# The Development of Selenium Catalyzed C-H Allylic Aminations and Palladium Catalyzed Aziridine Cross Coupling

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**Abstract**

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Allylic and homoallylic amines have long been valued as key synthetic intermediates in the production of nitrogen-containing compounds due to their ease of synthesis and the presence of a readily functionalizable alkene moiety. Despite the advancements in organic methodology, synthesizing these highly valuable nitrogen containing compounds remains challenging due to limitations in current existing methods. Herein, the synthesis of homoallylic amines with highly substituted alkenes was realized using a palladium catalyst starting from alkyl aziridines and alkenylboronic acid. This reaction provides facile access to highly regioselective homoallylic amines and provides an alternative to enantiospecific synthesis with a chiral starting aziridine. A metal free direct C-H allylic amination was achieved using a selenium-based catalyst. We discovered that the ligand plays a critical role, enabling the incorporation of nitrogen functionality

onto mono-, di-, tri-, and tetrasubstituted alkenes with high regioselectivity and diastereoselectivity. Biological active molecules were coupled to complex natural products demonstrating the utility of this developed reaction in late-stage functionalization.

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| Å: | Angstrom |
| Ac: | Acetyl |
| Ar: | Aryl |
| Bn: | Benzyl |
| Bz: | Benzoyl |
| Boc: | *tert*-Butyloxycarbonyl |
| Cbz: | Carbobenzyloxy |
| Cy: | Cyclohexyl |
| dba: | Dibenzylideneacetone |
| DCC: | N,N'-Dicyclohexylcarbodiimide |
| DCE: | Dichloroethane |
| DMSO: | Dimethyl sulfoxide |
| DMAP: | 4-Dimethylaminopyridine |
| dppf: | Bis(diphenylphosphino)ferrocene |
| ESI MS: | Electrospray Ionization Mass Spectrometry |
| Et: | Ethyl |
| GC/MS: | Gas Chromatography/ Mass Spectrometry |
| hr: | Hour |
| Hz: | Hertz |
| IMe: | 1,3-Di-methylimidazole-2-ylidine |
| IMes: | 1,3-Bis(2,4,6-trimethylphenyl)imidazole-2-ylidine |
| *i*-Pr: | *iso*-Propyl |
| IPr: | 1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidine |
| ItBu: | 1,3-Di-*tert*-butylimidazol-2-ylidine |
| L: | Ligand |
| Me: | Methyl |
| Mes: | Mesityl |
| MHz: | Megahertz |

| | |
|---|---|
| mp: | Melting Point |
| Ms: | Mesyl |
| Nbos: | ortho-Nitrobenzenesulfamyl |
| NHC: | *N*-Heterocyclic carbene |
| NFBS: | *N*-Fluorobenzenesulfonamide |
| NMR: | Nuclear Magnetic Resonance |

Abbreviations for NMR Splitting:

| | |
|---|---|
| s: | singlet |
| d: | doublet |
| t: | triplet |
| q: | quartet |
| quin: | quintet |
| m: | multiplet |
| br: | broad |
| Np: | Naphthalene |
| Ns: | 4-Nitrobenzenesulfonyl |
| Nu: | Nucleophile |
| Ph: | Phenyl |
| PG: | Protecting Group |
| ppm: | Parts Per Million |
| Pr: | Propyl |
| rt: | Room Temperature |
| *t*-Bu: | *tert*-Butyl |
| TBDPS: | *tert*-Butyldiphenylsilyl |
| Tces: | 2,2,2-Trichloroethoxysulfonyl |
| TEMPO: | 2,2,6,6-Tetramethylpiperidine 1-oxyl |
| Tf: | Trifluoromethanesulfonyl |
| Tfes: | 2,2,2-Trifluoroethoxysulfonyl |
| THF: | Tetrahydrofuran |
| TLC: | Thin Layer Chromatography |

| | |
|---|---|
| TMS: | Tetramethylsilane |
| Troc: | 2,2,2-Trichloroethoxycarbonyl |
| Ts: | para-Toluenesulfonyl |

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Next, I would like to thank my lab members: John Tabor, Derek Obenschain, Andrew Holtzen, Valerie Lesniak, Tianyi Zheng, Zach Stein, Jesse Spillane, Alex Dohoda, Parker Maloney, and Janna Berman. Thank you for making my time in lab so much more enjoyable and it is great to watch each one of you grow over these years. A great thanks to members of Lalic lab, especially Mitchell Lee and Avijit Hazra. Mitchell has help me tremendously in my projects with HPLC and Biotage auto column system when I am too busy with other things. Talking about chemistry with Avijit is always a huge pleasure as he is always so creative on solving problems and brainstorm new projects.

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Finally, I would like to thank my family for their love and constant support, I would not be here today without them.

# **Chapter 1.** PALLADIUM-CATALYZED CROSS-COUPLING OF N-SULFONYLAZIRIDINES AND BORONIC ACIDS: STEREOSPECIFIC SYNTHESIS OF HOMOALLYLIC WITH DI- AND TRISUBSTITUTED ALKENES

## 1.1 **INTRODUCTION**

Homoallylic amines have long been valued as key synthetic intermediates in the production of nitrogen-containing compounds due to their ease of synthesis and the presence of a readily functionalizable alkene moiety. One of the most common routes to homoallylic amines is the addition of allylmetal species to imines.[2] Although preparations of homoallylic amines through enantio- and diastereoselective allylation of imines are widely reported, several limitations are still plaguing this common approach. Preparation of homoallylic amines with highly substituted alkenes at the distal position via allylation remains challenging because of the difficulty of obtaining α-substituted allylmetal reagents and allylic transposition of these reagents. For example, a recent report by Hoveyda et. al. gives excellent results for the addition of allylboronates to aryl aldimines, but the allylmetal transposition favors the terminal alkene product (Figure 1.1).[3]

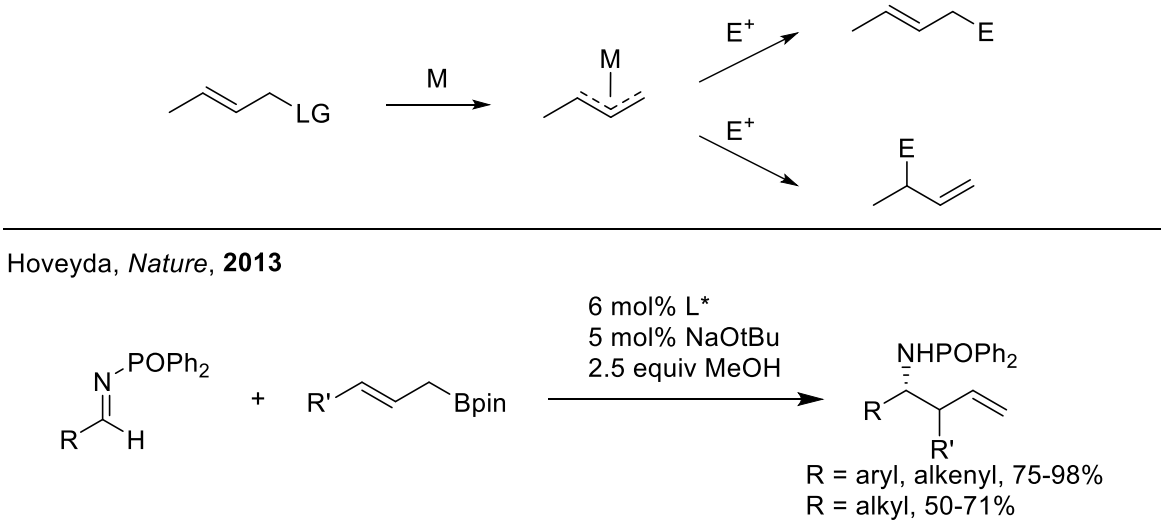



**Figure 1.1** Allyl Transposition of Metal-Assisted Reactions.

In addition to the limitations posed by allylmetal reagents, the yield from additions to alkyl substituted aldimines often suffers compared to their aryl counterparts due to competing tautomerization to the enamine. Buchwald and Niu have also reported highly enantioselective aldimine additions but these only work for aryl aldimines.[4b,4c]

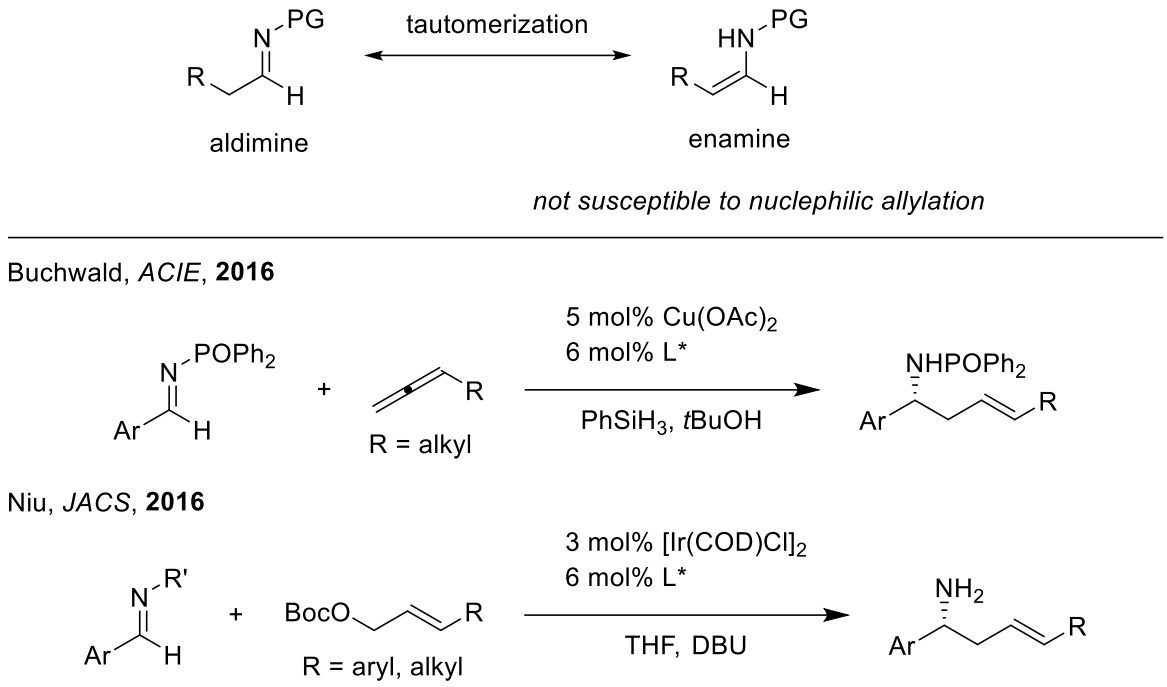



**Figure 1.2** Tautomerization of Aldimines Limits the Reaction.

Syzmoniak and Vasse have shown that cinnamyl zinc reagents have a preference towards linear products through the aldimine addition but the use of zinc reagents xxxx.[4a]

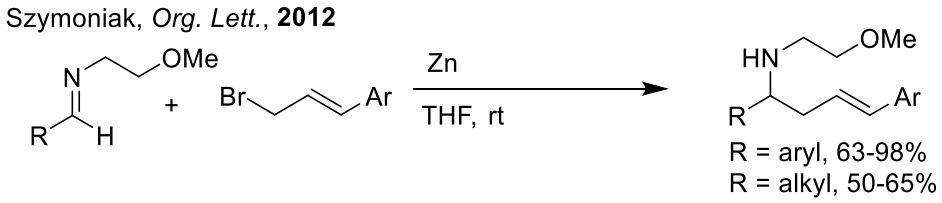



**Figure 1.3** Highly Selective Aldimine Allylation to Achieve Linear Homoallylic Amines.

The ring opening of aziridines with alkenylmetal species, usually lithium dialkenylcuprates, has been an alternative route to access homoallylic amines. While a few examples have been reported, these types of reactions often give poor moderate yields and suffers from functional group incompatibility due to the nature of the cuprate reagents. Specifically,

organocuprate reagents are not compatible with the nosyl protecting group,[4c] which is known for its ease of deprotection.

Recently, our group[6] and several others[7] have reported several Pd- and Ni- cross-couplings using aziridines as an electrophile with organozinc and organoboron nucleophiles (Figure 1.4). Doyle and Jamison have reported the cross coupling of aziridines and organozinc reagents employing nickel as catalyst, achieving arylation and alkylation of aziridines with moderate (Doyle) to high (Jamison) regioselectivity for linear over branched products. In addition to regioselectivity issues, the use of organozinc reagents presents another drawback for the reaction due to functional group compatibility and the use of air and moisture-sensitive alkyl/aryl zinc reagents.

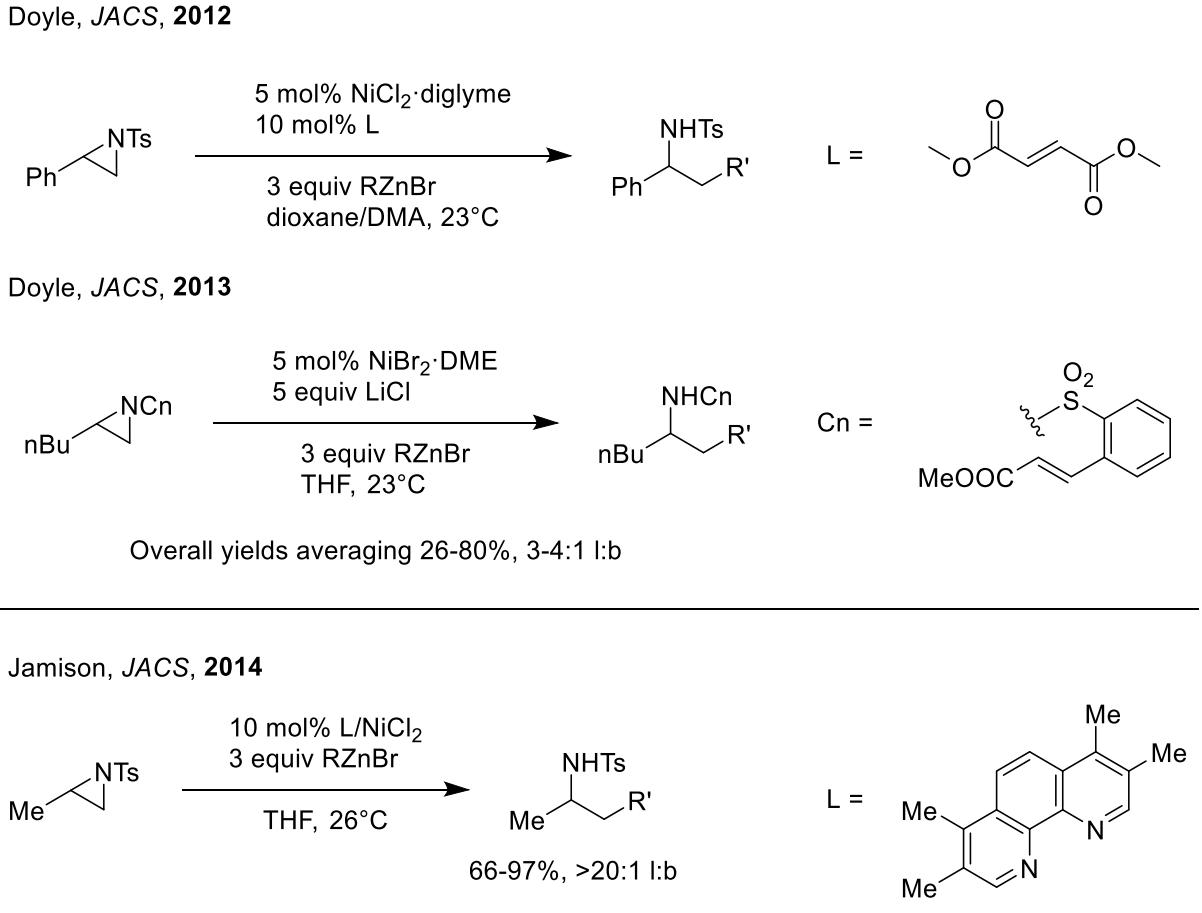



**Figure 1.4** Ring Opening of Aziridine using Aryl/Alkyl zinc reagents.

The development of aziridine cross coupling was further expanded by Dr. Megan Duda from our group using palladium as catalyst and arylboronic acids as the nucleophilic coupling

partner.[6] This discovery addressed several limitations imposed by previous work as our method drastically improved the regioselectivity of the products (l:b >20:1 for all cases) and eliminate the needs of using highly sensitive organozinc reagents, allowing a broader scope of substrates and functional groups. Minakata later has reported a complementary method to our work using palladium catalyst and arylboronic acids giving high selectivity to the branched regioisomer, albeit the scope is largely limited to aryl groups at the 2- position of aziridine.[7d]

Based on the prior success of our group and our understanding of palladium catalyzed cross coupling of aziridine and arylboronic acids, we envisioned that alkenylboronic acids could be a potential nucleophilic coupling partner, providing a straightforward access to a range of highly regioselective substituted homoallylic amines.

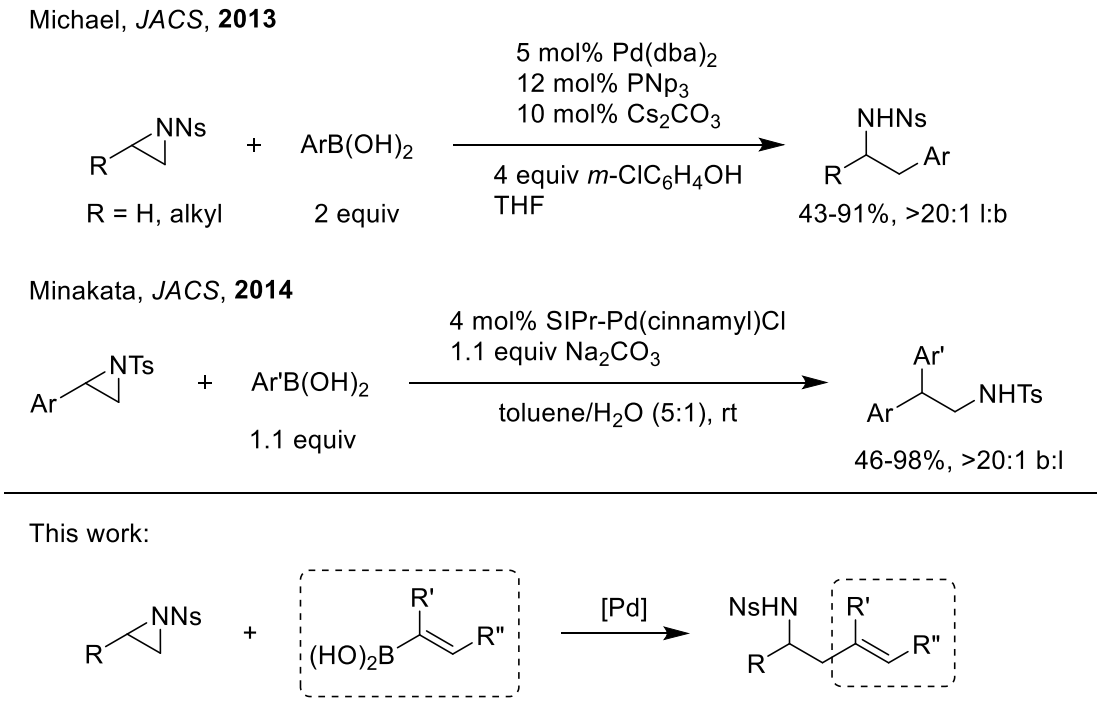



**Figure 1.5** Palladium Catalyzed Cross Couplings of Aziridine and Potential Extensions.

## 1.2 RESULTS AND DISCUSSION

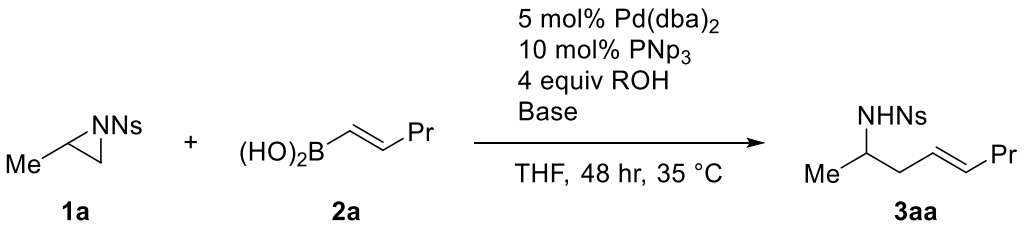
### 1.2.1 *Reaction Optimization*

We started the reaction development by testing the reaction between methyl aziridine **1a** and pentenyl boronic acid **2a** using previously optimized reaction conditions developed by former

member Dr. Megan Duda, giving the desired product **3aa** in a disappointing 29% yield (Table 1.1, entry 1). Valerie Lesniak, another former member from Forrest Michael laboratory, conducted a thorough screen on proton donors and identified that m-nitrophenol and methyl 4-hydroxybenzoate were a suitable proton donor for the reaction. With that information in hand, we screened the equivalents of base and found that the absence of $Cs_2CO_3$ improved the yields of the reaction to 91% yield (Table 1.1, entry 2) and ultimately settled on the use of m-nitrophenol due to the ease of purification of products.

A selection of experiment parameters such as proton donor (Table 1.2, entry 2&3), phosphine ligand(Table 1.2, entry 2), and alkenyl boronic acid derivatives(Table 1.2, 5-7) were also investigated. Notably, we only observed a slight decrease of 19% in yield when water (Table 1.2, entry 3) was used as proton donor for the reaction demonstrating the robustness of our reaction system in comparison to other established transition metal-catalyzed aziridine cross couplings. Boronic ester, trifluoroborate, and 9-borabicyclo[3.3.1]nonane derivatives that are widely employed in palladium catalyzed cross couplings did not give any reactivity.

**Table 1.1** Effects of Base for Aziridine Cross Coupling

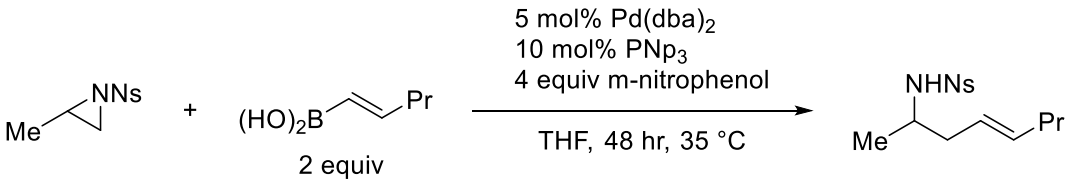


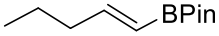
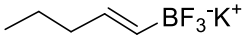
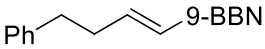

**1a** **2a** 2 equiv **3aa**

| Entry | ROH | Base | Yield %[a] |
|---|---|---|---|
| 1 | m-$ClC_6H_4OH$ | 10 mol% $Cs_2CO_3$ | 29 |
| 2 | m-NO2$C_6H_4OH$ | 10 mol% $Cs_2CO_3$ | 37 |
| 3 | m-$NO_2C_6H_4OH$ | - | 91(82) |
| 4 | m-$NO_2C_6H_4OH$ | 0.25 equiv of $Cs_2CO_3$ | 22 |
| 5 | m-$NO_2C_6H_4OH$ | 1 equiv. of $Cs_2CO_3$ | 0 |

[a]NMR yield was obtained using 1,3-dinitrobenzene as standard. Isolated yields in parenthesis.

**Table 1.2** Selected Parameters for Aziridine Cross Coupling




| Entry | Deviations from Optimal Conditions | Yield %[a] |
|---|---|---|
| 1 | no $Pd(dba)_2$ | n.r. |
| 2 | $P(o\text{-}tol)_3$ instead of $PNp_3$ | 56 |
| 3 | $H_2O$ instead of m-$NO_2C_6H_4OH$ | 72 |
| 4 | phenol instead of m-$NO_2C_6H_4OH$ | 66 |
| 5 |   | n.r. |
| 6 |   | n.r. |
| 7 |   | n.r. |

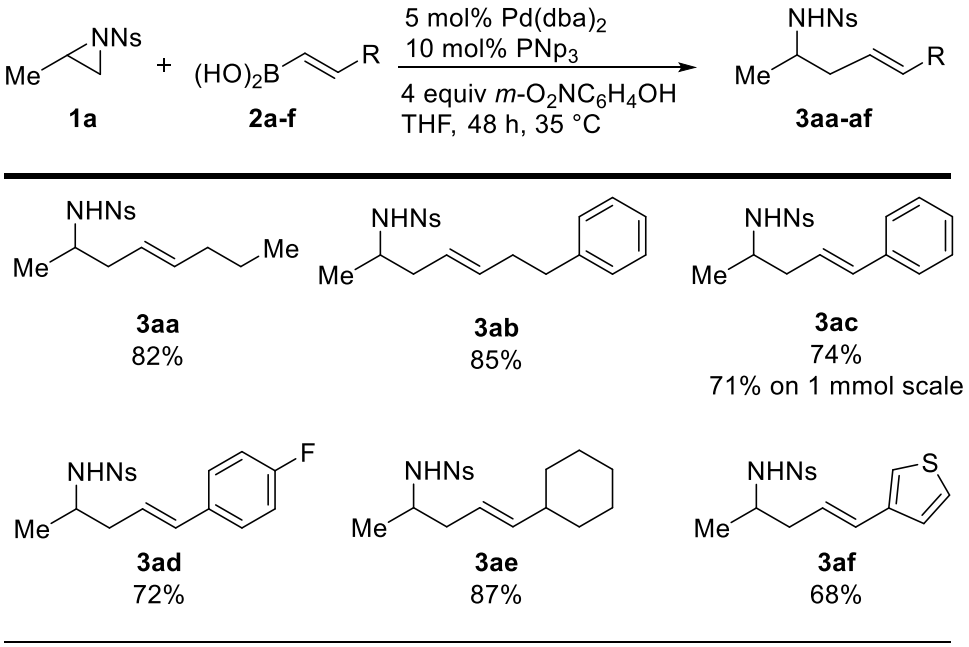
[a]NMR yield was obtained using 1,3-dinitrobenzene as standard.

### 1.2.2 *Substrate scope*

With the optimized reaction conditions in hand, we moved on to couple methyl aziridine **1a** with a wide array of terminal alkenylboronic acids (Scheme 1.1), including both alkyl and aryl-substituted alkenes. The yields are generally high and heteroaromatic substrate (Scheme 1.1, **3af**) was tolerated giving a moderate yield of 68%. The coupling of **1a** and trans-2-phenylvinylboronic acid **2c** was also conducted on a 1 mmol scale giving the product **3ac** with no significant loss in yield.

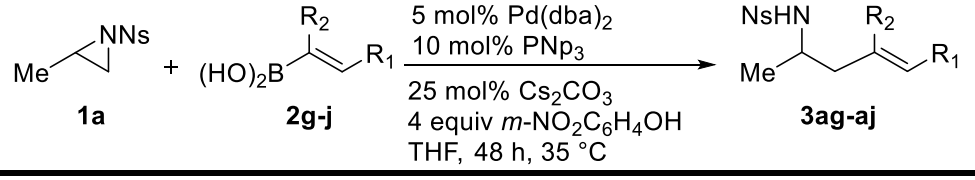
Unfortunately, when we applied the optimized reaction conditions to the internal alkenylboronic acid **2g**, **3ag** was obtained in a disappointing 21% yield (Scheme 1.2). The low yield of cross coupling product and complete consumption of limiting reagent aziridine **1a** suggested that the transmetallation of internal alkenylboronic acid onto our palladium catalyst was outcompeted by side reaction such as β-hydride elimination.

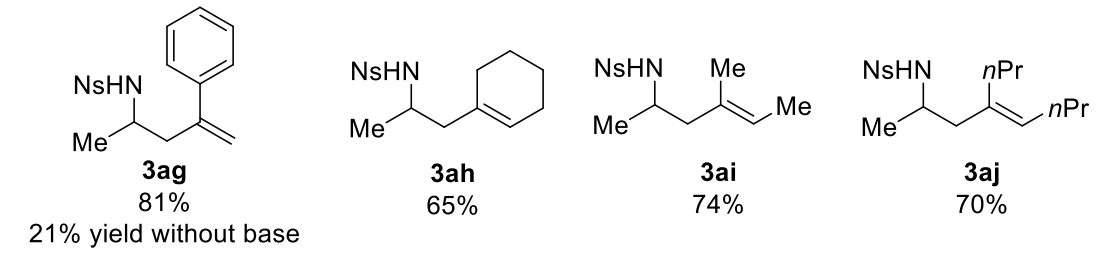
**Scheme 1.1** Substrate scope of Terminal Alkenylboronic Acids with Methylaziridine.




Interestingly, addition of 25 mol % of $Cs_2CO_3$ increased the yield to 81%. These differing requirements for inclusion of base were consistent, i.e., terminal boronic acids gave higher yields in the absence of base, and internal boronic acids gave higher yields in the presence of catalytic base. In the presence of base, a variety of 1,1-disubstituted and trisubstituted alkene products could be synthesized in good yield by coupling of the appropriate internal alkenylboronic acid (Scheme 1.2, **3ag-j**).

**Scheme 1.2** Substrate Scope of Internal Alkenylboronic Acids with Methylaziridine.

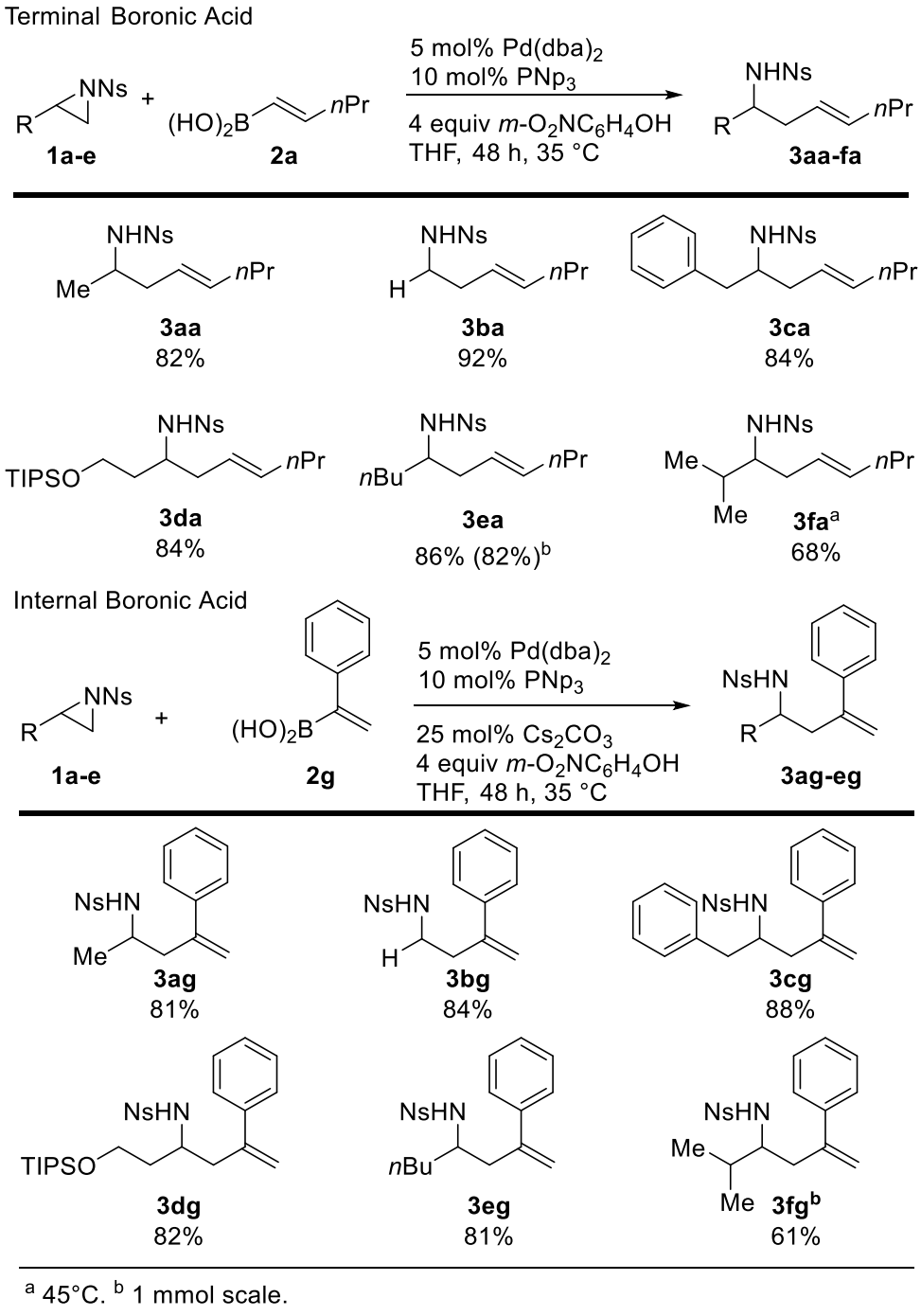



I then moved on to investigate the scope of the aziridine using model substrates 1-pentenylboronic acid (Scheme 1.3, **2a**) for terminal alkenylboronic acid and 1-phenylvinylboronic

acid(Scheme, **2g**) for internal alkenylboronic acid. Unsubstituted aziridine **1b** and several 2-alkyl substituted aziridines (**1c-1e**) coupled in excellent regioselectvity (>20:1 l:b) in all cases while

**Scheme 1.3** Substrate Scope of Aziridine with Internal and Terminal Alkenylboronic acids.




[a] 45°C. [b] 1 mmol scale.

giving good to excellent yields. Furthermore, a 2° alkyl substituent(**1g**) at the 2 position was tolerated which was not observed in our previously reported aziridine coupling. However, the reactivity was lower compared to other aziridines, presumably due to sterics of the substituent,

requiring higher temperature (45°C) and giving lower yields (**3fa, 3fg**). The regioselectivity of the coupling is excellent (>20:1) for all cases. Unfortunately, 2,2-disubstituted or 2,3-disubstituted aziridines gave little to no product under the present conditions.

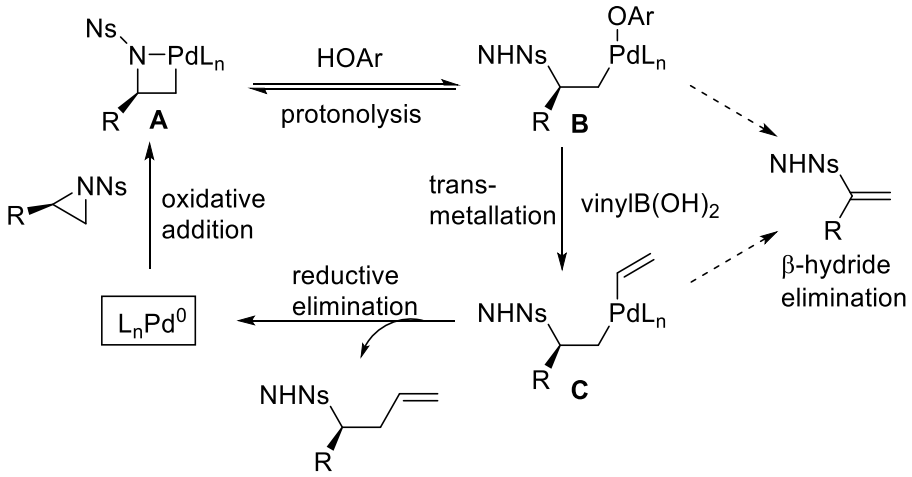


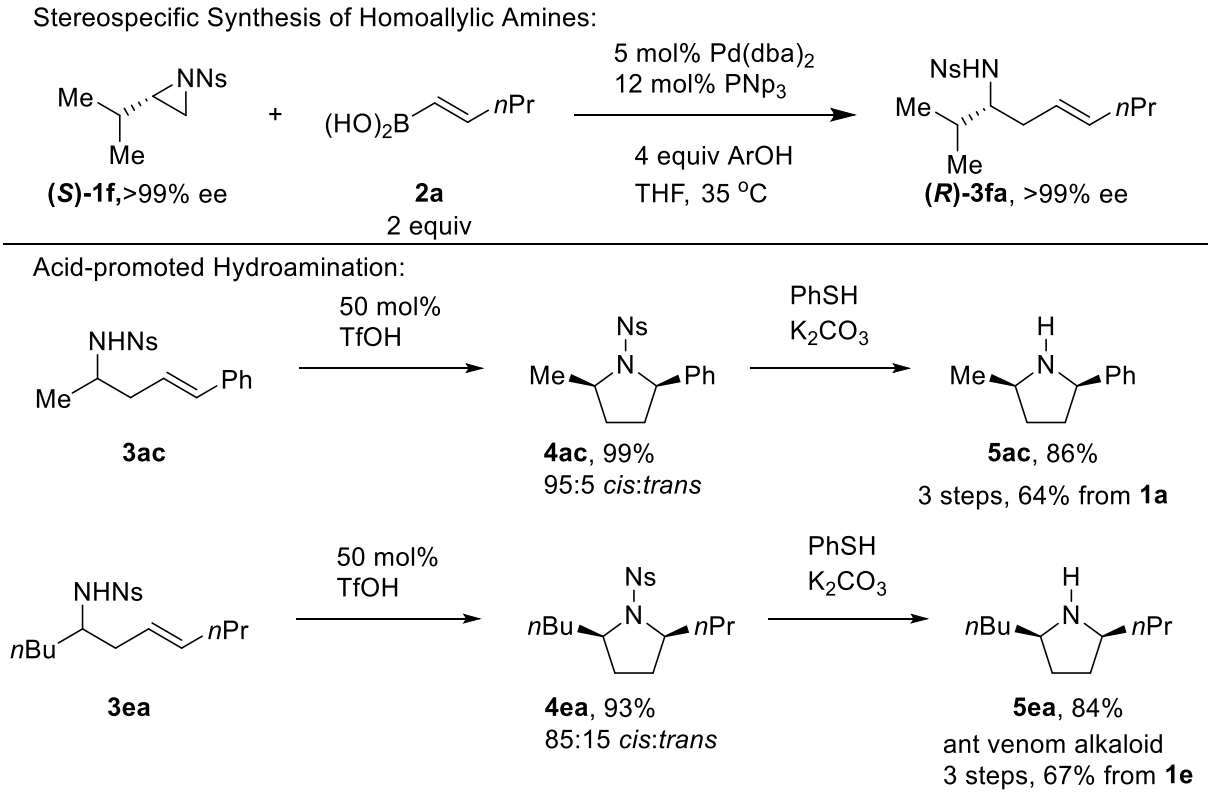

**Figure 1.6** Proposed Catalytic Cycle for Palladium Catalyzed Aziridine-Boronic Acids Cross Coupling.

A plausible catalytic cycle for this coupling reaction is depicted in Figure 1.6. As previously explored by Wolfe,[8] oxidative addition of the aziridine to Pd(0) gives the azametallacycle (**A)**. The high regioselectivity for addition of the unsubstituted C−N bond is consistent with our previous investigations. After oxidative addition, reversible protonolysis of the metallacycle with m-nitrophenol provides the Pd aryloxide (**B**) required for transmetalation of the boronic acid. Finally, rapid reductive elimination from intermediate C takes place to give the homoallylic amine product. Interestingly, the pKa of nitrophenol (pKa(DMSO) = 14.4)[9a] is nearly the same as that of the sulfonamide product (pKa(DMSO) = 13.9 for $NsNH_2$),[9b] which suggests that matching the acidity of the phenol and the sulfonamide is important.

To test the utility of this coupling reaction in the construction of enantiopure amine products, enantioenriched aziridine *(S)*-1f (>99% ee) was subjected to standard coupling conditions (Scheme 6). The homoallylic amine *(R)*-3fa was isolated with no loss of stereochemistry (>99% ee). To illustrate the utility of the homoallylic amine products, compounds **3ac** and **3ea** were cyclized to form 2,5-disubstituted pyrrolidines via acid-promoted hydroamination[10] (Scheme 7). The desired pyrrolidine products were formed in excellent yields and good diastereoselectivity. Compound **5ea** is one of a diverse class of 2,5-dialkylpyrrolidines

that are components of ant venom.[11] The modular sequence described here gave **5ea** in 3 steps and 67% overall yield from aziridine **1e**.

**Scheme 1.4** Synthetic Utilities of Palladium-Catalyzed Aziridine Cross Coupling with Alkenylboronic Acids.




## 1.3 CONCLUSION

In summary, we have developed a new method for coupling 2- alkyl-substituted *N*-nosylaziridines with alkenylboronic acid nucleophiles. This reaction takes place with high regioselectivity and stereospecificity to give enantioenriched homoallylic amines bearing the synthetically useful nosyl protecting group. Both terminal and internal alkenylboronic acids can be coupled in high yields in the presence or absence of catalytic $Cs_2CO_3$, respectively. The resulting homoallylic amines are versatile products and intermediates in the synthesis of nitrogen heterocycles, which we have demonstrated by synthesizing a pyrrolidine natural product.

## 1.4 EXPERIMENTAL

### 1.4.1 *General Procedures and materials*

All reactions were performed under a nitrogen atmosphere using oven-dried or flame-dried glassware unless otherwise indicated. Infrared spectra were acquired using a Perkin Elmer Spectrum RX I spectrometer. Mass spectra were acquired using a Bruker Esquire 1100 Liquid Chromatograph-Ion Trap Mass Spectrometer. Column chromatography was performed using silica gel (Whatman, 60 Å, 230-400 mesh). NMR spectra were recorded on a Bruker AV-300, AV-301, DRX-499, or AV-500 spectrometer. $^{1}$H NMR chemical shifts (δ) are reported in parts per million (ppm) and are referenced relative to TMS (0.00 ppm). $^{13}$C NMR chemical shifts (δ) are reported in parts per million (ppm) relative to the carbon resonance of $CDCl_3$ (77.23 ppm). Melting points were taken on a MEL-TEMP melting point apparatus and are uncorrected. Chiral HPLC analysis was performed on a Shimadzu LC-6AD with a SPD-20A UV/Vis-detector and a Daicel Chiralcel OD-H/AD-H column (.46 cm x 25 cm). Tetrahydrofuran was degassed and dried by passing through a column of neutral alumina. Deuterated solvent ($CDCl_3$) was obtained from Cambridge Isotope Laboratories, Inc. and stored over activated 3Å molecular sieves. Ethyl acetate, hexanes, and dichloromethane were obtained from Fisher Scientific or Sigma Aldrich and used without further purification. Bis(dibenzylideneacetone)palladium(0) was prepared according to the published procedure,[1] and spectroscopic ($^{1}$H NMR, ESI-MS) characterizations were consistent with reported values. Cesium carbonate was obtained from Sigma Aldrich and stored under nitrogen in a glovebox. Phosphine ligands were obtained from Strem, stored under nitrogen in a glovebox, and used without further purification. m-Nitrophenol and m-chlorophenol were obtained from Tokyo Chemical Industry or Sigma Aldrich and used without further purification. Boronic acids **2a, 2c, 2d, 2e,** and **2g** were obtained from Sigma Aldrich, Frontier Scientific, or Fisher Scientific, and used without further purification. Boronic acids **2b, 2f, 2h, 2i,** and **2j** were prepared according to previously published procedures and their respective spectroscopic signatures were found to be consistent with the values reported therein.[6] N-(4-nitrobenzenesulfonyl)-2-methylaziridine (**1a**), N-(4-nitrobenzenesulfonyl)aziridine (**1b**), N-(4-nitrobenzenesulfonyl)-2-benzylaziridine (**1c**), N-(4-nitrobenzenesulfonyl)-2-(2-triisopropylsilyloxyethyl)aziridine (**1d**), N-(4-nitrobenzenesulfonyl)-2-n-butylaziridine (**1e**), and N-(4-nitrobenzenesulfonyl)-2-

isopropylaziridine (**1f**) were prepared according to previously published procedures and their respective spectroscopic signatures were found to be consistent with values reported therein.[6,12]

### 1.4.2 *General Procedure and Characterization of Cross Coupling Products*

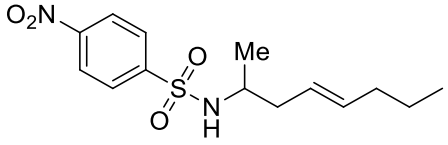
General Procedure A:

A flame-dried borosilicate glass vial equipped with a magnetic stirbar was charged with bis(dibenzylideneacetone)palladium(0) (5.8 mg, 0.010 mmol, 0.05 equiv), tri-1-naphthylphosphine (9.9 mg, 0.024 mmol, 0.12 equiv), aziridine (0.20 mmol, 1.0 equiv), and alkenylboronic acid (0.40 mmol, 2.0 equiv). The vial is thoroughly flushed with nitrogen and capped with a Teflon-lined screw cap. Dry tetrahydrofuran (0.5 mL) was added under nitrogen and the solution was heated to 35 °C and allowed to stir for 48 h. The mixture was then flushed through silica gel with ethyl acetate. The eluent was then concentrated on a rotary evaporator to afford the crude reaction product. 1,3-dinitrobenzene (16.8 mg, 0.10 mmol, 0.5 equiv) was added to the reaction mixture as an internal NMR standard where indicated.

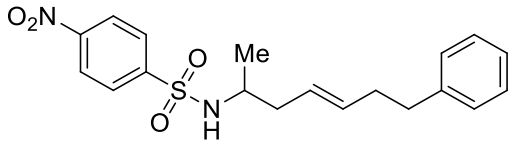
General Procedure B:

A flame-dried borosilicate glass vial equipped with a magnetic stirbar was charged with bis(dibenzylideneacetone)palladium(0) (5.8 mg, 0.010 mmol, 0.05 equiv), tri-1-naphthylphosphine (9.9 mg, 0.024 mmol, 0.12 equiv), aziridine (0.20 mmol, 1.0 equiv), alkenylboronic acid (0.40 mmol, 2.0 equiv) and cesium carbonate (16.3, 0.025 mmol, 0.25 equiv.). The vial is thoroughly flushed with nitrogen and capped with a Teflon-lined screw cap. Dry tetrahydrofuran (0.5 mL) was added under nitrogen and the solution was heated to 35 °C and allowed to stir for 48 h. The mixture was then flushed through silica gel with ethyl acetate. The eluent was then concentrated on a rotary evaporator to afford the crude reaction product. 1,3-dinitrobenzene (16.8 mg, 0.10 mmol, 0.5 equiv) was added to the reaction mixture as an internal NMR standard where indicated.

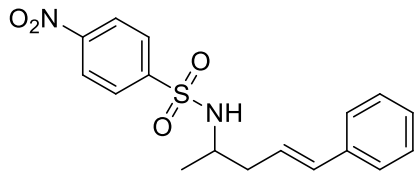
### 1.4.3 *Characterization of Products*



***(E)*-N-(4-nitrobenzenesulfonyl)pent-4-en-2-amine (3aa).** Prepared according to the general procedure A and purified by silica gel chromatography (95:5 hexane/ethyl acetate) to afford the product as yellow wax (51.0 mg, 82% yield). IR (thin film): 3377, 3287, 3104, 2960, 2929, 2872, 2341, 2253, 1607, 1531, 1309, 1166, 1903, 974, 907, 856, 731, 685, 650, 616, 570 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 8.35 (2H, d, J = 8.9 Hz), 8.05 (2H, d, J = 8.8 Hz), 5.42 (1H, dt, J = 14.5, 7.4 Hz), 5.13 (1H, dt, J = 14.8, 7.5 Hz), 4.45 (1H, d, J = 7.4 Hz), 3.52-3.37 (1H, m), 2.06-2.10 (2H, m), 1.91 (2H, q, J = 6.9 Hz), 1.36-1.18 (2H, m), 1.13 (3H, d, J = 6.6 Hz), 0.87 (3H, t, J = 7.3 Hz). $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 148.9, 146.1, 134.5, 127.3, 123.3, 123.2, 49.1, 39.2, 33.6, 21.4, 20.4, 12.6. MS (ESI, negative mode): $C_{14}H_{19}N_2O_4S$ $[M - H]^-$: 311.0.

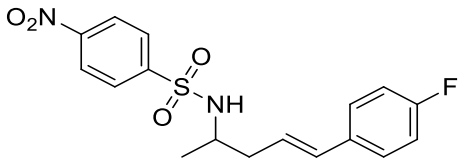



***(E)*-N-(4-nitrobenzenesulfonyl)-7-phenylhept-4-en-2-amine (3ab).** Prepared according to the general procedure A and purified by silica gel chromatography (95:5 to 90:10 hexane/ethyl acetate) to afford the product as an off-white solid (64.0 mg, 85% yield). mp: 124-126 °C. IR (thin film): 3293, 2941, 2873, 1530, 1422, 1350, 1309, 1095, 975, 736, 617 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 8.33 (2H, d, J = 9 Hz), 8.00 (2H, d, J = 9 Hz), 7.14-7.32 (5H, m), 5.42 (1H, dt, J = 14.1, 6.9 Hz), 5.13 (1H, dt, J = 14.7, 7.5 Hz), 4.48 (1H, d, J = 7.8 Hz), 3.35-3.44 (1H, septet, J = 6.6 Hz), 2.63-2.66 (2H, m), 2.29 (2H, q, J = 7.2 Hz), 2.05 (2H, t, J = 6.6 Hz) 1.00 (3H, d, J = 6.6 Hz). $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 150.1, 147.3, 141.7, 134.8, 128.6, 128.4, 126.2, 124.9, 124.5, 49.9, 40.1, 35.7, 34.3, 21.3. MS (ESI, negative mode): $C_{19}H_{22}N_2O_4S$ $[M - H]^-$: 373.8.

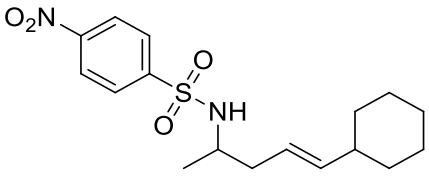



***(E)*-N-(4-nitrobenzenesulfonyl)-5-phenylpent-4-en-2-amine (3ac)**. Prepared according to the general procedure A and purified by silica gel chromatography (90:10 hexane/ethyl acetate) to afford the product as a yellow solid (51 mg, 74% yield). mp: 113-116 °C. IR (thin film): 3294, 3110, 2673, 1605, 1530, 1509, 1421, 1310, 1227, 1166, 1094, 912, 853, 737, 685, 617$cm^{-1}$. $^1H$

NMR (300 MHz, $CDCl_3$) δ 8.15 (d, J = 8.8 Hz, 2H), 7.97 (d, J = 8.8 Hz, 2H), 7.37 – 7.06 (m, 5H), 6.29 (d, J = 15.8 Hz, 1H), 5.78 (dt, J = 15.9, 7.5 Hz, 1H), 4.74 (d, J = 7.9 Hz, 1H), 3.52 (septet, J = 6.3 Hz, 1H), 2.46 – 2.13 (m, 2H), 1.24 (d, J = 6.6 Hz, 3H). $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 149.97, 146.95, 136.66, 134.20, 128.82, 128.35, 128.11, 126.21, 124.72, 124.48, 50.80, 40.86, 22.58. MS (ESI, negative mode): $C_{17}H_{18}N_2O_4S$ $[M - H]^-$: 345.3.

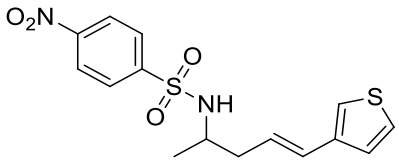



***(E)*-N-(4-nitrobenzenesulfonyl)-5-(4-fluorophenyl)pent-4-en-2-amine (3ad)**. Prepared according to the general procedure A and purified by silica gel chromatography (90:10 to 85:15 pentane/ether) to afford the product as an off-white solid (53 mg, 72%). mp: 114-117 °C. IR (thin film): 3294, 3106, 2675, 1602, 1530, 1509, 1421, 1350, 1310, 1227, 1166, 1094, 971, 909, 853, 736, 685, 617, 567 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$) δ 8.21 (d, J = 8.8 Hz, 2H), 8.00 (d, J = 8.8 Hz, 2H), 7.14 (dd, J = 8.6, 5.4 Hz, 2H), 6.96 (t, J = 8.6 Hz, 2H), 6.27 (d, J = 15.8 Hz, 1H), 5.70 (dt, J = 15.5, 7.5 Hz, 1H), 4.87 (d, J = 7.9 Hz, 1H), 3.52 (septet, J = 7 Hz, 1H), 2.33 (dt, J = 14, 7 Hz, 1H), 2.25 (dt, J = 14.5, 7 Hz, 1H), 1.20 (d, J = 6.6 Hz, 3H).$^{13}C$ NMR (126 MHz, $CDCl_3$) δ 162.52 (d, J = 248 Hz), 149.98, 146.96, 132.95, 128.36, 127.74, 127.51, 124.50, 115.54 (d, J = 22 Hz), 50.67, 40.81, 22.31. MS (ESI, negative mode): $C_{17}H_{17}FN_2O_4S$ $[M - H]^-$: 363.3.

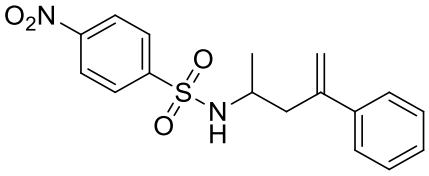



***(E)*-N-(4-nitrobenzenesulfonyl)-5-cyclohexylpent-4-en-2-amine (3ae)**. Prepared according to the general procedure A and purified by silica gel chromatography (90:10 to 80:20 pentane/ether) to afford the product as a clear oil (61 mg, 87% yield). IR (thin film): 3288, 2926, 2851, 1530, 1449, 1420, 1348, 1306, 1161, 1093, 969, 850, 730, 684, 616 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ 8.36 (d, J = 8.9 Hz, 2H), 8.06 (d, J = 8.9 Hz, 2H), 5.37 (dd, J = 15.4, 6.6 Hz, 1H), 5.17 – 4.94 (m,

1H), 4.59 (d, J = 7.4 Hz, 1H), 3.41 (septet, J = 6.6 Hz, 1H), 2.19 – 1.93 (m, 2H), 1.86-1.55 (m, 6H), 1.30 – 1.15 (m, 2H), 1.13 (d, J = 6.5 Hz, 3H), 1.07 – 0.87 (m, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 150.17, 147.33, 141.91, 128.48, 124.54, 121.66, 50.44, 40.88, 40.41, 33.19, 26.29, 26.16, 21.82. MS (ESI, negative mode): $C_{17}H_{24}N_2O_4S$ $[M - H]^-$: 351.4.

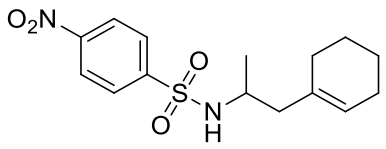


***(E)*-N-(4-nitrobenzenesulfonyl)-5-(3-thienyl)pent-4-en-2-amine (3af)**. Prepared according to the general procedure A and purified by silica gel chromatography (95:5 to 90:10 hexane/ethyl acetate) to afford the product as a yellow solid (48 mg, 68% yield). mp: 119-121 °C. IR (thin film): 3288, 3104, 2974, 2931, 1530, 1420, 1350, 1309, 1165, 1092, 968, 855, 771, 736, 685, 616, 566 $cm^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, J = 8.7 Hz, 2H), 7.99 (d, J = 8.7 Hz, 2H), 7.22 (dd, J = 4.8, 3.0 Hz, 1H), 7.01 (s, 1H), 6.94 (d, J = 4.9 Hz, 1H), 6.31 (d, J = 15.8 Hz, 1H), 5.65 (dt, J = 15, 7.5 Hz, 1H), 4.88 (d, J = 7.9 Hz, 1H), 3.50 (septet, J = 6.3 Hz, 1H), 2.37 – 2.12 (m, 2H), 1.21 (d, J = 6.5 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 150.02, 146.97, 139.41, 128.41, 128.38, 126.52, 124.74, 124.53, 124.47, 122.09, 50.74, 40.77, 22.44. MS (ESI, negative mode): $C_{15}H_{16}N_2O_4S_2$ $[M – H]^-$: 351.2.

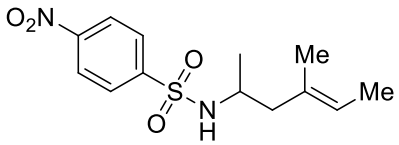


***N*-(4-nitrobenzenesulfonyl)-4-phenylpent-4-en-2-amine (3ag)**. Prepared according to the general procedure B and purified by silica gel chromatography (90:10 to 80:20 pentane/ether) to afford the product as a white solid (56 mg, 81% yield). mp: 108-110 °C. IR (thin film): 3294, 3103, 2920, 2876 1530, 1420, 1350, 1311, 1165, 951, 856, 780, 744, 708, 682 $cm^{-1}$ $^1$H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, J = 8.9 Hz, 2H), 7.83 (d, J = 8.9 Hz, 2H), 7.23 – 7.17 (m, 3H), 7.14 – 7.10 (m, 2H), 5.35 (d, J = 1.1 Hz, 1H), 5.07 (d, J = 0.9 Hz, 1H), 4.56 (d, J = 5.9 Hz, 1H), 3.30 (septet, J = 6.5 Hz, 1H), 2.69 (ddd, J = 14.3, 6.0, 1.0 Hz, 1H), 2.59 (ddd, J = 14.3, 8.3, 0.6 Hz, 1H), 1.22 (d, J

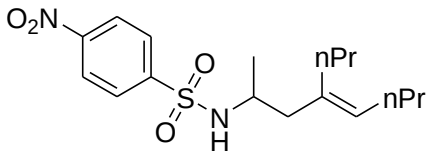
= 6.4 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 150.03, 145.97, 143.74, 138.58, 128.75, 128.32, 128.27, 125.94, 124.36, 116.51, 48.70, 43.47, 22.31. MS (ESI, negative mode): $C_{17}H_{18}N_2O_4S$ [M – H]$^-$: 345.1.



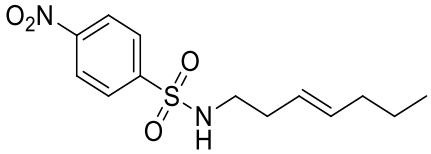
***N*-(4-nitrobenzenesulfonyl)-3-(1-cyclohexenyl)propan-2-amine (3ah)**. Prepared according to general procedure B and purified by silica gel chromatography (90:10 to 85:15 pentane/ether) to afford the product as a cloudy oil (42 mg, 65% yield). IR (thin film): 3288, 2986, 2877, 1530, 1420, 1349, 1310, 1164, 1092, 904, 855, 780, 736, 710, 685, 608, 584 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$) δ 8.36 (d, J = 8.9 Hz, 2H), 8.07 (d, J = 8.9 Hz, 2H), 5.41 (br s, 1H), 4.68 (d, J = 5.8 Hz, 1H), 3.54 – 3.30 (septet, J = 6.6 Hz, 1H), 2.05-1.85 (m, 4H), 1.79 – 1.63 (m, 1H), 1.63-1.34 (m, 5H), 1.15 (d, J = 6.4 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 150.02, 146.97, 133.48, 128.38, 126.12, 124.37, 48.29, 46.30, 27.97, 25.27, 22.64, 22.15, 22.15. MS (ESI, negative mode): $C_{15}H_{20}N_2O_4S$ [M – H]$^-$: 323.2.



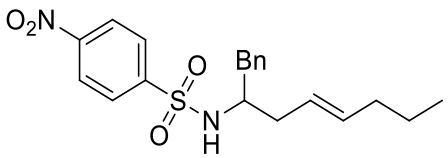
***(E)*-*N*-(4-nitrobenzenesulfonyl)-4-methylhex-4-en-2-amine (3ai)**. Prepared according to the general procedure B and purified by silica gel chromatography (90:10 to 80:20 pentane/ether) to afford the product as an off white wax (44 mg, 74% yield). IR (thin film): 3291, 2975, 2919, 2862, 1530, 1420, 1350, 1309, 1167, 1093, 993, 855, 736, 686, 617, 571, 511, 464 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, J = 8.8 Hz, 2H), 8.04 (d, J = 8.8 Hz, 2H), 5.22 (q, J = 6.6 Hz, 1H), 4.50 (d, J = 5.7 Hz, 1H), 3.52 – 3.27 (m, 1H), 2.10 (dd, J = 8.1, 13.7 Hz, 2H), 1.99 (dd, J = 8.7, 13.5 Hz, 1H) 1.52 (d, J = 6.6 Hz, 3H), 1.27 (s, 3H), 1.16 (d, J = 6.4 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 150.15, 147.06, 131.77, 128.58, 124.43, 123.77, 48.33, 47.87, 22.45, 15.41, 13.70. MS (ESI, negative mode): $C_{13}H_{18}N_2O_4S$ [M – H]$^-$: 297.4.



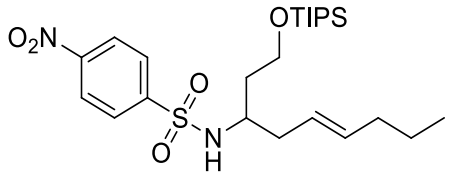

***(E)-N*-(4-nitrobenzenesulfonyl)-4-(n-propyl)oct-4-en-2-amine (3aj)**. Prepared according to general procedure B and purified by silica gel chromatography (90:10 to 80:20 pentane/ether) to afford the product as a yellow oil (51 mg, 70% yield). IR (thin film): 3290, 2947, 2864, 1529, 1451, 1348, 1306, 1161, 990, 891, 850, 735, 686, 617, 571 $cm^{-1}$. $^{1}H$ NMR (500 MHz, $CDCl_3$) δ 8.36 (d, J = 8.7 Hz, 2H), 8.04 (d, J = 8.7 Hz, 2H), 5.13 (t, J = 7.1 Hz, 1H), 4.61 (d, J = 5.6 Hz, 1H), 3.46 – 3.25 (m, 1H), 2.11 (dd, J = 13.8, 5.8 Hz, 1H), 1.98-1.87 (m, 3H), 1.76-1.65 (m, 1H), 1.54-1.44 (m, 1H), 1.33 (sextet, J = 7 Hz, 2H), 1.27 – 1.18 (m, 2H), 1.15 (d, J = 6.3 Hz, 2H), 0.89 (t, J = 7.4 Hz, 3H), 0.78 (t, J = 7.3 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 150.36, 147.33, 135.35, 130.52, 128.67, 124.53, 48.75, 45.27, 31.61, 30.17, 23.32, 22.32, 21.58, 14.25, 14.17. MS (ESI, negative mode): $C_{17}H_{26}N_2O_4S$ $[M - H]^-$: 353.0.



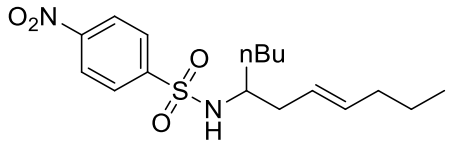

***(E)-N*-(4-nitrobenzenesulfonyl)hept-4-en-1-amine (3ba)**. Prepared according to the general procedure A and purified by silica gel chromatography (95:5 to 90:10 hexane/ethyl acetate) to afford the product as yellow oil (55.0 mg, 92% yield). IR (thin film): 3298, 2955, 1531, 1420, 1351, 1168, 1094, 972, 850, 736, 618 $cm^{-1}$. $^{1}H$ NMR (300 MHz, $CDCl_3$) δ 8.37 (d, J = 8.8 Hz, 2H), 8.05 (d, J = 8.8 Hz, 2H), 5.47 (dt, J = 15, 7.5 Hz, 1H), 5.19 (dt, J = 15, 7.5 Hz, 1H), 4.56 (br t, 1H), 3.06 (q, J = 6.4 Hz, 2H), 2.18 (q, J = 6.6 Hz, 2H), 1.94 (q, J = 7.0 Hz, 2H), 1.35 (sextet, J = 7.2 Hz, 2H), 0.87 (t, J = 7.3 Hz, 3H). $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 150.28, 146.27, 135.18, 128.53, 125.17, 124.62, 43.00, 34.79, 32.80, 22.59, 13.85. MS (ESI, negative mode): $C_{13}H_{18}N_2O_4S$ $[M - H]^-$: 297.2.



***(E)-N*-(4-nitrobenzenesulfonyl)-1-phenyloct-4-en-2-amine (3ca)**. Prepared according to the general procedure A and purified by silica gel chromatography (95:5 to 90:10 hexane/ethyl acetate) to afford the product as off white wax (67.0 mg, 87% yield). IR (thin film): 3300, 2958, 2926, 1529, 1457, 1420, 1347, 1306, 1156, 1093, 1052, 974, 855, 735, 699, 683, 616 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$) δ 8.17 (d, J = 7.5 Hz, 2H), 7.76 (d, J = 7.5 Hz, 2H), 7.17-7.14 (m, 3H), 6.99 (d, J = 6.6 Hz, 2H), 5.49 (dt, J = 14, 7 Hz, 1H), 5.22 (dt, J = 14, 7 Hz, 1H), 4.59 (d, J = 7.8 Hz, 1H), 3.47 (sextet, J = 7 Hz, 1H), 2.81 (dd, J = 13.8, 5.7 Hz, 1H), 2.63 (dd, J = 13.7, 7.8 Hz, 1H), 2.33 – 2.15 (m, 2H), 1.93 (q, J = 7.0 Hz, 2H), 1.34 (sextet, J = 7 Hz, 2H), 0.88 (t, J = 7.3 Hz, 3H).$^{13}C$ NMR (126 MHz, $C_6D_6$) δ 149.90, 146.51, 137.37, 136.16, 129.52, 128.83, 128.22, 126.99, 124.31, 56.11, 41.12, 38.58, 34.96, 22.66, 13.90. MS (ESI, negative mode): $C_{20}H_{24}N_2O_4S$ $[M - H]^-$: 387.3.

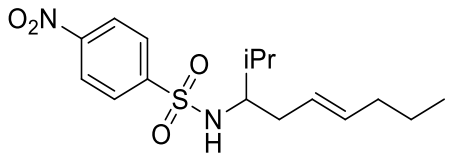



***(E)-N*-(4-nitrobenzenesulfonyl)-1-(triisopropylsilyloxy)non-5-en-3-amine (3da).** Prepared according to the general procedure A and purified by silica gel chromatography (90:10 to 80:20 pentane/ether) to afford the product as yellow wax (83.6 mg, 84% yield). IR (thin film): 3290, 2944, 2867, 1607, 1534, 1464, 1420, 1350, 1310, 1014, 971, 919, 883, 855, 737, 686, 617, 565 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ 8.34 (d, J = 8.7 Hz, 2H), 8.05 (d, J = 8.7 Hz, 2H), 5.85 (d, J = 6.9 Hz, 1H), 5.41 (dt, J = 15, 7.5 Hz, 1H), 5.22 (dt, J = 15, 7.5 Hz, 1H), 3.85-3.78 (m, 1H), 3.67 (dt, J = 10.5, 5.1 Hz, 1H), 3.48 (sextet, J = 6.3 Hz, 1H), 2.38 – 2.13 (m, 2H), 1.90 (q, J = 7.0 Hz, 2H), 1.74 – 1.54 (m, 2H), 1.32 (sextet, J = 7.5 Hz, 2H), 1.15 – 0.99 (m, 21H), 0.86 (t, J = 7.3 Hz, 3H). $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 150.05, 147.55, 135.06, 128.48, 124.91, 124.43, 60.89, 53.53, 37.99, 35.37, 34.88, 22.63, 18.20, 13.85, 11.99. MS (ESI, negative mode): $C_{24}H_{42}N_2O_4SSi$ $[M - H]^-$: 497.4.

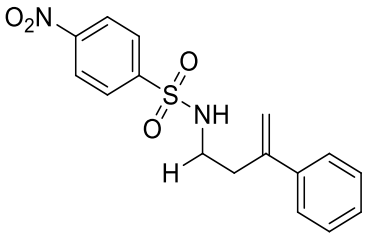



***(E)-N*-(4-nitrobenzenesulfonyl)undec-4-en-7-amine (3ea)**. Prepared according to the general procedure A and purified by silica gel chromatography (90:10 pentane/ether) to afford the product

as yellow oil (61.0 mg, 86% yield). IR (thin film): 3291, 2958, 2872, 1531, 1423, 1350, 1309, 1166, 1094, 972, 854, 736, 686, 618 $cm^{-1}$. $^{1}H$ NMR (500 MHz, $CDCl_3$) δ 8.37 (d, J = 8.3 Hz, 2H), 8.07 (d, J = 8.1 Hz, 2H), 5.36 (dt, J = 14, 7 Hz, 1H), 5.10 (dt, J = 14, 7 Hz, 1H), 4.76 (d, J = 8.3 Hz, 1H), 3.31 (sextet, J = 6.5 Hz, 1H), 2.07 (t, J = 6.3 Hz, 2H), 1.87 (q, J = 7.0 Hz, 2H), 1.51 – 1.35 (m, 2H), 1.35 – 1.26 (m, 2H), 1.26 – 1.10 (m, 4H), 0.85 (t, J = 7.3 Hz, 3H), 0.81 (t, J = 6.4 Hz, 3H).$^{13}C$ NMR (126 MHz, $CDCl_3$) δ 150.10, 147.47, 135.66, 128.47, 124.46, 124.25, 54.56, 38.12, 34.87, 34.65, 27.78, 22.62, 22.54, 14.08, 13.83. MS (ESI, negative mode): $C_{17}H_{26}N_2O_4S$ $[M – H]^-$: 353.5.

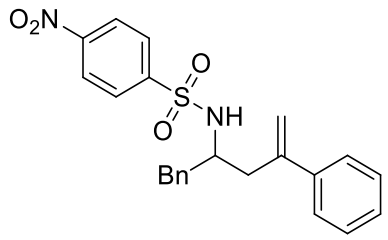



***(E)-N*-(4-nitrobenzenesulfonyl)-2-methylnon-5-en-3-amine (3fa)**. Prepared according to the general procedure A and purified by silica gel chromatography (90:10 to 75:25 pentane/ether) to afford the product as cloudy oil (46 mg, 68% yield). IR (thin film): 3293, 2961, 2873, 1530, 1424, 1350, 1310, 1166, 971, 854, 736, 686, 619 $cm^{-1}$. $^{1}H$ NMR (300 MHz, $CDCl_3$) δ 8.35 (d, J = 8.8 Hz, 2H), 8.05 (d, J = 8.8 Hz, 2H), 5.35 (dt, J = 13.8, 6.9 Hz, 1H), 5.02 (dt, J = 13.8, 6.9 Hz, 1H), 4.56 (d, J = 8.6 Hz, 1H), 3.20 – 3.05 (m, 1H), 2.05 (t, J = 6.5 Hz, 2H), 1.89 – 1.73 (m, 3H), 1.29 (sextet, J = 7.2 Hz, 2H), 0.84 (d, J = 6.6 Hz, 9H). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 150.36, 147.33, 135.35, 130.52, 128.67, 124.53, 48.75, 45.27, 31.61, 30.17, 23.32, 22.32, 21.58, 14.25. MS (ESI, negative mode): $C_{16}H_{24}N_2O_4S$ $[M – H]^-$: 331.0.

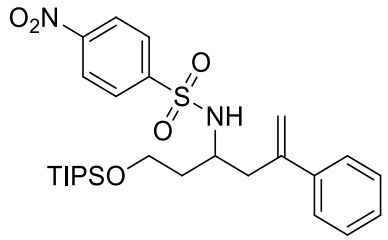



***N*-(4-nitrobenzenesulfonyl)-3-phenylbut-3-en-1-amine (3bg)**. Prepared according to the general procedure B and purified by silica gel chromatography (90:10 to 80:20 pentane/ether) to afford the product as off white solid (56.0 mg, 84% yield). mp: 105-106 °C. IR (thin film): 3294, 3103, 2948, 1530, 1420, 1350, 1311, 1165, 951, 855, 780, 745, 708, 685 $cm^{-1}$. $^{1}H$ NMR (500 MHz, $CDCl_3$) δ

8.25 (d, J = 8.7 Hz, 2H), 7.91 (d, J = 8.7 Hz, 2H), 7.31 – 7.19 (m, 5H), 5.38 (s, 1H), 5.08 (s, 1H), 4.59 (t, J = 5.5 Hz, 1H), 3.11 (q, J = 6.4 Hz, 2H), 2.73 (t, J = 6.5 Hz, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 150.15, 145.69, 144.02, 139.05, 128.83, 128.38, 128.32, 126.13, 124.52, 115.98, 41.46, 35.29. MS (ESI, negative mode): $C_{16}H_{16}N_2O_4S$ [M – H]$^-$: 331.2.

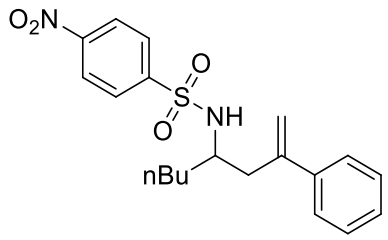



***N*-(4-nitrobenzenesulfonyl)-1,4-diphenylpent-4-en-2-amine (3cg)**. Prepared according to the general procedure and purified by silica gel chromatography (90:10 to 85:15 pentane/ether) to afford the product as yellow wax (74.0 mg, 88% yield). IR (thin film): 3294, 3105, 3029, 2929, 1530, 1454, 1418, 1350, 1311, 1165, 1094, 972, 909, 855, 782, 736, 703, 685, 617 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 8.8 Hz, 2H), 7.30 – 7.04 (m, 8H), 6.86 (dd, J = 7.5, 1.5 Hz, 2H), 5.34 (d, J = 0.9 Hz, 1H), 5.09 (s, 1H), 4.56 (s, 1H), 3.41 – 3.26 (sextet, J = 6.6 Hz, 1H), 2.86 (dd, J = 13.9, 6.0 Hz, 1H), 2.76-2.20 (m, 3H).$^{13}$C NMR (126 MHz, $CDCl_3$) δ 149.82, 145.27, 144.21, 138.91, 137.18, 129.41, 128.83, 128.75, 128.28, 128.14, 127.02, 126.23, 124.13, 116.41, 54.57, 41.73, 41.15. MS (ESI, negative mode): $C_{13}H_{22}N_2O_4S$ [M – H]$^-$: 422.1.

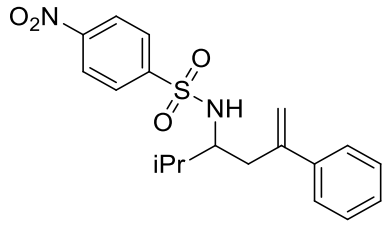



***N*-(4-nitrobenzenesulfonyl)-2-phenyl-6-(triisopropylsilyloxy)hex-1-en-4-amine (3dg).** Prepared according to the general procedure and purified by silica gel chromatography (90:10 to 75:25 pentane/ether) to afford the product as yellow wax (87.0 mg, 82% yield). IR (thin film): 3290, 2947, 2864, 1534, 1462, 1348, 1306, 1166, 1093, 1010, 881, 850, 782, 735, 684 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, J = 7.0 Hz, 2H), 7.81 (d, J = 6.9 Hz, 2H), 7.24-7.21 (m, 5H), 5.92 (d, J = 5.5 Hz, 1H), 5.24 (d, J = 1.1 Hz, 1H), 4.99 (s, 1H), 3.78 (dt, J = 10.8, 5.4 Hz, 1H), 3.52 (dt, J = 10.5, 5.1 Hz, 1H), 3.39 – 3.25 (m, 1H), 2.97 (dd, J = 13.9, 5.6 Hz, 1H), 2.67 (dd, J = 14.1,

8.7 Hz, 1H), 1.57 (q, J = 5.4 Hz, 2H), 1.07 – 0.77 (m, 21H).$^{13}$C NMR (126 MHz, $CDCl_3$) δ 149.95, 146.43, 144.45, 139.12, 128.72, 128.45, 128.19, 126.26, 124.29, 116.09, 60.95, 52.09, 41.17, 35.03, 18.20, 11.93. MS (ESI, negative mode): $C_{27}H_{40}N_2O_4SSi$ [M – H]$^-$: 531.3.



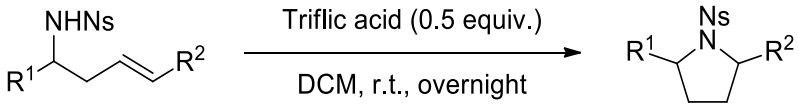

***N*-(4-nitrobenzenesulfonyl)-2-phenyloct-1-en-4-amine (3eg)**. Prepared according to the general procedure B and purified by silica gel chromatography (90:10 to 80:20 pentane/ether) to afford the product as yellow oil (63.0 mg, 81% yield). IR (thin film): 3291, 3104, 2933, 2862, 1530, 1444, 1420, 1350, 1311, 1166, 1093, 1039, 966, 904, 854, 781, 736, 711, 686, 570 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, J = 8.6 Hz, 2H), 7.86 (d, J = 8.6 Hz, 2H), 7.37 – 7.04 (m, 5H), 5.29 (s, 1H), 5.03 (s, 1H), 4.69 (dd, J = 16.3, 6.9 Hz, 1H), 3.24 (sextet, J = 6.6 Hz, 1H), 2.70 (dd, J = 6.3, 14.1 Hz, 1H), 2.60 (dd, J = 7.5, 14.1 Hz, 1H) 1.62 – 1.38 (m, 2H), 1.34 – 0.99 (m, 4H), 0.79 (t, J = 6.7 Hz, 3H).$^{13}$C NMR (126 MHz, $CDCl_3$) δ 149.82, 146.15, 143.83, 138.86, 128.50, 128.19, 127.99, 125.83, 124.08, 116.17, 52.81, 41.10, 34.68, 27.13, 22.34, 13.86. MS (ESI, negative mode): $C_{20}H_{24}N_2O_4S$ [M – H]$^-$: 387.3.



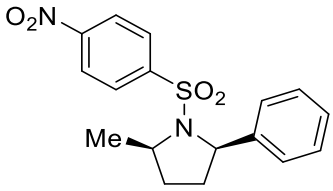

***N*-(4-nitrobenzenesulfonyl)-5-methyl-2-phenylhex-1-en-4-amine (3fg)**. Prepared according to the general procedure B and purified by silica gel chromatography (90:10 to 70:30 pentane/ether) to afford the product as cloudy oil (46 mg, 61% yield). IR (thin film): 3290, 2958, 2875, 1529, 1431, 1348, 1311, 1166, 1088, 1026, 907, 855, 782, 730, 709, 684, 616 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, J = 8.7 Hz, 2H), 7.83 (d, J = 8.7 Hz, 2H), 7.30 – 7.16 (m, 3H), 7.15 – 7.05 (m, 2H), 5.27 (s, 1H), 5.02 (s, 1H), 4.57 (d, J = 7.2 Hz, 1H), 3.27 – 3.11 (m, 1H), 2.74 (dd, J = 14.4,

5.8 Hz, 1H), 2.44 (dd, J = 14.3, 8.6 Hz, 1H), 2.11 – 1.95 (m, 1H), 0.91 (d, J = 6.9 Hz, 3H), 0.80 (d, J = 6.8 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 149.79, 145.98, 143.64, 138.39, 128.49, 128.24, 128.05, 125.71, 124.05, 116.05, 57.47, 36.78, 30.72, 17.54, 17.32. MS (ESI, negative mode): $C_{19}H_{22}N_2O_4S$ $[M - H]^-$:373.3.

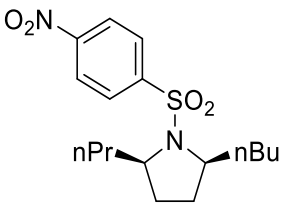
### 1.4.4 *General Procedure for Cyclization of Homoallylic Amines **3ac** and **3ea***



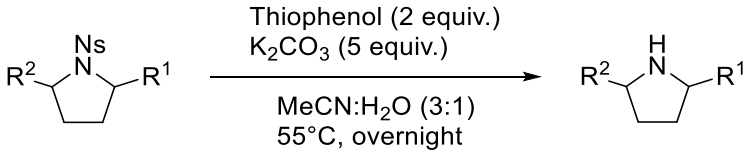

An oven-dried borosilicate glass vial equipped with a magnetic stirbar was charged with the homoallylic amine (1 equiv.) and dry dichloromethane (0.1 M in amine) was added under nitrogen. Triflic acid (0.5 equiv.) was added and the solution was stirred at room temperature overnight. The mixture was then diluted with ethyl acetate (10 mL) and washed with saturated sodium bicarbonate (3x5mL). Crude product was then purified through silica gel column chromatography.



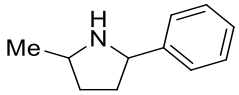

***cis*-*N*-(4-nitrobenzenesulfonyl)-5-methyl-2-phenylpyrrolidine (4ac)**. Prepared according to the general procedure with amine **3ac** (70 mg, 0.2 mmol) and purified by silica gel chromatography (80:20 hexane/ethyl acetate) to afford the product as white solid in a mixture of cis and trans isomers (71 mg, quantitative yield, 95:5 cis:trans). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.24 (d, J = 8.8 Hz, 2H), 7.83 (d, J = 8.8 Hz, 2H), 4.78 (t, J = 6.7 Hz, 1H), 4.20 – 3.99 (m, 1H), 2.13 – 1.78 (m, 3H), 1.70 – 1.54 (m, 1H), 1.49 (d, J = 6.4 Hz, 3H). This matches previously reported values.[13]



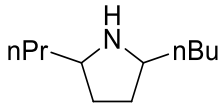
***cis*-*N*-(4-nitrobenzenesulfonyl)-2-n-butyl-5-n-propylpyrrolidine (4ea).** Prepared according to the general procedure with amine **4ea** (145 mg, 0.4 mmol) and purified by silica gel chromatography (90:10 hexane/ethyl acetate) to afford the product as yellow solid in a mixture of cis and trans isomers (135 mg, 93%, 85:15 cis:trans). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, J = 8.9 Hz, 2H), 8.02 (d, J = 8.9 Hz, 2H), 3.96 – 3.78 (m, 1H), 2.13 – 1.61 (m, 4H), 1.43 – 1.01 (m, 10H), 0.98 – 0.71 (m, 6H).




An oven dried borosilicate glass vial equipped with a magnetic stirbar was charged with the respective pyrrolidine (1 equiv.) and potassium carbonate (5 equiv.). A 3:1 mixture of acetonitrile/water was added to the vial to make a 0.1 M solution of pyrrolidine and the mixture was cooled to 0 °C. Thiophenol (2 equiv.) was added and the reaction mixture was allowed to warm to room temperature, and then heated at 55 °C until all the starting material were consumed by TLC. The reaction mixture was then diluted with ether and extracted with 0.5M citric acid (7x2 mL). The aqueous layers were combined and the pH of the solution was raised to approximately 11 using 10 M NaOH. The aqueous layer was then extracted with dichloromethane (5x4 mL) and the solvent was removed under a stream of $N_2$ gas.



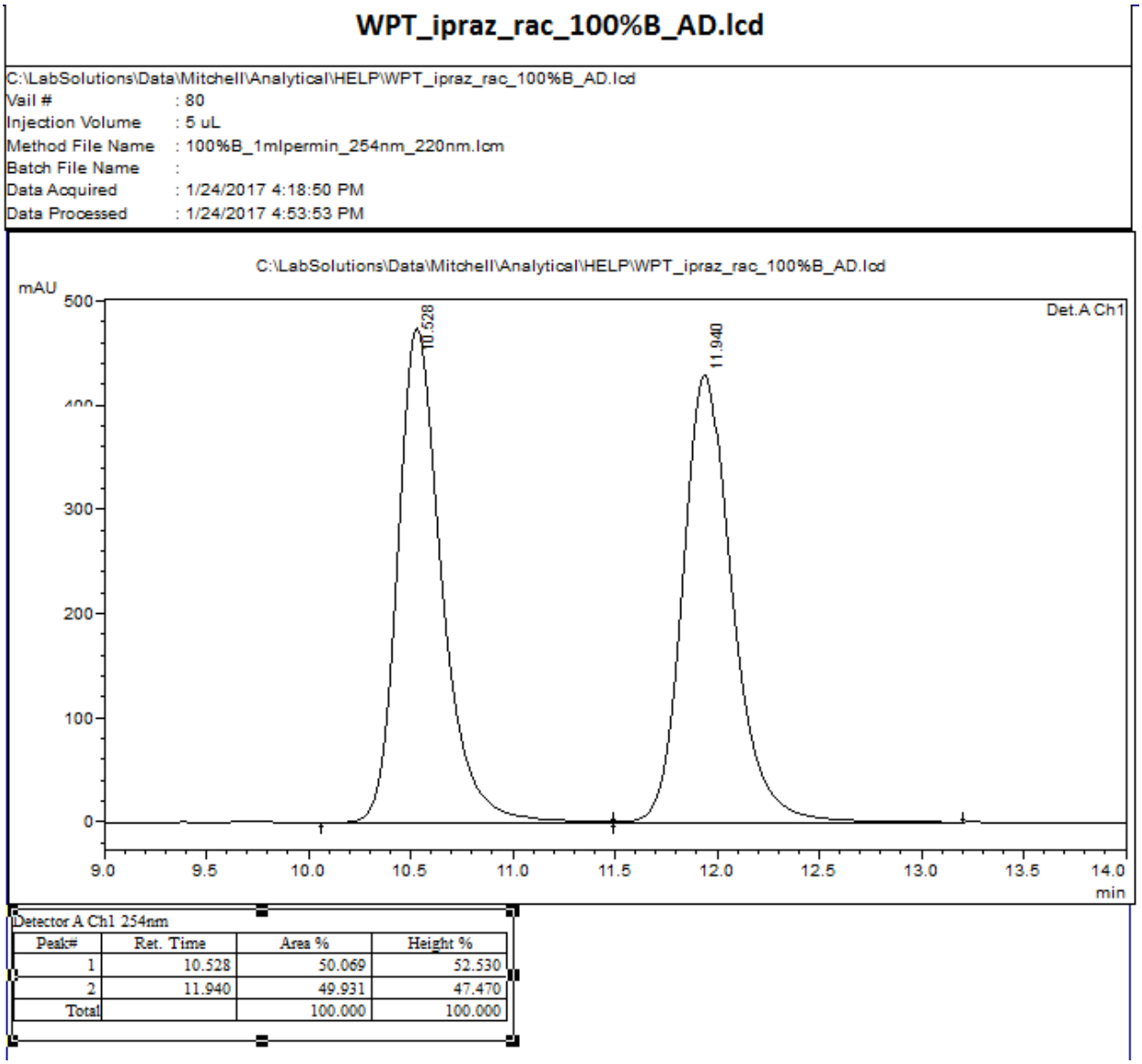

***cis*-2-Methyl-5-phenylpyrrolidine (5ac).** Prepared according to the deprotection procedure with pyrrolidine **4ac** (50 mg, 0.14 mmol) to afford the product as clear oil as a 95:5 mixture of cis and trans isomers (23 mg, 86%). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.49 – 7.15 (m, 5H), 4.14 (t, J = 7.9 Hz, 1H), 3.39 – 3.19 (m, 1H), 2.23 – 2.09 (m, 1H), 2.06 – 1.89 (m, 1H), 1.73 (dddd, J = 12.3, 10.1, 8.3, 5.8 Hz, 1H), 1.44 (dddd, J = 15.6, 9.7, 7.8, 3.8 Hz, 1H), 1.25 (d, J = 6.2 Hz, 3H). This matches previously reported values.[13]

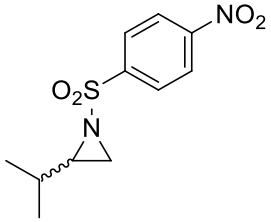



***cis*-2-n-Butyl-5-n-propylpyrrolidine (5ea)**. Prepared according to the deprotection procedure with pyrrolidine **4ea** (135 mg, 0.38 mmol) to afford the product as clear oil as an 85:15 mixture of cis and trans isomers (54 mg, 84% yield). $^{1}$H NMR (500 MHz, $CDCl_3$) δ 3.19 – 3.04 (m, 2H), 1.98 – 1.87 (m, 2H), 1.53 – 1.20 (m, 14H), 0.94 – 0.83 (m, 6H). This matches previously reported values.[7]

1.4.5 *Chiral HPLC Analysis of Aziridine **3f** and Homoallylic Amine **3fa***

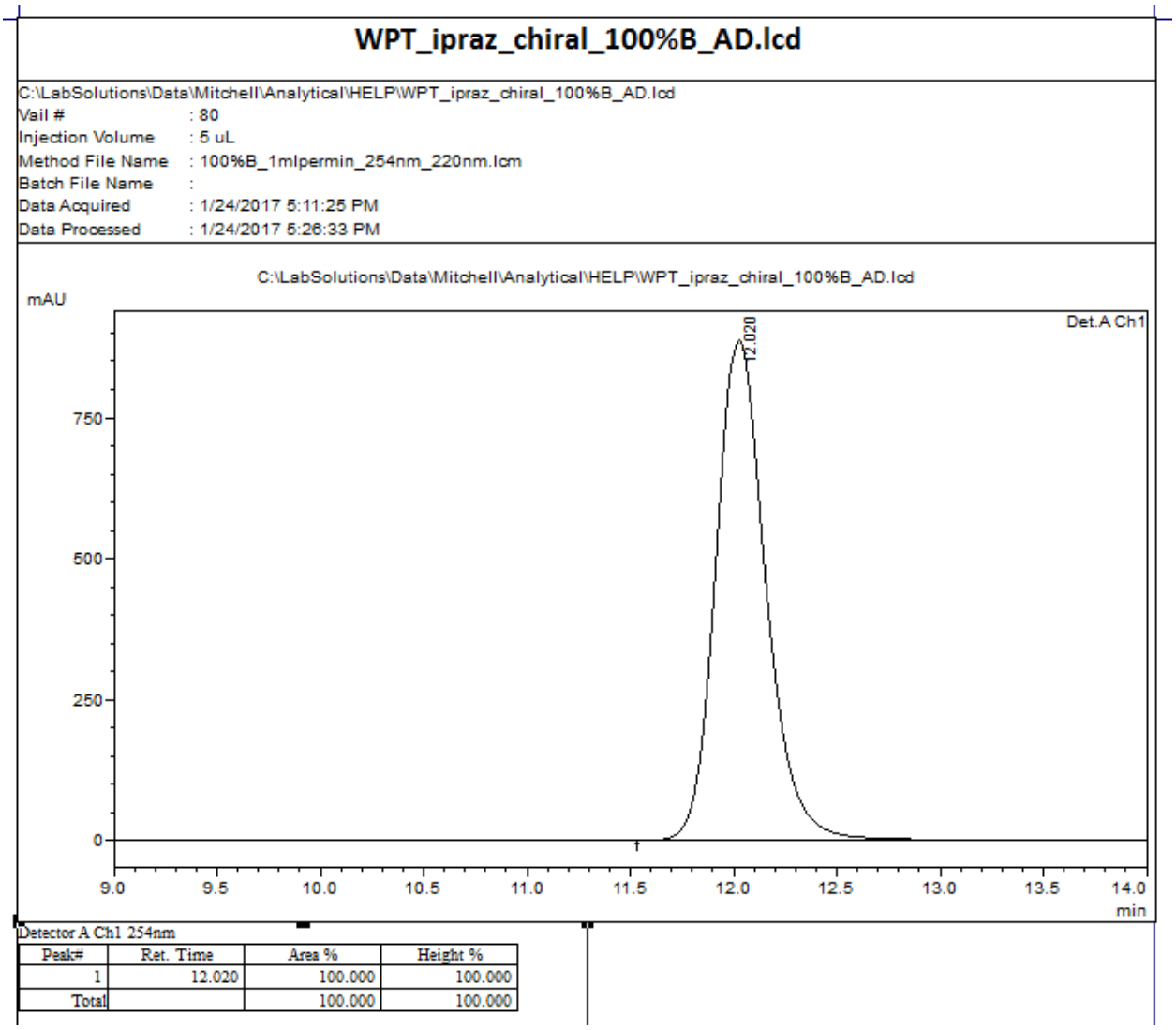
Parameters: 90:10 hexane:iPrOH, 1.0 mL/min



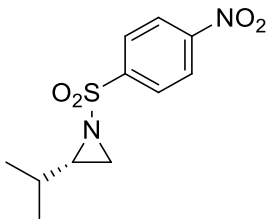

(RS)-Isopropyl aziridine **3f**

Parameters: 90:10 hexane:iPrOH, 1.0 mL/min



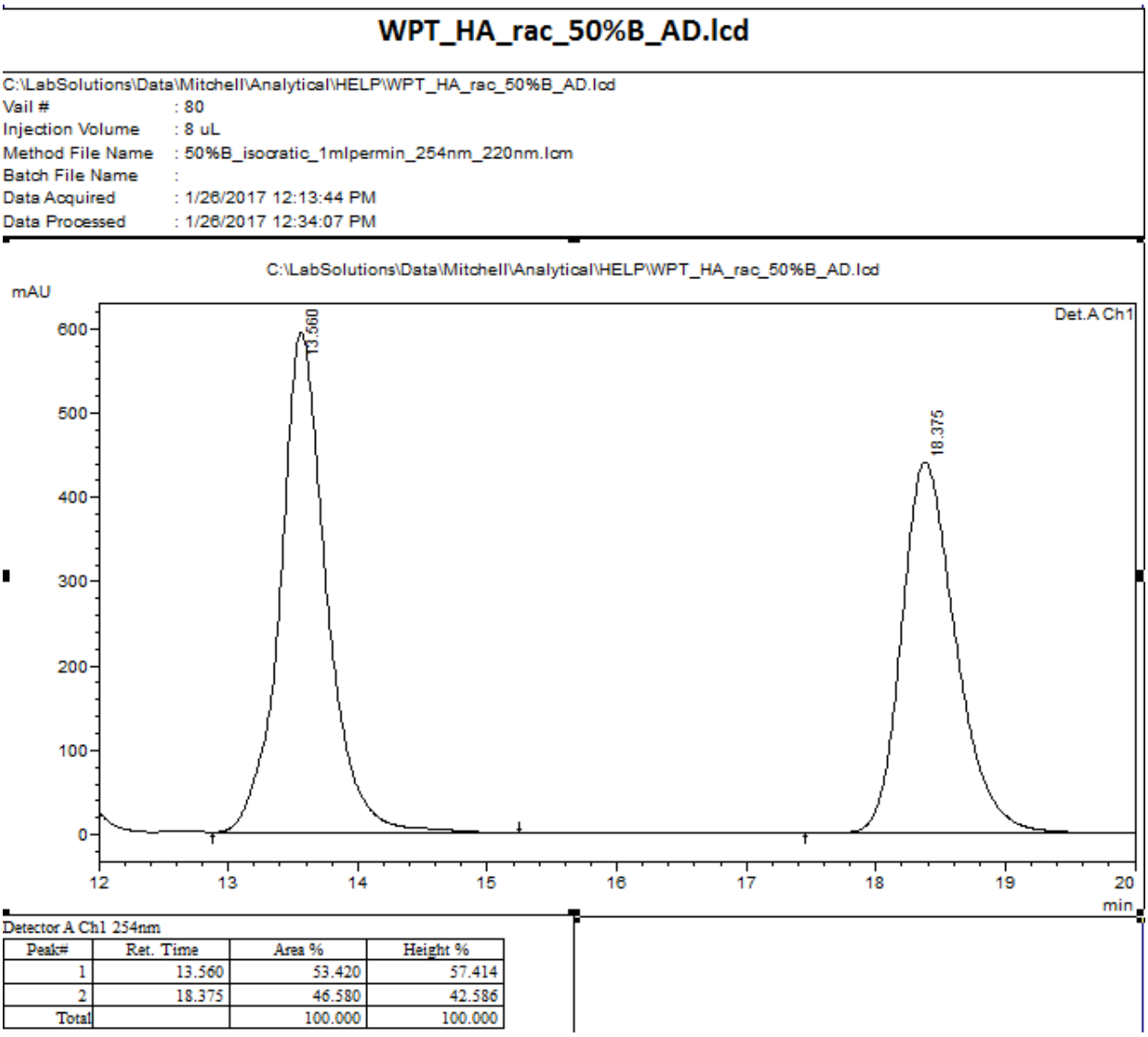

Detector A Ch1 254nm

| Peak# | Ret. Time | Area % | Height % |
|---|---|---|---|
| 1 | 12.020 | 100.000 | 100.000 |
| Total | | 100.000 | 100.000 |



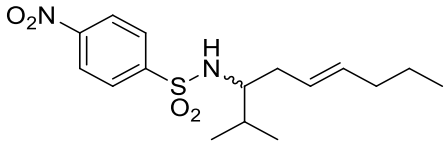

(S)-Isopropyl Aziridine **3f**

Parameters: 95:5 hexane:iPrOH, 1.0 mL/min



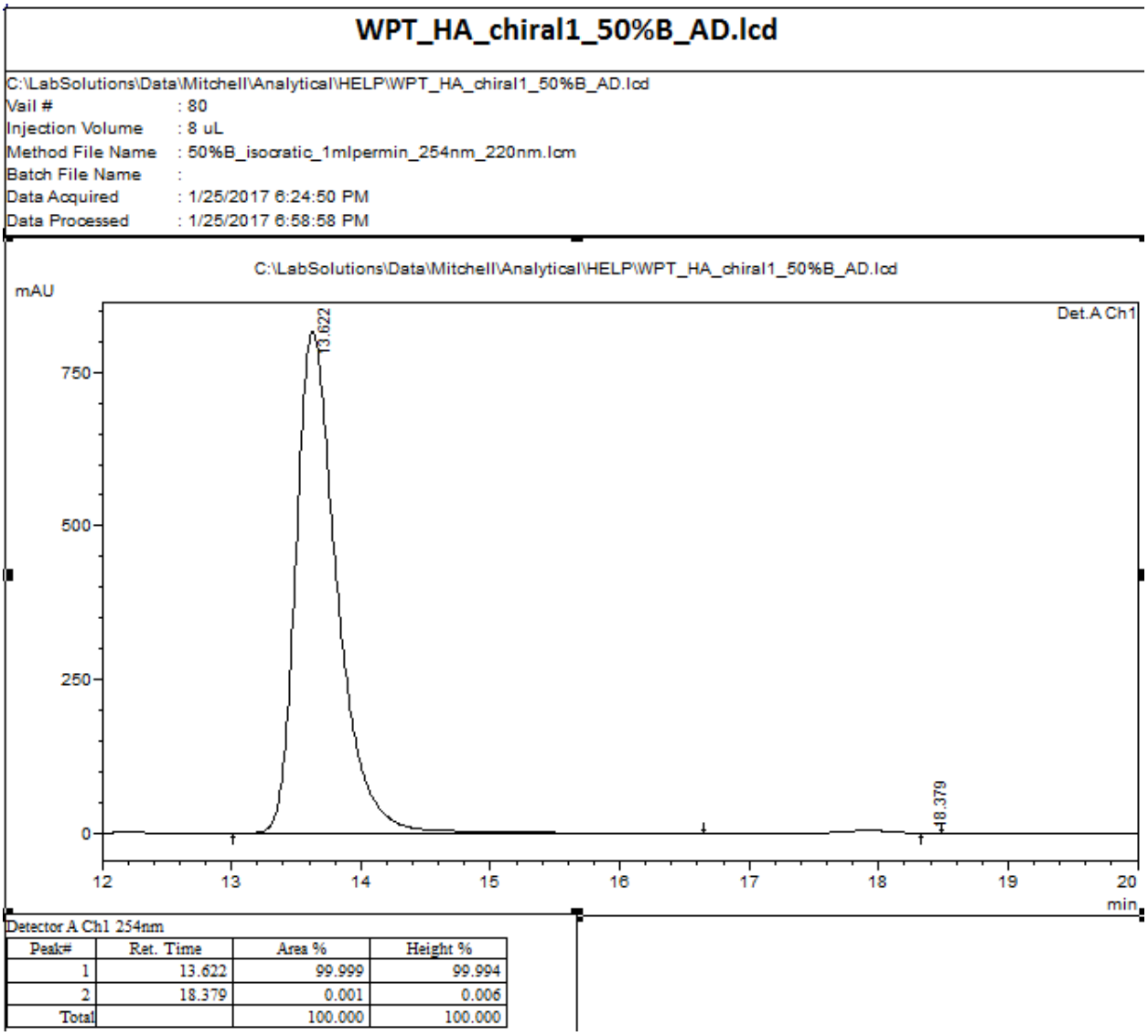

Detector A Ch1 254nm

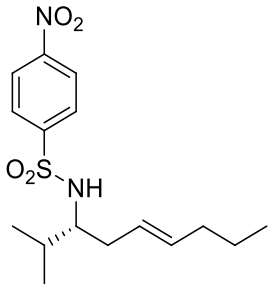
| Peak# | Ret. Time | Area % | Height % |
|---|---|---|---|
| 1 | 13.560 | 53.420 | 57.414 |
| 2 | 18.375 | 46.580 | 42.586 |
| Total | | 100.000 | 100.000 |



(RS)-(E)-N-(4-nitrobenzenesulfonyl)-2-methylnon-5-en-3-amine **3fa**

Parameters: 95:5 hexane, iPrOH, 1 mL/min




(R, E)-N-(4-nitrobenzenesulfonyl)-2-methylnon-5-en-3-amine **3fa**

## 1.5 REFERENCES FOR CHAPTER 1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# **Chapter 2.** CATALYTIC METAL-FREE ALLYLIC C-H AMINATION OF ALKENES

## 2.1 **INTRODUCTION**

The selective replacement of C–H bonds in organic molecules is a powerful tool for introducing new functionality, allowing an efficient and elegant construction of new molecular species. Furthermore, the employment of this technique enables one to achieve diversification at a later stage of synthesis, avoiding the need to for installation of leaving groups for modifications and carefully designed synthetic steps to prevent functional group incompatibility and potential side reactions. As such, this important problem has received significant attention over the last century, resulting in the rapid growth and development on methodology for the formation of new C–O, C–N, and C–C bonds through direct C-H functionalization.[2-4] Considering the well-documented importance of nitrogen in biologically active compounds, the formation of new C–N bonds via C–H amination reactions is a particularly promising application of this technology.[5-8]

Elegant construction of complex molecules is no stranger to biological systems, which is exemplified by the large array of bioactive terpene natural products. Organisms generate complex structures through concise cyclization of acyclic isoprenoid precursors, followed C-H oxidation reactions of exquisite selectivity to construct new C-O bonds, introducing functionality to these natural products to carry out essential biological process.[9,10] Selective C-H oxidation of complex molecules has been successfully achieved by several research groups carrying out total syntheses of natural products and late-stage functionalizations (Figure 2.1).[11-14] These methods employed various strategies to achieve high C-H selectivity, such as targeting the weakest C-H bonds through

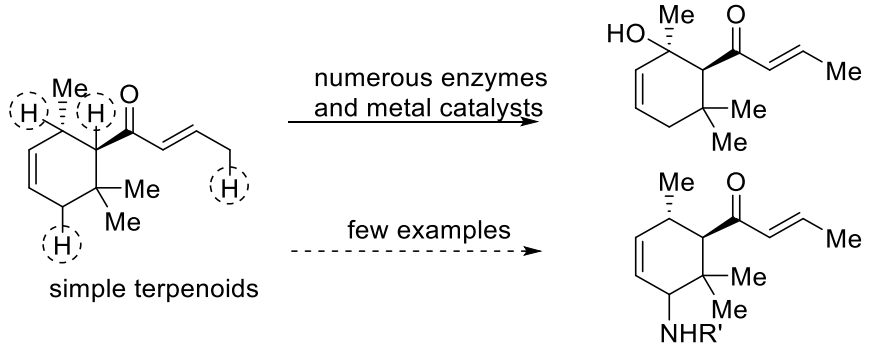



**Figure 2.1** Challenges in Direct C-H Functionalization and Amination

radicals or transition metals, stereoelectronic sensitivity of chemical reactions, or installation of labile directing groups to direct and activate specific C-H bond.

One of the biggest challenges on the development of C-H functionalization on complex molecules is achieving predictable and precise selectivity, due to the vast amount of C-H bonds present (Figure 2.1). Classically, selectivity in reactions is often obtained by activating the weakest C-H bond in the system through radical intermediates, which could be problematic when the desired target has multiple bonds with similar C-H bond dissociation energy. We envision that C-H bonds at the allylic position have the potentially to result in highly regioselective C-H amination as 1) the weakening C-H bond due to adjacent π-system allows the reaction system to distinguish it from other aliphatic C-H bonds, 2) the presence of the alkene potentially acting as a "directing" group though coordination or direct reaction to differentiate the allylic C-H bond from other weakened C-H bonds such as tertiary and benzylic systems. While the presence of the C-C double bond allows us to differentiate different C-H systems in complex molecules, regio- and chemo-selectivity could still be problematic due to the presence of multiple allylic C-H groups and competing side reaction of the alkene. For example, Schomaker reported a catalytic system using

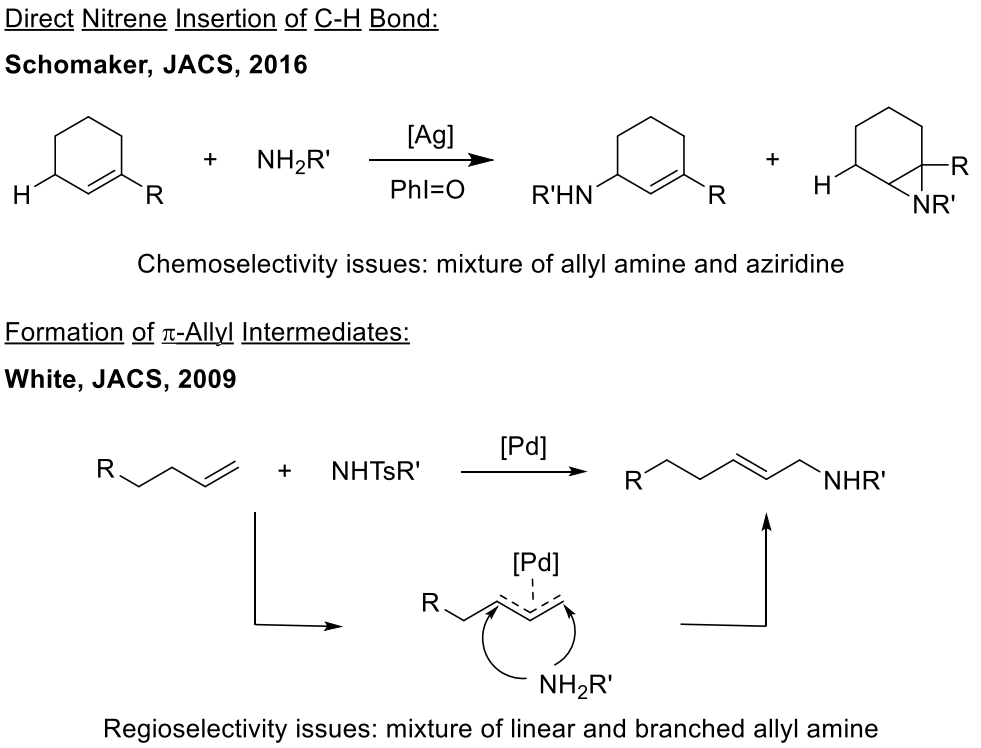



**Figure 2.2** Selected Examples of Transition Metal Catalyzed C-H Amination.[15,17]

a silver catalyst and a combination of nitrene precursor, iodosylbenzene (PhI=O), and sulfamates (Figure 2.2) to generate .[17] While the chemoselectivity can be controlled and tuned by ligand to an extent, the substrate scope is largely limited to symmetrical cyclic substrate to prevent regioisomeric issues. Similarly, radical mediated C-H allylic aminations also suffers from complications such as radical addition to alkenes or alkene transposition due to the nature of radicals, resulting in mixture of products and regioisomers (Figure 2.2). While methods that utilizes formation of π-allyl complexes avoid the formation of aziridines, selectivity could be challenging in unbiased allylic systems, limiting the scope of alkene substitution patterns and systems.[16] Furthermore, most of the systems are optimized to introduce unique or special pre-made nitrogen sources, limiting the scope of functionality that can be introduced through direct C-H allylic amination.[20,21]

In 1976, Sharpless and coworkers developed a C-H allylic amination of a range of simple alkenes with moderate yields.[22,23] This approach uses super-stoichiometric amounts of selenium metal and anhydrous chloroamine-T, generating a selenium bisimide intermediate, to install nitrogen groups in a highly regioselective fashion (Figure 2.3). Unfortunately, the need for explosive nitrogen source along with stoichiometric amounts of selenium hampers the development and application of this reaction. We envisioned that we could overcome these problems by using a catalytic quantity of a selenium catalyst and regenerate the selenium

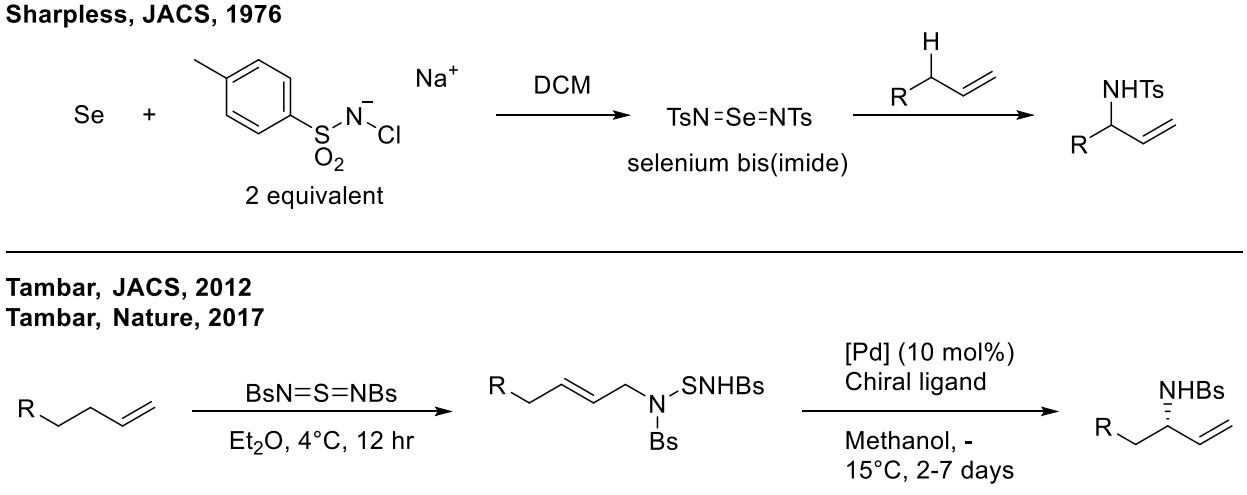


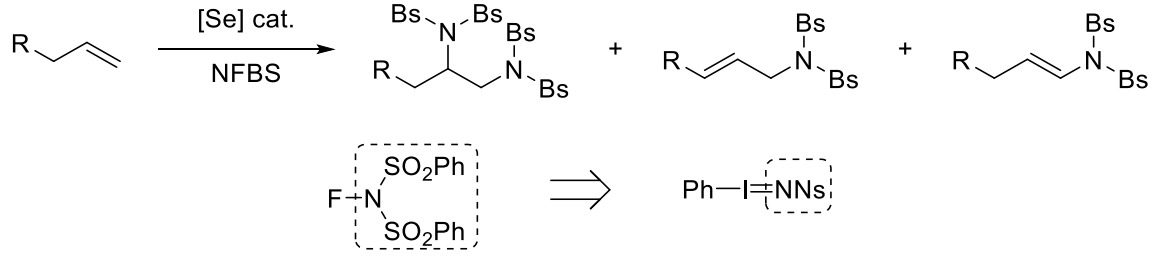

**Figure 2.3** Stoichiometric Selenium Bis(imide) and Sulfur Bis(imide) as Reagents for C-H Allylic Amination.[24,25]

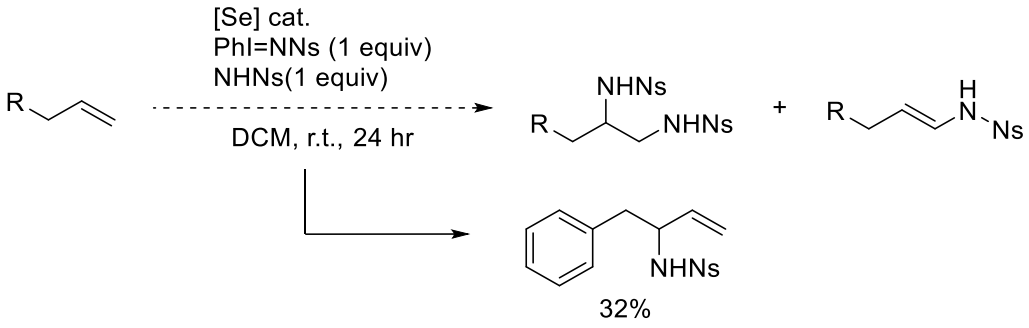
bis(imide) intermediate by using a combination of commercially available hypervalent iodine oxidant and amine source. Furthermore, in situ generation of nitrene allows us to expand the scope and enable us to introduce a wide variety of nitrogen substituents.

## 2.2 REACTION DISCOVERY AND OPTIMIZATION

The development of C-H allylic amination was inspired by a prior project led by Dr. John Tabor, where he was able to achieve diamination of alkenes using a phosphine selenide using N-fluorobenzenesulfonimide(NFBS) as an oxidant.[26, 27] Unfortunately, the reaction gave 2 major nitrogen containing products: diamine and enamine. We proposed that imidoiodinane, PhI=NNs, a hypervalent iodine oxidant may be capable of oxidizing the selenium catalyst without generating stoichiometric amounts of fluoride, which could be responsible for elimination to give enamine products. The absence of fluoride base could potentially improve the chemoselectivity of the reaction giving the desired diamine product. To our surprise, treatment of 4-phenyl-1-butene, PhI=NNs, and 4-nitrobenzenesulfonamide in the presence of catalytic amounts of phosphine

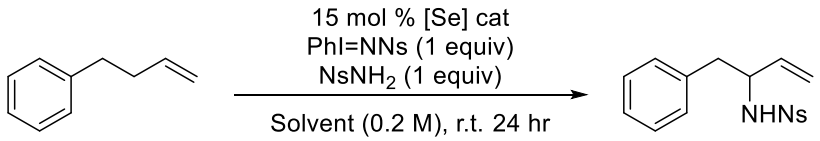
**Scheme 2.1** Comparison of Oxidant and The Discovery of Selenium Catalyzed C-H Allylic Amination.



selenide (Scheme 2.1) gave a branched allylic amine as a single product with a yield of 32%. We suspect that the low reactivity was due to the low solubility of PhI=NNs, which prompted us to screen a variety of solvents. We found that the choice of solvent has little to no effect in the catalytic system and we chose dichloromethane due to its low boiling point(Table 2.1). Low conversion of the starting material prompted us to screen various combination and equivalent of

**Table 2.1** Solvent Screen for Selenium Catalyzed C-H Allylic Amination.

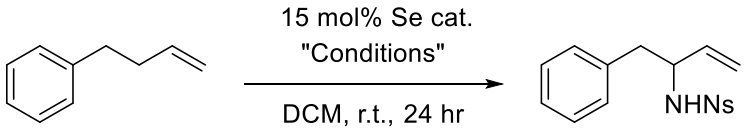



| Entry | Solvent | % Yield |
|---|---|---|
| 1 | DCM | 32 |
| 2 | THF | 33 |
| 3 | Toluene | 10 |
| 4 | MeCN | 34 |

NMR yields obtained using 1,3-dinitrobenzene as internal standard.

oxidant and nucleophile and we found that 2 equivalents of PhI=NNs and 4-nitrobenzenesulfonamide increased the yield of our allylic amine product from 30% to 72% (Table 2.2). A combination iodobenzene diacetate, $PhI(OAc)_2$, and nucleophile, $NsNH_2$, which

**Table 2.2** Equivalents Screen for Selenium Catalyzed C-H Allylic Amination.

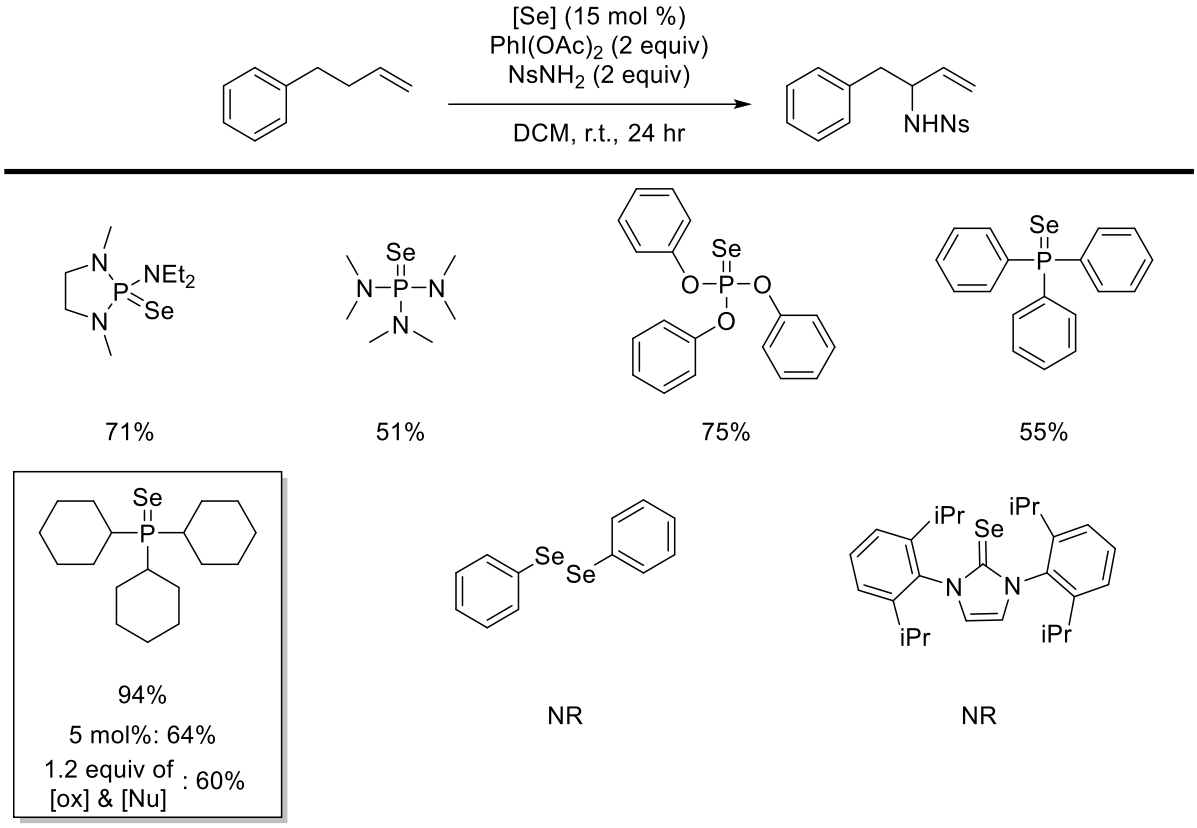



| Entry | Oxidant | Nucleophile | % Yield |
|---|---|---|---|
| 1 | PhI=NNs (1 equiv) | $NsNH_2$ (1 equiv) | 30 |
| 2 | PhI=NNs (2 equiv) | $NsNH_2$ (2 equiv) | 72 |
| 3 | $PhI(OAc)_2$ (1 equiv) | $NsNH_2$ (1 equiv) | 31 |
| 4 | $PhI(OAc)_2$ (2 equiv) | $NsNH_2$ (2 equiv) | 71 |

NMR yields obtained using 1,3-dinitrobenzene as internal standard.

presumably forming PhI=NNs in situ, gave comparable yields (Table 2.2) to the initial reaction conditions. This allows us to directly commercially available reagents, avoiding the need to pre-

**Scheme 2.2** Catalyst Screen for Terminal Alkene.




NMR yields obtained using 1,3-dinitrobenzene as internal standard.

make imidoiodinane, easing the process of incorporation of other nitrogen nucleophiles. A variety of phosphine selenide catalysts were investigated and found to be effective catalyst, with tricyclohexylphosphine selenide ($SePCy_3$), works best affording a nearly quantitative yield. Notably, diphenyl diselenide ($Se_2Ph_2$), a commonly used catalyst in selenium catalysis gave no desired reactivity, leaving a majority of starting alkene untouched (Scheme 2.2). Furthermore, we found that reducing the catalyst loading to 5 mol % resulted in a moderate decrease in yield, as did lowering the stoichiometry of $NH_2Ns/PhI(OAc)_2$ to 1.2 equivalents.

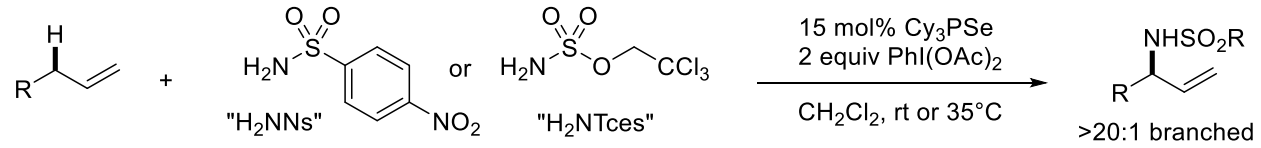
## 2.3 RESULTS AND DISCUSSION

With the optimized reaction conditions in hand, we screened a variety of terminal alkenes to probe the reaction scope with the help of my collaborators, Blaise Black and Derek Obenschain. The reaction tolerated a wide range of functional group and yields of the allylic amine products

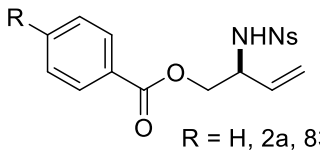
were generally high (37-99% yield). Electron rich aromatic (**9a**) and thiophene (**8b**) substrates can also be used under our mild reaction conditions without significant decrease in yields. Substrates bearing synthetically useful functional groups such as aryl boronic pinacol ester (**6a**), aryl and alkyl halides (**2a-5a, 11a**) can be safely used giving moderate yields, allowing subsequent orthogonal functionalization in transition metal catalyzed coupling reactions. Protected homoallylic alcohol and amine substrates afforded good yields, giving 1,2-aminoalcohols (**14a, 15a**) and 1,2-diamines (**10a**) which are important structural motifs in many synthetic intermediates. 1,1-Disubstituted alkenes and alkenes with tertiary C-H bonds (**17a-22b**) reacted well giving good yields which are hard to obtain through current existing methods due to sterics or their tendency to undergo alkene transposition. A large-scale reaction with reduced catalyst loading afforded a slight drop in yields, giving 4.39g of desired allylic amine product using less than 100 mg of selenium metal. Unfortunately, carboxylic acids, unprotected amines, amides, nitrogen heteroaromatics, and ketones failed to provide the desired products in appreciable yields (<10%).

To illustrate the flexibility of our C-H allylic amination to introduce nitrogen functionality, a wide range of amines were tested with our model alkene, 4-phenyl-1-butene (Scheme 2.4). Synthetically useful amine protecting groups were introduced in high yields, such as groups that are cleaved using mild nucleophilic substitution (Ns), Zn reduction (Tces), hydrolysis (Tfes), and photolysis (Nbos), allowing the installation of orthogonal protected amines in multistep synthesis. Furthermore, functional groups that are commonly used in cross-coupling reactions, including aryl halides, boronates, alkynes, and azides were also tolerated in our reaction which can pose chemoselectivity issues in transition metal catalyzed reactions. Lastly, amine groups with interesting physical properties such as solubility (Scheme 2.4, **1i** – **1f**) and fluorescence (Scheme 2.4, **1l**) can be introduced through appropriate choice of amine functional groups, potentially expand the utility of our reaction.

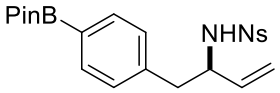
**Scheme 2.3** Terminal Alkene Scope for Selenium Catalyzed C-H Allylic Amination.



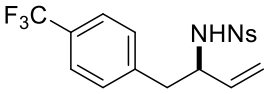

common functional groups



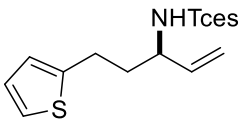

R = H, 2a, 83%
R = F, 3a, 75%
R = Br, 4a, 68%
R = I, 5a, 57%



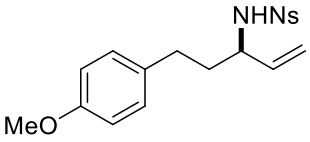

6a, 82%



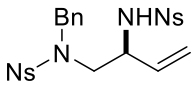

7a, 91%



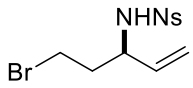

8b, 62%



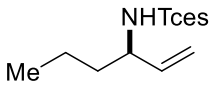

9a, 70%



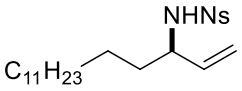

10a, 87%



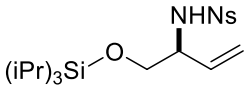

11a, 85%



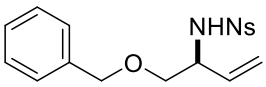

12b, 81%



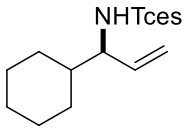

13a, 75%




14a, 83%

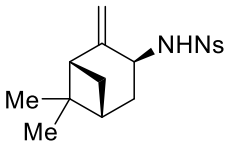



15a, 61%

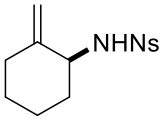



16b, 88%

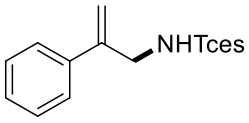
1,1-disubstituted alkenes



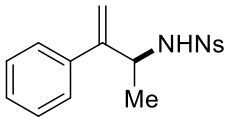

17a, 68%




18a, 92%

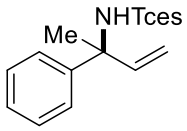



19b, 86%

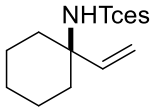



20a, 77%

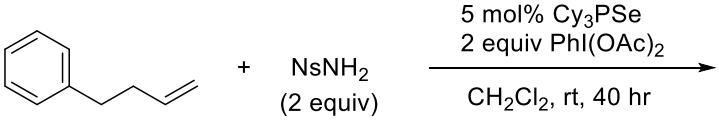
tertiary C-H bonds




21b, 74%

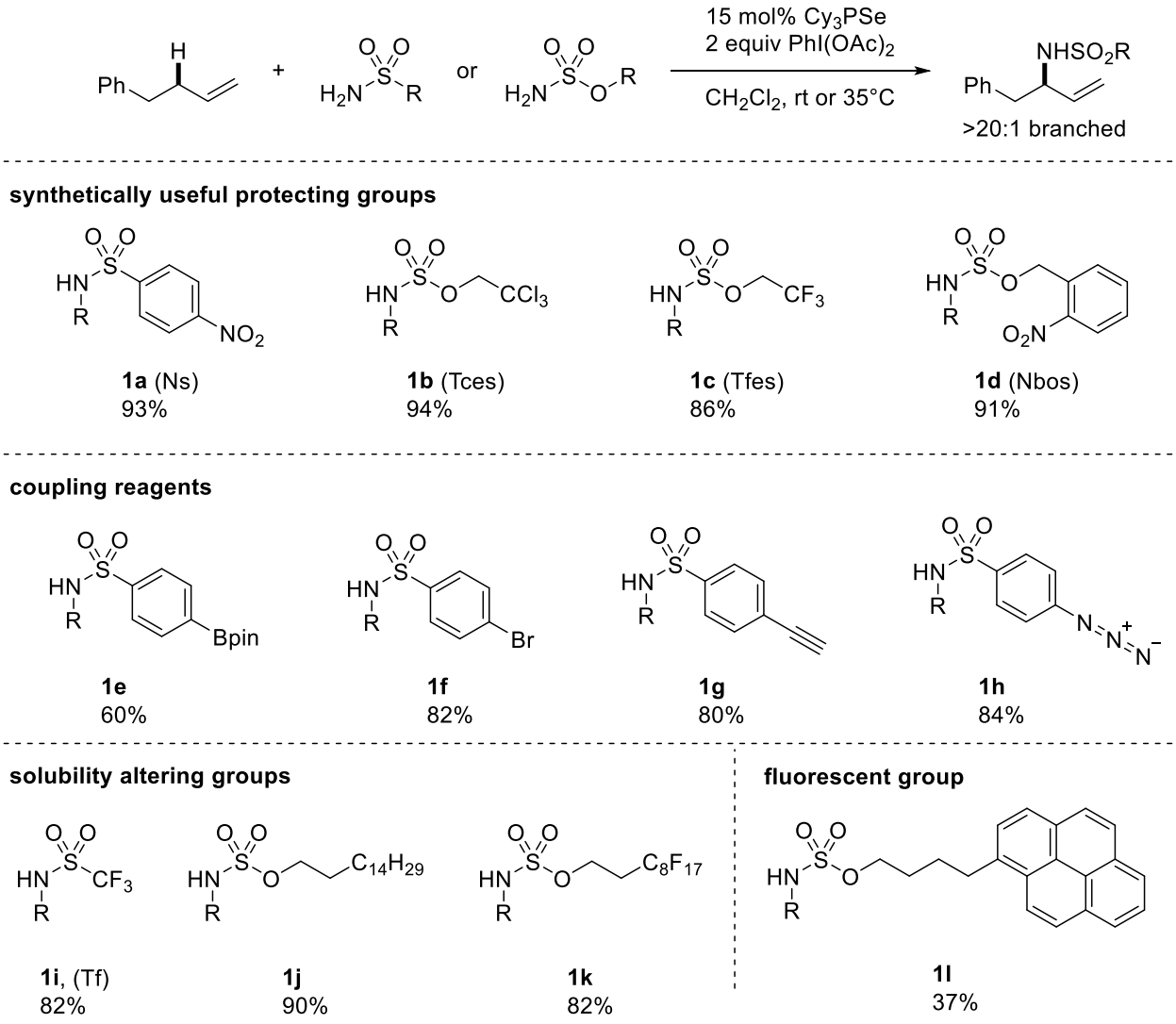



22b, 87%




20 mmol scale: 66%
4.39 g product from 79 mg Se

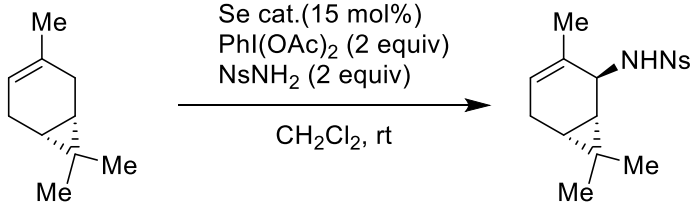
**Scheme 2.4** Amine Scope for Selenium Catalyzed C-H Allylic Amination.

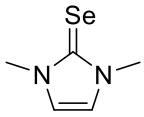
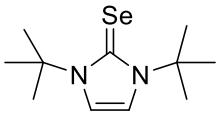



The success of our C-H allylic amination reaction on simple alkenes prompted us to tackle more complex substrates such as highly substituted alkenes and terpenoid natural products. Selectivity could pose a challenge due to multiple C-H or C=C bonds available in these substrates. A bicyclic trisubstituted monoterpene, 3-carene, was chosen to be the model substrate to test our C-H allylic amination. Unfortunately, a disappointing yield of 16% was obtained when we subjected it to our optimized reaction conditions (Table 2.3). A quick catalyst screen showed that selenourea based catalyst, specifically N,N-dimethylimidazolium selenide, SeIMe, drastically increase the yield to 87%. I also found that phosphine-based and imidazolium-based catalysts were

generally orthogonal, where SeIMe was more effective on electron rich alkenes and $SePCy_3$ was required for less electron rich alkenes.

**Table 2.3** Catalyst Screen for Highly Substituted Alkenes.




| Entry | Se cat. | % Yield[a] |
|---|---|---|
| 1 | $Cy_3PSe$ | 16 |
| 2 | $(Et_2N)_3PSe$ | 50 |
| 3 | $Ph_3PSe$ | 5 |
| 4 | $(PhO)_3PSe$ | 4 |
| 5 |  | 87 |
| 6 |  | 65 |

[a]NMR yields using 1,3-dinitrobenzene.

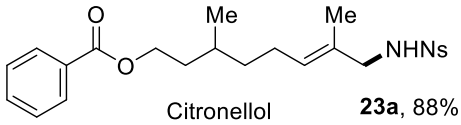
This discovery led us to the expansion and broadening of the scope of reaction, where a large variety of terpenoid natural products were able to couple with amine nucleophiles in moderate to excellent yields (Scheme 2.5). A single regioisomer was observed in most cases, which demonstrates the excellent selectivity of our C-H allylic amination. Acyclic trisubstituted alkenes such as citronellol and geraniol derivatives gave a single stereoisomer (**23a-29a**), where the primary C-H bond trans to the third substituent is preferentially aminated. In cases where multiple C=C bonds present within the compound, amination took place at the most electron-rich alkenes (**23a, 26a-28a**). Furthermore, cyclic substrates with trisubstituted alkenes generally prefers endocyclic substituted products (**32a-34a**), with the exception that exocyclic substitution occurs when the preferential site was blocked (**36b-38a**). High diastereoselectivity was observed in cyclic substrates due to the stereoelectronically more accessible axial C-H bonds. Notably, challenging

substrates such as highly sterically hindered tertiary allylic C-H bond in α-ionone (**33a)** and electronically unbiased 1,2-disubstituted alkenes such as methyl jasmonate (**39a)** reacted with high regioselectivity and moderate yields. Unfortunately, substrates bearing an exocyclic isoprepenyl group were problematic where our reaction is having a hard time to select between primary and tertiary C-H bond.

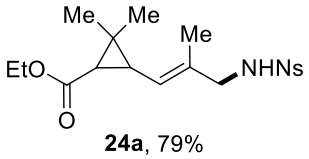
To demonstrate the late-stage diversification of complex molecules using our C-H allylic amination, a variety of biologically active compounds containing sulfamates and sulfonamides was coupled with several different alkenes in moderate to high yields (Scheme 2.5). Sulfamates can be easily prepared in a single step from biologically active compounds with an alcohol handle, allowing rapid diversification of these compounds.

**Scheme 2.5** Highly Substituted Internal Alkene Scope for Selenium Catalyzed C-H Allylic Amination.

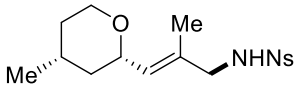

**Acyclic trisubstituted alkenes**



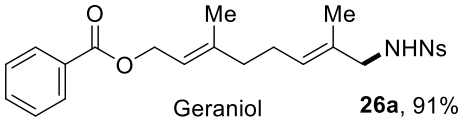

Citronellol **23a**, 88%



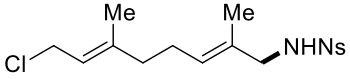

**24a**, 79%
Ethyl crysanthemate



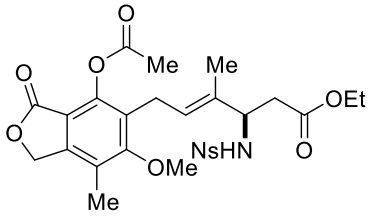

**25a**, 60%
Rose oxide



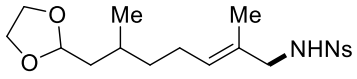

Geraniol **26a**, 91%




**28a**, 67%
Geranyl chloride

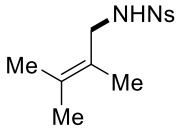



**29a**, 84% (2.5:1 rr)
Mycophenolic acid



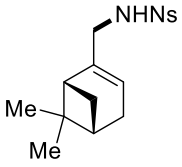

Citronellal **27a**, 84%

**Tetrasubstituted alkene**

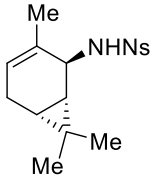



**30a**, 77%

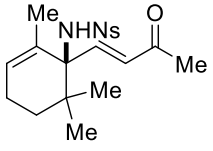
**Cyclic trisubstituted alkenes**



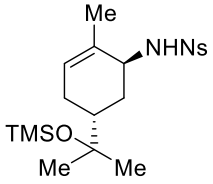

**31a**, 32%
α-Pinene



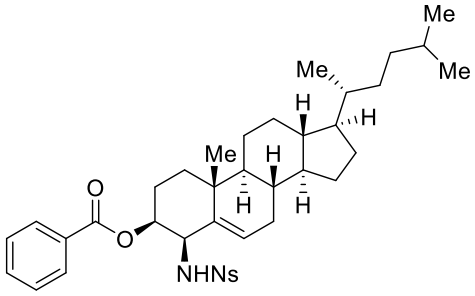

**32a**, 87% (>20:1 dr)
3-Carene



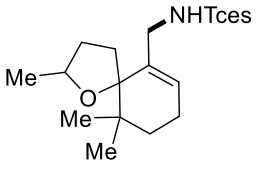

**33a**, 68%
α-Ionone



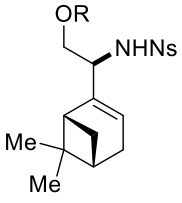

**34a**, 91% (6:1 dr)
rr = 4.4:1
α-Terpineol




**35a**, 83% (>20:1 dr)
Cholesteryl benzoate

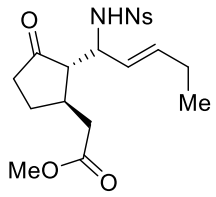



**36b**, 86%
Theaspirane

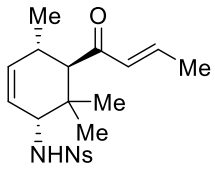



**37a**, R= Bn 79% (1.2:1 dr)
**38a**, R= Bz 77% (1.2:1 dr)
Nopol

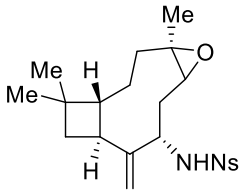
**Disubstituted alkenes**



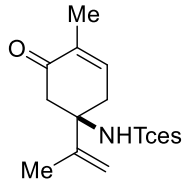
**39a**, 57% (3:1 dr)
Methyl jasmonate



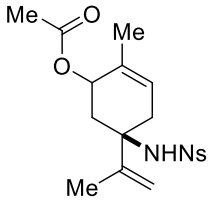
**40a**, 60% (>20:1 dr)
δ-Damascone



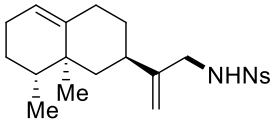
**41a**, 75% (10:1 dr)
Caryophyllene oxide



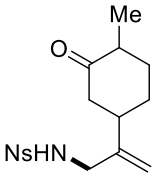
**42b**, 75% (1:1 rr)
Carvone



**43a**, 88% (1:1 rr)
Carvyl acetate

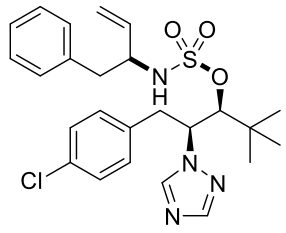


**44a**, 99% (1.5:1 rr)
Valencene

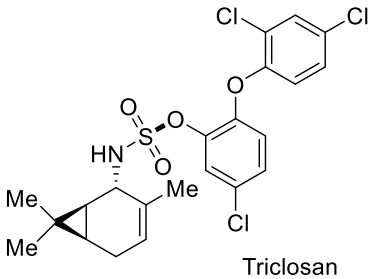


**45a**, 71% (2.7:1 rr)
Dihydrocarvone

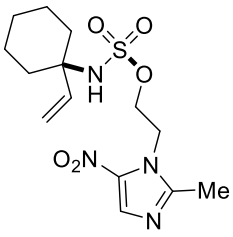
**Drug-derived sulfonamides/sulfamates**



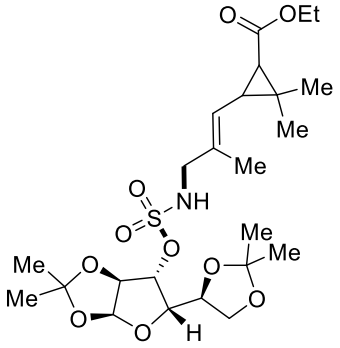
Paclobutrazol
**46**, 53%



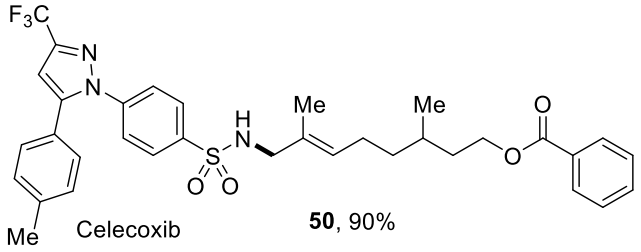
**47**, 94%
Triclosan



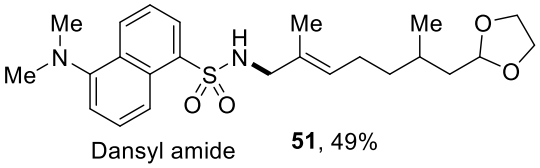
Metronidazole
**48**, 63%



Glucofuranose **49**, 72%



Celecoxib **50**, 90%



Dansyl amide **51**, 49%

## 2.4 MECHANISTIC STUDIES

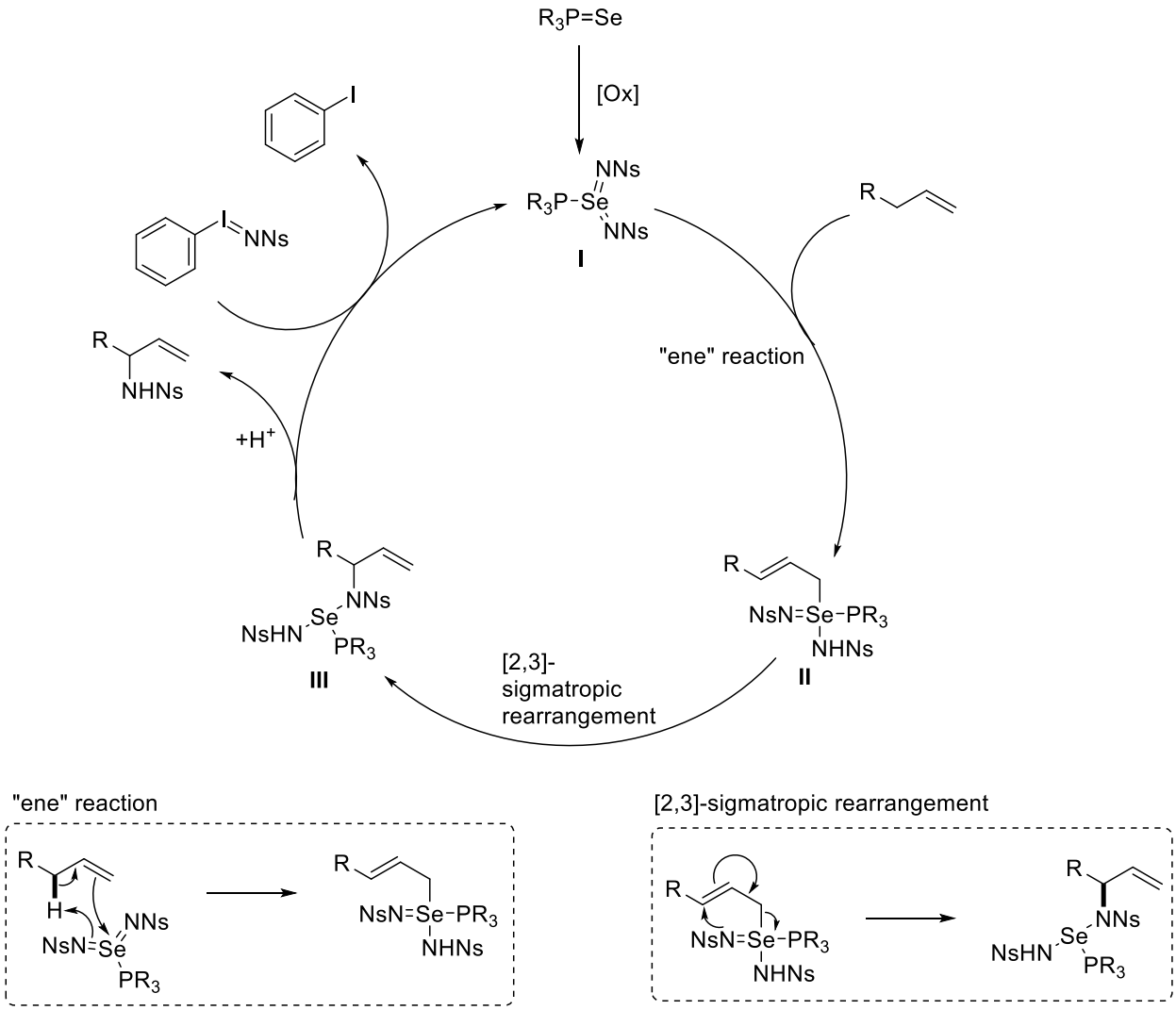



**Figure 2.4** Proposed Catalytic Cycle for Selenium Catalyzed Allylic Amination.

Consistent with the observed regio- and stereoselectivities reported by Sharpless[8], we proposed that our reaction undergoes a sequential ene/[2,3]-sigmatropic rearrangement (Figure 2.4). The two sequential rearrangements result in a net retention of the alkene position, which explains the absence of alkene transposition products observed in other allylic C-H functionalization. The phosphine selenide precatalyst undergoes oxidation by $PhI(OAc)_2$ presumably forming a reactive bis(imido) selenium intermediate **I**, which then undergoes the ene reaction with the alkene to form allylselenium species **II**. The allylselenium species would then undergo [2,3]-sigmatropic rearrangement to form allylic sulfonamide **III** follow by a protonolysis and reoxidation to continue the cycle.

Notably, high regioselectivity of complex molecule can be largely explained by the effects of electronic bias in the initial ene reaction (Figure 2.5, A). Like $SeO_2$ oxidations, the asynchronous nature of the ene reaction resulting in partial positive charge developed at the more substituted carbon prior to the abstraction of C-H bond. This allows our reaction to select and/or narrow down the allylic C-H bond for amination (Figure 2.5, **A**). In cases that have multiple preferred C-H bonds, other factors such as stability of the intermediates comes into play. For example, the abstraction of primary allylic C-H bond (Figure 2.5, **B**, $H_1$) in 3-carene leads to a disubstituted intermediate whereas the secondary allylic C-H bond leads to a trisubstituted intermediate (Figure 2.5, **B**, $H_2$). The trisubstituted intermediate is more thermodynamically favored than the disubstituted intermediates, leads to high selectivity in the abstraction of allylic C-H bonds. Furthermore, axial hydrogen in cyclic systems is often the preferred site of C-H amination due to the stereoelectronic overlapped with adjacent pi system for ene reaction to happen, resulting in high diastereoselectivity of certain products.

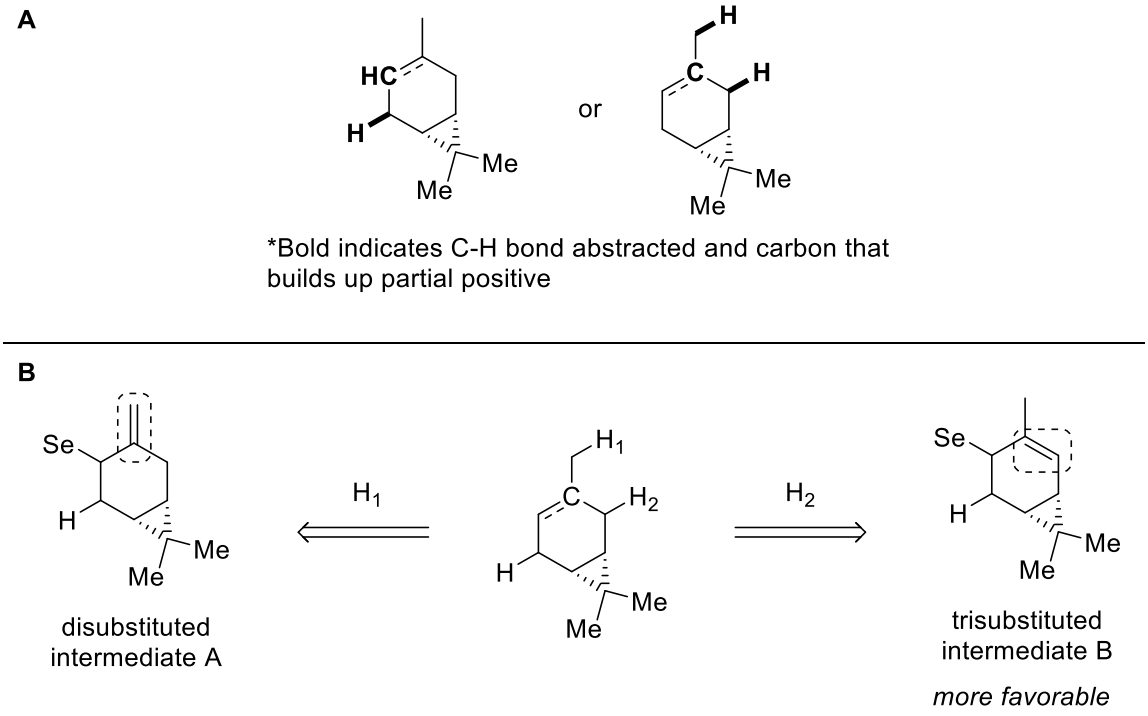
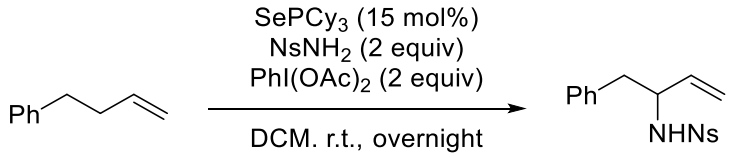



**Figure 2.5** Partial Positive Build up and Comparison of Intermediates to Achieve Selectivity.

A series of mechanistic experiments were performed to investigate the role of ligand, where neither elemental Se powder or $PCy_3$ alone gives any desired product (Table 2.4). Interestingly, pre-stirring Se and $PCy_3$ for as short as 5 minutes presumably forming $SePCy_3$ in situ before adding

other reagents gave similar yields to optimized reaction conditions, illustrate the importance of ligand in our C-H amination chemistry.

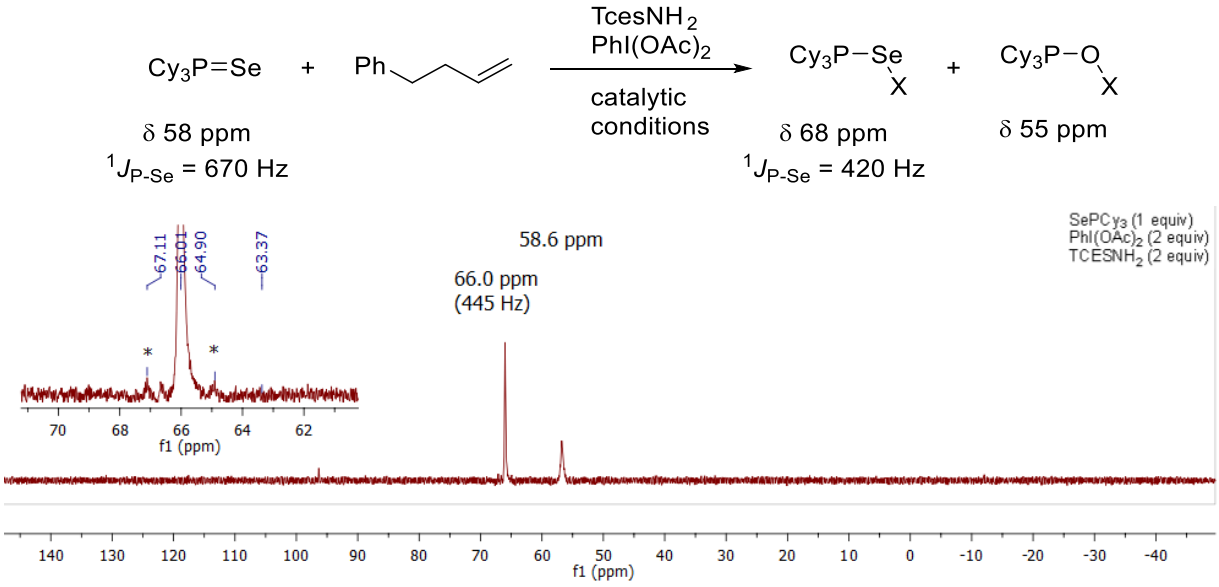
**Table 2.4** Control Reactions to Investigate the Role of Phosphine Selenium Catalyzed C-H Allylic Amination.




| Deviation from optimized reaction | Yield |
|---|---|
| none | 99 |
| no $SePCy_3$ | 0 |
| 15 mol% Se gray | 0 |
| 100 mol% Se gray | 0 |
| Pre stirring Se gray(15 mol%) and $PCy_3$(15 mol%) | 97 |
| Pre stirring Se gray(15 mol%) and $O{=}PCy_3$(15 mol%) | 0 |

In situ $^{31}P$ NMR spectroscopy revealed the formation of two new species upon mixing 1 equiv of $SePCy_3$, $PhI(OAc)_2$, and $TsNH_2$ (Scheme 2.6). The peak at x ppm was identified as tricyclohexylphosphine oxide, $OPCy_3$ by addition of an authentic sample. The downfield shift of the $OPCy_3$ resonance (56 vs 49 ppm) suggests the coordination of Lewis acid and/or hydrogen bonding with the oxygen(Scheme 2.6). The other new resonance at 68 ppm shows satellite peaks from coupling of $^{77}Se$ with a smaller coupling constant and downfield shift compared to starting catalyst $SePCy_3$. This is consistent with weakening of the Se-P bond through coordination at Se center (Scheme 2.6). Unfortunately, the exact species that is responsible for our C-H allylic amination was not identified through these series of NMR experiments.

**Scheme 2.6** $^{31}$P NMR Experiments to Investigate the Role of Phosphine Selenium Catalyzed C-H Allylic Amination.




## 2.5 CONCLUSION

In conclusion, I have developed a novel selenium-catalyzed allylic C–H amination of that can accommodate a broad range of alkenes allowing facile incorporation of nitrogen functionality. Alkene substitution patterns from mono- to tetrasubstituted coupled with a wide range of sulfonamides and sulfamates with moderate to high yields and predictable regioselectivity in an operationally simple and robust reaction. This reaction has been used to introduce new C–N bonds in an assortment of terpene natural products, thereby generating a new class of potentially bioactive products.

## 2.6 EXPERIMENTAL

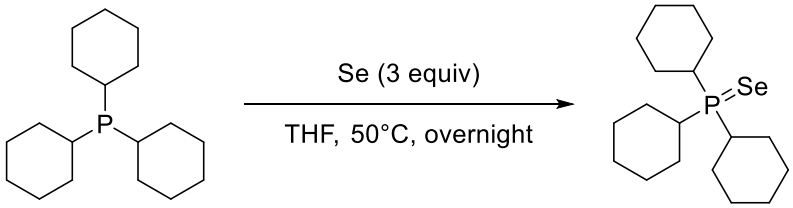
### 2.6.1 *General Procedure and Materials*

All reactions were performed under a nitrogen atmosphere using oven-dried or flame-dried glassware unless otherwise indicated. Dichloromethane ($CH_2Cl_2$) and tetrahydrofuran (THF) were degassed and dried by passing through a column of activated neutral alumina. Deuterated solvents ($CDCl_3$, acetone-$d^6$) were obtained from Cambridge Isotope Laboratories, Inc. and stored over activated 3A molecular sieves. Ethyl acetate (EtOAc), hexanes, and ether ($Et_2O$) were obtained

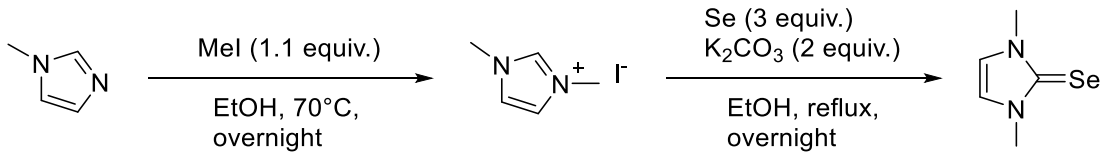
from Fisher Scientific or Sigma Aldrich and used without further purification. Reagents were purchased from Sigma Aldrich, Tokyo Chemical Industry, Fisher Scientific, Alfa Aesar, Oakwood chemicals and used without further purification unless otherwise indicated. Infrared spectra were acquired using a Perkin Elmer Spectrum RX I spectrometer. Mass spectra were acquired using a Bruker Esquire 1100 Liquid Chromatograph-Ion Trap Mass Spectrometer. Column chromatography was performed using silica gel (Whatman, 60 Å, 230-400 mesh). NMR spectra were recorded on a Bruker AV-300, AV-301, DRX-499, or AV-500 spectrometer. $^{1}H$ NMR chemical shifts (δ) are reported in parts per million (ppm) and are referenced relative to $Me_4Si$ (0.00 ppm), $CHCl_3$ (7.26 ppm) or acetone-$d^5$ (2.06 ppm). $^{13}C$ NMR chemical shifts (δ) are reported in parts per million (ppm) relative to the carbon resonance of $CDCl_3$ (77.26 ppm) or acetone-$d^6$ (29.92 ppm). Melting points were taken on a MEL-TEMP melting point apparatus and are uncorrected.

### 2.6.2 *General Procedure and Characterization of Starting Materials*

**General Procedure for Synthesis of Selenium Catalyst:**




Tricyclohexylphosphine selenide ($SePCy_3$). A flame-dried round bottom flask equipped with a magnetic stirbar was charged with tricyclohexylphosphine (10 mmol, 1 equiv.) and selenium powder (30 mmol, 3 equiv) in a glove box. The flask was capped with a rubber septum and transferred outside of the glove box. Dry tetrahydrofuran (20 mL, 0.5 M) was added using a syringe and the septum was replaced with a reflux condenser under nitrogen gas. The reaction was heated to 45 °C and allowed to stir overnight. After cooling to room temperature, the mixture was then flushed through Celite with dichloromethane to remove the residual selenium powder. The eluent was then concentrated on a rotary evaporator to afford the crude reaction product. The crude white solid was recrystallized from acetone and cooled in the freezer overnight to afford the product as white needles (3.05 g, 85% yield). $^{31}P$ NMR (121 MHz, $CDCl_3$) δ 57.65 (d, J = 674.5 Hz). $^{79}Se$ NMR (57 MHz, $CDCl_3$, 0.4 M) δ -464.45 (d, J = 674.9 Hz).[28]

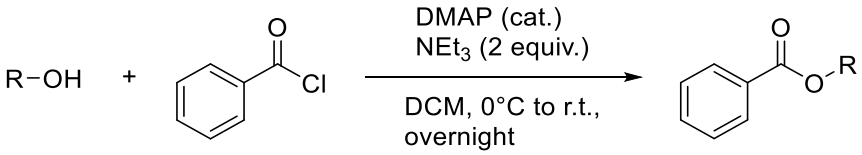



N,N'-dimethylimidazole-2-selenide (SeIMe). A flame-dried round bottom flask equipped with a magnetic stir bar was charged with 1-methylimidazole (2 mL, 25.1 mmol, 1 equiv.) and ethanol (50 mL, 0.5 M). Methyl iodide (1.72 mL, 27.6 mmol, 1.1 equiv.) was added to the flask, which was equipped with a water condenser. The reaction was heated to 70 °C and allowed to stir overnight. The reaction mixture was then concentrated on a rotary evaporator to afford the crude imidazolium salt. Potassium carbonate (6.9 g, 50.1 mmol, 2 equiv.), selenium powder (5.9 g, 74.3 mmol, 3 equiv.), and ethanol were added to the flask containing the crude reaction product and refluxed overnight. The reaction mixture was filtered through a pad of Celite and washed with dichloromethane (2 x 100 mL). The filtrate was concentrated on a rotary evaporator and recrystallized to afford the product as pale grey needles (3.25 g, 74%). The spectroscopic data were found to be consistent with reported literature.[29]

**General Information for Starting materials:**

Starting material alkenes and sulfonamides are purchased from commercial sources and used without further purification unless otherwise indicated. Terminal alkenes **2, 3, 4, 5, 6, 7, 8, 9, 10,** and **21** were synthesized according to literature procedure and the spectroscopic data were consistent with the reported values.[30-38] Internal alkenes **23, 26,** and **27** were synthesized according to general procedure for benzoate protection (see below) and the spectroscopic data were consistent with the literature values.[39-42] Sulfamates **b, c, d, j, k, l, 46, 47,** and **48** were synthesized according to literature procedure and spectroscopic data of known compounds were consistent with the reported values.[43-45]

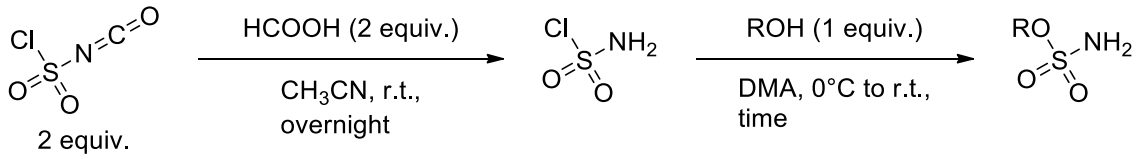
**General Procedure for Benzoate protection:**



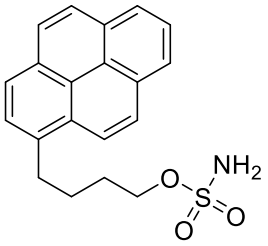

A flame-dried round bottom flask equipped with a magnetic stir bar was charged with alcohol (10 mmol, 1 equiv.) and 4-dimethylaminopyridine (0.2 mmol, 0.02 equiv.). Dry dichloromethane (20

mL, 0.5 M) was added and the reaction mixture was stirred and cooled to 0°C. Benzoyl chloride (11 mmol, 1.1 equiv.) was added to the reaction mixture followed by triethylamine (20 mmol, 2 equiv.). The round bottom flask was then allowed to warm to room temperature and stir overnight. The reaction was quenched with water (20 mL) and diluted with ether (30 mL). The organic layer was then washed with saturated sodium bicarbonate (2 x 20 mL) and brine (1 x 20 mL) and dried over sodium sulfate. The solvent was then removed under reduced pressure and silica gel chromatography was used to purify the crude products.

**General Procedure for Synthesis of Sulfamates:**




A flame-dried round bottom flask equipped with a magnetic stir bar was charged with a solution of formic acid (26.25 mmol, 3.5 equiv.) in $CH_3CN$ (2.5 M). Chlorosulfonyl isocyanate (3 equiv.) in $CH_3CN$ (2.5 M) was added to the reaction mixture over 10 min. The reaction mixture was stirred at room temperature overnight. A solution of alcohol (1 equiv.) in N, N-dimethylacetamide (0.5 M) was slowly added to the reaction mixture at 0°C. The reaction was monitored using TLC and quenched with water (~2 mL per 1 mmol of chlorosulfonyl isocyanate) upon completion. Ethyl acetate (3 x amount of water added) was used to extract the aqueous layer and the combined organic layers were further washed with water and brine then dried over sodium sulfate. The solvent was then removed under reduced pressure and purified through silica gel chromatography.




Pyrenebutanol sulfamate (k). Following the general procedure with 1-pyrenebutanol (1 g, 3.64 mmol) and purified with silica gel chromatography (70:30, hexanes:ethyl acetate) to afford a pale yellow solid (0.62 g, 48% yield).

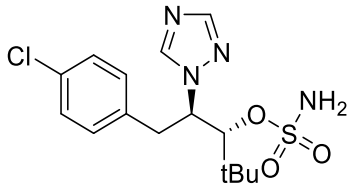
$^{1}$H NMR (300 MHz, Acetone) δ 8.41 (d, J = 9.3 Hz, 1H), 8.27 (m, 4H), , 8.12 (d, J = 0.8 Hz, 2H), 8.05 (t, J = 7.6 Hz, 1H), 7.98 (d, J = 7.8 Hz, 1H), 6.62 (s, 2H), 4.25 (t, J = 6.0 Hz, 2H), 3.45 (t, J = 7.4 Hz, 2H), 2.03 – 1.80 (m, 4H).

$^{13}$C NMR (75 MHz, Acetone) δ 137.69, 132.50, 132.00, 130.92, 129.61, 128.49, 128.41, 128.25, 127.56, 126.96, 125.89, 125.74, 124.46, 70.53, 33.45, 28.85.

IR (thin film): 3382, 3285, 3040, 2940, 2865, 1602, 1558, 1457, 1363, 1182, 940, 843, 760, 720, 553 cm$^{-1}$.

MS (ESI, positive mode): 376.5 (M+Na$^{+}$)

Melting point : 113 – 117 °C




Paclobutrazole sulfamate. Prepared via the general procedure using paclobutrazol (2.93 g, 10 mmol) and purified with silica gel chromatography (50:50, hexanes:ethyl acetate) to afford a white solid (1.26 g, 34% yield).

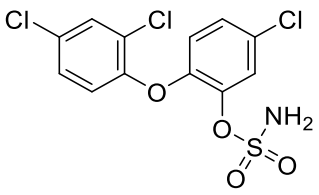
$^{1}$H NMR (500 MHz, Acetone) δ 8.50 (s, 1H), 7.73 (s, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 6.7 Hz, 4H), 5.14 (dd, J = 10.7, 4.3 Hz, 1H), 4.77 (s, 1H), 3.57 – 3.44 (m, 1H), 3.39 (dd, J = 14.1, 4.4 Hz, 1H), 0.84 (s, 9H).

$^{13}$C NMR (75 MHz, Acetone) δ 150.83, 144.69, 137.06, 133.06, 131.63, 129.26, 89.71, 63.05, 40.95, 36.32, 26.57.

IR (thin film): 3217, 2966, 1706, 1507, 1493, 1366, 1278, 1179, 1138, 1015, 927, 898, 855, 832, 738, 679, 578 cm$^{-1}$.

MS (ESI, negative mode): 371.6 (M-H$^{+}$)

Melting point : 189– 191°C



Triclosan sulfamate. Following the general procedure with triclosan (6.41 g, 22 mmol) and purified with silica gel chromatography (70:30, hexanes:ethyl acetate) to afford a pale yellow solid (3.8 g, 47% yield).

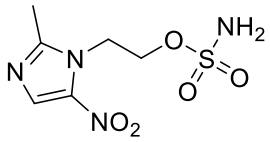
$^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.50 (s, 2H), 7.32 – 7.16 (m, 3H), 6.89 (d, J = 8.8 Hz, 1H), 6.83 (d, J = 8.8 Hz, 1H), 5.11 (s, 2H)

$^{13}$C NMR (75 MHz, Acetone) δ 151.72, 148.87, 141.99, 131.11, 130.50, 129.55, 129.09, 128.50, 127.12, 125.38, 122.81, 120.92.

IR (thin film): 3407, 3293, 3094, 1580, 1549, 1487, 1474, 1387, 1267, 1197, 1174, 1120, 1100, 923, 870, 804, 768, 750, 692, 584, 538 $cm^{-1}$.

MS (ESI, negative mode): 367.4 ($M-H^+$)

Melting point : 112 – 115°C




Metronidazole sulfamate. Following the general procedure with metronidazole (1.71 g, 10 mmol) and purified with silica gel chromatography (30:70 hexanes:ethyl acetate) to afford a white solid (1.85 g, 74% yield).

$^{1}$H NMR (300 MHz, DMSO) δ 8.04 (s, 1H), 7.58 (s, 2H), 4.62 (t, J = 4.8 Hz, 2H), 4.37 (t, J = 4.8 Hz, 2H), 2.46 (s, 3H).

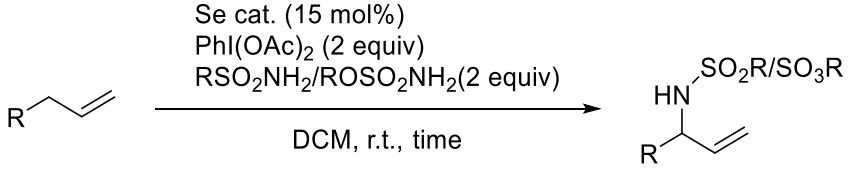
$^{13}$C NMR (75 MHz, DMSO) δ 151.82, 138.35, 133.06, 67.22, 45.00, 14.01.

IR (thin film): 3337, 3153, 2967, 1533, 1457, 1387, 1363, 1260, 1185, 1152, 1027, 943, 904, 828, 777, 744, 734, 611, 539, 475 $cm^{-1}$.

MS (ESI, negative mode): 249.5 ($M-H^+$)

Melting point : 165 – 170 °C

### 2.6.3 *General Procedure and Characterization for Allylic Amination Products*



**General procedure A**:

A flame-dried borosilicate glass vial equipped with a magnetic stir bar was charged with $SePCy_3$ (0.03 mmol, 0.15 equiv.), amine (0.4 mmol, 2 equiv.), and alkene (0.2 mmol, 1.0 equiv.). The vial was thoroughly flushed with nitrogen and capped with a Teflon-lined screw cap. Dry dichloromethane (1 mL, 0.2 M) was added, followed by iodobenzene diacetate (0.4 mmol, 2 equiv). The solution was stirred at the specified temperature and the reaction was monitored by TLC. Upon completion, an equal volume of ethyl acetate was added to the reaction and the mixture was flushed through a silica gel plug with ethyl acetate. The eluent was then concentrated on a rotary evaporator to afford the crude reaction product, which was then purified by column chromatography.

**General procedure B**:

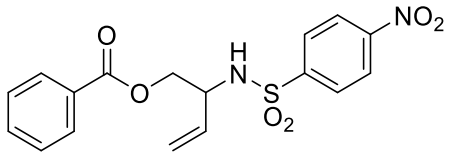
A flame-dried borosilicate glass vial equipped with a magnetic stir bar was charged with SeIMe (0.75 mmol, 0.15 equiv.), amine (1 mmol, 2 equiv.), and alkene (0.5 mmol, 1.0 equiv.). The vial was thoroughly flushed with nitrogen and capped with a Teflon-lined screw cap. Dry dichloromethane (0.2 M) was added followed by iodobenzene diacetate (1 mmol, 2 equiv). The solution was stirred at the specified temperature and the reaction was monitored by TLC. Upon completion, an equal volume of ethyl acetate was added to the reaction and the mixture was flushed through a silica gel plug with ethyl acetate. The eluent was then concentrated on a rotary evaporator to afford the crude reaction product, which was then purified by column chromatography.

**General procedure C**:

A flame-dried borosilicate glass vial equipped with a magnetic stir bar was charged with SeIMe (0.03 mmol, 0.15 equiv.), amine (0.4 mmol, 2 equiv.), and alkene (0.2 mmol, 1.0 equiv.). The vial was thoroughly flushed with nitrogen and capped with a Teflon-lined screw cap. Dry dichloromethane (1 mL, 0.2 M) was added followed by iodobenzene diacetate (0.4 mmol, 2 equiv). The solution was stirred at specified temperature and the reaction was monitored by TLC. Upon completion, an equal volume of ethyl acetate was added to the reaction and the mixture was flushed through a silica gel plug with ethyl acetate. The eluent was then concentrated on a rotary evaporator to afford the crude reaction product, which was then purified by column chromatography.

**Procedure for large scale reaction**:

A 250 mL flame-dried round bottom flask equipped with a magnetic stir bar was charged with $SePCy_3$ (1 mmol, 0.05 equiv.), amine (40 mmol, 2 equiv.), and alkene (20 mmol, 1.0 equiv.). The round bottom flask was thoroughly flushed with nitrogen and capped with a rubber septa. Dry dichloromethane (100 mL, 0.2 M) was added followed by iodobenzene diacetate (0.4 mmol, 2 equiv). The solution was stirred at room temperature and the reaction was monitored by TLC. Upon completion, the solvent was concentrated and the product purified by silica gel chromatography (95:5 to 80:20, hexanes/ethyl acetate).




**2a**. Prepared according to general procedure A and purified by silica gel chromatography (95:5 to 80:20, hexanes/ethyl acetate) to afford the product as a white solid (63 mg, 83%).

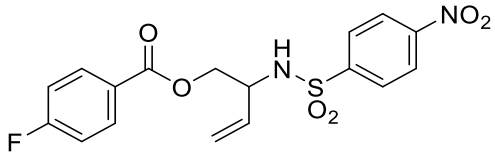
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.8 Hz, 2H), 7.95 (d, *J* = 8.8 Hz, 2H), 7.85 – 7.75 (m, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 2H), 5.76 (ddd, *J* = 16.9, 10.4, 5.4 Hz, 1H), 5.48 (d, *J* = 7.5 Hz, 1H), 5.36 (d, *J* = 17.2 Hz, 1H), 5.25 (d, *J* = 10.6 Hz, 1H), 4.37 – 4.31 (m, 2H), 4.24 (dd, *J* = 10.7, 3.2 Hz, 1H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 166.57, 149.87, 146.72, 133.94, 133.44, 129.77, 129.03, 128.64, 128.20, 124.42, 119.07, 65.67, 56.30.

**IR** (thin film): 3291, 3106, 1750, 1530, 1350, 1194, 1165, 1093, 934, 854, 738 $cm^{-1}$.

**MS** (ESI, negative mode): 375.8 ($M-H^+$)

**Melting point** : 123-125 °C




**3a**. Prepared according to general procedure A and purified by silica gel chromatography (95:5 to 80:20, hexanes/ethyl acetate) to afford the product as a white solid (59 mg, 75%).

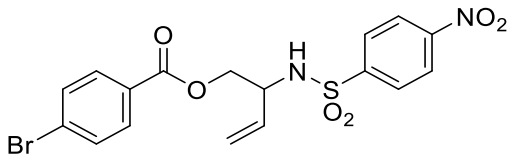
**$^{1}$H NMR** (300 MHz, Acetone) δ 8.31 (d, *J* = 8.9 Hz, 2H), 8.11 (d, *J* = 8.9 Hz, 2H), 7.96 (dd, *J* = 8.9, 5.5 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.21 (t, *J* = 8.8 Hz, 2H), 5.87 (ddd, *J* = 16.7, 10.5, 6.0 Hz, 1H), 5.33 (d, *J* = 17.2 Hz, 1H), 5.16 (d, *J* = 10.5 Hz, 1H), 4.50 – 4.39 (m, 1H), 4.40-4.26 (m, 2H).

**$^{13}$C NMR** (126 MHz, Acetone) δ 166.16 (d, J = 274.7 Hz), 165.25,, 150.27, 148.22, 134.80, 132.77, 132.70, 128.67, 126.70, 124.78, 117.94, 115.92 (d, J = 22.2 Hz), 66.41, 56.02.

**IR** (thin film): 3280, 3107, 1721, 1698, 1604, 1532, 1508, 1413, 1350, 1307, 1273, 1240, 1167, 1091, 1014, 988, 854, 767, 737, 684 cm$^{-1}$.

**MS** (ESI, negative mode): 393.8 (M-H$^{+}$)

**Melting point** : 116-120 °C




**4a**. Prepared according to general procedure A and purified by silica gel chromatography (90:10 to 70:30, hexanes/ethyl acetate) to afford the product as a white solid (62 mg, 68%).

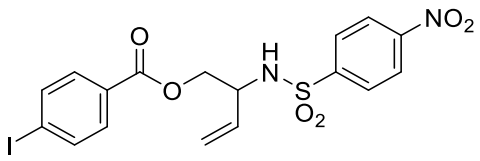
**$^{1}$H NMR** (300 MHz, Acetone) δ 8.31 (d, *J* = 8.9 Hz, 2H), 8.11 (d, *J* = 8.9 Hz, 2H), 7.81 (d, *J* = 8.6 Hz, 2H), 7.66 (d, *J* = 8.6 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 1H), 5.87 (ddd, *J* = 16.9, 10.5, 6.0 Hz, 1H), 5.33 (d, *J* = 17.2 Hz, 1H), 5.16 (d, *J* = 10.5 Hz, 1H), 4.51 – 4.41 (m, 1H), 4.36 (dd, *J* = 11.3, 4.5 Hz, 1H), 4.30 (dd, *J* = 11.3, 7.4 Hz, 1H)..

**$^{13}$C NMR** (126 MHz, Acetone) δ 165.78, 150.74, 148.68, 135.22, 132.67, 132.16, 129.82, 129.12, 128.70, 125.24, 118.42, 66.96, 56.44.

**IR** (thin film): 3267, 2924, 2849, 1694, 1515, 1457, 1397, 1340, 1274, 1149, 1089, 850, 758, 733 cm$^{-1}$.

**MS** (ESI, negative mode): 454.3 (M-H$^{+}$)

**Melting point** : 179-181 °C



**5a**. Prepared according to general procedure A and purified by silica gel chromatography (90:10 to 70:30, hexanes/ethyl acetate) to afford the product as a white solid (57 mg, 57%).

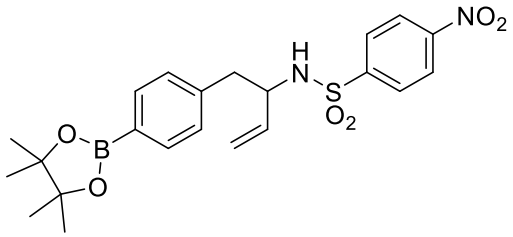
**$^1$H NMR** (300 MHz, Acetone) δ 8.23 (d, *J* = 8.9 Hz, 2H), 8.02 (d, *J* = 8.9 Hz, 2H), 7.79 (d, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 1H), 5.79 (ddd, *J* = 16.6, 10.5, 6.0 Hz, 1H), 5.25 (d, *J* = 17.2 Hz, 1H), 5.08 (d, *J* = 10.5 Hz, 1H), 4.41 – 4.32 (m, 1H), 4.27 (dd, *J* = 11.3, 4.4 Hz, 1H), 4.21 (dd, *J* = 11.3, 7.4 Hz, 1H).

**$^{13}$C NMR** (126 MHz, Acetone) δ 166.05, 150.74, 148.69, 138.79, 135.25, 131.93, 130.26, 129.12, 125.25, 118.41, 101.53, 66.92, 56.45.

**IR** (thin film): 3286, 2954, 2926, 1725, 1591, 1446, 1399, 1366, 1272, 1186, 1130, 1103, 1070, 1012, 988, 849, 756, 726, 683, 625, 593, 537 $cm^{-1}$.

**MS** (ESI, negative mode): 501.6 ($M-H^+$)

**Melting point** : 201-206 °C




**6a**. Prepared according to general procedure A and purified by silica gel chromatography (90:10 to 80:20, hexanes/ethyl acetate) to afford the product as a white solid (75 mg, 82%).

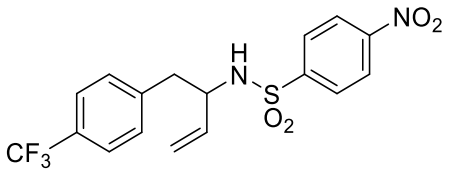
**$^1$H NMR** (300 MHz, Acetone) δ 8.20 (d, *J* = 8.8 Hz, 2H), 7.82 (d, *J* = 8.8 Hz, 2H), 7.49 (d, *J* = 7.8 Hz, 2H), 7.14 (d, *J* = 7.8 Hz, 2H), 7.03 (d, *J* = 8.8 Hz, 1H), 5.86 (ddd, *J* = 16.7, 10.4, 6.0 Hz, 1H), 5.17 (d, *J* = 17.1 Hz, 1H), 5.02 (d, *J* = 10.4 Hz, 1H), 4.28 – 4.13 (m, 1H), 2.92 (dd, *J* = 13.7, 5.6 Hz, 1H), 2.85 – 2.70 (m, 1H), 1.35 (s, 12H).

**$^{13}$C NMR** (126 MHz, Acetone) δ 150.43, 148.56, 141.85, 139.39, 135.37, 129.79, 128.83, 124.86, 115.98, 84.51, 59.11, 42.48, 25.28.

**IR** (thin film): 3289, 2981, 2932, 1612, 1532, 1400, 1361, 1273, 1165, 1144, 1091, 1022, 963, 857, 736, 685, 659, 618, 567 $cm^{-1}$.

**MS** (ESI, negative mode): 457.4 ($M-H^+$)

**Melting point** : 155-159 °C



**7a**. Prepared according to general procedure A and purified by silica gel chromatography (90:10 to 80:20, hexanes/ethyl acetate) to afford the product as a white solid (73 mg, 91%).

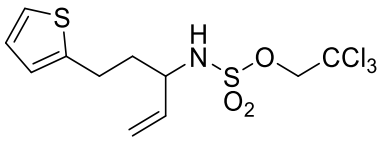
**$^1$H NMR** (300 MHz, Acetone) δ 8.26 (d, *J* = 8.8 Hz, 2H), 7.89 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.13 (d, *J* = 8.8 Hz, 1H), 5.85 (ddd, *J* = 16.8, 10.4, 6.1 Hz, 1H), 5.16 (d, *J* = 17.2 Hz, 1H), 5.02 (d, *J* = 10.4 Hz, 1H), 4.36 – 4.15 (m, 1H), 3.03 (dd, *J* = 13.7, 5.6 Hz, 1H), 2.87 (dd, *J* = 13.6, 9.1 Hz, 1H).

**$^{13}$C NMR** (126 MHz, Acetone) δ 150.17, 148.16, 142.99, 138.55, 130.75, 128.52, 125.43(q, *J* = 271.2 Hz), 125.41, 124.51, 115.93, 58.51, 41.60.

**IR** (thin film): 3280, 2930, 1607, 1531, 1420, 1350, 1325, 1162, 1121, 1093, 1067, 850, 747, 736, 684, 668 cm$^{-1}$.

**MS** (ESI, negative mode): 399.7 (M-H$^+$)

**Melting point** : 149-154 °C



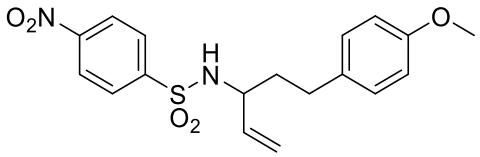
**8b**. Prepared according to general procedure A and purified by silica gel chromatography (90:10 to 80:20, hexanes/ethyl acetate) to afford the product as a clear oil (47 mg, 62%).

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.15 (d, *J* = 5.1 Hz, 1H), 6.93 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.83 (d, *J* = 3.3 Hz, 1H), 5.82 (ddd, *J* = 17.1, 10.3, 6.8 Hz, 1H), 5.40 – 5.27 (m, 2H), 4.67 – 4.62 (m, 1H), 4.61 (s, 2H), 4.17 – 3.94 (m, 1H), 2.96 (t, *J* = 7.7 Hz, 2H), 2.05 (dd, *J* = 7.6, 3.5 Hz, 1H), 2.00 (dd, *J* = 7.3, 3.2 Hz, 1H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 143.57, 136.76, 127.27, 125.05, 123.85, 118.27, 93.78, 78.52, 57.44, 37.22, 26.23.

**IR** (thin film): 3304, 2946, 2924, 1717, 1649, 1560, 1508, 1441, 1359, 1172, 1083, 1009, 927, 852, 725 cm$^{-1}$.

**MS** (ESI, negative mode): 375.6 (M-H$^+$)



**9a**. Prepared according to general procedure A and purified by silica gel chromatography (90:10 to 80:20, hexanes/ethyl acetate) to afford the product as a white solid (47 mg, 62%).

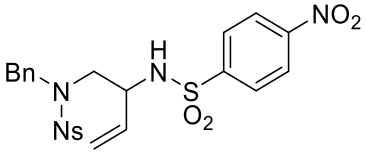
**$^1$H NMR** (300 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.8 Hz, 2H), 7.98 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 5.64 – 5.43 (m, 1H), 5.01 (d, *J* = 10.2 Hz, 2H), 5.00 (d, *J* = 17.3 Hz, 2H), 4.76 (d, *J* = 8.2 Hz, 1H), 3.87 (quin, *J* = 7.0 Hz, 1H), 3.79 (s, 3H), 2.56 (t, *J* = 7.5 Hz, 2H), 1.80 (q, *J* = 7.2 Hz, 2H)

**$^{13}$C NMR** (126 MHz, Acetone) δ 158.13, 149.92, 148.02, 137.95, 133.21, 129.20, 128.42, 124.15, 115.42, 113.75, 56.40, 54.55, 37.48, 30.59.

**IR** (thin film): 3285, 2932, 2858, 1609, 1529, 1215, 1444, 1419, 1349, 1306, 1246, 1163, 1092, 1033, 931, 853, 736, 684 $cm^{-1}$.

**MS** (ESI, negative mode): 375.9 ($M-H^+$)

**Melting point** : 71-74 °C



**10a**. Prepared according to general procedure A and purified by silica gel chromatography (85:15 to 70:30, hexanes/ethyl acetate) to afford the product as a pale yellow solid (95 mg, 87%).

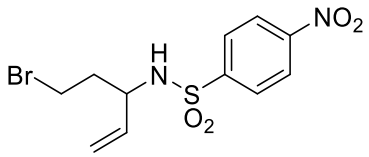
**$^1$H NMR** (300 MHz, Acetone) δ 8.43 (d, *J* = 9.0 Hz, 2H), 8.40 (d, *J* = 9.1 Hz, 2H), 8.14 (d, *J* = 8.8 Hz, 2H), 8.03 (d, *J* = 8.8 Hz, 2H), 7.48 – 7.14 (m, 5H), 6.94 (d, *J* = 8.4 Hz, 1H), 5.48 (ddd, *J* = 17.4, 10.4, 7.5 Hz, 1H), 4.85 (d, *J* = 11.5 Hz, 1H), 4.80 (d, *J* = 18.3 Hz, 1H), 4.60 (d, *J* = 15.1 Hz, 1H), 4.42 (d, *J* = 15.1 Hz, 1H), 3.91 (quin, *J* = 7.5 Hz, 1H), 3.52 – 3.23 (m, 2H).

**$^{13}$C NMR** (126 MHz, Acetone) δ 151.29, 151.08, 148.13, 146.63, 136.39, 135.49, 129.87, 129.74, 129.63, 129.49, 129.06, 125.45, 125.22, 118.85, 56.34, 53.47, 52.95.

**IR** (thin film): 3293, 3106, 2925, 1606, 1532, 1455, 1402, 1350, 1312, 1164, 1091, 1012, 936, 855, 784, 737, 685 $cm^{-1}$.

**MS** (ESI, negative mode): 545.9 ($M-H^+$)

**Melting point** : 153-155 °C




**11a**. Prepared according to general procedure A and purified by silica gel chromatography (90:10 to 80:20, hexanes/ethyl acetate) to afford the product as an off-white solid (59 mg, 85%).

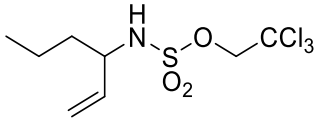
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.9 Hz, 2H), 8.07 (d, *J* = 8.8 Hz, 2H), 5.52 (ddd, *J* = 17.2, 10.3, 6.9 Hz, 1H), 5.13 (d, *J* = 8.6 Hz, 1H), 5.08 (d, *J* = 16.1 Hz, 1H), 5.05 (d, *J* = 9.8 Hz, 1H), 4.18 – 3.98 (m, 1H), 3.49 – 3.22 (m, 2H), 2.12 – 1.97 (m, 2H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 150.32, 146.74, 135.85, 128.71, 124.58, 118.01, 55.58, 38.33, 28.83.

**IR** (thin film): 3284, 3106, 2923, 1607, 1530, 1420, 1351, 1311, 1163, 1092, 1054, 934, 854, 737, 685, 616, 564 $cm^{-1}$.

**MS** (ESI, negative mode): 348.6 ($M-H^+$)

**Melting point** : 103-106 °C



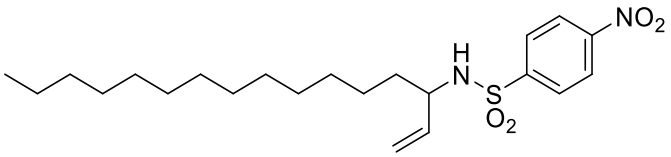

**12b**. Prepared according to general procedure A and purified by silica gel chromatography (90:10 to 80:20, hexanes/ethyl acetate) to afford the product as an oil (46 mg, 81%).

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 5.78 (ddd, *J* = 17.1, 10.3, 6.8 Hz, 1H), 5.30 (d, *J* = 17.1 Hz, 1H), 5.23 (d, *J* = 10.3 Hz, 1H), 4.70 (d, *J* = 8.0 Hz, 1H), 4.61 (s, 2H), 4.08 – 3.94 (m, 1H), 1.69 – 1.56 (m, 2H), 1.49 – 1.35 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 137.70, 117.78, 94.10, 78.77, 58.18, 37.84, 19.21, 14.25.

**IR** (thin film): 3301, 2962, 2936, 2875, 1447, 1432, 1363, 1183, 1089, 1048, 1015, 942, 856, 758, 726, 625, 588, 537 $cm^{-1}$.

**MS** (ESI, negative mode): 307.5 ($M-H^+$)



**13a**. Prepared according to general procedure A and purified by silica gel chromatography (90:10 to 80:20, hexanes/ethyl acetate) to afford the product as a white solid (64 mg, 75%).

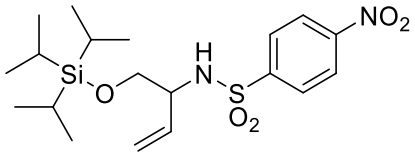
**$^1$H NMR** (300 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.8 Hz, 2H), 8.05 (d, *J* = 8.5 Hz, 2H), 5.48 (ddd, *J* = 17.1, 10.3, 6.9 Hz, 1H), 4.98 (d, *J* = 17.2 Hz, 1H), 4.95 (d, *J* = 10.3 Hz, 1H), 4.92 – 4.90 (m, 1H), 3.85 (quin, *J* = 6.9 Hz, 1H), 1.48 (t, *J* = 6.8 Hz, 2H), 1.35 – 1.03 (m, 22H), 0.88 (t, *J* = 6.6 Hz, 3H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 150.22, 147.42, 137.56, 128.73, 124.48, 116.74, 57.30, 36.02, 32.25, 29.97, 29.85, 29.76, 29.68, 29.46, 25.66, 23.01, 14.44.

**IR** (thin film): 3276, 2920, 2851, 1682, 1651, 1606, 1529, 1468, 1428, 1347, 1310, 1164, 1091, 1101, 927, 854, 738, 684, 620, 565 $cm^{-1}$.

**MS** (ESI, negative mode): 423.8 ($M-H^+$)

**Melting point** : 69-74 °C



**14a**. Prepared according to general procedure A and purified by silica gel chromatography (90:10 to 80:20, hexanes/ethyl acetate) to afford the product as a clear film (71 mg, 83%).

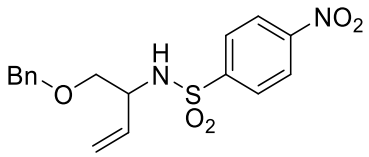
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.9 Hz, 2H), 8.04 (d, *J* = 8.9 Hz, 2H), 5.65 (ddd, *J* = 17.2, 10.3, 6.9 Hz, 1H), 5.23 (d, *J* = 6.3 Hz, 1H), 5.14 (d, *J* = 17.2 Hz, 1H), 5.09 (d, *J* = 10.4 Hz, 1H), 3.92 – 3.81 (m, 1H), 3.70 (dd, *J* = 9.9, 4.3 Hz, 1H), 3.63 (dd, *J* = 9.9, 5.5 Hz, 1H), 1.10 – 1.02 (m, 3H), 1.00 – 0.95 (m, 18H),

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 150.19, 146.90, 134.92, 128.70, 124.40, 118.30, 65.91, 58.50, 18.09, 12.02.

**IR** (thin film): 3296, 3106, 2944, 2867, 1607, 1532, 1463, 1403, 1349, 1310, 1249, 1168, 1118, 1093, 1069, 1014, 995, 922, 882, 854, 782, 736, 685, 618, 567 $cm^{-1}$.

**MS** (ESI, negative mode): 427.9 ($M-H^+$)

**Melting point** : 37-41 °C



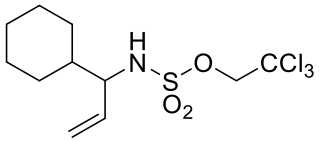
**15a**. Prepared according to general procedure A and purified by silica gel chromatography (90:10 to 80:20, hexanes/ethyl acetate) to afford the product as an off-white wax (44 mg, 61%).

**$^1$H NMR** (500 MHz, Acetone) δ 8.30 (d, *J* = 8.4 Hz, 2H), 8.11 (d, *J* = 8.2 Hz, 2H), 7.33 – 7.24 (m, 3H), 7.22 (d, *J* = 7.2 Hz, 2H), 7.12 (d, *J* = 7.9 Hz, 1H), 5.80 (ddd, *J* = 16.8, 10.3, 6.1 Hz, 1H), 5.24 (d, *J* = 17.2 Hz, 1H), 5.07 (d, *J* = 10.4 Hz, 1H), 4.39 (s, 2H), 4.20 – 4.13 (m, 1H), 3.55 – 3.39 (m, 2H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 150.06, 146.84, 137.32, 134.67, 128.73, 128.63, 128.34, 128.03, 124.29, 118.28, 73.55, 71.98, 56.52.

**IR** (thin film): 3285, 3105, 2864, 1529, 1453, 1402, 1349, 1311, 1166, 1091, 1027, 931, 853, 737, 699, 685 $cm^{-1}$.

**MS** (ESI, negative mode): 361.4 ($M-H^+$)



**16b**. Prepared according to general procedure A and purified by silica gel chromatography (90:10 to 80:20, hexanes/ethyl acetate) to afford the product as a white solid (61 mg, 88%).

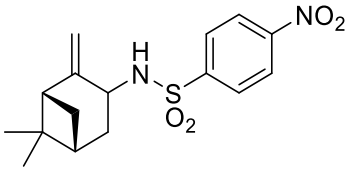
**$^1$H NMR** (300 MHz, $CDCl_3$) δ 5.75 (ddd, *J* = 17.3, 10.3, 7.2 Hz, 1H), 5.29 (d, *J* = 17.1 Hz, 1H), 5.26 (d, *J* = 10.3 Hz, 1H), 4.82 (d, *J* = 8.5 Hz, 1H), 4.60 (s, 2H), 3.83 (q, *J* = 7.2 Hz, 1H), 1.88 – 1.63 (m, 5H), 1.59 – 1.46 (m, 1H), 1.31 – 1.15 (m, 3H), 1.13 – 0.92 (m, 2H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 135.85, 118.21, 93.87, 78.45, 63.07, 42.51, 29.17, 29.08, 26.51, 26.27, 26.24.

**IR** (thin film): 3301, 2929, 2855, 1448, 1363, 1261, 1181, 1089, 1048, 1011, 945, 854, 758, 726, 595, 538 $cm^{-1}$.

**MS** (ESI, negative mode): 347.6 ($M-H^+$)

**Melting point** : 77-78 °C



**17a**. Prepared according to general procedure B and purified by silica gel chromatography (90:10 to 80:20, hexanes/ethyl acetate) to afford the product as a yellowish solid (114 mg, 68%).

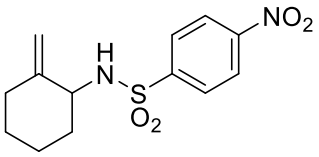
**$^{1}$H NMR** (300 MHz, $CDCl_3$) δ 8.39 (d, *J* = 8.8 Hz, 2H), 8.11 (d, *J* = 8.8 Hz, 2H), 4.86 (d, *J* = 6.1 Hz, 1H), 4.77 (s, 1H), 4.60 (s, 1H), 4.13 (t, *J* = 6.9 Hz, 1H), 2.59 – 2.37 (m, 2H), 2.36 – 2.16 (m, 1H), 2.03 – 1.83 (m, 2H), 1.28 – 1.17 (m, 4H), 0.66 (s, 3H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 152.49, 150.35, 147.05, 128.76, 124.75, 113.08, 51.35, 49.44, 40.46, 40.31, 35.20, 29.43, 25.97, 22.37.

**IR** (thin film): 3276, 3117, 2975, 2921, 1607, 1531, 1348, 1333, 1307, 1167, 1093, 961, 909, 854, 737, 684, 635, 597, 559 $cm^{-1}$.

**MS** (ESI, negative mode): 335.8 ($M-H^+$)

**Melting point** : 77-78 °C



**18a**. Prepared according to general procedure A and purified by silica gel chromatography (90:10 to 80:20, hexanes/ethyl acetate) to afford the product as an off white solid (55 mg, 92%).

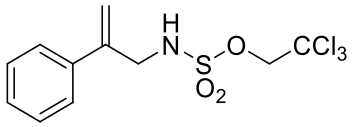
$^{1}$H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.6 Hz, 1H), 8.07 (d, *J* = 8.7 Hz, 1H), 5.11 (d, *J* = 8.3 Hz, 1H), 4.66 (s, 1H), 4.65 (s, 1H), 3.99 – 3.77 (m, 1H), 2.34 – 2.16 (m, 1H), 2.03 – 1.90 (m, 1H), 1.90 – 1.79 (m, 1H), 1.78 – 1.56 (m, 2H), 1.53 – 1.29 (m, 3H).

$^{13}$C NMR (126 MHz, $C_6D_6$) δ 149.93, 147.02, 128.26, 124.27, 108.03, 56.64, 35.77, 33.80, 27.17, 24.11.

IR (thin film): 3290, 3106, 2937, 2859, 1653, 1607, 1530, 1446, 1350, 1308, 1167, 1092, 1013, 969, 909, 854, 736, 685, 616, 562 $cm^{-1}$.

**MS** (ESI, negative mode): 295.4 ($M-H^+$)

**Melting point** : 119-122 °C



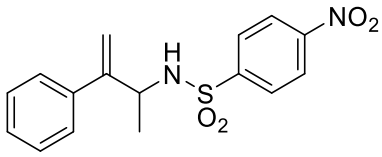
**19b**. Prepared according to general procedure A and purified by silica gel chromatography (90:10 to 80:20, hexanes/ethyl acetate) to afford the product as a clear film (59 mg, 86%).

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.49 – 7.31 (m, 5H), 5.54 (s, 1H), 5.39 (s, 1H), 4.75 – 4.64 (m, 1H), 4.54 (s, 2H), 4.29 (d, *J* = 5.2 Hz, 2H).

**$^{13}$C NMR** (126 MHz, $C_6D_6$) δ 142.70, 137.75, 129.23, 128.96, 126.53, 116.55, 78.56, 48.32

**IR** (thin film): 3313, 2950, 1428, 1368, 1181, 1087, 1018, 911, 856, 779, 758, 723, 617, 537, 486 $cm^{-1}$.

**MS** (ESI, negative mode): 342.0 ($M-H^+$)



**20a**. Prepared according to general procedure A and purified by silica gel chromatography (90:10 to 80:20, hexanes/ethyl acetate) to afford the product as a an solid (59 mg, 86%).

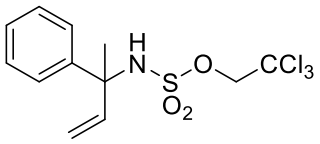
**$^1$H NMR** (300 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.8 Hz, 2H), 7.88 (d, *J* = 8.8 Hz, 2H), 7.29 – 7.13 (m, 3H), 7.09 (dd, *J* = 7.8, 1.5 Hz, 2H), 5.16 (s, 2H), 4.93 (d, *J* = 8.1 Hz, 1H), 4.61 – 4.37 (m, 1H), 1.40 (d, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 150.11, 149.65, 146.81, 139.68, 128.78, 128.47, 128.32, 126.96, 124.42, 114.51, 53.46, 22.50.

**IR** (thin film): 3288, 3105, 2981, 2933, 2870, 1607, 1530, 1427, 1350, 1311, 1166, 1089, 979, 911, 854, 779, 736, 685, 621 $cm^{-1}$.

**MS** (ESI, negative mode): 331.8 ($M-H^+$)

**Melting point** : 117-121 °C



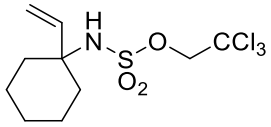
**21b**. Prepared according to general procedure A and purified by silica gel chromatography (90:10 to 80:20, hexanes/ethyl acetate) to afford the product as a clear oil (58 mg, 74%).

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.54 – 7.46 (m, 2H), 7.45 – 7.32 (m, 3H), 6.25 (dd, *J* = 17.3, 10.7 Hz, 1H), 5.37 (d, *J* = 10.7 Hz, 1H), 5.32 (d, *J* = 17.3 Hz, 1H), 5.17 (s, 1H), 4.53 (d, *J* = 2.4 Hz, 2H), 1.95 (s, 3H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 143.42, 141.83, 129.04, 128.35, 126.43, 115.69, 93.75, 78.55, 63.74, 25.84.

**IR** (thin film): 3297, 3061, 2992, 2948, 1494, 1446, 1410, 1358, 1181, 1124, 1088, 1046, 980, 931, 856, 763, 725, 700, 603, 539 $cm^{-1}$.

**MS** (ESI, negative mode): 355.6 ($M-H^+$)



**22b**. Prepared according to general procedure A and purified by silica gel chromatography (90:10 to 80:20, hexanes/ethyl acetate) to afford the product as a white solid (59 mg, 87%).

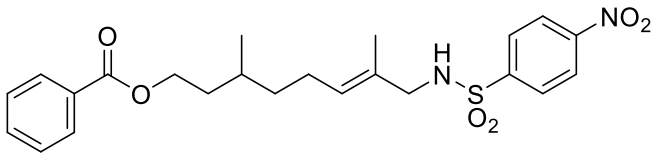
**$^1$H NMR** (300 MHz, $CDCl_3$) δ 6.01 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.30 (d, *J* = 17.6 Hz, 1H), 5.27 (d, *J* = 10.8 Hz, 1H), 4.85 (s, 1H), 4.60 (s, 2H), 2.04 – 1.88 (m, 2H), 1.82 – 1.69 (m, 2H), 1.69 – 1.47 (m, 5H), 1.47 – 1.31 (m, 1H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 141.79, 115.98, 93.90, 78.50, 60.59, 35.78, 25.54, 22.17.

**IR** (thin film): 3281, 2934, 2860, 1453, 1428, 1373, 1361, 1345, 1310, 1170, 1142, 1090, 1043, 1023, 996, 933, 903, 857, 763, 721, 593, 524 $cm^{-1}$.

**MS** (ESI, negative mode): 333.5 ($M-H^+$)

**Melting point** : 95-97 °C



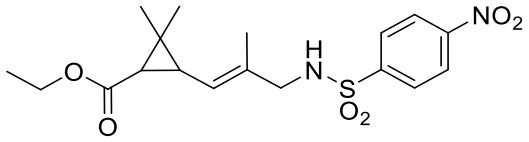
**23a.** Prepared according to the general procedure B and purified by silica gel chromatography (100:0 to 85:15, hexanes/ethyl acetate) to afford the product as a yellow oil (201 mg, 88% yield).

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.8 Hz, 2H), 8.03 (d, *J* = 8.8 Hz, 2H), 8.00 (d, *J* = 7.4 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 2H), 5.26 (t, *J* = 6.9 Hz, 1H), 5.14 (t, *J* = 6.1 Hz, 1H), 4.32 (m, 2H), 3.51 (d, *J* = 6.1 Hz, 2H), 2.03 – 1.87 (m, 2H), 1.80 – 1.68 (m, 1H), 1.63 – 1.54 (m, 2H), 1.52 (s, 3H), 1.37 – 1.28 (m, 1H), 1.20 – 1.10 (m, 1H), 0.93 (d, *J* = 6.3 Hz, 3H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 167.06, 150.24, 146.63, 133.22, 130.65, 130.01, 129.78, 129.63, 128.66, 128.60, 124.54, 63.69, 51.52, 36.51, 35.69, 29.86, 25.43, 19.80, 14.45.

**IR** (thin film): 3433, 1638, 1530, 1348, 1314, 1276, 1164, 1094, 1070, 853, 735, 714, 686, 614 $cm^{-1}$.

**MS** (ESI, negative mode): 459.0 ($M-H^+$)



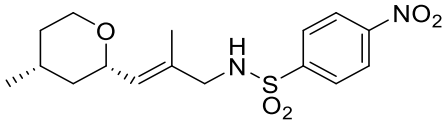

**24a.** Prepared according to the general procedure B and purified by silica gel chromatography (100:0 to 85:15, hexanes/ethyl acetate) to afford the product as a yellow oil (157 mg, 79%, 1.4:1 mixture of diastereomers from starting material).

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.1 Hz, 3.2H, both), 8.03 (d, *J* = 8.8 Hz, 1.2H, minor), 8.02 (d, *J* = 8.8 Hz, 2H, major), 5.57 (d, *J* = 8.5 Hz, 0.6H, minor), 5.07 (d, *J* = 6.1 Hz, 0.6H, minor), 5.06 (d, *J* = 6.0 Hz, 1H, major), 5.03 (d, *J* = 8.7 Hz, 1H, major), 4.11 (q, *J* = 7.1 Hz, 2H, major), 4.07 – 4.00 (m, 1.2H, minor), 3.56 (d, *J* = 6.1 Hz, 3.2H, both), 1.92 (dd, *J* = 8.4, 5.4 Hz, 1H, major), 1.75 (t, *J* = 8.5 Hz, 0.6H, minor), 1.67 (d, *J* = 8.6 Hz, 0.6H, minor), 1.64 (s, 1.8H, minor), 1.60 (s, 3H, major), 1.34 (d, *J* = 5.4 Hz, 1H, major), 1.24 (t, *J* = 7.1 Hz, 4.8H, both), 1.21 (s, 3H, major), 1.17 (s, 1.8H, minor), 1.14 (s, 1.8H, minor), 1.06 (s, 3H, major).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 172.15, 171.33, 150.33, 146.63, 146.47, 133.19, 132.67, 128.69, 128.63, 126.41, 124.61, 124.58, 123.79, 60.81, 60.36, 51.54, 51.16, 35.32, 31.87, 31.48, 28.90, 28.83, 26.94, 22.46, 20.58, 15.15, 15.03, 14.95, 14.63, 14.58.

**IR** (thin film): 3283, 2981, 2954, 2872, 1717, 1530, 1420, 1378, 1350, 1311, 1197, 1165, 1113, 1094, 1055, 1030, 912, 856, 736, 686, 614, 556 $cm^{-1}$.

**MS** (ESI, negative mode): 395.0 ($M-H^+$)



**25a.** Prepared according to the general procedure B and purified by silica gel chromatography (100:0 to 85:15, hexanes/ethyl acetate) to afford the product as a white solid (106 mg, 60% yield, 10:1 mixture of diastereomers from starting material).

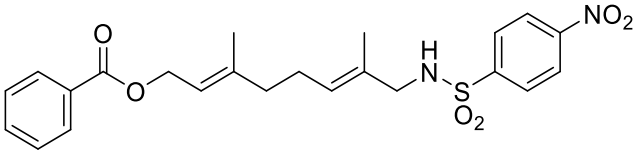
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.8 Hz, 2H), 8.03 (d, *J* = 8.8 Hz, 2H), 5.24 (d, *J* = 7.8 Hz, 1H), 5.09 (t, *J* = 6.2 Hz, 1H), 3.90 (ddd, *J* = 10.7, 9.2, 2.9 Hz, 2H), 3.54 (d, *J* = 6.1 Hz, 2H), 3.39 (td, *J* = 12.4, 2.0 Hz, 1H), 1.60 (s, 3H), 1.59 – 1.53 (m, 1H), 1.50 (dd, *J* = 13.3, 1.7 Hz, 1H), 1.40 (d, *J* = 13.3 Hz, 1H), 1.15 (qd, *J* = 12.5, 4.6 Hz, 1H), 0.90 (d, *J* = 6.5 Hz, 3H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 150.44, 146.62, 132.61, 130.24, 128.68, 124.68, 74.47, 68.21, 50.92, 40.56, 34.55, 30.33, 22.47, 15.15.

IR (thin film): 3279, 3106, 2952, 2925, 2869, 1606, 1530, 1456, 1441, 1349, 1311, 1257, 1165, 1091, 913, 854, 736, 686, 613 $cm^{-1}$.

**MS** (ESI, negative mode): 353.0 ($M-H^+$)

**Melting Point** : 139 – 144 °C



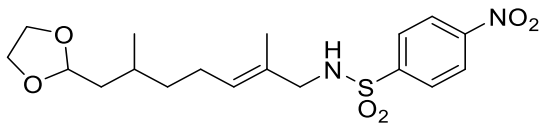
**26a.** Prepared according to the general procedure B and purified by silica gel chromatography (100:0 to 85:15, hexanes/ethyl acetate) to afford the product as a yellow oil (209 mg, 91% yield).

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.8 Hz, 2H), 8.03 (d, *J* = 8.6 Hz, 2H), 8.02 (d, *J* = 6.7 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 2H), 5.38 (t, *J* = 6.4 Hz, 1H), 5.23 (t, *J* = 6.6 Hz, 1H), 5.19 (t, *J* = 6.1 Hz, 1H), 4.81 (d, *J* = 6.8 Hz, 2H), 3.50 (d, *J* = 6.1 Hz, 2H), 2.08 (dd, *J* = 14.1, 7.0 Hz, 2H), 2.01 (t, *J* = 7.1 Hz, 2H), 1.71 (s, 3H), 1.52 (s, 3H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 167.18, 150.27, 146.70, 141.20, 133.30, 130.66, 130.58, 129.90, 128.85, 128.71, 128.62, 124.59, 119.69, 62.31, 51.57, 38.91, 25.96, 16.83, 14.56.

**IR** (thin film): 3627, 3280, 3105, 3068, 2922, 1746, 1604, 1585, 1528, 1451, 1349, 1313, 1273, 1165, 1094, 1028, 912, 855, 735, 688, 648, 615, 533 $cm^{-1}$.

**MS** (ESI, negative mode): 457.0 ($M-H^+$)



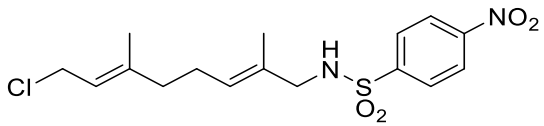
**27a.** Prepared according to the general procedure B and purified by silica gel chromatography (90:10 to 80:20, hexanes/ethyl acetate) to afford the product as a yellow oil (168 mg, 84%).

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.7 Hz, 2H), 8.03 (d, *J* = 8.6 Hz, 2H), 5.25 (t, *J* = 6.7 Hz, 1H), 5.17 (t, *J* = 5.5 Hz, 1H), 4.85 (t, *J* = 4.7 Hz, 1H), 3.94 (s, 2H), 3.81 (s, 2H), 3.51 (d, *J* = 5.7 Hz, 2H), 2.22 – 1.84 (m, 2H), 1.67 – 1.41 (m, 3H), 1.52 (s, 3H), 1.35 – 1.21 (m, 1H), 1.19 – 1.02 (m, 1H), 0.89 (d, *J* = 6.2 Hz, 3H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 150.23, 146.55, 129.88, 129.81, 128.59, 124.57, 103.85, 64.98, 64.92, 51.59, 40.90, 36.78, 29.09, 25.30, 20.07, 14.47.

**IR** (thin film): 3566, 3285, 3106, 2917, 1717, 1606, 1530, 1435, 1350, 1311, 1227, 1164, 1008, 1093, 1037, 949, 912, 855, 736, 686, 616, 548 $cm^{-1}$.

**MS** (ESI, negative mode): 397.3 ($M-H^+$)



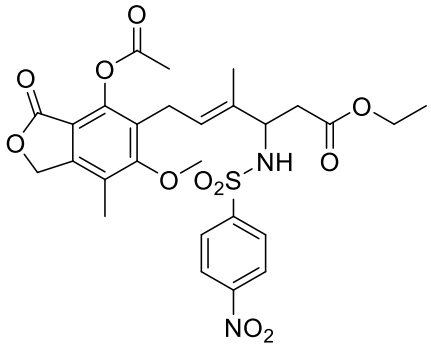
**28a.** Prepared according to the general procedure B and purified by silica gel chromatography (90:10 to 80:20, hexanes/ethyl acetate) to afford the product as a pale green oil (124 mg, 67%).

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.8 Hz, 2H), 8.05 (d, *J* = 8.8 Hz, 2H), 5.38 (t, *J* = 8.0 Hz, 1H), 5.25 (t, *J* = 7.0 Hz, 1H), 4.93 (t, *J* = 5.8 Hz, 1H), 4.08 (d, *J* = 8.0 Hz, 2H), 3.53 (d, *J* = 5.7 Hz, 2H), 2.21 – 1.90 (m, 4H), 1.69 (s, 3H), 1.55 (s, 3H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 150.32, 146.49, 142.09, 130.63, 128.70, 128.64, 124.62, 121.23, 51.52, 41.39, 38.87, 25.92, 16.23, 14.58.

**IR** (thin film): 3630, 3298, 3105, 2925, 2865, 1717, 1662, 1607, 1531, 1437, 1402, 1350, 1312, 1165, 1052, 855, 736, 686, 616, 463 $cm^{-1}$.

**MS** (ESI, negative mode): 371.9 ($M-H^+$)



**29a.** Prepared according to the general procedure B and purified by silica gel chromatography (90:10 to 70:30, hexanes/ethyl acetate) to afford the product as a white solid (248 mg, 84% yield. 2.5:1 mixture of regioisomers).

Major regioisomer (drawn above):

**$^{1}$H NMR** (500 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.8 Hz, 2H), 7.92 (d, *J* = 8.8 Hz, 2H), 5.90 (d, J = 7.6 Hz, 1H), 5.20-5.13 (m, 3H), 4.11 (dq, *J* = 14.4, 7.1 Hz, 2H), 4.02 (q, *J* = 7.1 Hz, 2H), 3.67 (s, 3H), 3.18 (d, *J* = 6.9 Hz, 2H), 2.57 (dd, *J* = 15.5, 7.3 Hz, 1H), 2.48 (dd, *J* = 15.3, 5.9 Hz, 1H), 2.37 (s, 3H), 2.19 (s, 3H), , 1.17 (t, *J* = 7.1 Hz, 3H).

Minor isomer (amination at methyl group):

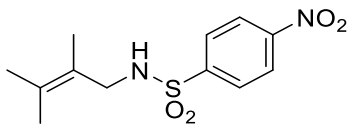
**$^{1}$H NMR** (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.8 Hz, 2H), 8.00 (d, *J* = 8.8 Hz, 2H), 5.32 (t, *J* = 6.2 Hz, 1H), 5.26 (t, *J* = 7.0 Hz, 1H), 3.76 (s, 3H), 3.55 (d, *J* = 6.0 Hz, 2H), 3.35 (d, *J* = 6.9 Hz, 2H), 2.37 (s, 3H), 2.19 (s, 3H), 1.23 (t, *J* = 7.7 Hz, 3H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 173.05, 170.70, 169.50, 169.16, 168.35, 168.31, 162.64, 150.05, 149.84, 146.95, 146.91, 146.67, 146.27, 146.01, 133.91, 133.26, 128.59, 128.44, 127.95, 125.78, 124.39, 124.09, 123.22, 113.62, 68.62, 61.39, 61.28, 61.20, 60.88, 60.52, 57.71, 48.76, 38.98, 32.72, 23.68, 23.30, 20.68, 14.36, 14.18, 12.91, 11.87.

**IR** (thin film): 3569, 3277, 3105, 2982, 1762, 1608, 1530, 1473, 1450, 1401, 1350, 1315, 1271, 1165, 1130, 1093, 1071, 1032, 1011, 967, 914, 855, 736, 686, 648, 618, 549 $cm^{-1}$.

**MS** (ESI, negative mode): 588.9 ($M-H^+$)

**Melting Point** : 44-51 °C



**30a.** Prepared according to the general procedure B and purified by silica gel chromatography (90:10 to 70:30, hexanes/ethyl acetate) to afford the product as a white solid (44 mg, 77%)

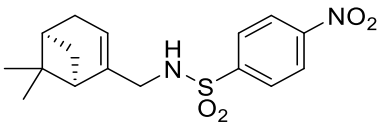
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.9 Hz, 2H), 8.05 (d, *J* = 8.9 Hz, 2H), 4.68 (t, *J* = 5.5 Hz, 1H), 3.64 (d, *J* = 5.7 Hz, 2H), 1.61 (s, 3H), 1.57 (s, 3H), 1.52 (s, 3H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 150.28, 146.53, 131.75, 128.54, 124.43, 122.28, 46.37, 20.98, 20.35, 17.09.

**IR** (thin film): 3310, 3109, 2322, 1606, 1528, 1346, 1327, 1311, 1155, 1090, 1035, 815, 746, 734, 615, 548 $cm^{-1}$.

**MS** (ESI, negative mode[M – H]$^-$): 283.1 (M-H$^+$)

**Melting Point** : 125 – 128 °C




**31a.** Prepared according to the general procedure B and purified by silica gel chromatography (90:10 to 80:20, hexanes/ethyl acetate) to afford the product as a white solid (53 mg, 32%)

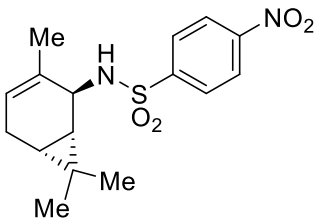
**$^1$H NMR** (300 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.6 Hz, 2H), 8.05 (d, *J* = 8.5 Hz, 2H), 5.38 (s, 1H), 4.65 (s, 1H), 3.53 (s, 2H), 2.40 – 2.23 (m, 1H), 2.18 (s, 2H), 2.08 – 1.87 (m, 2H), 1.24 (s, 3H), 0.97 (d, *J* = 8.7 Hz, 1H), 0.75 (s, 3H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 150.40, 146.45, 142.87, 128.69, 124.70, 121.30, 48.60, 44.19, 40.84, 38.33, 31.77, 31.46, 26.30, 21.34.

**IR** (thin film): 3290, 3106, 2919, 1606, 1530, 1428, 1349, 1311, 1165, 1093, 1050, 911, 854, 804, 736, 686, 611, 561, 507 $cm^{-1}$.

**MS** (ESI, negative mode): 335.6 (M-H$^+$)

**Melting Point** : 78 – 83 °C



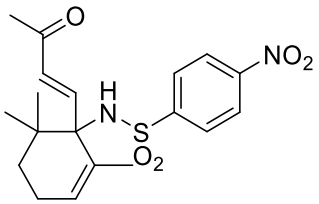
**32a.** Prepared according to the general procedure B and purified by silica gel chromatography (90:10 to 80:20, hexanes/ethyl acetate) to afford the product as yellow oil (146 mg, 87%)

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.8 Hz, 2H), 8.10 (d, *J* = 8.8 Hz, 2H), 5.39 (s, 1H), 4.80 (d, *J* = 9.7 Hz, 1H), 3.66 (d, *J* = 9.5 Hz, 1H), 2.35 (dd, *J* = 19.6, 4.9 Hz, 1H), 1.98 (d, *J* = 19.6 Hz, 1H), 1.51 (s, 3H), 0.82 (s, 3H), 0.79 (s, 3H), 0.64 (t, *J* = 8.2 Hz, 1H), 0.41 (d, *J* = 8.8 Hz, 1H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 150.22, 147.64, 130.26, 128.62, 126.23, 124.59, 50.58, 28.54, 26.53, 21.30, 21.15, 17.39, 16.16, 13.51.

**IR** (thin film): 3284, 3106, 2944, 2873, 1606, 1528, 1433, 1350, 1311, 1165, 1093, 1035, 311, 853, 820, 776, 736, 686, 648, 618, 581, 547 $cm^{-1}$.

**MS** (ESI, negative mode): 335.6 ($M-H^+$)




**33a.** Prepared according to the general procedure B and purified by silica gel chromatography (90:10 to 70:30, hexanes/ethyl acetate) to afford the product as a white solid (133 mg, 68%)

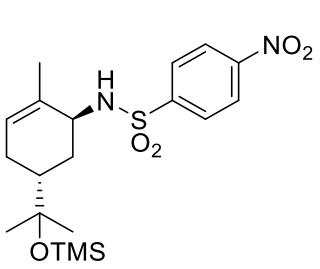
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.8 Hz, 2H), 8.07 (d, *J* = 8.8 Hz, 2H), 7.06 (d, *J* = 15.9 Hz, 1H), 6.07 (d, *J* = 15.9 Hz, 1H), 5.65 (s, 1H), 4.91 (s, 1H), 2.29 (s, 3H), 1.92 – 1.82 (m, 2H), 1.52 (s, 3H), 1.39 – 1.31 (m, 1H), 1.31 – 1.21 (m, 1H), 1.01 (s, 3H), 0.81 (s, 3H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 197.43, 150.23, 148.38, 143.65, 132.83, 131.74, 129.23, 128.82, 124.48, 70.62, 39.27, 32.32, 28.72, 24.84, 23.39, 22.73, 21.70.

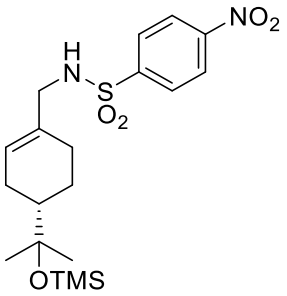
**IR** (thin film): 3289, 2969, 2927, 1672, 1623, 1531, 1454, 1350, 1256, 1163, 1092, 1056, 1003, 913, 854, 735, 686, 650, 609, 566 $cm^{-1}$.

**MS** (ESI, negative mode): 391.0 ($M-H^+$)

**Melting Point** : 167-171 °C




major




minor

**34a.** Prepared according to the general procedure B and purified by silica gel chromatography (90:10 to 80:20, hexanes/ethyl acetate) to afford the major regioisomer as clear sticky oil (148 mg, 74%, 6:1 mixture of diastereomers) and the minor regioisomer as a white solid (37 mg, 17%)

Major: **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.5 Hz, 2.34H, major + minor), 8.10 (d, *J* = 8.5 Hz, 2.34H, major + minor), 5.56 (s, 1.17H, major + minor), 4.93 (d, *J* = 8.7 Hz, 1.17H, major + minor), 3.89 (s, 0.17H, minor), 3.74 (d, *J* = 7.9 Hz, 1H, major), 2.00 (m, 1.17H, major + minor), 1.73 (m, 2.34H, major + minor), 1.52 – 1.41 (m, 3.51H, major + minor), 1.32 (m, 2.34H, major + minor), 1.07 (s, 3.51H, major + minor), 1.05 (s, 3.51H, major + minor), 0.03 (s, 10.53H, major + minor).

Major: **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 150.26, 150.22, 147.66, 147.45, 131.26, 130.99, 128.62, 128.56, 128.50, 128.27, 127.81, 124.68, 74.98, 72.31, 53.82, 53.61, 40.21, 39.25, 33.44, 31.18, 31.16, 27.72, 27.70, 27.63, 26.96, 26.85, 26.71, 26.64, 20.73, 20.69, 2.79.

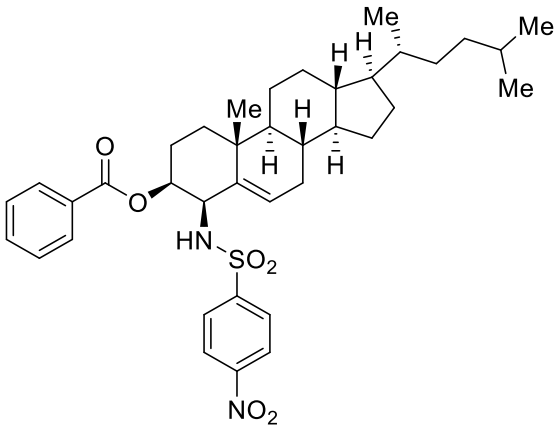
Minor: **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.3 Hz, 2H), 8.05 (d, *J* = 8.5 Hz, 2H), 5.58 (s, 1H), 4.79 (t, *J* = 6.0 Hz, 1H), 3.56 (d, *J* = 5.6 Hz, 2H), 2.03 – 1.59 (m, 5H), 1.50 – 1.19 (m, 1H), 1.14 (s, 3H), 1.13 (s, 3H), 1.08 – 0.91 (m, 1H), 0.08 (s, 9H).

Minor: **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 150.34, 146.66, 132.60, 128.74, 126.11, 124.61, 72.75, 49.63, 44.90, 27.67, 27.39, 26.88, 26.75, 23.64, 2.88, 2.27.

**IR** (thin film): 3292, 3106, 2970, 1606, 1531, 1449, 1350, 1309, 1249, 1161, 1093, 1061, 1040, 985, 914, 853, 840, 736, 686, 619, 565 $cm^{-1}$.

**MS** (ESI, negative mode): 425.2 ($M-H^+$)

**Melting Point** : major: (n/a); minor: 121 – 131 °C




**35a.** Prepared according to the general procedure B at 40 °C and purified by hot trituration with acetone to afford the product as a white solid (262 mg, 81% yield)

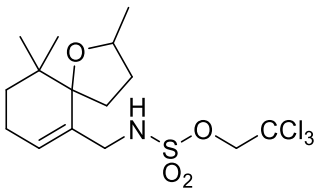
**$^{1}$H NMR** (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.8 Hz, 2H), 7.87 (d, *J* = 8.8 Hz, 2H), 7.80 (d, *J* = 7.4 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 2H), 5.72 (d, *J* = 2.7 Hz, 1H), 4.98 – 4.84 (m, 2H), 4.24 (t, *J* = 5.0 Hz, 1H), 2.08 (dt, *J* = 18.5, 5.2 Hz, 1H), 2.01 (d, *J* = 12.6 Hz, 1H), 1.94 – 1.79 (m, 4H), 1.64 – 1.49 (m, 2H), 1.45 – 1.31 (m, 6H), 1.29 – 1.06 (m, 8H), 1.05 (s, 3H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H), 0.64 (s, 3H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 165.31, 146.32, 137.94, 133.93, 131.58, 129.81, 129.53, 128.80, 128.40, 128.20, 124.29, 73.17, 60.20, 57.05, 56.41, 50.63, 42.56, 39.85, 36.91, 36.51, 36.09, 32.52, 31.95, 28.53, 28.37, 24.59, 24.17, 23.30, 23.17, 22.91, 21.21, 20.61, 19.06, 12.10.

**IR** (thin film): 3323, 2942, 2881, 1701, 1519, 1436, 1353, 1316, 1285, 1166, 1117, 738, 717, 687 $cm^{-1}$.

**MS** (ESI, negative mode): 648.1 ($M-H^+$)

**Melting Point** : 311-313 °C (decomposition)




**36b.** Prepared according to the general procedure B and purified by silica gel chromatography (90:10 to 70:30, hexanes/ethyl acetate) to afford the major diastereomer as a yellow oil (105 mg, 50%) and the minor diastereomer as a tan oil (79 mg, 36%). Diastereomers came from starting material.

Major: **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ 6.01 (d, *J* = 8.9 Hz, 1H), 5.67 (s, 1H), 4.67 – 4.55 (m, 2H), 4.22 – 4.06 (m, 1H), 3.83 (d, *J* = 12.8 Hz, 1H), 3.67 (dd, *J* = 12.8, 9.1 Hz, 1H), 2.15 – 2.03 (m, 2H), 2.02 – 1.89 (m, 2H), 1.84 – 1.70 (m, 1H), 1.63 – 1.50 (m, 1H), 1.46 – 1.36 (m, 1H), 1.33 – 1.21 (m, 4H), 0.93 (s, 3H), 0.87 (s, 3H).

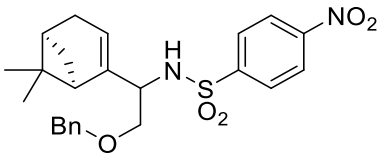
Major: **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 138.08, 128.94, 94.04, 90.20, 78.18, 77.50, 48.05, 36.87, 35.97, 34.77, 34.36, 24.98, 22.96, 21.65, 21.12.

Minor: **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ 5.91 (d, *J* = 8.9 Hz, 1H), 5.71 (t, *J* = 3.2 Hz, 1H), 4.60 (s, 2H), 4.28 – 4.13 (m, 1H), 3.83 (d, *J* = 12.8 Hz, 1H), 3.69 (dd, *J* = 12.8, 9.2 Hz, 1H), 2.28 – 2.07 (m, 3H), 2.04 – 1.94 (m, 1H), 1.87 – 1.72 (m, 1H), 1.68 – 1.56 (m, 1H), 1.55 – 1.45 (m, 1H), 1.31 (d, *J* = 6.0 Hz, 3H), 1.28 – 1.21 (m, 1H), 0.99 (s, 3H), 0.92 (s, 3H).

Minor: **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 137.38, 129.28, 94.03, 90.36, 78.21, 78.09, 48.58, 38.08, 35.32, 34.59, 34.02, 25.19, 23.10, 22.68, 21.92.

**IR** (thin film): 3307, 2973, 2924, 2874, 1472, 1453, 1411, 1362, 1326, 1260, 1226, 1181, 1085, 1048, 1009, 977, 940, 907, 884, 850, 755, 726, 680, 633, 586, 552, 536 $cm^{-1}$.

**MS** (ESI, negative mode): 419.8 ($M-H^+$)




**37a.** Prepared according to the general procedure B and purified by silica gel chromatography (90:10 to 80:20, hexanes/ethyl acetate) to afford the product as a white solid (160 mg 79% yield, 1.2:1 mixture of diastereomers)

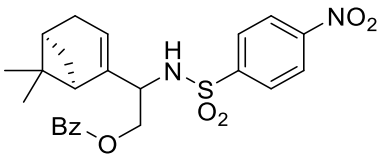
**$^{1}$H NMR** (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.8 Hz, 2H, major), 8.14 (d, *J* = 8.8 Hz, 1.6H, minor), 7.98 (d, *J* = 8.4 Hz, 2H, major), 7.97 (d, *J* = 8.4 Hz, 1.6H, minor), 7.34 – 7.28 (m, 5.4H, both), 7.22 – 7.17 (m, 1.8H, major), 7.17 – 7.12 (m, 1.8H, minor), 5.44 – 5.31 (m, 3.6H, both), 4.36 (d, *J* = 2.9 Hz, 2H, major), 4.32 (s, 1.6H, minor), 3.93 (q, *J* = 6.3 Hz, 1.8H, both), 3.43 (td, *J* = 9.4, 4.4 Hz, 1.6H, minor), 3.34 (ddd, *J* = 16.5, 9.8, 6.8 Hz, 2H, major), 2.35 (dt, *J* = 8.7, 5.6 Hz, .8H, minor), 2.21 (dt, *J* = 8.8, 5.7 Hz, 1H, major), 2.18 (s, 0.8H, minor), 2.14 (s, 2H, major), 2.12 – 2.09 (m, 1H, major), 2.05 (d, *J* = 5.2 Hz, 2H, major), 2.00 (s, 0.8H, minor), 1.24 (s, 2.4H, minor), 1.21 (s, 3H, major), 1.00 (d, *J* = 8.7 Hz, 0.8H, minor), 0.73 (s, 2.4H, minor), 0.70 (s, 3H, major), 0.67 (d, *J* = 8.7 Hz, 1H, major).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 150.08, 149.98, 147.14, 146.80, 144.37, 144.14, 137.54, 128.77, 128.72, 128.69, 128.60, 128.28, 128.07, 128.02, 124.25, 124.19, 121.57, 120.51, 73.44, 71.37, 70.89, 58.36, 58.13, 44.02, 43.06, 40.94, 40.77, 38.23, 31.98, 31.44, 31.36, 26.37, 26.32, 21.46, 21.40.

**IR** (thin film): 3286, 2985, 2918, 1717, 1606, 1528, 1454, 1349, 1312, 1165, 1093, 973, 911, 854, 736, 699, 685, 612, 570 $cm^{-1}$.

**MS** (ESI, negative mode): 455.1 ($M-H^+$)

**Melting Point** : 91 - 98 °C




**38a.** Prepared according to the general procedure B and purified by silica gel chromatography (90:10 to 80:20, hexanes/ethyl acetate) to afford the product as a white solid (181 mg, 77% yield, 1.2:1 mixture of diastereomers)

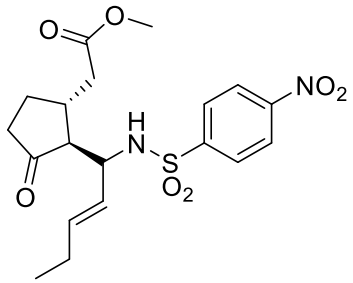
**$^{1}$H NMR** (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.8 Hz, 2H, major), 8.02 (d, *J* = 8.8 Hz, 1.6H, minor), 7.93 (d, *J* = 9.1 Hz, 2H, major), 7.92 (d, *J* = 9.1 Hz, 1.6H, minor), 7.81 (d, *J* = 7.3 Hz, 2H, major), 7.76 (d, *J* = 7.3 Hz, 1.6H, minor), 7.54 (t, *J* = 7.5 Hz, 1H, major), 7.53 (t, *J* = 7.5 Hz, 0.8H, minor), 7.37 (t, *J* = 5.9 Hz, 2H, major), 7.35 (t, *J* = 5.9 Hz, 1.6H, minor), 5.57 (d, *J* = 6.2 Hz, 1.8H, both), 5.32 (d, *J* = 7.6 Hz, 1H, major), 5.28 (d, *J* = 8.2 Hz, 0.8H, minor), 4.33 (d, *J* = 8.8 Hz, 0.8H, minor), 4.31 (d, *J* = 8.6 Hz, 1H, major), 4.21 – 4.16 (m, 3.6H, both), 2.41 (dt, *J* = 8.8, 5.6 Hz, 0.8, minor), 2.33 (dt, *J* = 8.7, 5.6 Hz, 1H, major), 2.25 – 2.20 (m, 2H, both), 2.18 (d, *J* = 5.6 Hz, 1H, major), 2.16 (d, *J* = 5.5 Hz, 1H, major), 2.08 (d, *J* = 16.2 Hz, 1.6H, minor), 1.28 (s, 2.4H, minor), 1.25 (s, 3H, major), 1.06 (d, *J* = 8.8 Hz, 0.8H, minor), 0.84 (d, *J* = 8.8 Hz, 1H, major), 0.77 (s, 2.4H, minor), 0.75 (s, 3H, major).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 166.44, 166.42, 149.62, 149.53, 146.76, 146.64, 143.34, 143.21, 133.61, 129.56, 129.50, 129.01, 128.97, 128.41, 128.37, 128.05, 127.89, 124.09, 121.67, 121.22, 65.12, 64.56, 58.15, 58.02, 43.61, 43.16, 40.62, 40.53, 38.08, 38.02, 31.75, 31.38, 31.17, 25.99, 21.14.

**IR** (thin film): 3432, 2918, 1702, 1654, 1528, 1451, 1431, 1349, 1314, 1273, 1163, 1092, 1027, 981, 853, 736, 713, 685, 616, 566 $cm^{-1}$.

**MS** (ESI, negative mode): 468.9 ($M-H^+$)

**Melting Point** : 138-140 °C



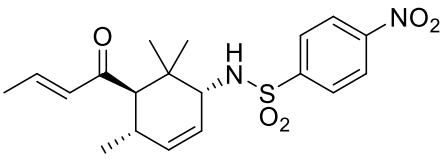
**39a.** Prepared according to the general procedure B and purified by silica gel chromatography (90:10 to 80:20, hexanes/ethyl acetate) to afford the product as a yellow oil (121 mg, 57%, 3:1 mixture of diastereomers)

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.6 Hz, 2H), 8.00 (d, *J* = 8.7 Hz, 2H), 5.74 (t, *J* = 11.6 Hz, 1H), 5.31 – 5.27 (m, 1H), 4.07 – 4.01 (m, 1H), 3.70 (s, 3H), 2.66 (dd, *J* = 15.1, 5.4 Hz, 1H), 2.60 – 2.43 (m, 2H), 2.40 – 2.27 (m, 2H), 2.26 – 2.14 (m, 2H), 2.12 – 2.05 (m, *J* = 14.6, 7.2 Hz, 1H), 1.78 – 1.71 (m, 2H), 1.62 – 1.52 (m, 1H), 0.70 (t, *J* = 7.4 Hz, 3H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 173.26, 172.43, 157.03, 150.29, 150.16, 147.93, 147.10, 138.74, 136.68, 128.91, 128.74, 125.69, 124.38, 124.29, 123.89, 59.58, 58.11, 55.83, 55.64, 52.22, 52.13, 38.85, 38.60, 38.16, 37.98, 35.75, 34.97, 27.41, 27.22, 25.19, 13.25, 13.18.

**IR** (thin film): 3450, 3275, 3107, 2963, 1732, 1607, 1529, 1437, 1350, 1311, 1166, 1092, 973, 914, 855, 738, 687, 648, 614 $cm^{-1}$.

**MS** (ESI, negative mode): 423.7 ($M-H^+$)



**40a.** Prepared according to the general procedure B and purified by silica gel chromatography (90:10 to 80:20, hexanes/ethyl acetate) to afford the product as a yellow solid (118 mg, 60%)

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.39 (d, *J* = 8.7 Hz, 2H), 8.10 (d, *J* = 8.7 Hz, 2H), 6.88 (dq, *J* = 13.9, 6.9 Hz, 1H), 6.21 (d, *J* = 15.6 Hz, 1H), 5.58 (d, *J* = 9.9 Hz, 1H), 5.17 (d, *J* = 9.6 Hz, 1H),

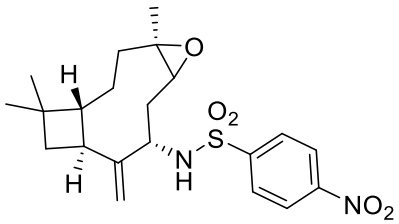
5.07 (ddd, *J* = 9.7, 5.2, 2.3 Hz, 1H), 3.23 (dd, *J* = 9.5, 5.3 Hz, 1H), 2.58 – 2.49 (m1H), 2.45 (d, *J* = 10.5 Hz, 1H), 1.88 (d, *J* = 6.8 Hz, 3H), 0.95 (s, 3H), 0.82 (d, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 202.29, 150.44, 147.39, 143.34, 137.28, 134.52, 128.56, 124.83, 123.33, 59.06, 55.45, 37.35, 31.65, 26.30, 21.53, 19.47, 18.60.

**IR** (thin film): 3273, 2968, 2933, 2875, 1734, 1685, 1650, 1623, 1531, 1441, 1349, 1310, 1165, 1093, 1043, 971, 912, 854, 738, 686, 617, 573, 515 $cm^{-1}$.

**MS** (ESI, negative mode): 391.2 ($M-H^+$)

**Melting Point** : 149 – 151 °C




**41a.** Prepared according to the general procedure B using 30% catalyst loading and purified by silica gel chromatography (90:10 to 80:20, hexanes/ethyl acetate) to afford the product as a yellow solid (157 mg, 75%, 10:1 mixture of diastereomers).

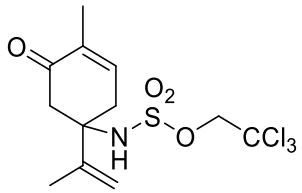
**$^{1}$H NMR** (300 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.5 Hz, 2.22H, maj + min), 8.03 (d, *J* = 8.6 Hz, 0.22H, min), 7.96 (d, *J* = 8.5 Hz, 2H, maj), 5.80 (d, *J* = 6.8 Hz, 0.11H, min), 5.67 (d, *J* = 7.3 Hz, 1H, maj), 5.05 (s, 2H, maj), 4.89 (s, 0.11H, min), 4.83 (s, 0.11H, min), 4.2-4.12 (m, 0.11H, min), 3.86 – 3.62 (m, 1H, maj), 2.91 (d, *J* = 8.7 Hz, 0.11H, min), 2.58 (dd, *J* = 8.6, 5.5 Hz, 1H, maj), 2.35 – 1.97 (m, 3.33H, maj + min), 1.74 (m, 1.11H, maj + min), 1.65 – 1.45 (m, 3.33H, maj + min), 1.44 – 1.21 (m, 5.55H, maj + min), 1.12 – 0.73 (m, 7.77H, maj + min).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 153.71, 150.15, 147.23, 128.65, 124.41, 112.83, 59.52, 59.30, 57.37, 57.28, 46.37, 39.80, 38.89, 36.46, 33.01, 29.99, 27.33, 22.61, 16.62.

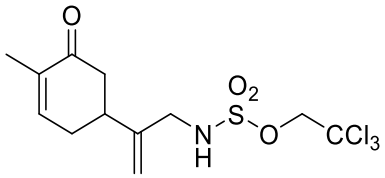
**IR** (thin film): 3272, 3106, 2934, 2862, 1639, 1607, 1530, 1454, 1402, 1385, 1310, 1274, 1260, 1166, 1126, 1093, 1063, 1014, 998, 980, 957, 939, 911, 854, 824, 763, 736, 685, 650, 603, 563, 537 $cm^{-1}$.

**MS** (ESI, negative mode): 419.4 ($M-H^+$)

**Melting Point** : 161 – 167 °C



major



minor

**42b.** Prepared according to the general procedure B and purified by silica gel chromatography (90:10 to 70:30, hexanes/ethyl acetate) to afford the major regioisomer as a tan solid (74 mg, 39%) and the minor regioisomer as a tan solid (68 mg, 36%).

Major: **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ 6.69 (s, 1H), 5.55 (s, 1H), 5.11 (s, 1H), 5.09 (s, 1H), 4.64 – 4.46 (m, 2H), 3.21 – 2.94 (m, 2H), 2.88 (s, 1H), 2.82 (s, 1H) 1.87 (s, 3H), 1.80 (s, 3H).

Major: **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 196.87, 143.81, 141.31, 136.14, 115.94, 93.70, 78.52, 64.10, 48.00, 34.51, 19.06, 15.67.

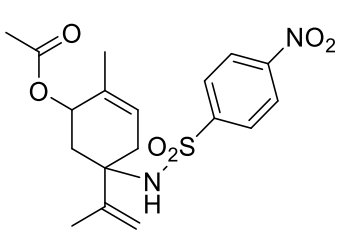
Minor: **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ 6.76 (s, 1H), 5.40 (t, *J* = 5.9 Hz, 1H), 5.21 (s, 1H), 5.06 (s, 1H), 4.64 (s, 2H), 3.87 (d, *J* = 5.8 Hz, 2H), 2.86 (t, *J* = 11.7 Hz, 1H), 2.70-2.50 (m, 2H), 2.49 – 2.19 (m, 2H), 1.78 (s, 3H).

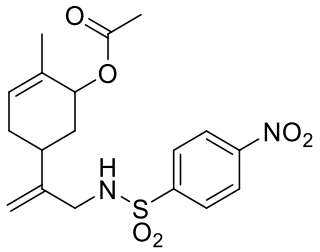
Minor: **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 199.56, 145.71, 144.67, 136.00, 114.03, 93.80, 78.54, 47.85, 43.25, 38.63, 31.62, 15.96.

**IR** (thin film): 3271, 2954, 2925, 1664, 1453, 1369, 1256, 1180, 1113, 1076, 1047, 1017, 987, 913, 855, 755, 727, 648, 572, 536 $cm^{-1}$.

**MS** (ESI, negative mode): 375.8 ($M-H^+$)

**Melting Point** : major: 114 – 122 °C; minor: 98 – 106 °C





**43a.** Prepared according to the general procedure B and purified by silica gel chromatography (90:10 to 70:30, hexanes/ethyl acetate) to afford the product as a sticky white oil (173 mg, 88%,

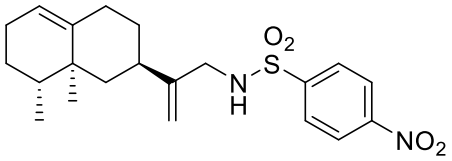
1.1:1 mixture of regioisomers, both regioisomers found as a mixture of diastereomers found in starting material).

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.38 – 8.33 (m, 2H, A), 8.32 – 8.26 (m, 2H, B), 8.08 – 8.03 (m, 2H, A), 8.02 – 7.98 (m, 1.4H, B), 7.98 – 7.94 (m, 0.6H, B), 5.66 (dd, *J* = 3.6, 1.7 Hz, 0.7H), 5.52 (d, *J* = 3.8 Hz, 0.3H), 5.46 – 5.36 (m, 1H), 5.35 – 5.25 (m, 2.3H), 5.17 (d, *J* = 12.0 Hz, 1H), 5.09 (t, *J* = 6.3 Hz, 0.7H), 5.06 (s, 0.3H), 5.00 (s, 0.7H), 4.94 (d, *J* = 4.4 Hz, 1H), 4.90 (s, 0.3H), 4.87 (s, 1H), 4.85 (s, 0.7H), 3.74 – 3.53 (m, 2H, A), 2.73 – 2.59 (m, 1H), 2.46 – 2.20 (m, 3.2H), 2.16 (s, 1.3H), 2.07 (s, 2H), 2.05 (s, 2H), 1.95 – 1.68 (m, 3.4H), 1.66 (s, 3.0H), 1.62 – 1.57 (m, 1.3H), 1.56 – 1.52 (m, 2.3H), 1.43 – 1.38 (m, 2.4H), 1.29 – 1.22 (m, 2.1H).

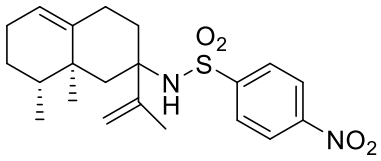
**$^{13}$C NMR** (126 MHz, c) δ 171.40, 171.18, 171.03, 150.30, 149.93, 147.87, 147.65, 147.59, 147.24, 146.22, 144.74, 143.11, 133.28, 133.13, 132.71, 131.46, 129.10, 128.96, 128.64, 128.57, 127.32, 125.47, 124.69, 124.01, 123.90, 123.06, 122.32, 115.99, 114.39, 112.13, 73.12, 70.92, 70.61, 69.57, 61.58, 58.65, 47.47, 47.16, 36.83, 36.45, 35.38, 34.06, 33.95, 32.33, 31.29, 31.19, 29.93, 21.60, 21.38, 21.30, 20.72, 19.94, 19.10, 18.94, 18.48, 18.43.

**IR** (thin film): 3441, 3106, 2922, 1731, 1716, 1644, 1607, 1530, 1437, 1371, 1350, 1311, 1242, 1163, 1092, 1060, 1027, 970, 914, 854, 736, 686, 614, 556, 464 $cm^{-1}$.

**MS** (ESI, negative mode): 393.5 ($M-H^+$)




major




minor

**44a.** Prepared according to the general procedure B and purified by silica gel chromatography (90:10 to 80:20, hexanes/ethyl acetate) to afford the product as a yellow solid (213 mg, quant, 1.5:1 mixture of regioisomers)

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.7 Hz, 2H, major), 8.29 (d, *J* = 8.7 Hz, 1.32H, minor), 8.07 (d, *J* = 8.7 Hz, 2H, maj), 7.99 (d, *J* = 8.7 Hz, 1.32H, min), 5.29 (s, 1.66H, maj + min), 5.18 (s, 0.66H, min), 5.14 (t, *J* = 6.2 Hz, 1H, maj), 5.07 (s, 0.66H, min), 4.93 (s, 0.66H, min), 4.86 (s, 1H, maj), 4.82 (s, 1H, maj), 3.63 (d, *J* = 6.1 Hz, 2H, maj), 2.70 (dq, *J* = 13.4, 2.9 Hz, 0.66H, min), 2.37 – 2.09 (m, 3.32H, maj + min), 2.09 – 1.82 (m, 4.98H, maj + min), 1.82 – 1.51 (m, 3.32H, maj

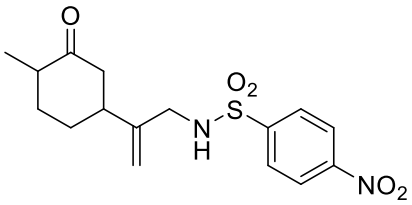
+ min), 1.43 – 1.25 (m, 7.20H, maj + min), 1.16 – 0.97 (m, 1.66H, maj + min), 0.92 – 0.72 (m, 10.96H, maj + min).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 150.32, 149.88, 149.05, 148.24, 146.37, 142.43, 142.24, 141.82, 129.08, 128.66, 124.66, 123.97, 120.97, 120.90, 116.80, 111.26, 62.91, 47.49, 47.36, 45.19, 41.93, 41.12, 38.67, 38.11, 37.38, 36.66, 33.55, 32.75, 29.90, 27.30, 26.60, 26.08, 25.83, 19.57, 18.53, 18.03, 16.00, 15.87.

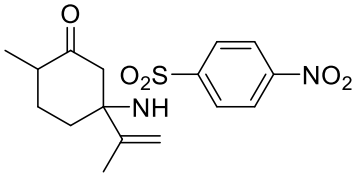
**IR** (thin film): 3289, 3105, 3037, 2965, 2923, 1644, 1607, 1530, 1435, 1349, 1310, 1163, 1093, 1062, 1010, 910, 854, 736, 686, 616, 561 $cm^{-1}$.

**MS** (ESI, negative mode): 404.3 ($M-H^+$)

**Melting Point** : 104 – 111 °C




major




minor

**45a.** Prepared according to the general procedure B and purified by silica gel chromatography (90:10 to 70:30, hexanes/ethyl acetate) to afford the major regioisomer as a tan solid (75 mg, 43%) and the minor regioisomer as a tan solid (20 mg, 11%)

Minor: **$^{1}$H NMR** (300 MHz, Acetone) δ 8.38 (d, *J* = 8.6 Hz, 2H), 8.05 (d, *J* = 8.6 Hz, 2H), 6.86 (s, 1H), 5.04 (s, 1H), 4.79 (s, 1H), 2.83 – 2.58 (m, 2H), 2.56 – 2.33 (m, 2H), 1.96 (dd, *J* = 19.7, 6.7 Hz, 2H), 1.80 (t, *J* = 11.9 Hz, 1H), 1.35 (s, 3H), 0.96 (d, *J* = 6.5 Hz, 3H).

Minor: **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 211.06, 150.03, 147.07, 144.07, 129.15, 123.92, 115.25, 66.52, 51.03, 44.77, 32.38, 30.25, 18.30, 14.51.

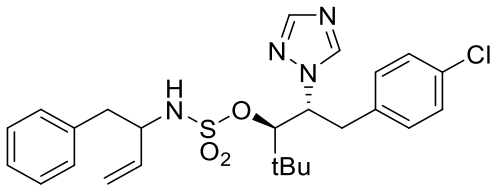
Major: **$^{1}$H NMR** (300 MHz, Acetone) δ 8.43 (d, *J* = 8.6 Hz, 2H), 8.14 (d, *J* = 8.6 Hz, 2H), 7.04 (s, 1H), 5.04 (s, 1H), 4.93 (s, 1H), 3.71 (d, *J* = 6.1 Hz, 2H), 2.50 – 2.36 (m, 1H), 2.33 (d, *J* = 8.8 Hz, 1H), 2.22 (t, *J* = 10.4 Hz, 1H), 2.14 – 2.07 (m, 1H), 1.89 (d, *J* = 13.9 Hz, 1H), 1.65 (q, *J* = 11.5 Hz, 1H), 1.38 – 1.15 (m, 2H), 0.92 (d, *J* = 6.5 Hz, 3H).

Major: **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 212.43, 150.41, 146.81, 146.18, 128.65, 124.76, 112.72, 47.23, 47.03, 45.03, 43.06, 34.98, 31.22, 14.55.

**IR** (thin film): 3275, 3106, 2966, 2932, 2864, 1709, 1650, 1606, 1530, 1448, 1402, 1350, 1311, 1220, 1165, 1093, 1055, 1014, 912, 854, 737, 686, 610, 557, 529 $cm^{-1}$.

**MS** (ESI, negative mode): 351.1 ($M-H^+$)

**Melting Point** : major: 125 - 129 °C; minor 148 °C decomp



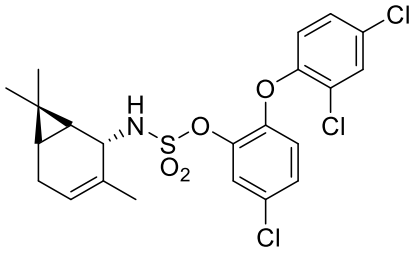

**46.** Prepared according to the general procedure and purified by silica gel chromatography(80:20 to 50:50, hexanes/ethyl acetate) to afford the product as a yellow oil (53 mg, 53%, 1:1 mixture of diastereomers at newly formed stereocenter)

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.36 (s, 1H, A+B), 7.77 (s, 0.5H, A), 7.72 (s, 0.5H, B), 7.35-7.28 (m,, 2H, A+B), 7.28 – 7.23 (m, 1H, A+B), 7.20 (d, *J* = 8.2 Hz, 4H, A+B), 6.99 (d, *J* = 7.8 Hz, 2H, A+B), 5.87 – 5.74 (m, 1H, A+B), 5.38 – 5.12 (m, 3H, A+B), 5.00 – 4.85 (m, 1H, A+B), 4.55 (s, 0.5H, A), 4.51 (s, 0.5H, B), 4.43 – 4.28 (m, 1H, A+B), 3.35 – 3.26 (m, 2H, A+B), 2.96 (t, *J* = 6.5 Hz, 2H, A+B), 0.77 (s, 4.5H, A), 0.74 (s, 4.5H, B).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 137.04, 136.97, 136.06, 134.77, 133.37, 130.53, 129.88, 129.85, 129.16, 128.98, 128.95, 127.39, 117.68, 117.16, 88.81, 88.15, 62.04, 58.67, 58.51, 42.31, 41.96, 40.46, 35.97, 26.34, 26.23.

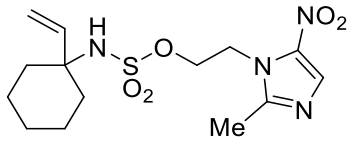
**IR** (thin film): 3280, 3087, 3029, 2965, 2876, 1601, 1494, 1454, 1353, 1277, 1173, 1136, 1015, 926, 909, 854, 831, 735, 701, 678 $cm^{-1}$.

**MS** (ESI, negative mode): 502.3 ($M-H^+$)

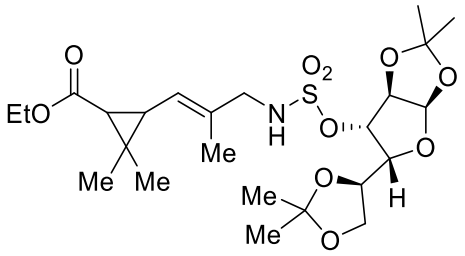



**47.** Prepared according to the general procedure and purified by silica gel chromatography (80:20 to 70:30, hexanes/ethyl acetate) to afford the product as a white solid (94 mg, 94%).

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 2.4 Hz, 1H), 7.47 (d, *J* = 2.4 Hz, 1H), 7.21 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.18 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 1H), 6.80 (d, *J* = 8.8 Hz, 1H), 5.43 (s, 1H), 4.71 (d, *J* = 9.3 Hz, 1H), 3.92 (d, *J* = 9.2 Hz, 1H), 2.44 – 2.34 (m, 1H), 2.05 (d, *J* = 19.5 Hz, 1H), 1.68 (s, 3H), 0.99 (d, *J* = 8.7 Hz, 1H), 0.92 (s, 3H), 0.80 (s, 3H), 0.66 (t, *J* = 8.0 Hz, 1H).
**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 151.10, 147.40, 141.67, 130.76, 130.47, 130.14, 129.64, 128.56, 127.79, 126.36, 126.14, 124.49, 121.03, 120.30, 52.15, 28.71, 25.89, 21.53, 21.03, 17.33, 16.08, 13.37.
**IR** (thin film): 3297, 3092, 2943, 2873, 2831, 1588, 1481, 1465, 1457, 1436, 1419, 1405, 1363, 1267, 1192, 1172, 915, 869, 736 $cm^{-1}$.
**MS** (ESI, negative mode): 502.1 ($M-H^+$)
**Melting Point** : 121 – 124 °C




**48.** Prepared according to the general procedure and purified by silica gel chromatography (80:20 to 70:30, hexanes/ethyl acetate) to afford the product as a white solid (45 mg, 63%).
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.99 (s, 1H), 5.72 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.18 (d, *J* = 17.6 Hz, 1H), 5.14 (d, *J* = 10.8 Hz, 1H), 4.62 (t, *J* = 4.9 Hz, 2H), 4.60 (s, 1H), 4.41 (t, *J* = 4.9 Hz, 2H), 2.54 (s, 3H), 1.80 – 1.70 (m, 2H), 1.68 – 1.59 (m, 2H), 1.52 – 1.45 (m, 4H), 1.44 – 1.32 (m, 2H).
**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 141.20, 138.59, 133.64, 115.90,68.10, 59.85, 45.67, 35.61, 25.40, 22.05, 14.75.
**IR** (thin film): 3291, 3089, 2936, 2862, 1533, 1471, 1428, 1365, 1262, 1190, 1177, 1148, 1035, 994, 905, 825, 764, 743 $cm^{-1}$.
**MS** (ESI, negative mode): 357.6 ($M-H^+$)
**Melting Point** : 98 – 103 °C



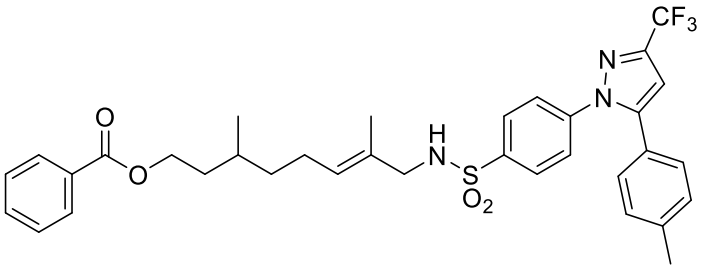
**49.** Prepared according to the general procedure and purified by silica gel chromatography (80:20, hexanes/ethyl acetate) to afford the product as a transparent oil (77 mg, 72%, mixture of 4 diastereomers from use of racemic and diastereomerically impure chrysanthemic acid).

**$^{1}$H NMR** (500 MHz, $CDCl_3$) δ 5.91 (t, *J* = 5.0 Hz, 1.7H, major + minor), 5.68 (d, *J* = 8.6 Hz, 0.7H, minor), 5.15 (d, *J* = 8.4 Hz, 1H, major), 4.89 (dd, *J* = 6.4, 3.1 Hz, 1.7H major + minor), 4.86 (t, *J* = 3.8 Hz, 1.7H major + minor), 4.80 (t, *J* = 5.6 Hz, 1.2H major + minor), 4.30 – 4.20 (m, 2H, major + minor), 4.17 – 4.00 (m, 6H), 3.77 – 3.72 (m, 1.31H, minor ), 3.72 – 3.68 (m, 2H, major), 2.06 (dd, *J* = 8.4, 3.0 Hz, 0.7H, minor), 2.03 (s, 1.8H, major + minor), 1.78 (s, 3H, major), 1.76 (s, 1.8H, minor), 1.71 (d, *J* = 8.6 Hz, 0.8H, minor), 1.50 (s, 3H), 1.45 (dd, *J* = 5.3, 2.4 Hz, 1H, major), 1.43 (s, 1.8H, minor), 1.41 (s, 3H, major), 1.32 (d, *J* = 2.1 Hz, 2H), 1.31 (s, 8H, major + minor), 1.28 – 1.20 (m, 15H, major + minor), 1.14 (s, 3H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 172.26, 172.17, 171.99, 171.17, 133.80, 133.60, 133.29, 133.13, 126.26, 126.19, 125.94, 125.82, 123.71, 123.52, 123.35, 112.79, 109.87, 105.33, 83.39, 83.20, 82.79, 82.63, 82.47, 80.24, 79.27, 72.29, 68.90, 68.73, 68.57, 67.69, 67.63, 64.63, 64.53, 64.25, 60.65, 60.50, 60.22, 52.29, 51.99, 51.73, 51.50, 35.33, 32.07, 31.93, 31.82, 31.62, 31.53, 31.43, 31.06, 29.87, 28.84, 27.10, 26.82, 26.45, 25.53, 25.45, 22.42, 20.55, 15.22, 15.14, 14.93, 14.54.

**IR** (thin film): 3265, 2986, 2936, 1722, 1446, 1373, 1257, 1216, 1181, 1076, 1024, 956, 881, 843, 757 $cm^{-1}$.

**MS** (ESI, negative mode): 532.8 ($M-H^+$)



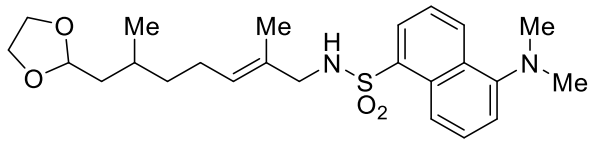
**50.** Prepared according to the general procedure and purified by silica gel chromatography (80:20 to 70:30, hexanes/ethyl acetate) to afford the product as a transparent oil (113 mg, 89%).

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.6 Hz, 2H), 7.83 (d, *J* = 8.6 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.48 – 7.39 (m, 4H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.74 (s, 1H), 5.27 (t, *J* = 7.0 Hz, 1H), 4.66 (t, *J* = 6.2 Hz, 1H), 4.43 – 4.26 (m, 2H), 3.44 (d, *J* = 6.1 Hz, 2H), 2.38 (s, 3H), 2.05-1.80 (m, 2H), 1.77 (dt, *J* = 12.2, 4.7 Hz, 1H), 1.64 – 1.55 (m, 1H), 1.54 (s, 3H), 1.44 – 1.32 (m, 1H), 1.25 – 1.15 (m, 1H), 0.96 (d, *J* = 6.4 Hz, 3H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 166.91, 145.50, 142.68, 140.08, 140.01, 133.10, 130.71, 130.23, 129.96, 129.75, 129.42, 128.96, 128.58, 128.32, 126.02, 125.71, 121.33 (q, J = 268.9 Hz), 106.49, 63.61, 51.47, 36.53, 35.70, 29.88, 25.42, 21.51, 19.73, 14.44.

**IR** (thin film): 3283, 3064, 2958, 2923, 2870, 1717, 1599, 1472, 1275, 1237, 1162, 1136, 1098, 976, 734, 714, 268 $cm^{-1}$.

**MS** (ESI, negative mode): 638.4 ($M-H^+$)



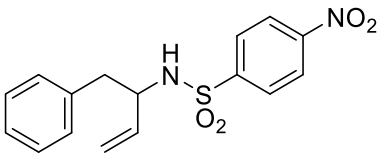

**51.** Prepared according to the general procedure **B** with 30 mol % catalyst and purified by silica gel chromatography (80:20, hexanes/ethyl acetate) to afford the product as a yellow oil (44 mg, 49%).

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.53 (d, *J* = 8.4 Hz, 1H), 8.30 (d, *J* = 8.6 Hz, 1H), 8.23 (dd, *J* = 7.3, 1.2 Hz, 1H), 7.61 – 7.48 (m, 1H), 7.18 (d, *J* = 7.5 Hz, 1H), 5.14 (t, *J* = 7.1, 1H), 4.85 (t, *J* = 5.0 Hz, 1H), 4.69 (t, *J* = 6.2 Hz, 1H), 3.97 – 3.94 (m, 2H), 3.84 – 3.81 (m, 2H), 3.39 (d, *J* = 6.2 Hz, 2H), 2.89 (s, 6H), 1.93 – 1.78 (m, 2H), 1.65 – 1.54 (m, 2H), 1.47 – 1.43 (m, 1H), 1.41 (s, 3H), 1.30 – 1.20 (m, 2H), 1.12 – 1.00 (m, 1H), 0.89 (d, *J* = 6.6 Hz, 3H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 152.23, 135.35, 130.56, 130.37, 130.14, 129.98, 129.91, 129.18, 128.51, 123.41, 119.09, 115.38, 103.92, 64.96, 64.90, 51.54, 45.65, 40.95, 36.80, 29.12, 25.26, 20.09, 14.39

**IR** (thin film): 3288, 2942, 2786, 1588, 1574, 1457, 1408, 1321, 1231, 1201, 1144, 1039, 945, 790, 627, 573 $cm^{-1}$.

**MS** (ESI, negative mode): 445.8 ($M\text{-}H^+$)




**1a**. Prepared according to general procedure A and purified by silica gel chromatography (95:5 to 80:20, hexanes/ethyl acetate) to afford the product as pale yellow solid (63 mg, 93%).

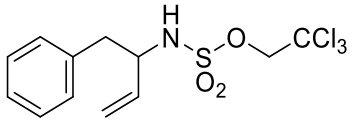
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 9.0 Hz, 2H), 7.78 (d, *J* = 9.0 Hz, 2H), 7.21 – 7.12 (m, 3H), 7.02 (dd, *J* = 6.4, 3.0 Hz, 2H), 5.73 (ddd, *J* = 17.0, 10.4, 6.1 Hz, 1H), 5.13 (d, *J* = 17.2 Hz, 1H), 5.09 (d, *J* = 10.6 Hz, 1H), 4.84 (d, *J* = 7.9 Hz, 1H), 4.09 (quin, *J* = 6.9 Hz, 1H), 2.89 (dd, *J* = 13.9, 5.6 Hz, 1H), 2.70 (dd, *J* = 13.9, 8.2 Hz, 1H).

**$^{13}$C NMR** (126 MHz, Acetone) δ 150.33, 148.38, 138.87, 138.26, 130.10, 128.81, 128.65, 126.93, 124.69, 115.80, 58.95, 42.23.

**IR** (thin film): 3292, 3106, 2923, 1529, 1427, 1350, 1311, 1165, 1094, 928, 855, 736, 617, 564 $cm^{-1}$.

**MS** (ESI, negative mode): 332.2 ($M\text{-}H^+$)

**Melting point** : 104-106°C



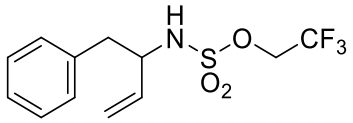

**1b.** Prepared according to general procedure A and purified by silica gel chromatography (90:10 to 80:20, hexanes/ethyl acetate) to afford the product as clear oil (67 mg, 94%).

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.19 (m, 5H), 5.88 (ddd, *J* = 17.0, 10.4, 6.4 Hz, 1H), 5.31 (d, *J* = 17.2 Hz, 1H), 5.25 (d, *J* = 10.4 Hz, 1H), 5.23 (d, *J* = 7.9 Hz, 1H), 4.39 (d, *J* = 10.8 Hz, 1H), 4.29 (quin, *J* = 6.0 Hz, 1H), 4.16 (d, *J* = 10.8 Hz, 1H), 3.01 (dd, *J* = 13.8, 6.4 Hz, 1H), 2.92 (dd, *J* = 13.8, 7.3 Hz, 1H).

$^{13}$C NMR (75 MHz, $CDCl_3$) δ 136.73, 136.37, 129.80, 128.95, 127.38, 117.36, 78.16, 58.58, 41.62, 31.08.

IR (thin film): 3306, 3088, 3066, 3030, 2952, 1497, 1455, 1362, 1266, 1179, 1121, 863, 751 $cm^{-1}$.

**MS** (ESI, negative mode): 358.5 ($M\text{-}H^+$)



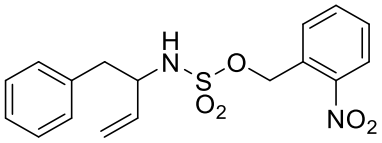
**1c.** Prepared according to general procedure A and purified by silica gel chromatography (90:10 to 80:20, hexanes/ethyl acetate) to afford the product as a clear oil (53 mg, 86%).

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.4 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.20 (d, *J* = 7.4 Hz, 2H), 5.83 (ddd, *J* = 17.0, 10.4, 6.5 Hz, 1H), 5.27 (d, *J* = 18.4 Hz, 1H), 5.24 (d, *J* = 11.5 Hz, 1H), 4.62 (s, 1H), 4.23 (quin, *J* = 6.9 Hz, 1H), 4.14 (dq, *J* = 16.3, 8.0 Hz, 1H), 3.95 (dq, *J* = 16.6, 8.1 Hz, 1H), 2.99 (dd, *J* = 13.8, 6.2 Hz, 1H), 2.86 (dd, *J* = 13.8, 7.4 Hz, 1H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 136.57, 136.10, 129.82, 129.09, 127.55, 117.62, 65.18 (q, J = 38.3 Hz), 58.60, 41.68.

**IR** (thin film): 3305, 3088, 3030, 2926, 1456, 1419, 1369, 1283, 1183, 1054, 964, 861, 806, 752, 702, 600, 557 $cm^{-1}$.

**MS** (ESI, negative mode): 308.0 ($M-H^+$)



**1d.** Prepared according to general procedure A and purified by silica gel chromatography (90:10 to 80:20, hexanes/ethyl acetate) to afford the product as a yellowish solid (66 mg, 91%).

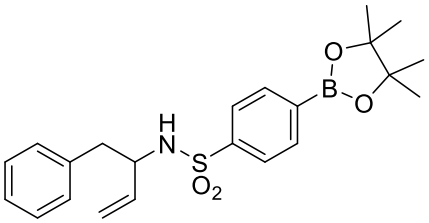
**$^1$H NMR** (500 MHz, Acetone) δ 8.17 (d, *J* = 8.2 Hz, 1H), 7.82 (t, *J* = 7.6 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 7.6 Hz, 2H), 7.18 (t, *J* = 7.4 Hz, 2H), 7.08 (t, *J* = 7.4 Hz, 1H), 5.94 (ddd, *J* = 17.1, 10.4, 6.7 Hz, 1H), 5.31 (d, *J* = 14.5 Hz, 1H), 5.25 (d, *J* = 17.1 Hz, 1H), 5.10 (d, *J* = 11.0 Hz, 1H), 5.08 (d, *J* = 13.6 Hz, 1H), 4.22 (quin, *J* = 7.3 Hz, 1H), 2.94 (d, *J* = 7.4 Hz, 2H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 147.99, 139.10, 138.92, 138.71, 135.08, 132.13, 130.44, 130.08, 129.49, 129.14, 127.24, 125.78, 116.51, 68.01, 59.75, 59.61, 42.24.

**IR** (thin film): 3314, 1516, 1358, 1340, 1175, 994, 966, 867, 801, 794, 731 $cm^{-1}$.

**MS** (ESI, negative mode): 363.2 ($M-H^+$)

**Melting point** : 116 – 120 °C



**1e.** Prepared according to general procedure A and purified by boric acid doped silica gel chromatography (70:30, pentane:ether) to afford the product as a white solid (50 mg, 60%).

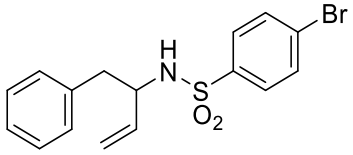
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.1 Hz, 2H), 7.71 (d, *J* = 8.1 Hz, 2H), 7.23 – 7.17 (m, 3H), 7.05 – 6.99 (m, 2H), 5.65 (ddd, *J* = 16.9, 10.4, 6.2 Hz, 1H), 5.02 (d, *J* = 17.3 Hz, 1H), 5.01 (d, *J* = 10.3 Hz, 1H), 4.61 (d, *J* = 7.4 Hz, 1H), 4.03 (quin, *J* = 6.7 Hz, 1H), 2.81 – 2.72 (m, 2H), 1.36 (s, 12H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 142.90, 137.26, 136.28, 135.43, 129.72, 128.79, 127.13, 126.24, 116.65, 84.61, 57.19, 42.17, 30.55, 25.12, 25.09.

**IR** (thin film): 3280, 3063, 3028, 2979, 2930, 1601, 1392, 1360, 1331, 1271, 1163, 1144, 1099, 1079, 857, 723, 700, 653, 610 $cm^{-1}$.

**MS** (ESI, negative mode): 412.6 ($M-H^+$)

**Melting point** : 129-134 °C



**1f.** Prepared according to general procedure A and purified by silica gel chromatography (90:10 to 80:20, hexanes/ethyl acetate) to afford the product as an off-white solid (60 mg, 82%).

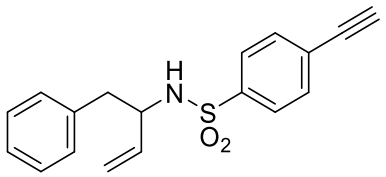
**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.51 (s, 4H), 7.25 – 7.18 (m, 3H), 7.06 – 6.94 (m, 2H), 5.71 (ddd, *J* = 17.0, 10.3, 6.1 Hz, 1H), 5.09 (d, *J* = 17.1 Hz, 1H), 5.06 (d, *J* = 10.4 Hz, 1H), 4.59 (d, *J* = 7.5 Hz, 1H), 4.02 (quin, *J* = 6.0 Hz, 1H), 2.85 (dd, *J* = 13.8, 6.0 Hz, 1H), 2.71 (dd, *J* = 13.8, 7.6 Hz, 1H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 139.75, 137.47, 136.30, 132.36, 129.63, 128.88, 128.77, 127.54, 127.18, 116.66, 57.45, 42.14.

**IR** (thin film): 3280, 3086, 3062, 3027, 3924, 3854, 1575, 1472, 1454, 1424, 1389, 1331, 1161, 1092, 1069, 1031, 1010, 927, 821, 739, 700, 668, 614, 567 $cm^{-1}$.

**MS** (ESI, negative mode): 365.4 ($M-H^+$)

**Melting point** : 74 – 78 °C



**1g.** Prepared according to general procedure A and purified by silica gel chromatography (90:10 to 80:20, hexanes/ethyl acetate) to afford the product as a white solid (50 mg, 80%).

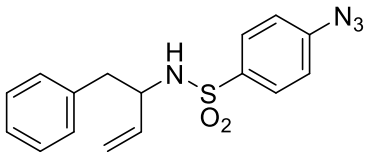
**$^{1}$H NMR** (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.6 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.24 – 7.18 (m, 3H), 7.02 (dd, *J* = 6.5, 2.9 Hz, 2H), 5.69 (ddd, *J* = 16.7, 10.4, 6.1 Hz, 1H), 5.06 (d, *J* = 17.1 Hz, 1H), 5.04 (d, *J* = 10.2 Hz, 1H), 4.59 (d, *J* = 7.5 Hz, 1H), 4.03 (quin, *J* = 7.4 Hz, 1H), 3.24 (s, 1H), 2.84 (dd, *J* = 13.7, 6.2 Hz, 1H), 2.73 (dd, *J* = 13.7, 7.3 Hz, 1H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 140.86, 137.46, 136.35, 132.75, 129.68, 128.88, 127.22, 126.73, 116.66, 82.36, 80.64, 57.41, 42.21.

**IR** (thin film): 3269, 3065, 1934, 1313, 1156, 1092, 833, 741, 695, 643, 635, 521 $cm^{-1}$.

**MS** (ESI, negative mode): 310.4 ($M-H^+$)

**Melting point** : 134 – 137 °C



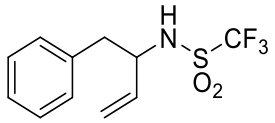
**1h.** Prepared according to general procedure A and purified by silica gel chromatography (90:10 to 70:30, hexanes/ethyl acetate) to afford the product as a yellow oil (55 mg, 82%).

**$^{1}$H NMR** (300 MHz, Acetone) δ 7.72 (d, *J* = 8.7 Hz, 2H), 7.32 – 6.96 (m, 7H), 6.65 (d, *J* = 8.3 Hz, 1H), 5.72 (ddd, *J* = 17.0, 10.4, 6.4 Hz, 1H), 5.02 (d, *J* = 17.2 Hz, 1H), 4.92 (d, *J* = 10.4 Hz, 1H), 4.06 (quin, *J* = 7.2 Hz, 1H), 2.80 (d, *J* = 7.2 Hz, 2H).

**$^{13}$C NMR** (126 MHz, Acetone) δ 144.70, 139.46, 139.01, 138.63, 130.42, 129.70, 129.12, 127.25, 120.20, 116.01, 58.85, 42.75.

**IR** (thin film): 3277, 3063, 3028, 2925, 2129, 2099, 1594, 1492, 1325, 1285, 1158, 1129, 1093, 911, 831, 735, 702, 625, 568, 511 $cm^{-1}$.

**MS** (ESI, negative mode): 327.6 ($M-H^+$)



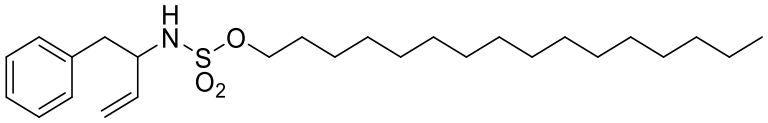
**1i.** Prepared according to general procedure A and purified by silica gel chromatography (90:10 to 80:20, hexanes/ethyl acetate) to afford the product as a clear oil (48 mg, 86%).

**$^{1}$H NMR** (300 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 3H), 7.22 – 7.15 (m, 2H), 5.83 (ddd, *J* = 17.2, 10.3, 6.0 Hz 1H), 5.23 (dd, *J* = 10.3, 1.2 Hz, 1H), 5.21 (dd, *J* = 17.2, 1.4 Hz, 1H), 4.85 (s, 1H), 4.39 (s, 1H), 2.96 (d, *J* = 6.3 Hz, 2H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 136.12, 135.32, 129.97, 129.00, 127.59, 119.6 (q, J = 320.7 Hz), 117.25, 58.60, 42.52.

**IR** (thin film): 3307, 3091, 3032, 2927, 1497, 1433, 1374, 1230, 1197, 1146, 1030, 933, 751, 701, 616, 576 $cm^{-1}$.

**MS** (ESI, negative mode): found: 278.3 ($M-H^+$)



**1j.** Prepared according to general procedure A and purified by silica gel chromatography (95:5, hexanes/ethyl acetate) to afford the product as a white solid (83 mg, 92%).

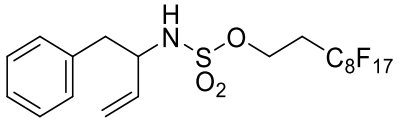
**$^{1}$H NMR** (500 MHz, $CDCl_3$) $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.31 (t, *J* = 7.3 Hz, 2H), 7.28 – 7.22 (m, 1H), 7.20 (d, *J* = 7.0 Hz, 2H), 5.81 (ddd, *J* = 17.0, 10.4, 6.4 Hz, 1H), 5.23 (d, *J* = 17.2 Hz, 1H), 5.18 (d, *J* = 10.4 Hz, 1H), 4.48 (d, *J* = 7.8 Hz, 1H), 4.17 (quin, *J* = 6.7 Hz, 1H), 3.92 (dt, *J* = 9.4, 6.7 Hz, 1H), 3.81 (dt, *J* = 9.4, 6.6 Hz, 1H), 2.94 (dd, *J* = 13.7, 6.5 Hz, 1H), 2.88 (dd, *J* = 13.7, 6.9 Hz, 1H), 1.63 – 1.54 (m, 2H), 1.35 – 1.20 (m, 28H), 0.88 (t, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 137.29, 136.54, 129.90, 128.88, 127.26, 116.94, 71.10, 58.00, 41.93, 32.16, 29.91, 29.77, 29.68, 29.58, 29.32, 29.02, 25.71, 22.91, 14.32.

**IR** (thin film): 3294, 3086, 3029, 2923, 2853, 1466, 1455, 1432, 1357, 1174, 945, 700 $cm^{-1}$.

**MS** (ESI, negative mode): found: 450.8 ($M-H^+$)

**Melting point** : 32-36 °C



**1k.** Prepared according to general procedure A and purified by silica gel chromatography (80:20, hexanes/ethyl acetate) to afford the product as a white solid (110 mg, 82%).

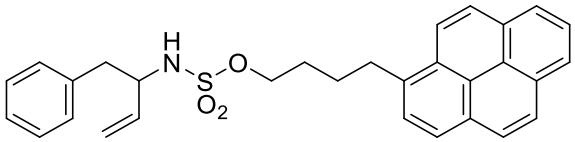
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.31 (t, *J* = 7.3 Hz, 2H), 7.25 (t, *J* = 7.4 Hz, 1H), 7.19 (d, *J* = 7.4 Hz, 2H), 5.81 (ddd, *J* = 17.0, 10.4, 6.4 Hz, 1H), 5.24 (d, *J* = 17.1 Hz, 1H), 5.20 (d, *J* = 10.4 Hz, 1H), 4.55 (d, *J* = 7.9 Hz, 1H), 4.26 – 4.10 (m, 2H), 4.06 – 3.93 (m, 1H), 2.96 (dd, *J* = 13.8, 6.1 Hz, 1H), 2.83 (dd, *J* = 13.8, 7.4 Hz, 1H), 2.53 – 2.29 (m, 2H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 137.09, 136.40, 129.88, 129.01, 127.45, 117.20, 62.03, 58.34, 41.84, 31.21 (t, J = 22.2 Hz).

**IR** (thin film): 3299, 3030, 2924, 1456, 1436, 1419, 1360, 1203, 1150, 1056, 998, 753, 703, 667, 656, 601 $cm^{-1}$.

**MS** (ESI, negative mode): 672.5 ($M-H^+$)

**Melting point** : 48 – 50 °C




**1l.** Prepared according to general procedure A and purified by silica gel chromatography (90:10 to 80:20, hexanes/ethyl acetate) to afford the product as a yellow film (36 mg, 37%).

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 9.2 Hz, 1H), 8.08 (d, *J* = 7.5 Hz, 2H), 8.02 (d, *J* = 7.5 Hz, 2H), 7.94 (s, 2H), 7.91 (t, *J* = 7.6 Hz, 1H), 7.75 (d, *J* = 7.7 Hz, 1H), 7.20 (d, *J* = 5.0 Hz, 1H), 7.16 (d, *J* = 7.9 Hz, 1H), 7.15 (d, *J* = 7.2 Hz, 1H), 7.10 (d, *J* = 6.6 Hz, 1H), 7.05 (d, *J* = 7.5 Hz, 2H), 5.66 (ddd, *J* = 16.9, 10.3, 6.4 Hz, 1H), 5.10 (d, *J* = 17.1 Hz, 1H), 5.02 (d, *J* = 10.4 Hz, 1H), 4.24 (d, *J* = 7.6 Hz, 1H), 4.06 (quin, *J* = 6.6 Hz, 1H), 3.93 – 3.86 (m, 1H), 3.83 – 3.69 (m, 1H), 3.26 (t, *J* = 7.6 Hz, 2H), 2.80 (dd, *J* = 13.7, 6.3 Hz, 1H), 2.72 (dd, *J* = 13.7, 7.0 Hz, 1H), 1.81 (quin, *J* = 7.6 Hz, 2H), 1.72 – 1.63 (m, 2H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 137.17, 136.38, 136.15, 131.66, 131.11, 130.17, 129.83, 128.87, 128.57, 127.72, 127.61, 127.46, 127.26, 126.96, 126.11, 125.35, 125.24, 125.20, 125.04, 125.02, 123.44, 116.98, 70.72, 57.96, 41.80, 33.04, 28.93, 27.81.

**IR** (thin film): 3299, 3028, 2929, 1735, 1602, 1454, 1432, 1357, 1243, 1172, 1030, 939, 847, 818, 752, 720, 700, 602 $cm^{-1}$.

**MS** (ESI, negative mode): 482.8 ($M-H^+$)

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# **Chapter 3.** C-H ALLYLIC AMINATION OF POLYNORBORNENES

## 3.1 **INTRODUCTION**

Functionalized polymers play an important role in the development of new materials as the incorporation of different functional groups allows the modification of their physical and electronic properties. Despite the advancements in various aspects of polymerization techniques and processing, synthesizing diverse classes of functionalized polymers with highly controlled molecular weight, architecture, dispersity, stereochemistry, and composition remains challenging. One of the commonly employed methods to achieve functionalized polymers is the direct polymerization of monomers containing desired functional groups. However, the functional groups that can be incorporated is often limited by the polymerization method (such as cationic polymerization) resulting in the lack of diversity in commodity polymers (Figure 3.1, **A**).[1] While the use of protecting groups in monomers could theoretically overcome functional group incompatibilities, the deprotection step may not proceed to completion, compromising the functionality due to structural defects of the polymer (Figure 3.1, **B**). Modern polymerization techniques such as controlled radical polymerization (ATRP, RAFT, NMP, SET)

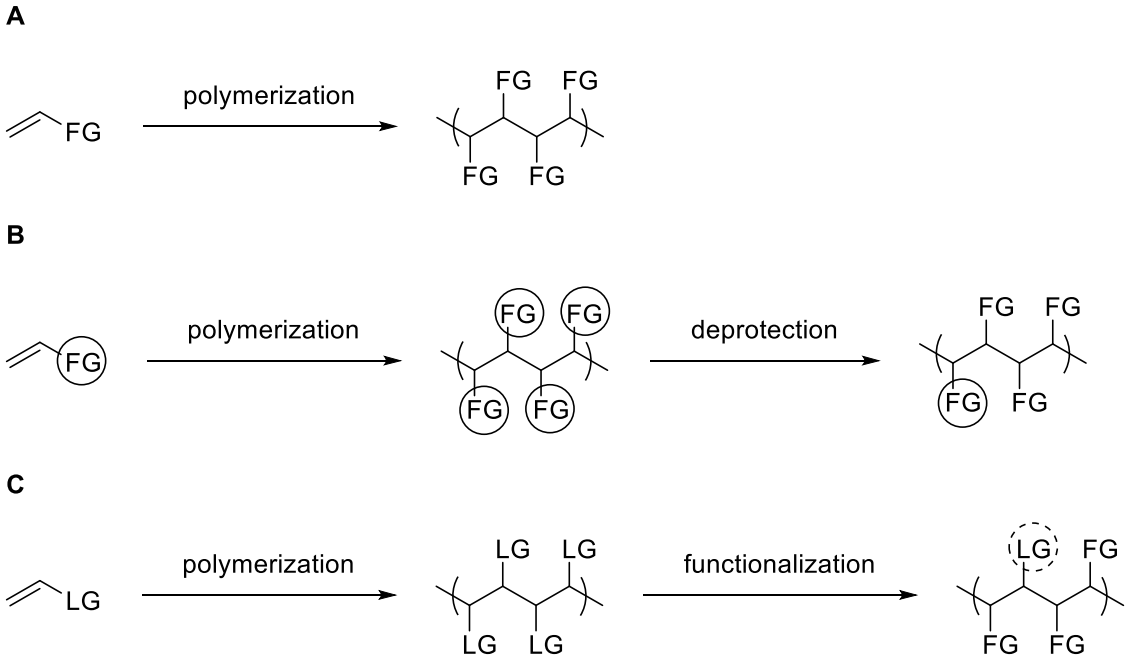



**Figure 3.1** Strategies to Access Functionalized Polymers.

and ring opening metathesis polymerization (ROMP) have expanded the functional groups that are compatible with the polymerization and allow access to a wider range of functionalized polymers.[2] Despite these advancements, there are still limitations to the types of side chain functionalities that can be introduced by polymerization and highly functionalized monomers may lead to decreasing reaction efficiency and poor control of key physical properties such as degree of polymerization. Furthermore, the use of novel functionalized monomers often require re-optimization of the polymerization process and/or catalyst selection to obtain the desired outcome, making installation of new functionality less flexible.

An alternative to direct polymerization of functionalized monomers is to chemically modify polymers after polymerization. In contrast to developing and optimizing new polymerization processes for each novel functional monomer, post-polymerization modification (PPM) allows the diversification and incorporation of functionality to common polymers prepared using well defined and preferred polymerization techniques (Figure 3.1, **C**). Common post polymerization modification often occurs in two major mechanistic pathways: nucleophilic addition and transition metal catalyzed cross couplings. Michael-type[3] (Figure 3.2, **A**) and thiol-ene[4] (Figure 3.2, **B**)

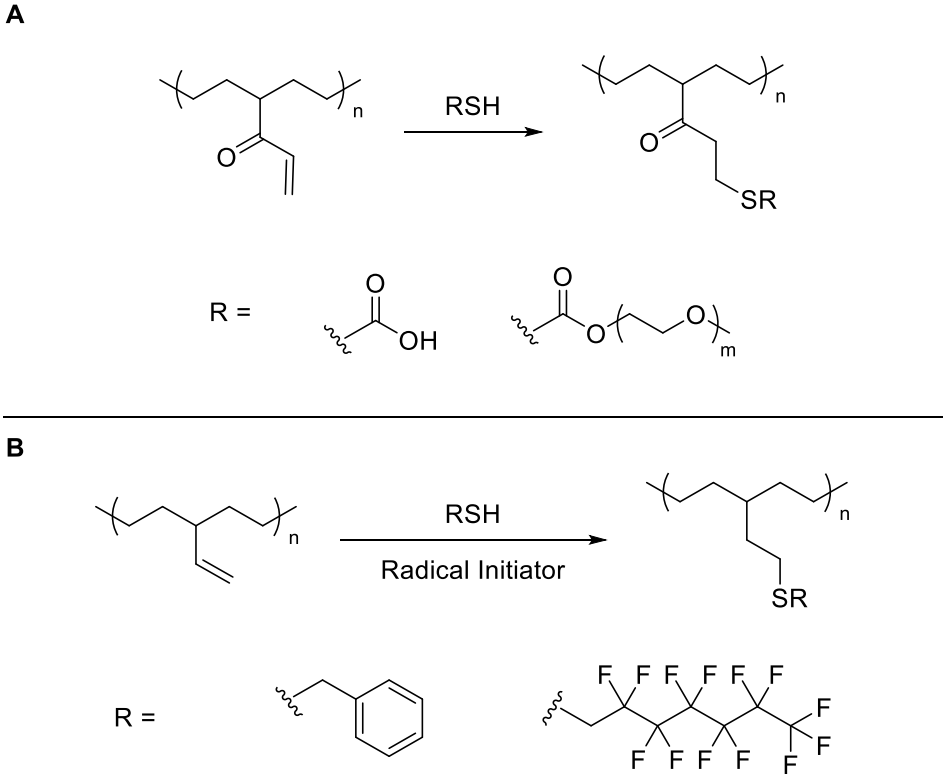



**Figure 3.2** Nucleophilic Addition Strategies to Functionalize Polymers.

addition to activated alkene systems such as acrylates, maleimides, and vinyl sulfones have been widely employed as post polymerization modifications to incorporate side chain functionalities into polymers. Moderate to quantitative functionalization was achieved without significant backbone degradation under mild reaction conditions making these methods a common modification tool. While this method is widely employed in PPM, one of the biggest draw backs is the requirement for an acrylate moiety which complicates the polymerization process to avoid unwanted side reaction such as cross-linking. Furthermore, polymer backbones containing alkene moieties may undergo competing thiol-ene reaction with the side chain resulting in irregularities in polymer structure. Huisgen 1,3-dipolar cycloaddition ("click chemistry"), a cycloaddition reaction between alkyne and azide using $Cu^{I}$ salts as catalyst to make 1,2,3-triazole (Figure 3.3), has been

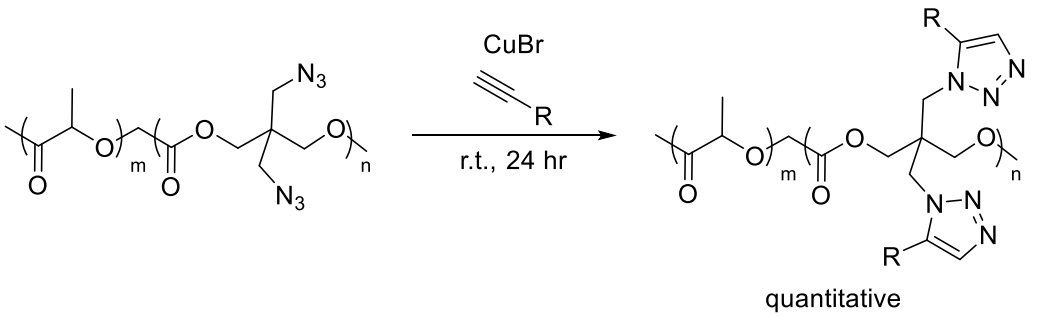



**Figure 3.3** "Click" Chemistry Side Chain Modification of Polymer.

extensively used in post polymerization modification to synthesize biodegradeable polymer drug conjugates.[5] The high efficiency of the reaction makes these types of PPM very attractive, allowing the conservation of the dispersity and uniformity of the starting polymer.[5,6] However, both post polymerization techniques suffer from one common drawback: to incorporate functionality to the polymer, the monomer itself needs to bear a suitable functional group, eg: acrylates for Michael type addition and alkyne/azide for "click" chemistry. The incorporation of these functional groups poses some incompatibility issues with certain well-established polymerization reactions such as ring opening metathesis polymerization (ROMP). These functionalized monomers often result in sluggish reactions, poor degree of polymerization, and large dispersities.

Direct C-H functionalization of polymers is a promising alternative to the previously described PPMs. This allows us to directly install functionality into polymers avoiding functional group incompatibilities during polymerization and also upcycle commodity polymers post-consumer usage.[7,8] Some of the early examples employs radical chemistry to incorporate halogens

at the benzylic position of polystyrene through halogenation (elemental chlorine or bromine and N-halosuccinimide) or azidation using hypervalent iodine reagents.

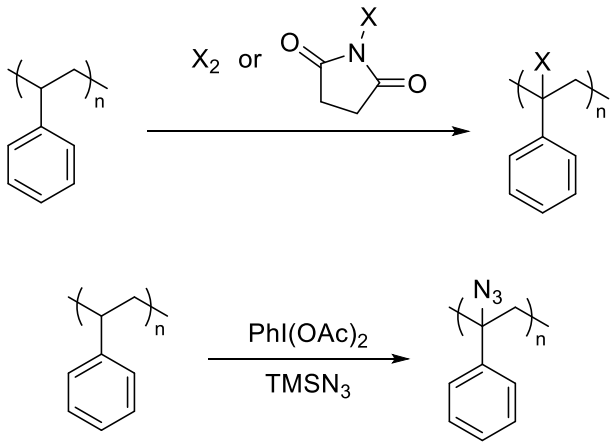



**Figure 3.4** Radical Mediated C-H Functionalization of Polystyrene.

Hartwig et al. have also shown several direct oxidations of various commodity polyolefins utilizing transition metal catalysts, specifically Mn and Ni, under mild conditions.[8] While this concept is promising, there are several challenges faced by radical-based C-H functionalization of polymers.[7] One of the most significant drawbacks is the degradation of the polymer backbone through chain scission making it challenging to control the physical properties of the functionalized polymer. Furthermore, chemoselectivity and degree of functionalization of these methods are poor (Figure 3.5), ranging from 1.4 – 4.0 hydroxyl groups per 100 monomer units. Furthermore, the reaction often incorporates multiple functional groups within the same polymer chain, which deters the use of these methods for post polymerization functionalization.

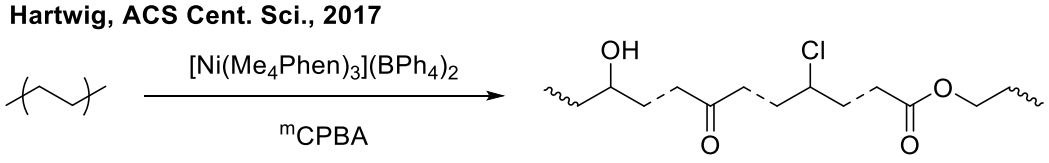



**Figure 3.5** Chemoselectivity Challenges in Direct C-H Oxidation of Polyethylene.

Polynorbornene (PNB) is often used commercially as a composite elastomer in the rubber industry due to its excellent shock absorbing properties. Furthermore, the vast number of well-established polymerization protocols to make PNB allows a range of polymer products with desired physical and chemical properties. However, existing methods to achieve functionalized PNB often rely on the installation of pendant linkers in the monomer, which then undergoes polymerization and functionalization.[9] This not only increases the number of synthetic steps

required to achieve functionalized polymer but also risks increasing physical defects and

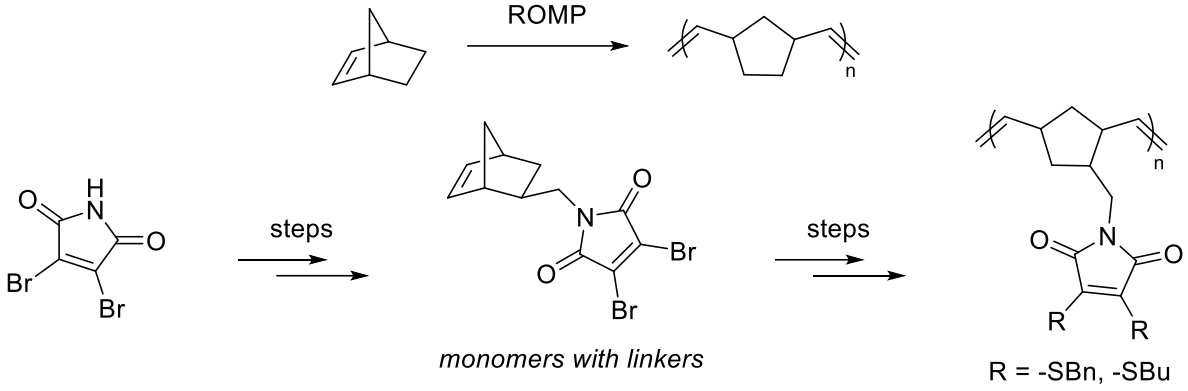



**Figure 3.6** Post-Polymerization Modification of Polynorbornene.

irregularities on the functionalized polymer due to incomplete functionalization. Furthermore, this method is limited to the side chain functionalization of polynorbornenes as functionalization at the bridge head of norbornene often slow or inhibits ROMP (Figure 3.7). Based on the success of our previously reported C-H allylic amination on a large range of olefins (Chapter 2), we envisioned using this as a method to introduce nitrogen functional groups to the backbone of polynorbornene, allowing access to backbone functionalized polynorbornene which cannot be achieved from direct polymerization of functionalized norbornene (Figure 3.7).

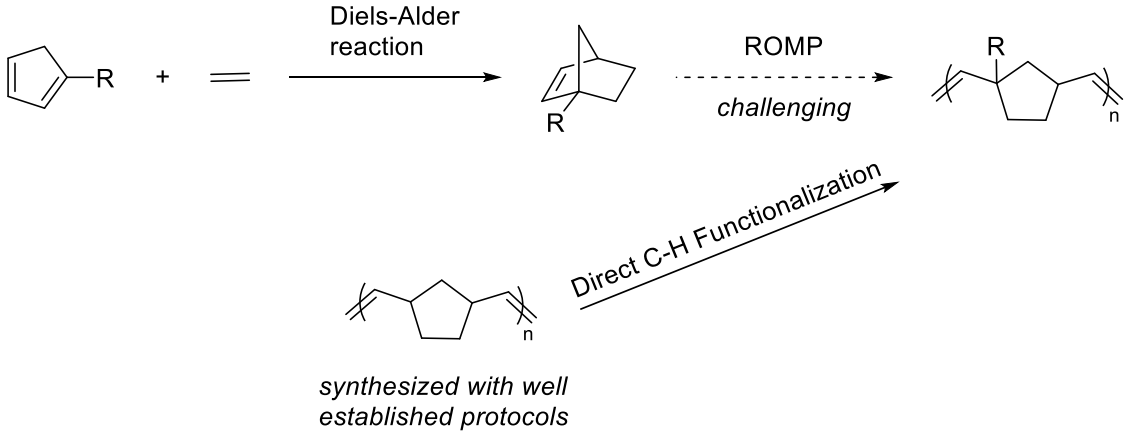


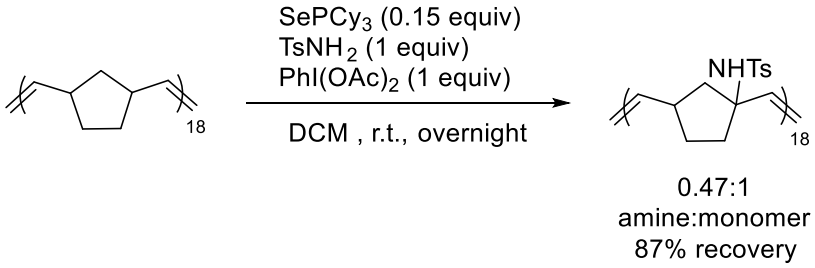

**Figure 3.7** Direct C-H Amination to Achieve Backbone Functionalization of Polynorbornene.

## 3.2 RESULTS AND DISCUSSIONS

The poly(norbornene) samples used in this project were supplied by our collaborators Victoria Kensy and Xuejin Yang from Boydston research group at University of Wisconsin,

Madison. We started off the project by subjecting PNB with a degree of polymerization of 18 (~1700 kDa) to our optimized reaction conditions, 15 mol% of $SePCy_3$, 2 equivalents of $PhI(OAc)_2$, and 2 equivalents of $NsNH_2$ in dichloromethane at room temperature overnight. We then precipitated the crude reaction into cold MeOH obtaining a yellowish solid that is highly insoluble in dichloromethane. A quick amine screen revealed the switch from $NsNH_2$ to toluenesulfonamide ($TsNH_2$) along with reducing the amount of amine and oxidant to 1 equivalent drastically improved the solubility of the labeled polymer in both dichloromethane and chloroform. The downshifted and broadened $TsNH_2$ aromatic peaks in the $^1H$ NMR spectrum of the labeled polymer suggested the successful allylic amination of polynorbornene. The reaction gave a satisfying yield of 87% and the degree of amination was calculated by comparing the relative integration of the alkene peaks in PNB to the broaden $TsNH_2$ peaks, giving an amine to monomer ratio of 0.47:1 (47 tosyl amine per 100 monomer units). With

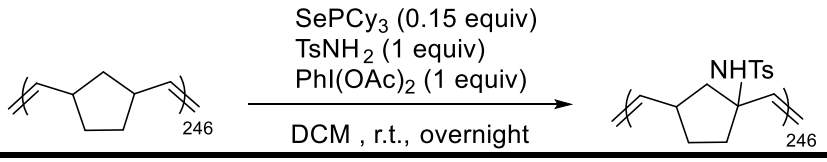
**Scheme 3.1** C-H Allylic Amination of Polynorbornene.




these results on hand, I tested our polymer labeling technique with a larger polymer chain. To our surprise, the reaction solution turned into a solid with gel like consistency after 4 hours of stirring, which maybe due to spontaneous cross-linking during the reaction. We revised our reaction protocol to carefully remove air from the reaction set up and added buylated hydroxytoluene (BHT) as a precaution to inhibit cross-linking of polynorbornene.

With the newly revised reaction conditions, we labeled the PNB with varying degree of polymerization and found that the molecular weight of the polymer does not have much effect on

**Table 3.1** C-H Allylic Amination of Polynorbornene with High Degree of Polymerization.




| Entry | Additive | Amine per Monomer | % Recovery |
|---|---|---|---|
| 1[a] | none | N/A | N/A |
| 2 | 10% BHT | 0.65 | 87 |
| 3[b] | 10% BHT | 0.72 | 91 |

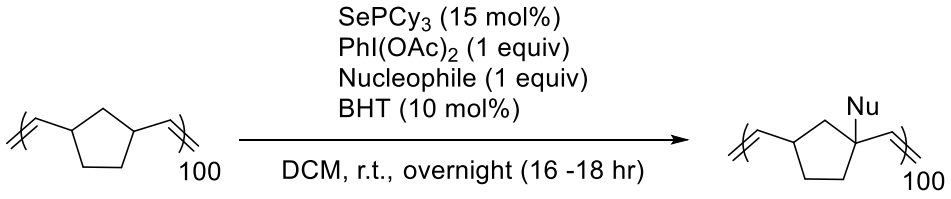
[a]The S.M. cross linked and formed a gel after 4 hours of stirring. [b] degree of polymerization of 100 instead of 246.

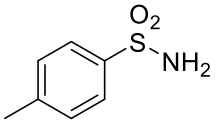
the degree of functionalization and polynorbonene (Table 3.1). Polynorbornene of ~10 kDa was selected as the model substrate due to the ease of precipitation (Table 3.1).

To test the if degree of functionalization could be varied, we tested our reaction conditions with varying amounts of $PhI(OAc)_2$ and $TsNH_2$ (Table 3.2). We found that increasing the stoichiometry of oxidant and nucleophile from 0.5 equivalents to 4 equivalents increases the degree of amination from 0.19 to 1.56 amine to monomer ratio. The control the degree of functionalization by simply changing the stoichiometry gives us an advantage over other C-H functionalization methods mentioned above (Figure 3.5). Furthermore, the efficiency of our C-H allylic amination is significantly higher in comparison to Hartwig's work[8] where they achieve a range of 1.4-4.0 hydroxy groups per 100 monomer units. Notably, the observation of amine to monomer ratio above 1 indicated both allylic positions in the monomer could be aminated, which was surprising because we had previously observed that functionalization of the same alkene twice was challenging.

Lastly, we tested a number of different sulfonamides to expand the scope of functional groups that are not compatible with ROMP. Notably, 4-ethynylbenzenesulfonamide (Table 3.3,

**Table 3.2** Varying Amounts of Oxidant and Amine for Polymer Labeling through C-H Allylic Amination.

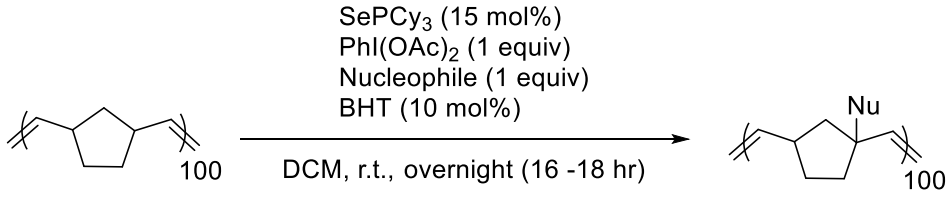



| Nucleophile | Amine per Monomer | Yield |
|---|---|---|
|  | 0.5 equiv: 0.19<br>1.0 equiv: 0.70<br>2.0 equiv: 1.03<br>4.0 equiv: 1.56 | 95<br>76<br>78<br>48 |

entry 3) and 4-azidobenzenesulfonamide (Table 3.3, entry 2) were coupled to the backbone of the polynorbornene with similar yields and high degree of amination. This installation of alkyne and azide handles allows further polynorbornene functionalization through "click chemistry". Labile and easily deprotected protecting groups such as 4-nitrobenzenesulfonamide (Table 3.3, entry 1) and 2-nitrobenzylsulfamate (Table 3.3, entry 4) were also well tolerated, opening up the possibility of obtaining free amines after deprotection.

Unfortunately, degree of amination calculated by the number average molecular weight ($M_n$) using gel permeation chromatography (GPC) experiments was not consistent with the NMR experiments (Table 3.4). GPC results shows that the average molecular weight of functionalized polymer is higher. We suspect that polymer aggregation due to hydrogen bonding could be the reason for the inconsistency in the molecular weight of functionalized PNB. Furthermore, control experiments done by our collaborator showed that incorporation of BHT into the polymer is possible in the absence of amine. Further experiments are planned to determine whether BHT is required to avoid cross-linking and explain the discrepancy between the molecular weights measured by GPC and NMR.

**Table 3.3** Amine Scope to Access New Functionality for Polynorbornene



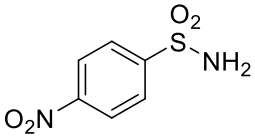
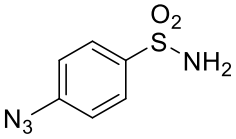
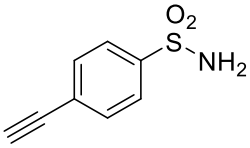
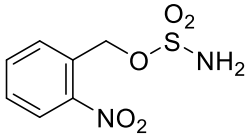
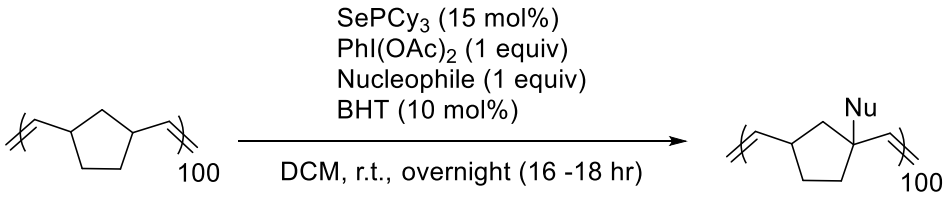

| Entry | Nucleophile | Amine per Monomer | Yield |
|---|---|---|---|
| 1 |  | 0.76 | 65 |
| 2 |  | 0.90 | 54 |
| 3 |  | 0.70 | 67 |
| 4 |  | 0.42 | 93 |

**Table 3.4** Comparison of Average Molecular Weight ($M_n$) of NMR and GPC.




| Entry | Amine:NB (NMR) | Calculated $M_n$ (kDa) | Measured $M_n$ (kDa) | % Difference |
|---|---|---|---|---|
| 1 | 0.19 | 12.55 | 43.64 | 347 |
| 2 | 0.70 | 21.23 | 32.99 | 155 |
| 3 | 1.03 | 26.85 | 31.85 | 118 |
| 4 | 1.56 | 35.87 | 49.13 | 137 |

## 3.3 CONCLUSION

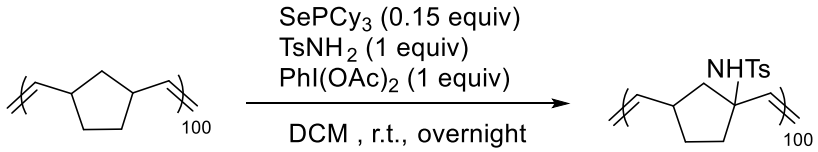
In conclusion, we demonstrated that our selenium catalyzed C-H allylic amination could be used to label poly(norbornene) with high yield and degree of incorporation. This new polymer labeling method is a promising alternative to achieve functionalized polynorbornene. The ability to control the amine to monomer ratio through a simple change in equivalents allows us to access a variety of labeled polynorbornenes. Furthermore, the expansion of the amine scope enables us to incorporate functional groups that are not tolerated in polymerization process, which allows access to new types of of functionalized materials.

## 3.4 EXPERIMENTAL

### 3.4.1 *General Procedure and Materials*

All reactions were performed under a nitrogen atmosphere using oven-dried or flame-dried glassware unless otherwise indicated. Dichloromethane ($CH_2Cl_2$) and tetrahydrofuran (THF) were degassed and dried by passing through a column of activated neutral alumina. Deuterated solvents ($CDCl_3$, acetone-$d^6$, DMSO-$d^6$) were obtained from Cambridge Isotope Laboratories, Inc. and stored over activated 3A molecular sieves. Methanol (MeOH) was obtained from Fisher Scientific or Sigma Aldrich and used without further purification. Reagents were purchased from Sigma Aldrich, Tokyo Chemical Industry, Fisher Scientific, Alfa Aesar, Oakwood chemicals and used without further purification unless otherwise indicated. NMR spectra were recorded on a Bruker AV-300, AV-301, DRX-499, or AV-500 spectrometer. $^1$H NMR chemical shifts (δ) are reported in parts per million (ppm) and are referenced relative to $Me_4Si$ (0.00 ppm), $CHCl_3$ (7.26 ppm) or acetone-$d^5$ (2.06 ppm). $^{13}$C NMR chemical shifts (δ) are reported in parts per million (ppm) relative to the carbon resonance of $CDCl_3$ (77.26 ppm) or acetone-$d^6$ (29.92 ppm).

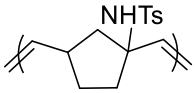
### 3.4.2 *General Procedure for Selenium Catalyzed C-H Allylic Amination of Polynorbornene*



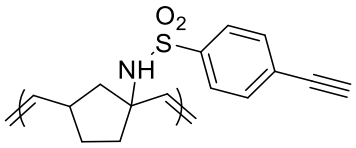

**General procedure A**:

A flame-dried borosilicate glass vial equipped with a magnetic stir bar was charged with $SePCy_3$ (0.75 mmol, 0.15 equiv.), amine (5 mmol, 1 equiv.), with or without BHT, and polynorbornene (5 mmol, 1.0 equiv.). The vial was thoroughly flushed with nitrogen and capped with a Teflon-lined screw cap. Dry dichloromethane (25 mL, 0.2 M) was added, followed by iodobenzene diacetate (5 mmol, 1 equiv). The solution was stirred at the room temperature overnight. Upon completion, the solvent concentrated on a rotary evaporator to approximately 1/5 of the original volume and the solution was precipitated into cold methanol at 1:10 ratio.

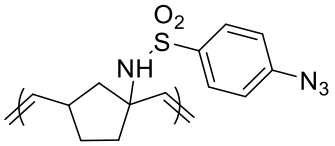
### 3.4.3 *Characterization of Selenium Catalyzed C-H Allylic Amination of Polynorbornene*




Prepared according to general procedure A and purified by precipitation to afford the product as a yellowish solid.
$^1$H NMR (500 MHz, $CDCl_3$) δ 8.11 – 7.51 (m, 1H), 7.26 (s, 1H), 5.66 – 4.90 (m, 1H), 2.78 (s, 0.15H), 2.42 (m, 2H), 2.00 – 1.66 (m, 2H), 1.50 – 1.14 (m, 2H), 1.14 – 0.93 (m, 2H).




Prepared according to general procedure A and purified by precipitation to afford the product as a yellowish solid.
$^1$H NMR (500 MHz, $CDCl_3$) δ 8.00 – 7.76 (m, 1H), 7.71 – 7.53 (m, 1H), 5.57 – 4.99 (m, 2H), 2.88 – 2.72 (m, 1H), 2.45 (s, 0.15H), 1.93 – 1.59 (m, 3H), 1.48 – 1.30 (m, 2H), 1.17 – 1.01 (m, 2H), 0.95 – 0.79 (m, 2H).




Prepared according to general procedure A and purified by precipitation to afford the product as a yellowish solid.
$^1$H NMR (500 MHz, $CDCl_3$) δ 8.19 – 7.51 (m, 1H), 7.25 – 6.83 (m, 1H), 5.66 – 4.94 (m, 2H), 2.80 (d, *J* = 11.2 Hz, 0.15H), 2.46 (s, 0.5H), 2.02 – 1.61 (m, 2H), 1.47 – 1.21 (m, 2H), 1.18 – 0.92 (m, 2H).

## 3.5 REFERENCES FOR CHAPTER 3

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# VITA

Born and raised in Malaysia, Wei Pin Teh moved to the Lakeland, Florida in 2012. He received his Bachelor of Science majoring chemistry at Florida Southern College. He then moved to Seattle in 2015 where he studies under Forrest Michael at University of Washington. He earned a Doctoral of Philosophy degree in Chemistry from the University of Washington in 2021.