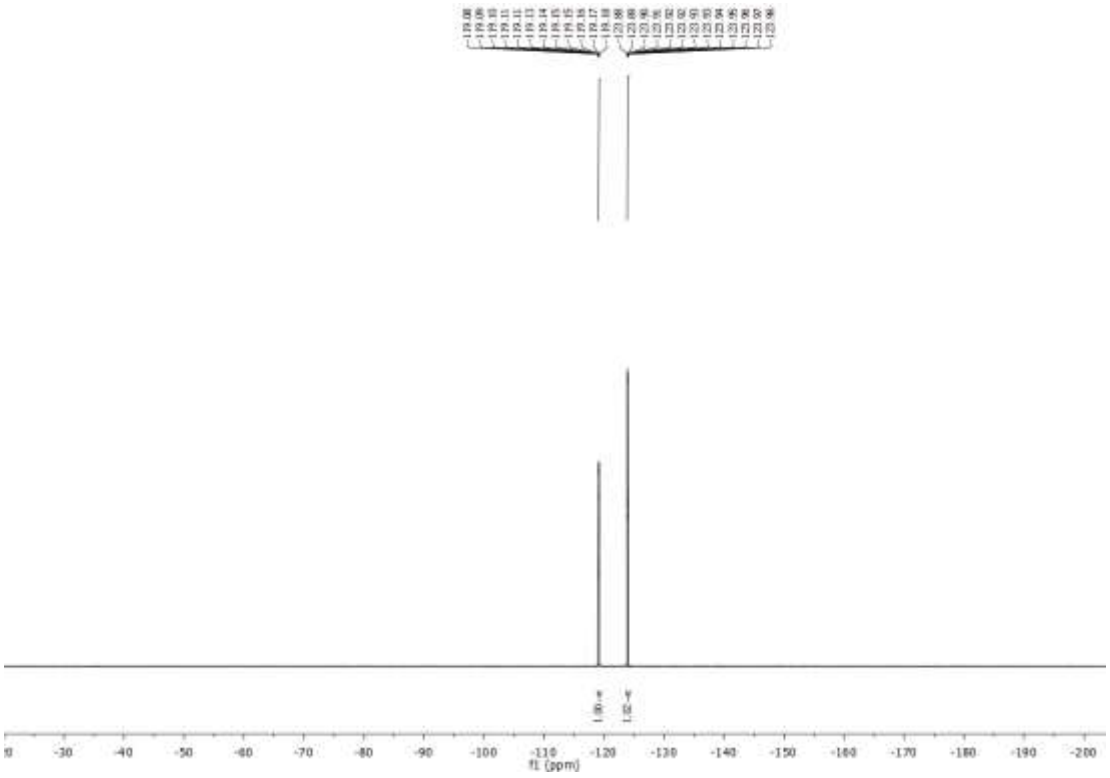
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 (ddd, *J* = 8.9, 5.8, 3.1 Hz, 1H), 7.00 (td, *J* = 9.4, 4.6 Hz, 1H), 6.96 – 6.86 (m, 1H), 6.75 (dq, *J* = 16.1, 1.5 Hz, 1H), 6.35 (dt, *J* = 16.1, 6.1 Hz, 1H), 4.75 (dd, *J* = 6.2, 1.5 Hz, 2H), 2.12 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 158.7 (dd, *J* = 242.0, 2.1 Hz), 156.3 (dd, *J* = 245.8, 2.3 Hz), 127.3 – 127.1 (m), 125.4 (dd, *J* = 14.8, 8.0 Hz), 125.2 (t, *J* = 2.6 Hz), 116.8 (dd, *J* = 25.1, 8.7 Hz), 115.7 (dd, *J* = 24.3, 8.8 Hz), 113.4 (dd, *J* = 24.6, 4.0 Hz), 64.6, 20.9.

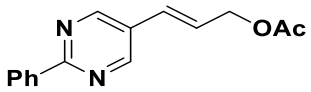
^{19}F NMR (376 MHz, $CDCl_3$): δ = –119.1 (m, 1F), –123.9 (m, 1F).


Parameter
Value
f1 (ppm)


Parameter
Value
f1 (ppm)


-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

(*E*)-3-(2-Phenylpyrimidin-5-yl)allyl acetate (2.1o)



The title compound was prepared by the general procedure (Horner–Wadsworth–Emmons reaction, DIBAL reduction, and acetylation of the corresponding aldehyde).

TLC (SiO_2) R_f = 0.56 (hexanes: ethyl acetate = 2:1).

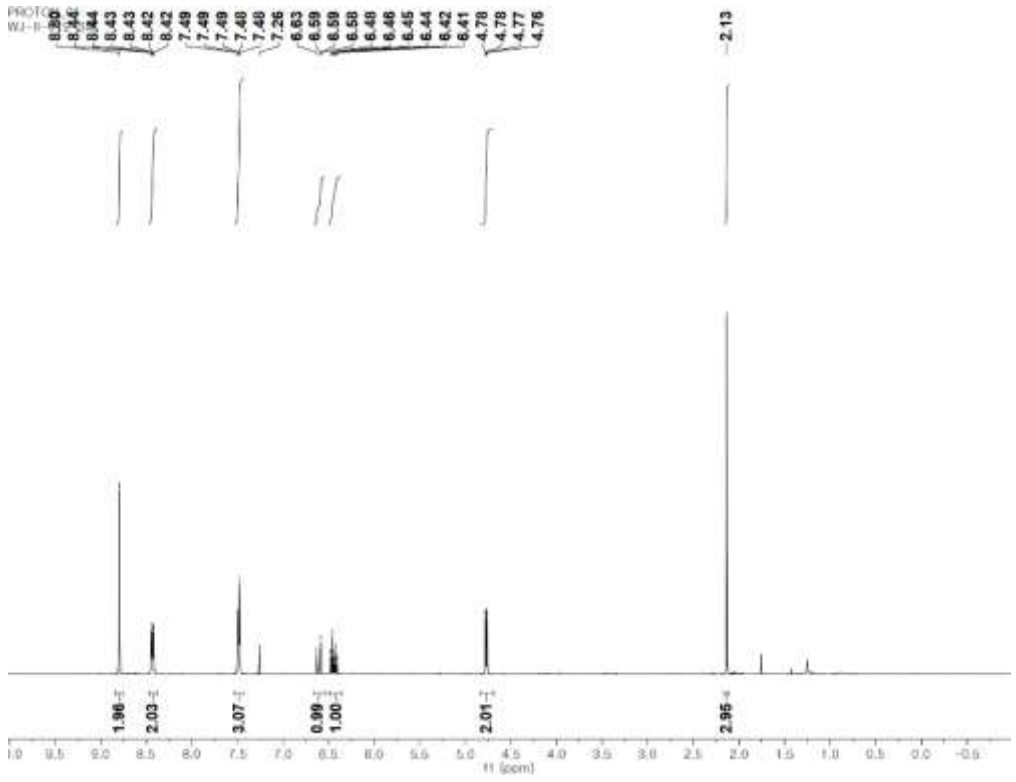
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.80 (s, 2H), 8.47 – 8.38 (m, 2H), 7.53 – 7.43 (m, 3H), 6.66 – 6.54 (m, 1H), 6.44 (dt, *J* = 16.1, 5.9 Hz, 1H), 4.77 (dd, *J* = 5.9, 1.4 Hz, 2H), 2.13 (s, 3H).

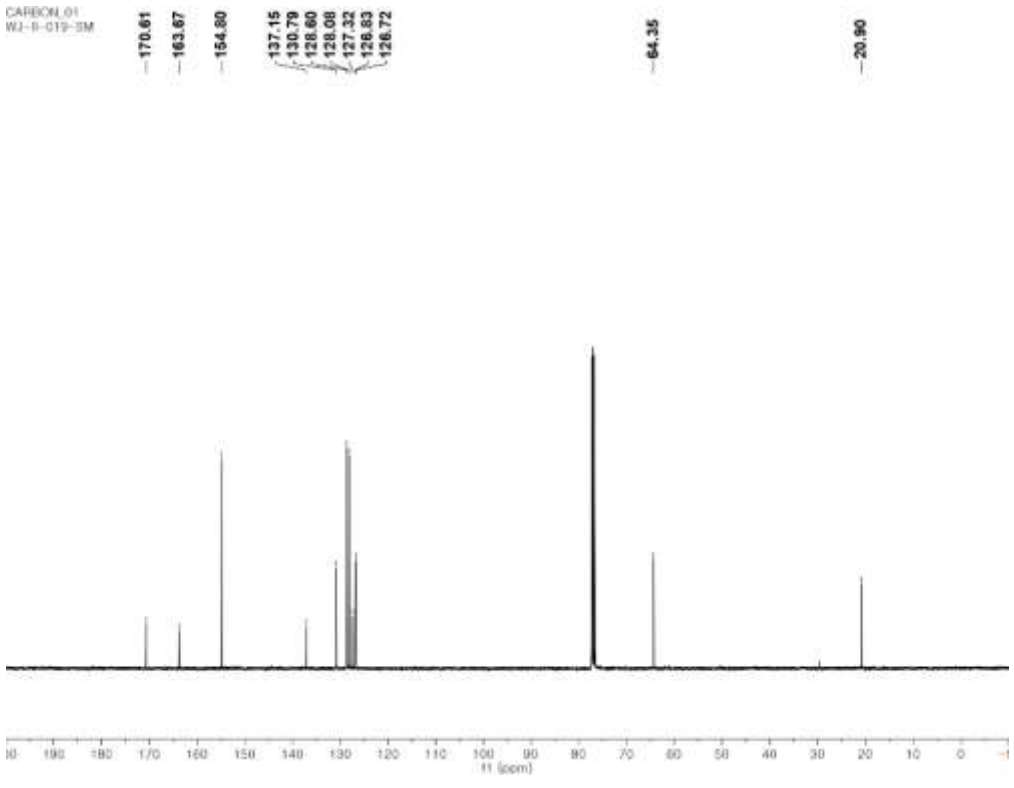
^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 163.7, 154.8, 137.2, 130.8, 128.6, 128.1, 127.3, 126.8, 126.7, 64.4, 20.9.

HRMS (ESI): Calculated for $C_{15}H_{14}N_2O_2$ $[M+H^+]$ = 255.1128, found 255.1128.

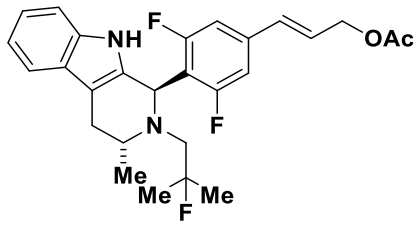
FTIR (neat): 3036, 2939, 1731,1662, 1582, 1540, 1450, 1432, 1385, 1366, 1328, 1316, 1297, 1250, 1228, 1170, 1077, 1065, 1021, 967, 942, 930, 906, 848, 820, 780, 747, 730, 697, 651 cm^{-1}.

Melting Point : 114–118 ˚C


8.43
8.42
7.49
7.49
7.49
7.48
7.48
7.26
6.63
6.59
6.59
6.58
6.46
6.46
6.45
6.44
6.42
6.41
4.78
4.78
4.77
4.76
2.13
1.96
2.03
3.07
0.99
1.00
2.01
2.95
f1 (ppm)


CARBON_01
WJ-5-019-SM
170.61
163.67
154.80
137.15
130.79
128.60
128.08
127.32
126.83
126.72
64.35
20.90
f1 (ppm)

(*E*)-3-(3,5-Difluoro-4-((*1R,3R*)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenyl)allyl acetate (2.1p)



Step 1: Borane-tetrahydrofuran complex (2.0 M in tetrahydrofuran, 16 mL, 33 mmol) was added to a solution of (E)-3-[3,5-difluoro-4-[(1R,3R)-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-1-yl]phenyl]prop-2-enoic acid (3.6 g, 8.1 mmol) in THF (16 mL) at rt. After 3 h, methanol was added and the reaction was allowed to stir for 20 minutes. The reaction was concentrated under reduced pressure, and the crude residue was purified by flash column chromatography (silica, 0% to 40% isopropyl acetate - heptane) to give (*E*)-3-[3,5-difluoro-4-[(*1R,3R*)-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-1-yl]phenyl]prop-2-en-1-ol (1.60 g, 3.73 mmol, 46% Yield).

TLC (SiO_2) R_f = 0.48 (hexanes: ethyl acetate = 1:1).

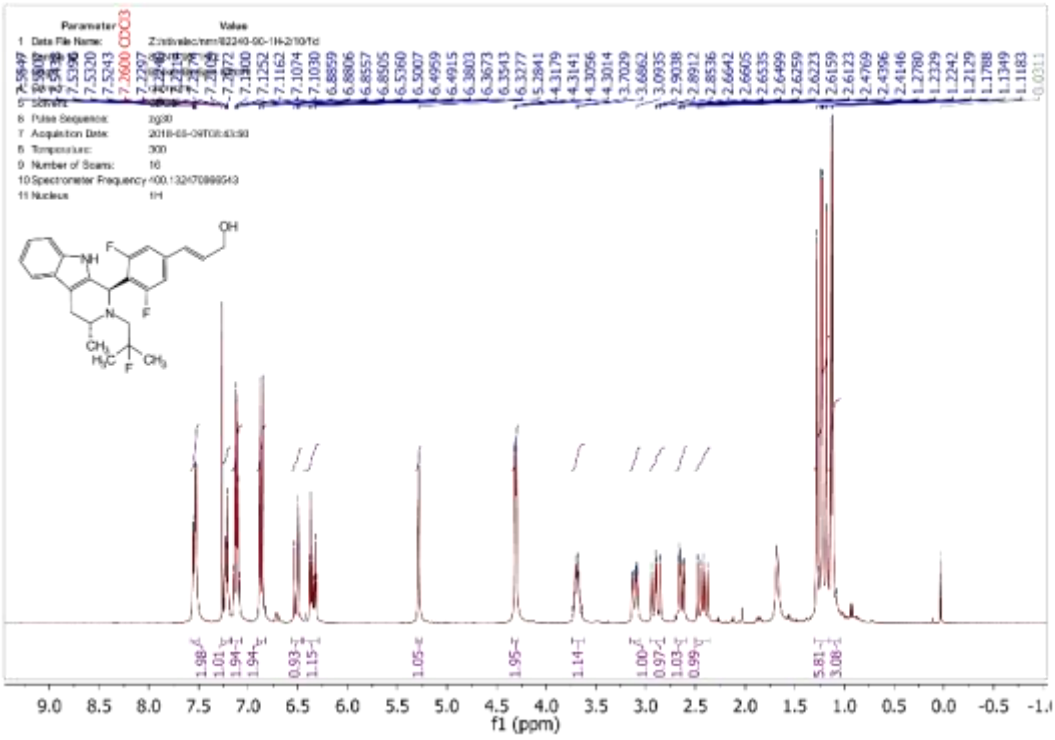
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 – 7.50 (m, 2H), 7.27 – 7.18 (m, 1H), 7.17 – 7.06 (m, 2H), 6.91 – 6.83 (m, 2H), 6.56 – 6.47 (m, 1H), 6.35 (dt, *J* = 15.9, 5.2 Hz, 1H), 5.28 (s, 1H), 4.34 – 4.28 (m, 2H), 3.74 – 3.62 (m, 1H), 3.11 (ddd, *J* = 15.2, 5.2, 2.0 Hz, 1H), 2.90 (dd, *J* = 20.0, 15.0 Hz, 1H), 2.64 (ddd, *J* = 15.1, 4.1, 1.5 Hz, 1H), 2.43 (dd, *J* = 25.0, 14.9 Hz, 1H), 1.23 (dd, *J* = 21.6, 18.1 Hz, 6H), 1.13 (d, *J* = 6.6 Hz, 3H).

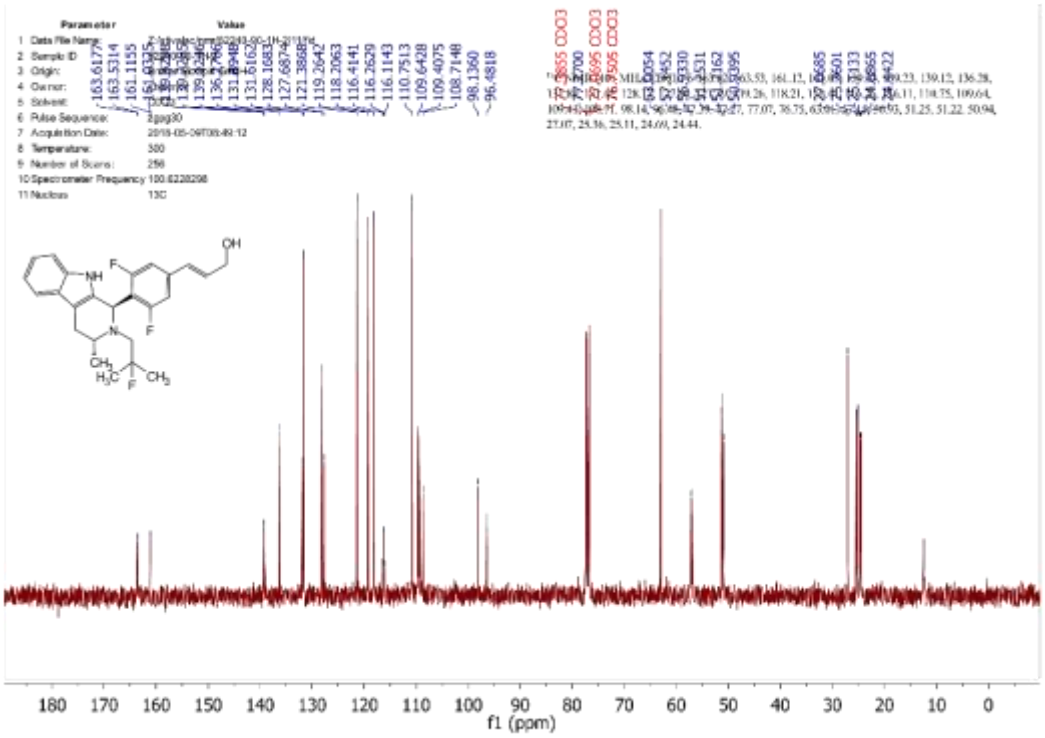
^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.3 (dd, *J* = 251.5, 8.3 Hz), 139.2 (t, *J* = 10.3 Hz), 136.3, 131.9, 131.6, 128.2 (t, *J* = 2.6 Hz), 127.7, 121.4, 119.3, 118.2, 116.3 (t, *J* = 15.0 Hz), 110.8, 109.5 (d, *J* = 22.1 Hz), 108.7, 98.1, 96.5, 63.0, 57.0 (d, *J* = 21.4 Hz), 51.2 (d, *J* = 3.7 Hz), 50.9, 27.1, 25.2 (d, *J* = 24.9 Hz), 24.6 (d, *J* = 24.6 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –139.4 (m).

HRMS (ESI): Calculated for $C_{25}H_{28}ON_2F_3$ [M+H$^+$] = 429.2148, found 429.2146.

FTIR (neat): 3413, 2979, 1629, 1449, 1372, 1202, 1132,, 1021, 908, 731 cm^{-1}.




Parameter
Value
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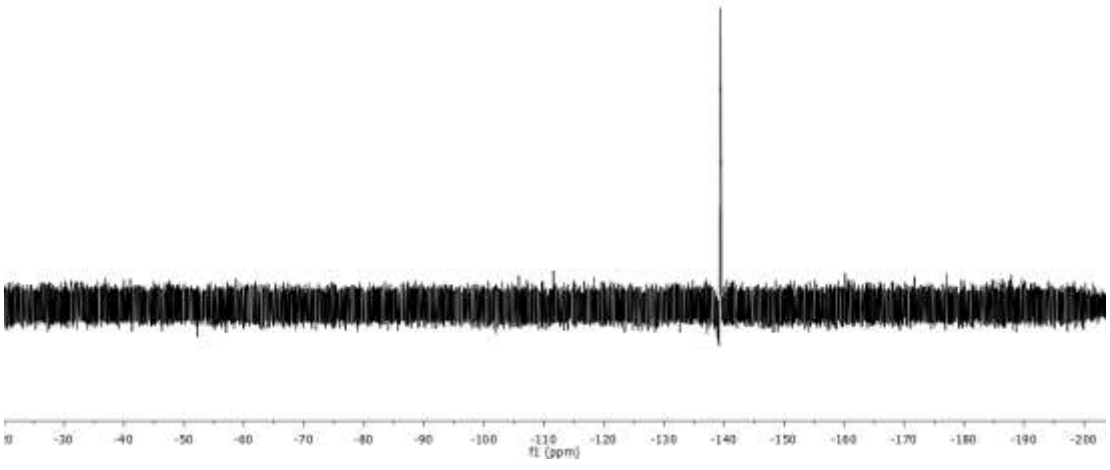
2 Sample ID
3 Origin:
4 Owner:
5 Solvent:
6 Pulse Sequence:
2pgpg30
7 Acquisition Date:
2019-05-04T08:49:12
8 Temperature:
300
9 Number of Scans:
256
10 Spectrometer Frequency:
100.6228298
11 Nucleus
13C
CDCl3
CDCl3
CDCl3
OH
NH
F
F
N
CH3
H3C
CH3
F
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


0 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

Step 2: 4-Dimethylaminopyridine (45.6 mg, 0.373 mmol) was added to a solution of the product of **Step 1** (1.60 g, 3.73 mmol) and acetic anhydride (0.420 mL, 4.48 mmol) in dichloromethane (75 mL) at rt. After 30 min, the reaction was concentrated under reduced pressure and the crude residue was purified by flash column chromatography (silica 0% to 30% isopropyl acetate - heptane) to give the desired product (1.64 g, 3.49 mmol, 93% Yield).

TLC (SiO_2) R_f = 0.61 (hexanes: ethyl acetate = 2:1).

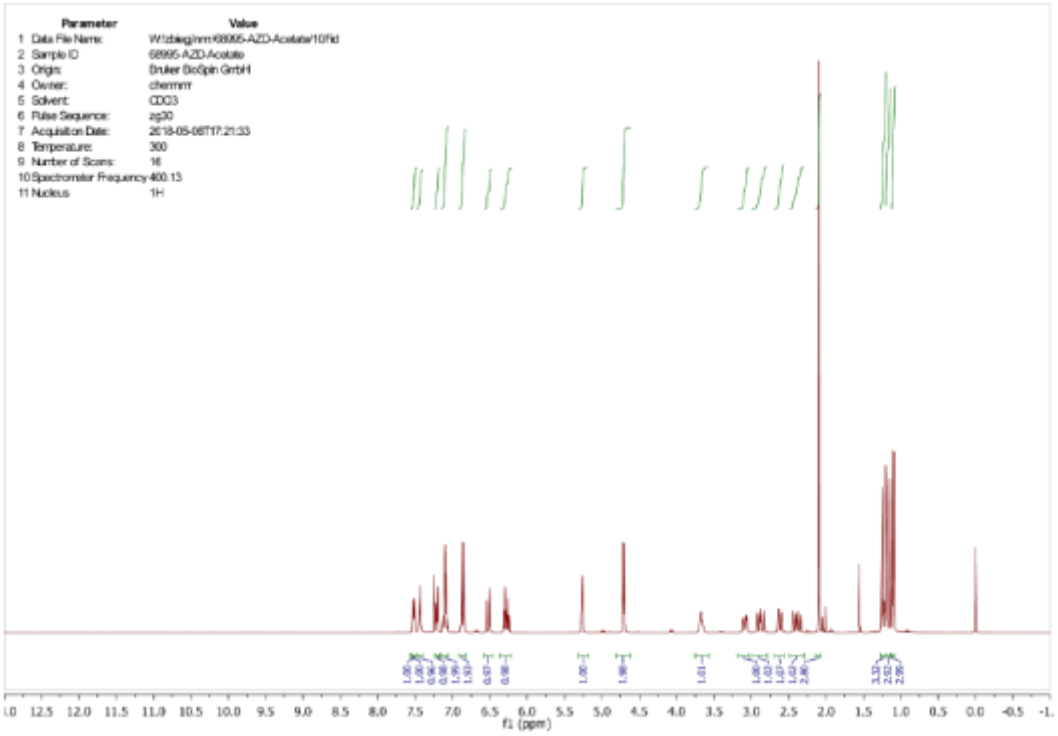
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 – 7.49 (m, 1H), 7.43 (s, 1H), 7.23 – 7.17 (m, 1H), 7.14 – 7.05 (m, 2H), 6.86 (d, *J* = 9.9 Hz, 2H), 6.52 (d, *J* = 16.0 Hz, 1H), 6.28 (dt, *J* = 15.9, 6.1 Hz, 1H), 5.26 (s, 1H), 4.71 (dd, *J* = 6.1, 1.4 Hz, 2H), 3.72 – 3.63 (m, 1H), 3.09 (ddd, *J* = 15.2, 5.0, 1.9 Hz, 1H), 2.88 (dd, *J* = 19.9, 15.0 Hz, 1H), 2.61 (ddd, *J* = 15.1, 4.1, 1.4 Hz, 1H), 2.39 (dd, *J* = 25.1, 15.0 Hz, 1H),1.23 (d, *J* = 18.2 Hz, 3H), 1.17 (d, *J* = 18.4 Hz, 3H), 1.10 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7 , 162.3 (dd, *J* = 251.8, 8.2 Hz), 138.6 (t, *J* = 10.3 Hz), 136.3, 131.7, 131.2 (d, *J* = 2.7 Hz), 127.7 , 126.4 , 121.4 , 119.3 , 118.2 , 116.7 (t, *J* = 14.9 Hz), 110.7 , 109.7 (dd, *J* = 23.8, 3.3 Hz), 108.8, 98.0, 96.4, 64.3, 57.1 (d, *J* = 21.7 Hz), 51.2 (d, *J* = 3.9 Hz), 50.9, 27.1, 25.2 (d, *J* = 24.9 Hz), 24.5 (d, *J* = 24.8 Hz), 20.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –139.3 (m).

HRMS (ESI): Calculated for $C_{27}H_{29}O_2N_2F_3$ $[M+H^+]$ = 471.2254, found 471.2247.

FTIR (neat): 3401, 2974, 1732, 1629, 1570, 1428, 1231, 1022, 964, 866, 736, 703 cm^{-1}.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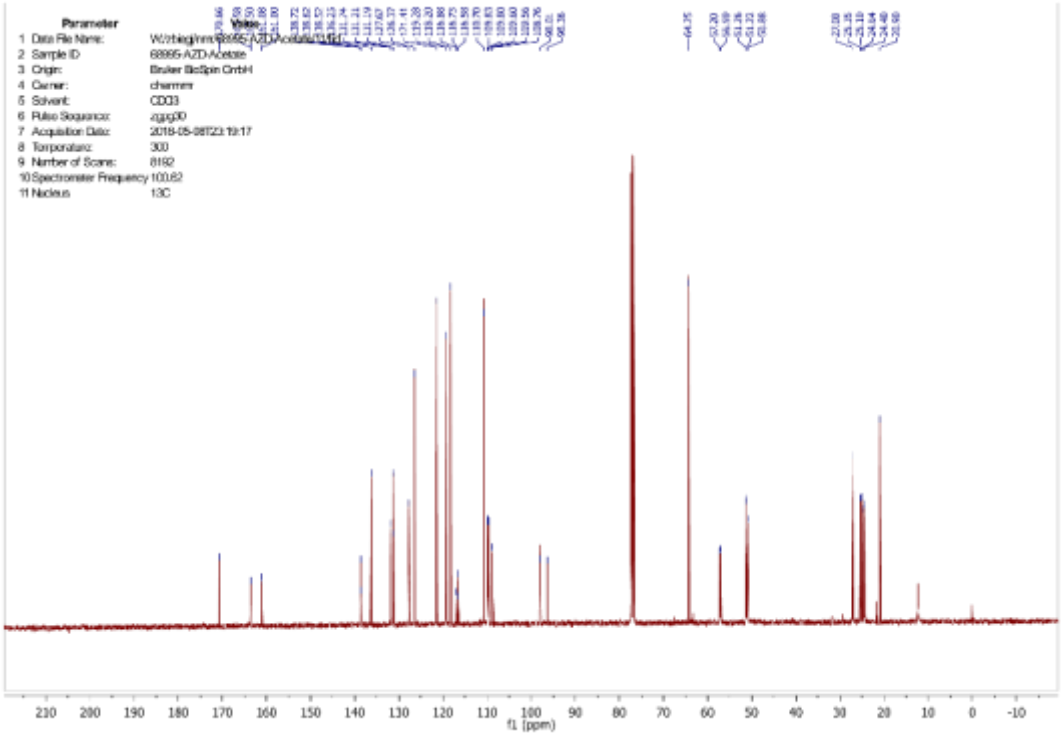
2 Sample ID 68995-AZD-Acetate
3 Origin: Bruker BioSpin GmbH
4 Owner: chemmr
5 Solvent: CDCl3
6 Pulse Sequence: zg30
7 Acquisition Date: 2018-05-08T17:21:33
8 Temperature: 300
9 Number of Scans: 16
10 Spectrometer Frequency 400.13
11 Nucleus 1H
f1 (ppm)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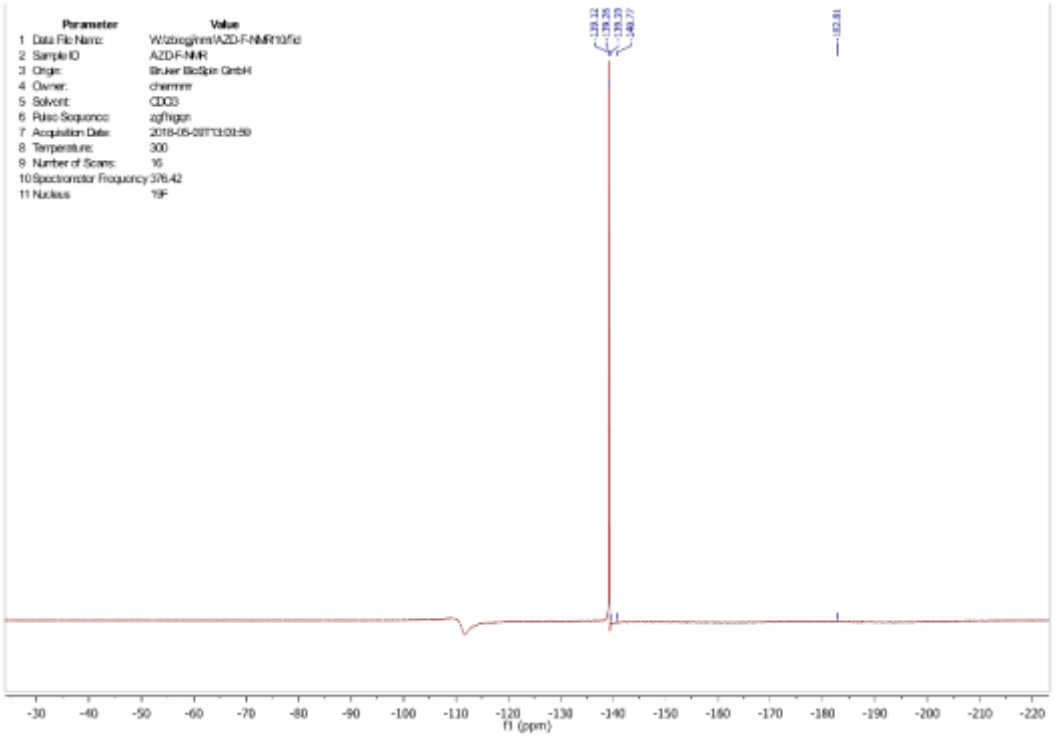
f1 (ppm)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4 Owner: chemmr
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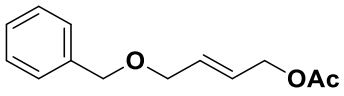
8 Temperature: 300
9 Number of Scans: 16
10 Spectrometer Frequency 376.42
11 Nucleus 19F
-139.32
-139.36
-139.39
-140.77
-182.81
-30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

(*E*)-4-(Benzyloxy)but-2-en-1-yl acetate (2.1r)



The title compound was prepared by the acetylation of the corresponding allylic alcohol.[32]

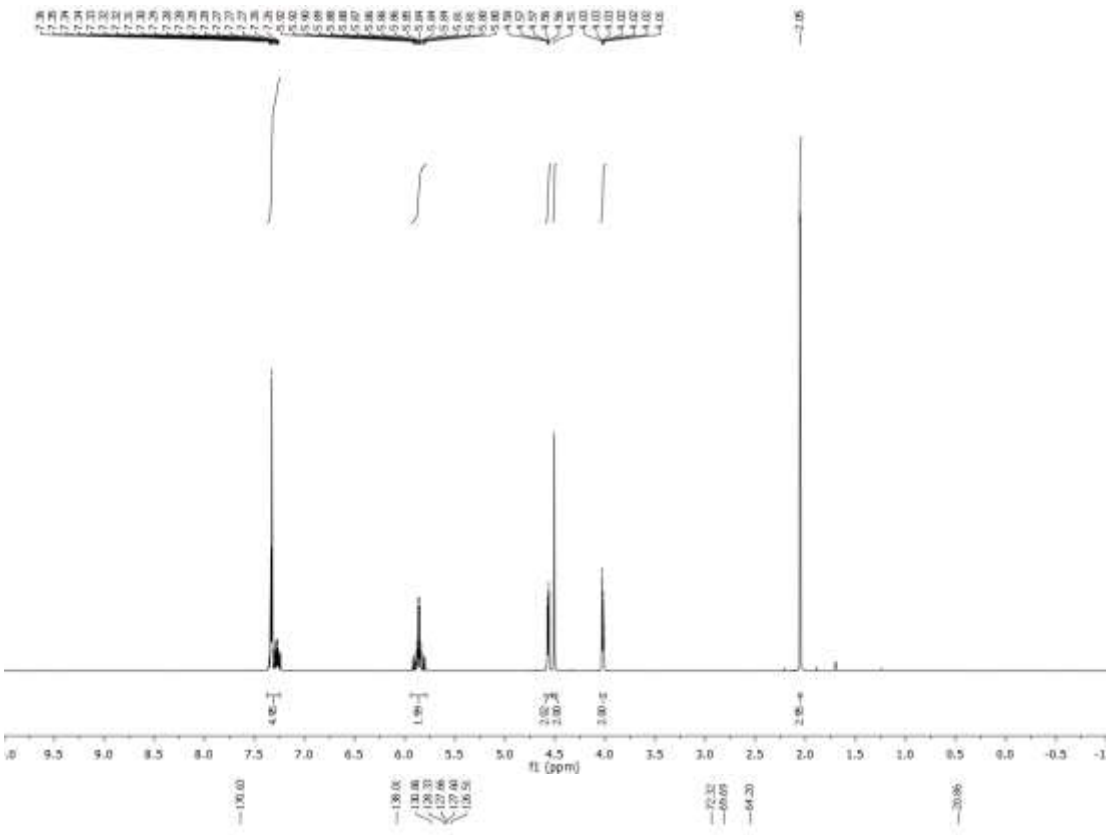
TLC (SiO_2) R_f = 0.45 (hexanes: ethyl acetate = 4:1).

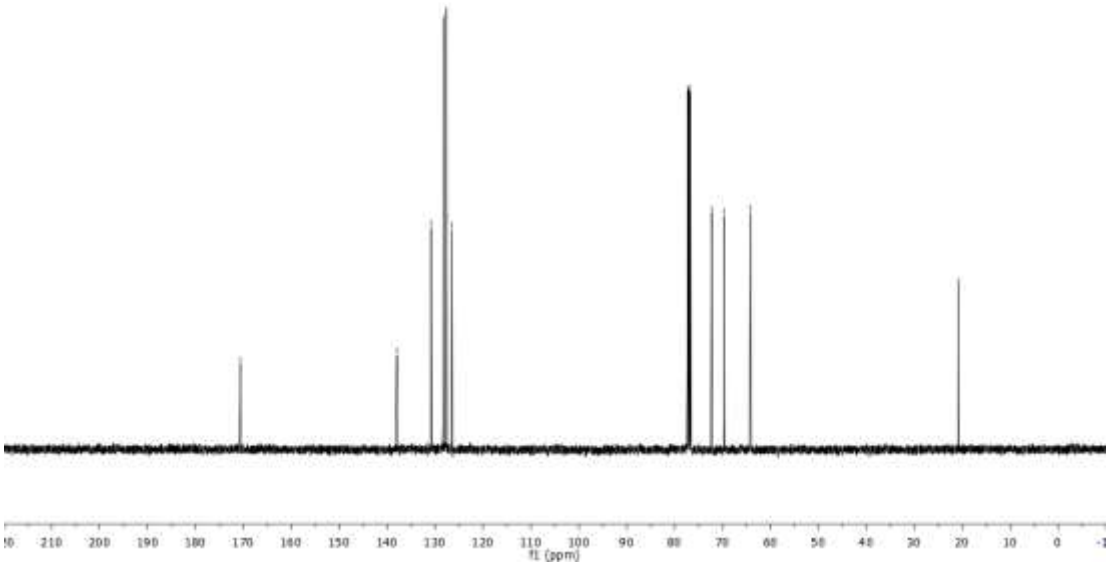
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 – 7.24 (m, 5H), 5.94 – 5.78 (m, 2H), 4.60 – 4.53 (m, 2H), 4.51 (s, 2H), 4.02 (dt, *J* = 3.9, 1.1 Hz, 2H), 2.05 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 138.0, 130.9, 128.3, 127.7, 127.6, 126.5, 72.3, 69.7, 64.2, 20.9.

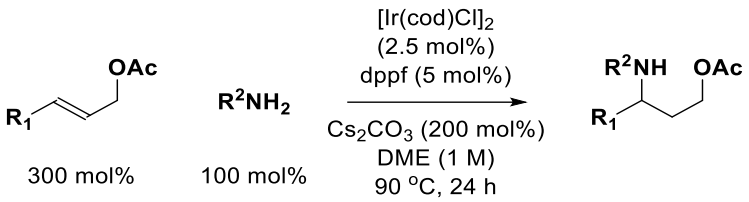
HRMS (ESI): Calculated for $C_{13}H_{16}O_3$ $[M+NH_4^+]$ = 238.1438, found 238.1442.

FTIR (neat): 2856, 1736, 1363, 1231, 1026, 908, 729, 669 cm^{-1}.


f1 (ppm)


f1 (ppm)

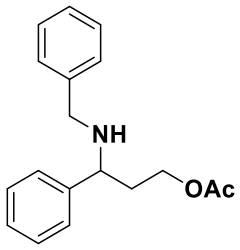
2.5.4 Procedures and Spectral Data for Synthesis of OAc-Amino Alcohols 2.3a-2.3r: Regioselective Ir-catalyzed hydroamination with primary amine nucleophiles



General Procedure

An oven-dried pressure tube equipped with a magnetic stir bar was charged with cesium carbonate (200 mol%), $[Ir(cod)Cl]_2$ (2.5 mol%), and dppf (5 mol%). The tube was purged with argon for 5 minutes. DME (1.0 M) was added followed by the allylic acetate (300 mol%) and the amine (100 mol%). The tube was sealed with a PTFE lined cap and was placed in an oil bath at 90 °C and stirred for 24 hours. After reaching ambient temperature, the crude reaction mixture was directly subjected to flash column chromatography under the noted conditions.

3-(Benzylamino)-3-phenylpropyl acetate (2.3a)



The allylic acetate (105.7 mg, 0.6 mmol, 300 mol%) and the primary amine (21.4 mg, 0.2 mmol, 100 mol%) were subject to standard reaction conditions. The title compound was obtained in 77% yield (43.6 mg, 0.15 mmol) as a light yellow oil after purification by flash column chromatography (SiO_2, dichloromethane: diethyl ether = 20:1–10:1).

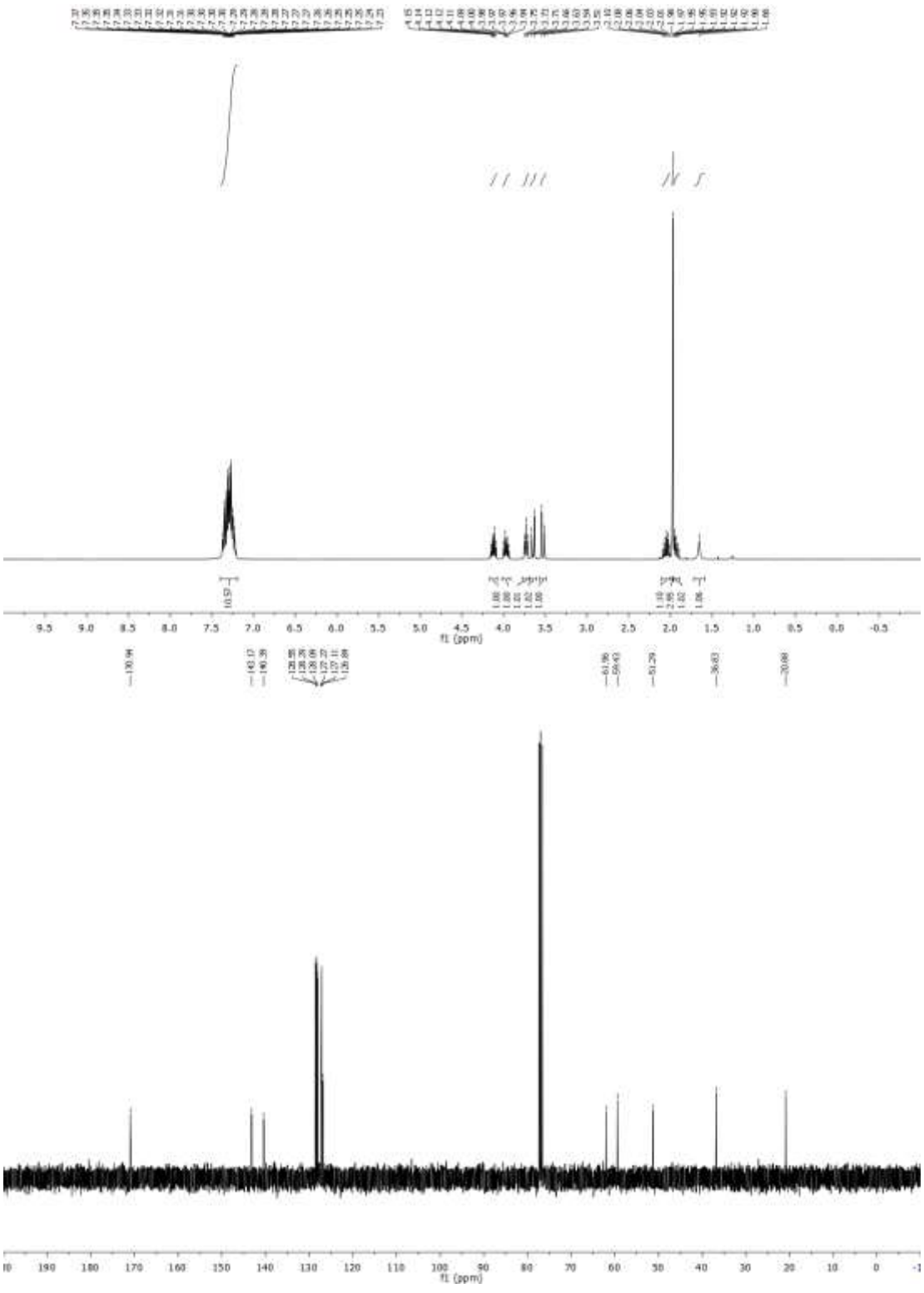
TLC (SiO_2) R_f = 0.22 (dichloromethane: diethyl ether = 5:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 – 7.19 (m, 10H), 4.12 (dt, *J* = 11.1, 6.4 Hz, 1H), 3.97 (dt, *J* = 11.1, 6.6 Hz, 1H), 3.73 (t, *J* = 7.0 Hz, 1H), 3.65 (d, *J* = 13.1 Hz, 1H), 3.53 (d, *J* = 13.1 Hz, 1H), 2.05 (dq, *J* = 13.5, 6.7 Hz, 1H), 1.97 (s, 3H), 1.97 – 1.89 (m, 1H), 1.66 (br, 1H).

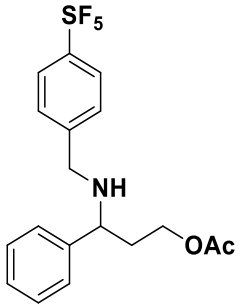
^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 143.2, 140.4, 128.6, 128.3, 128.1, 127.3, 127.1, 126.8, 62.0, 59.4, 51.3, 36.8, 20.9.

HRMS (ESI): Calculated for $C_{18}H_{21}NO_2$ [M+H$^+$] = 284.1654, found 284.1651.

FTIR (neat): 3029, 1735, 1453, 1364, 1235, 1028, 737, 698 cm^{-1}.



3-((4-(Pentafluoro-l6-sulfanyl)benzyl)amino)-3-phenylpropyl acetate (2.3b)



The allylic acetate (105.7 mg, 0.6 mmol, 300 mol%) and the primary amine (46.6 mg, 0.2 mmol, 100 mol%) were subject to standard reaction conditions. The title compound was obtained in 63% yield (51.6 mg, 0.13 mmol) as a light yellow oil after purification by flash column chromatography (SiO_2, dichloromethane: diethyl ether = 1:0–5:1).

TLC (SiO_2) R_f = 0.52 (dichloromethane: diethyl ether = 5:1).

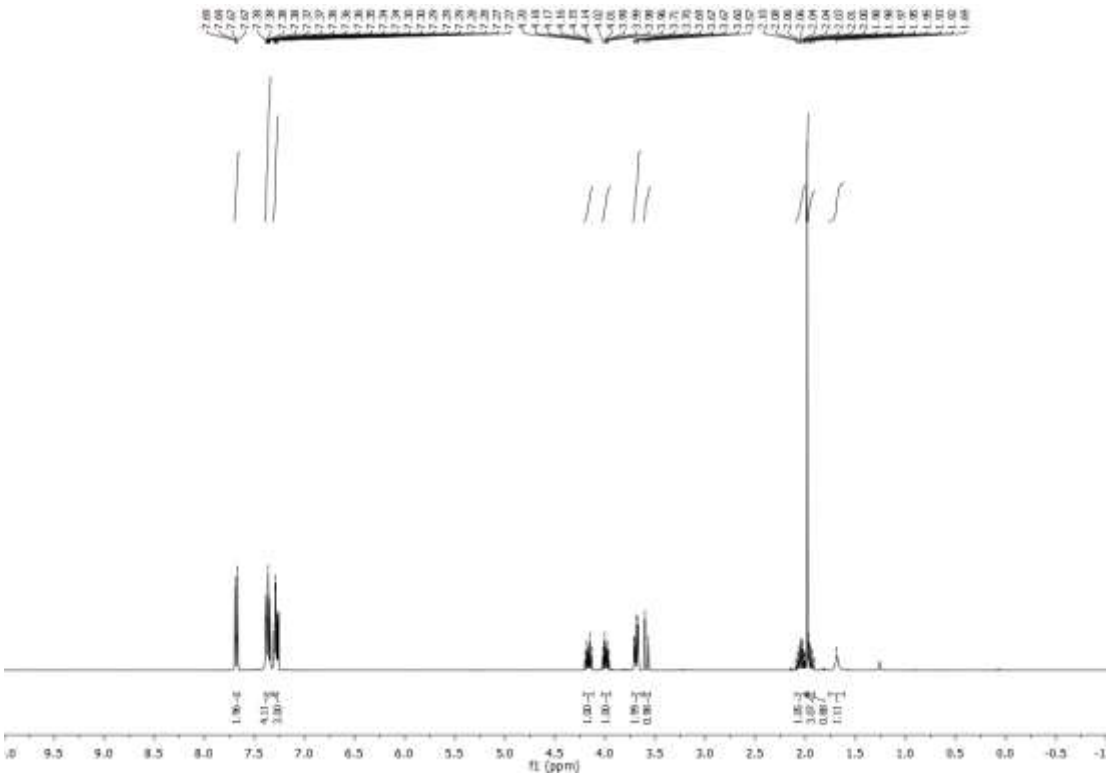
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 – 7.65 (m, 2H), 7.40 – 7.34 (m, 4H), 7.31 – 7.26 (m, 3H), 4.17 (dt, *J* = 11.1, 6.5 Hz, 1H), 3.99 (dt, *J* = 11.1, 6.5 Hz, 1H), 3.73 – 3.64 (m, 2H), 3.58 (d, *J* = 13.9 Hz, 1H), 2.10 – 2.01 (m, 1H), 1.98 (s, 3H), 1.98 – 1.91 (m, 1H), 1.69 (br, 1H).

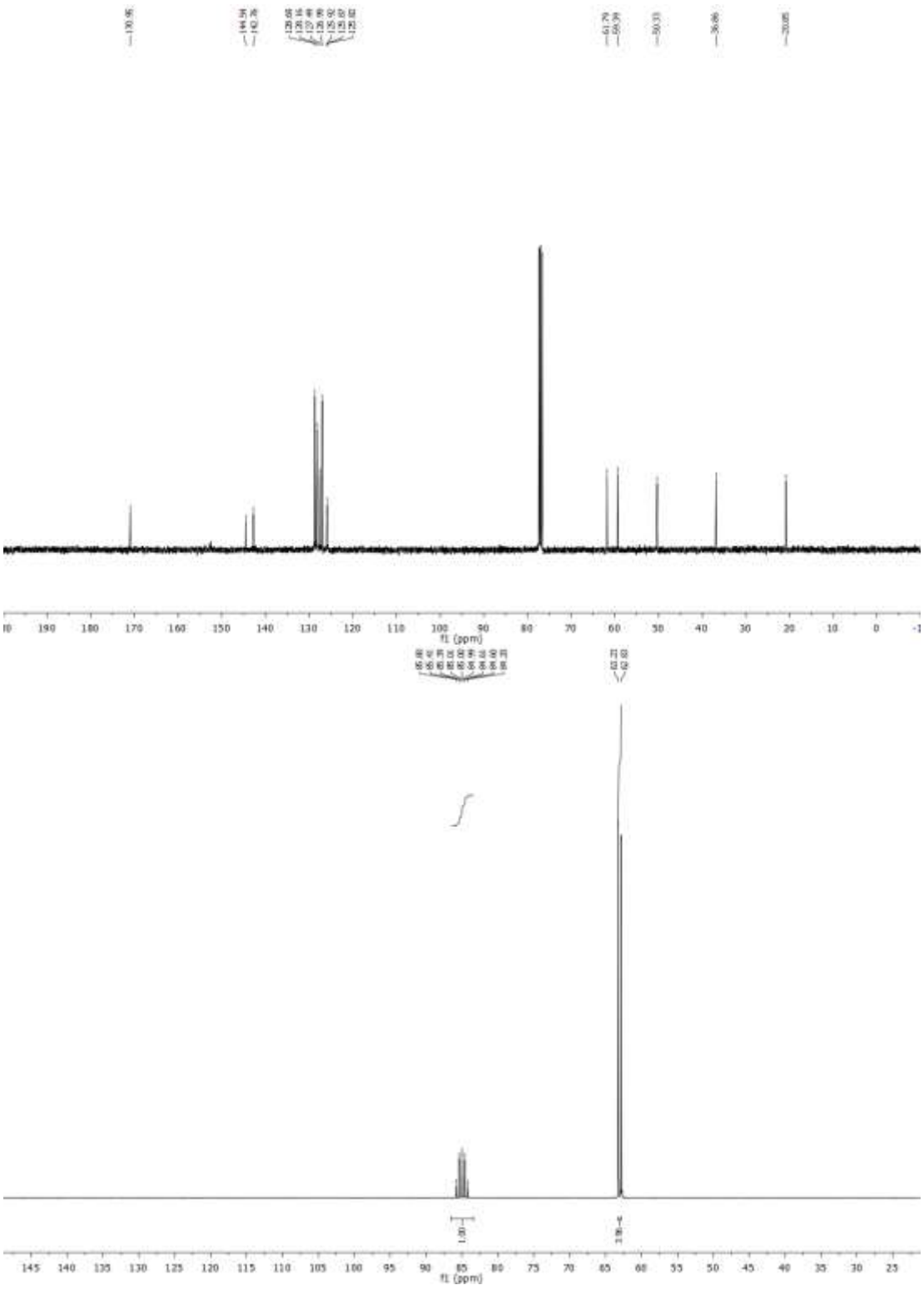
^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 144.5, 142.8, 128.7, 128.2, 127.5, 126.99, 125.87(t), 61.8, 59.4, 50.3, 36.9, 20.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ = 86.52 – 83.38 (m, 1F), 63.03 (d, *J* = 149.7 Hz, 4F).

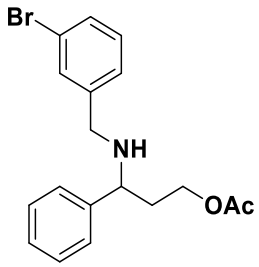
HRMS (ESI): Calculated for $C_{18}H_{20}F_5NO_2S$ [M+H$^+$] = 410.1208, found 410.1210.

FTIR (neat): 1736, 1366, 1239, 1039, 833, 701, 670 cm^{-1}.


f1 (ppm)



3-((3-Bromobenzyl)amino)-3-phenylpropyl acetate (2.3c)



The allylic acetate (105.7 mg, 0.6 mmol, 300 mol%) and the primary amine (37.2 mg, 0.2 mmol, 100 mol%) were subject to standard reaction conditions. The title compound was obtained in 65% yield (51.2 mg, 0.13 mmol) as a yellow oil after purification by flash column chromatography (SiO_2, hexanes: ethyl acetate = 4:1).

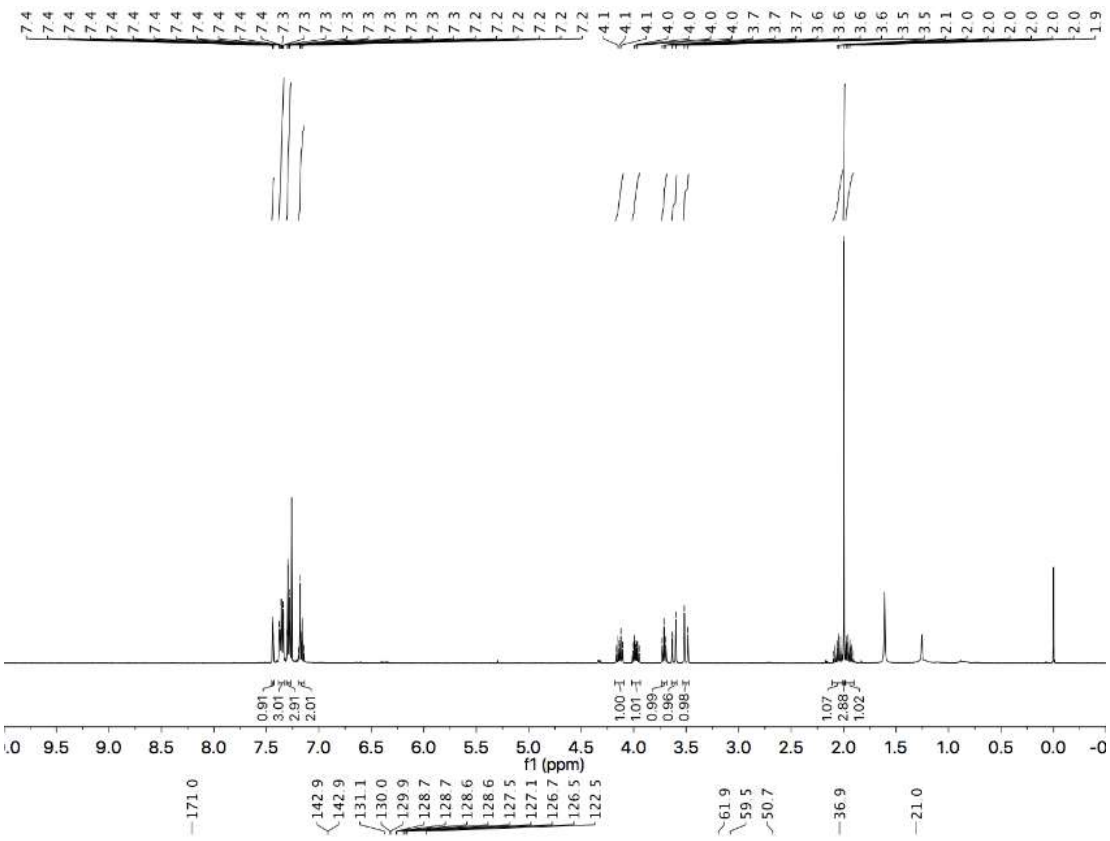
TLC (SiO_2) R_f = 0.20 (hexanes: ethyl acetate = 3:1).

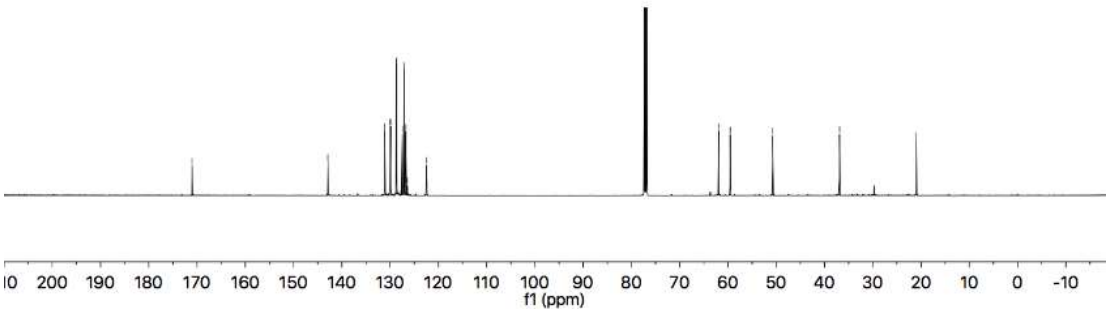
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 – 7.43 (m, 1H), 7.38 – 7.33 (m, 3H), 7.29 (dt, *J* = 7.8, 1.2 Hz, 3H), 7.20 – 7.14 (m, 2H), 4.14 (dt, *J* = 11.1, 6.4 Hz, 1H), 3.98 (ddd, *J* = 11.1, 7.0, 6.2 Hz, 1H), 3.71 (t, *J* = 7.0 Hz, 1H), 3.64 – 3.59 (m, 1H), 3.50 (d, *J* = 13.5 Hz, 1H), 2.06 (ddd, *J* = 14.0, 6.9, 6.2 Hz, 1H), 2.00 (s, 3H), 1.98 – 1.90 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 142.9, 142.9, 131.1, 130.0, 129.9, 128.7, 128.7, 128.7, 128.6, 127.5, 127.1, 126.7, 126.5, 122.5, 61.9, 59.5, 50.7, 36.9, 21.0.

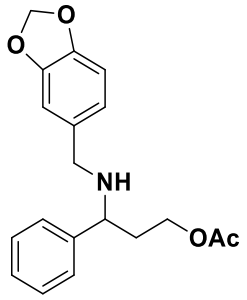
HRMS (ESI): Calculated for $C_{18}H_{20}BrNO_2$ [M+H$^+$] = 362.0750, Found 362.0754.

FTIR (neat): 3025, 2921, 1735, 1568, 1452, 1364, 1236, 1091, 1068, 1030, 996, 968,763, 700, 669 cm^{-1}.


f1 (ppm)


f1 (ppm)

3-((Benzo[d][1,3]dioxol-5-ylmethyl)amino)-3-phenylpropyl acetate (2.3d)



The allylic acetate (105.7 mg, 0.6 mmol, 300 mol%) and the primary amine (30.2 mg, 0.2 mmol, 100 mol%) were subject to standard reaction conditions. The title compound was obtained in 74% yield (48.5 mg, 0.15 mmol) as a light yellow oil after purification by flash column chromatography (SiO_2, dichloromethane: diethyl ether = 20:1–5:1).

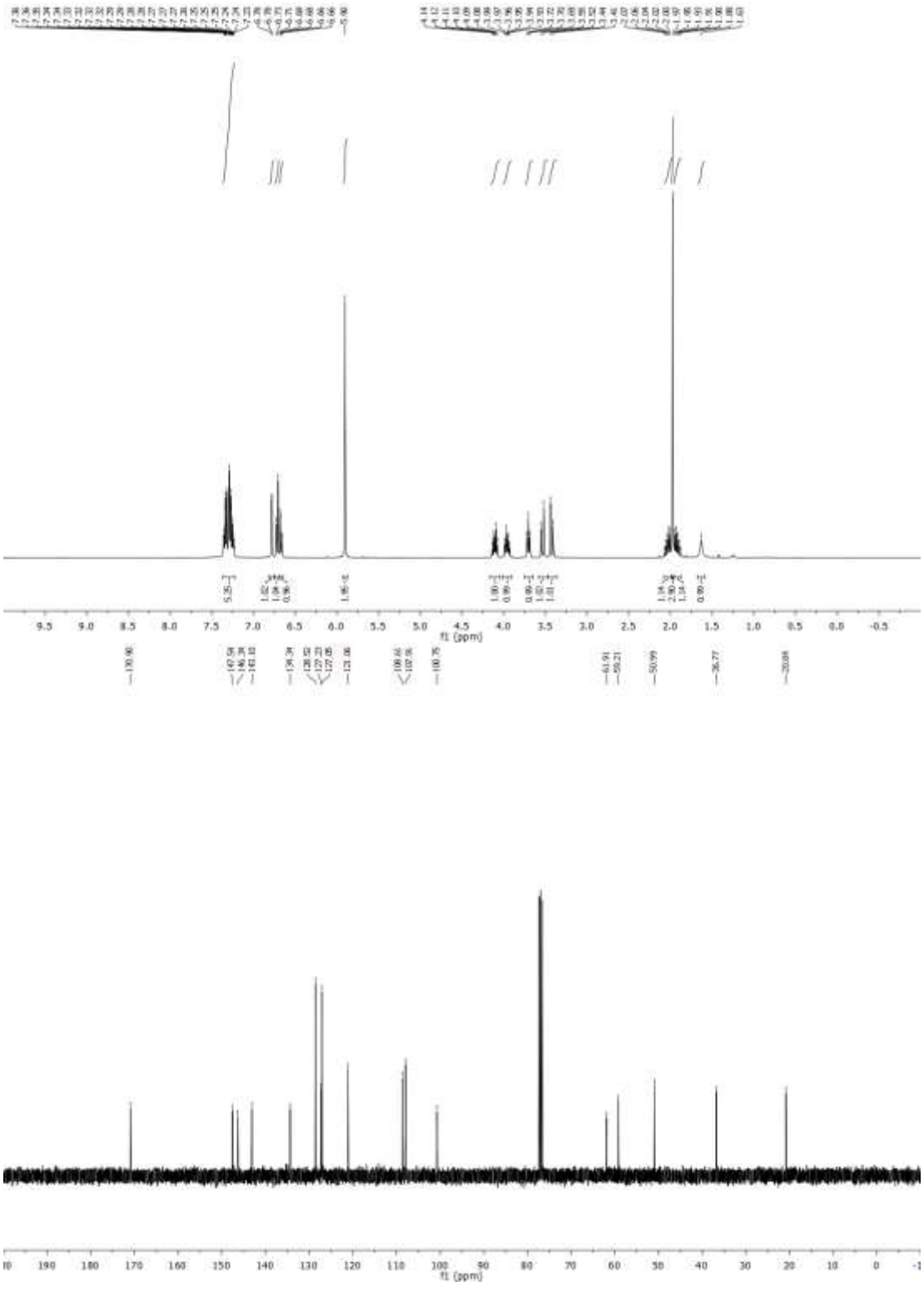
TLC (SiO_2) R_f = 0.19 (dichloromethane: diethyl ether = 5:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 – 7.22 (m, 5H), 6.78 (d, *J* = 1.6 Hz, 1H), 6.72 (d, *J* = 7.9 Hz, 1H), 6.67 (d, *J* = 7.9 Hz, 1H), 5.90 (s, 2H), 4.11 (dt, *J* = 11.1, 6.4 Hz, 1H), 3.96 (dt, *J* = 11.1, 6.7 Hz, 1H), 3.70 (t, *J* = 7.0 Hz, 1H), 3.54 (d, *J* = 13.0 Hz, 1H), 3.42 (d, *J* = 13.0 Hz, 1H), 2.04 (dt, *J* = 13.7, 6.8 Hz, 1H), 1.97 (s, 3H), 1.91 (dt, *J* = 13.7, 6.8 Hz, 1H), 1.63 (br, 1H).

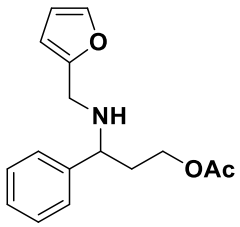
^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 147.5, 146.3, 143.1, 134.3, 128.5, 127.2, 127.1, 121.1, 108.6, 107.9, 100.8, 61.9, 59.2, 51.0, 36.8, 20.8.

HRMS (ESI): Calculated for $C_{19}H_{21}NO_4$ [M+H$^+$] = 328.1543, found 328.1551.

FTIR (neat): 2984, 1733, 1488, 1440, 1365, 1236, 1036, 929, 808, 734, 701 cm^{-1}.



3-((Furan-2-ylmethyl)amino)-3-phenylpropyl acetate (2.3e)



The allylic acetate (105.7 mg, 0.6 mmol, 300 mol%) and the primary amine (19.4 mg, 0.2 mmol, 100 mol%) were subject to standard reaction conditions. The title compound was obtained in 68% yield (37.1 mg, 0.14 mmol) as a light yellow oil after purification by flash column chromatography (SiO_2, dichloromethane: diethyl ether = 30:1–10:1).

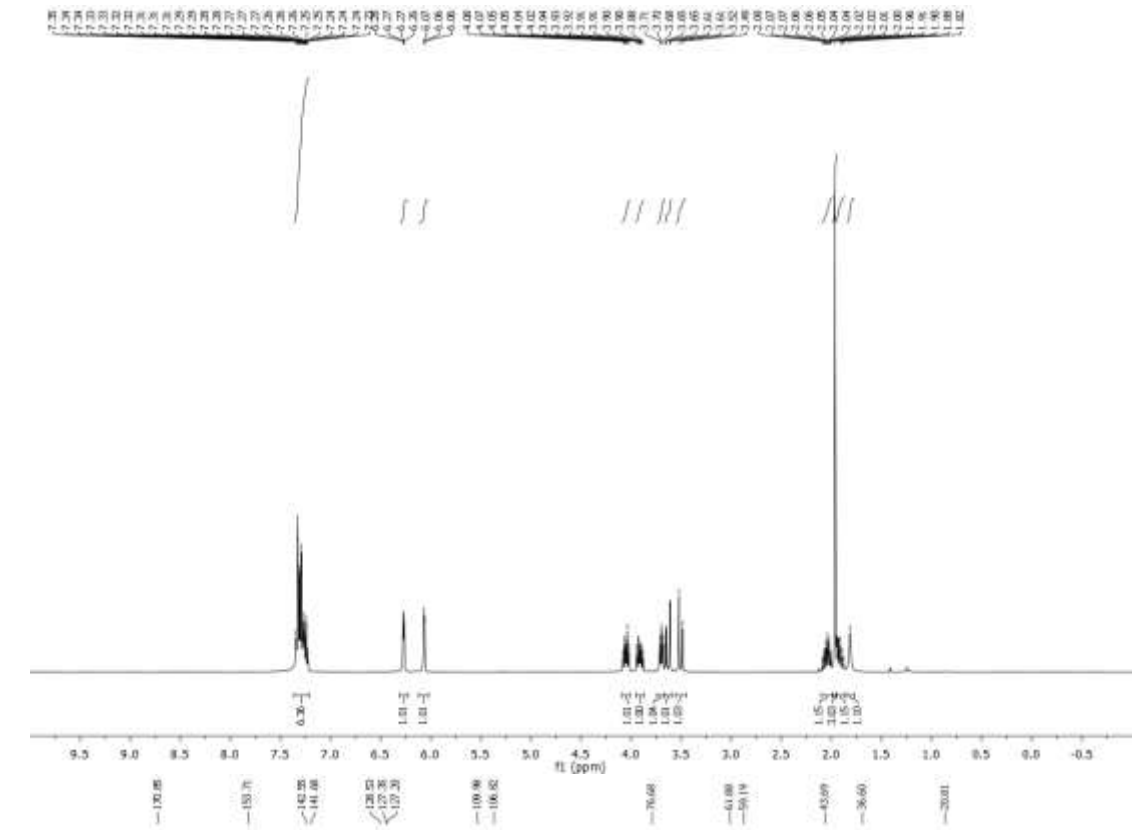
TLC (SiO_2) R_f = 0.33 (dichloromethane: diethyl ether = 5:1).

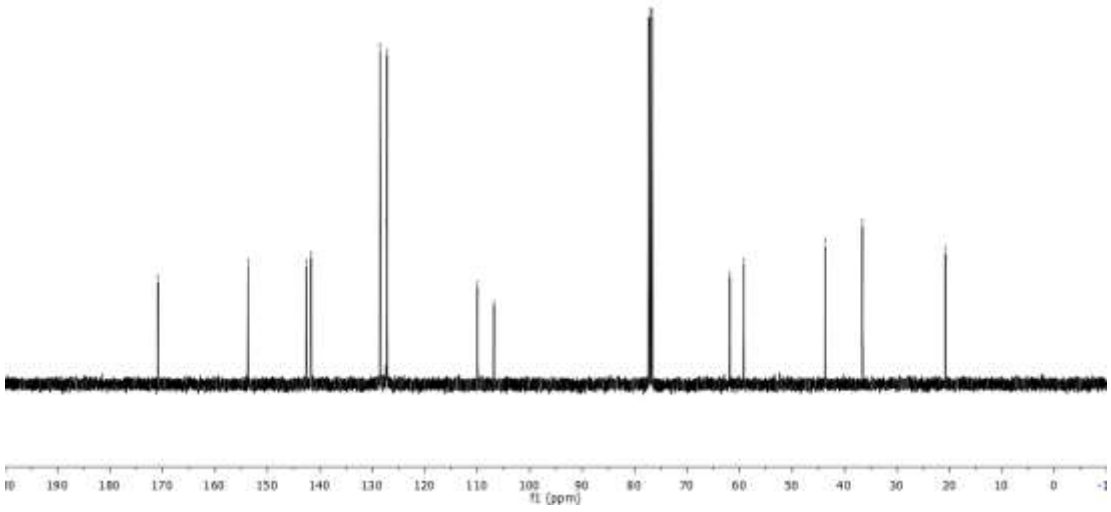
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 – 7.21 (m, 6H), 6.27 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.12 – 6.02 (m, 1H), 4.05 (dt, *J* = 11.1, 6.2 Hz, 1H), 3.91 (dt, *J* = 11.1, 6.2 Hz, 1H), 3.70 (t, *J* = 6.8 Hz, 1H), 3.63 (d, *J* = 14.5 Hz, 1H), 3.50 (d, *J* = 14.5 Hz, 1H), 2.05 (td, *J* = 13.8, 6.3 Hz, 1H), 1.96 (s, 3H), 1.95 – 1.87 (m, 1H), 1.82 (br, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 153.7, 142.6, 141.7, 128.5, 127.4, 127.2, 110.0, 106.8, 76.7, 61.9, 59.2, 43.7, 36.6, 20.8.

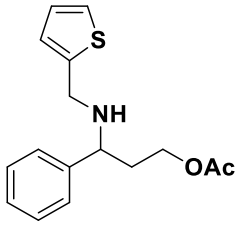
HRMS (ESI): Calculated for $C_{16}H_{19}NO_3$ [M+H$^+$] = 274.1438, found 274.1445.

FTIR (neat): 2919, 1735, 1365, 1235, 1036, 918, 735, 700 cm^{-1}.





3-Phenyl-3-((thiophen-2-ylmethyl)amino)propyl acetate (2.3f)



The allylic acetate (105.7 mg, 0.6 mmol, 300 mol%) and the primary amine (22.6 mg, 0.2 mmol, 100 mol%) were subject to standard reaction conditions. The title compound was obtained in 71% yield (41.1 mg, 0.14 mmol) as a light yellow oil after purification by flash column chromatography (SiO_2, dichloromethane: diethyl ether = 20:1–10:1).

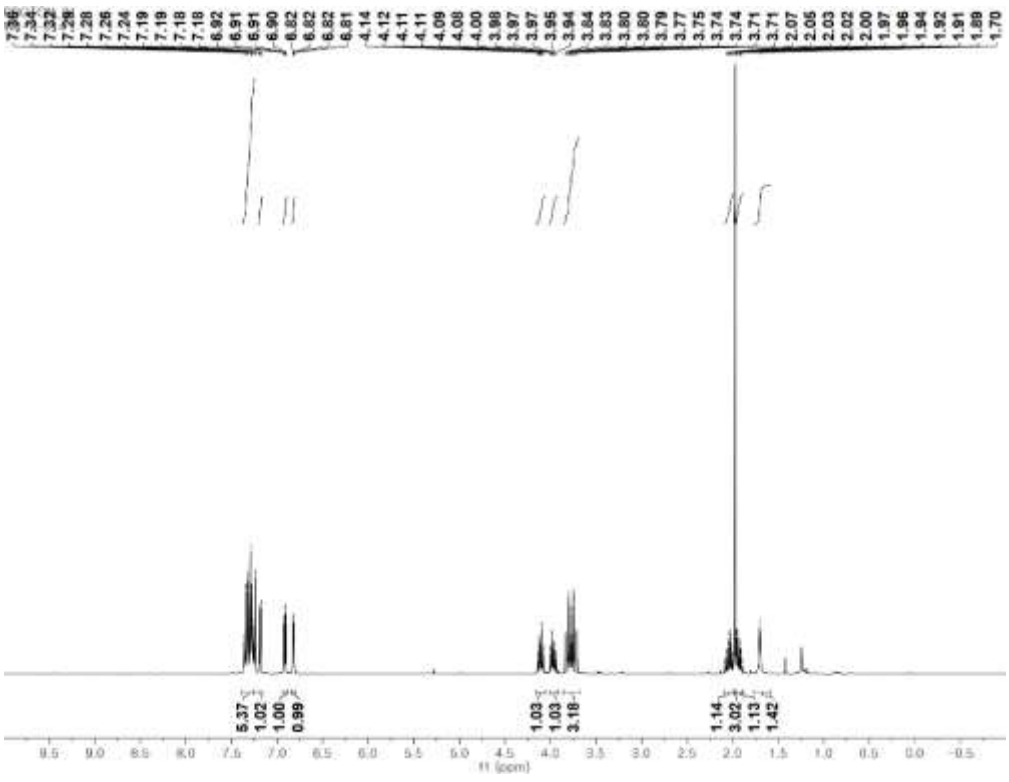
TLC (SiO_2) R_f = 0.52 (dichloromethane: diethyl ether = 5:1).

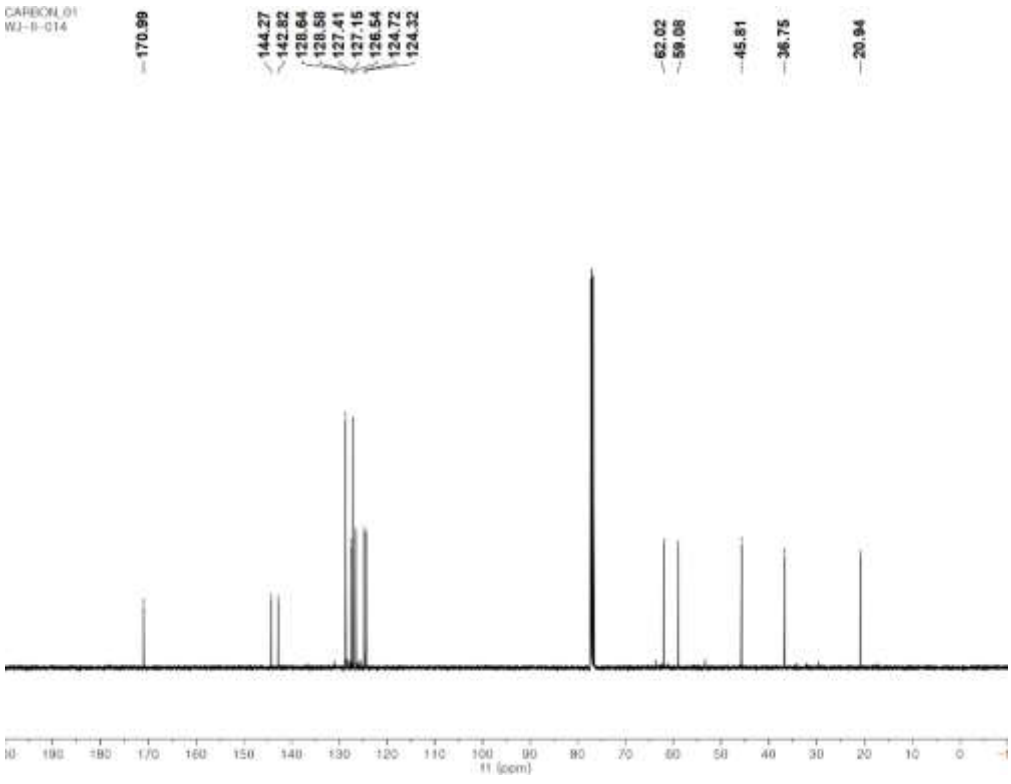
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 – 7.25 (m, 5H), 7.18 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.91 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.82 (dd, *J* = 3.4, 1.0 Hz, 1H), 4.11 (dt, *J* = 11.1, 6.4 Hz, 1H), 3.97 (dt, *J* = 11.1, 6.6 Hz, 1H), 3.86 – 3.68 (m, 3H), 2.04 (dq, *J* = 13.5, 6.9 Hz, 1H), 1.97 (s, 3H), 1.93 (dd, *J* = 13.9, 7.2 Hz, 1H), 1.70 (br, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 144.3, 142.8, 128.6, 128.6, 127.4, 127.2, 126.5, 124.7, 124.3, 62.0, 59.1, 45.8, 36.8, 20.9.

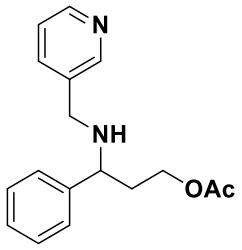
HRMS (ESI): Calculated for $C_{16}H_{19}NO_2S$ [M+H$^+$] = 290.1209, found 290.1213.

FTIR (neat): 2919, 2849,1735, 1493, 1454, 1387, 1365, 1237, 1110, 1037, 852, 829, 761, 700 cm^{-1}.


7.36
7.34
7.32
7.28
7.26
7.24
7.19
7.19
7.18
7.18
6.92
6.91
6.91
6.90
6.82
6.82
6.82
6.81
4.14
4.12
4.11
4.11
4.09
4.08
4.00
3.98
3.97
3.97
3.95
3.94
3.84
3.83
3.80
3.80
3.79
3.77
3.75
3.74
3.74
3.71
3.71
2.07
2.05
2.03
2.02
2.00
1.97
1.96
1.94
1.92
1.91
1.89
1.70
5.37
1.02
1.00
0.99
1.03
1.03
3.18
1.14
3.02
1.13
1.42
f1 (ppm)


CARBON_01
W2-5-014
170.99
144.27
142.82
128.64
128.58
127.41
127.15
126.54
124.72
124.32
62.02
59.08
45.81
36.75
20.94
f1 (ppm)

3-Phenyl-3-((pyridin-3-ylmethyl)amino)propyl acetate (2.3g)



The allylic acetate (105.7 mg, 0.6 mmol, 300 mol%) and the primary amine (21.6 mg, 0.2 mmol, 100 mol%) were subject to standard reaction conditions. The title compound was obtained in 67% yield (38 mg, 0.14 mmol) as a light yellow oil after purification by flash column chromatography (4g SiO_2, Isopropyl Acetate / Heptane = 0% - 100% over 30 min).

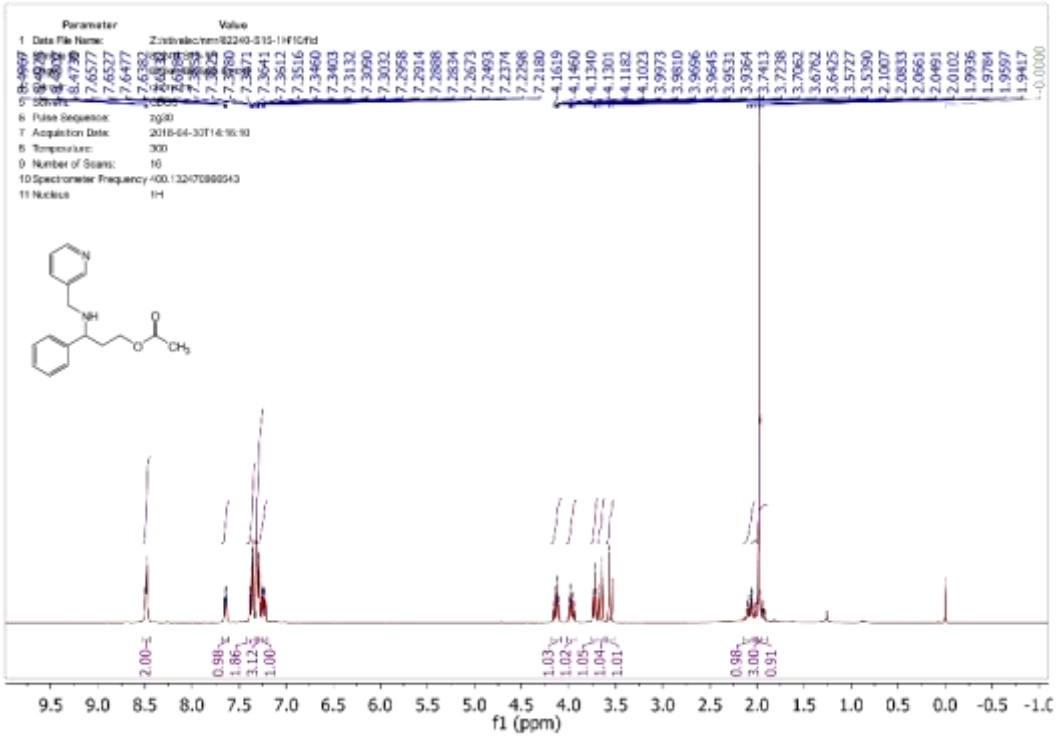
TLC (SiO_2) R_f = 0.30 (ethyl acetate: methanol = 15:1).

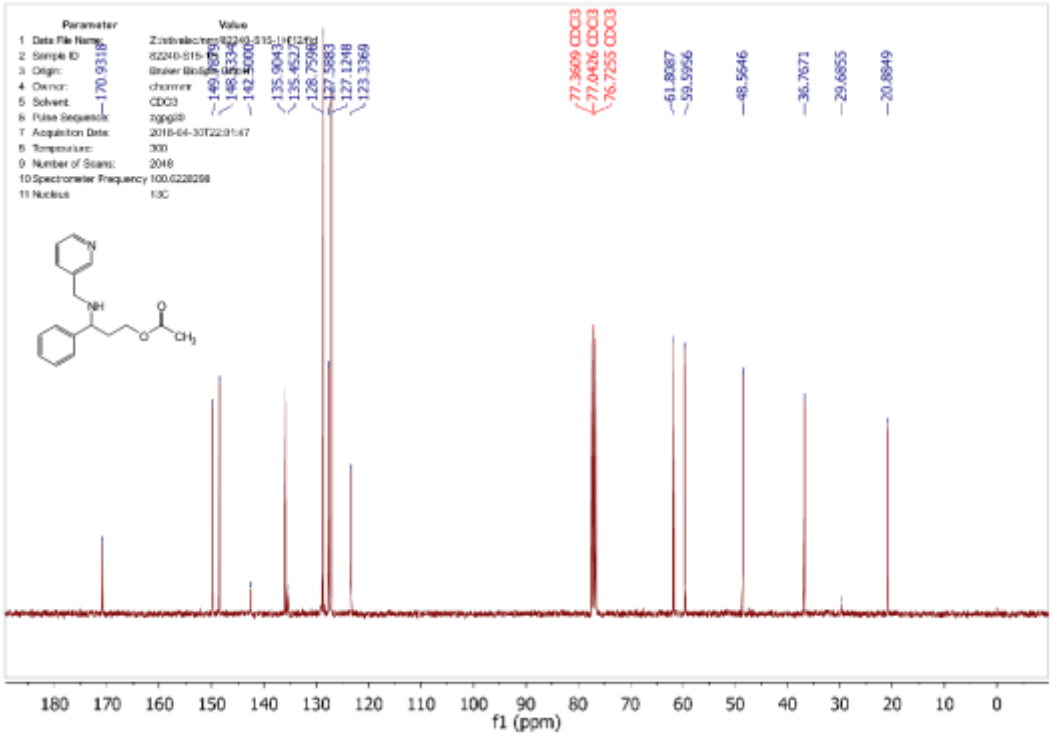
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 – 8.45 (m, 2H), 7.64 (dt, *J* = 7.7, 2.0 Hz, 1H), 7.42 – 7.33 (m, 2H), 7.33 – 7.24 (m, 3H), 7.23 (dd, *J* = 7.8, 4.7 Hz, 1H), 4.13 (dt, *J* = 11.1, 6.4 Hz, 1H), 3.97 (dt, *J* = 11.2, 6.6 Hz, 1H), 3.72 (t, *J* = 7.0 Hz, 1H), 3.66 (d, *J* = 13.5 Hz, 1H), 3.56 (d, *J* = 13.5 Hz, 1H), 2.08 (dt, *J* = 13.7, 6.7 Hz, 1H), 2.05 – 1.89 (m, 1H), 1.98 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 149.5, 149.2, 134.8, 128.5, 128.3, 127.4, 123.8, 61.4, 57.2, 51.1, 36.3 20.8.

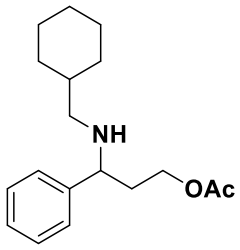
HRMS (ESI): Calculated for $C_{17}H_{21}N_2O_2$ $[M+H^+]$ =285.1598, found 285.1595.

FTIR (neat): 220, 1735, 1424, 13365, 1237, 1028, 762, 702 cm^{-1}.


f1 (ppm)


f1 (ppm)

3-((Cyclohexylmethyl)amino)-3-phenylpropyl acetate (2.3h)



The cinnamyl acetate (105.7 mg, 0.6 mmol, 300 mol%) and the cyclohexylmethanamine (22.6 mg, 0.2 mmol, 100 mol%) were subject to standard reaction conditions (90 ^{o}C, 24 hr). The title compound was obtained in 54% yield (31.2 mg, 0.11 mmol) as a yellow oil after purification by flash column chromatography (SiO_2, hexanes: ethylacetate = 3:1).

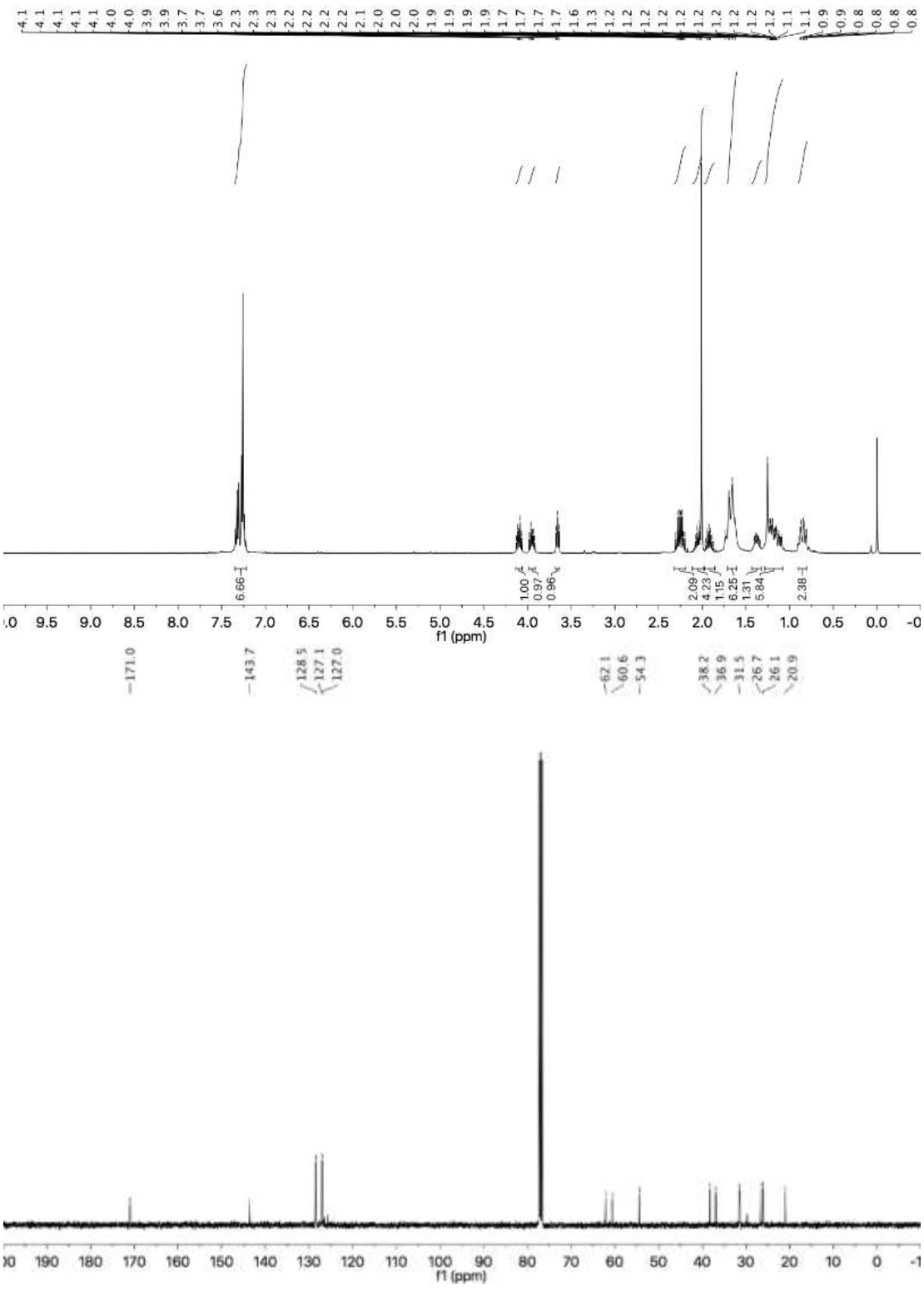
TLC (SiO_2) R_f = 0.19 (hexanes: ethyl acetate = 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 – 7.21 (m, 7H), 4.10 (dt, *J* = 11.1, 6.3 Hz, 1H), 3.95 (dt, *J* = 11.1, 6.8 Hz, 1H), 3.66 (t, *J* = 6.9 Hz, 1H), 2.25 (qd, *J* = 11.5, 6.6 Hz, 2H), 2.01 (s, 4H), 1.97 – 1.86 (m, 1H), 1.71 – 1.61 (m, 6H), 1.38 (ddt, *J* = 11.1, 7.6, 3.4 Hz, 1H), 1.28 – 1.08 (m, 6H), 0.90 – 0.80 (m, 2H).

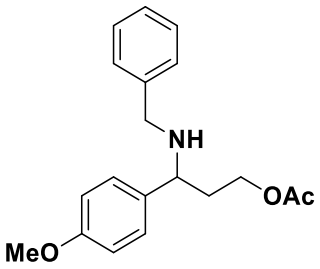
^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 143.7, 128.5, 127.1, 127.0, 62.1, 60.6, 54.3, 38.2, 36.9, 31.5, 26.7, 26.1, 20.9.

HRMS (ESI): Calculated for $C_{18}H_{27}NO_2$ [M+H$^+$] = 290.2115, Found 290.2119.

FTIR (neat): 2920, 2850, 1739, 1450, 1356, 1237, 1037, 761, 700 cm^{-1}.


f1 (ppm)
f1 (ppm)

3-(Benzylamino)-3-(4-methoxyphenyl)propyl acetate (2.3i)



The allylic acetate (123.7 mg, 0.6 mmol, 300 mol%) and the benzyl amine (21 mg, 0.2 mmol, 100 mol%) were subject to standard reaction conditions (90 ^{o}C, 24 hr). The title compound was obtained in 64% yield (40.1 mg, 0.13 mmol) as a yellow oil after purification by flash column chromatography (SiO_2, hexanes: ethylacetate = 2:1).

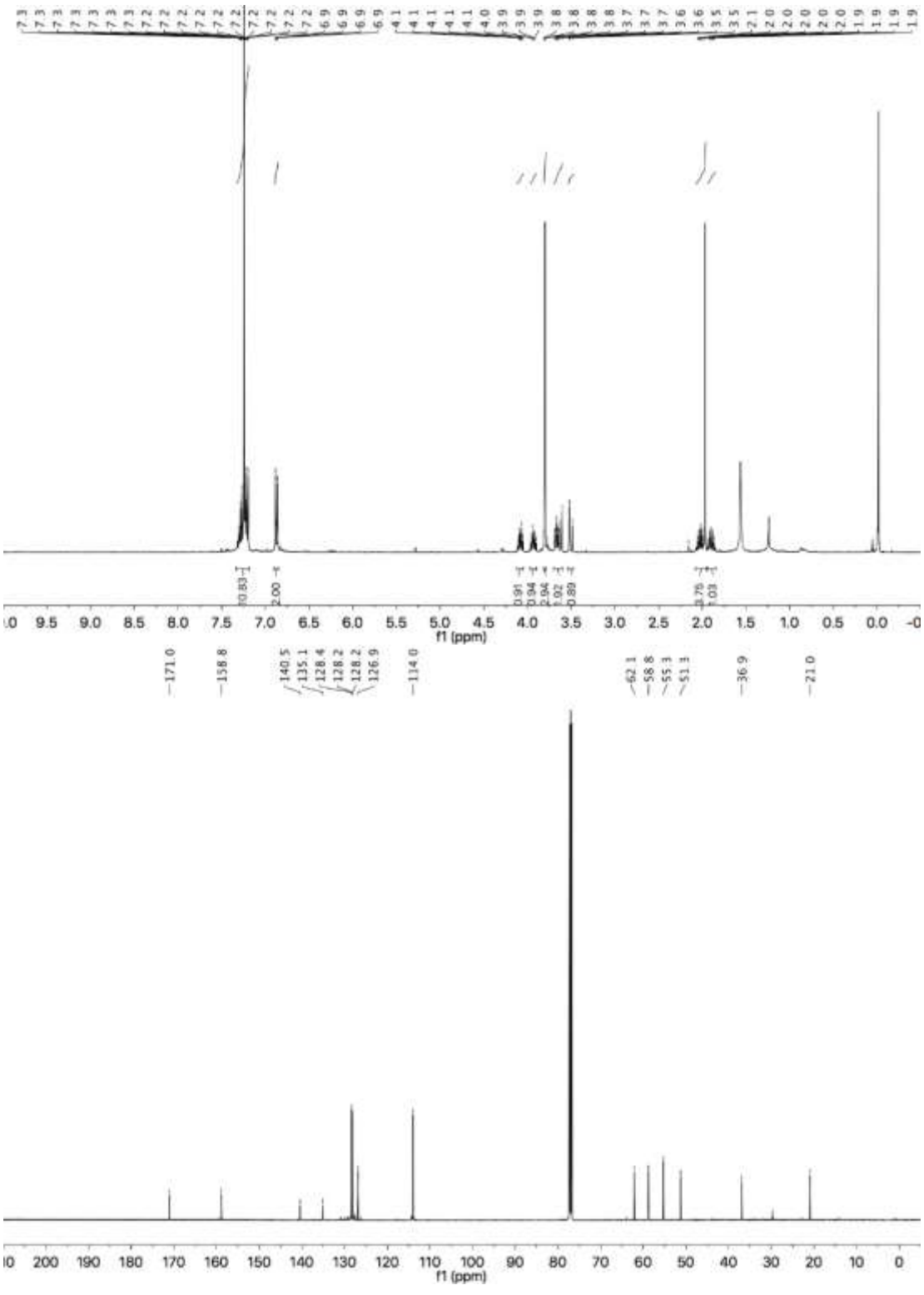
TLC (SiO_2) R_f = 0.17 (hexanes: ethyl acetate = 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 – 7.18 (m, 11H), 6.90 – 6.85 (m, 2H), 4.08 (dt, *J* = 11.0, 6.3 Hz, 1H), 3.93 (dt, *J* = 11.1, 6.7 Hz, 1H), 3.80 (d, *J* = 0.5 Hz, 3H), 3.70 – 3.60 (m, 2H), 3.50 (d, *J* = 13.1 Hz, 1H), 2.08 – 1.95 (m, 4H), 1.90 (dt, *J* = 14.0, 6.9 Hz, 1H).

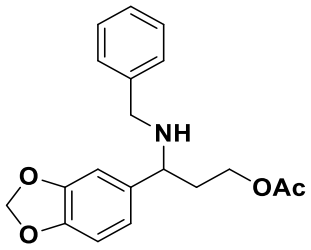
^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.0, 158.8, 140.5, 135.1, 128.4, 128. 2, 128.2, 126.9, 114.0, 62.1, 58.8, 55.3, 51.3, 36.9, 21.0.

HRMS (ESI): Calculated for $C_{19}H_{23}NO_3$ [M+H^{+}] = 314.1751, Found 313.1751.

FTIR (neat): 2931, 2836, 1735, 1584, 1511, 1454, 1302, 1243, 1176, 1033, 831, 735, 699 cm^{-1}.


f1 (ppm)
f1 (ppm)

3-(Benzo[d][1,3]dioxol-5-yl)-3-(benzylamino)propyl acetate (2.3j)



The allylic acetate (132.1 mg, 0.6 mmol, 300 mol%) and the primary amine (21.4 mg, 0.2 mmol, 100 mol%) were subject to standard reaction conditions for 48 h. The title compound was obtained in 67% yield (43.9 mg, 0.13 mmol) as a light yellow oil after purification by flash column chromatography (SiO_2, dichloromethane: diethyl ether = 25:1–5:1).

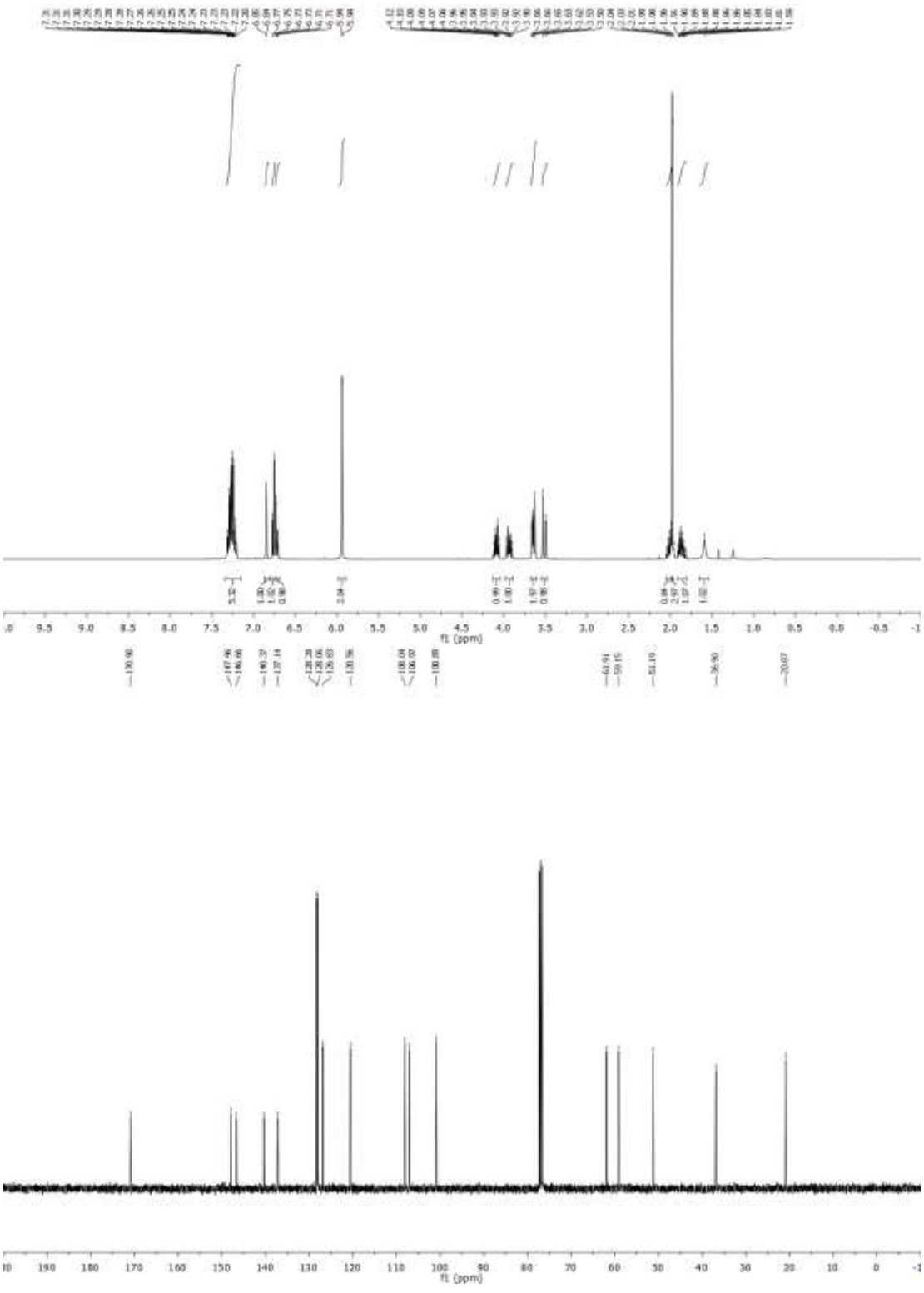
TLC (SiO_2) R_f = 0.30 (dichloromethane: diethyl ether = 3:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 – 7.15 (m, 5H), 6.85 (d, *J* = 1.6 Hz, 1H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.72 (dd, *J* = 7.9, 1.7 Hz, 1H), 5.94 (d, *J* = 0.8 Hz, 2H), 4.09 (dt, *J* = 11.1, 6.3 Hz, 1H), 3.93 (dt, *J* = 11.1, 6.3 Hz, 1H), 3.68 – 3.61 (m, 2H), 3.51 (d, *J* = 13.2 Hz, 1H), 2.05 – 1.95 (m, 1H), 1.98 (s, 3H), 1.87 (ddt, *J* = 13.8, 7.5, 6.3 Hz, 1H), 1.59 (br, 1H).

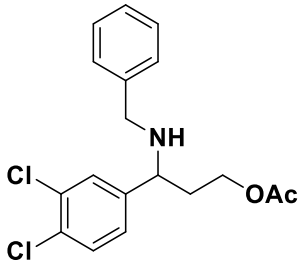
^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 148.0, 146.7, 140.4, 137.1, 128.3, 128.1, 126.8, 120.6, 108.0, 107.0, 100.9, 61.9, 59.2, 51.2, 36.9, 20.9.

HRMS (ESI): Calculated for $C_{19}H_{21}NO_4$ [M+H$^+$] = 328.1543, found 328.1551.

FTIR (neat): 2917, 1732, 1486, 1365, 1236, 1036, 908, 728, 698 cm^{-1}.



3-(Benzylamino)-3-(3,4-dichlorophenyl)propyl acetate (2.3k)



The allylic acetate (147 mg, 0.6 mmol, 300 mol%) and the primary amine (21.6 mg, 0.2 mmol, 100 mol%) were subject to standard reaction conditions. The title compound was obtained in 78% yield (55 mg, 0.16 mmol) as a light yellow oil after purification by flash column chromatography (4g SiO_2, Isopropyl Acetate / Heptane = 0% - 100% over 30 min).

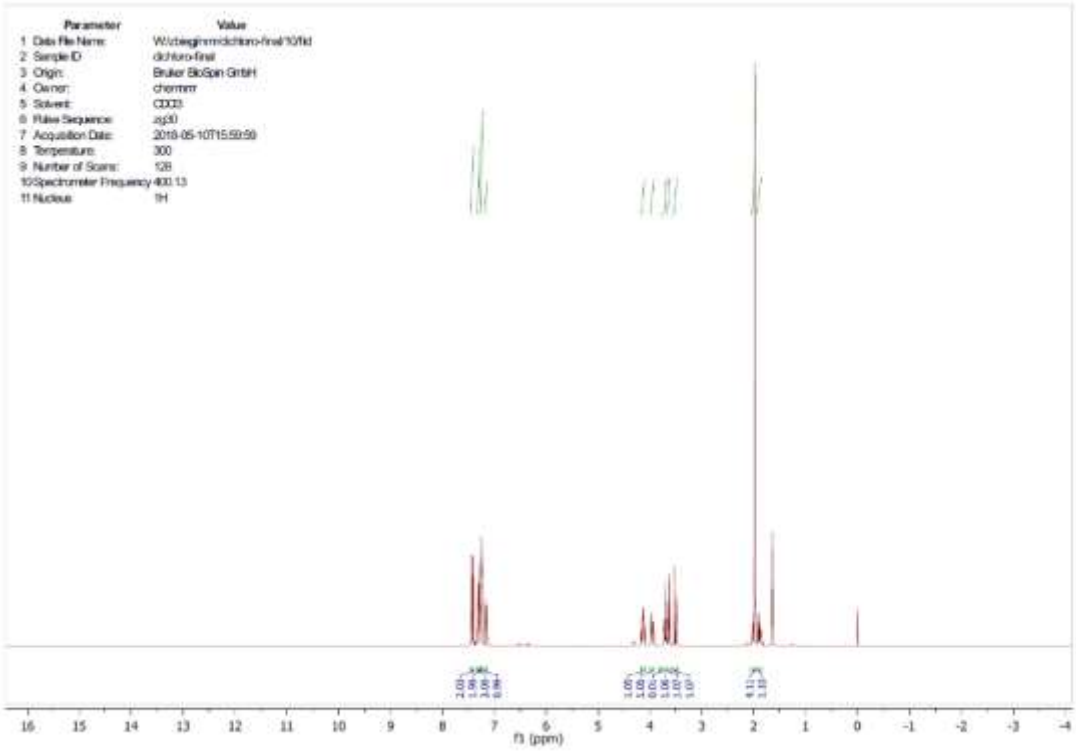
TLC (SiO_2) R_f = 0.42 (hexanes: ethyl acetate = 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 – 7.39 (m, 2H), 7.34 – 7.28 (m, 2H), 7.24 (td, *J* = 4.8, 2.8 Hz, 3H), 7.16 (dd, *J* = 8.2, 2.0 Hz, 1H), 4.13 (dt, *J* = 11.2, 6.5 Hz, 1H), 3.95 (dt, *J* = 11.2, 6.5 Hz, 1H), 3.71 (t, *J* = 6.9 Hz, 1H), 3.64 (d, *J* = 13.2 Hz, 1H), 3.51 (d, *J* = 13.2 Hz, 1H), 2.05-1.95 (m, 4H), 1.95 – 1.84 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 143.9, 139.9, 132.7, 131.1, 130.6, 129.2, 128.5, 128.1, 127.1, 126.6, 61.5, 58.7, 51.4, 36.8, 20.9.

HRMS (ESI): Calculated for $C_{18}H_{19}Cl_2NO_2$ [M+H$^+$] = 352.0866, found 352.0858.

FTIR (neat): 1735, 1464, 1364, 1236, 1130, 1028, 824, 737, 699 cm^{-1}.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4 Owner:
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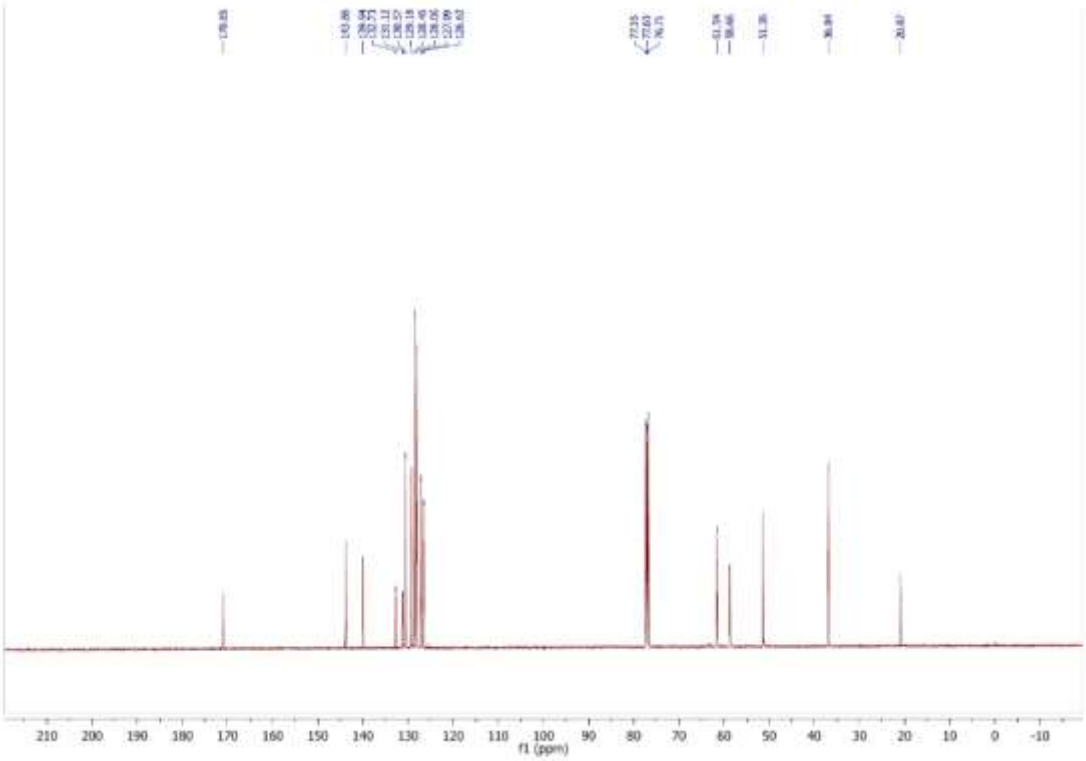
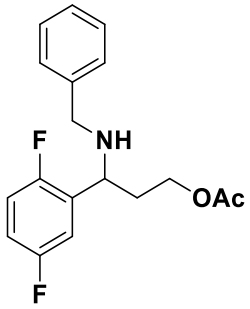
1H
f1 (ppm)


f1 (ppm)

3-(Benzylamino)-3-(2,5-difluorophenyl)propyl acetate (2.3l)



The allylic acetate (127 mg, 0.6 mmol, 300 mol%) and the primary amine (21.6 mg, 0.2 mmol, 100 mol%) were subject to standard reaction conditions. The title compound was obtained in 52% yield (33 mg, 0.10 mmol) as a light yellow oil after purification by flash column chromatography (4g SiO_2, Isopropyl Acetate / Heptane = 0% - 100% over 30 min).

TLC (SiO_2) R_f = 0.61 (hexanes: ethyl acetate = 2:1).

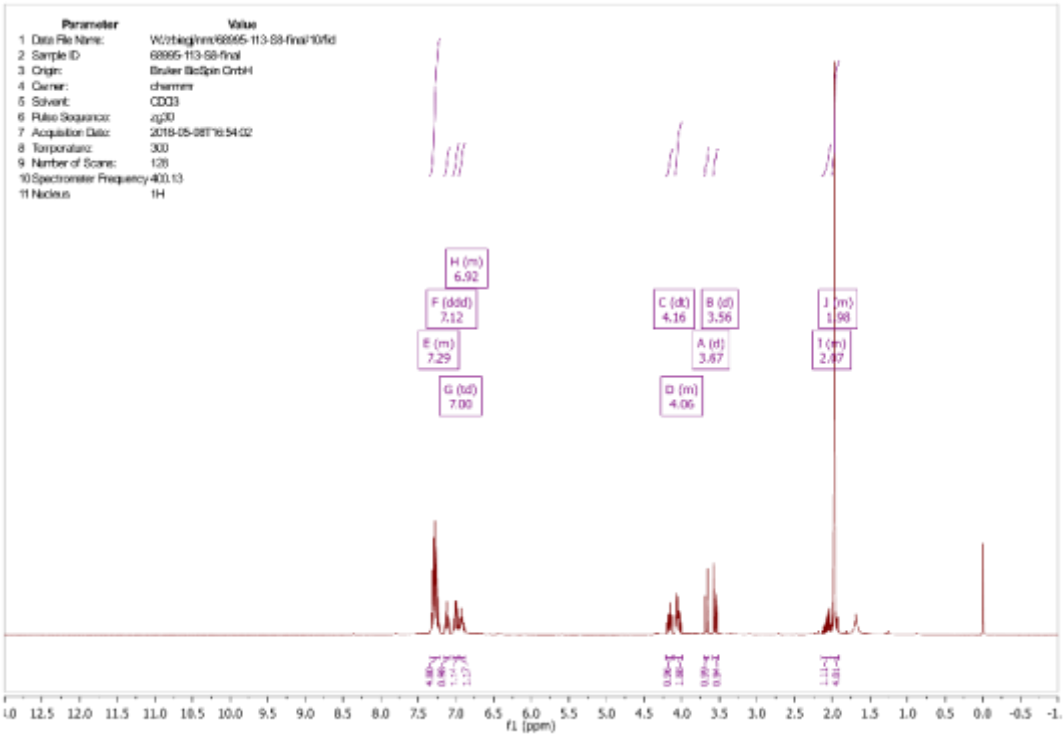
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 – 7.20 (m, 5H), 7.12 (ddd, *J* = 8.8, 5.5, 3.1 Hz, 1H), 7.00 (td, *J* = 9.2, 4.4 Hz, 1H), 6.99 – 6.87 (m, 1H), 4.16 (dt, *J* = 11.1, 6.4 Hz, 1H), 4.11 – 3.99 (m, 2H), 3.67 (d, *J* = 13.0 Hz, 1H), 3.56 (d, *J* = 13.1 Hz, 1H), 2.14 – 2.02 (m, 1H), 1.97 (s, 3H), 2.05 – 1.90 (m, 1H).

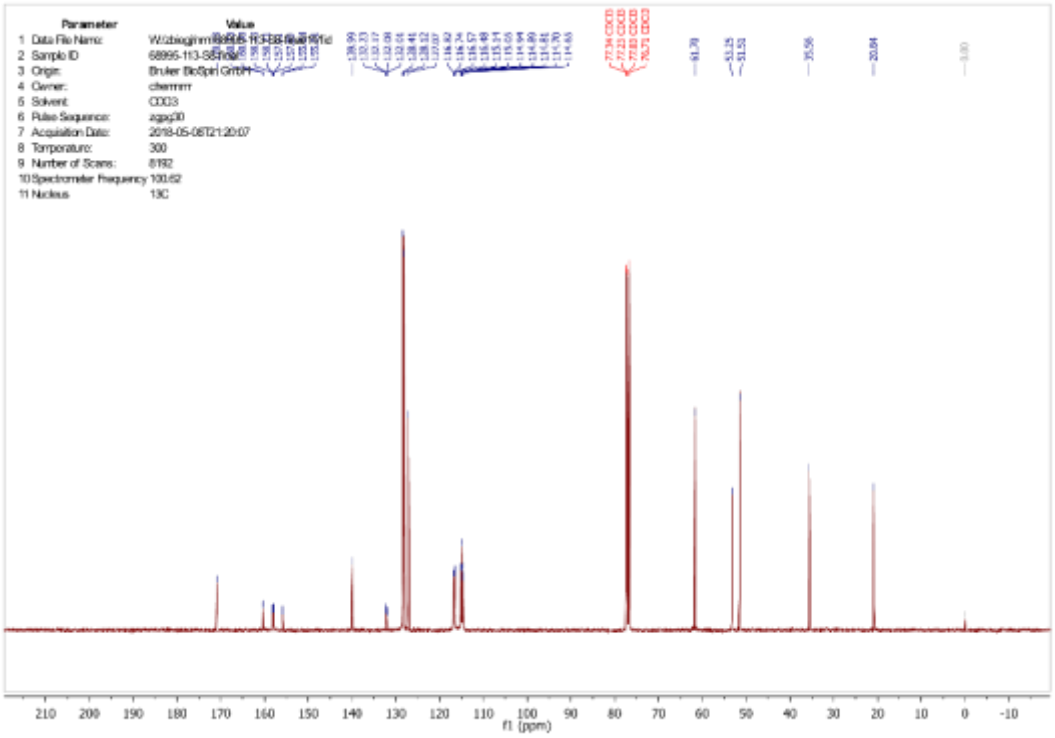
^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 159.3 (dd, *J* = 210, 2.3 Hz, 1C), 156.9 (dd, J= 210, 2.3 Hz, 1C) 140.0, 132.2 (dd, *J* = 15.7, 6.5 Hz, 1C), 128.4, 128.1, 127.1, 116.7 (dd, *J* =25.5, 8.4, 1C), 115.1-114.7 (m, 2C), 61.7, 53.3, 51.5, 35.6, 20.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -121.9 (dd, *J* = 2644, 18.5 Hz, 1F), -278.1 (dd, J=2244, 18.5 Hz, 1F).

HRMS (ESI): Calculated for $C_{18}H_{19}F_2NO_2$ [M+H$^+$] = 320.1457, found 320.1452.

FTIR (neat): 2960, 1736, 1489, 1366, 1236, 1177, 1040, 874, 814, 737, 699 cm^{-1}.

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Value
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4 Owner:
5 Solvent
6 Pulse Sequence:
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9 Number of Scans:
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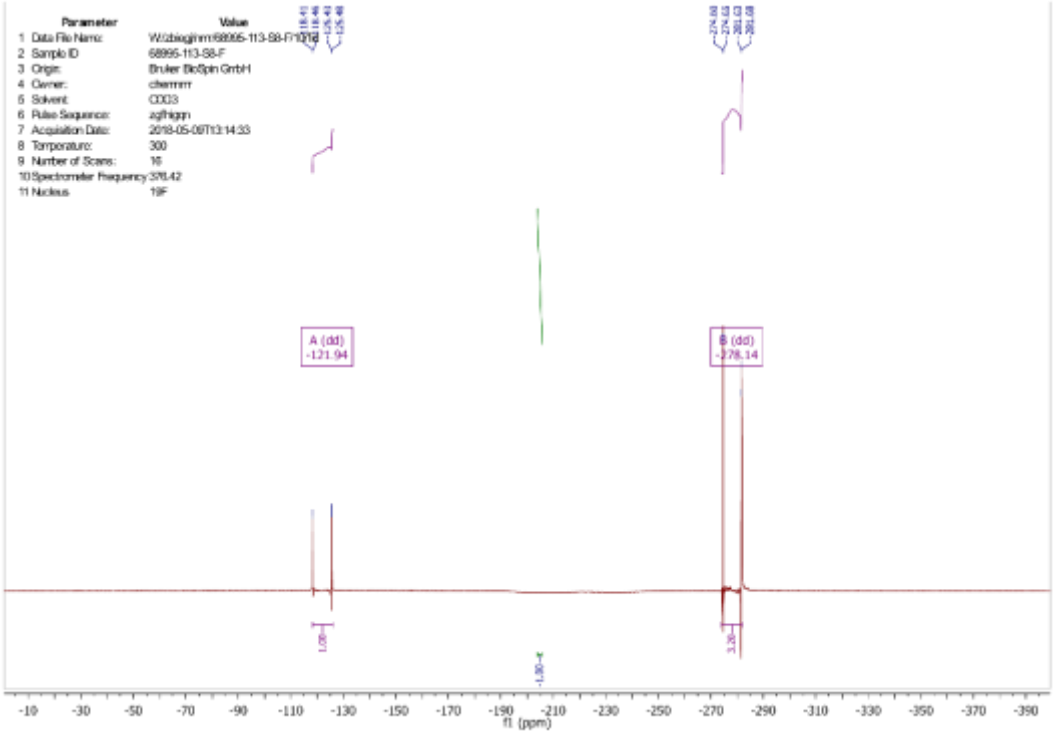
13C
f1 (ppm)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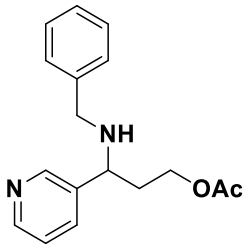
B (dd)
-278.14
f1 (ppm)

3-(Benzylamino)-3-(pyridin-3-yl)propyl acetate (2.3m)



The allylic acetate (106 mg, 0.6 mmol, 300 mol%) and the primary amine (21.6 mg, 0.2 mmol, 100 mol%) were subject to standard reaction conditions. The title compound was obtained in 81% yield (46 mg, 0.16 mmol) as a light yellow oil after purification by flash column chromatography (4g SiO_2, Methanol / DCM = 0% - 10% over 30 min).

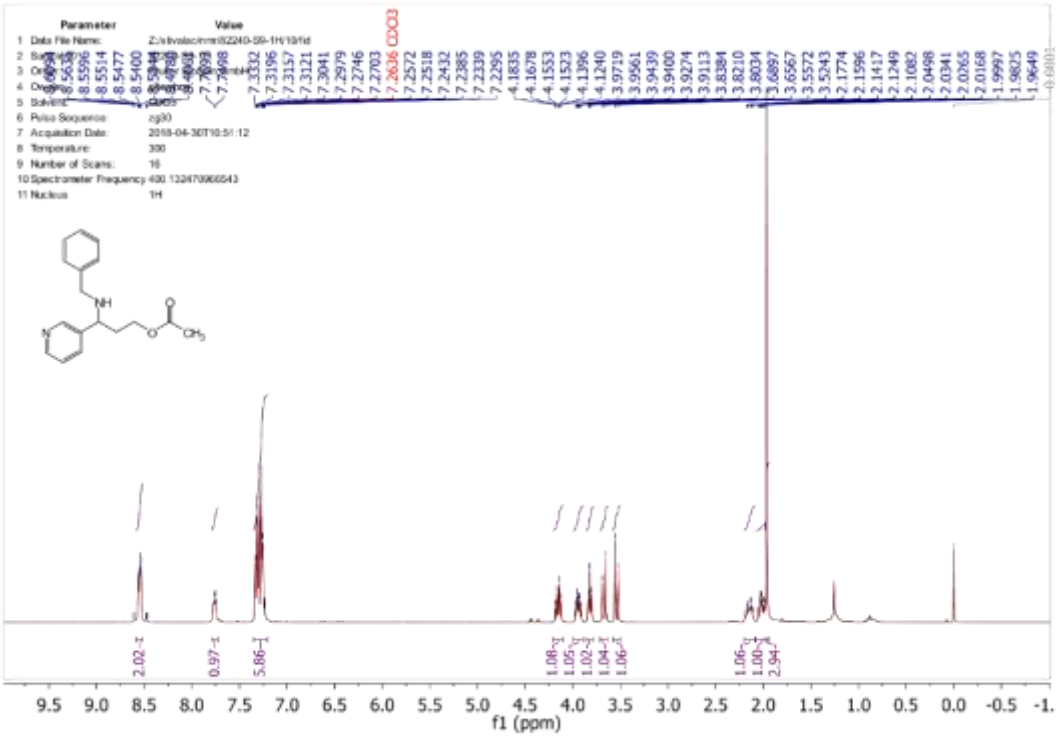
TLC (SiO_2) R_f = 0.45 (ethyl acetate: methanol = 15:1).

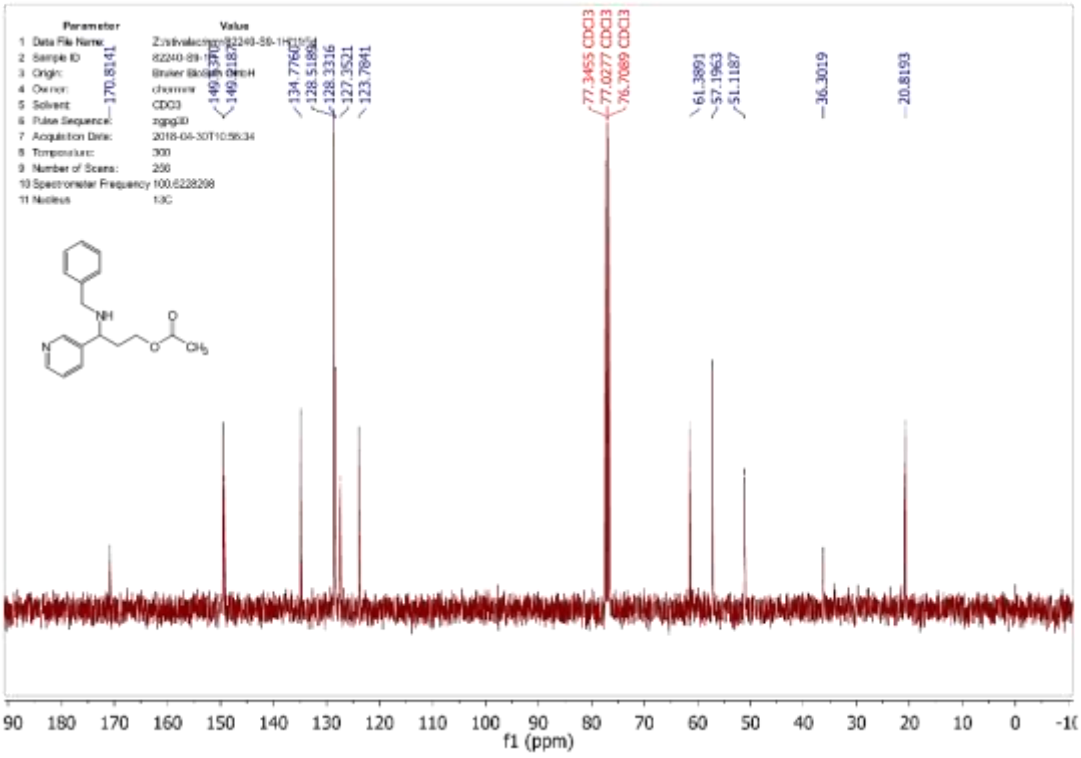
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.59 – 8.51 (m, 2H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.36 – 7.21 (m, 6H), 4.15 (dt, *J* = 11.3, 6.3 Hz, 1H), 3.94 (dt, *J* = 11.5, 6.4 Hz, 1H), 3.82 (t, *J* = 7.0 Hz, 1H), 3.67 (d, *J* = 13.2 Hz, 1H), 3.54 (d, *J* = 13.2 Hz, 1H), 2.14 (dt, *J* = 13.4, 6.9 Hz, 1H), 2.08 – 1.96 (m, 1H), 1.96 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 149.5, 149.2, 134.8, 128.5, 128.3, 127.4, 123.8, 61.4, 57.2, 51.1, 36.3 20.8.

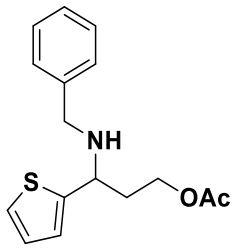
HRMS (ESI): Calculated for $C_{17}H_{21}N_2O_2$ $[M+H^+]$ =285.1598, found 285.1598.

FTIR (neat): 2924, 1735, 1426, 1365, 1237, 1026, 810, 737, 717, 700 cm^{-1}.


f1 (ppm)


f1 (ppm)

3-(Benzylamino)-3-(thiophen-2-yl)propyl acetate (2.3n)



The allylic acetate (109.3 mg, 0.6 mmol, 300 mol%) and the primary amine (21.4 mg, 0.2 mmol, 100 mol%) were subject to standard reaction conditions for 48 h. The title compound was obtained in 71% yield (41.1 mg, 0.14 mmol) as a light yellow oil after purification by flash column chromatography (SiO_2, hexanes: ethyl acetate = 10:1–5:1).

TLC (SiO_2) R_f = 0.40 (hexanes: ethyl acetate = 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 – 7.19 (m, 6H), 6.95 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.91 (ddd, *J* = 3.4, 1.3, 0.5 Hz, 1H), 4.16 (dt, *J* = 11.1, 6.2 Hz, 1H), 4.07 – 3.96 (m, 2H), 3.77 (d, *J* = 13.2 Hz, 1H), 3.61 (d, *J* = 13.1 Hz, 1H), 2.11 (dtd, *J* = 14.0, 7.0, 6.1 Hz, 1H), 2.02 (dt, *J* = 7.5, 6.2 Hz, 1H), 1.98 (s, 3H), 1.63 (s, 1H).

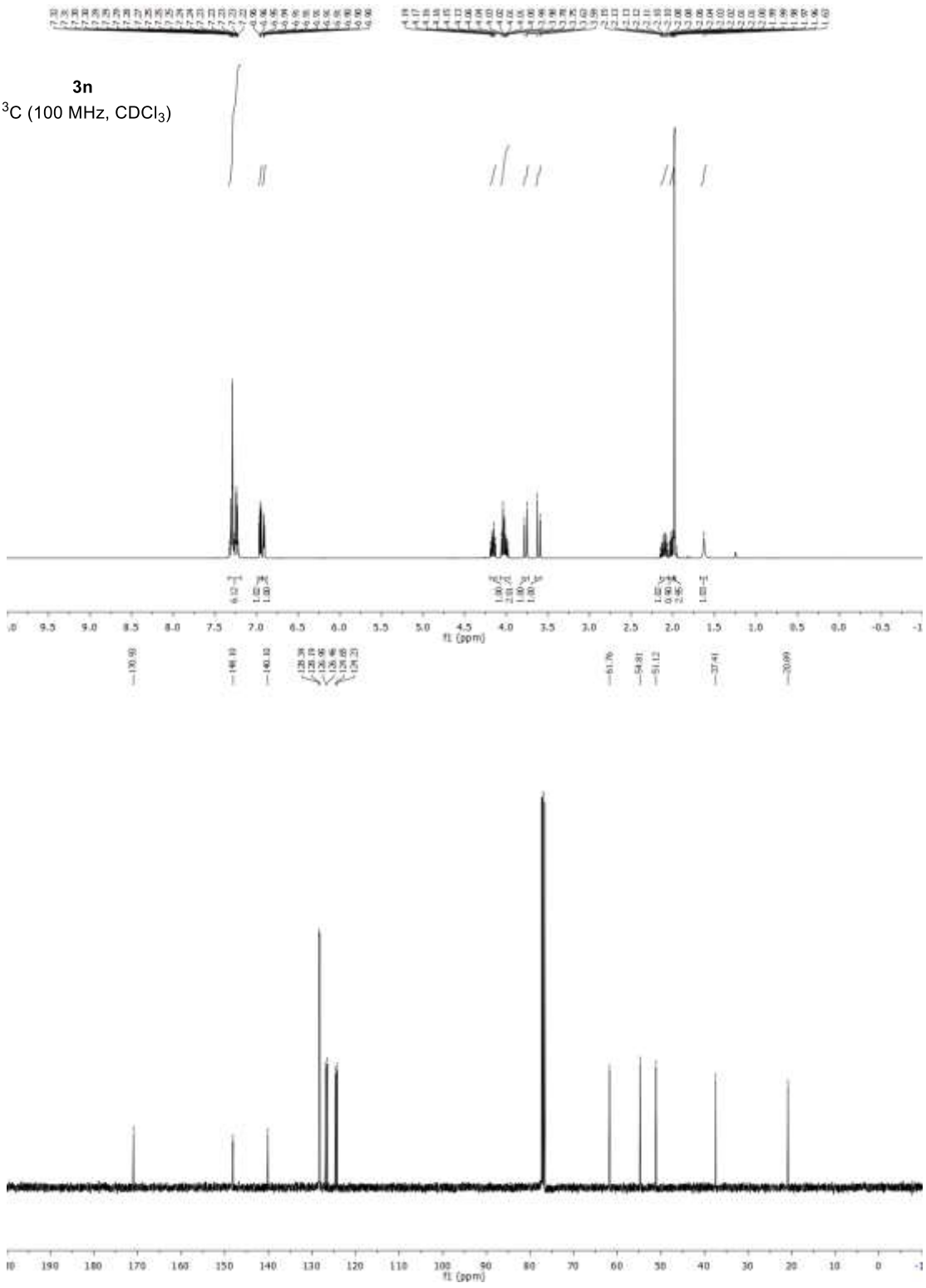
^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 148.1, 140.1, 128.3, 128.2, 127.0, 126.5, 124.7, 124.2, 61.8, 54.8, 51.1, 37.4, 20.9.

HRMS (ESI): Calculated for $C_{16}H_{19}NO_2S$ $[M+H^+]$ = 290.1209, found 290.1211.

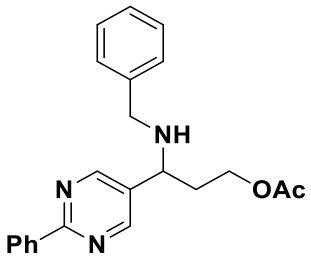
FTIR (neat): 2917, 1735, 1365, 1235, 1036, 907, 731, 697 cm^{-1}.

3n

^{13}C (100 MHz, $CDCl_3$)



3-(Benzylamino)-3-(2-phenylpyrimidin-5-yl)propyl acetate (2.3o)



The allylic acetate (152.1 mg, 0.6 mmol, 300 mol%) and the primary amine (21.4 mg, 0.2 mmol, 100 mol%) were subject to standard reaction conditions with Cs_2CO_3 (300 mol%). The title compound was obtained in 52% yield (37.6 mg, 0.10 mmol) as a light yellow oil after purification by flash column chromatography (SiO_2, toluene: ethyl acetate = 10:1–3:1).

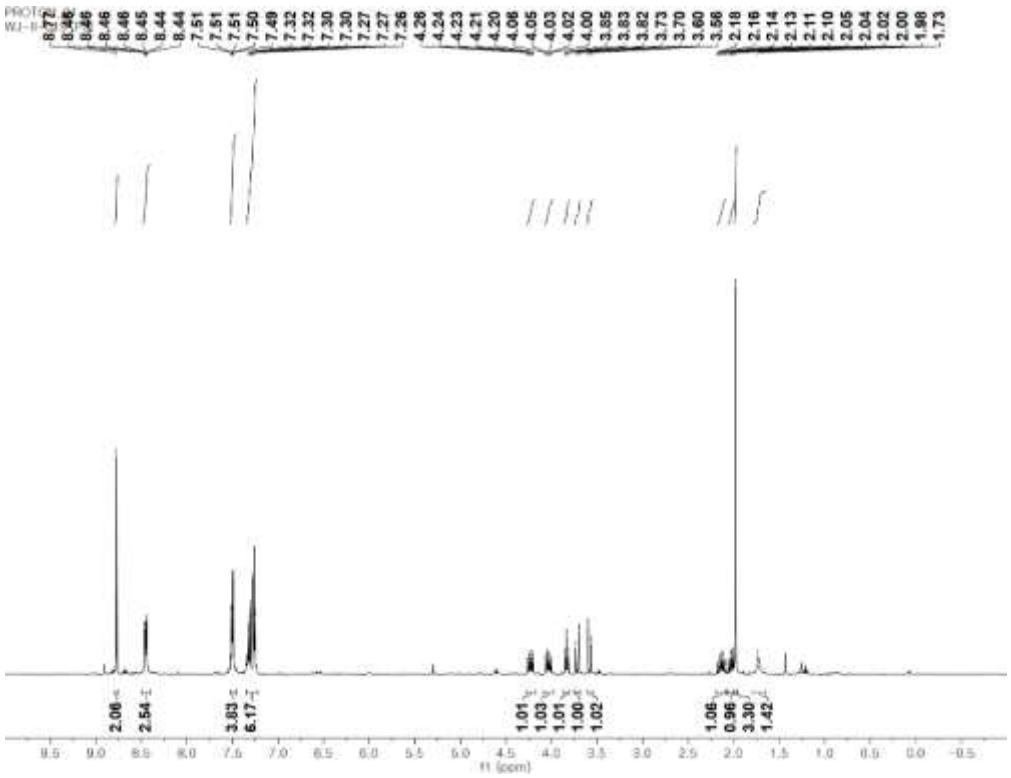
TLC (SiO_2) R_f = 0.55 (toluene: ethyl acetate = 1:1).

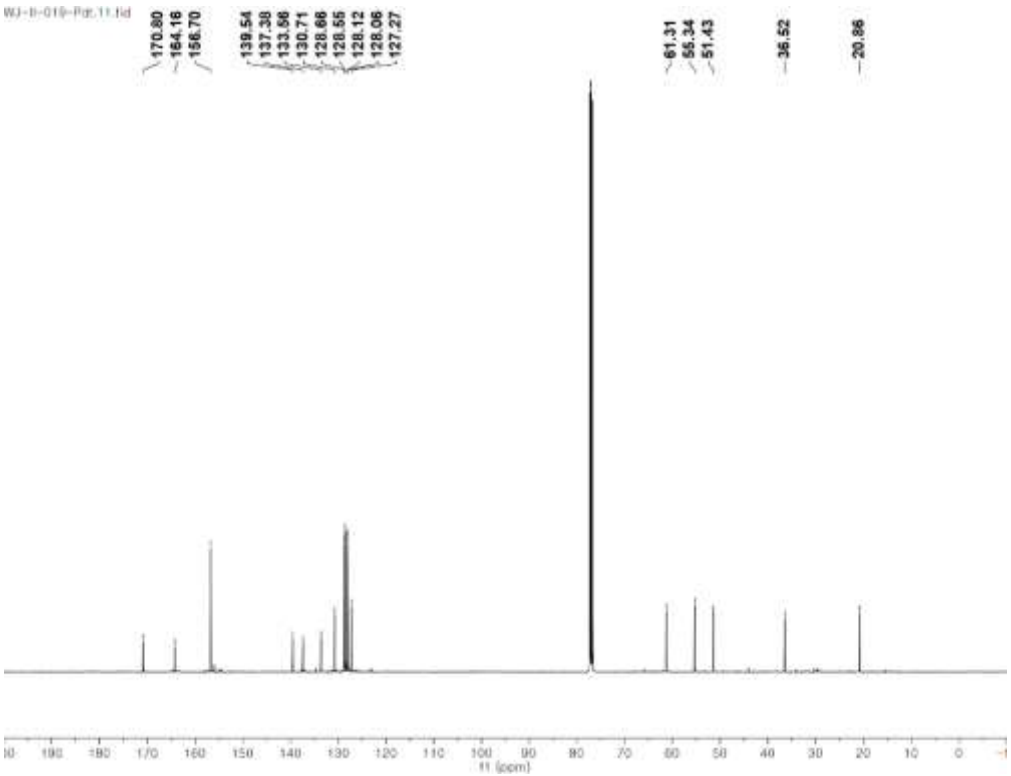
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.77 (s, 2H), 8.49 – 8.40 (m, 3H), 7.50 (dd, *J* = 5.2, 2.1 Hz, 4H), 7.35 – 7.23 (m, 6H), 4.28 – 4.18 (m, 1H), 4.08 – 3.98 (m, 1H), 3.83 (t, *J* = 6.9 Hz, 1H), 3.71 (d, *J* = 13.2 Hz, 1H), 3.58 (d, *J* = 13.2 Hz, 1H), 2.19 – 2.08 (m, 1H), 2.03 (dd, *J* = 12.7, 7.0 Hz, 1H), 1.98 (s, 3H), 1.73 (br, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 164.2, 156.7, 139.5, 137.4, 133.6, 130.7, 128.7, 128.6, 128.1, 128.1, 127.3, 61.3, 55.3, 51.4, 36.5, 20.9.

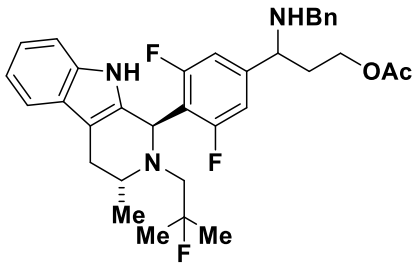
HRMS (ESI): Calculated for $C_{22}H_{23}N_3O_2$ $[M+H^+]$ = 362.1863, found 362.1867.

FTIR (neat): 3026, 2926, 1737, 1583, 1543, 1494, 1428, 1322, 1240, 1172, 1025, 927, 749, 694 cm^{-1}.





3-(Benzylamino)-3-(3,5-difluoro-4-((1R,3R)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenyl)propyl acetate (2.3p)



The allylic acetate (282 mg, 0.6 mmol, 300 mol%) and the primary amine (21.4 mg, 0.2 mmol, 100 mol%) were subject to standard reaction conditions with Cs_2CO_3 (300 mol%). The title compound was obtained in 53% yield (61 mg, 0.11 mmol) as a light yellow oil after purification by flash column chromatography (12g SiO_2, Isopropyl Acetate / Heptane = 0% - 100% over 30 min).

TLC (SiO_2) R_f = 0.30 (hexanes: ethyl acetate = 2:1).

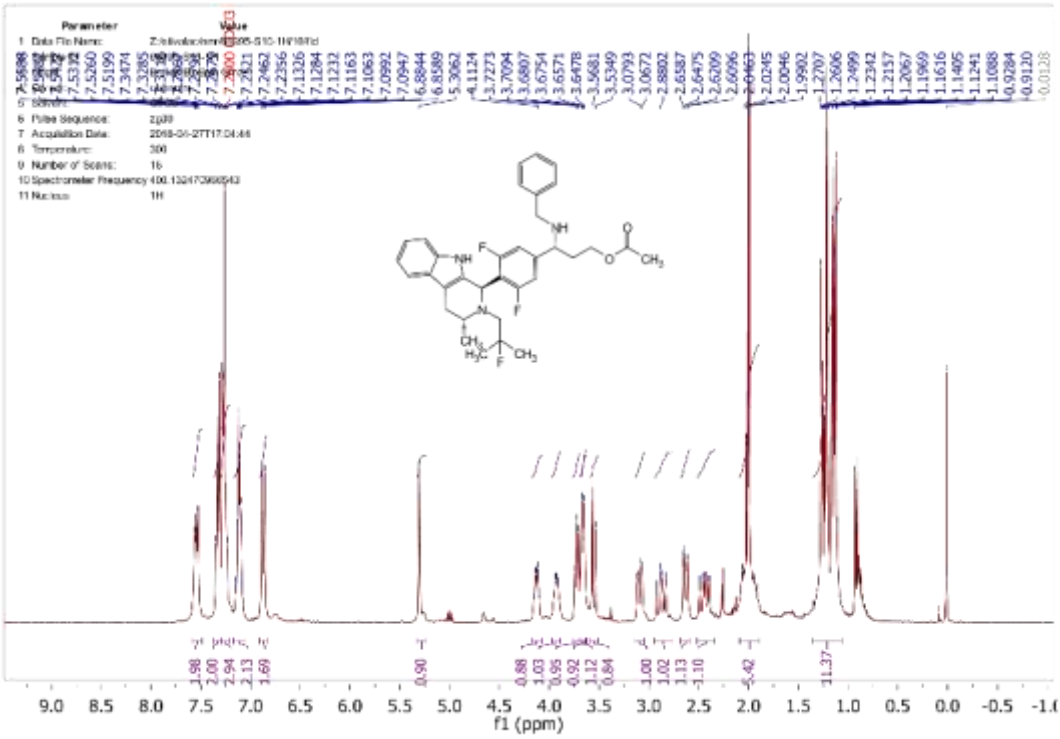
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 – 7.49 (m, 2H), 7.37 – 7.30 (m, 2H), 7.30 – 7.21 (m, 3H), 7.17 – 7.05 (m, 2H), 6.91 – 6.83 (m, 2H), 5.31 (s, 1H), 4.19 – 4.06 (m, 1H), 3.98 – 3.86 (m, 1H), 3.76 – 3.60 (m, 3H), 3.59 – 3.51 (m, 1H), 3.14 – 3.04 (m, 1H), 2.95 – 2.79 (m, 1H), 2.68 – 2.57 (m, 1H), 2.52 – 2.35 (m, 1H), 2.08 - 1.89 (m, 5H), 1.32 – 1.06 (m, 9H).

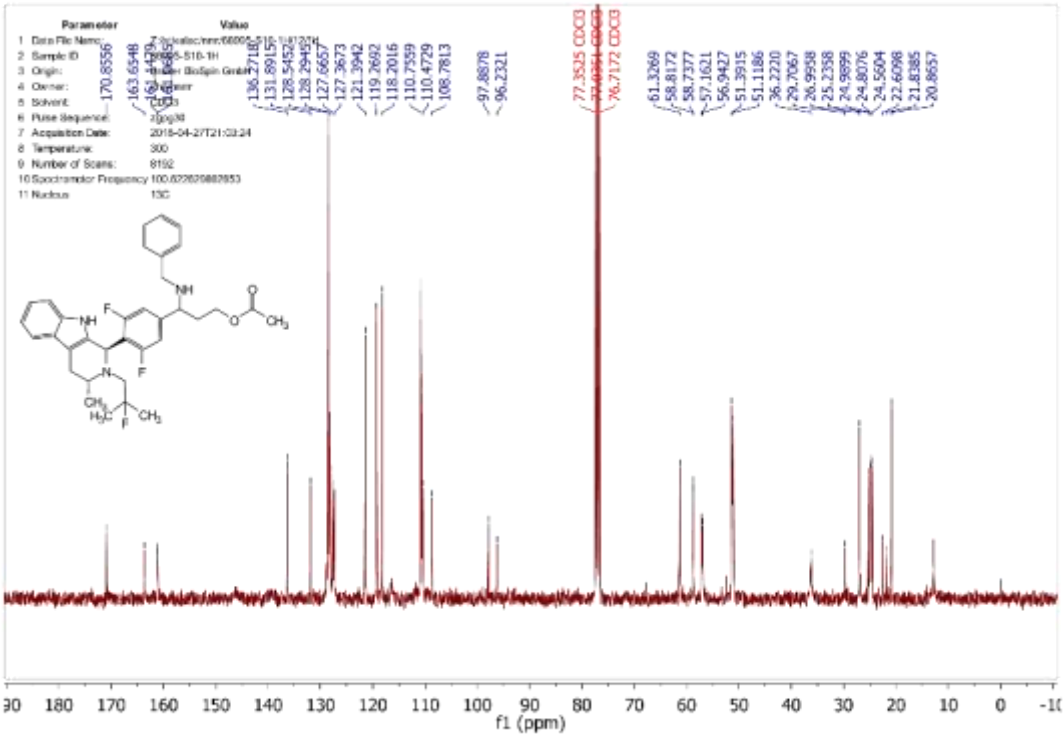
^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 162.4 (dd, *J* = 252.4, 7.8 Hz), 136.3, 131.9, 128.6, 128.3, 127.7, 127.4, 121.4, 119.3, 118.2, 110.8, 110.5, 108.8, 97.9, 96.2, 61.3, 58.8 (d, *J* = 8.0 Hz), 57.1 (d, *J* = 22.1 Hz), 51.6 – 50.8 (m, 2C), 36.2, 29.7, 27.0, 25.1 (d, *J* = 24.7 Hz), 24.7 (d, *J* = 24.9 Hz), 22.6, 21.8, 20.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –139.7 (m).

HRMS (ESI): Calculated for $C_{34}H_{39}N_3O_2F_3$ [M+H$^+$] = 578.2989, found 578.2984.

FTIR (neat): 2973, 2926, 1729, 1631, 1578, 1433, 1367, 1239, 1019, 908, 732 cm^{-1}.

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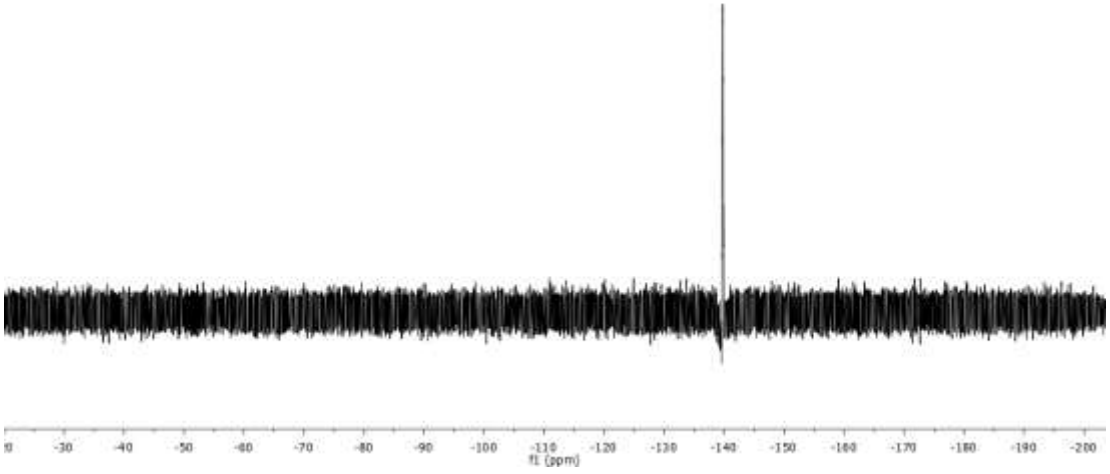
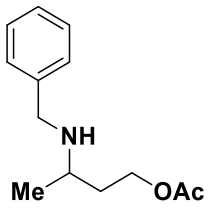
13C
f1 (ppm)


f1 (ppm)

3-(Benzylamino)butyl acetate (2.3q)



The allylic acetate (68.5 mg, 0.6 mmol, 300 mol%) and the primary amine (21.4 mg, 0.2 mmol, 100 mol%) were subject to standard reaction conditions. The title compound was obtained in 30% yield (13.3 mg, 0.06 mmol) as a light yellow oil after purification by flash column chrmmatography (SiO_2, hexanes: ethyl acetate = 5:1–1:1).

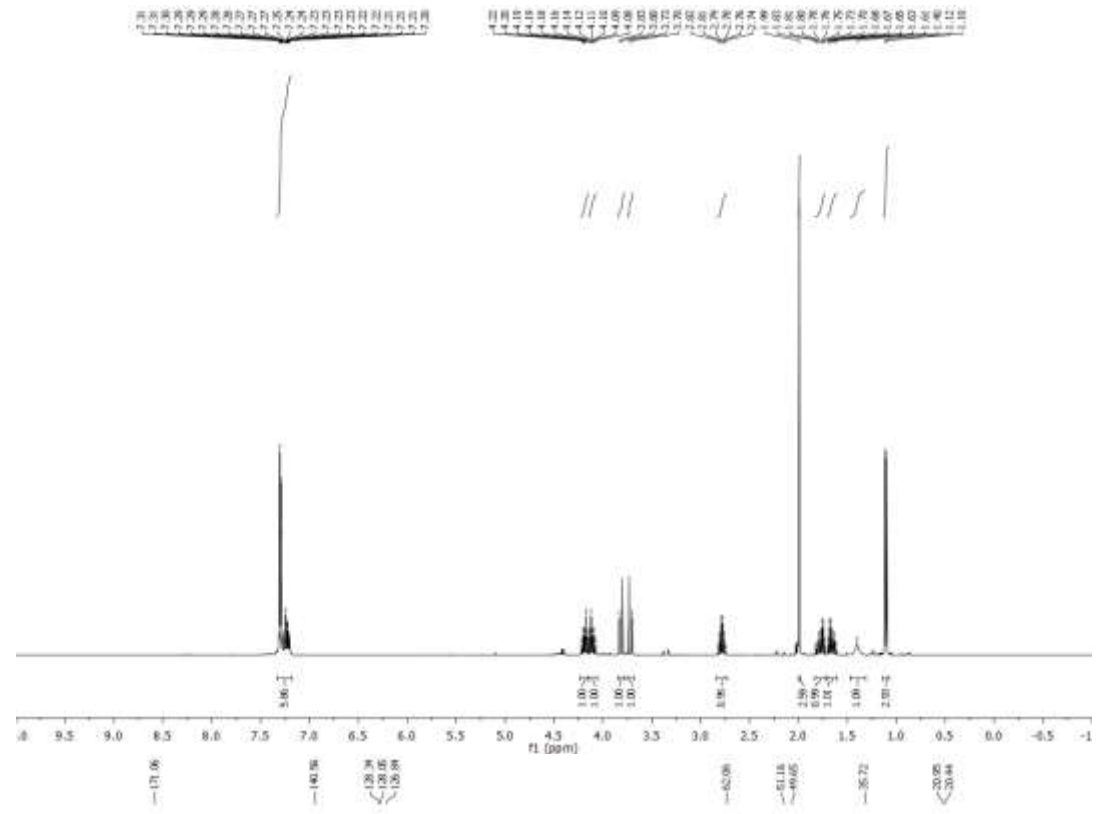
TLC (SiO_2) R_f = 0.24 (ethyl acetate: methanol = 10:1).

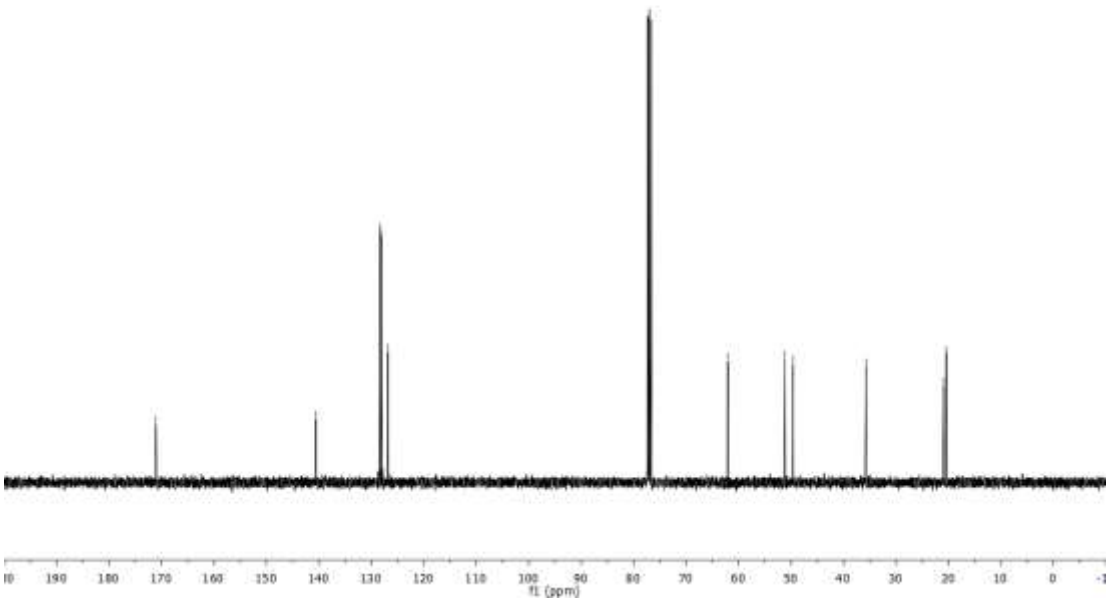
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 – 7.18 (m, 5H), 4.19 (dt, *J* = 11.1, 6.6 Hz, 1H), 4.11 (dt, *J* = 11.1, 6.7 Hz, 1H), 3.82 (d, *J* = 13.0 Hz, 1H), 3.72 (d, *J* = 13.0 Hz, 1H), 2.78 (h, *J* = 6.3 Hz, 1H), 1.99 (s, 3H), 1.83 – 1.72 (m, 1H), 1.71 – 1.61 (m, 1H), 1.40 (br, 1H), 1.11 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 140.6, 128.3, 128.1, 126.8, 62.1, 51.2, 49.7, 35.7, 21.0, 20.4.

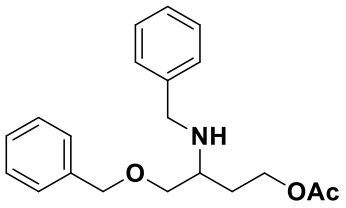
HRMS (ESI): Calculated for $C_{13}H_{19}NO_2$ [M+H$^+$] = 222.1489, found 222.1495.

FTIR (neat): 2962, 1734, 1453, 1365, 1238, 1045, 731, 698 cm^{-1}.


f1 (ppm)


f1 (ppm)

3-(Benzylamino)-4-(benzyloxy)butyl acetate (2.3r)



The allylic acetate (132.2 mg, 0.6 mmol, 300 mol%) and the primary amine (21.4 mg, 0.2 mmol, 100 mol%) were subject to standard reaction conditions with Cs_2CO_3 (300 mol%). The title compound was obtained in 53% yield (34.7 mg, 0.11 mmol) as a light yellow oil after purification by flash column chromatography (SiO_2, hexanes: ethyl acetate = 5:1–2:1).

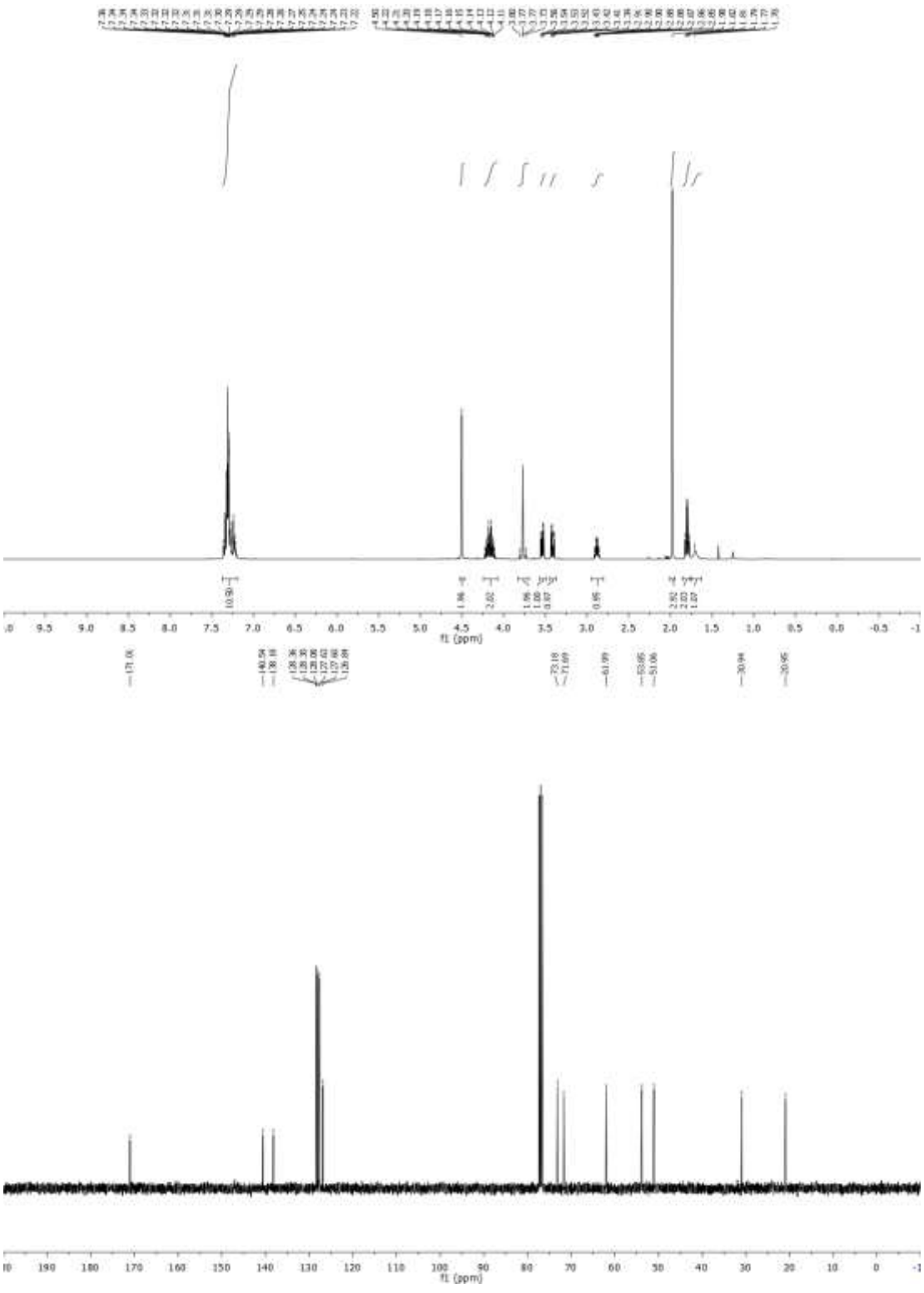
TLC (SiO_2) R_f = 0.30 (hexanes: ethyl acetate = 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 – 7.19 (m, 10H), 4.50 (s, 2H), 4.17 (qt, *J* = 11.0, 6.6 Hz, 2H), 3.77 (d, *J* = 1.5 Hz, 2H), 3.54 (dd, *J* = 9.4, 4.3 Hz, 1H), 3.41 (dd, *J* = 9.4, 5.8 Hz, 1H), 2.88 (qd, *J* = 6.2, 4.3 Hz, 1H), 1.98 (s, 3H), 1.80 (q, *J* = 6.6 Hz, 2H), 1.70 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 140.5, 138.2, 128.4, 128.3, 128.1, 127.6, 127.6, 126.8, 73.2, 71.7, 62.0, 53.9, 51.1, 30.9, 21.0.

HRMS (ESI): Calculated for $C_{20}H_{25}NO_3$ [M+H$^+$] = 328.1907, found 328.1907.

FTIR (neat): 1735, 1453, 1364, 1238, 1093, 1027, 734, 697 cm^{-1}.



Chapter 3: Enantioselective Iridium-Catalyzed Allylation of Acetylenic Ketones via 2-Propanol-Mediated Reductive Coupling of Allyl Acetate: C14-C23 of Pladienolide D

3.1 INTRODUCTION

The catalytic enantioselective addition of *C*-nucleophiles to ketones remains as a challenge in chemical synthesis[1] due to low C=O π-facial enantioselectivities, which resulted by incomplete differentiation of the acyl substituents by the chiral. Additionally, carbonyl addition of stabilized *C*-nucleophiles to construct C-C bonds is reversible, which diminishes kinetic stereoselectivity. Consequently, work in this area is relegated to the use of non-stabilized *C*-nucleophiles in the form of stoichiometric organometallic reagents, which are often prepared via successive transmetallation.[2,3] In the specific context of enantioselective ketone allylation, reagents based on B, Si, and Sn have been described.[4] Metal-catalyzed carbonyl reductive couplings of π-unsaturated feedstocks potentially provides an alternative to the use of premetalated *C*-nucleophiles.[5] However, the requisite reductants utilized in these processes are typically metallic (Zn, Mn), pyrophoric ($ZnEt_2$, BEt_3), or mass-intensive (R_3SiH).[6] To address these limitations, we have developed metal-catalyzed carbonyl reductive couplings that utilize hydrogen gas, 2-propanol or formates as terminal reductant, as well as related hydrogen auto-transfer processes wherein alcohols serve as hydrogen donor and carbonyl proelectrophile.[7] While this methodology has enabled diverse catalytic enantioselective aldehyde allylations[7f] and propargylations,[7g]

*This chapter is based on the previously published works: Brito, G. A.; Jung, W.-O.; Yoo, M.; Krische, M. J. *Angew. Chem. Int. Ed.* **2019**, *58*, 18803.
W. J. contributed to reaction optimization (Table 3.1), substrate scope (Tables 3.2), equations 3.1 and 3.2, and preparation of manuscript and supporting information.

asymmetric transfer hydrogenative allylations of ketones are restricted to vicinal dicarbonyl compounds.[8]

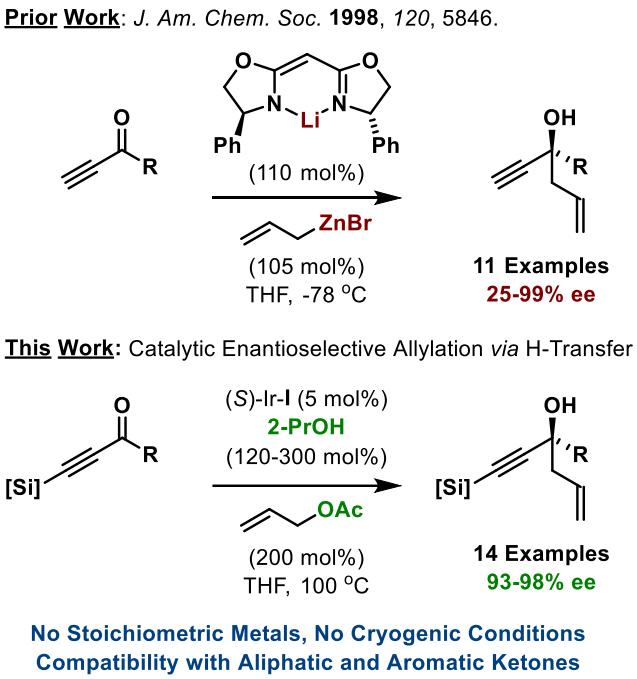


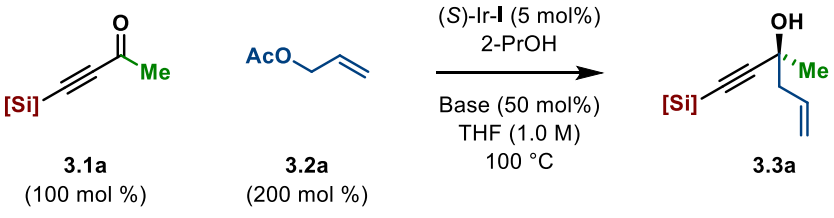
Figure 3. 1 Asymmetric allylation of acetylenic ketones.

It was postulated that acetylenic ketones might participate in alcohol-mediated carbonyl allylation efficiently due to the negative inductive effect of the alkyne.[9] Although isolated examples have been reported,[10] only one systematic study on the asymmetric allylation of acetylenic ketones is reported, which requires the use of an allylzinc reagent with a stoichiometric quantities of a chiral modifier.[11] Given this lack of prior art and the diverse utility of the resulting 1,5-enynes,[12] the 2-propanol-mediated transfer hydrogenative allylation of acetylenic ketones was explored. Here, we report that such

processes not only occur with high levels of enantioselectivity but conduct in a chemoselective manner in the presence of aliphatic and aromatic ketones (Figure 3.1).

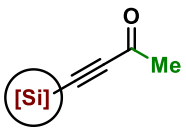
3.2 Reaction Development and Scope

Table 3. 1 Selected optimization experiments in the enantioselective π-allyliridium-*C*,*O*-benzoate catalyzed allylation of acetylenic ketone **3.1a**.[a]

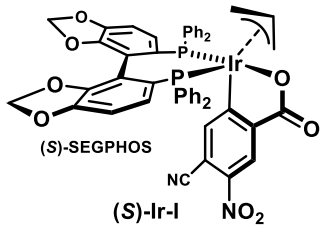


3.1a (100 mol %) **3.2a** (200 mol %) **3.3a**

Entry	[Si]	Base	2-PrOH	H_2O	Yield (%)	ee (%)
1	$^{i}Pr_3Si$	Cs_2CO_3	200 mol%	---	---	---
2	$^{i}Pr_3Si$	Cs_2CO_3	200 mol%	100	44	96
3	Ph_3Si	Cs_2CO_3	200 mol%	100	---	---
4	$^{t}BuPh_2Si$	Cs_2CO_3	200 mol%	100	48	94
5	$^{t}BuPh_2Si$	Cs_2CO_3	200 mol%	200	37	94
6	$^{t}BuPh_2Si$	Cs_2CO_3	200 mol%	50	39	94
7	$^{t}BuPh_2Si$	Cs_2CO_3	120 mol%	100	50	94
8	$^{t}BuPh_2Si$	K_2CO_3	120 mol%	100	53	94
9[b]	$^{t}BuPh_2Si$	K_2CO_3	120 mol%	100	66	94



[Si] Too Electron Rich: Insufficient C=O Electrophilicity
[Si] Too Electron Deficient: Silyl Cleavage Forms Acetylenic C-H, a Catalyst Poison



[a]Yields are of material isolated by silica gel chromatography. Enantioselectivities were determined by chiral stationary phase HPLC analysis. [b]3-NO_2-4-CN-BzOH (10 mol%).

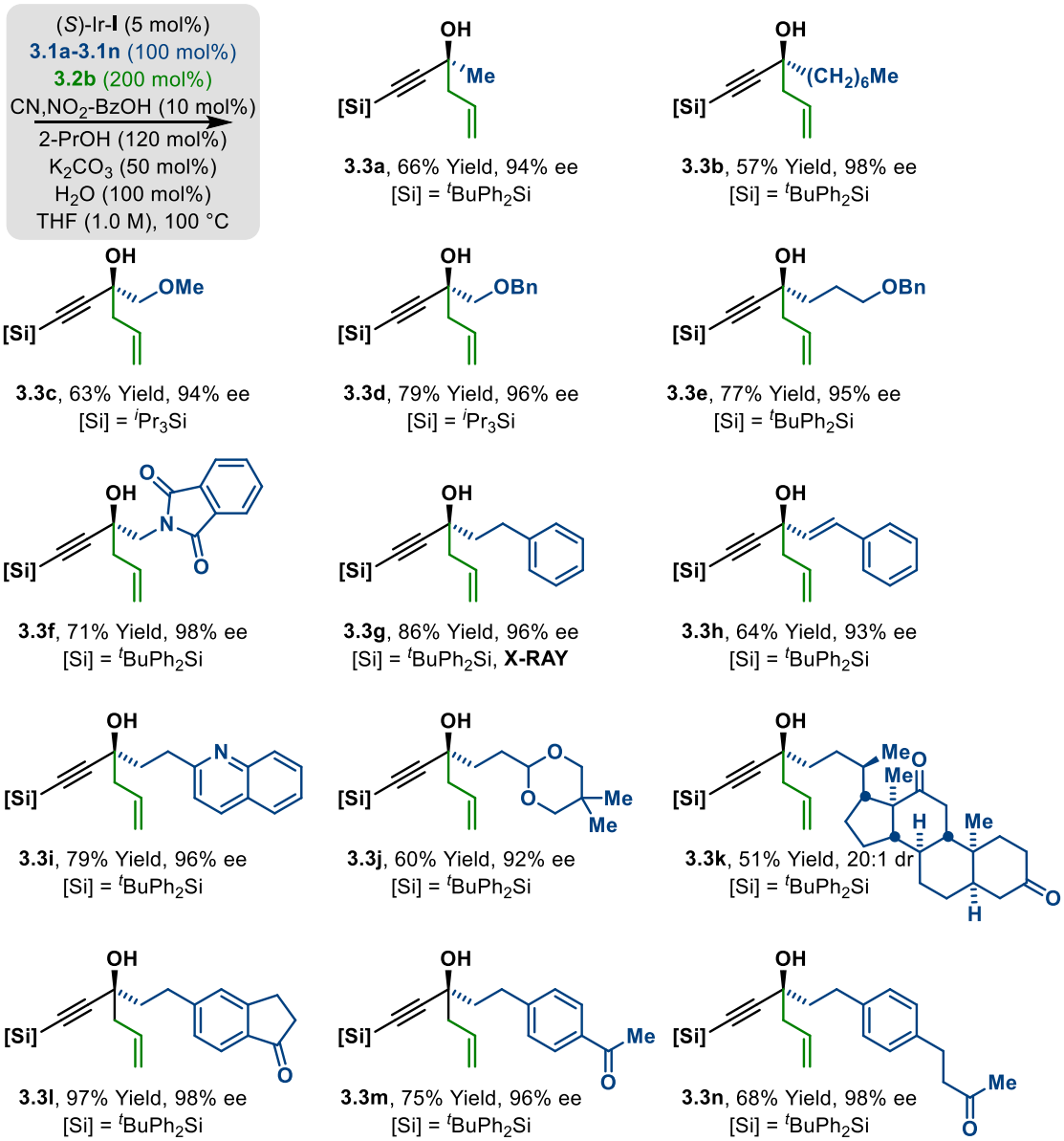
Guided by our prior work on the transfer hydrogenative allylation of acetylenic aldehydes,[9] methyl ketone **3.1a** (100 mol%, [Si] = $^{i}Pr_3Si$) was subjected to allyl acetate **3.2a** (200 mol%) and 2-propanol (200 mol%) in the presence of Cs_2CO_3 (50 mol%) and π-

allyliridium-*C*,*O*-benzoate modified by (*S*)-SEGPHOS, (S)-Ir-**I** (5 mol%), in anhydrous THF (Table 3.1, entry 1). The desired allylation product **3.3a** was not observed. However, addition of water (100 mol%), which may facilitate alkoxide exchange at the metal center and solubilize the heterogeneous carbonate base, the tertiary homoallylic alcohol **3.3a** was obtained in 44% yield and 96% ee (Entry 2). The mass balance in this experiment consisted primarily of unreacted **3.1a** and the corresponding product of silyl cleavage. As acetylenic C-H moieties are not tolerated under the reaction conditions, an effort was made to accelerate carbonyl addition with respect silyl cleavage through the introduction of a more inductive silyl groups. While use of the triphenylsilyl group, as in **3.1a** ([Si] = Ph_3Si), only exacerbated silyl cleavage to prevent formation of **3.3a** (Entry 3), the corresponding *tert*-butyl-diphenylsilyl compound, **3.1a** ([Si] = $^tBuPh_2Si$), better balanced inductive activation and stability toward cleavage, enabling formation of **3.3a** in 48% yield with a high level of enantioselectivity (Entry 4). While adjusting the loading of water did not increase efficiency (Entries 5 and 6), decreased loadings of 2-propanol (120 mol%) and use of a slightly weaker base, K_2CO_3 (50 mol%) each led to modest improvements (Entries 7 and 8). Finally, introduction of 3-NO_2-4-CN-BzOH (10 mol%), which presumably stabilizes the catalyst and attenuates silyl cleavage by buffering the medium, led to a much cleaner reaction, delivering **3.3a** in 66% yield and 96% enantiomeric excess (Entry 9).

With these optimal conditions in hand, the enantioselective allylation of diverse acetylenic ketones was explored (Table 3.2). While simple alkyl-substituted acetylenic exert a negative σ-inductive effect, deliver the tertiary homoallylic alcohols **3.3c**-**3.3g**, respectively, excellent yields. For α-alkoxy ketones **3.1c** and **3.1d**, which exert a relatively strong negative σ-inductive effect, the less inductive and more stable $^iPr_3Si$ ketones **3.1a**

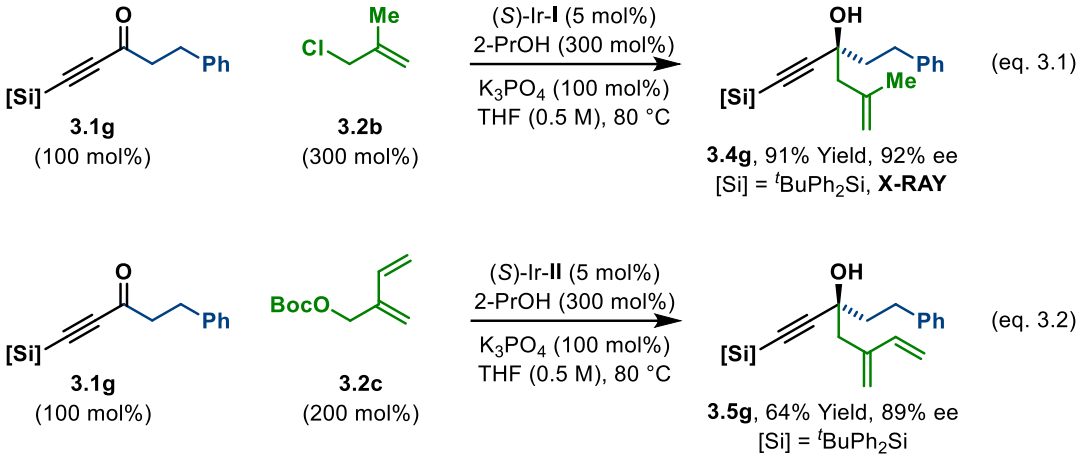
and **3.1b** provide moderate yields of the corresponding tertiary homoallylic alcohols **3.3a** and **3.3b**, acetylenic ketones **3.1c**-**3.1g**, which incorporate substituents that

Table 3. 2 Enantioselective π-allyliridium-*C*,*O*-benzoate catalyzed allylation of acetylenic ketones **3.1a-3.1n** via 2-propanol-mediated reductive coupling with allyl acetate **3.2b**.[a]



[a]Yields are of material isolated by silica gel chromatography. Enantioselectivities were determined by chiral stationary phase HPLC analysis.

moiety can be used instead of the ^{t}BuPh$_2$Si moiety. Remarkably, ketone **3.1h**, which incorporate acetylenic and vinylic acyl substituents, is an effective partner of carbonyl allylation, forming the tertiary propargylic-allylic-homoallylic alcohol **3.3h** in good yield. Tolerance of *N*-heterocycles and acetals are illustrated by the formation of **3.3i** and **3.3j**, respectively. Perhaps most significant, however, are the reactions of ketones **3.1k**-**3.1n**. The acetylic ketone moieties of **3.1k**-**3.1n** undergo completely chemoselective allylation in the presence of aliphatic or aromatic ketone moieties to form **3.3k**-**3.3n** as single constitutional isomers. For all adducts **3.3a**-**3.3n**, uniformly high levels of enantioselectivity are observed. In lower yielding transformations, unreacted ketone along with trace quantities of *tert*-butyldiphenylsilanol (<5 %) were observed. The absolute stereochemistry of tertiary alcohols **3.3a**-**3.3n** was assigned in analogy to that determined for adducts **3.3g**, which was determined by single crystal X-ray diffraction analysis. Aryl substituted acetylenic ketones did not participate in allylation. Additionally, formation of compounds **3.3a**-**3.3n** from the propargyl alcohols corresponding to ketones **3.1k**-**3.1n** via hydrogen auto-transfer was inefficient, as the negative inductive effect of the alkyne impedes dehydrogenation.



Finally, acetylenic ketones are competent partners in related enantioselective transfer hydrogenative allylations. For example, exposure of acetylenic ketone **3.1g** to methallyl chloride **3.2b** and 2-propanol (300 mol%) in the presence of (S)-Ir-**I** (5 mol%) provides the product of methallylation **3.4g** in 91% yield and 92% ee (eq. 1).[13] Additionally, the reductive coupling of acetylenic ketone **3.1g** with isoprenyl *tert*-butoxy carbonate **3.2c** mediated by 2-propanol (300 mol%) and catalyzed by the corresponding (*S*)-DM-SEGPHOS-modified catalyst (*S*)-Ir-**II** (5 mol%) provides the product of isoprenylation **3.5g** in 64% yield and 89% ee (eq. 1).[14]

3.3 Discussion

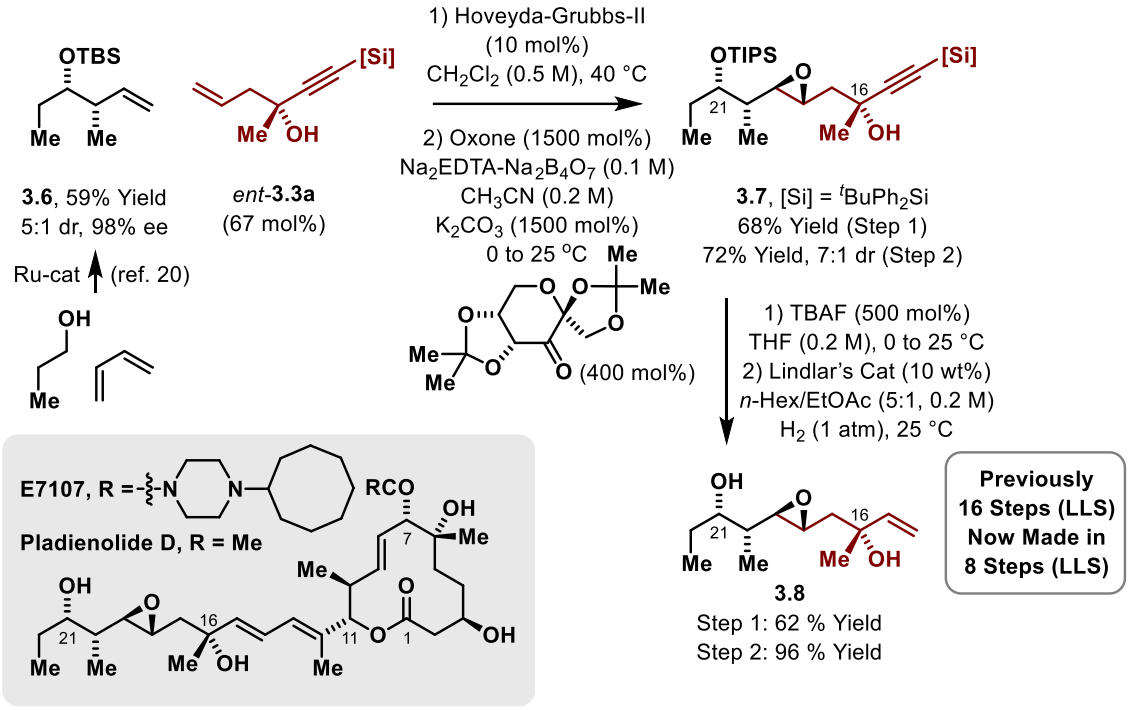
The utility of the present ketone allylation method to natural product total synthesis is illustrated by the rapid conversion of adduct *ent*-**3.3a** to the C14-C23 side chain of pladienolide D (Scheme 3.1). The pladienolides were isolated in 2004 from the culture broth of Mer-11107, an engineered strain of Streptomyces platensis,[15] and were found to inhibit the proliferation of multiple drug resistant human cancer cells with low nanomolar

IC_{50} values.[16] These compounds operate through a novel mechanism of action, involving binding to the splicing factor 3b (SF3b) subunit of the spliceosome.[17] Clinical evaluation of pladienolide analogue E7107 was undertaken but discontinued due to vision loss.[18] More recently, however, clinical trials were initiated with another pladienolide analogue, H3B-8800, which was granted orphan drug status by the FDA in August 2017 for treatment of myelogenous leukemia and chronic myelomonocytic leukemia.[19] Cross-metathesis of *ent*-**3.3a** with compound **3.6** (conveniently prepared via butadiene-mediated crotylation of propanal),[20] followed by Shi epoxidation[21] of the resulting olefin, delivers acetylenic epoxide **3.7** with high levels of stereocontrol. To corroborate the stereochemical assignment of acetylenic epoxide **3.7**, it was subjected to silyl deprotection and Lindlar reduction to furnish the previously reported tertiary allylic alcohol **3.8**,[21] which embodies C14-C23 of pladienolide D. Whereas the prior synthesis of tertiary allylic alcohol **3.8** required 16 steps (LLS), the present synthesis of **3.8** is completed in only 8 steps (LLS).

3.4 CONCLUSION

In summary, we report the first catalytic enantioselective allylations of acetylenic ketones. Specifically, using the π-allyliridium-*C*,*O*-benzoate modified by (*S*)-SEGPHOS, (*S*)-Ir-**I**, as catalyst, allyl acetate **3.2a** engages acetylenic ketones **3.1a**-**3.1n** in enantioselective 2-propanol-mediated reductive coupling to form tertiary propargyl alcohols **3.3a**-**3.3n**. Additionally, owing the highly chemoselective nature of this process, we demonstrate that acetylenic ketones undergo allylation in the presence of aliphatic or aromatic ketone functional groups to form single constitutional isomers. Using this protocol, a concise enantioselective synthesis of C14-C23 side chain of

pladienolide D is achieved. More broadly, these studies contribute to a growing body of alcohol-mediated carbonyl additions that collectively signify a departure from the use of premetalated reagents C-C bond formation.[5d]



Scheme 3. 1 Enantioselective synthesis of C14-C23 side chain of pladienolide D.

3.5 Experimental Details

3.5.1 General Information

All reactions were run under an atmosphere of argon. Sealed tubes (13x100 mm) were purchased from Fischer Scientific (catalog number 14-959-35C) and were flame dried

followed by cooling in a desiccator. Tetrahydrofuran, toluene and diethyl ether were distilled from sodium-benzophenone immediately prior to use. Dichloromethane was distilled from calcium hydride under a nitrogen atmosphere prior to use. Anhydrous solvents were transferred by oven-dried syringes. All commercial reagents and anhydrous solvents were used as received from vendors (Fischer Scientific, Sigma Aldrich and Combi Blocks) without further purification. Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates (Dynanmic Absorbents F254). Visualization was accomplished with UV light followed by dipping in potassium permanganate or *p*-anisaldehyde stain solution and then heating. Purification of reactions were carried out by flash chromatography using silica gel (40-63 μm).

3.5.2 Spectroscopy, Spectrometry, and Data Collection

Infrared spectra were recorded on a Thermo Scientific Nicolet 380 spectrometer. High-resolution mass spectra (HRMS) were obtained on an Agilent Technologies 6530 Accurate-Mass Q-TOF LC/MS (ESI and APPI analysis) or on a Waters Micromass AutoSpec Ultima GC/MS (CI analysis) and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M+H, M+Na), or a suitable fragment ion. Nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR) were recorded on Bruker AVANCE III (500 MHz), Varian Gemini (400 MHz) or Varian INOVA (500 MHz). Chemical shifts (δ) for protons are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to the proton resonance of residual $CHCl_3$ in the NMR solvent (δ = 7.27 ppm). Chemical shifts (δ) for carbon are reported in ppm downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent peak (δ = 77.0

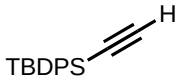
ppm). NMR data are represented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant in Hertz (Hz), and integration. Uncorrected melting points were measured on a Stuart SMP3 Melting Point Apparatus. Specific optical rotations were recorded on an Atago AP-300 automatic polarimeter at the sodium line (589.3 nm). X-ray diffraction data were collected and analyzed by the UT Austin X-ray Diffraction Facility.

3.5.3 Experimental Details and Spectra Data for compounds 3.1a-3.1n

Preparation of (*S*)-Ir-I

Catalyst modified with (*S*)-SEGPHOS ligand was prepared according to the published procedure: Gao, X.; Townsend, I. A.; Krische, M. J. *J. Org. Chem.* **2011**, *76*, 2350.

***tert*-Butyl(ethynyl)diphenylsilane**

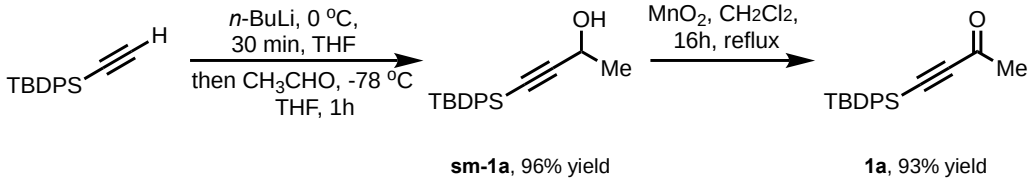


To an oven-dried round-bottomed flask charged with trimethylsilylacetylene (6.90 mL, 50 mmol, 100 mol%) and THF (83 mL, 0.6 M) at 0 ^{o}C was added *n*-BuLi (20 mL, 50 mmol, 100 mol%, 2.5 M in hexanes). The mixture was allowed to stir at this temperature for 30 min at which point TBDPSCl (13.5 mL, 57.5 mmol, 115 mol%) was added and the reaction mixture was allowed to stir overnight at room temperature. To the reaction mixture was added saturated aqueous ammonium chloride solution (40 mL). The reaction mixture

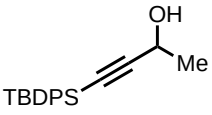
was transferred to a separatory funnel and the aqueous phase extracted with EtOAc (3 x 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The solid residue was dissolved in methanol (50 mL), K_2CO_3 (17.3 g, 125 mmol, 250 mol%) was added and the heterogenous solution was stirred at room temperature for 2 h. The reaction mixture was filtered through a plug of celite with the aid of EtOAc and the filtrate was concentrated in vacuo. The resulting residue was diluted with EtOAc (50 mL) and water (50 mL) and the mixture transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting residue was subjected to flash column chromatography (SiO_2, hexanes/ethyl acetate = 20:1) to furnish the title compound (7.54 g, 28.5 mmol) as white solid in 57% yield over two steps. The spectroscopic properties of this compound were consistent with the data available in literature.[22]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 – 7.82 (m, 4H), 7.44 – 7.39 (m, 6H), 2.73 (s, 1H), 1.13 (s, 9H).

4-(*tert*-Butyldiphenylsilyl)but-3-yn-2-one (3.1a)

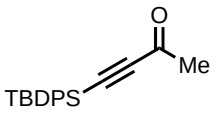


sm-1a, 96% yield **1a**, 93% yield



To an oven-dried round-bottomed flask charged with *tert*-butyl(ethynyl)diphenylsilane (1.32 g, 5.0 mmol, 100 mol%) and THF (17 mL, 0.3 M) at 0 °C was added *n*-BuLi (2.5 M, 2.0 mL, 5.0 mmol, 100 mol%). The reaction mixture was allowed to stir at 0 °C for 30 min. The reaction vessel was cooled to -78 °C and a solution of acetaldehyde (0.37 mL, 6.5 mmol, 130 mol%) in THF (3 mL) was added dropwise. The mixture was allowed to warm to room temperature and saturated aqueous NH_4Cl (5 mL) was added. The reaction mixture was transferred to a separatory funnel and the aqueous phase extracted with EtOAc (3 x 5 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was subjected to flash column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to furnish the title compound **sm-3.1a** (1.48 g, 4.80 mmol) in 96% yield as a pale oil. The spectroscopic properties of this compound were consistent with the data available in literature.[23]

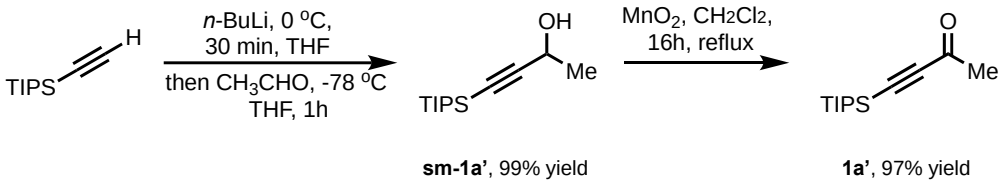
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 – 7.75 (m, 4H), 7.41 – 7.34 (m, 6H), 4.72 – 4.64 (m, 1H), 1.87 (d, *J* = 5.4 Hz, 1H), 1.58 (d, *J* = 6.6 Hz, 3H), 1.08 (s, 9H).



To an oven-dried round-bottomed flask charged with **sm-3.1a** (1.30 g, 4.20 mmol, 100 mol%) and CH_2Cl_2 (15 mL, 0.3 M) at room temperature was added MnO_2 (7.30 g, 84 mmol, 20 equiv). The reaction mixture was allowed to stir at reflux overnight. The reaction mixture was cooled to room temperature, filtered through a celite plug with the aid of CH_2Cl_2, and the filtrate concentrated in vacuo. The residue was subjected to flash column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to furnish title compound **3.1a** (1.20 g, 3.91 mmol) in 93% yield as a white solid. The spectroscopic properties of this compound were consistent with the data available in literature.[24]

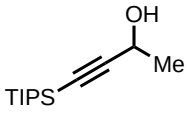
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 – 7.73 (m, 4H), 7.45 – 7.37 (m, 6H), 2.45 (s, 3H), 1.12 (s, 9H).

4-(Triisopropylsilyl)but-3-yn-2-one (3.1a')



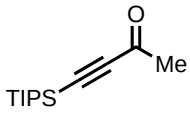
sm-1a', 99% yield

1a', 97% yield



The title compound was prepared according to general procedure described in section 3.2 using ethynyltriisopropylsilane (0.91 g, 5.0 mmol, 100 mol%), THF (15 mL, 0.3 M), *n*-BuLi (2.0 mL, 5.0 mmol, 100 mol%, 2.5 M in hexanes) and acetaldehyde (0.34 mL, 6.0 mmol, 120 mol%). Upon flash column chromatography (SiO_2, hexanes/ethyl acetate = 9:1) the title compound **sm-3.1a'** (1.12 g, 4.95 mmol) was obtained in 99% yield as a pale oil. The spectroscopic properties of this compound were consistent with the data available in literature.[25]

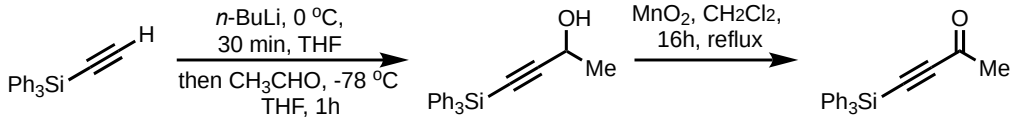
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.58 – 4.50 (m, 1H), 1.74 (d, *J* = 5.2 Hz, 1H), 1.55 (s, 1H), 1.47 (d, *J* = 6.5 Hz, 3H), 1.07-1.06 (m, 21H).



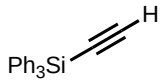
The title compound was prepared according to general procedure described in section 3.2 using **sm-3.1a'** (1.12 g, 4.95 mmol, 100 mol%), CH_2Cl_2 (17 mL, 0.3 M) and MnO_2 (8.70 g, 100 mmol, 20 equiv.). Upon flash column chromatography (SiO_2, hexanes/ethyl acetate = 9:1) the title compound **3.1a'** (1.08 g, 4.80 mmol) was obtained in 97% yield as a yellow oil. The spectroscopic properties of this compound were consistent with the data available in literature.[26]

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.36 (s, 3H), 1.12 – 1.08 (m, 21H).

4-(Triphenylsilyl)but-3-yn-2-one (3.1a'')

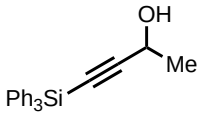


sm-1a'', 87% yield **1a''**, 91% yield



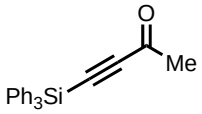
To a 50 mL round-bottomed flask charged with a solution of ethynyl-Grignard reagent (24 mL, 120 mol%, 0.5 M in THF) in 20 mL of THF was added chlorotriphenylsilane (2.95 g, 10.0 mmol, 100 mol%) in THF (10 mL) *via* an addition funnel over a period of 1 h. The reaction mixture was stirred at refluxed for 3 h. The reaction mixture was cooled to room temperature, diluted with water (20 mL), and the mixture transferred to a separatory funnel. The phases were separated and the aqueous layer extracted with ether (3 x 20 mL). The organic layers were combined, washed with water (20 mL), dried (Na_2SO_4) and the solvents removed under reduced pressure. The resulting residue was subjected to flash column chromatography (SiO_2, hexanes/ethyl acetate = 20:1) to furnish the title compound **sm-3.1a''** (1.60 g, 5.60 mmol) in 56% yield as a white solid. The spectroscopic properties of this compound were consistent with the data available in literature.[26]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.6 Hz, 6H), 7.40 (dq, *J* = 14.3, 7.4 Hz, 10H), 2.77 (s, 1H) ppm.



The title compound was prepared according to general procedure described in section 3.2 using ethynyltriphenylsilane (0.71 g, 2.50 mmol, 100 mol%), THF (4.2 mL, 0.6 M), *n*-BuLi (1.00 mL, 2.50 mmol, 100 mol%, 2.5 M in hexanes) and acetaldehyde (0.20 mL, 2.63 mmol, 105 mol %). Upon flash column chromatography (SiO_2, hexanes/ethyl acetate = 4:1) title compound **sm-3.1a''** (0.71 g, 2.17 mmol) was obtained in 87% yield as a pale oil. The spectroscopic properties of this compound were consistent with the data available in literature.[27]

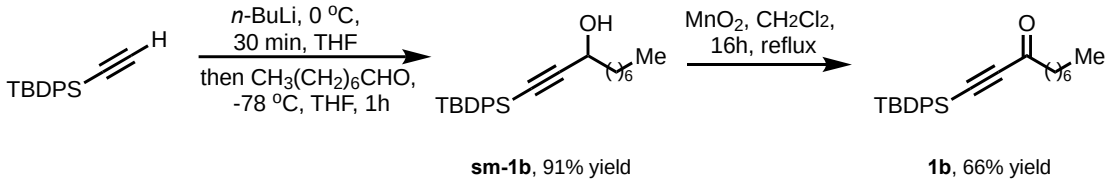
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.58 (m, 6H), 7.38 (ddd, *J* = 14.6, 7.9, 6.5 Hz, 9H), 4.65 (q, *J* = 6.6 Hz, 1H), 1.61 (s, 2H), 1.54 (d, *J* = 6.7 Hz, 3H) ppm.



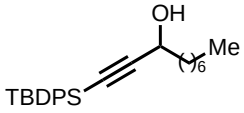
The title compound was prepared according to general procedure described in section 3.2 using **sm-3.1a''** (0.23 g, 0.70 mmol, 100 mol%), CH_2Cl_2 (3.5 mL, 0.2 M) and MnO_2 (1.22 g, 14 mmol, 20 equiv). Upon flash column chromatography (SiO_2, hexanes/ethyl acetate = 4:1) title compound **3.1a''** (0.21 g, 0.64 mmol) was obtained in 91% yield as a yellow oil. The spectroscopic properties of this compound were consistent with the data available in literature.[28]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.59 (m, 6H), 7.48 – 7.36 (m, 10H), 2.41 (s, 3H) ppm.

1-(*tert*-Butyldiphenylsilyl)dec-1-yn-3-one (3.1b)



sm-1b, 91% yield **1b**, 66% yield



The title compound was prepared according to general procedure using *tert*-butyl(ethynyl)diphenylsilane (1.32 g, 5.0 mmol, 100 mol%), THF (15 mL, 0.3 M), *n*-BuLi (2.0 mL, 5.0 mmol, 100 mol%, 2.5 M in hexanes) and octanaldehyde (0.78 mL, 5.0 mmol, 100 mol%). Upon flash column chromatography (SiO_2, hexanes/ethyl acetate = 9:1) title compound **sm-3.1b** (1.78 g, 4.55 mmol) was obtained in 91% yield as a yellow oil.

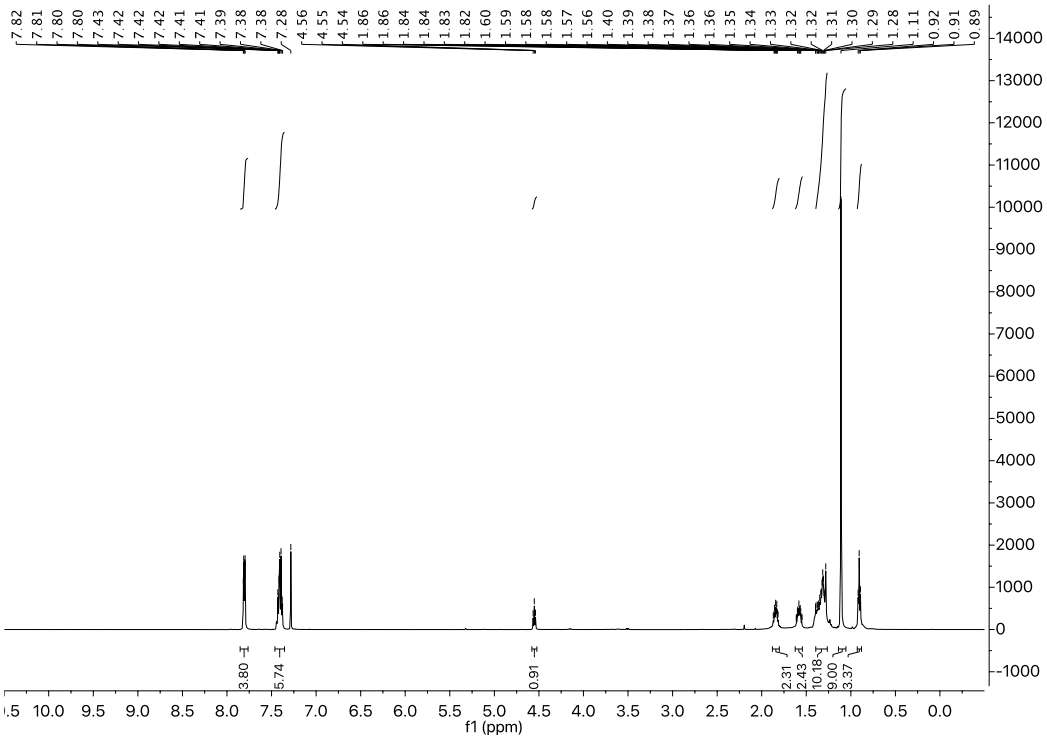
TLC (SiO_2) R_f = 0.36 (hexanes/ethyl acetate = 9:1).

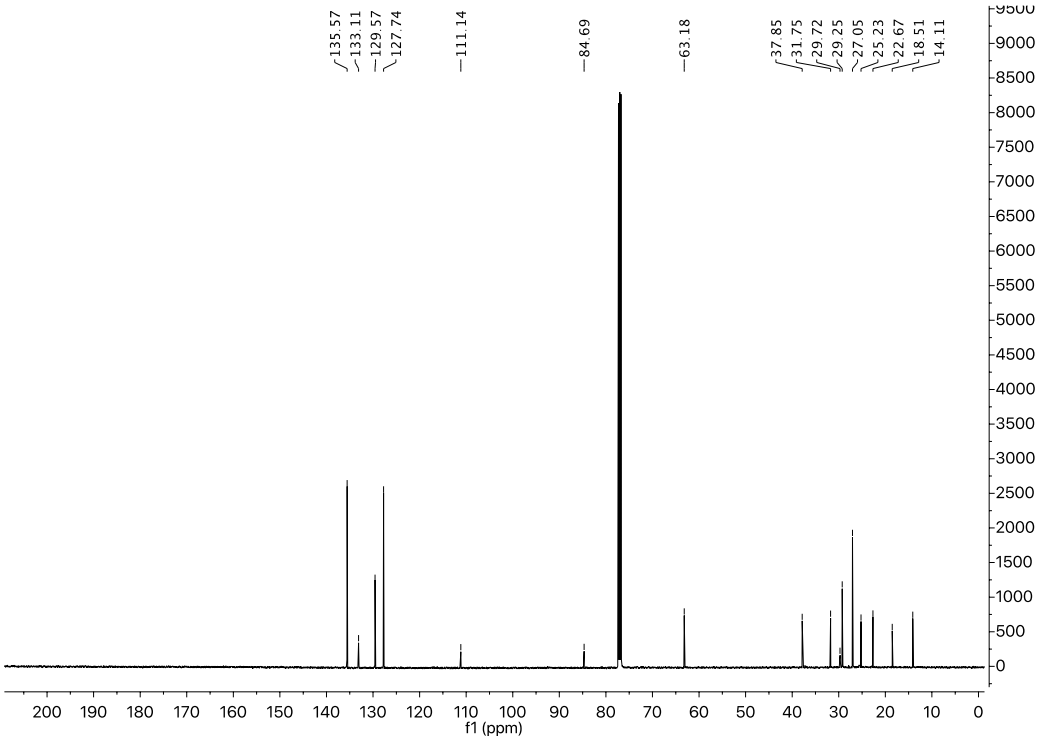
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 – 7.76 (m, 4H), 7.46 – 7.35 (m, 6H), 4.55 (t, *J* = 6.6 Hz, 1H), 1.84 (qd, *J* = 7.0, 4.0 Hz, 2H), 1.62 – 1.54 (m, 2H), 1.39 – 1.26 (m, 10H), 1.11 (s, 9H), 0.91 (t, *J* = 6.7 Hz, 3H) ppm.

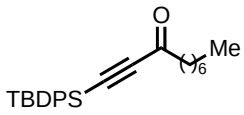
^{13}C NMR (101 MHz, $CDCl_3$) δ 135.6, 133.1, 129.6, 127.7, 111.1, 84.7, 63.2, 37.9, 31.8, 29.7, 29.3, 27.1, 25.2, 22.7, 18.5, 14.1 ppm.

HRMS (ESI) m/z: [M-H$^+$] calcd for $C_{26}H_{36}OSi$ 391.2457, found 391.2455.

FTIR (ATR) 3412, 3070, 2928, 2855, 1707, 1462, 1428, 1361, 1109, 1008, 998, 819, 741, 698 cm^{-1}.


7.82
7.81
7.80
7.80
7.43
7.42
7.42
7.42
7.41
7.41
7.39
7.38
7.38
7.28
4.56
4.55
4.54
1.86
1.86
1.84
1.84
1.83
1.82
1.60
1.59
1.58
1.58
1.57
1.56
1.40
1.39
1.38
1.37
1.36
1.36
1.35
1.34
1.33
1.32
1.32
1.31
1.30
1.29
1.28
1.11
0.92
0.91
0.89
3.80
5.74
0.91
2.31
2.43
10.18
9.00
3.37
f1 (ppm)


135.57
133.11
129.57
127.74
111.14
84.69
63.18
37.85
31.75
29.72
29.25
27.05
25.23
22.67
18.51
14.11
f1 (ppm)



The title compound was prepared according to general procedure using **sm-3.1b** (1.78 g, 4.53 mmol, 100 mol%), CH_2Cl_2 (23 mL, 0.2 M) and MnO_2 (7.88 g, 90.7 mmol, 20 equiv). Upon flash column chromatography (SiO_2, hexanes/ethyl = 20:1) title compound **3.1b** (1.16 g, 2.99 mmol) was obtained in 66% yield as a yellow oil.

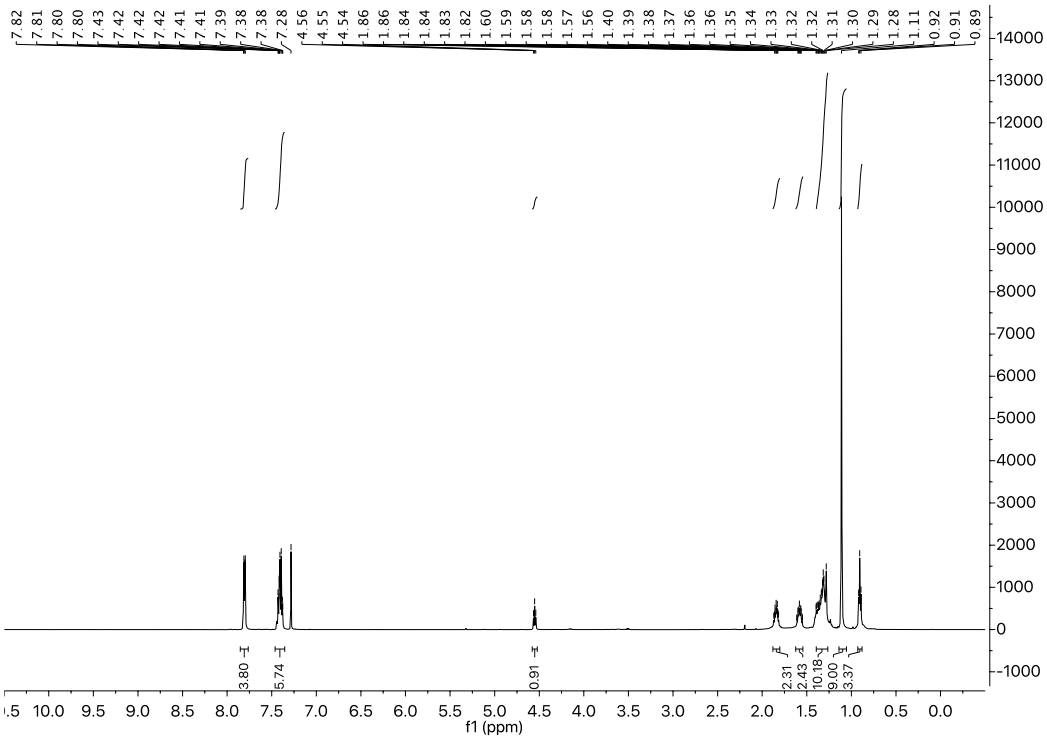
TLC (SiO_2) R_f = 0.36 (hexanes/ethyl acetate = 20:1).

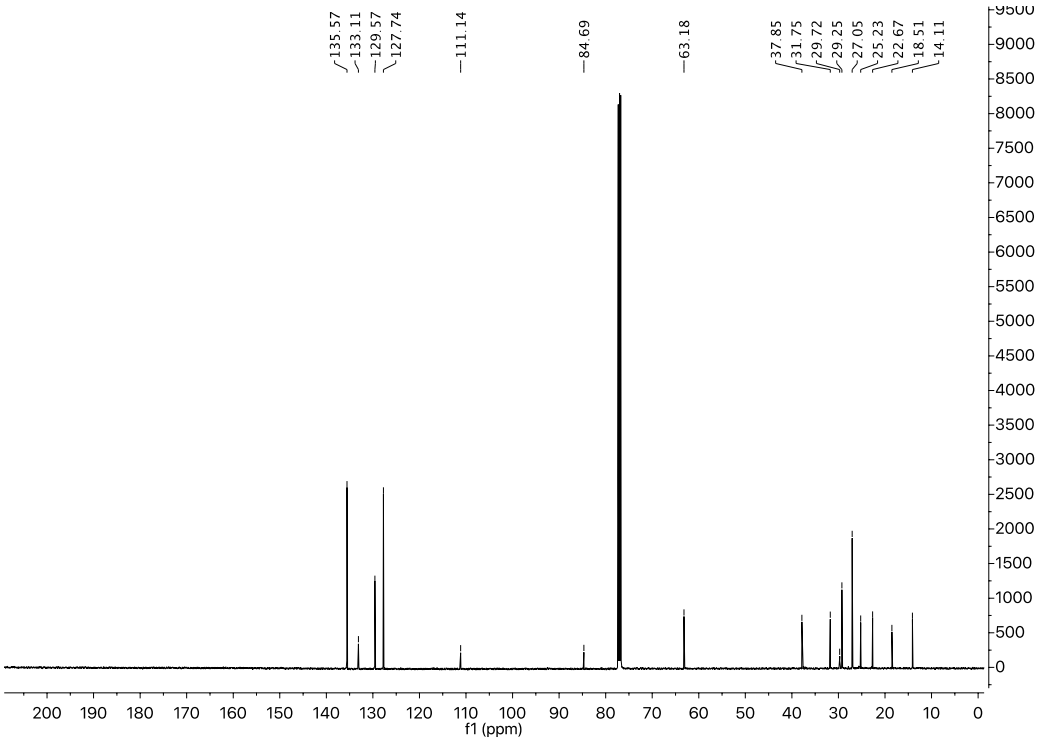
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 – 7.75 (m, 4H), 7.49 – 7.38 (m, 6H), 2.68 (t, *J* = 7.4 Hz, 2H), 1.78 (p, *J* = 7.4 Hz, 2H), 1.41 – 1.27 (m, 8H), 1.15 (s, 9H), 0.90 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 187.89, 135.6, 131.5, 130.0, 128.0, 128.0, 105.4, 93.3, 45.7, 31.6, 29.0, 29.0, 27.0, 24.2, 22.6, 18.7, 14.1.

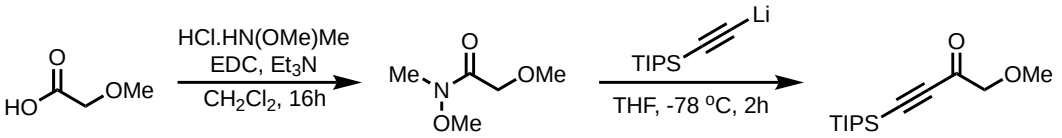
HRMS (ESI) m/z: [M+H$^+$] calcd for $C_{26}H_{34}OSi$ 391.2457, found 391.2446.

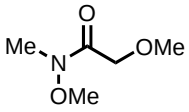
FTIR (ATR) 2956, 2930, 2858, 1715, 1676, 1470, 1428, 1362, 1218, 1132, 1110, 1028, 819, 698 cm^{-1}.


7.82
7.81
7.80
7.80
7.43
7.42
7.42
7.42
7.41
7.41
7.39
7.38
7.38
7.28
4.56
4.55
4.54
1.86
1.86
1.84
1.84
1.83
1.82
1.60
1.59
1.58
1.58
1.57
1.56
1.40
1.39
1.38
1.37
1.36
1.36
1.35
1.34
1.33
1.32
1.32
1.31
1.30
1.29
1.28
1.11
0.92
0.91
0.89
3.80
5.74
0.91
2.31
2.43
10.18
9.00
3.37
f1 (ppm)


135.57
133.11
129.57
127.74
111.14
84.69
63.18
37.85
31.75
29.72
29.25
27.05
25.23
22.67
18.51
14.11
f1 (ppm)

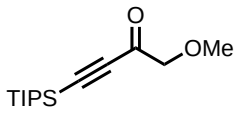
1-Methoxy-4-(triisopropylsilyl)but-3-yn-2-one (3.1c)





To a dried round-bottomed flask charged with methoxy acetic acid (3.0 mL, 40 mmol, 100 mol%) and CH_2Cl_2 (50 mL, 0.8 M) at 0 ^oC were added DMF (0.040 mL, 0.4 mmol) and oxalyl chloride (4.4 mL, 52 mmol, 130 mol%). The reaction mixture was allowed to stir at this temperature for 3 hours. The solvents were removed at reduced pressure and the residue was dissolved in 50 mL of CH_2Cl_2. *N,O*-Dimethyl hydroxylamine hydrochloride (4.4 g, 44 mmol, 110 mol%) and K_2CO_3 (11.0 g, 80 mmol, 200 mol%) were added and the heterogeneous mixture was stirred for 16 h at room temperature. The inorganic solids were removed by filtration and the filtrate was concentrated at reduced pressure to furnish the title compound **sm-3.1c** (2.8 g, 21.0 mmol) in 53% yield as pale yellow oil. The spectroscopic properties of this compound were consistent with the data available in literature.[29]

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.21 (s, 2H), 3.68 (s, 3H), 3.46 (s, 3H), 3.19 (s, 3H) ppm.



The title compound was prepared according to general procedure described in section 3.2 using ethynyltriisopropylsilane (4.3 mL, 19.6 mmol, 100 mol%), THF (65 mL, 0.3 M), *n*-BuLi (7.84 mL, 19.6 mmol, 100 mol%, 2.5 M in hexanes) and **sm-3.1c** (2.61 g, 19.6 mmol, 100 mol%). Upon flash column chromatography (SiO_2, hexanes/ethyl acetate = 9:1) the title compound **sm-3.1c** (3.79 g, 13.1 mmol) was obtained in 67% yield as a yellow oil.

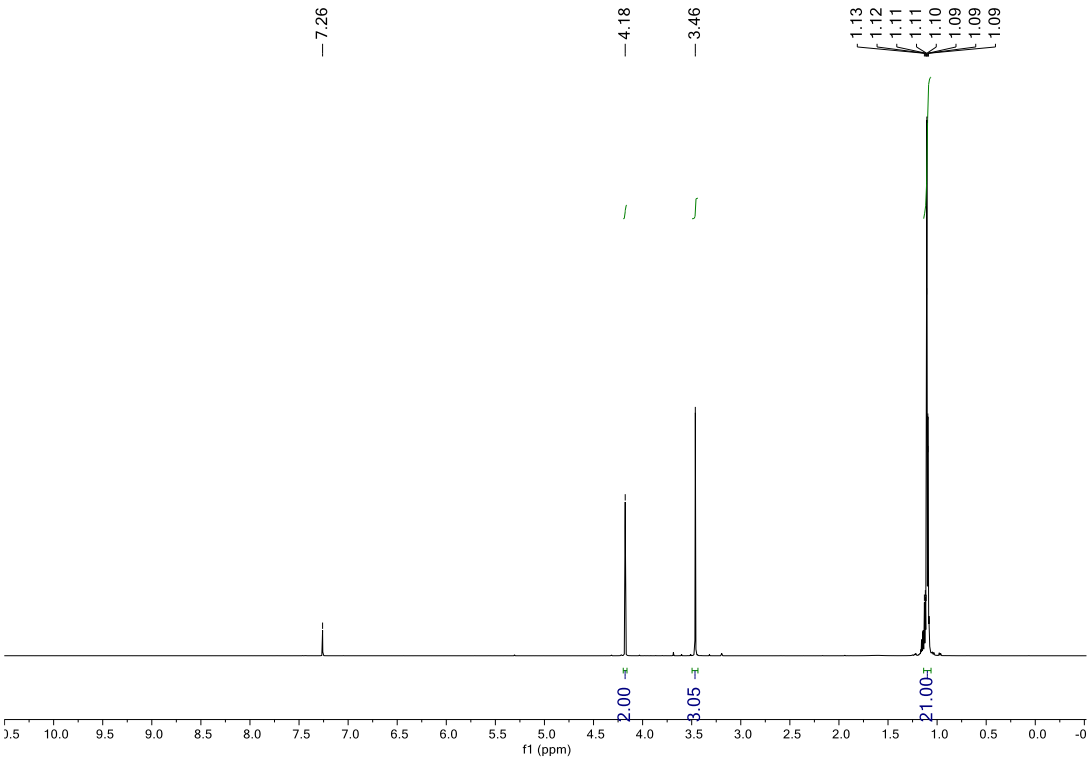
TLC (SiO_2) R_f = 0.36 (hexanes/ethyl acetate = 9:1).

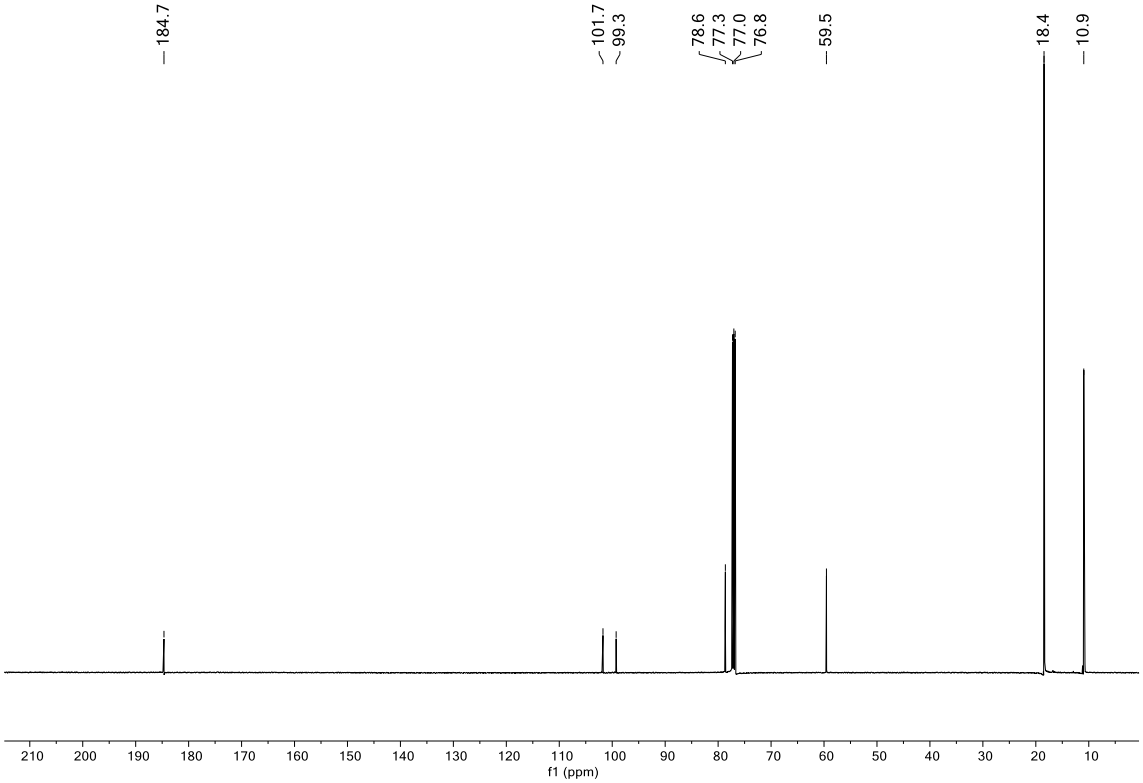
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 – 7.76 (m, 4H), 7.46 – 7.35 (m, 6H), 4.55 (t, *J* = 6.6 Hz, 1H), 1.84 (qd, *J* = 7.0, 4.0 Hz, 2H), 1.62 – 1.54 (m, 2H), 1.39 – 1.26 (m, 10H), 1.11 (s, 9H), 0.91 (t, *J* = 6.7 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.6, 133.1, 129.6, 127.7, 111.1, 84.7, 63.2, 37.9, 31.8, 29.7, 29.3, 27.1, 25.2, 22.7, 18.5, 14.1 ppm.

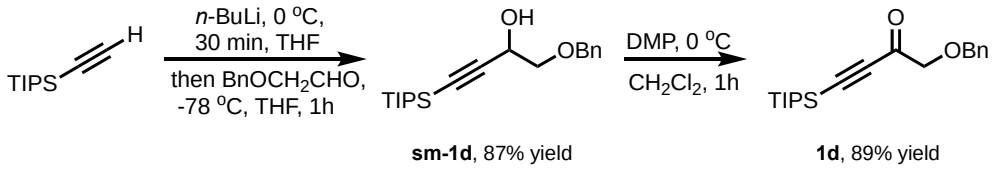
HRMS (ESI) m/z: [M+Na^+] calcd for $C_{14}H_{26}O_2Si$ 277.1594, found 277.1598.

FTIR (ATR) 2956, 2930, 2858, 1715, 1676, 1470, 1428, 1362, 1218, 1132, 1110, 1028, 819, 698 cm^{-1}.

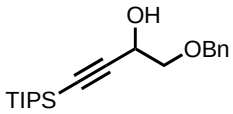

7.26
4.18
3.46
1.13
1.12
1.11
1.11
1.10
1.09
1.09
1.09
2.00
3.05
21.00
f1 (ppm)


184.7
101.7
99.3
78.6
77.3
77.0
76.8
59.5
18.4
10.9
f1 (ppm)

1-(Benzyloxy)-4-(triisopropylsilyl)but-3-yn-2-one (3.1d)



sm-1d, 87% yield **1d**, 89% yield



The title compound was prepared according to general procedure described in section 3.2 using ethynyltriisopropylsilane (0.99 mL, 4.40 mmol, 100 mol%), THF (4.4 mL, 1.0 M), *n*-BuLi (1.9 mL, 4.84 mmol, 110 mol%, 2.5 M in hexanes) and benzyloxyethanal (0.69 g, 4.62 mmol, 105 mol%).[22] Upon flash column chromatography (SiO_2, hexanes/ethyl acetate = 13:1) the title compound **sm-3.1d** (0.91 g, 3.83 mmol) was obtained in 87% yield as a colorless oil.

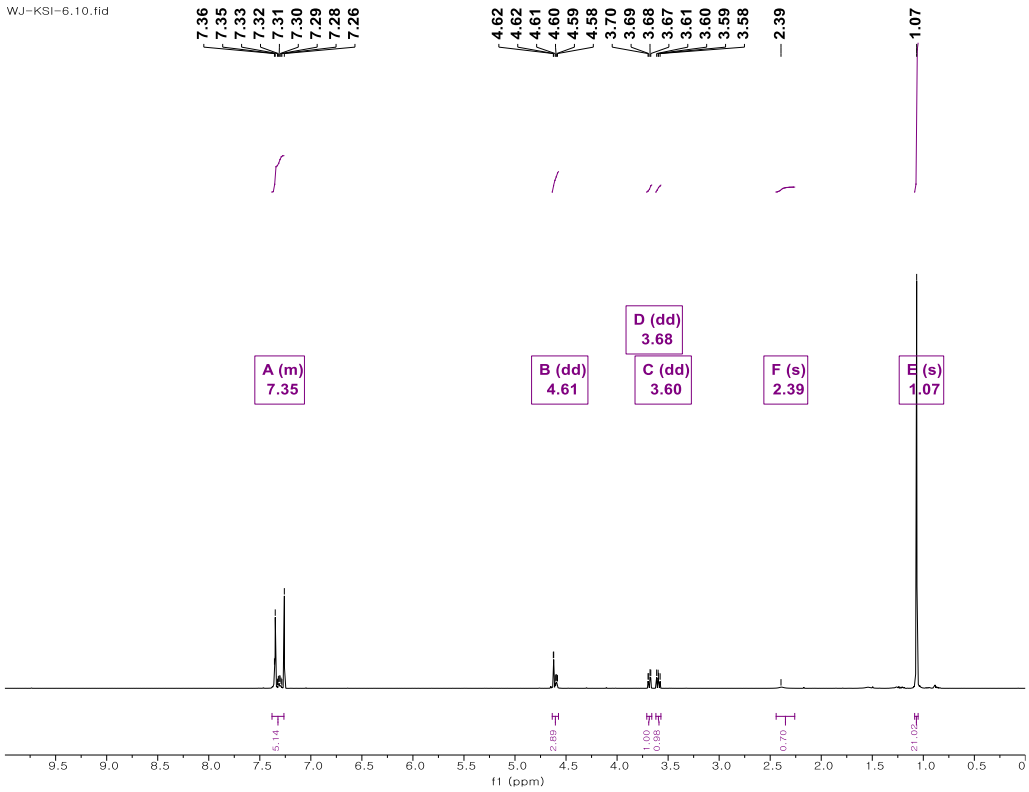
TLC (SiO_2) R_f = 0.38 (hexanes/ethyl acetate = 4:1).

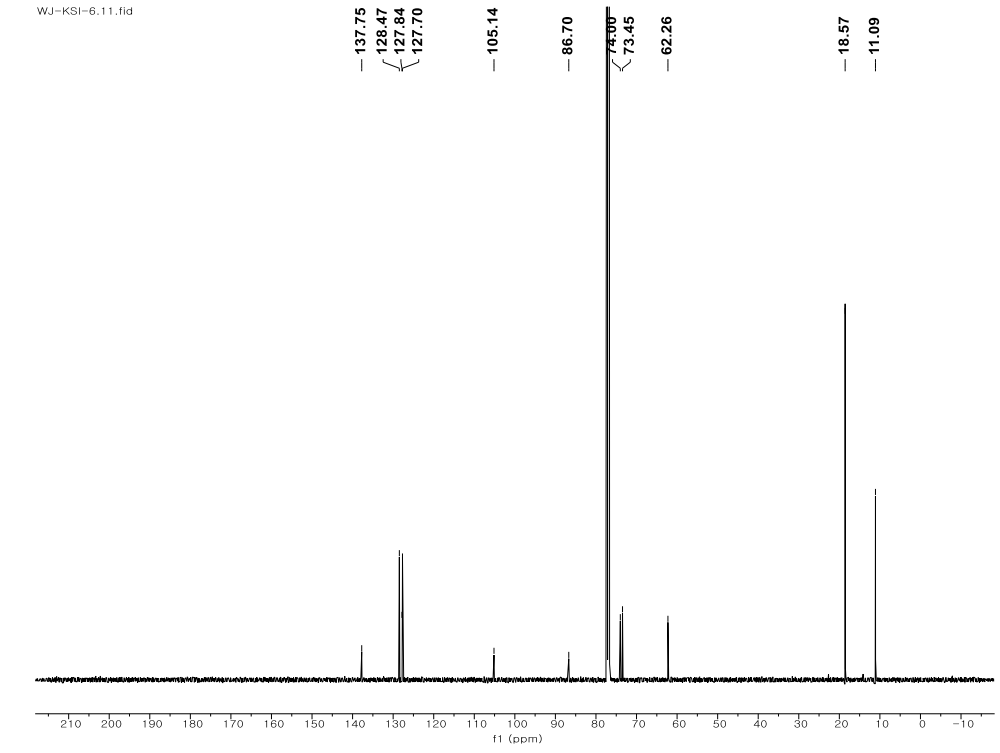
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 5H), 4.61 (dd, J = 14.0, 2.7 Hz, 3H), 3.68 (dd, J = 9.8, 3.6 Hz, 1H), 3.60 (dd, J = 9.8, 7.3 Hz, 1H), 2.39 (s, 1H), 1.07 (s, 21H) ppm.

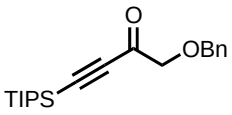
^{13}C NMR (126 MHz, $CDCl_3$) δ 137.8, 128.5, 127.8, 127.7, 105.1, 86.7, 74.0, 73.5, 62.3, 18.6, 11.1 ppm.

HRMS (ESI) m/z: [(M+Na)+] calcd for $C_{20}H_{32}O_2Si$ 355.2064, found 355.2074.

FTIR (ATR) 2942, 2891, 2865, 1462, 1094, 1074, 1017, 997, 883, 733, 697, 677 cm^{-1}.


WJ-KSI-6.10.fid
7.36
7.35
7.33
7.32
7.31
7.30
7.29
7.28
7.26
4.62
4.62
4.61
4.60
4.59
4.58
3.70
3.69
3.68
3.67
3.61
3.60
3.59
3.58
2.39
1.07
A (m)
7.35
B (dd)
4.61
D (dd)
3.68
C (dd)
3.60
F (s)
2.39
E (s)
1.07
5.14
2.89
1.00
0.98
0.70
21.02
f1 (ppm)


WJ-KSI-6.11.fid
137.75
128.47
127.84
127.70
105.14
86.70
74.00
73.45
62.26
18.57
11.09
f1 (ppm)



To a dried round-bottomed flask charged with 1-(benzyloxy)-4-(triisopropylsilyl)but-3-yn-2-ol (**sm-3.1d**, 1.20 g, 3.6 mmol, 100 mol%), CH_2Cl_2 (18 mL, 0.2 M) and $NaHCO_3$ (1.21 g, 14.4 mmol, 400 mol%) at 0 ^oC, was added Dess–Martin periodinane (DMP, 1.68 g, 3.96 mmol, 110 mol%). The reaction mixture was allowed to stir at room temperature for 2 hours. The mixture was filtered through a celite plug with the aid of DCM. The filtrate was transferred to a separatory funnel and washed with saturated Na_2CO_3 and brine. The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was subjected to flash column chromatography (SiO_2, hexanes/ethyl acetate = 20:1) to furnish the title compound **3.1d** (1.06 g, 3.20 mmol) in 89% yield as a colorless oil.

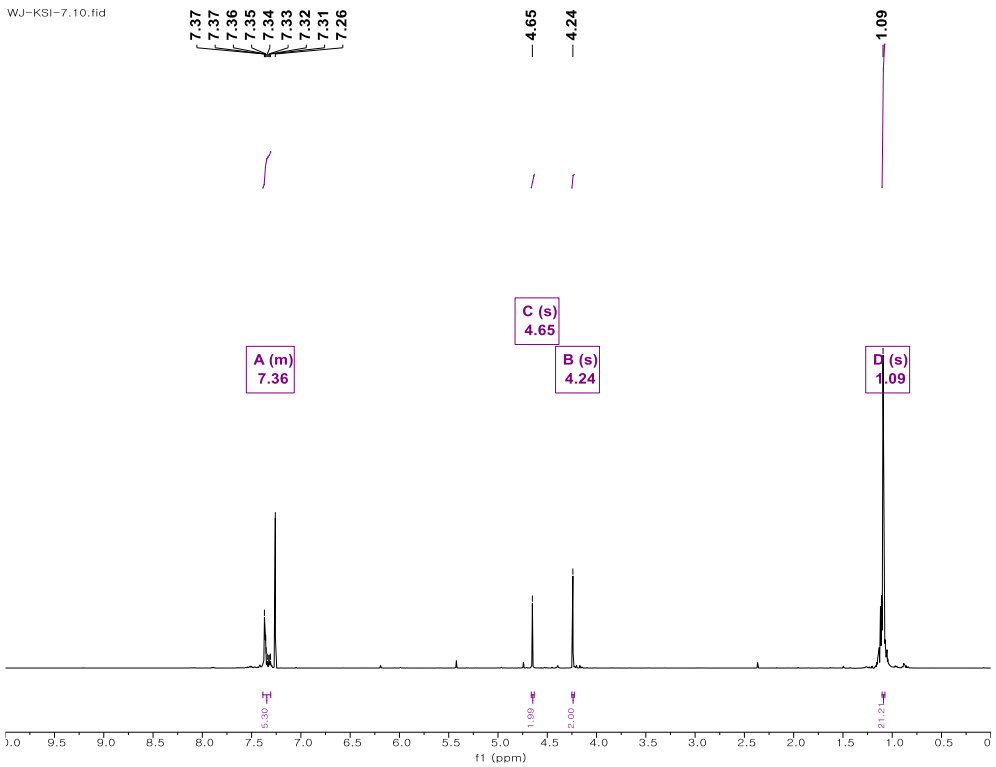
TLC (SiO_2) R_f = 0.66 (hexanes/ethyl acetate = 4:1).

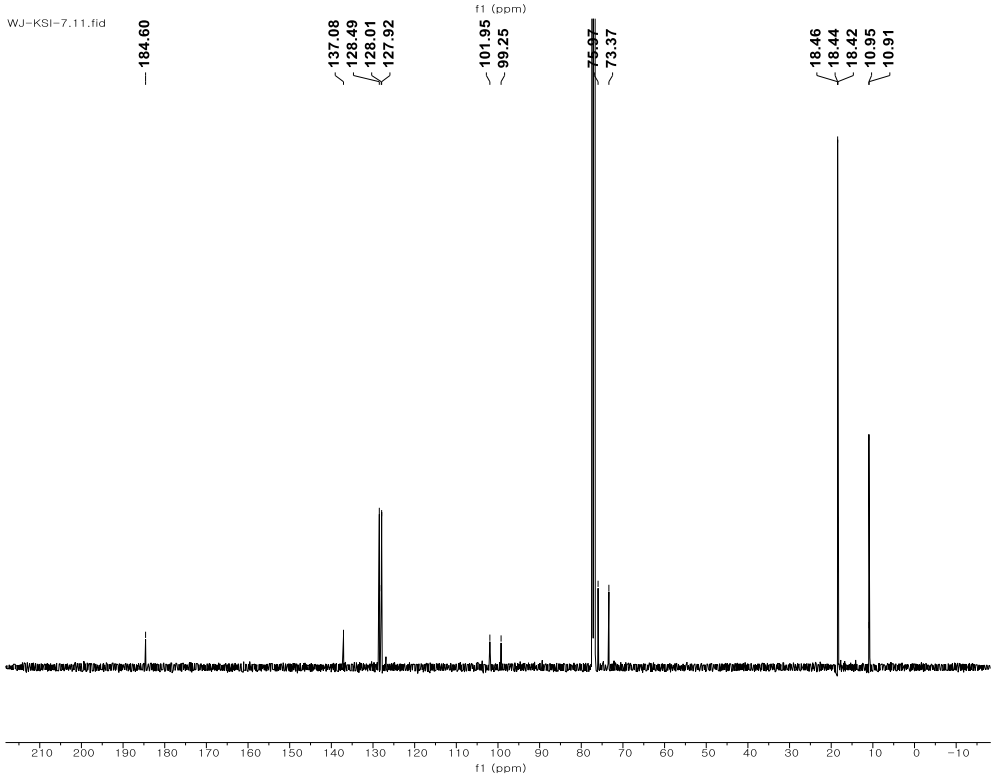
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 5H), 4.65 (s, 2H), 4.24 (s, 2H), 1.09 (s, 21H). ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 184.6, 137.1, 128.5, 128.0, 127.9, 102.0, 99.3, 76.0, 73.4, 18.5, 18.4, 18.4, 11.0, 10.9 ppm.

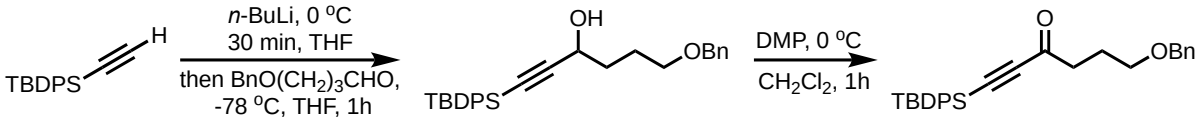
HRMS (ESI) m/z: [(M+Na)+] calcd for $C_{20}H_{30}O_2Si$ 353.1907, found 353.1917.

FTIR (ATR) 2944, 2891, 2866, 1693, 1678, 1463, 1385, 1368, 1202, 1071, 1018, 997, 883, 853, 817, 737, 697, 679 cm^{-1}.

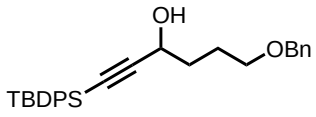

WJ-KSI-7.10.fid
7.37
7.37
7.36
7.35
7.34
7.33
7.32
7.31
7.26
4.65
4.24
1.09
C (s)
4.65
A (m)
7.36
B (s)
4.24
D (s)
1.09
5.30
1.99
2.00
21.2
f1 (ppm)


WJ-KSI-7.11.fid
184.60
137.08
128.49
128.01
127.92
101.95
99.25
75.07
73.37
18.46
18.44
18.42
10.95
10.91
f1 (ppm)

6-(Benzyloxy)-1-(*tert*-butyldiphenylsilyl)hex-1-yn-3-one (3.1e)



sm-1e, 57% yield **1e**, 68% yield



The title compound was prepared according to general procedure using *tert*-butyl(ethynyl)diphenylsilane (1.10 g, 4.16 mmol, 100 mol%), THF (14 mL, 0.3 M), *n*-BuLi (1.66 mL, 4.16 mmol, 100 mol%) and 4-(benzyloxy)butanal (0.81 mL, 4.58 mmol, 110 mol%). Upon flash column chromatography (SiO_2, hexanes/ethyl acetate 9:1) title compound **sm-3.1e** (1.05 g, 2.37 mmol) was obtained in 57% yield as a yellow oil.

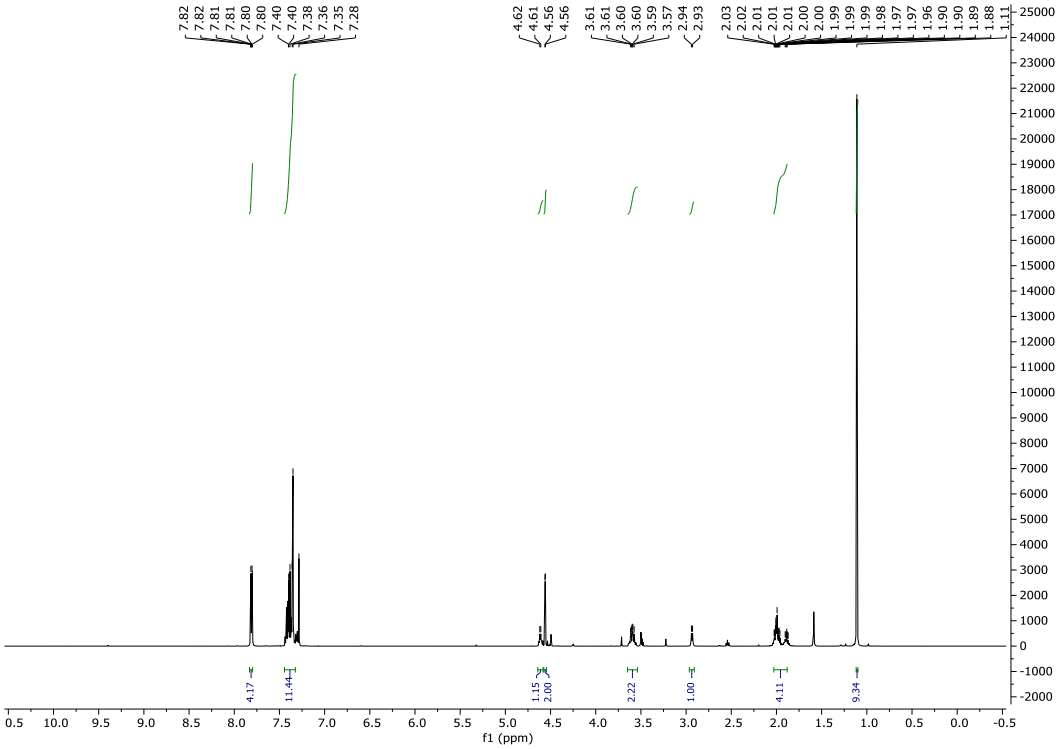
TLC (SiO_2) R_f = 0.35 (hexanes/ethyl acetate = 9:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ.84 – 7.78 (m, 4H), 7.44 – 7.32 (m, 11H), 4.61 (d, *J* = 5.7 Hz, 1H), 4.56 (d, *J* = 2.1 Hz, 2H), 3.65 – 3.54 (m, 2H), 2.93 (d, *J* = 6.1 Hz, 1H), 2.04 – 1.86 (m, 5H), 1.11 (s, 10H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.1, 135.6, 133.1, 129.5, 128.4, 127.7, 127.7, 127.7, 111.0, 73.0, 70.0, 62.7, 35.4, 27.1, 25.6, 18.5 ppm.

HRMS (ESI) m/z: [M+Na^+] calcd for $C_{29}H_{34}O_2Si$ 456.2220, found 456.2216.

FTIR (ATR) 2929, 2856, 2171, 1470, 1453, 1428, 1351, 1198, 1108, 1008, 937, 819, 738, 696 cm^{-1}.


7.82
7.82
7.81
7.81
7.80
7.80
7.40
7.40
7.38
7.36
7.35
7.28
4.62
4.61
4.56
4.56
3.61
3.61
3.60
3.60
3.59
3.57
2.94
2.93
2.03
2.02
2.01
2.01
2.01
2.00
2.00
1.99
1.99
1.99
1.98
1.97
1.96
1.90
1.90
1.89
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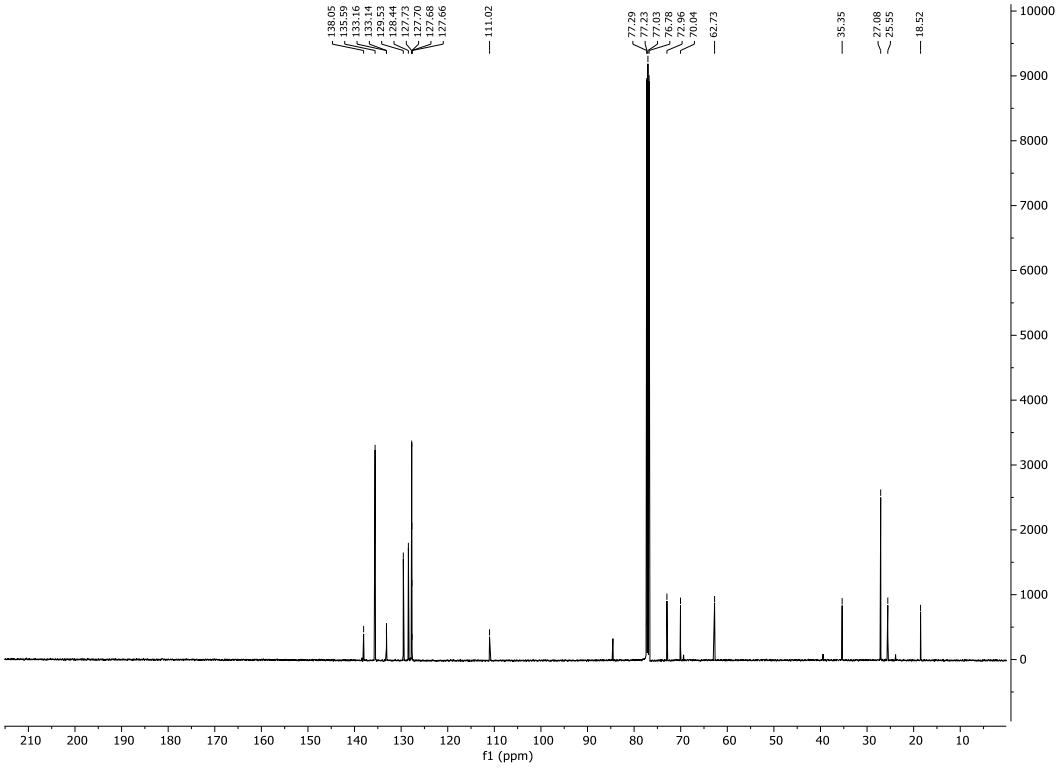
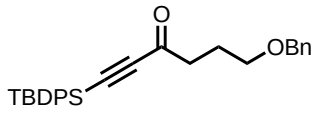
2.00
2.22
1.00
4.11
9.34
f1 (ppm)


138.05
135.59
133.16
131.14
129.53
128.44
127.73
127.70
127.68
127.66
111.02
77.29
77.23
77.03
76.78
72.96
70.04
62.73
35.35
27.08
25.55
18.52
f1 (ppm)



The title compound **3.1e** was prepared according to general procedure using **sm-3.1e** (0.58 g, 1.29 mmol, 100 mol%), DMP (0.66 g, 1.54 mmol, 120 mol%), $NaHCO_3$ (0.43 g, 5.16 mmol, 400 mol%) and DCM (6.5 mL, 0.2 M). Upon flash column chromatography (hexanes/ethyl acetate 9:1) title compound (0.39 g, 0.88 mmol) was obtained in 68% yield as a yellow oil.

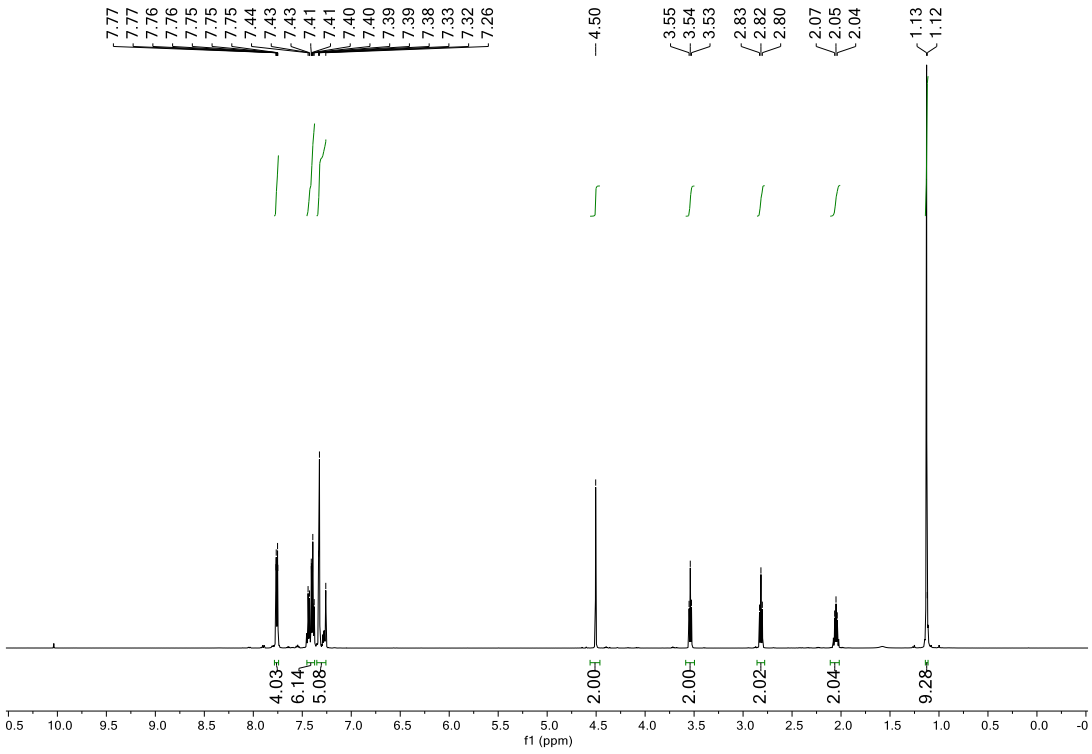
TLC (SiO_2) R_f = 0.41 (hexanes/ethyl acetate = 9:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (dt, *J* = 6.8, 1.3 Hz, 4H), 7.45 – 7.37 (m, 6H), 7.33 (d, *J* = 4.5 Hz, 5H), 4.50 (s, 2H), 3.54 (t, *J* = 6.1 Hz, 2H), 2.82 (t, *J* = 7.2 Hz, 2H), 2.05 (t, *J* = 6.7 Hz, 2H), 1.13 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 187.0, 135.6, 131.5, 130.1, 128.4, 128.0, 127.6, 127.6, 72.9, 68.9, 42.5, 27.0, 24.1, 18.7 ppm.

HRMS (ESI) m/z: [$M+Na^+$] calcd for $C_{29}H_{32}O_2Si$ 463.2064, found 463.2070.

FTIR (ATR) 3068, 2929, 2857, 1675, 1470, 1428, 1361, 1221, 1110, 1065, 819, 738, 696 cm^{-1}.


7.77
7.77
7.76
7.76
7.75
7.75
7.75
7.44
7.43
7.43
7.41
7.41
7.40
7.40
7.39
7.39
7.38
7.33
7.32
7.26
4.50
3.55
3.54
3.53
2.83
2.82
2.80
2.07
2.05
2.04
1.13
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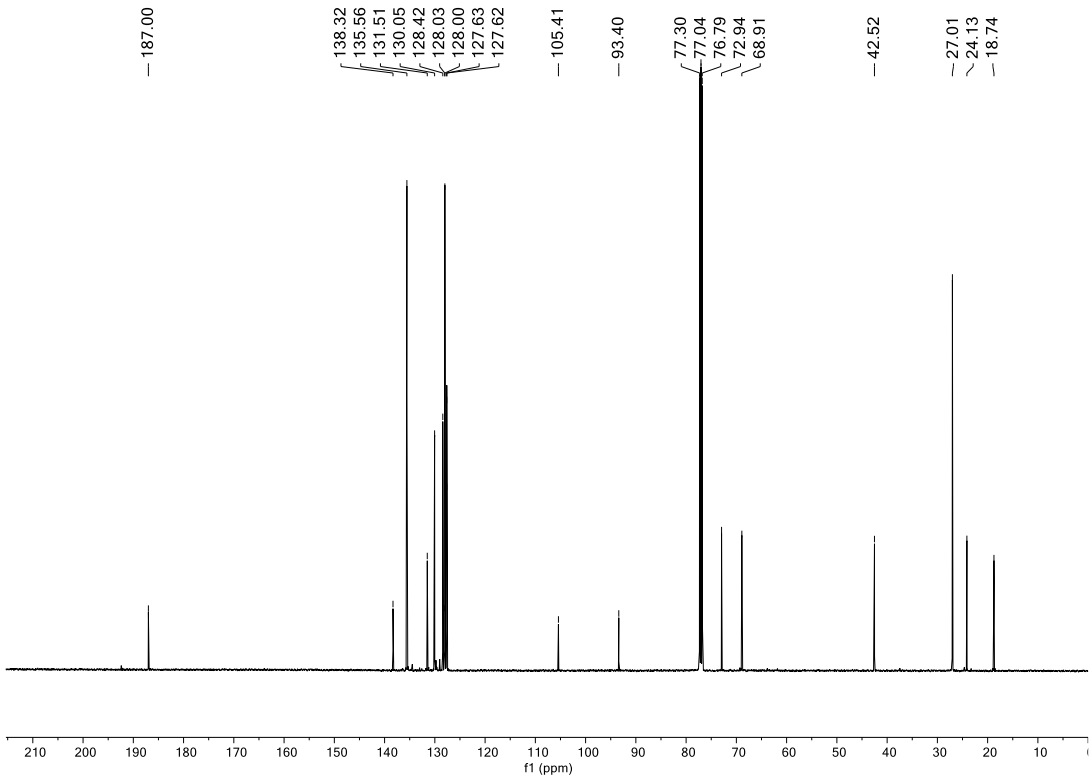
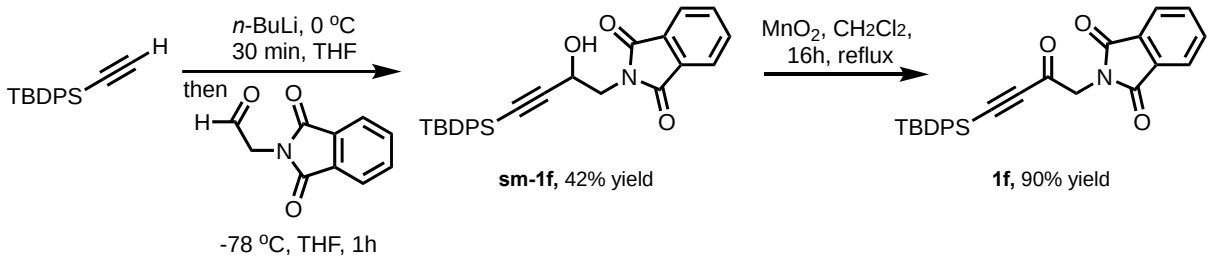
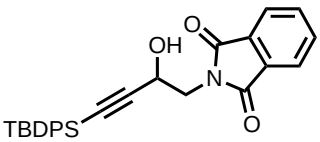
4.03
6.14
5.08
2.00
2.00
2.02
2.04
9.28
f1 (ppm)


187.00
138.32
135.56
131.51
130.05
128.42
128.03
128.00
127.63
127.62
105.41
93.40
77.30
77.04
76.79
72.94
68.91
42.52
27.01
24.13
18.74
f1 (ppm)

2-(4-(*tert*-Butyldiphenylsilyl)-2-oxobut-3-yn-1-yl)isoindoline-1,3-dione (3.1f)





The title compound was prepared according to general procedure using *tert*-butyl(ethynyl)diphenylsilane (1.41 g, 5.33 mmol, 100 mol%), THF (10 mL, 0.5 M), *n*-BuLi (2.13 mL, 5.33 mmol, 100 mol%, 2.5 M in hexanes) and 2-(1,3-dioxoisoindolin-2-yl)acetaldehyde (1.09 mL, 5.33 mmol, 100 mol%). Upon flash column chromatography (SiO_2, hexanes/ethyl acetate = 1:1) title compound **sm-3.1f** (1.01 g, 2.24 mmol) was obtained in 42% yield as a colorless oil.

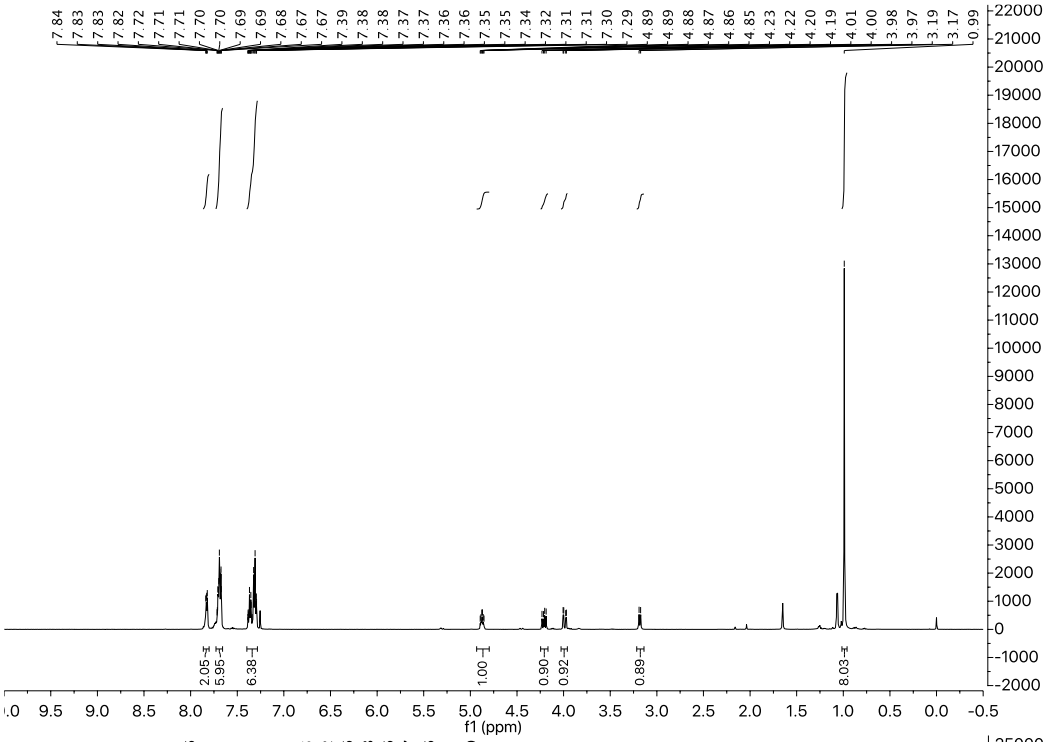
TLC (SiO_2) R_f = 0.37 (hexanes/ethyl acetate = 3:1).

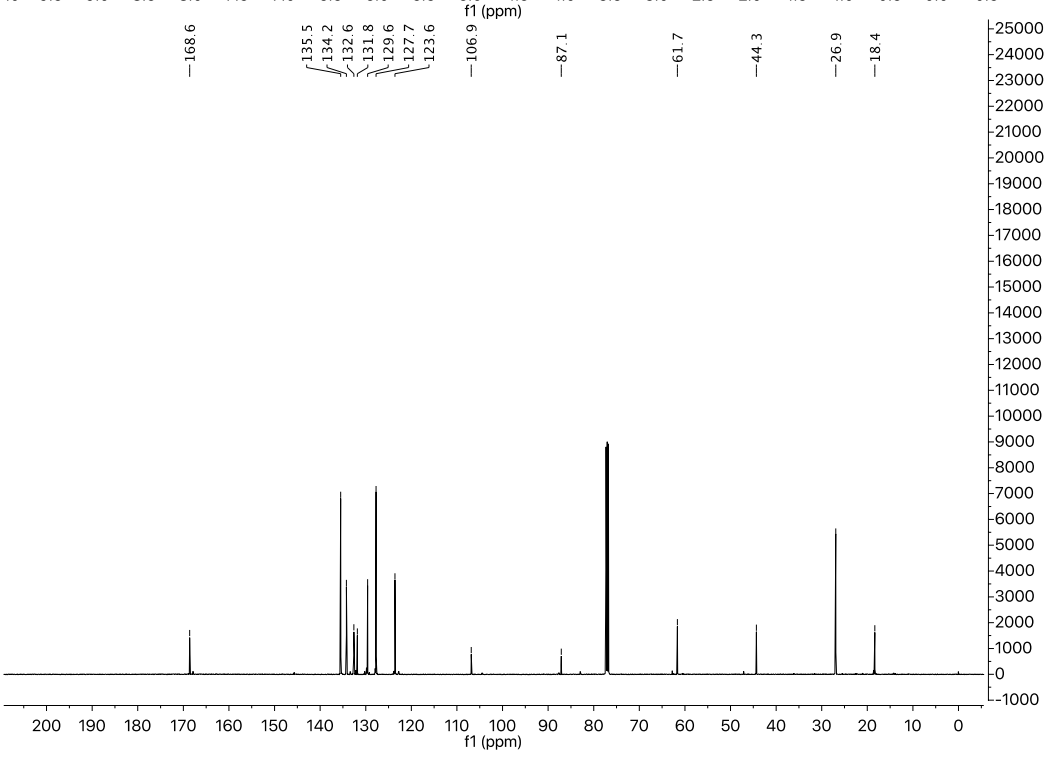
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.69 (ddd, *J* = 8.4, 6.0, 2.5 Hz, 6H), 7.40 – 7.28 (m, 6H), 4.87 (td, *J* = 8.2, 3.7 Hz, 1H), 4.21 (dd, *J* = 14.2, 7.9 Hz, 1H), 3.99 (dd, *J* = 14.3, 3.7 Hz, 1H), 3.18 (d, *J* = 8.4 Hz, 1H), 0.99 (s, 8H).

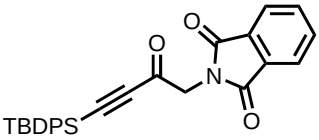
^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6, 135.5, 134.2, 132.6, 131.9, 129.6, 127.7, 123.6, 106.9, 87.1, 61.7, 44.3, 26.9, 18.4.

HRMS (ESI) m/z: [M+Na^+] calcd for $C_{28}H_{27}NO_3Si$ 476.1652, found 476.1655.

FTIR (ATR) 2930, 2857, 1773, 1708, 1469, 1428, 1394, 1361, 1110, 974, 906, 727, 715, 698, 674 cm^{-1}.


7.84 7.83 7.83 7.82 7.72 7.71 7.71 7.70 7.70 7.69 7.69 7.68 7.67 7.67 7.39 7.38 7.38 7.37 7.37 7.36 7.36 7.35 7.35 7.34 7.32 7.31 7.31 7.30 7.29 4.89 4.89 4.88 4.87 4.86 4.85 4.23 4.22 4.20 4.19 4.01 4.00 3.98 3.97 3.19 3.17 0.99
2.05 5.95 6.38 1.00 0.90 0.92 0.89 8.03
f1 (ppm)


168.6 135.5 134.2 132.6 131.8 129.6 127.7 123.6 106.9 87.1 61.7 44.3 26.9 18.4
f1 (ppm)



The title compound was prepared according to general procedure using **sm-3.1f** (1.0 g, 2.20 mmol, 100 mol%), CH_2Cl_2 (8 mL, 0.3 M) and MnO_2 (3.83 g, 44.1 mmol, 20 equiv). Upon flash column chromatography (SiO_2, hexanes/ethyl acetate 3:1) title compound **3.1f** (0.89 g, 1.98 mmol) was obtained in 90% yield as a white solid.

TLC (SiO_2) R_f = 0.38 (hexanes/ethyl acetate = 3:1).

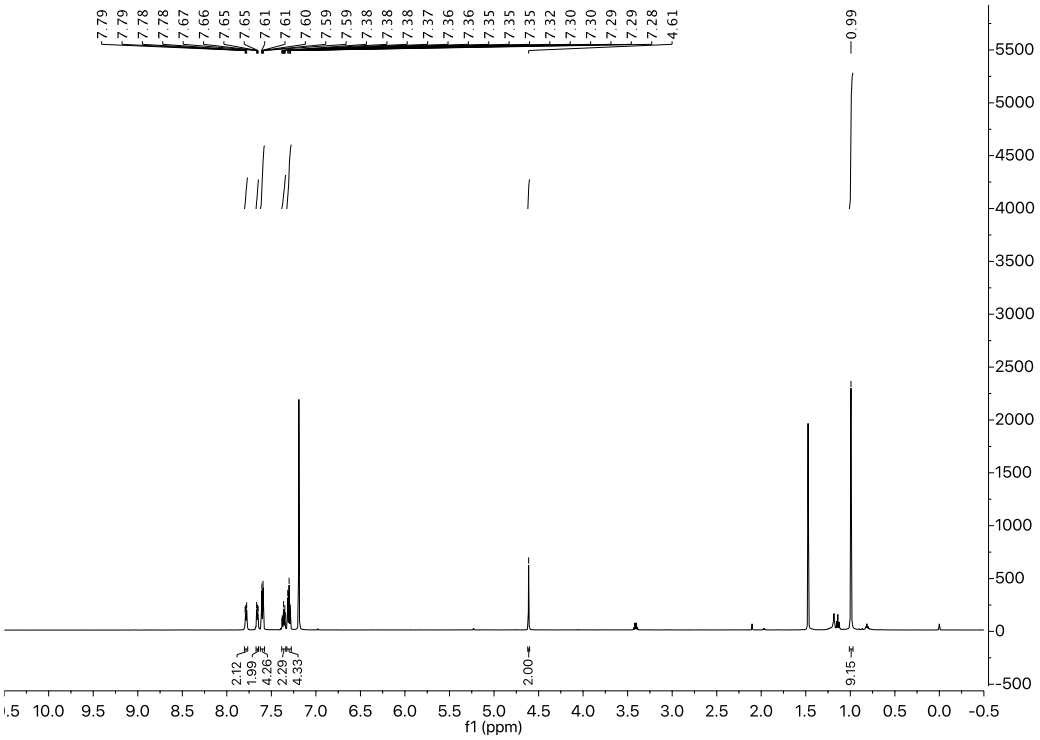
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.66 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.62 – 7.58 (m, 4H), 7.38 – 7.34 (m, 2H), 7.33 – 7.28 (m, 4H), 4.61 (s, 2H), 0.99 (s, 9H) ppm.

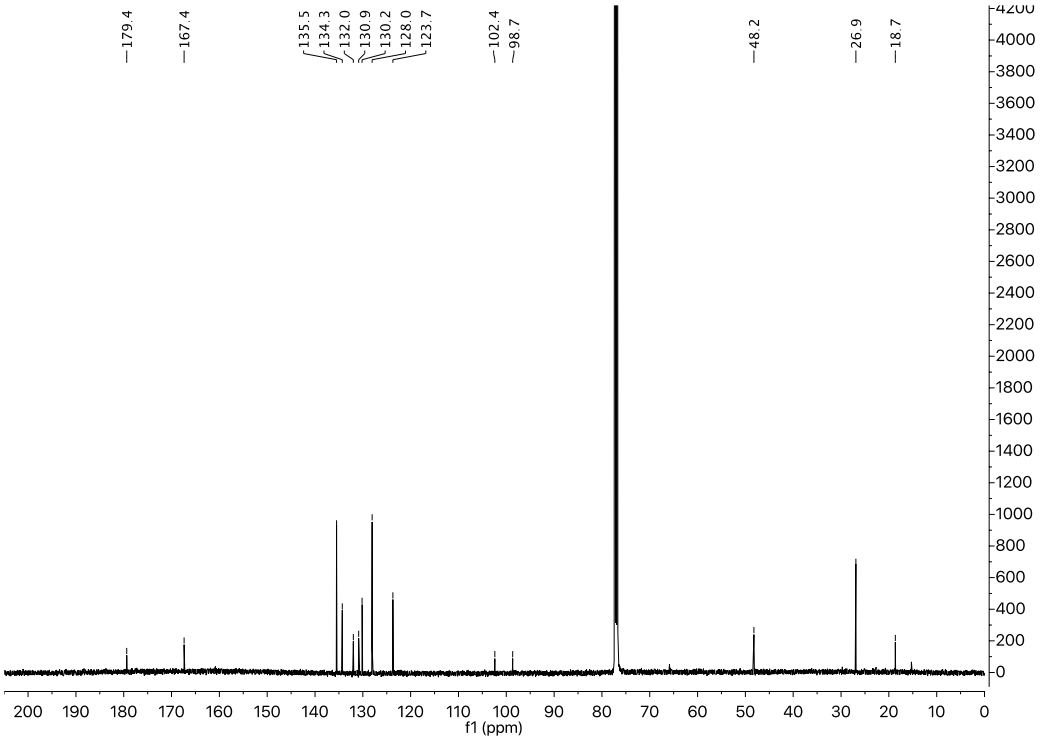
^{13}C NMR (126 MHz, $CDCl_3$) δ 179.4, 167.4, 135.5, 134.3, 132.0, 130.9, 130.2, 128.1, 123.7, 102.4, 98.7, 48.2, 26.9, 18.7 ppm.

HRMS (ESI) m/z: [M+Na^+] calcd for $C_{28}H_{25}NO_3Si$ 474.1496, found 474.1503.

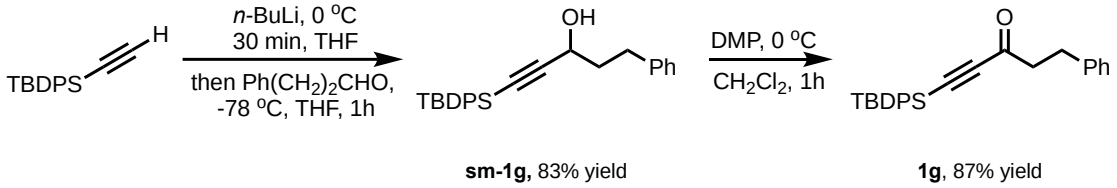
FTIR (ATR) 2963, 2930, 1772, 1720, 1683, 1466, 1429, 1406, 1383, 1307, 1113, 1100, 1088, 943, 739, 700 cm^{-1}.

MP: 145-147 °C


7.79
7.79
7.78
7.78
7.67
7.66
7.65
7.65
7.61
7.61
7.60
7.59
7.59
7.38
7.38
7.38
7.37
7.36
7.36
7.35
7.35
7.35
7.32
7.30
7.30
7.29
7.29
7.28
4.61
0.99
2.12
1.99
4.26
2.29
4.33
2.00
9.15
f1 (ppm)

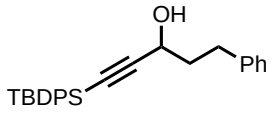

179.4
167.4
135.5
134.3
132.0
130.9
130.2
128.0
123.7
102.4
98.7
48.2
26.9
18.7
f1 (ppm)

1-(*tert*-Butyldiphenylsilyl)-5-phenylpent-1-yn-3-one (3.1g)



sm-1g, 83% yield

1g, 87% yield



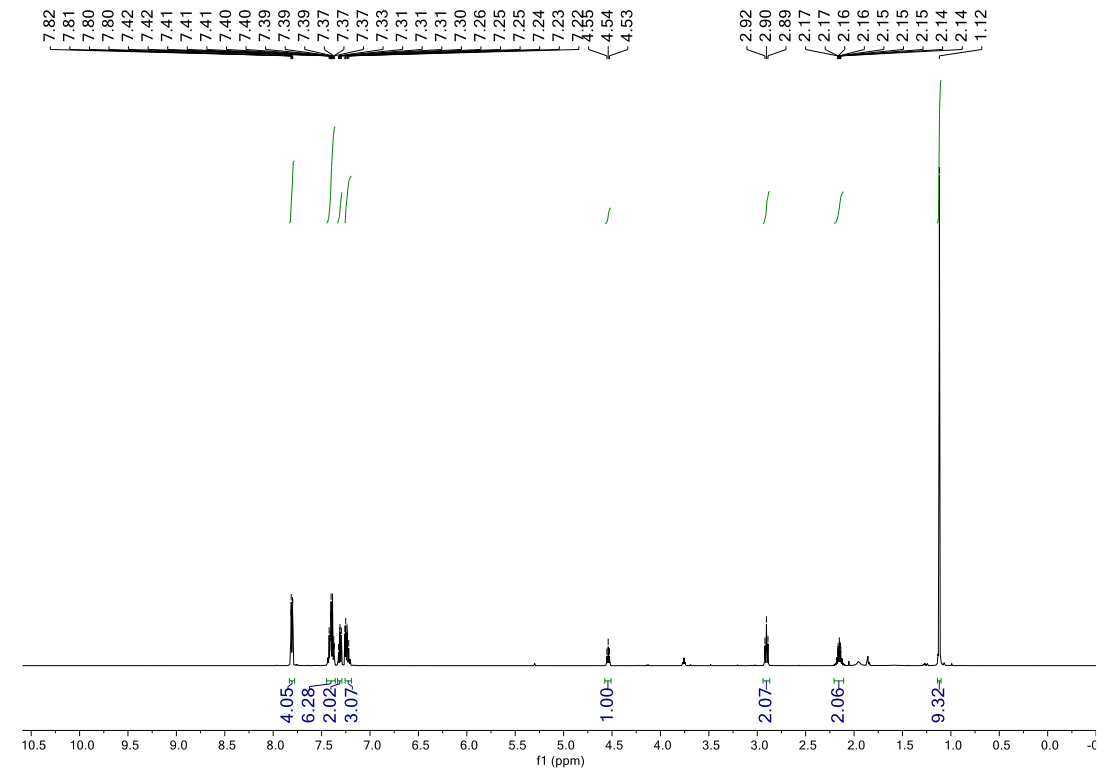
The title compound **sm-3.1g** was prepared according to general procedure using *tert*-butyl(ethynyl)diphenylsilane (4.62 g, 17.5 mmol, 100 mol%) 3-phenylpropanal (2.57 g, 19.3 mmol, 110 mol%), *n*-BuLi (7.0 mL, 17.5 mmol, 100 mol%, 2.5 M in hexanes) and THF (88 mL, 0.2 M). Upon flash column chromatography (SiO_2, hexanes/ethylacetate = 9:1) title compound **sm-3.1g** (5.79 g, 14.5 mmol) was obtained in 83% yield as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 7.8, 1.7 Hz, 4H), 7.45 – 7.36 (m, 6H), 7.34 – 7.29 (m, 2H), 7.26 – 7.19 (m, 3H), 4.54 (t, *J* = 6.5 Hz, 1H), 2.90 (t, *J* = 7.9 Hz, 2H), 2.21 – 2.11 (m, 2H), 1.12 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.3, 135.6, 133.0, 129.6, 128.6, 128.5, 127.8, 126.1, 110.7, 62.4, 39.5, 31.6, 27.1, 18.5 ppm.

HRMS (ESI) m/z: [M+Na^+] calcd for $C_{27}H_{30}OSi$ 421.1958, found 421.1971.

FTIR (ATR) 2928, 2856, 1470, 1428, 1109, 1044, 1008, 819, 740, 696 cm^{-1}.


7.82
7.81
7.80
7.80
7.42
7.42
7.41
7.41
7.41
7.40
7.40
7.39
7.39
7.39
7.37
7.37
7.37
7.33
7.31
7.31
7.31
7.30
7.26
7.25
7.25
7.24
7.23
4.55
4.54
4.53
2.92
2.90
2.89
2.17
2.17
2.16
2.16
2.15
2.15
2.15
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2.14
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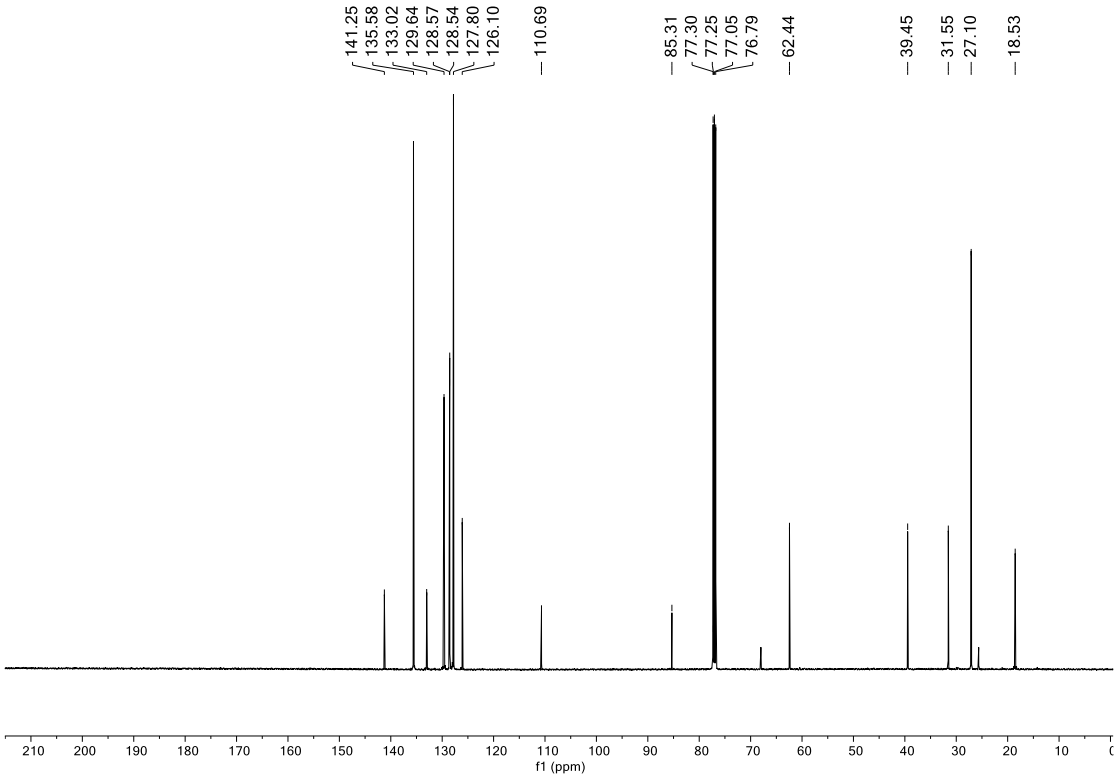
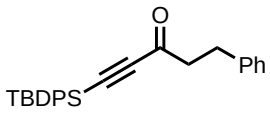
4.05
6.28
2.02
3.07
1.00
2.07
2.06
9.32
f1 (ppm)


141.25
135.58
133.02
129.64
128.57
128.54
127.80
126.10
110.69
85.31
77.30
77.25
77.05
76.79
62.44
39.45
31.55
27.10
18.53
f1 (ppm)



The title compound **3.1g** was prepared according to general procedure using **sm-3.1g** (3.0 g, 7.53 mmol, 100 mol%), DMP (3.83 g, 9.03 mmol, 120 mol%), $NaHCO_3$ (2.53 g, 30.12 mmol, 400 mol%) and CH_2Cl_2 (38 mL, 0.2 M). Upon flash column chromatography (SiO_2, hexanes/ethyl acetate = 9:1) the title compound (2.60 g, 6.55 mmol) was obtained in 87% yield as a pale yellow oil.

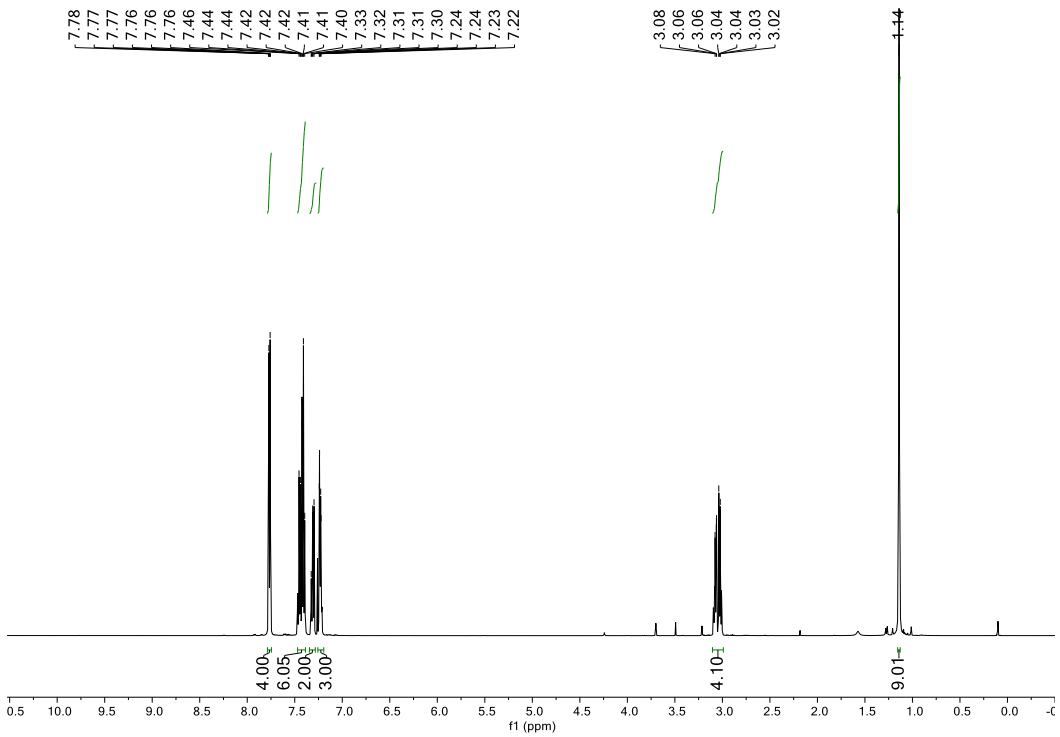
TLC (SiO_2) R_f = 0.56 (hexanes/ethyl acetate = 9:1).

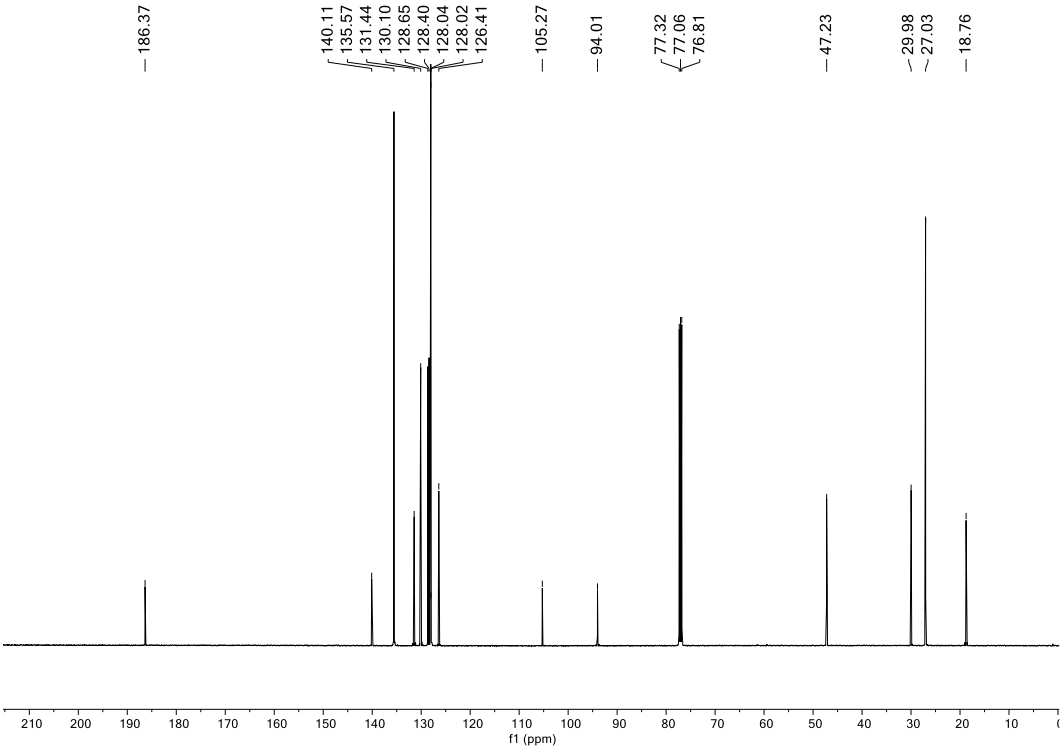
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (dt, *J* = 6.7, 1.5 Hz, 4H), 7.47 – 7.39 (m, 6H), 7.35 – 7.28 (m, 2H), 7.26 – 7.19 (m, 3H), 3.10 – 2.99 (m, 4H), 1.14 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 186.4, 140.1, 135.6, 131.4, 130.1, 128.7, 128.4, 128.0, 126.4, 105.3, 94.0, 47.2, 30.0, 27.0, 18.8 ppm.

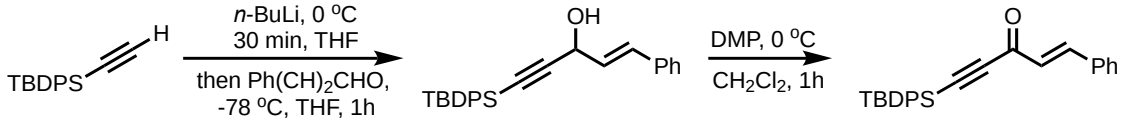
HRMS (ESI) m/z: [M+Na^+] calcd for $C_{27}H_{28}OSi$ 419.1802, found 419.1814.

FTIR (ATR) 2930, 2857, 1676, 1428, 1192, 1103, 818, 741, 696 cm^{-1}.


7.78
7.77
7.77
7.76
7.76
7.76
7.46
7.44
7.44
7.42
7.42
7.42
7.41
7.41
7.40
7.33
7.32
7.31
7.31
7.30
7.24
7.23
7.22
3.08
3.06
3.06
3.04
3.04
3.03
3.02
1.14
4.00
6.05
2.00
3.00
4.10
9.01
f1 (ppm)

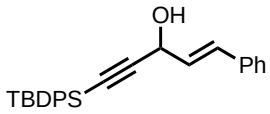

186.37
140.11
135.57
131.44
130.10
128.65
128.40
128.04
128.02
126.41
105.27
94.01
77.32
77.06
76.81
47.23
29.98
27.03
18.76
f1 (ppm)

(*E*)-5-(*tert*-Butyldiphenylsilyl)-1-phenylpent-1-en-4-yn-3-one (3.1h)



sm-1h, 90% yield

1h, 97% yield



The title compound **sm-3.1h** was prepared according to general procedure using *tert*-butyl(ethynyl)diphenylsilane (0.40 g, 1.50 mmol, 100 mol%) cinnamaldehyde (0.22 g, 1.66 mmol, 110 mol%), *n*-BuLi (0.60 mL, 1.50 mmol, 100 mol%, 2.5 M in hexanes) and THF (7.5 mL, 0.2 M). Upon flash column chromatography (SiO_2, hexanes/ethyl acetate = 9:1) the title compound **sm-3.1h** (0.54 g, 1.35 mmol) was obtained in 90% yield as a pale yellow oil.

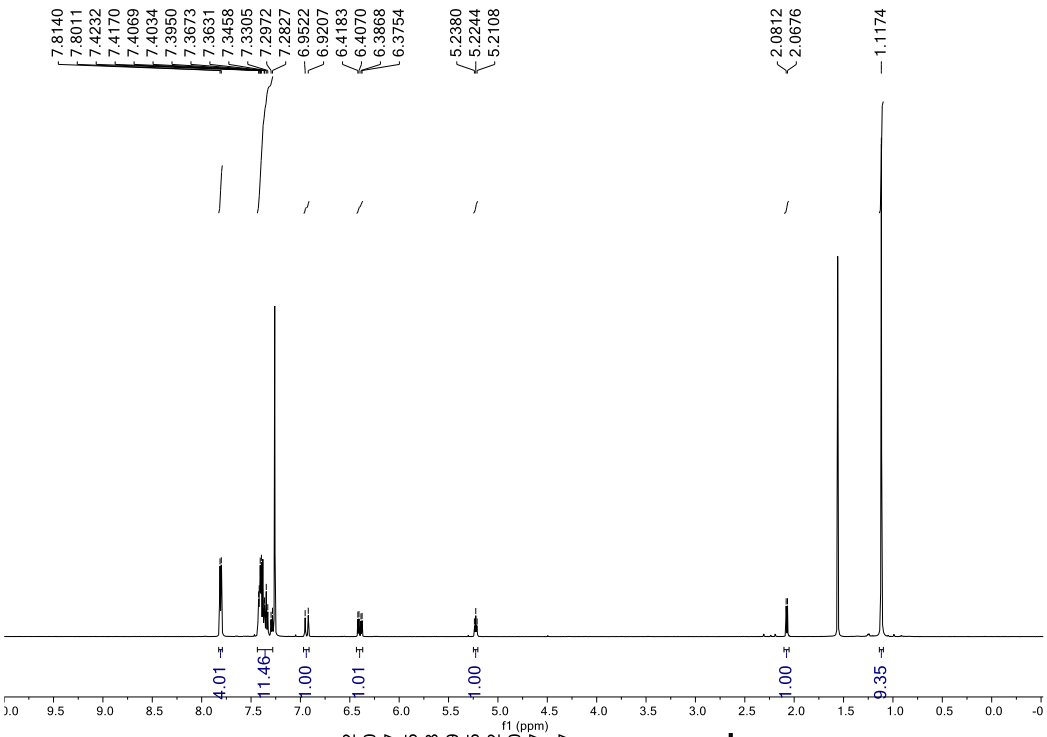
TLC (SiO_2) R_f = 0.22 (hexanes/ethyl acetate = 9:1).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.81 (d, *J* = 6.4 Hz, 4H), 7.44 – 7.28 (m, 11H), 6.94 (d, *J* = 15.7 Hz, 1H), 6.40 (dd, *J* = 15.8, 5.7 Hz, 1H), 5.22 (t, *J* = 6.8 Hz, 1H), 2.07 (d, *J* = 6.8 Hz, 1H), 1.12 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.0, 135.6, 132.9, 132.6, 129.7, 128.7, 128.3, 127.8, 127.6, 126.9, 108.3, 87.0, 63.6, 27.1, 18.6 ppm.

HRMS (ESI) m/z: [M+Na^+] calcd for $C_{27}H_{30}OSi$ 421.1958, found 421.1970.

FTIR (ATR) 2929, 2857, 1736, 1626, 1595, 1428, 1363, 1232, 1198, 1110, 859, 819, 741, 762, 696 cm^{-1}.


7.8140
7.8011
7.4232
7.4170
7.4069
7.4034
7.3950
7.3673
7.3631
7.3458
7.3305
7.2972
7.2827
6.9522
6.9207
6.4183
6.4070
6.3868
6.3754
5.2380
5.2244
5.2108
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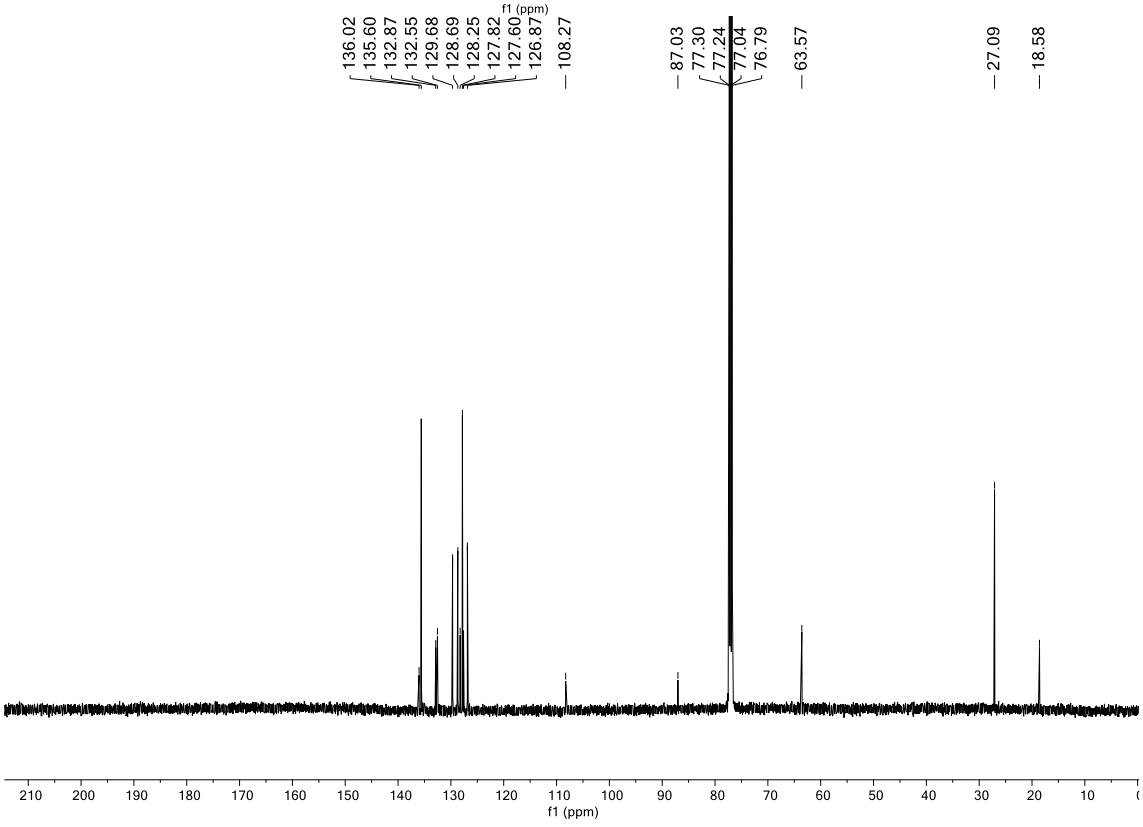
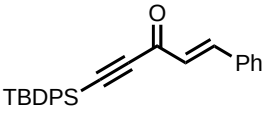
1.00
1.01
1.00
1.00
9.35
f1 (ppm)


136.02
135.60
132.87
132.55
129.68
128.69
128.25
127.82
127.60
126.87
108.27
87.03
77.30
77.24
77.04
76.79
63.57
27.09
18.58
f1 (ppm)



The title compound **3.1h** was prepared according to general procedure using **sm-3.1h** (0.22 g, 0.55 mmol, 100 mol%), DMP (0.28 g, 0.66 mmol, 120 mol%), $NaHCO_3$ (0.18 g, 2.20 mmol, 400 mol%) and CH_2Cl_2 (3 mL, 0.2 M). Upon flash column chromatography (SiO_2, hexanes/ethyl acetate = 9:1) the title compound **3.1h** (0.21 g, 0.53 mmol) was obtained in 97% yield as a pale yellow oil.

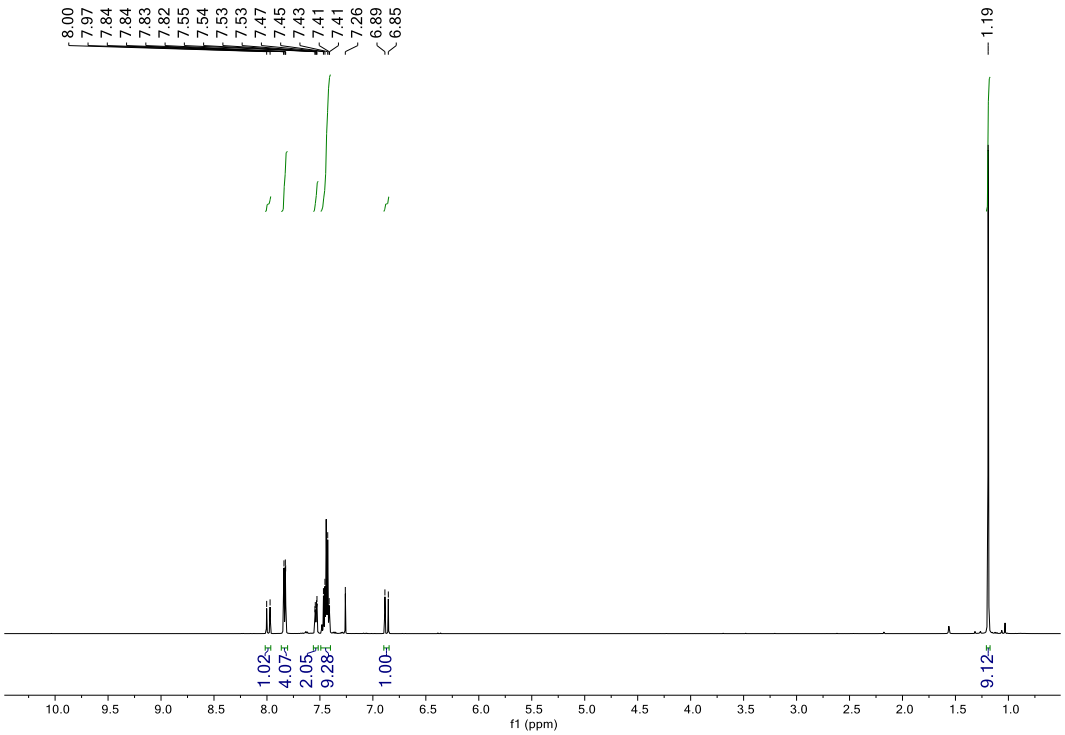
TLC (SiO_2) R_f = 0.49 (hexanes/ethyl acetate = 9:1).

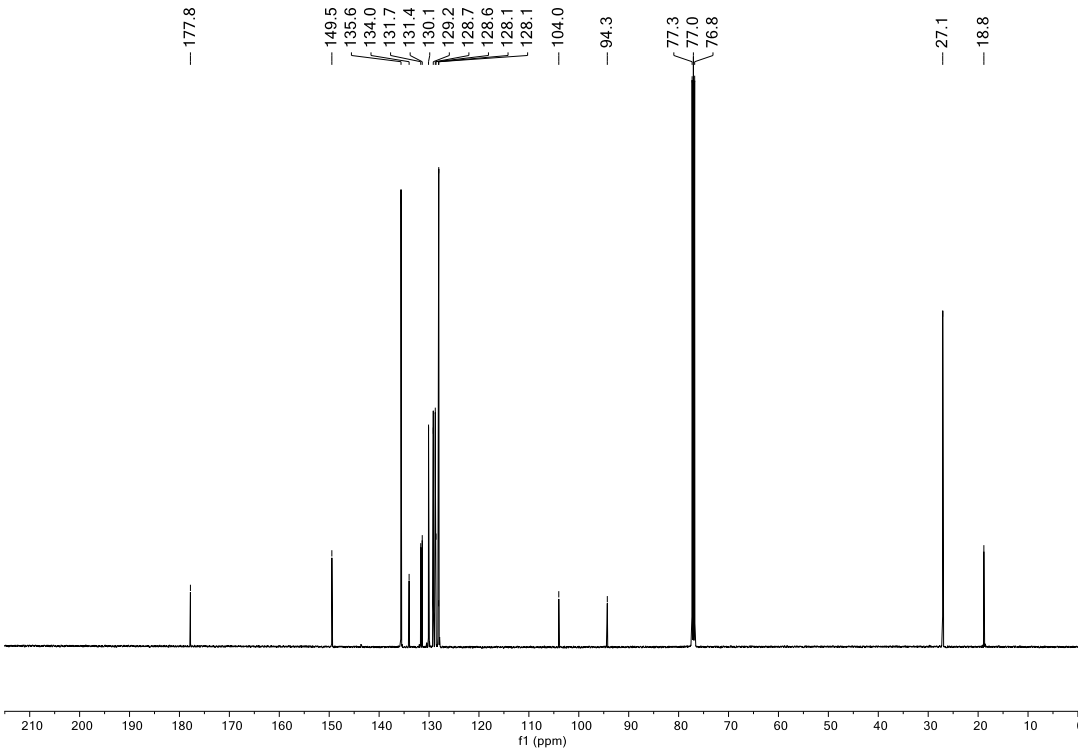
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.99 (d, *J* = 16.1 Hz, 1H), 7.83 (dd, *J* = 7.9, 1.5 Hz, 4H), 7.54 (dd, *J* = 7.5, 1.9 Hz, 2H), 7.49 – 7.40 (m, 9H), 6.87 (d, *J* = 16.1 Hz, 1H), 1.19 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.80, 149.47, 135.61, 133.99, 131.66, 131.36, 130.10, 129.15, 128.75, 128.59, 128.06, 104.01, 94.28, 27.09, 18.85 ppm.

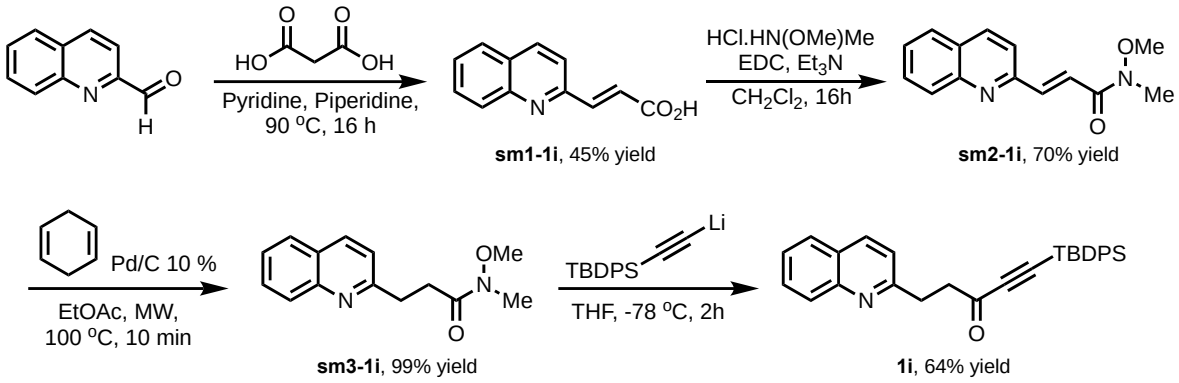
HRMS (ESI) m/z: [M+Na^+] calcd for $C_{27}H_{26}OSi$ 417.1645, found 417.1653.

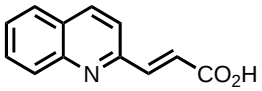
FTIR (ATR) 2929, 2857, 1627, 1596, 1428, 1233, 1195, 1110, 974, 858, 762, 741, 696, 678 cm^{-1}.


8.00
7.97
7.84
7.84
7.83
7.82
7.55
7.54
7.53
7.53
7.47
7.45
7.43
7.41
7.41
7.26
6.89
6.85
1.19
1.02
4.07
2.05
9.28
1.00
9.12
f1 (ppm)


177.8
149.5
135.6
134.0
131.7
131.4
130.1
129.2
128.7
128.6
128.1
128.1
104.0
94.3
77.3
77.0
76.8
27.1
18.8
f1 (ppm)

1-(*tert*-Butyldiphenylsilyl)-5-(quinolin-2-yl)pent-1-yn-3-one (3.1i)

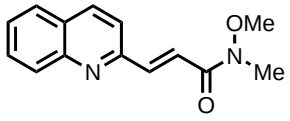




A flame-dried round-bottom flask equipped with a magnetic stir bar was charged with 2-quinolinecarboxaldehyde (1.0 g, 6.40 mmol, 100 mol%) and malonic acid (0.66 g, 6.40 mmol, 100 mol%). The reaction vessel was placed under an atmosphere of argon and pyridine (2.6 mL, 32 mmol, 500 mol%) and piperidine (0.031 mL, 0.31 mmol, 5 mol%) were added by syringe. The reaction mixture was stirred at 90 °C for 16 h. The reaction mixture was cooled to room temperature and diethyl ether (20 mL) and HCl (5 mL or until pH 5) were added. The reaction mixture was transferred to a separatory funnel and the aqueous phase extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was subjected to flash column chromatography (SiO_2, hexanes/EtOAc = 3:1 – EtOAc 100%) to furnish the title compound **sm1-3.1i** (0.57 g, 2.88 mmol) in 45% yield as a brown solid. The spectroscopic properties of this compound were consistent with the data available in literature.[31]

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.69 (s, 1H), 8.39 (dd, J = 8.6, 0.8 Hz, 1H), 8.01 (dq, J = 8.6, 0.9 Hz, 1H), 7.98 – 7.94 (m, 1H), 7.93 (d, J = 8.5 Hz, 1H), 7.76 (ddd, J = 8.4, 6.9,

1.5 Hz, 1H), 7.70 (d, *J* = 16.0 Hz, 1H), 7.60 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 6.98 (d, *J* = 16.0 Hz, 1H) ppm.



A flame-dried round-bottom flask equipped with a magnetic stir bar was charged with **sm1-3.1i** (0.44 g, 2.20 mmol, 100 mol%), *N*,*O*-dimethylhydroxylamine (0.24 g, 2.43 mmol, 110 mol%), triethylamine (0.92 mL, 6.63 mol, 300 mol%), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC, 3.31 g, 0.63 mmol, 150 mol%) and CH_2Cl_2 (8 mL, 0.3 M). The reaction mixture was allowed to stir at room temperature for 16 h. Saturated aqueous ammonium chloride (10 mL) was added and the reaction mixture was transferred to a separatory funnel. The aqueous phase extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was subjected to flash column chromatography (SiO_2, hexanes/ethyl acetate = 1:1 – ethyl acetate 100 %) to furnish the title compound **sm2-3.1i** (0.37 g, 1.53 mmol) in 70% yield as a brown oil.

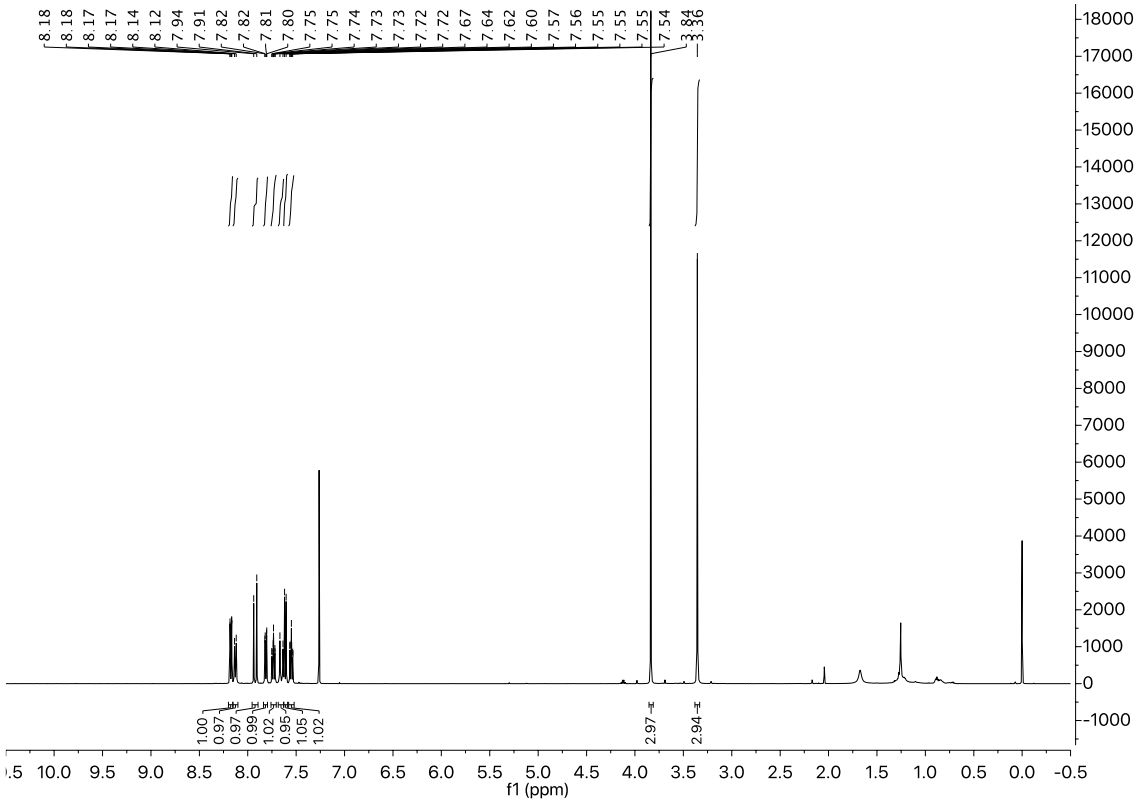
TLC (SiO_2) R_f = 0.46 (ethyl acetate 100%).

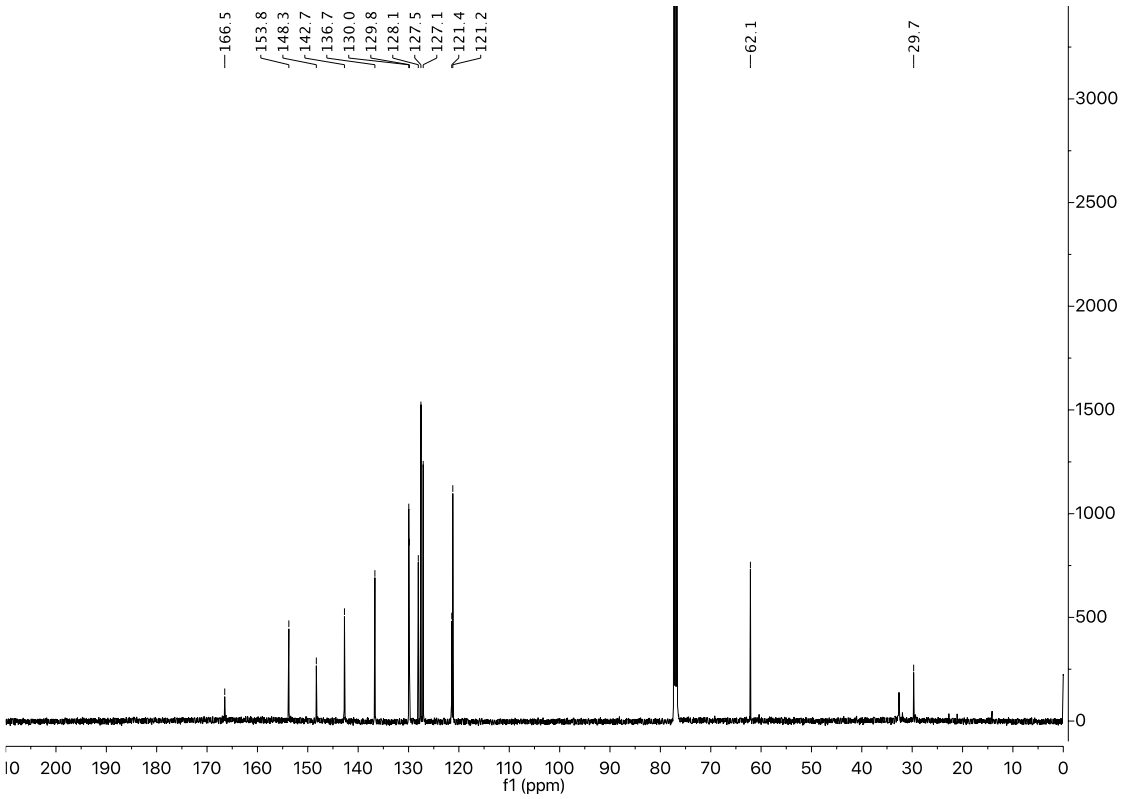
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (dd, *J* = 8.4, 0.8 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.92 (d, *J* = 15.6 Hz, 1H), 7.81 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.73 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.65 (d, *J* = 15.6 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.55 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 3.84 (s, 3H), 3.36 (s, 3H) ppm.

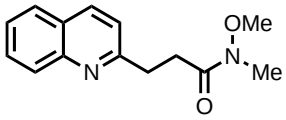
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5, 153.8, 148.3, 142.7, 136.7, 130.0, 129.8, 128.1, 127.5, 127.1, 121.4, 121.2, 62.1, 29.7 ppm.

HRMS (ESI) m/z: [(M+H)+] calcd for $C_{14}H_{14}N_2O_2$ 243.1128, found 243.1126.

FTIR (ATR) 3502, 3056, 2924, 2853, 1654, 1623, 1593, 1427, 1377, 998, 869, 756 cm^{-1}.







A flame-dried pressure tube equipped with a magnetic stir bar was charged with **sm2-3.1i** (0.30 g, 1.24 mmol, 100 mol%), Pd/C (0.030 g, 10% m/m), 1,4-cyclohexadiene (0.59 mL, 6.20 mmol, 500 mol%) and ethyl acetate (2.40 mL, 0.50 M). The reaction vessel was submitted to microwave irradiation (300 W) for 10 min. The mixture was cooled to room temperature, filtered through a celite plug with the aid of CH_2Cl_2 and the filtrate was concentrated at reduced pressure. The title compound **sm3-3.1i** (0.30 g, 1.24 mmol) was obtained with 99% as a brown oil.

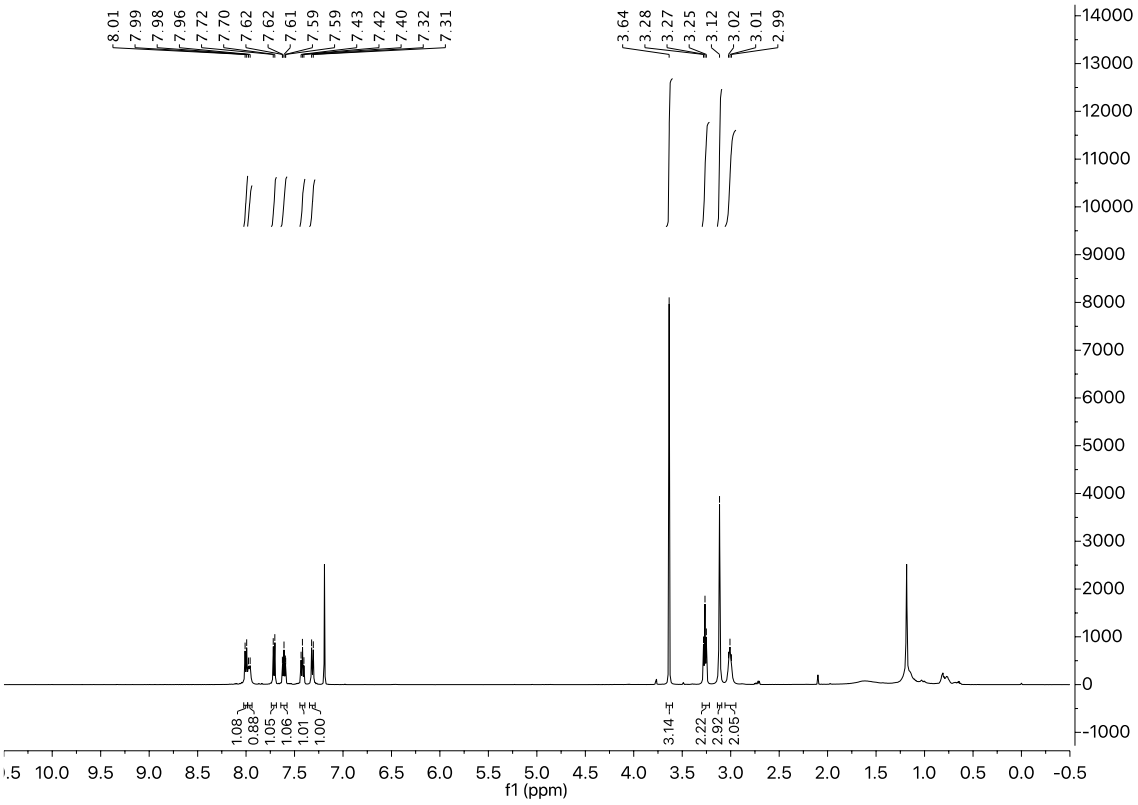
TLC (SiO_2) R_f = 0.46 (ethyl acetate 100%).

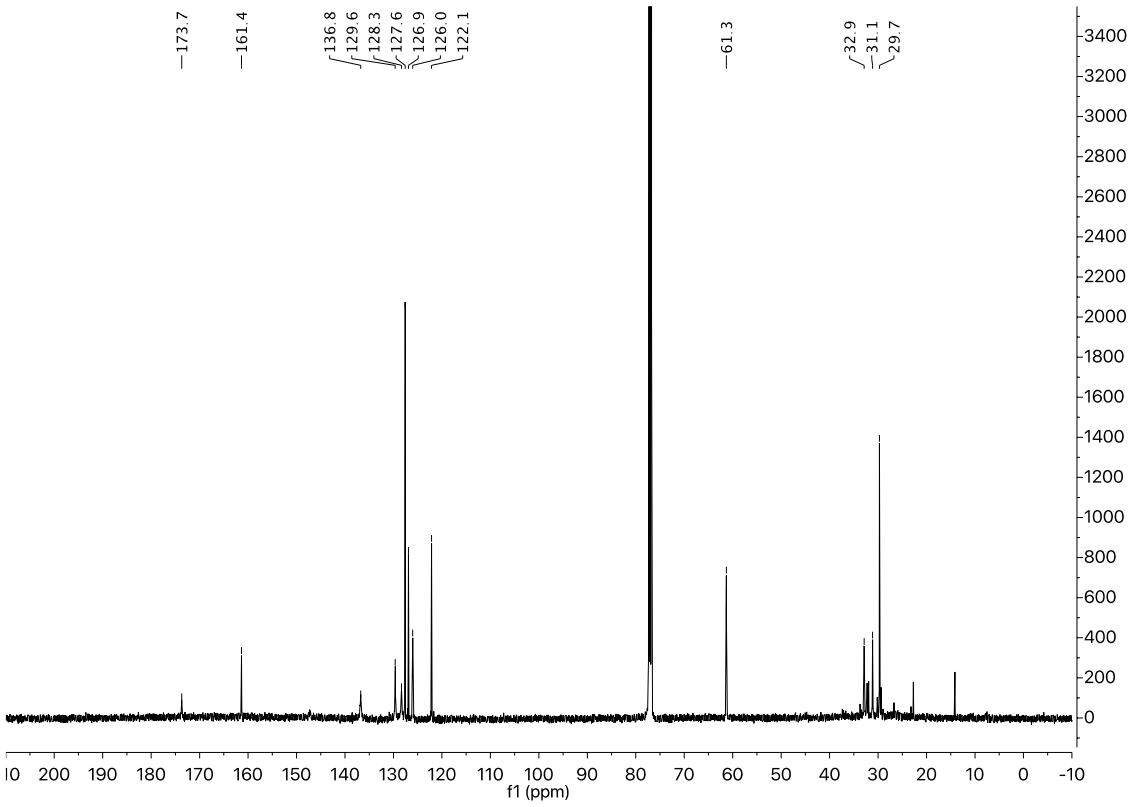
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 8.5 Hz, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.64 – 7.58 (m, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 3.64 (s, 3H), 3.27 (t, *J* = 7.4 Hz, 2H), 3.12 (s, 3H), 3.01 (d, *J* = 7.5 Hz, 2H) ppm.

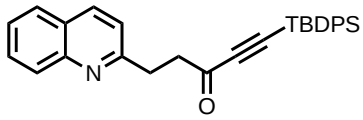
^{13}C NMR (126 MHz, $CDCl_3$) δ 173.7, 161.4, 136.8, 129.6, 128.3, 127.6, 126.9, 126.0, 122.1, 61.3, 32.9, 31.1, 29.7 ppm.

HRMS (ESI) m/z: [(M+H)+] calcd for $C_{14}H_{16}N_2O_2$ 245.1285, found 245.1285.

FTIR (ATR) 3056, 2923, 2853, 1657, 1600, 1503, 1426, 1385, 1177, 1114, 990, 826, 755 cm^{-1}.







The title compound was prepared according to general procedure using *tert*-butyl(ethynyl)diphenylsilane (0.36 g, 1.35 mmol, 100 mol%), THF (5 mL, 0.3 M), *n*-BuLi (0.54 mL, 1.35 mmol, 100 mol%, 2.5 M in hexanes) and **sm3-3.1i** (0.33 g, 1.35 mmol, 100 mol%). Upon flash column chromatography (SiO_2, hexanes/ethyl acetate = 5:1) the title compound **3.1i** (0.39 g, 0.87 mmol) was obtained in 64% yield as a brown oil.

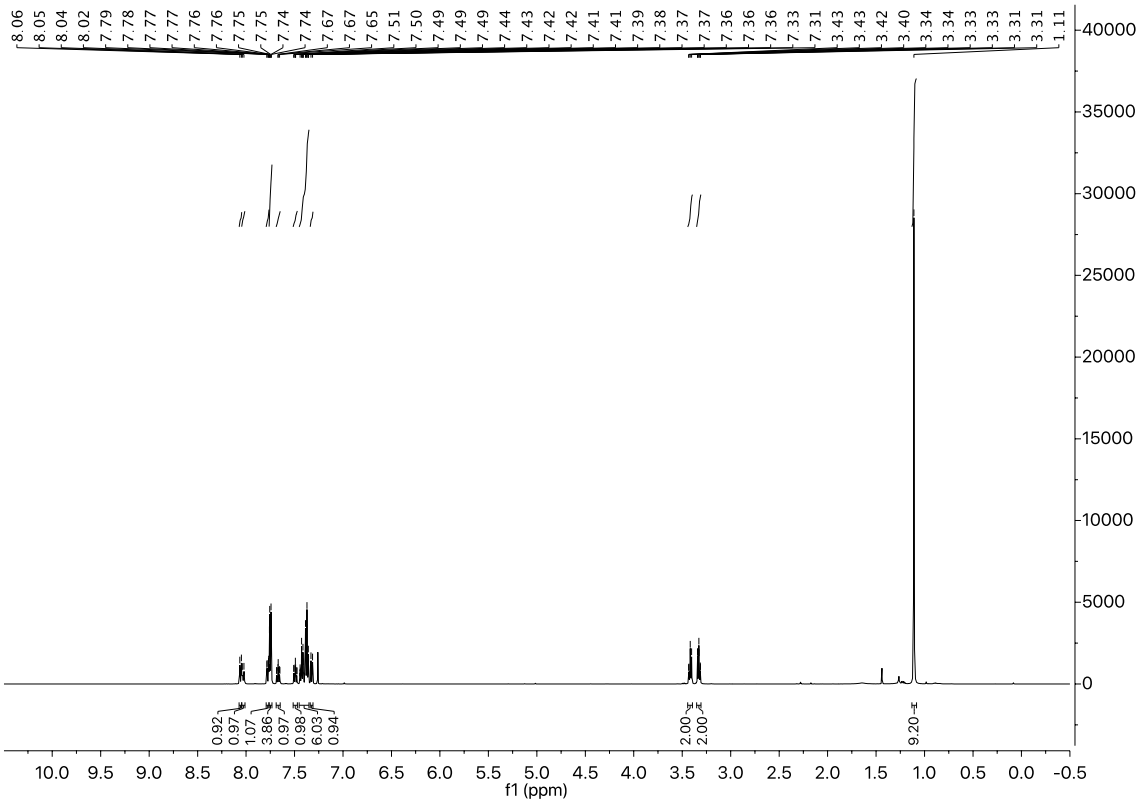
TLC (SiO_2) R_f = 0.41 (hexanes/ethyl acetate = 5:1).

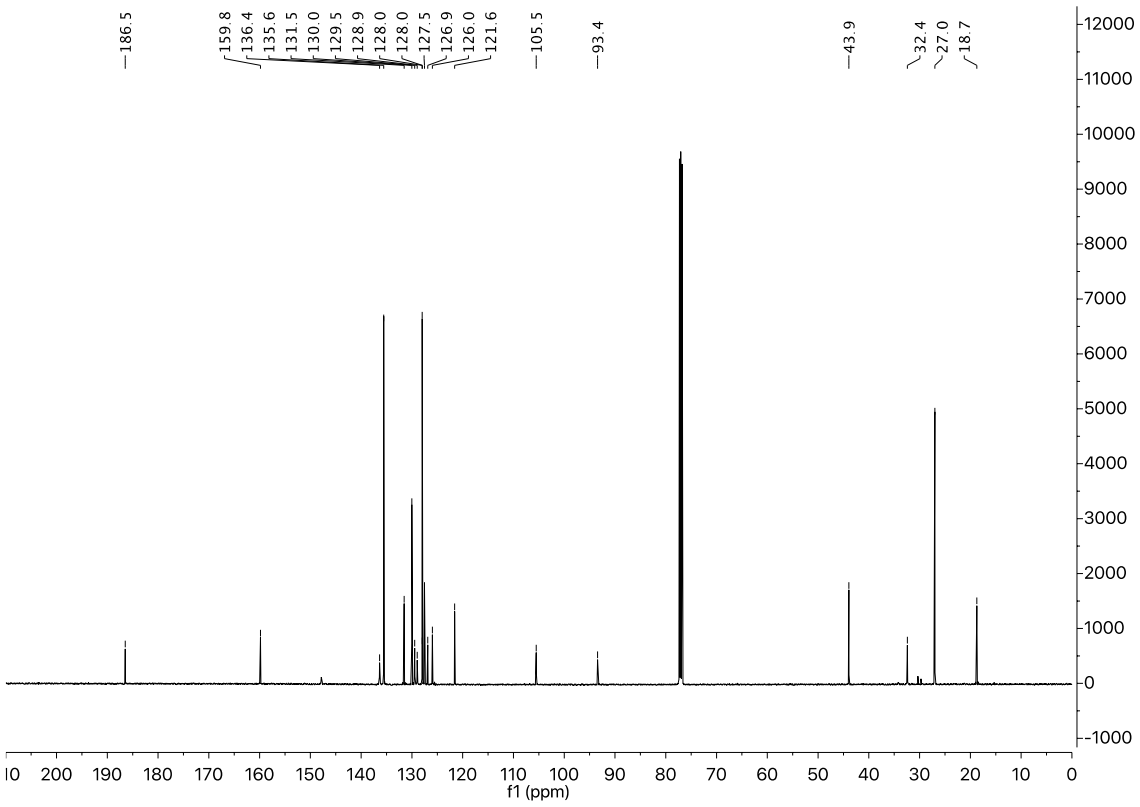
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.4 Hz, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.78 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.75 (dt, *J* = 6.7, 1.5 Hz, 4H), 7.67 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.49 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.45 – 7.35 (m, 6H), 7.32 (d, *J* = 8.4 Hz, 1H), 3.42 (t, *J* = 7.4 Hz, 2H), 3.33 (td, *J* = 6.8, 1.1 Hz, 2H), 1.11 (s, 9H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 186.5, 159.8, 136.4, 135.6, 131.5, 130.0, 129.5, 129.0, 128.0, 128.0, 127.5, 126.9, 126.0, 121.6, 105.5, 93.4, 43.9, 32.4, 27.0, 18.7 ppm.

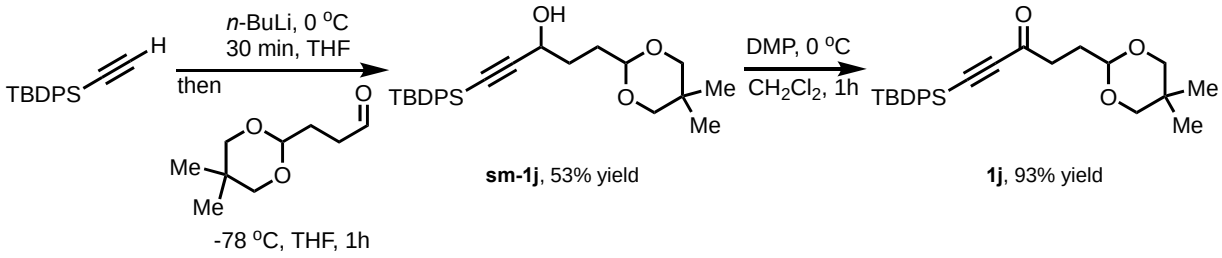
HRMS (ESI) m/z: [(M+H)+] calcd for $C_{30}H_{29}NOSi$ 448.2091, found 448.2088.

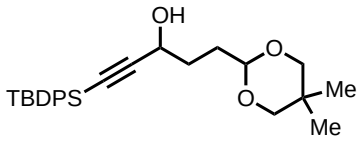
FTIR (ATR) 2926, 2855, 1676, 1618, 1427, 1104, 820, 714 cm^{-1}.




186.5
159.8
136.4
135.6
131.5
130.0
129.5
128.9
128.0
128.0
127.5
126.9
126.0
121.6
105.5
93.4
43.9
32.4
27.0
18.7
f1 (ppm)

1-(*tert*-Butyldiphenylsilyl)-5-(5,5-dimethyl-1,3-dioxan-2-yl)pent-1-yn-3-one (3.1j)





The title compound **sm-3.1j** was prepared according to general procedure using *tert*-butyl(ethynyl)diphenylsilane (1.06 g, 4.0 mmol, 100 mol%) aldehyde (0.69 g, 4.0 mmol, 100 mol%),[24] *n*-BuLi (1.6 mL, 4.0 mmol, 100 mol%, 2.5 M in hexanes) and THF (20 mL, 0.2 M). Upon flash column chromatography (SiO_2, hexanes/ethyl acetate = 9:1) the title compound **sm-3.1j** (0.93 g, 2.13 mmol) was obtained in 53% yield as a pale yellow oil.

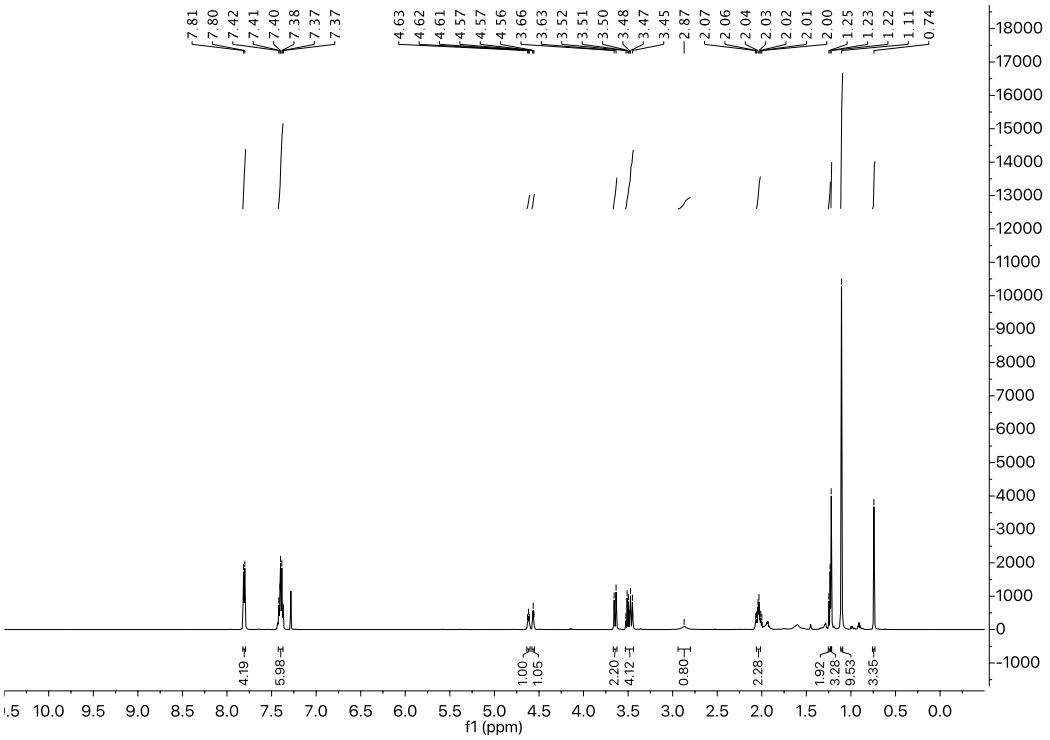
TLC (SiO_2) R_f = 0.10 (hexanes/ethyl acetate = 9:1).

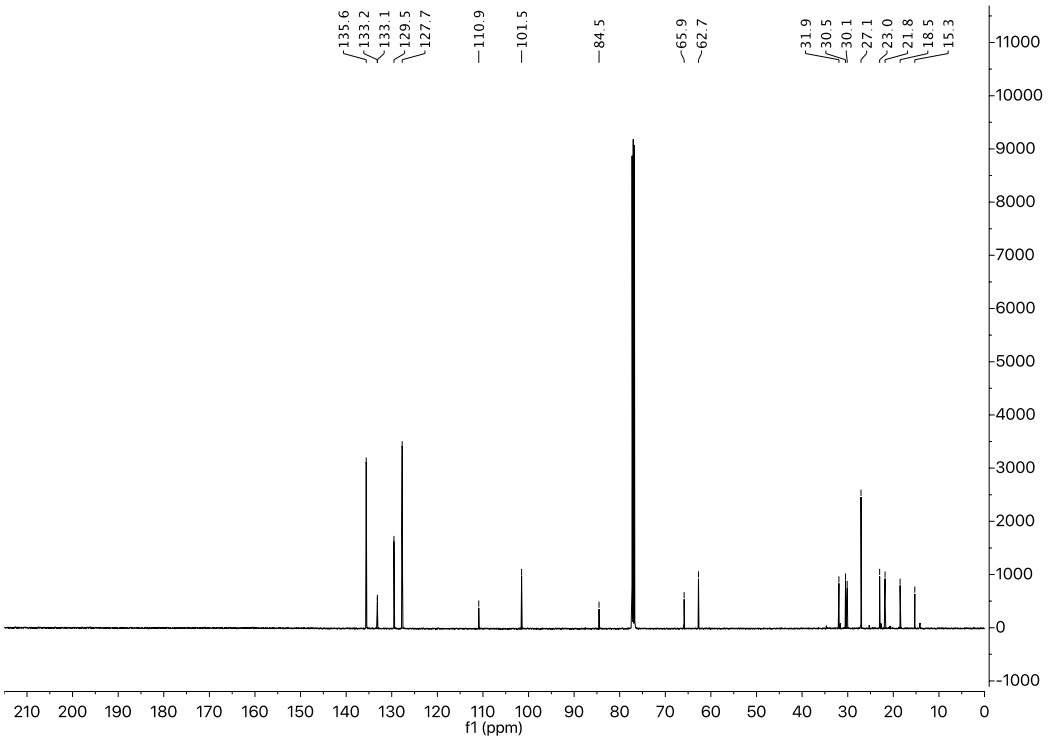
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 6.9 Hz, 4H), 7.40 (dd, *J* = 10.5, 6.8 Hz, 6H), 4.62 (d, *J* = 5.9 Hz, 1H), 4.56 (d, *J* = 4.5 Hz, 1H), 3.65 (d, *J* = 10.8 Hz, 2H), 3.49 (dt, *J* = 16.0, 9.0 Hz, 4H), 2.87 (s, 1H), 2.04 (q, *J* = 7.0, 5.5 Hz, 2H), 1.24 (d, *J* = 7.1 Hz, 2H), 1.22 (s, 3H), 1.11 (s, 10H), 0.74 (s, 3H) ppm.

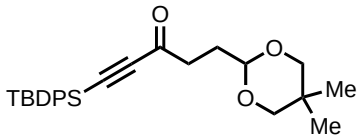
^{13}C NMR (126 MHz, $CDCl_3$) δ 135.6, 133.2, 133.1, 129.5, 127.7, 110.9, 101.5, 84.5, 65.9, 62.7, 31.9, 30.5, 30.1, 27.1, 23.0, 21.8, 18.5, 15.3 ppm.

HRMS (ESI) m/z: [(M+Na)+] calcd for $C_{27}H_{36}O_3Si$ 459.2326, found 459.2333.

FTIR (ATR) 3423, 2932, 2818, 1439, 1372, 1241, 1081, 1045, 984, 948, 702 cm^{-1}.


7.81
7.80
7.42
7.41
7.40
7.38
7.37
7.37
4.63
4.62
4.61
4.57
4.57
4.56
3.66
3.63
3.52
3.51
3.50
3.48
3.47
3.45
2.87
2.07
2.06
2.04
2.03
2.02
2.01
2.00
1.25
1.23
1.22
1.11
0.74
4.19
5.98
1.00
1.05
2.20
4.12
0.80
2.28
1.92
3.28
9.53
3.35
f1 (ppm)


135.6
133.2
133.1
129.5
127.7
110.9
101.5
84.5
65.9
62.7
31.9
30.5
30.1
27.1
23.0
21.8
18.5
15.3
f1 (ppm)



The title compound **3.1j** was prepared according to general procedure using **sm-3.1j** (0.92 g, 2.12 mmol, 100 mol%), DMP (1.08 g, 2.54 mmol, 120 mol %), $NaHCO_3$ (0.71 g, 8.48 mmol, 400mol%) and DCM (11 mL, 0.2 M). Upon flash column chromatography (SiO_2, hexanes/ethyl acetate = 9:1) the title compound **3.1j** (0.86 g, 1.97 mmol) was obtained in 93% yield as a pale yellow oil.

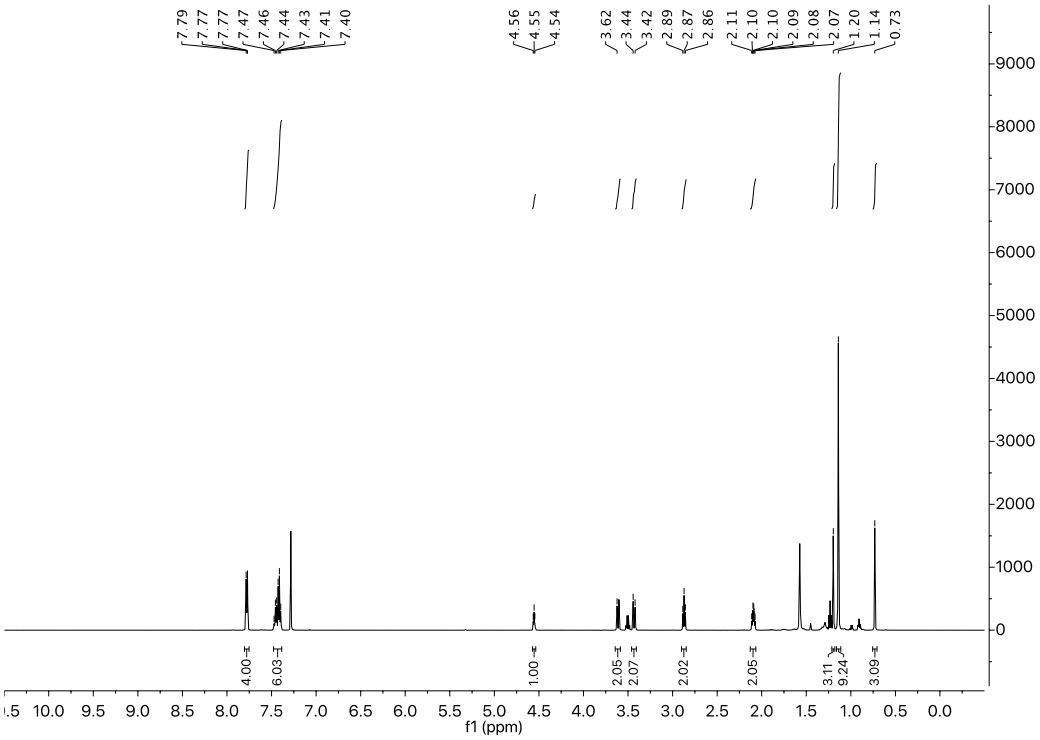
TLC (SiO_2) R_f = 0.36 (hexanes/ethyl acetate = 9:1).

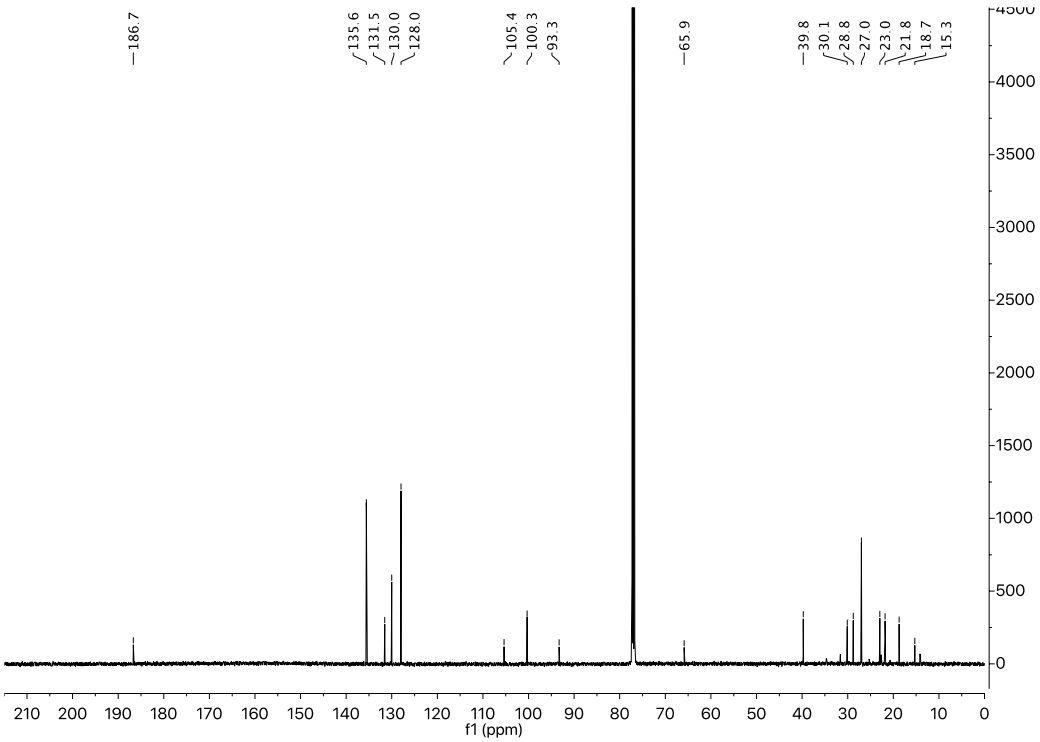
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 – 7.75 (m, 4H), 7.43 (dt, *J* = 14.5, 7.2 Hz, 6H), 4.55 (t, *J* = 4.7 Hz, 1H), 3.62 (s, 2H), 3.43 (d, *J* = 10.8 Hz, 2H), 2.87 (t, *J* = 7.2 Hz, 2H), 2.09 (td, *J* = 7.2, 4.7 Hz, 2H), 1.20 (s, 3H), 1.14 (s, 9H), 0.73 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 186.7, 135.6, 131.5, 130.0, 128.0, 105.4, 100.3, 93.3, 65.9, 39.8, 30.1, 28.8, 27.0, 23.0, 21.8, 18.7, 15.3 ppm.

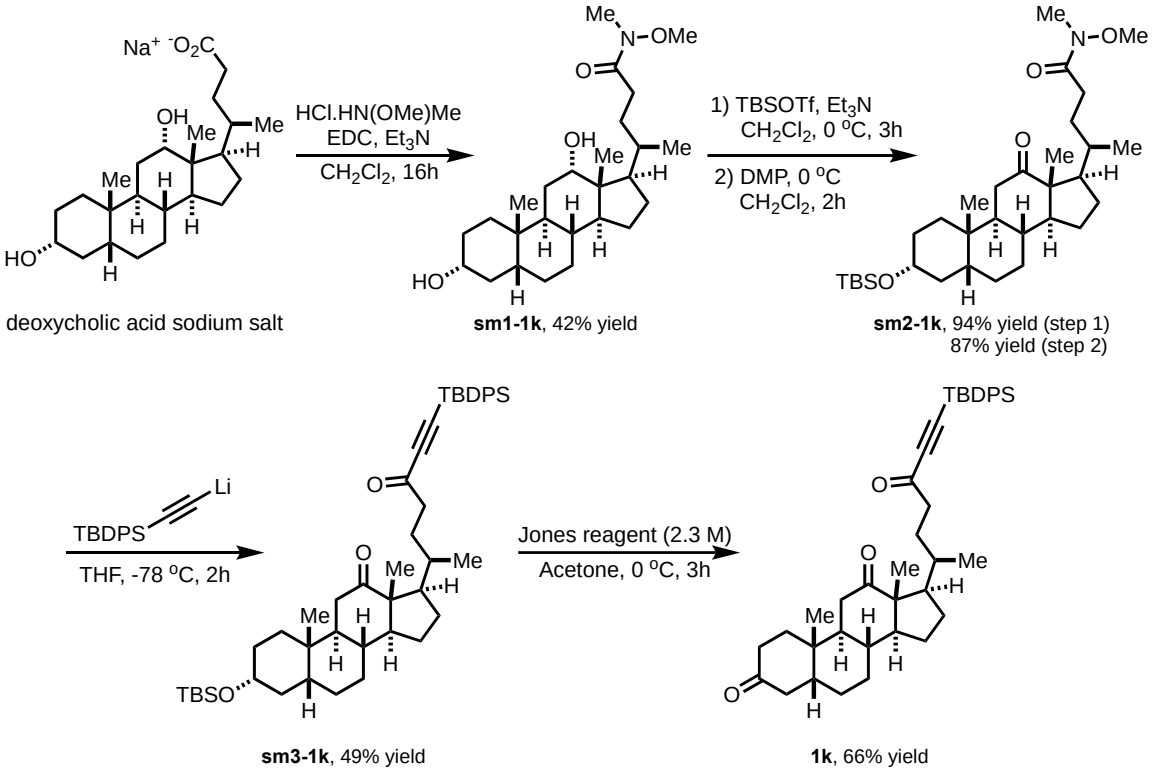
HRMS (ESI) m/z: [(M+H)+] calcd for $C_{27}H_{34}O_3Si$ 435.2350, found 435.2363.

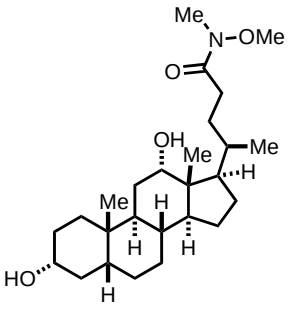
FTIR (ATR) 2954, 2856, 1677, 1470, 1428, 1393, 1132, 1108, 1036, 792, 698 cm^{-1}.


7.79
7.77
7.77
7.47
7.46
7.44
7.43
7.41
7.40
4.56
4.55
4.54
3.62
3.44
3.42
2.89
2.87
2.86
2.11
2.10
2.10
2.09
2.08
2.07
1.20
1.14
0.73
4.00
6.03
1.00
2.05
2.07
2.02
2.05
3.11
9.24
3.09
f1 (ppm)


186.7
135.6
131.5
130.0
128.0
105.4
100.3
93.3
65.9
39.8
30.1
28.8
27.0
23.0
21.8
18.7
15.3
f1 (ppm)

(5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-17-((*R*)-7-(*tert*-butyldiphenylsilyl)-5-oxohept-6-yn-2-yl)-10,13-dimethyltetradecahydro-3*H*-cyclopenta[*a*]phenanthrene-3,12(2*H*)-dione (3.1k)





The title compound **sm1-3.1k** was prepared according to general procedure using deoxycholic acid sodium salt (6.60 g, 16 mmol, 100 mol%), *N*,*O*-dimethylhydroxylamine (1.70 g, 17.5 mmol, 110 mol%), EDC (3.68 g, 19.2 mmol, 120 mol%), Et_3N (4.50 mL, 32 mmol, 200 mol%) and CH_2Cl_2 (54 mL, 0.3 M). Upon flash column chromatography (SiO_2, ethyl acetate 100%) the title compound **sm-3.1k** (0.2.96 g, 6.79 mmol) was obtained in 42% yield as a white solid.

TLC (SiO_2) R_f = 0.35 (ethyl acetate 100%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.03 – 3.98 (m, 1H), 3.71 (s, 3H), 3.68 – 3.60 (m, 1H), 3.20 (s, 3H), 2.49 (ddd, *J* = 15.3, 10.2, 5.1 Hz, 1H), 2.36 (dq, *J* = 15.6, 8.8, 7.6 Hz, 1H), 1.94 – 1.07 (m, 26H), 1.02 (d, *J* = 6.5 Hz, 3H), 0.93 (s, 3H), 0.71 (s, 3H) ppm.

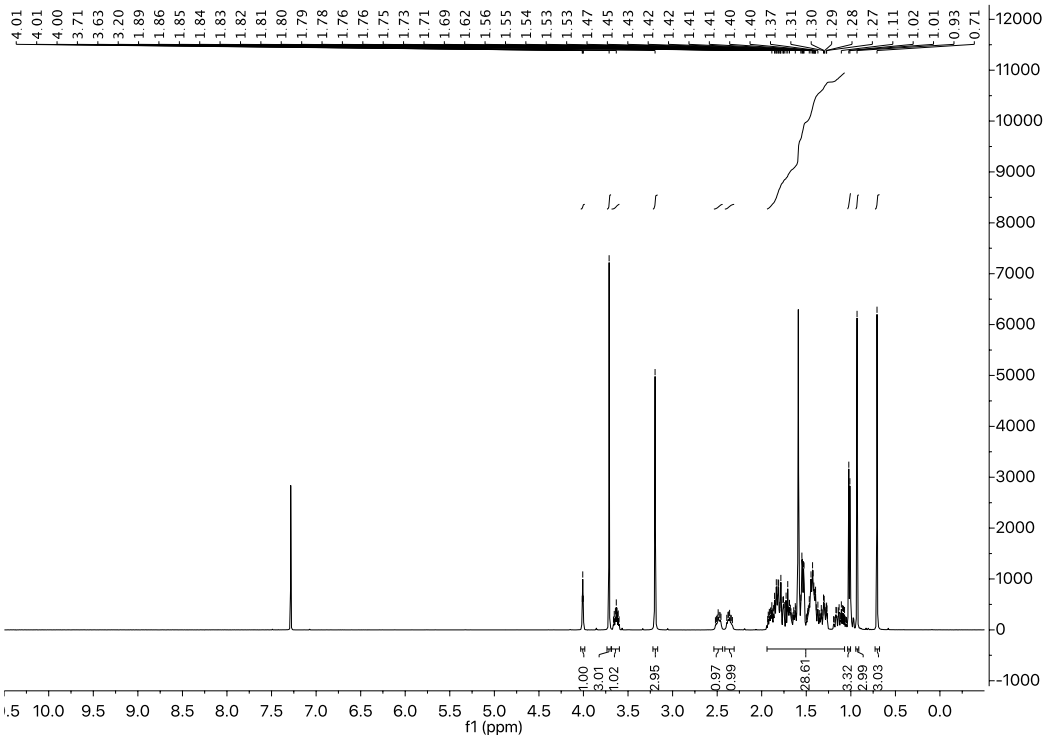
^{13}C NMR (126 MHz, $CDCl_3$) ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.3, 73.2, 71.8, 61.3, 48.3, 47.3, 46.5, 42.1, 36.4, 36.0, 35.3, 35.3, 34.1, 33.7, 32.3, 30.6, 30.5, 28.8, 28.6, 27.5, 27.2, 26.1, 23.7, 23.2, 17.5, 12.8 ppm.

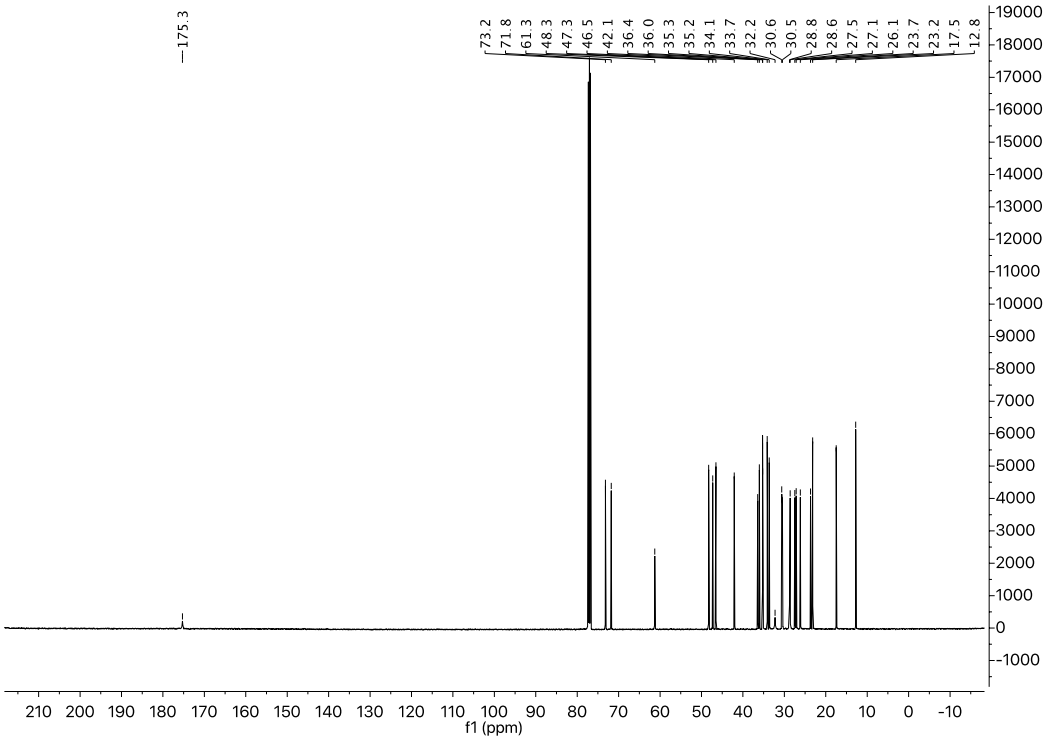
HRMS (ESI) m/z: [(M+H)+] calcd for $C_{26}H_{45}NO_4$ 436.3421, found 436.345.

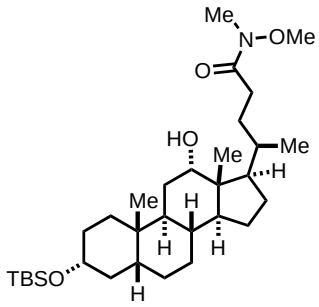
FTIR (ATR) 3246, 3141, 2935, 2863, 1644, 1447, 1378, 1089, 1043, 1011, 735 cm^{-1}.

$[\alpha]_D^{28}$: +26.7 (*c* 1.0, $CHCl_3$).

MP: 134-137 °C


4.01 4.01 4.00 3.71 3.63 3.20 1.89 1.86 1.85 1.84 1.83 1.82 1.81 1.80 1.79 1.78 1.76 1.76 1.75 1.73 1.71 1.69 1.62 1.56 1.55 1.54 1.53 1.53 1.47 1.45 1.43 1.42 1.42 1.41 1.41 1.40 1.40 1.37 1.31 1.30 1.29 1.28 1.27 1.11 1.02 1.01 0.93 0.71
1.00 3.01 1.02 2.95 0.97 0.99 28.61 3.32 2.99 3.03
f1 (ppm)


175.3
73.2 71.8 61.3 48.3 47.3 46.5 42.1 36.4 36.0 35.3 35.2 34.1 33.7 32.2 30.6 30.5 28.8 28.6 27.5 27.1 26.1 23.7 23.2 17.5 12.8
f1 (ppm)



To a dried round-bottomed flask charged with **sm1-3.1k** (2.96 g, 6.79 mmol, 100 mol%), CH_2Cl_2 (35 mL, 0.2 M) and triethylamine (2.40 mL, 17.0 mmol, 250 mol%) at 0 °C, *tert*-Butyldimethylsilyl trifluoromethanesulfonate (TBSOTf, 1.87 mL, 8.15 mmol, 120 mol%) was added and the mixture was allowed to stir at 0 °C for 2 hours. The mixture was allowed to warm to room temperature, and saturated aqueous ammonium chloride (15 mL) was added. The reaction mixture was transferred to a separatory funnel and the aqueous phase extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was subjected to flash column chromatography (SiO_2, hexanes/ethyl acetate = 3:1) to furnish the title compound (**sm1-3.1k**) in 94% yield (3.50 g, 6.38 mmol) as a white solid.

TLC (SiO_2) R_f = 0.20 (hexanes/ethyl acetate = 3:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.95 – 3.90 (m, 1H), 3.65 (d, *J* = 1.7 Hz, 3H), 3.52 (tt, *J* = 10.7, 4.3 Hz, 1H), 3.13 (s, 3H), 2.47 – 2.25 (m, 2H), 1.87 – 1.64 (m, 7H), 1.61 – 1.43 (m, 8H), 1.35 (tt, *J* = 9.2, 5.8 Hz, 6H), 1.25 – 0.98 (m, 4H), 0.95 (dd, *J* = 6.4, 1.5 Hz, 3H), 0.87 – 0.82 (m, 11H), 0.65 – 0.61 (m, 3H), -0.00 (s, 5H) ppm.

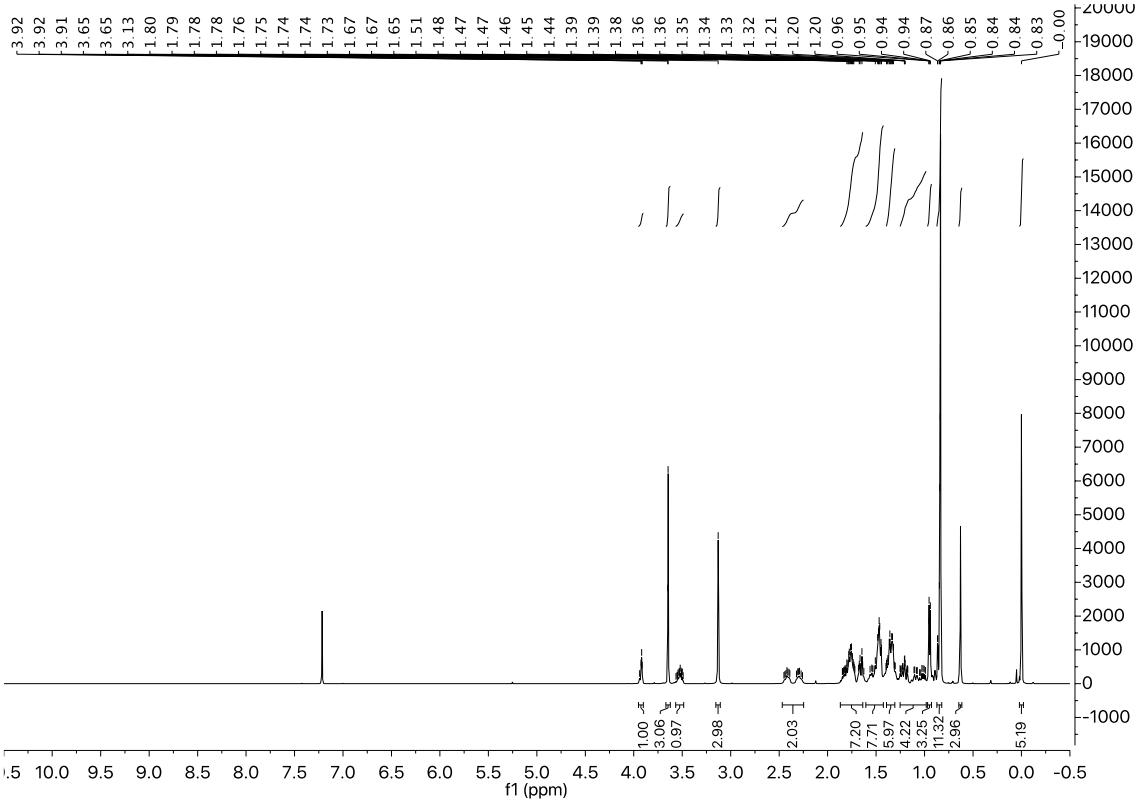
^{13}C NMR (126 MHz, $CDCl_3$) δ 175.3, 73.3, 72.8, 61.3, 48.3, 47.2, 46.5, 42.3, 36.9, 36.1, 35.4, 35.2, 34.2, 33.7, 33.7, 30.9, 30.6, 28.7, 28.6, 27.4, 27.3, 26.1, 26.0, 23.7, 23.7, 23.3, 18.3, 17.5, 12.8, 12.8, -4.6, -4.6 ppm.

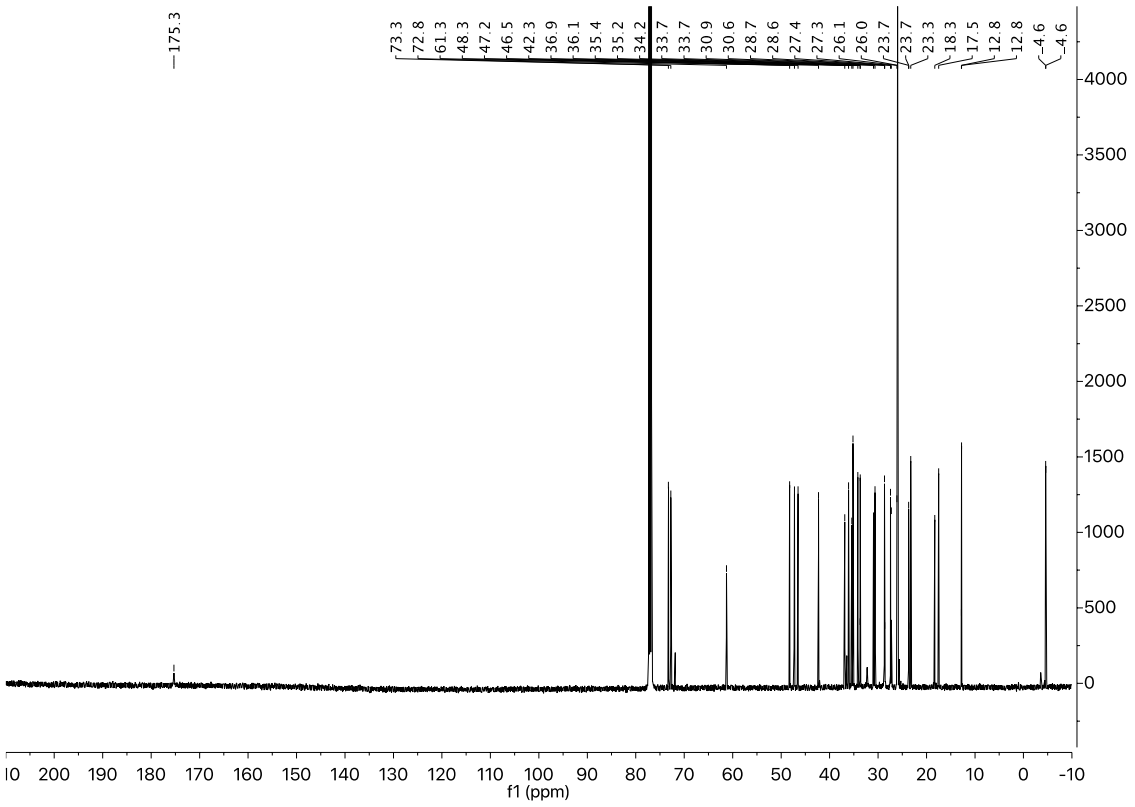
HRMS (ESI) m/z: [(M+H)+] calcd for $C_{32}H_{59}NO_4Si$ 550.4286, found 550.4293.

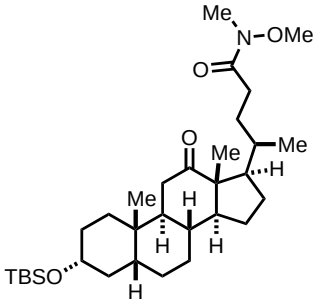
FTIR (ATR) 3482, 2926, 2859, 1650, 1470, 1462, 1445, 1378, 1092, 923, 777 cm^{-1}.

$[\alpha]_D^{28}$: +31.3 (*c* 0.25, $CHCl_3$).

MP: 175-177 °C







The title compound **sm2-3.1k** was prepared according to general procedure described in section 3.7 using **sm1-3.1k** (3.40 g, 6.18 mmol, 100 mol%), DMP (3.15 g, 7.42 mmol, 120 mol%), $NaHCO_3$ (2.10 g, 24.7 mmol, 400 mol%) and DCM (32 mL, 0.2 M). Upon flash column chromatography (SiO_2, hexanes/ethyl acetate = 3:1) the title compound **sm2-3.1k** (2.93 g, 5.83 mmol) was obtained in 87% yield as a white solid.

TLC (SiO_2) R_f = 0.29 (hexanes/ethyl acetate = 3:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.66 (s, 3H), 3.53 (ddt, *J* = 15.2, 10.5, 4.6 Hz, 1H), 3.14 (s, 3H), 2.49 – 2.29 (m, 3H), 2.04 – 1.95 (m, 2H), 1.96 – 1.48 (m, 9H), 1.49 – 1.21 (m, 10H), 1.15 – 1.03 (m, 1H), 0.97 (s, 3H), 0.95 (s, 3H), 0.83 (d, *J* = 2.5 Hz, 12H), 0.00 (s, 6H) ppm.

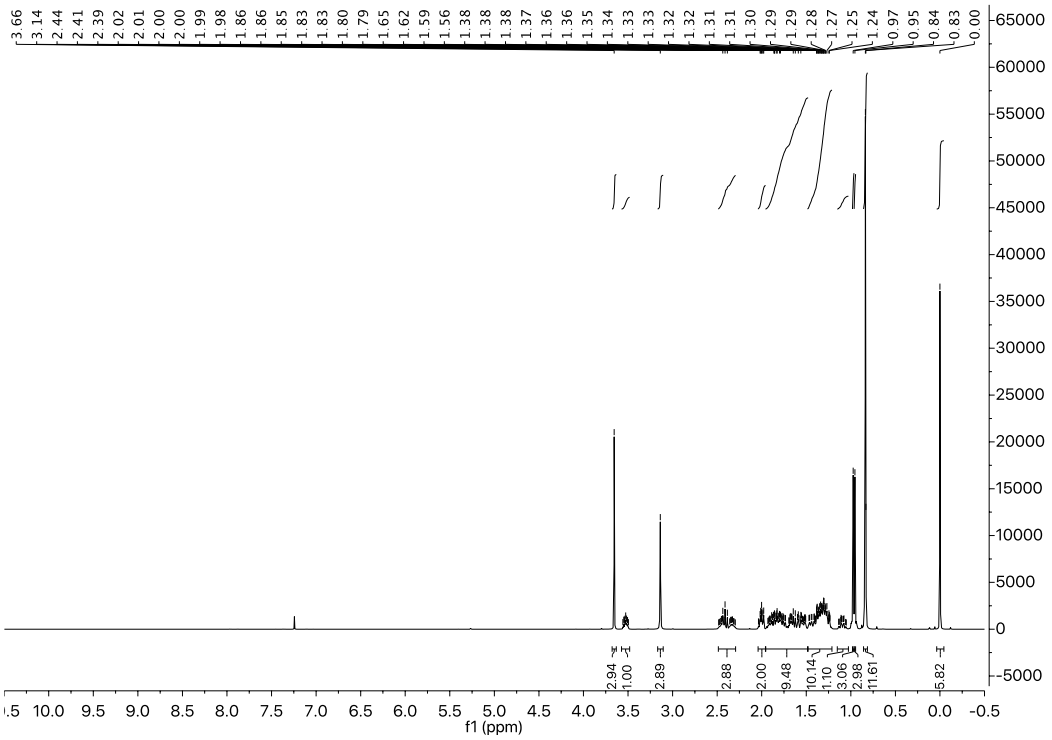
^{13}C NMR (126 MHz, $CDCl_3$) δ ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.9, 175.2, 72.2, 61.2, 58.6, 57.5, 46.4, 43.9, 41.7, 38.1, 36.8, 35.7, 35.7, 35.5, 35.3, 32.2, 30.7, 30.1, 28.9, 27.5, 27.2, 26.1, 25.9, 24.4, 22.8, 18.8, 18.2, 11.7, -4.6, -4.6 ppm.

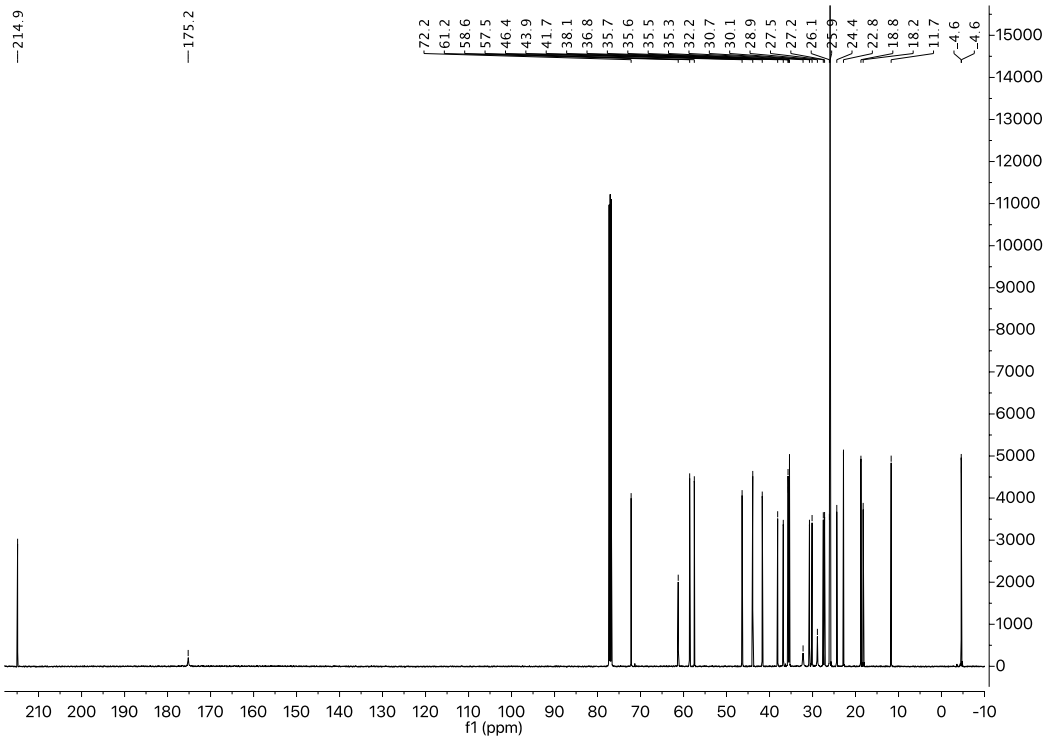
HRMS (ESI) m/z: [(M+H)+] calcd for $C_{32}H_{57}NO_4Si$ 548.4130, found 548.4140.

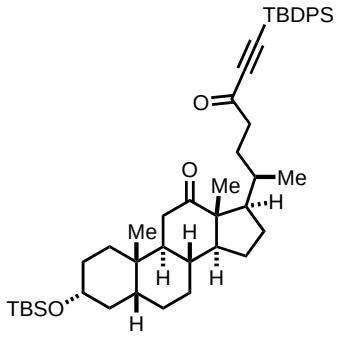
FTIR (ATR) 2927, 2858, 2866, 1698, 1655, 1463, 1380, 1247, 1101, 1089, 882, 833, 776 cm^{-1}.

$[\alpha]_D^{28}$: +54.7 (*c* 1.0, $CHCl_3$).

MP: 174-176 ^{o}C


3.66
3.14
2.44
2.41
2.39
2.02
2.01
2.00
2.00
1.99
1.98
1.86
1.86
1.85
1.83
1.83
1.80
1.79
1.65
1.62
1.59
1.56
1.38
1.38
1.38
1.37
1.36
1.36
1.35
1.34
1.33
1.33
1.32
1.32
1.31
1.31
1.30
1.29
1.29
1.28
1.27
1.25
1.24
0.97
0.95
0.84
0.83
0.00
2.94
1.00
2.89
2.88
2.00
9.48
10.14
1.10
3.06
2.98
11.61
5.82
f1 (ppm)


214.9
175.2
72.2
61.2
58.6
57.5
46.4
43.9
41.7
38.1
36.8
35.7
35.6
35.5
35.3
32.2
30.7
30.1
28.9
27.5
27.2
26.1
25.9
24.4
22.8
18.8
18.2
11.7
-4.6
-4.6
f1 (ppm)



The title compound **sm3-3.1k** was prepared according to general procedure using *tert*-butyl(ethynyl)diphenylsilane (1.33 g, 5.0 mmol, 95 mol%) **sm2-3.1k** (2.90 g, 5.30 mmol, 100 mol%), *n*-BuLi (2.0 mL, 5.0 mmol, 95 mol%, 2.5 M in hexanes) and toluene (54 mL, 0.1 M). Upon flash column chromatography (SiO_2, hexanes/ethyl acetate = 10:1) the title compound **sm3-3.1k** (1.97 g, 2.62 mmol) was obtained in 49% yield as a pale yellow oil.

TLC (SiO_2) R_f = 0.49 (hexanes/ethyl acetate = 10:1).

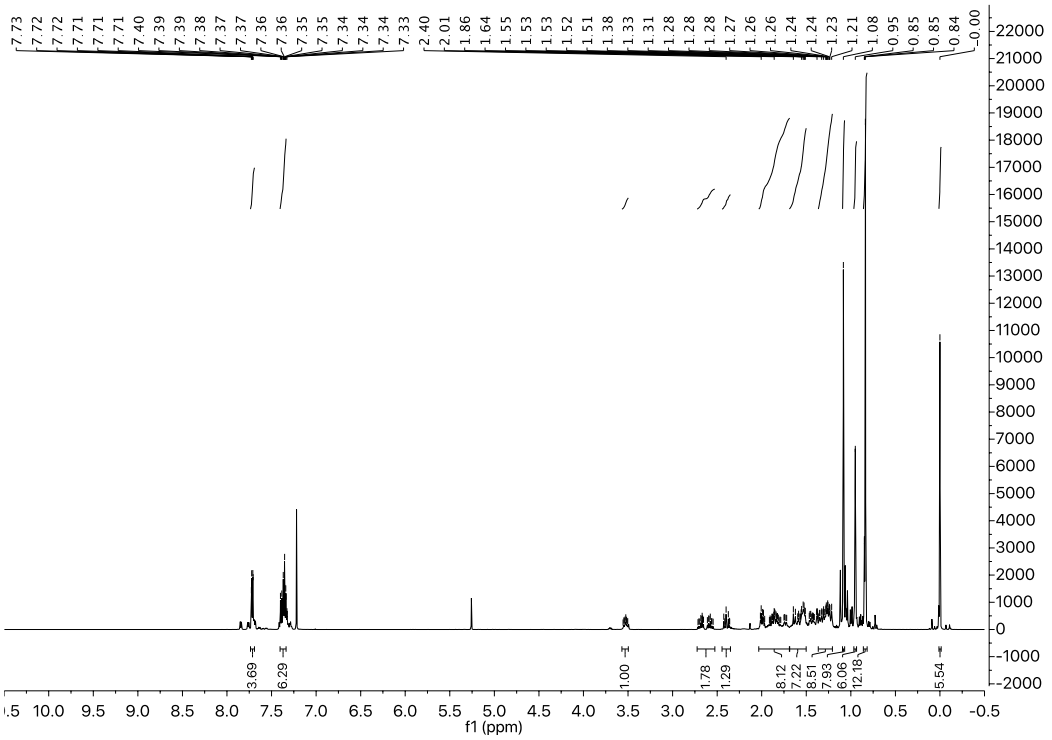
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (dt, *J* = 6.6, 1.6 Hz, 4H), 7.40 – 7.34 (m, 6H), 3.53 (dq, *J* = 10.7, 6.2, 5.4 Hz, 1H), 2.72 – 2.53 (m, 2H), 2.45 – 2.35 (m, 1H), 2.03 – 1.69 (m, 8H), 1.69 – 1.50 (m, 7H), 1.36 – 1.21 (m, 9H), 1.08 (s, 8H), 0.95 (s, 6H), 0.84 (d, *J* = 5.5 Hz, 12H), -0.00 (s, 6H) ppm.

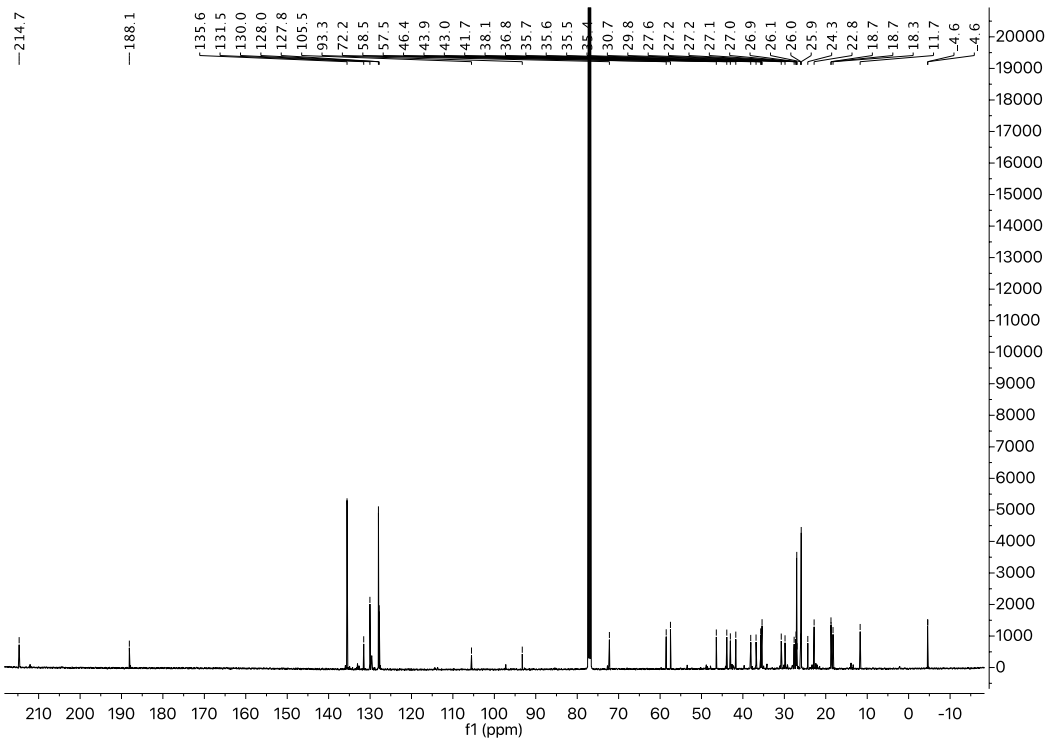
^{13}C NMR (126 MHz, $CDCl_3$) δ 214.7, 188.1, 135.6, 131.5, 130.0, 128.0, 127.8, 105.5, 93.3, 72.2, 58.5, 57.5, 46.4, 43.9, 43.0, 41.7, 38.1, 36.8, 35.7, 35.6, 35.5, 35.4, 30.7, 29.8, 27.6, 27.2, 27.2, 27.1, 27.0, 26.9, 26.1, 26.0, 25.9, 24.3, 22.8, 18.7, 18.7, 18.3, 11.7, -4.6, -4.6 ppm.

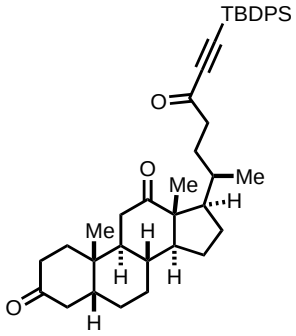
HRMS (ESI) m/z: [(M+Na)+] calcd for $C_{48}H_{70}O_3Si_2$ 773.4756, found 773.4769.

FTIR (ATR) 2928, 2857, 1705, 1676, 1428, 1249, 1104, 1085, 819, 774, 699 cm^{-1}.

$[\alpha]_D^{28}$: +108.8 (*c* 0.1, $CHCl_3$).


f1 (ppm)


f1 (ppm)



To a dried round-bottomed flask charged with **sm3-3.1k** (1.97 g, 2.62 mmol, 100 mol%) and acetone (14 mL, 0.2 M) at 0 °C, Jones reagent (2.3 M, 0.35 mL, 200 mol%) was dropwise over the period of 15 min and the mixture was allowed to stir at 0 °C for 2 hours. Isopropanol (2 mL) was added, and the mixture was stirred for an additional of 15 min. The excess of solvent was removed by reduced pressure and water (10 mL) was added. The reaction mixture was transferred to a separatory funnel and the aqueous phase extracted with EtOAc (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was subjected to flash column chromatography (SiO_2, hexanes/ethyl acetate = 4:1) to furnish the title compound (**3.1k**) in 96% yield (1.48 g, 4.80 mmol) as a white solid.

TLC (SiO_2) R_f = 0.14 (hexanes/ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 – 7.75 (m, 4H), 7.48 – 7.39 (m, 6H), 2.79 – 2.54 (m, 5H), 2.45 – 2.32 (m, 2H), 2.24 – 2.02 (m, 6H), 1.98 – 1.90 (m, 7H), 1.44 – 1.33 (m, 6H), 1.14 (s, 9H), 1.13 (s, 3H), 1.07 (s, 3H), 0.93 – 0.90 (m, 3H) ppm.

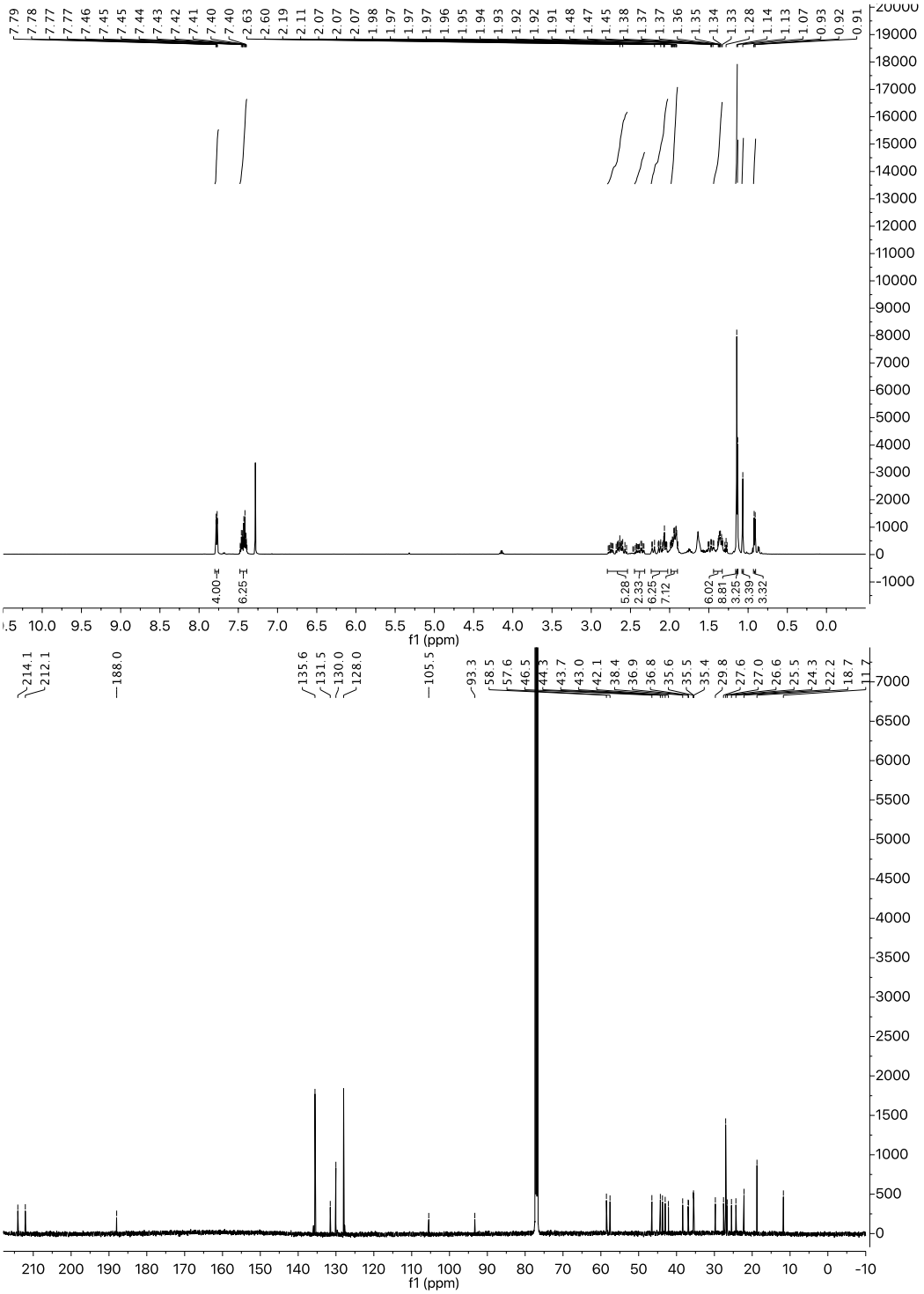
^{13}C NMR (126 MHz, $CDCl_3$) δ 214.1, 212.1, 188.0, 135.6, 131.5, 130.0, 128.0, 105.5, 93.3, 58.5, 57.6, 46.5, 44.3, 43.7, 43.0, 42.1, 38.4, 36.9, 36.8, 35.6, 35.5, 35.5, 29.8, 27.6, 27.5, 27.0, 26.6, 25.5, 24.3, 22.2, 18.7, 11.8 ppm.

HRMS (ESI) m/z: [(M+Na)+] calcd for $C_{42}H_{54}O_3Si$ 657.3734, found 657.3749.

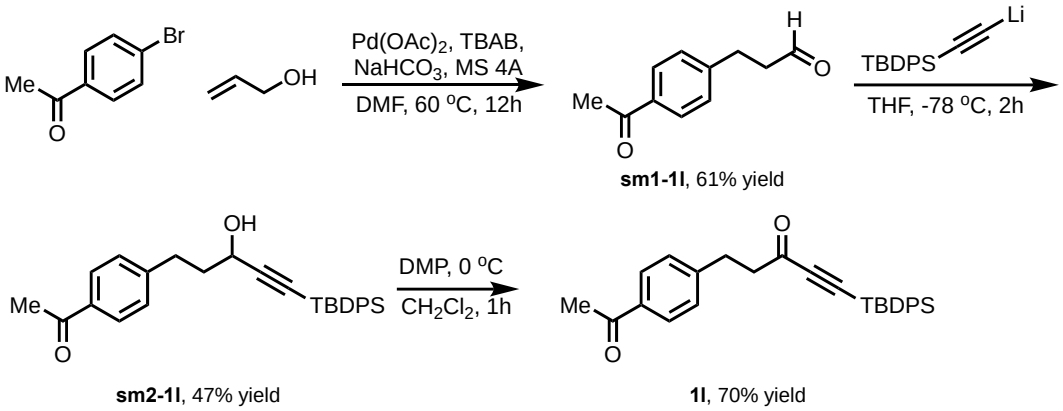
FTIR (ATR) 2930, 2861, 1704, 1673, 1462, 1428, 1110, 909, 819, 729 cm^{-1}.

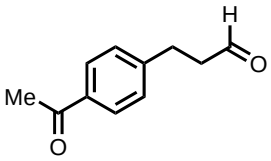
$[\alpha]_D^{28}$: +75.8 (*c* 1.0, $CHCl_3$).

MP: 62-64 °C


7.79 7.78 7.77 7.77 7.46 7.45 7.45 7.44 7.43 7.42 7.41 7.40 7.40 2.63 2.60 2.19 2.11 2.07 2.07 2.07 1.98 1.97 1.97 1.97 1.96 1.95 1.94 1.93 1.92 1.92 1.91 1.48 1.47 1.45 1.38 1.37 1.37 1.36 1.35 1.34 1.33 1.28 1.14 1.13 1.07 0.93 0.92 0.91
4.00 6.25 5.28 2.33 6.25 7.12 6.02 8.81 3.25 3.39 3.32
f1 (ppm)
214.1 212.1 188.0 135.6 131.5 130.0 128.0 105.5 93.3 58.5 57.6 46.5 44.3 43.7 43.0 42.1 38.4 36.9 36.8 35.6 35.5 35.4 29.8 27.6 27.0 26.6 25.5 24.3 22.2 18.7 11.7
f1 (ppm)

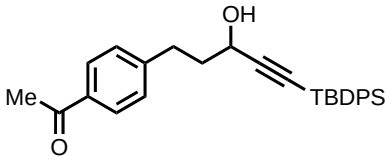
5-(4-Acetylphenyl)-1-(*tert*-butyldiphenylsilyl)pent-1-yn-3-one (3.1l)





To a flame-dried pressure tube equipped with a magnetic stir bar under an argon atmosphere charged with 4-bromoacetophenone (1.99 g, 10 mmol, 100 mol%), tetrabutylammonium bromide (TBAB, 3.22 g, 10 mmol, 100 mol%), $NaHCO_3$ (1.68 g, 20 mmol, 200 mol%), $Pd(OAc)_2$ (0.11 g, 0.5 mmol, 5 mol%) and pre-activated molecular sieves 4A (0.5 g, 50 mg/mmol) was added DMF (16 mL, 0.6 M) and allyl alcohol (1.02 mL, 15 mmol, 150 mol%). The reaction vessel was sealed and the reaction mixture was allowed to stir in an oil bath at 60 ^oC overnight and cooled to room temperature. Ethyl acetate (30 mL) was added and the mixture was filtered through a pad of celite. The resulting solution was transferred to a separatory funnel, washed with brine (4 x 25 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was subjected to flash column chromatography (SiO_2, hexanes/ethyl acetate = 3:1) to afford the title compound **sm1-3.1l** (1.07 g, 6.10 mmol) as yellow oil in 61% yield. The spectroscopic properties of this compound were consistent with the data available in literature.[25]

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.85 (t, J = 1.2 Hz, 1H), 7.94 – 7.90 (m, 2H), 7.33 – 7.30 (m, 2H), 3.04 (t, J = 7.5 Hz, 2H), 2.85 (td, J = 7.5, 1.2 Hz, 2H), 2.61 (s, 3H) ppm.



The title compound **sm2-3.1l** was prepared according to general procedure using *tert*-butyl(ethynyl)diphenylsilane (1.24 g, 4.7 mmol, 100 mol%) **sm1-3.1l** (0.83 g, 4.70 mmol, 100 mol%), *n*-BuLi (1.90 mL, 4.70 mmol, 100 mol%, 2.5 M in hexanes) and toluene (47 mL, 0.1 M). Upon flash column chromatography (SiO_2, hexanes/ethyl acetate = 3:1) the title compound (0.39 g, 2.21 mmol) was obtained in 47% yield as a yellow oil.

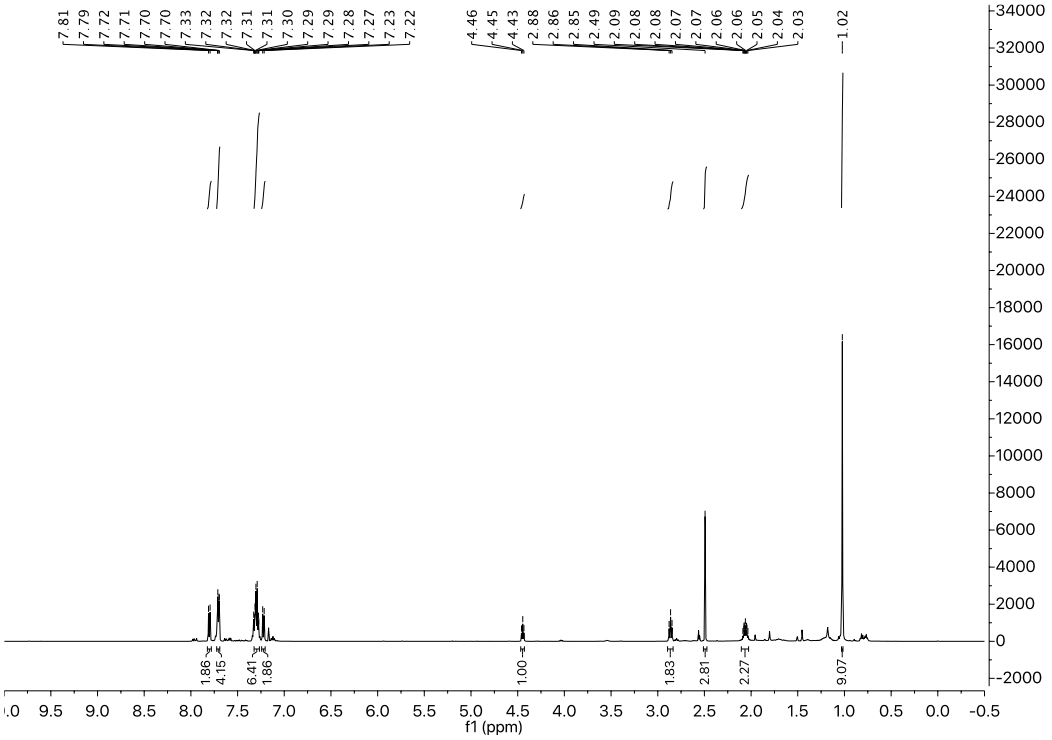
TLC (SiO_2) R_f = 0.39 (hexanes/ethyl acetate = 3:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.3 Hz, 2H), 7.72 – 7.69 (m, 4H), 7.32 – 7.27 (m, 6H), 7.22 (d, *J* = 8.1 Hz, 2H), 4.45 (t, *J* = 6.5 Hz, 1H), 2.86 (t, *J* = 7.9 Hz, 2H), 2.49 (s, 3H), 2.10 – 2.03 (m, 2H), 1.02 (s, 9H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 197.9, 147.2, 147.2, 135.6, 132.9, 129.7, 128.8, 128.7, 127.8, 127.8, 110.4, 85.6, 62.2, 38.9, 31.5, 27.1, 26.6, 18.5 ppm.

HRMS (ESI) m/z: [(M+K)+] calcd for $C_{29}H_{32}O_2Si$ 479.1803, found 479.1791.

FTIR (ATR) 2959, 2929, 2916, 2855, 1683, 1606, 1428, 1268, 1109, 703 cm^{-1}.


7.81
7.79
7.72
7.71
7.70
7.70
7.33
7.32
7.32
7.31
7.31
7.30
7.29
7.29
7.28
7.27
7.23
7.22
4.46
4.45
4.43
2.88
2.86
2.85
2.49
2.09
2.08
2.08
2.07
2.07
2.06
2.06
2.05
2.04
2.03
1.02
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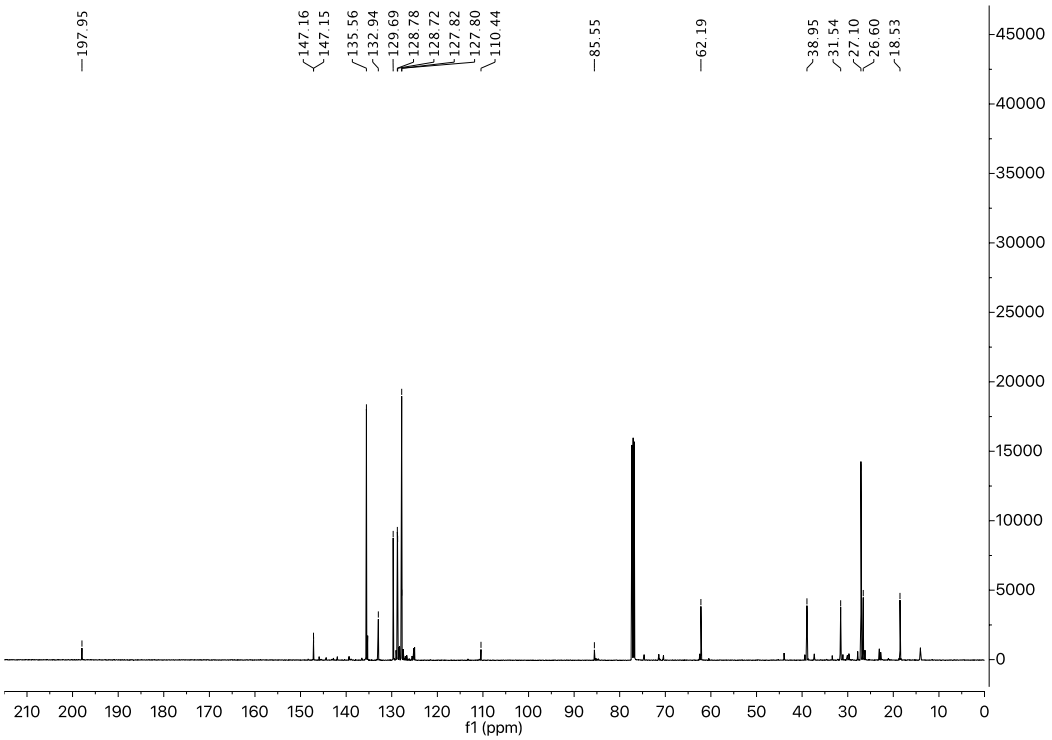
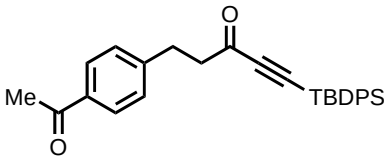
4.15
6.41
1.86
1.00
1.83
2.81
2.27
9.07
f1 (ppm)


197.95
147.16
147.15
135.56
132.94
129.69
128.78
128.72
127.82
127.80
110.44
85.55
62.19
38.95
31.54
27.10
26.60
18.53
f1 (ppm)



The title compound **3.1l** was prepared according to general procedure using **sm2-3.1l** (0.38 g, 0.84 mmol, 100 mol%), DMP (0.38 g, 0.90 mmol, 105 mol%), $NaHCO_3$ (0.28 g, 3.40 mmol, 400 mol%) and CH_2Cl_2 (4.2 mL, 0.2 M). Upon flash column chromatography (SiO_2, hexanes/ethyl acetate = 3:1) the title compound **3.1l** (0.26 g, 0.59 mmol) was obtained in 70% yield as a yellow oil.

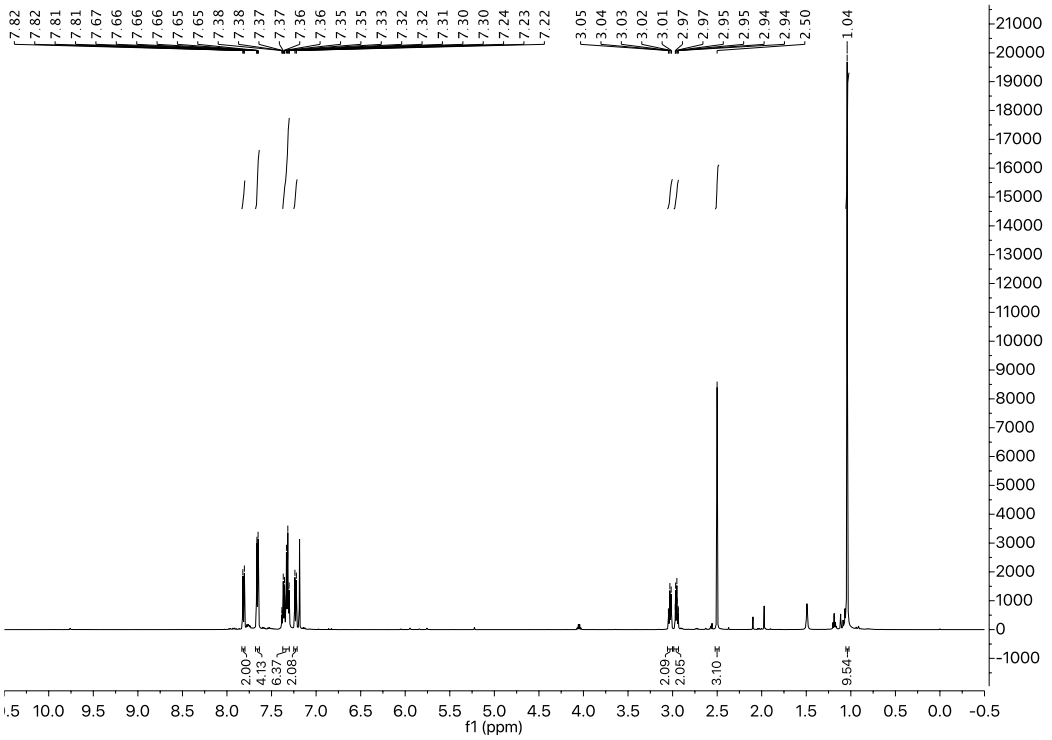
TLC (SiO_2) R_f = 0.54 (hexanes/ethyl acetate = 3:1).

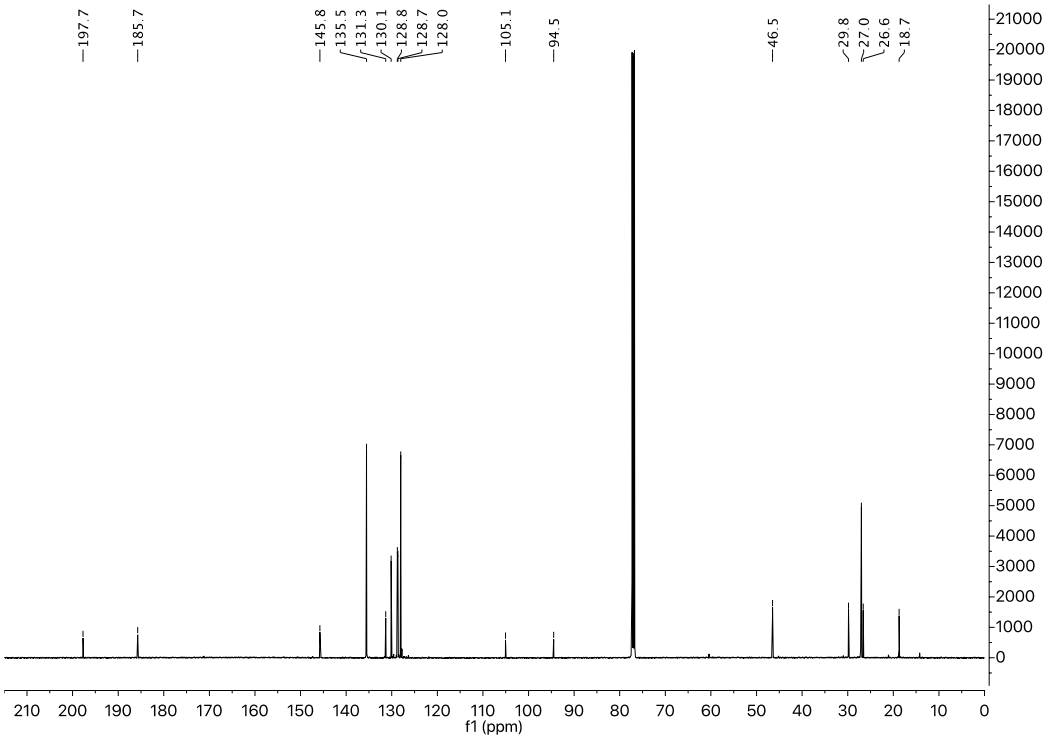
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 – 7.80 (m, 2H), 7.68 – 7.64 (m, 4H), 7.37 – 7.30 (m, 6H), 7.23 (d, *J* = 8.2 Hz, 2H), 3.03 (t, *J* = 7.6 Hz, 2H), 2.99 – 2.93 (m, 2H), 2.50 (s, 3H), 1.04 (s, 10H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 197.7, 185.7, 145.8, 135.5, 131.3, 130.1, 128.8, 128.7, 128.0, 105.1, 94.5, 46.5, 29.8, 27.0, 26.6, 18.7 ppm.

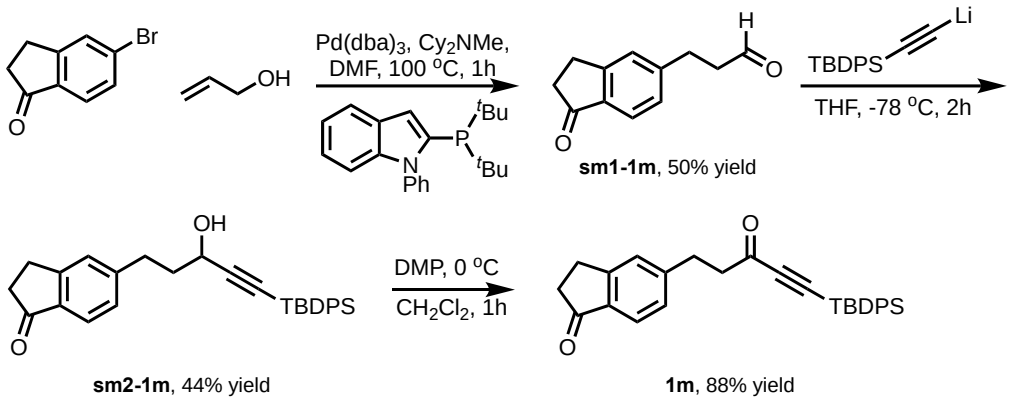
HRMS (ESI) m/z: [(M+Na)+] calcd for $C_{29}H_{30}O_2Si$ 461.1907, found 461.1904.

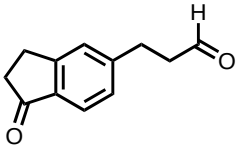
FTIR (ATR) 2929, 2857, 1678, 1606, 1428, 1358, 1266, 1102, 1017, 819 cm^{-1}.


7.82 7.82 7.81 7.81 7.67 7.66 7.66 7.66 7.65 7.65 7.38 7.38 7.37 7.37 7.36 7.36 7.35 7.35 7.33 7.32 7.32 7.31 7.30 7.30 7.24 7.23 7.22
3.05 3.04 3.03 3.02 3.01 2.97 2.97 2.95 2.95 2.94 2.94 2.50
1.04
2.00 4.13 6.37 2.08 2.09 2.05 3.10 9.54
f1 (ppm)


197.7 185.7 145.8 135.5 131.3 130.1 128.8 128.7 128.0 105.1 94.5 46.5 29.8 27.0 26.6 18.7
f1 (ppm)

5-(5-(*tert*-Butyldiphenylsilyl)-3-oxopent-4-yn-1-yl)-2,3-dihydro-1*H*-inden-1-one (3.1m)





To a flame-dried pressure tube equipped with a magnetic stir bar under an argon atmosphere charged with 5-bromoindanone (2.11 g, 10 mmol, 100 mol%), $Pd(dba)_3$ (0.21 g, 0.20 mmol, 2 mol%) and *N*-phenyl-2-(di-*t*-butylphosphino)indol (0.20 g, 0.60 mmol, 6 mol%) was added DMF (25 mL, 0.4 M), *N*,*N*-dicyclohexylmethylamine (2.40 mL, 11 mmol, 110 mol%) and allyl alcohol (0.75 mL, 11 mmol, 110 mol%). The reaction vessel was sealed and the reaction mixture was allowed to stir in an oil bath at 100 °C for 1 h and cooled to room temperature. Ethyl acetate (30 mL) was added and the mixture was filtered through a pad of celite. The resulting solution was transferred to a separatory funnel, washed with brine (4 x 25 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was subjected to flash column chromatography (SiO_2, hexanes/ethyl acetate = 2:1) to afford the title compound **sm1-3.1m** (1.03 g, 5.50 mmol) as yellow oil in 50% yield.

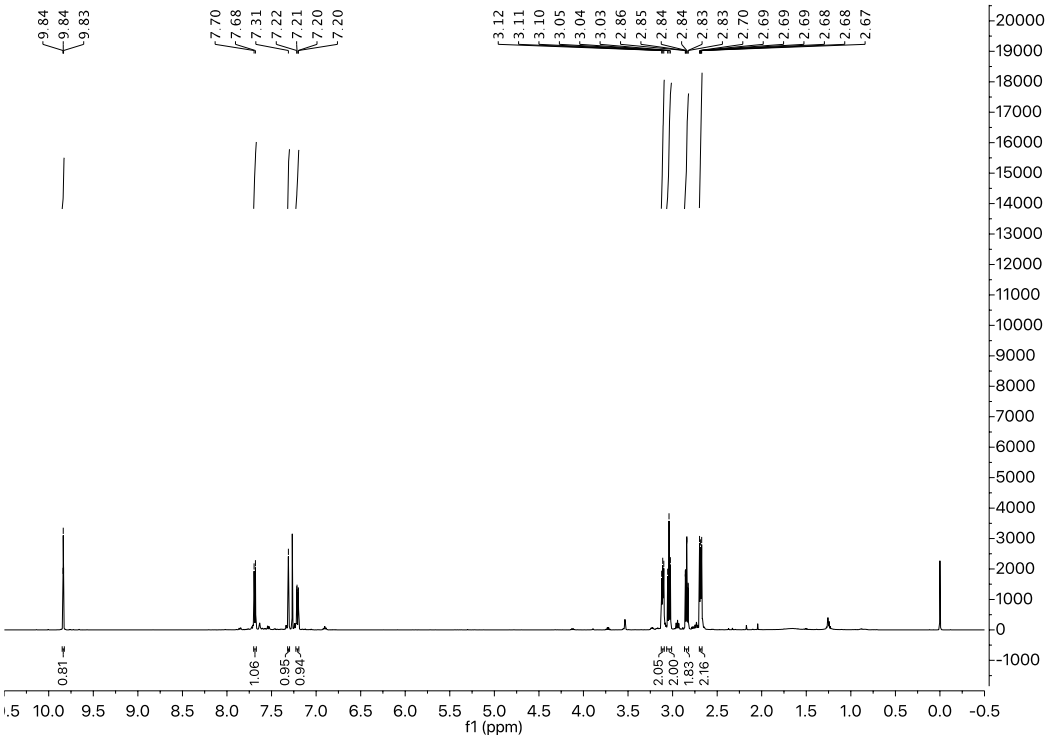
TLC (SiO_2) R_f = 0.23 (hexanes/ethyl acetate = 2:1).

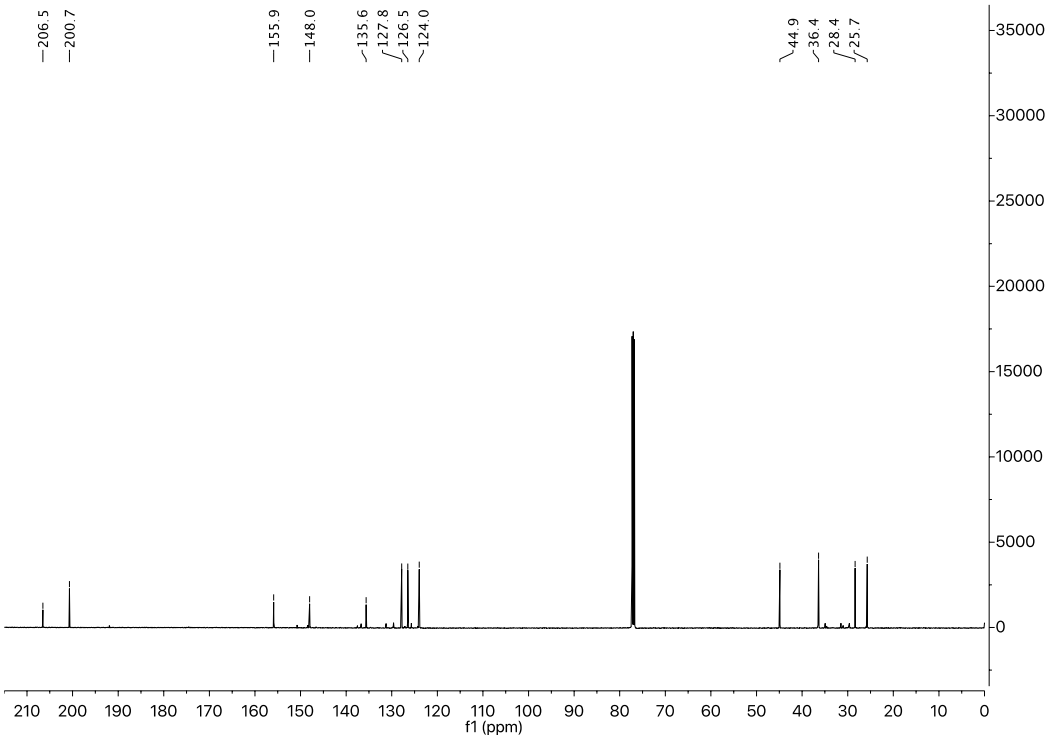
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.84 (t, *J* = 1.2 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.31 (s, 1H), 7.21 (dd, *J* = 8.0, 1.4 Hz, 1H), 3.13 – 3.09 (m, 2H), 3.04 (t, *J* = 7.4 Hz, 2H), 2.84 (td, *J* = 7.4, 1.2 Hz, 2H), 2.70 – 2.67 (m, 2H) ppm.

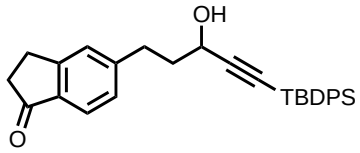
^{13}C NMR (126 MHz, $CDCl_3$) δ 206.5, 200.7, 155.9, 148.0, 135.6, 127.8, 126.5, 124.0, 44.9, 36.4, 28.4, 25.7 ppm.

HRMS (ESI) m/z: [(M+H)+] calcd for $C_{12}H_{12}O_2$ 189.0910, found 189.0909.

FTIR (ATR) 2921, 2735, 1698, 1648, 1606, 1441, 1404, 1290, 1104, 1028, 815 cm^{-1}.







The title compound **sm2-3.1m** was prepared according to general procedure using *tert*-butyl(ethynyl)diphenylsilane (0.56 g, 2.11 mmol, 100 mol%) **sm1-3.1m** (0.44 g, 2.34 mmol, 110 mol%), *n*-BuLi (0.84 mL, 2.11 mmol, 100 mol%, 2.5 M in hexanes) and toluene (21 mL, 0.1 M). Upon flash column chromatography (SiO_2, hexanes/ethyl acetate = 3:1) the title compound (0.47 g, 1.03 mmol) was obtained in 44% yield as a yellow oil.

TLC (SiO_2) R_f = 0.23 (hexanes/ethyl acetate = 3:1).

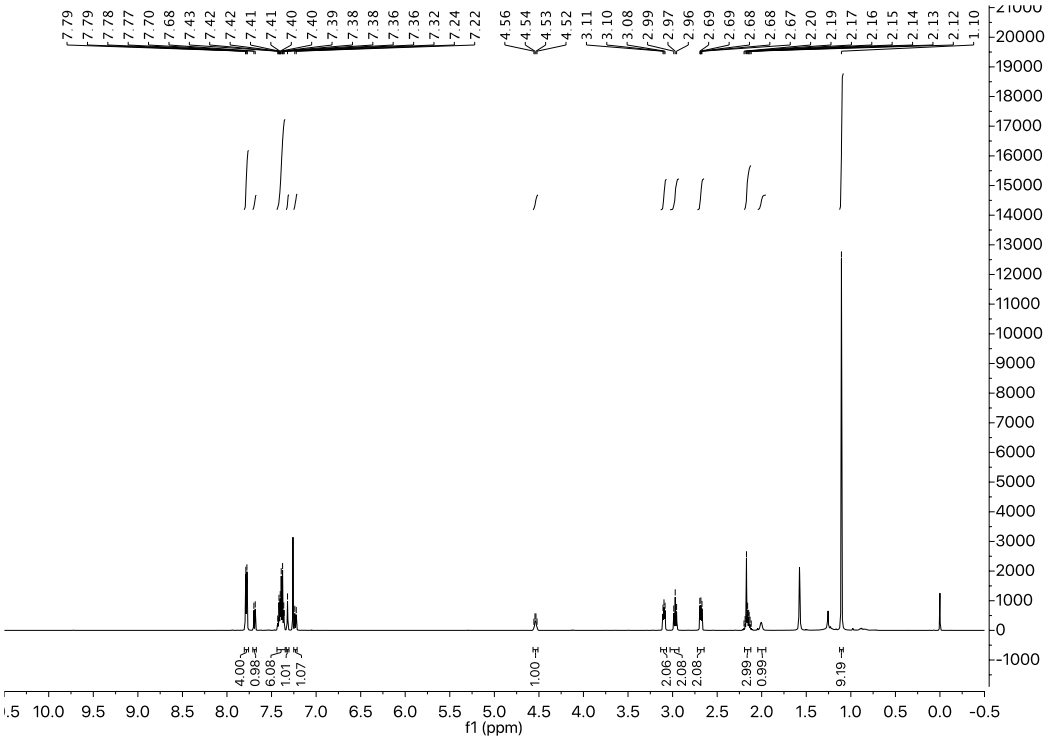
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 – 7.76 (m, 4H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.39 (ddd, *J* = 14.1, 7.7, 6.1 Hz, 6H), 7.32 (s, 1H), 7.23 (d, *J* = 7.9 Hz, 1H), 4.54 (q, *J* = 5.9 Hz, 1H),

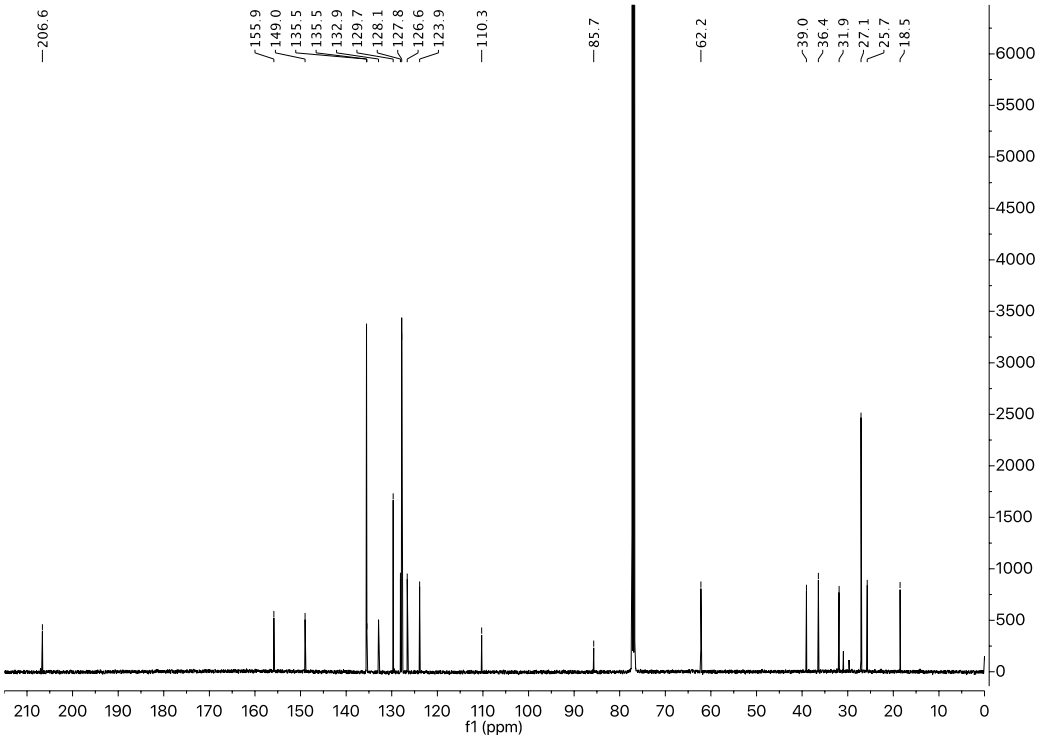
3.13 – 3.07 (m, 2H), 2.97 (t, *J* = 7.8 Hz, 2H), 2.72 – 2.65 (m, 2H), 2.19 – 2.12 (1, 3H), 2.01 (s, 1H), 1.10 (s, 9H) ppm.

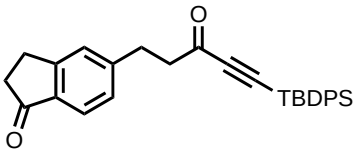
^{13}C NMR (126 MHz, $CDCl_3$) δ 206.6, 155.9, 149.0, 135.5, 135.5, 132.9, 129.7, 128.1, 127.8, 126.6, 123.9, 110.3, 85.7, 62.2, 39.0, 36.4, 31.9, 27.1, 25.7, 18.5 ppm.

HRMS (ESI) m/z: [(M+K)+] calcd for $C_{30}H_{32}O_2Si$ 491.1803, found 491.1802.

FTIR (ATR) 3400, 2925, 2854, 1706, 1608, 1429, 1328, 1261, 1105, 1030, 816 cm^{-1}.







The title compound **3.1m** was prepared according to general procedure using **sm2-3.1m** (0.41 g, 0.91 mmol, 100 mol%), DMP (0.44 g, 1.05 mmol, 115 mol%), $NaHCO_3$ (0.31 g, 3.64 mmol, 400 mol%) and DCM (5.0 mL, 0.2 M). Upon flash column chromatography (SiO_2, hexanes/ethyl acetate = 3:1) the title compound **3.1m** (0.36 g, 0.80 mmol) was obtained in 88% yield as a white solid.

TLC (SiO_2) R_f = 0.34 (hexanes/ethyl acetate = 3:1).

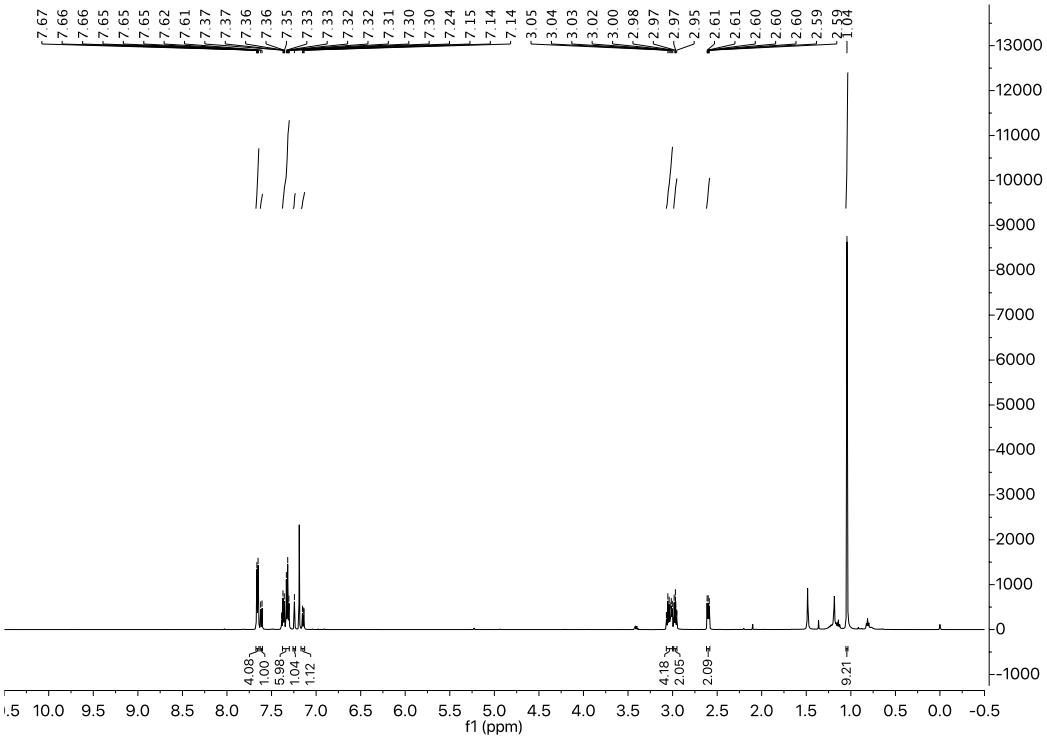
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (dt, *J* = 6.7, 1.5 Hz, 4H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.38 – 7.30 (m, 6H), 7.24 (s, 1H), 7.17 – 7.13 (m, 1H), 3.07 – 3.00 (m, 4H), 2.97 (dd, *J* = 7.8, 6.2 Hz, 2H), 2.62 – 2.58 (m, 2H), 1.04 (s, 9H) ppm.

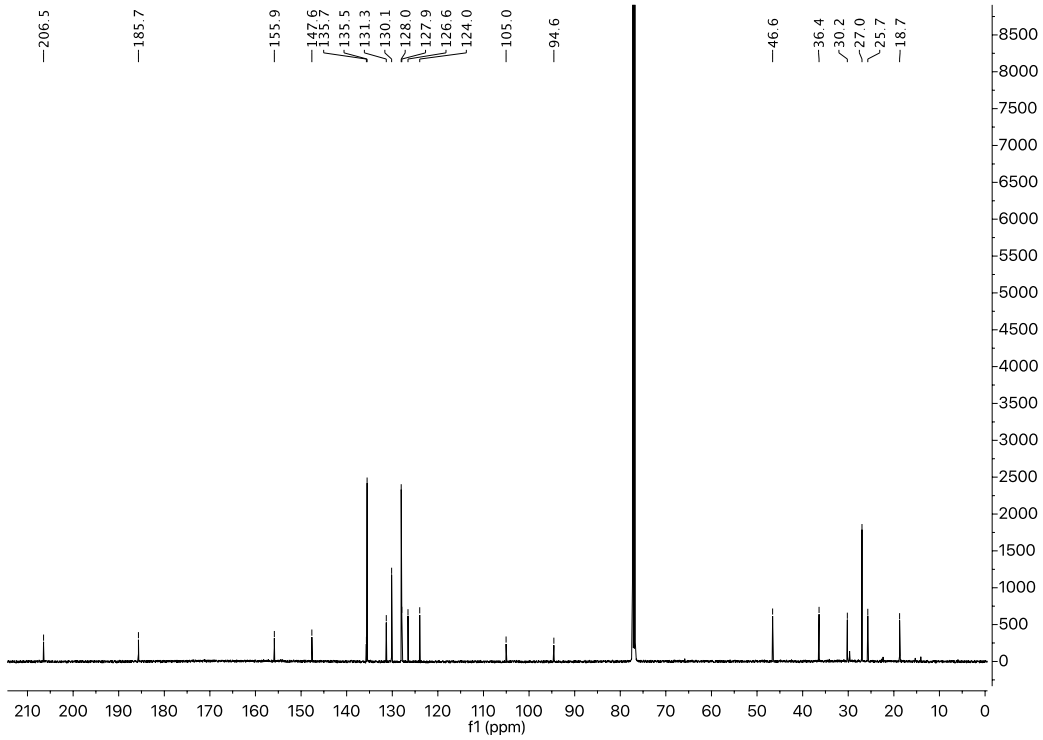
^{13}C NMR (126 MHz, $CDCl_3$) δ 206.5, 185.7, 155.9, 147.6, 135.7, 135.5, 131.3, 130.1, 128.0, 127.9, 126.6, 124.0, 105.0, 94.6, 46.6, 36.4, 30.2, 27.0, 25.7, 18.7 ppm.

HRMS (ESI) m/z: [(M+K)+] calcd for $C_{30}H_{30}O_2Si$ 489.1647, found 489.1647.

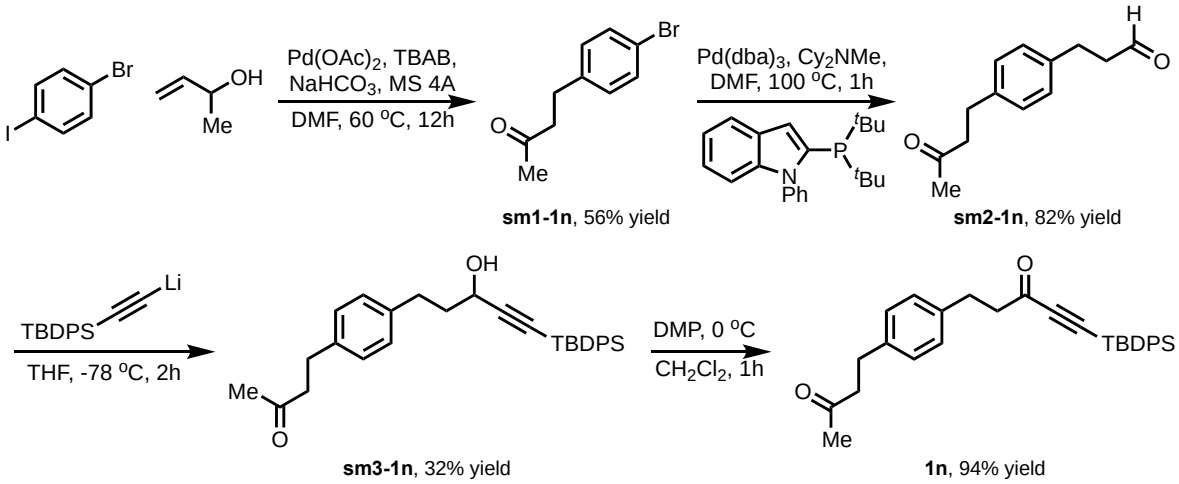
FTIR (ATR) 2959, 2927, 2360, 2340, 1710, 1606, 1428, 1284, 1108, 818, 703 cm^{-1}.

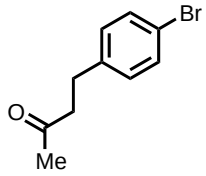
MP: 117-119 ^{o}C





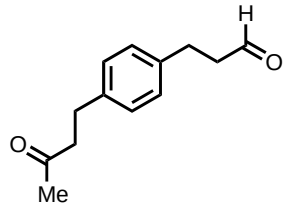
1-(*tert*-Butyldiphenylsilyl)-5-(4-(3-oxobutyl)phenyl)pent-1-yn-3-one (3.1n)





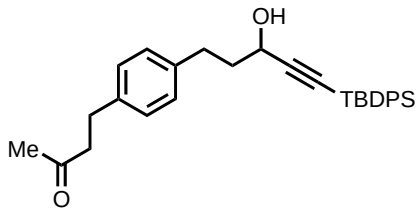
The title compound **sm1-3.1n** was prepared according to general procedure using 4-iodobromobenzene (5.66 g, 20 mmol, 100 mol%), TBAB (6.44 g, 20 mmol, 100 mol%), $Pd(OAc)_2$ (0.22 g, 1.0 mmol, 5 mol%) and $NaHCO_3$ (2.52 g, 30 mmol, 150 mol%), 3-buten-2-ol (1.75 mL, 20 mmol, 100 mol%) and DMF (34 mL, 0.6 M). Upon flash column chromatography (SiO_2, hexanes/ethyl acetate = 9:1) the title compound **sm1-3.1n** (2.52 g, 11.1 mmol) was obtained in 56% yield as a yellow oil. The spectroscopic properties of this compound were consistent with the data available in literature.[26]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42, 7.41, 7.40, 7.09, 7.07, 2.88, 2.87, 2.85, 2.77, 2.76, 2.74, 2.16 ppm.



The title compound **sm2-3.1n** was prepared according to general procedure using **sm1-3.1n** (2.12 g, 9.34 mmol, 100 mol%), $Pd(dba)_3$ (0.19 g, 0.19 mmol, 2 mol%), *N*-phenyl-2-(di-*t*-butylphosphino)indol (0.19 g, 0.56 mmol, 6 mol%), DMF (19 mL, 0.5 M), N,N-dicyclohexylmethylamine (2.20 mL, 10.3 mmol, 110 mol%) and allyl alcohol (0.70 mL, 10.3 mmol, 110 mol%). Upon flash column chromatography (SiO_2, hexanes/ethyl acetate = 3:1) the title compound **sm2-3.1n** (1.57 g, 7.66 mmol) was obtained in 82% yield as a white solid. The spectroscopic properties of this compound were consistent with the data available in literature.[27]

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.84 (d, *J* = 1.6 Hz, 1H), 7.13 (s, 4H), 2.95 (t, *J* = 7.5 Hz, 2H), 2.88 (t, *J* = 7.6 Hz, 2H), 2.78 (dd, *J* = 9.4, 7.4 Hz, 4H), 2.16 (s, 3H) ppm.



The title compound **sm3-3.1n** was prepared according to general procedure using *tert*-butyl(ethynyl)-diphenylsilane (1.49 g, 5.65 mmol, 100 mol%) **sm2-3.1n** (1.27 g, 6.22 mmol, 110 mol%), *n*-BuLi (2.30 mL, 5.65 mmol, 100 mol%, 2.5 M in hexanes) and toluene (55 mL, 0.1 M). Upon flash column chromatography (SiO_2, hexanes/ethyl acetate = 3:1) the title compound (0.85 g, 1.81 mmol) was obtained in 32% yield as a clear oil.

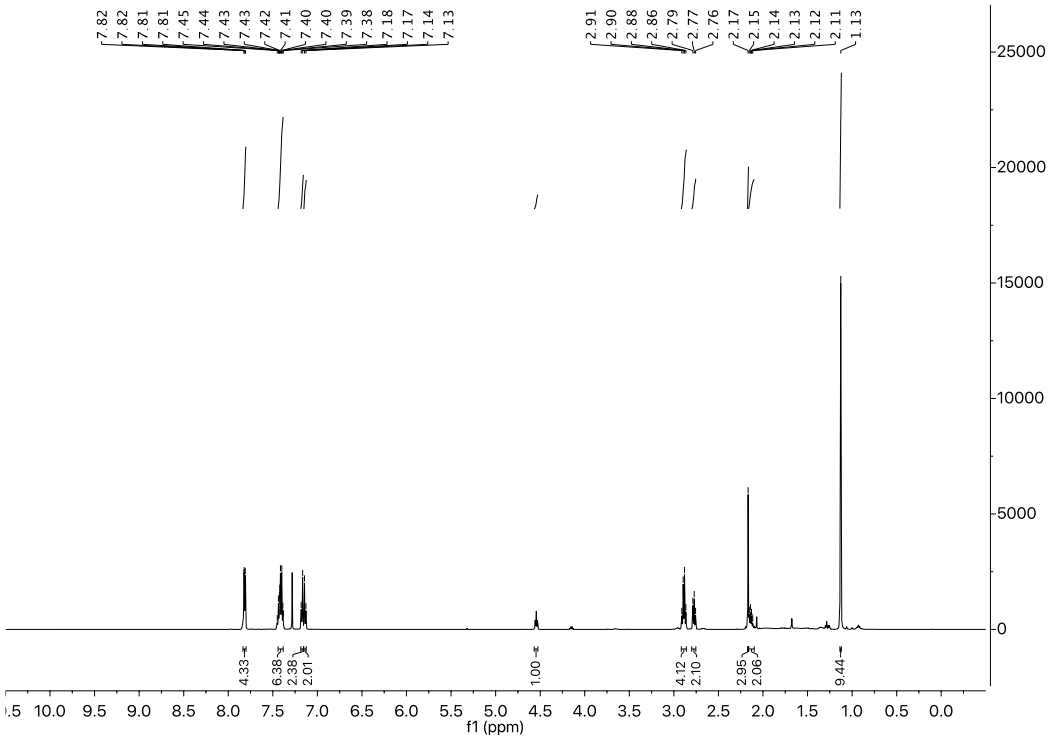
TLC (SiO_2) R_f = 0.30 (hexanes/ethyl acetate = 3:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 – 7.80 (m, 4H), 7.44 – 7.38 (m, 6H), 7.17 (d, *J* = 7.9 Hz, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 4.54 (t, *J* = 6.5 Hz, 1H), 2.89 (q, *J* = 7.7 Hz, 4H), 2.77 (t, *J* = 7.6 Hz, 2H), 2.17 (s, 3H), 2.16 – 2.10 (m, 2H), 1.13 (s, 9H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.1, 139.0, 138.7, 135.6, 133.0, 129.6, 128.7, 128.5, 127.8, 110.7, 85.3, 62.4, 45.3, 39.5, 31.1, 30.1, 29.3, 27.1, 18.5 ppm.

HRMS (ESI) m/z: [(M+K)+] calcd for $C_{31}H_{36}O_2Si$ 507.2116, found 507.2105.

FTIR (ATR) 3410, 2928, 2856, 1708, 1514, 1471, 1428, 1361, 1109, 1057, 1008, 819, 698 cm^{-1}.


7.82
7.82
7.81
7.81
7.45
7.44
7.43
7.43
7.42
7.41
7.40
7.40
7.39
7.38
7.18
7.17
7.14
7.13
2.91
2.90
2.88
2.86
2.79
2.77
2.76
2.17
2.15
2.14
2.13
2.12
2.11
1.13
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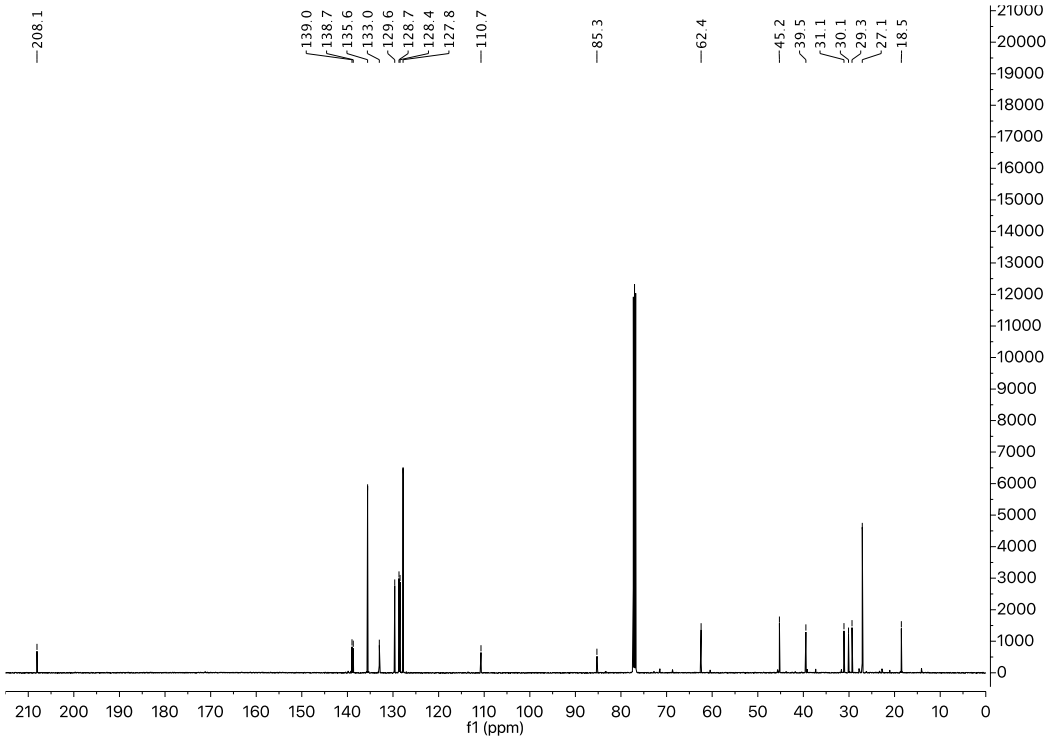
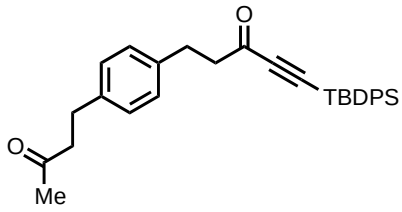
2.01
1.00
4.12
2.10
2.95
2.06
9.44
f1 (ppm)


208.1
139.0
138.7
135.6
133.0
129.6
128.7
128.4
127.8
110.7
85.3
62.4
45.2
39.5
31.1
30.1
29.3
27.1
18.5
f1 (ppm)



The title compound **3.1n** was prepared according to general procedure using **sm3-3.1n** (0.51 g, 1.09 mmol, 100 mol%), DMP (0.55 g, 1.31 mmol, 120 mol%), $NaHCO_3$ (0.37 g, 4.36 mmol, 400 mol%) and DCM (6.0 mL, 0.2 M). Upon flash column chromatography (SiO_2, hexanes/ethyl acetate = 5:1) the title compound **3.1n** (0.48 g, 1.03 mmol) was obtained in 94% yield as a pale yellow oil.

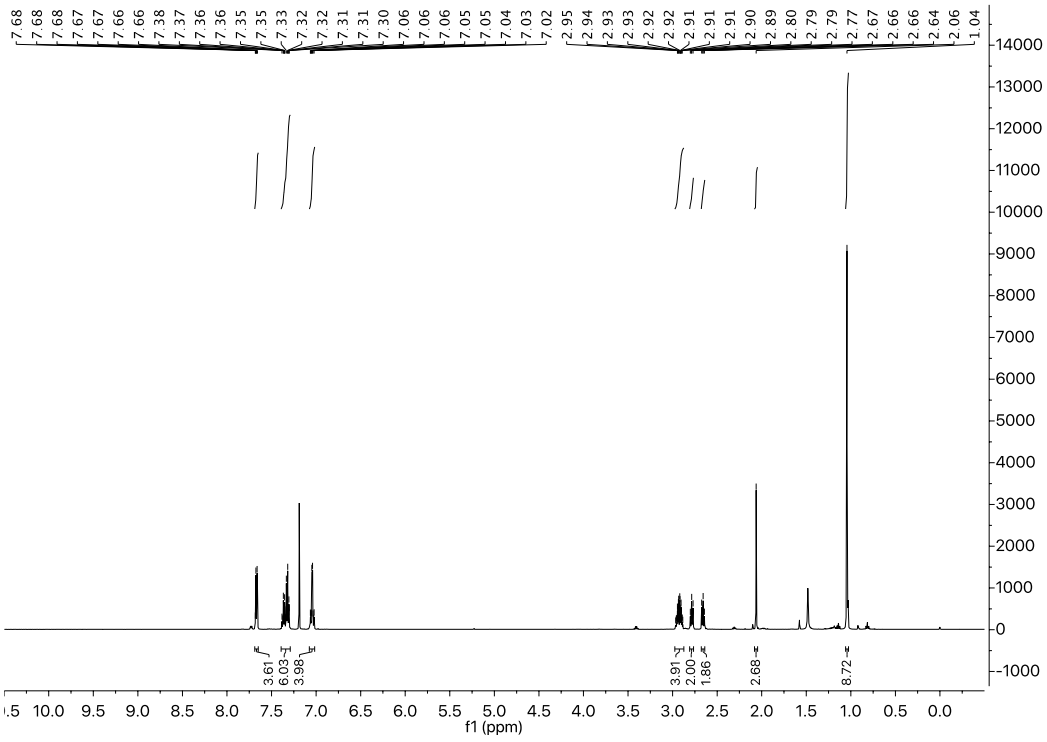
TLC (SiO_2) R_f = 0.35 (hexanes/ethyl acetate = 5:1).

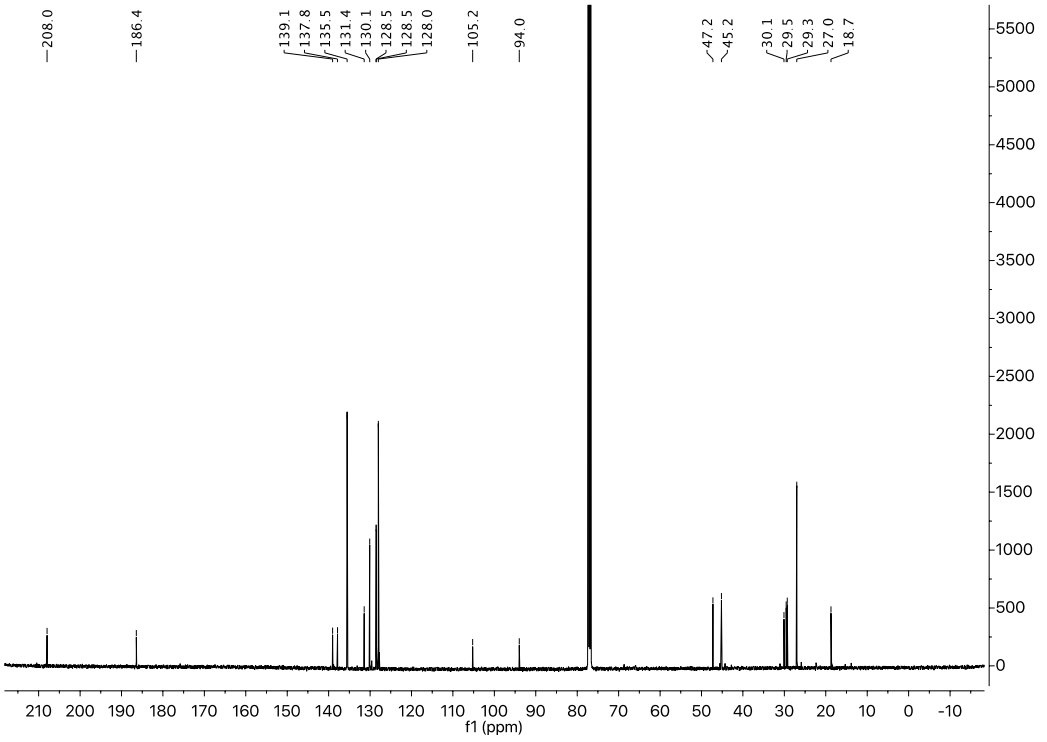
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.65 (m, 4H), 7.39 – 7.29 (m, 6H), 7.08 – 7.02 (m, 4H), 2.97 – 2.87 (m, 4H), 2.79 (t, *J* = 7.6 Hz, 2H), 2.66 (dd, *J* = 8.3, 6.9 Hz, 2H), 2.06 (s, 3H), 1.04 (s, 9H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 208.0, 186.4, 139.1, 137.9, 135.5, 131.4, 130.1, 128.5, 128.5, 128.0, 105.2, 94.0, 47.2, 45.2, 30.1, 29.5, 29.3, 27.0, 18.7 ppm.

HRMS (ESI) m/z: [(M+H)+] calcd for $C_{31}H_{34}O_2Si$ 468.2401, found 468.2414.

FTIR (ATR) 2930, 2857, 1714, 1676, 1428, 1361, 1103, 910, 818, 737, 698 cm^{-1}.


7.68 7.68 7.68 7.67 7.67 7.66 7.66 7.38 7.37 7.36 7.36 7.35 7.35 7.33 7.32 7.32 7.31 7.31 7.30 7.06 7.06 7.06 7.05 7.05 7.04 7.03 7.02
2.95 2.94 2.93 2.93 2.92 2.92 2.91 2.91 2.91 2.90 2.89 2.80 2.79 2.79 2.77 2.67 2.66 2.66 2.64 2.06 1.04
3.61 6.03 3.98 3.91 2.00 1.86 2.68 8.72
f1 (ppm)

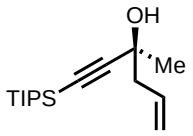

208.0 186.4 139.1 137.8 135.5 131.4 130.1 128.5 128.5 128.0 105.2 94.0 47.2 45.2 30.1 29.5 29.3 27.0 18.7
f1 (ppm)

3.5.4 Experimental Details and Spectra Data for tertiary alcohols 3.3a-3.3n

General procedure

To a pressure tube equipped with a magnetic stir bar under an argon atmosphere charged with K_2CO_3 (14 mg, 0.10 mmol, 50 mol%), (*S*)-Ir-I (10.3 mg, 0.01 mmol, 5 mol%), 3-nitro-4-cyano-benzoic acid (3.84 mg, 0.02, 10 mol%) and the acetylenic ketone (0.2 mmol, 100 mol%) was added anhydrous THF (0.2 mL, 1.0 M), 2-propanol (0.018 mL, 0.24 mmol, 120 mol%), allyl acetate (0.043 mL, 0.4 mmol, 200 mol%) and water (0.0036 mL, 0.20 mmol, 100 mol%) *via* syringe. The reaction vessel was sealed and the reaction mixture was placed in an oil bath at 100 °C for 48 hours. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. The resulting residue was subjected to flash column chromatography (SiO_2, hexanes/ethyl acetate as eluent) to furnish the desired tertiary alcohols.

(*S*)-3-Methyl-1-(triisopropylsilyl)hex-5-en-1-yn-3-ol (3.3a')



3a'

The title compound **3.3a'** was prepared according to general procedure using **3.1a'** (45 mg, 0.20 mmol, 100 mol%). Upon flash chromatography (SiO_2, hexanes/ethyl acetate = 40:1) the title compound (24 mg, 0.09 mmol) was obtained in 44% yield as a yellow oil.

TLC (SiO_2) R_f = 0.17 (hexanes/ethyl acetate = 30:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (dddd, *J* = 16.9, 10.4, 8.1, 6.5 Hz, 1H), 5.28 – 5.12 (m, 2H), 2.53 – 2.34 (m, 2H), 2.11 (s, 1H), 1.50 (s, 3H), 1.06-1.07 (m, 21H).

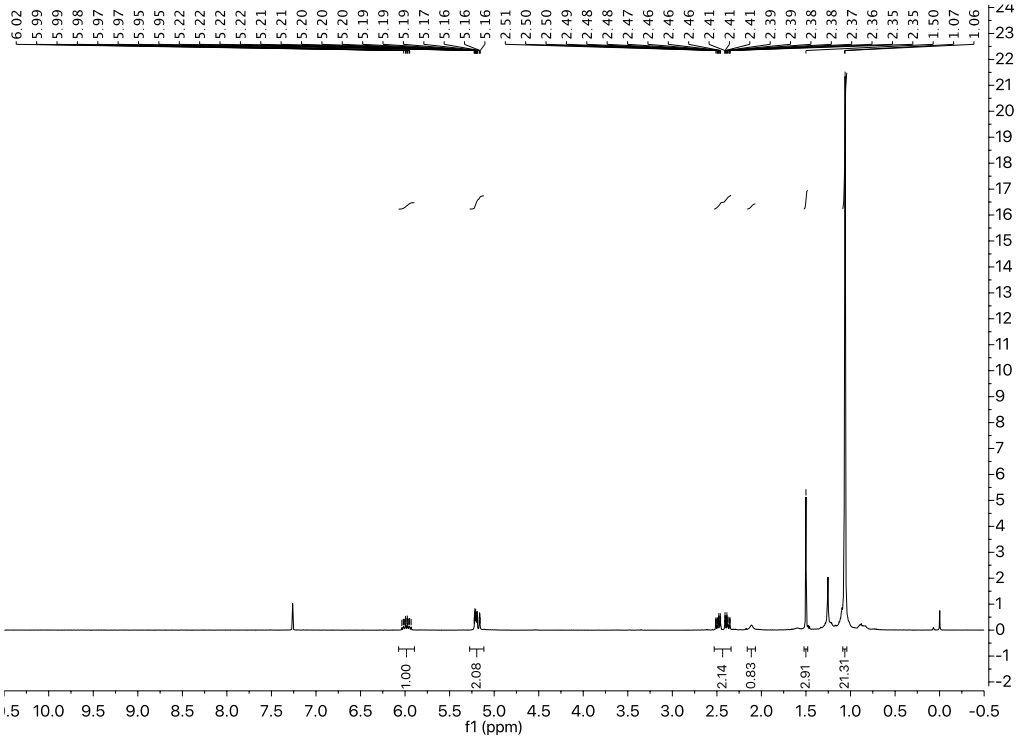
^{13}C NMR (101 MHz, $CDCl_3$) ^{13}C NMR (101 MHz, Chloroform-*d*) δ 133.4, 119.5, 111.1, 83.7, 67.4, 48.3, 29.7, 29.5, 18.6, 11.1.

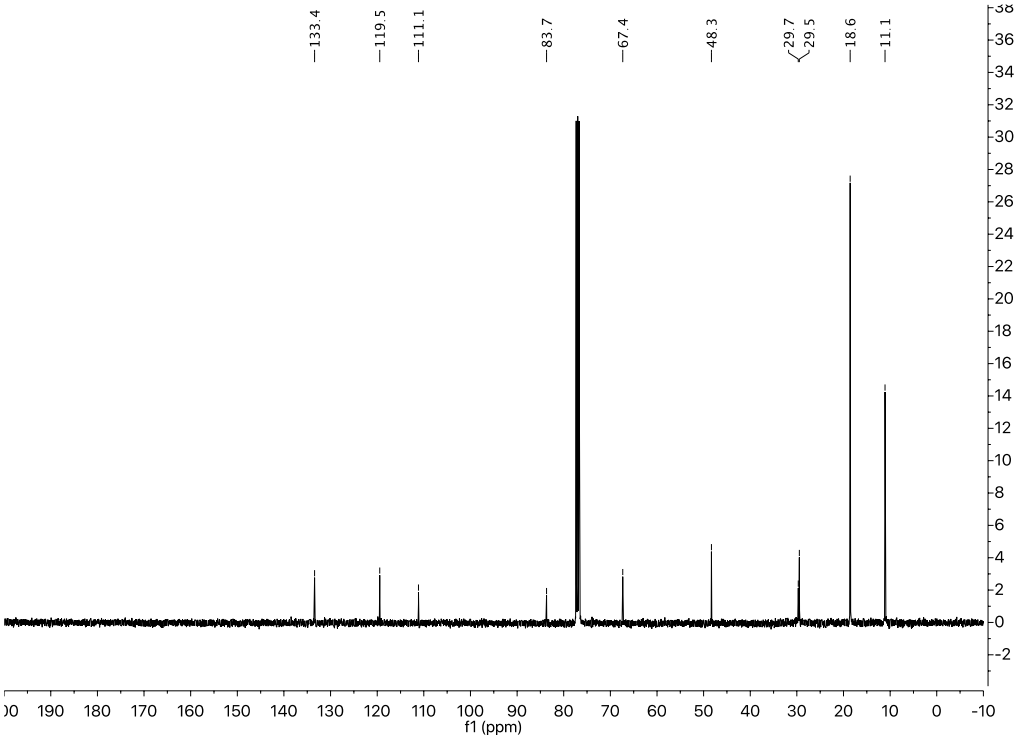
HRMS (ESI) m/z: [M+Na^+] calcd for $C_{16}H_{30}OSi$ 289.1958, found 289.1956.

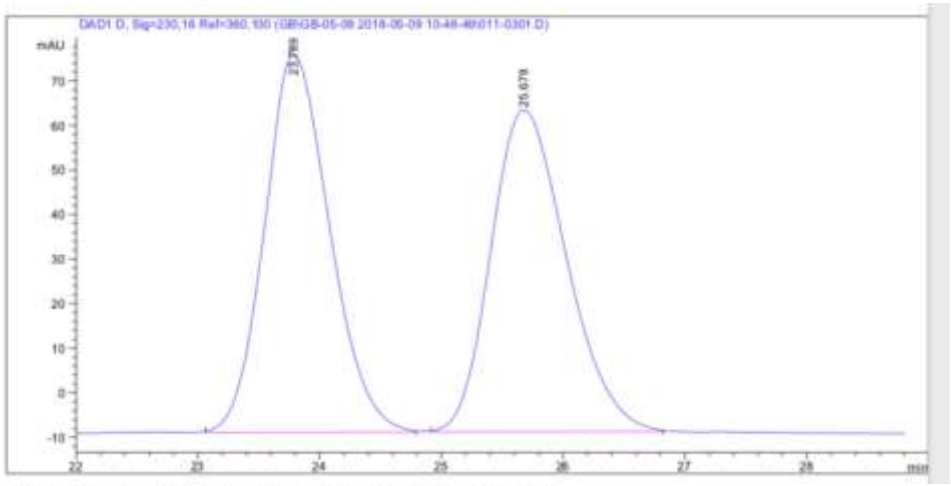
FTIR (ATR) 3434, 2942, 2892, 2865, 1463, 1382, 1367, 1260, 1111, 995, 883, cm^{-1}.

$[\alpha]_D^{28}$: -18.9 (*c* 1.0, $CHCl_3$).

HPLC: Enantiomeric excess was determined by HPLC analysis (OD-H column, hexanes:*i*-PrOH = 99.5:0.5, 0.5 mL/min, 230 nm), t_{major} = 24.45 min, t_{minor} = 26.50 min; *ee* = 96%.

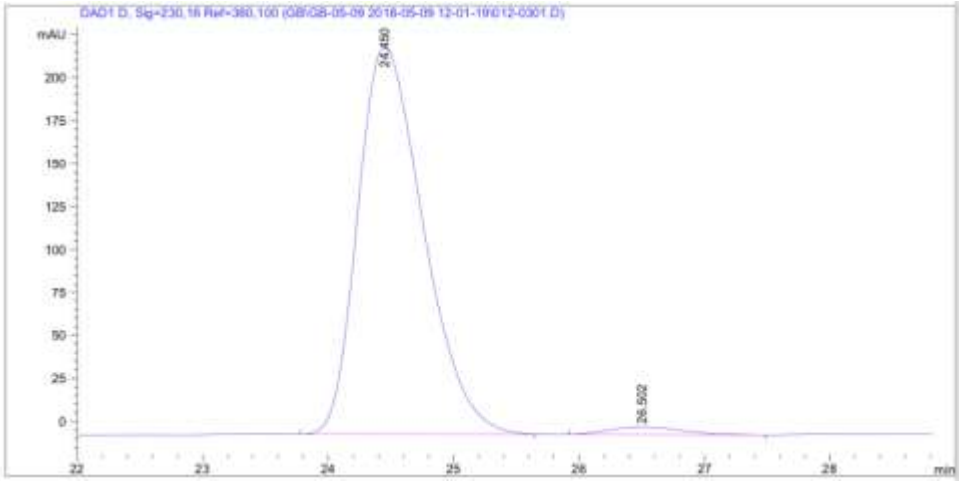

6.02 5.99 5.99 5.98 5.97 5.97 5.95 5.95 5.22 5.22 5.22 5.21 5.21 5.20 5.20 5.20 5.19 5.19 5.19 5.17 5.16 5.16 5.16
2.51 2.50 2.50 2.49 2.48 2.48 2.47 2.46 2.46 2.46 2.41 2.41 2.41 2.39 2.39 2.38 2.38 2.37 2.36 2.35 2.35 1.50 1.07 1.06
1.00 2.08 2.14 0.83 2.91 21.31
f1 (ppm)


133.4 119.5 111.1 83.7 67.4 48.3 29.7 29.5 18.6 11.1
f1 (ppm)



Signal 1: DAD1 D, Sig=230,16 Ref=360,100

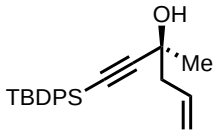
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.789	BB	0.5538	3145.35327	84.59978	50.2934
2	25.678	BB	0.6640	3108.64917	72.24621	49.7066
Totals :				6254.00244	156.84599	



Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.450	BB	0.5672	8173.89746	225.33690	97.8603
2	26.502	BB	0.4788	178.72311	4.52477	2.1397
Totals :				8352.62057	229.86167	

(*S*)-1-(*tert*-Butyldiphenylsilyl)-3-methylhex-5-en-1-yn-3-ol (3.3a)



3a

The title compound **3.3a** was prepared according to general procedure using **3.1a** (61.3 mg, 0.20 mmol, 100 mol%). Upon flash chromatography (SiO_2, hexanes/ethyl acetate = 20:1) the title compound (46 mg, 0.13 mmol) was obtained in 66% yield as a yellow oil.

TLC (SiO_2) R_f = 0.12 (hexanes/ethyl acetate = 20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.74 (m, 4H), 7.38 (ddd, *J* = 12.1, 7.6, 5.8 Hz, 6H), 6.05 (dddd, *J* = 16.8, 10.5, 8.1, 6.6 Hz, 1H), 5.28 – 5.21 (m, 2H), 2.60 (ddt, *J* = 13.5, 6.5, 1.3 Hz, 1H), 2.48 (dd, *J* = 13.5, 8.1 Hz, 1H), 2.22 (s, 1H), 1.61 (s, 3H), 1.08 (s, 9H) ppm

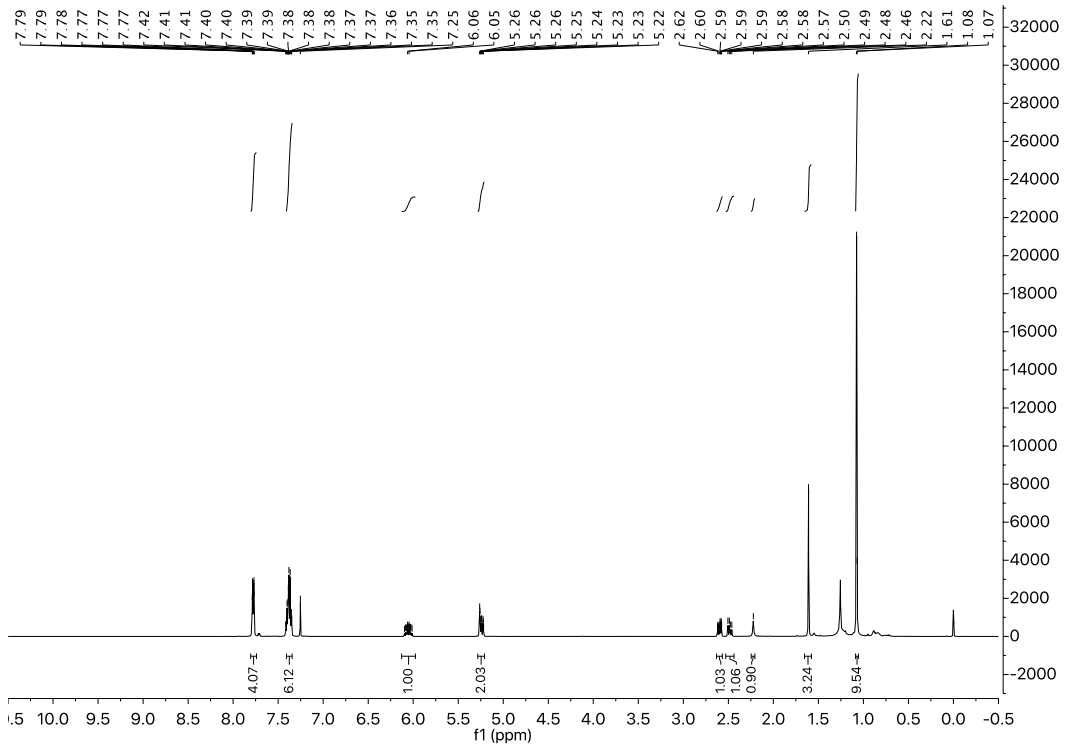
^{13}C NMR (126 MHz, $CDCl_3$) δ 135.5, 133.2, 133.1, 129.5, 127.7, 119.9, 113.4, 83.0, 67.6, 48.2, 29.4, 27.0, 18.5 ppm

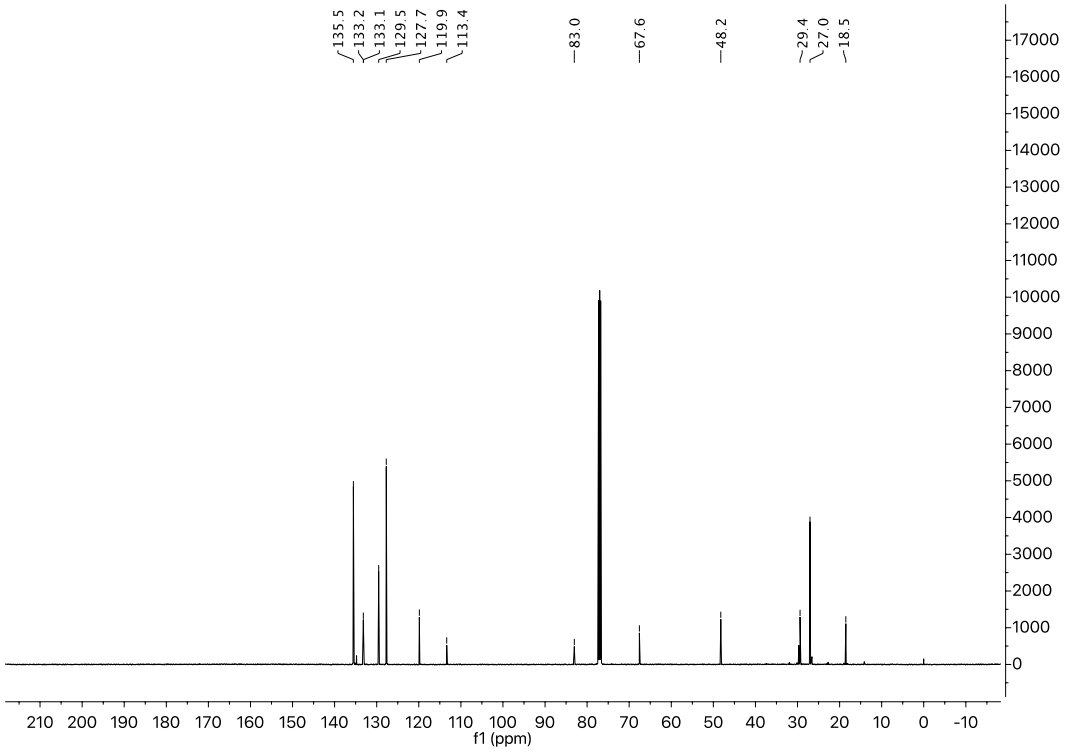
HRMS (ESI) m/z: [M+K^+] calcd for $C_{23}H_{28}OSi$ 387.1541, found 387.1549.

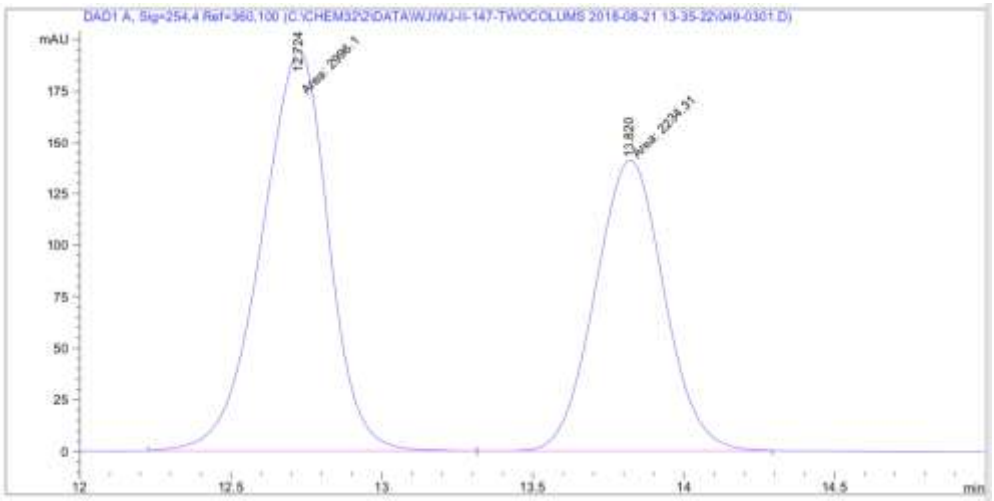
FTIR (ATR) 3432, 3070, 2928, 2856, 1471, 1428, 1361, 1259, 1109, 997, 886, 819 cm^{-1}.

$[\alpha]_D^{28}$: -19.6 (*c* 1.0, $CHCl_3$).

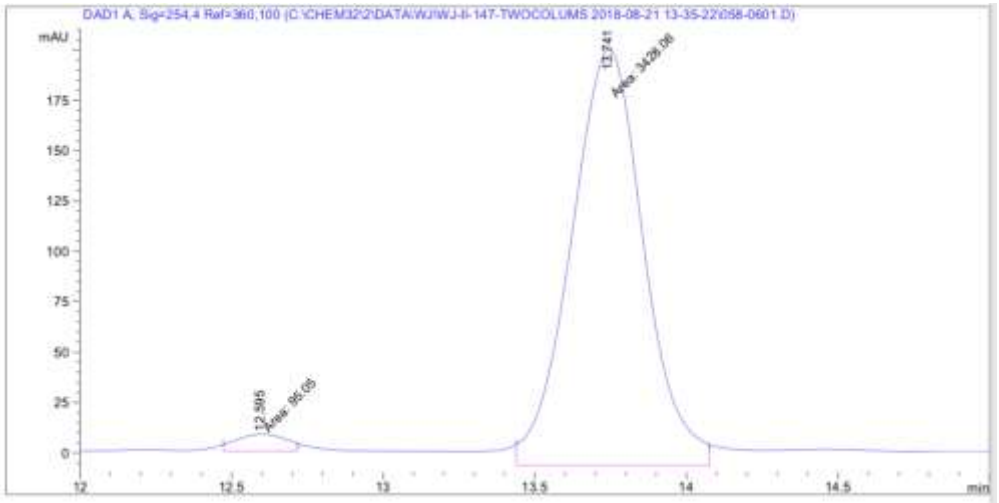
HPLC: Enantiomeric excess was determined by HPLC analysis (two Chiralcel OD-H columns, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 254 nm), t_{major} = 13.74 min, t_{minor} = 12.59 min; *ee* = 95%.


7.79 7.79 7.78 7.77 7.77 7.77 7.42 7.41 7.41 7.40 7.40 7.39 7.39 7.38 7.38 7.38 7.37 7.37 7.36 7.35 7.35 7.25 6.06 6.05 5.26 5.26 5.25 5.24 5.23 5.23 5.22 2.62 2.60 2.59 2.59 2.59 2.58 2.58 2.57 2.50 2.49 2.48 2.46 2.22 1.61 1.08 1.07
4.07 6.12 1.00 2.03 1.03 1.06 0.90 3.24 9.54
f1 (ppm)


135.5 133.2 133.1 129.5 127.7 119.9 113.4 83.0 67.6 48.2 29.4 27.0 18.5
f1 (ppm)

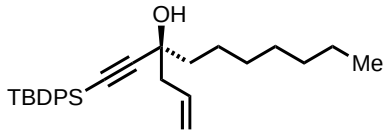


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.724	MF	0.2571	2996.09985	194.19370	57.2824
2	13.820	FM	0.2643	2234.30566	140.91716	42.7176
Totals :				5230.40552	335.11086	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.595	MM	0.1895	95.05002	8.36135	2.6979
2	13.741	MM	0.2765	3428.05884	206.61024	97.3021
Totals :				3523.10886	214.97160	

(*S*)-4-((*tert*-Butyldiphenylsilyl)ethynyl)undec-1-en-4-ol (3.3b)



3b

The title compound **3.3b** was prepared according to general procedure **3.1b** (78.3 mg, 0.20 mmol, 100 mol%). Upon flash chromatography (SiO_2, hexanes/ethyl acetate = 20:1) the title compound (49.3 mg, 0.11 mmol) was obtained in 57% yield as a yellow oil.

TLC (SiO_2) R_f = 0.37 (hexanes/ethyl acetate = 12:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 – 7.69 (m, 4H), 7.30 (tt, *J* = 8.3, 5.9 Hz, 6H), 5.99 (dddd, *J* = 16.8, 10.4, 8.1, 6.4 Hz, 1H), 5.20 – 5.13 (m, 2H), 2.57 – 2.50 (m, 1H), 2.36 (dd, *J* = 13.6, 8.2 Hz, 1H), 1.72 – 1.65 (m, 2H), 1.57 (ddd, *J* = 12.5, 9.1, 5.9 Hz, 3H), 1.29 – 1.19 (m, 8H), 1.00 (s, 9H), 0.82 – 0.78 (m, 3H) ppm.

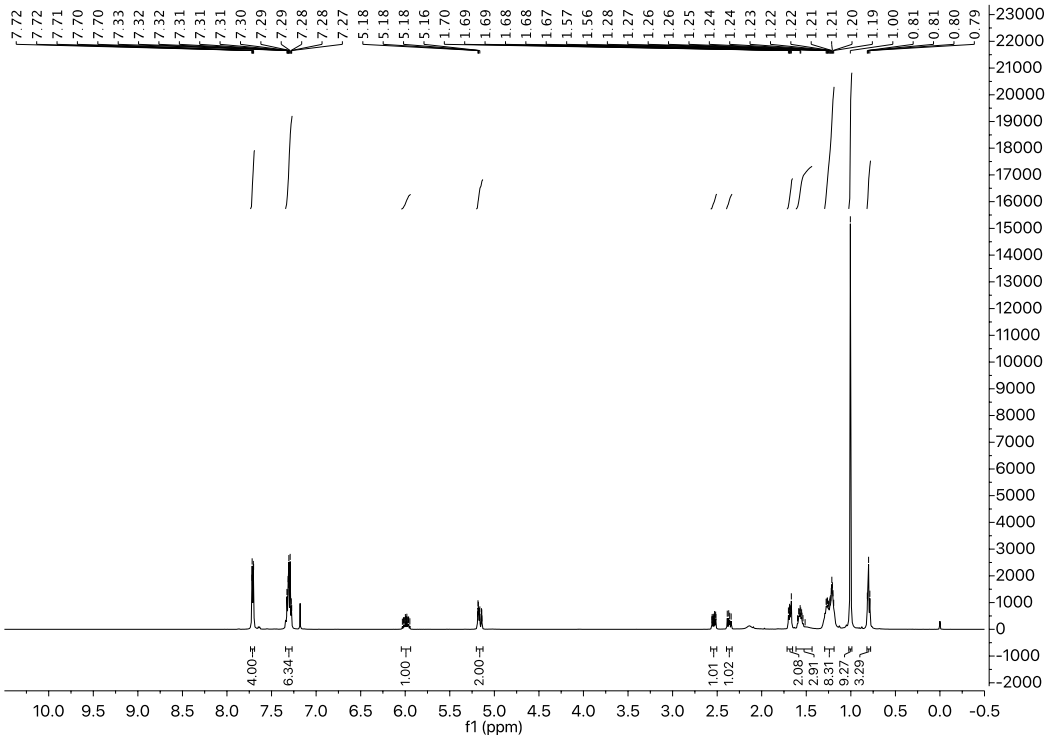
^{13}C NMR (126 MHz, $CDCl_3$) δ 135.6, 133.2, 133.2, 129.5, 127.7, 119.8, 112.7, 84.1, 70.8, 46.8, 41.8, 31.8, 29.7, 29.3, 27.0, 24.5, 22.7, 18.5, 14.1 ppm.

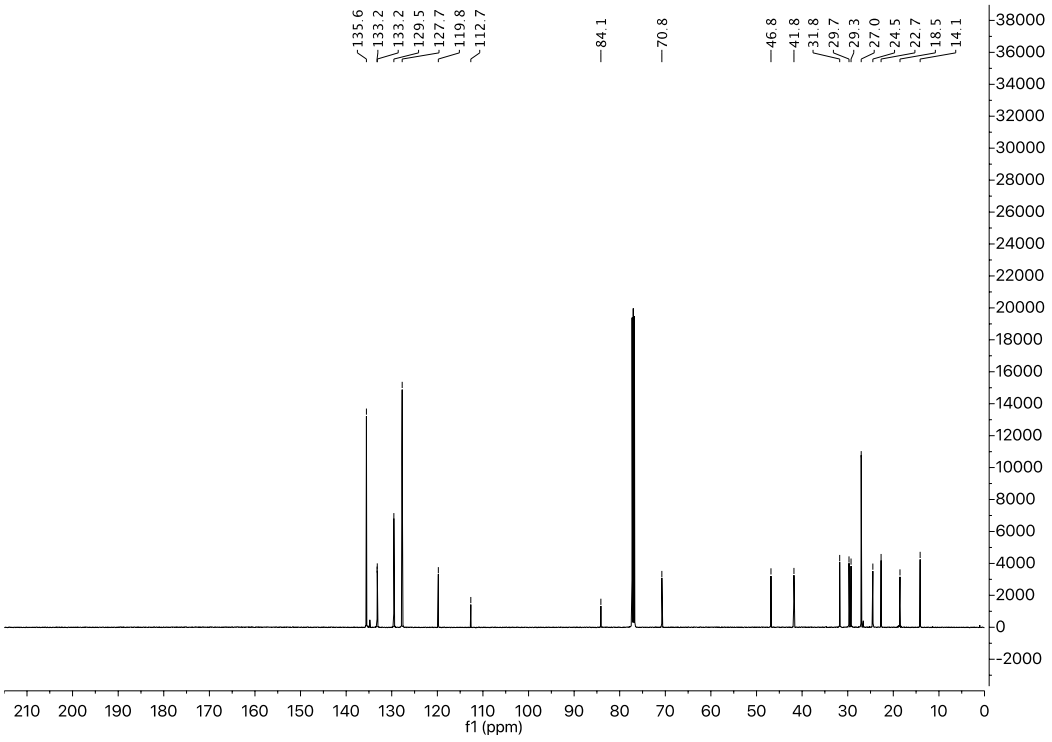
HRMS (ESI) m/z: [M+H$^+$] calcd for $C_{29}H_{40}OSi$ 433.2927, found 433.2913.

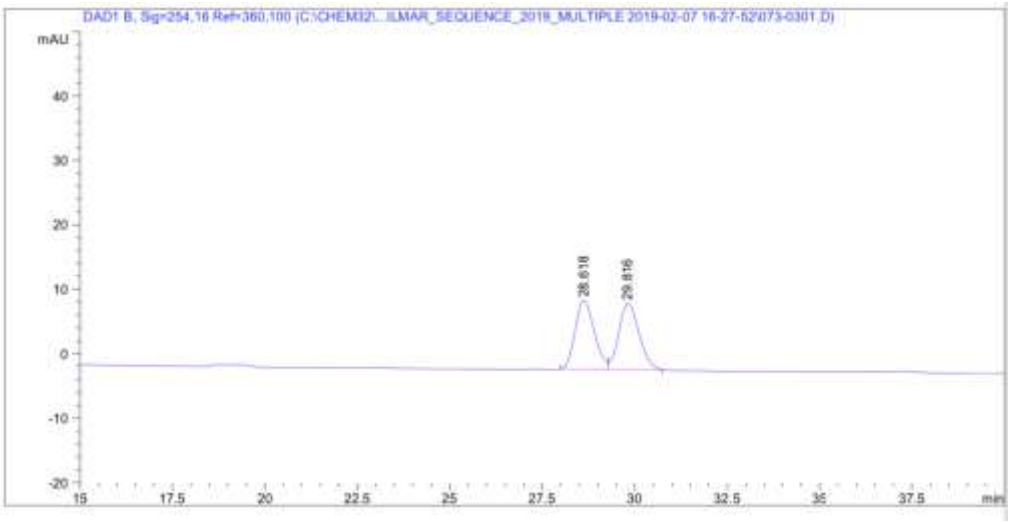
FTIR (ATR) 3421, 3070, 2928, 2856, 1470, 1428, 1109, 996, 819 cm^{-1}.

$[\alpha]_D^{28}$: -12.1 (*c* 1.0, $CHCl_3$).

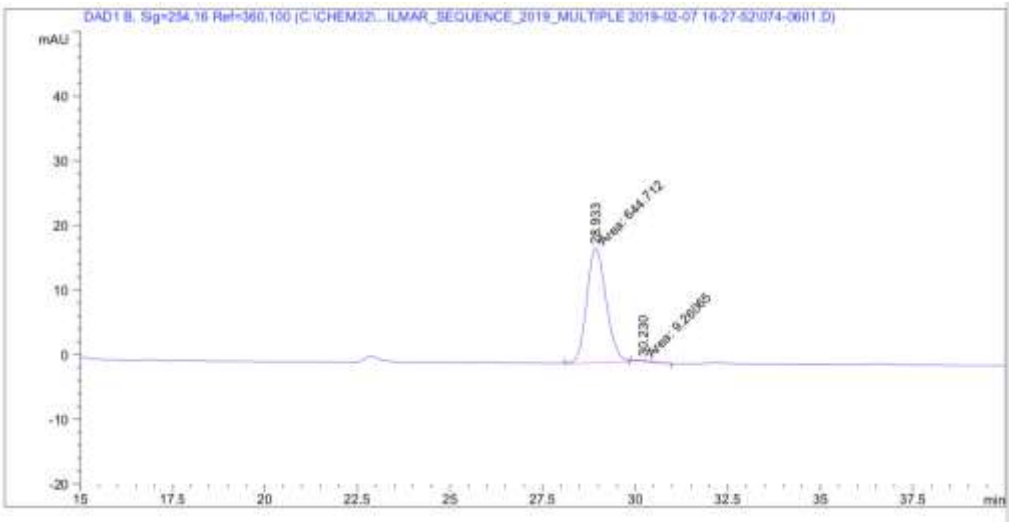
HPLC: Enantiomeric excess was determined by HPLC analysis (two Chiralcel AD-H columns, hexanes:*i*-PrOH = 98:2, 0.5 mL/min, 254 nm), t_{major} = 28.93 min, t_{minor} = 30.23 min; *ee* = 98%.


7.72 7.72 7.71 7.70 7.70 7.33 7.32 7.32 7.31 7.31 7.31 7.30 7.29 7.29 7.28 7.28 7.27
5.18 5.18 5.18 5.16 1.70 1.69 1.69 1.68 1.68 1.67 1.57 1.56 1.28 1.27 1.26 1.26 1.25 1.24 1.24 1.23 1.22 1.22 1.21 1.21 1.20 1.19 1.00 0.81 0.81 0.80 0.79
4.00 6.34 1.00 2.00 1.01 1.02 2.08 2.91 8.31 9.27 3.29
f1 (ppm)


135.6 133.2 133.2 129.5 127.7 119.8 112.7
84.1 70.8 46.8 41.8 31.8 29.7 29.3 27.0 24.5 22.7 18.5 14.1
f1 (ppm)

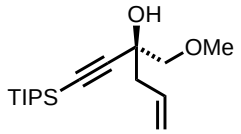


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.618	BV	0.5503	382.48779	10.66660	49.4534
2	29.816	VB	0.5814	390.94330	10.28540	50.5466
Totals :				773.43109	20.95200	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.933	MM	0.6050	644.71228	17.75994	98.5839
2	30.230	MM	0.6076	9.26065	2.54030e-1	1.4161
Totals :				653.97293	18.01397	

(*S*)-3-(Methoxymethyl)-1-(triisopropylsilyl)hex-5-en-1-yn-3-ol (3.3c)



3c

The title compound **3.3c** was prepared according to general procedure using **3.1c** (59.3 mg, 0.20 mmol, 100 mol%). Upon flash chromatography (SiO_2, hexanes/ethyl acetate = 9:1) the title compound (38 mg, 0.13 mmol) was obtained in 63% yield as a yellow.

TLC (SiO_2) R_f = 0.35 (hexanes/ethyl acetate = 9:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02 – 5.90 (m, 1H), 5.21 – 5.14 (m, 2H), 3.48 – 3.42 (m, 5H), 2.52 – 2.42 (m, 2H), 1.06 (d, *J* = 3.2 Hz, 21H) ppm.

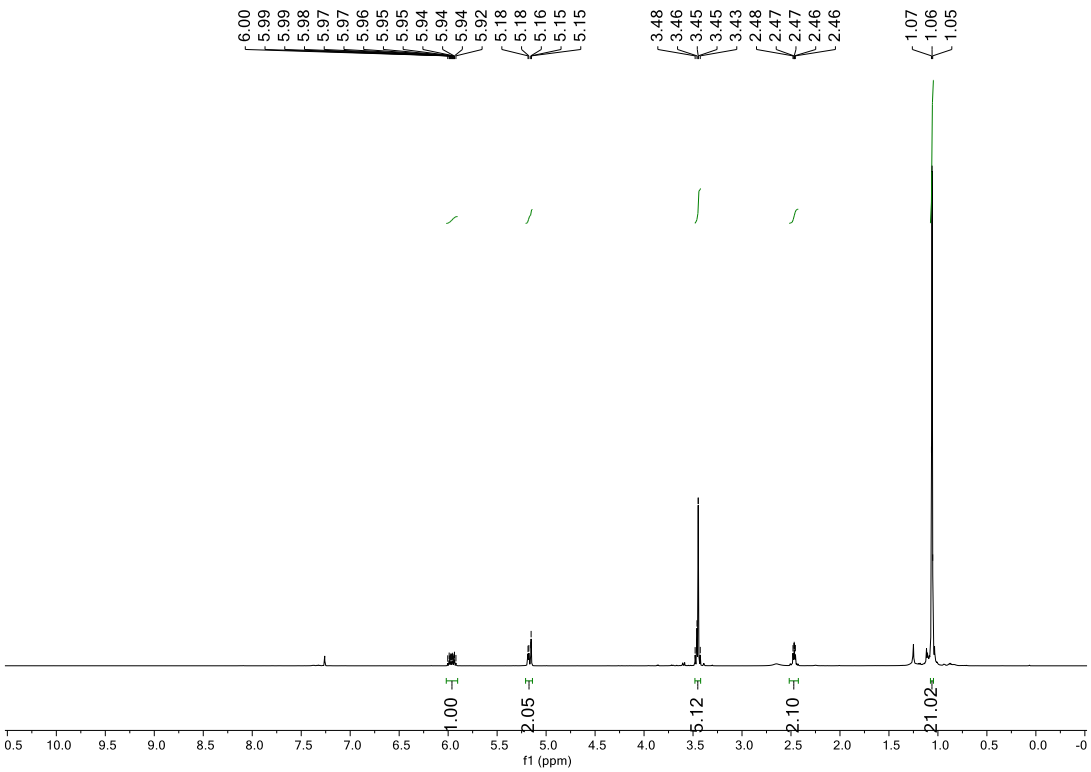
^{13}C NMR (101 MHz, $CDCl_3$) δ 132.9, 119.1, 108.2, 85.6, 78.5, 70. 0, 59.6, 43.3, 18.6, 11.1 ppm.

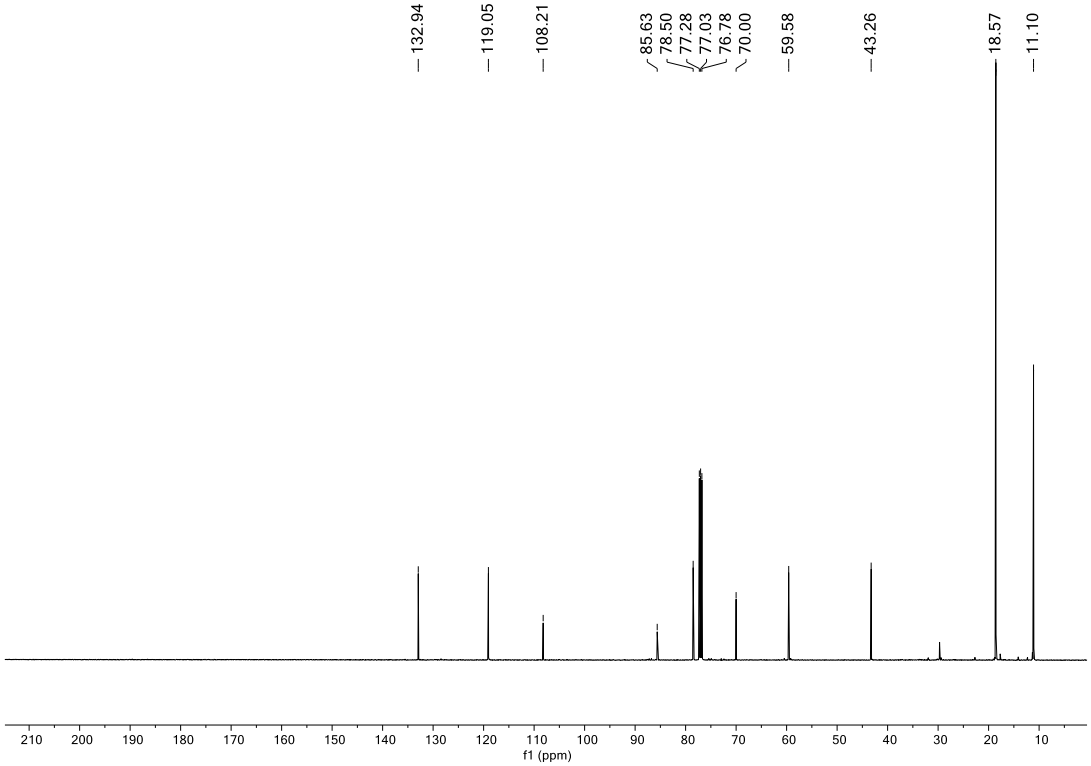
HRMS (ESI) m/z: [M+Na^+] calcd for $C_{17}H_{32}O_2Si$ 319.2064, found 319.2068.

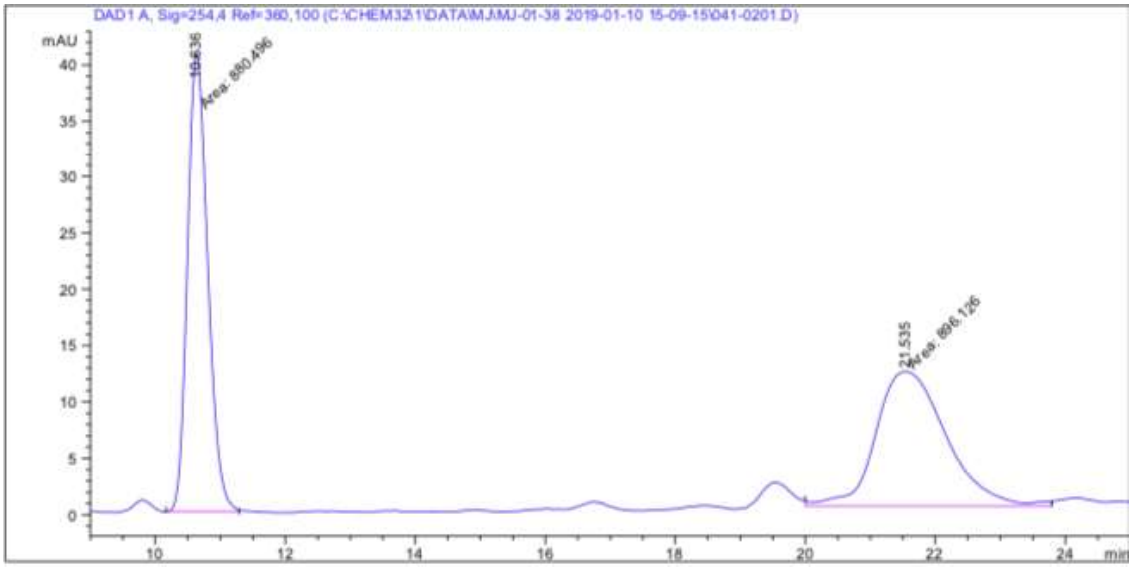
FTIR (ATR) 2941.66, 2865.04, 1462.86, 1383.30, 1199.73, 1108.30, 1072.69, 995.53, 917.38, 882.34, 813.99, 676.17cm^{-1}.

$[\alpha]_D^{28}$: -4.08 (*c* 1.25, $CHCl_3$).

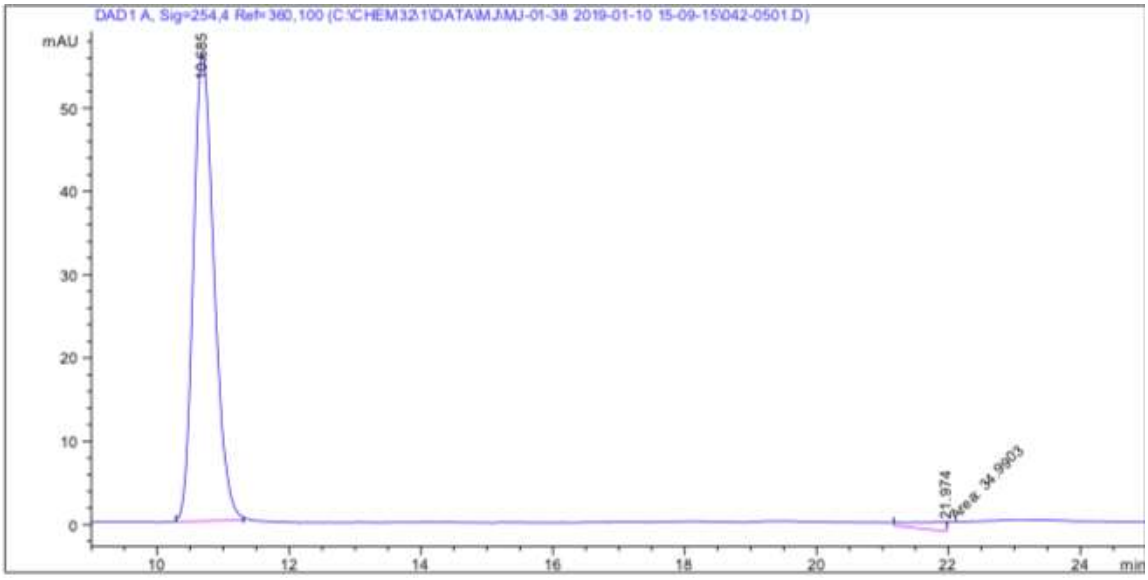
HPLC: Enantiomeric excess was determined by HPLC analysis (OD-H columns, hexanes:*i*-PrOH = 99:1, 1.0 mL/min, 230 nm), t_{major} = 10.68 min, t_{minor} = 21.97 min; *ee* = 94%.


6.00
5.99
5.99
5.98
5.97
5.97
5.96
5.95
5.95
5.94
5.94
5.94
5.92
5.18
5.16
5.15
5.15
3.48
3.46
3.45
3.45
3.43
2.48
2.47
2.47
2.46
2.46
1.07
1.06
1.05
1.00
2.05
5.12
2.10
21.02
f1 (ppm)


132.94
119.05
108.21
85.63
78.50
77.28
77.03
76.78
70.00
59.58
43.26
18.57
11.10
f1 (ppm)

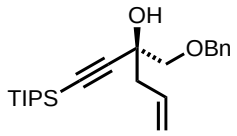


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.636	MM	0.3608	880.49567	40.66941	49.5601
2	21.535	MM	1.2526	896.12628	11.92375	50.4399



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.685	BB	0.3384	1220.00891	55.95818	97.2119
2	21.974	MM	0.5395	34.99030	1.08098	2.7881

(*S*)-3-((Benzyloxy)methyl)-1-(triisopropylsilyl)hex-5-en-1-yn-3-ol (3.3d)



3d

The title compound **3.3d** was prepared according to general procedure using **3.1d** (66.1 mg, 0.20 mmol, 100 mol%). Upon flash chromatography (SiO_2, hexanes/ethyl acetate = 4:1) the title compound (59 mg, 0.16 mmol) was obtained in 79% yield as a pale yellow oil.

TLC (SiO_2) R_f = 0.60 (hexanes/ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 6H), 5.97 (ddt, J = 16.4, 11.0, 7.2 Hz, 1H), 5.20 – 5.12 (m, 2H), 4.71 – 4.59 (m, 2H), 3.62 – 3.50 (m, 2H), 2.76 (s, 1H), 2.50 (d, J = 7.2 Hz, 2H), 1.08 (s, 22H). ppm.

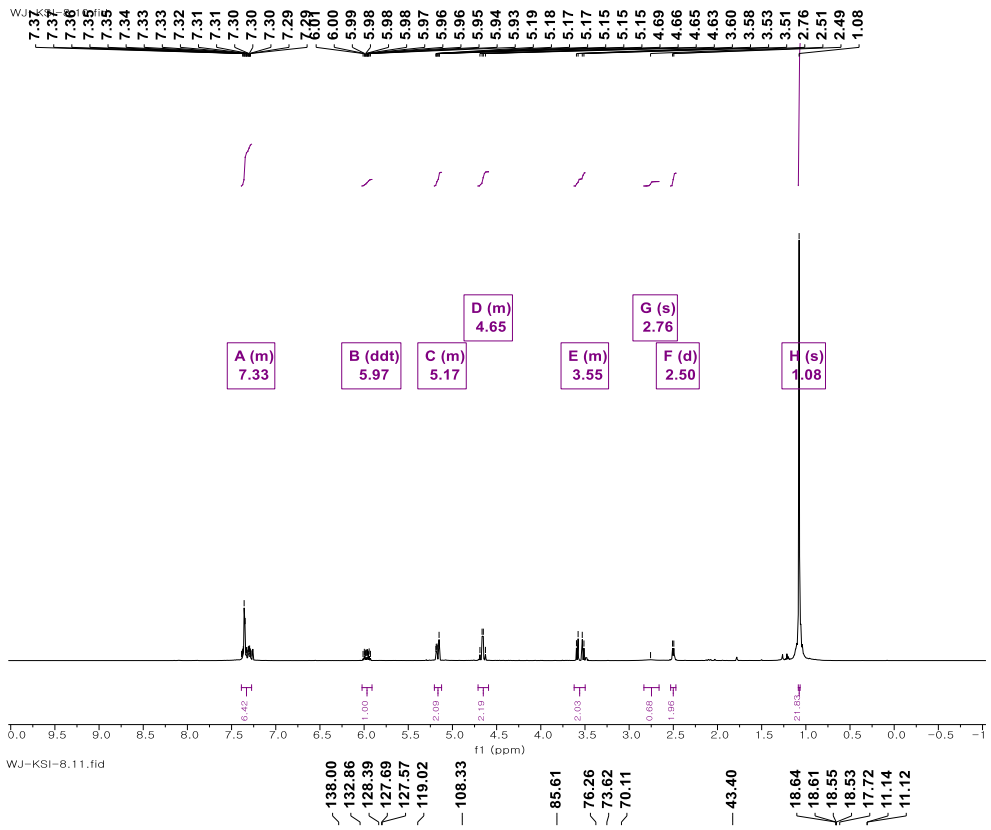
^{13}C NMR (126 MHz, $CDCl_3$) δ 138.0, 132.9, 128.4, 127.7, 127.6, 119.0, 108.3, 85.6, 76.3, 73.6, 70.1, 43.4, 18.6, 18.6, 18.6, 18.5, 17.7, 11.1, 11.1 ppm.

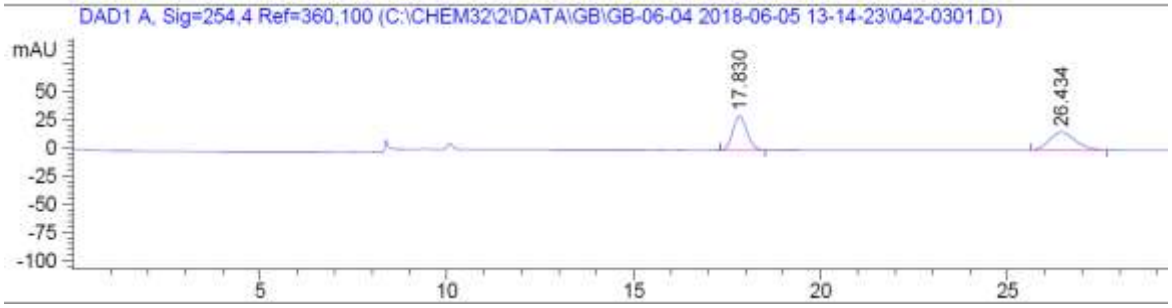
HRMS (ESI) m/z: [(M+Na)+] calcd for $C_{23}H_{36}O_2Si$ 395.2377, found 395.2389.

FTIR (ATR) 2943, 1260, 1383, 1243, 1103, 1073, 1016, 996, 883, 735, 697, 678 cm^{-1}.

$[\alpha]_D^{28}$**:** -5.5 (c = 1.0, $CHCl_3$).

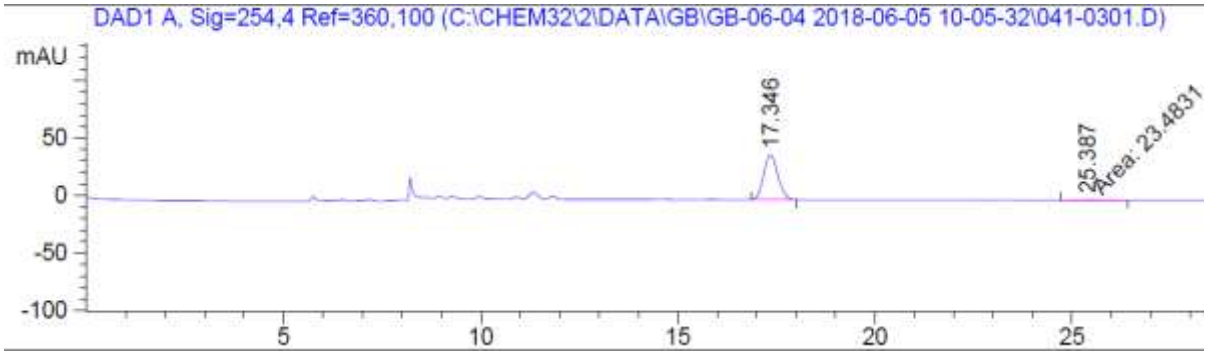
HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H column, hexanes:2-PrOH = 95:5, 0.5 mL/min, 254 nm), tmajor = 17.8 min, tminor = 26.4 min; ee = 96%.


7.37 7.37 7.36 7.35 7.35 7.34 7.33 7.33 7.32 7.31 7.31 7.30 7.30 7.30 7.29 7.29
6.01 6.00 5.99 5.98 5.98 5.98 5.97 5.96 5.96 5.95 5.94 5.93 5.19 5.18 5.17 5.17 5.15 5.15 5.15 4.69 4.66 4.65 4.63 3.60 3.58 3.53 3.51 2.76 2.51 2.49 1.08
A (m) 7.33
B (ddt) 5.97
C (m) 5.17
D (m) 4.65
E (m) 3.55
F (d) 2.50
G (s) 2.76
H (s) 1.08
6.42 1.00 2.09 2.19 2.03 0.68 1.96 21.83
f1 (ppm)
WJ-KSI-8.11.fid
138.00 132.86 128.39 127.69 127.57 119.02 108.33 85.61 76.26 73.62 70.11 43.40 18.64 18.61 18.55 18.53 17.72 11.14 11.12
f1 (ppm)



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

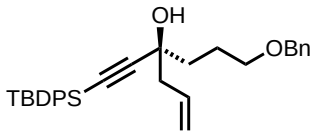
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.830	BB	0.4007	789.79376	30.04381	51.0548
2	26.434	BB	0.6663	757.16064	15.65354	48.9452
Totals :				1546.95441	45.69735	



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.346	BB	0.3945	980.92816	38.86221	97.6620
2	25.387	MM	0.8324	23.48306	4.70179e-1	2.3380
Totals :				1004.41122	39.33238	

(*S*)-7-(Benzyloxy)-4-((*tert*-butyldiphenylsilyl)ethynyl)hept-1-en-4-ol (3.3e)



3e

The title compound **3.3e** was prepared according to general procedure using **3.1e** (88.1 mg, 0.20 mmol, 100 mol%). Upon flash chromatography (SiO_2, hexanes/ethyl acetate = 9:1) the title compound (74.0 mg, 0.15 mmol) was obtained in 77% yield as a yellow oil.

TLC (SiO_2) R_f = 0.34 (hexanes/ethyl acetate = 9:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 6.3 Hz, 4H), 7.43 – 7.37 (m, 6H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.21 (dd, *J* = 18.0, 7.3 Hz, 3H), 6.09 (dddd, *J* = 16.7, 10.3, 8.1, 6.5 Hz, 1H), 5.30 – 5.24 (m, 2H), 3.03 – 2.98 (m, 2H), 2.66 (dd, *J* = 13.6, 6.5 Hz, 1H), 2.51 (dd, *J* = 13.6, 8.1 Hz, 1H), 2.10 – 2.05 (m, 2H), 1.12 (s, 9H) ppm.

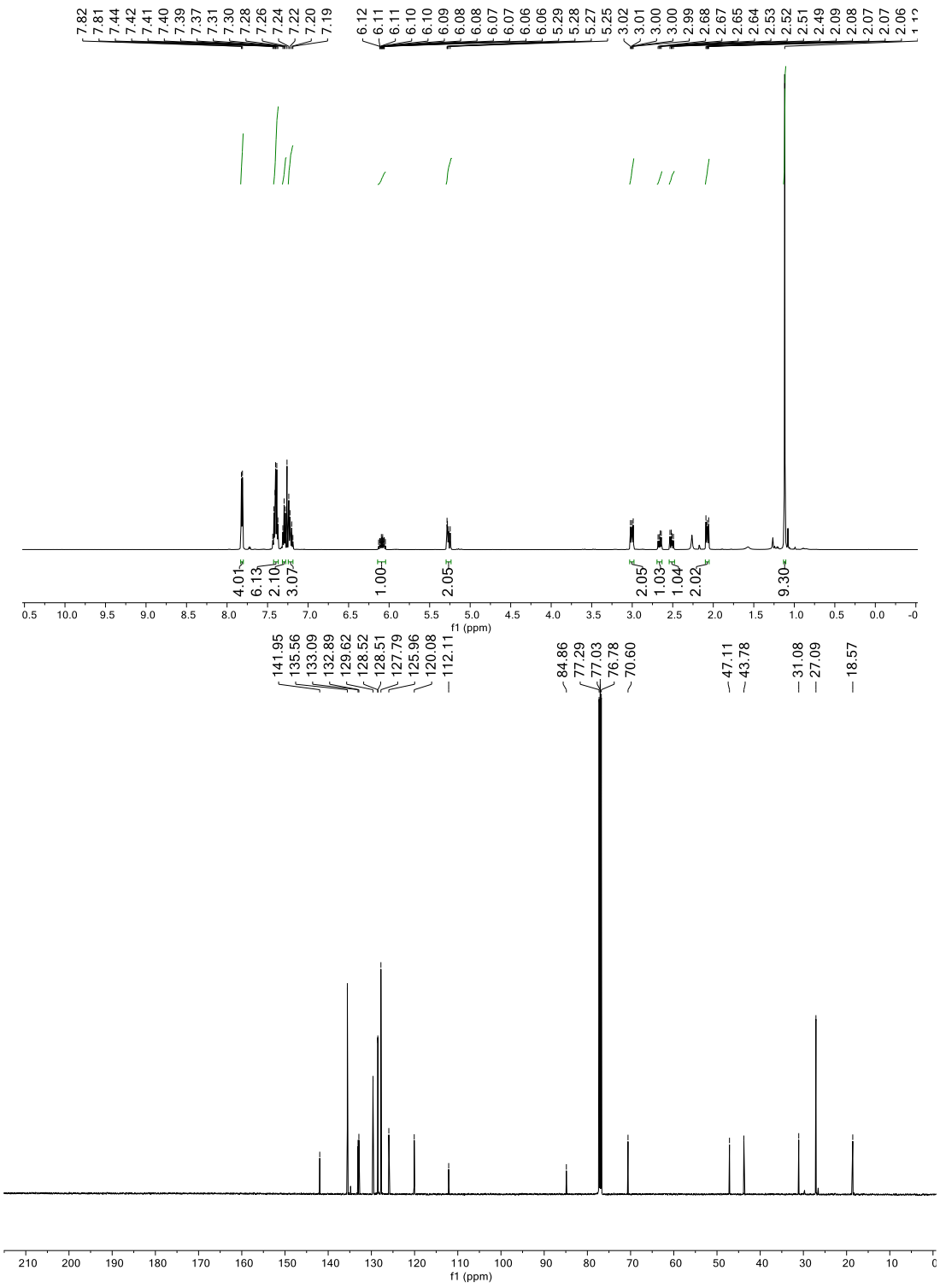
^{13}C NMR (101 MHz, $CDCl_3$) δ 142.0, 135.6, 133.1, 132.9, 129.6, 128.5, 128.5, 127.8, 126.0, 120.1, 112.1, 84.9, 70.6, 47.1, 43.8, 31.1, 27.1, 18.6 ppm.

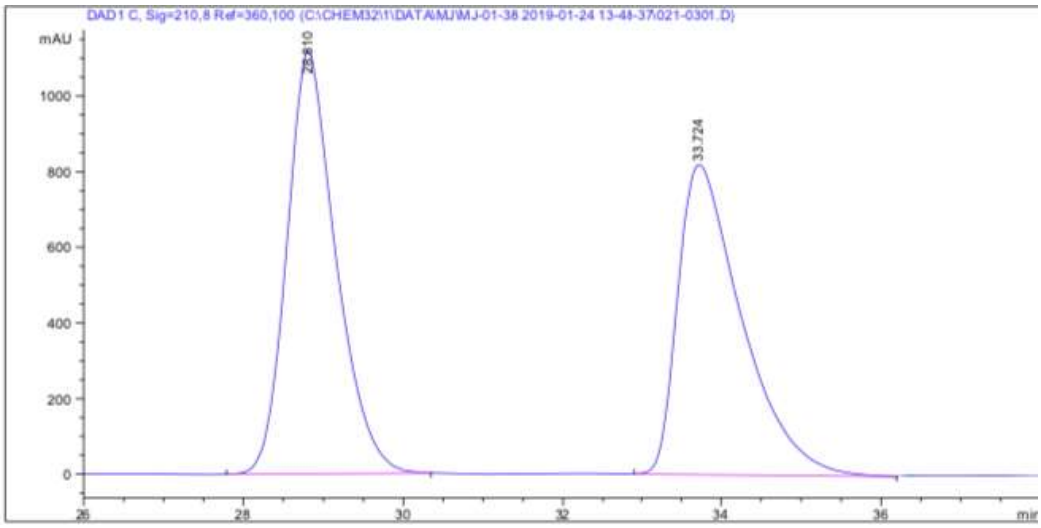
HRMS (ESI) m/z: [M+Na^+] calcd for $C_{30}H_{38}O_2Si$ 461.2328, found 461.2331.

FTIR (ATR) 2927, 2855, 1428, 1109, 1042, 997, 819, 741, 697 cm^{-1}.

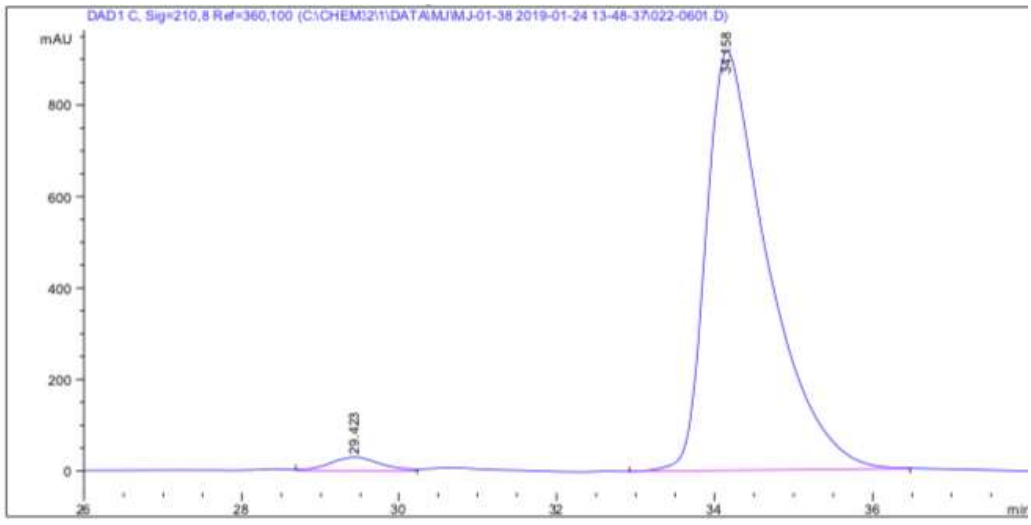
$[\alpha]_D^{28}$: -6.75 (*c* 0.62, $CHCl_3$).

HPLC: (OD-H columns, hexanes:*i*-PrOH = 99:1, 1.0 mL/min, 230 nm), t_{major} = 26.14 min, t_{minor} = 43.36 min; *ee* = 95%.


7.82 7.81 7.44 7.42 7.41 7.40 7.39 7.37 7.31 7.30 7.28 7.26 7.24 7.22 7.20 7.19
6.12 6.11 6.11 6.10 6.10 6.09 6.08 6.08 6.07 6.07 6.06 6.06 5.29 5.28 5.27 5.25
3.02 3.01 3.00 3.00 2.99 2.68 2.67 2.65 2.64 2.53 2.52 2.51 2.49 2.09 2.08 2.07 2.07 2.06
4.01 6.13 2.10 3.07 1.00 2.05 2.05 1.03 1.04 2.02 9.30
f1 (ppm)
141.95 135.56 133.09 132.89 129.62 128.52 128.51 127.79 125.96 120.08 112.11
84.86 77.29 77.03 76.78 70.60
47.11 43.78
31.08 27.09
18.57
f1 (ppm)

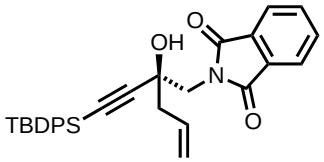


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.810	BB	0.6233	4.76389e4	1117.53735	51.1472
2	33.724	BB	0.8258	4.55018e4	819.41638	48.8528



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.423	VV	0.6583	1325.72363	29.49904	2.5843
2	34.158	VB	0.7879	4.99739e4	916.85492	97.4157

(*S*)-2-(2-((*tert*-Butyldiphenylsilyl)ethynyl)-2-hydroxypent-4-en-1-yl)isoindoline-1,3-dione (3.3f)



3f

The title compound **3.3f** was prepared according to general procedure using **3.1f** (90.3 mg, 0.20 mmol, 100 mol%). Upon flash chromatography (SiO_2, hexanes/ethyl acetate = 4:1) the title compound (70.1 mg, 0.14 mmol) was obtained in 71% yield as a yellow oil.

TLC (SiO_2) R_f = 0.28 (hexanes/ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.62 (dt, *J* = 6.8, 3.3 Hz, 2H), 7.55 (t, *J* = 6.0 Hz, 4H), 7.27 (td, *J* = 7.3, 4.1 Hz, 2H), 7.24 – 7.16 (m, 6H), 6.04 (ddt, *J* = 17.3, 10.2, 7.2 Hz, 1H), 5.26 – 5.17 (m, 2H), 4.29 (s, 1H), 4.24 (d, *J* = 14.5 Hz, 1H), 3.77 (d, *J* = 14.4 Hz, 1H), 2.58 (d, *J* = 7.1 Hz, 2H), 0.85 (s, 9H) ppm

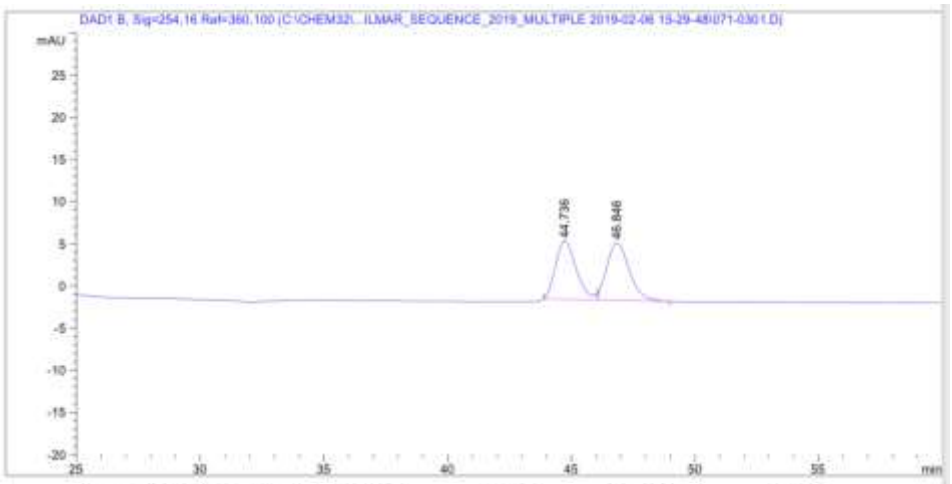
^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 135.5, 135.4, 134.3, 132.7, 132.4, 131.8, 129.4, 129.4, 128.1, 127.6, 123.7, 119.7, 109.0, 86.5, 71.3, 48.2, 44.7, 29.7, 26.8, 18.3 ppm

HRMS (ESI) m/z: [M+Na^+] calcd for $C_{31}H_{31}NO_3Si$ 516.1965, found 516.1974.

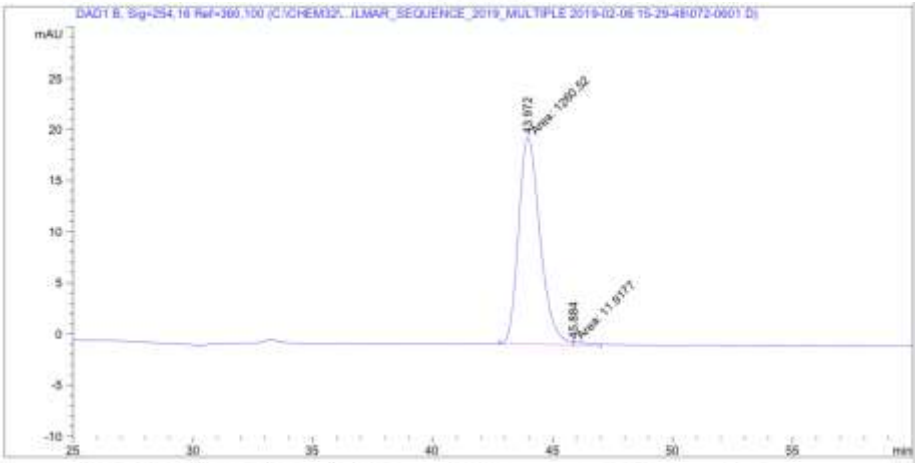
FTIR (ATR) 3432, 2926, 2855, 1774, 1708, 1468, 1428, 1110, 1029, 997, 908, 732 cm^{-1}.

$[\alpha]_D^{28}$: +5.75 (*c* 1.0, $CHCl_3$).

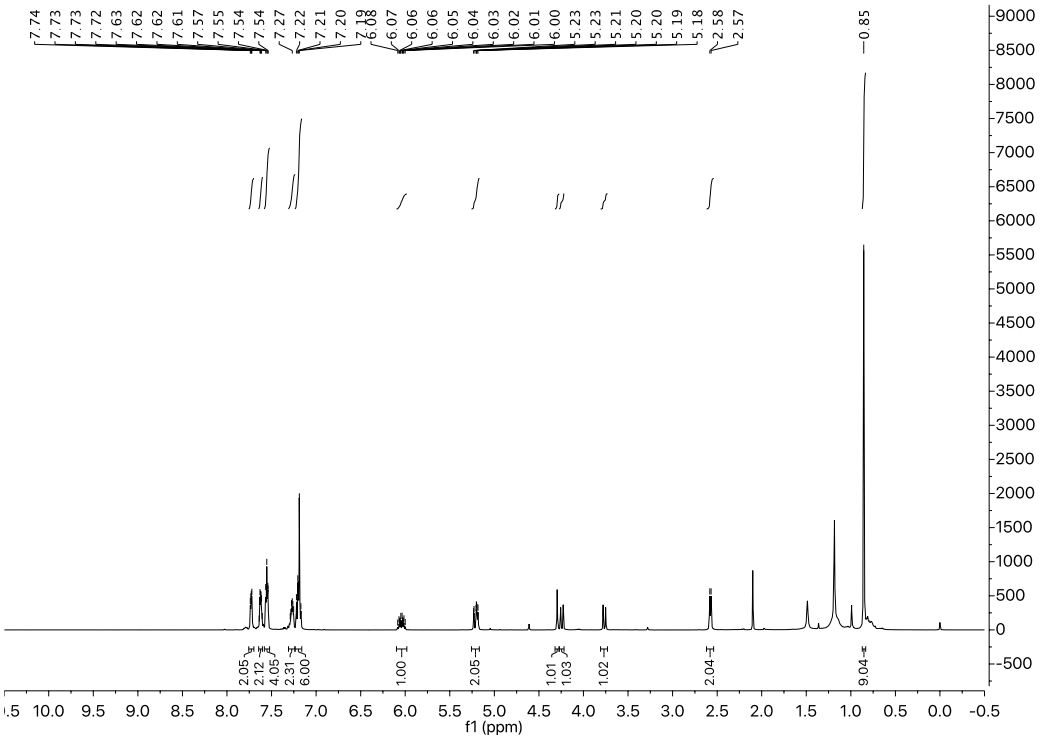
HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralcel AD-H column, hexanes:*i*-PrOH = 97:3, 0.5 mL/min, 254 nm), t_{major} = 43.97 min, t_{minor} = 45.88 min; *ee* = 98%.

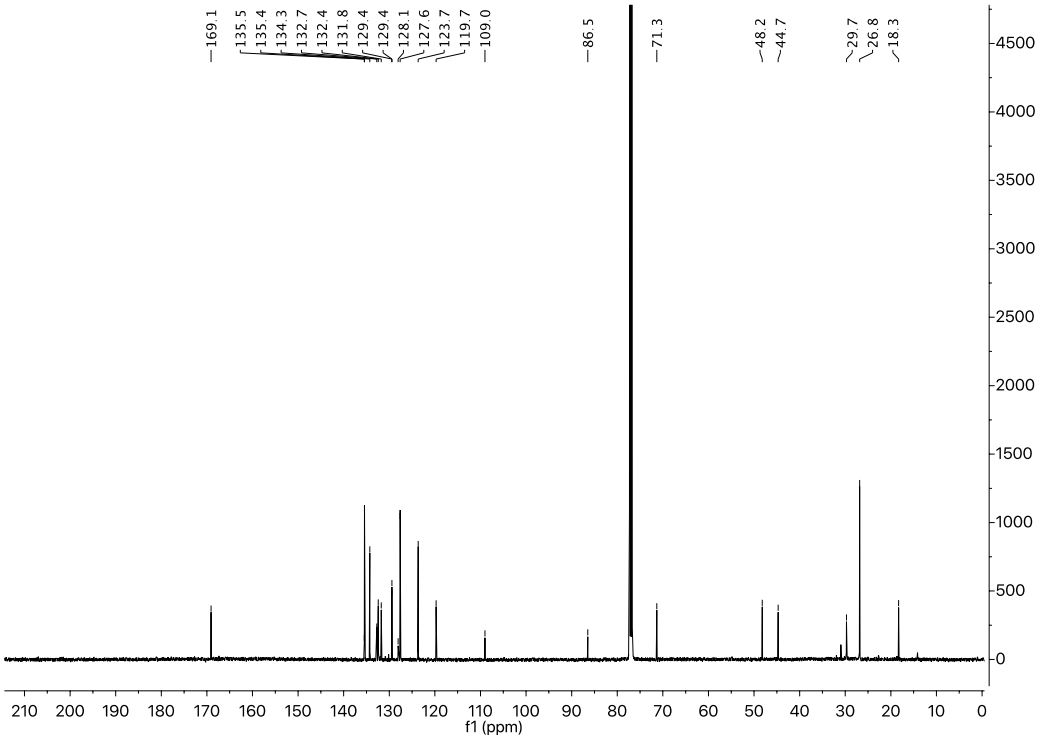


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	44.736	BB	0.7766	400.20435	6.90113	48.1421
2	46.846	BB	0.8064	431.09439	6.84791	51.8579
Totals :				831.29874	13.74904	

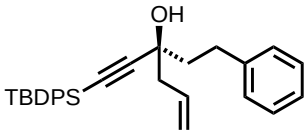


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	43.972	MF	1.0372	1260.51501	20.25544	99.0634
2	45.884	FM	0.6880	11.91770	2.88693e-1	0.9366
Totals :				1272.43271	20.54413	


7.74
7.73
7.73
7.72
7.63
7.62
7.62
7.61
7.57
7.55
7.54
7.54
7.27
7.22
7.21
7.20
7.19
6.08
6.07
6.06
6.06
6.05
6.04
6.03
6.02
6.01
6.00
5.23
5.21
5.20
5.20
5.19
5.18
2.58
2.57
0.85
2.05
2.12
4.05
2.31
6.00
1.00
2.05
1.01
1.03
1.02
2.04
9.04
f1 (ppm)


169.1
135.5
135.4
134.3
132.7
132.4
131.8
129.4
129.4
128.1
127.6
123.7
119.7
109.0
86.5
71.3
48.2
44.7
29.7
26.8
18.3
f1 (ppm)

(*S*)-1-(*tert*-Butyldiphenylsilyl)-3-phenethylhex-5-en-1-yn-3-ol (3.3g)



3g

The title compound **3.3g** was prepared according to general procedure using **3.1g** (79.3 mg, 0.20 mmol, 100 mol%). Upon flash chromatography (SiO_2, hexanes/ethyl acetate = 9:1) the title compound (76 mg, 0.17 mmol) was obtained in 86% yield as a yellow oil.

TLC (SiO_2) R_f = 0.34 (hexanes/ethyl acetate = 9:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 6.3 Hz, 4H), 7.43 – 7.37 (m, 6H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.21 (dd, *J* = 18.0, 7.3 Hz, 3H), 6.09 (dddd, *J* = 16.7, 10.3, 8.1, 6.5 Hz, 1H), 5.30 – 5.24 (m, 2H), 3.03 – 2.98 (m, 2H), 2.66 (dd, *J* = 13.6, 6.5 Hz, 1H), 2.51 (dd, *J* = 13.6, 8.1 Hz, 1H), 2.10 – 2.05 (m, 2H), 1.12 (s, 9H) ppm.

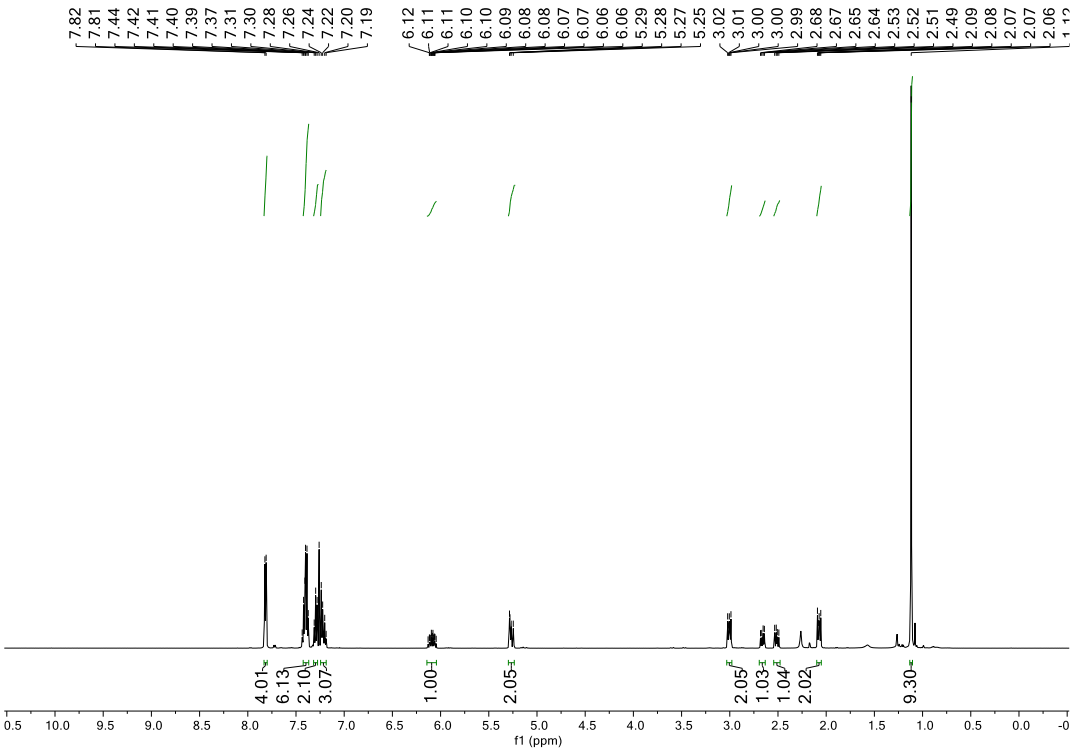
^{13}C NMR (101 MHz, $CDCl_3$) δ 142.0, 135.6, 133.1, 132.9, 129.6, 128.5, 128.5, 127.8, 126.0, 120.1, 112.1, 84.9, 70.6, 47.1, 43.8, 31.1, 27.1, 18.6 ppm.

HRMS (ESI) m/z: [M+Na^+] calcd for $C_{30}H_{34}OSi$ 461.2271, found 461.2268.

FTIR (ATR) 2927, 2855, 1428, 1109, 1042, 997, 819, 741, 697 cm^{-1}.

$[\alpha]_D^{28}$: -6.75 (*c* 0.3, $CHCl_3$).

HPLC: (OD-H columns, hexanes:*i*-PrOH = 99:1, 1.0 mL/min, 230 nm), t_{major} = 26.14 min, t_{minor} = 43.36 min; *ee* = 96%.


7.82
7.81
7.44
7.42
7.41
7.40
7.39
7.37
7.31
7.30
7.28
7.26
7.24
7.22
7.20
7.19
6.12
6.11
6.11
6.10
6.10
6.09
6.08
6.08
6.07
6.07
6.06
6.06
5.29
5.28
5.27
5.25
3.02
3.01
3.00
3.00
2.99
2.68
2.67
2.65
2.64
2.53
2.52
2.51
2.49
2.09
2.08
2.07
2.07
2.06
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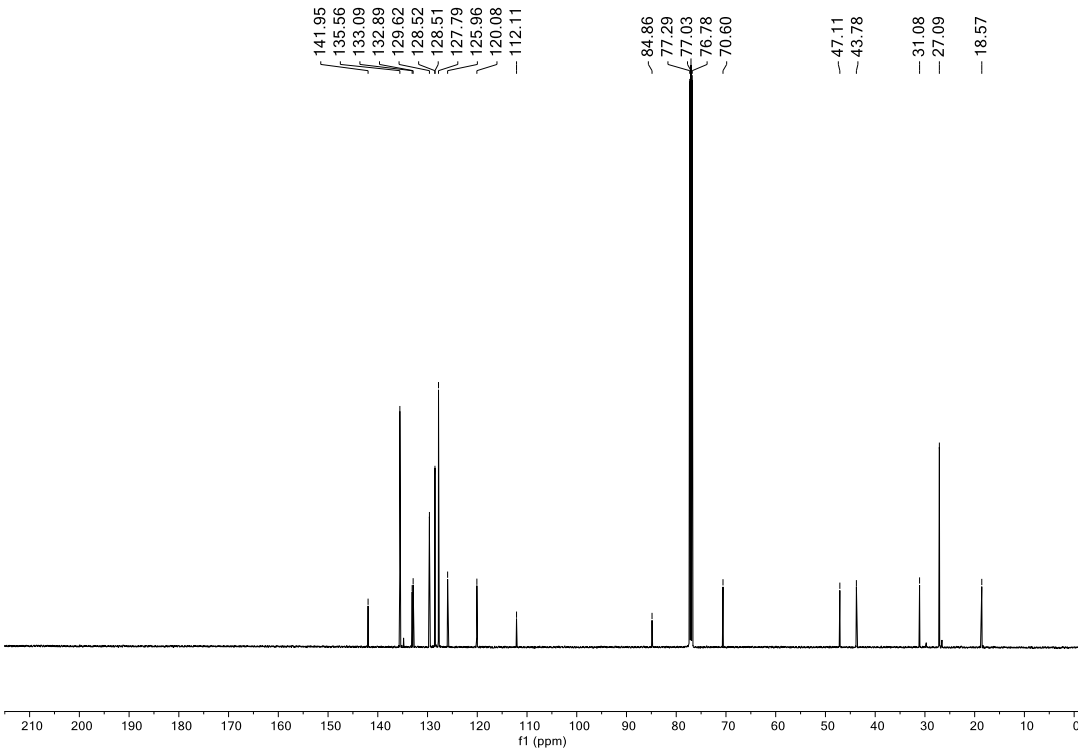
2.05
1.03
1.04
2.02
9.30
f1 (ppm)


141.95
135.56
133.09
132.89
129.62
128.52
128.51
127.79
125.96
120.08
112.11
84.86
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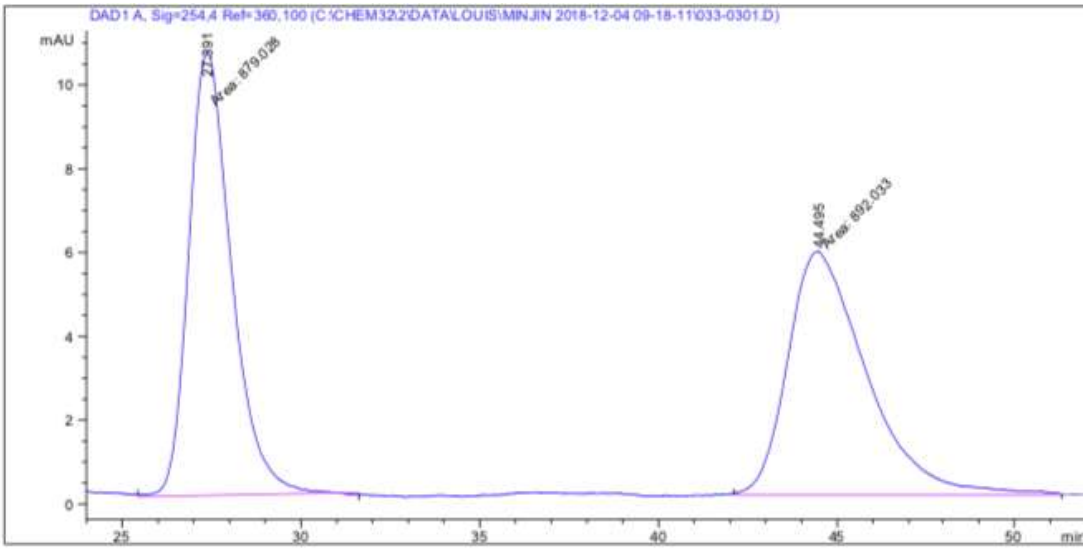
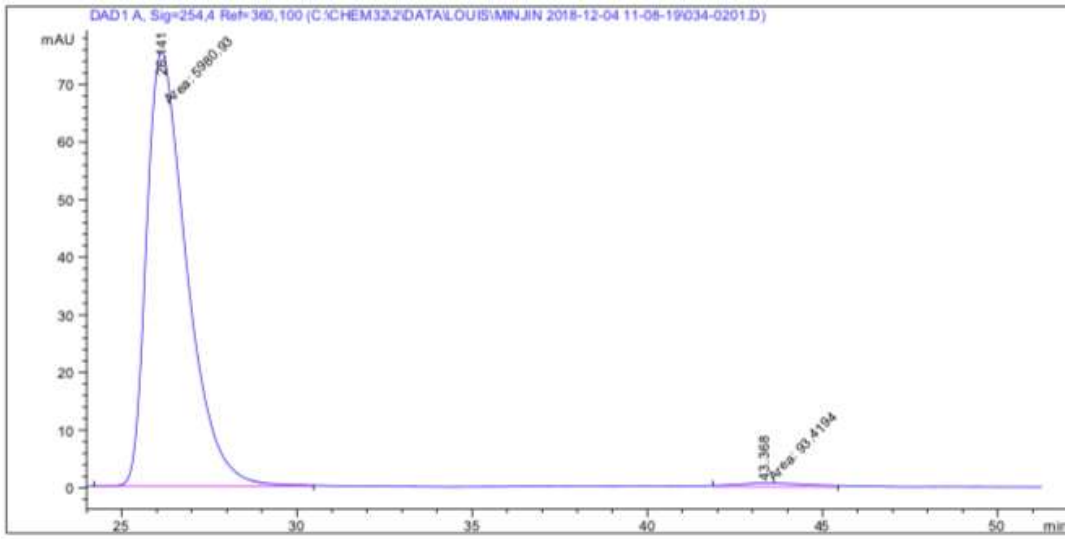
77.03
76.78
70.60
47.11
43.78
31.08
27.09
18.57
f1 (ppm)

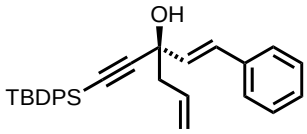


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.391	MM	1.3871	879.02814	10.56158	49.6329
2	44.495	MM	2.5564	892.03278	5.81577	50.3671



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.141	MF	1.3243	5980.92627	75.27267	98.4621
2	43.368	MF	2.3690	93.41938	6.57244e-1	1.5379

(*R*,*E*)-3-((*tert*-Butyldiphenylsilyl)ethynyl)-1-phenylhexa-1,5-dien-3-ol (3.3h)



3h

The title compound **3.3h** was prepared according to general procedure using **3.1h** (79.0 mg, 0.20 mmol, 100 mol %). Upon flash chromatography (SiO_2, hexanes/ethyl acetate = 9:1) the title compound (55.2 mg, 0.13 mmol) was obtained in 64% yield as a yellow oil.

TLC (SiO_2) R_f = 0.38 (hexanes/ethyl acetate = 9:1).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.82 (d, *J* = 7.1 Hz, 4H), 7.44 – 7.31 (m, 13H), 7.05 (d, *J* = 15.8 Hz, 1H), 6.33 (d, *J* = 15.8 Hz, 1H), 6.09 – 5.99 (m, 1H), 5.30 – 5.22 (m, 2H), 2.73 – 2.67 (m, 2H), 1.12 (s, 9H) ppm.

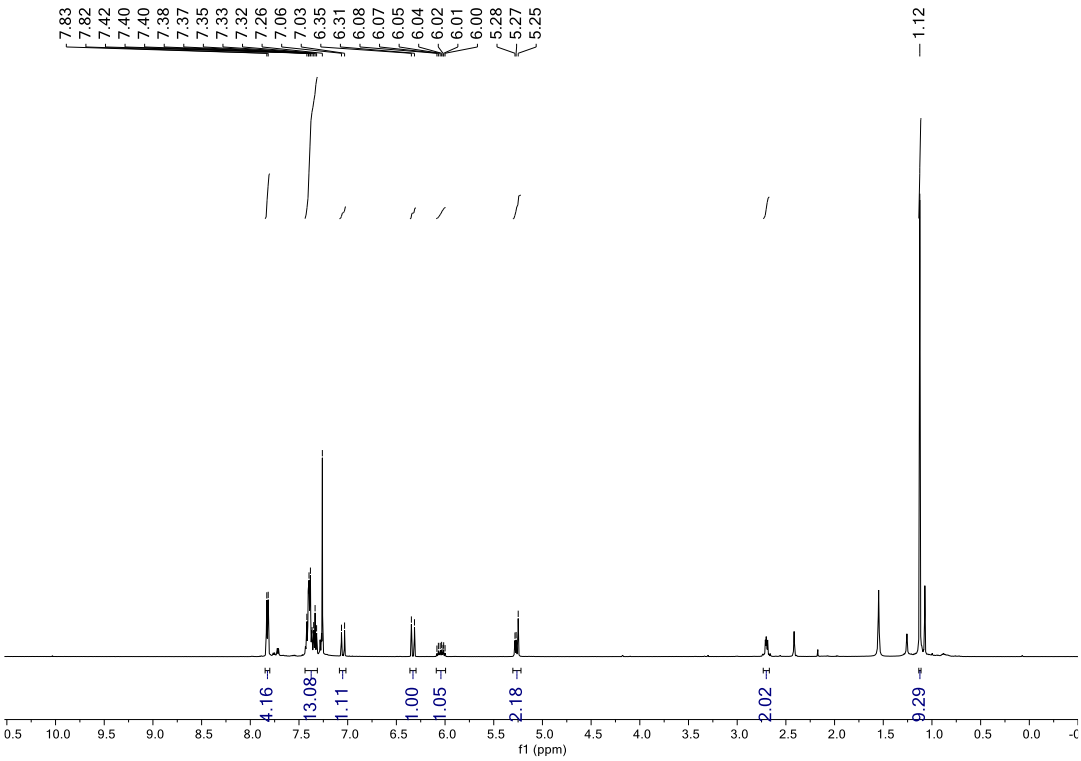
^{13}C NMR (101 MHz, $CDCl_3$) δ 136.2, 135.6, 134.8, 133.0, 132.5, 131.5, 130.9, 129.6, 128.7, 128.1, 127.8, 126.9, 120. 0, 110. 3, 71.2, 47.6, 27.1, 18.6 ppm.

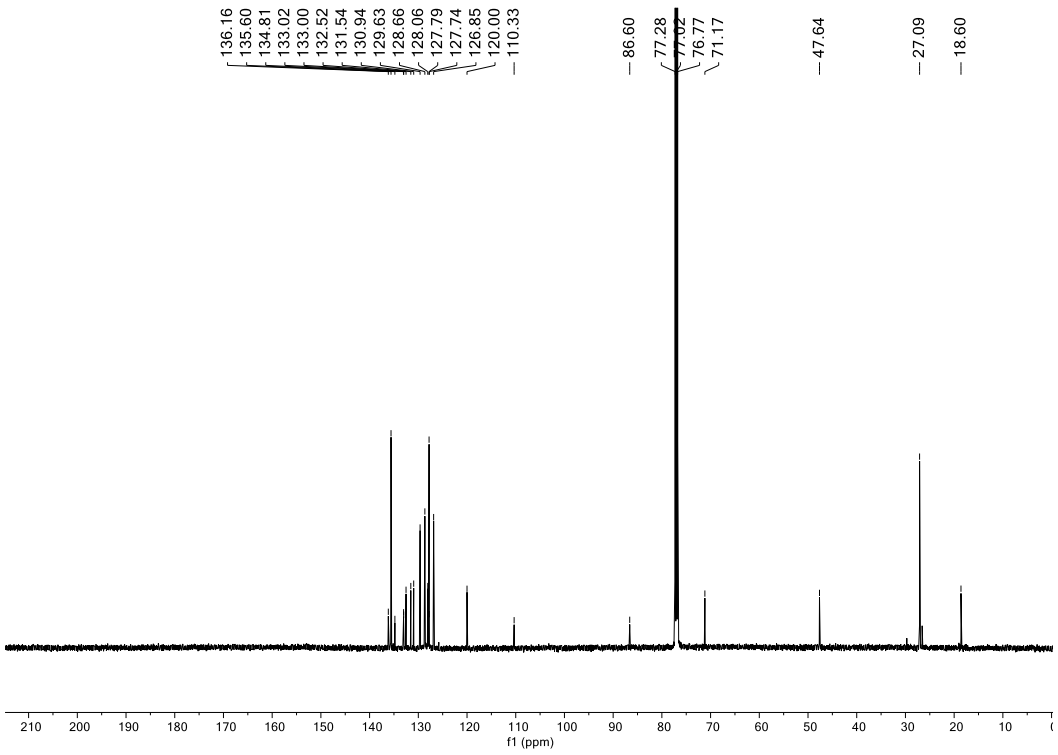
HRMS (ESI) m/z: [M+Na^+] calcd for $C_{30}H_{32}OSi$ 459.2115, found 459.2126

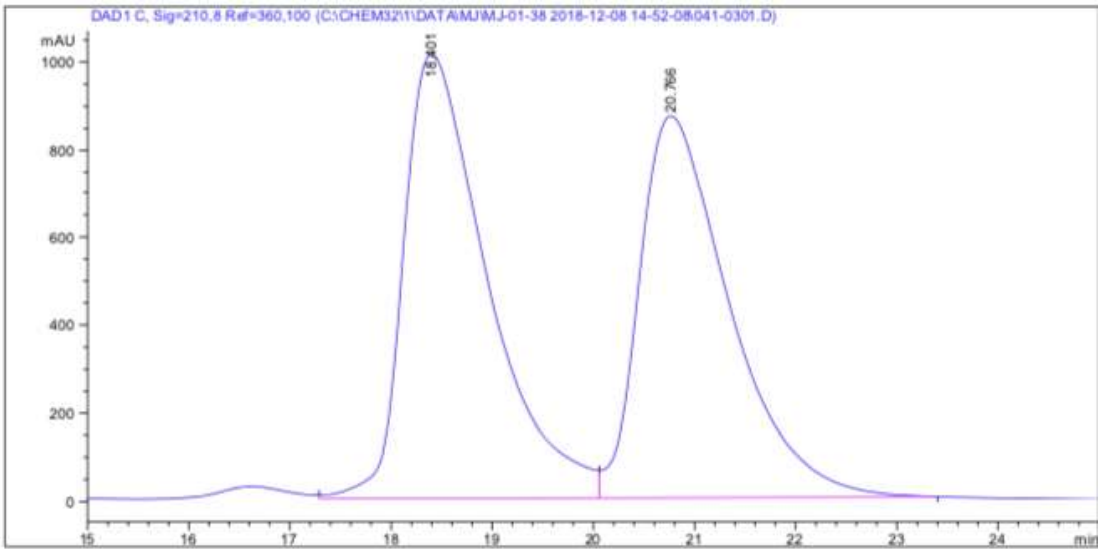
FTIR (ATR) 2928, 2856, 1428, 1109, 997, 966, 818, 742, 696 cm^{-1}.

$[\alpha]_D^{28}$: -9.2 (*c* 1.06, $CHCl_3$).

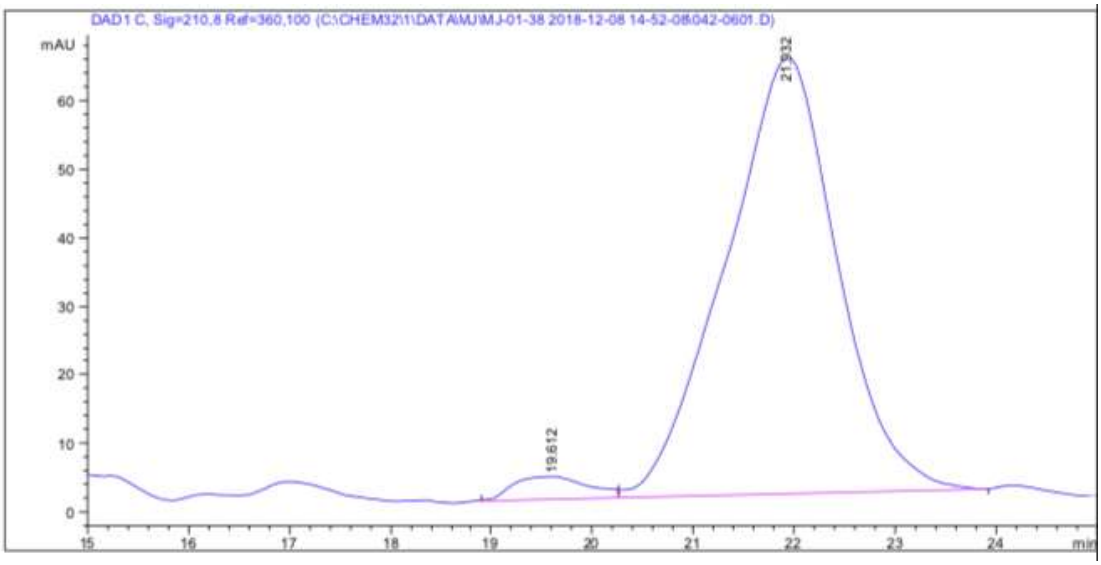
HPLC: (OD-H columns, hexanes:*i*-PrOH = 99:1, 1.0 mL/min, 230 nm), t_{major} = 21.93 min, t_{minor} = 19.61 min; *ee* = 93%.


7.83
7.82
7.42
7.40
7.40
7.38
7.37
7.35
7.33
7.32
7.26
7.06
7.03
6.35
6.31
6.08
6.07
6.05
6.04
6.02
6.01
6.00
5.28
5.27
5.25
1.12
4.16
13.08
1.11
1.00
1.05
2.18
2.02
9.29
f1 (ppm)


136.16
135.60
134.81
133.02
133.00
132.52
131.54
130.94
129.63
128.66
128.06
127.79
127.74
126.85
120.00
110.33
86.60
77.28
77.02
76.77
71.17
47.64
27.09
18.60
f1 (ppm)

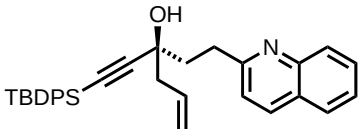


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.401	VV	0.8177	5.79373e4	1012.39990	51.9154
2	20.766	VB	0.9217	5.36621e4	869.87366	48.0846



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.612	BV	0.6049	169.88029	3.30929	3.3607
2	21.932	VB	1.0361	4885.04883	63.60214	96.6393

(*S*)-1-(*tert*-Butyldiphenylsilyl)-3-(2-(quinolin-2-yl)ethyl)hex-5-en-1-yn-3-ol (3.3i)



3i

The title compound **3.3i** was prepared according to general procedure using **3.1i** (89.6 mg, 0.20 mmol, 100 mol%). Upon flash chromatography (SiO_2, hexanes/ethyl acetate = 5:1) the title compound (77.4 mg, 0.16 mmol) was obtained in 79% yield as a brown oil.

TLC (SiO_2) R_f = 0.25 (hexanes/ethyl acetate = 5:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.4 Hz, 2H), 7.70 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.67 (ddd, *J* = 8.1, 3.2, 1.4 Hz, 4H), 7.61 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.43 (ddd, *J* = 8.0, 6.8, 1.1 Hz, 1H), 7.28 – 7.17 (m, 7H), 6.11 (ddt, *J* = 17.3, 10.2, 7.2 Hz, 1H), 5.20 – 5.13 (m, 2H), 3.65 (dt, *J* = 16.6, 6.7 Hz, 1H), 3.26 (dt, *J* = 16.7, 5.3 Hz, 1H), 2.68 – 2.55 (m, 2H), 2.24 (dd, *J* = 7.3, 5.2 Hz, 2H), 0.95 (s, 9H) ppm

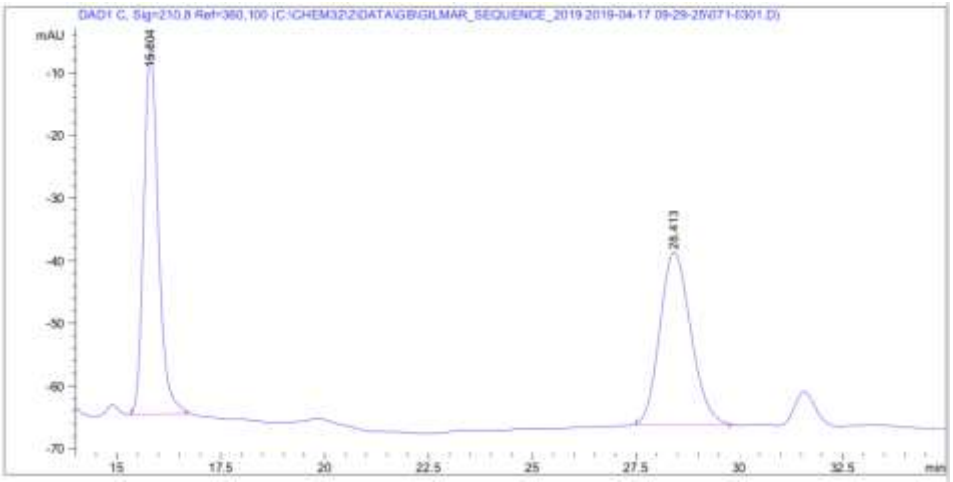
^{13}C NMR (126 MHz, $CDCl_3$) δ 161.7, 146.6, 137.0, 135.6, 134.1, 133.5, 133.4, 129.9, 129.4, 128.1, 127.6, 127.6, 127.5, 126.6, 126.2, 121.9, 118.6, 113.5, 84.1, 70.6, 48.1, 38.9, 34.7, 27.1, 18.5 ppm

HRMS (ESI) m/z: [M+H$^+$] calcd for $C_{33}H_{35}NOSi$ 490.2561, found 490.2555.

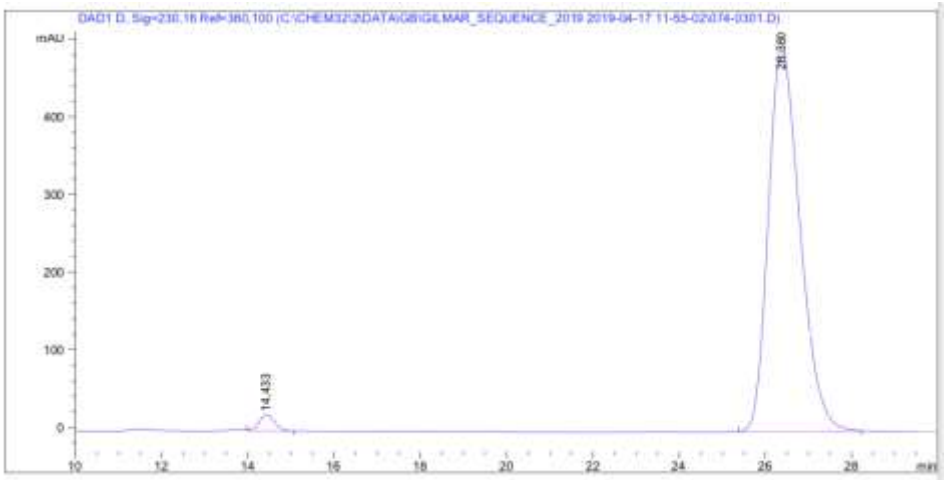
FTIR (ATR) 3069, 2926, 2854, 1601, 1505, 1264, 1141, 1109, 819, 771 cm^{-1}.

$[\alpha]_D^{28}$: +118.4 (*c* 1.0, $CHCl_3$).

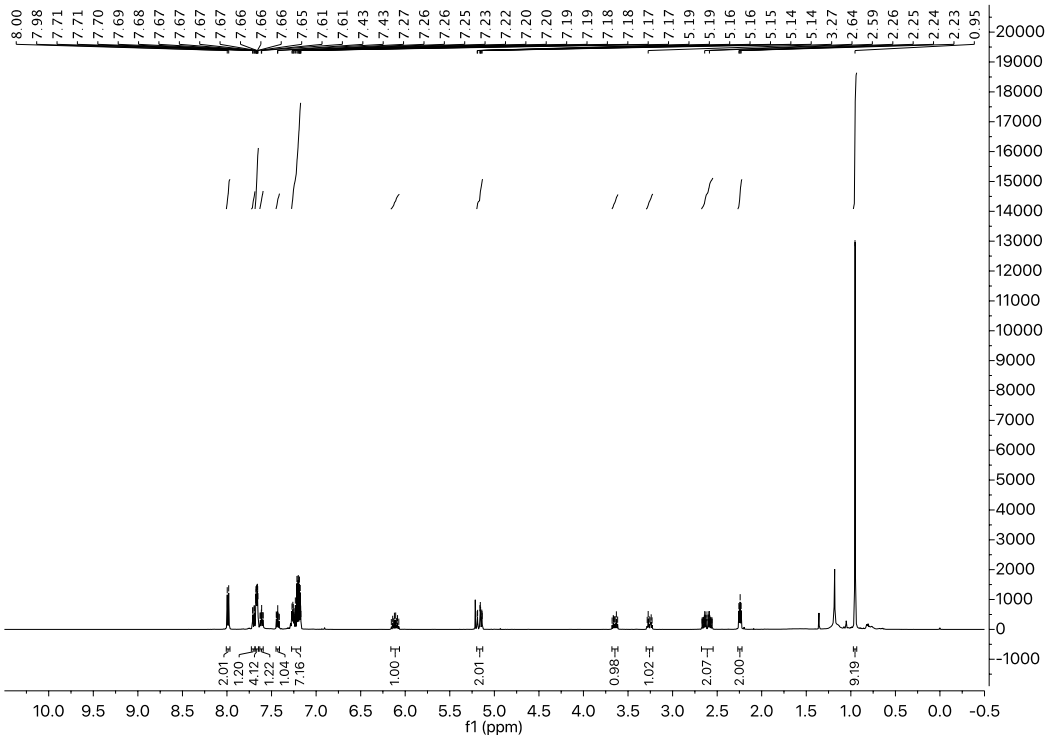
HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H column, hexanes:*i*-PrOH = 97:3, 0.7 mL/min, 230 nm), t_{major} = 26.38 min, t_{minor} = 14.43 min; *ee* = 96%.

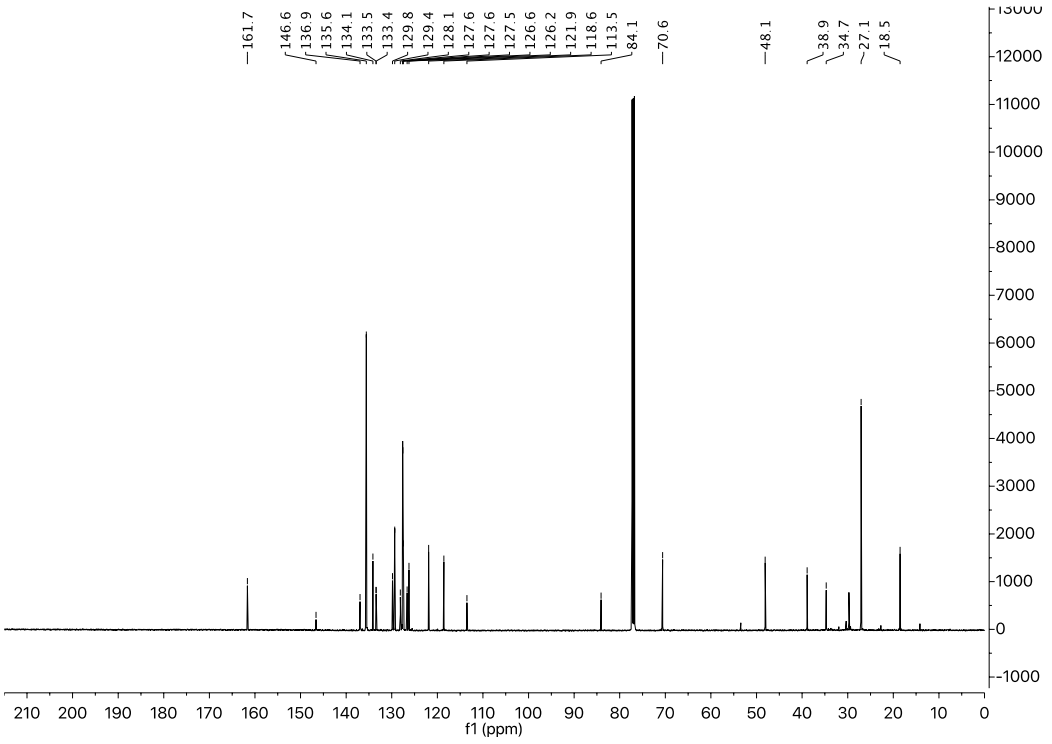


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.804	BB	0.3749	1430.59509	58.57870	50.0312
2	28.413	BB	0.6856	1428.80933	27.52510	49.9688
Totals :				2859.40442	86.10381	

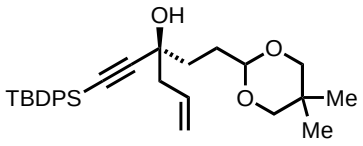


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.433	BB	0.3949	543.85858	20.94599	2.1104
2	26.380	BB	0.7962	2.52264e4	492.00983	97.8896
Totals :				2.57703e4	512.95581	


8.00 7.98 7.71 7.71 7.70 7.69 7.68 7.67 7.67 7.67 7.67 7.66 7.66 7.66 7.65 7.61 7.61 7.43 7.43 7.27 7.26 7.26 7.25 7.23 7.22 7.20 7.20 7.19 7.19 7.18 7.18 7.17 7.17 5.19 5.19 5.16 5.16 5.15 5.14 5.14 3.27 2.64 2.59 2.26 2.25 2.24 2.23 0.95
2.01 1.20 4.12 1.22 1.04 7.16 1.00 2.01 0.98 1.02 2.07 2.00 9.19
f1 (ppm)


161.7 146.6 136.9 135.6 134.1 133.5 133.4 129.8 129.4 128.1 127.6 127.6 127.5 126.6 126.2 121.9 118.6 113.5 84.1 70.6 48.1 38.9 34.7 27.1 18.5
f1 (ppm)

(*S*)-1-(*tert*-Butyldiphenylsilyl)-3-(2-(5,5-dimethyl-1,3-dioxan-2-yl)ethyl)hex-5-en-1-yn-3-ol (3.3j)



3j

The title compound **3.3j** was prepared according to general using **3.1j** (86.9 mg, 0.20 mmol, 100 mol%). Upon flash chromatography (SiO_2, hexanes/ethyl acetate = 9:1) the title compound (58.2 mg, 0.12 mmol) was obtained in 60% yield as a yellow oil.

TLC (SiO_2) R_f = 0.28 (hexanes/ethyl acetate = 9: 1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 – 7.67 (m, 4H), 7.29 (qd, *J* = 8.6, 7.8, 3.7 Hz, 6H), 6.06 – 5.93 (m, 1H), 5.17 – 5.11 (m, 2H), 4.48 (t, *J* = 4.5 Hz, 1H), 3.54 (d, *J* = 10.9 Hz, 2H), 3.35 (d, *J* = 10.9 Hz, 2H), 2.46 (qd, *J* = 13.6, 7.2 Hz, 2H), 2.12 – 2.05 (m, 1H), 1.95 – 1.84 (m, 3H), 1.12 (s, 3H), 1.00 (s, 9H), 0.63 (s, 3H) ppm.

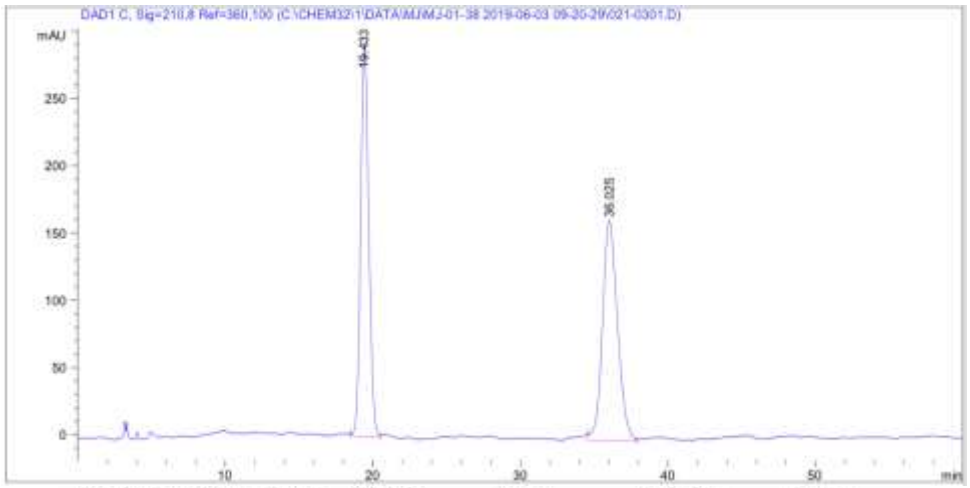
^{13}C NMR (126 MHz, $CDCl_3$) δ 135.6, 133.41, 133.27, 129.46, 127.69, 119.26, 112.53, 101.81, 84.28, 70.33, 47.17, 35.72, 30.10, 30.08, 27.07, 22.99, 21.80, 18.56 ppm.

HRMS (ESI) m/z: [M+K^+] calcd for $C_{30}H_{40}NO_3Si$ 515.2378, found 515.2392.

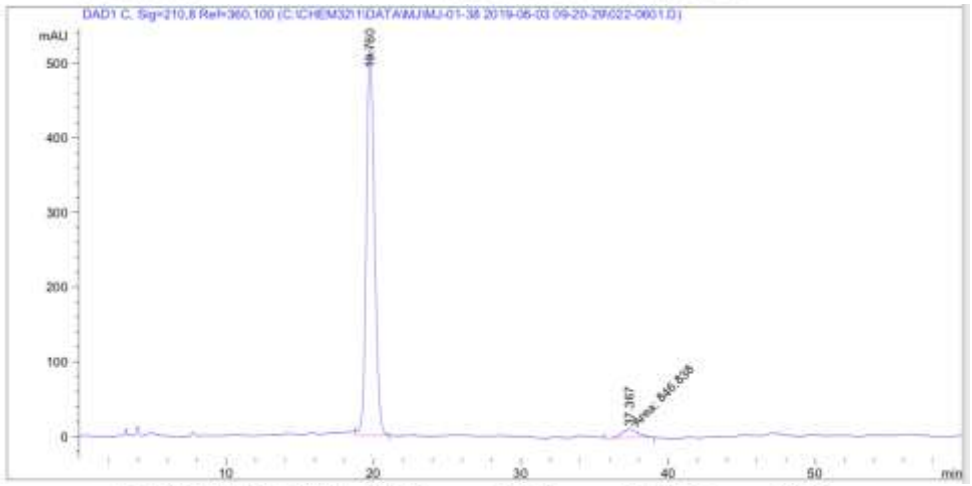
FTIR (ATR) 3415, 2957, 2856, 1471, 1428, 1393, 1131, 1109, 1015, 990, 907, 729 cm^{-1}.

$[\alpha]_D^{28}$: +8.5 (*c* 1.0, $CHCl_3$).

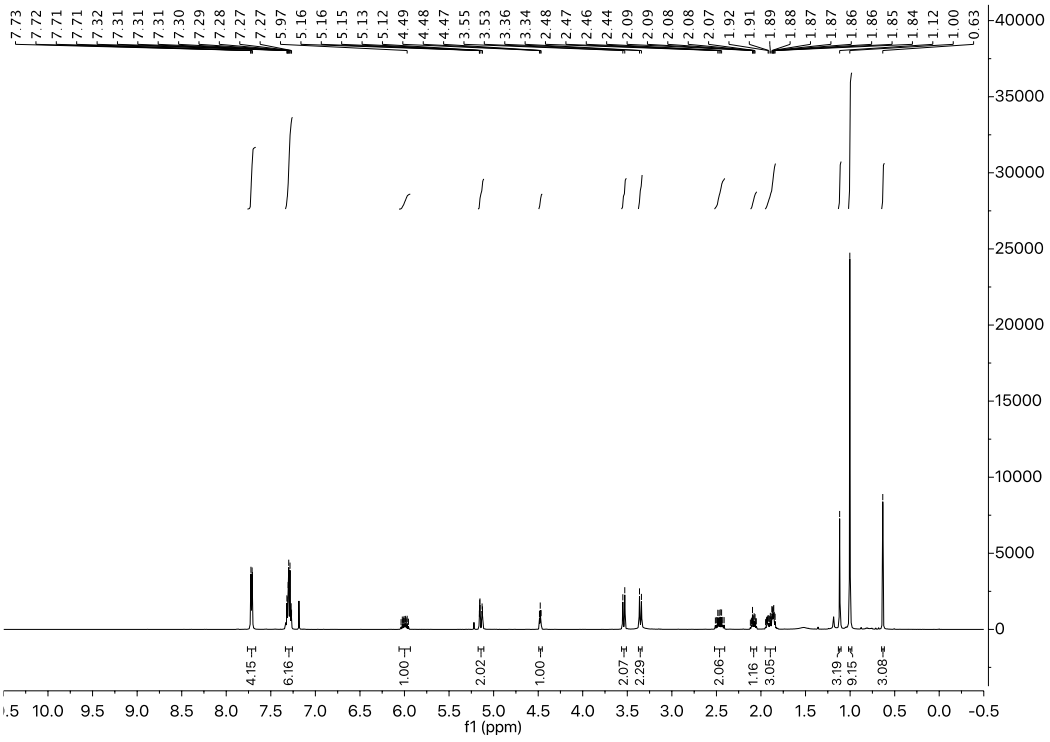
HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralcel AD-H column, hexanes:*i*-PrOH = 99:1, 1 mL/min, 210 nm), t_{major} = 19.76 min, t_{minor} = 37.37 min; *ee* = 92%.

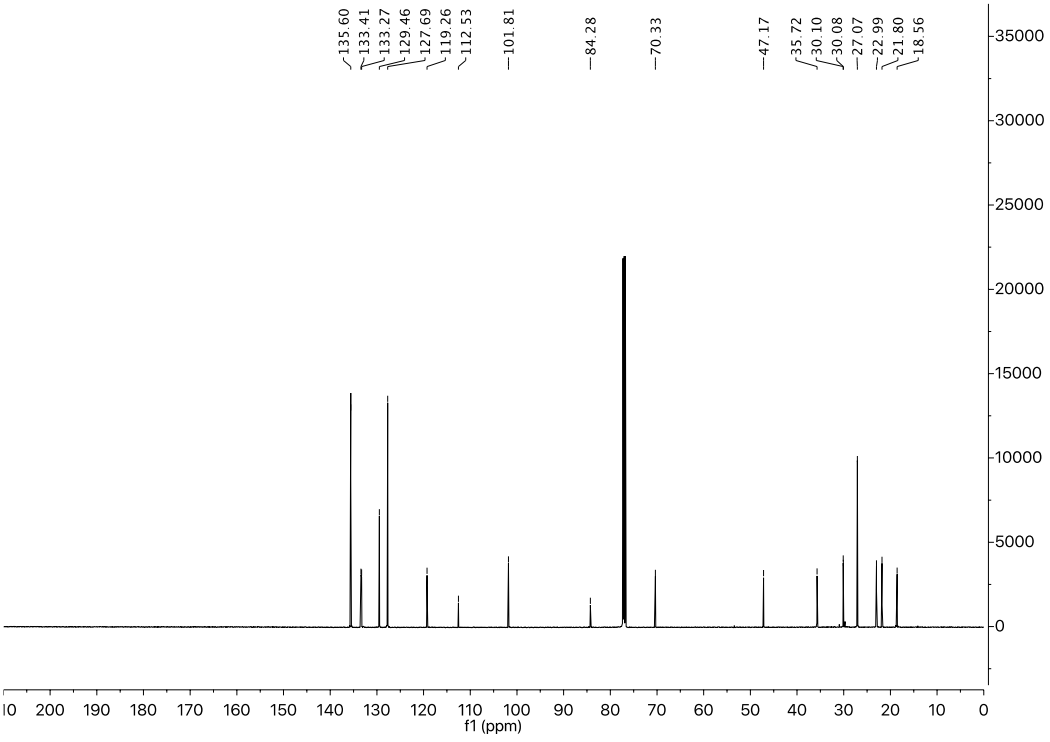


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.433	BV	0.5926	1.11645e4	289.08853	49.2719
2	36.025	VV	0.8415	1.14944e4	163.62955	50.7281
Totals :				2.26589e4	452.71808	

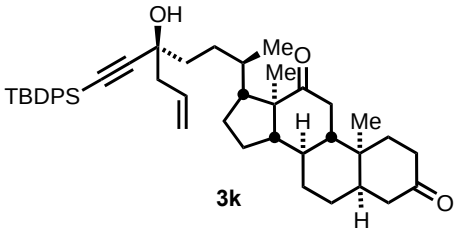


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.760	VB	0.5849	1.98715e4	518.81128	95.9126
2	37.367	MM	1.2382	846.83832	11.39850	4.0874
Totals :				2.07183e4	530.20978	


7.73 7.72 7.71 7.71 7.32 7.31 7.31 7.31 7.30 7.29 7.28 7.27 7.27 5.97 5.16 5.16 5.15 5.13 5.12 4.49 4.48 4.47 3.55 3.53 3.36 3.34 2.48 2.47 2.46 2.44 2.09 2.09 2.08 2.08 2.07 1.92 1.91 1.89 1.88 1.87 1.87 1.86 1.86 1.85 1.84 1.12 1.00 0.63
4.15 6.16 1.00 2.02 1.00 2.07 2.29 2.06 1.16 3.05 3.19 9.15 3.08
f1 (ppm)


135.60 133.41 133.27 129.46 127.69 119.26 112.53 101.81 84.28 70.33 47.17 35.72 30.10 30.08 27.07 22.99 21.80 18.56
f1 (ppm)

(5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*S*)-17-((2*R*,5*S*)-5-((*tert*-Butyldiphenylsilyl)ethynyl)-5-hydroxyoct-7-en-2-yl)-10,13-dimethyltetradecahydro-3*H*-cyclopenta[*a*]phenanthrene-3,12(2*H*)-dione (3.3k)



The title compound **3.3k** was prepared according to general using **3.1k** (127 mg, 0.20 mmol, 100 mol%). Upon flash chromatography (SiO_2, hexanes/ethyl acetate = 4:1) the title compound (69.1 mg, 0.10 mmol, 20:1 *dr*) was obtained in 51% yield as a white solid.

TLC (SiO_2) R_f = 0.14 (hexanes/ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (dt, *J* = 6.5, 1.6 Hz, 4H), 7.31 (tt, *J* = 8.2, 5.7 Hz, 6H), 5.99 (dddd, *J* = 16.8, 10.4, 8.3, 6.3 Hz, 1H), 5.21 – 5.15 (m, 2H), 2.60 – 2.49 (m, 3H), 2.36 (dd, *J* = 13.7, 8.3 Hz, 1H), 2.31 – 2.24 (m, 1H), 2.16 – 1.93 (m, 6H), 1.84 (tdd, *J* = 14.8, 10.1, 4.9 Hz, 8H), 1.61 (d, *J* = 6.8 Hz, 2H), 1.37 (tt, *J* = 11.9, 3.6 Hz, 4H), 1.25 (dd, *J* = 11.8, 3.1 Hz, 4H), 1.04 (s, 3H), 1.01 (s, 9H), 0.98 (s, 3H), 0.83 (d, *J* = 6.6 Hz, 3H) ppm.

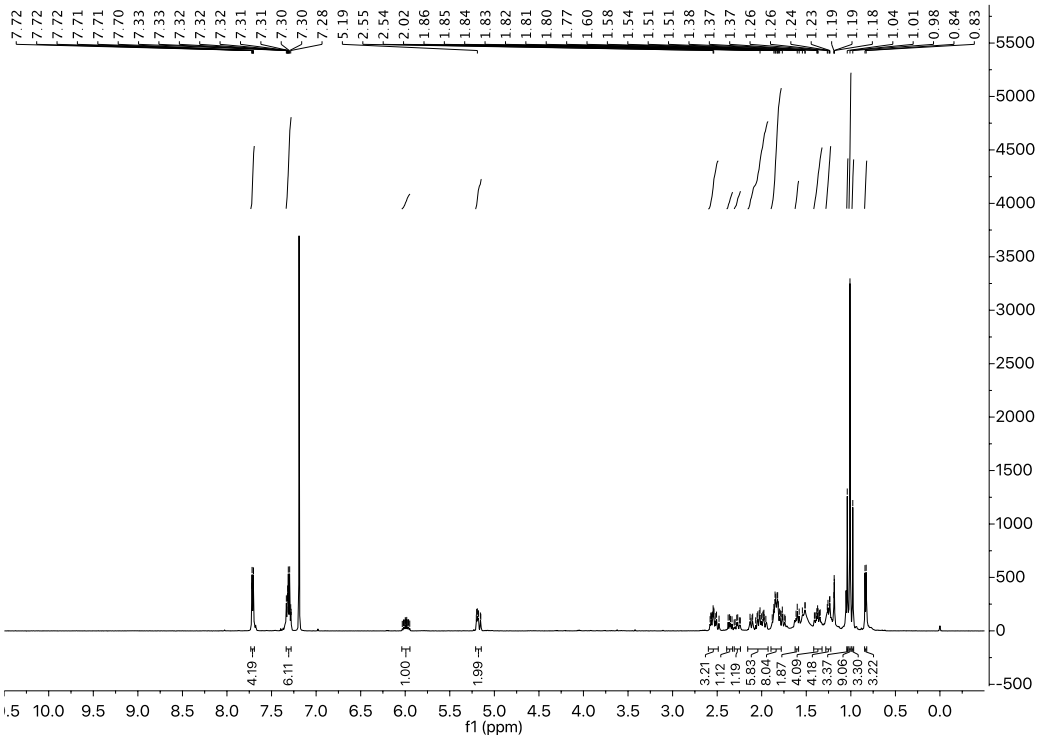
^{13}C NMR (126 MHz, $CDCl_3$) δ 214.2, 212.2, 135.6, 133.0, 129.5, 127.7, 120.0, 112.6, 84.2, 70.9, 58.6, 57.6, 46.9, 46.5, 44.3, 43.8, 42.2, 38.6, 38.4, 37.0, 36.8, 36.1, 35.6, 35.5, 30.0, 29.7, 27.6, 27.1, 27.0, 26.6, 25.5, 24.3, 22.2, 19.1, 18.5, 11.8 ppm.

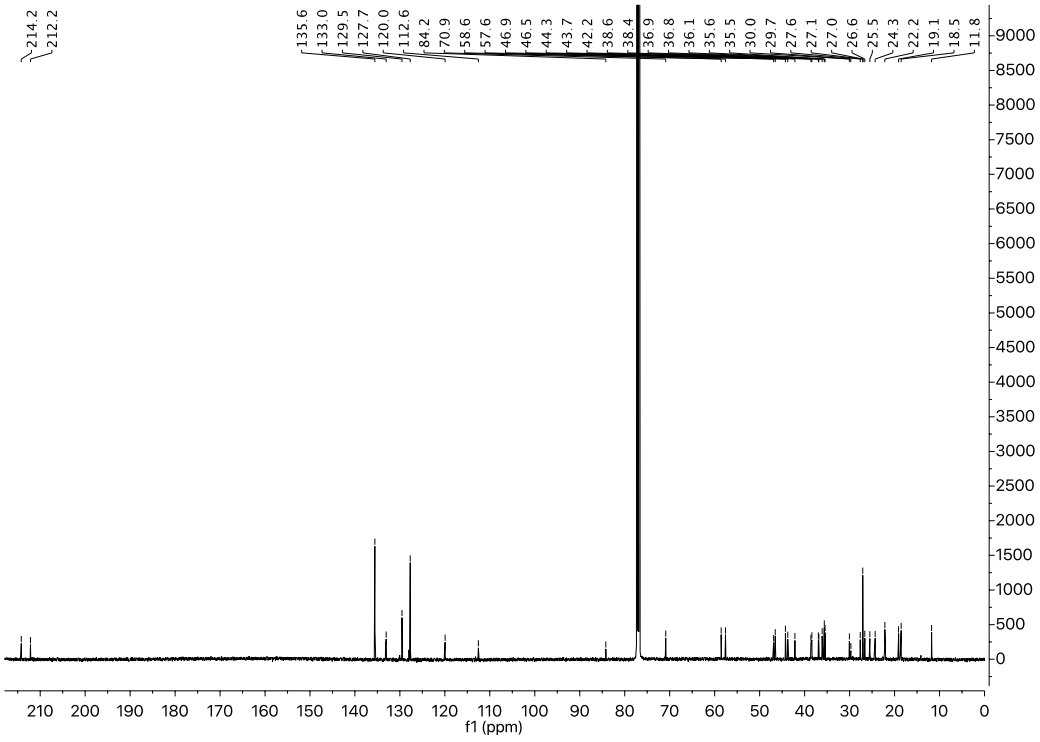
HRMS (ESI) m/z: [M+K^+] calcd for $C_{46}H_{60}O_3Si$ 715.3943, found 715.3936.

FTIR (ATR) 3240, 2926, 2859, 1699, 1462, 1446, 1428, 1107, 1009, 917, 820 cm^{-1}.

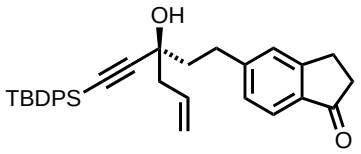
$[\alpha]_D^{28}$: +30.8 (*c* 1.0, $CHCl_3$).

MP: 127-129 ^oC


7.72 7.72 7.72 7.71 7.71 7.70 7.33 7.33 7.32 7.32 7.32 7.31 7.31 7.30 7.30 7.28 5.19 2.55 2.54 2.02 1.86 1.85 1.84 1.83 1.82 1.81 1.80 1.77 1.60 1.58 1.54 1.51 1.51 1.38 1.37 1.37 1.26 1.26 1.24 1.23 1.19 1.19 1.18 1.04 1.01 0.98 0.84 0.83
4.19 6.11 1.00 1.99 3.21 1.12 1.19 5.83 8.04 1.87 4.09 4.18 3.37 9.06 3.30 3.22
f1 (ppm)


214.2 212.2
135.6 133.0 129.5 127.7 120.0 112.6 84.2 70.9 58.6 57.6 46.9 46.5 44.3 43.7 42.2 38.6 38.4 36.9 36.8 36.1 35.6 35.5 30.0 29.7 27.6 27.1 27.0 26.6 25.5 24.3 22.2 19.1 18.5 11.8
f1 (ppm)

(*S*)-5-(3-((*tert*-butyldiphenylsilyl)ethynyl)-3-hydroxyhex-5-en-1-yl)-2,3-dihydro-1*H*-inden-1-one (3.3l)



3l

The title compound **3.3l** was prepared according to general procedure using **3.1l** (90.1 mg, 0.20 mmol, 100 mol%). Upon flash chromatography (SiO_2, hexanes/ethyl acetate = 3:1) the title compound (95.6 mg, 0.19 mmol) was obtained in 97% yield as a yellow oil.

TLC (SiO_2) R_f = 0.23 (hexanes/ethyl acetate = 3:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (dt, *J* = 8.0, 1.8 Hz, 4H), 7.68 (d, *J* = 7.9 Hz, 1H), 7.44 – 7.36 (m, 6H), 7.30 (s, 1H), 7.22 (d, *J* = 7.8 Hz, 1H), 6.13 – 6.03 (m, 1H), 5.33 – 5.23 (m, 2H), 3.12 – 3.03 (m, 4H), 2.70 – 2.64 (m, 3H), 2.55 – 2.47 (m, 1H), 2.29 (s, 1H), 2.11 – 2.03 (m, 2H), 1.11 (s, 9H) ppm.

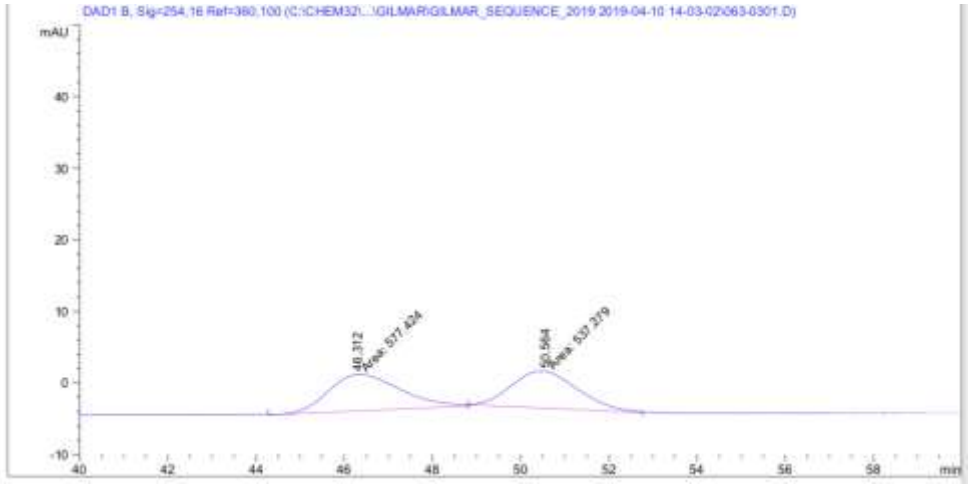
^{13}C NMR (126 MHz, $CDCl_3$) δ 206.6, 155.9, 149.8, 135.5, 135.3, 133.0, 133.0, 132.7, 129.7, 128.1, 127.8, 126.5, 123.9, 120.3, 111.8, 85.2, 70.4, 47.2, 43.4, 36.4, 31.5, 29.7, 27.1, 25.7, 18.6 ppm.

HRMS (ESI) m/z: [M+H$^+$] calcd for $C_{33}H_{36}O_2Si$ 493.2557, found 493.2553.

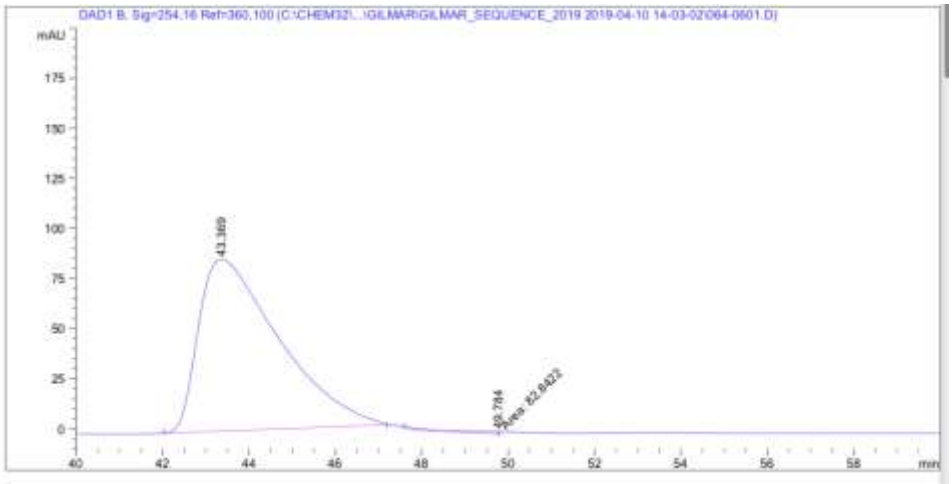
FTIR (ATR) 3401, 3071, 2928, 2856, 1693, 1608, 1428, 1361, 1008, 819, 737 cm^{-1}.

$[\alpha]_D^{28}$: -29.5 (*c* 1.0, $CHCl_3$).

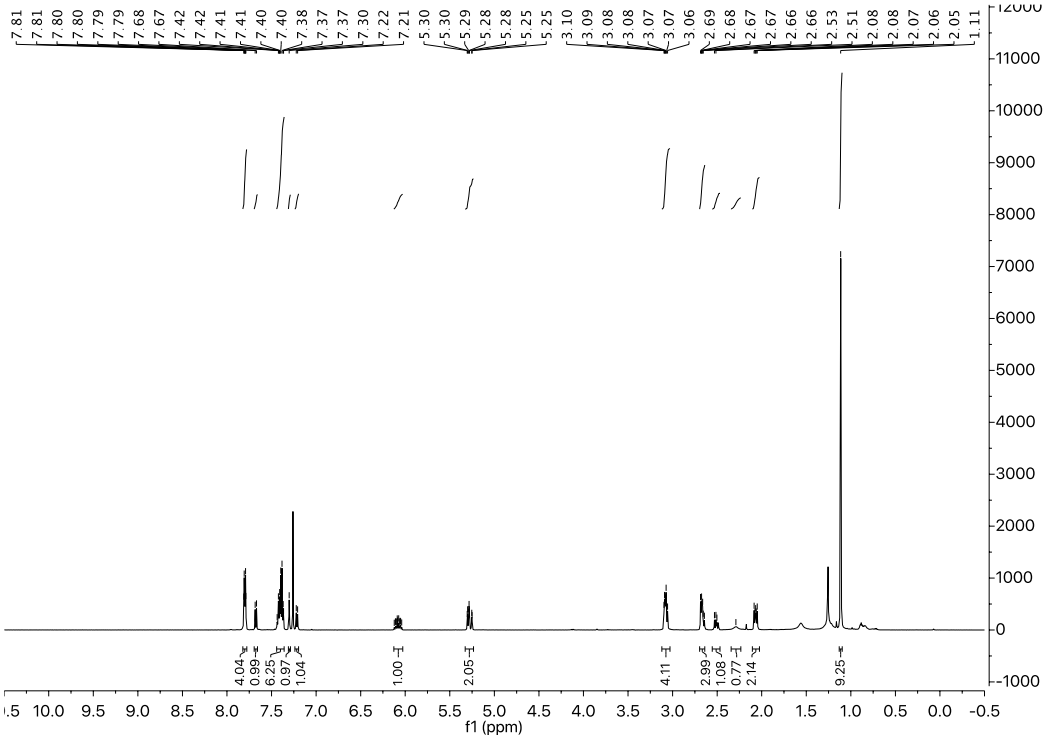
HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H column, hexanes:*i*-PrOH = 97:3, 0.5 mL/min, 254 nm), t_{major} = 43.37 min, t_{minor} = 49.78 min; *ee* = 98%.

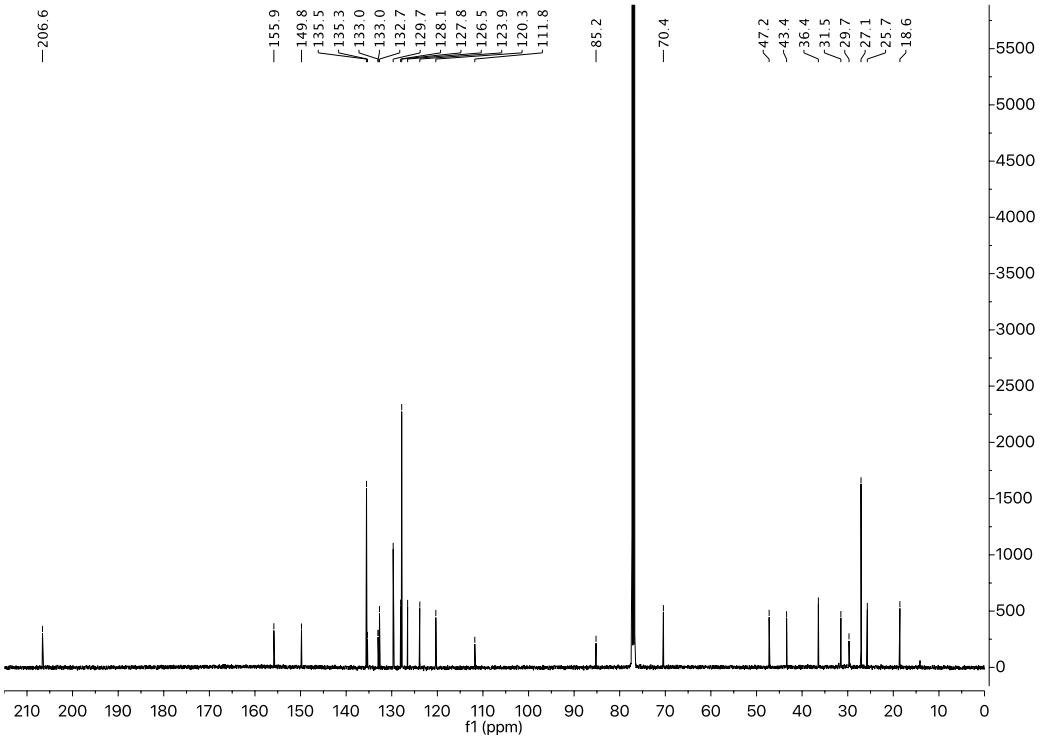


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	46.312	MM	1.8792	577.42395	5.12130	51.8007
2	50.564	MM	1.7401	537.27930	5.14598	48.1993
Totals :				1114.70325	10.26728	

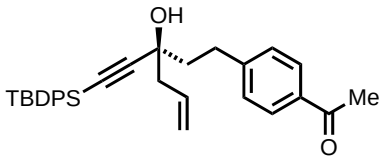


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	43.369	BB	1.6857	1.10631e4	85.83488	99.2568
2	49.784	MM	1.1199	82.84223	1.23286	0.7432
Totals :				1.11460e4	87.06774	


7.81
7.81
7.80
7.80
7.79
7.79
7.68
7.67
7.42
7.42
7.41
7.41
7.40
7.40
7.38
7.37
7.37
7.30
7.22
7.21
5.30
5.30
5.29
5.28
5.28
5.25
5.25
3.10
3.09
3.08
3.08
3.07
3.07
3.06
2.69
2.68
2.67
2.67
2.66
2.66
2.53
2.51
2.08
2.08
2.07
2.06
2.05
1.11
4.04
0.99
6.25
0.97
1.04
1.00
2.05
4.11
2.99
1.08
0.77
2.14
9.25
f1 (ppm)


206.6
155.9
149.8
135.5
135.3
133.0
133.0
132.7
129.7
128.1
127.8
126.5
123.9
120.3
111.8
85.2
70.4
47.2
43.4
36.4
31.5
29.7
27.1
25.7
18.6
f1 (ppm)

(*S*)-1-(4-(3-((*tert*-Butyldiphenylsilyl)ethynyl)-3-hydroxyhex-5-en-1-yl)phenyl)ethan-1-one (3.3m)



3m

The title compound **3.3m** was prepared according to general procedure using **3.1m** (87.7 mg, 0.20 mmol, 100 mol%). Upon flash chromatography (SiO_2, hexanes/ethyl acetate = 20:1) the title compound (72.1 mg, 0.15 mmol) was obtained in 75% yield as a yellow oil.

TLC (SiO_2) R_f = 0.32 (hexanes/ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 – 7.78 (m, 2H), 7.76 – 7.70 (m, 4H), 7.32 (ddd, *J* = 13.9, 7.7, 6.0 Hz, 6H), 7.23 (d, *J* = 8.0 Hz, 2H), 6.01 (dddd, *J* = 16.8, 10.3, 8.2, 6.5 Hz, 1H), 5.26 – 5.12 (m, 2H), 3.02 – 2.94 (m, 2H), 2.59 (dd, *J* = 13.6, 6.5 Hz, 1H), 2.51 (s, 3H), 2.43 (dd, *J* = 13.6, 8.2 Hz, 1H), 2.23 (s, 1H), 2.03 – 1.94 (m, 2H), 1.04 (s, 9H) ppm.

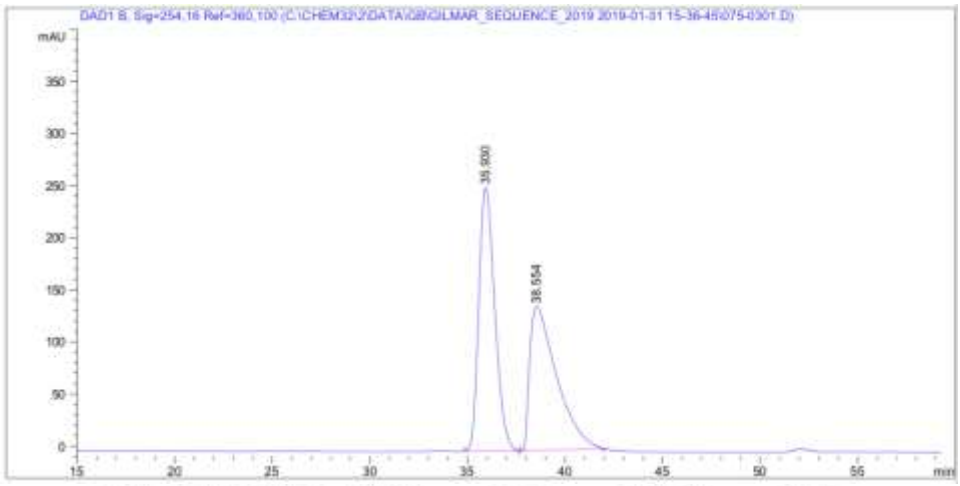
^{13}C NMR (126 MHz, $CDCl_3$) δ 197.8, 147.9, 135.5, 135.2, 133.0, 133.0, 132.7, 129.7, 128.7, 127.8, 120.3, 111.8, 85.2, 70.4, 47.2, 43.3, 31.1, 27.1, 26.6, 18.6 ppm.

HRMS (ESI) m/z: [M+Na^+] calcd for $C_{32}H_{36}O_2Si$ 503.2377, found 503.2376.

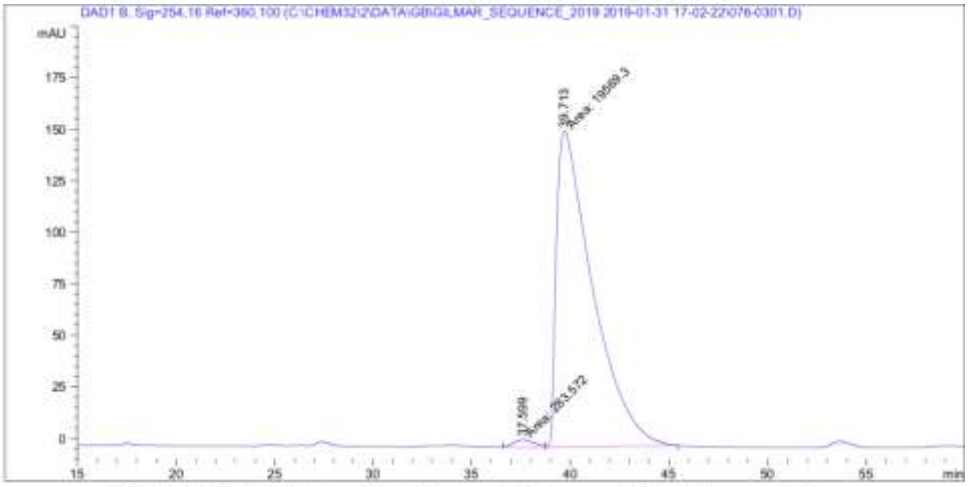
FTIR (ATR) 3434, 3071, 2929, 2856, 1680, 1605, 1428, 1359, 1266, 819, 736 cm^{-1}.

$[\alpha]_D^{28}$: -25.1 (*c* 1.0, $CHCl_3$).

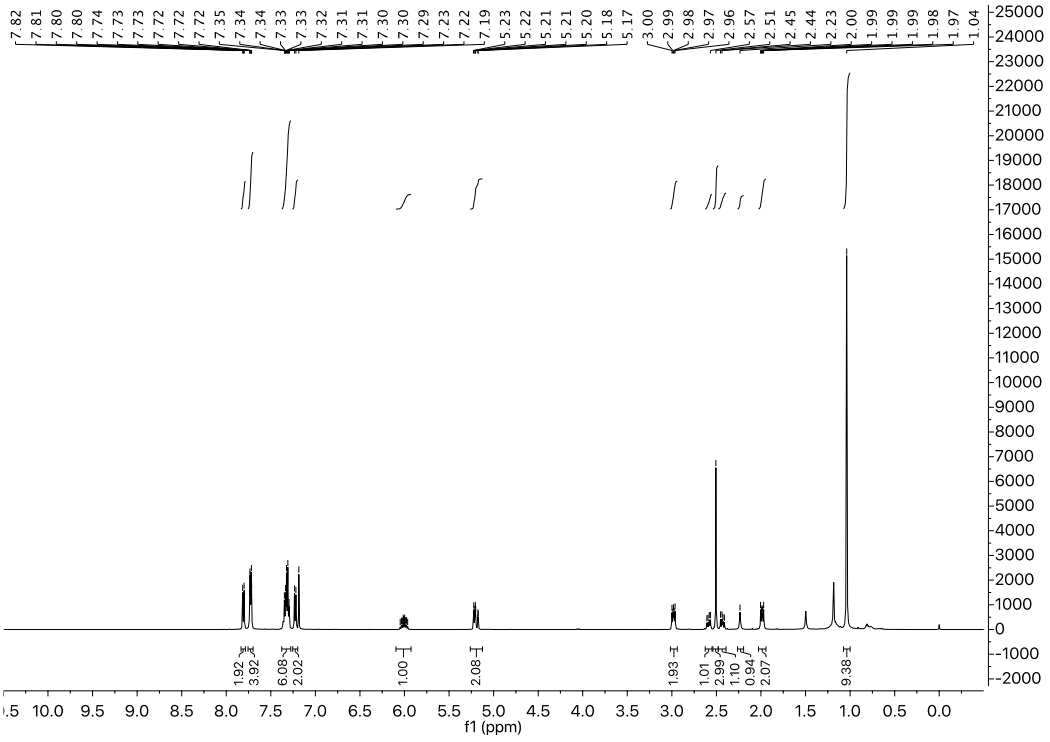
HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H column, hexanes:*i*-PrOH = 97:3, 0.5 mL/min, 254 nm), t_{major} = 39.71 min, t_{minor} = 37.60 min; *ee* = 96%.

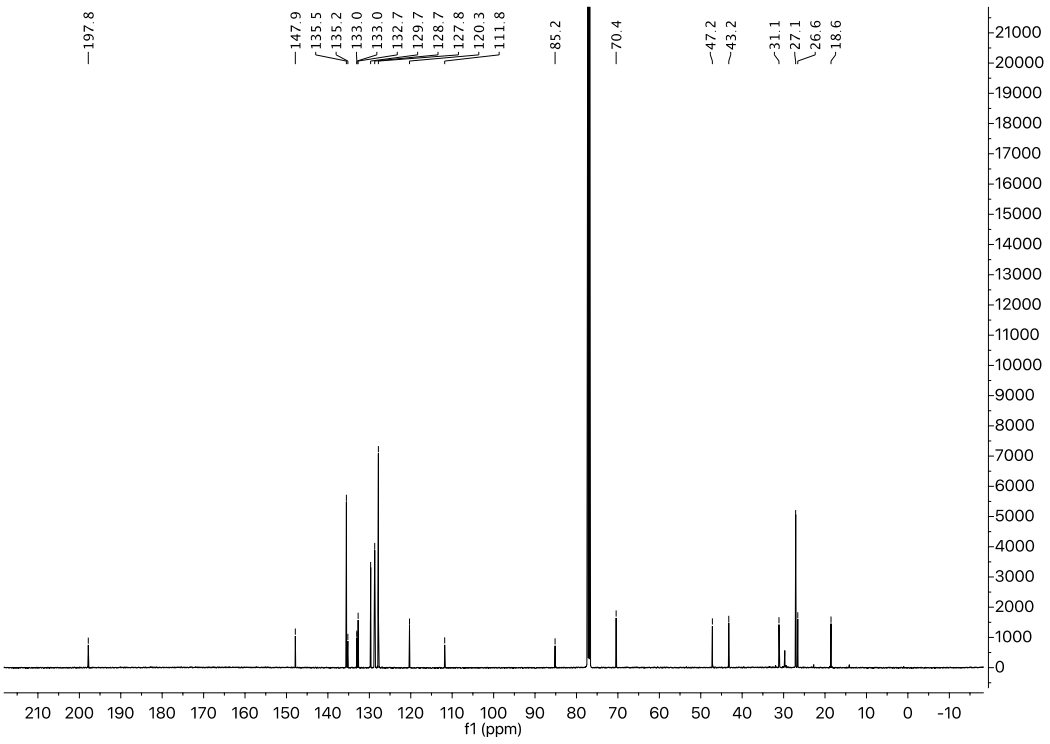


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	35.930	BB	0.8798	1.43517e4	253.01143	52.0508
2	38.554	BB	1.3619	1.32207e4	137.96875	47.9492
Totals :				2.75724e4	390.98018	

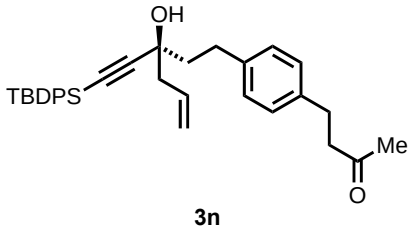


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	37.599	MF	1.2333	283.57239	3.83206	1.4284
2	39.713	FM	2.1280	1.95693e4	153.27097	98.5716
Totals :				1.98528e4	157.10303	


7.82 7.81 7.80 7.80 7.74 7.73 7.73 7.72 7.72 7.72 7.35 7.34 7.34 7.33 7.33 7.32 7.31 7.31 7.30 7.30 7.29 7.23 7.22 7.19 5.23 5.22 5.21 5.21 5.20 5.18 5.17 3.00 2.99 2.98 2.97 2.96 2.57 2.51 2.45 2.44 2.23 2.00 1.99 1.99 1.99 1.98 1.97 1.04
1.92 3.92 6.08 2.02 1.00 2.08 1.93 1.01 2.99 1.10 0.94 2.07 9.38
f1 (ppm)


197.8 147.9 135.5 135.2 133.0 133.0 132.7 129.7 128.7 127.8 120.3 111.8 85.2 70.4 47.2 43.2 31.1 27.1 26.6 18.6
f1 (ppm)

(*S*)-4-(4-(3-((*tert*-Butyldiphenylsilyl)ethynyl)-3-hydroxyhex-5-en-1-yl)phenyl)butan-2-one (3.3n)



3n

The title compound **3.3n** was prepared according to general procedure using **3.1n** (93.3 mg, 0.20 mmol, 100 mol%). Upon flash chromatography (SiO_2, hexanes/ethyl acetate = 4:1) the title compound (69.2 mg, 0.14 mmol) was obtained in 68% yield as a yellow oil.

TLC (SiO_2) R_f = 0.23 (hexanes/ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (dt, *J* = 6.5, 1.7 Hz, 4H), 7.36 – 7.28 (m, 6H), 7.09 – 7.01 (m, 4H), 6.00 (dddd, *J* = 16.8, 10.4, 8.1, 6.5 Hz, 1H), 5.21 – 5.15 (m, 2H), 2.91 – 2.85 (m, 2H), 2.79 (dd, *J* = 8.4, 6.8 Hz, 2H), 2.67 (dd, *J* = 8.3, 6.9 Hz, 2H), 2.57 (ddt, *J* = 13.6, 6.5, 1.3 Hz, 1H), 2.43 (dd, *J* = 13.6, 8.1 Hz, 1H), 2.19 (d, *J* = 9.7 Hz, 1H), 2.07 (s, 3H), 2.00 – 1.93 (m, 2H), 1.03 (s, 9H) ppm.

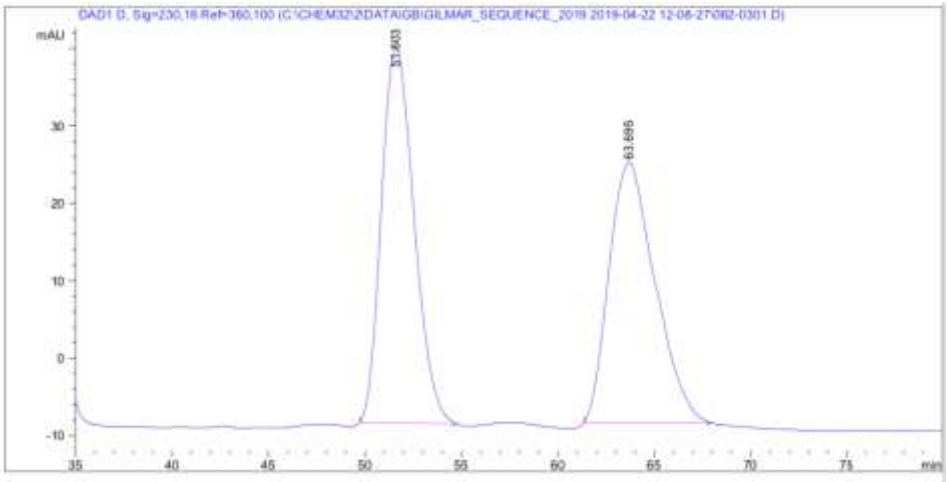
^{13}C NMR (126 MHz, $CDCl_3$) δ 208.1, 139.7, 138.6, 135.6, 133.1, 132.9, 129.6, 128.6, 128.4, 127.8, 120.1, 112.1, 84.8, 70.6, 47.1, 45.3, 43.8, 30.6, 30.1, 29.3, 27.1, 18.6 ppm.

HRMS (ESI) m/z: [M+Na^+] calcd for $C_{34}H_{40}O_2Si$ 531.2690, found 531.2711.

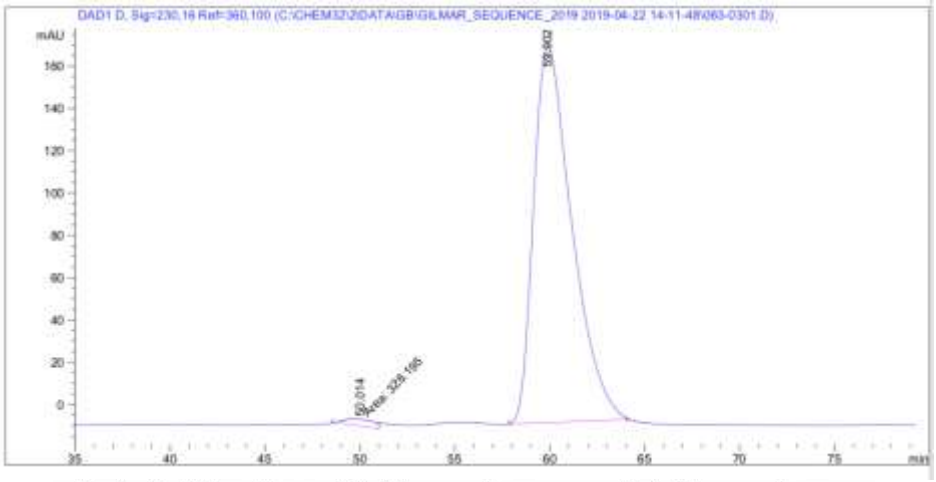
FTIR (ATR) 3456, 2928, 2856, 1709, 1514, 1428, 1361, 1108, 853, 742 cm^{-1}.

$[\alpha]_D^{28}$: -24.6 (*c* 1.0, $CHCl_3$).

HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H column, hexanes:*i*-PrOH = 97:3, 0.5 mL/min, 230 nm), t_{major} = 59.90 min, t_{minor} = 50.01 min; *ee* = 98%.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	51.603	BB	1.4702	5717.33740	48.53750	50.6473
2	63.695	BB	1.9452	5571.20703	33.62143	49.3527
Totals :				1.12885e4	82.15892	



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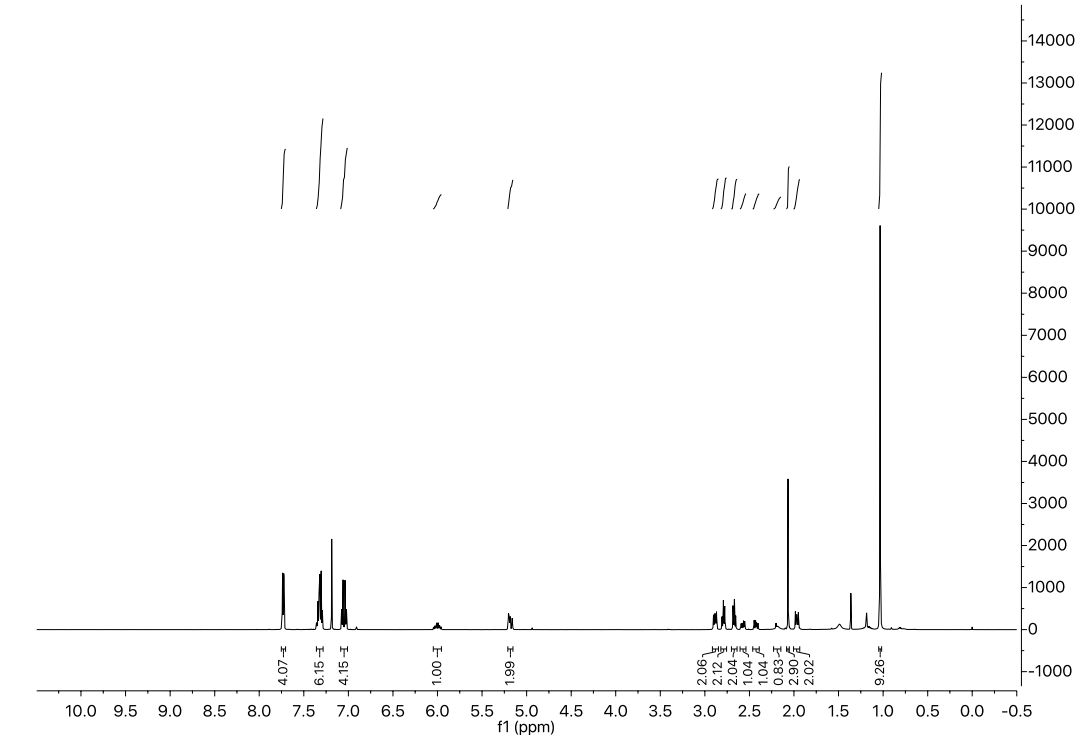
2	59.902	BB	2.0303	2.49536e4	177.48051	98.7019
Totals :				2.52818e4	180.63007	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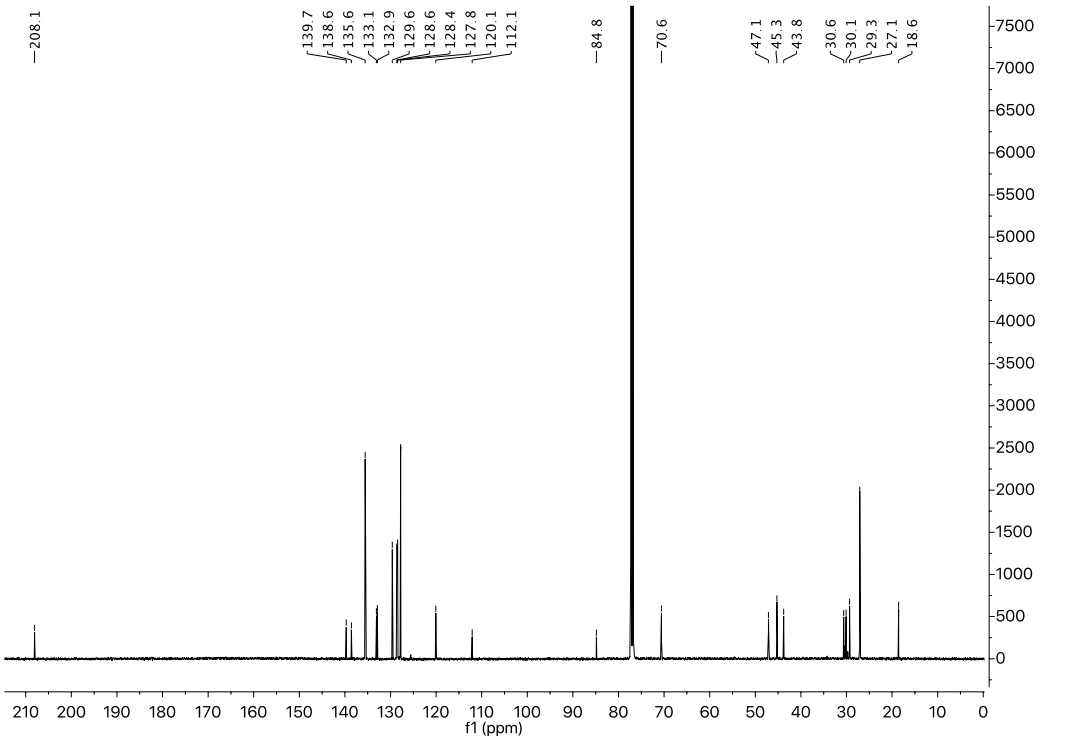
6.15
4.15
1.00
1.99
2.06
2.12
2.04
1.04
1.04
0.83
2.90
2.02
9.26
f1 (ppm)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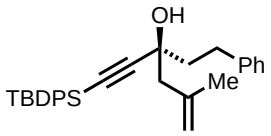
135.6
133.1
132.9
129.6
128.6
128.4
127.8
120.1
112.1
84.8
70.6
47.1
45.3
43.8
30.6
30.1
29.3
27.1
18.6
f1 (ppm)

(*S*)-1-(*tert*-Butyldiphenylsilyl)-5-methyl-3-phenethylhex-5-en-1-yn-3-ol (3.4g)



4g

A pressure tube was equipped with a magnetic stir bar and charged with 1-(tert-butyldiphenylsilyl)-5-phenylpent-1-yn-3-one (**3.1g**, 79.3 mg, 0.20 mmol, 100 mol%), K_3PO_4 (42.5 mg, 0.20 mmol, 100 mol%) and (*S*)-Ir-I (10.3 mg, 0.01 mmol, 5 mol%). The pressure tube was purged with argon. Anhydrous THF (0.4 mL, 0.5 M), 2-propanol (0.046 mL, 0.6 mmol, 300 mol%) and methallyl chloride (0.059 mL, 0.60 mmol, 300 mol%) were added via syringe. The reaction vessel was sealed, and the reaction mixture was placed in an oil bath at 80 °C for 24 hours. The reaction vessel was allowed to reach ambient temperature and the reaction mixture was concentrated *in vacuo*. The resultant residue was subjected to flash column chromatography (SiO_2, hexanes/ethyl acetate as eluent) to furnish the title compound in 91% yield (82 mg, 0.18 mmol) as a pale yellow oil.

TLC (SiO_2) R_f = 0.56 (hexanes/ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, J = 7.6 Hz, 4H), 7.42 (dq, J = 13.8, 6.9, 6.5 Hz, 6H), 7.32 (t, J = 7.4 Hz, 2H), 7.23 (d, J = 11.2 Hz, 2H), 5.02 (d, J = 39.7 Hz, 2H), 3.06 (t, J = 8.6 Hz, 2H), 2.63 (d, J = 13.4 Hz, 1H), 2.53 (d, J = 13.4 Hz, 1H), 2.49 (s, 1H), 2.16 – 2.06 (m, 2H), 2.01 (s, 3H), 1.15 (s, 9H). ppm.

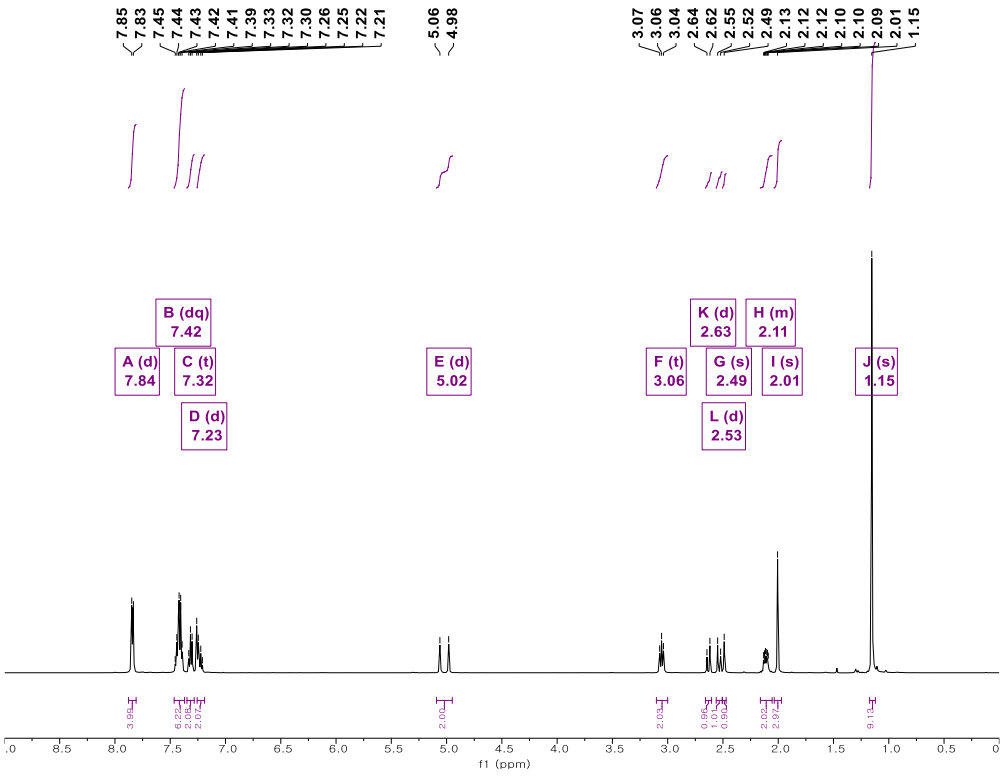
^{13}C NMR (126 MHz, $CDCl_3$) δ 142.1, 141.5, 135.6, 133.2, 129.6, 128.5, 128.5, 127.8, 125.9, 116.2, 112.7, 85.0, 77.3, 77.1, 76.8, 69.9, 50.1, 44.9, 31.2, 27.2, 24.7, 18.6 ppm.

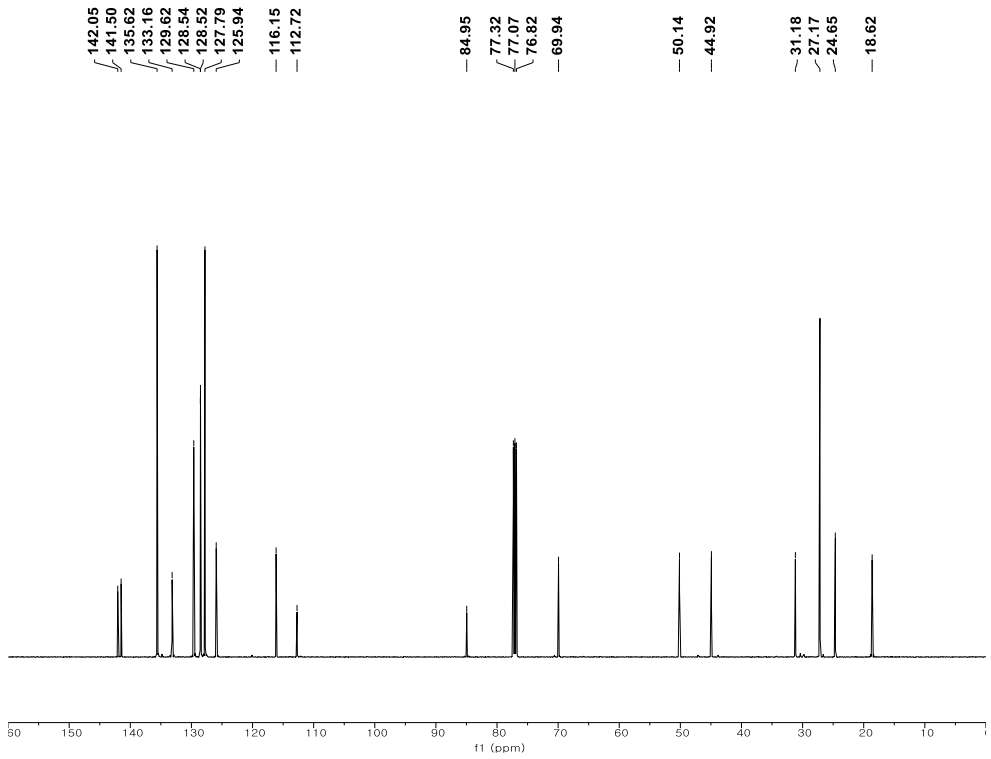
HRMS (ESI) m/z: [(M+Na)+] calcd for $C_{31}H_{36}OSi$ 475.2428, found 475.2426.

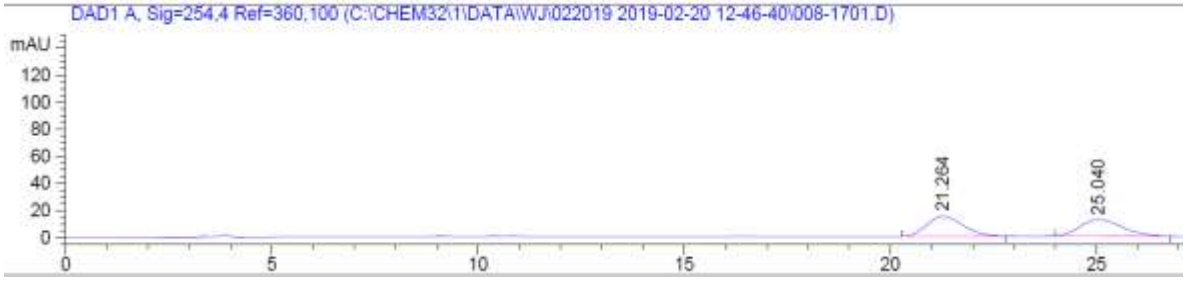
FTIR (ATR) 2942, 2865, 1459, 1381, 1366, 1107, 1016, 997, 884, 733, 697, 678, 662 cm^{-1}.

$[\alpha]_D^{28}$: + 211 (c = 0.25, $CHCl_3$).

HPLC: Enantiomeric excess was determined by HPLC analysis of the 3,5-dinitrobenzoate derivative of the product (Chiralcel OD-H column, hexanes:2-PrOH = 99:1, 1.0 mL/min, 254 nm), tmajor = 20.6 min, tminor = 23.8 min; ee = 92 %.

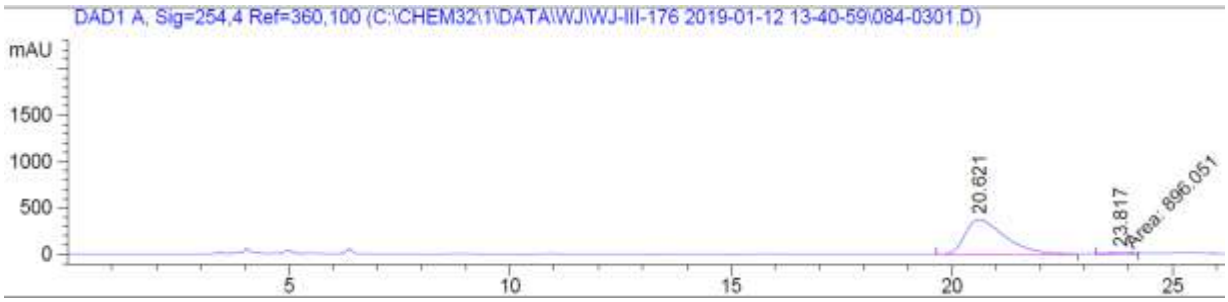






Signal 1: DAD1 A, Sig=254,4 Ref=360,100

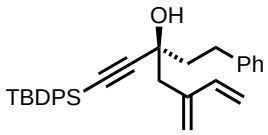
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.264	BB	0.7259	912.37866	14.91072	51.0291
2	25.040	BB	0.8486	875.57928	12.23903	48.9709
Totals :				1787.95795	27.14974	



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.621	BB	0.9343	2.33016e4	373.26385	96.2970
2	23.817	MF	0.7881	896.05072	18.95066	3.7030
Totals :				2.41977e4	392.21452	

(*S*)-1-(*tert*-Butyldiphenylsilyl)-5-methylene-3-phenethylhept-6-en-1-yn-3-ol (3.5g)



5g

A pressure tube was equipped with a magnetic stir bar and charged with 1-(tert-butyldiphenylsilyl)-5-phenylpent-1-yn-3-one (**3.1g**, 79.3 mg, 0.20 mmol, 100 mol%), K_3PO_4 (42.5 mg, 0.20 mmol, 100 mol%) and (*S*)-Ir-DM-SEGPHOS (10.3 mg, 0.01 mmol, 5 mol%). The pressure tube was purged with argon. Anhydrous THF (0.4 mL, 0.5 M), 2-propanol (0.046 mL, 0.6 mmol, 300 mol%) and *tert*-butyl (2-methylenebut-3-en-1-yl) carbonate (73.4 mg, 0.40 mmol, 200 mol%) were added via syringe. The reaction vessel

was sealed and the reaction mixture was placed in an oil bath at 80 °C for 48 hours. The reaction vessel was allowed to reach ambient temperature and the reaction mixture was concentrated *in vacuo*. The resultant residue was subjected to flash column chromatography (SiO_2, hexanes/ethyl acetate = 20:1) to furnish the title compound in 64% yield (59.6 mg, 0.13 mmol) as a pale yellow oil.

TLC (SiO_2) R_f = 0.56 (hexanes/ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 7.6 Hz, 4H), 7.31 (dt, J = 13.9, 6.8 Hz, 7H), 7.21 (t, J = 7.5 Hz, 2H), 7.17 – 7.09 (m, 3H), 6.40 (dd, J = 17.5, 10.9 Hz, 1H), 5.34 (d, J = 17.5 Hz, 1H), 5.25 (d, J = 13.9 Hz, 2H), 5.01 (d, J = 10.8 Hz, 1H), 2.96 (t, J = 8.7 Hz, 2H), 2.74 – 2.59 (m, 2H), 2.27 (s, 1H), 2.04 (q, J = 8.3 Hz, 2H), 1.03 (s, 10H). ppm.

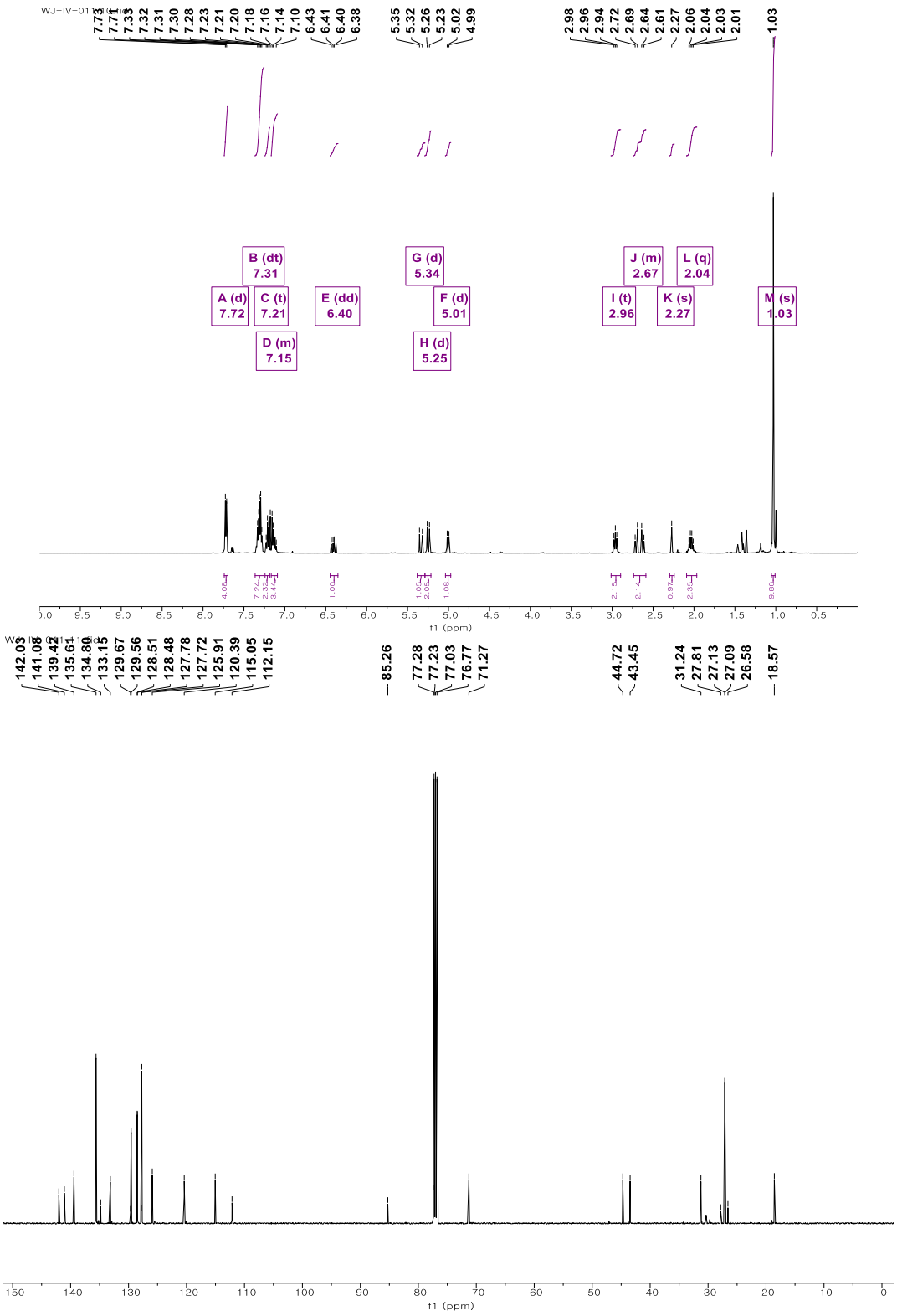
^{13}C NMR (126 MHz, $CDCl_3$) δ 142.0, 141.1, 139.4, 135.6, 134.8, 133.2, 129.7, 129.6, 128.5, 128.5, 127.8, 127.7, 125.9, 120.4, 115.1, 112.2, 85.3, 77.3, 77.2, 77.0, 76.8, 71.3, 44.7, 43.5, 31.2, 27.8, 27.1, 27.1, 26.6, 18.6 ppm.

HRMS (ESI) m/z: [(M+Na)+] calcd for $C_{32}H_{36}OSi$ 487.2428, found 487.2427.

FTIR (ATR) 2929, 2857, 1739, 1591, 1497, 1458, 1429, 1392, 1368, 1277, 1254, 1160, 1110, 1009, 998, 901, 858, 820, 794, 742, 699 cm^{-1}.

$[\alpha]_D^{28}$: + 95 (c = 0.25, $CHCl_3$).

HPLC: Chiralcel OD-H column, hexanes:2-PrOH = 95:5, 1.0 mL/min, 254 nm, tmajor = 4.5 min, tminor = 5.0 min; ee = 89%.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7.72
7.35
7.32
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7.30
7.28
7.23
7.21
7.20
7.18
7.16
7.14
7.10
6.43
6.41
6.40
6.38
5.35
5.32
5.26
5.23
5.02
4.99
2.98
2.96
2.94
2.72
2.69
2.64
2.61
2.27
2.06
2.04
2.03
2.01
1.03
B (dt) 7.31
A (d) 7.72
C (t) 7.21
D (m) 7.15
E (dd) 6.40
G (d) 5.34
F (d) 5.01
H (d) 5.25
J (m) 2.67
I (t) 2.96
L (q) 2.04
K (s) 2.27
M (s) 1.03
f1 (ppm)
142.03
141.08
139.42
135.61
134.80
133.15
129.67
129.56
128.51
128.48
127.78
127.72
125.91
120.39
115.05
112.15
85.26
77.28
77.23
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76.77
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44.72
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31.24
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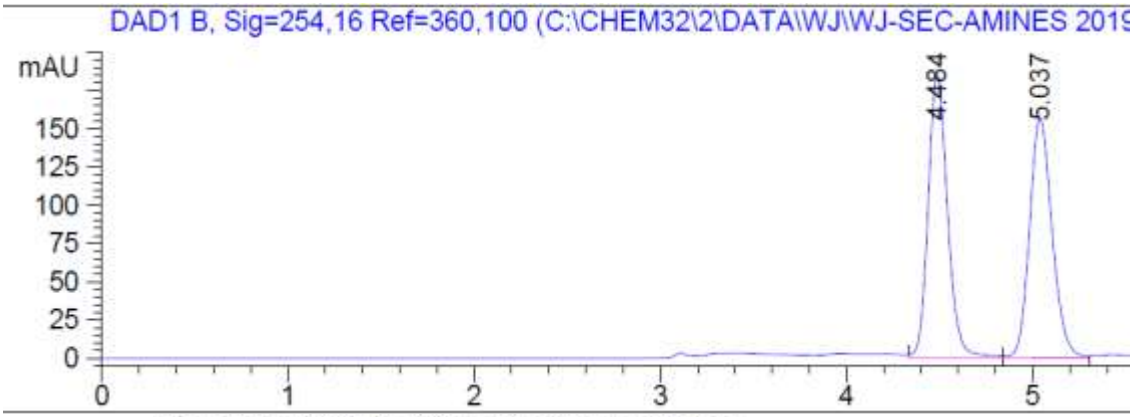
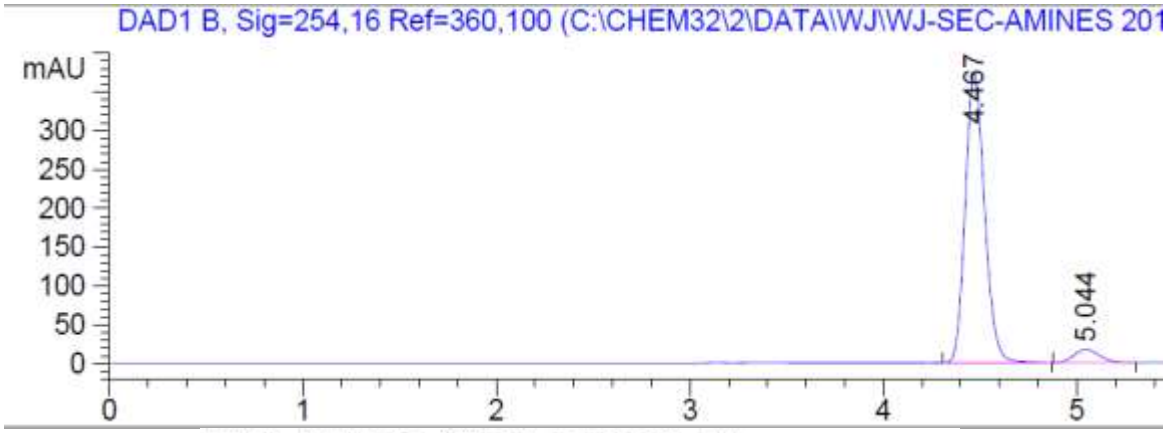
27.13
27.09
26.58
18.57
f1 (ppm)



Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.484	BV	0.1102	1335.01416	184.96469	50.3697
2	5.037	VV	0.1281	1315.41931	156.51157	49.6303
Totals :				2650.43347	341.47626	



Signal 2: DAD1 B, Sig=254,16 Ref=360,100

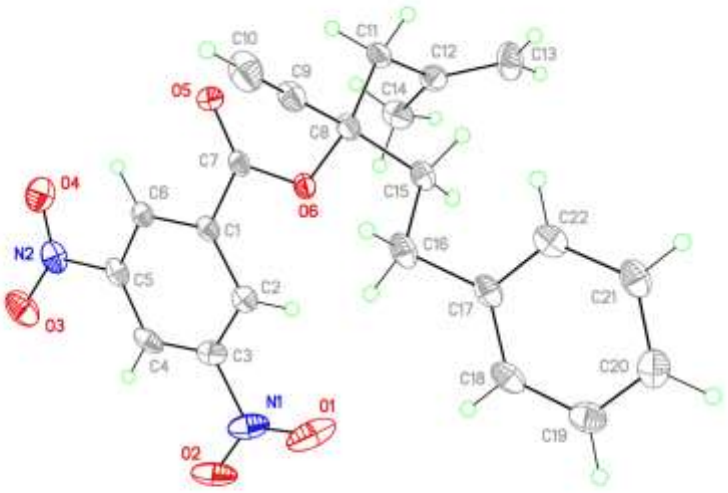
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.467	BB	0.1088	2583.34692	372.90732	94.4525
2	5.044	BB	0.1444	151.72900	16.63083	5.5475
Totals :				2735.07593	389.53814	

3.5.5 Single Crystal Diffraction Data for 3.4g

Empirical formula	C23 H22 Cl0 N2 O6.33	
Formula weight	427.76	
Temperature	100(2) K	
Wavelength	1.54184 Å	
Crystal system	monoclinic	
Space group	P 21	
Unit cell dimensions	a = 20.3961(3) Å	α= 90°.
	b = 7.65640(10) Å	β= 104.537(2)°.
	c = 20.9340(3) Å	γ = 90°.
Volume	3164.41(8) $Å^3$	
Z	6	
Density (calculated)	1.347 Mg/m^3	
Absorption coefficient	0.825 mm^{-1}	
F(000)	1348	
Crystal size	0.270 x 0.150 x 0.050 mm^3	
Theta range for data collection	2.704 to 68.247°.	
Index ranges	-24<=h<=20, -9<=k<=9, -25<=l<=25	
Reflections collected	37067	
Independent reflections	11588 [R(int) = 0.0420]	
Completeness to theta = 67.684°	99.9 %	
Absorption correction	Gaussian + multi-scan	
Max. and min. transmission	1.00 and 0.725	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	11588 / 1 / 852
Goodness-of-fit on F^2	0.994
Final R indices [I>2sigma(I)]	R1 = 0.0588, wR2 = 0.1521
R indices (all data)	R1 = 0.0615, wR2 = 0.1566
Absolute structure parameter	-0.05(8)
Extinction coefficient	n/a
Largest diff. peak and hole	0.596 and -0.428 e.$Å^{-3}$

View of the molecule 1 in **3.4g** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.



Chapter 4: Enantioselective Iridium-Catalyzed Allylation of Nitroalkanes: Entry to β-Stereogenic α-Quaternary Primary Amines

4.1 INTRODUCTION

Chiral amines are prevalent among FDA approved drugs,[1] as are protocols for their synthesis.[2] The vast majority of present catalytic enantioselective methods for the construction of chiral amines deliver *N*-substituted carbon stereocenters.[2] Catalytic enantioselective methods to form acyclic chiral β-stereogenic amines are far less common and include asymmetric hydrogenation of enamines,[3] allylic amines/amides[4] or nitrolefins,[5] 1,4-reductions and 1,4-additions to nitroolefins,[6,7] and dynamic kinetic resolutions via aldehyde reductive amination.[8] These methods do not deliver chiral β-stereogenic α-quaternary primary amines. Catalytic enantioselective Tsuji–Trost allylic alkylation of nitronate, followed by reduction potentially provides acyclic chiral β-stereogenic amines, but such methods are underdeveloped.[9-12] Palladium-catalyzed allylic alkylations typically display linear regioselectivity, and consequently focus on reactions that proceed via symmetric π-allylpalladium intermediates[9] or prochiral nucleophiles (α-nitroesters).[12] Beyond vinyl epoxides,[10a] only a single catalytic system for catalytic asymmetric nitronate allylic alkylation of mono-substituted π-allyl precursors with branched regioselectivity has been described.[10b,c] Only three examples of corresponding iridium-catalyzed nitronate allylic alkylations are reported.[11] Both the palladium- and iridium-based catalyst systems rely on linear aryl-substituted π-allyl precursors and display incomplete diastereo- and regioselectivity (Figure 4.1).

*This chapter is based on the previously published works: Jung, W.-O.; Mai, B. K.; Spinello, B. J.; Dubey, Z. J.; Kim, S. W.; Zbieg, J. R.; Stivala, C. E.; Liu, P.; Krische, M. J. *J. Am. Chem. Soc.* **2021**, *143*, 9343. W. J. contributed to reaction discovery and optimization (Table 4.1), substrate scope (Tables 4.2 and 4.3), and preparation of manuscript and supporting information.

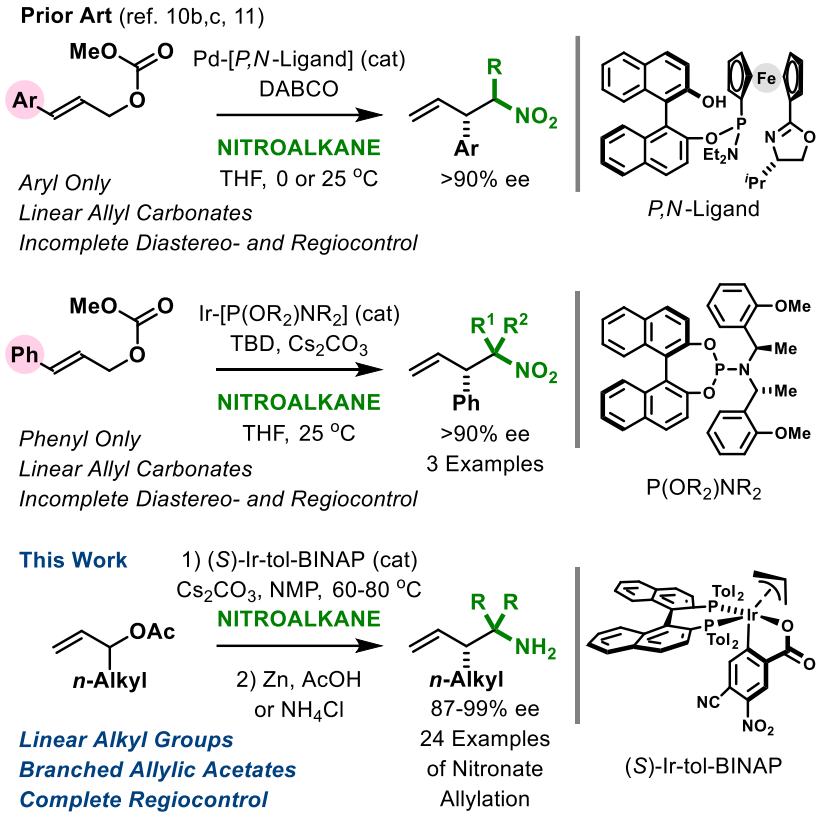


Figure 4. 1 Catalytic enantioselective nitronate allylic alkylation of mono-substituted π-allyl precursors.

In connection with studies of π-allyliridium *C,O*-benzoate-catalyzed *nucleophilic* allylations of carbonyl compounds,[13] we recently found these same complexes are competent catalysts for *electrophilic* allylation, as demonstrated in regio- and enantioselective aminations of racemic branched alkyl-substituted allylic acetates to form acyclic chiral α-stereogenic amines.[14] Aspiring to access corresponding chiral β-stereogenic amines, a study of nitronate nucleophiles was undertaken. Here, we demonstrate that α,α-disubstituted nitroalkanes participate in highly enantioselective allylic alkylation with racemic branched alkyl-substituted allylic acetates. Despite forming

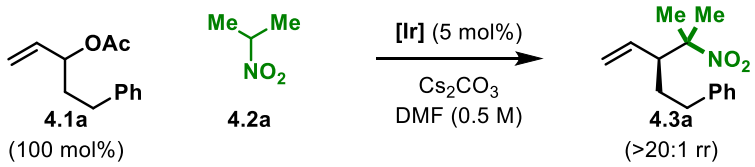
congested contiguous quaternary-tertiary C-C bonds, complete branched regioselectivities are observed. DFT calculations reveal early transition states that render the reaction less sensitive to steric effects and distinct trans-effects of diastereomeric chiral-at-iridium π-allyl complexes that facilitate formation of congested tertiary-quaternary C-C bonds.

4.2 Reaction Development and Scope

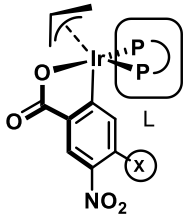
In initial experiments, allylic acetate **4.1a** (100 mol%) was exposed to 2-nitropropane **4.2a** (1125 mol%) as solvent (1.0 M) in the presence of Cs_2CO_3 (500 mol%) and the π-allyliridium *C,O*-benzoate complex modified by (*S*)-tol-BINAP, Ir-**I**, at 100 °C. The homoallylic nitroalkane **4.3a** was formed in 51% yield and 95% ee (Table 1, entry 1). Lower loading of 2-nitropropane **4.2a** (450 mol%) with DMF (0.5 M) as solvent improved yield and enantioselectivity (Table 4.1, entry 2), but further reduction in the loading of **4.2a** led to a small decrease in yield (Entry 3). A slight decrease in temperature (80 °C) improved the yield of **4.3a** without diminishing enantioselectivity (Entry 4). Lower loading of Cs_2CO_3 decreased the yield of **4.3a** (Entry 5) and water (100 mol%) dramatically decreased conversion of **4.1a** (Entry 6). Other π-allyliridium *C,O*-benzoates were evaluated but did not improve the yield of **4.3a** (Entries 7-10).

To evaluate reaction scope, optimal conditions for the formation of **4.3a** (Table 4.1, entry 4) were applied to the allylic alkylation of α,α-disubstituted nitroalkanes **4.2a**-**4.2j** with racemic branched alkyl substituted allylic acetates **4.1a**-**4.1n** (Table 4.2). As illustrated by the conversion of 2-nitropropane **4.2a** to adducts **4.3a**-**4.3h**, diverse (hetero)aromatic groups (**4.3a**-**4.3e**), (thio)ethers (**4.3f**, **4.3g**), cyclopropyl groups (**4.3h**)

Table 4. 1 Selected optimization experiments in the enantioselective iridium-catalyzed allylic alkylation of racemic branched alkyl-substituted allylic acetate **4.1a** with nitronate **4.2a**.[a]



Entry	4.2a (mol%)	catalyst	Cs_2CO_3 (mol%)	T °C	Yield (%)	ee (%)
1[b]	1125	Ir-**I**	500 mol%	100	51	95
2	450	Ir-**I**	500 mol%	100	67	99
3	240	Ir-**I**	500 mol%	100	35	99
4	450	Ir-**I**	500 mol%	80	71	99
5	450	Ir-**I**	300 mol%	80	56	99
6[c]	450	Ir-**I**	500 mol%	80	<10	-
7	450	Ir-**II**	500 mol%	80	51	99
8	450	Ir-**III**	500 mol%	80	53	99
9	450	Ir-**IV**	500 mol%	80	43	99
10	450	Ir-**V**	500 mol%	80	50	99

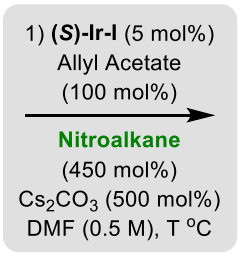


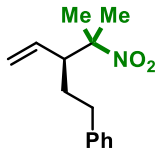
Ir-**I** L = (*S*)-tol-BINAP, X = CN
Ir-**II** L = (*S*)-tol-BINAP, X = NO_2
Ir-**III** L = (*S*)-BINAP, X = CN
Ir-**IV** L = (*S*)-SEGPHOS, X= CN
Ir-**V** L = (*S*)-MeO-BIPHEP, X= CN

[a]Yields are of material isolated by silica gel chromatography. Diastereoselectivities were determined by ^{1}H NMR of crude reaction mixtures. Enantioselectivities were determined by HPLC analysis. [b]**4.2a** = solvent (1.0 M). [c]H_2O (100 mol%).

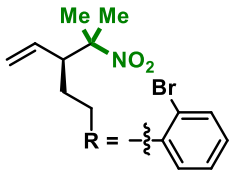
are tolerated. As demonstrated by the formation of adducts **4.3i-4.3x**, cyclic nitroalkanes **4.2b-4.2h** are also competent partners for allylic alkylation. This includes nitrocyclobutane (**4.2b**), nitrocyclopentane (**4.2c**), *N*-Cbz- and *N*-Boc-4-nitropiperidines (**4.2d** and **4.2g**, respectively), as well as 1,1-disubstituted 4-nitrocyclohexanes (**4.2e**, **4.2f**), nitrocycloheptane (**4.2h**) and the spirocyclic nitroalkanes (**4.2i**, **4.2j**). In all cases, good to excellent yields of adducts **4.3a-4.3x** were obtained with high levels of

Table 4. 2 Iridium-catalyzed allylation nitroalkanes **4.2a-4.2j** using allylic acetates **4.1a-4.1n** to form homoallylic nitroalkanes **4.3a-4.3x**.[a]

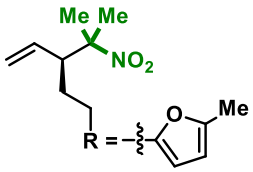




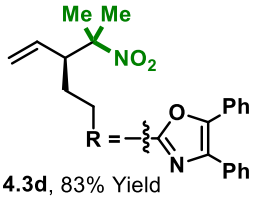
4.3a, 71% Yield
99% ee (80 °C)



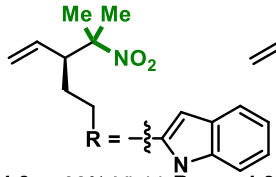
4.3b, 74% Yield
90% ee (60 °C)[b]



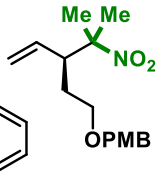
4.3c, 84% Yield
96% ee (60 °C)



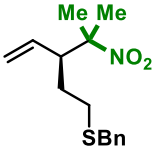
4.3d, 83% Yield
95% ee (60 °C)



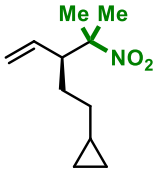
4.3e, 62% Yield
90% ee (70 °C)



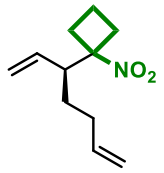
4.3f, 70% Yield
94% ee (60 °C)



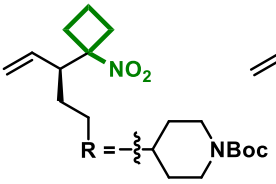
4.3g, 83% Yield
90% ee (60 °C)



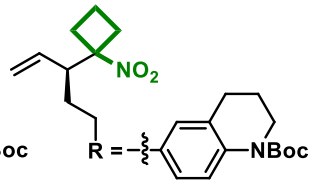
4.3h, 73% Yield
89% ee (80 °C)



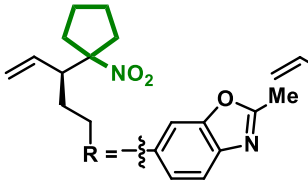
4.3i, 72% Yield
88% ee (60 °C)



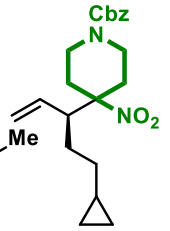
4.3j, 84% Yield
88% ee (60 °C)[b-d]



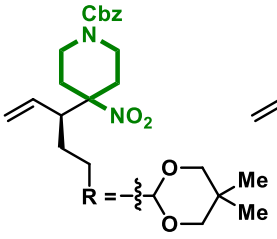
4.3k, 85% Yield
96% ee (80 °C)



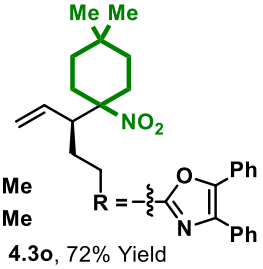
4.3l, 74% Yield
89% ee (80 °C)[b,c]



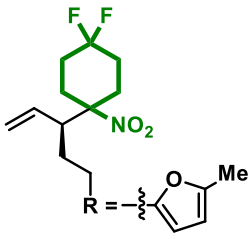
4.3m, 72% Yield
93% ee (60 °C)[b-d]



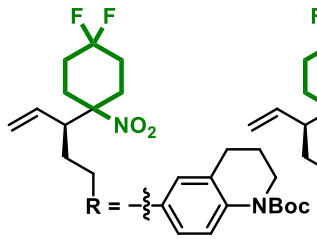
4.3n, 68% Yield
92% ee (60 °C)



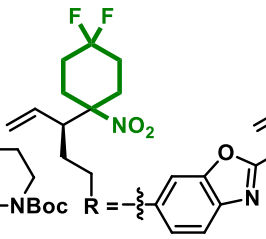
4.3o, 72% Yield
88% ee (60 °C)[b]



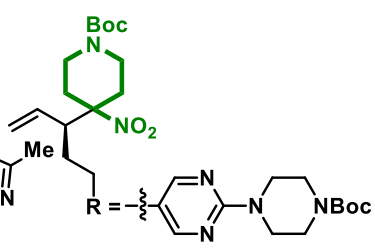
4.3p, 98% Yield
90% ee (60 °C)



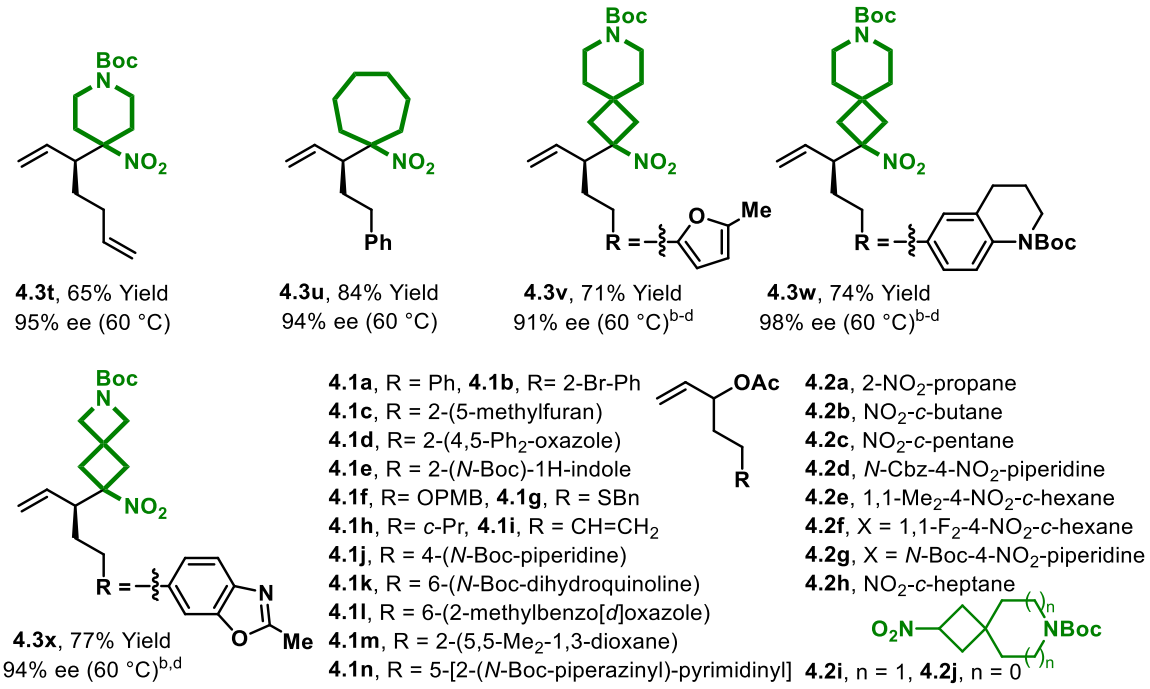
4.3q, 94% Yield
87% ee (60 °C)



4.3r, 91% Yield
88% ee (60 °C)



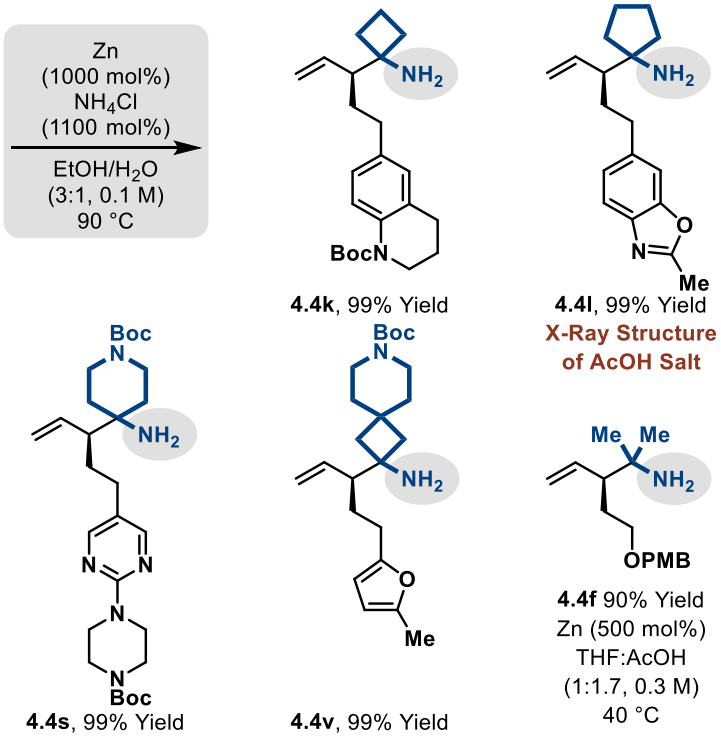
4.3s, 82% Yield
89% ee (80 °C)



[a]Yields are of material isolated by silica gel chromatography. Enantioselectivities were determined by chiral stationary phase HPLC analysis. [b]NMP was used as the reaction solvent. [c](*S*)-Ir-tol-BINAP, X= OMe. [d]Ir-catalyst (10 mol%).

enantiomeric enrichment (87-99% ee) and complete branched regioselectivity. Low conversion was observed using allylic acetates bearing α- or β-branched alkyl moieties. As revealed by the conversion of **4.3f**, **4.3k**, **4.3l**, **4.3s** and **4.3v** to amines **4.4f**, **4.4k**, **4.4l**, **4.4s** and **4.4v**, respectively, conversion of the allylation products to chiral β-stereogenic α-quaternary primary amines is readily achieved through zinc-mediated reduction (Table 4.3).

Table 4. 3 Zinc-mediated reduction of **4.3f**, **4.3k**, **4.3l**, **4.3s** and **4.3v** to form β-stereogenic α-quaternary primary amines **4.4f**, **4.4k**, **4.4l**, **4.4s** and **4.4v**.[a]



[a]Yields are of material isolated after filtration through celite.

4.3 Discussion

Density functional theory (DFT) calculations were carried out to investigate the origin of regio- and enantioselectivity of the Ir-catalyzed allylic alkylation.[15,16] As numerous diastereomeric π-allyliridium *C*,*O*-benzoate complexes may exist in equilibration prior to the allylation, the relative stabilities, reactivities and regioselectivities of all 16 possible stereoisomers of the π-crotyliridium(III) complex were computed (Figure 4.2). These include diastereomers **A**, **B**, **C**, and **D**, where the *C*,*O*-benzoate resides in different coordination sites of the octahedral Ir complex,[17] with four

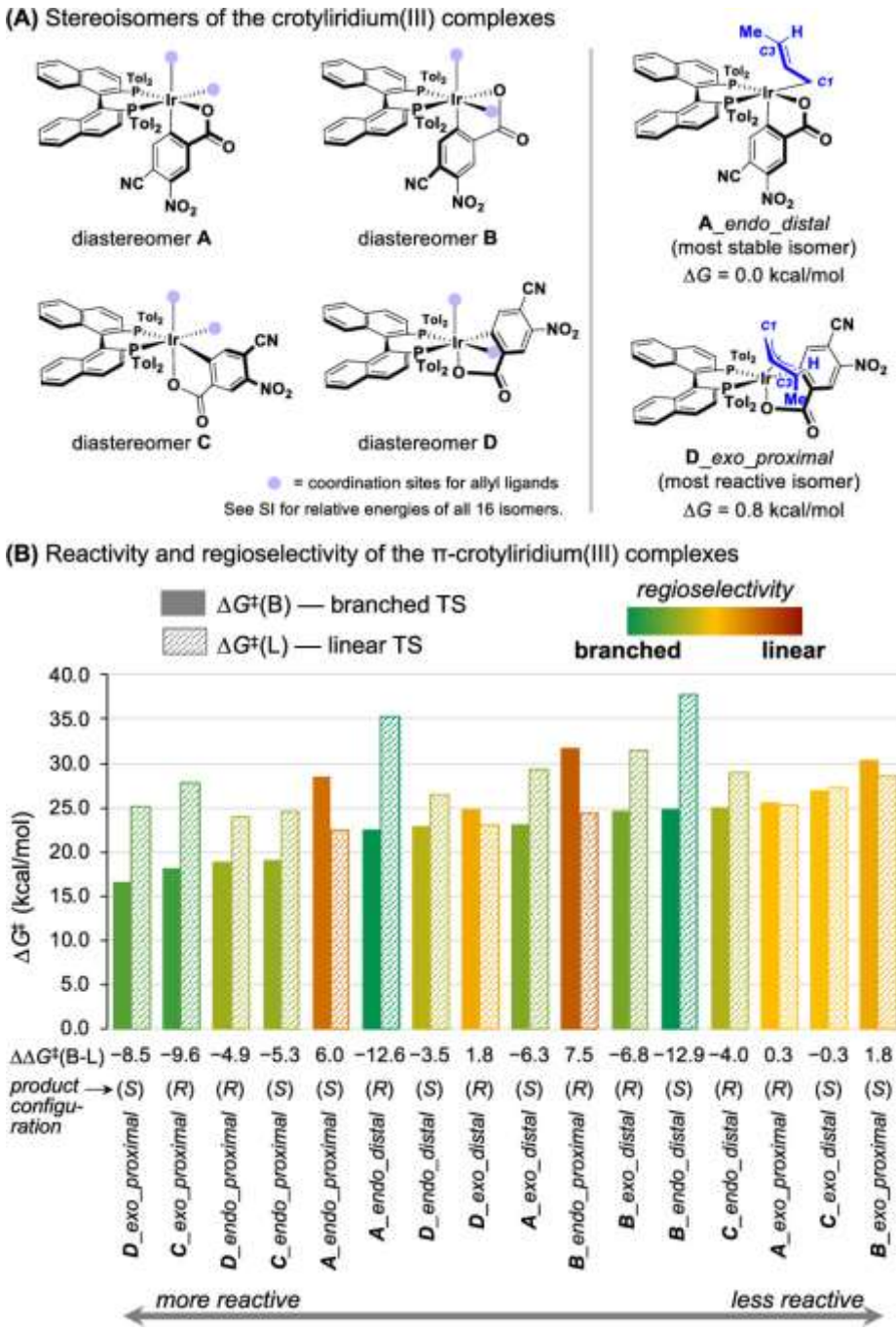


Figure 4. 2 Computed activation free energies of the addition of $^{-}CMe_2NO_2$ to different π-crotyliridium(III) isomers. All activation barriers ($\Delta G^{‡}$) are with respect to **A**_*endo_distal*.

different coordination modes of the π-crotyl ligand for each diastereomer. Here, the suffix *exo* or *endo* describes whether the allyl C2−H points away or towards the *C,O*-benzoate ligand, and *distal* or *proximal* describes if the C3−methyl points away or towards the *C,O*-benzoate. Computed activation barriers for the addition of $^{-}CMe_2NO_2$ anion to each π-crotyliridium(III) isomer leading to branched and linear products are shown in Figure 2B. The 16 π-crotyliridium(III) isomers exhibited very different reactivity and regioselectivity. The most reactive isomer, **D**_*exo_proximal*, strongly favors the branched product ($\Delta\Delta G^{\ddagger}$(B-L) = − 8.5 kcal/mol), while some less reactive isomers, such as **A**_*endo_proximal* and **B**_*endo_proximal*, prefer the linear product. These results suggest stereogenicity at iridium not only affects reactivity but also regioselectivity. To assess the origin of these effects, computational analysis on the electronic and structural properties of the diastereomeric π-crotyliridium(III) complexes were performed.

The computed transition state structures of the outer sphere addition of the nitronate nucleophile all involve long forming C–C distances (usually >2.4 Å in branch-selective TSs and >2.2 Å in linear-selective TSs. (Figure 4.3). These early transition states suggest that the addition is not sensitive to steric effects, and thus, the regioselectivity is mainly controlled by the electronic properties of the π-allyl complexes. The computed ground state properties of the π-crotyliridium(III) isomers and the distortion/interaction model analysis of the allylation transition states revealed enormously different electronic properties and their influences on the regioselectivity. In branch-selective isomers, such as **D**_*exo_proximal* (Figure 4.3A), the Ir−C3 distance is much longer than Ir−C1. This geometry leads to weaker d→π* backbonding at C3 and more positive charge on C3 compared to C1 (Figure 4.3A),[18] making the more substituted C3 terminus more electrophilic.[19] In addition, the transition state of nitronate addition to

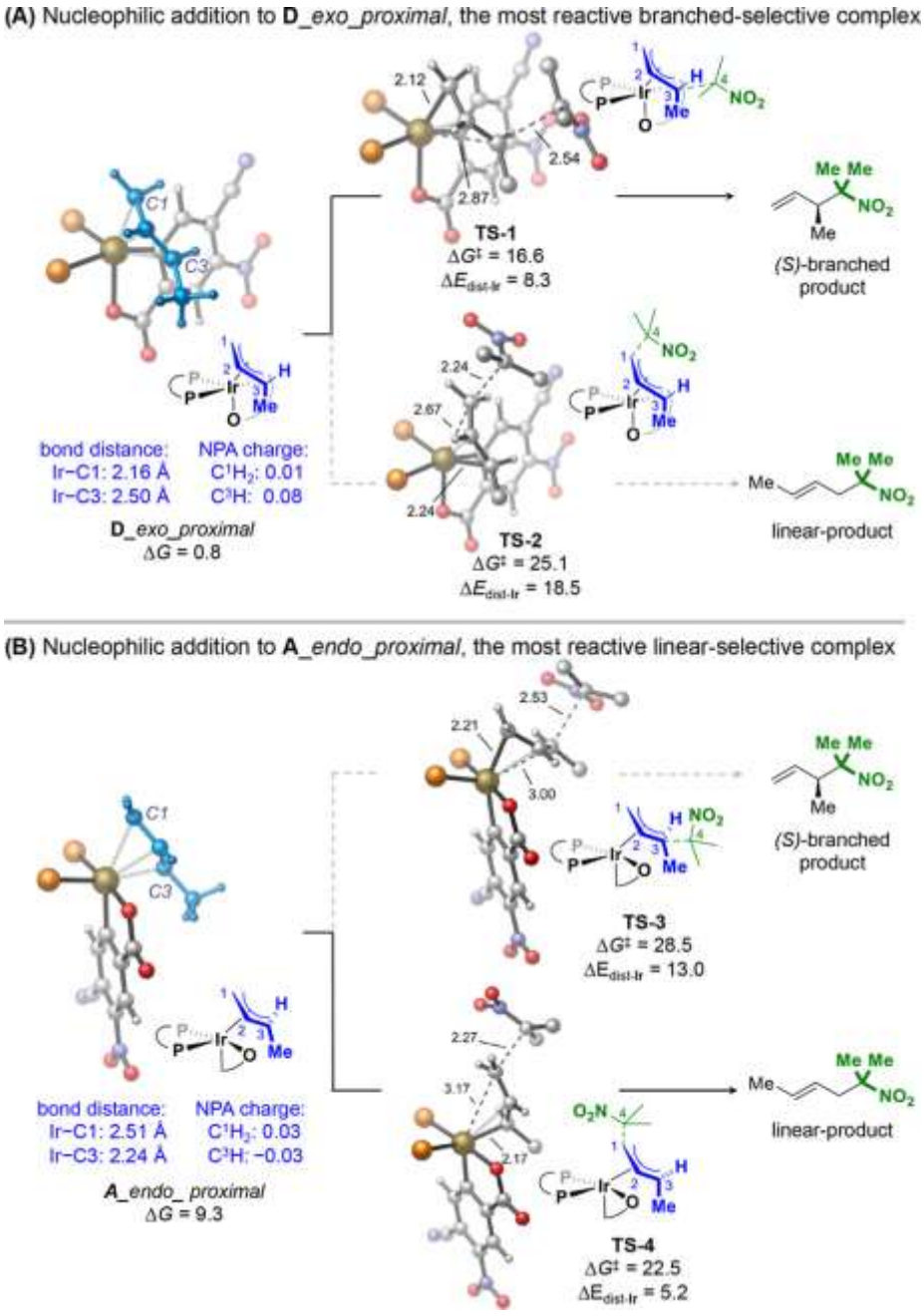


Figure 4. 3 Origin of regioselectivity. Bisphosphine ligand and some H-atoms are omitted for clarity. All Gibbs free energies are in kcal/mol with respect to **A**_*endo_distal*. $\Delta E_{\text{dist-Ir}}$: distortion energy of the π-crotyliridium complex to reach its geometry in the TS for nucleophilic addition.

C3 (**TS-1**) is promoted by the smaller distortion energy of the π-crotyliridium complex ($\Delta E_{\text{dist-Ir}}$) as the ground state Ir−C3 bond of **D**_*exo_proximal* is predistorted to a longer distance (2.50 Å) that is closer to that in **TS-1** (2.87 Å). In contrast, electronic effects strongly disfavor branch-selective addition with **A**_*endo_proximal* (Figure 4.2B), because the more substituted terminus C3 is less electrophilic than C1, as evidenced by the negative charge on C3. In addition, the Ir−C3 bond becomes shorter than Ir−C1, leading to greater distortion energy ($\Delta E_{\text{dist-Ir}}$) to elongate the Ir−C3 bond in the branch-selective transition state (**TS-3**).

The same analyses on all 16 isomers of the π-crotyliridium complex revealed good correlations between the computed regioselectivity for each isomer and the C3/C1 difference in NPA charge and Ir−C3 bond distance, i.e. diastereomers with more positive charge on C3 and a longer Ir−C3 bond give higher branch-selectivity (Figure 4.4).[20] These results are consistent with our findings that regioselectivity is controlled by electronic effects, including the allyl electrophilicity and the distortion of the π-allyl complex. The electronic properties of the diastereomeric π-crotyl complexes also are affected by the trans-effect[21] of the bisphosphine and the chelating *C,O*-benzoate ligands on the stereogenic Ir center. In diastereomers **A** and **B**, due to the stronger trans-effect of the aryl vs phosphine groups, addition occurs at sites *trans* to the aryl group, leading to branched products in "*distal*" isomers and linear products in "*proximal*" isomers. In disastereomers **C** and **D**, "*proximal*" isomers, in which C3 is *trans* to a phosphorus atom, give higher branched regioselectivity. This is consistent with the stronger trans-effects of phosphine vs carboxylate ligands. These branch-selective "*proximal*" isomers of **C** and **D** are also among the most reactive in all 16 stereoisomers (Figure 4.2B), as the π-acceptor ability of the phosphine ligand promotes addition at sites *trans* to phosphorus.[22]

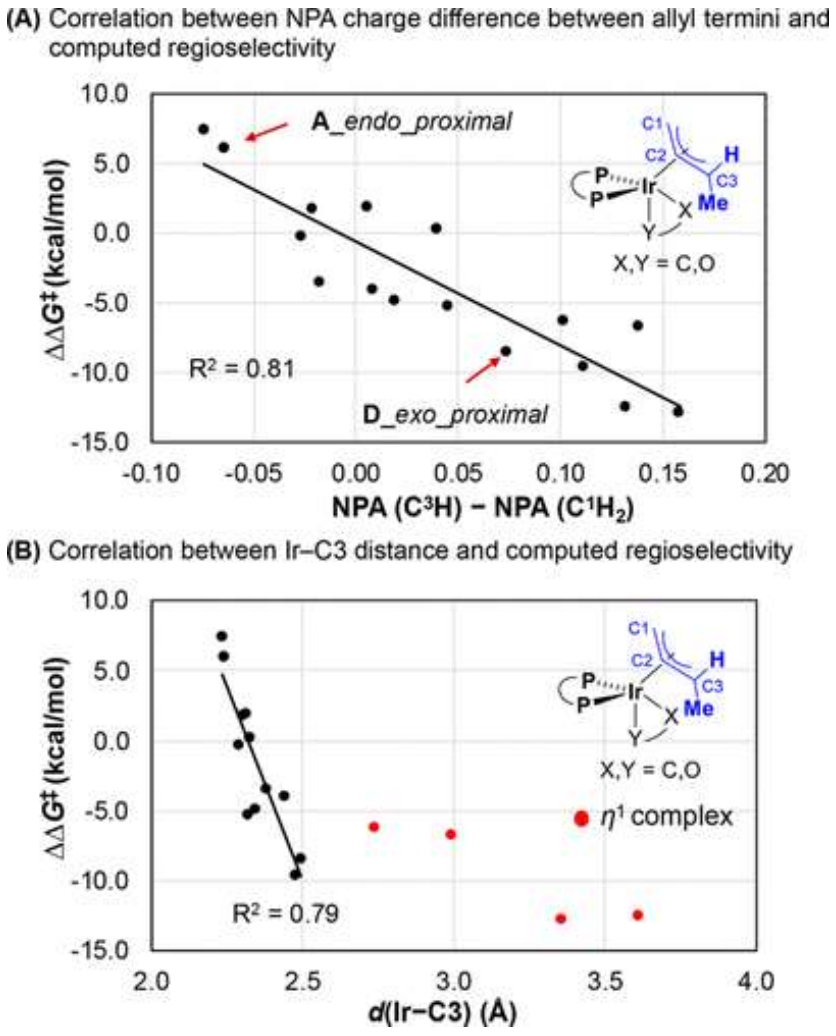


Figure 4. 4 Electronic effects on allylation regioselecitivy of different stereoisomers of the π-crotyliridium complex.

Stereogenicity at iridium is also a critical determinant of enantioselectivity. Due to trans-effects (*vide supra*), the "*proximal*" isomers of **C** and **D** are the most reactive among all 16 stereoisomers. The four most favorable pathways involve **D**_*exo_proximal* (**TS-1**) and **C**_*endo_proximal* (**TS-7**), which give (*S*)-product, and **D**_*endo_proximal* (**TS-6**) and

C_*exo_proximal* (**TS-5**), which give (*R*)-product. Optimized structures of these branch-selective transition states are shown in Figure 4.5. The two transition states leading to the (*R*)-product, **TS-5** and **TS-6**, are destabilized because the allyl C2−H moiety in **TS-5** and the C3−methyl in **TS-6** clash with a *P*-tolyl group of (*S*)-tol-BINAP. Thus, **TS-5** and **TS-6** are 1.6 and 1.8 kcal/mol less stable than the lowest-energy transition state, **TS-1** that gives the (*S*)-product. In **TS-1**, the steric repulsions between tol-BINAP and the allyl group are absent. Our calculations are consistent with the experimentally observed enantioselectivity for the (*S*)-product.

4.4 CONCLUSION

In summary, we report iridium-catalyzed allylic alkylations of nitronate nucleophiles. This method, which employs an air and water stable π-allyliridium *C,O*-benzoate catalyst modified by tol-BINAP, enables highly regio- and enantioselective substitution of racemic branched alkyl-substituted allylic acetates by α,α-disubstituted nitronates and, hence, entry to β-stereogenic α-quaternary primary amines. As revealed by DFT calculations, early transition states that render the reaction less sensitive to steric effects and distinct trans-effects of diastereomeric chiral-at-iridium π-allyl complexes facilitate formation of congested tertiary-quaternary C-C bonds. Related asymmetric allylic alkylations of non-stabilized carbanions are currently underway.[23]

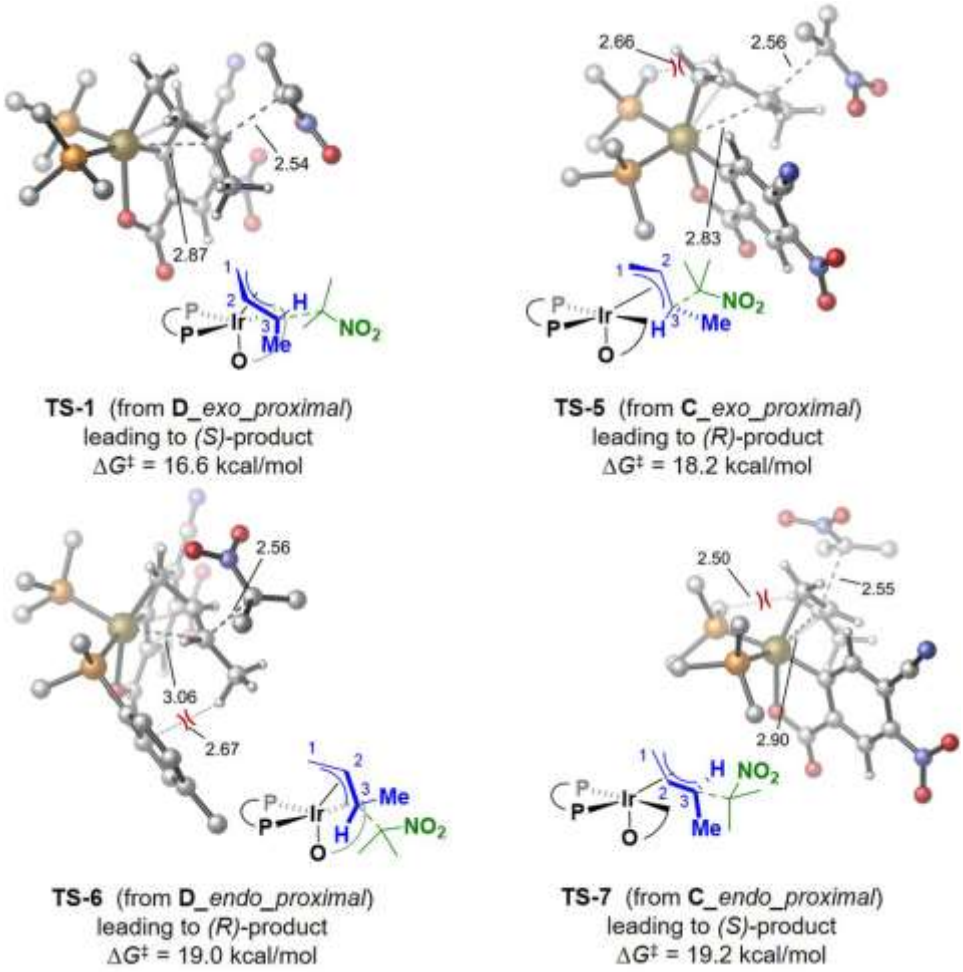


Figure 4. 5 Optimized structures for additions of $^{-}CMe_2NO_2$ anion giving branched product. Gibbs free energies are with respect to **A**_*endo_distal*.

4.5 EXPERIMENTAL DETAILS

4.5.1 General Information

All reactions were carried out under inert gas atmosphere (nitrogen or argon) unless otherwise indicated. Re-sealable pressure tubes (13x100 mm) were purchased from Fischer Scientific (catalog number 14-959-35C) and were flame dried followed by cooling in a desiccator or under a stream of inert gas prior to use. All commercial reagents and anhydrous solvents were used as received from vendors (Fischer Scientific, Sigma Aldrich, TCI America, Combi Blocks and Enamine) without further isolation. The used Iridium catalyst (*S*)-Ir-tol-BINAP was prepared according to literature known procedures.[24] Cs_2CO_3 was used as received from Rockwell Lithium. Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates (Dynamic Absorbents F). Visualization was accomplished with UV light followed by dipping in CAM, p- Anisaldehyde (PAA), or $KMnO_4$ stain solution followed by heating.

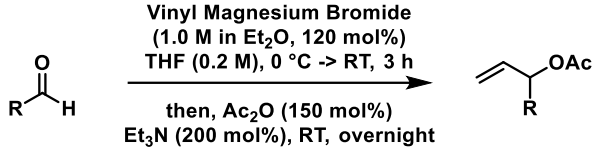
4.5.2 Spectroscopy, Spectrometry and Data Collection

Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer using a diamond ATR unit. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M+H, M+Na), or a suitable fragment ion. Nuclear magnetic resonance (1H, 13C, 19F NMR) spectra were recorded with a Bruker BioSpin GmbG, Varian Gemini (400 MHz) or Varian INOVA (500 MHz) spectrometer equipped with a Bruker cryoprobe. The chemical shifts are given as parts per million (ppm) and were referenced to the residual solvent signal (Acetone: $\delta H = 2.05$ ppm, $\delta C = 206.3$ ppm, $CDCl_3$: $\delta H = 7.26$ ppm, $\delta C = 77.2$ ppm). Specific optical rotations were recorded on an Atago AP-300 automatic polarimeter at the sodium line (589 nm) in $CHCl_3$. Solution concentrations are given in the units of 10^{-2} g mL^{-1}.

4.5.3 Synthesis of Allylic Acetates 4.1a-4.1n

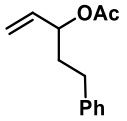
General procedure for the synthesis of allylic acetates.

The allylic acetates **4.1a-4.1k** were prepared by the Grignard reaction and acetylation as shown below. The allylic acetates were identical with respect to the reported materials (*vide infra*).



To a round-bottomed flask charged with aldehyde (100 mol%) under argon atmosphere was added THF (0.2 M). The reaction flask was placed in an ice bath. After 10 mins, vinyl magnesium bromide (120 mol%, 1.0 M in Et_2O) was added slowly via syringe and the mixture was allowed to stir at room temperature for 3 h, at which point acetic anhydride (150 mol%) and triethylamine (200 mol%) were added and the reaction was stirred vigorously overnight. Water was added and the mixture was transferred to a separatory funnel. The organic layer was extracted with diethyl ether and the combined organic layers were washed with HCl (1 N), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting oily residue was subjected to flash column chromatography to give Allylic acetate over 2 steps.

5-Phenylpent-1-en-3-yl acetate (4.1a)

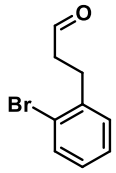


Procedures

The title compound was prepared by the general procedure and it is identical with respect to the reported materials.[25]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (dt, J = 38.0, 7.6 Hz, 5H), 5.81 (ddd, J = 17.6, 10.9, 6.9 Hz, 1H), 5.31 – 5.16 (m, 3H), 2.65 (dt, J = 9.7, 5.0 Hz, 3H), 2.06 (s, 3H), 1.95 (dtt, J = 20.9, 14.5, 7.1 Hz, 3H) ppm.

3-(2-Bromophenyl)propanal (4.1b-CHO)



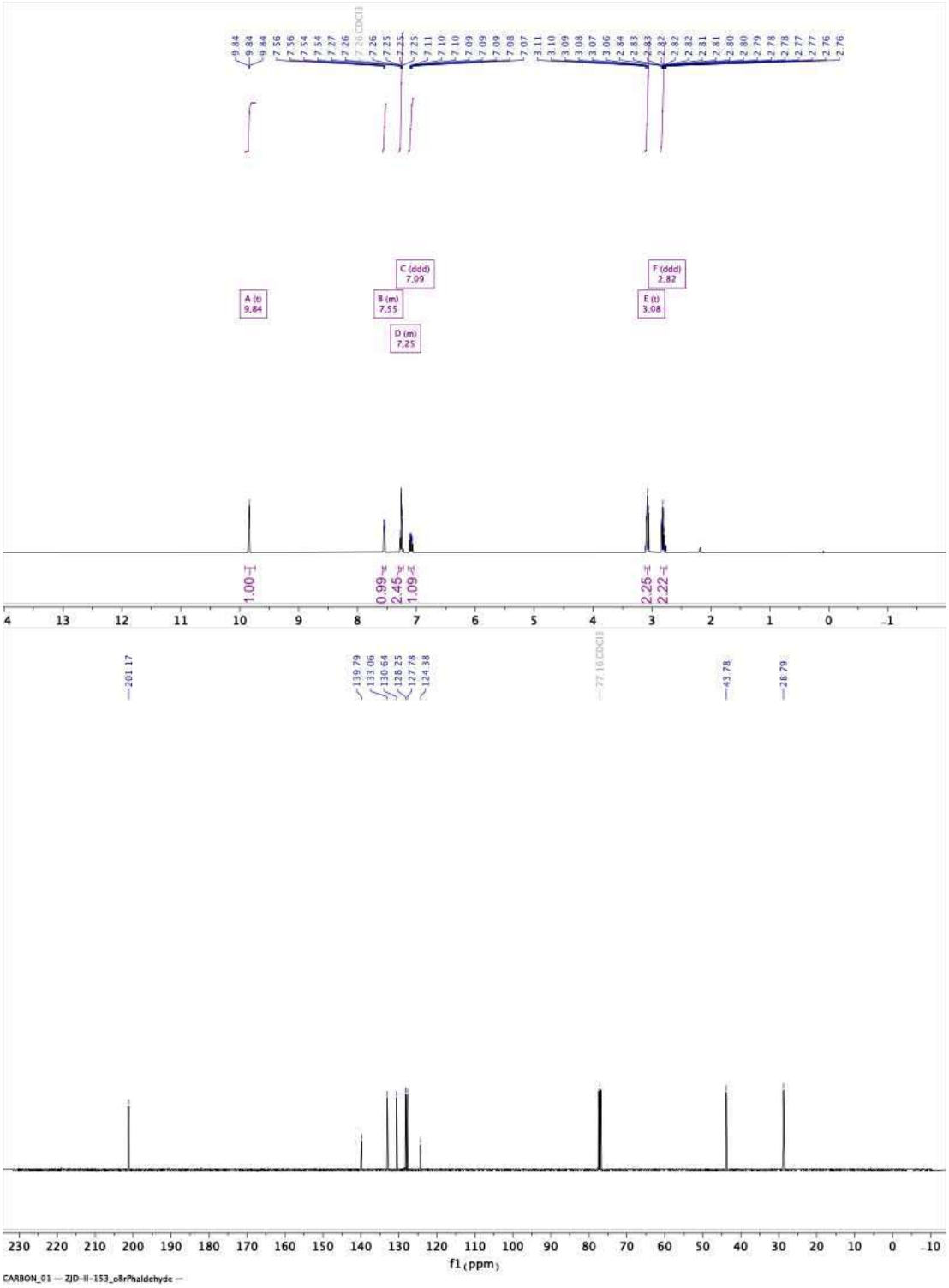
Procedures

Dess-Martin periodinane (10.9 g, 25.6 mmol, 110 mol%), sodium bicarbonate (7.8 g, 93 mmol, 400 mol%), and dichloromethane (233 mL, 0.1 M) were added to a round-bottom flask equipped with a magnetic stir bar followed by 3-(2-bromophenyl)propan-1-ol (5 g, 23.3 mmol, 100 mol%). The reaction mixture was allowed to stir overnight, at which point the reaction mixture was filtered through celite with the aid of ethyl acetate. The filtrate was transferred to a separatory funnel and the organic layer was separated. The aqueous layer was washed with ethyl acetate (2 x 100 mL) and the combined organic layers were washed with water (2 x 100 mL). The organic layer was dried over sodium sulfate, and the solvent was removed *in vacuo*. The title compound was isolated in 55% yield (2.7 g, 12.9 mmol) as a yellow oil after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate 20 : 1).[26]

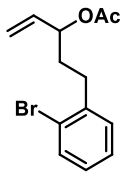
TLC (SiO_2) R_f = 0.54 (hexane : ethyl acetate = 4:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (t, J = 1.2 Hz, 1H), 7.58 – 7.51 (m, 1H), 7.29 – 7.22 (m, 2H), 7.09 (ddd, J = 8.0, 5.5, 3.7 Hz, 1H), 3.08 (t, J = 7.6 Hz, 2H), 2.82 (ddd, J = 8.5, 7.1, 1.3 Hz, 2H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 201.2, 139.8, 133.1, 130.6, 128.3, 127.8, 124.4, 43.8, 28.8 ppm.


A (t) 9.84
B (m) 7.55
C (ddd) 7.09
D (m) 7.25
E (t) 3.08
F (ddd) 2.82
1.00
0.99
2.45
1.09
2.25
2.22
201.17
139.79
133.06
130.64
128.25
127.78
124.38
77.16 CDCl3
43.78
28.79
f1 (ppm)
CARBON_01 — ZJD-II-153_oBrPhaldehyde —

5-(2-Bromophenyl)pent-1-en-3-yl acetate (4.1b)



Procedures

The title compound was prepared by the general procedure and was obtained as a yellow oil (1.7 g, 6.1 mmol) in 27% yield over 2 steps.

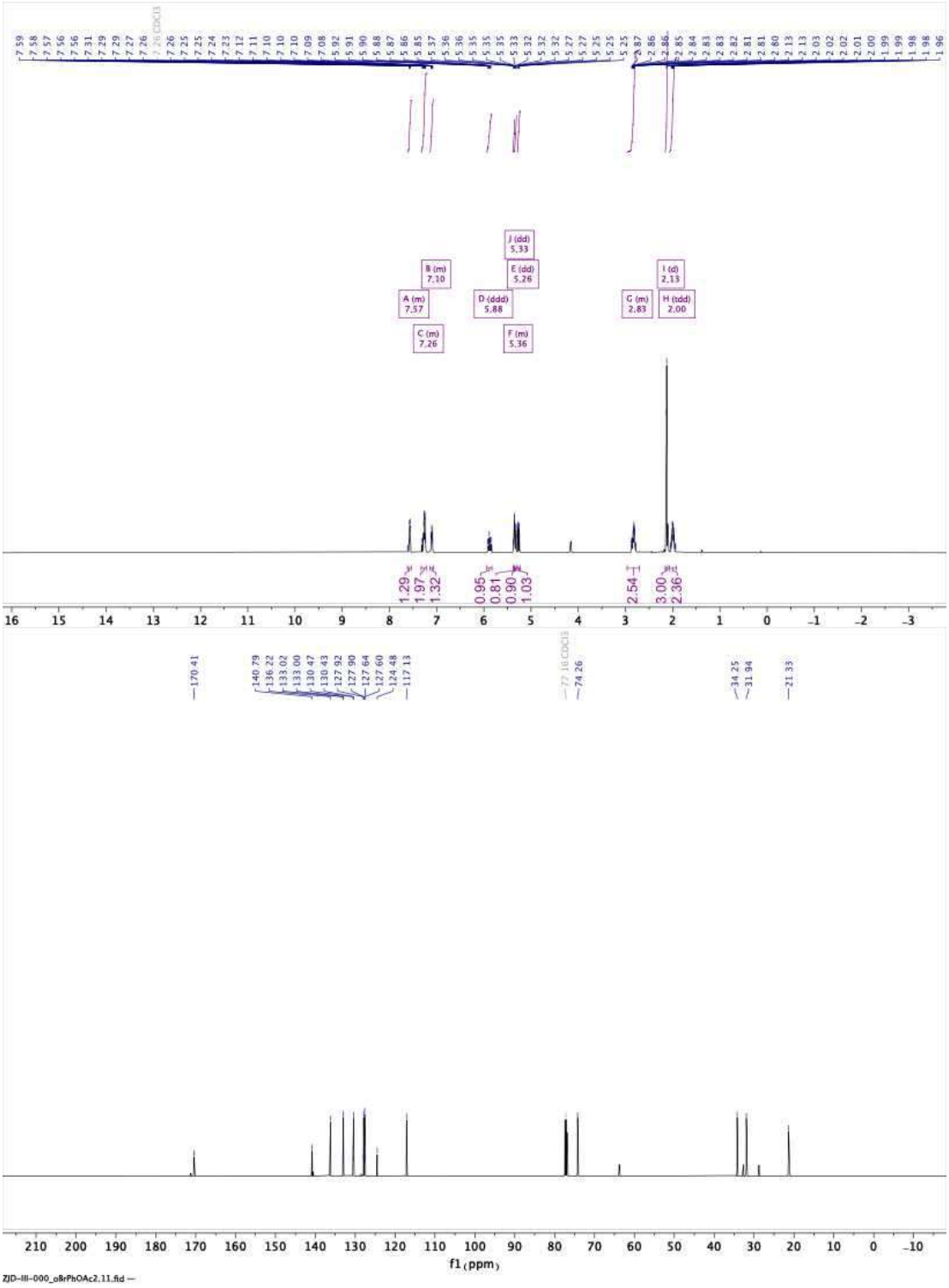
TLC (SiO_2) R_f = 0.63 (hexane : ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 – 7.54 (m, 1H), 7.33 – 7.21 (m, 2H), 7.14 – 7.07 (m, 1H), 5.88 (ddd, J = 17.1, 10.5, 6.3 Hz, 1H), 5.38 – 5.35 (m, 1H), 5.33 (dd, J = 14.5, 1.5 Hz, 1H), 5.26 (dd, J = 10.6, 1.3 Hz, 1H), 2.96 – 2.71 (m, 3H), 2.13 (d, J = 1.2 Hz, 3H), 2.00 (tdd, J = 12.6, 7.2, 4.9 Hz, 2H) ppm.

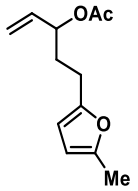
^{13}C NMR (101 MHz, $CDCl_3$): δ 170.4, 140.8, 136.2, 133.0, 130.4, 127.9, 127.6, 124.5, 117.1, 74.3, 34.3, 32.0, 21.3 ppm.

HRMS (ESI) m/z: [(M+Na)+] calcd for $C_{13}H_{15}BrO_2$ 305.0148, found 305.0149.

FTIR (Neat): 2936, 1735, 1567, 1471, 1439, 1370, 1232, 1103, 1020, 989, 923, 871, 749, 724, 658 cm^{-1}.


J (dd) 5.33
B (m) 7.10
E (dd) 5.26
I (d) 2.13
A (m) 7.57
D (ddd) 5.88
G (m) 2.83
H (ddd) 2.00
C (m) 7.26
F (m) 5.36
1.29
1.97
1.32
0.95
0.81
0.90
1.03
2.54
3.00
2.36
f1 (ppm)
ZJD-III-000_oBrPhOAc2.11.fid

Methylfuran-2-yl)pent-1-en-3-yl acetate (4.1c)



Procedures

The title compound was prepared by the general procedure and was obtained as light-yellow oil (2.8 g, 13.8 mmol) in 69% yield over 2 steps.

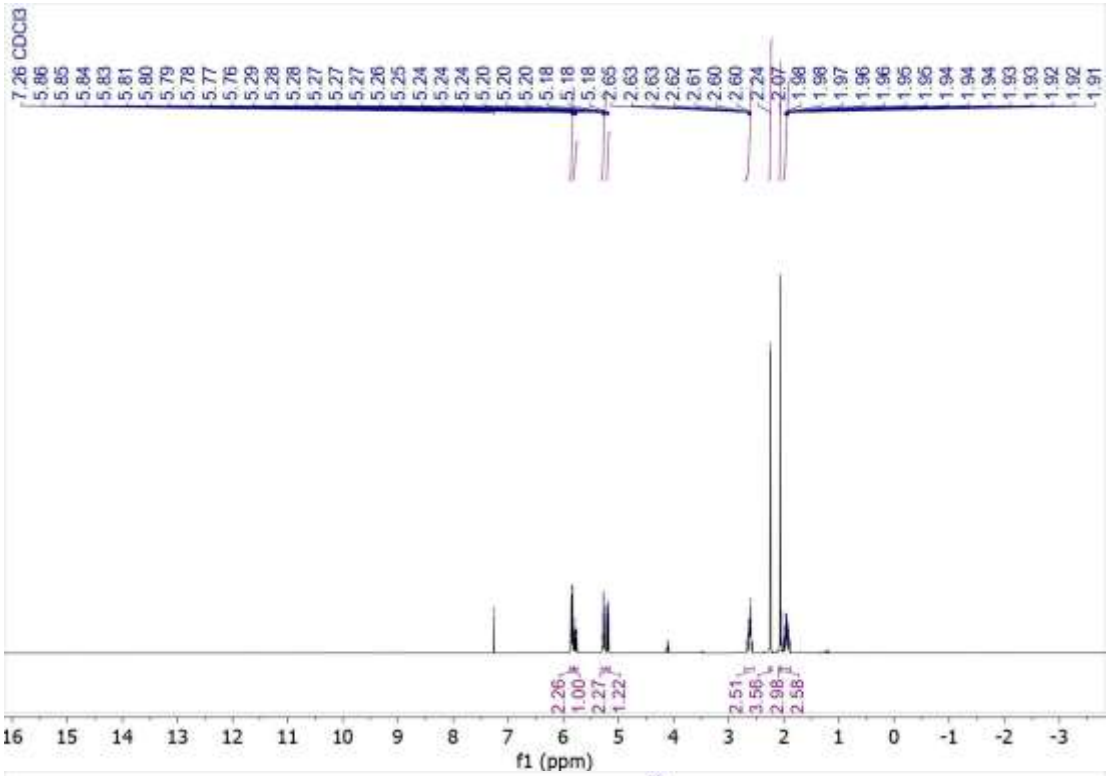
TLC (SiO_2) R_f = 0.67 (hexane: ethyl acetate = 4:1).

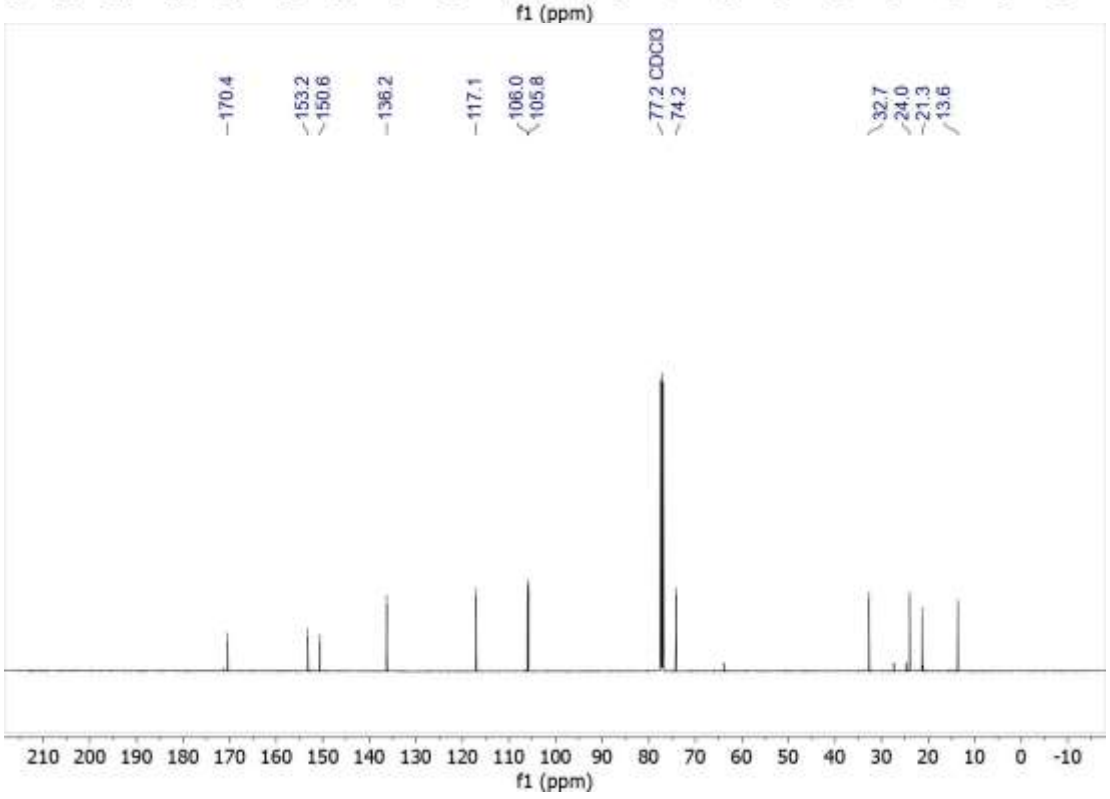
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 – 5.81 (m, 2H), 5.82 – 5.75 (m, 1H), 5.31 – 5.22 (m, 2H), 5.19 (dt, J = 10.6, 1.2 Hz, 1H), 2.71 – 2.55 (m, 3H), 2.24 (s, 4H), 2.07 (s, 3H), 2.01 – 1.88 (m, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 153.1, 150.5, 136.1, 117.0, 105.9, 105.7, 74.0, 32.6, 23.8, 21.2, 13.5 ppm.

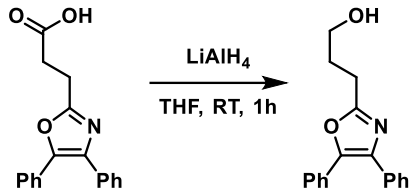
HRMS (ESI): Calculated for $C_{12}H_{16}O_3$ $[M+Na]^+$ = 231.0992, Found 231.1000.

FTIR (neat): 2925, 2860, 1736, 15707, 1437, 1371, 1235, 1109, 1020, 909, 781, 730, 669 cm^{-1}.


7.26 CDCl3
5.86
5.85
5.84
5.83
5.81
5.80
5.79
5.78
5.77
5.76
5.29
5.28
5.28
5.27
5.27
5.27
5.26
5.25
5.24
5.24
5.24
5.20
5.20
5.20
5.18
5.18
2.65
2.63
2.63
2.62
2.61
2.60
2.60
2.24
2.07
1.98
1.98
1.97
1.96
1.96
1.95
1.95
1.94
1.94
1.94
1.93
1.93
1.92
1.92
1.91
2.26
1.00
2.27
1.22
2.51
3.56
2.98
2.58
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)


170.4
153.2
150.6
136.2
117.1
106.0
105.8
77.2 CDCl3
74.2
32.7
24.0
21.3
13.6
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-(4,5-Diphenyloxazol-2-yl)propan-1-ol (4.1d-OH)



Procedures

To a round-bottom flask charged with $LiAlH_4$ (655 mg, 17.3 mmol, 150 mol%) under an argon atmosphere was added THF (20 mL, 0.5 M). The reaction vessel was placed in an ice bath and a THF (3 mL, 6 M) solution of oxaprozin (3.37 g, 11.5 mmol, 100 mol%) was added dropwise. The reaction vessel was removed from the ice bath and allowed to stir for 1 hour reaching ambient temperature. To the reaction mixture was added ice-water (25 mL). The reaction mixture was transferred to a separatory funnel, and the aqueous layer was extracted with dichloromethane (3 x 25 mL). The combined organic layers were washed with brine (2 x 25 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The crude title compound was obtained in 61% yield (1.9669 g, 7.0 mmol) as a light orange solid and used directly without isolation.

TLC (SiO_2) R_f = 0.22 (hexane : ethyl acetate = 1:1).

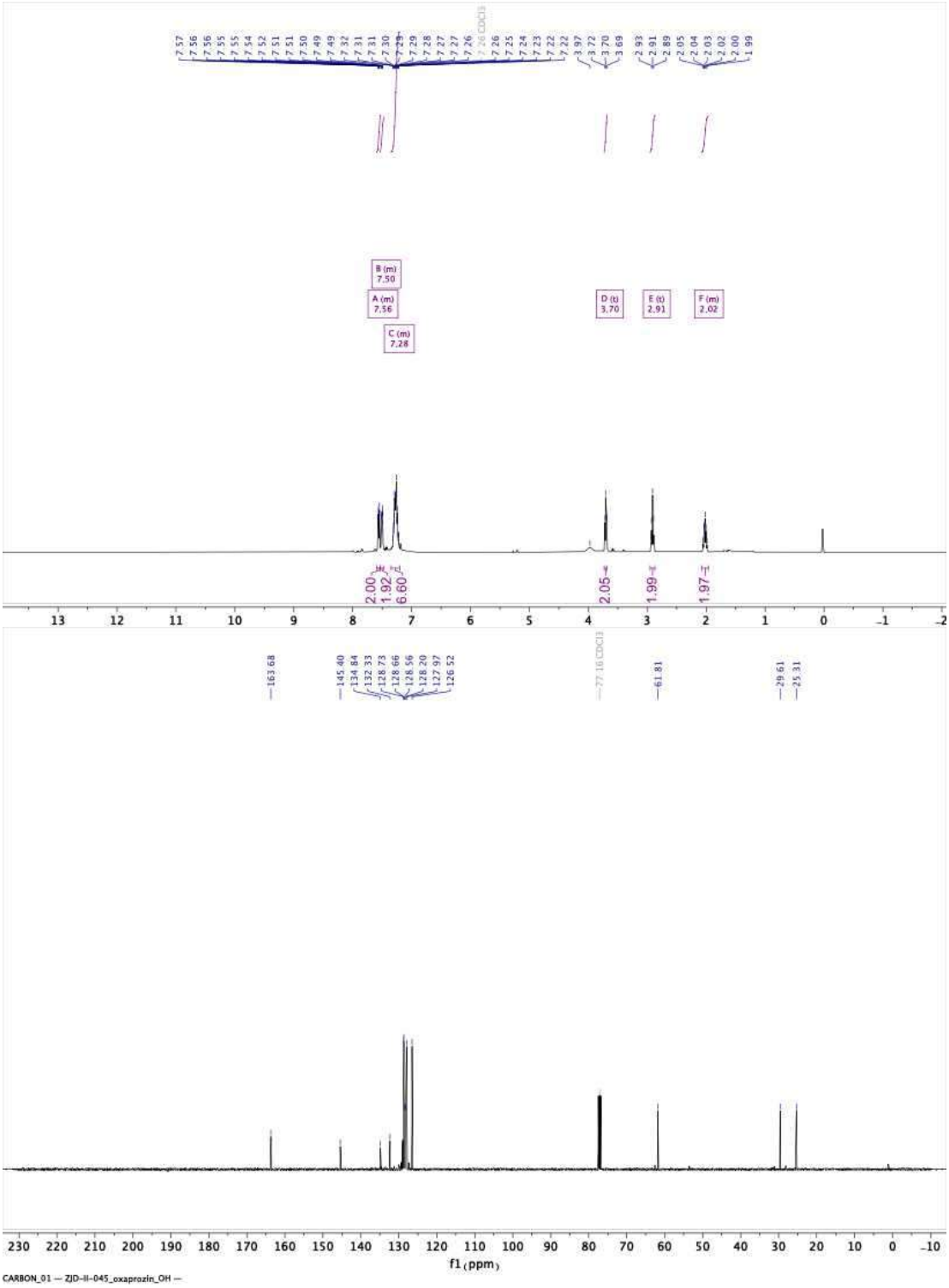
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 – 7.53 (m, 2H), 7.53 – 7.48 (m, 2H), 7.37 – 7.15 (m, 6H), 3.97 (s, 1H), 3.70 (t, *J* = 5.9 Hz, 2H), 2.91 (t, *J* = 7.1 Hz, 2H), 2.07 – 1.96 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 163.7, 145.4, 134.8, 132.3, 129.0, 128.7, 128.7, 128.6, 128.20, 127.97, 126.52, 61.81, 29.61, 25.3.

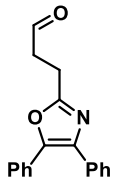
HRMS (ESI) m/z: [(M+H)+] calcd for $C_{18}H_{15}NO_2$ 280.1332, found 280.1338.

FTIR (Neat): 3321, 2872, 1680, 1569, 1444, 1324, 1177, 1060, 989, 933, 757, 675 cm^{-1}.

Melting Point 86-88°C


B (m) 7.50
A (m) 7.56
C (m) 7.28
D (t) 3.70
E (t) 2.91
F (m) 2.02
2.00
1.92
6.60
2.05
1.99
1.97
f1 (ppm)
CARBON_01 — ZJD-II-045_oxaprozin_OH —

3-(4,5-Diphenyloxazol-2-yl)propanal (4.1d-CHO)



Procedures

Dess-Martin periodinane (2.93 mg, 6.9 mmol, 110 mol%) sodium bicarbonate (2.11 g, 25.1 mmol, 400 mol%), and dichloromethane (63 mL, 0.1 M) were added to a round-bottom flask equipped with a magnetic stir bar followed by the reduced Oxaprozin **4.1d-OH** (1.76 g, 6.3 mmol, 100 mol%). The reaction mixture was allowed to stir overnight, at which point the reaction mixture was filtered through celite with the aid of ethyl acetate. The filtrate was transferred to a separatory funnel and the organic layer was separated. The aqueous layer was washed with ethyl acetate (2 x 100 mL) and the combined organic layers were washed with water (2 x 100 mL). The organic layer was dried over sodium sulfate, and the solvent was removed in vacuo. The title compound was isolated in 69% yield (1.2 g, 4.3 mmol) as a yellow oil after isolation by flash column chromatography (SiO2, hexane : ethyl acetate 5 : 1).

TLC (SiO_2) R_f = 0.44 (hexane : ethyl acetate = 4:1).

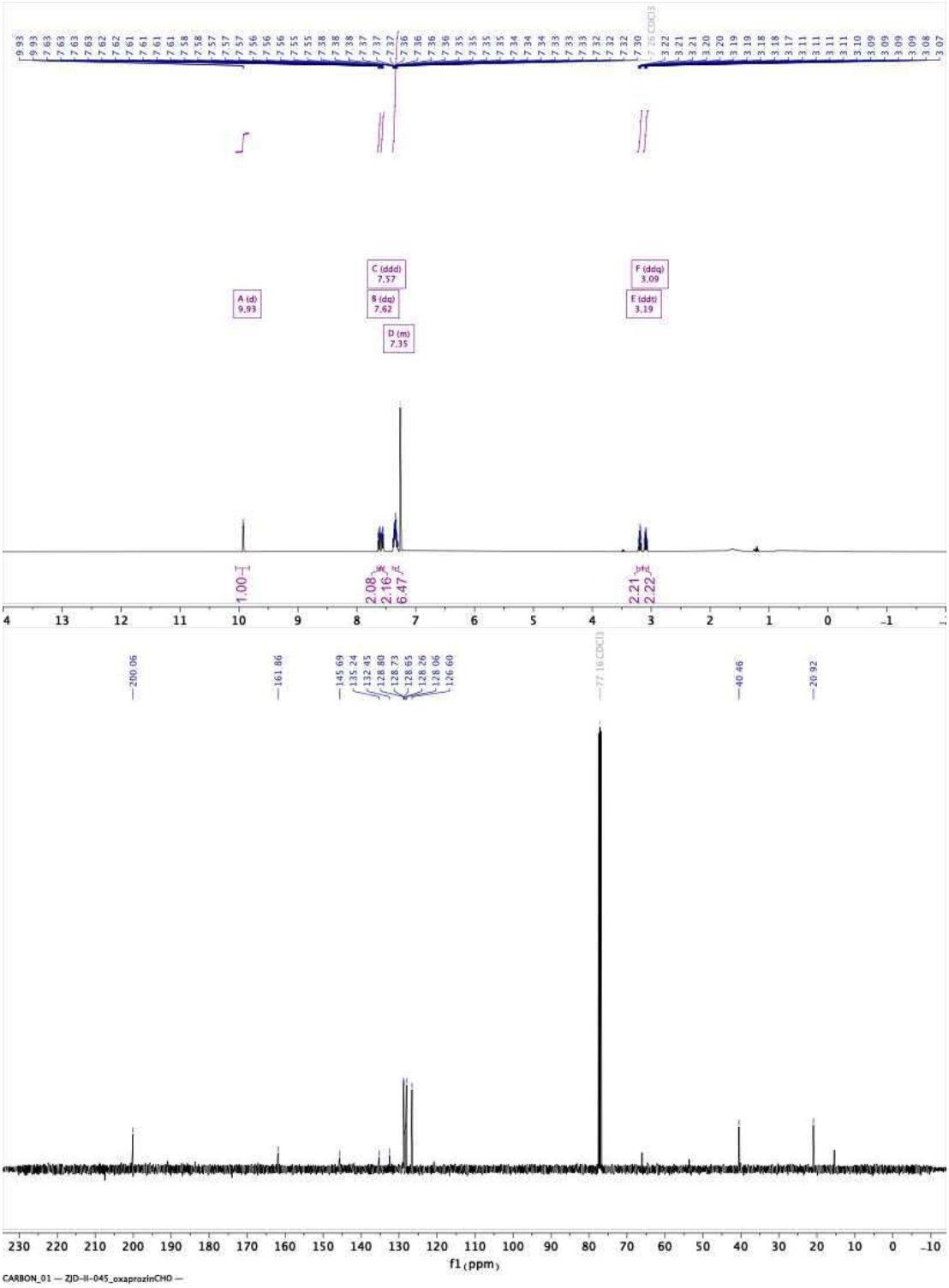
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.93 (q, *J* = 0.9 Hz, 1H), 7.62 (dq, *J* = 8.0, 1.1 Hz, 2H), 7.57 (ddd, *J* = 7.9, 2.0, 1.0 Hz, 2H), 7.41 – 7.30 (m, 6H), 3.20 (ddt, *J* = 8.1, 7.0, 1.2 Hz, 2H), 3.10 (ddq, *J* = 7.7, 6.7, 1.2 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 200.1, 128.8, 128.7, 128.7, 128.3, 128.1, 126.6, 40.5, 20.9.

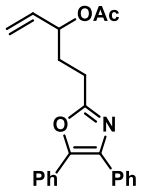
HRMS (ESI) m/z: [(M+H)+] calcd for $C_{18}H_{15}NO_2$ 278.1176, found 278.1182.

FTIR (Neat): 2909, 2827, 2731, 1981, 1720, 1605, 1580, 1570, 1503, 1434, 1408, 1388, 1360, 1313, 1217, 1172, 1145, 1057, 1025, 993, 978, 967, 921, 860, 779, 766, 711, 696, 673 cm^{-1}.

Melting Point 97 – 99 °C


A (d)
9.93
B (dq)
7.62
C (ddd)
7.57
D (m)
7.35
E (ddt)
3.19
F (ddq)
3.09
1.00
2.08
2.16
6.47
2.21
2.22
f1 (ppm)
CARBON_01 — ZJD-II-045_oxaprozinCHO —

5-(4,5-Diphenyloxazol-2-yl)pent-1-en-3-yl acetate (4.1d)



Procedures

The title compound was prepared by the general procedure and was obtained as a yellow oil (674 mg, 1.9 mmol) in 46% yield over 2 steps.

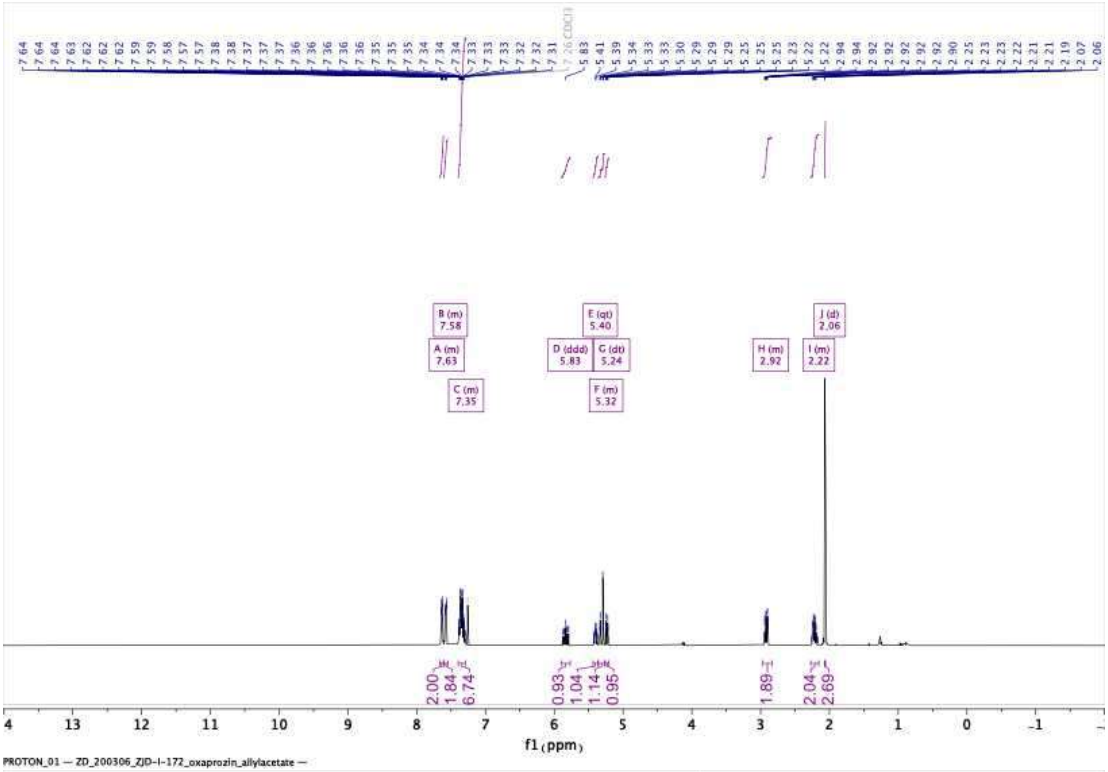
TLC (SiO_2) R_f = 0.73 (hexane : ethyl acetate = 1:1).

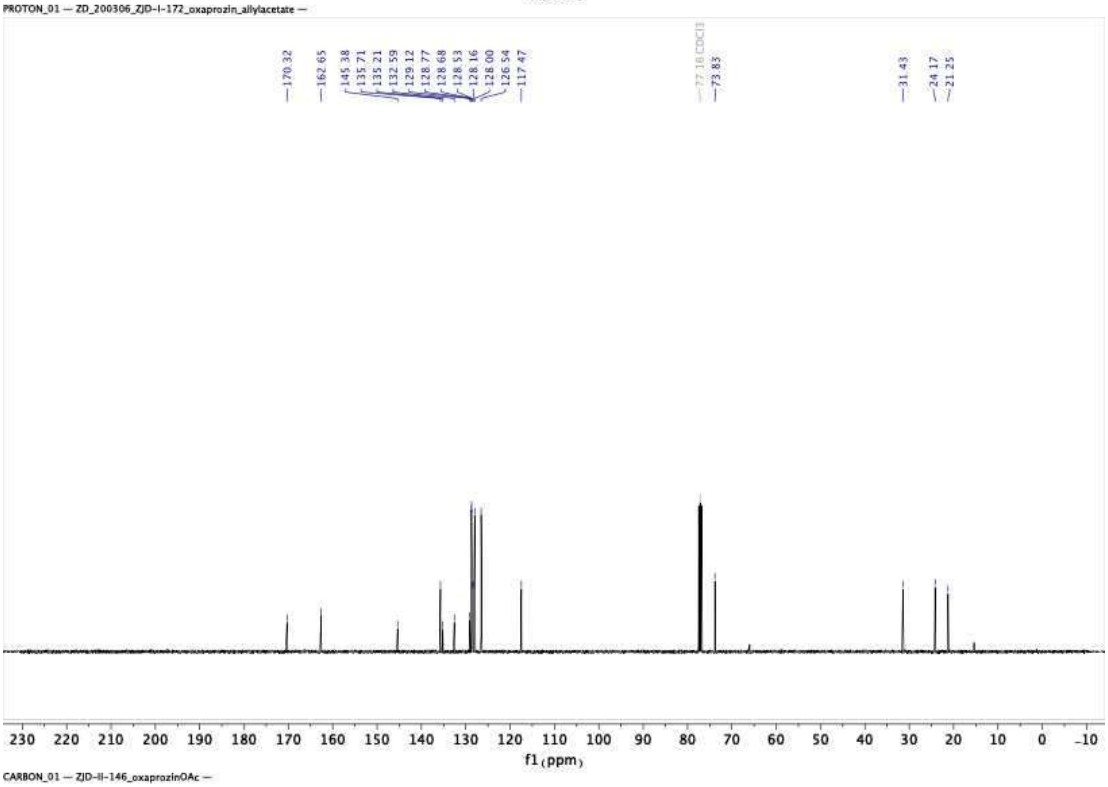
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.61 (m, 2H), 7.60 – 7.55 (m, 2H), 7.40 – 7.29 (m, 7H), 5.83 (ddd, J = 17.0, 10.5, 6.2 Hz, 1H), 5.40 (qt, J = 6.3, 1.3 Hz, 1H), 5.36 – 5.26 (m, 1H), 5.24 (dt, J = 10.6, 1.2 Hz, 1H), 2.97 – 2.84 (m, 2H), 2.27 – 2.15 (m, 2H), 2.06 (d, J = 0.5 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 162.7, 145.4, 135.7, 135.2, 132.6, 129.1, 128.8, 128.7, 128.5, 128.2, 128.0, 126.5, 117.5, 73.8, 31.4, 24.2, 21.3 ppm.

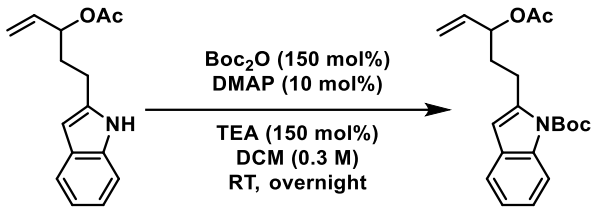
HRMS (ESI) m/z: [(M+H)+] calcd for $C_{22}H_{21}NO_3$ 348.1594, found 348.1603.

FTIR (Neat): 2930, 2353, 1738, 1699, 1683, 1651, 1605, 1570, 1558, 1538, 1503, 1486, 1444, 1370, 1232, 1103, 1059, 1024, 962, 928, 763, 693, 674 cm^{-1}.


B (m) 7.58
A (m) 7.63
C (m) 7.35
E (qt) 5.40
D (dddd) 5.83
G (dt) 5.24
F (m) 5.32
H (m) 2.92
J (d) 2.06
I (m) 2.22
2.00
1.84
6.74
0.93
1.04
1.14
0.95
1.89
2.04
2.69
f1 (ppm)
PROTON_01 — ZD_200306_ZJD-I-172_oxaprozin_allylacetate —


170.32
162.65
145.38
135.71
135.21
132.59
129.12
128.77
128.68
128.53
128.16
128.00
126.54
117.47
77.16 CDCl3
73.83
31.43
24.17
21.25
f1 (ppm)
CARBON_01 — ZJD-II-146_oxaprozinOAc —

***tert*-Butyl 2-(3-acetoxypent-4-en-1-yl)-1*H*-indole-1-carboxylate (4.1e)**



Procedures

To a round-bottomed flask charged with the corresponding allyl acetate (225 mg, 0.92 mmol, 100 mol%)[4] was added dichloromethane (3 mL, 0.3 M). Boc_2O (0.32 mg, 1.38 mmol, 150 mol%), DMAP (12 mg, 0.1 mmol, 10 mol%) and triethylamine (0.19 mL, 1.38 mmol, 150 mol%) were added and the reaction was stirred at room temperature overnight. After water was added, the mixture was transferred to a separatory funnel. The organic layer was extracted with diethyl ether and the combined organic layers were washed with 1 N HCl, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The title compound was obtained in 95% yield (302 mg, 0.88 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate = 30:1).

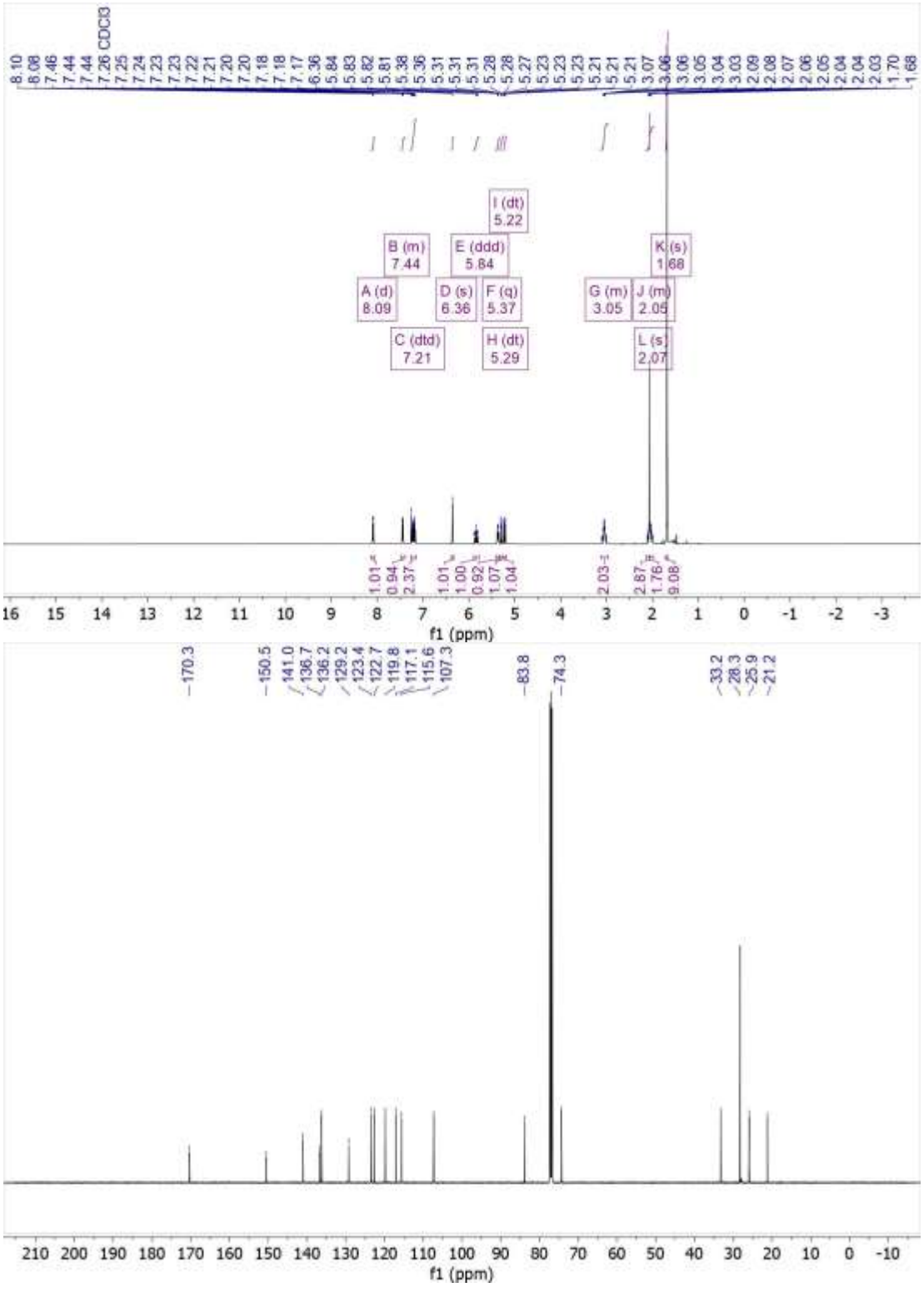
TLC (SiO_2) R_f = 0.54 (hexane: ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, J = 8.2 Hz, 1H), 7.48 – 7.39 (m, 1H), 7.21 (dtd, J = 23.0, 7.3, 1.2 Hz, 2H), 6.36 (s, 1H), 5.84 (ddd, J = 17.1, 10.5, 6.4 Hz, 1H), 5.37 (q, J = 6.5 Hz, 1H), 5.29 (dt, J = 17.3, 1.3 Hz, 1H), 5.22 (dt, J = 10.5, 1.2 Hz, 1H), 3.12 – 2.97 (m, 2H), 2.07 (s, 3H), 2.14 – 1.98 (m, 2H), 1.68 (s, 9H) ppm.

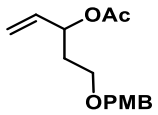
^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 150.5, 141.0, 136.7, 136.2, 129.2, 123.4, 122.7, 119.8, 117.1, 115.6, 107.3, 83.8, 74.3, 33.2, 28.3, 25.9, 21.2 ppm.

HRMS (ESI): Calculated for $C_{20}H_{25}NO_4$ $[M+Na]^+$ = 366.1676, Found 366.1678.

FTIR (Neat): 2979, 1729, 1568, 1454, 1327, 1157, 1087, 990, 849, 803, 769, 746 cm^{-1}.


8.10 8.08 7.46 7.44 7.44 7.26 CDCl3 7.25 7.24 7.23 7.23 7.22 7.21 7.20 7.20 7.18 7.18 7.17 6.36 5.84 5.83 5.82 5.81 5.38 5.36 5.31 5.31 5.31 5.28 5.27 5.23 5.23 5.23 5.21 5.21 5.21 3.07 3.06 3.06 3.05 3.04 3.03 2.09 2.08 2.07 2.06 2.05 2.04 2.04 2.03 1.70 1.68
I (dt) 5.22
B (m) 7.44
E (ddd) 5.84
K (s) 1.68
A (d) 8.09
D (s) 6.36
F (q) 5.37
G (m) 3.05
J (m) 2.05
C (dtd) 7.21
H (dt) 5.29
L (s) 2.07
1.01 0.94 2.37 1.01 1.00 0.92 1.07 1.04 2.03 2.87 1.76 9.08
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)
170.3 150.5 141.0 136.7 136.2 129.2 123.4 122.7 119.8 117.1 115.6 107.3 83.8 74.3 33.2 28.3 25.9 21.2
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)

5-((4-Methoxybenzyl)oxy)pent-1-en-3-yl acetate (4.1f)



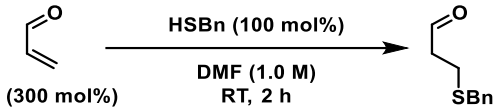
Procedures

The title compound was prepared by the general procedure and it is identical with respect to the reported materials.[28]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, J = 2.1 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 5.81 (ddd, J = 17.0, 10.5, 6.3 Hz, 1H), 5.43 (q, J = 6.6 Hz, 1H), 5.30 – 5.15 (m, 1H), 4.43 (d, J = 3.0 Hz, 2H), 3.83 (s, 3H), 3.50 (q, J = 6.6 Hz, 3H), 2.05 (s, 3H), 1.99 – 1.87 (m, 2H), 1.23 (t, J = 7.0 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 159.2, 136.3, 130.4, 129.3, 116.7, 113.8, 72.7, 72.2, 65.9, 65.8, 55.29, 34.4, 21.2, 15.3 ppm.

3-(Benzylthio)propanal (4.1g-CHO)



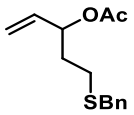
Procedures

The title compound was prepared according to literature procedure.[5] The aldehyde was obtained in quantitative yield as a light yellow oil and used in subsequent steps without further isolation. Spectral data are consistent with reported literature.[29]

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (t, *J* = 1.3 Hz, 1H), 7.36 – 7.22 (m, 5H), 3.74 (s, 2H), 2.78 – 2.58 (m, 4H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 200.6, 138.1, 129.0, 128.7, 127.3, 43.5, 36.7, 23.8 ppm.

5-(Benzylthio)pent-1-en-3-yl acetate (4.1g)



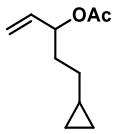
Procedures

The title compound was prepared by the general procedure and it is identical with respect to the reported materials.[30]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.20 (m, 5H), 5.72 (ddd, *J* = 17.2, 10.5, 6.3 Hz, 1H), 5.32 – 5.25 (m, 1H), 5.25 – 5.14 (m, 2H), 3.71 (s, 2H), 2.41 (ddd, *J* = 8.3, 6.7, 1.7 Hz, 2H), 2.03 (s, 3H), 1.96 – 1.76 (m, 2H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 1 δ 170.3, 138.4, 135.9, 129.0, 128.6, 127.1, 117.3, 73.7, 36.3, 33.9, 26.8, 21.3 ppm.

5-Cyclopropylpent-1-en-3-yl acetate (4.1h)



Procedures

The title compound was prepared by the general procedure and was obtained as a light yellow oil (0.59 g, 3.51 mmol) in 41% yield over 2 steps.

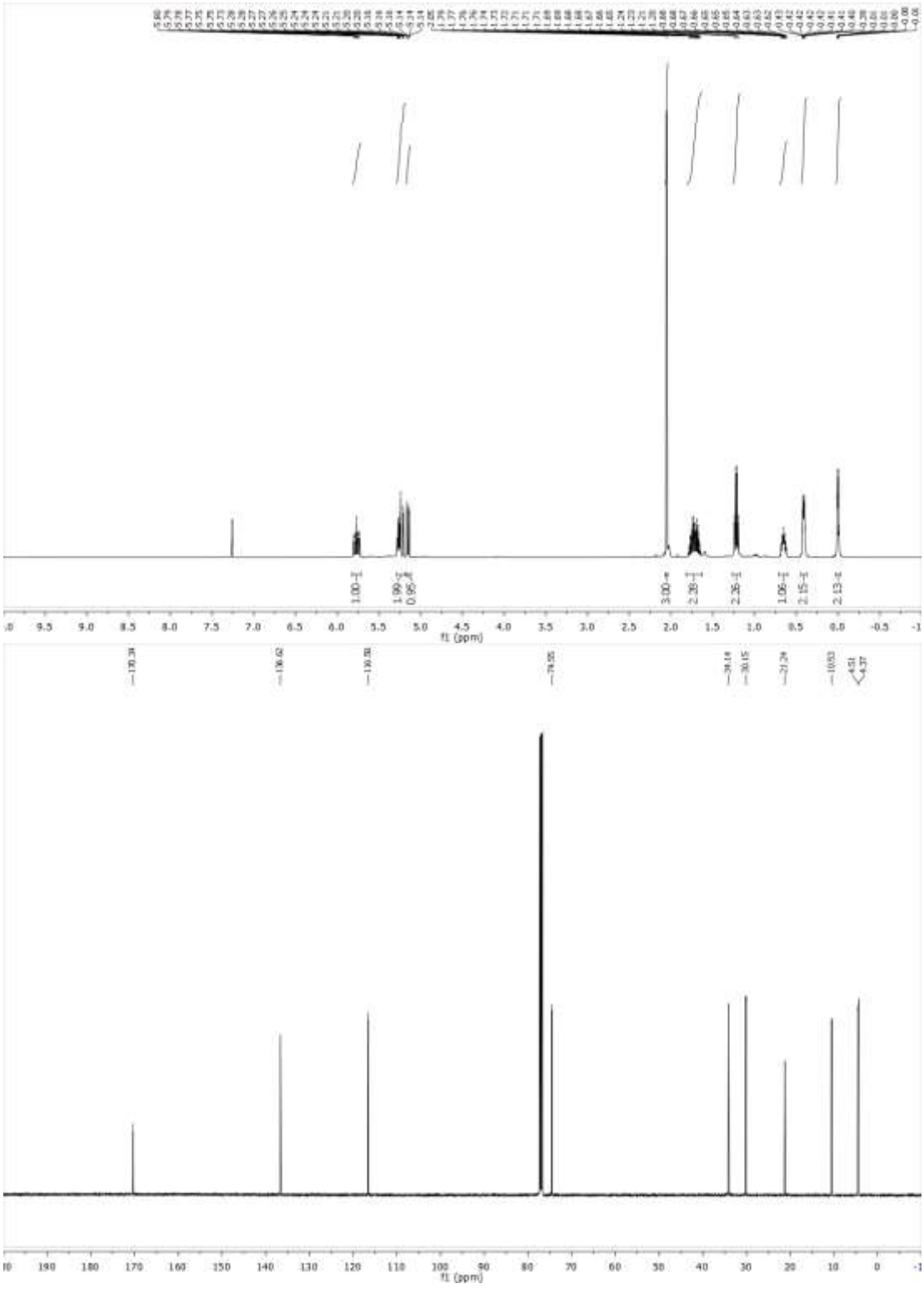
TLC (SiO_2) R_f = 0.57 (hexane: ethyl acetate = 10:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.77 (ddd, J = 17.1, 10.5, 6.4 Hz, 1H), 5.29 – 5.18 (m, 2H), 5.15 (dt, J = 10.5, 1.1 Hz, 1H), 2.05 (s, 3H), 1.82 – 1.63 (m, 2H), 1.22 (q, J = 7.5 Hz, 2H), 0.71 – 0.60 (m, 1H), 0.44 – 0.37 (m, 2H), 0.03 – -0.03 (m, 2H) ppm.

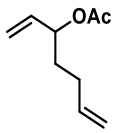
^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.3, 136.6, 116.5, 74.6, 34.1, 30.2, 21.2, 10.5, 4.5, 4.4 ppm.

HRMS (ESI): Calculated for C_8H_{12} $[M–OAc]^+$ = 109.1012, Found 109.1012.

FTIR (Neat): 2928, 1737, 1427, 1371, 1233, 1016, 924, 822 cm^{-1}.



Hepta-1,6-dien-3-yl acetate (4.1i)

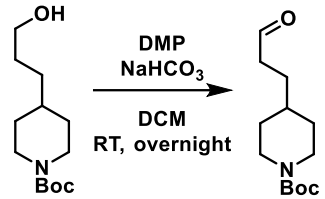


Procedures

The title compound was prepared by the general procedure and it is identical with respect to the reported materials.[31]

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.79 (dddd, J = 16.9, 13.2, 10.4, 6.5 Hz, 2H), 5.25 (dd, J = 7.4, 1.1 Hz, 1H), 5.22 (t, J = 1.4 Hz, 0H), 5.18 (dt, J = 10.5, 1.2 Hz, 1H), 5.05 (q, J = 1.7 Hz, 0H), 5.00 (dq, J = 3.3, 1.6 Hz, 1H), 4.97 (q, J = 1.4 Hz, 0H), 2.09 (dt, J = 6.8, 1.6 Hz, 1H), 2.07 (s, 3H), 1.83 – 1.59 (m, 2H) ppm.

***tert*-butyl 4-(3-oxopropyl)piperidine-1-carboxylate (4.1j-CHO)**



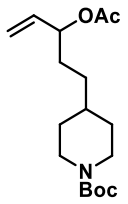
Procedures

The title compound was prepared according to literature procedure.[8] The aldehyde was obtained in 95% yield as a colorless oil and used in subsequent steps without further isolation. Spectral data are consistent with reported literature.[32]

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.8 (t, *J* = 1.5 Hz, 1H), 4.1 (d, *J* = 13.4 Hz, 2H), 2.6 (t, *J* = 12.8 Hz, 2H), 2.4 (td, *J* = 7.6, 2.0 Hz, 2H), 1.7 – 1.5 (m, 5H), 1.4 (s, 9H), 1.2 – 1.0 (m, 2H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.4, 154.9, 79.4, 43.9, 41.2, 35.6, 32.0, 28.6, 28.5 ppm.

***tert*-butyl 4-(3-acetoxypent-4-en-1-yl)piperidine-1-carboxylate (4.1j)**



Procedures

The title compound was prepared by the general procedure and was obtained as a light yellow oil (0.273 g, 0.88 mmol) in 31% yield over 2 steps

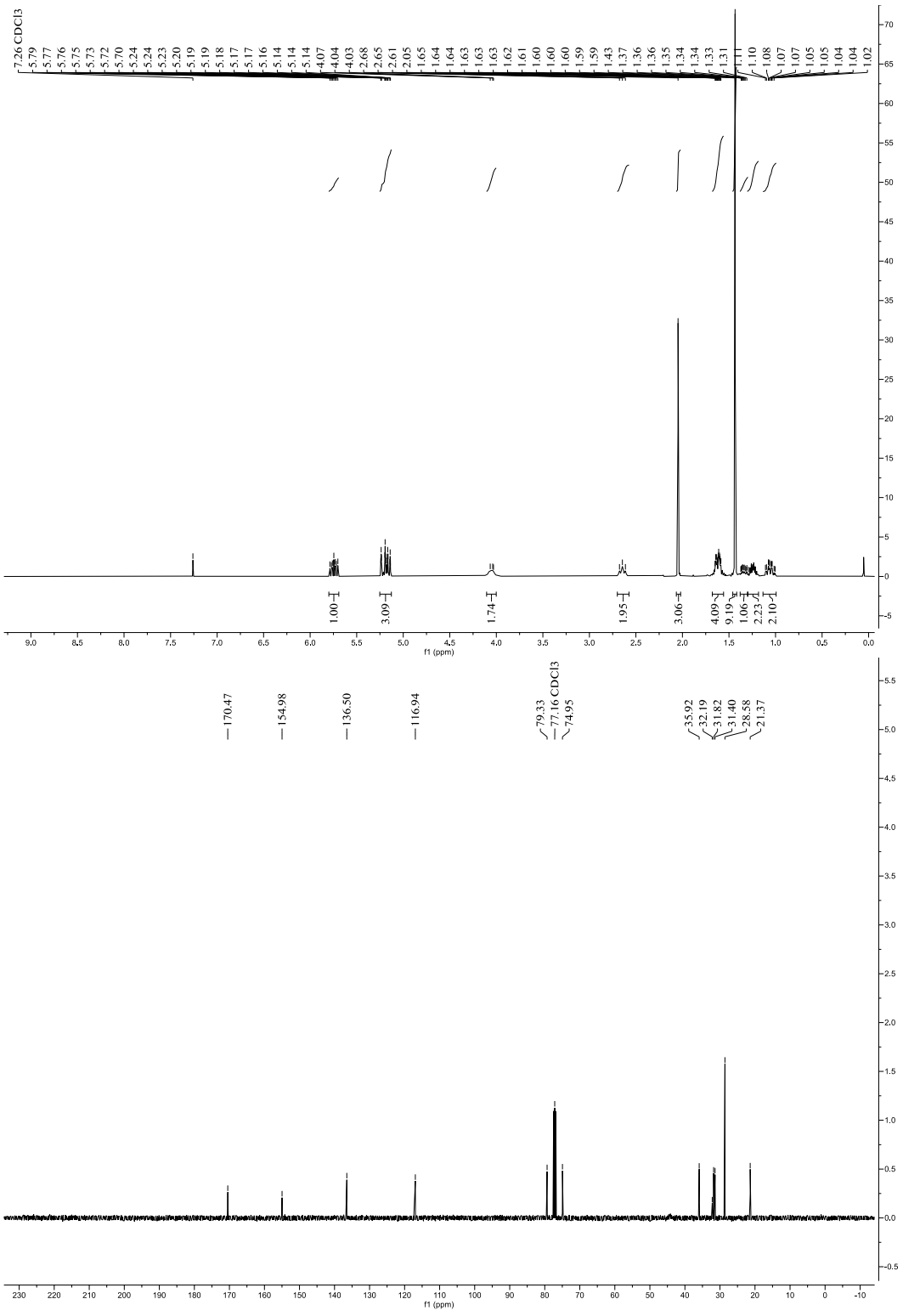
TLC (SiO_2) R_f = 0.34 (hexane: ethyl acetate = 10:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.75 (ddd, *J* = 17.2, 10.5, 6.5 Hz, 1H), 5.26 – 5.12 (m, 3H), 4.13 – 3.98 (m, 2H), 2.65 (t, *J* = 12.7 Hz, 2H), 2.05 (s, 3H), 1.77 – 1.55 (m, 4H), 1.43 (s, 9H), 1.39 – 1.29 (m, 1H), 1.16 – 0.95 (m, 2H) ppm.

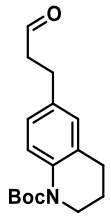
^{13}C NMR (101 MHz, $CDCl_3$): δ 170.5, 155.0, 136.5, 116.9, 79.3, 75.0, 35.9, 32.2, 31.8, 31.4, 28.6, 21.4 ppm.

HRMS (ESI): Calculated for $C_{17}H_{29}NO_4$ $[M+Na]^+$ = 334.1989, Found 334.1998.

FTIR (Neat): 2925, 2853, 1737, 1689, 1365, 1235, 1168 cm^{-1}.


7.26 CDCl3
5.79
5.77
5.76
5.75
5.73
5.72
5.70
5.24
5.24
5.23
5.20
5.19
5.19
5.18
5.17
5.17
5.16
5.14
5.14
5.14
4.07
4.04
4.03
2.68
2.65
2.61
2.05
1.65
1.64
1.64
1.63
1.63
1.63
1.62
1.61
1.60
1.60
1.60
1.59
1.43
1.37
1.36
1.36
1.35
1.34
1.34
1.33
1.31
1.11
1.10
1.08
1.07
1.07
1.05
1.05
1.04
1.04
1.02
1.00
3.09
1.74
1.95
3.06
4.09
9.19
1.06
2.23
2.10
f1 (ppm)
170.47
154.98
136.50
116.94
79.33
77.16 CDCl3
74.95
35.92
32.19
31.82
31.40
28.58
21.37
f1 (ppm)

***tert*-Butyl 6-(3-oxopropyl)-3,4-dihydroquinoline-1(2*H*)-carboxylate (4.1k-CHO)**



Procedures

To a round-bottomed flask charged with *tert*-butyl 6-bromo-3,4-dihydroquinoline-1(2*H*)-carboxylate (3.12 g, 10 mmol, 100 mol%), tris(dibenzylideneacetone)dipalladium(0) (183 mg, 0.20 mmol, 2 mol%), 2-(di-tert-butylphosphino)-1-phenylindole (202.5 mg, 0.60 mmol, 6 mol%) was added anhydrous DMF (25 mL, 0.4 M). Allylic alcohol (1.16 mL, 20.0 mmol, 200 mol%), and *N*,*N*-dicyclohexylmethylamine (2.15 mL, 11.0 mmol, 110 mol%) were added and the reaction was stirred at 100 °C for 2 h. After cooling down to room temperature, the mixture was transferred to a separatory funnel and water was added. The aqueous layer was extracted with diethyl ether three times and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The title compound was obtained in 66% yield (1.9 g, 6.6 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate = 15:1).

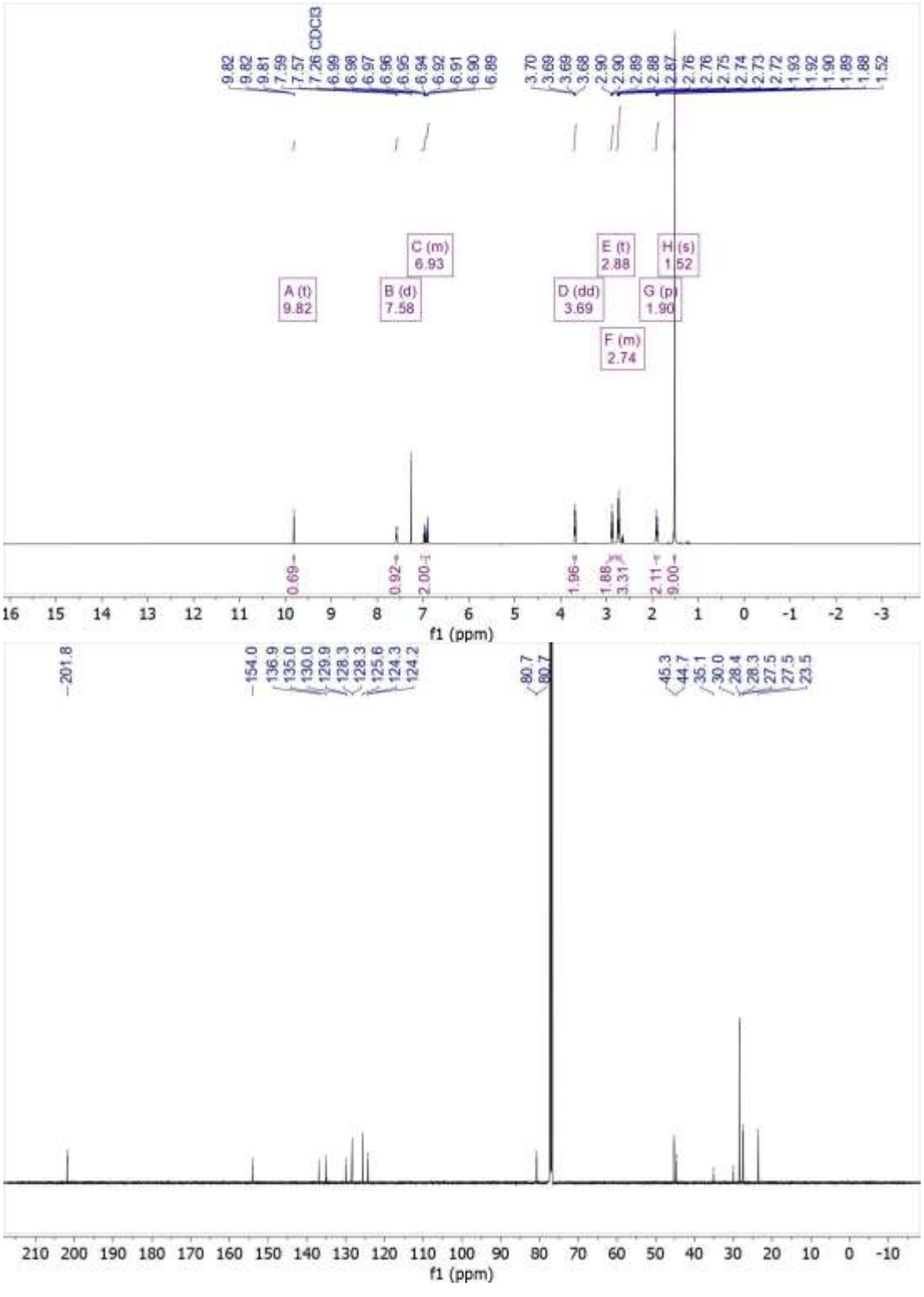
TLC (SiO_2) R_f = 0.30 (hexane: ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.82 (t, J = 1.5 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.03 – 6.86 (m, 2H), 3.69 (dd, J = 7.0, 5.1 Hz, 2H), 2.88 (t, J = 7.4 Hz, 2H), 2.79 – 2.70 (m, 3H), 1.90 (p, J = 6.5 Hz, 2H), 1.52 (s, 9H) ppm.

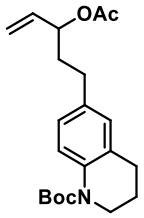
^{13}C NMR (126 MHz, $CDCl_3$) δ 201.8, 154.0, 136.9, 135.0, 129.9, 129.8, 128.3, 128.3, 125.6, 124.3, 124.2, 80.7, 80.7, 45.3, 44.7, 35.1, 29.9, 28.4, 28.3, 27.5, 27.5, 23.5 ppm.

HRMS (ESI): Calculated for $C_{17}H_{23}NO_3$ $[M+Na]^+$ = 312.1570, Found 312.1582.

FTIR (Neat): 3461, 3016, 2970, 1739, 1435, 1366, 1229, 1217, 1011, 896, 768 cm^{-1}.


9.82
9.82
9.81
7.59
7.57
7.26 CDCl3
6.99
6.98
6.97
6.96
6.95
6.94
6.92
6.91
6.90
6.89
3.70
3.69
3.69
3.68
2.90
2.90
2.89
2.88
2.87
2.76
2.76
2.75
2.74
2.73
2.72
1.93
1.92
1.90
1.89
1.88
1.52
A (t) 9.82
B (d) 7.58
C (m) 6.93
D (dd) 3.69
E (t) 2.88
F (m) 2.74
G (p) 1.90
H (s) 1.52
0.69
0.92
2.00
1.96
1.88
3.31
2.11
9.00
f1 (ppm)
201.8
154.0
136.9
135.0
130.0
129.9
128.3
128.3
125.6
124.3
124.2
80.7
80.7
45.3
44.7
35.1
30.0
28.4
28.3
27.5
27.5
23.5
f1 (ppm)

***tert*-Butyl 6-(3-acetoxypent-4-en-1-yl)-3,4-dihydroquinoline-1(2*H*)-carboxylate (4.1k)**



Procedures

The title compound was prepared by the general procedure and was obtained as light-yellow oil (1.9 g, 5.4 mmol) in 82% yield over 2 steps.

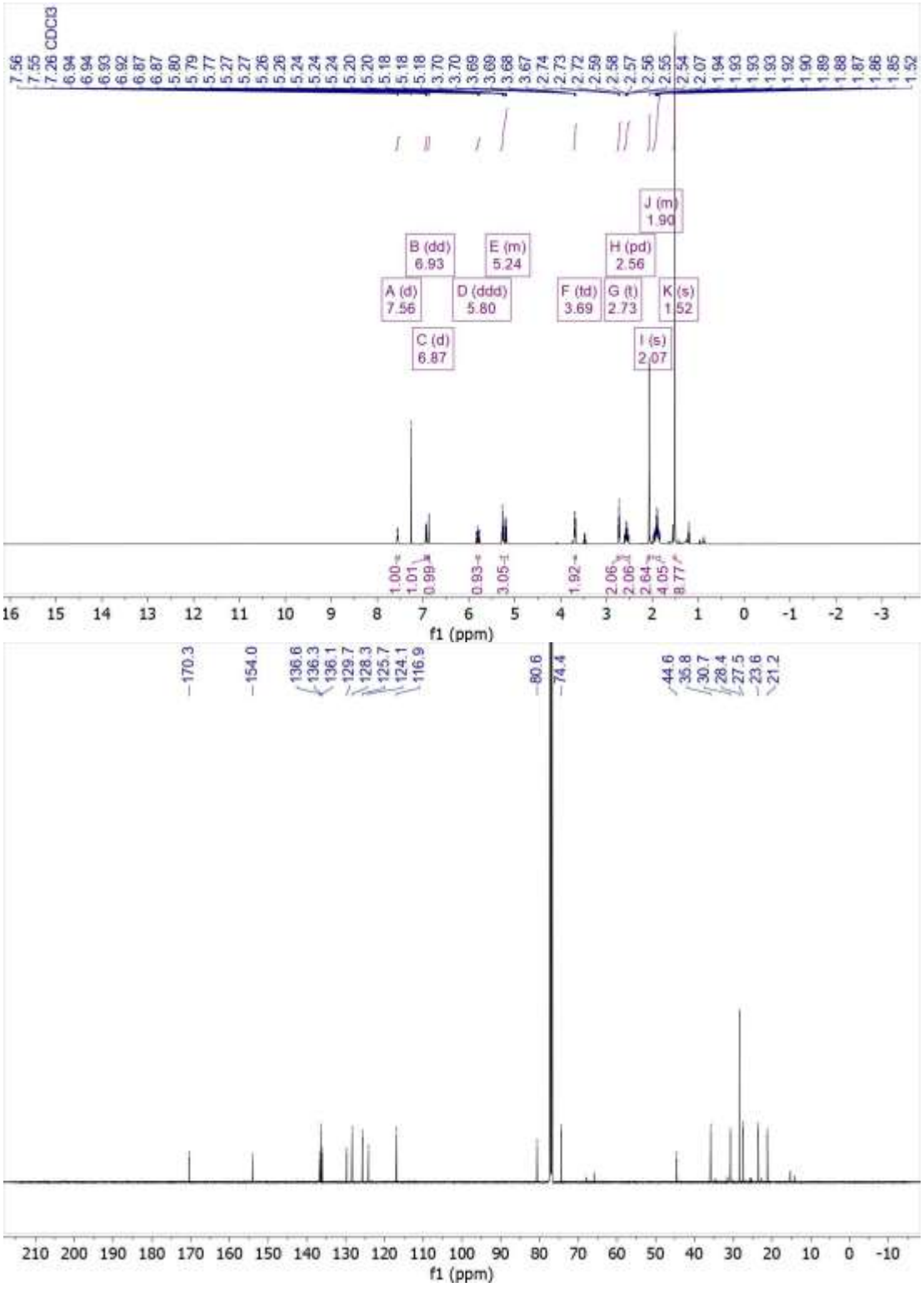
TLC (SiO_2) R_f = 0.52 (hexane: ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 8.4 Hz, 1H), 6.93 (dd, J = 8.5, 2.2 Hz, 1H), 6.87 (d, J = 2.1 Hz, 1H), 5.80 (ddd, J = 17.0, 10.5, 6.3 Hz, 1H), 5.31 – 5.16 (m, 3H), 3.69 (td, J = 5.6, 1.3 Hz, 2H), 2.73 (t, J = 6.6 Hz, 2H), 2.56 (pd, J = 14.1, 6.3 Hz, 2H), 2.07 (s, 3H), 2.00 – 1.83 (m, 4H), 1.52 (s, 9H) ppm.

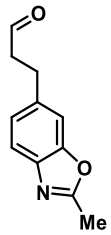
^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 154.0, 136.6, 136.3, 136.1, 129.7, 128.3, 125.7, 124.1, 116.9, 80.6, 74.4, 44.6, 35.9, 30.7, 28.4, 27.5, 23.6, 21.2 ppm.

HRMS (ESI): Calculated for $C_{21}H_{29}NO_4$ $[M+Na]^+$ = 382.1989, Found 382.2003.

FTIR (Neat): 3454, 3016, 2970, 2945, 1738, 1501, 1448, 1366, 1229, 1217 1158, 1136, 1010, 895, 854, 823, 766 cm^{-1}.


7.56 7.55 CDCl3 7.26 6.94 6.93 6.92 6.87 6.87 5.80 5.79 5.77 5.27 5.27 5.26 5.26 5.24 5.24 5.24 5.20 5.20 5.18 5.18 5.18 3.70 3.70 3.69 3.69 3.68 3.67 2.74 2.73 2.72 2.59 2.58 2.57 2.56 2.55 2.54 2.07 1.94 1.93 1.93 1.93 1.92 1.90 1.89 1.88 1.87 1.86 1.85 1.52
J (m) 1.90
B (dd) 6.93
E (m) 5.24
H (pd) 2.56
A (d) 7.56
D (ddd) 5.80
F (td) 3.69
G (t) 2.73
K (s) 1.52
C (d) 6.87
I (s) 2.07
1.00 1.01 0.99 0.93 3.05 1.92 2.06 2.06 2.64 4.05 8.77
f1 (ppm)
170.3 154.0 136.6 136.3 136.1 129.7 128.3 125.7 124.1 116.9 80.6 74.4 44.6 35.8 30.7 28.4 27.5 23.6 21.2
f1 (ppm)

3-(2-Methylbenzo[*d*]oxazol-6-yl)propanal (4.1l-CHO)



Procedures

To a round-bottomed flask charged with 6-bromo-2-methylbenzo[*d*]oxazole (2.12 g, 10 mmol, 100 mol%), tris(dibenzylideneacetone)dipalladium(0) (183 mg, 0.20 mmol, 2 mol%), 2-(di-tert-butylphosphino)-1-phenylindole (202.5 mg, 0.60 mmol, 6 mol%) was added anhydrous DMF (25 mL, 0.4 M). Allylic alcohol (1.16 mL, 20.0 mmol, 200 mol%), and *N*,*N*-dicyclohexylmethylamine (2.15 mL, 11.0 mmol, 110 mol%) were added and the reaction was stirred at 100 °C for 2 h. After cooling down to room temperature, the mixture was transferred to a separatory funnel and water was added. The aqueous layer was extracted with diethyl ether three times and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The title compound was obtained in 81% yield (1.53 g, 8.1 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate = 10:1).

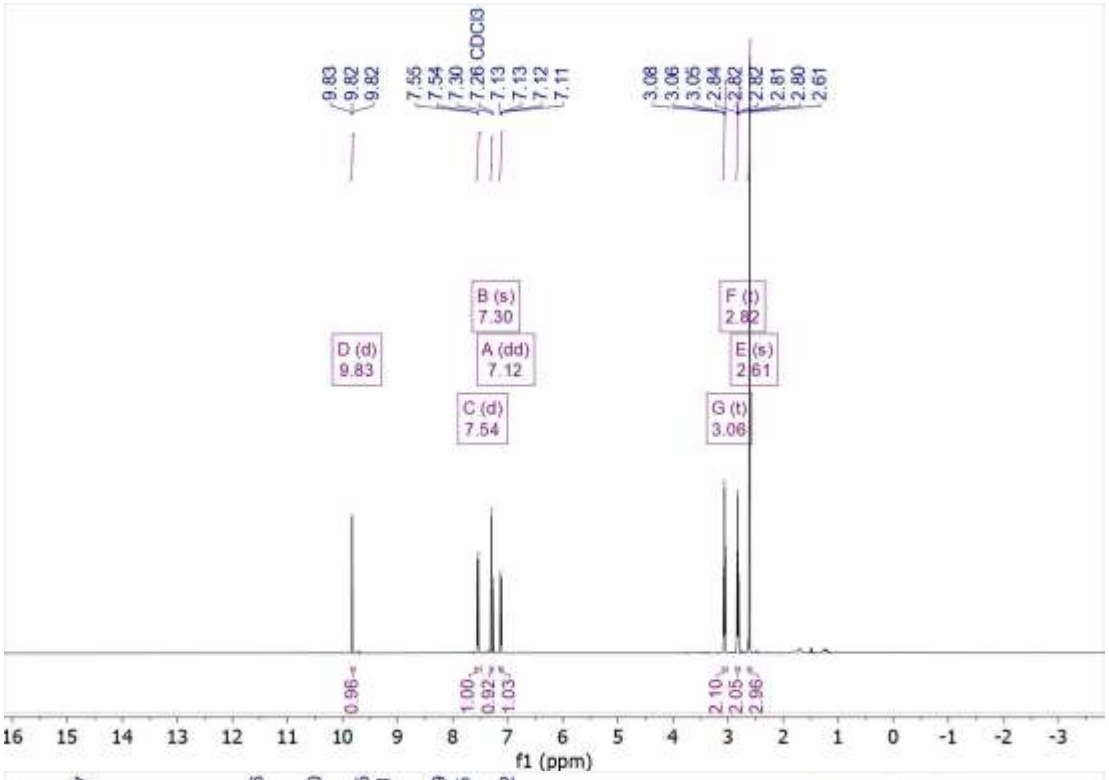
TLC (SiO_2) R_f = 0.18 (hexane: ethyl acetate = 4:1).

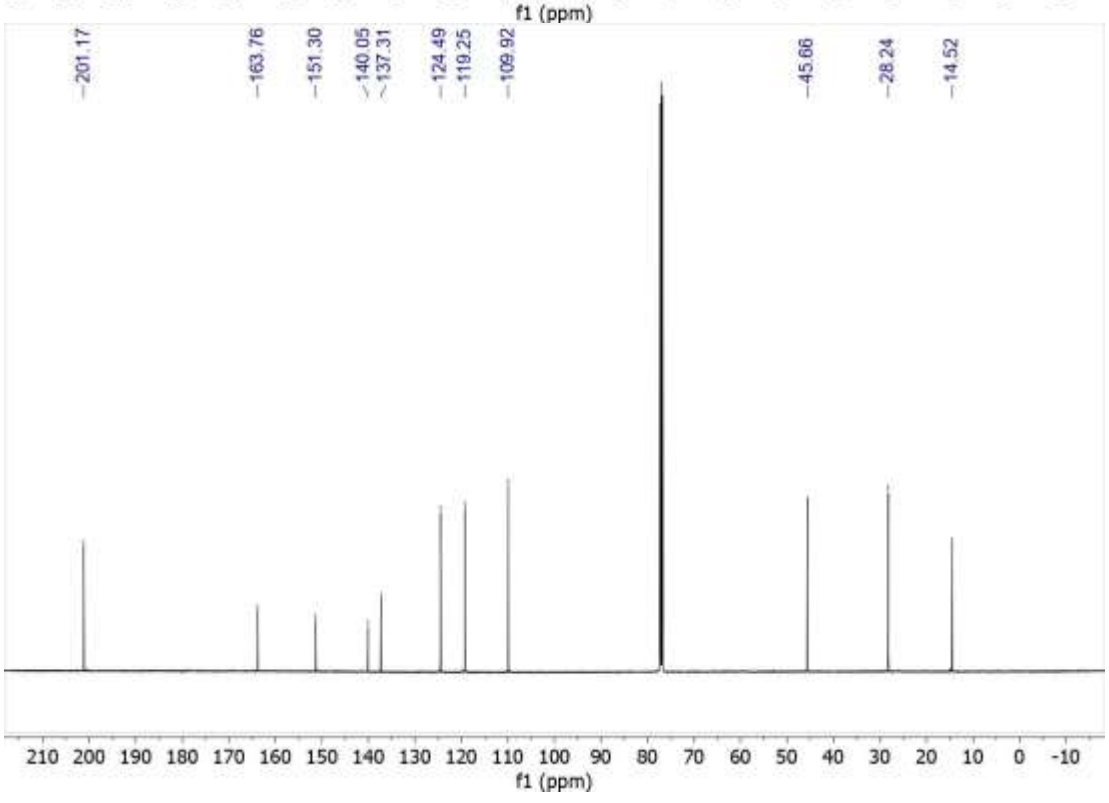
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.83 (d, J = 1.5 Hz, 1H), 7.54 (d, J = 8.1 Hz, 1H), 7.30 (s, 1H), 7.12 (dd, J = 8.2, 1.7 Hz, 1H), 3.06 (t, J = 7.5 Hz, 2H), 2.82 (t, J = 7.4 Hz, 2H), 2.61 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.2, 163.8, 151.3, 140.1, 137.3, 124.5, 119.3, 109.9, 45.7, 28.2, 14.5 ppm.

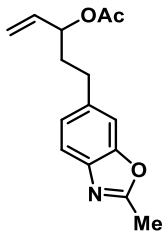
HRMS (ESI): Calculated for $C_{11}H_{11}NO_2$ $[M+H]^+$ = 190.0863, Found 190.0867.

FTIR (Neat): 3461, 3015, 2970, 2945, 2362, 2133, 1738, 1614, 1575, 1434, 1365, 1228, 1216, 1116, 1092, 911, 820 cm^{-1}.


9.83
9.82
9.82
7.55
7.54
7.30
7.26 CDCl3
7.13
7.13
7.12
7.11
3.08
3.06
3.05
2.84
2.82
2.82
2.81
2.80
2.61
B (s)
7.30
F (t)
2.82
D (d)
9.83
A (dd)
7.12
E (s)
2.61
C (d)
7.54
G (t)
3.06
0.96
1.00
0.92
1.03
2.10
2.05
2.96
f1 (ppm)


201.17
163.76
151.30
140.05
137.31
124.49
119.25
109.92
45.66
28.24
14.52
f1 (ppm)

5-(2-Methylbenzo[*d*]oxazol-6-yl)pent-1-en-3-yl acetate (4.1l)



Procedures

The title compound was prepared by the general procedure and was obtained as light-yellow oil (1.9 g, 7.3 mmol) in 90% yield over 2 steps.

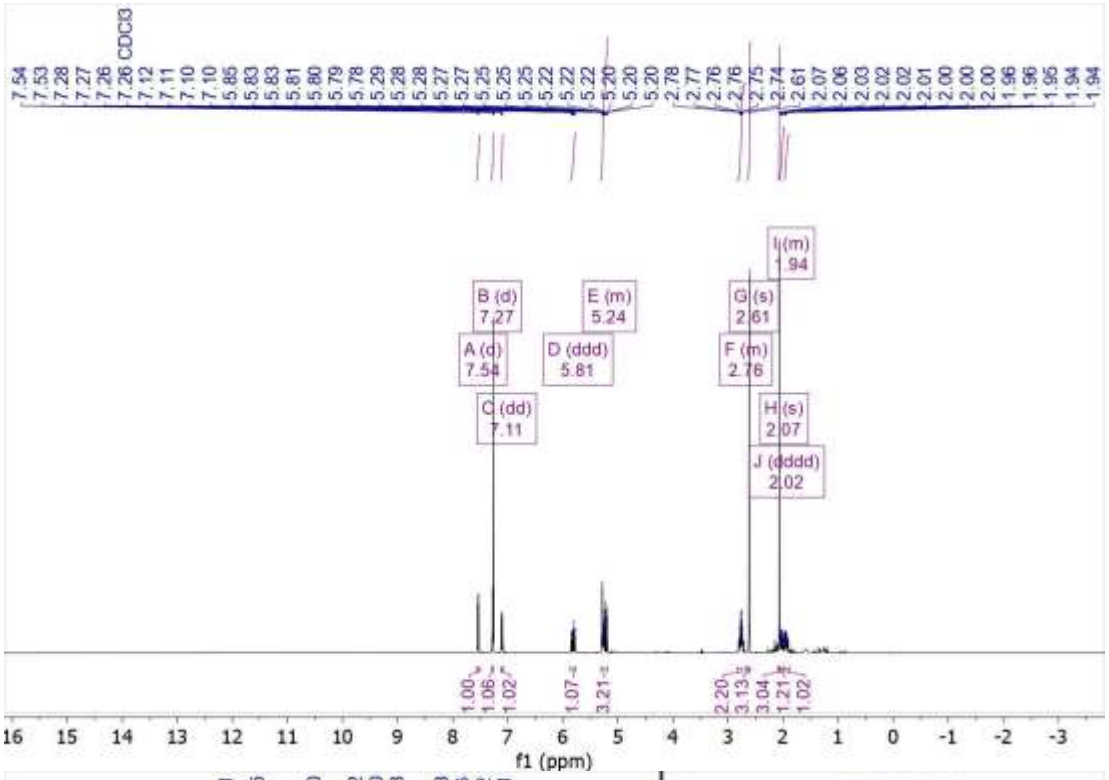
TLC (SiO_2) R_f = 0.48 (hexane: ethyl acetate = 2:1).

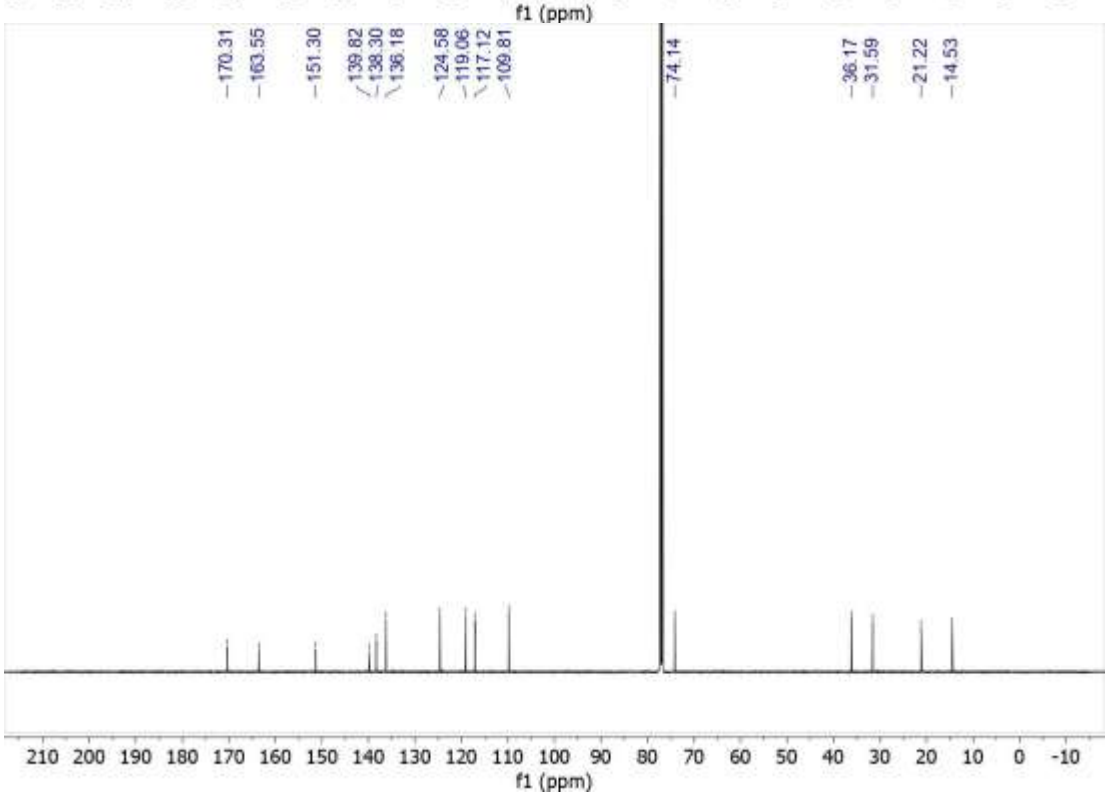
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 1.6 Hz, 1H), 7.11 (dd, J = 8.1, 1.6 Hz, 1H), 5.81 (ddd, J = 17.0, 10.5, 6.3 Hz, 1H), 5.31 – 5.18 (m, 3H), 2.84 – 2.69 (m, 2H), 2.61 (s, 3H), 2.07 (s, 3H), 2.02 (dddd, J = 13.8, 9.5, 7.9, 6.6 Hz, 1H), 1.98 – 1.88 (m, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 163.6, 151.3, 139.8, 138.3, 136.2, 124.6, 119.1, 117.1, 109.8, 74.1, 36.2, 31.6, 21.2, 14.5 ppm.

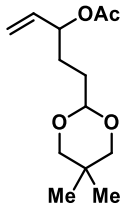
HRMS (ESI): Calculated for $C_{15}H_{17}NO_3$ $[M+H]^+$ = 260.1281, Found 260.1290.

FTIR (Neat): 3456, 3015, 2970, 2946, 2362, 2132, 1738, 1614, 1576, 1434, 1366, 1229, 1216, 1092, 1020, 911, 822 cm^{-1}.


7.54 7.53 7.28 7.27 7.26 CDCl3 7.12 7.11 7.10 7.10 5.85 5.83 5.81 5.80 5.79 5.78 5.29 5.28 5.28 5.27 5.27 5.25 5.25 5.22 5.22 5.22 5.20 5.20 5.20 2.78 2.77 2.76 2.76 2.75 2.74 2.61 2.07 2.06 2.03 2.02 2.02 2.01 2.00 2.00 2.00 1.96 1.96 1.95 1.94 1.94
I (m) 1.94
B (d) 7.27
E (m) 5.24
G (s) 2.61
A (d) 7.54
D (ddd) 5.81
F (m) 2.76
C (dd) 7.11
H (s) 2.07
J (dddd) 2.02
1.00 1.06 1.02 1.07 3.21 2.20 3.13 3.04 1.21 1.02
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)


170.31 163.55 151.30 139.82 138.30 136.18 124.58 119.06 117.12 109.81 74.14 36.17 31.59 21.22 14.53
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)

5-(5,5-Dimethyl-1,3-dioxan-2-yl)pent-1-en-3-yl acetate (4.1m)



Procedures

The title compound was prepared by the general procedure and was obtained as light-yellow oil (2.1 g, 8.6 mmol) in 86% yield over 2 steps.

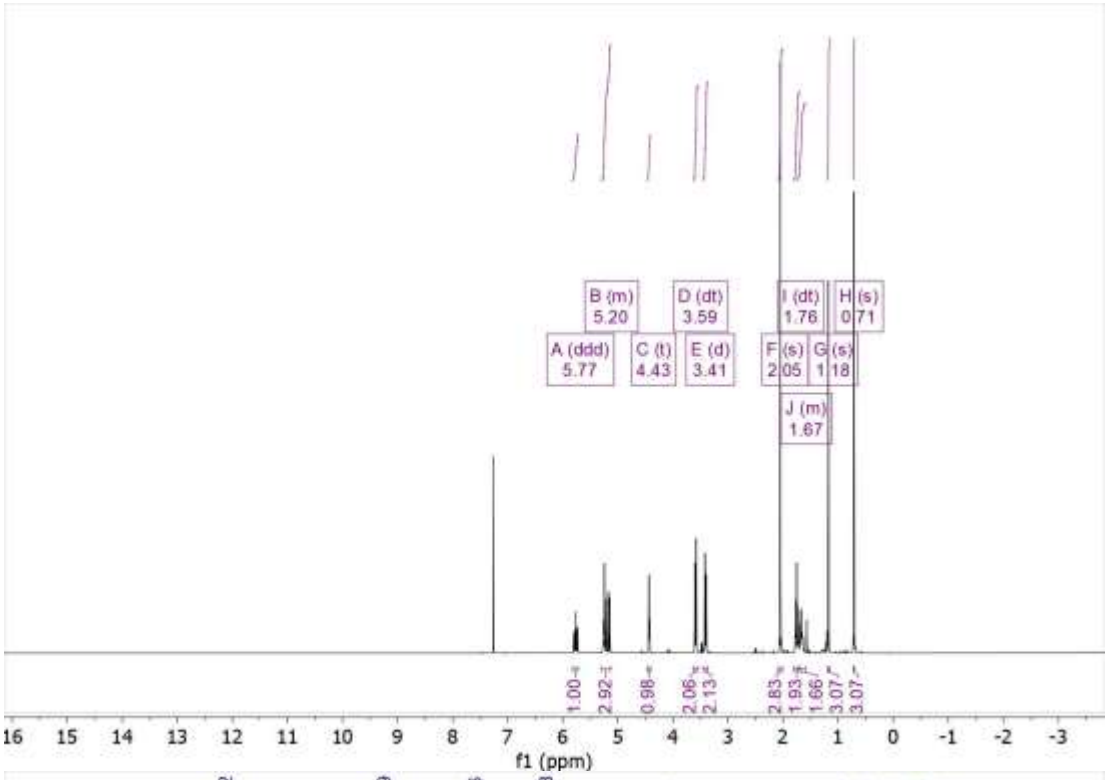
TLC (SiO_2) R_f = 0.42 (hexane: ethyl acetate = 4:1).

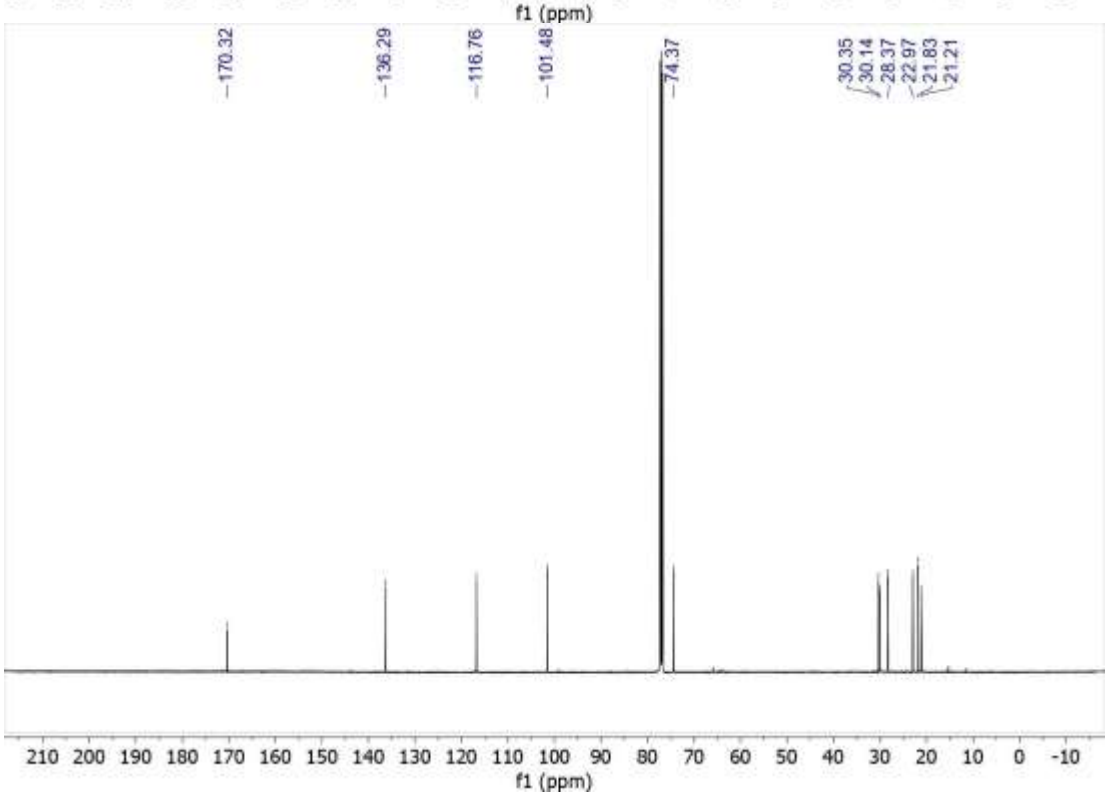
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77 (ddd, J = 16.9, 10.5, 6.3 Hz, 1H), 5.29 – 5.13 (m, 3H), 4.43 (t, J = 4.7 Hz, 1H), 3.59 (dt, J = 11.3, 1.5 Hz, 2H), 3.41 (d, J = 10.9 Hz, 2H), 2.05 (s, 3H), 1.76 (dt, J = 9.4, 5.7 Hz, 2H), 1.73 – 1.59 (m, 2H), 1.18 (s, 3H), 0.71 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 136.3, 116.8, 101.5, 74.4, 30.4, 30.1, 28.4, 23.0, 21.8, 21.2 ppm.

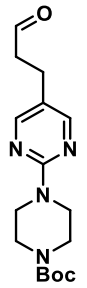
HRMS (ESI): Calculated for $C_{13}H_{22}O_4$ $[M+Na]^+$ = 265.1410, Found 265.1408.

FTIR (Neat): 3464, 2969, 2951, 2848, 1737, 1435, 1365, 1231, 1217, 1129, 1112, 1017, 975, 918, 791, 665 cm^{-1}.


B (m)
5.20
D (dt)
3.59
I (dt)
1.76
H (s)
0.71
A (ddd)
5.77
C (t)
4.43
E (d)
3.41
F (s)
2.05
G (s)
1.18
J (m)
1.67
1.00
2.92
0.98
2.06
2.13
2.83
1.93
1.66
3.07
3.07
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)


170.32
136.29
116.76
101.48
74.37
30.35
30.14
28.37
22.97
21.83
21.21
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)

***tert*-Butyl 4-(5-(3-oxopropyl)pyrimidin-2-yl)piperazine-1-carboxylate (4.1n-CHO)**



Procedures

To a round-bottomed flask charged with *tert*-butyl 4-(5-bromopyrimidin-2-yl)piperazine-1-carboxylate (3.43 g, 10 mmol, 100 mol%), tris(dibenzylideneacetone)dipalladium(0) (183 mg, 0.20 mmol, 2 mol%), 2-(di-tert-butylphosphino)-1-phenylindole (202.5 mg, 0.60 mmol, 6 mol%) was added anhydrous DMF (25 mL, 0.4 M). Allylic alcohol (1.16 mL, 20.0 mmol, 200 mol%), and *N*,*N*-dicyclohexylmethylamine (2.15 mL, 11.0 mmol, 110 mol%) were added and the reaction was stirred at 100 °C for 2 h. After cooling down to room temperature, the mixture was transferred to a separatory funnel and water was added. The aqueous layer was extracted with diethyl ether three times and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The title compound was obtained in 30% yield (0.96 g, 3.0 mmol) as a light yellow solid after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate = 5:1).

TLC (SiO_2) R_f = 0.30 (hexane: ethyl acetate = 1:1).

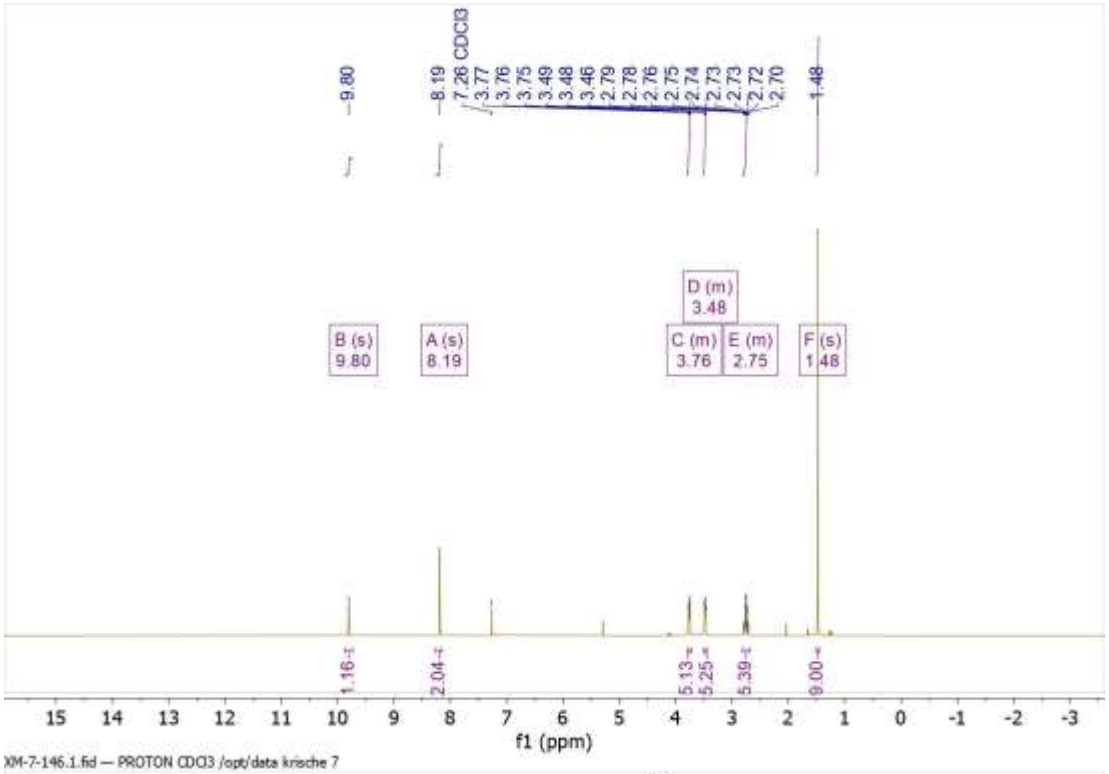
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 8.19 (s, 2H), 3.79 – 3.72 (m, 5H), 3.51 – 3.44 (m, 5H), 2.81 – 2.68 (m, 5H), 1.48 (s, 9H) ppm.

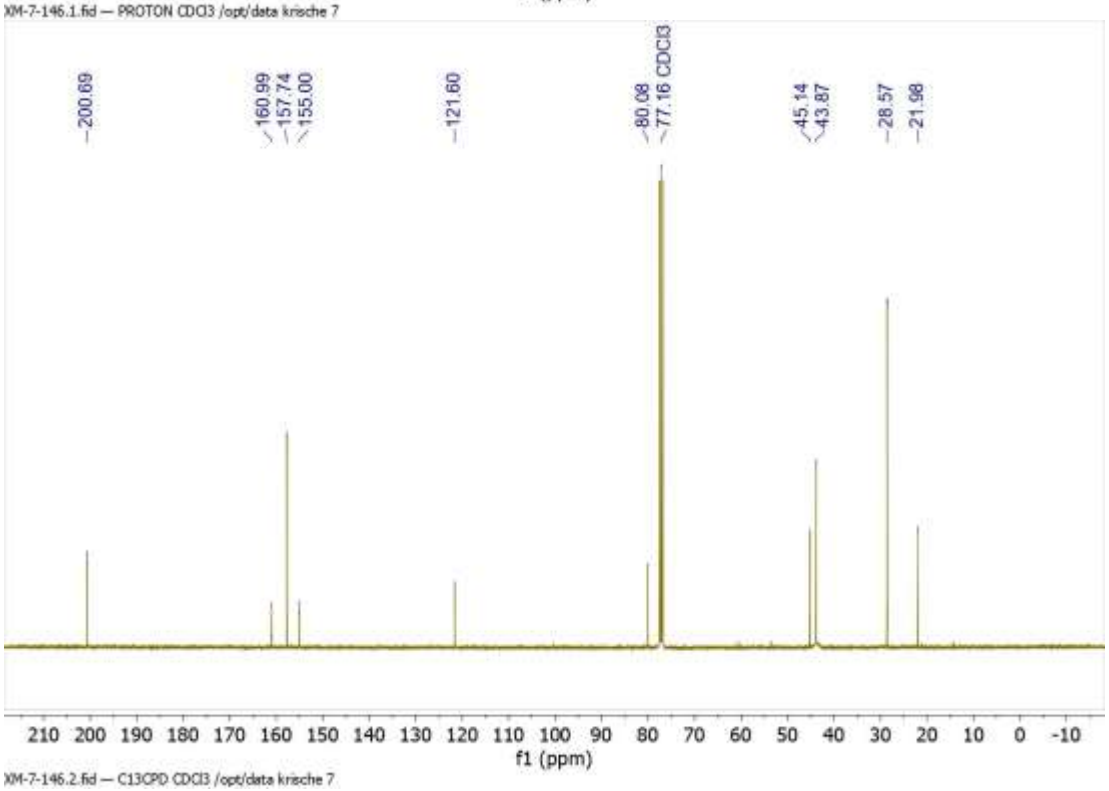
^{13}C NMR (101 MHz, $CDCl_3$) δ 200.7, 161.0, 157.7, 155.0, 121.6, 80.1, 45.1, 43.9, 28.6, 22.0 ppm.

HRMS (ESI): Calculated for C16H24N4O3 $[M+Na]^+$ = 343.1741, Found 343.1736.

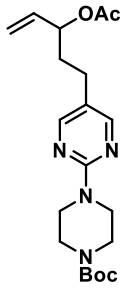
Melting Point 96 - 98 °C

FTIR (Neat): 2976, 2929, 2861, 1725, 1683, 1605, 1537, 1505, 1449, 1421, 1360, 1304, 1278, 1244, 1166, 1126, 1083, 999, 948, 895, 866, 794, 764, 657 cm^{-1}.


9.80
8.19
7.26 CDCl3
3.77
3.76
3.75
3.49
3.48
3.46
2.79
2.78
2.76
2.75
2.74
2.73
2.73
2.72
2.70
1.48
D (m)
3.48
B (s)
9.80
A (s)
8.19
C (m)
3.76
E (m)
2.75
F (s)
1.48
1.16
2.04
5.13
5.25
5.39
9.00
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)
XM-7-146.1.fid — PROTON CDCl3 /opt/data krische 7


200.69
160.99
157.74
155.00
121.60
80.08
77.16 CDCl3
45.14
43.87
28.57
21.98
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)
XM-7-146.2.fid — C13CPD CDCl3 /opt/data krische 7

***tert*-Butyl 4-(5-(3-acetoxypent-4-en-1-yl)pyrimidin-2-yl)piperazine-1-carboxylate (4.1n)**



Procedures

The title compound was prepared by the general procedure and was obtained as light-yellow solid (589 mg, 1.5 mmol) in 51% yield over 2 steps.

TLC (SiO_2) R_f = 0.59 (hexane: ethyl acetate = 1:1).

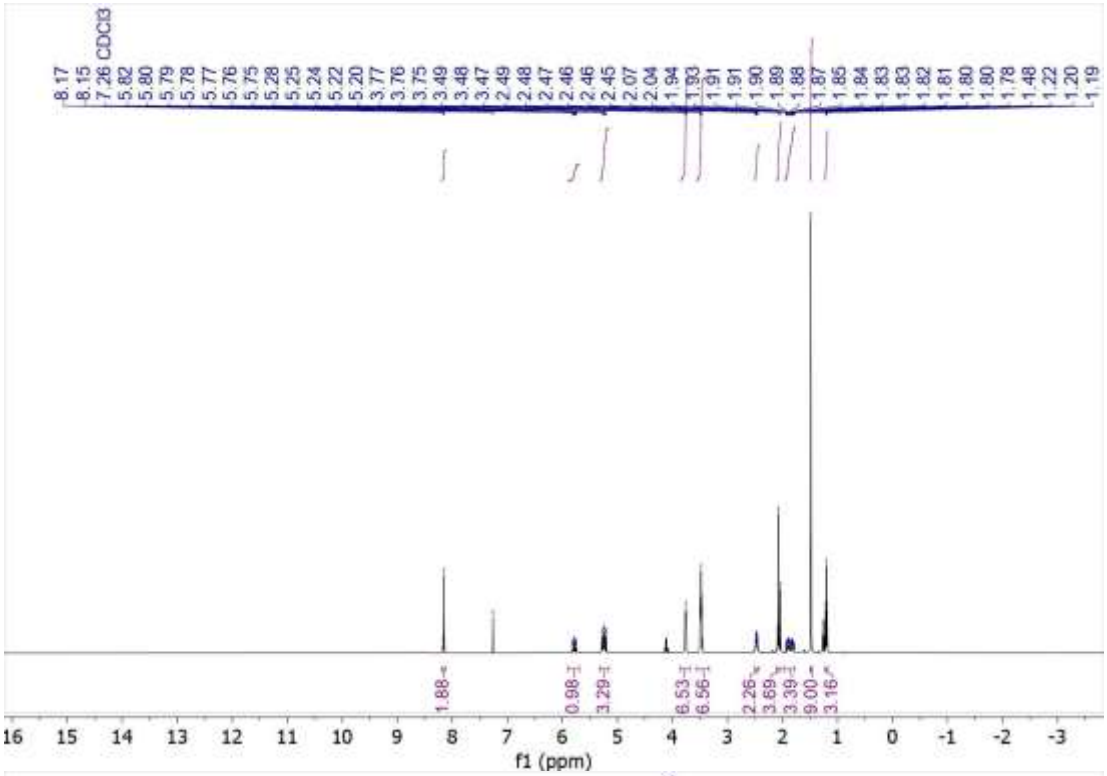
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 2H), 5.78 (ddd, J = 17.1, 10.5, 6.5 Hz, 1H), 5.32 – 5.15 (m, 3H), 3.86 – 3.69 (m, 7H), 3.48 (t, J = 6.9 Hz, 7H), 2.47 (dt, J = 8.7, 6.0 Hz, 2H), 2.05 (d, J = 16.0 Hz, 4H), 1.95 – 1.77 (m, 3H), 1.48 (s, 9H), 1.20 (t, J = 7.0 Hz, 3H) ppm.

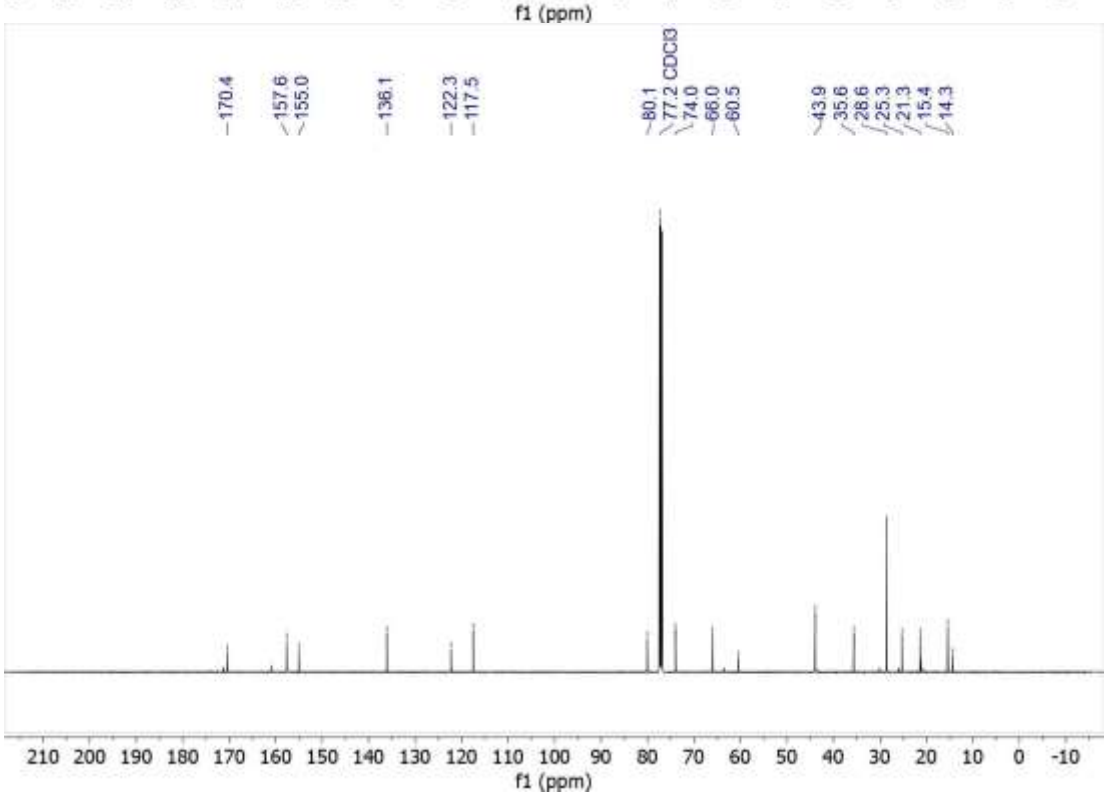
^{13}C NMR (126 MHz, $CDCl_3$) 13C δ 170.4, 157.6, 155.0, 136.1, 122.3, 117.5, 80.1, 74.0, 66.0, 60.5, 43.9, 35.6, 28.6, 25.3, 21.3, 15.4, 14.3 ppm.

HRMS (ESI): Calculated for C20H30N4O4 $[M+H]^+$ = 391.2340, Found 391.2341.

Melting Point 62 - 66 °C

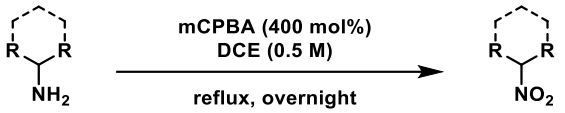
FTIR (Neat): 2975, 2932, 1740, 1677, 1605, 1541, 1499, 1457, 1404, 1360, 1306, 1279, 1237, 1163, 1113, 1096, 1019, 999, 956, 919, 898, 856, 795, 772, 656 cm^{-1}.


8.17
8.15
7.26 CDCl3
5.82
5.80
5.79
5.78
5.77
5.76
5.75
5.28
5.25
5.24
5.22
5.20
3.77
3.76
3.75
3.49
3.48
3.47
2.49
2.48
2.47
2.46
2.46
2.45
2.07
2.04
1.94
1.93
1.91
1.91
1.90
1.89
1.88
1.87
1.85
1.84
1.83
1.83
1.82
1.81
1.80
1.80
1.78
1.48
1.22
1.20
1.19
1.88
0.98
3.29
6.53
6.56
2.26
3.69
3.39
9.00
3.16
f1 (ppm)


170.4
157.6
155.0
136.1
122.3
117.5
80.1
77.2 CDCl3
74.0
66.0
60.5
43.9
35.6
28.6
25.3
21.3
15.4
14.3
f1 (ppm)

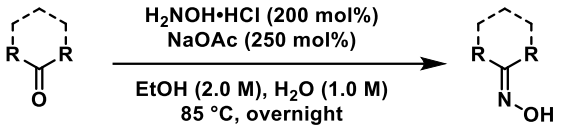
4.5.4 Synthesis of Nitroalkanes 4.2a-4.2j

General procedure A



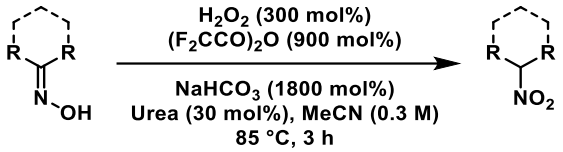
A round-bottom flask equipped with a magnetic stir bar was charged with mCPBA (85 wgt%, 400 mol%) and dichloroethane (0.5 M). The corresponding amine was added, and the reaction mixture was refluxed overnight. After reaching ambient temperature, the mixture was transferred to a separatory funnel. The organic layer was washed with saturated sodium bicarbonate, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting oily residue was subjected to flash column chromatography to give the nitroalkane.

General procedure for synthesis of oxime intermediate



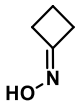
A round-bottom flask equipped with a magnetic stir bar was charged with $H_2NOH{\cdot}HCl$ (200 mol%), NaOAc (250 mol%), ethanol (2.0 M) and water (1.0 M). Ketone (100 mol%) was added, and the flask was placed in an oil bath at 85 °C and allowed to stir overnight. After reaching ambient temperature, the solid oxime was collected by filtration, washed with water and dried *in vacuo*. The resulting crystalline solid was subjected to next step without further isolations.

General procedure B



A freshly prepared solution of hydrogen peroxide (30 wgt% in water, 300 mol%) and trifluoroacetic anhydride (900 mol%) was added dropwise to a mixture of oxime (100 mol%), sodium bicarbonate (1800 mol%), urea (30 mol%) and acetonitrile (0.3 M). The resulting mixture was stirred at 85 °C for 3 h. The reaction mixture was cooled to room temperature and transferred to a separatory funnel. The organic layer was washed with saturated sodium bicarbonate, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting oily residue was subjected to flash column chromatography to give the nitroalkane.

Cyclobutanone oxime (4.2b-Oxime)



Procedures

The cyclobutanone (3 g, 43 mmol, 100 mol%) was subject to the reaction conditions for the oxime synthesis. The title compound was obtained in 85% yield (2.9 g, 34.4 mmol) as a light yellow solid.

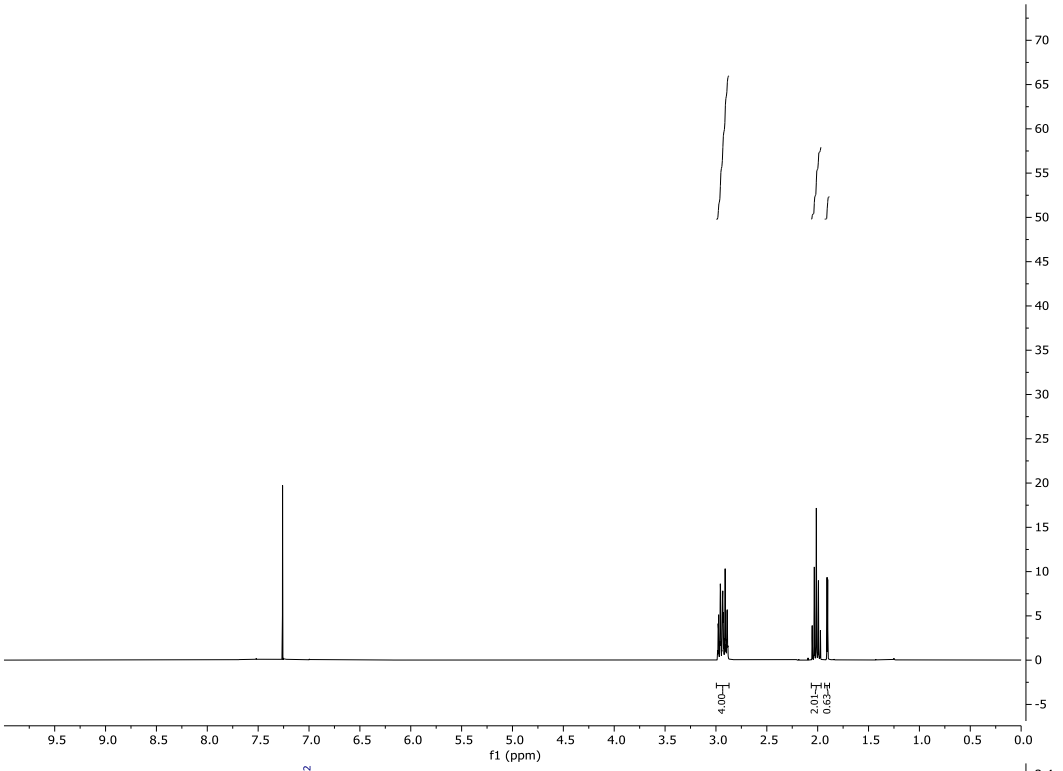
TLC (SiO_2) R_f = 0.3 (hexane : ethyl acetate = 5:1).

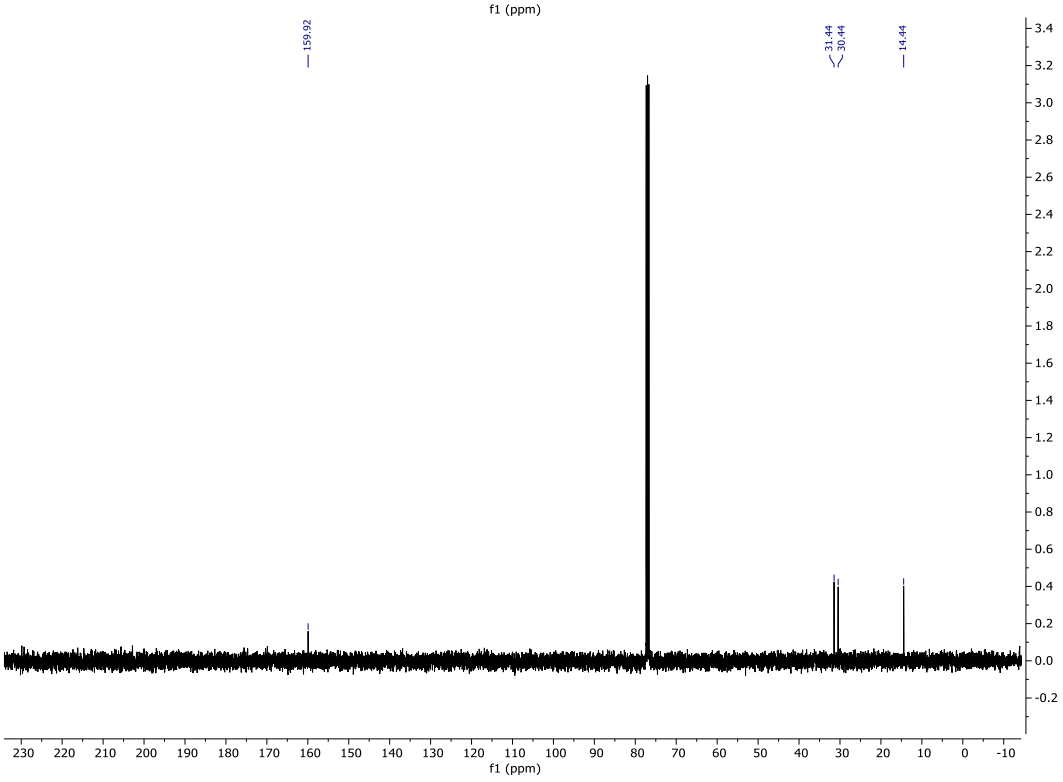
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.07 – 2.80 (m, 4H), 2.08 – 1.95 (m, 2H), 1.90 (d, J = 2.5 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 31.4, 30.4, 14.4 ppm.

HRMS (CI) m/z: [(M+H)]+] calcd for C_4H_8NO 86.0606, found 86.0608.

FTIR (Neat): 3123, 2881, 970, 934, 778, 721 cm^{-1}.


4.00
2.01
0.63
f1 (ppm)


159.92
31.44
30.44
14.44
f1 (ppm)

Nitrocyclobutane (4.2b)

Procedures

The cyclobutanone oxime **4.2b-Oxime (**680 mg, 8 mmol, 100 mol%) was subject to general procedure B. The title compound was obtained in 25% yield (200 mg, 2.0 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate = 30:1).

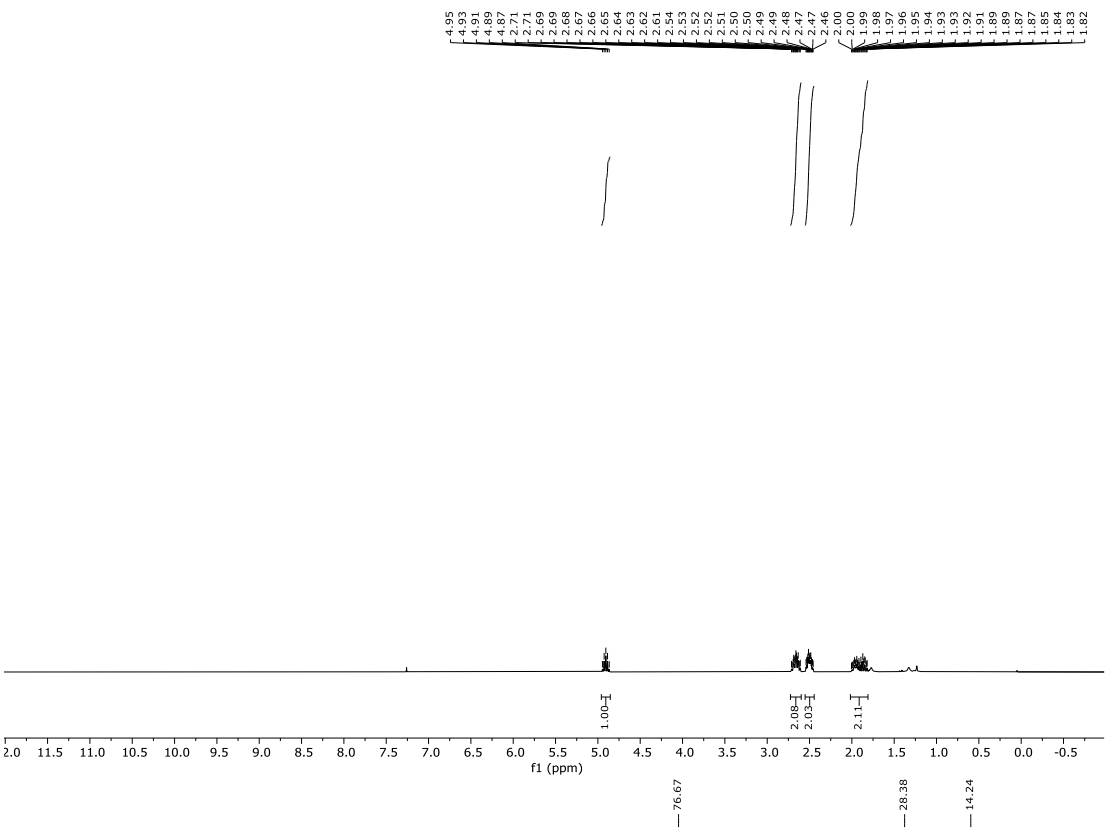
TLC (SiO_2) R_f = 0.6 (hexane: ethyl acetate = 5:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.91 (p, J = 8.0 Hz, 1H), 2.87 – 2.59 (m, 2H), 2.50 (tdd, J = 11.2, 8.1, 3.3 Hz, 2H), 2.07 – 1.80 (m, 2H) ppm.

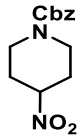
^{13}C NMR (100 MHz, $CDCl_3$): δ 76.7, 28.4, 14.2 ppm.

HRMS (Analyzed as the oxime) (CI) m/z: [(M+H)]+] calcd for C_4H_8NO 86.0606, found 86.0608.

FTIR (Neat): 1540, 1373, 1313, 1197, 912, 801, 732, 691 cm^{-1}.


4.95 4.93 4.91 4.89 4.87 2.71 2.71 2.69 2.69 2.68 2.67 2.66 2.65 2.64 2.63 2.62 2.61 2.54 2.53 2.52 2.52 2.51 2.50 2.50 2.49 2.49 2.48 2.47 2.47 2.46 2.00 2.00 1.99 1.98 1.97 1.96 1.95 1.94 1.93 1.93 1.92 1.91 1.89 1.89 1.87 1.87 1.85 1.84 1.83 1.82
1.00
2.08
2.03
2.11
f1 (ppm)
76.67
28.38
14.24
f1 (ppm)

Benzyl 4-nitropiperidine-1-carboxylate (4.2d)



Procedures

The benzyl 4-aminopiperidine-1-carboxylate (2.3 g, 10.0 mmol, 100 mol%) was subject to general procedure A. The title compound was obtained in 54% yield (1.4 g, 5.4 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate = 5:1).

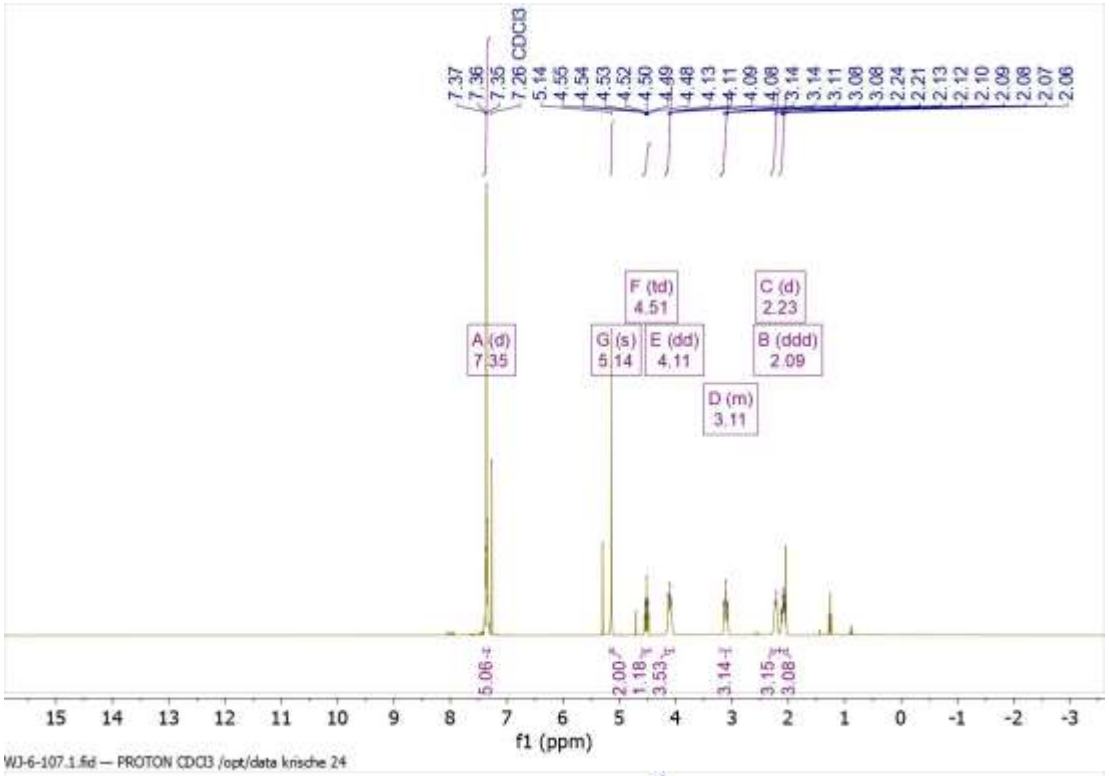
TLC (SiO_2) R_f = 0.24 (hexane: ethyl acetate = 4:1).

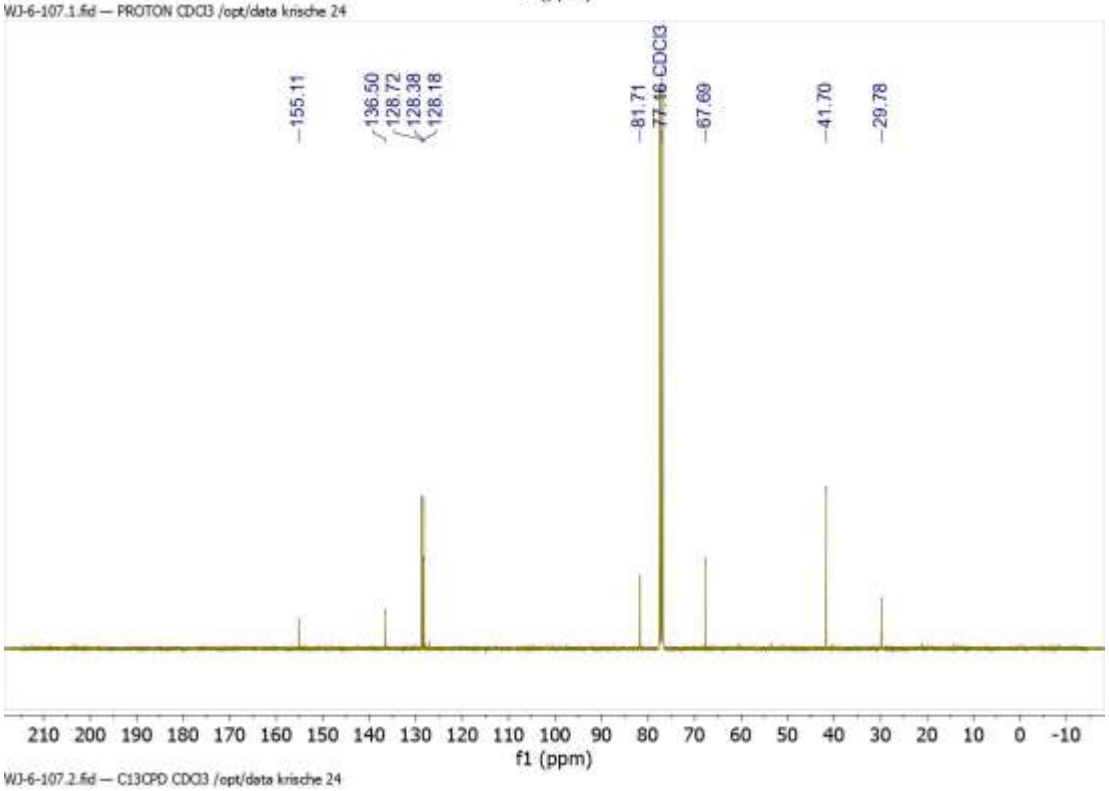
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 4.7 Hz, 5H), 5.14 (s, 2H), 4.51 (td, J = 9.9, 4.9 Hz, 1H), 4.11 (dd, J = 12.8, 5.6 Hz, 4H), 3.20 – 3.03 (m, 3H), 2.23 (d, J = 10.0 Hz, 3H), 2.09 (ddd, J = 13.2, 8.5, 3.8 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1, 136.5, 128.7, 128.4, 128.2, 81.7, 67.7, 41.7, 29.8 ppm.

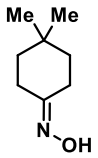
HRMS (ESI) m/z: [M-Na]+ calcd for C13H16N2O4 287.1002, found 287.0998.

FTIR (Neat): 2866, 1694, 1543, 1497, 1471, 1427, 1374, 1294, 1273, 1225, 1131, 1073, 1016, 914, 842, 763, 735, 697 cm^{-1}.


7.37
7.36
7.35
7.26 CDCl3
5.14
4.55
4.54
4.53
4.52
4.50
4.49
4.48
4.13
4.11
4.09
4.08
3.14
3.14
3.11
3.08
3.08
2.24
2.21
2.13
2.12
2.10
2.09
2.08
2.07
2.06
A (d) 7.35
G (s) 5.14
F (td) 4.51
E (dd) 4.11
D (m) 3.11
C (d) 2.23
B (ddd) 2.09
5.06
2.00
1.18
3.53
3.14
3.15
3.08
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)
WJ-6-107.1.fid — PROTON CDCl3 /opt/data krische 24


155.11
136.50
128.72
128.38
128.18
81.71
77.16 CDCl3
67.60
41.70
29.78
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)
WJ-6-107.2.fid — C13CPD CDCl3 /opt/data krische 24

4,4-Dimethylcyclohexan-1-one oxime (4.2e-Oxime)



Procedures

The cyclohexanone (2.5 g, 19.8 mmol, 100 mol%) was subject to the reaction conditions for the oxime synthesis. The title compound was obtained in 81% yield (2.3 g, 16.0 mmol) as a white solid.

TLC (SiO_2) R_f = 0.28 (hexane : ethyl acetate = 4:1)

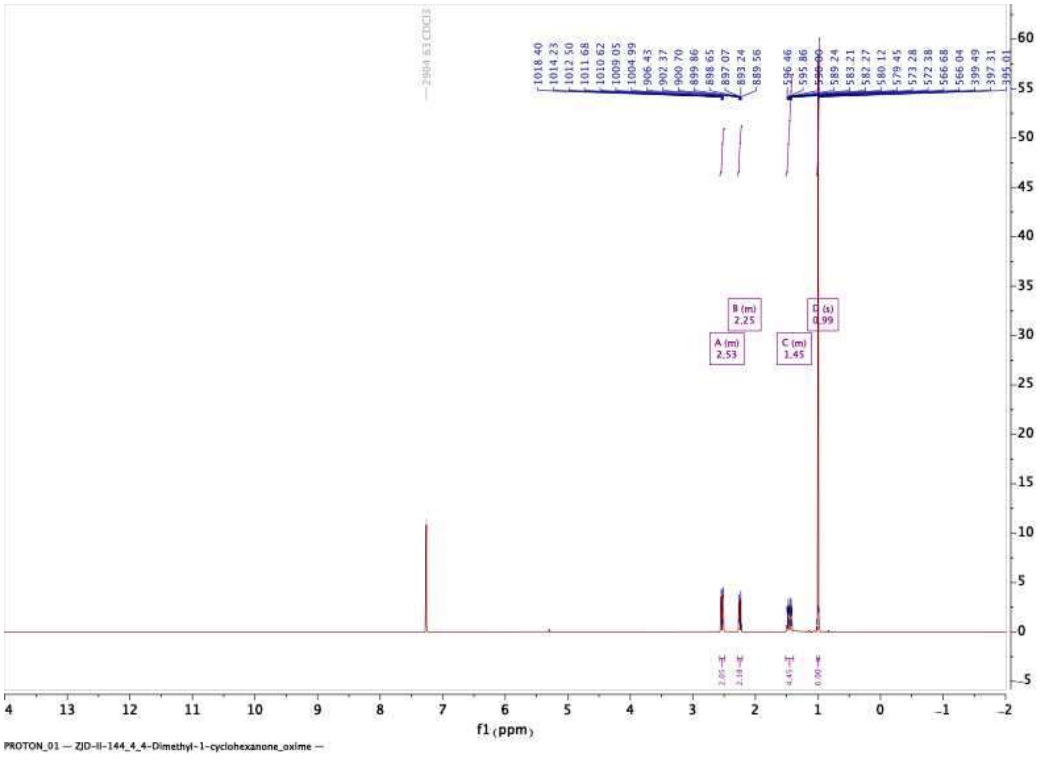
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.57 – 2.49 (m, 2H), 2.29 – 2.21 (m, 2H), 1.51 – 1.39 (m, 4H), 0.99 (s, 6H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 160.9, 53.6, 39.2, 38.0, 30.5, 28.2, 27.8, 20.7 ppm.

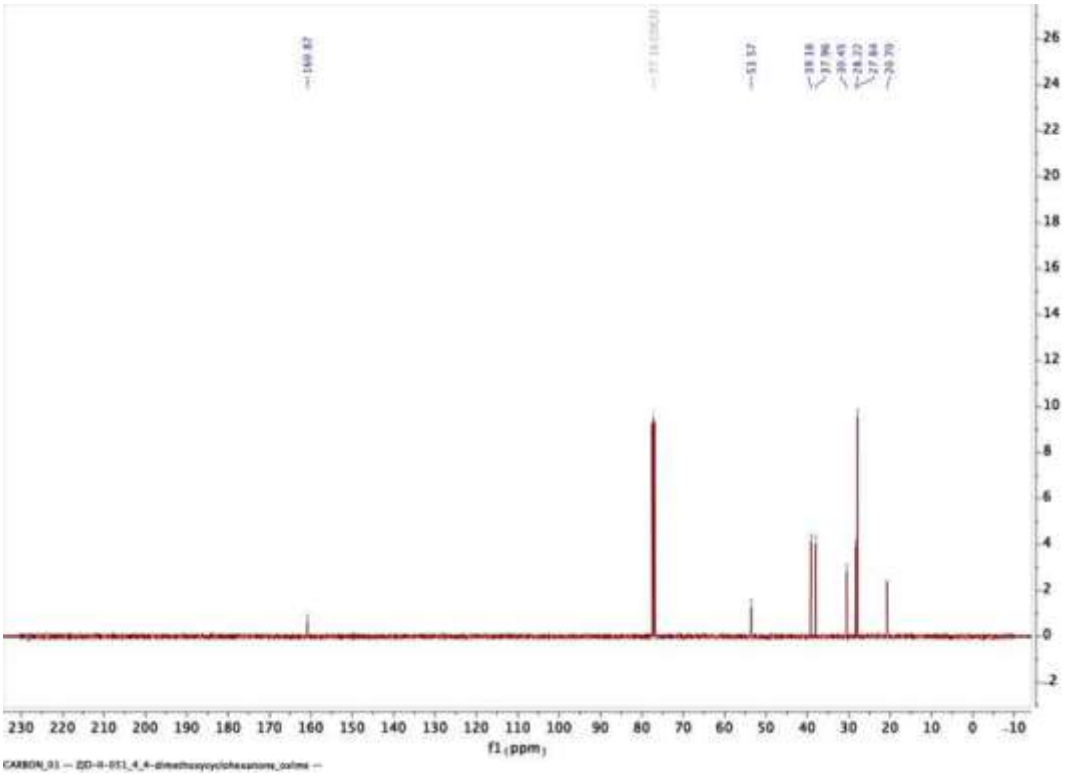
HRMS (ESI) m/z: [(M+H)+] calcd for $C_8H_{15}NO$ 142.1226, found 142.1229.

FTIR (Neat): 3193, 3099, 2950, 2915, 2848, 1662, 1472, 1444, 1386, 1364, 1338, 1235, 1166, 1142, 1017, 967, 942, 885, 780, 709, 685 cm^{-1}.

Melting Point 87 - 88 °C

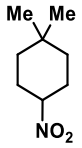


PROTON_01 — ZJD-II-144_4_4-Dimethyl-1-cyclohexanone_oxime —



CARBON_01 — ZJD-II-151_4_4-dimethoxycyclohexanone_oxime —

1,1-Dimethyl-4-nitrocyclohexane (4.2e)



Procedures

The 4,4-Dimethylcyclohexan-1one oxime **4.2e-oxime** (1 g, 7.1 mmol, 100 mol%) was subject to general procedure B. The title compound was obtained in 21% yield (235 mg, 1.49 mmol) as a colorless oil after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate 40 : 1).

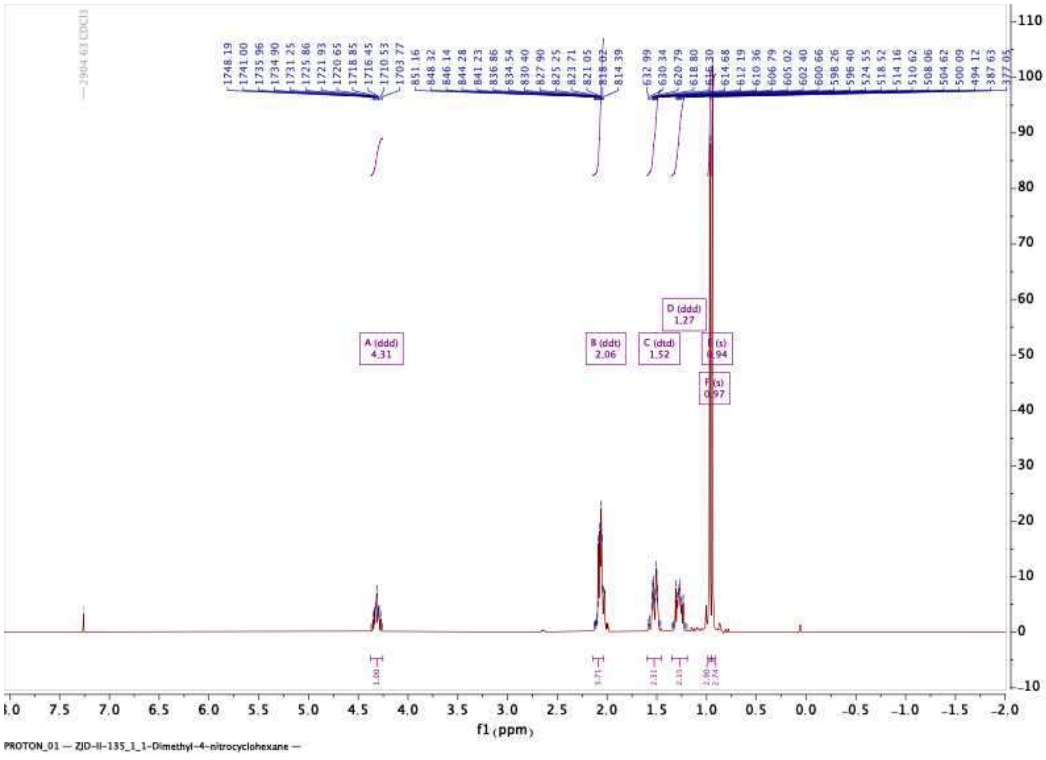
TLC (SiO_2) R_f = 0.83 (hexane : ethyl acetate = 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.31 (ddd, *J* = 15.3, 9.9, 6.0 Hz, 1H), 2.06 (ddt, *J* = 9.3, 6.7, 3.9 Hz, 4H), 1.52 (dtd, *J* = 14.0, 4.4, 1.9 Hz, 2H), 1.27 (ddd, *J* = 13.9, 10.4, 6.0 Hz, 2H), 0.97 (s, 3H), 0.94 (s, 3H) ppm.

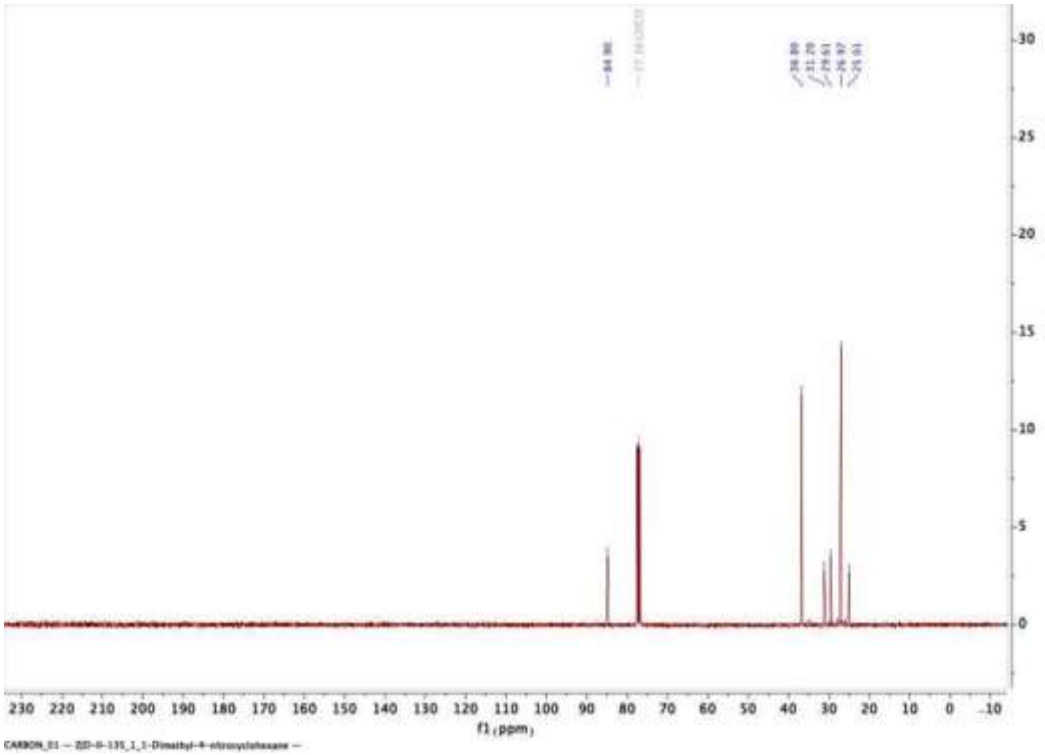
^{13}C NMR (101 MHz, $CDCl_3$): δ 84.9, 36.8, 31.2, 29.6, 27.0, 25.0 ppm.

HRMS (CI) m/z: [(M-NO_2)] calcd for C_8H_{15} 111.1174, found 111.1177.

FTIR (Neat): 2952, 1737, 1542, 1471, 1375, 1234, 1168, 1022, 994, 938, 837, 757 cm^{-1}.

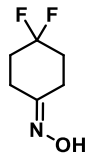


PROTON_01 — ZJD-II-135_1_1-Dimethyl-4-nitrocyclohexane —



CARBON_01 — ZJD-II-135_1_1-Dimethyl-4-nitrocyclohexane —

4,4-Difluorocyclohexan-1-one oxime (4.2f-Oxime)



Procedures

4,4-Difluorocyclohexan-1-one (15 mmol, 100 mol%) was subject to the reaction conditions for the oxime synthesis. The title compound was obtained in 72% yield (1.6 g, 10.8 mmol) as a white solid.

TLC (SiO_2) R_f = 0.77 (hexane : ethyl acetate = 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.7 (t, *J* = 7.0 Hz, 2H), 2.5 (td, *J* = 6.8, 1.3 Hz, 2H), 2.3 – 2.0 (m, 4H) ppm.

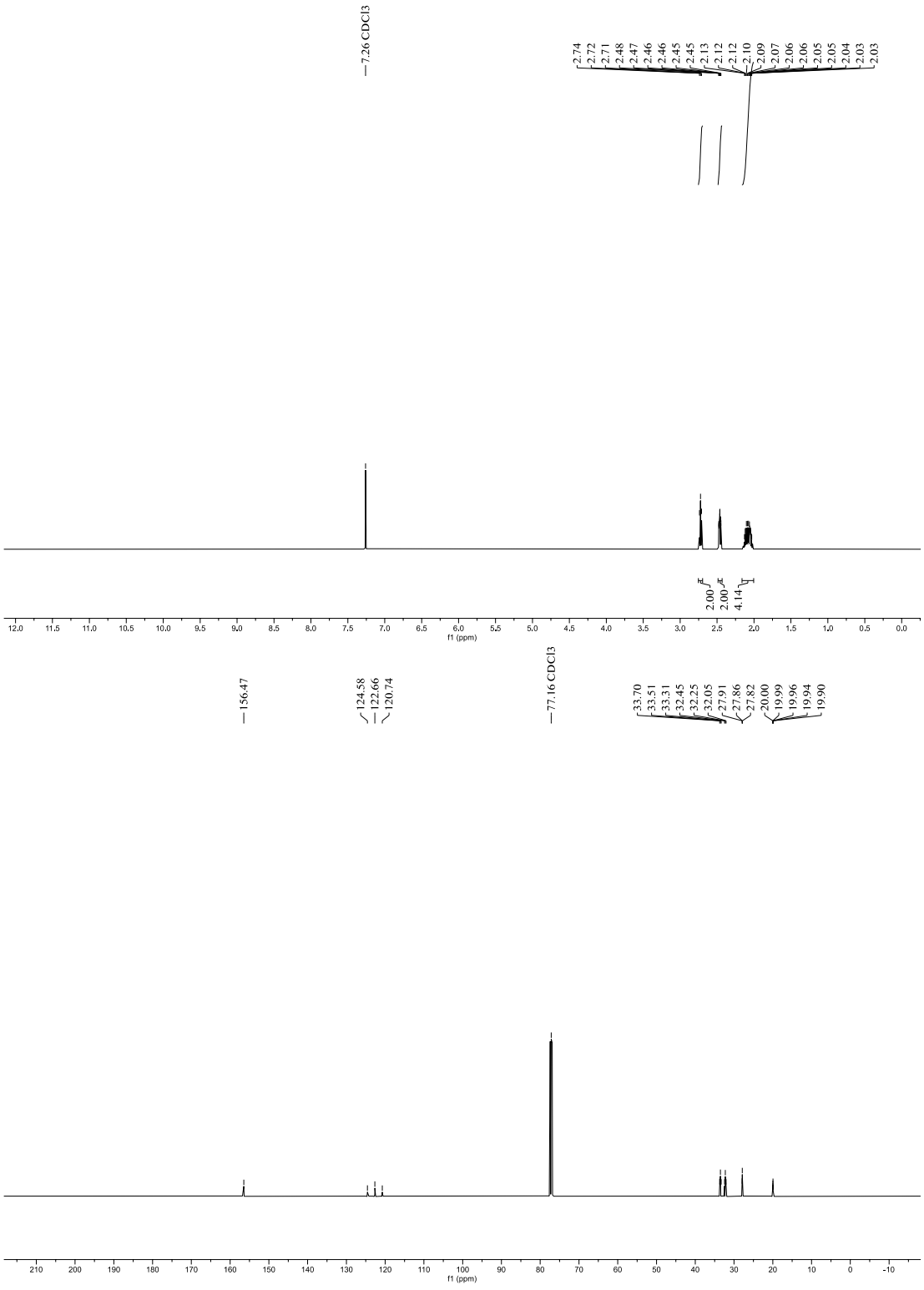
^{13}C NMR (100 MHz, $CDCl_3$): δ 156.5, 122.7 (t, *J* = 241.4 Hz), 33.5 (t, *J* = 24.8 Hz), 32.2 (t, *J* = 25.2 Hz), 27.9 (t, *J* = 5.4 Hz), 20.0 (dt, *J* = 7.0, 3.4 Hz) ppm.

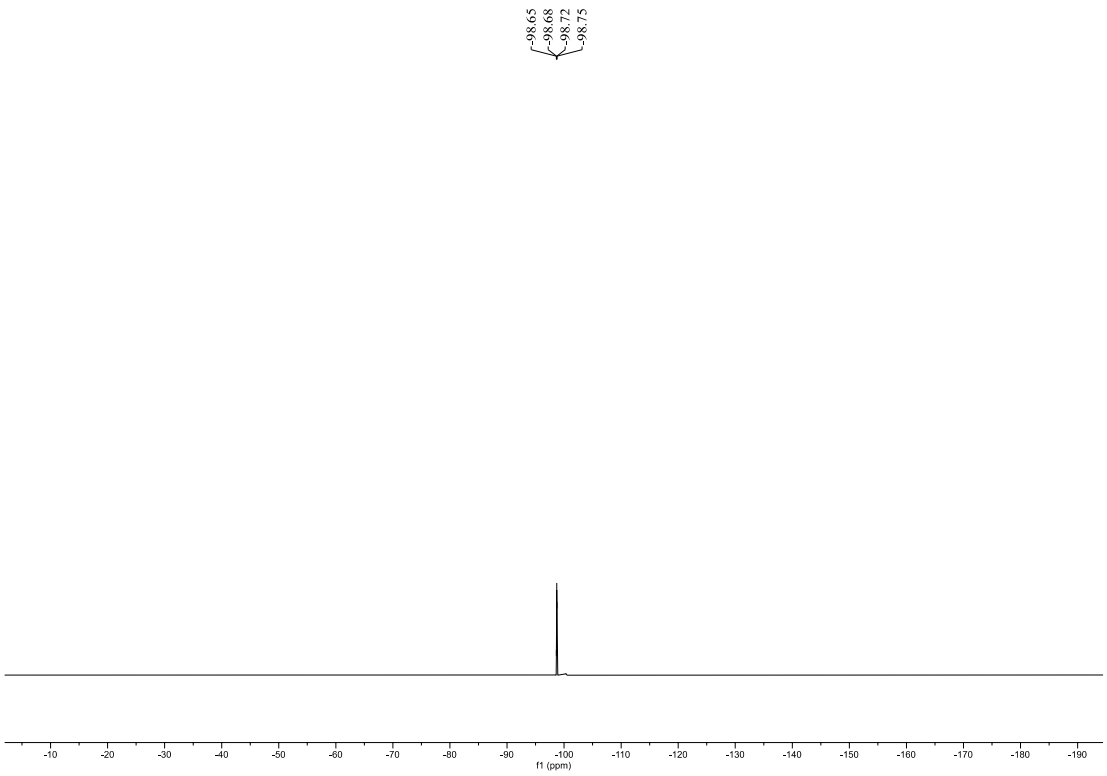
^{19}F NMR (376 MHz, $CDCl_3$): δ -98.6 – -98.8 (q) ppm.

HRMS (ESI) m/z: [(M+H)]+] calcd for $C_6H_9F_2NO$ 150.0725, found 150.0727.

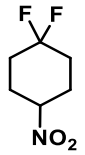
FTIR (Neat): 3186, 1669, 1396, 1092, 951, 928 cm^{-1}.

M.P 111-115 ^oC


7.26 CDCl3
2.74
2.72
2.71
2.48
2.47
2.46
2.46
2.45
2.45
2.13
2.12
2.12
2.10
2.09
2.07
2.06
2.06
2.05
2.05
2.04
2.03
2.03
2.00
2.00
4.14
f1 (ppm)
156.47
124.58
122.66
120.74
77.16 CDCl3
33.70
33.51
33.31
32.45
32.25
32.05
27.91
27.86
27.82
20.00
19.99
19.96
19.94
19.90
f1 (ppm)


-98.65
-98.68
-98.72
-98.75
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

1,1-Difluoro-4-nitrocyclohexane (4.2f)



Procedures

The 4,4-difluorocyclohexan-1-one oxime **4.2f-Oxime** (1.90 g, 12.75 mmol, 100 mol%) was subject to general procedure B. The title compound was obtained in 21% yield (435 mg, 2.64 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate = 100:1–10:1).

TLC (SiO_2) R_f = 0.54 (hexane: ethyl Acetate = 10:1)

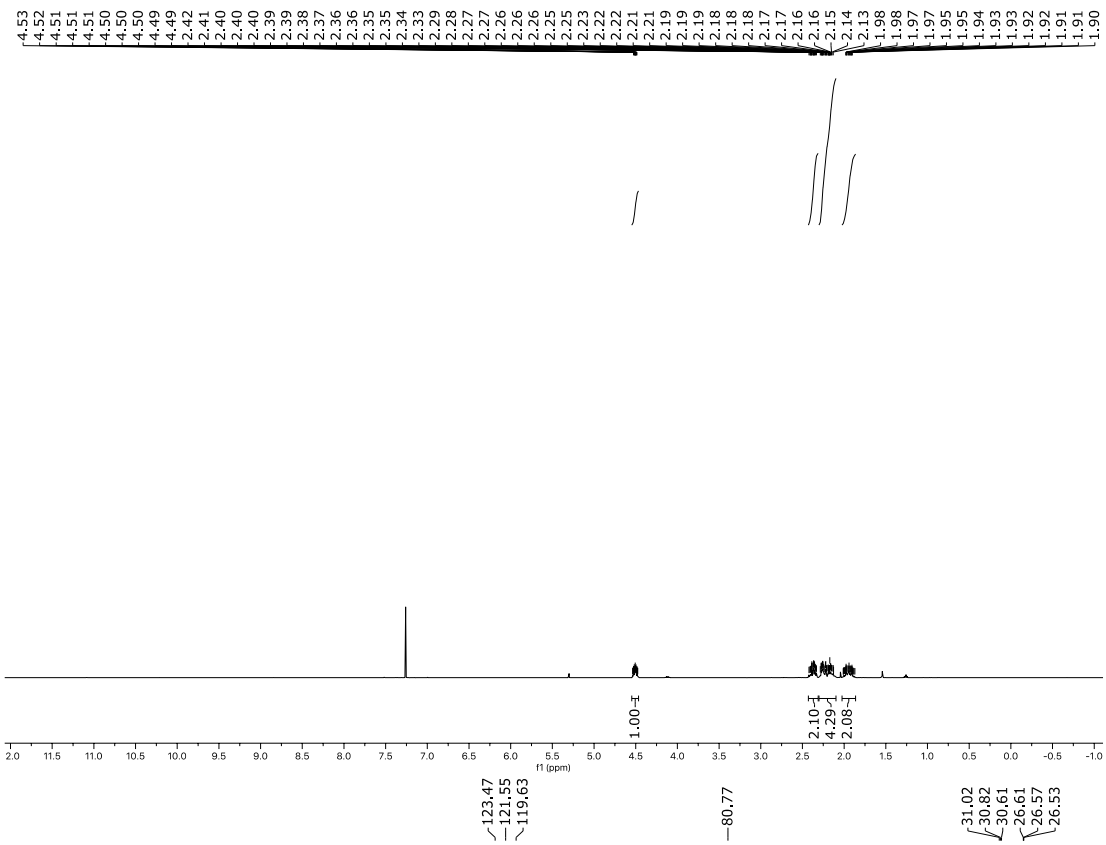
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.51 (tddd, *J* = 8.3, 4.2, 2.7, 1.4 Hz, 1H), 2.49 – 2.30 (m, 3H), 2.29 – 2.08 (m, 5H), 2.03 – 1.83 (m, 2H) ppm.

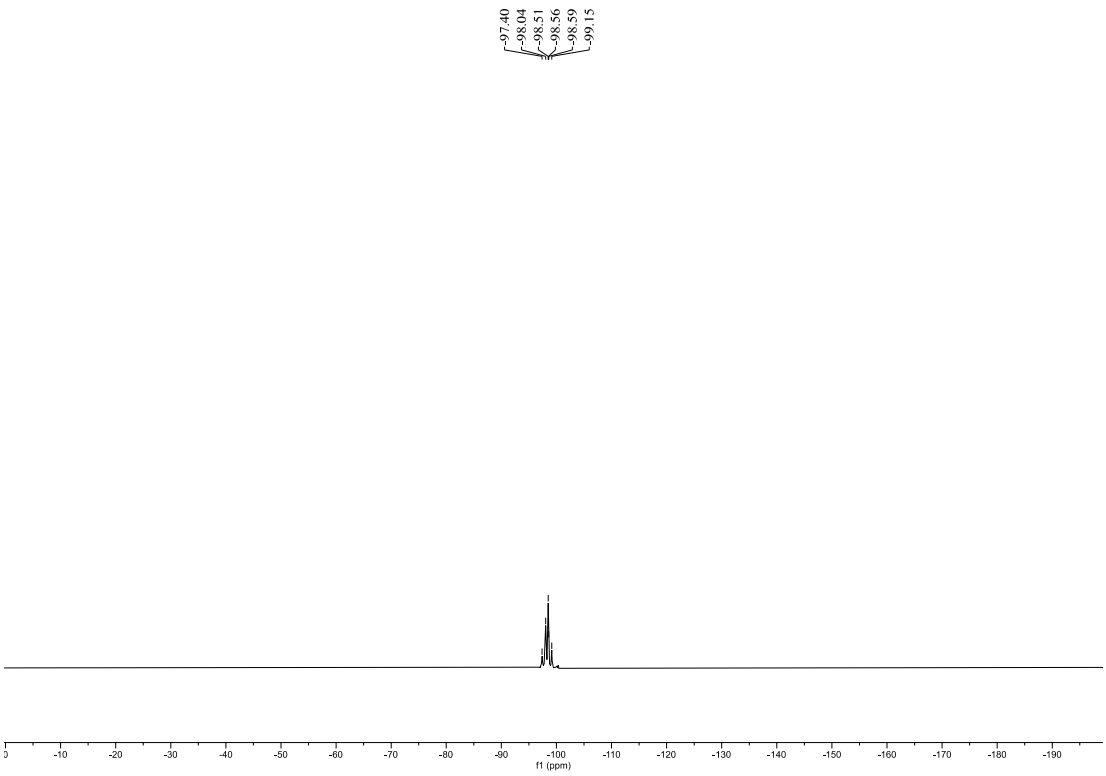
^{13}C NMR (126 MHz, $CDCl_3$): δ 121.5 (t, *J* = 241.8 Hz), 80.8, 30.8 (t, *J* = 25.5 Hz), 26.6 (t, *J* = 5.2 Hz) ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ -96.8 – -99.4 (q) ppm.

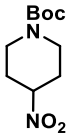
HRMS (Analyzed as the oxime) (ESI) m/z: [(M+H)]+] calcd for $C_6H_9F_2NO$ 150.0725, found 150.0727.

FTIR (Neat): 2954, 1545, 1187, 1111, 955 cm^{-1}.


4.53 4.52 4.51 4.51 4.51 4.50 4.50 4.50 4.49 4.49 4.42 2.41 2.40 2.40 2.40 2.39 2.39 2.38 2.37 2.36 2.36 2.35 2.35 2.34 2.33 2.29 2.28 2.27 2.27 2.26 2.26 2.26 2.25 2.25 2.23 2.22 2.22 2.21 2.21 2.19 2.19 2.19 2.18 2.18 2.18 2.17 2.16 2.16 2.15 2.14 2.13 1.98 1.98 1.97 1.97 1.95 1.95 1.94 1.93 1.93 1.92 1.92 1.91 1.91 1.90
1.00
2.10
4.29
2.08
f1 (ppm)
123.47
121.55
119.63
80.77
31.02
30.82
30.61
26.61
26.57
26.53
f1 (ppm)


-97.40
-98.04
-98.51
-98.56
-98.59
-99.15
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

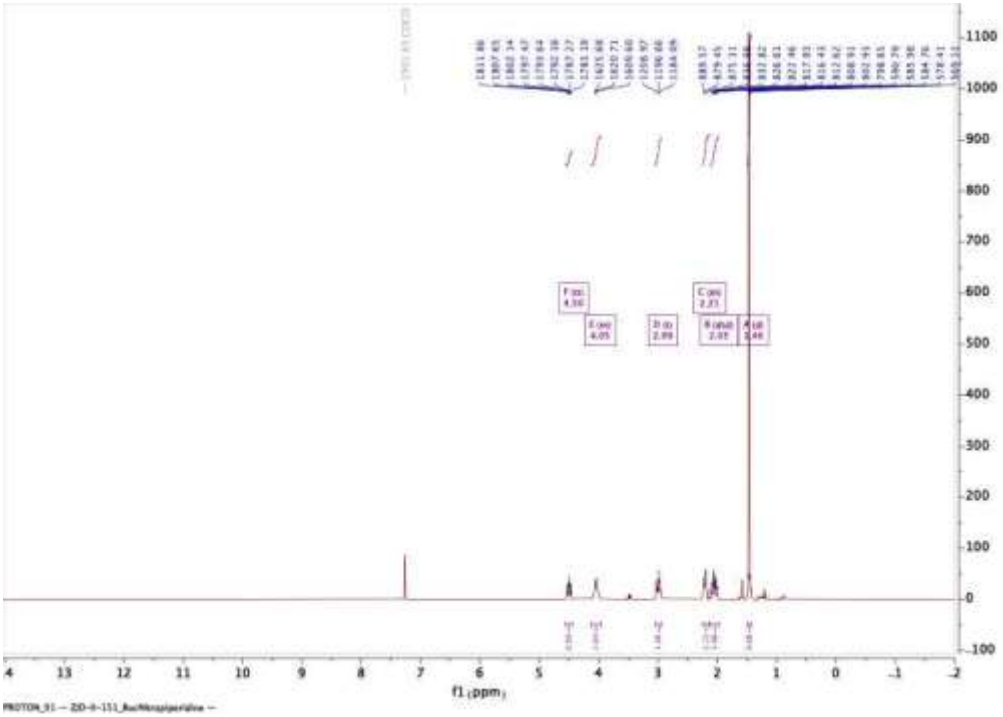
***tert*-Butyl 4-nitropiperidine-1-carboxylate (4.2g)**



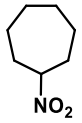
Procedures

tert-Butyl 4-aminopiperidine-1-carboxylate (2 g, 10 mmol, 100 mol%) was subject to general procedure A. The title compound was obtained in 19% yield (434 mg, 1.9 mmol) as a colorless oil after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate 20 : 1). Spectral data are consistent with reported literature.[33]

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.50 (tt, *J* = 9.2, 4.1 Hz, 1H), 4.13 – 3.96 (m, 2H), 2.99 (t, *J* = 12.4 Hz, 2H), 2.25 – 2.12 (m, 2H), 2.05 (dtd, *J* = 14.0, 10.3, 4.2 Hz, 2H), 1.46 (d, *J* = 1.2 Hz, 9H) ppm.



Nitrocycloheptane (4.2h)

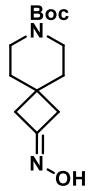


Procedures

Cycloheptylamine (1.70 g, 15.0 mmol, 100 mol%) was subject to general procedure A. The title compound was obtained in 75% yield (1.62 g, 11.3 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate = 10:1). Spectral data are consistent with reported literature.[11]

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.57 (tt, J = 9.3, 4.8 Hz, 1H), 2.28 – 2.17 (m, 2H), 2.15 – 2.04 (m, 2H), 1.80 (dddtd, J = 14.1, 7.7, 4.3, 3.2, 1.7 Hz, 2H), 1.59 (dddd, J = 6.7, 5.3, 4.3, 3.3 Hz, 4H), 1.55 – 1.45 (m, 2H) ppm.

***tert*-Butyl 2-(hydroxyimino)-7-azaspiro[3.5]nonane-7-carboxylate (4.2i-Oxime)**



Procedures

2-Oxo-7-azaspiro[3.5]nonane-7-carboxylate *tert*-butyl ester (4.79 g, 20.0 mmol, 100 mol%) was subject to the reaction conditions for the oxime synthesis. The title compound was obtained in 99% yield (5.0 g, 20.0 mmol) as a white solid.

TLC (SiO_2) R_f = 0.27 (hexane: ethyl acetate = 1:1)

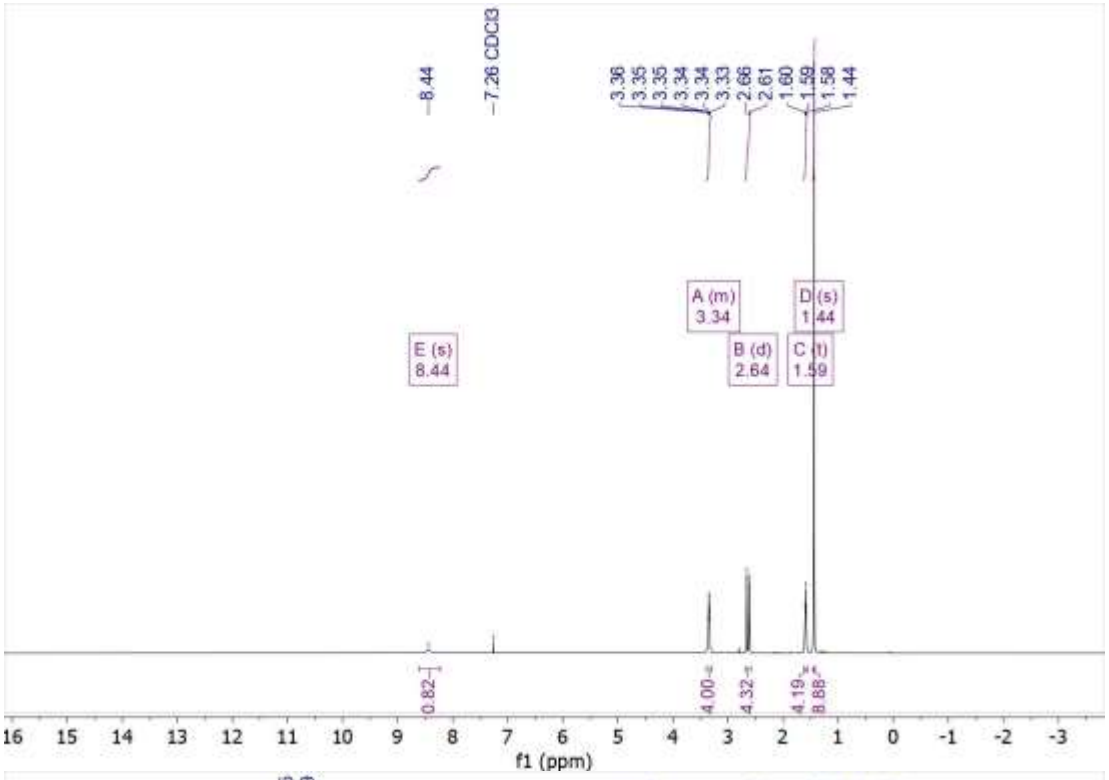
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (s, 1H), 3.39 – 3.30 (m, 4H), 2.64 (d, J = 23.6 Hz, 4H), 1.59 (t, J = 5.5 Hz, 4H), 1.44 (s, 9H) ppm.

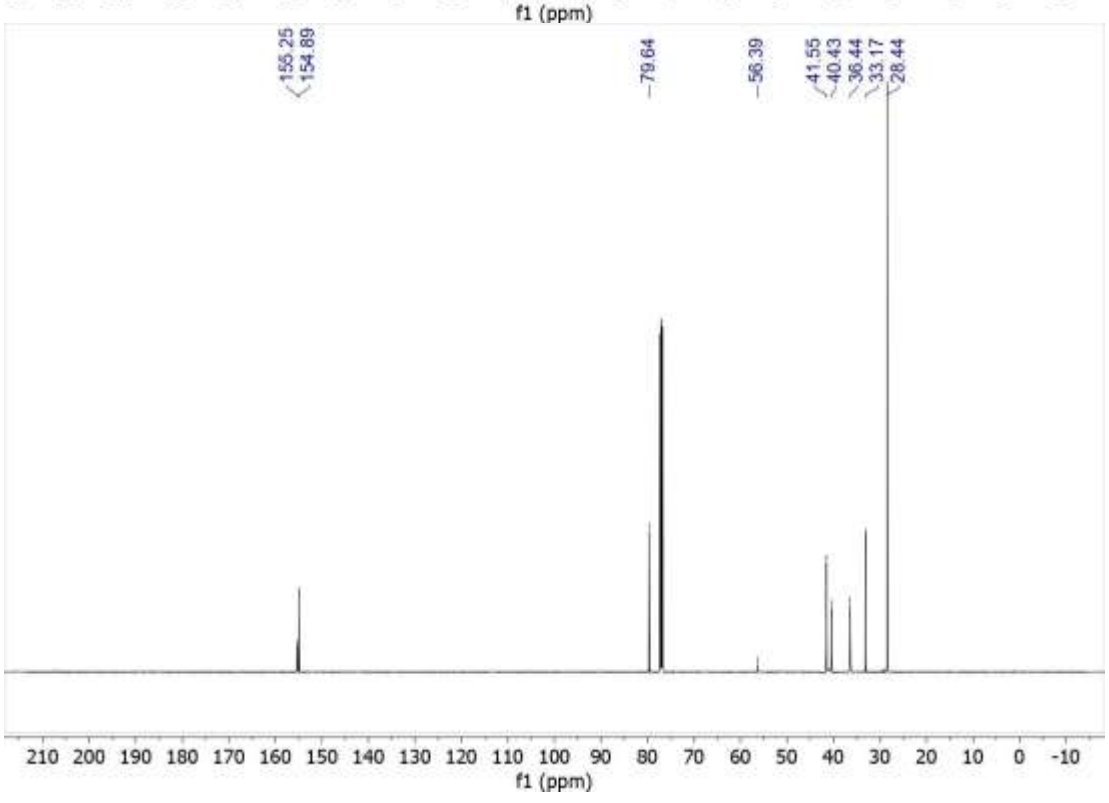
^{13}C NMR (126 MHz, $CDCl_3$) δ 155.3, 154.9, 79.6, 56.4, 41.6, 40.4, 36.4, 33.2, 28.4 ppm.

HRMS (ESI) m/z: [M-Cl]+ calcd for $C_{13}H_{22}N_2O_3$ 254.1630, found 254.1628.

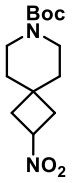
FTIR (Neat): 2972, 2915, 1681, 1409, 1362, 1268, 1241, 1211, 1170, 1099, 991, 904, 770, 725 cm^{-1}.

Melting Point 124 - 125 °C


8.44
7.26 CDCl3
3.36
3.35
3.35
3.34
3.34
3.33
2.66
2.61
1.60
1.59
1.58
1.44
A (m)
3.34
D (s)
1.44
m (s)
8.44
B (d)
2.64
C (t)
1.59
0.82
4.00
4.32
4.19
8.88
f1 (ppm)


155.25
154.89
79.64
56.39
41.55
40.43
36.44
33.17
28.44
f1 (ppm)

tert-Butyl 2-nitro-7-azaspiro[3.5]nonane-7-carboxylate (4.2i)



Procedures

tert-Butyl 2-(hydroxyimino)-7-azaspiro[3.5]nonane-7-carboxylate **4.2i-Oxime** (2.03 g, 8.0 mmol, 100 mol%) was subject to general procedure B. The title compound was obtained in 56% yield (1.2 g, 4.5 mmol) as a white solid after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate = 10:1).

TLC (SiO_2) R_f = 0.48 (hexane: ethyl acetate = 2:1)

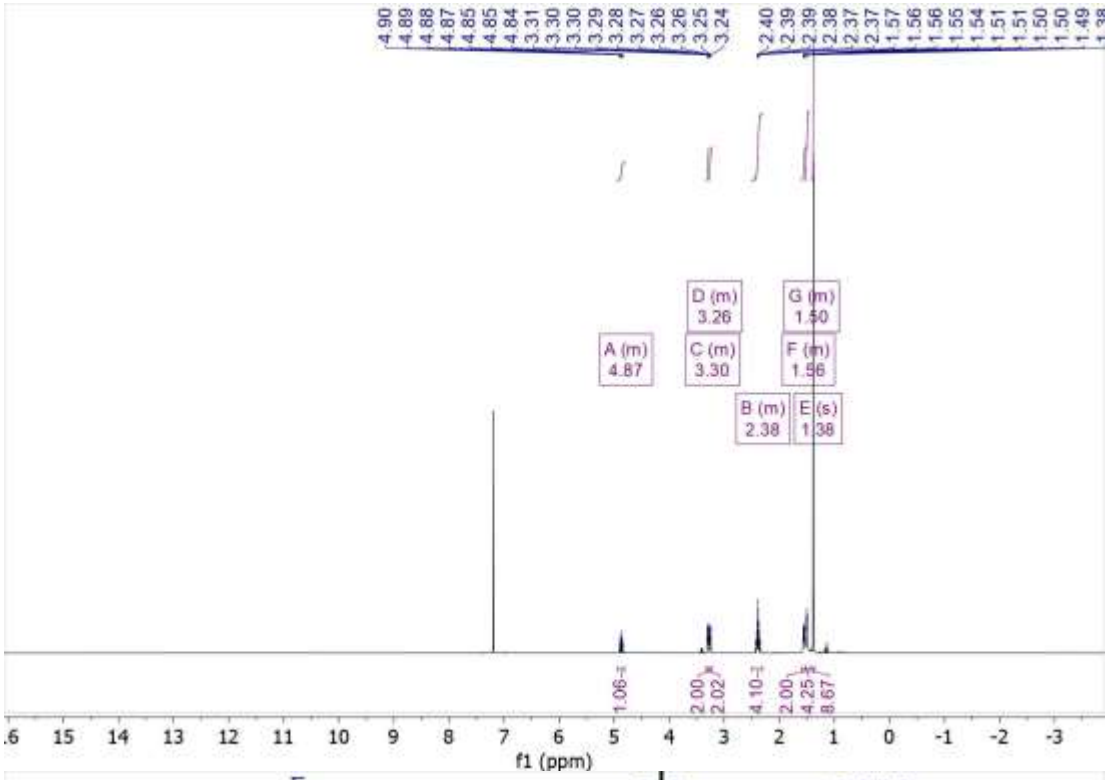
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.94 – 4.81 (m, 1H), 3.33 – 3.28 (m, 2H), 3.28 – 3.22 (m, 2H), 2.49 – 2.31 (m, 4H), 1.60 – 1.53 (m, 2H), 1.53 – 1.46 (m, 4H), 1.38 (s, 9H) ppm.

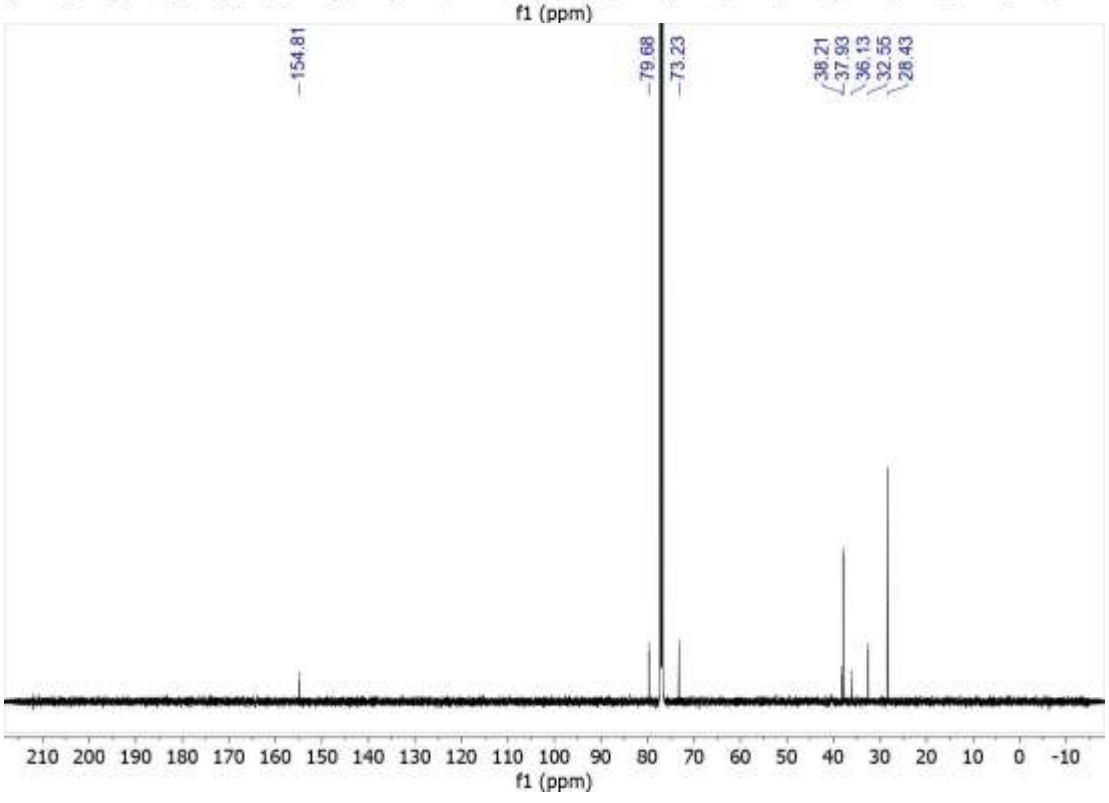
^{13}C NMR (126 MHz, $CDCl_3$) δ 154.8, 79.7, 73.2, 38.2, 37.9, 36.1, 32.6, 28.4 ppm.

HRMS (ESI) m/z: [M-Cl]+ calcd for $C_{13}H_{21}N_2O_4$ 269.1501, found 269.1501.

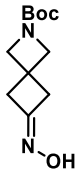
FTIR (Neat): 2976, 2927, 2860, 1783, 1672, 1532, 1423, 1363, 1242, 1146, 1116, 963, 856, 769 cm^{-1}.

Melting Point 114 - 116 °C


4.90
4.89
4.88
4.87
4.85
4.85
4.84
3.31
3.30
3.30
3.29
3.28
3.27
3.26
3.26
3.25
3.24
2.40
2.39
2.39
2.38
2.37
2.37
1.57
1.56
1.56
1.55
1.54
1.51
1.51
1.50
1.50
1.49
A (m)
4.87
D (m)
3.26
C (m)
3.30
G (m)
1.50
F (m)
1.56
B (m)
2.38
E (s)
1.38
1.06
2.00
2.02
4.10
2.00
4.25
8.67
f1 (ppm)


154.81
79.68
73.23
38.21
37.93
36.13
32.55
28.43
f1 (ppm)

***tert*-Butyl 6-(hydroxyimino)-2-azaspiro[3.3]heptane-2-carboxylate (4.2j-Oxime)**



Procedures

tert-Butyl 6-oxo-2-azaspiro[3.3]heptane-2-carboxylate (3.17 g, 15.0 mmol, 100 mol%) was subject to the reaction conditions for the oxime synthesis. The title compound was obtained in 99% yield (3.9 g, 15.0 mmol) as a white solid.

TLC (SiO_2) R_f = 0.14 (hexane: ethyl acetate = 2:1)

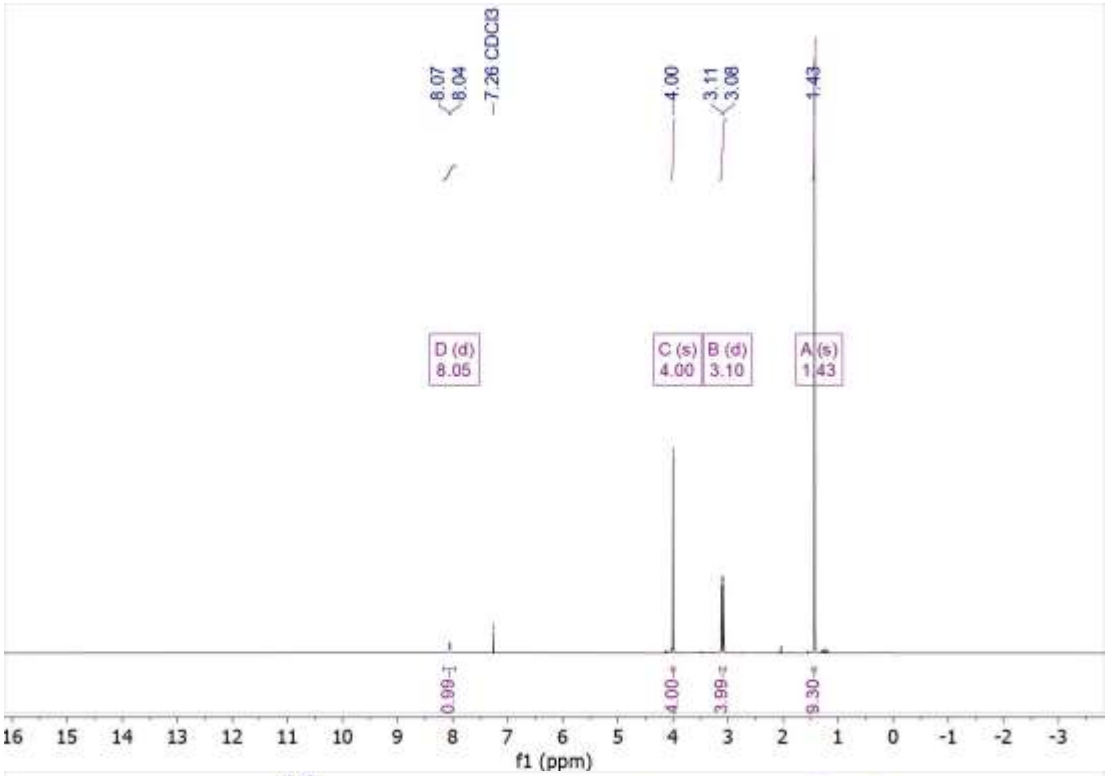
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, J = 13.8 Hz, 1H), 4.00 (s, 4H), 3.10 (d, J = 16.0 Hz, 4H), 1.43 (s, 9H) ppm.

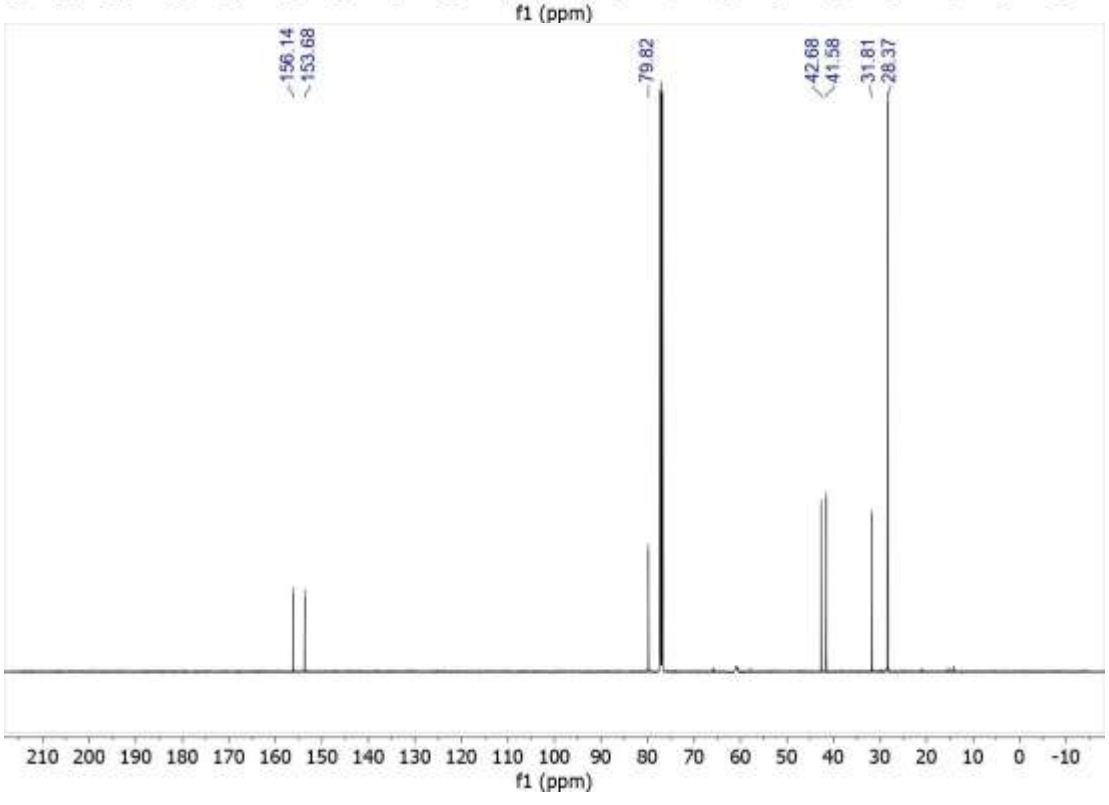
^{13}C NMR (126 MHz, $CDCl_3$) δ 156.1, 153.7, 79.8, 42.7, 41.6, 31.8, 28.4 ppm.

HRMS (ESI) m/z: [M-Cl]+ calcd for $C_{11}H_{18}N_2O_3$ 226.1317, found 226.1318.

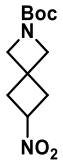
FTIR (Neat): 2972, 2919, 2879, 1683, 1463, 1411, 1387, 1362, 1312, 1268, 1253, 1230, 1157, 1096, 936, 921, 901, 858, 768, 748, 699 cm^{-1}.

Melting Point 157 - 159 °C


8.07
8.04
7.26 CDCl3
4.00
3.11
3.08
1.43
D (d)
8.05
C (s)
4.00
B (d)
3.10
A (s)
1.43
0.99
4.00
3.99
9.30
f1 (ppm)


156.14
153.68
79.82
42.68
41.58
31.81
28.37
f1 (ppm)

***tert*-Butyl 6-nitro-2-azaspiro[3.3]heptane-2-carboxylate (4.2j)**



Procedures

tert-Butyl 6-(hydroxyimino)-2-azaspiro[3.3]heptane-2-carboxylate **4.2j-Oxime** (1.81 g, 8.0 mmol, 100 mol%) was subject to general procedure B. The title compound was obtained in 28% yield (545 mg, 2.25 mmol) as a white solid after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate = 4:1).

TLC (SiO_2) R_f = 0.14 (hexane: ethyl acetate = 2:1)

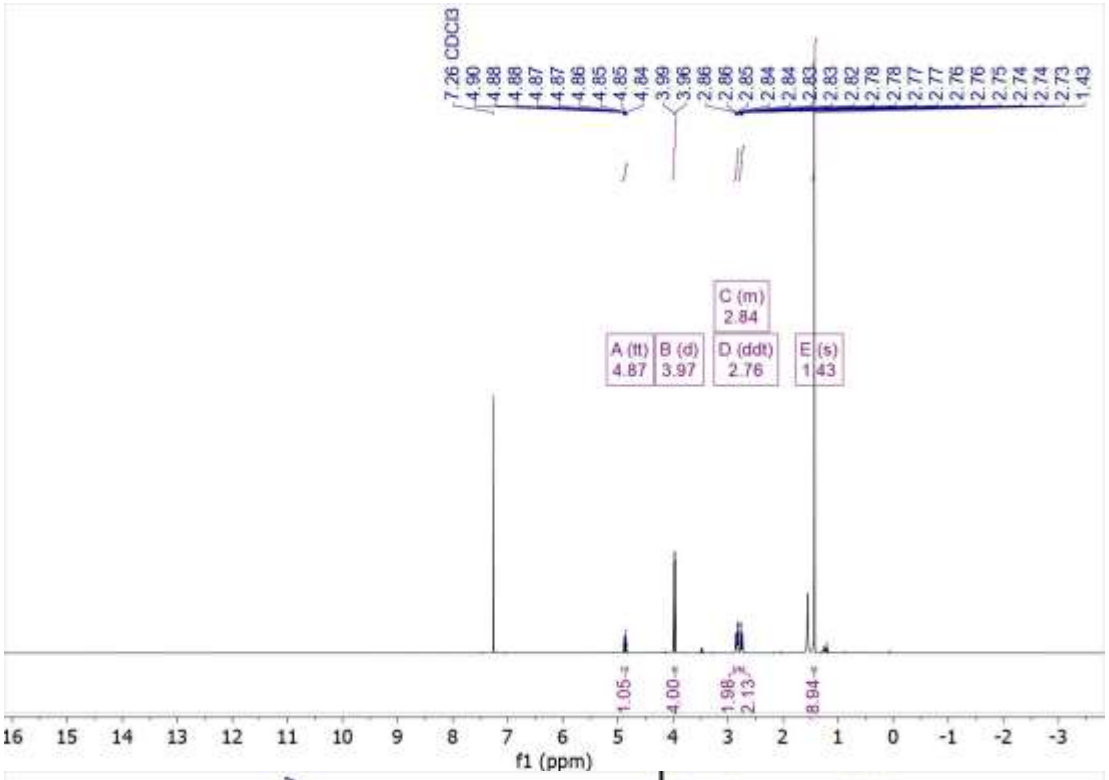
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.87 (tt, J = 8.0, 6.8 Hz, 1H), 3.97 (d, J = 15.8 Hz, 4H), 2.90 – 2.80 (m, 2H), 2.76 (ddt, J = 10.8, 8.0, 2.3 Hz, 2H), 1.43 (s, 9H) ppm.

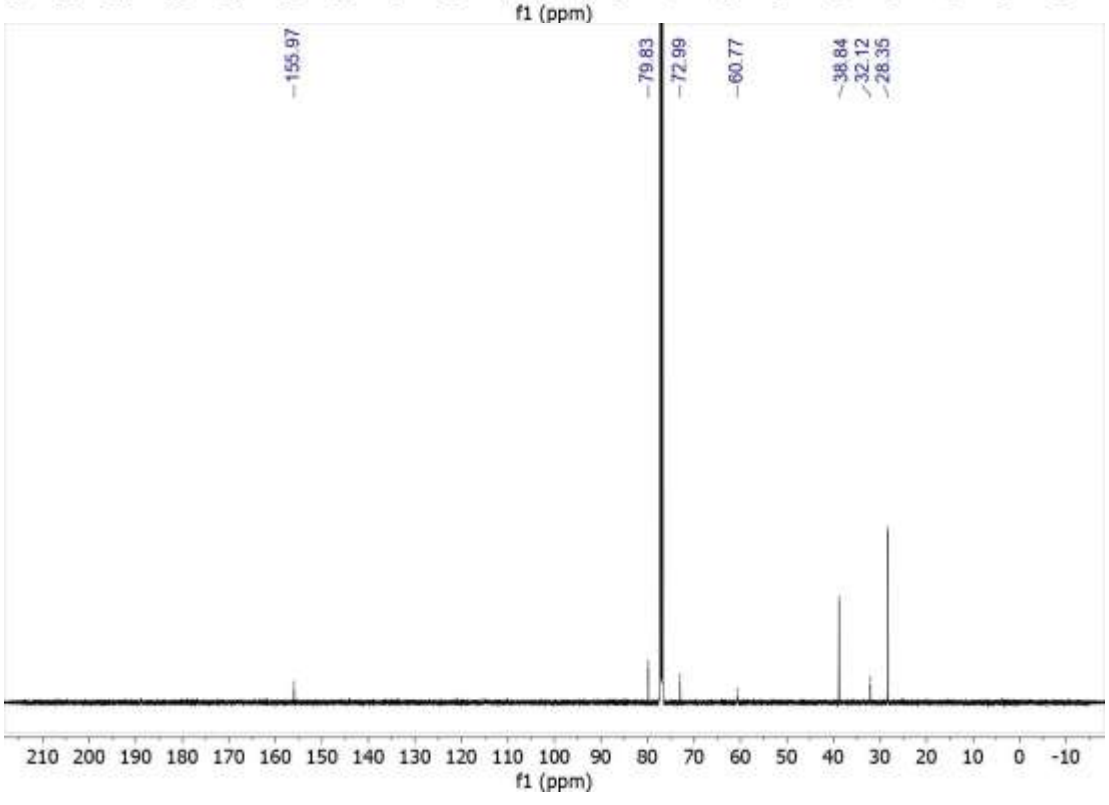
^{13}C NMR (126 MHz, $CDCl_3$) δ 156.0, 79.8, 73.0, 60.8, 38.8, 32.1, 28.4 ppm.

HRMS (ESI) m/z: [M-Cl]+ calcd for $C_{11}H_{18}N_2O_4$ 242.1267, found 242.1266.

FTIR (Neat): 2975, 2878, 1785, 1682, 1526, 1461, 1481, 1393, 1362, 1312, 1273, 1251, 1164, 1136, 1099, 929, 855, 788, 772, 757, 692 cm^{-1}.

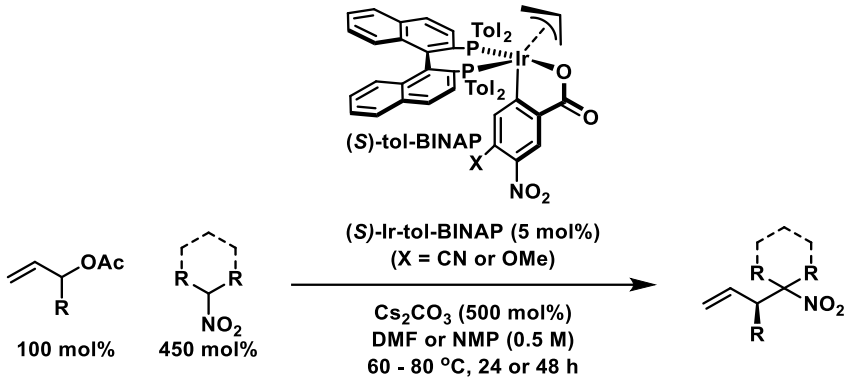
Melting Point 100 - 103 °C


7.26 CDCl3
4.90
4.88
4.88
4.87
4.87
4.86
4.85
4.85
4.84
3.99
3.96
2.86
2.86
2.85
2.84
2.84
2.83
2.83
2.82
2.78
2.78
2.77
2.77
2.76
2.76
2.75
2.74
2.74
2.73
1.43
C (m)
2.84
A (tt)
4.87
B (d)
3.97
D (ddt)
2.76
E (s)
1.43
1.05
4.00
1.98
2.13
8.94
f1 (ppm)


155.97
79.83
72.99
60.77
38.84
32.12
28.35
f1 (ppm)

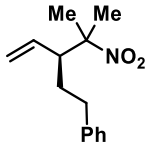
4.5.5 Procedures and Spectral Data for the Products 4.3a-4.3x

General Procedure



A pressure tube equipped with a magnetic stir bar was charged with cesium carbonate (500 mol%) and (*S*)-Ir-tol-BINAP (5 mol%). The reaction vessel was purged with argon. DMF or NMP (0.5 M) was added followed by the allylic acetate (100 mol%) and nitroalkane (450 mol%). The tube was sealed with a PTFE lined cap and was placed in an oil bath at 60 - 80 °C and stirred for 24 - 48 hours. After reaching ambient temperature, the crude reaction mixture was directly subjected to flash column chromatography.

(*S*)-(3-(2-Nitropropan-2-yl)pent-4-en-1-yl)benzene (4.3a)



Procedure

Allylic acetate **4.1a** (40.9 mg, 0.2 mmol, 100 mol%) and 2-nitropropane **4.2a** (80 µL, 0.9 mmol, 450 mol%) were subject to standard reaction conditions (DMF, 80 °C, 24 h). The title compound was obtained in 71% yield (33.2 mg, 0.14 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate = 20:1–10:1).

TLC (SiO_2) R_f = 0.73 (hexane : ethyl acetate = 1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 3H), 7.25 – 7.09 (m, 6H), 5.69 – 5.47 (m, 1H), 5.29 (dd, J = 10.4, 1.9 Hz, 1H), 5.19 (dd, J = 16.8, 1.7 Hz, 1H), 2.66 (td, J = 7.5, 4.1 Hz, 4H), 2.54 (d, J = 7.3 Hz, 2H), 2.34 (q, J = 7.5 Hz, 2H), 1.50 (s, 7H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.5, 141.4, 135.7, 135.50, 133.9, 128.4, 128.4, 128.3, 126.0, 126.0, 125.9, 123.3, 122.4, 120.8, 91.25, 88.1, 52.6, 43.9, 38.3, 35.7, 35.6, 34.2, 33.6, 30.8, 29.4, 25.5, 25.4, 24.6, 22.3 ppm.

HRMS (ESI) m/z: [(M+Na)+] calcd for $C_{14}H_{19}NO_2$ 256.1308, found 256.1310.

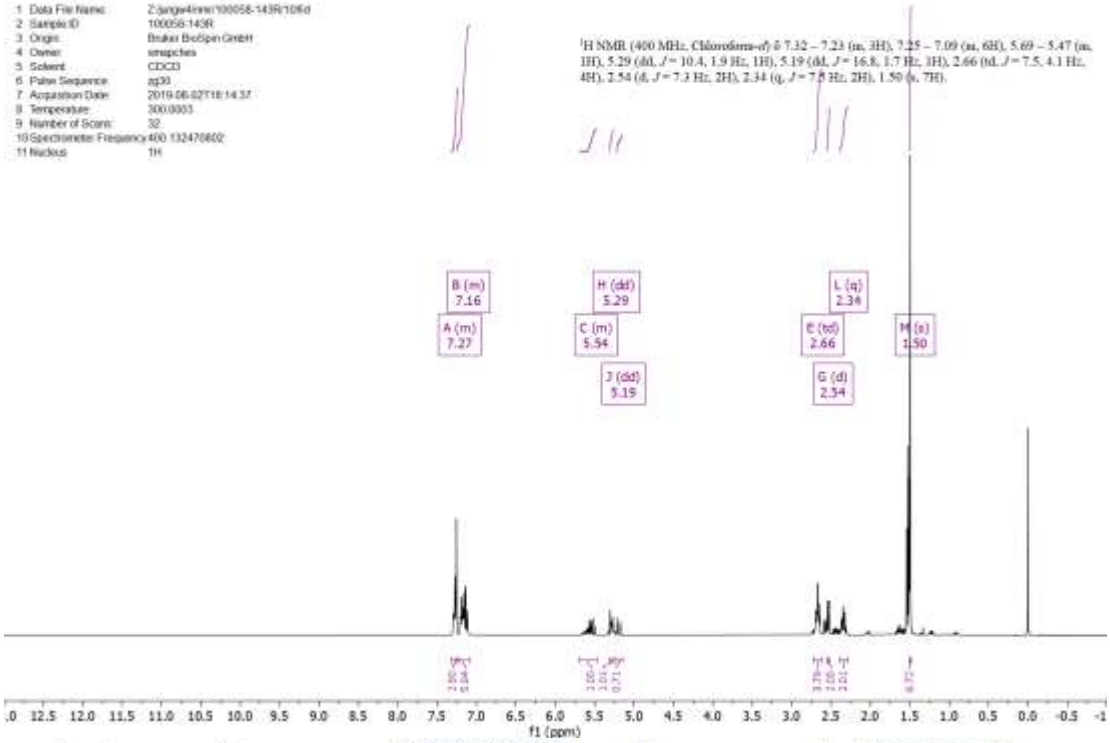
FTIR (Neat): 2961, 1537, 1496, 1397, 1373, 1347, 1258, 1011, 862, 790, 699 cm^{-1}.

$[\alpha]_D^{28}$: - 24.0 (c = 0.5, $CHCl_3$).

HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralcel OJ-3 column, hexane : 2-PrOH = 99:1, 1.0 mL/min, 210 nm), t_{major} = 12.8 min, t_{minor} = 11.2 min; ee = 99 %.

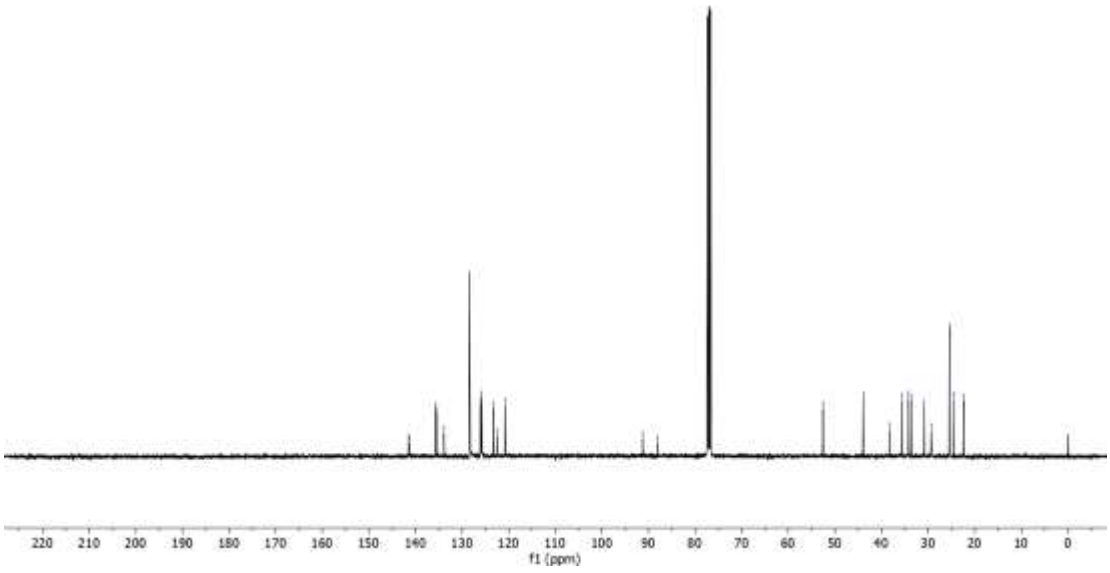
Parameter	Value
1 Data File Name:	Z:\jungw4\nmr\100058-143R\10\fid
2 Sample ID:	100058-143R
3 Origin:	Bruker BioSpin GmbH
4 Owner:	nmrpchas
5 Solvent:	CDCl3
6 Pulse Sequence:	zg30
7 Acquisition Date:	2019-08-02T18:14:37
8 Temperature:	300.0003
9 Number of Scans:	32
10 Spectrometer Frequency:	400.132478802
11 Nucleus:	1H

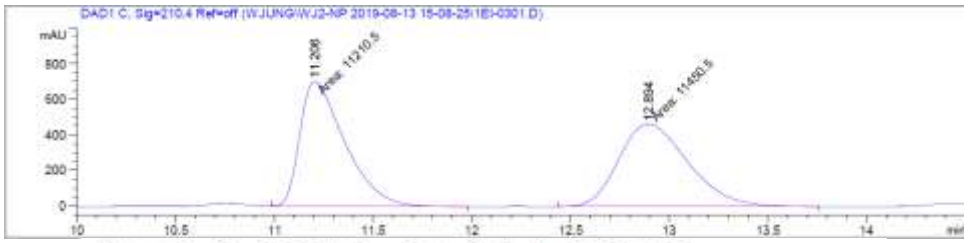
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32 – 7.23 (m, 3H), 7.25 – 7.09 (m, 6H), 5.69 – 5.47 (m, 1H), 5.29 (dd, *J* = 10.4, 1.9 Hz, 1H), 5.19 (dd, *J* = 16.8, 1.7 Hz, 1H), 2.66 (td, *J* = 7.5, 4.1 Hz, 4H), 2.54 (d, *J* = 7.3 Hz, 2H), 2.34 (q, *J* = 7.5 Hz, 2H), 1.50 (s, 7H).



Parameter	Value
1 Data File Name:	Z:\jungw4\nmr\100058-143R\15\fid
2 Sample ID:	100058-143R
3 Origin:	Bruker BioSpin GmbH
4 Owner:	nmrpchas
5 Solvent:	CDCl3
6 Pulse Sequence:	zgpg30
7 Acquisition Date:	2019-08-02T21:04:01
8 Temperature:	300.0003
9 Number of Scans:	8192
10 Spectrometer Frequency:	100.623638459
11 Nucleus:	13C

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.51, 141.36, 135.65, 135.50, 133.88, 128.43, 128.36, 128.31, 126.03, 125.96, 125.85, 123.27, 122.43, 120.76, 91.24, 88.06, 52.58, 43.92, 38.29, 35.66, 35.60, 34.21, 33.63, 30.84, 29.37, 25.47, 25.41, 24.57, 22.33.

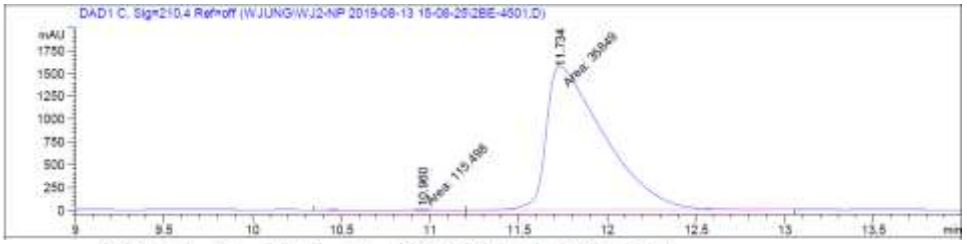




Signal 2: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	11.206	MF	0.2649	1.12105e4	49.4704
2	12.894	MF	0.4099	1.14505e4	50.5296

Totals : 2.26610e4

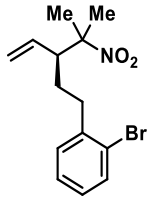


Signal 2: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	10.960	MM	0.5601	115.49792	0.3211
2	11.734	MM	0.3786	3.58490e4	99.6789

Totals : 3.59645e4

1-Bromo-2-(3-(2-nitropropan-2-yl)pent-4-en-1-yl)benzene (4.3b)



Procedure

Allylic acetate **4.1b** (22 μL, 0.1 mmol, 100 mol%) and 2-nitropropane **4.2a** (40 μL, 0.45 mmol, 450 mol%) were subject to standard reaction conditions (NMP, 60 °C, 48 h). The nitroalkane compound was obtained in 74% yield (23.2 mg, 0.07 mmol) was a yellow oil after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate = 80:1-70:1).

TLC (SiO_2) R_f = 0.70 (hexane : ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 – 7.52 (m, 1H), 7.30 – 7.23 (m, 1H), 7.20 (dd, J = 7.7, 1.8 Hz, 1H), 7.10 (td, J = 7.6, 1.9 Hz, 1H), 5.64 (dt, J = 16.8, 9.9 Hz, 1H), 5.35 (dd, J = 10.2, 1.7 Hz, 1H), 5.29 (dd, J = 16.9, 1.6 Hz, 1H), 2.92 – 2.70 (m, 2H), 2.59 (ddd, J = 13.6, 10.7, 6.0 Hz, 1H), 1.68 (tdd, J = 11.1, 6.0, 2.4 Hz, 1H), 1.57 (s, 3H), 1.55 (s, 3H).

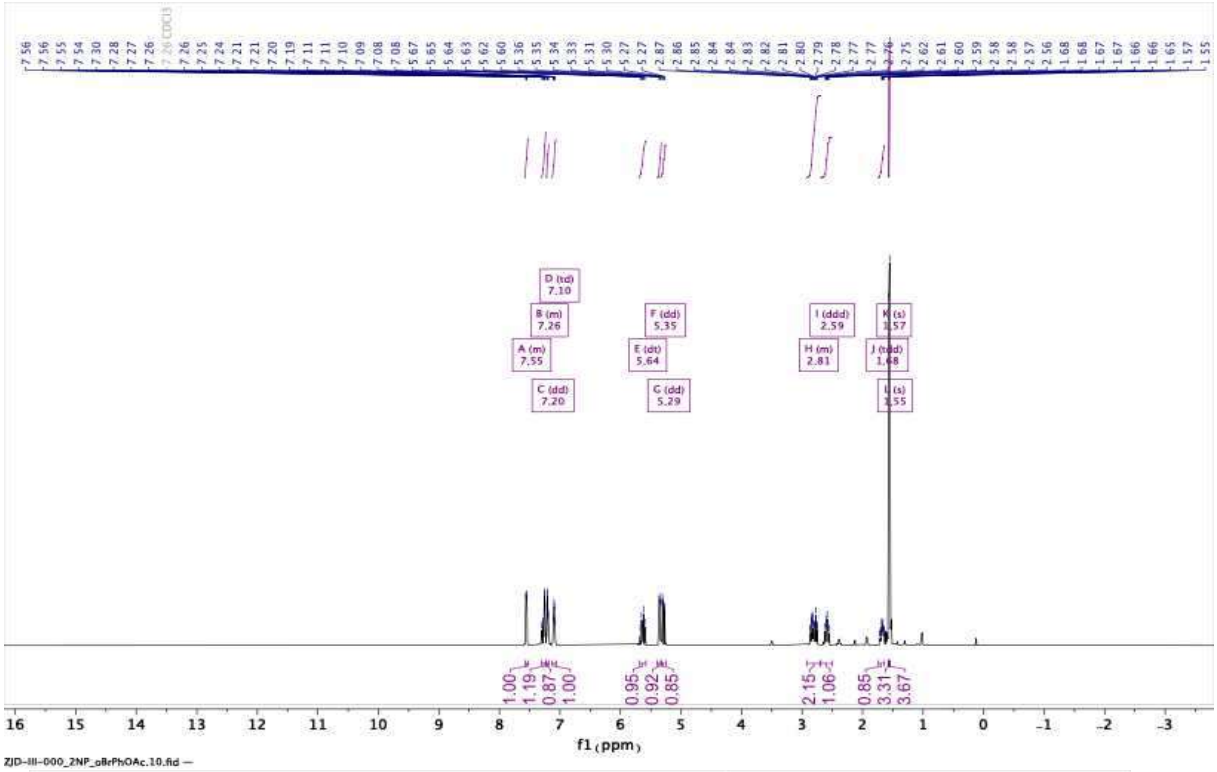
^{13}C NMR (126 MHz, $CDCl_3$) δ 141.0, 135.5, 133.0, 130.5, 128.0, 127.6, 124.4, 121.0, 91.4, 53.1, 34.5, 29.5, 24.5, 22.6.

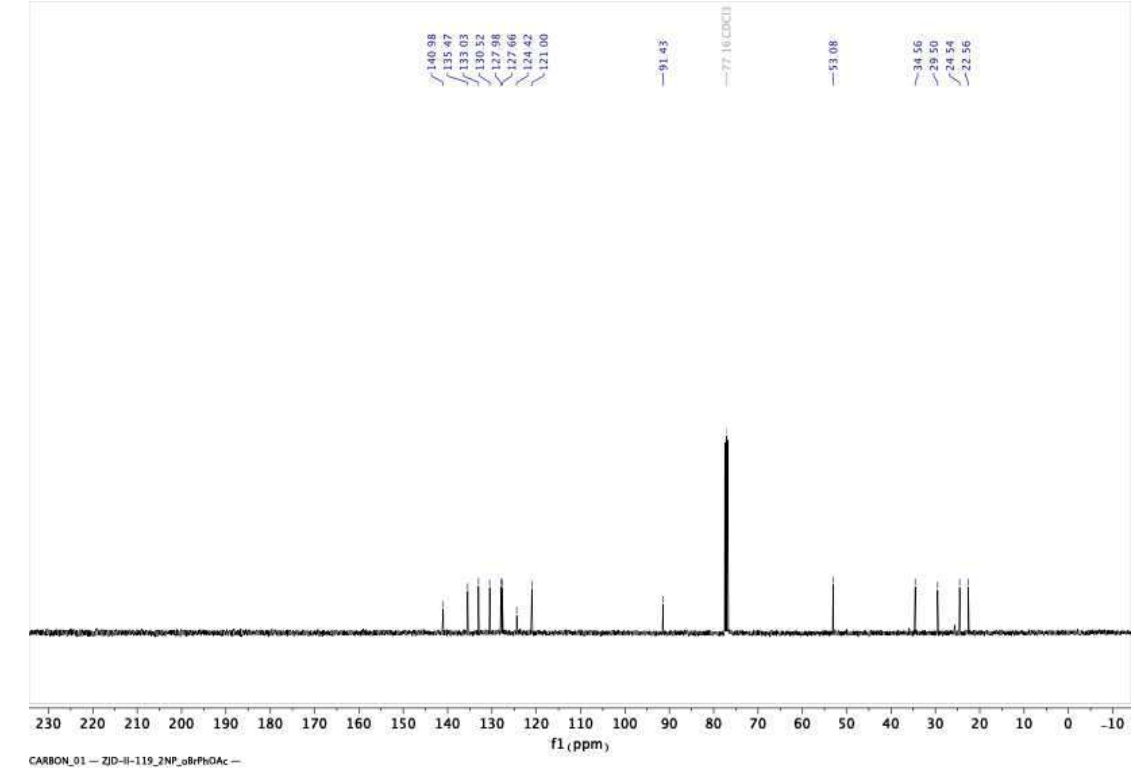
HRMS (ESI) m/z: [(M+Na)+] calcd for $C_{14}H_{18}BrNO_2$ 334.0413, found 334.0415.

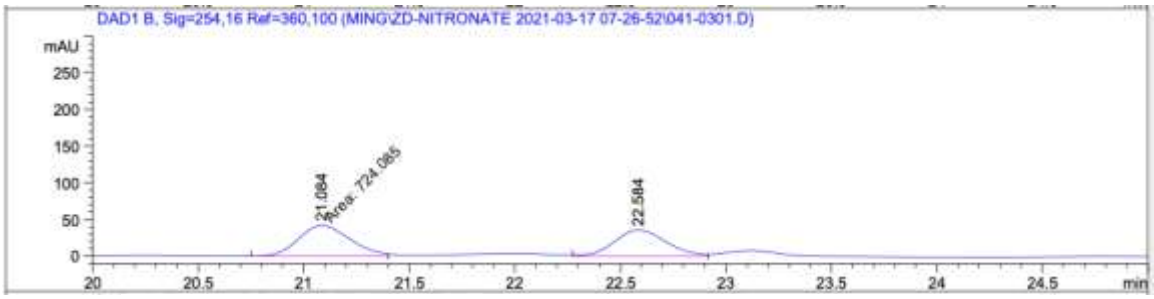
FTIR (Neat): 2934, 1737, 1535, 1469, 1439, 1396, 1372, 1346, 1229, 1116, 1022, 996, 927, 854, 750, 721, 658 cm^{-1}.

$[\alpha]_D^{28}$**:** -16.0 (c = 1.0, $CHCl_3$).

HPLC: Enantiomeric excess was determined by HPLC analysis (Lux Amylose-3 and Cellulose-5, hexane : 2-PrOH = 98 : 2, 0.5 mL/min, 254 nm), t_{major} = 21.1 min, t_{minor} = 22.6 min; ee = 90%.

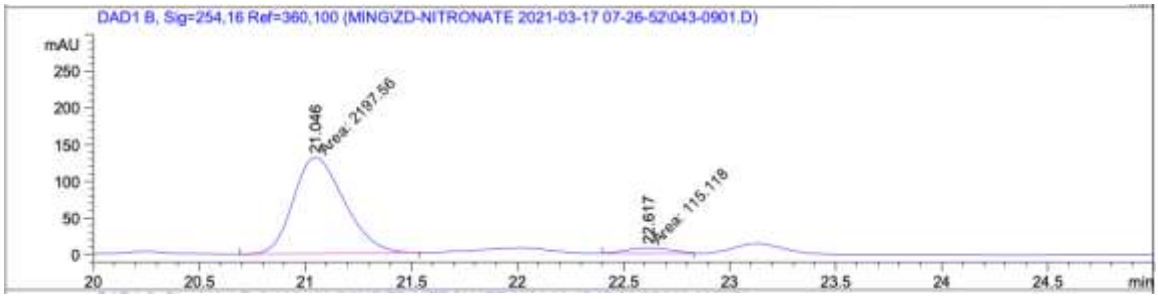

D (td) 7.10
B (m) 7.26
A (m) 7.55
C (dd) 7.20
F (dd) 5.35
E (dt) 5.64
G (dd) 5.29
I (ddd) 2.59
H (m) 2.81
K (s) 1.57
J (tdd) 1.48
L (s) 1.55
1.00 1.19 0.87 1.00 0.95 0.92 0.85 2.15 1.06 0.85 3.31 3.67
f1 (ppm)
ZJD-III-000_2NP_oBrPhOAc.10.fid


140.98
135.47
133.03
130.52
127.98
127.66
124.42
121.00
91.43
77.16 CDCl3
53.08
34.56
29.50
24.54
22.56
f1 (ppm)
CARBON_01 — ZJD-II-119_2NP_oBrPhOAc



Signal 2: DAD1 B, Sig=254,16 Ref=360,100

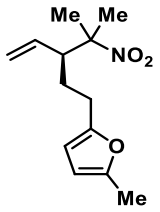
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.084	MF	0.2857	724.08478	42.24177	53.3853
2	22.584	VV	0.2690	632.25385	36.33403	46.6147
Totals :				1356.33862	78.57580	



Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.046	MM	0.2790	2197.55835	131.28494	95.0223
2	22.617	MM	0.2422	115.11832	7.92284	4.9777
Totals :				2312.67667	139.20778	

(*S*)-2-Methyl-5-(3-(2-nitropropan-2-yl)pent-4-en-1-yl)furan (4.3c)



Procedures

Allylic acetate **4.1c** (41.7 mg, 0.2 mmol, 100 mol%) and 2-nitropropane **4.2a** (80 µL, 0.9 mmol, 450 mol%) were subject to standard reaction conditions (DMF, 60 °C, 48 h). The title compound was obtained in 84% yield (39.7 mg, 0.16 mmol) as a light yellow oil after isolation by flash column chromatography (SiO2, hexane : ethyl acetate = 10:1).

TLC (SiO_2) R_f = 0.70 (hexane : ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (s, 2H), 5.51 (dt, J = 17.0, 9.9 Hz, 1H), 5.27 – 5.21 (m, 1H), 5.17 (d, J = 17.0 Hz, 1H), 2.69 – 2.58 (m, 2H), 2.43 (dt, J = 15.7, 8.3 Hz, 1H), 2.24 (s, 3H), 1.73 – 1.63 (m, 1H), 1.52 (d, J = 10.6 Hz, 7H) ppm.

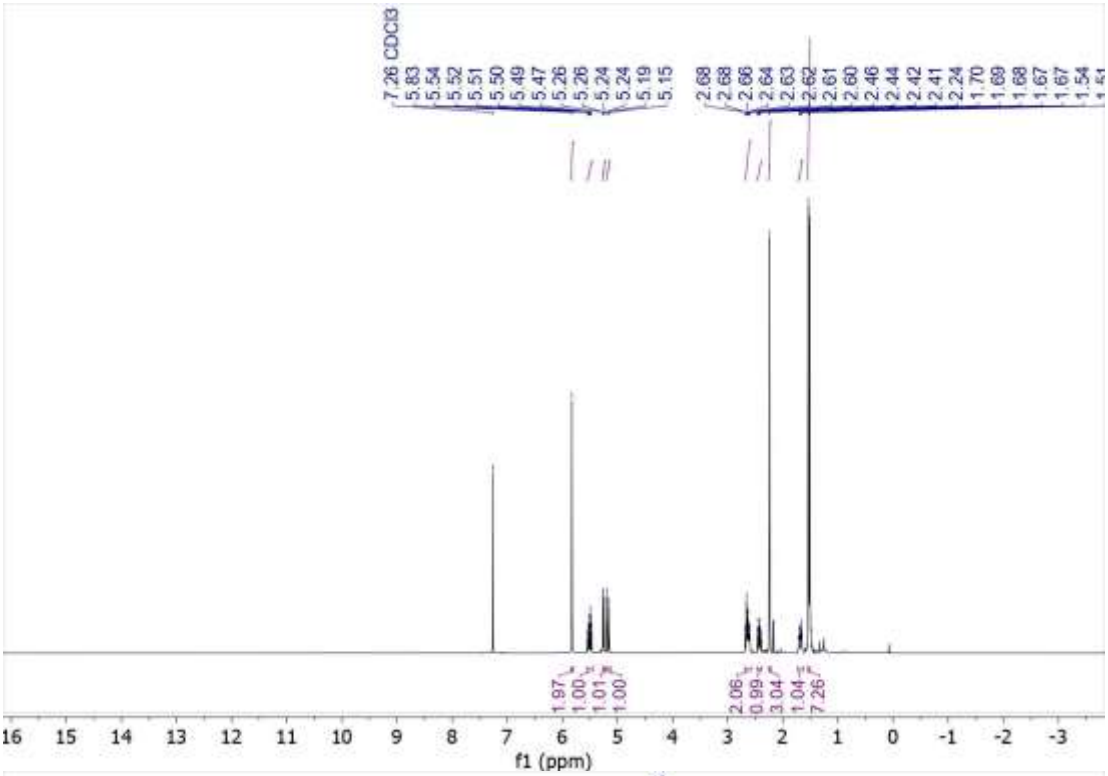
^{13}C NMR (126 MHz, $CDCl_3$) δ 153.2, 150.7, 135.3, 120.9, 106.0, 105.9, 91.4, 52.6, 27.7, 26.1, 24.6, 22.7, 13.6 ppm.

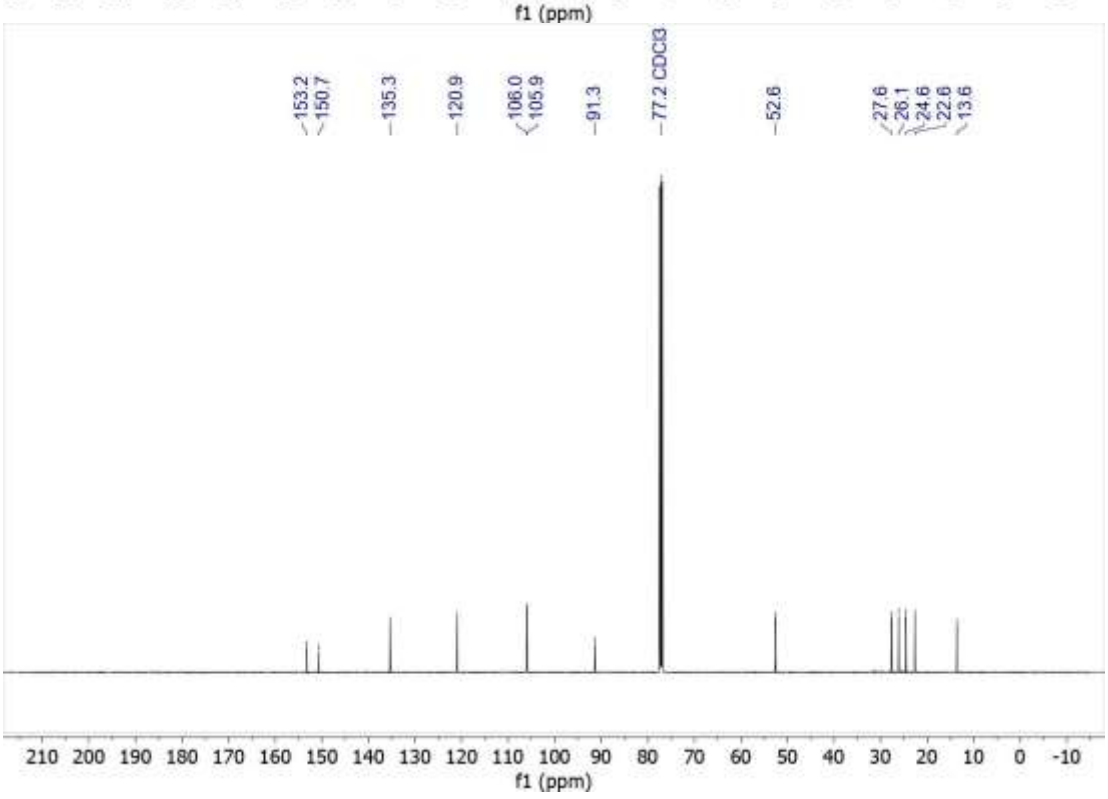
HRMS (ESI) m/z: [$(M+Na)^+$] calcd for $C_{13}H_{19}NO_3$ 260.1257, found 260.1261.

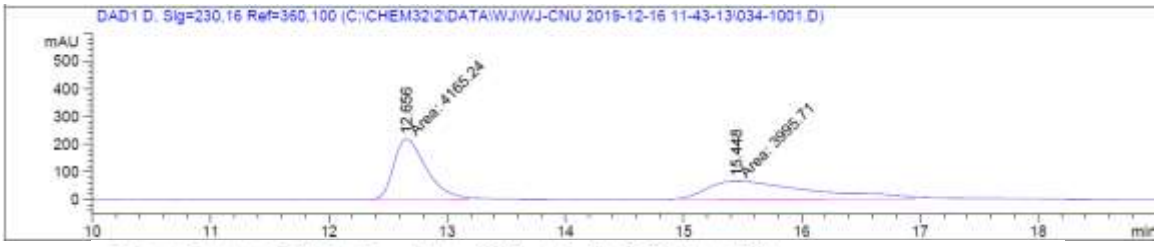
FTIR (Neat): 2924, 1710, 1569, 1535, 1455, 1397, 1373, 1346, 1218, 1138, 1019, 997, 929, 854, 782, 690, 660 cm–1.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{28}}$: - 6.0 (c = 0.5, $CHCl_3$).

HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralcel AD-H column, hexane : 2-PrOH = 99.5:0.5, 1.0 mL/min, 230 nm), tmajor = 12.6 min, tminor = 16.3 min; ee = 96 %.

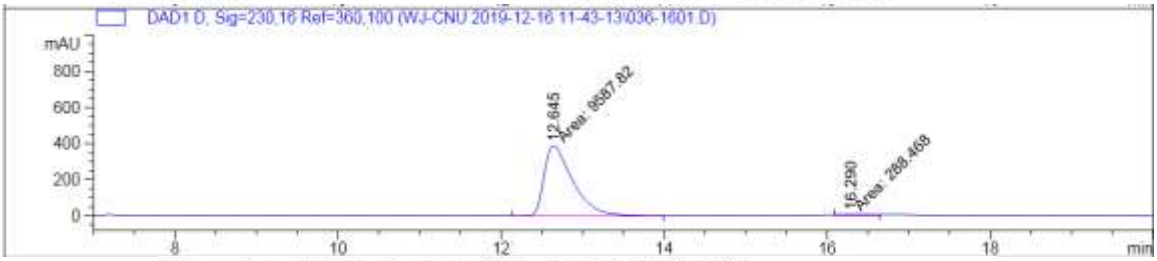

7.26 CDCl3
5.83
5.54
5.52
5.51
5.50
5.49
5.47
5.26
5.26
5.24
5.24
5.19
5.15
2.68
2.68
2.66
2.64
2.63
2.62
2.61
2.60
2.46
2.44
2.42
2.41
2.24
1.70
1.69
1.68
1.67
1.67
1.54
1.97
1.00
1.01
1.00
2.06
0.99
3.04
1.04
7.26
f1 (ppm)


153.2
150.7
135.3
120.9
106.0
105.9
91.3
77.2 CDCl3
52.6
27.6
26.1
24.6
22.6
13.6
f1 (ppm)



Signal 4: DAD1 D, Sig=230,16 Ref=360,100

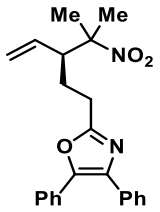
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.656	MF	0.3181	4165.24170	218.22577	51.0387
2	15.448	FM	1.0102	3995.70947	65.92092	48.9613
Totals :				8160.95117	284.14669	



Signal 4: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.645	MF	0.4122	9587.81543	387.63541	97.0792
2	16.290	MF	0.5393	288.46762	8.91552	2.9208
Totals :				9876.28305	396.55092	

(*S*)-2-(3-(2-Nitropropan-2-yl)pent-4-en-1-yl)-4,5-diphenyloxazole (4.3d)



Procedure

Allylic acetate **4.1d** (69.5 mg, 0.2 mmol, 100 mol%) and 2-nitropropane **4.2a** (80 µL, 0.9 mmol, 450 mol%) was subjected to standard reaction conditions (DMF, 60 ºC, 48 h). The nitroalkane product was obtained in 83% yield (62.5 mg, 0.16 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate = 8:1 – 4:1).

TLC (SiO_2) R_f = 0.39 (hexane : ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 – 7.61 (m, 2H), 7.60 – 7.55 (m, 2H), 7.40 – 7.28 (m, 6H), 5.55 (dt, J = 16.8, 9.9 Hz, 1H), 5.29 (dd, J = 10.2, 1.6 Hz, 1H), 5.24 (dd, J = 16.9, 1.6 Hz, 1H), 2.91 (ddd, J = 15.2, 9.7, 5.1 Hz, 1H), 2.85 – 2.68 (m, 2H), 2.02 – 1.92 (m, 1H), 1.84 – 1.68 (m, 1H), 1.59 (s, 3H), 1.56 (s, 3H) ppm.

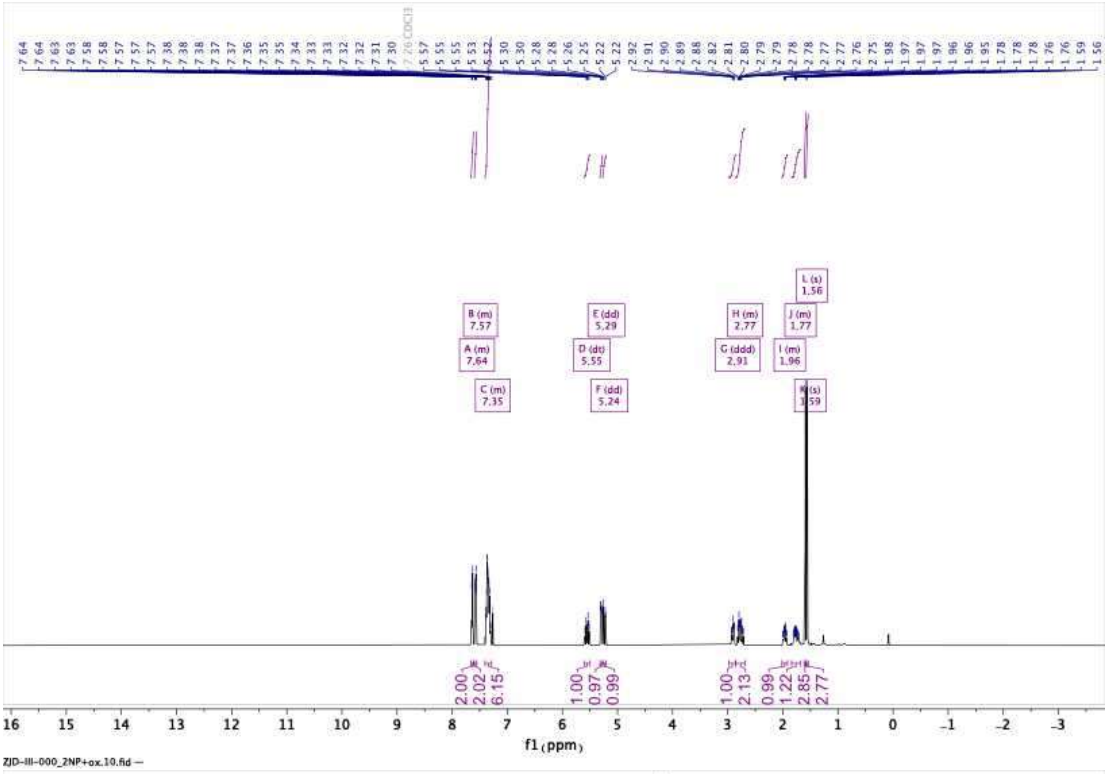
^{13}C NMR (126 MHz, $CDCl_3$) δ 162.6, 145.4, 135.2, 134.8, 132.6, 129.1, 128.8, 128.7, 128.6, 128.2, 128.0, 126.6, 121.5, 91.2, 52.8, 26.6, 26.4, 24.6, 22.7 ppm.

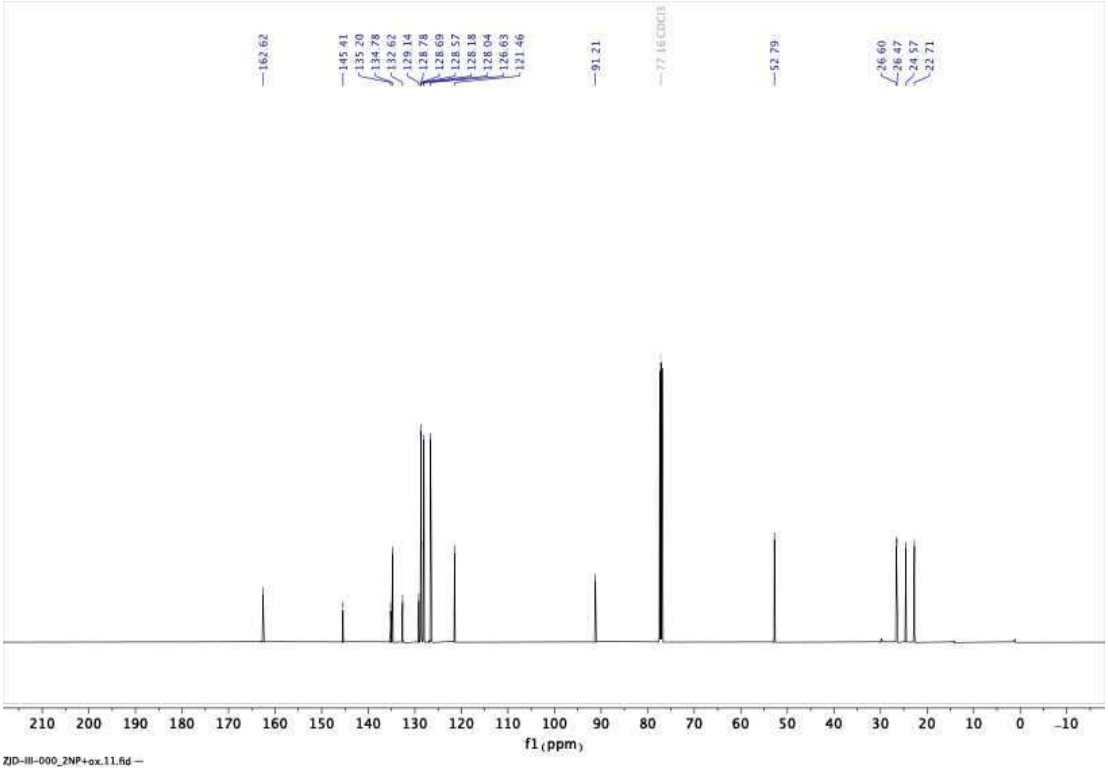
HRMS (ESI) m/z: [(M+Na)+] calcd for $C_{23}H_{24}N_2O_3$ 399.1679, found 399.1672.

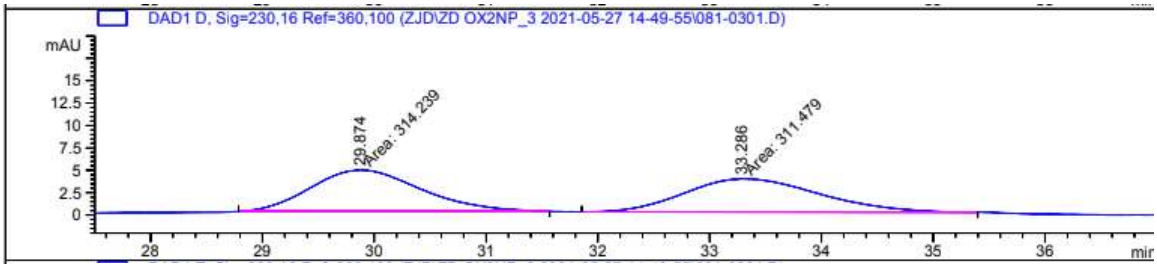
FTIR (Neat): 2938, 1604, 1570, 1536, 1501, 1444, 1397, 1373, 1346, 1219, 1142, 1059, 1025, 1000, 961, 928, 848, 762, 732, 692, 673 cm^{-1}.

$[\alpha]_D^{28}$**:** -10.0 (c = 1.0, $CHCl_3$).

HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralcel OJH column, hexane : 2-PrOH = 99 : 1, 1.0mL/min, 230 nm), t_{major} = 36.4 min, t_{minor} = 40.6 min; ee = 95%.

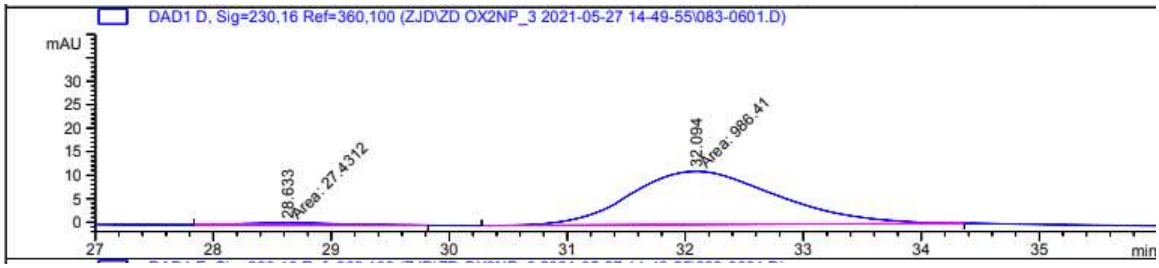

B (m) 7.57
A (m) 7.64
C (m) 7.35
E (dd) 5.29
D (dt) 5.55
F (dd) 5.24
H (m) 2.77
G (dddd) 2.91
L (s) 1.56
J (m) 1.77
I (m) 1.96
M (s) 3.59
2.00 2.02 6.15 1.00 0.97 0.99 1.00 2.13 0.99 1.22 2.85 2.77
f1 (ppm)
ZJD-III-000_2NP+ox.10.fid


162.62
145.41
135.20
134.78
132.62
129.14
128.78
128.69
128.57
128.18
128.04
126.63
121.46
91.21
77.16 CDCl3
52.79
26.60
26.47
24.57
22.71
f1 (ppm)
ZJD-III-000_2NP+ox.11.fid



Signal 3: DAD1 D, Sig=230,16 Ref=360,100

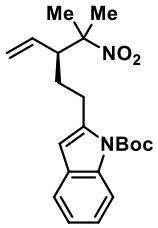
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.874	MM	1.1366	314.23865	4.60772	50.2205
2	33.286	MM	1.3968	311.47864	3.71654	49.7795
Totals :				625.71729	8.32426	



Signal 3: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.633	MM	1.0306	27.43122	4.43596e-1	2.7057
2	32.094	MM	1.4481	986.41034	11.35286	97.2943
Totals :				1013.84156	11.79646	

***tert*-Butyl (*S*)-2-(3-(2-nitropropan-2-yl)pent-4-en-1-yl)-1H-indole-1-carboxylate (4.3e)**



Procedure

Allylic acetate **4.1e** (68.7 mg, 0.2 mmol, 100 mol%) and 2-nitropropane **4.2a** (80 µL, 0.9 mmol, 450 mol%) were subject to standard reaction conditions (DMF, 70 °C, 24 h). The title compound was obtained in 62% yield (45.9 mg, 0.12 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate = 10:1).

TLC (SiO_2) R_f = 0.64 (hexane : ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 – 8.05 (m, 1H), 7.48 – 7.42 (m, 1H), 7.28 – 7.15 (m, 2H), 6.36 – 6.30 (m, 1H), 5.58 (dt, J = 16.9, 10.0 Hz, 1H), 5.35 – 5.18 (m, 2H), 3.13 – 3.02 (m, 1H), 2.91 – 2.82 (m, 1H), 2.77 (ddd, J = 11.8, 9.6, 2.5 Hz, 1H), 1.79 (dddd, J = 16.0, 10.1, 5.5, 2.4 Hz, 1H), 1.68 (s, 9H), 1.65 – 1.56 (m, 1H), 1.55 (d, J = 10.7 Hz, 6H) .

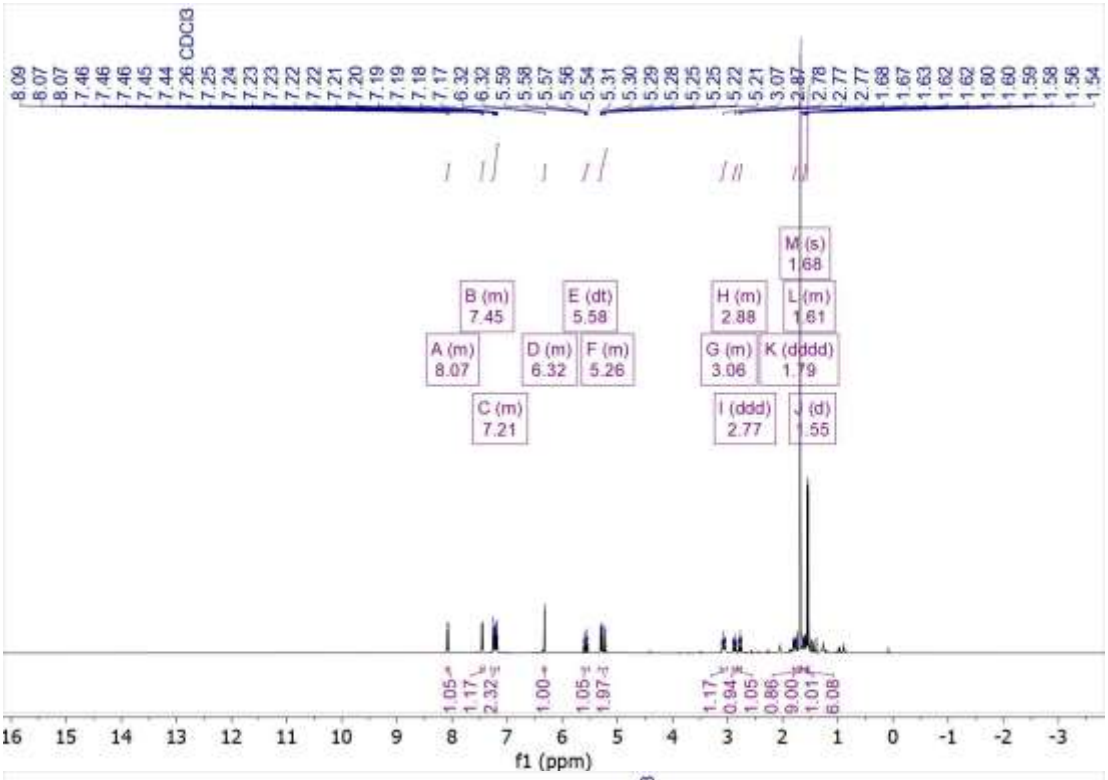
^{13}C NMR (126 MHz, $CDCl_3$) δ 150.5, 141.1, 136.6, 135.5, 129.2, 123.4, 122.7, 120.8, 119.8, 115.6, 107.3, 91.2, 83.8, 52.7, 28.3, 28.1, 28.1, 24.6, 22.5.

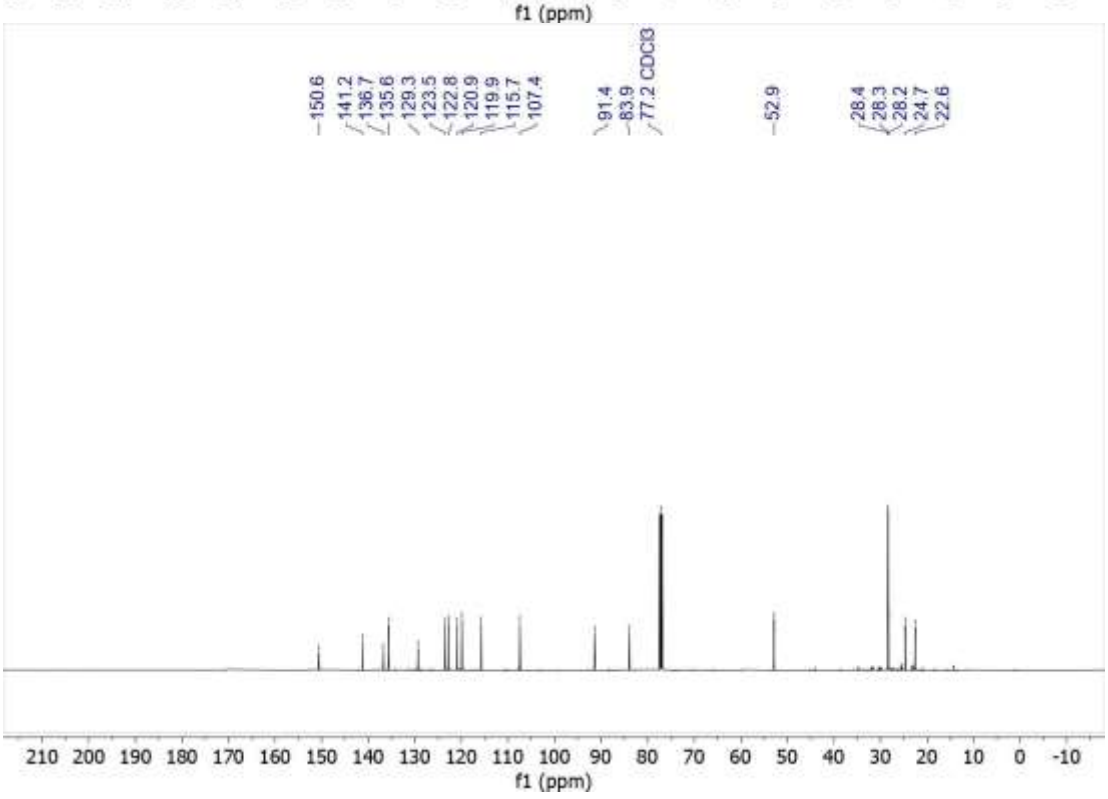
HRMS (ESI) m/z: [(M+Na)+] calcd for $C_{21}H_{28}N_2O_4$ 395.1941, found 395.1948.

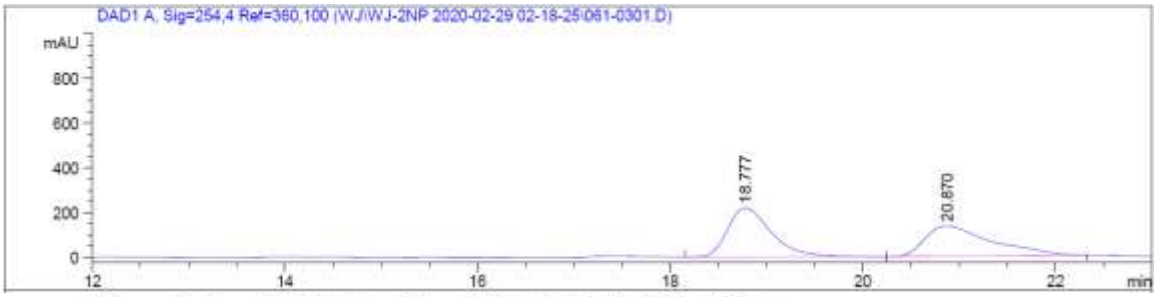
FTIR (Neat): 2947, 1691, 1530, 1500, 1452, 1366, 1334, 1253, 1227, 1158, 1137, 1075, 1010, 924, 854, 824, 752, 665 cm^{-1}.

$[\alpha]_D^{28}$: - 34.0 (c = 0.5, $CHCl_3$).

HPLC: Enantiomeric excess was determined by HPLC analysis (Lux Amylose-3 column, hexane : 2-PrOH = 99:1, 0.5 mL/min, 254 nm), t_{major} = 18.97 min, t_{minor} = 21.46 min; ee = 90 %.

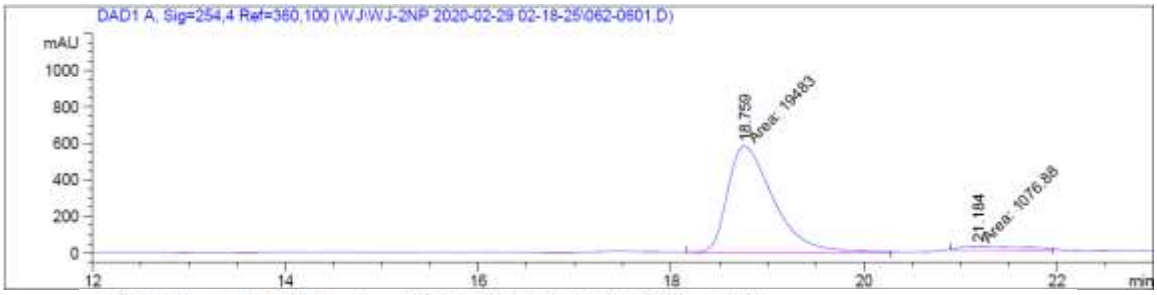

8.09 8.07 8.07 7.46 7.46 7.46 7.45 7.44 7.26 CDCl3 7.25 7.24 7.23 7.23 7.22 7.22 7.21 7.20 7.19 7.19 7.18 7.17 6.32 6.32 5.59 5.58 5.57 5.56 5.54 5.31 5.30 5.29 5.28 5.25 5.25 5.22 5.21 3.07 2.87 2.78 2.77 2.77 1.68 1.67 1.63 1.62 1.62 1.60 1.60 1.59 1.58 1.56 1.54
M (s) 1.68
B (m) 7.45
E (dt) 5.58
H (m) 2.88
L (m) 1.61
A (m) 8.07
D (m) 6.32
F (m) 5.26
G (m) 3.06
K (dddd) 1.79
C (m) 7.21
I (ddd) 2.77
J (d) 1.55
1.05 1.17 2.32 1.00 1.05 1.97 1.17 0.94 1.05 0.86 9.00 1.01 6.08
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)


150.6 141.2 136.7 135.6 129.3 123.5 122.8 120.9 119.9 115.7 107.4 91.4 83.9 77.2 CDCl3 52.9 28.4 28.3 28.2 24.7 22.6
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)



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

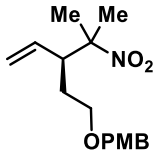
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.777	VB	0.4848	7030.27197	219.99678	51.7188
2	20.870	BB	0.7127	6562.98340	136.06107	48.2812
Totals :				1.35933e4	356.05785	



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.759	MF	0.5559	1.94830e4	584.08435	94.7622
2	21.184	MF	0.7785	1076.87842	23.05590	5.2378
Totals :				2.05599e4	607.14025	

(*S*)-1-Methoxy-4-(((3-(2-nitropropan-2-yl)pent-4-en-1-yl)oxy)methyl)benzene (4.3f)



Procedures

Allylic acetate **4.1f** (52.8 mg, 0.2 mmol, 100 mol%) and 2-nitropropane **4.2a** (80 µL, 0.9 mmol, 450 mol%) were subject to standard reaction conditions (DMF, 60 °C, 48 h). The title compound was obtained in 70% yield (41 mg, 0.14 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate = 30:1–10:1).

TLC (SiO_2) R_f = 0.6 (hexane : ethyl acetate = 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 5.48 (dt, J = 16.9, 9.9 Hz, 1H), 5.21 – 5.08 (m, 2H), 4.38 (q, J = 11.5 Hz, 2H), 3.80 (s, 3H), 3.44 (ddd, J = 9.4, 7.3, 4.2 Hz, 1H), 3.35 (td, J = 9.0, 6.3 Hz, 1H), 2.81 (ddd, J = 11.9, 9.6, 2.5 Hz, 1H), 1.78 – 1.67 (m, 1H), 1.54 (s, 3H), 1.52 (s, 3H), 1.44 (dddd, J = 13.4, 11.5, 6.3, 4.2 Hz, 1H) ppm.

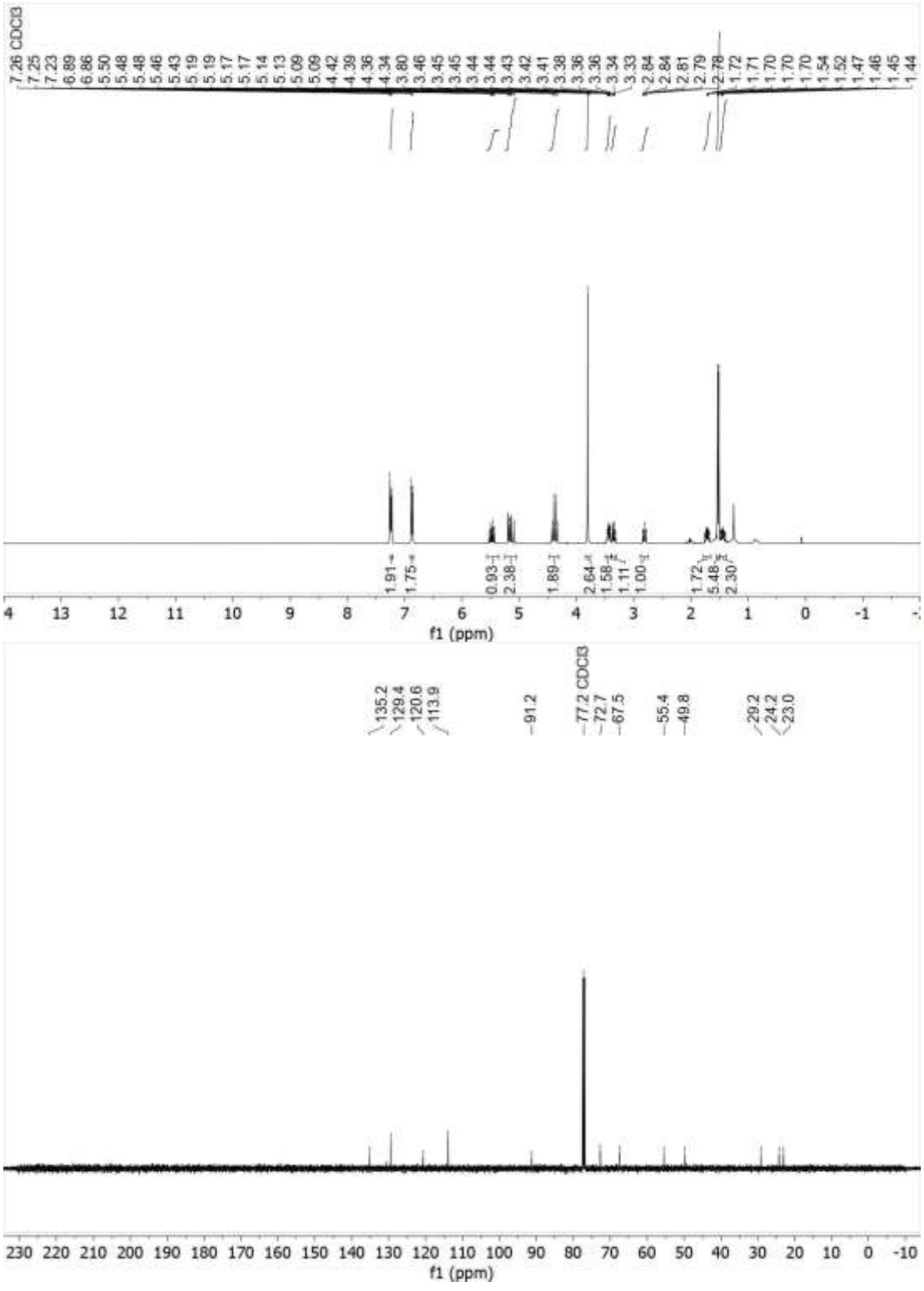
^{13}C NMR (100 MHz, $CDCl_3$): δ 135.1, 129.3, 120.5, 113.8, 91.1, 72.5, 67.4, 55.3, 49.6, 29.1, 24.1, 22.8 ppm.

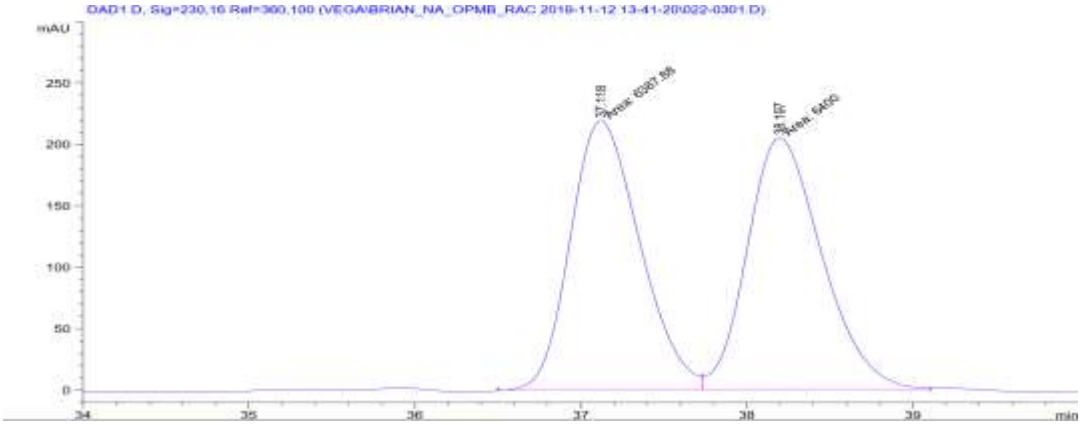
HRMS (ESI) m/z: [(M+Na)]+ calcd for $C_{16}H_{23}NO_4$ 316.1519, found 316.1530

FTIR (Neat): 1536, 1512, 1245, 1096, 1033, 819 cm^{-1}

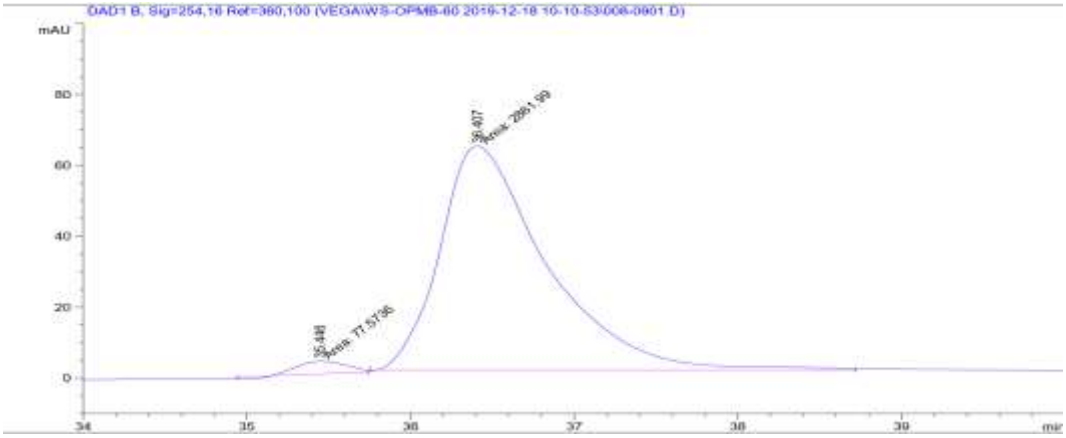
$[\alpha]_D^{28}$: - 18.5 (c = 1.0, $CHCl_3$).

HPLC: Enantiomeric excess was determined by HPLC analysis (two Chiralcel OD-H columns, hexane : 2-PrOH = 99:1, 1.0 mL/min, 254 nm), t_{major} = 36.40 min, t_{minor} = 35.45 min; ee = 94 %.


7.26 CDCl3
7.25
7.23
6.89
6.86
5.50
5.48
5.48
5.46
5.43
5.19
5.19
5.17
5.17
5.14
5.13
5.09
5.09
4.42
4.39
4.36
4.34
3.80
3.46
3.45
3.45
3.44
3.44
3.43
3.42
3.41
3.38
3.36
3.36
3.34
3.33
2.84
2.84
2.81
2.79
2.78
1.72
1.71
1.70
1.70
1.70
1.54
1.52
1.47
1.46
1.45
1.44
1.91
1.75
0.93
2.38
1.89
2.64
1.58
1.11
1.00
1.72
5.48
2.30
f1 (ppm)
135.2
129.4
120.6
113.9
91.2
77.2 CDCl3
72.7
67.5
55.4
49.8
29.2
24.2
23.0
f1 (ppm)

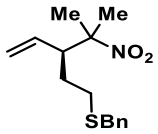


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	37.118	MF	0.4857	6387.87988	219.19226	49.9526
2	38.197	FM	0.5203	6400.00195	204.99922	50.0474



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	35.446	MM	0.3594	77.57357	3.59702	2.6389
2	36.407	MM	0.7553	2861.99048	63.15498	97.3611

(*S*)-Benzyl(3-(2-nitropropan-2-yl)pent-4-en-1-yl)sulfane (4.3g)



Procedures

Allylic acetate **4.1g** (50.0 mg, 0.20 mmol**,** 100 mol%) and 2-nitropropane **4.2a** (80 µL, 0.9 mmol, 450 mol%) were subject to standard reaction conditions (DMF, 60 °C, 48 h). The title compound was obtained in 83% yield (46.1 mg, 0.17 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate = 100:1–20:1).

TLC (SiO_2) R_f = 0.72 (hexane : ethyl acetate = 10:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.20 (m, 5H), 5.39 (ddd, J = 16.8, 9.9, 9.9 Hz, 1H), 5.19 (dd, J = 10.2, 1.7 Hz, 1H), 5.12 (dd, J = 16.8, 1.7 Hz, 1H), 3.66 (s, 2H), 2.76 (ddd, J = 11.1, 9.6, 2.7 Hz, 1H), 2.46 (ddd, J = 13.2, 8.7, 4.5 Hz, 1H), 2.28 – 2.14 (m, 1H), 1.56 – 1.51 (m, 1H), 1.49 (d, J = 1.8 Hz, 6H), 1.47 – 1.37 (m, 1H) ppm.

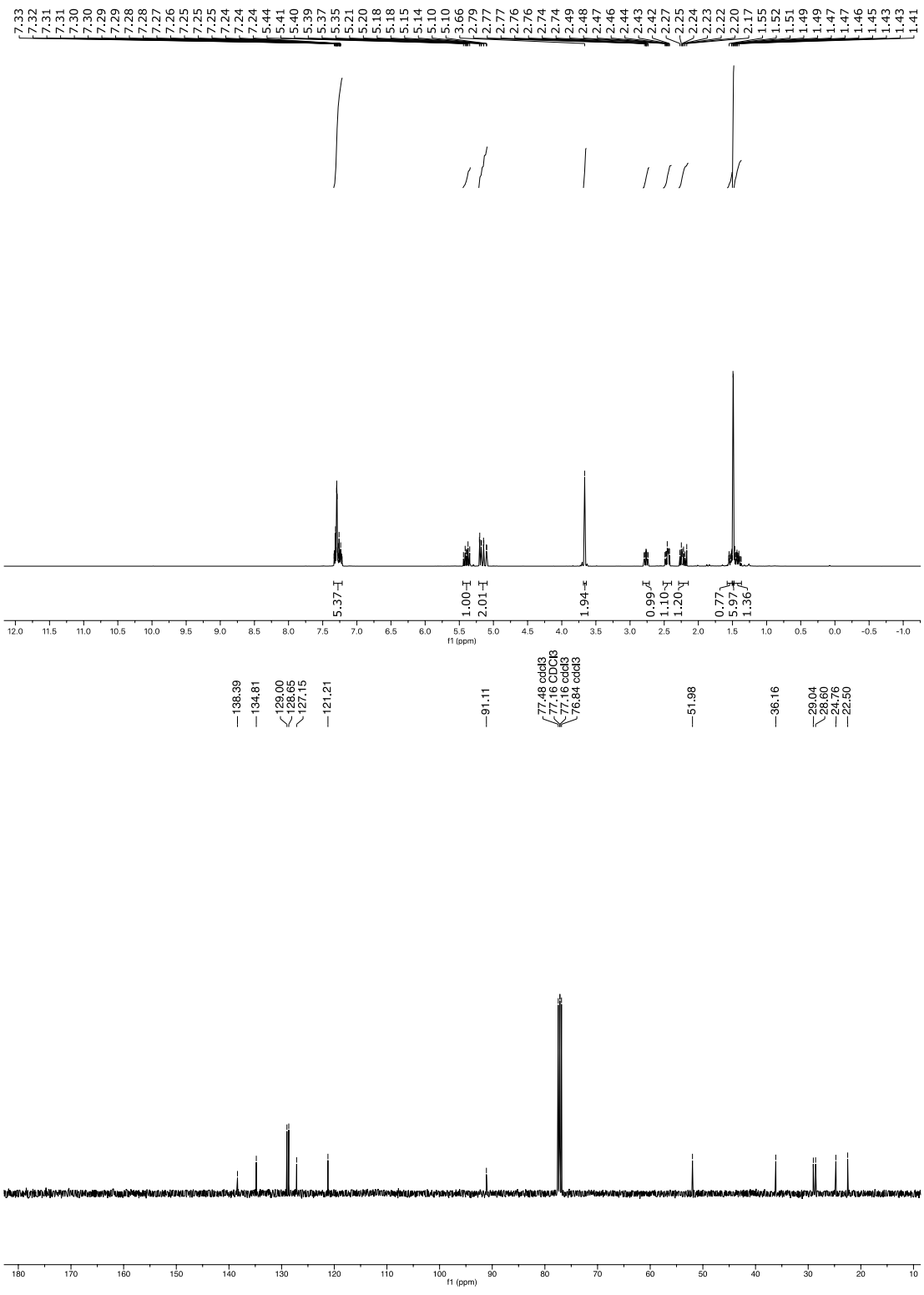
^{13}C NMR (101 MHz, $CDCl_3$) δ 138.4, 134.8, 129.0, 128.6, 127.2, 121.2, 91.1, 52.0, 36.2, 29.0, 28.6, 24.8, 22.5 ppm.

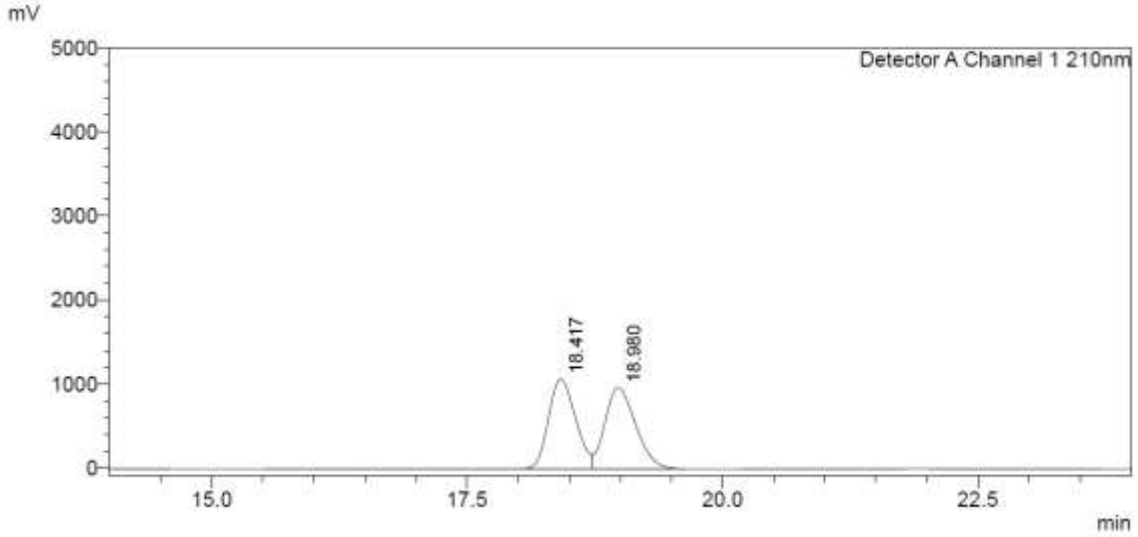
HRMS (CI) m/z: [(M-H)+] calcd for $C_{15}H_{20}NO_2S$ 278.1215, found 278.1205.

FTIR (Neat) 2923, 1534, 1420, 1346, 699 cm^{-1}.

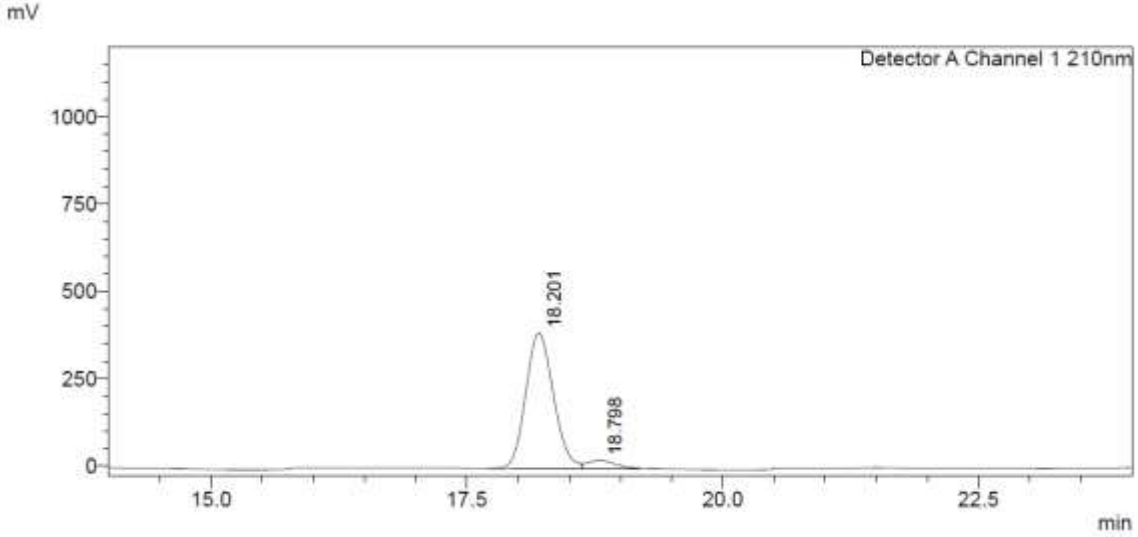
$[\alpha]_D^{28}$: + 8.0 (c = 0.25, $CHCl_3$).

HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H column, hexane : 2-PrOH = 99:1, 1.0 mL/min, 210 nm), t_{major} = 18.20 min, t_{minor} = 18.80 min; ee = 90 %.


7.33 7.32 7.31 7.31 7.30 7.29 7.28 7.28 7.27 7.26 7.25 7.25 7.24 7.24 7.24 5.44 5.41 5.40 5.39 5.37 5.35 5.21 5.20 5.18 5.15 5.14 5.10 3.66 2.79 2.77 2.77 2.76 2.76 2.74 2.74 2.49 2.48 2.47 2.46 2.44 2.43 2.42 2.27 2.25 2.24 2.23 2.22 2.20 2.17 1.55 1.52 1.51 1.49 1.49 1.47 1.47 1.46 1.45 1.43 1.43 1.41
5.37 1.00 2.01 1.94 0.99 1.10 1.20 0.77 5.97 1.36
f1 (ppm)
138.39 134.81 129.00 128.65 127.15 121.21 91.11 77.48 cdcl3 77.16 CDCl3 76.84 cdcl3 51.98 36.16 29.04 28.60 24.76 22.50
f1 (ppm)

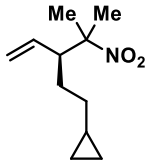


Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark
1	18.417	19660248	1064173	49.442		M
2	18.980	20104290	961992	50.558		V M
Total		39764539	2026165			



Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark
1	18.201	7330489	388491	94.283		M
2	18.798	444483	23342	5.717		V M
Total		7774972	411833			

(*S*)-(3-(2-Nitropropan-2-yl)pent-4-en-1-yl)cyclopropane (4.3h)



Procedures

Allylic acetate **4.1h** (33.6 mg, 0.20 mmol, 100 mol%) and 2-nitropropane **4.2a** (80 µL, 0.9 mmol, 450 mol%) were subject to standard reaction conditions (DMF, 80 °C, 24 h). The title compound was obtained in 73% yield (28.8 mg, 0.15 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate = 80:1–50:1).

TLC (SiO_2) R_f= 0.64 (hexane: ethyl acetate = 10:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = δ 5.44 (dt, J = 16.9, 9.9 Hz, 1H), 5.18 (dd, J = 10.2, 1.8 Hz, 1H), 5.12 (dd, J = 16.9, 1.7 Hz, 1H), 2.66 (ddd, J = 11.8, 9.7, 2.6 Hz, 1H), 1.53 (s, 3H), 1.51 (s, 3H), 1.44 – 1.26 (m, 2H), 1.18 – 1.09 (m, 2H), 0.68 – 0.54 (m, 1H), 0.39 (dddd, J = 11.4, 7.8, 4.8, 2.4 Hz, 2H), 0.00 (dtd, J = 9.0, 4.7, 3.3 Hz, 1H), -0.06 (dtd, J = 9.9, 4.8, 3.3 Hz, 1H) ppm.

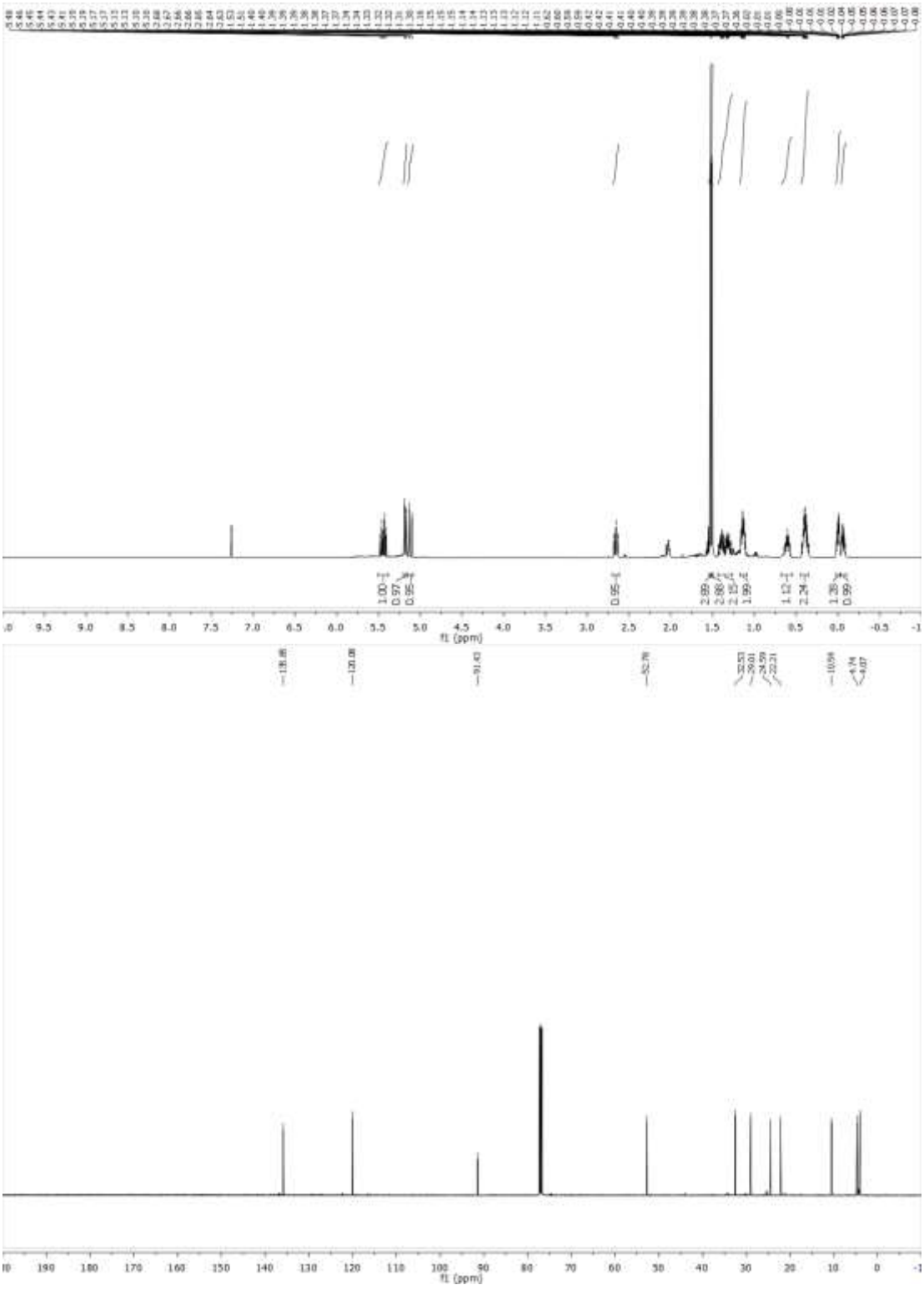
^{13}C NMR (125 MHz, $CDCl_3$): δ = 135.9, 120.1, 91.4, 52.8, 32.5, 29.0, 24.6, 22.2, 10.5, 4.7, 4.1 ppm.

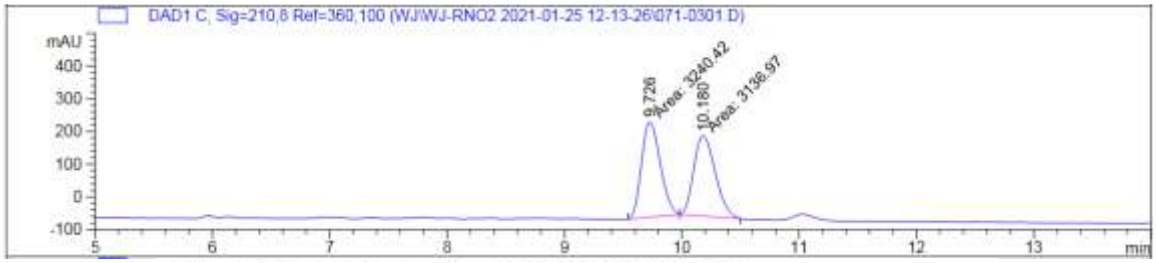
HRMS (ESI): Calculated for $C_{11}H_{19}NO_2$ [M+Ag^+] = 304.0461, Found 304.0471.

FTIR (neat): 2927, 1736, 1537, 1347, 1216, 1015, 926, 753 cm^{-1}.

$[\alpha]_D^{28}$= – 23.0 (*c* 1.0, $CHCl_3$).

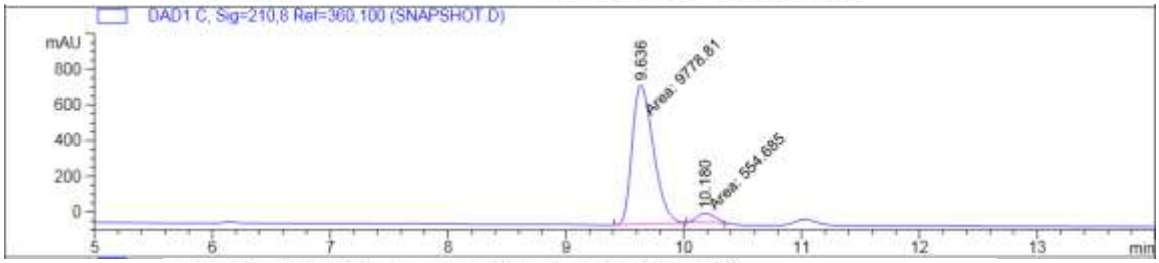
HPLC Enantiomeric excess was determined by HPLC analysis (Chiralcel OJH column, hexane:2-PrOH = 100:0, 1.00 mL/min, 210 nm), t_{major} = 9.64 min, t_{minor} = 10.18 min; *ee* = 89%.





Signal 2: DAD1 C, Sig=210,8 Ref=360,100

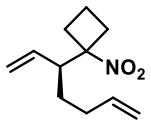
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.726	MM	0.1844	3240.42358	292.86072	50.8111
2	10.180	MM	0.2129	3136.97461	245.60954	49.1889
Totals :				6377.39819	538.47026	



Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.636	MM	0.2088	9778.81055	780.43768	94.6322
2	10.180	MM	0.1774	554.68500	52.12165	5.3678
Totals :				1.03335e4	832.55933	

(*S*)-1-(Hepta-1,6-dien-3-yl)cyclobutan-1-amine (4.3i)



Procedures

Allylic acetate **4.1i** (30.8 mg, 0.2 mmol, 100 mol%) and nitrocyclobutane **4.2b** (103.6 mg, 0.90 mmol, 450 mol%) were subject to standard reaction conditions (DMF, 60 °C, 48 h). The title compound was obtained in 72% yield (28.3 mg, 0.14 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate = 80:1–50:1).

TLC (SiO_2) R_f = 0.53 (hexane: ethyl acetate = 10:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.67 (ddt, J = 17.1, 10.2, 6.7 Hz, 1H), 5.47 (dt, J = 16.9, 9.9 Hz, 1H), 5.21 (dd, J = 10.1, 1.7 Hz, 1H), 5.12 (dd, J = 17.0, 1.6 Hz, 1H), 4.98 – 4.89 (m, 2H), 2.66 (tdd, J = 13.5, 9.3, 2.5 Hz, 2H), 2.47 (ddd, J = 11.8, 9.7, 2.6 Hz, 1H), 2.32 (tdt, J = 11.2, 5.5, 2.4 Hz, 2H), 2.08 (ddt, J = 12.3, 9.3, 5.7 Hz, 1H), 1.85 (dq, J = 13.7, 7.0, 6.2 Hz, 1H), 1.77 (ddt, J = 15.4, 10.4, 5.2 Hz, 1H), 1.70 – 1.59 (m, 1H), 1.47 (dtd, J = 13.5, 8.2, 2.7 Hz, 1H), 1.25 – 1.20 (m, 1H) ppmn.

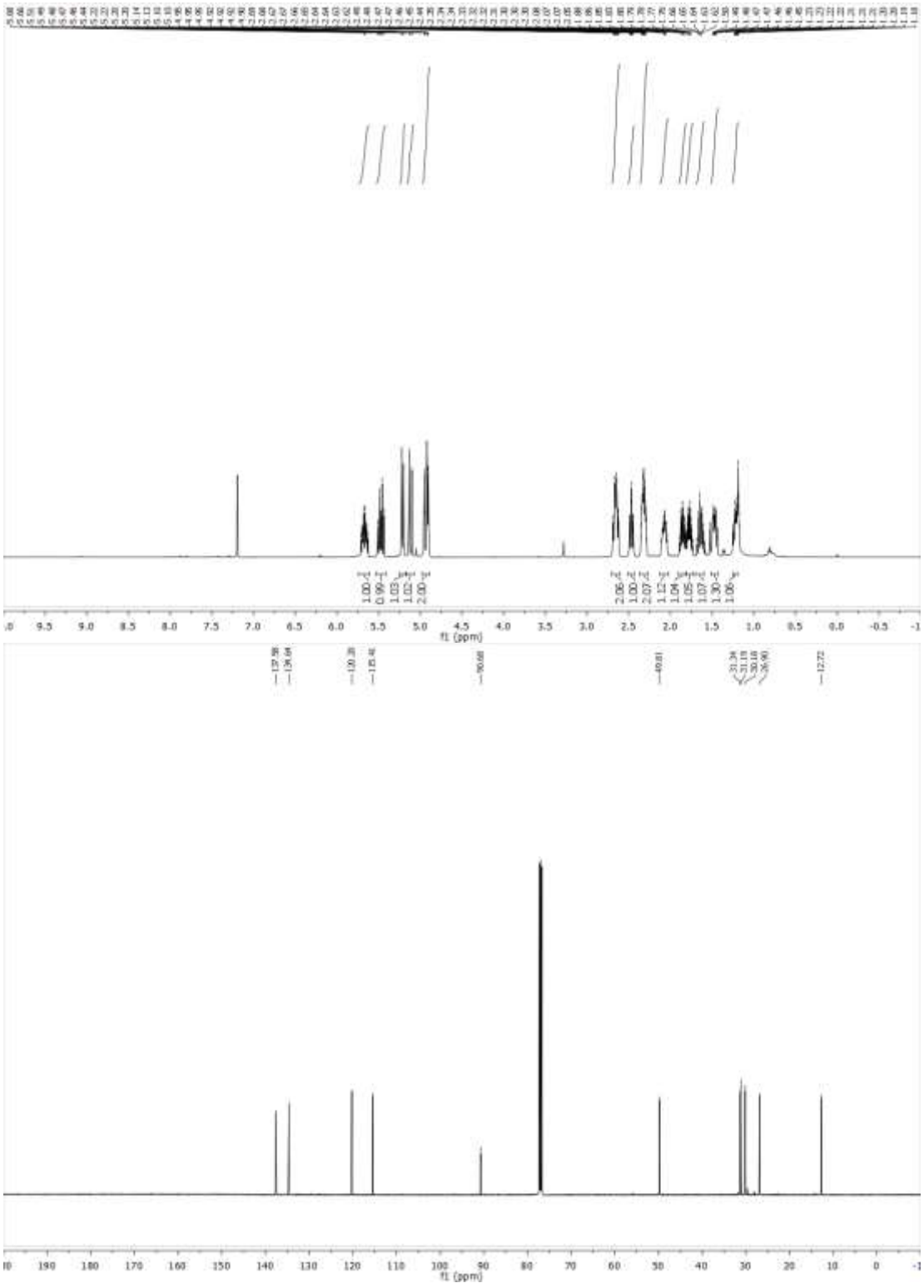
^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.6, 134.6, 120.2, 115.4, 90.7, 49.8, 31.3, 31.2, 30.2, 26.9, 12.7 ppm.

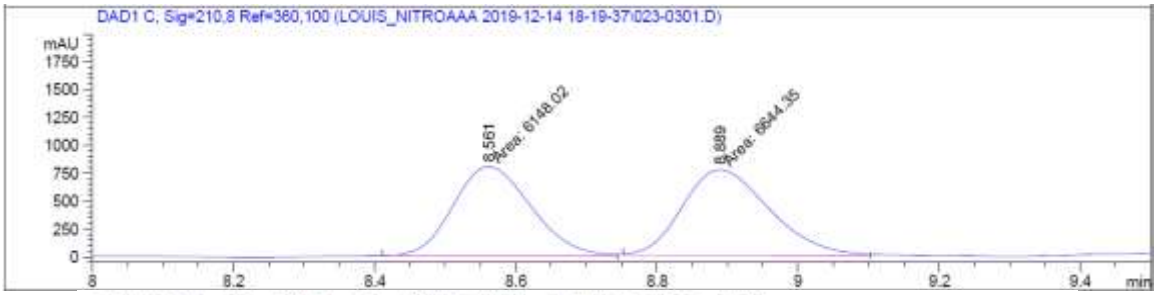
HRMS (ESI): Calculated for $C_{11}H_{17}NO_2$ [M+Ag^+] = 302.0305, Found 302.0314.

FTIR (Neat): 2950, 1640, 1531, 1360, 1216, 995, 920, 754, 667 cm^{-1}.

$[\alpha]_D^{28}$= – 6.0 (*c* 1.0, $CHCl_3$).

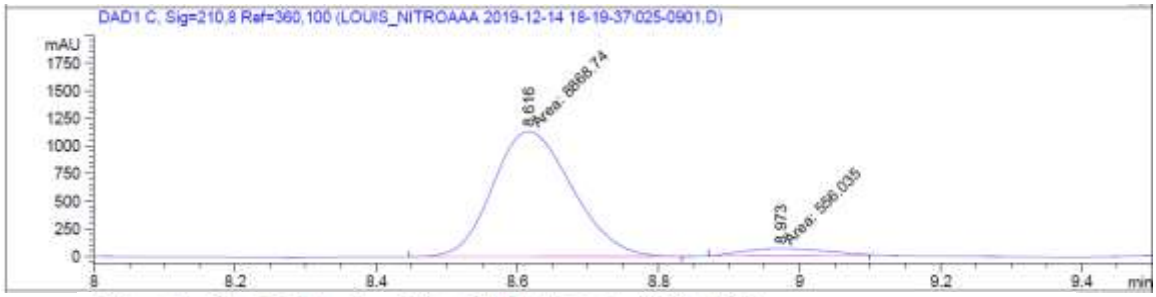
HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralpak AD-H column, hexane : 2-PrOH = 959:1, 1.0 mL/min, 210 nm), t_{major} = 8.62 min, t_{minor} = 8.97 min; ee = 88 %.





Signal 2: DAD1 C, Sig=210,8 Ref=360,100

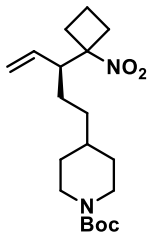
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.561	MF	0.1276	6148.01611	802.76221	48.0600
2	8.889	FM	0.1433	6644.34766	772.74329	51.9400
Totals :				1.27924e4	1575.50549	



Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.616	FM	0.1302	8868.74316	1135.44885	94.1003
2	8.973	MF	0.1367	556.03485	67.77323	5.8997
Totals :				9424.77802	1203.22208	

***(S)-tert*-Butyl-4-(3-(1-nitrocyclobutyl)pent-4-en-1-yl)piperidine-1-carboxylate (4.3j)**



Procedures

Allylic acetate **4.1j** (31.0 mg, 0.10 mmol**,** 100 mol%) and nitrocyclobutane **4.2b** (45 mg, 0.45 mmol, 450 mol%) were subject to standard reaction conditions (60 °C, 48 h, NMP) utilizing (*S*)-Ir-Tol-BINAP-OMe-NO_2 (11.0 mg, 0.10 mmol, 10 mol%). The title compound was obtained in 84% yield (29.4 mg, 0.084 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate = 10:1).

TLC (SiO_2) R_f = 0.43 (hexane : ethyl acetate = 10:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.5 (ddd, *J* = 16.9, 10.2, 9.6 Hz, 1H), 5.3 (dd, *J* = 10.2, 1.7 Hz, 1H), 5.2 (ddd, *J* = 16.9, 1.8, 0.7 Hz, 1H), 4.1 (d, *J* = 13.2 Hz, 2H), 2.8 – 2.6 (m, 4H), 2.5 – 2.3 (m, 3H), 1.9 – 1.7 (m, 1H), 1.7 – 1.5 (m, 4H), 1.4 (s, 9H), 1.3 – 0.9 (m, 6H) ppm.

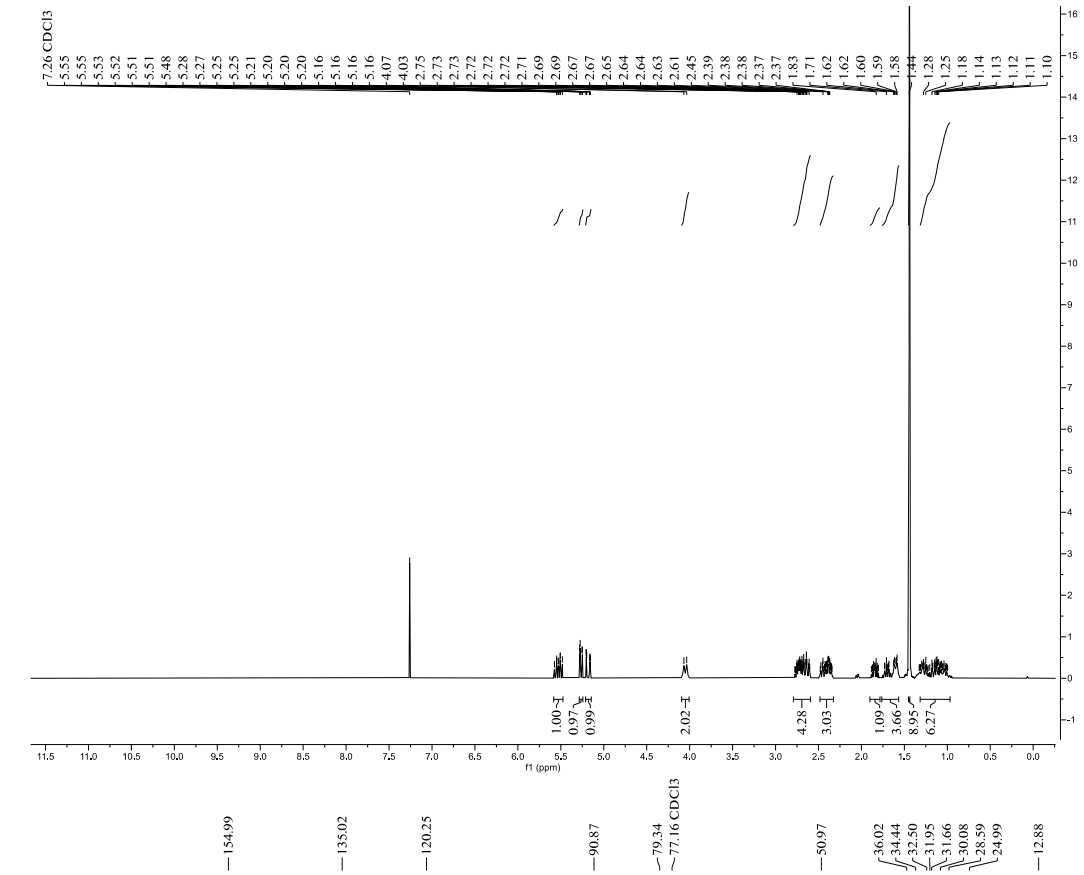
^{13}C NMR (101 MHz, $CDCl_3$) δ 155.0, 135.0, 120.2, 90.9, 79.3, 51.0, 36.0, 34.4, 32.5, 32.0, 31.7, 30.1, 28.6, 25.0, 12.9 ppm.

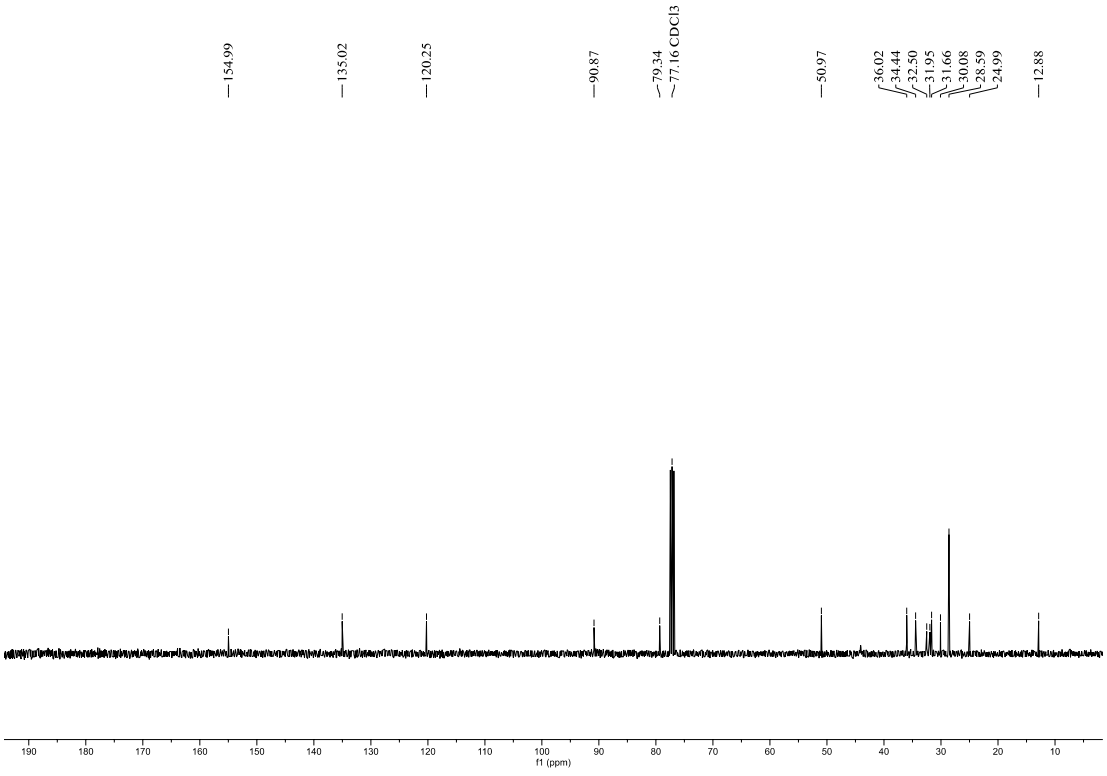
HRMS (ESI) m/z: [(M+Na)+] calcd for $C_{19}H_{32}N_2O_4$ 375.2254, found 375.2261.

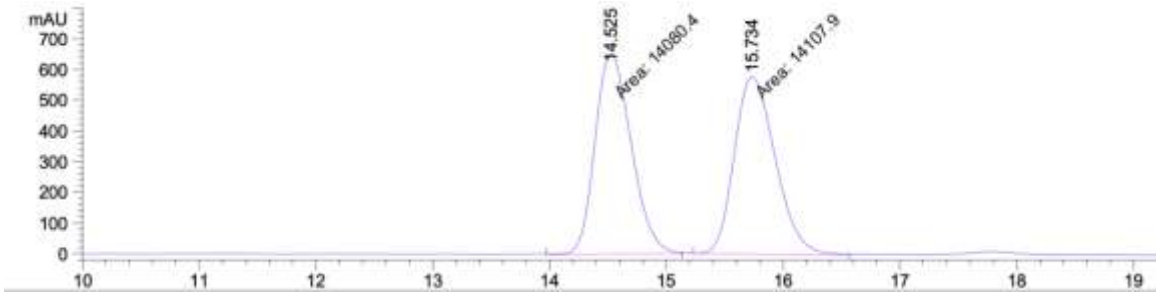
FTIR (Neat) 2927, 2852, 1687, 1530, 1421, 1153 cm^{-1}.

$[\alpha]_D^{28}$: - 24 (c = 0.25, $CHCl_3$).

HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H column, hexane : 2-PrOH = 97:3, 1.0 mL/min, 210 nm), t_{major} = 16.00 min, t_{minor} = 14.85 min; ee = 88 %.

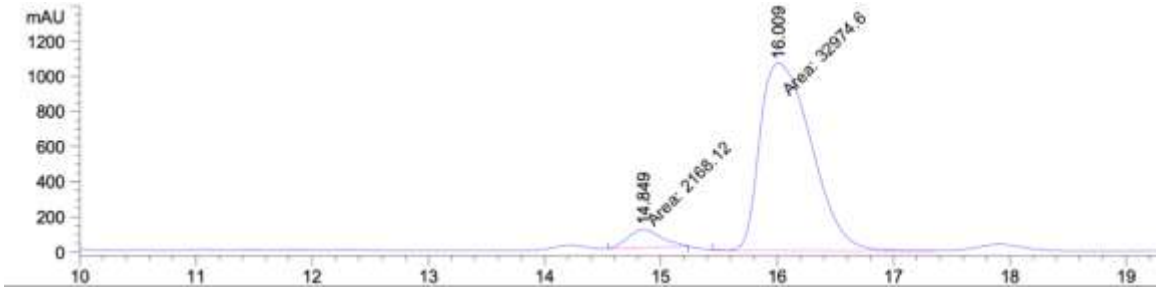

7.26 CDCl3
5.55
5.55
5.53
5.52
5.51
5.51
5.48
5.28
5.27
5.25
5.25
5.21
5.20
5.20
5.20
5.16
5.16
5.16
5.16
4.07
4.03
2.75
2.73
2.73
2.72
2.72
2.72
2.72
2.71
2.69
2.69
2.67
2.67
2.65
2.64
2.64
2.63
2.61
2.45
2.39
2.38
2.38
2.37
2.37
1.83
1.71
1.62
1.62
1.60
1.59
1.58
1.44
1.28
1.25
1.18
1.14
1.13
1.12
1.11
1.10
1.00
0.97
0.99
2.02
4.28
3.03
1.09
3.66
8.95
6.27
f1 (ppm)


154.99
135.02
120.25
90.87
79.34
77.16 CDCl3
50.97
36.02
34.44
32.50
31.95
31.66
30.08
28.59
24.99
12.88
f1 (ppm)



Signal 2: DAD1 C, Sig=210,8 Ref=360,100

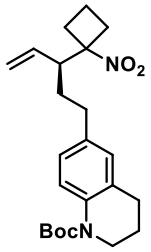
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.525	MM	0.3596	1.40804e4	652.56836	49.9512
2	15.734	MM	0.4069	1.41079e4	577.80859	50.0488
Totals :				2.81883e4	1230.37695	



Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.849	MM	0.3432	2168.12451	105.29306	6.1695
2	16.009	MM	0.5130	3.29746e4	1071.31250	93.8305
Totals :				3.51427e4	1176.60556	

***tert*-Butyl (*S*)-6-(3-(1-nitrocyclobutyl)pent-4-en-1-yl)-3,4-dihydroquinoline-1(2*H*)-carboxylate (4.3k)**



Procedures

Allylic acetate **4.1k** (35.9 mg, 0.1 mmol, 100 mol%) and nitrocyclobutane **4.2b** (45.5 mg, 0.45 mmol, 450 mol%) were subject to standard reaction conditions (DMF, 80 °C, 24 h). The title compound was obtained in 85% yield (34.2 mg, 0.085 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate = 20:1).

TLC (SiO_2) R_f = 0.55 (hexane : ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56 (d, J = 8.4 Hz, 1H), 6.90 (dd, J = 8.4, 2.1 Hz, 1H), 6.84 (d, J = 2.2 Hz, 1H), 5.61 (dt, J = 16.9, 9.9 Hz, 1H), 1.56 – 1.41 (m, 1H), 5.33 (dd, J = 10.2, 1.7 Hz, 1H), 5.21 (dd, J = 16.9, 1.7 Hz, 1H), 3.74 – 3.65 (m, 2H), 2.76 – 2.60 (m, 4H), 2.52 (ddd, J = 11.7, 9.5, 2.6 Hz, 1H), 2.44 – 2.28 (m, 3H), 1.95 – 1.87 (m, 2H), 1.87 – 1.71 (m, 2H), 1.66 (dtt, J = 12.2, 9.7, 8.4 Hz, 1H), 1.52 (s, 9H) ppm.

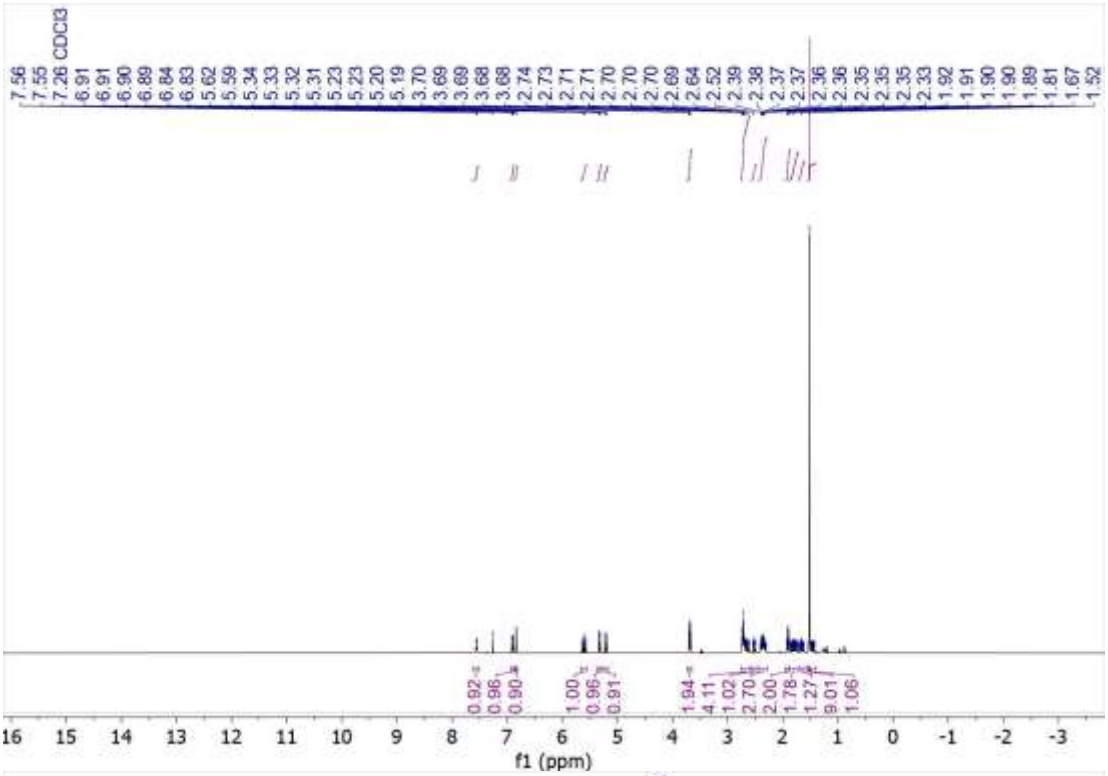
^{13}C NMR (126 MHz, $CDCl_3$) δ 154.0, 136.7, 136.1, 134.8, 129.8, 128.3, 125.7, 124.1, 120.4, 90.8, 80.6, 50.1, 44.6, 32.7, 31.3, 30.3, 29.6, 28.4, 27.5, 23.6, 12.8 ppm.

HRMS (ESI) m/z: [(M+Na)+] calculated for $C_{23}H_{32}N_2O_4$ 423.2254 found 423.2258.

FTIR (Neat): 3016, 1727, 1537, 1454, 1370, 1214, 1157, 116, 1086, 747, 667 cm^{-1}.

$[\alpha]_D^{28}$: - 10.0 (c = 0.5, $CHCl_3$).

HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralpak AD-H column, hexane : 2-PrOH = 99:1, 1.0 mL/min, 230 nm), t_{major} = 20.69 min, t_{minor} = 36.22 min; ee = 96 %.


7.56
7.55
7.26 CDCl3
6.91
6.91
6.90
6.89
6.84
6.83
5.62
5.59
5.34
5.33
5.32
5.31
5.23
5.23
5.20
5.19
3.70
3.69
3.69
3.68
3.68
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2.73
2.71
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2.70
2.70
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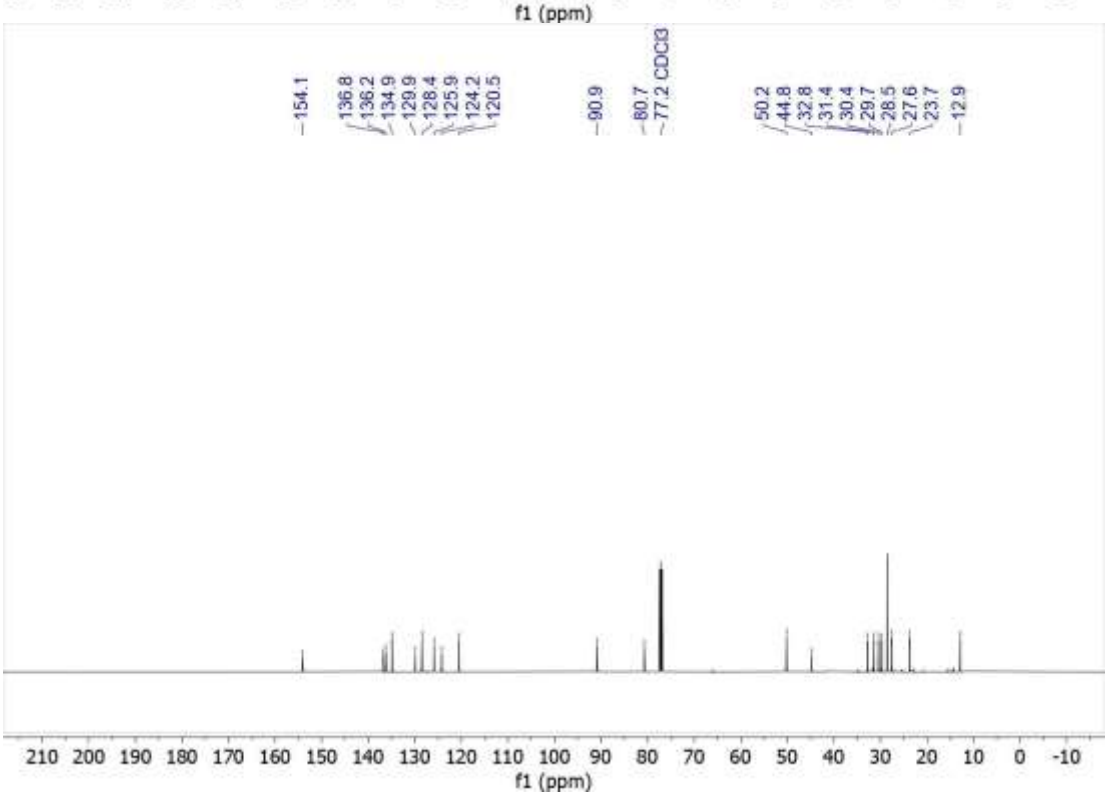
2.35
2.33
1.92
1.91
1.90
1.90
1.89
1.81
1.67
1.52
0.92
0.96
0.90
1.00
0.96
0.91
1.94
4.11
1.02
2.70
2.00
1.78
1.27
9.01
1.06
f1 (ppm)


154.1
136.8
136.2
134.9
129.9
128.4
125.9
124.2
120.5
90.9
80.7
77.2 CDCl3
50.2
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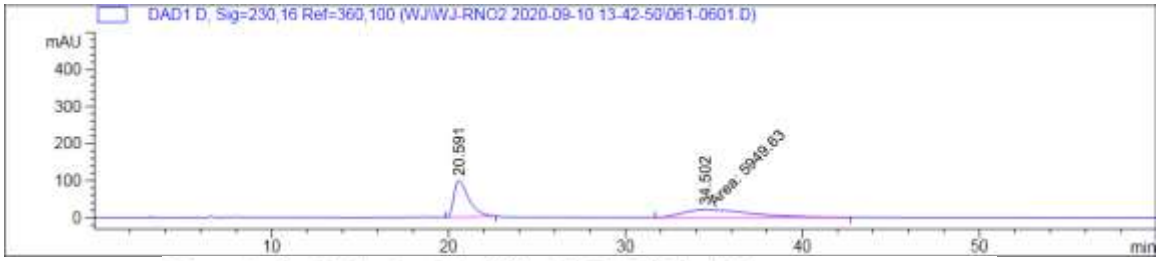
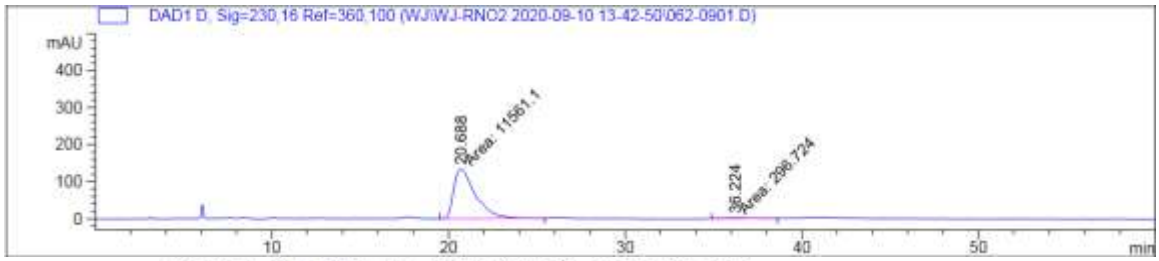
32.8
31.4
30.4
29.7
28.5
27.6
23.7
12.9
f1 (ppm)



Signal 3: DAD1 D, Sig=230,16 Ref=360,100

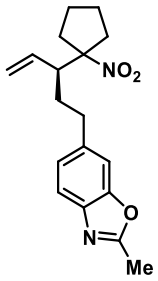
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.591	BB	0.8476	5818.23682	99.01282	49.4417
2	34.502	MF	4.6076	5949.63477	21.52117	50.5583
Totals :				1.17679e4	120.53399	



Signal 3: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.688	MM	1.4387	1.15611e4	133.93050	97.4976
2	36.224	FM	1.9779	296.72366	2.50028	2.5024
Totals :				1.18578e4	136.43078	

(*S*)-2-Methyl-6-(3-(1-nitrocyclopentyl)pent-4-en-1-yl)benzo[*d*]oxazole (**4.3l**)



Procedures

Allylic acetate **4.1l** (25.9 mg, 0.1 mmol, 100 mol%) and nitrocyclopentane **4.2b** (48 µL, 0.45 mmol, 450 mol%) were subject to standard reaction conditions (NMP, 80 °C, 24 h) with (*S*)-Ir-tol-BINAP-OMe,NO_2 (5.5 mg, 0.05 mmol, 5 mol%). The title compound was obtained in 74% yield (23.6 mg, 0.07 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate = 20:1–10:1).

TLC (SiO_2) R_f = 0.34 (hexane : ethyl acetate = 4:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 8.1 Hz, 1H), 7.23 (s, 1H), 7.08 – 7.03 (m, 1H), 5.58 (dt, J = 16.9, 9.9 Hz, 1H), 5.30 (dd, J = 10.1, 1.5 Hz, 1H), 5.18 (dd, J = 16.9, 1.3 Hz, 1H), 2.81 (ddd, J = 14.2, 9.6, 4.7 Hz, 1H), 2.70 – 2.63 (m, 1H), 2.62 (s, 3H), 2.56 – 2.49 (m, 2H), 1.87 – 1.68 (m, 4H), 1.64 (ddq, J = 11.0, 7.8, 4.4, 3.3 Hz, 4H), 1.57 – 1.49 (m, 1H) ppm.

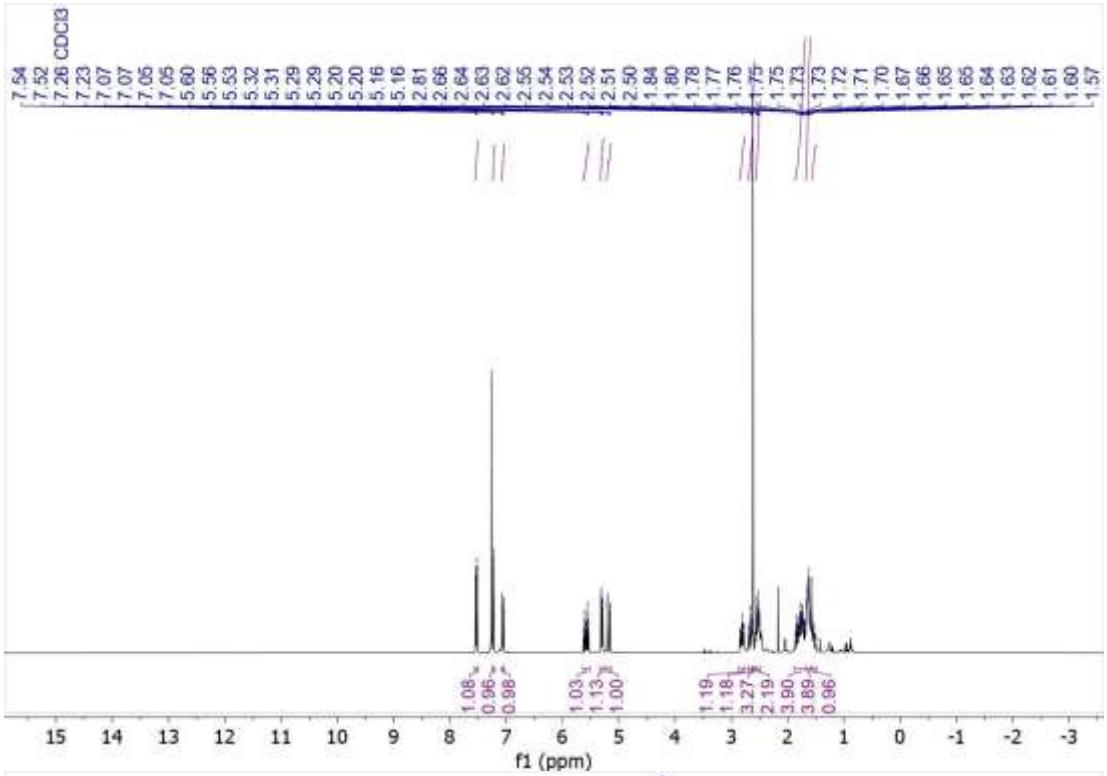
^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7, 151.4, 134.0 138.5, 136.1, 124.8, 120.6, 119.2, 110.0, 103.7, 51.1, 35.8, 33.9, 33.7, 31.9, 24.1, 24.1, 14.7 ppm.

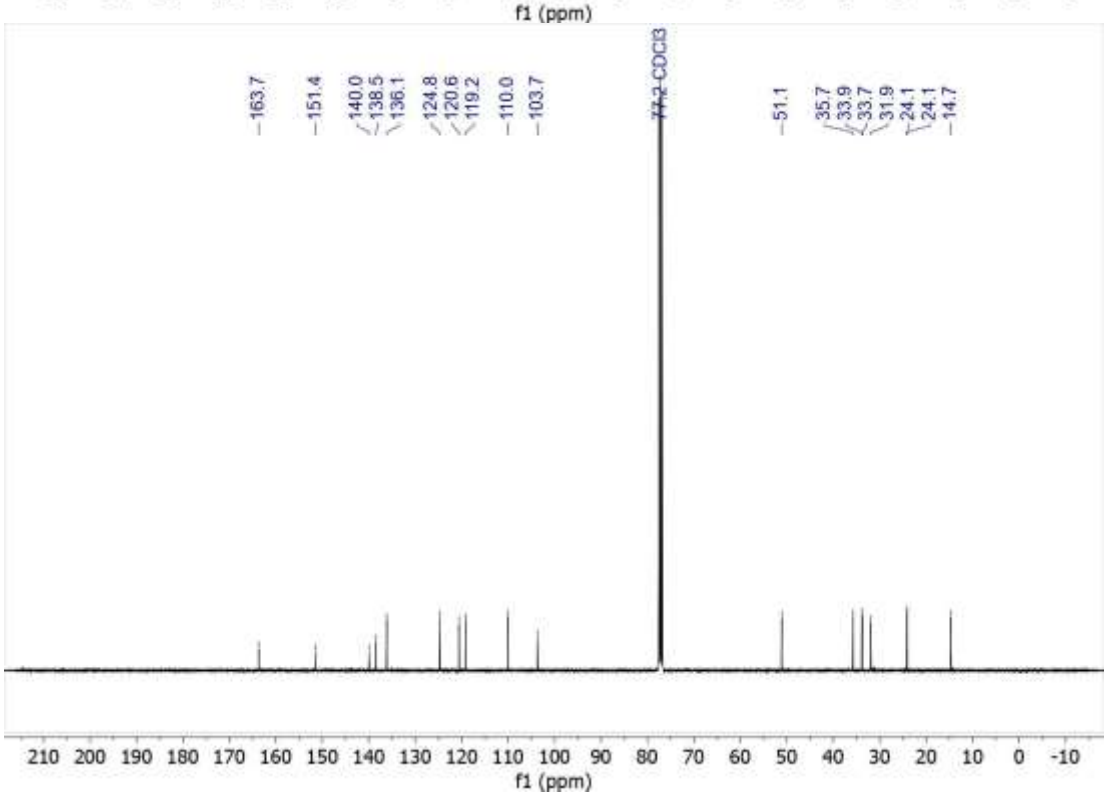
HRMS (ESI) m/z: [(M+Na)+] calcd for $C_{18}H_{22}N_2O_3$ 337.1523, found 337.1533

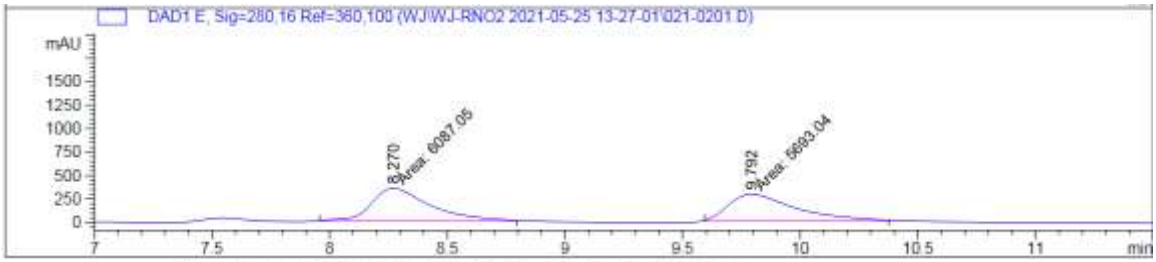
FTIR (Neat): 2949, 1614, 1531, 1484, 1355, 1243, 1189, 1117, 996, 925, 849, 821 cm^{-1}.

$[\alpha]_D^{28}$: - 9.3 (c = 2.0, $CHCl_3$).

HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralcel ADH column, hexane : 2-PrOH = 80:10, 1.0 mL/min, 280 nm), t_{major} = 8.27 min, t_{minor} = 9.79 min; ee = 89%.

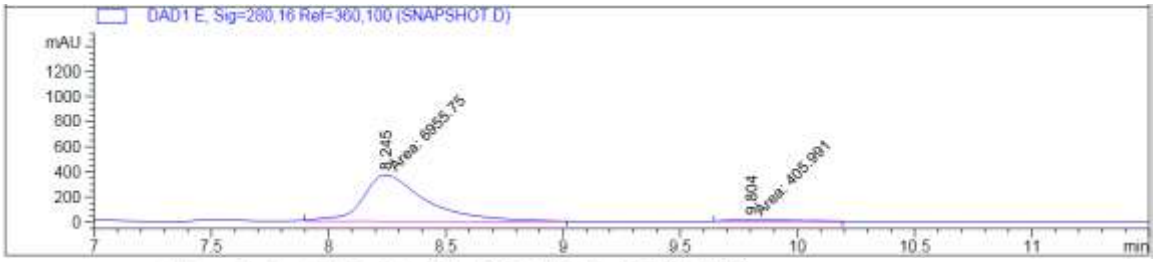

7.54
7.52
7.26 CDCl3
7.23
7.07
7.07
7.05
7.05
5.60
5.56
5.53
5.32
5.31
5.29
5.29
5.20
5.20
5.16
5.16
2.81
2.66
2.64
2.63
2.62
2.55
2.54
2.53
2.52
2.51
2.50
1.84
1.80
1.78
1.77
1.76
1.75
1.75
1.73
1.73
1.72
1.71
1.70
1.67
1.66
1.65
1.65
1.64
1.63
1.62
1.61
1.60
1.57
1.08
0.96
0.98
1.03
1.13
1.00
1.19
1.18
3.27
2.19
3.90
3.89
0.96
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)


163.7
151.4
140.0
138.5
136.1
124.8
120.6
119.2
110.0
103.7
77.2 CDCl3
51.1
35.7
33.9
33.7
31.9
24.1
24.1
14.7
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)



Signal 4: DAD1 E, Sig=280,16 Ref=360,100

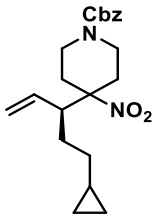
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.270	MF	0.2906	6087.05420	349.12973	51.6724
2	9.792	FM	0.3329	5693.03711	285.00653	48.3276
Totals :				1.17801e4	634.13626	



Signal 4: DAD1 E, Sig=280,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.245	FM	0.3128	6955.75098	370.57996	94.4851
2	9.804	FM	0.3354	405.99142	20.17389	5.5149
Totals :				7361.74240	390.75384	

Benzyl (*S*)-4-(5-cyclopropylpent-1-en-3-yl)-4-nitropiperidine-1-carboxylate (4.3m)



Procedures

Allylic acetate **4.1h** (33.6 mg , 0.2 mmol, 100 mol%) and nitroalkane **4.2d** (237.9 mg, 0.9 mmol, 450 mol%) were subject to standard reaction conditions (NMP, 60 °C, 48 h) with (*S*)-Ir-tol-BINAP-OMe,NO_2 (22.1 mg, 0.02 mmol, 10 mol%). The title compound was obtained in 72% yield (53.8 mg, 0.14 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate = 20:1–10:1).

TLC (SiO_2) R_f = 0.67 (hexane : ethyl acetate = 2:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H), 5.41 (dt, J = 16.9, 9.9 Hz, 1H), 5.22 (d, J = 1.6 Hz, 1H), 5.12 (s, 2H), 5.08 (dd, J = 16.9, 1.7 Hz, 1H), 4.12 (dd, J = 14.5, 7.4 Hz, 2H), 2.81 (s, 2H), 2.45 (d, J = 14.3 Hz, 2H), 2.38 (ddd, J = 11.9, 9.7, 2.5 Hz, 1H), 2.03 (dtd, J = 5.8, 4.0, 1.6 Hz, 0H), 1.87 – 1.65 (m, 2H), 1.55 – 1.45 (m, 1H), 1.32 – 1.17 (m, 2H), 1.11 (dddd, J = 16.3, 13.7, 11.6, 5.9 Hz, 2H), 0.58 (ddt, J = 10.0, 7.4, 3.8 Hz, 1H), 0.46 – 0.33 (m, 2H), -0.01 (dtd, J = 9.3, 4.8, 3.4 Hz, 1H), -0.04 – -0.10 (m, 1H) ppm.

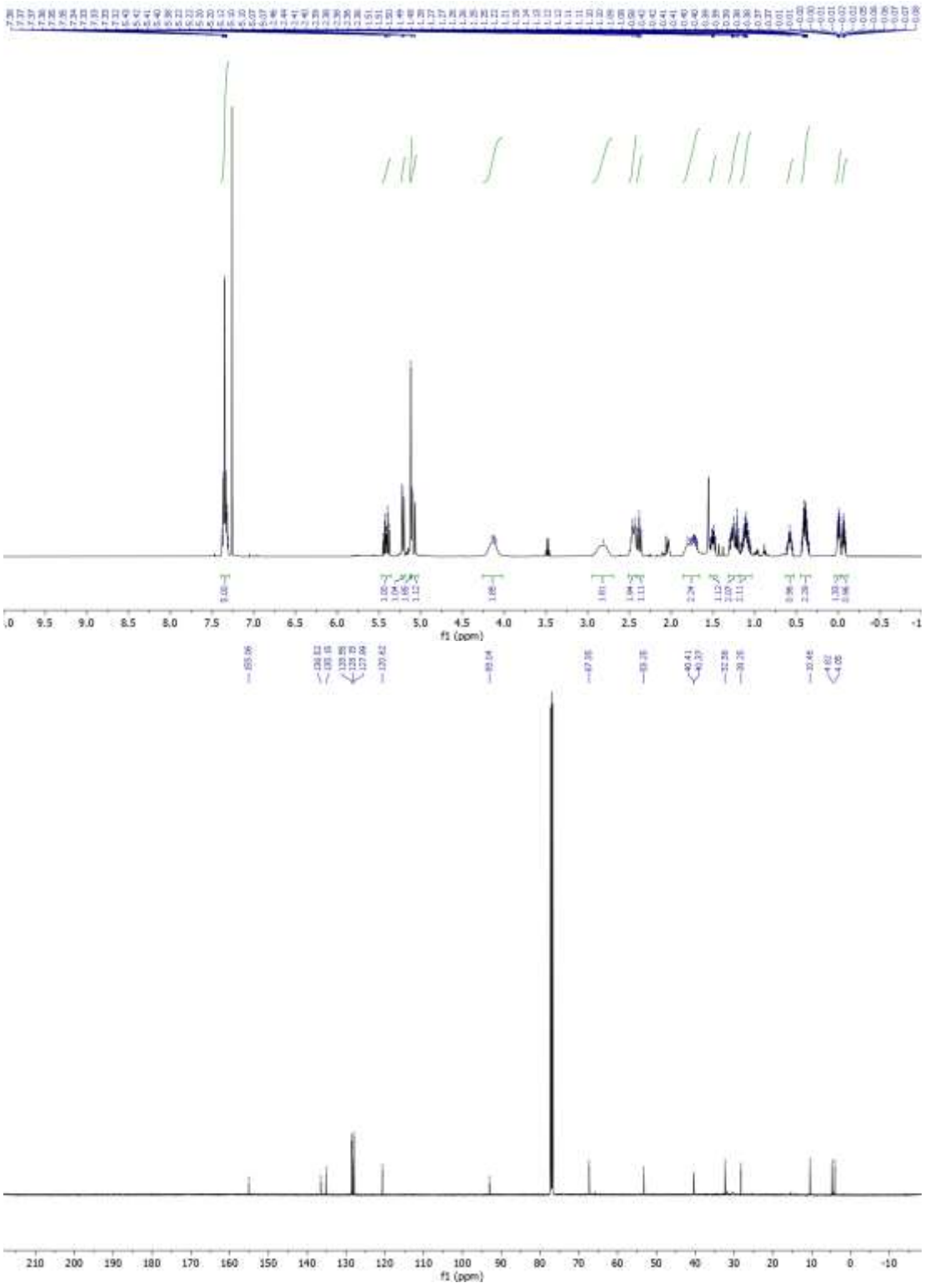
^{13}C NMR (126 MHz, $CDCl_3$) δ 155.1, 136.5, 135.2, 128.6, 128.2, 128.0, 120.6, 93.0, 67.4, 53.3, 40.4, 40.4, 32.4, 28.3, 10.5, 4.8, 4.1 ppm.

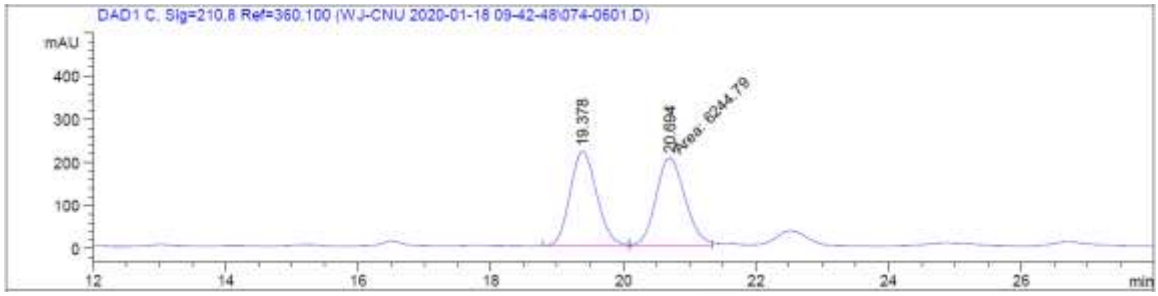
HRMS (ESI) m/z: [(M+Na)+] calcd for $C_{21}H_{28}N_2O_4$ 395.1941, found 395.1948.

FTIR (Neat): 2927, 1698, 1536, 1430, 1363, 1235, 1129, 1013, 927, 751, 697 cm^{-1}.

$[\alpha]_D^{28}$: + 6.0 (c = 0.5, $CHCl_3$).

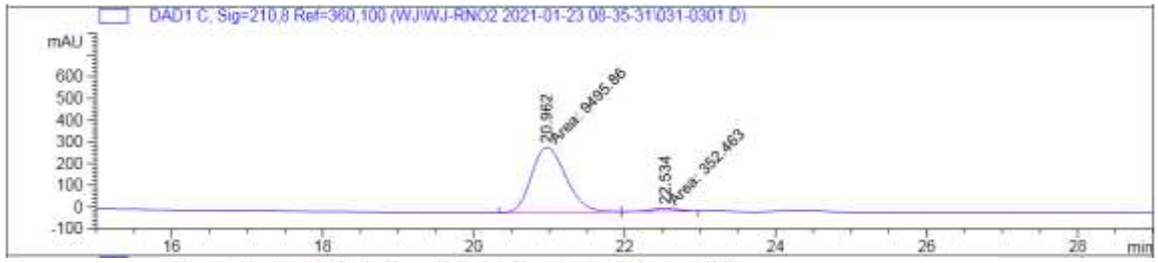
HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H column, hexane : 2-PrOH = 90:10, 1.0 mL/min, 210 nm), t_{major} = 20.96 min, t_{minor} = 22.53min; ee = 93 %.





Signal 3: DAD1 C, Sig=210,8 Ref=360,100

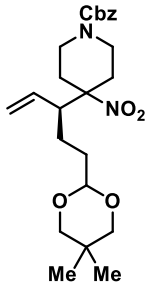
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.378	BV	0.4393	6155.41406	219.44031	49.6396
2	20.694	MF	0.5101	6244.79004	204.05780	50.3604
Totals :				1.24002e4	423.49811	



Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.962	MM	0.5289	9495.85645	299.23465	96.4211
2	22.534	MM	0.4717	352.46280	12.45394	3.5789
Totals :				9848.31924	311.68859	

Benzyl (*S*)-4-(5-(5,5-dimethyl-1,3-dioxan-2-yl)pent-1-en-3-yl)-4-nitropiperidine-1-carboxylate (4.3n)



Procedures

Allylic acetate **4.1m** (24.2 mg, 0.10 mmol, 100 mol%) and nitroalkane **4.2d** (118.9 mg, 0.45 mmol, 450 mol%) were subject to standard reaction conditions (DMF, 60 °C, 48 h). The title compound was obtained in 68% yield (28.0 mg, 0.07 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate = 20:1–10:1).

TLC (SiO_2) R_f = 0.67 (hexane: ethyl acetate = 2:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (hd, J = 6.8, 2.1 Hz, 5H), 5.43 (dt, J = 16.9, 10.0 Hz, 1H), 5.23 (dd, J = 10.1, 1.4 Hz, 1H), 5.15 – 5.06 (m, 3H), 4.36 (t, J = 4.8 Hz, 1H), 4.12 (s, 2H), 3.57 (d, J = 11.1 Hz, 2H), 3.38 (d, J = 10.7 Hz, 2H), 2.91 – 2.74 (m, 2H), 2.44 (d, J = 11.5 Hz, 2H), 2.38 – 2.30 (m, 1H), 1.84 – 1.70 (m, 2H), 1.70 – 1.62 (m, 1H), 1.62 – 1.54 (m, 2H), 1.43 (ddt, J = 12.7, 9.5, 4.7 Hz, 1H), 1.26 (tq, J = 11.5, 7.2, 5.6 Hz, 1H), 1.16 (s, 3H), 0.71 (s, 3H) ppm.

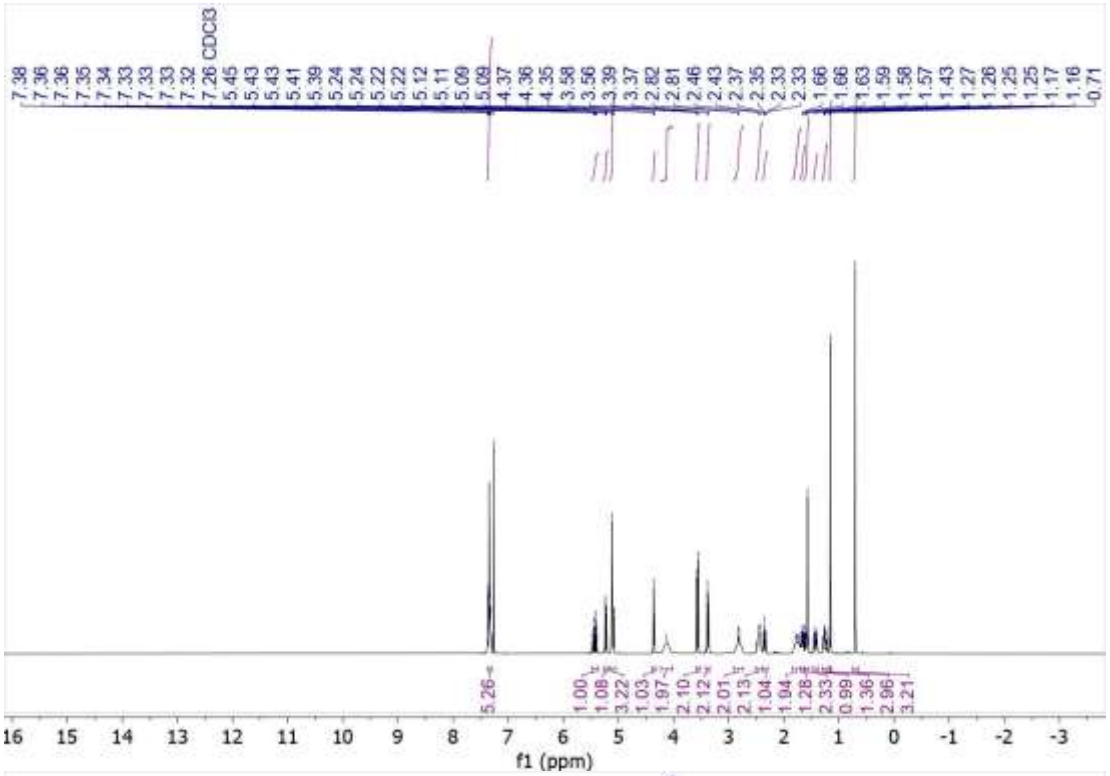
^{13}C NMR (126 MHz, $CDCl_3$): δ 155.2, 136.7, 134.8, 128.7, 128.3, 128.1, 121.2, 101.6, 93.1, 77.3, 67.5, 53.6, 40.5, 40.5, 32.9, 30.3, 23.1, 22.6, 22.0 ppm.

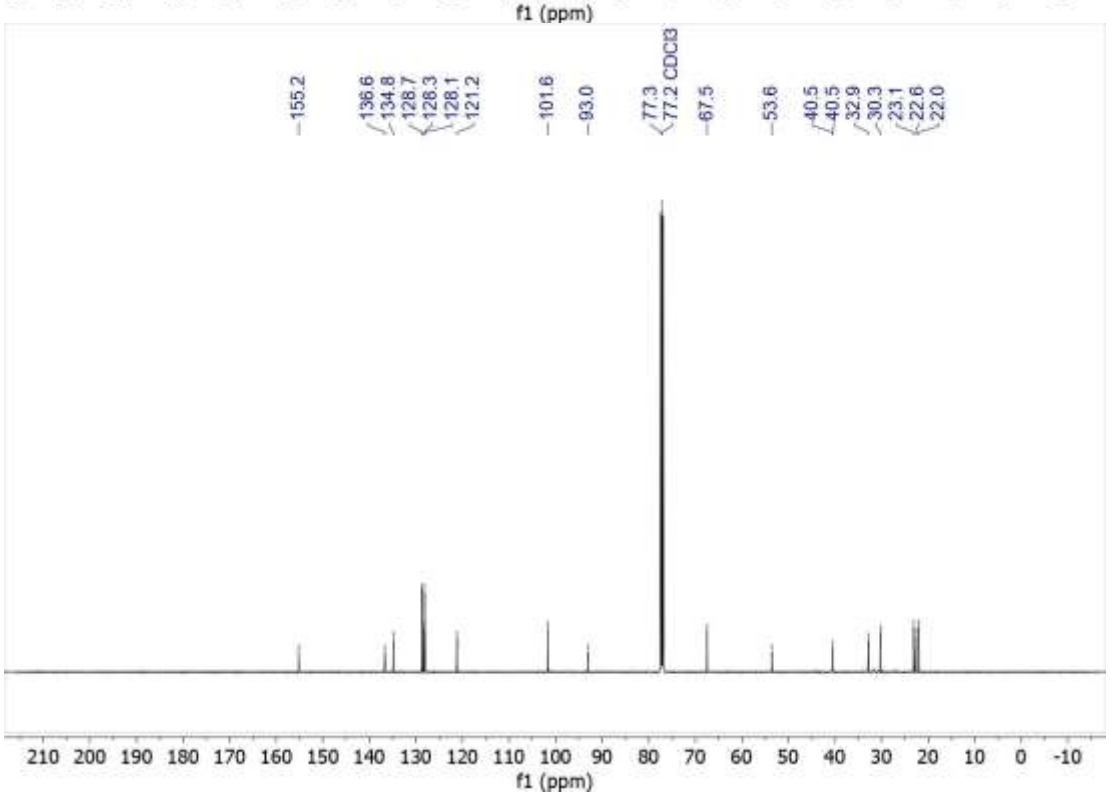
HRMS (ESI): Calculated for $C_{24}H_{34}N_2O_6$ [M+H$^+$] = 447.2490, Found 447.2493.

FTIR (Neat): 2954, 1699, 1536, 1471, 1234, 1123, 1085, 1014, 972, 762, 697 cm^{-1}.

$[\alpha]_D^{28}$ = - 5.0 (*c* 0.5, $CHCl_3$).

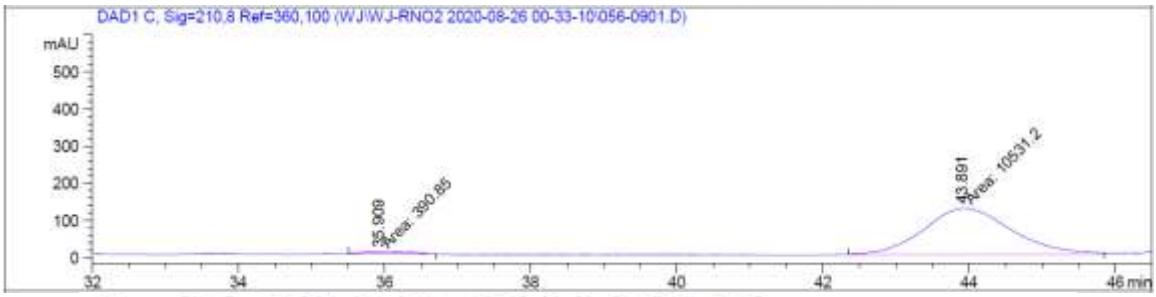
HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H column, hexane : 2-PrOH = 90:10, 1.0 mL/min, 210 nm), t_{major} = 43.89 min, t_{minor} = 35.91 min; ee = 92 %.


7.38
7.36
7.36
7.35
7.34
7.33
7.33
7.33
7.32
7.26 CDCl3
5.45
5.43
5.43
5.41
5.39
5.24
5.24
5.22
5.22
5.12
5.11
5.09
5.09
4.37
4.36
4.35
3.58
3.56
3.39
3.37
2.82
2.81
2.46
2.43
2.37
2.35
2.33
2.33
1.66
1.66
1.63
1.59
1.58
1.57
1.43
1.27
1.26
1.25
1.25
1.17
1.16
0.71
5.26
1.00
1.08
3.22
1.03
1.97
2.10
2.12
2.01
2.13
1.04
1.94
1.28
2.33
0.99
1.36
2.96
3.21
f1 (ppm)


155.2
136.6
134.8
128.7
128.3
128.1
121.2
101.6
93.0
77.3
77.2 CDCl3
67.5
53.6
40.5
40.5
32.9
30.3
23.1
22.6
22.0
f1 (ppm)

Signal 2: DAD1 C, Sig=210,8 Ref=360,100

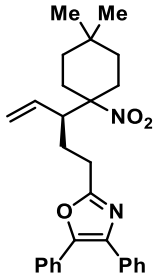
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	36.357	FM	1.1414	7524.03369	109.86549	50.0846
2	48.249	FM	1.5613	7498.60059	80.04494	49.9154
Totals :				1.50226e4	189.91042	



Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	35.909	FM	0.9230	390.84976	7.05767	3.5785
2	43.891	FM	1.4083	1.05312e4	124.63325	96.4215
Totals :				1.09221e4	131.69092	

(*S*)-2-(3-(4,4-Dimethyl-1-nitrocyclohexyl)pent-4-en-1-yl)-4,5-diphenyloxazole (4.3o)



Procedure:

Allylic acetate **4.1d** (34.7 mg, 0.1 mmol, 100 mol%) and nitroalkane **4.2d** (70.7 mg, 0.45 mmol, 450 mol%) was subjected to standard reaction conditions (NMP, 60 ºC, 48 h). The nitroalkane product was obtained in 72% yield (32.1 mg, 0.07 mmol) as a yellow oil after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate = 20:1).

TLC (SiO_2) R_f = 0.56 (hexane : ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (dt, *J* = 6.4, 1.5 Hz, 2H), 7.60 – 7.55 (m, 2H), 7.40 – 7.29 (m, 6H), 5.57 (dt, *J* = 17.0, 10.0 Hz, 1H), 5.29 (dd, *J* = 10.1, 1.7 Hz, 1H), 5.19 (dd, *J* = 16.9, 1.7 Hz, 1H), 2.88 (ddd, *J* = 15.5, 9.3, 5.2 Hz, 1H), 2.70 (ddd, *J* = 15.8, 9.1, 7.3 Hz, 1H), 2.50 (ddd, *J* = 12.0, 9.7, 2.4 Hz, 1H), 2.09 (dddd, *J* = 13.4, 9.6, 7.3, 2.4 Hz, 1H), 1.91 – 1.64 (m, 3H), 1.29 – 1.21 (m, 2H), 0.89 (s, 6H) ppm.

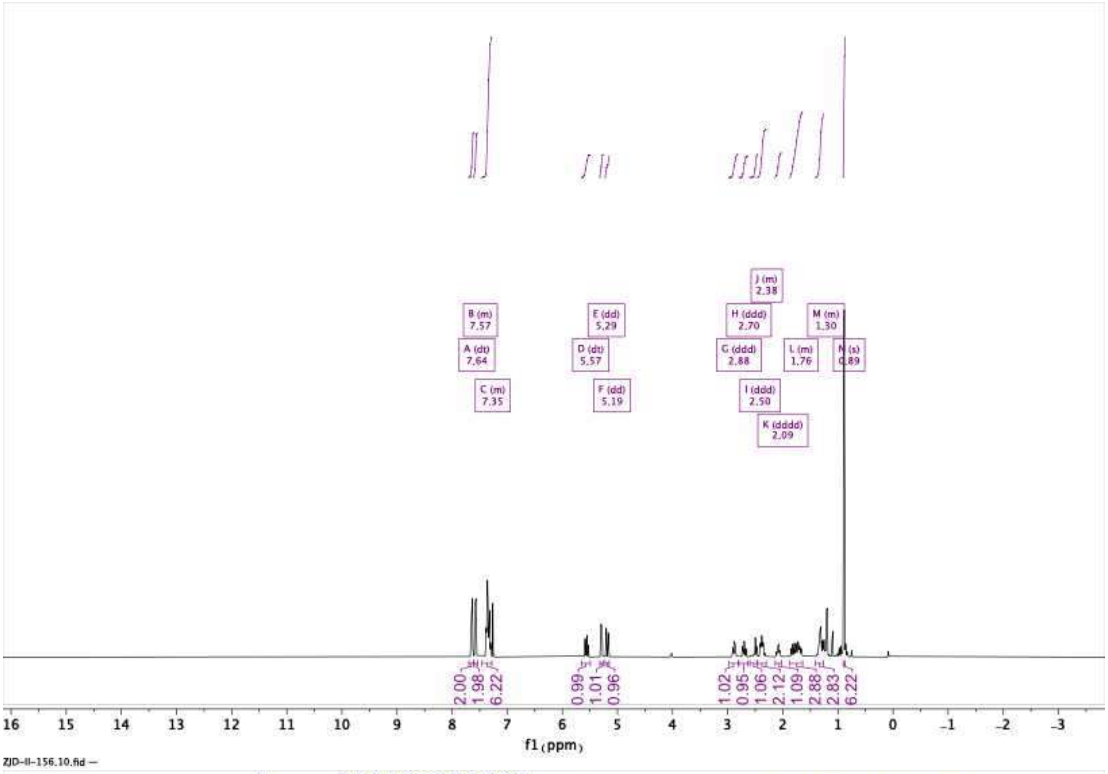
^{13}C NMR (126 MHz, $CDCl_3$): δ 162.7, 145.4, 135.2, 134.9, 132.6, 129.1, 128.8, 128.7, 128.6, 128.1, 128.0, 126.6, 121.0, 94.3, 53.1, 35.0, 35.0, 31.9, 29.3, 28.5, 27.5, 26.4, 26.0, 25.5 ppm.

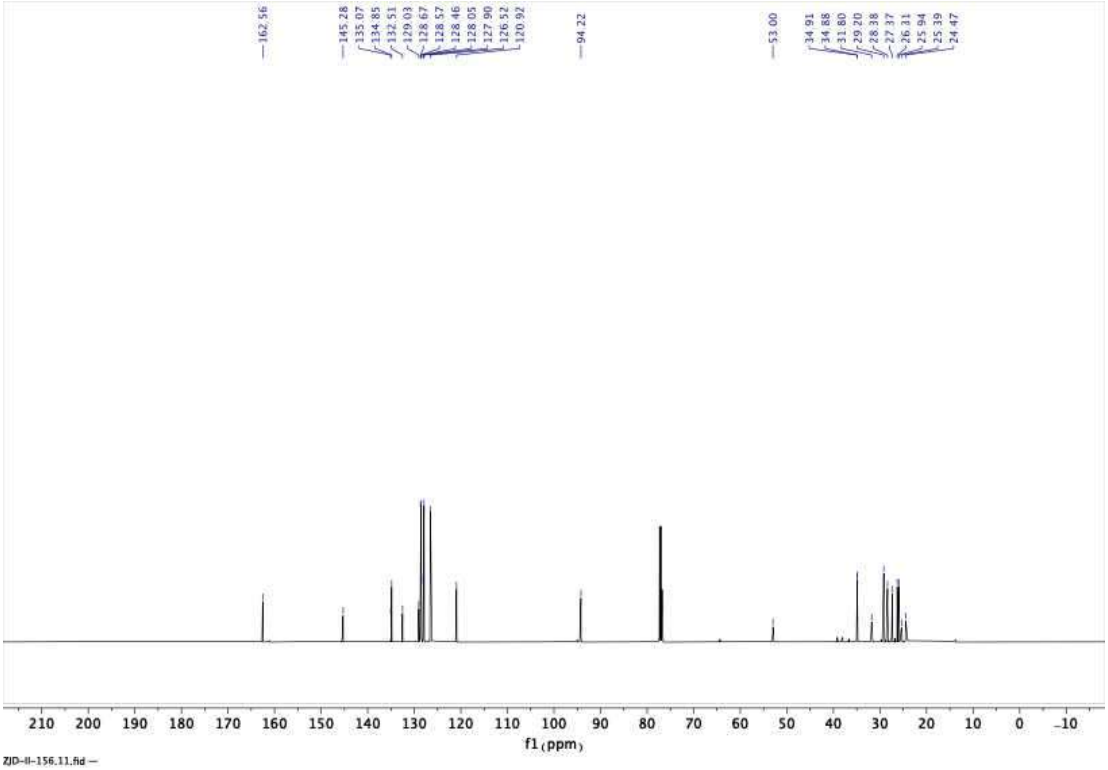
HRMS (ESI) m/z: [(M+Na)+] calcd for $C_{28}H_{32}N_2O_3$ 467.2305, found 467.2311.

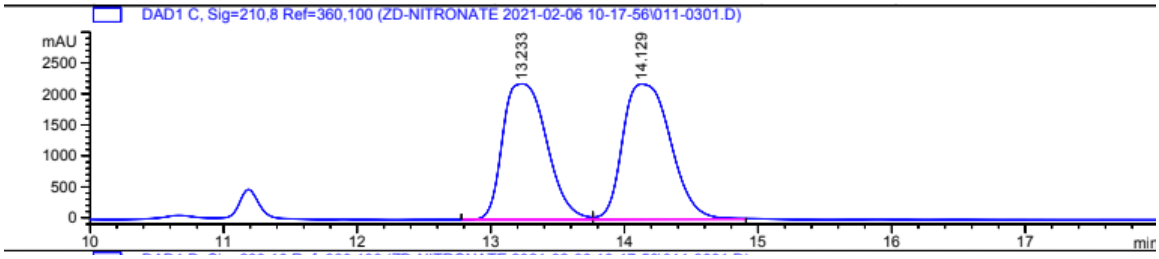
FTIR (Neat): 2951, 2858, 1569, 1533, 1502, 1446, 1427, 1366, 1343, 1220, 1178, 1156, 1059, 1024, 999, 961, 925, 858, 844, 791, 762, 693, 674 cm^{-1}.

$[\alpha]_D^{28}$**:** -2.0 (c = 1.0, $CHCl_3$).

HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H column, hexane : 2-PrOH = 90:10, 1.0 mL/min, 210 nm), t_{major} = 13.25 min, t_{minor} = 14.13 min; ee = 88%.

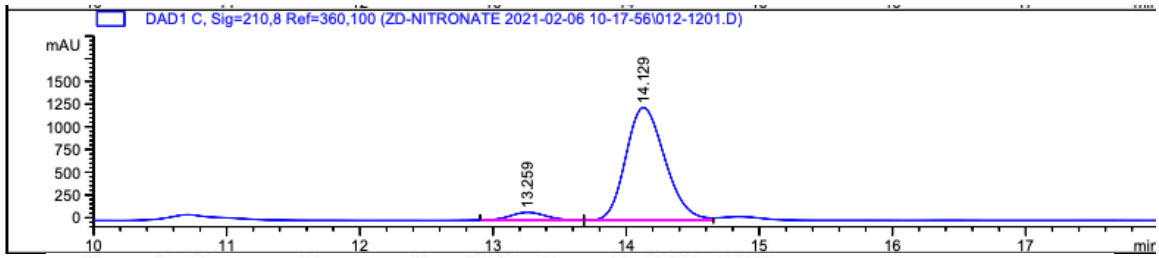

B (m) 7,57
A (dt) 7,64
C (m) 7,35
E (dd) 5,29
D (dt) 5,57
F (dd) 5,19
J (m) 2,38
H (ddd) 2,70
G (ddd) 2,88
I (ddd) 2,50
K (dddd) 2,09
M (m) 1,30
L (m) 1,76
N (s) 0,89
2.00 1.98 6.22 0.99 1.01 0.96 1.02 0.95 1.06 2.12 1.09 2.88 2.83 6.22
f1 (ppm)
ZJD-II-156.10.fid


162.56
145.28
135.07
134.85
132.51
129.03
128.67
128.57
128.46
128.05
127.90
126.52
120.92
94.22
53.00
34.91
34.88
31.80
29.20
28.38
27.37
26.31
25.94
25.39
24.47
f1 (ppm)
ZJD-II-156.11.fid



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

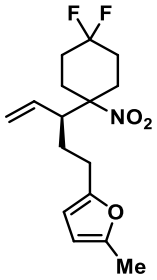
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.233	BV	0.3675	5.01809e4	2188.67139	47.9145
2	14.129	VB	0.3995	5.45492e4	2183.19165	52.0855
Totals :				1.04730e5	4371.86304	



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.259	BV	0.2962	1696.50684	88.26499	6.2447
2	14.129	VV	0.3212	2.54708e4	1242.05408	93.7553
Totals :				2.71673e4	1330.31907	

***(S)*-2-(3-(4,4-Difluoro-1-nitrocyclohexyl)pent-4-en-1-yl)-5-methylfuran (4.3p)**



Procedures

Allylic acetate **4.1c** (41.7 mg, 0.2 mmol, 100 mol%) and nitroalkane **4.2f** (149 mg, 0.9 mmol, 450 mol%) were subject to standard reaction conditions (DMF, 60 °C, 48 h). The title compound was obtained in 98% yield (61.4 mg, 0.20 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate = 100:1–50:1).

TLC (SiO_2) R_f = 0.72 (hexane : ethyl acetate = 10:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 – 5.80 (m, 2H), 5.50 (dt, J = 16.8, 9.9 Hz, 1H), 5.29 (dd, J = 10.1, 1.6 Hz, 1H), 5.15 (dd, J = 16.9, 1.3 Hz, 1H), 2.67 – 2.53 (m, 3H), 2.44 – 2.36 (m, 2H), 2.24 (s, 3H), 2.06 (dddd, J = 16.9, 10.6, 5.4, 3.0 Hz, 2H), 1.97 – 1.66 (m, 5H), 1.46 (dddd, J = 13.3, 11.6, 8.7, 4.7 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.7, 150.8, 134.6, 122.1 (dd, J = 243.9, 238.5 Hz), 121.4, 106.2, 106.0, 92.9, 92.9, 52.4, 52.4, 30.2 (ddd, J = 26.0, 24.3, 2.3 Hz), 29.1 (d, J = 9.6 Hz), 28.1 (d, J = 9.6 Hz), 27.2, 25.9, 13.6 ppm.

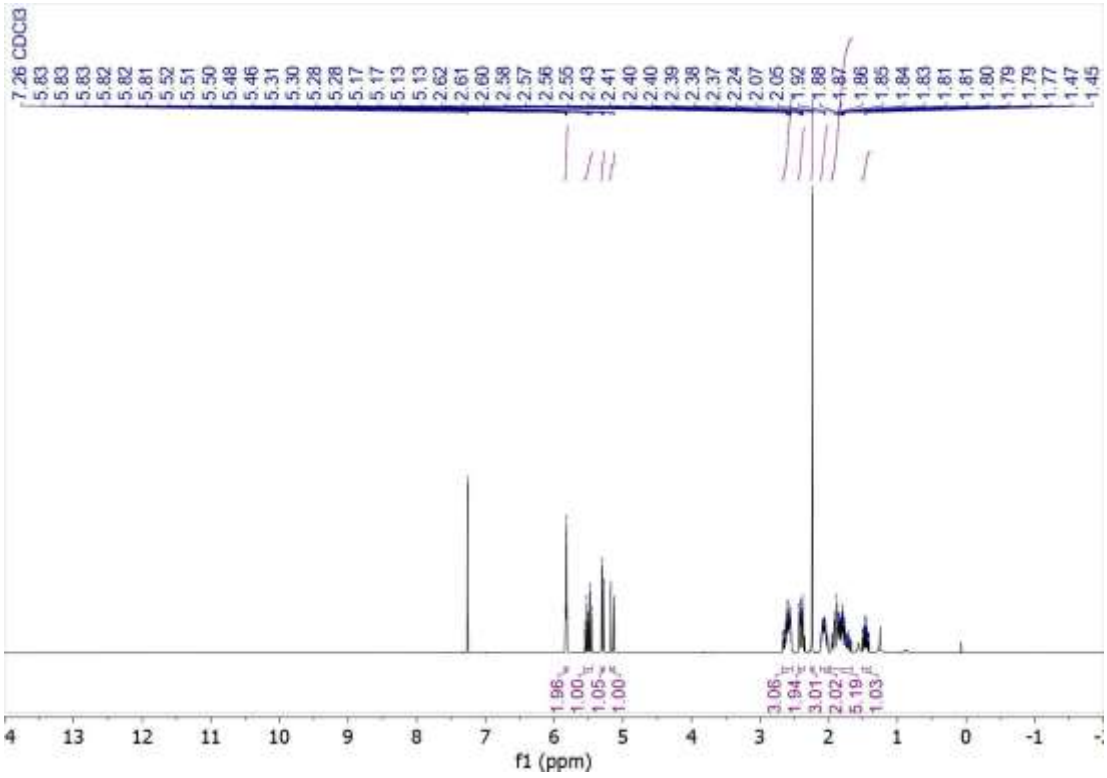
^{19}F NMR (471 MHz, CDCl3) δ -93.27 (d, J = 238.3 Hz), -103.58 (dddt, J = 238.3, 33.2, 23.6, 10.1 Hz) ppm.

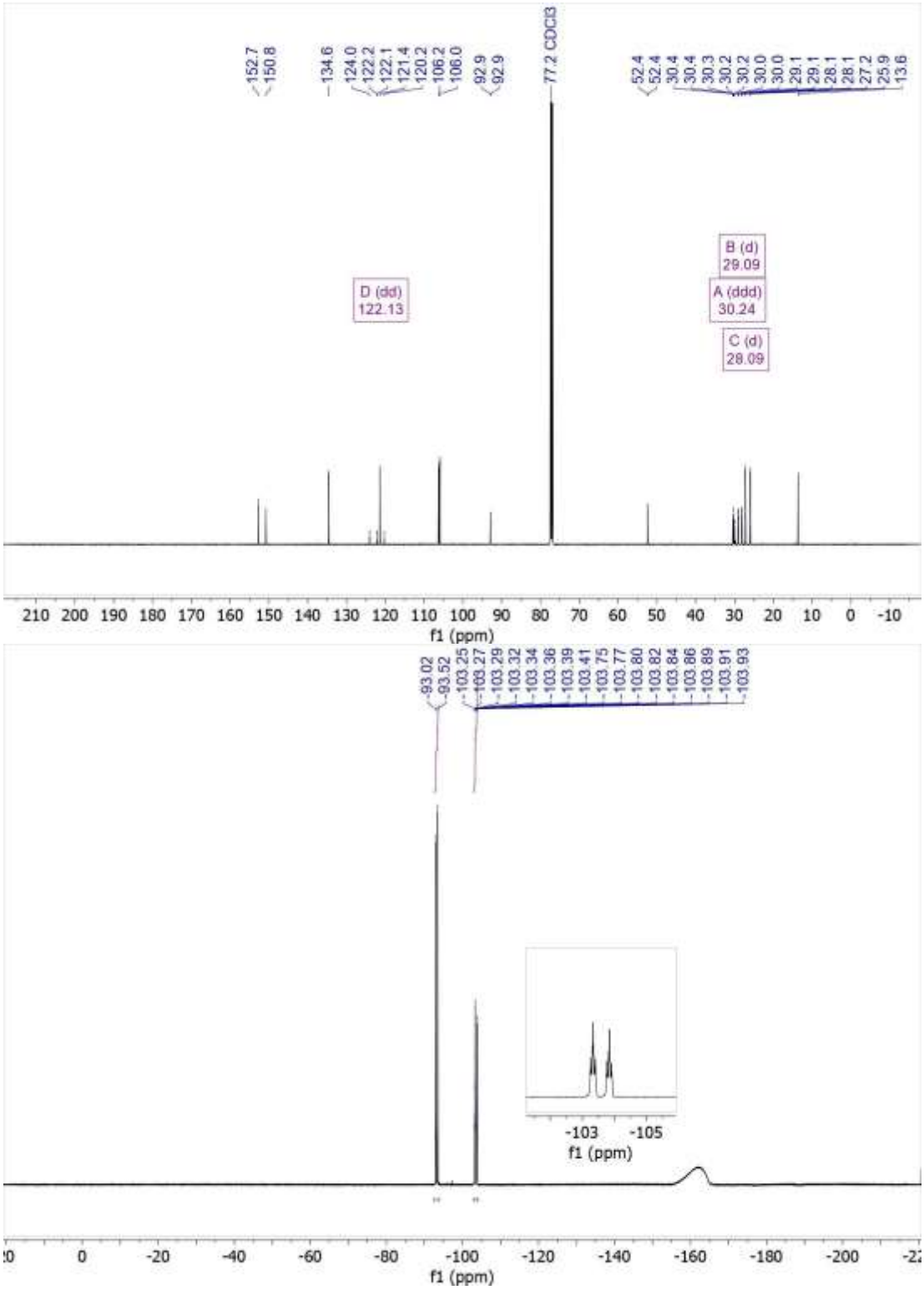
HRMS (ESI) m/z: [(M+Na)+] calcd for $C_{16}H_{21}F_2NO_3$ 336.1382, found 336.1382

FTIR (Neat) 2950, 1538, 1441, 1126, 933, 782 cm^{-1}.

$[\alpha]_D^{28}$: +12.0 (c = 1.0, $CHCl_3$).

HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H column, hexane : 2-PrOH = 95:5, 0.5 mL/min, 210 nm), t_{major} = 17.64 min, t_{minor} = 17.10 min; ee = 90 %.




152.7
150.8
134.6
124.0
122.2
122.1
121.4
120.2
106.2
106.0
92.9
92.9
77.2 CDCl3
52.4
52.4
30.4
30.4
30.3
30.2
30.2
30.0
30.0
29.1
29.1
28.1
28.1
27.2
25.9
13.6
D (dd)
122.13
B (d)
29.09
A (ddd)
30.24
C (d)
28.09
f1 (ppm)
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-93.52
-103.25
-103.27
-103.29
-103.32
-103.34
-103.36
-103.39
-103.41
-103.75
-103.77
-103.80
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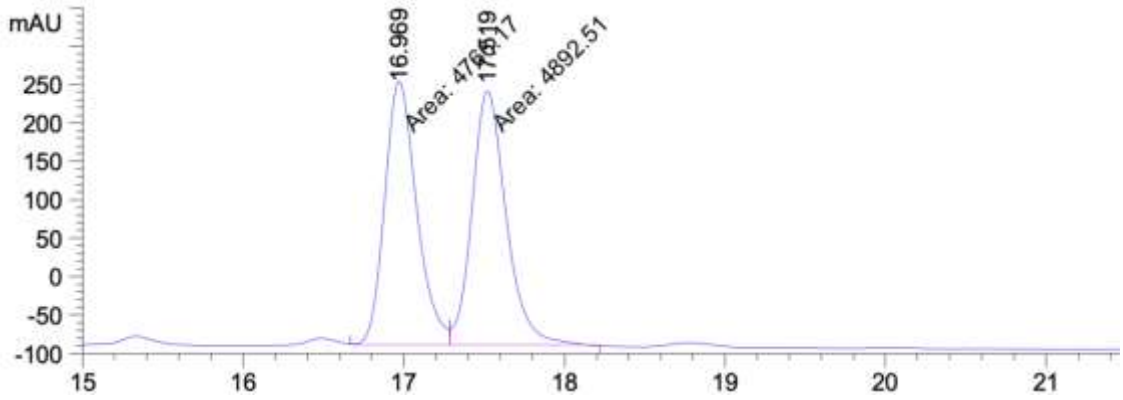
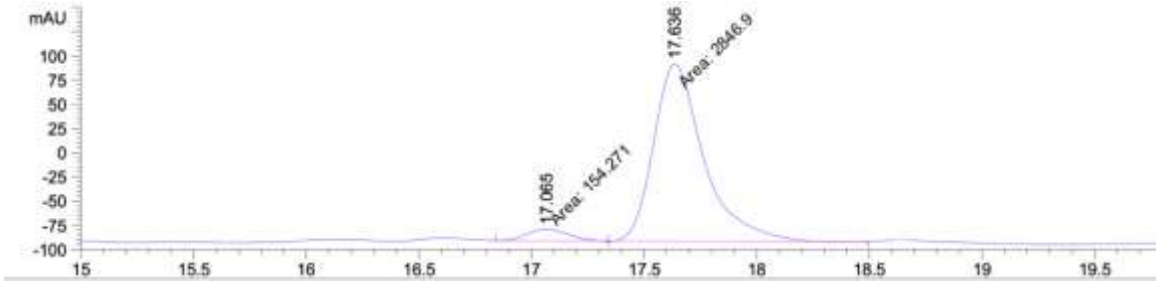
-103.93
-103
-105
f1 (ppm)
f1 (ppm)



Signal 2: DAD1 C, Sig=210,8 Ref=360,100

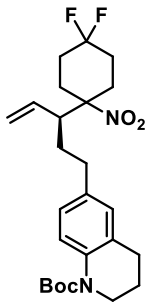
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.969	MF	0.2304	4766.17432	344.80087	49.3460
2	17.519	FM	0.2458	4892.51025	331.76285	50.6540
Totals :				9658.68457	676.56372	



Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.065	MF	0.2098	154.27129	12.25603	5.1404
2	17.636	FM	0.2583	2846.89941	183.68439	94.8596
Totals :				3001.17070	195.94041	

***tert*-Butyl (*S*)-6-(3-(4,4-difluoro-1-nitrocyclohexyl)pent-4-en-1-yl)-3,4-dihydroquinoline-1(2*H*)-carboxylate (4.3q)**



Procedures

Allylic acetate **4.1k** (35.9 mg, 0.1 mmol, 100 mol%) and 1,1-difluoro-4-nitrocyclohexane **4.2f** (74.3 mg, 0.45 mmol, 450 mol%) were subject to standard reaction conditions (DMF, 60 °C, 24 h). The title compound was obtained in 94% yield (43.6 mg, 0.09 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate = 20:1).

TLC (SiO_2) R_f = 0.59 (hexane : ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 8.4 Hz, 1H), 6.87 (dd, J = 8.5, 2.2 Hz, 1H), 6.81 (d, J = 2.2 Hz, 1H), 5.53 (dt, J = 16.9, 9.9 Hz, 1H), 5.32 (dd, J = 10.2, 1.6 Hz, 1H), 5.16 (dd, J = 16.9, 1.7 Hz, 1H), 3.73 – 3.65 (m, 2H), 2.72 (t, J = 6.6 Hz, 2H), 2.67 – 2.51 (m, 3H), 2.41 (ddd, J = 11.8, 9.7, 2.4 Hz, 1H), 2.30 (ddd, J = 14.0, 9.7, 7.3 Hz, 1H), 2.13 – 1.99 (m, 2H), 1.98 – 1.66 (m, 6H), 1.52 (s, 9H), 1.51 – 1.41 (m, 1H), 1.35 – 1.24 (m, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 154.0, 136.8, 135.7, 134.9, 129.8, 128.3, 125.7, 124.1, 122.0 (dd, J = 243.9, 238.7 Hz), 121.2, 92.9, 92.9, 80.7, 52.5, 44.6, 32.7, 30.3, 30.1, 29.9, 29.0 (d, J = 9.7 Hz), 28.4, 27.9 (d, J = 9.8 Hz), 27.5, 23.5 ppm.

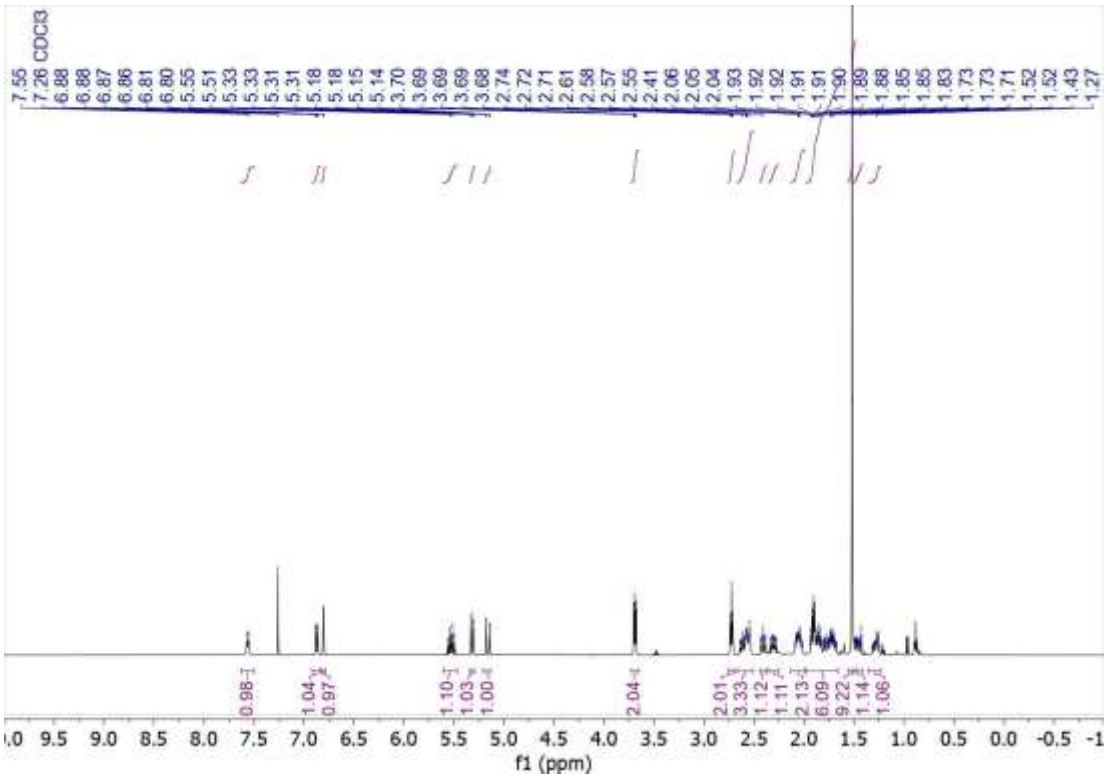
^{19}F NMR (471 MHz, $CDCl_3$) δ -93.16 (d, J = 238.1 Hz), -103.65 (dtt, J = 238.1, 33.5, 10.7 Hz) ppm.

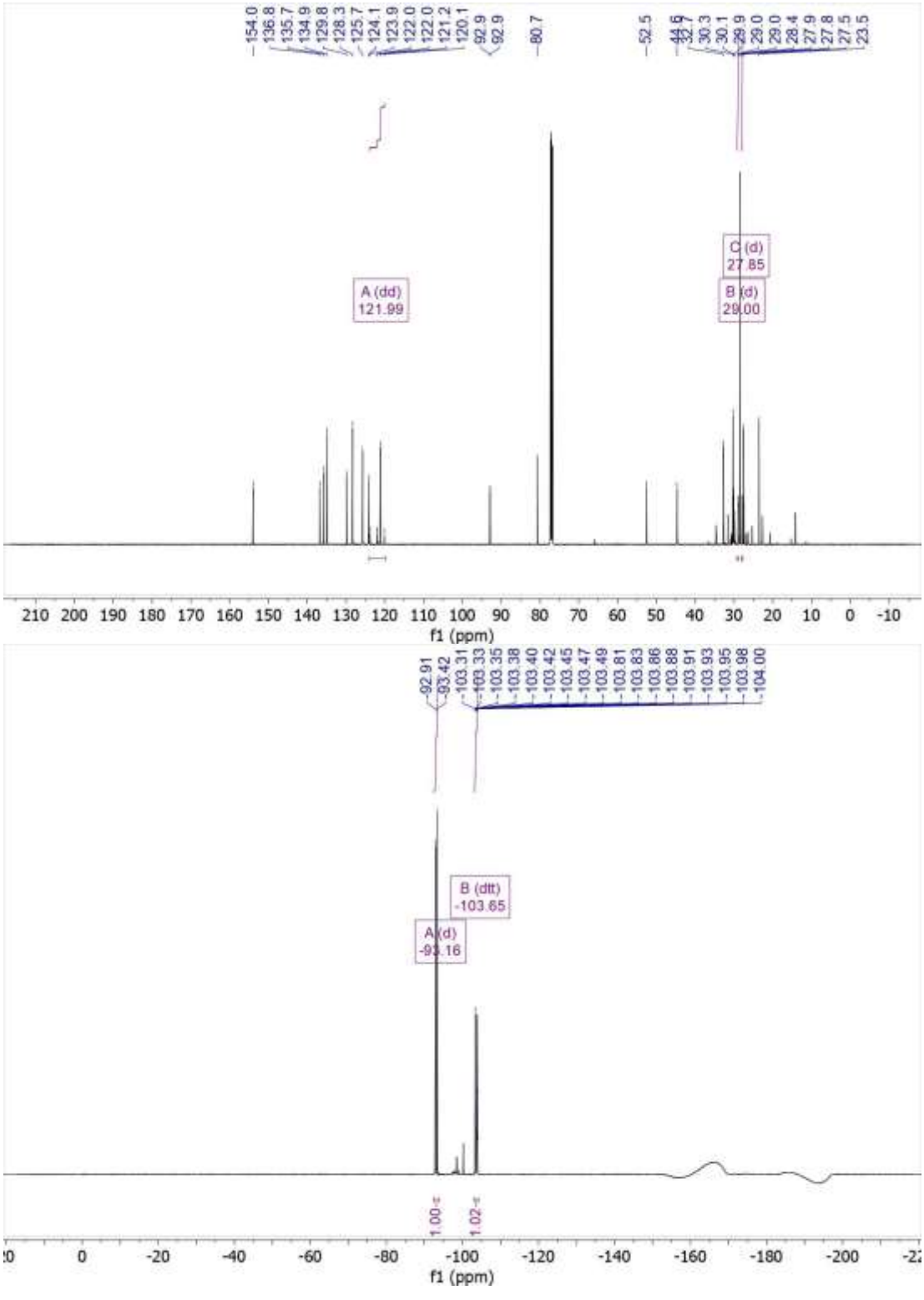
HRMS (ESI) m/z: [(M+Na)+] calculated for $C_{25}H_{34}F_2N_2O_4$ 487.2379, found 487.2383.

FTIR (Neat): 2937, 1692, 1538, 1501, 1440, 1367, 1334, 1257, 1157, 1133, 1010, 965, 931, 753 cm^{-1}.

$[\alpha]_D^{28}$: + 3.0 (c = 0.5, $CHCl_3$).

HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralpak AD-H column, hexane : 2-PrOH = 93:7, 1.0 mL/min, 280 nm), t_{major} = 5.86 min, t_{minor} = 6.51 min; ee = 87 %.

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124.1
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122.0
121.2
120.1
92.9
92.9
80.7
52.5
44.6
32.7
30.3
30.1
29.9
29.0
29.0
28.4
27.9
27.8
27.5
23.5
A (dd)
121.99
C (d)
27.85
B (d)
29.00
f1 (ppm)
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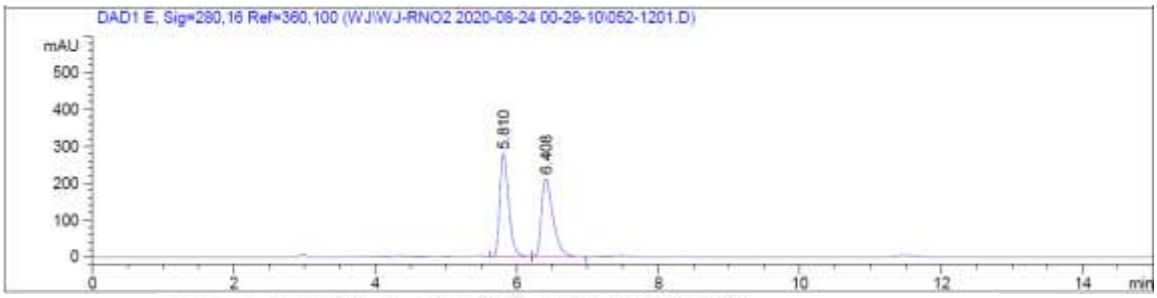
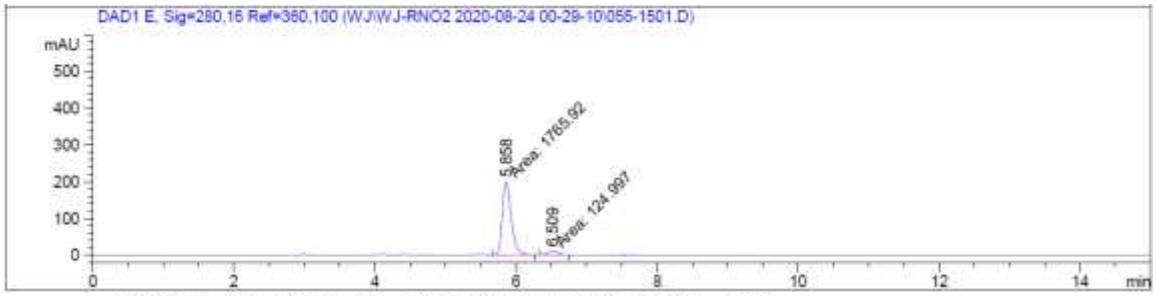
103.40
103.42
103.45
103.47
103.49
103.81
103.83
103.86
103.88
103.91
103.93
103.95
103.98
104.00
B (dtt)
-103.65
A (d)
-93.16
1.00
1.02
f1 (ppm)



Signal 4: DAD1 E, Sig=280,16 Ref=360,100

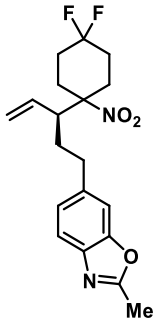
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.810	VV	0.1345	2455.98853	279.49927	50.2757
2	6.408	VB	0.1737	2429.05225	211.99008	49.7243
Totals :				4885.04077	491.48935	



Signal 4: DAD1 E, Sig=280,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.858	VB	0.1355	1766.37402	199.19420	93.3024
2	6.509	BB	0.1731	126.79659	11.11489	6.6976
Totals :				1893.17061	210.30909	

(*S*)-6-(3-(4,4-Difluoro-1-nitrocyclohexyl)pent-4-en-1-yl)-2-methylbenzo[d]oxazole (4.3r)



Procedures

Allylic acetate **4.1l** (25.9 mg, 0.1 mmol, 100 mol%) and 1,1-difluoro-4-nitrocyclohexane **4.2f** (74.3 mg, 0.45 mmol, 450 mol%) were subject to standard reaction conditions (DMF, 60 °C, 24 h). The title compound was obtained in 91% yield (33.0 mg, 0.09 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate = 20:1).

TLC (SiO_2) R_f = 0.46 (hexane : ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, J = 8.0 Hz, 1H), 7.20 (d, J = 1.6 Hz, 1H), 7.04 (dd, J = 8.1, 1.6 Hz, 1H), 5.54 (dt, J = 16.9, 9.9 Hz, 1H), 5.34 (dd, J = 10.1, 1.5 Hz, 1H), 5.17 (dd, J = 17.0, 1.6 Hz, 1H), 2.81 (ddd, J = 14.0, 9.3, 4.7 Hz, 1H), 2.61 (s, 3H), 2.58 – 2.44 (m, 3H), 2.39 (ddd, J = 11.8, 9.7, 2.4 Hz, 1H), 2.09 – 1.98 (m, 2H), 1.93 – 1.63 (m, 4H), 1.55 (dddd, J = 13.5, 11.5, 9.0, 4.7 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 163.7, 151.3, 140.0, 137.8, 134.8, 124.6, 121.9 (dd, J = 243.9, 238.4 Hz), 121.4, 119.2, 109.8, 92.8, 92.8, 52.8, 52.3, 33.4, 30.6, 30.1 (t, J = 25.0 Hz), 28.4 (dd, J = 163.9, 9.7 Hz), 14.5 ppm.

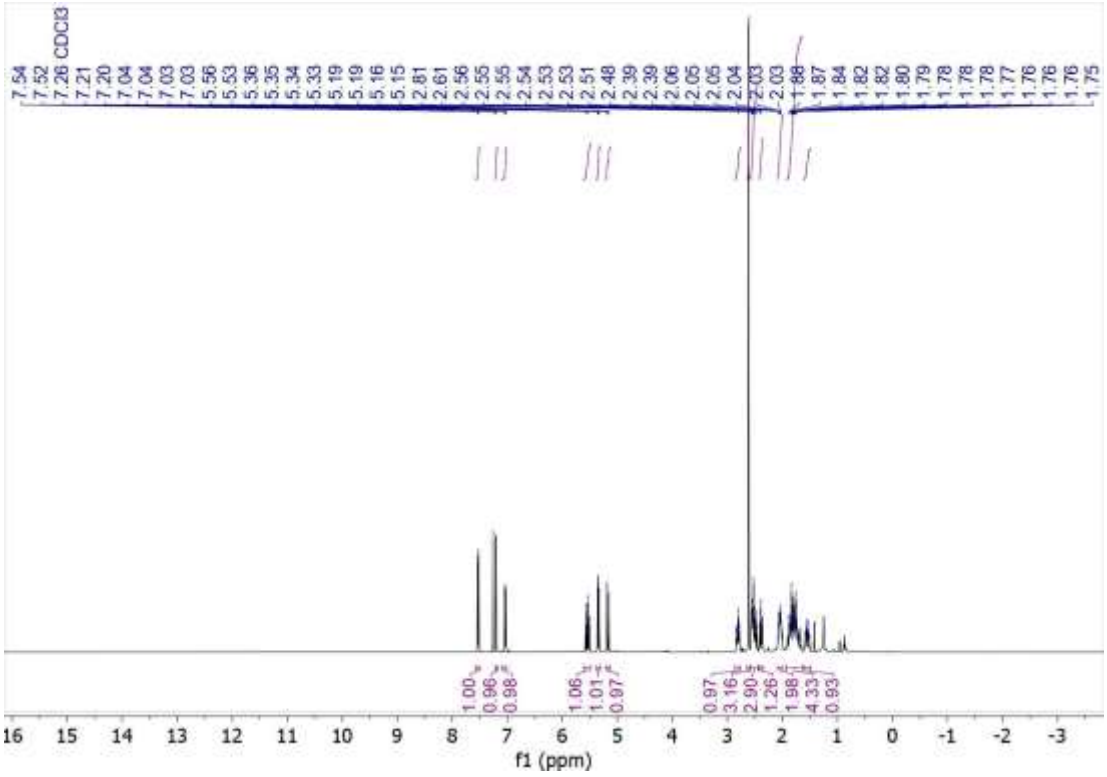
^{19}F NMR (471 MHz, $CDCl_3$) δ -93.20 (d, J = 238.4 Hz), -103.71 (dtt, J = 238.4, 34.0, 10.3 Hz) ppm.

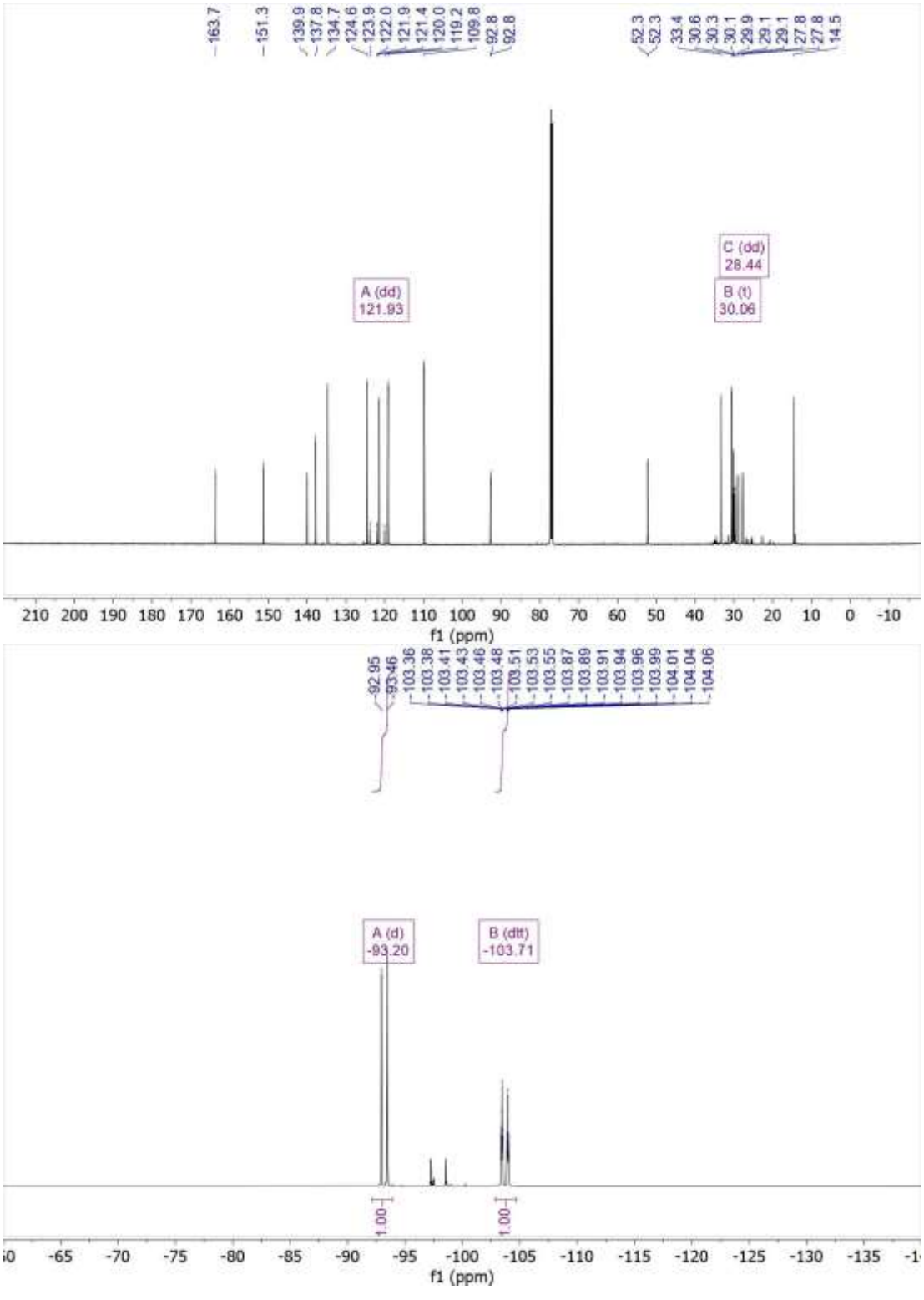
HRMS (ESI) m/z: [(M+H)+] calculated for $C_{19}H_{22}F_2N_2O_3$ 365.1671, found 365.1678.

FTIR (Neat): 2923, 1614, 1537, 1439, 1385, 1244, 1117, 964, 928, 862, 754 cm^{-1}.

$[\alpha]_D^{28}$: + 11.0 (c = 0.5, $CHCl_3$).

HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralpak AD-H column, hexane : 2-PrOH = 90:10, 1.0 mL/min, 230 nm), t_{major} = 14.87 min, t_{minor} = 18.19 min; ee = 88 %.

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121.4
120.0
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92.8
92.8
52.3
52.3
33.4
30.6
30.3
30.1
29.9
29.1
29.1
27.8
27.8
14.5
A (dd)
121.93
C (dd)
28.44
B (t)
30.06
f1 (ppm)
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103.38
103.41
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103.46
103.48
103.51
103.53
103.55
103.87
103.89
103.91
103.94
103.96
103.99
104.01
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104.06
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B (dtt)
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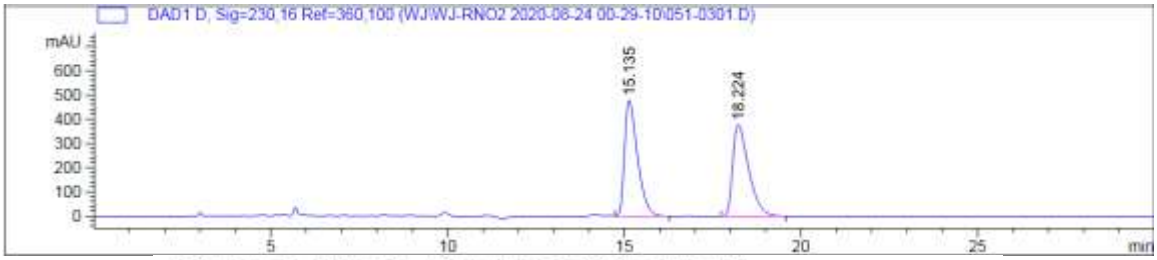
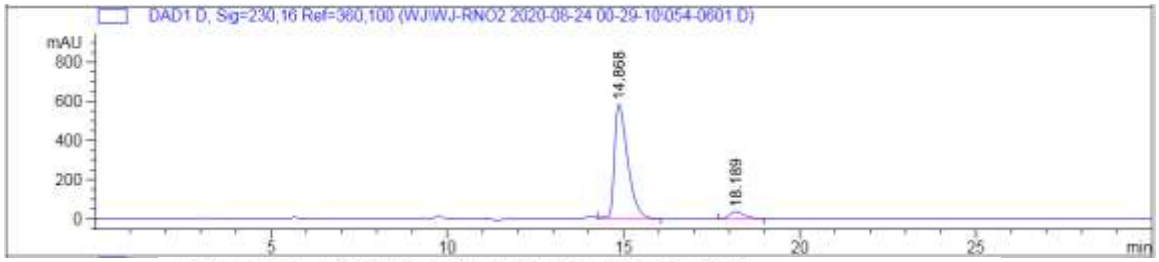
1.00
1.00
f1 (ppm)



Signal 3: DAD1 D, Sig=230,16 Ref=360,100

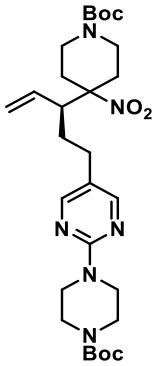
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.135	BB	0.3846	1.21650e4	478.55576	50.5215
2	18.224	BB	0.4774	1.19139e4	378.34940	49.4785
Totals :				2.40789e4	856.90515	



Signal 3: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.868	VB	0.3938	1.53308e4	584.83936	93.4620
2	18.189	BB	0.4426	1072.45032	36.73043	6.5380
Totals :				1.64032e4	621.56979	

***tert*-Butyl (*S*)-4-(5-(3-(1-(tert-butoxycarbonyl)-4-nitropiperidin-4-yl)pent-4-en-1-yl)pyrimidin-2-yl)piperazine-1-carboxylate (4.3s)**



Procedures

Allylic acetate **4.1n** (39.0 mg, 0.10 mmol, 100 mol%) and nitroalkane **4.2g** (103.6 mg, 0.45 mmol, 450 mol%) were subject to standard reaction conditions (DMF, 80 °C, 48 h). The title compound was obtained in 82% yield (45.9 mg, 0.08 mmol) as a light yellow solid after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate = 9:1).

TLC (SiO_2) R_f = 0.24 (hexane: ethyl acetate = 2:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (s, 2H), 5.50 (dt, J = 16.9, 9.9 Hz, 1H), 5.34 (dd, J = 10.1, 1.4 Hz, 1H), 5.21 – 5.12 (m, 1H), 3.80 – 3.72 (m, 4H), 3.51 – 3.44 (m, 4H), 2.56 – 2.45 (m, 1H), 2.40 (dd, J = 19.2, 9.0 Hz, 2H), 2.36 – 2.29 (m, 2H), 2.29 – 2.16 (m, 2H), 2.10 – 1.97 (m, 1H), 1.67 (dqt, J = 24.1, 9.8, 4.5 Hz, 3H), 1.49 (s, 9H), 1.44 (s, 9H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 157.7, 155.0, 154.6, 134.7, 121.9, 121.7, 92.8, 80.2, 80.1, 52.7, 43.9, 29.6, 28.6, 28.6, 28.5, 27.1, 17.8 ppm.

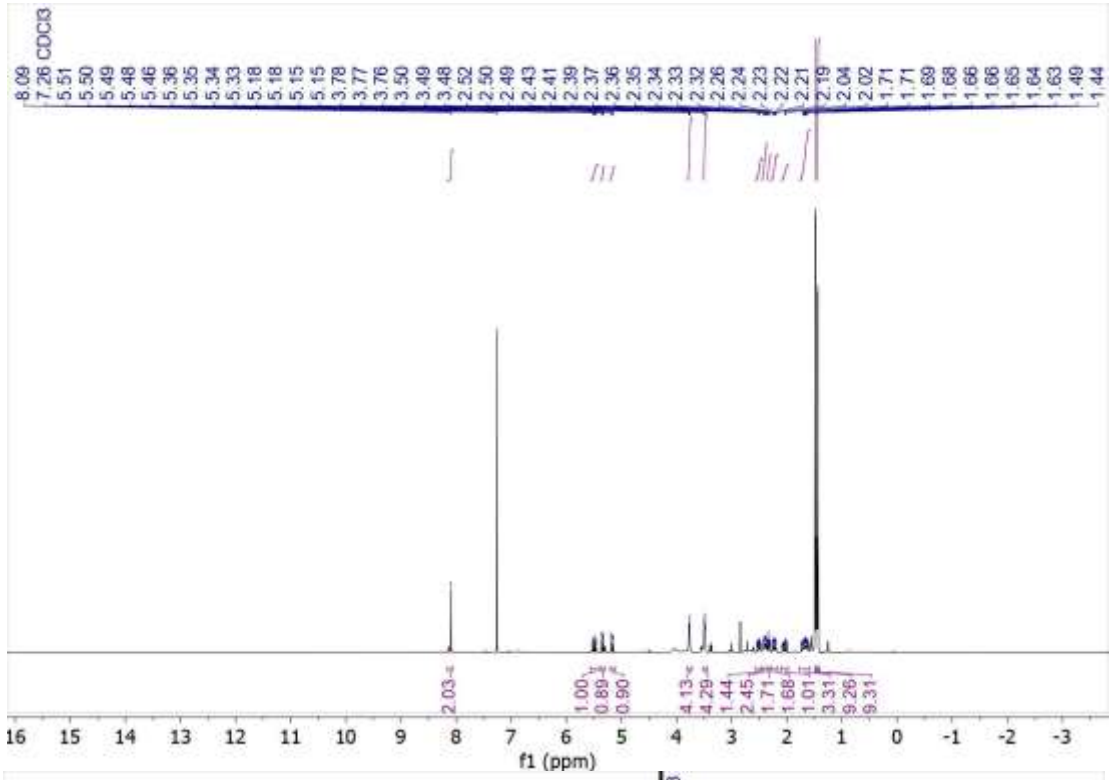
HRMS (ESI): Calculated for $C_{28}H_{44}N_6O_6$ [M+Na^+] = 583.3215, Found 583.3221.

FTIR (Neat): 2977, 2929, 1689, 1603, 1538, 1478, 1417, 1364, 1242, 1165, 1131, 997, 752, 665 cm^{-1}.

$[\alpha]_D^{28}$= + 3.0 (*c* 1.0, $CHCl_3$).

Melting point 104 – 108 °C

HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralpak AD-H column, hexane : 2-PrOH = 85:15, 1.0 mL/min, 210 nm), t_{major} = 8.48 min, t_{minor} = 9.26 min; ee = 89 %.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5.50
5.49
5.48
5.46
5.36
5.35
5.34
5.33
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5.15
5.15
3.78
3.77
3.76
3.50
3.49
3.48
2.52
2.50
2.49
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2.41
2.39
2.37
2.36
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2.34
2.33
2.32
2.26
2.24
2.23
2.22
2.21
2.19
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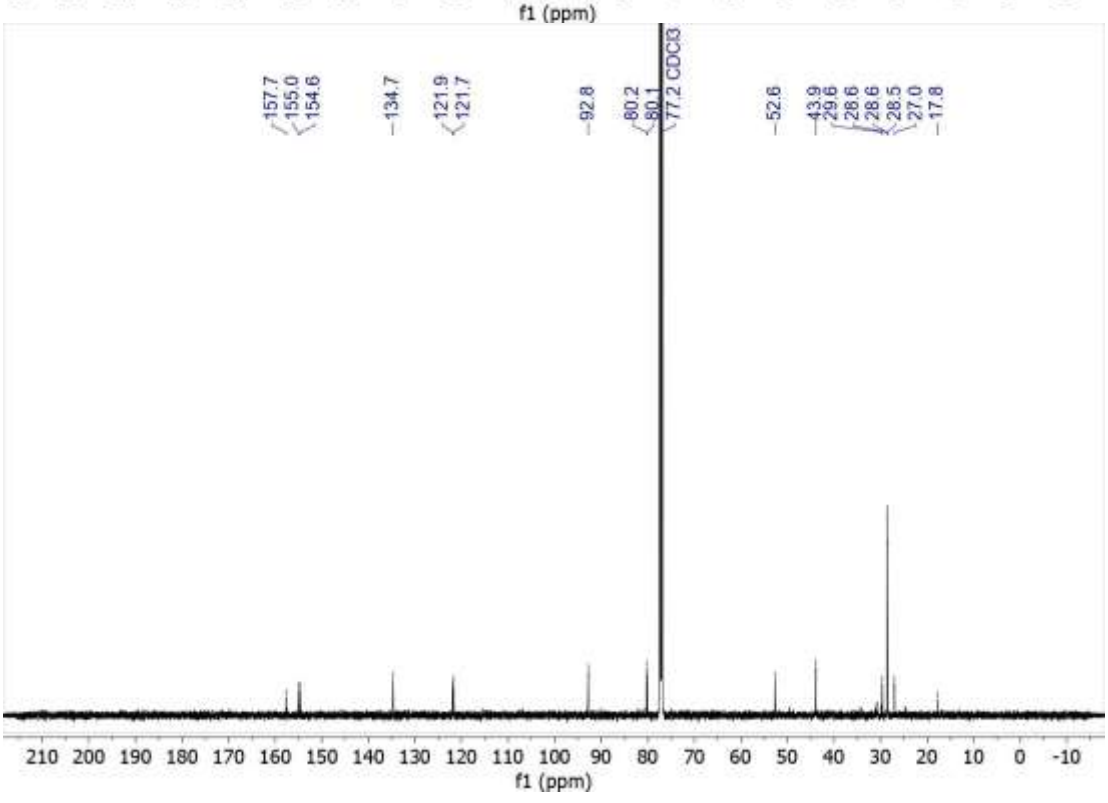
1.71
1.69
1.68
1.66
1.66
1.65
1.64
1.63
1.49
1.44
2.03
1.00
0.89
0.90
4.13
4.29
1.44
2.45
1.71
1.68
1.01
3.31
9.26
9.31
f1 (ppm)


157.7
155.0
154.6
134.7
121.9
121.7
92.8
80.2
80.1
77.2 CDCl3
52.6
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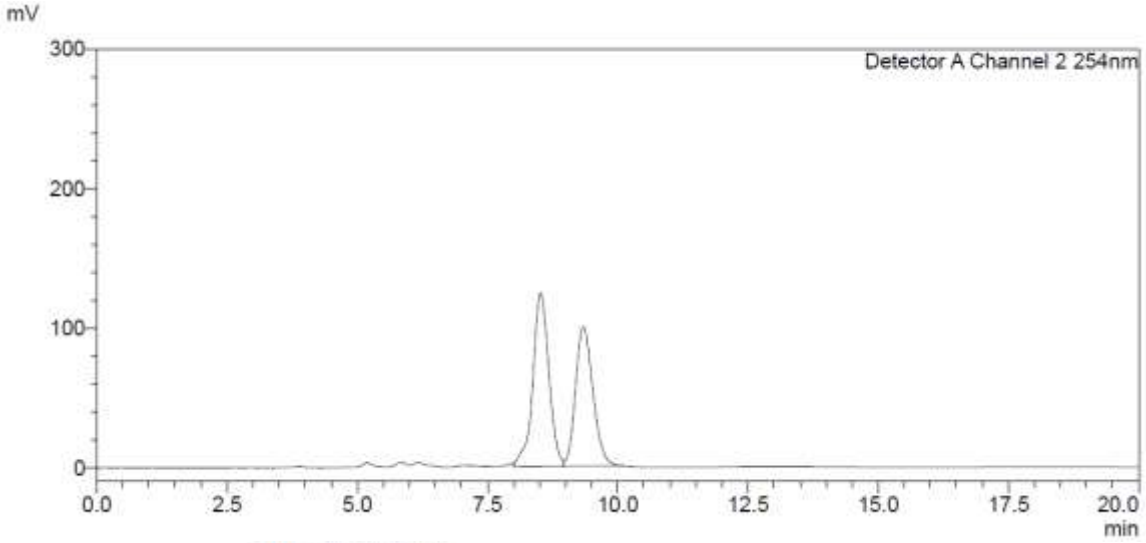
28.6
28.5
27.0
17.8
f1 (ppm)



<Peak Table>

Detector A Channel 2 254nm

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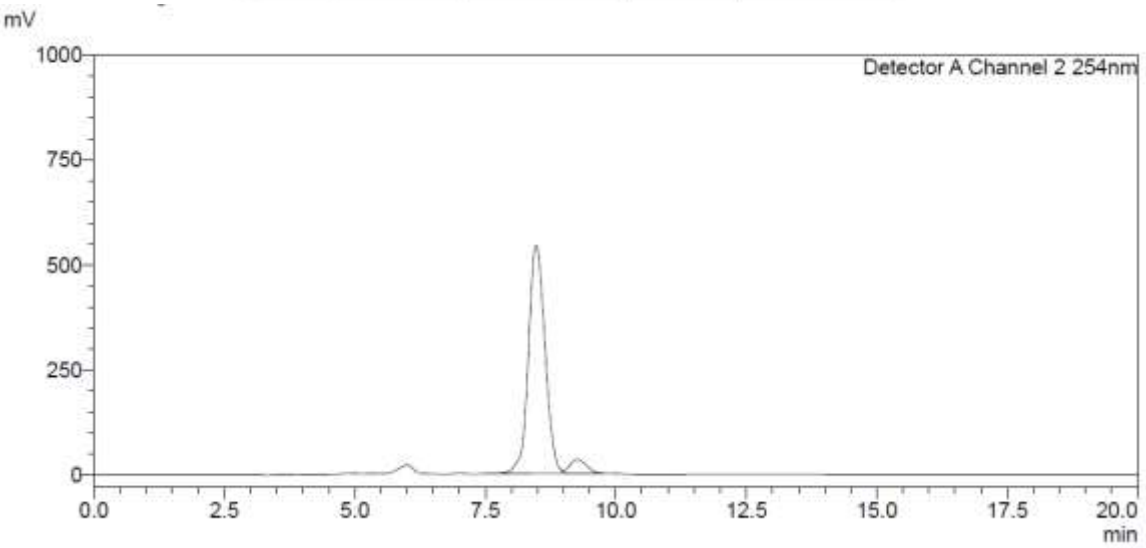
2	9.337	2321229	V M	46.453
Total		4996902		100.000

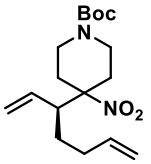


<Peak Table>

Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Mark	Area%
1	8.475	12022539	M	94.417
2	9.262	710965	V M	5.583
Total		12733505		100.000

***tert*-Butyl (*S*)-4-(hepta-1,6-dien-3-yl)-4-nitropiperidine-1-carboxylate (4.3t)**



Procedures

Allylic acetate **4.1i** (30.8 mg, 0.20 mmol, 100 mol%) and nitroalkane **4.2g** (207.2 mg, 0.90 mmol, 450 mol%) were subject to standard reaction conditions (DMF, 60 °C, 48 h). The title compound was obtained in 65% yield (42.3 mg, 0.13 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate = 20:1–10:1).

TLC (SiO_2) R_f = 0.30 (hexane: ethyl acetate = 10:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.70 – 5.57 (m, 1H), 5.37 (dt, J = 16.9, 9.9 Hz, 1H), 5.19 (dd, J = 10.1, 1.6 Hz, 1H), 5.05 (dd, J = 16.9, 1.7 Hz, 1H), 4.96 – 4.86 (m, 2H), 3.97 (br, 2H), 2.81 – 2.53 (m, 2H), 2.46 – 2.23 (m, 3H), 2.11 – 1.96 (m, 1H), 1.86 – 1.74 (m, 1H), 1.74 – 1.56 (m, 2H), 1.47 – 1.40 (m, 1H), 1.38 (s, 9H), 1.23 – 1.16 (m, 1H) ppm.

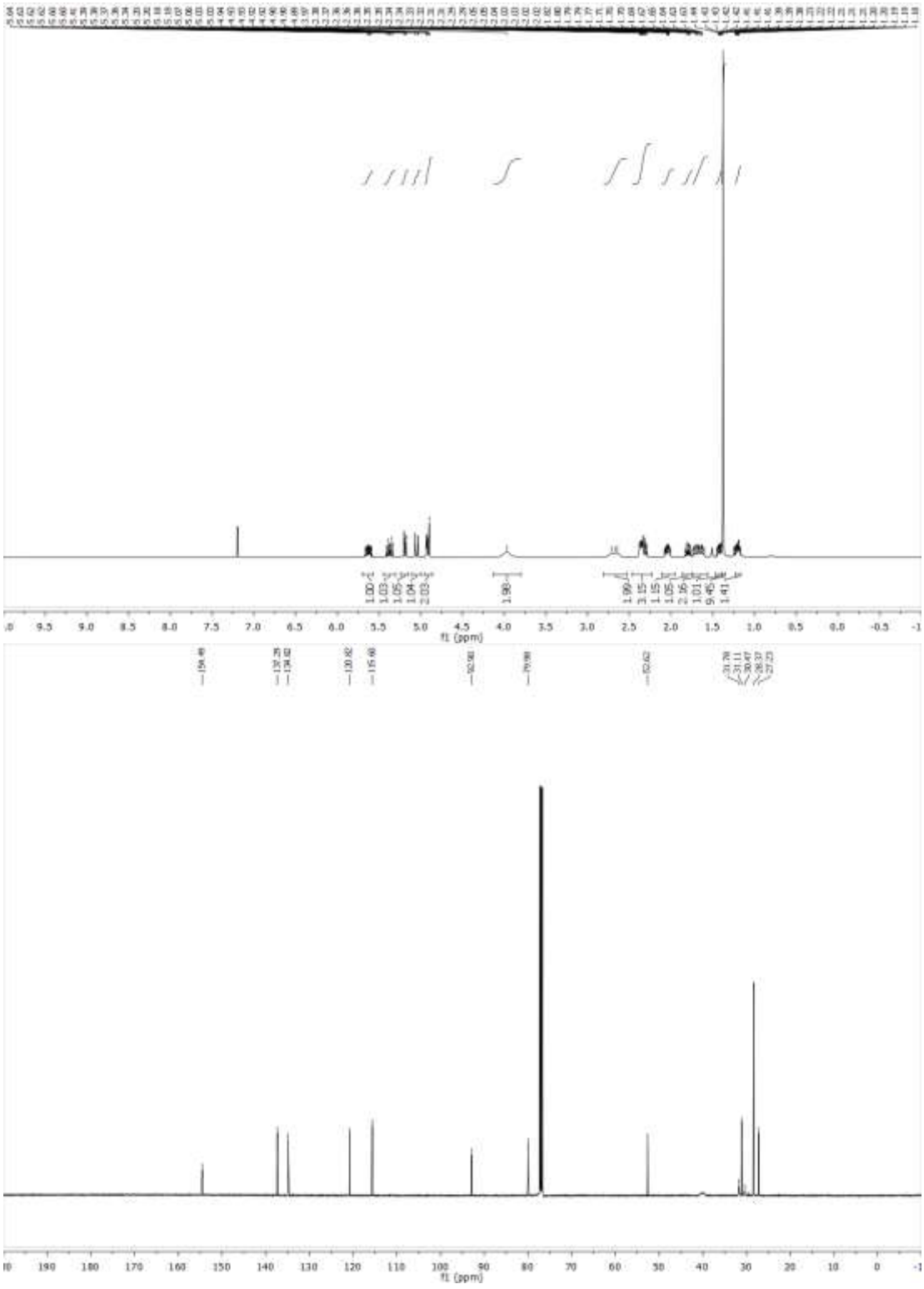
^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.5, 137.3, 134.8, 120.8, 115.6, 92.9, 80.0, 52.6, 31.8, 31.1, 30.5, 28.4, 27.2 ppm.

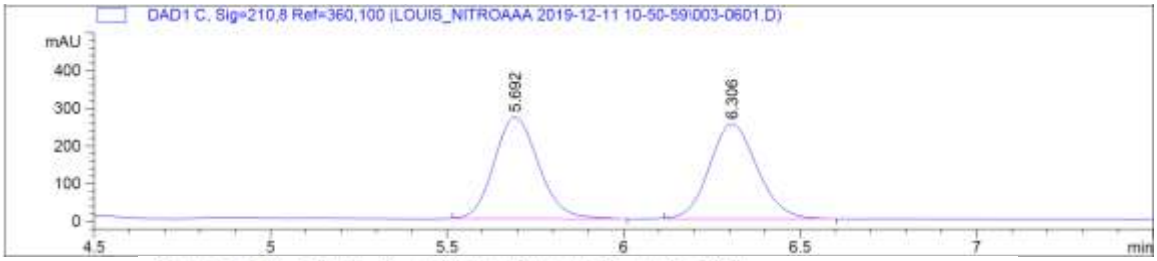
HRMS (ESI): Calculated for $C_{17}H_{28}N_2O_4$ [M+Na^+] = 347.1941, Found 347.1952.

FTIR (Neat): 2979, 1685, 1538, 1421, 1367, 1245, 1216, 1171, 926, 753 cm^{-1}.

$[\alpha]_D^{28}$ = –5.0 (*c* 1.0, $CHCl_3$).

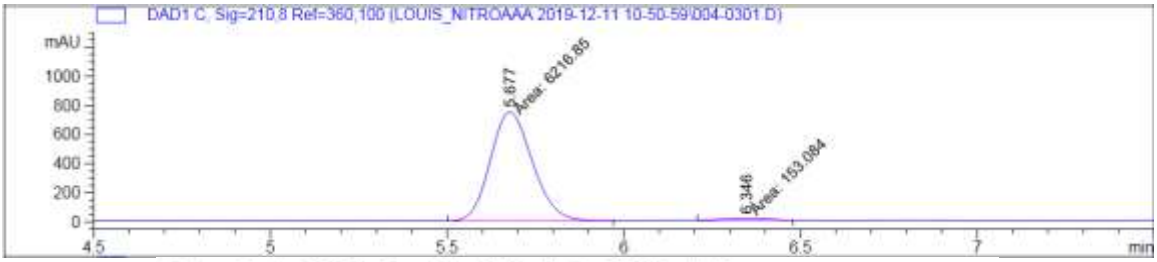
HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H column, hexane : 2-PrOH = 100:0, 1.0 mL/min, 210 nm), t_{major} = 5.68 min, t_{minor} = 6.35 min; ee = 95 %.





Signal 2: DAD1 C, Sig=210,8 Ref=360,100

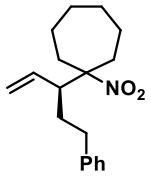
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.692	BB	0.1342	2370.05127	270.44446	49.9848
2	6.306	BB	0.1457	2371.49512	252.17542	50.0152
Totals :				4741.54639	522.61987	



Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.677	FM	0.1382	6216.85449	749.56787	97.5968
2	6.346	FM	0.1901	153.08368	13.42453	2.4032
Totals :				6369.93817	762.99240	

(*S*)-1-Nitro-1-(5-phenylpent-1-en-3-yl)cycloheptane (4.3u)



Procedure

Allylic acetate **4.1a** (40.9 mg, 0.2 mmol, 100 mol%) and nitrocycloheptane **4.2h** (128 mg, 0.9 mmol, 450 mol%) were subject to standard reaction (NMP, 60 ºC, 48 h). The title compound was obtained in 84% yield (48.1 mg, 0.17 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate = 50:1–10:1).

TLC (SiO_2) R_f= 0.80 (hexane : ethyl acetate = 4 : 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 – 7.09 (m, 5H), 5.59 (dt, *J* = 16.9, 9.9 Hz, 1H), 5.27 (dd, *J* = 10.1, 1.8 Hz, 1H), 5.15 (dd, *J* = 17.0, 1.1 Hz, 1H), 2.71 – 2.65 (m, 1H), 2.53 – 2.35 (m, 4H), 1.61 – 1.41 (m, 12H) ppm.

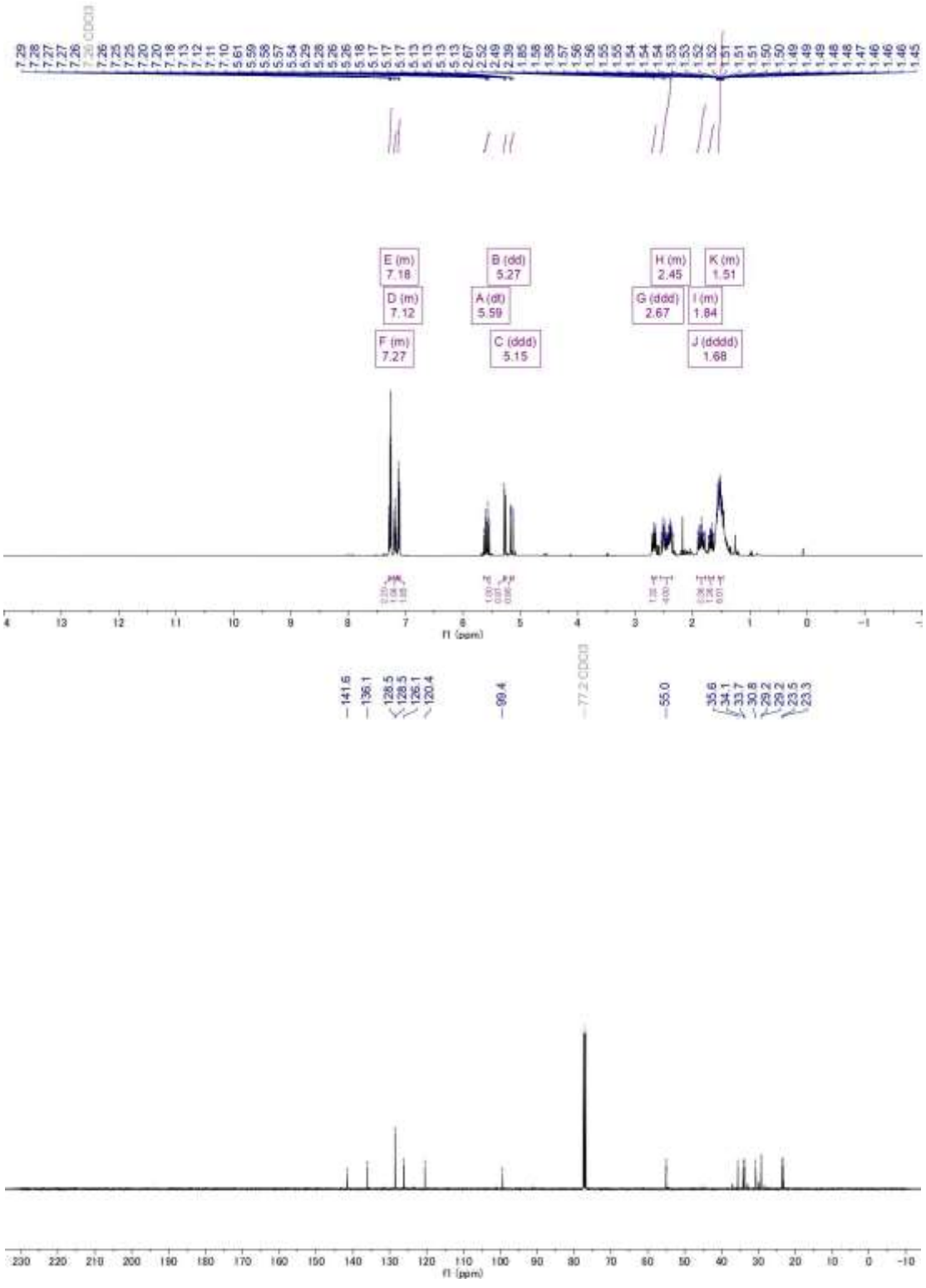
^{13}C NMR (100 MHz, $CDCl_3$): δ141.4, 135.9, 128.4, 128.4, 126.0, 120.3, 99.3, 77.3, 77.0, 76.7, 54.9, 35.4, 34.0, 33.6, 30.6, 29.1, 29.1, 23.4, 23.2 ppm.

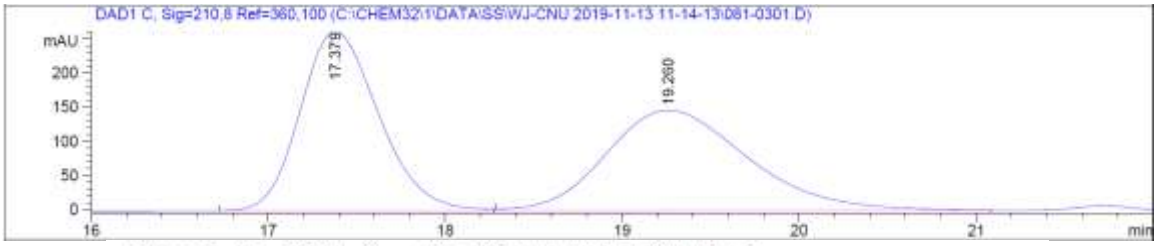
HRMS (ESI) m/z: [(M+Na)+] calcd for $C_{18}H_{25}NO_2$ 310.1778, found 310.1781.

FTIR (Neat): 2928, 2858, 2357, 2342, 1533, 1458, 1344, 999, 923, 844, 748, 699 cm^{-1}

$[\alpha]_D^{28}$: - 14.0 (c = 1.0, $CHCl_3$).

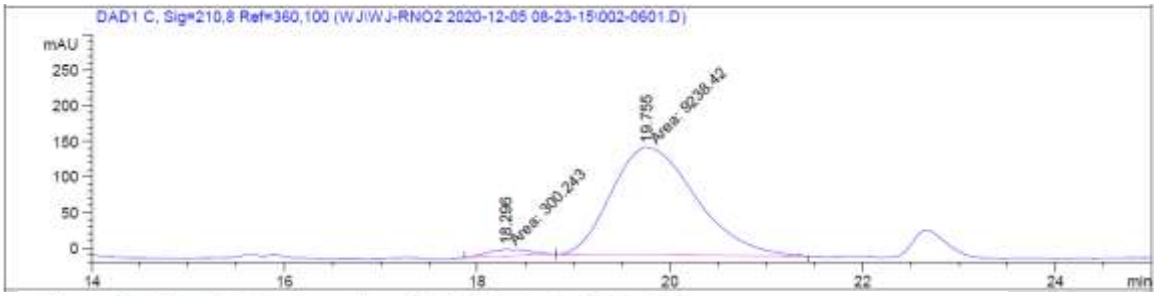
HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralcel OJ-H column, hexane : 2-PrOH = 99: 1, 1.0 mL/min, 210 nm), t_{major} =19.76 min, t_{minor}=18.30 min; ee =94 %


E (m) 7.18
D (m) 7.12
F (m) 7.27
B (dd) 5.27
A (dt) 5.59
C (ddd) 5.15
H (m) 2.45
G (ddd) 2.67
K (m) 1.51
I (m) 1.84
J (dddd) 1.68
f1 (ppm)
141.6
136.1
128.5
128.5
126.1
120.4
99.4
77.2 CDCl3
55.0
35.6
34.1
33.7
30.8
29.2
29.2
23.5
23.3
f1 (ppm)



Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.379	BB	0.4780	8117.10889	263.05658	49.6069
2	19.260	BB	0.8635	8245.73926	147.20137	50.3931
Totals :				1.63628e4	410.25795	

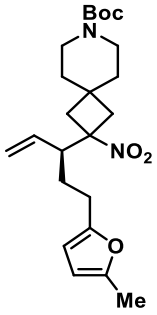


Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.296	MM	0.4916	300.24277	10.17899	3.1476
2	19.755	MM	1.0163	9238.41895	151.50507	96.8524
Totals :				9538.66171	161.68406	

***tert*-Butyl**

(*S*)-2-(5-(5-methylfuran-2-yl)pent-1-en-3-yl)-2-nitro-7-azaspiro[3.5]nonane-7-carboxylate (4.3v)



Procedures

Allylic acetate **4.1c** (20.8 mg, 0.1 mmol, 100 mol%) and corresponding nitroalkane **4.2i** (121.6 mg, 0.45 mmol, 450 mol%) were subject to standard reaction conditions (NMP, 60 °C, 48 h) with (*S*)-Ir-tol-BINAP-OMe,NO_2 (11.1 mg, 10 mol%, 0.01 mmol). The title compound was obtained in 71% yield (29.9 mg, 0.07 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate = 15:1).

TLC (SiO_2) R_f = 0.70 (hexane : ethyl acetate = 2:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (s, 2H), 5.50 (dt, J = 17.0, 9.8 Hz, 1H), 5.30 (dd, J = 10.1, 1.2 Hz, 1H), 5.16 (d, J = 16.9 Hz, 1H), 3.28 (ddq, J = 14.9, 11.2, 6.4, 4.8 Hz, 7H), 2.69 – 2.53 (m, 4H), 2.47 – 2.35 (m, 3H), 2.23 (s, 3H), 2.28 – 2.15 (m, 2H), 1.84 (dtd, J = 13.4, 8.4, 2.2 Hz, 1H), 1.43 (s, 9H) ppm.

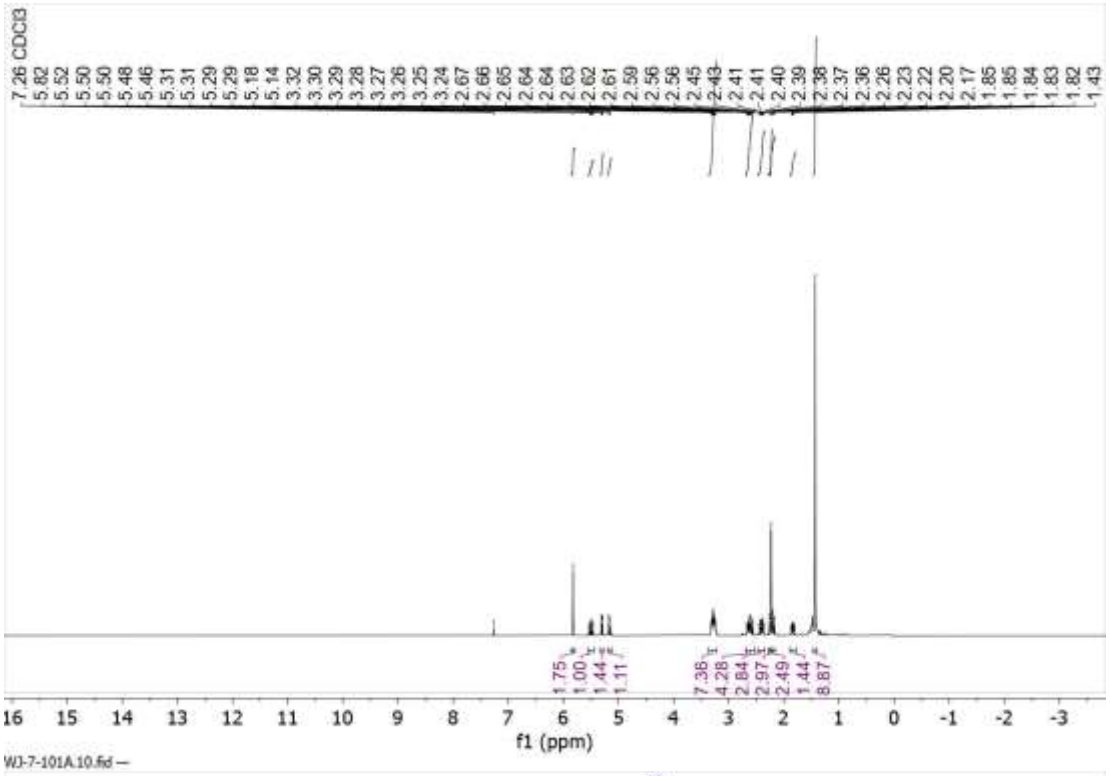
^{13}C NMR (126 MHz, $CDCl_3$) δ 154.9, 153.0, 150.7, 134.5, 120.8, 106.3, 105.9, 87.8, 79.7, 52.1, 41.9, 40.9, 30.8, 28.6, 28.5, 26.6, 25.8, 13.6 ppm.

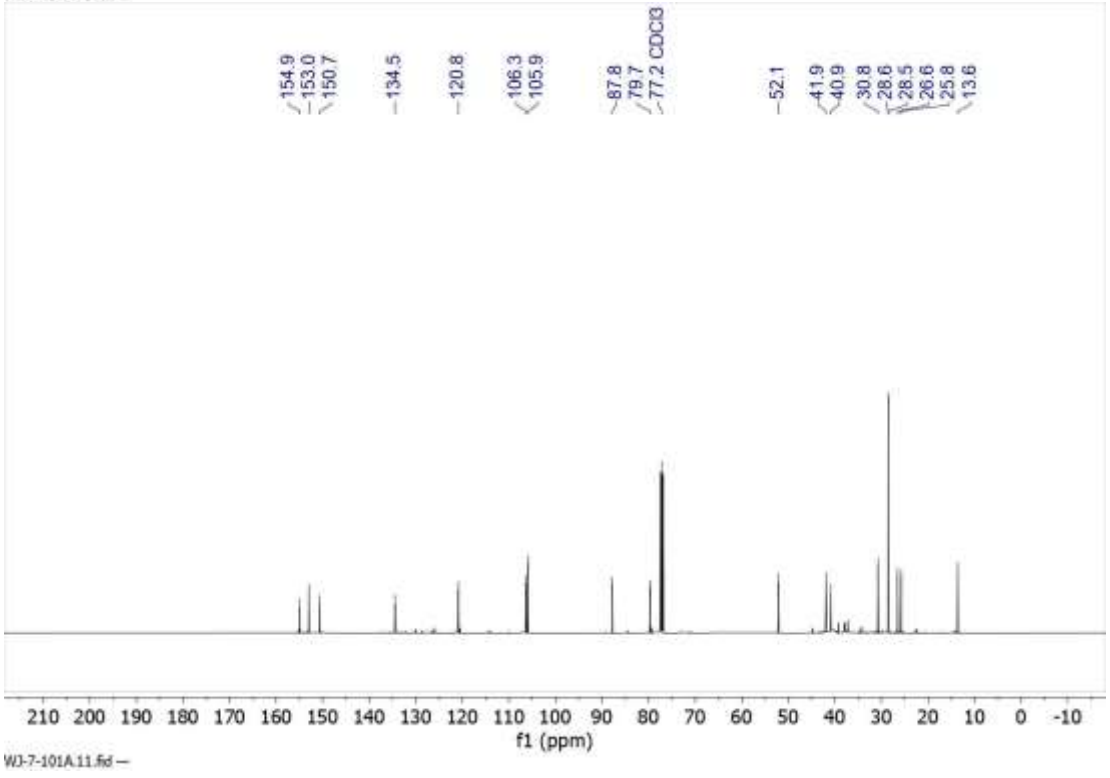
HRMS (ESI) m/z: [(M+Na)+] calcd for $C_{23}H_{34}N_2O_5$ 441.2360, found 441.2377.

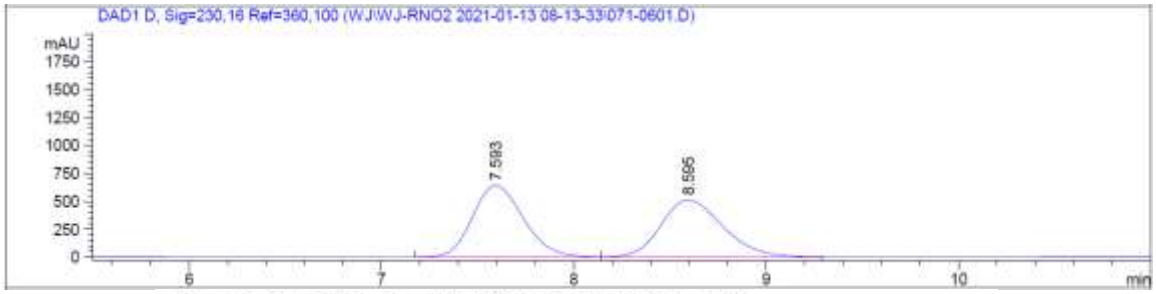
FTIR (Neat): 2927, 1680, 1533, 1424, 1271, 1151, 967, 928, 750, 666 cm^{-1}.

$[\alpha]_D^{28}$: + 22.0 (c = 0.5, $CHCl_3$).

HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H column, hexane : 2-PrOH = 95:5, 1.0 mL/min, 230 nm), t_{major} = 7.57 min, t_{minor} = 8.56 min; ee = 91 %.

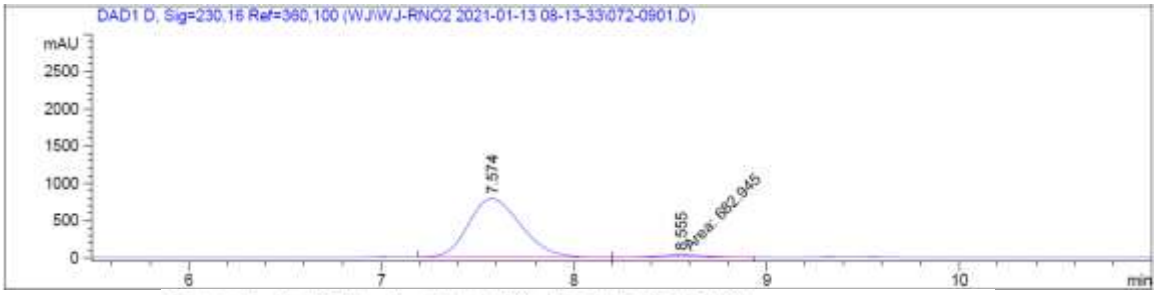

7.26 CDCl3
5.82
5.52
5.50
5.50
5.48
5.46
5.31
5.31
5.29
5.29
5.18
5.14
3.32
3.30
3.29
3.28
3.27
3.26
3.25
3.24
2.67
2.66
2.65
2.64
2.64
2.63
2.62
2.61
2.59
2.56
2.56
2.45
2.43
2.41
2.41
2.40
2.39
2.38
2.37
2.36
2.26
2.23
2.22
2.20
2.17
1.85
1.85
1.84
1.83
1.82
1.43
1.75
1.00
1.44
1.11
7.38
4.28
2.84
2.97
2.49
1.44
8.87
f1 (ppm)
WJ-7-101A.10.fid


154.9
153.0
150.7
134.5
120.8
106.3
105.9
87.8
79.7
77.2 CDCl3
52.1
41.9
40.9
30.8
28.6
28.5
26.6
25.8
13.6
f1 (ppm)
WJ-7-101A.11.fid



Signal 3: DAD1 D, Sig=230,16 Ref=360,100

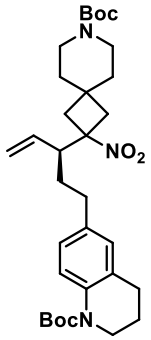
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.593	VV	0.2836	1.17526e4	642.06238	50.6389
2	8.595	VB	0.3480	1.14561e4	510.12424	49.3611
Totals :				2.32087e4	1152.18661	



Signal 3: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.574	VV	0.2997	1.51198e4	788.64386	95.5636
2	8.555	VV	0.3589	701.91498	29.36200	4.4364
Totals :				1.58217e4	818.00586	

***tert*-Butyl (*S*)-6-(3-(7-(tert-butoxycarbonyl)-2-nitro-7-azaspiro[3.5]nonan-2-yl)pent-4-en-1-yl)-3,4-dihydroquinoline-1(2*H*)-carboxylate (4.3w)**



Procedures

Allylic acetate **4.1k** (35.9 mg, 0.1 mmol, 100 mol%) and nitroalkane **4.2i** (121.6 mg, 0.45 mmol, 450 mol%) were subject to standard reaction conditions (NMP, 60 °C, 48 h) with (*S*)-Ir-tol-BINAP-OMe,NO_2 (11.1 mg, 10 mol%, 0.01 mmol). The title compound was obtained in 77% yield (46.2 mg, 0.08 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate = 9:1).

TLC (SiO_2) R_f = 0.64 (hexane : ethyl acetate = 2:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.4 Hz, 1H), 6.89 (dd, J = 8.4, 1.7 Hz, 1H), 6.82 (s, 1H), 5.54 (dt, J = 16.9, 9.8 Hz, 1H), 5.33 (dd, J = 10.1, 1.4 Hz, 1H), 5.21 – 5.13 (m, 1H), 3.73 – 3.64 (m, 2H), 3.26 (ddt, J = 19.4, 9.2, 5.7 Hz, 4H), 2.72 (t, J = 6.6 Hz, 2H), 2.63 – 2.54 (m, 3H), 2.47 – 2.28 (m, 3H), 2.17 (dd, J = 22.4, 14.3 Hz, 2H), 1.90 (p, J = 6.5 Hz, 2H), 1.78 – 1.68 (m, 1H), 1.51 (s, 9H), 1.49 – 1.45 (m, 2H), 1.43 (s, 9H) ppm.

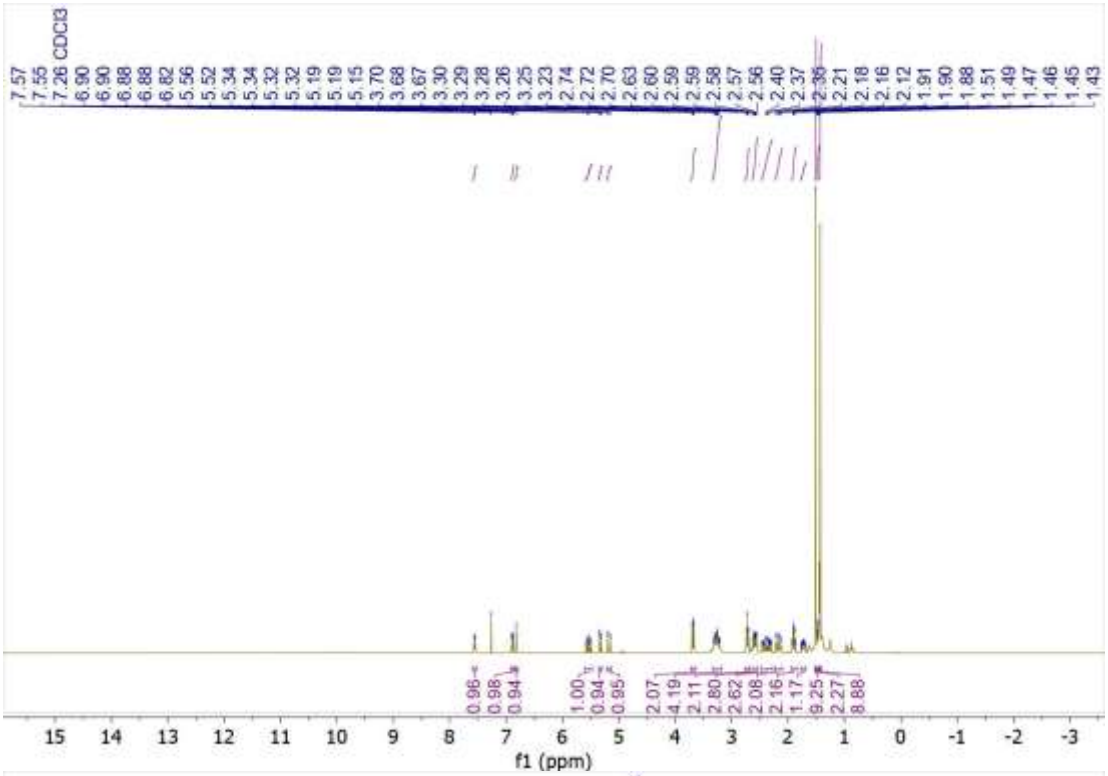
^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9, 154.1, 136.8, 136.1, 134.9, 129.9, 128.5, 125.9, 124.3, 120.8, 88.0, 80.8, 79.7, 73.4, 52.1, 44.8, 41.8, 40.8, 38.1, 37.8, 37.2, 32.7, 30.9, 29.9, 28.5, 27.6, 23.7, 14.3 ppm.

HRMS (ESI) m/z: [(M+Na)+] calcd for $C_{32}H_{47}N_3O_6$ 592.3357, found 592.3352.

FTIR (Neat): 2977, 1689, 1500, 1421, 1364, 1242, 1153, 1009, 919, 730 cm^{-1}.

$\mathbf{[\alpha]_D^{28}}$**:** + 4.8 (c = 2.0, $CHCl_3$).

HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralpak AS-H column, hexane : 2-PrOH = 98:2, 0.5 mL/min, 254 nm), t_{major} = 52.4 min, t_{minor} = 40.7 min; ee = 99 %.


7.57
7.55
7.26 CDCl3
6.90
6.90
6.88
6.88
6.82
5.56
5.52
5.34
5.34
5.32
5.32
5.19
5.19
5.15
3.70
3.68
3.67
3.30
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3.28
3.26
3.25
3.23
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2.70
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2.60
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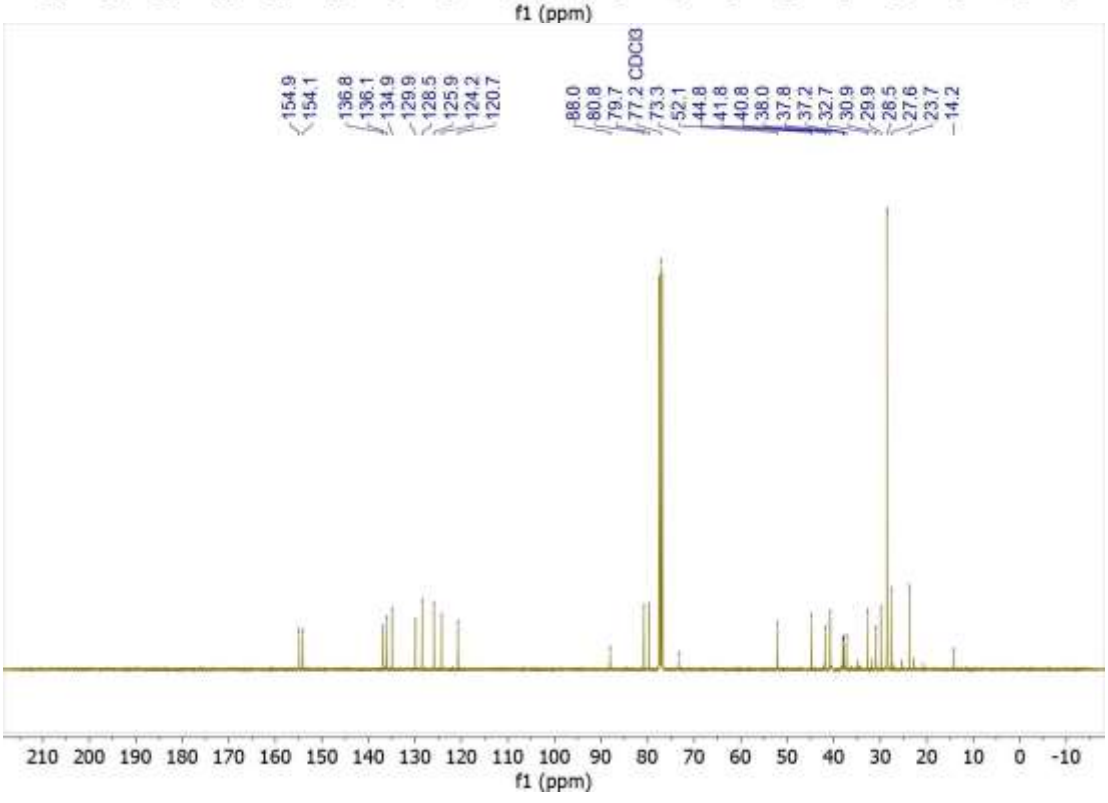
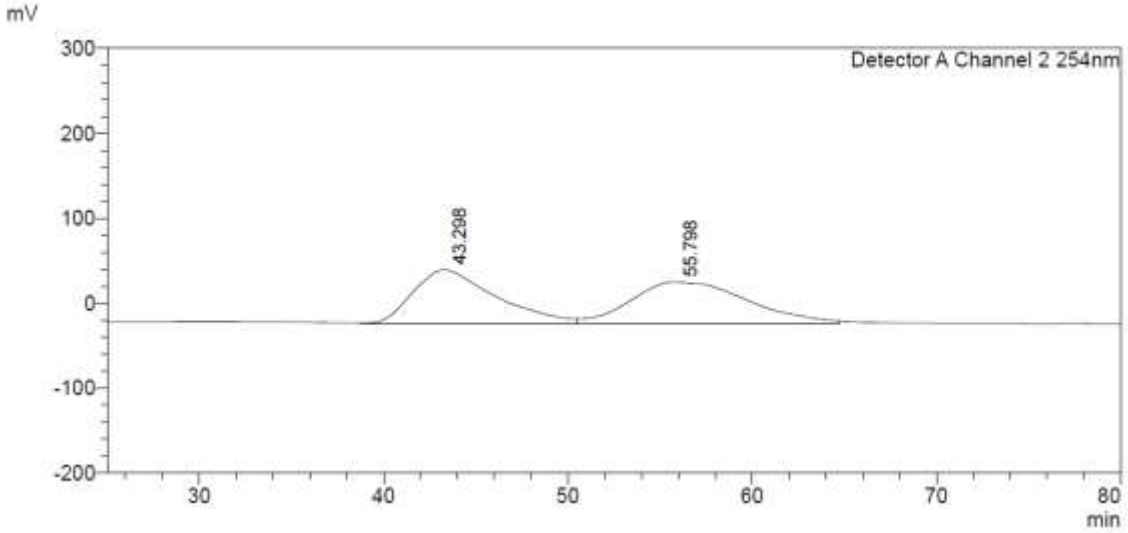
2.58
2.57
2.56
2.40
2.37
2.36
2.21
2.18
2.16
2.12
1.91
1.90
1.88
1.51
1.49
1.47
1.46
1.45
1.43
0.96
0.98
0.94
1.00
0.94
0.95
2.07
4.19
2.11
2.80
2.62
2.08
2.16
1.17
9.25
2.27
8.88
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)


154.9
154.1
136.8
136.1
134.9
129.9
128.5
125.9
124.2
120.7
88.0
80.8
79.7
77.2 CDCl3
73.3
52.1
44.8
41.8
40.8
38.0
37.8
37.2
32.7
30.9
29.9
28.5
27.6
23.7
14.2
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)



Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
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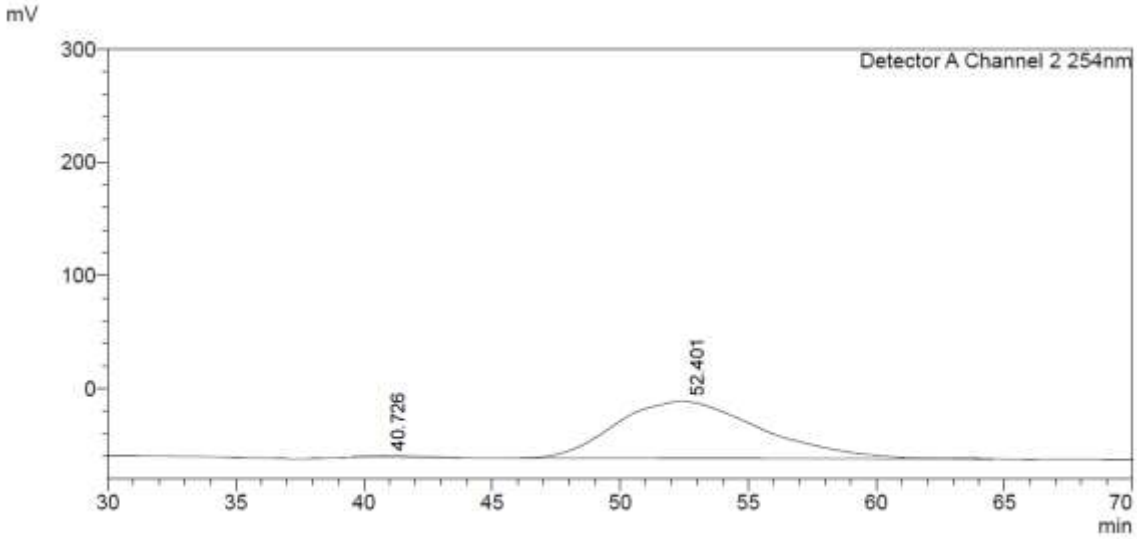
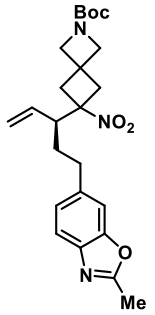
2	55.798	21105861	48250	52.253		V M	
Total		40391833	111080				



Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	40.726	114532	1046	0.573		M	
2	52.401	19884822	50524	99.427		M	
Total		19999354	51570				

***tert*-Butyl (*S*)-6-(5-(2-methylbenzo[d]oxazol-6-yl)pent-1-en-3-yl)-6-nitro-2-azaspiro[3.3]heptane-2-carboxylate (4.3x)**



Procedures

Allylic acetate **4.1l** (25.9 mg, 0.1 mmol, 100 mol%) and nitroalkane **4.2j** (109.0 mg, 0.45 mmol, 450 mol%) were subject to standard reaction conditions (NMP, 60 °C, 48 h) with (*S*)-Ir-tol-BINAP-CN,NO_2 (11.0 mg, 10 mol%, 0.01 mmol). The title compound was obtained in 77% yield (34.2 mg, 0.08 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane : ethyl acetate = 5:1).

TLC (SiO_2) R_f = 0.36 (hexane : ethyl acetate = 1:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 8.1 Hz, 1H), 7.22 (s, 1H), 7.05 (d, J = 8.1 Hz, 1H), 5.56 (dt, J = 16.9, 9.9 Hz, 1H), 5.39 (d, J = 10.1 Hz, 1H), 5.22 (d, J = 16.9 Hz, 1H), 3.89 – 3.83 (m, 2H), 3.79 (d, J = 8.8 Hz, 1H), 3.67 (d, J = 8.3 Hz, 1H), 2.85 (dd, J = 26.2, 14.0 Hz, 3H), 2.61 (s, 3H), 2.59 – 2.48 (m, 3H), 2.37 (t, J = 9.9 Hz, 1H), 1.72 (dt, J = 14.8, 8.6 Hz, 1H), 1.57 – 1.48 (m, 1H), 1.41 (s, 9H) ppm.

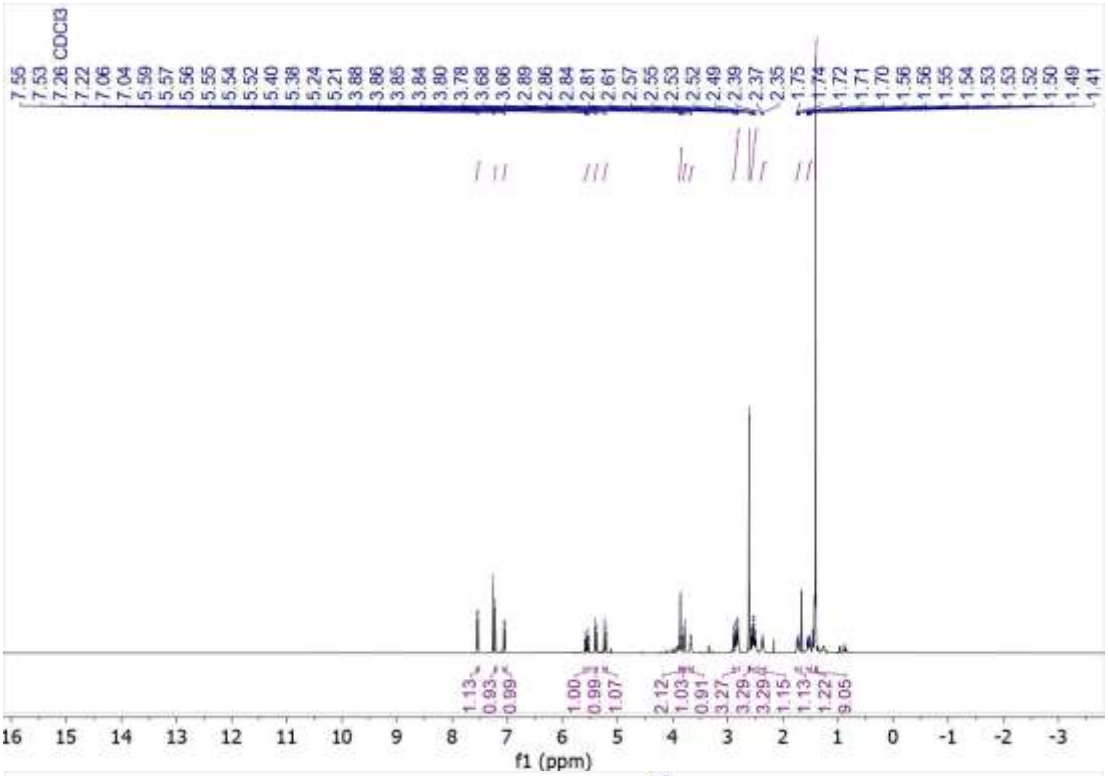
^{13}C NMR (101 MHz, $CDCl_3$) δ 163.8, 156.0, 151.5, 140.1, 138.0, 134.4, 124.7, 121.7, 119.3, 110.0, 79.9, 49.8, 42.8, 41.0, 33.3, 30.1, 29.9, 28.5, 14.7 ppm.

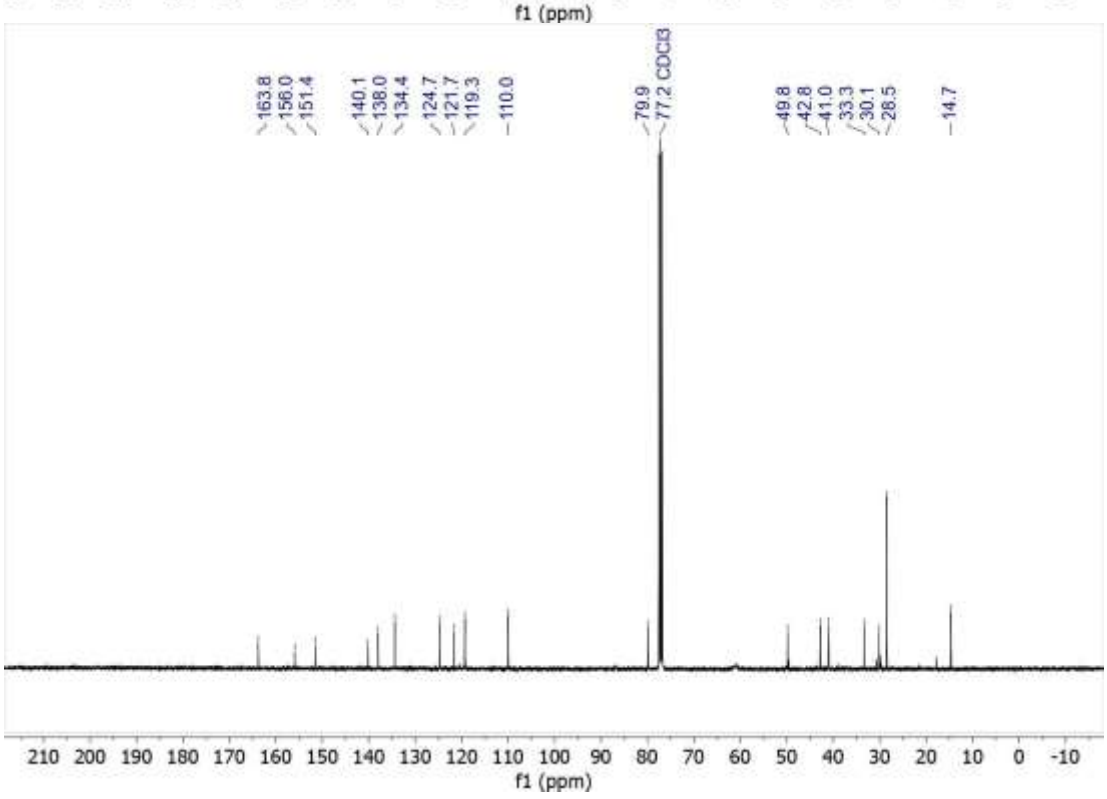
HRMS (ESI) m/z: [(M+Na)+] calcd for $C_{24}H_{31}N_3O_5$ 464.2156, found 464.2161.

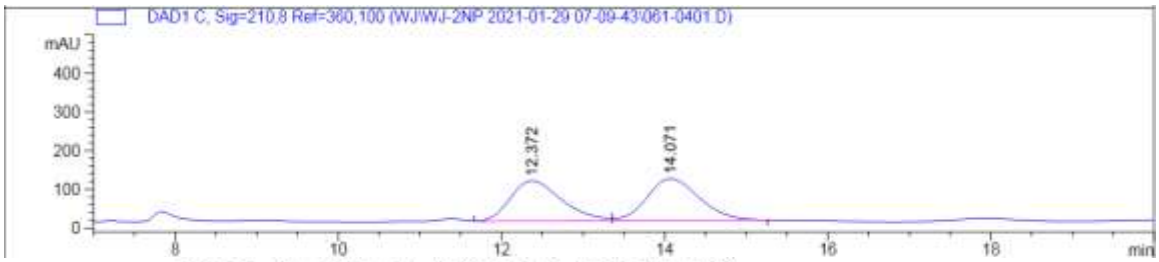
FTIR (Neat): 2935, 1788, 1698, 1533, 1394, 1365, 1245, 1167, 1116, 930, 857 cm^{-1}.

$[\alpha]_D^{28}$: + 8.0 (c = 0.25, $CHCl_3$).

HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H column, hexane : 2-PrOH = 85:15, 1.0 mL/min, 210 nm), t_{major} = 13.90 min, t_{minor} = 12.40 min; ee = 94 %.

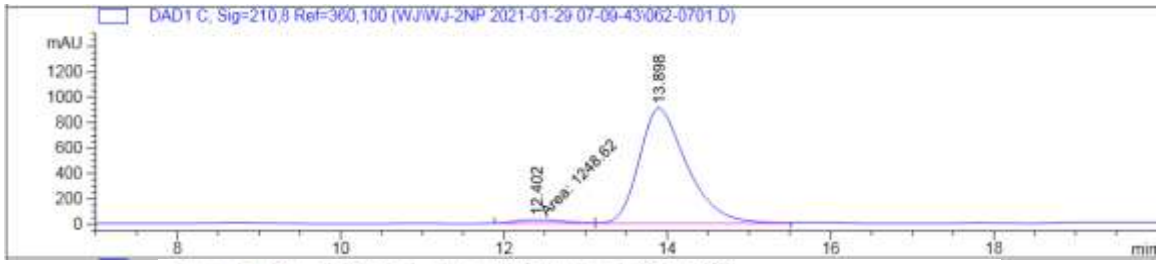

7.55
7.53
7.26 CDCl3
7.22
7.06
7.04
5.59
5.57
5.56
5.55
5.54
5.52
5.40
5.38
5.24
5.21
3.88
3.86
3.85
3.84
3.80
3.78
3.68
3.66
2.89
2.86
2.84
2.81
2.61
2.57
2.55
2.53
2.52
2.49
2.39
2.37
2.35
1.75
1.74
1.72
1.71
1.70
1.56
1.56
1.55
1.54
1.53
1.53
1.52
1.50
1.49
1.41
1.13
0.93
0.99
1.00
0.99
1.07
2.12
1.03
0.91
3.27
3.29
3.29
1.15
1.13
1.22
9.05
f1 (ppm)


163.8
156.0
151.4
140.1
138.0
134.4
124.7
121.7
119.3
110.0
79.9
77.2 CDCl3
49.8
42.8
41.0
33.3
30.1
28.5
14.7
f1 (ppm)



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.372	VV	0.6743	4600.37109	104.76878	48.4407
2	14.071	VB	0.6925	4896.54834	108.91638	51.5593
Totals :				9496.91943	213.68516	

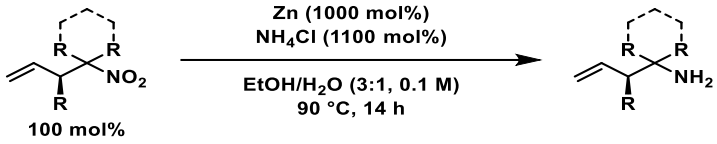


Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.402	FM	0.7135	1248.62280	29.16797	3.2479
2	13.898	VB	0.6100	3.71957e4	907.77319	96.7521
Totals :				3.84444e4	936.94116	

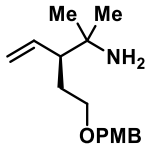
4.5.6 Procedures and Spectral Data for the Amines 4.4f, 4.4k, 4.4l, 4.4s, and 4.4v

General procedure



A sealed tube equipped with a magnetic stir bar was charged with Zn dust (1000 mol%) and NH_4Cl (1100 mol%). The mixture of EtOH and water (3:1, 0.1 M) was added followed by corresponding products (**4.3k, 4.3m,** and **4.3aa**). The tube was purged with argon. Then the tube was sealed with a PTFE lined cap and was placed in an oil bath at 90 °C and stirred for 14 hours. After reaching ambient temperature, the mixture was filtered through celite with ethyl acetate and dried *in vacuo*.

(*S*)-3-(2-((4-Methoxybenzyl)oxy)ethyl)-2-methylpent-4-en-2-amine (4.4f)



Procedures

A round-bottom flask equipped with a magnetic stir bar was charged with Zn dust (45.8 mg, 0.70 mmol, 500 mol%). The mixture of acetic acid (0.28 mL, 0.5 M) and THF (0.18 mL, 0.8 M) was added followed by corresponding products nitroalkane product **4.3f** (41 mg, 0.14 mmol, 100 mol%). The flask was sealed with a PTFE cap and stirred at 40 °C. After 14 h, the crude reaction mixture was directly filtered through alumina (Al_2O_3) with dichloromethane/methanol (9:1) mixture. The title compound was obtained in 90% (31 mg, 0.12 mmol) as a light-yellow oil.

TLC (SiO_2) R_f = 0.4 (dichloromethane : methanol = 1:1).

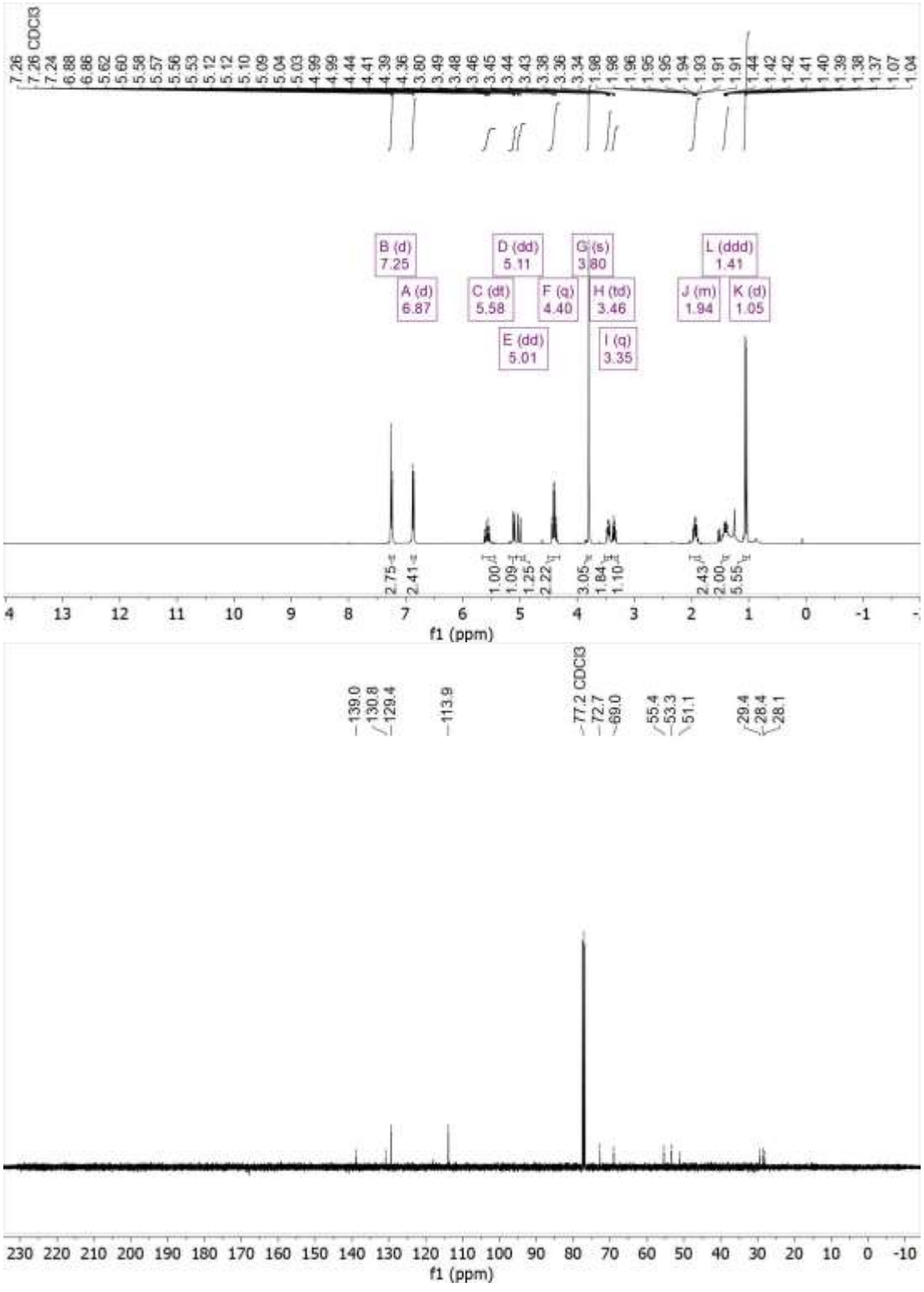
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 2.1 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 5.58 (dt, J = 17.0, 10.0 Hz, 1H), 5.11 (dd, J = 10.2, 2.1 Hz, 1H), 5.01 (dd, J = 17.0, 1.8 Hz, 1H), 4.40 (q, J = 11.4 Hz, 2H), 3.80 (s, 3H), 3.46 (td, J = 8.5, 8.0, 4.4 Hz, 2H), 3.35 (q, J = 7.8 Hz, 1H), 2.01 – 1.87 (m, 2H), 1.42 (dtd, J = 17.6, 7.3, 4.6 Hz, 2H), 1.05 (d, J = 11.0 Hz, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 130.8, 129.4, 113.9, 72.8, 69.0, 55.4, 53.3, 51.1, 29.4, 28.4, 28.1 ppm.

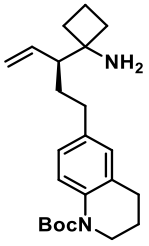
HRMS (ESI) m/z: [(M+H)]+ calcd for $C_{16}H_{25}NO_2$ 264.1958, found 264.1966

FTIR (Neat): 3021, 2854, 2360, 1513, 1246, 1089, 820 cm^{-1}.

$[\alpha]_D^{28}$: - 37.5 (c = 0.2, $CHCl_3$).


7.26
7.26 CDCl3
7.24
6.88
6.86
5.62
5.60
5.58
5.57
5.56
5.53
5.12
5.12
5.10
5.09
5.04
5.03
4.99
4.99
4.44
4.41
4.39
4.36
3.80
3.49
3.48
3.46
3.45
3.44
3.43
3.38
3.36
3.34
1.98
1.98
1.96
1.95
1.95
1.94
1.93
1.91
1.91
1.44
1.42
1.42
1.41
1.40
1.39
1.38
1.37
1.07
1.04
B (d) 7.25
A (d) 6.87
D (dd) 5.11
C (dt) 5.58
E (dd) 5.01
F (q) 4.40
G (s) 3.80
H (td) 3.46
I (q) 3.35
L (ddd) 1.41
J (m) 1.94
K (d) 1.05
2.75
2.41
1.00
1.09
1.25
2.22
3.05
1.84
1.10
2.43
2.00
5.55
f1 (ppm)
139.0
130.8
129.4
113.9
77.2 CDCl3
72.7
69.0
55.4
53.3
51.1
29.4
28.4
28.1
f1 (ppm)

***tert*-Butyl (*S*)-6-(3-(1-aminocyclobutyl)pent-4-en-1-yl)-3,4-dihydroquinoline-1(2*H*)-carboxylate (4.4k)**



Procedures

Nitroalkane product **4.3k** (40.1 mg, 0.10 mmol, 100 mol%) was subjected to general procedure. The title compound was obtained in 99% yield (36.6 mg, 0.10 mmol) as yellow oil after filtration (acetone).

TLC (SiO_2) R_f = 0.30 (acetone).

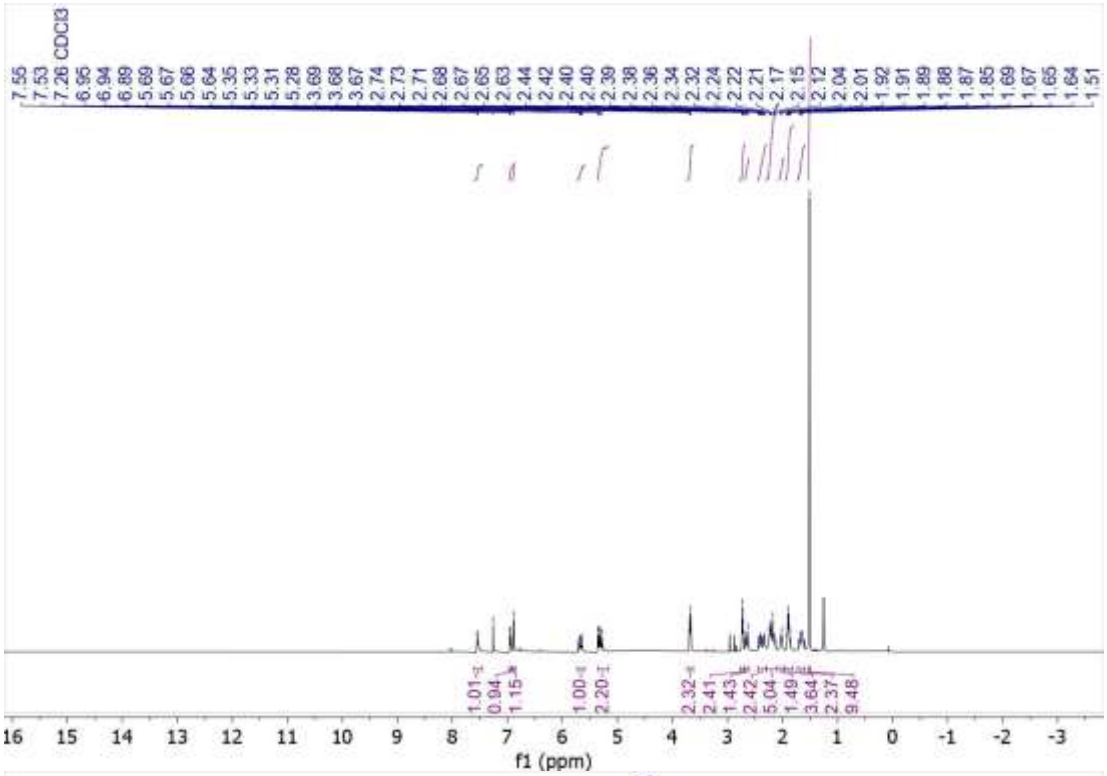
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 8.1 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 6.89 (s, 1H), 5.68 (dt, J = 17.4, 9.8 Hz, 1H), 5.32 (dd, J = 24.7, 13.7 Hz, 2H), 3.73 – 3.62 (m, 2H), 2.73 (t, J = 6.4 Hz, 2H), 2.69 – 2.61 (m, 1H), 2.45 – 2.30 (m, 2H), 2.19 (dq, J = 25.4, 12.4, 10.2 Hz, 5H), 2.03 (d, J = 13.4 Hz, 1H), 1.89 (dq, J = 16.6, 10.1, 8.2 Hz, 4H), 1.65 (dt, J = 23.9, 14.2 Hz, 2H), 1.51 (s, 9H) ppm.

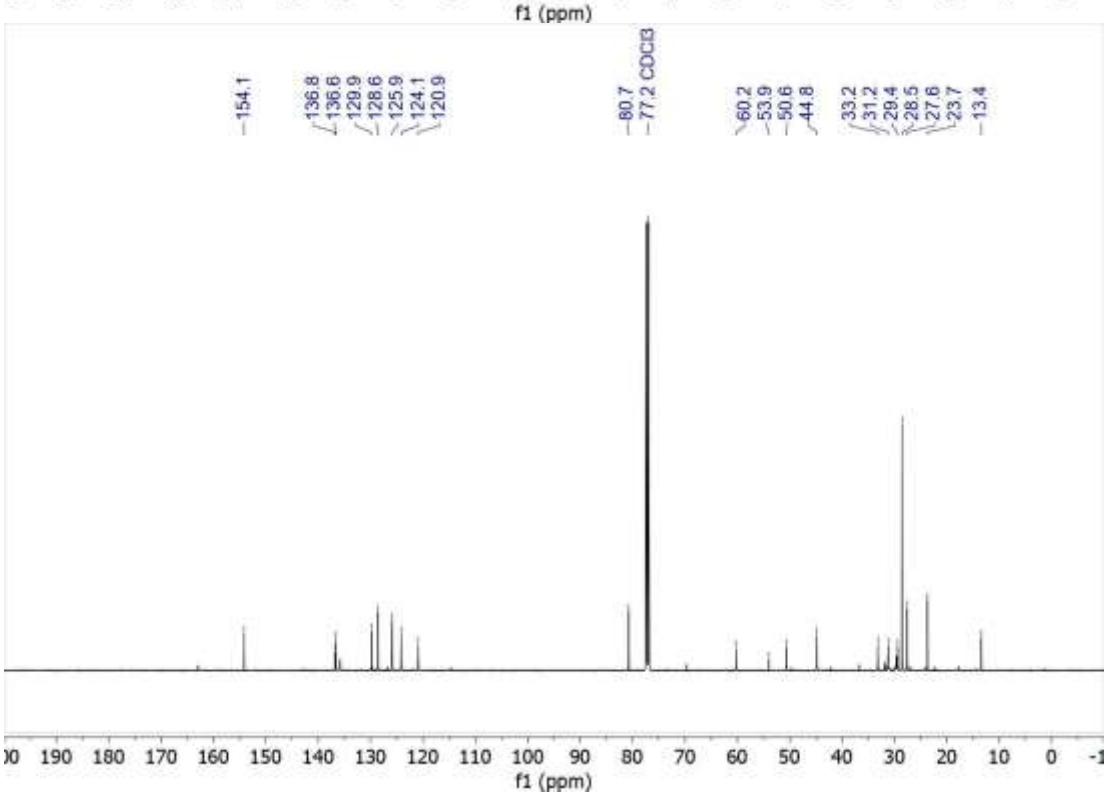
^{13}C NMR (126 MHz, $CDCl_3$) δ 154.1, 136.8, 136.6, 129.9, 128.6, 125.9, 124.2, 120.9, 80.7, 60.2, 53.9, 50.6, 44.8, 33.2, 31.2, 29.4, 28.5, 27.6, 23.7, 13.4 ppm.

HRMS (ESI) m/z: [(M+H)+] calcd for $C_{23}H_{34}N_2O_2$ 371.2693, found 371.2699.

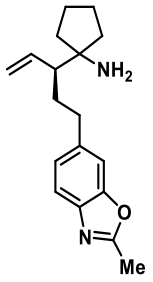
FTIR (Neat): 2981, 1735, 1372, 1238, 1046, 1033, 1012, 735, 702 cm^{-1}.

$[\alpha]_D^{28}$: - 17.0 (c = 0.5, $CHCl_3$).


7.55
7.53
7.26 CDCl3
6.95
6.94
6.89
5.69
5.67
5.66
5.64
5.35
5.33
5.31
5.28
3.69
3.68
3.67
2.74
2.73
2.71
2.68
2.67
2.65
2.63
2.44
2.42
2.40
2.40
2.39
2.38
2.36
2.34
2.32
2.24
2.22
2.21
2.17
2.15
2.12
2.04
2.01
1.92
1.91
1.89
1.88
1.87
1.85
1.69
1.67
1.65
1.64
1.51
1.01
0.94
1.15
1.00
2.20
2.32
2.41
1.43
2.42
5.04
1.49
3.64
2.37
9.48
f1 (ppm)


154.1
136.8
136.6
129.9
128.6
125.9
124.1
120.9
80.7
77.2 CDCl3
60.2
53.9
50.6
44.8
33.2
31.2
29.4
28.5
27.6
23.7
13.4
f1 (ppm)

(*S*)-1-(5-(2-Methylbenzo[*d*]oxazol-6-yl)pent-1-en-3-yl)cyclopentan-1-amine (4.4l)



Procedures

Nitroalkane product **4.3l** (31.4 mg, 0.10 mmol, 100 mol%) was subjected to general procedure B. The title compound was obtained in 99% yield (28.2 mg, 0.10 mmol) as a yellow oil after filtration.

TLC (Al_2O_3) R_f = 0.18 (Acetone).

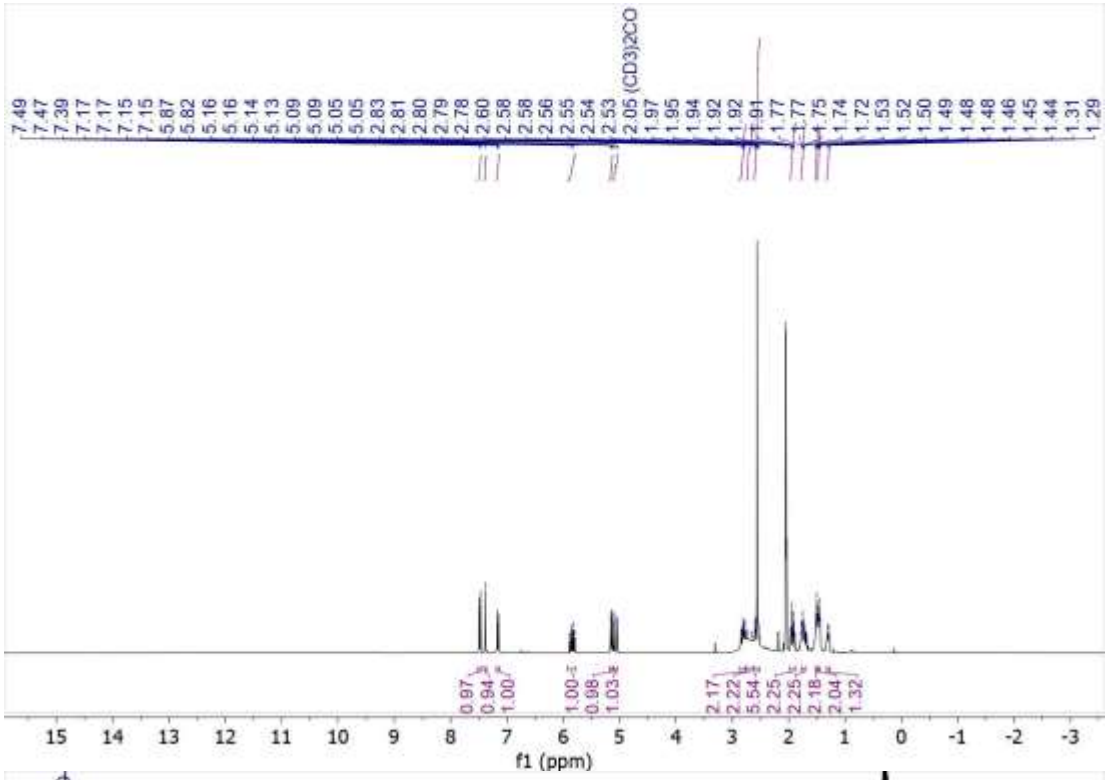
^{1}H NMR (400 MHz, Acetone) δ 7.48 (d, J = 8.1 Hz, 1H), 7.39 (s, 1H), 7.16 (dd, J = 8.1, 1.1 Hz, 1H), 5.84 (dt, J = 17.2, 9.9 Hz, 1H), 5.15 (dd, J = 10.3, 2.3 Hz, 1H), 5.07 (dd, J = 17.2, 2.3 Hz, 1H), 2.82 (ddd, J = 14.0, 9.8, 4.8 Hz, 2H), 2.69 (d, J = 23.0 Hz, 2H), 2.61 – 2.51 (m, 6H), 1.97 – 1.88 (m, 2H), 1.78 – 1.71 (m, 2H), 1.53 – 1.48 (m, 2H), 1.48 – 1.44 (m, 2H), 1.30 (d, J = 8.5 Hz, 1H) ppm.

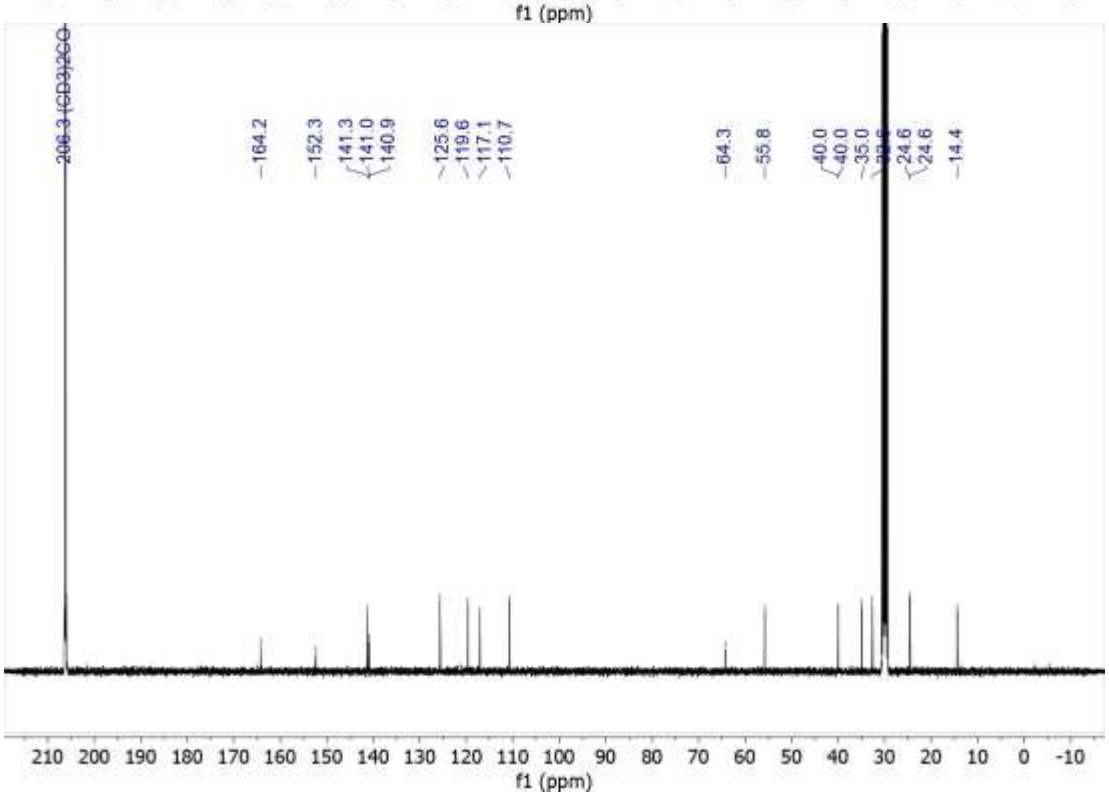
^{13}C NMR (101 MHz, Acetone) δ 164.2, 152.3, 141.3, 141.0, 140.9, 125.7, 119.7, 117.1, 110.7, 64.3, 55.8, 40.0, 40.0, 35.0, 32.6, 24.7, 24.6, 14.4 ppm.

HRMS (ESI) m/z: [(M+H)+] calcd for $C_{18}H_{24}N_2O$ 285.1961, found 285.1965.

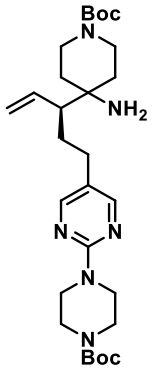
FTIR (Neat): 2941, 1528, 1426, 1117, 1024 cm^{-1}.

$[\alpha]_D^{28}$: + 10.0 (c = 0.5, $CHCl_3$).


7.49
7.47
7.39
7.17
7.17
7.15
7.15
5.87
5.82
5.16
5.16
5.14
5.13
5.09
5.09
5.05
5.05
2.83
2.81
2.80
2.79
2.78
2.60
2.58
2.58
2.56
2.55
2.54
2.53
2.05 (CD3)2CO
1.97
1.95
1.94
1.92
1.92
1.91
1.77
1.77
1.75
1.74
1.72
1.53
1.52
1.50
1.49
1.48
1.48
1.46
1.45
1.44
1.31
1.29
0.97
0.94
1.00
1.00
0.98
1.03
2.17
2.22
5.54
2.25
2.25
2.18
2.04
1.32
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)


206.3 (CD3)2CO
164.2
152.3
141.3
141.0
140.9
125.6
119.6
117.1
110.7
64.3
55.8
40.0
40.0
35.0
24.6
24.6
14.4
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)

***tert*-Butyl (*S*)-4-(5-(3-(4-amino-1-(*tert*-butoxycarbonyl)piperidin-4-yl)pent-4-en-1-yl)pyrimidin-2-yl)piperazine-1-carboxylate (4.4s)**



Procedures

Nitroalkane product **4.3s** (28.0 mg, 0.05 mmol, 100 mol%) was subjected to general procedure B. The title compound was obtained in 99% yield (26.4 mg, 0.05 mmol) as a yellow oil after filtration.

TLC (Al_2O_3) R_f = 0.41 (Acetone).

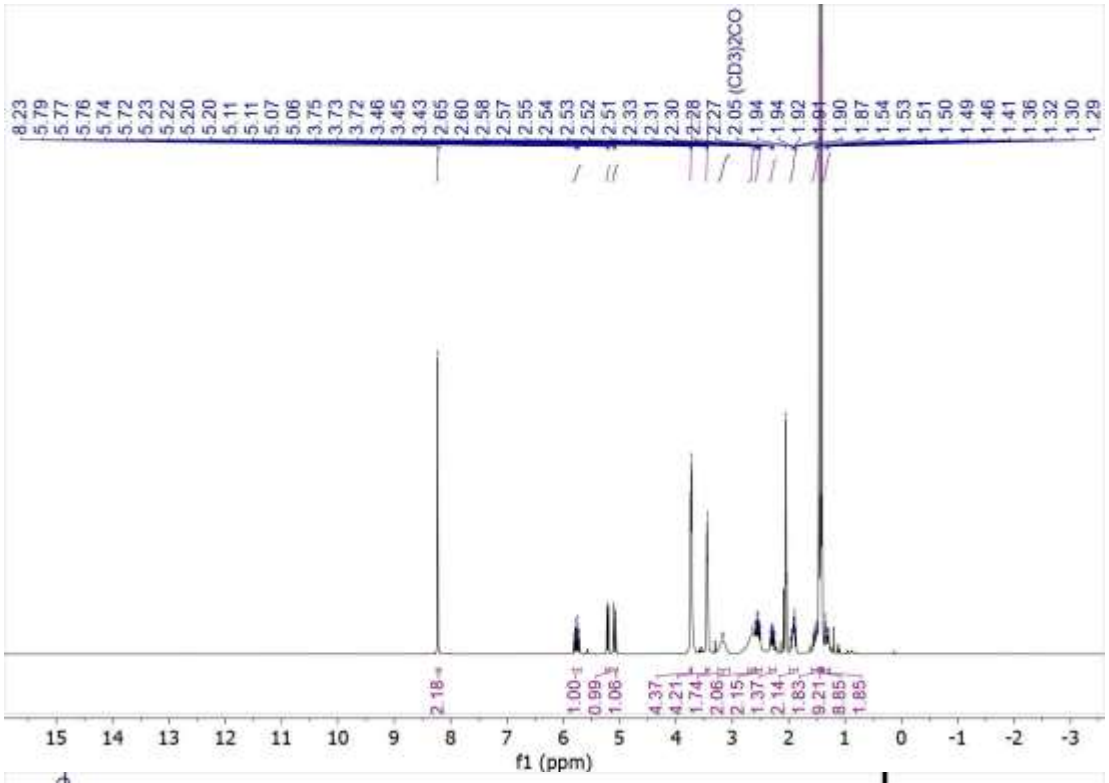
^{1}H NMR (400 MHz, Acetone) δ 8.23 (s, 2H), 5.76 (dt, J = 17.1, 10.0 Hz, 1H), 5.21 (dd, J = 10.3, 2.2 Hz, 1H), 5.09 (dd, J = 17.1, 2.0 Hz, 1H), 3.75 – 3.72 (m, 4H), 3.47 – 3.42 (m, 4H), 3.25 – 3.06 (m, 2H), 2.65 (s, 2H), 2.54 (ddd, J = 14.3, 9.8, 4.7 Hz, 2H), 2.29 (ddd, J = 14.2, 9.4, 7.4 Hz, 1H), 1.92 (ddd, J = 19.1, 12.7, 8.7 Hz, 2H), 1.53 (ddd, J = 17.0, 10.0, 3.4 Hz, 2H), 1.46 (s, 9H), 1.41 (s, 9H), 1.38 – 1.27 (m, 2H) ppm.

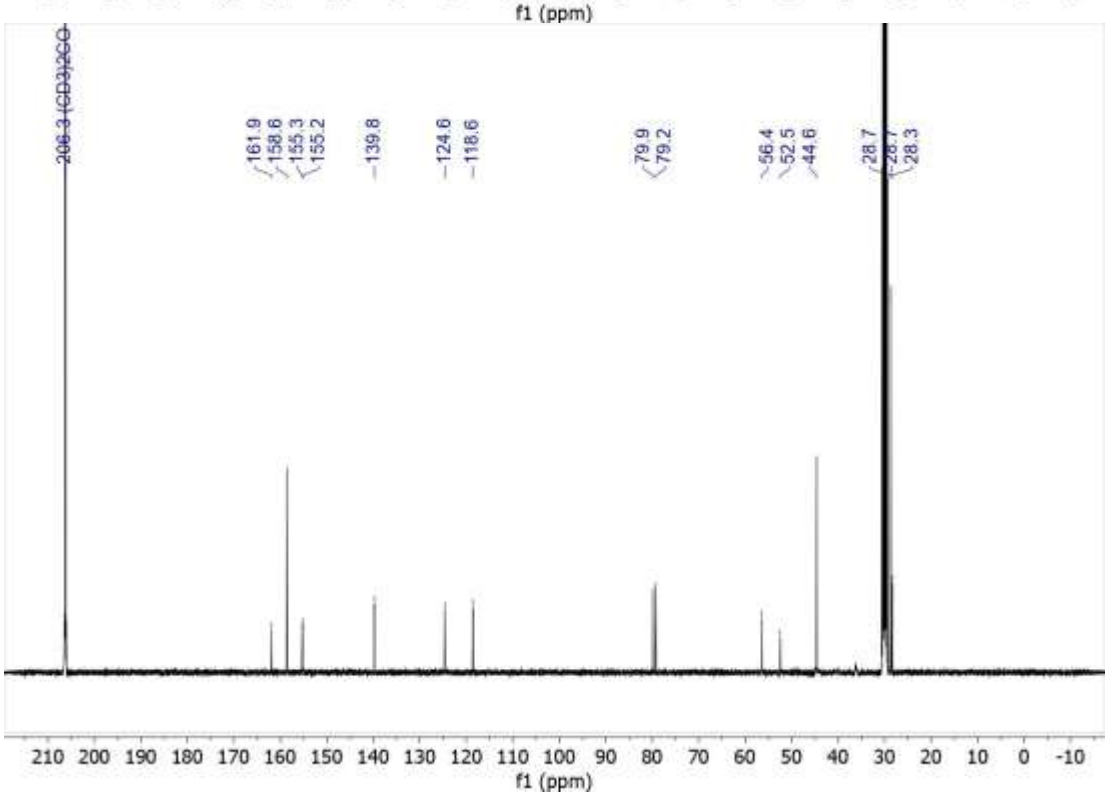
^{13}C NMR (101 MHz, Acetone) δ 161.9, 158.6, 155.3, 155.2, 139.8, 124.6, 118.6, 79.9, 79.2, 56.4, 52.5, 44.6, 28.7, 28.7, 28.4 ppm.

HRMS (ESI) m/z: [(M+Na)+] calcd for $C_{28}H_{46}N_6O_4$ 553.3473, found 553.3458.

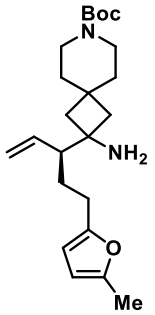
FTIR (Neat): 2979, 1680, 1423, 1366, 1246, 1215, 1162, 998, 747, 666 cm^{-1}.

$[\alpha]_D^{28}$: - 17.0 (c = 1.0, $CHCl_3$).


8.23
5.79
5.77
5.76
5.74
5.72
5.23
5.22
5.20
5.20
5.11
5.11
5.07
5.06
3.75
3.73
3.72
3.46
3.45
3.43
2.65
2.60
2.58
2.57
2.55
2.54
2.53
2.52
2.51
2.33
2.31
2.30
2.28
2.27
2.05 (CD3)2CO
1.94
1.94
1.92
1.91
1.90
1.87
1.54
1.53
1.51
1.50
1.49
1.46
1.41
1.36
1.32
1.30
1.29
2.18
1.00
0.99
1.06
4.37
4.21
1.74
2.06
2.15
1.37
2.14
1.83
9.21
8.85
1.85
f1 (ppm)


206.3 (CD3)2CO
161.9
158.6
155.3
155.2
139.8
124.6
118.6
79.9
79.2
56.4
52.5
44.6
28.7
28.3
f1 (ppm)

***tert*-Butyl (*S*)-2-amino-2-(5-(5-methylfuran-2-yl)pent-1-en-3-yl)-7-azaspiro[3.5]nonane-7-carboxylate (4.4v)**



Procedures

Nitroalkane product **4.3v** (41.9 mg, 0.10 mmol, 100 mol%) was subjected to general procedure B. The title compound was obtained in 99% yield (38.6 mg, 0.10 mmol) as a yellow oil after filtration.

TLC (Al_2O_3) R_f = 0.23 (hexane : EA = 1:1).

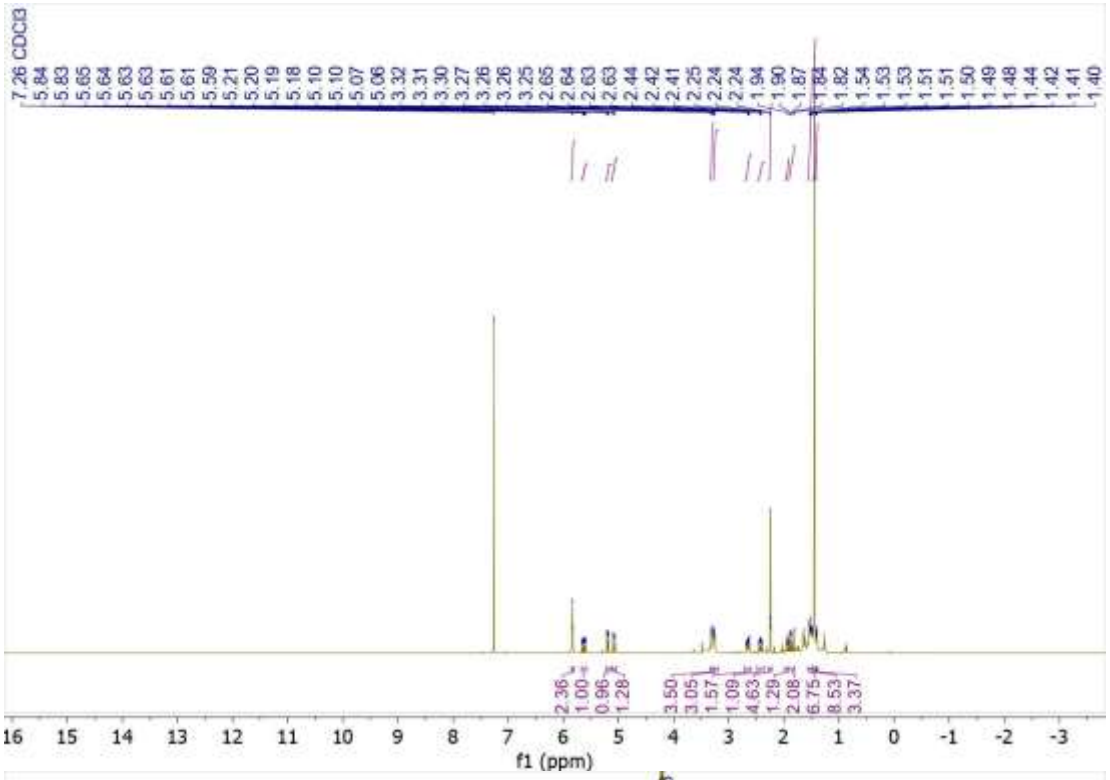
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.83 (d, J = 4.9 Hz, 2H), 5.63 (ddd, J = 17.2, 10.3, 9.0 Hz, 1H), 5.20 (dd, J = 10.3, 2.0 Hz, 1H), 5.08 (dd, J = 17.2, 1.5 Hz, 1H), 3.34 – 3.28 (m, 4H), 3.26 (dd, J = 6.5, 3.9 Hz, 3H), 2.65 (ddd, J = 14.3, 9.2, 4.5 Hz, 2H), 2.42 (dt, J = 15.5, 8.5 Hz, 1H), 2.24 (d, J = 2.8 Hz, 5H), 1.98 – 1.91 (m, 1H), 1.86 (dd, J = 26.9, 12.4 Hz, 2H), 1.51 (ddd, J = 15.8, 7.8, 4.5 Hz, 7H), 1.44 (s, 9H), 1.42 – 1.39 (m, 3H) ppm.

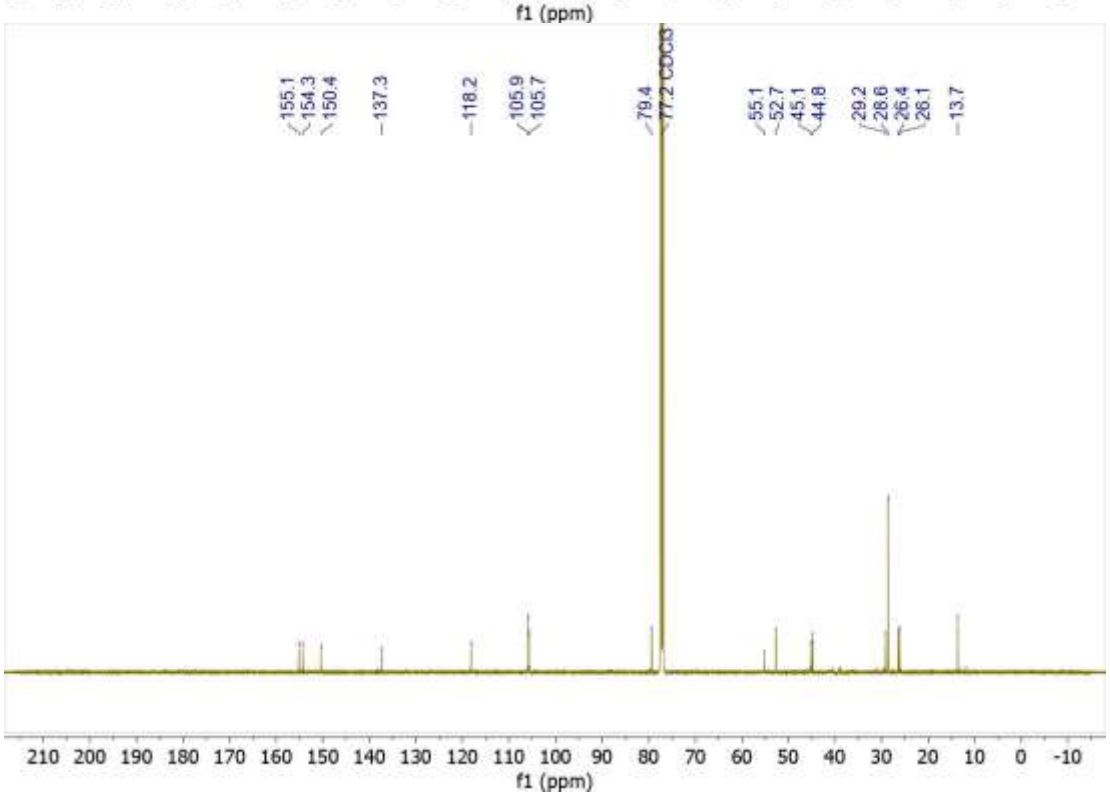
^{13}C NMR (126 MHz, $CDCl_3$): δ 155.1, 154.3, 150.4, 137.3, 118.2, 105.9, 105.7, 79.4, 55.2, 52.7, 45.1, 44.8, 29.2, 28.6, 26.4, 26.1, 13.7 ppm.

HRMS (ESI) m/z: [(M+H)+] calcd for $C_{23}H_{36}N_2O_3$ 389.2799, found 389.2798.

FTIR (Neat): 2924, 1664, 1425, 1245, 1151, 909, 729 cm^{-1}.

$[\alpha]_D^{28}$: - 22.0 (c = 1.0, $CHCl_3$).


7.26 CDCl3
5.84
5.83
5.65
5.64
5.63
5.63
5.61
5.61
5.59
5.21
5.20
5.19
5.18
5.10
5.10
5.07
5.06
3.32
3.31
3.30
3.27
3.26
3.26
3.25
2.65
2.64
2.63
2.63
2.44
2.42
2.41
2.25
2.24
2.24
1.94
1.90
1.87
1.84
1.82
1.54
1.53
1.53
1.51
1.51
1.50
1.49
1.48
1.44
1.42
1.41
1.40
2.36
1.00
0.96
1.28
3.50
3.05
1.57
1.09
4.63
1.29
2.08
6.75
8.53
3.37
f1 (ppm)


155.1
154.3
150.4
137.3
118.2
105.9
105.7
79.4
77.2 CDCl3
55.1
52.7
45.1
44.8
29.2
28.6
26.4
26.1
13.7
f1 (ppm)

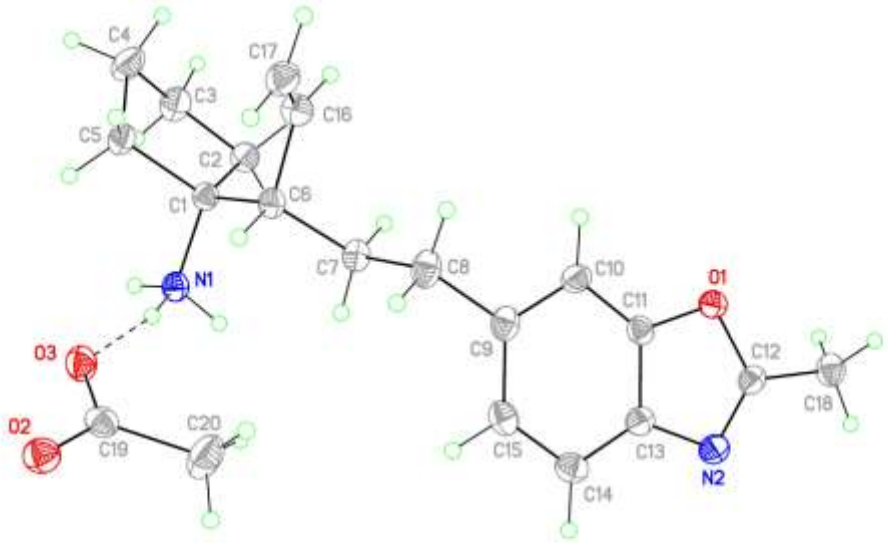
4.5.7 Single Crystal X-Ray Diffraction Analysis of Adduct 4.4l

Crystal data and structure refinement for **4.4l**.

Empirical formula	C20 H28 N2 O3	
Formula weight	344.44	
Temperature	100.0 K	
Wavelength	1.54184 Å	
Crystal system	orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 6.04900(10) Å	a= 90°.
	b = 11.2868(3) Å	b= 90°.
	c = 27.7367(6) Å	g = 90°.
Volume	1893.69(7) $Å^3$	
Z	4	
Density (calculated)	1.208 Mg/m^3	
Absorption coefficient	0.649 mm^{-1}	
F(000)	744	
Crystal size	0.105 x 0.012 x 0.012 mm^3	
Theta range for data collection	3.187 to 74.571°.	
Index ranges	-7<=h<=7, -13<=k<=14, -34<=l<=34	
Reflections collected	55514	
Independent reflections	3872 [R(int) = 0.0368]	
Completeness to theta = 67.684°	100.0 %	
Absorption correction	Semi-empirical from equivalents	

Max. and min. transmission	0.982 and 0.893
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3872 / 0 / 311
Goodness-of-fit on F^2	1.042
Final R indices [I>2sigma(I)]	R1 = 0.0262, wR2 = 0.0661
R indices (all data)	R1 = 0.0269, wR2 = 0.0667
Absolute structure parameter	0.00(4)
Extinction coefficient	0.0012(3)
Largest diff. peak and hole	0.180 and -0.168 e.$Å^{-3}$

View of **4.4l** showing the heteroatom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level. Dashed lines are indicative of a H-bonding interaction.



Chapter 5: Regio- and Enantioselective Iridium-Catalyzed Amination of Alkyl-Substituted Allylic Acetates with Secondary Amines

5.1 INTRODUCTION

Nearly 50 years since its discovery, the Tsuji-Trost reaction continues to serve as an important method in asymmetric synthesis.[1-3] Iridium-catalyzed variants of the Tsuji-Trost reaction have proven especially useful *vis-à-vis* enantioselective C-N bond formation in acyclic systems.[4] Following initial reports by Takeuchi,[5,6] the laboratories of Helmchen,[7,8] Hartwig,[9,10] Carreira[11,12] You[13,14] and others[15] have advanced chiral phosphoramidite-modified iridium complexes for diverse asymmetric allylic aminations.[4-15] Helmchen has defined Type I and Type II catalysts (Figure 5.1).[8c] Whereas Type I catalysts operate under basic conditions and require linear π-allyl precursors (as branched proelectrophiles react stereospecifically),[16] Type II catalysts operate under acidic conditions and may be applied to branched π-allyl precursors (as π-enantiofacial interconversion is rapid with respect to alkylation).[17] For both Type I and II iridium catalysts, allylic alkylation proceeds by way of cationic π-allyliridium intermediates.

We have developed a novel class of cyclometallated π-allyliridium *C,O*-benzoates as neutral π-allyliridium intermediates.[18,19] Remarkably, these catalysts display amphiphilic properties: *nucleophilic* carbonyl allylation occurs via inner sphere addition[18] and *electrophilic N*-allylation occurs via outer-sphere addition, as corroborated by isotopic labeling studies.[19b,c] In the latter context, the π-allyliridium-*C,O*-benzoates were

*This chapter is based on the previously published works: Jung, W.-O.; Yoo, M.; Migliozzi, M. M.; Zbieg, J. R.; Stivala, C. E.; Krische, M. J. *Org. Lett.* **2022,** *24*, 441.
W. J. contributed to reaction discovery and optimization (Scheme5.1), substrate scope (Table 5.1, equations 5.1 and 5.2), and preparation of manuscript and supporting information.

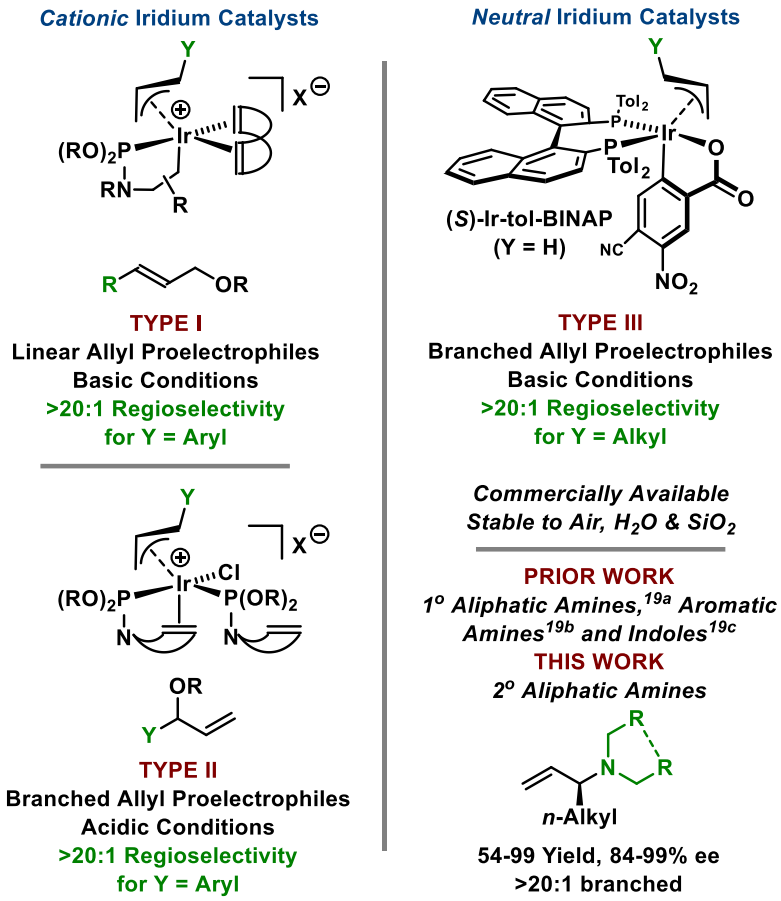


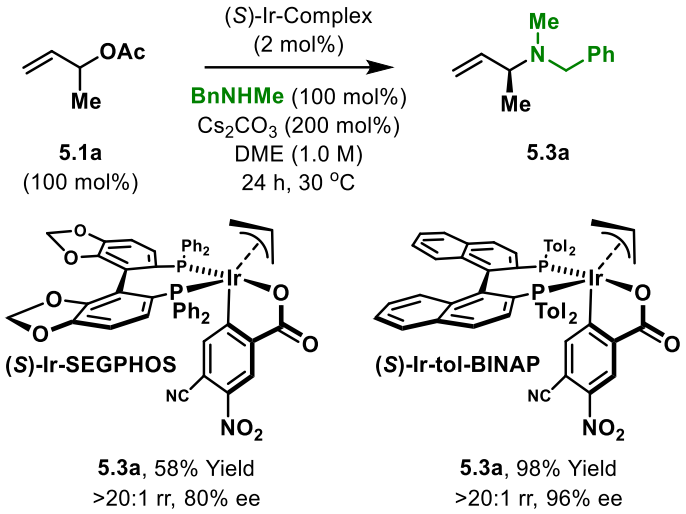
Figure 5. 1 Cationic vs neutral chiral iridium complexes for regio- and enantioselective allylic amination.

shown to catalyze enantioselective aminations of branched π-allyl precursors under basic conditions.[19a-c,20] Complementing the scope of Type I and II catalysts, our "Type III" iridium catalysts enable highly enantioselective allylic substitutions of π-allyl proelectrophiles bearing alkyl groups with complete branched regioselectivity. This capability has been demonstrated in asymmetric allylations of primary aliphatic amines,[19a] (hetero)aromatic amines,[19b] indoles/azoles,[19c] and *C*-nucleophiles (nitronates[19d] and malonates[19e]). Here, we report that secondary aliphatic amines participate in highly

enantioselective allylic amination with complete branched regioselectivity despite formation of more highly substituted C-N bonds. This method enables access chiral α-stereogenic tertiary amines that are challenging to access by other means.[20,21]

5.2 Reaction Development and Scope

In our initial discovery, the SEGPHOS-modified π-allyliridium-*C,O*-benzoate was reported to catalyze highly regio- and enantioselective aminations of branched alkyl substituted allylic acetates using primary aliphatic amine nucleophiles.[19a] The corresponding tol-BINAP-modified complex was found to be a superior catalyst, enabling the use of aromatic amine[19b] and indole[19c] nucleophiles. The SEGPHOS-modified π-allyliridium-*C,O*-benzoates were not efficient catalysts for asymmetric allylic aminations employing secondary aliphatic amine nucleophiles. However, based on enhanced performance of the tol-BINAP-modified complexes, the use of secondary aliphatic amine nucleophiles was revisited. Specifically, a cross-comparison was conducted in which equimolar quantities of allylic acetate **5.1a** and *N*-methyl benzyl amine **5.2a** were exposed to the indicated SEGPHOS- and tol-BINAP complexes (2 mol%) in the presence of Cs_2CO_3 (200 mol%) in DME (1.0 M) at 30 °C for 24 hours (Scheme 5.1). Remarkably, while the reaction catalyzed by (*S*)-Ir-SEGPHOS gave a relatively low isolated yield of the allylic amination product **5.3a**, the reaction catalyzed by (*S*)-Ir-tol-BINAP delivered **5.3a** in 98% yield as a single regioisomer with a 96% enantiomeric excess.

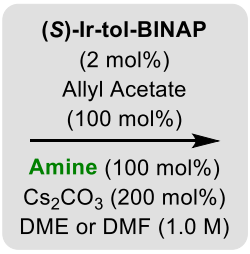


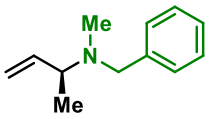
[a]Yields are of material isolated by silica gel chromatography. Enantioselectivity was determined by chiral stationary phase HPLC analysis. See Supporting Information for further experimental details.

Scheme 5. 1 Comparison of SEGPHOS- and tol-BINAP-modified π-allyliridium-*C,O*-benzoate catalysts for asymmetric allylic aminations employing secondary aliphatic amine nucleophiles.[a]

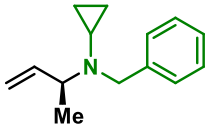
To assess reaction scope, these conditions were applied to the allylation of diverse secondary aliphatic amines **5.2a**-**5.2t** using branched alkyl substituted allylic acetates **5.1a**-**5.1j** (Table 5.1). All targeted products (**5.3a-5.3ab**) were formed with complete branched-regioselectivity and consistently high enantioselectivity. Acyclic amines bearing primary and secondary alkyl substituents are effective nucleophilic partners (**5.3a-5.3e**). As illustrated by the conversion of **5.2f** to **5.3f**, secondary aliphatic amines undergo chemoselective allylation in the presence of secondary Boc-amides. Additionally, *N*-benzyl ethanolamine **5.2g** undergoes *N*-allylation to furnish **5.3g** without competing dehydrogenative carbonyl crotylation of the primary alcohol moiety.[18] As

Table 5. 1 Iridium-catalyzed amination of branched alkyl substituted allyl acetates **5.1a-5.1j** with secondary aliphatic amines **5.2a-5.2t** to form enantiomerically enriched allylic amines **5.3a-5.3ab**.[a]

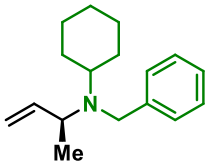




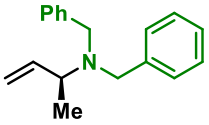
5.3a, 98% Yield, >20:1 rr
96% ee (30 °C, DME)
(86% Yield, 1.0 mmol)



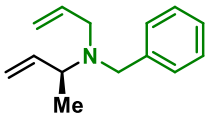
5.3b, 65% Yield, >20:1 rr,
99% ee (60 °C, DMF)



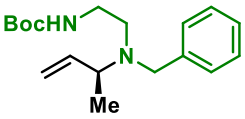
5.3c, 58% Yield, >20:1 rr
88% ee (70 °C, DMF)



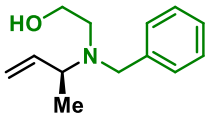
5.3d, 78% Yield, >20:1 rr
88% ee (70 °C, DMF)[b]



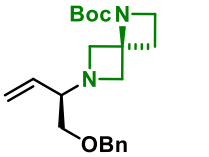
5.3e, 82% Yield, >20:1 rr
92% ee (50 °C, DMF)



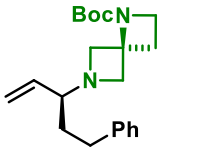
5.3f, 75% Yield, >20:1 rr
88% ee (90 °C, DMF)[b,c]



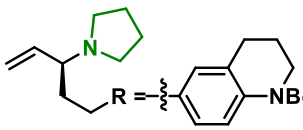
5.3g, 70% Yield, >20:1 rr
93% ee (70 °C, DMF)



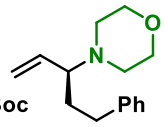
5.3h, 54% Yield, >20:1 rr
84% ee (70 °C, DMF)[c,d]
from oxalate salt



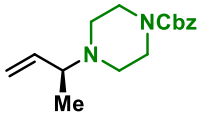
5.3i, 87% Yield, >20:1 rr
89% ee (90 °C, DMF)[d]
from oxalate salt



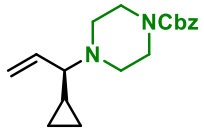
5.3j, 94% Yield, >20:1 rr
92% ee (50 °C, DMF)



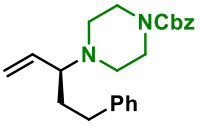
5.3k, 79% Yield, >20:1 rr
98% ee (50 °C, DME)



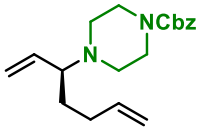
5.3l, 98% Yield, >20:1 rr
98% ee (30 °C, DME)



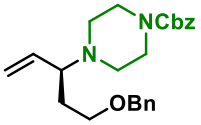
5.3m, 81% Yield, >20:1 rr
92% ee (50 °C, DMF)



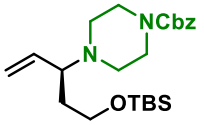
5.3n, 91% Yield, >20:1 rr
93% ee (50 °C, DMF)



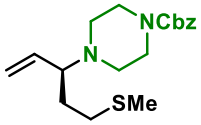
5.3o, 64% Yield, >20:1 rr
94% ee (50 °C, DMF)



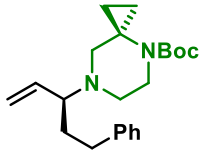
5.3p, 57% Yield, >20:1 rr
98% ee (50 °C, DMF)



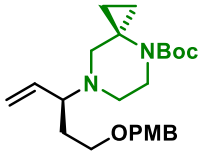
5.3q, 82% Yield, >20:1 rr
92% ee (50 °C, DMF)



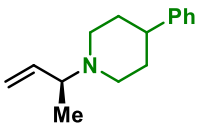
5.3r, 76% Yield, >20:1 rr
92% ee (50 °C, DMF)



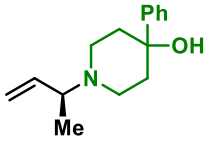
5.3s, 98% Yield, >20:1 rr
95% ee (70 °C, DMF)



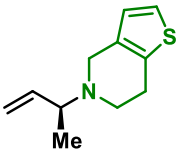
5.3t, 97% Yield, >20:1 rr
99% ee (70 °C, DMF)



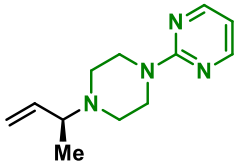
5.3u, 95% Yield, >20:1 rr
96% ee (40 °C, DME)



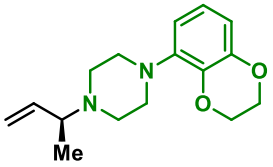
5.3v, 94% Yield, >20:1 rr
93% ee (90 °C, DME)[d]
(X-Ray)



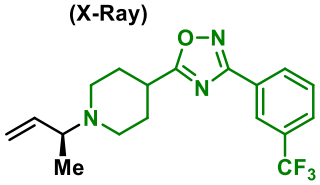
5.3w, 98% Yield, >20:1 rr
98% ee (30 °C, DME)



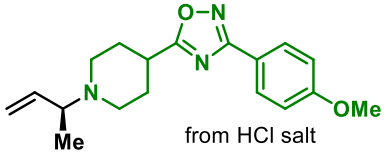
5.3x, 94% Yield, >20:1 rr
93% ee (30 °C, DME)



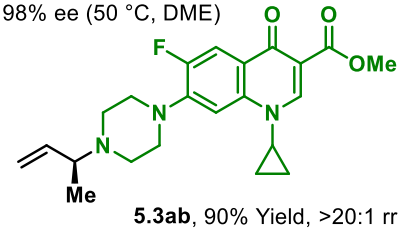
5.3y, 97% Yield, >20:1 rr
95% ee (30 °C, DME)



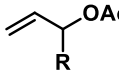
5.3z, 99% Yield, >20:1 rr
98% ee (50 °C, DME)



from HCl salt
5.3aa, 92% Yield, >20:1 rr
97% ee (50 °C, DME)[d]



5.3ab, 90% Yield, >20:1 rr
95% ee (80 °C, DME)[e]



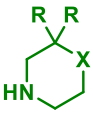
5.1a, R = Me, **5.1b**, R = CH_2OBn, **5.1c**, R = $(CH_2)_2Ph$
5.1d, R = $(CH_2)_2$-6-(*N*-Boc-dihydroquinoline)
5.1e, R = *c*-Pr, **5.1f**, R = $(CH_2)_2CH{=}CH_2$

ALLYLIC ACETATES

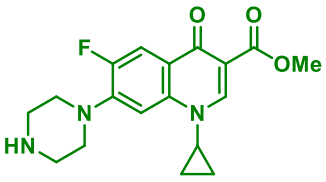
5.1g, R = $(CH_2)_2OBn$
5.1h, R = $(CH_2)_2OTBS$
5.1i, R = $(CH_2)_2SMe$
5.1j, R = $(CH_2)_2OPMB$

SECONDARY AMINES

R–NHBn
5.2a, R = Me
5.2b, R = *c*-Pr
5.2c, R = *c*-Hex
5.2d, R = Bn
5.2e, R = $CH_2CH{=}CH_2$
5.2f, R = $(CH_2)_2NHBoc$
5.2g, R = $(CH_2)_2OH$



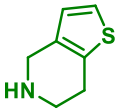
5.2j, R = H, X = O
5.2k, R = H, X = NCbz
5.2l, R = $(CH_2)_2$, X = NBoc
5.2m, R = H, X = CHPh
5.2n, R = H, X = C(OH)Ph
5.2p, R = H, X = N-(2-pyrimidinyl)
5.2q, R = H, X = N-(5-benzodioxanyl)



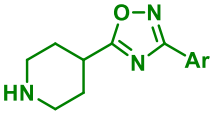
5.2t

5.2h

5.2i



5.2o



5.2r, Ar = 3-CF_3Ph
5.2s, Ar = 4-MeOPh

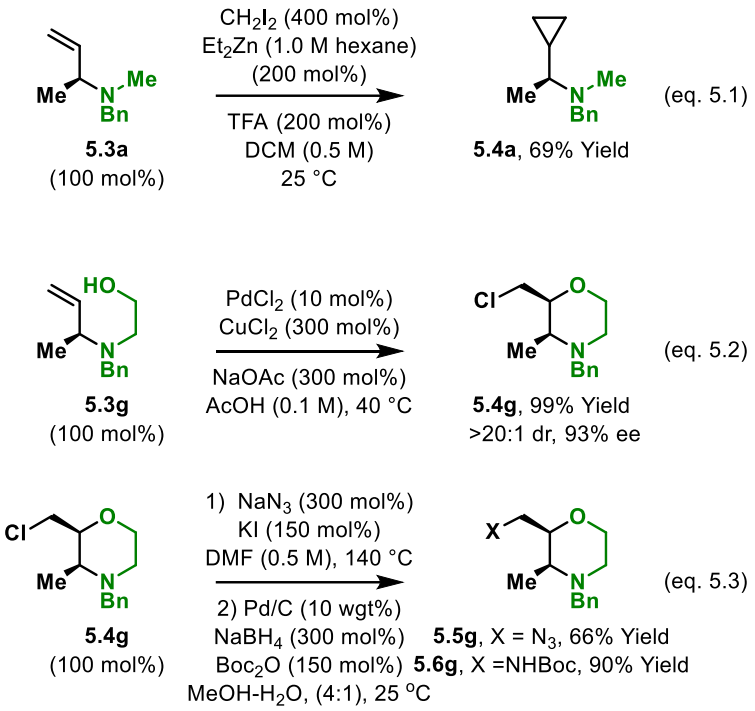
[a]Yields are of material isolated by silica gel chromatography. Enantioselectivity was determined by chiral stationary phase HPLC analysis.

illustrated by the formation of **5.3h**, **5.3i**, **5.3s**, and **5.3t**, spirocyclic amines engage in highly enantioselective C-N bond formation in the presence of strained 3- and 4-membered rings. The allylation of amine oxalate or hydrochloric acid salts **5.2h** and **5.2s** proceeded smoothly with additional Cs_2CO_3 to form adducts **5.3h**, **5.3i**, and **5.3aa**. Branched allyl acetates that are functionalized at the α (**5.1b**, **5.1e**), β (**5.1c, 5.1d**, **5.1g**-**5.1j**), and γ-positions (**5.1f**) are tolerated, as demonstrated by the formation of **5.3h** and **5.3m**, **5.3n, 5.3p**-**5.3t**, and **5.3o**, respectively. Secondary amines **5.2o**-**5.2q** correspond to substructures of clopidogrel, buspirone, and lecozotan, respectively. The oxadiazole-containing piperidines **5.2r** and **5.2s** are farnesoid X receptor (FXR) antagonists,[22] and piperazine **5.2t** is the methyl ester of the antibiotic ciprofloxacin. The allylation of **5.2o**-**5.2t**, which are FDA approved drugs or clinical candidates, highlights the feasibility of utilizing this method for late-stage functionalization.[23] The absolute stereochemical assignment of adducts **5.3a**-**5.3ab** is made in analogy to that determined for compound **5.3v**, which was determined by single crystal X-ray diffraction analysis.

5.3 DISCUSSION

To briefly illustrate the utility of the reaction products, adducts **5.3a** and **5.3g** were converted to compounds **5.4a** and **5.6g**, respectively (eq. 5.1, 5,2 and 5.3). Simmons-Smith cyclopropanation of allylic amine **5.3a** occurred uneventfully to deliver the cyclopropyl carbinyl amine in good yield.[24] Given the importance of saturated nitrogen-containing heterocycles in drug discovery,[25] the cyclization of adduct **5.3g** was attempted under a variety of conditions. Attempted haloetherification using diverse electrophilic halogen sources failed. Eventually, it was found that palladium-catalyzed-chlorocyclization in

acetic acid solvent provided the *cis*-2,3-disubstituted morpholine **5.4g** as a single diastereomer.[26,27] The relative stereochemistry of **5.4g** was assigned by NOE experiments. Treatment of **5.4g** with sodium azide followed by reduction of the resulting organic azide **5.5g** in the presence of Boc-anhydride[28] delivered the orthogonally protected 3-methyl-2-(methylamino)-morpholine **5.6g** in good yield, a potentially valuable synthon for medicinal chemistry campaigns.



5.4 Conclusion

In conclusion, we report highly regio- and enantioselective π-allyliridium *C,O*-benzoate-catalyzed allylic aminations of racemic branched alkyl-substituted allylic acetates using secondary aliphatic amines. The observation of complete branched

regioselectivity in the present enantioselective reactions of hindered secondary amines is noteworthy[29] and, as corroborated by prior computational studies,[19d] may be attributed to early transition states for allylic alkylation that mitigate the influence of steric effects. From our collective studies,[19a-d] it is evident that Type III iridium catalysts offer broad new capabilities for asymmetric allylic amination, providing a powerful new tool for industrial and academic chemists to forge stereogenic C-N bonds, a long-standing challenge in both communities.[21]

5.5 Experimental Details

5.5.1 General Information

All reactions were carried out under inert gas atmosphere (nitrogen or argon) unless otherwise indicated. Re-sealable pressure tubes (13x100 mm) were purchased from Fischer Scientific (catalog number 14-959-35C) and were flame dried followed by cooling in a desiccator or under a stream of inert gas prior to use. All commercial reagents and anhydrous solvents were used as received from vendors (Fischer Scientific, Sigma Aldrich, TCI America, Combi Blocks and Enamine) without further purification. The used Iridium catalyst (*S*)-Ir-SEGPHOS and (*S*)-Ir-tol-BINAP was prepared according to literature known procedures.[30] Cs_2CO_3 was used as received from Rockwell Lithium. Preparative column chromatography employing Silicycle silica gel (40-63 μm) was performed according to the method of Still[31] or on a Teledyne Isco Combiflash Rf utilizing Silicycle HP columns using a mobile phase composed of either heptane/isopropyl acetate or dichloromethane/methanol. Reactions were monitored by a Shimadzu LCMS/UV system

with LC-30AD solvent pump, 2020 MS, Sil-30AC autosampler, SPD-M30A UV detector, CTO-20A column oven, using a 2-98% acetonitrile/0.1% formic acid (or 0.001% ammonia) gradient over 2.5 minutes. Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates (Dynamic Absorbents F). Visualization was accomplished with UV light followed by dipping in CAM, p-Anisaldehyde (PAA), or KMnO4 stain solution followed by heating.

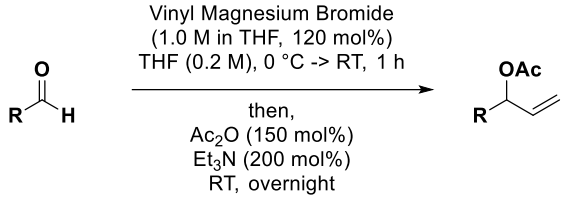
5.5.2 Spectroscopy, Spectrometry and Data Collection

Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer using a diamond NEAT unit. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M+H, M+Na), or a suitable fragment ion. Nuclear magnetic resonance (1H, 13C, 19F NMR) spectra were recorded with a Bruker BioSpin GmbG, Varian Gemini (400 MHz) or Varian INOVA (500 MHz) spectrometer equipped with a Bruker cryoprobe. The chemical shifts are given as parts per million (ppm) and were referenced to the residual solvent signal (DMSO: δH = 2.50 ppm, δC = 39.52 ppm, CDCl3: δH = 7.26 ppm, δC = 77.16 ppm). Specific optical rotations were recorded on an Atago AP-300 automatic polarimeter at the sodium line (589 nm) in either $CHCl_3$ or methanol. Solution concentrations are given in the units of 10^{-2} g mL^{-1}.

5.5.3 Synthesis of Allylic Acetates 5.1a-5.1j

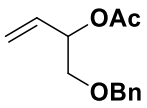
General procedure for the synthesis of allylic acetates.

The allylic acetates **5.1a-5.1i** were prepared by the Grignard reaction followed by acetylation as shown below. The allylic acetates were identical with respect to the reported material.



To a round-bottomed flask charged with the corresponding aldehyde under argon atmosphere was added THF (0.2 M). The reaction flask was placed in an ice bath. After 10 minutes, vinyl magnesium bromide solution (120 mol%, 1.0 M in THF) was added slowly and the mixture was stirred at room temperature for 1 hour, at which point acetic anhydride (150 mol%) and triethylamine (200 mol%) were added and the reaction was stirred vigorously overnight. After water was added, the mixture was transferred to a separatory funnel. The organic layer was extracted with diethyl ether and the combined organic layers were washed with 1 N HCl, dried (MgSO4), filtered and concentrated under reduced pressure. The resulting residue was subjected to flash column chromatography to give the corresponding allylic acetate over 2 steps.

1-(Benzyloxy)but-3-en-2-yl acetate (5.1b)



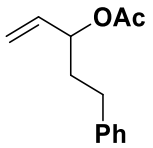
Procedures

The title compound was prepared by the general procedure, and it is identical with respect to the reported material.[32]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 – 7.29 (m, 5H), 5.86 (ddd, J = 17.1, 10.6, 6.0 Hz, 1H), 5.51 (q, J = 6.3, 5.6 Hz, 1H), 5.39 – 5.24 (m, 1H), 4.59 (q, J = 12.3 Hz, 3H), 3.60 (dd, J = 5.5, 2.6 Hz, 2H), 2.13 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.2, 137.9, 133.3, 128.4, 127.7, 127.7, 118.0, 73.2, 73.2, 71.3, 21.2 ppm.

5-Phenylpent-1-en-3-yl acetate (5.1c)

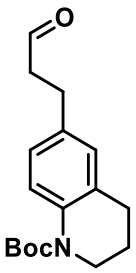


Procedures

The title compound was prepared by the general procedure, and it is identical with respect to the reported material.[33]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (dt, J = 38.0, 7.6 Hz, 5H), 5.81 (ddd, J = 17.6, 10.9, 6.9 Hz, 1H), 5.31 – 5.16 (m, 3H), 2.65 (dt, J = 9.7, 5.0 Hz, 3H), 2.06 (s, 3H), 1.95 (dtt, J = 20.9, 14.5, 7.1 Hz, 3H) ppm.

***tert*-Butyl 6-(3-oxopropyl)-3,4-dihydroquinoline-1(2*H*)-carboxylate (5.1d-CHO)**



Procedures

To a round-bottomed flask charged with *tert*-butyl 6-bromo-3,4-dihydroquinoline-1(2*H*)-carboxylate (3.12 g, 10 mmol, 100 mol%), tris(dibenzylideneacetone)dipalladium(0) (183 mg, 0.20 mmol, 2 mol%), 2-(di-*tert*-butylphosphino)-1-phenylindole (202.5 mg, 0.60 mmol, 6 mol%) was added anhydrous DMF (25 mL, 0.4 M). Allylic alcohol (1.16 mL, 20.0 mmol, 200 mol%), and *N*,*N*-dicyclohexylmethylamine (2.15 mL, 11.0 mmol, 110 mol%) were added and the reaction was stirred at 100 °C for 2 h. After cooling down to room temperature, the mixture was transferred to a separatory funnel and water was added. The aqueous layer was extracted with diethyl ether three times and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The title compound was obtained in 66% yield (1.9 g, 6.6 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane: ethyl acetate = 15:1).

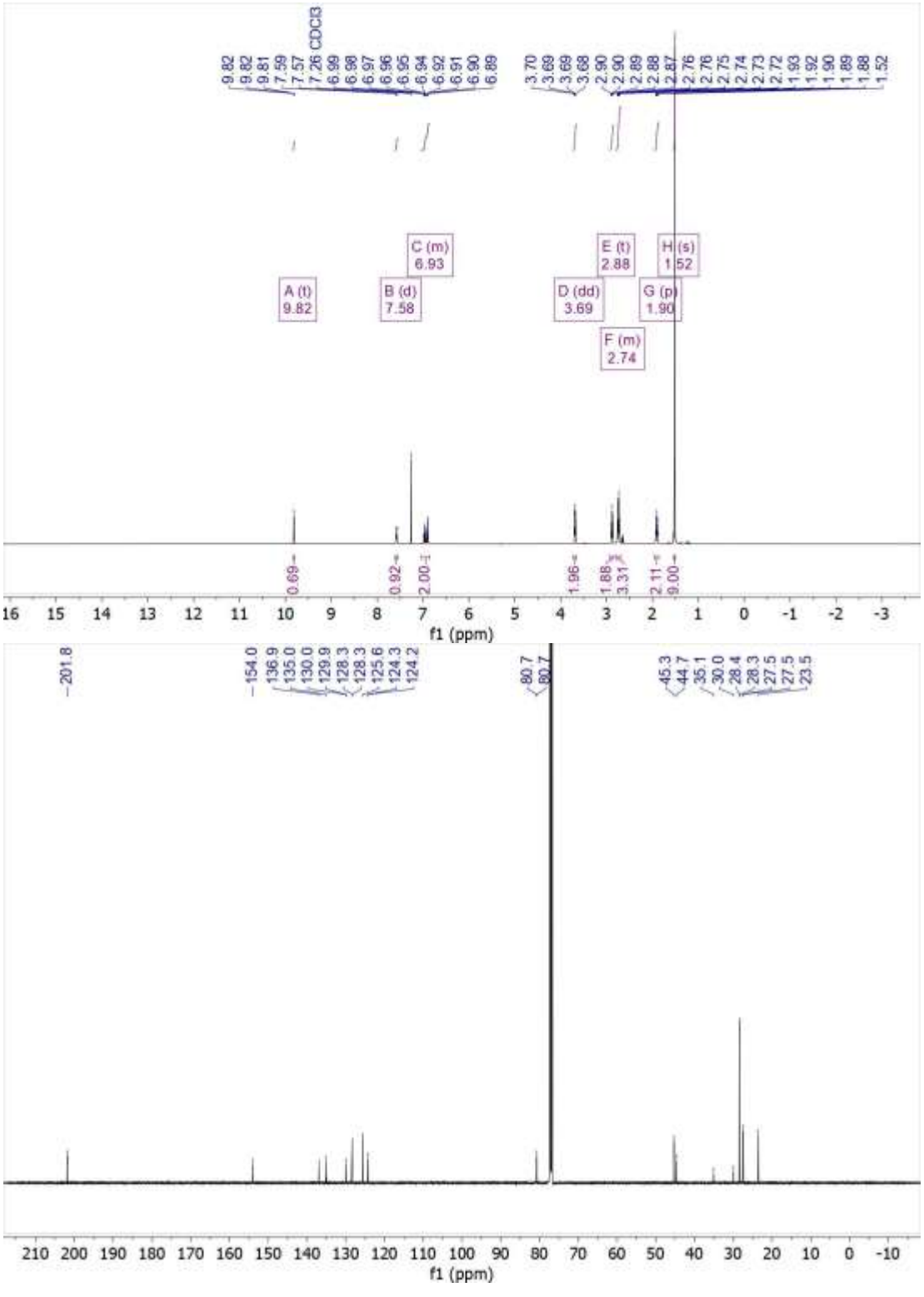
TLC (SiO_2) R_f = 0.30 (hexane: ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.82 (t, J = 1.5 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.03 – 6.86 (m, 2H), 3.69 (dd, J = 7.0, 5.1 Hz, 2H), 2.88 (t, J = 7.4 Hz, 2H), 2.79 – 2.70 (m, 3H), 1.90 (p, J = 6.5 Hz, 2H), 1.52 (s, 9H) ppm.

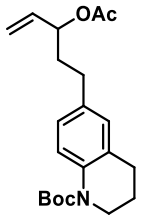
^{13}C NMR (126 MHz, $CDCl_3$): δ 201.8, 154.0, 136.9, 135.0, 129.9, 129.8, 128.3, 128.3, 125.6, 124.3, 124.2, 80.7, 80.7, 45.3, 44.7, 35.1, 29.9, 28.4, 28.3, 27.5, 27.5, 23.5 ppm.

HRMS (ESI): Calculated for $C_{17}H_{23}NO_3Na$ $[M+Na]^+$ = 312.1570, Found 312.1582.

FTIR (neat): 3461, 3015, 2970, 1738, 1435, 1365, 1216, 1010, 768 cm^{-1}.


9.82
9.82
9.81
7.59
7.57
7.26 CDCl3
6.99
6.98
6.97
6.96
6.95
6.94
6.92
6.91
6.90
6.89
3.70
3.69
3.69
3.68
2.90
2.90
2.89
2.88
2.87
2.76
2.76
2.75
2.74
2.73
2.72
1.93
1.92
1.90
1.89
1.88
1.52
A (t) 9.82
B (d) 7.58
C (m) 6.93
D (dd) 3.69
E (t) 2.88
F (m) 2.74
G (p) 1.90
H (s) 1.52
0.69
0.92
2.00
1.96
1.88
3.31
2.11
9.00
f1 (ppm)
201.8
154.0
136.9
135.0
130.0
129.9
128.3
128.3
125.6
124.3
124.2
80.7
80.7
45.3
44.7
35.1
30.0
28.4
28.3
27.5
27.5
23.5
f1 (ppm)

***tert*-Butyl 6-(3-acetoxypent-4-en-1-yl)-3,4-dihydroquinoline-1(2*H*)-carboxylate (5.1d)**



Procedures

The title compound was prepared by the general procedure and was obtained as light-yellow oil (1.9 g, 5.4 mmol) in 82% yield over 2 steps.

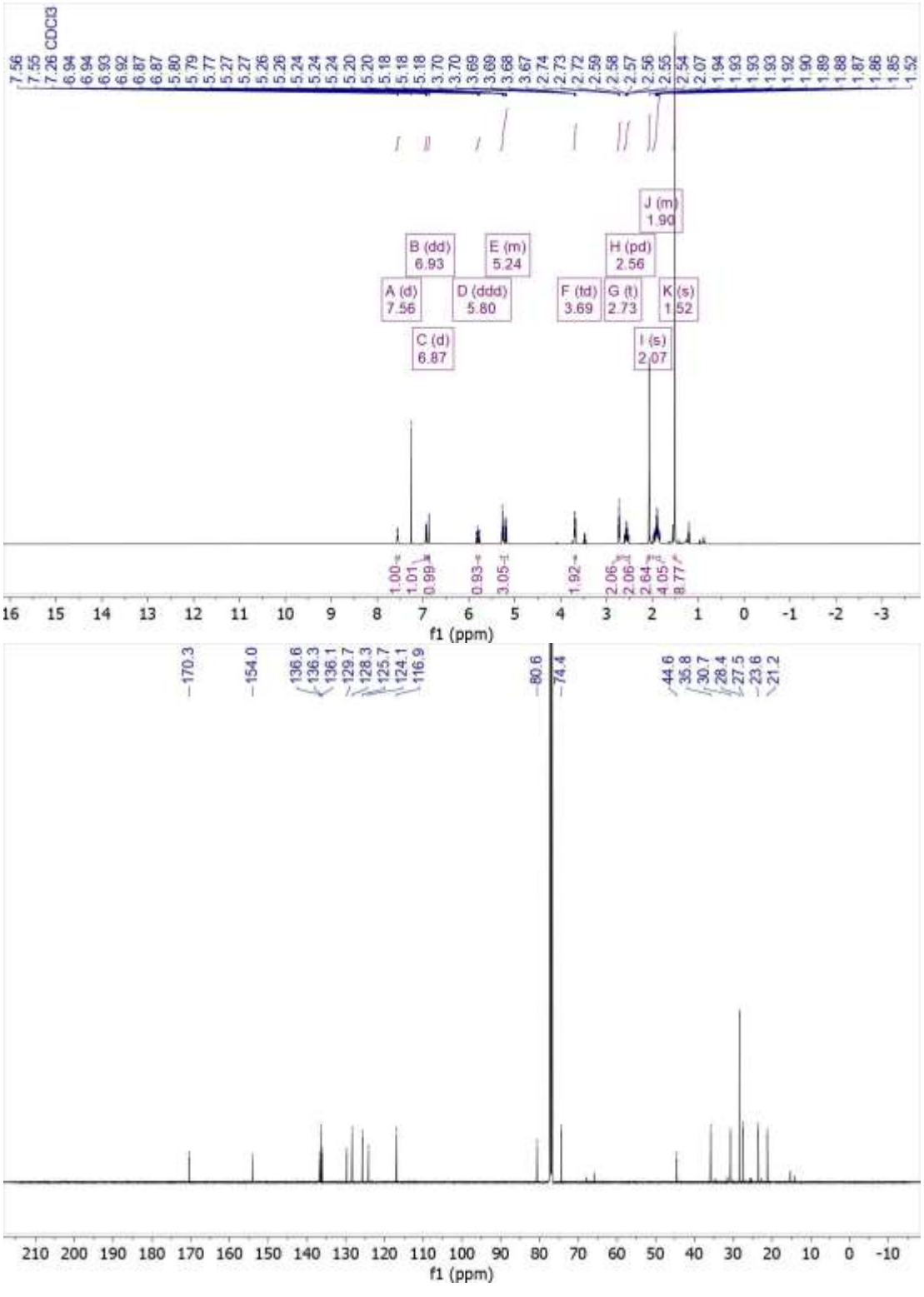
TLC (SiO_2) R_f = 0.52 (hexane: ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56 (d, J = 8.4 Hz, 1H), 6.93 (dd, J = 8.5, 2.2 Hz, 1H), 6.87 (d, J = 2.1 Hz, 1H), 5.80 (ddd, J = 17.0, 10.5, 6.3 Hz, 1H), 5.31 – 5.16 (m, 3H), 3.69 (td, J = 5.6, 1.3 Hz, 2H), 2.73 (t, J = 6.6 Hz, 2H), 2.56 (pd, J = 14.1, 6.3 Hz, 2H), 2.07 (s, 3H), 2.00 – 1.83 (m, 4H), 1.52 (s, 9H) ppm.

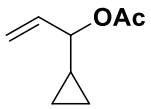
^{13}C NMR (126 MHz, $CDCl_3$): δ 170.3, 154.0, 136.6, 136.3, 136.1, 129.7, 128.3, 125.7, 124.1, 116.9, 80.6, 74.4, 44.6, 35.9, 30.7, 28.4, 27.5, 23.6, 21.2 ppm.

HRMS (ESI): Calculated for $C_{21}H_{29}NO_4Na$ $[M+Na]^+$ = 382.1989, Found 382.2003.

FTIR (neat): 3454, 2970, 1738, 1500, 1365, 1217, 1157, 1010, 895, 766 cm^{-1}.


7.56 7.55 CDCl3 7.26 6.94 6.93 6.92 6.87 6.87 5.80 5.79 5.77 5.27 5.27 5.26 5.26 5.24 5.24 5.24 5.20 5.20 5.18 5.18 5.18 3.70 3.70 3.69 3.69 3.68 3.67 2.74 2.73 2.72 2.59 2.58 2.57 2.56 2.55 2.54 2.07 1.94 1.93 1.93 1.93 1.92 1.90 1.89 1.88 1.87 1.86 1.85 1.52
J (m) 1.90
B (dd) 6.93
E (m) 5.24
H (pd) 2.56
A (d) 7.56
D (ddd) 5.80
F (td) 3.69
G (t) 2.73
K (s) 1.52
C (d) 6.87
I (s) 2.07
1.00 1.01 0.99 0.93 3.05 1.92 2.06 2.06 2.64 4.05 8.77
f1 (ppm)
170.3 154.0 136.6 136.3 136.1 129.7 128.3 125.7 124.1 116.9 80.6 74.4 44.6 35.8 30.7 28.4 27.5 23.6 21.2
f1 (ppm)

1-Cyclopropylallyl acetate (5.1e)

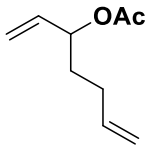


Procedures

The title compound was prepared by the general procedure, and it is identical with respect to the reported material.[34]

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85 (ddd, J = 16.9, 10.6, 6.0 Hz, 1H), 5.22 (dd, J = 41.8, 13.8 Hz, 2H), 4.75 – 4.68 (m, 1H), 2.09 (s, 3H), 1.06 (ddq, J = 13.1, 8.5, 5.1 Hz, 1H), 0.56 (qp, J = 8.6, 4.6 Hz, 2H), 0.42 (dq, J = 9.8, 4.5 Hz, 1H), 0.31 (dq, J = 8.1, 4.4 Hz, 1H) ppm.

Hepta-1,6-dien-3-yl acetate (5.1f)

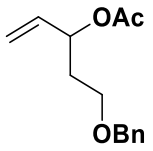


Procedures

The title compound was prepared by the general procedure, and it is identical with respect to the reported material.[35]

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.79 (dddd, J = 16.9, 13.2, 10.4, 6.5 Hz, 2H), 5.25 (dd, J = 7.4, 1.1 Hz, 1H), 5.22 (t, J = 1.4 Hz, 0H), 5.18 (dt, J = 10.5, 1.2 Hz, 1H), 5.05 (q, J = 1.7 Hz, 0H), 5.00 (dq, J = 3.3, 1.6 Hz, 1H), 4.97 (q, J = 1.4 Hz, 0H), 2.09 (dt, J = 6.8, 1.6 Hz, 1H), 2.07 (s, 3H), 1.83 – 1.59 (m, 2H) ppm.

5-(Benzyloxy)pent-1-en-3-yl acetate (5.1g)

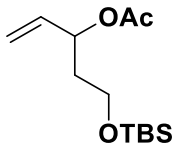


Procedures

The title compound was prepared by the general procedure, and it is identical with respect to the reported material.[36]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.25 (m, 5H), 5.79 (ddd, J = 17.1, 10.5, 6.4 Hz, 1H), 5.49 – 5.37 (m, 1H), 5.24 (dt, J = 17.2, 1.3 Hz, 1H), 5.21 (d, J = 1.0 Hz, 0H), 5.16 (dt, J = 10.6, 1.3 Hz, 1H), 4.48 (d, J = 1.8 Hz, 2H), 3.51 (t, J = 6.4 Hz, 2H), 2.02 (s, 3H), 1.98 – 1.86 (m, 2H) ppm.

5-((*tert*-Butyldimethylsilyl)oxy)pent-1-en-3-yl acetate (5.1h)

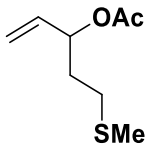


Procedures

The title compound was prepared by the general procedure, and it is identical with respect to the reported material.[27]

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.80 (ddd, J = 17.0, 10.5, 6.3 Hz, 1H), 5.40 – 5.32 (m, 1H), 5.29 – 5.12 (m, 2H), 3.65 (t, J = 6.6 Hz, 2H), 2.06 (s, 3H), 1.92 – 1.76 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H) ppm.

5-(Methylthio)pent-1-en-3-yl acetate (5.1i)

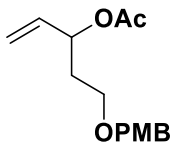


Procedures

The title compound was prepared by the general procedure, and it is identical with respect to the reported material.[28]

^{1}H NMR (400 MHz, $CDCl_3$): 5.78 (ddd, J = 17.1, 10.5, 6.4 Hz, 1H), 5.40 – 5.31 (m, 1H), 5.27 (dt, J = 17.3, 1.3 Hz, 1H), 5.20 (dt, J = 10.5, 1.2 Hz, 1H), 2.62 – 2.57 (m, 2H), 2.50 (ddd, J = 8.4, 6.7, 1.8 Hz, 2H), 2.10 (s, 3H), 2.07 (s, 3H) ppm.

5-((4-Methoxybenzyl)oxy)pent-1-en-3-yl acetate (5.1j)



Procedures

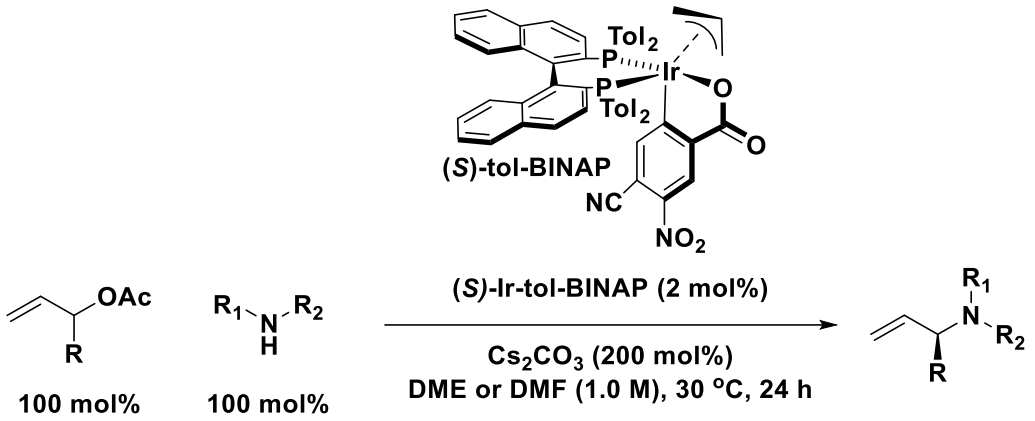
The title compound was prepared by the general procedure, and it is identical with respect to the reported material.[39]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (d, J = 2.1 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 5.81 (ddd, J = 17.0, 10.5, 6.3 Hz, 1H), 5.43 (q, J = 6.6 Hz, 1H), 5.30 – 5.15 (m, 1H), 4.43 (d, J = 3.0 Hz, 2H), 3.83 (s, 3H), 3.50 (q, J = 6.6 Hz, 3H), 2.05 (s, 3H), 1.99 – 1.87 (m, 2H), 1.23 (t, J = 7.0 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.2, 159.2, 136.3, 130.4, 129.3, 116.7, 113.8, 72.7, 72.2, 65.9, 65.8, 55.29, 34.4, 21.2, 15.3 ppm.

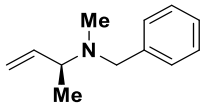
5.5.4 Procedures and Spectral Data for Products 5.3a-5.3ab

General procedure



A pressure tube equipped with a magnetic stir bar was charged with Cs_2CO_3 (130.3 mg, 0.4 mmol, 200 mol%) and (*S*)-Ir-tol-BINAP (4.4 mg, 0.004 mmol, 2 mol%). The tube was purged with argon for 2 minutes. DME (0.2 mL, 1.0 M) or DMF (0.2 mL, 1.0 M) was added followed by the allylic acetate (0.2 mmol, 100 mol%) and the amine (0.2 mmol, 100 mol%). The tube was sealed with a PTFE lined cap and was placed in an oil bath at 30 °C and stirred for 24 hours. After reaching ambient temperature, the crude reaction mixture was directly subjected to flash column chromatography.

(*S*)-*N*-Benzyl-*N*-methylbut-3-en-2-amine (5.3a)



Procedures (0.2 mmol scale)

The crotyl acetate (22.8 mg, 0.2 mmol, 100 mol%) and *N*-benzylmethylamine (24.2 mg, 0.2 mmol, 100 mol%) were subject to standard reaction conditions (DME). The title compound was obtained in 98% yield (34.4 mg, 0.20 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane: ethyl acetate = 20:1–10:1).

Procedures (1.0 mmol scale)

The crotyl acetate (114.1 mg, 1.0 mmol, 100 mol%) and *N*-benzylmethylamine (121.2 mg, 1.0 mmol, 100 mol%) were subject to standard reaction conditions (DME, 1.0 M). The title compound was obtained in 86% yield (151.2 mg, 0.86 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane: ethyl acetate = 20:1–10:1).

TLC (SiO_2) R_f = 0.52 (hexane: ethyl acetate = 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 – 7.23 (m, 3H), 7.22 – 7.15 (m, 1H), 5.87 (ddd, J = 17.3, 10.5, 7.0 Hz, 1H), 5.16 – 5.03 (m, 2H), 3.54 (d, J = 13.3 Hz, 1H), 3.41 (d, J = 13.3 Hz, 1H), 3.15 (pt, J = 6.7, 1.2 Hz, 1H), 2.12 (s, 3H), 1.15 (d, J = 6.7 Hz, 3H) ppm.

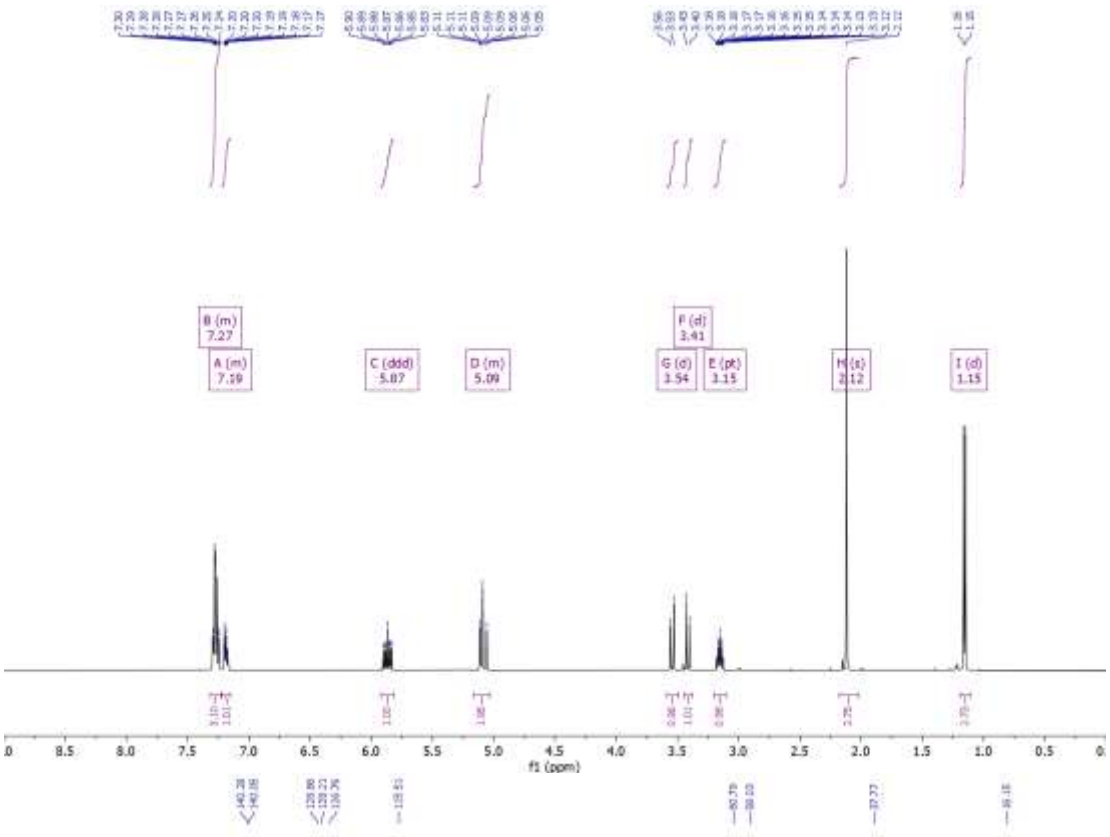
^{13}C NMR (126 MHz, $CDCl_3$): δ 140.3, 140.1, 128.9, 128.2, 126.8, 115.5, 60.8, 58.3, 37.8, 16.2 ppm.

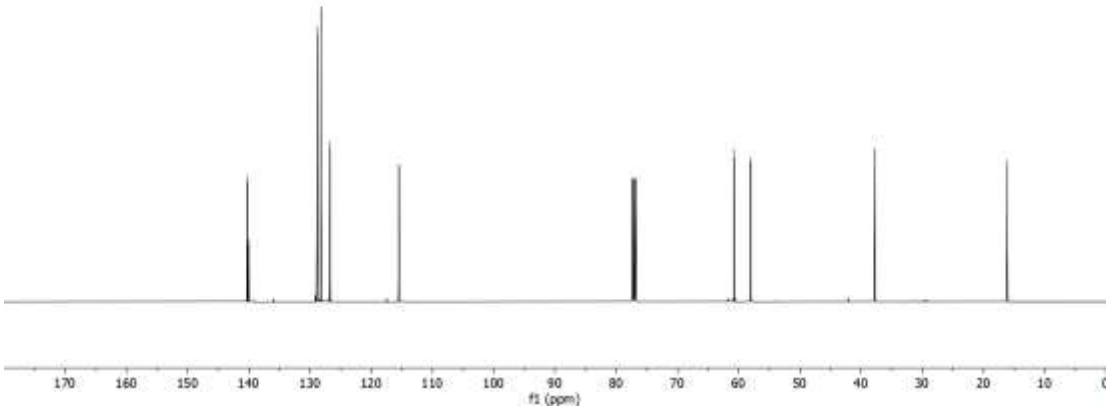
HRMS (ESI) m/z: [(M+H)+] calcd for $C_{12}H_{18}N$ 176.1434, found 176.1431.

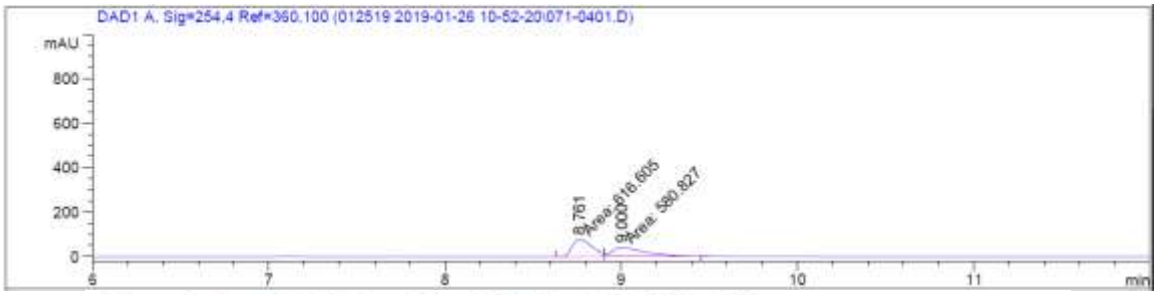
FTIR (neat): 697, 825, 954, 1027, 1156, 1363, 1637, 2371, 2788, 2931, 3027 cm^{-1}.

$\mathbf{[\alpha]_D^{28}}$**:** - 3.5 (c = 1.0, $CHCl_3$).

HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralcel OJ-H column, hexane: 2-PrOH = 99:1, 1.0 mL/min, 254 nm), t_{major} = 8.71 min, t_{minor} = 9.28 min; ee = 96 %.

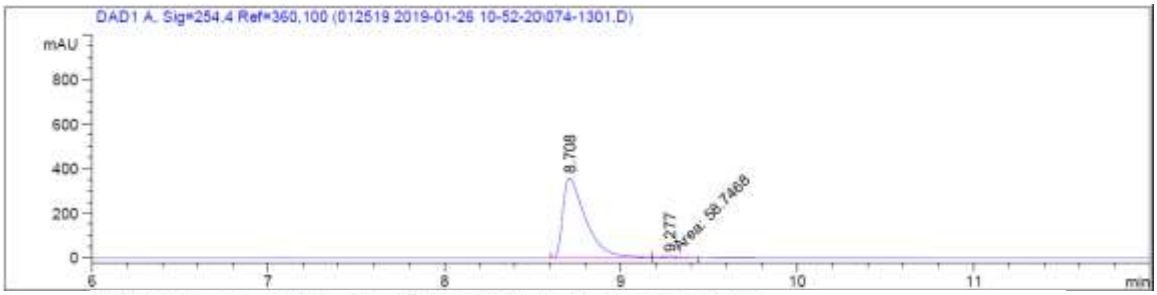

B (m)
7.27
A (m)
7.19
C (ddd)
5.07
D (m)
5.09
F (d)
3.41
G (d)
3.54
E (pt)
3.15
H (s)
2.12
I (d)
1.15
f1 (ppm)


f1 (ppm)



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

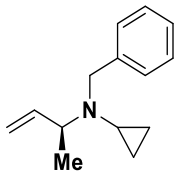
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.761	MF	0.1304	616.60547	78.83508	51.4939
2	9.000	FM	0.2319	580.82745	41.74364	48.5061
Totals :				1197.43292	120.57871	



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.708	BV	0.1332	3236.72339	358.97678	98.2173
2	9.277	MF	0.1426	58.74683	6.86435	1.7827
Totals :				3295.47021	365.84112	

(S)-*N*-Benzyl-*N*-(but-3-en-2-yl)cyclopropanamine (5.3b)



Procedures

The allyl acetate (22.8 mg, 0.2 mmol, 100 mol%) and *N*-cyclopropyl benzylamine (29.4 mg, 0.2 mmol, 100 mol%) were subject to standard reaction conditions (60 °C, 48 h, DMF). The title compound was obtained in 65% yield (26.0 mg, 0.13 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane: ethyl acetate = 20:1–10:1).

TLC (SiO_2) R_f = 0.77 (hexane: ethyl acetate = 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 – 7.18 (m, 5H), 5.88 (ddd, *J* = 17.4, 10.4, 7.0 Hz, 1H), 5.07 – 4.94 (m, 2H), 3.71 – 3.59 (m, 2H), 3.27 (s, 1H), 1.84 (t, *J* = 3.6 Hz, 1H), 1.12 (d, *J* = 6.8 Hz, 3H), 0.35 – 0.17 (m, 4H) ppm.

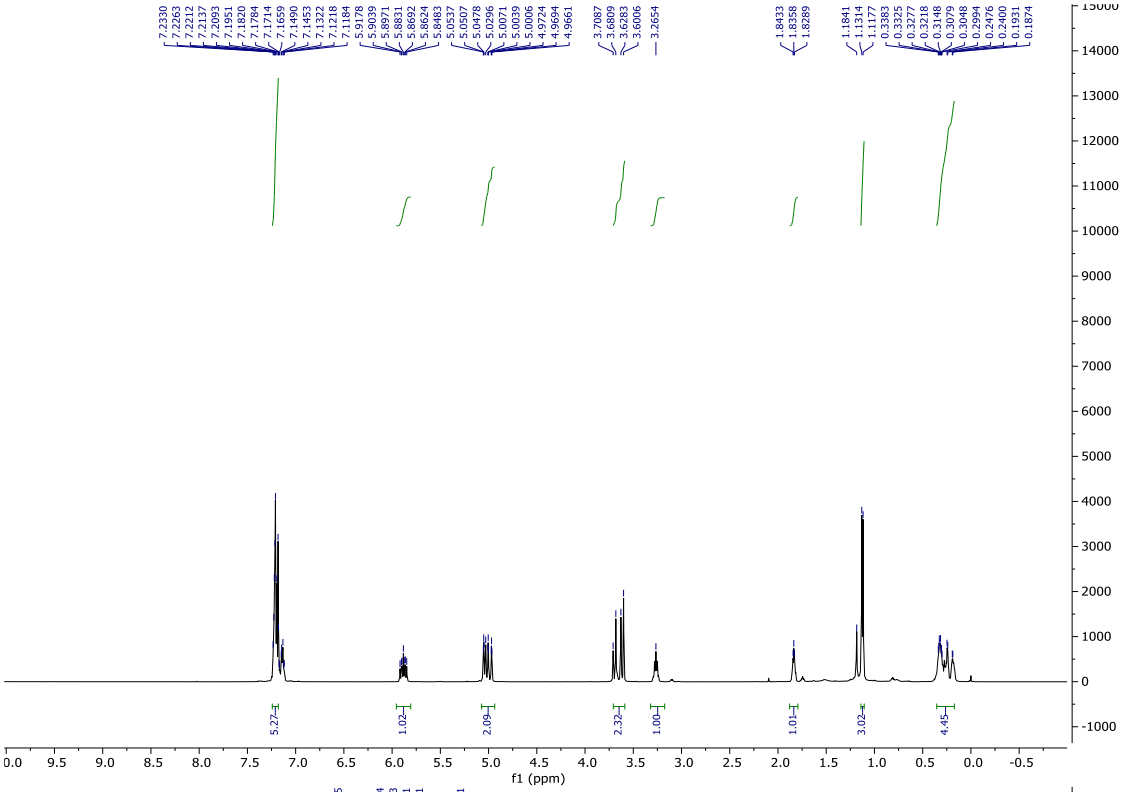
^{13}C NMR (100 MHz, $CDCl_3$): δ 140.5, 128.9, 128.0, 127.9, 126.5, 115.1, 59.3, 55.9, 33.5, 17.1, 7.7, 7.1 ppm.

HRMS (ESI) m/z: [(M+H)+] calcd for $C_{14}H_{20}N$ 201.1517, found 202.1588.

FTIR (neat): 2971, 1493, 1134, 1146, 1018, 997, 730, 697 cm^{-1}.

$[\alpha]_D^{28}$: -11.0 (c= 1.0, $CHCl_3$).

HPLC: Enantiomeric excess was determined by HPLC analysis (two Chiralcel OD-H columns, hexane: 2-PrOH = 99:1, 1.0 mL/min, 254 nm), t_{major} = 7.71 min, t_{minor} = 7.536 min; ee = 99 %.


7.2330
7.2263
7.2212
7.2137
7.2093
7.1951
7.1820
7.1784
7.1714
7.1659
7.1490
7.1453
7.1322
7.1218
7.1184
5.9178
5.9039
5.8971
5.8831
5.8692
5.8624
5.8483
5.0537
5.0507
5.0478
5.0296
5.0071
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5.0006
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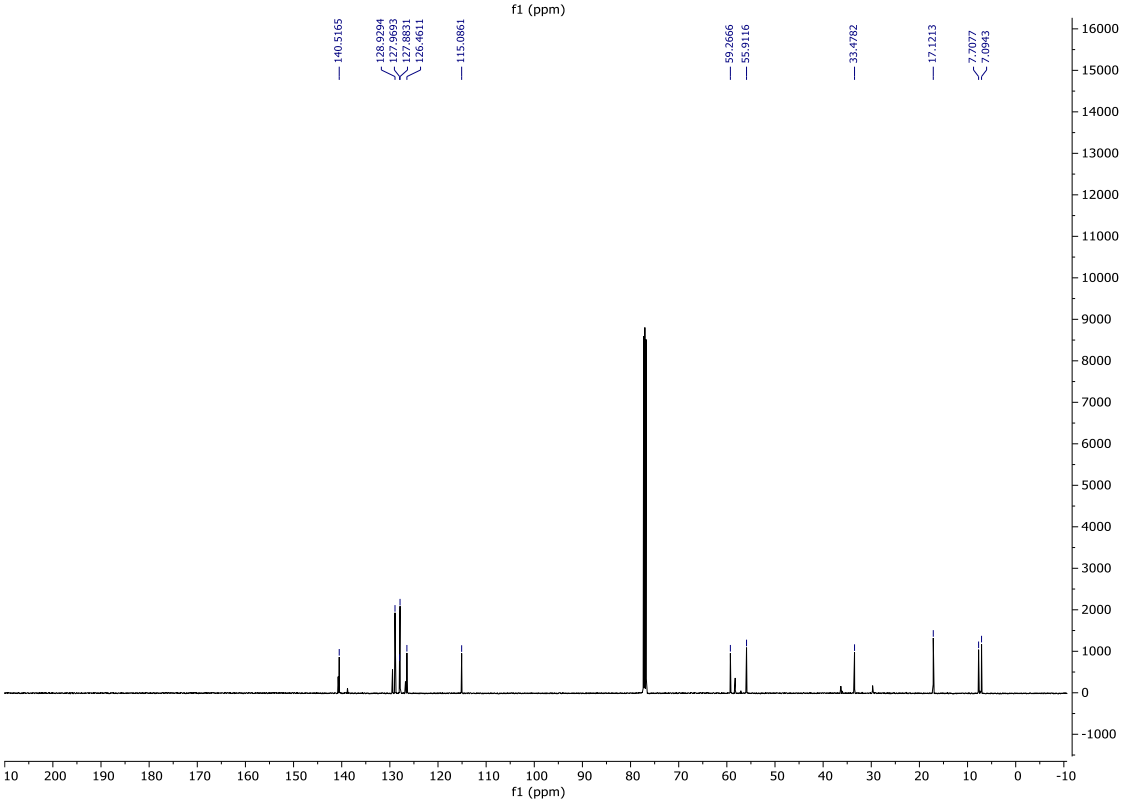
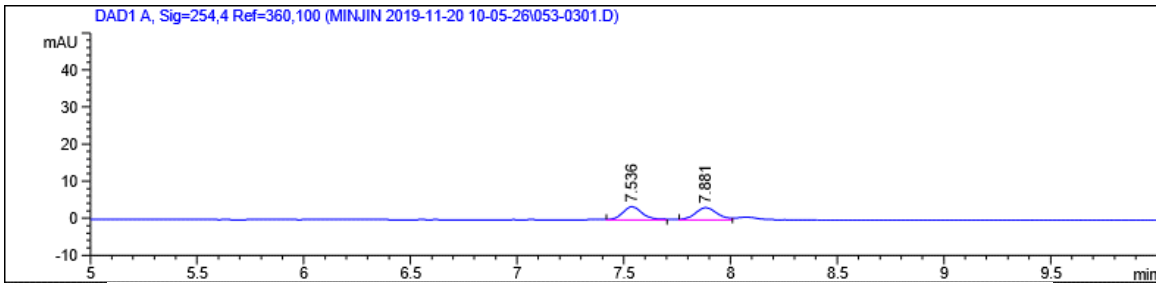
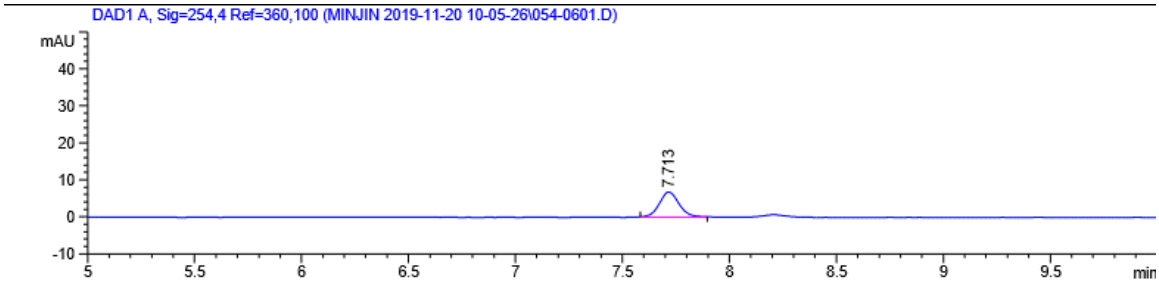
3.6809
3.6283
3.6006
3.2654
1.8433
1.8358
1.8289
1.1841
1.1314
1.1177
0.3383
0.3325
0.3277
0.3218
0.3148
0.3079
0.3048
0.2994
0.2476
0.2400
0.1931
0.1874
5.27
1.02
2.09
2.32
1.00
1.01
3.02
4.45
f1 (ppm)


140.5165
128.9294
127.9693
127.8831
126.4611
115.0861
59.2666
55.9116
33.4782
17.1213
7.7077
7.0943
f1 (ppm)



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

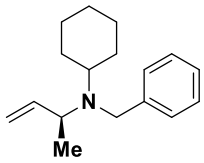
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.536	BB	0.0990	22.58928	3.51169	49.2797
2	7.881	BV	0.1087	23.24959	3.27799	50.7203
Totals :				45.83886	6.78968	



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.713	BB	0.1004	44.47564	6.78965	100.0000
Totals :				44.47564	6.78965	

(*S*)-*N*-Benzyl-*N*-(but-3-en-2-yl)cyclohexanamine (5.3c)



Procedures

The crotyl acetate (22.8 mg, 0.2 mmol, 100 mol%) and *N*-benzylcyclohexylamine (37.9 mg, 0.2 mmol, 100 mol%) were subject to standard reaction conditions (70 °C, DMF). The title compound was obtained in 58% yield (28.3 mg, 0.34 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane: ethyl acetate = 20:1–10:1).

TLC (SiO_2) R_f = 0.76 (hexane: ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 – 7.26 (m, 2H), 7.24 – 7.17 (m, 3H), 7.15 – 7.08 (m, 1H), 5.83 (ddd, J = 17.0, 10.6, 6.1 Hz, 1H), 4.99 – 4.91 (m, 2H), 3.73 – 3.55 (m, 2H), 3.31 (ddt, J = 8.2, 6.7, 3.3 Hz, 1H), 2.51 (tt, J = 11.4, 3.4 Hz, 1H), 2.10 (s, 1H), 1.78 – 1.62 (m, 3H), 1.25 – 1.07 (m, 4H), 1.05 (d, J = 6.7 Hz, 3H), 0.95 (qt, J = 12.7, 3.6 Hz, 1H) ppm.

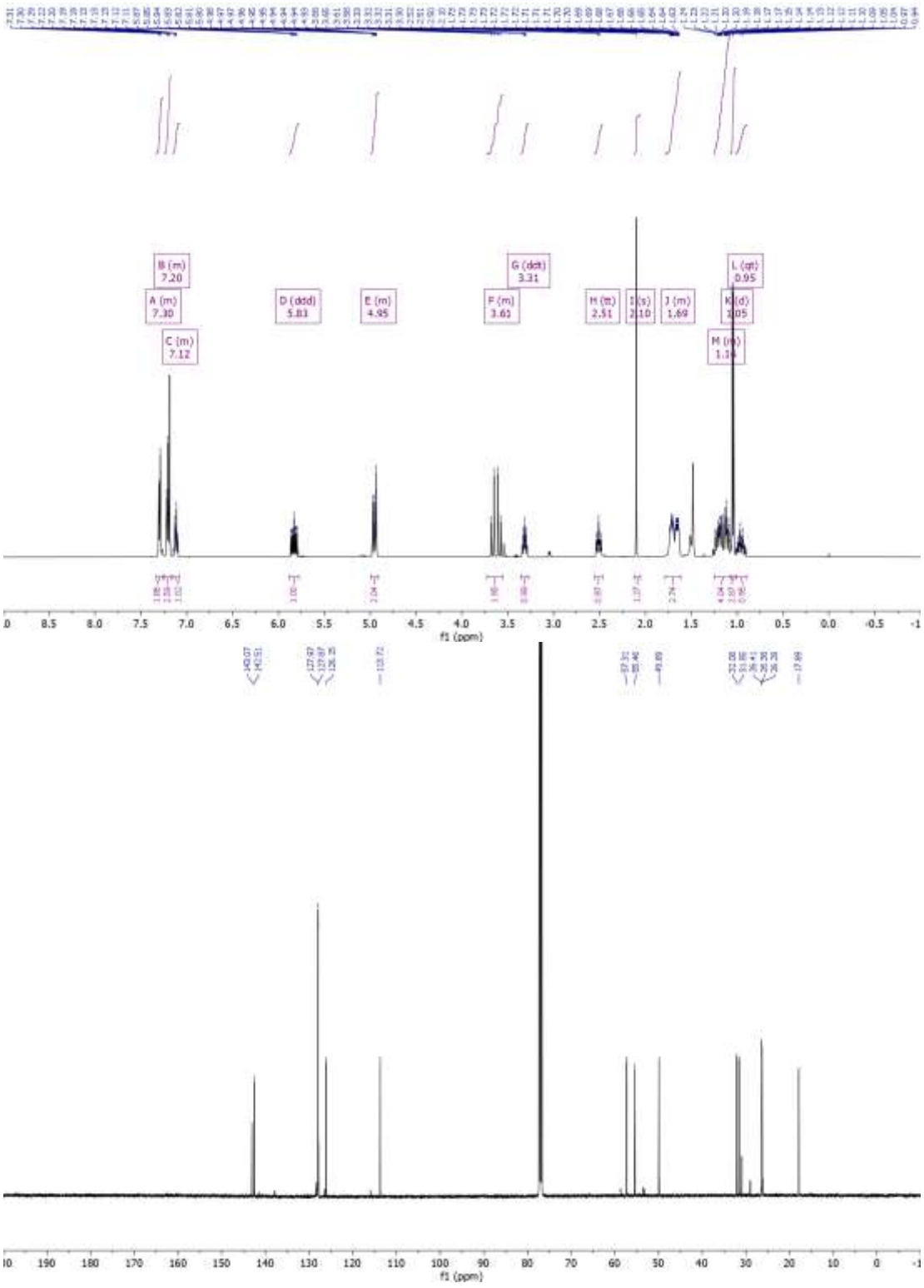
^{13}C NMR (126 MHz, $CDCl_3$): δ 143.1, 142.5, 128.0, 127.9, 126.2, 113.7, 57.3, 55.5, 49.9, 32.1, 31.6, 26.4, 26.4, 26.3, 17.9 ppm.

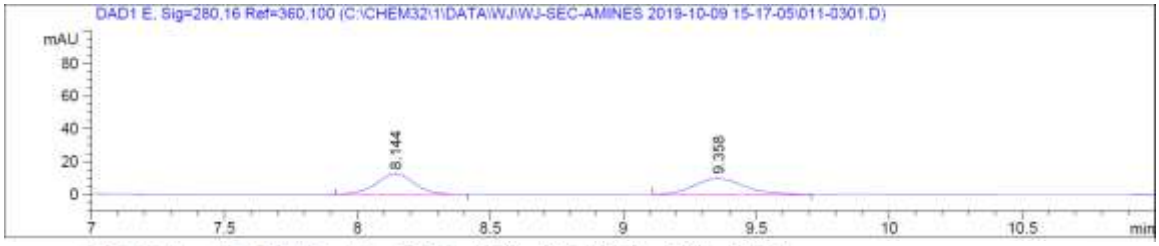
HRMS (ESI) m/z: [(M+H)+] calcd for $C_{17}H_{26}N$ 244.2060, found 244.2061.

FTIR (neat): 668, 751, 916, 1027, 1215, 1366, 1450, 2853, 2929 cm^{-1}.

$[\alpha]_D^{28}$: - 22.5 (c = 1.0, $CHCl_3$).

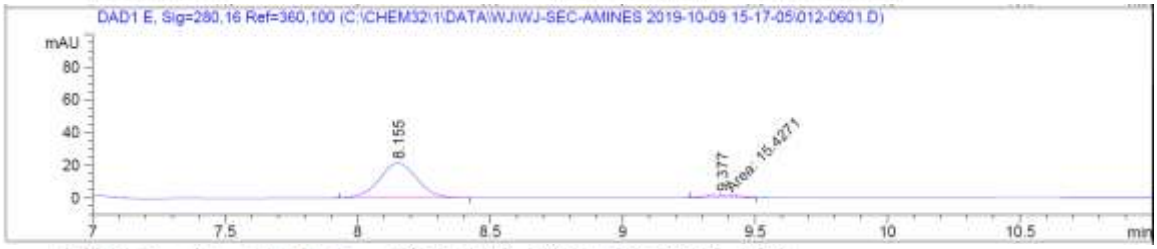
HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralcel OJ-H column, hexane: 2-PrOH = 99:1, 1.0 mL/min, 280 nm), t_{major} = 8.16 min, t_{minor} = 3.78 min; ee = 88 %.


B (m)
7.20
A (m)
7.30
C (m)
7.12
D (ddd)
5.83
E (m)
4.95
G (dqt)
3.31
F (m)
3.61
H (tt)
2.51
I (s)
2.10
J (m)
1.69
L (qt)
0.95
K (d)
1.05
M (m)
1.14
f1 (ppm)
f1 (ppm)



Signal 4: DAD1 E, Sig=280,16 Ref=360,100

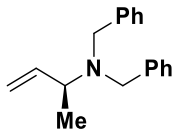
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.144	BB	0.1540	127.38074	12.59140	50.9901
2	9.358	BB	0.2028	122.43414	9.47342	49.0099
Totals :				249.81487	22.06482	



Signal 4: DAD1 E, Sig=280,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.155	BB	0.1552	214.78493	21.37455	93.2987
2	9.377	FM	0.1766	15.42710	1.45562	6.7013
Totals :				230.21203	22.83017	

(*S*)-*N*,*N*-Dibenzylbut-3-en-2-amine (5.3d)



Procedures

The allylic acetate (22.8 mg, 0.2 mmol, 100 mol%) and dibenzylamine (39.5 mg, 0.2 mmol, 100 mol%) were subject to standard reaction conditions (70 °C, DMF) with 5 mol% catalyst (0.01 mmol, 11.0 mg). The title compound was obtained in 78% yield (40.2 mg, 0.16 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane: ethyl acetate = 50:1–10:1).

TLC (SiO_2) R_f = 0.71 (hexane: ethyl acetate = 95:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 7.6 Hz, 4H), 7.30 (t, *J* = 7.6 Hz, 4H), 7.21 (t, *J* = 7.3 Hz, 2H), 5.93 (td, *J* = 10.6, 5.2 Hz, 1H), 5.13 (dd, *J* = 39.6, 13.9 Hz, 2H), 3.65 – 3.53 (m, 4H), 3.31 (t, *J* = 6.7 Hz, 1H), 1.18 (d, *J* = 6.7 Hz, 3H) ppm.

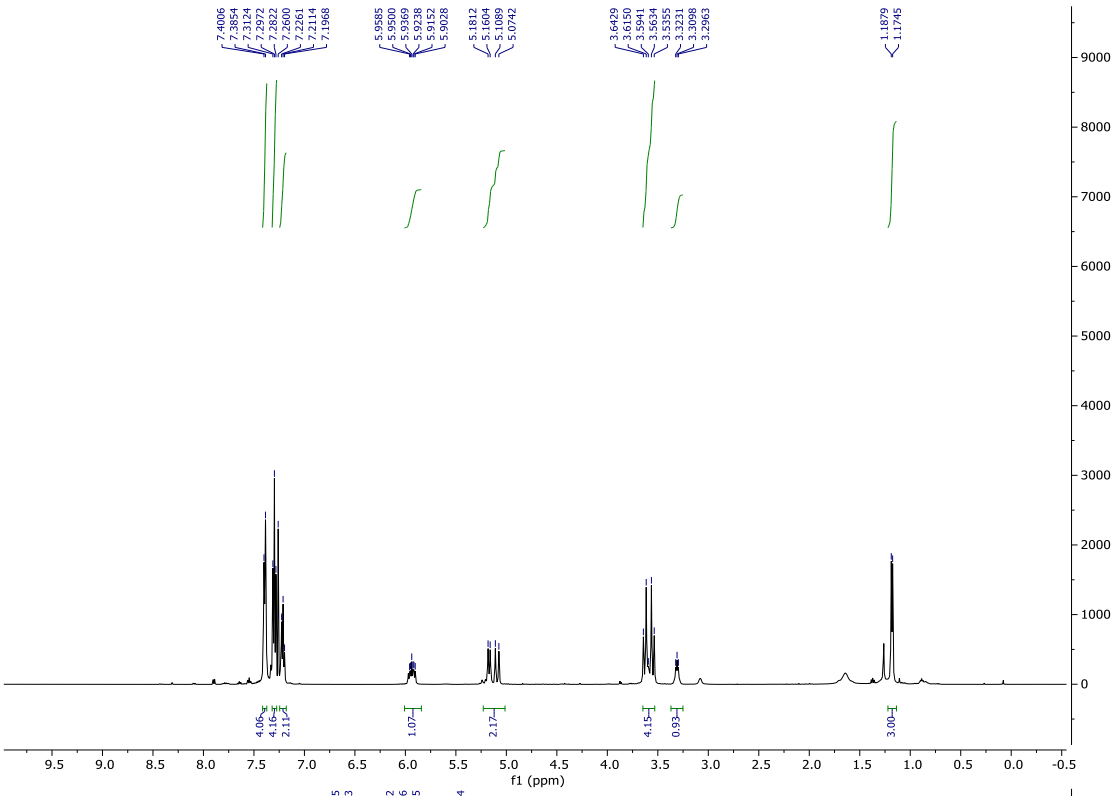
^{13}C NMR (100 MHz, $CDCl_3$): δ 140.7, 139.8, 128.5, 128.2, 126.7, 115.6, 55.0, 53.5, 14.7 ppm.

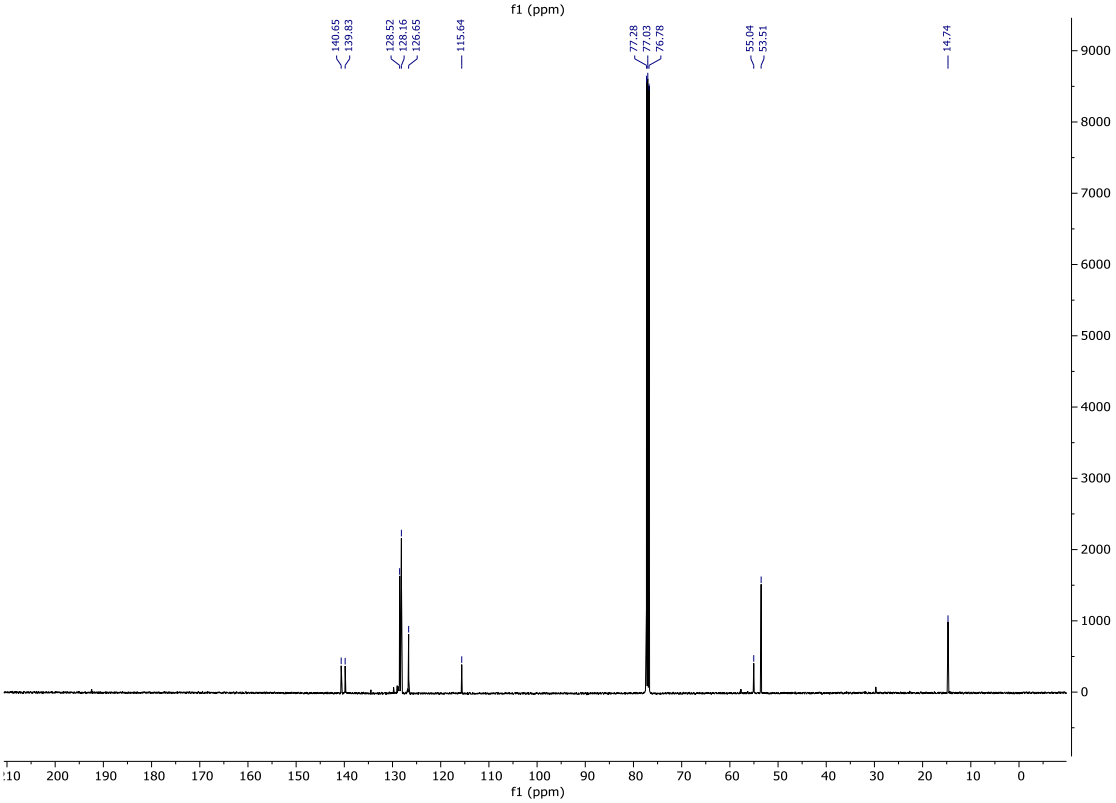
HRMS (ESI) m/z: [(M+H)+] calcd for $C_{18}H_{22}N$ 251.3730, found 252.1756.

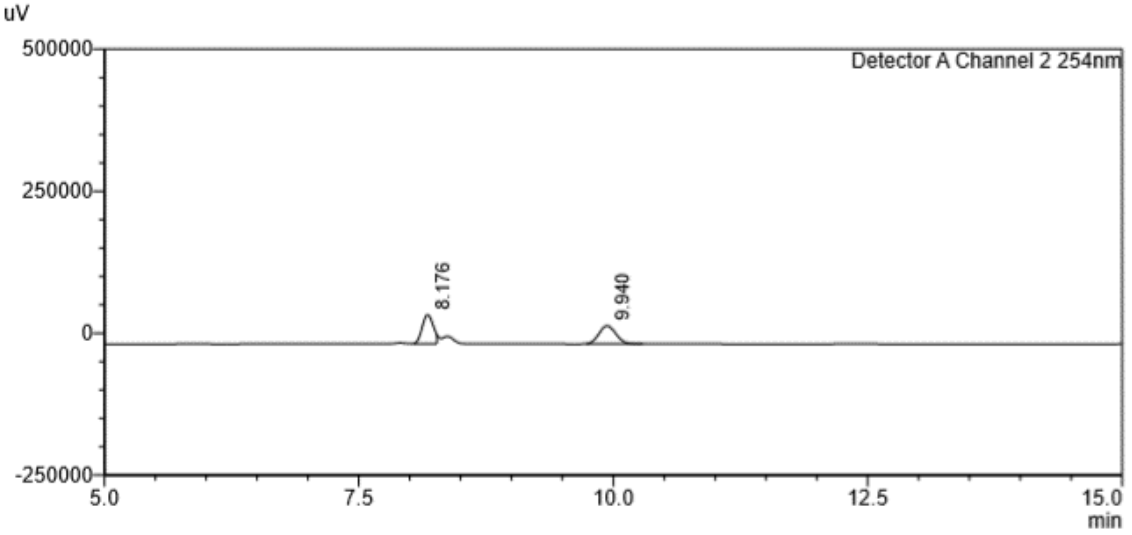
FTIR (neat): 2969, 2800, 1493, 1367, 1142, 917, 742, 696 cm^{-1}.

$[\alpha]_D^{28}$: - 21.0 (c = 1.0, $CHCl_3$).

HPLC: Enantiomeric excess was determined by HPLC analysis (two Chiralcel OD-H columns, hexane: 2-PrOH = 99:1, 1.0 mL/min, 254 nm), t_{major} = 8.26 min, t_{minor} = 9.87 min; ee = 88 %.

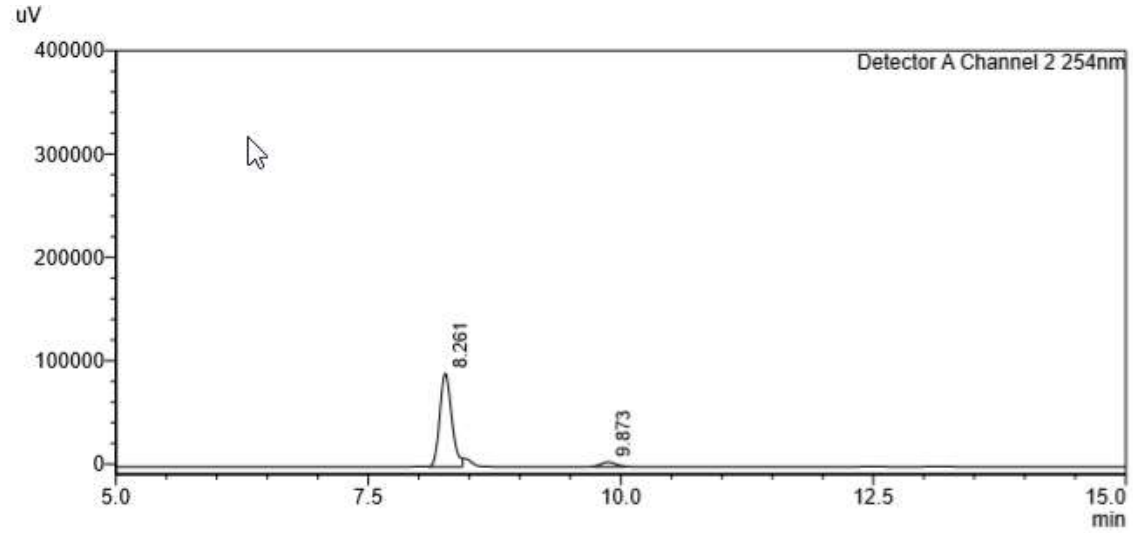

7.4006
7.3854
7.3734
7.2972
7.2822
7.2600
7.2261
7.2114
7.1968
5.9585
5.9500
5.9369
5.9238
5.9152
5.9028
5.1812
5.1604
5.1099
5.0742
3.6429
3.6150
3.5941
3.5624
3.5355
3.3231
3.3098
3.2963
1.1879
1.1745
4.06
4.16
2.11
1.07
2.17
4.15
0.93
3.00
f1 (ppm)


140.65
139.83
128.52
128.16
126.65
115.64
77.28
77.03
76.78
55.04
53.51
14.74
f1 (ppm)



Detector A Channel 2 254nm

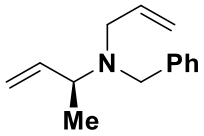
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	8.176	378288	50636	50.858		M	
2	9.940	365530	32025	49.142		M	
Total		743818	82662				



Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	8.261	749990	90414	93.758		M	
2	9.873	49935	4604	6.242		M	
Total		799925	95018				

(*S*)-*N*-Allyl-*N*-benzylbut-3-en-2-amine (5.3e)



Procedures

The crotyl acetate (22.8 mg, 0.2 mmol, 100 mol%) and allylbenzylamine (29.4 mg, 0.2 mmol, 100 mol%) were subject to standard reaction conditions (50 °C, DMF). The title compound was obtained in 82% yield (33.2 mg, 0.24 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane: ethyl acetate = 20:1–10:1).

TLC (SiO_2) R_f = 0.73 (hexane: ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 – 7.27 (m, 4H), 7.24 – 7.17 (m, 1H), 5.95 – 5.75 (m, 2H), 5.24 – 5.02 (m, 4H), 3.66 – 3.50 (m, 2H), 3.40 – 3.30 (m, 1H), 3.08 (qd, J = 13.9, 5.5 Hz, 2H), 1.14 (d, J = 6.7 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 140.3, 137.3, 128.5, 128.1, 126.6, 116.4, 115.3, 77.3, 77.2, 77.0, 76.8, 56.1, 53.5, 52.6, 15.2 ppm.

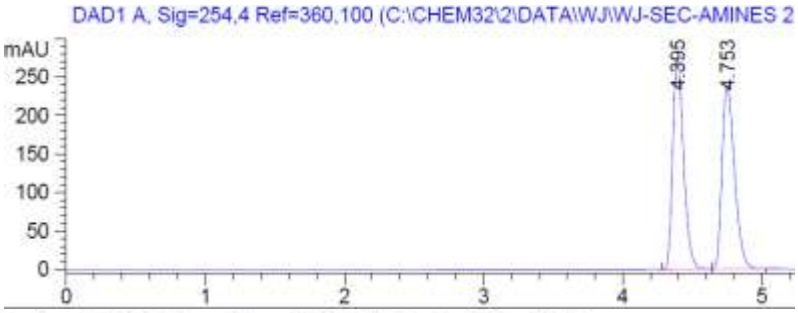
HRMS (ESI) m/z: [(M+H)+] calcd for $C_{14}H_{20}N$ 202.1590, found 202.1591.

FTIR (neat): 681, 738, 917, 1961, 1996, 2149, 2330, 2971, 3440, 3648 cm^{-1}.

$[\alpha]_D^{28}$: - 50 (c = 0.1, $CHCl_3$).

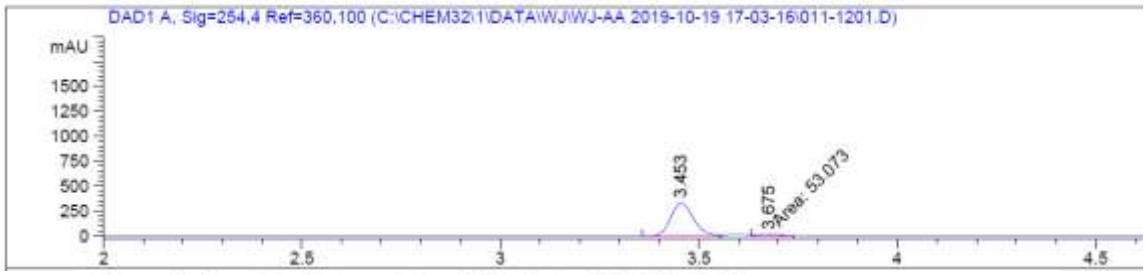
HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H column, hexane: 2-PrOH = 99:1, 1.0 mL/min, 254 nm), t_{major} = 3.5 min, t_{minor} = 3.7 min; ee = 92 %.


7.36 7.35 7.31 7.29 7.28 7.23 7.21 7.20 5.91 5.89 5.89 5.87 5.85 5.84 5.82 5.80 5.79 5.20 5.16 5.14 5.12 5.11 5.08 5.07 3.63 3.60 3.56 3.53 3.37 3.36 3.35 3.13 3.12 3.10 3.09 3.07 3.06 3.04 3.03 1.15 1.13
H (m) 7.21
G (m) 7.32
A (m) 5.86
B (m) 5.12
D (m) 3.36
C (m) 3.58
E (qd) 3.08
F (d) 1.14
4.39 1.08 1.99 4.18 2.01 0.88 2.09 2.89
f1 (ppm)
WJ-2AASI-2.11.fid
140.25 137.26 128.49 128.12 126.58 116.43 115.31 77.27 77.22 77.01 76.76 56.05 53.48 52.61 15.18
f1 (ppm)



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

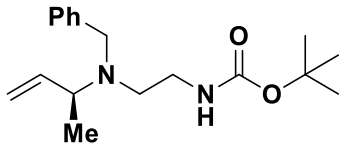
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.395	VV	0.0852	1490.11548	274.92905	50.0997
2	4.753	VB	0.0966	1484.18396	238.55099	49.9003
Totals :				2974.29944	513.48004	



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.453	BV	0.0619	1278.90735	325.31973	96.0155
2	3.675	MF	0.0673	53.07305	13.13486	3.9845
Totals :				1331.98040	338.45459	

***tert*-Butyl (*S*)-(2-(benzyl(but-3-en-2-yl)amino)ethyl)carbamate (5.3f)**



Procedures

The crotyl acetate (45.7 mg, 0.4 mmol, 100 mol%) and (100.1 mg, 0.4 mmol, 100 mol%) were subject to standard reaction conditions with 5 mol% of catalyst (22.0 mg, 0.02 mmol, 5 mol%) in DMF (1.5 M, 3.0 ml) at 90 °C. The title compound was obtained in 75% yield (91.3 mg, 0.30 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, heptane: isopropyl acetate = 20:1-5:1).

TLC (SiO_2) R_f = 0.52 (heptane: isopropyl acetate = 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, J = 4.6 Hz, 5H), 7.25 – 7.18 (m, 1H), 5.85 (ddd, J = 17.0, 10.6, 6.4 Hz, 1H), 5.15 (d, J = 10.2 Hz, 1H), 5.07 (d, J = 17.3 Hz, 1H), 4.79 (s, 1H), 3.66 – 3.55 (m, 1H), 3.58 – 3.44 (m, 1H), 3.30 (p, J = 6.9 Hz, 1H), 3.09 (t, J = 6.4 Hz, 2H), 2.56 (dtt, J = 24.5, 12.7, 6.0 Hz, 2H), 1.92 (s, 1H), 1.43 (d, J = 3.8 Hz, 11H), 1.31 – 1.11 (m, 4H), 0.87 (hept, J = 6.4, 5.7 Hz, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.1, 140.4, 139.4, 135.3, 128.9, 128.8, 128.6, 128.3, 128.3, 127.9, 127.17, 127.0, 126.9, 117.9, 115.9, 78.9, 77.2, 65.9, 58.4, 58.1, 56.7, 56.6, 54.5, 52.5, 48.9, 38.6, 38.0, 29.7, 28.44, 15.3, 15.3 ppm.

HRMS (ESI) m/z: [(M+H)+] calcd for $C_{18}H_{29}N_2O_2$ 305.2151, found 305.2221.

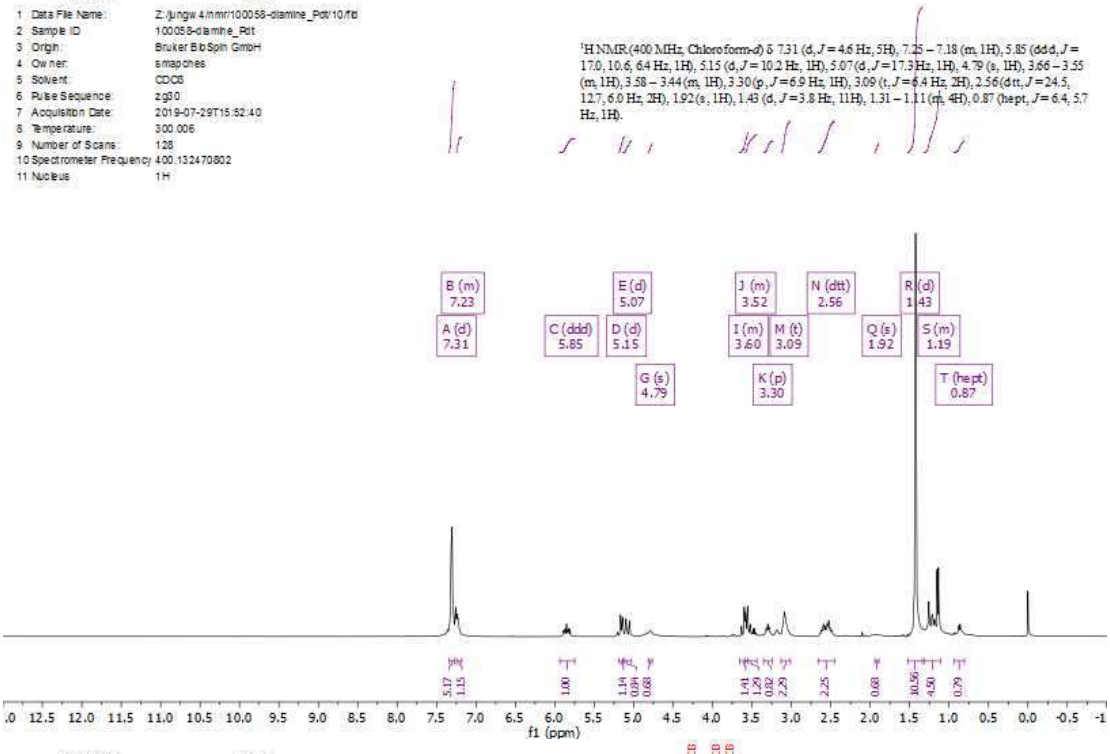
FTIR (neat): 3025, 2927, 2359, 1698, 1454, 1240, 997, 731, 696 cm^{-1}.

$[\alpha]_D^{28}$: + 16.9 (c = 2.0, methanol).

HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralcel OJ-H column, hexane: 2-PrOH = 97:3, 1.0 mL/min, 220 nm), t_{major} = 5.55 min, t_{minor} = 6.12 min; ee = 88%.

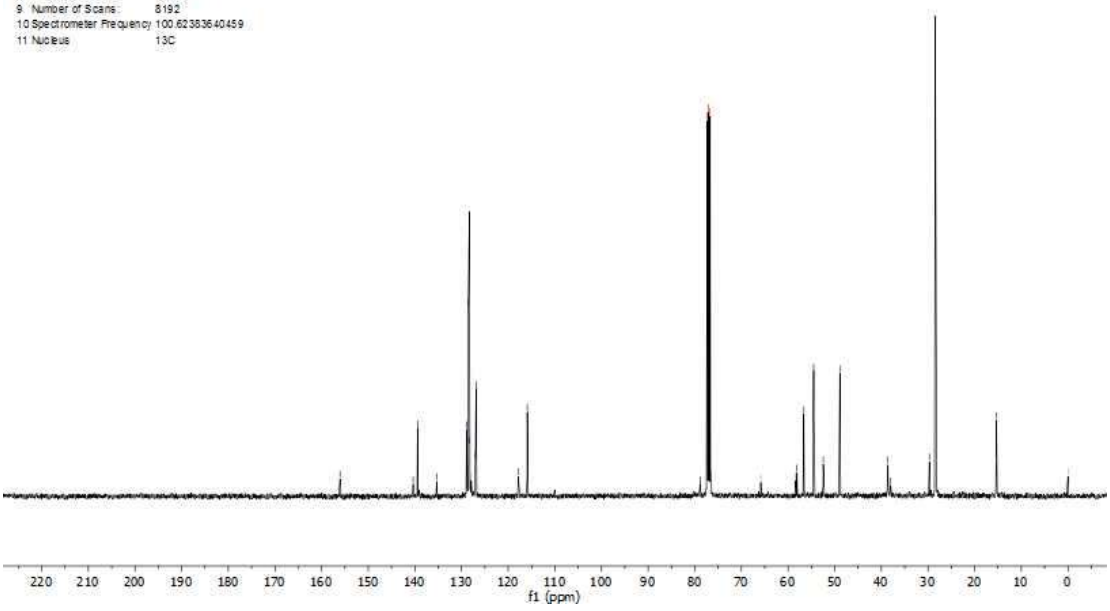
Parameter	Value
1 Data File Name:	Z:\jungw 4\nmr\100058-diamine_Pdt\10\fid
2 Sample ID	100058-diamine_Pdt
3 Origin:	Bruker BioSpin GmbH
4 Owner:	smapches
5 Solvent:	CDCl3
6 Pulse Sequence:	zg30
7 Acquisition Date:	2019-07-29T15:52:40
8 Temperature:	300.006
9 Number of Scans:	128
10 Spectrometer Frequency:	400.132470802
11 Nucleus	1H

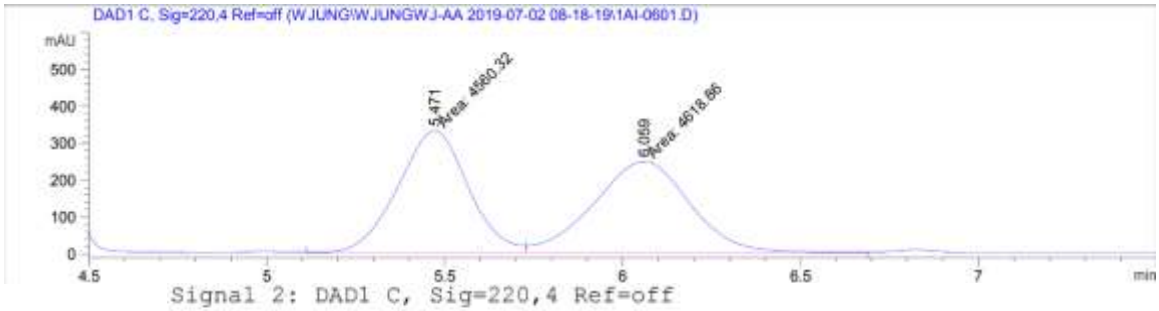
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.31 (d, *J* = 4.6 Hz, 5H), 7.25 – 7.18 (m, 1H), 5.85 (ddd, *J* = 17.0, 10.6, 6.4 Hz, 1H), 5.15 (d, *J* = 10.2 Hz, 1H), 5.07 (d, *J* = 17.3 Hz, 1H), 4.79 (s, 1H), 3.66 – 3.55 (m, 1H), 3.58 – 3.44 (m, 1H), 3.30 (p, *J* = 6.9 Hz, 1H), 3.09 (t, *J* = 6.4 Hz, 2H), 2.56 (dtt, *J* = 24.5, 12.7, 6.0 Hz, 2H), 1.92 (s, 1H), 1.43 (d, *J* = 3.8 Hz, 11H), 1.31 – 1.11 (m, 4H), 0.87 (hept, *J* = 6.4, 5.7 Hz, 1H).



Parameter	Value
1 Data File Name:	Z:\jungw 4\nmr\100058-diamine_Pdt\20\fid
2 Sample ID	100058-diamine_Pdt
3 Origin:	Bruker BioSpin GmbH
4 Owner:	smapches
5 Solvent:	CDCl3
6 Pulse Sequence:	zgpg30
7 Acquisition Date:	2019-07-29T23:04:09
8 Temperature:	299.9984
9 Number of Scans:	8192
10 Spectrometer Frequency:	100.623836340459
11 Nucleus	13C

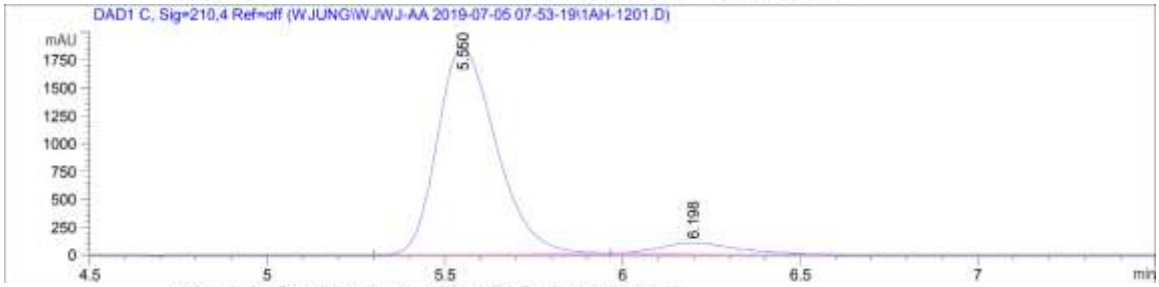
^{13}C NMR (101 MHz, $CDCl_3$) δ 156.05, 140.38, 139.43, 135.33, 128.90, 128.77, 128.55, 128.32, 128.27, 127.93, 127.17, 127.03, 126.88, 117.85, 115.90, 78.88, 77.34, 77.22, 77.02, 76.70, 65.86, 58.36, 58.09, 56.69, 56.63, 54.52, 52.45, 48.90, 38.60, 38.02, 29.71, 28.44, 15.33, 15.28, 0.00.





Signal 2: DAD1 C, Sig=220,4 Ref=off

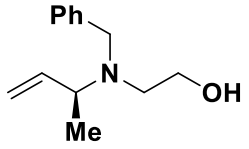
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.471	MF	0.2296	4560.32178	331.06525	49.6812
2	6.059	FM	0.3121	4618.85693	246.63123	50.3188
Totals :				9179.17871	577.69647	



Signal 2: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.550	BB	0.1778	2.11884e4	1847.17297	93.8846
2	6.198	BB	0.2263	1380.16760	93.45277	6.1154
Totals :				2.25686e4	1940.62575	

(*S*)-2-(Benzyl(but-3-en-2-yl)amino)ethan-1-ol (5.3g)



Procedures

The crotyl acetate (45.7 mg, 0.4 mmol, 100 mol%) and 2-(benzylamino)ethan-1-ol (60.5 mg, 0.4 mmol, 100 mol%) were subject to standard reaction conditions (70 °C, DMF). The title compound was obtained in 70% yield (57.5 mg, 0.28 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, heptane: isopropyl acetate = 5:1-1:1).

TLC (SiO_2) R_f = 0.57 (heptane: isopropyl acetate = 1:1).

^{1}H NMR (400 MHz, CDCl3): δ 7.37 – 7.20 (m, 5H), 5.86 (ddd, J = 17.2, 10.5, 6.5 Hz, 1H), 5.18 (dt, J = 10.5, 1.5 Hz, 1H), 5.09 (dt, J = 17.3, 1.5 Hz, 1H), 3.70 – 3.54 (m, 2H), 3.49 (d, J = 1.6 Hz, 1H), 3.33 (pt, J = 6.7, 1.4 Hz, 1H), 2.72 (ddd, J = 13.1, 6.3, 5.2 Hz, 1H), 2.60 (dt, J = 13.1, 4.9 Hz, 1H), 1.16 (d, J = 6.7 Hz, 3H) ppm.

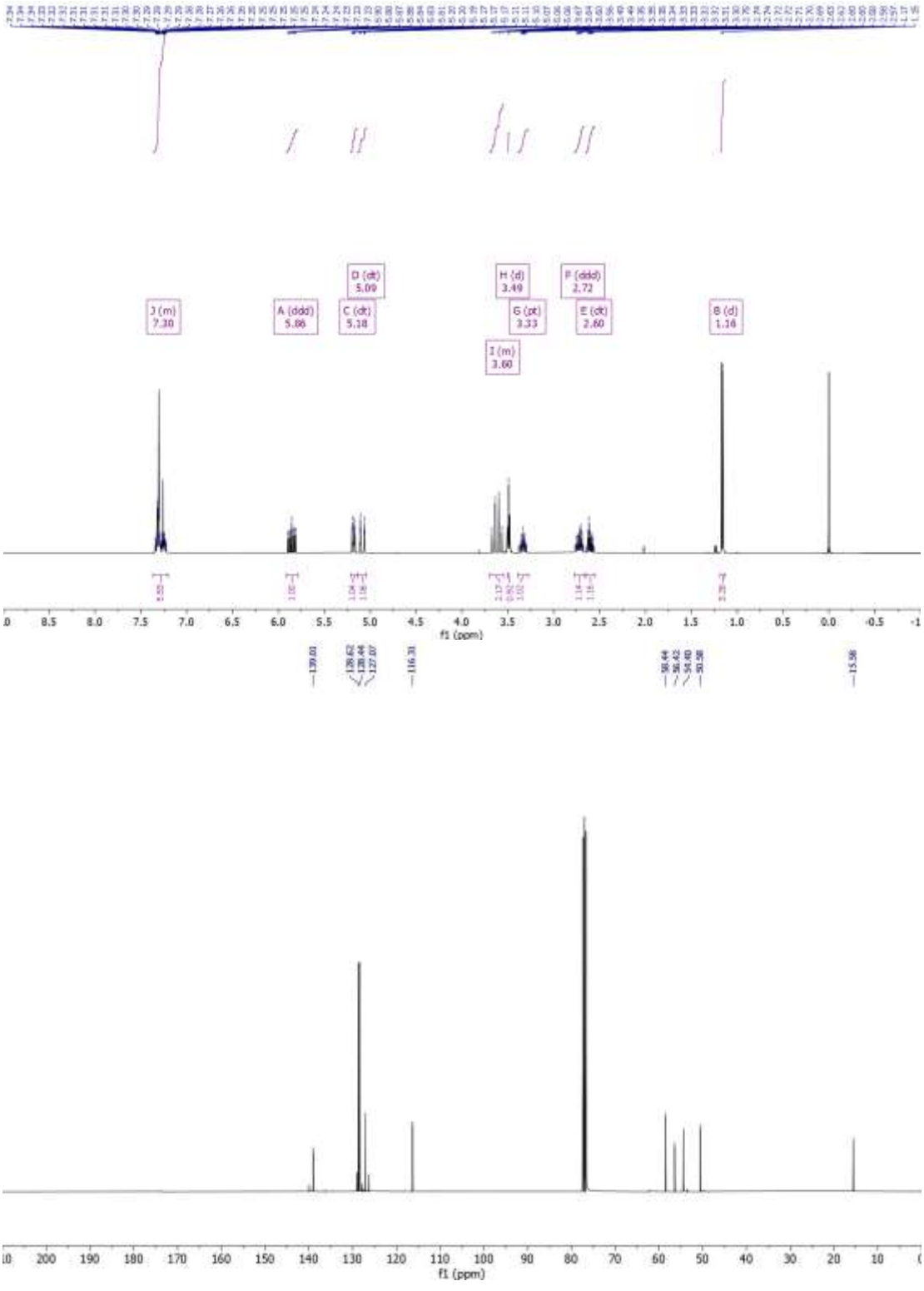
^{13}C NMR (101 MHz, $CDCl_3$): δ 139.8, 139.0, 128.6, 128.5, 127.1, 116.4, 58.4, 56.4, 54.4, 50.6, 15.6 ppm.

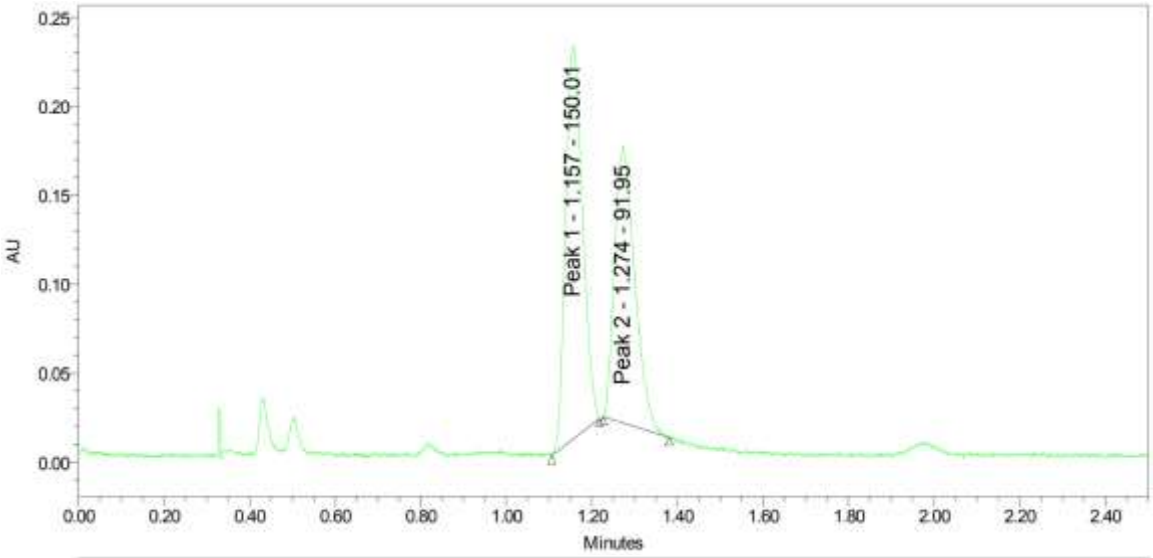
HRMS (ESI) m/z: [(M+H)+] calcd for $C_{13}H_{20}NO$ 206.1467, found 206.1535.

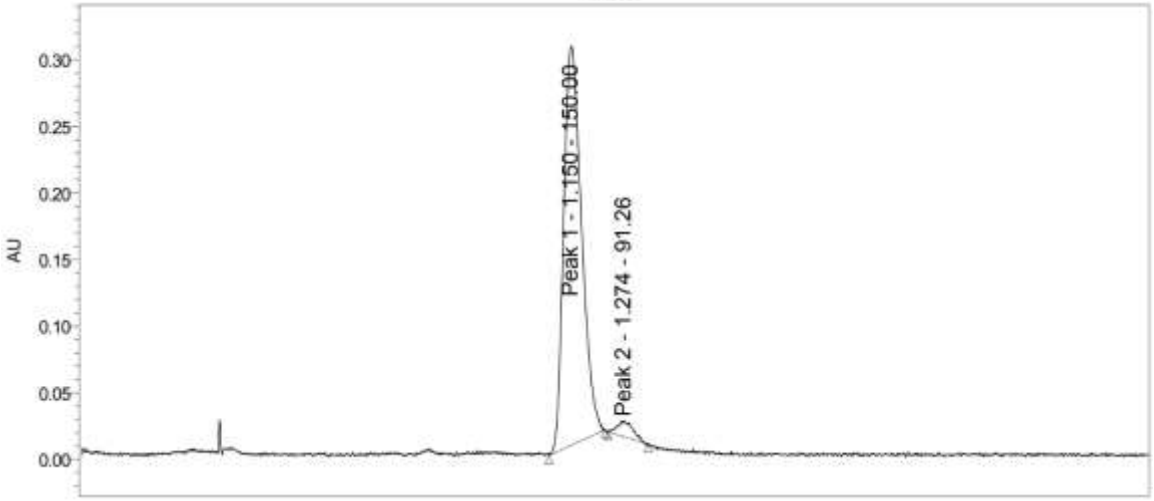
FTIR (neat): 3388, 2969, 1494, 1370, 1146, 997, 733, 698 cm^{-1}.

$[\alpha]_D^{28}$: - 8.5 (c = 2.0, methanol).

SFC: Enantiomeric excess was determined by SFC analysis (Chiralpak IG column, 10 % of methanol with 0.1% NH_4OH, 4.0 mL/min, 40 °C, 220 nm), t_{major} = 1.15 min, t_{minor} = 1.27 min; ee = 93 %.

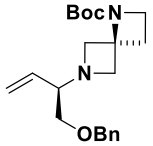

J (m)
7.30
A (ddd)
5.86
D (dt)
5.09
C (dt)
5.18
I (m)
3.60
H (d)
3.49
G (pt)
3.33
F (ddd)
2.72
E (dt)
2.60
B (d)
1.16
f1 (ppm)
f1 (ppm)





	Peak Name	SampleName	Ret. Time	% Area	Base Peak (m/z)
1	Peak 1	MM CHIRAL PURE	1.150	96.54	150.00
2	Peak 2	MM CHIRAL PURE	1.274	3.46	91.26
3	Peak 2	MM RACEMIC	1.274	45.74	91.95
4	Peak 1	MM RACEMIC	1.157	54.26	150.01

***tert*-Butyl (*R*)-6-(1-(benzyloxy)but-3-en-2-yl)-1,6-diazaspiro[3.3]heptane-1-carboxylate (5.3h)**



Procedures

The allyl acetate (44.1 mg, 0.2 mmol, 100 mol%) and 2,6-diazaspiro[3.3]heptane-2-carboxylic acid *tert*-butyl ester hemioxalate (48.7 mg, 0.2 mmol, 100 mol%) were subject to standard reaction conditions (70 °C, DMF) with 300 mol% of Cs_2CO_3 (195.5 mg, 0.60 mmol). The title compound was obtained in 54% yield (39.0 mg, 0.11 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane: ethyl acetate = 20:1–10:1).

TLC (SiO_2) R_f = 0.17 (hexane: ethyl acetate = 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 – 7.20 (m, 5H), 5.53 (ddd, J = 17.1, 10.3, 8.2 Hz, 1H), 5.22 – 5.09 (m, 2H), 4.43 (d, J = 1.5 Hz, 2H), 3.90 (s, 4H), 3.38 – 3.29 (m, 2H), 3.28 (s, 4H), 2.82 (q, J = 5.7 Hz, 1H), 1.35 (s, 9H) ppm.

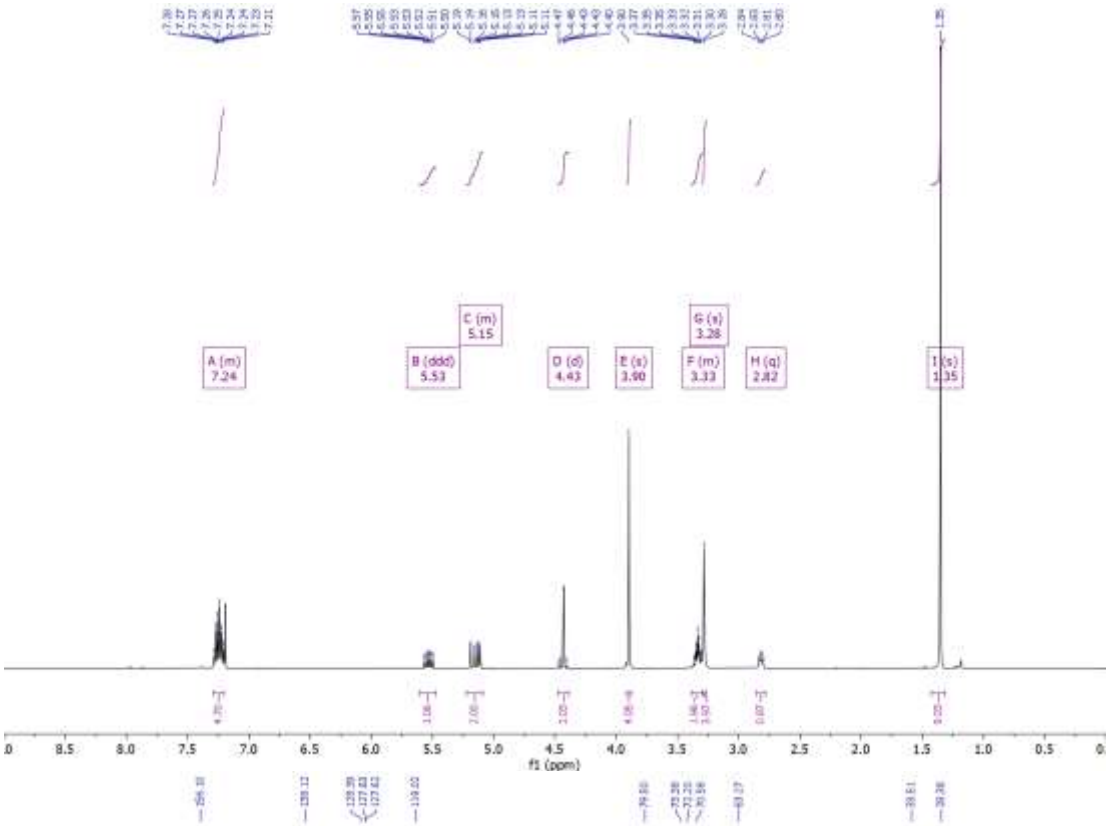
^{13}C NMR (126 MHz, $CDCl_3$): δ 156.1, 138.1, 128.4, 127.6, 127.6, 119.0, 79.5, 73.4, 72.2, 70.6, 63.27, 33.5, 28.4 ppm.

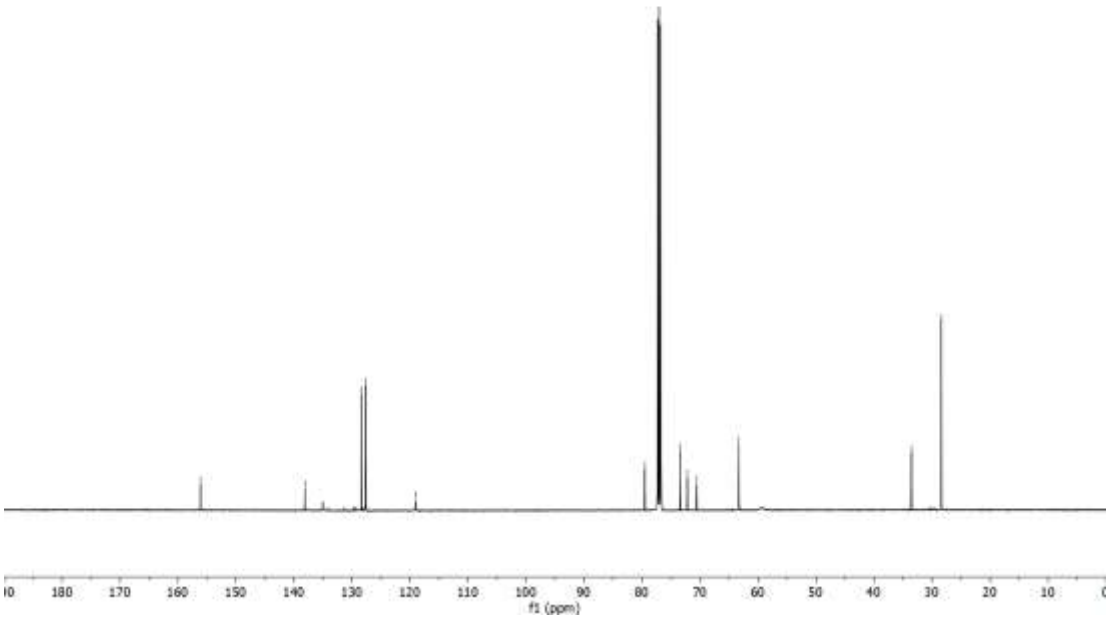
HRMS (ESI) m/z: [(M+Na)+] calcd for $C_{21}H_{30}N_2O_3Na$ 381.2149, found 381.2157.

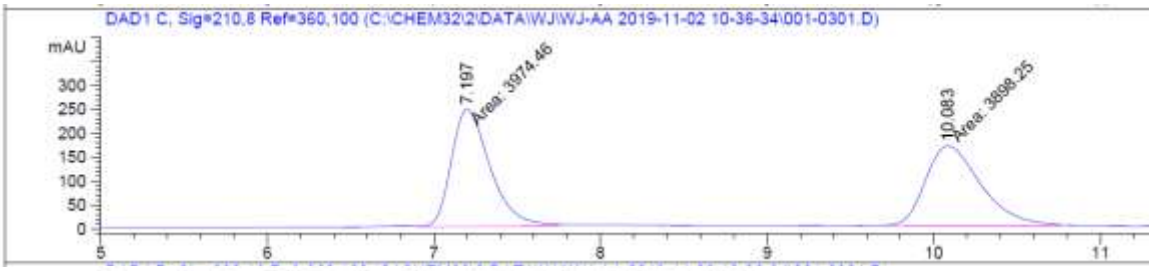
FTIR (neat): 665, 859, 1028, 1216, 1406, 1692, 2367, 2930 cm^{-1}.

$[\alpha]_D^{28}$: - 20.5 (c = 1.0, $CHCl_3$).

HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H column, hexane: 2-PrOH = 90:10, 1.0 mL/min, 210 nm), t_{major} = 6.95 min, t_{minor} = 9.76 min; ee = 84 %.

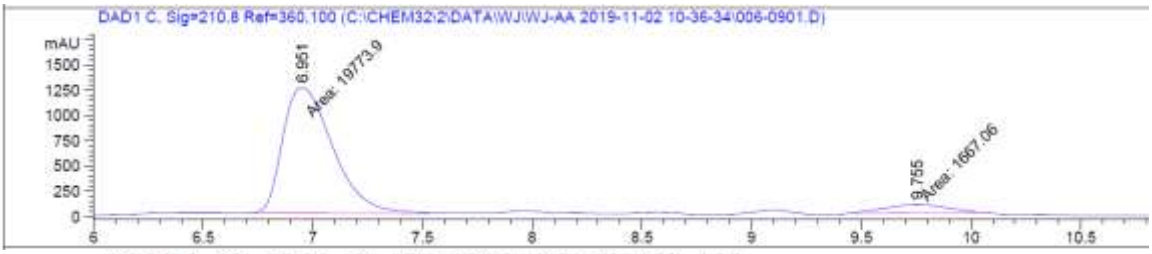

A (m)
7.24
B (ddd)
5.53
C (m)
5.15
D (d)
4.43
E (s)
3.90
F (m)
3.33
G (s)
3.28
H (q)
2.82
I (s)
1.35
f1 (ppm)


f1 (ppm)



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

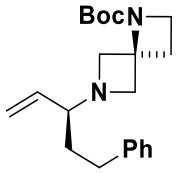
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.197	FM	0.2708	3974.46436	244.65134	50.4840
2	10.083	FM	0.3889	3898.25146	167.08406	49.5160
Totals :				7872.71582	411.73540	



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.951	MF	0.2647	1.97739e4	1244.98352	92.2249
2	9.755	MM	0.3254	1667.05530	85.38869	7.7751
Totals :				2.14410e4	1330.37222	

***tert*-Butyl (*S*)-6-(5-phenylpent-1-en-3-yl)-1,6-diazaspiro[3.3]heptane-1-carboxylate (5.3i)**



Procedures

The allyl acetate (40.9 mg, 0.2 mmol, 100 mol%) and 2,6-diazaspiro[3.3]heptane-2-carboxylic acid *tert*-butyl ester hemioxalate (48.7 mg, 0.2 mmol, 100 mol%) were subject to standard reaction conditions (90 °C, DMF) with 300 mol% of Cs_2CO_3 (195.5 mg, 0.60 mmol). The title compound was obtained in 87% yield (59.8 mg, 0.17 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane: ethyl acetate = 20:1–10:1).

TLC (SiO_2) R_f = 0.26 (hexane: ethyl acetate = 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 – 7.16 (m, 2H), 7.14 – 7.05 (m, 3H), 5.47 (ddd, J = 17.0, 10.2, 8.4 Hz, 1H), 5.15 – 5.05 (m, 2H), 3.88 (s, 4H), 3.19 (d, J = 7.7 Hz, 2H), 3.12 (d, J = 7.7 Hz, 2H), 2.62 – 2.53 (m, 1H), 2.44 (td, J = 9.2, 3.3 Hz, 1H), 2.37 (ddd, J = 13.9, 10.1, 7.0 Hz, 1H), 1.67 (dddd, J = 13.5, 10.3, 6.9, 3.3 Hz, 1H), 1.53 – 1.43 (m, 1H), 1.35 (s, 9H) ppm.

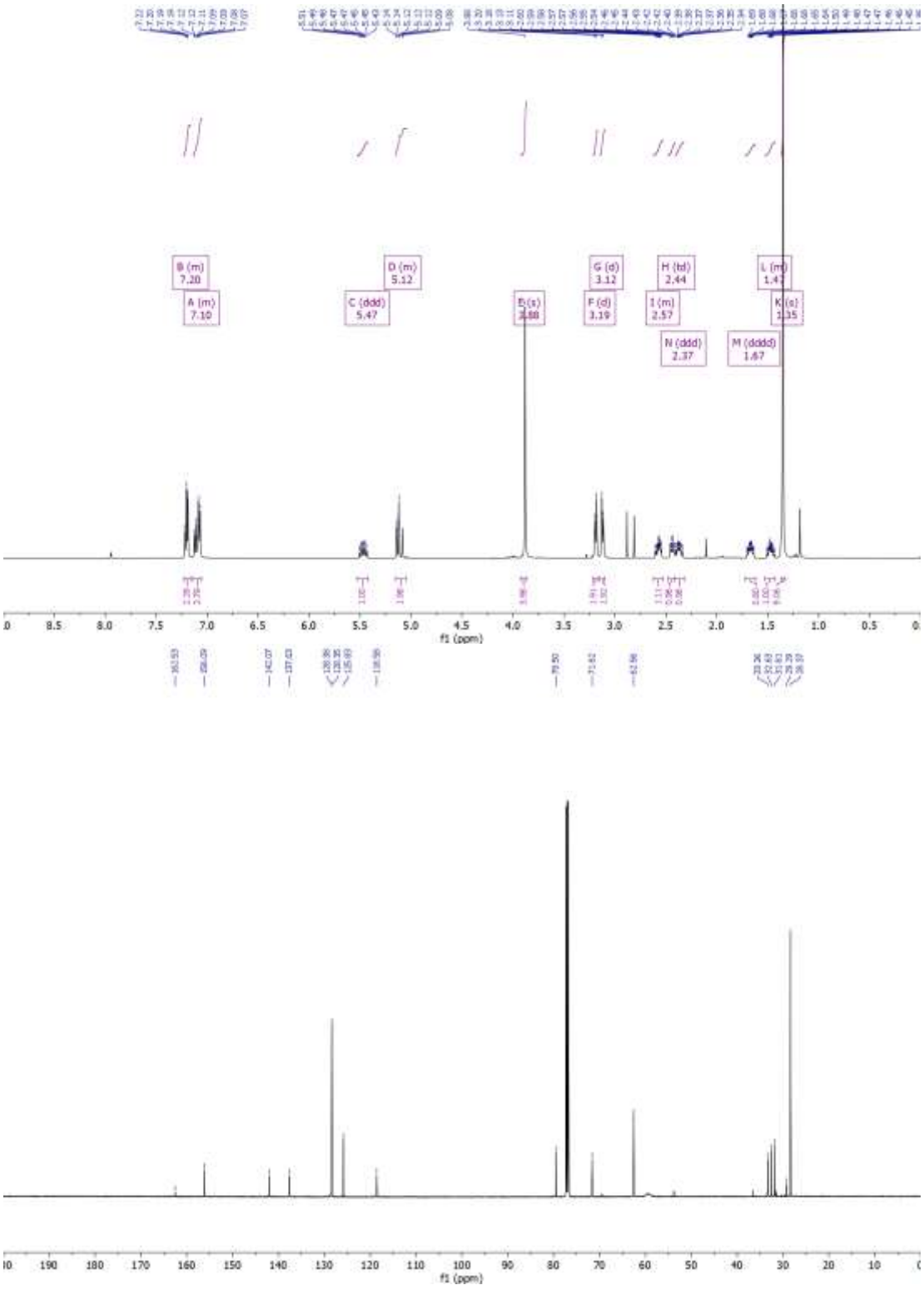
^{13}C NMR (126 MHz, $CDCl_3$): δ 162.5, 156.1, 142.1, 137.6, 128.4, 128.4, 125.8, 118.6, 79.5, 71.6, 62.6, 33.4, 32.6, 31.8, 29.3, 28.4 ppm.

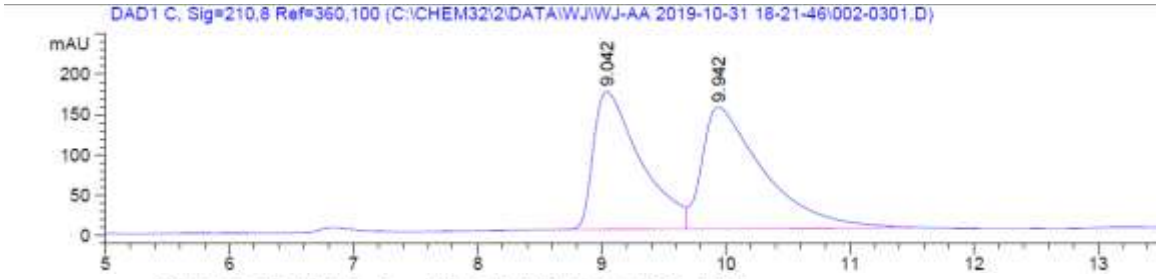
HRMS (ESI) m/z: [(M+H)+] calcd for $C_{21}H_{31}N_2O_2$ 343.2380, found 343.2389.

FTIR (neat): 698, 922, 1152, 1365, 1496, 1736, 2342, 2931, 3025 cm^{-1}.

$[\alpha]_D^{28}$: + 3.5 (c = 1.0, $CHCl_3$).

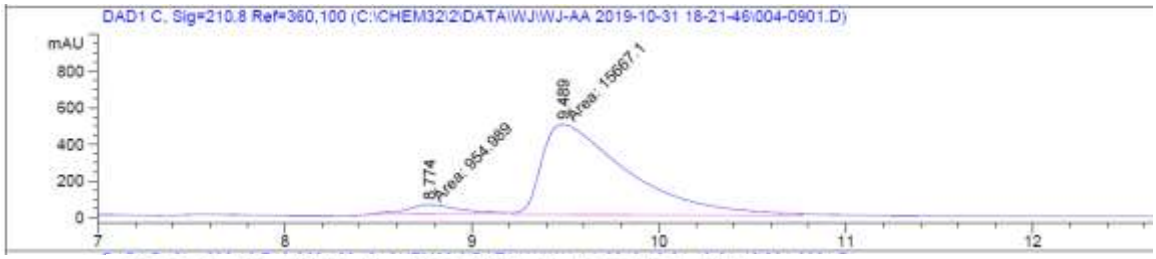
HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralcel AD-H column, hexane: 2-PrOH = 95:5, 1.0 mL/min, 210 nm), t_{major} = 8.77 min, t_{minor} = 9.49 min; ee = 89 %.


B (m)
7.20
A (m)
7.10
D (m)
5.12
C (ddd)
5.47
E (s)
3.88
G (d)
3.12
F (d)
3.19
H (td)
2.44
I (m)
2.57
N (ddd)
2.37
L (m)
1.47
K (s)
1.35
M (dddd)
1.67
f1 (ppm)
f1 (ppm)



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

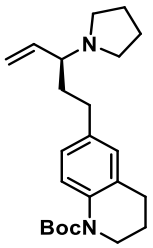
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.042	BV	0.3837	4508.95850	170.95067	46.5075
2	9.942	VB	0.4751	5186.16553	150.83438	53.4925
Totals :				9695.12402	321.78505	



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.774	MM	0.3185	954.98865	49.96769	5.7453
2	9.489	MF	0.5299	1.56671e4	492.73984	94.2547
Totals :				1.66221e4	542.70753	

***tert*-Butyl (*S*)-6-(3-(pyrrolidin-1-yl)pent-4-en-1-yl)-3,4-dihydroquinoline-1(2*H*)-carboxylate (5.3j)**



Procedures

The corresponding allyl acetate (**1d**, 71.9 mg, 0.2 mmol, 100 mol%) and pyrrolidine (14.2 mg, 0.2 mmol, 100 mol%) were subject to standard reaction conditions (50 °C, DMF). The title compound was obtained in 94% yield (69.8mg, 0.11 mmol) as a light yellow oil after isolation by flash column chromatography (AlO_2, hexane: acetone = 1:1–1:10).

TLC (SiO_2) R_f = 0.12 (acetone)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, J = 8.3 Hz, 1H), 6.94 (dd, J = 8.4, 1.9 Hz, 1H), 6.88 (s, 1H), 5.78 (dt, J = 18.6, 9.7 Hz, 1H), 5.22 – 5.08 (m, 2H), 3.71 – 3.67 (m, 2H), 2.73 (t, J = 6.6 Hz, 2H), 2.60 (ddd, J = 24.7, 13.4, 7.8 Hz, 6H), 2.43 (ddd, J = 14.1, 10.7, 6.3 Hz, 1H), 1.98 (d, J = 16.4 Hz, 1H), 1.90 (p, J = 6.5 Hz, 3H), 1.76 (s, 4H), 1.60 (s, 1H), 1.52 (s, 9H) ppm.

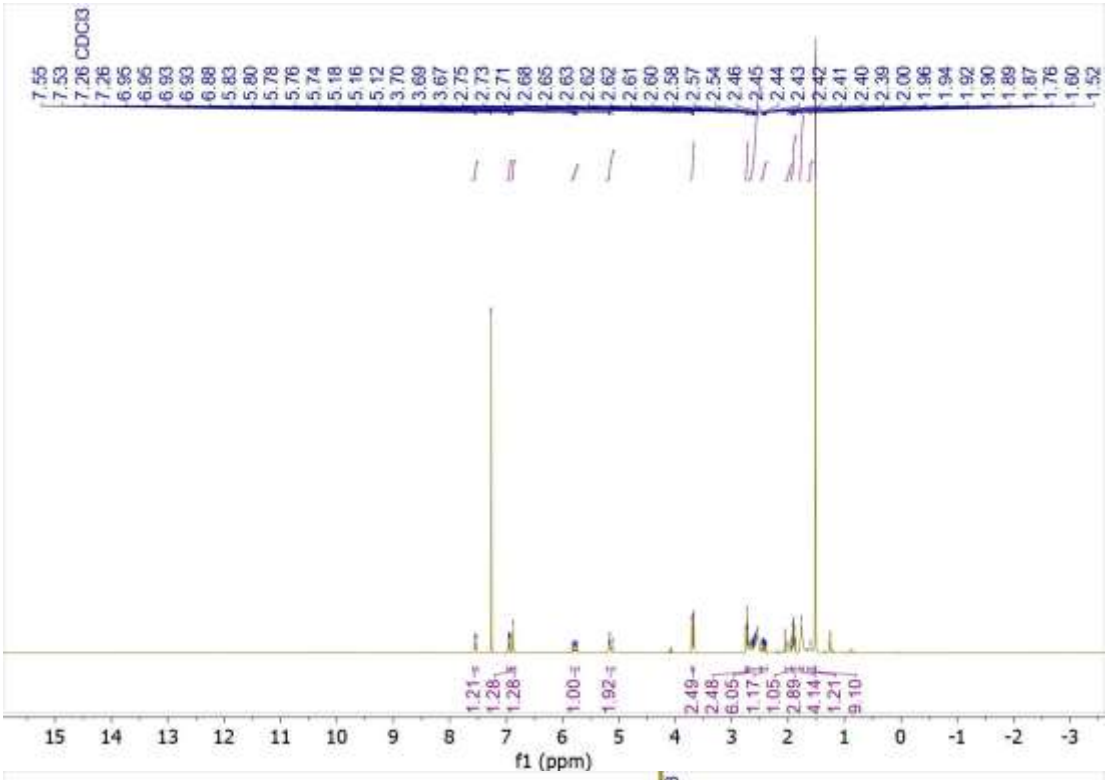
^{13}C NMR (101 MHz, $CDCl_3$): δ 154.2, 129.8, 128.5, 125.9, 124.1, 80.7, 68.4, 51.6, 44.8, 31.7, 28.6, 27.6, 23.7, 23.4 ppm.

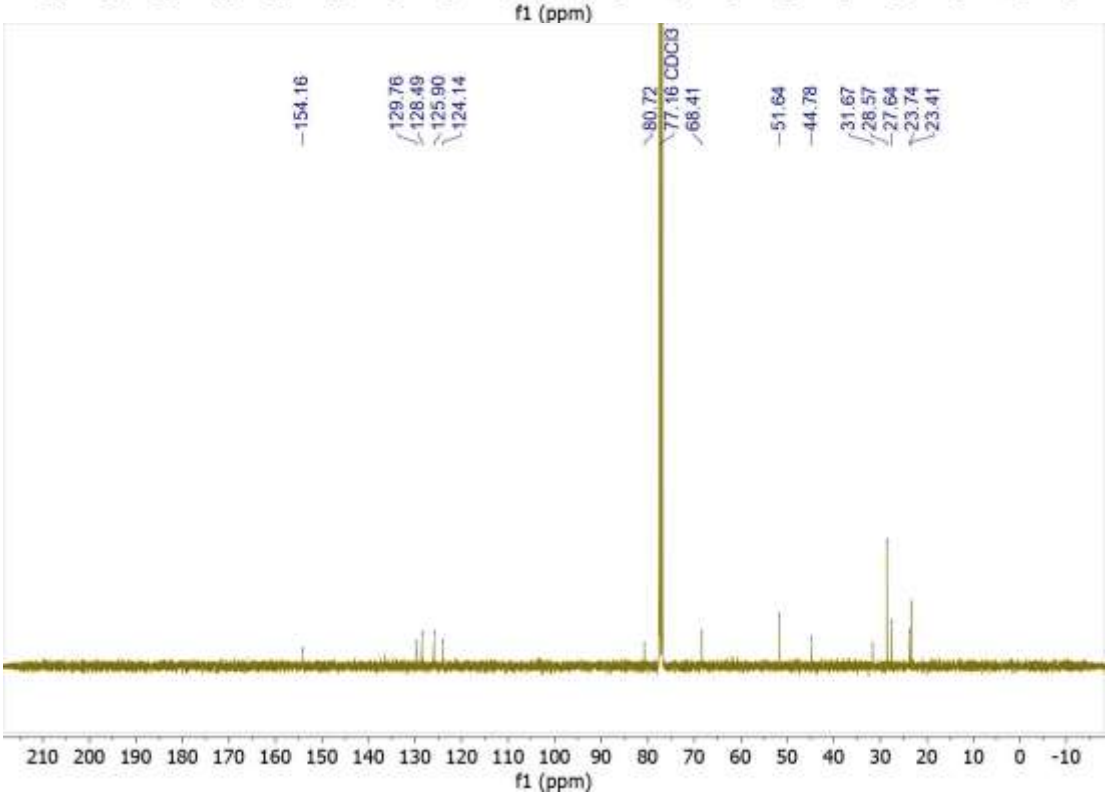
HRMS (ESI) m/z: [(M+H)+] calcd for $C_{23}H_{35}N_2O_2$ 371.2693, found 371.2697.

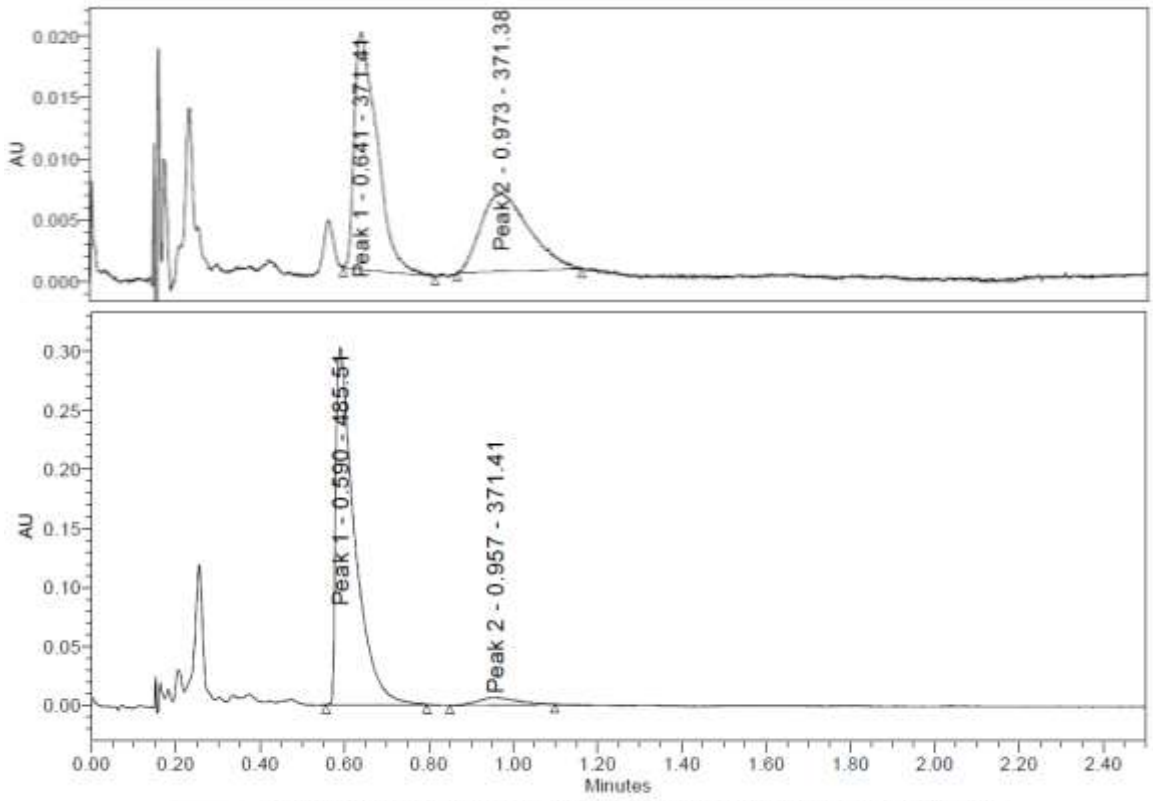
FTIR (neat): 2931, 1692, 1331, 1134, 915, 821, 765 cm^{-1}.

$[\alpha]_D^{28}$: - 2.0 (c = 0.5, $CHCl_3$).

SFC: Enantiomeric excess was determined by SFC analysis (Reflect I-Amylose A column, 10 % of methanol with 0.1 % NH_4OH, 4.0 mL/min, 220 nm), t_{major} = 0.59 min, t_{minor} = 0.96 min; ee = 92 %.

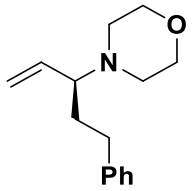

7.55
7.53
7.26 CDCl3
7.26
6.95
6.95
6.93
6.93
6.88
5.83
5.80
5.78
5.76
5.74
5.18
5.16
5.12
3.70
3.69
3.67
2.75
2.73
2.71
2.68
2.65
2.63
2.62
2.62
2.61
2.60
2.58
2.57
2.54
2.46
2.45
2.44
2.43
2.42
2.41
2.40
2.39
2.00
1.96
1.94
1.92
1.90
1.89
1.87
1.76
1.60
1.52
1.21
1.28
1.28
1.00
1.92
2.49
2.48
6.05
1.17
1.05
2.89
4.14
1.21
9.10
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)


154.16
129.76
128.49
125.90
124.14
80.72
77.16 CDCl3
68.41
51.64
44.78
31.67
28.57
27.64
23.74
23.41
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)



	Peak Name	SampleName	Ret. Time	% Area	Base Peak (m/z)
1	Peak 1	16C racemic	0.641	59.12	371.41
2	Peak 2	16C racemic	0.973	40.88	371.38
3	Peak 1	16A	0.590	95.93	485.51
4	Peak 2	16A	0.957	4.07	371.41

(*S*)-4-(5-Phenylpent-1-en-3-yl)morpholine (5.3k)



Procedures

The 5-phenylpent-1-en-3-yl acetate (81.7 mg, 0.4 mmol, 100 mol%) and morpholine (34.8 mg, 0.4 mmol, 100 mol%) were subject to standard reaction conditions (50 °C, DME). The title compound was obtained in 79% yield (72.9 mg, 0.32 mmol) as a light yellow oil after isolation by flash column chromatography (Al_2O_3, heptane: isopropyl acetate = 20:1–5:1).

TLC (SiO_2) R_f = 0.63 (dichloromethane: methanol = 9:1)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (dd, J = 33.4, 6.8 Hz, 5H), 5.74 (dt, J = 18.1, 9.6 Hz, 1H), 5.25 (d, J = 10.2 Hz, 1H), 5.12 (d, J = 17.2 Hz, 1H), 3.70 (h, J = 7.9 Hz, 4H), 2.75 (q, J = 8.8 Hz, 1H), 2.71 – 2.63 (m, 1H), 2.58 (dd, J = 11.3, 4.7 Hz, 3H), 2.45 (dd, J = 10.4, 5.1 Hz, 2H), 1.97 (ddd, J = 15.6, 11.4, 5.6 Hz, 1H), 1.78 – 1.65 (m, 1H) ppm.

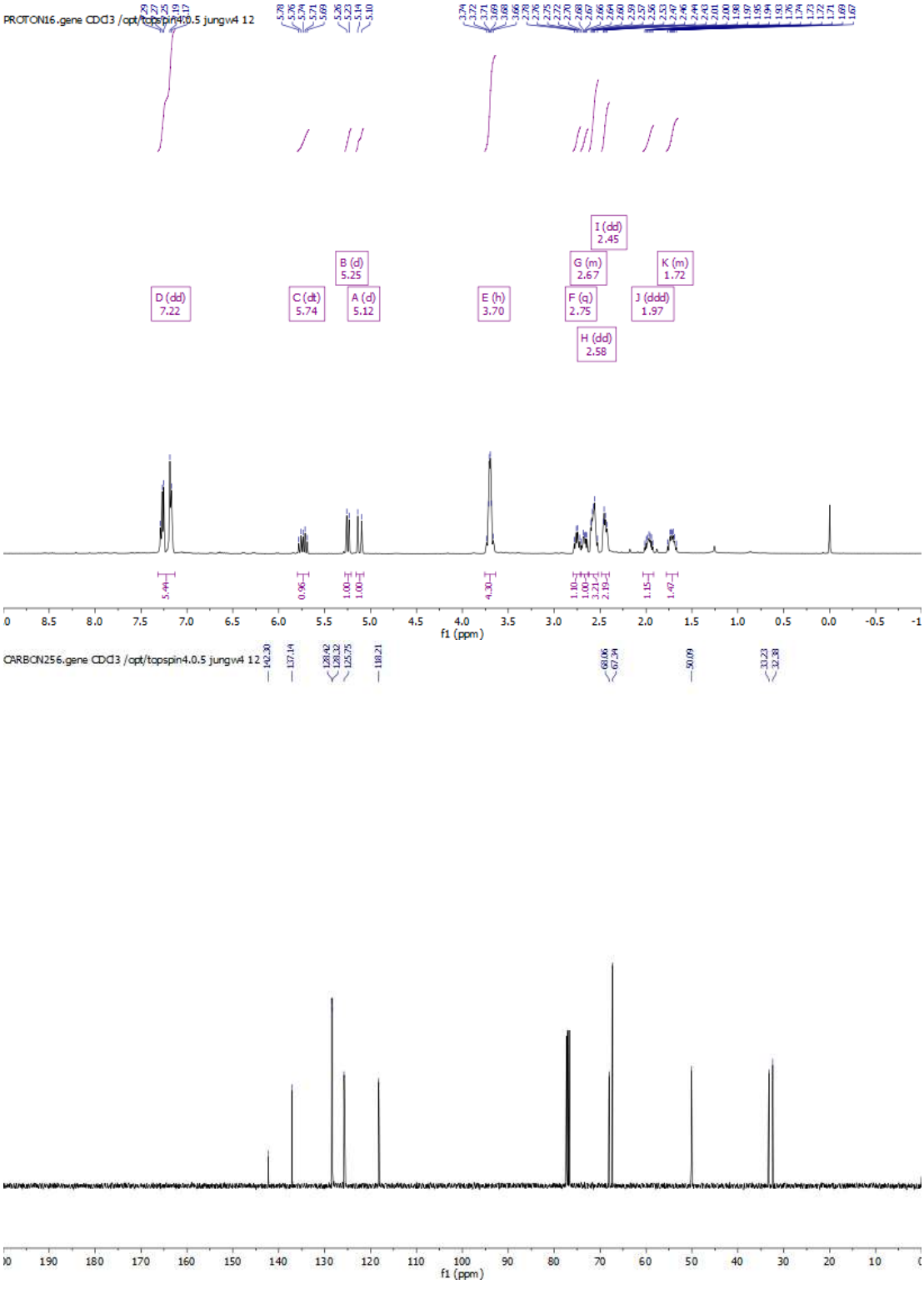
^{13}C NMR (101 MHz, $CDCl_3$): δ 142.3, 137.1, 128.4, 128.32 125.8, 118.2, 68.1, 67.3, 50.1, 33.2, 32.4 ppm.

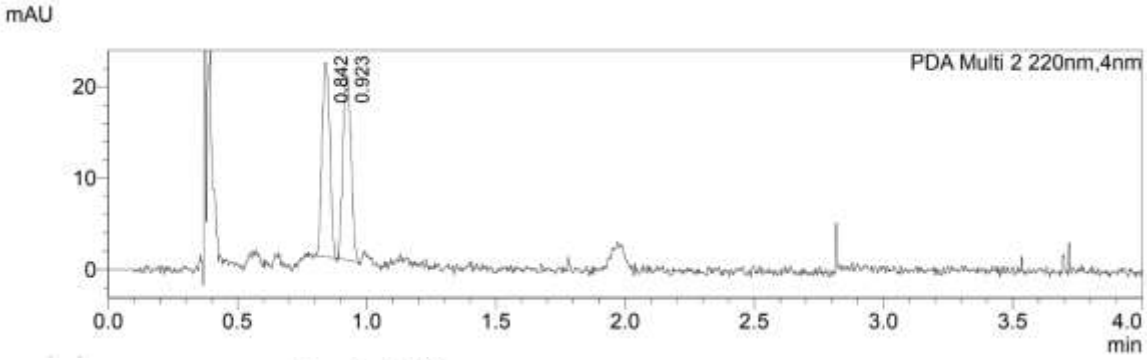
HRMS (ESI) m/z: [(M+H)+] calcd for $C_{15}H_{22}NO$ 232.1623, found 232.1693.

FTIR (neat): 415, 481, 749, 1029, 1328, 1700, 2167, 2852, 3062 cm^{-1}.

$[\alpha]_D^{28}$: - 16.4 (c = 2.0, methanol).

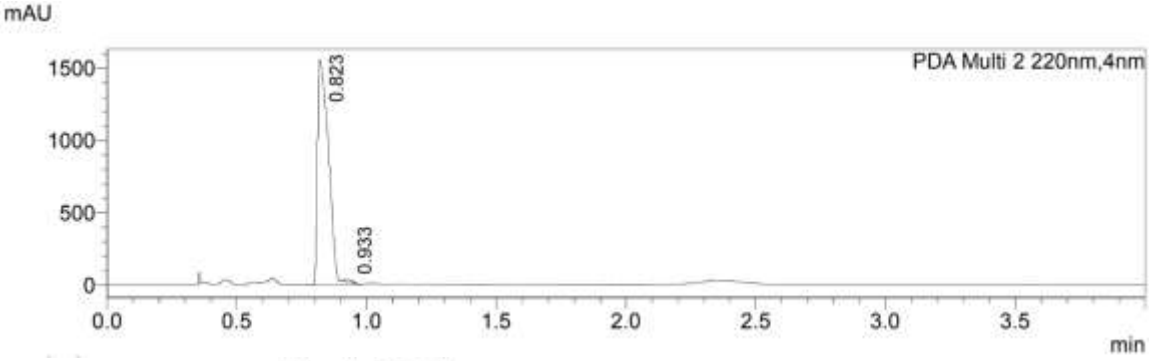
SFC: Enantiomeric excess was determined by SFC analysis (Chiralcel OJ column, 3 % of methanol with 0.1 % NH_4OH, 2.0 mL/min, 220 nm), t_{major} = 8.2 min, t_{minor} = 9.3 min; ee = 98 %.


PROTON16.gene CDCl3 /opt/topspin4.0.5 jungw4 12
D (dd) 7.22
C (dt) 5.74
B (d) 5.25
A (d) 5.12
E (h) 3.70
I (dd) 2.45
G (m) 2.67
F (q) 2.75
H (dd) 2.58
K (m) 1.72
J (ddd) 1.97
f1 (ppm)
CARBON256.gene CDCl3 /opt/topspin4.0.5 jungw4 12
f1 (ppm)



Peak Table
PDA Ch2 220nm

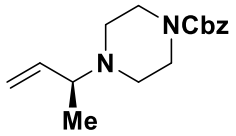
Peak#	Ret. Time	Area%
1	0.842	50.12
2	0.923	49.88
Total		100.00



Peak Table
PDA Ch2 220nm

Peak#	Ret. Time	Area%
1	0.823	99.24
2	0.933	0.76
Total		100.00

Benzyl (*S*)-4-(but-3-en-2-yl)piperazine-1-carboxylate (5.3l)



Procedures

The crotyl acetate (22.8 mg, 0.2 mmol, 100 mol%) and benzyl piperazine-1-carboxylate (44.1 mg, 0.2 mmol, 100 mol%) were subject to standard reaction conditions (DME). The title compound was obtained in 98% yield (53.8 mg, 0.20 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane: ethyl acetate = 8:1).

TLC (SiO_2) R_f = 0.12 (hexane: ethyl acetate = 1:2).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 – 7.28 (m, 5H), 5.76 (ddd, J = 16.7, 10.8, 7.7 Hz, 1H), 5.12 (s, 2H), 5.12 – 5.06 (m, 2H), 3.51 (t, J = 5.1 Hz, 4H), 2.98 – 2.92 (m, 1H), 2.49 (s, 4H), 1.16 (d, J = 6.6 Hz, 3H) ppm.

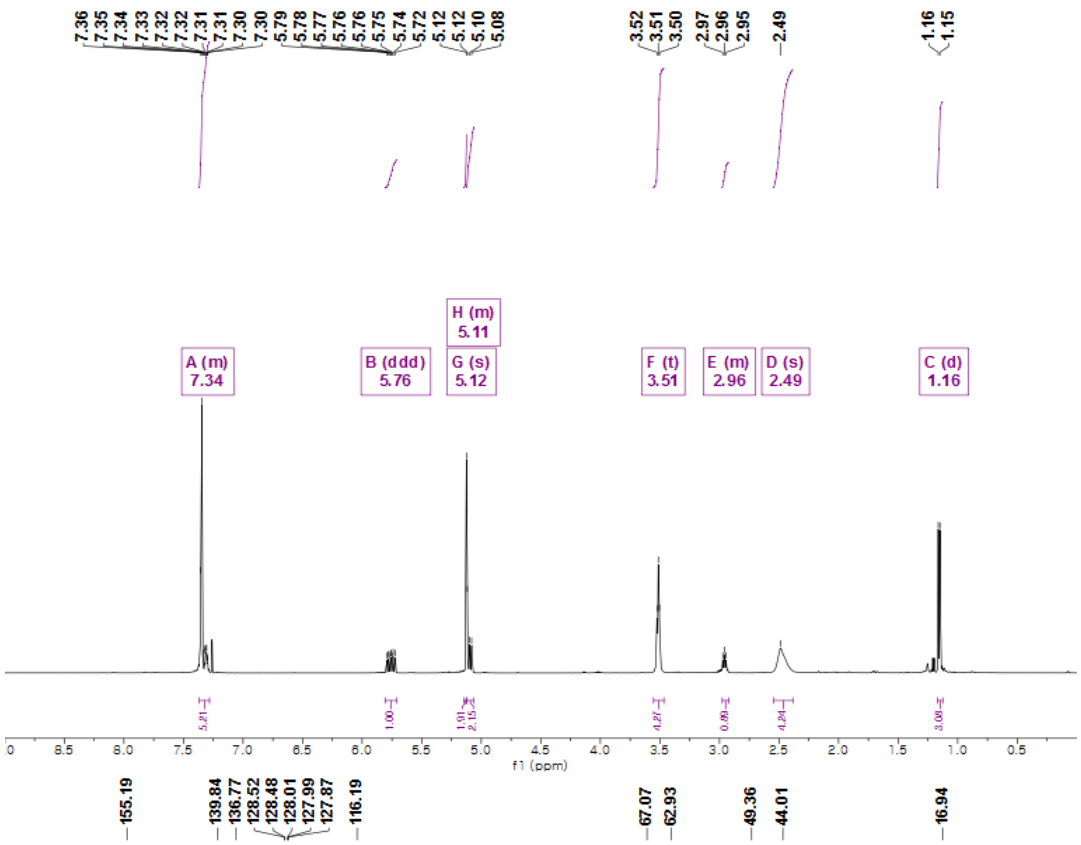
^{13}C NMR (126 MHz, $CDCl_3$): δ 155.2, 139.8, 136.8, 128.5, 128.5, 128.0, 128.0, 127.9, 116.2, 67.1, 62.9, 49.4, 44.0, 16.9 ppm.

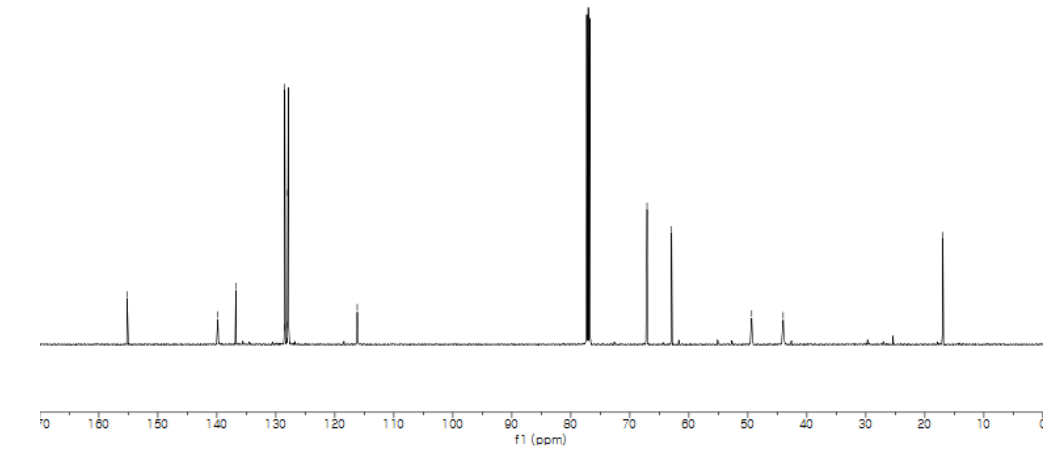
HRMS (ESI) m/z: [(M+H)+] calcd for $C_{16}H_{23}N_2O_2$ 275.1754, found 275.1762.

FTIR (neat): 698, 920, 1242, 1428, 1701, 2811, 2971 cm^{-1}.

$[\alpha]_D^{28}$: - 97 (c = 0.5, $CHCl_3$).

HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H column, hexane: 2-PrOH = 75:25, 1.0 mL/min, 254 nm), t_{major} = 4.8 min, t_{minor} = 6.3 min; ee = 98 %.


7.36
7.35
7.34
7.33
7.32
7.32
7.31
7.31
7.30
7.30
5.79
5.78
5.77
5.76
5.76
5.75
5.74
5.72
5.12
5.12
5.10
5.08
3.52
3.51
3.50
2.97
2.96
2.95
2.49
1.16
1.15
A (m)
7.34
B (ddd)
5.76
H (m)
5.11
G (s)
5.12
F (t)
3.51
E (m)
2.96
D (s)
2.49
C (d)
1.16
f1 (ppm)


155.19
139.84
136.77
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127.87
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49.36
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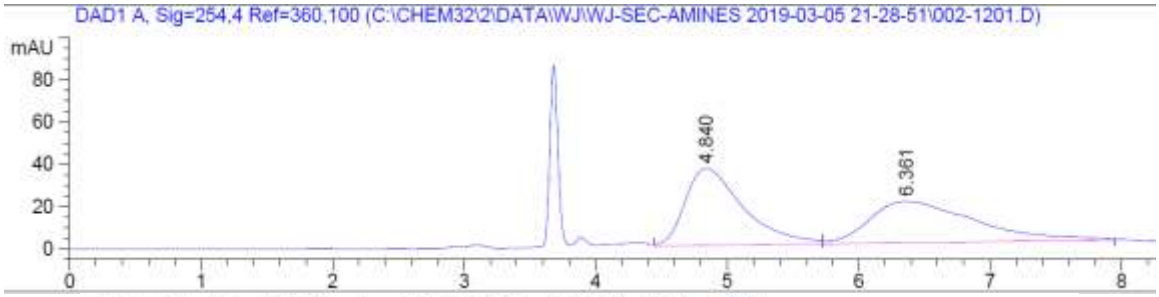
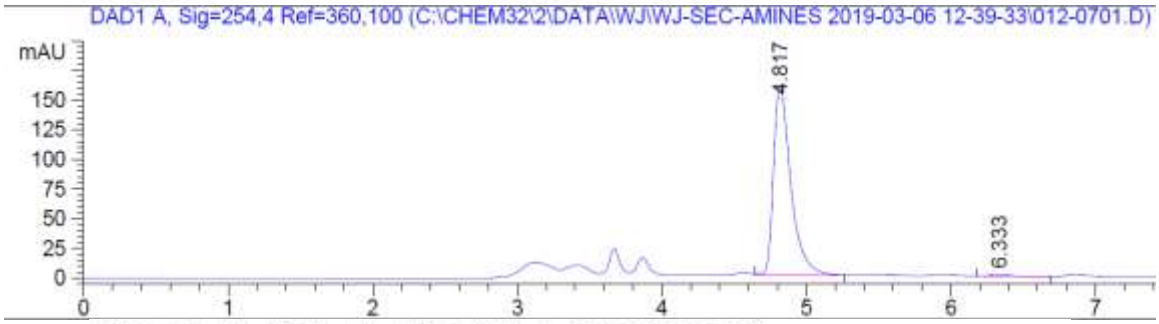
16.94
f1 (ppm)



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

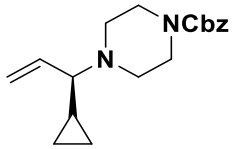
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.840	VB	0.4561	1114.49219	36.30567	50.5315
2	6.361	BB	0.7630	1091.04651	19.61379	49.4685
Totals :				2205.53870	55.91945	



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.817	VB	0.1269	1326.66638	159.71442	99.0597
2	6.333	VB	0.1347	12.59316	1.48848	0.9403
Totals :				1339.25954	161.20290	

Benzyl (*R*)-4-(1-cyclopropylallyl)piperazine-1-carboxylate (5.3m)



Procedures

The allylic acetate (56.1 mg, 0.4 mmol, 100 mol%) and benzyl piperazine-1-carboxylate (88.1 mg, 0.4 mmol, 100 mol%) were subject to standard reaction conditions (50 °C, DMF). The title compound was obtained in 81% yield (94.7 mg, 0.32 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, heptane: isopropyl acetate = 20:1–5:1).

TLC (SiO_2) R_f = 0.22 (heptane: isopropyl acetate = 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.23 (m, 5H), 5.76 (ddd, J = 17.1, 10.3, 8.2 Hz, 1H), 5.13 (s, 2H), 5.20 – 4.98 (m, 2H), 3.52 (dd, J = 6.0, 4.7 Hz, 5H), 2.65 (s, 2H), 2.53 (s, 2H), 1.90 (t, J = 8.5 Hz, 1H), 1.29 – 1.19 (m, 1H), 0.80 (qt, J = 8.5, 5.0 Hz, 1H), 0.66 (dddd, J = 9.1, 7.8, 5.9, 4.4 Hz, 1H), 0.48 (tdd, J = 9.0, 5.7, 4.7 Hz, 1H), 0.37 – 0.26 (m, 1H), 0.05 (dtd, J = 9.3, 4.7, 1.6 Hz, 1H) ppm.

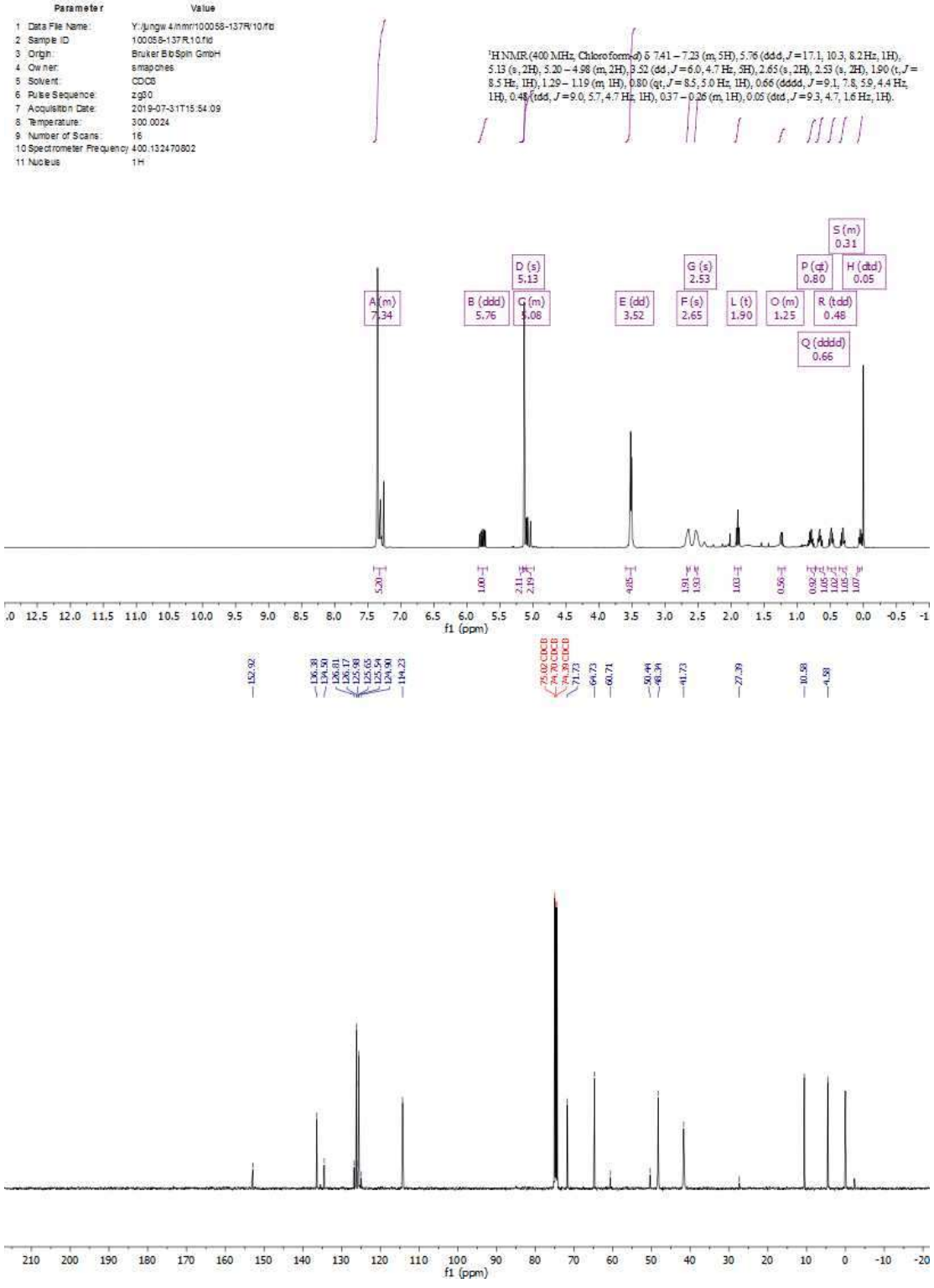
^{13}C NMR (101 MHz, $CDCl_3$): δ 152.9, 136.4, 134.5, 126.8, 126.2, 126.0, 125.7, 125.5, 124.9, 114.2, 71.7, 64.7, 60.7, 50.4, 48.3, 41.7, 27.4, 10.6, 4.6 ppm.

HRMS (ESI) m/z: [(M+H)+] calcd for $C_{18}H_{25}N_2O_2$ 301.1838, found 301.1910.

FTIR (neat): 2861, 1697, 1427, 1116, 918, 734, 697 cm^{-1}.

$[\alpha]_D^{28}$: + 4.5 (c = 2.0, methanol).

SFC: Enantiomeric excess was determined by SFC analysis (Lux Cellulose-1 column, 5 % of methanol with 0.1 % NH_4OH, 2.0 mL/min, 220 nm), t_{major} = 1.76 min, t_{minor} = 1.62 min; ee = 92 %.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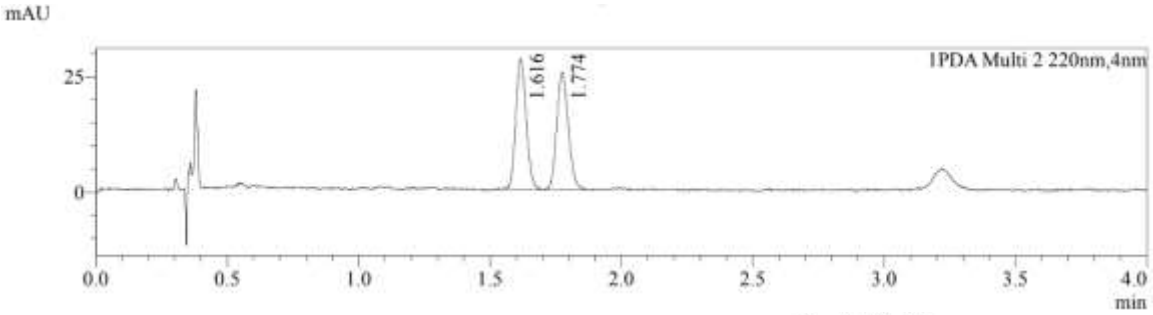
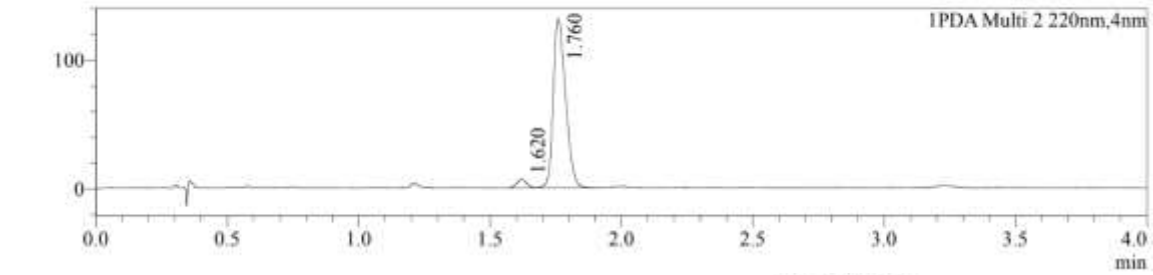
1 Data File Name: Y:/jungw4/nmr/100058-137R/10/fid
2 Sample ID 100058-137R.10.fid
3 Origin: Bruker BioSpin GmbH
4 Owner: smapches
5 Solvent: CDCl3
6 Pulse Sequence: zg30
7 Acquisition Date: 2019-07-31T15:54:09
8 Temperature: 300.0024
9 Number of Scans: 16
10 Spectrometer Frequency 400.132470802
11 Nucleus 1H
1H NMR (400 MHz, Chloroform-d) δ 7.41 – 7.23 (m, 5H), 5.76 (dddd, J = 17.1, 10.3, 8.2 Hz, 1H), 5.13 (s, 2H), 5.20 – 4.98 (m, 2H), 3.52 (dd, J = 6.0, 4.7 Hz, 5H), 2.65 (s, 2H), 2.53 (s, 2H), 1.90 (t, J = 8.5 Hz, 1H), 1.29 – 1.19 (m, 1H), 0.80 (qt, J = 8.5, 5.0 Hz, 1H), 0.66 (dddd, J = 9.1, 7.8, 5.9, 4.4 Hz, 1H), 0.48 (tdd, J = 9.0, 5.7, 4.7 Hz, 1H), 0.37 – 0.26 (m, 1H), 0.05 (dtd, J = 9.3, 4.7, 1.6 Hz, 1H).
A (m) 7.34
B (ddd) 5.76
C (m) 5.08
D (s) 5.13
E (dd) 3.52
F (s) 2.65
G (s) 2.53
L (t) 1.90
O (m) 1.25
P (qt) 0.80
Q (dddd) 0.66
R (tdd) 0.48
S (m) 0.31
H (dtd) 0.05
f1 (ppm)
152.92
136.38
134.50
126.01
125.77
125.98
125.65
125.54
124.90
114.23
75.92 CDCl3
74.70 CDCl3
74.39 CDCl3
71.73
64.73
60.71
50.44
48.34
41.73
27.39
10.58
4.58
f1 (ppm)



Peak Table

PDA Ch2 220nm

Peak#	Ret. Time	Area	Height	Area%
1	1.616	77830	27452	50.169
2	1.774	77305	24775	49.831
Total		155135	52226	100.000

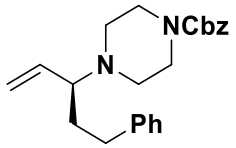


Peak Table

PDA Ch2 220nm

Peak#	Ret. Time	Area	Height	Area%
1	1.620	17848	6635	4.010
2	1.760	427249	129102	95.990
Total		445097	135736	100.000

Benzyl *(S)*-4-(5-phenylpent-1-en-3-yl)piperazine-1-carboxylate (5.3n)



Procedures

The allylic acetate (81.7 mg, 0.4 mmol, 100 mol%) and benzyl piperazine-1-carboxylate (88.1 mg, 0.4 mmol, 100 mol%) were subject to standard reaction conditions (50 °C, DMF). The title compound was obtained in 91% yield (132.9 mg, 0.36 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, heptane: isopropyl acetate = 20:1–5:1).

TLC (SiO_2) R_f = 0.27 (heptane: isopropyl acetate = 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.22 (m, 4H), 7.17 (d, J = 7.4 Hz, 2H), 5.71 (dt, J = 18.0, 9.4 Hz, 1H), 5.23 (d, J = 10.3 Hz, 1H), 5.10 (d, J = 17.6 Hz, 2H), 3.49 (h, J = 9.1 Hz, 3H), 2.82 (td, J = 8.3, 5.3 Hz, 1H), 2.65 (ddd, J = 25.2, 14.9, 6.1 Hz, 1H), 2.55 (dt, J = 15.7, 5.8 Hz, 2H), 2.40 (s, 1H), 1.95 (ddt, J = 15.4, 10.9, 5.9 Hz, 1H), 1.73 (qd, J = 9.3, 5.6 Hz, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 155.2, 142.2, 136.8, 136.7, 128.5, 128.4, 128.3, 128.0, 127.9, 125.8, 118.25, 67.5, 67.0, 49.1, 44.2, 33.5, 32.5 ppm.

HRMS (ESI) m/z: [(M+H)+] calcd for $C_{23}H_{29}N_2O_2$ 365.2151, found 365.2226.

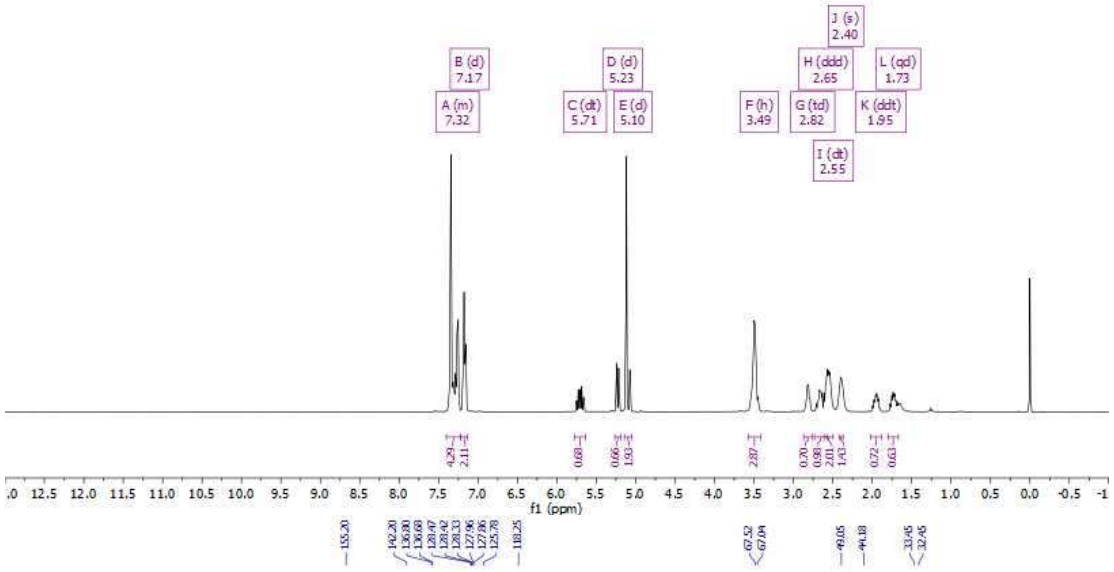
FTIR (neat): 2931, 1698, 1362, 1129, 997, 750, 696 cm^{-1}.

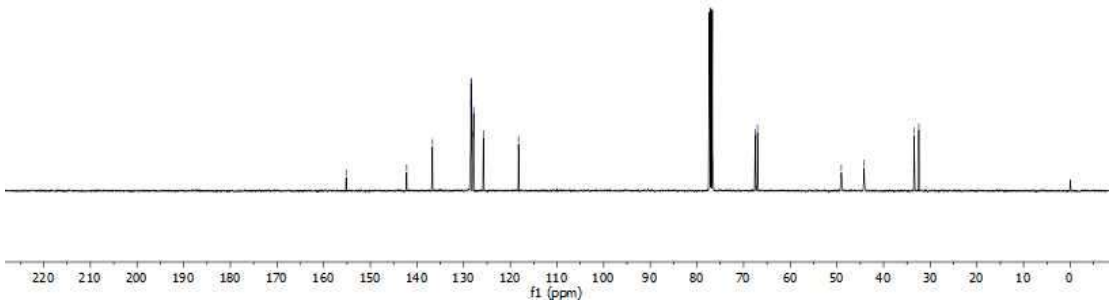
$[\alpha]_D^{28}$: + 13.9 (c = 2.0, methanol).

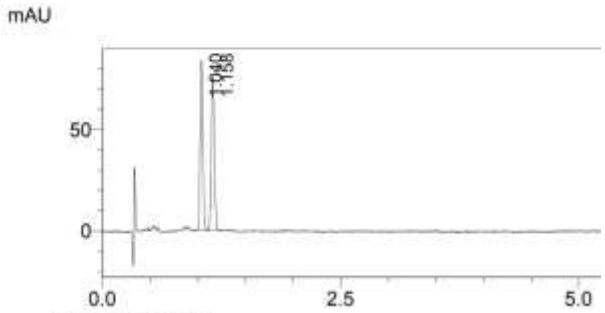
SFC: Enantiomeric excess was determined by SFC analysis (Chiralcel OJ-H column, 25 % of methanol with 0.1 % NH_4OH, 2.0 mL/min, 220 nm), t_{major} = 1.02 min, t_{minor} = 1.14 min; ee = 93 %.

	Parameter	Value
1	Data File Name:	Z:\jungw 4\nmr\100058-134A\10\fid
2	Sample ID	100058-134A
3	Origin:	Bruker BioSpin GmbH
4	Owner:	smapches
5	Solvent:	CDCl3
6	Pulse Sequence:	zg30
7	Acquisition Date:	2019-07-29T15:12:47
8	Temperature:	300.0015
9	Number of Scans:	128
10	Spectrometer Frequency:	400.132470802
11	Nucleus	1H

^{1}H NMR (400 MHz, Chloroform-d) δ 7.40 – 7.22 (m, 4H), 7.17 (d, J = 7.4 Hz, 2H), 5.71 (dt, J = 18.0, 9.4 Hz, 1H), 5.23 (d, J = 10.3 Hz, 1H), 5.10 (d, J = 17.6 Hz, 2H), 3.49 (h, J = 9.1 Hz, 3H), 2.82 (td, J = 8.3, 5.3 Hz, 1H), 2.65 (ddd, J = 25.2, 14.9, 6.1 Hz, 1H), 2.55 (dt, J = 15.7, 5.8 Hz, 2H), 2.40 (s, 1H), 1.95 (ddt, J = 15.4, 10.9, 5.9 Hz, 1H), 1.73 (qd, J = 9.3, 5.6 Hz, 1H).







Peak Table
PDA Ch2 220nm

Peak#	Ret. Time	Area%
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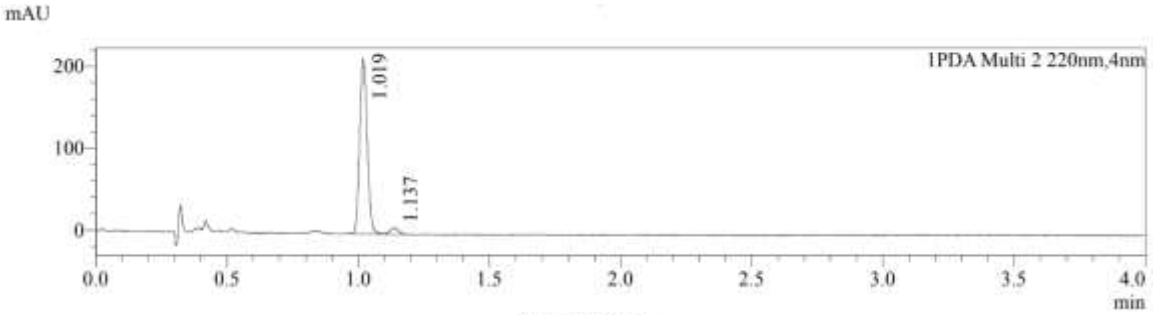
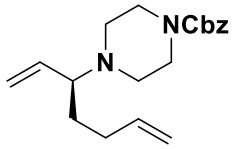
Total		100.00



Peak Table
PDA Ch2 220nm

Peak#	Ret. Time	Area	Height	Area%
1	1.019	426998	207343	95.916
2	1.137	18183	7739	4.084
Total		445182	215082	100.000

Benzyl (*S*)-4-(hepta-1,6-dien-3-yl)piperazine-1-carboxylate (5.3o)



Procedures

The allylic acetate (61.7 mg, 0.4 mmol, 100 mol%) and benzyl piperazine-1-carboxylate (88.1 mg, 0.4 mmol, 100 mol%) were subject to standard reaction conditions (50 °C, DMF). The title compound was obtained in 64% yield (80.6 mg, 0.26 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, heptane: isopropyl acetate = 20:1–5:1).

TLC (SiO_2) R_f = 0.42 (heptane: isopropyl acetate = 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.27 (m, 2H), 5.80 (ddt, J = 16.9, 10.1, 6.6 Hz, 1H), 5.65 (ddd, J = 17.1, 10.3, 8.9 Hz, 1H), 5.19 (dd, J = 10.3, 1.8 Hz, 1H), 5.12 (s, 2H), 5.07 (dd, J = 17.0, 1.9 Hz, 1H), 5.04 – 4.91 (m, 2H), 3.57 – 3.42 (m, 4H), 2.80 (td, J = 8.8, 5.1 Hz, 1H), 2.54 (s, 2H), 2.40 (s, 2H), 2.18 – 1.94 (m, 2H), 1.71 (dddd, J = 13.2, 9.5, 6.3, 5.1 Hz, 1H), 1.50 (dtd, J = 13.3, 9.0, 5.7 Hz, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 155.2, 138.4, 136.8, 128.5, 128.0, 127.9, 118.0, 114.7, 67.7, 67.0, 49.1, 44.1, 30.8, 30.4 ppm.

HRMS (ESI) m/z: [(M+H)+] calcd for $C_{19}H_{27}N_2O_2$ 315.1994, found 315.2066.

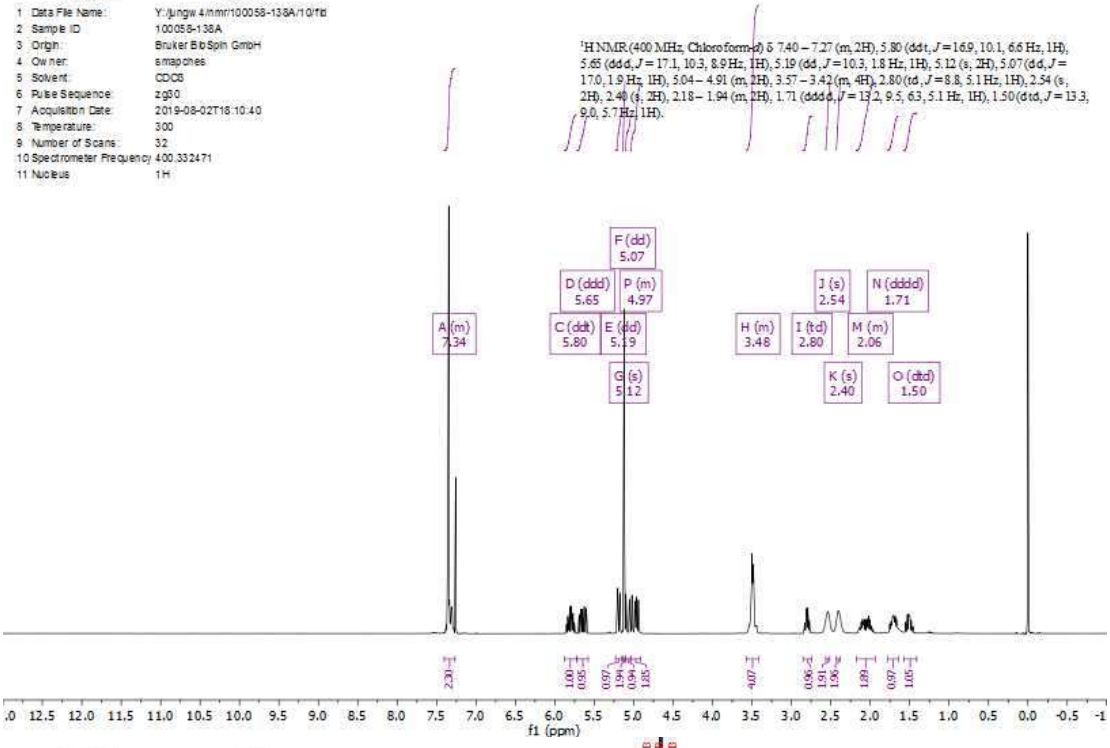
FTIR (neat): 2932, 2360, 1698, 1428, 1239, 998, 733, 696 cm^{-1}.

$[\alpha]_D^{28}$: + 19.4 (c = 2.0, methanol).

SFC: Enantiomeric excess was determined by SFC analysis (Chiralcel OJ-H column, 1 % of 2-PrOH with 0.1% NH_4OH, 4.0 mL/min, 40 °C, 220 nm), t_{major} = 1.49 min, t_{minor} = 1.39 min; ee = 94 %.

Parameter	Value
1 Data File Name:	Y:/jungw4/nmr/100058-138A/10/fid
2 Sample ID	100058-138A
3 Origin:	Bruker BioSpin GmbH
4 Owner:	smapches
5 Solvent:	CDCl3
6 Pulse Sequence:	zg30
7 Acquisition Date:	2019-08-02T18:10:40
8 Temperature:	300
9 Number of Scans:	32
10 Spectrometer Frequency	400.332471
11 Nucleus	1H

^{1}H NMR (400 MHz, Chloroform-d) δ 7.40 – 7.27 (m, 2H), 5.80 (ddt, J = 16.9, 10.1, 6.6 Hz, 1H), 5.65 (ddd, J = 17.1, 10.3, 8.9 Hz, 1H), 5.19 (dd, J = 10.3, 1.8 Hz, 1H), 5.12 (s, 2H), 5.07 (dd, J = 17.0, 1.9 Hz, 1H), 5.04 – 4.91 (m, 2H), 3.57 – 3.42 (m, 4H), 2.80 (td, J = 8.8, 5.1 Hz, 1H), 2.54 (s, 2H), 2.40 (s, 2H), 2.18 – 1.94 (m, 2H), 1.71 (dddd, J = 13.2, 9.5, 6.3, 5.1 Hz, 1H), 1.50 (dtd, J = 13.3, 9.0, 5.7 Hz, 1H).



Parameter	Value
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4 Owner:	smapches
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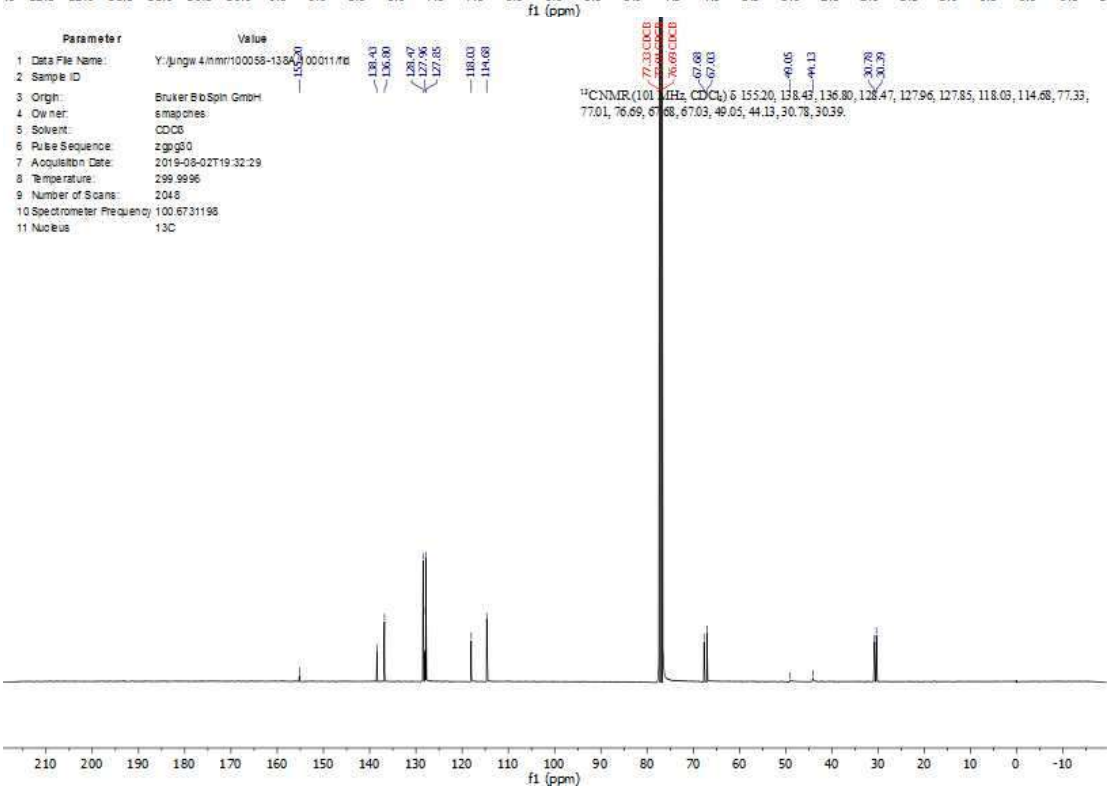
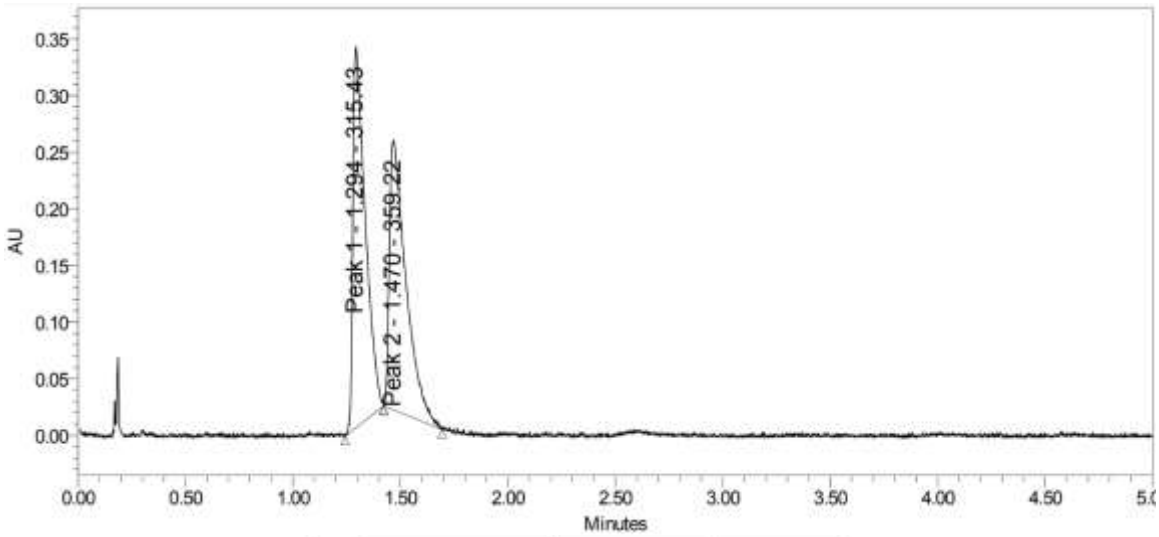
6 Pulse Sequence:	zgpg30
7 Acquisition Date:	2019-08-02T19:32:29
8 Temperature:	299.9996
9 Number of Scans:	2048
10 Spectrometer Frequency	100.6731198
11 Nucleus	13C

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.20, 138.43, 136.80, 128.47, 127.96, 127.85, 118.03, 114.68, 77.33, 77.01, 76.69, 67.68, 67.03, 49.05, 44.13, 30.78, 30.39.





	Peak Name	Ret. Time	% Area
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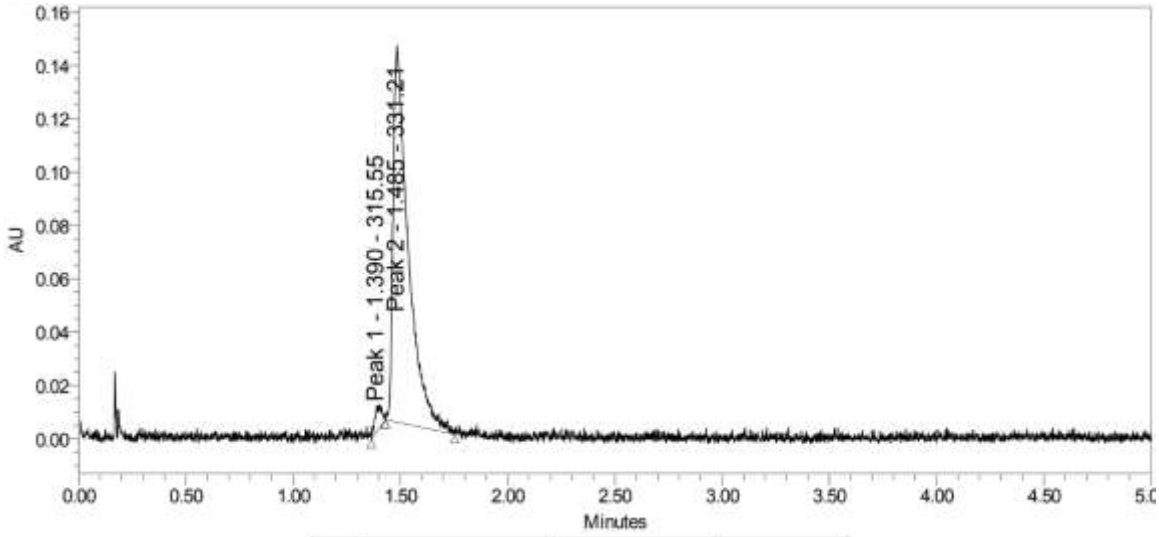
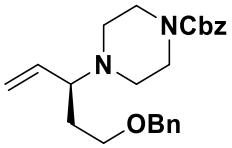
2	Peak 2	1.470	48.66



	Peak Name	Ret. Time	% Area
1	Peak 1	1.390	2.81
2	Peak 2	1.485	97.19

Benzyl (*S*)-4-(5-(benzyloxy)pent-1-en-3-yl)piperazine-1-carboxylate (5.3p)



Procedures

The allylic acetate (93.7 mg, 0.4 mmol, 100 mol%) and benzyl piperazine-1-carboxylate (88.1 mg, 0.4 mmol, 100 mol%) were subject to standard reaction conditions (50 °C, DMF). The title compound was obtained in 57% yield (90.1 mg, 0.23 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, heptane: isopropyl acetate = 20:1–5:1).

TLC (SiO_2) R_f = 0.11 (heptane: isopropyl acetate = 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (dd, J = 8.4, 4.4 Hz, 8H), 7.32 – 7.24 (m, 1H), 5.65 (dt, J = 17.8, 9.5 Hz, 1H), 5.16 (d, J = 10.2 Hz, 1H), 5.11 (s, 2H), 5.06 (d, J = 17.1 Hz, 1H), 4.47 (s, 2H), 3.53 (t, J = 6.7 Hz, 1H), 3.45 (dq, J = 13.1, 5.2, 4.6 Hz, 5H), 3.00 (q, J = 8.2 Hz, 1H), 2.53 (dd, J = 13.1, 6.4 Hz, 2H), 2.44 – 2.34 (m, 3H), 1.96 (dt, J = 13.3, 6.7 Hz, 1H), 1.69 (dq, J = 13.7, 6.8 Hz, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 155.2, 138.5, 136.8, 136.4, 128.4, 128.3, 127.9, 127.8, 127.6, 127.5, 118.01, 72.9, 67.6, 67.3, 67.0, 64.9, 52.7, 49.1, 44.1, 31.6, 21.8 ppm.

HRMS (ESI) m/z: [(M+H)+] calcd for $C_{24}H_{31}N_2O_3$ 395.2256, found 395.2331.

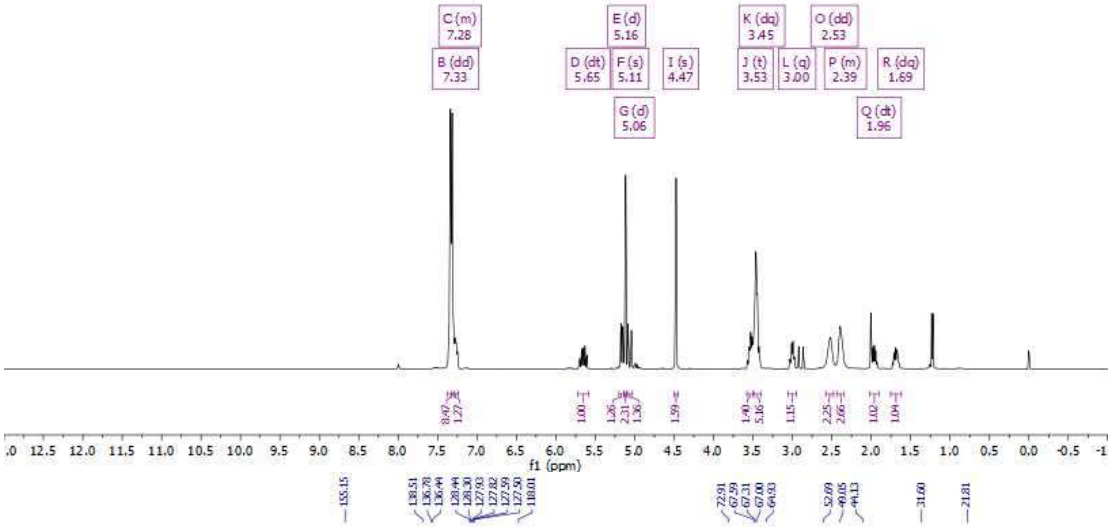
FTIR (neat): 2858, 1697, 1428, 1280, 998, 734, 696 cm^{-1}.

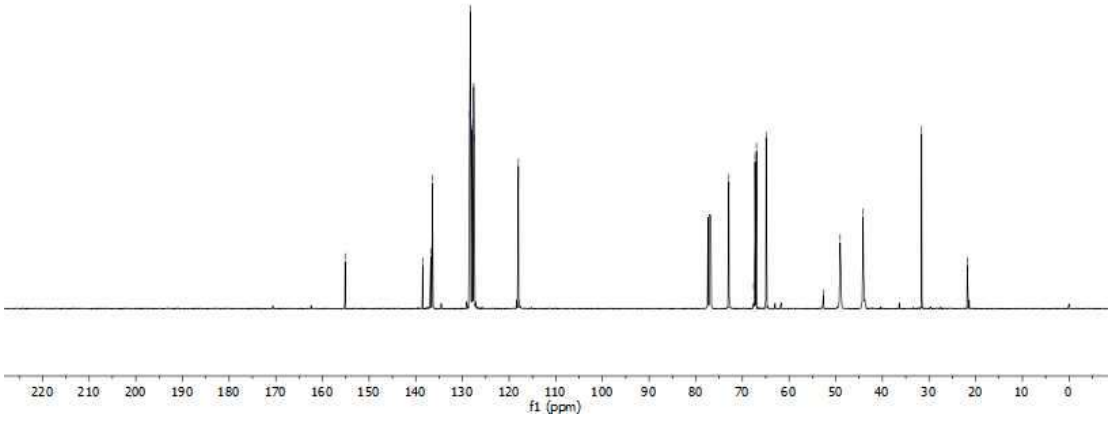
$[\alpha]_D^{28}$: + 25.4 (c = 2.0, methanol).

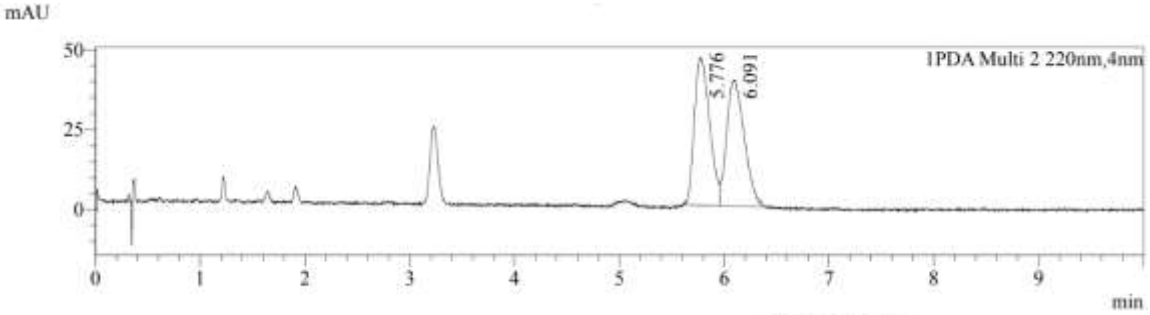
SFC: Enantiomeric excess was determined by SFC analysis (Lux Cellulose-1 column, 5 % of methanol with 0.1 % NH_4OH, 2.0 mL/min, 220 nm), t_{major} = 6.07 min, t_{minor} = 5.85 min; ee = 98 %.

	Parameter	Value
1	Data File Name:	Z:\jungw4\nmr\100058-136A\10\fid
2	Sample ID	100058-136A
3	Origin:	Bruker BioSpin GmbH
4	Owner:	smapches
5	Solvent:	CDCl3
6	Pulse Sequence:	zg30
7	Acquisition Date:	2019-07-30T17:19:32
8	Temperature:	299.9992
9	Number of Scans:	128
10	Spectrometer Frequency	400.13247080Z
11	Nucleus	1H

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 (dd, *J* = 8.4, 4.4 Hz, 8H), 7.32 – 7.24 (m, 1H), 5.65 (dt, *J* = 17.8, 9.5 Hz, 1H), 5.16 (d, *J* = 10.2 Hz, 1H), 5.11 (s, 2H), 5.06 (d, *J* = 17.1 Hz, 1H), 4.47 (s, 2H), 3.53 (t, *J* = 6.7 Hz, 1H), 3.45 (dq, *J* = 13.1, 5.2, 4.6 Hz, 5H), 3.00 (q, *J* = 8.2 Hz, 1H), 2.53 (dd, *J* = 13.1, 6.4 Hz, 2H), 2.44 – 2.34 (m, 3H), 1.96 (dt, *J* = 13.3, 6.7 Hz, 1H), 1.69 (dq, *J* = 13.7, 6.8 Hz, 1H).







Peak Table

PDA Ch2 220nm

Peak#	Ret. Time	Area	Height	Area%
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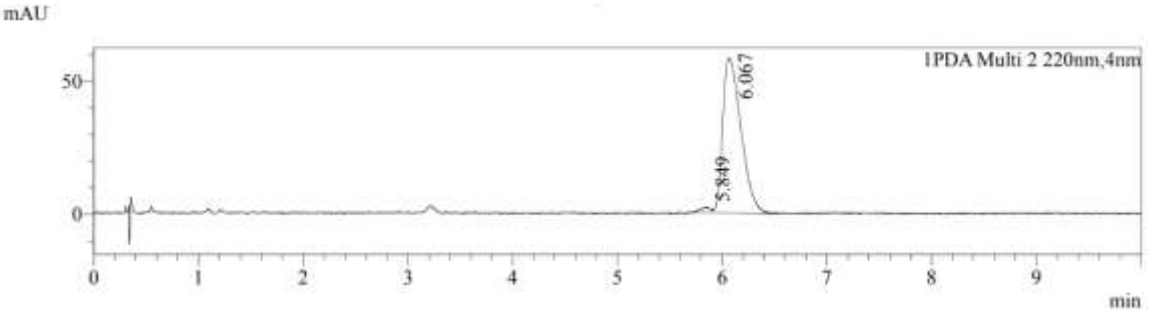
2	6.091	459976	39180	49.631
Total		926787	85175	100.000

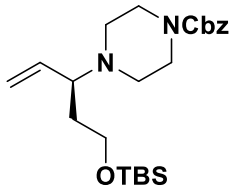


Peak Table

PDA Ch2 220nm

Peak#	Ret. Time	Area	Height	Area%
1	5.849	12503	1863	1.741
2	6.067	705730	57791	98.259
Total		718232	59654	100.000

Benzyl (*S*)-4-(5-((*tert*-butyldimethylsilyl)oxy)pent-1-en-3-yl)piperazine-1-carboxylate (5.3q)



Procedures

The allylic acetate (103 mg, 0.4 mmol, 100 mol%) and benzyl piperazine-1-carboxylate (88.1 mg, 0.4 mmol, 100 mol%) were subject to standard reaction conditions (50 °C, DMF). The title compound was obtained in 82% yield (138 mg, 0.33 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, heptane: isopropyl acetate = 20:1–5:1).

TLC (SiO_2) R_f = 0.66 (heptane: isopropyl acetate = 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.26 (m, 5H), 5.66 (ddd, J = 17.1, 10.3, 8.8 Hz, 1H), 5.18 (dd, J = 10.3, 1.9 Hz, 1H), 5.12 (s, 2H), 5.08 (dd, J = 17.2, 1.9 Hz, 1H), 3.68 (ddd, J = 10.0, 6.9, 5.7 Hz, 1H), 3.63 – 3.46 (m, 4H), 3.45 (dd, J = 12.9, 3.7 Hz, 1H), 2.99 (td, J = 8.6, 5.6 Hz, 1H), 2.53 (s, 2H), 2.41 (s, 2H), 1.93 – 1.80 (m, 1H), 1.66 – 1.53 (m, 1H), 1.57 (s, 4H), 0.88 (s, 9H) ppm.

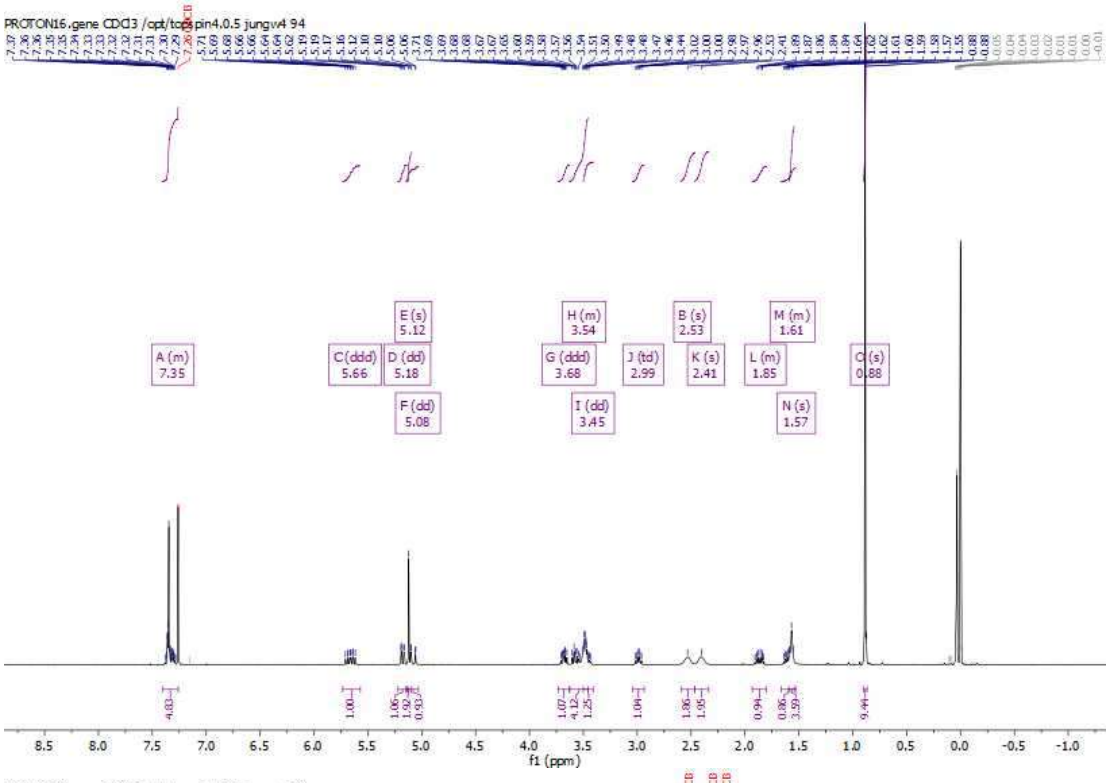
^{13}C NMR (101 MHz, $CDCl_3$): δ 155.2, 136.8, 136.6, 128.5, 128.0, 127.9, 117.9, 77.2, 67.0, 64.6, 60.1, 49.1, 44.2, 34.4, 26.0, 18.3 ppm.

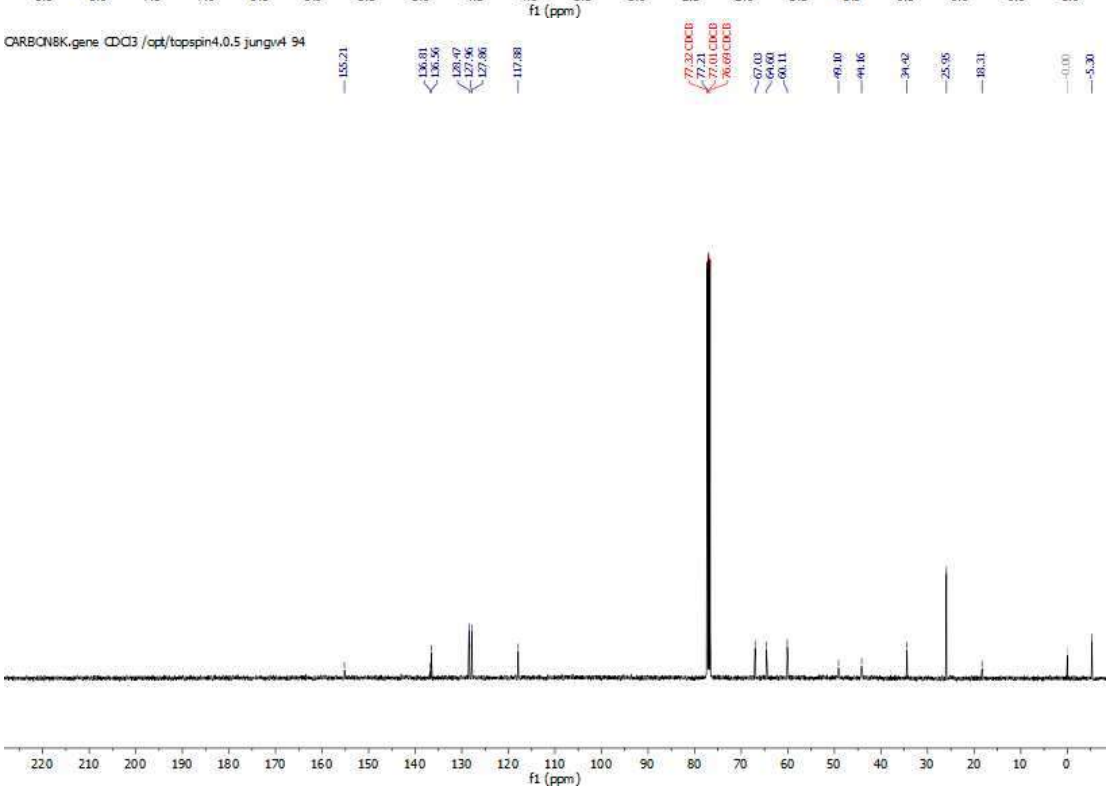
HRMS (ESI) m/z: [(M+H)+] calcd for $C_{23}H_{39}N_2O_3Si$ 419.2652, found 419.2727.

FTIR (neat): 2952, 1703, 1387, 1096, 834, 730, 696 cm^{-1}.

$[\alpha]_D^{28}$: + 25.8 (c = 2.0, methanol).

SFC: Enantiomeric excess was determined by SFC analysis (Lux Cellulose-1 column, 5 % of 2-PrOH (with 0.1 % NH_4OH), 4.0 mL/min, 40 ºC, 220 nm), t_{major} = 1.40 min, t_{minor} = 1.27 min; ee = 92 %.


PROTON16.gene CDCl3 /opt/topspin4.0.5 jungv4 94
A (m) 7.35
C (ddd) 5.66
D (dd) 5.18
E (s) 5.12
F (dd) 5.08
G (ddd) 3.68
H (m) 3.54
I (dd) 3.45
J (td) 2.99
K (s) 2.41
B (s) 2.53
L (m) 1.85
M (m) 1.61
N (s) 1.57
O (s) 0.88
f1 (ppm)


CARBON8K.gene CDCl3 /opt/topspin4.0.5 jungv4 94
155.21
136.81
136.56
128.47
127.96
127.86
117.88
77.32 CDCl3
77.21
77.01 CDCl3
76.69 CDCl3
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44.16
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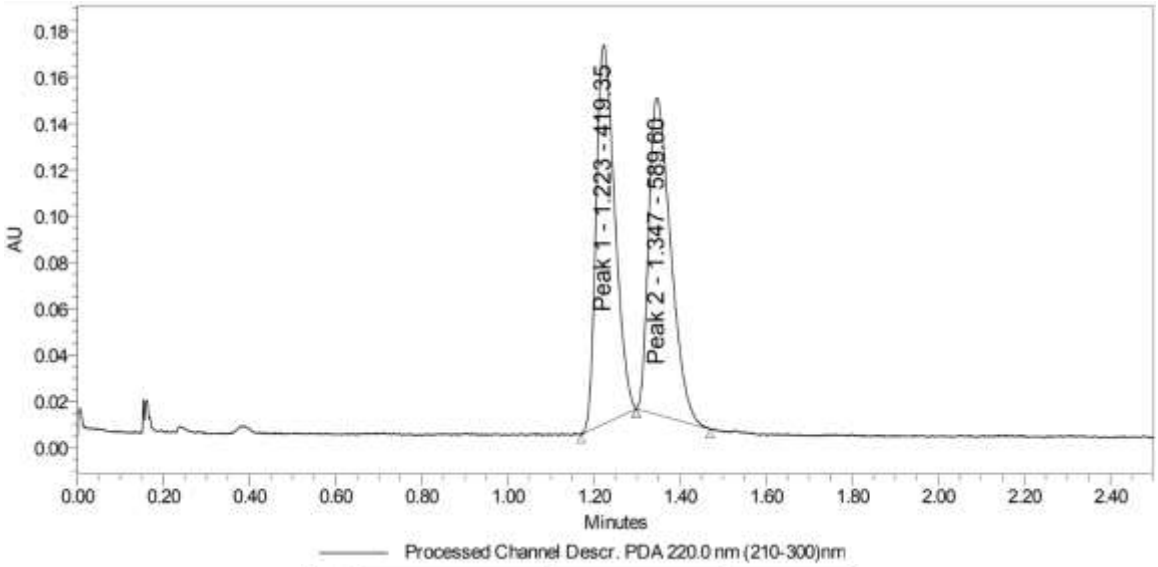
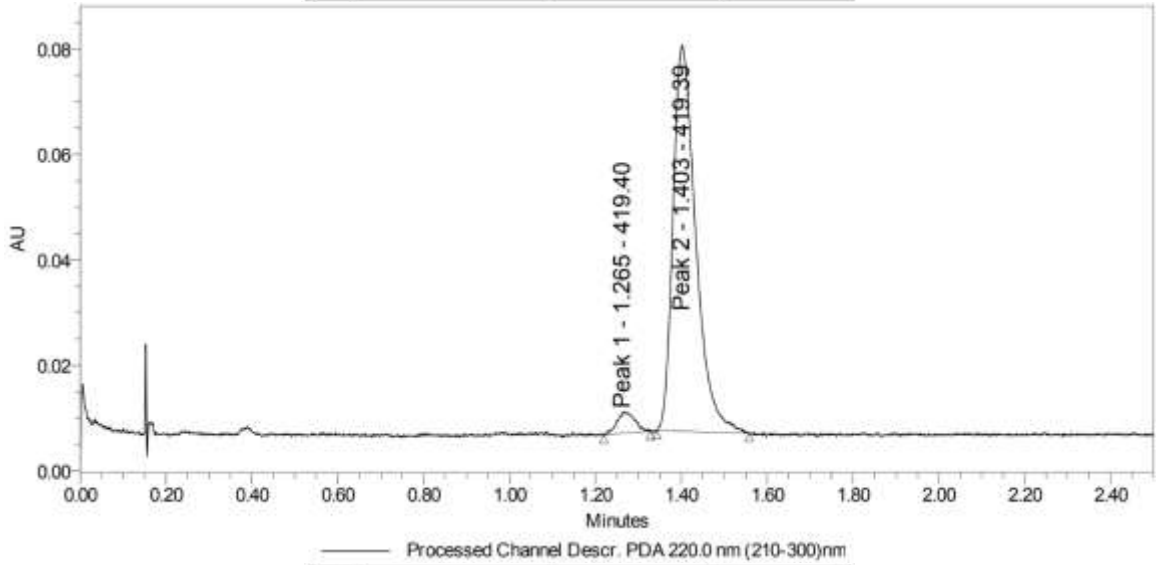
25.95
18.31
-0.00
-5.30
f1 (ppm)

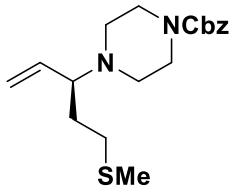


	Peak Name	Ret. Time	% Area
1	Peak 1	1.223	50.35
2	Peak 2	1.347	49.65



	Peak Name	Ret. Time	% Area
1	Peak 1	1.265	4.10
2	Peak 2	1.403	95.90

Benzyl (*S*)-4-(5-(methylthio)pent-1-en-3-yl)piperazine-1-carboxylate (5.3r)



Procedures

The allylic acetate (69.7 mg, 0.4 mmol, 100 mol%) and benzyl piperazine-1-carboxylate (88.1 mg, 0.4 mmol, 100 mol%) were subject to standard reaction conditions (50 °C, DMF). The title compound was obtained in 76% yield (101.1 mg, 0.30 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, heptane: isopropyl acetate = 20:1–5:1).

TLC (SiO_2) R_f = 0.58 (isopropyl acetate).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (s, 2H), 7.41 – 7.26 (m, 2H), 5.66 (ddd, J = 17.1, 10.3, 8.8 Hz, 1H), 5.21 (dd, J = 10.3, 1.9 Hz, 1H), 5.12 (s, 2H), 5.11 (dd, J = 17.4, 1.9 Hz, 1H), 3.49 (td, J = 6.3, 3.5 Hz, 4H), 2.95 (td, J = 8.3, 5.8 Hz, 1H), 2.54 (ddd, J = 12.9, 9.2, 5.9 Hz, 2H), 2.51 – 2.41 (m, 1H), 2.41 (s, 1H), 2.09 (s, 3H), 1.91 (ddt, J = 12.3, 9.1, 6.2 Hz, 1H), 1.77 – 1.62 (m, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 155.2, 136.8, 136.2, 128.5, 128.0, 127.9, 118.5, 67.1, 49.1, 44.2, 31.1, 31.00, 15.6 ppm.

HRMS (ESI) m/z: [(M+H)+] calcd for $C_{18}H_{27}N_2O_2S$ 335.1788, found 335.1795.

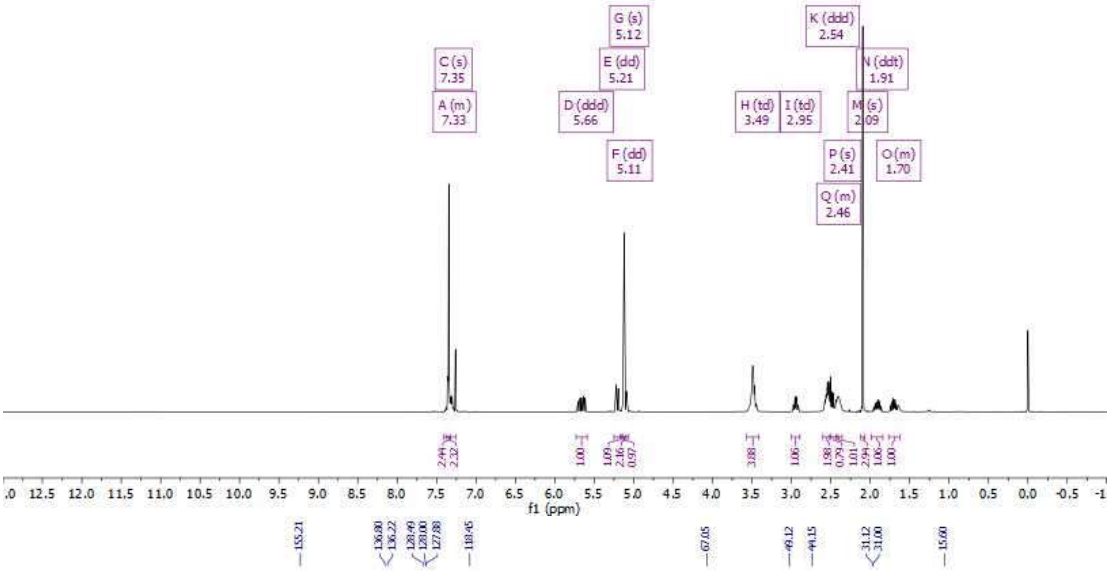
FTIR (neat): 2914, 2358, 1427, 1241, 999, 734, 696 cm^{-1}.

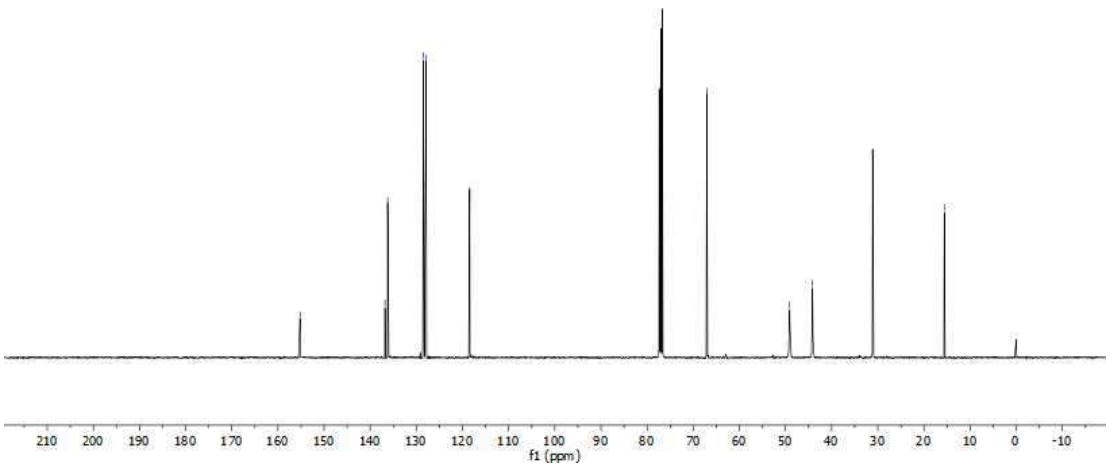
$[\alpha]_D^{28}$: + 21.9 (c = 2.0, methanol).

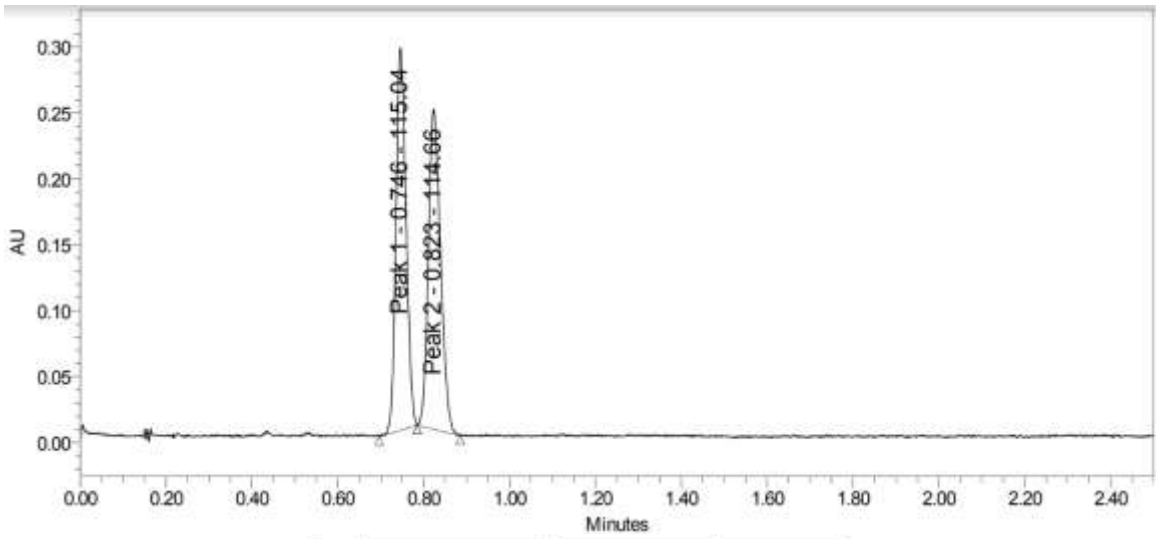
SFC: Enantiomeric excess was determined by SFC analysis (Chiralpak IA column, 10 % of methanol with 0.1 % NH_4OH, 4.0 mL/min, 40 ºC, 220 nm), t_{major} = 0.73 min, t_{minor} = 0.82 min; ee = 92 %.

	Parameter	Value
1	Data File Name:	Y:/jungw4/nmr/100058-161/10/fid
2	Sample ID	100058-161
3	Origin:	Bruker BioSpin GmbH
4	Owner:	smapches
5	Solvent:	CDCl3
6	Pulse Sequence:	zg30
7	Acquisition Date:	2019-08-12T14:53:31
8	Temperature:	300.0018
9	Number of Scans:	16
10	Spectrometer Frequency:	400.332471
11	Nucleus	1H

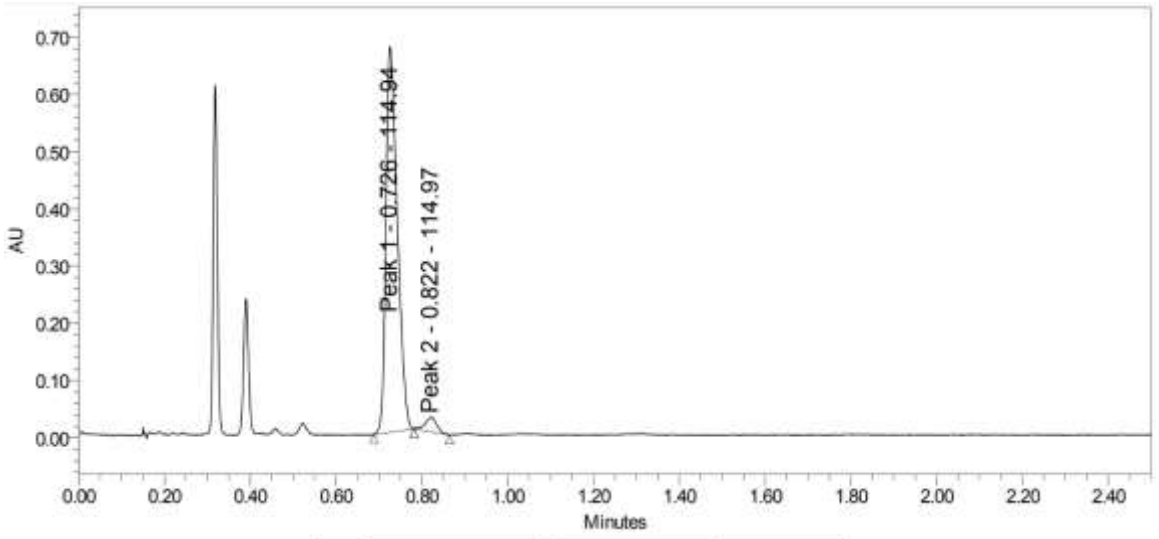
^{1}H NMR (400 MHz, Chloroform-d) δ 7.35 (s, 2H), 7.41 – 7.26 (m, 2H), 5.66 (ddd, J = 17.1, 10.3, 8.8 Hz, 1H), 5.21 (dd, J = 10.3, 1.9 Hz, 1H), 5.12 (s, 2H), 5.11 (dd, J = 17.4, 1.9 Hz, 1H), 3.49 (td, J = 6.3, 3.5 Hz, 4H), 2.95 (td, J = 8.3, 5.8 Hz, 1H), 2.34 (ddd, J = 12.9, 9.2, 5.9 Hz, 2H), 2.51 – 2.41 (m, 1H), 2.41 (s, 1H), 2.09 (s, 3H), 1.91 (ddt, J = 12.3, 9.1, 6.2 Hz, 1H), 1.77 – 1.62 (m, 1H).





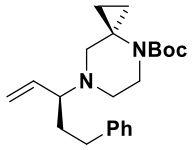


	Peak Name	Ret. Time	% Area
1	Peak 1	0.746	49.79
2	Peak 2	0.823	50.21



	Peak Name	Ret. Time	% Area
1	Peak 1	0.726	96.23
2	Peak 2	0.822	3.77

***tert*-Butyl (*S*)-7-(5-phenylpent-1-en-3-yl)-4,7-diazaspiro[2.5]octane-4-carboxylate (5.3s)**



Procedures

The allyl acetate (40.9 mg, 0.2 mmol, 100 mol%) and 4-Boc-4,7-diazaspiro[2.5]octane (42.5 mg, 0.2 mmol, 100 mol%) were subject to standard reaction conditions (70 °C, DMF). The title compound was obtained in 98% yield (70.1 mg, 0.20 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane: ethyl acetate = 20:1–10:1).

TLC (SiO_2) R_f = 0.29 (hexane: ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 – 7.04 (m, 5H), 5.62 (ddd, J = 17.1, 10.3, 8.9 Hz, 1H), 5.14 (dd, J = 10.3, 1.9 Hz, 1H), 5.00 (dd, J = 17.1, 1.8 Hz, 1H), 3.55 – 3.39 (m, 2H), 2.68 (td, J = 8.7, 5.4 Hz, 1H), 2.58 (ddd, J = 13.6, 10.2, 5.9 Hz, 1H), 2.49 (ddd, J = 13.7, 9.9, 5.9 Hz, 2H), 2.35 (ddd, J = 11.7, 7.6, 3.9 Hz, 1H), 2.23 (s, 2H), 1.85 (ddt, J = 13.3, 10.2, 5.8 Hz, 1H), 1.66 – 1.55 (m, 1H), 1.37 (s, 8H), 0.94 (dt, J = 10.5, 5.8 Hz, 1H), 0.85 (dt, J = 10.7, 5.4 Hz, 1H), 0.71 – 0.57 (m, 2H) ppm.

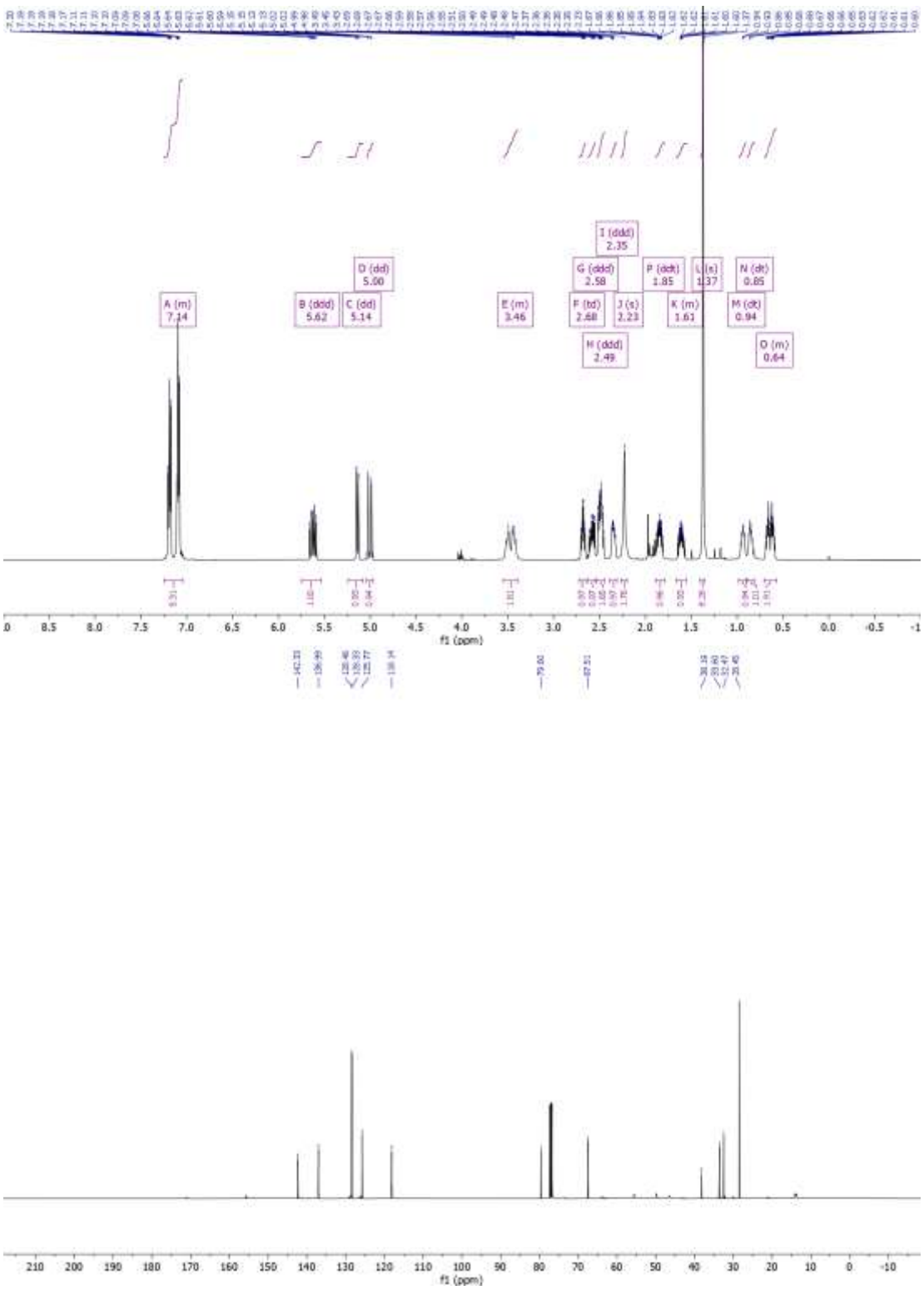
^{13}C NMR (126 MHz, $CDCl_3$): δ 142.3, 137.0, 128.5, 128.3, 125.8, 118.1, 79.6, 67.5, 38.2, 33.6, 32.5, 28.5. ppm.

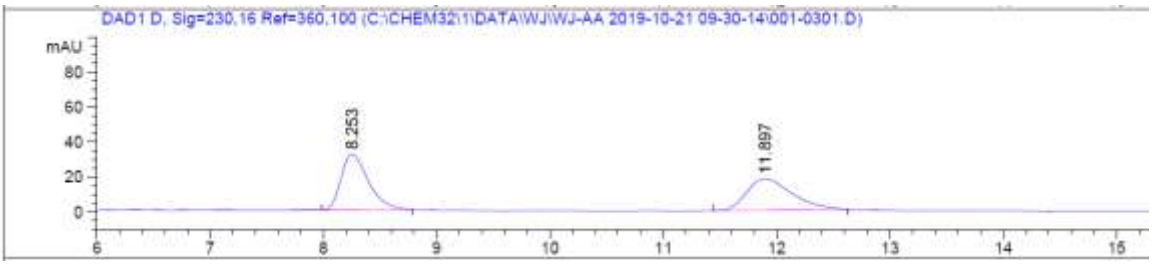
HRMS (ESI) m/z: [(M+H)+] calcd for $C_{22}H_{33}N_2O_2$ 357.2537, found 357.2544.

FTIR (neat): 666, 749, 1029, 1240, 1455, 1734, 2364, 3016 cm^{-1}.

$[\alpha]_D^{28}$: + 5.0 (c = 1.0, $CHCl_3$).

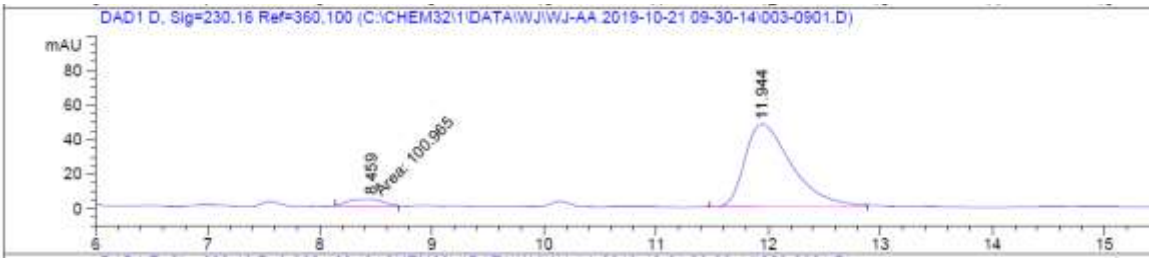
HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H column, hexane: 2-PrOH = 99:1, 1.0 mL/min, nm), t_{major} = 11.94 min, t_{minor} = 8.46 min; ee = 95 %.


A (m)
7.14
B (ddd)
5.62
C (dd)
5.14
D (dd)
5.60
E (m)
3.46
F (bd)
2.68
G (ddd)
2.58
H (ddd)
2.49
I (ddd)
2.35
J (s)
2.23
K (m)
1.61
L (s)
1.37
M (dt)
0.94
N (dt)
0.85
O (m)
0.64
P (ddt)
1.85
f1 (ppm)



Signal 3: DAD1 D, Sig=230,16 Ref=360,100

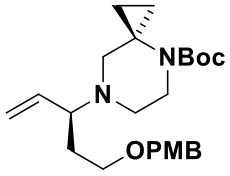
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.253	BB	0.2594	542.41888	32.04993	51.5661
2	11.897	BB	0.4275	509.47229	18.15073	48.4339
Totals :				1051.89117	50.20066	



Signal 3: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.459	MM	0.3870	100.96476	4.34844	6.7966
2	11.944	BB	0.4394	1384.54688	47.87353	93.2034
Totals :				1485.51163	52.22197	

***tert*-Butyl (*S*)-7-(5-((4-methoxybenzyl)oxy)pent-1-en-3-yl)-4,7-diazaspiro[2.5]octane-4-carboxylate (5.3t)**



Procedures

The allyl acetate (52.9 mg, 0.2 mmol, 100 mol%) and 4-Boc-4,7-diazaspiro[2.5]octane (42.5 mg, 0.2 mmol, 100 mol%) were subject to standard reaction conditions (70 °C, DMF). The title compound was obtained in 97% yield (81.0 mg, 0.20 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane: ethyl acetate = 20:1–10:1).

TLC (SiO_2) R_f = 0.34 (hexane: ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 5.66 (ddd, J = 17.0, 10.2, 8.7 Hz, 1H), 5.17 (dd, J = 10.2, 1.9 Hz, 1H), 5.07 (dd, J = 17.3, 2.0 Hz, 1H), 4.43 (d, J = 1.6 Hz, 2H), 4.14 (q, J = 7.2 Hz, 1H), 3.82 (s, 3H), 3.57 – 3.40 (m, 4H), 2.92 (td, J = 8.7, 5.5 Hz, 1H), 2.57 (dd, J = 11.0, 4.9 Hz, 1H), 2.44 (dt, J = 10.8, 4.6 Hz, 1H), 2.31 (s, 2H), 2.07 (s, 1H), 1.96 (dq, J = 13.3, 6.7 Hz, 1H), 1.71 – 1.62 (m, 3H), 1.47 (s, 8H), 1.28 (t, J = 7.1 Hz, 1H), 0.99 (s, 1H), 0.94 (s, 1H), 0.70 (ddt, J = 20.0, 9.4, 4.9 Hz, 2H) ppm.

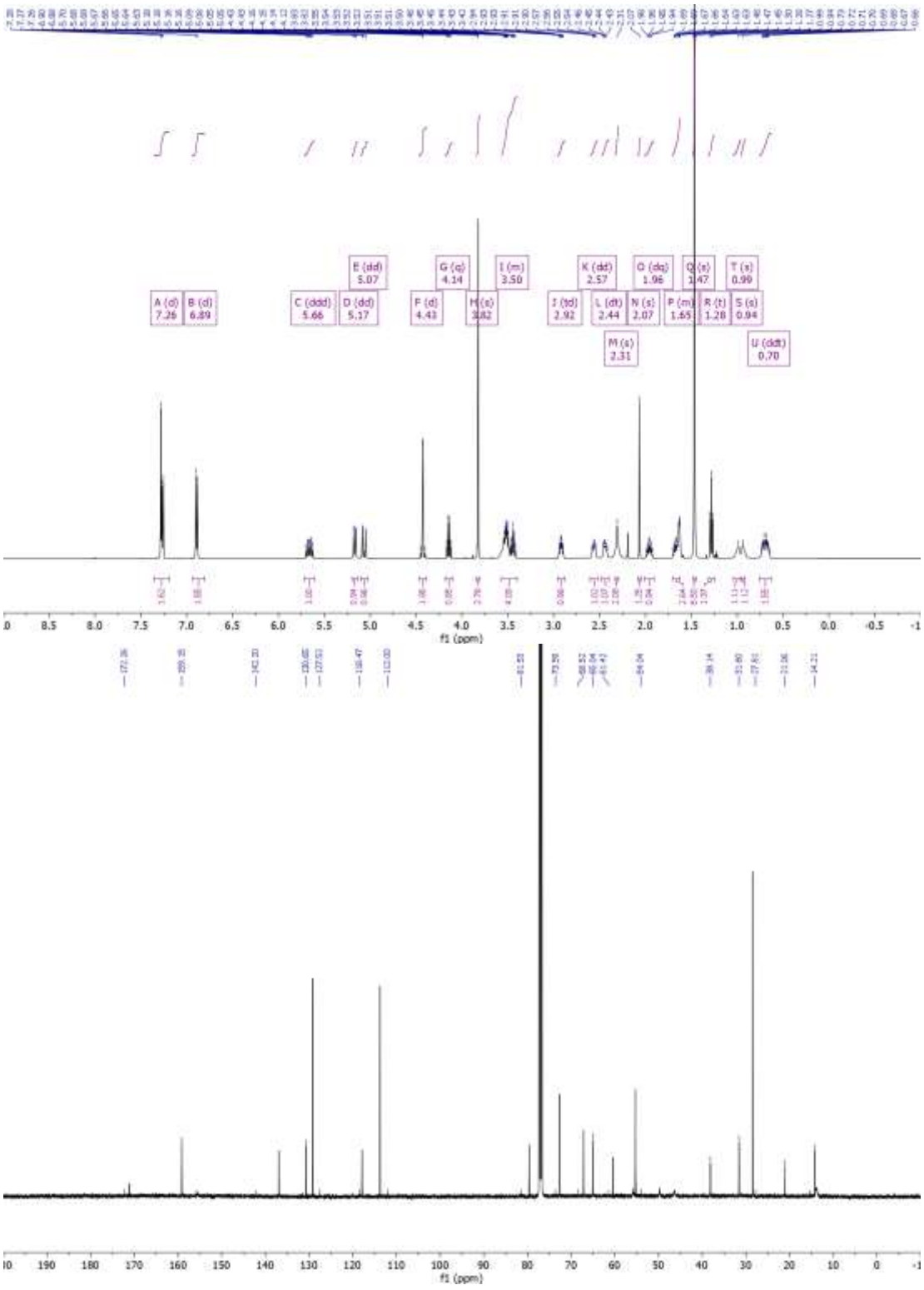
^{13}C NMR (126 MHz, $CDCl_3$): δ 172.3, 159.2, 142.2, 130.7, 127.5, 118.5, 112.0, 81.5, 73.6, 68.5, 65.0, 61.4, 54.0, 38.1, 31.6, 27.8, 21.1, 14.2 ppm.

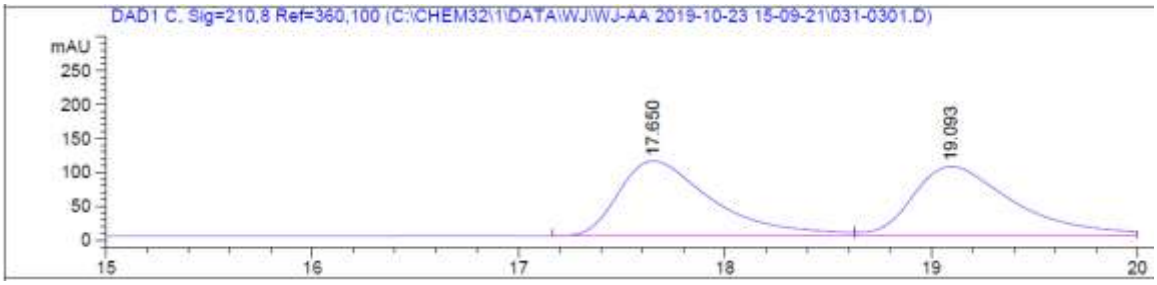
HRMS (ESI) m/z: [(M+H)+] calcd for $C_{24}H_{37}N_2O_4$ 417.2748, found 417.2754.

FTIR (neat): 666, 821, 1035, 1216, 1319, 1513, 1687, 3007 cm^{-1}.

$[\alpha]_D^{28}$: + 12.0 (c = 1.0, $CHCl_3$).

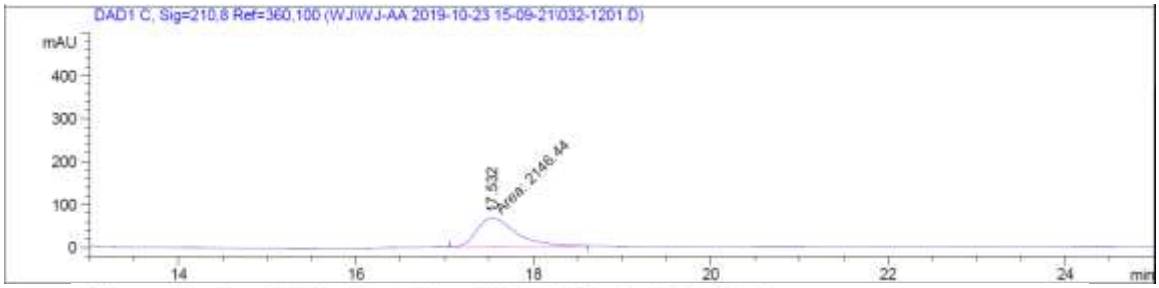
HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralcel AD-H column, hexane: 2-PrOH = 99:1, 1.0 mL/min, 210 nm), t_{major} = 17.65 min, t_{minor} = 19.09 min; ee = 99 %.


A (d) 7.26
B (d) 6.89
C (ddd) 5.66
D (dd) 5.17
E (dd) 5.07
F (d) 4.43
G (q) 4.14
H (s) 3.82
I (m) 3.50
J (td) 2.92
K (dd) 2.57
L (dt) 2.44
M (s) 2.31
N (s) 2.07
O (dq) 1.96
P (m) 1.65
Q (s) 1.47
R (t) 1.28
S (s) 0.94
T (s) 0.99
U (ddt) 0.70
f1 (ppm)
f1 (ppm)



Signal 2: DAD1 C, Sig=210,8 Ref=360,100

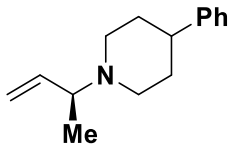
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.650	BV	0.4760	3498.36060	110.29546	50.0095
2	19.093	VBA	0.5130	3497.02905	102.25587	49.9905
Totals :				6995.38965	212.55133	



Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.532	FM	0.5219	2146.44482	68.54509	100.0000
Totals :				2146.44482	68.54509	

(*S*)-1-(But-3-en-2-yl)-4-phenylpiperidine (5.3u)



Procedures

The crotyl acetate (45.7 mg, 0.4 mmol, 100 mol%) and 4-phenylpiperidine (64.5 mg, 0.4 mmol, 100 mol%) were subject to standard reaction conditions (40 °C, DME). The title compound was obtained in 95% yield (81.8 mg, 0.38 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, heptane: isopropyl acetate = 5:1-1:1).

TLC (SiO_2) R_f = 0.61 (isopropyl acetate).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.15 (m, 6H), 5.91 – 5.80 (m, 1H), 5.13 – 5.10 (m, 1H), 5.09 – 5.08 (m, 1H), 3.11 (dddd, J = 11.4, 3.8, 3.0, 2.0 Hz, 1H), 3.07 – 2.94 (m, 2H), 2.47 (tt, J = 11.7, 4.3 Hz, 1H), 2.22 – 2.10 (m, 2H), 1.89 – 1.69 (m, 5H), 1.20 (d, J = 6.6 Hz, 3H) ppm.

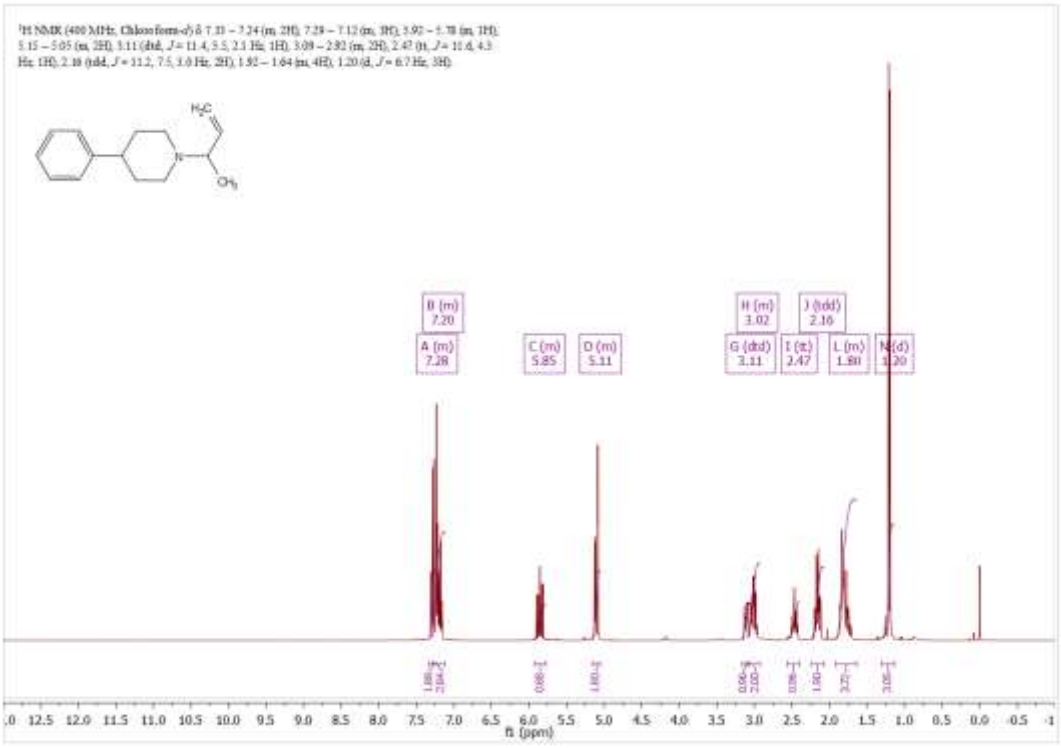
^{13}C NMR (101 MHz, $CDCl_3$): δ 146.6, 140.7, 128.4, 126.9, 126.1, 115.5, 63.3, 50.7, 50.5, 43.0, 33.8, 33.8, 17.3 ppm.

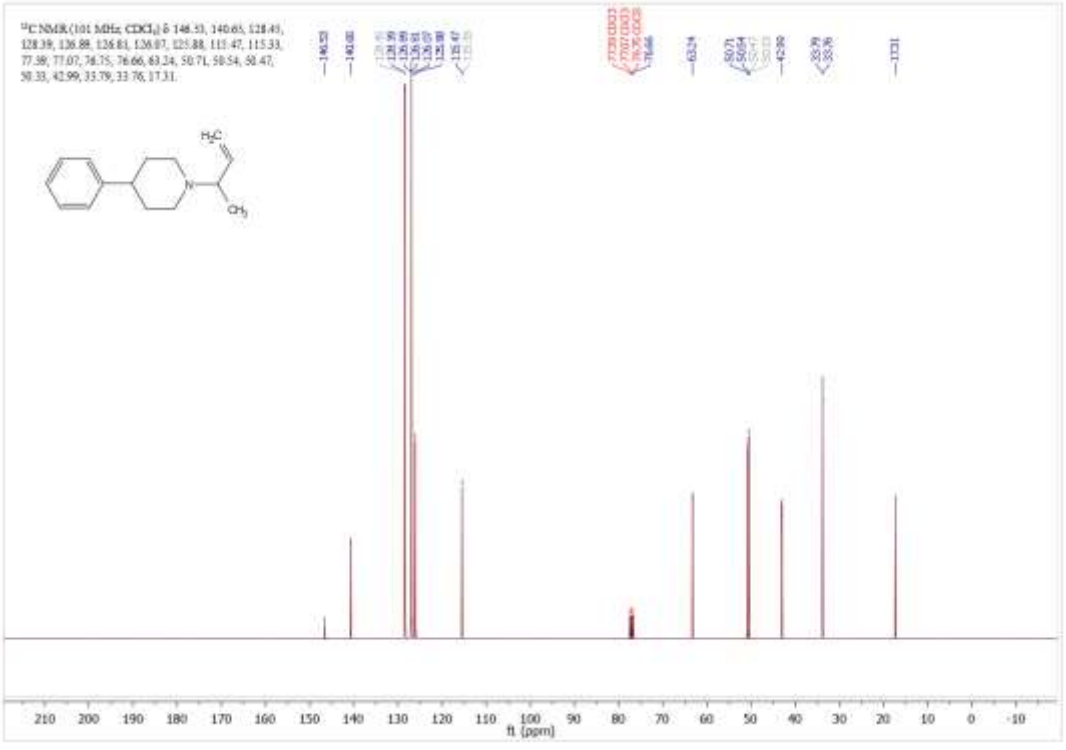
HRMS (ESI) m/z: [(M+H)+] calcd for $C_{15}H_{23}N$ 216.1747, found 216.1745.

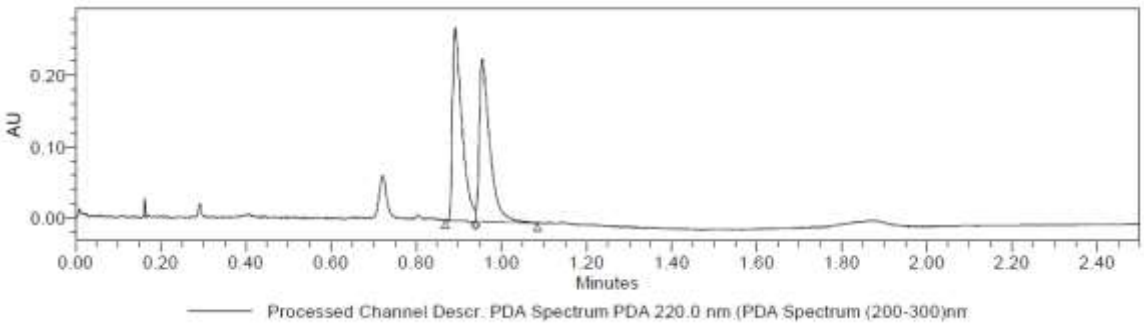
FTIR (neat): 3061, 2795, 1602, 1450, 1328, 1129, 983, 754, 635, 472 cm^{-1}.

$[\alpha]_D^{28}$: + 8.6 (c = 2.0, methanol).

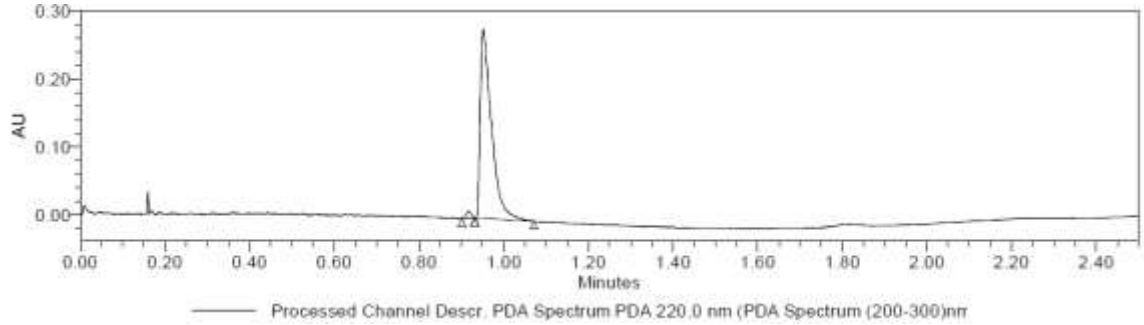
SFC: Enantiomeric excess was determined by SFC analysis (Chiralcel OX column, 5 % of methanol with 0.1% NH_4OH, 4.0 mL/min, 40 °C, 220 nm), t_{major} = 0.95 min, t_{minor} = 0.92 min; ee = 97 %.


B (m)
7.20
A (m)
7.28
C (m)
5.85
D (m)
5.11
H (m)
3.02
G (ddd)
3.11
J (tdd)
2.16
I (tt)
2.47
L (m)
1.80
K (d)
1.20
f1 (ppm)


f1 (ppm)

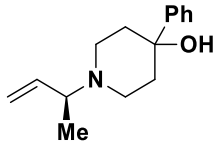


	Ret. Time	% Area
1	0.892	51.54
2	0.955	48.46



	Ret. Time	% Area
1	0.918	1.60
2	0.952	98.40

(*S*)-1-(But-3-en-2-yl)-4-phenylpiperidin-4-ol (5.3v)



Procedures

The allylic acetate (22.8 mg, 0.2 mmol, 100 mol%) and the 4-hydroxy-4-phenylpiperidine (35.4 mg, 0.2 mmol, 100 mol%). were subject to standard reaction conditions (90 °C, DME) with 5 mol% catalyst (0.01 mmol, 11.0 mg) and 300 mol% Cs_2CO_3 (0.6 mmol, 391 mg). The title compound was obtained in 94% yield (43.5 mg, 0.19 mmol) as a light yellow solid after isolation by flash column chromatography (SiO2, dichloromethane: methanol = 30:1–10:1).

TLC (SiO_2) R_f = 0.12 (dichloromethane: methanol = 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 – 7.50 (m, 2H), 7.35 (t, *J* = 7.7 Hz, 2H), 7.27 (m, 1H), 5.90 (d, *J* = 9.8 Hz, 1H), 5.24 – 5.13 (m, 2H), 3.17 (s, 1H), 2.96 (dd, *J* = 37.0, 11.4 Hz, 2H), 2.68 (d, *J* = 12.7 Hz, 2H), 2.31 (s, 2H), 1.83 – 1.77 (m, 2H), 1.30 (d, *J* = 6.6 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 128.4, 127.2, 124.5, 71.1, 63.4, 46.0, 45.6, 17.0 ppm.

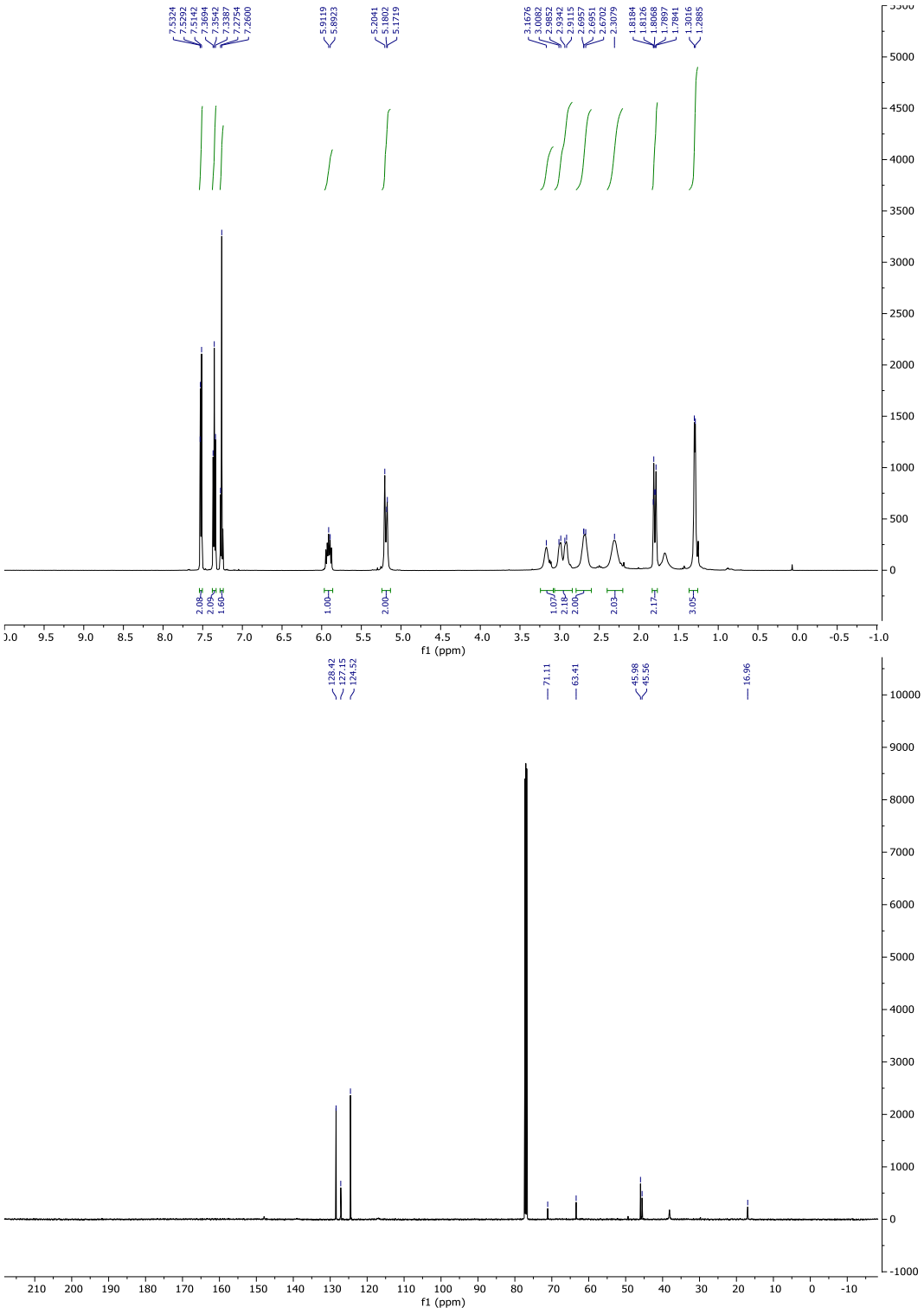
HRMS (ESI) m/z: [(M+H)+] calcd for $C_{15}H_{22}NO$ 231.3390, found 232.1700.

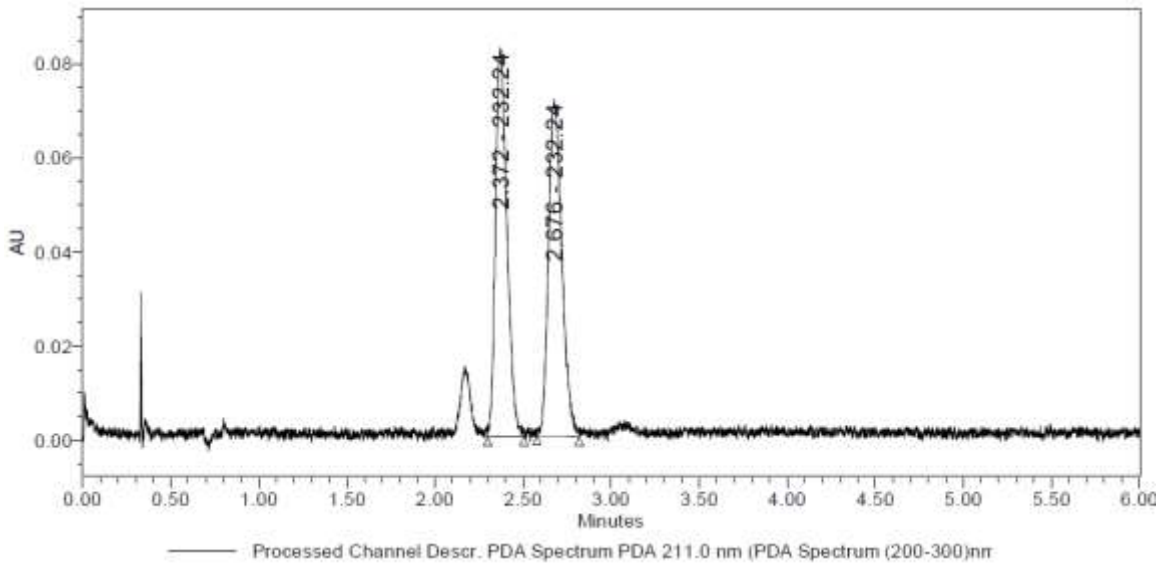
FTIR (neat): 3262, 2811, 1446, 1221, 921, 768, 699 cm^{-1}.

Melting Point: 96.7 °C

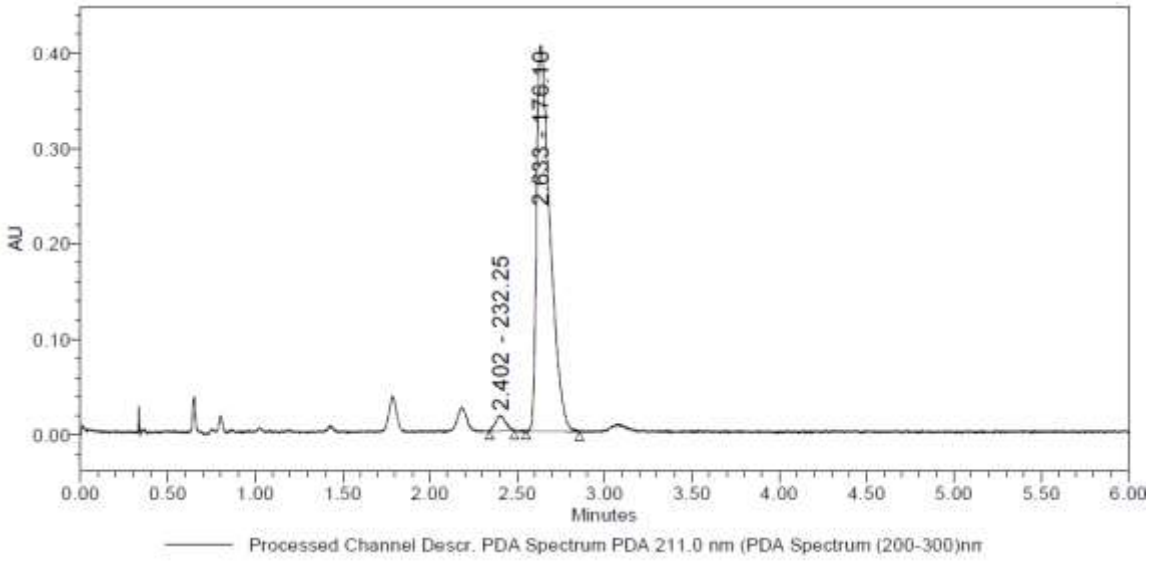
$[\alpha]_D^{28}$: + 32.0 (c = 0.5, $CHCl_3$).

HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralcel OX column, 15% methanol with 0.1% NH_4OH, t_{major} = 2.633 min, t_{minor} = 2.402 min; ee = 94 %.


7.5324
7.5292
7.5142
7.3694
7.3542
7.3387
7.2754
7.2600
5.9119
5.8923
5.2041
5.1802
5.1719
3.1676
3.0082
2.9852
2.9342
2.9115
2.6957
2.6951
2.6702
2.3079
1.8184
1.8126
1.8068
1.7897
1.7841
1.3016
1.2885
2.08
2.09
1.60
1.00
2.00
1.07
2.18
2.00
2.03
2.17
3.05
f1 (ppm)
128.42
127.15
124.52
71.11
63.41
45.98
45.56
16.96
f1 (ppm)

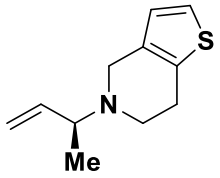


	Ret. Time	% Area
1	2.372	49.96
2	2.676	50.04



	Ret. Time	% Area
1	2.402	2.82
2	2.633	97.18

(*S*)-5-(But-3-en-2-yl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (5.3w)



Procedures

The crotyl acetate (22.8 mg, 0.2 mmol, 100 mol%) and 4,5,6,7-tetrahydrothieno[3,2-c]pyridine (27.8 mg, 0.2 mmol, 100 mol%) were subject to standard reaction conditions (DME). The title compound was obtained in 98% yield (37.7 mg, 0.20 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane: ethyl acetate = 5:1).

TLC (SiO_2) R_f = 0.55 (hexane: ethyl acetate = 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.06 (d, J = 5.1 Hz, 1H), 6.72 (d, J = 5.1 Hz, 1H), 5.89 (ddd, J = 17.8, 10.3, 7.6 Hz, 1H), 5.19 – 5.11 (m, 2H), 3.72 – 3.57 (m, 2H), 3.19 (p, J = 6.7 Hz, 1H), 2.93 (dt, J = 10.6, 5.7 Hz, 1H), 2.87 (t, J = 5.3 Hz, 2H), 2.79 – 2.72 (m, 1H), 1.26 (d, J = 6.6 Hz, 3H) ppm.

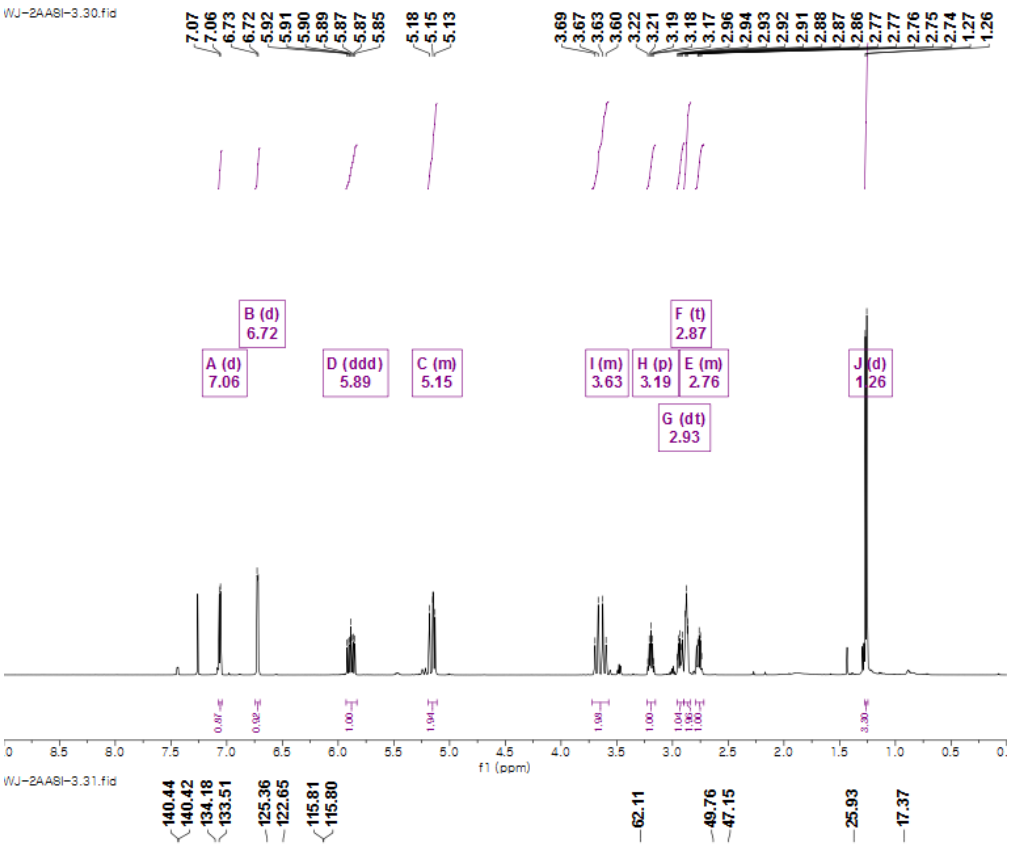
^{13}C NMR (126 MHz, $CDCl_3$): δ 140.4, 140.4, 134.2, 133.5, 125.4, 122.7, 115.8, 115.8, 62.1, 49.8, 47.2, 25.9, 17.4 ppm.

HRMS (ESI) m/z: [(M+H)+] calcd for $C_{11}H_{16}NS$ 194.0998, found 194.1003.

FTIR (neat): 661, 830, 1049, 1235, 1419, 1972, 2808, 3068 cm^{-1}.

$[\alpha]_D^{28}$: -88 (c = 0.5, $CHCl_3$).

SFC: Enantiomeric excess was determined by SFC analysis (Chiralpak IH column, 20 % of methanol with 0.1 % NH_4OH, 2 mL/min, 254 nm), t_{major} = 1.29 min, t_{minor} = 1.13 min; ee = 98 %.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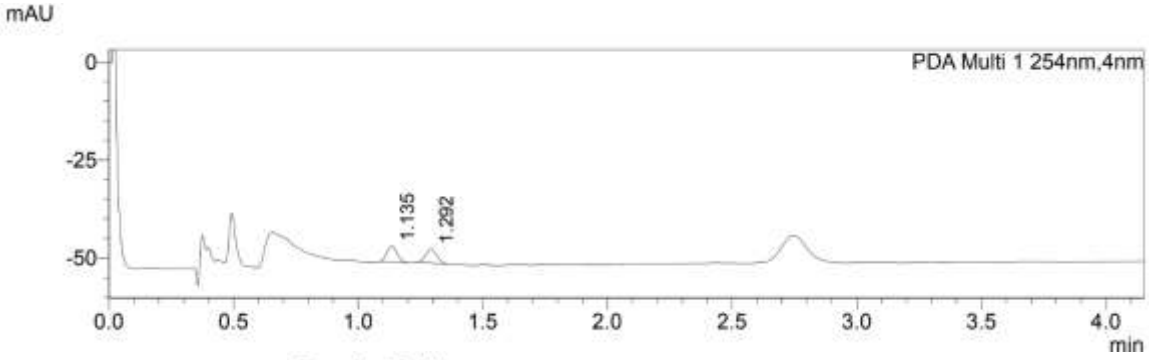
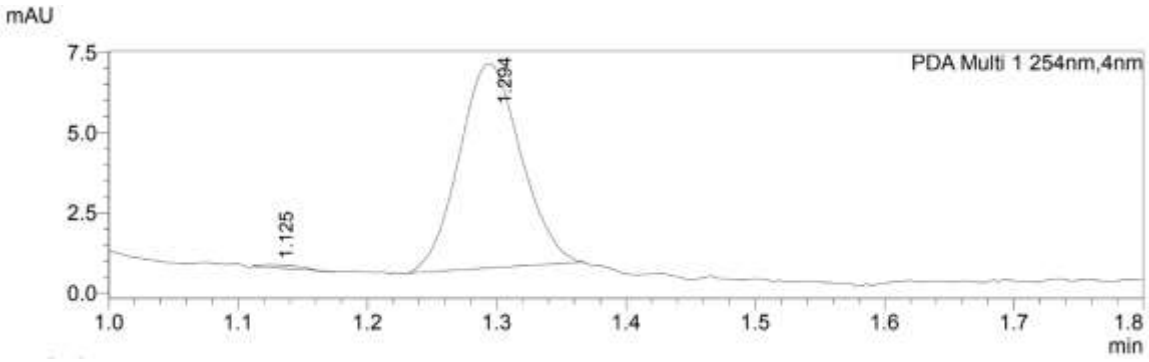
7.06
6.73
6.72
5.92
5.91
5.90
5.89
5.87
5.87
5.85
5.18
5.15
5.13
3.69
3.67
3.63
3.60
3.22
3.21
3.19
3.18
3.17
2.96
2.94
2.93
2.92
2.91
2.88
2.87
2.86
2.77
2.77
2.76
2.75
2.74
1.27
1.26
B (d)
6.72
A (d)
7.06
D (ddd)
5.89
C (m)
5.15
F (t)
2.87
I (m)
3.63
H (p)
3.19
E (m)
2.76
G (dt)
2.93
J (d)
1.26
0.87
0.92
1.00
1.94
1.98
1.00
1.01
1.90
1.00
3.30
f1 (ppm)
WJ-2AABI-3.31.fid
140.44
140.42
134.18
133.51
125.36
122.65
115.81
115.80
62.11
49.76
47.15
25.93
17.37
f1 (ppm)



Peak Table
PDA Ch1 254nm

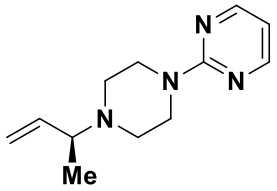
Peak#	Ret. Time	Area%
1	1.135	50.99
2	1.292	49.01
Total		100.00



Peak Table
PDA Ch1 254nm

Peak#	Ret. Time	Area%
1	1.125	0.88
2	1.294	99.12
Total		100.00

(*S*)-2-(4-(But-3-en-2-yl)piperazin-1-yl)pyrimidine (5.3x)



Procedures

The crotyl acetate (22.8 mg, 0.2 mmol, 100 mol%) and *N*-(2-pyridinyl)piperazine (32.8 mg, 0.2 mmol, 100 mol%) were subject to standard reaction conditions (DME). The title compound was obtained in 94% yield (41.2 mg, 0.19 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, hexane: acetone = 5:1).

TLC (SiO_2) R_f = 0.70 (acetone).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27 (d, J = 4.7 Hz, 2H), 6.44 (t, J = 4.7 Hz, 1H), 5.79 (ddd, J = 17.7, 9.8, 7.8 Hz, 1H), 5.12 – 5.05 (m, 2H), 3.80 (t, J = 5.1 Hz, 4H), 2.96 (p, J = 6.7 Hz, 1H), 2.55 (dtd, J = 16.5, 11.2, 5.1 Hz, 4H), 1.17 (d, J = 6.6 Hz, 3H) ppm.

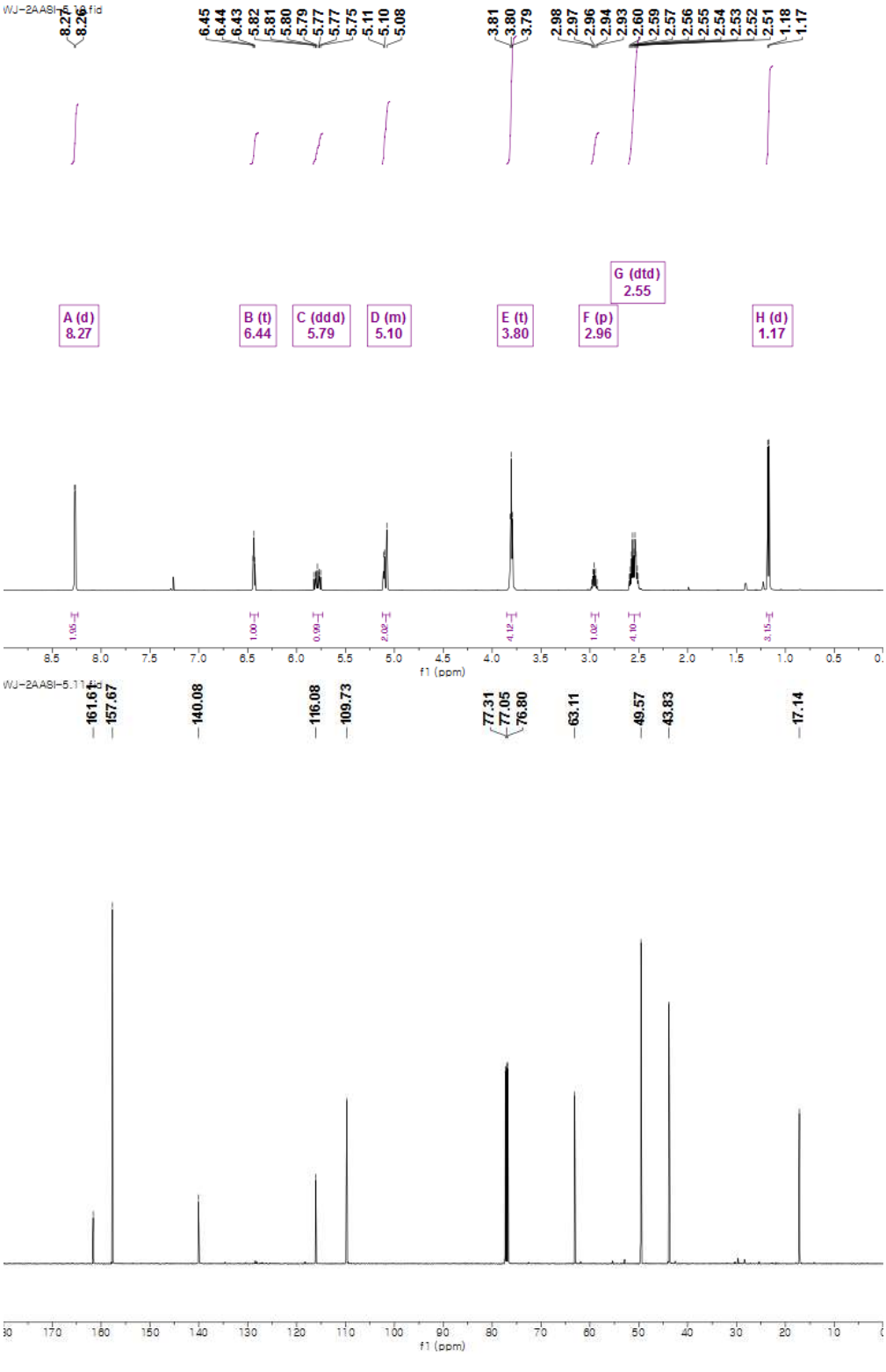
^{13}C NMR (126 MHz, $CDCl_3$): δ 161.6, 157.7, 140.1, 116.1, 109.7, 77.3, 77.1, 76.8, 63.1, 49.6, 43.8, 17.1 ppm.

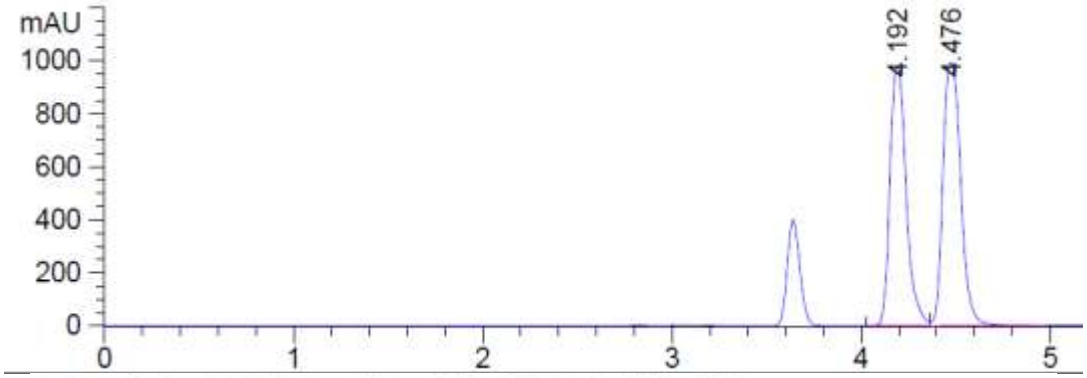
HRMS (ESI) m/z: [(M+H)+] calcd for $C_{12}H_{19}N_4$ 219.1604, found 219.1603.

FTIR (neat): 684, 918, 1135, 1306, 1496, 1583, 2971 cm^{-1}.

$[\alpha]_D^{28}$: - 19 (c = 1.0, $CHCl_3$).

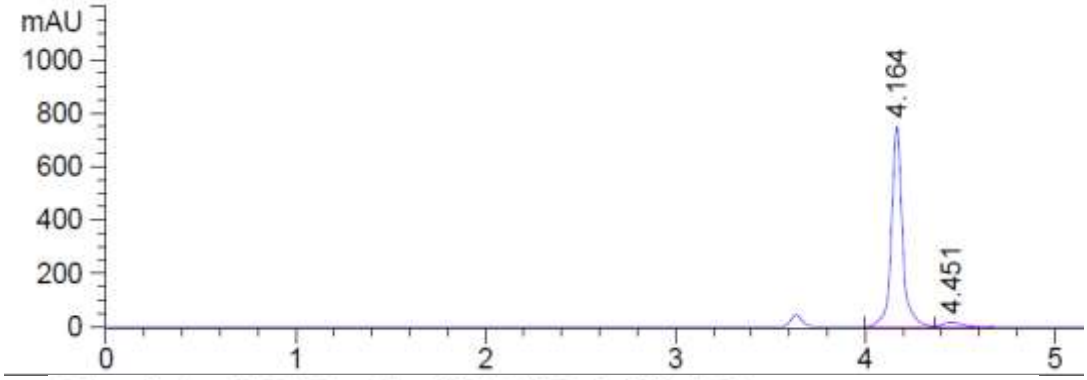
HPLC: Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H column, hexane: 2-PrOH = 85:15, 1.0 mL/min, 280 nm), t_{major} = 17.8 min, t_{minor} = 26.4 min; ee = 93 %.


8.27
8.26
6.45
6.44
6.43
5.82
5.81
5.80
5.79
5.77
5.77
5.75
5.11
5.10
5.08
3.81
3.80
3.79
2.98
2.97
2.96
2.94
2.93
2.60
2.59
2.57
2.56
2.55
2.54
2.53
2.52
2.51
1.18
1.17
A (d) 8.27
B (t) 6.44
C (ddd) 5.79
D (m) 5.10
E (t) 3.80
F (p) 2.96
G (dtd) 2.55
H (d) 1.17
f1 (ppm)
161.61
157.67
140.08
116.08
109.73
77.31
77.05
76.80
63.11
49.57
43.83
17.14
f1 (ppm)



Signal 4: DAD1 E, Sig=280,16 Ref=360,100

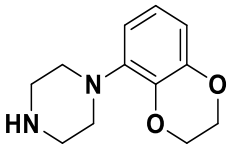
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.192	BV	0.0949	5792.11328	980.34021	47.3119
2	4.476	VB	0.1038	6450.28418	992.53748	52.6881
Totals :				1.22424e4	1972.87769	



Signal 4: DAD1 E, Sig=280,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.164	BV	0.0605	3003.84912	753.80725	96.5513
2	4.451	VB	0.0959	107.29356	16.94050	3.4487
Totals :				3111.14268	770.74775	

1-(2,3-Dihydrobenzo[b][1,4]dioxin-5-yl)piperazine (5.2q)



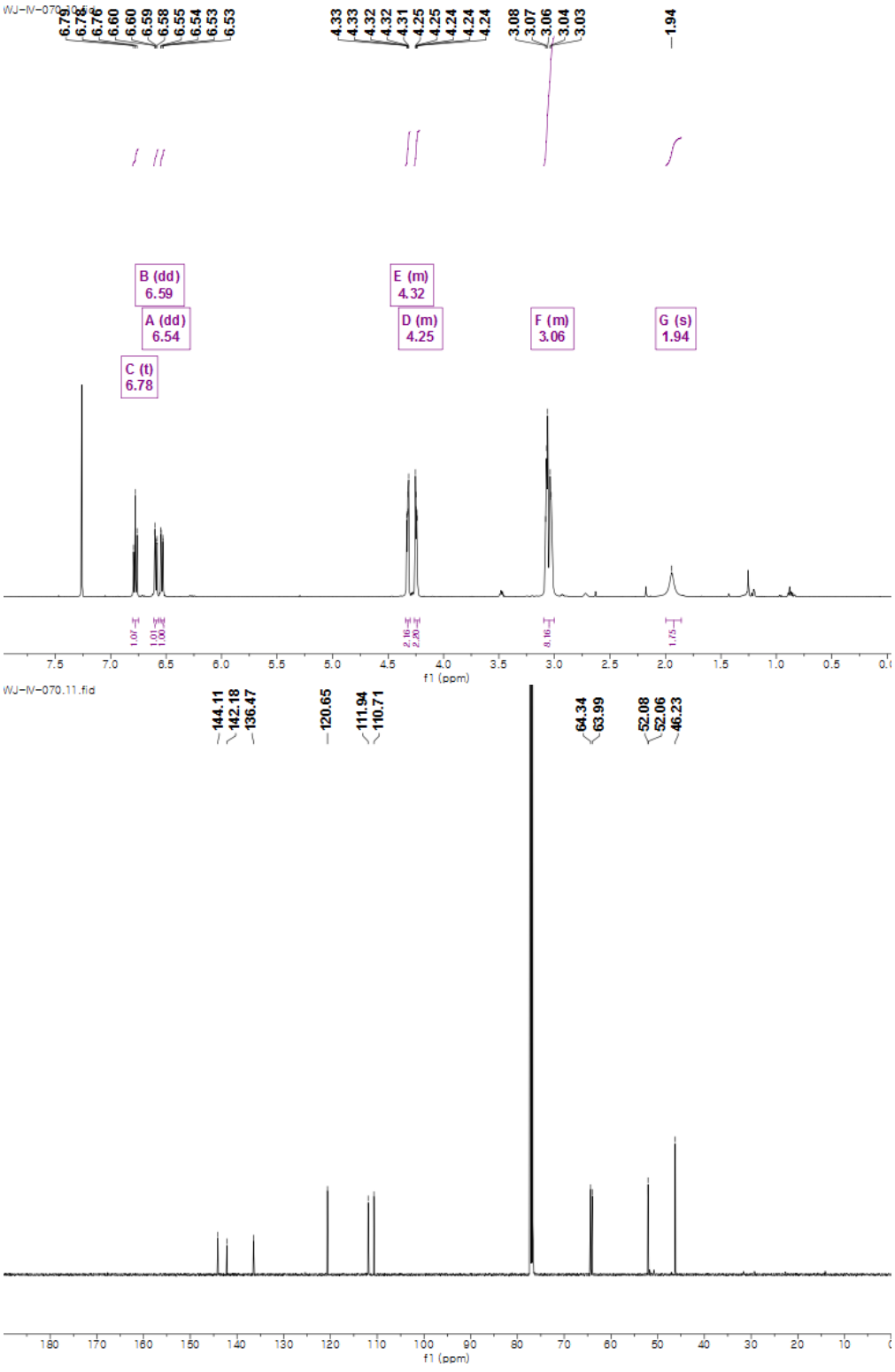
Procedures

A round-bottom flask equipped with a magnetic stir bar was charged with 1,4-benzodioxan-5-amine (1.16 g, 11.0 mmol, 100 mol%) and bis(2-chloroethyl)amine hydrochloride salt (2.55 g, 14.3 mmol, 130 mol%). Chlorobenzene (36.7 ml, 0.3 M) was added and refluxed overnight. The title compound was obtained in 84% yield (2.0 g, 9.2 mmol) as a purple solid after isolation by flash column chromatography (Al_2O_3, hexane: acetone = 5:1). The title compound is identical in all respects to the reported material.[40]

TLC (Al_2O_3) R_f = 0.55 (dichloromethane: methanol = 10:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.78 (t, J = 8.1 Hz, 1H), 6.59 (dd, J = 8.2, 1.4 Hz, 1H), 6.54 (dd, J = 8.0, 1.4 Hz, 1H), 4.34 – 4.30 (m, 2H), 4.26 – 4.22 (m, 2H), 3.09 – 3.00 (m, 8H), 1.94 (s, 2H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 144.1, 142.2, 136.5, 120.7, 111.9, 110.7, 64.3, 64.0, 52.1, 52.1, 46.2 ppm.


6.79
6.78
6.76
6.60
6.60
6.59
6.58
6.55
6.54
6.53
6.53
4.33
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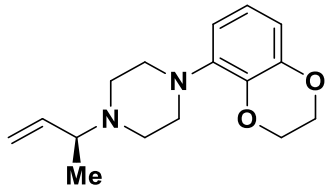
4.32
4.32
4.31
4.25
4.25
4.24
4.24
4.24
3.08
3.07
3.06
3.04
3.03
1.94
B (dd)
6.59
A (dd)
6.54
C (t)
6.78
E (m)
4.32
D (m)
4.25
F (m)
3.06
G (s)
1.94
1.07
1.01
1.00
2.16
2.20
8.16
1.75
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
WJ-IV-070.11.fid
144.11
142.18
136.47
120.65
111.94
110.71
64.34
63.99
52.08
52.06
46.23
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

(*S*)-1-(But-3-en-2-yl)-4-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)piperazine (5.3y)



Procedures

The crotyl acetate (22.8 mg, 0.2 mmol, 100 mol%) and 1-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)piperazine (44.1 mg, 0.2 mmol, 100 mol%) were subject to standard reaction conditions (DME). The title compound was obtained in 97% yield (53.4 mg, 0.19 mmol) as a light yellow oil after isolation by flash column chromatography (Al_2O_3, hexane: acetone = 5:1).

TLC (Al_2O_3) R_f = 0.91 (acetone).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.77 (t, J = 8.1 Hz, 1H), 6.56 (dd, J = 22.1, 8.1 Hz, 2H), 5.84 (ddd, J = 17.7, 10.3, 7.9 Hz, 1H), 5.16 – 5.06 (m, 2H), 4.34 – 4.30 (m, 2H), 4.26 – 4.22 (m, 2H), 3.10 (s, 4H), 2.99 (p, J = 6.9 Hz, 1H), 2.72 (s, 4H), 1.21 (d, J = 6.5 Hz, 3H).

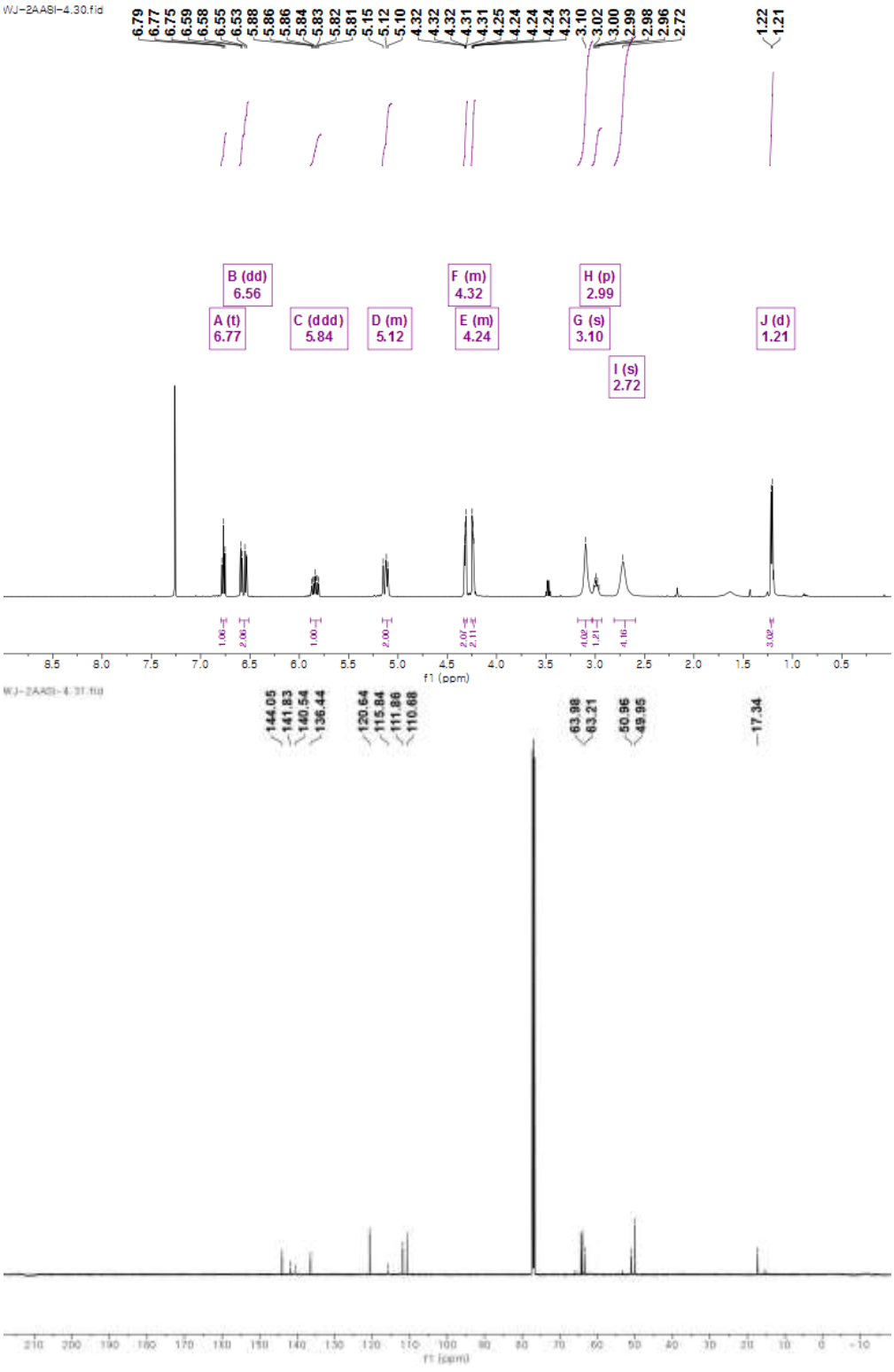
^{13}C NMR (126 MHz, $CDCl_3$): δ 144.1, 141.8, 140.6, 136.4, 120.6, 115.8, 111.9, 110.7, 64.0, 63.2, 51.0, 50.0, 17.3.

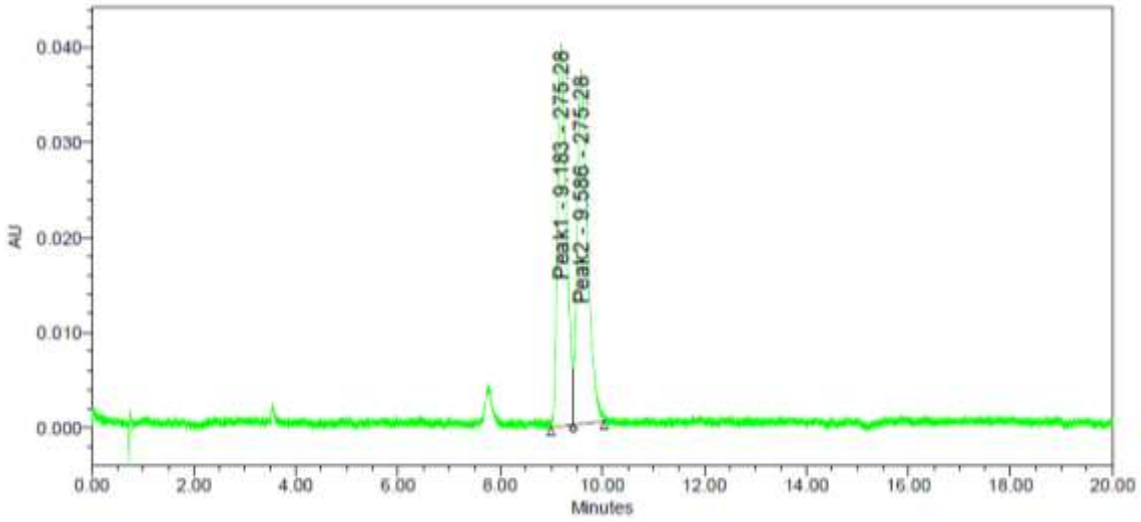
HRMS (ESI) m/z: [(M+H)+] calcd for $C_{16}H_{23}N_2O_2$ 275.1754, found 275.1759.

FTIR (neat): 722, 921, 1103, 1236, 1472, 1972, 2759, 2971 cm^{-1}.

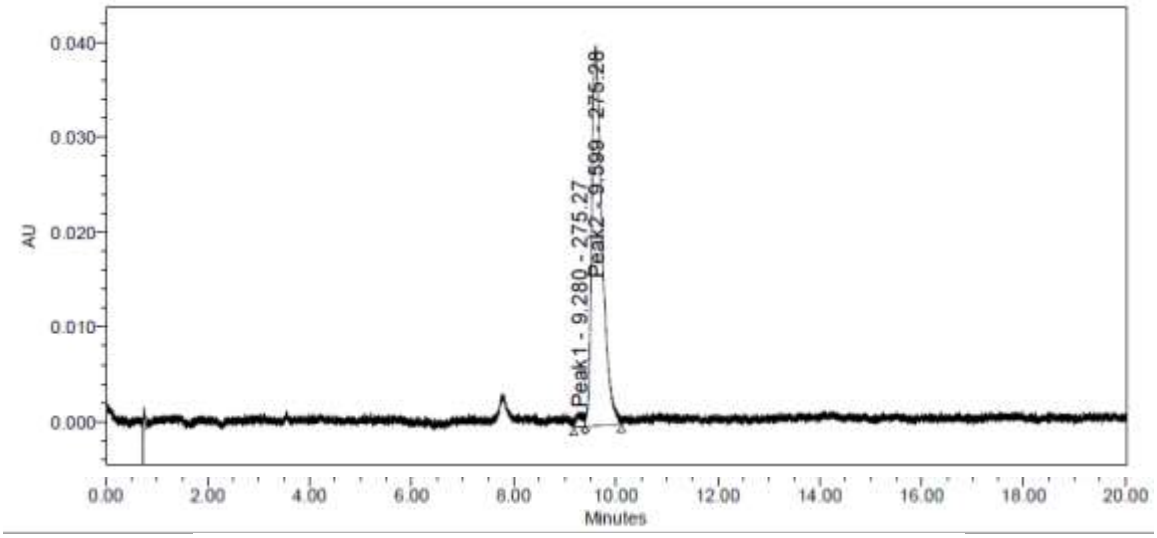
$[\alpha]_D^{28}$: - 55 (c = 0.5, $CHCl_3$).

SFC: Enantiomeric excess was determined by SFC analysis (Chiralcel OX column, 5 % methanol with 0.1% NH_4OH = 95:5, 4.0 mL/min, 40 °C, 220 nm), t_{major} = 9.60 min, t_{minor} = 9.28 min; ee = 95 %.


WJ-2AASI-4.30.fid
6.79 6.77 6.75 6.59 6.58 6.55 6.53 5.88 5.86 5.86 5.84 5.83 5.82 5.81 5.15 5.12 5.10 4.32 4.32 4.32 4.31 4.31 4.25 4.24 4.24 4.24 4.23 3.10 3.02 3.00 2.99 2.98 2.96 2.72 1.22 1.21
B (dd) 6.56
A (t) 6.77
C (ddd) 5.84
D (m) 5.12
F (m) 4.32
E (m) 4.24
H (p) 2.99
G (s) 3.10
I (s) 2.72
J (d) 1.21
f1 (ppm)
144.05 141.83 140.54 136.44 120.64 115.84 111.86 110.68 63.98 63.21 50.96 49.95 17.34
f1 (ppm)

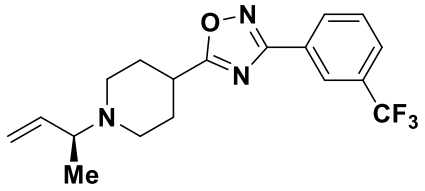


	Peak Name	SampleName	Ret. Time	% Area	Base Peak (m/z)
1	Peak1	WJ-3Y Racemic	9.183	48.80	275.28
2	Peak2	WJ-3Y Racemic	9.586	51.20	275.28



	Peak Name	SampleName	Ret. Time	% Area	Base Peak (m/z)
3	Peak1	WJ-3Y Chiral	9.280	2.34	275.27
4	Peak2	WJ-3Y Chiral	9.599	97.66	275.28

(*S*)-5-(1-(But-3-en-2-yl)piperidin-4-yl)-3-(3-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (5.3z)



Procedures

The crotyl acetate (45.7 mg, 0.4 mmol, 100 mol%) and 5-(piperidin-4-yl)-3-(3-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (118.9 mg, 0.4 mmol, 100 mol%) were subject to standard reaction conditions (50 °C, DME). The title compound was obtained in 99% yield (139.1 mg, 0.40 mmol) as a light yellow oil after isolation by flash column chromatography (SiO_2, heptane: isopropyl acetate = 5:1-1:1).

TLC (SiO_2) R_f = 0.6 (isopropyl acetate).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (tt, J = 1.5, 0.7 Hz, 1H), 8.27 (ddt, J = 7.9, 1.7, 0.8 Hz, 1H), 7.75 (ddd, J = 7.9, 1.7, 0.9 Hz, 1H), 7.63 – 7.58 (m, 1H), 5.82 (dddd, J = 17.6, 9.8, 7.5, 0.7 Hz, 1H), 5.15 – 5.08 (m, 2H), 3.09 – 2.93 (m, 4H), 2.27 (tdd, J = 11.5, 5.6, 2.6 Hz, 2H), 2.20 – 2.11 (m, 2H), 2.08 – 1.94 (m, 2H), 1.19 (dd, J = 6.6, 0.8 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 182.6, 167.2, 140.2, 131.4 (q, J = 32.8 Hz), 130.5, 130.5, 129.4, 127.6 (q, J = 4.0 Hz), 124.4 (q, J = 4.1 Hz), 123.8 (q, J = 272.6 Hz), 115.7, 62.9, 49.1, 49.0, 34.9, 29.8, 29.7, 16.9 ppm.

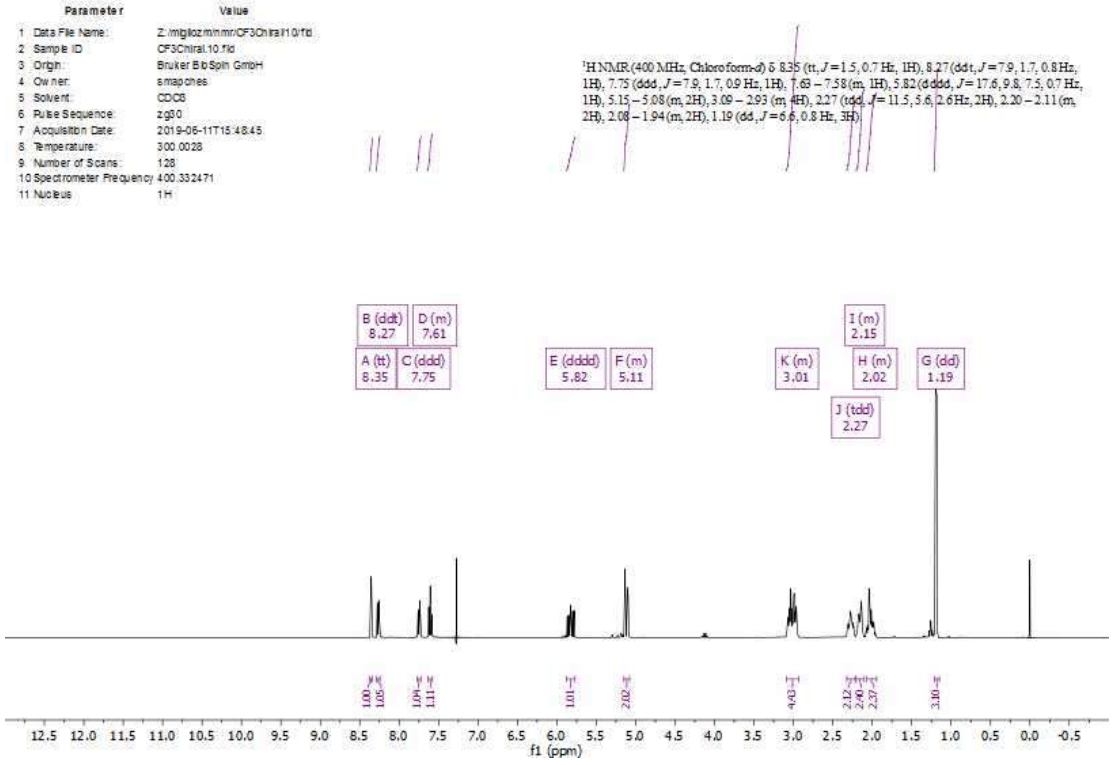
^{19}F NMR (376 MHz, $CDCl_3$): δ - 62.86 ppm.

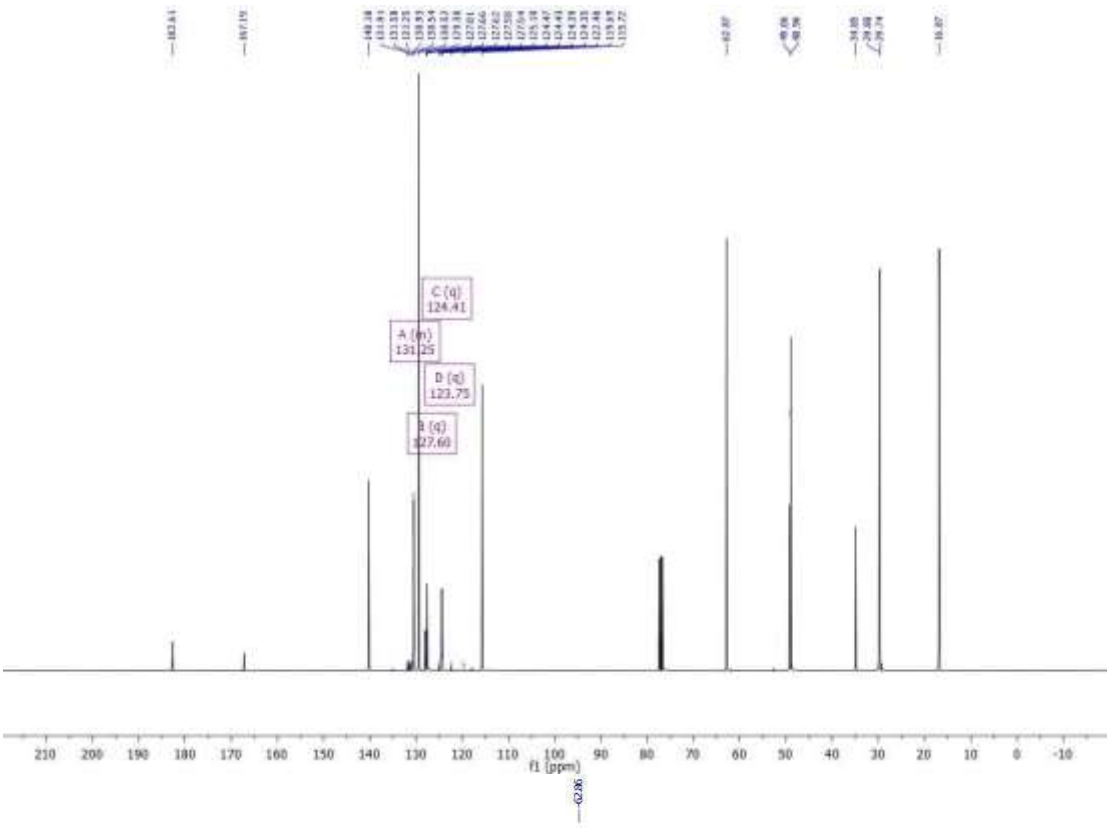
HRMS (ESI) m/z: [(M+H)+] calcd for $C_{18}H_{22}ON_3F_3$ 352.1631, found 352.1629.

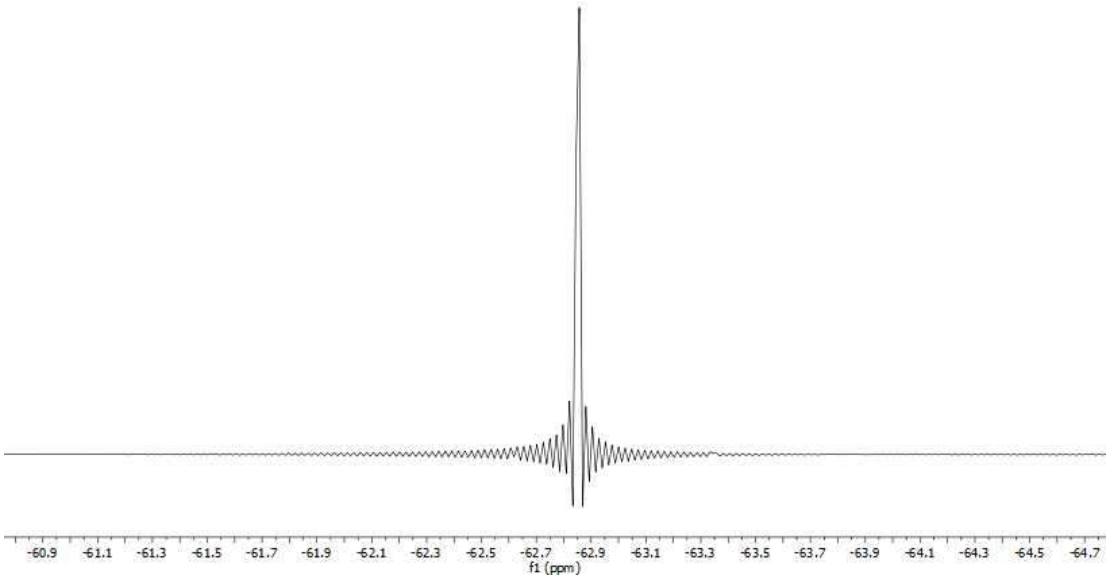
FTIR (neat): 2932, 1570, 1308, 949, 756, 651, 526 cm^{-1}.

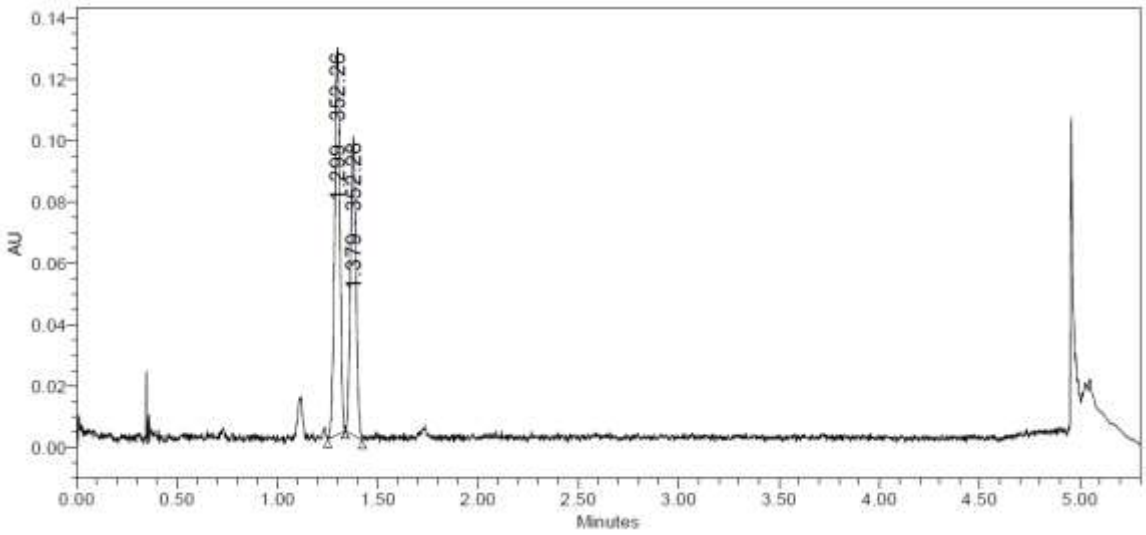
$[\alpha]_D^{28}$: + 11.7 (c = 2.0, methanol).

SFC: Enantiomeric excess was determined by SFC analysis (Chiralcel OX column, methanol with 0.1% NH_4OH = linear gradient over 5 min from 5 to 10 %, 4.0 mL/min, 40 °C, 220 nm), t_{major} = 1.37 min, t_{minor} = 1.30 min; ee = 97 %.

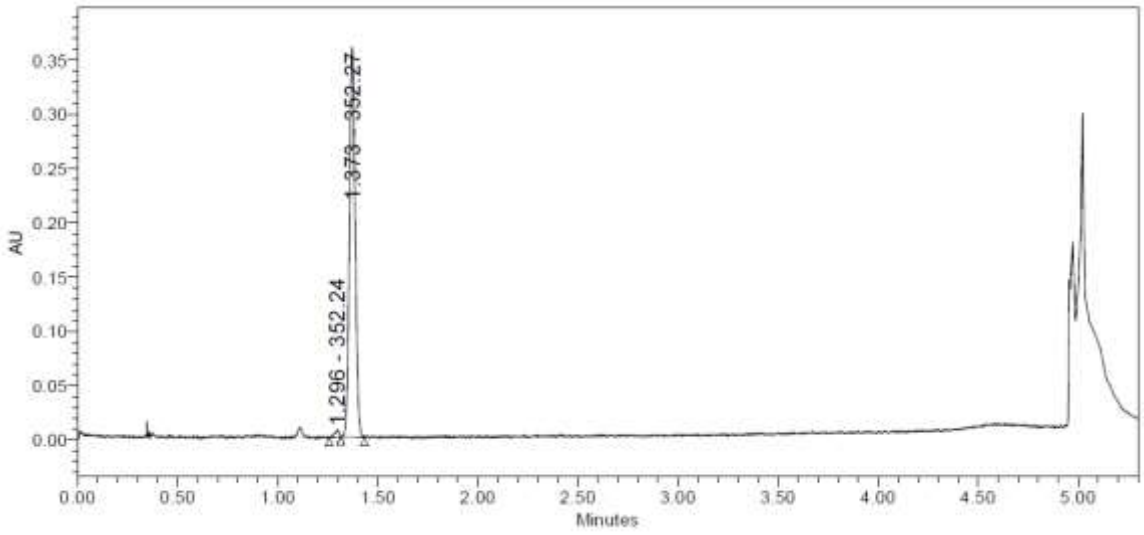



C (q)
124.41
A (m)
131.25
D (q)
123.75
B (q)
127.60
f1 (ppm)


f1 (ppm)

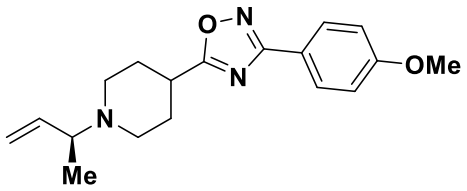


	Ret. Time	% Area
1	1.299	55.53
2	1.379	44.47



	Ret. Time	% Area
1	1.296	1.41
2	1.373	98.59

(*S*)-5-(1-(But-3-en-2-yl)piperidin-4-yl)-3-(4-methoxyphenyl)-1,2,4-oxadiazole (5.3aa)



Procedures

The crotyl acetate (45.7 mg, 0.4 mmol, 100 mol%) and 3-(4-methoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole · HCl salt (118.3 mg, 0.4 mmol, 100 mol%) were subject to standard reaction conditions (50 °C, DME) with 300 mol% of Cs_2CO_3 (391.0 mg, 1.2 mmol). The title compound was obtained in 92% yield (128.7 mg, 0.37 mmol) as a light yellow oil after isolation by flash column chromatography (heptane: isopropyl acetate = 5:1-1:1).

TLC (SiO_2) R_f = 0.55 (isopropyl acetate).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 – 7.97 (m, 2H), 7.00 – 6.94 (m, 2H), 5.87 – 5.76 (m, 1H), 5.14 – 5.06 (m, 2H), 3.08 – 2.89 (m, 4H), 2.30 – 1.91 (m, 7H), 1.18 (dd, J = 6.7, 1.0 Hz, 3H) ppm.

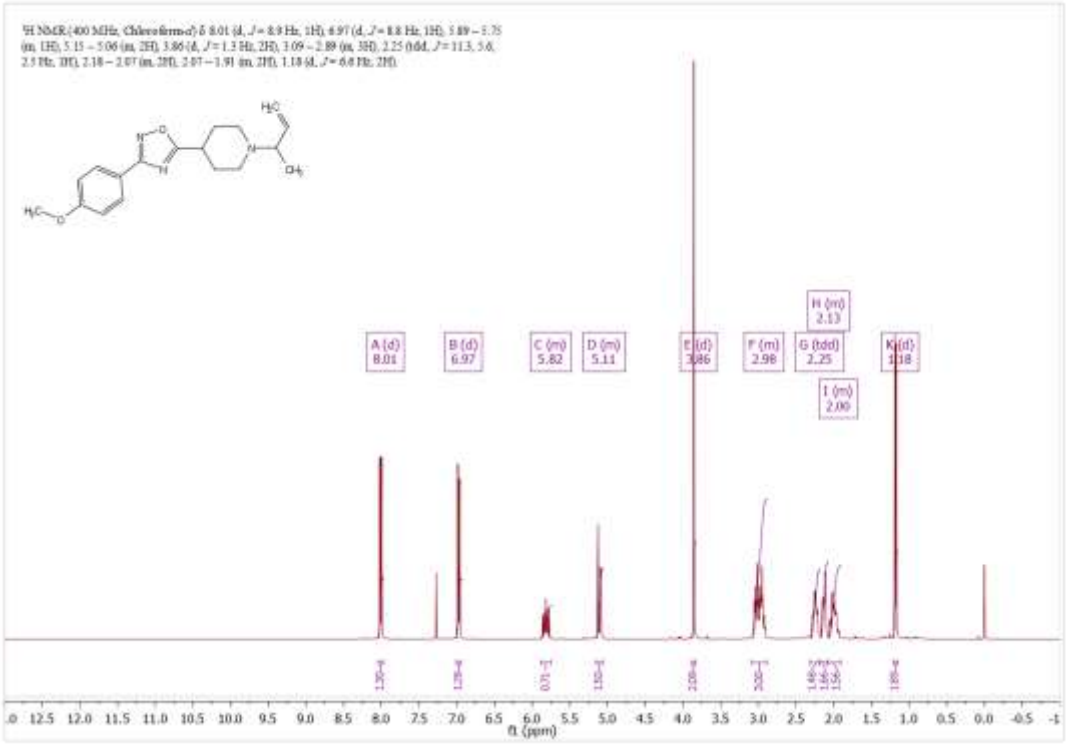
^{13}C NMR (101 MHz, $CDCl_3$): δ 181.8, 167.9, 161.8, 140.3, 129.0, 119.5, 115.7, 114.2, 62.9, 55.4, 49.1, 49.0, 34.8, 29.8, 29.8, 16.9 ppm.

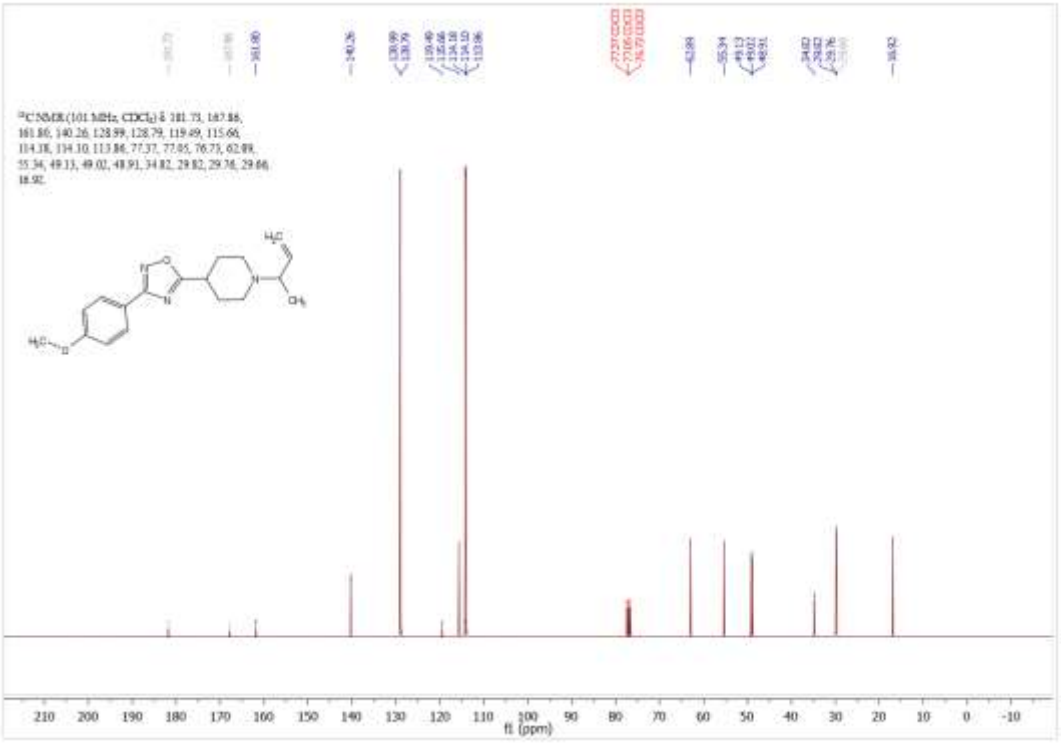
HRMS (ESI) m/z: [(M+H)+] calcd for $C_{18}H_{25}O_2N_3$ 314.1863, found 314.1861.

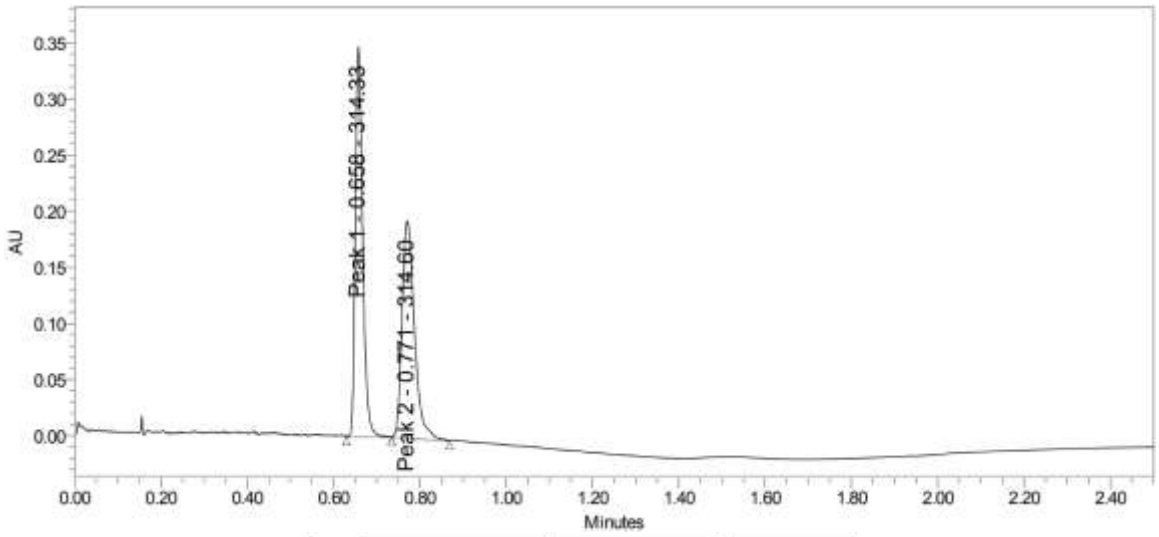
FTIR (neat): 2936, 1565, 1354, 1104, 916, 752, 616, 528 cm^{-1}.

$[\alpha]_D^{28}$: + 6.9 (c = 2.0, methanol).

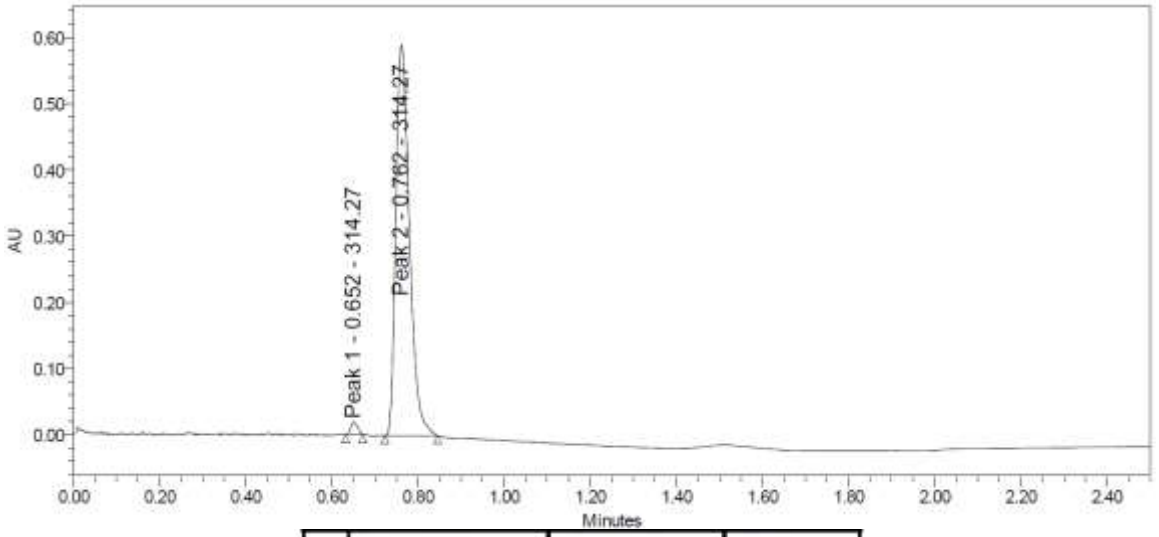
SFC: Enantiomeric excess was determined by SFC analysis (Chiralpak IH column, methanol with 0.1% NH_4OH = linear gradient over 1.8 min from 5 to 60 %, 4.0 mL/min, 40 °C, 220 nm), t_{major} = 0.76 min, t_{minor} = 0.65 min; ee = 97 %.


A (d) 8.01
B (d) 6.97
C (m) 5.82
D (m) 5.11
E (d) 3.86
F (m) 2.98
G (tdd) 2.25
H (m) 2.13
I (m) 2.00
K (d) 1.18
f1 (ppm)


f1 (ppm)

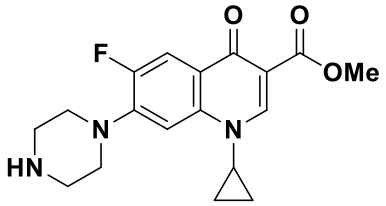


	Peak Name	Ret. Time	% Area
1	Peak 1	0.658	51.72
2	Peak 2	0.771	48.28



	Peak Name	Ret. Time	% Area
1	Peak 1	0.652	1.61
2	Peak 2	0.762	98.39

Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate (5.2t)

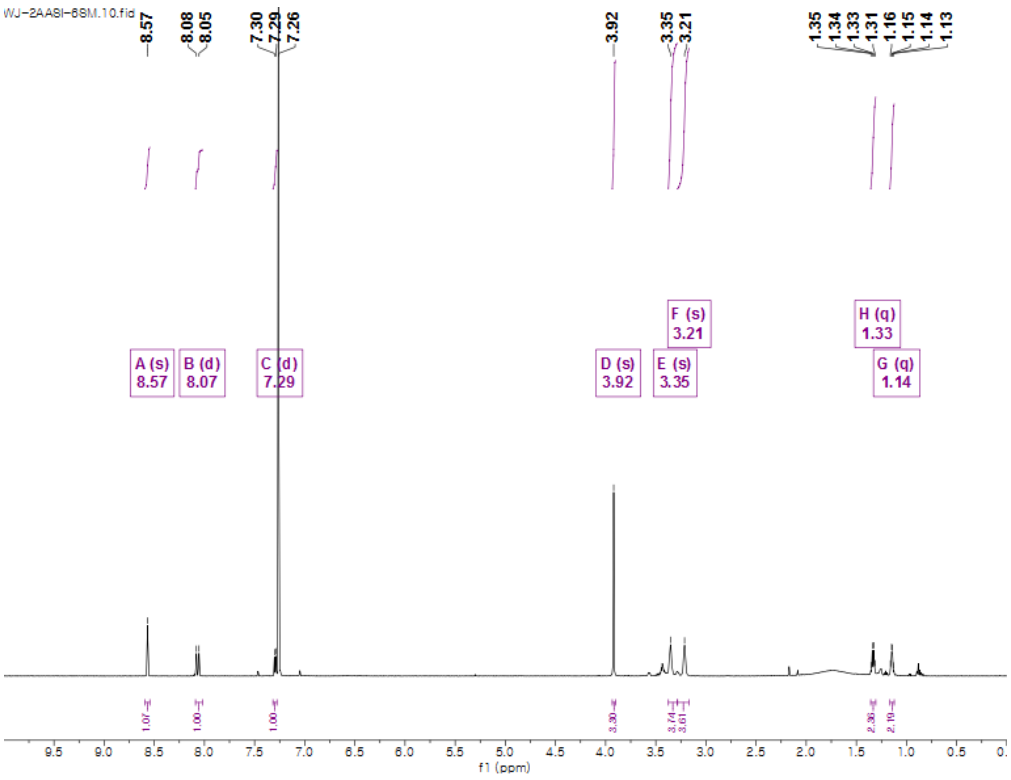


Procedures

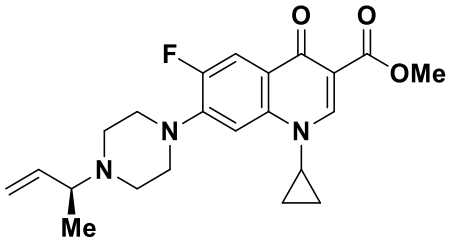
A round-bottom flask equipped with a magnetic stir bar was charged with Ciprofloxacin (1.99 mg, 6.0 mmol, 100 mol%), sulfuric acid (3.2 ml, 60 mmol, 1000 mol%) and methanol (75.0 ml, 0.08 M) and refluxed overnight. After reaching ambient temperature, the solvent was removed under reduced pressure. Then the crude mixture was transferred to a separatory funnel and sat. $NaHCO_3$ was added. The mixture was extracted with dichloromethane and washed with water, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The title compound was obtained in 97% yield (2.0 g, 5.8 mmol) as a light yellow solid after isolation by flash column chromatography (Al_2O_3, dichloromethane: methanol = 10:1). The title compound is identical in all respects to the reported material.[41]

TLC (AlO_2) R_f = 0.67 (dichloromethane: methanol = 10:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.57 (s, 1H), 8.07 (d, J = 13.1 Hz, 1H), 7.29 (d, J = 7.1 Hz, 1H), 3.92 (s, 3H), 3.35 (s, 4H), 3.21 (s, 4H), 1.33 (q, J = 6.8 Hz, 2H), 1.14 (q, J = 6.8, 6.3 Hz, 2H) ppm.


WJ-2AASI-6SM.10.fid
8.57
8.08
8.05
7.30
7.29
7.26
3.92
3.35
3.21
1.35
1.34
1.33
1.31
1.16
1.15
1.14
1.13
A (s) 8.57
B (d) 8.07
C (d) 7.29
D (s) 3.92
E (s) 3.35
F (s) 3.21
G (q) 1.14
H (q) 1.33
f1 (ppm)

Methyl (*S*)-7-(4-(but-3-en-2-yl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (5.3ab)



Procedures

The crotyl acetate (22.8 mg, 0.2 mmol, 100 mol%) and methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate (69.1 mg, 0.2 mmol, 100 mol%) were subject to standard reaction conditions at 80 °C in DME (0.5 M, 0.4 ml). The title compound was obtained in 90% yield (71.7 mg, 0.18 mmol) as a light yellow oil after isolation by flash column chromatography (Al_2O_3, hexane: acetone = 5:1).

TLC (SiO_2) R_f = 0.27 (acetone).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.44 (s, 1H), 7.90 (d, J = 13.4 Hz, 1H), 7.20 (d, J = 7.0 Hz, 1H), 5.79 (ddd, J = 17.0, 10.4, 7.8 Hz, 1H), 5.16 – 5.09 (m, 2H), 3.85 (s, 3H), 3.40 (tt, J = 7.1, 3.9 Hz, 1H), 3.24 (t, J = 4.9 Hz, 4H), 3.00 (p, J = 6.8 Hz, 1H), 2.71 (dtd, J = 16.5, 11.3, 5.5 Hz, 3H), 1.27 (d, J = 6.8 Hz, 2H), 1.19 (d, J = 6.6 Hz, 3H), 1.12 – 1.07 (m, 2H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 173.0 (d, J = 2.2 Hz), 166.3, 154.4, 152.4, 148.3, 144.6 (d, J = 10.7 Hz), 139.8, 138.0, 122.8 (d, J = 7.0 Hz), 116.3, 113.0 (d, J = 22.9 Hz), 109.8, 104.8 (d, J = 3.1 Hz), 63.0, 52.0, 50.1 (d, J = 4.4 Hz), 49.4, 34.5, 17.1, 8.1 ppm.

^{19}F NMR (471 MHz, $CDCl_3$): δ -123.49 (dd, J = 13.1, 7.0 Hz) ppm.

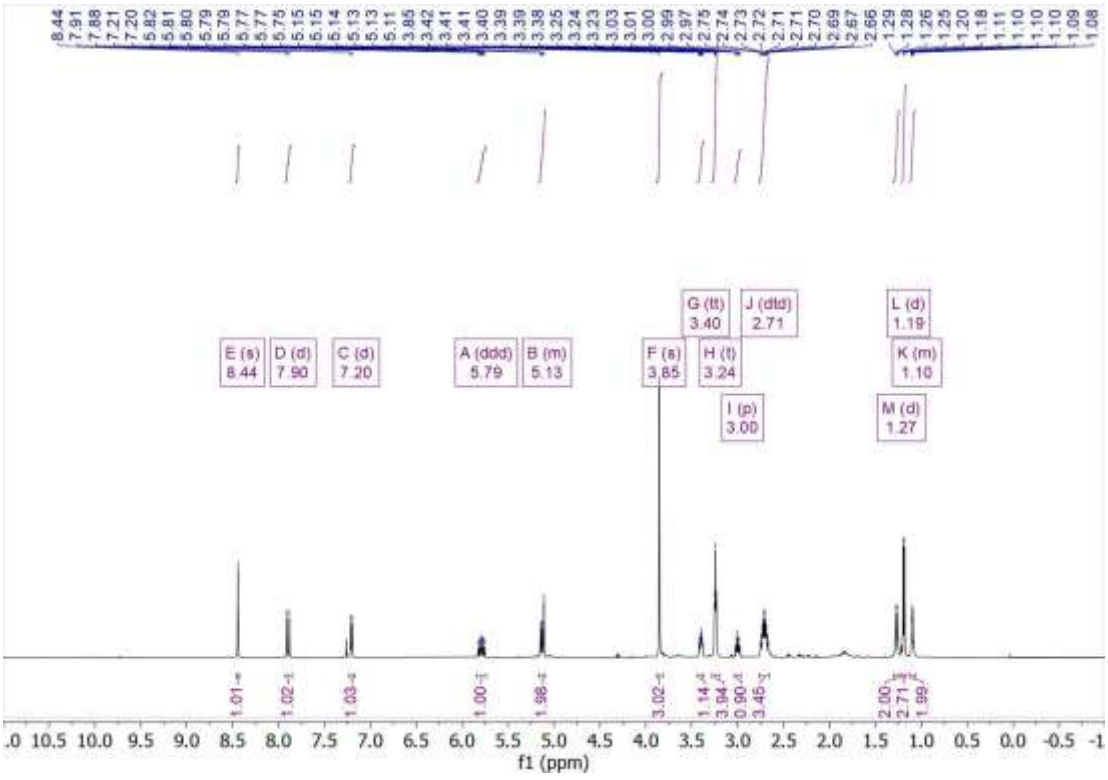
HRMS (ESI) m/z: [(M+H)+] calcd for $C_{22}H_{27}FN_3O_3$ 400.2031, found 400.2036.

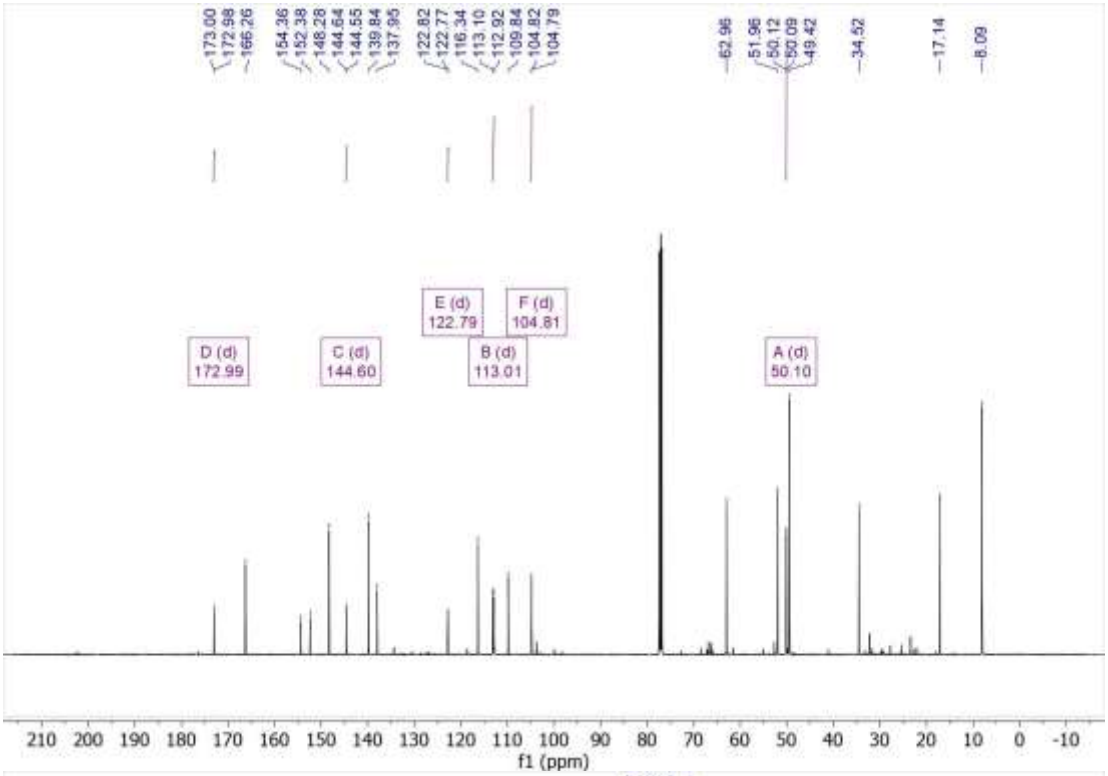
FTIR (neat): 662, 899, 1316, 1585, 1721, 2830, 2987 cm^{-1}.

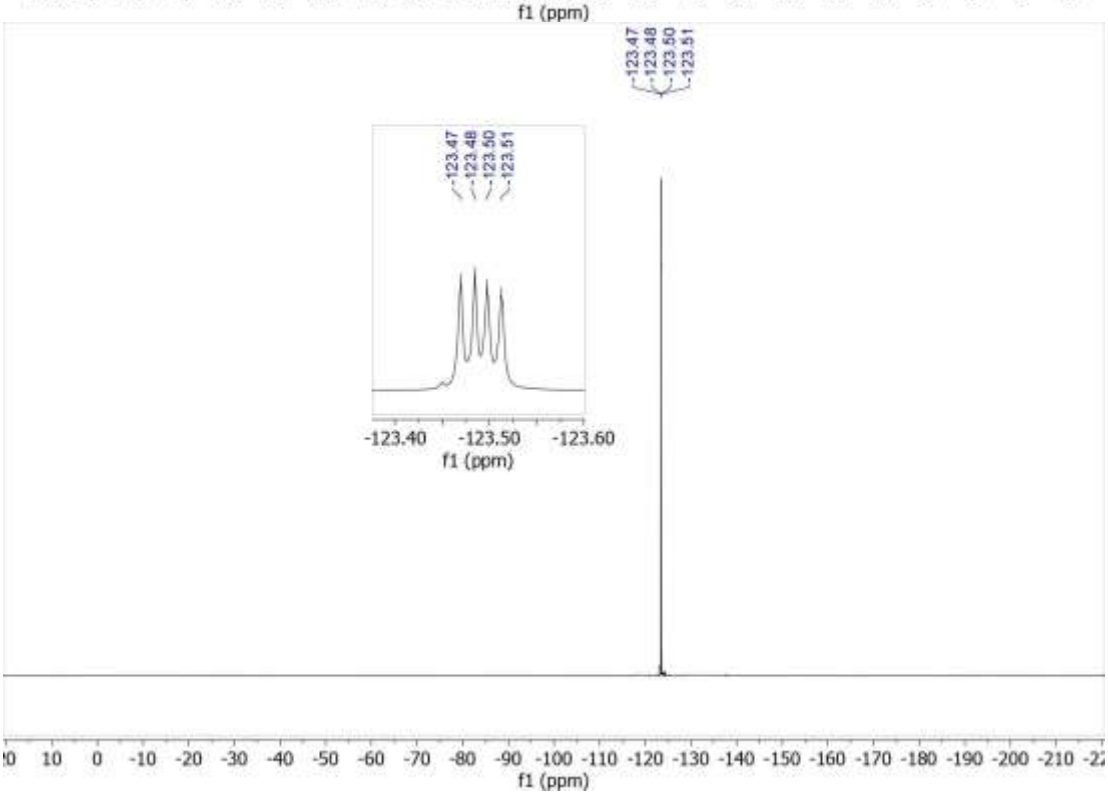
Melting Point: 189 - 192 °C

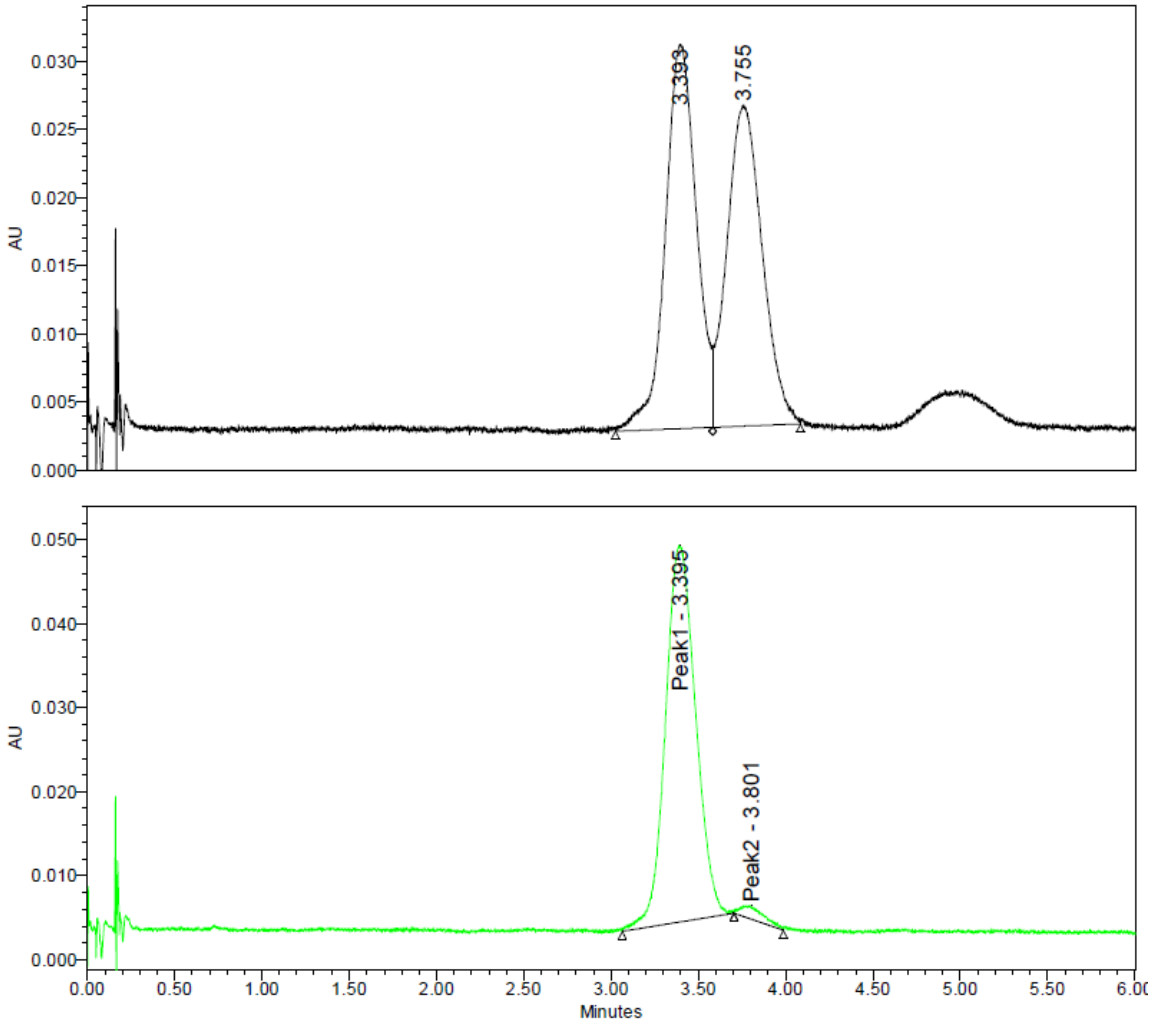
$[\alpha]_D^{28}$: - 100 (c = 1.0, $CHCl_3$).

SFC: Enantiomeric excess was determined by SFC analysis (Chiralpak IG column, 25 % of methanol with 20 nM ammonium formate, 4.0 mL/min, 280 nm), t_{major} = 3.40 min, t_{minor} = 3.80 min; ee = 95 %.




173.00
172.98
166.26
154.36
152.38
148.28
144.64
144.55
139.84
137.95
122.82
122.77
116.34
113.10
112.92
109.84
104.82
104.79
62.96
51.96
50.12
50.09
49.42
34.52
17.14
8.09
D (d)
172.99
C (d)
144.60
E (d)
122.79
F (d)
104.81
B (d)
113.01
A (d)
50.10
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)


123.47
123.48
123.50
123.51
-123.40
-123.50
-123.60
f1 (ppm)
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

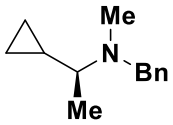


	Ret. Time	% Area
1	3.800	48.92
2	4.253	51.08

	Peak Name	SampleName	Ret. Time	% Area
1	Peak1	69A 0.3mg/ml	3.395	97.35
2	Peak2	69A 0.3mg/ml	3.801	2.65

5.5.5. Synthesis and Spectral Data for Adducts 5.4a, 5.4g, 5.5g and 5.6g

(*S*)-*N*-Benzyl-1-cyclopropyl-*N*-methylethan-1-amine (5.4a)



Procedures

A round-bottom flask equipped with a magnetic stir bar was charged with argon. Diethyl zinc solution (1.0 M in hexane, 0.4 mL, 0.4 mmol, 200 mol%) was added at 0 °C, followed by diiodomethane (65 µL, 0.8 mmol, 400 mol%) and stirred for 15 min at the same temperature. A solution of *N*-benzyl-*N*-methylbuten amine (**5.3a**, 35.1 mg, 0.2 mmol, 100 mol%) and trifluoroacetic acid (31 µL, 0.4 mmol, 200 mol%) in dichloromethane (0.5 M, 0.4 mL) was added to the prepared reaction mixture at 0 °C. The mixture was stirred overnight at room temperature. The solution was transferred to a separatory funnel. Saturated $NaHCO_3$ aqueous solution was added to the reaction mixture and extracted with dichloromethane three times. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting oily residue was subjected to flash column chromatography (SiO_2, hexane: ethyl acetate = 1:1) to give the title compound in 69% yield (26.0 mg, 0.14 mmol) as a light yellow oil.

TLC (SiO_2) R_f = 0.15 (hexane: ethyl acetate = 2:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (d, J = 7.5 Hz, 2H), 7.31 (t, J = 7.5 Hz, 2H), 7.23 (t, J = 7.2 Hz, 1H), 3.65 (s, 2H), 2.27 (s, 3H), 1.96 (dt, J = 13.2, 6.6 Hz, 1H), 1.14 (d, J = 6.6

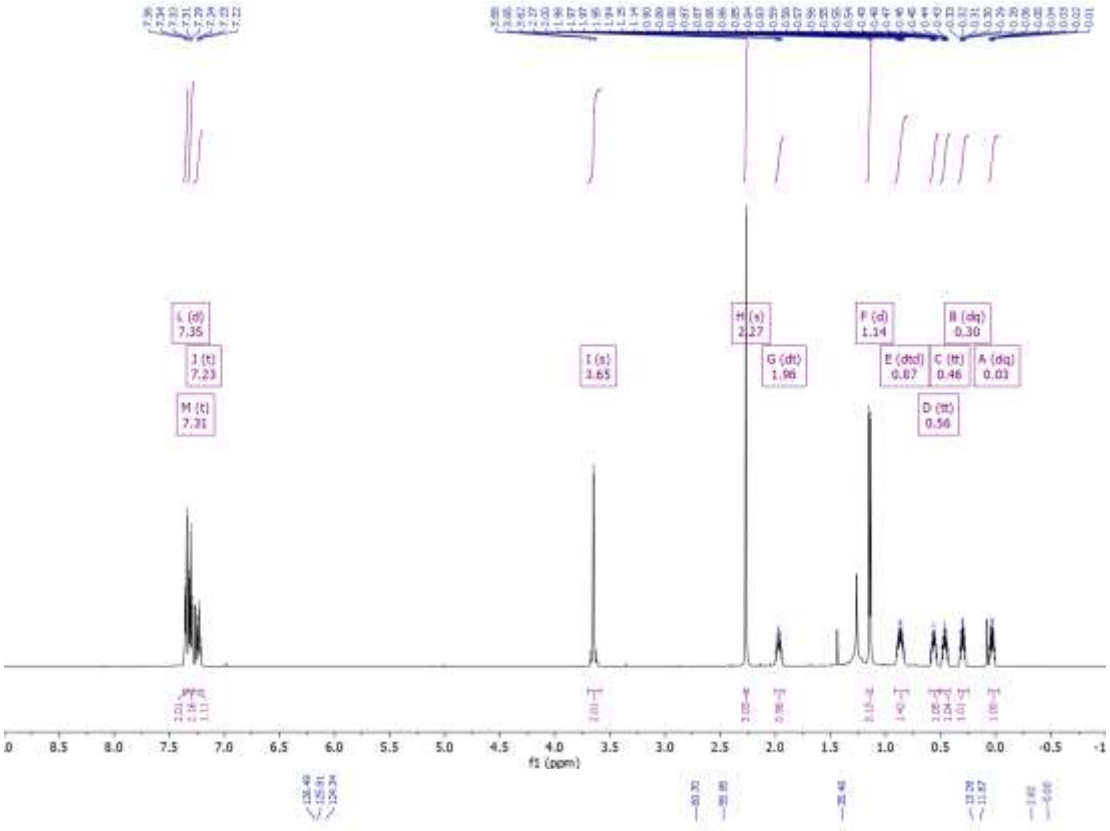
Hz, 3H), 0.87 (dtd, J = 11.8, 8.3, 4.4 Hz, 1H), 0.56 (tt, J = 8.6, 4.8 Hz, 1H), 0.46 (tt, J = 8.9, 4.9 Hz, 1H), 0.30 (dq, J = 9.9, 5.0 Hz, 1H), 0.03 (dq, J = 9.7, 5.0 Hz, 1H) ppm.

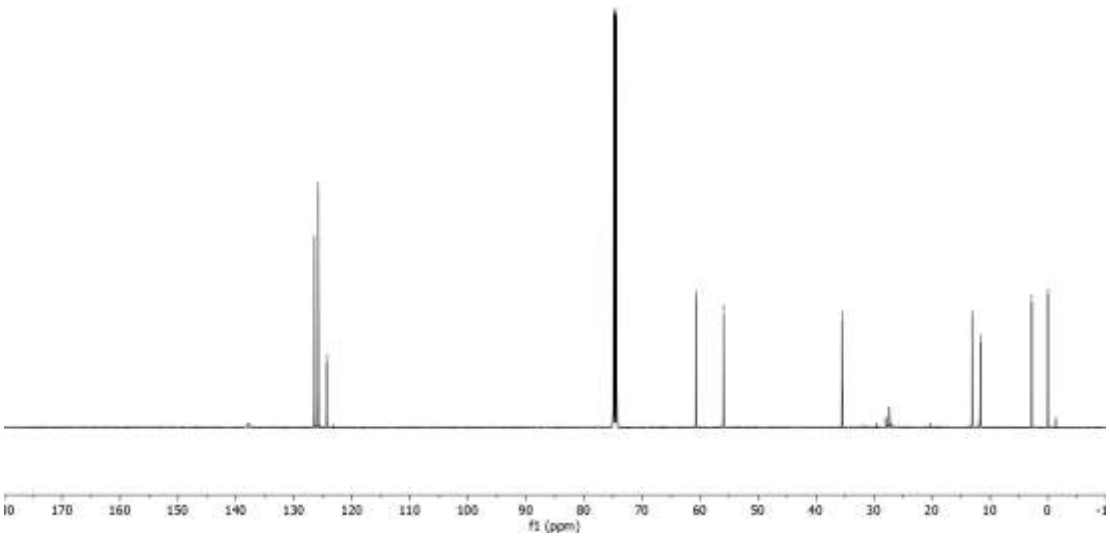
^{13}C NMR (126 MHz, $CDCl_3$): δ 126.5, 125.8, 124.3, 60.7, 56.0, 35.5, 13.1, 11.7, 2.8, 0.0 ppm.

HRMS (ESI) m/z: [(M+H)+] calcd for $C_{13}H_{20}N$ 190.1590, found 190.1588.

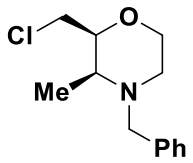
FTIR (neat): 666, 818, 1017, 1216, 1572, 2789, 2928 cm^{-1}.

$[\alpha]_D^{28}$: + 20 (c = 0.5, $CHCl_3$).


L (d)
7.35
J (t)
7.23
M (t)
7.31
I (s)
3.65
H (s)
2.27
G (dt)
1.96
F (d)
1.14
E (dtd)
0.87
C (tt)
0.46
B (dq)
0.30
A (dq)
0.03
D (tt)
0.56
f1 (ppm)


f1 (ppm)

(*2S,3S*)-4-Benzyl-2-(chloromethyl)-3-methylmorpholine (5.4g)



Procedures

A round-bottom flask equipped with a magnetic stir bar was charged with (*S*)-2-(benzyl(but-3-en-2-yl)amino)ethan-1-ol (**5.3g**, 82.1 mg, 0.4 mmol, 100 mol%), anhydrous cupric chloride (161 mg, 1.2 mmol, 300 mol%), palladium (II) chloride (7.2 mg, 0.04 mmol, 10 mol%) and sodium acetate (98.4 mg, 1.2 mmol, 300 mol%). The tube was purged with argon for 1 minute. Glacial acetic acid (0.1 M, 4.0 ml) was added, and the tube was sealed with a PTFE lined cap. The tube was placed in an oil bath at 40 °C and stirred for 14 hours. The reaction vessel was removed from the oil bath and allowed to reach ambient temperature. To the reaction mixture was added 1 N NaOH (pH>11). The reaction mixture was transferred to a separatory funnel, and the aqueous layer was extracted with extracted with isopropyl acetate three times. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The resulting oily residue was subjected to flash column chromatography (SiO_2, heptane: isopropyl acetate = 20:1–5:1) to give the title compound in 99% yield (94.9 mg, 0.40 mmol) as a light yellow oil.

TLC (SiO_2) R_f = 0.85 (heptane: isopropyl acetate = 1:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.36 – 7.28 (m, 4H), 7.26 – 7.20 (m, 1H), 3.77 (ddd, J = 11.1, 3.6, 1.7 Hz, 1H), 3.71 (ddd, J = 7.9, 5.3, 2.6 Hz, 1H), 3.65 – 3.54 (m, 2H), 3.58 –

3.45 (m, 3H), 2.88 (qd, J = 6.6, 2.6 Hz, 1H), 2.57 (td, J = 11.6, 3.6 Hz, 1H), 2.25 (ddd, J = 11.6, 3.2, 1.6 Hz, 1H), 0.88 (d, J = 6.6 Hz, 3H) ppm.

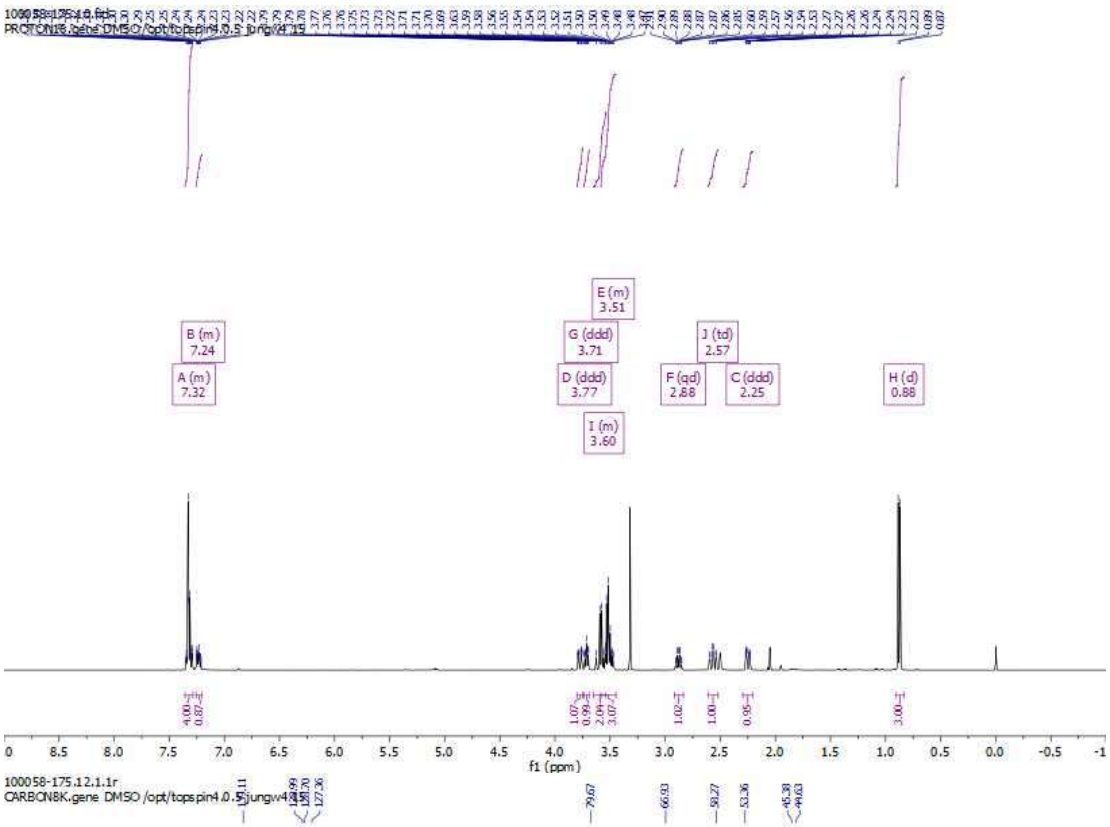
^{13}C NMR (101 MHz, DMSO-d_6): δ 139.1, 129.0, 128.7, 127.4, 79.7, 66.9, 58.3, 53.4, 45.4, 44.6 ppm.

HRMS (ESI) m/z: [(M+H)+] calcd for $C_{13}H_{19}ClNO$ 240.1077, found 240.1147.

FTIR (neat): 2969, 2159, 1452, 1128, 746, 698 cm^{-1}.

$[\alpha]_D^{28}$: - 8.5 (c = 2.0, methanol).

SFC: Enantiomeric excess was determined by SFC analysis (Chiralpak AD-H column, 3 % of methanol with 0.1 % of NH_4OH, 2.0 mL/min, 220 nm), t_{major} = 17.8 min, t_{minor} = 26.4 min; ee = 93 %.


E (m)
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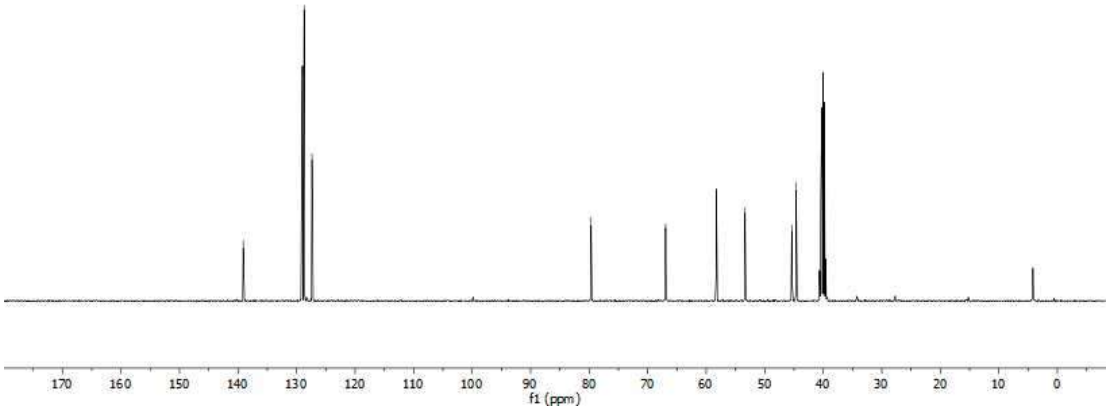
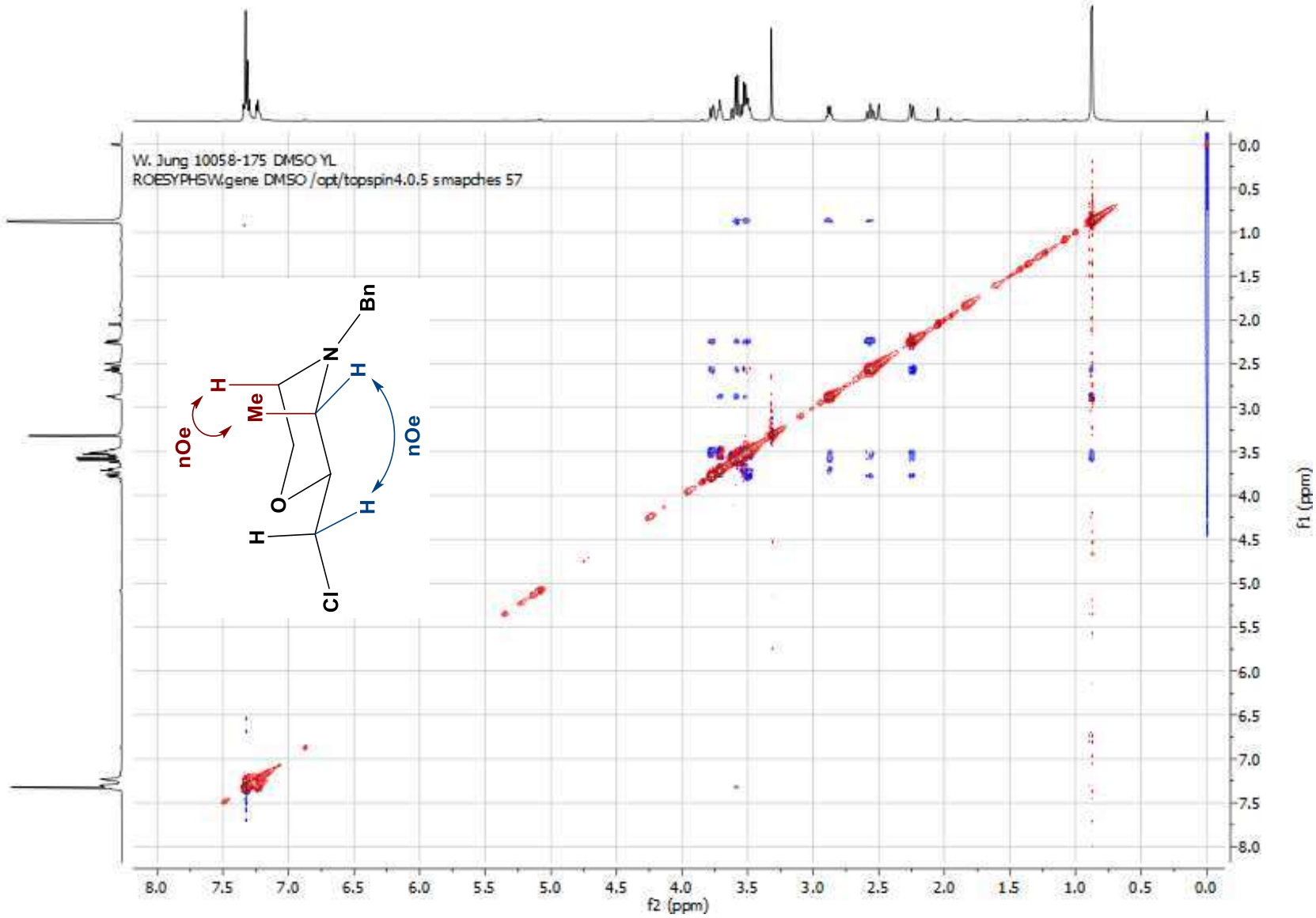
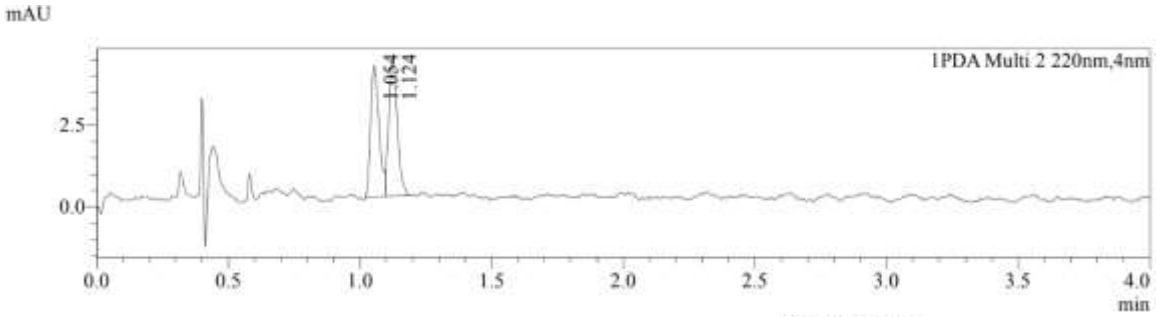
B (m)
7.24
G (ddd)
3.71
J (td)
2.57
A (m)
7.32
D (ddd)
3.77
F (qd)
2.88
C (ddd)
2.25
H (d)
0.88
I (m)
3.60
f1 (ppm)


f1 (ppm)

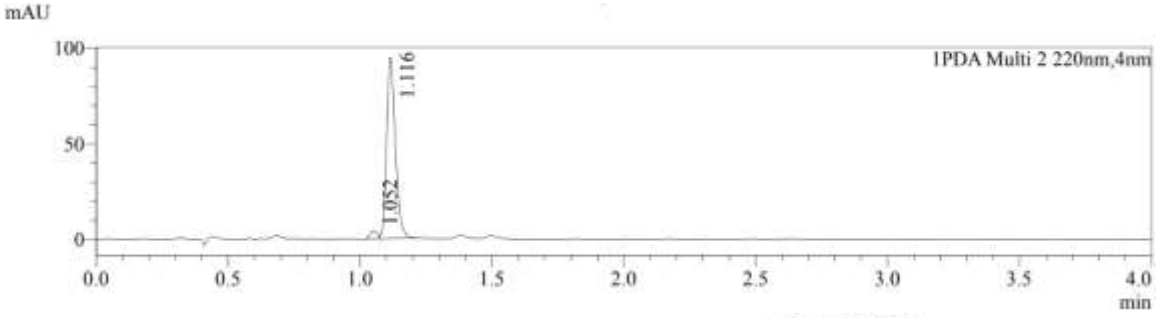

W. Jung 10058-175 DMSO YL
ROESYPHSW.gene DMSO /opt/topspin4.0.5 smapches 57
Bn
N
H
Me
H
nOe
nOe
O
H
H
Cl
f2 (ppm)
f1 (ppm)



Peak Table

PDA Ch2 220nm

Peak#	Ret. Time	Area	Height	Area%
1	1.054	8957	3972	48.966
2	1.124	9335	4108	51.034
Total		18292	8080	100.000

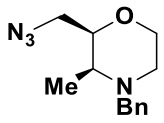


Peak Table

PDA Ch2 220nm

Peak#	Ret. Time	Area	Height	Area%
1	1.052	7636	4011	3.400
2	1.116	216949	92758	96.600
Total		224585	96769	100.000

(*2R,3S*)-2-(Azidomethyl)-4-benzyl-3-methylmorpholine (5.5g)



Procedures

A dried pressure tube equipped with a magnetic stir bar under an argon atmosphere was charged with sodium azide (19.5 mg, 0.3 mmol, 300 mol%), potassium iodide (24.9 mg, 0.15 mmol, 150 mol%), and (*S*)-*N*-allyl-*N*-benzylbut-3-en-2-amine (**5.4g**, 24.0 mg, 0.1 mmol, 100 ml%) in DMF (0.2 mL, 0.5 M). The tube was sealed with a PTFE lined cap and the reaction mixture was allowed to stir for 48 hours at 140 °C. After reaching ambient temperature, the mixture was transferred to a separatory funnel and added diethyl ether. The organic layer was washed with water and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting oily residue was subjected to flash column chromatography (SiO_2, hexane: ethyl acetate =20:1-10:1) to give the title compound in 66% yield (16.3 mg, 0.066 mmol) as a light yellow oil.

TLC (SiO_2) R_f = 0.33 (hexane: ethyl acetate = 4:1).

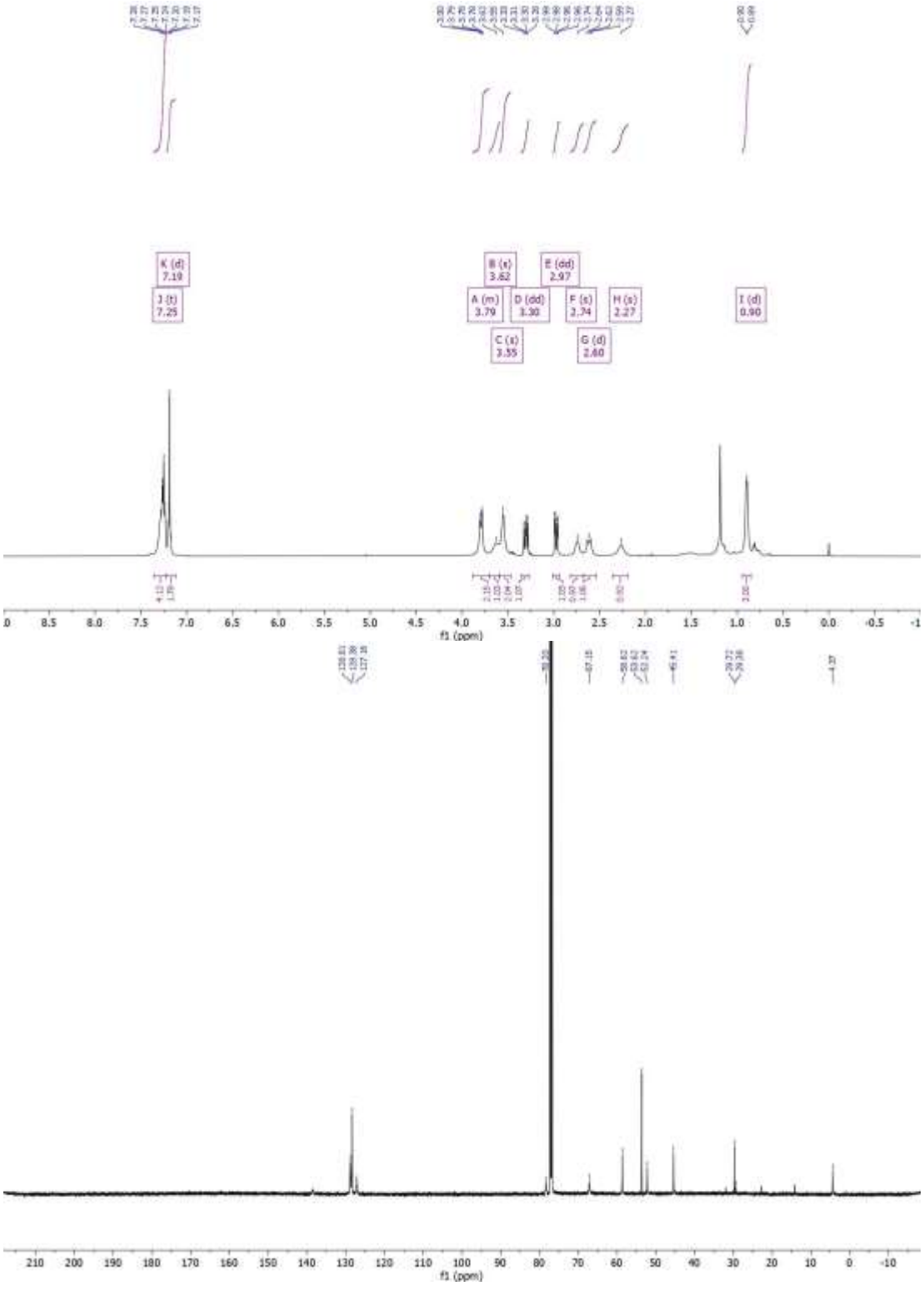
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (t, J = 7.3 Hz, 4H), 7.19 (d, J = 7.1 Hz, 2H), 3.88 – 3.70 (m, 2H), 3.62 (s, 1H), 3.55 (s, 2H), 3.30 (dd, J = 12.9, 8.7 Hz, 1H), 2.97 (dd, J = 12.8, 4.2 Hz, 1H), 2.74 (s, 1H), 2.60 (d, J = 11.5 Hz, 1H), 2.27 (s, 1H), 0.90 (d, J = 6.6 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 128.8, 128. 4, 127.2, 78.3, 67.2, 58.6, 53.6, 52.2, 45.4, 29.7, 29.4, 4.4 ppm.

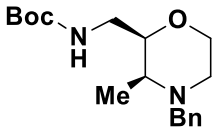
HRMS (ESI) m/z: [(M+H)+] calcd for $C_{13}H_{19}N_4O$ 247.1553, found 247.1556.

FTIR (neat): 667, 908, 1135, 1348, 1668, 2358, 2922 cm^{-1}.

$[\alpha]_D^{28}$: - 20 (c = 1.0, $CHCl_3$).


K (d) 7.19
J (t) 7.25
B (s) 3.62
E (dd) 2.97
A (m) 3.79
D (dd) 3.30
F (s) 2.74
H (s) 2.27
I (d) 0.90
C (s) 3.55
G (d) 2.60
f1 (ppm)
f1 (ppm)

***tert*-Butyl (((*2R,3S*)-4-benzyl-3-methylmorpholin-2-yl)methyl)carbamate (5.6g)**



Procedures

A round-bottom flask equipped with a magnetic stir bar under an argon atmosphere was charged with Pd/C (10 wt.%, 1.0 mg), $NaBH_4$ (4.5 mg, 0.12 mmol, 300 mol%), and H_2O (0.1 mL, 0.4 M) and stirred for 10 min at room temperature. A solution of (*2R,3S*)-2-(azidomethyl)-4-benzyl-3-methylmorpholine (**5.5g**, 9.9 mg, 0.04 mmol, 100 mol%) and Boc_2O (14 µL, 0.06 mmol, 150 mol%) in methanol (0.5 mL, 0.08 M) was added to the prepared reaction mixture. After stirring 2 h at room temperature, the mixture was filtered through Celite with ethyl acetate and transferred to a separatory funnel. The organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting oily residue was subjected to flash column chromatography (SiO_2, hexane: ethyl acetate = 5:1) to give the title compound in 90% yield (11.5 mg, 0.036 mmol) as a pale yellow oil.

TLC (SiO_2) R_f = 0.61 (hexane: ethyl acetate = 1:1).

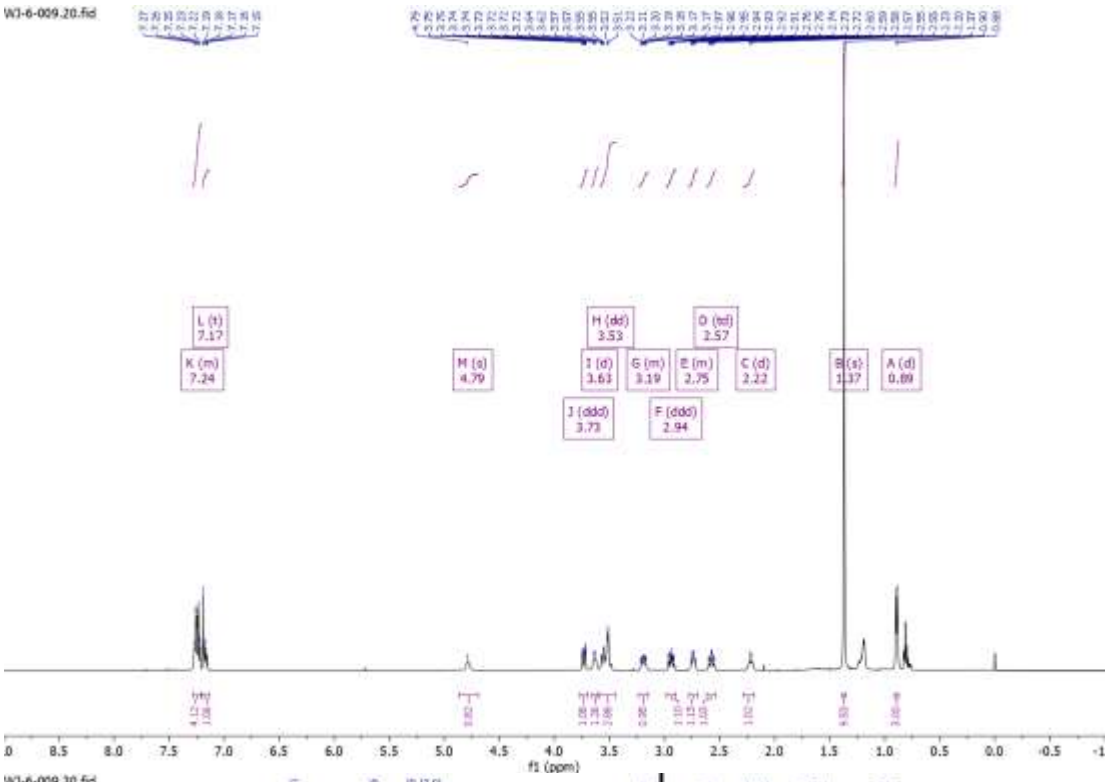
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 – 7.21 (m, 4H), 7.17 (t, J = 7.0 Hz, 1H), 4.79 (s, 1H), 3.73 (ddd, J = 11.1, 3.5, 2.1 Hz, 1H), 3.63 (d, J = 9.4 Hz, 1H), 3.53 (dd, J = 17.6, 4.1 Hz, 3H), 3.24 – 3.15 (m, 1H), 2.94 (ddd, J = 13.3, 9.3, 3.4 Hz, 1H), 2.78 – 2.70 (m, 1H), 2.57 (td, J = 11.4, 3.5 Hz, 1H), 2.22 (d, J = 12.0 Hz, 1H), 1.37 (s, 10H), 0.89 (d, J = 6.5 Hz, 3H) ppm.

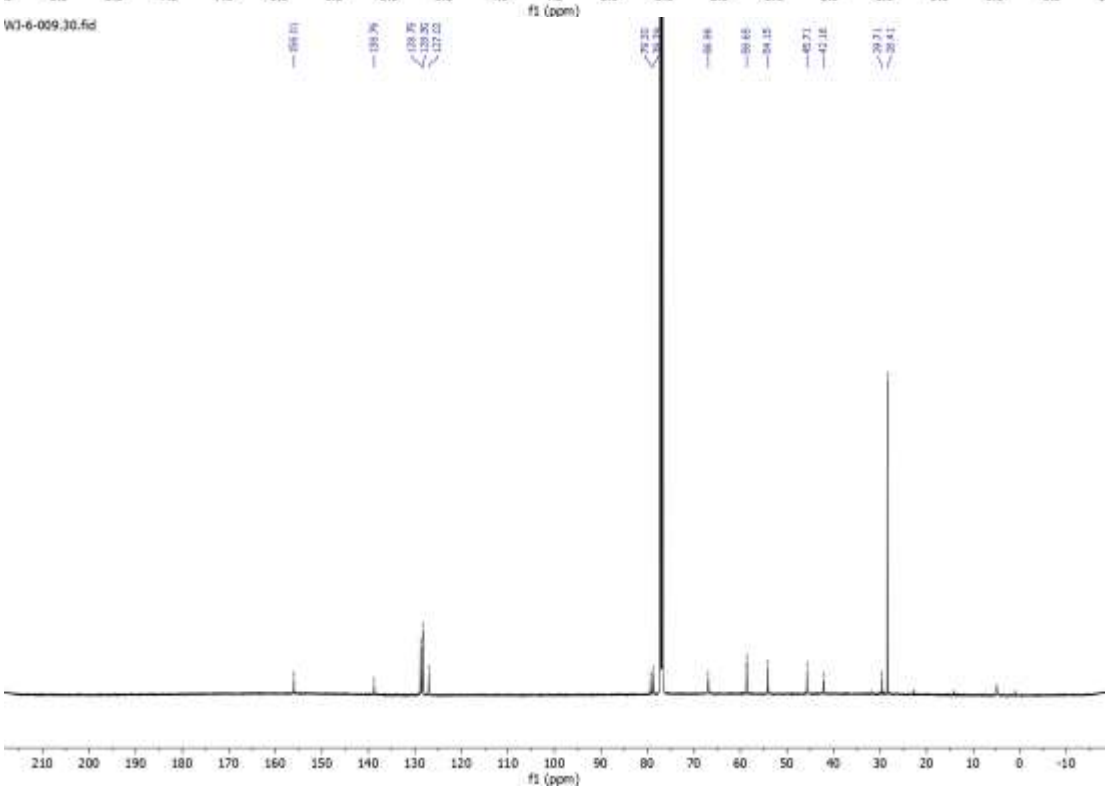
^{13}C NMR (126 MHz, $CDCl_3$): δ 156.0, 138.8, 128.8, 128.3, 127.0, 79.3, 78.8, 67.0, 58.7, 54.2, 45.7, 42.2, 29.7, 28.4 ppm.

HRMS (ESI) m/z: [(M+Na)+] calcd for $C_{18}H_{28}N_2O_3Na$ 343.1998, found 343.1992.

FTIR (neat): 659, 822, 1027, 1267, 1453, 1712, 2814, 2973, 3335 cm^{-1}.

$[\alpha]_D^{28}$: + 26 (c = 1.0, $CHCl_3$).


WJ-6-009.20.fid
L (t) 7.17
K (m) 7.24
M (s) 4.79
H (dd) 3.53
I (d) 3.63
J (ddd) 3.73
G (m) 3.19
F (ddd) 2.94
D (td) 2.57
E (m) 2.75
C (d) 2.22
B (s) 1.37
A (d) 0.89
f1 (ppm)

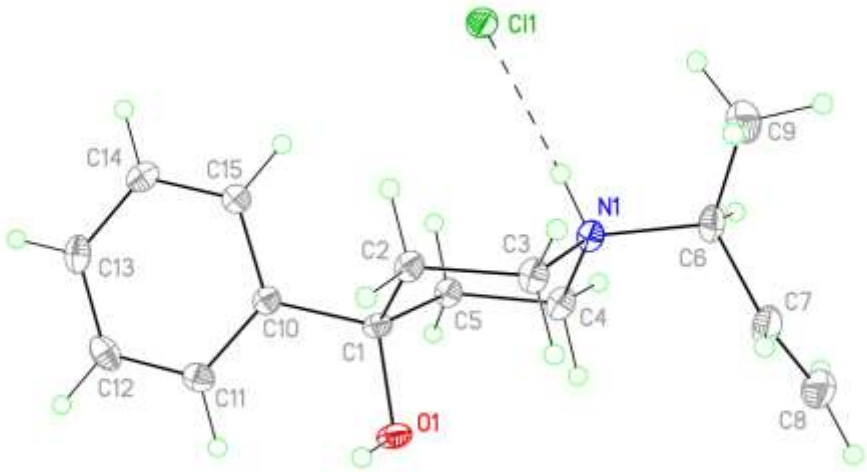

WJ-6-009.30.fid
f1 (ppm)

5.5.6. Single Crystal X-Ray Diffraction Analysis of HCl Salt of Adduct 5.3v

Empirical formula	C15 H22 Cl N O	
Formula weight	267.78	
Temperature	100.15 K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 8.9762(5) Å	a= 90°.
	b = 10.0543(5) Å	b= 90.317(2)°.
	c = 15.9177(8) Å	g = 90°.
Volume	1436.54(13) $Å^3$	
Z	4	
Density (calculated)	1.238 Mg/m^3	
Absorption coefficient	0.255 mm^{-1}	
F(000)	576	
Crystal size	0.59 x 0.37 x 0.14 mm^3	
Theta range for data collection	2.269 to 30.625°.	
Index ranges	-12<=h<=12, -14<=k<=14, -22<=l<=22	
Reflections collected	42697	
Independent reflections	8307 [R(int) = 0.0419]	
Completeness to theta = 25.242°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00 and 0.8933	

Refinement method	Full-mneatix least-squares on F^2
Data / restraints / parameters	8307 / 5 / 355
Goodness-of-fit on F^2	1.085
Final R indices [I>2sigma(I)]	R1 = 0.0321, wR2 = 0.0772
R indices (all data)	R1 = 0.0373, wR2 = 0.0785
Absolute structure parameter	0.01(4)
Extinction coefficient	n/a
Largest diff. peak and hole	0.347 and -0.202 e.$Å^{-3}$

View of complex 1 of **5.3v** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level. Dashed lines are indicative of a hydrogen bonding interaction.



Chapter 6: Kinetic, ESI-MS and Computational Studies of π-Allyliridium *C,O*-Benzoate-Catalyzed Allylic Amination: Understanding the Unique Effect of Cesium Ion

6.1 INTRODUCTION

Enantioselective metal-catalyzed allylic amination has emerged as an important method for the synthesis of chiral amines, which are ubiquitous structural motifs in FDA-approved drugs.[1] Among metal catalysts for allylic amination,[2] chiral phosphoramidite-modified iridium complexes have proven especially effective due to their ability to promote high levels of branched regioselectivity and enantioselectivity (Figure 6.1).[3] Pursuant to initial data obtained by Takeuchi,[4,5] catalysts of this type were developed in the laboratories of Helmchen,[6] Hartwig,[7] Carreira,[8] You[9] and others.[10] These iridium-phosphoramidite-catalyzed allylic aminations proceed by way of cationic π-allyliridium intermediates. In collaboration with Genentech, our laboratory has advanced an alternate class of iridium catalysts for allylic amination, cyclometallated π-allyliridium *C,O*-benzoates, that react by way of neutral π-allyliridium intermediates,[11] as demonstrated in reactions of primary aliphatic amines,[1a] (hetero)aromatic amines,[11b] indoles/azoles,[11c] secondary amines,[11d] as well as *C*-nucleophiles (nitronates[11e] and malonates[11f]). These π-allyliridium *C,O*-benzoate complexes were originally developed as catalysts for the nucleophilic carbonyl allylation.[12] The ability of these catalysts to promote both *nucleophilic* and *electrophilic* allylation (via inner sphere vs outer sphere addition, respectively) establishes unique amphiphilic properties of neutral π-allyliridium species.

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*This chapter is based on the previously published works: Jung, W.-O.; Mai, B. K.; Yoo, M.; Shields, S. W. J.; Zbieg, J. R.; Stivala, C. E.; Liu, P.; Krische, M. J. *ACS Catal.* **2022**, *12*, 3660.
W. J. contributed to kinetic studies (Figure 6.2 and 6.3), sample preparation and mass spectrometry studies (Figure 6.4 and 6.5 and Scheme 6.2) and preparation of manuscript and supporting information.

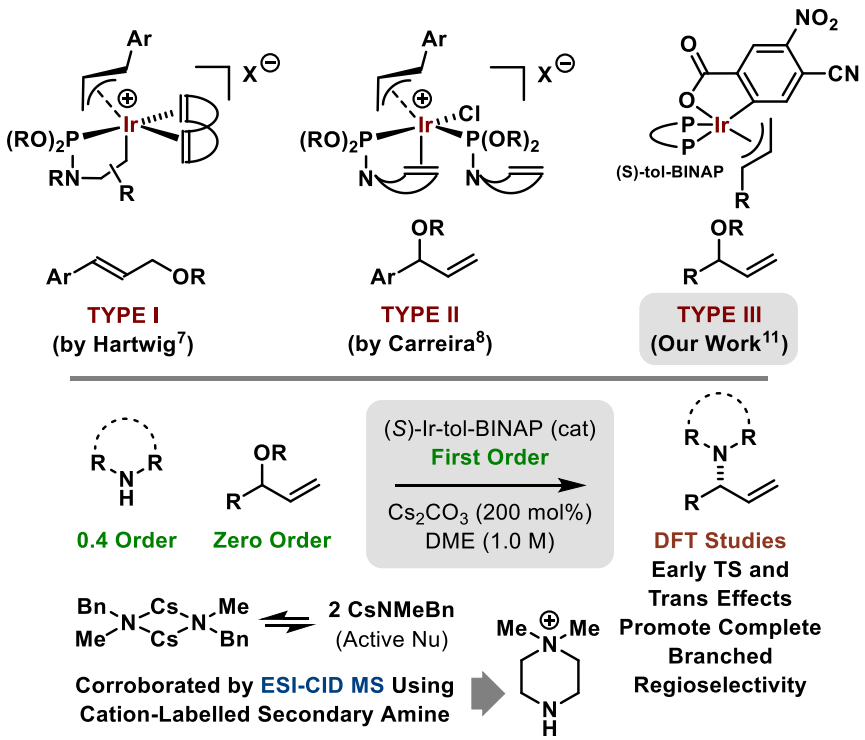


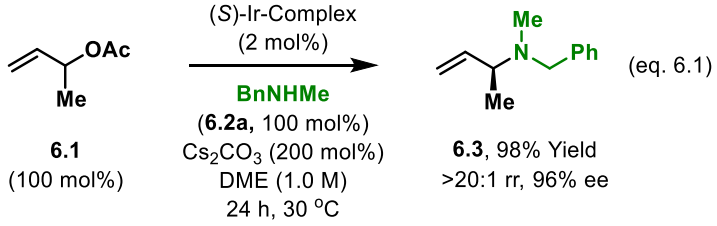
Figure 6. 1 Cationic vs neutral chiral iridium complexes for regio- and enantioselective allylic alkylation.

The π-allyliridium *C,O*-benzoate catalysts for allylic amination display several unique features that warranted further understanding. First, complementing the scope of iridium-phosphoramidite catalysts, complete levels of branched regioselectivity are observed in reactions of allylic acetates bearing linear alkyl groups, even in reactions of sterically demanding secondary amine nucleophiles.[11d] Secondly, in all π-allyliridium *C,O*-benzoate-catalyzed allylic aminations, cesium carbonate is vastly superior to all other bases. Here, we report kinetic, ESI mass spectrometric and DFT computational studies on π-allyliridium *C,O*-benzoate-catalyzed allylic aminations that illuminate the origins of regio- and enantioselectivity, and provide insight into the unique role of cesium ion.[13]

6.2 Reaction Development

6.2.1 Reaction Progress Kinetic Analysis (RPKA).

In our studies of π-allyliridium *C,O*-benzoate-catalyzed allylic aminations of aliphatic and aromatic amine partners,[11a,b] cesium carbonate is required as base. Allylic amination does not proceed in the presence of other carbonate bases. To gain further insight into the catalytic mechanism and the unique effect of cesium ion, reaction progress kinetic analysis (RPKA) using the "different excess" protocol[14] was applied to the reaction of allylic acetate **6.1** with secondary amine **6.2a** based on standard conditions employing the π-allyliridium *C,O*-benzoate modified by (*S*)-tol-BINAP (eq. 6.1).[11d] Selected RPKA data is depicted in Figures 6.2 and 6.3.



Higher concentrations of branched allyl acetate **6.1** show the same rate of product formation, suggesting a zero-order rate dependence on **6.1**, and that **6.1** is not involved in the turnover-limiting step of the catalytic mechanism (Figure 6.2, top). Doubling catalyst concentration results in a doubling of rate, corroborating a first-order rate dependence on catalyst (Figure 6.2, middle). The results of a set of experiments performed using the "same excess" protocol demonstrate minimal catalyst deactivation occurs (Figure 6.2, bottom). Finally, doubling the initial concentration of amine **6.2a** increases the rate of product formation (Figure 6.3, top). Analysis of these data using Burés's method[15] indicates the reaction has a fractional order of 0.4 in amine (Figure 6.3, middle).

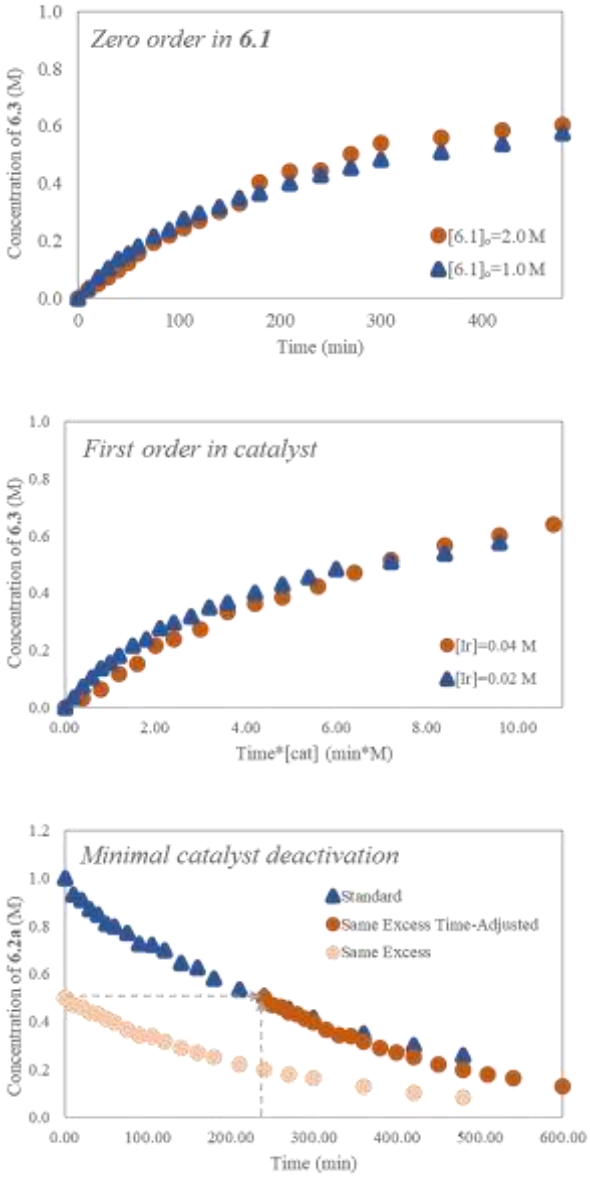


Figure 6. 2 Kinetic profile of allylic amination catalyzed by π-allyliridium *C,O*-benzoate. (Top) Different excess reaction carried out with [**6.1**]$_0$ = as noted and [**6.2a**]$_0$ = 1.0 M; Standard conditions: [**6.1**]$_0$ = 1.0 M, [**6.2a**]$_0$ = 1.0 M, [Ir] = 0.02 M and [Cs_2CO_3] = 2.0 M. (Middle) Different excess reaction carried out with [Ir] = as noted. (Bottom) Same excess reaction carried out with [excess] = 0.0 M. Standard condition: [**6.1**]$_0$ = 1.0 M, [**6.2a**]$_0$ = 1.0 M; same excess: [**6.1**]$_0$ = 0.5 M, [**6.2a**]$_0$ = 0.5 M.

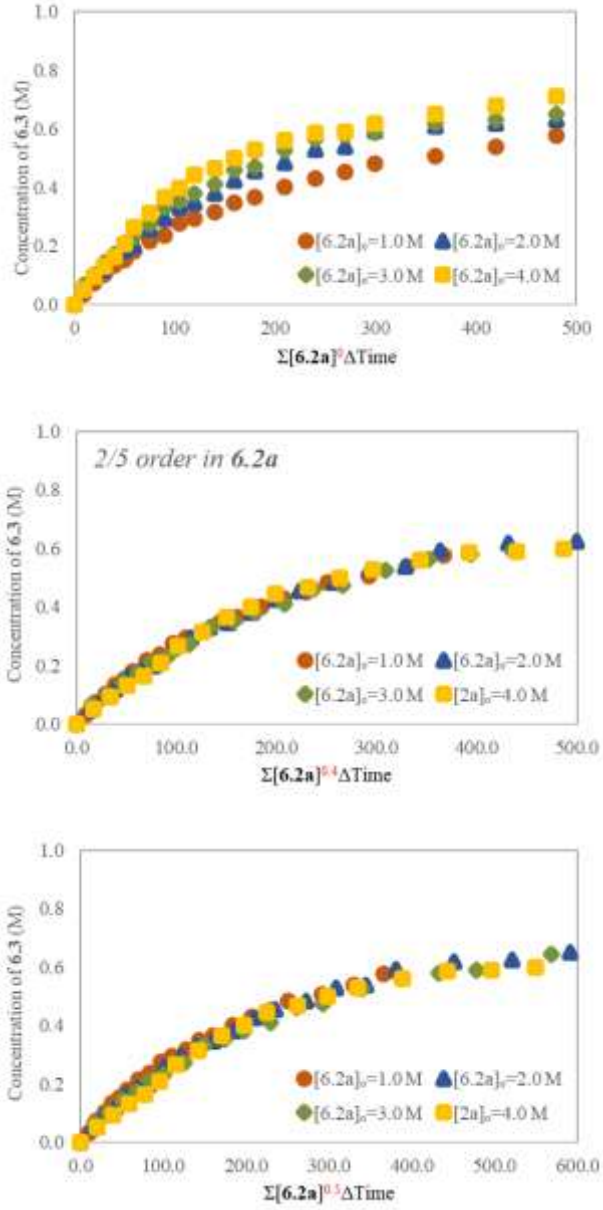
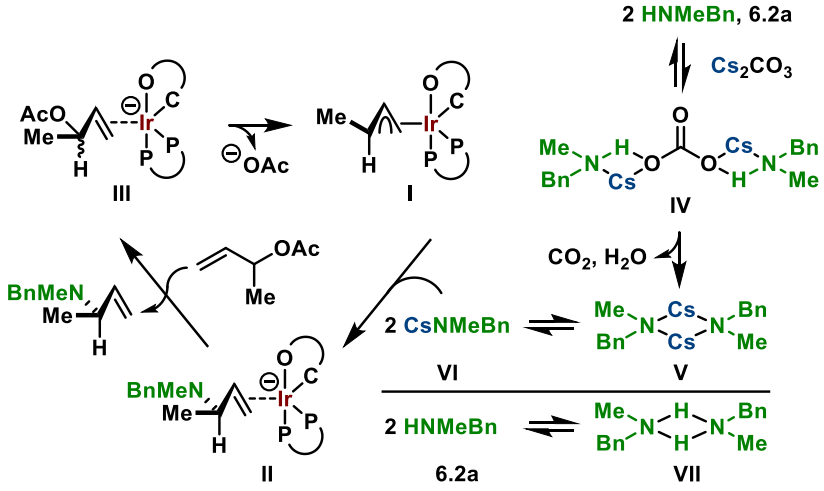


Figure 6. 3 The normalized timescale method shows that the allylic amination is 0.4 order in amine. Formation of product **6.3** was monitored by ^{1}H NMR in reactions conducted using the "different excess" protocol: [**6.1**] $_0$ = 1.0 M, [Ir] = 0.02 M and [Cs_2CO_3] = 2.0 M, with [**6.2a**]$_0$ = as noted. Four different traces corresponding to amine **6.2a** loadings of 100, 200, 300, and 400 mol% are shown and the overlay of all the curves indicates the reaction order in amine is 0.4 (middle).[15]

It was recognized that the apparent fractional 0.4 order dependence on amine **6.2a** may reflect "saturation kinetics," that is, the kinetic order of amine **6.2a** may change as substrate concentration changes over the course of the reaction. To corroborate the fractional 0.4 order dependence on amine, "different excess" experiments were conducted using 200, 300 and 400 mol% of amine **6.2a** (Figure 6.3, middle). The 2/5 kinetic order on amine persisted across these experiments. "Different excess" experiments involving higher loadings of amine **6.2a** were not possible due to the highly concentrated reaction conditions (1.0 M DME).



Scheme 6. 1 General catalytic mechanism for enantioselective iridium-catalyzed allylic amination.

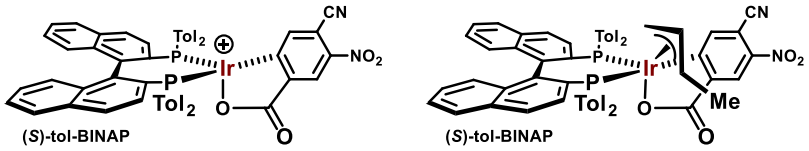
The collective data corroborate the indicated catalytic mechanism (Scheme 6.1). Cesium ion is coordinating the secondary amine to provide the bis(amine) carbonate complex **IV**, which due to Lewis acid enhanced Brønsted acidification of the amine[13] undergoes decarboxylative deprotonation to form the cesium-bridged amine dimer **V**. Related cesium-bridged amine dimers derived from tetramethylpiperidine have been

characterized via single crystal x-ray diffraction.[16] Dissociation of the cesium-bridged dimer **V** forms the monomeric cesium-amide **VI**. To account for the 0.4 kinetic order dependence of reaction rate on the concentration of amine **6.2a**, we propose that the monomeric cesium-amide **VI** is the active *N*-nucleophile in the addition to the π-allyliridium intermediate **I**. Addition of monomer **VI** to the π-allyliridium(III) complex **I** is the rate-limiting step of the catalytic cycle. An outer-sphere addition pathway was corroborated by previously reported deuterium labeling studies.[11b,c] Alkene exchange with allylic acetate releases the amination product and forms the olefin complex **III**, which rapidly ejects acetate ion to regenerate the resting state of the catalyst, π-allyliridium complex **I**. It should be noted that another explanation for the fractional order dependence on amine concentration was considered, which involves dissociation of hydrogen-bonded amine dimer **VII** followed by addition of the neutral monoamine **6.2a** to the π-allyliridium intermediate **I**. Here, deprotonation must occur irreversibly after C-N bond formation to preserve kinetic regio- and enantioselectivity.[17] This latter pathway was ruled out by the fact that allylic amination does not occur in the absence of cesium carbonate or in the presence of any other carbonate base.

6.2.2 Mass Spectrometry Experiments.

To corroborate our interpretation of the kinetic data, a series of mass spectrometry experiments were performed. To evaluate the catalyst resting state, an aliquot of the crude reaction mixture was analyzed by LCMS (Figure 6.4). Under standard ionization conditions, two diastereomers of the stereogenic-at-metal iridium complexes[18] lacking the allyl moiety were observed as major components along with small quantities of the

indicated π-crotyliridium-*C,O*-benzoate. Under milder LCMS conditions, a greater quantity of Ir-complex **I** was observed as a single stereogenic-at-metal diastereomer, although the iridium complex without allyl ligand was still the dominant component. These LCMS data suggest that the iridium complexes lacking the crotyl moiety are fragments of the relatively unstable π-crotyliridium-*C,O*-benzoate complex **I**. As previously reported, the parent π-allyliridium-*C,O*-benzoate is a robust, chromatographically stable compound that has been isolated and characterized by LCMS, NMR, and X-Ray analysis, whereas the corresponding π-crotyliridium-*C,O*-benzoate is not isolable.[19] These results suggest the π-crotyliridium-*C,O*-benzoate complex **I** is the major iridium complex in the reaction mixture and the resting state in the catalytic cycle; a conclusion that is in alignment with kinetic data implicating C-N bond formation as the turnover-limiting event.



Ir-complex I lacking allyl ligand
$C_{56}H_{41}IrN_2O_4P_2$: 1061.2249
Found: 1061.2239 $[M+H]^+$

Ir-complex I
$C_{60}H_{49}IrN_2O_4P_2$: 1117.2875
Found: 1117.2798 $[M+H]^+$

Figure 6. 4 Ions observed by LCMS that implicate Ir-complex **I** as the resting state of the catalyst.

Next, ESI-MS analyses were performed with multistage collision induced dissociation (CID) on solutions of cation-labelled amine **6.2b** in DME in the presence of Cs_2CO_3 to detect the putative cesium amide dimer akin to **V** (Figure 6.5). Detection of the cesium amide dimer using cation-labelled amine **6.2b** was challenging due to its propensity to eliminate in the presence of base under the conditions of ESI analysis, and the intrinsic moisture sensitivity of such cesium amides. Despite these difficulties, an ion

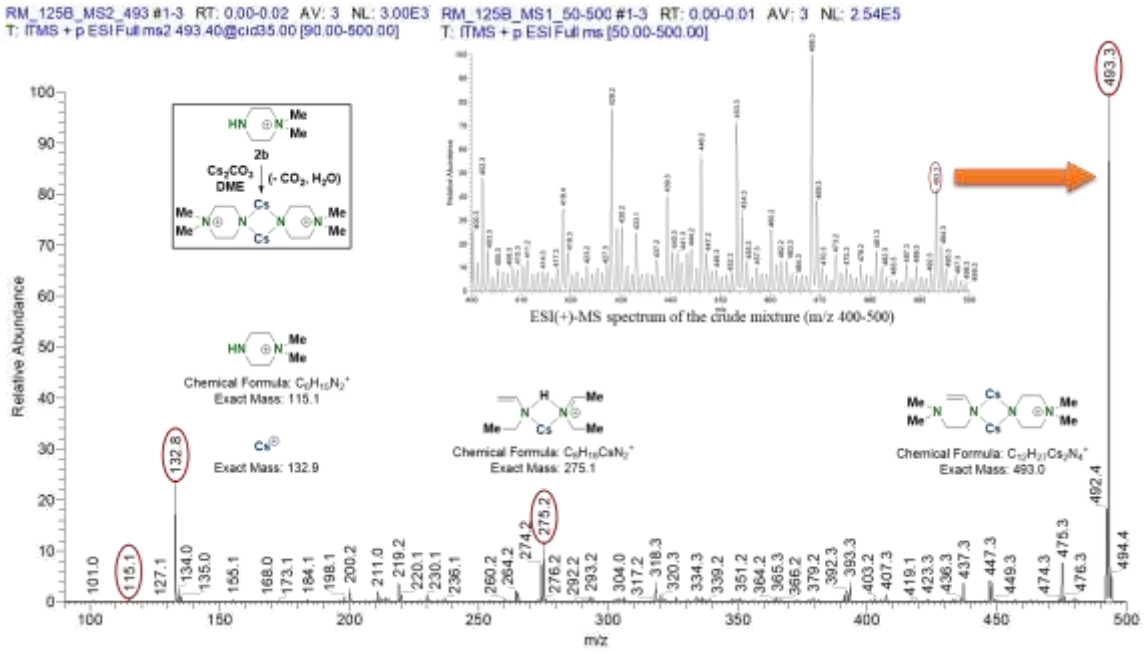
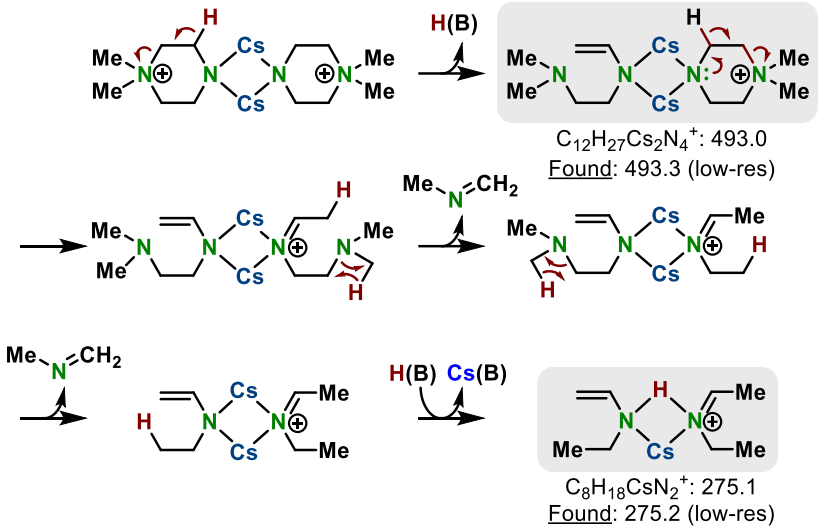


Figure 6. 5 ESI-CID-MS spectrum of the cesium-amide dimer as $[M-H]^+$ = m/z 493.3 at NCE=35 and ESI(+)-MS spectrum of the crude reaction mixture (m/z 400-500).

matching the weight of a cesium amide dimer derived from **6.2b** lacking one hydrogen atom was detected (m/z 493.3), which was assigned the indicated structure (Scheme 6.2). This structural assignment was confirmed by a multistage CID experiment, which provided fragmentation fingerprint of this ion to reveal the fragment $[C_8H_{18}CsN_2]^+$ (m/z =275.2) and the parent ammonium ion **6.2b** (m/z 115.1) The indicated mechanism accounts for formation of the major fragment (m/z =275.2) and involves sequential C-N bond cleavage[20] followed by metal ion transfer.[21]



Scheme 6. 2 Proposed fragmentation pathway of the cesium-amide dimer.

6.3 DISCUSSION

To further explore the mechanistic details of the allylic amination and the origins of regio- and enantioselectivity, density functional theory (DFT) calculations were carried out.[22,23] There are 16 possible stereoisomers of the π-crotyliridium-*C*,*O*-benzoate complex **I** derived from (*S*)-Ir-tol-BINAP and α-methyl allyl acetate **6.1**.[11e,18,24] We computed the activation free energies leading to branched and linear amination products from each of these isomers using monomeric cesium-pyrrolidide **6.4** as the active nucleophile (32 transition states in total. Figure 6.6). Here, **A**-**D** indicates one of the four possible diastereomeric arrangements of the *C*,*O*-benzoate ligand around the stereogenic Ir, *proximal* indicates the methyl on the crotyl ligand points towards the *C*,*O*-benzoate, and *exo* or *endo* describes whether the allyl C2−H moiety points away from or towards the *C*,*O*-benzoate. The most reactive isomer is **D**_*exo*_*proximal*, which prefers the

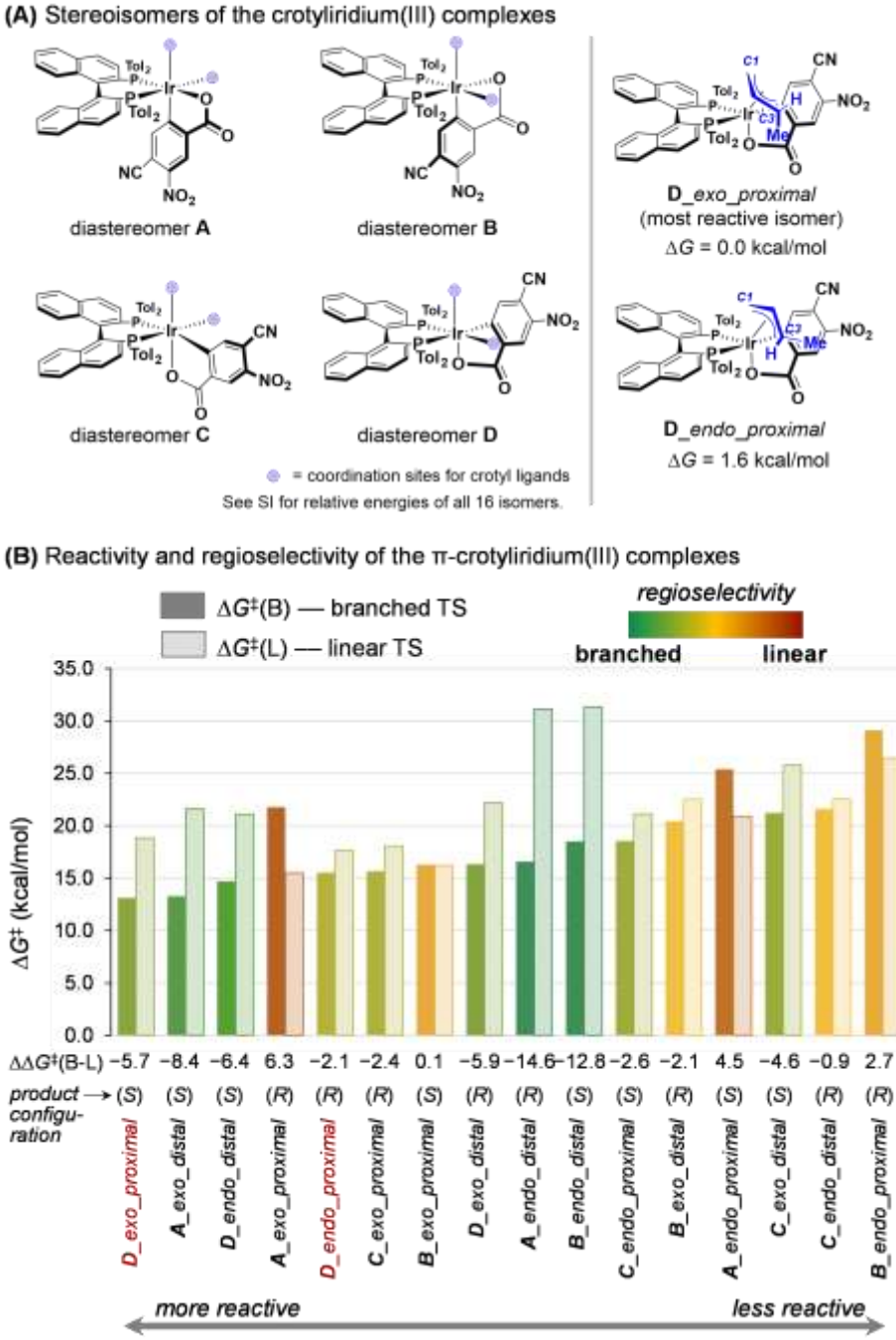


Figure 6. 6 Stereoisomers of the π-crotyliridium(III) complex and computed activation free energies for the addition of the monomeric cesium-pyrrolidide **6.4** leading to linear and branched amination products. Gibbs free energies are with respect to **D**_*exo_proximal*.

branched product, whereas, some less reactive isomers, e.g., **A**_*exo_proximal*, favor the linear product. Our calculations indicate that both reactivity and regioselectivity are affected by the stereogenicity at iridium center of each isomer.

The high reactivity and branched selectivity of **D**_*exo_proximal* are due to trans-effect of the bisphosphine ligand that facilitates nucleophilic addition occurring *trans* to the phosphorus.[11e,25] The trans-effect in **D**_*exo_proximal* leads to the longer, and thus weakened, Ir–C3 bond compared to Ir–C1 and the smaller negative charge on C3 than that on C1, both consistent with the greater electrophilicity of the more substituted C3 carbon (Figure 6.7). Our DFT calculations show that the addition of monomeric cesium-pyrrolidide **6.4** to **D**_*exo_proximal* strongly prefers the attack at the internal allylic carbon (C3) (**TS1**). The C1-attack transition state leading to the linear product (**TS2**) is 5.7 kcal/mol higher in energy than **TS1**.[26] The early amination transition state, as evidenced by the long forming C–N bond length (2.90 Å in **TS1**) decreases the sensitivity to steric effects and provides another important factor promoting the branched-selectivity.

Next, we examined the enantioselectivity of the amination, which is determined by the π-facial selectivity in the outer-sphere nucleophilic attack. Among the 16 possible branched-selective pathways, the most favorable transition states leading to the (*S*)- and (*R*)-enantiomers of the allylic amine product are **TS1** and **TS3**, which involve the additions of the cesium-amide **6.4** to **D**_*exo_proximal* and **D**_*endo_proximal*, respectively (Figure 6.7). The nucleophilic addition to the more stable *exo* isomer **D**_*exo_proximal* via **TS1** requires a 2.4 kcal/mol lower barrier. The predicted (*S*)-enantioselectivity via **TS1** is consistent with the absolute configuration of the product determined by X-ray crystallography.[11d] Here, the *endo* transition state **TS3** is destabilized by steric repulsions between the allyl C3−H/C1−H and the bisphosphine

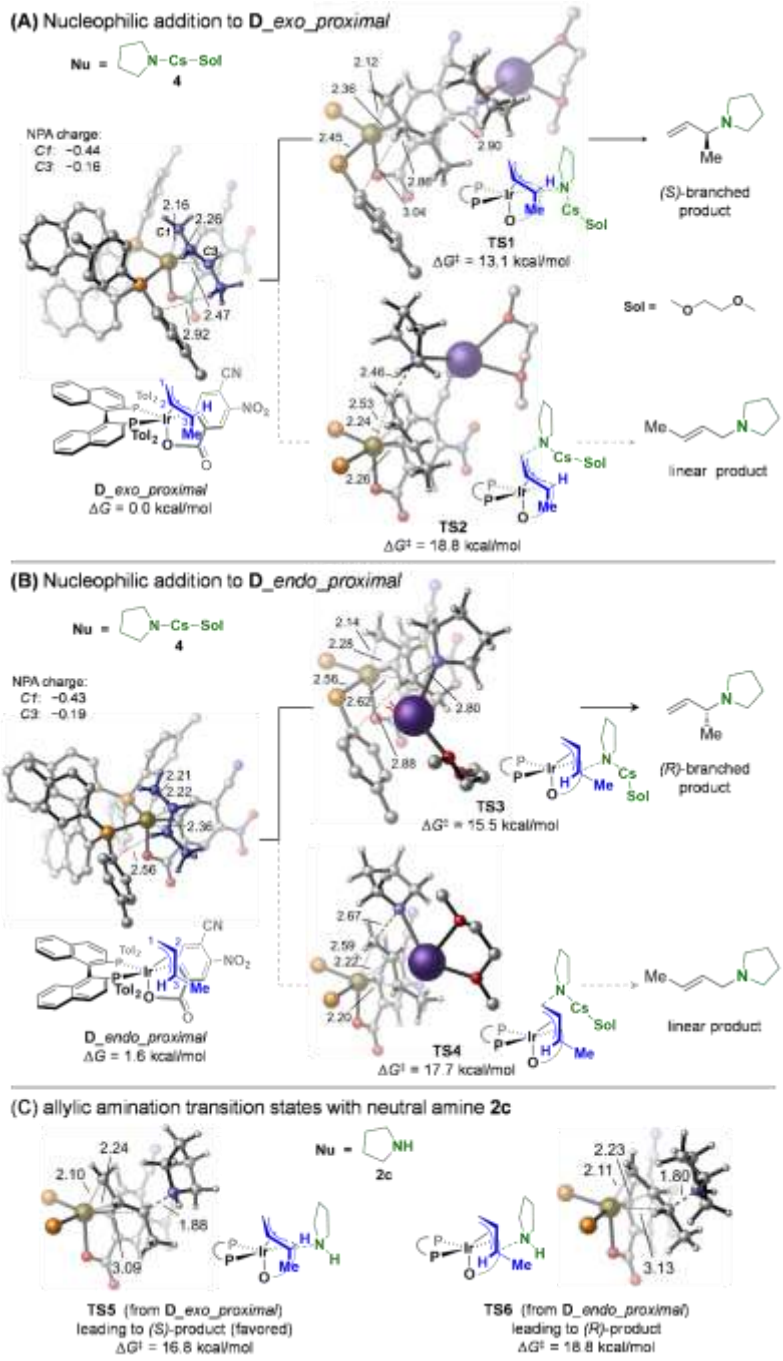


Figure 6. 7 Computational studies of the origins of regio- and enantioselectivities and the identity of the active nucleophile. Gibbs free energies are with respect to **D**_*exo_proximal*. Amination transition states with other π-crotyliridium(III) isomers are less favorable.

ligand, in particular, the arm *cis* to both allyl termini. These repulsions are evidenced by the much longer Ir−P distance in **TS3** (2.56 Å) than that in **TS1** (2.45 Å). Similar steric effects destabilize the ground state π-crotyliridium complex **D**_*endo_proximal*,[27] which has a short distance (2.56 Å) between allyl C3−H and the *ipso* carbon of a *p*-tolyl group. In **D**_*exo_proximal*, this repulsion is diminished with a much longer distance (2.92 Å) between the C3-methyl and the same *ipso* carbon. In addition, the NPA charge on C3 of **D**_*exo_proximal* is slightly less negative than that of **D**_*endo_proximal*, suggesting the former is also kinetically more reactive due to the longer and weaker Ir–C3 bond in the ground state.

The stereogenicity of the iridium center is critical for the high enantioselectivity. An inversion of enantioselectivity would be anticipated if diastereomer **C** were the active intermediate in the catalytic cycle. Because π-allyl complexes of diastereomer **C** are at least 4 kcal/mol less stable than **D**_*exo_proximal*, the nucleophilic addition with **C** are much less favorable (Figure 6.6B). Similarly, the less stable diastereomers **A** and **B** are not catalytically relevant either in the amination reaction.

The alternative pathway involving nucleophilic addition with neutral amine was ruled out experimentally (*vide supra*). Our DFT calculations indicated that the reaction with neutral amine **6.2c** requires a higher activation energy than the addition with the sterically more hindered but more nucleophilic cesium amide **6.4** (Figures 6.7C). Although it is not feasible to calculate the equilibrium between the cesium-amide and the neutral amine, the DFT calculations identified the cesium amide as a reactive nucleophile for the amination. Moreover, the computed transition state energies using neutral pyrrolidine **6.2c** as the nucleophile predict the same regio- and enantioselectivity trends, suggesting the selectivities are not affected by the active nucleophile.

6.4 CONCLUSION

In summary, we report kinetic, ESI-CID-MS and computational studies of the regio- and enantioselective π-allyliridium *C,O*-benzoate-catalyzed allylic amination of racemic branched alkyl-substituted allylic acetates using secondary aliphatic amine nucleophiles that provide insight into the critical role of cesium carbonate in these transformations and a rational for the observed regio- and enantioselectivity. Reaction progress kinetic analysis (RPKA) corroborates a first-order dependence on catalyst, zero-order dependence on allylic acetate, and a 0.4-order dependence on amine. The fractional-order dependence on amine suggests intervention of a dimeric cesium-amide complex that must dissociate to form the active monomeric cesium-amide nucleophile. ESI-CID-MS analysis of quaternary ammonium-labelled piperazine **6.2b** provides evidence for the formation of such species. Thus, we postulate that the requirement of cesium carbonate stems from its high basicity and capacity for Lewis-acid enhanced Brønsted acidification of the amine, which enables formation of cesium-bridged amine dimers. Analysis of reaction mixtures by LCMS reveals the presence of the π-allyliridium intermediate, corroborating its role as the catalyst resting state, as suggested by RPKA.

Computational studies reveal that neutral amine nucleophiles are less reactive than corresponding monomeric cesium amide-amine complexes in the outer-sphere nucleophilic addition and that the monomer is more reactive than the dimeric cesium-amide. The observation of complete branched regioselectivity in the present reactions of hindered secondary amines is especially noteworthy.[28] Computational studies provide insight into the origins of regioselectivity by revealing early transition states for C-N bond formation that mitigate steric effects, as well as trans-effects of the stereogenic-at-metal π-crotyliridium *C,O*-benzoate complexes that direct outer-sphere nucleophilic addition to the

more substituted allyl terminus. In the most stable and most reactive stereoisomers of the π-crotyliridium complex, the Ir–C bond with the more substituted allyl terminus is elongated, which increases its electrophilicity. The facial selectivity of the π-crotyl moiety is controlled by steric interactions between the bisphosphine ligand and the allyl termini, ultimately defining enantioselectivity. The mechanistic understanding gained from these studies will facilitate the design of new catalytic processes that are of high interest to both academic and industrial communities.

6.5 Experimental Details

6.5.1 General Information

All reactions were carried out under inert gas atmosphere unless otherwise indicated. Re-sealable pressure tubes (13x100 mm) were purchased from Fischer Scientific (catalog number 14-959-35C) and were flame dried followed by cooling in a desiccator or under a stream of inert gas prior to use. All commercial reagents and anhydrous solvents were used as received from vendors (Fischer Scientific, Sigma Aldrich, TCI America, Combi Blocks and Enamine) without further purification. The used Iridium catalyst (*S*)-Ir-tol-BINAP was prepared according to literature known procedures.[29] Cesium carbonate was used as received from Rockwell Lithium. Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates (Dynamic Absorbents F). Visualization was accomplished with UV light followed by dipping in $KMnO_4$ stain solution followed by heating.

6.5.2 Spectroscopy, Spectrometry and Data Collection

High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M+H, M+Na), or a suitable fragment ion. Nuclear magnetic resonance (^{1}H and ^{13}C) spectra were recorded with a Bruker BioSpin GmbG, Varian Gemini (400 MHz) or Varian INOVA (500 MHz) spectrometer equipped with a Bruker cryoprobe. The chemical shifts are given as parts per million (ppm) and were referenced to the residual solvent signal (DMSO-d_6: δH = 2.50 ppm, δC = 39.5 ppm, Acetone-d_6: δH = 2.05 ppm, δC = 29.8 ppm).

5.6.3. Kinetic Studies

Standard Conditions: To a dried 4-dram vial under an argon atmosphere charged with (*S*)-Ir-tol-BINAP (44 mg, 0.04 mmol, 2.0 mol%), cesium carbonate (1.30 g, 4.0 mmol, 200 mol%), durene (67.1 mg, 0.50 mmol, 25 mol%), *N*-methylbenzylamine (**6.2a**, 0.26 mL, 1.0 mmol, 100 mol%), and crotyl acetate (**6.1**, 0.25 mL, 2.0 mmol, 100 mol%) was added DME (2.0 mL, 1.0 M). The reaction mixture was then allowed to stir at 30 °C and checked every 10 min to 1 h for analysis.

Reaction progress was monitored by ^{1}H NMR analysis using durene as internal standard. 0.1 mL of the reaction mixture was extracted each hour and diluted with acetone-d_6, and the concentration of product was determined by NMR analysis.

Reaction order determined by submitting data to Burés's plot analysis.[30,31]

Experiment	[Ir] (M)	[6.1] (M)	[6.2a] (M)	[excess] [6.1] – [6.2a] (M)

Standard	0.02	1.0	1.0	0.0
Different excess 1	0.02	2.0	1.0	1.0
Different excess 2	0.02	1.0	2.0	-1.0
Different excess 3	0.02	1.0	3.0	-2.0
Different excess 4	0.02	1.0	4.0	-3.0
Same excess	0.02	0.5	0.5	0.0
Increased catalyst	0.04	1.0	1.0	0.0

Table 6. 1 Further reaction conditions for the kinetic experiments.

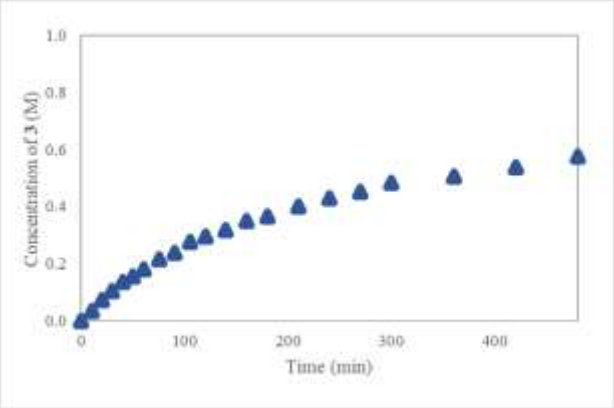


Figure 6. 8 Product formation under standard conditions.

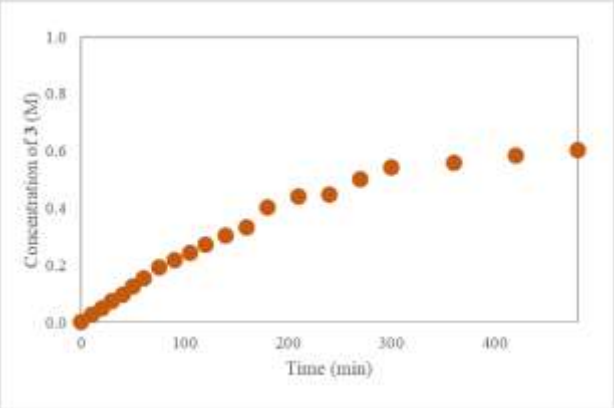


Figure 6. 9 Product formation under different excess 1 conditions.

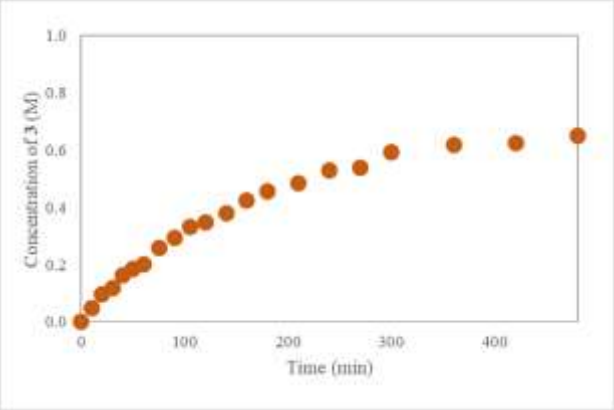


Figure 6. 10 Product formation under different excess 2 conditions.

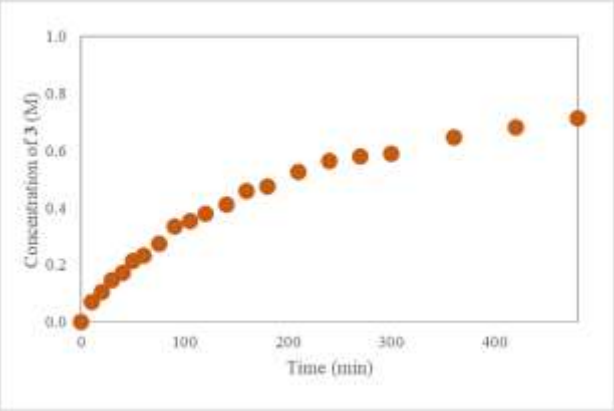


Figure 6. 11 Product formation under different excess 3 conditions.

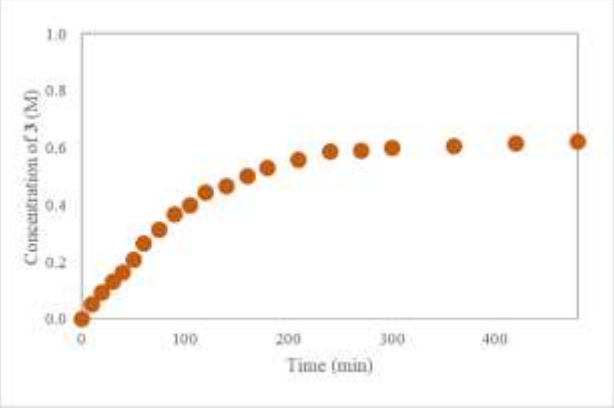


Figure 6. 12 Product formation under different excess 4 conditions.

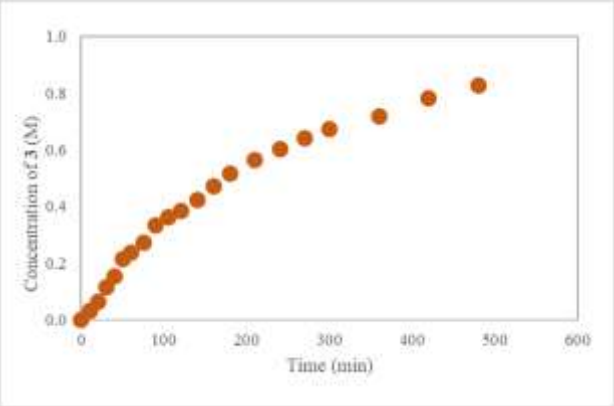


Figure 6. 13 Product formation under same excess conditions.

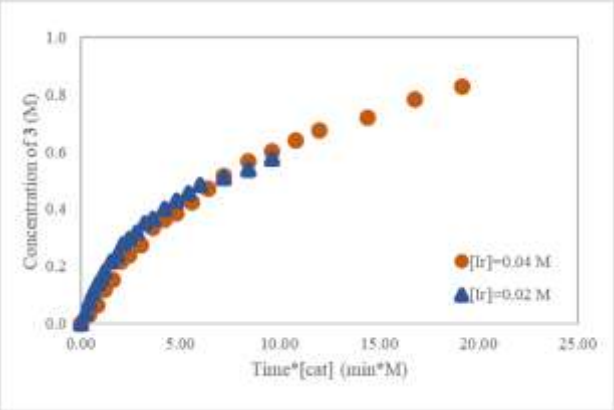


Figure 6. 14 Product formation under increased catalyst conditions.

To determine if any catalyst deactivation occurred during the reaction the same excess protocol was utilized. The collected product formation data for both the standard and same excess data sets were converted to amine concentration data ($[Amine]_t = [Amine]_0 - [Product]_t$). Since the standard data set has a starting concentration of amine that is half that in the same excess experiment, the standard data was time adjusted to reflect this. This method is representative of starting the reaction from two different starting points. At the point where the same excess data set matches the half starting point of the standard data set, they then represent a reaction with the same conditions. The relative

overlap of the two data sets that is observed here indicates that minimal catalyst deactivation occurs throughout the process of the reaction.

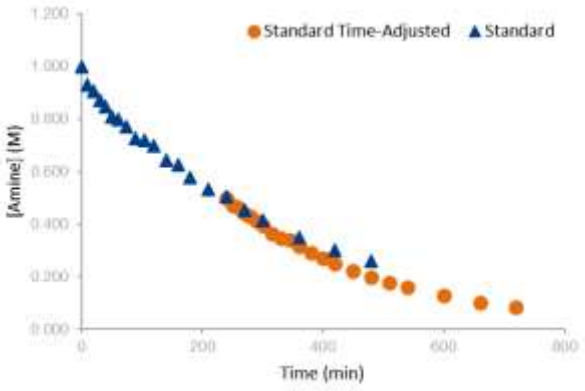
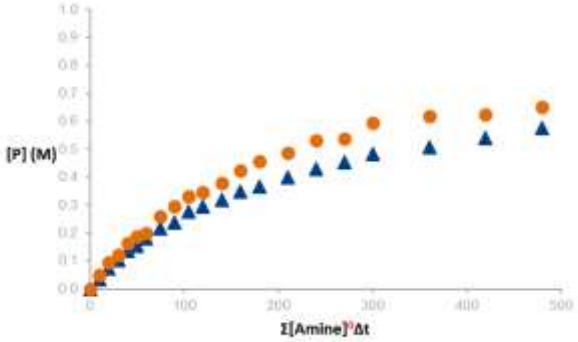
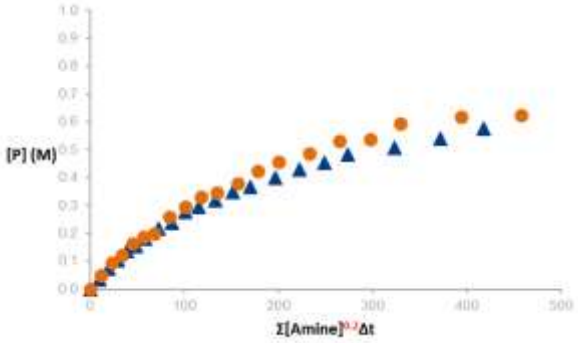


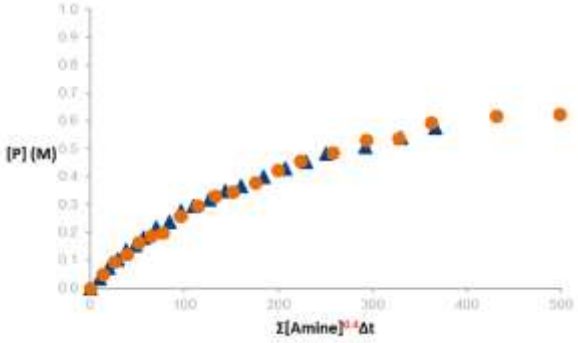
Figure 6. 15 Evaluation of catalyst performance utilizing same excess protocol.

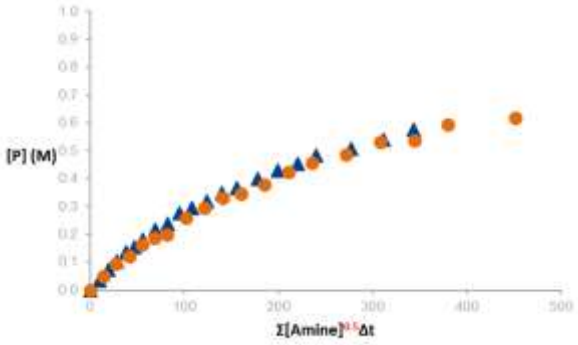
The analysis for amines indicates that positive order in amine. In order to elucidate the exact order in amine of the reaction, the time scale should be substituted by $\sum[\text{Amine}]^{\beta}\Delta t$ based on variable time normalization analysis (VTNA).[31b]

$$\sum [Amine]^{\beta} \Delta t = \sum_{i=0}^{n} (\frac{[B]_i + [B]_{i-1}}{2})^{\beta} (t_i - t_{i-1})$$


[P] (M)
Σ[Amine]^3Δt


[P] (M)
Σ[Amine]^2.2Δt


[P] (M)
Σ[Amine]^2.4Δt


[P] (M)
Σ[Amine]^2.5Δt

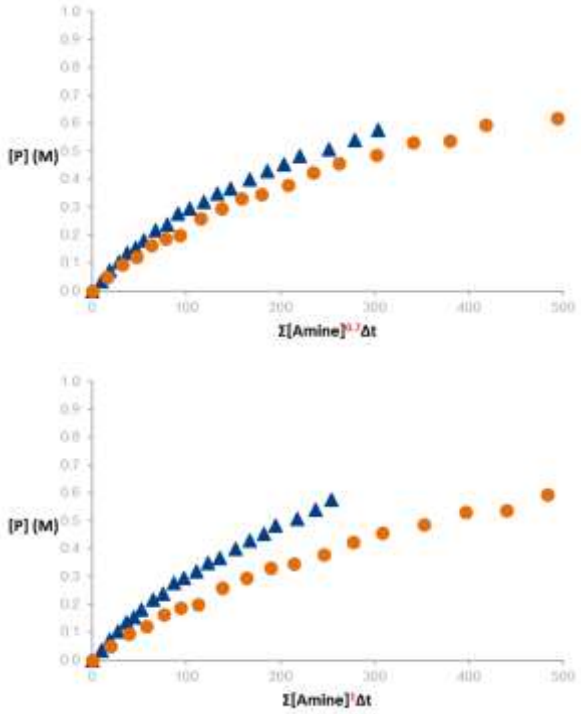
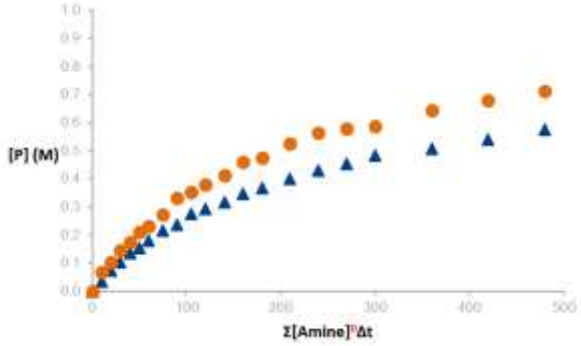
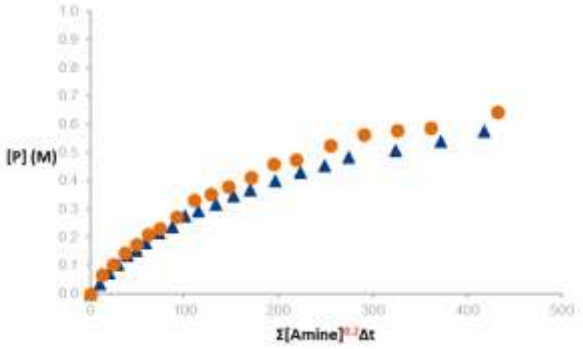
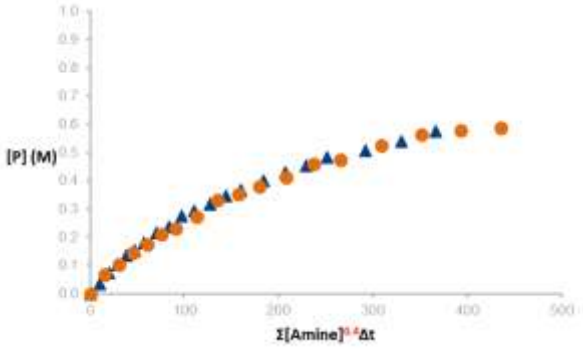
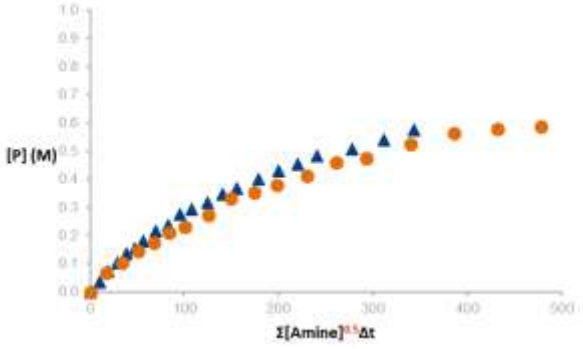


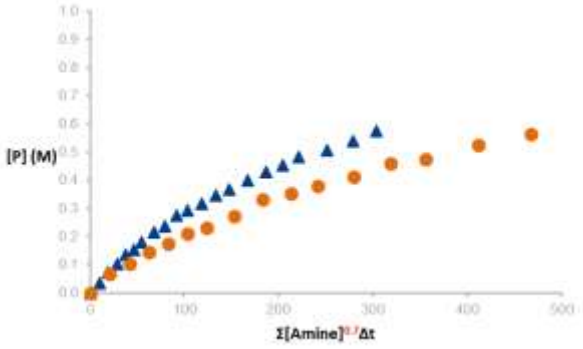
Figure 6. 16 Variable time normalization analysis for the determination of the order in amine (different excess 2 experiment).




[P] (M)
Σ[Amine]^0.7Δt


[P] (M)
Σ[Amine]^0.6Δt


[P] (M)
Σ[Amine]^0.5Δt


[P] (M)
Σ[Amine]^0.7Δt

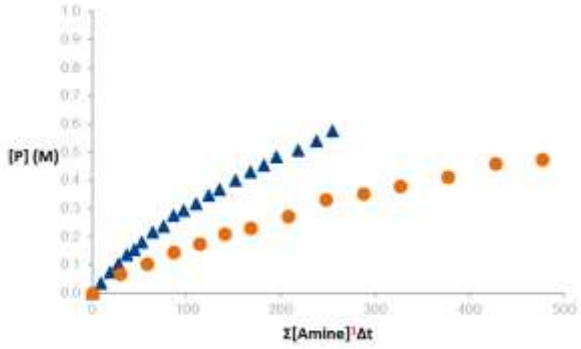
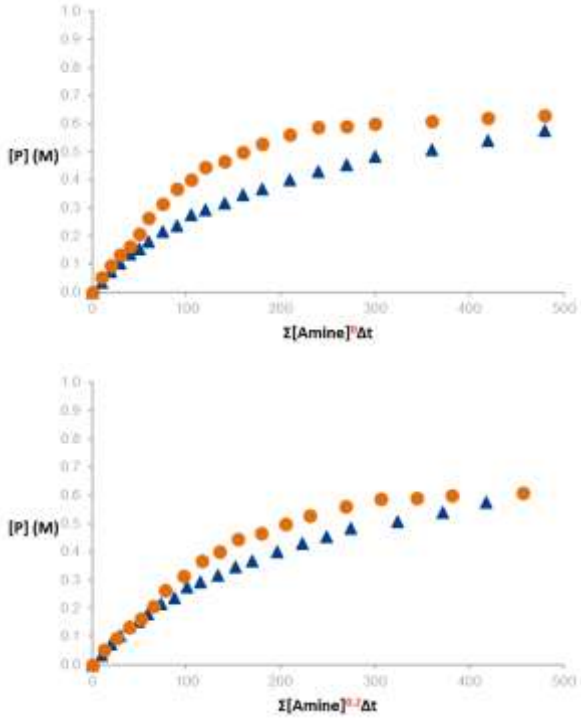
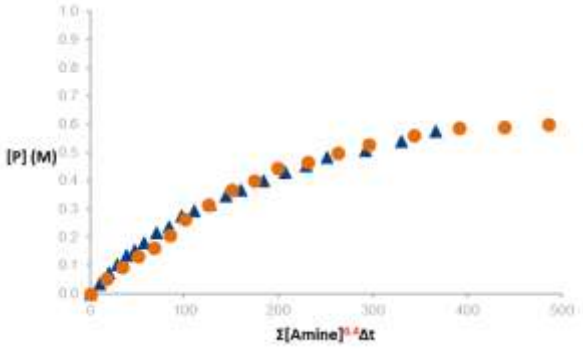
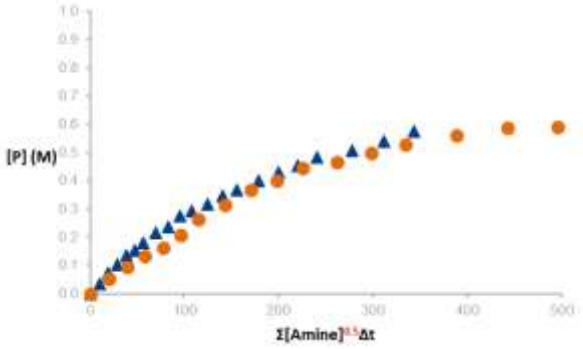
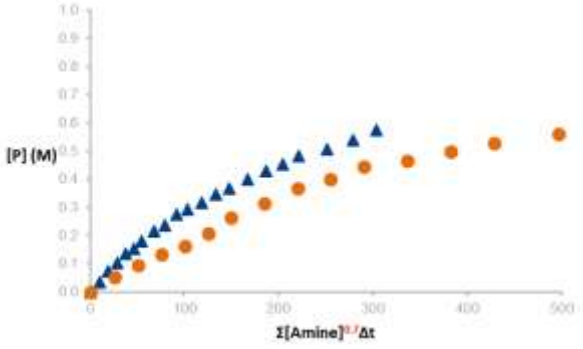


Figure 6. 17 Variable time normalization analysis for the determination of the order in amine (different excess 3 experiment).




[P] (M)
Σ[Amine]^1.4Δt


[P] (M)
Σ[Amine]^1.5Δt


[P] (M)
Σ[Amine]^1.7Δt

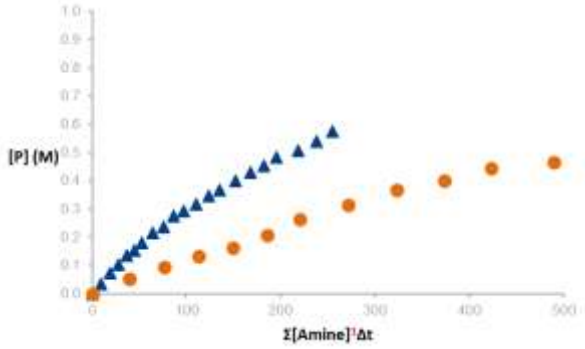


Figure 6. 18 Variable time normalization analysis for the determination of the order in amine (different excess 4 experiment).

Figure 6.16-6.18 demonstrate the overlay for an order of amine using the product concentration profiles. The curves with 0.4 order in amine overlap with the standard curve and other orders in amine do not overlap with the standard. These results corroborate a fractional 0.4 order in amine.

5.4.4. LCMS Analysis of Ir-Complex I

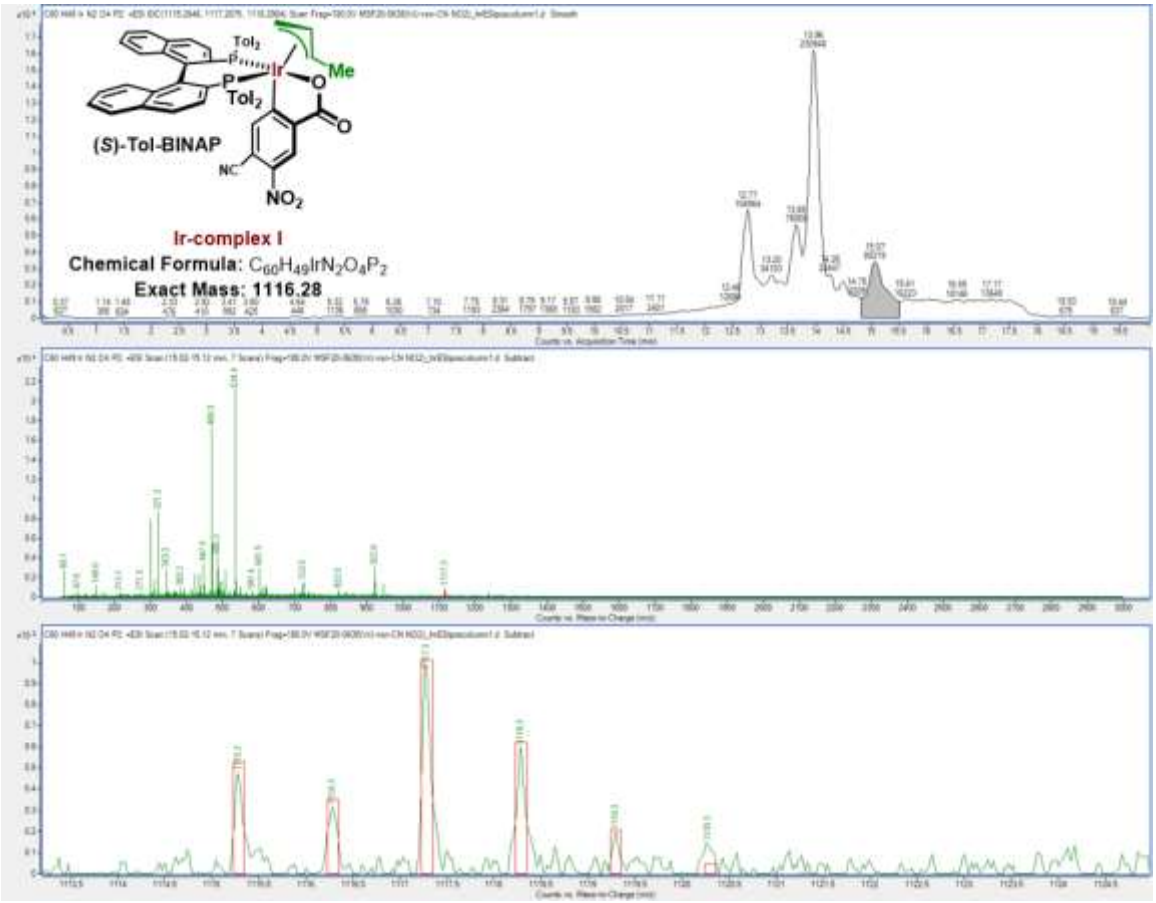


Figure 6. 19 Under the standard ionization conditions of LCMS, target (Ir-complex **I**) is only slightly observed as $[M+H]^+$ at 1117. Ignore the unhighlighted peaks. They are not isomers.

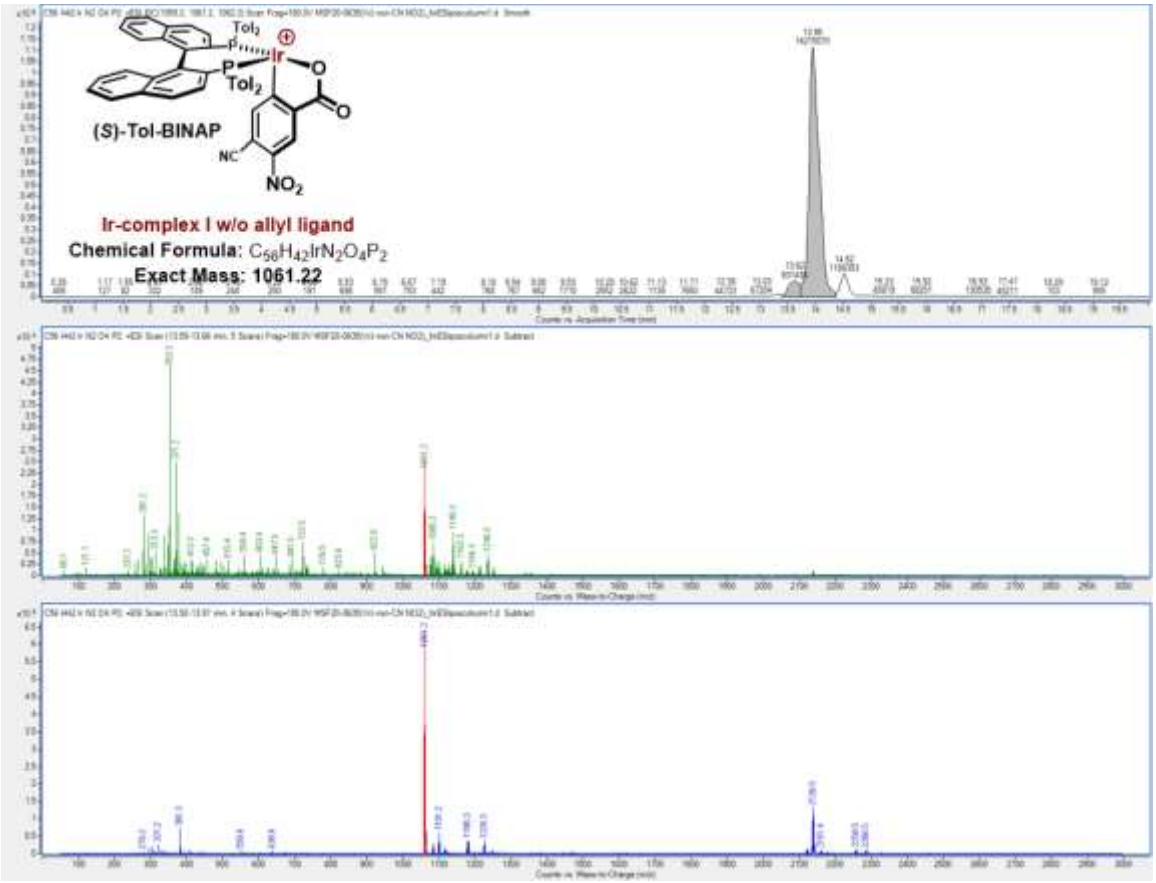


Figure 6. 20 Under the standard ionization conditions of LCMS, the main peak is the catalyst with no C_4H_7 ligand (Ir-complex **I** w/o allyl ligand) as $[M]^+$ at 1061 (two isomers observed). Ignore the unhighlighted peaks. They are not isomers.

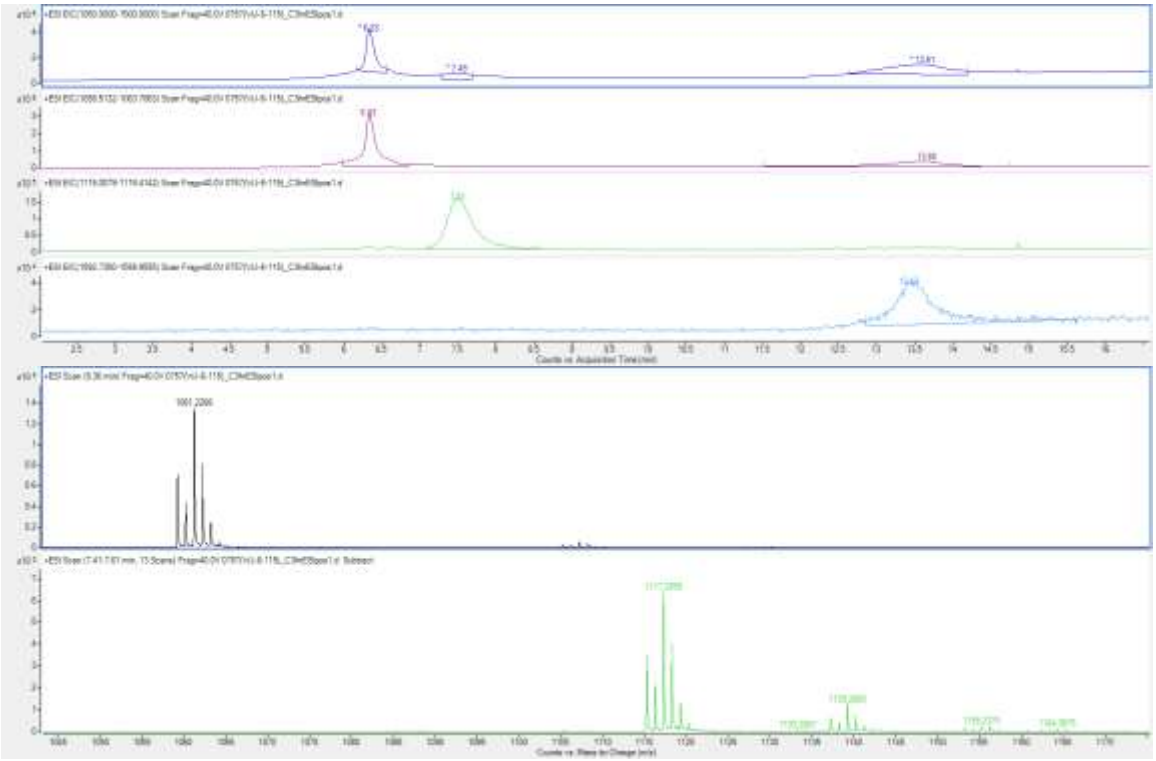
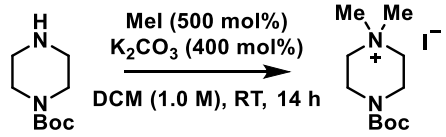


Figure 6. 21 Under very gentle source conditions, the peak at 6.33 min is Ir-complex **I** w/o allyl ligand $[C_{56}H_{42}IrN_2O_4P_2]^+$ (m/z= 1061.2266) and the peak at 7.51 min is from the target (Ir-complex **I**) $[M+H]^+$ at 1117.2858 and $[M+Na]^+$ at 1139.2688.

6.5.5. Mass Spectrometric Analysis

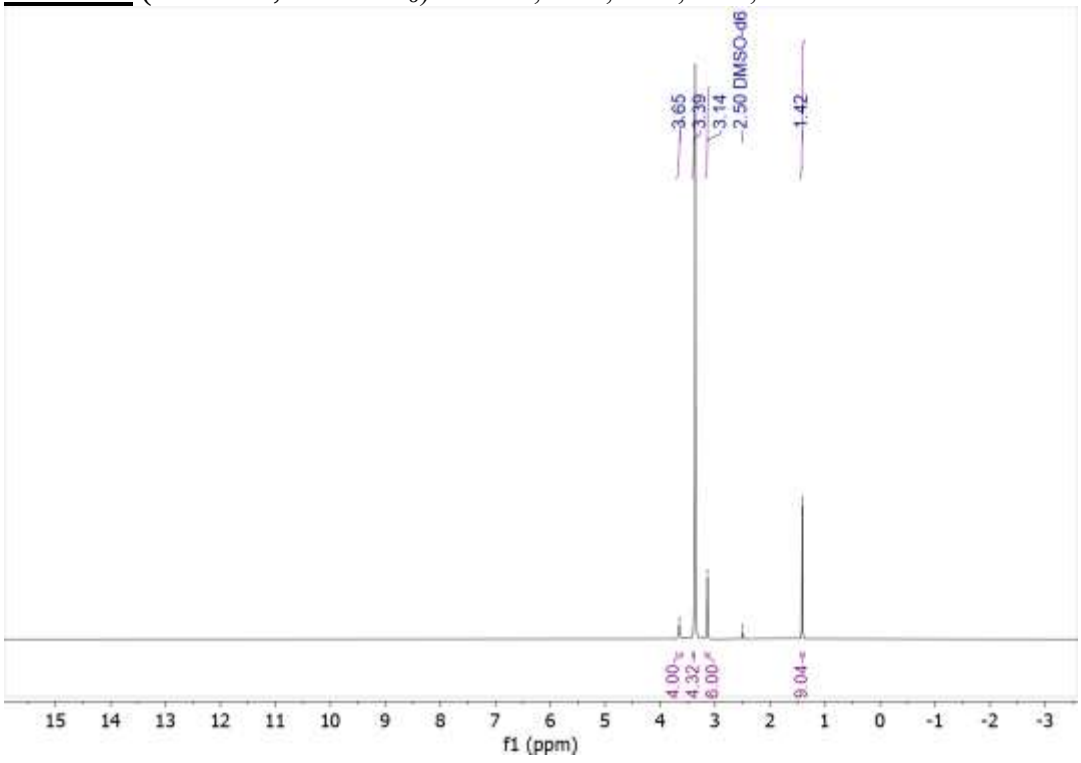
4-(*tert*-Butoxycarbonyl)-1,1-dimethylpiperazin-1-ium iodide (**6.2b-SM**)



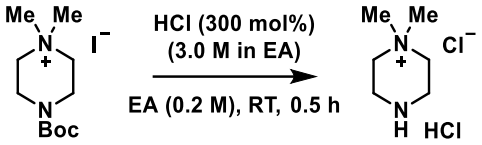
Procedure To a round-bottomed flask charged with 1-Boc-piperazine (0.93 g, 5.0 mmol, 100 mol%), and potassium carbonate (2.8 g, 20 mmol, 400 mol%) was added DCM (2.5 mL, 2.0 M). Iodomethane (1.6 mL, 25 mmol, 500 mol%) were added and the reaction was stirred at room temperature for 14 h. The salt was filtered from the crude mixture using diethyl ether and the title compound obtained in 99% yield (1.7 g, 5.0 mmol) as white powder. The title compound is identical with respect to the reported material.[32]

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.65 (s, 4H), 3.39 (s, 4H), 3.14 (s, 6H), 1.42 (s, 9H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 153.4, 80.0, 59.9, 50.3, 28.0.



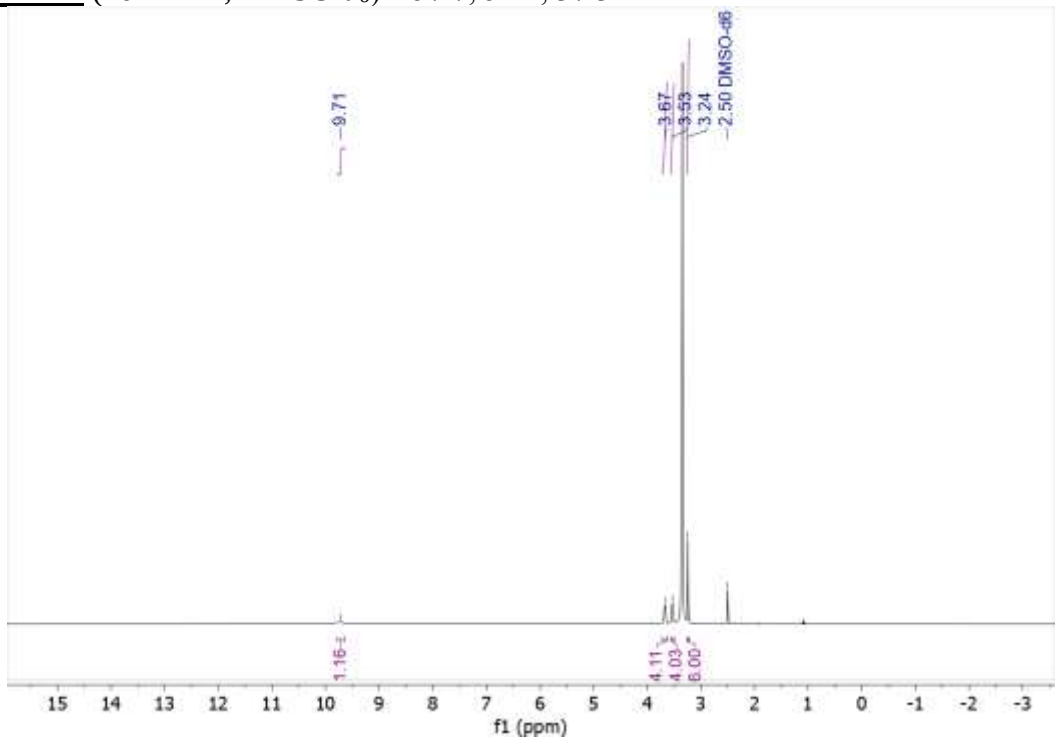
1,1-Dimethylpiperazin-1-ium chloride • HCl (6.2b• HCl)



Procedure To a round-bottomed flask charged with 4-(*tert*-butoxycarbonyl)-1,1-dimethylpiperazin-1-ium iodide (**2b-SM**, 0.34 g, 1.0 mmol, 100 mol%) was added EA (5.0 mL, 0.2 M). HCl solution in EA (3.0 M, 1.0 mL, 3.0 mmol, 300 mol%) were slowly added and the reaction was stirred at room temperature for 0.5 h. The salt was filtered from the crude mixture using diethyl ether and the title compound obtained in 99% yield (0.19 g, 1.0 mmol) as white powder. The title compound is identical with respect to the reported material.[32]

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.71 (s, 1H), 3.67 (s, 4H), 3.53 (s, 4H), 3.24 (s, 6H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 57.7, 51.4, 37.3.



Sample preparation

A pressure tube equipped with a magnetic stir bar was charged with cesium carbonate (0.49 g, 1.5 mmol, 300 mol%) and 1,1-dimethylpiperazin-1-ium chloride•HCl (**6.2b**•HCl, 94 mg, 0.5 mmol, 100 mol%). The tube was purged with argon for 2 minutes. Dry DME (0.5 mL, 1.0 M) was added, and the tube was sealed with a PTFE lined cap and was placed in an oil bath at 60 °C and stirred for 14 hours. After reaching ambient temperature, the crude reaction mixture was filtered and diluted with 2.0 mL of dry DME.

Mass spectrometry and data collection

The crude reaction mixture was further diluted two-fold with dry DME and directly infused into Velos Pro dual linear ion trap mass spectrometer (Thermo Scientific, San Jose, CA) at a rate of 5 uL/min. Analytes were ionized in positive ion mode using 4.5 kV ionization voltage at 300 °C. All MS2 scans were performed in positive ion mode using collisional activation with a normalized collision energy of 25-35% and activation time of 10-20 ms.

Mass spectra

Figure 6. 22. ESI(+)-MS spectrum: Blank Experiment with DME (solvent).

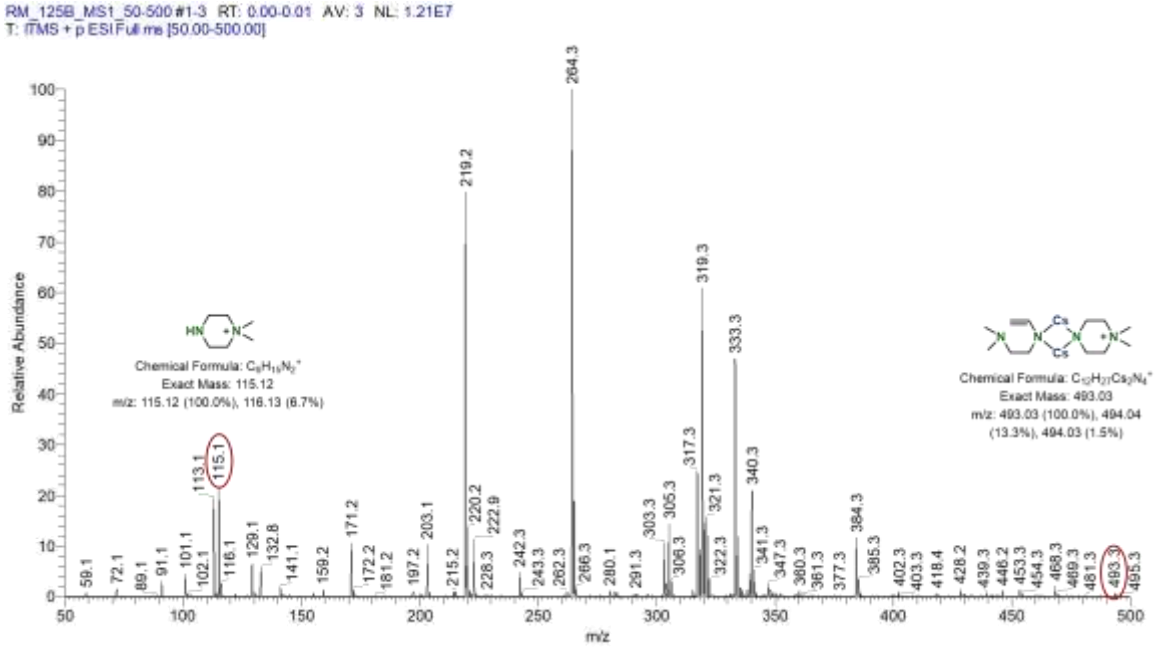


Figure 6. 23 . ESI(+)-MS spectrum from m/z 50 to 500. The parent amine **6.2b** is observed at m/z 115.1.

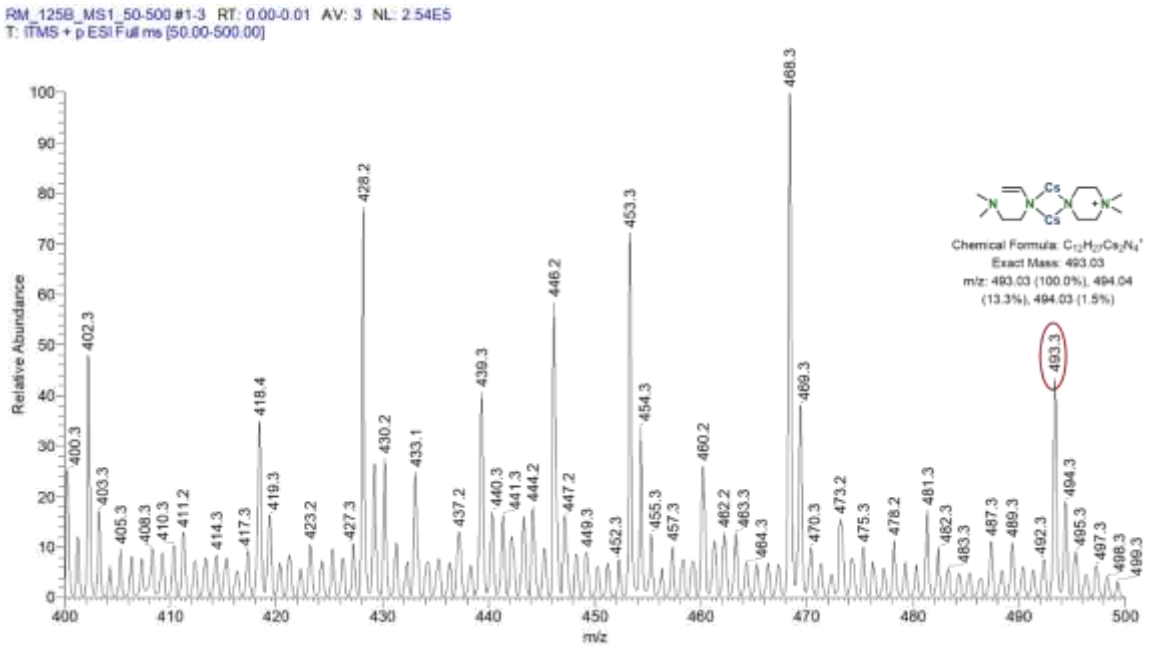


Figure 6. 24 ESI(+)-MS Spectrum from m/z 400 to 500. The proposed cesium-amid dimer is observed as $[M-H]^+$ at m/z 493.3.

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