Selenium Catalyzed C-N bond formation

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Abstract

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Carbon-nitrogen bonds are an ubiquitous structural motif in natural products, biologically active compounds, and organic materials. Our ability to design molecules that address modern problems requires an array of methods that allow us access to a myriad of carbon-nitrogen bonds. Herein, the development of two selenium catalyzed carbon-nitrogen bond forming reactions are described which add to the pantheon of methods to make this structural motif; the propagylic C-H amination of alkynes and the regioselective C-H allylic amination of heteroatom substituted alkenes.

The propagylic C-H amination of alkynes generated propargyl amines in good to excellent yields. The reaction functionalizes a wide variety of unactivated alkynes with a broad functioal group tolerance. The regiochemical trends of C-H amination of internal alkynes were explored and a mechanistic model was developed to predict the reactivity of different types of propargyl C-H bonds. kinetic isotope labeling experiments were carried out in conjunction to support our mechanistic model.

The regioselective C-H allylic amination of heteroatom substituted alkenes generates allylic amines from a wide variety of enolate derivatives and alkenyl halides in good yields. The reaction is stereoconvergent to the Z-alkene and gives a single regio isomer. We demonstrate how thermodynamic and kinetic enolization correlates to subsequent regiochemical control of C-H amination. Additionally we measured relative reaction rates of differing alkenyl substiutents to compare different functional group reactivities.

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LIST OF SCHEMES

Nomenclature

Ac: Acetyl

Ar: Aryl

Bn: Benzyl

br broad

Cbz: Carbobenzyloxy

Cy: Cyclohexyl

d: doublet

dba: Dibenzylideneacetone

DCC: N,N'-Dicyclohexylcarbodiimide

DCM: Dichloromethane

DMSO: Dimethyl sulfoxide

ESI MS: Electrospray Ionization Mass Spectrometry

Et: Ethyl

hr: Hour

Hz: Hertz

IMe: 1,3-Di-methylimidazole-2-ylidine

L: Ligand

m multiplet

Me: Methyl

MHz: Megahertz

MIDA: N-Methyliminodiacetate

NHC: N-Heterocyclic carbene

NMR: Nuclear Magnetic Resonance

Ns: 4-Nitrobenzenesulfonyl

Ph: Phenyl

ppm: Parts Per Million

q quartet

rt: Room Temperature

s: singlet

t triplet

TBDPS: tert-Butyldiphenylsilyl

TBS: tert-butyl dimethyl silane

Tces: 2,2,2-Trichloroethoxysulfonyl

TES: Triethylsilane

Tfes: 2,2,2-Trifluoroethoxysulfonyl

THF: Tetrahydrofuran

TLC: Thin Layer Chromatography

TMS: Trimethylsilane

DEDICATION

To my parents Richard and Valerie, and my brothers Jeffrey and Nicholas.

Chapter 1

PROPAGYLIC C-H AMINATION OF ALKYNES

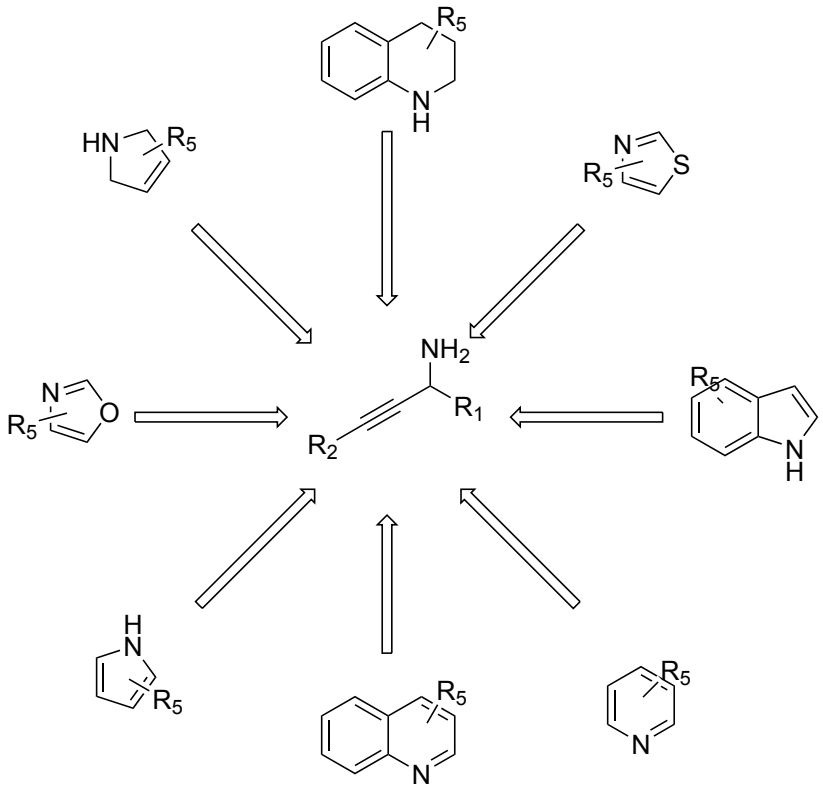


Figure 1.1: Propargyl amines and their synthetic utility

1.1 Introduction

Propargyl amines are known precursors to Pyridines[1], Quinolines[2], Oxazoles[3], and a variety of other nitrogen containing heterocycles prevalent as pharmacophores in drug design. These versatile synthetic intermediates are commonly generated from two methods. The first method takes an amine and displaces a propargyl leaving group. This method is

effective for making primary progargyl amines but more difficult for higher substitutions as the nucleophilic attack becomes hard.

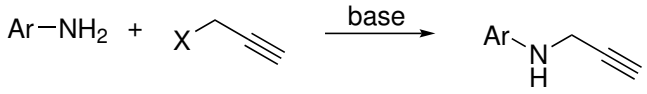


Figure 1.2: Nucleophilic substitution

The second method is the addition of terminal alkynes into imines both stoichiometrically and catalytically, refered to broadly as an A^3 coupling. While this synthetic pathway is versatile it requires a terminal alkyne. Both methods require a preoxidized carbon skeleton.

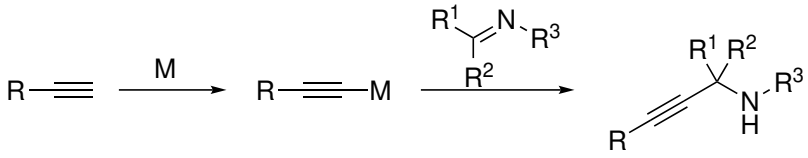


Figure 1.3: A^3 coupling

An alternative strategy could involve a direct C-H amination of a propargyl C-H bond. This would allow the preconstruction of internal alkynes prior to propargyl amine formation and introduce aliphatic internal alkynes as a chemical precursor to propargyl amines; this method would serve a complimentary role to established A^3 coupling methods[4].

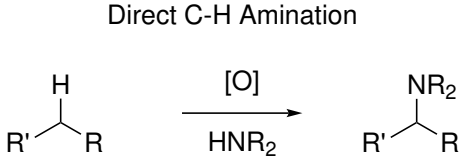


Figure 1.4: C-H amination

This methodological pathway has been explored using transition metal catalysis but remains underdeveloped. Methods include a Rhodium catalyzed report developed by Schomaker

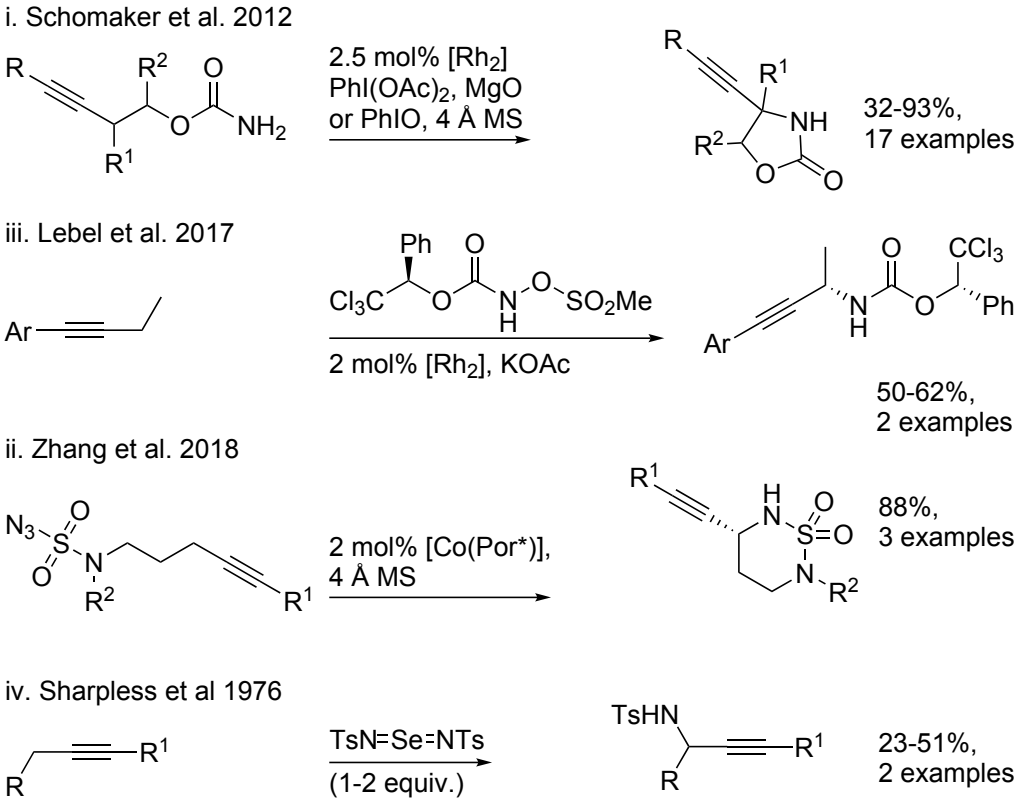
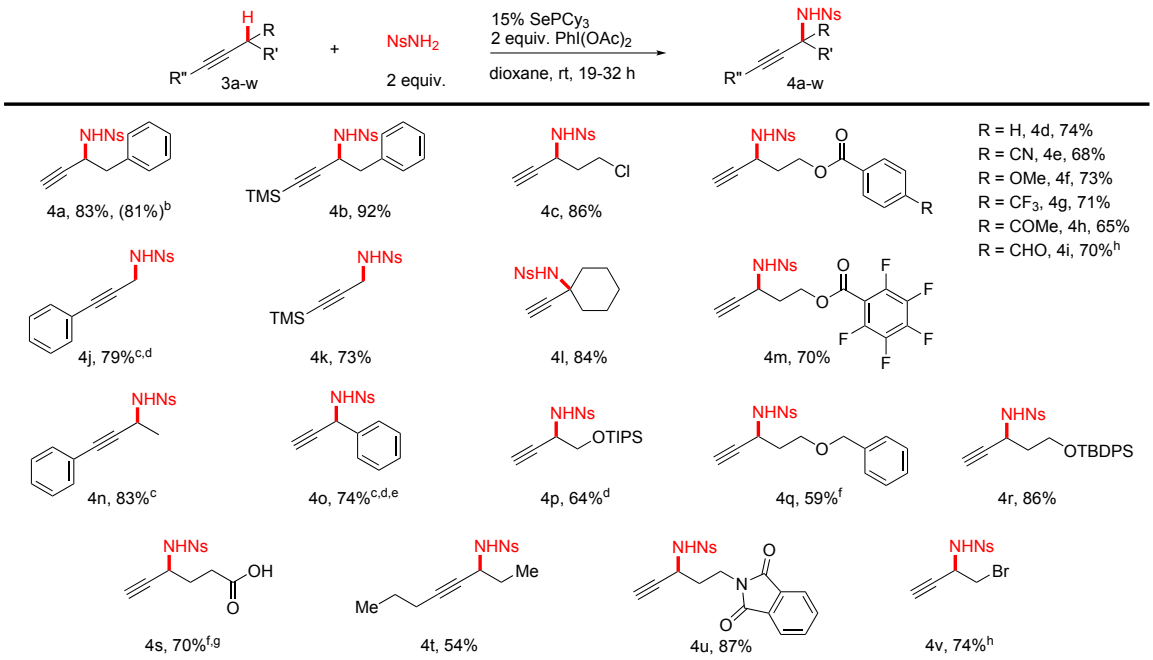


Figure 1.5: Background

and coworkers[5] and Cobalt catalyzed report by Zhang[6]. Both of these methods are intramolecular in scope which fundamentally limits the utility of these methods. Lebel[7] and Zhang[8] have reported intermolecular enantioselective propargyl C-H amination reactions on activated propargyl C-H bonds with a limited number of examples. Our group recently published a selenium catalyzed allylic C-H amination reaction that produced allylic amines. This reaction is intermolecular and functionalizes a large number of unactivated alkenes. Our group saw an opportunity in an unaddressed area of functionalization and thought to use our recent Selenium methodology to tackle it. Working with Parker Maloney and Alec Zhu we developed and published an extension of our selenium catalysis to propargyl C-H amination.



1.2 Scope

Parker's initial optimization found that nosyl sulfonamide worked preferentially over other nitrene precursors and that the reaction functioned well in dioxane, dichloromethane, and toluene. Certain substrates saw complete conversion but poor mass balance. The addition of metal oxide bases such as MgO and CaO improved mass recovery and thus yields albeit with an increase in reaction time. However gentle heating at 35C or 45C brought reaction times back to a reasonable range. Other substrates were sluggish to react under the normal conditions. The addition of p-nitrobenzoic acid as an additive restored reactivity. With this set of conditions in hand I joined Parker and Alec to explore the functional group scope and probe the regiochemical trends of internal alkynes. Prior art outlined in figure 1.5 saw propargyl C-H amination work mostly in intramolecular examples with few intermolecular examples. Additionally internal activated alkynes in conjugation with phenyl rings were usually required to C-H aminate. We sought to explore how well our method intermolecularly C-H aminated and if it could do so on unactivated internal alkynes. We were pleased to see our method successfully aminate propargyl C-H bonds intermolecularly. Our method

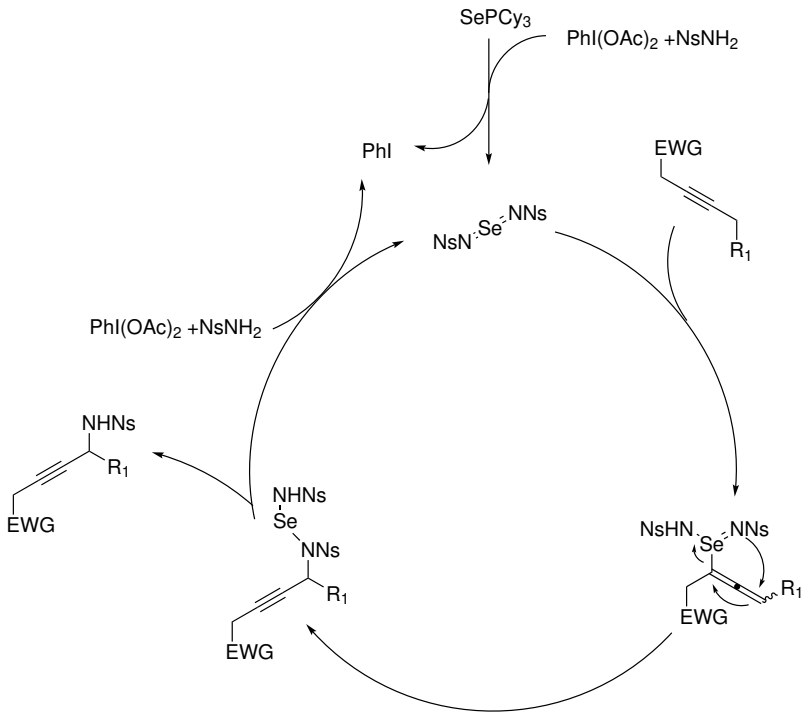


Figure 1.6: Proposed Catalytic Cycle

also worked in the presence of a variety of functional groups, including alkyl halides, aldehydes, and free carboxylic acids. Additionally our method functionalized terminal and internal alkyne unactivated alkynes along with alkynes activiated by phenyl rings.

We hypothesized that the alkyne substrates would undergo an analogous catalytic cycle as the alkene reaction. With this model in mind we thought that the initial ene reaction would be the regiochemical determining step and that any observed preference for C-H amination would be the result of one ene being faster than the other one. Given a choice of internal of several internal propargyl C-H bonds we thought to probe what properties governed regioselectivity. We hypothesized our ene reaction has a late transition state and is

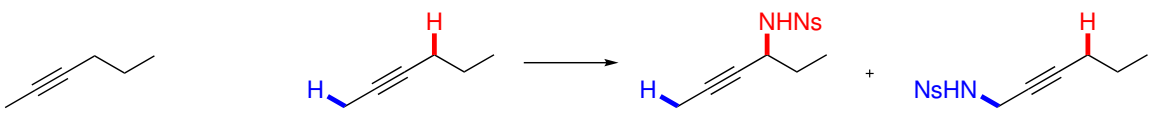
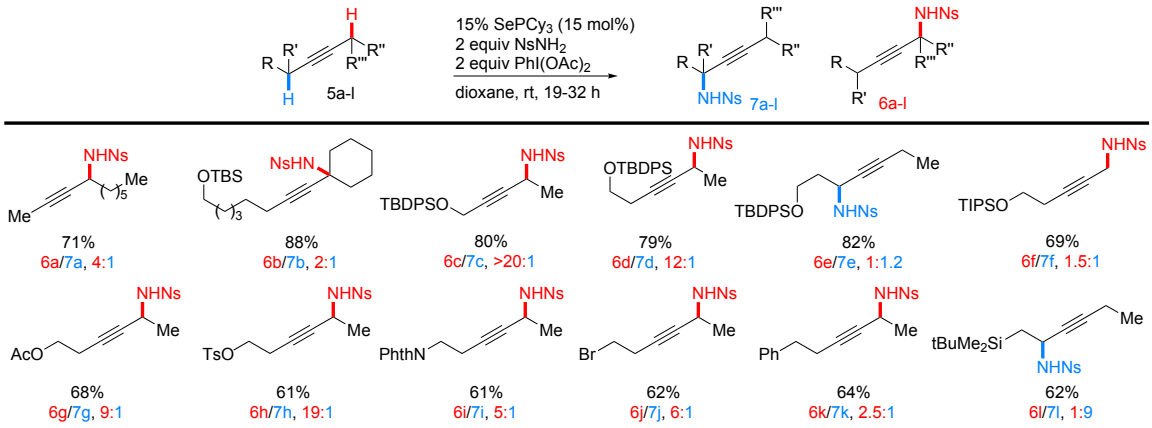


Figure 1.7: Regiochemical Outcomes



Scheme 1.1: Regioselectivity

asynchronous (figure 1.8), meaning it looks more like the product than the starting material. We then thought that ground state thermodynamic stability of the allenyl selenide product of the ene reaction would correlate to a lower energy transition state, thus a faster C-H amination, and ultimately a regiochemical preference. With this model in mind I designed and synthesized a series a internal alkynes to probe our hypothesis.

1.3 Regioselectivity

I examined the C-H amination of internal alkynes. We observed preference for the more substituted propargyl position to be aminated (tertiary: secondary: primary 8:4:1). This preference for amination at the more substituted propargyl position is consistent with the ene reaction generating a more substituted and thus more thermodynamically stable allene, consistent with our mechanistic hypothesis. Amination also occurs distal to electron withdrawing substituents at the propargylic and homo-propargylic positions. We suggest that there may be asynchronicity during the ene reaction where the C-Se bond develops faster than the propargyl C-H deprotonation occurs, allowing for positive charge development to occur at the formerly SP hybridized carbon proximal to the C-H bond being aminated. The electron withdrawing groups destabilize

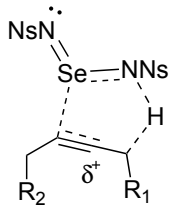
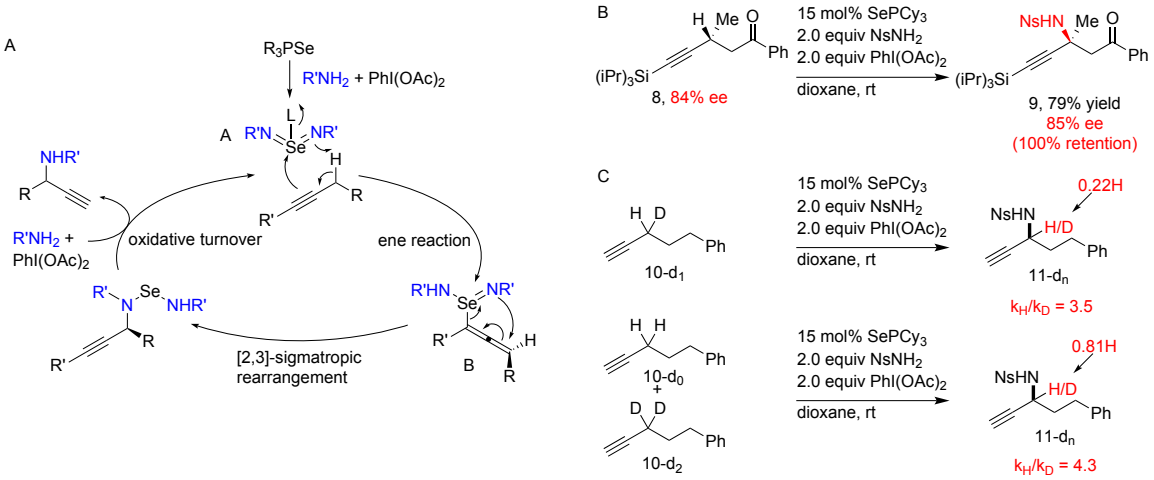


Figure 1.8: asychronous TS

this charge development causing amination to occur distal to the electron withdrawing groups. Gratifyingly we found that an electron rich hetero atom carbon bond (Si-C) directed amination towards the heteroatom, a result consistent with our hypothesis.

1.4 Mechanistic experiments



Scheme 1.2: Mechanistic experiments

To further probe the mechanism I conducted a series of mechanistic studies to probe the ene reaction. I synthesized an enantioenriched substrate and subjected it to our reaction conditions. Our hypothesized allene intermediate should maintain stereochemistry during the ene reaction giving retention of our chiral center and we observed a complete retention of stereochemistry consistent with this step being stereospecific. I conducted intramolecular and intermolecular competition experiments and observed KIEs of 4.3 and 3.5 respectively. This is consistent with the ene reaction being the product determining step while the intermolecular experiment rules out irreversible pre-coordination of the catalyst before the ene reaction. These results in conjunction with our observed regiochemical trends support an asynchronous ene reaction as our product determining step that is the source of our substrate controlled regioselectivity of internal alkynes.

1.5 Conclusions

In summary Parker, Alec, and I helped develop a general intermolecular propargyl amination procedure using our previously reported selenium catalysis. We elucidated regiochemical trends of internal alkynes determining that amination occurs distall to electron withdrawing groups and proximal electron donating groups. We developed a mechanistic model where the product determining ene reaction affords a substrate controlled regioselectivity. Finally, We conducted several mechanistic experiments elucidated the mechanism of propargyl amination and establishing it as enantiospecific.

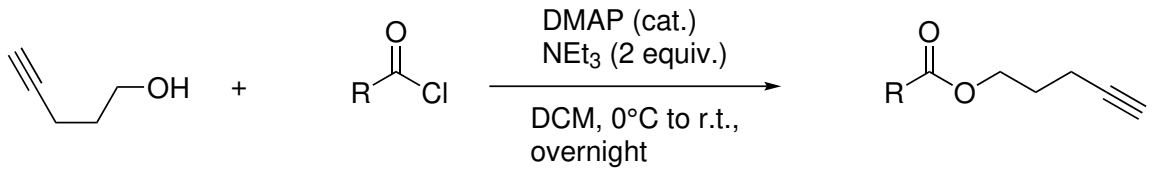
1.6 Experimental

1.6.1 General Procedures 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 TMS (0.00ppm), $CHCl_3$ (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.

1.6.2 ***Preparation of alkyne substrates***

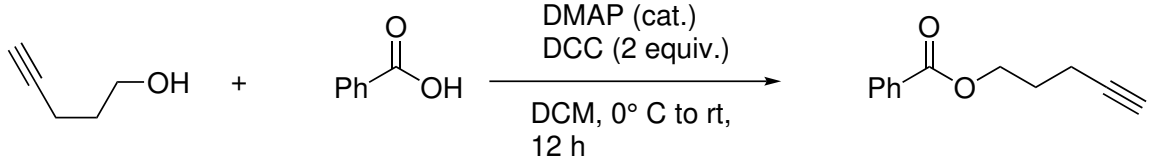
General Procedure A for alcohol protection



Scheme 1.3: General Procedure A for alcohol protection

A flame-dried round-bottomed flask equipped with a magnetic stir bar was charged with 4-pentyn-1-ol (5 mmol, 1 equiv.) and 4-dimethylaminopyridine (0.1 mmol, 0.02 equiv.). Dry dichloromethane (10 mL, 0.5 M) was added and the reaction mixture was stirred and cooled to 0o C. Benzoyl chloride (5.5 mmol, 1.1 equiv.) was added to the reaction mixture followed by triethylamine (10 mmol, 2 equiv.). The mixture 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 the crude products were purified by silica gel chromatography.

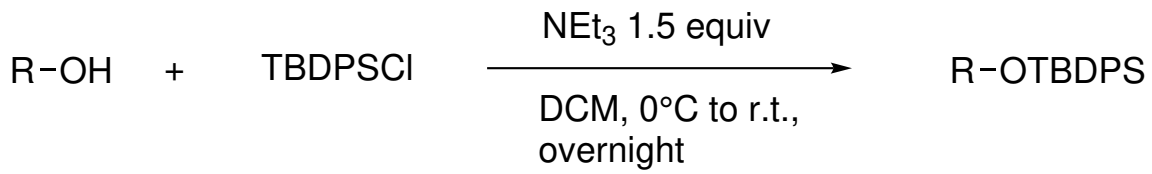
General Procedure B for alcohol protection



Scheme 1.4: General Procedure B for alcohol protection

In a 200 ml round bottom flask, mixture of benzoic acid (5.5 mmol), 4-pentyn-1-ol (0.466 mL, 5.0 mmol), DCC (2.67 g, 11.00 mmol) dissolved in dry dichloromethane (50 mL), was stirred at 0°C under an nitrogen atmosphere for 30 min. Then, a solution of 4-dimethylaminopyridine (0.49 g, 4.0 mmol) in dry dichloromethane (20 mL) was added and the mixture was stirred at 0 oC for 1 h and allowed to warm to room temperature and stirred 12 h. The mixture was filtered and the filtrate was washed with 0.5M HCl (2 x 50 mL), NaHCO3 (2 x 50 mL), and brine (1 x 50 mL). The solvent was removed under reduced pressure and the crude product was purified by chromatography on a silica gel column.

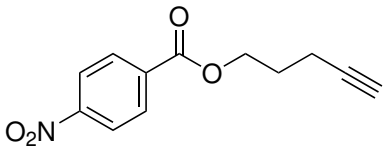
General Procedure C for alcohol protection



Scheme 1.5: General Procedure C for alcohol protection

A flame-dried round-bottomed flask equipped with a magnetic stir bar was charged with a mixture of alcohol (1.0 equiv) and triethylamine (1.5 equiv) dissolved in dry dichloromethane (0.25 M), then was stirred at 0°C under an nitrogen atmosphere for 10 min. TBDPSCl (1.2 equiv) was added dropwise and the mixture was stirred at 0°C for 1 h then allowed to warm to room temperature. The reaction was monitored by TLC until starting alcohol was consumed. After that, the mixture was washed with 0.5M HCl (2 x 25 mL), NaHCO3 (2 x

25 mL), and brine (1 x 25 mL). The solvent was removed under reduced pressure and the crude product was purified by chromatography on a silica gel column.



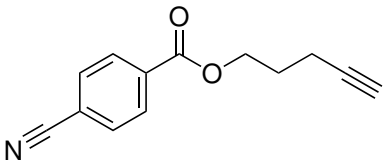
Pent-4-ynyl 4-nitrobenzoate (1e): Prepared according to general procedure A using 5 mmol of 4-pentyn-1-ol. Purified by silica gel chromatography (80:20, hexanes/ethyl acetate) to afford the product as a clear liquid (1.000 g, 85%).

^{1}H NMR (500 MHz, CDCl3) δ 8.33 (d, J = 9.0 Hz, 2H), 8.22 (d, J = 9.0 Hz, 2H), 4.49 (t, J = 6.0 Hz, 2H), 2.40 (td, J = 6.5, 3.0 Hz, 2H), 2.03 (quin, J = 6.5 Hz, 2H) 2.00 (t. J = 2.5 Hz, 1H)

^{13}C NMR (126 MHz, CDCl3) δ 164.69, 150.65, 135.67, 130.83, 123.61, 82.81, 69.43, 64.56, 27.57, 15.44.

IR (thin film): 3263, 1719, 1598, 1517, 1344, 1274, 1121, 1022, 877, 852, 825, 784, 717 cm^{-1}

MS (ESI positive mode): m/z 256.1 $[M+Na]^+$



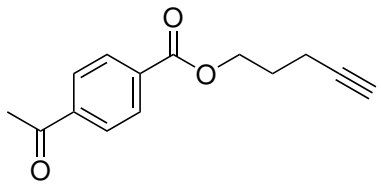
Pent-4-ynyl 4-cyanobenzoate (1f): Prepared according to general procedure B using 5.5 mmol of 4-pentyn-1-ol. Purified by silica gel chromatography (80:20, hexanes/ethyl acetate) to afford the product as a white solid (823 mg, 77%).

^{1}H NMR (500 MHz, CDCl3) δ 8.14 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.0 Hz, 2H), 4.47 (t, 6.5 Hz, 2H), 2.38 (td, J = 7.0, 3.0 Hz, 2H), 2.01 (quin, J = 7.0 Hz, 2H), 1.99 (t, J = 2.0 Hz, 1H)

^{13}C NMR (126 MHz, CDCl3) δ 164.84, 134.02, 132.21, 130.01, 117.97, 116.43, 82.77, 69.37, 64.33, 27.50, 15.35..

IR (thin film): 3284, 3061, 2962, 2853, 2118, 1718, 1687, 1573, 1502, 1406, 1358, 1275, 1178, 1121, 1017, 959, 860, 769, 696 cm^{-1}

MS (ESI positive mode): m/z 236.4 $[M+Na]^+$



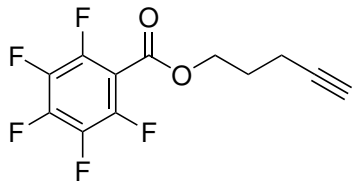
Pent-4-ynyl 4-acetylbenzoate (1i): Prepared according to general procedure B using 5.0 mmol of 4-pentyn-1-ol. Purified by silica gel chromatography (80:20, hexanes/ethyl acetate) to afford the product as a white solid (937 mg, 81%).

^{1}H NMR (500 MHz, CDCl3) δ 8.00 (d, J = 9.0 Hz, 2H), 7.89 (d, J = 9.0 Hz, 2H), 4.34 (t, J = 6.0 Hz, 2H), 2.53 (s, 3H), 2.28 (td, J = 7.0, 2.5 Hz, 2H), 1.94 (t, J = 3.0 Hz, 1H), 1.91 (quin, J = 7.0 Hz, 2H)

^{13}C NMR (126 MHz, CDCl3) δ 197.21, 165.38, 140.10, 133.79, 129.64, 128.05, 82.80, 69.25, 63.83, 27.46, 26.68, 15.21.

IR (thin film): 3260, 2967, 1956, 1714, 1683, 1574, 1501, 1405, 1358, 1277, 1123, 1018, 958, 856, 768, 743, 694, 612 cm^{-1}

MS (ESI positive mode): m/z 253.2 $[M+Na]^+$



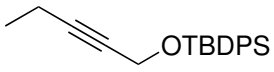
Pent-4-ynyl 2,3,4,5,6-pentafluorobenzoate (1n):Prepared according to general procedure A using 5 mmol of the 4-pentyn-1-ol. Purified by silica gel chromatography (80:20, hexanes/ethyl acetate) to afford the product as a clear liquid (1.187 g, 85%).

^{1}H NMR (500 MHz, CDCl3) δ 4.46 (t, J = 6.0 Hz, 2H), 2.33 (td, J = 7.0, 2.5 Hz, 2H), 1.95 (t, J = 3.0 Hz, 1H), 1.95 (quint, J = 7.0 Hz, 2H)

^{13}C NMR (126 MHz, CDCl3) δ 158.85, 145.38 (d, J = 263 Hz), 143.25 (d, J = 272 Hz), 137.69 (d, J = 255 Hz)108.17, 82.34, 77.02, 69.20, 65.13, 27.24, 14.95

IR (thin film): 3307, 2966, 2120, 1741, 1652, 1525, 1422, 1388, 1328, 1230, 1107, 1003, 953, 813, 763, 644 cm^{-1}

MS (ESI positive mode): m/z 301.4 $[M+Na]^+$



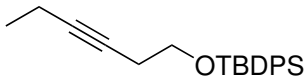
t-Butyl(pent-2-ynyloxy)diphenylsilane (5c):Prepared according to general procedure C for alcohol protection using 6.5 mmol of 2-penytn-1-ol. Purified by silica gel chromatography (95:5, hexanes/ethyl acetate) to afford the product as a clear liquid (1.61 g, 76%).

^{1}H NMR (500 MHz, CDCl3) δ 7.83 (m, 4H), 7.47 (m, 6H), 4.42 (m, 2H), 2.25 (q, J = 7.5, 2.0 Hz, 2H), 1.18 (m, 12H)

^{13}C NMR (126 MHz, CDCl3) δ 135.66, 133.47, 129.68, 127.62, 87.17, 77.83, 53.04, 26.81, 19.23, 13.78, 12.52.

IR (thin film): 3070, 3048, 2958, 2931, 2857, 2234, 1589, 1461, 1373, 1318, 1261, 1188, 1110, 1075, 998, 822, 702, 611 cm^{-1}

MS (ESI positive mode): m/z 345.3 $[M+Na]^+$



t-Butyl(hex-3-ynyloxy)diphenylsilane (5d):Prepared according to general procedure for alcohol protection using 6.0 mmol of 3-hexyn-1-ol. Purified by silica gel chromatography (95:5, hexanes/ethyl acetate) to afford the product as a clear liquid (1.510 g, 74%).

^{1}H NMR (500 MHz, CDCl3) δ 7.72 (m, 4H), 7.41 (m, 6H), 3.78 (t, J = 7.0 Hz, 2H), 2.46 (tt, J = 7.0, 2.5 Hz, 2H), 2.17 (qt, J = 7.5, 2.5 Hz, 2H), 1.13 (t, 3H), 1.09 (s, 9H)

^{13}C NMR (126 MHz, CDCl3) δ 135.76, 134.02, 129.79, 127.81, 83.07, 76.50, 63.18, 27.02,

23.15, 19.46, 14.41, 12.64.

IR (thin film): 3069, 2931, 2856, 1959, 1889, 1825, 1589, 1462, 1427, 1387, 1360, 1263, 1188, 1109, 998, 917, 823, 738, 702, 613, 506 cm^{-1}

MS (ESI positive mode): m/z 359.3 $[M+Na]^+$

t-Butyl(hept-4-ynyloxy)diphenylsilane (5e): Silyl ether intermediate was prepared by general procedure for alcohol protection using 5.0 mmol of the 4-pentyn-1-ol. Purified by silica gel chromatography (95:5, hexanes/ethyl acetate) to afford the product as a clear liquid (1.001 g, 72%). This protected alcohol was added to a flame-dried round-bottomed flask equipped with a magnetic stir bar, which was then charged with HMPA (1 equiv) dissolved in dry THF (0.25 M) and was cooled at -78 °C under a nitrogen atmosphere. n-BuLi (2.1 ml, 2.5 M) was added dropwise and the reaction was allowed to warm to room temperature and then stirred for 20 minutes. The mixture was cooled to -78 °C and bromoethane was added dropwise. The reaction was allowed to warm to room temperature and stirred overnight. The reaction was quenched slowly with water and extracted with dichloromethane, then washed with water (2 x 25 ml), and brine (1 x 25 ml). The solution was dried over sodium sulfate and the solvent removed under reduced pressure to give the crude alkyne. This was purified by silica gel chromatography (95:5, hexanes/ethyl acetate) to afford the product as a clear liquid (1.260 g, 72%).

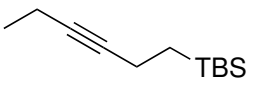
^{1}H NMR (500 MHz, CDCl3) δ 7.72 (m, 4H), 7.43 (m, 6H), 3.78 (t, J = 7.0 Hz, 2H), 2.46 (tt, J = 7.0, 2.0 Hz, 2H), 2.17 (qt, J = 7.5, 2.0 Hz, 2H), 1.13 (t, 3H), 1.09 (s, 9H)

^{13}C NMR (126 MHz, CDCl3) δ 135.76, 134.02, 129.79, 127.81, 83.07, 76.50, 63.18, 27.02, 23.15, 19.46, 14.41, 12.64.

IR (thin film): 3071, 2932, 2858, 1969, 1889, 1823, 1678, 1589, 1472, 1428, 1389, 1361, 1322, 1189, 1109, 979, 823, 739, 702, 613 cm^{-1}

MS (ESI positive mode): m/z 373.4 $[M+Na]^+$

t-Butyl(4-hexyn-1-yl)dimethylsilane (5l): 1-Iodo-3-hexyne (832 mg, 4.0 mmol) was



dissolved in dry ether (20 mL) and was cooled at -78 °C under an nitrogen atmosphere. t-BuLi (5.2 ml, 1.7 M, 2.2 equiv) was added dropwise and the reaction was allowed to warm to room temperature and stirred for 30 min. The mixture was cooled back down to -78 °C and TBSCl (2.4 g, 16.0 mmol, 4 equiv) in 10 ml of ether was added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched slowly with water and extracted with 2 times with ether. The organic extracts were then washed with water (2x) and brine (1x), dried over sodium sulfate and the solvent was removed under reduced pressure to give the crude product. This was purified by silica gel chromatography (95:5, hexanes/ethyl acetate) to afford the product as a clear liquid (255 mg, 65%).

^{1}H NMR (500 MHz, CDCl3) δ 2.20 (m, 4H), 1.09 (t, J = 7.5 Hz, 3H), 0.85 (s, 9H), 0.78 (m, 2H), -0.05 (s, 6H)

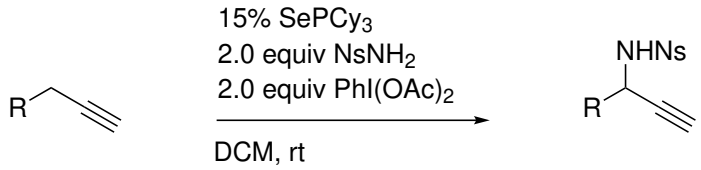
^{13}C NMR (126 MHz, CDCl3) δ 81.75, 80.91, 26.46, 16.46, 14.28, 13.59, 12.56, 12.41, -6.37

IR (thin film): 2954, 2884, 2857, 1905, 1711, 1594, 1469, 1362, 1254, 1169, 1051, 1006, 937 834 cm^{-1}

MS (ESI positive mode): m/z 219.2 $[M+Na]^{+}$

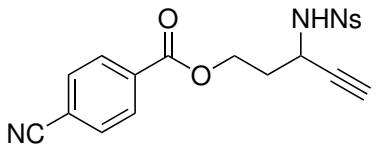
1.6.3 ***Alkyne Products***

General Procedure for Propargyl Amination



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, 2.0 equiv.), and alkyne (0.2 mmol, 1.0 equiv.). The vial was thoroughly flushed with nitrogen and capped with a Teflon-lined

screw cap. Dry dioxane (1 mL, 0.2 M) was added, followed by iodobenzene diacetate (0.4 mmol, 2.0 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.



4e: Prepared according to standard amination conditions with dichloromethane as solvent. Purified by silica gel chromatography (85:15, hexanes/ethyl acetate) to afford the product as a clear liquid (46 mg, 68%).

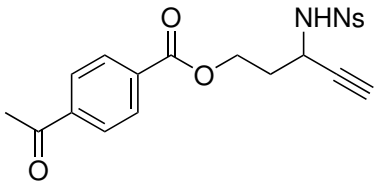
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.76 (d, J = 8.5 Hz, 1H), 8.34 (d, J = 9.0 Hz, 2H), 8.06 (m, 4H), 8.05 (d, J = 9.0 Hz, 2H), 4.32 (m, 2H), 4.25 (m, 1H), 3.14 (d, J = 2.5 Hz, 1H), 2.06 (m, 2H)

^{13}C NMR (126 MHz, DMSO-d_6) δ 164.26, 149.46, 146.40, 133.34, 132.75, 129.83, 128.36, 124.30, 118.03, 115.51, 81.48, 75.41, 61.45, 41.96, 34.29

IR (thin film): 3273, 3103, 2859, 1724, 1608, 1530, 1404, 1350, 1312, 1277, 1167, 1120, 1092, 1019, 856, 768, 738, 685, 663, 617 cm^{-1}

MS (ESI positive mode): m/z 436.0 $[M+Na]^+$

MP 137-140C



4h: Prepared according to standard amination conditions. Purified by silica gel chromatography (98:2 dichloromethane/MeOH) to afford the product as a white solid (56 mg,

65%).

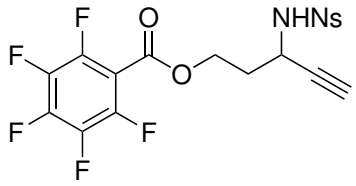
^{1}H NMR (500 MHz, CDCl3) δ 8.31 (d, J = 9.0 Hz, 2H), 8.10 (d, J = 8.5 Hz, 2H), 8.07 (d, J = 8.5 Hz, 2H), 8.02 (d, J = 8.5 Hz, 2H), 5.25 (d, J = 9.0 Hz, 1H), 4.56 (dt, J = 11.5, 6.0 Hz, 1H), 4.49 (dt, J = 11.5, 6.0 Hz, 1H), 4.42 (m, 1H), 2.65 (s, 3H), 2.24 (q, J = 6.1 Hz, 2H), 2.11 (d, J = 2.5 Hz, 1H).

^{13}C NMR (126 MHz, CDCl3) δ 197.63, 165.76, 150.36, 146.01, 140.69, 133.57, 130.03, 128.81, 128.48, 124.40, 80.33, 74.18, 61.15, 43.37, 35.62, 27.04.

IR (thin film): 3261, 1718, 1686, 1530, 1349, 1268, 1166, 1091, 1015, 912, 855, 737, 615 cm^{-1}

MS (ESI positive mode): m/z 453.2 $[M+Na]^+$

MP 155-157C



4m: Prepared according to standard amination conditions. Purified by silica gel chromatography (85:15 hexanes/ethyl acetate) to afford the product as a clear liquid (67 mg, 70%).

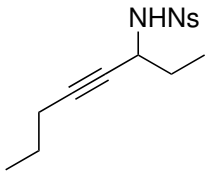
^{1}H NMR (500 MHz, CDCl3) δ 8.37 (d, J = 8.5 Hz, 2H), 8.10 (d, J = 9.0 Hz, 2H), 5.24 (d, J = 9.5 Hz, 1H), 4.55 (m, 2H), 4.38 (m, 1H), 2.19 (m, 2H), 2.15 (d, J = 2.5 Hz, 1H)

^{13}C NMR (126 MHz, CDCl3) δ 158.89, 150.42, 145.86, 128.86, 124.42, 79.76, 74.49, 62.54, 43.20, 35.21.

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

MS (ESI positive mode): m/z 501.1 $[M+Na]^+$

4t: Prepared according to standard amination conditions. Purified by silica gel chromatography (85:15, hexanes/ethyl acetate) to afford the product as a white solid (33 mg, 54%).



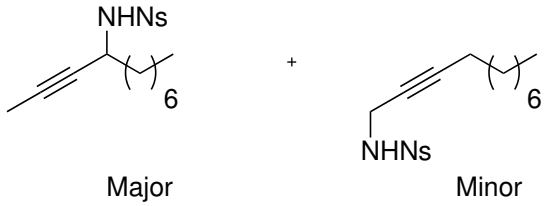
^{1}H NMR (500 MHz, CDCl3) δ 8.33 (d, J = 9.0 Hz, 2H), 8.08 (d, J = 9.0 Hz, 2H), 4.90 (d, J = 9.5 Hz, 1H), 4.05 (m, 1H), 1.83 (dt, J = 2.0, 7.0 Hz, 2H), 1.69 (m, 2H), 1.23 (sextet, J = 7.0 Hz, 2H), 0.98 (t, J = 7.5 Hz, 3H), 0.77 (t, J = 7.5 Hz, 3H).

^{13}C NMR (126 MHz, CDCl3) δ 150.18, 146.61, 128.85, 124.16, 85.87, 77.64, 47.86, 30.46, 21.87, 20.40, 13.39, 9.98.

IR (thin film): 3280, 3106, 2967, 2936, 2875, 1607, 1531, 1428, 1350, 1311, 1168, 1091, 996, 854, 738, 685, 619, 560 cm^{-1}

MS (ESI positive mode): m/z 333.1 $[M+Na]^+$

MP 101-104 oC



6a/7a: Prepared according to standard amination conditions. Purified by silica gel chromatography (80:20, hexanes/ethyl acetate) to afford a 4:1 mixture of regioisomeric products as a liquid (50mg, 71%).

^{1}H NMR (500 MHz, CDCl3) δ 8.34 (d, J = 9 Hz, 2H) (major + minor), 8.10 (d, J = 9 Hz, 2H) (major + minor), 5.20 (t, J = 6 Hz, 1H) (minor), 5.13 (d, J = 9.5 Hz, 1H) (major), 4.05 (qt, J = 7, 2.5 Hz, 1H) (major), 3.89 (td, J = 4.5, 2.5 Hz, 2H) (minor), 1.9-1.8 (m, 2H) (minor), 1.7-1.5 (m, 2H) (major), 1.45 (d, J = 2 Hz, 3H) (major), 1.4-1.3 (m, 2H) (major), 1.3-1.1 (m, 10H) (major + minor), 1.0-0.8 (m, 3H) (major + minor).

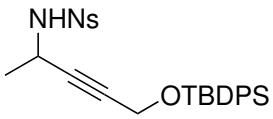
^{13}C NMR (126 MHz, CDCl3) δ 150.18, 150.06, 146.53, 146.16, 129.14, 128.89, 124.19, 124.00, 86.28, 81.27, 77.41, 73.61, 46.41, 36.80, 33.54, 31.84, 31.75, 29.17, 29.13, 29.03,

28.92, 28.85, 28.37, 25.44, 22.67, 22.64, 18.45, 14.13, 14.10, 3.19.

IR (thin film): 3280, 3106, 2927, 2857, 1607, 1531, 1428, 1349, 1311, 1166, 1092, 1054, 855, 738, 685, 619 cm^{-1}

MS (ESI positive mode): m/z 375.1 $[M+Na]^+$

MP



4h: Prepared according to standard amination conditions. Purified by silica gel chromatography (98:2 dichloromethane/MeOH) to afford the product as a white solid (56 mg, 65%).

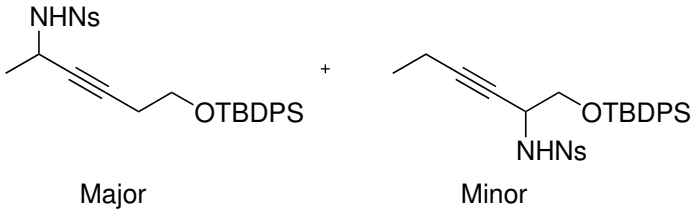
^{1}H NMR (500 MHz, CDCl3) δ 8.24 (d, J = 9 Hz, 2H), 7.98 (d, J = 9 Hz, 2H), 7.63 (m, 4H), 7.46 (m, 2H), 7.40 (m, 4H), 4.59 (d, J = 8.5 Hz, 1H), 4.17 (m, 1H), 4.08 (dd, J = 16, 1.5 Hz 1H), 4.02 (dd, J = 16, 1.5 Hz 1H), 1.32 (d, J = 7.0 Hz, 3H), 1.00 (s, 9H).

^{13}C NMR (126 MHz, CDCl3) δ 150.23, 146.38, 135.86, 135.81, 133.24, 133.22, 130.25, 130.21, 128.81, 127.99, 127.97, 124.27, 83.61, 83.05, 52.41, 41.98, 26.83, 23.50, 19.29.

IR (thin film): 3280, 3104, 3071, 2931, 2859, 2255, 1961, 1892, 1826, 1710, 1606, 1530, 1471, 1427, 1348, 1311, 1158, 1109, 1071, 1011, 955, 909, 853, 823, 736, 703, 618, 571 cm^{-1}

MS (ESI positive mode): m/z 545.0 $[M+Na]^+$

MP



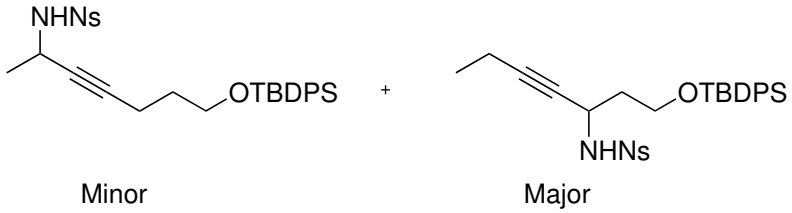
6d: Prepared according to standard amination conditions. Purified by silica gel chromatography (85:15, hexanes/ethyl acetate) to afford a 12:1 mixture of products as a liquid (84 mg, 79%).

^{1}H NMR (500 MHz, CDCl3) δ 8.31 (d, J = 9 Hz, 2H) (minor), 8.26 (d, J = 9 Hz, 2H) (major), 8.09 (d, J = 9 Hz, 2H) (minor), 8.02 (d, J = 9 Hz, 2H) (major), 7.63 (d, J = 8 Hz, 4H) (major + minor), 7.45 (t, J = 7.5 Hz, 2H) (major + minor), 7.40 (t, J = 8 Hz, 4H) (major + minor), 5.18 (d, J = 8.5 Hz, 1H) (minor), 4.82 (d, J = 8.5 Hz, 1H) (major), 4.25-4.20 (m, 1H) (major + minor), 4.16 (dd, J = 11, 4.5 Hz, 2H) (minor), 3.87 (m, 2H) (major+minor), 2.20 (tt, J = 7, 2 Hz, 2H) (major), 2.06 (s, 3H) (minor), 2.02 (s, 3H) (major), 1.91 (qd, J = 7.5, 2 Hz, 2H) (minor), 1.42 (d, J = 8 Hz, 3H) (major), 0.87 (t, J = 7.5 Hz, 3H) (minor)

^{13}C NMR (126 MHz, CDCl3) δ 170.83, 150.25, 146.50, 128.81, 124.21, 80.61, 80.38, 65.72, 61.81, 45.71, 41.96, 23.69, 20.88, 18.99, 13.37, 12.12

IR (thin film): 3279, 3070, 2931, 2857, 2247, 1606, 1530, 1471, 1427, 1348, 1311, 1160, 1111, 1012, 965, 911, 853, 823 737, 703, 614 cm^{-1}

MS (ESI positive mode): m/z 537.4 $[M+H]^+$



6e/7e: : Prepared according to standard amination conditions. Purified by silica gel chromatography (85:15 hexanes/ethyl acetate) to afford a 1.2:1 mixture of regioisomeric products as a liquid (92 mg, 82%).

^{1}H NMR (500 MHz, CDCl3) δ 8.31 (d, J = 9.0 Hz, 2H, major), 8.26 (d, J = 9.0 Hz, 2H, minor) 8.01 (m, 4H, major + minor), 7.64 (m, 8H, major + minor), 7.41 (m, 12H, major + minor), 6.14 (d, J = 8.5 Hz, 1H, major), 4.74 (d, J = 8.5 Hz, 1H, minor), 4.55 (m, 1H, major), 4.20 (m, 1H, minor), 4.02 (dt, J = 9.0, 2.5 Hz, 2H, major), 3.76 (dt, J = 9.0, 2.5 Hz, 2H, major), 3.54 (m, 2H, minor), 2.03 (m, 3H, major + minor), 1.83 (m, 3H, major + minor), 1.50 (sextet, J = 6.0 Hz, 2H, minor), 1.38 (d, J = 7.0 Hz, 3H, minor), 1.09 (s, 9H, major), 1.03 (s, 9H, minor), 1.09 (t, J = 7.5 Hz, 3H, major)

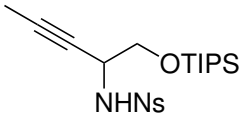
^{13}C NMR (126 MHz, CDCl3) δ 150.12, 150.00, 147.11, 146.47, 135.69, 135.66, 135.58,

133.82, 133.78, 133.00, 132.63, 130.14, 130.09, 129.84, 128.90, 128.77, 127.99, 127.98, 127.82, 124.10, 123.94, 87.91, 84.65, 78.82, 76.16, 62.18, 61.31, 45.18, 42.09, 37.38, 31.20, 26.96, 26.92, 24.02, 19.31, 19.23, 14.92, 13.58, 12.16.

IR (thin film): 3284, 3071, 2932, 2858, 1607, 1531, 1472, 1428, 1349, 1312, 1166, 1110, 1010, 966, 910, 854, 823, 737, 704, 616 cm^{-1}

MS (ESI positive mode): m/z $[M+Na]^+$

MP



6f/7f:Prepared according to standard amination conditions. Purification by silica gel chromatography (85:15 hexanes/ethyl acetate) allowed separation of the 2:1 mixture of regioisomers to afford product 7f as a white solid (25 mg, 28%) and 6f as a white solid (37 mg, 41%).

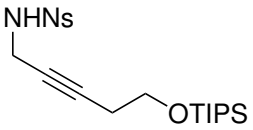
^{1}H NMR (500 MHz, CDCl3) δ 8.33 (d, J = 9.0 Hz, 2H), 8.10 (d, J = 9.0 Hz, 2H), 5.13 (d, J = 7.5 Hz, 1H), 4.17 (m, 1H), 3.84 (dd, J = 9.5, 4.0 Hz, 1H), 3.75 (d, J = 9.5, 4.0 Hz, 1H), 1.50 (d, J = 2.0 Hz, 3H), 1.06 (m, 21H).

^{13}C NMR (126 MHz, CDCl3) δ 150.15, 146.69, 128.96, 124.02, 82.00, 74.97, 66.2148.07, 18.08, 17.96, 12.00, 3.32.

IR (thin film): 3280, 3104, 3071, 2931, 2859, 2255, 1961, 1892, 1826, 1710, 1606, 1530, 1471, 1427, 1348, 1311, 1158, 1109, 1071, 1011, 955, 909, 853, 823, 736, 703, 618, 571 cm^{-1}

MS (ESI positive mode): m/z 463.1 $[M+Na]^+$

MP 70-72 C



^{1}H NMR (500 MHz, CDCl3) δ 8.34 (d, J = 9.0 Hz, 2H), 8.08 (d, J = 9.0 Hz, 2H), 4.92 (t, J = 6.0 Hz, 1H), 3.90 (dt, J = 5.5, 2.5 Hz, 1H), 3.58 (t, J = 7.0 Hz, 2H), 2.17 (tt, J =

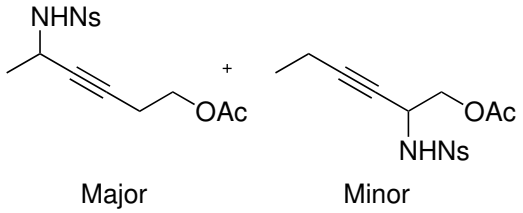
7.0, 2.5 Hz, 2H), 1.03 (m, 21H).

^{13}C NMR (126 MHz, CDCl3) δ 150.28, 146.10, 128.83, 124.28, 83.51, 74.76, 61.74, 33.61, 23.05, 18.01, 12.04.

IR (thin film): 3280, 3104, 3071, 2931, 2859, 2255, 1961, 1892, 1826, 1710, 1606, 1530, 1471, 1427, 1348, 1311, 1158, 1109, 1071, 1011, 955, 909, 853, 823, 736, 703, 618, 571 cm^{-1}

MS (ESI positive mode): m/z 463.1 $[M+Na]^+$

MP 62-63 C



6g: Prepared according to standard amination conditions with dichloromethane as solvent. Purified by silica gel chromatography (85:15 hexanes/ethyl acetate) to afford a 9:1 mixture of regioisomeric products as a clear liquid (46 mg, 68%).

^{1}H NMR (500 MHz, CDCl3) δ 8.36 (d, J = 9.0 Hz, 2H, major + minor), 8.10 (d, J = 9.0 Hz, 2H, major + minor), 5.31 (d, J = 9.0 Hz, 1H, minor), 5.11 (d, J = 9.0 Hz, 1H, major), 4.5-4.4 (m, 1H, minor), 4.3-4.2 (m, 1H, major + minor), 4.16 (dd, J = 11.0, 4.5 Hz, 2H, minor), 3.9-3.8 (m, 2H, major), 2.20 (tt, J = 7.0, 2.0 Hz, 2H, major), 2.06 (s, 3H, minor), 2.02 (s, 3H, major), 1.91 (qd, J = 7.5, 2.0 Hz, 2H, minor), 1.42 (d, J = 8.0 Hz, 3H, major), 0.87 (t, J = 7.5 Hz, 3H, minor)

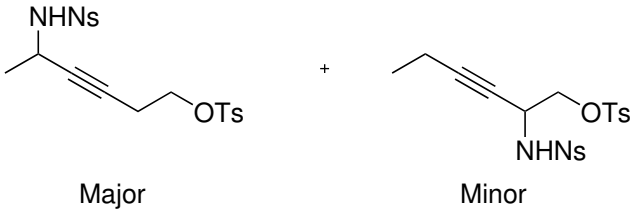
^{13}C NMR (126 MHz, CDCl3) δ 170.83, 150.25, 146.50, 128.81, 124.21, 80.61, 80.38, 65.72, 61.81, 45.71, 41.96, 23.69, 20.88, 18.99, 13.37, 12.12

IR (thin film): 3270, 2984, 1739, 1531, 1350, 1241, 1160, 1089, 1043, 854, 738, 685, 618 cm^{-1}

MS (ESI positive mode): m/z 573.3 $[M+Na]^+$

MP

6h: Prepared according to standard amination conditions. Purified by silica gel chromatography (80:20 hexanes/ethyl acetate) to afford a 19:1 mixture of regioisomeric products



as a solid (49 mg, 62%)

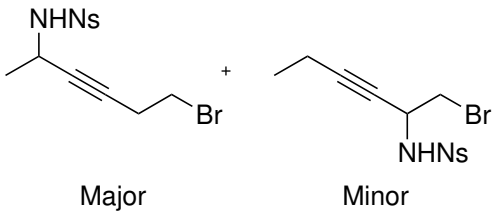
^{1}H NMR (500 MHz, CDCl3) δ 8.33 (d, J = 9 Hz, 2H, major + minor), 8.07 (d, J = 9 Hz, 2H, major + minor), 7.76 (d, J = 8 Hz, 2H, major + minor), 7.36 (d, J = 8 Hz, 2H, major + minor), 5.03 (d, J = 8.5 Hz, 1H, major), 4.4-4.3 (m, 1H, minor), 4.2-4.1 (m, 1H, major), 4.1-4.0 (m, 2H, minor), 3.9-3.8 (m, 2H, major), 2.46 (s, 3H, major + minor), 2.3-2.2 (m, 2H, major), 1.90 (qd, J = 7.5, 2.0 Hz, 2H minor), 1.41 (d, J = 7 Hz, 3H, major), 0.88 (t, J = 7.5 Hz, 3H, minor)

^{13}C NMR (126 MHz, CDCl3) δ 150.35, 146.49, 145.46, 133.08, 130.23, 128.93, 128.06, 124.39, 81.36, 79.60, 67.53, 42.05, 23.85, 21.90, 19.81, 0.23.

IR (thin film): 3279, 3070, 2931, 2857, 2247, 1606, 1530, 1471, 1427, 1348, 1311, 1160, 1111, 1012, 965, 911, 853, 823 737, 703, 614 cm^{-1}

MS (ESI positive mode): m/z 475.0 $[M+Na]^+$

MP 154-157



6i/7i: Prepared according to standard amination conditions with dichloromethane as solvent. Purified by silica gel chromatography (85:15 hexanes/ethyl acetate) to afford a 5:1 mixture of regioisomeric products as a clear liquid (44 mg, 61%).

^{1}H NMR (500 MHz, CDCl3) δ 8.36 (d, J = 9.0 Hz, 2H, major + minor), 8.11 (d, J = 9.0 Hz, 2H, major + minor), 5.38 (d, J = 9.0 Hz, 1H, minor), 5.14 (d, J = 9.0 Hz, 1H, major),

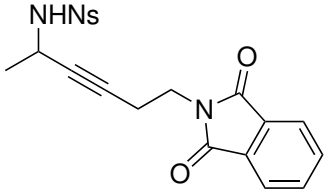
4.5-4.4 (m, 1H, minor), 4.3-4.2 (m, 1H, major), 3.54 (dd, J = 10.5, 5.0 Hz, 1H, minor), 3.50 (dd, J = 10.5, 5.0 Hz, 1H, minor), 3.17 (t, J = 7.0 Hz, 2H, major), 2.64 (m, 2H, major), 1.92 (qd, J = 7.5, 2.0 Hz, 2H, minor), 1.44 (d, J = 7 Hz, 3H, major), 0.89 (t, J = 7.5 Hz, 3H, minor)

^{13}C NMR (126 MHz, CDCl3) δ 150.21, 146.36, 146.06, 128.82, 124.28, 88.94, 81.74, 80.80, 74.35, 46.89, 41.95, 36.61, 29.38, 23.73, 22.85, 13.31, 12.14

IR (thin film): 3282, 3106, 2983, 2935, 2872, 1607, 1530, 1421, 1350, 1312, 1161, 1089, 958, 911, 854, 738, 685, 617, 551 cm^{-1}

MS (ESI positive mode): m/z 383.0 $[M+Na]^+$

MP 107-109 C



6j/7j: Prepared according to standard amination conditions. Crude mixture was obtained in a 6:1 ratio of isomers in 62% yield. Purified by silica gel chromatography (40:40:20 hexanes/toluene/ethyl acetate) to afford pure isomer 7j as a white solid (45 mg, 53%)

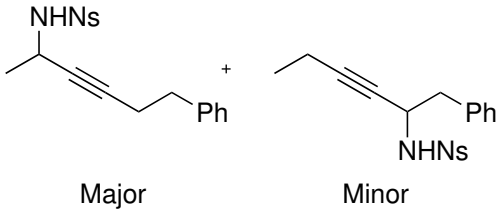
^{1}H NMR (500 MHz, CDCl3) δ 8.32 (d, J = 9.0 Hz, 2H), 8.06 (d, J = 9.0 Hz, 2H), 7.9-7.8 (m, 2H), 7.8-7.7 (m, 2H), 5.00 (d, J = 7.5 Hz, 1H), 4.2-4.1 (m, 1H), 3.7-3.6 (m, 2H), 2.4-2.3 (m, 1H), 2.2-2.1 (m, 1H), 1.34 (d, J = 7.0 Hz, 3H)

^{13}C NMR (126 MHz, CDCl3) δ 168.26, 150.23, 146.45, 134.44, 131.93, 128.81, 124.19, 123.58, 81.52, 80.77, 42.06, 36.64, 23.83, 18.74.

IR (thin film): 3266, 2935, 1772.1, 1710, 1608, 1530, 1432, 1397, 1349, 1160, 1114, 1087, 1001, 913, 854, 738, 720 cm^{-1}

MS (ESI positive mode): m/z 450.1 $[M+Na]^+$

MP 184-187



6k/7k: Prepared according to amination conditions with toluene as the solvent. Purified by silica gel chromatography (85:15 hexanes/ethyl acetate) to afford a 2.5:1 mixture of regioisomeric products as a liquid (48 mg, 64%)

^{1}H NMR (500 MHz, CDCl3) δ 8.28 (d, J = 9.0 Hz, 2H, minor), 8.25 (d, J = 9.0 Hz, 2H, major), 7.98 (d, J = 9.0 Hz, 2H, major + minor), 7.3-7.2 (m, 3H, major + minor), 7.1-7.0 (m, 2H, major) 4.7-4.6 (m, 1H, major + minor), 4.4-4.3 (m, 1H, minor), 4.3-4.2 (m, 1H, major), 2.98 (dd, J = 6.5, 2.0 Hz, 2H, minor), 2.57 (t, J = 7.0 Hz, 2H, major), 2.20 (tt, J

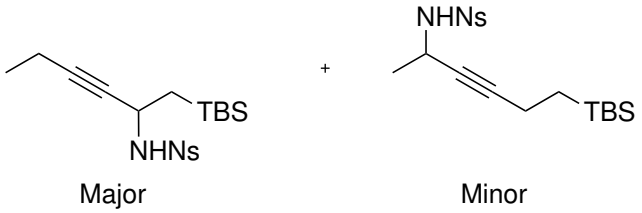
= 7.0, 2.0 Hz, 2H, major), 1.91 (qd, J = 7.5, 2.0 Hz, 2H, minor), 1.42 (d, J = 7.0 Hz, 3H, major), 0.87 (t, J = 7.5 Hz, 3H, minor)

^{13}C NMR (126 MHz, CDCl3) δ 150.13, 146.36, 140.22, 135.47, 130.03, 128.80, 128.62, 128.56, 128.53, 127.44, 126.67, 124.14, 124.11, 84.46, 79.67, 47.22, 42.96, 42.14, 34.65, 23.98, 20.66, 13.50, 12.16.

IR (thin film): 3282, 2935, 1606, 1530, 1427, 1349, 1312, 1162, 1089, 1014, 960, 854, 738, 700, 618 cm^{-1}

MS (ESI positive mode): m/z 359.2 $[M+H]^+$

MP



6l/7l: Prepared according to standard amination conditions. Purified by silica gel chromatography (90:10 hexanes/ethyl acetate) to afford a 9:1 mixture of regioisomeric products as a liquid (49 mg, 62%)

^{1}H NMR (500 MHz, CDCl3) δ 8.35 (d, J = 9 Hz, 2H, major + minor), 8.10 (d, J = 9 Hz, 2H, major + minor), 4.79 (m, 1H, major + minor), 4.21 (m, 1H, major + minor), 1.9-1.8 (m, 2H, minor), 1.80 (dq, J = 7.5, 2Hz, 2H, major), 1.43 (d, 3H, minor), 1.2-1.0 (m, 2H, major), 0.83 (m, 9H, major + minor), 0.6-0.5 (m, 2H, minor), 0.04 (m, 6H, major), -0.13 (s, 6H, minor)

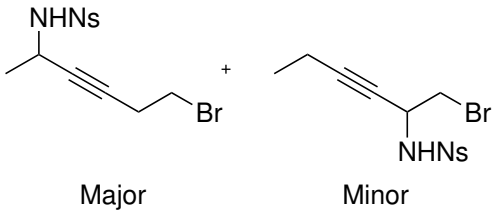
^{13}C NMR (126 MHz, CDCl3) δ 150.24, 146.90, 129.07, 129.01, 87.08, 78.87, 44.41, 42.32, 26.59, 26.49, 24.06, 22.81, 16.64, 13.46, 12.20, 12.07, -5.27, -5.78, -6.24

IR (thin film): 2988, 2361, 2341, 1756, 1725, 1600, 1463, 1348, 1174, 749, 668 cm^{-1}

MS (ESI positive mode): m/z 419.1 $[M+Na]^+$

MP

6i/7i: Prepared according to standard amination conditions with dichloromethane as solvent. Purified by silica gel chromatography (85:15 hexanes/ethyl acetate) to afford a 5:1



mixture of regioisomeric products as a clear liquid (44 mg, 61%).

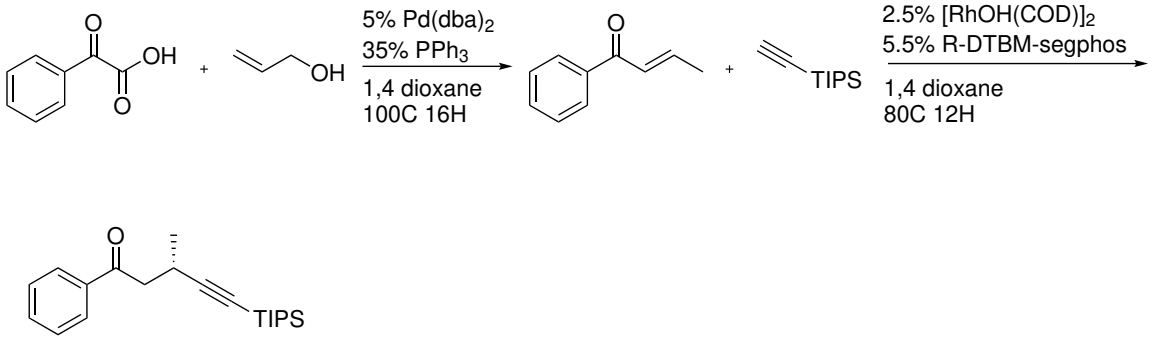
^{1}H NMR (500 MHz, CDCl3) δ

^{13}C NMR (126 MHz, CDCl3) δ

IR (thin film): cm^{-1}

MS (ESI positive mode): m/z $[M+Na]^{+}$

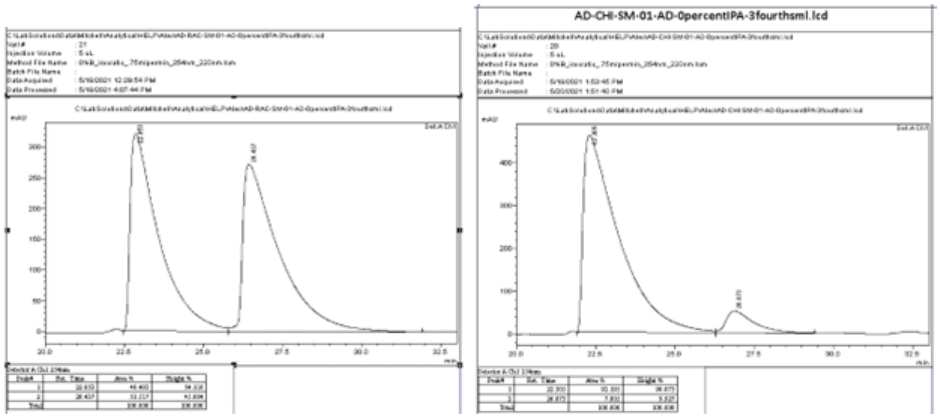
Stereochemistry Retention

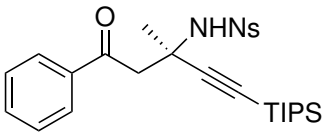


A 25 ml flame dried round-bottomed flask was charged with bis(dibenzylideneacetone) palladium(0) (28.8 mg, 0.05 mmol) and triphenylphosphine (91.8 mg, 0.35 mmol). A solution of the carboxylic acid (1.0 mmol) in 1,4-dioxane (8 mL) and allyl alcohol (104 μL, 1.5 mmol) were added via syringe. The reaction mixture was stirred at 100°C for 16 h and was then cooled to room temperature. The solvent was removed and the remaining residue was further purified by flash chromatography (90:10 hexane/ethyl acetate), giving (E)-1-phenylbut-2-en-1-one in 89% yield (130 mg)

A mixture of $[Rh(OH)(COD)]_2$ (10 mg, 0.022 mmol) and (R)-DTBM-Segphos (58.5 mg, 0.05 mmol) in 1,4-dioxane (2.0 mL) was stirred at room temperature for 5 min. Triiso-

propylsilylacetylene (328.5 mg, 018 mmol) and enone (0.89 mmol) were then added, and the mixture was stirred at 80°C for 12 h. After cooling, the mixture was passed through a short column of silica gel with ethyl acetate and concentrated under vacuum. The resulting residue was subjected to column chromatography (95:5 hexane/ethyl acetate) to give compound in 74% yield (216 mg). The NMR spectrum was consistent with literature values. **HPLC:** (Chiralcel AD, 100% hexanes, 0.75 ml/min): 22.3 and 26.9 min, 84% ee.





9: Prepared according to amination conditions with 2 equiv. benzoic acid in toluene at 35°C. Purified by silica gel chromatography (90:10 hexanes/ethyl acetate) to afford the product as a liquid (84 mg, 79%).

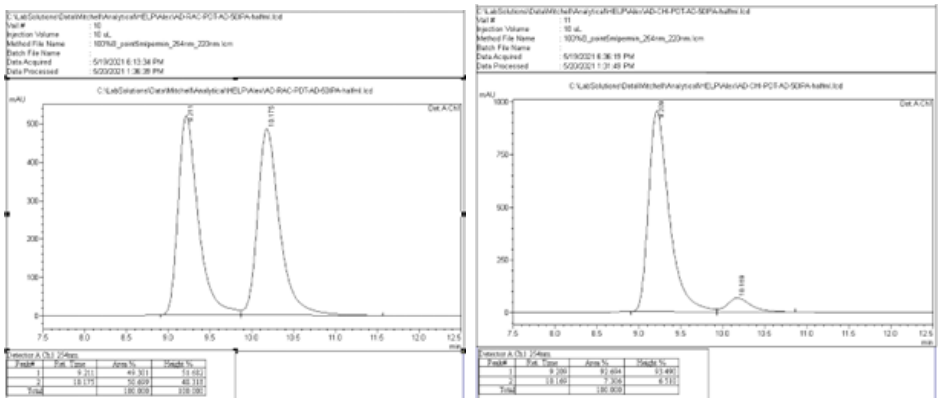
^{1}H NMR (500 MHz, CDCl3) δ8.29 (d, J = 8.9 Hz, 2H), 8.14 (d, J = 8.8 Hz, 2H), 7.93–7.87 (m, 2H), 7.60 (t, J = 7.5 Hz, 1H), 7.47 (t, J = 7.5 Hz, 2H), 6.94 (s, 1H), 3.65 (d, J = 17.0 Hz, 1H), 3.26 (d, J = 17.0 Hz, 1H), 0.9-0.8 (m, 18H), 0.80–0.71 (m, 3H).

^{13}C NMR (126 MHz, CDCl3) δ 198.63, 149.94, 147.85, 136.67, 134.21, 128.93, 128.71, 128.35, 124.19, 106.74, 86.52, 52.38, 49.78, 29.29, 18.45, 11.06.

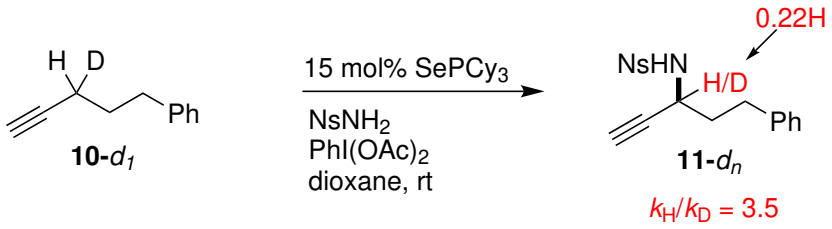
IR (thin film): 3289, 2943, 2865, 1678, 1597, 1531, 1449, 1349, 1226, 1166, 1094, 998, 882, 854, 736, 685, 610 cm^{-1}

MS (ESI positive mode): m/z 529.4 $[M+H]^+$

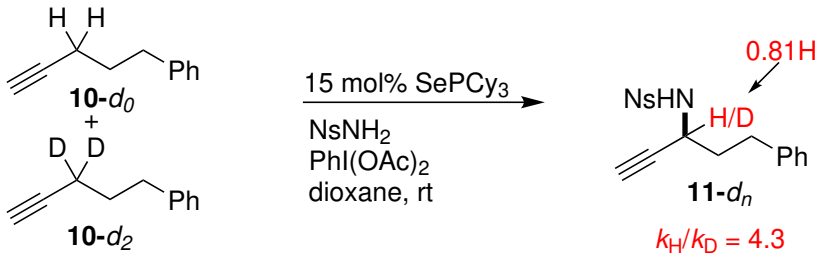
HPLC: (Chiralcel AD, 50% isopropanol/hexanes, 5 mL/min): 9.2 and 10.2 min, 84% ee.



Intramolecular competition KIE: 3-deuterio-5-phenyl-1-pentyne was subjected to the standard propargyl amination conditions. Upon consumption of the starting material the product was purified by silica gel chromatography (85:15 hexanes/ethyl acetate). The KIE was determined by product ratio using ^{1}H NMR spectroscopy.



One-pot Intermolecular competition KIE: A 1:1 mixture of 5-phenyl-1-pentyne and 3,3-dideuterio-5-phenyl-1-pentyne was subjected to the standard propargyl amination conditions. After 15% conversion the product was purified by silica gel chromatography (85:15 hexanes/ethyl acetate). The KIE was determined by product ratio using ^{1}H NMR spectroscopy.


H H
Ph
10-d_0
+
D D
Ph
10-d_2
15 mol% SePCy3
NsNH2
PhI(OAc)2
dioxane, rt
0.81H
NsHN
H/D
Ph
11-d_n
k_H/k_D = 4.3

Chapter 2

C-H AMINATION OF ALKENYL SUBSTITUTED ALKENES

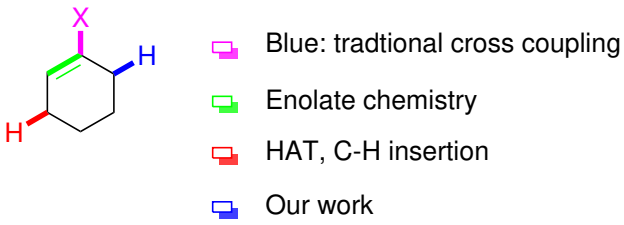


Figure 2.1: Alkenyl-X reactivity

2.1 Introduction

Enol derivatives are fundamental intermediates due to the reactivity imparted by the heteroatom in a variety of organic transformations[9]. Alkenyl phosphates, tosylates, halides, and acetates serve as electrophiles in transition metal catalyzed cross coupling reactions[10, 11, 12]. Alkenyl acetate and carbonates serve as carbon nucleophiles in allylic alkylation

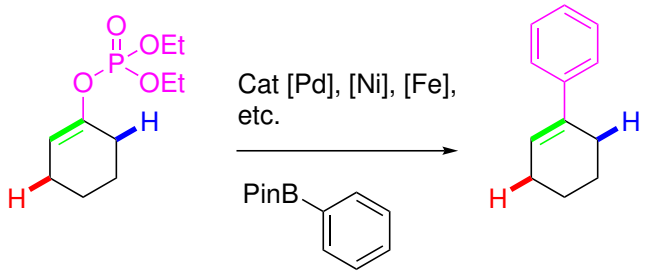


Figure 2.2: Alkenyl electrophile in cross-coupling

reactions, generating a C-C bond alpha to a ketone.

Silyl enol ethers are carbon nucleophiles in traditional enolate chemistry which returns

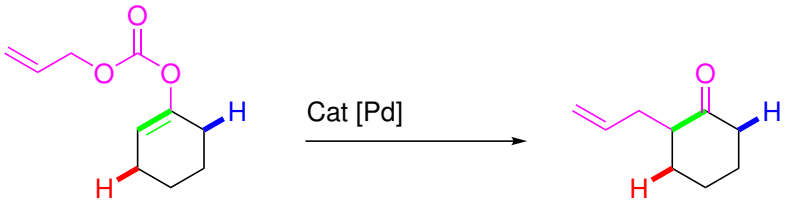


Figure 2.3: Tsuji-Trost allylation

a carbonyl group with its corresponding alpha carbon functionalized with a variety of heteroatom and carbon electrophiles.

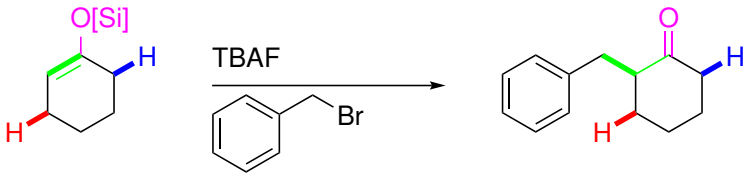


Figure 2.4: Silyl enol ether nucleophile

The pi-bond itself can also be functionalized by epoxidation, aziridination, cyclopropanation, and hydrogenation. In all of these transformations the enol equivalent is consumed in

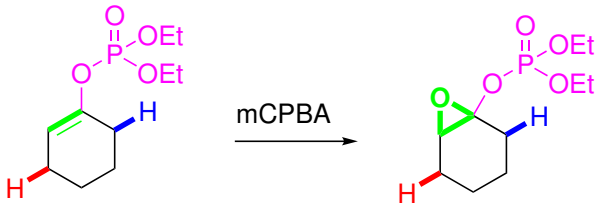


Figure 2.5: Example of Epoxidation

the functionalization, either as the removal of the carbon-hetero atom bond or the pi system itself. Functionalizations that engage enolate derivatives without consuming the functional group would be a powerful tool orthogonal to the native reactivity of these motifs. These types of transformations are rare however as the it is well established that transition metal catalyzed reactions engage carbon-heteroatom bond or pi bond system preferentially over C-H functionalization.

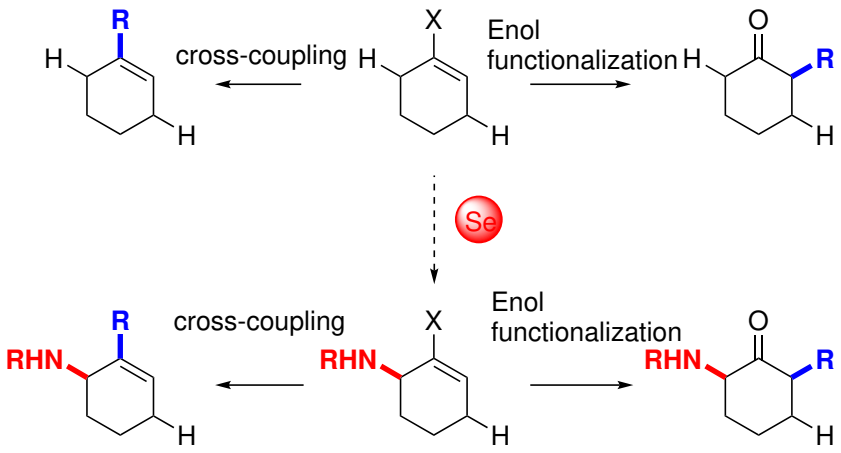


Figure 2.6: Alkenyl-X preserving C-H amination

C-H amination is a powerful tool to functionalize unreactive carbon-hydrogen bonds. The tradeoff here is this reactivity can be incompatible with reactive functional groups, such as enolate derivatives. A C-H amination reaction that reacts orthogonally to this class of reactive pi bond and carbon-hetero atom bonds would complement and expand the established C-H amination methodologies. Furthermore this orthogonality would allow these aminated products to be derivatized further by the vast array of transformations ubiquitous with enolate derivatives.

2.2 Background

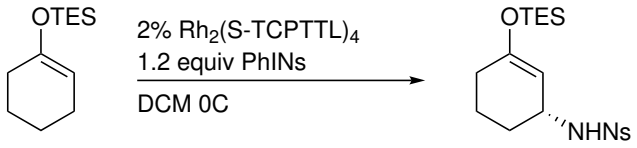


Figure 2.7: Hashimoto 2008

Magnus used stoichiometric selenium and chloramine-T to C-H aminate silyl enol ethers proximal to the carbon-oxygen bond, this reaction was stoichiometric and limited to silyl enol ethers[13]. Hashimoto developed an asymmetric rhodium catalyzed allylic C-H amination to C-H bonds distal to the carbon-oxygen bond of TES protected silyl enol ethers[14].

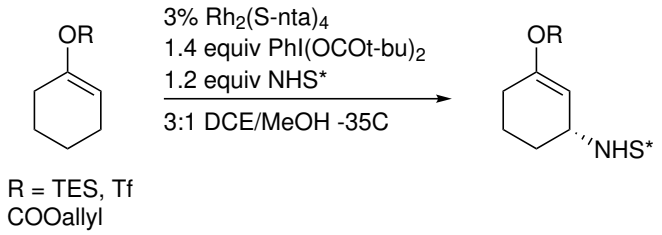


Figure 2.8: Dauban 2012

Dauban expanded this asymmetric rhodium methodology to enol triflates and carbonates. To highlight the challenges of C-H amination of enolate derivatives both observed competitive functionalization at the pi system of the enolate derivative and are limited in scope[15].

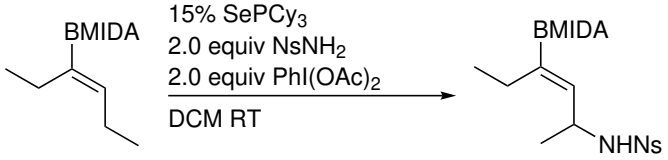


Figure 2.9: Michael 2022

Our group previously reported a selenium-catalyzed allylic C-H amination method that tolerates a wide range functional groups. We recently reported a functional group preserving C-H amination of vinyl BMIDAs and silanes that aminates at the distal position[16]. We hypothesized that our groups selenium catalyzed allylic amination protocol could be applied to other enolate equivalents, circumvent traditional transition metal reactivity, presevering the alkenyl functional group as it did in the BMIDA and silane case.

We further hypothesized that these enolate derivatives will direct C-H amination to the proximal C-H bond by stabilizing the transition state via resonance while inductive withdrawing would destabilize the transition state leading to distal amination. With this precedent in mind Nicole Rishwain, Y-Nhi Tran, and I set out to develop a regioselective C-H amination of enolate equivalents.

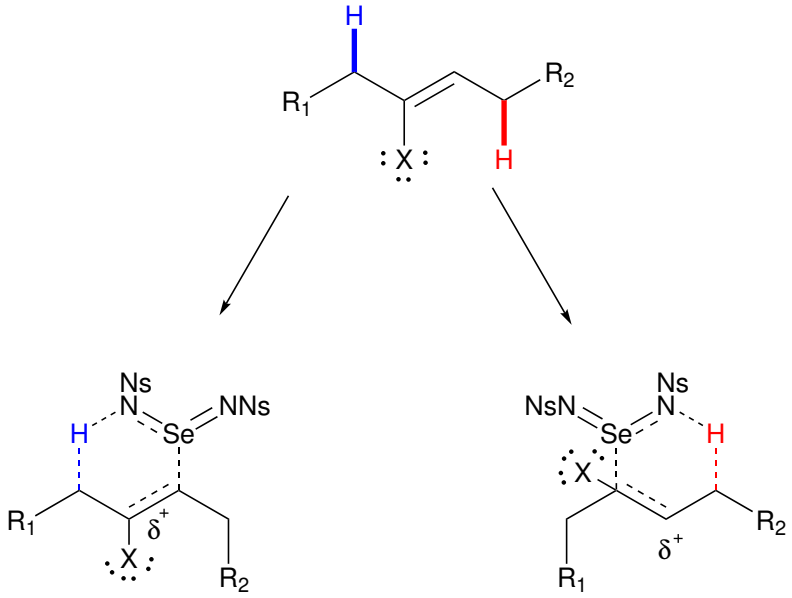
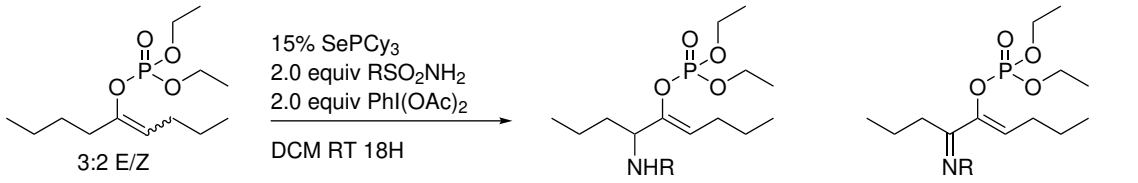


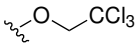
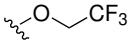
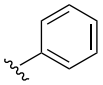
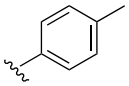
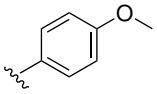
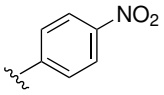
Figure 2.10: Transition State Models

2.3 Optimization

Optimization began on 1-butyl-1-penten-1-yl diethyl phosphate (3:2 mixture of E/Z isomers) as a model substrate. Our original amination conditions gave a 10% yield with 20% overoxidation to the imine after 24 hours(scheme 2.1 final entry). A screen of sulfonamides and sulfamates found that sulfonamides routinely gave over oxidation to alpha-beta unsaturated imines while electron poor sulfamates gave solely the desired C-H amination product. Imine formation seemed to be correlated to electron richness of the sulfonamide with para-methoxy benzenesulfonamide giving the highest yield of imine and $NsNH_2$ giving the lowest.

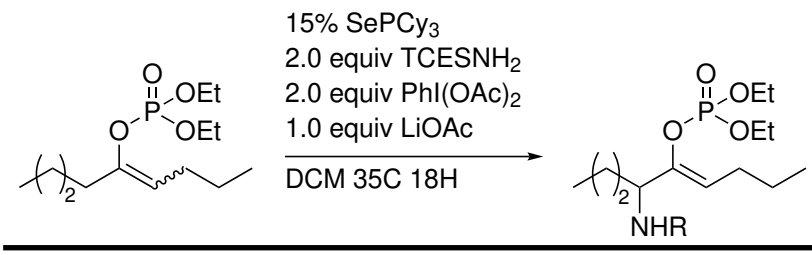
A screen of catalysts found that $SePCy_3$ and SeIMe were competent catalysts. Other NHC and aryl phosphine ligands on selenium gave 100% conversion and catalytic turnover, albeit with lower yields. Hydrolysis of the alkenyl phosphate was observed and it was hypothesized acetic acid generated in the course of the reaction was catalyzing this. A screen of bases found that several increased mass balance while slowing the reaction down. Gentle heating at 35°C restored reactivity and the allylic amine product was formed in 79%.



R =	(%)	(%)
	63	0
	61	0
	53	0
	20	33
	15	48
	15	46
	10	20

Scheme 2.1: Nucleophile Screen

Knowing that our reaction proceeded well in toluene and dichloromethane in conjunction with several different insoluble bases we moved to examine the scope of enolate equivalents tolerated in our chemistry.

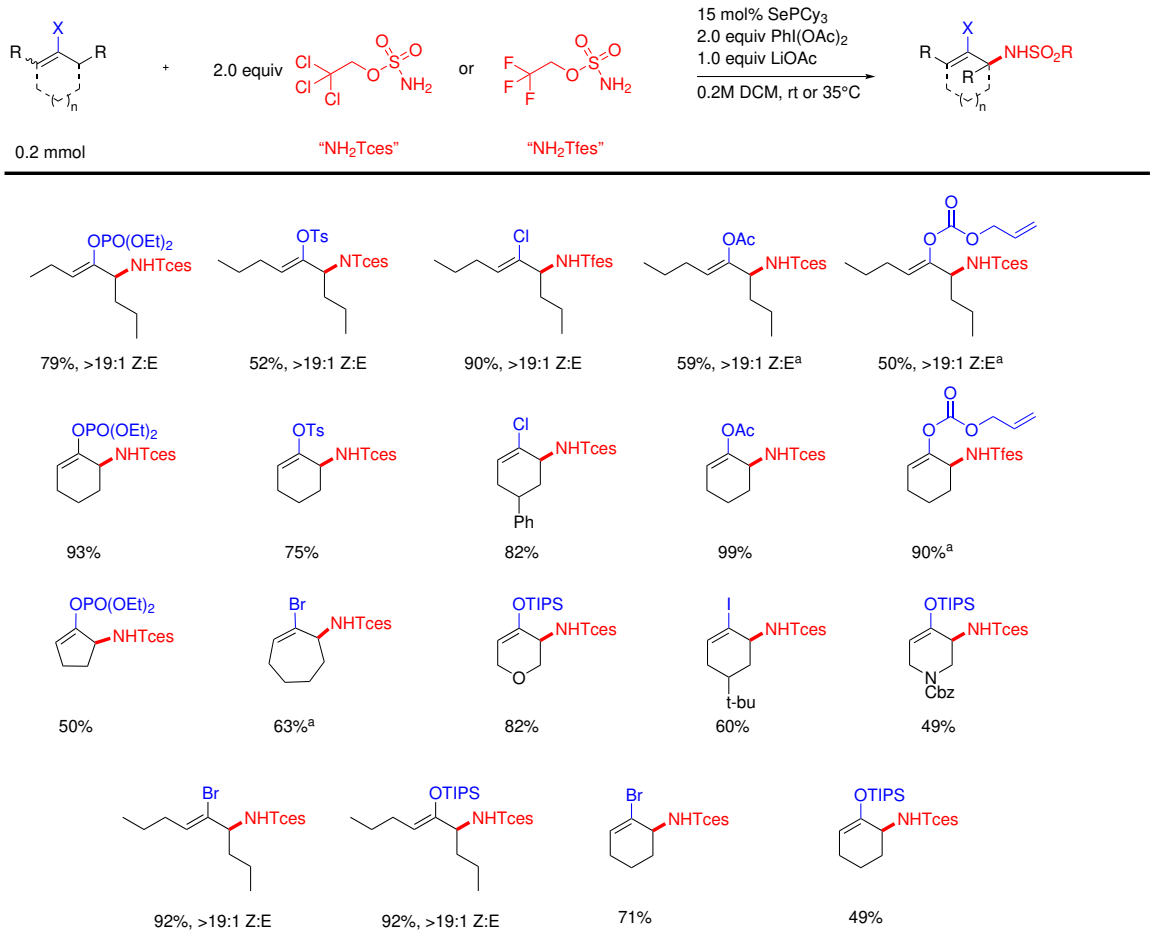


Standard Conditions	79%
$NsNH_2$ instead of $TCESNH_2$, no base	10%
Trifilamide instead of $TCESNH_2$, no base	53%
SeIMe instead of $SePCy_3$	71%
$SePPh_3$ instead of $SePCy_3$	53%
$SePNp_3$ instead of $SePCy_3$	57%
CaO instead of LiOAc	64%
MgO instead of LiOAc	76%

Scheme 2.2: Optimization

2.4 Scope

We wanted to test whether acyclic and cyclic structural motifs were tolerated in our reaction conditions. We found that acyclic motifs were easily transformed and E/Z mixtures strereoconverged to the Z isomer. Cylic alkenyl-X groups were also well tolerated with 5, 6, and 7 member rings reacting readily. We then examined which electron withdrawing enolate derivatives were tolerated in the reaction. We found that enol phosphates, tosylates, acetates, and carbonates perfomred well under our reaction conditions. Additionally silyl enol ethers performed well under our reaction conditions. TIPS enol ether performed optimally over TMS, TBS, and TES enol ethers. Next we wanted to examine what other heteroatom substitutions could be tolerated as alkenyl substituents. Gratifyingly we found



Scheme 2.3: Alkenyl-X Group Scope

that alkenyl chlorides, bromides, and iodides also underwent our allylic amination reaction in decent yields. Since ring systems were functionalized well by our reaction we wanted to see if oxygen and nitogren containing heterocycles were tolerated. Our previous work with alkynes saw that having electron withdrawing groups adjacent to the pi system we were reacting with deactivated it toward our C-H amination method. Having allylic oxygens and nitrogens deactivated the pi system towards reacting with our selenium system, with the enol phosphate giving no reaction and recovery of starting material.

With starting material still present we hypothesized that the pi system of the enol phosphate was too deactivated. We then switched to a more electron rich TIPS silyl enol ether

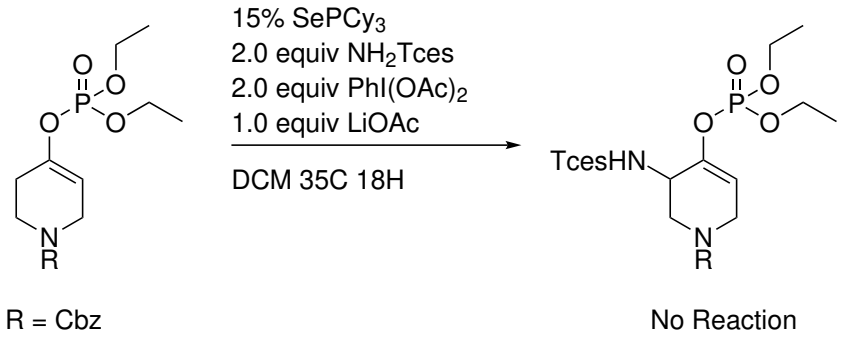


Figure 2.11: Unreactive electron poor pi system

to increase the reactivity of pi system. Upon switching to a more electron rich silyl enol ether we were able restore reactivity and C-H aminate a pair of silyl enol ether containing heterocycles. Our mechanistic hypothesis predicted that C-H amination should be directed

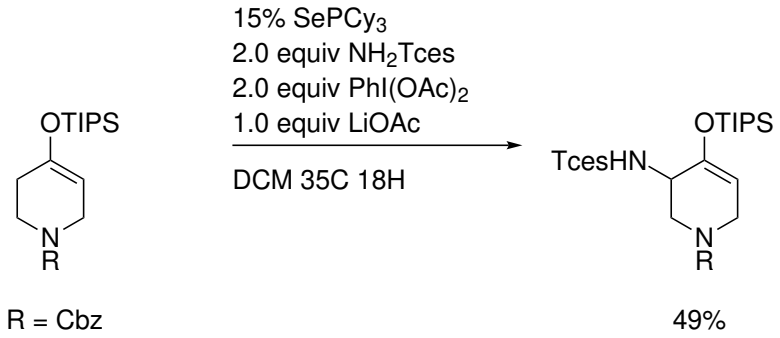


Figure 2.12: Restoring reactivity

towards the proximal C-H bond relative to the alkenyl substituent. In all cases C-H aminations gave selectivity proximal to the carbon-heteroatom bond on the enolate while the distal product was not observed, consistent with our hypothesis.

Seeing that the regioselectivity of C-H amination was consistent with our mechanistic hypothesis we thought to leverage this trait to make difficult to access C-N bonds. We envisioned that our C-H amination protocol could be used to translate kinetic and thermodynamic enolate control into C-N bond regiochemical control. By choosing which enolate derivative we generated we can use the directing effects of the carbon hetero-atom bond to

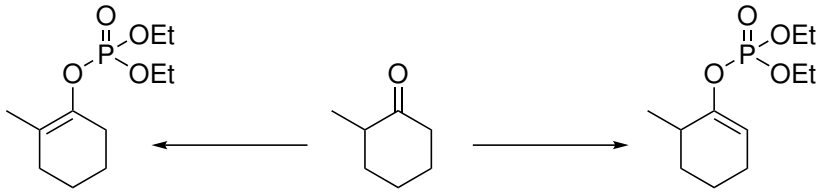
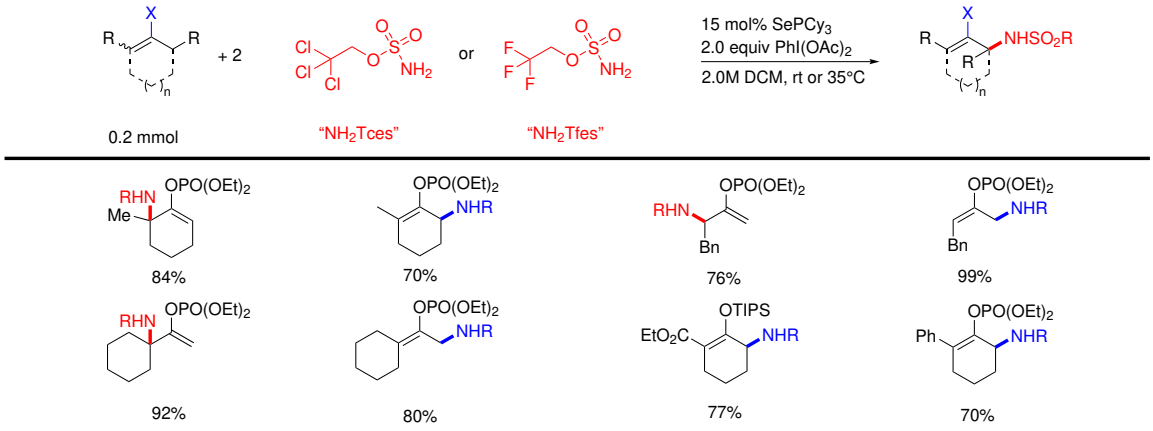


Figure 2.13: Thermodynamic and kinetic enol phosphates

functionalize specific C-H bonds. This C-N bond forming reaction would by construction be regiochemically orthogonal to traditional enolate C-N forming reactions allowing for further derivatization of these groups.



Scheme 2.4: Enolate scope

We were pleased to see that our C-H amination method transformed these pairs of alkenyl phosphates smoothly and with no detectable isomerization of the pi system. We demonstrated that primary, secondary, and tertiary C-H bonds can be aminated. Furthermore this application gives us C-N bond products orthogonal to traditional alpha-keto amination methods which utilize the pi system of an enol, enolate, or enolate equivalent. Additionally our method in specific substrates gives us C-N bond formation that would be difficult to access due to the inability to form the corresponding kinetic enol. With our proximal selectivity and orthogonality to alpha-keto amination in mind our C-H amination method is complimentary to existing transition metal catalyzed C-H insertion and alpha-keto C-N

bond forming methods.

2.5 Conclusions

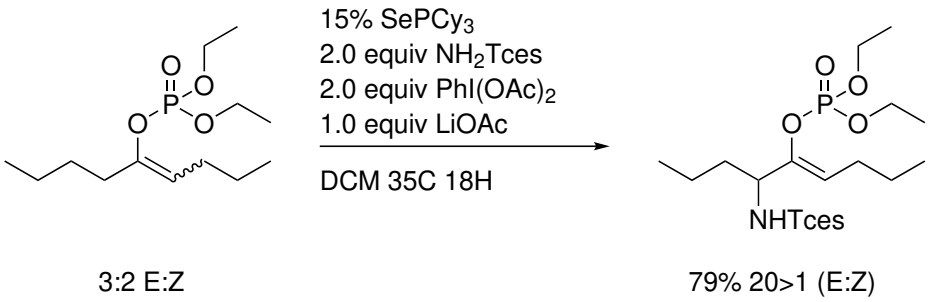
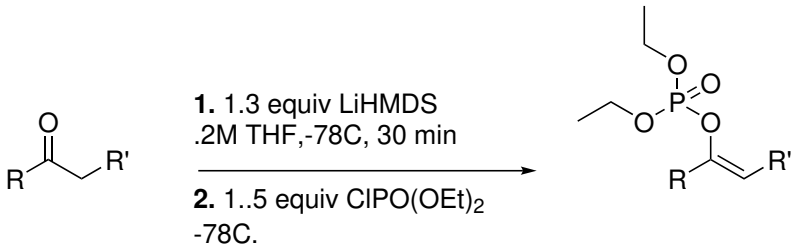


Figure 2.14: Selenium catalyzed C-H amination of enolate equivalents

Nicole, Y-Nhi, and I developed a selenium catalyzed C-H amination reaction of enloate equivalents. This reaction regioselectively aminates the C-H bond proximal to the alkenyl substituents and stereoconverges to the Z-alkene. It tolerates a variety of enolate derivatives and halides. This methodology has been demonstrated to translate control of enolization to control of C-H functionalization and is complementary to other reactions of enolate equivalents, in some cases givng C-N bond formation at positions largely inaccessible to traditional methods.

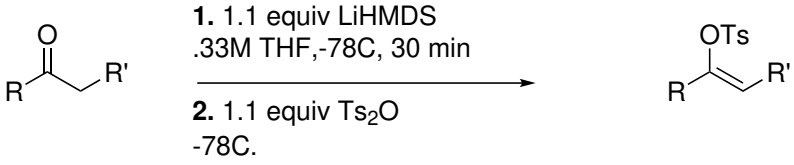
2.6 Experimental

2.6.1 Preparation of enol derivative substrates



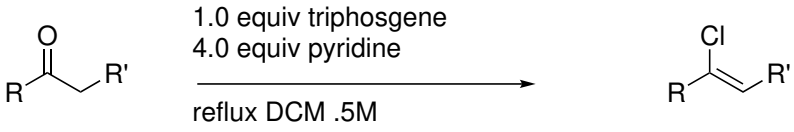
Scheme 2.5: General procedure for enol phosphates

To a stirred solution of ketone (5.0 mmol, 1.0 equiv.) in anhydrous THF at –78 ºC and under an inert atmosphere of nitrogen LiHMDS (6.5 mL of a 1 M solution in THF, 6.5 mmol, 1.3 equiv.) was added dropwise. After 30 min, diethyl chlorophosphate (1.09 mL, 7.5 mmol, 1.5 equiv.) was added dropwise and the reaction mixture was stirred at -78°C for 2 h. The reaction mixture was warmed up to room temperature for 15 min, quenched with saturated ammonium chloride solution and then extracted with ethyl acetate (3 x 25 mL). The combined organics were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography affording pure enol phosphate.



Scheme 2.6: General procedure for enol tosylates

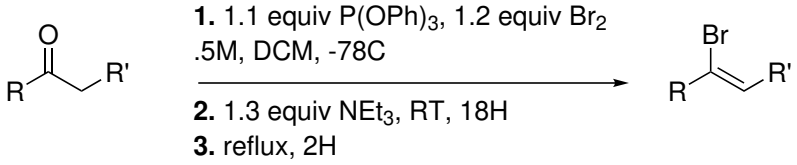
LiHMDS (11.0 ml of a 1.0 M, 11 mmol, 1.1 equiv) was dissolved in 30 mL of THF and the solution was cooled to -78°C . After 15 min, ketone (10 mmol) added slowly and stirred for 30 min at -78°C. p-Toluenesulfonic anhydride (3.6 g, 11.0 mmol, 11.0 equiv) was dissolved in 15 mL THF and added slowly. The reaction then warmed to RT and stirred over night. The reaction mixture was quenched with saturated ammonium chloride solution and then extracted with dichloromethane. The combined organics were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography affording pure enol tosylate.



Scheme 2.7: General procedure for alkenyl chlorides

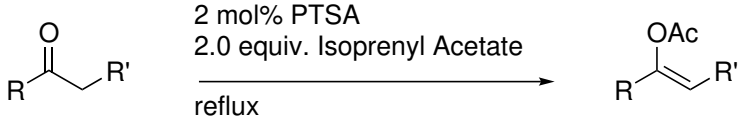
Dissolved ketone (20.0 mmol, 1.0 equiv) in anhydrous dichloromethane (0.2 M) in a

flamed dried RB with stir bar. Triphosgene (5.9 g, 20.0 mmol, 1.0 equiv) was added in one portion, followed by pyridine (6.5 ml, 80.0 mmol, 4.0 equiv). The mixture was then warmed to a gentle reflux at 35°C. Upon completion crude mixture was partition with 1.0 M HCl and dichloromethane (1:1 ratio, 20 mL). The aqueous layer was further extracted with dichloromethane (3 × 10 mL). The combined organic layers were then dried over Na_2SO_4 and concentrated under vacuum. The resulting residue was then purified by flash column chromatography.



Scheme 2.8: General procedure for alkenyl bromides

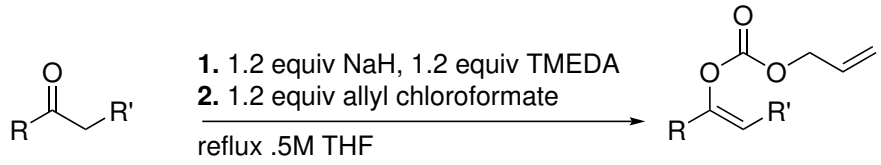
To a cold solution of triphenyl phosphite (5.7 mL, 22 mmol, 1.1 equiv) in anhydrous dichloromethane (20 mL) maintained at -78°C under N_2 flow, bromine (1.2 ml, 24.0 mmol, 1.2 equiv) was dropped in. Anhydrous trimethylamine (3.7 mL, 26.2 mmol, 1.3 equiv) and ketone (20 mmol, 1 equiv) were added to the faint orange solution. The reaction mixture was stirred for 18 h, while warming to rt, and heated to reflux for further 2 h. At this time, the reaction mixture was diluted with water (20 mL) and extracted with ether (2 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. Resulting vinyl bromides were purified by column chromatography.



Scheme 2.9: General procedure for enol acetates

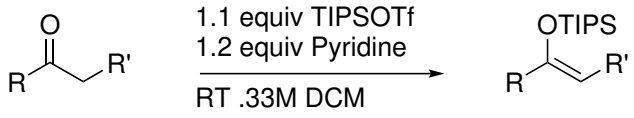
In a flame dried round bottom equipped with reflux condenser the ketone (1 equiv. 20mmol) PTSA (2 mol%, .4 mmol) and isoprenyl acetate (2 equiv, 40 mmol) were mixed

and refluxed overnight. The reaction was diluted with ethyl acetate, washed 3 times with DI water, and once with $NaHCO_3$ and finally with Brine. The organic layer was collected and dried over Na_2SO_4. The drying reagent was filtered off and solvent removed in vacuo. The crude was purified by column chromatography.



Scheme 2.10: General procedure for enol carbonates

To a clean dry 100 mL of three-neck flask with a magnetic stirring bar and a refluxing condenser was loaded 0.96 g (24 mmol) suspension of 60% sodium hydride in mineral oil and was purged with nitrogen. The sodium hydride was washed three times with anhydrous hexane under nitrogen. 3.6 mL of TMEDA and 20 mL of anhydrous THF was added into the flask and the suspension was heated in a 80°C oil bath. A solution of 2.07 mL of cyclohexanone (20 mmol) in 10 mL of THF was added slowly via a cannula over 15 min. The reaction mixture was stirred for 1 h at 80 °C and then cooled to 0°C in an ice-bath. The enolate solution was transferred through a cannula into a solution of 2.56 mL of allyl chloroformate in 10 mL of THF at 0°C. After stirring for another 15 min, 50 mL of saturated aqueous ammonium chloride was poured into the reaction flask. The mixture was extracted with diethyl ether twice; the organic layer was combined and dried over anhydrous magnesium sulfate. After filtration and concentration the residue was purified by column chromatography.

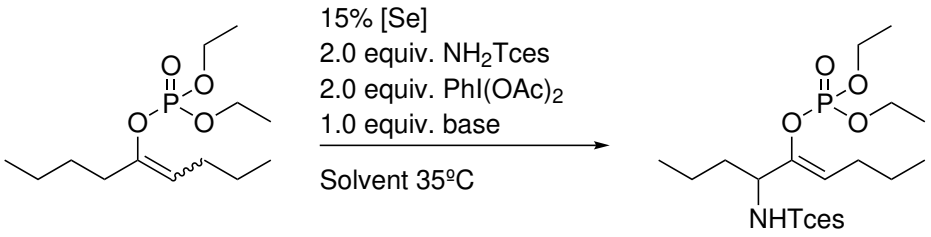


Scheme 2.11: General procedure for silyl enol ether

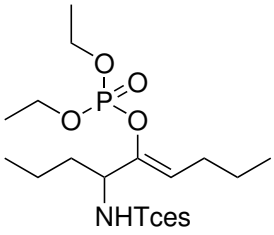
A flame-dried round bottom flask was charged with the cyclohexanone (0.52 mL, 5.0

mmol) and dichloromethane (0.33 M) at room temperature. TIPSOTf (1.1 eq.) was added slowly via syringe, followed immediately by freshly distalled pyridine (1.2 eq.) dropwise via syringe. The reaction mixture was stirred at room temperature overnight and quenched with DI water. The reaction mixture was transfered to a separatory funnel and extracted with dichloromethane. The combined organics layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude was purify the residue by column chromatography on (99:1 hexane:NEt_3).

2.6.2 ***Products***



A flame-dried borosilicate glass vial equipped with a magnetic stir bar was charged with $SePCy_3$ or SeIMe (0.03 mmol, 0.15 equiv.), amine (0.4 mmol, 2 equiv.), and substrate (0.2 mmol, 1.0 equiv.). The vial was thoroughly flushed with nitrogen and capped with a Teflon-lined screw cap. Dry dichloromethane or toluene (1 mL, 0.2 M) was added, followed by iodobenzene diacetate (0.4 mmol, 2.0 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.



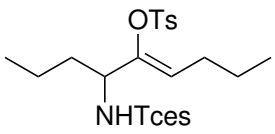
Prepared according to standard amination conditions. Purified by silica gel chromatography hexanes/ethyl acetate to afford the product liquid (62.1mg, 79%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, J = 10.0 Hz, 1H), 5.26 (t, J =7.0 Hz, 1H), 4.61 (d, J = 11.0 Hz, 1H), 4.58 (d, J = 11.0 Hz, 1H), 4.26 – 4.15 (m, 4H), 4.01 (q, J = 9.0 Hz, 1H) 2.19 – 2.11 (m, 1H) 2.07 – 2.01 (m, 1H), 1.78 – 1.66 (m, 2H), 1.41 – 1.34 (m, 10H), 0.92 (t, J = 7.5 Hz, 3H), 0.90 (t, J = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.36, 121.61, 121.56, 93.86, 78.14, 65.54, 65.49, 65.21, 65.16, 58.60, 35.03, 27.30, 22.17, 22.16, 19.23, 16.29, 16.23, 16.20, 16.15, 13.90, 13.66.

IR (thin film): 3135, 2961, 2874, 1686, 1456, 1372, 1245, 1183, 1022, 982, 847, 751, 723, 535 cm^{-1}

MS (ESI positive mode): m/z 526.0 $[M+Na]^+$



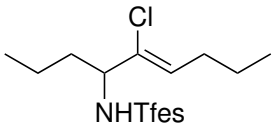
Prepared according to standard amination conditions. Purified by silica gel chromatography hexanes/ethyl acetate to afford the product liquid (54.4mg, 52%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 5.74 (d, J = 10.0 Hz, 1H), 5.51 (dd, J = 8.0, 7.0 Hz, 1H), 4.71 (d, J=11.0, 1H), 4.66 (d, J = 11.0, 1H), 4.17 (q, J = 8.5 Hz, 1H), 2.48 (s, 3H), 1.92 – 1.85 (m, 1H), 1.80 – 1.71 (m, 3H), 1.43 – 1.31 (m, 2H), 1.31 – 1.20 (m, 3H), 0 .92 (t, J = 7.5 Hz, 3H), 0.80 (t, J = 7.5 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 145.90, 144.47, 132.54, 130.06, 128.21, 126.65, 93.61, 78.29, 77.24, 57.70, 34.84, 27.83, 21.77, 18.95, 13.69, 13.50.

IR (thin film): 3324.9, 3054.1, 2962.4, 2933.2, 2874.0, 2684.8, 2410.3, 2305.8, 1920.6, 1682.4, 1597.6, 1431.8, 1367.9, 1265.3, 1180.3, 1091.3, 1047.6, 1019.0, 948.0, 914.1, 856.9, 815.1, 740.5, 631.6, 551.3 cm^{-1}

MS (ESI positive mode): m/z 521.9 $[M+H]^+$



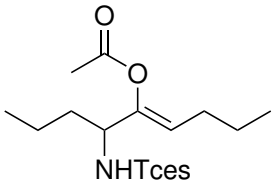
Prepared according to standard amination conditions. Purified by silica gel chromatography hexanes/ethyl acetate to afford the product liquid (60.8 mg, 90%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (t, J = 7.0 Hz, 1H), 4.83 (d, J = 8.5 Hz, 1H), 4.08 (t, J = 8.0 Hz, 1H), 4.08 (t, J = 8.0 Hz, 1H), 2.21-2.16 (m, 2H), 1.67 (q, J = 7.5 Hz, 2H), 1.46 - 1.41 (m, 2H), 1.35 – 1.30 (m, 2H), 0.94 (t, J = 7.5 Hz, 3H), 0.93 (t, J = 7.5 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 132.03, 130.50, 122.01 (q, J=278.46 Hz, 1C) 65.10 (q, J=37.8Hz, 1C), 60.89, 35.29, 30.14, 21.46, 18.89, 13.64, 13.38.

IR (thin film): 3302.9, 2963.4, 2875.6, 1711.2, 1658.3, 1429.0, 1373.0, 1283.0, 1187.0, 1105.4, 1054.6, 964.0, 889.4, 858.7, 810.0, 667.4, 614.0, 561.8 cm^{-1}

MS (ESI positive mode): m/z 360.0 $[M+Na]^+$



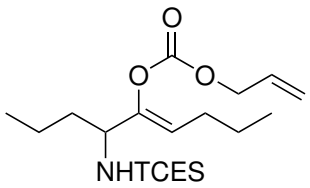
Prepared according to standard amination conditions. Purified by silica gel chromatography hexanes/ethyl acetate to afford the product liquid (48.4mg, 59%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.50 (d, J =8.0 Hz, 1H), 5.42 (t, J =7.5 Hz, 2H), 4.64 (d, J = 11.0 Hz, 1H), 4.62 (d, J = 11.0 Hz, 1H), 4.07 (q, J = 7.5Hz, 1H) 2.22 (s, 3H) 1.97 – 1.86 (m, 2H), 1.66 – 1.54 (m, 2H), 1.43 – 1.35 (m, 2H), 0.93 (t, J = 7.0 Hz, 3H), 0.89 (t, J = 7.5 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.25, 145.09, 122.38, 93.72, 78.34, 58.22, 34.92, 27.80, 21.90, 20.65, 19.12, 13.93, 13.74.

IR (thin film): 3296, 2961, 2934, 2874, 1760, 1738, 1436, 1368, 1207, 1178, 1089, 1017, 943, 851, 757, 724, 579 cm^{-1}

MS (ESI positive mode): m/z 432.0 $[M+Na]^+$



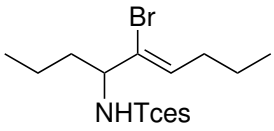
Prepared according to standard amination conditions. Purified by silica gel chromatography hexanes/ethyl acetate to afford the product liquid (45.3 mg, 50%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.99-5.91 (m, 1H), 5.54 (d, J = 8.0 Hz 1H), 5.43 (t, J = 7.5 Hz 1H), 5.40 (dq, J = 17.0, 1.5 Hz 1H), 5.32 (dq, J = 10.5, 1.0 Hz 1H), 4.68 (dt, J = 5.5, 1.5 Hz 2H), 4.64 (d, J = 10.5 1H), 4.61 (d, J = 10.5 1H) 2.03-1.92 (m, 2H), 1.67-1.61 (m, 2H), 1.43-1.35 (m, 4H), 0.92 (t, J = 7.0 Hz, 3H), 0.89 (t, J = 7.5 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.75, 145.08, 130.97, 122.63, 119.86, 93.69, 78.35, 77.41, 77.16, 76.90, 69.58, 58.04, 34.82, 27.45, 21.84, 19.08, 13.86, 13.66.

IR (thin film): 2963.98, 2254.39, 2050.51, 2036.20, 1982.05, 1752.14, 1426.22, 1368.35, 1229.66, 1182.60, 1090.03, 1049.26, 1016.75, 990.34, 947.54, 904.32, 855.14, 726.09, 649.98, 571.05, 562.96, 536.53, 518.44, 506.77, 499.78, 497.83, 494.31, 482.96, 480.42, 477.70, 474.34, 471.76, 468.82, 465.52, 461.30, 458.00, 455.73 cm^{-1}

MS (ESI positive mode): m/z 475.9 $[M+Na]^+$



Prepared according to standard amination conditions. Purified by silica gel chromatography hexanes/ethyl acetate to afford the product liquid (79.4mg, 90%).

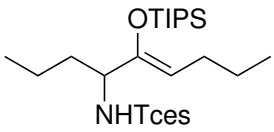
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.04 (t, J = 7.0 Hz, 1H), 5.07 (d, J = 8.5 Hz, 1H), 4.59 (s, 2H), 4.04 (q, J = 8.0 Hz, 1H), 2.22 – 2.10 (m, 3H), 1.66 (q, J = 8.0 Hz, 2H), 1.50 – 1.23

(m, 4H), 0.93 (t, J = 7.5, 3H), 0.92 (t, J = 7.5, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 133.34, 127.39, 93.44, 78.34, 61.86, 36.36, 32.85, 21.42, 18.86, 13.71, 13.43.

IR (thin film): 4252.3, 4195.7, 3942.5, 3691.0, 3369.0, 3053.7, 2986.4, 2916.6, 2848.5, 2685.0, 2410.5, 2304.6, 1576.0, 1541.7, 1421.6, 1384.0, 1264.6, 1184.6, 1156.6, 895.7 cm^{-1}

MS (ESI positive mode): m/z 430.3 $[M+NH]^+$



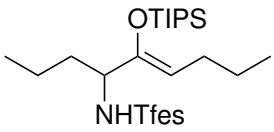
Prepared according to standard amination conditions. Purified by silica gel chromatography hexanes/ethyl acetate to afford the product liquid (96.6mg, 92%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.77 (d, J =8.5 Hz, 1H), 4.62 (t, J =7.5 Hz, 1H), 4.60 (s, 2H), 3.85 (q, J = 7.0Hz, 1H) 2.07-1.94 (m, 2H) 1.80 – 1.73 (m, 1H), 1.65 – 1.58 (m, 1H), 1.48 – 1.33 (m, 4H), 1.25 – 1.20 (m, 3H), 1.12 – 1.07 (m, 18H), 0.93 (t, J = 7.5 Hz, 3H), 0.90 (t, J = 7.5 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.76, 107.97, 93.68, 78.24, 60.12, 36.37, 27.63, 23.06, 19.05, 18.29, 18.25, 14.03, 13.91, 13.86.

IR (thin film): 3300, 2959, 2865, 1714, 1463, 1376, 1187, 1108, 648, 570 cm^{-1}

MS (ESI positive mode): m/z 546.1 $[M+Na]^+$



Prepared according to standard amination conditions. Purified by silica gel chromatography hexanes/ethyl acetate to afford the product liquid (96.6mg, 87%)

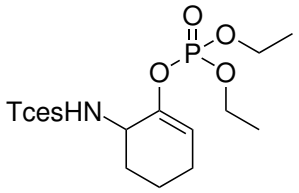
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.81 (d, J = 8.5 Hz, 1H), 4.58 (t, J = 7.5 Hz, 1H), 4.36 (q,

J = 8.0 Hz 2H), 3.79 (q, J = 7.0Hz, 1H) 2.07-1.93 (m, 2H) 1.78 – 1.69 (m, 1H), 1.63 – 1.54 (m, 1H), 1.45 – 1.29 (m, 4H), 1.22 – 1.15 (m, 3H), 1.13 – 1.07 (m, 18H), 0.93 (t, J = 7.0 Hz, 3H), 0.90 (t, J = 7.5 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.73, 107.93, 65.16, 64.86, 60.16, 36.32, 27.58, 22.98, 19.02, 18.19, 18.17, 17.82, 13.94, 13.89, 13.76, 12.43.

IR (thin film): 3309, 2956, 2870, 1708, 1672, 1462, 1421, 1374, 1283, 1177, 1057, 963, 739, 678, 560. cm^{-1}

MS (ESI positive mode): m/z 498.1 $[M+Na]^+$



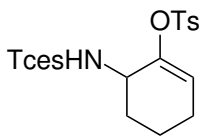
Prepared according to standard amination conditions. Purified by silica gel chromatography hexanes/ethyl acetate to afford the product as a white solid (85.6 mg, 93%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.67(d, J = 4.5 Hz, 1H), 5.80 - 5.77 (m, 1H), 4.67 (d, J = 11.0 Hz 1H), 4.63 (d, J = 11.0 Hz 1H), 4.24 -4.15 (m, 4H), 4.13-4.12 (m, 1H), 2.20-2.14 (m, 2H), 2.09-2.05 (m, 1H), 1.84-1.77 (m, 1H), 1.65-1.60 (m, 2H), 1.38-1.34 (m, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.61, 143.54, 118.93, 118.89, 93.75, 78.30, 65.20, 65.15, 65.11, 52.08, 52.06, 29.67, 23.86, 17.29, 16.26, 16.21, 16.19, 16.13.

IR (thin film): 3112, 2986, 2939, 1680, 1453, 1371, 1253, 1181, 1025, 984, 915, 846, 749, 721, 533 cm^{-1}

MS (ESI positive mode): m/z 434 $[M+Na]^+$



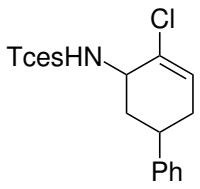
Prepared according to standard amination conditions. Purified by silica gel chromatography hexanes/ethyl acetate to afford the product as a white solid (71.8 mg, 75%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, J = 9.5 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 5.75 (t, J = 4.0 Hz, 1H), 5.40 (d, J = 6.5 Hz, 1 H), 4.69 (d, J = 10.0 Hz, 1H), 4.65 (d, J = 10.0 Hz, 1H), 4.06 (q, J = 5.0 Hz, 1H), 2.40 (s, 3H), 2.19-2.11 (m, 2H), 2.07-2.02 (m, 1H), 1.85-1.78 (m, 1H), 1.68-1.53 (m, 2H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 145.85, 143.47, 132.67, 130.04, 128.37, 123.90, 93.51, 78.39, 51.53, 29.89, 24.03, 21.77, 16.95.

IR (thin film): 3315.0, 3056.0, 2918.0, 2306.1, 1674.6, 1598.3, 1541.5, 1447.4, 1373.0, 1265.5, 1191.8, 1179.1, 1090.4, 1070.6, 1005.5, 944.0, 875.5, 851.4, 815.0, 739.0, 704.7, 667.7, 610.1, 537.1 cm^{-1}

MS (ESI positive mode): m/z 477 $[M+Na]^+$



Prepared according to standard amination conditions. Purified by silica gel chromatography hexanes/ethyl acetate to afford the product as a white solid (68.7 mg, 82%) Mixture of diastereomers: 1:1.4.

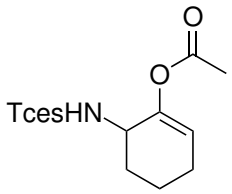
^{1}H NMR (500 MHz, C_6D_6) δ 7.22 – 7.04 (m, 3H) major + minor, 6.87 (tt, J = 6.4, 1.3 Hz, 2H) major + minor, 5.54 (td, , J = 4.5, 1.5, 0.42H) minor, 5.48 (dd, , J = 5.5, 2.5, 0.57H) major, 4.52 – 4.37 (m, 2H) major + minor, 4.22 (s, .56H) major, 4.06 (s, .43H) minor, 4.00 (s, .57H) major, 3.90 (s, .37H) minor, 2.33 – 2.18 (m, 2H)major + minor, 1.80 – 1.68 (m, 1.46H) major + minor, 1.61 – 1.53 (m, 0.62H) major, 1.37 (td, J = 14.0, 4.4 Hz, 1H)major + minor.

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.46, 143.25, 131.19, 130.20, 129.73, 128.88, 128.75, 128.61, 127.04, 126.93, 126.90, 126.72, 93.35, 78.38, 55.94, 55.81, 38.94, 38.28, 36.91, 34.14,

33.81, 33.45

IR (thin film): 4252.2, 4195.4, 3943.3, 3689.5, 3371.0, 3053.5, 2986.2, 2916.9, 2848.4, 2684.7, 2409.8, 2304.8, 1549.4, 1421.5, 1384.0, 1266.4, 1181.7, 1021.5, 895.8, 738.5 cm^{-1}

MS (ESI negative mode): m/z 403.2 $[M\text{-}Na]^+$



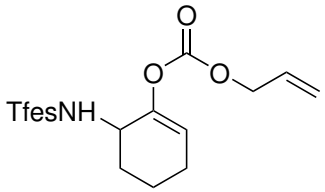
Prepared according to standard amination conditions. Purified by silica gel chromatography hexanes/ethyl acetate to afford the product as a clear liquid (72.4 mg, 99%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65-563(m, 1H), 5.40 (s, 1H), 4.62 (d, J = 11.0 Hz 1H), 4.59 (d, J = 11.0 Hz 1H), 4.13 (bs, 1H), 2.25-2.07 (m, 3H), 2.18 (s, 3H), 1.92-1.86 (m, 1H), 1.72-1.60 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.33, 143.90, 122.19, 93.62, 78.14, 52.41, 37.97, 31.90, 31.23, 27.47, 25.43, 21.07

IR (thin film): 3284, 2943, 1744, 1686, 1447, 1368, 1214, 1182, 1124, 1065, 1003, 940, 849, 753, 721, 597, 532 cm^{-1}

MS (ESI positive mode): m/z 387.9 $[M+Na]^+$



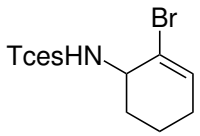
Prepared according to standard amination conditions. Purified by silica gel chromatography hexanes/ethyl acetate to afford the product as a clear liquid (90%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.97-5.85 (m, 1H), 5.80-5.78 (m, 1H), 5.39 (dq, J = 17.0,

1.5 Hz 1H), 5.34-5.29 (m, 2H), 4.65 (d, J = 5.5 Hz, 2H), 4.64 (d, J = 6.0, 1H), 4.40 (q, J = 8.0, 2H) 4.15 (m, 1H), 2.25-2.02 (m, 3H), 1.92-1.87 (m, 1H), 1.75-1. 65 (m, 2H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.44, 144.39, 130.91, 123.33, 122.03, 121.12, 119.95, 69.62, 65.65, 65.35, 65.04, 64.74, 51.47, 30.18, 23.71, 17.28.

MS (ESI positive mode): m/z 360.1 $[M+H]^+$



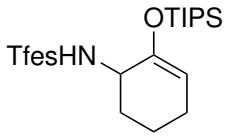
Prepared according to standard amination conditions. Purified by silica gel chromatography hexanes/ethyl acetate to afford the product as a clear liquid (71%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.34 (t, J = 4.5Hz, 1H), 4.97 (d, J = 5.0 Hz 1H), 4.76 (d, J = 11.0 Hz, 1H), 4.69 (d, J = 11.0 Hz, 1H), 4.18-4.16 (m, 1H), 2.23-2.05 (m, 3H), 2.00-1.93 (m, 1H), 1.76-1.70 (m, 1H), 1.65-1.57 (m, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.27, 119.35, 93.49, 78.50, 56.63, 30.84, 27.57, 16.73.

IR (thin film): 3302, 2945, 2868, 1440, 1367, 1182, 1087, 999, 951, 917, 837, 755, 735, 707. cm^{-1}

MS (ESI positive mode): m/z 407.8 $[M+Na]^+$

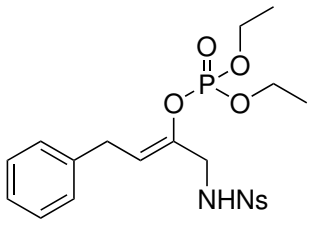


Prepared according to standard amination conditions. Purified by silica gel chromatography hexanes/ethyl acetate to afford the product as a clear liquid (49%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.04 (t, J = 3.5 Hz, 1H), 4.98 (d, J = 4.5 Hz, 1H), 4.21-4.09 (m, 2H, Minor), 4.07 (q, J = 4.5 Hz, 1H), 2.32-2.30 (m, 2H), 2.07-2.02 (m, 2H), 1.83-1.77 (m, 1H), 1.66-1.58 (m, 2H), 1.86-1.82 (m, 1H), 1.27-1.21(m, 6H), 1.10-1.08 (m, 18H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.79, 117.82, 115.61, 101.86, 59.98, 59.68, 59.38, 59.07, 48.68, 24.08, 18.10, 12.87, 12.52, 7.16.

MS (ESI positive mode): m/z 353.3 $[M+Na]^+$



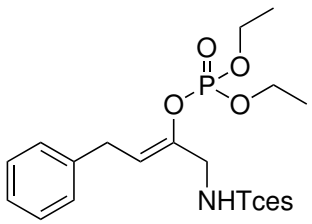
Prepared according to standard amination conditions. Purified by silica gel chromatography hexanes/ethyl acetate to afford the product as a clear liquid (92%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, J = 8.5 Hz, 2H), 8.00 (d, J = 8.5 Hz, 1H), 7.25 (t, J = 8.0 Hz, 2H), 7.20 (t, J = 7.0 Hz, 1H), 4.05 (d, J = 7.0 Hz, 2H), 6.59 (t, J = 6.0 Hz, 1H), 5.20 (t, J = 7.5 Hz, 1H) 4.16 – 4.09 (m, 4H), 3.88 (d, J = 7.0 Hz, 2H), 3.30 (d, J = 7.5 Hz, 2H), 6.59 (t, J = 7.5 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.93, 146.71, 142.38, 142.32, 138.85, 128.70, 128.37, 128.28, 126.62, 124.19, 118.28, 118.21, 65.20, 65.15, 60.51, 46.31, 31.27, 21.15, 16.18, 16.13, 14.30.

IR (thin film): 3106, 2995, 1695, 1607, 1530, 1349, 1311, 1259, 1164, 1094, 1026, 905, 730. cm^{-1}

MS (ESI positive mode): m/z 485.3 $[M+H]^+$



Prepared according to standard amination conditions. Purified by silica gel chromatog-

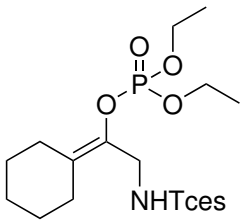
raphy hexanes/ethyl acetate to afford the product as a clear liquid (99%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (m, J = 8.5 Hz, 2H), 7.24-7.17 (m, 3H), 6.94 (t, J = 6.0 Hz, 1H), 5.43 (t, J = 7.5 Hz, 1H), 4.61 (s, 2H), 4.25 – 4.15 (m, 4H), 3.98 (d, J = 6.0 Hz, 2H), 3.48 (d, J = 7.0 Hz, 2H), 1.36 (t, J = 7.5 Hz, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.55, 142.49, 139.05, 128.74, 128.42, 126.56, 119.16, 119.10, 93.70, 78.29, 65.34, 65.29, 47.02, 31.48, 16.23, 16.17.

IR (thin film): cm^{-1}

MS (ESI positive mode): m/z 510.1 $[M+H]^+$



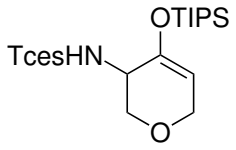
Prepared according to standard amination conditions. Purified by silica gel chromatography hexanes/ethyl acetate to afford the product as a clear liquid (80%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (t, J = 6.0 Hz, 1H), 4.62 (s, 2H), 4.22 – 4.12 (m, 4H), 4.03 (d, J = 6.0 Hz, 2H), 2.24-2.22 (m, 4H) 1.59-1.53 (m, 6H), 1.36 (t, J = 7.0 Hz, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 133.98, 133.91, 132.60, 132.54, 93.80, 78.29, 65.02, 64.97, 43.40, 29.60, 27.93, 27.91, 27.60, 27.59, 27.08, 26.25, 16.28, 16.22.

IR (thin film): 3121, 2983, 2931, 2856, 1447, 1374, 1246, 1181, 1026, 988, 846, 751, 722, 535 cm^{-1}

MS (ESI positive mode): m/z 510.0 $[M+Na]^+$



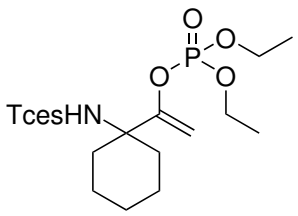
Prepared according to standard amination conditions. Purified by silica gel chromatography hexanes/ethyl acetate to afford the product as a clear liquid (82%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.18 (d, J = 7.5Hz, 1H), 4.99 (m, 1H), 4.66 (s, 2H), 4.21 - 4.06 (m, 3H), 3.87-3.86 (m, 1H) 3.77 (dd, J = 12.0, 2.5 Hz), 1.25-1.18 (m, 3H), 1.11-1.09 (m, 18H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 145.51, 104.85, 93.74, 78.49, 77.52, 77.26, 77.01, 69.35, 64.83, 53.50, 18.20, 12.86.

IR (thin film): 2948, 2868, 1672, 1463, 1366, 1217, 1181, 1104, 991, 850, 823, 649, 536. cm^{-1}

MS (ESI positive mode): m/z 504.3 $[M+Na]^+$



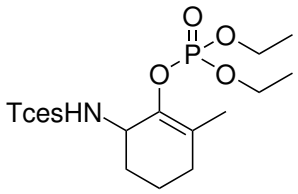
Prepared according to standard amination conditions. Purified by silica gel chromatography hexanes/ethyl acetate to afford the product as a clear liquid (92%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72(s, 1H), 5.18 - 5.17 (m, 1H), 4.91 - 4.90 (m, 1H), 4.62 (s, 1H), 4.25 -4.14 (m, 4H), 2.09-2.05 (m, 2H), 1.88-1.86 (m, 2H), 1.69-1.615 (m, 2H), 1.56-1.47 (m, 3H), 1.40-1.33 (m, 7H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.69, 99.52, 93.81, 78.45, 76.91, 64.94, 64.90, 61.51, 61.46, 33.45, 25.32, 21.91, 16.24, 16.19.

IR (thin film): 3109, 2938, 1720, 1651, 1461, 1369, 1260, 1234, 1180, 1145, 1009, 928, 848, 746, 722, 584 cm^{-1}

MS (ESI positive mode): m/z 510.0 $[M+Na]^+$



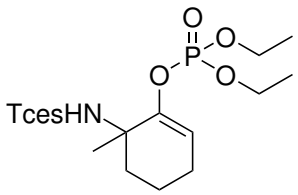
Prepared according to standard amination conditions. Purified by silica gel chromatography hexanes/ethyl acetate to afford the product as a clear liquid (70%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95(d, J = 2.0 Hz, 1H), 4.70 (d, J = 6.0 Hz 1H), 4.62 (d, J = 6.0 Hz 1H), 4.25-4.15 (m, 5H), 2.86 -2.49 (m, 1H), 2.08-2.03 (m, 2H), 1.74 (s, 3H), 1.69-1.60 (m, 3H), 1.37 (t, J = 7.0 Hz 3H), 1.36 (t, J = 7.0 Hz 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.93, 137.87, 128.36, 128.32, 93.80, 78.33, 65.08, 65.03, 64.90, 64.85, 52.99, 30.88, 30.87, 29.43, 17.31, 17.27, 17.26, 16.24, 16.18, 16.12.

IR (thin film): 3114.04, 2932.86, 1695.02, 1450.11, 1370.52, 1264.77, 1173.75, 1086.63, 1029.03, 974.10, 849.11, 732.97 cm^{-1}

MS (ESI negative mode): m/z 474.0 $[M-H]^-$



Prepared according to standard amination conditions. Purified by silica gel chromatography hexanes/ethyl acetate to afford the product as a clear liquid (84%)

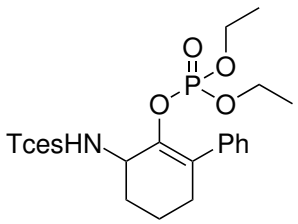
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.84 (s, 1H), 5.69-5.68 (m, 1H), 4.66 (d, J = 10.5 Hz 1H), 4.63 (d, J = 12.0 Hz 1H), 4.25-4.16 (m, 4H), 2.58 -2.55 (m, 1H), 2.19-2.04 (m, 2H), 1.81-1.74 (m, 1H), 1.63 (s, 3H), 1.60 (m, 2H), 1.38 (t, J = 7.5 Hz 3H), 1.35 (t, J = 5.5 Hz 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.46, 147.39, 117.38, 117.34, 93.82, 78.04, 65.26, 65.21, 65.10, 65.05, 58.63, 58.61, 35.76, 24.43, 24.42, 24.05, 17.99, 16.26, 16.22, 16.21, 16.17.

IR (thin film): 3750.19, 3726.30, 3689.46, 3154.11, 2987.80, 2940.82, 2205.00, 2175.66,

2043.69, 2019.03, 2001.58, 1979.37, 1674.53, 1626.00, 1565.70, 1453.95, 1371.20, 1350.56, 1256.89, 1177.53, 1147.68, 1121.01, 1093.21, 1032.67, 986.56, 934.38, 906.70, 850.97, 791.43, 779.97, 752.65, 740.05, 725.64, 669.73, 617.69, 613.54, 602.95, 538.54, 521.60, 516.70, 505.93, 502.50 cm^{-1}

MS (ESI positive mode): m/z 475.6 $[M+H]^+$



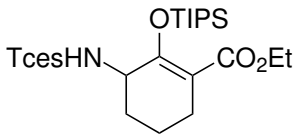
Prepared according to standard amination conditions. Purified by silica gel chromatography hexanes/ethyl acetate to afford the product as a clear liquid (70%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 -7.27 (m, 5H), 7.13 (d, J = 2.0 Hz, 1H), 4.72 (d, J = 10.5Hz, 1H), 4.66 (d, J = 10.5Hz, 1H), 4.40 (m, 1H), 4.07-3.96 (m, 2H), 3.56-3.40 (m, 2H), 2.54-2.51 (m, 1H), 2.39-2.49 (m, 2H), 1.87-1.76 (m, 2H), 1.26 (t, J = 7.0 Hz, 3H), 0.94 (t, J = 7.0 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.44, 144.39, 130.91, 123.33, 122.03, 121.12, 119.95, 69.62, 65.65, 65.35, 65.04, 64.74, 51.47, 30.18, 23.71, 17.28.

IR (thin film): 2941.90, 2253.44, 1446.33, 1371.90, 1257.24, 1180.03, 1034.58, 967.45, 905.07, 855.43, 725.67 cm^{-1}

MS (ESI negative mode): m/z 535.9 $[M-H]^-$

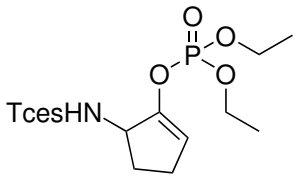


Prepared according to standard amination conditions. Purified by silica gel chromatography hexanes/ethyl acetate to afford the product as a clear liquid (77%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.18 (d, , J = 5.0 Hz, 1H), 4.46-4.36 (m, 2H), 4.21-4.09 (m, 2H, Minor), 4.07 (q, J = 4.5 Hz, 1H), 2.32-2.30 (m, 2H), 2.07-2.02 (m, 2H), 1.83-1.77 (m, 1H), 1.66-1.58 (m, 2H), 1.86-1.82 (m, 1H), 1.27-1.21(m, 6H), 1.10-1.08 (m, 18H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.52, 150.81, 123.34, 121.13, 114.74, 65.54, 65.24, 64.94, 64.64, 60.51, 55.45, 28.46, 25.73, 18.08, 18.01, 17.02, 14.36, 13.77.

MS (ESI positive mode): m/z 575.0 $[M+Na]^+$



Prepared according to standard amination conditions. Purified by silica gel chromatography hexanes/ethyl acetate to afford the product as a clear liquid (50%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.53(d, J = 7.5 Hz, 1H), 5.56 (m, 1H), 4.46 -4.39 (m, 3H), 4.23-4.15 (m, 4H), 2.45-2.38 (m, 2H), 2.31-2.24 (m, 1H), 1.97-1.91 (m, 1H), 1.36 (t, J = 7.0 Hz, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.33, 146.26, 125.68, 123.47, 121.26, 119.06, 116.22, 116.19, 65.45, 65.31, 65.30, 65.26, 65.25, 65.15, 64.85, 64.55, 58.71, 58.68, 30.05, 25.93, 16.17, 16.11, 16.07, 16.02.

IR (thin film): 3112, 2986, 2939, 1680, 1453, 1371, 1253, 1181, 1025, 984, 915, 846, 749, 721, 533 cm^{-1}

MS (ESI positive mode): m/z 434.0 $[M+Na]^+$

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