C-H Functionalisation of Alkenes via Organoselenium Catalysis

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Abstract

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C-H functionalisation of simple, abundant, and inexpensive alkenes is a privileged strategy for rapid construction of complex molecular architectures in organic synthesis and industrial chemical processes. Although this area is dominated by transition-metal catalysis, organoselenium catalysis has emerged as a powerful alternative framework for oxidative functionalisation of alkenes. This dissertation introduces phosphine/NHC selenides as a novel class of catalysts which enable controlled reactivity and selectivity of reactions catalysed by these selenides through wise choice of phosphine/NHC ligands on selenium. The power of these catalysts is manifested in the context of C-H amination and C-H alkylation of unactivated alkenes through mechanistically different reactivity modes.

An aza-Heck reaction of unactivated terminal alkenes catalysed by phosphine selenides was developed via seleniranium catalysis. The reaction proceeds via an *anti*-addition/*syn*-elimination mechanism. Although it has been documented that a Se-Se bond is essential to catalytic reactivity, this work has demonstrated that monoselenides are also effective catalysts. Proper choice of phosphine ligands allows for improved regioselectivity of the reaction and isolation of desired aza-Heck products.

A diastereoconvergent synthesis of *anti*-1,2-amino alcohols bearing N-containing quaternary stereocentres from homoallylic alcohol derivatives catalysed by phosphine/NHC selenides was disclosed. Unlike the aza-Heck reaction, this transformation proceeds via a sequence of ene reaction and [2,3]-sigmatropic rearrangement. The destruction of allylic stereocentre in the ene reaction enables diastereoconvergence. The *anti* diastereoselectivity is controlled by an unexpected inside alkoxy effect in the [2,3]-sigmatropic rearrangement. This system was successfully expanded to allylic alcohol derivatives bearing internal *Z* alkene to access *syn*-1,4-amino alcohols. This work is the first example of synthesis of *anti*-1,2-amino alcohols and *syn*-1,4-amino alcohols via direct C-H amination.

Preliminary success was achieved in allylic alkylation using NHC selenides. Allylic alkylation product was obtained in moderate yield using methyl cyanoacetate as nucleophile. Mechanistic studies revealed the presence of a background reaction among terminal oxidant, nucleophile, and selenium catalyst. Further optimisation is ongoing in our laboratory to improve the reaction performance.

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Å	Angstrom
Ac	Acetyl
Ar	Aryl
Bn	Benzyl
Bu	Butyl
Bz	Benzoyl
Cy	Cyclohexyl
DCE	Dichloroethane
DCM	Dichloromethane
DFT	Density functional theory
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
d.r.	Diastereomeric ratio
equiv	Equivalents
ESI MS	Electrospray Ionization Mass Spectrometry
Et	Ethyl
FTIR	Fourier transform infrared spectroscopy
GC-MS	Gas Chromatography-Mass Spectrometry
Hr	hour
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
IMe	1,3-Di-methylimidazole-2-ylidine
*i*Pr	*iso*-Propyl
IPr	1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidine
I*t*Bu	1,3-Di-tert-butylimidazol-2-ylidine
KIE	Kinetic isotope effect

L	Ligand
Me	Methyl
MHz	Megahertz
mmol	millimole
mp	melting point
NFBS	*N*-Fluorobenzenesulfonamide
NHC	*N*-Heterocyclic carbene
NMR	Nuclear Magnetic Resonance

Abbreviations for NMR Splitting:

s	singlet
d	doublet
t	triplet
q	quartet
quin	quintet
m	multiplet
br	broad

NOE	Nuclear Overhauser Effect
NOSEY	Nuclear Overhauser Effect Spectroscopy
n-Pr	n-propyl
Np	Naphthyl
Ns	4-Nitrobenzenesulfonyl
Nu, NuH	Nucleophile
o-Tol	2-methyl(phenyl)
PG	Protecting group
Ph	Phenyl
Piv	Pivaloyl
ppm	parts per million
Py	Pyridine
rt	room temperature
SM	Starting material

TBAF	Tetra-n-butylammonium fluoride
TBDPS	tert-butyldiphenylsilyl
t-Bu	tert-Butyl
TEA	Triethylamine
TfO	Trifluoromethanesulfonate
TLC	Thin Layer Chromatography
TM	Transition Metal
Tol, p-Tol	4-methyl(phenyl)
Troc	2,2,2-Trichloroethoxycarbonyl
Trt	triphenylmethyl
Ts	p-Toluenesulfonyl

ACKNOWLEDGEMENTS

First, I would like to thank my supervisor, Prof. Forrest E. Michael, for his dedication and guidance to help me succeed in my graduate career. His genuine passion for science truly inspired me along the way and his incredible knowledge of organic chemistry has always been a great source of ideas. Thank you for giving me the freedom to tackle problems that interest me, bringing me back to the big picture, and keeping me on track to success.

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I would also like to offer my appreciation to previous supervisors who sparked my interest and led me to the world of chemistry including Prof. Yan Zhang, Prof. Matthew Todd, and Prof. Alice Williamson.

Of course, I must express my greatest gratitude to my family for their love and support. I would not have been here today without them.

Chapter 1. REGIOSELECTIVE AZA-HECK REACTION OF TERMINAL ALKENES CATALYSED BY PHOSPHINE SELENIDES

Portions of this chapter as well as figures, schemes, and tables were adapted or reproduced from the following manuscript, with permission from Zheng, T.; Tabor, J. R.; Stein, Z. L.; Michael, F. E. Regioselective Metal-Free Aza-Heck Reactions of Terminal Alkenes Catalyzed by Phosphine Selenides. *Org. Lett.* **2018**, *20* (21), 6975–6978.

1.1 INTRODUCTION

Nitrogen-containing molecules are at the centre of drug discovery. In this regard, the aza-Heck[1] reaction and aza-Wacker[2] reaction are powerful methods for the construction of C-N bonds from alkenes. Most of these reactions are realised via transition metal catalysis, with predominant use of Pd catalysts. These reactions proceed via aminopalladation of an alkene, followed by β-hydride elimination. As a result, one of the challenges in the development of aza-Heck and aza-Wacker reaction is to control the regioselectivity of these two steps. The combination of the two steps can give up to four isomeric products (Figure 1.1).

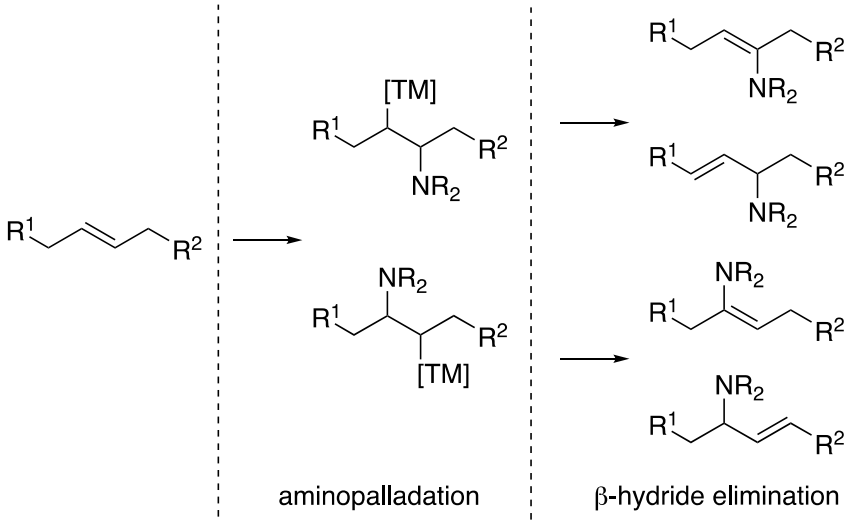
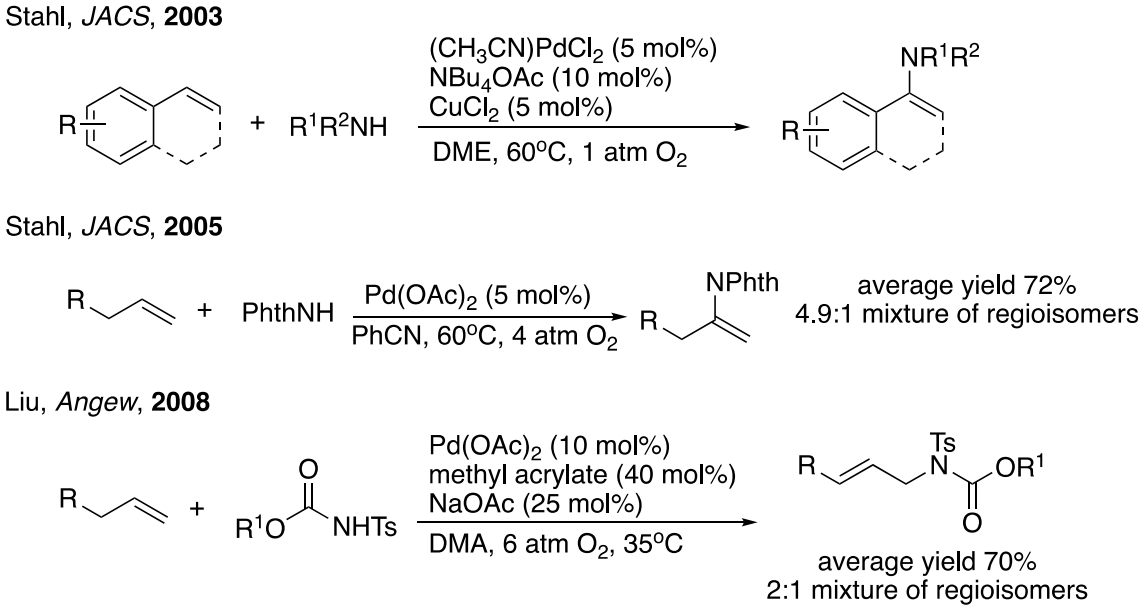


Figure 1.1 Conceptual Mechanism of the Aza-Heck Reaction

One way to solve this regioselectivity issue is to deliver the nitrogen nucleophile intramolecularly by tethering the nitrogen group to the substrates. By employing this strategy, many intramolecular reactions are reported with excellent regioselectivity, allowing for exclusive formation of one of the possible products. These intramolecular transformations are primarily applied to synthesis of N-containing heterocycles[3,4]. However, substrate scopes of these reactions lack generality and thus intermolecular variants of such reactions are highly desirable. Unfortunately, simply applying these protocols intermolecularly gives rise to severe regioselectivity issues (Scheme 1.1). In 2003 and 2005, Stahl and co-workers reported selective formation of internal aza-Heck products for styrene[5] and unactivated terminal alkenes[6,7], respectively. In 2008, Liu and co-workers disclosed selective formation of allyl regioisomers[8]. However, not only does poor regioselectivity render the reaction low yielding, but also makes the isolation of the pure desired regioisomer impossible due to similar polarity.

Scheme 1.1 Previous Intermolecular Aza-Heck Reactions



In recent years, organoselenium catalysis has emerged as a promising alternative to transition metal catalysis. Organoselenium compounds have been demonstrated to be effective catalysts for oxidative functionalisation of alkenes[9–15]. These reactions occur via an addition-elimination sequence conceptually analogous to that of transition-metal catalysed reactions (Figure 1.2). The reaction initiates with the oxidative generation of an electrophilic selenium species which interacts with an alkene to generate a seleniranium ion intermediate (Figure 1.2, Int-I). External or internal nucleophiles can be incorporated via nucleophilic attack on the seleniranium ion to give Int-II. Elimination or displacement of the selenium moiety with another nucleophile finally closes the catalytic cycle and releases the product.

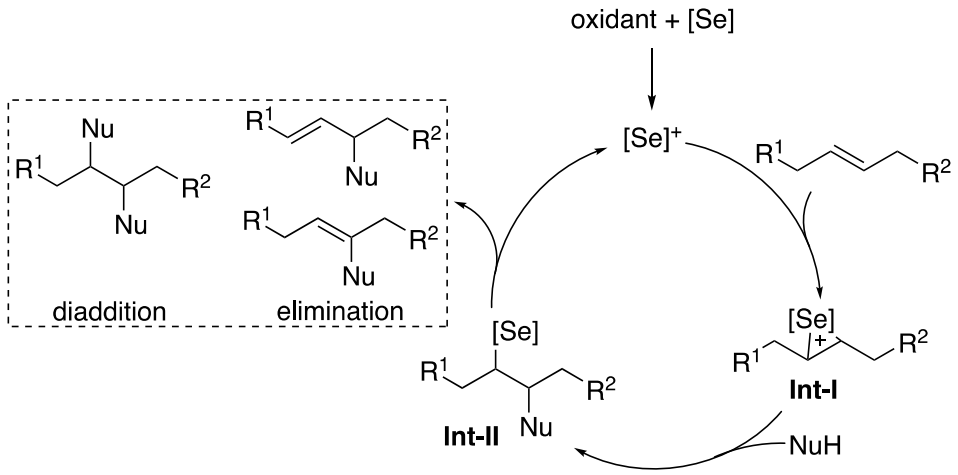
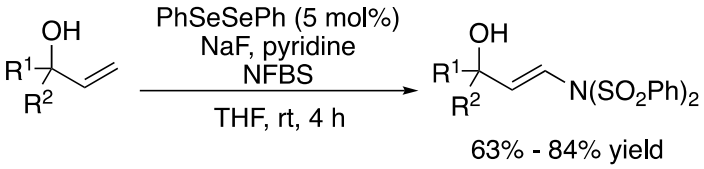


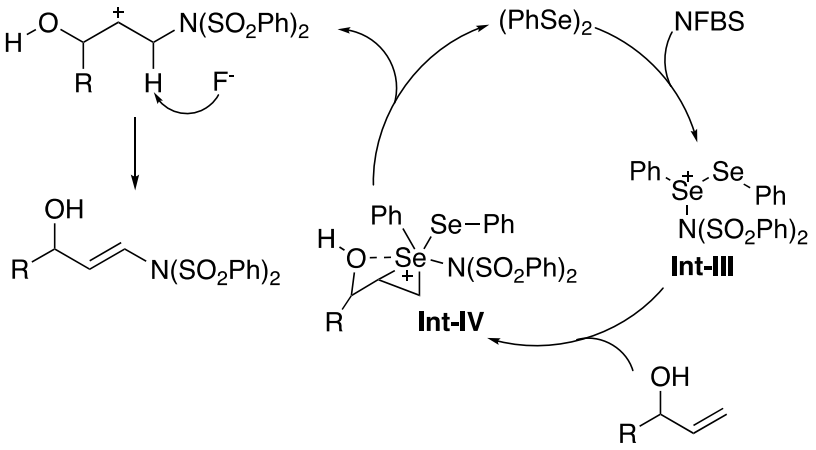
Figure 1.2 Mechanism of Oxidative Functionalisation of Alkenes via Organoselenium Catalysis

Both intramolecular and intermolecular aza-Heck reactions have been developed using organoselenium catalysis. In 2015, Breder[16] and Zhao[17] reported synthesis of indoles via intramolecular aza-Heck reactions catalysed by diphenyl diselenide. In 2013, Breder and co-workers reported a direct vinylic C-H amination of alkenes using diphenyl diselenide as the catalyst under oxidative conditions[18]. Although the nitrogen group is delivered intermolecularly, the substrate scope is limited to styrene and cyclic alkenes to avoid regioselectivity issues (Scheme 1.2). In 2015, the Zhao group achieved a vinylic amination of allylic alcohols catalysed by diphenyl diselenide[19]. They proposed that the regioselectivity is probably controlled through stabilisation of the intermediate (Scheme 1.2, Int-II) by the lone pair of the hydroxyl group at the allylic position. Unfortunately, when these reactions are applied to unactivated terminal alkene 1a, the regioselectivity issue emerges again, leading to a mixture of inseparable regioisomers (Table 1.1).

Scheme 1.2 Vinylic Amination of Alkenes via Oxidative Organoselenium Catalysis

Zhao, *Org. Lett.* , **2015**





Breder, *Angew. Chem. Int. Ed*, **2013**

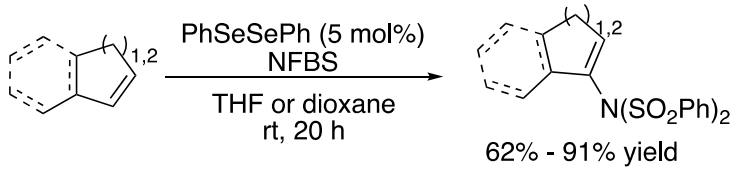
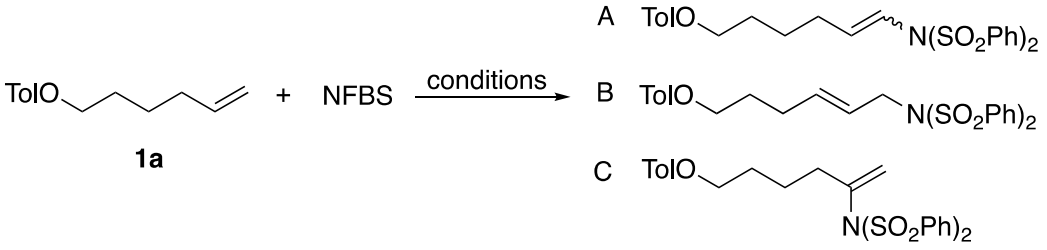


Table 1.1 Application of Reported Methods to Unactivated Terminal Alkenes



entry	conditions	A (%) (*E*/*Z*)	B (%)	C (%)
1	Breder	47 (1.8:1)	17	13
2	Zhao	41 (1.9:1)	14	13

[a]Yields and E/Z ratios determined by ^{1}H NMR using 1,3-dinitrobenzene as internal standard.

Among these two and other known reports on oxidative functionalisation of alkenes via organoselenium catalysis, commercially available diphenyl diselenide is predominantly used as the catalyst. We wondered if manipulation of the substituents in diphenyl diselenide would open the possibility of tuneable reactivity and selectivity. However, synthesis of functionalised diselenides requires harsh conditions[20,21], limiting the diversity of groups that can be incorporated on selenium.

Although it has been suggested that the Se-Se bond is essential to the catalytic reactivity[18], we wondered if monoselenides could also be effective catalysts. Recognising the vital role of electronic and steric effects of ligands in transition-metal catalysis and the analogy between organoselenium catalysis and transition-metal counterparts, we hypothesised that the selectivity of this and other reactions catalysed by organoselenium compounds could be improved by conceiving of the phenyl group as a ligand for selenium rather than a substituent (Figure 1.3). Replacement of this group by common ligands such as phosphines and N-heterocyclic carbenes (NHC) would suggest that phosphine selenides and selenoureas might also function as catalysts for these transformations. One advantage is that preparation of these phosphine selenides and selenoureas requires just one step from the corresponding phosphines or NHCs. Notably, the diversity of phosphines and NHC ligands allow for access to a large library of sterically and electronically diverse catalysts. Thus, tuneable reactivity and selectivity of reactions catalysed by these monoselenides would be feasible. Based on our hypothesis, we envisioned that the regioselectivity issue with aza-Heck reaction of unactivated terminal alkenes could be addressed by tuned reactivity and selectivity of phosphine/NHC selenides.

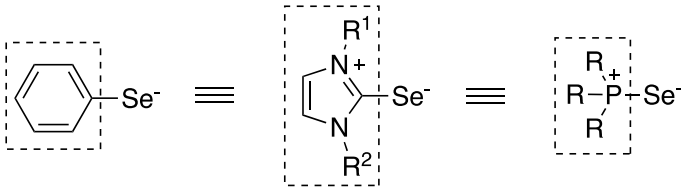


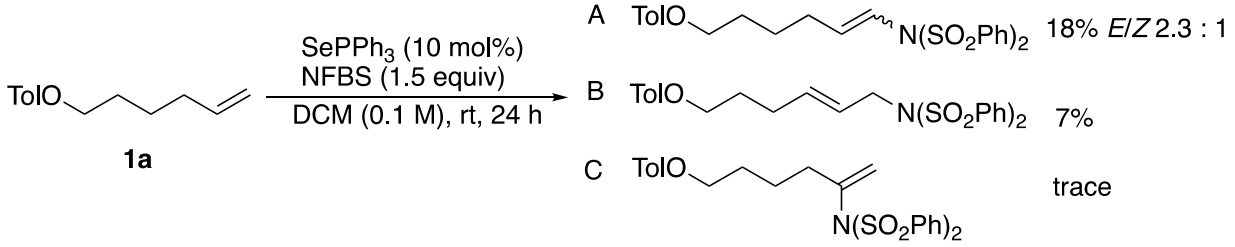
Figure 1.3 Phosphine Selenides as Catalysts via Analogy to Aryl Selenides

1.2 Results and Discussion

1.2.1 *Initial Results*

Initial reaction conditions are detailed in Scheme 1.3. Terminal alkene 1a was treated with *N*-fluorobenzenesulfonimide (NFBS) using 10 mol% triphenylphosphine selenide as the catalyst in DCM at room temperature. As expected, the internal aza-Heck product, terminal aza-Heck product, and allylic amination product were identified in low yields. Notably, the desired terminal aza-Heck product was generated as the major regioisomer in 18% yield with an *E/Z* ratio of 2.3:1. This proves that monoselenides are effective alternative catalysts to diphenyl diselenide.

Scheme 1.3 Initial Results for Aza-Heck Reaction of Terminal Alkenes

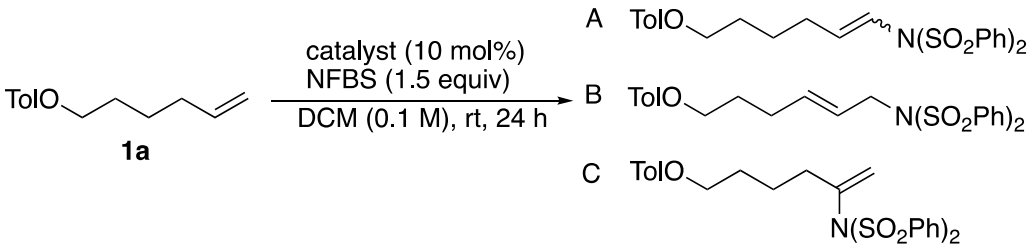


1.2.2 *Reaction Optimisation*

As discussed, the goal of this project was to demonstrate that phosphine/NHC selenides are effective catalysts, and that reactivity and selectivity promoted by these catalysts can be tuned by choice of ligands on selenium. Thus, a catalyst screen was performed (Table 1.2). The results show that phosphine selenides are superior to NHC selenides in terms of reactivity, and that catalysts

with bulky aryl phosphine ligands outperform others. Tri(*o*-tolyl)phosphine selenide was found to give the highest yield and selectivity for the terminal aza-Heck product (Table 1.2, entry 4). These results justify our hypothesis that ligands on selenium have significant impact on reactivity and selectivity of reactions catalysed by these monoselenides.

Table 1.2 Catalyst Screen



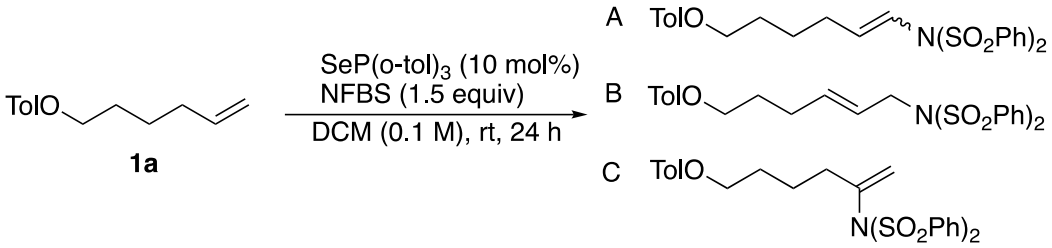
entry	catalyst	A (%) (*E/Z*)	B (%)	C (%)
1	$SePPh_3$	18 (2.3:1)	7	trace
2	IPrSe	trace	trace	trace
3	$SePCy_3$	16 (2.6:1)	6	trace
4	$SeP(o\text{-}tol)_3$	31 (4.1:1)	9	trace

[a]Yields and E/Z ratios determined by ^1H NMR using 1,3-dinitrobenzene as internal standard.

Noticing that NFBS serves as both terminal oxidant and nitrogen source, we proposed that adding extra external nucleophile might help improve the yield. Indeed, adding 1 equiv of benzenesulfonimide salt, boosted the yield of terminal aza-Heck product to 74% (Table 1.3, entry 1 and 2). The *E/Z* ratio was also improved from 4.1:1 to 5.7:1. More importantly, little changes in yields of the other two products were observed. Although decent yield and stereoselectivity were achieved, the generation of allyl isomer remained an obstacle to isolation of pure terminal aza-Heck products due to its similar polarity to that of the desired aza-Heck product. Re-examining the structure of allyl isomer, we wondered if a second amination could occur on the internal alkene to generate a more polar molecule that can be separated from the desired product. Extending the reaction time from 24 hours to 48 hours aminated the allyl isomer further to bis(sulfonamide)

without affecting the yield of aza-Heck product (Table 1.3, entry 2 and 3). This feature allows for isolation of pure aza-Heck product.

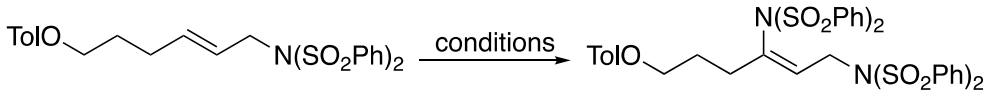
Table 1.3 Effects of External Nucleophile and Reaction Time



entry	changes	A (%) (*E*/*Z*)	B (%)	C (%)
1	none	31 (4.1:1)	9	trace
2	1 equiv $Et_3NHN(SO_2Ph)_2$	74 (5.7:1)	12	4
3	1 equiv $Et_3NHN(SO_2Ph)_2$, 48 h	74 (5.7:1)	0	4

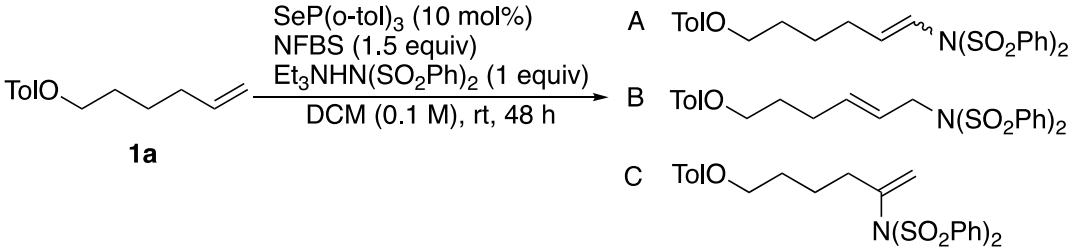
[a]Yields and E/Z ratios determined by ^1H NMR using 1,3-dinitrobenzene as internal standard.

allyl sulfonamide to bis(sulfonamide)



Control experiments were performed to ensure that all reaction components are indispensable. No reactivity was observed in the absence of catalyst or oxidant (Table 1.4, entry 2 and 3). We found that phosphine selenides could be generated in situ by stirring Se powder with the corresponding phosphine for 3 h prior to addition of the remaining reagents, although further amination of the allyl isomer did not occur in this case (Table 1.4, entry 4). Selenium powder in the absence of phosphine did not catalyse the reaction (Table 1.4, entry 5).

Table 1.4 Control Experiments



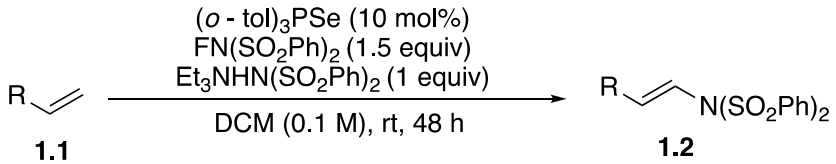
entry	changes	A (%) (*E/Z*)	B (%)	C (%)
1	none	74 (4.1:1)	0	4
2	no catalyst	NR	NR	NR
3	no oxidant	NR	NR	NR
4	15 mol% Se + 10 mol% $P(o\text{-tol})_3$ pre-stirred for 3 h	70 (4.8:1)	14	5
5	10 mol% Se	NR	NR	NR

[a]Yields and E/Z ratios determined by ^{1}H NMR using 1,3-dinitrobenzene as internal standard.

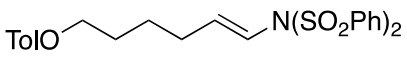
1.2.3 *Substrate Scope*

The optimised conditions were applied to the amination of a variety of terminal alkenes (Table 1.5). Yields and *E/Z* ratios are generally high. The reaction conditions show excellent functional group compatibility. The conditions tolerate esters, ethers, electron-rich and electron-deficient aromatics, silyl ethers, sulfonamides, and nitriles. Notably, aliphatic and aromatic halides could also be successfully used as substrates. The reaction of 1a was performed under an ambient atmosphere on 4 mmol scale and gave the desired product with no significant loss of yield or selectivity.

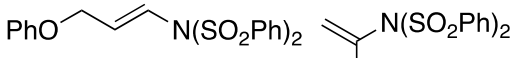
Table 1.5 Substrate Scope for the Aza-Heck Reaction



1.1 **1.2**

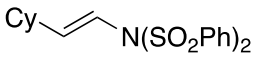


1.2a, 78%, 5.9 : 1 *E/Z*
76%, 11 : 1 *E/Z* (4 mmol)

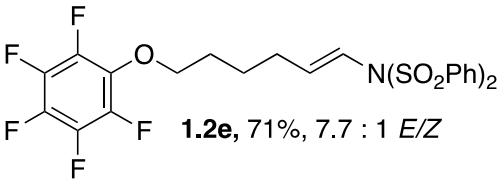


1.2b, 80%, 7.6 : 1 *E/Z*

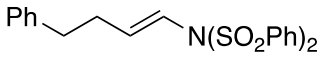
1.2c, 97%



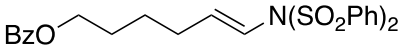
1.2d, 76%, 17 : 1 *E/Z*



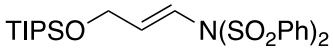
1.2e, 71%, 7.7 : 1 *E/Z*



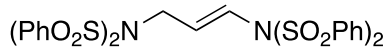
1.2f, 71%, 5.5 : 1 *E/Z*



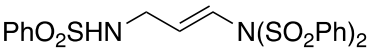
1.2g, 70%, 7.6 : 1 *E/Z*



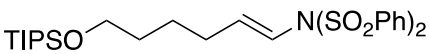
1.2h, 77%, 15 : 1 *E/Z*



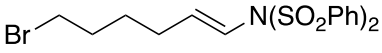
1.2i, 87%, 12 : 1 *E/Z*



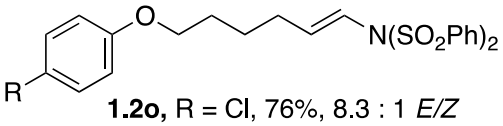
1.2j, 84%, 8.3 : 1 *E/Z*



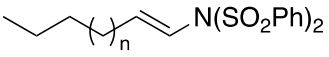
1.2k, 73%, 6.2 : 1 *E/Z*



1.2l, 75%, 6.2 : 1 *E/Z*



1.2o, R = Cl, 76%, 8.3 : 1 *E/Z*
1.2p, R = I, 81%, 6.6 : 1 *E/Z*
1.2q, R = CF_3, 68%, 6.4 : 1 *E/Z*
1.2r, R = NO_2, 62%, 8.4 : 1 *E/Z*
1.2s, R = CN, 73%, 7.4 : 1 *E/Z*



1.2m, n = 11, 65%, 9.1 : 1 *E/Z*
1.2n, n = 1, 71%, 5.7 : 1 *E/Z*

[a] isolated yields.

1.2.4 *Mechanistic Studies*

Although it has been suggested that the Se-Se bond is essential to the catalytic reactivity and many plausible mechanisms have been reported in literature[18], no detailed mechanistic studies

have been presented. We proposed that phosphine selenides might also occur through a sequence of addition and elimination processes analogous to that of diphenyl diselenide. However, several questions about the mechanism remain elusive and need to be addressed:

1) Does the reaction proceed via an *anti*-addition/*syn*-elimination sequence?

2) What is the rate-determining step of the reaction?

3) What is the product-determining step (i.e., first irreversible step) of the reaction?

At this point, John Tabor, another member of our lab, joined this project. We sought to address these questions through a series of deuterium labelling experiments and kinetic isotope effects (KIE) experiments.

1.2.4.1 Deuterium Labelling Experiment

A deuterium labelling experiment was designed to investigate the stereochemistry of both addition and elimination steps. Consider all possible combinations of stereochemistry of addition and elimination steps using deuterated substrate 1.3-*d* as a model (Figure 1.4). If the reaction proceeded via *anti*-addition/*syn*-elimination or *syn*-addition/*anti*-elimination, we would expect the set of boxed products. On the contrary, if the reaction proceeded via *anti*-addition/*anti*-elimination or *syn*-addition/*syn*-elimination, we would expect the unboxed products.

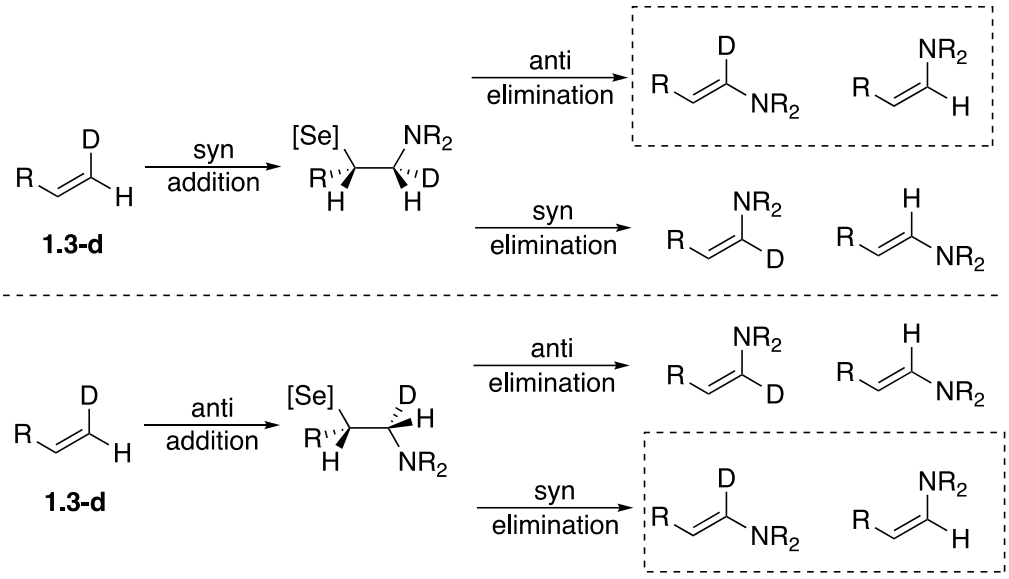
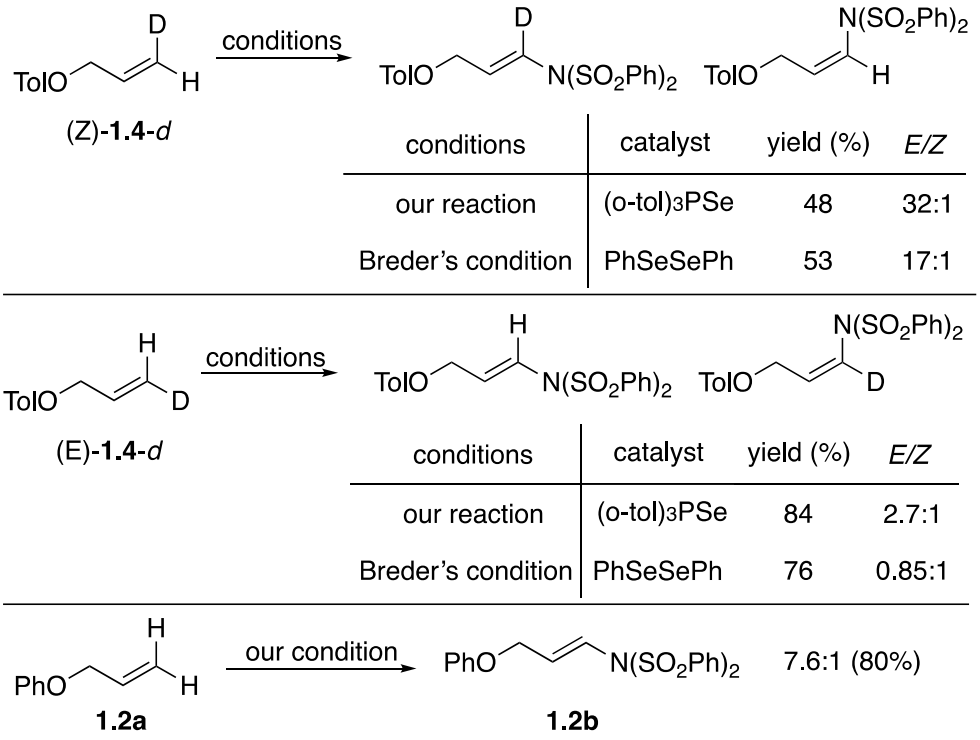


Figure 1.4 Analysis of Expected Products of Deuterium Labelling Experiments

Substrates (*Z*)-1.4-*d* and (*E*)-1.4-*d* were synthesised. Both our conditions and conditions reported by Breder[18] using diphenyl diselenide as the catalyst were applied to these deuterated substrates (Scheme 1.4). In all cases, the reactions generated the set of products expected of either syn-addition/anti-elimination or anti-addition/syn-elimination, ruling out the possibility of the other two pathways. Notably, the *E/Z* ratio of (*Z*)-1.4-*d* is about 4 times greater than that of the non-deuterated substrate 1.2a, which can be rationalised by the primary kinetic isotope effect in the elimination step (k_H/k_D = 3~4). To clarify, this kinetic isotope effect reflects the intramolecular competition of terminal proton and deuterium in the elimination step. The primary KIE is comparable to that measured for the well-known selenoxide elimination (k_H/k_D = 5.2)[22], suggesting that the elimination in our reaction occurs in *syn* fashion which is isoelectronic to selenoxide elimination. Thus, we proposed that the reaction proceeds via *anti*-addition followed by *syn*-elimination (Figure 1.5): phosphine selenides are oxidised to generate an electrophilic selenium species which reacts with an alkene to give the seleniranium ion intermediate. This intermediate is then trapped by an external nucleophile during a ring-opening event to deliver a net *anti* addition.

Syn-elimination of the terminal proton and selenium moiety through an intramolecular process affords the aza-Heck product.

Scheme 1.4 Deuterium Labelling Experiment



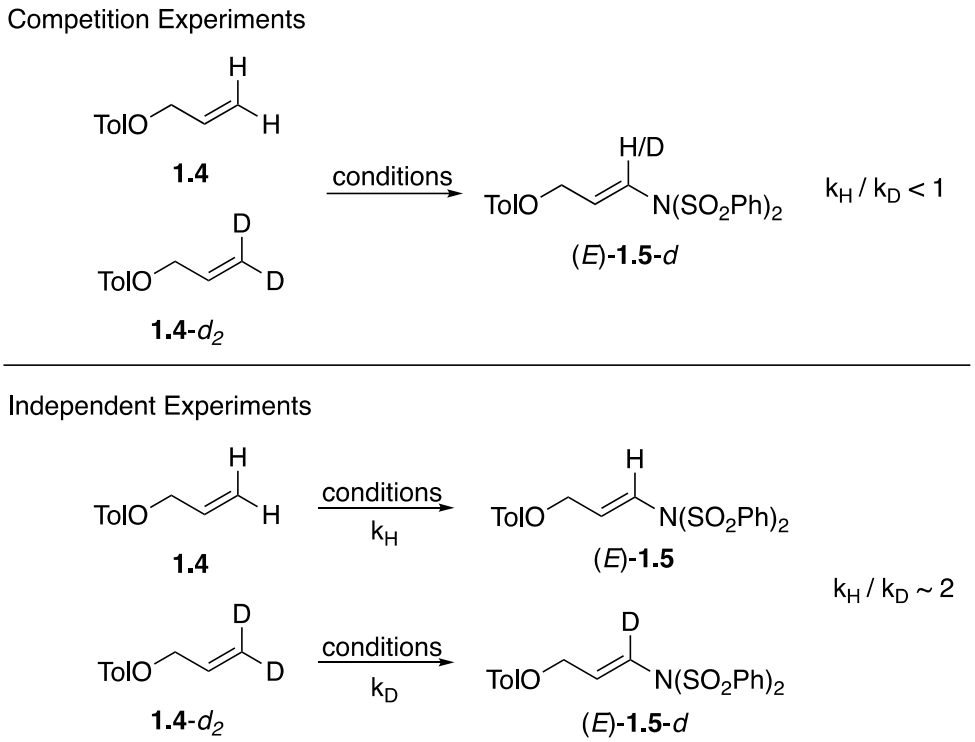
1.2.4.2 Kinetic Isotope Effect Experiment

To probe the rate-determining step of the reaction, the kinetic isotope effect was measured for substrates with deuterium substitution at the terminal position. The reaction rates of 1.4 and 1.4-d_2 were measured independently (Scheme 1.5). A primary KIE of 2 was observed under these reactions, indicating that *syn*-elimination where C-H bond cleavage event occurs is the rate-determining step (RDS).

To probe the product-determining step, an intermolecular competition experiment was conducted between 1.4 and 1.4-d_2 (Scheme 1.5). The product distribution gave a small inverse KIE of ~0.95, which is typical of alkene addition reactions[23]. This is consistent with the scenario that

the addition of electrophilic selenium species to the alkene is irreversible, rendering it the product-determining step.

Scheme 1.5 Kinetic Isotope Effect Experiments



1.2.4.3 Proposed Mechanism

Based on the results above, the following mechanism was proposed (Figure 1.5). Oxidative addition of NFBS to phosphine selenides generates an electrophilic selenium species A. This species irreversibly adds to an alkene to give a seleniranium ion B, followed by nucleophilic attack of nucleophile to afford the alkylselenium fluoride C. This intermediate finally eliminates to give the product via a *syn*-elimination process isoelectronic to selenoxide elimination.

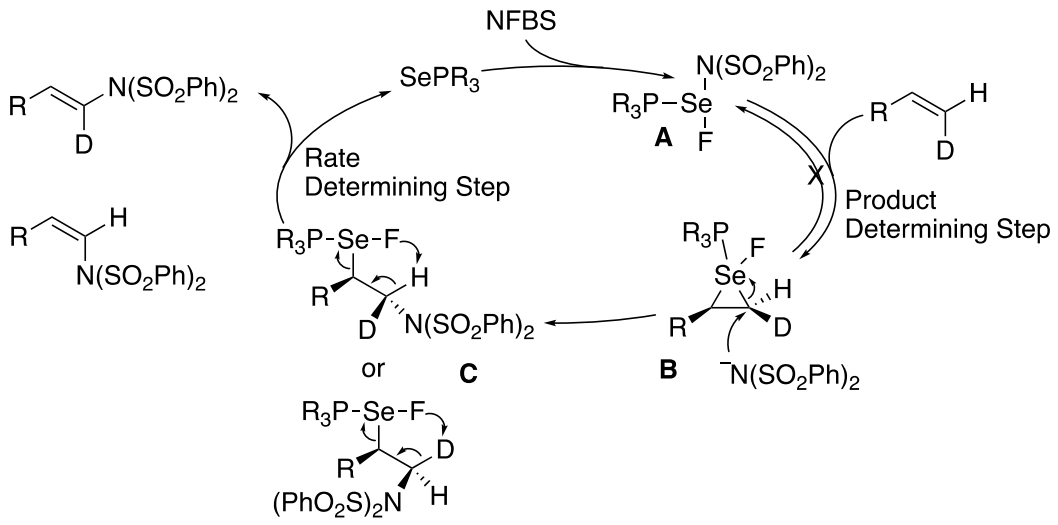


Figure 1.5 Proposed Mechanism for Aza-Heck Reaction Catalysed by Phosphine Selenides

1.3 CONCLUSION

A regioselective metal-free aza-Heck reaction of unactivated terminal alkenes was developed. This work demonstrated that phosphine selenides can be used as effective alternative catalysts to the predominately used diphenyl diselenide in organoselenium catalysis. We showed that the reactivity and selectivity of reactions catalysed by these phosphine/NHC selenides can be tuned by proper choice of sterically and electronically diverse phosphine or NHC ligands on selenium. This reaction resolves the regioselectivity issue associated with previous methods, allowing for the isolation of pure aza-Heck product in high yields and good stereoselectivity. The reaction exhibits good functional group compatibility. Mechanistic study reveals that the basic mechanistic outline is the same for both phosphine selenides and diphenyl diselenide, that is, the reaction occurs via *anti*-addition followed by *syn*-elimination. The proposed mechanism is supported by the products obtained from deuterium labelling experiments. Kinetic isotope effects measured in competition experiments and in individual rate measurements suggest that the overall rate determining step is

the *syn*-elimination step and that the product-determining step is the irreversible addition of electrophilic selenium species to the alkene.

1.4 EXPERIMENTAL

1.4.1 *General Procedures and Materials*

All reactions were performed under a nitrogen atmosphere using flame-dried glassware unless otherwise noted. Infrared spectra were measured on a Perkin Elmer Spectrum RX I spectrometer. Mass spectra were collected on a Hewlett Packard 5971A Gas Chromatograph-Mass Spectrometer or Bruker Esquire 1100 Liquid Chromatograph-Ion Trap Mass Spectrometer. Column chromatography was performed using silica gel (Whatman, 60 Å, 230-400 mesh). NMR spectra were recorded on a Bruker AV-300, AV-301, DRX-499 or AV-500 spectrometer. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) and are referenced relative to TMS (0.00 ppm) or residual protonated $CHCl_3$ (7.26 ppm). ^{13}C NMR chemical shifts (δ) are reported in parts per million (ppm) relative to the carbon resonance of $CDCl_3$ (77.16 ppm). Melting points were taken on a MEL-TEMP melting point apparatus and are uncorrected.

All commercial reagents were used as received, unless otherwise noted. All solvents were degassed and dried on solvent columns of neutral alumina. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc., stored over 4 Å molecular sieves, and were used without further purification. Vinyl cyclohexane, allyl phenyl ether, allyl tolyl ether, styrene, 1-hexene and 1-hexadecene were purified by distillation from calcium hydride and stored over 4 Å molecular sieves. N-allylbenzenesulfonamide[24], N-allylbenzenesulfonimide[25], (hex-5-enyloxy)triisopropylsilane[26], hex-5-en-1-yl benzoate[27], triethylammonium benzenesulfonimide[28] and all phosphine selenide catalysts[29] were prepared according to previously published procedures

and their respective spectroscopic signatures (^{1}H NMR) were found to be consistent with values reported therein.

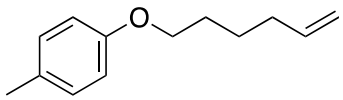
1.4.2 *Synthesis and Characterisation of Alkene Starting Materials*

General Procedure A: Synthesis of Terminal Alkenes

In a flamed dried 250 mL two-neck round bottom flask, 6-bromo-1-hexene (10 mmol, 1 equiv) was added dropwise to a solution of p-substituted phenol (12 mmol, 1.2 equiv) and K_2CO_3 (30 mmol, 3 equiv) in acetonitrile (80 mL). The reaction mixture was heated at reflux for 12 hours. After the reaction was complete, it was cooled to room temperature, white solids were filtered off, and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding alkene.

Characterisation of Terminal Alkenes

1-(hex-5-enyloxy)-4-methylbenzene (1.1a)



Synthesised according to General Procedure A to afford the product as a colourless oil (1.7 g, 90% yield). Purified by column chromatography (EtOAc/Hexanes = 1/50).

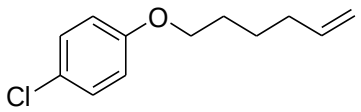
IR (thin film) 2940, 2865, 1641, 1615, 1586, 1512, 1474, 1390, 1291, 1244, 1176, 1110, 1037, 995, 910, 818, 511 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (d, *J* = 8.4 Hz, 2H), 6.79 (d, J = 8.5 Hz, 2H), 5.83 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.11 – 4.88 (m, 2H), 3.94 (t, *J* = 6.5 Hz, 2H), 2.28 (s, 3H), 2.13 (q, *J* = 7.1 Hz, 2H), 1.87 – 1.71 (m, 2H), 1.67 – 1.47 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.10, 138.74, 129.99, 129.83, 114.83, 114.48, 67.94, 33.61, 28.93, 25.50, 20.60.

GC-MS m/z 190 (1, M^+), 108 (3.2, C_7H_7OH), 55(100, $C_4H_7^+$).

1-chloro-4-(hex-5-enyloxy)benzene (1.1o)



Synthesised according to General Procedure A to afford the product as a colourless oil (1.85 g, 88% yields). Purified by column chromatography (EtOAc/Hexanes = 1/50).

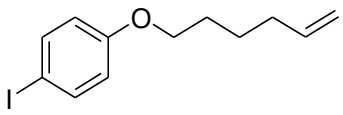
IR (thin film) 2940, 1597, 1493, 1473, 1287, 1244, 1170, 1092, 1006, 913, 823, 668 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.82 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.18 – 4.89 (m, 2H), 4.01 (t, *J* = 6.4 Hz, 2H), 2.13 (q, *J* = 7.1 Hz, 2H), 1.96 – 1.71 (m, 2H), 1.66 – 1.48 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.84, 138.59, 129.40, 125.46, 115.88, 114.95, 68.21, 33.54, 28.77, 25.42.

GC-MS (m/z) 210/212 (15/5, M^+), 128/130 (100/33, C_6H_4ClOH).

1-(hex-5-enyloxy)-4-iodobenzene (1.1p)



Synthesised according to General Procedure A to afford the product as a white solid (2.6 g, 86% yield). Purified by column chromatography (EtOAc/Hexanes = 1/50).

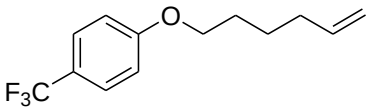
IR (thin film) 2937, 1586, 1487, 1283, 1244, 1174, 819 cm^{-1}.

^{1}H NMR (300 MHz, CDCl3) δ 7.54 (d, *J* = 8.8 Hz, 2H), 6.67 (d, *J* = 8.8 Hz, 2H), 5.90 – 5.73 (m, 1H), 5.16 – 4.88 (m, 2H), 3.92 (t, *J* = 6.4 Hz, 2H), 2.12 (q, *J* = 7.2 Hz, 2H), 1.90 – 1.67 (m, 2H), 1.64 – 1.45 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.10, 138.57, 138.29, 117.05, 114.96, 82.59, 68.01, 33.53, 28.71, 25.40.

GC-MS (m/z) 302 (26, M^+), 220 (100, C_6H_4IOH)

1-(hex-5-enyloxy)-4-(trifluoromethyl)benzene (1.1q)



Synthesised according to General Procedure A to afford the product as a colourless oil (2.13 g, 87% yield). Purified by column chromatography (EtOAc/Hexanes = 1/50).

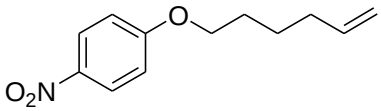
IR (thin film) 2941, 1617, 1567, 1520, 1331, 1258, 1161, 1110, 1068, 913, 836 cm^{-1}.

^{1}H NMR (300 MHz, CDCl3) δ 7.53 (d, *J* = 8.6 Hz, 2H), 6.94 (d, *J* = 8.6 Hz, 2H), 5.83 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.12 – 4.90 (m, 2H), 4.00 (t, *J* = 6.4 Hz, 2H), 2.14 (q, *J* = 7.1 Hz, 2H), 1.92 – 1.72 (m, 2H), 1.69 – 1.46 (m, 2H).

^{13}C NMR (126 MHz, CDCl3) δ 161.74, 138.51, 126.98, 124.69 (q, *J* = 271.0 Hz), 122.78 (q, *J* = 32.6 Hz), 114.98, 114.55, 68.12, 33.53, 28.67, 25.39.

GC-MS (m/z) 244 (13, M^+), 162 (81, $C_6H_4CF_3OH$), 55(100, $C_4H_7^+$)

1-(hex-5-enyloxy)-4-nitrobenzene (1.1r)



Synthesised according to General Procedure A to afford the product as a dark orange oil (1.77 g, 80% yield). Purified by column chromatography (EtOAc/Hexanes = 1/50).

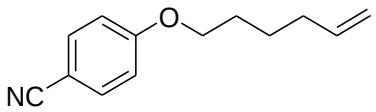
IR (thin film) 2940, 1640, 1593, 1510, 1340, 1260, 1172, 1110, 994, 913, 844, 751, 690 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, *J* = 9.2 Hz, 2H), 6.94 (d, *J* = 9.1 Hz, 2H), 5.96 – 5.68 (m, 1H), 5.14 – 4.88 (m, 2H), 4.06 (t, *J* = 6.4 Hz, 2H), 2.14 (q, *J* = 7.2 Hz, 2H), 1.97 – 1.76 (m, 2H), 1.68 – 1.46 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.30, 141.42, 138.33, 125.99, 115.09, 114.49, 68.76, 33.40, 28.48, 25.25.

GC-MS (m/z) 221 (10, M^+), 139 (10, $C_6H_4NO_2OH$), 55 (100, $C_4H_7^+$).

4-(hex-5-enyloxy)benzonitrile (1.1s)



Synthesised according to General Procedure A to afford the product as an orange oil (1.83 g, 91% yield). Purified by column chromatography (EtOAc/Hexanes = 1/50).

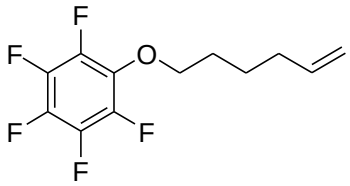
IR (thin film) 2940, 2224, 1606, 1508, 1302, 1258, 1171, 913, 834, 748 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 5.82 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.11 – 4.93 (m, 2H), 4.01 (t, *J* = 6.4 Hz, 2H), 2.13 (q, *J* = 7.2 Hz, 2H), 1.91 – 1.76 (m, 2H), 1.65 – 1.48 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.52, 138.39, 134.10, 119.45, 115.30, 115.10, 103.84, 68.31, 33.45, 28.53, 25.31.

GC-MS (m/z) 201 (21, M^+), 119 (53, C_6H_4CNOH), 55(100, $C_4H_7^+$).

1,2,3,4,5-pentafluoro-6-(hex-5-enyloxy)benzene (1.1e)



Synthesised according to General Procedure A to afford the product as a colourless oil (2.26 g, 85% yield). Purified by column chromatography (EtOAc/Hexanes = 1/50).

IR (thin film) 3081, 2947, 1643, 1514, 1469, 1388, 1314, 1162, 1032, 997, 914 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 16.9, 10.0, 6.6 Hz, 1H), 5.11 – 4.89 (m, 2H), 4.16 (t, *J* = 6.4 Hz, 2H), 2.12 (q, *J* = 7.1 Hz, 2H), 1.91 – 1.68 (m, 2H), 1.71 – 1.43 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.07 (ddd, *J* = 248.1, 10.9, 3.8 Hz), 138.50 (d, *J* = 255.9 Hz), 138.37, 138.61 – 136.14 (m), 133.98 (t, *J* = 11.2 Hz), 114.95, 75.78, 33.42, 29.41, 24.98.

GC-MS (m/z) 266 (1, M^+), 184 (13, C_6F_5OH), 55 (100, $C_4H_7^+$).

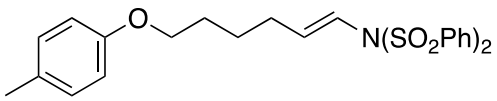
1.4.3 *Synthesis and Characterisation of Aza-Heck Products*

General Procedure B: Aza-Heck Reaction of Terminal Alkenes

To an oven-dried 1-dram vial was added phosphine selenide (0.01 equiv), DCM (2 mL), alkene (0.2 mmol, 1 equiv), triethylammonium benzenesulfonimide (79.4 mg, 0.2 mmol, 1 equiv) and NFBS (94.6 mg, 0.3 mmol, 1.5 equiv), in that order. The vial was then flushed with nitrogen and capped with a Telfon-lined screw cap and the reaction was stirred at room temperature for 24 or 48 hours. To the reaction mixture was added deionised water (2 mL) and dimethyl sulphide (66 µL, 4.5 equiv). After stirring for an additional 20 min, the reaction mixture was diluted with diethyl ether (15 mL) and washed with citric acid (1 M), saturated $NaHCO_3$, and brine. The organic layer was dried over sodium sulphate, filtered, and concentrated in vacuo. An ^1H NMR was taken with 1, 3-dinitrobenzene as internal standard to obtain NMR yield. The crude product was purified by column chromatography to afford the corresponding product.

Characterisation of Aza-Heck Products

(*E*)-N-(6-(p-tolyloxy)hex-1-enyl)benzenesulfonimide (1.2a)



Synthesised according to general procedure B to afford the product as a pale, white solid (77 mg, 78% yield, *E:Z* = 8.7:1). Purified by column chromatography (EtOAc/Hexanes = 1/9).

Melting point 92.8-94.6 °C

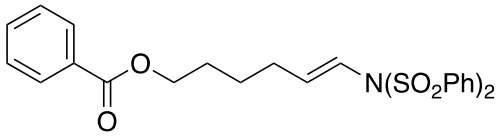
IR (thin film) 3066, 2944, 2867, 1614, 1585, 1512, 1477, 1449, 1378, 1360, 1312, 1292, 1243, 1172, 1122, 1087, 1026, 1000, 961, 916, 818, 754, 740, 722, 686, 608, 577, 551, 513 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.3 Hz, 4H), 7.65 (t, *J* = 7.3 Hz, 2H), 7.54 (t, *J* = 7.5 Hz, 4H), 7.10 (d, *J* = 8.1 Hz, 2H), 6.81 (d, *J* = 8.3 Hz, 2H), 6.01 – 5.76 (m, 2H), 3.93 (t, *J* = 6.1 Hz, 2H), 2.30 (s, 3H), 2.25 – 2.14 (q, *J* = 13.6, 6.9 Hz, 2H), 1.84 – 1.69 (m, 2H), 1.65 – 1.50 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.92, 142.49, 139.64, 133.96, 129.98, 129.13, 128.78, 128.21, 120.67, 114.39, 67.52, 29.74, 28.62, 25.16, 20.55.

HRMS (ESI) ($M+H^+$) calculated 486.1403, found 486.1392

(*E*)-6-(N-phenylsulfonimido)hex-5-enyl benzoate (1.2g)



Synthesised according to general procedure B to afford the product as a white solid (69.9 mg, 70% yield, *E:Z* = 7.6:1). Purified by column chromatography (EtOAc/Hexanes = 1/4).

Melting point 60-63 °C.

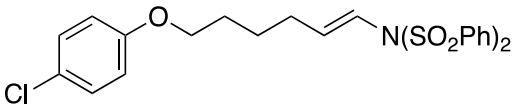
IR (thin film) 3074, 2937, 2860, 1716, 1448, 1378, 1275, 1171, 1114, 1086, 1026, 957, 914, 754, 720, 686, 576, 550 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.2 Hz, 2H), 7.96 (d, *J* = 7.5 Hz, 4H), 7.64 (t, *J* = 7.4 Hz, 2H), 7.58 – 7.49 (m, 5H), 7.45 (t, *J* = 7.5 Hz, 2H), 5.98 – 5.73 (m, 2H), 4.32 (t, *J* = 6.4 Hz, 2H), 2.20 (q, *J* = 7.1 Hz, 2H), 1.82 – 1.71 (m, 2H), 1.62 – 1.48 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.71, 142.16, 139.70, 134.00, 133.08, 130.45, 129.66, 129.16, 128.52, 128.26, 120.89, 64.59, 29.67, 28.13, 25.14.

HRMS (ESI) ($M+H^+$) calculated 500.1196, found 500.1185

(*E*)-N-(6-(4-chlorophenoxy)hex-1-enyl)benzenesulfonimide (1.2o)



Synthesised according to general procedure B to afford the product as a white solid (76.9 mg, 76% yield, *E:Z* = 8.3:1). Purified by column chromatography (EtOAc/Hexanes = 1/4).

Melting point 86-87 °C

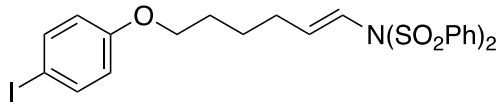
IR (thin film) 2944, 1596, 1492, 1448, 1378, 1358, 1288, 1244, 1171, 1086, 915, 826, 753, 722, 686, 576, 550 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.2 Hz, 4H), 7.65 (t, *J* = 7.4 Hz, 2H), 7.53 (t, *J* = 7.6 Hz, 4H), 7.22 (d, *J* = 9.0 Hz, 2H), 6.81 (d, *J* = 9.0 Hz, 2H), 6.05 – 5.63 (m, 2H), 3.91 (t, *J* = 6.2 Hz, 2H), 2.27 – 2.12 (q, *J* = 7.1 Hz, 2H), 1.82 – 1.69 (m, 2H), 1.64 – 1.49 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.72, 142.31, 139.73, 134.01, 129.46, 129.17, 128.28, 125.63, 120.85, 115.86, 67.89, 29.77, 28.55, 25.15.

HRMS (ESI) ($M+NH_4^+$) calculated 523.1123, found 523.1107

(*E*)-N-(6-(4-iodophenoxy)hex-1-enyl)benzenesulfonimide (1.2p)



Synthesised according to general procedure B to afford the product as a white solid (96.8 mg, 81% yield, *E:Z* = 6.6:1). Purified by column chromatography (EtOAc/Hexanes = 1/4).

Melting point 107.8-108.2 °C

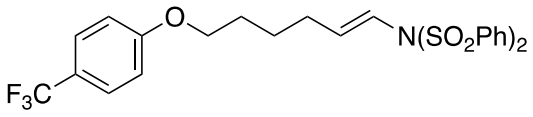
IR (thin film) 2941, 1586, 1486, 1448, 1378, 1358, 1284, 1243, 1171, 1085, 915, 821, 753, 722, 686, 576, 550 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.3 Hz, 4H), 7.64 (t, *J* = 7.4 Hz, 2H), 7.58 – 7.44 (m, 6H), 6.66 (d, *J* = 8.8 Hz, 2H), 5.99 – 5.65 (m, 2H), 3.90 (t, *J* = 6.2 Hz, 2H), 2.18 (q, *J* = 7.0 Hz, 2H), 1.82 – 1.67 (m, 2H), 1.62 – 1.45 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.95, 142.29, 139.68, 138.32, 133.99, 129.15, 128.24, 120.81, 117.00, 82.73, 67.66, 29.73, 28.47, 25.10.

HRMS (ESI) ($M+NH_4^+$) calculated 615.0479, found 615.0461

(*E*)-N-(6-(4-(trifluoromethyl)phenoxy)hex-1-enyl)benzenesulfonimide (1.2q)



Synthesised according to general procedure B to afford the product as a colourless oil (73.4 mg, 68% yield, *E:Z* = 6.4:1). Purified by column chromatography (EtOAc/Hexanes = 1/4).

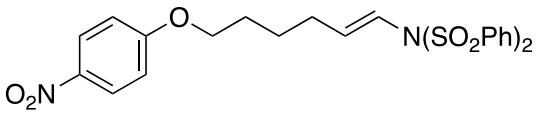
IR (thin film) 2942, 1616, 1519, 1449, 1379, 1330, 1258, 1172, 1112, 1086, 1068, 916, 837, 754, 722, 686, 638, 576, 551cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.6 Hz, 4H), 7.65 (t, *J* = 7.3 Hz, 2H), 7.59 – 7.43 (m, 6H), 6.94 (d, *J* = 8.5 Hz, 2H), 6.03 – 5.70 (m, 2H), 3.99 (t, *J* = 6.2 Hz, 2H), 2.20 (d, *J* = 7.0 Hz, 2H), 1.85 – 1.74 (m, 2H), 1.67 – 1.53 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.56, 142.19, 139.75, 134.01, 129.16, 128.28, 127.03, 124.60 (q, J = 270.8 Hz), 122.94 (q, J = 32.8 Hz), 120.92, 114.55, 67.83, 29.74, 28.45, 25.12.

HRMS (ESI) ($M+NH_4^+$) calculated 557.1386, found 557.1372

(*E*)-N-(6-(4-nitrophenoxy)hex-1-enyl)benzenesulfonimide (1.2r)



Synthesised according to general procedure B to afford the product as an off-white solid (64.1 mg, 62% yield, *E:Z* = 8.4:1). Purified by column chromatography (EtOAc/Hexanes = 1/4).

Melting point 93-96.3 °C

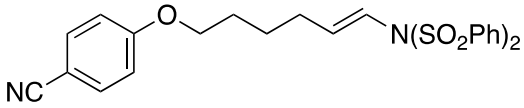
IR (thin film) 3066, 2942, 1607, 1593, 1511, 1448, 1378, 1341, 1297, 1263, 1172, 1111, 1085, 1024, 961, 914, 846, 753, 722, 686, 656, 608, 576, 551 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 9.2 Hz, 2H), 7.96 (d, *J* = 7.5 Hz, 4H), 7.65 (t, *J* = 7.4 Hz, 2H), 7.54 (t, *J* = 7.7 Hz, 4H), 6.93 (d, *J* = 9.2 Hz, 2H), 5.98 – 5.76 (m, 2H), 4.04 (t, *J* = 6.2 Hz, 2H), 2.21 (q, *J* = 13.8, 7.0 Hz, 2H), 1.89 – 1.75 (m, 2H), 1.66 – 1.52 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.12, 142.01, 139.69, 134.02, 129.15, 128.36, 128.24, 126.04, 120.98, 114.51, 68.47, 29.68, 28.31, 25.01.

HRMS (ESI) ($M+H^+$) calculated 517.1098, found 517.1085

(*E*)-N-(6-(4-cyanophenoxy)hex-1-enyl)benzenesulfonimide (1.2s)



Synthesised according to general procedure B to afford the product as a white solid (72.8 mg, 73% yield, *E:Z* = 7.4:1). Purified by column chromatography (EtOAc/Hexanes = 1/4).

Melting point 112.5-115.3 °C

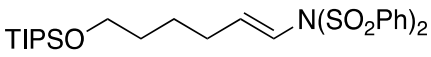
IR (thin film) 3068, 2945, 2872, 2225, 1606, 1574, 1509, 1477, 1448, 1378, 1303, 1260, 1172, 1116, 1086, 1024, 961, 914, 836, 722, 686, 607, 576, 550 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.4 Hz, 4H), 7.65 (t, *J* = 7.4 Hz, 2H), 7.60 – 7.46 (m, 6H), 6.92 (d, *J* = 8.8 Hz, 2H), 5.98 – 5.75 (m, 2H), 3.99 (t, *J* = 6.2 Hz, 2H), 2.20 (q, *J* = 13.8, 7.0 Hz, 2H), 1.86 – 1.73 (m, 2H), 1.65 – 1.51 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.35, 142.05, 139.68, 134.10, 134.01, 129.14, 128.23, 120.94, 119.32, 115.27, 103.99, 67.99, 29.68, 28.31, 25.02.

HRMS (ESI) ($M+H^+$) calculated 497.1199, found 497.1192

(*E*)-N-(6-(triisopropylsilyloxy)hex-1-enyl)benzenesulfonimide (1.2k)



Synthesised according to general procedure B to afford the product as a yellow oil (80 mg, 73% yield, *E:Z* = 6.2:1). Purified by column chromatography (EtOAc/Hexanes = 1/19).

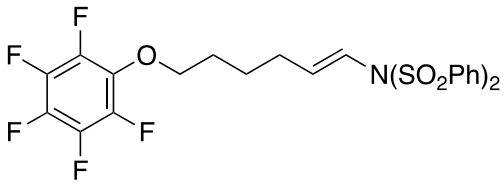
IR (thin film) 2942, 2865, 1451, 1381, 1173, 1091, 916, 722, 686, 577, 551 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.8 Hz, 4H), 7.64 (t, *J* = 7.2 Hz, 2H), 7.54 (t, *J* = 7.6 Hz, 4H), 5.94 – 5.68 (m, 2H), 3.68 (t, *J* = 5.8 Hz, 2H), 2.14 (q, *J* = 12.9, 6.5 Hz, 2H), 1.60 – 1.41 (m, 2H), 1.15-0.97 (m, 23H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.87, 139.67, 133.82, 129.01, 128.16, 120.29, 62.93, 32.24, 29.84, 24.93, 18.06, 12.01.

HRMS (ESI) ($M+H^+$) calculated 552.2268, found 552.2275

(*E*)-N-(6-(perfluorophenoxy)hex-1-enyl)benzenesulfonimide (1.2e)



Synthesised according to general procedure B to afford the product as colourless oil (79.7 mg, 71% yield, *E:Z* = 7.7:1). Purified by column chromatography (EtOAc/Hexanes = 1/4).

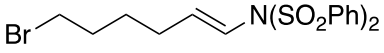
IR (thin film) 1514, 1449, 1379, 1172, 1086, 1028, 996, 915, 754, 722, 686, 577, 551 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.3 Hz, 4H), 7.66 (t, *J* = 7.4 Hz, 2H), 7.55 (t, *J* = 7.6 Hz, 4H), 6.00 – 5.72 (m, 1H), 4.14 (t, *J* = 6.1 Hz, 2H), 2.20 (q, *J* = 7.0 Hz, 2H), 1.83 – 1.69 (m, 2H), 1.66 – 1.50 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.33 – 140.67 (m), 142.09, 139.71, 139.38 – 136.96 (m), 138.81 –135.98 (m), 134.42 – 133.74 (m, 2C), 129.16, 128.26, 120.99, 75.40, 29.61, 29.14, 24.67.

HRMS (ESI) ($M+H^+$) calculated 562.0776, found 562.0803

(*E*)-N-(6-bromohex-1-enyl) benzenesulfonimide (1.2l)



Synthesised according to general procedure B to afford the product as a white solid (77.9 mg, 85% yield, *E*:*Z*:Allyl = 6.2:1:1). Purified by column chromatography (EtOAc/Hexanes = 1/4).

Melting point 70-73 °C

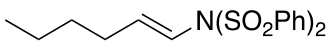
IR (thin film) 2939, 1448, 1378, 1171, 1086, 916, 723, 686, 577, 550 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.3 Hz, 4H), 7.66 (t, *J* = 7.4 Hz, 2H), 7.56 (t, *J* = 7.6 Hz, 4H), 5.97 – 5.72 (m, 2H), 3.40 (t, *J* = 6.6 Hz, 2H), 2.16 (q, *J* = 7.0 Hz, 2H), 1.91 – 1.77 (m, 2H), 1.65 – 1.46 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.93, 139.69, 134.04, 129.20, 128.27, 120.99, 33.36, 31.92, 29.19, 27.05.

HRMS (ESI) ($M+NH_4^+$) calculated 475.0355, found 475.0346

(*E*)-N-(hex-1-enyl)benzenesulfonimide (1.2n)



Synthesised according to general procedure B to afford the product as a yellow oil (53.5 mg, 71% yield, *E:Z* = 5.7:1). Purified by column chromatography (EtOAc/Hexanes = 1/19).

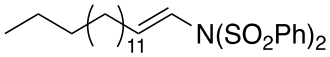
IR (thin film) 2932, 2864, 1450, 1380, 1173, 1088, 953, 914, 751, 723, 686, 576, 551 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.7 Hz, 4H), 7.65 (t, *J* = 7.4 Hz, 2H), 7.54 (t, *J* = 7.6 Hz, 4H), 6.01 – 5.59 (m, 2H), 2.11 (q, *J* = 12.9, 6.6 Hz, 1H), 1.43 – 1.16 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.20, 139.78, 133.94, 129.12, 128.27, 120.25, 30.63, 29.76, 22.10, 13.87.

HRMS (ESI) ($M+H^+$) calculated 380.0985, found 380.0988

(*E*)-N-(hexadec-1-enyl)benzenesulfonimide (1.2m)



Synthesised according to general procedure B to afford the product as a white solid (67.6 mg, 65% yield, *E:Z* = 9.1:1). Purified by column chromatography (EtOAc/Hexanes = 1/19).

Melting point 47.2-50.5 ºC

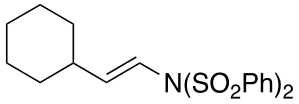
IR (thin film) 2926, 2854, 1450, 1381, 1173, 1088, 915, 722, 687, 576, 551 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.8 Hz, 4H), 7.65 (t, *J* = 7.3 Hz, 2H), 7.54 (t, *J* = 7.6 Hz, 4H), 5.98 – 5.69 (m, 2H), 2.11 (q, *J* = 12.8, 6.5 Hz, 1H), 1.41 – 1.16 (m, 24H), 0.88 (t, *J* = 6.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.22, 139.80, 133.92, 129.11, 128.28, 120.23, 36.23, 32.05, 30.10, 29.81, 29.81, 29.78, 29.71, 29.48, 29.07, 28.56, 27.70, 26.97, 22.81, 14.24.

HRMS (ESI) ($M+H^+$) calculated 520.2550, found 520.2539

(*E*)-N-(2-cyclohexylvinyl)benzenesulfonimide (1.2d)



Synthesised according to general procedure B to afford the product as a white solid (61.2 mg, 76% yield, *E:Z* = 17.1:1). Purified by column chromatography (EtOAc/Hexanes = 1/19).

Melting point 104.8-106.4 °C

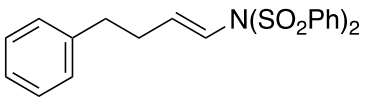
IR (thin film) 3067, 2927, 2853, 1585, 1480, 1449, 1380, 1360, 1313, 1292, 1171, 1130, 1086, 1025, 1000, 958, 916, 794, 754, 741, 722, 686, 635, 619, 578, 550 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.6 Hz, 4H), 7.65 (t, *J* = 7.3 Hz, 2H), 7.54 (t, *J* = 7.6 Hz, 4H), 5.73 (dt, *J* = 13.4, 10.4 Hz, 2H), 2.14-2.05 (m, 1H), 1.79 – 1.58 (m, 4H), 1.39 – 0.97 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.15, 139.61, 133.82, 128.98, 128.20, 118.67, 38.93, 32.00, 25.83, 25.55.

HRMS (ESI) ($M+H^+$) calculated 406.1141, found 406.1142

(*E*)-N-(4-phenylbut-1-enyl)-N-benzenesulfonimide (1.2f)



Synthesised according to general procedure B to afford the product as a colourless oil (71.8 mg, 84% yield, *E*:*Z*:Allyl = 5.5:1:0.9). Purified by column chromatography (EtOAc/Hexanes = 1/19).

IR (thin film) 3061, 3030, 2926, 2854, 1592, 1498, 1450, 1379, 1171, 1119, 1083, 1026, 912, 782, 741, 684, 575, 549.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.4 Hz, 4H), 7.62 (t, *J* = 6.9 Hz, 2H), 7.49 (t, *J* = 7.6 Hz, 4H), 7.34 – 7.13 (m, 5H), 5.99 – 5.75 (m, 2H), 2.72 (t, *J* = 7.4 Hz, 2H), 2.46 (q, *J* = 12.2, 6.9 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.58, 140.59, 139.67, 133.91, 129.10, 128.60, 128.33, 128.18, 126.28, 120.98, 34.74, 31.63.

HRMS (ESI) ($M+Na^+$) calculated 450.0804, found 450.0796

N-(1-phenylvinyl)benzenesulfonimide (1.2c)

Synthesised according to general procedure B to afford the product as an off-white solid (77.5 mg, 97% yield). Purified by column chromatography (EtOAc/Hexanes = 1/6).

Melting point 148-149 °C

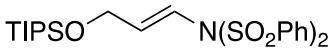
IR (thin film) 3061, 1623, 1576, 1488, 1449, 1379, 1263, 1170, 1086, 1019, 932, 756, 722, 686, 593, 545 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.6 Hz, 4H), 7.62 (t, *J* = 7.4 Hz, 2H), 7.48 (t, *J* = 7.8 Hz, 4H), 7.39 (d, *J* = 7.1 Hz, 2H), 7.32 – 7.12 (m, 3H), 5.90 (s, 1H), 5.05 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.12, 139.43, 135.40, 134.10, 129.18, 129.18, 128.90, 128.40, 127.19, 120.30.

HRMS (ESI) (M+H+) calculated 400.0672, found 400.0665

(*E*)-N-(3-(triisopropylsilyloxy)prop-1-enyl)benzenesulfonimide (1.2h)



Synthesised according to general procedure B to afford the product as a white solid (78.5 mg, 77% yield, *E:Z* = 15.4:1). Purified by column chromatography (EtOAc/Hexanes = 1/4).

Meilting point 43-45 °C

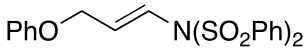
IR (thin film) 2943, 2866, 1448, 1383, 1351, 1171, 1126, 1086, 883, 811, 754, 722, 685, 624, 579, 550 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.5 Hz, 4H), 7.65 (t, *J* = 7.4 Hz, 2H), 7.53 (t, *J* = 7.6 Hz, 4H), 6.18 (dt, *J* = 13.2, 1.9 Hz, 1H), 5.96 (dt, *J* = 13.2, 4.0 Hz, 1H), 4.35 (dd, *J* = 3.9, 2.0 Hz, 2H), 1.18 – 1.01 (m, 21H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.73, 139.66, 133.98, 129.16, 128.32, 120.71, 61.56, 18.09, 12.07.

HRMS (ESI) (M+H+) calculated 510.1799, found 510.1808

(*E*)-N-(3-phenoxyprop-1-enyl)benzenesulfonimide (1.2b)



Synthesised according to general procedure B to afford the product as a white solid (61.6 mg, 71% yield, pure *E*). Purified by column chromatography (EtOAc/Hexanes = 1/19).

Melting point 90.1-91.9 ºC

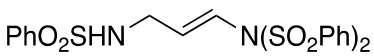
IR (thin film) 3066, 1599, 1587, 1496, 1448, 1379, 1241, 1171, 1136, 1085, 1032, 913, 753, 722, 685, 574, 548 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.6 Hz, 4H), 7.65 (t, *J* = 7.4 Hz, 2H), 7.51 (t, *J* = 7.7 Hz, 4H), 7.32 (t, *J* = 8.0 Hz, 2H), 7.01 (t, *J* = 7.4 Hz, 1H), 6.91 (d, *J* = 7.9 Hz, 2H), 6.30 (d, *J* = 13.5 Hz, 1H), 6.08 (dt, *J* = 13.5, 5.0 Hz, 1H), 4.64 (dd, *J* = 5.0, 1.5 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.01, 139.45, 134.52, 134.11, 129.69, 129.20, 128.26, 123.33, 121.48, 115.01, 65.39.

HRMS (ESI) ($M+H^+$) calculated 430.0777, found 430.0783

(*E*)-N-(3-(phenylsulfonamido)prop-1-enyl)benzenesulfonimide (1.2j)



Synthesised according to general procedure B to afford the product as a white solid (82.8 mg, 84% yield, *E:Z* = 8.3:1). Purified by column chromatography (EtOAc/Hexanes = 1/3).

Melting point 121.6-124.5 °C.

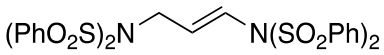
IR (thin film) 3300, 3067, 1480, 1448, 1379, 1332, 1170, 1086, 914, 754, 740, 722, 686 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 – 7.82 (m, 6H), 7.67 – 7.58 (m, 3H), 7.58 – 7.44 (m, 6H), 6.11 (d, *J* = 13.5 Hz, 1H), 5.83 (dt, *J* = 13.4, 6.7 Hz, 1H), 5.17 (t, *J* = 6.2 Hz, 1H), 3.64 (t, *J* = 6.2 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.64, 139.26, 134.22, 134.03, 133.04, 129.40, 129.26, 128.24, 127.15, 123.71, 42.63.

HRMS (ESI) ($M+H^+$) calculated 493.0556, found 493.0560

(*E*)-N-(3-phenylsulfonimido)prop-1-enyl)benzenesulfonamide) (1.2i)



Synthesised according to general procedure B to afford the product as a white, bubbly solid (109.4 mg, 87% yield, *E:Z* = 12.4:1). Purified by column chromatography (EtOAc/Hexanes = 75/25).

Melting point 42.3-47 °C

IR (thin film) 3072, 1449, 1377, 1171, 1087, 911, 816, 728, 686, 579, 549 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.5 Hz, 4H), 7.92 (d, *J* = 7.6 Hz, 4H), 7.65 (t, *J* = 6.9 Hz, 4H), 7.6-7.48 (m, 8H), 6.28 (d, *J* = 13.6 Hz, 1H), 6.02 (dt, *J* = 13.6, 6.8 Hz, 1H), 4.36 (d, *J* = 6.8 Hz, 2H).

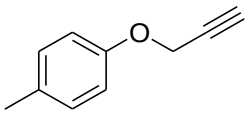
^{13}C NMR (126 MHz, $CDCl_3$) δ 139.39, 139.28, 134.22, 134.19, 131.60, 129.33, 129.27, 128.44, 128.27, 125.95, 47.51.

HRMS (ESI) ($M+H^+$) calculated 633.0488, found 633.0491

1.4.4 *Experimental Procedures for Mechanistic Studies*

Synthesis of Materials for Mechanistic Studies

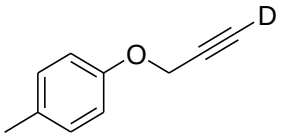
1-methyl-4-(prop-2-ynyloxy)benzene



Synthesised according to general procedure A. The crude product was dissolved in ether and washed with 2 M NaOH(aq). The organic layer was dried over sodium sulphate, filtered, and concentrated under reduced pressure. The product was used for the next step without further purification. (2.3 g, 85% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.3 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 4.66 (d, *J* = 2.4 Hz, 2H), 2.50 (t, *J* = 2.4 Hz, 1H), 2.29 (s, 3H).

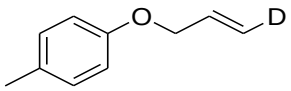
1-methyl-4-(3-deuterio-2-propynyloxy)benzene[30].



1-methyl-4-(prop-2-ynyloxy)benzene was dissolved in dry THF under nitrogen at -78 °C followed by addition of 2.5 M nBuLi in THF (2 equiv). After being stirred for additional 2 hours, the reaction mixture was cooled down to -78 °C, quenched with D_2O (excess), diluted with ether, and washed with water. After extraction, the organic layer was dried over sodium sulphate, filtered, and concentrated in vacuo. The crude product was purified through column chromatography (EtOAc/Hexanes = 1/50) to afford a colourless oil (2.03 g, 89% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.3 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 4.66 (s, 2H), 2.29 (s, 3H).

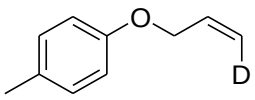
(*E*)-1-(3-deuterio-prop-2-enyloxy)-4-methylbenzene ((*E*)-1.4-*d*)



To Cp_2ZrCl_2 (1.5 equiv) in THF was added $LiAlH_4$ (0.4 equiv) powder. The reaction mixture was stirred at room temperature for 3 hours and 1-methyl-4-(prop-2-ynyloxy)benzene (1 equiv) was added. The reaction mixture was stirred for additional 5 hours, quenched with D_2O, and was allowed to stir overnight. The reaction mixture was diluted with ether and was washed with 1 M HCl (aq), saturated $NaHCO_3$ (aq), and brine. The organic layer was dried over sodium sulphate, filtered, and concentrated under reduced pressure. The crude was purified through column chromatography (EtOAc/Hexanes = 1/50) to afford a pale-yellow oil (727.2 mg, 50% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.2 Hz, 2H), 6.82 (d, *J* = 8.4 Hz, 2H), 6.05 (dt, *J* = 16.9, 4.8 Hz, 1H), 5.39 (d, *J* = 17.2 Hz, 1H), 4.64 – 4.33 (m, 2H), 2.29 (s, 3H).

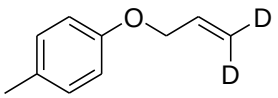
(*Z*)-1-(3-deuterio-prop-2-enyloxy)-4-methylbenzene ((*Z*)-1.4-*d*)



To Cp_2ZrCl_2 (1.5 equiv) in THF was added $LiAlH_4$ (0.4 equiv) powder. The reaction mixture was stirred at room temperature for 3 hours and 1-methyl-4-(3-deuterio-2-propynyloxy)benzene (1 equiv) was added. The reaction mixture was stirred for additional 5 hours, quenched with deionised water, and was allowed to stir overnight. The reaction mixture was diluted with ether and was washed with 1 M HCl (aq), saturated $NaHCO_3$ (aq), and brine. The organic layer was dried over sodium sulphate, filtered, and concentrated under reduced pressure. The crude was purified through column chromatography (EtOAc/Hexanes = 1/50) to afford a pale-yellow oil (600 mg, 40% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.2 Hz, 2H), 6.82 (d, *J* = 8.4 Hz, 2H), 6.05 (d, *J* = 5.2 Hz, 1H), 5.26 (d, *J* = 10.6 Hz, 1H), 4.51 (d, *J* = 4.0 Hz, 2H), 2.28 (s, 3H).

1-(3,3-di-deuterio-prop-2-enyloxy)-4-methylbenzene (1.4-d_2)



To Cp_2ZrCl_2 (1.5 equiv) in THF was added $LiAlH_4$ (0.4 equiv) powder. The reaction mixture was stirred at room temperature for 3 hours and 1-methyl-4-(3-deuterio-2-propynyloxy)benzene (1 equiv) was added. The reaction mixture was stirred for additional 5 hours, quenched with D_2O, and was allowed to stir overnight. The reaction mixture was diluted with ether and was washed with 1 M HCl (aq), saturated $NaHCO_3$ (aq), and brine. The organic layer was dried over sodium sulphate, filtered, and concentrated under reduced pressure. The crude was purified through column chromatography (EtOAc/Hexanes = 1/50) to give a yellow oil (1.54 g, 74% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.4 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 6.13 – 5.90 (m, 1H), 4.51 (d, *J* = 5.3 Hz, 2H), 2.29 (s, 3H).

Procedure for Deuterium Labelling Experiment

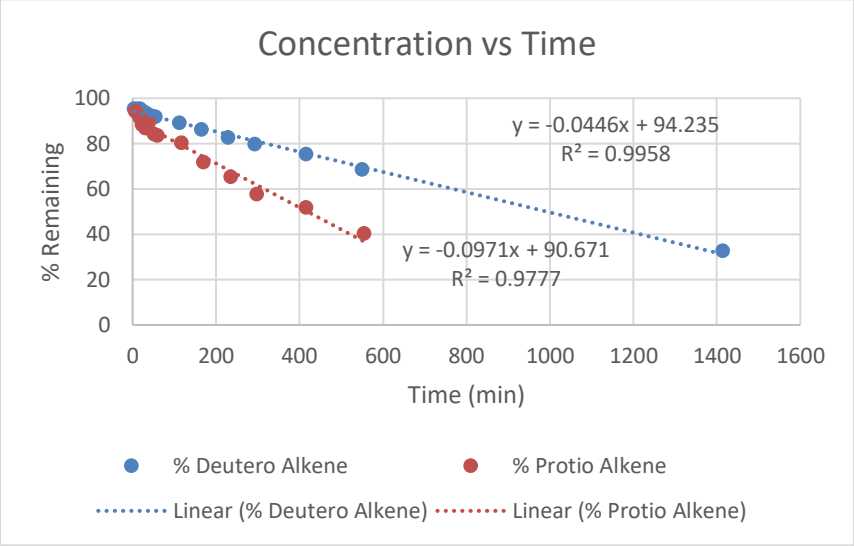
Both (*E*)-1.4-*d* and (*Z*)-1.4-*d* were subjected to the conditions described in General Procedure B and Breder's conditions[18], respectively. Crude ^{1}H NMRs were taken and analysed for mechanistic studies.

Procedure for KIE Experiment: Competition Experiment

A competition experiment was run in which a mixture of 1:1 molar ratio of 1.4 and 1.4-d_2 was subjected to the reaction conditions described in General Procedure B and Breder's conditions[18], respectively. Crude ^{1}H NMRs were taken and analysed for mechanistic studies.

Procedure for KIE Experiment: Independent Rate Measurement

Both 1.4 and 1.4-d_2 were independently subjected to the reaction conditions described in General Procedure B in an NMR tube with $CDCl_3$ as solvent. Spectra were taken at various time points and the results are shown in the graph below.



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Chapter 2. DIASTEREOCONVERGENT SYNTHESIS OF ANTI-1,2-AMINO ALCOHOLS BEARING QUATERNARY N-CONTAINING STEREOCENTRE VIA INTERMOLECULAR DIRECT C-H AMINATION CATALYSED BY PHOSPHINE SELENIDES

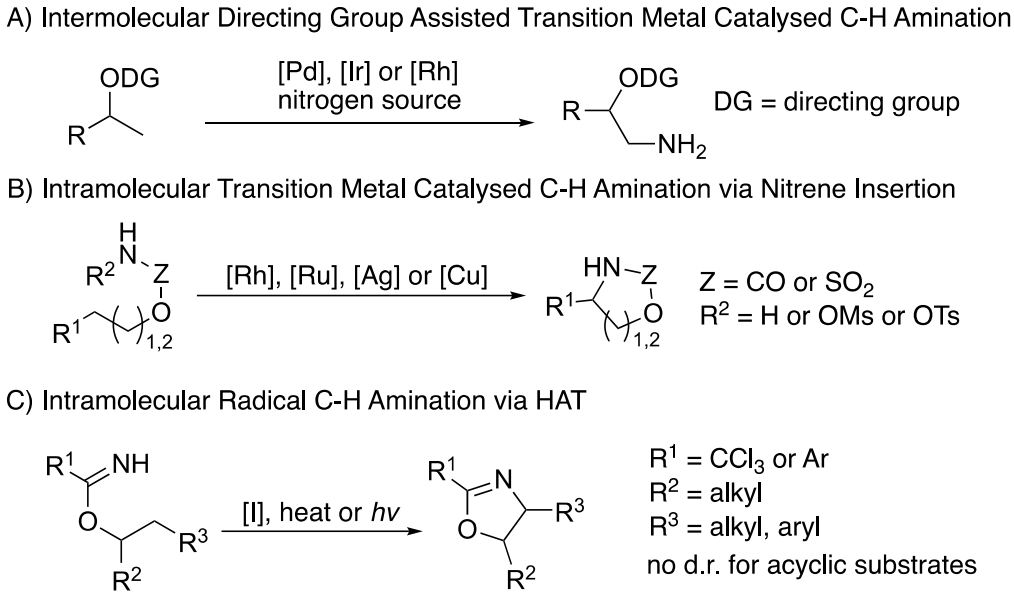
2.1 INTRODUCTION

Vicinal amino alcohols are ubiquitous motifs in a wide range of pharmaceuticals[1,2], ligands, and organocatalysts in asymmetric catalysis[3,4]. Traditional synthesis of 1,2-amino alcohols is accomplished through functional group interconversion and C-C bond formation. For example, numerous methods have been reported including ring opening of epoxides[5–10] or aziridines[11], hydroboration of enamines[12], reduction of α-amino ketones/α-hydroxyl imines[12,13], aminohydroxylation of olefins[14], etc. Extensive studies have also been conducted on the development of asymmetric Mannich reaction giving 1,2-amino alcohols through C-C bond formation[15–20]. Although these well-established methods are robust, pre-oxidised materials are often required, requiring additional steps for functional group manipulations.

Direct C-H functionalisation offers a powerful alternative strategy to overcome these inherent drawbacks, streamline synthesis of complex molecules, and enable late-stage modification[21–23]. In this context, state-of-the-art strategies for the synthesis of 1,2-amino alcohols are transition-metal catalysed and radical-mediated direct C-H functionalisation (Scheme 2.1). Intramolecular transition-metal catalysed direct C-H amination via nitrene insertion using Rh[24–26], Ru[27,28], Ag[29,30], and Cu[31] catalysts has been reported. However, the competing aziridination of alkene must be thoroughly considered in the development of these reactions. Intermolecular transformations were also accomplished using Rh[32], Pd[33], and Ir[34] catalysts via directing group assisted C-H activation.

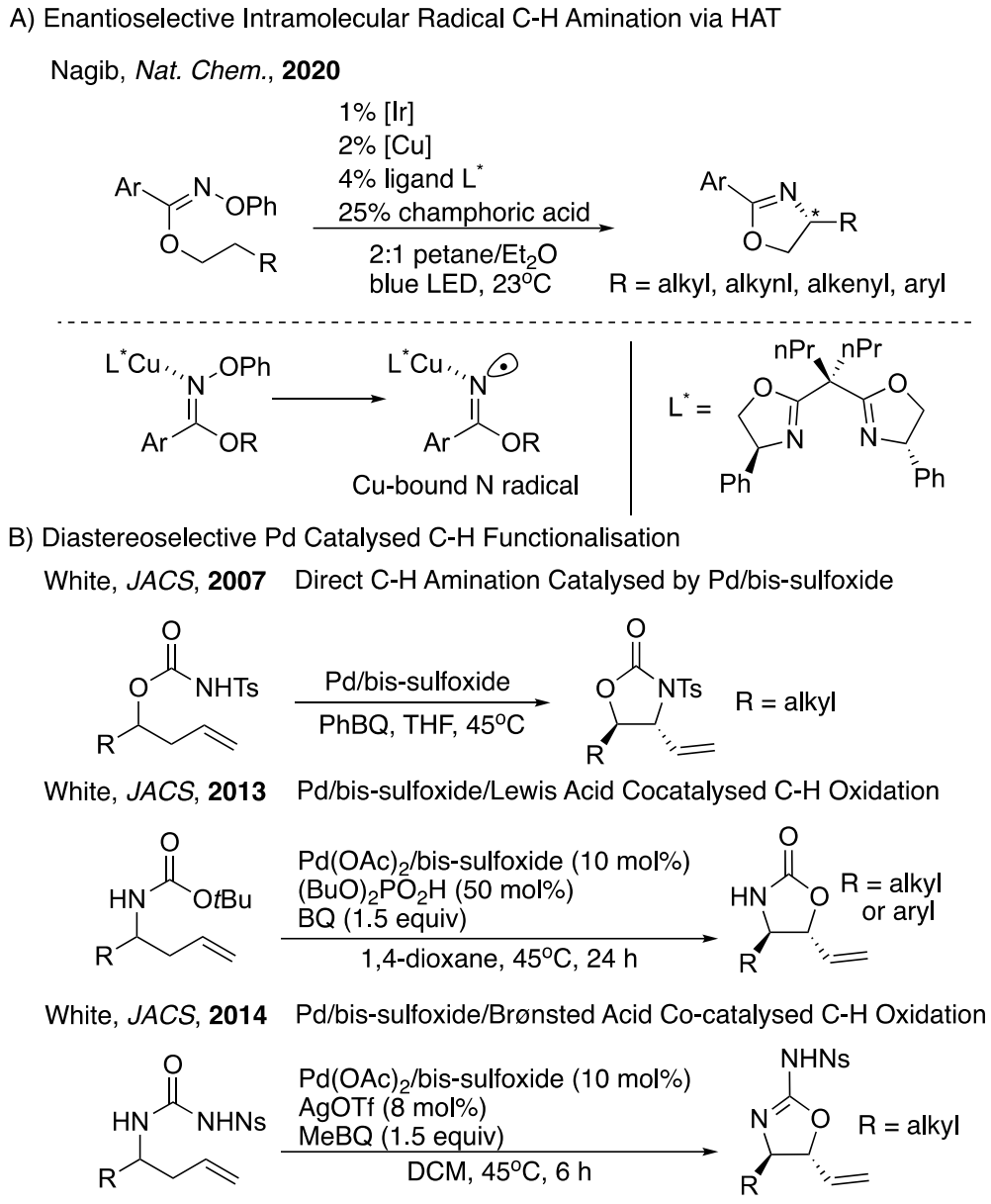
Alternatively, intramolecular radical C-H amination via 1,5-hydrogen atom transfer (HAT) under thermal and photocatalytic conditions has been developed[35–38].

Scheme 2.1 Strategies for Amino Alcohol Synthesis via Direct C-H Amination



Although these methods can be applied to accessing 1,2-amino alcohols, most of these reactions require intramolecular delivery of nitrogen group and little attention had been paid to diastereoselectivity. In 2007, White and co-workers reported an intramolecular synthesis of *syn*-1,2-amino alcohols by allylic amination via direct cleavage of an allylic C-H bond promoted by Pd(II)/bis-sulfoxide catalytic system (Scheme 2.2B)[39]. In the following years, this catalytic system was further extended to allylic C-H oxidation with co-catalysis of Brønsted acid or Lewis acid (Scheme 2.2B)[40,41]. However, all these transformations are intramolecular and give *syn*-1,2-amino alcohols as the major diastereomer. Notably, these reactions do not tolerate tertiary C-H bond at the allylic position. Thus, 1,2-amino alcohols bearing N-containing quaternary stereocentre cannot be synthesised using these protocols. To the best of our knowledge, intermolecular transformations giving *anti*-1,2-amino alcohols bearing N-containing quaternary stereocentre via direct C-H amination remain elusive.

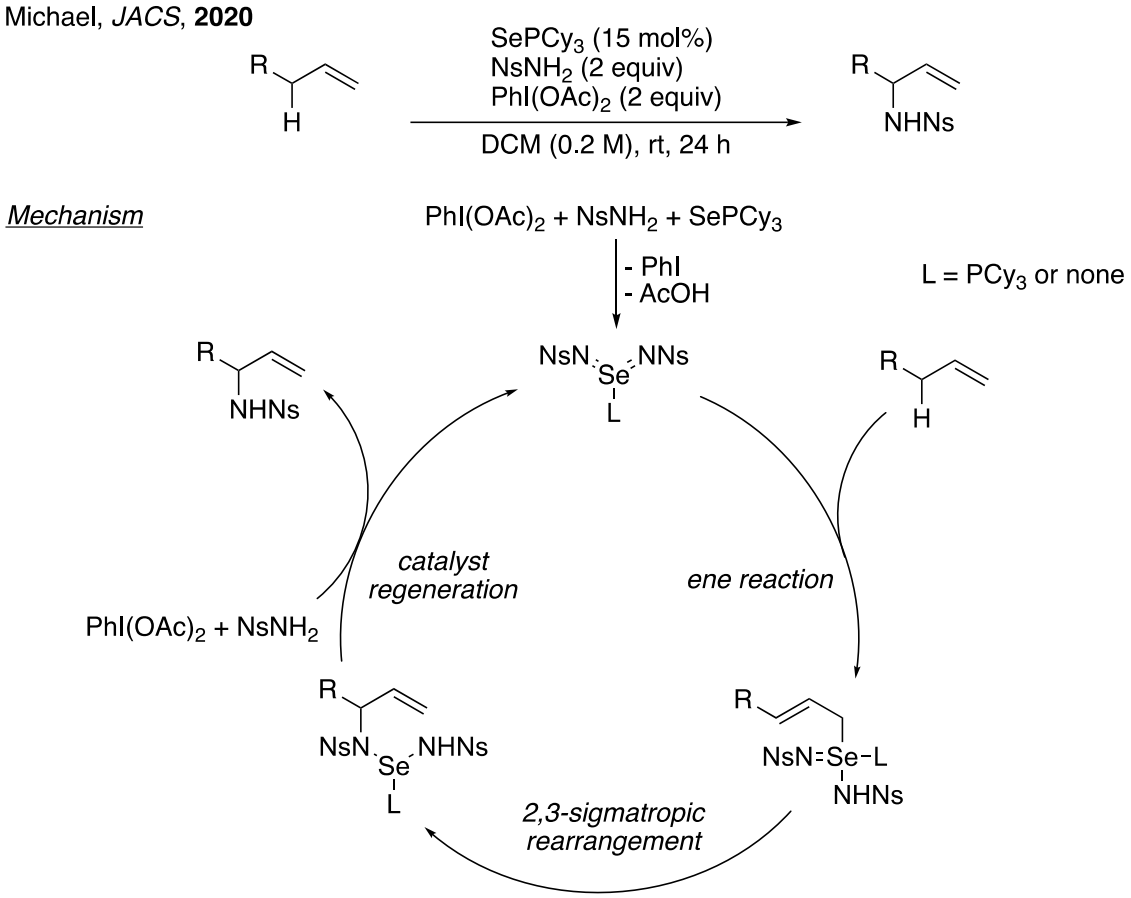
Scheme 2.2 Stereoselective Synthesis of 1,2-Amino Alcohols via Direct C-H Activation



Although C-H amination via nitrene insertion[42] has been demonstrated as an effective approach to constructing N-containing quaternary stereocentre, these reactions occur with retention of stereochemistry of C-H bonds. Therefore, diastereomerically pure starting materials are required for diastereoselective synthesis of 1,2-amino alcohols bearing N-containing quaternary stereocentre from homoallylic alcohols via nitrene insertion. However, diastereoselective synthesis of homoallylic alcohol derivatives is often challenging.

In 2020, our group reported a metal-free allylic amination catalysed by phosphine selenides (Scheme 2.3)[43]. The reaction proceeds via an ene reaction between an imidoselenium species and an alkene, followed by a 2,3-sigmatropic rearrangement.

Scheme 2.3 Previous Work - Allylic Amination Catalysed by Phosphine Selenides



Careful analysis of the mechanism reveals that the allylic stereocentre in homoallylic alcohol derivatives is destroyed in the ene reaction, opening up the possibility of a diastereoconvergent process, which would allow for diastereoselective formation of a N-containing quaternary stereocentre from either diastereomer of the starting material (Figure 2.1). In this chapter, we disclose a diastereoconvergent synthesis of *anti*-1,2-amino alcohols bearing N-containing quaternary stereocentre via intermolecular direct C-H amination of homoallylic alcohol derivatives catalysed by phosphine selenides under metal-free conditions.

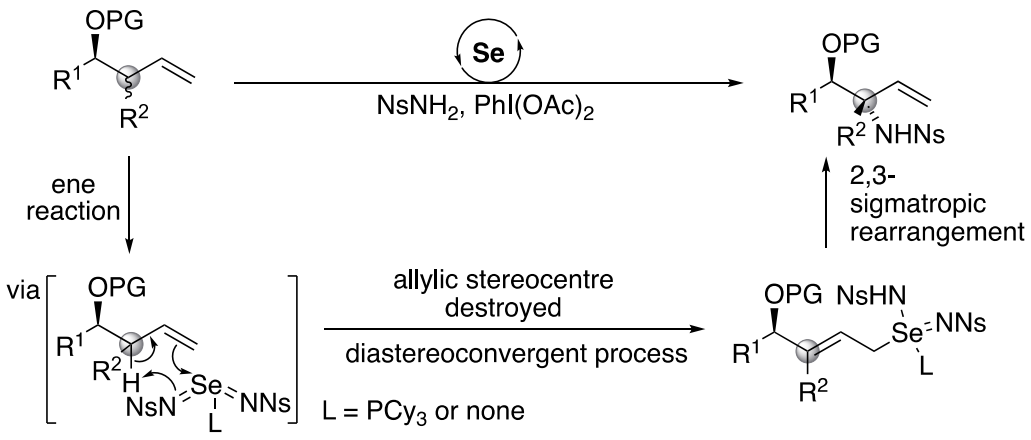


Figure 2.1 Working Hypothesis for Diastereoconvergent Synthesis of 1,2-Amino Alcohols

Remote stereocontrol has been a difficult task in organic synthesis. In the case of substrate control, direct interactions between the chiral group and the prochiral group are required to impose effective conformational restrictions to the transition states of these reactions. However, direct interactions can only be accomplished when the chiral group and the prochiral group are at most 2 bonds apart (Figure 2.2A). Thus, remote stereocontrol such as 1,4-asymmetric induction is particularly challenging. We hypothesised that our reaction mechanism would enable a relay process of chirality transfer where 1,2-asymmetric induction would occur in the ene reaction, followed by 1,3-asymmetric induction in the 2,3-sigmatropic rearrangement (Figure 2.2B). Based on this hypothesis, we demonstrated that this reaction protocol can be applied to the synthesis of *syn*-1,4-amino alcohols from allylic alcohol derivatives bearing internal *Z*-alkene. To the best of our knowledge, this is the first example of diastereoselective synthesis of 1,4-amino alcohols via direct C-H amination.

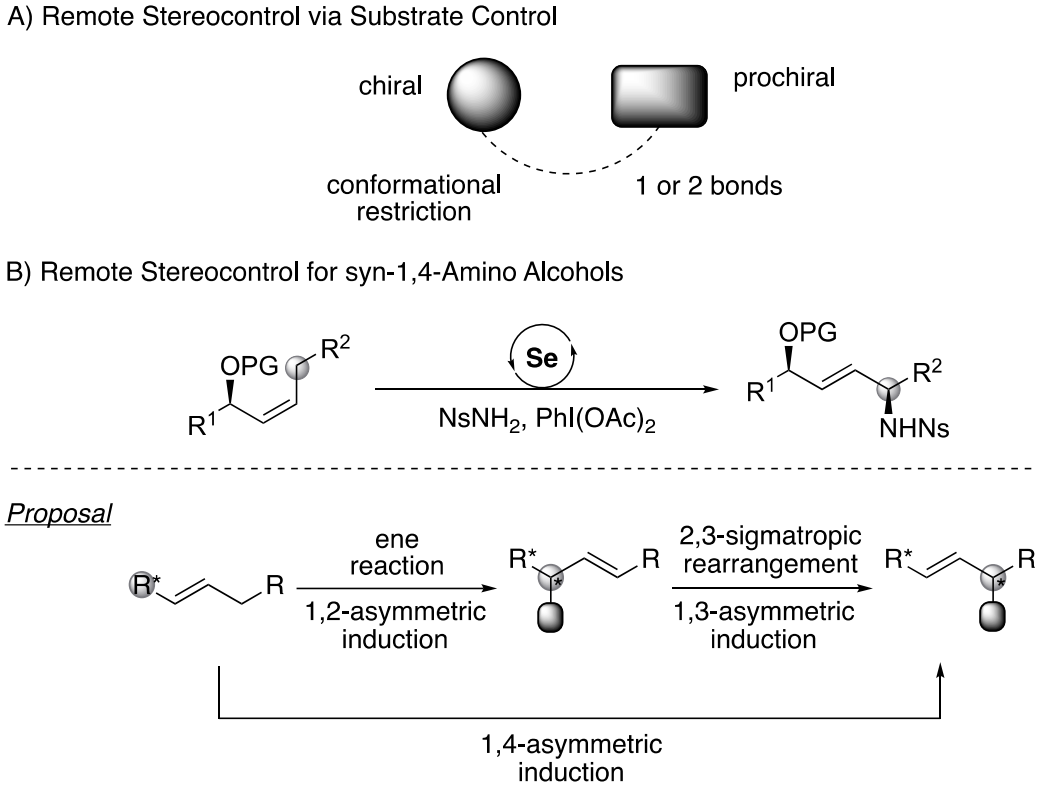


Figure 2.2 Working Hypothesis for Diastereoselective Synthesis of 1,4-Amino Alcohols

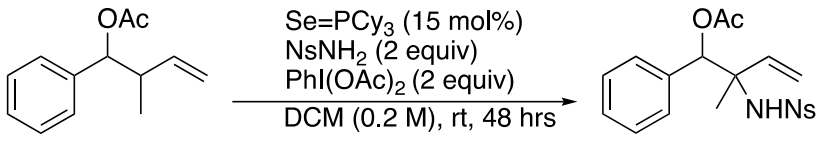
2.2 RESULTS AND DISCUSSION

2.2.1 *Reaction Optimisation for 1,2-Amino Alcohols*

Initial investigation started by applying our previous allylic amination conditions to model substrate 2.1 (Table 2.1). Although the desired aminated product 2.2 was identified in 21% yield, substantial amount of starting material was observed (Table 2.1, entry 1). Several variants of reaction conditions were tested to improve the reaction. Running the reaction at elevated temperature resulted in even lower yield and substrate recovery (Table 2.1, entry 3). Using less oxidant and nitrogen nucleophile at 35ºC did not improve the reaction (Table 2.1, entry 2). The reaction was sluggish when p-nitrobenzoic acid was added as an additive (Table 2.1, entry 4). To our delight, when magnesium oxide or calcium oxide was added at 35ºC, the yield was boosted to

around 50%. Conversion of starting material to product was also improved (Table 2.1, entries 5 and 6).

Table 2.1 Initial Investigation of Reaction Condition



2.1
anti:syn = 1:1

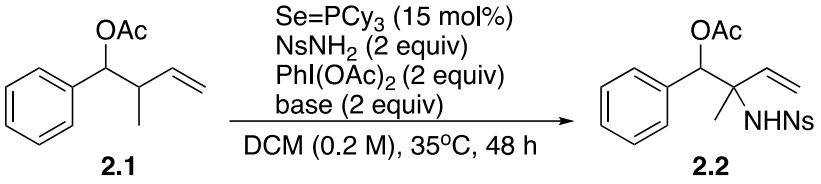
2.2

entry	changes to conditions above	substrate (%)[a]	yield (%)[a]
1	none	26	21 (11:1)
2	1.5 eq $NsNH_2$, 1.5 eq $PhI(OAc)_2$, 35°C	18	15
3	35°C	17	13
4	2 equiv p-nitrobenzoic acid, 35°C	32	15
5	2 equiv CaO, 35°C	14	47
6	2 equiv MgO, 35°C	14	54

[a] Yields determined by ^1H NMR using 1,3-dinitrobenzene as internal standard.

A base screen was performed to further improve the reaction. Among all the tested inorganic bases, lithium carbonate was identified as the optimal base additive. We found that adding 2 equiv of lithium carbonate enabled full conversion of starting material to product in 70% yield with a d.r. of 6:1 (Table 2.2, entry 3).

Table 2.2 Base Screen



2.1
anti:syn = 1:1

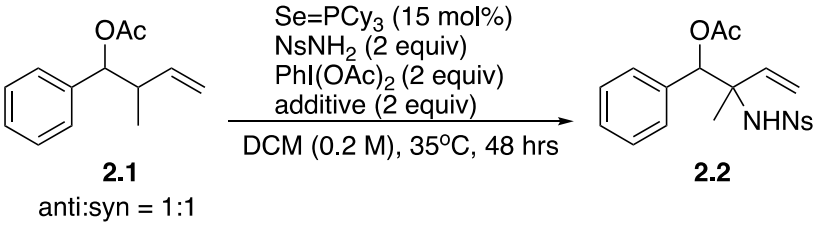
2.2

entry	base	substrate (%)[a]	yield (%)[a]
1	BaO	62	0
2	Cs_2CO_3	42	0
3	Li_2CO_3	0	70 (6:1)
4	K_2CO_3	71	0
5	Na_2CO_3	75	0
6	K_3PO_4	82	0
7	K_2HPO_4	50	0
8	KH_2PO_4	8	17

[a] Yields and d.r. were determined by ^1H NMR using 1,3-dinitrobenzene as internal standard.

The role of lithium carbonate was explored (Table 2.3). Lithium carbonate was initially proposed to be an acid scavenger since reduction of (diacetoxyiodo)benzene generates acetic acid. However, this hypothesis was disputed by the lack of efficacy of other similar carbonate base additives (Table 2.2, entries 2, 4, and 5). To verify if lithium cation is the key, lithium triflate and lithium acetate were tested. Although lithium acetate showed effects similar to that of lithium carbonate, lower conversion of substrate was observed (Table 2.3, entry 2). However, when lithium triflate was used, all starting materials decomposed and no product was identified (Table 2.3, entry 3). We then hypothesised that lithium carbonate might be a drying agent due to its powdery structure. However, addition of other drying agents such as powdered molecular sieves and anhydrous calcium chloride, did not give any product (Table 2.3, entries 4 and 5). The role of lithium carbonate remains unclear.

Table 2.3 Potential Role of Lithium Carbonate



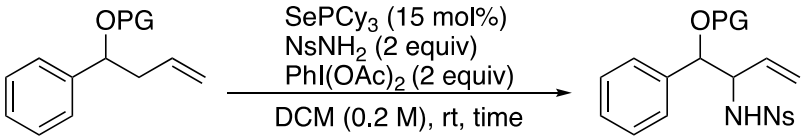
2.1
anti:syn = 1:1

2.2

entry	additive	substrate (%)[a]	yield (%)[a]
1	Li_2CO_3	0	70 (6:1)
2	LiOAc	20	62 (14:1)
3	LiOTf	0	0
4	4 Å Molecular Sieves	88	0
5	$CaCl_2$	0	0

[a] Yields and d.r. were determined by ^{1}H NMR using 1,3-dinitrobenzene as internal standard.

Table 2.4 Protecting Group Screen



entry	PG	yield (%)[a]	time (h)
1	Ac	79 (7:1)	24
2	Bn	58	48
3	TBDPS	61 (18:1)	48
4	Piv	70 (16:1)	44
5[c]	Trt	trace	50
6	Troc	69 (6:1)	24

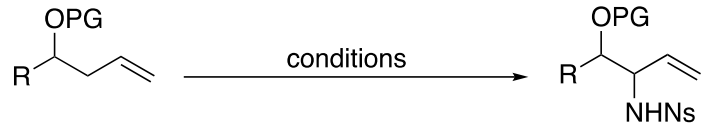
[a] Yields and d.r. were determined by ^{1}H NMR using 1,3-dinitrobenzene as internal standard. [b] PG = protecting group. [c] Reaction was incomplete after 50 hours. [d] d.r. was provided in the parenthesis when applicable.

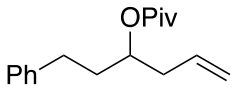
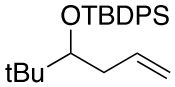
Effect of protecting groups was explored using substrates without allylic substituents (Table 2.4). A series of protecting groups was tested under our previous allylic amination conditions. Unlike substrates with allylic substituents, these reactions proceeded smoothly without lithium

carbonate. Trityl group gave incomplete conversion due to steric hindrance, resulting in only trace amount of product after 50 hours (Table 2.4, entry 5). As a result, pivalate was chosen as the optimal protecting group as it gave both decent diastereoselectivity and yield (Table 2.4, entry 4).

The effect of lithium carbonate for substrates with allylic substituents was also manifested in substrates without allylic substituents. Improved diastereoselectivity and yield were observed when lithium carbonate was added at 35°C (Table 2.5).

Table 2.5 Improved Diastereoselectivity and Yields with Lithium Carbonate

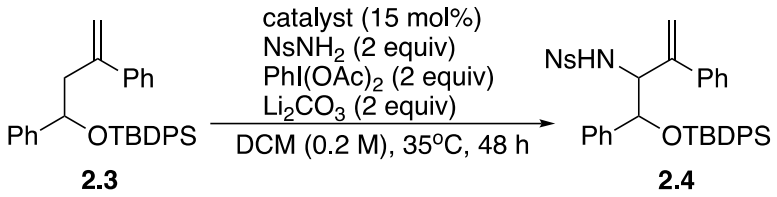


entry	substrate	yield (%) without Li_2CO_3	yield (%) with Li_2CO_3
1		66 (6:1)	79 (8:1)
2		62 (single diastereomer)	72 (single diastereomer)

[a] Yields and d.r. were determined by ^1H NMR using 1,3-dinitrobenzene as internal standard. [b] d.r. is reported in parenthesis.

Next, 1,1-disubstituted alkenes were examined. A catalyst screen revealed that NHC selenides were more effective than phosphine selenides in general (Table 2.6). For example, when $SePCy_3$ was used without lithium carbonate, the desired product was given in only 32% yield (Table 2.6, entry 1). Replacing phosphine ligands with NHC counterparts boosted the yield to as high as 54% (Table 2.6, entry 7). When lithium carbonate was added, both yield and diastereoselectivity were improved (Table 2.6).

Table 2.6 Optimisation for 1,1-Disubstituted Alkene



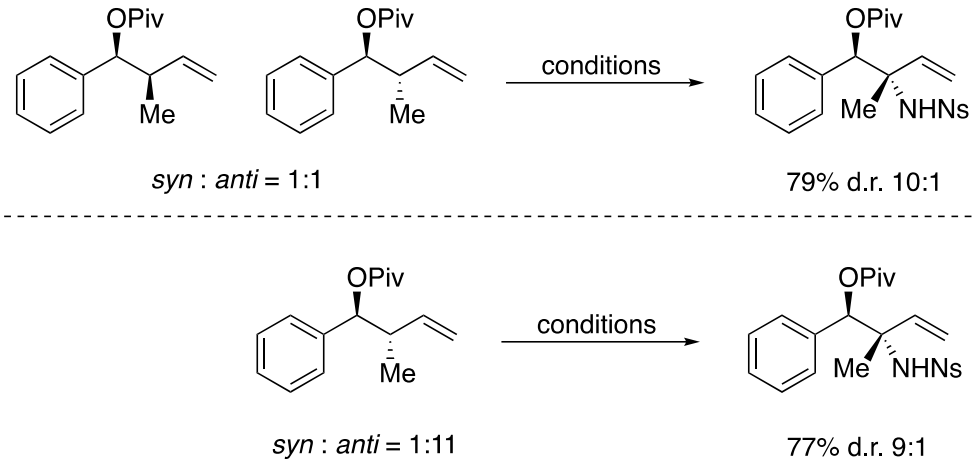
2.3 **2.4**

entry	catalyst	yield (%)[a] w Li_2CO_3	yield (%)[a] w/o Li_2CO_3
1	$SePCy_3$	48 (10:1)	32
2	$SePNp_3$	N/A	26
3	$SeP(o\text{-}tol)_3$	N/A	28
4	$SeP(tBu)_3$	N/A	38
5	$SeP(OPh)_3$	N/A	22
6	$SeP(NEt_2)_3$	N/A	26
7	SeIMe	58 (10:1)	54 (10:1)
8	SeItBu	62 (11:1)	53 (9:1)
9	SeICy	62 (11:1)	53 (8:1)
10	SeIMe (saturated)	55 (10:1)	44 (9:1)

[a] Yields and d.r. were determined by ^1H NMR using 1,3-dinitrobenzene as internal standard.
[b] d.r. is reported in parenthesis where applicable.

As discussed, we hypothesised that the reaction would be diastereoconvergent due to the destruction of allylic stereocentre of the starting material in the ene reaction. To verify our hypothesis, reactions of two mixtures of diastereomers of different d.r. were carried out separately under optimised conditions (Scheme 2.4). Both reactions gave almost the same results, suggesting that the reaction is diastereoconvergent.

Scheme 2.4 Diastereoconvergence - Impact of Diastereomeric Ratio of Substrate on Stereochemical Outcome



[a] Conditions: See Table 2.7.

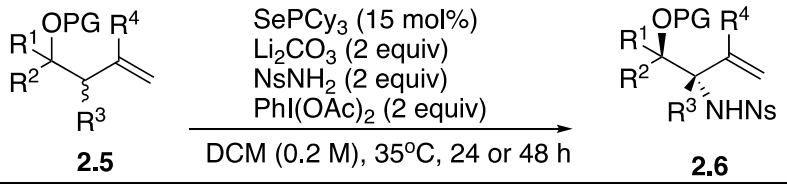
To summarise, optimisation shows that pivalate is optimal protecting group for most substrate classes. Lithium carbonate is essential to the success in reactions of substrates with allylic substituents. However, the effect of lithium carbonate is universally observed across all investigated substrate classes. The optimised conditions are presented in Table 2.7.

2.2.2 *Substrate Scope for 1,2-Amino Alcohols*

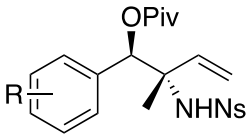
Substrate scope for 1,2-amino alcohols was examined by applying the optimised conditions to a variety of homoallylic alcohol derivatives (Table 2.7). Yields and diastereoselectivity were generally high. The reaction features excellent compatibility with common functional groups including ester, alkyl halides, nitrile, aryl halides, ether, silyl ether, etc. Notably, our reaction tolerates a variety of heterocycles, especially pharmaceutically important nitrogen-containing heteroaromatics, including thiophene (2.6j), indole (2.6r), pyrazole (2.6k), quinoline (2.6l) and pyridine (2.6m). The substitution pattern of substrates was also thoroughly explored. The reaction tolerates aryl, primary alkyl, secondary alkyl, and tertiary alkyl groups at homoallylic position. The reaction also tolerates various alkyl groups at the allylic position, giving aminated quaternary

stereocentre in decent yields and diastereoselectivity (2.6h, 2.6i). Additionally, diastereoselectivity increases as homoallylic groups becomes more sterically hindered. Notably, when *tert*-butyl group is used, the reaction furnishes a single diastereomer in 77% yield (2.6p). This trend applies to both substrates without allylic substituents (2.6n, 2.6o, 2.6q and 2.6p) and substrates with allylic substituents (2.6e, 2.6a, and 2.6d). Furthermore, the reaction is also effective for 1,1-disubstitued alkenes (2.6x) and cyclic alkenes (2.6w). However, NHC selenides are required as the catalyst to make the reaction work for 1,1-disubstituted alkenes.

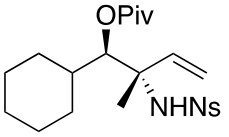
Table 2.7 Substrate Scope for Anti-1,2-Amino Alcohols



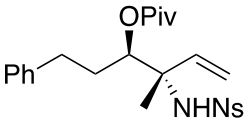
2.5 **2.6**



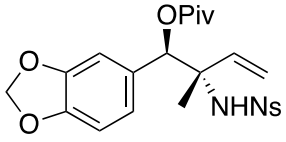
2.6a, R = H, 79% (10:1)
2.6b, R = 3-Br, 82% (15:1)
2.6c, R = 4-CN, 77% (single)



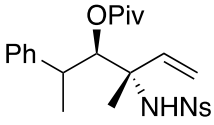
2.6d, 75% (11:1)



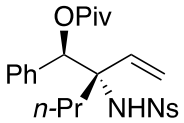
2.6e, 85% (4.2:1)



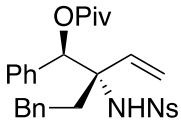
2.6f, 76% (11:1)



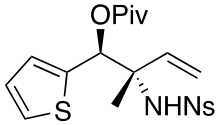
2.6g, 78% (16.6:1)



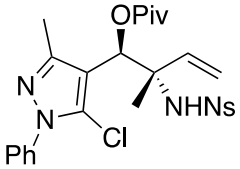
2.6h, 72% (7:1)[a]



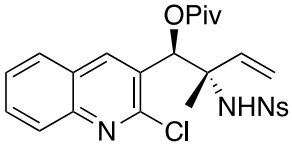
2.6i, 78% (12:1)[a]



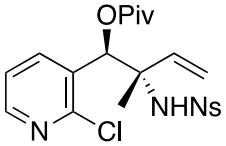
2.6j, 72% (10:1)



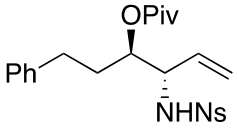
2.6k, 60% (12:1)[a]



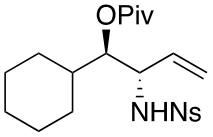
2.6l, 67% (13:1)[a]



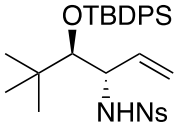
2.6m, 75% (17:1)[a]



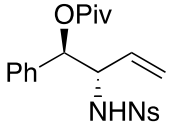
2.6n, 79% (8:1)



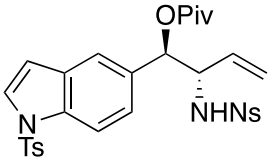
2.6o, 80% (8:1)



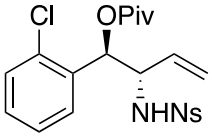
2.6p, 77% (1 isomer)



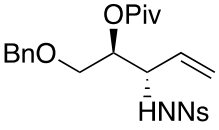
2.6q, 86% (11:1)



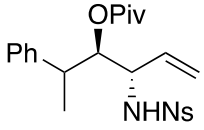
2.6r, 69% (13:1)



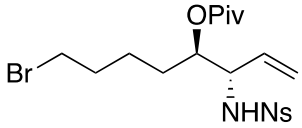
2.6s, 83% (7.2:1)



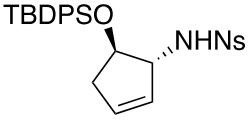
2.6t, 64% (10:1)



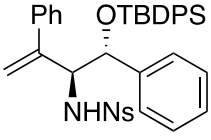
2.6u, 88% (3:1)



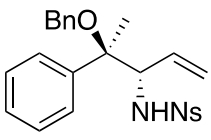
2.6v, 86% (10:1)



2.6w, 73% (10:1)



2.6x, 64% (10:1)[d]



2.6y, 74% (2.3:1)

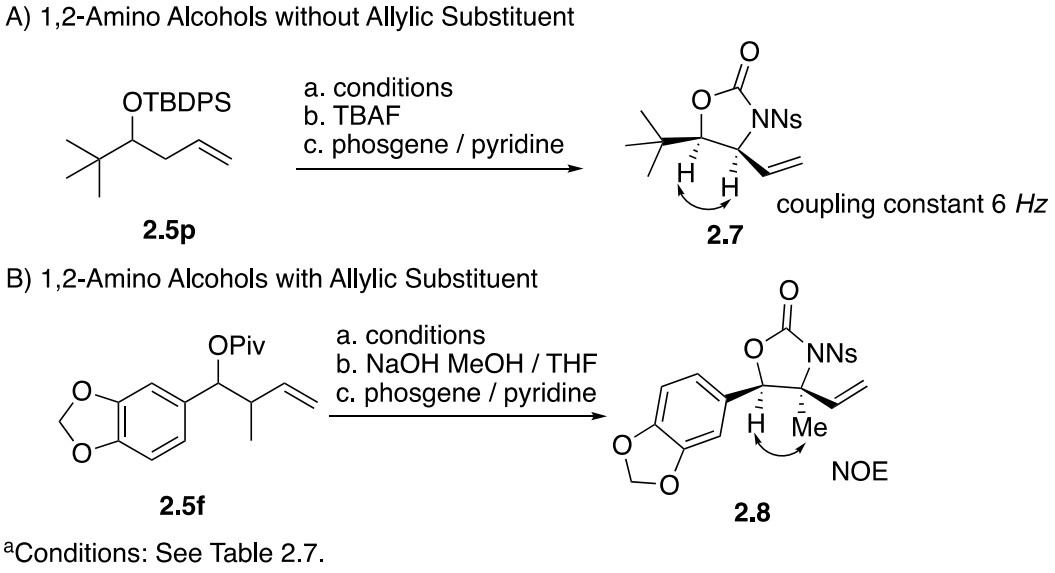
[a]Reaction was performed by using $SePCy_3$ (30 mol%) in DCE at 50°C. [b]Isolated yields. [c]Diastereomeric ratio (d.r.) determined by ^1H NMR spectroscopy. [d]ItBuSe was used as the catalyst. [e]PG = Protecting Group.

2.2.3 *Mechanistic Studies for 1,2-Amino Alcohols*

2.2.3.1 Experimental Evidence

To probe the stereochemistry of 1,2-amino alcohols, 2.5p and 2.5f were deprotected and cyclised to 2.7 and 2.8, respectively (Scheme 2.5). The ^{1}H NMR of 2.7 showed a coupling constant of 6 Hz of the two adjacent protons (Scheme 2.5A). Comparison of coupling constant to known literature value[44] indicated that the protons are *cis* in 2.7, suggesting that the reaction affords *anti*-1,2-amino alcohols without allylic substituents as the major diastereomer. A NOSEY experiment was performed for 2.8 (Scheme 2.5B). An NOE between the benzylic proton and the allylic methyl group was observed, indicating that the two groups are spatially proximal to each other and that the major product bearing allylic substituents is also *anti*-1,2-amino alcohol.

Scheme 2.5 Determination of Relative Stereochemistry of 1,2-Amino Alcohols



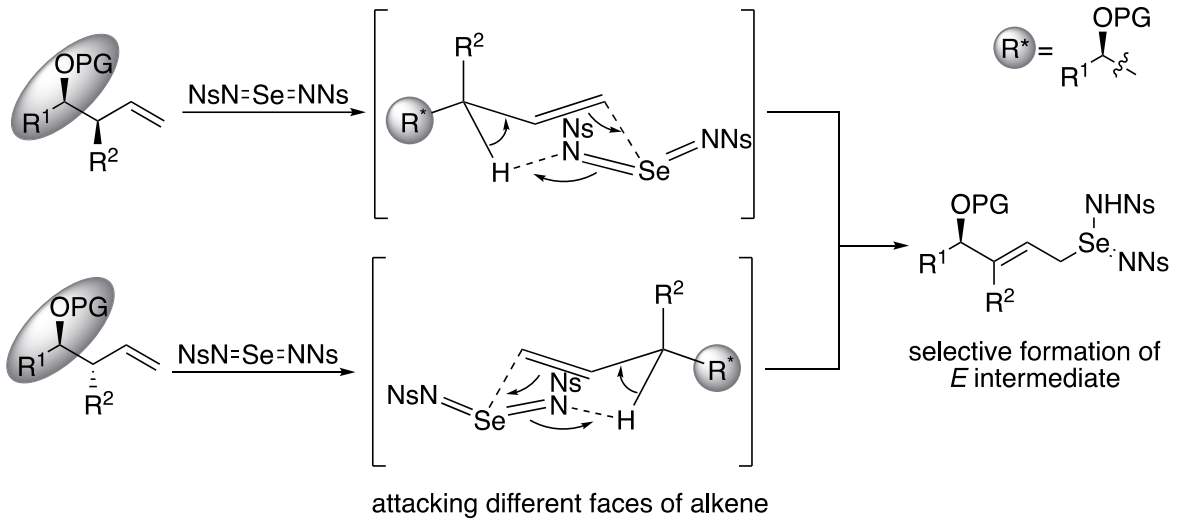
[a]Conditions: See Table 2.7.

2.2.3.2 Computational Study and Stereochemical Model – The Inside Alkoxy Effect

We sought to explain the diastereoselectivity by building a stereochemical model based on the proposed mechanism (Scheme 2.3) and computation. To understand the ene reaction, careful conformational analysis was performed for the six-membered-ring transition states for homoallylic

alcohol derivatives with different relative stereochemistry (Scheme 2.6). Analysis revealed that diastereoconvergence can be explained by the favourable formation of *E* intermediate in the ene reaction regardless of the original relative stereochemistry of the homoallylic alcohol derivatives. The favourable transition state places the bulky chiral group at the equatorial position, which is accomplished by having the diimido selenium species approach the alkene from different sides of the alkene.

Scheme 2.6 Conformational Analysis of the Ene Reaction for 1,2-Amino Alcohols



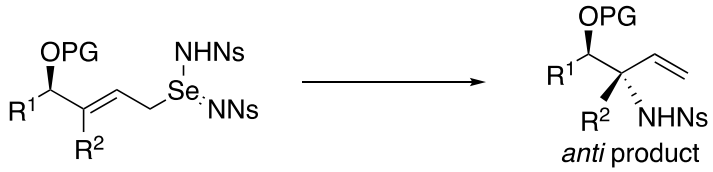
To gain insights into 2,3-sigmatropic rearrangement, computational study was performed in collaboration with Janna Berman (Scheme 2.7). The results revealed that the relative stereochemistry of the product is stereoelectronically controlled by inside alkoxy effect[45]. It has been documented that, in electrophilic addition reactions of alkenes, the presence of a C-O bond or other polar substituents at the allylic stereocentre adjacent to a prochiral sp^2 carbon has significant impact on the stereochemistry of products via both steric and stereoelectronic effects. The inside alkoxy effect states that the allylic C-O bond prefers to adopt the inside position over outside position and anti position in the transition state of the electrophilic addition reaction of the alkene. Inside, outside, and anti are terms describing orientations that the three allylic substituents

can take relative to the alkene and the incoming electrophilic reagent in the transition state. The inside position is defined as the spot coplanar with the alkene. The anti position is defined as the spot opposite to the incoming electrophilic reagent. The outside position is defined as the spot pointing away from the alkene. DFT calculations showed that the π bond becomes electron-deficient during the rearrangement and that electron-donating substituents on the alkene stabilise the transition state. This finding is consistent with the inside alkoxy effect. The protected hydroxyl group is coplanar with the alkene in the most stable transition state, minimising the overlap of electron-withdrawing σ^*_{CO} orbital with π bond. More importantly, this orientation maximises the overlap of electron-donating σ_{CH} and σ_{CR} with the π bond, stabilising the transition state and allowing for the stereoselection of the two alkene faces. The nitrogen group approaches the alkene from the H side more readily than from the other side blocked by R^1, leading to the *anti*-diastereomer. The calculations revealed that TS-I is more stable than TS-II by 2.6 kcal/mol, which correlates well with experimental observation of single diastereomer (Table 2.7, 2.5p and 2.6p).

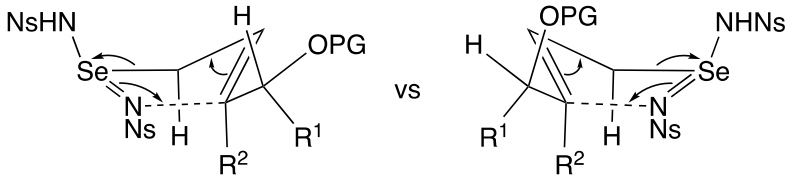
The stereochemical model is further justified by several observations. First, it is consistent with the trend that diastereoselectivity is improved as R^1 becomes bulkier (primary < secondary <tertiary) (Table 2.7, 2.6n, 2.6o, 2.6p). When *tert*-butyl group was used, a single diastereomer was obtained (Table 2.7, 2.6p). Second, substrates with flipped ester group do not show any diastereoselectivity (Scheme 2.8). This evidence strongly supports the presence of a stereoelectronic effect imposed by the allylic C-O bond and that the diastereoselectivity is not primarily controlled by steric effects of the substituents.

Scheme 2.7 The Inside Alkoxy Effect in 2,3-Sigmatropic Rearrangement

A) 2,3-Sigmatropic Rearrangement

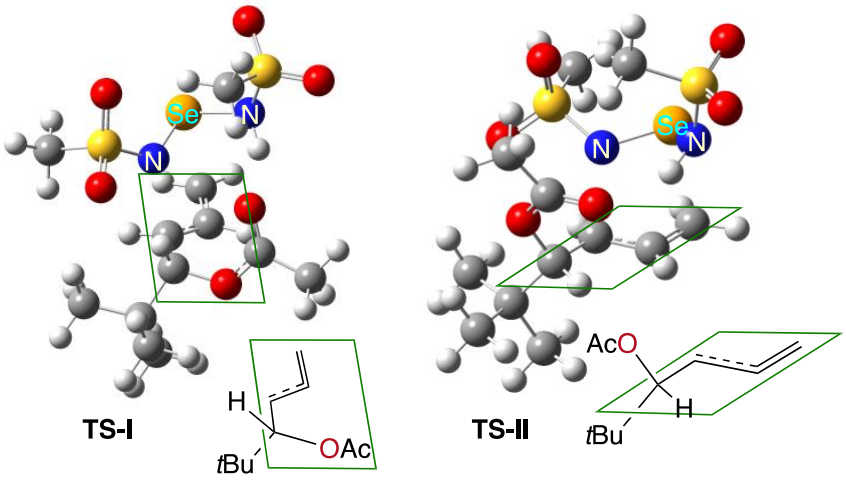


Transition State of 2,3-Sigmatropic Rearrangement



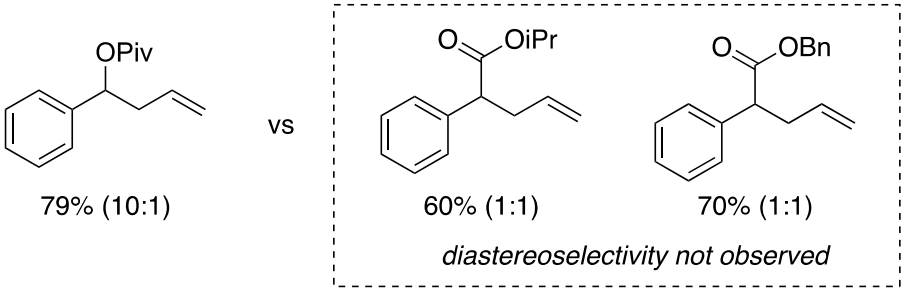
- inside alkoxy effect
- protected hydroxyl group coplanar with alkene
- minimised overlap of σ^*_{CO} with π
- maximised overlap of σ_{CC} and σ_{CH} with π

B) DFT Calculations for Transition State of 2,3-Sigmatropic Rearrangement



TS-I is more stable than TS-II by 2.6 kcal/mol

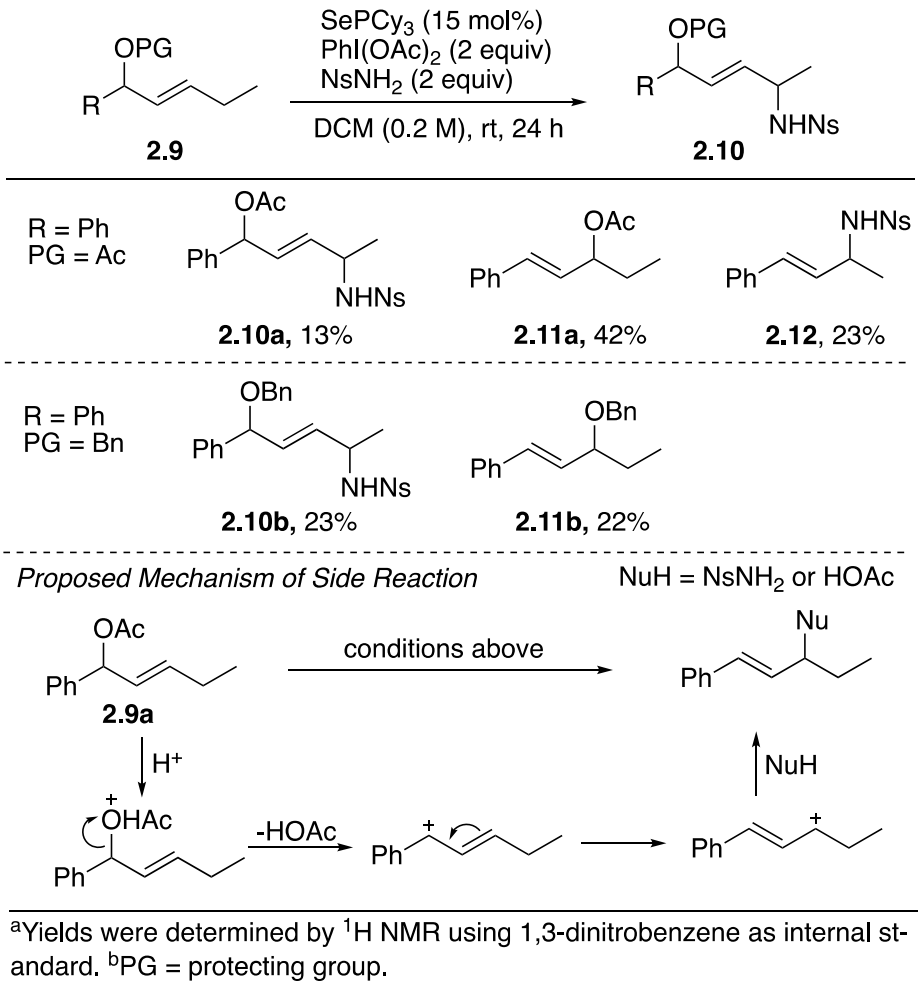
Scheme 2.8 Experimental Evidence for Presence of Inside Alkoxy Effect



2.2.4 *Reaction Optimisation for 1,4-Amino Alcohols*

Investigation started with our previous allylic amination conditions (Scheme 2.9). In the case of acetate 2.9a, two rearranged products (2.11a and 2.12) with alkene transposition were detected in substantial amount. However, the desired product 2.10a was only given in 13% yield. The same side reaction was also observed for benzyl protecting group. Re-examining the reaction condition, we noticed that the reaction mixture would be acidic as reduction of (diacetoxyiodo)benzene generates acetic acid as by-product. We proposed that, under this acidic condition, cleavage of benzylic C-O bond would occur, promoted by protonation of acetate/benzyl ether and stabilisation of carbocation by conjugation with the adjacent phenyl group (Scheme 2.9).

Scheme 2.9 Initial Results

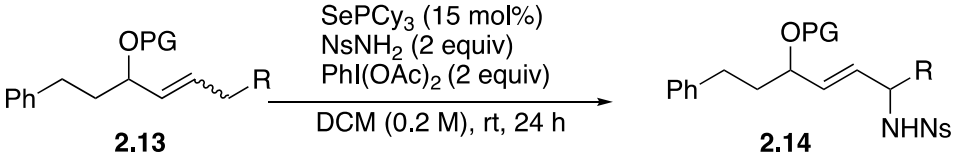


[a]Yields were determined by ^{1}H NMR using 1,3-dinitrobenzene as internal standard. [b]PG = protecting group.

We proposed that breaking the conjugation would prevent the decomposition of substrates. Thus, a series of substrates bearing *E* alkene with different protecting groups was prepared and tested (Table 2.8, entries 1-4). To our delight, decomposition of substrate was prevented. However, little to no diastereoselectivity was observed for these substrates (Table 2.8, entries, 1-4).

Allylic strain plays a critical role in stereoselective reactions[46]. We hypothesised that a *Z* alkene would potentially improve the diastereoselectivity by introducing direct steric interactions between the chiral group and the other allylic substituent across the alkene. This interaction would impose more conformational restriction to the orientation of the chiral group through 1,3-allylic strain, thereby allowing for stereoselection of the two alkene faces (Scheme 2.10). To our delight, using *Z* alkene and pivalate protecting group significantly improved the diastereoselectivity to 4.9:1 (Table 2.8, entry 5). In this process, the alkene isomerised from *cis* to *trans*, which was confirmed by a coupling constant of 15.5 Hz between the two vinylic protons.

Table 2.8 Optimisation for Syn-1,4-Amino Alcohols



2.13 **2.14**

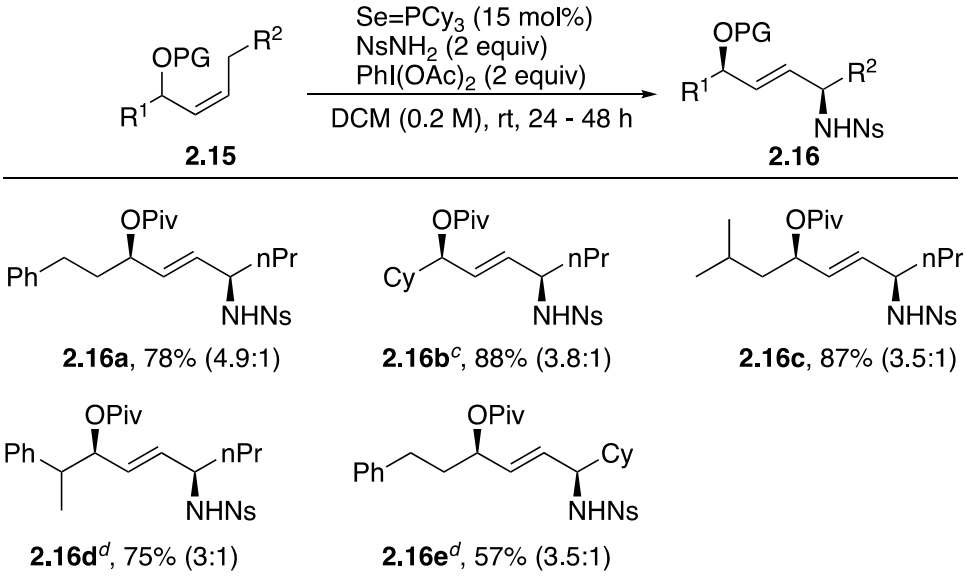
entry	PG and R	*E* or *Z*	yield (%)	d.r.
1	Ac, Me	*E*	75	1:1
2	Bz, Me	*E*	75 (76)	1.5:1
3	Piv, Me	*E*	76	1.7:1
4	TBDPS, Me	*E*	62	1.9:1
5	Piv, nPr	*Z*	78	4.9:1

[a]Yields and diastereomeric ratios were determined by ^{1}H NMR using 1,3-dinitrobenzene as internal standard. [b]PG = protecting group. [c]Yields in parathesis were isolated yields.

2.2.5 *Substrate Scope for 1,4-Amino Alcohols*

Investigation of substrate scope for 1,4-amino alcohols focuses on substitution pattern across the alkene (Table 2.9). In general, the reaction tolerates both primary and secondary groups on both sides of alkene. We found that the reaction is sensitive to steric effect of these groups. However, extending the reaction time or using higher catalyst loading pushed the reaction to completion in reasonable amount of time with decent yield and diastereoselectivity.

Table 2.9 Substrate Scope for Syn-1,4-Amino Alcohols



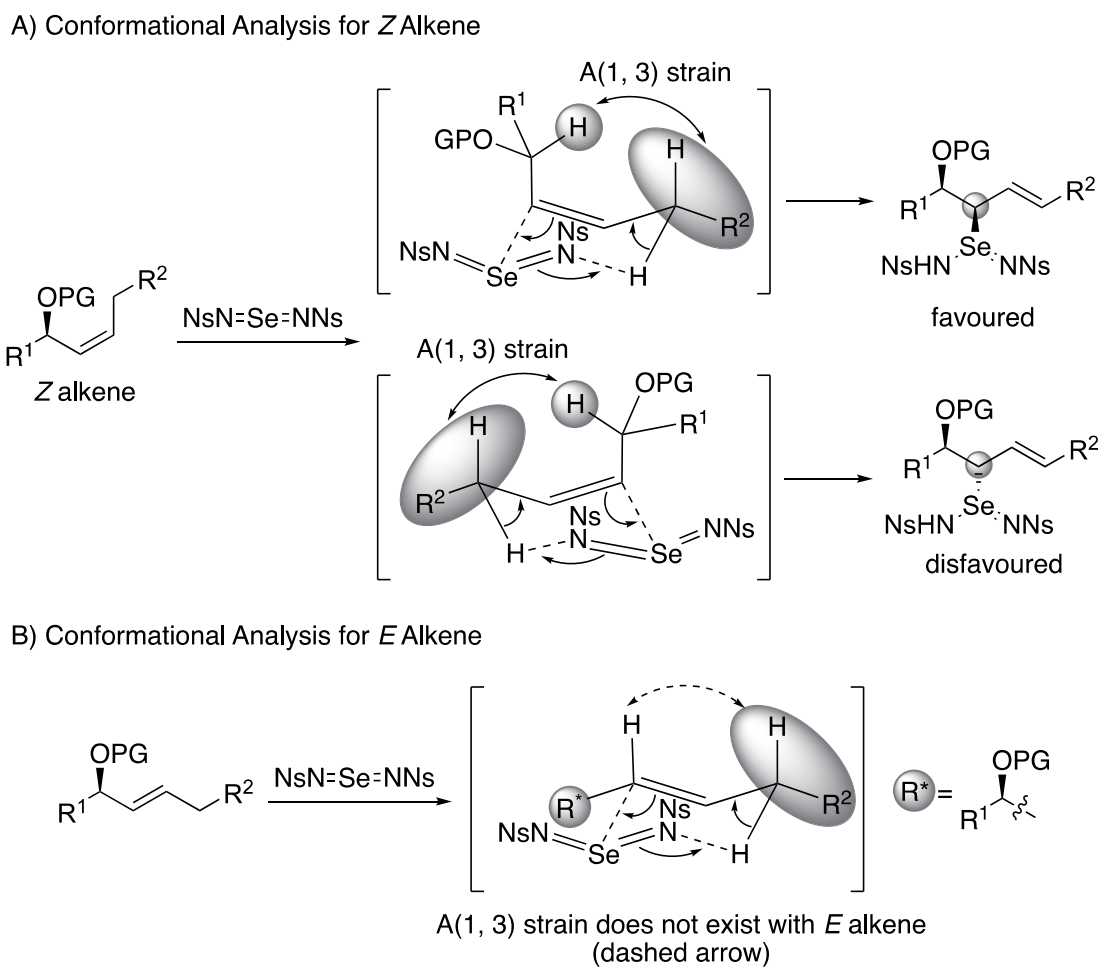
[a]Isolated yields. [b]Diastereomeric ratio (d.r.) determined by ^{1}H NMR spectroscopy. [c]Reaction time 70 h. [d]30 mol % catalyst used.

2.2.6 *Determination of Stereochemistry for 1,4-Amino Alcohols*

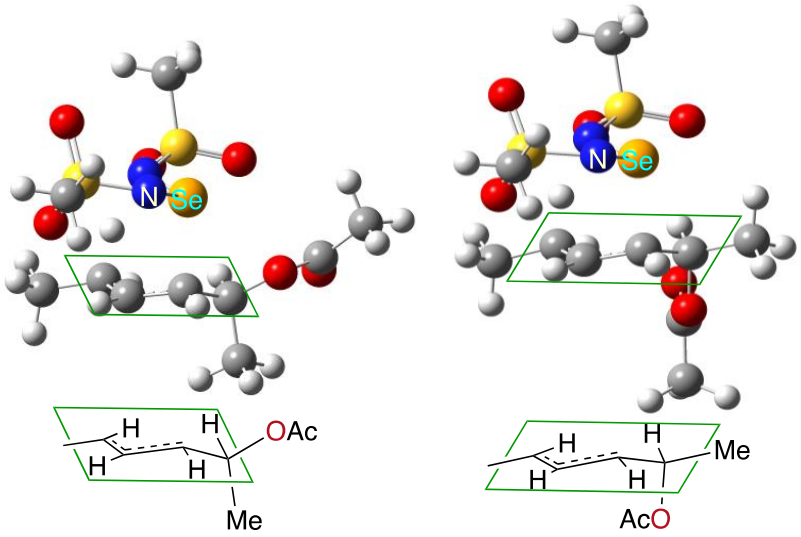
The stereochemistry of the two allylic stereocentres of 1,4-amino alcohols is assigned using a stereochemical model built on knowledge obtained from the synthesis of *anti*-1,2-amino alcohols. The model shows that the major product is *syn*-1,4-amino alcohols and that the stereochemistry of the product is determined in the ene reaction, controlled by 1,3-allylic strain between the H of the chiral group and the other allylic substituent across the alkene (Scheme 2.10). The steric effects of

R^1 and pivalate allow for stereoselection of the two alkene faces. The approach of nitrogen group to the alkene from the less bulky pivalate side is more favourable, leading to the intermediate with the newly generated selenium moiety being *syn* to the pivalate. The improved performance of *Z* alkene over *E* alkene (Table 2.8, entry 3 and 5) can be justified by the fact that such a 1,3-allylic strain does not exist when an *E* alkene is used. The 1,3-allylic strain imposes more conformational restriction to the chiral group, because the H of the chiral group must be coplanar with the other allylic substituent across the alkene to minimise this 1,3-allylic strain. This model is supported by our computational study for the transition states of the ene reaction that TS-III is more than TS-IV by about 0.4 kcal/mol (Scheme 2.11), which is consistent with experimental results (Table 2.9).

Scheme 2.10 Conformational Analysis for Ene Reaction for 1,4-Amino Alcohols



Scheme 2.11 Computational Study for Transition States of Ene Reaction

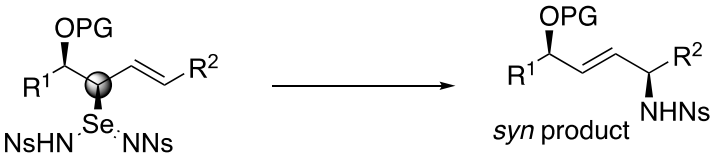


TS-III **TS-IV**

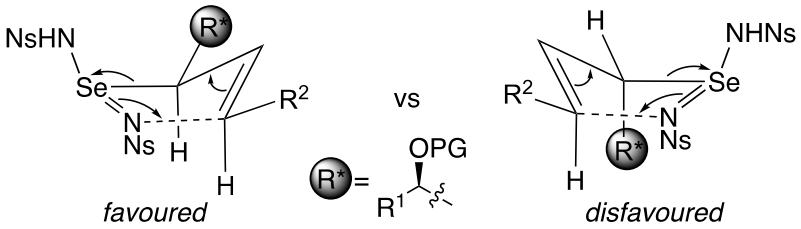
TS-III is more favourable than TS-IV by 0.4 kcal/mol

In 2,3-sigmatropic rearrangement, the transition state is more favourable when the bulky chiral group is placed at the equatorial position, leading to *syn*-1,4-amino alcohols with an *E* alkene as the major diastereomer (Scheme 2.12). The other disfavoured transition state, however, gives *syn*-1,4-amino alcohol with a *Z* alkene, which is inconsistent with the observed isomerisation of alkene over the course of reaction. This further justifies our stereochemical model.

Scheme 2.12 Conformational Analysis for 2,3-Sigmatropic Rearrangement for 1,4-Amino Alcohols



Transition State of 2,3-Sigmatropic Rearrangement



2.3 CONCLUSION

We have developed a diastereoconvergent synthesis of *anti*-1,2-amino alcohols bearing quaternary N-containing stereocentre via intermolecular direct allylic C-H amination catalysed by phosphine selenides, complementary to existing approaches to *syn*-1,2-amino alcohols. Experimental and computational studies reveal that the diastereoselectivity of *anti*-1,2-amino alcohols is controlled by inside alkoxy effect of the protected hydroxyl group in the transition state of 2,3-sigmatropic rearrangement. The diastereoconvergent ene reaction eliminates the need of challenging preparation of diastereomerically pure homoallylic alcohol derivatives to ensure high diastereoselectivity of amino alcohol products. The extension of this system to *syn*-1,4-amino alcohols presents the first example of diastereoselective synthesis of 1,4-amino alcohols via direct C-H amination. This method may streamline the synthesis of complex molecules via direct C-H functionalisation and the ease of preparation of starting materials.

2.4 EXPERIMENTAL

2.4.1 *General Procedures and Materials*

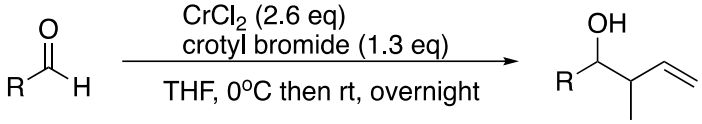
All reactions were performed under a nitrogen atmosphere using flame-dried glassware unless otherwise noted. Infrared spectra were measured on a Perkin Elmer Spectrum RX I spectrometer. Mass spectra were collected on a Hewlett Packard 5971A Gas Chromatograph-Mass Spectrometer or Bruker Esquire 1100 Liquid Chromatograph-Ion Trap Mass Spectrometer. Column chromatography was performed using silica gel (Whatman, 60 Å, 230-400 mesh). NMR spectra were recorded on a Bruker AV-300, AV-301, DRX-499 or AV-500 spectrometer. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) and are referenced relative to TMS (0.00 ppm) or residual protonated $CHCl_3$ (7.26 ppm). ^{13}C NMR chemical shifts (δ) are reported in parts

per million (ppm) relative to the carbon resonance of $CDCl_3$ (77.16 ppm). Melting points were taken on a MEL-TEMP melting point apparatus and are uncorrected.

All commercial reagents were used as received, unless otherwise noted. All solvents were degassed and dried on solvent columns of neutral alumina. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc., stored over 4Å molecular sieves, and were used without further purification.

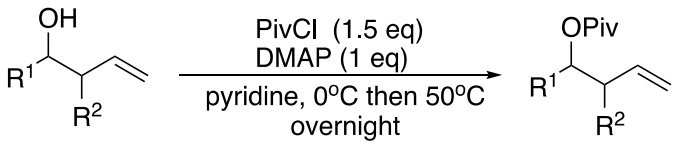
2.4.2 *Synthesis and Characterisation of Homoallylic Alcohol Pivalates*

General Procedure A: Cr Promoted Crotylation of Aldehydes



Anhydrous chromium (II) chloride (2.6 equiv) suspended in THF (50 mL) at 0 °C under an argon atmosphere. Spontaneous hydrogen evolution was observed, and a dark brown suspension was obtained. To this suspension aldehyde (1 equiv) and subsequently crotyl bromide (1.3 equiv) were added dropwise, and the mixture was stirred overnight at room temperature. Upon completion, the reaction was quenched with water. The reaction mixture was extracted with ether three times. The collected organic layers were dried over sodium sulphate and solvent was removed under reduced pressure. The crude product was purified by column chromatograph.

General Procedure B: Synthesis of Pivalates

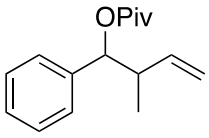


Pivaloyl chloride (1.5 equiv) was added to a solution of alcohol and DMAP (1 equiv) in pyridine at 0°C. The mixture was stirred overnight at 50°C. Upon completion, the reaction was quenched

with 1 M HCl at room temperature. The aqueous phase was extracted with diethyl ether three times. The combined organic layers were washed with saturated aqueous sodium bicarbonate, brine and dried over magnesium sulphate. The solvent was removed under reduced pressure to give a crude which was purified through column chromatography to afford pure product.

Characterisation of Homoallylic Alcohols

2-methyl-1-phenylbut-3-enyl pivalate (2.5a)



Prepared according to literature procedure[47] and General Procedure B. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:20) to afford the product as a colourless oil (70% yield, d.r. 1:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.15 (m, 5 * 0.50H + m, 5 * 0.5H), 5.75 (ddd, *J* = 17.6, 9.8, 7.9 Hz, 1 * 0.5H), 5.71 – 5.60 (m, 1*0.5H, 1 * 0.5H), 5.56 (d, *J* = 7.4 Hz, 1 * 0.5H), 5.07 – 4.92 (m, 2* 0.5H, + m, 2* 0.5H), 2.73 – 2.58 (m, 1 * 0.5H, + m, 1 * 0.5H), 1.22 (s, 9 * 0.5H), 1.19 (s, 9 * 0.5H), 1.04 (d, *J* = 6.8 Hz, 3 * 0.5H), 0.91 (d, *J* = 6.9 Hz, 3 * 0.5H). (both diastereomers reported)

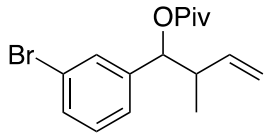
^{13}C NMR (75 MHz, $CDCl_3$) δ 177.25, 139.69, 139.46, 139.35, 128.11, 128.01, 127.67, 127.54, 126.94, 126.84, 115.52, 115.39, 78.61, 78.40, 43.80, 43.15, 38.92, 38.83, 27.16, 16.43, 14.97. (both diastereomers reported)

IR (thin film) 3067, 3033, 2974, 2933, 2872, 1732, 1480, 1456, 1281, 1154, 1031, 915 cm^{-1}.

GC-MS (m/z) 266 (1, M^+), 184 (13, C_6F_5OH), 55(100, $C_4H_7^+$).

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 269.1512, found 269.1515

1-(3-bromophenyl)-2-methylbut-3-enyl pivalate (2.5b)



Prepared according to General Procedure A and B. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:25) to afford the product as a colourless oil (61% yield, d.r. 1:11).

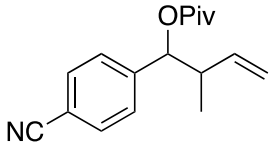
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.37 (m, 2H), 7.22 – 7.15 (m, 2H), 5.72 (ddd, *J* = 17.1, 10.4, 7.9 Hz, 1H), 5.51 (d, *J* = 7.3 Hz, 1H), 5.24 – 4.85 (m, 2H), 2.61 (m, 1H), 1.20 (s, 9H), 0.92 (d, *J* = 6.9 Hz, 3H). (major diastereomer reported)

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.26, 141.84, 139.09, 130.86, 129.90, 129.76, 125.64, 122.35, 116.06, 77.82, 43.73, 38.85, 27.13, 16.44. (major diastereomer reported)

IR (thin film) 2975, 2935, 2873, 1732, 1643, 1572, 1479, 1282, 1153, 997, 918, 783, 697 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[C_{11}H_{12}Br]^+$ 223.0122, found 223.0117

1-(4-cyanophenyl)-2-methylbut-3-enyl pivalate (2.5c)



Prepared according to General Procedure A and B. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:5) to afford the product as a colourless oil (73% yield, single diastereomer).

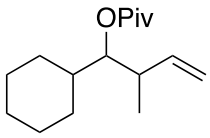
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 5.71 (ddd, *J* = 17.2, 10.3, 7.9 Hz, 1H), 5.59 (d, *J* = 6.7 Hz, 1H), 5.05 (d, *J* = 10.3 Hz, 1H), 5.00 (d, *J* = 17.1 Hz, 1H), 2.69 – 2.57 (m, 1H), 1.21 (s, 9H), 0.94 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.25, 144.84, 138.45, 132.08, 127.53, 118.66, 116.51, 111.69, 77.85, 43.59, 38.89, 27.11, 16.34.

IR (thin film) 2970, 2936, 2874, 2229, 1732, 1642, 1612, 1480, 1460, 1397, 1367, 1281, 1154, 1033, 996, 920, 829 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+H]^+$ 272.1650, found 272.1650

1-cyclohexyl-2-methylbut-3-enyl pivalate (2.5d)



Prepared according to literature procedure[47] and General Procedure B. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:20) to afford the product as a colourless oil (78% yield, d.r. 1:3).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 (m, 1H), 5.09 – 4.95 (m, 2H), 4.72 – 4.62 (m, 1H), 2.50 (m, 1H), 1.82 – 1.41 (m, 6H), 1.21 (s, 9H), 1.14 (m, 5H), 0.96 (d, *J* = 6.9 Hz, 3H). (major diastereomer reported)

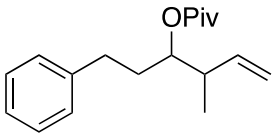
^{13}C NMR (126 MHz, $CDCl_3$) δ 178.09, 139.86, 115.16, 79.57, 39.60, 39.25, 29.60, 27.68, 27.45, 26.42, 26.12, 25.97, 17.64. (major diastereomer reported)

IR (thin film) 3075, 2971, 2930, 2854, 1727, 1480, 1450, 1281, 1160, 913 cm^{-1}.

GC-MS (m/z) 266 (1, M^+), 184 (13, C_6F_5OH), 55(100, $C_4H_7^+$).

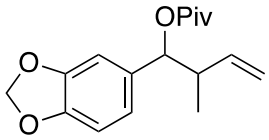
HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 275.1982, found 275.1984

4-methyl-1-phenylhex-5-en-3-yl pivalate (2.5e)



Prepared according to literature procedure[48] and General Procedure B. Product was isolated as a colourless oil (80% yield, d.r. 1:1). The characterisation data is consistent with literature[49].

1-(benzo[d][1,3]dioxol-5-yl)-2-methylbut-3-enyl pivalate (2.5f)



Prepared according to literature procedure[47] and General Procedure B. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:10) to afford the product as a colourless oil (65% yield, d.r. 2:3).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.80 – 6.70 (m, 3H), 5.97 – 5.92 (m, 2H), 5.74 (ddd, *J* = 17.1, 10.4, 7.9 Hz, 1H * 0.40), 5.64 (ddd, *J* = 17.0, 10.6, 7.3 Hz, 1H * 0.60), 5.49 (d, *J* = 6.8 Hz, 1H * 0.60), 5.44 (d, *J* = 7.8 Hz, 1H * 0.40), 5.07 – 5.01 (m, 2H * 0.40), 5.00 – 4.93 (m, 2H * 0.60), 2.67 – 2.54 (m, 1H), 1.21 (s, 9H * 0.60), 1.18 (s, 9H * 0.40), 1.04 (d, *J* = 6.8 Hz, 3H * 0.60), 0.89 (d, *J* = 6.9 Hz, 3H * 0.40). (both diastereomers reported)

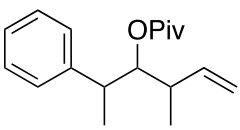
^{13}C NMR (126 MHz, $CDCl_3$) δ 177.36, 177.33, 147.56, 147.45, 147.07, 146.96, 139.79, 139.21, 133.42, 133.29, 120.72, 120.57, 115.61, 115.55, 107.93, 107.86, 107.32, 107.24, 101.03, 101.00, 78.52, 78.42, 43.91, 43.21, 38.91, 38.82, 27.17, 27.15, 16.52, 15.31. (both diastereomers reported)

IR (thin film) 2934, 1727, 1504, 1490, 1444, 1282, 1250, 1156, 1039, 937, 808 cm^{-1}.

GC-MS (m/z) 266 (1, M^+), 184 (13, C_6F_5OH), 55(100, $C_4H_7^+$).

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 313.1410 found 313.1415

4-methyl-2-phenylhex-5-en-3-yl pivalate (2.5g)



Prepared according to literature procedure[47] and General Procedure B. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:20) to afford the product as a colourless oil (85% yield, d.r. 1:3).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 2 * 0.2H + m, 2 * 0.8H), 7.26 – 7.18 (m, 3 * 0.2H + m, 3 * 0.8H), 5.78 (ddd, *J* = 17.3, 10.3, 8.9 Hz, 1 * 0.8H), 5.72 (ddd, *J* = 17.2, 10.6, 6.7 Hz, 1 * 0.2H), 5.17 (dd, *J* = 8.4, 4.2 Hz, 1 * 0.2H), 5.12 (dd, *J* = 9.8, 3.0 Hz, 1 * 0.8H), 5.06 (dd, *J* = 10.3, 2.0 Hz, 1 * 0.8H), 4.97 (dd, *J* = 2.1, 1.4 Hz, 1 * 0.2H), 4.95 (dt, *J* = 10.1, 1.5 Hz, 1 * 0.2H), 4.88 (dd, *J* = 17.2, 1.2 Hz, 1 * 0.8H), 3.08 – 2.93 (m, 1 * 0.2H + m, 1 * 0.8H), 2.27 – 2.12 (m, 1 * 0.2H + m, 1 * 0.8H), 1.25 (s, 9* 0.8H), 1.23 (d, *J* = 7.0 Hz, 3* 0.2H), 1.20 (s, 9* 0.2H), 1.18 (d, *J* = 7.0 Hz, 3* 0.8H), 0.97 (d, *J* = 6.8 Hz, 3* 0.2H), 0.89 (d, *J* = 7.0 Hz, 3* 0.8H). (both diastereomers reported)

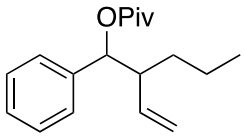
^{13}C NMR (126 MHz, $CDCl_3$) δ 178.14, 143.83, 138.81, 128.57, 127.88, 126.58, 116.13, 79.81, 42.24, 40.05, 39.21, 27.46, 18.37, 18.27. (major diastereomer reported)

IR (thin film) 3074, 3029, 1727, 1479, 1454, 1396, 1369, 1280, 1158, 1101, 999, 940, 914, 762, 702 cm^{-1}.

GC-MS (m/z) 266 (1, M^+), 184 (13, C_6F_5OH), 55(100, $C_4H_7^+$).

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 297.1825, found 297.1826

1-**phenyl-2-vinylpentyl pivalate (2.5h)**



Prepared according to literature procedure[50] and General Procedure B. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:30) to afford the product as a colourless oil (64% yield overall, d.r. 1:3).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.21 (m, 5H), 5.64 (d, *J* = 6.9 Hz, 1H), 5.58 (ddd, *J* = 17.1, 10.2, 9.2 Hz, 1H), 5.06 (dd, *J* = 10.2, 1.9 Hz, 1H), 4.97 (ddd, *J* = 17.2, 1.9, 0.6 Hz, 1H), 2.45 (tdd,

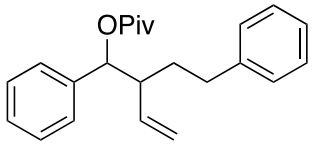
J = 9.1, 6.9, 4.4 Hz, 1H), 1.41 – 1.29 (m, 4H), 1.19 (s, 9H), 0.81 (t, *J* = 7.2 Hz, 3H). (major diastereomer reported)

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.33, 139.72, 138.23, 128.12, 127.61, 126.95, 117.32, 77.62, 50.06, 38.86, 32.76, 27.18, 20.09, 13.90. (major diastereomer reported)

IR (thin film) 3069, 3034, 2960, 2934, 2873, 1732, 1480, 1457, 1281, 1154, 1032, 995, 969, 915, 763, 699 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+NH_4]^+$ 292.2271, found 292.2268

2-phenethyl-1-phenylbut-3-enyl pivalate (2.5i)



Prepared according to literature procedure[50] and General Procedure B. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:30) to afford the product as a colourless oil (61% yield overall, d.r. 1:2.6).

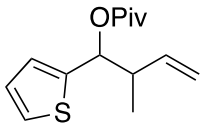
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.21 (m, 7H), 7.20 – 6.97 (m, 3H), 5.69 (d, *J* = 6.8 Hz, 1H), 5.64 (ddd, *J* = 17.1, 8.7, 7.7 Hz, 1H), 5.15 (dd, *J* = 10.3, 1.8 Hz, 1H), 5.02 (ddd, *J* = 17.1, 1.8, 0.6 Hz, 1H), 2.67 (ddt, *J* = 14.5, 10.0, 5.6 Hz, 1H), 2.46 (m, 2H), 1.65 (m, 2H), 1.18 (s, 9H). (major diastereomer reported)

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.30, 141.93, 139.33, 137.87, 128.41, 128.31, 128.17, 127.72, 126.98, 125.78, 118.08, 77.41, 49.60, 38.86, 33.11, 32.06, 27.17. (major diastereomer reported)

IR (thin film) 3065, 3029, 2975, 2933, 2870, 1732, 1643, 1496, 1479, 1455, 1396, 1366, 1281, 1154, 1031, 998, 917, 763, 749, 699 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+NH_4]^+$ 354.2427, found 354.2429

2-methyl-1-(thiophen-2-yl)but-3-enyl pivalate (2.5j)



Prepared according to literature procedure[47] and General Procedure B. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:10) to afford the product as a colourless oil (60% yield, d.r. 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 – 7.18 (m, 1 * 0.50H + m, 1 * 0.50H), 7.02 – 6.89 (m, 2 * 0.50H + m, 2 * 0.50H), 5.92 (d, *J* = 6.8 Hz, 1 * 0.50H), 5.88 (d, *J* = 7.5 Hz, 1 * 0.50H), 5.86 – 5.64 (m, 1 * 0.50H + m, 1 * 0.50H), 5.15 – 4.97 (m, 2 * 0.50H + m, 2 * 0.50H), 2.80 – 2.63 (m, 1 * 0.50H + m, 1 * 0.50H), 1.21 (s, 9* 0.50H), 1.19 (s, 9 * 0.50H), 1.09 (d, *J* = 6.8 Hz, 3 * 0.50H), 0.97 (d, *J* = 6.8 Hz, 3 * 0.50H). (both diastereomers reported)

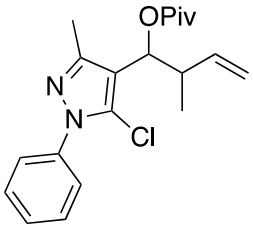
^{13}C NMR (126 MHz, $CDCl_3$) δ 177.16, 177.13, 142.32, 142.18, 139.39, 138.82, 126.35, 126.31, 125.82, 125.66, 124.95, 124.80, 116.07, 115.98, 74.40, 74.35, 44.27, 43.44, 38.94, 38.86, 27.13, 27.11, 16.55, 15.41. (both diastereomers reported)

IR (thin film) 3078, 2975, 2934, 2872, 1732, 1479, 1280, 1150, 1032, 994, 966, 918, 700 cm^{-1}.

GC-MS (m/z) 266 (1, M^+), 184 (13, C_6F_5OH), 55(100, $C_4H_7^+$).

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 275.1076, found 275.1075

1-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-methylbut-3-enyl pivalate (2.5k)



Prepared according to General Procedure A and B. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:4) to afford the product as a colourless oil (62% yield, d.r. 1:4).

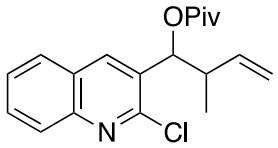
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 – 7.50 (m, 2H), 7.50 – 7.43 (m, 2H), 7.39 (d, *J* = 7.4 Hz, 1H), 5.78 (ddd, *J* = 17.2, 10.3, 8.0 Hz, 1H), 5.55 (d, *J* = 9.9 Hz, 1H), 5.14 (ddd, *J* = 17.1, 1.5, 1.0 Hz, 1H), 5.08 (ddd, *J* = 10.3, 1.6, 0.6 Hz, 1H), 2.93 – 2.84 (m, 1H), 2.40 (s, 3H), 1.20 (s, 9H), 0.95 (d, *J* = 6.9 Hz, 3H). (major diastereomer reported)

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.37, 148.48, 140.15, 138.20, 128.94, 128.07, 126.11, 124.98, 115.78, 115.55, 71.13, 42.21, 39.00, 27.23, 16.60, 13.44. (major diastereomer reported)

IR (thin film) 2974, 2933, 2873, 1730, 1599, 1557, 1503, 1479, 1459, 1417, 1281, 1154, 997, 920, 762, 694 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+H]^+$ 361.1677, found 361.1686

1-(2-chloroquinolin-3-yl)-2-methylbut-3-enyl pivalate (2.5l)



Prepared according to General Procedure A and B. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:5) to afford the product as a colourless oil (62% yield, single diastereomer).

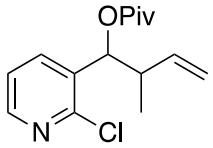
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (m, 2H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.72 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1H), 7.56 (ddd, *J* = 8.0, 6.8, 0.9 Hz, 1H), 6.13 (d, *J* = 5.3 Hz, 1H), 5.82 (ddd, *J* = 17.2, 10.3, 8.2 Hz, 1H), 5.03 (d, *J* = 10.4 Hz, 1H), 4.91 (d, *J* = 17.2 Hz, 1H), 2.91 – 2.80 (m, 1H), 1.27 (s, 9H), 1.15 (d, *J* = 6.9 Hz, 3H). (major diastereomer reported)

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.11, 149.07, 147.02, 137.84, 136.32, 132.20, 130.51, 128.38, 127.57, 127.21, 126.94, 116.96, 74.93, 42.78, 39.01, 27.18, 17.20. (major diastereomer reported)

IR (thin film) 2973, 1734, 1479, 1330, 1280, 1137, 1041, 995, 917, 754 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 332.1417, found 332.1412

1-(2-chloropyridin-3-yl)-2-methylbut-3-enyl pivalate (2.5m)



Prepared according to General Procedure A and B. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:4) to afford the product as a colourless oil (58% yield, single diastereomer).

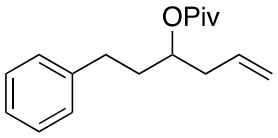
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (dd, *J* = 4.7, 1.9 Hz, 1H), 7.58 (dd, *J* = 7.6, 1.9 Hz, 1H), 7.22 (dd, *J* = 7.7, 4.7 Hz, 1H), 5.99 (d, *J* = 5.4 Hz, 1H), 5.76 (ddd, *J* = 17.2, 10.3, 8.2 Hz, 1H), 5.03 (dd, *J* = 10.3, 1.0 Hz, 1H), 4.91 (d, *J* = 17.2 Hz, 1H), 2.79 – 2.65 (m, 1H), 1.23 (s, 9H), 1.10 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.06, 149.53, 148.63, 137.83, 136.51, 134.59, 122.31, 116.88, 74.62, 42.62, 38.94, 27.13, 17.01.

IR (thin film) 2974, 2873, 1735, 1582, 1566, 1480, 1460, 1413, 1348, 1281, 1149, 1122, 1068, 996, 921, 804, 751, 726 cm^{-1}.

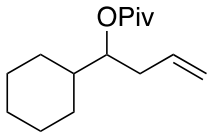
HRMS (ESI, positive mode) calculated for $[M+H]^+$ 282.1255, found 282.126

1-phenylhex-5-en-3-yl pivalate (2.5n)



Prepared according to literature procedure[48] and General Procedure B. The characterisation data is consistent with literature[49].

1-cyclohexylbut-3-enyl pivalate (2.5o)



Prepared according to literature procedure[48] and General Procedure B. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:30) to afford the product as a colourless oil (70% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 – 5.67 (m, 1H), 5.08 – 4.99 (m, 2H), 4.75 (ddd, *J* = 7.8, 6.0, 4.5 Hz, 1H), 2.38 – 2.22 (m, 2H), 1.77 – 1.71 (m, 3H), 1.70 – 1.61 (m, 2H), 1.57 – 1.48 (m, 1H), 1.27 – 1.08 (m, 12H), 1.08 – 0.95 (m, 2H).

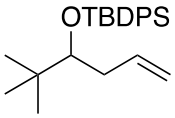
^{13}C NMR (126 MHz, $CDCl_3$) δ 178.07, 141.66, 133.59, 128.47, 128.35, 125.98, 117.79, 72.25, 38.91, 38.73, 35.59, 31.78, 27.27.

IR (thin film) 2975, 2929, 2854, 1727, 1480, 1450, 1283, 1163 cm^{-1}.

GC-MS (m/z) 210/212 (15/5, M^+), 128/130 (100/33, C_6H_4ClOH).

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 261.1825, Found 261.1822

tert-butyl(2,2-dimethylhex-5-en-3-yloxy)diphenylsilane (2.5p)



Prepared according to literature procedure[48,51] as a colourless oil (75% yield).

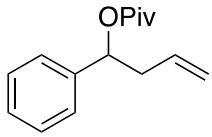
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 – 7.66 (m, 4H), 7.47 – 7.31 (m, 6H), 5.59 – 5.39 (m, 1H), 4.72 – 4.58 (m, 2H), 3.54 – 3.41 (m, 1H), 2.39 – 2.24 (m, 1H), 2.24 – 2.11 (m, 1H), 1.04 (s, 9H), 0.90 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.16, 136.27, 136.15, 135.07, 133.98, 129.49, 129.34, 127.45, 127.29, 115.31, 81.55, 38.44, 36.79, 27.23, 26.73, 19.86.

IR (thin film) 3072, 2955, 2857, 1474, 1428, 1391, 1362, 1110, 1079, 1027, 999, 908, 821, 739, 702, 610 cm^{-1}.

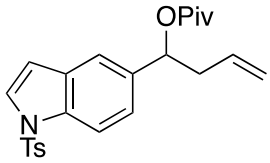
GC-MS (m/z) 302 (26, M^+), 220 (100, C_6H_4IOH)

1-phenylbut-3-enyl pivalate (2.5q)



Prepared according to literature procedure[48] and General Procedure B. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:30) to afford the product as a colourless oil (75% yield). The spectroscopic signatures were found to be consistent with literature data[52].

1-(1-tosyl-1H-indol-5-yl)but-3-enyl pivalate (2.5r)



Prepared according to literature procedure[48,53] and General Procedure B. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:3) to afford the product as a pale-yellow semi solid (57% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.6 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 3.7 Hz, 1H), 7.47 (s, 1H), 7.26 (d, *J* = 6.4 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 6.62 (d, *J* = 3.7 Hz, 1H), 5.82 (dd, *J* = 8.0, 5.4 Hz, 1H), 5.69 (ddt, *J* = 17.1, 10.1, 7.0 Hz, 1H), 5.04 (m, 2H), 2.63 (dt, *J* = 15.1, 7.7 Hz, 1H), 2.54 (ddd, *J* = 13.4, 6.5, 5.5 Hz, 1H), 2.35 (s, 3H), 1.19 (s, 9H).

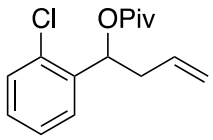
^{13}C NMR (126 MHz, $CDCl_3$) δ 177.51, 144.99, 135.82, 135.43, 134.36, 133.46, 130.72, 129.93, 126.87, 126.76, 122.92, 119.20, 117.94, 113.47, 109.00, 74.80, 41.39, 38.82, 27.17, 21.54.

IR (thin film) 2976, 1726, 1372, 1280, 1173, 1128, 996, 676 cm^{-1}.

GC-MS (m/z) 266 (1, M^+), 184 (13, C_6F_5OH), 55(100, $C_4H_7^+$).

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 448.1553, found 448.1543

1-(2-chlorophenyl)but-3-enyl pivalate (2.5s)



Prepared according to literature procedure[48] and General Procedure B. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:20) to afford the product as a colourless oil (80% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.32 (m, 2H), 7.29 – 7.17 (m, 2H), 6.17 (dd, *J* = 8.0, 4.6 Hz, 1H), 5.77 (ddt, *J* = 17.1, 10.3, 7.0 Hz, 1H), 5.11 – 5.04 (m, 2H), 2.67 – 2.58 (m, 1H), 2.55 (dt, *J* = 14.6, 7.7 Hz, 1H), 1.23 (s, 9H).

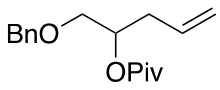
^{13}C NMR (75 MHz, $CDCl_3$) δ 177.08, 138.44, 133.07, 132.10, 129.60, 128.66, 126.90, 126.85, 118.05, 71.44, 39.59, 38.81, 27.16.

IR (thin film) 3076, 2975, 2933, 2906, 2872, 1733, 1478, 1441, 1396, 1366, 1282, 1152, 1035, 986, 918, 756 cm^{-1}.

GC-MS (m/z) 221 (10, M^+), 139 (10, $C_6H_4NO_2OH$), 55(100, $C_4H_7^+$).

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 289.0966, found 289.0966

1-(benzyloxy)pent-4-en-2-yl pivalate (2.5t)



Prepared according to literature procedure[48,54] and General Procedure B. Purified through column chromatograph (silica get, ethyl acetate/hexanes 1:15) to afford the product as a colourless oil (60% yield).

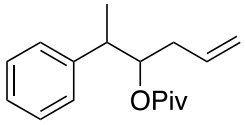
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 5H), 5.74 (ddt, *J* = 17.0, 10.2, 7.1 Hz, 1H), 5.13 – 5.02 (m, 3H), 4.56 (d, *J* = 12.1 Hz, 2H), 4.51 (d, *J* = 12.1 Hz, 2H), 3.58 – 3.47 (m, 2H), 2.43 (dddt, *J* = 14.7, 6.7, 5.3, 1.3 Hz, 1H), 2.35 (dtt, *J* = 14.5, 7.3, 1.3 Hz, 1H), 1.19 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.98, 138.21, 133.37, 128.40, 127.65, 127.56, 117.92, 73.16, 71.35, 70.84, 38.83, 35.58, 27.21.

IR (thin film) 3076, 3030, 2975, 2933, 2869, 1727, 1480, 1454, 1366, 1283, 1163, 1120, 917, 737, 698 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 299.1618, found 299.1617

2-phenylhex-5-en-3-yl pivalate (2.5u)



Prepared according to literature procedure[48] and General Procedure B. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:30) to afford the product as a colourless oil (73%, d.r. 1:3).

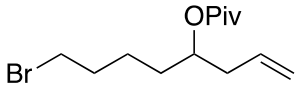
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.15 (m, 5H), 5.79 – 5.62 (m, 1H), 5.18 – 5.05 (m, 1H), 5.05 – 4.86 (m, 2H), 3.04 – 2.91 (m, 1H), 2.35 (d, *J* = 14.6 Hz, 1H * 0.27), 2.27 – 2.19 (m, 1H), 2.08 (dt, *J* = 15.5, 8.3 Hz, 1H * 0.73), 1.30 – 1.21 (m, 4H), 1.20 (s, 9H * 0.73), 1.03 (s, 9H * 0,27). (both diastereomers reported)

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.94, 177.75, 143.45, 143.06, 133.85, 128.50, 128.18, 128.12, 127.86, 126.66, 126.45, 117.62, 117.56, 76.38, 75.87, 43.33, 43.08, 38.96, 38.78, 36.91, 36.52, 27.30, 27.05, 17.72, 17.63. (both diastereomers reported)

IR (thin film) 3078, 3029, 2974, 2934, 2907, 2874, 1726, 1495, 1479, 1454, 1396, 1366, 1282, 1160, 1031, 985, 915, 761, 701 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 283.1669, found 283.1671

8-bromooct-1-en-4-yl pivalate (2.5v)



Prepared according to literature procedure[55,56] and General Procedure B. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:30) to afford the product as a colourless oil (57% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 5.11 – 5.03 (m, 2H), 4.90 (p, *J* = 6.0 Hz, 1H), 3.52 (t, *J* = 6.6 Hz, 2H), 2.38 – 2.24 (m, 2H), 1.90 – 1.70 (m, 2H), 1.68 – 1.38 (m, 2H), 1.19 (s, 9H).

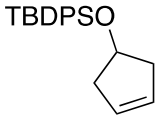
^{13}C NMR (126 MHz, $CDCl_3$) δ 178.06, 133.61, 117.70, 72.26, 44.74, 38.83, 38.66, 32.79, 32.24, 27.19, 22.54.

IR (thin film) 3078, 2957, 2870, 1725, 1643, 1480, 1460, 1284, 1162, 917, 652 cm^{-1}.

GC-MS (m/z) 266 (1, M^+), 184 (13, C_6F_5OH), 55(100, $C_4H_7^+$).

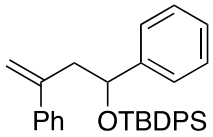
HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 313.0774, found 313.0774

tert-butyl(cyclopent-3-enyloxy)diphenylsilane (2.5w)



Prepared according to literature procedure[57]. Characterisation data was found to be consistent with data reported therein.

tert-butyl(1,3-diphenylbut-3-enyloxy)diphenylsilane (2.5x)



Prepared according to literature procedure[47] and General Procedure B. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:30) to afford the product as a colourless oil (67% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 – 7.64 (m, 2H), 7.52 – 7.26 (m, 6H), 7.23 – 7.02 (m, 10H), 6.95 – 6.85 (m, 2H), 5.05 (d, *J* = 1.3 Hz, 1H), 4.72 – 4.61 (m, 2H), 3.07 (dd, *J* = 13.6, 5.1 Hz, 1H), 2.73 (dd, *J* = 13.5, 8.7 Hz, 1H), 1.00 (s, 9H).

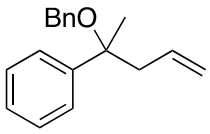
^{13}C NMR (126 MHz, $CDCl_3$) δ 141.43, 141.33, 137.84, 133.54, 133.42, 131.75, 131.02, 127.10, 126.85, 125.66, 125.15, 125.05, 124.81, 124.57, 124.45, 123.98, 123.52, 113.21, 72.02, 44.18, 24.46, 16.77.

IR (thin film) 3070, 3030, 2956, 2930, 2891, 2856, 1493, 1471, 1427, 1390, 1363, 1265, 1111, 1083, 1063, 942, 900, 848, 822, 777, 740, 700, 614 cm^{-1}.

GC-MS (m/z) 266 (1, M^+), 184 (13, C_6F_5OH), 55(100, $C_4H_7^+$).

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 485.2271, found 485.2266

(2-(benzyloxy)pent-4-en-2-yl)benzene (2.5y)



The homoallylic alcohol was prepared according to literature procedure[48], which was subjected to the following procedure for benzylation. To a flamed dried round bottom flask charged with NaH (60% suspension in mineral oil) (1.5 equiv) and THF (50ml) at 0 ^{o}C under nitrogen atmosphere was added the alcohol (1 equiv) dropwise. After 30 min, benzyl bromide (1.3 equiv) was added

dropwise. The reaction mixture was refluxed overnight. The reaction was cooled to room temperature and was quenched with saturated aqueous NH_4Cl. The mixture was extracted with diethyl ether three times. The combined organic layers were washed with brine, dried over sodium sulphate, and filtered. The solvent was removed under reduced pressure, and the crude was purified through column chromatography (silica gel, ether/hexanes 1:20) to afford the product as a colourless oil (73% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.14 (m, 10H), 5.83 – 5.58 (m, 1H), 5.09 – 4.96 (m, 2H), 4.32 (d, *J* = 11.3 Hz, 1H), 4.21 (d, *J* = 11.3 Hz, 1H), 2.68 (dd, *J* = 13.9, 7.2 Hz, 1H), 2.59 (dd, *J* = 14.0, 7.2 Hz, 1H), 1.63 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 145.03, 139.48, 134.24, 128.26, 128.20, 127.26, 127.12, 127.03, 126.32, 117.61, 79.00, 64.63, 47.68, 23.47.

IR (thin film) 3063, 3029, 2978, 2933, 1494, 1447, 1381, 1288, 1219, 1171, 1091, 1067, 1028, 998, 915, 733, 699 cm^{-1}.

GC-MS (m/z) 266 (1, M^+), 184 (13, C_6F_5OH), 55(100, $C_4H_7^+$).

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 275.1406, found 275.1409

2.4.3 *Synthesis and Characterisation of Anti-1,2-Amino Alcohols*

General Procedure C: Allylic Amination of Homoallylic Alcohols

To an oven-dried 1-dram vial was added alkene (0.2 mmol, 1 equiv), tricyclohexylphosphine selenide (15 mol %), 4-nitrobenzenesulfonamide (0.4 mmol, 2 equiv), Li_2CO_3 (0.4 mmol, 2 equiv), DCM (1 mL) and (diacetoxyiodo)benzene (0.4 mmol, 2 equiv), in that order. The vial was capped with a Teflon-lined screw cap and the reaction was stirred at 35°C for 24 or 48 hours. Upon completion, the reaction mixture was diluted with 2 ml ethyl acetate and was pushed through a silica plug. An ^{1}H NMR spectrum was taken with 1,3-dinitrobenzene as internal standard to obtain

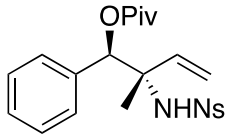
NMR yield. The crude product was purified by column chromatography to afford the corresponding product.

General Procedure D: Allylic Amination of Homoallylic Alcohols

To an oven-dried 1-dram vial was added alkene (0.2 mmol, 1 equiv), tricyclohexylphosphine selenide (30 mol%), 4-nitrobenzenesulfonamide (0.4 mmol, 2 equiv), Li_2CO_3 (0.4 mmol, 2 equiv), DCE (1 mL) and (diacetoxyiodo)benzene (0.4 mmol, 2 equiv), in that order. The vial was capped with a Teflon-lined screw cap and the reaction was stirred at 50°C for 24 or 48 hours. Upon completion, the reaction mixture was diluted with 2 ml ethyl acetate and was pushed through a silica plug. An ^{1}H NMR spectrum was taken with 1,3-dinitrobenzene as internal standard to obtain NMR yield. The crude product was purified by column chromatography to afford the corresponding product.

Characterisation of 1,2-Amino Alcohol Products

2-methyl-2-(4-nitrophenylsulfonamido)-1-phenylbut-3-enyl pivalate (2.6a)



Prepared according to General Procedure C. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:5) as a yellow semi solid (70.3 mg, 79% yield, d.r. 1:10).

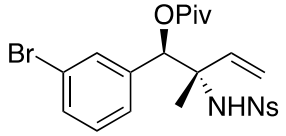
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.6 Hz, 2H), 7.95 (d, *J* = 8.6 Hz, 2H), 7.37 – 7.26 (m, 5H), 5.71 (s, 1H), 5.64 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.24 – 5.11 (m, 2H), 5.01 (s, 1H), 1.36 (s, 3H), 1.20 (s, 9H). (major diastereomer reported)

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.73, 149.83, 148.39, 136.86, 135.17, 128.82, 128.52, 128.28, 128.13, 124.06, 118.17, 79.69, 62.85, 38.95, 27.06, 20.67. (major diastereomer reported)

IR (thin film) 3276, 1736, 1530, 1349, 1219, 1158, 1092, 1003, 854, 772 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 469.1404, found 469.1400

1-(3-bromophenyl)-2-methyl-2-(4-nitrophenylsulfonamido)but-3-enyl pivalate (2.6b)



Prepared according to General Procedure D. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:5) as a yellow waxy solid (86.2 mg, 82% yield, d.r. 1:15).

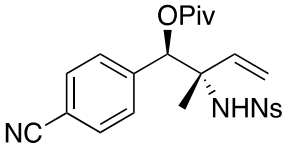
^{1}H NMR (500 MHz, Acetone) δ 8.40 (d, *J* = 8.8 Hz, 2H), 8.07 (d, *J* = 8.8 Hz, 2H), 7.65 (s, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 2H), 7.34 (t, *J* = 7.9 Hz, 1H), 6.01 (dd, *J* = 17.4, 10.9 Hz, 1H), 5.97 (s, 1H), 5.16 (d, *J* = 10.8 Hz, 1H), 5.15 (d, *J* = 17.5 Hz, 1H), 1.37 (s, 3H), 1.21 (s, 9H). (major diastereomer reported)

^{13}C NMR (126 MHz, Acetone) δ 176.74, 150.70, 150.12, 140.17, 138.44, 132.24, 132.04, 130.65, 129.29, 128.30, 124.98, 122.29, 118.13, 78.88, 62.93, 39.38, 27.30, 19.89. (major diastereomer reported)

IR (thin film) 3276, 2105, 2976, 2934, 2873, 1738, 1532, 1479, 1350, 1309, 1279, 1165, 1093, 1035, 1006, 939, 855, 757, 736, 686, 608 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+NH_4]^+$ 542.0954, found 542.0961

1-(4-cyanophenyl)-2-methyl-2-(4-nitrophenylsulfonamido)but-3-enyl pivalate (2.6c)



Prepared according to General Procedure D. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:5) as a yellow oil (72.6 mg, 77% yield, single diastereomer).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.5 Hz, 2H), 8.00 (d, *J* = 8.6 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 5.87 (s, 1H), 5.77 (dd, *J* = 17.5, 10.9 Hz, 1H), 5.27 (s, 1H), 5.20

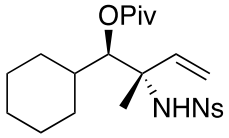
(d, *J* = 10.9 Hz, 1H), 5.09 (d, *J* = 17.4 Hz, 1H), 1.29 (s, 3H), 1.21 (s, 9H). (major diastereomer reported)

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.63, 149.97, 148.12, 140.83, 136.01, 131.93, 129.00, 128.52, 124.18, 118.72, 118.24, 112.66, 78.86, 62.48, 38.94, 27.01, 20.53. (major diastereomer reported)

IR (thin film) 3273, 3106, 2976, 2935, 2874, 2231, 1737, 1609, 1532, 1350, 1310, 1280, 1165, 1093, 1036, 1007, 855, 757, 736, 686, 617 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+NH_4]^+$ 489.1802, found 489.1791

1-cyclohexyl-2-methyl-2-(4-nitrophenylsulfonamido)but-3-enyl pivalate (2.6d)



Prepared according to General Procedure C. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:5) as a colourless solid (67.5 mg, 75% yield, d.r. 1:11).

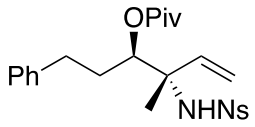
^{1}H NMR (500 MHz, Acetone) δ 8.43 (d, *J* = 8.9 Hz, 2H), 8.12 (d, *J* = 8.9 Hz, 2H), 6.79 (s, 1H), 5.91 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.11 (d, *J* = 17.5 Hz, 1H), 5.05 (d, *J* = 10.9 Hz, 1H), 4.84 (d, *J* = 3.4 Hz, 1H), 1.97 – 1.52 (m, 6H), 1.41 (s, 3H), 1.34 – 0.95 (m, 14H).

^{13}C NMR (126 MHz, Acetone) δ 177.79, 150.73, 150.21, 139.74, 129.51, 124.99, 116.83, 80.76, 63.81, 39.60, 38.97, 33.92, 30.76, 29.02, 27.63, 27.24, 26.94, 20.03. (major diastereomer reported)

IR (thin film) 3274, 2929, 2853, 1729, 1531, 1480, 1349, 1163, 1092, 854, 749 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 475.1873, found 475.1869

4-methyl-4-(4-nitrophenylsulfonamido)-1-phenylhex-5-en-3-yl pivalate (2.6e)



Prepared according to General Procedure C. Purified through column chromatograph (silica gel, ethyl acetate / hexanes 1:5) as a yellow oil (80.4 mg, 85% yield, d.r. 1:4.2).

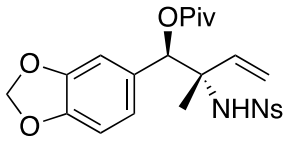
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.9 Hz, 2H), 7.99 (d, *J* = 8.9 Hz, 2H), 7.27 (t, *J* = 7.4 Hz, 2H), 7.19 (t, *J* = 7.4 Hz, 1H), 7.09 (d, *J* = 7.0 Hz, 2H), 5.72 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.20 (d, *J* = 10.9 Hz, 1H), 5.18 (d, *J* = 17.5 Hz, 1H), 4.91 (dd, *J* = 10.4, 2.4 Hz, 1H), 2.57 (ddd, *J* = 14.2, 10.4, 5.1 Hz, 1H), 2.46 (ddd, *J* = 13.7, 10.2, 6.4 Hz, 1H), 1.92 – 1.83 (m, 1H), 1.82 – 1.73 (m, 1H), 1.33 (s, 3H), 1.22 (s, 9H). (major diastereomer reported)

^{13}C NMR (126 MHz, $CDCl_3$) δ 178.46, 149.85, 148.47, 140.74, 136.67, 128.60, 128.56, 128.28, 126.34, 124.13, 118.07, 77.52, 63.58, 39.13, 32.15, 31.44, 27.25, 21.04. (major diastereomer reported)

IR (thin film) 3266, 2969, 1729, 1606, 1530, 1479, 1349, 1162, 1092, 1035, 854, 747, 685 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 497.1717, found 497.1713

1-(benzo[*d*][1,3]dioxol-5-yl)-2-methyl-2-(4-nitrophenylsulfonamido)but-3-enyl pivalate (2.6f)



Prepared according to General Procedure C. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:3) as a white semi solid (69.5 mg, 76% yield, d.r. 1:11).

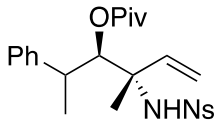
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.8 Hz, 2H), 7.98 (d, *J* = 8.8 Hz, 2H), 6.8-6.7 (m, 3H), 5.97 (s, 2H), 5.64 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.60 (s, 1H), 5.20 (d, *J* = 10.8 Hz, 1H), 5.16 (d, *J* = 17.4 Hz, 1H), 4.95 (s, 1H), 1.35 (s, 3H), 1.19 (s, 9H). (major diastereomer reported)

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.72, 149.86, 148.37, 148.00, 147.62, 136.92, 128.80, 128.57, 124.08, 122.04, 118.18, 108.29, 108.06, 101.38, 79.55, 62.91, 38.94, 27.05, 20.64. (major diastereomer reported)

IR (thin film) 3281, 2974, 1734, 1530, 1490, 1444, 1349, 1249, 1159, 1093, 1036, 935, 854, 735 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 513.1302, found 513.1299

4-methyl-4-(4-nitrophenylsulfonamido)-2-phenylhex-5-en-3-yl pivalate (2.6g)



Prepared according to General Procedure C. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:5) as a yellow oil (74 mg, 78% yield, d.r. 1:17).

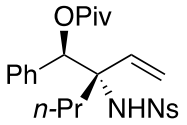
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.7 Hz, 2H), 7.90 (d, *J* = 8.9 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.26 – 7.17 (m, 3H), 5.67 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.20 – 5.09 (m, 3H), 4.92 – 4.83 (m, 1H), 3.12 (quin, *J* = 7.2 Hz, 1H), 1.28 (s, 3H), 1.21 (s, 9H), 1.19 (d, *J* = 7.1 Hz, 3H). (major diastereomer reported)

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.86, 149.80, 148.47, 144.20, 137.07, 129.07, 128.59, 127.64, 127.19, 124.03, 117.73, 80.39, 64.22, 40.49, 39.22, 27.34, 21.28, 19.13. (major diastereomer reported)

IR (thin film) 3274, 2959, 1726, 1531, 1349, 1280, 1166, 1092, 938, 854, 738 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 497.1717, found 497.1711

2-(4-nitrophenylsulfonamido)-1-phenyl-2-vinylpentyl pivalate (2.6h)



Prepared according to General Procedure D. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:5) as a pale yellow oil (68.3 mg, 72% yield, d.r. 1:7).

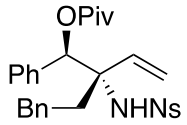
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.7 Hz, 2H), 7.99 (d, *J* = 8.7 Hz, 2H), 7.45 – 7.13 (m, 5H), 5.89 (s, 1H), 5.64 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.24 (d, *J* = 11.0 Hz, 1H), 5.10 (d, *J* = 17.5 Hz, 1H), 5.00 (s, 1H), 1.96 – 1.57 (m, 2H), 1.39 – 1.21 (m, 2H), 1.16 (s, 9H), 0.82 (s, 3H). (major diastereomer reported)

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.93, 149.79, 148.50, 135.40, 135.13, 128.70, 128.49, 128.19, 128.13, 124.03, 118.58, 77.99, 66.37, 38.93, 35.80, 27.00, 16.88, 14.10. (major diastereomer reported)

IR (thin film) 3284, 3106, 3035, 2967, 2935, 2875, 1734, 1608, 1532, 1350, 1308, 1164, 1094, 1033, 1004, 940, 912, 856, 736, 617 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+NH_4]^+$ 492.2162, found 492.2170

2-(4-nitrophenylsulfonamido)-2-phenethyl-1-phenylbut-3-enyl pivalate (2.6i)



Prepared according to General Procedure D. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:7) as a pale-yellow oil (83.7 mg, 78% yield, d.r. 1:12).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.9 Hz, 2H), 7.99 (d, *J* = 8.8 Hz, 2H), 7.32 (m, 5H), 7.28 – 6.97 (m, 5H), 5.97 (s, 1H), 5.69 (dd, *J* = 17.6, 11.0 Hz, 1H), 5.29 (d, *J* = 11.0 Hz, 1H), 5.17

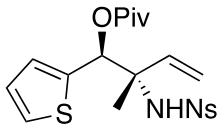
(s, 1H)， 5.16 (d, *J* = 17.6 Hz, 2H), 3.05 – 2.57 (m, 2H), 2.23 – 1.84 (m, 2H), 1.17 (s, 9H). (major diastereomer reported)

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.01, 149.84, 148.30, 140.87, 135.14, 134.91, 128.91, 128.57, 128.52, 128.25, 128.22, 128.17, 126.27, 124.11, 119.03, 78.24, 66.27, 38.96, 35.43, 29.78, 27.03. (major diastereomer reported)

IR (thin film) 3282, 2972, 1736, 1606, 1531, 1349, 1308, 1162, 1092, 855, 736, 700 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+NH_4]^+$ 554.2319, found 554.2329

2-methyl-2-(4-nitrophenylsulfonamido)-1-(thiophen-2-yl)but-3-enyl pivalate (2.6j)



Prepared according to General Procedure C. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:5) as a yellow oil (62.8 mg, 72% yield, d.r. 1:10).

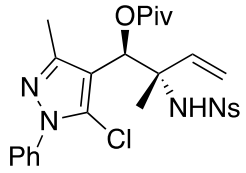
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.8 Hz, 2H), 7.99 (d, *J* = 8.9 Hz, 2H), 7.29 (dd, *J* = 5.1, 0.8 Hz, 1H), 7.05 (d, *J* = 3.4 Hz, 1H), 6.98 (dd, *J* = 5.0, 3.6 Hz, 1H), 6.02 (s, 1H), 5.67 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.25 (d, *J* = 17.4 Hz, 1H), 5.23 (d, *J* = 10.8 Hz, 1H), 5.07 (s, 1H), 1.43 (s, 3H), 1.18 (s, 9H). (major diastereomer reported)

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.40, 149.88, 148.22, 137.32, 136.60, 128.64, 128.20, 126.68, 126.32, 124.07, 118.83, 76.10, 62.76, 38.97, 27.00, 20.75. (major diastereomer reported)

IR (thin film) 3276, 2974, 1737, 1530, 1479, 1399, 1349, 1308, 1160, 1092, 1033, 1000, 854, 735, 685 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 475.0968, found 475.0966

1-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-methyl-2-(4-nitrophenylsulfonamido) but-3-enyl pivalate (2.6k)



Prepared according to General Procedure D. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:4) as a yellow oil (67.3 mg, 60% yield, d.r. 1:12).

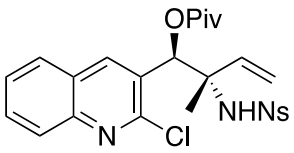
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.7 Hz, 2H), 8.02 (d, *J* = 8.9 Hz, 2H), 7.61 – 7.36 (m, 5H), 5.72 (m, 1H), 5.43 – 5.21 (m, 3H), 2.34 (s, 3H), 1.25 (s, 12H). (major diastereomer reported)

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.88, 149.93, 148.29, 137.83, 136.66, 135.82, 129.09, 128.63, 128.57, 125.54, 125.13, 124.13, 118.71, 112.01, 73.68, 64.22, 39.25, 34.25, 30.35, 27.26. (major diastereomer reported)

IR (thin film) 3271, 3106, 2971, 2932, 2873, 1734, 1605, 1532, 1503, 1349, 1310, 1278, 1163, 1093, 1034, 1006, 941, 855, 761, 686, 609 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+H]^+$ 561.1574, found 561.1569

1-(2-chloroquinolin-3-yl)-2-methyl-2-(4-nitrophenylsulfonamido)but-3-enyl pivalate (2.6l)



Prepared according to General Procedure D. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:5) as a yellow oil (71.3 mg, 67% yield, d.r. 1:13).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.5 Hz, 2H), 8.04 (s, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 2H), 7.77 (m, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 6.28 (s, 1H), 5.82 (dd, *J* = 17.3,

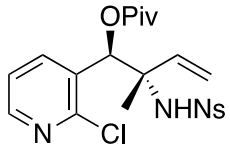
10.7 Hz, 1H), 5.44 (s, 1H), 5.32 (d, *J* = 10.7 Hz, 1H), 5.21 (d, *J* = 17.4 Hz, 1H), 1.47 (s, 3H), 1.22 (s, 9H). (major diastereomer reported)

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.46, 149.78, 149.70, 147.90, 147.24, 137.86, 136.06, 131.48, 128.39, 128.36, 127.69, 127.53, 126.29, 124.04, 118.83, 75.31, 63.85, 38.87, 26.96, 19.74. (major diastereomer reported)

IR (thin film) 3273, 2976, 2933, 2873, 1738, 1531, 1350, 1165, 1136, 1092, 1050, 854, 756, 735, 686 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+H]^+$ 532.1309, found 532.1300

1-(2-chloropyridin-3-yl)-2-methyl-2-(4-nitrophenylsulfonamido)but-3-enyl pivalate (2.6m)



Prepared according to General Procedure D. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:3) as a yellow oil (72.3 mg, 75% yield, d.r. 1:17).

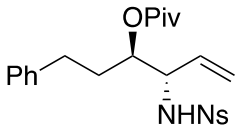
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 4.6, 1.8 Hz, 1H), 8.31 (d, *J* = 8.8 Hz, 2H), 8.01 (d, *J* = 8.8 Hz, 2H), 7.64 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.22 (dd, *J* = 7.7, 4.7 Hz, 1H), 6.15 (s, 1H), 5.80 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.42 (s, 1H), 5.29 (d, *J* = 10.8 Hz, 1H), 5.14 (d, *J* = 17.4 Hz, 1H), 1.38 (s, 3H), 1.20 (s, 9H). (major diastereomer reported)

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.50, 151.13, 149.96, 149.77, 148.08, 137.92, 135.61, 130.68, 128.55, 124.21, 122.15, 119.01, 75.34, 63.64, 38.86, 26.96, 19.97. (major diastereomer reported)

IR (thin film) 3272, 2976, 1738, 1531, 1350, 1165, 1136, 1092, 1033, 1004, 855, 736, 686 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+H]^+$ 482.1147, found 482.1154

4-(4-nitrophenylsulfonamido)-1-phenylhex-5-en-3-yl pivalate (2.6n).



Prepared according to General Procedure C. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:5) as a yellow semi solid (72.3 mg, 79% yield, d.r. 1:8).

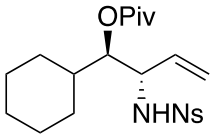
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.8 Hz, 2H), 7.89 (d, *J* = 8.9 Hz, 2H), 7.18 (dd, *J* = 9.0, 5.7 Hz, 2H), 7.11 (t, *J* = 7.3 Hz, 1H), 6.98 (d, *J* = 7.2 Hz, 2H), 5.45 (m, 2H), 5.06 – 4.98 (m, 2H), 4.61 (dt, *J* = 9.5, 3.6 Hz, 1H), 3.99 (td, *J* = 8.3, 3.2 Hz, 1H), 2.58 (ddd, *J* = 14.3, 9.3, 5.3 Hz, 1H), 2.44 (ddd, *J* = 14.0, 8.8, 7.5 Hz, 1H), 1.90 – 1.81 (m, 1H), 1.70 (dddd, *J* = 11.2, 9.4, 7.2, 3.9 Hz, 1H), 1.14 (s, 9H). (major diastereomer reported)

^{13}C NMR (126 MHz, $CDCl_3$) δ 178.96, 149.91, 146.82, 140.31, 132.01, 128.58, 128.26, 128.24, 126.33, 124.22, 119.25, 74.78, 59.72, 39.05, 32.77, 31.44, 27.18. (major diastereomer reported)

IR (thin film) 3280, 2972, 1726, 1530, 1479, 1454, 1349, 1310, 1282, 1166, 1092, 933, 854, 738, 684 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 483.156, found 483.1555

1-**cyclohexyl-2-(4-nitrophenylsulfonamido)but-3-enyl pivalate (2.6o)**



Prepared according to General Procedure C. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:5) as a yellow oil (70 mg 80% yield, d.r. 1:8).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.9 Hz, 2H), 8.03 (d, *J* = 8.9 Hz, 2H), 5.68 (d, *J* = 8.2 Hz, 1H), 5.51 (ddd, *J* = 17.1, 10.3, 6.9 Hz, 1H), 5.13 – 5.04 (m, 2H), 4.47 (dd, *J* = 7.1, 3.4 Hz,

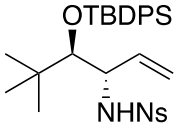
1H), 4.18 (ddd, *J* = 8.3, 7.1, 3.5 Hz, 1H), 1.75 – 1.68 (m, 3H), 1.68 – 1.56 (m, 4H), 1.27 – 1.03 (m, 7H), 1.01 – 0.85 (m, 11H). (major diastereomer reported)

^{13}C NMR (126 MHz, $CDCl_3$) δ 179.23, 149.94, 147.12, 132.38, 128.43, 124.19, 118.89, 79.73, 57.72, 39.10, 38.86, 29.63, 27.68, 27.23, 26.03, 25.78, 25.59. (major diastereomer reported)

IR (thin film) 3270, 2929, 2854, 1708, 1531, 1479, 1449, 1349, 1310, 1282, 1165, 1092, 854, 738, 685 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 461.1717, found 461.1713

***N*-(4-(*tert*-butyldiphenylsilyloxy)-5,5-dimethylhex-1-en-3-yl)-4 nitrobenzenesulfonamide (2.6p)**



Prepared according to General Procedure C. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:10) as a yellow solid (87.5 mg 77% yield, single isomer).

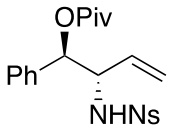
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.8 Hz, 2H), 7.73 (d, *J* = 6.8 Hz, 2H), 7.67 – 7.60 (m, 4H), 7.58 – 7.51 (m, 1H), 7.51 – 7.44 (m, 3H), 7.41 (t, *J* = 7.4 Hz, 2H), 5.97 (ddd, *J* = 17.5, 10.3, 8.3 Hz, 1H), 4.98 (d, *J* = 10.4 Hz, 1H), 4.84 (d, *J* = 17.3 Hz, 1H), 4.65 (d, *J* = 9.5 Hz, 1H), 4.04 (t, *J* = 8.8 Hz, 1H), 3.58 (d, *J* = 1.3 Hz, 1H), 1.14 (s, 9H), 0.82 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.65, 147.29, 136.69, 136.25, 134.95, 134.00, 131.70, 130.31, 130.26, 128.20, 128.12, 127.85, 123.90, 118.82, 85.14, 59.13, 35.65, 27.55, 26.97, 20.04.

IR (thin film) 3319, 2957, 2859, 1531, 1474, 1427, 1349, 1311, 1166, 1107, 1032, 997, 930, 854, 822, 804, 737, 704, 685 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 589.2163, found 589.2156

2-(4-nitrophenylsulfonamido)-1-phenylbut-3-enyl pivalate (2.6q)



Prepared according to General Procedure C. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:5) as a white waxy solid (78.6 mg 86% yield, d.r. 1:11).

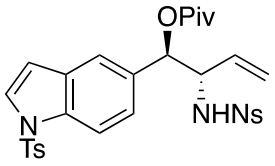
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.8 Hz, 2H), 7.90 (d, *J* = 8.8 Hz, 2H), 7.36 – 7.28 (m, 3H), 7.23 (dd, *J* = 6.8, 2.8 Hz, 2H), 5.71 (d, *J* = 4.5 Hz, 1H), 5.59 (ddd, *J* = 17.0, 10.4, 6.4 Hz, 1H), 5.10 (d, *J* = 10.4 Hz, 1H), 5.00 (d, *J* = 17.2 Hz, 1H), 4.94 (d, *J* = 8.7 Hz, 1H), 4.40 – 4.33 (m, 1H), 1.23 (s, 9H). (major diastereomer reported)

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.62, 149.91, 146.77, 135.63, 132.54, 128.70, 128.67, 128.21, 126.84, 124.23, 118.96, 76.41, 60.39, 38.99, 27.12. (major diastereomer reported)

IR (thin film) 3280, 2973, 1733, 1530, 1349, 1311, 1282, 1166, 1092, 1033, 991, 937, 854, 737, 684 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 455.1247, found 455.1244

2-(4-nitrophenylsulfonamido)-1-(1-tosyl-1*H*-indol-5-yl)but-3-enyl pivalate (2.6r)



Prepared according to General Procedure C. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:2) as a yellow oil (85.7 mg, 69% yield, d.r. 1:13).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.8 Hz, 2H), 7.87 (d, *J* = 8.6 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 2H), 7.75 (d, *J* = 8.7 Hz, 2H), 7.56 (d, *J* = 3.7 Hz, 1H), 7.34 (s, 1H), 7.28 – 7.24 (m, 3H), 7.17 (d, *J* = 9.0 Hz, 1H), 6.54 (d, *J* = 3.6 Hz, 1H), 5.71 (d, *J* = 5.4 Hz, 1H), 5.62 (ddd, *J* = 17.0, 10.4,

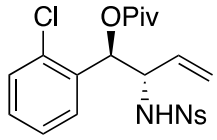
6.4 Hz, 1H), 5.12 (d, *J* = 10.3 Hz, 1H), 5.06 (d, *J* = 17.1 Hz, 1H), 4.90 (d, *J* = 6.7 Hz, 1H), 4.38 – 4.30 (m, 1H), 2.36 (s, 3H), 1.21 (s, 9H). (major diastereomer reported)

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.48, 149.75, 146.47, 145.33, 135.22, 134.51, 133.03, 130.93, 130.68, 130.07, 127.99, 127.16, 126.97, 123.93, 123.38, 119.77, 118.96, 113.49, 108.49, 76.35, 60.57, 38.92, 27.09, 21.59. (major diastereomer reported)

IR (thin film) 3321, 1732, 1530, 1461, 1349, 1170, 1092, 854, 737 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 648.1445, found 648.1442

1-(2-chlorophenyl)-2-(4-nitrophenylsulfonamido)but-3-enyl pivalate (2.6s)



Prepared according to General Procedure C. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:5) as a yellow semi solid (76.8 mg, 83% yield, d.r. 1:7.2).

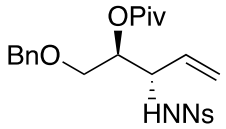
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.9 Hz, 2H), 7.93 (d, *J* = 8.9 Hz, 2H), 7.29 – 7.16 (m, 4H), 6.06 (d, *J* = 5.2 Hz, 1H), 5.71 (ddd, *J* = 16.9, 10.4, 6.4 Hz, 1H), 5.33 – 5.21 (m, 1H), 5.17 (d, *J* = 10.4 Hz, 1H), 5.10 (d, *J* = 17.1 Hz, 1H), 4.35 (dt, *J* = 8.9, 6.3 Hz, 1H), 1.22 (s, 9H). (major diastereomer reported)

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.22, 149.94, 146.57, 134.48, 132.54, 132.13, 129.75, 129.68, 128.26, 127.71, 127.04, 124.23, 119.31, 73.11, 59.53, 38.96, 27.08. (major diastereomer reported)

IR (thin film) 3284, 1736, 1530, 1349, 1167, 1092, 855, 770, 738 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 489.0858, found 489.0856

1-(benzyloxy)-3-(4-nitrophenylsulfonamido)pent-4-en-2-yl pivalate (2.6t)



Prepared according to General Procedure C. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:4) as a yellow oil (61 mg, 64% yield, d.r. 1:10).

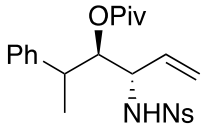
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.9 Hz, 2H), 7.96 (d, *J* = 8.9 Hz, 2H), 7.42 – 7.27 (m, 5H), 6.10 (d, *J* = 8.4 Hz, 1H), 5.54 (ddd, *J* = 16.9, 10.3, 6.4 Hz, 1H), 5.12 (d, *J* = 17.1 Hz, 1H), 5.09 (d, *J* = 10.4 Hz, 1H), 4.76 (q, *J* = 4.1 Hz, 1H), 4.53 (d, *J* = 11.8 Hz, 1H), 4.49 (d, *J* = 11.8 Hz, 1H), 4.39 (ddd, *J* = 8.5, 6.6, 4.7 Hz, 1H), 3.67 (dd, *J* = 10.7, 3.6 Hz, 1H), 3.56 (dd, *J* = 10.7, 4.5 Hz, 1H), 1.19 (s, 9H). (major diastereomer reported)

^{13}C NMR (126 MHz, $CDCl_3$) δ 178.22, 149.82, 147.39, 137.08, 132.74, 128.67, 128.22, 127.80, 124.15, 118.89, 73.80, 72.58, 68.78, 57.86, 38.92, 27.10. (major diastereomer reported)

IR (thin film) 3280, 2973, 1727, 1530, 1349, 1166, 854, 738 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 499.1509, found 499.1504

4-(4-nitrophenylsulfonamido)-2-phenylhex-5-en-3-yl pivalate (2.6u)



Prepared according to General Procedure C. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:5) as a white semi solid (80.9 mg, 88% yield, d.r. 1:3). This d.r. is inherited from the d.r. of the starting material 1u.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.7 Hz, 2 * 0.27H), 8.23 (d, *J* = 8.8 Hz, 2 * 0.73H), 7.98 (d, *J* = 8.8 Hz, 2 * 0.27H), 7.75 (d, *J* = 8.9 Hz, 2 * 0.73H), 7.32 – 7.20 (m, 3H), 7.15 – 7.10 (m, 2 * 0.27H), 7.02 – 6.94 (m, 2 * 0.73H), 5.70 – 5.55 (m, 1 * 0.73H + 1 * 0.73H + 1 * 0.27H),

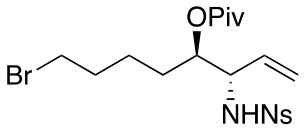
5.41 (ddd, *J* = 17.2, 10.2, 6.9 Hz, 1 * 0.27H), 5.25 – 5.07 (m, 2 * 0.73H + 2 * 0.27H), 4.88 (dd, *J* = 8.3, 2.3 Hz, 1 * 0.27H), 4.81 (dd, *J* = 10.2, 1.6 Hz, 1 * 0.73H), 4.29 (t, *J* = 6.9 Hz, 1 * 0.27H), 3.75 (t, *J* = 6.9 Hz, 1 * 0.73H), 3.02 – 2.88 (m, 1 * 0.27H + 1 * 0.73H), 1.25 – 1.21 (m, 9* 0.73H + 3 * 0.27H), 1.18 (d, *J* = 6.9 Hz, 3 * 0.73H), 0.93 (s, 9 * 0.27H). (both diastereomers reported)

^{13}C NMR (126 MHz, $CDCl_3$) δ 179.68, 149.80, 146.39, 141.91, 131.48, 129.07, 128.27, 127.51, 127.38, 124.20, 119.74, 80.36, 57.86, 41.56, 39.27, 27.24, 18.44. (major diastereomer reported)

IR (thin film) 3257, 2973, 1709, 1531, 1349, 1166, 1092, 936, 854, 766, 738 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 483.156, found 483.1554

8-bromo-3-(4-nitrophenylsulfonamido)oct-1-en-4-yl pivalate (2.6v)



Prepared according to General Procedure C. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:5) as a colourless oil (84.5 mg, 86% yield, d.r. 1:10).

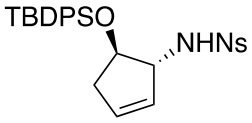
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.5 Hz, 2H), 8.03 (d, *J* = 8.9 Hz, 2H), 5.59 – 5.42 (m, 2H), 5.07 (m, 2H), 4.74 (dt, *J* = 8.4, 4.0 Hz, 1H), 4.06 (td, *J* = 7.5, 3.5 Hz, 1H), 3.50 (t, *J* = 6.3 Hz, 2H), 1.93 – 1.32 (m, 6H), 1.19 (s, 9H). (major diastereomer reported)

^{13}C NMR (126 MHz, $CDCl_3$) δ 178.92, 150.03, 146.89, 132.04, 128.41, 124.28, 119.35, 75.20, 59.69, 44.51, 39.02, 31.84, 30.09, 27.14, 22.56. (major diastereomer reported)

IR (thin film) 3274, 2959, 1726, 1531, 1349, 1280, 1166, 1092, 938, 854, 738 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 513.0665, found 513.066

***N*-(5-(*tert*-butyldiphenylsilyloxy)cyclopent-2-enyl)-4-nitrobenzenesulfonamide (2.6w)**



Prepared according to General Procedure C. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:10) as a yellow oil (76.4 mg, 73% yield, d.r. 1:10).

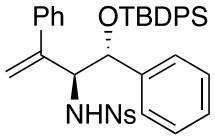
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.9 Hz, 2H), 7.92 (d, *J* = 8.9 Hz, 2H), 7.61 (dd, *J* = 8.0, 1.4 Hz, 2H), 7.56 (dd, *J* = 8.0, 1.4 Hz, 2H), 7.49 – 7.33 (m, 6H), 5.74 (ddd, *J* = 6.2, 4.1, 2.3 Hz, 1H), 5.42 (dq, *J* = 6.0, 2.0 Hz, 1H), 4.36 – 4.31 (m, 1H), 4.25 (d, *J* = 7.5 Hz, 1H), 4.14 (dt, *J* = 6.8, 4.5 Hz, 1H), 2.38 – 2.30 (m, 1H), 2.23 (dtd, *J* = 6.7, 4.1, 2.1 Hz, 1H), 0.99 (s, 9H). (major diastereomer reported)

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.89, 146.57, 135.76, 135.71, 133.40, 133.25, 133.03, 130.06, 130.00, 128.65, 128.23, 127.84, 127.76, 124.27, 79.24, 67.62, 39.85, 26.73, 19.02. (major diastereomer reported)

IR (thin film) 3288, 2930, 2856, 1606, 1530, 1428, 1348, 1311, 1165, 1111, 889, 854, 823, 738, 703, 686 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 545.1537, found 545.1531

***N*-(1-(*tert*-butyldiphenylsilyloxy)-1,3-diphenylbut-3-en-2-yl)-4-nitrobenzenesulfonamide (2.6x)**



Prepared according to General Procedure C using ItBuSe catalyst. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:10) as a pale-yellow solid (82.5 mg, 64 % yield, d.r. 1:10).

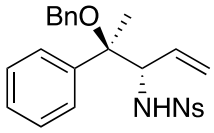
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.9 Hz, 2H), 7.90 (d, *J* = 8.9 Hz, 2H), 7.70 – 7.66 (m, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.4 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.30 – 7.22 (m, 5H), 7.21 – 7.14 (m, 3H), 7.14 – 7.06 (m, 4H), 6.81 – 6.74 (m, 2H), 5.01 (s, 1H), 4.85 – 4.76 (m, 3H), 4.38 (d, *J* = 0.9 Hz, 1H), 0.99 (s, 9H). (major diastereomer reported)

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.70, 147.04, 144.41, 138.85, 137.51, 136.10, 135.82, 133.23, 132.50, 130.08, 129.76, 128.69, 128.16, 127.99, 127.89, 127.81, 127.56, 127.23, 126.11, 123.98, 116.34(2C overlapped), 74.52, 62.38, 26.97, 19.30. (major diastereomer reported)

IR (thin film) 2930, 1530, 1427, 1349, 1219, 1167, 1111, 1066, 913, 854, 772, 701 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 685.2163, found 685.216

***N*-(4-(benzyloxy)-4-phenylpent-1-en-3-yl)-4-nitrobenzenesulfonamide (2.6y)**



Prepared according to General Procedure C. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:10) as a pale-yellow semi solid (67 mg, 74% yield, d.r. 1:2.3).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.9 Hz, 2H), 7.87 (d, *J* = 8.9 Hz, 2H), 7.39 – 7.20 (m, 10H), 5.51 (ddd, *J* = 17.6, 10.3, 7.5 Hz, 1H), 5.16 – 5.09 (m, 1H), 4.88 (d, *J* = 10.4 Hz, 2H), 4.76 (d, *J* = 17.2 Hz, 2H), 4.41 (d, *J* = 11.3 Hz, 1H), 4.27 (d, *J* = 11.3 Hz, 1H), 3.99 (t, *J* = 8.1 Hz, 1H), 1.79 (s, 3H). (major diastereomer)

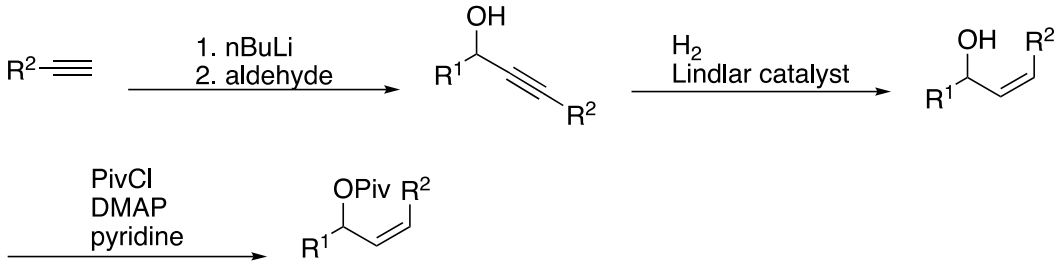
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.8 Hz, 2H), 7.72 (d, *J* = 8.9 Hz, 2H), 7.39 – 7.20 (m, 10H), 5.75 (ddd, *J* = 17.4, 10.4, 7.1 Hz, 1H), 5.20 (d, *J* = 3.8 Hz, 1H), 5.16 – 5.09 (m, 1H), 5.05 (d, *J* = 17.2 Hz, 1H), 4.32 (d, *J* = 10.9 Hz, 1H), 4.15 (d, *J* = 10.9 Hz, 1H), 3.89 (t, *J* = 7.2 Hz, 1H), 1.65 (s, 3H). (minor diastereomer)

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.68, 146.83, 140.30, 138.19, 133.69, 128.49, 128.38, 128.29, 127.64, 127.53, 127.16, 126.84, 123.94, 118.59, 81.36, 66.47, 64.86, 21.57. (major diastereomer reported)

IR (thin film) 1528, 1348, 1219, 1166, 854, 772, 737 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 475.1298, found 475.1294

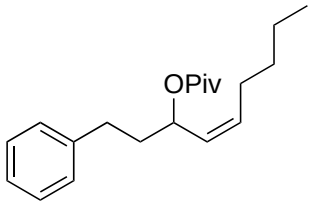
2.4.4 *Synthesis and Characterisation of Allylic Alcohol Pivalates*



The *cis* allylic alcohols were prepared according to literature procedure[58]. The alcohols were subjected to General Procedure B to afford pivalates.

Characterisation of Allylic Alcohol Pivalates

(*Z*)-1-phenylnon-4-en-3-yl pivalate (2.15a)



Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:25) as a colourless oil (70% yield).

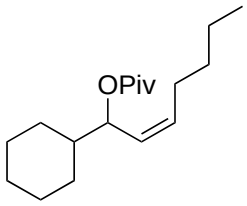
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 2H), 7.22 – 7.14 (m, 3H), 5.59 – 5.49 (m, 2H), 5.33 (ddt, *J* = 10.8, 9.0, 1.6 Hz, 1H), 2.70 – 2.56 (m, 2H), 2.11 (m, 2H), 2.06 – 1.95 (m, 1H), 1.86 – 1.76 (m, 1H), 1.38 – 1.24 (m, 4H), 1.20 (s, 9H), 0.88 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.71, 141.59, 134.26, 128.44, 128.34, 127.98, 125.95, 69.74, 38.78, 36.66, 31.73, 31.52, 27.66, 27.20, 22.34, 13.95.

IR (thin film) 3026, 2957, 2930, 2870, 1726, 1479, 1456, 1281, 1030, 748, 699 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 325.2138, found 325.214

(*Z*)-1-cyclohexylhept-2-enyl pivalate (2.15b)



Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:30) as a colourless oil (77% yield).

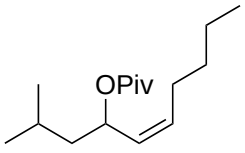
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.55 (dt, *J* = 10.1, 7.4 Hz, 1H), 5.32 – 5.21 (m, 2H), 2.25 – 1.98 (m, 1H), 1.81 – 1.59 (m, 5H), 1.55 – 1.47 (m, 1H), 1.39 – 1.29 (m, 4H), 1.18 (m, 12H), 1.05 – 0.93 (m, 2H), 0.90 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.66, 134.57, 126.74, 73.87, 42.07, 38.84, 31.79, 28.59, 28.53, 27.77, 27.21, 26.47, 26.08, 25.96, 22.41, 13.99.

IR (thin film) 2927, 2854, 1726, 1479, 1451, 1395, 1365, 1281, 1161, 1030, 972, 937, 880, 769, 739 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 303.2295, found 303.2297

(*Z*)-2-methyldec-5-en-4-yl pivalate (2.15c)



Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:30) as a colourless oil (81% yield).

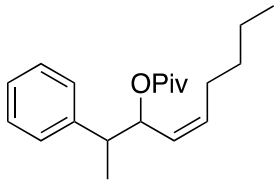
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.57 (q, *J* = 7.5 Hz, 1H), 5.49 (dt, *J* = 11.0, 7.5 Hz, 1H), 5.26 (dd, *J* = 11.1, 9.0 Hz, 1H), 2.22 – 2.12 (m, 2H), 1.66 – 1.55 (m, 2H), 1.41 – 1.26 (m, 5H), 1.17 (s, 9H), 0.98 – 0.85 (m, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.74, 133.59, 128.66, 68.73, 43.91, 38.68, 31.76, 27.59, 27.14, 24.52, 22.95, 22.43, 22.34, 13.96.

IR (thin film) 2958, 2931, 2872, 1727, 1480, 1466, 1396, 1367, 1282, 1159, 1033, 963, 935, 770, 751 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 277.2138, found 277.2138

(*Z*)-1-phenyloct-3-en-2-yl pivalate (2.15d)



Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:25) as a colourless oil (64% yield).

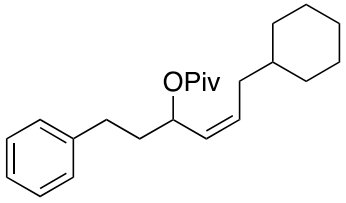
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.23 (m, 2H), 7.22 – 7.15 (m, 3H), 5.59 (t, *J* = 8.0 Hz, H), 5.41 (dt, *J* = 10.9, 7.5 Hz, 1H), 5.15 (t, *J* = 10.2 Hz, 1H), 3.00 (quin, *J* = 6.8 Hz, 1H), 2.05 (dq, *J* = 14.5, 7.2 Hz, 1H), 1.90 (dt, *J* = 14.5, 7.4 Hz, 1H), 1.32 (d, *J* = 7.1 Hz, 3H), 1.29 – 1.11 (m, 13H), 0.83 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.58, 142.74, 134.77, 128.29, 128.11, 126.55, 126.27, 73.92, 44.19, 38.86, 31.47, 27.66, 26.94, 22.37, 16.88, 13.96.

IR (thin film) 3028, 2960, 2930, 2871, 1727, 1479, 1454, 1280, 1156, 1031, 957, 761, 700cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 325.2138, found 325.214

(*Z*)-6-cyclohexyl-1-phenylhex-4-en-3-yl pivalate (2.15e)



Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:25) as a colourless oil (78% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 2H), 7.22 – 7.14 (m, 3H), 5.60 – 5.49 (m, 2H), 5.42 – 5.34 (m, 1H), 2.70 – 2.55 (m, 2H), 2.05 – 1.94 (m, 3H), 1.86 – 1.75 (m, 1H), 1.70 – 1.59 (m, 5H), 1.30 – 1.06 (m, 13H), 0.93 – 0.79 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.72, 141.63, 132.93, 128.58, 128.44, 128.37, 125.95, 69.69, 38.79, 38.08, 36.68, 35.60, 33.13, 33.03, 31.53, 27.21, 26.49, 26.36.

IR (thin film) 3025, 2923, 2851, 1726, 1496, 1479, 1450, 1395, 1365, 1281, 1157, 1030 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 365.2451, found 365.2455

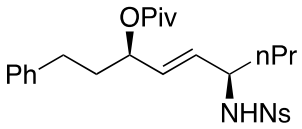
2.4.5 *Synthesis and Characterisation of Syn-1,4-Amino Alcohols*

General Procedure E: Allylic Amination of Internal Allylic Alcohols

To an oven-dried 1-dram vial was added alkene (0.2 mmol, 1 equiv), phosphine selenide (15 mol%), 4-nitrobenzenesulfonamide (0.4 mmol, 2 equiv), DCM (1 mL) and (diacetoxyiodo)benzene (0.4 mmol, 2 equiv), in that order. The vial was capped with a Teflon-lined screw cap and the reaction was stirred at room temperature for 48 hours. Upon completion, the reaction mixture was diluted with 2 mL ethyl acetate and was pushed through a silica plug. An ^{1}H NMR spectrum was taken with 1,3-dinitrobenzene as internal standard to obtain NMR yield. The crude product was purified by column chromatography to afford the corresponding product.

Characterisation of syn-1,4-Amino Alcohol Products

(*E*)-6-(4-nitrophenylsulfonamido)-1-phenylnon-4-en-3-yl pivalate (2.16a)



Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:8) as a yellow oil (78.4 mg, 78% yield, d.r. 1:4.9).

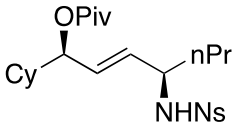
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.8 Hz, 2H), 8.02 (d, *J* = 8.9 Hz, 2H), 7.28 (t, *J* = 7.5 Hz, 2H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.10 (d, *J* = 7.1 Hz, 2H), 5.47 (dd, *J* = 15.7, 6.0 Hz, 1H), 5.38 (dd, *J* = 15.7, 6.9 Hz, 1H), 5.14 – 5.03 (m, 1H), 4.76 (d, *J* = 7.6 Hz, 1H), 3.89 (quin, *J* = 6.8 Hz, 1H), 2.62 – 2.44 (m, 2H), 1.88 – 1.76 (m, 1H), 1.76 – 1.66 (m, 1H), 1.51 – 1.38 (m, 2H), 1.31 – 1.20 (m, 2H), 1.18 (s, 9H), 0.85 (t, *J* = 7.2 Hz, 3H). (major diastereomer reported)

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.50, 149.91, 147.17, 140.99, 131.34, 130.92, 128.55, 128.24, 128.22, 126.15, 124.28, 72.26, 55.62, 38.82, 37.91, 36.18, 31.40, 27.12, 18.61, 13.56. (major diastereomer reported)

IR (thin film) 3276, 2964, 1726, 1530, 1348, 1164 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 525.203, found 525.2028

(*E*)-1-cyclohexyl-4-(4-nitrophenylsulfonamido)hept-2-enyl pivalate (2.16b)



Prepared according to General Procedure C. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:10) as a yellow oil (84.6 mg, 88% yield, d.r. 1:3).

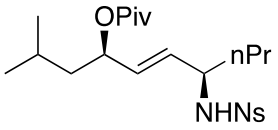
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.8 Hz, 2H), 8.04 (d, *J* = 8.9 Hz, 2H), 5.55 – 5.29 (m, 2H), 4.94 – 4.77 (m, 2H), 4.02 – 3.80 (m, 2H), 1.79 – 0.43 (m, 27H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.51, 149.91, 147.27, 132.06, 129.64, 128.21, 124.32, 76.90, 55.64, 41.81, 38.92, 38.23, 30.34, 28.79, 28.17, 27.17, 26.29, 25.89, 25.83, 18.61, 13.60. (major diastereomer reported)

IR (thin film) 2930, 1726, 1531, 1348, 1165 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 503.2186, found 503.2179

(*E*)-2-methyl-7-(4-nitrophenylsulfonamido)dec-5-en-4-yl pivalate (2.16c)



Prepared according to General Procedure C. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:10) as a yellow semi solid (79 mg, 87% yield, d.r. 1:3.5).

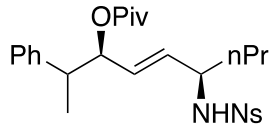
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.7 Hz, 2H), 8.03 (d, *J* = 8.7 Hz, 2H), 5.50 – 5.27 (m, 2H), 5.12 (dt, *J* = 10.5, 5.4 Hz, 1H), 4.68 (s, 1H), 3.94 – 3.84 (m, 1H), 1.55 – 1.35 (m, 3H), 1.35 – 1.17 (m, 4H), 1.15 (s, 9H), 0.93 – 0.75 (m, 9H). (major diastereomer reported)

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.57, 149.95, 147.25, 131.56, 130.81, 128.31, 124.31, 71.22, 55.66, 43.42, 38.76, 38.06, 27.10, 24.44, 22.89, 22.00, 18.60, 13.58. (major diastereomer reported)

IR (thin film) 3276, 2959, 1726, 1531, 1349, 1165, 856, 737 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 477.2030, found 477.2025

(*E*)-6-(4-nitrophenylsulfonamido)-2-phenylnon-4-en-3-yl pivalate (2.16d)



Prepared according to General Procedure C. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:10) as a yellow semi solid (78 mg, 75% yield, d.r. 1:3).

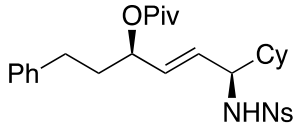
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.9 Hz, 1H), 7.94 (d, *J* = 8.8 Hz, 1H), 7.33 – 7.18 (m, 3H), 7.16 – 7.06 (m, 2H), 5.32 – 5.14 (m, 3H), 4.66 (br s, 1H), 3.72 (quin, *J* = 7.1 Hz, 1H), 2.90 (quin, *J* = 6.7 Hz, 1H), 1.40 – 1.20 (m, 6H), 1.17 (d, *J* = 0.8 Hz, 9H), 1.10 – 0.98 (m, 1H), 0.75 (t, *J* = 7.3 Hz, 3H). (major diastereomer reported)

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.44, 149.89, 147.08, 142.30, 132.32, 129.69, 128.41, 128.15, 128.09, 126.86, 124.32, 77.15, 55.57, 44.21, 38.92, 37.89, 27.16, 18.35, 17.28, 13.57. (major diastereomer reported)

IR (thin film) 3276, 2964, 1726, 1530, 1348, 1164, 1093, 967, 855, 737, 701 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 525.203, found 525.2021

(*E*)-6-cyclohexyl-6-(4-nitrophenylsulfonamido)-1-phenylhex-4-en-3-yl pivalate (2.16e)



Prepared according to General Procedure C. Purified through column chromatograph (silica gel, ethyl acetate/hexanes 1:10) as a yellow semi solid (61.9 mg, 57% yield, d.r. 1:3.5).

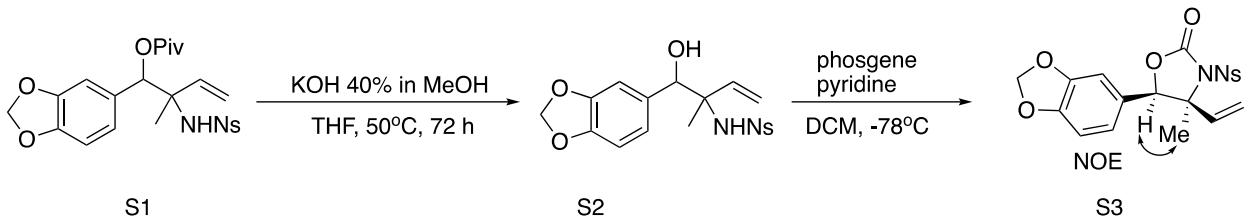
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.6 Hz, 2H), 8.01 (d, *J* = 8.7 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 7.09 (d, *J* = 7.3 Hz, 2H), 5.41 – 5.30 (m, 2H), 5.14 – 5.00 (m, 1H), 4.84 – 4.72 (m, 1H), 3.71 (dt, *J* = 8.3, 4.0 Hz, 1H), 2.60 – 2.44 (m, 2H), 1.85 – 1.74 (m, 1H), 1.75 – 1.59 (m, 5H), 1.55 (m, 1H), 1.42 – 1.33 (m, 1H), 1.16 (m, 12H), 0.96 – 0.81 (m, 2H). (major diastereomer reported)

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.45, 149.90, 147.16, 140.98, 131.57, 129.99, 128.60, 128.27, 128.22, 126.20, 124.27, 72.27, 60.70, 42.76, 38.84, 36.26, 31.45, 28.95, 28.78, 27.15, 26.11, 25.89, 25.86. (major diastereomer reported)

IR (thin film) 3276, 2926, 1726, 1531, 1348, 1163, 1092, 855, 737 cm^{-1}.

HRMS (ESI, positive mode) calculated for $[M+Na]^+$ 565.2343, found 565.2337

2.4.6 *Stereochemistry Determination*

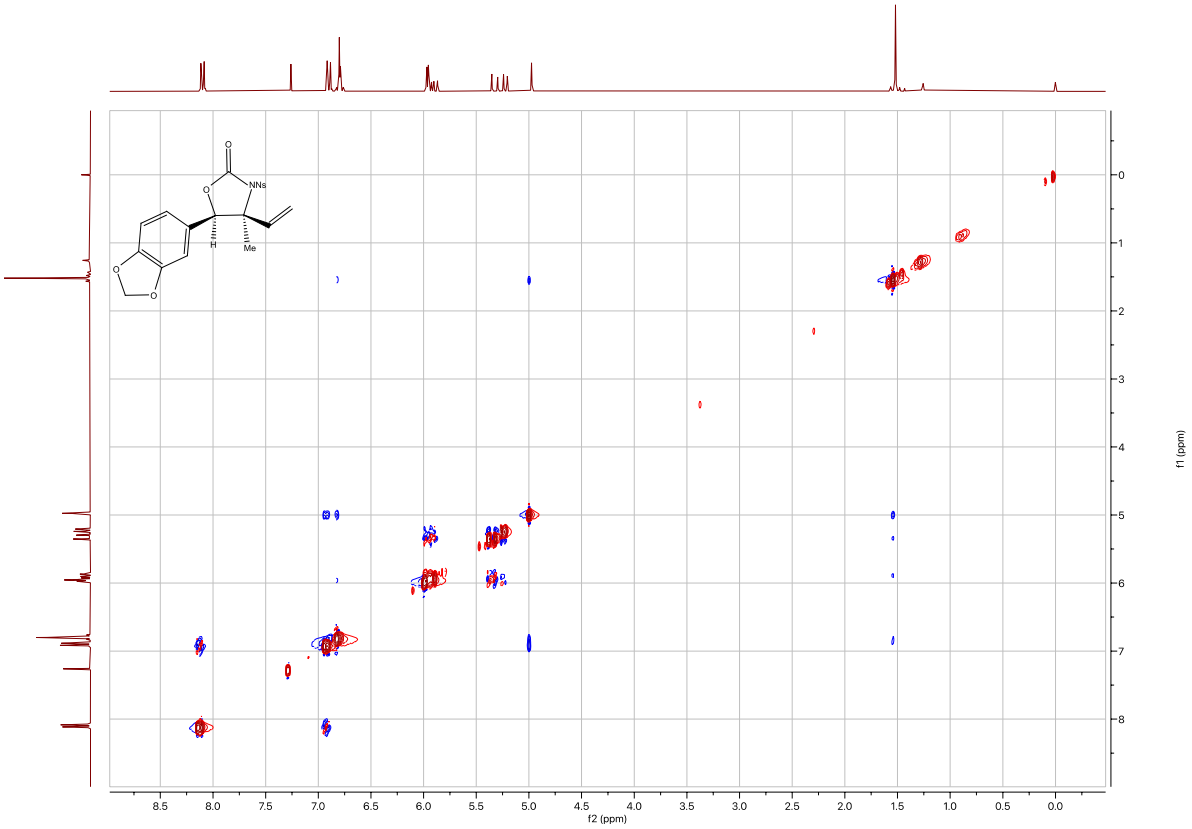


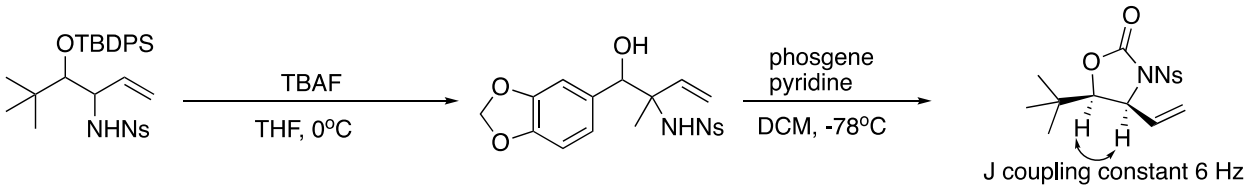
S1 S2 S3

Deprotection of S1: In a round-bottom flask charged with S1 (1 equiv) was added THF. A solution of KOH (40% in MeOH, excess) was added. The reaction was heated at 50 °C for 72 hours. The reaction mixture was diluted with water and extracted with ethyl acetate three times. The organic layer was then washed with water and brine, dried over sodium sulphate, and removed under reduced pressure. The crude product was then purified on column to afford S2 as a colourless oil which was used in next step.

Cyclisation of S2: In a flame dried round-bottom flask was added S2 (1 equiv), pyridine (20 equiv) and DCM at -78°C. A solution of phosgene (15wt% in toluene, 1.5 equiv) was added dropwise. The reaction was allowed to stir at the same temperature for 2 hours. The reaction was quenched with water and diluted with ether. The reaction was extracted with ether, washed with 1 M HCl and brine. The solvent was dried over sodium sulphate and removed under reduced pressure. The crude product was purified on column to afford S3 as a colourless oil.

The pure product of S3 was subject to NOESY experiment to confirm the stereochemistry.





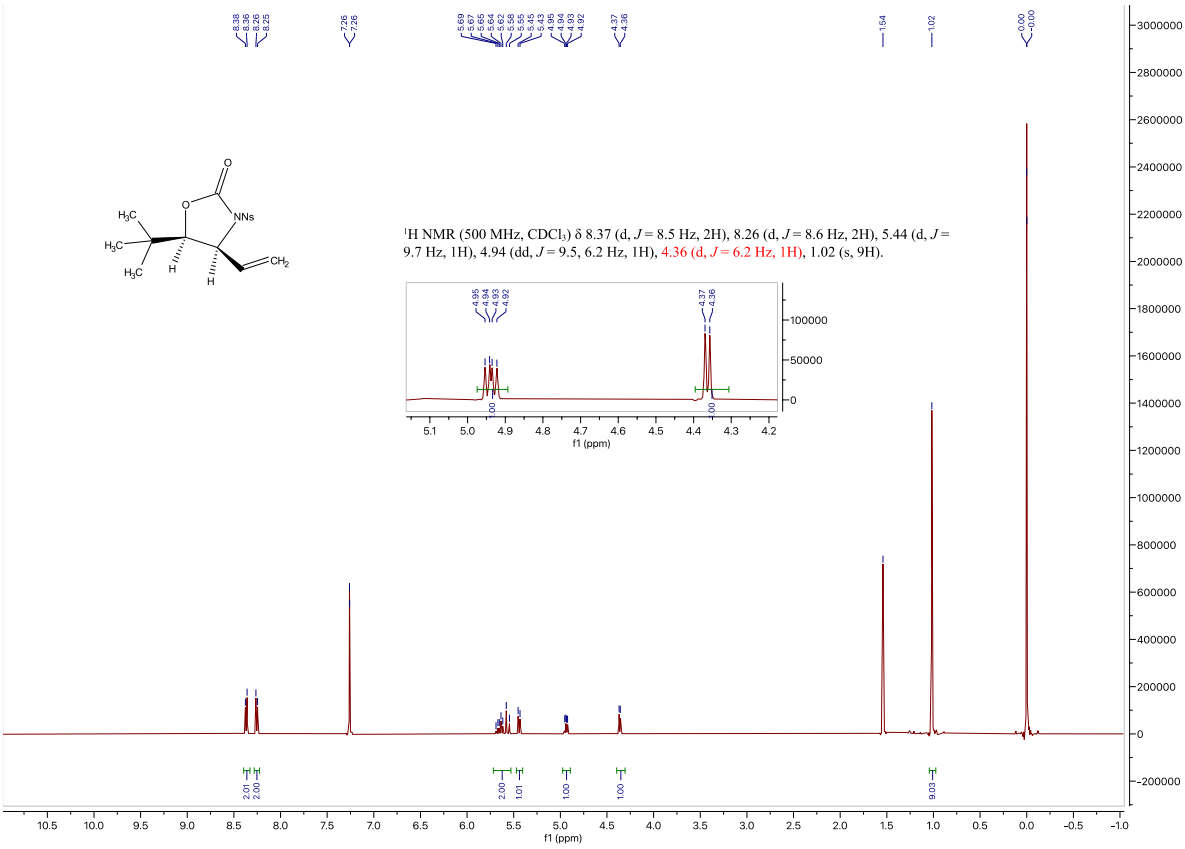
S4 S5 S6

Deprotection of S4: S4 (1 equiv) was dissolved in 10 mL of dry THF. To the solution was added TBAF (3 equiv). The resulting solution was stirred at room temperature for 4 h and then quenched by addition of a saturated aqueous solution of NH_4Cl (10 mL). The reaction mixture was extracted with ethyl acetate three times. The organic layers were combined, washed with brine (20 mL), dried with sodium sulphate, and concentrated in vacuo. The crude product was purified on column to afford S5.

Cyclisation of S5: S5 was subjected to the same cyclisation procedure for S2 to give S6.

An ^{1}H NMR was taken for S6 to confirm the stereochemistry. By comparing the *J* coupling constant to literature value[44], the stereochemistry is confirmed to be *cis* in the cyclised product. Therefore, the reaction gives *anti*-1,2-amino alcohol.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.5 Hz, 2H), 8.26 (d, *J* = 8.6 Hz, 2H), 5.44 (d, *J* = 9.7 Hz, 1H), 4.94 (dd, *J* = 9.5, 6.2 Hz, 1H), **4.36 (d, *J* = 6.2 Hz, 1H),** 1.02 (s, 9H).



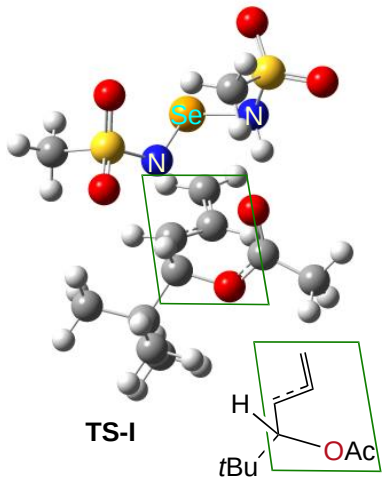
2.4.7 *Computational Study*

DFT calculations were performed using the Gaussian-16 software package. Structures were optimised at the ωB97-XD/6-311++G(d,p) level of theory, using the PCM model with CH_2Cl_2 as solvent. Frequency calculations were performed on all structures and enthalpies and free energies were calculated using the harmonic approximation at standard state (1 M concentration). Free energies have also been adjusted and recorded for 0.04 M concentration to better reflect the

experimental conditions. All structures had zero negative frequencies, and the transition state had one negative frequency whose motions corresponded to the expected reaction coordinate.

Computational Study for [2,3]-Sigmatropic Rearrangement for 1,2-Amino Alcohol

Anti-Conformation for [2,3]-Sigmatropic Rearrangement Transition State (TS-I)



TS-I

C -0.13250400 -0.03918600 2.94582000

C -0.93916600 0.59820300 2.03008700

C -1.57681000 -0.15821200 1.05419300

H -0.84556000 1.67049500 1.90816900

C -2.32943200 0.44620800 -0.09911600

H -1.84336600 -1.17658100 1.29998400

C -3.82894500 0.05187700 -0.13663100

C -3.95020800 -1.47484600 -0.25816700

H -3.32155100 -1.85987700 -1.06521000

H -4.98871700 -1.73697100 -0.47585700

H -3.68144500 -1.98904200 0.66885600

C -4.45598100 0.69120300 -1.38304000

H -3.95260200 0.34738700 -2.29193200

H -4.39706600 1.78059600 -1.34646100

H -5.51014100 0.40979800 -1.45309700

C -4.55341600 0.53655400 1.12430800

H -4.12531700 0.09220500 2.02824500

H -5.60796400 0.25079700 1.07918000

H -4.49908300 1.62337900 1.21954600

O -2.28345600 1.88658000 -0.05477100

H -1.85738800 0.10909000 -1.02377800

C -1.21053500 2.53122000 -0.51721500

C -1.42220000 4.01452100 -0.50745600

H -1.72203500 4.33987300 0.49035100

H -2.23135100 4.26787200 -1.19575900

H -0.50746200 4.51929700 -0.80886700

O -0.20112800 1.97147900 -0.88126300

Se 1.61597300 -0.83950900 1.24624800

H -0.29477000 -1.08432800 3.18710900

H 0.47567100 0.52284500 3.64500200

N 0.22270100 -1.02740700 0.17819600

N 2.15225600 0.88136900 0.75790200

S 0.13644200 -2.18530900 -0.96562700

S 3.32437900 1.10445700 -0.41902200

H 1.33491200 1.45779700 0.54841800

O -0.92190100 -1.77132200 -1.88520200

O 1.44542600 -2.48658800 -1.54516400

O 3.54442100 2.54121000 -0.46434100

O 4.42555900 0.22102000 -0.07346200

C 2.62352900 0.59228800 -1.96936500

H 2.44200900 -0.48195800 -1.93288600

H 3.35677900 0.84035200 -2.73655800

H 1.69673000 1.14677000 -2.11139400

C -0.43831700 -3.66396400 -0.14626500

H -0.55434100 -4.43356400 -0.90864400

H 0.30244700 -3.96610300 0.59296000

H -1.39678300 -3.44514100 0.32259800

Imaginary frequencies = 1 at -288 cm^{-1}

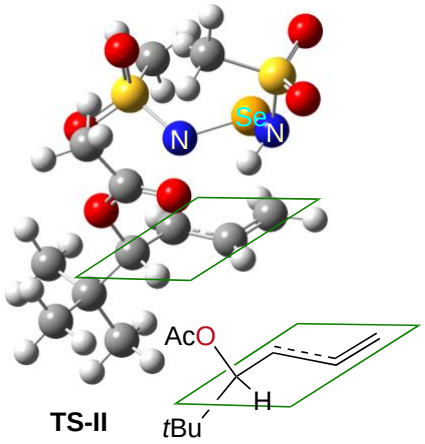
Energy = -4230.3534

Enthalpy = -4229.9513

Free Energy (1 M) = -4230.0383

Free Energy (0.04 M) = -4230.0353

Syn-Conformation for [2,3]-Sigmatropic Rearrangement Transition State (TS-II)



TS-II

C 0.15417200 0.66752000 2.99261800

C 0.96239500 -0.20861800 2.30438600

C 1.65256500 0.21359700 1.17181800

H 0.81648100 -1.27469600 2.44971300

C 2.40409700 -0.85096200 0.38852700

H 2.01009800 1.23288800 1.10516500

C 3.93226800 -0.63171200 0.34341600

C 4.44852500 -0.52666400 1.78527000

H 4.06658700 0.36277200 2.29364800

H 5.53989200 -0.46396600 1.78002600

H 4.16314700 -1.40340800 2.37534900

C 4.30527700 0.62983000 -0.44200400

H 3.92082400 1.53671100 0.03046500

H 3.90988900 0.59352600 -1.45797000

H 5.39453800 0.71647400 -0.49202100

C 4.56638900 -1.85889200 -0.32634700

H 4.31096500 -2.77796700 0.21074600

H 5.65533700 -1.76041600 -0.32681400

H 4.23421100 -1.96128600 -1.36157800

O 1.94481100 -0.97702400 -0.96400700

H 2.21368900 -1.80784800 0.88138200

C 0.85344400 -1.69942700 -1.19588200

O 0.19880300 -2.23400600 -0.32385900

C 0.53937000 -1.74862600 -2.65954400

H 0.00190400 -0.83150200 -2.91930700

H 1.45406800 -1.78326500 -3.25012200

H -0.08843600 -2.61096100 -2.87684600

Se -1.48259800 0.97884800 1.09499600

H 0.34291300 1.73556600 2.95093600

H -0.48315000 0.32714600 3.80057200

N -0.04724800 0.88701700 0.06327600

N -2.06471400 -0.79015300 1.02394000

S 0.08062800 1.87594000 -1.24288100

S -3.37536400 -1.17578300 0.05793100

H -1.28053000 -1.43254800 0.87797100

O -4.34797100 -0.11521700 0.26529900

O -3.72165800 -2.54568100 0.39424500

O -0.83375600 1.44624000 -2.30394600

O 1.49847700 1.93785900 -1.57004800

C -0.42166700 3.52041900 -0.74952500

H -0.22952500 4.16890700 -1.60369900

H 0.18335200 3.82349300 0.10387500

H -1.48414900 3.52027200 -0.51020600

C -2.81492700 -1.13392600 -1.62773500

H -3.69091300 -1.30122500 -2.25396700

H -2.36107600 -0.16310300 -1.83345900

H -2.09335200 -1.93955100 -1.74648900

Imaginary frequencies = 1 at -255 cm^{-1}

Energy = -4230.3507

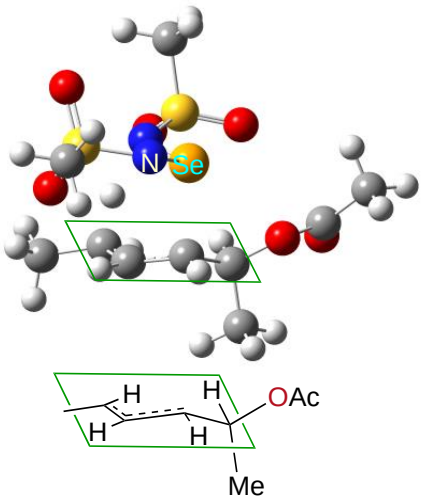
Enthalpy = -4229.9486

Free Energy (1 M) = -4230.0340

Free Energy (0.04 M) = -4230.0310

<u>Computational Study for Ene Reaction for 1,4-Amino Alcohol</u>

<u>Syn-Conformation for Ene Reaction Transition State (TS-III)</u>



TS-III

C -1.98080800 -1.52682800 0.39753100

C -0.49938900 -1.79852900 0.20459800

C 0.39079100 -1.76991500 1.29563600

C 0.26916700 -0.89238300 2.39825200

C 1.25766300 -0.98220500 3.54117700

H 0.52958500 0.07506900 1.69919900

H -0.74630700 -0.62902100 2.69557200

H 2.26328800 -1.17334500 3.16483600

H 0.97558700 -1.78493700 4.22693300

H 1.26980900 -0.04819700 4.10421700

H -0.29045500 -2.55788400 -0.54721300

H 1.34309800 -2.27343200 1.16310600

Se 0.26474800 -0.01192500 -0.94953000

N 1.83169400 -0.48872200 -1.49910300

N 0.48372900 1.06240200 0.43542400

S 3.20211700 -0.25568100 -0.63736500

S -0.71401800 2.18991800 0.66573900

O 3.08976700 -0.80036600 0.72152300

O 3.68045700 1.12176700 -0.73804300

C 4.31116100 -1.29274900 -1.56498400

H 5.28835300 -1.19602900 -1.09251900

H 3.95363900 -2.31893500 -1.51384500

H 4.34298100 -0.93447600 -2.59192600

O -0.90056600 2.31506500 2.10337900

C 0.01786500 3.69108600 0.05463200

H -0.70476600 4.48775500 0.22939300

H 0.93900700 3.86867300 0.60585900

H 0.21240100 3.56863000 -1.00943900

O -1.88586400 1.87487000 -0.15364900

H -2.15362200 -0.65782300 1.03590000

O -2.49354200 -1.21612500 -0.90747400

C -3.65568200 -0.53297400 -0.97365800

C -3.94525800 -0.10955300 -2.37998300

H -3.75815300 -0.92712200 -3.07665800

H -4.97486000 0.23215200 -2.45817900

H -3.27017100 0.71236100 -2.63173000

O -4.33410800 -0.29773800 -0.00783300

C -2.66489800 -2.75491600 0.98277100

H -2.51359000 -3.61954600 0.33250500

H -2.24501300 -2.97836600 1.96586300

H -3.73263000 -2.56959000 1.09483800

Imaginary frequencies = 1 at 465 cm^{-1}

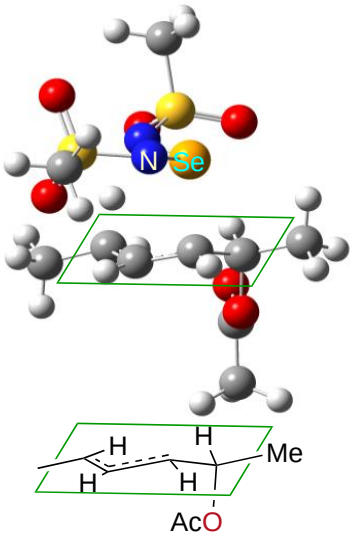
Energy = -4151.6949

Enthalpy = -4151.3558

Free Energy (1 M) = -4151.4385

Free Energy (0.04 M) = -4151.4355

Anti-Conformation for Ene Reaction Transition State (TS-IV)



TS-IV

C -2.29337600 -0.11902300 -2.53800800

C -2.11514600 -0.45389100 -1.07015100

H -3.25883200 0.36686800 -2.68498800

H -1.52060900 0.57427000 -2.87537700

H -2.25357700 -1.02256900 -3.15065400

C -0.84827700 -1.24494500 -0.76607300

C -0.54282100 -1.61714600 0.55983000

C -0.85539800 -0.83380500 1.69477200

C -0.54961100 -1.36181200 3.08030400

H -0.02978100 0.00044800 1.38051900

H -1.75891600 -0.22608300 1.62489900

H 0.40204000 -1.89477000 3.08835100

H -1.33967600 -2.04020500 3.41137600

H -0.49262500 -0.53887800 3.79357100

H -0.57966700 -1.97854900 -1.52459700

H 0.16870600 -2.42624700 0.69234800

Se 0.82934500 0.22321400 -1.13904000

N 2.25566200 -0.74877700 -1.16901000

N 0.77046700 1.04463300 0.42168400

S 3.12863300 -1.09216400 0.17395900

S -0.03156200 2.50006600 0.43580600

O 2.28912800 -1.66615300 1.23273700

O 3.98420800 0.02505900 0.56700300

C 4.16762600 -2.38108300 -0.47738800

H 4.83016800 -2.67943000 0.33479100

H 3.53821500 -3.21087000 -0.79158400

H 4.73845800 -1.97764500 -1.31125000

O -0.67876900 2.60477400 1.73364400

C 1.28096400 3.69797400 0.35905100

H 0.81412400 4.68031200 0.42561500

H 1.94806500 3.52283800 1.20056100

H 1.80215400 3.57890900 -0.58918800

O -0.86301400 2.63960700 -0.76257500

H -2.16478400 0.45808400 -0.47435100

O -3.20476300 -1.31436000 -0.66797300

C -4.14686600 -0.81713300 0.15599200

C -5.21416000 -1.83535900 0.41971200

H -4.76560700 -2.73729000 0.84022600

H -5.94931000 -1.42686700 1.10902500

H -5.69651400 -2.11081800 -0.52009700

O -4.10971700 0.29846300 0.61153200

Imaginary frequencies = 1 at -379 cm^{-1}

Energy = -4151.6920

Enthalpy = -4151.3528

Free Energy (1 M) = -4151.4378

Free Energy (0.04 M) = -4151.4348

2.5 REFERENCES TO CHAPTER 2

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Chapter 3. THE DEVELOPMENT OF ALLYLIC ALKYLATION CATALYSED BY NHC SELENIDES

3.1 INTRODUCTION

The formation of C-C bonds is at the heart of organic synthesis. Allylic alkylation is among the most powerful methods to forge $C(sp^3)$-$C(sp^3)$ bonds. In the past decades, transition metal catalysed allylic alkylation via allylic substitution has experienced an explosive growth and development, predominated by Pd π-allyl chemistry (Figure 3.1)[1]. These reactions occur via a π allyl intermediate generated by oxidative addition of an allylic C-X bond to the catalyst. The π-allyl species is then trapped by a carbon nucleophile to give a net allylic substitution. This mechanism allows for allylic substitution under redox neutral conditions. However, nearly all such transformations require a leaving group at the allylic position of the substrate, necessitating the preparation of pre-oxidised starting materials. As a result, these reactions often suffer low atom economy and compromised efficiency.

One approach to improving efficiency of traditional allylic alkylation is direct transformation of an allylic C-H bond to $C(sp^3)$-$C(sp^3)$ bond under oxidative conditions (Figure 3.1)[2–11]. This powerful strategy eliminates the need of pre-installation of allylic leaving groups, streamlines the synthesis of complex molecules, and enables late-stage functionalisation. In contrast to traditional Pd π-allyl chemistry, these reactions proceed through direct cleavage of an allylic C-H bond promoted by the Pd(II) catalyst to form the π allyl species. The π allyl species is then attacked by a carbon nucleophile to give the allylic substitution product with concurrent reduction of Pd(II) to Pd(0). Finally, the catalyst is re-oxidised back to Pd(II) by terminal oxidant to close the catalytic cycle.

Although these two protocols are fundamentally different, two closely related problems are shared. Since the π-allyl species has two positions susceptible to nucleophilic attack, these reactions often suffer regioselectivity issues and thus branched/linear selectivity must be thoroughly considered in the development of reactions. Another problem is allylic transposition where the alkene of the starting materials is shifted to the next carbon in the products due to the poor regioselectivity of nucleophilic attack on the Pd π-allyl species. However, this feature may not be desirable in some scenarios.

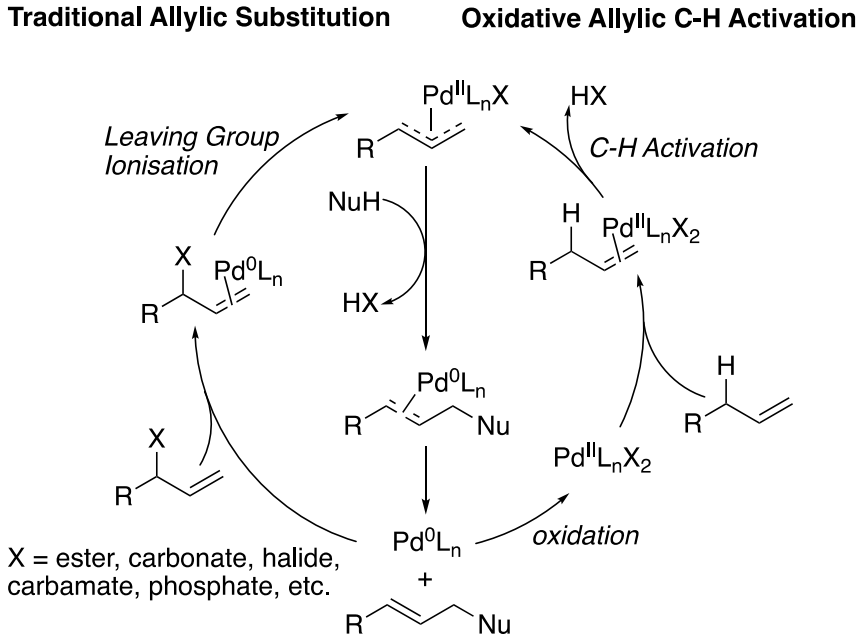
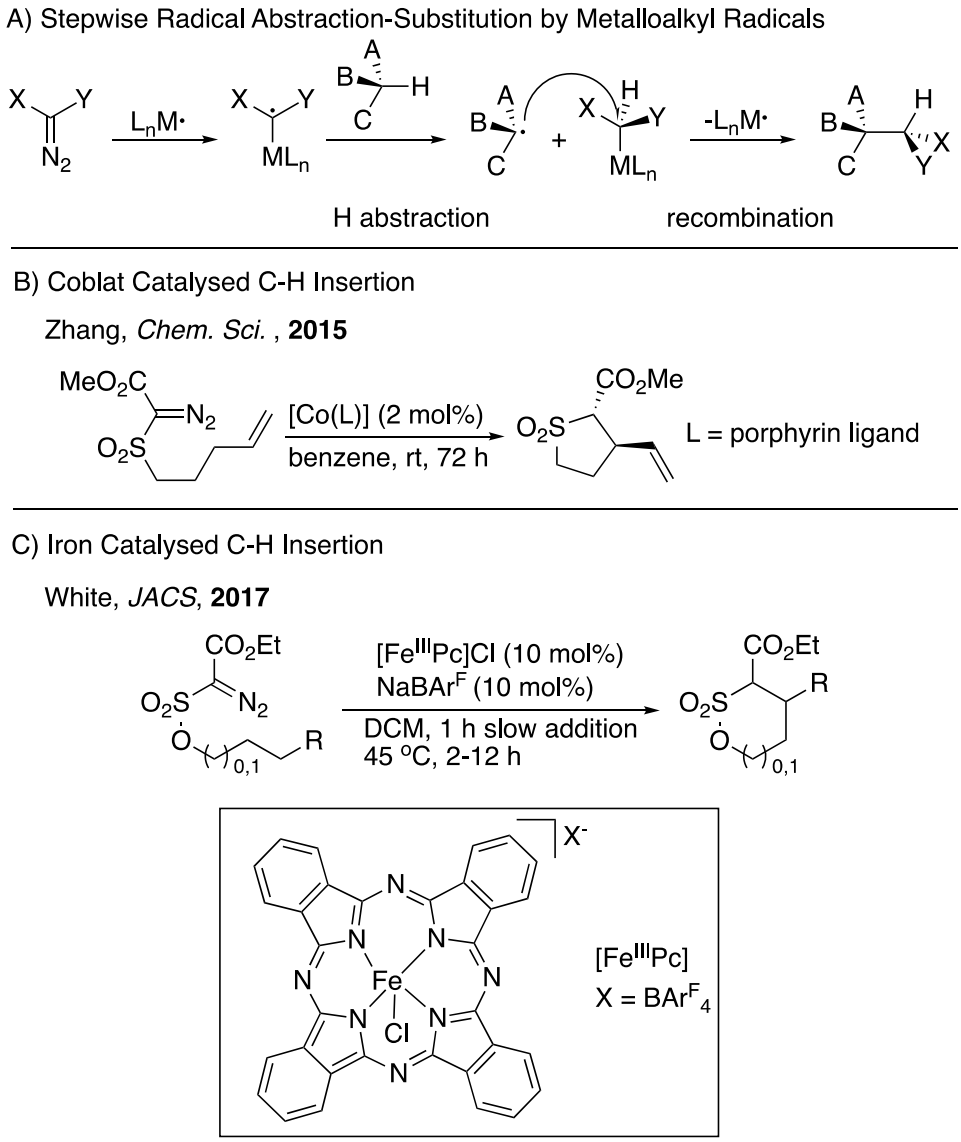


Figure 3.1 Mechanisms of Traditional Pd-catalysed Allylic Substitution and Oxidative Allylic C-H Activation

Another mechanistically different strategy for direct C-H allylic alkylation is carbene insertion into C-H bond (Scheme 3.1)[12]. Although carbene insertion is an established process, application of this framework to allylic alkylation is rare due to difficult control over regioselectivity and competing cyclopropanation pathway. In 2015, Zhang reported a direct C-H allylic alkylation using cobalt catalysts[13]. In contrast to the well-known concerted electrophilic insertion mechanism, this reaction proceeds via stepwise radical abstraction-substitution by

metalloalkyl radicals. In 2017, White demonstrated that iron carbene intermediate can also promote catalytic allylic alkylation via a similar mechanism[14]. Unlike the cobalt catalysis, this iron-catalysed reaction is less reactive to electron-deficient substrates due to the electrophilic nature of the iron carbene intermediate and thus substrate scope is limited. Despite both reactions showing high selectivity for allylic C-H bonds, the excellent regioselectivity is accomplished through intramolecular delivery of the carbon nucleophile and intrinsic favourable ring size for ring-closure process.

Scheme 3.1 Allylic C-H Alkylation via Carbenoid Insertion



Inspired by the success in the development of allylic amination[15], we wondered whether an allylic alkylation is feasible by replacing the nitrogen source with an appropriate carbon nucleophile (Figure 3.2). By analogy, the key is to generate carbene intermediates that can be transferred to selenium catalysts to generate selenium ylides. Subsequently, the selenium ylides would undergo an ene reaction with an alkene, followed by a 2,3-sigmatropic rearrangement to give the desired product. We envisioned that such a transformation could potentially solve the issues discussed above. First, the reaction is expected to give allylic alkylated product without transposition of alkene by mechanism. Second, since we previously observed exclusive formation of a single regioisomer in the allylic amination for most trisubstituted and disubstituted alkenes, we hypothesised that this could be a potential solution to the regioselectivity issue when multiple allylic C-H bonds are available to functionalisation, without needing to carry out the reaction intramolecularly.

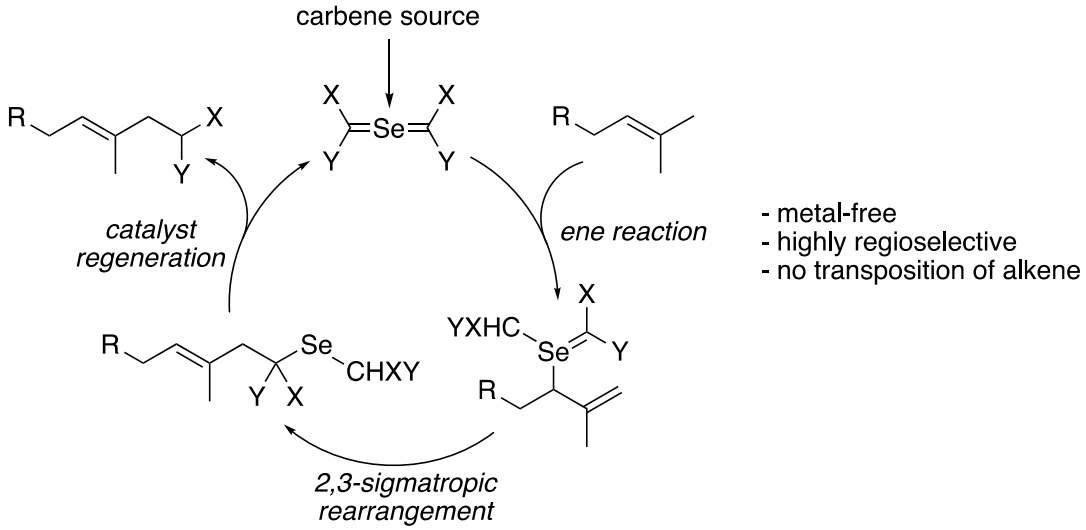


Figure 3.2 Working Hypothesis for Allylic Alkylation via Organoselenium Catalysis

3.2 REACTION DEVELOPMENT

3.2.1 *Generation of Carbene under Redox Neutral Conditions*

To begin with, we sought to generate carbenes from α-bromoesters under redox neutral conditions. Two possible pathways were examined (Figure 3.3): 1) deprotonation of α-bromoester and 2) halide abstraction of α-bromoester. We hypothesised that the generated carbene would be transferred to the selenium catalyst to produce the desired selenium ylides.

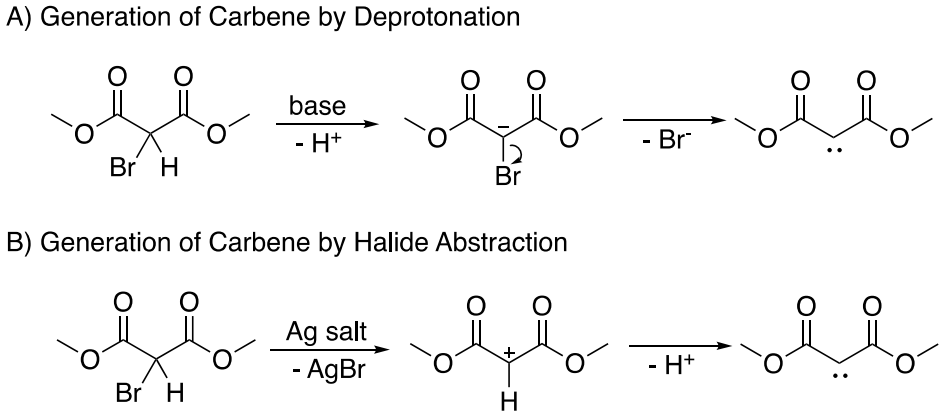
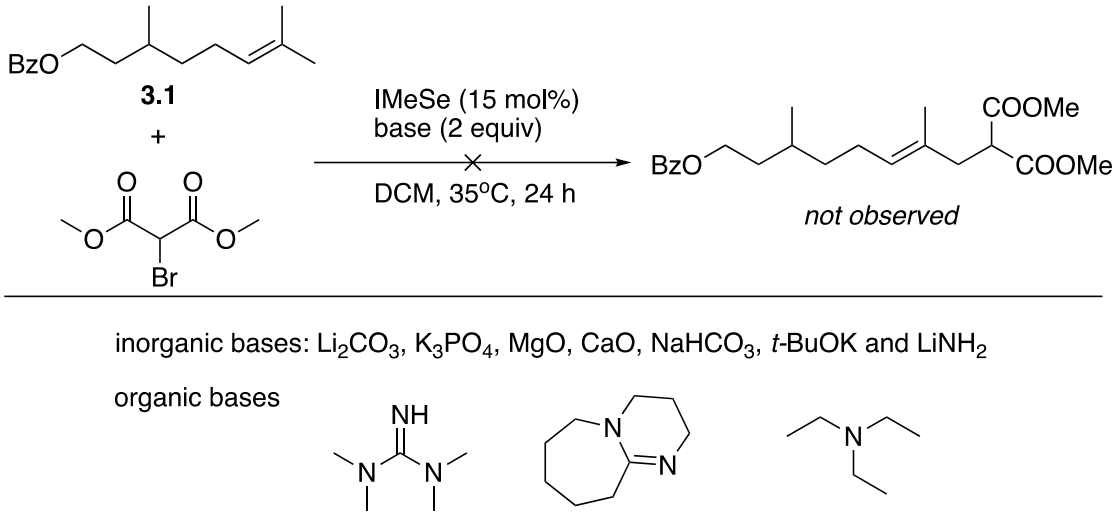


Figure 3.3 Generation of Carbene from α-Bromoester

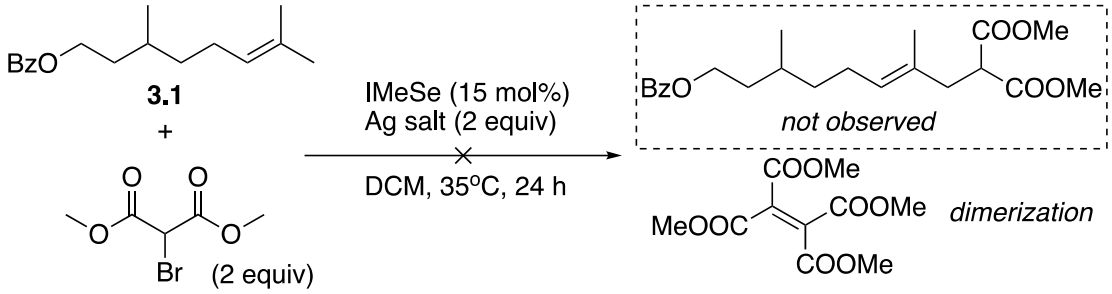
To verify deprotonation, model substrate 3.1 was treated with IMeSe (15 mol%), dimethyl bromomalonate (2 equiv), and a base additive (2 equiv) in DCM at 35 °C. A screen of inorganic base was performed (Scheme 3.2). Unfortunately, no alkylated products were observed probably due to low solubility of these inorganic bases in organic solvents. Thus, tetramethyl guanidine, triethylamine and DBU were tested under otherwise same conditions. However, no desired product was observed in all cases.

Scheme 3.2 Base Screen for Generating Carbene from α-Bromoester by Deprotonation



To test halide abstraction, a screen of silver salts was performed (Table 3.1). However, no desired product was observed in all cases with varying degree of consumption of substrate and nucleophile. Notably, when silver carbonate was used, dimerization of dimethyl bromomalonate was observed in 44% yield (Table 3.1, entry 2). The dimer appears as a singlet at 3.87 ppm by ^{1}H NMR, supporting the formation of free carbene or selenium ylide intermediates, though the expected alkylation did not occur.

Table 3.1 Silver Salt Screen for Generating Carbenes from α-Bromoesters by Halide Abstraction



entry	Ag salt	substrate (%)[c]	nucleophile (%)[b]	dimer (%)[b]	product (%)[c]
1	AgOAc	77	22	0	0
2	Ag_2CO_3	69	0	44	0
3	$AgBF_4$	56	77	0	0
4	$AgBF_4 + Na_2CO_3$	79	74	0	0

[a]Yields determined by ^1H NMR using 1,3-dinitrobenzene as internal standard. [b]Yields were calculated based on nucleophile. [c]Yields were calculated based on substrate.

3.2.2 *Generation of Carbene under Oxidative Conditions*

By analogy to allylic amination, we wondered if selenium ylides could be produced from methylene nucleophiles bearing electron-withdrawing groups under oxidative conditions (Figure 3.4).

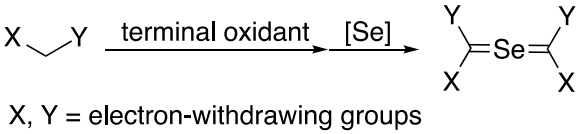
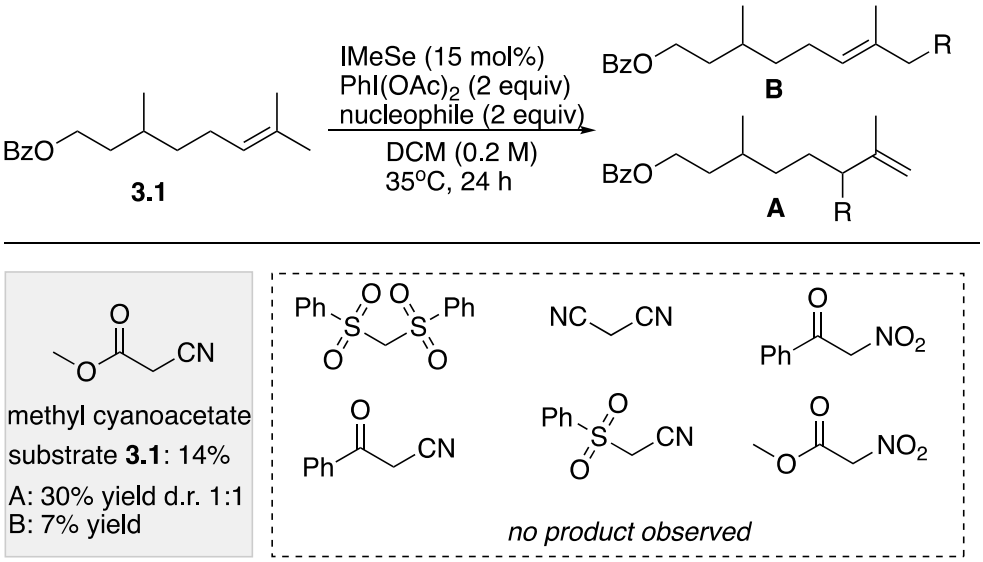


Figure 3.4 Working Hypothesis for Oxidative Generation of Selenium Ylides

A series of methylene nucleophiles bearing two electron-withdrawing groups was tested under conditions shown in Table 3.2. To our delight, allylic alkylation was observed with methyl cyanoacetate, though the reaction was incomplete. Counterintuitively, transposed alkylated product was generated as the major regioisomer in 30% yield as a 1:1 mixture of diastereomers whereas non-transposed alkylated product was given in 7% yield.

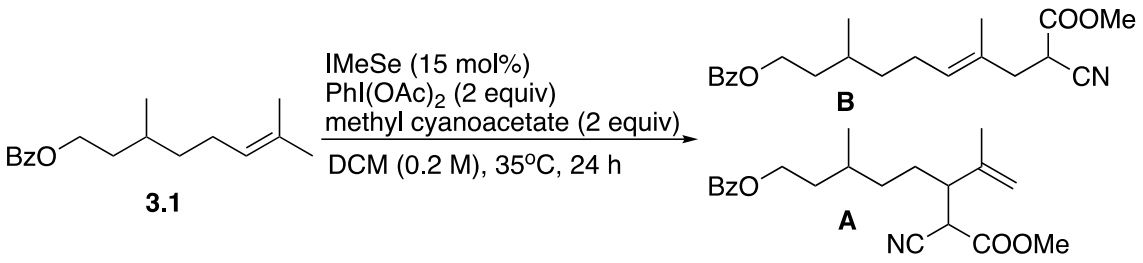
Table 3.2 Nucleophile Screen



[a]Yields determined by ^{1}H NMR using 1,3-dinitrobenzene as internal standard.

Control experiments revealed that no alkylated product was formed in the absence of catalyst, oxidant, methyl cyanoacetate, or substrate, suggesting that all reaction components are essential (Table 3.3). Notably, when substrate was left out, methyl cyanoacetate was completely consumed (Table 3.3, entry 2), which was not true for other scenarios (Table 3.3, entries 1, 3, and 4). This interesting result led us to consider the presence of a background reaction among selenium catalyst, (diacetoxyiodo)benzene, and methyl cyanoacetate. We wondered if this competing pathway consumes the nucleophile, causing incomplete conversion of substrate and low yield. Thus, optimisation continued with a focus on achieving complete conversion of substrate.

Table 3.3 Control Experiments

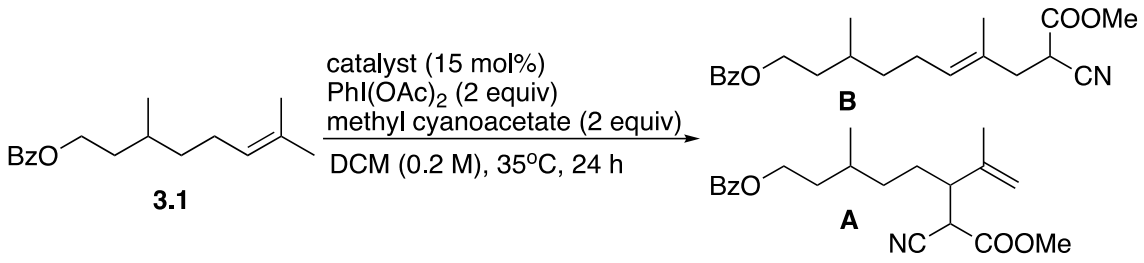


entry	deviation from conditions above	A (%)	B (%)
1	no IMeSe	0	0
2[b]	no substrate	0	0
3	no $PhI(OAc)_2$	0	0
4	no methyl cyanoacetate	0	0

[a]Yields determined by ^1H NMR using 1,3-dinitrobenzene as internal standard. [b]All methyl cyanoacetate was completely consumed.

Our previous work has demonstrated that reactivity of reactions catalysed by phosphine/NHC based selenides can be tuned by altering ligands on selenium. To push the reaction to completion, a catalyst screen was performed (Table 3.4). Compared to NHC selenides, phosphine selenides did not show catalytic reactivity (Table 3.4, entries 5-7). When phosphine selenides were used, methyl cyanoacetate was not consumed. We also observed that reactivity of NHC selenides correlates with steric effects of substitutes on NHC ligands (Table 3.4, entries 1-4). As the substituents became bulkier, conversion of substrate decreased and yield of product increased. These observations were consistent with the hypothesis that a background reaction among selenium catalyst, methyl cyanoacetate, and (diacetoxyiodo)benzene may exist, causing incomplete conversion of staring material and low yield. It is worth noting that the non-transposed product was only observed in small amount when IMeSe was used. Other NHC based selenides suppressed the formation of non-transposed product. However, IMeSe was optimal from the perspective of yield.

Table 3.4 Catalyst Screen

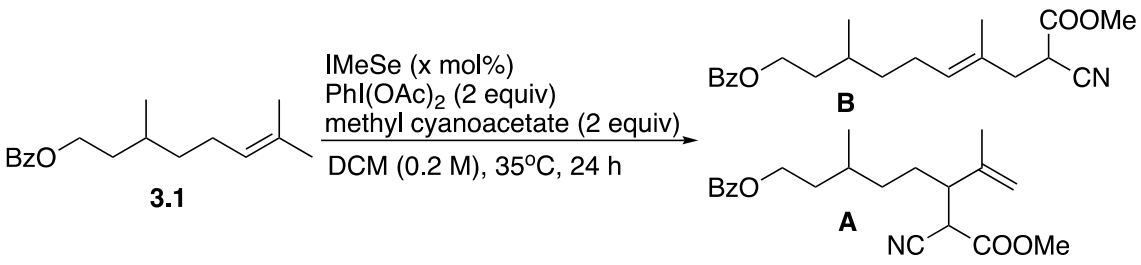


entry	catalyst	substrate (%)	A (%)	B(%)
1	IMeSe	14	30	7
2	ICySe	26	28	0
3	ItBuSe	35	12	0
4	IPrSe	55	0	0
5	$SeP(o\text{-}tol)_3$	62	0	0
6	$SeP(OPh)_3$	60	0	0
7	$SePCy_3$	62	0	0

[a]Yields determined by ^1H NMR using 1,3-dinitrobenzene as internal standard.

Catalyst loading screen showed that 15 mol% was optimal for the highest yield of product (Table 3.5). When 5 mol% IMeSe was used, methyl cyanoacetate was not completely consumed after 24 hours (Table 3.5, entry 1). As catalyst loading increased from 5 mol% to 15 mol%, more product was generated, and more substrate was consumed. However, as catalyst loading continued increasing to stoichiometric amount, yield of product decreased drastically and more substrate left-over was observed. This trend once again indicated the presence of the previously mentioned background reaction. One possible explanation for this trend is that excessive selenium catalyst accelerates the background reaction which eventually outcompetes the desired allylic alkylation pathway.

Table 3.5 Catalyst Loading Screen

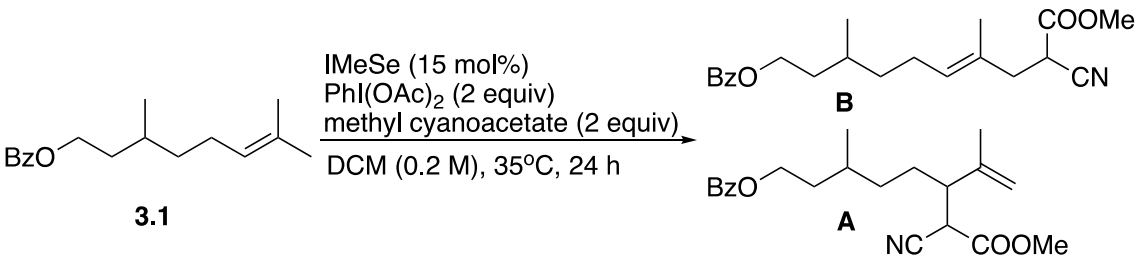


entry	catalyst loading (x mol%)	substrate (%)	A (%)	B (%)
1[b]	5	47	15	0
2	10	25	25	0
3	15	16	30	7
4	30	27	22	0
5	50	34	16	0
6	75	45	11	0
7	100	52	6	0
8	200	71	0	0

[a]Yields determined by ^{1}H NMR using 1,3-dinitrobenzene as internal standard. [b]Methyl cyanoacetate was not fully consumed.

Another possible reason for low conversion of substrate might be inadequate oxidant and nucleophile. A stoichiometry screen showed that increasing the amount of oxidant and nucleophile did not improve the reaction (Table 3.6, entries 1, 2, and 4). Excessive oxidant and nucleophile promoted substrate decomposition (Table 3.6, entries 1 and 2). We sought to use more substrate to increase the chance of trapping activated carbon nucleophile. Unfortunately, we observed diminished yield of the product (Table 3.6, entry 3). Given that some selenium ylides are unstable at elevated temperature, the reaction was run at room temperature. However, no significant improvement was observed (Table 3.6, entry 5).

Table 3.6 Stoichiometry Screen



entry	changes	substrate (%)	A (%)	B (%)
1	3 equiv oxidant and nucleophile	trace	30	trace
2	4 equiv oxidant and nucleophile	0	24	16
3	2 equiv substrate	59	14	0
4	4 equiv nucleophile	15	30	5
5	room temp	19	30	0

[a]Yields determined by ^{1}H NMR using 1,3-dinitrobenzene as internal standard.

To improve the performance of the reaction, base, concentration, oxidant, and solvent were also screened (see experimental section). Unfortunately, no improvements were observed.

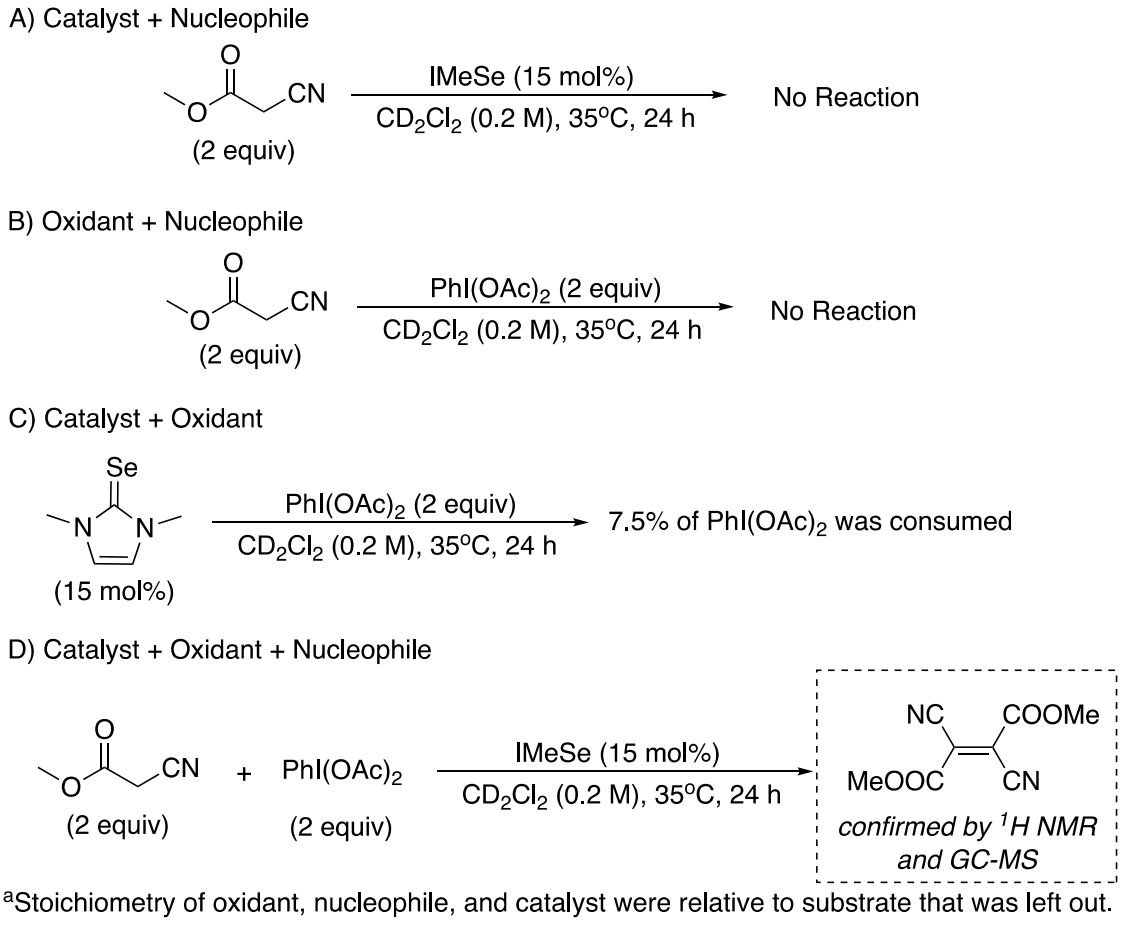
3.2.3 *Identification of Dimerization*

The convergence of control experiments, catalyst screen, and catalyst loading screen clearly suggests the presence of a background reaction among selenium catalyst, (diacetoxyiodo)benzene, and methyl cyanoacetate, which causes incomplete conversion of substrate and low yield. Thus, understanding of this background reaction is crucial to further optimisation.

First, reactions between any two of selenium catalyst, (diacetoxyiodo)benzene, and methyl cyanoacetate as well as the reaction of all three were run in deuterated methylene chloride (Scheme 3.3). The progresses of these reactions were monitored by ^{1}H NMR spectroscopy. No reaction occurred between methyl cyanoacetate and IMeSe (Scheme 3.3A). Methyl cyanoacetate did not react with (diacetoxyiodo)benzene, either (Scheme 3.3B). When IMeSe was mixed with

(diacetoxyiodo)benzene, the reaction started immediately, and 7.5% (diacetoxyiodo)benzene was consumed in less than 30 min. The conversion of (diacetoxyiodo)benzene did not change thereafter, suggesting stochiometric oxidation of IMeSe by (diacetoxyiodo)benzene (Scheme 3.3C). When all three components were mixed, the reaction immediately started and methyl cyanoacetate was completely consumed in less than 30 min. Although several unknown new peaks appeared on ^{1}H NMR spectroscopy during the first three hours, all these peaks eventually evolved to a singlet peak appeared at 4.05 ppm after 24 hours (Scheme 3.3D). The crude mixture was subjected to GC-MS, together with ^{1}H NMR, to confirm that the new compound was a dimer of methyl cyanoacetate.

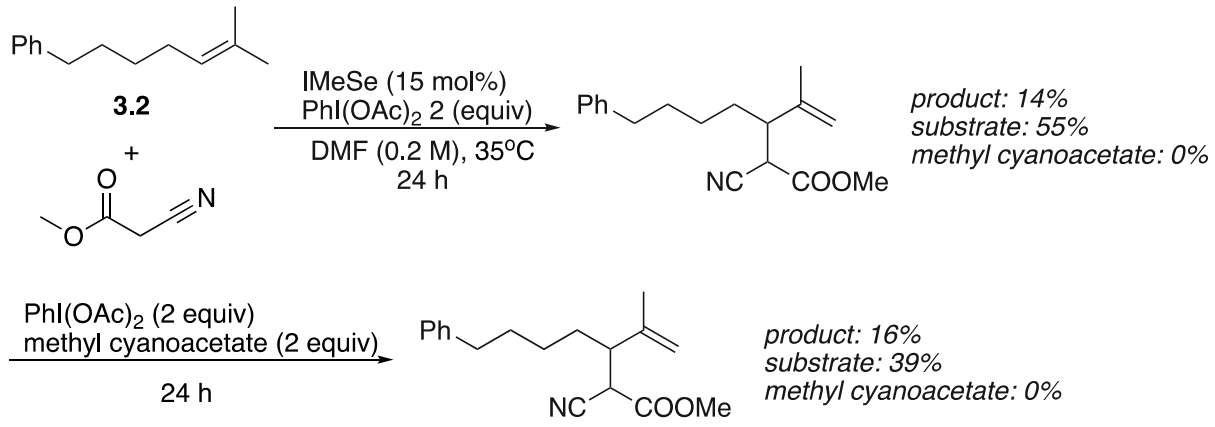
Scheme 3.3 Identification of Background Reaction



[a]Stoichiometry of oxidant, nucleophile, and catalyst were relative to substrate that was left out.

Another possible explanation for incomplete conversion of substrate is catalyst deactivation. To verify this hypothesis, the experiment shown in Scheme 3.4 was performed. Substrate 3.2 was treated with 15 mol% IMeSe, 2 equiv (diacetoxyiodo)benzene, and 2 equiv methyl cyanoacetate in DMF at 35 °C. After 24 hours, crude ^{1}H NMR showed that the desired product was generated in 14% yield and 55% starting material was left in the reaction. However, all methyl cyanoacetate was consumed. At this point, another 2 equiv methyl cyanoacetate in 1 ml DMF was added, followed by addition of another 2 equiv (diacetoxyiodo)benzene. After another 24 hours, there was no significant increase in the yield of desired product, although residual substrate decreased by 16%. Notably, the second portion of methyl cyanoacetate was completely consumed again. This experiment indicated that catalytic active species survived the reaction conditions over a period of at least 48 hours, which supports that the background reaction among selenium catalyst, diacetoxyiodobenzene, and methyl cyanoacetate is the major pathway for nucleophile consumption and thus results in incomplete conversion of starting material.

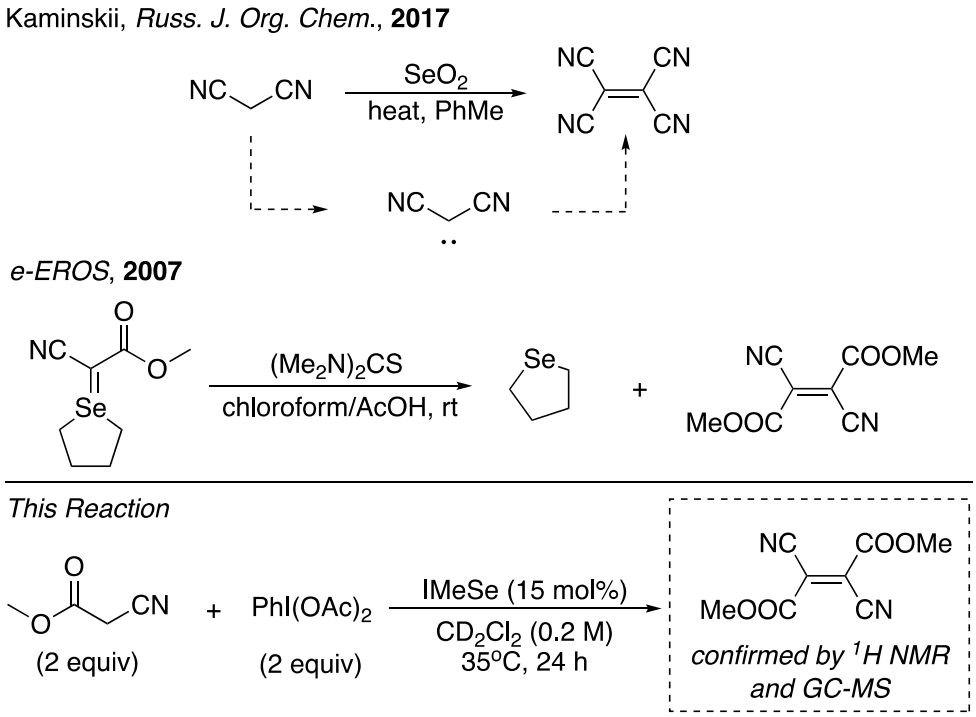
Scheme 3.4 Exploration of Catalyst Deactivation



Kaminskii showed that malononitrile dimerises in the presence of selenium dioxide via a carbene intermediate at elevated temperatures in toluene (Scheme 3.5)[16]. Another report[17] shows that dimerization of selenium ylides at room temperature is possible (Scheme 3.5). Based on these

reports, we proposed that two competing pathways exist in this reaction system (Figure 3.5): 1) allylic alkylation via seleniranium ion (path a) and 2) oxidative dimerization of nucleophile (path b). The reaction starts with oxidation of IMeSe to generate an electrophilic selenium species. At this point, this electrophilic selenium species could engage in oxidation of alkenes to afford a seleniranium ion. Nucleophilic attack by the carbon nucleophile on the seleniranium ion gives the alkylated selenide intermediate. Elimination of the selenium moiety regenerates the catalyst and releases the product. This mechanism is consistent with the predominant formation of transposed product. The electrophilic selenium species could also participate in dimerization of nucleophile. IMeSe based selenium ylides are generated under this oxidative condition, which undergoes dimerization of methyl cyanoacetate. Experiment described in Scheme 3.4 suggests that dimerization occurs faster than allylic alkylation, as the second addition of nucleophile was also completely consumed without improving the yield of desired product.

Scheme 3.5 Proposed Mechanism for Dimerization of Nucleophile



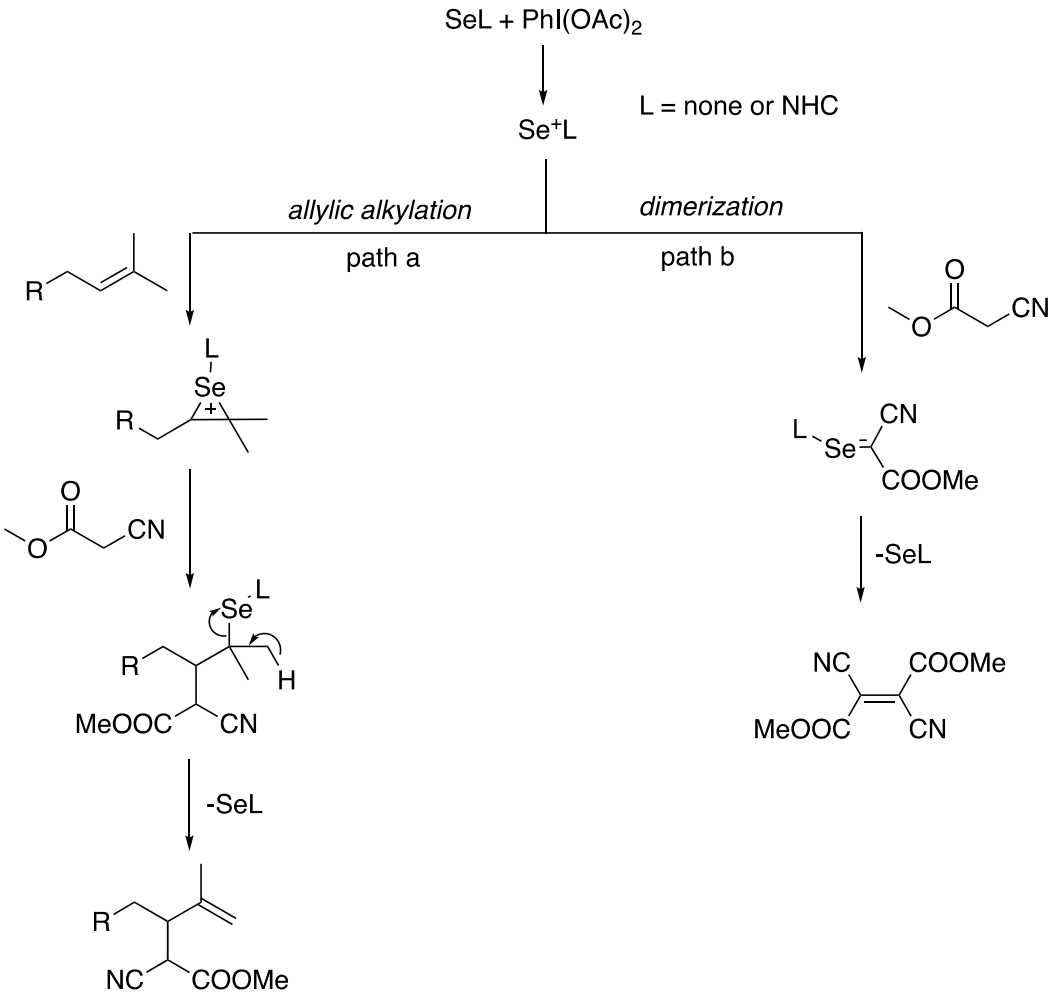


Figure 3.5 Proposed Mechanism for Allylic Alkylation

3.3 CONCLUSION

The development of allylic alkylation catalysed by NHC selenides was described. The product with alkene transposition was isolated in 30% yield. Mechanistic study reveals the presence of background reaction among selenium catalyst, nucleophile, and oxidant. This background reaction consumes nucleophile via catalytic dimerization of nucleophile, competing with the desired allylic alkylation pathway. This competition might be the cause to incomplete conversion of starting material and low yield of product. Further optimisation is required to suppress the dimerization of nucleophile to improve the performance of the reaction.

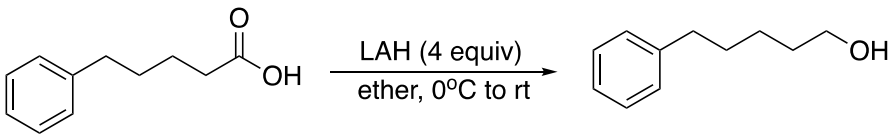
3.4 EXPERIMENTAL

3.4.1 *General Procedures and Materials*

All reactions were performed under a nitrogen atmosphere using flame-dried glassware unless otherwise noted. Infrared spectra were measured on a Perkin Elmer Spectrum RX I spectrometer. Mass spectra were collected on a Hewlett Packard 5971A Gas Chromatograph - Mass Spectrometer or Bruker Esquire 1100 Liquid Chromatograph - Ion Trap Mass Spectrometer. Column chromatography was performed using silica gel (Whatman, 60 Å, 230-400 mesh). NMR spectra were recorded on a Bruker AV-300, AV-301, DRX-499 or AV-500 spectrometer. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) and are referenced relative to TMS (0.00 ppm) or residual protonated $CHCl_3$ (7.26 ppm). ^{13}C NMR chemical shifts (δ) are reported in parts per million (ppm) relative to the carbon resonance of $CDCl_3$ (77.16 ppm). Melting points were taken on a MEL-TEMP melting point apparatus and are uncorrected.

All commercial reagents were used as received, unless otherwise noted. All solvents were degassed and dried on solvent columns of neutral alumina. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc., stored over 4 Å molecular sieves, and were used without further purification.

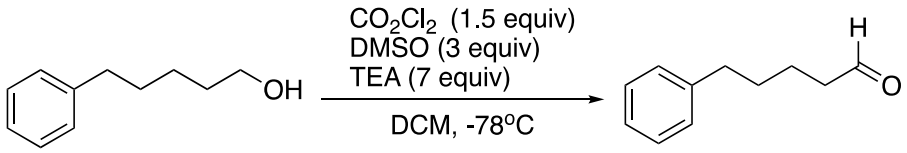
3.4.2 *Synthesis and Characterisation of Alkene Starting Materials*



5-Phenylpentan-1-ol. $LiAlH_4$ (120 mmol, 4 equiv) was suspended in dry diethyl ether. The mixture was cooled to 0 °C and a solution of 5-phenylvaleric acid (30 mmol, 1 equiv) in dry diethyl ether was added dropwise. The mixture was stirred at room temperature for 4 h. The reaction was

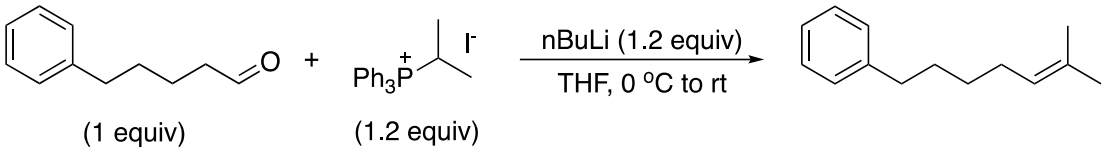
quenched following the procedure of Fieser work-up (see below). The resulting solution was concentrated to dryness and the crude was purified on column (ethyl acetate/hexanes 1:5) to afford 5-phenylpentan-1-ol as a colourless oil (86% yield). Fieser work-up: To work up a reaction containing x g lithium aluminium hydride, dilute the reaction with ether and cool the reaction mixture to 0°C. Slowly add x mL water, x mL 15% aqueous sodium hydroxide, and 3x mL water, in that order. Warm the mixture to room temperature and let it stir for 15 min. Add some anhydrous magnesium sulphate. Let the reaction stir for another 15 min and filter to remove the resulting salts.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.15 (m, 5H), 3.59 (t, *J* = 6.8 Hz, 2H), 2.60 (t, *J* = 6.8 Hz, 2H), 2.14 (s, 1H), 1.67 – 1.53 (m, 4H), 1.42 – 1.34 (m, 2H).



5-Phenylpentanal. Dimethyl sulfoxide (DMSO) (45 mmol, 3 equiv) was added slowly to a solution of oxalyl chloride (22.5 mmol, 1.5 equiv) in DCM (50 mL) at -78 ℃ over 10 min, and the mixture was stirred at -78 ℃. After 10 min, a solution of alcohol (15 mmol, 1 equiv) in DCM (5 mL) was added dropwise, and the reaction was stirred at -78 ℃. After 15 min, Et_3N (105 mmol, 7 equiv) was added over 5 min. The reaction mixture was allowed to stir at -78 ℃ for 5 min and at room temperature overnight. The solid was filtered off and washed with DCM. Then 50 mL of water was added. The organic phase was separated, and the aqueous phase was extracted with DCM (20 mL × 2). The combined organic layer was then washed with 0.5 M HCl (30 mL), water (30 mL) and brine (30 mL). Drying ($MgSO_4$) and evaporation gave the crude product. Purification of the residue by silica gel chromatography yields the desired aldehyde as a colourless oil (95% yield).

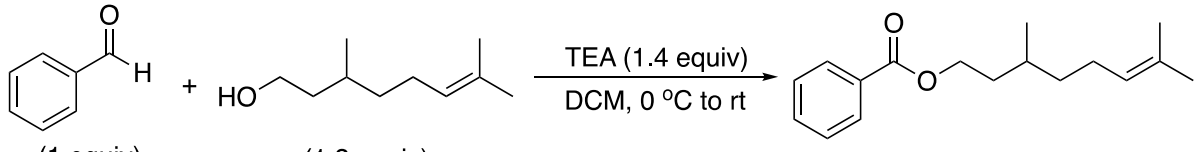
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.67-1.73 (m, 4H), 2.44-2.52 (m, 2H), 2.60-2.71 (m, 2H), 7.16-7.35 (m, 5H), 9.78 (t, *J* = 1.8 Hz, 1H).



(1 equiv) (1.2 equiv)

(6-Methylhept-5-en-1-yl)benzene (3.2). To a stirred solution of triphenyl phosphonium salt (18 mmol, 1.2 equiv) in THF (35 mL) was added nBuLi (18 mmol, 2.5 M in hexanes, 1.2 equiv) dropwise at 0 ℃. After addition, the resulting solution was stirred at 0 ℃ for 30 min, warmed to room temperature and stirred for another 2 h. A solution of aldehyde (15 mmol, 1 equiv) in anhydrous THF (5 mL) was added via syringe at 0 ℃. The mixture was stirred for 20 min at this temperature and then warmed to room temperature and stirred for 5 h. The progress of the reaction was monitored by TLC. The reaction mixture was then treated with water (20 mL) and extracted with Et_2O (3 × 40 mL). The organic layer was washed with brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to give the corresponding compound (87% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.21 (m, 2H), 7.20 – 7.14 (m, 3H), 5.11 (t, *J* = 7.2 Hz, 1H), 2.60 (t, *J* = 7.8 Hz, 2H), 2.00 (q, *J* = 7.4 Hz, 2H), 1.68 (s, 3H), 1.67 – 1.57 (m, 5H), 1.37 (m, 2H).



(1 equiv) (1.2 equiv)

3,7-Dimethyloct-6-enyl benzoate (3.1). To a flame-dried round bottom flask was added (-)-β-citronellol (31.35 mmol, 1.4 equiv) in dry DCM (100 mL), followed by addition of Et_3N (28.3 mmol, 1.3 equiv). Benzoyl chloride (22.65 mmol, 1 equiv) was added into the reaction mixture at 0 °C dropwise. The reaction was allowed to warm to room temperature and stirred until the reaction

was complete by TLC. The reaction was quenched by adding 1 M HCl. The organic layer was washed with 1 M HCl, saturated $NaHCO_3$, and brine. The organic layer was dried over sodium sulphate, filtered, and evaporated under reduced pressure to give the crude product as a colourless oil. The crude was purified by column chromatography to give the desired compound as a colourless oil (99% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.2 Hz, 2H), 7.55 (t, *J* = 7.4 Hz 1H), 7.44 (t, *J* = 7.4 Hz, 2H), 5.10 (t, *J* = 7.4, 1H), 4.43-4.30 (m, 2H), 2.09- 1.94 (m, 2H), 1.88-1.77 (m, 1H), 1.72-1.52 (m, 8H), 1.47-1.35 (m, 1H), 1.30-1.18 (m, 1H), 0.97 (d, *J* = 7.2 Hz, 3H).

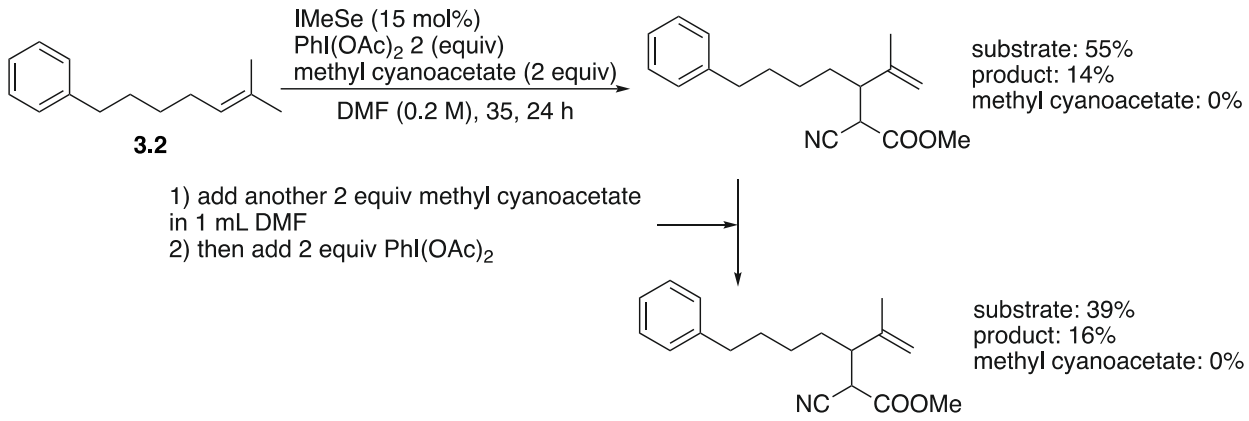
3.4.3 *General Procedure for Allylic Alkylation Catalysed by NHC Selenides*

To an oven-dried 1-dram vial was added alkene (0.2 mmol, 1 equiv), catalyst (15 mol%), a solution of carbon nucleophile in 1 mL DCM (0.4 mmol, 2 equiv), and oxidant (0.4mmol, 2 equiv), in that order. The vial was then flushed with nitrogen and capped with a Telfon-lined screw cap and the reaction was stirred at 35 ^{o}C for 24 hours. The reaction mixture was diluted with ethyl acetate (1 mL). The reaction mixture was pushed through a silica plug and was concentrated in vacuo. A crude ^{1}H NMR was taken with 1, 3-dinitrobenzene as internal standard to obtain NMR yield.

3.4.4 *Experimental Procedures for Mechanistic Studies*

3.4.4.1 Catalyst Deactivation

Scheme 3.6 Experiment for Catalyst Deactivation



Two reactions were set up side by side. In these experiments, DMF was chosen as the solvent instead of DCM, because DMF results in higher substrate recovery compared to other solvents. Since the goal of this experiment is to study 1) catalyst deactivation and 2) whether adding nucleophile portionwise would lead to higher conversion of substrate and improve yield of product, DMF would be a better solvent than DCM for this purpose.

Reaction 1: To an oven-dried 1-dram vial was added alkene (0.2 mmol, 1 equiv), NHC selenide (15 mol%), a solution of methyl cyanoacetate in 1 mL DMF (0.4 mmol, 2 equiv), and (diacetoxyiodo)benzene (0.4mmol, 2 equiv), in that order. The vial was then flushed with nitrogen and capped with a Telfon-lined screw cap and the reaction was stirred at 35 ^{o}C for 24 hours. The reaction mixture was diluted with ethyl acetate (15 mL), washed with water and brine. The organic layer was dried over sodium sulphate, filtered, and concentrated in vacuo. An ^{1}H NMR was taken with 1, 3-dinitrobenzene as internal standard to obtain NMR yield.

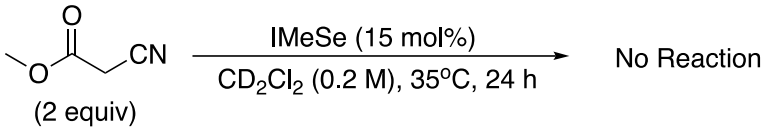
Reaction 2: The reaction was set up in the same way as Reaction 1. After 24 hours, another solution of methyl cyanoacetate in 1 mL DMF was added into the reaction mixture, followed by

addition of another portion of (diacetoxyiodo)benzene (0.4 mmol, 2 equiv). The reaction mixture was allowed to continue to stir for another 24 hours. The reaction mixture was diluted with ethyl acetate (15 mL) and washed with water and brine. The organic layer was dried over sodium sulphate, filtered, and concentrated in vacuo. An ^{1}H NMR was taken with 1, 3-dinitrobenzene as internal standard to obtain NMR yield.

3.4.4.2 Background Reaction

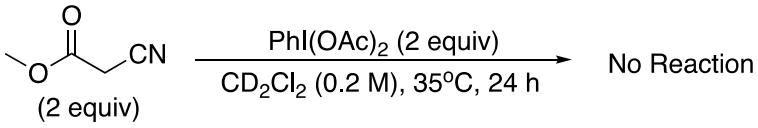
Note that stoichiometry in the following procedures is relative to the omitted alkene substrate (1 equiv) in a standard reaction, not to the limiting reagents in each individual case.

Reaction A: Nucleophile + Catalyst



To an oven-dried 1-dram vial was added NHC selenide (15 mol%) and a solution of methyl cyanoacetate in 1 mL CD_2Cl_2 (0.4 mmol, 2 equiv). The vial was then flushed with nitrogen and capped with a Telfon-lined screw cap and the reaction was stirred at 35°C. The reaction was monitored by ^{1}H NMR. Aliquot was taken, diluted with $CDCl_3$, and subjected to ^{1}H NMR every 30 minutes for the first 3 hours. After 24 hours, a final ^{1}H NMR was taken.

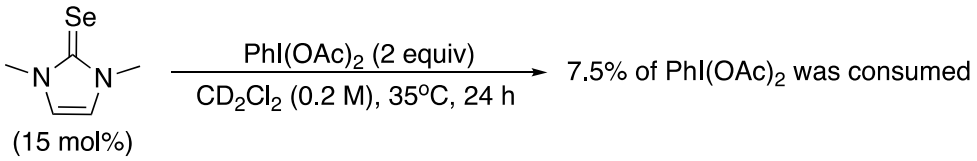
Reaction B: Nucleophile + Oxidant



To an oven-dried 1-dram vial was added a solution of methyl cyanoacetate in 1 mL CD_2Cl_2 (0.4 mmol, 2 equiv) and (diacetoxyiodo)benzene (0.4mmol, 2 equiv). The vial was then flushed with nitrogen and capped with a Telfon-lined screw cap and the reaction was stirred at 35°C. The

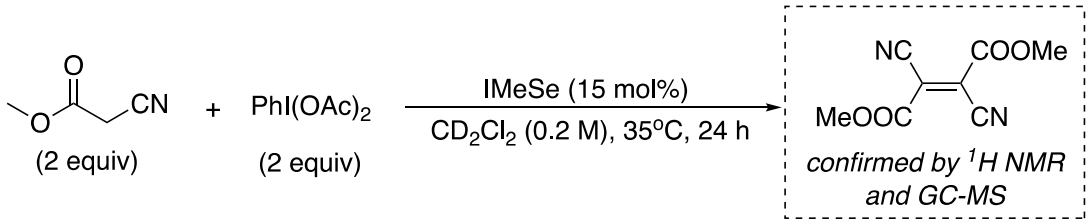
reaction was monitored by ^{1}H NMR. Aliquot was taken, diluted with $CDCl_3$, and subjected to ^{1}H NMR every 30 minutes for the first 3 hours. After 24 hours, a final ^{1}H NMR was taken.

Reaction C: Catalyst + Oxidant



To an oven-dried 1-dram vial was added NHC selenide (15 mol%), 1 mL CD_2Cl_2, and (diacetoxyiodo)benzene (0.4mmol, 2 equiv). The vial was then flushed with nitrogen and capped with a Telfon-lined screw cap and the reaction was stirred at 35°C. The reaction was monitored by ^{1}H NMR. Aliquot was taken, diluted with $CDCl_3$, and subjected to ^{1}H NMR every 30 minutes for the first 3 hours. After 24 hours, a final ^{1}H NMR was taken.

Reaction D: Nucleophile + Oxidant + Catalyst

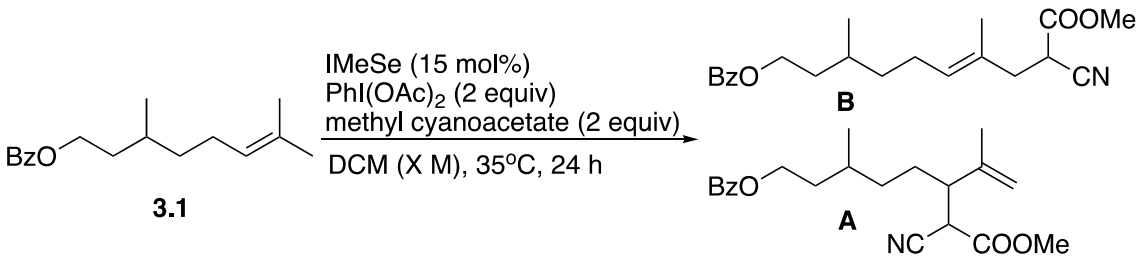


To an oven-dried 1-dram vial was added NHC selenide (15 mol%), a solution of methyl cyanoacetate in 1 mL CD_2Cl_2 (0.4 mmol, 2 equiv), and (diacetoxyiodo)benzene (0.4mmol, 2 equiv). The vial was then flushed with nitrogen and capped with a Telfon-lined screw cap and the reaction was stirred at 35°C. The reaction was monitored by ^{1}H NMR. Aliquot was taken, diluted with $CDCl_3$, and subjected to ^{1}H NMR every 30 minutes for the first 3 hours. After 24 hours, a final ^{1}H NMR was taken. The reaction mixture was also subjected to GC-MS analysis.

3.4.5 *Other Reaction Optimisation Details*

3.4.5.1 Concentration Screen

Table 3.7 Concentration Screen

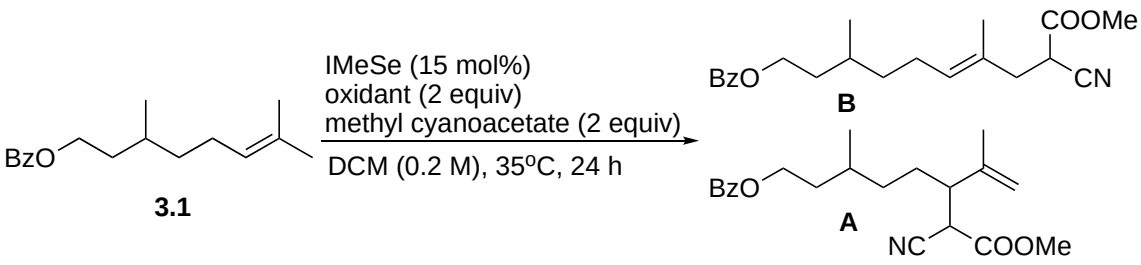


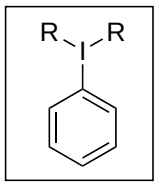
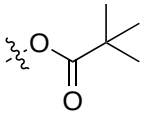
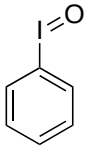
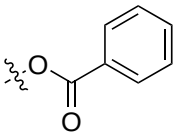
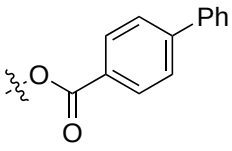
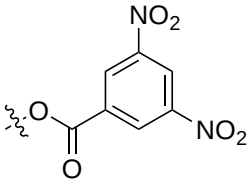
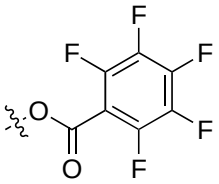
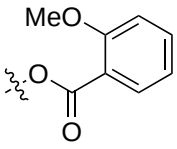
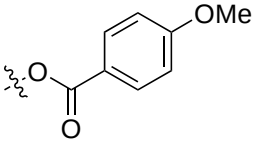
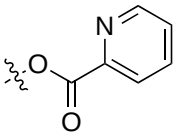
entry	concentration (M)	substrate (%)	A (%)	B (%)
1[b]	0.02	44	0	0
2	0.1	48	12	trace
3	0.2	16	30	7
4	0.3	31	20	8

[a]Yields determined by ^{1}H NMR using 1,3-dinitrobenzene as internal standard. [b]Nucleophile was not fully consumed.

3.4.5.2 Oxidant Screen

Table 3.8 Oxidant Screen

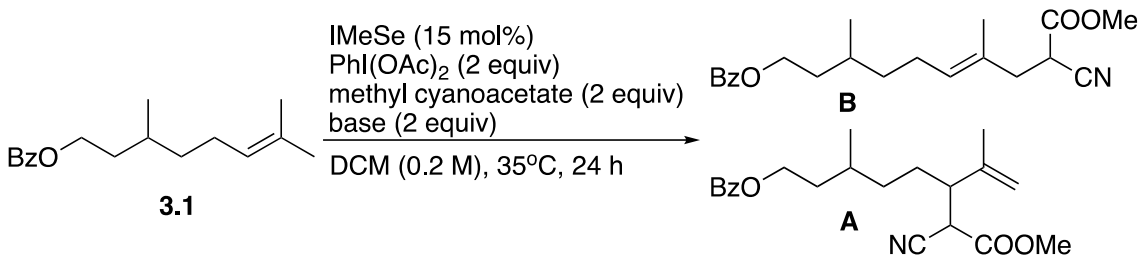


	 substrate 29% A 16% B 8% no nucelphile	 substrate 42% A 16% B 0% nucleophile observed	 substrate 45% A 0% B 0% nucleophile observed
	 substrate 45% A 15% B trace nucleophile observed	 substrate 28% A 0% B 0% nucleophile observed	 substrate 0% A 0% B 0% no nucleophile
	 substrate 35% A 23% B 0% no nucleophile	 substrate 42% A 15% B 4% nucleophile observed	 substrate 62% A 15% B 0% nucleophile observed

[a]Yields determined by ^{1}H NMR using 1,3-dinitrobenzene as internal standard.

3.4.5.3 Base Screen

Table 3.9 Base Screen



entry	base	substrate (%)	A (%)	B (%)
1	none	14	30	7
2	Li_2CO_3	17	30	6
3	LiOAc	18	29	4
4	Na_2CO_3	35	25	2
5	$NaHCO_3$	17	28	6
6	CaO	20	27	3
7	MgO	15	30	6
8	K_3PO_4	49	12	4

[a]Yields determined by ^{1}H NMR using 1,3-dinitrobenzene as internal standard.

3.5 REFERENCES TO CHAPTER 3

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VITA

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