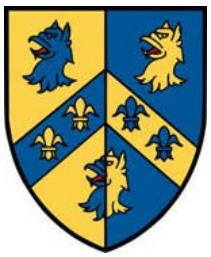

'Applications of the Heck reaction for the syntheses of substituted pyridines and β,β-disubstituted vinyl Weinreb amides'

'Studies towards the syntheses of inthomycin B and inthomycin C'

A thesis submitted to the Board of the Faculty of the Mathematical, Physical, and Life Sciences Division for the degree of Doctor of Philosophy

David Bawden Baker

Trinity College, University of Oxford

Trinity 2014

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Declaration

This thesis and the work of which it is a record has been carried out by the author, except where the author has either acknowledged help from a co-worker or given a reference to a published source.

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Trinity College, University of Oxford

Trinity 2014

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Special thanks also go to my industrial supervisor at Eli Lilly, Dr Peter Gallagher. I especially enjoyed my industrial placement during my second year and Peter was always at hand to support me during that time. I also managed to play a copious amount of football during that summer, enjoying all of the things that Eli Lilly had to offer!

Thanks must also be given to the Donohoe group, especially those in F7 (or 'F Heaven' as the indigenous folk refer to it). I will miss the horrendous, yet varied, taste in the music that was on offer, as well as the stimulating 'life' conversations. F7 teaches you more than just chemistry, it teaches you about the world! A special mention must go to my less skilled rival of four years in the Donohoe group, Matthew Tatton. In all seriousness though, it is strange to think how quickly four years has passed.

I want to thank my army of proofreaders, Alice, Leo, Anatol, and Johannes, for kindly agreeing to meticulously check through their respective sections, and to Tim for proofreading everything! It has become apparent that my use of definite and indefinite articles requires some 'fine-tuning'.

Finally, I would like to thank my parents for their support during my time in Oxford. My Mum's cooking has fuelled me all of this time. I also want to thank Katie for her love and support which kept me going even when things were not always going to plan.

Abstract

'Applications of the Heck reaction for the syntheses of substituted pyridines and β,β-disubstituted vinyl Weinreb amides'

'Studies towards the syntheses of inthomycin B and inthomycin C'

A thesis submitted for the degree of Doctor of Philosophy

David Bawden Baker, Trinity College, TT 2014

The Heck reaction has become a fundamental reaction for synthetic organic chemists over the last half century and is utilised heavily in the fine chemical industry and for natural product synthesis. This thesis describes some of the applications of the Heck reaction to modern day organic synthesis.

Introduction

This section presents an overview of the Heck reaction starting from its conception during the late 1960s to present day understanding. A variety of ligand classes are described along with commonly accepted catalytic cycles for their activity during the reaction.

Results and Discussion

In the first part of the thesis, the use of a cross-metathesis/Heck reaction protocol to synthesise a range of 2,4,6-trisubstituted pyridines is described. Attempts were made to expand the scope of the methodology by employing vinyl Weinreb amides, but this proved unsuccessful for the synthesis of pyridines. Nevertheless, the Heck reaction on vinyl Weinreb amides worked efficiently and the scope of this arylation was explored. Following on, the functionalisation of the Weinreb amide products was studied to generate a range of enone products, some of which would be difficult to synthesise *via* direct Heck reaction on the respective precursor enone.

In the second part of the thesis, previous syntheses of inthomycin B and inthomycin C are described. The synthesis of inthomycin B and inthomycin C were then attempted using an unprecedented Mukaiyama aldol/cross-metathesis based approach to generate the triene core of both natural products.

Abbreviations

aq.	aqueous
Binap	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
b.p.	boiling point
Bu	butyl
C	Celsius
Cbz	benzyloxycarbonyl
cm^{-1}	wavenumbers
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
d.e.	diasteromeric excess
DIBAL-H	diisobutyl aluminium hydride
DMAc	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
d.r.	diastereomeric ratio
dtbpf	1,1'-bis(di-*tert*-butylphosphino)ferrocene
e.e.	enantiomeric excess

equiv.	equivalents
EI	electron ionisation
ESI^-	electrospray ionisation (negative ion detection)
ESI^+	electrospray ionisation (positive ion detection)
Et	ethyl
FTIR	Fourier transform infrared
GC	gas-chromatography
h	hour(s)
HATU	1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HMPA	hexamethylphosphoramide
HRMS	high-resolution mass spectrometry
Hz	hertz
i	iso
J	coupling constant (Hz)
K	Kelvin
KHMDS	potassium bis(trimethylsilyl)amide
L	ligand
LRMS	low-resolution mass spectrometry
M	molar or metal
Me	methyl

Mes	mesityl
min	minute(s)
mL	millilitre(s)
mol	mole
MP	melting point
Ms	methanesulfonyl
n	*normal*
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NQ	naphthoquinone
PCC	pyridinium chlorochromate
Ph	phenyl
pH	$-\log_{10}[H_3O^+]$
pK_a	$-\log_{10}K_a$
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl

R	alkyl group
r.t.	room temperature
S	solvent
t	*tert*
TBS	*tert*-butyldimethylsilyl
Tedicyp	*cis,cis,cis,cis*-tetrakis(diphenylphosphinomethyl)cyclopentane
TEMPOL	4-hydroxy-2,2,6,6-tetramethylpiperidin-1-oxyl
Tf	trifluoromethanesulfonate
TFA	trifluoroacetic acid
TIPS	triisopropylsilyl
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMS	trimethylsilyl
THF	tetrahydrofuran
TPAP	tetra-*n*-propylammonium perruthenate
Ts	*para*-toluenesulfonyl
UV	ultraviolet
X	halogen or functional group
XPhos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

Chapter 1 Introduction to the Heck reaction

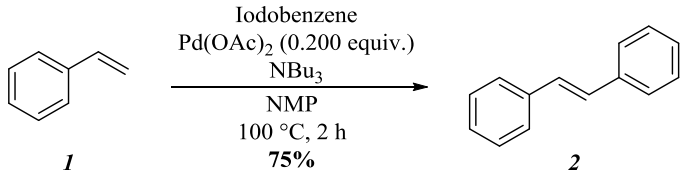
1.1 Palladium catalysed cross-coupling reactions

The functionalisation of aryl halides has become a feature of synthetic organic chemistry over the last five decades, with much of this driven by the frequent occurrence of aromatic and heteroaromatic compounds in the chemical industry, such as in agrochemicals, and in particular the pharmaceutical industry.[1,2] Furthermore, palladium-catalysed cross-coupling reactions have been extensively utilised in natural product synthesis.[3] A range of different palladium-catalysed cross-coupling reactions have been developed for the functionalisation of aryl halides/trifluoromethanesulfonate precursors, such as the Suzuki,[4] Sonogashira,[5,6] Negishi, Stille,[7,8] Kumada,[9] Hiyama,[10] Buchwald-Hartwig amination,[11] and the Heck reaction,[12,13] which act as useful tools for a synthetic organic chemist. The main advantages of these methods include material availability, functional group tolerance, and robustness—a feature which is especially important when scaling-up a process.

1.2 Overview of the Heck reaction

1.2.1 General catalytic cycle for the non-polar Heck reaction

In general, the Heck reaction (sometimes referred to as the Mizoroki-Heck reaction) is a coupling reaction between an aryl halide/pseudo-halide and an olefin carried out in the presence of a palladium catalyst, ligand, base, and solvent, to generate a substituted olefin. Examples of pseudo-halides include trifluoromethanesulfonates,[14] iodonium salts,[15] and aryl diazonium salts,[16] to name a few. For example, styrene (***1***) (olefin) was reacted with iodobenzene (aryl halide/pseudo-halide) in the presence of palladium acetate (catalyst and spectator ligand), tributylamine (base), and *N*-methyl-2-pyrrolidone (solvent). The reaction furnished (*E*)-stilbene (***2***) in 75% yield (*Scheme* ***1.1***).[17] This reaction can be termed 'ligand-free' although this can be misleading as the substrate, solvent, base, and/or spectator ligand may fill a vacant coordination site on the palladium during the catalytic cycle, effectively acting as ancillary ligands. This system is better referred to as 'phosphine-free' as typically phosphines are used as ligands for palladium, although not used in this instance.



Scheme 1.1 *Synthesis of (E)-stilbene (**2**) via Heck reaction*

Since first being reported by Heck and co-workers in 1972, a vast collection of studies have been reported detailing/hypothesising the specific intermediates present during the Heck reaction depending on the nature of the catalytic species utilised, in spite of this however, Heck's original proposal of the catalytic cycle, which describes the monophosphine ligand-accelerated Heck reaction with palladium acetate, still provides a general overview (*Figure **1.1***).[17]

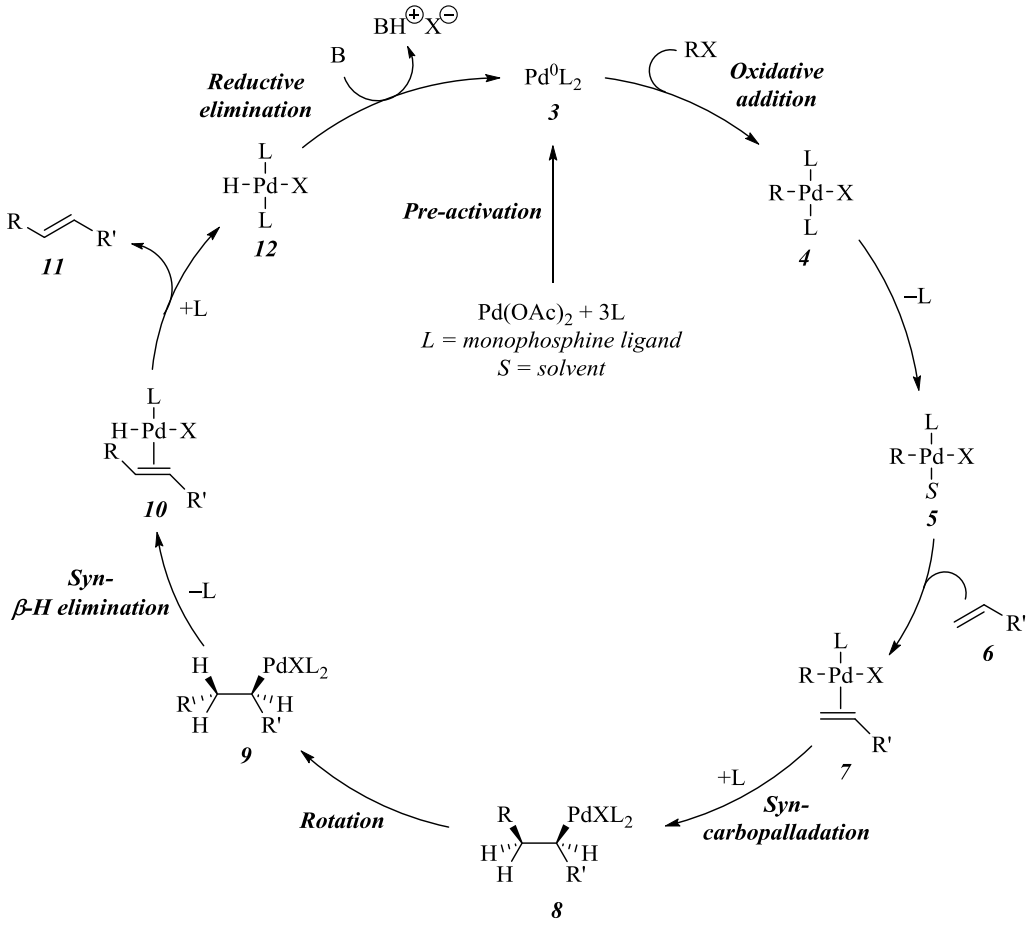
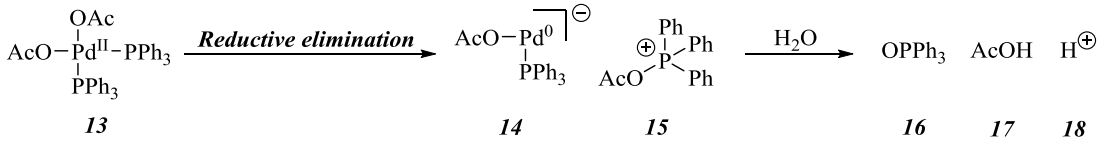


Figure 1.1 *Catalytic cycle for the non-polar ligand-accelerated Heck reaction proposed by Heck*

1.2.2 Pre-activation

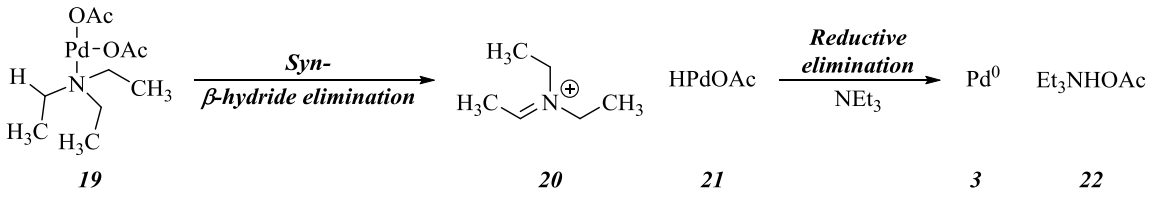
Prior to the beginning of the catalytic cycle, Pd^0L_2 (***3***), a fourteen electron complex, is hypothesised to be formed from the reduction of palladium acetate by monophosphine ligands. This step is known

as *pre-activation*. The *pre-activation* step is known to occur by three methods: Firstly, when phosphine ligands are present, phosphine assisted reduction of palladium(II) to palladium(0) occurs.[18,19] For example, when three equivalents of triphenylphosphine are employed, the phosphine ligands coordinate to the metal centre to generate $Pd(OAc)_2(PPh_3)_2$ (***13***) and *reductive elimination* with an acetate ligand generates $[Pd^0(OAc)(PPh_3)]^-$ (***14***)—a palladium(0) complex which can presumably bind another phosphine ligand and lose the acetate ligand to generate $Pd^0(PPh_3)_2$, the active catalytic species as proposed by Heck (*Scheme* ***1.2***). More recent studies have shown however, that $[Pd^0(OAc)(PPh_3)_2]^-$ (***52***) is actually formed from this procedure and is the active catalytic species (*Figure* ***1.3****, vide infra*).[20,21] This mechanism also generates $[PPh_3OAc]^+$ (***15***), which can convert to triphenylphosphine oxide (***16***) and acetic acid (***17***) in the presence of trace amounts of water. A proton (***18***) is also liberated during this transformation.[18]



Scheme 1.2 *Reduction of palladium(II) to palladium(0) by phosphine ligands*

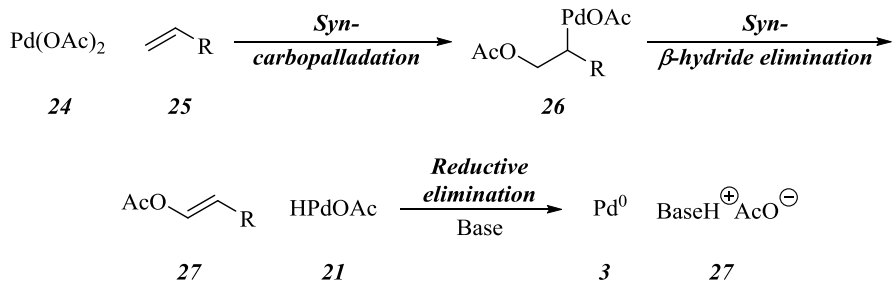
Secondly, amines are known to be able to reduce palladium(II) to palladium(0) *via* coordination of the amine to the metal centre and subsequent *syn-β-hydride elimination* to generate HPdOAc (***21***). *Reductive elimination* then generates Pd^0 (***3***) —the active catalytic species (*Scheme* ***1.3***).[22]



Scheme 1.3 *Reduction of palladium(II) to palladium(0) by amines*

Lastly, a 'Wacker-type' mechanism has also been proposed for the reduction of palladium(II) to palladium(0).[23,24] Coordination of the olefin to palladium acetate (***24***) and *syn-carbopalladation* generate *intermediate* ***26***. *Syn-β-hydride elimination* then produces *alkene* ***27***and HPdOAc (***21***), which undergoes *reductive elimination* to generate Pd^0 (***3***)—the active catalytic species (*Scheme* ***1.4***). Interestingly, in the presence of phosphine ligands, the reduction rate of palladium(II) to

palladium(0) is not influenced by changes in the amine or olefin concentration, indicating that the phosphine reduction is the dominant pathway.[20]



Scheme 1.4 *'Wacker-type' mechanism for palladium(0) generation*

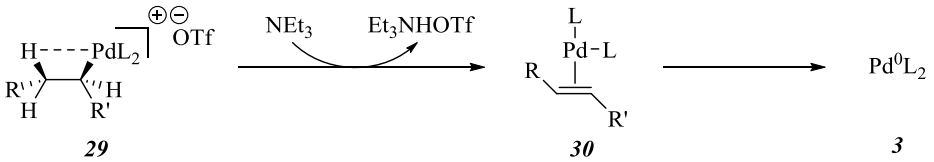
1.2.3 Oxidative addition

Pd^0L_2 (***3***) then undergoes *oxidative addition* with an aryl/alkenyl halide/pseudo-halide to form *cis*-$RPdXL_2$, which then rapidly isomerises to *trans*-$RPdXL_2$ (***4***), although it is thought that *cis*-$RPdXL_2$ may also participate in the remainder of the catalytic cycle.[25] This has been shown to be the case for transmetallation based cross-coupling reactions, such as the Suzuki reaction and Negishi reaction, where *transmetallation* is faster than the *cis-trans* isomerisation.[26] It is thought that in the Heck reaction however, that olefin coordination is slower than the *cis-trans* isomerisation. The rate of *oxidative addition* for respective aryl halides is aryl iodides > aryl bromides >> aryl chlorides, which follows the experimentally determined bond dissociation energies, which are 65, 81, and 91 kcal mol^{-1}, respectively.[27] Aryl trifluoromethanesulfonates have similar reactivity to aryl bromides. Within each class of aryl halide there exists a spectrum of reactivity which is determined by the electronic properties of the substituents on the aromatic ring. Electron-withdrawing groups such as esters are known to increase reactivity towards *oxidative addition* and are termed 'activating'. Conversely, electron-donating groups such as ethers are known to decrease the reactivity towards *oxidative addition* and are termed 'deactivating'. *Oxidative addition* is considered to be the rate-determining step for the least reactive aryl halides, whereas the *syn-carbopalladation* step is thought to be rate-determining for the most reactive aryl halides.

1.2.4 Syn-carbopalladation and syn-β-H elimination

Dissociation of a ligand is important as it frees a coordination site on the metal,[28] which is then filled by *alkene* ***6***. This then undergoes a *syn-carbopalladation* to generate *intermediate* ***7***. Theoretical studies on the insertion of ethylene into the Pt–H bond, an analogous mechanism, determined that this step is stereoselective and requires a *syn*-co-planar arrangement of the metal, hydride, and ethylene. This report also showed that a pentacoordinated intermediate, resulting from olefin association without ligand dissociation, would have a much higher energy profile compared to a tetracoordinated intermediate.[29] Therefore, it is unlikely that the pentacoordinated intermediate takes part in the catalytic cycle, although it has been invoked in some instances where strongly coordinating bidentate ligands and halides are present.[30] Furthermore, kinetic studies conducted independently by Hoffman[31] and Norman[32] have demonstrated that a tetracoordinated intermediate is required and that the *syn-carbopalladation* step is concerted. The reactivity for olefins follows a trend of steric hindrance with monosubstituted > disubstituted >> trisubstituted. Trisubstituted olefins typically do not undergo intermolecular Heck reactions.[33]

After rotation, *syn-β-H elimination* occurs to generate *alkene* ***11***, which is released from *intermediate* ***10***. A *syn*-disposition of the palladium and hydride is a requirement for the *syn-β-H elimination* step, and this has been studied through computational modelling.[34,35] An *E*-geometry for *alkene* ***11*** is thermodynamically favoured where possible, but the mechanistic requirement for palladium and hydrogen to be *syn*-disposed ultimately controls stereoselectivity. Association of a ligand, *trans-cis* isomerisation, and *reductive elimination* regenerates Pd^0L_2 (***3***), which then continues in the catalytic cycle. A base is essential to scavenge *palladium hydride* ***12***, which is thought to be involved in alkene isomerisation,[28] allowing the *reductive elimination* step to proceed and thus complete the catalytic cycle. The base is thought to quench the hydrogen halide species generated from this step.[36]



Scheme 1.5 *Base-assisted deprotonation of the agostic β-hydrogen*

There is however, debate about the existence of *palladium hydride* ***12***. Computational studies suggest that there is a strong agostic interaction between palladium and the β-hydrogen(s) after *syn-carbopalladation* takes place.[37,38] A base-assisted deprotonation of the agostic β-hydrogen then occurs, and this is the most computationally-supported mechanism for the regeneration of palladium(0) (*Scheme* ***1.5***), rather than through classical *syn-β-H elimination* to give *palladium hydride* ***12*** and subsequent *reductive elimination* to regenerate Pd^0L_2 (***3***).[39] Alternatively, 'E2-like' elimination, although unlikely, cannot be fully excluded and may be one of the reasons for the observation of alkene geometric isomers.

1.2.5 General catalytic cycle for the polar Heck reaction

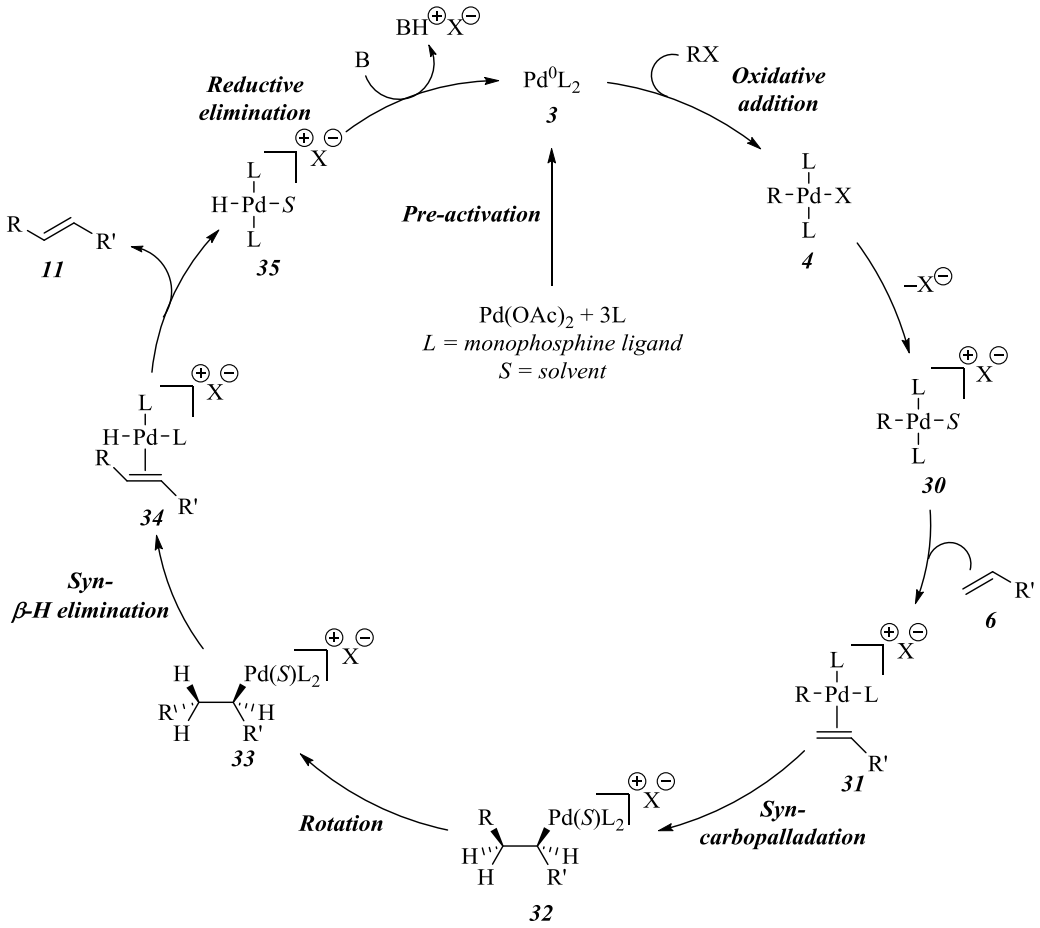


Figure 1.2 *Catalytic cycle for the polar ligand-accelerated Heck reaction*

The general catalytic cycle described previously (*Figure* ***1.1****, vide supra*) is commonly referred to as the 'non-polar' pathway for the Heck reaction, involving formally neutral intermediates throughout the cycle. Instead of the dissociation of a phosphine ligand from tetracoordinated *intermediate* ***4***, the

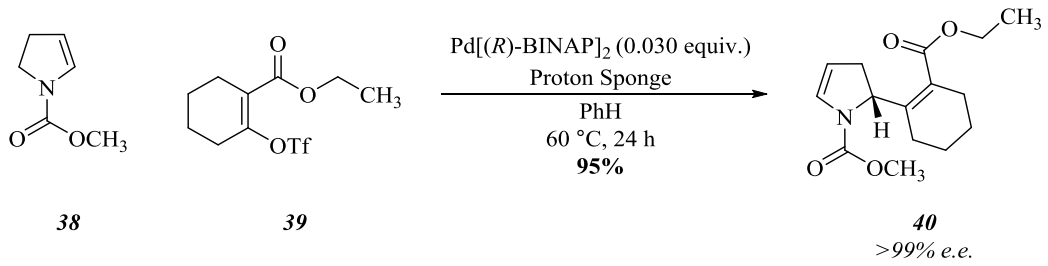
halide or pseudo-halide may dissociate instead giving rise to cationic $[RPd(S)L_2]^+X^-$ (***30***) (*Figure **1.2***). This leads to a slightly modified catalytic cycle known as the 'polar' pathway for the Heck reaction.

Pre-activation and *oxidative addition* occur in a similar manner to the non-polar pathway, but at this point the mechanisms diverge. Instead of neutral ligand dissociation, dissociation of a halide or pseudo-halide occurs readily to generate $[RPd(S)L_2]^+X^-$ (***30***),[40] which is formally cationic in nature and has two ligands bound to the palladium centre. The anion remains loosely coordinated to the cationic complex although it is outside of the metal coordination sphere. $[RPd(S)L_2]^+X^-$ (***30***) coordinates *alkene **6*** and isomerises to *cis-intermediate **31***, which then undergoes *syn-carbopalladation*. The remainder of the catalytic cycle is analogous to the non-polar pathway.

The polar pathway is typically favoured when the coordination sphere of the palladium is undefined, in that the exact ligating species are unknown. This occurs in the absence of strongly coordinating ligands such as phosphine ligands or N-heterocyclic carbene ligands. The polar pathway can be induced by two methods: Firstly, the use of aryl/alkenyl trifluoromethanesulfonates can allow the polar pathway to dominate as the trifluoromethanesulfonate anion is more labile than a halide, thus will dissociate readily from the metal centre.[41] Secondly, when aryl/alkenyl halides are used, silver or thallium salts are commonly employed as halide scavengers as the halide anion has a greater affinity for polarised metals such as these.[42,43] Conversely, the addition of a halide source, such as a tetraalkylammonium halide, can favour the non-polar pathway when aryl/alkenyl trifluoromethanesulfonates are employed.[44] Finally, although not strong enough effects in their own right, the use of polar solvents, such as *N,N*-dimethylformamide, and bidentate ligands can assist in favouring the polar pathway over the non-polar pathway.

Examination of the catalytic cycle for the polar pathway for the Heck reaction leads to its first important application—the asymmetric Heck reaction (*Scheme **1.6***). *Dihydropyrrole **38*** and *triflate **39*** were reacted in the presence of a chiral palladium catalyst based on (*R*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl to furnish *(R)-dihydropyrrole **40*** in 95% yield and

with >99% enantiomeric excess.[45] Furthermore, the asymmetric intramolecular Heck reaction has been utilised extensively in natural product synthesis.[46,47]



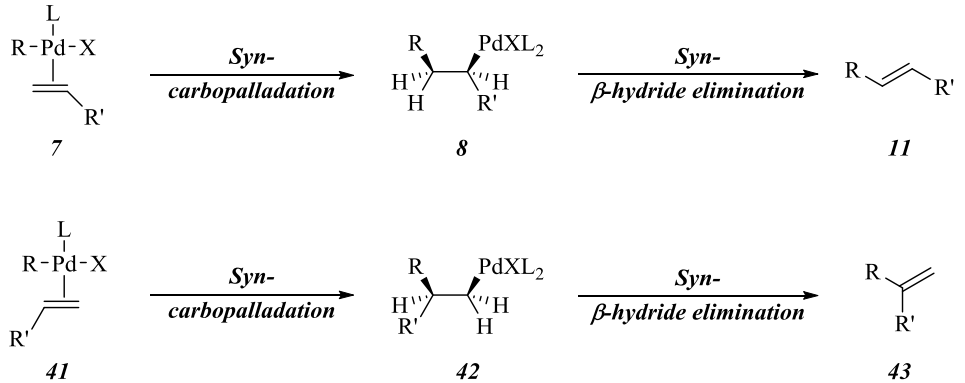
38 ***39*** ***40***
>99% e.e.

Scheme 1.6 *Synthesis of (R)-dihydropyrrole* ***40*** *via asymmetric intermolecular Heck reaction*

The most effective chiral ligands for palladium in the asymmetric Heck reaction are usually chiral bidentate phosphine ligands such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl. In the polar pathway for the Heck reaction, both phosphine 'arms' of a bidentate ligand can remain coordinated to the metal centre, resulting in high enantioselectivity. Diminished enantioselectivity is usually attributed to ligand dissociation from palladium and entry to the non-polar pathway for the Heck reaction.

1.2.6 Olefin regioselectivity in the Heck reaction

The second important application of the polar pathway is to aid in the control of olefin regioselectivity in the Heck reaction. During the *syn-carbopalladation* step in the catalytic cycle of the Heck reaction (*Figure* ***1.1*** and *Figure* ***1.2***), there is a regioselectivity consideration as the palladium and migrating group, *R'*, can add across an unsymmetrical olefin in two different ways. The result of this is two different olefin regioisomers—*alkene* ***11*** and *alkene* ***43*** (*Scheme* ***1.7***).

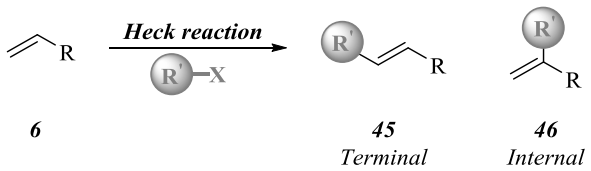


7 ***8*** ***11***

41 ***42*** ***43***

Scheme 1.7 *Regioselectivity of syn-carbopalladation*

Proceeding selectively down the non-polar pathway or polar pathway for the Heck reaction can give control over the regioselectivity for some olefins (*Table* ***1.1***).[48] In the case of electron-deficient olefins such as methyl acrylate (***47***) however, the non-polar and polar pathways both result in the isolation of the terminal Heck product (*Entry 1*). This is due to the polarisation of the Pd–R bond. The migrating group, *R*, will behave formally as an anion and add to the olefin at the position of least electron density. Furthermore, the steric effects of the Pd–R bond, where the migrating group, *R*, is likely to be larger than palladium, result in *R* adding preferentially to the least sterically hindered end of the olefin. Electron-deficient olefins suffer minimal conflict as the site of least electron density and least steric hindrance coincides. This is not true for electron-rich olefins. When *amide* ***48*** was exposed to the Heck reaction, a 60:40 mixture of the terminal and internal Heck products was observed from the non-polar pathway. Conversely, the polar pathway resulted in the isolation of predominantly the internal Heck product (*Entry 2*).



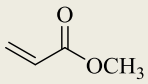
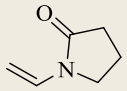
Entry	*Olefin*	*Non-polar pathway*	*Polar pathway*
1	 ***47***	100:0 *Terminal:Internal substitution*	100:0 *Terminal:Internal substitution*
2	 ***48***	60:40 *Terminal:Internal substitution*	0:100 *Terminal:Internal substitution*

Table 1.1 *Product distribution from the non-polar and polar pathways of the Heck reaction*

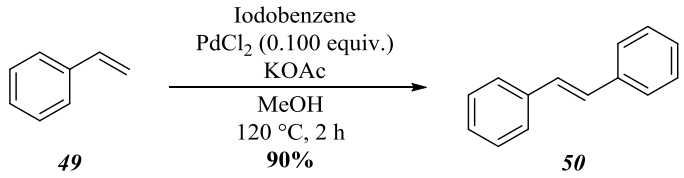
These results can be rationalised by the catalytic cycles for the non-polar and polar pathways. In the non-polar pathway, the steric effects outweigh the electronic effects and this leads to predominant isolation of the terminal Heck product. In the polar pathway, the olefin coordinates to a formally cationic palladium species— $[RPdSL_2]^+X^-$ (***30***). This polarises the π-system in the olefin and favours electronic effects over steric effects, leading to isolation of the internal Heck product.[49] It follows

that under the non-polar pathway, electron-deficient olefins react faster than electron-rich olefins, and this can be understood by the partial anionic character of the migrating group, *R*. The opposite is true for the polar pathway, electron-rich olefins are known to react faster than electron-deficient olefins.[50] This is thought to be due to the reluctance of an electron-deficient olefin to coordinate to a cationic palladium complex.[51]

1.3 Historical perspective and specific catalytic cycles

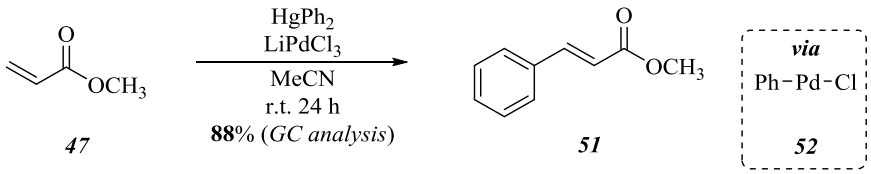
1.3.1 Phosphine-free catalytic systems

The first Heck reaction was performed in 1971 by Mizoroki and co-workers and employed palladium chloride and potassium acetate for the arylation of alkenes, such as styrene (***49***) by iodobenzene (*Scheme* ***1.8***).[52]



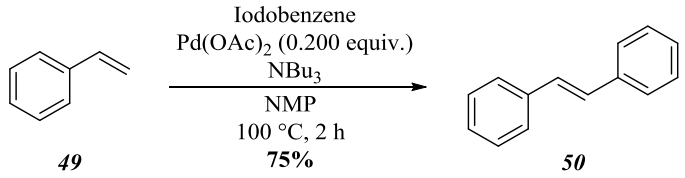
Scheme 1.8 *Mizoroki's phosphine-free conditions for the Heck reaction*

Even though this was the first reported Heck reaction, Heck and co-workers had performed initial stoichiometric studies in 1968 detailing that *in situ* generated [Ar–Pd–Cl] or [Ar–Pd–OAc] could undergo *syn-carbopalladation* with an alkene, leading to arylated alkenes after *syn-β-H elimination* (*Scheme* ***1.9***).[53]



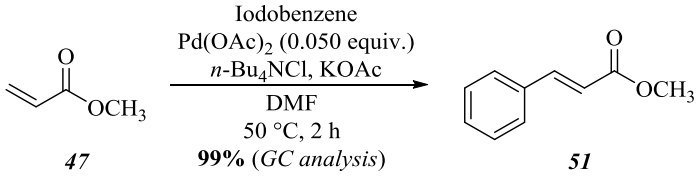
Scheme 1.9 *Synthesis of ester* ***51*** *via stoichiometric Heck reaction*

In 1972, Heck and co-workers reported similar conditions to those described by Mizoroki. Their conditions utilised palladium acetate as the catalyst and were performed solvent-free or in *N*-methyl-2-pyrrolidone (*Scheme* ***1.10***). Heck went on to propose a catalytic cycle for the palladium catalysed reaction (*Figure* ***1.1****, vide supra*).[17]



Scheme 1.10 *Heck's phosphine-free conditions for the Heck reaction*

A significant contribution to the Heck reaction was made in 1996 by Jeffrey, who reported that the use of tetraalkylammonium salts and palladium acetate in the presence of a base, could accelerate the Heck reaction of aryl iodides, especially in the absence of phosphine ligands. For example, treatment of methyl acrylate (***47***) and iodobenzene in the presence of palladium acetate, potassium acetate, and tetra-*n*-butylammonium chloride furnished *ester* ***51*** in 99% yield as observed by gas-chromatography analysis (*Scheme* ***1.11***).[54]



Scheme 1.11 *Jeffrey's conditions for the Heck reaction*

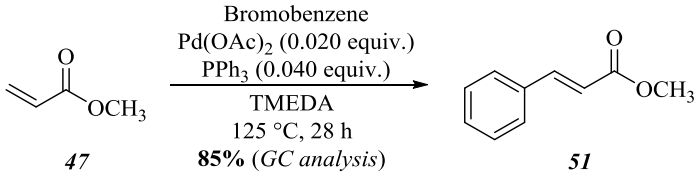
It was hypothesised by Jeffrey, that after decomposition of the Pd–OAc bond in palladium acetate occurs, the resultant palladium(0)-nanoparticles are stabilised by the quaternary ammonium salt, thus generating soluble active clusters of palladium(0). These nanoparticles are known to catalyse the Heck reaction and undergo *oxidative addition* rapidly.[55] It was also noted that tetraalkylammonium chlorides worked better than tetraalkylammonium bromides, and it was hypothesised that organopalladium chlorides are more reactive in the *syn-β-H elimination* step than their bromide counterparts. This suggested that the tetraalkylammonium salts were acting as halide donors. A further accelerating effect was described when inorganic bases were employed with the tetraalkylammonium salts. It was proposed that the beneficial solid-liquid phase-transfer properties of quaternary ammonium salts[56] may be important in explaining this effect and this further accelerating effect was not observed when amine bases were utilised in the Heck reaction. The overall mechanism for phosphine-free Heck reaction systems however, has been difficult to fully

elucidate due to the absence of ligands to stabilise important intermediates throughout the catalytic cycle, although a polar-based mechanism is thought to be involved.[57]

Although improvements had been made with these phosphine-free systems, only aryl iodides had been successfully coupled with olefins. The use of ligands with predictable binding ability would be essential to allow for the coupling of more challenging aryl bromides and aryl chlorides.

1.3.2 Catalytic systems with monophosphine ligands

In 1973, Mizoroki and co-workers made their final contribution to the Heck reaction and reported that the use of triphenylphosphine as a ligand was beneficial to allow aryl iodides and, in some cases, aryl bromides to react with olefins.[58] Building upon these results, Heck and co-workers further developed the use of palladium acetate with triphenylphosphine. Using this protocol, aryl iodides reacted at a faster rate when compared to phosphine-free catalysis, and importantly, aryl bromides were successfully employed in the Heck reaction, although temperatures of 100−135 ºC were required depending on the electronic nature of the aryl bromide used. Aryl chlorides however, were still unreactive under these conditions.



47 *51*

Scheme 1.12 *Heck's triphenylphosphine based conditions for the Heck reaction*

For example, treatment of methyl acrylate (***47***) and bromobenzene in the presence of palladium acetate, triphenylphosphine, and tetramethylethylenediamine furnished *ester* ***51*** in 85% yield as observed by gas-chromatography analysis (*Scheme* ***1.12***).[59]

The general catalytic cycle described previously (*Figure* ***1.1****, vide supra*) provides a suitable overview of the key aspects in the Heck reaction, however, Amatore and Jutand proposed an updated catalytic cycle specific for the use of palladium acetate and triphenylphosphine in tetrahydrofuran or *N,N*-dimethylformamide (*Figure* ***1.3***). When three equivalents of triphenylphosphine were used as the ligand with palladium acetate, Heck proposed that the active catalytic species was $Pd^0(PPh_3)_2$.

Amatore and Jutand have shown that $[Pd^0(OAc)(PPh_3)_2]^-$ (***52***) is the active catalytic species generated under these conditions, but only in the presence of a base which serves to prevent protonation of the acetate anion if dissociation from the palladium complex occurs.[60]

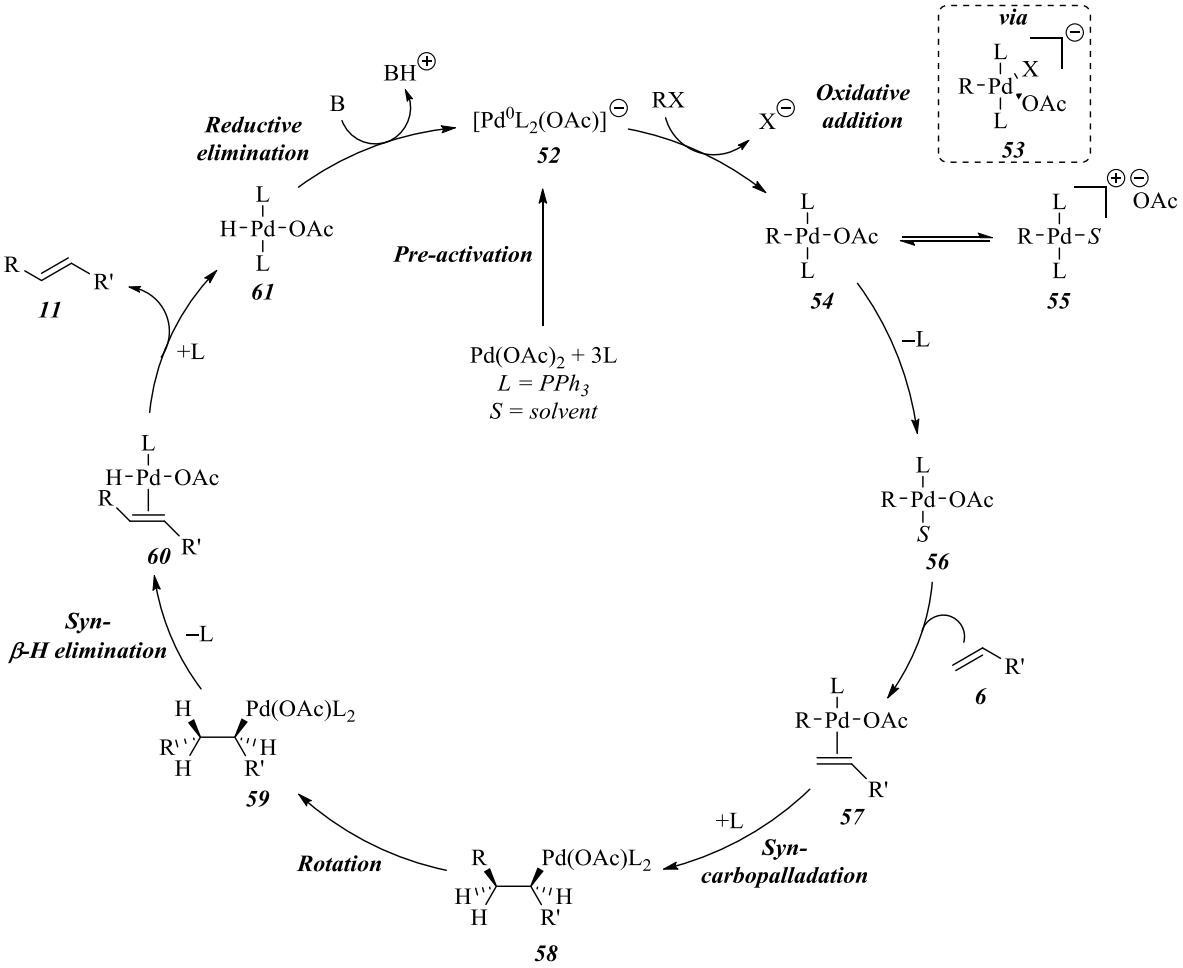
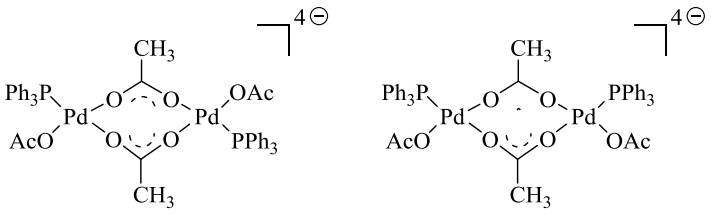


Figure 1.3 *Catalytic cycle for the Heck reaction with palladium acetate and triphenylphosphine*

Once protonated to acetic acid by the proton generated from the hydrolysis of $[PPh_3OAc]^+$ (***15***) to triphenylphosphine oxide (***16***) (*Scheme **1.2**, vide supra*), the acetate anion can no longer coordinate to palladium and the unstable $Pd^0(PPh_3)_2$ complex remains.[21] Reported computational studies support the presence of $[Pd^0(OAc)(PPh_3)_2]^-$ (***52***).[61]

When two equivalents of triphenylphosphine are used with palladium acetate, *intermediate **63*** and *intermediate **64*** are formed (*Figure **1.4***). As a result of one equivalent of triphenylphosphine being used for reduction of palladium(II) to palladium(0), only one ligand is bound to the generated

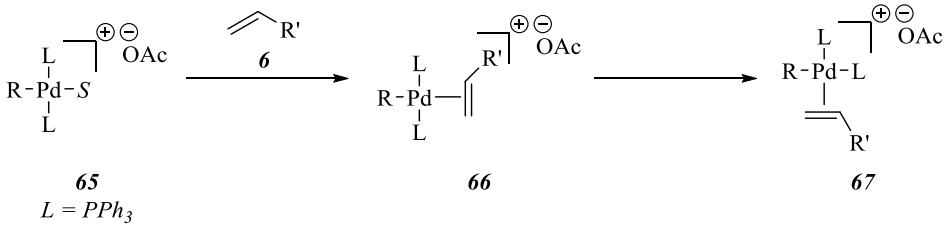
palladium complex. It is thought that *intermediate* ***63*** and *intermediate* ***64*** are active catalysts for the Heck reaction, although the complexes themselves are less stable than $[Pd^0(OAc)(PPh_3)_2]^-$ (***52***).[18]



63 ***64***

Figure 1.4 *Intermediate* ***63*** *and intermediate* ***64***

Oxidative addition to form $RPd(OAc)(PPh_3)_2$ (***54***) proceeds *via* pentacoordinated anionic intermediate $[RPdX(OAc)(PPh_3)_2]^-$ (***53***), as shown by computational studies for *oxidative addition* to iodobenzene. Interestingly, the *oxidative addition* step does not produce the iodide complex, instead forming $RPd(OAc)(PPh_3)_2$ (***54***).[21] In addition, the presence of *alkene* ***6*** retards the rate of *oxidative addition* by coordination to $[Pd^0(OAc)(PPh_3)_2]^-$ (***52***).[62] Excess triphenylphosphine is also known to retard the rate of *oxidative addition* by formation of unreactive $[Pd^0(OAc)(PPh_3)_3]^-$.[21] Acetate-assisted ligand dissociation frees a coordination site for *alkene* ***6*** to bind *cis*- to the *R* group on palladium, and this leads to fast a *syn-carbopalladation* step. $RPd(OAc)(PPh_3)_2$ (***54***) exists in equilibrium with $[RPd(S)(PPh_3)_2]^+$ (***55***), and the presence of base prevents the acetate anion from protonating on dissociation and thus shifting the equilibrium towards $[RPd(S)(PPh_3)_2]^+$ (***55***).[63] $[RPd(S)(PPh_3)_2]^+$ (***55***) is thought to undergo alkene coordination and *syn-carbopalladation*, but at a slower rate due to the requirement of a *trans-cis* isomerisation before *syn-carbopalladation* (*Scheme* ***1.13***).[21] The use of aryl triflates gives a similar equilibrium to that observed when aryl halides are employed, indicating that a non-polar pathway is active.[64] The remainder of the catalytic cycle proceeds in the similar manner to Heck's proposed mechanism.

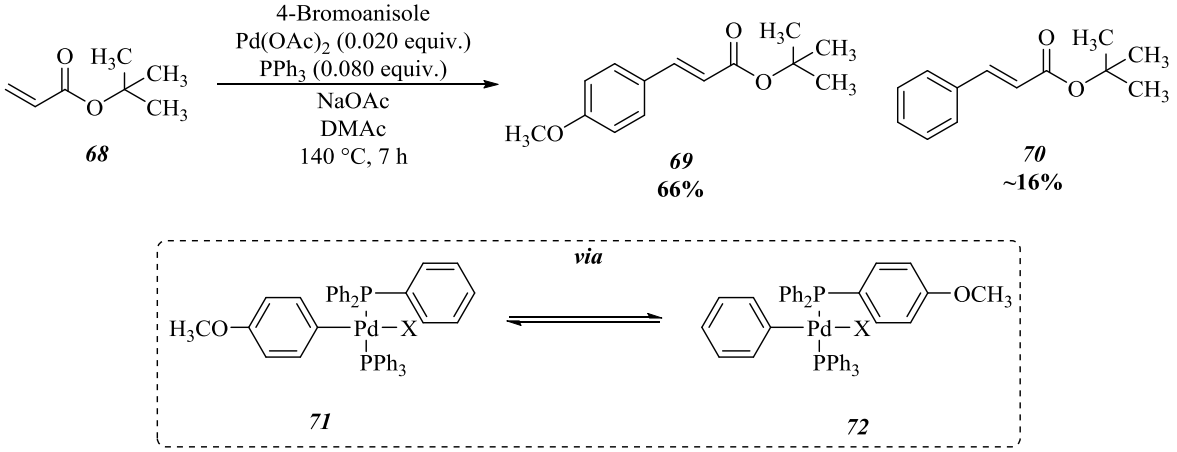


65 ***66*** ***67***

L = PPh3

Scheme 1.13 *Trans-cis isomerisation on coordination of alkene* ***6*** *to* $[RPd(S)(PPh_3)_2]^+AcO^-$ (***65***)

An issue with the palladium acetate and triphenylphosphine catalysed system is quarternarisation of the triphenylphosphine ligand by the arylating moiety, which can lead to deactivation of the catalytic system as the newly generated phosphonium salt will no longer bind to palladium thus generating inactive palladium black.[65] Furthermore, this can be extended to an effect known as *aryl scrambling*, where the aryl group on the ligand is switched with the arylating moiety on palladium.[66,67] For example, the reaction of 4-bromoanisole with *tert*-butylacrylate (***68***) in the presence of palladium acetate and triphenylphosphine generated *ester* ***69*** in 66% yield, but the phenyl analogue, *ester* ***70***, is furnished in ~16% yield (*Scheme* ***1.14***).[65] Systems are prone to aryl scrambling when unhindered phosphine ligands are employed with electron-rich aryl halides at elevated reaction temperatures.

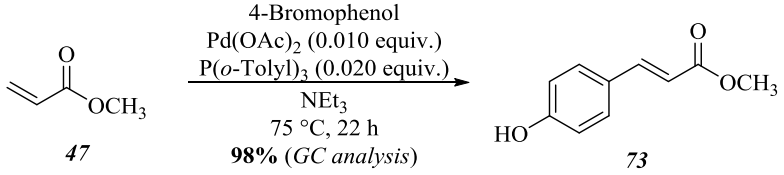


Scheme 1.14 *Aryl scrambling in the Heck reaction*

1.3.3 Catalytic systems with P,C-palladacycles and P,C,P-palladacycles

When palladium acetate and tri(*o*-tolyl)phosphine are used in the Heck reaction, the system is much less prone to aryl scrambling and formation of inactive palladium black, even at elevated temperatures.[68] It was initially hypothesised that this was a result of the extra steric hindrance provided by the *ortho*-methyl groups, which stabilise $Pd^0\{P(o\text{-Tolyl})_3\}_2$, but in fact this palladium(0) complex is not the active catalytic species. Tri(*o*-tolyl)phosphine is not capable of reducing palladium(II) to palladium(0) in the way that triphenylphosphine behaves, due to the extra steric hindrance, instead *palladacycle* ***74*** is formed and is thought to be the precursor to the active catalytic species $Pd^0\{P(o\text{-Tolyl})_2(o\text{-benzyl-OAc})\}(S)$ (***76***) (*Scheme* ***1.17****, vide infra*).

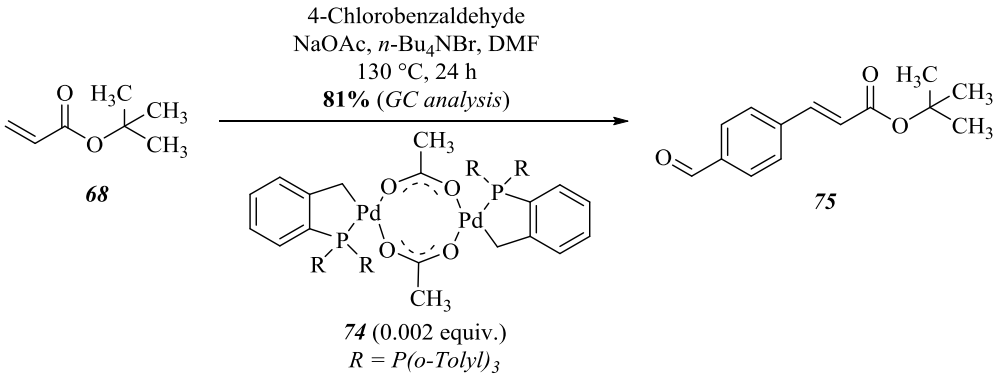
Nevertheless, this catalytic system was far more robust and in 1978, Heck and co-workers reported the use of palladium acetate and tri(*o*-tolyl)phosphine for the Heck reactions of aryl bromides. For example, 4-bromophenol was reacted with methyl acrylate (***47***) to give *ester **73*** in 98% yield as observed by gas-chromatography analysis (*Scheme **1.15***).[69]



47 ***73***

Scheme 1.15 *Heck's tri(o-tolyl)phosphine based conditions for the Heck reaction*

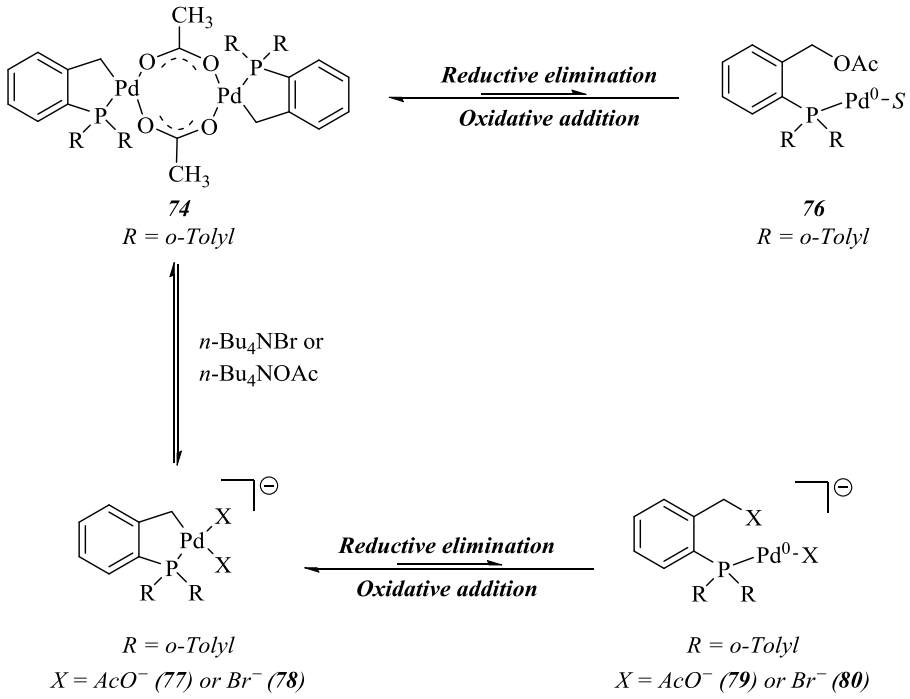
Spencer followed up this work with similar Heck reactions of aryl bromides in 1984,[70] before Herrmann and co-workers attempted to use aryl chlorides in the sequence in 1995.[71] This was met with limited success, with poor conversions and mixtures of geometric isomers observed. It was not until Herrmann and co-workers employed *palladacycle **74*** (sometimes referred to as the Herrmann-Beller catalyst) did activated aryl chlorides become viable substrates in the Heck reaction. *Palladacycle **74*** is formed when palladium acetate undergoes cyclometalation with one of the *ortho*-methyl groups on tri(*o*-tolyl)phosphine,[72] Using this protocol, 4-chlorobenzaldehyde was coupled with *tert*-butylacrylate (***68***) to furnish *ester **75*** in 81% yield as observed by gas-chromatography analysis (*Scheme **1.16***).[68] The presence of tetra-*n*-butylammonium bromide was found to be essential in order to obtain a good yield, and without it only 12% yield was observed by gas-chromatography analysis, even with a ten-fold increase the catalyst loading. *Palladacycle **74*** has also been successfully employed for the Heck reactions of aryl bromides.[73]



68 ***75***

Scheme 1.16 *Herrmann's palladacycle **74** based conditions for the Heck reaction*

The mechanism by which *palladacycle* ***74*** takes part in the Heck catalytic cycle has been debated. It was initially thought by Shaw that a palladium(II)/palladium(IV) catalytic cycle may be invoked,[74] but computational studies have shown that the *oxidative addition* of iodobenzene to a palladium(II) complex has a high activation energy due to the presence of a tetracoordinated palladium complex.[75]



74
R = o-Tolyl

76
R = o-Tolyl

R = o-Tolyl
X = AcO⁻ (77) or Br⁻ (78)

R = o-Tolyl
X = AcO⁻ (79) or Br⁻ (80)

Scheme 1.17 *Activation of palladacycle* ***74*** *by reductive elimination*

In 2005, d'Orlyé and Jutand showed that *palladacycle* ***74*** is actually a slow releasing source of palladium(0) complex, $Pd^0\{P(o\text{-Tolyl})_2(o\text{-benzyl-OAc})\}(S)$ (***76***), formed from *reductive elimination* of the benzylic carbon and an acetate ligand in *N,N*-dimethylformamide. This endergonic process is relatively slow, but the rate of *reductive elimination* can be increased by the addition of acetate anions or bromide anions, which are why these types of Heck reaction are performed using acetate derived bases. It also explains Herrmann's observation that the presence of tetra-*n*-butylammonium bromide gave increased conversions. Addition of such anions to *palladacycle* ***74*** generates anionic *palladacycle* ***77*** or anionic *palladacycle* ***78***, which undergo *reductive elimination* at a faster rate than *palladacycle* ***74*** to form $[Pd^0\{P(o\text{-Tolyl})_2(o\text{-benzyl-OAc})\}(OAc)]^-$ (***79***) or $[Pd^0\{P(o\text{-Tolyl})_2(o\text{-benzyl-Br})\}(Br)]^-$ (***80***) which are the active species in the catalytic cycle (*Scheme* ***1.17***).[76]

A catalytic cycle has been proposed for the Heck reaction using $[Pd^0\{P(o\text{-Tolyl})_2(o\text{-benzyl-OAc})\}(OAc)]^-$ (***79***), generated from *reductive elimination* of *palladacycle 77* in the presence of acetate anions (*Figure **1.4***).[13]

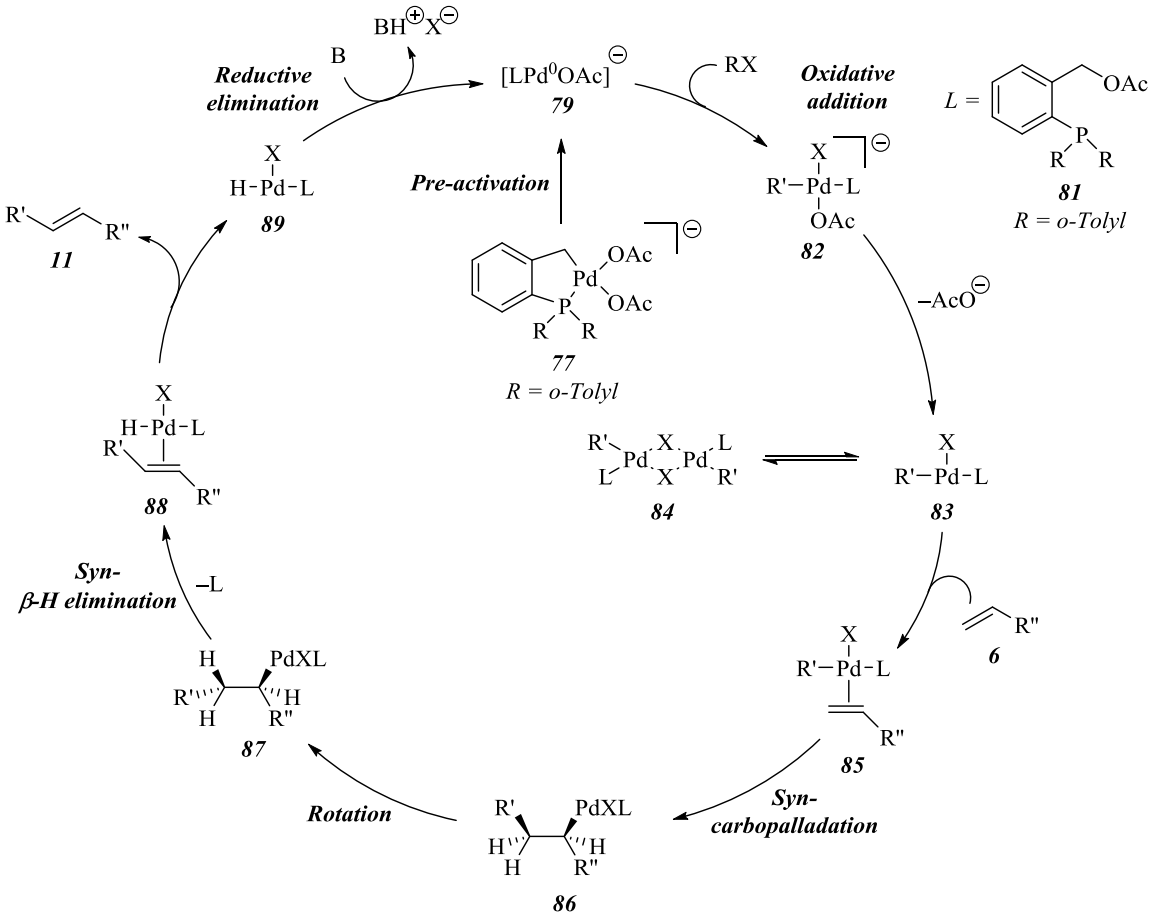
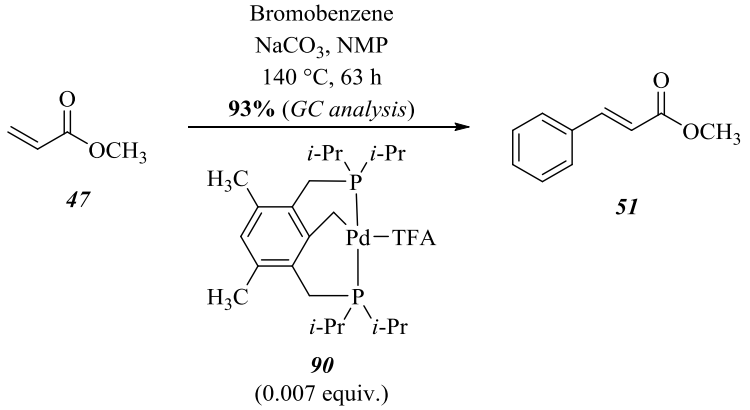


Figure 1.4 *Catalytic cycle for the Heck reaction catalysed by palladacycle 77*

$[Pd^0\{P(o\text{-Tolyl})_2(o\text{-benzyl-OAc})\}(OAc)]^-$ (***79***) is formed in the *pre-activation* step from the treatment of *palladacycle 77* and acetate anions. Hartwig and Paul reported the *oxidative addition* products observed from $Pd^0\{P(o\text{-Tolyl})_3$ with aryl bromides, and it is assumed that a similar mechanism can be invoked in this instance.[77] *Oxidative addition* and acetate dissociation generates $Pd\{P(o\text{-Tolyl})_2(o\text{-benzyl-OAc})\}(R')X$ (8***3***), which is equilibrium with dimeric *palladacycle **84***.[78] The remainder of the catalytic cycle is proposed to proceed in a similar manner to Heck's proposal, although kinetic studies on this mechanism are limited.

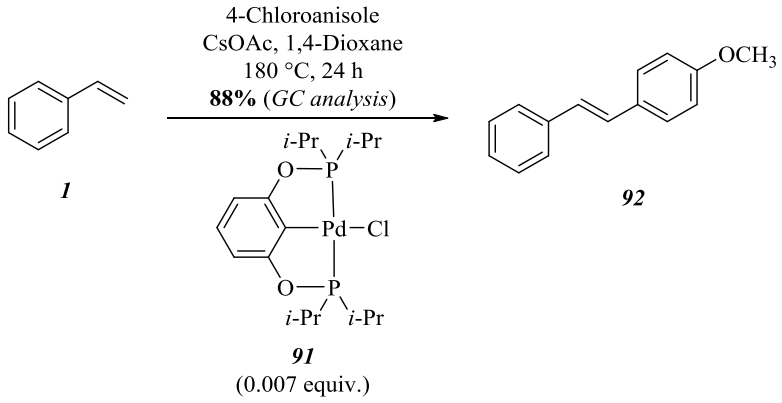
Another class of palladium system known as pincer complexes or P,C,P-palladacycles were initially developed by Milstein and co-workers in 1997 and have proved very active for Heck reactions of

aryl bromides. They were found to be very stable at elevated temperatures and were also stable under aerobic conditions. For example, treatment of methylacrylate (***47***) with bromobenzene in the presence of *palladacycle* ***90*** furnished *ester* ***51*** in 93% yield as observed by gas-chromatography analysis (*Scheme* ***1.18***). *Palladacycle* ***90*** has also proven to be effective for the Heck reaction of aryl iodides, although Heck reactions of aryl chlorides were not viable.[79]



Scheme 1.18 *Milstein's P,C,P-palladacycle based conditions for the Heck reaction*

Building upon the work of Milstein, in 2000, Jensen and co-workers were able to couple aryl chlorides with olefins in the Heck reaction, using a modified P,C,P-palladacycle utilising a phosphite based ligand. Using *palladacycle* ***91***, it was possible for styrene and 4-chloroanisole to be coupled in 88% yield as observed by gas-chromatography analysis (*Scheme* ***1.19***).[80]



Scheme 1.19 *Jensen's P,C,P-palladacycle based conditions for the Heck reaction*

The mechanism of how these P,C,P-palladacycles react in the Heck reaction is a topic of much debate. Due to the strong dual-chelate of the phosphine ligands, palladium(II)/palladium(IV) catalytic cycles have been hypothesised by Shaw[74] and Jensen (*Figure* ***1.5***).[80] *Oxidative addition* of

alkene ***6*** to *palladacycle* ***93*** gives palladium(IV) *palladacycle* ***94***, which in turn releases HX (***95***) by *reductive elimination*. *Oxidative addition* to *palladacycle* ***96*** with RX (***97***) furnishes palladium(IV) *palladacycle* ***98*** and then *reductive elimination* of *alkene* ***11*** regenerates starting *palladacycle* ***93***.

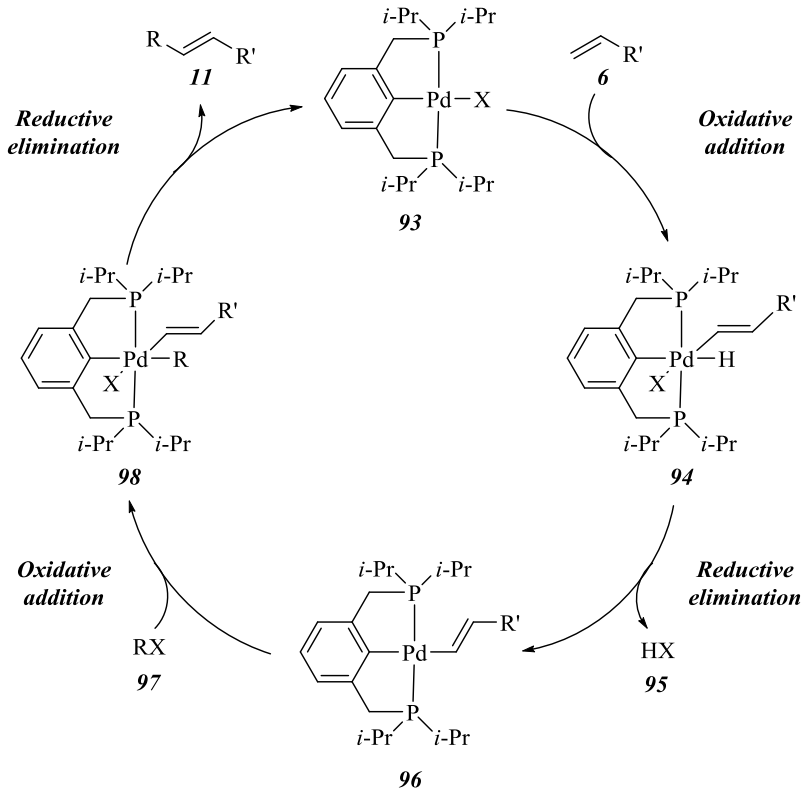


Figure 1.5 *Jensen's palladium(II)/palladium(IV) catalytic cycle for the Heck reaction*

Recent computational studies have supported the viability of this type of catalytic cycle[81] and furthermore, *oxidative addition* to a palladium(II) complex has been characterised by Vicente and co-workers in 2011.[82] However, there is no conclusive evidence that these intermediates exist during the catalytic cycle of the Heck reaction and attempts to isolate palladium(IV) intermediates have typically proven fruitless.[83,84]

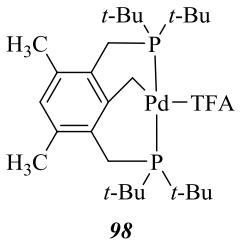
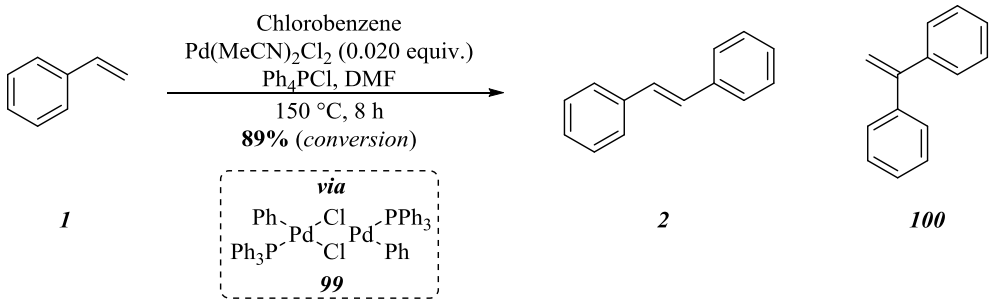


Figure 1.6 *Palladacycle* ***98***

A palladium(0)/palladium(II) catalytic system cannot be fully disregarded, and it was hypothesised by Beletskaya and Cheprakov that dissociation of one phosphine ligand would leave a system that could undergo similar palladium-based chemistry to *palladacycle **74***—the Herrmann-Beller catalyst. Indeed *palladacycle **98*** (*Figure **1.6***) has been shown by X-ray crystallographic studies to have a bite angle as small as 152º, which would indicate a significant amount of ring strain that could be relieved on dissociation of a phosphine ligand, especially at the elevated temperatures at which these P,C,P-palladacycles are utilised.[85]

Addition of tetraarylphosphonium salts to the Heck reaction was reported by Reetz and co-workers in 2000. Impressively, the authors found that chlorobenzene could be coupled with styrene (***1***) in the presence of bis(acetonitrile)dichloropalladium and tetraphenylphosphium chloride. This protocol gave a conversion of 89% for the formation of *(E)-stilbene* (***1***) although a small amount of *alkene **100*** was also formed, indicative of the polar pathway for the Heck reaction playing a role (*Scheme **1.20***). There has been limited study on the mechanism of the catalytic system, but it is thought that *palladacycle **99*** may be the active catalytic species, which arises from *oxidative addition* of the phosphonium salt.[86]

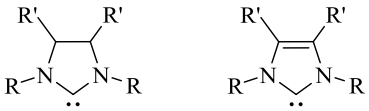


Scheme 1.20 *Synthesis of (E)-stilbene (**2**) via Heck reaction*

1.3.4 Catalytic systems with N-heterocyclic carbene ligands

N-Heterocyclic carbene ligands (NHC), such as *NHC **101*** and *NHC **102*** (*Figure **1.7***), have emerged as an interesting ligand class in the search for catalytic systems to perform the Heck reaction with aryl chlorides. Not only are they air-stable, but N-heterocyclic carbene ligands offer different binding interactions with palladium compared to traditional phosphine based ligands. They are known to be stronger σ-donors to metal centres than phosphine ligands, but are significantly less

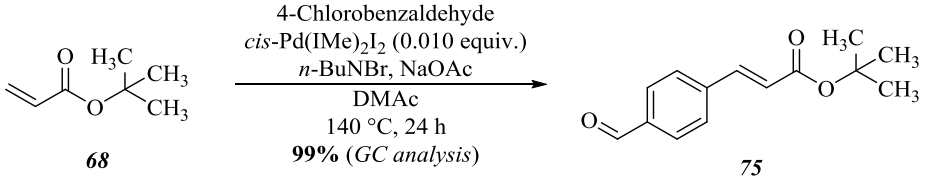
available for π-back donation compared to phosphine ligands, as observed by infrared studies on metal carbonyl complexes.[87,88] The π-back donation component to the bond is typically small, although not totally irrelevant, and this makes the resultant palladium complex relatively electron-rich and more effective for *oxidative addition* of aryl chlorides. Additionally, the strong σ-donor effect present in N-heterocyclic carbene ligands results in the ligand being non-dissociative. This is in direct comparison to phosphine ligands, which can easily dissociate from metal centres. Furthermore, saturated N-heterocyclic carbene ligands have been shown to be better σ-donors and π-acceptors than their unsaturated counterparts. This leads to a more stable, but less reactive metal complex due to the metal centre being a worse σ-acceptor and π-donor.[89]



101 ***102***

Figure 1.7 *Saturated NHC* ***101*** *and unsaturated NHC* ***102***

For example, Herrmann and co-workers described the use of *cis*-$Pd(IMe)_2I_2$ for the Heck reaction of *tert*-butylacrylate (***68***) with 4-chlorobenzaldehyde. This furnished *ester* ***75*** in 99% yield as observed by gas-chromatography analysis (*Scheme* ***1.21***.[90] The addition of *n*-butylammonium bromide assisted in the *pre-activation* of catalyst by reduction of palladium(II) to palladium(0). Without the additive, only a 12% yield was observed. This catalyst system was also suitable for the use of aryl bromides, but attempts to utilise deactivated aryl chlorides, such as 4-chloroanisole, were unsuccessful.



68 ***75***

Scheme 1.21 *Herrmann's N-Heterocyclic carbene ligand complexes for the Heck reaction*

A catalytic cycle for the Heck reaction catalysed by N-heterocyclic carbene ligated palladium complexes has been proposed (*Figure* ***1.8***).[13] Caddick,[91] Green,[92] and Jutand[93] have shown that the active catalytic species for the reaction is either a Pd^0(NHC) or $Pd^0(NHC)_2$ complex depending on

the steric bulk possessed by the N-heterocyclic carbene ligand. This is generated from the reduction of a precursor palladium(II) complex. The result from the *oxidative addition* and subsequent *cis-trans* isomerisation is a bis-ligated palladium complex such as $PdR(NHC)_2X$ (***104***), even if the active catalytic species before *oxidative addition* is mono-ligated. As N-heterocyclic carbene ligands are strongly bound to the palladium centre, it is likely that a halide anion dissociates to generate cationic $[PdR(NHC)_2S]^+X^-$ (***105***), which would then undergo *syn-carbopalladation* after coordination of *alkene* ***6*** and *trans-cis* isomerisation. Dissociation of the ligand has been supported by both computational studies[94] and experimental work.[95] It is interesting to note that cationic carbene complexes have been shown to not be particularly stable at room temperature, and this study would suggest that this may be a major pathway for catalyst degradation.[95] The remainder of the catalytic cycle is analogous to the catalytic cycle of the polar Heck reaction.

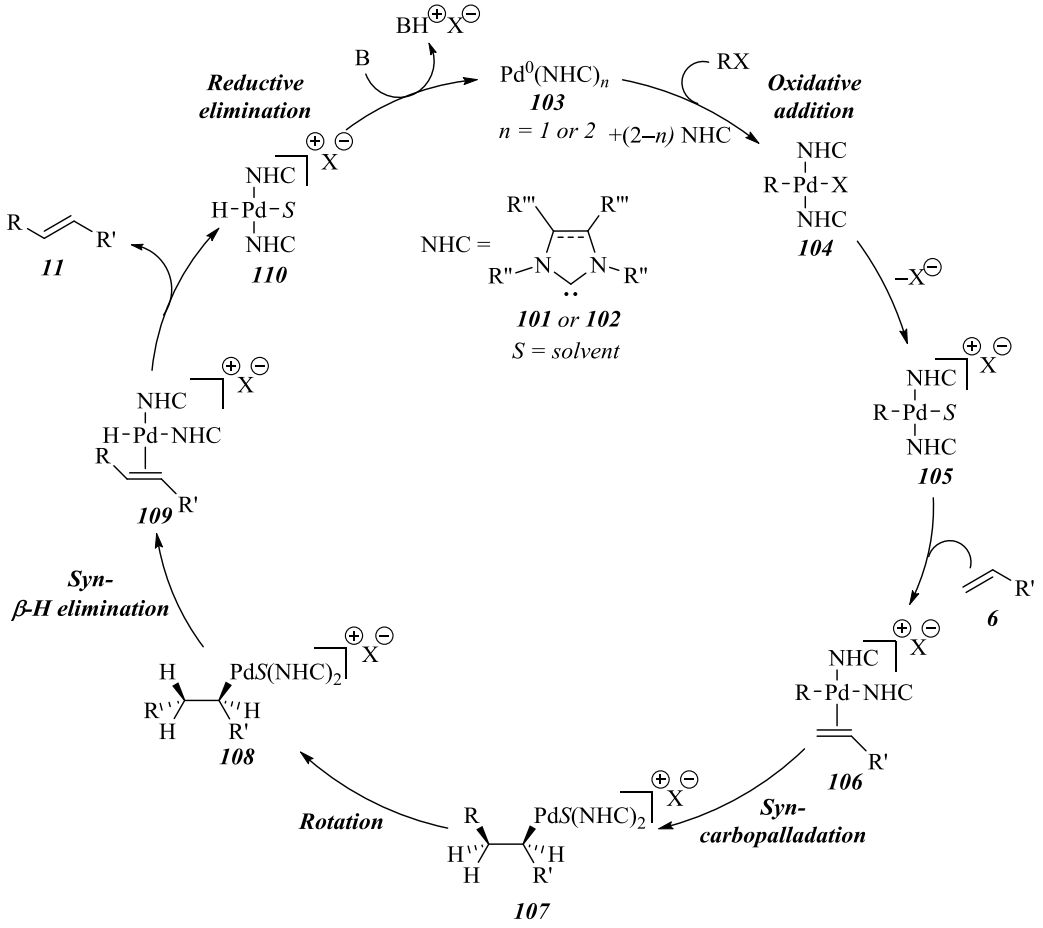
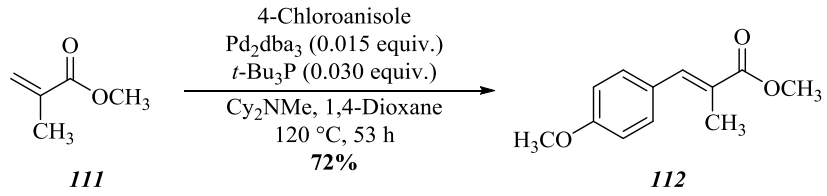


Figure 1.8 *Catalytic cycle for the Heck reaction catalysed by N-heterocyclic carbene ligands*

1.3.5 Catalytic systems with bulky and electron-rich phosphine ligands

In 2001, Fu and co-workers successfully introduced the use of bulky, electron-rich phosphine ligands such as tri-*tert*-butylphosphine in order to allow deactivated aryl chlorides to undergo *oxidative addition* in the Heck reaction. Significantly, 4-chloroanisole was coupled with methyl methacrylate (***111***) in the presence of tris(dibenzylideneacetone)dipalladium and tri-*tert*-butylphosphine to generate *ester* ***112*** in 72% yield (*Scheme* ***1.22***).[96] The use of *N,N*-dicyclohexylmethylamine as base aided in the reactivity and proved more efficient than caesium carbonate. Aryl bromides and activated aryl chlorides were also successfully coupled in excellent yields at room temperature. A range of analogs of tri-*tert*-butylphosphine, where the tri-*tert*-butyl groups have been substituted out, have been utilised in the Heck reaction offering marginal improvements in catalyst activity.[97]

Following on from this work, Fu recognised that the tri-*tert*-butylphosphine was prone to oxidation in air and developed an air stable phosphonium precursor—tri-*tert*-butylphosphonium tetrafluoroborate—which was found to be equally as effective as its parent phosphine compound upon deprotonation with a Brønsted base *in situ*.[98]



111 ***112***

Scheme 1.22 *Fu's tri-tert-butylphosphine ligand for the Heck reaction*

A catalytic cycle has been proposed for the Heck reaction catalysed by tris(dibenzylideneacetone)dipalladium and tri-*tert*-butylphosphine with a 1:1 palladium/phosphine ratio (*Figure* ***1.9***).[13] *Pre-activation* occurs by displacement of the ancillary dibenzylideneacetone ligands, which are themselves known to have catalytic activity in the Heck reaction, with tri-*tert*-butylphosphine ligands. A formal reduction is no longer necessary as the precursor palladium complex is already palladium(0), which is required for *oxidative addition*. *Oxidative addition* is thought to occur from the mono-ligated $Pd^0Pt\text{-}Bu_3$ (***113***), which is equilibrium with $Pd^0(Pt\text{-}Bu_3)_2$.[99] This gives the T-shaped $RPdX(Pt\text{-}Bu_3)$ (***114***) and the free coordination site on palladium is stabilised

by an agostic interaction from a C–H bond on the ligand.[100] Less bulky ligands such as tricyclohexylphosphine are active ligands for aryl chlorides, although they are not as efficient as tri-*tert*-butylphosphine. With a decrease in steric hindrance, these ligands react through $Pd^0(PCy_3)_2$, rather than by dissociation of a ligand prior to *oxidative addition*.[101] Association of *alkene* ***6***, *trans-cis* isomerisation, *syn-carbopalladation* and *syn-β-H elimination* occur successively to generate HPdX(P*t*-Bu_3) (***120***) and *alkene* ***11***. Studies by Fu and co-workers have shown that the *reductive elimination* step readily occurs from this complex when *N,N*-dicyclohexylmethylamine is utilised as a base, re-generating the active catalytic species. In contrast, caesium carbonate does not perform efficiently in this role, highlighting the importance of choice of base for the Heck reaction. Furthermore, it has also been shown that HPdCl(P*t*-$Bu_3)_2$ performs far more efficiently in the *reductive elimination* step compared to $HPdCl(PCy_3)_2$, which is relatively reluctant, and this explains the superiority of tri-*tert*-butylphosphine as a ligand in the Heck reaction of aryl chlorides.[102]

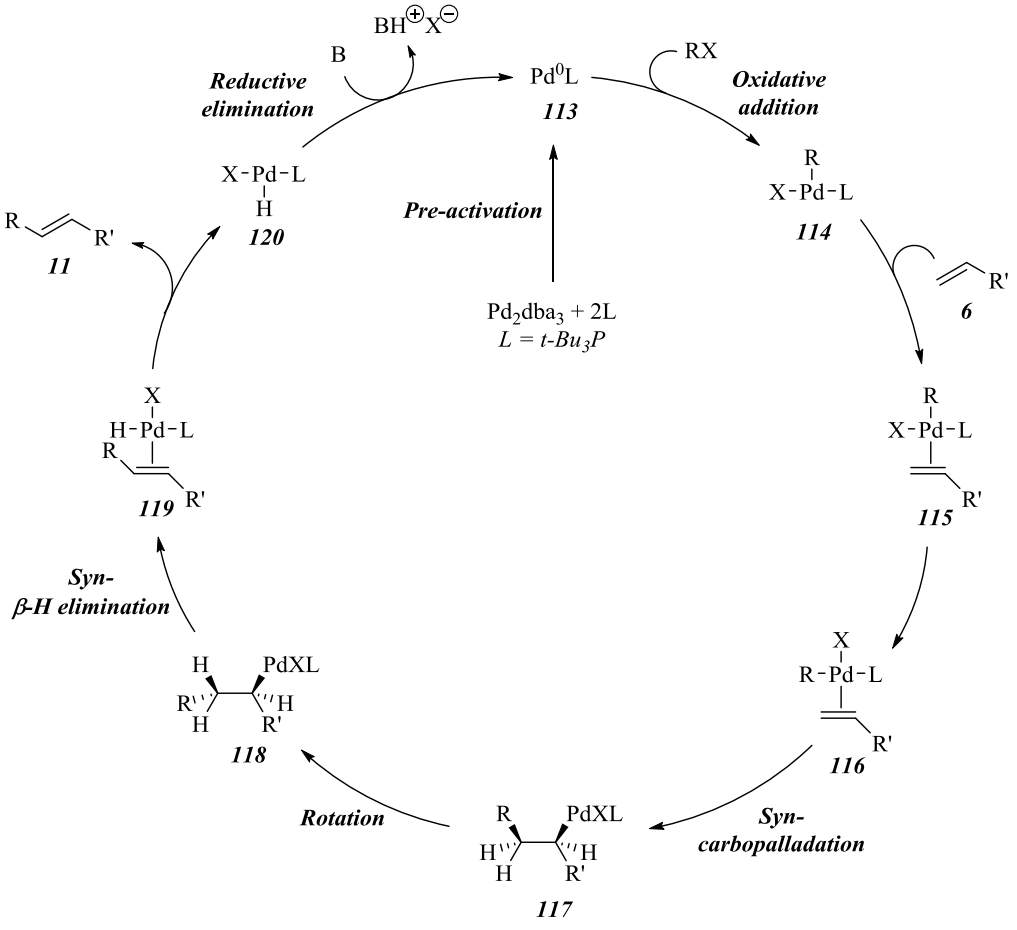


Figure 1.9 *Catalytic cycle for the Heck reaction catalysed by tri-tert-butylphosphine ligands*

Chapter 2

The de novo synthesis of 2,4,6-trisubstituted pyridines

*The synthesis of sulfonamide **158**, enones **160** and **162**, dihydropyridine **168**, pyridines **169**, **172**, **178**, and **181**, and acrylates **253** and **254** had all been performed previously by co-workers in the group. These results, however, were unpublished and were repeated by the author for validation and optimisation studies. A selection of the work described in this chapter has been published in Chemical Communications.*[103]

2.1 De novo heterocycle synthesis in the Donohoe group

2.1.1 Introduction

The synthesis of substituted heterocycles has been an extremely important area of chemistry. This is because aromatic heterocycles typically appear in a range of natural products and pharmaceutical targets.[104] Furthermore, pyridines in particular, are useful ligands in transition metal chemistry[105] and an interesting area currently being explored is photo-redox catalysis for organic synthesis.[106]

Typically, the syntheses of these heterocycles are performed by modification of a pre-existing aromatic core, with the natural reactivity of the aromatic cores being exploited. More recently however, an important area of research has been focussed around the functionalisation of aromatic carbocycles and aromatic heterocycles beyond traditional electrophilicity or nucleophilicity. As a result of this research, two key areas have emerged:[107,108] Palladium-catalysed cross-coupling methods, which have been used for the functionalisation of a pre-installed carbon−halogen bond, and more recently, metal catalysed functionalisation of the carbon−hydrogen bond, usually aided by a directing group (*Figure **2.1***).

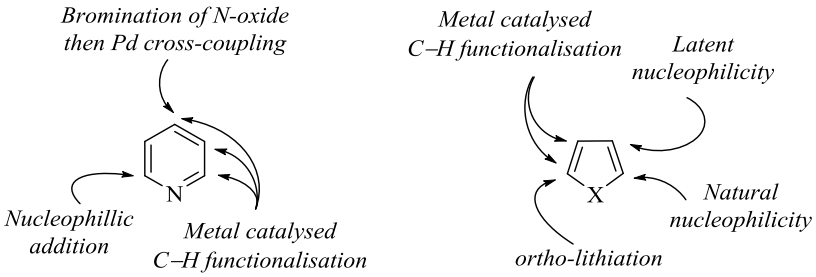
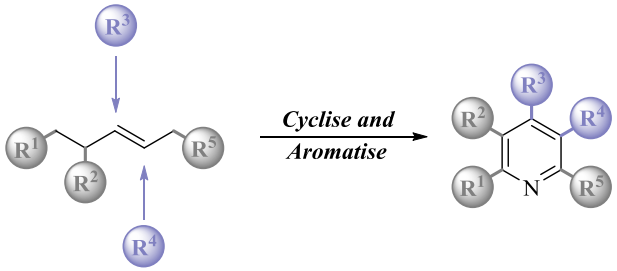


***Figure 2.1** Functionalisation of aromatic heterocycles*

A research theme in the Donohoe laboratory has taken a complementary *de novo* approach to aromatic heterocycle synthesis. This fundamentally implies that these heterocyclic motifs are

designed from small and simple acyclic building blocks, which are then attached to one another using state-of-the-art organic chemistry techniques. Functionalisation of the acyclic core would allow for the introduction of substituents with pre-determined regiochemistry in the resultant heterocycle. Another significant advantage is that it can also provide a way of overcoming the natural reactivity of a heterocycle by functionalising the acyclic core before cyclisation and aromatisation is attempted (*Scheme* ***2.1***). This novel methodology for generating heterocycles was employed with great success by co-workers in the Donohoe laboratory.



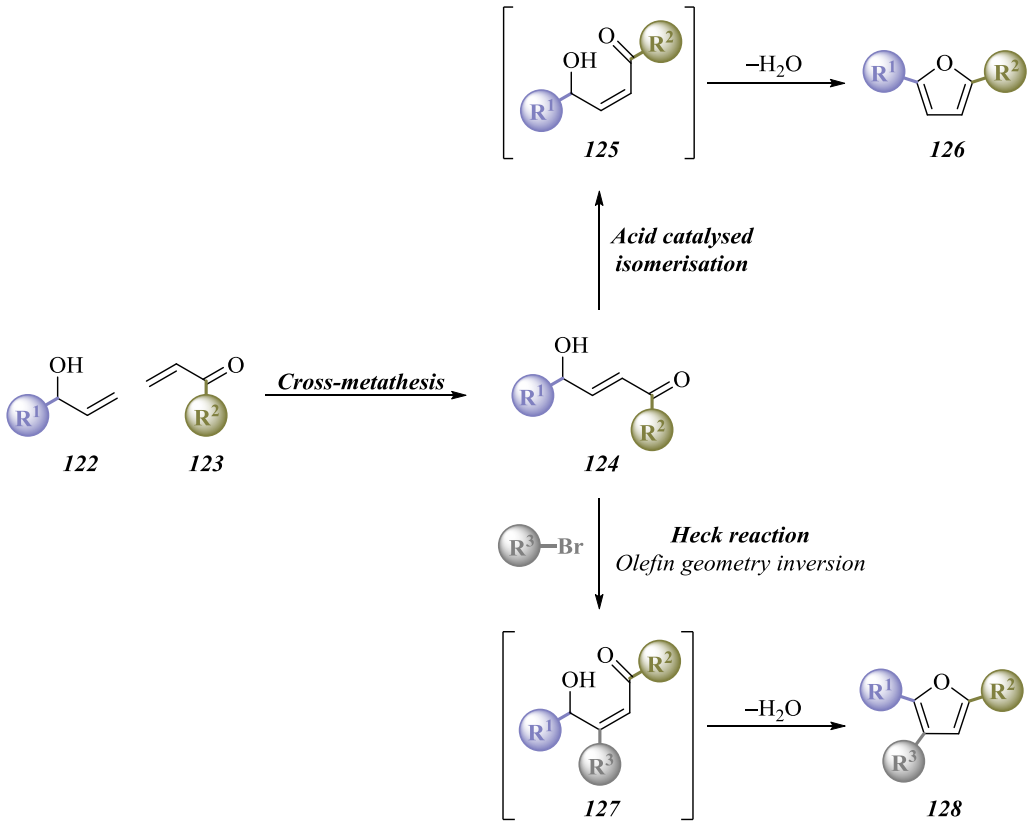
Functionalisation of acyclic building block results in regiocontrolled aromatic heterocycle synthesis

Scheme 2.1 *Concept of the de novo approach to synthesis of substituted pyridines*

2.1.2 De novo furan synthesis (2010)

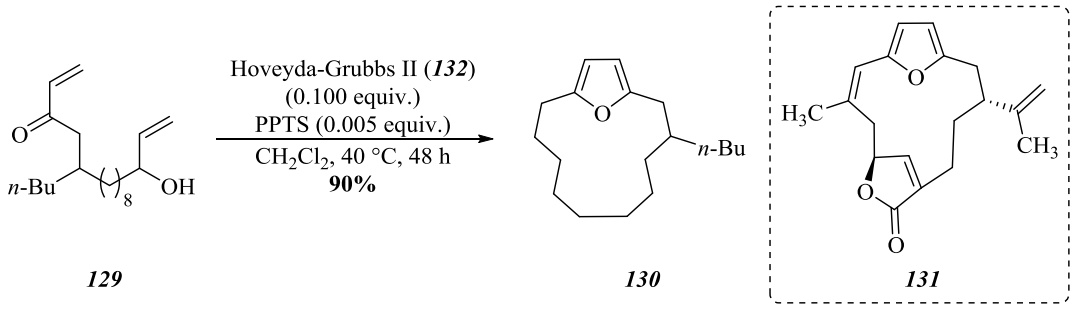
Research conducted in the Donohoe laboratory had previously demonstrated the use of a cross-metathesis reaction protocol in the generation of a range of 2,5-disubstituted furans (*furan* ***126***) and 2,3,5-trisubstituted furans (*furan* ***128***) with a varied scope of substitution.[109] Importantly, the *de novo* approach taken for this synthesis allowed for the incorporation of substituents onto the non-aromatic precursors, which led to specifically defined regiochemistry in the resultant furans (*Scheme* ***2.2***).

The protocol began with the cross-metathesis reaction of *alcohol* ***122*** and *enone* ***123*** to generate *enone* ***124***. *Enone* ***124*** was then either treated with a Brønsted acid to encourage olefin isomerisation, or subjected to a Heck reaction, which has been shown to be effective for the isomerisation of olefins (*Figure* ***2.5****, vide infra*). Subsequent *in situ* dehydration furnished *furan* ***126*** or *furan* ***128*** in good to excellent yields.



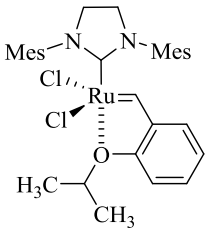
Scheme 2.2 *Synthesis of furans via cross-metathesis reaction protocol*

The (ring-closing) cross-metathesis reaction protocol is exemplified in the synthesis of the core of (+)-(*Z*)-deoxypukalide (***131***)[110] (*Scheme* ***2.3***).



Scheme 2.3 *Synthesis of furan* ***130*** *via ring-closing metathesis*

Diene ***129*** was treated with Hoveyda-Grubbs second generation catalyst (***132***)[111,112] (*Figure* ***2.2***) to furnish *furan* ***130*** in an excellent 90% yield. It was found that the cross-metathesis reaction was tolerant of Brønsted acidic conditions and the presence of pyridinium *para*-toluenesulfonamide allowed for the *in situ* condensation reaction to occur after the (ring-closing) cross-metathesis reaction had completed.

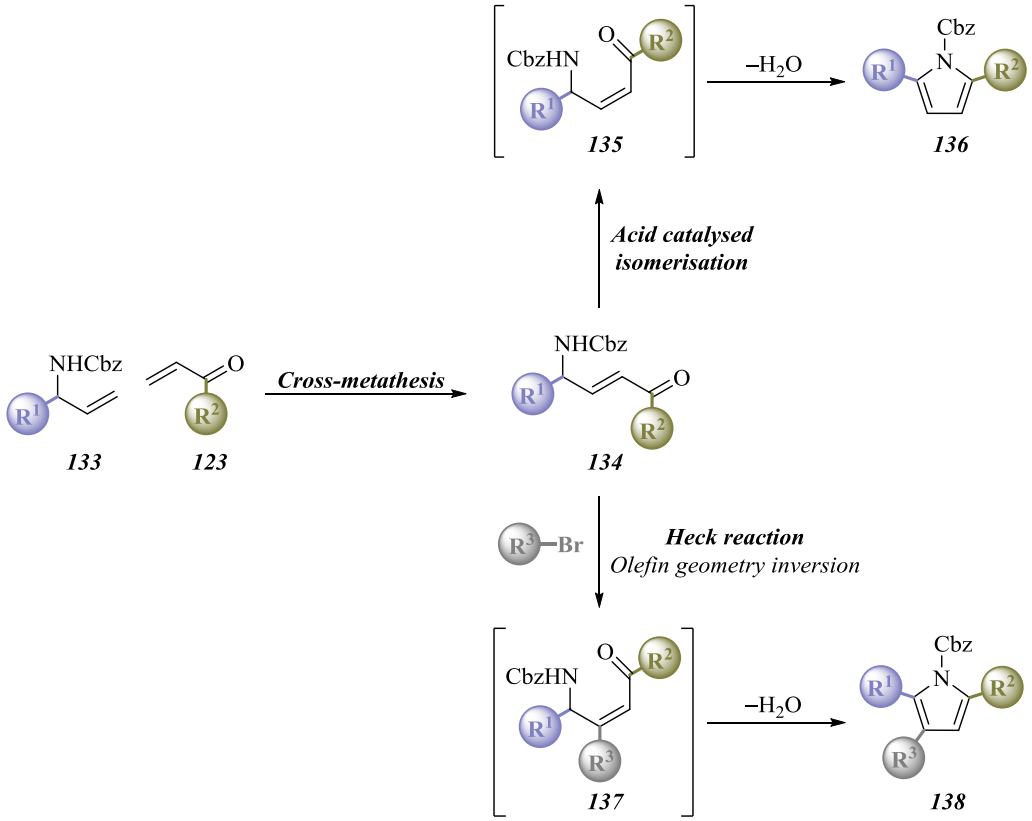


132

Figure 2.2 *Hoveyda-Grubbs second generation catalyst (**132**)*

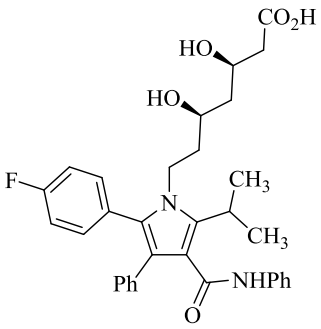
2.1.3 De novo pyrrole synthesis (2010)

The cross-metathesis reaction protocol described for the synthesis of substituted furans was then extended to produce 2,5-disubstituted pyrroles (*pyrrole **136***) and 2,3,5-trisubstituted pyrroles (*pyrrole **138***) (*Scheme **2.4***).[113] The protocol began with the cross-metathesis reaction of *amine **133*** and *enone **123*** to generate *enone **134***. *Enone **134*** was then either treated with a Brønsted acid or under the Heck reaction, to encourage olefin isomerisation and introduce additional functionality. Subsequent *in situ* dehydration furnished *pyrrole **136*** or *pyrrole **138*** in good to excellent yields.



Scheme 2.4 *Synthesis of pyrroles via cross-metathesis reaction protocol*

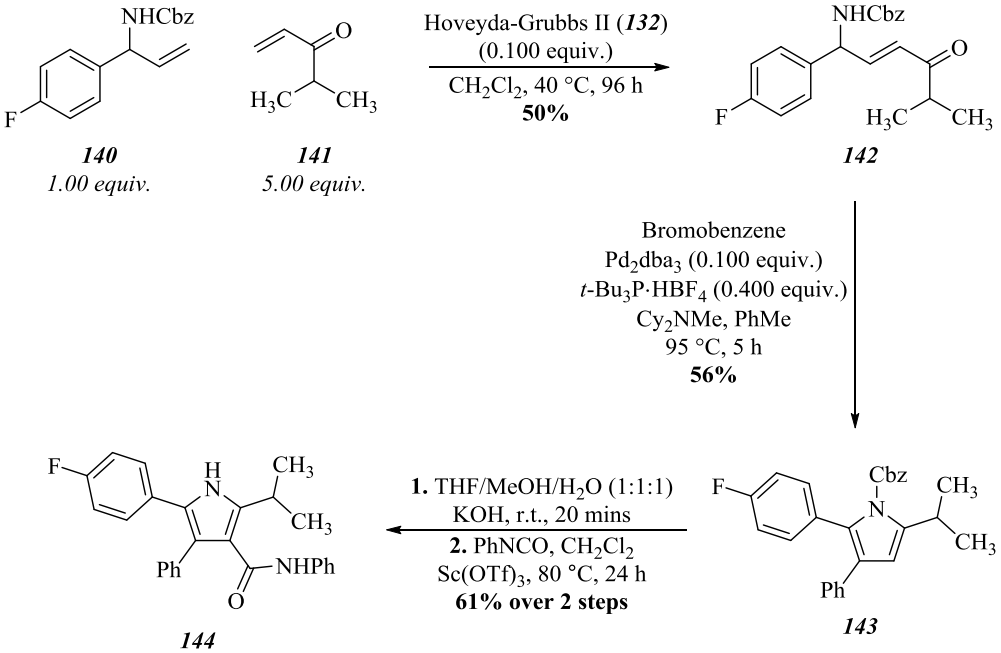
To highlight the utility of this protocol, the synthesis of the pyrrole core of Atorvastatin (***139***)[114] (*Figure* ***2.3***), the largest selling pharmaceutical for the treatment of cholesterol, was attempted.



139

Figure 2.3 *Atorvastatin (**139**)*

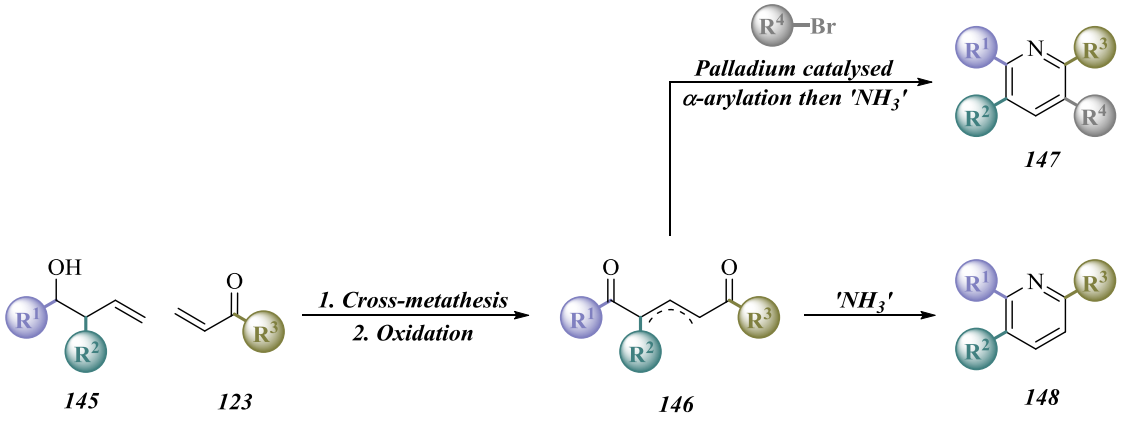
Carbamate ***140*** was treated with Hoveyda-Grubbs second generation catalyst (***132***) and *enone* ***141*** to furnish *enone* ***142*** in 50% yield, with 40% of *carbamate* ***140*** being isolated on termination of the reaction, which could be recycled. The Heck reaction, employing conditions developed by Fu and co-workers,[98] was then used to simultaneously install a phenyl substituent and invert the olefin geometry, and was successfully performed in 56% yield to generate *pyrrole* ***143***. Subsequent deprotection and functionalisation using phenylisocyanate generated *pyrrole* ***144*** in 61% yield over two steps.



Scheme 2.5 *Synthesis of pyrrole* ***144*** *via cross-metathesis/Heck reaction protocol*

2.1.4 First generation de novo pyridine synthesis (2011)

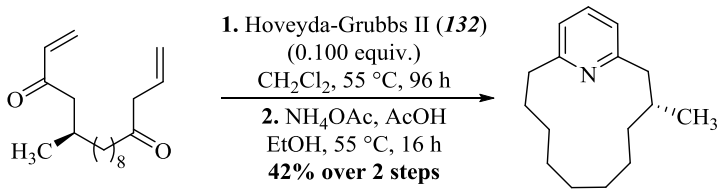
With pyridines being more widely utilised in the pharmaceutical industry than furans or pyrroles, the synthesis of trisubstituted pyridines (*pyridine* ***147***) and tetrasubstituted pyridines (*pyridine* ***148***) was next attempted using the cross-metathesis reaction protocol (*Scheme* ***2.6***).[115]



Scheme 2.6 *Synthesis of pyridines via cross-metathesis reaction protocol*

The protocol began with the cross-metathesis reaction of *alcohol* ***145*** and *enone* ***123*** to generate *diketone* ***146***. *Diketone* ***146*** was then cyclised with an ammonia source, such as ammonium chloride or ammonium acetate to furnish *pyridine* ***147***. *Diketone* ***146*** could also be treated under α-arylation conditions and followed subsequently with an ammonia equivalent to generate *pyridine* ***148***. Interestingly, the presence of acidic α-protons made it difficult to perform a Heck reaction on the olefin and thus α-arylation reactions were observed instead. This presented a major issue with the methodology as it would have been desirable to install functionality at the *C-4* position of the resultant pyridine. Attempts were made to carry out this transformation using the rhodium catalysed conjugate addition of boronic acids, but the conditions were found to be relatively harsh and not suitable for many sensitive functional groups.

The synthesis of a natural product, (*R*)-(+)-muscopyridine (***150***),[116] once again provided a useful testing ground for the methodology. *Diene* ***149*** was treated with Hoveyda-Grubbs second generation catalyst (***132***) in a (ring-closing) cross-metathesis reaction. Ammonium acetate was then added to the reaction mixture to afford (*R*)-(+)-muscopyridine (***150***) in 42% yield over two steps (*Scheme* ***2.7***).

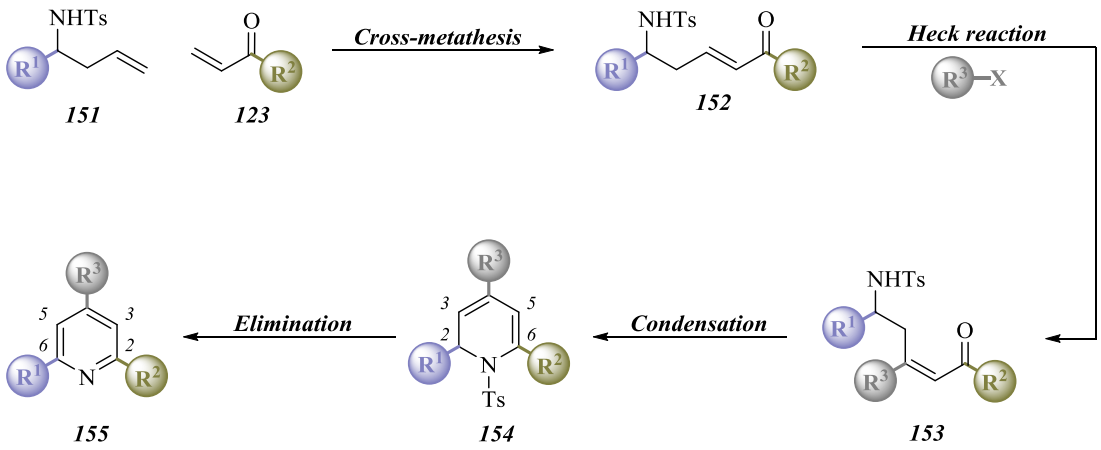


Scheme 2.7 *Synthesis of* (*R*)-(+)-*muscopyridine* ***(150)*** *via ring-closing metathesis*

2.2 Research outline

2.2.1 Second generation de novo pyridine synthesis

A severe limitation of the first generation pyridine synthesis was that *C-4* functionalisation of the resultant pyridine was not readily accessible, although a few attempts had been made through rhodium catalysed conjugate addition of boronic acids. This was of particular interest as direct functionalisation methods, which complement this *de novo* approach, are commonly employed to functionalise the *C-2* and *C-3* positions of the resultant pyridine,[117,118] but there are only limited examples of *C-4* functionalisation.[119] With this in mind, the second generation pyridine synthesis was designed to allow facile access to the *C-4* position of the resultant pyridine, and this was made possible *via* the Heck reaction (*Scheme* ***2.8***).



Scheme 2.8 *Proposed second generation pyridine synthesis via cross-metathesis/Heck reaction protocol*

Sulfonamide ***151*** could be reacted with *enone* ***123*** in a cross-metathesis reaction to generate *enone* ***152***. Subsequent Heck reaction, followed by condensation and elimination of a sulfinate group would generate a range of 2,4,6-trisubstituted pyridines (*pyridine* ***155***). Preliminary studies by

co-workers in the group had shown that it was possible to perform the sequence described above and, in fact, the Heck reaction and condensation reaction could be telescoped into a single-pot. It was discovered that if the substituent at the *C-6* (R^1) position of the resultant pyridine was electron-withdrawing or aromatic, the proton at *C-2* of *dihydropyridine* ***154*** would be readily acidified and the Heck, condensation, and elimination reactions could be performed sequentially in a single-pot. If the substituent at the *C-6* (R^1) position of the resultant pyridine was not electron-withdrawing or aromatic, then the elimination reaction needed to be carried out in a separate step.

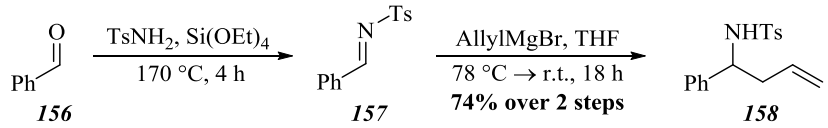
2.2.2 Project aims

The aims of the project were to validate and optimise previous work on the second generation pyridine synthesis and then expand the scope at each position of the resultant 2,4,6-trisubstituted pyridine. This would be achieved by alteration of the precursor sulfonamide (***151***) or enone (***123***) for *C-6* (R^1) or *C-2* (R^2) substituents, respectively. The Heck reaction would also be explored for a range of halides and thus functionalise the *C-4* (R^3) position of the resultant pyridine.

2.3 Optimisation and validation of the second generation pyridine synthesis

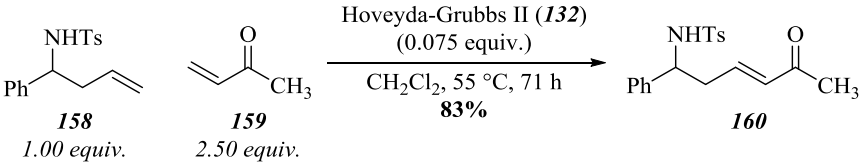
2.3.1 Optimisation of the cross-metathesis reaction

Initial studies were focussed around the optimisation of the cross-metathesis reaction of homoallylic sulfonamides (***151***) with enones (***123***) and this began with the synthesis of *sulfonamide* ***158*** from benzaldehyde (***156***) (*Scheme* ***2.8***). Following a reported literature procedure,[120] benzaldehyde (***156***) and *p*-toluene sulfonamide were heated in the presence of tetraethyl orthosilicate to furnish *imine* ***157*** as a white crystalline solid without the need for further purification. Ethanol was distilled off to ensure full completion of the reaction ($Si(OEt)_4 + 2H_2O \rightarrow SiO_2 + 4EtOH$). *Imine* ***157*** was subsequently reacted with an excess of allyl magnesium bromide to give *sulfonamide* ***158*** in 74% yield over two steps from benzaldehyde (***156***) on a multi-gram scale (*Scheme* ***2.9***). The identity of *sulfonamide* ***158*** was confirmed by the absence of a singlet at 10.01 ppm in the ^{1}H nuclear magnetic resonance (NMR) spectrum and the presence of a quartet (J = 6.5 Hz) at 4.38 ppm and a singlet at 2.37 ppm in the ^{1}H NMR spectrum, which corresponded to $CH_2C\underline{H}NH$ and $ArC\underline{H_3}$, respectively.



Scheme 2.9 *Synthesis of sulfonamide* ***158***

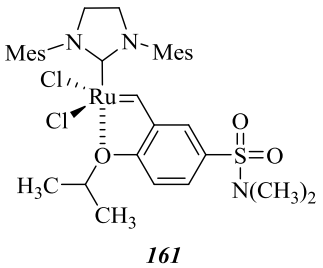
With *sulfonamide* ***158*** in hand, the cross-metathesis reaction with methyl vinyl ketone (***159***) was attempted using Hoveyda-Grubbs second generation catalyst (***132***). Pleasingly, *enone* ***160*** was synthesised in 83% yield, and exclusively as a single geometric isomer as observed by ^{1}H NMR spectroscopy (*Scheme* ***2.10***).



Scheme 2.10 *Synthesis of enone* ***160*** *via cross-metathesis reaction*

The identity of *enone* ***160*** was confirmed by the presence of a signal at 1647 cm^{-1} in the infrared spectrum, which corresponded to the carbonyl stretch. The double-bond geometry was confirmed to be *E* by the diagnostic coupling constant (J = 16.0 Hz) for the olefin protons observed in the ^{1}H NMR spectrum.

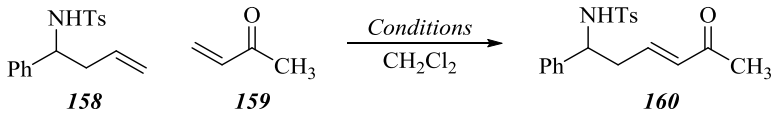
Unfortunately, the cross-metathesis reaction to form *enone* ***160*** required relatively harsh conditions, with the use of 0.075 equivalents of Hoveyda-Grubbs second generation catalyst (***132***), and an extended reaction time of 71 h. Therefore, attempts were made to optimise the conditions for this transformation (*Table* ***2.1***).



161

Figure 2.4 *Zhan 1-B catalyst* ***(161)***

Zhan 1-B catalyst (***161***) (*Figure **2.4***) had been used effectively during the first generation pyridine synthesis (*Scheme **2.6**, vide supra*) however this change led to a disappointing reduction of yield to 70% for this substrate (*Entry 2*). It would be desirable to lower the overall loading of Hoveyda-Grubbs second generation catalyst (***132***) and yields of 74% and 68% were obtained when 0.050 equivalents and 0.030 equivalents were employed, respectively (*Entry 3 and Entry 4*). Altering the reaction temperature had a profound effect, with a reduced yield of 42% obtained after three days at room temperature (*Entry 5*). Promisingly, shortening of the reaction time only led to a small reduction in yield to 76% (*Entry 6*). The stoichiometry of methyl vinyl ketone (***159***) had a large effect on the reaction with yields of 56% and 88% observed when 1.00 equivalent and 5.00 equivalents were employed, respectively (*Entry 7 and Entry 8*). This, however, presented another issue in using potentially toxic and volatile substrates in large excess.



158 ***159*** ***160***

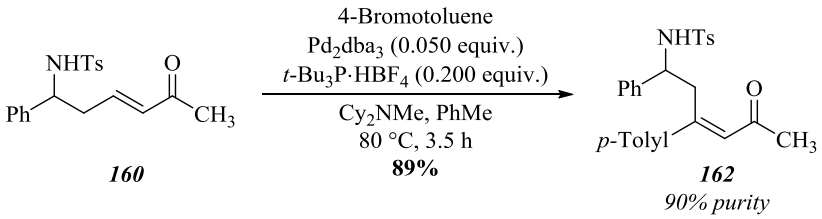
Entry	*Catalyst*	*Methyl vinyl ketone (159)*	*Temperature*	*Time*	*Yield*
1	Hoveyda-Grubbs II (***132***) (0.075 equiv.)	2.50 equiv.	55 °C	3 d	83%
2	Zhan 1-B (***161***) (0.075 equiv.)	2.50 equiv.	55 °C	3 d	70%
3	Hoveyda-Grubbs II (***132***) (0.050 equiv.)	2.50 equiv.	55 °C	3 d	74%
4	Hoveyda-Grubbs II (***132***) (0.030 equiv.)	2.50 equiv.	55 °C	3 d	68%
5	Hoveyda-Grubbs II (***132***) (0.075 equiv.)	2.50 equiv.	r.t.	3 d	42%
6	Hoveyda-Grubbs II (***132***) (0.075 equiv.)	2.50 equiv.	55 °C	1 d	76%
7	Hoveyda-Grubbs II (***132***) (0.075 equiv.)	1.00 equiv.	55 °C	3 d	56%
8	Hoveyda-Grubbs II (***132***) (0.075 equiv.)	5.00 equiv.	55 °C	2 d	88%
9	Hoveyda-Grubbs II (***132***) (0.050 equiv.)	5.00 equiv.	55 °C	2 d	84%
10	Hoveyda-Grubbs II (***132***) (0.030 equiv.)	5.00 equiv.	55 °C	4 d	83%

Table 2.1 *Optimisation of the cross-metathesis reaction*

The hypotheses for the requirement of a large excess of methyl vinyl ketone (***159***) were twofold: Firstly, methyl vinyl ketone (***159***) has been found to polymerise when heated for prolonged periods of time. A large excess was therefore essential to ensure it could engage in a cross-metathesis reaction. Secondly, some evidence of methyl vinyl ketone homodimerisation was observed. Even though the homodimers of type two olefins are known to form slowly, the homodimers themselves are sparingly consumed during the cross-metathesis reaction, and hence a large quantity of methyl vinyl ketone (***159***) is required to counteract this effect.[121] Nevertheless, with an increase in yield observed with a large excess of methyl vinyl ketone (***159***), a reduction in the loading of Hoveyda-Grubbs second generation catalyst (***132***) to 0.050 equivalents or 0.030 equivalents was possible and *enone* ***159*** was furnished in yields of 84% and 83%, respectively (*Entry 9 and Entry 10*).

2.3.2 Step-wise synthesis of pyridines via Heck/condensation/elimination protocol

With a range of conditions for the cross-metathesis having been screened, studies were then focused on the synthesis of *pyridine* ***169*** from *enone* ***160*** utilising the Heck/condensation/elimination protocol.



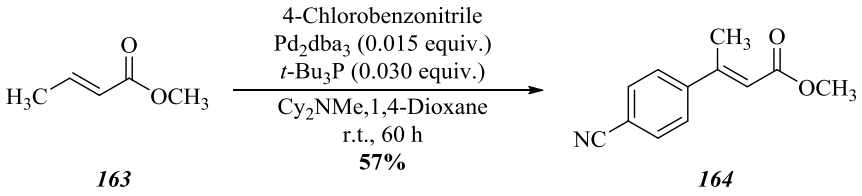
Scheme 2.11 *Synthesis of enone* ***162*** *via Heck reaction*

Enone ***160*** was subjected to Heck conditions similar to those developed by Fu and co-workers,[98] which utilised tris(dibenzylideneacetone)dipalladium and tri-*tert*-butylphosphonium tetrafluoroborate, an air stable precursor of tri-*tert*-butylphosphine (*Chapter* ***1.3.5****, vide supra*), as the catalytic system (*Scheme* ***2.11***). *Enone* ***162*** was isolated in 89% yield, although a small amount (10% by ^{1}H NMR analysis) of inseparable olefin regio/geometric isomers were thought to contaminate *enone* ***162***, even after repeated flash-column chromatography. This was not a major concern as it was hypothesised that the double-bond regioisomer impurities might equilibrate under

the subsequent Brønsted acid condensation conditions used to furnish *dihydropyridine* ***168***. It was also hypothesised that unless the minor geometric isomer could isomerise under the Brønsted acid condensation conditions, this impurity could be removed after purification.

The identity of *enone* ***162*** was confirmed by the absence of a double triplet (J = 16.0, 7.0 Hz) at 6.54 ppm and a doublet (J = 16.0 Hz) at 5.99 ppm in the ^{1}H NMR spectrum, which corresponded to the olefin protons present in *enone* ***160***. Further confirmation was obtained by the presence of a singlet at 6.51 ppm in the ^{1}H NMR spectrum, which corresponded to the olefin proton. The *E*-geometry of the double-bond was inferred from nuclear Overhauser effect (nOe) based NMR experiments performed during previous studies,[109] observed from the proposed mechanism of *syn-carbopalladation* during the Heck reaction, and from analogous nOe based NMR experiments conducted during later studies on the Heck reactions of β-substituted vinyl Weinreb amides (*Figure* ***3.4***, *vide infra*).

Furthermore, this inversion of olefin geometry has been described previously in the literature. For example, Fu and co-workers have shown that treatment of methyl crotonate (***163***) with 4-chlorobenzonitrile in the presence of tris(dibenzylideneacetone)dipalladium and tri-*tert*-butylphosphine furnished *ester* ***164*** in 57% yield (*Scheme* ***2.12***).[96]



163 ***164***

Scheme 2.12 *Example of olefin geometry inversion during the Heck reaction*

The mechanism for the olefin geometry inversion can be proposed (*Figure* ***2.5***). After completion of *oxidative addition*—the first step of the catalytic cycle—*enone* ***152*** was subjected to *syn-carbopalladation*, which allowed for the *syn*-addition of palladium and the R^3 group across the olefin to generate *intermediate* ***166***. Similarly, a mechanistic requirement of the Heck reaction dictates that *β-H elimination* of palladium hydride must occur in a *syn*-fashion, and thus rotation to *intermediate* ***167*** occurs before generation of *enone* ***153***, the desired Heck reaction product.

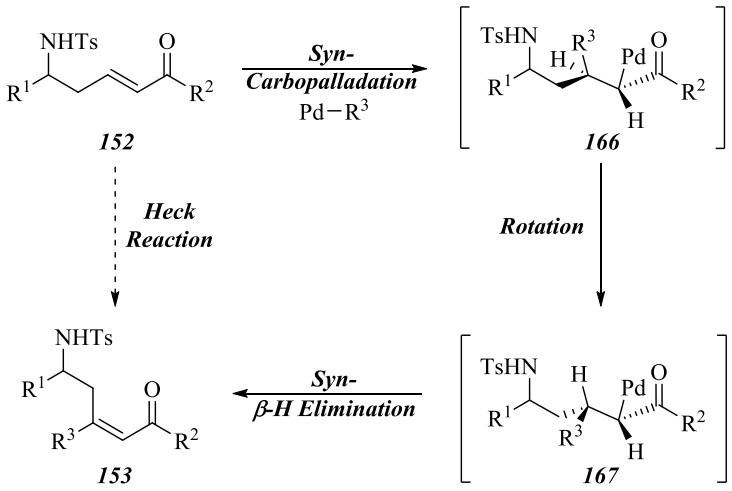
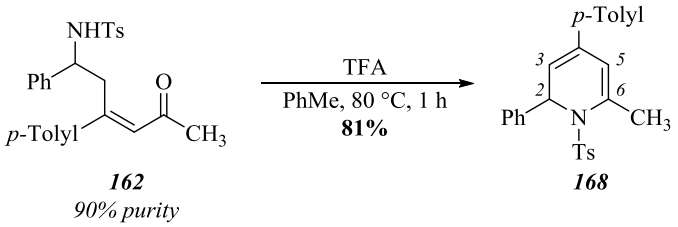


Figure 2.5 *Inversion of double-bond geometry during syn-carbopalladation*

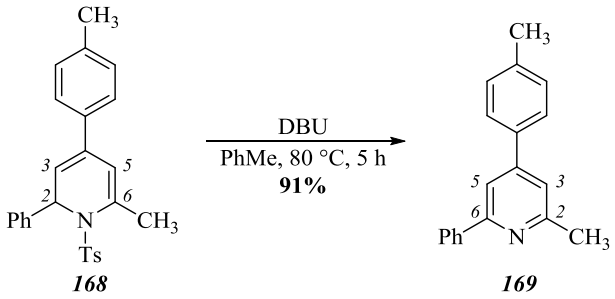
With the ketone and sulfonamide portions of *enone* ***162*** (90% purity) being *cis*-disposed, condensation with trifluoroacetic acid afforded *dihydropyridine* ***168*** in 81% yield, although an inseparable unknown impurity, with peaks at ~0.1 ppm (^{1}H NMR) and ~0.5 ppm (^{13}C NMR), was thought to contaminate *dihydropyridine* ***168***, even after repeated flash-column chromatography (*Scheme* ***2.13***). This impurity has been observed in a small selection of compounds synthesised during the metatheses projects. The olefin regio/geometric isomers observed during the Heck reaction to synthesise *enone* ***162*** were no longer present, indicating that they had isomerised and reacted, or were left on completion of the reaction and removed during purification.



Scheme 2.13 *Synthesis of dihydropyridine* ***168*** *via condensation*

The identity of *dihydropyridine* ***168*** was confirmed by the absence of a singlet at 201.0 ppm in the ^{13}C NMR spectrum and a signal at 1668 cm^{-1} in the infrared spectrum, which corresponded to the carbonyl stretch and the carbon atom in the carbonyl group, respectively, both present in *enone* ***162***. Further confirmation was obtained by the presence of two mutually coupled doublets (J = 6.5 Hz) at 6.02 ppm and 5.75 ppm in the ^{1}H NMR spectrum, which corresponded to C$\underline{H}^{3}$ and C$\underline{H}^{2}$, respectively.

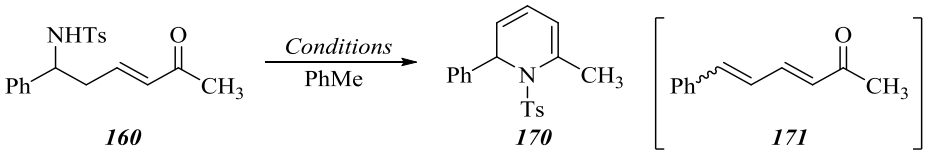
The final step of the protocol to generate the resultant 2,4,6-trisubstituted pyridine was the elimination of the sulfinate group from *dihydropyridine* ***168*** by treatment with 1,8-diazabicycloundec-7-ene. This reaction furnished *pyridine* ***169*** in 91% yield, or 66% yield over three steps from *enone* ***160*** (*Scheme* ***2.14***).



Scheme 2.14 *Synthesis of pyridine* ***169*** *via elimination*

The identity of *pyridine* ***169*** was confirmed by the absence of a doublet at 5.75 ppm in the ^{1}H NMR spectrum, which corresponded to C$\underline{H}^{2}$ present in *dihydropyridine* ***168***, and the presence of a doublet (J = 1.0 Hz) at 7.74 ppm in the ^{1}H NMR spectrum, which corresponded to Ar$\underline{H}^{5}$. The regiochemistry of *pyridine* ***169*** was inferred from the mechanism of the transformation, which is based upon the *de novo* approach. Furthermore, X-ray crystallographic studies were later used to elucidate the structure of *pyridine* ***175*** (*Figure* ***2.6***, *vide infra*), which confirmed the substitution pattern around the aromatic ring.

2.3.3 Removing substitution at the C-4 of the pyridine



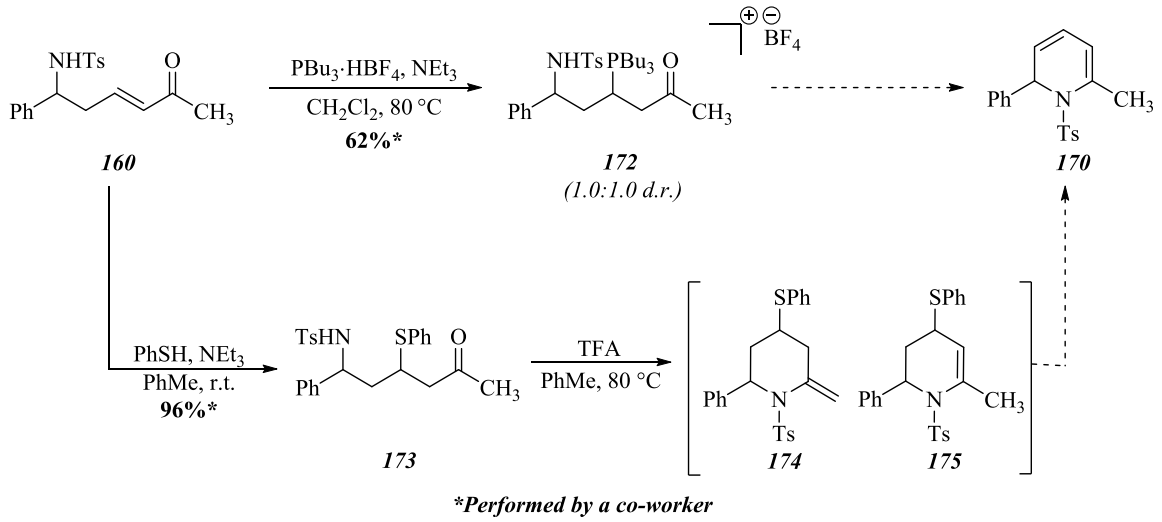
Entry	*Reagent*	*Temperature*	*Time*	*Result*
1	TFA (1.00 equiv.)	80 °C	3 h	Recovered ***160*** + trace ***171***
2	TFA (1.00 equiv.)	110 °C	4 h	Recovered ***160*** + trace ***171***
3	$AlMe_3$ (1.00 equiv.)	40 °C	1 h	Recovered ***160*** + trace ***171***

Table 2.2 *Screen of condensation conditions*

The main focus of the second generation pyridine synthesis was to install functionality at the *C-4* position of the resultant 2,4,6-trisubstituted pyridine, however, the opportunity to leave the *C-4* position unsubstituted was briefly explored for completion. It was hypothesised that an olefin isomerisation would be required to allow the condensation step to occur, however, it was hoped that the use of acid would suffice to affect this transformation (*Table* ***2.2***).

Treatment of *enone* ***160*** with trifluoroacetic acid at 80 °C led largely to the recovery of *enone* ***160*** with trace amounts of sulfonamide elimination product, *diene* ***171***, observed in the ^{1}H NMR spectrum and low-resolution mass spectrum of the crude reaction mixture (*Entry 1*). *Dihydropyridine* ***170*** was not observed. When the reaction was performed at 110 °C, *enone* ***160*** was observed again with trace amounts of *diene* ***171*** present in the reaction mixture (*Entry 2*). A similar reaction mixture distribution was seen under Lewis acid promoted condensation conditions, with the use of trimethylaluminium (*Entry 3*). These unsuccessful results provide evidence to show that it is likely that the minor olefin geometric isomer observed during the isolation of *enone* ***160*** would not condense under the Brønsted acid condensation conditions.

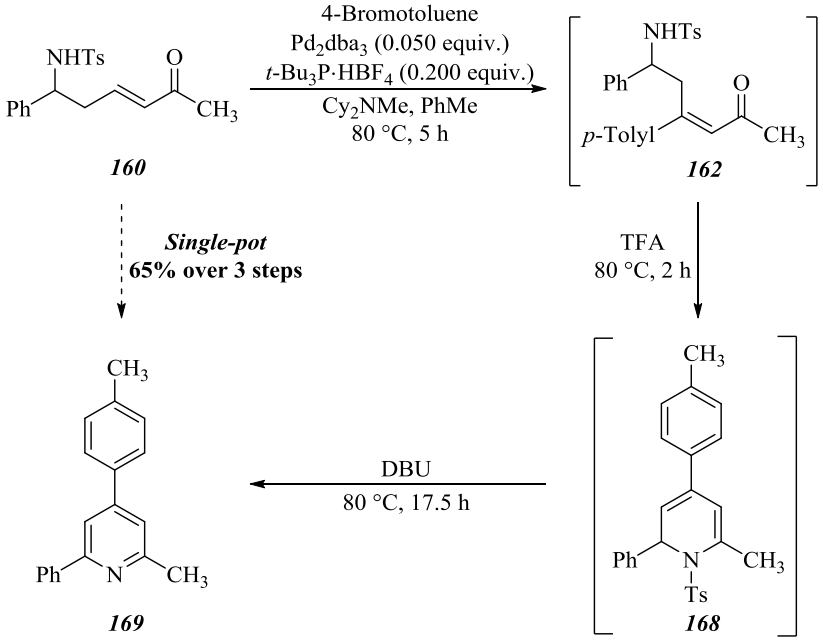
Co-workers in the group attempted to use a conjugate addition approach to generate 2,6-disubstituted pyridines by facilitating alkene isomerisation. Treatment of *enone* ***160*** with tributylphosphine generated *phosphonium* ***172*** in 62% yield, however attempts to effect the cyclisation proved unsuccessful. Similarly, *enone* ***160*** was treated with thiophenol which furnish *sulfide* ***173*** in an excellent 96% yield. Exposing *sulfide* ***173*** to trifluoroacetic acid led to a mixture of *exo-cyclic enamine* ***174*** and *endo-cyclic enamine* ***175*** which decomposed when exposed to prolonged reaction conditions (*Scheme* ***2.15***)



Scheme 2.15 *Conjugate addition approach to 2,6-disubstituted pyridines*

2.3.4 Single-pot synthesis of pyridines via Heck/condensation/elimination protocol

After the step-wise synthesis had been explored, studies were focussed on attempting the single-pot Heck/condensation/elimination protocol beginning with the synthesis of *pyridine* ***169*** (*Scheme* ***2.16***). As described previously, the single-pot procedure was made possible by the presence of the phenyl substituent, which acidified the neighbouring proton in *dihydropyridine* ***168*** and thus aided in its elimination (*Chapter* ***2.2.1***, *vide supra*).



Scheme 2.16 *Synthesis of pyridine* ***169*** *via Heck/condensation/elimination protocol*

Enone ***160*** was treated with 4-bromotoluene under Fu's Heck conditions to generate *enone* ***162***. When the Heck reaction was judged to be complete by thin-layer chromatography analysis, trifluoroacetic acid was added to the reaction mixture to allow for the formation of *dihydropyridine* ***168*** under condensation conditions. When the condensation reaction was judged to be complete by thin-layer chromatography analysis, excess 1,8-diazabicycloundec-7-ene was added to encourage the elimination of the sulfinate group. *Pyridine* ***169*** was furnished in a pleasing 65% yield over three steps (*c.f. 66% yield for step-wise approach*) with the spectroscopic data of *pyridine* ***169*** identical to the step-wise approach. The importance of reaction time during the single-pot Heck/condensation/elimination protocol cannot be understated, and low yields were found when reaction mixtures were heated for prolonged periods of time. In particular, disappointing yields of *pyridine* ***169*** were observed when carrying out the Heck reaction for greater than 6 h, presumably due to the increased chance of palladium hydride mediated isomerisation of the Heck product and/or *enone* ***160***.

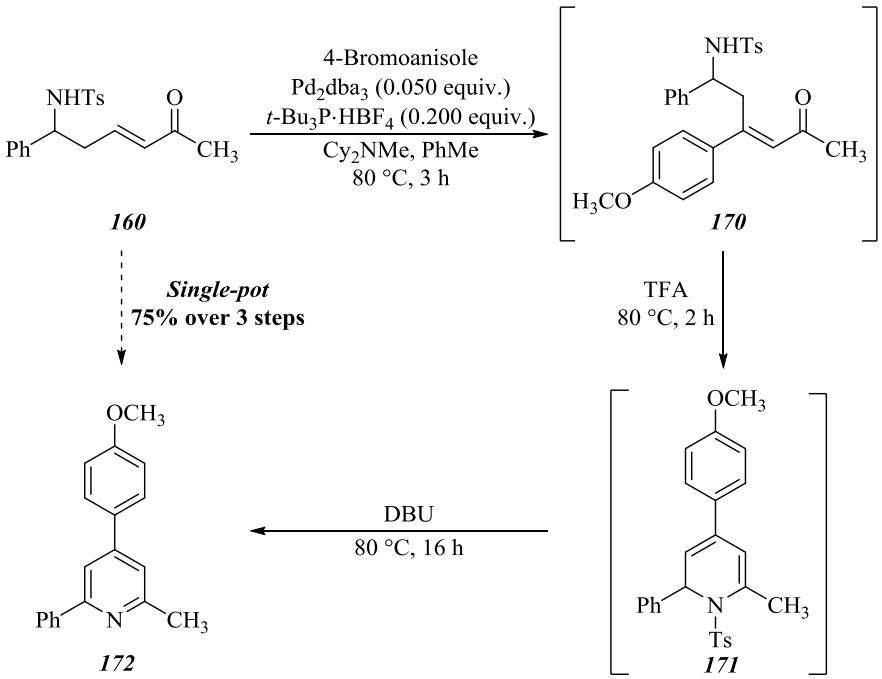
2.4 Expansion of the scope at the C-4 (R^3) position

2.4.1 Accessing the C-4 (R^3) position of the 2,4,6-trisubstituted pyridines

The next part of the project focussed on expansion of the scope of substitution at the *C-4* (R^3) position of the resultant 2,4,6-trisubstituted pyridines. The substitution at this position was accessed by altering the aryl, vinyl, or alkyl bromide used in the Heck component of the single-pot Heck/condensation/elimination protocol. Preliminary studies had so far revealed that the synthesis of *pyridine* ***169*** was possible with the use of the single-pot Heck/condensation/elimination protocol, but the opportunity to add electron-rich, electron-deficient, biaryl, heteroaromatic, vinyl, and aliphatic substituents had yet to be explored. To this end, a range of aryl, heteroaryl, vinyl, and alkyl bromides were employed during the Heck component of the single-pot Heck/condensation/elimination protocol.

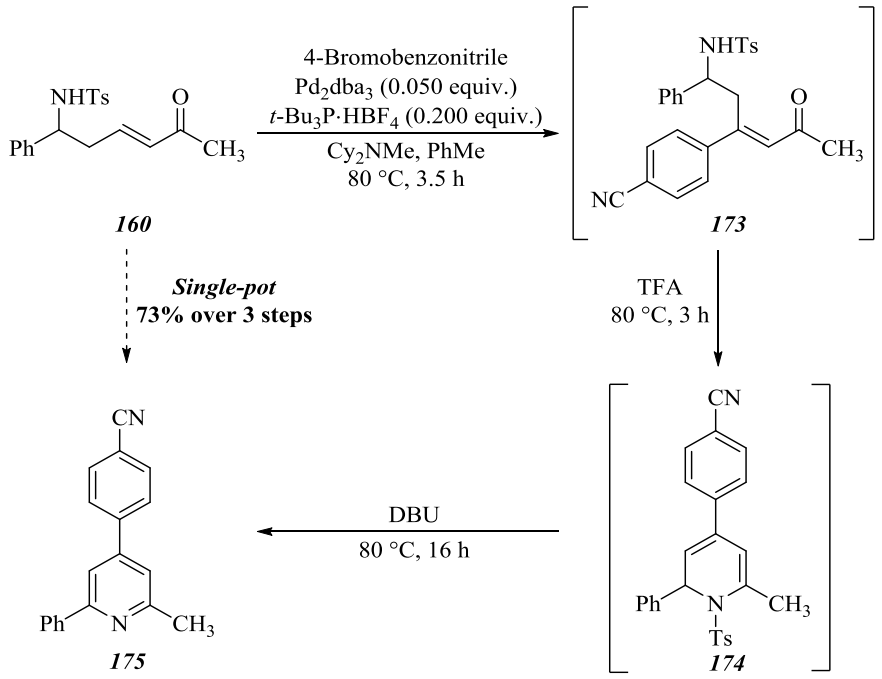
2.4.2 Electron-rich and electron-deficient substituents

Enone ***160*** was treated with 4-bromoanisole under the single-pot Heck/condensation/elimination protocol to furnish *pyridine* ***172*** in 75% yield over three steps from *enone* ***160*** (*Scheme* ***2.17***).



Scheme 2.17 *Synthesis of pyridine* ***172*** *via single-pot Heck/condensation/elimination protocol*

The identity of *pyridine* ***172*** was confirmed by the presence of a singlet at 3.88 ppm in the ^{1}H NMR spectrum, which corresponded to ArOC$\underline{H}_3$.

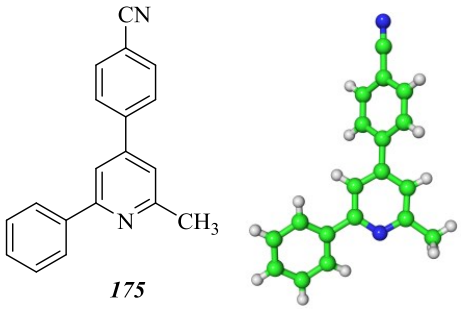


Scheme 2.18 *Synthesis of pyridine* ***175*** *via single-pot Heck/condensation/elimination protocol*

With installation of electron-rich substituents successfully demonstrated, studies focussed on the installation of electron-deficient substituents. *Enone* ***160*** was treated with 4-bromobenzonitrile under

the single-pot Heck/condensation/elimination protocol to furnish *pyridine* ***175*** in 73% yield over three steps (*Scheme* ***2.18***).

The identity of *pyridine* ***175*** was confirmed by the presence of a signal at 2228 cm^{-1} in the infrared spectrum, which corresponded to the nitrile stretch. The regiochemistry of *pyridine* ***175*** was confirmed by X-ray crystallographic studies (*Figure* ***2.6***), and this crystal structure was employed to infer the regiochemistry of other pyridines made by the Heck/condensation/elimination protocol.

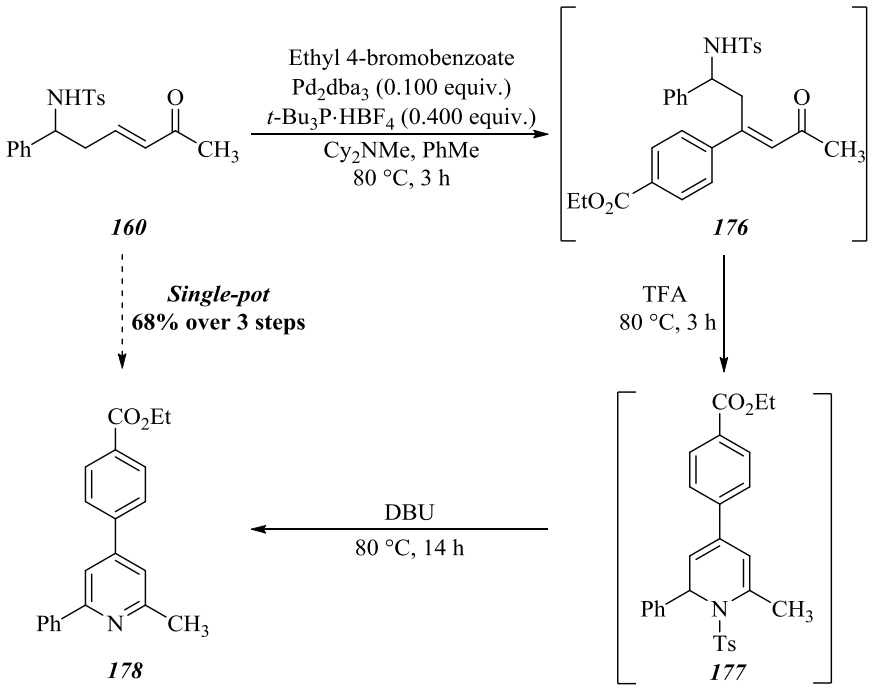


175

Figure 2.6 *X-ray crystallographic studies of pyridine* ***175***

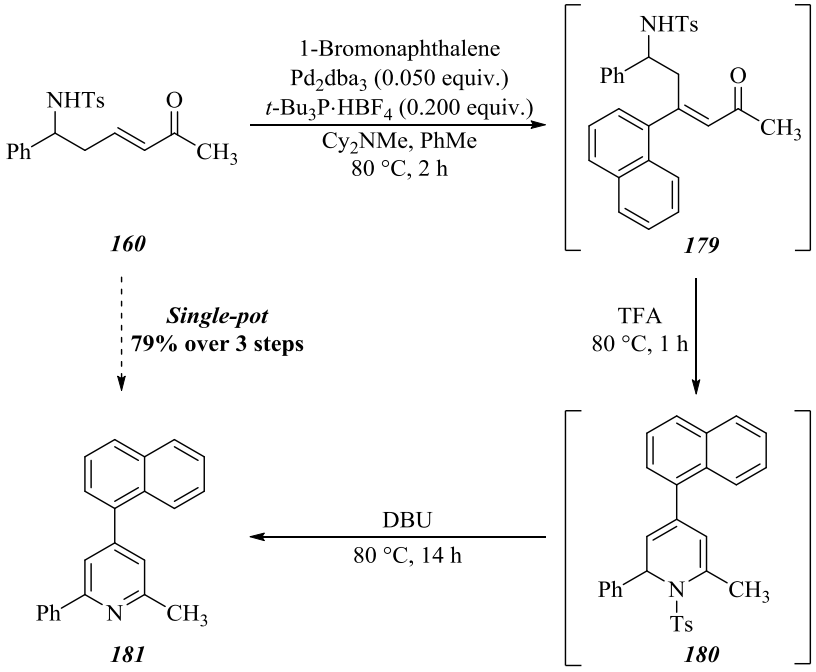
Initial attempts to treat *enone* ***160*** with ethyl 4-bromobenzoate under the single-pot Heck/condensation/elimination protocol proved challenging and *pyridine* ***178*** was isolated in a 28% yield over three steps from *enone* ***160***. Careful observation of the reaction mixture by thin-layer chromatography indicated that a significant quantity of *enone* ***160*** still remained after extended reaction times. Pleasingly, it was found that an increase in the amount of tris(dibenzylideneacetone)dipalladium and tri-*tert*-butylphosphonium tetrafluoroborate from 0.050 equivalents and 0.200 equivalents to 0.100 equivalents and 0.400 equivalents, respectively solved this issue by encouraging the Heck component of the protocol to go towards completion and *pyridine* ***178*** was isolated in a pleasing 68% yield over three steps from *enone* ***160*** (*Scheme* ***2.19***).

The identity of *pyridine* ***178*** was confirmed by the presence of a singlet at 166.2 ppm in the ^{13}C NMR spectrum and a signal at 1715 cm^{-1} in the infrared spectrum which corresponded to the carbon atom in the carbonyl group and the carbonyl stretch, respectively, present in the ester.



Scheme 2.19 *Synthesis of pyridine* ***178*** *via single-pot Heck/condensation/elimination protocol*

2.4.3 Biaryl substituents



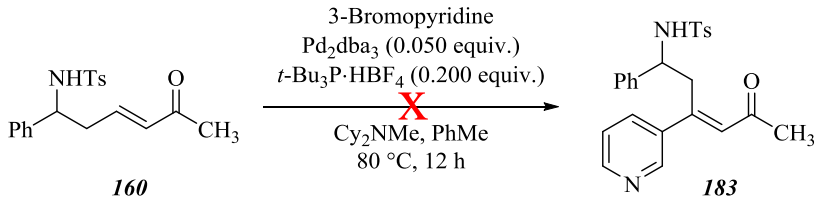
Scheme 2.20 *Synthesis of pyridine* ***181*** *via single-pot Heck/condensation/elimination protocol*

Enone ***160*** was treated with 1-bromonaphthalene under the single-pot Heck/condensation/elimination protocol to furnish *pyridine* ***181*** in 79% yield over three steps from *enone* ***160*** (*Scheme* ***2.20***). The identity of *pyridine* ***181*** was confirmed by the presence of a signal in

the high-resolution mass spectrum at 296.1437 ($\Delta = -1.0$ ppm), which corresponded to the $[M+H]^+$ ion of *pyridine* ***181***.

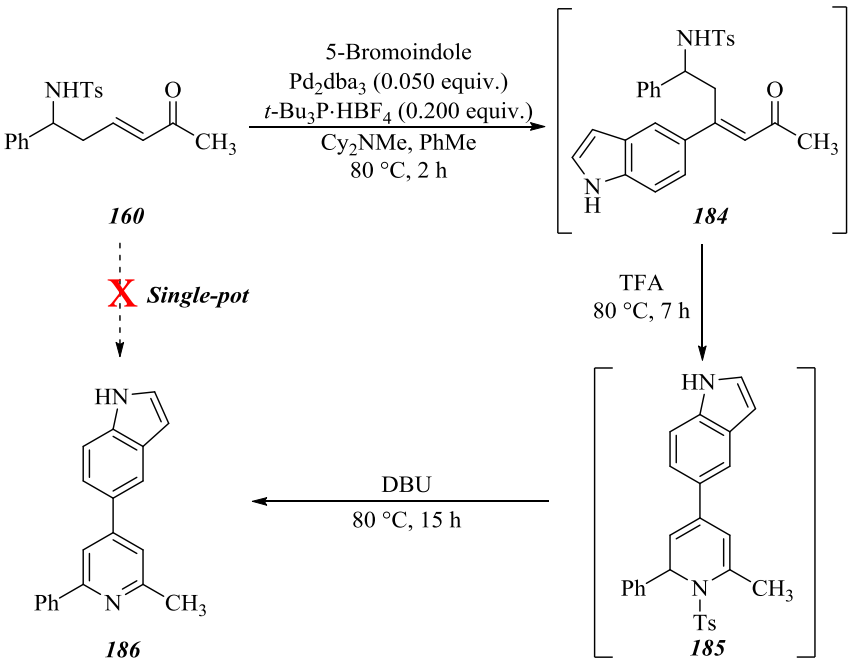
2.4.4 Heteroaromatic substituents

The synthesis of bipyridine substrates would prove very useful and so studies focussed on installing heterocycles such as pyridines during the Heck component of the single-pot Heck/condensation/elimination protocol. Initial attempts to treat *enone* ***160*** with 3-bromopyridine under the single-pot Heck/condensation/elimination protocol proved unsuccessful, with *enone* ***160*** being observed after the Heck reaction in the ^{1}H NMR spectrum of the crude reaction mixture, therefore the last two steps of the protocol were not attempted. The nitrogen atom in acrylonitrile is thought to coordinate[122] to the active palladium species and it is hypothesised that this coordination deactivates the catalytic system thus halting the Heck reaction. It is possible that a similar type of catalyst deactivation by the nitrogen atom in 3-bromopyridine may have been present in this system as well (*Scheme* ***2.21***).



Scheme 2.21 *Failed synthesis of enone* ***183***

Using the knowledge gained from the failed synthesis of *enone* ***183***, another nitrogen based heterocycle was chosen for the Heck component of the single-pot Heck/condensation/elimination protocol. 5-Bromoindole (***187***) was selected as it was hypothesised that the nitrogen lone pair would be delocalised within the aromatic ring and be less likely to coordinate and disrupt the catalytic cycle of the Heck reaction. Disappointingly however, treatment of *enone* ***160*** with 5-bromoindole under the single-pot Heck/condensation/elimination protocol gave *pyridine* ***186*** in trace quantities as observed from the ^{1}H NMR spectrum of the crude reaction mixture (*Scheme* ***2.22***). Furthermore, analysis of the product distribution from the crude reaction mixture was not possible due to extensive decomposition.

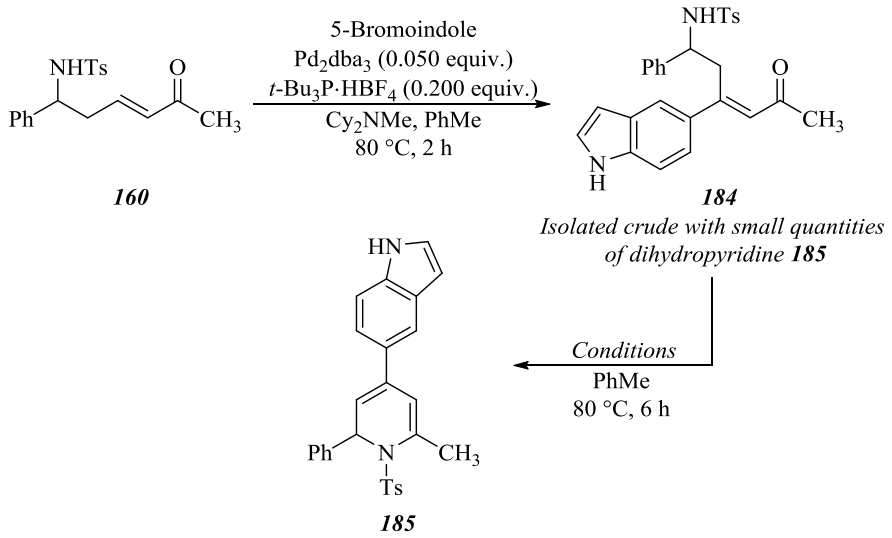


Scheme 2.22 *Failed synthesis of pyridine* ***186***

Subsequent studies into this reaction focussed upon isolation of the problematic step and so the single-pot Heck/condensation/elimination protocol of *enone* ***160*** with 5-bromoindole was performed without the final elimination. Observation of the reaction mixture by thin-layer chromatography analysis indicated sufficient completion of the Heck component to generate *enone* ***184***. Subsequent addition of trifluoroacetic acid, however, led to extensive decomposition. The ^{1}H NMR spectrum of the crude reaction mixture confirmed the observation made by thin-layer chromatography analysis. It was hypothesised that the final elimination component was not likely to be problematic, and that the decomposition is likely to occur during the acidic condensation component, although decomposition during the Heck component could not be completely ruled out.

To investigate further, the Heck component of the single-pot Heck/condensation/elimination protocol was performed in isolation. Investigation of the Heck reaction revealed that *enone* ***160*** had been mostly consumed during the Heck component, as observed by thin-layer chromatography analysis, and *enone* ***184*** was observed in the ^{1}H NMR spectrum of the crude reaction mixture. Surprisingly, a small amount of *dihydropyridine* ***185*** was also observed, and in an attempt to encourage the formation of *dihydropyridine* ***185***, a subsequent attempt at the Heck reaction was left for 5 days, which led to extensive decomposition. The crude reaction mixture of *enone* ***184*** was

divided into equal portions and treated with a range of condensation conditions in an attempt to generate *dihydropyridine* ***185*** (*Table* ***2.3***). Previous studies had shown that decomposition was observed when using a strong Brønsted acid such as trifluoroacetic acid ($pK_a = 0.23$), and so a milder acid was chosen. Pyridinium *p*-toluene sulfonamide ($pK_a = 5.2$) had been used previously for condensation reactions to generate furans (*Scheme* ***2.3****, vide supra*) and so it was utilised for the condensation of *enone* ***184*** to *dihydropyridine* ***185***. Similar to trifluoroacetic acid, large amounts of decomposition was observed in the ^{1}H NMR spectrum of the crude reaction mixture (*Entry 1*). A base-mediated condensation was attempted using potassium carbonate but this led to recovery of *enone* ***184*** (*Entry 2*). Finally, 3 Å molecular sieves were employed to induce the condensation reaction by removal of water, but this also led to recovery of *enone* ***184*** (*Entry 3*).

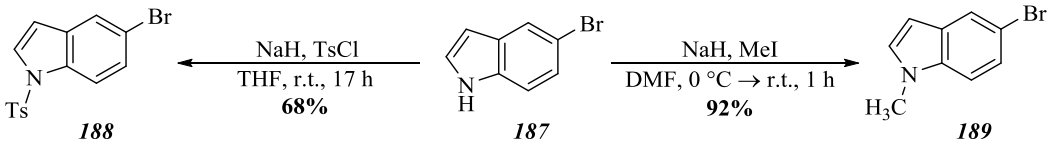


Entry	*Reagent*	*Result*
1	PPTS (1.00 equiv.)	Decomposition
2	K_2CO_3 (1.00 equiv.)	Recovered ***184***
3	3 Å Molecular Sieves	Recovered ***184***

Table 2.3 *Screen of condensation conditions*

It was hypothesised that the free hydrogen on the indole may be interfering with the single-pot Heck/condensation/elimination protocol. In order to investigate this effect, installation of a *p*-toluenesulfonate group and a methyl group were attempted. Following a reported literature procedure,[123] 5-bromoindole (***187***) was treated with sodium hydride and *p*-toluenesulfonyl chloride

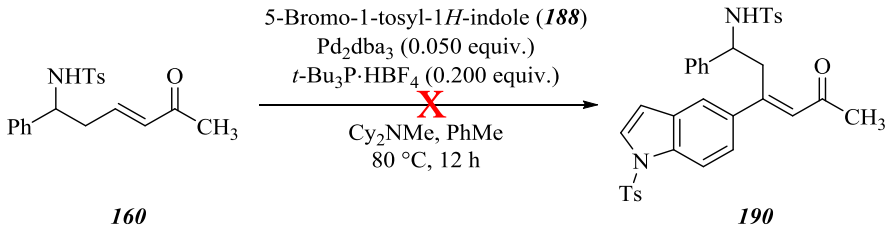
in tetrahydrofuran. This reaction furnished *indole* ***188*** in 68% yield. Similarly, following a reported literature procedure,[124] 5-bromoindole (***187***) was treated with sodium hydride and methyl iodide in *N,N*-dimethylformamide, which furnished *indole* ***189*** in 92% yield (*Scheme* ***2.23***).



Scheme 2.23 *Synthesis of indole* ***188*** *and indole* ***189***

The identity of *indole* ***188*** was confirmed by the presence of a singlet at 2.34 ppm in the ^{1}H NMR spectrum, which corresponded to Ar$C\underline{H_3}$. The identity of *indole* ***189*** was confirmed by the presence of a singlet at 3.77 ppm in the ^{1}H NMR spectrum, which corresponded to $NC\underline{H_3}$. Further confirmation was obtained when the spectroscopic data were found to be consistent with those reported in the literature for both *indole* ***188***[125] and *indole* ***189***.[126]

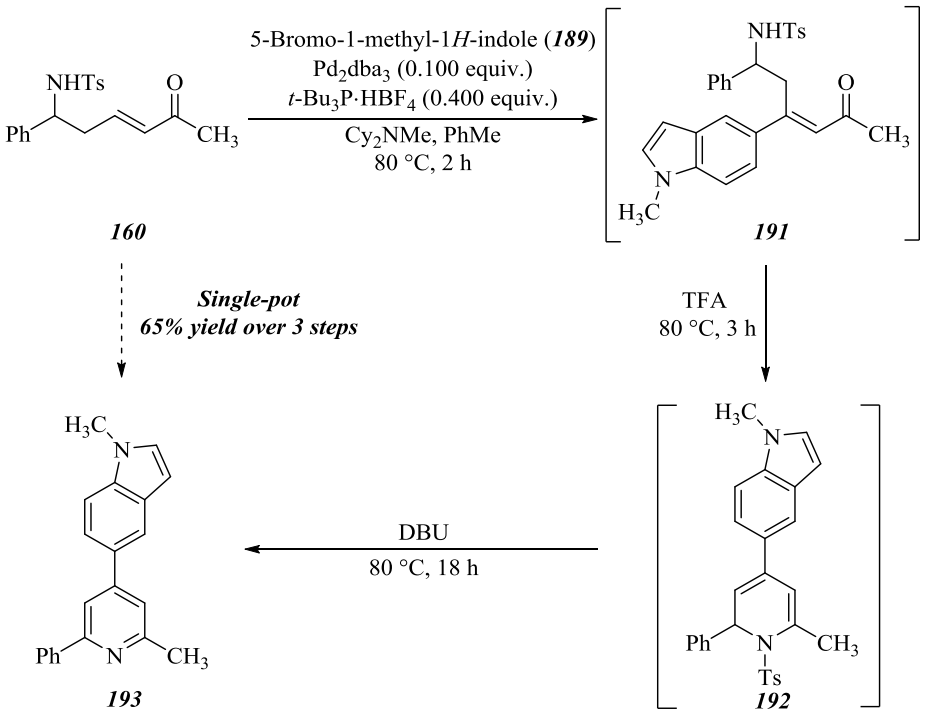
With *indole* ***188*** and *indole* ***189*** in hand, the single-pot Heck/condensation/elimination was attempted. Disappointingly, treatment of *enone* ***160*** with *indole* ***188*** led only to recovery of *enone* ***160*** and decomposition after the Heck reaction as observed in the ^{1}H NMR spectrum of the crude reaction mixture (*Scheme* ***2.24***).



Scheme 2.24 *Failed synthesis of enone* ***190***

Encouragingly, treatment of *enone* ***160*** with *indole* ***189*** in the single-pot Heck/condensation/elimination protocol led to a 15% yield of *pyridine* ***193*** over three steps from *enone* ***160***. *Enone* ***160*** was also recovered from the reaction mixture indicating that the Heck component had not gone to full conversion. Increasing the amounts of tris(dibenzylideneacetone)dipalladium and tri-*tert*-butylphosphonium tetrafluoroborate from 0.050 equivalents and 0.200 equivalents to 0.100 equivalents and 0.400 equivalents, respectively, resulted

in the isolation of *pyridine* ***193*** in a pleasing 65% yield over three steps from *enone* ***160*** (*Scheme* ***2.25***).



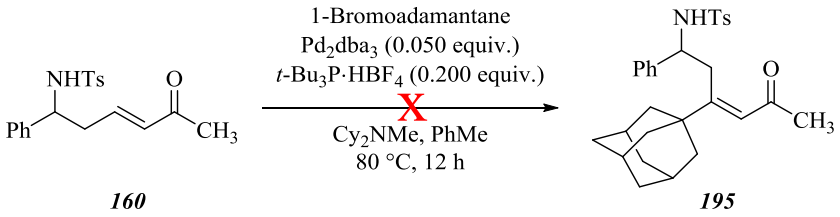
Scheme 2.25 *Synthesis of pyridine* ***193*** *via single-pot Heck/condensation/elimination protocol*

The identity of *pyridine* ***193*** was confirmed by the presence of a singlet at 3.86 ppm in the ^{1}H NMR spectrum, which corresponded to NC$\underline{H}_3$. Further confirmation was obtained by the presence of a signal in the high-resolution mass spectrum at 296.1543 (Δ = +1.3 ppm), which corresponded to the $[M+H]^+$ ion of *pyridine* ***193***.

2.4.5 Sp^3 and vinyl substituents

A range of different aromatic substituents had been successfully installed onto the *C-4* (R^3) position of the resultant 2,4,6-trisubstituted pyridines, and now studies focused on the installation of more unusual substituents. It would be interesting to incorporate sp^2-sp^3 couplings into the methodology but these substrates typically are unsuccessful in the Heck reaction due to rapid *syn-β-hydride elimination* after *oxidative addition* of palladium into the carbon–halogen bond has taken place. It was thought, however, that this issue could be circumvented by the use of a substrate that did not have protons at the β-position and thus could not undergo *syn-β-hydride elimination*. 1-Bromoadamantane was chosen as a suitable substrate for investigation in the Heck reaction.

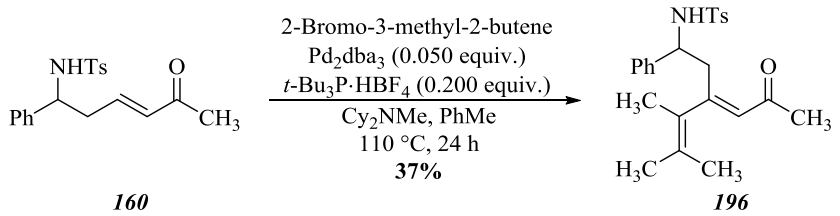
Treatment of *enone* ***160*** with 1-bromoadamantane under Fu's Heck conditions led to recovery of *enone* ***160*** and 1-bromoadamantane, as observed from the ^{1}H NMR of the crude reaction mixture, which suggested that 1-bromoadamantane was too sterically hindered for palladium insertion to occur, although it could be hypothesised that after *oxidative addition* had taken place, the palladium intermediate is too sterically hindered to coordinate *enone* ***160*** and undergo *syn-carbopalladation* (*Scheme* ***2.26***).



160 ***195***

Scheme 2.26 *Failed synthesis of enone* ***195***

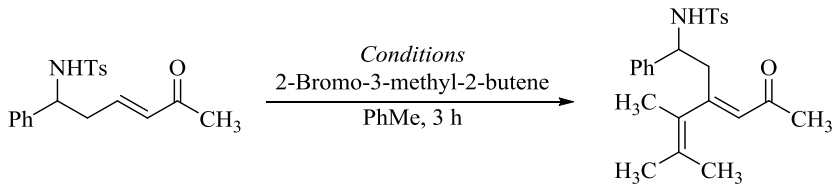
With the failed attempt to add sp^3 substituents to the *C-4* (R^3) position of the resultant pyridine, focus was diverted onto performing Heck reactions with vinyl bromides. Surprisingly, intermolecular vinyl Heck reactions are not commonly employed and where they are reported, they are typically describing protocols for cyclic vinyl bromides/triflates or intramolecular Heck reactions. To this end, *enone* ***160*** was treated with 2-bromo-3-methyl-2-butene under Fu's Heck conditions, which furnished *enone* ***196*** in 37% yield (*Scheme* ***2.27***).



160 ***196***

Scheme 2.27 *Synthesis of enone* ***196*** *via Heck reaction*

The identity of *enone* ***196*** was confirmed by the presence of a singlet at 6.21 ppm in the ^{1}H NMR spectrum, which corresponded to the olefin proton. Further confirmation was found by the presence of nine protons between 1.83–1.74 ppm, which corresponded to three alkenyl C$\underline{H_3}$ groups.



160 ***196***

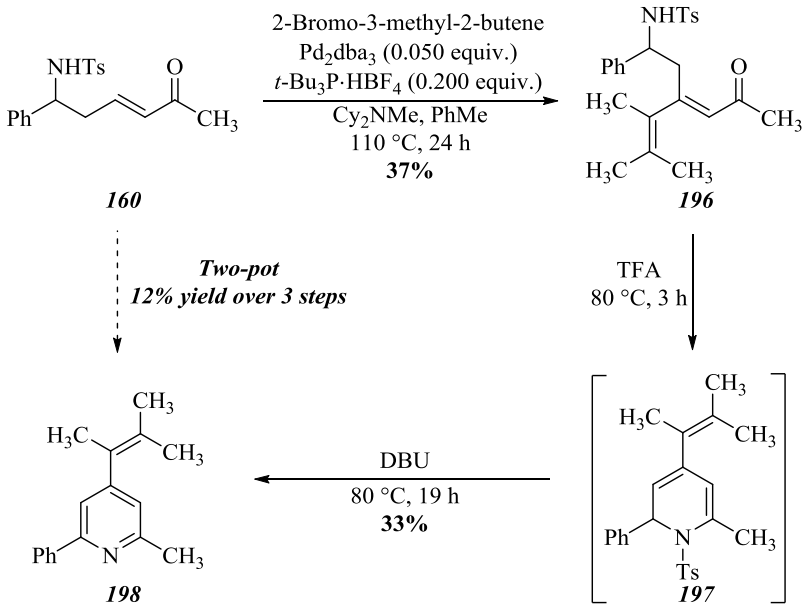
Entry	*Catalyst*	*Ligand*	*Base*	*Temperature*	*Conversion (^{1}H NMR)*
1	Pd_2dba_3 (0.050 equiv.)	*t*-$Bu_3P{\cdot}HBF_4$ (0.200 equiv.)	Cy_2NMe (1.50 equiv.)	110 °C	20%
2	Pd_2dba_3 (0.075 equiv.)	*t*-$Bu_3P{\cdot}HBF_4$ (0.300 equiv.)	Cy_2NMe (1.50 equiv.)	110 °C	20%
3	$PdCl_2$(dtbpf) (0.100 equiv.)	N/A	Cy_2NMe (1.50 equiv.)	110 °C	15%
4	Pd_2dba_3 (0.050 equiv.)	*t*-$Bu_3P{\cdot}HBF_4$ (0.200 equiv.)	Cy_2NMe (2.50 equiv.)	110 °C	24%
5	Pd_2dba_3 (0.050 equiv.)	*t*-$Bu_3P{\cdot}HBF_4$ (0.200 equiv.)	*i*-Pr_2NEt (1.50 equiv.)	110 °C	18%
6	Pd_2dba_3 (0.050 equiv.)	*t*-$Bu_3P{\cdot}HBF_4$ (0.200 equiv.)	K_3PO_4 (1.50 equiv.)	110 °C	14%
7	Pd_2dba_3 (0.050 equiv.)	*t*-$Bu_3P{\cdot}HBF_4$ (0.200 equiv.)	Cs_2CO_3 (1.50 equiv.)	110 °C	17%
8	Pd_2dba_3 (0.050 equiv.)	*t*-$Bu_3P{\cdot}HBF_4$ (0.200 equiv.)	*t*-BuONa (1.50 equiv.)	110 °C	11%
9	Pd_2dba_3 (0.050 equiv.)	*t*-$Bu_3P.HBF_4$ (0.200 equiv.)	Cy_2NMe (1.50 equiv.)	80 °C	22%

Table 2.4 *Optimisation of the intermolecular acyclic vinyl Heck reaction*

Despite obtaining a low yield of *enone* ***196***, it was pleasing to note that intermolecular acyclic vinyl Heck reactions could be performed. In an attempt to improve this yield, a range of different conditions were explored (*Table* ***2.4***). Similar conditions to those utilised for the Heck reaction above (*Scheme* ***2.27***) were found to give 20% conversion as measured in the ^{1}H NMR spectrum (*Entry 1*). The remainder of the material was largely composed of recovered *enone* ***160***. Increasing the quantities of tris(dibenzylideneacetone)dipalladium and tri-*tert*-butylphosphonium tetrafluoroborate to 0.075 equivalents and 0.300 equivalents, respectively, led to no change in conversion (*Entry 2*). With no change in conversion observed when the catalyst and ligand stoichiometry was altered, [1,1′-bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II), a bulky, bidentate palladium catalyst that has been used in a range of cross-coupling reactions was utilised. Unfortunately, a decrease in conversion to 15% was observed (*Entry 3*). Promisingly, an increase in

the quantity of *N,N*-dicyclohexylmethylamine to 2.50 equivalents gave a small improvement with a 24% conversion obtained (*Entry 4*). Furthermore, alteration of the base to *N,N*-diisopropylethylamine, potassium phosphate, caesium carbonate, or sodium *tert*-butoxide all led to a decrease in conversion (*Entries 5−8*). Lastly, a decrease in temperature to 80 °C had little effect with a conversion of 22% obtained after 3 h (*Entry 9*). Disappointingly, attempts to increase the yield of the acyclic vinyl Heck reaction proved unsuccessful and due to their limited reports in the literature, it was concluded that vinyl halides are less reactive substrates for the Heck reaction than their aryl halide counterparts.

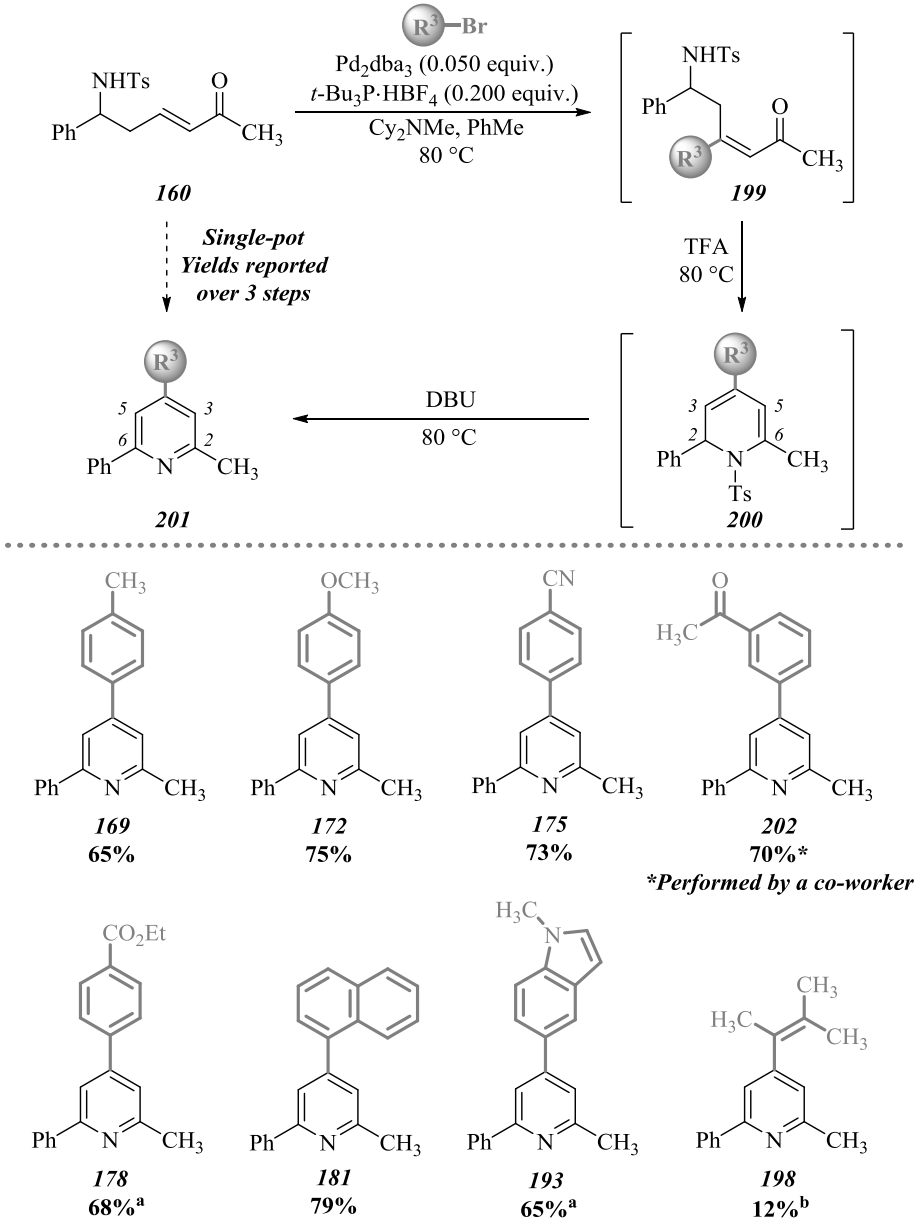
With the knowledge that the formation of *enone* ***196*** was now possible, the single-pot Heck/condensation/elimination protocol to generate *pyridine* ***198*** was attempted using *enone* ***160*** and 2-bromo-3-methyl-2-butene. Unfortunately, the reaction mixture proved too difficult to purify due to the presence of a large amount of side-products generated during the course of the protocol. It was decided that splitting the protocol into the Heck component and the condensation/elimination component may be beneficial to solve these issues. Pleasingly, this solution proved successful and treatment of *enone* ***196*** with trifluoroacetic acid and subsequently with 1,8-diazabicycloundec-7-ene furnished *pyridine* ***198*** in 33% yield, or 12% yield over three steps from *enone* ***160*** (*Scheme* ***2.28***).



Scheme 2.28 *Synthesis of pyridine* ***198*** *via two-pot Heck/condensation/elimination protocol*

The identity of *pyridine* ***198*** was confirmed by the absence of a signal at 1670 cm^{-1} in the infrared spectrum, which corresponded to the carbonyl group in *enone* ***160***. Further confirmation was obtained by the presence of a signal in the high-resolution mass spectrum at 238.1592 (Δ = −0.84 ppm), which corresponded to the $[M+H]^+$ ion of *pyridine* ***198***.

2.4.6 Summary



Scheme 2.29 *Scope of the Heck component in the single-pot Heck/condensation/elimination protocol.* [a] *Pd_2dba_3 (0.100 equiv.) and t-Bu_3P·HBF_4 (0.400 equiv.) used in Heck component.* [b] *Protocol carried out in two pots and Heck component carried out separately at 110 °C.*

In summary, *enone* ***160*** was treated with a range of aryl bromides and vinyl bromides in the Heck component of the single-pot Heck/condensation/elimination protocol to generate *pyridine* ***201***. These pyridines all differ by their substitution at the *C-4* (R^3) position, which is introduced during the Heck component. The synthesis began by reacting *enone* ***160*** under Fu's Heck conditions[98] to generate *enone* ***199***.

When the Heck reaction was judged to be complete by thin-layer chromatography analysis, trifluoroacetic acid was added to the reaction mixture to allow for the formation of *dihydropyridine* ***200*** under condensation conditions. When the condensation reaction was judged to be complete by thin-layer chromatography analysis, excess 1,8-diazabicycloundec-7-ene was added to encourage the elimination of the sulfinate group to generate 2,4,6-trisubstituted *pyridine* ***201***. The successful syntheses of eight different 2,4,6-trisubstituted pyridines with varying *C-4* (R^3) substitution are described (*Scheme* ***2.29***).

Using this protocol, it was possible to install electron-neutral (*pyridine* ***169***), electron-rich (*pyridine* ***172***), and electron-deficient (*pyridine* ***175****, pyridine* ***202****, and pyridine* ***178***) substituents in excellent yields over three steps from *enone* ***160***. Pleasingly, the generation of pyridines with biaryl (*pyridine* ***181***) or heteroaromatic (*pyridine* ***193***) substituents was also possible, however attempts to install vinyl (*pyridine* ***198***) substituents proved challenging and the developed methodology currently works optimally when introducing aryl substituents at *C-4* (R^3)

2.5 Expansion of the scope at the C-6 (R^1) and C-2 (R^2) position

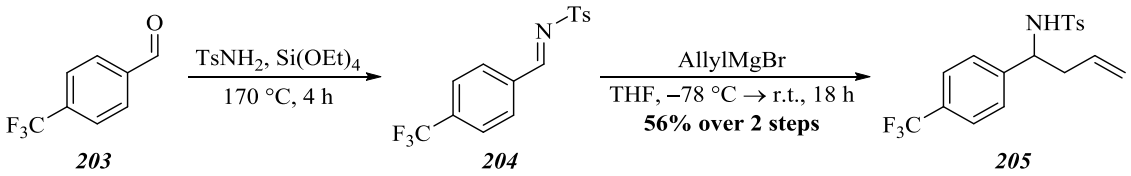
2.5.1 Accessing the C-6 (R^1) and C-2 (R^2) positions of the 2,4,6-trisubstituted pyridines

After exploring the scope at the *C-4* (R^3) position of the resultant pyridine, it was also important to assess the scope at the *C-6* (R^1) and *C-2* (R^2) positions of the pyridine, which were accessed from substitution of the homoallylic sulfonamide precursor and enone precursor, respectively. The precursor alkenes were reacted in the presence of Hoveyda-Grubbs second generation catalyst (***132***) in a cross-metathesis reaction. The resultant enone was then subjected to the single-pot Heck/condensation/elimination protocol to generate a range of 2,4,6-trisubstituted pyridines. The

synthesis of various homoallylic sulfonamide precursors and enone precursors was attempted using this protocol.

2.5.2 Scope at the C-6 (R^1) position: Electron-deficient substituents

Co-workers in the group had shown that it was possible to generate pyridines with electron-rich substitution or biaryl substitution at the *C-6* (R^1) position (*Scheme* ***2.45***, *vide infra*), however, no attempts had been made to install electron-deficient substituents or heteroaromatic substituents. To this end, it was decided that addition of a *p*-trifluoromethylbenzene would be appropriate, providing the necessary scope for the methodology as well as the opportunity to add significant functionality relevant to the pharmaceutical industry.

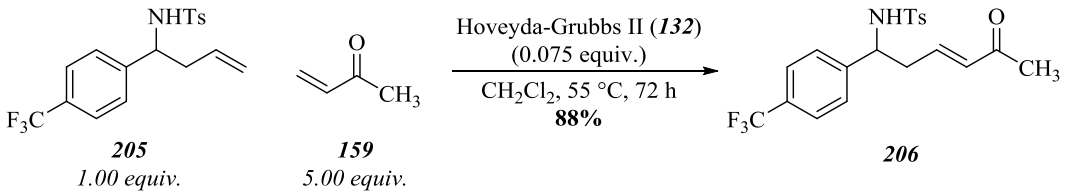


203 ***204*** ***205***

Scheme 2.30 *Synthesis of sulfonamide* ***205***

Studies began with the synthesis of *sulfonamide* ***205*** from 4-(trifluoromethyl)benzaldehyde (***203***) (*Scheme* ***2.30***). 4-(Trifluoromethyl)benzaldehyde (***203***) and *p*-toluene sulfonamide were heated in the presence of tetraethyl orthosilicate to furnish *imine* ***204*** as a white crystalline solid without the need for further purification. *Imine* ***204*** was subsequently reacted with an excess of allyl magnesium bromide to give *sulfonamide* ***205*** in 56% yield over two steps from 4-(trifluoromethyl)benzaldehyde (***203***) on a multi-gram scale. The identity of *sulfonamide* ***205*** was confirmed by the absence of a singlet at 10.12 ppm in the ^{1}H NMR spectrum and the presence of three quartets at 129.5 ppm ($^2J_{C–F} = 32$ Hz), 125.2 ppm ($^3J_{C–F} = 4$ Hz), and 124.0 ppm ($^1J_{C–F} = 272$ Hz) in the ^{13}C NMR spectrum, which corresponded to the carbon atoms *ipso* and *ortho* to CF_3, and $\underline{C}F_3$, respectively.

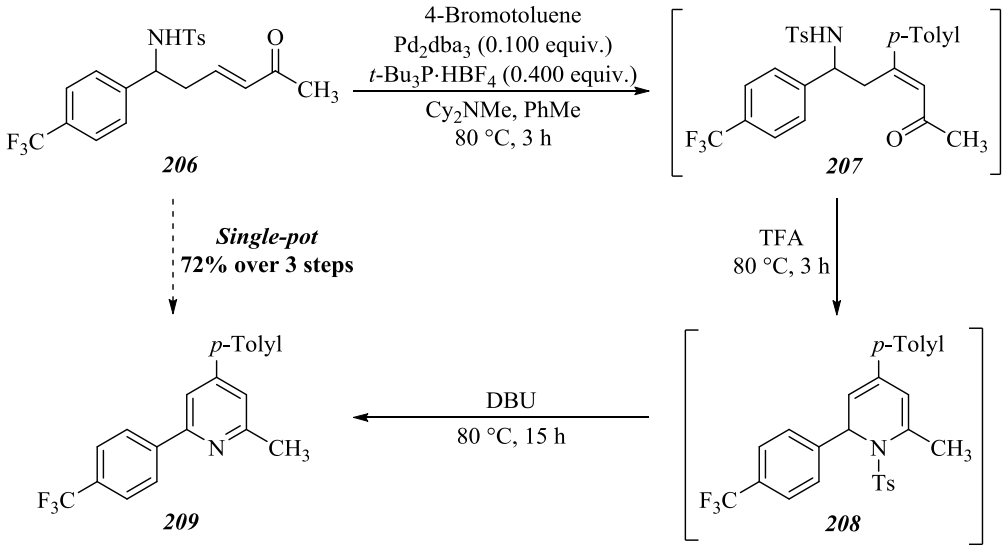
With *sulfonamide* ***205*** in hand, the cross-metathesis reaction with methyl vinyl ketone (***159***) was attempted using Hoveyda-Grubbs second generation catalyst (***132***). Pleasingly, *enone* ***206*** was generated in 88% yield after 72 h, and exclusively as a single geometric isomer as observed by ^{1}H NMR spectroscopy (*Scheme* ***2.31***). However, this reaction required the use of 5.00 equivalents of methyl vinyl ketone (***159***).



Scheme 2.31 *Synthesis of enone* ***206*** *via cross-metathesis reaction*

The identity of *enone* ***206*** was confirmed by the presence of a singlet at 198.1 ppm in the ^{13}C NMR spectrum, which corresponded to the carbon atom in the carbonyl group. The double-bond geometry was confirmed to be *E* by the diagnostic coupling constant (J = 16.0 Hz) for the olefin protons in the ^{1}H NMR spectrum.

After the cross-metathesis reaction had been performed, *enone* ***206*** was subjected to the single-pot Heck/condensation/elimination protocol with 4-bromotoluene utilised in the Heck component. Disappointingly, *pyridine* ***209*** was only formed in 49% yield over three steps from *enone* ***206***. Increasing the quantities of tris(dibenzylideneacetone)dipalladium and tri-*tert*-butylphosphonium tetrafluoroborate from 0.050 equivalents and 0.200 equivalents to 0.100 equivalents and 0.400 equivalents, respectively led to an increase in yield to 72% over three steps from *enone* ***206*** (*Scheme* ***2.32***).

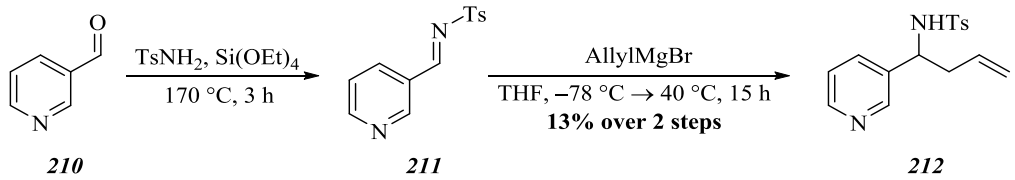


Scheme 2.32 *Synthesis of pyridine* ***209*** *via Heck/condensation/elimination protocol*

The identity of *pyridine* ***209*** was confirmed by the presence of a singlet at 2.71 ppm in the ^{1}H NMR spectrum, which corresponded to $Ar_{(py)}C\underline{H}_3$, and a singlet at −62.5 ppm in the ^{19}F NMR spectrum, which corresponded to $C\underline{F}_3$.

2.5.3 Scope at the C-6 (R^1) position: Heteroaromatic substituents

After the successful installation of a *p*-trifluoromethylbenzene substituent, studies were then focussed once again on the generation of bipyridine substrates by installation of a pyridine substituent at the *C-6* (R^1) position of the resultant 2,4,6-trisubstituted pyridine. The synthesis of the desired bipyridine started with the formation of *sulfonamide* ***212*** from 3-pyridinecarboxaldehyde (***210***) using a similar procedure to that described previously. 3-Pyridinecarboxaldehyde (***210***) and *p*-toluenesulfonamide were heated in the presence of tetraethyl orthosilicate to furnish *imine* ***211*** as a white crystalline solid without the need for further purification. *Imine* ***211*** was subsequently reacted with an excess of allyl magnesium bromide to give *sulfonamide* ***212*** in a disappointing 13% yield over two steps from 3-pyridinecarboxaldehyde (***210***) (*Scheme* ***2.33***).

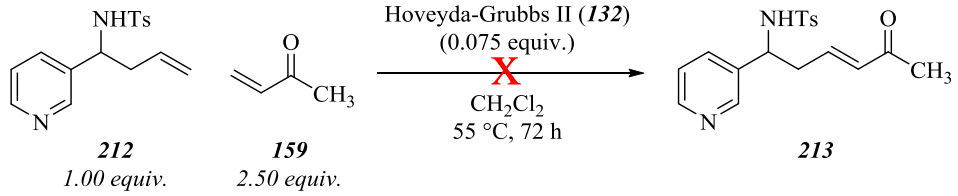


210 ***211*** ***212***

Scheme 2.33 *Synthesis of sulfonamide* ***212***

The identity of *sulfonamide* ***212*** was confirmed by the presence of a double doublet of triplets at 5.49 ppm (J = 17.0, 10.0, 7.0 Hz) and a doublet at 5.68 ppm (J = 6.5 Hz) in the ^{1}H NMR spectrum, which corresponded to $C\underline{H}$=CH_2 and $N\underline{H}$, respectively.

Despite a poor yield of *sulfonamide* ***212*** being obtained, scale-up of the process afforded sufficient material to attempt the subsequent cross-metathesis reaction using Hoveyda-Grubbs second generation catalyst (***132***).



Scheme 2.34 *Failed synthesis of enone* ***213***

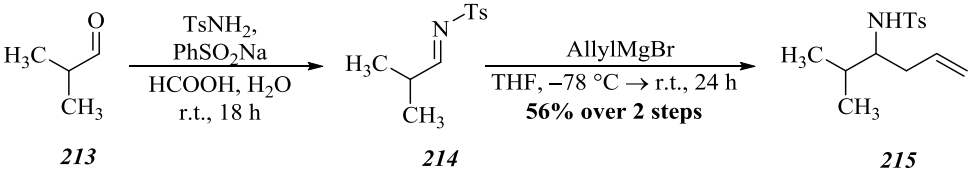
Thin-layer chromatography analysis indicated that only *sulfonamide* ***212*** remained on completion of the reaction. This was confirmed by the ^{1}H NMR spectrum of the crude reaction mixture. It was hypothesised that the free lone pair on the nitrogen atom in the pyridine ring could deactivate the metathesis catalyst by coordination (*Scheme* ***2.34***).

2.5.4 Scope at the C-6 (R^1) position: Aliphatic substituents

For consistency between 2,4,6-trisubstituted pyridines, atom numbering in pyridine ***219*** *is inconsistent with International Union of Pure and Applied Chemistry naming conventions.*

Co-workers in the group had successfully incorporated primary aliphatic substituents into the resultant 2,4,6-trisubstituted pyridine, but it would also be desirable to expand the scope of this methodology to encompass secondary aliphatic and tertiary aliphatic substituents. To this end, installation of an isopropyl group was attempted and studies began with the synthesis of *sulfonamide* ***215***.

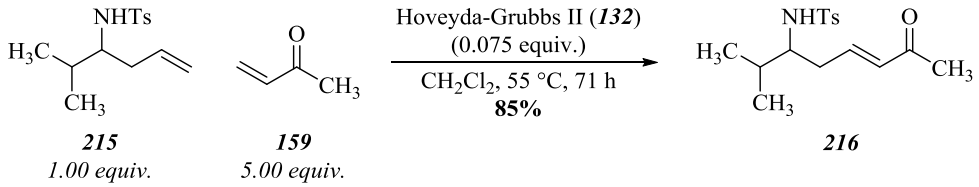
Following a reported literature procedure,[127] isobutyraldehyde (***213***) was treated with *p*-toluenesulfonamide in the presence of sodium benzenesulfinate to generate *imine* ***214*** as a white crystalline solid without the need for further purification. *Imine* ***214*** was subsequently reacted with an excess of allyl magnesium bromide to give *sulfonamide* ***215*** in a respectable 56% yield over two steps from isobutyraldehyde (***213***) on a multi-gram scale (*Scheme* ***2.35***).



Scheme 2.35 *Synthesis of sulfonamide* ***215***

The identity of *sulfonamide* ***215*** was confirmed by the presence of a doublet at 0.83 ppm (J = 7.0 Hz) in the ^{1}H NMR spectrum, which corresponded to $CH(C\underline{H_3})_2$.

With *sulfonamide* ***215*** in hand, attention turned to performing the cross-metathesis reaction with methyl vinyl ketone (***159***) using Hoveyda-Grubbs second generation catalyst (***132***). Pleasingly, *enone* ***216*** was generated in 85% yield after 71 h, and exclusively as a single geometric isomer as observed by ^{1}H NMR spectroscopy. However, this reaction required the use of 5.00 equivalents of methyl vinyl ketone (***159***) (*Scheme* ***2.36***).



215 *1.00 equiv.* ***159*** *5.00 equiv.* ***216***

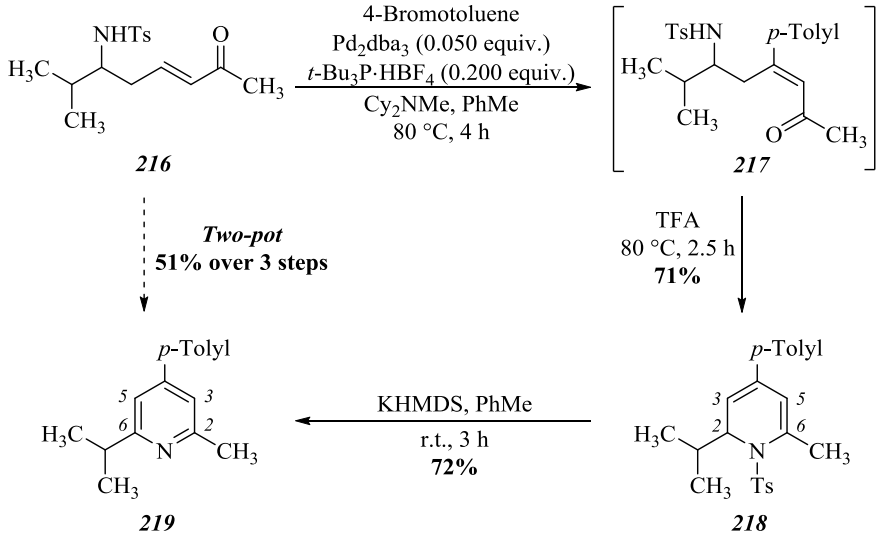
Scheme 2.36 *Synthesis of enone* ***216*** *via cross-metathesis reaction*

The identity of *enone* ***216*** was confirmed by the presence of a singlet at 198.2 ppm in the ^{13}C NMR spectrum, which corresponded to carbon atom in the carbonyl group, and a signal at 1673 cm^{-1} in the infrared spectrum, which corresponded to the carbonyl stretch. The double-bond geometry was confirmed to be *E* by the diagnostic coupling constant (J = 16.0 Hz) for the olefin protons observed in the ^{1}H NMR spectrum.

After generation of *enone* ***216***, work focused on the synthesis of *pyridine* ***219*** using the Heck/condensation/elimination protocol. As described previously (*Chapter* ***2.2.1***, *vide supra*), the single-pot Heck/condensation/elimination protocol was not applicable to this substrate due to the isopropyl substituent present in *dihydropyridine* ***218***. This substituent did not suitably acidify the neighbouring proton for subsequent elimination with 1,8-diazabicycloundec-7-ene. Therefore, the protocol was split into a single-pot Heck/condensation component, and a separate elimination component using potassium bis(trimethylsilyl)amide, a stronger base than 1,8-diazabicycloundec-7-ene.

Enone ***216*** was treated with Fu's Heck conditions to generate *enone* ***217***. When the Heck reaction was judged to be complete by thin-layer chromatography analysis, trifluoroacetic acid was added to

the reaction mixture to allow for the formation of *dihydropyridine* ***218*** under condensation conditions. This protocol furnished *dihydropyridine* ***218*** in 71% yield over two steps from *enone* ***216***. *Dihydropyridine* ***218*** was subsequently eliminated with potassium bis(trimethylsilyl)amide in toluene to afford *pyridine* ***219*** in 72% yield, or 51% yield over three steps from *enone* ***216*** (*Scheme* ***2.37***).

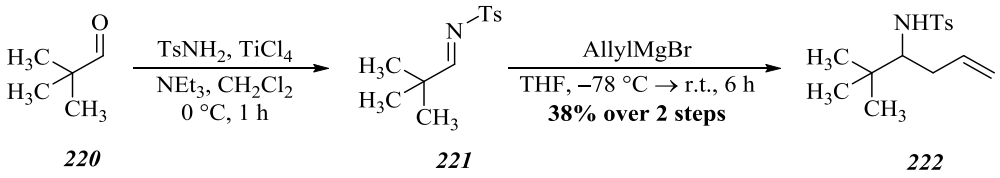


Scheme 2.37 *Synthesis of pyridine* ***219*** *via Heck/condensation/elimination protocol*

The identity of *dihydropyridine* ***218*** was confirmed by the absence of a signal at 1673 cm^{-1} in the infrared spectrum, which corresponded to the carbonyl stretch in *enone* ***216***. Further confirmation was obtained by the presence of a doublet at 5.47 ppm (J = 6.0 Hz) in the ^{1}H NMR spectrum, which corresponded to C$\underline{H}^3$. The identity of *pyridine* ***219*** was confirmed by the absence of a double doublet at 4.29 ppm (J = 9.0, 6.0 Hz) in the ^{1}H NMR spectrum, which corresponded to C$\underline{H}^2$ in *dihydropyridine* ***218***. Further confirmation was obtained by the presence of a signal in the high-resolution mass spectrum at 226.1588 (Δ = +0.88 ppm), which corresponded to the $[M+H]^+$ ion of *pyridine* ***219***.

After successful installation of a secondary aliphatic substituent onto the resultant 2,4,6-trisubstituted pyridine, attention turned to the installation of a tertiary aliphatic substituent, *tert*-butyl. Studies began with the synthesis of *sulfonamide* ***222***. Following a reported literature procedure,[128] pivaldehyde (***220***) was treated subsequently with triethylamine and titanium tetrachloride in the presence of *p*-toluenesulfonamide to furnish *imine* ***221*** as a white crystalline

solid after recrystallisation from acetone. *Imine* ***221*** was subsequently reacted with an excess of allyl magnesium bromide to give *sulfonamide* ***222*** in a respectable 38% yield over two steps from pivaldehyde (***220***) (*Scheme* ***2.38***).

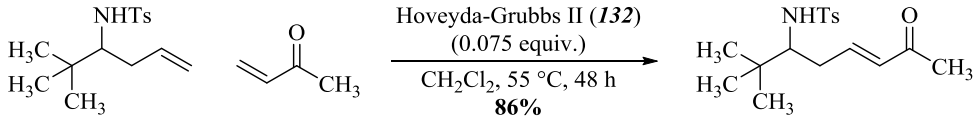


220 ***221*** ***222***

Scheme 2.38 *Synthesis of sulfonamide* ***222***

The identity of *sulfonamide* ***222*** was confirmed by the presence of a signal at 3285 cm^{-1} in the infrared spectrum, which corresponded to the N−H stretch. Further confirmation was obtained by the presence of a signal in the high-resolution mass spectrum at 304.1332 (Δ = +3.3 ppm), which corresponded to the $[M+Na]^+$ ion of *sulfonamide* ***222***.

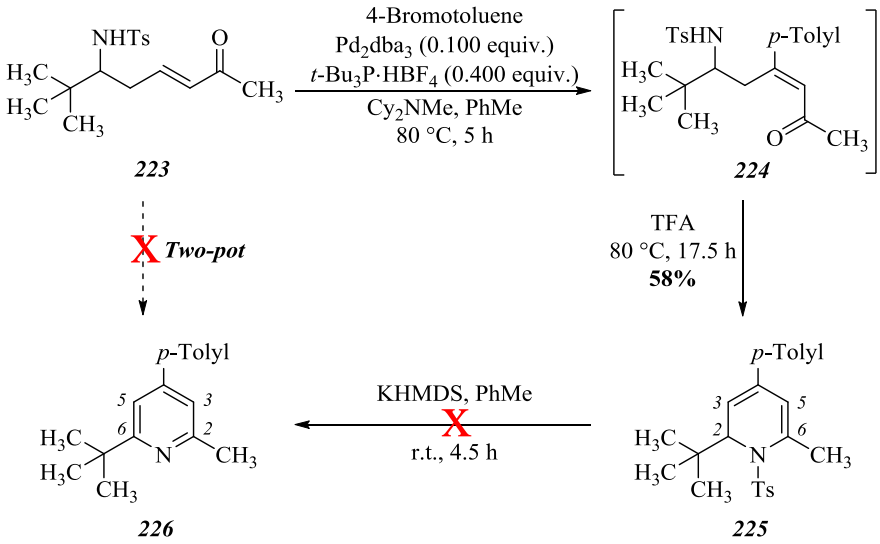
Next, the cross-metathesis reaction of *sulfonamide* ***222*** and methyl vinyl ketone (***159***) was explored using Hoveyda-Grubbs second generation catalyst (***132***). It was hypothesised that the extra steric bulk provided by the *tert*-butyl substituent may cause problems in the cross-metathesis reaction, gratifyingly however, *enone* ***223*** was generated in 86% yield and exclusively as a single geometric isomer as observed by ^{1}H NMR spectroscopy, when 5.00 equivalents of methyl vinyl ketone (***159***) were employed (*Scheme* ***2.39***).



222 *1.00 equiv.* ***159*** *5.00 equiv.* ***223***

Scheme 2.39 *Synthesis of enone* ***223*** *via cross-metathesis reaction*

The identity of *enone* ***223*** was confirmed by the presence of a singlet at 198.5 ppm in the ^{13}C NMR spectrum, which corresponded to carbon atom in the carbonyl group, and a signal at 1672 cm^{-1} in the infrared spectrum, which corresponded to the carbonyl stretch. The double-bond geometry was confirmed to be *E* by the diagnostic coupling constant (J = 16.0 Hz) for the olefin protons observed in the ^{1}H NMR spectrum.

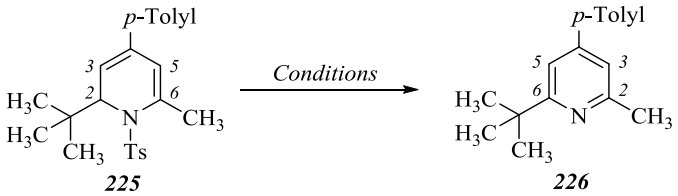


Scheme 2.40 *Failed synthesis of pyridine* ***226*** *via Heck/condensation/elimination protocol*

Enone ***223*** was then exposed to the single-pot Heck/condensation protocol using 4-bromotoluene in the Heck component. This protocol proceeded smoothly generating *dihydropyridine* ***225*** in a satisfying 58% yield over two steps from *enone* ***223*** (*Scheme* ***2.40***). The identity of *dihydropyridine* ***225*** was confirmed by the absence of a signal at 3283 cm^{-1} in the infrared spectrum, which corresponded to the N−H stretch. Further confirmation was obtained by the presence of a doublet at 4.59 ppm (J = 6.0 Hz), which corresponded to C$\underline{H}^2$.

Disappointingly, subsequent elimination to generate *pyridine* ***226*** proved challenging with only *dihydropyridine* ***225*** being isolated after treatment with potassium bis(trimethylsilyl)amide. Further conditions were explored to effect the formation of *pyridine* ***226*** (*Table* ***2.5***). In an attempt to entropically favour the elimination, *dihydropyridine* ***225*** was treated with potassium bis(trimethylsilyl)amide at 95 °C, which unfortunately led only to recovery of *dihydropyridine* ***225*** with some minor decomposition as observed by ^{1}H NMR spectrum of the crude reaction mixture (*Entry 1*). Utilisation of 1,8-diazabicycloundec-7-ene also returned *dihydropyridine* ***225*** (*Entry 2*). A co-worker had discovered that the elimination reaction could be achieved by heating *dihydropyridine* ***225*** in the presence of potassium hydroxide and ethanol in a screw-top reaction tube, unfortunately, this only led to recovery of *dihydropyridine* ***225*** (*Entry 3*). A similar result was obtained with the use of potassium trimethylsilanoate as the base (*Entry 4*). The failed elimination

attempts indicated that *dihydropyridine* ***225*** was particularly resistant to deprotonation, and this was hypothesised to be due to the extra steric hindrance provided by the *tert*-butyl group.



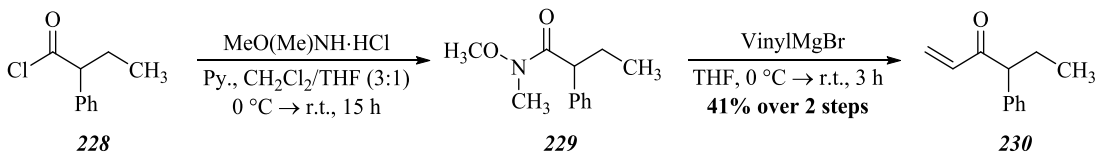
225 ***226***

Entry	*Reagent*	*Solvent*	*Temperature*	*Time*	*Result*
1	KHMDS (1.20 equiv.)	PhMe (0.100 M)	95 °C	3 h	Recovered ***225***
2	DBU (5.00 equiv.)	PhMe (0.100 M)	80 °C	5 h	Recovered ***225***
3	KOH (42.3 equiv.)	EtOH (0.100 M)	90 °C	24 h	Recovered ***225***
4	Me_3SiOK (1.50 equiv.)	THF (0.100 M)	r.t.	2.5 h	Recovered ***225***

Table 2.5 *Screen of elimination conditions*

2.5.5 Scope at the C-2 (R^2) position: Substituents with α-stereogenic centres

Co-workers in the group had demonstrated that simple primary aliphatic and secondary aliphatic substituents could be installed onto the *C-2* (R^2) position of the resultant 2,4,6-trisubstituted pyridine, however, the complexity of these substituents was very limited and so it was desirable to increase this complexity by installation of an α-stereogenic centre, which would be incorporated from the vinyl ketone precursor. Studies began with the synthesis of an appropriate vinyl ketone precursor, and *enone* ***230*** was chosen to avoid the practical issues of dealing with extremely volatile substrates. The synthesis of *enone* ***230*** began with the treatment of 2-phenylbutyryl chloride (***228***) with *N*,*O*-dimethylhydroxylamine hydrochloride, following a reported literature procedure,[129] which furnished *amide* ***229*** as colourless oil without the need for further purification. *Amide* ***229*** was subsequently reacted with vinyl magnesium bromide to generate *enone* ***230*** in 41% yield over two steps (*Scheme* ***2.41***).

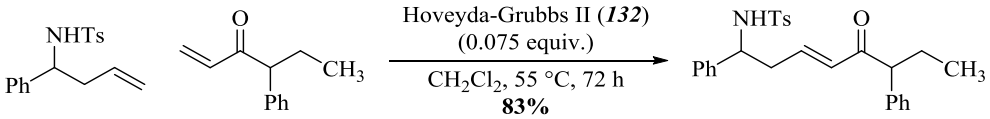


228 ***229*** ***230***

Scheme 2.41 *Synthesis of enone* ***230***

The identity of *enone* ***230*** was confirmed by the presence of a double doublet (J = 17.5, 10.0 Hz) at 6.36 ppm in the ^{1}H NMR spectrum which corresponded to C***H***=CH_2. Further confirmation was obtained by the presence of a singlet at 199.5 ppm in the ^{13}C NMR spectrum, which corresponded to the carbon atom in the carbonyl group.

With the synthesis of *enone* ***230*** complete, the cross-metathesis reaction with *sulfonamide* ***158*** was attempted using Hoveyda-Grubbs second generation catalyst (***132***). This afforded *enone* ***231*** as an inseparable 1.0:1.0 mixture (by ^{1}H NMR analysis) of diastereoisomers in an excellent 83% yield and exclusively as a single geometric isomer as observed by ^{1}H NMR spectroscopy, when 5.00 equivalents of *enone* ***230*** was employed. Encouragingly, a yield of 65% was obtained when 2.50 equivalents of *enone* ***230*** were employed (*Scheme* ***2.42***).

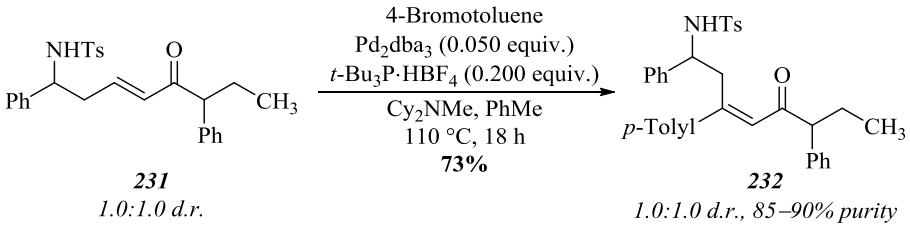


158 *1.00 equiv.* ***230*** *5.00 equiv.* ***231*** *1.0:1.0 d.r.*

Scheme 2.42 *Synthesis of enone* ***231*** *via cross-metathesis reaction*

The identity of *enone* ***231*** was confirmed by the presence of a signal at 3271 cm^{-1} in the infrared spectrum, which corresponded to the N−H stretch. The double-bond geometry was confirmed to be *E* by the diagnostic coupling constant (J = 15.5 Hz) for the olefin protons observed in the ^{1}H NMR spectrum.

Subsequently, *enone* ***231*** (1.0:1.0 mixture of diastereoisomers) was treated with 4-bromotoluene under Fu's Heck conditions to generate *enone* ***231*** as an inseparable 1.0:1.0 mixture (by ^{1}H NMR analysis) of diastereoisomers in 73% yield, although a small amount (10−15% by ^{1}H NMR analysis) of inseparable olefin regio/geometric isomers were thought to contaminate *enone* ***232***, even after repeated flash-column chromatography (*Scheme* ***2.43***).

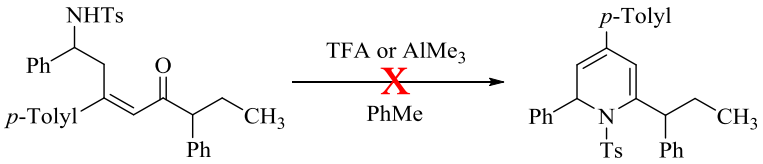


231
1.0:1.0 d.r.

232
1.0:1.0 d.r., 85–90% purity

Scheme 2.43 *Synthesis of enone* ***232*** *via Heck reaction*

The identity of *enone* ***232*** was confirmed by the presence of two singlets at 6.40 ppm (*diastereoisomer 1*) and 6.35 ppm (*diastereoisomer 2*) in the ^{1}H NMR spectrum, which corresponded to the olefin proton. The *E*-geometry of the double-bond was inferred from nOe based NMR experiments performed during previous studies,[109] observed from the proposed mechanism of *syn-carbopalladation* during the Heck reaction, and from analogous nOe based NMR experiments conducted during later studies on the Heck reactions of β-substituted vinyl Weinreb amides (*Figure* ***3.4***, *vide infra*).



232
1.0:1.0 d.r., 85–90% purity

233

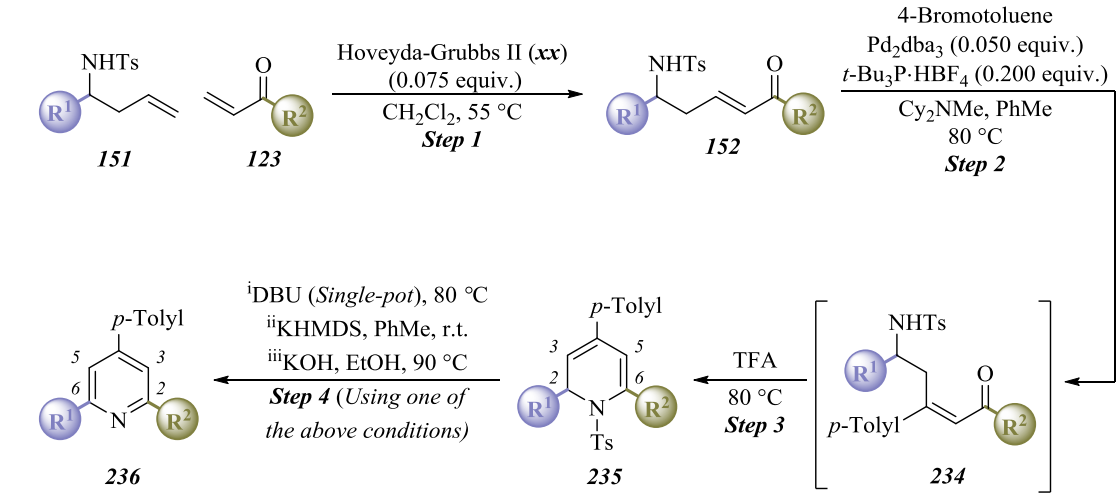
Scheme 2.44 *Failed condensation of enone* ***232***

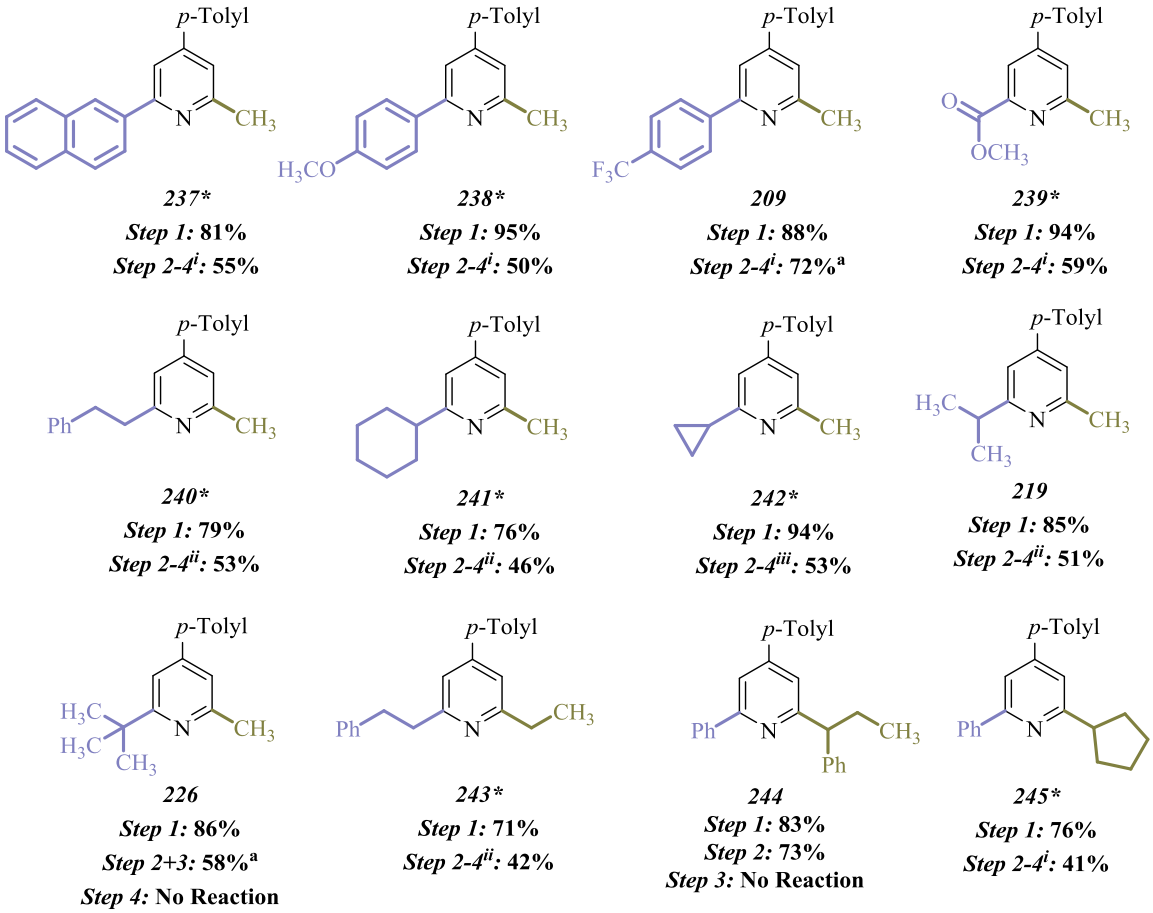
The condensation of *enone* ***232*** (85−90% purity) to form *dihydropyridine* ***233*** was then attempted using trifluoroacetic acid or trimethylaluminium. Unfortunately, neither set of conditions proved successful in the formation of *dihydropyridine* ***233***, even after heating to reflux, with *enone* ***232*** being observed in the ^{1}H NMR spectrum of the crude reaction mixture. It was hypothesised that the carbonyl α-protons were very enolisable under the Brønsted acid Lewis acid conditions employed and this keto/enol tautomerism would prevent nucleophilic attack of the sulfonamide portion of the molecule to the carbonyl group (*Scheme* ***2.44***). Condensation under basic conditions was also thought to be problematic for a similar reason as above, but also due to the possibility of sulfonamide elimination, and thus was not attempted.

2.5.6 Summary

In summary, the synthesis began by the treatment of *sulfonamide* ***151*** with *enone* ***123*** under cross-metathesis reaction conditions using Hoveyda-Grubbs second generation catalyst (***132***) to generate *enone* ***152***. Subsequently, Fu's Heck conditions were employed to generate *enone* ***234***. When the Heck reaction was judged to be complete by thin-layer chromatography analysis, trifluoroacetic acid was added to the reaction mixture to allow for the formation of *dihydropyridine* ***235*** under condensation conditions. At this point, depending on the nature of the *C-6* (R^1) substituent of the resultant pyridine, either excess 1,8-diazabicycloundec-7-ene was added directly to the reaction mixture (when the substituent was aromatic or electron-withdrawing), or the reaction was first purified and then *dihydropyridine* ***235*** was exposed to potassium bis(trimethylsilyl)amide (when the substituent was aliphatic). Both sets of conditions furnished *pyridine* ***236*** in good to moderate yields over three steps. The attempted syntheses of eight different 2,4,6-trisubstituted pyridines with varying *C-6* (R^1) or *C-2* (R^2) substitution are described (*Scheme* ***2.45***). These pyridines all differ by their substitution at the *C-6* (R^1) position, which is introduced from *sulfonamide* ***151***, or by their substitution at the *C-2* (R^2) position, which is introduced from *enone* ***123***.

Using this protocol, it was possible to install biaryl (*pyridine* ***237***), electron-rich (*pyridine* ***238***), and electron-deficient (*pyridine* ***209*** *and pyridine* ***239***) substituents at the *C-6* (R^1) in good yields over three steps from the respective *enone* ***152***, which were in turn synthesised in very good yields from respective *sulfonamide* ***151*** and respective *enone* ***123***. Pleasingly, the generation of pyridines with primary aliphatic (*pyridine* ***240***) and secondary aliphatic (*pyridine* ***241****, pyridine* ***242*** *and pyridine* ***219***) substituents was also possible, however attempts to install a tertiary aliphatic (*pyridine* ***226***) substituent proved challenging. Ultimately, this methodology works optimally when introducing aryl substituents at the *C-6* (R^1) position. The scope at the *C-2* (R^2) position is relatively small, with the installation of only primary aliphatic (*pyridine* ***243***) and secondary aliphatic (*pyridine* ***245***) substituents possible, albeit in good yields over three steps. Unfortunately, attempts to increase the complexity of the secondary aliphatic substituent proved unsuccessful and the synthesis of 2,4,6-trisubstituted pyridines was limited to simple aliphatic groups at the *C-2* (R^2) position.



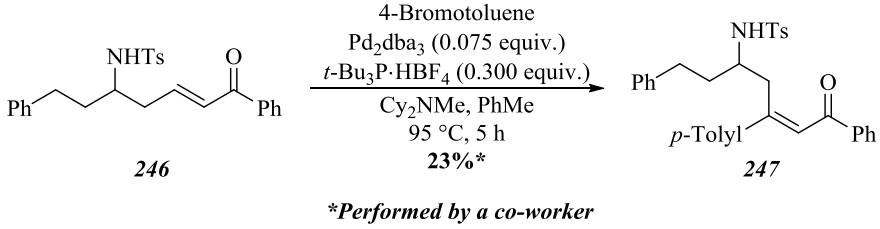


Scheme 2.45 *Scope at the C-6 (R^1) and C-2 (R^2) in the single-pot Heck/condensation/elimination protocol. [a] Pd_2dba_3 (0.100 equiv.) and t-Bu_3P·HBF_4 (0.400 equiv.) used in Heck component.*

2.6 Synthesis of substituted 2-hydroxypyridines

2.6.1 Limitations of the second generation pyridine synthesis

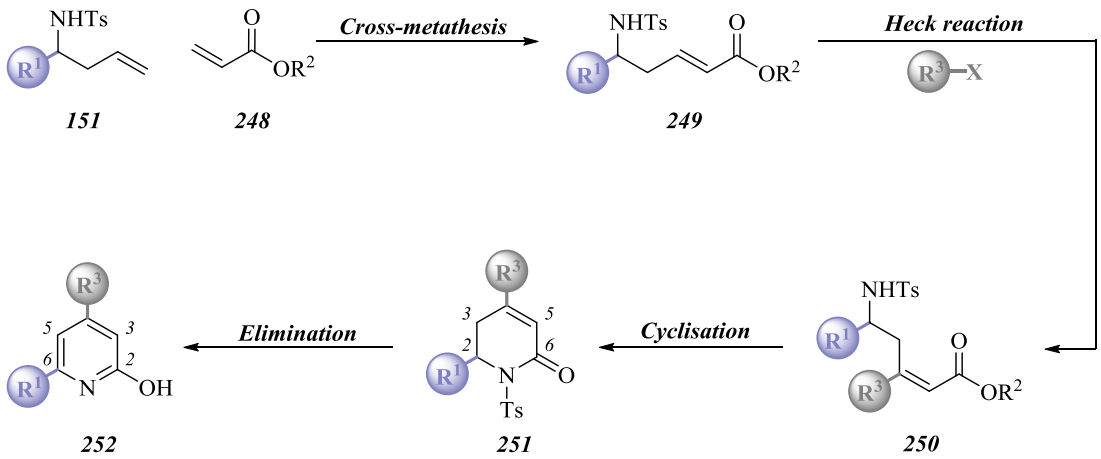
Although the second generation pyridine synthesis successfully addressed the issue of *C-4* (R^3) substitution, and also allowed for excellent scope at the *C-6* (R^1) position, the scope at the *C-2* (R^2) position of the resultant 2,4,6-trisubstituted pyridines was limited to simple aliphatic substituents. Co-workers had investigated this issue and it was found that the Heck reaction was poor yielding when aromatic substituents were present on the enone portion of the molecule. A disappointing 23% yield was obtained when a phenyl substituent was incorporated, and thus the methodology was limited to the use of primary and secondary aliphatic vinyl ketones (*Scheme* ***2.46***).



Scheme 2.46 *Synthesis of enone* ***247*** *via Heck reaction*

2.6.2 Proposed synthetic route to substituted 2-hydroxypyridines

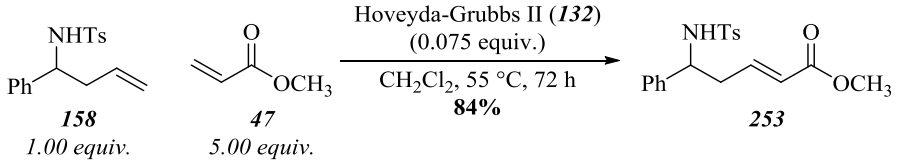
After obtaining this result, studies focussed on the design of a synthesis that would avoid this issue and that allowed incorporation of complex functionality into the *C-2* position of the resultant pyridine. It was hypothesised that installation of a hydroxyl group at the *C-2* position would provide a handle for further functionalisation through formation of the trifluoromethylsulfonate and subsequent palladium-catalysed cross-coupling reaction. It was proposed that this could be achieved by treatment of *sulfonamide* ***151*** with *acrylate* ***248*** in the cross-metathesis reaction to generate *acrylate* ***249***. *Acrylate* ***249*** would then be exposed subsequently to the Heck, cyclisation, and elimination reactions to furnish *pyridine* ***252*** (*Scheme* ***2.47***).



Scheme 2.47 *Proposed synthetic route to substituted 2-hydroxypyridines*

2.6.3 Step-wise synthesis of substituted 2-hydroxypyridines

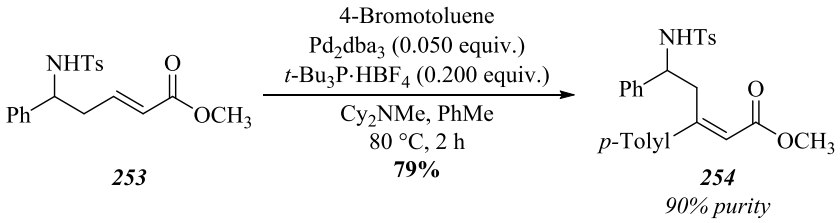
Therefore the synthesis of substituted 2-hydroxypyridines began with the cross-metathesis reaction of *sulfonamide* ***158*** and methyl acrylate (***47***) using Hoveyda-Grubbs second generation catalyst (***132***), which furnished *acrylate* ***253*** in 84% yield when 5.00 equivalents of methyl acrylate (***47***) were employed (*Scheme* ***2.48***).



Scheme 2.48 *Synthesis of acrylate* ***253*** *via cross-metathesis reaction*

The identity of *acrylate* ***253*** was confirmed by the presence of a singlet 3.69 ppm in the ^{1}H NMR spectrum, which corresponded to OC$\underline{H}_3$. The double-bond geometry was confirmed to be *E* by the diagnostic coupling constant (J = 15.5 Hz) for the olefin protons observed in the ^{1}H NMR spectrum.

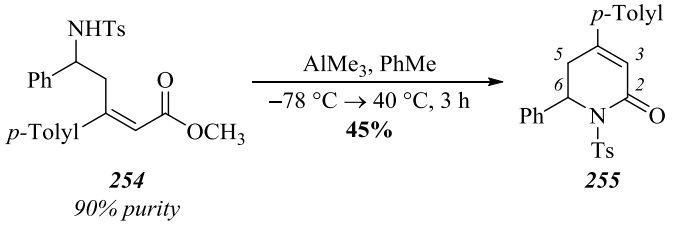
Acrylate ***253*** was subsequently treated with 4-bromotoluene using Fu's Heck conditions to generate *acrylate* ***254*** in 79% yield, although a small amount (10% by ^{1}H NMR analysis) of inseparable olefin regio/geometric isomers were thought to contaminate the *acrylate* ***254***, even after repeated flash-column chromatography (*Scheme* ***2.49***).



Scheme 2.49 *Synthesis of acrylate* ***254*** *via Heck reaction*

The identity of *acrylate* ***254*** was confirmed by the absence of a double triplet (J = 15.5, 7.5 Hz) at 6.66 ppm in the ^{1}H NMR spectrum, which corresponded to $CH_2C\underline{H}$=CH in *acrylate* ***253***. Further confirmation was obtained by presence of a singlet at 6.08 ppm in the ^{1}H NMR spectrum which corresponded to the olefin proton. The *E*-geometry of the double-bond was inferred from nOe based NMR experiments performed during previous studies,[109] observed from the proposed mechanism of *syn-carbopalladation* during the Heck reaction, and from analogous nOe based NMR experiments conducted during later studies on the Heck reactions of β-substituted vinyl Weinreb amides (*Figure* ***3.4***, *vide infra*).

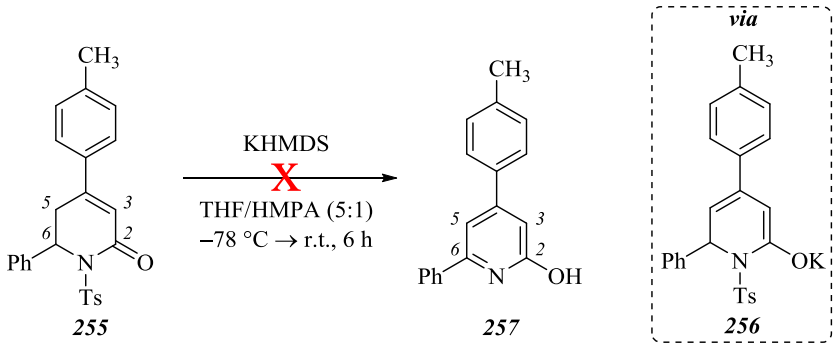
With *acrylate* ***254*** (90% purity) in hand, the cyclisation was attempted using trifluoroacetic acid. Unfortunately, this only led to recovery of *acrylate* ***254*** and no trace of condensation product—*dihydropyridone* ***255***. Gratifyingly, treatment of *acrylate* ***254*** (90% purity) with trimethylaluminium led to the successful synthesis of *dihydropyridone* ***255***, albeit in a moderate 45% yield. The moderate yield was thought to be a result of the decreased rate of cyclisation onto an acrylate rather than an enone carbonyl. *Acrylate* ***254*** was observed at the end of the reaction and it was thought that this reaction could be fully completed with high temperatures and an extended reaction time. However, the protocol produced sufficient material to attempt the subsequent elimination (*Scheme* ***2.50***).



Scheme 2.50 *Synthesis of dihydropyridone* ***255*** *via cyclisation*

The identity of *dihydropyridone* ***255*** was confirmed by the presence of a singlet at 163.5 ppm in the ^{13}C NMR spectrum, which corresponded to the carbon atom in the carbonyl group. Further confirmation was obtained by the presence of a mutually coupled double doublet of doublets (J = 17.5, 7.0, 3.0 Hz) at 3.53 ppm and a double doublet (J = 17.5, 1.5 Hz) at 3.15 ppm in the ^{1}H NMR spectrum, which corresponded to the two protons at C$\underline{H}^{5}$.

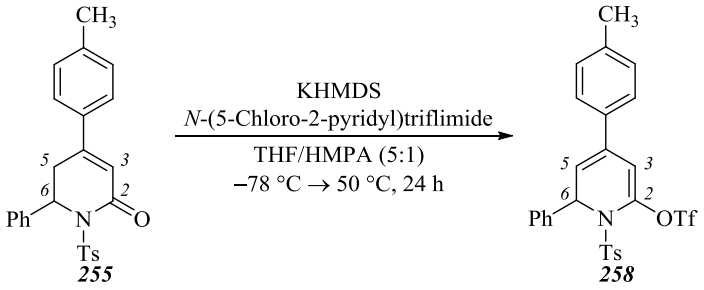
Dihydropyridone ***255*** was then treated with potassium bis(trimethylsilyl)amide, however this reaction led to recovery of *dihydropyridone* ***255*** as observed in the ^{1}H NMR spectrum of the crude reaction mixture. It was hypothesised that this elimination would be quite challenging for two reasons: Firstly, the protons at the *C-5* position of were thought to have greater acidity than the protons at the *C-6* position. Secondly, once the potassium stabilised anion of oxygen, *hydropyridine* ***256***, is formed by deprotonation of a proton at the *C-5* position, a second deprotonation to form a dianion and subsequent sulfinate elimination would be relatively unlikely (*Scheme* ***2.51***).



255 ***257*** ***256***

Scheme 2.51 *Failed synthesis of pyridine* ***257***

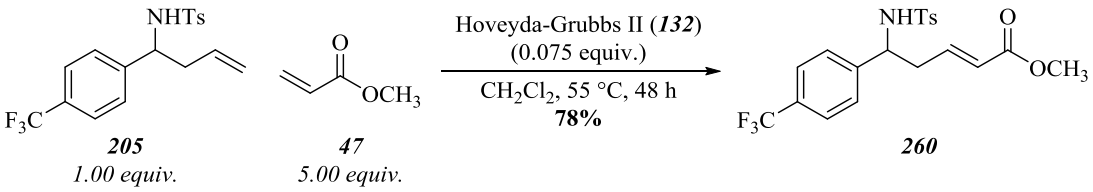
To overcome the issue described above, it was proposed that the formation of the trifluoromethylsulfonate at this stage would be useful and, conveniently, the resultant pyridine would have a pre-installed handle for further functionalisation. To this end, *dihydropyridone* ***255*** was treated with potassium bis(trimethylsilyl)amide in the presence of *N*-(5-chloro-2-pyridyl)triflimide (*Scheme* ***2.52***).



Scheme 2.52 *Synthesis of triflate* ***258***

Pleasingly, a small amount of *triflate* ***258*** was isolated (*ca. 10%*) from the reaction although this decomposed within a few hours of isolation and thus was not viable for further studies. It was hoped that *triflate* ***258***, upon being formed in the reaction mixture, would then undergo sulfinate elimination to generate a pyridine, but this was not observed.

The identity of *triflate* ***258*** was indicated by the presence of a doublet (J = 6.0 Hz) at 6.05 ppm and a double doublet (J = 6.0, 0.5 Hz) at 5.66 ppm in the ^{1}H NMR spectrum, which corresponded to C$\underline{H}^6$ and C$\underline{H}^5$, respectively. Full confirmation and assignment of *triflate* ***258*** was not obtained due to the rapid decomposition described above.



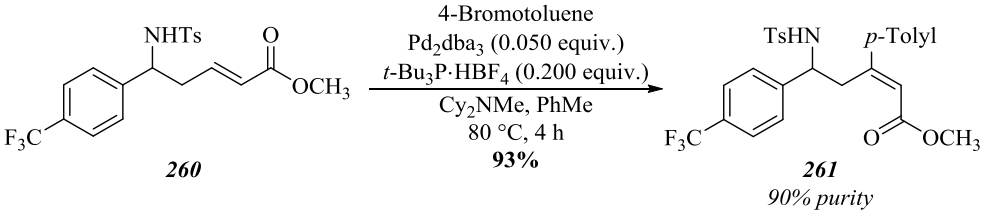
Scheme 2.53 *Synthesis of acrylate* ***260*** *via cross-metathesis reaction*

As *triflate* ***258*** was deemed to be problematic, it was decided that studies would focus on the generation of 2-hydroxypyridines, rather than the trifluoromethylsulfonate analogues. It was theorised that substituting the phenyl substituent at the *C-6* position of *dihydropyridone* ***255*** to another more electron-deficient aromatic substituent would suitably acidify the proton at the *C-6* position and thus allow for facile elimination of the sulfinate. To test this hypothesis, the synthesis of the 4-trifluoromethylphenyl analogue of *dihydropyridone* ***262*** would be conducted and this began with the synthesis of *acrylate* ***260*** by the cross-metathesis reaction of *sulfonamide* ***205*** and methyl acrylate (***47***) using Hoveyda-Grubbs second generation catalyst (***132***). As expected, *acrylate* ***260***

was generated in 78% yield when 5.00 equivalents of methyl acrylate (***47***) were employed (*Scheme* ***2.53***).

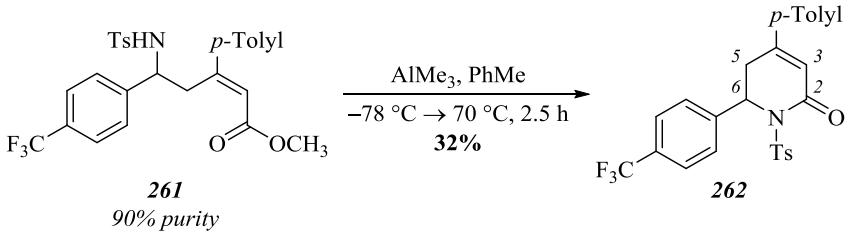
The identity of *acrylate* ***260*** was confirmed by the presence of a signal at 1703 cm^{-1} in the infrared spectrum, which corresponded to the carbonyl stretch. The double-bond geometry was confirmed to be *E* by the diagnostic coupling constant (J = 15.5 Hz) for the olefin protons observed in the ^{1}H NMR spectrum.

Acrylate ***260*** was subsequently treated with 4-bromotoluene using Fu's Heck conditions to generate *acrylate* ***261*** in an excellent 93% yield, although a small amount (10% by ^{1}H NMR analysis) of inseparable olefin regio/geometric isomers were thought to contaminate the *acrylate* ***261***, even after repeated flash-column chromatography (*Scheme* ***2.54***).



Scheme 2.54 *Synthesis of acrylate* ***261*** *via Heck reaction*

The identity of *acrylate* ***261*** was confirmed by the absence of a double triplet (J = 15.5, 7.0 Hz) at 6.67 ppm in the ^{1}H NMR spectrum, which corresponded to $CH_2C\underline{H}$=CH in *acrylate* ***260***. Further confirmation was obtained by the presence of a singlet 6.11 ppm in the ^{1}H NMR spectrum which corresponded to the olefin proton. The *E*-geometry of the double-bond was inferred from nOe based NMR experiments performed during previous studies,[109] observed from the proposed mechanism of *syn-carbopalladation* during the Heck reaction, and from analogous nOe based NMR experiments conducted during later studies on the Heck reactions of β-substituted vinyl Weinreb amides (*Figure* ***3.4***, *vide infra*).



261
90% purity

262

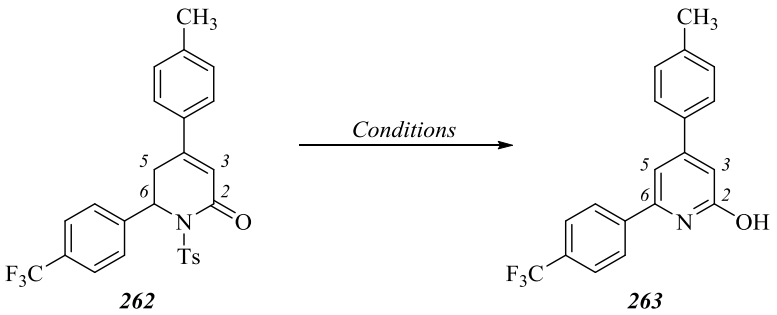
Scheme 2.55 *Synthesis of dihydropyridone* ***262*** *via cyclisation*

With *acrylate* ***261*** in hand, the cyclisation conditions developed for the synthesis of *dihydropyridone* ***262*** were utilised. Treatment of *acrylate* ***261*** (90% purity) with trimethylaluminium afforded *dihydropyridon*e ***262*** in a disappointing 32% yield. In comparison to the synthesis of *dihydropyridon*e ***255***, the synthesis of *dihydropyridon*e ***262*** proceeded at a slower rate and required an increase in temperature to 70 °C to obtain a reasonable conversion. This is likely to be a result of the electron-deficient aromatic substituent which decreases the nucleophilicity of the sulfonamide, thus inhibiting nucleophilic attack into the carbonyl group (*Scheme* ***2.55***).

The identity of *dihydropyridon*e ***262*** was confirmed by the absence of a signal at 3305 cm^{-1} in the infrared spectrum, which corresponded to the N−H stretch in *acrylate* ***261***. Further confirmation was obtained by the presence of a signal in the high-resolution mass spectrum at 508.1156 (Δ = +1.8 ppm), which corresponded to the $[M+Na]^+$ ion of *dihydropyridon*e ***262***. Interestingly, when comparing the ^{1}H NMR spectra of *dihydropyridon*e ***255*** and *dihydropyridon*e ***262***, it was found that the C$\underline{H}^6$ chemical shifts were 6.10 ppm and 6.15 ppm, respectively. From this data, it was inferred that the C$\underline{H}^6$ in *dihydropyridon*e ***262*** was more de-shielded than in *dihydropyridon*e ***255*** and thus may be more susceptible to deprotonation.

With the synthesis of *dihydropyridon*e ***262*** complete, a range of conditions were employed in order to encourage the elimination to generate *pyridine* ***263*** (*Table* ***2.6***). Treatment of *dihydropyridon*e ***262*** with potassium bis(trimethylsilyl)amide led only to recovery of *dihydropyridon*e ***262*** as observed in the ^{1}H NMR of the crude reaction mixture (*Entry 1*). Unfortunately, similar outcomes were obtained with all attempted conditions, including 1,8-diazabicycloundec-7-ene in either toluene (*Entry 2*) or tetrahydrofuran (*Entry 3*), sodium methoxide (*Entry 4*), potassium carbonate (*Entry 5*), sodium hydroxide with a phase transfer catalyst (*Entry 6*), or with

1,8-bis(dimethylamino)naphthalene (Proton Sponge), a sterically hindered and strong amine base (*Entry 7*).



Entry	*Reagent*	Solvent	*Temperature*	*Time*	*Result*
1	KHMDS (2.00 equiv.)	PhMe (0.100 M)	70 °C	18.5 h	Recovered ***262***
2	DBU (5.00 equiv.)	PhMe (0.100 M)	70 °C	18.5 h	Recovered ***262***
3	DBU (5.00 equiv.)	THF (0.100 M)	40 °C	6 h	Recovered ***262***
4	NaOMe (3.00 equiv.)	PhMe (0.100 M)	70 °C	18.5 h	Recovered ***262***
5	K_2CO_3 (3.00 equiv.)	PhMe (0.100 M)	70 °C	18.5 h	Recovered ***262***
6	NaOH (125 equiv.) *n*-Bu_4NBF_4	PhMe (0.100 M)	110 °C	5 h	Recovered ***262***
7	Proton Sponge (5.00 equiv.)	PhMe (0.100 M)	110 °C	12 h	Recovered ***262***

Table 2.6 *Screen of elimination conditions*

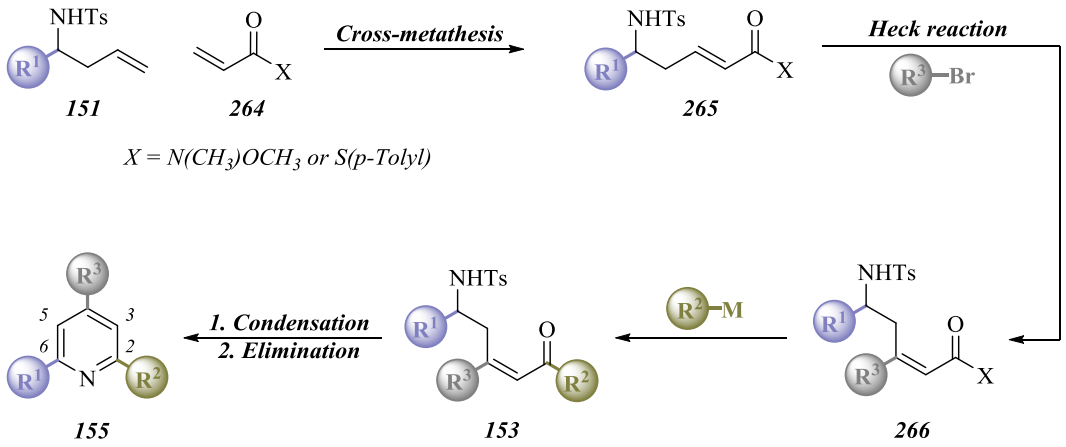
With the elimination to generate *pyridine* ***257*** and *pyridine* ***263*** proving challenging, it was decided that substitution of the enone component in the cross-metathesis should be attempted with other functional groups that could 'mask' an enone.

2.7 Enone Surrogates

2.7.1 Proposed synthetic route to 2,4,6-trisubstituted pyridines using enone surrogates

After the synthesis of substituted 2-hydroxypyridines had been explored and had shown to be unsuccessful, another synthetic route was designed to overcome the Heck reaction issues found in the second generation pyridine synthesis. It was proposed that the enone could be masked using another functional group and then converted back to the enone at a later stage of the synthetic route. A vinyl Weinreb amide or a thioacrylate was thought to be suitable for this role. It was proposed that

sulfonamide ***151*** could be treated with *alkene* ***264*** in the cross-metathesis reaction using Hoveyda-Grubbs second generation catalyst (***132***). Subsequent Heck reaction would be performed to generate *sulfonamide* ***266***. It was envisaged that *enone* ***153*** could be generated by addition of an organometallic reagent or by palladium-catalysed cross-coupling—Fukuyama coupling[130] or Liebeskind-Srogl coupling.[131] Once *enone* ***153*** had been generated, the condensation/elimination protocol previously described could be utilised to generate *pyridine* ***155*** (*Scheme* ***2.56***).

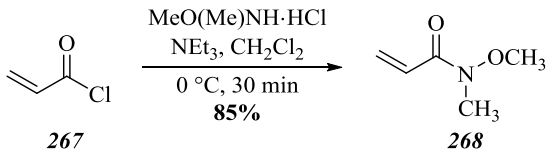


Scheme 2.56 *Proposed synthetic route to 2,4,6-trisubstituted pyridines*

2.7.2 Enone surrogates: vinyl Weinreb amides

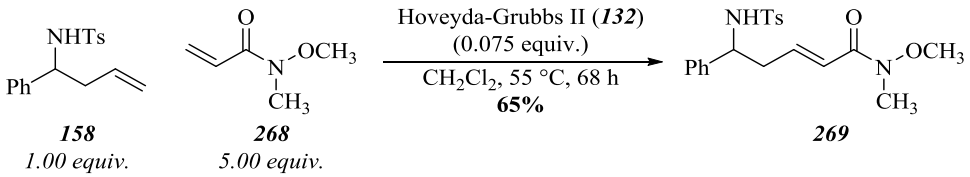
Work to test the hypothesis began with the synthesis of *amide* ***268*** from acryloyl chloride (***267***). Following a reported literature procedure,[132] acryloyl chloride (***267***) was treated with *N,O*-dimethylhydroxylamine hydrochloride in the presence of triethylamine to furnish *amide* ***268*** in 85% yield on a multi-gram scale after purification by vacuum distillation (*Scheme* ***2.57***).

The identity of *amide* ***268*** was confirmed by the presence two singlets at 61.7 ppm and 32.3 ppm in the ^{13}C NMR spectrum, which corresponded to O<u>C</u>H$_3$ and <u>C</u>H$_3$, respectively. Further confirmation was obtained when the spectroscopic data was found to be consistent with those reported in the literature for *amide* ***268***.[132]



Scheme 2.57 *Synthesis of amide* ***268***

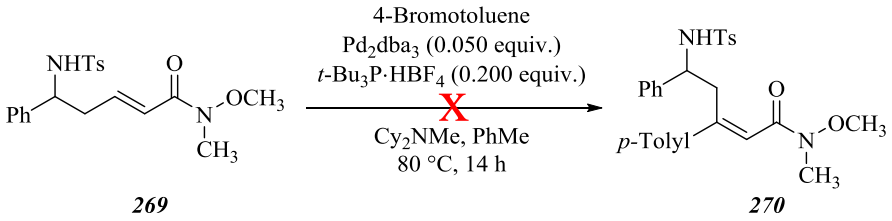
Amide ***268*** was then treated with *sulfonamide* ***158*** in the cross-metathesis using Hoveyda-Grubbs second generation catalyst (***132***), which furnished *amide* ***269*** in a respectable 65% yield and exclusively as a single geometric isomer as observed by ^{1}H NMR spectroscopy, when 5.00 equivalents of *amide* ***268*** were employed (*Scheme* ***2.58***). The reduced yield compared to the cross-metathesis with methyl vinyl ketone (***159***) or methyl acrylate (***47***) is proposed to be twofold: Firstly, *amide* ***268*** has extra steric bulk compared to methyl vinyl ketone (***159***) or methyl acrylate (***47***), and the cross-metathesis has been shown to be sensitive to increases in steric bulk. Secondly, and most importantly, the oxygen atom is thought to coordinate to the ruthenium centre of Hoveyda-Grubbs second generation catalyst (***132***), thus hindering catalytic activity and potentially decomposing the catalyst. This effect has been reported for the cross-metathesis reaction of acrylonitrile and it was thought that the extra nucleophilicity of the oxygen atom in a Weinreb amide may replicate this effect.[122] In response to this issue, titanium isopropoxide had been shown to increase yields when cross-metathesis reactions are performed with acrylonitrile and this is thought to be due to the coordination of the Lewis acid to the nitrogen atom, however this additive had no significant effect on the system investigated. Cossy and co-workers have also described an elegant method for the preparation of amides similar to *amide* ***269*** through the cross-metathesis reaction with acryloyl chloride and subsequent treatment with an amine.[133]



158 *1.00 equiv.* ***268*** *5.00 equiv.* ***269***

Scheme 2.58 *Synthesis of amide* ***269*** *via cross-metathesis reaction*

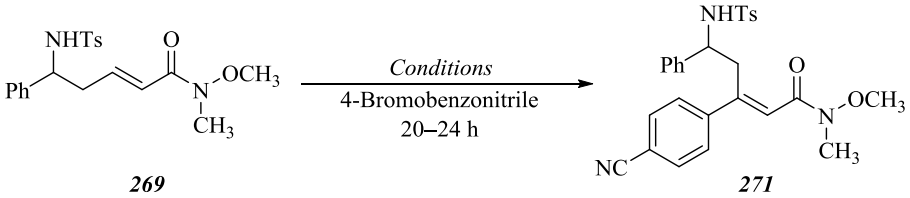
The identity of *amide* ***269*** was confirmed by the presence of a signal at 1661 cm^{-1} in the infrared spectrum, which corresponded to the carbonyl stretch. The double-bond geometry was confirmed to be *E* by the diagnostic coupling constant (J = 15.5 Hz) for the olefin protons observed in the ^{1}H NMR spectrum.



269 ***270***

Scheme 2.59 *Failed synthesis of amide* ***270*** *via Heck reaction*

Amide ***269*** was then treated with 4-bromotoluene using Fu's Heck conditions, however, this led only to the recovery of *amide* ***269*** (*Scheme* ***2.59***). It was proposed that the extra electron-donation into the carbonyl group from the amide compared to an enone reduced the electrophilicity of the double-bond, and this would reduce the rate of *syn-carbopalladation* as electron-deficient olefins typically perform better in the Heck reaction. Nevertheless, it was felt that altering the reaction conditions could lead to the generation of *amide* ***270*** (*Table* ***2.7***).



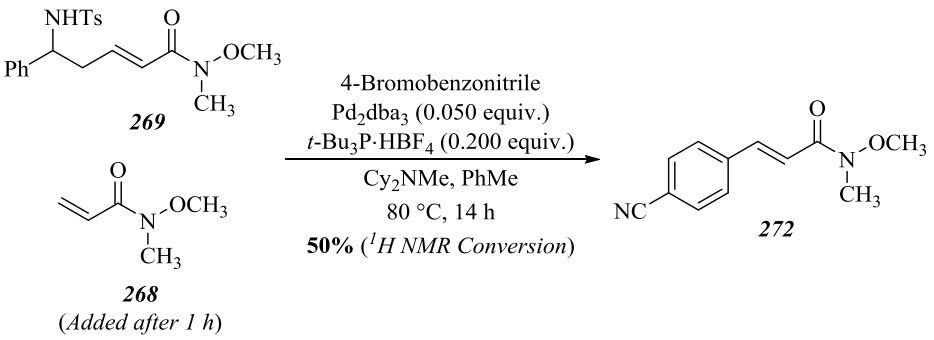
269 ***271***

Entry	*Catalyst*	*Base*	*Solvent*	*Temperature*	*Result*
1	$Pd(OAc)_2$ (0.050 equiv.), P(*o*-Tolyl)$_3$ (0.100 equiv.)	NaOAc (2.00 equiv.)	DMF (0.100 M)	120 °C	Sulfonamide elimination
2	Pd_2dba_3 (0.050 equiv.) *t*-$Bu_3P{\cdot}HBF_4$ (0.200 equiv.)	Cy_2NMe (1.50 equiv.)	PhMe (0.100 M)	80 °C	Recovered ***269***
3	Pd_2dba_3 (0.050 equiv.) ^{t}$Bu_3P{\cdot}HBF_4$ (0.200 equiv.)	Cy_2NMe (1.50 equiv.)	DMF (0.100 M)	80 °C	Recovered ***269***
4	Pd_2dba_3 (0.050 equiv.) *t*-$Bu_3P{\cdot}HBF_4$ (0.200 equiv.)	Cy_2NMe (1.50 equiv.)	1,4-Dioxane (0.100 M)	80 °C	42%
5	Pd_2dba_3 (0.050 equiv.) *t*-$Bu_3P{\cdot}HBF_4$ (0.200 equiv.)	Cy_2NMe (1.50 equiv.)	1,4-Dioxane (0.500 M)	80 °C	48%

Table 2.7 *Screen of cyclisation conditions*

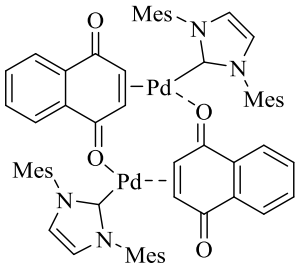
During these studies, it was found that the residual ruthenium present from the cross-metathesis reaction could interfere with the Heck reaction and led to the observation of reduced yields.

Removal of the ruthenium residues after the cross-metathesis reaction was essential to obtain good yields from the Heck reaction, and was achieved by decomposition with dimethylsulfoxide and subsequent flash-column chromatography.[134] Conditions described in Heck's seminal publications[59] which utilised palladium acetate and tri(*o*-tolyl)phosphine furnished the sulfonamide elimination product as observed in the ^{1}H NMR spectrum of the crude reaction mixture (*Entry 1*). Fu's Heck conditions were employed but once again only resulted in the recovery of *amide* ***269*** (*Entry 2*). It was proposed that *amide* ***269***, rather than just being unreactive to the catalytic system, may actually inhibit any further catalytic activity by coordination to palladium. To test this hypothesis, *amide* ***269*** was once again exposed to Fu's Heck conditions but *amide* ***268*** was added after 1 h. It was found that *amide* ***268*** had undergone conversion to *amide* ***272*** (*ca*. 50% by ^{1}H NMR spectrum of the crude reaction mixture), which indicated that the catalytic system was still active and that *amide* ***269*** was simply unreactive (*Scheme* ***2.60***).



Scheme 2.60 *Synthesis of amide* ***272*** *via Heck reaction*

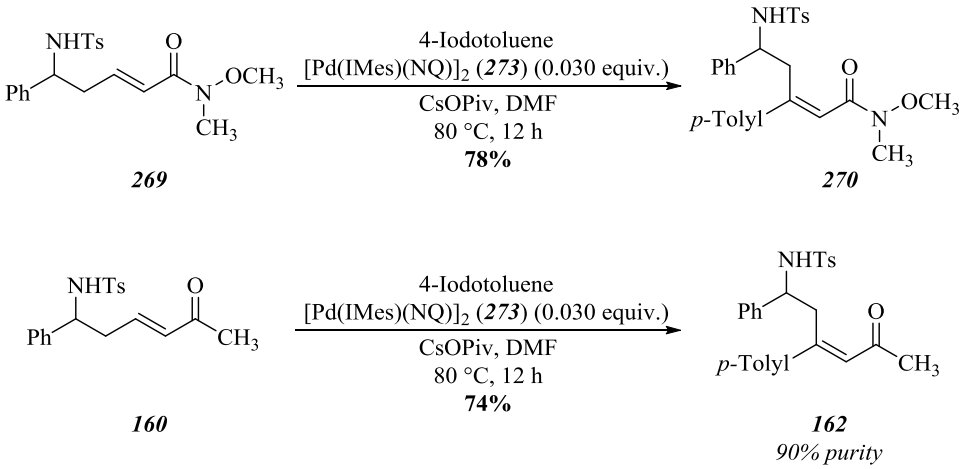
Utilising Fu's Heck conditions with a change of solvent initially had little effect when *N,N*-dimethylformamide was employed (*Entry 3*), however, encouragingly when 1,4-dioxane was used, *amide* ***271*** was generated in 42% yield (*Entry 4*), which was optimised to 48% yield when the concentration of 1,4-dioxane was increased from 0.100 M to 0.500 M (*Entry 5*). After further screening had been performed on *amide* ***269*** (*Scheme* ***3.14***, *vide infra*), novel conditions reported by De Vries,[135] which used a catalyst developed by Beller[136] and co-workers—1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (1,4-naphthoquinone)palladium(0) dimer (***273***) (*Figure* ***2.7***)—were employed to perform the Heck reaction.



273

Figure 2.7 *1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (1,4-naphthoquinone)palladium(0) dimer (**273**)*

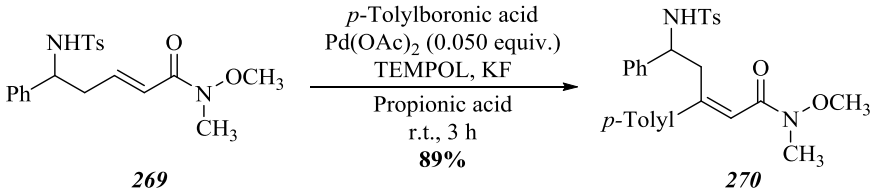
Pleasingly, *amide **270*** was furnished in 78% yield and exclusively as a single geometric isomer as observed by ^{1}H NMR spectroscopy, although 4-iodotoluene was required for this transformation to occur. As a control experiment, *enone **160*** was treated under the same conditions to furnish *enone **162*** in 74% yield with spectroscopic data identical to those reported earlier, although a small amount (10% by ^{1}H NMR analysis) of inseparable olefin regio/geometric isomers were thought to contaminate *enone **162***, even after repeated flash-column chromatography (*Scheme **2.61***). This result suggests that the presence of the Weinreb amide instead of the methyl ketone plays a key role in preventing olefin isomerisation.



Scheme 2.61 *Synthesis of amide **270** and enone **162** via Heck reaction*

The Fujiwara-Moritani reaction was also found to be effective in performing this transformation and conditions developed by Studer and co-workers,[137] which used palladium acetate and 4-hydroxy-2,2,6,6-tetramethylpiperidin-1-oxyl as the reoxidant. This procedure furnished *amide **270***

in 89% yield and exclusively as a single geometric isomer as observed by ^{1}H NMR spectroscopy (*Scheme* ***2.62***).

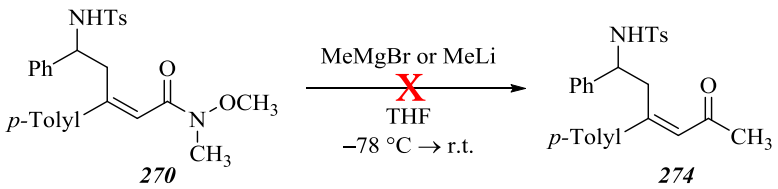


269 ***270***

Scheme 2.62 *Synthesis of amide* ***270*** *via Fujiwara-Moritani reaction*

The identity of *amide* ***270*** was confirmed by the presence of a singlet at 6.53 ppm in the ^{1}H NMR spectrum, which corresponded to the olefin proton. Further confirmation was obtained by the presence of a signal in the high-resolution mass spectrum at 501.1794 (Δ = +4.8 ppm), which corresponded to the $[M+Na]^+$ ion of *amide* ***270***. The *E*-geometry of the double-bond was inferred from nOe based NMR experiments performed during previous studies,[109] observed from the proposed mechanism of *syn-carbopalladation* during the Heck reaction, and from analogous nOe based NMR experiments conducted during later studies on the Heck reactions of β-substituted vinyl Weinreb amides (*Figure* ***3.4***, *vide infra*).

With the synthesis of *amide* ***270*** complete, the next step of the sequence was to unmask the Weinreb amide and furnish a ketone which would undergo subsequent cyclisation and elimination to generate a pyridine. However, treatment of *amide* ***270*** with either methylmagnesium bromide or methyllithium led to return of starting material along with some decomposition, which was proposed to be partly made up of sulfonamide elimination, although this could not be confirmed (*Scheme* ***2.63***).



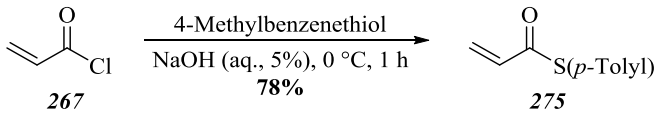
270 ***274***

Scheme 2.63 *Failed synthesis of enone* ***274***

Although Heck reactions on vinyl Weinreb amides could be performed successfully, functionalisation of *amide* ***270*** was not possible due to the presence of a sulfonamide leaving group. It was decided that thioacrylates may be easier to functionalise as the sulfonamide moiety was known to be stable to palladium-catalysed reaction conditions.

2.7.3 Enone surrogates: Thioacrylates

After exploring the use of Weinreb amides as enone surrogates, attention turned to the use of thioesters for this purpose. Studies began with the synthesis of *thioacrylate* ***275***, which was thought to be a suitable substrate for Liebeskind-Srogl coupling that would take place after the Heck reaction. 4-Methylbenzenethiol was treated with acryloyl chloride (***267***) in the presence of sodium hydroxide, which generated *thioacrylate* ***275*** in 78% yield (*Scheme* ***2.64***).



267 ***275***

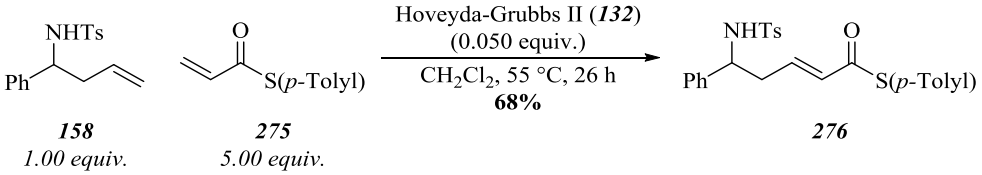
Scheme 2.64 *Synthesis of thioacrylate* ***275***

The identity of *thioacrylate* ***275*** was confirmed by the presence of a singlet at 2.42 ppm in the ^{1}H NMR spectrum, which corresponded to Ar$C\underline{H}_3$. Further confirmation was obtained when the spectroscopic data was found to be consistent with those reported in the literature for *thioacrylate* ***275***.[138]

Thioacrylate ***275*** was then treated with *sulfonamide* ***158*** in the cross-metathesis using Hoveyda-Grubbs second generation catalyst (***132***), which furnished *thioacrylate* ***276*** in an acceptable 68% yield and exclusively as a single geometric isomer as observed by ^{1}H NMR spectroscopy, when 5.00 equivalents of *thioacrylate* ***275*** were employed (*Scheme* ***2.65***).

The identity of *thioacrylate* ***276*** was confirmed by the absence of two double doublets at 6.42 ppm (J = 17.0, 1.5 Hz) and 5.79 ppm (J = 10.0, 1.5 Hz) in the ^{1}H NMR spectrum, which corresponded to the geminal protons on the olefin in *thioacrylate* ***275***. Further confirmation was obtained by the presence of a signal at 3274 cm^{-1} in the infrared spectrum, which corresponded to the N−H stretch.

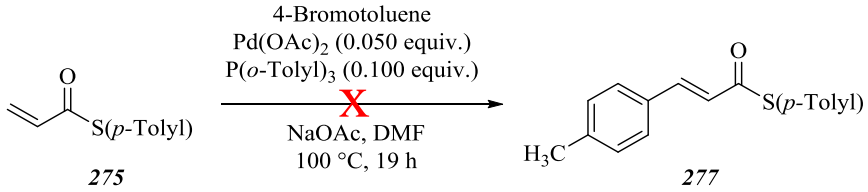
The double-bond geometry was confirmed to be *E* by the diagnostic coupling constant (J = 15.5 Hz) for the olefin protons observed in the ^{1}H NMR spectrum.



158 *1.00 equiv.* ***275*** *5.00 equiv.* ***276***

Scheme 2.65 *Synthesis of thioacrylate* ***276*** *via cross-metathesis reaction*

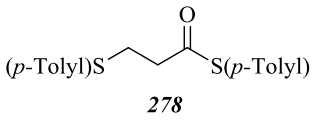
Even though a small amount of *thioacrylate* ***276*** had been synthesised, it was felt that attempting the Heck reaction on *thioacrylate* ***275*** would lead to simpler optimisation.



275 ***277***

Scheme 2.66 *Failed synthesis of thioacrylate* ***277*** *via Heck reaction*

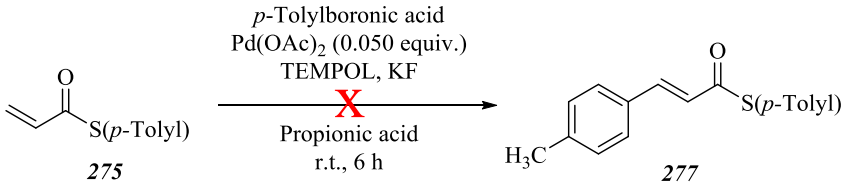
Thioacrylate ***275*** was treated with 4-bromotoluene using Heck's conditions (*Scheme* ***2.66***), disappointingly, no trace of *thioacrylate* ***277*** was present but recovery of *thioacrylate* ***275*** along with a small amount of *thioacrylate* ***278*** (*Figure* ***2.8***) was observed in the ^{1}H NMR spectrum and low-resolution mass spectrum of the crude reaction mixture. It was proposed that this could occur through palladium insertion into the C–S bond, which could eventually lead to generation of 4-methylbenzenethiolate and subsequent conjugate addition.



278

Figure 2.8 *Thioacrylate* ***278****—observed during the failed Heck reaction of thioacrylate* ***275***

Studer's Fujiwara-Moritani reaction conditions were also used in an attempt to generate *thioacrylate* ***277***. This reaction, however, led to extensive decomposition and it was hypothesised that the sulfur atom may oxidise under the reaction conditions (*Scheme* ***2.67***).



Scheme 2.67 *Failed synthesis of thioacrylate* ***277*** *via Fujiwara-Moritani reaction*

2.8 Conclusions

2.8.1 Summary

In summary, the *de novo* syntheses of a range of 2,4,6-trisubstituted pyridines have been described. Installation of the substituents arises from the precursor sulfonamide (R^1), enone (R^2), or from the aryl/vinyl bromide (R^3) employed in the Heck reaction. The scope of substitution was found to be excellent at *C-6* (R^1) and *C-4* (R^3), however the scope at *C-2* (R^2) was limited to simple aliphatic substrates. To circumvent this issue, acrylates, vinyl Weinreb amides, and thioacrylates were employed successfully in the cross-metathesis reaction, but ultimately, the formation of 2,4,6-trisubstituted pyridines was not possible using these protocols

2.8.2 Future work

Even though vinyl Weinreb amides were not appropriate substrates for the synthesis of 2,4,6-trisubstituted pyridines, due to sulfonamide elimination when treated with organometallic reagents, the Heck reaction of vinyl Weinreb amides was conducted successfully and is an interesting, yet under-utilised substrate for this type of reaction. It would be useful to explore and understand the reactivity of vinyl Weinreb amides in the Heck reaction, and then explore the possible scope of reactivity.

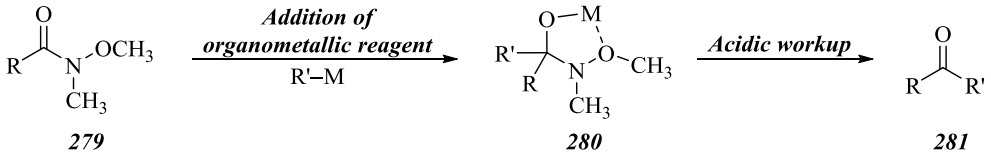
Chapter 3

Vinyl Weinreb amides as versatile substrates in the Heck reaction

A selection of the work described in this chapter has been published in Tetrahedron.[139]

3.1 The use of Weinreb amides in chemistry

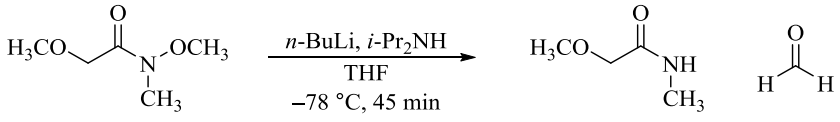
Since their discovery in 1981 by Weinreb and Nahm,[140] Weinreb amides have become an essential component of a synthetic organic chemists' toolkit, having use in the arena of natural product synthesis and for small-molecule synthesis.[141] The main reason for the use of a Weinreb amide is to prevent the over-addition reaction seen when organometallic reagents are added into the carbonyl group of a molecule. Typically, treatment of a generic ester with an organometallic reagent, such as methylmagnesium bromide, will result in significant amounts of the tertiary alcohol. The Weinreb amide, however, will furnish the desired ketone as the major product. Aldehydes can also be generated by treatment of the Weinreb amide with a reducing agent such as lithium aluminium hydride.[140]



279 ***280*** ***281***

Scheme 3.1 *Addition of an organometallic reagent to amide* ***279***

This reactivity is a result of the stability of *metallocycle* ***280*** formed after addition of an organometallic reagent to the carbonyl group has occurred. *Metallocycle* ***280*** then collapses only after the addition of a mild acid, which also quenches any remaining organometallic reagent, thus preventing over-addition (*Scheme* ***3.1***). In addition, Weinreb amides are easy to prepare from acid chlorides,[140] carboxylic acids,[142,143] or from aryl bromides by aminocarbonylation.[144] Furthermore, they undergo very few side reactions, and are easily cleaved during an acidic workup.



282 ***283*** ***284***

Scheme 3.2 *Generation of amide* ***283*** *and formaldehyde (****284****) from amide* ***282***

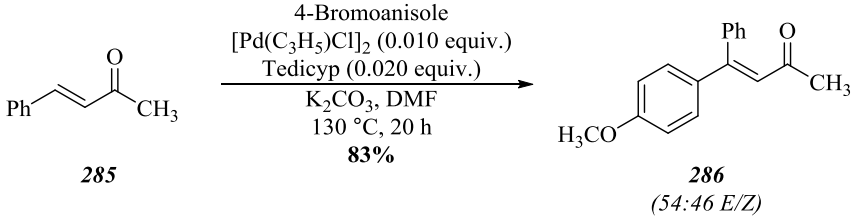
One notable side reaction pathway, however, makes Weinreb amides incompatible with the use of strong, sterically hindered bases (*Scheme* ***3.2***). It was reported that when *amide* ***282*** was treated with lithium diisopropylamide, elimination of *amide* ***283*** occurred generating formaldehyde (***284***).[145] It was hypothesised that this could either occur through an E2 mechanism or *via* concerted elimination from the enolate. E2 elimination was concluded to be the more likely mechanism after control experiments had been performed.

3.2 Literature reported Heck reactions on enones and vinyl Weinreb amides

3.2.1 Introduction

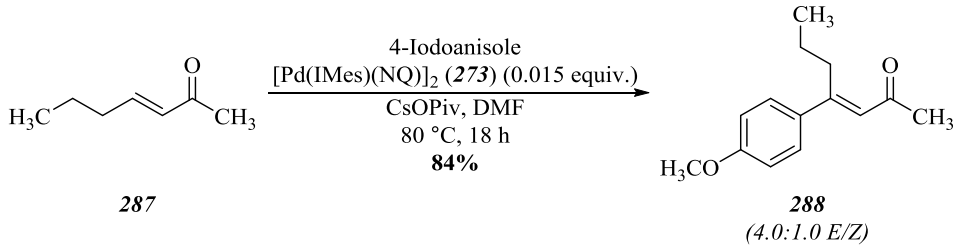
To date, methods for introducing additional substituents onto an enone with retention of the alkene oxidation level typically involve exposing the enone to Heck reaction conditions. While this type of reaction of enones has been described in the literature, enones are not nearly as commonly employed as their acrylate counterparts, with the first Heck reaction on an aryl vinyl ketone being claimed in 2003.[146] The reason for their underuse is likely to be a practical issue as low molecular weight enones are typically difficult to handle. Some enones have been shown to polymerise rapidly when heated, and can be volatile and toxic.

In addition, whilst not necessarily occurring in every case, examples have been reported in the literature where mixtures of olefin geometric isomers have been observed when performing Heck reaction on β-substituted vinyl ketones. For example, Doucet and Santelli obtained an 83% yield of *enone* ***286*** with a 54:46 mixture of geometric isomers when benzalacetone (***285***) was coupled with 4-bromoanisole using *cis,cis,cis,cis*-tetrakis(diphenylphosphinomethyl)cyclopentane and the dimer of allylpalladium chloride (*Scheme* ***3.3***).[147]



Scheme 3.3 *Mixtures of geometric isomers observed in the Heck reaction of benzalacetone* ***(285)***

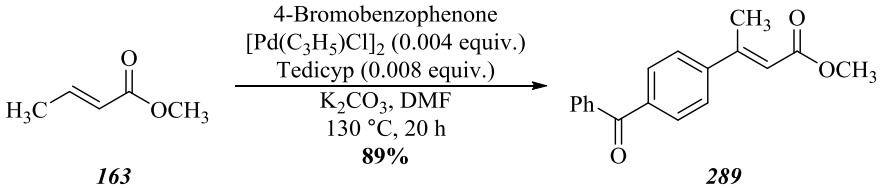
These mixtures have also been observed in the work of De Vries and co-workers.[135] The Heck reaction of hept-3-en-2-one (***287***) and 4-iodoanisole gave *enone* ***288*** in 84% yield and as a 4.0:1.0 mixture of geometric isomers (*Scheme* ***3.4***). This was hypothesised to be a result of the fast carbon-bound to oxygen-bound palladium enolate conversion present in these α,β-unsaturated carbonyl systems



287 ***288*** *(4.0:1.0 E/Z)*

Scheme 3.4 *Mixtures of geometric isomers observed in the Heck reaction of hept-3-en-2-one (**287**)*

When acrylates are employed in the Heck reaction, mixtures of geometric isomers are also sometimes observed, although much less frequently and much less severely compared to their enone counterparts with a 10.1.0 mixture of geometric isomers observed when *acrylate* ***289*** was synthesised *via* the Heck reaction (*Scheme* ***3.5***).[147]



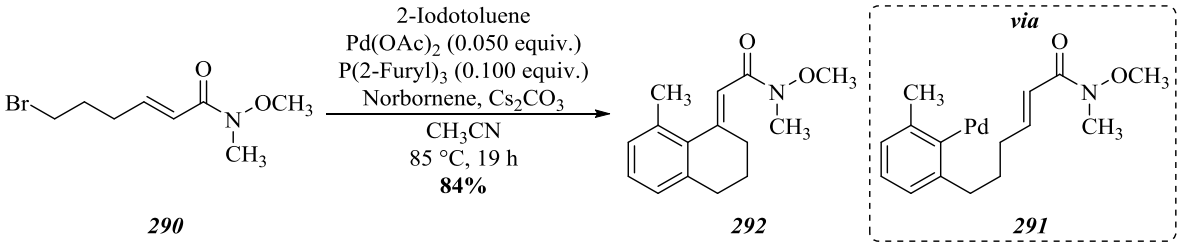
163 ***289*** *(10:1.0 E/Z)*

Scheme 3.5 *Mixtures of geometric isomers observed in the Heck reaction of methyl crotonate (**163**)*

It was hypothesised that vinyl Weinreb amides may be suitable alternatives to enones in the Heck reaction, as they could be further functionalised back to enones after the Heck reaction. However, within the large amount of research reported on the Heck reaction, it was surprising to discover only a few isolated reports of the successful use of vinyl Weinreb amides as substrates, thus representing a significant absence from the literature.

3.2.2 Intramolecular Heck reactions on vinyl Weinreb amides—Lautens (2001 and 2006)

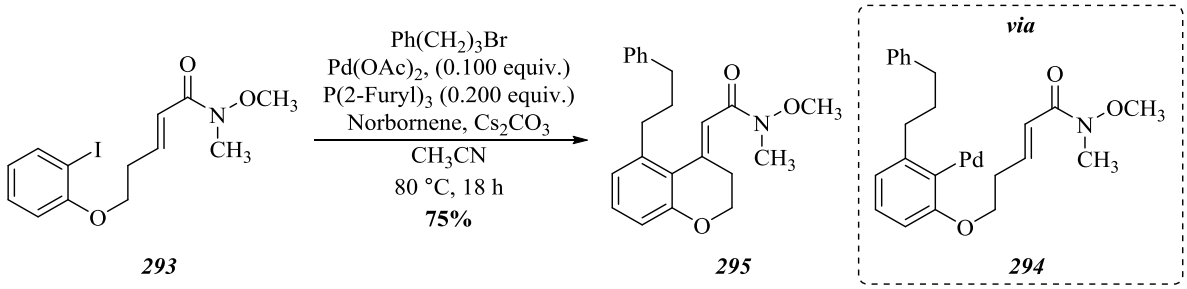
In 2001, Lautens and co-workers reported a novel sequential alkylation/Heck reaction protocol, with the scope inclusive of an unprecedented intramolecular Heck reaction onto a vinyl Weinreb amide[148] (*Scheme* ***3.6***).



Scheme 3.6 *Synthesis of amide* ***292*** *via sequential alkylation/Heck reaction protocol*

2-Iodotoluene and *bromide* ***290*** were coupled in the presence of palladium acetate, tri(2-furyl)phosphine, and norbornene to furnish *amide* ***292*** in an excellent 84% yield. The reaction was thought to proceed *via intermediate* ***291***, which then underwent an intramolecular Heck reaction onto the vinyl Weinreb amide.

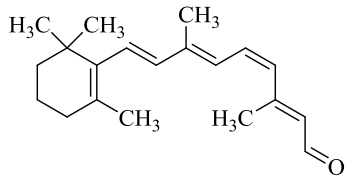
Following on from this work, in 2006, Lautens and co-workers performed a novel domino *ortho*-alkylation/Heck reaction protocol to generate a range of substituted benzoxacycles in excellent yields, with an intramolecular Heck reaction onto a vinyl Weinreb amide included as a key component of the reaction[149] (*Scheme* ***3.7***). Treatment of *iodide* ***293*** with (3-bromopropyl)benzene in the presence of palladium acetate, tri(2-furyl)phosphine, and norbornene furnished *amide* ***295*** in 75% yield. The reaction was thought to proceed *via intermediate* ***294***, which then undergoes an intramolecular Heck reaction onto the vinyl Weinreb amide.



Scheme 3.7 *Synthesis of amide* ***295*** *via domino ortho-alkylation/Heck reaction protocol*

3.2.3 Intermolecular Heck reactions on unsubstituted vinyl Weinreb amides—Brown (2011)

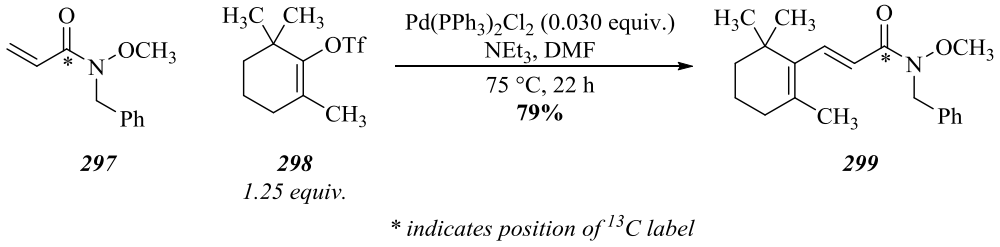
In 2011, Brown and co-workers reported a synthesis of the $^{13}C_2$-labelled (11*Z*)-retinals (***296***) (*Figure **3.1***), the synthesis of which involved a novel intermolecular Heck reaction onto an unsubstituted vinyl Weinreb amide[150] (*Scheme **3.8***).



296

Figure 3.1 *(11Z)-retinal (**296**)*

*Triflate **298*** was reacted with ^{13}C-labelled *amide **297***, a Weinreb amide analogue, in the presence of bis(triphenylphosphine)palladium dichloride to generate ^{13}C-labelled *amide **299*** in 79% yield.



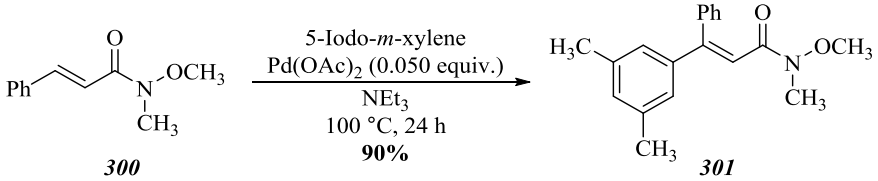
297 ***298*** *1.25 equiv.* ***299***

** indicates position of ^{13}C label*

Scheme 3.8 *Synthesis of amide **299** via Heck reaction*

3.2.4 Intermolecular Heck reactions on β-aryl-substituted vinyl Weinreb amides—Kim (2013)

In 2013, Kim and co-workers reported a novel Heck reaction on β-aryl-substituted vinyl Weinreb amides,[151] which was coincidental in time with similar work published by the Donohoe group.[139] Kim had discovered that treatment of β-aryl-substituted vinyl Weinreb amides, using Heck conditions developed by Fabrizi and co-workers,[152,153] with aryl iodides generated a range of β,β-disubstituted vinyl Weinreb amides.



300 ***301***

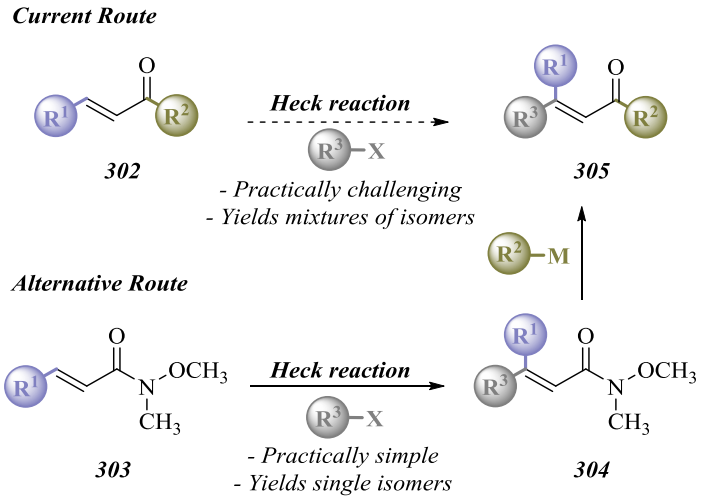
Scheme 3.9 *Synthesis of amide **301** via Heck reaction*

For example, treatment of *amide* ***300*** with 5-iodo-*m*-xylene using Fabrizi's Heck conditions afforded *amide* ***301*** in an excellent 90% yield, although trace amounts of the olefin geometric isomer were present (*Scheme* ***3.9***). The scope of the Heck reaction, however, was limited to only β-aryl-substituted vinyl Weinreb amides and the scope of the aryl iodide had not been fully explored. Furthermore, in some of the examples, the olefin geometric isomer was also isolated although this was not a major downfall as it was never observed in more than 10% yield, and typically below 5% yield.

3.3 Research outline

3.3.1 Vinyl Weinreb amides as enone surrogates in the Heck reaction

Even though the incorporation of Weinreb amides into the synthesis of 2,4,6-trisubstituted pyridines was unsuccessful, the results obtained when performing Heck reactions with vinyl Weinreb amides as substrates was pleasing (*Scheme* ***2.61***, *vide supra*). In contrast to the use of *enone* ***160*** and *acrylate* ***253***, conditions were developed which allowed the Heck reaction of *amide* ***269*** to generate pure material without any visible sign of regioisomers or geometric isomers, as observed by ^{1}H nuclear magnetic resonance (NMR) spectroscopy. Furthermore as mentioned above, from a practical standpoint, low molecular weight enones are typically difficult to handle. Some of them have been shown to polymerise rapidly, and can be volatile and toxic. With the extra molecular weight added from the amide moiety, vinyl Weinreb amides may be a more practical solution for organic synthesis, however overall atom economy would decrease.



Scheme 3.10 *Concept—Heck reaction on vinyl Weinreb amides*

It was therefore proposed that instead of carrying out these direct Heck reactions on enones, a Heck reaction on *amide* ***303*** could be performed to give a single geometric isomer. It was then reasoned that the Heck reaction would be followed by a functionalisation of *intermediate* ***304*** to furnish *enone* ***305*** as single a geometric isomer, which may be difficult to access by a direct Heck reaction on the *enone* ***302*** itself. The vinyl Weinreb amide would effectively act as an enone surrogate (*Scheme* ***3.10***).

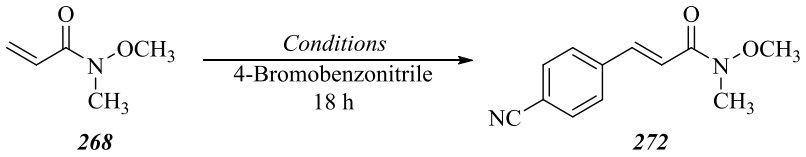
3.3.2 Project aims

The aims of the project were to assess the viability of performing Heck reactions on vinyl Weinreb amides. After finding suitable conditions for the Heck reaction, the scope of the halide and the vinyl Weinreb amide would be explored. Following on, once the Heck reactions of vinyl Weinreb amides had been successfully completed, functionalisation of the Weinreb amide would be attempted to generate a range of enones, some of which may be difficult to access by direct Heck reaction on the precursor enone.

3.4 Scope of the Heck reaction on unsubstituted vinyl Weinreb amides

3.4.1 Optimisation of the Heck reaction on unsubstituted vinyl Weinreb amides

Studies began with the optimisation of conditions for the Heck reaction on unsubstituted vinyl Weinreb amides and 4-bromobenzonitrile was chosen as a suitable substrate for *amide* ***268*** (*Table* ***3.1***). Palladium acetate was initially used as catalyst but this reaction only returned mostly *amide* ***268*** (*Entry 1*). More success was found when phosphine based ligands were employed with a 45% yield being obtained with tetrakis(triphenylphosphine)palladium (*Entry 2*). Heck conditions similar to those developed by Fu and co-workers[98] gave *amide* ***272*** in an excellent 89% yield (*Entry 3*) and an 85% yield was obtained when [1,1′-bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II) was employed (*Entry 4*). 2-Di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl has been used extensively by Buchwald[154] for the Buchwald-Hartwig amination and it was hoped that this ligand would prove effective in the Heck reaction. Disappointingly, only a 77% yield of *amide* ***272*** was obtained using this catalytic system (*Entry 5*). Pleasingly, conditions developed by Heck[59] proved very effective for the synthesis of *amide* ***272*** with a 93% yield isolated exclusively as a single geometric isomer as observed by ^{1}H NMR spectroscopy (*Entry 6*).



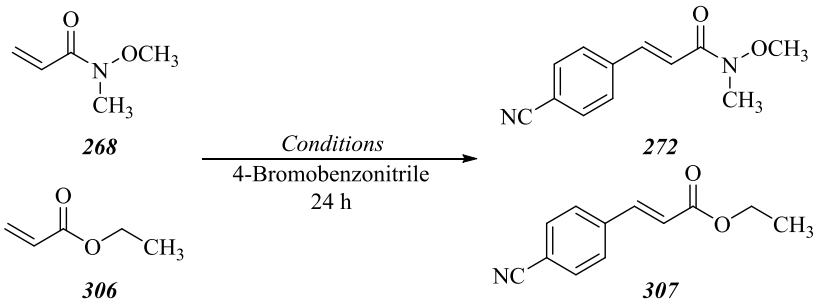
268 ***272***

Entry	*Catalyst*	*Base*	*Solvent*	*Temperature*	*Yield*
1	$Pd(OAc)_2$ (0.050 equiv.)	NaOAc (2.00 equiv.)	DMF (0.100 M)	120 °C	10%[a]
2	$Pd(PPh_3)_4$ (0.050 equiv.)	NaOAc (2.00 equiv.)	DMF (0.100 M)	80 °C	45%
3	Pd_2dba_3 (0.050 equiv.) *t*-$Bu_3P{\cdot}HBF_4$ (0.200 equiv.)	Cy_2NMe (1.50 equiv.)	PhMe (0.100 M)	80 °C	89%
4	$PdCl_2$(dtbpf) (0.050 equiv.)	NaOAc (2.00 equiv.)	DMF (0.100 M)	80 °C	85%
5	$Pd(OAc)_2$ (0.050 equiv.) XPhos (0.100 equiv.)	NaOAc (2.00 equiv.)	DMF (0.100 M)	80 °C	77%
6	$Pd(OAc)_2$ (0.050 equiv.) P(*o*-Tolyl)$_3$ (0.100 equiv.)	NaOAc (2.00 equiv.)	DMF (0.100 M)	120 °C	93%

Table 3.1 *Optimisation of the Heck reaction on amide* ***268****.* [a]*Conversion as observed in* ^{1}*H NMR of crude reaction mixture*

The identity of *amide* ***272*** was confirmed by the presence of a signal at 2224 cm^{-1} in the infrared spectrum, which corresponded to the nitrile stretch. Further confirmation was obtained by the presence of a signal in the high-resolution mass spectrum at 216.0898 (Δ = +0.46 ppm), which corresponded to the $[M]^+$ ion of *amide* ***272***. The double-bond geometry was confirmed to be *E* by the diagnostic coupling constant (J = 16.0 Hz) for the olefin protons observed in the ^{1}H NMR spectrum. This olefin geometry is the expected outcome of the Heck reaction as the *E* isomer is the thermodynamically most stable diastereoisomer due to minimisation of steric clashes.

3.4.2 Reactivity of unsubstituted vinyl Weinreb amides



Entry	*Catalyst*	*Base*	*Solvent*	*Temperature*	*Result*
1	$Pd(OAc)_2$ (0.050 equiv.) P(*o*-Tolyl)$_3$ (0.100 equiv.)	NaOAc (2.00 equiv.)	DMF (0.100 M)	120 °C	1.0:1.2 ***272***/***307***
2	Pd_2dba_3 (0.050 equiv.) *t*-$Bu_3P{\cdot}HBF_4$ (0.200 equiv.)	Cy_2NMe (1.50 equiv.)	PhMe (0.100 M)	80 °C	1.4:1.0 ***272***/***307***

Table 3.2 *Competition experiment for amide* ***268*** *and ethyl acrylate (****306****)*

It was of considerable interest to investigate how the reactivity of *amide* ***268*** in the Heck reaction compared to an acrylate counterpart. Electron-deficient olefins are known to be more reactive than electron-rich olefins in the non-polar Heck reaction[50] and for this reason it was thought that *amide* ***268*** would be less reactive than ethyl acrylate (***306***). To test the hypothesis, a competition experiment was designed where 4-bromobenzonitrile (1.00 equivalent) was treated under Heck's and Fu's Heck conditions in the presence of *amide* ***268*** (5.00 equivalents) and ethyl acrylate (***306***) (5.00 equivalents), with the product distribution observed from the ^{1}H NMR of the crude reaction mixture (*Table* ***3.2***). Interestingly, it was found that under Heck's conditions, a ratio of 1.0:1.2 of *amide* ***272***/*acrylate* ***307*** was obtained whereas Fu's Heck conditions gave a ratio of 1.4:1.0 of *amide* ***272***/*acrylate* ***307***. Within experimental error, these results show that *amide* ***268*** has similar reactivity in the Heck reaction as ethyl acrylate (***306***). The product ratios were calculated from the integration of the singlets at 3.74 or 3.69 ppm, and 3.28 or 3.23 ppm in the ^{1}H NMR spectrum, which corresponded to OC$\underline{H}_3$ and NC$\underline{H}_3$ in *amide* ***272***, respectively, and from the integration of the quartet at 4.22 ppm or 4.19 ppm, which corresponded to OC$\underline{H}_2$ in *acrylate* ***307*** (*Figure* ***3.2*** and *Figure* ***3.3***).

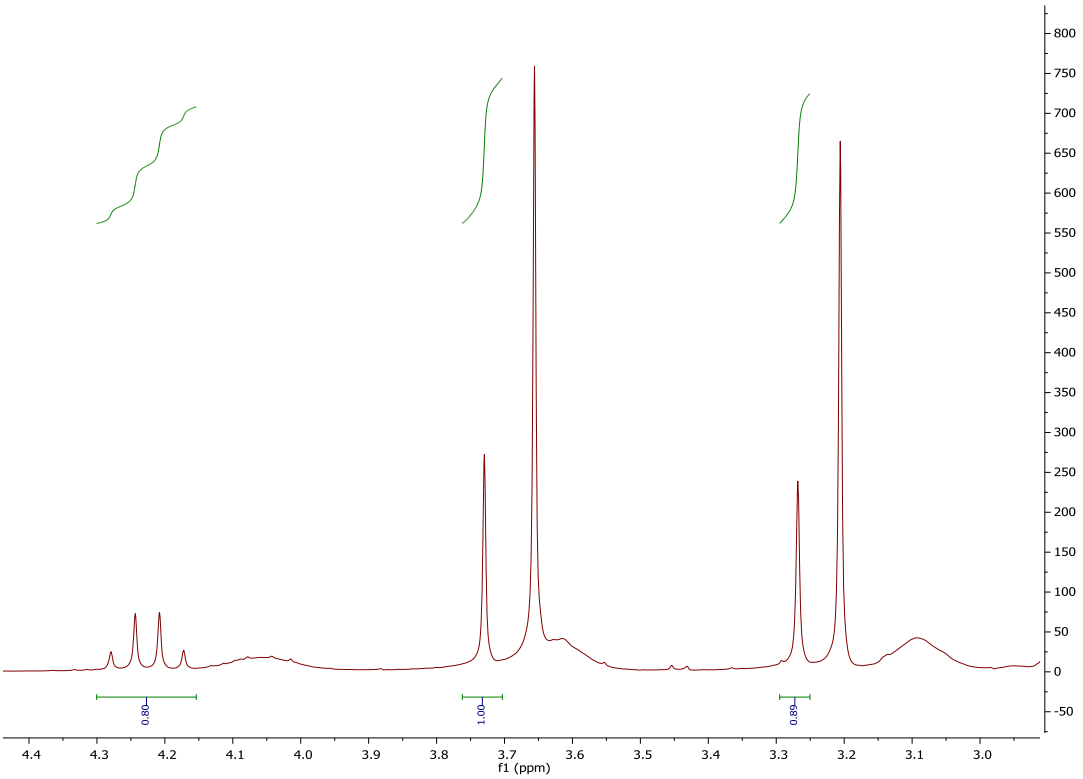


Figure 3.2 *^{1}H NMR spectrum for the competition experiment (Table **3.2**, Entry 1)*

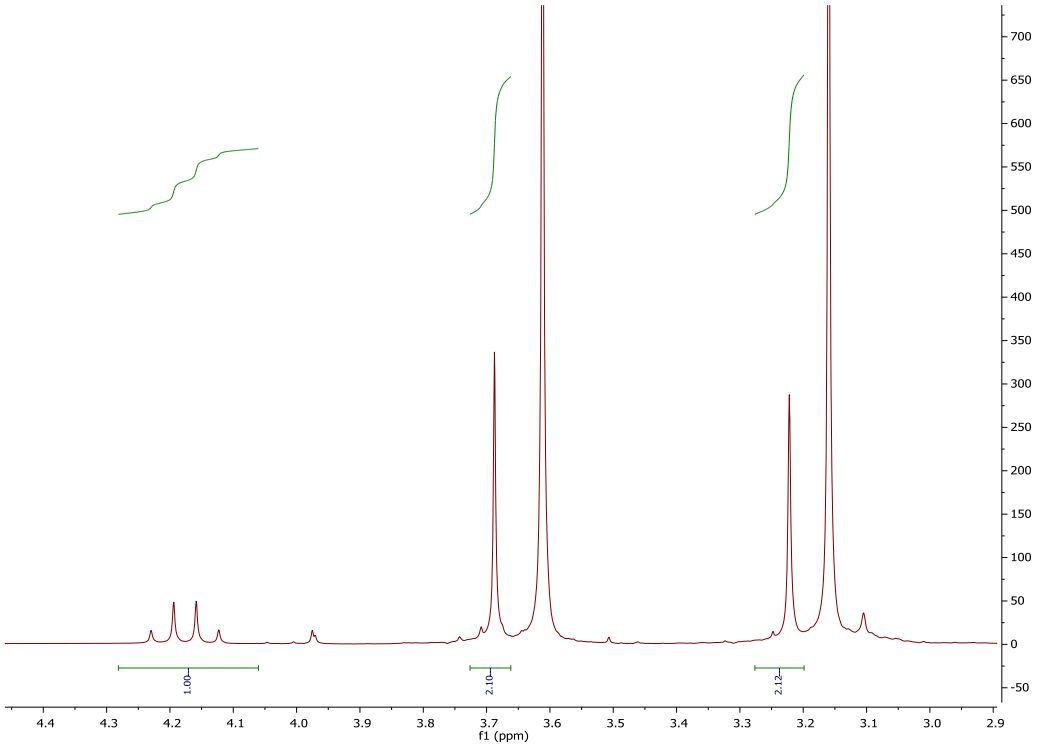
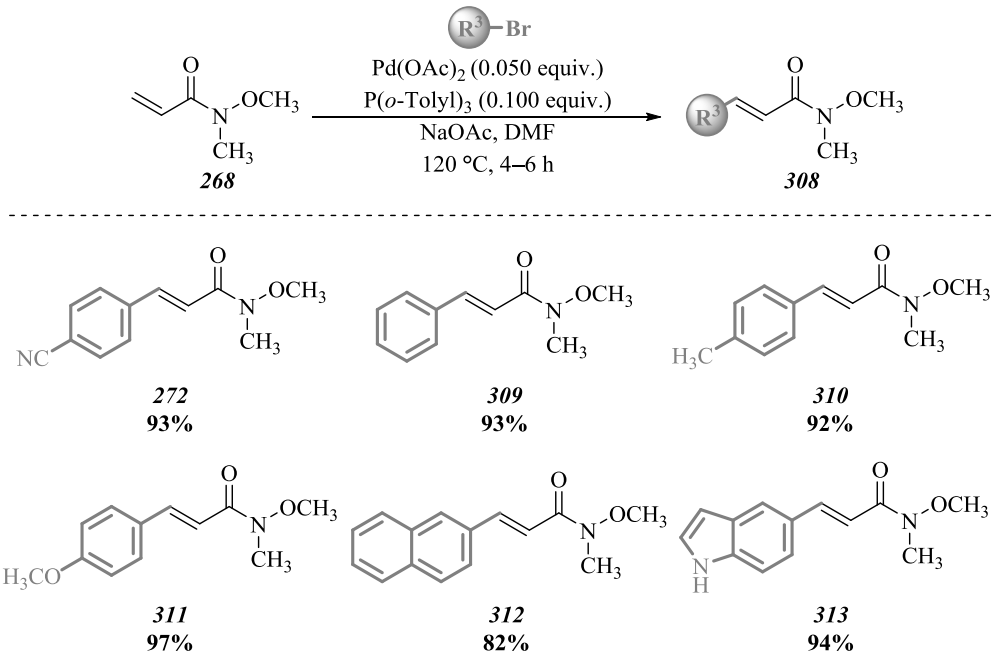


Figure 3.3 *^{1}H NMR spectrum for the competition experiment (Table **3.2**, Entry 2)*

3.4.3 Exploring the scope of the Heck reaction on amide 268

Focus turned to the synthesis of a range of β-substituted vinyl Weinreb amides from *amide* ***268***, and it was desirable to explore the scope using different aryl bromides. To this end, Heck's conditions, which utilised palladium acetate and tri(*o*-tolyl)phosphine, were employed (*Scheme* ***3.11***).



Scheme 3.11 *Scope of the Heck reaction on amide* ***268***

Pleasingly, bromobenzene and 4-bromotoluene with successfully coupled with *amide* ***268***. These conditions generated *amide* ***309*** and *amide* ***310*** in 93% yield and 92% yield, respectively. After generating β-aryl-substituted vinyl Weinreb amides with electron-neutral substituents, electron-rich substituents were attempted. *Amide* ***268*** was reacted with 4-bromoanisole under Heck's conditions to furnish *amide* ***311*** in 97% yield. Biaryl substituents were also suitable substrates and *amide* ***268*** was reacted under Heck's conditions with 2-bromonaphthalene to synthesise *amide* ***312*** in 82% yield. A slight decrease in yield was observed for this substrate which was proposed to be due to the extra steric bulk present in the aryl bromide. Finally, a heteroaromatic substituent was attempted in the protocol. Heteroaromatic substituents are known to be useful in medicinal chemistry due to their desirable physical properties, such as increased polarity and their ability to form hydrogen-bonds.[155] Heck's conditions were utilised for coupling of *amide* ***268*** and 5-bromoindole, and these conditions

furnished *amide* ***313*** in an excellent 94% yield. All of the reported amides were formed exclusively as single geometric isomers as observed by ^{1}H NMR spectroscopy

The identities of the synthesised amides were confirmed by appropriate spectroscopic methods, and in some cases, comparison to literature reported data. The double-bond geometries of the amides were confirmed to be *E* by the diagnostic coupling constant (J = 15.5–16.0 Hz) for the olefin protons observed in the ^{1}H NMR spectrum. The *E* geometric isomer is the thermodynamically favoured product from the Heck reaction performed on an unsubstituted vinyl Weinreb amide.

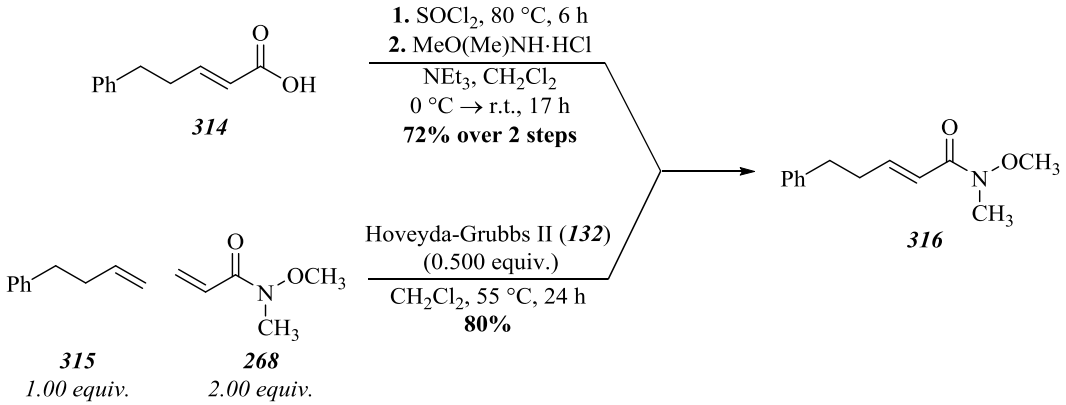
After assessing the scope of the Heck reaction on unsubstituted vinyl Weinreb amides using Heck's conditions, attention turned to performing Heck reactions onto more challenging monosubstituted vinyl Weinreb amides.

3.5 Scope of the Heck reaction on β-substituted vinyl Weinreb amides

3.5.1 Optimisation of the Heck reaction on β-substituted vinyl Weinreb amides

After accessing the scope of the Heck reaction on unsubstituted vinyl Weinreb amides, it was thought to be advantageous to expand the scope to performing Heck reactions on β-substituted vinyl Weinreb amides. This began with the synthesis of *amide* ***316*** and *amide* ***318*** which would be used as substrates to assess this protocol.

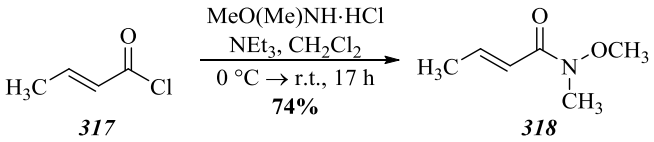
Following a reported literature procedure,[129,156] (*E*)-5-phenylpent-2-enoic acid (***314***) was treated first with thionyl chloride at reflux and then subsequently reacted with *N*,*O*-dimethylhydroxylamine hydrochloride to afford *amide* ***316*** in 72% yield over two steps. An alternative method for the synthesis of *amide* ***316*** involved the cross-metathesis reaction of 4-phenyl-1-butene (***315***) with *amide* ***268*** using Hoveyda-Grubbs second generation catalyst (***132***)[111,112] which furnished *amide* ***316*** in 80% yield exclusively as a single geometric isomer as observed by ^{1}H NMR spectroscopy (*Scheme* ***3.12***).



Scheme 3.12 *Syntheses of amide* ***316***

The identity of *amide* ***316*** was confirmed by the presence of two singlets at 3.63 ppm and 3.24 ppm in the ^{1}H NMR spectrum, which corresponded to OC$\underline{H_3}$ and NC$\underline{H_3}$, respectively. Further confirmation was obtained by the presence of a signal at 1662 cm^{-1} in the infrared spectrum, which corresponded to the carbonyl stretch. The double-bond geometry was confirmed to be *E* by the diagnostic coupling constant (J = 15.5 Hz) for the olefin protons observed in the ^{1}H NMR spectrum.

Secondly, following a reported literature procedure,[129] (*E*)-but-2-enoyl chloride (***317***) was treated with *N*,*O*-dimethylhydroxylamine hydrochloride in the presence of triethylamine to afford *amide* ***318*** in 74% yield (*Scheme* ***3.13***).

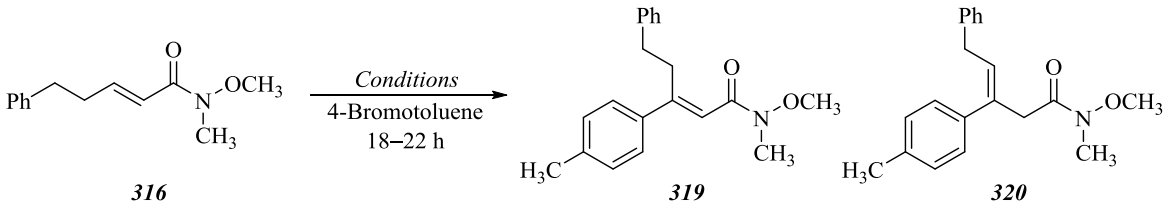


Scheme 3.13 *Synthesis of amide* ***318***

The identity of *amide* ***318*** was confirmed by the presence of two singlets at 3.68 ppm and 3.240 ppm in the ^{1}H NMR spectrum, which corresponded to OC$\underline{H_3}$ and C$\underline{H_3}$, respectively. Further confirmation was obtained when the spectroscopic data was found to be consistent with those reported in the literature for *amide* ***318***.[129] The double-bond geometry was confirmed to be *E* by the diagnostic coupling constant (J = 15.5 Hz) for the olefin protons observed in the ^{1}H NMR spectrum.

With the synthesis of the starting substrates in hand, attention turned to finding conditions that would promote the Heck reaction on β-substituted vinyl Weinreb amides, starting with *amide* ***316*** (*Table* ***3.3***).

Studies began with palladium acetate being used as the catalyst but this only led to the recovery of *amide* ***316*** as observed in the ^{1}H NMR of the crude reaction mixture (*Entry 1*). Heck's conditions with sodium acetate as the base, which had been successfully utilised for the Heck reaction of unsubstituted vinyl Weinreb amides (*Entry 2*) gave Heck coupling products in 23% yield, with the ^{1}H NMR of the crude reaction mixture indicating a 1.5:1.0 ratio of *amide* ***319***/*amide* ***320***, with the generation of *amide* ***320*** hypothesised to have come from palladium hydride mediated isomerisation. Heck's conditions when triethylamine was used as the base gave a reversal in product distribution with a 1.0:3.5 ratio of *amide* ***319***/*amide* ***320*** observed in the ^{1}H NMR of the crude reaction mixture (*Entry 3*).

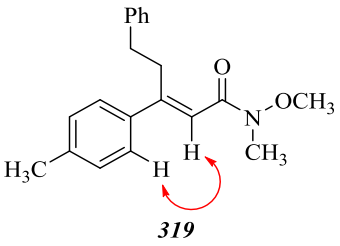


316 ***319*** ***320***

Entry	*Catalyst*	*Base*	*Solvent*	*Temperature*	*Result*
1	$Pd(OAc)_2$ (0.050 equiv.)	NaOAc (2.00 equiv.)	DMF (0.100 M)	120 °C	Recovered ***316***
2	$Pd(OAc)_2$ (0.050 equiv.) P(*o*-Tolyl)$_3$ (0.100	NaOAc (2.00 equiv.)	DMF (0.100 M)	120 °C	23% ***319*** (1.5:1.0 ***319***/***320***)[a]
3	$Pd(OAc)_2$ (0.050 equiv.) P(*o*-Tolyl)$_3$ (0.100	NEt_3 (2.00 equiv.)	DMF (0.100 M)	120 °C	(1.0:3.5 ***319***/***320***)[a]
4	$PdCl_2$(dtbpf) (0.100 equiv.)	Cs_2CO_3 (1.50 equiv.)	1,4-Dioxane (0.100 M)	80 °C	33% ***319*** + ***320*** (1.5:1.0 ***319***/***320***)
5	Pd_2dba_3 (0.050 equiv.) *t*-$Bu_3P{\cdot}HBF_4$ (0.200 equiv.)	Cy_2NMe (1.50 equiv.)	1,4-Dioxane (0.100 M)	80 °C	89% ***319*** + ***320*** (1.0:1.2 ***319***/***320***)

Table 3.3 *Optimisation of the Heck reaction on amide* ***316***. [a]*Ratio as observed in* ^{1}*H NMR of crude reaction mixture*

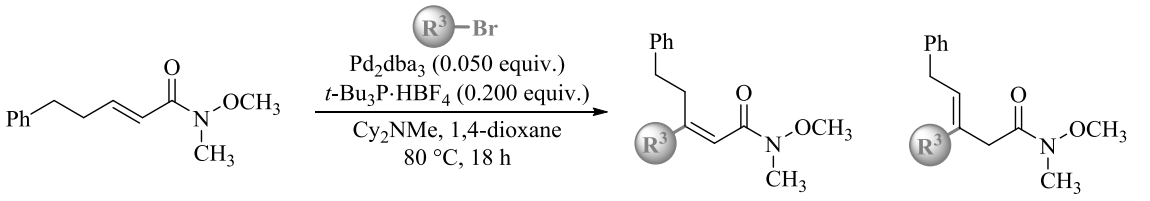
Increasing the steric bulk on the ligand had a beneficial effect and [1,1′-bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II) gave a combined 33% yield of *amide* ***319*** and of *amide* ***320***. Disappointingly, a 1.5:1.0 ratio of *amide* ***319***/*amide* ***320*** was observed (*Entry 4*). Another increase in the steric bulk of the ligand gave another increase in the combined yield to 89%, but once again, a 1.0:1.2 ratio of *amide* ***319***/*amide* ***320*** was observed (*Entry 5*). It was hoped that a reduction in temperature may improve the yield of *amide* ***319*** but decreasing the reaction temperature to 50 °C led only to *amide* ***316***.



319

Figure 3.4 *Confirmation of double-bond geometry in amide* ***319*** *by nOe based NMR experiments*

The identity of *amide* ***319*** was confirmed by the presence of a singlet at 6.51 ppm in the ^{1}H NMR spectrum, which corresponded to the olefin proton. The double-bond geometry was confirmed by nuclear Overhauser effect (nOe) based NMR experiments performed on *amide* ***319*** (*Figure* ***3.4***). The identity of *amide* ***320*** was confirmed by the presence of a triplet (J = 7.5 Hz) at 6.12 ppm in the ^{1}H NMR spectrum, which corresponded to the olefin proton.



316

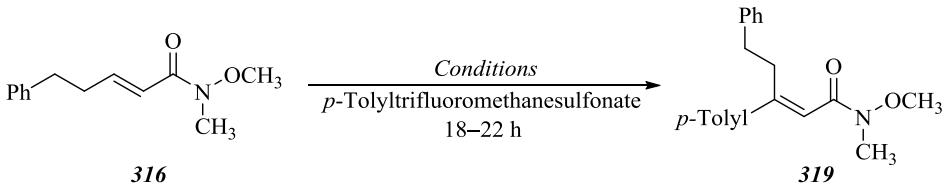
*R^3 = p-Tolyl (**319**), Ph (**321**), 2-Naphthyl (**323**)*

*R^3 = p-Tolyl (**320**), Ph (**322**), 2-Naphthyl (**324**)*

Entry	R^3	*Yield*
1	*p*-Tolyl	89% ***319*** + ***320*** (1.0:1.2 ***319***/***320***)
2	Ph	81% ***321*** + ***322*** (1.2:1.0 ***321***/***322***)
3	2-Naphthyl	87% ***323*** + ***324*** (4.4:1.0 ***323***/***324***)

Table 3.4 *Effect of aryl bromide on regioselectivity*

With a good yield of coupling product obtained, studies focussed on trying to control the palladium hydride mediated isomerisation by altering the aryl bromide (*Table **3.4***). Interestingly, even though a similar yield and ratio of *amide **321**/amide **322*** was obtained when bromobenzene was employed (*Entry 2*), significantly less isomerisation was seen when 2-bromonaphthalene (*Entry 3*) was used. It was proposed that bulky aryl bromides would provide extra steric hindrance to the olefin and thus reduce the rate of palladium hydride addition, which is thought to be a pathway for olefin isomerisation.



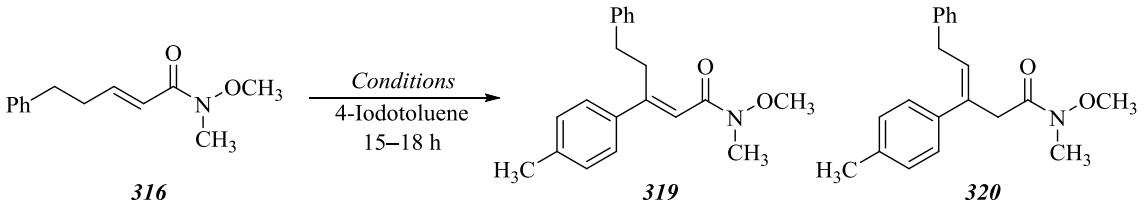
316 ***319***

Entry	*Catalyst*	*Base*	*Solvent*	*Temperature*	*Result*
1	$Pd(OAc)_2$ (0.050 equiv.) $P(o\text{-Tolyl})_3$ (0.100 equiv.)	NaOAc (2.00 equiv.)	DMF (0.100 M)	120 °C	Recovered ***316***
2	$Pd(OAc)_2$ (0.050 equiv.) $P(o\text{-Tolyl})_3$ (0.100 equiv.)	NEt_3 (2.00 equiv.)	DMF (0.100 M)	120 °C	Recovered ***316***
3	Pd_2dba_3 (0.050 equiv.) $t\text{-Bu}_3P\cdot HBF_4$ (0.200 equiv.)	Cy_2NMe (1.50 equiv.)	1,4-Dioxane (0.100 M)	80 °C	Recovered ***316***

Table 3.5 *Polar Heck conditions on amide **316***

With mixtures of *amide **319*** and *amide **320*** observed when reactions were performed with various aryl bromides, it was decided that a change in Heck conditions may prove beneficial as the polar Heck reaction is known to have different reactivity from the non-polar Heck reaction (*Chapter **1.2.6***, *vide supra*). To this end, Heck reactions were performed with *p*-tolyltrifluoromethanesulfonate (*Table **3.5***), which unlike a halide, is thought to dissociate rapidly to free a coordination site for *syn-carbopalladation* to occur. This species would be cationic in nature due to the loss of the trifluoromethanesulfonate anion. Unfortunately, attempts to employ Heck's (*Entry 1 and Entry 2*) or Fu's Heck conditions (*Entry 3*) led only to the recovery of *amide **316*** as observed by thin-layer chromatography.

Even though aryl bromides and aryl chlorides are generally considered desirable for cross-coupling reactions, it was important to assess the use of aryl iodides for this Heck reaction (*Table **3.6***). Heck's conditions gave a 28% yield of *amide **319***, with the ^{1}H NMR of the crude reaction mixture indicating a 1.4:1.0 ratio of *amide **319***/*amide **320*** (*Entry 1*). Disappointingly, Fu's Heck conditions with *N,N*-dicyclohexylmethylamine (*Entry 2*) or caesium carbonate (*Entry 3*) both returned *amide **316*** with minimal amounts of *amide **319*** observed by thin-layer chromatography.

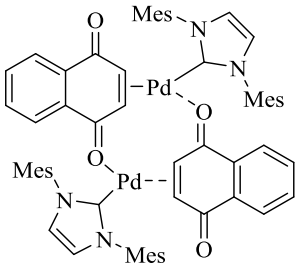


316 ***319*** ***320***

Entry	*Catalyst*	*Base*	*Solvent*	*Temperature*	*Result*
1	$Pd(OAc)_2$ (0.050 equiv.) P(*o*-Tolyl)$_3$ (0.100 equiv.)	NaOAc (2.00 equiv.)	DMF (0.100 M)	120 °C	28% ***319*** (1.4:1.0 ***319***/***320***)
2	Pd_2dba_3 (0.050 equiv.) *t*-$Bu_3P{\cdot}HBF_4$ (0.200 equiv.)	Cy_2NMe (1.50 equiv.)	1,4-Dioxane (0.100 M)	80 °C	Recovered ***316***
3	Pd_2dba_3 (0.050 equiv.) *t*-$Bu_3P{\cdot}HBF_4$ (0.200 equiv.)	Cs_2CO_3 (1.50 equiv.)	1,4-Dioxane (0.100 M)	80 °C	Recovered ***316***

Table 3.6 *Heck reaction on amide **316** with 4-iodotoluene*

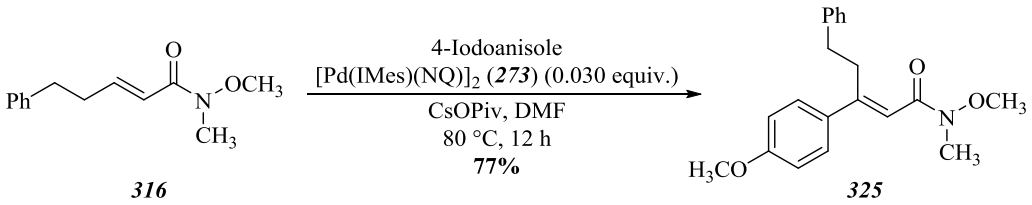
Novel conditions developed by De Vries,[135] which used a catalyst developed by Beller and co-workers—1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (1,4-naphthoquinone)palladium(0) dimer (***273***) (*Figure **3.5***)—were developed at this point and employed to promote the Heck reaction.



273

Figure 3.5 *1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (1,4-naphthoquinone)palladium(0) dimer (**273**)*

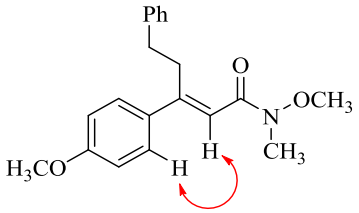
*Amide **325*** was generated in 77% yield when treated under De Vries' Heck conditions, although this required the use of 4-iodoanisole (*Scheme **3.14***). Pleasingly, *amide **325*** was isolated exclusively as a single geometric isomer and without the presence of any regioisomers as observed by ^{1}H NMR spectroscopy.



316 ***325***

Scheme 3.14 *Synthesis of amide **325** via Heck reaction*

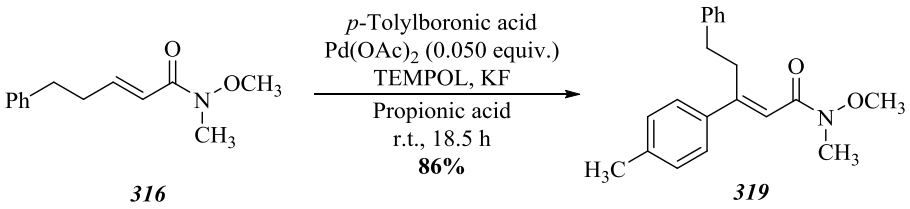
The identity of *amide **325*** was confirmed by the presence of a two singlets at 6.47 ppm and 3.82 ppm in the ^{1}H NMR spectrum, which corresponded to the olefin proton and ArOC<u>*H*</u>$_3$, respectively. The double-bond geometry was confirmed to be *E* by nOe based NMR experiments performed on *amide **325*** (*Figure **3.6***).



325

Figure 3.6 *Confirmation of double-bond geometry in amide **325** by nOe based NMR experiments*

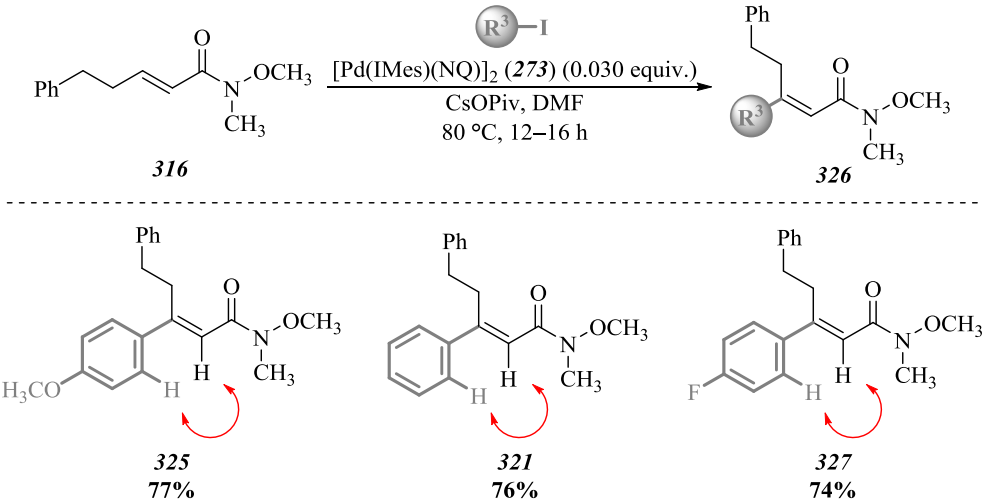
The Fujiwara-Moritani reaction was also found to be effective in performing this transformation and conditions developed by Studer and co-workers,[137] which used palladium acetate and 4-hydroxy-2,2,6,6-tetramethylpiperidin-1-oxyl as the reoxidant. This procedure furnished *amide* ***319*** in 86% yield and exclusively as a single geometric isomer as observed by ^{1}H NMR spectroscopy (*Scheme* ***3.15***), with spectroscopic data identical to those reported earlier.



Scheme 3.15 *Synthesis of amide* ***319*** *via Fujiwara-Moritani reaction*

3.5.2 Exploring the scope of the Heck reaction on amide 316

After discovering suitable conditions for the Heck reaction, work turned to assessing the scope of aryl iodides in the Heck reaction on β-substituted vinyl Weinreb amides. This began with exploration of the scope of Heck reactions on *amide* ***316*** using De Vries' Heck conditions (*Scheme* ***3.16***).

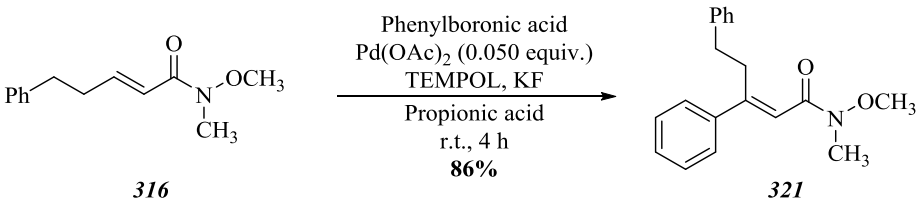


Scheme 3.16 *Scope of the Heck reaction on amide* ***316****. Red arrows indicate a significant nOe enhancement as observed by nOe based NMR experiments.*

As well as installing an anisole group during the Heck reaction, the installation of an electron-neutral substituent was also possible, with De Vries' Heck conditions used to furnish *amide* ***321*** in 76%

yield. To make this methodology more applicable to medicinal chemistry, it was decided that the addition of a fluorine group at the *para*- position of a phenyl ring would be useful as it acts as a metabolic blocker, typically being substituted in when the corresponding unsubstituted benzene derivatives at that position undergo oxidation by cytochrome P450 enzymes. To this end, *amide* ***316*** was reacted with 1-fluoro-4-iodobenzene under De Vries' Heck conditions to afford *amide* ***327*** in 74% yield. All of the reported amides were formed exclusively as single geometric isomers as observed by ^{1}H NMR spectroscopy. The identities of the synthesised amides were confirmed by appropriate spectroscopic methods and the double-bond geometries were confirmed to be *E* by nOe based NMR experiments.

Studer's Fujiwara-Moritani conditions (*Scheme* ***3.17***) also proved successful in performing the arylation of *amide* ***316*** to generate *amide* ***321***. This protocol furnished *amide* ***321*** in 86% yield, and exclusively as a single geometric isomer as observed by ^{1}H NMR spectroscopy with spectroscopic data identical to the previous reported method.

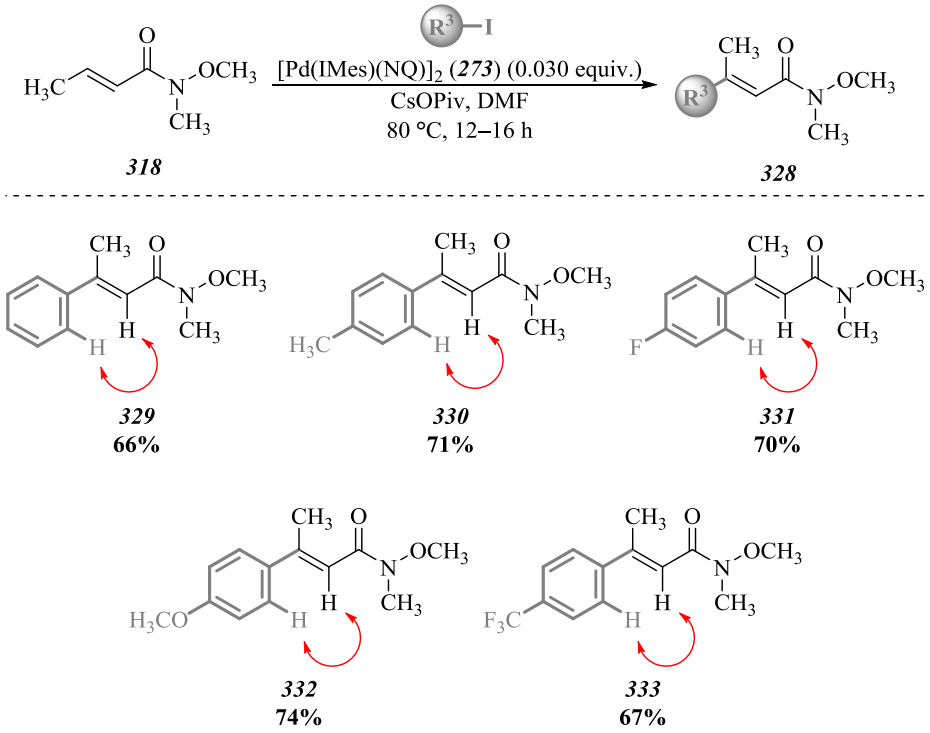


Scheme 3.17 *Synthesis of amide* ***321*** *via Fujiwara-Moritani reaction*

3.5.3 Exploring the scope of the Heck reaction on amide 318

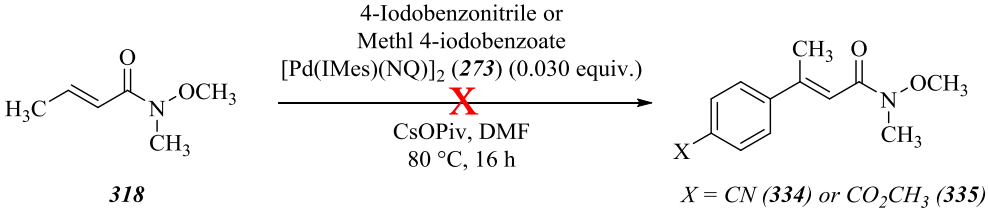
The scope of the Heck reaction on *amide* ***318*** using De Vries' Heck conditions was also explored to assess the generality of this protocol (*Scheme* ***3.18***). Electron-neutral substituents were installed successfully, with *amide* ***329*** and *amide* ***330*** generated in 66% yield and 71% yield, respectively. It was also possible to functionalise the olefin with a fluorine group at the *para*- position of a phenyl ring with *amide* ***331*** furnished in 70% yield. Electron-rich substituents were also compatible with the methodology and *amide* ***332*** was synthesised in 74% yield. Finally, addition of electron-deficient substituents was attempted and a trifluoromethyl group on the *para* position of the aromatic ring was thought to be desirable due to its application in medicinal chemistry as a metabolic blocker for methyl or chlorine groups. This protocol furnished *amide* ***333*** in a pleasing 67% yield. All of the

reported amides were formed exclusively as single geometric isomers as observed by ^{1}H NMR spectroscopy. The identities of the synthesised amides were confirmed by appropriate spectroscopic methods and the double-bond geometries were confirmed to be *E* by nOe based NMR experiments.



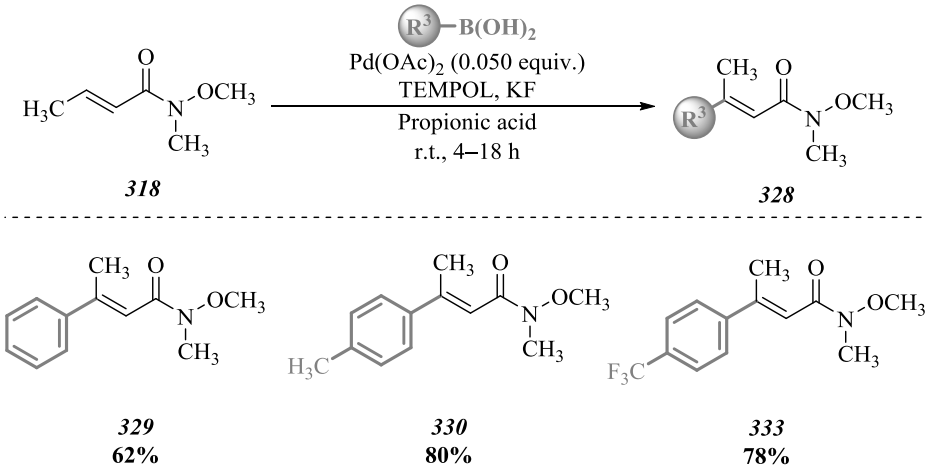
Scheme 3.18 *Scope of the Heck reaction on amide* ***318****. Red arrows indicate a significant nOe enhancement as observed by nOe based NMR experiments.*

It was disappointing to find that the attempted coupling of *amide* ***318*** and 4-iodobenzonitrile only returned *amide* ***318*** as observed by thin-layer chromatography. An identical result was obtained when methyl 4-iodobenzoate was employed (*Scheme* ***3.19***). It was hypothesised that the carbonyl and the nitrile groups on the aromatic ring may be susceptible to hydrolysis under the reaction conditions, and that the resultant carboxylate anions may not be suitable substrates for catalytic cycle.



Scheme 3.19 *Failed synthesis of amide* ***334*** *and amide* ***335*** *via Heck reaction*

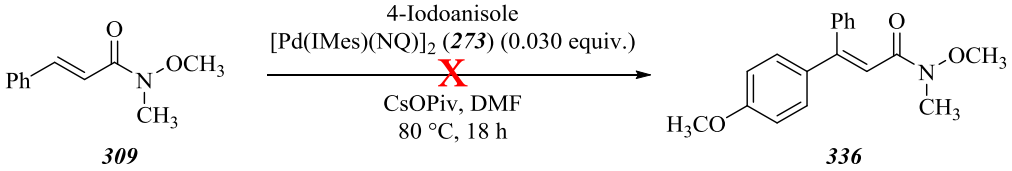
Studer's Fujiwara-Moritani conditions (*Scheme* ***3.20***) also proved successful in performing the arylations of *amide* ***318***. This protocol furnished *amide* ***329***, *amide* ***330***, and *amide* ***333*** in 62% yield, 80% yield, and 78% yield, respectively. All of the synthesised amides were formed exclusively as single geometric isomers as observed by ^{1}H NMR spectroscopy with spectroscopic data identical to the previous reported method.



Scheme 3.20 *Scope of the Fujiwara-Moritani reaction on amide* ***318***

3.5.4 β-aryl-substituted vinyl Weinreb amides

It had been demonstrated that De Vries' Heck conditions could successfully be performed on substrates with primary alkyl groups, and it was of interest to explore if an aryl substituent could be tolerated during the Heck reaction. To this end, *amide* ***309***, which had been successfully synthesised previously when exploring the scope of the Heck reaction on unsubstituted vinyl Weinreb amides (*Scheme* ***3.11***, *vide supra*), was treated with 4-iodoanisole under De Vries' Heck conditions. However, this protocol only returned *amide* ***309*** as observed in the ^{1}H NMR spectrum of the crude reaction mixture (*Scheme* ***3.21***).



Scheme 3.21 *Failed synthesis of amide* ***309*** *via Heck reaction*

It was thought that the increase in steric bulk provided by the phenyl group hindered the *syn-carbopalladation* step and thus led to the recovery of *amide* ***309***. This highlights the current limitations of the methodology in that only primary alkyl substituents are tolerated on the starting β-substituted vinyl Weinreb amide.

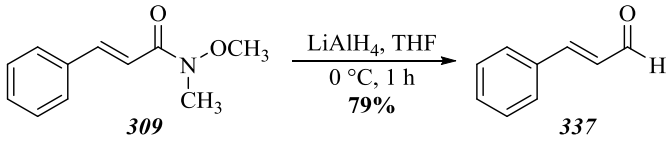
3.5.5 Summary

In summary, a range of aryl iodides were treated with β-substituted vinyl Weinreb amides under De Vries' Heck conditions to generate a varied scope of disubstituted vinyl Weinreb amides in good yields. It was pleasing to find that electron-neutral (*amide* ***321***, *amide* ***327***, *amide* ***329***, *amide* ***330***, *and amide* ***331***), electron-rich (*amide* ***325*** *and amide* ***332***), and electron-deficient (*amide* ***333***) substituents were all tolerated in the methodology, and it was especially encouraging to find that the addition of fluorine groups was possible as these frequently are used in medicinal chemistry. Furthermore, all of the vinyl Weinreb amides were isolated as single geometric isomers as observed by ^{1}H NMR spectroscopy. The products were identified as *E*-isomers as observed by nOe based NMR experiments studies. This presents a significant advantage over direct Heck reactions on enones, which have been shown to occasionally give mixtures of geometric isomers because of fast carbon-bound to oxygen-bound palladium enolate conversion present in these α,β-unsaturated carbonyl systems. It is hypothesised that the presence of the Weinreb amide functionality would stabilise a carbon-bound palladium enolate and prevent this conversion.

3.6 Scope of functionalisation of the vinyl Weinreb amide

3.6.1 Functionalisation of vinyl Weinreb amides with reducing agents

After assessing the scope of the Heck reaction on unsubstituted and β-substituted vinyl Weinreb amides, studies then focussed on the functionalisation of the resultant amides to generate enals and enones, which in some cases would have been difficult to synthesise selectively *via* direct Heck reaction on the precursor enone.



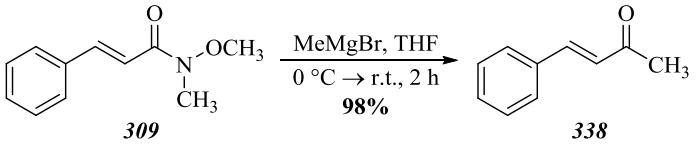
309 ***337***

Scheme 3.22 *Synthesis of enal* ***337***

Amide ***309*** was treated with lithium aluminium hydride in tetrahydrofuran to generate *enal* ***337*** in 79% yield. This transformation was also accomplished with the use of diisobutylaluminium hydride, which generated *enal* ***337*** in 72% yield (*Scheme* ***3.22***). The identity of *enal* ***337*** was confirmed by the absence of two singlets at 3.76 ppm and 3.31 ppm in the ^{1}H NMR spectrum, which corresponded to OC$\underline{H}_3$ and NC$\underline{H}_3$ in *amide* ***309***, respectively. Further confirmation was obtained by the presence of a doublet (J = 7.5 Hz) at 9.71 ppm in the ^{1}H NMR spectrum, which corresponded to C$\underline{H}$O.

3.6.2 Functionalisation of vinyl Weinreb amides with aliphatic or aromatic substituents

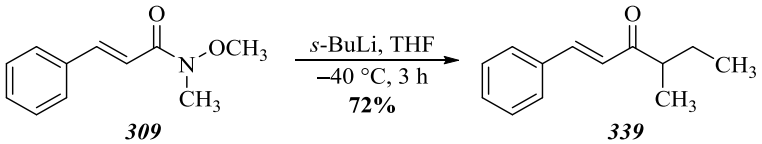
Studies were then focussed on the addition of simple aliphatic and aromatic organometallic reagents. To this end, *amide* ***309*** was treated with methylmagnesium bromide to generate *enone* ***338*** in an excellent 98% yield (*Scheme* ***3.23***).



309 ***338***

Scheme 3.23 *Synthesis of enone* ***338***

The identity of *enone* ***338*** was confirmed by the presence of a singlet at 2.38 ppm in the ^{1}H NMR spectrum, which corresponded to COC$\underline{H}_3$.



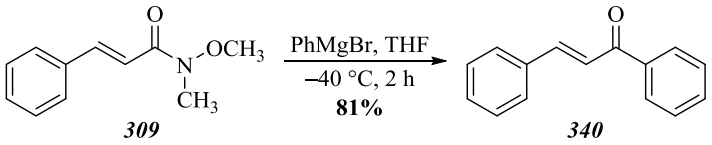
309 ***339***

Scheme 3.24 *Synthesis of enone* ***339***

Amide ***309*** was also treated with *sec*-butyllithium to generate *enone* ***339*** in a good 72% yield (*Scheme* ***3.24***). The identity of *enone* ***339*** was confirmed by the presence of a doublet (J = 7.5 Hz) at 1.17 ppm in the ^{1}H NMR spectrum, which corresponded to COCHC$\underline{H}_3$. Further confirmation was

obtained when the spectroscopic data was found to be consistent with those reported in the literature for *enone* ***339***.[157]

As described previously, Heck reactions of phenyl enones were found to be low yielding (*Scheme* ***3.25***, *vide supra*). Furthermore, phenyl vinyl ketone was found to be unstable, polymerized rapidly in air and was, therefore, not a suitable substrate for the Heck reaction. However, using the methodology detailed above, the Heck reaction may be performed on a vinyl Weinreb amide and then functionalised to generate the phenyl substituted enone, thus circumventing the need to handle phenyl vinyl ketone. To validate this approach, *amide* ***309*** was reacted with phenylmagnesium bromide. This reaction furnished *enone* ***340*** in a pleasing 81% yield.

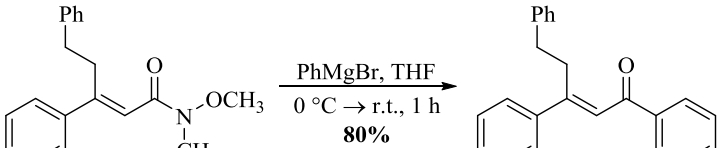


309 ***340***

Scheme 3.25 *Synthesis of enone* ***340***

The identity of *enone* ***340*** was confirmed by the presence of ten protons in the aromatic region of the ^{1}H NMR spectrum.

After proving that this methodology would work to functionalise β-substituted vinyl Weinreb amides, it was important to assess how the methodology would work to functionalise trisubstituted vinyl Weinreb amides. To achieve this goal, *amide* ***321*** was treated with phenylmagnesium bromide which generated *enone* ***341*** in a very good 80% yield (*Scheme* ***3.26***).



321 ***341***

Scheme 3.26 *Synthesis of enone* ***341***

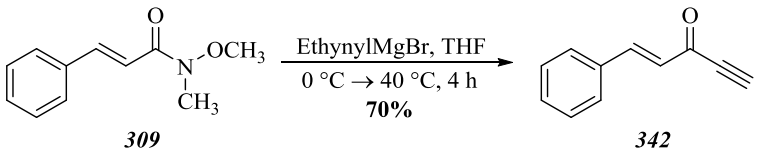
The identity of *enone* ***341*** was confirmed by the presence of fifteen protons in the aromatic region of the ^{1}H NMR spectrum. Further confirmation was obtained by the presence of a signal in the

high-resolution mass spectrum at 335.1407 ($\Delta = -0.30$ ppm), which corresponded to the $[M+Na]^+$ ion of *enone* ***341***.

3.6.3 Functionalisation of vinyl Weinreb amides with unsaturated non-aromatic substituents

After the successful addition of a range of aliphatic and aromatic substituents to the Weinreb amides had been demonstrated, attention turned to the addition of unsaturated non-aromatic substituents to generate substrates that may be difficult to access selectively by direct Heck reaction.

Studies began with the addition of a propargyl group to *amide* ***309***, which furnished *enone* ***342*** in 70% yield (*Scheme* ***3.27***).

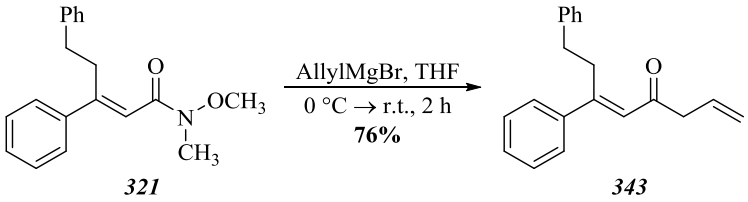


309 ***342***

Scheme 3.27 *Synthesis of enone* ***342***

The identity of *enone* ***342*** was confirmed by the presence of a singlet at 3.33 ppm in the ^{1}H NMR spectrum, which corresponded to C≡C*H*, and the presence of two singlets at 80.0 ppm and 79.3 ppm in the ^{13}C NMR spectrum, which corresponded to the alkyne carbon atoms. Further confirmation was obtained when the spectroscopic data was found to be consistent with those reported in the literature for *enone* ***342***.[158]

After the successful installation of a propargyl group, attempts were made to add olefin groups to the vinyl Weinreb amide, starting with an allyl group. *Amide* ***321*** was treated with allylmagnesium bromide to generate *enone* ***343*** in pleasing 76% yield (*Scheme* ***3.28***). It was pleasing to note that that isomerisation of the allyl olefin into conjugation with the carbonyl group was not present. This is a significant advantage over performing a direct arylation using the Heck reaction onto a requisite enone as isomerisation of the allyl olefin would be expected by a palladium hydride species formed during the catalytic cycle.

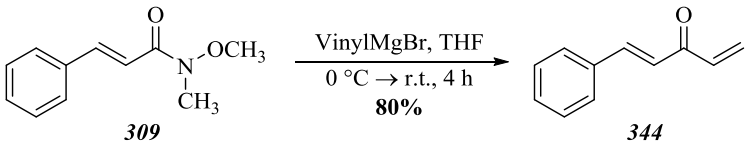


321 ***343***

Scheme 3.28 *Synthesis of enone* ***343***

The identity of *enone* ***343*** was confirmed by the presence of a signal in the high-resolution mass spectrum at 299.1405 (Δ = +0.38 ppm), which corresponded to the $[M+Na]^+$ ion of *enone* ***343***.

Vinyl groups were thought to be desirable substituents to showcase the methodology as it is almost certain that these types of enones would not readily undergo clean and regioselective Heck reactions. To this end, *amide* ***309*** was treated with vinylmagnesium bromide to furnish *enone* ***344*** in 80% yield (*Scheme* ***3.29***).

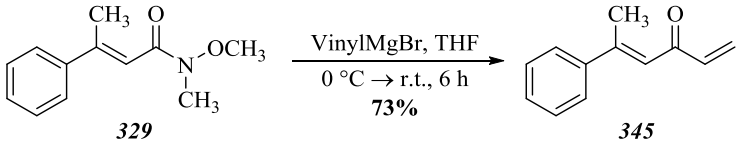


309 ***344***

Scheme 3.29 *Synthesis of enone* ***344***

The identity of *enone* ***344*** was confirmed by the presence of a double doublet (J = 17.5, 11.0 Hz) at 6.72 ppm in the ^{1}H NMR spectrum, which corresponded to C<u>*H*</u>=CH_2. Further confirmation was obtained when the spectroscopic data was found to be consistent with those reported in the literature for *enone* ***344***.[159]

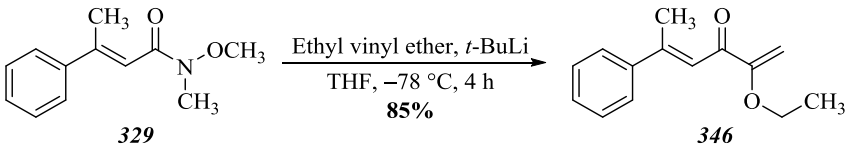
Amide ***329*** was treated vinylmagnesium bromide to furnish *enone* ***345*** in 73% yield although a small amount (10% by ^{1}H NMR analysis) of inseparable impurities were thought to contaminate *enone* ***345***, even after repeated flash-column chromatography (*Scheme* ***3.30***). This example shows the possibility of obtaining the opposite regioselectivity by performing the Heck reaction on the vinyl Weinreb amide compared to a direct Heck reaction on the precursor enone. This is due to the additional steric hindrance of the methyl group which would disfavour the formation of a trisubstituted olefin in the direct Heck reaction. The identity of *enone* ***345*** was confirmed by the presence of a double doublet (J = 17.5, 10.5 Hz) at 6.51 ppm in the ^{1}H NMR spectrum, which corresponded to C<u>*H*</u>=CH_2.



329 ***345***

Scheme 3.30 *Synthesis of enone* ***345***

Finally, *amide* ***329*** was treated with the lithium anion of ethyl vinyl ether, which was pre-generated from *tert*-butyllithium and ethyl vinyl ether, to furnish *enone* ***346*** in an excellent 85% yield (*Scheme* ***3.31***). The identity of *enone* ***346*** was confirmed by the presence of a quartet (J = 7.0 Hz) at 3.85 ppm and a triplet (J = 7.0 Hz) at 1.41 ppm in the ^{1}H NMR spectrum, which corresponded to OC$\underline{H}_2$CH$_3$ and OCH$_2$C$\underline{H}_3$, respectively.

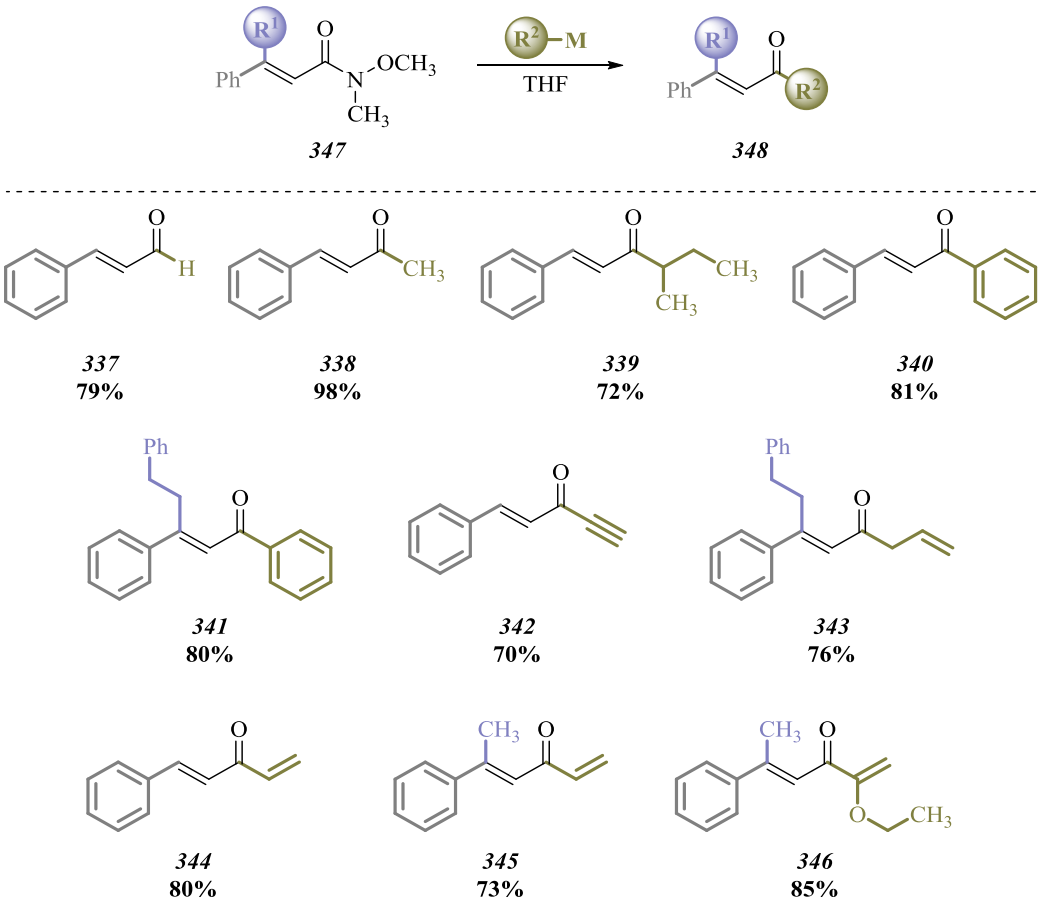


329 ***346***

Scheme 3.31 *Synthesis of enone* ***346***

3.6.4 Summary

In summary, *amide* ***347*** was treated with a range of organometallic reagents in tetrahydrofuran to generate *enone* ***348***, some of which would be difficult to access by direct Heck reaction on the corresponding precursor enone. It was encouraging to find that a hydrogen (*enal* ***337***) as well as aliphatic (*enone* ***338*** *and enone* ***339***) substituents were added to the Weinreb amide in good yields. It was found that aromatic (*enone* ***340*** *and enone* ***341***) substituents were also added in very good yields, thus circumventing the issue of performing Heck reactions on phenyl enones, which were previously found to be problematic (*Scheme* ***2.46***, *vide supra*). Finally, unsaturated (*enone* ***342***, *enone* ***343***, *enone* ***344***, *enone* ***345***, *and enone* ***346***) substituents were added to the Weinreb amide in good to excellent yields. It would be challenging to perform direct Heck reactions on the precursor enone regioselectively thus highlighting a significant advantage of performing Heck reactions on vinyl Weinreb amides and then functionalising the resultant Heck product (*Scheme* ***3.32***).



Scheme 3.32 *Scope of the functionalisation of vinyl Weinreb amides*

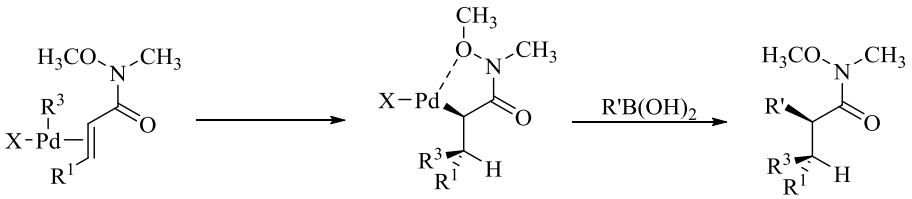
3.7 Conclusions

3.7.1 Summary

Heck reactions on unsubstituted and β-aryl-substituted vinyl Weinreb amides have been performed using conditions developed by Heck and De Vries, respectively. A range of aryl bromides and aryl iodides were successfully added to the olefin portion of the molecule in good to excellent yields, with only a single geometric isomer being observed. After completion of the Heck reaction, the vinyl Weinreb amides were functionalized using a range of organometallic reagents in good to excellent yields. Overall this methodology provides the option to circumvent troublesome Heck reactions on enone precursors, and replace them with pragmatic and reliable Heck reactions on vinyl Weinreb amides which can then be functionalised at a later stage to generate a varied scope of trisubstituted enones.

3.7.2 Future work

It has been hypothesised that the Weinreb amide group can stabilise the palladium species after *syn-carbopalladation*,[151] and this results in excellent diastereoselectivity in the Heck reaction. Following on from *oxidative addition*, *palladium intermediate* ***349*** could be formed from the association of the ligand with palladium. *Syn-carbopalladation* would follow and it was thought that *palladium intermediate* ***350*** could be further functionalised by a Suzuki reaction if a suitable boronic acid could transmetallate with palladium. This would furnish *amide* ***351*** (*Scheme* ***3.33***).



349 ***350*** ***351***

Scheme 3.33 *Second functionalisation of palladium intermediate* ***350***

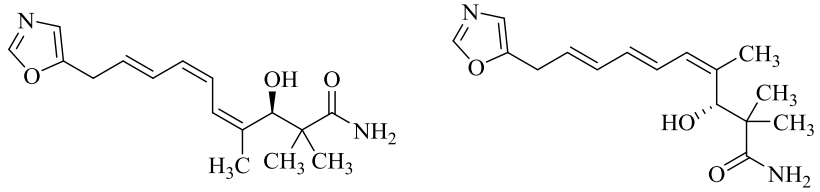
Chapter 4

Studies towards the syntheses of (±)-inthomycin B and (±)-inthomycin C

4.1 Introduction

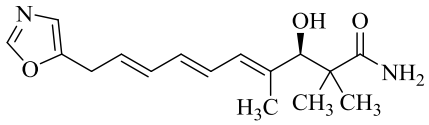
4.1.1 Background

(+)-Inthomycin A (***353***), (+)-inthomycin B (***354***), and (+)-inthomycin C (***355***) (*Figure* ***4.1***) were first isolated in 1991 by Henkel and Zeeck[160] from the *Streptomyces species* (Strain Gö 2), although (+)-inthomycin A (***353***) had been previously isolated by Omura and co-workers[161,162] in 1990 and given the name phthoxazolin A (***353***). The inthomycins are selective inhibitors of cellulose biosynthesis and have shown activity against *Phytophthora parasitica* and *Phytophthora cactorum* during *in vitro* studies.[161,162] (+)-Inthomycin A (***353***), in particular, has shown notable herbicidal activity against velvet leaf[163] and radish seedlings,[164] and interestingly, it has also been shown to inhibit the growth of prostate cancer cells.[165]



353

354



355

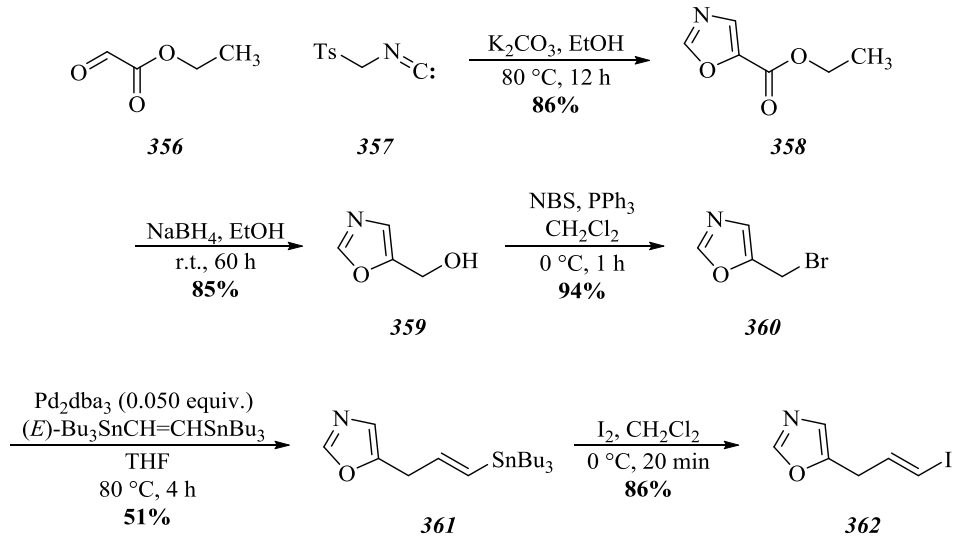
Figure 4.1 *(+)-Inthomycin A (**353**), (+)-inthomycin B (**354**), and (+)-inthomycin C (**355**)*

To date, there have been only two syntheses of (+)-inthomycin B (***354***) and five syntheses of (+)-inthomycin C (***355***), which generally employ palladium cross-coupling methods, most frequently the Stille coupling.

4.1.2 Previous synthesis of (+)-inthomycin B (354) and (+)-inthomycin C (355)—Taylor (2008)

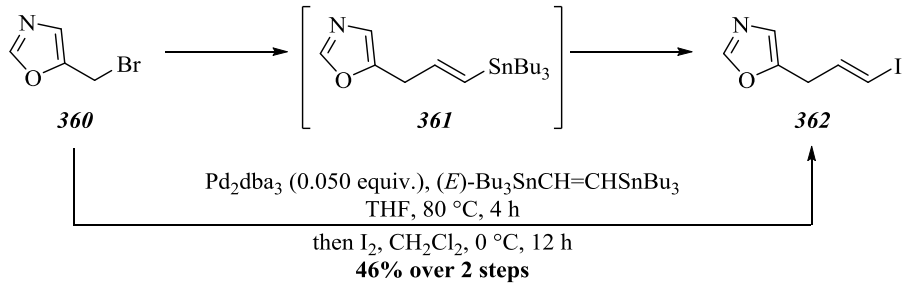
In 2008, Taylor and co-workers reported the first syntheses of (+)-inthomycin B (***354***) and (+)-inthomycin C (***355***),[166] as well as a synthesis of (+)-inthomycin A (***353***). The syntheses began with the preparation of *iodide* ***362***, a general intermediate for the synthesis of all three inthomycins. A protocol developed by Van Leusen and co-workers,[167] which employed toluenesulfonylmethyl

isocyanide (***357***) and ethyl glycoxylate (***356***) in the presence of potassium carbonate, was used to furnish *oxazole* ***358*** in 86% yield. *Oxazole* ***358*** was reduced with sodium borohydride to give *alcohol* ***359*** in 85% yield, which was subsequently brominated with *N*-bromosuccinimide and triphenylphosphine to generate *bromide* ***360*** in 94% yield. Stille coupling with tris(dibenzylideneacetone)dipalladium and (*E*)-1,2-bis-(tri-*n*-butylstannyl)ethylene furnished *stannane* ***361*** in a moderate 51% yield before subsequent iodination gave *iodide* ***362*** in 86% yield (*Scheme* ***4.1***).



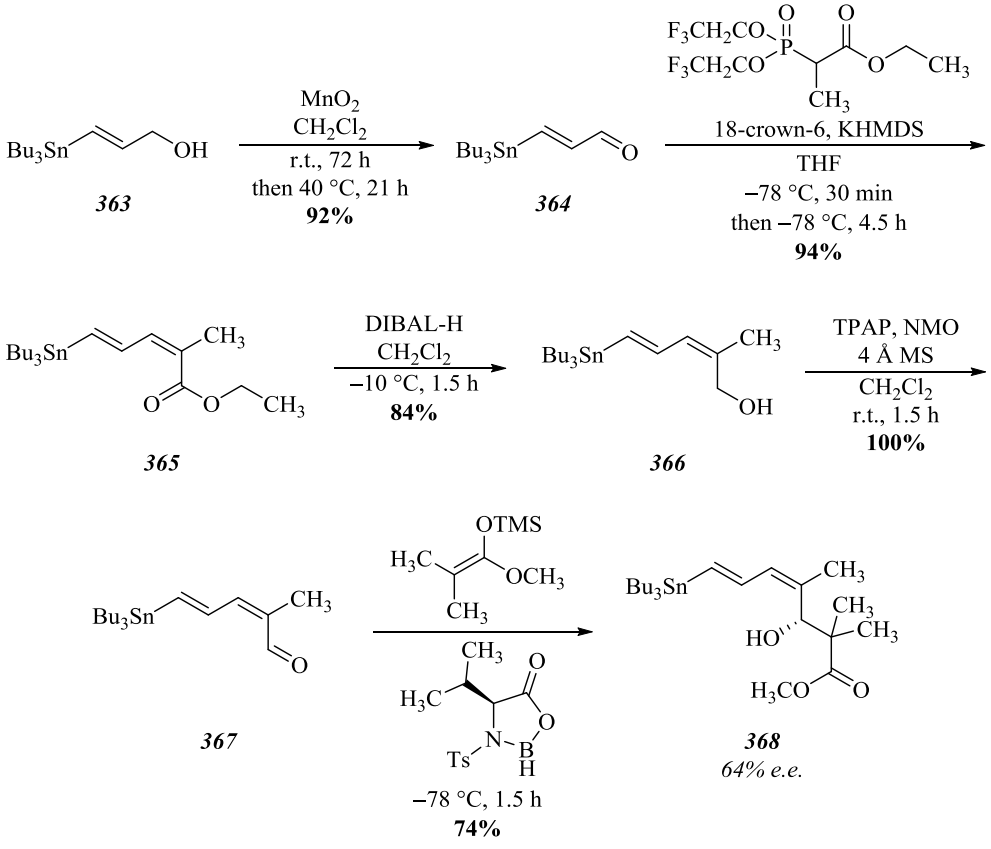
Scheme 4.1 *Preparation of iodide* ***362***

An improvement to the final stages of the synthesis of *iodide* ***3.62*** was made when the Stille coupling and iodination were telescoped into a single-pot. This protocol gave *iodide* ***3.62*** with a slightly improved 46% yield over two steps compared to the step-wise synthesis, which gave *iodide* ***362*** in 44% yield over two steps (*Scheme* ***4.2***).



Scheme 4.2 *Preparation of iodide* ***362*** *via telescoped Stille coupling/iodination protocol*

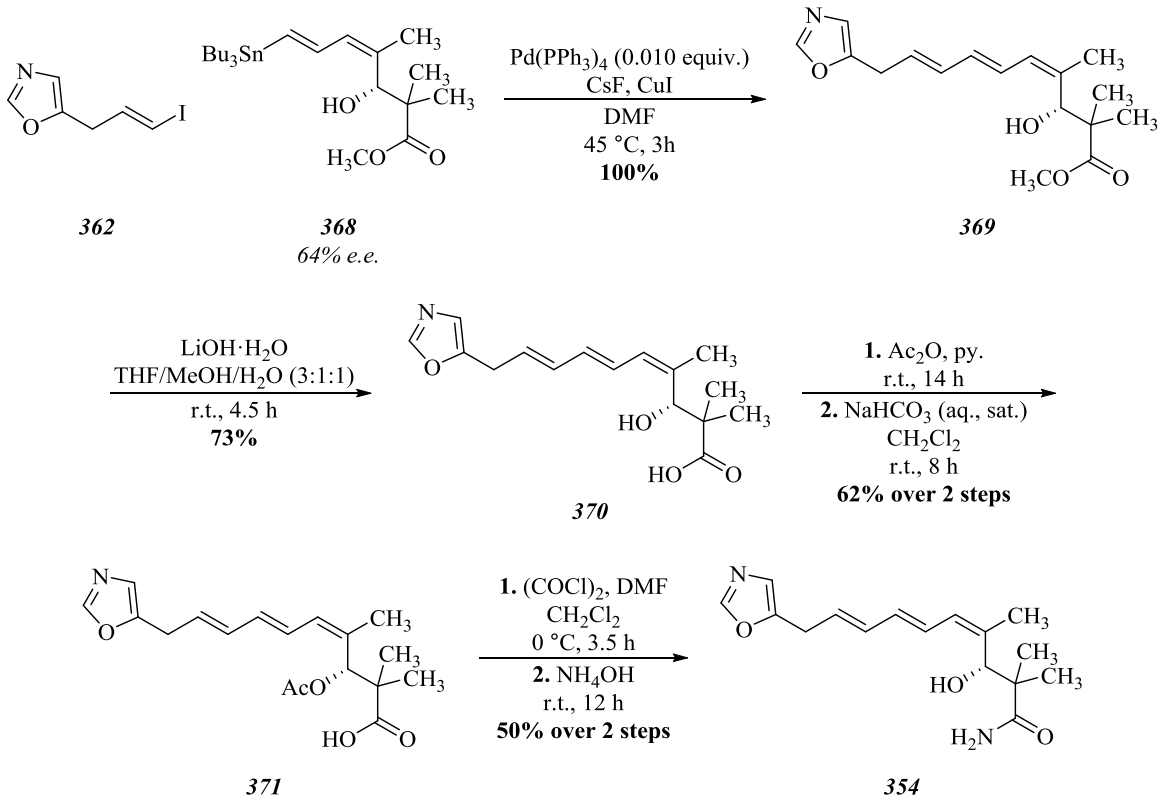
With *iodide* ***362***, a general intermediate, in hand, the synthesis of the other fragments was attempted, beginning with *stannane* ***368*** (*Scheme* ***4.3***). *Stannane* ***363*** was prepared from propargyl alcohol using the reported literature procedure described by Wender and co-workers,[168] before being oxidised using manganese dioxide to generate *enal* ***364*** in 92% yield. The Still-Gennari modification[169] of the Horner-Wadsworth-Emmons reaction was then utilised to furnish *ester* ***365*** in 94% yield, with excellent *Z*-selectivity observed. *Ester* ***366*** was reduced with diisobutylaluminium hydride and then oxidised using the Ley-Griffiths reagent[170] and *N*-methylmorpholine *N*-oxide to furnish *enal* ***367*** in 84% over two steps. Finally, the synthesis of *stannane* ***368*** was completed by treatment of *enal* ***367*** with *N*-tosyl-L-valine and the tetrahydrofuran complex of borane under asymmetric Mukaiyama-Kiyooka aldol conditions[171,172] to give *stannane* ***368*** in 74% yield with a 64% enantiomeric excess as observed by Mosher's ester analysis.



Scheme 4.3 *Preparation of stannane* ***368***

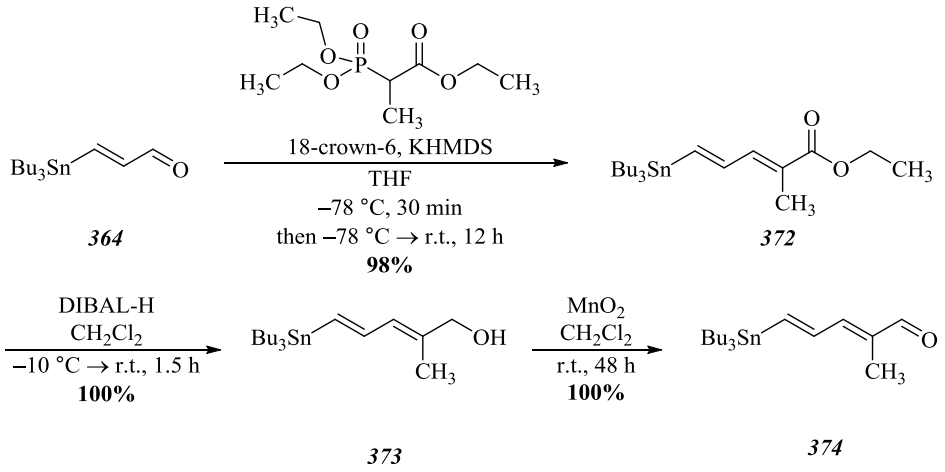
With both *iodide* ***362*** and *stannane* ***368*** prepared, the Stille coupling was employed using tetrakis(triphenylphosphine)palladium to generate *triene* ***369*** in quantitative yield. *Triene* ***369*** was hydrolysed with lithium hydroxide monohydrate to generate *acid* ***370*** in 73% yield, before being

acetylated to give *acetate* ***371*** in 62% over two steps. Finally, *acetate* ***371*** was activated with oxalyl chloride to generate the acid chloride before treatment with ammonium hydroxide to synthesise (+)-inthomycin B (***354***) in 50% yield over two steps, and in 7% overall yield over nine steps from ethyl glycoxylate (***356***) and *stannane* ***363*** (*Scheme* ***4.4***).



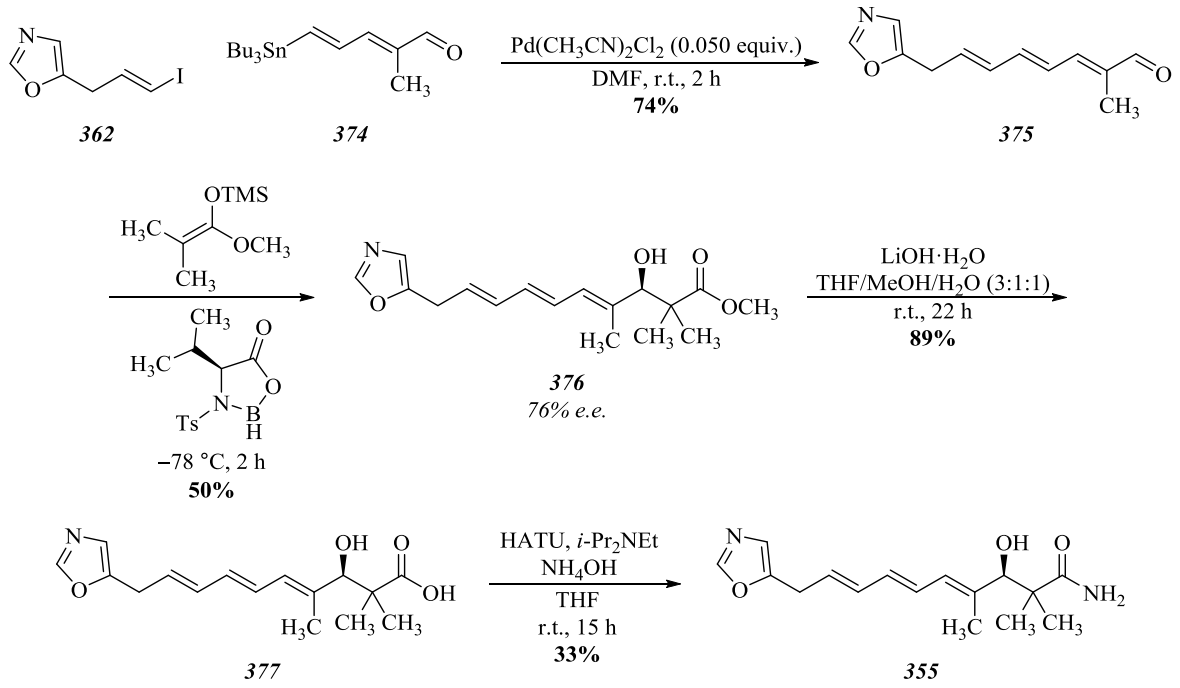
Scheme 4.4 *Synthesis of (+)-inthomycin B (**354**)*

At this point, attention turned to the synthesis of (+)-inthomycin C (***355***), which would employ *iodide* ***362*** previously prepared during the synthesis of (+)-inthomycin B (***354***). Firstly, the synthesis of the coupling partner for *iodide* ***362***—*stannane* ***374***—was carried out (*Scheme* ***4.5***). *Enal* ***364***, which had been previously prepared during the synthesis of (+)-inthomycin B (***354***), was treated under Horner-Wadsworth-Emmons reaction conditions using triethyl 2-phophonopropionate to give *ester* ***372*** in 98% yield with 19:1 *E*/*Z*-selectivity. *Ester* ***372*** was reduced with diisobutylaluminium hydride and then oxidised using manganese dioxide to furnish *stannane* ***374*** in quantitative yield over two steps.



Scheme 4.5 *Preparation of stannane **374***

With *iodide **362*** and *stannane **374*** in hand, the synthesis of (+)-inthomycin C (***355***) was completed (*Scheme **4.6***). This began with the Stille coupling of *iodide **362*** and *stannane **374*** using dichlorobis(acetonitrile) palladium, which generated *triene **375*** in 74% yield. Subsequent treatment of *triene **375*** with *N*-tosyl-L-valine and the tetrahydrofuran complex of borane under asymmetric Mukaiyama-Kiyooka aldol conditions to give *triene **376*** in 50% yield with a 76% enantiomeric excess as observed by Mosher's ester analysis.

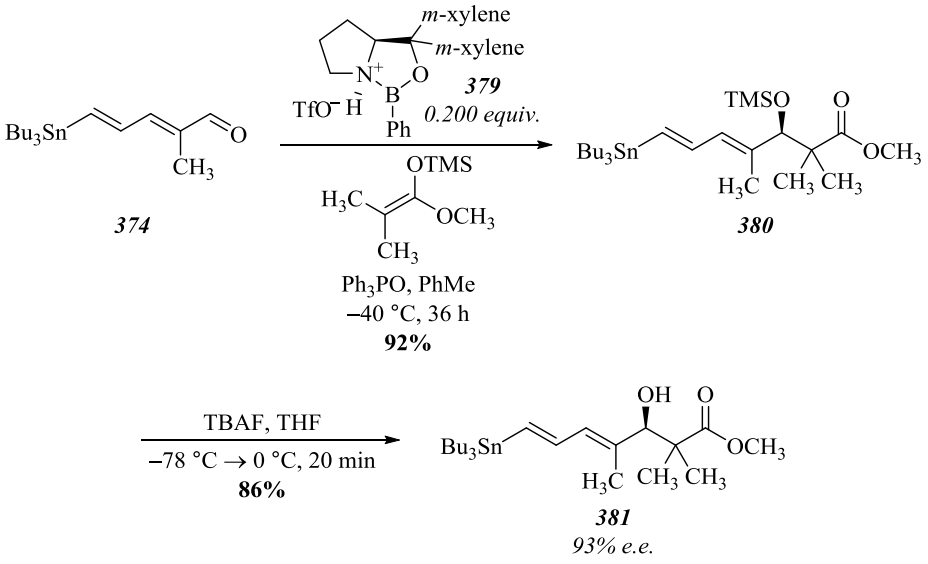


Scheme 4.6 *Synthesis of (+)-inthomycin C (**355**)*

The ester functionality in *triene* ***376*** was then hydrolysed with lithium hydroxide monohydrate to give *acid* ***377*** in 89% yield. Subsequent amide bond formation using ammonium hydroxide and 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU) furnished (+)-inthomycin C (***355***) in 33% yield, and in 3% overall yield over eight steps from ethyl glycoxylate (***356***) and *stannane* ***363***.

4.1.3 Previous synthesis of (−)-inthomycin C (355)—Ryu (2010)

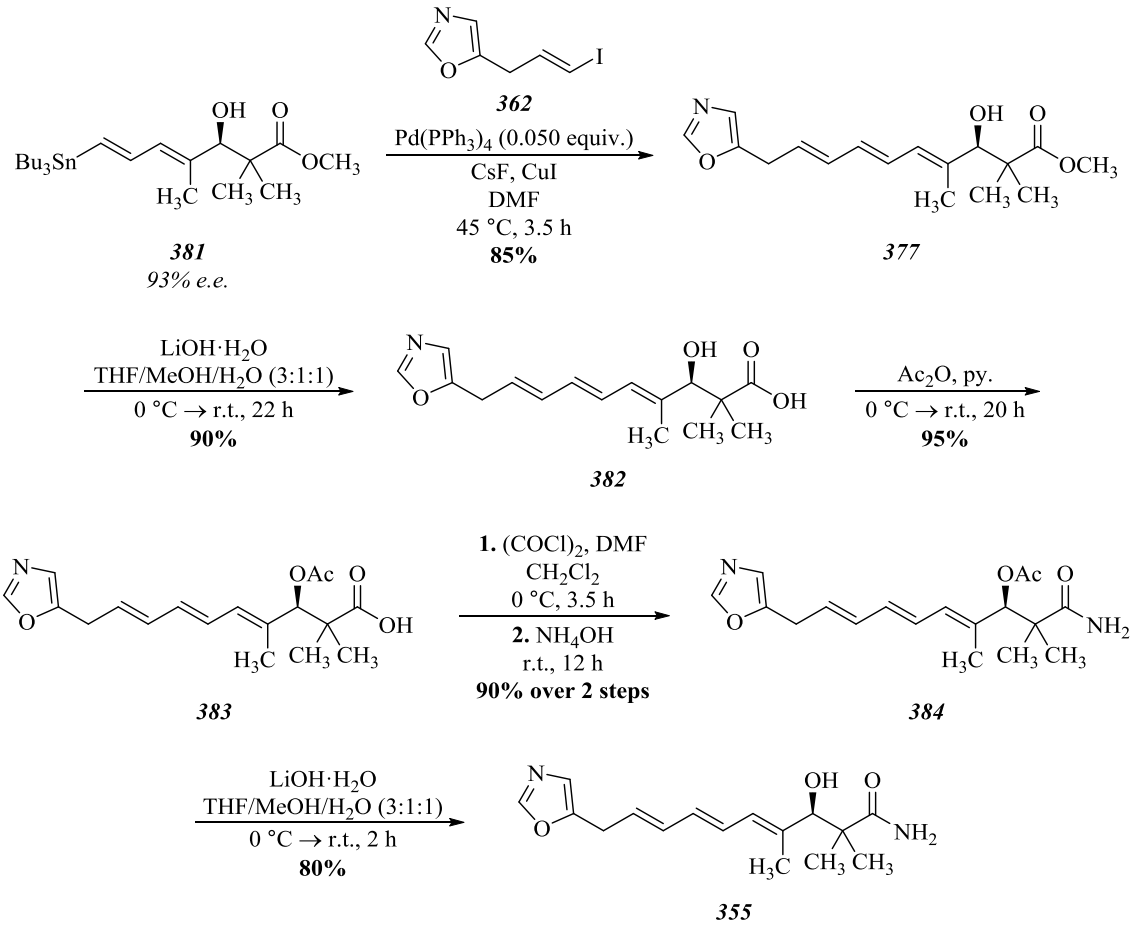
In 2010, Ryu and co-workers[173] reported a similar route for the synthesis of (−)-inthomycin C (***355***), but utilised a more effective catalyst for the asymmetric Mukaiyama-Kiyooka aldol reaction. Utilising *stannane* ***374***, which had been previously synthesised by Taylor and co-workers (*Scheme* ***4.3***, *vide supra*), and chiral catalyst *(S)-oxazaborolidinium* ***379*** furnished *stannane* ***380*** in 92% yield. Deprotection gave *stannane* ***380*** in 86% yield and in 93% enantiomeric excess as observed by chiral high-performance liquid-chromatography (*Scheme* ***4.7***).



Scheme 4.7 *Preparation of stannane* ***381***

Iodide ***362***, which had been previously synthesised by Taylor and co-workers (*Scheme* ***4.1***, *vide supra*), was coupled with *stannane* ***381*** using the Stille coupling under conditions developed by Baldwin and co-workers.[174,175] This protocol furnished *alcohol* ***377*** in 85% yield and was followed by hydrolysis of the methyl ester with lithium hydroxide monohydrate to generate *acid* ***382*** in 90%. Subsequent acetylation of *acid* ***382*** furnished *acetate* ***383*** in 95% yield. *Acetate* ***383*** was activated

with oxalyl chloride to generate the acid chloride before treatment with ammonium hydroxide to synthesise *amide* ***384***, which was acetate deprotected with lithium hydroxide monohydrate to generate (−)-inthomycin C (***355***) in 80% yield, and 11% yield over fourteen steps from propargyl alcohol (*Scheme* ***4.8***).



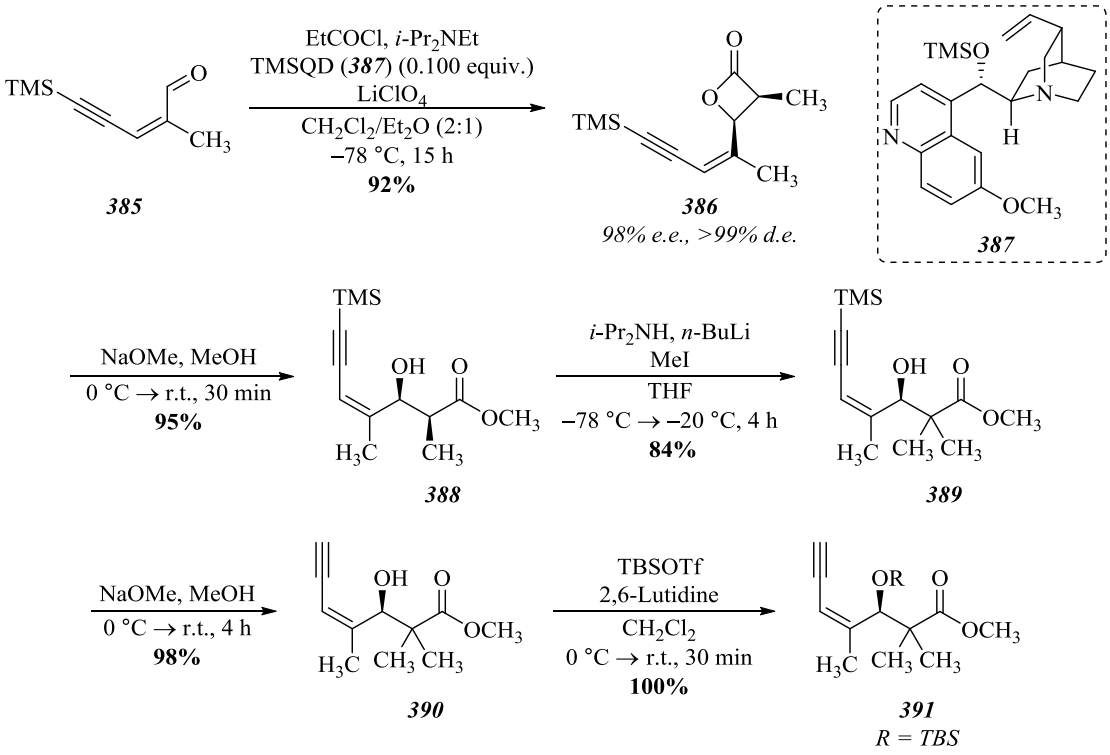
Scheme 4.8 *Synthesis of (−)-inthomycin C (**355**)*

4.1.4 Previous synthesis of (+)-inthomycin B (354) and (–)-inthomycin C (355)—Hatakeyama (2012)

In 2012, Hatakeyama and co-workers reported a similar, but slightly modified route to (+)-inthomycin B (***354***) and (−)-inthomycin C (***355***).[176] The synthesis of (+)-inthomycin A (***353***) was also reported in this paper. The Hatakeyama group utilised an asymmetric [2+2] cycloaddition as the key step.

Firstly, the synthesis of (+)-inthomycin B (***354***) was carried out, and this began with the preparation of *enal* ***385***, which was synthesised as reported previously by Hatakeyama and co-workers.[177] *Enal* ***385*** was then treated under conditions developed by Nelson and co-workers for the asymmetric

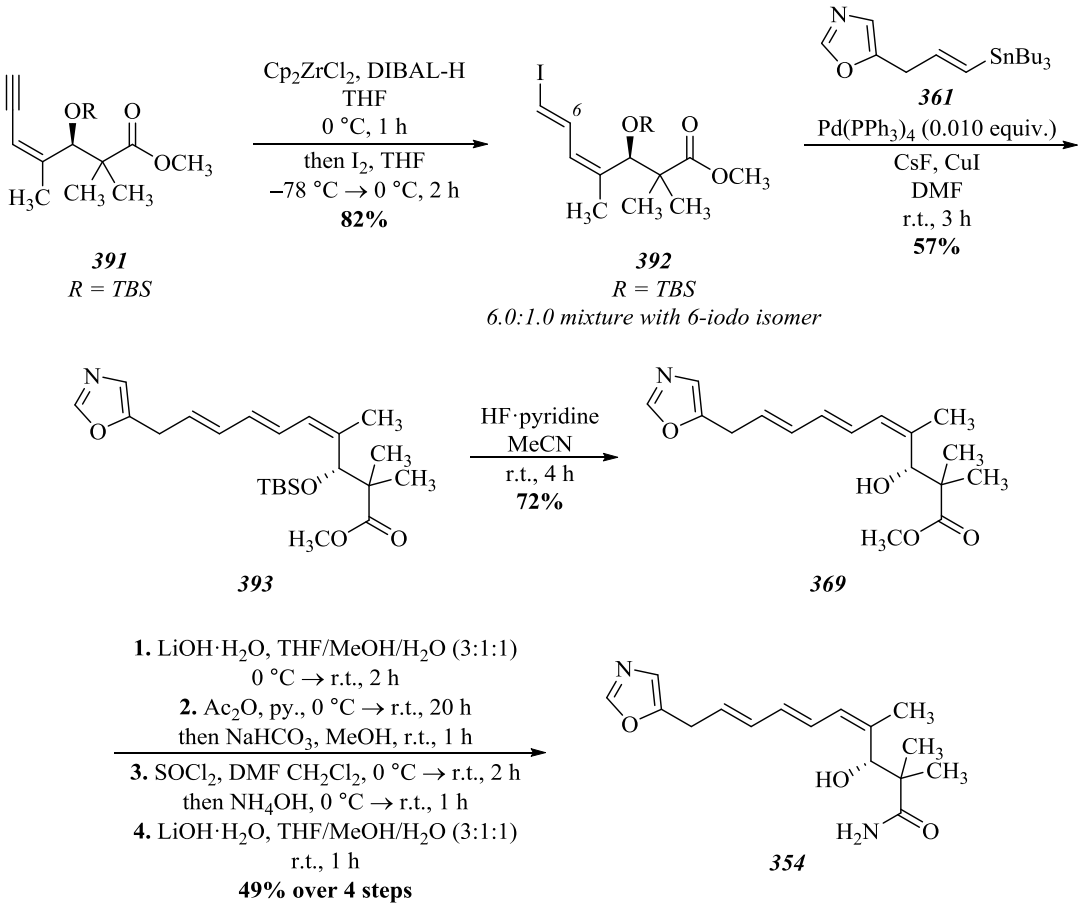
[2+2] cycloaddition.[178,179] This protocol furnished *lactone* ***386*** in 92% yield with a 98% enantiomeric excess and 99% diastereomeric excess as observed by chiral high-performance liquid-chromatography. Ring-opening of *lactone* ***386*** was then performed using sodium methoxide in methanol to give *ester* ***388*** in 95% yield. Methylation to generate *ester* ***389***, silicon deprotection to give *alkyne* ***390***, and alcohol protection to furnish protected *alcohol* ***391*** were performed in 82% yield over three steps (*Scheme* ***4.9***).



Scheme 4.9 *Preparation of protected alcohol* ***391***

Protected alcohol ***391*** was then subjected to hydrozirconation using Swartz's reagent,[180] which was generated *in situ* from zirconene dichloride and diisobutylaluminium hydride. This was followed by iodination to generate *iodide* ***392*** in 82% yield, although this was isolated as a 6.0:1.0 mixture with the 6-iodo isomer of *iodide* ***392***. Stille coupling with *stannane* ***361***, which had been previously prepared by Taylor and co-workers (*Scheme* ***4.1***, *vide supra*), under Baldwin's conditions furnished *triene* ***393*** in 57% yield, which was subsequently silicon deprotected to generate *triene* ***369*** in 72% yield. In a similar manner to previous syntheses, *triene* ***369*** was hydrolysed and acetate protected before formation of the amide bond from the acid chloride. Finally, acetate deprotection was

performed to generate (+)-inthomycin B (***354***) in 49% yield over four steps, and in 7% yield over fifteen steps from propargyl alcohol (*Scheme* ***4.10***).

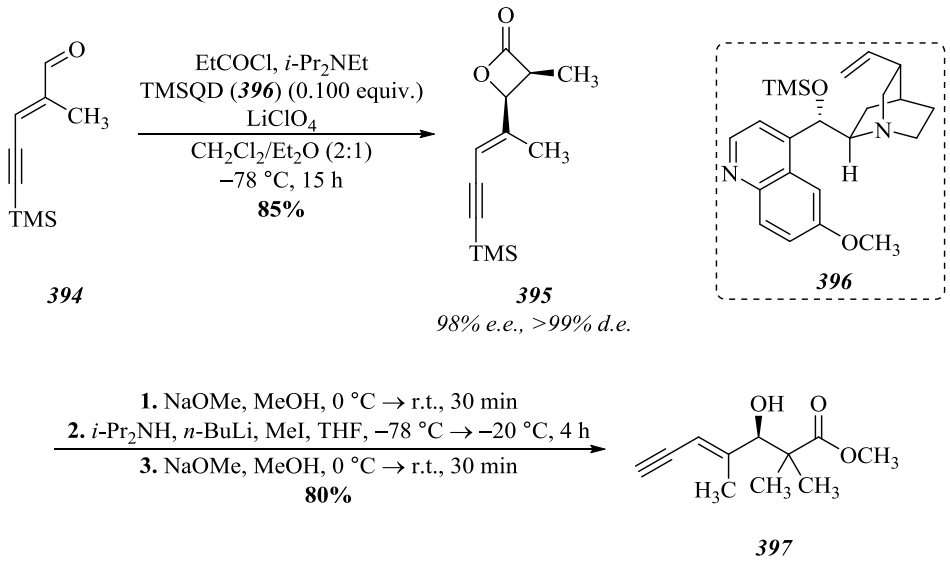


Scheme 4.10 *Synthesis of (+)-inthomycin B (**354**)*

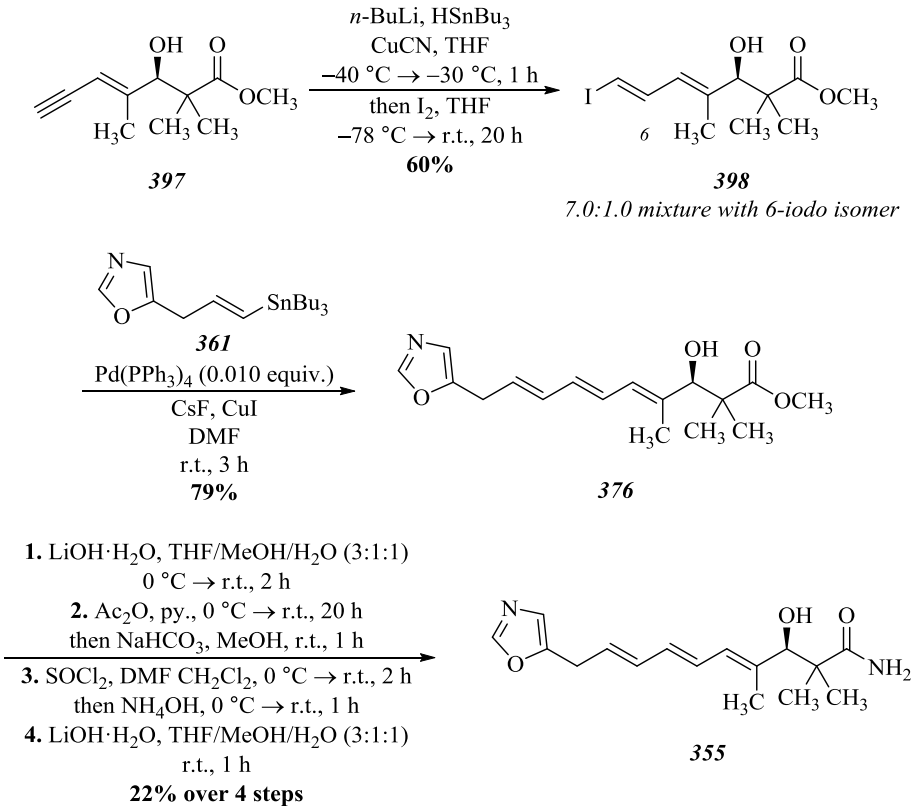
Focus next turned to the synthesis of (−)-inthomycin C (***355***) starting from *enal* ***394***, which had been previously synthesised by Hatakeyama and co-workers.[177] *Enal* ***394*** was subjected to Nelson's conditions for the asymmetric [2+2] cycloaddition to generate *lactone* ***395*** in 85% yield with a 98% enantiomeric excess and >99% diastereomeric excess as observed by chiral high-performance liquid-chromatography. Subsequent ring-opening of *lactone* ***395***, methylation and silicon deprotection furnished *alkyne* ***397*** in 80% yield (*Scheme* ***4.11***).

Alkyne ***397*** was then exposed to stannyl-cupration/iodination conditions[181] to furnish *iodide* ***398*** in 60% yield, although this was isolated as a 7.0:1.0 mixture with the 6-iodo isomer of *iodide* ***398***. Stille coupling with *stannane* ***361***, which had been previously prepared by Taylor and co-workers (*Scheme* ***4.1***, *vide supra*), under Baldwin's conditions furnished *triene* ***376*** in 79% yield. In a similar

manner to previous syntheses, *triene* ***376*** was hydrolysed and acetate protected before formation of amide bond from the acid chloride. Finally, acetate deprotection was performed to generate (−)-inthomycin C (***355***) in 22% yield over four steps, and in 4% yield over thirteen steps from propargyl alcohol (*Scheme* ***4.12***).



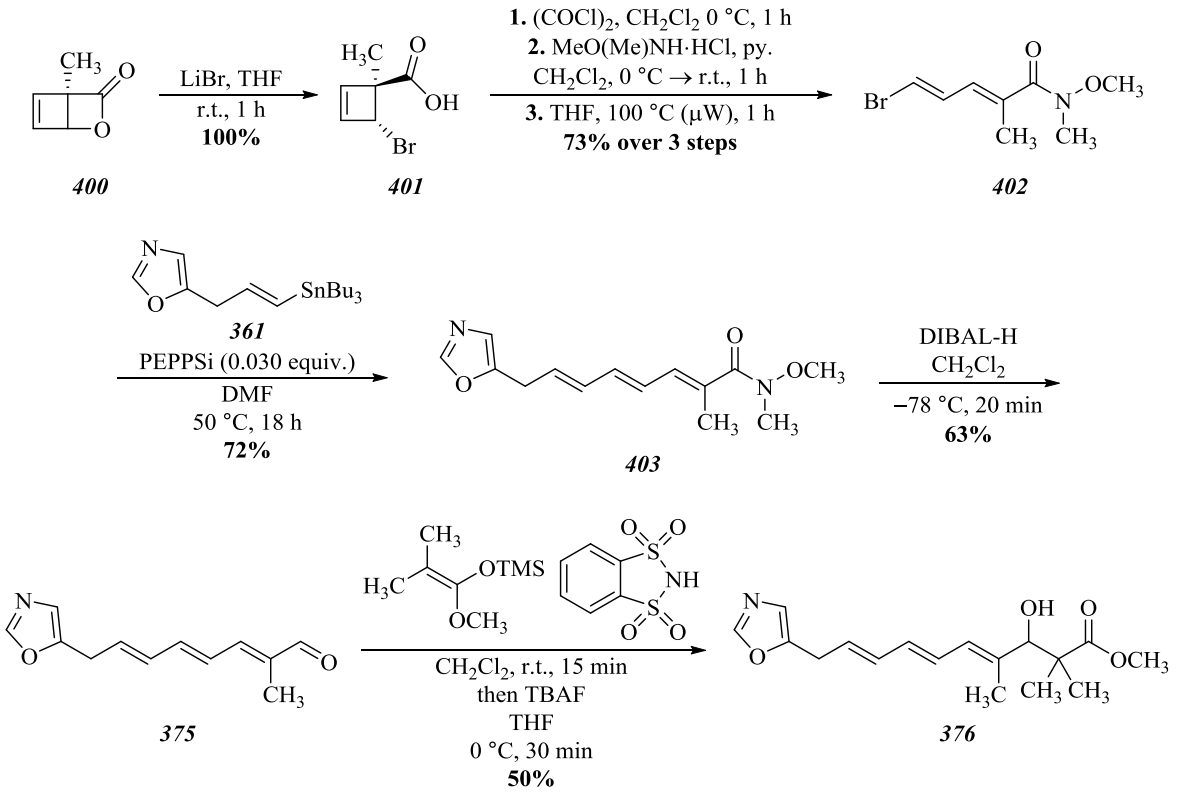
Scheme 4.11 *Preparation of alkyne* ***397***



Scheme 4.12 *Synthesis of (−)-inthomycin C (****355****)*

It should be noted that there is some debate over the absolute configuration of (+)-inthomycin C (***355***) and (−)-inthomycin C (***355***). Zeeck, Taylor (*Chapter* ***4.1.2***, *vide supra*), and Hale (*Chapter* ***4.1.6***, *vide infra*) claim that (+)-inthomycin C (***355***) has (*R*) configuration at the 3-position, whereas Ryu (*Chapter* ***4.1.3***, *vide supra*) and Hatakeyama (claimed that (−)-inthomycin C (***355***) has (*R*) configuration at this 3-position. A recent report by Hale and co-workers[182] has indicated that Ryu and Hatakeyama have actually made the (*S*) enantiomer in their synthesis of (−)-inthomycin C (***355***), which is consistent with the assignments of Zeeck and Taylor.

4.1.5 Previous formal synthesis of (±)-inthomycin C (355)—Maulide (2013)

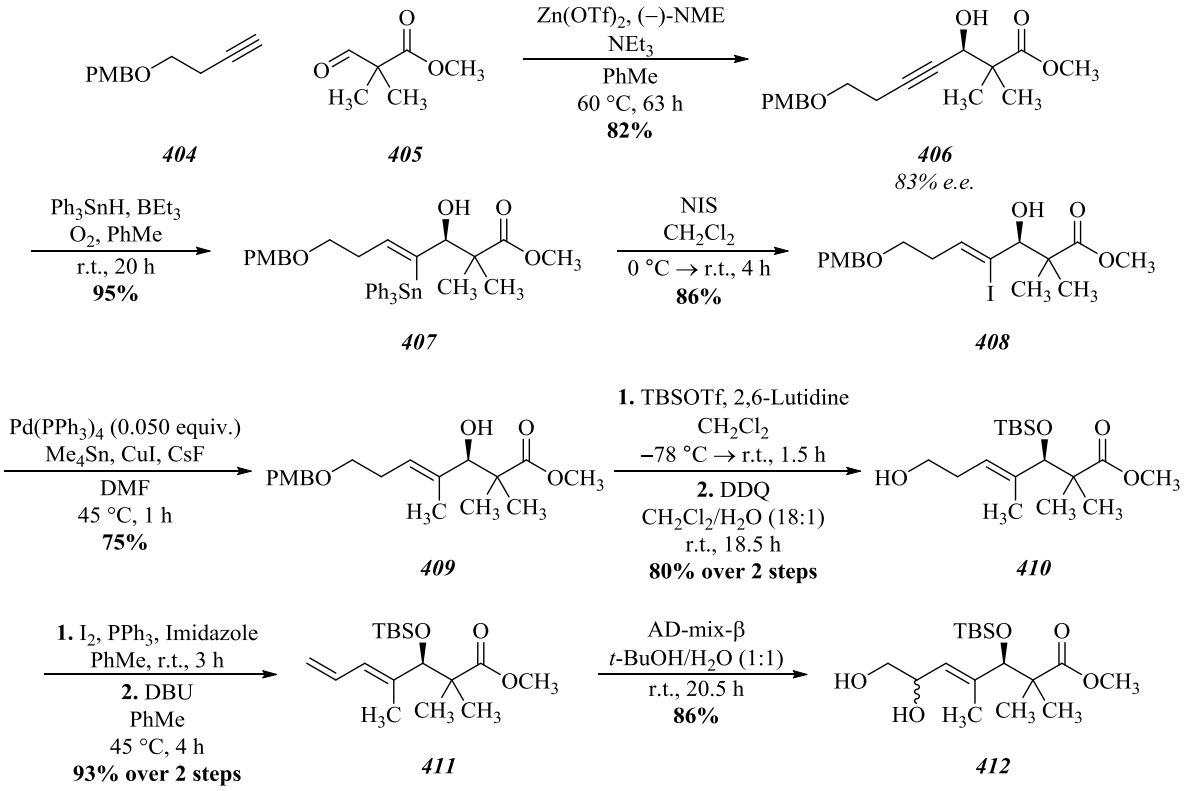


Scheme 4.13 *Formal synthesis of (±)-inthomycin C (355)*

In 2013, Maulide and co-workers employed a new approach to the synthesis of one of the building blocks, which utilised protocol for the ring-opening of a halocyclobutene to provide dienyl carboxylate derivatives.[183] The synthesis began with the opening of *lactone* ***400*** by lithium bromide, which opened the lactone to generate *acid* ***401*** in quantitative yield. Formation of the Weinreb amide was followed with conrotatory thermal cyclobutene electrocyclic ring-opening to furnish *amide* ***402*** in 73% yield over three steps. The Stille coupling was then employed with *stannane* ***361***, which had

been previously prepared by Taylor and co-workers (*Scheme* ***4.1***, *vide supra*), and *amide* ***402*** to generate *triene* ***403*** in 72% yield. Reduction with diisobutylaluminium hydride gave *triene* ***375*** in 63% yield. Finally, the organocatalytic Mukaiyama aldol reaction was employed to generate *triene* ***376*** in 50% yield. The synthesis of *triene* ***376*** represents a formal synthesis of (±)-inthomycin C (***355***) (*Scheme* ***4.13***).

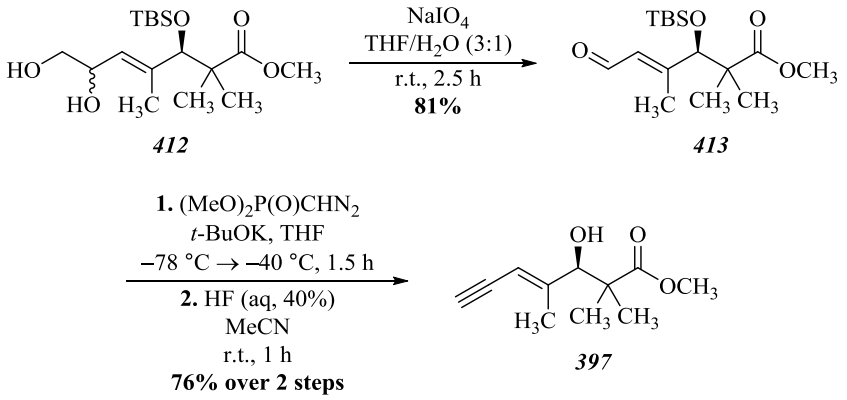
4.1.6 Previous synthesis of (+)-inthomycin C (355)—Hale (2014)



Scheme 4.14 *Preparation of diol* ***412***

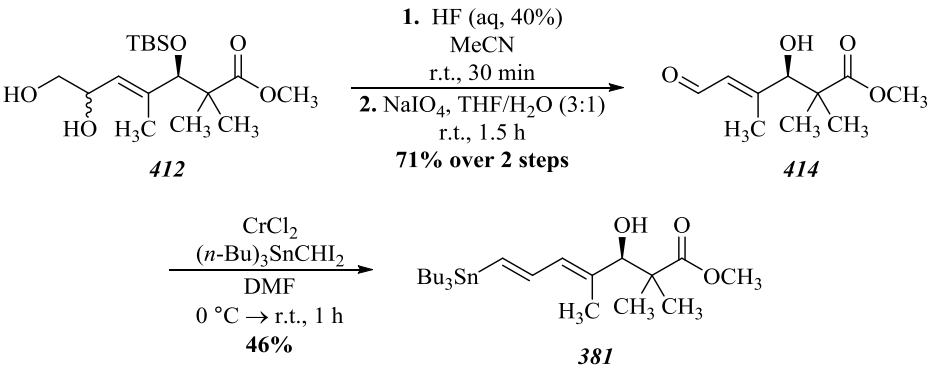
In 2014, Hale and co-workers reported the synthesis of (+)-inthomycin C (***355***), which utilised the group's oxygen-directed hydrostannation methodology.[182] Their synthesis began with the Carreira reaction[184,185] of *protected alcohol* ***404*** and *aldehyde* ***405*** using (−)-*N*-methylephedrine as the chiral ligand for zinc trifluoromethanesulfonate. The protocol furnished *alcohol* ***406*** in 82% yield with an 83% enantiomeric excess as observed by Mosher's ester analysis. Treatment of *alcohol* ***406*** under radical hydrostannation conditions gave *stannane* ***407*** in 95% yield. Subsequent iodination and Stille coupling under Baldwin's conditions generated protected *alcohol* ***409*** in 65% yield over two steps. Following on, the secondary alcohol was silicon protected and then the primary alcohol deprotected

using 2,3-dichloro-5,6-dicyano-*p*-benzoquinone to give *alcohol* ***410*** in 80% yield over two steps. Displacement of the activated alcohol with iodine and elimination synthesised *diene* ***411*** in 93% yield over two steps. Finally, osmium-catalysed dihydroxylation gave *diol* ***412*** in 86% yield (*Scheme* ***4.14***).



Scheme 4.15 *Preparation of alkyne* ***397***

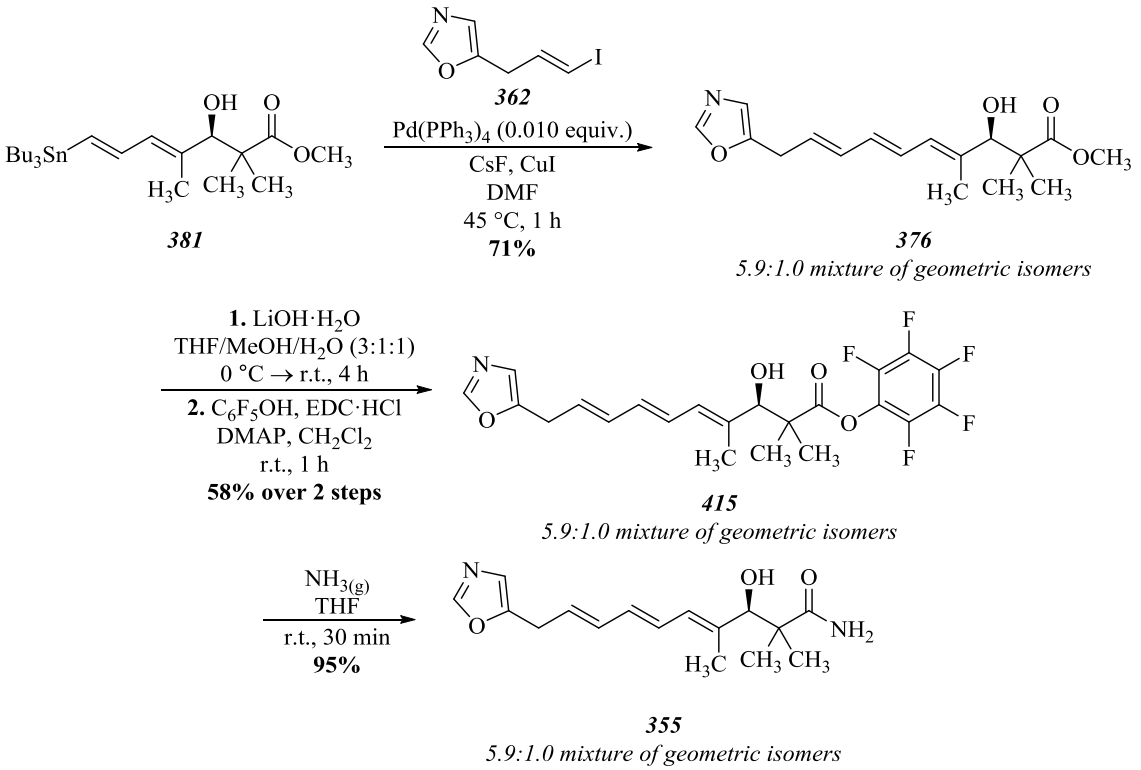
With *diol* ***412*** in hand, Hale and co-workers next attempted the synthesis of *alkyne* ***397***, a compound which had been previously prepared by Hatakeyama (*Scheme* ***4.11***, *vide supra*). *Diol* ***412*** was treated with sodium periodate to furnish *enal* ***413*** in 81% yield. The Seyferth-Gilbert homologation and silicon deprotection were then performed to generate *alkyne* ***397*** in 76% yield over two steps. Interestingly, Hatakeyama had reported an $[\alpha]_D$ −15.9 10^{-1} deg g^{-1} cm^2 (*c*. 1.04, $CHCl_3$) for *alkyne* ***397***, whereas Hale reported an $[\alpha]_D$ +12.6 10^{-1} deg g^{-1} cm^2 (*c*. 0.71, $CHCl_3$), giving strong evidence that Hatakeyama had indeed synthesised the (*S*) enantiomer of inthomycin C (***355***) and not the (*R*) enantiomer as they had previously believed (*Scheme* ***4.15***).



Scheme 4.16 *Preparation of stannane* ***381***

In a similar manner, the synthesis of *stannane* ***381***, which had been previously prepared by Ryu and co-workers (*Scheme* ***4.7***, *vide supra*), was attempted. *Diol* ***412*** was silicon deprotected and exposed to sodium periodate to furnish *enal* ***414*** in 71% yield over two steps. Treatment of *enal* ***414*** with Hodgson's vinylstannation[186] gave *stannane* ***381*** in 46% yield. Interestingly, Ryu had reported that the $[\alpha]_D$ $-17.5\ 10^{-1}$ deg g^{-1} cm^2 (*c*. 0.12, $CHCl_3$) for *stannane* ***381***, whereas Hale reported $[\alpha]_D$ $+5.6\ 10^{-1}$ deg g^{-1} cm^2 (*c*. 0.18, $CHCl_3$), again suggesting that Ryu had synthesised the (*S*) enantiomer of inthomycin C (***355***) and not the (*R*) enantiomer as they had previously believed (*Scheme* ***4.16***).

To complete the synthesis of (+)-inthomycin C (***355***), *stannane* ***381*** was subjected to the Stille reaction under Baldwin's conditions with *iodide* ***362***, which had been previously prepared by Taylor and co-workers (*Scheme* ***4.1***, *vide supra*). This protocol furnished *triene* ***376*** in 71% yield and as a 5.9:1.0 mixture of inseparable geometric isomers, which were carried through the remainder of the synthesis. A two-step transesterification furnished *ester* ***415*** in 58% yield over two steps and finally, treatment with ammonia generated (+)-inthomycin C (***355***) in 95% yield and in 13% yield over thirteen steps from *protected alcohol* ***404*** (*Scheme* ***4.17***).

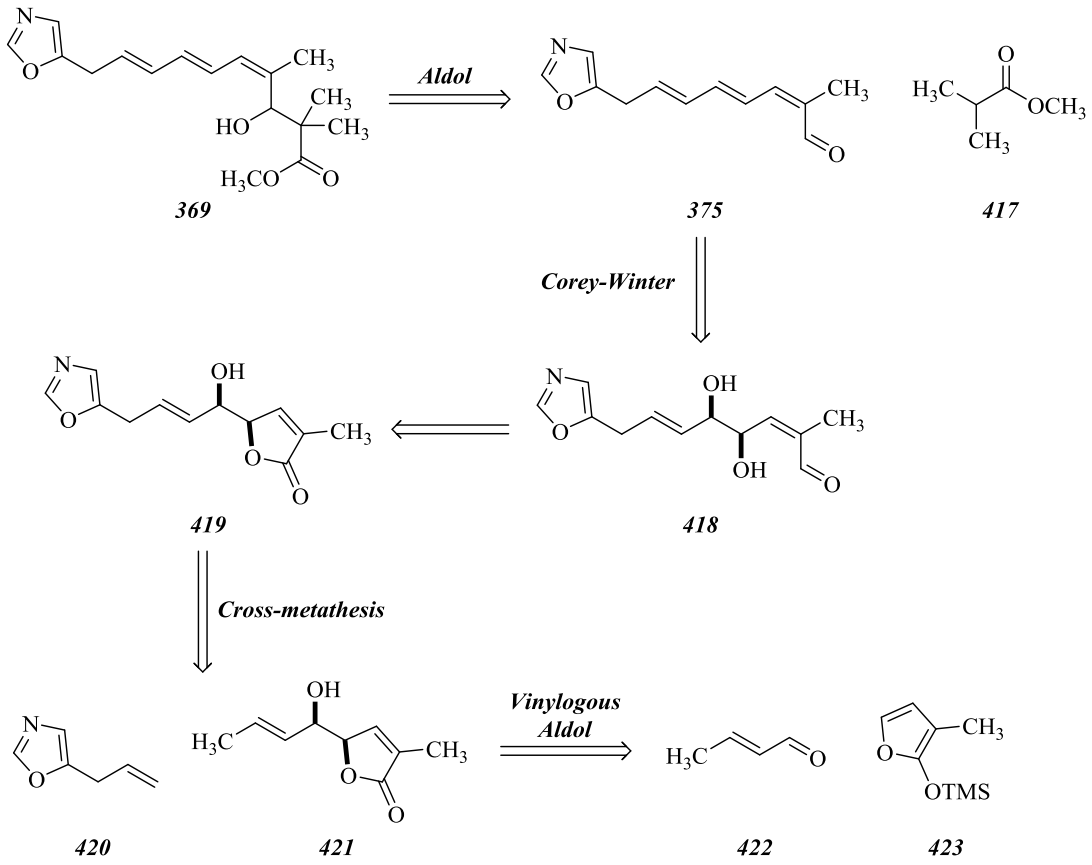


Scheme 4.17 *Synthesis of (+)-inthomycin C (**355**)*

4.2 Studies towards the synthesis of (±)-inthomycin B

4.2.1 Research outline and project aims

Attempts to repeat the syntheses of (±)-inthomycin B (***354***) and (±)-inthomycin C (***355***) had proven unsuccessful within the group, and it was found that many of the steps were capricious and not robust. To this end, it was decided that new syntheses to these compounds would be attempted. A retrosynthetic analysis was proposed to generate *triene* ***369*** which would provide a formal synthesis of (±)-inthomycin B (***354***) (*Scheme* ***4.18***). *Triene* ***369*** would be generated from an aldol reaction between *triene* ***375*** and methyl isobutyrate (***417***). A Corey-Winter olefination[187] was proposed to generate *triene* ***375*** from *syn-diol* ***418***, which itself would be synthesised from the ring-opening reduction of *oxazole* ***419***. We hoped that *oxazole* ***419*** could be furnished from the cross-metathesis reaction of *oxazole* ***420*** and *furanone* ***421***. Finally, *furanone* ***421*** could be generated from the vinylogous Mukaiyama aldol reaction of crotonaldehyde (***422***), which was chosen for its stability and ease of use compared to acrolein, and *furan* ***423***, a compound whose synthesis had been previously described in the literature.[188]

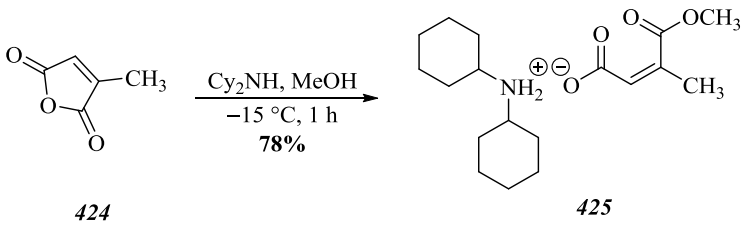


Scheme 4.18 *Proposed retrosynthetic analysis of (±)-inthomycin B (**354**)*

The aim of the project was to carry out the forward synthesis proposed from the retrosynthetic analysis, starting with the synthesis of *furan* ***423***.

4.2.2 Synthesis of furan 423

Following a reported literature procedure,[189] the synthesis of *furan* ***423*** began with ring-opening of citraconic anhydride (***424***) with methanol in the presence of dicyclohexylamine. This procedure generated *carboxylate salt* ***425*** in 78% yield on a multi-gram scale (*Scheme* ***4.19***).

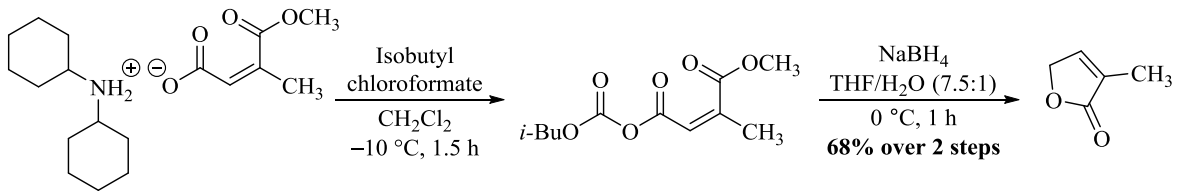


424 ***425***

Scheme 4.19 *Synthesis of carboxylate salt* ***425***

The identity of *carboxylate salt* ***425*** was confirmed by the presence of a singlet at 3.68 ppm in ^{1}H nuclear magnetic resonance (NMR) spectrum, which corresponded to O$C\underline{H}_3$. Further confirmation was obtained by the presence of a signal in the positive high-resolution mass spectrum at 182.1902 (Δ = +0.55 ppm), which corresponded to the amine cation of *carboxylate salt* ***425***, and the presence of a signal in the negative high-resolution mass spectrum at 143.0344 (Δ = +4.2 ppm), which corresponded to the carboxylate anion of *carboxylate salt* ***425***. Furthermore, spectroscopic data were found to be consistent with those reported in the literature for *carboxylate salt* ***425***.[189] Interestingly, the regioselectivity observed in this reaction shows the addition of methanol to, what appears to be, the most sterically hindered carbonyl. This was hypothesised to be due to the Bürgi-Dunitz angle of attack by the nucleophile into the carbonyl group. Approach to the carbonyl group over the C−H bonds of the CH_3 group would be considerably less favourable compared to approach adjacent to the CH_3 group, therefore formation of *carboxylate salt* ***425*** dominates.

Carboxylate salt ***425*** was treated with isobutyl chloroformate to generate *carbonate* ***426***, which was used in the next step without further purification. The reduction of *carbonate* ***426*** was performed using sodium borohydride to afford *furanone* ***427*** in a 68% yield over two steps on multi-gram scale after purification by vacuum distillation (*Scheme* ***4.20***).

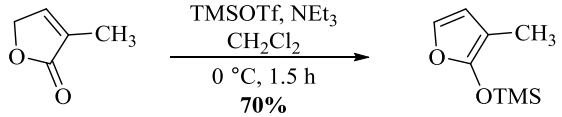


425 ***426*** ***427***

Scheme 4.20 *Synthesis of furanone* ***427***

The identity of *furanone* ***427*** was confirmed by the presence of a singlet at 174.9 ppm in the ^{13}C NMR spectrum, which corresponded to the carbon atom in the carbonyl group. Further confirmation was obtained when the spectroscopic data were found to be consistent with those reported in the literature for *furanone* ***427***.[190]

Finally, the synthesis of *furan* ***423*** was completed when *furanone* ***427*** was treated with trimethylsilyl trifluoromethanesulfonates in the presence of triethylamine following a reported literature procedure.[188] *Furan* ***423*** was thus furnished in 70% yield on a multi-gram scale after purification by vacuum distillation (*Scheme* ***4.21***).



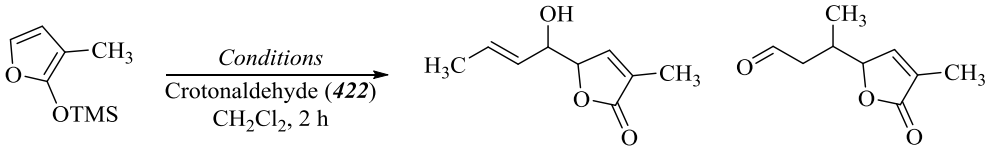
427 ***423***

Scheme 4.21 *Synthesis of furan* ***423***

The identity of *furan* ***423*** was confirmed by the presence of a singlet at 0.29 ppm in the ^{1}H NMR spectrum, which corresponded to the $Si(C\underline{H}_3)_3$. Further confirmation was obtained when the spectroscopic data were found to be consistent with those reported in the literature for *furan* ***423***.[188]

4.2.3 Optimisation of the vinylogous Mukaiyama aldol reaction

With *furan* ***423*** in hand, the planned formal synthesis of (±)-inthomycin B (***354***) was attempted starting with the vinylogous Mukaiyama aldol reaction with crotonaldehyde (***422***), which was a stable substitute for acrolein (*Table* ***4.1***).



423 ***421*** ***428***

Entry	*Furan 423*	*Crotonaldehyde (422)*	*Lewis Acid*	*Temperature*	*Yield*
1	1.00 equiv.	1.00 equiv.	$BF_3{\cdot}OEt_2$ (1.00 equiv.)	−78 °C	54% ***421*** (3.5:1.0 d.r.)
2	1.00 equiv.	1.00 equiv.	$ZnBr_2$ (1.00 equiv.)	−78 °C	20% ***421*** (2.0:1.0 d.r.), 45% ***428*** (5.0:1.0 d.r.)
3	1.00 equiv.	1.00 equiv.	TMSOTf (1.00 equiv.)	0 °C	Decomposition
4	2.00 equiv.	1.00 equiv.	$BF_3{\cdot}OEt_2$ (1.00 equiv.)	−78 °C	25% ***421*** (3.0:1.0 d.r.), 52% ***428***[a,b]
5	1.00 equiv.	5.00 equiv.	$BF_3{\cdot}OEt_2$ (1.00 equiv.)	−78 °C	40% ***421*** (3.5:1.0 d.r.)
6	1.00 equiv.	1.00 equiv.	$BF_3{\cdot}OEt_2$ (2.00 equiv.)	−78 °C	28% ***421*** (3.0:1.0 d.r.)
7	1.00 equiv.	1.00 equiv.	$BF_3{\cdot}OEt_2$ (1.00 equiv.)	−78 °C → 0 °C	59% ***421*** (3.0:1.0 d.r.)
8	1.00 equiv.	1.00 equiv.	$BF_3{\cdot}OEt_2$ (1.00 equiv.)	−78 °C → −40 °C	52% ***421*** (3.5:1.0 d.r.)
9	1.00 equiv.	1.00 equiv.	$BF_3{\cdot}OEt_2$ (1.00 equiv.)	0 °C	48% ***421*** (1.0:1.0 d.r.)
10	1.00 equiv.	1.00 equiv.	$BF_3{\cdot}OEt_2$ (1.00 equiv.)	−78 °C → 0 °C	42% ***421***[c] (3.5:1.0 d.r.)

Table 4.1 *Optimisation of the vinylogous Mukaiyama aldol reaction.* [a]*Contaminated with 20% inseparable impurities.* [b]*d.r. not obtained due to signal overlap.* [c]*Gram scale reaction.*

Boron trifluoride diethyl etherate was thought to be a suitable Lewis acid for this reaction because the presence of fluoride should aid in the removal of the silicon protecting group. Furthermore, these conditions had been reported in the literature for the vinylogous Mukaiyama aldol reaction of analogues of *furan* ***423***.[191] Treatment of *furan* ***423*** with crotonaldehyde (***422***) in the presence of boron trifluoride diethyl etherate furnished *furanone* ***421*** as an inseparable 3.5:1.0 mixture (by ^{1}H NMR analysis) of diastereoisomers in a promising 54% yield and exclusively as a single geometric isomer as observed by ^{1}H NMR spectroscopy (*Entry 1*). The remainder of the reaction material was a mixture which contained *furanone* ***428*** and uncharacterised minor impurities. It has been reported[191] that a switch in Lewis acid to zinc bromide could reverse the diastereomeric ratio, but instead a reversal in product distribution was observed with *furanone* ***428*** isolated as an inseparable 5.0:1.0 mixture (by ^{1}H NMR analysis) of diastereoisomers in 45% yield (*Entry 2*). *Furanone* ***421*** was also isolated during this reaction as an inseparable 2.0:1.0 mixture (by ^{1}H NMR analysis) of diastereoisomers in 20% yield. Unfortunately, switching to trimethylsilyl trifluoromethanesulfonates as Lewis acid led only to decomposition (*Entry 3*). Increasing the stoichiometry of *furan* ***423*** to 2.00 equivalents also led to a reversal in product distribution with 52% yield of *furanone* ***428*** observed, although a small amount (20% by ^{1}H NMR analysis) of inseparable impurities contaminated *furanone* ***428*** (*Entry 4*). Increasing the stoichiometry of crotonaldehyde (***422***) (*Entry* 5) or boron trifluoride diethyl etherate (*Entry* 6) led to a decrease in yield with little change in diastereomeric ratio.

Interestingly, the reaction was sensitive to alterations in temperature and it was found that warming the reaction to 0 ºC after addition of boron trifluoride diethyl etherate at −78 ºC gave *furanone* ***421*** as an inseparable 3.0:1.0 mixture (by ^{1}H NMR analysis) of diastereoisomers in 59% yield (*Entry 7*). Little change was observed when warming the reaction to −40 ºC after addition of boron trifluoride diethyl etherate at −78 ºC (*Entry 8*). Performing the whole procedure at 0 ºC led to a decrease in reaction yield to 48%, but importantly *furanone* ***421*** was isolated as an inseparable 1.0:1.0 mixture (by ^{1}H NMR analysis) of diastereoisomers, once again indicating a significant temperature dependency (*Entry 9*). Finally, the optimised conditions were utilised to perform the transformation

on a gram scale. This protocol furnished *furanone* ***421*** as an inseparable 3.5:1.0 mixture (by ^{1}H NMR analysis) of diastereoisomers in a slightly decreased 42% yield (*Entry 10*).

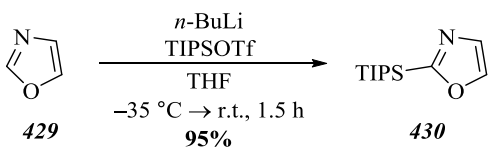
The identity of *furanone* ***421*** was confirmed by the presence of a triplet (J = 5.5 Hz) at 4.34 ppm in the ^{1}H NMR spectrum, which corresponded to C*H*OH in the major diastereoisomer. A similar triplet was observed (J = 7.0 Hz) at 4.09 ppm in the ^{1}H NMR spectrum, which corresponded to C*H*OH in the minor diastereoisomer. It has been reported that the *syn*-isomer is expected from the reaction[192] but unambiguous confirmation of the relative stereochemistry was unsuccessfully attempted by comparison of the ^{1}H NMR chemical shifts, ^{13}C NMR chemical shifts, and coupling constants of *furanone* ***421*** to literature sources.[191]

The identity of *furanone* ***428*** was confirmed by the presence of a singlet at 200.5 ppm in the ^{13}C NMR spectrum, which corresponded to carbon atom in the aldehyde in the major diastereoisomer. A similar singlet was observed at 200.7 ppm in the ^{13}C NMR spectrum, which corresponded to the carbon atom in the aldehyde in the in the minor diastereoisomer.

4.2.4 Optimisation of the cross-metathesis reaction

Even though the relative stereochemistry of *furanone* ***421*** could not be confirmed, it was proposed that the resultant alkene from the Corey-Winter olefination would indicate the relative stereochemistry, retrospectively. The next step in the proposed synthesis was to couple *oxazole* ***420*** and *furanone* ***421*** in a cross-metathesis reaction and this began with the synthesis of *oxazole* ***429***. The acidity of the protons at the *C-2* position prevented direct allylation to form *oxazole* ***420***, and so a silicon protecting group was added to oxazole (***429***).

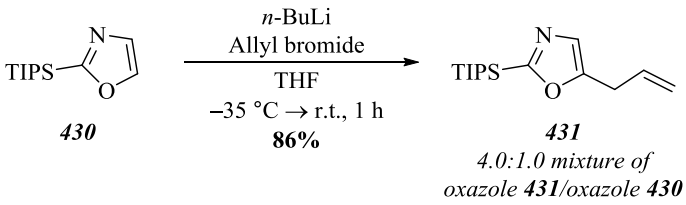
Following a reported literature procedure,[193] oxazole (***429***) was treated subsequently with *n*-butyllithium and triisopropylsilyl trifluoromethanesulfonate in tetrahydrofuran to generate *oxazole* ***430*** in a pleasing 95% yield on a multi-gram scale (*Scheme* ***4.22***).



Scheme 4.22 *Synthesis of oxazole* ***430***

The identity of *oxazole* ***430*** was confirmed by the presence of a septet (J = 7.5 Hz) at 1.40 ppm in the ^{1}H NMR spectrum, which corresponded to SiC<u>*H*</u>$(CH_3)_2$. Further confirmation was obtained when the spectroscopic data were found to be consistent with those reported in the literature for *oxazole* ***430***.[193]

With *oxazole* ***430*** in hand, the allylation reaction to form *oxazole* ***431*** was attempted. Following a reported literature procedure,[194] *oxazole* ***430*** was treated with sequentially with *n*-butyllithium and allyl bromide, which had been filtered through potassium carbonate, to furnish *oxazole* ***431*** as an inseparable 4.0:1.0 mixture (by ^{1}H NMR analysis) of *oxazole* ***431***/*oxazole* ***430*** and in an excellent 86% yield (*Scheme* ***4.23***). *Oxazole* ***431***/*oxazole* ***430*** mixtures varying from 2.0:1.0 to 5.0:1.0 were achieved and employed in subsequent reactions as indicated.



Scheme 4.23 *Synthesis of oxazole* ***431***

The identity of *oxazole* ***431*** was confirmed by the presence of a double quarter (J = 6.5, 1.5 Hz) at 3.45 ppm in the ^{1}H NMR spectrum, which corresponded to C<u>*H*</u>$_2$CH=CH_2. Further confirmation was obtained when the spectroscopic data were found to be consistent with those reported in the literature for *oxazole* ***431***.[194]

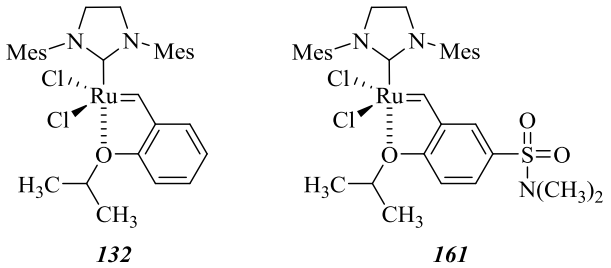
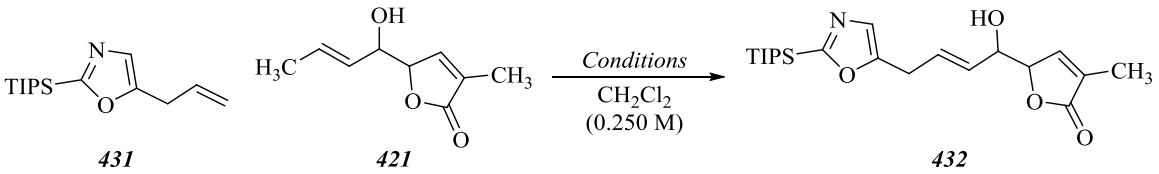


Figure 4.2 *Hoveyda-Grubbs second generation catalyst (****132****) and Zhan 1-B catalyst (****161****)*

With the synthesis of *oxazole* ***431*** complete, the cross-metathesis with *furanone* ***421*** was attempted (*Table* ***4.2***). Treatment of 2.00 equivalents of *oxazole* ***431*** (4.0:1.0 *oxazole* ***431***/*oxazole* ***430*** mixture)

with 1.00 equivalent of *furanone* ***421*** (3.5:1.0 d.r.) using Hoveyda-Grubbs second generation catalyst (***132***)[111,112] (*Figure* ***4.2***) furnished *oxazole* ***432*** as an inseparable 4.0:1.0 mixture (by ^{1}H NMR analysis) of diastereoisomers in 36% yield and exclusively as a single geometric isomer as observed by ^{1}H NMR spectroscopy (*Entry 1*).



431 ***421*** ***432***

Entry	*Oxazole 431*	*Furanone 421*	*Catalyst*	*Temperature*	*Time*	*Yield*
1	2.00 equiv. (4.0:1.0 ***431***:***430***)	1.00 equiv. 3.5:1.0 d.r.	Hoveyda-Grubbs II (***132***) (0.050 equiv.)	40 °C	16 h	36% (4.0:1.0 d.r.)
2	2.00 equiv. (4.0:1.0 ***431***:***430***)	1.00 equiv. 3.0:1.0 d.r.	Zhan 1-B (***161***) (0.050 equiv.)	50 °C	18 h	23% (3.0:1.0 d.r.)
3	2.00 equiv. (4.0:1.0 ***431***:***430***)	1.00 equiv. 3.5:1.0 d.r.	Hoveyda-Grubbs II (***132***) (0.050 equiv.)	r.t.	24 h	28% (3.5:1.0 d.r.)
4	2.00 equiv. (4.0:1.0 ***431***:***430***)	1.00 equiv. 3.5:1.0 d.r.	Hoveyda-Grubbs II (***132***) (0.050 equiv.)	r.t.	24 h	32%[a] (4.0:1.0 d.r.)
5	1.00 equiv. (4.0:1.0 ***431***:***430***)	2.50 equiv. 3.5:1.0 d.r.	Hoveyda-Grubbs II (***132***) (0.050 equiv.)	40 °C	21 h	33% (3.5:1.0 d.r.)
6	1.00 equiv. (4.0:1.0 ***431***:***430***)	2.50 equiv. 3.5:1.0 d.r.	Hoveyda-Grubbs II (***132***) (0.050 equiv.)	r.t.	21 h	29% (3.5:1.0 d.r.)

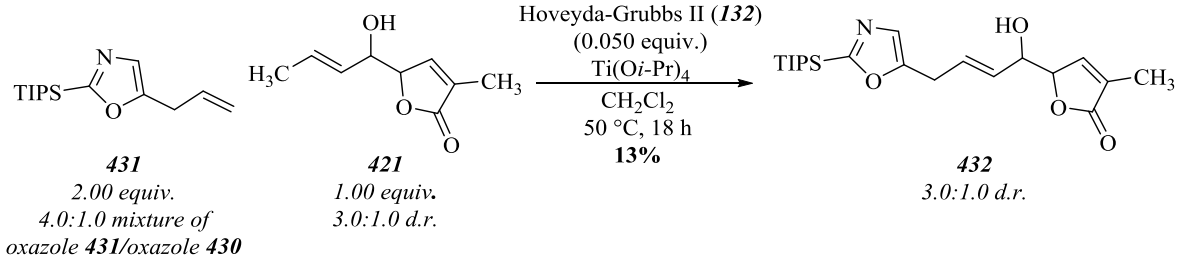
Table 4.2 *Optimisation of the cross-metathesis reaction.* [a]*Reaction performed with CH_2Cl_2 (1.00 M)*

In an attempt to improve the yield, Zhan 1-B catalyst (***161***) (*Figure* ***4.2***) was used instead of Hoveyda-Grubbs second generation catalyst (***132***), however this gave a reduction in yield to 23% (*Entry 2*). Cross-metathesis reactions have been known to perform more efficiently at lower temperatures because the catalyst is thought to undergo less decomposition.[195] In this case, however,

performing the reaction at room temperature led to decrease in yield to 28% (*Entry 3*), although performing the reaction at 1.00 M concentration gave a slight improvement on this yield with *oxazole* ***432*** being isolated in 32% yield (*Entry 4*).

Alternating the stoichiometry of the reaction with 1.00 equivalent of *oxazole* ***431*** (4.0:1.0 *oxazole* ***431***/*oxazole* ***430*** mixture) and 2.50 equivalents of *furanone* ***421*** (3.5:1.0 d.r) gave *oxazole* ***432*** as an inseparable 3.5.0:1.0 mixture (by ^{1}H NMR analysis) of diastereoisomers in 36% yield (*Entry 5*). As observed previously, performing the reaction at room temperature led to a decrease in yield to 29% (*Entry 6*).

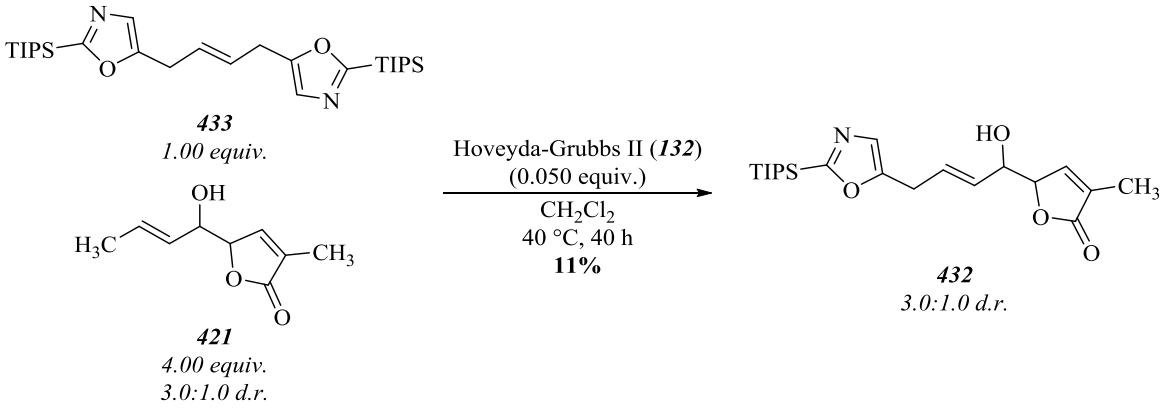
It was hypothesised that the nitrogen atom in *oxazole* ***431*** may be coordinating to the ruthenium catalyst and causing it to deactivate. Titanium isopropoxide has been shown to stop this type of coordination for the cross-metathesis reaction with acrylonitrile and so it was thought that this may act as a useful additive for this reaction.[122] However, using these modified conditions, *oxazole* ***432*** was furnished in a decreased yield of 13% indicating that titanium isopropoxide was retarding the reaction in this instance (*Scheme* ***4.24***).



Scheme 4.24 *Synthesis of oxazole* ***432*** *via cross-metathesis reaction using Ti(Oi-Pr)$_4$ as an additive*

It was also observed that a 27% yield of *oxazole dimer* ***433*** was isolated (*Table* ***4.2***, *Entry 1*) and this was typical of all reactions performed. It was hypothesised that *oxazole* ***432*** may initially form *oxazole dimer* ***433*** before taking part in a productive cross-metathesis event and it was thought that employing *oxazole dimer* ***433*** in the cross-metathesis reaction may be beneficial as ethylene had already been removed. However, treatment of *oxazole dimer* ***433*** with *furanone* ***421*** (3.0:1.0 d.r.) using Hoveyda-Grubbs second generation catalyst (***132***) furnished *oxazole* ***432*** as an inseparable 3.0:1.0 mixture (by ^{1}H NMR analysis) of diastereoisomers in 11% yield (*Scheme* ***4.25***). This

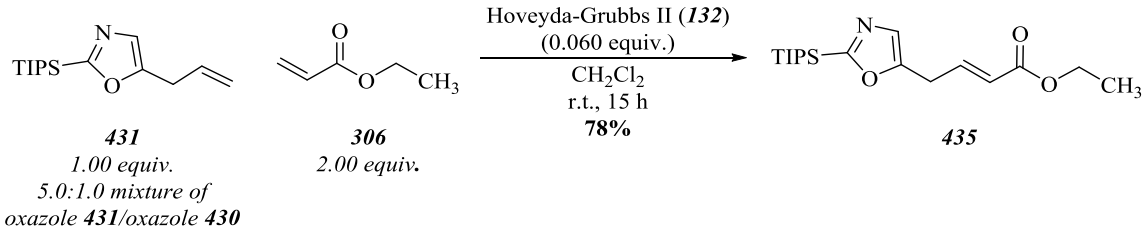
indicated that *oxazole dimer* ***433*** is a relatively inefficient coupling partner in the cross-metathesis reaction, presumably because of the increased steric hindrance of the disubstituted alkene.



Scheme 4.25 *Cross-metathesis reaction to form oxazole* ***432*** *using oxazole dimer* ***433***

The identity of *oxazole* ***432*** was confirmed by the absence of a doublet (J = 6.5 Hz) at 1.74 ppm in the ^{1}H NMR spectrum, which corresponded to C$\underline{H}_3$CH in both the major and minor diastereoisomer of *furanone* ***421***. Further confirmation was obtained by the presence of a signal in the high-resolution mass spectrum at 414.2078 (Δ = −1.7 ppm), which corresponded to the $[M+Na]^+$ ion of *oxazole* ***432***. The double-bond geometry was confirmed to be *E* by the diagnostic coupling constant (*J* = 15.5 Hz) for the olefin protons observed in the ^{1}H NMR spectrum.

With little insight gained from these experiments, it was decided that *oxazole* ***431*** would be treated in a cross-metathesis reaction with a coupling partner that was known to be tolerated by the reaction conditions. To this end *oxazole* ***431*** (5.0:1.0 *oxazole* ***431***/*oxazole* ***430*** mixture) was treated with ethyl acrylate (***306***) using Hoveyda-Grubbs second generation catalyst (***132***) to furnish *oxazole* ***435*** in a good 78% yield and exclusively as a single geometric isomer as observed by ^{1}H NMR spectroscopy (*Scheme* ***4.26***). This significant result indicated that *oxazole* ***431*** was well tolerated by the reaction conditions, and it was therefore inferred that *furanone* ***421*** was the problematic coupling partner, evidence for which can be observed by the recovery of *furanone* ***421*** from the cross-metathesis reaction even when used as the limiting reagent. It was concluded that *oxazole* ***431*** was successfully activating onto the ruthenium catalyst, and either slowly coupled with *furanone* ***421*** to generate *oxazole* ***432***, or being coupled with another equivalent of *oxazole* ***431*** to generate *oxazole dimer* ***433***, which itself was only sparingly consumed during a cross-metathesis reaction.



431
1.00 equiv.
*5.0:1.0 mixture of oxazole **431**/oxazole **430***

306
2.00 equiv.

435

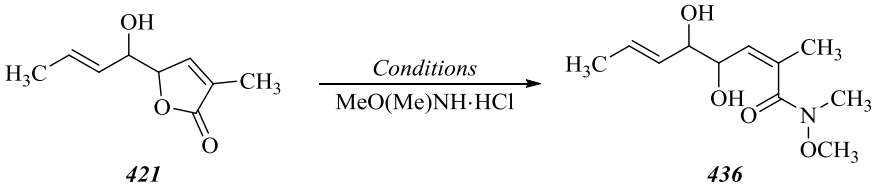
Scheme 4.26 *Synthesis of oxazole **435** via cross-metathesis reaction*

The identity of *oxazole **435*** was confirmed by the presence of a signal at 1723 cm^{-1} in the infrared spectrum, which corresponded to the carbonyl stretch. Further confirmation was obtained by the presence of a signal in the high-resolution mass spectrum at 360.1964 (Δ = +0.28 ppm), which corresponded to the $[M+Na]^+$ ion of *oxazole **435***. The double-bond geometry was confirmed to be *E* by the diagnostic coupling constant (J = 15.5 Hz) for the olefin protons observed in the ^1H NMR spectrum.

4.2.5 Ring-opening of furanone 421

Before further studies were conducted into the cross-metathesis reaction, it was decided that confirmation of the diastereoselectivity of the vinylogous Mukaiyama aldol reaction would be beneficial. This would be confirmed from the observed product ratio from the Corey-Winter olefination and to achieve this goal, the opening of *furanone **421*** was attempted. *Oxazole **432*** was not used as the substrate due to limited material available *via* the cross-metathesis reaction.

*Furanone **421*** was exposed to *N*,*O*-dimethylhydroxylamine hydrochloride under a range of different conditions to try and generate *amide **436***, which could be converted to the aldehyde when required (*Table **4.3***). Treatment of *furanone **421*** with *N*,*O*-dimethylhydroxylamine hydrochloride using diethyl aluminium chloride led only to recovery of *furanone **421*** (*Entry 1*). Similarly, using trimethylaluminium also led to recovery of *furanone **421*** (*Entry 2*). Switching to isopropylmagnesium chloride initially gave *furanone **421*** at 0 ºC (*Entry 3*), but increasing the temperature to 50 ºC led to decomposition (*Entry 4*).



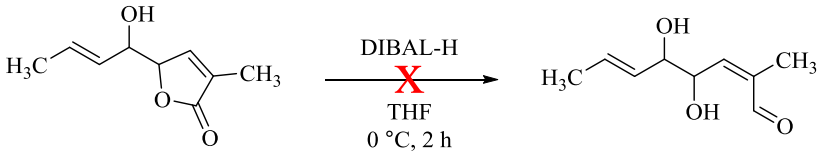
421
2.0:1.0 d.r.

436

Entry	*Lewis acid*	*Solvent*	*Temperature*	*Time*	*Result*
1	Et_2AlCl 2.20 equiv.	CH_2Cl_2	r.t.	12 h	Recovered *furanone* ***421***
2	$AlMe_3$ 4.00 equiv.	CH_2Cl_2	40 °C	12 h	Recovered *furanone* ***421***
3	*i*-PrMgCl 3.00 equiv.	THF	0 °C	2 h	Recovered *furanone* ***421***
4	*i*-PrMgCl 4.00 equiv.	THF	50 °C	12 h	Decomposition

Table 4.3 *Optimisation of the ring-opening of furanone* ***421***

With the attempts to open *furanone* ***421*** to *amide* ***436*** unsuccessful, direct formation of *enal* ***437*** was attempted (*Scheme* ***4.27***). Treatment of *furanone* ***421*** with diisobutylaluminium hydride led to the recovery of a unknown product that was hypothesised to arise from reduction of the cyclic olefin, due to loss of a signal from 7.15–7.00 ppm in the ^{1}H NMR spectrum which corresponded to C*H*=CCH$_3$.



421
2.0:1.0 d.r.

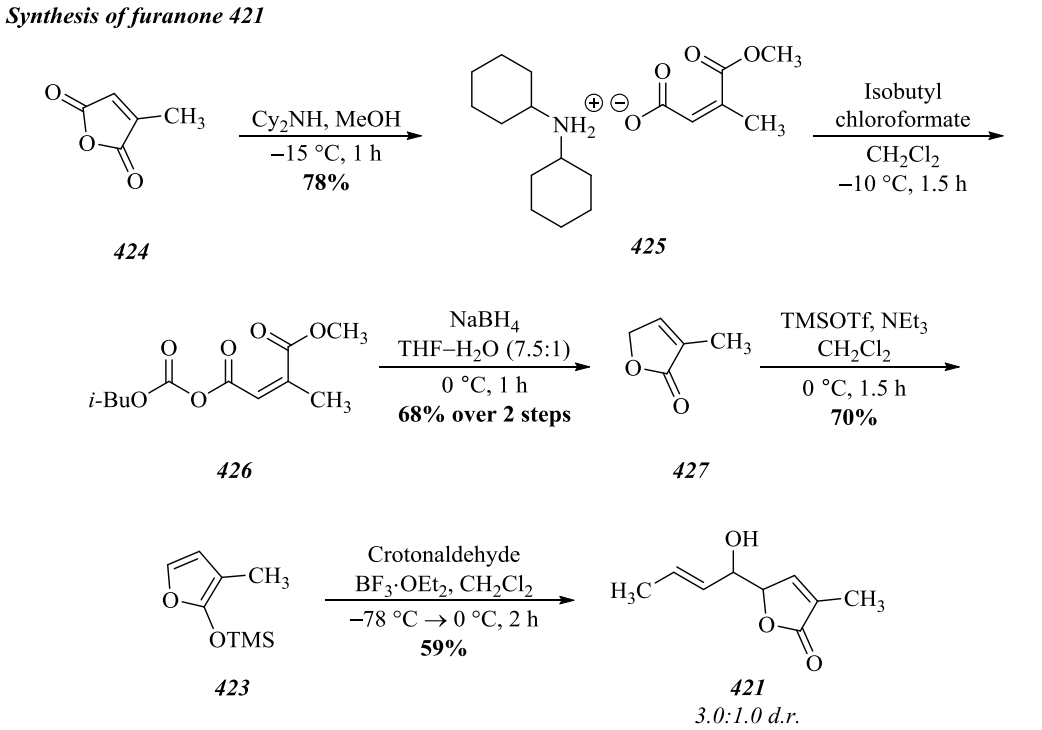
437

Scheme 4.27 *Failed synthesis of enal* ***437***

4.2.6 Summary

In summary, the formal synthesis of (±)-inthomycin B (***354***) was attempted (*Scheme* ***4.28***). *Furanone* ***421*** was generated in 22% yield over five steps from citraconic anhydride (***424***), but unfortunately the vinylogous Mukaiyama aldol reaction gave only a moderate 59% yield, and

produced *furanone* ***421*** as an inseparable 3.0:1.0 mixture (by ^{1}H NMR analysis) of diastereoisomers, the identity of which could not be confirmed by comparison to reported literature compounds.



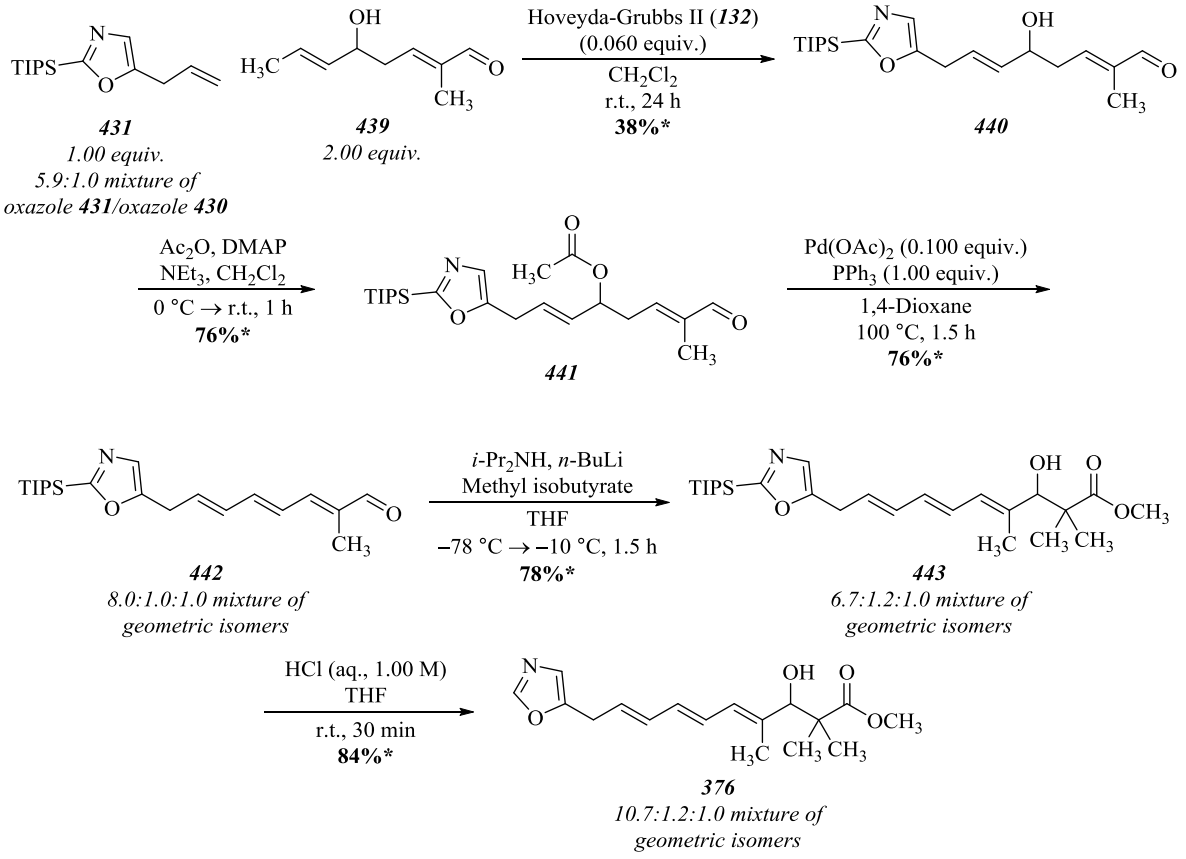
Scheme 4.28 *Summary of the attempted synthesis of (±)-inthomycin B* ***(354)***

Oxazole ***431*** was furnished in a pleasing 82% yield over two steps, however this was produced as an inseparable 4.0:1.0 mixture (by ^{1}H NMR analysis) of *oxazole* ***431***/*oxazole* ***430***. Attempts were made to carry out the cross-metathesis reaction with Hoveyda-Grubbs second generation catalyst (***132***), which furnished *oxazole* ***432*** in a disappointing 36% yield.

Due to the unsuccessful attempts at ring-opening *oxazole* ***432***, the low yield of the cross-metathesis reaction, and the unknown mixture of diastereoisomers produced from the vinylogous Mukaiyama aldol reaction, the synthesis of (±)-inthomycin B (***354***) was halted at this point and attention turned to optimising the synthesis of (±)-inthomycin C (***355***).

4.3 Optimisation of the synthesis of (±)-inthomycin C

4.3.1 Research outline and project aims



Scheme 4.29 *First generation formal synthesis of (±)-inthomycin C (**355**)*

After focussing on the synthesis of (±)-inthomycin B (***354***), attention turned to the optimisation of the formal synthesis of (±)-inthomycin C (***355***). Studies by an undergraduate co-worker in the group

had shown that a first generation formal synthesis of (±)-inthomycin C (***355***) was possible in a promising 9% yield over seven steps (*Scheme* ***4.29***).

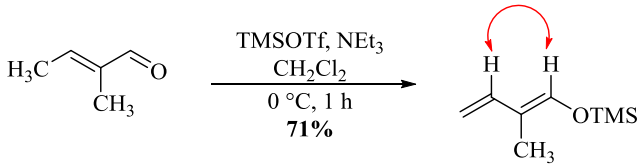
The synthesis began with the cross-metathesis reaction of 1.00 equivalent of *oxazole* ***431*** (5.9:1.0 *oxazole* ***431***/*oxazole* ***430*** mixture) and 2.00 equivalents of *enal* ***439*** using Hoveyda-Grubbs second generation catalyst (***132***), to generate *oxazole* ***440*** in disappointing 38% yield. Acetylation followed by the Tsuji-Trost reaction generated *triene* ***442*** in 58% yield over two steps. The formal synthesis of (±)-inthomycin C (***355***) was completed by subjecting *enal* ***441*** to the aldol reaction with methyl isobutyrate using pre-generated lithium diisopropylamide. This protocol furnished *triene* ***376*** in 66% over two steps once silicon deprotection had been performed with hydrochloric acid (aq., 1.00 M).

Overall, the first generation formal synthesis of (±)-inthomycin C (***355***) was encouraging, however, some of the key steps in reaction required optimisation. Firstly, the allylation of *oxazole* ***430*** did not go fully to completion and resulted in an inseparable mixture of *oxazole* ***431*** and *oxazole* ***430***. Secondly, the cross-metathesis reaction of *oxazole* ***431*** and *enal* ***439*** required significant optimisation as this was by far the lowest yielding step in the synthesis. Lastly, the Tsuji-Trost reaction, whilst generating *triene* ***442*** in a pleasing 76% yield, also produced an 8.0:1.0:1.0 mixture of geometric isomers, which was carried through the remainder of the synthesis.

The aims of the project were to address the three issues described above and generate an optimised second generation formal synthesis of (±)-inthomycin C (***355***).

4.3.2 Validation of the cross-metathesis reaction

Studies focussed on the validation of the co-worker's previous results for the cross-metathesis reaction and this began with the synthesis of *enal* ***439***, which would be coupled with *oxazole* ***431***. Firstly, tiglic aldehyde (***444***) was treated with trimethylsilyl trifluoromethanesulfonate in the presence of triethylamine to generate *enol ether* ***445*** in 71% yield on a multi-gram scale after purification by vacuum distillation. Distillation of *enol ether* ***445*** was found to significantly increase the robustness of the subsequent vinylogous Mukaiyama aldol reaction (*Scheme* ***4.30***).

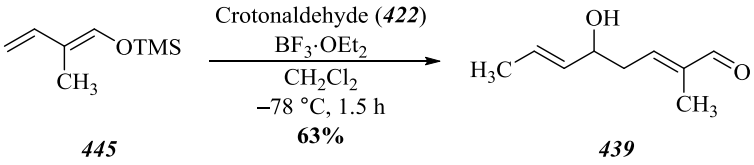


444 ***445***

Scheme 4.30 *Synthesis of enol ether* ***445***

The identity of *enol ether* ***445*** was confirmed by the presence of a singlet at 0.22 ppm in the ^{1}H NMR spectrum, which corresponded to Si(C$\underline{H}_3$)$_3$. Further confirmation was obtained when the spectroscopic data were found to be consistent with those reported in the literature for *enol ether* ***445***.[196] The diene geometry was confirmed by nuclear Overhauser effect (nOe) based NMR experiments performed on *enol ether* ***445***, which were performed by a co-worker.

With *enol ether* ***445*** in hand, the vinylogous Mukaiyama aldol reaction with crotonaldehyde (***422***) was attempted using boron trifluoride diethyl etherate as a Lewis acid. This protocol furnished *enal* ***439*** in a moderate 63% yield and exclusively as a single geometric isomer as observed by ^{1}H NMR spectroscopy on a gram scale (*Scheme* ***4.31***). The trisubstituted double-bond geometry was inferred from nOe based NMR experiments performed on *enal* ***442*** (*Scheme* ***4.33****, vide infra*), which were performed by a co-worker.



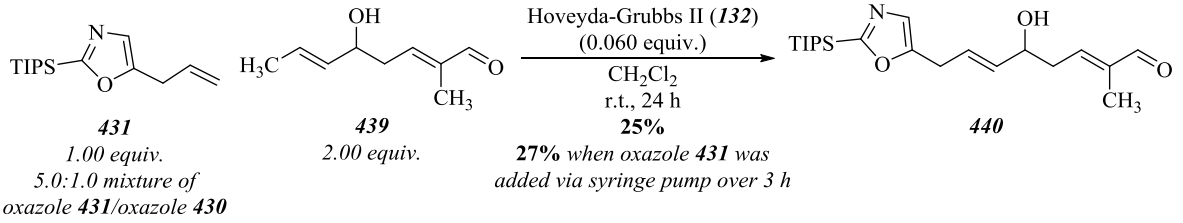
445 ***439***

Scheme 4.31 *Synthesis of enal* ***439***

The identity of *enal* ***439*** was confirmed by the presence of a signal at 3240 cm^{-1} in the infrared spectrum, which corresponded to the hydroxyl stretch. Further confirmation was obtained by the presence of a singlet at 195.3 ppm in the ^{13}C NMR spectrum, which corresponded to the carbon atom in the carbonyl group.

The cross-metathesis of *enal* ***439*** and *oxazole* ***431*** (5.0:1.0 *oxazole* ***431***/*oxazole* ***430*** mixture) was attempted using Hoveyda-Grubbs second generation catalyst (***132***), which furnished *oxazole* ***440*** in a low 25% yield and exclusively as a single geometric isomer as observed by ^{1}H NMR spectroscopy,

which was similar to that obtained by a co-worker (*Scheme* ***4.32***). This result was optimised to 27% yield when *oxazole* ***431*** was added *via* syringe-pump over 3 h.



431 *1.00 equiv. 5.0:1.0 mixture of oxazole* ***431****/oxazole* ***430***

439 *2.00 equiv.*

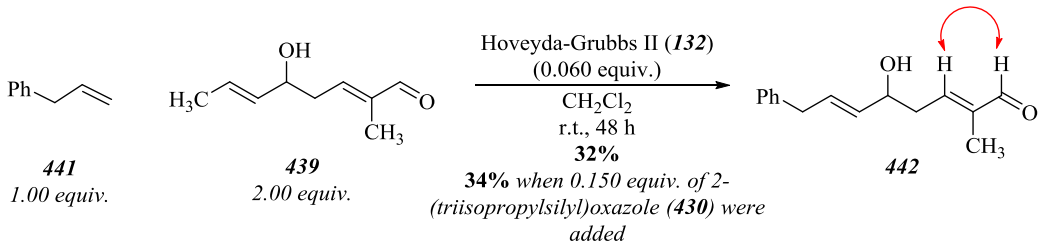
25% **27%** *when oxazole* ***431*** *was added via syringe pump over 3 h*

440

Scheme 4.32 *Synthesis of oxazole* ***440*** *via cross-metathesis reaction*

The identity of *oxazole* ***440*** was confirmed by presence of a signal in the high-resolution mass spectrum at 400.2285 ($\Delta = -1.7$ ppm), which corresponded to the $[M+Na]^+$ ion of *oxazole* ***440***. The disubstituted double-bond geometry was confirmed to be *E* by the diagnostic coupling constant ($J = 15.5$ Hz) for the olefin protons observed in the ^{1}H NMR spectrum.

After obtaining a poor yield of *oxazole* ***440*** from the cross-metathesis reaction, the reactivity of the coupling partners was investigated in order to fully understand the reaction. As previously described *oxazole* ***431*** was treated with ethyl acrylate (***306***) using Hoveyda-Grubbs second generation catalyst (***132***) to furnish *oxazole* ***435*** in a good 78% yield and exclusively as a single geometric isomer as observed by ^{1}H NMR spectroscopy (*Scheme* ***4.26****, vide supra*), which indicated that *oxazole* ***431*** was tolerated during the cross-metathesis reaction. However, treatment of *enal* ***439*** with allyl benzene (***441***) only generated *enal* ***442*** in 32% yield and exclusively as a single geometric isomer as observed by ^{1}H NMR spectroscopy (*Scheme* ***4.33***), which indicated that *enal* ***439*** was not well tolerated in the cross-metathesis reaction. Lastly, it was hypothesised that *oxazole* ***430***, which was present during the cross-metathesis reaction, may hinder the catalytic cycle. To this end, 0.150 equivalents of *oxazole* ***430*** were doped into the cross-metathesis reaction of allylbenzene (***441***) and *enal* ***439***, which furnished *enal* ***442*** in a similar 34% yield. This indicated that the presence of *oxazole* ***430*** in the reaction mixture was not detrimental.

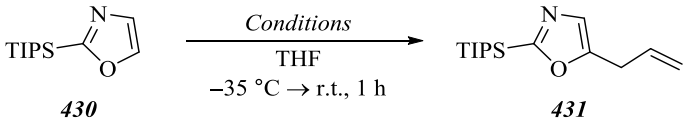


Scheme 4.33 *Synthesis of enal* ***442*** *via cross-metathesis reaction*

The identity of *enal* ***442*** was confirmed by presence of a signal in the high-resolution mass spectrum at 253.1198 (Δ = +0.40 ppm), which corresponded to the $[M+Na]^+$ ion of *enal* ***442***. The disubstituted double-bond geometry was confirmed to be *E* by the diagnostic coupling constant (*J* = 15.5 Hz) for the olefin protons observed in the ^{1}H NMR spectrum. The trisubstituted double-bond geometry was confirmed by nOe based NMR experiments performed on *enal* ***442***, which were performed by a co-worker.

4.3.3 Optimisation of the allylation reaction of oxazole 430

After validation of previous results, attention turned to switching *enal* ***439*** with a less problematic coupling partner in the cross-metathesis reaction. Firstly, however, attempts were made to optimise the synthesis of *oxazole* ***431***, which was produced as a mixture with *oxazole* ***430*** (*Table* ***4. 4***).



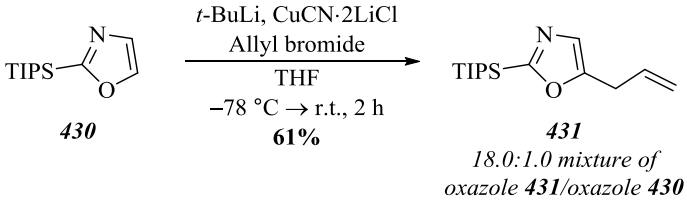
Entry	*n-BuLi*	*Allyl Bromide*	*Yield*
1	1.10 equiv.	2.00 equiv.	86% (4.0:1.0 ***431:430***)
2	2.00 equiv.	3.00 equiv.	79% (4.5:1.0 ***431:430***)

Table 4.4 *Optimisation of the synthesis of oxazole* ***431***

A small decrease in yield to 79% was observed when increasing the stoichiometry of n-butyllithium and allyl bromide, although a slight increase in the observed ratio of *oxazole* ***431***:*oxazole* ***430*** to 4.5:1.0 was also observed (*Entry 2*). Attempts to optimise the purification of the *oxazole* ***431***:*oxazole* ***430*** mixture were made using silver nitrate doped silicon dioxide in flash-column chromatography,

which has been used previously for the separation of olefin geometric isomers. Unfortunately, this proved unsuccessful in this instance with no separation of *oxazole* ***431*** and *oxazole* ***430*** observed.

Preliminary studies by a co-worker indicated that performing a transmetallation from lithium to copper may generate a softer organometallic reagent which would be more reactive in the S_N2 (or S_N2') reaction with allyl bromide. Following this procedure, *oxazole* ***430*** was treated with *tert*-butyllithium and copper cyanide to generate the requisite organocuprate. This was then treated with allyl bromide to furnish *oxazole* ***431*** as an inseparable 18.0:1.0 mixture (by ^{1}H NMR analysis) of *oxazole* ***431***/*oxazole* ***430*** and in 61% yield (*Scheme* ***4.34***), with spectroscopic data identical to the previous reported method (*Scheme* ***4.23****, vide supra*). The yield of this reaction was optimised by a co-worker, with the generation of *oxazole* ***431*** as an inseparable 19.0:1.0 mixture (by ^{1}H NMR analysis) of *oxazole* ***431***/*oxazole* ***430*** and in 89% yield on a multi-gram scale.

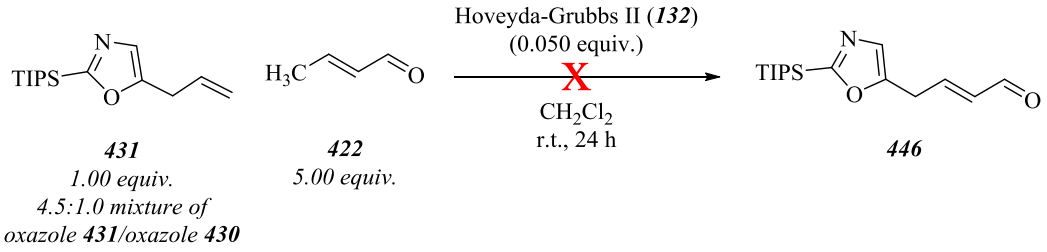


Scheme 4.34 *Synthesis of oxazole* ***431***

4.3.4 Exploring alternative coupling partners for oxazole 431 in the cross-metathesis reaction

With the optimisation of *oxazole* ***431*** completed, attention turned to exploring alternative coupling partners for *oxazole* ***431*** in the cross-metathesis reaction. It was hypothesised that instead of using *enal* ***439***, which had been derived from crotonaldehyde (***422***) and *enol ether* ***445***, it may be beneficial to simply use acrolein or crotonaldehyde (***422***) in the cross-metathesis reaction, and then perform the Mukaiyama aldol reaction subsequently. Treatment of *oxazole* ***431*** (4.5:1.0 *oxazole* ***431***/*oxazole* ***430*** mixture) with a large excess of acrolein using Hoveyda-Grubbs second generation catalyst (***132***) led only to the recovery of *oxazole* ***431***. It was thought that acrolein had rapidly polymerised under the reaction conditions and thus was not available during the cross-metathesis reaction. Treatment of *oxazole* ***431*** (4.5:1.0 *oxazole* ***431***/*oxazole* ***430*** mixture) with a large excess of crotonaldehyde (***422***) was more promising with observation of *oxazole* ***444*** in the ^{1}H NMR of the crude reaction mixture. This, however, decomposed upon purification by flash-column

chromatography, even after treatment of silicon dioxide with a pH 7 buffer (potassium phosphate monobasic/potassium phosphate dibasic). Furthermore, *oxazole* ***444*** could not be used as a crude reaction mixture due to the significant amount of by-products from the cross-metathesis reaction (*Scheme* ***4.35***).



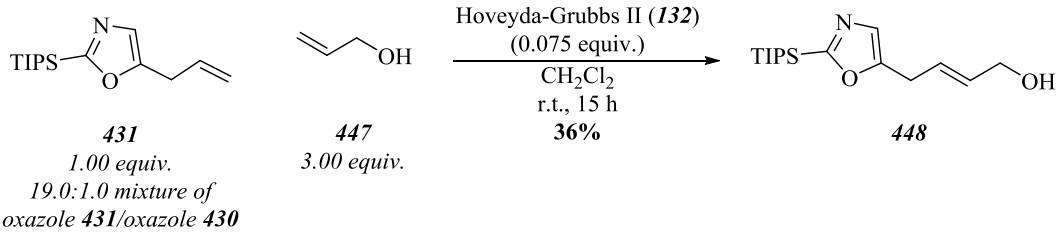
431 *1.00 equiv. 4.5:1.0 mixture of oxazole* ***431****/oxazole* ***430***

422 *5.00 equiv.*

446

Scheme 4.35 *Failed synthesis of oxazole* ***446***

The synthesis of *oxazole* ***446*** *via* cross-metathesis proved problematic and so studies focussed on generating *oxazole* ***446*** under milder conditions. It was hoped that oxidation of *oxazole* ***448*** may prove mild enough to afford *oxazole* ***446*** without the need for purification. To this end *oxazole* ***431*** was treated with allyl alcohol (***447***) in a cross-metathesis reaction using Hoveyda-Grubbs second generation catalyst (***132***). This furnished *oxazole* ***448*** exclusively as a single geometric isomer as observed by ^{1}H NMR spectroscopy but in a disappointing 36% yield (*Scheme* ***4.36***).



431 *1.00 equiv. 19.0:1.0 mixture of oxazole* ***431****/oxazole* ***430***

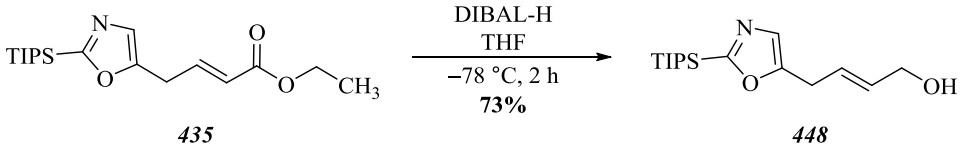
447 *3.00 equiv.*

448

Scheme 4.36 *Synthesis of oxazole* ***448*** *via cross-metathesis reaction*

The identity of *oxazole* ***448*** was confirmed by the presence of a multiplet between 4.19−4.10 ppm in the ^{1}H NMR spectrum, which corresponded to C*H*$_2$OH. Further confirmation was obtained by the presence of a signal at 3332 cm^{-1} in the infrared spectrum, which corresponded to the hydroxyl stretch. Due to extensive signal overlap in the ^{1}H NMR spectrum, the double-bond geometry was inferred to be *E* by comparison to the outcome of similar cross-metathesis reactions, and from comparison to material derived from the reduction of *oxazole* ***435*** (*Scheme* ***4.37****, vide infra*).

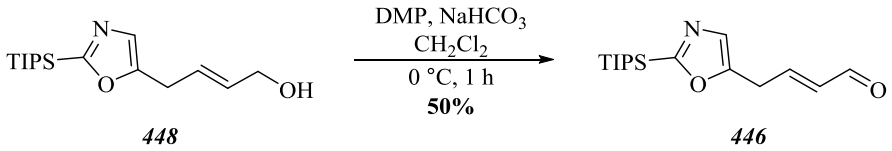
With a low yield of *oxazole* ***448*** obtained from the direct cross-metathesis reaction with allyl alcohol (***447***), it was decided that the reduction of the ester moiety in *oxazole* ***435***, generated from the cross-metathesis reaction of *oxazole* ***431*** and ethyl acrylate (***306***) in 78% yield (*Scheme* ***4.26****, vide supra*) may provide an overall greater yield of *oxazole* ***448***. It followed that the reduction of *oxazole* ***435*** with diisobutylaluminium hydride was attempted and this protocol furnished *oxazole* ***448*** in a pleasing 73% yield, and 57% yield over two steps from *oxazole* ***431*** (*Scheme* ***4.37***). Spectroscopic data was identical to that described previously for *oxazole* ***448***.



435 ***448***

Scheme 4.37 *Synthesis of oxazole* ***448***

Subsequently, *oxazole* ***448*** was oxidised to *oxazole* ***446*** using the Dess-Martin periodinane. This furnished *oxazole* ***446*** exclusively as a single geometric isomer as observed by ^{1}H NMR spectroscopy in 50% yield after purification by *rapid* flash-column chromatography, although the crude reaction material was observed to be mostly pure by ^{1}H NMR spectroscopy (*Scheme* ***4.38***). It was found that the addition of sodium bicarbonate to neutralise the acetic acid by-product was beneficial to the reaction yield as it was concluded from previous failed purification attempts that *oxazole* ***446*** was not acid-stable.

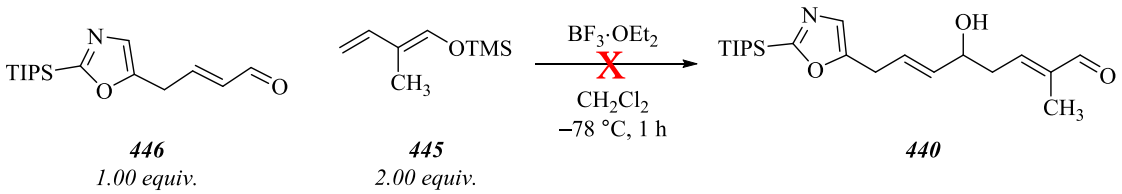


448 ***446***

Scheme 4.38 *Synthesis of oxazole* ***446***

The identity of *oxazole* ***446*** was confirmed by the presence of a singlet at 193.3 ppm in the ^{13}C NMR spectrum, which corresponded to the carbon atom in the carbonyl group. Further confirmation was obtained by the presence of a signal at 1696 cm^{-1} in the infrared spectrum, which corresponded to the carbonyl stretch. The double-bond geometry was confirmed to be *E* by the diagnostic coupling constant (J = 15.5 Hz) for the olefin protons observed in the ^{1}H NMR spectrum.

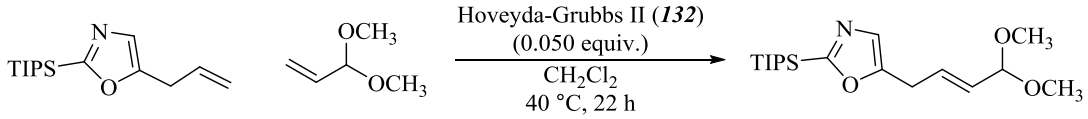
With *oxazole* ***446*** in hand, the vinylogous Mukaiyama aldol reaction was attempted. Treatment of *oxazole* ***446*** with *enol ether* ***445*** in the presence of boron trifluoride diethyl etherate led only to the generation of trace amounts of *oxazole* ***446*** (*Scheme* ***4.39***), with a large amount of silicon deprotection observed from starting *oxazole* ***446***.



446 *1.00 equiv.* ***445*** *2.00 equiv.* ***440***

Scheme 4.39 *Failed synthesis of oxazole* ***440***

With *oxazole* ***446*** proving unsuitable towards the vinylogous Mukaiyama aldol reaction, generation of the dimethylacetal was thought to provide a solution. To this end, acrolein dimethylacetal (***449***) and *oxazole* ***431*** (4.5:1.0 *oxazole* ***431***/*oxazole* ***430*** mixture) were employed in the cross-metathesis reaction using Hoveyda-Grubbs second generation catalyst (***132***), which furnished *oxazole* ***450*** in 72% yield and exclusively as a single geometric isomer as observed by ^{1}H NMR spectroscopy (*Scheme* ***4.40***).



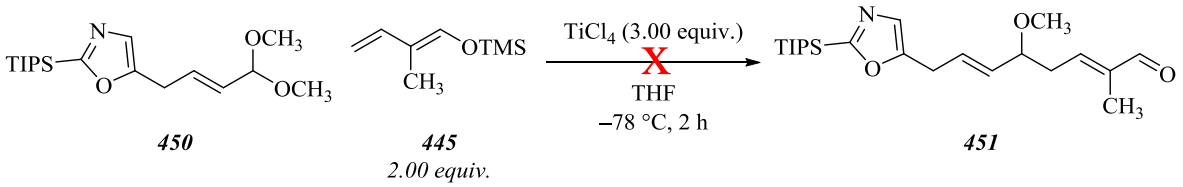
431 *1.00 equiv. 4.5:1.0 mixture of oxazole* ***431***/*oxazole* ***430*** ***449*** *5.00 equiv.* ***450***

Scheme 4.40 *Synthesis of oxazole* ***450*** *via cross-metathesis reaction*

The identity of *oxazole* ***450*** was confirmed by the presence of a singlet at 3.31 ppm in the ^{1}H NMR spectrum, which corresponded to OC$\underline{H}_3$ × 2. The double-bond geometry was confirmed to be *E* by the diagnostic coupling constant (J = 15.5 Hz) for the olefin protons observed in the ^{1}H NMR spectrum.

It was hoped that treatment of *oxazole* ***450*** with hydrochloric acid (aq., 1.00 M) would un-mask *oxazole* ***446***, but this only led to decomposition. However, direct vinylogous Mukaiyama aldol

reactions with vinyl acetals had been reported in the literature[197] and the protocol was employed for the reaction with *oxazole* ***450***.



450 ***445*** *2.00 equiv.* ***451***

Scheme 4.41 *Failed synthesis of oxazole* ***451***

Treatment of *oxazole* ***450*** with *enol ether* ***445*** in the presence of titanium chloride led only to a slurry-like solution with extensive decomposition observed in the ^{1}H NMR of the crude reaction mixture (*Scheme* ***4.41***).

4.3.5 The synthesis of oxazole 440 and oxazole 465 via relay cross-metathesis

Having established that *enal* ***439*** was likely to be the unreactive coupling partner in the cross-metathesis reaction with *oxazole* ***431***, it was hypothesised that relay cross-metathesis could afford better reactivity to generate *oxazole* ***440***.[198] This would be accomplished by extension of *enal* ***439*** with the addition of a pendant terminal alkene moiety (*Figure* ***4.3***).

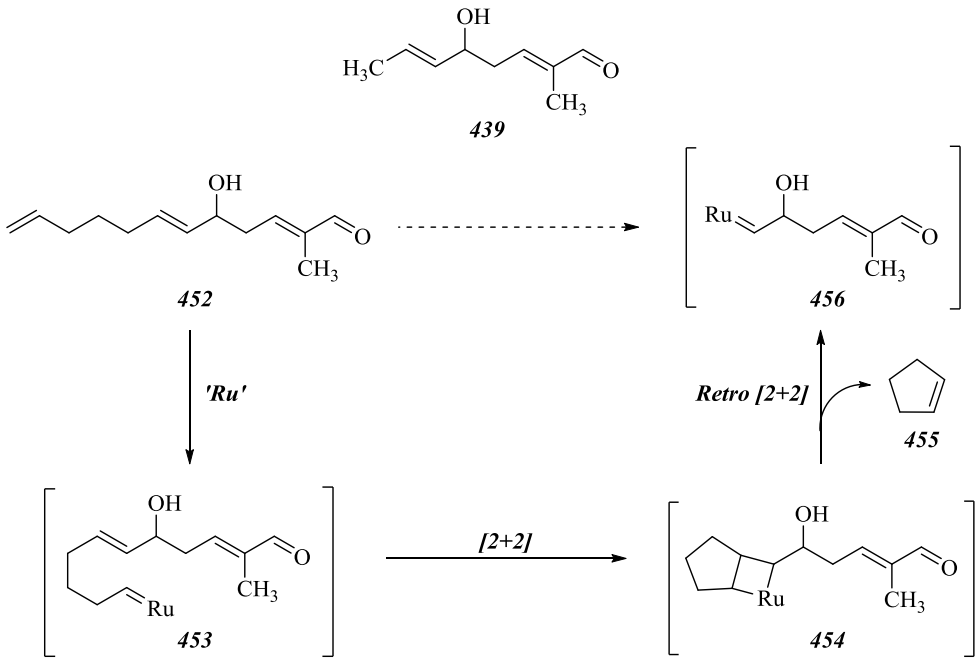
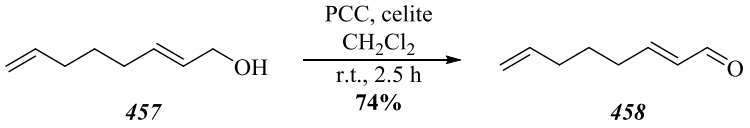


Figure 4.3 *Proposed relay cross-metathesis mechanism*

The ruthenium catalyst would activate on the terminal alkene in *enal* ***452***, which is sterically more accessible than the disubstituted alkene present in *enal* ***439***. A [2+2] cycloaddition would form *ruthenium metallocycle* ***454***, which could then undergo a retro [2+2] cycloaddition to generate *ruthenium carbene* ***456***. The removal of cyclopentene (***455***) (b.p. 44–46 ºC) would provide a suitable entropic driving force to thermodynamically favour this reaction pathway.

To test the proposed hypothesis, the synthesis of *enal* ***452*** was carried out starting from (*E*)-2,7-octadien-1-ol (***457***). (*E*)-2,7-Octadien-1-ol (***457***) was reacted with a mixture of pyridinium chlorochromate and celite in dichloromethane to generate *enal* ***458*** in 74% yield on a multi-gram scale (*Scheme* ***4.42***).

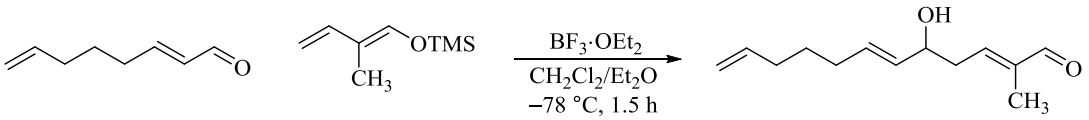


457 ***458***

Scheme 4.42 *Synthesis of enal* ***458***

The identity of *enal* ***458*** was confirmed by the presence of a doublet (J = 8.0 Hz) at 9.49 ppm in the ^{1}H NMR spectrum, which corresponded to C*H*O. Further confirmation was obtained when the spectroscopic data were found to be consistent with those reported in the literature for *enal* ***458***.[199]

Enal ***458*** was then exposed to the vinylogous Mukaiyama aldol reaction (*Table* ***4.5***). Treatment of 1.00 equivalent of *enal* ***458*** with 2.00 equivalents of distilled *enol ether* ***445*** in the presence of boron trifluoride diethyl etherate furnished *enal* ***452*** in a moderate 49% yield (*Entry 1*). A notable improvement in yield to 61% was observed when the solvent ratio was altered from 7:1 to 3:1 dichloromethane/diethyl ether. It was hypothesised that increasing the quantity of diethyl ether present in the reaction mixture would attenuate the reactivity of the Lewis acid (*Entry 2*). Pleasingly, reversing the stoichiometry of the reaction led to another improvement with a 74% yield observed (*Entry 3*).

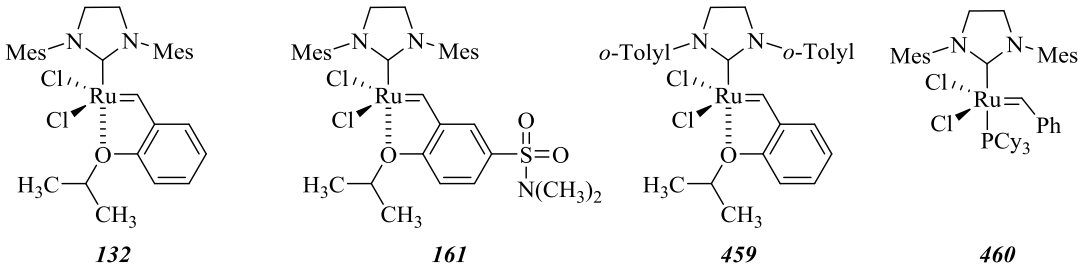


458 ***445*** ***452***

Entry	*Enal 458*	*Enol ether 445*	*Solvent*	*Yield*
1	1.00 equiv.	2.00 equiv.	7:1 CH_2Cl_2/Et_2O (0.100 M)	49%
2	1.00 equiv.	2.00 equiv.	3:1 CH_2Cl_2/Et_2O (0.100 M)	61%
3	2.00 equiv.	1.00 equiv.	3:1 CH_2Cl_2/Et_2O (0.100 M)	74%

Table 4.5 *Optimisation of the vinylogous Mukaiyama aldol reaction*

The identity of *enal* ***452*** was confirmed by the presence of a singlet at 71.7 ppm in the ^{13}C NMR spectrum, which corresponded to *C*OH. Further confirmation was obtained by the presence of a signal at 3423 cm^{-1} in the infrared spectrum, which corresponded to the hydroxyl stretch.

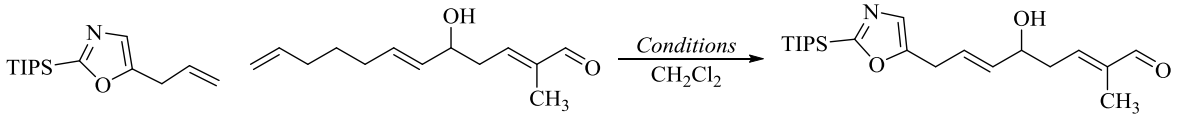


132 ***161*** ***459*** ***460***

Figure 4.4 *Hoveyda-Grubbs second generation catalyst (**132**), Zhan 1-B catalyst (**161**), Stuart-Grubbs catalyst (**459**), and Grubbs second generation catalyst (**460**)*

With *enal* ***452*** in hand, the relay cross-metathesis reaction with *oxazole* ***431*** was attempted to generate *oxazole* ***440*** (*Table* ***4.6***). Treatment of 1.00 equivalent of *enal* ***452*** and 2.00 equivalents of *oxazole* ***431*** in the presence of Hoveyda-Grubbs second generation catalyst (***132***) (*Figure* ***4.4***) gave *oxazole* ***440*** in 33% yield and exclusively as a single geometric isomer as observed by ^1H NMR spectroscopy, with spectroscopic data identical to those reported earlier (*Entry 1*). Analysis of the remainder of the reaction mixture indicated the presence of starting *oxazole* ***431*** and *enal* ***452***, as well as *oxazole dimer* ***433*** and *enal* ***461***. Furthermore, low-resolution mass spectrum of the crude reaction mixture indicated the presence of a small quantity of *oxazole* ***462***, where the ruthenium

catalyst has activated onto *oxazole* ***431*** and then undergone a standard cross-metathesis reaction with the terminal olefin in *enal* ***452*** (*Figure* ***4.5***).



431 *18.0:1.0 mixture of oxazole* ***431****/oxazole* ***430***

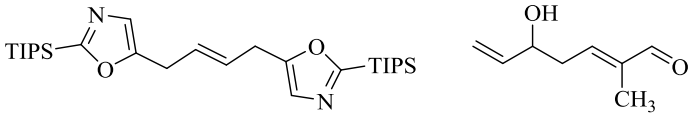
452

440

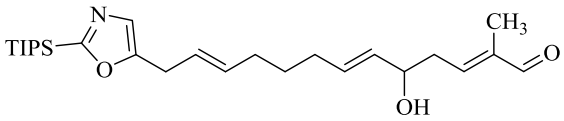
Entry	*Oxazole 431*	*Enal 452*	*Catalyst*	*Temperature*	*Time*	*Yield*
1	1.00 equiv.	2.00 equiv.	Hoveyda-Grubbs II (***132***) (0.075 equiv.)	40 °C	19 h	33%
2	1.00 equiv.	2.00 equiv.	Zhan 1-B (***161***) (0.075 equiv.)	40 °C	21 h	31%
3	1.00 equiv.	2.00 equiv.	Stuart-Grubbs (***459***) (0.075 equiv.)	40 °C	21 h	27%
4	1.00 equiv.	2.00 equiv.	Grubbs II (***460***) (0.075 equiv.)	40 °C	24 h	12%
5	2.00 equiv.	1.00 equiv.	Hoveyda-Grubbs II (***132***) (0.075 equiv.)	40 °C	21 h	10%[a]
6	1.00 equiv.	2.00 equiv.	Hoveyda-Grubbs II (***132***) (0.075 equiv.)	60 °C	23 h	28%
7	1.00 equiv.	2.00 equiv.	Hoveyda-Grubbs II (***132***) (0.075 equiv.)	r.t.	23 h	35%
8	1.00 equiv.	2.00 equiv.	Hoveyda-Grubbs II (***132***) (0.075 equiv.)	r.t.	24 h	21%[b]
9	1.00 equiv.	4.00 equiv.	Hoveyda-Grubbs II (***132***) (0.075 equiv.)	r.t.	24 h	30%[c]
10	1.00 equiv.	2.00 equiv.	Hoveyda-Grubbs II (***132***) (0.075 equiv.)	r.t.	24 h	24%[d]

Table 4.6 *Optimisation of the relay cross-metathesis reaction.* [a]*Contaminated with 50% impurities.* [b]*Syringe-pump addition of oxazole* ***431*** *over 3 h.* [c]*Syringe-pump addition of enal* ***452*** *over 3 h.* [d]*Syringe-pump addition of Hoveyda-Grubbs second generation catalyst (**132**) over 3 h.*

Spectroscopic data for *oxazole dimer* ***433*** were identical to those reported earlier. The identity of *enal* ***461*** was confirmed by the presence of a double doublet of doublets (J = 17.0, 10.5, 6.0 Hz) in the ^{1}H NMR spectrum, which corresponded to CH_2=C<u>*H*</u>. Further confirmation was obtained by the presence of a singlet at 195.0 ppm in the ^{13}C NMR spectrum, which corresponded to the carbon atom in the carbonyl group.



433 ***461***

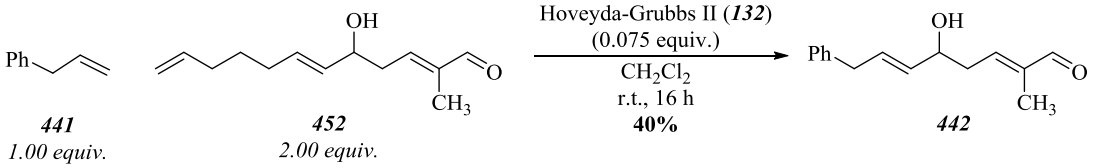


462

Figure 4.5 *Observed impurities in the relay cross-metathesis reaction*

Altering the catalyst to either Zhan 1-B catalyst (***161***) (*Entry 2*) or Stuart-Grubbs catalyst (***459***) (*Entry 3*) led to a minimal change in the yield, but use of Grubbs second generation catalyst (***460***) resulted in a significant reduction in yield to 12% (*Entry 4*). Reversing the stoichiometry of the reaction resulted in a 10% yield, although impurities (50% by ^{1}H NMR analysis) contaminated *oxazole* ***440*** (*Entry 5*). This result indicated that *enal* ***452*** was still the unreactive partner in the relay cross-metathesis reaction. Performing the reaction at 60 ºC gave a small reduction in yield to 28% (*Entry 6*), and conversely performing the reaction at room temperature gave a small increase in yield to 35% (*Entry 7*), indicating a small temperature dependence which is likely a result of catalyst stability. The presence of *oxazole* ***431*** indicated that the ruthenium catalyst may not be efficiently activating onto *enal* ***452*** when the more reactive *oxazole* ***431*** was present. To counteract this, syringe-pump addition of *oxazole* ***431*** over 3 h was attempted to allow the ruthenium catalyst to activate on *enal* ***452***, remove cyclopentene (***455***), and then react with *oxazole* ***431***. This however led to a reduced 21% yield (*Entry 8*). It was thought that *enal* ***452*** may be unstable to the cross-metathesis reaction conditions, and a control experiment exposing *enal* ***452*** to the reaction conditions without *oxazole* ***431*** led to decomposition. To overcome this issue, a large excess of *enal* ***452*** was added *via* syringe-pump over 3 h, however no notable change in yield was observed (*Entry*

9). Finally, syringe-pump addition of Hoveyda-Grubbs second generation catalyst (***132***) over 3 h was attempted in order to prevent decomposition of *enal* ***452***, but this only led to a 24% yield (*Entry 10*). Even though the relay cross-metathesis reaction could not be optimised to a suitable extent, it was pleasing to note the slightly increased yields when using the relay cross-metathesis reaction, compared to the standard cross-metathesis reaction.

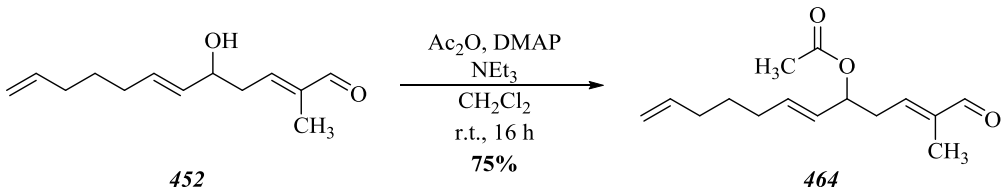


441 *1.00 equiv.* ***452*** *2.00 equiv.* ***442***

Scheme 4.43 *Synthesis of enal* ***442*** *via relay cross-metathesis reaction*

To further confirm the reactivity, *enal* ***452*** was treated in a relay cross-metathesis reaction with allyl benzene (***441***) in the presence of Hoveyda-Grubbs second generation catalyst (***132***). This protocol generated *enal* ***442*** in 40% yield and exclusively as a single geometric isomer as observed by ^{1}H NMR spectroscopy, with spectroscopic data identical to those reported earlier (*Scheme* ***4.43***).

Lastly, it was thought that the free hydroxyl group, which has been known to beneficially hydrogen bond to the chloride ions on the ruthenium catalyst,[200] may actually be hindering reactivity in this instance. To this end, attempts to acetate protect the free hydroxyl group were carried out. Treatment of *enal* ***452*** with acetic anhydride in the presence of a nucleophilic catalyst and triethylamine furnished *acetate* ***464*** in 75% yield (*Scheme* ***4.44***).

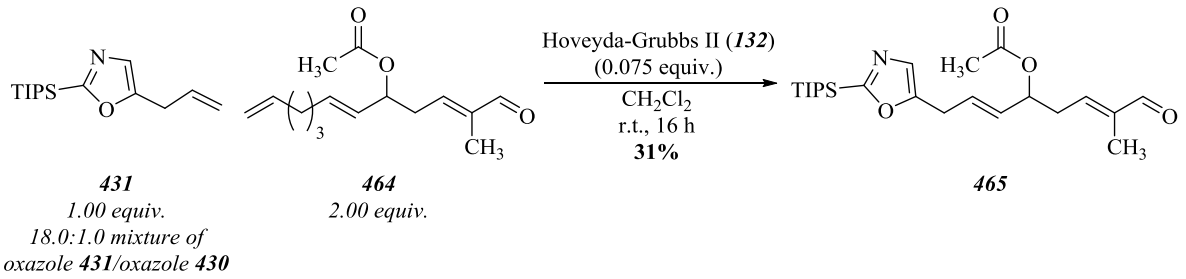


452 ***464***

Scheme 4.44 *Synthesis of enal* ***464***

The identity of *acetate* ***464*** was confirmed by the presence of a singlet at 170.2 ppm in the ^{13}C NMR spectrum, which corresponded to the carbon atom in the carbonyl group of the ester. Further confirmation was obtained by the absence of a signal at 3423 cm^{-1} in the infrared spectrum, which corresponded to the hydroxyl stretch in *acetate* ***464***.

With *acetate* ***464*** in hand, the relay cross-metathesis reaction with *oxazole* ***431*** was attempted in the presence of Hoveyda-Grubbs second generation catalyst (***132***). Disappointingly the absence of the hydroxyl group had little effect and *oxazole* ***465*** was generated in 31% yield and exclusively as a single geometric isomer as observed by ^{1}H NMR spectroscopy (*Scheme* ***4.45***). Analysis of the remainder of the reaction mixture indicated the presence of starting *oxazole* ***431*** and *acetate* ***464***, as well as *oxazole dimer* ***433***.



431 *1.00 equiv. 18.0:1.0 mixture of oxazole* ***431****/oxazole* ***430***

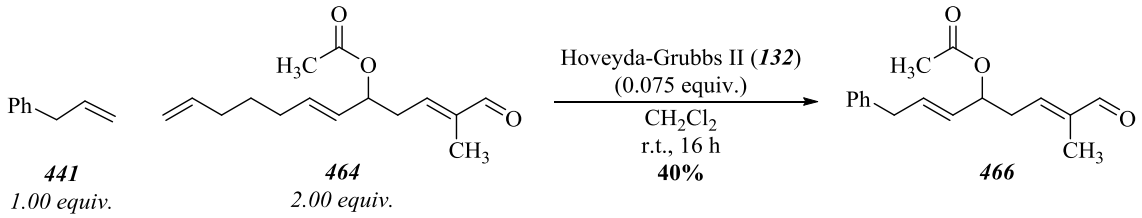
464 *2.00 equiv.*

465

Scheme 4.45 *Synthesis of oxazole* ***465*** *via relay cross-metathesis reaction*

The identity of *oxazole* ***465*** was confirmed by the presence of a signal in the high-resolution mass spectrum at 442.2387 ($\Delta = -0.67$ ppm), which corresponded to the $[M+Na]^+$ ion of *oxazole* ***465***. The double-bond geometry was confirmed to be *E* by the diagnostic coupling constant ($J = 15.0$ Hz) for the olefin protons observed in the ^{1}H NMR spectrum.

Once again, to confirm the reactivity, *enal* ***464*** was treated in a relay cross-metathesis reaction with allyl benzene (***441***) in the presence of Hoveyda-Grubbs second generation catalyst (***132***). This protocol generated *enal* ***466*** in 40% yield and exclusively as a single geometric isomer as observed by ^{1}H NMR spectroscopy (*Scheme* ***4.46***).



441 *1.00 equiv.*

464 *2.00 equiv.*

466

Scheme 4.46 *Synthesis of enal* ***466*** *via relay cross-metathesis reaction*

The identity of *enal* ***466*** was confirmed by the presence of a signal in the high-resolution mass spectrum at 295.1299 ($\Delta = +2.0$ ppm), which corresponded to the $[M+Na]^+$ ion of *enal* ***466***. The

double-bond geometry was inferred to be *E* by comparison to the outcome of similar cross-metathesis reactions (*Scheme* ***4.45****, vide supra*).

After exploring the use of different coupling partners in the cross-metathesis reaction, it was felt that a modified route to inthomycin C (***355***) may be required. The project was handed over to a co-worker at this point.

4.3.6 Summary

In summary, alternative coupling partners were trialed in order to improve the yield of the cross-metathesis reaction. It was hoped that performing the cross-metathesis reaction on simpler molecules than *enal* ***439*** would allow for increased yields. Subsequent vinylogous Mukaiyama aldol reaction would follow the cross-metathesis reaction. Unfortunately, attempts to encourage this transformation were unsuccessful, either due to the cross-metathesis reaction itself, or the subsequent vinylogous Mukaiyama aldol reaction.

Relay cross-metathesis was then employed with the hypothesis that *enal* ***439*** was unreactive in the cross-metathesis reaction. Attachment of the relay portion to form *enal* ***452*** would allow quick activation to form the desired ruthenium carbene. Even though the relay cross-metathesis reaction did afford improved yields compared to the standard cross-metathesis reaction, a maximum yield of 35% was obtained for the transformation. Attempts to optimise this reaction any further proved unsuccessful.

Chapter 5

Experimental

5.1 Experimental Techniques

5.1.1 Reagents and Reaction Solvents

All reagents and reaction solvents were obtained from Acros, Alfa Aesar, Fluorochem, Sigma-Aldrich, and Strem fine chemicals suppliers. They were used directly as supplied or after purification procedures as described by Perrin and Armarego,[201] apart from dichloromethane, toluene, diethyl ether, methanol, and tetrahydrofuran which were dried by filtration through an activated alumina purification column under a pressure of nitrogen.[202] Petrol refers to petroleum ether that boils in the range of 40−60 °C.

5.1.2 Reactions

All reactions were performed in flame-dried glassware and under an inert atmosphere after being evacuated and refilled with argon or nitrogen (×3). Syringes and needles for the transfer of reagents were dried in an oven before being cooled in a desiccator over self-indicating silicon dioxide gel, except for disposal needles and syringes which were used directly out of the sealed wrapping. All stated temperatures refer to external bath temperatures and not internal reaction mixture temperatures.

5.1.3 Flash-column chromatography

Flash-column chromatography was performed using Merck Kieselgel 60 (40−63 μm) using head pressure by means of a positive pressure from a nitrogen line, employing the method of Still *et al.*[203] Solvent systems are reported as percentages of polar solvent in non-polar solvent. Thin-layer chromatography analyses were performed on Merck Kiesegel 60 F_{254} 0.25 mm precoated aluminium plates. Product spots were visualised under ultraviolet light (λ_{max} =254 nm) and/or by staining with potassium permanganate, vanillin, or phosphomolybdic acid solution.

5.1.4 Nuclear Magnetic Resonance

Nuclear magnetic resonance (NMR) spectroscopy was recorded at room temperature on a Bruker Avance AV300, AV400, or AV500 spectrometer. ^{1}H NMR spectroscopy was recorded at 300 MHz, 400 MHz, or 500 MHz as stated. ^{13}C NMR spectroscopy was recorded at 75 MHz, 101 MHz, or 126 MHz as stated with broadband proton decoupling. ^{19}F NMR spectroscopy was recorded at

376 MHz or 471 MHz, as stated, and was externally calibrated to $CFCl_3$. Chemical shifts (δ) are reported in ppm to the nearest 0.01 ppm for ^{1}H NMR spectra, 0.1 ppm for ^{13}C NMR spectra, and 0.1 ppm for ^{19}F NMR spectra. Chemical shifts are reported relative to residual deuterated solvent peaks or tetramethylsilane internal standard. Coupling constants (*J*) are reported in Hz to the nearest 0.5 Hz for ^{1}H NMR spectra and 1 Hz for ^{13}C NMR spectra. Where required, assignments were aided by the use of distortionless enhancement by polarisation transfer (DEPT), correlation spectroscopy (COSY), and heteronuclear single quantum coherence (HSQC) experiments. Nuclear Overhauser effect (nOe) enhancement based NMR experiments and nuclear Overhauser enhancement spectroscopy (2D NOESY) correlation based NMR experiments were used to aid in olefin geometry assignment. Where numbers have been used to aid in atom assignment, these follow the International Union of Pure and Applied Chemistry naming conventions.

5.1.5 Mass Spectrometry

Low-resolution mass spectrometry (LRMS), under the conditions of electrospray ionisation (ESI), was recorded on a Fisons Platform II spectrometer. High-resolution mass spectrometry (HRMS), under conditions of ESI, was recorded on a Bruker MicroTof spectrometer. HRMS, under the conditions of field ionisation (FI), was recorded on a Micromass LCT spectrometer. Values are reported as a ratio of mass to charge in Daltons.

5.1.6 Infrared Spectroscopy

Fourier transform infrared (FTIR) spectroscopy was recorded on a Bruker Tensor 27 FTIR spectrometer as evaporated films using the Infrared Diamond ATR Module. Selected absorption peaks are given in cm^{-1}.

5.1.7 Melting Points

Melting points (MP) were obtained using a Leica VMTG heated-stage microscope and are uncorrected.

5.2 General Procedures

5.2.1 General Procedure A: The cross-metathesis of homoallylic sulfonamides with enones

The synthesis of the desired cross-metathesis product followed a procedure developed by a co-worker; this procedure was based upon optimisation of a reported literature procedure that was used for the preparation of related compounds[121]

Hoveyda-Grubbs 2nd generation catalyst (***132***)[111,112] (0.075 equiv.) and, if solid, the appropriate homoallylic sulfonamide (1.00 equiv.) were added to a screw-top reaction tube fitted with a magnetic follower. The screw-top reaction tube was sealed with a rubber septum. Dichloromethane (0.250 M), if liquid, the appropriate homoallylic sulfonamide, and the appropriate enone (2.50−5.00 equiv.) were sequentially added *via* syringe. The rubber septum was replaced with a screw cap. The reaction mixture was heated to the stated temperature and stirred at this temperature for the stated time until thin-layer chromatography analysis indicated full consumption of the appropriate homoallylic sulfonamide. On completion, the reaction mixture was cooled to room temperature and concentrated *in vacuo*. The crude material was purified by flash-column chromatography under the stated conditions, to afford the desired cross-metathesis product.

5.2.2 General Procedure B: The cross-metathesis of homoallylic sulfonamides with acrylates/thioacrylates/amides

The synthesis of the desired cross-metathesis product was adapted from a procedure developed by a co-worker, used for the cross-metathesis of homoallylic sulfonamides with enones; this procedure was based upon optimisation of a reported literature procedure that was used for the preparation of related compounds[121]

Hoveyda-Grubbs 2nd generation catalyst (***132***) [111,112] (0.075 equiv.) and, if solid, the appropriate homoallylic sulfonamide (1.00 equiv.) were added to a screw-top reaction tube fitted with a magnetic follower. The screw-top reaction tube was sealed with a rubber septum. Dichloromethane (0.250 M), if liquid, the appropriate homoallylic sulfonamide, and the appropriate acrylate/thioacrylate/amide (2.50−5.00 equiv.) were sequentially added *via* syringe. The rubber septum was replaced with a screw cap. The reaction mixture was heated to the stated temperature and stirred at this temperature for the stated time until thin-layer chromatography analysis indicated

full consumption of the appropriate homoallylic sulfonamide. On completion, the reaction mixture was cooled to room temperature and concentrated *in vacuo*. The crude material was purified by flash-column chromatography under the stated conditions, to afford the desired cross-metathesis product.

5.2.3 General Procedure C: The Heck reaction of δ-sulfonamido enones with aryl bromides

The synthesis of the desired Heck product followed a procedure developed by a co-worker; this procedure was based upon optimisation of a reported literature procedure that was used for preparation of related compounds[98]

Tris(dibenzylideneacetone)dipalladium (0.050 equiv.), tri-*tert*-butylphosphonium tetrafluoroborate (0.200 equiv.), and, if solid, the appropriate aryl bromide (2.50−5.00 equiv.) were added to a boiling tube fitted with magnetic follower. The boiling tube was sealed with a rubber septum. The appropriate δ-sulfonamido enone (1.00 equiv.), if liquid, the appropriate aryl bromide (2.50−5.00 equiv.), toluene (0.100 M), and *N*,*N*-dicyclohexylmethylamine (2.50 equiv.) were sequentially added *via* syringe. The reaction mixture was heated to the stated temperature and stirred at this temperature for the stated time until thin-layer chromatography analysis indicated full consumption of the appropriate δ-sulfonamido enone. On completion, the reaction mixture was cooled to room temperature and filtered [silicon dioxide, 50% ethyl acetate in petrol]. The fractions that contained the desired coupling product were combined and concentrated *in vacuo*. The crude material was purified by flash-column chromatography under the stated conditions, to afford the desired Heck product.

5.2.4 General Procedure D: The Heck reaction of δ-sulfonamido acrylates with aryl bromides

The synthesis of the desired Heck product was adapted from a procedure developed by a co-worker, for the Heck reaction of δ-sulfonamido enones with aryl bromides; this procedure was based upon optimisation of a reported literature procedure that was used for the preparation of related compounds[98]

Tris(dibenzylideneacetone)dipalladium (0.050 equiv.), tri-*tert*-butylphosphonium tetrafluoroborate (0.200 equiv.), and, if solid, the appropriate aryl bromide (2.50−5.00 equiv.) were added to a boiling tube fitted with magnetic follower. The boiling tube was sealed with a rubber septum. The

appropriate δ-sulfonamido acrylate (1.00 equiv.), if liquid, the appropriate aryl bromide (2.50−5.00 equiv.), toluene (0.100 M), and *N*,*N*-dicyclohexylmethylamine (2.50 equiv.) were sequentially added *via* syringe. The reaction mixture was heated to the stated temperature and stirred at this temperature for the stated time until thin-layer chromatography analysis indicated full consumption of the appropriate δ-sulfonamido acrylate. On completion, the reaction mixture was cooled to room temperature and filtered [silicon dioxide, 50% ethyl acetate in petrol]. The fractions that contained the desired coupling product were combined and concentrated *in vacuo*. The crude material was purified by flash-column chromatography under the stated conditions, to afford the desired Heck product.

5.2.5 General Procedure E: The single-pot Heck/condensation/elimination formation of pyridines

The synthesis of the desired pyridine product followed a procedure developed by a co-worker; this procedure was based upon optimisation of a reported literature procedure that was used for preparation of related compounds[98]

Tris(dibenzylideneacetone)dipalladium (0.050 equiv.), tri-*tert*-butylphosphonium tetrafluoroborate (0.200 equiv.), and, if solid, the appropriate aryl bromide (2.50 equiv.) were added to a boiling tube fitted with magnetic follower. The boiling tube was sealed with a rubber septum. The appropriate δ-sulfonamido enone (1.00 equiv.), if liquid, the appropriate aryl bromide (2.50 equiv.), toluene (0.100 M), and *N*,*N*-dicyclohexylmethylamine (1.50 equiv.) were sequentially added *via* syringe. The reaction mixture was heated to the stated temperature and stirred at this temperature for the stated time until thin-layer chromatography analysis indicated full consumption of the appropriate δ-sulfonamido enone. Trifluoroacetic acid (1.00 equiv.) was added *via* syringe and the reaction mixture was stirred at this temperature for the stated time until thin-layer chromatography analysis indicated full consumption of the appropriate Heck product. At this stage, elimination to the desired pyridine product was achieved *via* one of two alternative conditions:

Conditions A

1,8-Diazabicycloundec-7-ene (5.00 equiv.) was added *via* syringe and the reaction mixture was stirred at this temperature for the stated time until thin-layer chromatography analysis indicated full

consumption of the appropriate condensation product. On completion, the reaction mixture was cooled to room temperature and filtered [silicon dioxide, 33% ethyl acetate in petrol]. The fractions that contained the desired pyridine were combined and concentrated *in vacuo*. The crude material was purified by flash-column chromatography under the stated conditions, to afford the desired pyridine.

Conditions B

Step 1

The reaction mixture was cooled to room temperature and filtered [silicon dioxide, 33% ethyl acetate in petrol]. The fractions that contained the desired condensation product were combined and concentrated *in vacuo*. The crude material was purified by flash-column chromatography under the stated conditions, to afford the desired condensation product.

Step 2

The appropriate condensation product (1.00 equiv.) was added *via* syringe to a round-bottom flask fitted with a magnetic follower. The round-bottom flask was sealed with a rubber septum. Toluene (0.100 M) and potassium bis(trimethylsilyl)amide (0.500 M in toluene) (1.20 equiv.) were sequentially added *via* syringe. The reaction mixture was left at room temperature and stirred at this temperature for the stated time until thin-layer chromatography analysis indicated full consumption of the appropriate condensation product. On completion, the reaction mixture was quenched with brine (sat.) and extracted with dichloromethane (×3). The combined organic phases were dried over magnesium sulphate or sodium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by flash-column chromatography under the stated conditions, to afford the desired pyridine.

5.2.6 General Procedure F: The Heck reaction of unsubstituted vinyl Weinreb amides with aryl bromides

The synthesis of the desired Heck product was adapted from a reported literature procedure that was used for the preparation of related compounds[59]

Palladium acetate (0.050 equiv.), tri(*ortho*-tolyl)phosphine (0.100 equiv.), sodium acetate (2.00 equiv.), and, if solid, the appropriate aryl bromide (1.50 equiv.) were added to a microwave

vial fitted with a magnetic follower. The microwave vial was sealed with a crimped microwave lid with a septum and *N*,*N*-dimethylformamide (0.200 M) was added *via* syringe. If liquid, the appropriate aryl bromide (1.50 equiv.) and *amide* ***268*** (1.00 equiv.) were sequentially added *via* syringe. The reaction mixture was heated to the stated temperature and stirred at this temperature for the stated time until thin-layer chromatography analysis indicated full consumption of *amide* ***268***. On completion, the reaction mixture was cooled to room temperature. The reaction mixture was diluted with ethyl acetate. The organic phase was washed with ammonium chloride (aq., sat.) (×2), water (×2), and brine (sat.). The organic phase was dried over magnesium/sodium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by flash-column chromatography under the stated conditions, to afford the desired Heck product.

5.2.7 General Procedure G: The Heck reaction of β-substituted vinyl Weinreb amides with aryl iodides

*The synthesis of the desired Heck product was adapted from a reported literature procedure used for the preparation of related compound*s[135]

1,3-Bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (1,4-naphthoquinone)palladium(0) dimer (***273***)[136] (0.030 equiv.), caesium pivalate (2.00 equiv.), and, if solid, the appropriate aryl iodide (2.00 equiv.) were added to a microwave vial fitted with a magnetic follower. The microwave vial was sealed with a crimped microwave lid with a septum and *N*,*N*-dimethylformamide (0.500 M) were added *via* syringe. If liquid, the appropriate aryl iodide (2.00 equiv.) and the appropriate vinyl Weinreb amide (1.00 equiv.) were sequentially added *via* syringe. The reaction mixture was heated to the stated temperature and stirred at this temperature for the stated time until thin-layer chromatography analysis indicated full consumption of the appropriate vinyl Weinreb amide. On completion, the reaction mixture was cooled to room temperature. The reaction mixture was diluted with ethyl acetate. The organic phase was washed with ammonium chloride (aq., sat.) (×2), water (×2), and brine (sat.). The organic phase was dried over magnesium/sodium sulphate, filtered and concentrated *in vacuo*. The crude material was purified by flash-column chromatography under the stated conditions, to afford the desired Heck product.

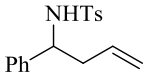
5.2.8 General Procedure H: The Fujiwara-Moritani of β-substituted vinyl Weinreb amides with arylboronic acids

The synthesis of the desired Heck product was adapted from a reported literature procedure used for the preparation of related compounds[137]

Palladium acetate (0.050 equiv.), potassium fluoride (4.00 equiv.), 4-hydroxy-2,2,6,6-tetramethylpiperidin-1-oxyl (2.00 equiv.), and the appropriate aryl boronic acid (4.00 equiv.), were added to a microwave vial fitted with a magnetic follower. The microwave vial was sealed with a crimped microwave lid with a septum. Propionic acid (0.250 M) and the appropriate vinyl Weinreb amide (1.00 equiv.) were sequentially added *via* syringe. The reaction mixture was left at room temperature and stirred at this temperature for the stated time. On completion, the reaction mixture was quenched by addition into a conical flask that contained sodium bicarbonate (aq., sat.) and extracted with dichloromethane (×3). The combined organic phases were dried over magnesium/sodium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by flash-column chromatography under the stated conditions, to afford the desired Fujiwara-Moritani product.

5.3 Experimental Details and Characterisation

4-Methyl-N-(1-phenylbut-3-en-1-yl)benzenesulfonamide (158)



Step 1

*The synthesis of imine **157** followed a reported literature procedure*[120]

Benzaldehyde (***156***) (5.23 g, 49.2 mmol), tetraethyl orthosilicate (11.0 mL, 54.2 mmol), and *p*-toluenesulfonamide (9.28 g, 54.2 mmol) were added to a 25 mL round-bottom flask fitted with a magnetic follower. A short path distillation head was fitted. The reaction mixture was heated to 170 °C and stirred at this temperature for 4 h. Ethanol was distilled off during the course of the reaction. On completion, the reaction mixture was cooled to room temperature. The crude material was filtered and washed with 50% diethyl ether in petrol to afford *imine **157*** as a white crystalline solid. *Imine **157*** was used in the next step of the transformation without further purification.

Step 2

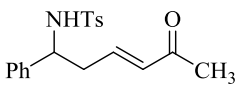
*The synthesis of sulfonamide **158** followed a procedure developed by a co-worker*

*Imine **157*** was added to a 1000 mL round-bottom flask fitted with a magnetic follower. The round-bottom flask was sealed with a rubber septum. Tetrahydrofuran (250 mL, 0.197 M) was added directly from the activated alumina purification column and the reaction mixture was cooled to −78 °C. Allylmagnesium bromide (1.00 M in diethyl ether) (73.8 mL, 73.8 mmol) was added drop-wise *via* syringe. The reaction mixture was warmed to room temperature and stirred at this temperature for 18 h. On completion, the reaction mixture was quenched with ammonium chloride (aq., sat.) and extracted with ethyl acetate (×3). The combined organic phases were washed with brine (sat.), dried over sodium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 20% ethyl acetate in petrol] to afford *sulfonamide **158*** as a white solid (11.0 g, 74% over two steps).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.57 (d, *J* = 8.5 Hz, 2 H, Ar$\underline{H}_{(m\text{-}CH_3)}$), 7.19−7.05 (m, 7 H, Ar$\underline{H}$), 5.57−5.46 (m, 1 H, C$\underline{H}$=CH$_2$), 5.12−5.01 (m, 3 H, CH=C$\underline{H}_2$ and N$\underline{H}$), 4.38 (q, *J* = 6.5 Hz, 1 H, C$\underline{H}$NH), 2.52−2.43 (m, 2 H, C$\underline{H}_2$CH), and 2.37 ppm (s, 3 H, ArC$\underline{H}_3$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 143.1, 140.3, 137.5, 133.1, 129.3, 128.3, 127.3, 127.1, 126.6, 119.2, 57.2, 41.9, and 21.5 ppm; **HRMS** (ESI$^+$) Calculated for $C_{17}H_{19}NO_2S$. $[M+Na]^+$ requires 324.1029; found 324.1019 (Δ = +3.1 ppm); **FTIR** ν_{max} (thin film): 3275, 3064, 2922, 1644, 1599, 1497, 1459, 1323, 1159, 1096, 1060, 992, 920, 843, 813, 763, 705, and 700 cm^{-1}; **MP** 59−61 °C (dichloromethane/petrol)

*NMR assignments for sulfonamide **158** were aided by DEPT, COSY, and HSQC based NMR experiments*

(E)-4-Methyl-N-(5-oxo-1-phenylhex-3-en-1-yl)benzenesulfonamide (160)



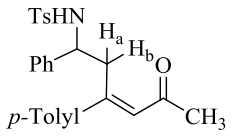
Using General Procedure A

*Sulfonamide **158*** (400 mg, 1.33 mmol) and methyl vinyl ketone (***159***) (0.273 mL, 3.33 mmol) were employed. The reaction mixture was heated to 55 °C and stirred at this temperature for 71 h. The

crude material was purified by flash-column chromatography [silicon dioxide, 20% to 50% ethyl acetate in petrol] to afford *enone **160*** as a white solid (380 mg, 83%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.57 (d, *J* = 8.5 Hz, 2 H, Ar$\underline{H}_{(m\text{-}CH_3)}$), 7.31−7.19 (m, 5 H, Ar$\underline{H}$), 7.12−7.01 (m, 2 H, Ar$\underline{H}$), 6.54 (dt, *J* = 16.0, 7.0 Hz, 1 H, $CH_2C\underline{H}$=CH), 5.99 (d, *J* = 16.0 Hz, 1 H, CH=C$\underline{H}COCH_3$), 5.75 (d, *J* = 8.0 Hz, 1 H, N$\underline{H}$), 4.44 (q, *J* = 7.5 Hz, 1 H, C$\underline{H}$NH), 2.71−2.58 (m, 2 H, $C\underline{H}_2$CH=CH), 2.35 (s, 3 H, ArC$\underline{H}_3$), and 2.12 ppm (s, 3 H, COC$\underline{H}_3$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 198.3, 143.3, 142.4, 139.7, 137.4, 134.1, 129.4, 128.6, 127.8, 127.0, 126.3, 57.2, 40.3, 26.8, and 21.4 ppm; **HRMS** (ESI^+) Calculated for $C_{19}H_{21}NO_3S$. $[M+Na]^+$ requires 366.1134; found 366.1144 (Δ = −2.7 ppm); **FTIR** ν_{max} (thin film): 3270, 2360, 1673, 1456, 1327, 1258, 1159, 1092, 980, 815, 760, 702, and 668 cm^{-1}; **MP** 104−106 °C (dichloromethane/petrol)

(E)-4-Methyl-N-(5-oxo-1-phenyl-3-(p-tolyl)hex-3-en-1-yl)benzenesulfonamide (162)



Using General Procedure C

*Enone **160*** (70.0 mg, 0.204 mmol) and 4-bromotoluene (86.5 mg, 0.510 mmol), were employed. The reaction mixture was heated to 80 °C and stirred at this temperature for 3.5 h. The crude material was purified by flash-column chromatography [silicon dioxide, 20% to 40% ethyl acetate in petrol] to afford *enone **162*** as a yellow oil (78.5 mg, 89%).

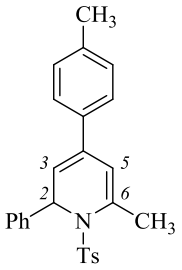
*Enone **162** was contaminated with 10% inseparable olefin regio/geometric isomers (by ^{1}H NMR analysis)*

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.37 (d, *J* = 8.0 Hz, 2 H, $Ar_{(Ts)}\underline{H}_{(m\text{-}CH_3)}$), 7.20−7.15 (m, 9 H, Ar$\underline{H}$), 7.01 (d, *J* = 8.0 Hz, 2 H, Ar$\underline{H}$, $Ar_{(Ts)}\underline{H}_{(o\text{-}CH_3)}$), 6.85 (d, *J* = 6.5 Hz, N$\underline{H}$), 6.51 (s, 1 H, C=C$\underline{H}COCH_3$), 4.37 (ddd, *J* = 11.5, 6.5, 3.5 Hz, 1 H, C$\underline{H}$NH), 3.58 (dd, *J* = 13.5, 11.5 Hz, 1 H, $C\underline{H}_aH_b$CHNH), 2.85 (dd, *J* = 13.5, 3.5 Hz, 1 H, $CH_a\underline{H}_b$CHNH), 2.42 (s, 3 H, C$\underline{H}_3$), 2.35 (s, 3 H, $Ar_{(Ts)}C\underline{H}_3$), and 2.33 ppm (s, 3 H, C$\underline{H}_3$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 201.0, 153.5, 142.2, 142.1, 140.1, 138.5, 136.5, 129.6, 129.0, 128.4, 127.3 (2), 126.9, 126.8, 126.3, 57.4, 39.1, 31.8, and 21.4 (2) ppm; **HRMS** (ESI^+) Calculated for $C_{26}H_{27}NO_3S$. $[M+Na]^+$ requires 456.1604;

found 456.1609 (Δ = −1.0 ppm); **FTIR** ν_{max} (thin film): 2923, 1668, 1596, 1455, 1330, 1183, 1159, 1091, 955, 813, 732, 700, and 667 cm^{-1}

*NMR assignments for enone **162** were aided by COSY and HSQC based NMR experiments*

6-Methyl-2-phenyl-4-(p-tolyl)-1-tosyl-1,2-dihydropyridine (168)



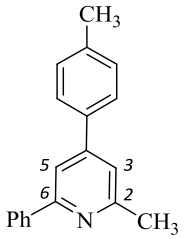
*The synthesis of dihydropyridine **168** followed a procedure developed by a co-worker*

*Enone **162*** (90% purity) (100 mg, 0.231 mmol) was added to a boiling tube fitted with a magnetic follower. The boiling tube was sealed with a rubber septum. Toluene (2.30 mL, 0.100 M) and trifluoroacetic acid (17.7 μL, 0.231 mmol) were added *via* syringe. The reaction mixture was heated to 80 °C and stirred at this temperature for 1 h. On completion, the reaction mixture was cooled to room temperature. The crude material was purified by flash-column chromatography [silicon dioxide, 15% ethyl acetate in petrol] to afford *dihydropyridine **168*** as a yellow oil (77.6 mg, 81%).

*Dihydropyridine **168** was contaminated by an inseparable compound with peaks at ~0.1 ppm (^{1}H NMR) and ~0.5 ppm (^{13}C NMR)*

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.68 (d, *J* = 8.5 Hz, 2 H, $Ar_{(Ts)}\underline{H}_{(m\text{-}CH_3)}$), 7.46 (d, *J* = 7.5 Hz, 2 H, Ar$\underline{H}$), 7.36−7.28 (m, 3 H, Ar$\underline{H}$), 7.15 (d, *J* = 8.5 Hz, 2 H, $Ar_{(Ts)}\underline{H}_{(o\text{-}CH_3)}$), 7.10 (d, *J* = 8.0 Hz, 2 H, $Ar_{(p\text{-Tolyl})}\underline{H}_{(m\text{-}CH_3)}$), 6.99 (d, *J* = 8.5 Hz, 2 H, $Ar_{(p\text{-Tolyl})}\underline{H}_{(o\text{-}CH_3)}$), 6.02 (d, *J* = 6.5 Hz, 1 H, C$\underline{H}^3$), 5.89 (s, 1 H, C$\underline{H}^5$), 5.75 (d, *J* = 6.5 Hz, 1 H, C$\underline{H}^2$), 2.35 (s, 3 H, ArC$\underline{H}_3$), 2.30 (s, 3 H, ArC$\underline{H}_3$), and 2.14 ppm (s, 3 H, C$\underline{H}_3$); **^{13}C NMR** (*chloroform-d*, 126 MHz): δ = 143.3, 139.0, 137.3, 136.1, 135.4, 134.9, 134.8, 128.9, 128.7, 128.0, 127.6, 127.0, 126.9, 125.4, 117.4, 116.2, 57.1, 23.0, 21.2, and 20.9 ppm; **HRMS** (ESI^+) Calculated for $C_{26}H_{25}NO_2S$. $[M+Na]^+$ requires 438.1498; found 438.1497 (Δ = +0.23 ppm); **FTIR** ν_{max} (thin film): 2920, 1598, 1456, 1348, 1301, 1261, 1243, 1163, 1065, 978, 734, and 691 cm^{-1}

2-Methyl-6-phenyl-4-(p-tolyl)pyridine (169)



Procedure 1

Using General Procedure E and Conditions A

Enone ***160*** (100 mg, 0.291 mmol) and 4-bromotoluene (124 mg, 0.728 mmol) were employed. The reaction mixture was heated to 80 °C and stirred at this temperature for the following times: The Heck reaction was carried out for 5 h, the condensation reaction was carried out for 2 h, and the elimination reaction was carried out for 17.5 h. The crude material was purified by flash-column chromatography [silicon dioxide, 5% ethyl acetate in petrol] to afford *pyridine* ***169*** as a yellow solid (49.5 mg, 65%).

Procedure 2

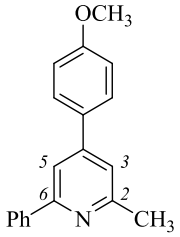
Dihydropyridine ***168*** (50 mg, 0.120 mmol) was added to a boiling tube fitted with a magnetic follower. The boiling tube was sealed with a rubber septum. Toluene (1.20 mL, 0.100 M) and 1,8-diazabicycloundec-7-ene (90.1 μL, 0.602 mmol) were sequentially added *via* syringe. The reaction mixture was heated at 80 °C and stirred at this temperature for 5 h. On completion, the reaction mixture was cooled to room temperature. The crude material was purified by flash-column chromatography [silicon dioxide, 5% ethyl acetate in petrol] to afford *pyridine* ***169*** as a yellow solid (28.4 mg, 91%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 8.05 (d, *J* = 7.0 Hz, 2 H, $Ar_{(Ph)}\underline{H}_{(o\text{-}py)}$), 7.74 (d, *J* = 1.0 Hz, 1 H, $Ar\underline{H}^{5}$), 7.61 (d, *J* = 8.5 Hz, 2 H, $Ar\underline{H}_{(m\text{-}CH_3)}$), 7.51 (dd, *J* = 7.0 Hz, 2 H, $Ar_{(Ph)}\underline{H}_{(m\text{-}py)}$), 7.44 (t, *J* = 7.5 Hz, 1 H, $Ar_{(Ph)}\underline{H}_{(p\text{-}py)}$), 7.33−7.31 (m, 3 H, $Ar\underline{H}^{3}$ and $Ar\underline{H}_{(o\text{-}CH_3)}$), 2.71 (s, 3 H, $Ar_{(py)}C\underline{H}_3$), and 2.45 ppm (s, 3 H, $Ar_{(p\text{-}Tolyl)}C\underline{H}_3$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 158.8, 157.6, 149.4, 140.0, 138.9, 135.9, 129.8, 128.7 (2), 127.2, 126.9, 119.6, 115.9, 24.9, and 21.2 ppm; **HRMS** (ESI^{+}) Calculated for $C_{19}H_{17}N$. $[M+H]^{+}$ requires 260.1434; found 260.1438 (Δ = −1.5 ppm); **FTIR** ν_{max}

(thin film): 3059, 2920, 2360, 2342, 1600, 1580, 1548, 1516, 1496, 1449, 1417, 1393, 1261, 1223, 1114, 1074, 1030, 873, 815, 774, 736, 695, 669, and 649 cm^{-1}; **MP** 57−59 °C (dichloromethane/petrol)

*NMR assignments for pyridine **169** were aided by COSY and HSQC based NMR experiments*

4-(4-Methoxyphenyl)-2-methyl-6-phenylpyridine (172)

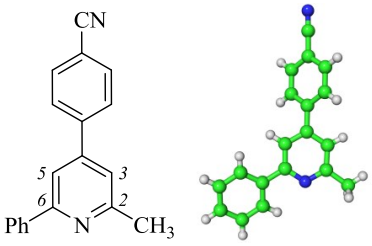


Using General Procedure E and Conditions A

*Enone **160*** (100 mg, 0.291 mmol) and 4-bromoanisole (136 mg, 0.728 mmol) were employed. The reaction mixture was heated to 80 °C and stirred at this temperature for the following times: The Heck reaction was carried out for 3 h, the condensation reaction was carried out for 2 h, and the elimination reaction was carried out for 16 h. The crude material was purified by flash-column chromatography [silicon dioxide, 10% ethyl acetate in petrol] to afford *pyridine **172*** as a yellow oil (59.6 mg, 75%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 8.05 (d, *J* = 7.5 Hz, 2 H, $Ar_{(Ph)}\underline{H}_{(o\text{-}py)}$), 7.70 (s, 1 H, $Ar\underline{H}^{5}$), 7.65 (d, *J* = 8.5 Hz, 2 H, $Ar\underline{H}_{(m\text{-}OCH_3)}$), 7.50 (t, *J* = 7.5 Hz, 2 H, $Ar_{(Ph)}\underline{H}_{(m\text{-}py)}$), 7.43 (t, *J* = 7.5 Hz, 1 H, $Ar_{(Ph)}\underline{H}_{(p\text{-}py)}$), 7.30 (s, 1 H, $Ar\underline{H}^{3}$), 7.03 (d, *J* = 9.0 Hz, 2 H, $Ar\underline{H}_{(o\text{-}OCH_3)}$), 3.88 (s, 3 H, $ArOC\underline{H}_3$), and 2.70 ppm (s, 3 H, $ArC\underline{H}_3$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 160.8, 159.2, 158.0, 149.3, 140.4, 131.5, 129.1 (2), 128.6, 127.6, 119.7, 116.0, 114.9, 55.8, and 25.3 ppm; **HRMS** (ESI^{+}) Calculated for $C_{19}H_{17}NO$. $[M+H]^{+}$ requires 276.1388; found 276.1392 (Δ = −1.5 ppm); **FTIR** ν_{max} (thin film): 2924, 2360, 1607, 1550, 1516, 1461, 1396, 1291, 1253, 1181, 1032, 829, 777, 695, and 612 cm^{-1}

4-(2-Methyl-6-phenylpyridin-4-yl)benzonitrile (175)



Using General Procedure E and Conditions A

Enone ***160*** (100 mg, 0.291 mmol) and 4-bromobenzonitrile (132.4 mg, 0.728 mmol) were employed. The reaction mixture was heated to 80 °C and stirred at this temperature for the following times: The Heck reaction was carried out for 3.5 h, the condensation reaction was carried out for 3 h, and the elimination reaction was carried out for 16 h. The crude material was purified by flash-column chromatography [silicon dioxide, 100% dichloromethane] followed by subsequent flash-column chromatography [silicon dioxide, 10% ethyl acetate in petrol] to afford *pyridine* ***175*** as a colourless solid (57.1 mg, 73%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 8.06−8.01 (m, 2 H, $Ar_{(Ph)}\underline{H}_{(o\text{-}py)}$), 7.82−7.76 (m, 4 H, $Ar_{(CN)}\underline{H}$), 7.70 (d, *J* = 1.5 Hz, 1 H, $Ar\underline{H}^{5}$), 7.50 (t, *J* = 7.5 Hz, 2 H, $Ar_{(Ph)}\underline{H}_{(m\text{-}py)}$), 7.44 (t, *J* = 7.5 Hz, 1 H, $Ar_{(Ph)}\underline{H}_{(p\text{-}py)}$), 7.30 (d, *J* = 1.5 Hz, 1 H, $Ar\underline{H}^{3}$), and 2.72 ppm (s, 3 H, $ArC\underline{H}_{3}$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 159.4, 158.1, 147.5, 143.4, 139.4, 132.8, 129.1, 128.8, 127.9, 127.1, 119.7, 118.5, 115.9, 112.6, and 24.9 ppm; **HRMS** (ESI^{+}) Calculated for $C_{19}H_{14}N_{2}$. $[M+H]^{+}$ requires 271.1230; found 271.1226 (Δ = +1.5 ppm); **FTIR** ν_{max} (thin film): 3062, 2228, 1600, 1573, 1545, 1509, 1449, 1391, 1029, 836, 776, 730, 695, and 645 cm^{-1}; **MP** 87−89 °C (dichloromethane/petrol)

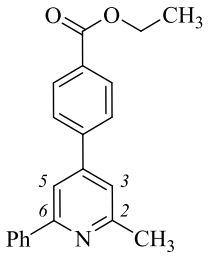
NMR assignments for pyridine ***175*** *were aided by COSY and HSQC based NMR experiments*

Single crystal diffraction data were collected at 150 K[204] using a Nonius Kappa CCD Diffractometer (λ = 0.71073Å). Data were reduced using DENZO/SCALEPACK.[205] The structure was solved with SuperFlip[206] and refined by full-matrix least squares on F^{2} using CRYSTALS.[207] Non-hydrogen atoms were refined with anisotropic displacement parameters and hydrogen atoms were treated in the usual manner.[208] See the CIF (*Appendix* ***1***) for full refinement details.

Single Crystal Data: $C_{19}H_{14}N_{2}$, M_r = 270.33, triclinic, $P\bar{1}$. *a* = 8.0582(2) Å, *b* = 9.9181(3) Å, *c* = 9.9557(3) Å, α = 62.2103(15)°, *β* = 85.9715(14)°, γ = 87.9363(12)°, *V* = 702.17(4) Å,

Data/restraints/parameters = 3194/0/190, R_{int} = 0.019, R = 0.0431 (I>2σ(I)), wR = 0.1084 (I>2σ(I)), $\Delta P_{min,max}$ = −0.22+0.29 e.Å^3

Ethyl 4-(2-methyl-6-phenylpyridin-4-yl)benzoate (178)



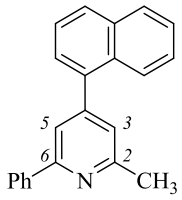
Using General Procedure E and Conditions A

Enone ***160*** (100 mg, 0.291 mmol) and ethyl 4-bromobenzoate (118 μL, 0.728 mmol) were employed. In a modification to the general procedure, tris(dibenzylideneacetone)dipalladium (26.6 mg, 29.1 μmol) and tri-*tert*-butylphosphonium tetrafluoroborate (33.8 mg, 0.116 mmol) were employed. The reaction mixture was heated to 80 °C and stirred at this temperature for the following times: The Heck reaction was carried out for 3 h, the condensation reaction was carried out for 3 h, and the elimination reaction was carried out for 14 h. The crude material was purified by flash-column chromatography [silicon dioxide, 4% ethyl acetate in petrol] and followed by subsequent flash-column chromatography [silicon dioxide, 2% ethyl acetate in petrol] to afford *pyridine* ***178*** as a colourless oil (61.3 mg, 68%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 8.17 (d, *J* = 8.0 Hz, 2 H, Ar$\underline{H}_{(o\text{-}CO_2CH_2CH_3)}$), 8.04 (d, *J* = 7.5 Hz, 2 H, Ar$_{(Ph)}\underline{H}_{(o\text{-}py)}$), 7.77−7.73 (m, 3 H, Ar$\underline{H}^5$ and Ar$\underline{H}_{(m\text{-}CO_2CH_2CH_3)}$), 7.50 (t, *J* = 7.5 Hz, 2 H, Ar$_{(Ph)}\underline{H}_{(m\text{-}py)}$), 7.43 (t, *J* = 7.5 Hz, 1 H, Ar$_{(Ph)}\underline{H}_{(p\text{-}py)}$), 7.34 (d, *J* = 1.5 Hz, 1 H, Ar$\underline{H}^3$), 4.43 (q, *J* = 7.0 Hz, 2 H, $CH_3C\underline{H}_2O$), 2.72 (s, 3 H, $ArC\underline{H}_3$), and 1.44 ppm (t, *J* = 7.0 Hz, 3 H, $C\underline{H}_3CH_2O$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 166.2, 159.1, 157.9, 148.4, 143.1, 139.6, 130.7, 130.3, 129.0, 128.8, 127.1 (2), 119.8, 116.1, 61.2, 24.9, and 14.4 ppm; **HRMS** (ESI$^+$) Calculated for $C_{21}H_{19}NO_2$. $[M+H]^+$ requires 318.1489; found 318.1493 (Δ = −1.3 ppm); **FTIR** ν_{max} (thin film): 2981, 1715, 1600, 1547, 1447, 1391, 1368, 1273, 1183, 1104, 1020, 851, 769, 735, 695, and 638 cm^{-1}

NMR assignments for pyridine ***178*** *were aided by COSY and HSQC based NMR experiments*

2-Methyl-4-(naphthalen-1-yl)-6-phenylpyridine (181)



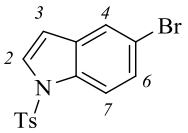
Using General Procedure E and Conditions A

Enone ***160*** (100 mg, 0.291 mmol) and 1-bromonaphthalene (202 mg, 0.728 mmol) were employed. The reaction mixture was heated to 80 °C and stirred at this temperature for the following times: The Heck reaction was carried out for 2 h, the condensation reaction was carried out for 1 h, and the elimination reaction was carried out for 14 h. The crude material was purified by flash-column chromatography [silicon dioxide, 5% ethyl acetate in petrol] to afford *pyridine* ***181*** as a yellow solid (67.8 mg, 79%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 8.17 (s, 1 H, Ar$\underline{H}^{5}$), 8.13 (d, *J* = 7.5 Hz, 2 H, Ar$_{(Ph)}\underline{H}_{(o\text{-}py)}$), 8.00−7.90 (m, 3 H, Ar$\underline{H}$), 7.88 (s, 1 H, Ar$\underline{H}^{3}$), 7.81 (dd, *J* = 8.5, 1 H, Ar$\underline{H}$), 7.59−7.52 (m, 4 H, Ar$\underline{H}$), 7.50−7.44 (m, 2 H, Ar$\underline{H}$), and 2.77 ppm (s, 3 H, ArC$\underline{H}_{3}$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 159.4, 158.2, 149.8, 140.4, 136.5, 133.9, 133.8, 129.3, 129.2, 128.9, 128.2, 127.6, 127.1 (2), 126.8, 125.2, 120.4, 116.7, and 25.3 ppm; **HRMS** (ESI^{+}) Calculated for $C_{22}H_{17}N$. $[M+H]^{+}$ requires 296.1434; found 296.1437 (Δ = −1.0 ppm); **FTIR** ν_{max} (thin film): 3058, 1651, 1595, 1574, 1494, 1448, 1338, 1255, 1185, 1096, 977, 881, 802, 779, and 696 cm^{-1}; **MP** 97−99 °C (dichloromethane/petrol)

Only 19 signals (signal overlap) observed in ^{13}C NMR (20 signals should be observed)

5-Bromo-1-tosyl-1H-indole (188)



The synthesis of indole ***188*** *followed a reported literature procedure*[123]

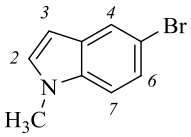
5-Bromoindole (***187***) (1.00 g, 5.10 mmol) and *p*-toluenesulfonyl chloride (1.95 g, 10.2 mmol) were added to a 100 mL round-bottom flask fitted with a magnetic follower. The round-bottom flask was

sealed with a rubber septum. Tetrahydrofuran (25.0 mL, 0.204 M) was added *via* syringe. Sodium hydride (60% dispersion in mineral oil) (408 mg, 10.2 mmol) was added slowly and the round-bottom flask was sealed with a rubber septum. The reaction mixture was left at room temperature and stirred at this temperature for 17 h. On completion, the reaction mixture was cooled to 0 °C. The reaction mixture was quenched with water and extracted with dichloromethane (×3). The combined organic phases were concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 5% ethyl acetate in petrol] to afford *indole* ***188*** as a white solid (1.21 g, 68%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.88 (d, *J* = 9.0 Hz, 1 H, Ar$\underline{H}^{7}$), 7.75 (d, *J* = 8.5 Hz, 2 H, Ar$\underline{H}_{(m\text{-}CH_3)}$), 7.65 (d, *J* = 2.0 Hz, 1 H, Ar$\underline{H}^{4}$), 7.57 (d, *J* = 3.5 Hz, 1 H, Ar$\underline{H}^{2}$), 7.40 (dd, *J* = 9.0, 2.0 Hz, 1 H, Ar$\underline{H}^{6}$), 7.23 (d, *J* = 8.0 Hz, 2 H, Ar$\underline{H}_{(o\text{-}CH_3)}$), 6.59 (dd, *J* = 3.5, 1.0 Hz, 1 H, Ar$\underline{H}^{3}$), and 2.34 ppm (s, 3 H, ArC$\underline{H}_{3}$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 145.3, 135.0, 133.5, 132.5, 130.0, 127.6, 127.5, 126.8, 124.1, 116.8, 115.0, 108.3, and 21.6 ppm; **MP** 137−139 °C (dichloromethane/petrol)

Spectroscopic data are consistent with those reported in the literature for indole ***188***[125]

5-Bromo-1-methyl-1H-indole (189)



The synthesis of indole ***189*** *followed a reported literature procedure*[124]

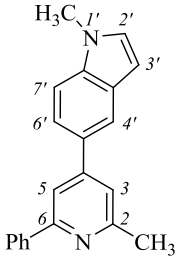
5-Bromoindole (***187***) (500 mg, 2.55 mmol) and sodium hydride (60% dispersion in mineral oil) (112 mg, 2.81 mmol) were added to a 50 mL round-bottom flask fitted with a magnetic follower. The round-bottom flask was sealed with a rubber septum. *N*,*N*-Dimethylformamide (10.0 mL, 0.255 M) was added *via* syringe. The reaction mixture was left room temperature and stirred at this temperature for 15 mins. The reaction mixture was cooled to 0 °C and methyl iodide (0.190 mL, 3.06 mmol) was added drop-wise *via* syringe. The reaction mixture was warmed to room temperature and stirred at this temperature for 1 h. On completion, the reaction mixture was quenched with water and extracted with diethyl ether (×3). The combined organic phases were

washed with brine (sat.), dried over magnesium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 20% ethyl acetate in petrol] to afford *indole* ***189*** as a white solid (490 mg, 92%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.80 (d, *J* = 2.0 Hz, 1 H, Ar$\underline{H}^4$), 7.34 (dd, *J* = 8.5, 2.0 Hz, 1 H, Ar$\underline{H}^6$), 7.20 (d, *J* = 8.5 Hz, 1 H, Ar$\underline{H}^7$), 7.07 (d, *J* = 3.0 Hz, 1 H, Ar$\underline{H}^2$), 6.46 (d, *J* = 3.0 Hz, 1 H, Ar$\underline{H}^3$), and 3.77 ppm (s, 3 H, NC$\underline{H}_3$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 135.4, 130.2, 130.1, 124.3, 123.3, 112.7, 110.8, 100.6, and 33.0 ppm; **MP** 39−41 °C (dichloromethane/petrol)

Spectroscopic data are consistent with those reported in the literature for indole ***189***[126]

1-Methyl-5-(2-methyl-6-phenylpyridin-4-yl)-1H-indole (193)



Using General Procedure E and Conditions A

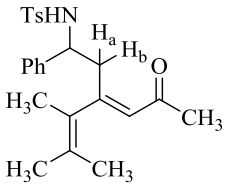
Enone ***160*** (100 mg, 0.291 mmol) and *N*-methyl-5-bromoindole (153 mg, 0.728 mmol) were employed. In a modification to the general procedure, tris(dibenzylideneacetone)dipalladium (26.6 mg, 29.1 μmol) and tri-*tert*-butylphosphonium tetrafluoroborate (33.8 mg, 0.116 mmol) were employed. The reaction mixture was heated to 80 °C and stirred at this temperature for the following times: The Heck reaction was carried out for 2 h, the reaction was carried out for 3 h, and the elimination reaction was carried out for 18 h. The crude material was purified by flash-column chromatography [silicon dioxide, 100% dichloromethane] and followed by subsequent flash-column chromatography [silicon dioxide, 20% ethyl acetate in petrol] to afford *pyridine* ***193*** as a yellow oil (56.1 mg, 65%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 8.07 (d, *J* = 8.5 Hz, 2 H, Ar$_{(Ph)}\underline{H}_{(o\text{-py})}$), 7.99 (d, *J* = 1.5 Hz, 1 H, Ar$\underline{H}^{4'}$), 7.82 (s, 1 H, Ar$\underline{H}^5$), 7.59 (dd, *J* = 8.5, 2.0 Hz, 1 H, Ar$\underline{H}^{6'}$), 7.55−7.47 (m, 2 H, Ar$_{(Ph)}\underline{H}_{(m\text{-py})}$), 7.45 (s, 1 H, Ar$\underline{H}^3$), 7.43 (m, 2 H, Ar$\underline{H}^{7'}$ and Ar$_{(Ph)}\underline{H}_{(p\text{-py})}$), 7.13 (d, *J* = 3.0 Hz, 1 H, Ar$\underline{H}^{2'}$), 6.59 (d, *J* = 3.0 Hz, 1 H, Ar$\underline{H}^{3'}$), 3.86 (s, 3 H, NC$\underline{H}_3$), and 2.72 ppm (s, 3 H, ArC$\underline{H}_3$);

^{13}C NMR (*chloroform-d*, 75 MHz): δ = 158.6, 157.5, 150.8, 140.3, 137.1, 130.1, 129.9, 129.0, 128.7, 128.6, 127.2, 120.9, 120.0, 119.7, 116.4, 109.8, 101.7, 33.0, and 24.9 ppm; **HRMS** (ESI^+) Calculated for $C_{21}H_{18}N_2$. $[M+H]^+$ requires 299.1543; found 299.1539 (Δ = +1.3 ppm); **FTIR** ν_{max} (thin film): 2291, 1598, 1551, 1513, 1493, 1448, 1409, 1347, 1327, 1284, 1249, 1080, 1029, 867, 801, 776, 717, 695, and 644 cm^{-1}

*NMR assignments for pyridine **193** were aided by COSY and HSQC based NMR experiments*

(E)-4-Methyl-N-(3-(3-methylbut-2-en-2-yl)-5-oxo-1-phenylhex-3-en-1-yl)benzenesulfonamide (196)

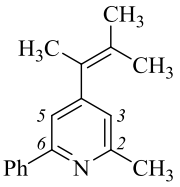


Using General Procedure C

*Enone **160*** (750 mg, 2.18 mmol) and 2-bromo-3-methyl-2-butene (0.634 mL, 5.46 mmol) were employed. The reaction mixture was heated to 110 °C and stirred at this temperature for 24 h. The crude material was purified by flash-column chromatography [silicon dioxide, 20% ethyl acetate in petrol] to afford *enone **196*** as a yellow oil (335 mg, 37%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.29 (d, *J* = 8.0 Hz, 2 H, Ar$\underline{H}_{(m\text{-}CH_3)}$), 7.09−7.00 (m, 5 H, Ar$\underline{H}$), 6.98−6.90 (m, 3 H, Ar$\underline{H}$ and N$\underline{H}$), 6.21 (s, 1 H, C=C$\underline{H}$COCH$_3$), 4.58−4.50 (m, 1 H, C$\underline{H}$NH), 3.30 (t, *J* = 12.5 Hz, 1 H, C$\underline{H}_a$H$_b$CHNH), 2.38 (dd, *J* = 12.5, 4.0 Hz, 1 H, CH$_a$$\underline{H}_b$CHNH), 2.32−2.24 (m, 6 H, ArC$\underline{H}_3$ and COC$\underline{H}_3$), and 1.83−1.74 ppm (m, 9 H, C$\underline{H}_3$C=C(C$\underline{H}_3$)$_2$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 201.7, 158.0, 141.9, 141.2, 138.9, 131.1, 129.1, 128.7, 128.4, 128.1, 127.0, 126.6 (2), 57.2, 39.4, 31.5, 22.5, 21.3, 20.7, and 17.9 ppm; **HRMS** (ESI^+) Calculated for $C_{24}H_{29}NO_3S$. $[M+H]^+$ requires 412.1941; found 412.1927 (Δ = +3.4 ppm); **FTIR** ν_{max} (thin film): 3271, 2923, 1670, 1597, 1455, 1329, 1157, 1092, 1069, 954, 813, 761, 732, 700, and 666 cm^{-1}

2-Methyl-4-(3-methylbut-2-en-2-yl)-6-phenylpyridine (198)

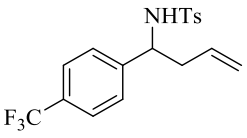


The synthesis of pyridine ***198*** *was adapted from General Procedure E and Conditions A*

Enone ***196*** (90.3 mg, 0.220 mmol) was added to a 10 mL round-bottom flask fitted with a magnetic follower. The round-bottom flask was sealed with a rubber septum. Toluene (2.20 mL, 0.100 M) and trifluoroacetic acid (16.2 μL, 0.220 mmol) were sequentially added *via* syringe. The reaction mixture was heated to 80 °C and stirred at this temperature for 3 h. 1,8-Diazabicycloundec-7-ene (0.163 mL, 1.10 mmol) was added *via* syringe and stirred at this temperature for 19 h. On completion, the reaction mixture was cooled to room temperature. The crude material was purified by flash-column chromatography [silicon dioxide, 5% diethyl ether in petrol] to afford *pyridine* ***198*** as a colourless oil (17.1 mg, 33%).

^{1}H NMR (*chloroform-d*, 500 MHz): δ = 7.99−7.95 (m, 2 H, Ar$\underline{H}_{(o\text{-py})}$), 7.46 (t, *J* = 7.5 Hz, 2 H, Ar$\underline{H}_{(m\text{-py})}$), 7.39 (t, *J* = 7.5 Hz, 1 H, Ar$\underline{H}_{(p\text{-py})}$), 7.29 (s, 1 H, Ar$\underline{H}^5$), 6.88 (s, 1 H, Ar$\underline{H}^3$), 2.62 (s, 3 H, ArC$\underline{H}_3$), 1.98 (s, 3 H, C$\underline{H}_3$), 1.84 (s, 3 H, C$\underline{H}_3$), and 1.66 ppm (d, *J* = 1.5 Hz, 3 H, C$\underline{H}_3$); **^{13}C NMR** (*chloroform-d*, 126 MHz): δ = 158.0, 156.8, 154.2, 140.1, 129.1, 128.6, 128.5, 128.2, 127.0, 121.6, 117.9, 24.7, 22.1, 20.6, and 20.1 ppm; **HRMS** (ESI$^+$) Calculated for $C_{17}H_{19}N$ $[M+H]^+$ requires 238.1590; found 238.1592 (Δ = −0.84 ppm); **FTIR** ν_{max} (thin film): 2921, 1599, 1547, 1497, 1449, 1401, 1374, 1225, 1164, 1030, 873, 776, 742, 695, 660, and 645 cm^{-1}

4-Methyl-N-(1-(4-(trifluoromethyl)phenyl)but-3-en-1-yl)benzenesulfonamide (205)



Step 1

The synthesis of imine ***204*** *was adapted from a reported literature procedure that was used for the preparation of imine* ***157***[120]

4-(Trifluoromethyl)benzaldehyde (***203***) (880 mg, 5.05 mmol), tetraethyl orthosilicate (1.24 mL, 5.56 mmol), and *p*-toluenesulfonamide (952 mg, 5.56 mmol) were added to a 10 mL round-bottom flask fitted with a magnetic follower. A short path distillation head was fitted. The reaction mixture was heated to 170 °C and stirred at this temperature for 4 h. Ethanol was distilled off during the course of the reaction. On completion, the reaction mixture was cooled to room temperature. The crude material was filtered and washed with 50% diethyl ether in petrol to afford *imine* ***204*** as a white crystalline solid. *Imine* ***204*** was used in the next step of the transformation without further purification.

Step 2

The synthesis of sulfonamide ***205*** *was adapted from a procedure developed by a co-worker that was used for the preparation sulfonamide* ***158***

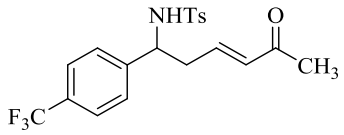
Imine ***204*** was added to a 250 mL round-bottom flask fitted with a magnetic follower. The round-bottom flask was sealed with a rubber septum. Tetrahydrofuran (100 mL 0.051 M) was added directly from the activated alumina purification column and the reaction mixture was cooled to −78 °C. Allylmagnesium bromide (1.00 M in diethyl ether) (10.1 mL, 10.1 mmol) was added drop-wise *via* syringe. The reaction mixture was warmed to room temperature and stirred at this temperature for 18 h. On completion, the reaction mixture was quenched with ammonium chloride (aq., sat.) and extracted with ethyl acetate (×3). The combined organic phases were washed with brine (sat.), dried over sodium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 15% to 20% ethyl acetate in petrol] to afford *sulfonamide* ***205*** as a white solid (1.06 g, 56% over two steps).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.51 (d, *J* = 8.5 Hz, 2 H, Ar$\underline{H}_{(m\text{-}CH_3)}$), 7.37 (d, *J* = 8.0 Hz, 2 H, Ar$\underline{H}_{(o\text{-}CF_3)}$), 7.18 (d, *J* = 8.0 Hz, 2 H, Ar$\underline{H}_{(m\text{-}CF_3)}$), 7.09 (d, *J* = 8.0 Hz, 2 H, Ar$\underline{H}_{(o\text{-}CH_3)}$), 5.57−5.46 (m, 2 H, C$\underline{H}$=CH$_2$ and N$\underline{H}$), 5.09−5.03 (m, 2 H, CH=C$\underline{H}_2$), 4.45 (q, *J* = 7.0 Hz, 1 H, C$\underline{H}$NH), 2.50−2.40 (m, 2 H, C$\underline{H}_2$CH), and 2.35 ppm (s, 3 H, ArC$\underline{H}_3$); **^{13}C NMR** (*chloroform-d*, 126 MHz): δ = 144.3, 143.4, 137.1, 132.3, 129.5 (q, $^{2}J_{C-F}$ = 32 Hz), 129.3, 127.1, 125.2 (q, $^{3}J_{C-F}$ = 4 Hz), 124.0 (q, $^{1}J_{C-F}$ = 272 Hz), 122.9, 119.9, 56.7, 41.6, and 21.3 ppm; **^{19}F NMR** (*chloroform-d*, 376 MHz): δ = −62.6 ppm (s, 1 F); **HRMS** (ESI^{+}) Calculated for $C_{18}H_{18}F_3NO_2S$.

$[M+Na]^+$ requires 392.0903; found 392.0896 (Δ = +1.8 ppm); **FTIR** ν_{max} (thin film): 3276, 2927, 1620, 1599, 1430, 1327, 1161, 1125, 1068, 1018, 923, 840, 814, and 669 cm^{-1}; **MP** 67−69 °C (dichloromethane/petrol)

*NMR assignments for sulfonamide **205** were aided by DEPT, COSY, and HSQC based NMR experiments*

(E)-4-Methyl-N-(5-oxo-1-(4-(trifluoromethyl)phenyl)hex-3-en-1-yl)benzenesulfonamide (206)



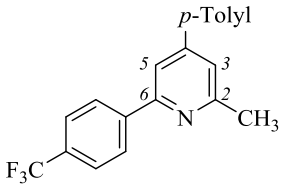
Using General Procedure A

*Sulfonamide **205*** (500 mg 1.35 mmol) and methyl vinyl ketone (***159***) (0.552 mL, 6.77 mmol) were employed. The reaction mixture was heated to 55 °C and stirred at this temperature for 72 h. The crude material was purified by flash-column chromatography [silicon dioxide, 30% to 50% ethyl acetate in petrol] to afford *enone **206*** as a white solid (490 mg, 88%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.50 (d, *J* = 8.0 Hz, 2 H, Ar$\underline{H}_{(m\text{-}CH_3)}$), 7.39 (d, *J* = 8.0 Hz, 2 H, Ar$\underline{H}_{(o\text{-}CF_3)}$), 7.17 (d, *J* = 8.0 Hz, 2 H, Ar$\underline{H}_{(m\text{-}CF_3)}$), 7.09 (d, *J* = 8.0 Hz, 2 H, Ar$\underline{H}_{(o\text{-}CH_3)}$), 6.53 (dt, *J* = 16.0, 8.0 Hz, 1 H, $CH_2C\underline{H}$=CH), 6.05 (d, *J* = 16.0 Hz, 1 H, CH=C$\underline{H}COCH_3$), 5.85 (d, *J* = 8.0 Hz, 1 H, N$\underline{H}$), 4.55 (q, *J* = 7.5 Hz, 1 H, C$\underline{H}$NH), 2.73−2.57 (m, 2 H, C$\underline{H}_2$CH=CH), 2.36 (s, 3 H, ArC$\underline{H}_3$), and 2.15 ppm (s, 3 H, COC$\underline{H}_3$); **^{13}C NMR** (*chloroform-d*, 126 MHz): δ = 198.1, 143.7, 143.6, 141.2, 137.0, 134.4, 129.9 (q, $^2J_{C-F}$ = 33 Hz), 129.5, 127.0, 126.9, 125.5 (q, $^3J_{C-F}$ = 4 Hz), 123.8 (q, $^1J_{C-F}$ = 273 Hz) 56.8, 39.9, 27.0, and 21.3 ppm; **^{19}F NMR** (*chloroform-d*, 376 MHz): δ = −62.8 ppm (s, 3 F); **HRMS** (ESI^+) Calculated for $C_{20}H_{20}F_3NO_3S$. $[M+Na]^+$ requires 434.1008; found 434.1008 (Δ = 0.0 ppm); **FTIR** ν_{max} (thin film): 3272, 1675, 1424, 1326, 1160, 1120, 1068, 1018, 815, and 670 cm^{-1}; **MP** 132−134 °C (dichloromethane/petrol)

*NMR assignments for enone **206** were aided by COSY and HSQC based NMR experiments*

2-Methyl-4-(p-tolyl)-6-(4-(trifluoromethyl)phenyl)pyridine (209)

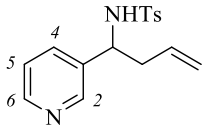


Using General Procedure E and Conditions A

Enone ***206*** (100 mg, 0.243 mmol) and 4-bromotoluene (104 mg, 0.608 mmol) were employed. In a modification to the general procedure, tris(dibenzylideneacetone)dipalladium (22.3 mg, 24.4 μmol) and tri-*tert*-butylphosphonium tetrafluoroborate (28.2 mg, 97.2 μmol) were employed. The reaction mixture was heated to 80 °C and stirred at this temperature for the following times: The Heck reaction was carried out for 3 h, the condensation reaction was carried out for 3 h, and the elimination reaction was carried out for 15 h. The crude material was purified by flash-column chromatography [silicon dioxide, 4% ethyl acetate in petrol] and followed by subsequent flash-column chromatography [silicon dioxide, 2% ethyl acetate in petrol] to afford *pyridine* ***209*** as a white solid (57.0 mg, 72%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 8.16 (d, *J* = 8.0 Hz, 2 H, Ar$\underline{H}_{(m\text{-}CF_3)}$), 7.77−7.72 (m, 3 H, Ar$\underline{H}^{5}$ and Ar$\underline{H}_{(o\text{-}CF_3)}$), 7.60 (d, *J* = 8.0 Hz, 2 H, Ar$\underline{H}_{(m\text{-}CH_3)}$), 7.37 (d, *J* = 1.5 Hz, 1 H, Ar$\underline{H}^{3}$), 7.33 (d, *J* = 8.0 Hz, 2 H, Ar$\underline{H}_{(o\text{-}CH_3)}$), 2.71 (s, 3 H, Ar$_{(py)}C\underline{H}_3$), and 2.45 ppm (s, 3 H, Ar$_{(p\text{-}Tolyl)}$C$\underline{H}_3$); **^{13}C NMR** (*chloroform-d*, 75 MHz): δ = 159.2, 156.0, 149.7, 143.3, 139.2, 135.6, 130.5 (q, $^{2}J_{C-F}$ = 32 Hz), 129.8, 127.4, 126.9, 125.5 (q, $^{3}J_{C-F}$ = 4 Hz), 124.2 (q, $^{1}J_{C-F}$ = 272 Hz), 120.4, 116.2, 24.8, and 21.2 ppm; **^{19}F NMR** (*chloroform-d*, 376 MHz): δ = −62.5 ppm (s, 3 F); **HRMS** (ESI^{+}) Calculated for $C_{20}H_{16}F_3N$. $[M+H]^{+}$ requires 328.1308; found 328.1299 (Δ = +2.7 ppm); **FTIR** ν_{max} (thin film): 1602, 1548, 1390, 1324, 1165, 1124, 1064, 1017, 848, and 814 cm^{-1}; **MP** 75−77 °C (dichloromethane/petrol)

4-Methyl-N-(1-(pyridin-3-yl)but-3-en-1-yl)benzenesulfonamide (212)



Step 1

The synthesis of imine ***211*** *was adapted from a reported literature procedure that was used for the preparation of imine* ***157***[120]

Pyridine-3-carboxaldehyde (***210***) (1.00 mL, 10.6 mmol), tetraethyl orthosilicate (2.61 mL, 11.7 mmol), and *p*-toluenesulfonamide (2.00 g, 11.7 mmol) were added to a 25 mL round-bottom flask fitted with a magnetic follower. A short path distillation head was fitted. The reaction mixture was heated to 170 °C and stirred at this temperature for 3 h. Ethanol was distilled off during the course of the reaction. On completion, the reaction mixture was cooled to room temperature. The crude material was filtered and washed with 50% diethyl ether in petrol to afford *imine* ***211*** as a white crystalline solid. *Imine* ***211*** was used in the next step of the transformation without further purification.

Step 2

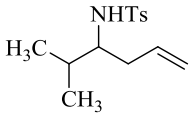
The synthesis of sulfonamide ***212*** *was adapted from a procedure developed by a co-worker that was used for the preparation sulfonamide* ***158***

Imine ***211*** was added to a 250 mL round-bottom flask fitted with a magnetic follower. The round-bottom flask was sealed with a rubber septum. Tetrahydrofuran (100 mL 0.051 M) was added directly from the activated alumina purification column and the reaction mixture was cooled to −78 °C. Allyl magnesium chloride (2.00 M in tetrahydrofuran) (7.95 mL, 15.9 mmol) was added drop-wise *via* syringe. The reaction mixture was warmed to 40 °C and stirred at this temperature for 15 h. On completion, the reaction mixture was quenched with ammonium chloride (aq., sat.) and extracted with diethyl ether (×3). The combined organic phases were washed with brine (sat.), dried over sodium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 100% diethyl ether] to afford *sulfonamide* ***212*** as a white solid (404 mg, 13% over two steps).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 8.40 (dd, *J* = 5.0, 2.0 Hz, 1 H, Ar*H*^{6}), 8.35 (d, *J* = 2.5 Hz, 1 H, Ar*H*^{2}), 7.56 (d, *J* = 8.5 Hz, 2 H, Ar*H*$_{(m\text{-}CH_3)}$), 7.46 (dt, *J* = 8.0, 2.0 Hz, 1 H, Ar*H*^{4}), 7.15 (d, *J* = 8.0 Hz, 2 H, Ar*H*$_{(o\text{-}CH_3)}$), 7.10 (dd, *J* = 8.0, 5.0 Hz, 1 H, Ar*H*^{5}), 5.68 (d, *J* = 6.5 Hz, 1 H, N*H*), 5.49 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1 H, C*H*=CH$_2$), 5.09−5.01 (m, 2 H, CH=C*H*$_2$), 4.40 (q, *J* = 6.5 Hz, 1 H, C*H*NH), 2.53−2.40 (m, 2 H, C*H*$_2$CH), and 2.36 ppm (s, 3 H, ArC*H*$_3$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 148.6, 148.4, 143.4, 137.1, 136.1, 134.2, 132.3, 129.5, 127.1, 123.2, 119.9, 55.0, 41.6, 21.5 ppm; **HRMS** (ESI$^+$) Calculated for $C_{16}H_{19}N2O_2S$. $[M+H]^+$ requires 303.1162; found 303.1166 (Δ = −1.3 ppm); **FTIR** ν_{max} (thin film): 3273, 3076, 1642, 1597, 1580, 1480, 1430, 1330, 1184, 1159, 1094, 1070, 1028, 993, 921, 814, 715, 666, and 616 cm^{-1}; **MP** 71−73 °C (dichloromethane/petrol)

*NMR assignments for sulfonamide **212** were aided by DEPT, COSY, and HSQC based NMR experiments*

4-Methyl-N-(2-methylhex-5-en-3-yl)benzenesulfonamide (215)



Step 1

*The synthesis of imine **214** followed a reported literature procedure*[127]

p-Toluenesulfonamide (2.62 g, 15.3 mmol) and sodium benzenesulfinate (2.51 g, 15.3 mmol) were added to a 150 mL round-bottom flask fitted with a magnetic follower. The round-bottom flask was sealed with a rubber septum. Water (14.0 mL, 0.993 M), formic acid (14.0 mL, 0.993 M), and isobutyraldehyde (***213***) (1.27 mL, 13.9 mmol) were sequentially added *via* syringe. The reaction mixture was left at room temperature and stirred at this temperature for 18 h. The resultant solid was filtered and sequentially washed with water and petrol. The solid was added to a 250 mL round-bottom flask fitted with a magnetic follower. Dichloromethane and sodium bicarbonate (aq., sat.) were added. The reaction mixture was left at room temperature and stirred at this temperature for 2 h. On completion, the organic phase was separated and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried over magnesium sulphate and

concentrated *in vacuo* to afford *imine* ***214*** as a white crystalline solid. *Imine* ***214*** was used in the next step of the transformation without further purification.

Step 2

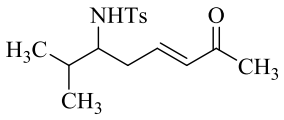
The synthesis of sulfonamide ***215*** *was adapted from a procedure developed by a co-worker that was used for the preparation sulfonamide* ***158***

Imine ***214*** was added to a 250 mL round-bottom flask fitted with a magnetic follower. The round-bottom flask was sealed with a rubber septum. Tetrahydrofuran (150 mL, 0.093 M) was added directly from the activated alumina purification column and the reaction mixture was cooled to −78 °C. Allyl magnesium chloride (2.00 M in tetrahydrofuran) (5.00 mL, 10.0 mmol) was added drop-wise *via* syringe. The reaction mixture was warmed to room temperature and stirred at this temperature for 24 h. On completion, the reaction mixture was quenched with ammonium chloride (aq., sat.) and extracted with ethyl acetate (×3). The combined organic phases were washed with brine (sat.), dried over sodium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 5% to 10% ethyl acetate in petrol] to afford *sulfonamide* ***215*** as a white solid (1.13 g, 56% over two steps).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.75 (d, *J* = 8.5 Hz, 2 H, Ar$\underline{H}_{(m\text{-}CH_3)}$), 7.29 (d, *J* = 8.5 Hz, 2 H, Ar$\underline{H}_{(o\text{-}CH_3)}$), 5.48 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1 H, C$\underline{H}$=CH$_2$), 5.00−4.88 (m, 2 H, CH=C$\underline{H}_2$), 4.57 (d, *J* = 8.5 Hz, 1 H, N$\underline{H}$), 3.09 (dq, *J* = 8.5, 6.0 Hz, 1 H, C$\underline{H}$NH), 2.42 (s, 3 H, ArC$\underline{H}_3$), 2.10−2.01 (m, 2 H, C$\underline{H}_2$CH), 1.80−1.72 (m, 1 H, C$\underline{H}$(CH$_3$)$_2$), and 0.83 ppm (d, *J* = 7.0 Hz, 6 H, CH(C$\underline{H}_3$)$_2$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 143.1, 138.2, 133.8, 129.5, 127.1, 118.4, 58.7, 36.1, 30.8, 21.5, 18.6, and 17.8 ppm; **HRMS** (ESI$^+$) Calculated for $C_{14}H_{21}NO_2S$. $[M+Na]^+$ requires 290.1185; found 290.1180 (Δ = +1.7 ppm); **FTIR** ν_{max} (thin film): 3283, 2963, 2875, 1642, 1599, 1496, 1429, 1389, 1370, 1324, 1289, 1159, 1094, 1029, 995, 945, 916, 842, 814, and 707 cm^{-1}; **MP** 51−53 °C (dichloromethane/petrol)

NMR assignments for sulfonamide ***215*** *were aided by DEPT, COSY, and HSQC based NMR experiments*

(E)-4-Methyl-N-(2-methyl-7-oxooct-5-en-3-yl)benzenesulfonamide (216)



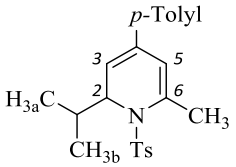
Using General Procedure A

Sulfonamide ***215*** (200 mg, 0.749 mmol) and methyl vinyl ketone (***159***) (0.306 mL, 3.74 mmol) were employed. The reaction mixture was heated to 55 °C and stirred at this temperature for 71 h. The crude material was purified by flash-column chromatography [silicon dioxide, 20% ethyl acetate in petrol] to afford *enone* ***216*** as an off-white solid (197 mg, 85%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.75 (d, *J* = 8.5 Hz, 2 H, Ar$\underline{H}_{(m\text{-}CH_3)}$), 7.29 (d, *J* = 8.0 Hz, 2 H, Ar$\underline{H}_{(o\text{-}CH_3)}$), 6.56 (dt, *J* = 16.0, 7.0 Hz, 1 H, $CH_2C\underline{H}$=CH), 5.97 (d, *J* = 16.0 Hz, 1 H, CH=C$\underline{H}$COCH$_3$), 4.82 (d, *J* = 9.0 Hz, 1 H, N$\underline{H}$), 3.28−3.16 (m, 1 H, C$\underline{H}$NH), 2.42 (s, 3 H, ArC$\underline{H}_3$), 2.40−2.21 (m, 2 H, C$\underline{H}_2$CH=CH), 2.14 (s, 3 H, COC$\underline{H}_3$), 1.73 (m, 1 H, CH(CH$_3$)$_2$), and 0.81 ppm (d, *J* = 7.0 Hz, 6 H, CH(C$\underline{H}_3$)$_2$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 198.2, 143.5, 138.0, 133.7, 129.7, 127.0, 58.4, 35.4, 31.5, 26.7, 21.5, 18.5, and 17.7 ppm; **HRMS** (ESI$^+$) Calculated for $C_{16}H_{23}NO_3S$. $[M+H]^+$ requires 310.1471; found 310.1472 (Δ = −0.32 ppm); **FTIR** ν_{max} (thin film): 3282, 3005, 2964, 2876, 1673, 1627, 1599, 1495, 1427, 1391, 1362, 1325, 1305, 1276, 1260, 1159, 1094, 1038, 981, 862, 816, 764, 750, and 707 cm^{-1}; **MP** 85−87 °C (dichloromethane/petrol)

NMR assignments for enone ***216*** *were aided by DEPT, COSY, and HSQC based NMR experiments*

2-Isopropyl-6-methyl-4-(p-tolyl)-1-tosyl-1,2-dihydropyridine (218)



Using General Procedure E and Conditions B: Step 1

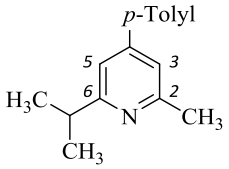
Enone ***216*** (100 mg, 0.322 mmol) and 4-bromotoluene (139 mg, 0.805 mmol) were employed. The reaction mixture was heated to 80 °C and stirred at this temperature for the following times:

The Heck reaction was carried out for 4 h and the condensation reaction was carried out for 2.5 h. The crude material was purified by flash-column chromatography [silicon dioxide, 50% dichloromethane in petrol] to afford *dihydropyridine **218*** as a yellow oil (82.3 mg, 71%).

^{1}H NMR (*chloroform-d*, 300 MHz): δ = 7.52 (d, *J* = 8.0 Hz, 2 H, $Ar_{(Ts)}\underline{H}_{(m\text{-}CH_3)}$), 7.06−6.94 (m, 4 H, $Ar_{(Ts)}\underline{H}_{(o\text{-}CH_3)}$ and $Ar_{(p\text{-}Tolyl)}\underline{H}_{(m\text{-}CH_3)}$), 6.79 (d, *J* = 8.0 Hz, 2 H, $Ar_{(p\text{-}Tolyl)}\underline{H}_{(o\text{-}CH_3)}$), 5.79 (s, 1 H, $C\underline{H}^5$), 5.47 (d, *J* = 6.0 Hz, 1 H, $C\underline{H}^3$), 4.29 (dd, *J* = 9.0, 6.0 Hz, 1 H, $C\underline{H}^2$), 2.24 (s, 3 H, $C\underline{H}_3$), 2.21−2.14 (m, 6 H, $C\underline{H}_3$ ×2), 1.80−1.71 (m, 1 H, $CH_{3a}CH_{3b}C\underline{H}$), 0.96 (d, *J* = 6.5 Hz, $C\underline{H}_{3a}$), and 0.90 ppm (d, *J* = 6.5 Hz, $C\underline{H}_{3b}$); **^{13}C NMR** (*chloroform-d*, 75 MHz): δ = 143.2, 137.2, 136.5, 135.6, 134.6, 133.9, 129.0, 128.9, 127.1, 125.6, 118.3, 117.6, 61.9, 30.9, 23.2, 21.4, 21.1, 19.0, and 18.8 ppm; **HRMS** (ESI^+) Calculated for $C_{23}H_{27}NO_2S$. $[M+H]^+$ requires 382.1835; found 382.1828 (Δ = +1.8 ppm); **FTIR** ν_{max} (thin film): 2960, 1597, 1514, 1449, 1342, 1166, 1087, 971, 871, 800, 736, 705, 674, and 629 cm^{-1}

*NMR assignments for dihydropyridine **218** were aided by COSY and HSQC experiments*

2-Isopropyl-6-methyl-4-(p-tolyl)pyridine (219)



*For consistency between 2,4,6-trisubstituted pyridines, atom numbering in pyridine **219** is inconsistent with International Union of Pure and Applied Chemistry naming conventions.*

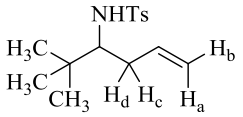
Using General Procedure E and Conditions B: Step 2

*Dihydropyridine **218*** (34.0 mg, 89.1 μmol) was employed. The elimination reaction was carried out for 3 h. The crude material was purified by flash-column chromatography [silicon dioxide, 5% ethyl acetate in petrol] to afford pyridine ***219*** as a yellow oil (14.4 mg, 72%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.53 (d, *J* = 8.0 Hz, 2 H, $Ar\underline{H}_{(m\text{-}CH_3)}$), 7.33−7.25 (m, 2 H, $Ar\underline{H}_{(o\text{-}CH_3)}$), 7.18 (s, 2 H, $Ar\underline{H}^3$ and $Ar\underline{H}^5$), 3.10 (spt, *J* = 7.0 Hz, 1 H, $(CH_3)_2C\underline{H}$), 2.60 (s, 3 H, $Ar_{(py)}C\underline{H}_3$), 2.42 (s, 3 H, $Ar_{(p\text{-}Tolyl)}C\underline{H}_3$), and 1.35 ppm (d, *J* = 7.0 Hz, 6 H, $(C\underline{H}_3)_2CH$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 167.4, 157.8, 149.0, 138.7, 136.2, 129.6, 126.9, 118.6, 115.0, 36.6,

24.7, 22.8, and 21.2 ppm; **HRMS** (ESI^+) Calculated for $C_{16}H_{19}N$. $[M+H]^+$ requires 226.1590; found 226.1588 (Δ = +0.88 ppm); **FTIR** ν_{max} (thin film): 2961, 1602, 1552, 1516, 1457, 1094, 872, and 814 cm^{-1}

N-(2,2-Dimethylhex-5-en-3-yl)-4-methylbenzenesulfonamide (222)



Step 1

*The synthesis of imine **221** followed a reported literature procedure*[128]

Pivaldehyde (***220***) (0.619 mL, 5.57 mmol) and *p*-toluenesulfonamide (1.05 g, 6.13 mmol) were added to a 150 mL round-bottom flask fitted with a magnetic follower. The round-bottom flask was sealed with a rubber septum. Dichloromethane (50.0 mL, 0.111 M) and triethylamine (3.10 mL, 22.3 mmol) were sequentially added *via* syringe. The reaction mixture was cooled to 0 °C and titanium tetrachloride (1.00 M in dichloromethane) (2.79 mL, 2.79 mmol) was added drop-wise *via* syringe. The reaction mixture was stirred at this temperature for 1 h. On completion, the reaction mixture was warmed to room temperature. The resultant solid was filtered and the filtrate concentrated *in vacuo*. Toluene was added to the residue and the resultant solid filtered once again. The filtrate was concentrated *in vacuo*. The crude material was recrystallized from acetone to afford *imine **221*** a white crystalline solid. *Imine **221*** was used in the next step of the transformation without further purification.

Step 2

*The synthesis of sulfonamide **222** was adapted from a procedure developed by a co-worker that was used for the preparation sulfonamide **158***

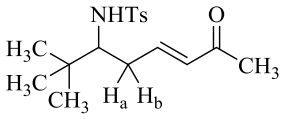
*Imine **221*** (500 mg, 2.21 mmol) was added to a 250 mL round-bottom flask fitted with a magnetic follower. The round-bottom flask was sealed with a rubber septum. Tetrahydrofuran (100 mL, 0.022 M) was added directly from the activated alumina purification column and the reaction mixture was cooled to −78 °C. Allylmagnesium bromide (2.00 M in diethyl ether) (2.09 mL, 4.18 mmol) was added drop-wise *via* syringe. The reaction mixture was warmed to room

temperature and stirred at this temperature for 6 h. On completion, the reaction mixture was quenched with ammonium chloride (aq., sat.) and extracted with ethyl acetate (×3). The combined organic phases were washed with brine (sat.), dried over sodium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 5% to 20% ethyl acetate in petrol] to afford *sulfonamide* ***222*** as a white solid (588 mg, 38% over two steps).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.75 (d, *J* = 8.0 Hz, 2 H, Ar$\underline{H}_{(m\text{-}CH_3)}$), 7.26 (d, *J* = 8.0 Hz, 2 H, Ar$\underline{H}_{(o\text{-}CH_3)}$), 5.52−5.36 (m, 1 H, C$\underline{H}$=CH$_aH_b$), 4.82 (d, *J* = 17.0 Hz, 1 H, CH=C$\underline{H}_a$H$_b$), 4.75 (d, *J* = 10.0 Hz, 1 H, CH=CH$_a\underline{H}_b$), 4.67 (d, *J* = 9.5 Hz, 1 H, N$\underline{H}$), 3.18−3.09 (m, 1 H, C$\underline{H}$NH), 2.41 (s, 3 H, ArC$\underline{H}_3$), 2.32−2.21 (m, 1 H, CHC$\underline{H}_c$H$_d$), 2.05−1.96 (m, 1 H, CHCH$_c\underline{H}_d$), and 0.86 ppm (s, 9 H, CC$\underline{H}_3$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 142.9, 139.0, 135.2, 129.4, 127.2, 117.4, 62.6, 36.0, 35.2, 26.9, and 21.5 ppm; **HRMS** (ESI$^+$) Calculated for $C_{15}H_{23}NO_2S$. $[M+Na]^+$ requires 304.1342; found 304.1332 (Δ = +3.3 ppm); **FTIR** ν_{max} (thin film): 3285, 2973, 1598, 1425, 1369, 1321, 1155, 1095, 1025, 989, 909, 814, 708, and 667 cm^{-1}; **MP** 59−61 °C (dichloromethane/petrol)

NMR assignments for sulfonamide ***222*** *were aided by COSY and HSQC based NMR experiments*

(E)-N-(2,2-Dimethyl-7-oxooct-5-en-3-yl)-4-methylbenzenesulfonamide (223)



Using General Procedure A

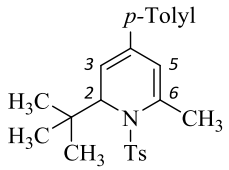
Sulfonamide ***222*** (400 mg, 1.42 mmol) and methyl vinyl ketone (***159***) (0.593 mL, 7.12 mmol) were employed. The reaction mixture was heated to 55 °C and stirred at this temperature for 48 h. The crude material was purified by flash-column chromatography [silicon dioxide, 30% ethyl acetate in petrol] to afford *enone* ***223*** as an off-white solid (393 mg, 86%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.73 (d, *J* = 8.5 Hz, 2 H, Ar$\underline{H}_{(m\text{-}CH_3)}$), 7.26 (d, *J* = 8.5 Hz, 2 H, Ar$\underline{H}_{(o\text{-}CH_3)}$), 6.69−6.58 (m, 1 H, CH$_aH_bC\underline{H}$=CH), 5.89 (d, *J* = 16.0 Hz, 1 H, CH=C$\underline{H}$COCH$_3$), 4.98 (d, *J* = 9.5 Hz, 1 H, N$\underline{H}$), 3.22 (td, *J* = 9.5, 4.0 Hz, 1 H, C$\underline{H}$NH), 2.60−2.49 (m, 1 H, C$\underline{H}_a$H$_b$CH=CH) 2.40 (s, 3 H, ArC$\underline{H}_3$), 2.25−2.14 (m, 1 H, CH$_a\underline{H}_b$CH=CH), 2.11 (s, 3 H, COC$\underline{H}_3$),

and 0.84 ppm (s, 9 H, C(C<u>*H*</u>$_3$)$_3$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 198.5, 145.4, 143.3, 138.7, 133.3, 129.6, 126.9, 62.4, 35.3, 35.1, 26.7, 26.4, and 21.5 ppm; **HRMS** (ESI$^+$) Calculated for $C_{17}H_{25}NO_3S$. $[M+Na]^+$ requires 346.1447; found 346.1436 (Δ = +3.2 ppm); **FTIR** ν_{max} (thin film): 3283, 2964, 1672, 1427, 1366, 1323, 1255, 1156, 1092, 1026, 979, 815, and 666 cm^{-1}; **MP** 90−92 °C (dichloromethane/petrol)

*NMR assignments for enone **223** were aided by COSY and HSQC based NMR experiments*

2-(t-Butyl)-6-methyl-4-(p-tolyl)-1-tosyl-1,2-dihydropyridine (225)



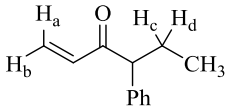
Using General Procedure E and Conditions B: Step 1

*Enone **223*** (200 mg, 0.624 mmol) and 4-bromotoluene (265 mg, 1.55 mmol) were employed. In a modification to the general procedure, tris(dibenzylideneacetone)dipalladium (56.7 mg, 61.9 μmol) and tri-*tert*-butylphosphonium tetrafluoroborate (71.8 mg, 0.248 mmol) were employed. The reaction mixture was heated to 80 °C and stirred at this temperature for the following times: The Heck reaction was carried out for 5 h and the condensation reaction was carried out for 17.5 h. The crude material was purified by flash-column chromatography [silicon dioxide, 100% dichloromethane] to afford *dihydropyridine **225*** as a yellow oil (142 mg, 58%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.61 (d, *J* = 8.0 Hz, 2 H, Ar$_{\mathbf{(Ts)}}$<u>*H*</u>$_{\mathbf{(}\boldsymbol{m}\mathbf{-CH_3)}}$), 7.11 (d, *J* = 8.5 Hz, 2 H, Ar$_{\mathbf{(Ts)}}$<u>*H*</u>$_{\mathbf{(}\boldsymbol{o}\mathbf{-CH_3)}}$), 7.08 (d, *J* = 8.5 Hz, 2 H, Ar$_{\mathbf{(}\boldsymbol{p}\mathbf{-Tolyl)}}$<u>*H*</u>$_{\mathbf{(}\boldsymbol{m}\mathbf{-CH_3)}}$), 6.91 (d, *J* = 8.0 Hz, 2 H, Ar$_{\mathbf{(}\boldsymbol{p}\mathbf{-Tolyl)}}$<u>*H*</u>$_{\mathbf{(}\boldsymbol{o}\mathbf{-CH_3)}}$), 5.84−5.73 (m, 1 H, C<u>*H*</u>^{5}), 5.50 (d, *J* = 6.0 Hz, 1 H, C<u>*H*</u>^{3}), 4.59 (d, *J* = 6.0 Hz, 1 H, C<u>*H*</u>^{2}), 2.34 (s, 3 H, C<u>*H*</u>$_3$), 2.29 (s, 3 H, C<u>*H*</u>$_3$), 2.26 (s, 3 H, C<u>*H*</u>$_3$), and 0.99 ppm (s, 9 H, C(C<u>*H*</u>$_3$)$_3$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 143.3, 137.2, 135.9, 135.8, 135.7, 135.1, 129.0, 128.9, 127.2, 125.6, 118.2, 116.5, 64.4, 37.9, 25.8, 23.4, 21.4, and 21.1 ppm; **HRMS** (ESI$^+$) Calculated for $C_{24}H_{29}NO_2S$. $[M+H]^+$ requires 396.1992; found 396.2001 (Δ = −2.3 ppm); **FTIR** ν_{max} (thin film): 2962, 1597, 1514, 1342, 1162, 1088, 967, 910, 865, 809, 732, 705, 672, and 626 cm^{-1}

*NMR assignments for dihydropyridine **225** were aided by COSY and HSQC based NMR experiments*

4-Phenylhex-1-en-3-one (230)



Step 1

*The synthesis of amide **229** was adapted from a reported literature procedure that was used for the preparation of related compounds*[129]

N,*O*-Dimethylhydroxylamine hydrochloride (1.44 g, 14.7 mmol) was added to a 50 mL round-bottom flask fitted with a magnetic follower. The round-bottom flask was sealed with a rubber septum. Dichloromethane (18.0 mL, 0.628 M), tetrahydrofuran (6.00 mL, 1.88 M), and pyridine (1.94 mL, 22.7 mmol) were sequentially *via* syringe. The reaction mixture was cooled to 0 °C and 2-phenylbutyryl chloride (***228***) (2.01 mL, 11.3 mmol) was added drop-wise *via* syringe. The reaction mixture was warmed to room temperature and stirred at this temperature for 15 h. On completion, the reaction mixture was quenched with water and extracted with dichloromethane (×3). The combined organic phases were washed with hydrochloric acid (aq., 1.00 M), sodium hydroxide (aq., 1.00 M), and brine (sat.). The organic phase was dried over sodium sulphate, filtered, and concentrated *in vacuo* to afford *amide **229*** as a colourless oil. *Amide **229*** was used in the next step of the transformation without further purification.

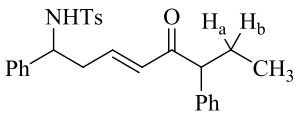
Step 2

*Amide **229*** was added to a 500 mL round-bottom flask fitted with a magnetic follower. The round-bottom flask was sealed with a rubber septum. Tetrahydrofuran (150 mL, 0.075 M) was added *via* syringe. The reaction mixture was cooled to 0 °C and vinyl magnesium bromide (1.00 M in diethyl ether) (14.7 mL, 14.7 mmol) was added drop-wise *via* syringe. The reaction mixture was warmed to room temperature and stirred at this temperature for 3 h. On completion, the reaction mixture was quenched with ammonium chloride (aq., sat.) and extracted with ethyl acetate (×3). The combined organic phases were washed with brine (sat.), dried over sodium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon

dioxide, 5% ethyl acetate in petrol] to afford *enone **230*** as a colourless oil (638 mg, 41% over two steps).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.37−7.19 (m, 5 H, Ar*H*), 6.36 (dd, *J* = 17.5, 10.0 Hz, 1 H, C*H*=CH_aH_b), 6.27 (dd, *J* = 17.5, 1.5 Hz, 1 H, CH=C*H*$_a$$H_b$), 5.66 (dd, *J* = 10.0, 2.0 Hz, 1 H, CH=CH_aH_b), 3.77 (t, *J* = 7.5 Hz, 1 H, C*H*CH_cH_d), 2.18−2.05 (m, 1 H, C*H*$_c$$H_dCH_3$), 1.80−1.69 (m, 1 H, $CH_cH_dCH_3$), and 0.87 ppm (t, *J* = 7.5 Hz, 3 H, $CH_cH_dCH_3$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 199.5, 138.7, 135.3, 128.9, 128.5, 128.2, 127.2, 58.4, 25.4, and 12.1 ppm; **HRMS** (FI) Calculated for $C_{12}H_{14}O$. $[M]^+$ requires 174.1045; found 174.1049 (Δ = −2.3 ppm); **FTIR** ν_{max} (thin film): 2965, 1697, 1675, 1613, 1492, 1454, 1399, 1138, 1059, 983, 749, and 700 cm^{-1}

(E)-4-Methyl-N-(5-oxo-1,6-diphenyloct-3-en-1-yl)benzenesulfonamide (231)



Using General Procedure A

*Sulfonamide **158*** (120 mg, 0.398 mmol) and *enone **230*** (347 mg, 1.99 mmol) were employed. The reaction mixture was heated to 55 °C and stirred at this temperature for 72 h. The crude material was purified by flash-column chromatography [silicon dioxide, 20% to 30% ethyl acetate in petrol] to afford *enone **231*** as a brown oil and an inseparable 1.0:1.0 mixture (by ^{1}H NMR analysis) of diastereoisomers (147 mg, 83%).

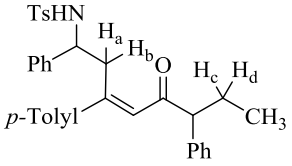
Data for both diastereoisomers are reported simultaneously

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.59−7.49 (m, 2 H, Ar*H*$_{(m\text{-}CH_3)}$), 7.34−7.19 (m, 3 H, Ar*H*), 7.18−7.04 (m, 7 H, Ar*H*), 7.00−6.90 (m, 2 H, Ar*H*), 6.65−6.55 (m, 1 H, CH_2C*H*=CH), 5.98 (dd, *J* = 15.5, 4.0 Hz, 1 H, CH=C*H*COCHPh), 5.86−5.71 (m, 1 H, N*H*), 4.54−4.25 (m, 1 H, C*H*NH), 3.63 (td, *J* = 7.0, 3.5 Hz, 1 H, COC*H*Ph), 2.68−2.43 (m, 2 H, C*H*$_2$CH=CH), 2.35 (s, 3 H, ArC*H*$_3$), 2.10−1.92 (m, 1 H, C*H*$_a$$H_bCH_3$), 1.78−1.61 (m, 1 H, $CH_aH_bCH_3$), and 0.84−0.73 ppm (m, 3 H, $CH_aH_bCH_3$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 199.1 (2), 143.2, 141.3 (2), 139.6, 139.5, 138.9 (2), 137.4, 132.2, 129.4, 128.8, 128.5, 128.4, 127.6 (2), 127.1, 127.0, 126.5, 58.2, 57.2, 57.0, 40.2, 40.1, 25.4, 25.3, 21.5, and 12.0 ppm; **HRMS** (ESI^+) Calculated for $C_{27}H_{29}NO_3S$. $[M+Na]^+$

requires 470.1760; found 470.1747 (Δ = +2.8 ppm); **FTIR** ν_{max} (thin film): 3271, 2926, 1672, 1627, 1598, 1495, 1363, 1326, 1258, 1157, 1093, 1019, 978, 816, and 663 cm^{-1}

Only 29 signals (signal overlap) observed in ^{13}C NMR (42 signals should be observed including both diastereoisomers)

(E)-4-Methyl-N-(5-oxo-1,6-diphenyl-3-(p-tolyl)oct-3-en-1-yl)benzenesulfonamide (232)



Using General Procedure C

*Enone **231*** (1.0:1.0 mixture of diastereoisomers) (71.1 mg, 0.159 mmol) and 4-bromotoluene (67.9 mg, 0.398 mmol) were employed. In a modification to the general procedure, *N*,*N*-dicyclohexylmethylamine (51.1 μL, 0.239 mmol) was employed. The reaction mixture was heated to 110 °C and stirred at this temperature for 18 h. The crude material was purified by flash-column chromatography [silicon dioxide, 15% ethyl acetate in petrol] to afford *enone **232*** as a yellow oil and an inseparable 1.0:1.0 mixture (by ^{1}H NMR analysis) of diastereoisomers (62.3 mg, 73%).

*Enone **232** was contaminated with 10−15% inseparable olefin regio/geometric isomers (by ^{1}H NMR analysis)*

Data for both diastereoisomers are reported simultaneously

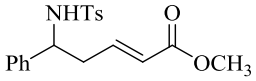
^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.37−6.87 (m, 18 H, Ar*H*), 6.86−6.75 (m, 1 H, N*H*), 6.40 (s, 0.5 H, C=C*H*COCHPh), 6.35 (s, 0.5 H, C=C*H*COCHPh), 4.32 (m, 0.5 H, C*H*NH), 4.21 (m, 0.5 H, C*H*NH), 3.69−3.61 (m, 1 H, COC*H*Ph), 3.59−3.47 (m, 1 H, C$H_a$$H_b$CHNH), 2.85−2.73 (m, 1 H, CH$_a$$H_b$CHNH), 2.38 (s, 1.5 H, ArCH_3), 2.37 (s, 1.5 H, ArCH_3), 2.34 (s, 1.5 H, ArCH_3), 2.30 (s, 1.5 H, ArCH_3), 2.23−2.10 (m, 1 H, C$H_c$$H_dCH_3$), 1.88−1.77 (m, 1 H, CH$_c$$H_dCH_3$), 0.93 (t, *J* = 7.5 Hz, 1.5 H, CH$_c$H$_d$CH_3), and 0.87 ppm (t, *J* = 7.5 Hz, 1.5 H, CH$_c$H$_d$CH_3); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 202.7, 202.4, 154.2, 153.0, 142.9, 142.4, 142.2, 142.1, 139.9, 138.7, 138.4, 138.0, 136.4, 136.3, 129.4 (2), 129.3, 129.0, 128.9 (2), 128.7, 128.4 (2), 127.6, 127.3, 126.9, 126.8, 126.6,

126.2, 61.6, 57.4, 39.2, 39.1, 25.2 (2), 21.3, and 12.1 ppm; **LRMS** (ESI^+) 560 $[M+Na]^+$; **FTIR** ν_{max} (thin film): 3268, 3075, 2868, 1642, 1597, 1580, 1480, 1430, 1330, 1184, 1158, 1093, 1070, 1028, 993, 921, 814, 715, and 667 cm^{-1}

Only 37 signals (signal overlap) observed in ^{13}C NMR (52 signals should be observed including both diastereoisomers)

HRMS failed for this compound

(E)-Methyl 5-(4-methylphenylsulfonamido)-5-phenylpent-2-enoate (253)



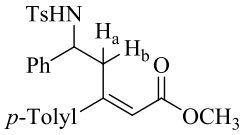
Using General Procedure B

*Sulfonamide **158*** (400 mg, 1.33 mmol) and methylacrylate (***47***) (0.612 mL, 6.65 mmol) were employed. The reaction mixture was heated to 55 °C and stirred at this temperature for 72 h. The crude material was purified by flash-column chromatography [silicon dioxide, 10% to 30% ethyl acetate in petrol] to afford *acrylate **253*** as an off-white solid (401 mg, 84%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.58 (d, *J* = 8.0 Hz, 2 H, Ar$\underline{H}_{(m\text{-}CH_3)}$), 7.24−7.12 (m, 5 H, Ar$\underline{H}$), 7.10−6.99 (m, 2 H, Ar$\underline{H}$), 6.66 (dt, *J* = 15.5, 7.5 Hz, 1 H, $CH_2C\underline{H}$=CH), 5.78 (d, *J* = 15.5 Hz, 1 H, CH=C$\underline{H}$$COOCH_3$), 4.98 (d, *J* = 7.0 Hz, 1 H, N$\underline{H}$), 4.44 (q, *J* = 7.0 Hz, 1 H, C$\underline{H}$NH), 3.69 (s, 3 H, OC$\underline{H_3}$), 2.78−2.57 (m, 2 H, CH_2CH=CH), and 2.38 ppm (s, 3 H, ArC$\underline{H_3}$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 166.3, 143.3, 143.2, 139.5, 137.3, 129.4, 128.6, 127.7, 127.0, 126.4, 124.3, 57.0, 51.5, 39.9, and 21.5 ppm; **HRMS** (ESI^+) Calculated for $C_{19}H_{21}NO_4S$. $[M+Na]^+$ requires 382.1083; found 382.1069 (Δ = +3.7 ppm); **FTIR** ν_{max} (thin film): 3276, 1723, 1659, 1599, 1496, 1437, 1326, 1201, 1160, 1092, 1060, 981, 951, 916, 814, 762, 731, 702, 668, and 562 cm^{-1}; **MP** 90−92 °C (dichloromethane/petrol)

*NMR assignments for acrylate **253** were aided by COSY and HSQC based NMR experiments*

(E)-Methyl 5-(4-methylphenylsulfonamido)-5-phenyl-3-(p-tolyl)pent-2-enoate (254)



Using General Procedure D

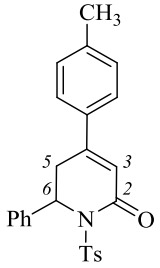
Acrylate ***253*** (359 mg, 1.00 mmol) and 4-bromotoluene (428 mg, 2.50 mmol) were employed. The reaction mixture was heated to 80 °C and stirred at this temperature for 2 h. The crude material was purified by flash-column chromatography [silicon dioxide, 30% ethyl acetate in petrol] to afford *acrylate* ***254*** as a yellow oil (354 mg, 79%).

Acrylate ***254*** *was contaminated with 10% inseparable olefin regio/geometric isomers (by* ^{1}*H NMR analysis)*

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.40 (d, *J* = 8.5 Hz, 2 H, $Ar_{(Ts)}\underline{H}_{(m\text{-}CH_3)}$), 7.21−7.14 (m, 9 H, Ar$\underline{H}$), 7.03 (d, *J* = 8.0 Hz, 2 H, $Ar_{(Ts)}\underline{H}_{(o\text{-}CH_3)}$), 6.49 (d, *J* = 6.5 Hz, 1 H, N$\underline{H}$), 6.08 (s, 1 H, C=C$\underline{H}$COOCH$_3$), 4.36 (ddd, *J* = 11.0, 7.0, 4.0 Hz, 1 H, C$\underline{H}$NH), 3.81 (s, 3 H, OC$\underline{H_3}$), 3.77 (dd, *J* = 13.5, 11.0 Hz, 1 H, C$\underline{H_a}$H$_b$CHNH), 2.94 (dd, *J* = 13.5, 4.0 Hz, 1 H, CH$_a$$\underline{H_b}$CHNH), 2.40 (s, 3 H, ArC$\underline{H_3}$), and 2.35 ppm (s, 3 H, ArC$\underline{H_3}$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 168.6, 155.6, 142.4, 142.0, 139.8, 138.2, 136.3, 129.5, 129.0, 128.4, 127.3, 126.8, 126.7, 126.2, 118.9, 57.3, 51.9, 38.9, 21.4, and 21.3 ppm; **HRMS** (ESI^{+}) Calculated for $C_{26}H_{27}NO_4S$. $[M+Na]^{+}$ requires 472.1553; found 472.1544 (Δ = +1.9 ppm); **FTIR** ν_{max} (thin film): 3274, 3030, 2951, 2255, 1693, 1625, 1606, 1567, 1511, 1495, 1455, 1434, and 1329 cm^{-1}

NMR assignments for acrylate ***254*** *were aided by DEPT, COSY, and HSQC based NMR experiments*

6-Phenyl-4-(p-tolyl)-1-tosyl-5,6-dihydropyridin-2(1H)-one (255)



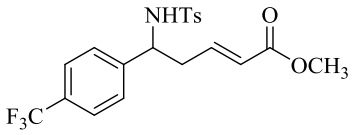
The synthesis of dihydropyridone ***255*** *followed a procedure developed by a co-worker*

Acrylate ***254*** (90% purity) (900 mg, 2.00 mmol) was added to a 50 mL round-bottom flask fitted with a magnetic follower. The round-bottom flask was sealed with a rubber septum and toluene (20.0 mL, 0.100 M) was added *via* syringe. The reaction mixture was cooled to −78 °C and trimethylaluminium (2.00 M in hexanes) (3.00 mL, 6.00 mmol) was added drop-wise *via* syringe. The reaction mixture was heated to 40 °C and stirred at this temperature for 3 h. On completion, the reaction mixture was cooled to room temperature. The reaction mixture was quenched with sodium bicarbonate (aq., sat.) and extracted with dichloromethane (×3). The combined organic phases were dried over sodium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 100% dichloromethane] to afford *dihydropyridone* ***255*** as an off-white solid (377 mg, 45%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.67 (d, *J* = 8.5 Hz, 2 H, $Ar_{(Ts)}\underline{H}_{(m\text{-}CH_3)}$), 7.29−7.16 (m, 11 H, Ar$\underline{H}$), 6.26 (d, *J* = 3.0 Hz, 1 H, C$\underline{H}^{3}$), 6.10 (dd, *J* = 7.0, 1.0 Hz, 1 H, C$\underline{H}^{6}$), 3.53 (ddd, *J* = 17.5, 7.0, 3.0 Hz, 1 H, C$\underline{H}^{5}$), 3.15 (dd, *J* = 17.5, 1.5 Hz, 1 H, C$\underline{H}^{5}$), 2.39 (s, 3 H, ArC$\underline{H}_3$), and 2.34 ppm (s, 3 H, ArC$\underline{H}_3$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 163.5, 151.0, 144.6, 141.0, 139.6, 135.8, 133.6, 129.6, 129.4, 128.9, 128.6, 127.9, 126.5, 126.0, 118.1, 57.4, 35.2, 21.6, and 21.3 ppm; **HRMS** (ESI^{+}) Calculated for $C_{25}H_{23}NO_3S$. $[M+Na]^{+}$ requires 440.1291; found 440.1279 (Δ = +2.7 ppm); **FTIR** ν_{max} (thin film): 1675, 1608, 1351, 1230, 1167, 1088, 1023, 875, 815, 701, 669, and 641 cm^{-1}; **MP** 178−180 °C (dichloromethane/petrol)

NMR assignments for dihydropyridone ***255*** *were aided by DEPT, COSY, and HSQC based NMR experiments*

(E)-Methyl 5-(4-methylphenylsulfonamido)-5-(4-(trifluoromethyl)phenyl)pent-2-enoate (260)



Using General Procedure B

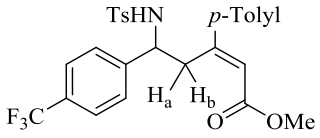
Sulfonamide ***205*** (1.13 g, 3.07 mmol) and methylacrylate (***47***) (1.42 mL, 15.4 mmol) were employed. The reaction mixture was heated to 55 °C and stirred at this temperature for 48 h. The crude material was purified by flash-column chromatography [silicon dioxide, 20% to 40% ethyl acetate in petrol] to afford *acrylate* ***260*** as an off-white solid (897 mg, 78%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.49 (d, *J* = 8.0 Hz, 2 H, Ar$\underline{H}_{(m\text{-}CH_3)}$), 7.37 (d, *J* = 8.5 Hz, 2 H, Ar$\underline{H}_{(o\text{-}CF_3)}$), 7.15 (d, *J* = 8.0 Hz, 2 H, Ar$\underline{H}_{(m\text{-}CF_3)}$), 7.08 (d, *J* = 8.5 Hz, 2 H, Ar$\underline{H}_{(m\text{-}CH_3)}$), 6.67 (dt, *J* = 15.5, 7.0 Hz, 1 H, $CH_2C\underline{H}$=CH), 5.85−5.78 (m, 2 H, CH=C$\underline{H}$COOCH$_3$ and N$\underline{H}$), 4.53 (q, *J* = 7.0 Hz, 1 H, C$\underline{H}$NH), 3.69 (s, 3 H, OC$\underline{H}_3$), 2.73−2.53 (m, 2 H, C$\underline{H}_2$CH=CH), and 2.34 ppm (s, 3 H, ArC$\underline{H}_3$); **^{13}C NMR** (*chloroform-d*, 126 MHz): δ = 166.1, 143.6, 143.4, 142.3, 136.9, 129.8 (q, $^{2}J_{C-F}$ = 33 Hz), 129.4, 127.0, 125.4 (q, $^{3}J_{C-F}$ = 4 Hz), 124.8, 123.8 (q, $^{1}J_{C-F}$ = 273 Hz), 56.6, 51.6, 39.6, and 21.3 ppm; **^{19}F NMR** (*chloroform-d*, 376 MHz): δ = −62.7 ppm (s, 3 F); **HRMS** (ESI^{+}) Calculated for $C_{20}H_{20}F_3NO_4S$. $[M+Na]^+$ requires 450.0957; found 450.0954 (Δ = +0.66 ppm); **FTIR** ν_{max} (thin film): 3275, 1709, 1435, 1324, 1156, 1118, 913, 844, 812, and 732 cm^{-1}; **MP** 110−112 °C (dichloromethane/petrol)

Only 15 signals (signal overlap) observed in ^{13}C NMR (16 signals should be observed)

NMR assignments for acrylate ***260*** *were aided by DEPT, COSY, and HSQC based NMR experiments*

(E)-Methyl 5-(4-methylphenylsulfonamido)-3-(p-tolyl)-5-(4-(trifluoromethyl)phenyl)pent-2enoate (261)



Using General Procedure D

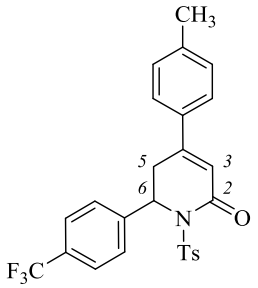
*Acrylate **260*** (820 mg, 1.92 mmol) and 4-bromotoluene (1.64 g, 9.60 mmol) were employed. The reaction mixture was heated to 80 °C and stirred at this temperature for 4 h. The crude material was purified by flash-column chromatography [silicon dioxide, 20% ethyl acetate in petrol] to afford *acrylate **261*** as a yellow solid (923 mg, 93%).

*Acrylate **261** was contaminated with 10% inseparable olefin regio/geometric isomers (by ^{1}H NMR analysis)*

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.40 (d, *J* = 8.0 Hz, 2 H, $Ar_{(Ts)}\underline{H}_{(m\text{-}CH_3)}$), 7.37 (d, *J* = 8.0 Hz, 2 H, $Ar\underline{H}_{(o\text{-}CF_3)}$), 7.27 (d, *J* = 8.5 Hz, 2 H, $Ar\underline{H}_{(m\text{-}CF_3)}$), 7.17 (d, *J* = 8.0 Hz, 2 H, $Ar_{(p\text{-Tolyl})}\underline{H}_{(m\text{-}CH_3)}$), 7.13 (d, *J* = 8.5 Hz, 2 H, $Ar_{(p\text{-Tolyl})}\underline{H}_{(o\text{-}CH_3)}$), 7.02 (d, *J* = 8.0 Hz, 2 H, $Ar_{(Ts)}\underline{H}_{(o\text{-}CH_3)}$), 6.64 (d, *J* = 6.5 Hz, 1 H, N*H*), 6.11 (s, 1 H, C=C*H*COOCH$_3$), 4.40 (ddd, *J* = 11.0, 6.5, 4.0 Hz, 1 H, C*H*NH), 3.82 (s, 3 H, OC$\underline{H_3}$), 3.72 (dd, *J* = 13.5, 11.0 Hz, 1 H, C$\underline{H_a}$H$_b$CHNH), 2.91 (dd, *J* = 13.5, 4.0 Hz, 1 H, CH$_a\underline{H_b}$CHNH), 2.40 (s, 3 H, ArC$\underline{H_3}$), and 2.34 ppm (s, 3 H, ArC$\underline{H_3}$); **^{13}C NMR** (*chloroform-d*, 126 MHz): δ = 168.6, 155.1, 145.8, 142.7, 140.0, 137.8, 136.1, 129.6, 129.3 (q, $^{2}J_{C-F}$ = 32 Hz), 129.1, 126.8, 126.7, 126.6, 125.3 (q, $^{3}J_{C-F}$ = 4 Hz), 124.1 (q, $^{1}J_{C-F}$ = 273 Hz), 119.3, 56.9, 52.0, 38.5, 21.3, and 21.2 ppm; **^{19}F NMR** (*chloroform-d*, 376 MHz): δ = −62.5 ppm (s, 3 F); **HRMS** (ESI$^+$) Calculated for $C_{27}H_{26}F_3NO_4S$. $[M+Na]^+$ requires 540.1427; found 540.1426 (Δ = +0.19 ppm); **FTIR** ν_{max} (thin film): 3305, 2941, 1694, 1551, 1412, 1326, 1162, 1123, and 815 cm^{-1}; **MP** 91−93 °C (dichloromethane/petrol)

*NMR assignments for acrylate **261** were aided by a DEPT based NMR experiment*

4-(p-Tolyl)-1-tosyl-6-(4-(trifluoromethyl)phenyl)-5,6-dihydropyridin-2(1H)-one (262)



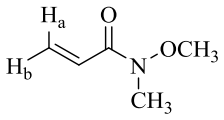
*The synthesis of dihydropyridone **262** was adapted from a procedure developed by a co-worker that was used for the preparation of dihydropyridone **255***

*Acrylate **261*** (90% purity) (865 mg, 1.67 mmol) was added to a 50 mL round-bottom flask fitted with a magnetic follower. The round-bottom flask was sealed with a rubber septum and toluene (16.7 mL, 0.100 M) was added *via* syringe. The reaction mixture was cooled to −78 °C and trimethylaluminium (2.00 M in hexanes) (2.51 mL, 5.02 mmol) was added drop-wise *via* syringe. The reaction mixture was heated to 70 °C and stirred at this temperature for 2.5 h. On completion, the reaction mixture was cooled to room temperature. The reaction mixture was quenched with sodium bicarbonate (aq., sat.) and extracted with dichloromethane (×3). The combined organic phases were dried over sodium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 100% dichloromethane] to afford *dihydropyridone **261*** as an off-white solid (262 mg, 32%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.71 (d, *J* = 8.5 Hz, 2 H, $Ar_{(Ts)}\underline{H}_{(m\text{-}CH_3)}$), 7.50 (d, *J* = 8.5 Hz, 2 H, $Ar\underline{H}_{(o\text{-}CF_3)}$), 7.32 (d, *J* = 8.5 Hz, 2 H, $Ar\underline{H}_{(m\text{-}CF_3)}$), 7.27 (d, *J* = 8.0 Hz, 2 H, $Ar_{(p\text{-Tolyl})}\underline{H}_{(m\text{-}CH_3)}$), 7.20 (d, *J* = 8.5 Hz, 2 H, $Ar_{(Ts)}\underline{H}_{(o\text{-}CH_3)}$), 7.16 (d, *J* = 8.0 Hz, 2 H, $Ar_{(p\text{-Tolyl})}\underline{H}_{(o\text{-}CH_3)}$), 6.27 (d, *J* = 2.5 Hz, 1 H, C$\underline{H}^{3}$), 6.15 (d, *J* = 7.0 Hz, 1 H, C$\underline{H}^{6}$), 3.56 (ddd, *J* = 17.5, 7.0, 2.5 Hz, 1 H, C$\underline{H}^{5}$), 3.15 (dd, *J* = 17.5, 1.5 Hz, 1 H, C$\underline{H}^{5}$), 2.41 (s, 3 H, ArC$\underline{H}_3$), and 2.34 ppm (s, 3 H, ArC$\underline{H}_3$); **^{13}C NMR** (*chloroform-d*, 126 MHz): δ = 163.1, 150.7, 145.0, 143.6, 141.3, 135.6, 133.1, 130.2 (q, $^{2}J_{C-F}$ = 32 Hz), 129.7, 129.2, 129.0, 126.9, 126.0, 125.6 (q, $^{3}J_{C-F}$ = 4 Hz), 123.8 (q, $^{1}J_{C-F}$ = 272 Hz), 118.0, 57.0, 34.8, 21.6, and 21.3 ppm; **^{19}F NMR** (*chloroform-d*, 376 MHz): δ = −62.7 ppm (s, 3 F); **HRMS** (ESI^{+}) Calculated for $C_{26}H_{22}F_3NO_3S$ $[M+Na]^{+}$ requires 508.1165; found 508.1156

(Δ = +1.8 ppm); **FTIR** ν_{max} (thin film): 1678, 1326, 1229, 1167, 1116, 1070, 1016, 881, 815, and 670 cm^{-1}; **MP** 185−187 °C (dichloromethane/petrol)

N-Methoxy-N-methylacrylamide (268)



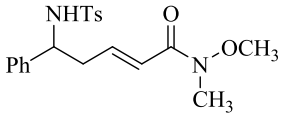
*The synthesis of amide **268** followed a reported literature procedure*[132]

N,*O*-Dimethylhydroxylamine hydrochloride (15.6 g, 161 mmol) was added to a 500 mL round-bottom flask fitted with a magnetic follower. The round-bottom flask was sealed with a rubber septum. Dichloromethane (250 mL, 0.494 M) was added directly from the activated alumina purification column and the reaction mixture was cooled to 0 °C. Triethylamine (34.6 mL, 247 mmol) and acryloyl chloride (***267***) (10.0 mL, 124 mmol) were sequentially added drop-wise *via* syringe. The reaction mixture was stirred at this temperature for 30 mins. On completion, the reaction mixture was warmed to room temperature. The reaction mixture was diluted with dichloromethane and washed with hydrochloric acid (aq., 1.00 M), sodium bicarbonate (aq., sat.), and brine (sat.). The organic phase were dried over sodium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by vacuum distillation [96 °C at 52 mmHg] to afford *amide **268*** as a colourless oil (12.1 g, 85%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 6.70 (dd, *J* = 17.0, 10.5 Hz, 1 H, CH_aH_b=C<u>*H*</u>), 6.39 (d, *J* = 17.0 Hz, 1 H, C<u>*H*</u>$_a$$H_b$=CH), 5.72 (d, *J* = 10.5 Hz, 1 H, CH_a<u>*H*</u>$_b$=CH), 3.68 (s, 3 H, OC<u>*H*</u>$_3$), and 3.23 ppm (s, 3 H, NC<u>*H*</u>$_3$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 166.4, 128.9, 125.9, 61.7, and 32.3 ppm

*Spectroscopic data are consistent with those reported in the literature for amide **268***

(E)-N-Methoxy-N-methyl-5-((4-methylphenyl)sulfonamido)-5-phenylpent-2-enamide (269)

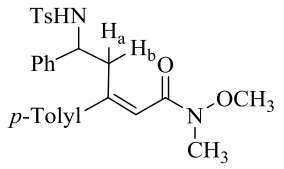


Using General Procedure B

Sulfonamide ***158*** (200 mg, 0.664 mmol) and *amide* ***268*** (0.374 mL, 3.32 mmol) were employed. The reaction mixture was heated 55 °C and stirred at this temperature for 68 h. The crude material was purified by flash-column chromatography [silicon dioxide, 60% ethyl acetate in petrol] to afford *amide* ***269*** as a colourless oil (167 mg, 65%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.56 (d, *J* = 8.0 Hz, 2 H, Ar$\underline{H}_{(m\text{-}CH_3)}$), 7.19−7.11 (m, 5 H, Ar$\underline{H}$), 7.08−7.02 (m, 2 H, Ar$\underline{H}$), 6.71−6.61 (m, 1 H, $CH_2C\underline{H}$=CH), 6.37 (d, *J* = 15.5 Hz, 1 H, CH=C$\underline{H}$CON(CH_3)OCH_3), 5.24 (d, *J* = 7.5 Hz, 1 H, N$\underline{H}$), 4.47 (q, *J* = 7.0 Hz, 1 H, C$\underline{H}$NH), 3.59 (s, 3 H, OC$\underline{H_3}$), 3.20 (s, 3 H, NC$\underline{H_3}$), 2.80−2.61 (m, 2 H, C$\underline{H_2}$CH=CH), and 2.36 ppm (s, 3 H, ArC$\underline{H_3}$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 166.0, 143.2, 141.0, 139.6, 137.3, 129.4, 128.6, 127.6, 127.1, 126.6, 122.5, 61.7, 57.0, 40.1, 32.3, and 21.5 ppm; **HRMS** (ESI^+) Calculated for $C_{20}H_{24}N_2O_4S$. $[M+Na]^+$ requires 411.1349; found 411.1334 (Δ = +3.7 ppm); **FTIR** ν_{max} (thin film): 3187, 1661, 1615, 1457, 1386, 1328, 1159, 1092, 993, 814, 761, 702, and 668 cm^{-1}

(E)-N-methoxy-N-methyl-5-((4-methylphenyl)sulfonamido)-5-phenyl-3-(p-tolyl)pent-2-enamide (270)



Procedure 1

Using General Procedure G

Amide ***269*** (50.0 mg, 0.129 mmol) and 4-iodotoluene (56.3 mg, 0.258 mmol) were employed. The reaction mixture was heated to 80 °C and stirred at this temperature for 12 h. The crude material was purified by flash-column chromatography [silicon dioxide, 30% ethyl acetate in petrol] to afford *amide* ***270*** as a colourless oil (48.1 mg, 78%).

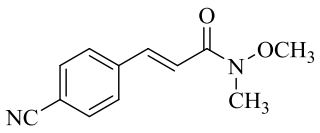
Procedure 2

Using General Procedure H

p-Tolylboronic acid (70.1 mg, 0.515 mmol) and *amide* ***316*** (50.0 mg, 0.129 mmol) were employed. The Fujiwara-Moritani reaction was carried out for 3 h. The crude material was purified by flash-column chromatography [silicon dioxide, 35% ethyl acetate in petrol] to afford *amide* ***270*** as a colourless oil (54.9 mg, 89%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 8.12 (d, *J* = 5.5 Hz, 1 H, N*H*), 7.41 (d, *J* = 7.5 Hz, 2 H, Ar$_{(Ts)}$*H*$_{(m\text{-}CH_3)}$), 7.25−7.10 (m, 9 H, Ar*H*), 7.01 (d, *J* = 7.5 Hz, 2 H, Ar*H*), 6.53 (s, 1 H, C=C*H*CON(CH$_3$)OCH$_3$), 4.29 (ddd, *J* = 12.0, 5.0, 3.0 Hz, 1 H, C*H*NH), 3.71−3.53 (m, 4 H, OC*H*$_3$ and C*H*$_a$H$_b$CHNH), 3.33 (s, 3 H, NC*H*$_3$), 2.74 (dd, *J* = 13.5, 3.0 Hz, 1 H, CH$_a$*H*$_b$CHNH), 2.41 (s, 3 H, ArC*H*$_3$), and 2.35 ppm (s, 3 H, ArC*H*$_3$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 168.0, 152.3, 142.9, 141.9, 139.3, 138.7, 136.9, 129.4, 128.9, 128.3, 127.0, 126.9, 126.8, 126.3, 118.7, 61.8, 56.7, 39.7, 32.4, 21.4, and 21.3 ppm; **HRMS** (ESI$^+$) Calculated for $C_{27}H_{30}N_2O_4S$. $[M+Na]^+$ requires 501.1818; found 501.1794 (Δ = +4.8 ppm); **FTIR** ν_{max} (thin film): 3151, 2954, 1629, 1457, 1331, 1160, 1093, 960, 814, 701 and 665 cm^{-1}

(E)-3-(4-Cyanophenyl)-N-methoxy-N-methylacrylamide (272)



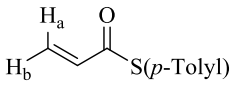
Using General Procedure F

Amide ***268*** (50.0 mg, 0.435 mmol) and 4-bromobenzonitrile (119 mg, 0.653 mmol) were employed. The reaction mixture was heated to 120 °C and stirred at this temperature for 4 h. The crude material was purified by flash-column chromatography [silicon dioxide, 50% ethyl acetate in petrol] to afford *amide* ***272*** as a white solid (87.8 mg, 93%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.71−7.48 (m, 5 H, Ar*H* and ArC*H*=CH), 7.05 (d, *J* = 16.0 Hz, 1 H, ArCH=C*H*), 3.71 (s, 3 H, OC*H*$_3$), and 3.25 ppm (s, 3 H, NC*H*$_3$); **^{13}C NMR** (*chloroform-d*, 126 MHz): δ = 165.9, 141.1, 139.5, 132.6, 128.4, 119.3, 118.5, 112.9, 62.1, and 32.5 ppm; **HRMS** (EI$^+$) Calculated for $C_{12}H_{12}N_2O_2$. $[M]^+$ requires 216.0899; found 216.0898

(Δ = +0.46 ppm); **FTIR** ν_{max} (thin film): 2976, 2224, 1655, 1616, 1603, 1412, 1384, 1193, 1005, 956, and 829 cm^{-1}; **MP** 142−144 °C (dichloromethane/petrol)

S-(p-Tolyl)-prop-2-enethioate (275)



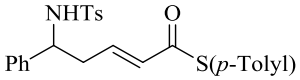
*The synthesis of thioacrylate **275** was adapted from a reported literature procedure that was used for the preparation of related compounds*[209]

4-Methylbenzenethiol (***267***) (868 mg, 7.00 mmol) was added to a 50 mL round-bottom flask fitted with a magnetic follower. The round-bottom flask was sealed with a rubber septum. Sodium hydroxide (aq., 5%) (20.0 mL, 25.0 mmol) was added *via* syringe and the reaction mixture was cooled to 0 °C. Acryloyl chloride (***267***) (1.14 mL, 14.1 mmol) was added drop-wise *via* syringe. The reaction mixture stirred at this temperature for 1 h. On completion, the reaction mixture was warmed to room temperature. The reaction mixture was extracted with dichloromethane (×2). The organic phase was washed with sodium bicarbonate (aq., sat.), brine (sat.), dried over sodium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 5% diethyl ether in petrol] to afford *thioacrylate **275*** as a colourless oil (972 mg, 78%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.37 (d, *J* = 8.0 Hz, 2 H, Ar$\underline{H}_{(m\text{-}CH_3)}$), 7.28 (d, *J* = 8.0 Hz, 2 H, Ar$\underline{H}_{(o\text{-}CH_3)}$), 6.49 (dd, *J* = 17.0, 10.0 Hz, 1 H, CH_aH_b=C$\underline{H}$), 6.42 (dd, *J* = 17.0, 1.5 Hz, 1 H, C$\underline{H}_a$$H_b$=CH), 5.79 (dd, *J* = 10.0, 1.5 Hz, 1 H, $CH_a\underline{H}_b$=CH), and 2.42 ppm (s, 3 H, ArC$\underline{H}_3$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 189.0, 139.9, 134.6, 134.4, 130.1, 127.3, 123.6, and 21.4 ppm

*Spectroscopic data are consistent with those reported in the literature for thioacrylate **272***

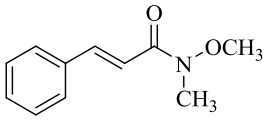
S-(p-Tolyl)-(E)-5-((4-methylphenyl)sulfonamido)-5-phenylpent-2-enethioate (276)



Using General Procedure B

*Sulfonamide **158*** (100 mg, 0.332 mmol) and *thioacrylate **275*** (295 mg, 1.66 mmol) were employed. In a modification to the general procedure, Hoveyda-Grubbs 2nd generation catalyst (***132***)[111,112] (11.0 mg, 16.6 μmol) was employed. The reaction mixture was heated 55 °C and stirred at this temperature for 26 h. The crude material was purified by flash-column chromatography [silicon dioxide, 20% ethyl acetate in petrol] to afford sulfon*amide **276*** as an off-white solid (102 mg, 68%). **^{1}H NMR** (*chloroform-d*, 400 MHz): δ = 7.61 (d, *J* = 8.5 Hz, 2 H, $Ar_{(Ts)}\underline{H}_{(m\text{-}CH_3)}$), 7.33−7.16 (m, 9 H, Ar*H*), 7.10−7.04 (m, 2 H, Ar*H*), 6.75−6.59 (m, 1 H, $CH_2C\underline{H}$=CH), 6.12 (d, *J* = 15.5 Hz, 1 H, CH=C*H*COS(*p*-Tolyl)), 5.26 (d, *J* = 7.5 Hz, 1 H, N*H*), 4.48 (q, *J* = 7.0 Hz, 1 H, C*H*NH), 2.80−2.61 (m, 2 H, $C\underline{H}_2$CH=CH), 2.40 (s, 3 H, $ArC\underline{H}_3$), and 2.38 ppm (s, 3 H, $ArC\underline{H}_3$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 188.0, 143.4, 140.0, 139.8, 139.4, 137.2, 134.5, 130.8, 130.0, 129.6, 128.8, 127.9, 127.1, 126.4, 123.8, 57.0, 40.0, 21.5, and 21.4 ppm; **HRMS** (ESI^+) Calculated for $C_{25}H_{25}NO_3S_2$. $[M+Na]^+$ requires 474.1168; found 474.1168 (Δ = 0.0 ppm); **FTIR** ν_{max} (thin film): 3274, 1681, 1633, 1599, 1494, 1455, 1325, 1158, 1092, 1030, 977, 809, 732, 701, and 667 cm^{-1}; **MP** 130−132 °C (dichloromethane/petrol)

(E)-N-Methoxy-N-methylcinnamamide (309)



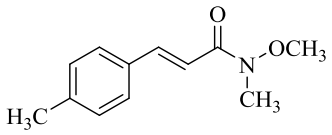
Using General Procedure F

*Amide **268*** (50.0 mg, 0.435 mmol) and bromobenzene (103 mg, 0.653 mmol) were employed. The reaction mixture was heated to 120 °C and stirred at this temperature for 5 h. The crude material was purified by flash-column chromatography [silicon dioxide, 40% ethyl acetate in petrol] to afford *amide **309*** as a white solid (77.3 mg, 93%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.74 (d, *J* = 16.0 Hz, 1 H, PhC*H*=CH), 7.62−7.52 (m, 2 H, Ar*H*), 7.45−7.33 (m, 3 H, Ar*H*), 7.04 (d, *J* = 16.0 Hz, 1 H, PhCH=C*H*), 3.76 (s, 3 H, OCH_3), and 3.31 ppm (s, 3 H, NCH_3); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 166.9, 143.4, 135.1, 129.9, 128.8, 128.0, 115.8, 61.9, and 32.5 ppm; **MP** 58−60 °C (dichloromethane/petrol)

*Spectroscopic data are consistent with those reported in the literature for amide **309***[210]

(E)-N-Methoxy-N-methyl-3-(p-tolyl)acrylamide (310)



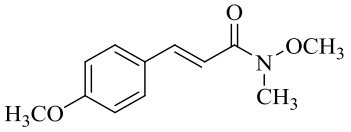
Using General Procedure F

*Amide **268*** (100 mg, 0.870 mmol) and 4-bromotoluene (223 mg, 1.305 mmol) were employed. The reaction mixture was heated to 120 °C and stirred at this temperature for 5 h. The crude material was purified by flash-column chromatography [silicon dioxide, 40% ethyl acetate in petrol] to afford *amide **310*** as a colourless oil (163 mg, 92%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.71 (d, *J* = 16.0 Hz, 1 H, *p*-TolylC*H*=CH), 7.46 (d, *J* = 8.5 Hz, 2 H, Ar$H_{(m\text{-}CH_3)}$), 7.17 (d, *J* = 8.5 Hz, 2 H, Ar$H_{(o\text{-}CH_3)}$), 6.99 (d, *J* = 16.0 Hz, 1 H, *p*-TolylCH=C*H*), 3.74 (s, 3 H, OCH_3), 3.29 (s, 3 H, NCH_3), and 2.35 ppm (s, 3 H, ArCH_3); **^{13}C NMR** (*chloroform-d*, 126 MHz): δ = 167.2, 143.4, 140.2, 132.4, 129.5, 128.0, 114.7, 61.8, 32.5, and 21.4 ppm

*Spectroscopic data are consistent with those reported in the literature for amide **310***[211]

(E)-N-Methoxy-3-(4-methoxyphenyl)-N-methylacrylamide (311)



Using General Procedure F

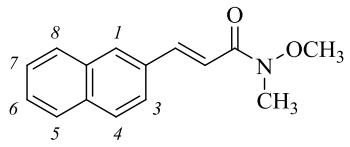
*Amide **268*** (50.0 mg, 0.435 mmol) and 4-bromoanisole (82.6 μL, 0.653 mmol) were employed. The reaction mixture was heated to 120 °C and stirred at this temperature for 5 h. The crude material was

purified by flash-column chromatography [silicon dioxide, 40% ethyl acetate in petrol] to afford *amide **311*** as a colourless oil (94.2 mg, 97%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.69 (d, *J* = 15.5 Hz, 1 H, ArC*H*=CH), 7.52 (d, *J* = 9.0 Hz, 2 H, Ar$H_{(m\text{-}OCH_3)}$), 6.97−6.85 (m, 3 H, Ar$H_{(o\text{-}OCH_3)}$ and ArCH=C*H*), 3.82 (s, 3 H, ArOCH_3), 3.75 (s, 3 H, OCH_3), and 3.29 ppm (s, 3 H, NCH_3); **^{13}C NMR** (*chloroform-d*, 126 MHz): δ = 167.3, 161.1, 143.1, 129.6, 127.9, 114.2, 113.3, 61.8, 55.3, and 32.5 ppm

*Spectroscopic data are consistent with those reported in the literature for amide **311***[211]

(E)-N-Methoxy-N-methyl-3-(naphthalen-2-yl)acrylamide (312)



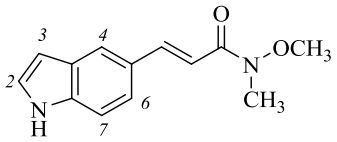
Using General Procedure F

*Amide **268*** (50.0 mg, 0.435 mmol) and 2-bromonaphthalene (137 mg, 0.653 mmol) were employed. The reaction mixture was heated to 120 °C and stirred at this temperature for 5 h. The crude material was purified by flash-column chromatography [silicon dioxide, 40% ethyl acetate in petrol] to afford *amide **312*** as a white solid (88.0 mg, 82%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.95 (s, 1 H, ArH^1), 7.90 (d, *J* = 15.5 Hz, 1 H, ArC*H*=CH), 7.87−7.78 (m, 3 H, Ar*H*), 7.72 (dd, *J* = 8.5, 1.5 Hz, 1 H, Ar*H*), 7.55−7.42 (m, 2 H, Ar*H*), 7.15 (d, *J* = 15.5 Hz, 1 H, ArCH=C*H*), 3.78 (s, 3 H, OCH_3), and 3.33 ppm (s, 3 H, NCH_3); **^{13}C NMR** (*chloroform-d*, 126 MHz): δ = 167.0, 143.5, 134.1, 133.4, 132.7, 129.7, 128.5 (2), 127.8, 127.0, 126.6, 123.8, 116.0, 62.0, and 32.6 ppm; **MP** 85−87 °C (dichloromethane/petrol)

*Spectroscopic data are consistent with those reported in the literature for amide **312***[212]

(E)-3-(1H-Indol-5-yl)-N-methoxy-N-methylacrylamide (313)

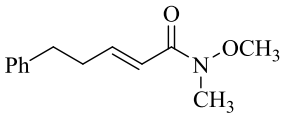


Using General Procedure F

*Amide **268*** (50.0 mg, 0.435 mmol) and 5-bromoindole (129 mg, 0.653 mmol) were employed. The reaction mixture was heated to 120 °C and stirred at this temperature for 4 h. The crude material was purified by flash-column chromatography [silicon dioxide, 50% ethyl acetate in petrol] to afford *amide **313*** as a colourless oil (95.0 mg, 95%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 9.27 (s, 1 H, N*H*), 7.91 (d, *J* = 15.5 Hz, 1 H, ArC*H*=CH), 7.81 (s, 1 H, ArH^4), 7.42 (dd, *J* = 8.5, 1.5 Hz, 1 H, ArH^6), 7.35 (d, *J* = 8.5 Hz, 1 H, ArH^7), 7.18 (t, *J* = 2.5 Hz, 1 H, ArH^2), 7.02 (d, *J* = 15.5 Hz, 1 H, ArCH=C*H*), 6.57−6.50 (m, 1 H, ArH^3), 3.75 (s, 3 H, OCH_3), and 3.31 ppm (s, 3 H, NCH_3); **^{13}C NMR** (*chloroform-d*, 126 MHz): δ = 168.0, 145.7, 137.2, 128.2, 126.8, 125.7, 122.1, 121.6, 112.4, 111.8, 103.0, 61.9, and 32.7 ppm; **HRMS** (ESI^+) Calculated for $C_{13}H_{14}N_2O_2$. $[M+Na]^+$: requires 253.0947; found 253.0955 (Δ = −3.2 ppm); **FTIR** ν_{max} (thin film): 1642, 1593, 1475, 1420, 1385, 1349, 1332, 1295, 1095, 1002, 909, 806, 769, and 730 cm^{-1}

(E)-N-Methoxy-N-methyl-5-phenylpent-2-enamide (316)



Procedure 1

Step 1

The synthesis of the acid chloride followed a reported literature procedure[156]

(*E*)-5-Phenylpent-2-enoic acid (***314***) (2.50 g, 14.2 mmol) was added to a 10 mL round-bottom flask fitted with a magnetic follower. A reflux condenser, sealed with a rubber septum, was attached to the round-bottom flask. Thionyl chloride (2.06 mL, 28.4 mmol) was added *via* syringe. The reaction

mixture was heated to 80 °C and stirred at this temperature for 6 h. On completion, the reaction mixture was cooled to room temperature and concentrated *in vacuo* to afford an acid chloride as a colourless oil.

Step 2

The synthesis of amide ***316*** *was adapted from a reported literature procedure used for the preparation of related compounds*[132]

N,*O*-Dimethylhydroxylamine hydrochloride (1.39 g, 14.2 mmol) was added to a 100 mL round-bottom flask fitted with a magnetic follower. The round-bottom flask was sealed with a rubber septum. Dichloromethane (30.0 mL, 0.473 M) was added *via* syringe and the reaction mixture was cooled to 0 °C. Triethylamine (2.12 mL, 15.6 mmol) and the acid chloride were sequentially added drop-wise *via* syringe. The reaction mixture was stirred at this temperature for 1 h. The reaction mixture was warmed to room temperature and stirred at this temperature for 16 h. On completion, the reaction mixture was quenched with ammonium chloride (aq., sat.) and extracted with dichloromethane (×3). The combined organic phases were washed with brine (sat.), dried over sodium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 40% ethyl acetate in petrol] to afford *amide* ***316*** as a colourless oil (1.37 g, 72% over two steps).

Procedure 2

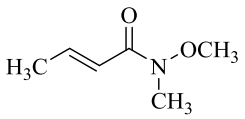
The synthesis of amide ***316*** *was adapted from a reported literature procedure that was used for the preparation of related compounds*[121]

Hoveyda-Grubbs 2nd generation catalyst (***132***)[111,112] (125 mg, 0.200 mmol) was added to a microwave vial fitted with a magnetic follower. The microwave vial was sealed with a crimped microwave lid with a septum. Dichloromethane (8.00 mL, 0.499 M), 4-phenyl-1-butene (***315***) (600 μL, 3.99 mmol), and *amide* ***268*** (900 μL, 7.99 mmol) were sequentially added *via* syringe. The reaction mixture was heated to 40 °C and stirred at this temperature for 24 h. On completion, the reaction mixture was cooled to room temperature. The crude material was purified by flash-column chromatography [silicon dioxide, 40% ethyl acetate in petrol] followed by subsequent flash-column

chromatography [silicon dioxide, 10% diethyl ether in dichloromethane) to afford *amide **316*** as a colourless oil (700 mg, 80%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.32−7.26 (m, 2 H, Ar*H*), 7.22−7.17 (m, 3 H, Ar*H*), 7.02 (dt, *J* = 15.5, 7.0 Hz, 1 H, Ph(CH$_2$)$_2$)C*H*=CH), 6.39 (d, *J* = 15.5 Hz, 1 H, Ph(CH$_2$)$_2$)CH=C*H*), 3.63 (s, 3 H, OC*H*$_3$), 3.24 (s, 3 H, NC*H*$_3$), 2.84−2.75 (m, 2 H, PhCH$_2$C*H*$_2$), and 2.61−2.53 ppm (m, 2 H, PhC*H*$_2$CH$_2$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 166.8, 146.5, 141.0, 128.4 (2), 126.1, 119.4, 61.7, 34.6, 34.2, and 32.3 ppm; **HRMS** (ESI$^+$) Calculated for $C_{13}H_{17}NO_2$. $[M+Na]^+$ requires 242.1151; found 242.1155 (Δ = −1.7 ppm); **FTIR** ν_{max} (thin film): 2935, 1662, 1632, 1414, 1382, 1179, 990, 749, and 700 cm^{-1}

(E)-N-Methoxy-N-methylbut-2-enamide (318)



*The synthesis of amide **318** followed a reported literature procedure*[132]

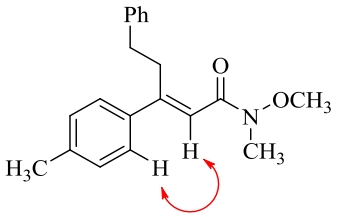
N,*O*-Dimethylhydroxylamine hydrochloride (4.62 g, 47.3 mmol) was added to a 500 mL round-bottom flask fitted with a magnetic follower. The round-bottom flask was sealed with a rubber septum. Dichloromethane (125 mL, 0.344 M) was added directly from the activated alumina purification column and the reaction mixture was cooled to 0 °C. Triethylamine (9.00 mL, 64.6 mmol) and (*E*)-but-2-enoyl chloride (***317***) (4.49 g, 43.0 mmol) were sequentially added drop-wise *via* syringe. The reaction mixture was stirred at this temperature for 1 h. The reaction mixture was warmed to room temperature and stirred at this temperature for 16 h. On completion, the reaction mixture was quenched with ammonium chloride (aq., sat.) and extracted with dichloromethane (×3). The combined organic phases were washed with brine (sat.), dried over sodium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 50% ethyl acetate in petrol] to afford *amide **318*** as a colourless oil (4.10 g, 74%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.00−6.90 (m, 1 H, CH$_3$C*H*=CH), 6.39 (dd, *J* = 15.5, 1.5 Hz, 1 H, CH$_3$CH=C*H*), 3.68 (s, 3 H, OC*H*$_3$), 3.20 (s, 3 H, NC*H*$_3$), and 1.88 ppm (dd, *J* = 7.0, 2.0 Hz,

3 H, C*H*$_3$CH=CH); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 166.9, 142.9, 120.1, 61.6, 32.3, and 18.2 ppm

Spectroscopic data are consistent with those reported in the literature for amide ***318***

(E)-N-Methoxy-N-methyl-5-phenyl-3-(p-tolyl)pent-2-enamide (319)



Procedure 1

The synthesis of amide ***319*** *was adapted from a reported literature procedure that was used for the preparation of related compounds*[98]

Tris(dibenzylideneacetone)dipalladium (10.5 mg, 11.5 µmol), tri-*tert*-butylphosphonium tetrafluoroborate (13.3 mg, 46.0 µmol), and 4-bromotoluene (59.0 mg, 0.345 mmol) were added to a microwave vial fitted with magnetic follower. The microwave vial was sealed with a crimped microwave lid. *Amide* ***316*** (50.0 mg, 0.228 mmol), 1,4-dioxane (2.30 mL, 0.100 M), and *N*,*N*-dicyclohexylmethylamine (73.2 µL, 0.345 mmol) were sequentially added *via* syringe. The reaction mixture was heated to 80 °C and stirred at this temperature for 22 h. On completion, the reaction mixture was cooled to room temperature and filtered [silicon dioxide, 50% ethyl acetate in petrol]. The fractions that contained the desired coupling product were combined and concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 20% ethyl acetate in petrol] to afford *amide* ***319*** as a colourless oil (29.0 mg, 41%).

Procedure 2

Using General Procedure H

p-Tolylboronic acid (250 mg, 1.84 mmol) and *amide* ***316*** (100 mg, 0.456 mmol) were employed. The Fujiwara-Moritani reaction was carried out for 18.5 h. The crude material was purified by flash-column chromatography [silicon dioxide, 15% to 25% ethyl acetate in petrol] to afford *amide* ***319*** as a colourless oil (122 mg, 86%).

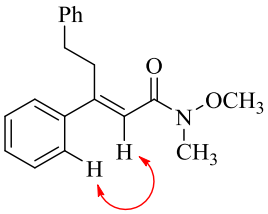
^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.39 (d, *J* = 7.0 Hz, 2 H, Ar$\underline{H}_{(m\text{-}CH_3)}$), 7.31−7.14 (m, 7 H, Ar$\underline{H}$), 6.51 (s, 1 H, *p*-Tolyl(Ph(CH$_2$)$_2$)C=C$\underline{H}$), 3.63 (s, 3 H, OC$\underline{H}_3$), 3.43−3.32 (m, 2 H, PhCH$_2$C$\underline{H}_2$), 3.26 (s, 3 H, NC$\underline{H}_3$), 2.81−2.71 (m, 2 H, PhC$\underline{H}_2$CH$_2$), and 2.41 ppm (s, 3 H, ArC$\underline{H}_3$)

7.52−7.32 (m, 5 H, Ar$\underline{H}$), 7.26−7.10 (m, 5 H, Ar$\underline{H}$), 6.49 (s, 1 H, Ph(Ph(CH$_2$)$_2$)C=C$\underline{H}$), 3.61 (s, 3 H, OC$\underline{H}_3$), 3.40−3.32 (m, 2 H, PhCH$_2$C$\underline{H}_2$), 3.24 (s, 3 H, NC$\underline{H}_3$), and 2.79−2.69 ppm (m, 2 H, PhC$\underline{H}_2$CH$_2$); **^{13}C NMR** (*methanol-d$_4$*, 126 MHz): δ = 169.1, 157.6, 142.9, 129.9, 129.8, 129.6, 129.3, 127.9, 127.0, 118.0, 101.4, 62.1, 36.0, 34.0, and 32.6 ppm; **HRMS** (ESI$^+$) Calculated for $C_{19}H_{21}NO_2$. $[M+Na]^+$ requires 318.1465; found 318.1472 (Δ = −2.2 ppm); **FTIR** ν_{max} (thin film): 3663, 2538, 2074, 1633, 1495, 1383, 1296, 1149, 1120, 984, and 699 cm^{-1}

*NMR assignments for amide **319** were aided by COSY and HSQC based NMR experiments*

Red arrows indicate a significant nOe enhancement as observed by a 1D nOe based NMR experiment

(E)-N-Methoxy-N-methyl-3,5-diphenylpent-2-enamide (321)



Procedure 1

Using General Procedure G

*Amide **316*** (50.0 mg, 0.228 mmol) and iodobenzene (93.8 mg, 0.456 mmol) were employed. The reaction mixture was heated to 80 °C and stirred at this temperature for 15 h. The crude material was purified by flash-column chromatography [silicon dioxide, 15% ethyl acetate in petrol] to afford *amide **321*** as a colourless oil (51.1 mg, 76%).

Procedure 2

Using General Procedure H

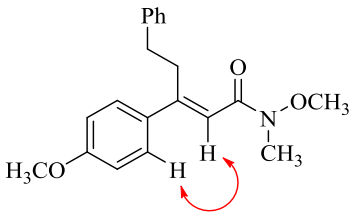
Phenylboronic acid (1.12 g, 9.12 mmol) and *amide **316*** (500 mg, 2.28 mmol) were employed. The Fujiwara-Moritani reaction was carried out for 4 h. The crude material was purified by flash-column

chromatography [silicon dioxide, 10% to 30% ethyl acetate in petrol] to afford *amide **321*** as a colourless oil (579 mg, 86%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.52−7.32 (m, 5 H, Ar*H*), 7.26−7.10 (m, 5 H, Ar*H*), 6.49 (s, 1 H, Ph(Ph(CH$_2$)$_2$)C=C*H*), 3.61 (s, 3 H, OC*H*$_3$), 3.40−3.32 (m, 2 H, PhCH$_2$C*H*$_2$), 3.24 (s, 3 H, NC*H*$_3$), and 2.79−2.69 ppm (m, 2 H, PhC*H*$_2$CH$_2$); **^{13}C NMR** (*methanol-d*$_4$, 126 MHz): δ = 167.5, 156.2, 142.0, 138.8, 138.7, 129.3, 128.6, 128.2, 126.7, 125.8, 116.1, 61.5, 35.1, 33.1, 32.5, and 21.2 ppm; **HRMS** (ESI$^+$) Calculated for $C_{20}H_{23}NO_2$. $[M+Na]^+$ requires 332.1621; found 332.1627 (Δ = −1.8 ppm); **FTIR** ν_{max} (thin film): 2933, 1645, 1607, 1511, 1496, 1454, 1412, 1379, 1178, 1099, 984, 750, and 700 cm^{-1}

Red arrows indicate a significant nOe enhancement as observed by 2D NOESY correlation based NMR experiments

(E)-N-Methoxy-3-(4-methoxyphenyl)-N-methyl-5-phenylpent-2-enamide (325)



Using General Procedure G

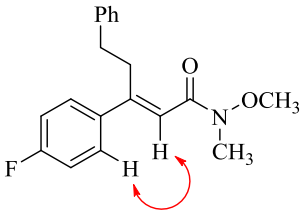
*Amide **316*** (85.0 mg, 0.388 mmol) and 4-iodoanisole (183 mg, 0.776 mmol) were employed. The reaction mixture was heated to 80 °C and stirred at this temperature for 12 h. The crude material was purified by flash-column chromatography [silicon dioxide, 20% ethyl acetate in petrol] to afford *amide **325*** as a colourless oil (97.1 mg, 77%).

^{1}H NMR (*chloroform-d*, 500 MHz): δ = 7.42 (d, *J* = 8.5 Hz, 2 H, Ar*H*$_{(m\text{-}OCH_3)}$), 7.29−7.19 (m, 4 H, Ar$_{(Ph)}$*H*$_{(o\text{-}CH_2)}$ and Ar$_{(Ph)}$*H*$_{(m\text{-}CH_2)}$), 7.14 (tt, *J* = 6.0, 3.0 Hz, 1 H, Ar$_{(Ph)}$*H*$_{(p\text{-}CH_2)}$), 6.92 (d, *J* = 8.5 Hz, 2 H, Ar*H*$_{(o\text{-}OCH_3)}$), 6.47 (s, 1 H, Ar(Ph(CH$_2$)$_2$)C=C*H*), 3.82 (s, 3 H, ArOC*H*$_3$), 3.60 (s, 3 H, OC*H*$_3$), 3.38−3.32 (m, 2 H, PhCH$_2$C*H*$_2$), 3.23 (s, 3 H, NC*H*$_3$), and 2.79−2.70 ppm (m, 2 H, PhC*H*$_2$CH$_2$); **^{13}C NMR** (*chloroform-d*, 126 MHz): δ = 167.7, 160.2, 155.8, 142.0, 133.9, 128.6, 128.3, 128.1, 125.8, 115.2, 114.0, 61.5, 55.4, 35.3, 33.0, and 32.5 ppm; **HRMS** (ESI$^+$) Calculated for $C_{20}H_{23}NO_3$.

$[M+Na]^+$ requires 348.1566; found 348.1570 ($\Delta = -1.2$ ppm); **FTIR** ν_{max} (thin film): 1644, 1602, 1511, 1454, 1380, 1289, 1246, 1180, 1099, 1029, 984, 833, and 702 cm^{-1}

Red arrows indicate a significant nOe enhancement as observed by a 2D NOESY correlation based NMR experiment

(E)-3-(4-Fluorophenyl)-N-methoxy-N-methyl-5-phenylpent-2-enamide (327)



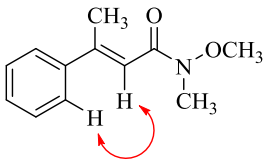
Using General Procedure G

Amide ***316*** (50.0 mg, 0.228 mmol) and 1-fluoro-4-iodobenzene (102 mg, 0.456 mmol) were employed. The reaction mixture was heated to 80 °C and stirred at this temperature for 15 h. The crude material was purified by flash-column chromatography [silicon dioxide, 20% to 30% ethyl acetate in petrol] to afford *amide* ***327*** as a colourless oil (52.8 mg, 74%).

^{1}H NMR (*chloroform-d*, 500 MHz): $\delta = 7.45-7.37$ (m, 2 H, Ar$\underline{H}_{(m\text{-}F)}$), 7.28−7.12 (m, 5 H, Ar$_{(Ph)}\underline{H}$), 7.11−7.02 (m, 2 H, Ar$\underline{H}_{(o\text{-}F)}$), 6.44 (s, 1 H, Ar(Ph$(CH_2)_2$)C=C$\underline{H}$), 3.61 (s, 3 H, OC$\underline{H}_3$), 3.37−3.31 (m, 2 H, PhCH_2C$\underline{H}_2$), 3.24 (s, 3 H, NC$\underline{H}_3$), and 2.77−2.68 ppm (m, 2 H, PhC$\underline{H}_2$CH_2); **^{13}C NMR** (*chloroform-d*, 126 MHz): $\delta = 167.3$, 163.0 (d, $^1J_{C-F} = 249$ Hz), 155.1, 141.6, 137.8, 128.6, 128.6, 128.5 (d, $^3J_{C-F} = 8$ Hz), 125.9, 116.9, 115.5 (d, $^2J_{C-F} = 22$ Hz), 61.5, 35.0, 33.2, and 32.4 ppm; **^{19}F NMR** (*chloroform-d*, 471 MHz): $\delta = -113.3$ ppm (m, 1 F); **HRMS** (ESI^+) Calculated for $C_{19}H_{20}FNO_2$. $[M+Na]^+$ requires 336.1370; found 336.1380 ($\Delta = -3.0$ ppm); **FTIR** ν_{max} (thin film): 1646, 1601, 1508, 1454, 1380, 1233, 1161, 1101, 1013, 913, 833, 748, 745, and 700 cm^{-1}

Red arrows indicate a significant nOe enhancement as observed by a 2D NOESY correlation based NMR experiment

(E)-N-Methoxy-N-methyl-3-phenylbut-2-enamide (329)



Procedure 1

Using General Procedure G

Amide ***318*** (50.0 mg, 0.388 mmol) and iodobenzene (86.8 µL, 0.776 mmol) were employed. The reaction mixture was heated to 80 °C and stirred at this temperature for 16 h. The crude material was purified by flash-column chromatography [silicon dioxide, 20% to 30% ethyl acetate in petrol] to afford *amide* ***329*** as a colourless oil (52.7 mg, 66%).

Procedure 2

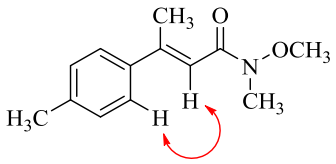
Using General Procedure H

Phenylboronic acid (1.89 g, 15.5 mmol) and *amide* ***318*** (500 mg, 3.88 mmol) were employed. The Fujiwara-Moritani reaction was carried out for 18 h. The crude material was purified by flash-column chromatography [silicon dioxide, 20% ethyl acetate in petrol] to afford *amide* ***329*** as a colourless oil (490 mg, 62%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.51−7.43 (m, 2 H, Ar$\underline{H}_{(o\text{-alkene})}$), 7.41−7.33 (m, 3 H, Ar$\underline{H}_{(m\text{-alkene})}$ and Ar$\underline{H}_{(p\text{-alkene})}$), 6.57 (s, 1 H, Ph(CH$_3$)C=C$\underline{H}$), 3.71 (s, 3 H, OC$\underline{H}_3$), 3.27 (s, 3 H, NC$\underline{H}_3$), and 2.51 ppm (d, *J* = 1 Hz, 3 H, Ph(C$\underline{H}_3$)C=CH); **^{13}C NMR** (*chloroform-d*, 126 MHz): δ = 168.0, 152.3, 143.0, 128.6, 128.5, 126.3, 116.0, 61.6, 32.4, and 18.0 ppm; **HRMS** (ESI$^+$) Calculated for $C_{12}H_{15}NO_2$. $[M+Na]^+$ requires 228.0995; found 228.1005 (Δ = −4.4 ppm); **FTIR** ν_{max} (thin film): 1647, 1620, 1446, 1368, 1178, 1151, 1107, 978, 913, and 696 cm^{-1}

Red arrows indicate a significant nOe enhancement as observed by a 2D NOESY correlation based NMR experiment

(E)-N-Methoxy-N-methyl-3-(p-tolyl)but-2-enamide (330)



Procedure 1

Using General Procedure G

Amide ***318*** (50.0 mg, 0.388 mmol) and 4-iodotoluene (170 mg, 0.776 mmol) were employed. The reaction mixture was heated to 80 °C and stirred at this temperature for 16 h. The crude material was purified by flash-column chromatography [silicon dioxide, 20% to 30% ethyl acetate in petrol] to afford *amide* ***330*** as a colourless oil (60.7 mg, 71%).

Procedure 2

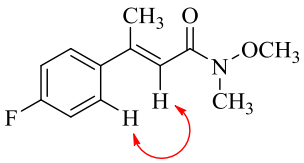
Using General Procedure H

p-Tolylboronic acid (211 mg, 1.55 mmol) and *amide* ***318*** (50.0 mg, 0.388 mmol) were employed. The Fujiwara-Moritani reaction was carried out for 20 h. The crude material was purified by flash-column chromatography [silicon dioxide, 20% ethyl acetate in petrol] to afford *amide* ***330*** as a colourless oil (68.0 mg, 80%).

^{1}H NMR (*chloroform-d*, 500 MHz): δ = 7.40 (d, *J* = 8.0 Hz, 2 H, Ar$\underline{H}_{(m\text{-}CH_3)}$), 7.18 (d, *J* = 8.0 Hz, 2 H, Ar$\underline{H}_{(o\text{-}CH_3)}$), 6.56 (s, 1 H, *p*-Tolyl(CH_3)C=C$\underline{H}$), 3.70 (s, 3 H, OC$\underline{H}_3$), 3.26 (s, 3 H, NC$\underline{H}_3$), 2.52 (s, 3 H, *p*-Tolyl(C$\underline{H}_3$)C=CH), and 2.37 ppm (s, 3 H, ArC$\underline{H}_3$); **^{13}C NMR** (*chloroform-d*, 126 MHz): δ = 168.1, 152.2, 140.1, 138.7, 129.2, 126.2, 115.2, 61.6, 32.3, 21.2, and 17.9 ppm; **HRMS** (ESI^+) Calculated for $C_{13}H_{17}NO_2$. $[M+Na]^+$ requires 242.1151; found 242.1157 (Δ = −2.5 ppm); **FTIR** ν_{max} (thin film): 1647, 1618, 1367, 1177, 1102, 1017, 978, 913, 814, 732 cm^{-1}

Red arrows indicate a significant nOe enhancement as observed by a 2D NOESY correlation based NMR experiment

(E)-3-(4-Fluorophenyl)-N-methoxy-N-methylbut-2-enamide (331)



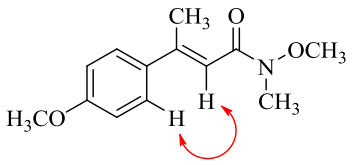
Using General Procedure G

Amide ***318*** (50.0 mg, 0.388 mmol) and 1-fluoro-4-iodobenzene (89.5 µL, 0.776 mmol) were employed. The reaction mixture was heated to 80 °C and stirred at this temperature for 15 h. The crude material was purified by flash-column chromatography [silicon dioxide, 20% to 30% ethyl acetate in petrol] to afford *amide* ***331*** as a colourless oil (60.4 mg, 70%).

^{1}H NMR (*chloroform-d*, 500 MHz): δ = 7.49−7.42 (m, 2 H, Ar*H*$_{(m\text{-}F)}$), 7.10−7.01 (m, 2 H, Ar*H*$_{(o\text{-}F)}$), 6.53 (s, 1 H, Ar(CH$_3$)C=C*H*), 3.71 (s, 3 H, OC*H*$_3$), 3.27 (s, 3 H, NC*H*$_3$), and 2.51 ppm (s, 3 H, Ar(C*H*$_3$)C=CH); **^{13}C NMR** (*chloroform-d*, 126 MHz): δ = 167.8, 163.0 (d, $^{1}J_{C-F}$ = 249 Hz), 151.1, 139.0, 128.0 (d, $^{3}J_{C-F}$ = 8 Hz), 115.9, 115.3 (d, $^{2}J_{C-F}$ = 21 Hz), 61.6, 32.3, and 18.1 ppm; **^{19}F NMR** (*chloroform-d*, 471 MHz): δ = −113.2 ppm (m, 1 F); **HRMS** (ESI$^+$) Calculated for $C_{12}H_{14}FNO_2$. $[M+Na]^+$ requires 246.0901; found 246.0905 (Δ = −1.6 ppm); **FTIR** ν_{max} (thin film): 1647, 1509, 1369, 1233, 1162, 1105, 979, 913, 831, 748, 743, and 680 cm^{-1}

Red arrows indicate a significant nOe enhancement as observed by a 2D NOESY correlation based NMR experiment

(E)-N-Methoxy-3-(4-methoxyphenyl)-N-methylbut-2-enamide (332)

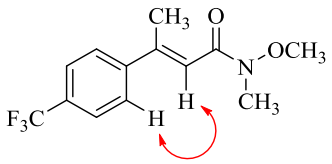


Using General Procedure G

Amide ***318*** (50.0 mg, 0.388 mmol) and 4-iodoanisole (183 mg, 0.776 mmol) were employed. The reaction mixture was heated to 80 °C and stirred at this temperature for 15 h. The crude material was purified by flash-column chromatography [silicon dioxide, 25% ethyl acetate in petrol] to afford *amide* ***332*** as a colourless oil (67.7 mg, 74%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.45 (d, *J* = 8.5 Hz, 2 H, Ar$\underline{H}_{(m\text{-}OCH_3)}$), 6.90 (d, *J* = 8.5 Hz, 2 H, Ar$\underline{H}_{(o\text{-}OCH_3)}$), 6.55 (s, 1 H, Ar($CH_3$)C=C$\underline{H}$), 3.81 (s, 3 H, ArOC$\underline{H}_3$), 3.72 (s, 3 H, OC$\underline{H}_3$), 3.26 (s, 3 H, NC$\underline{H}_3$), and 2.52 ppm (s, 3 H, Ar(C$\underline{H}_3$)C=CH); **^{13}C NMR** (*chloroform-d*, 126 MHz): δ = 168.2, 160.1, 151.8, 135.2, 127.6, 114.2, 113.8, 61.6, 55.3, 32.4, and 17.8 ppm; **HRMS** (ESI$^+$) Calculated for $C_{13}H_{17}NO_3$. $[M+Na]^+$ requires 258.1101; found 258.1111 (Δ = −3.9 ppm); **FTIR** ν_{max} (thin film): 1644, 1602, 1513, 1290, 1247, 1181, 1031, 979, 829, 807 and 679 cm^{-1}

(E)-N-Methoxy-N-methyl-3-(4-(trifluoromethyl)phenyl)but-2-enamide (333)



Procedure 1

Using General Procedure G

*Amide **318*** (50.0 mg, 0.388 mmol) and 4-(trifluoromethyl)iodobenzene (110 μL, 0.776 mmol) were employed. The reaction mixture was heated to 80 °C and stirred at this temperature for 15 h. The crude material was purified by flash-column chromatography [silicon dioxide, 20% to 30% ethyl acetate in petrol] to afford *amide **333*** as a colourless oil (71.0 mg, 67%).

Procedure 2

Using General Procedure H

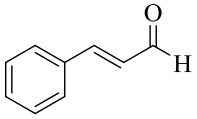
4-(Trifluoromethyl)phenylboronic acid (1.18 g, 6.20 mmol) and *amide **318*** (200 mg, 1.55 mmol) were employed. The Fujiwara-Moritani reaction was carried out for 20 h. The crude material was purified by flash-column chromatography [silicon dioxide, 40% ethyl acetate in petrol] to afford *amide **333*** as a colourless oil (330 mg, 78%).

^{1}H NMR (*chloroform-d*, 500 MHz): δ = 7.64 (d, *J* = 8.5 Hz, 2 H, Ar$\underline{H}_{(o\text{-}CF_3)}$), 7.57 (d, *J* = 8.5 Hz, 2 H, Ar$\underline{H}_{(m\text{-}CF_3)}$), 6.59 (s, 1 H, Ar($CH_3$)C=C$\underline{H}$), 3.72 (s, 3 H, OC$\underline{H}_3$), 3.28 (s, 3 H, NC$\underline{H}_3$), and 2.53 ppm (s, 3 H, Ar(C$\underline{H}_3$)C=CH); **^{13}C NMR** (*chloroform-d*, 126 MHz): δ = 167.5, 150.6, 146.5, 130.5 (q, $^{2}J_{C-F}$ = 33 Hz), 126.7, 125.5 (q, $^{3}J_{C-F}$ = 4 Hz), 124.0 (q, $^{1}J_{C-F}$ = 272 Hz), 117.9, 61.7, 32.3, and 18.0 ppm; **^{19}F NMR** (*chloroform-d*, 471 MHz): δ = −62.6 ppm (s, 3 F); **HRMS** (ESI$^+$)

Calculated for $C_{13}H_{14}F_3NO_2$. $[M+Na]^+$ requires 296.0869; found 296.0876 ($\Delta = -2.4$ ppm); **FTIR** ν_{max} (thin film): 1651, 1617, 1325, 1167, 1117, 1079, 1065, 1015, 980, 852, and 689 cm^{-1}

Red arrows indicate a significant nOe enhancement as observed by a 2D NOESY correlation based NMR experiment

Cinnamaldehyde (337)



Procedure 1

*Amide **309*** (100 mg, 0.524 mmol) was added *via* syringe to a 100 mL round-bottom flask sealed with a rubber septum and fitted with a magnetic follower. Tetrahydrofuran (25.0 mL, 0.021 M) was added *via* syringe and the reaction mixture was cooled to 0 °C. Lithium aluminium hydride (1.00 M in tetrahydrofuran) (1.04 mL, 1.04 mmol) was added drop-wise *via* syringe. The reaction mixture was stirred at this temperature for 1 h. On completion, the reaction mixture was warmed to room temperature. The reaction mixture was quenched with ammonium chloride (aq., sat.) and extracted with ethyl acetate (×3). The combined organic phases were washed with brine (sat.), dried over magnesium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 5% ethyl acetate in petrol] to afford *enal **337*** as a colourless oil (54.4 mg, 79%).

Procedure 2

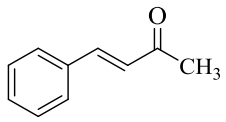
*Amide **309*** (100 mg, 0.524 mmol) was added *via* syringe to a 100 mL round-bottom flask sealed with a rubber septum and fitted with a magnetic follower. Tetrahydrofuran (25.0 mL, 0.021 M) was added *via* syringe and the reaction mixture was cooled to −15 °C. Diisobutylaluminium hydride (1.00 M in tetrahydrofuran) (2.62 mL, 2.62 mmol) was added drop-wise *via* syringe. The reaction mixture was stirred at this temperature for 3 h. On completion, the reaction mixture was warmed to room temperature. The reaction mixture was quenched with hydrochloric acid (aq., 1.00 M) and extracted with ethyl acetate (×3). The combined organic phases were washed with brine (sat.), dried over magnesium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by

flash-column chromatography [silicon dioxide, 5% ethyl acetate in petrol] to afford *enal **337*** as a colourless oil (49.8 mg, 72%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 9.71 (d, *J* = 7.5 Hz, 1 H, C*H*O), 7.59−7.53 (m, 2 H, Ar*H*$_{(o\text{-alkene})}$), 7.51−7.39 (m, 4 H, Ar*H*$_{(m\text{-alkene})}$, Ar*H*$_{(p\text{-alkene})}$ and PhC*H*=CH), and 6.72 ppm (dd, *J* = 15.5, 7.5 Hz, 1 H, PhCH=C*H*); **^{13}C NMR** (*chloroform-d*, 126 MHz): δ = 193.7, 152.8, 134.0, 131.3, 129.1, 128.6, and 128.5 ppm

*Spectroscopic data are consistent with a commercially available sample of enal **337** purchased from Sigma Aldrich*

(E)-4-Phenylbut-3-en-2-one (338)

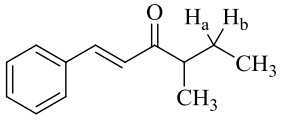


*Amide **309*** (100 mg, 0.524 mmol) was added *via* syringe to a 100 mL round-bottom flask sealed with a rubber septum and and fitted with a magnetic follower. Tetrahydrofuran (25.0 mL, 0.021 M) was added *via* syringe and the reaction mixture was cooled to 0 °C. Methyl magnesium bromide (3.00 M in diethyl ether) (0.53 mL, 1.56 mmol) was added drop-wise *via* syringe. The reaction mixture was warmed to room temperature and stirred at this temperature for 2 h. On completion, the reaction mixture was quenched with ammonium chloride (aq., sat.) and extracted with ethyl acetate (×3). The combined organic phases were washed with brine (sat.), dried over sodium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 10% ethyl acetate in petrol] to afford *enone **338*** as a colourless oil (75.0 mg, 98%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.60−7.48 (m, 3 H, Ar*H*$_{(o\text{-alkene})}$ and PhC*H*=CH), 7.42−7.36 (m, 3 H, Ar*H*$_{(m\text{-alkene})}$ and Ar*H*$_{(p\text{-alkene})}$), 6.72 (d, *J* = 16.0 Hz, 1 H, PhCH=C*H*), and 2.38 ppm (s, 3 H, COC*H*$_3$); **^{13}C NMR** (*chloroform-d*, 126 MHz): δ = 198.2, 143.4, 134.4, 130.5, 129.0, 128.3, 127.1, and 27.5 ppm; **MP** 38−40 °C (dichloromethane/petrol)

*Spectroscopic data are consistent with a commercially available sample of enone **338** purchased from Sigma Aldrich*

(E)-4-Methyl-1-phenylhex-1-en-3-one (339)

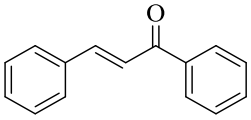


*Amide **309*** (100 mg, 0.524 mmol) was added *via* syringe to a 100 mL round-bottom flask sealed with a rubber septum and fitted with a magnetic follower. Tetrahydrofuran (25.0 mL, 0.021 M) was added *via* syringe and the reaction mixture was cooled to −40 °C. *sec*-Butyllithium (1.40 M in cyclohexane) (1.11 mL, 1.56 mmol) was added drop-wise *via* syringe. The reaction mixture was stirred at this temperature for 3 h. On completion, the reaction mixture was warmed to room temperature. The reaction mixture was quenched with ammonium chloride (aq., sat.) and extracted with ethyl acetate (×3). The combined organic phases were washed with brine (sat.), dried over magnesium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 5% ethyl acetate in petrol] to afford *enone **339*** as a colourless oil (70.9 mg, 72%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.64−7.56 (m, 3 H, Ar$\underline{H}_{(o\text{-alkene})}$ and PhC$\underline{H}$=CH), 7.44−7.32 (m, 3 H, Ar$\underline{H}_{(m\text{-alkene})}$ and Ar$\underline{H}_{(p\text{-alkene})}$), 6.81 (d, J = 15.5 Hz, 1 H, PhCH=C$\underline{H}$), 2.78 (sxt, J = 7.0 Hz, 1 H, COC$\underline{H}$(CH_3)$CH_aH_bCH_3$), 1.78 (dquin, J = 14.0, 7.0 Hz, 1 H, COCH(CH_3)C$\underline{H_a}H_bCH_3$), 1.49 (dquin, J = 14.0, 7.0 Hz, 1 H, COCH(CH_3)$CH_a\underline{H_b}CH_3$), 1.17 (d, J = 7.0 Hz, 3 H, COCH(C$\underline{H_3}$)$CH_aH_bCH_3$), and 0.92 ppm (t, J = 7.0 Hz, 3 H, COCH(CH_3)$CH_aH_bC\underline{H_3}$); **^{13}C NMR** (*chloroform-d*, 126 MHz): δ = 203.8, 142.4, 134.7, 130.4, 128.9, 128.3, 125.0, 46.3, 26.3, 16.2, and 11.8 ppm

*Spectroscopic data are consistent with those reported in the literature for enone **339***

(E)-Chalcone (340)

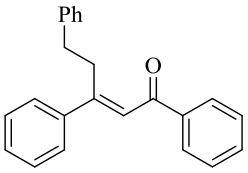


Amide ***309*** (100 mg, 0.524 mmol) was added *via* syringe to a 100 mL round-bottom flask sealed with a rubber septum and fitted with a magnetic follower. Tetrahydrofuran (25.0 mL, 0.021 M) was added *via* syringe and the reaction mixture was cooled to −40 °C. Phenyl magnesium bromide (3.00 M in diethyl ether) (0.530 mL, 1.56 mmol) was added drop-wise *via* syringe. The reaction mixture was stirred at this temperature for 2 h. On completion, the reaction mixture was warmed to room temperature. The reaction mixture was quenched with ammonium chloride (aq., sat.) and extracted with ethyl acetate (×3). The combined organic phases were washed with brine (sat.), dried over sodium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 10% ethyl acetate in petrol] to afford *enone* ***340*** as a colourless oil (88.3 mg, 81%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 8.05−7.98 (m, 2 H, Ar$\underline{H}_{(o\text{-alkene})}$), 7.80 (d, *J* = 15.5 Hz, 1 H, PhC$\underline{H}$=CH), 7.66−7.45 (m, 6 H, Ar$\underline{H}$ and PhCH=C$\underline{H}$), and 7.42−7.36 ppm (m, 3 H, Ar$\underline{H}$); **^{13}C NMR** (*chloroform-d*, 126 MHz): δ = 190.5, 144.9, 138.2, 134.9, 132.8, 130.6, 129.0, 128.7, 128.6, 128.5, and 122.1 ppm; **MP** 56−58 °C (dichloromethane/petrol)

Spectroscopic data are consistent with a commercially available sample of enone ***340*** *purchased from Sigma Aldrich*

(E)-1,3,5-Triphenylpent-2-en-1-one (341)

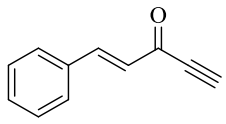


Amide ***321*** (50.0 mg, 0.172 mmol) was added *via* syringe to a 25 mL round-bottom flask sealed with a rubber septum and fitted with a magnetic follower. Tetrahydrofuran (1.72 mL, 0.100 M) was added *via* syringe and the reaction mixture was cooled to 0 °C. Phenyl magnesium bromide (3.00 M

in diethyl ether) (0.172 mL, 0.516 mmol) was added drop-wise *via* syringe. The reaction mixture was warmed to room temperature and stirred at this temperature for 1 h. On completion, the reaction mixture was quenched with ammonium chloride (aq., sat.) and extracted with ethyl acetate (×3). The combined organic phases were washed with brine (sat.), dried over sodium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 50% dichloromethane in petrol] to afford *enone* ***341*** as a colourless oil (42.2 mg, 80%).

^{1}H NMR (*chloroform-d*, 300 MHz): δ = 8.05−7.88 (m, 2 H, Ar$\underline{H}_{(o\text{-alkene})}$), 7.66−7.37 (m, 8 H, Ar$\underline{H}$), 7.30−7.24 (m, 5 H, Ar$\underline{H}$), 7.10 (s, 1 H, Ph(Ph($CH_2$)$_2$)C=C$\underline{H}$), 3.46−3.31 (m, 2 H, PhCH_2C$\underline{H}_2$), and 2.89−2.74 ppm (m, 2 H, PhC$\underline{H}_2$CH_2); **^{13}C NMR** (*chloroform-d*, 126 MHz): δ = 191.5, 158.8, 141.6, 141.5, 139.3, 132.5, 129.1, 128.7, 128.5 (2), 128.3 (2), 126.9, 125.9, 122.9, 35.1, and 34.0 ppm; **HRMS** (ESI^+) Calculated for $C_{23}H_{20}O$. $[M+Na]^+$ requires 335.1406; found 335.1407 (Δ = −0.30 ppm); **FTIR** ν_{max} (thin film): 1656, 1599, 1571, 1495, 1449, 1214, 913, 745, 729, 697, and 688 cm^{-1}

(E)-1-Phenylpent-1-en-4-yn-3-one (342)

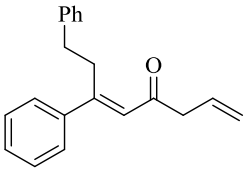


Amide ***309*** (100 mg, 0.524 mmol) was added *via* syringe to a 100 mL round-bottom flask sealed with a rubber septum and fitted with a magnetic follower. Tetrahydrofuran (25.0 mL, 0.021 M) was added *via* syringe and the reaction mixture was cooled to 0 °C. Ethynyl magnesium bromide (0.500 M in tetrahydrofuran) (3.12 mL, 1.56 mmol) was added drop-wise *via* syringe. The reaction mixture was heated to 40 °C for 4 h. On completion, the reaction mixture was cooled to room temperature. The reaction mixture was quenched with ammonium chloride (aq., sat.) and extracted with ethyl acetate (×3). The combined organic phases were washed with brine (sat.), dried over sodium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 10% ethyl acetate in petrol] to afford *enone* ***342*** as a white solid (57.2 mg, 70%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.89 (d, *J* = 16.0 Hz, 1 H, PhC*H*=CH), 7.65−7.53 (m, 2 H, Ar$H_{(o\text{-alkene})}$), 7.51−7.36 (m, 3 H, Ar$H_{(m\text{-alkene})}$ and Ar$H_{(p\text{-alkene})}$), 6.81 (d, *J* = 16.0 Hz, 1 H, PhCH=C*H*), and 3.33 ppm (s, 1 H, C≡C*H*); **^{13}C NMR** (*chloroform-d*, 126 MHz): δ = 177.6, 149.7, 133.9, 131.4, 129.1, 128.8, 128.0, 80.0, and 79.3 ppm; **MP** 50−52 °C (dichloromethane/petrol)

*Spectroscopic data are consistent with those reported in the literature for enone **342***[213]

(E)-6,8-Diphenylocta-1,5-dien-4-one (343)

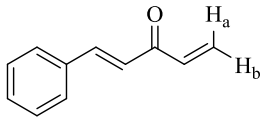


*Amide **321*** (50.0 mg, 0.172 mmol) was added *via* syringe to a 25 mL round-bottom flask sealed with a rubber septum and fitted with a magnetic follower. Tetrahydrofuran (1.72 mL, 0.100 M) was added *via* syringe and the reaction mixture was cooled to 0 °C. Allyl magnesium bromide (2.00 M in diethyl ether) (0.258 mL, 0.516 mmol) was added drop-wise *via* syringe. The reaction mixture was warmed to room temperature and stirred at this temperature for 2 h. On completion, the reaction mixture was quenched with ammonium chloride (aq., sat.) and extracted with ethyl acetate (×3). The combined organic phases were washed with brine (sat.), dried over sodium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 40% dichloromethane in petrol] to afford *enone **343*** as a colourless oil (35.4 mg, 76%).

^{1}H NMR (*chloroform-d*, 300 MHz): δ = 7.59−7.12 (m, 10 H, Ar*H*), 6.47 (s, 1 H, Ph(Ph$(CH_2)_2$)C=C*H*), 6.15−5.84 (m, 1 H, CH_2CH=CH_2), 5.51−5.07 (m, 2 H, CH_2CH=CH_2), 3.48−3.19 (m, 4 H, $PhCH_2CH_2$ and CH_2CH=CH_2), and 2.79−2.65 ppm (m, 2 H, $PhCH_2CH_2$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 198.2, 158.6, 141.6, 141.3, 131.1, 129.2, 128.7, 128.6, 128.3, 126.9, 125.9, 124.1, 118.9, 49.6, 35.1, and 33.7 ppm; **HRMS** (ESI^+) Calculated for $C_{20}H_{20}O$. $[M+Na]^+$ requires 299.1406; found 299.1405 (Δ = +0.38 ppm); **FTIR** ν_{max} (thin film): 1666, 1608, 1576, 1495, 1450, 1358, 1328, 1255, 1204, 1175, 974, 748, and 690 cm^{-1}

*NMR assignments for enone **343** were aided by COSY and HSQC based NMR experiments*

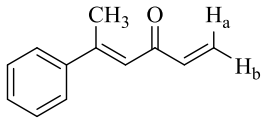
(E)-1-Phenylpenta-1,4-dien-3-one (344)



*Amide **309*** (100 mg, 0.524 mmol) was added *via* syringe to a 100 mL round-bottom flask sealed with a rubber septum and fitted with a magnetic follower. Tetrahydrofuran (25.0 mL, 0.021 M) was added *via* syringe and the reaction mixture was cooled to 0 °C. Vinyl magnesium bromide (1.00 M in diethyl ether) (1.04 mL, 1.04 mmol) was added drop-wise *via* syringe. The reaction mixture was warmed to room temperature and stirred at this temperature for 4 h. On completion, the reaction mixture was quenched with ammonium chloride (aq., sat.) and extracted with ethyl acetate (×3). The combined organic phases were washed with brine (sat.), dried over magnesium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 10% ethyl acetate in petrol] to afford *enone **344*** as a colourless oil (66.2 mg, 80%). **^{1}H NMR** (*chloroform-d*, 400 MHz): δ = 7.70 (d, *J* = 16.0 Hz, 1 H, PhC*H*=CH), 7.63−7.50 (m, 2 H, Ar$H_{(o\text{-alkene})}$), 7.49−7.36 (m, 3 H, Ar$H_{(m\text{-alkene})}$ and Ar$H_{(p\text{-alkene})}$), 7.02 (d, *J* = 15.5 Hz, 1 H, PhCH=C*H*), 6.72 (dd, *J* = 17.5, 11.0 Hz, 1 H, C*H*=CH_aH_b), 6.38 (dd, *J* = 17.5, 1.0 Hz, 1 H, CH=C$H_a$$H_b$), and 5.89 ppm (dd, *J* = 11.0, 1.0 Hz, 1 H, CH=$CH_a$$H_b$); **^{13}C NMR** (*chloroform-d*, 126 MHz): δ = 188.5, 142.9, 134.4, 133.6, 129.6, 127.9, 127.5, 127.4, and 123.1 ppm

*Spectroscopic data are consistent with those reported in the literature for enone **344***

(E)-5-Phenylhexa-1,4-dien-3-one (345)



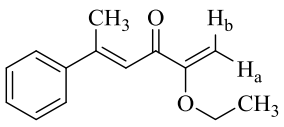
*Amide **329*** (75.0 mg, 0.366 mmol) was added *via* syringe to a 25 mL round-bottom flask sealed with a rubber septum and fitted with a magnetic follower. Tetrahydrofuran (3.70 mL, 0.099 M) was added *via* syringe and the reaction mixture was cooled to 0 °C. Vinyl magnesium bromide (1.00 M in diethyl ether) (1.10 mL, 1.10 mmol) was added drop-wise *via* syringe. The reaction mixture was warmed to room temperature and stirred at this temperature for 6 h. On completion, the reaction

mixture was quenched with ammonium chloride (aq., sat.) and extracted with ethyl acetate (×3). The combined organic phases were washed with brine (sat.), dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 15% ethyl acetate in petrol] to afford *enone* ***345*** as a colourless oil (46.0 mg, 73%).

Enone ***345*** *was contaminated with 10% inseparable impurities (by* ^{1}*H NMR analysis)*

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.55−7.48 (m, 2 H, Ar$\underline{H}_{(o\text{-alkene})}$), 7.42−7.36 (m, 3 H, Ar$\underline{H}_{(m\text{-alkene})}$ and Ar$\underline{H}_{(p\text{-alkene})}$), 6.70 (s, 1 H, Ph($CH_3$)C=C$\underline{H}$), 6.51 (dd, *J* = 17.5, 10.5 Hz, 1 H, C$\underline{H}$=CH_aH_b), 6.34−6.26 (d, *J* = 17.5 Hz, 1 H, CH=C$\underline{H}_a$$H_b$), 5.81 (dd, *J* = 10.5, 1.0 Hz, 1 H, CH=$CH_a$$\underline{H}_b$), and 2.58 ppm (d, *J* = 1.0 Hz, 3 H, Ph(C$\underline{H}_3$)C=CH); **^{13}C NMR** (*chloroform-d*, 126 MHz): δ = 190.8, 155.7, 142.7, 138.5, 129.2, 128.6, 127.6, 126.5, 122.7, and 18.8 ppm; **HRMS** (ESI^+) Calculated for $C_{12}H_{12}O$. $[M+Na]^+$ requires 195.0780; found 195.0781 (Δ = −0.51 ppm); **FTIR** ν_{max} (thin film): 1657, 1613, 1592, 1573, 1446, 1400, 1201, 1113, 960, 913, 748, and 693 cm^{-1}

(E)-2-Ethoxy-5-phenylhexa-1,4-dien-3-one (346)



Step 1

The synthesis of the organolithium reagent followed a reported literature procedure[214]

Ethyl vinyl ether (0.110 mL, 1.15 mmol) was added *via* syringe to a 50 mL round-bottom flask sealed with a rubber septum and fitted with a magnetic follower. Tetrahydrofuran (5.00 mL, 0.230 M) was added *via* syringe and the reaction mixture was cooled to −78 °C. *tert*-Butyllithium (1.70 M in pentane) (0.653 mL, 1.11 mmol) was added drop-wise *via* syringe. The reaction mixture was warmed to 0 °C and stirred at this temperature for 20 mins to afford the *organolithium* reagent.

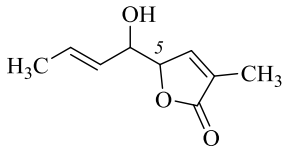
Step 2

Amide ***329*** (75.0 mg, 0.366 mmol) was added *via* syringe to a 50 mL round-bottom flask sealed with a rubber septum and fitted with a magnetic follower. Tetrahydrofuran (5.00 mL, 0.732 M) was added *via* syringe and the reaction mixture was cooled to −78 °C. The *organolithium* reagent was

added drop-wise *via* syringe. The reaction mixture was stirred at this temperature for 4 h. On completion, the reaction mixture was warmed to room temperature. The reaction mixture was quenched with ammonium chloride (aq., sat.) and extracted with diethyl ether (×3). The combined organic phases were dried over magnesium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 10% ethyl acetate in petrol] to afford *enone* ***346*** as a colourless oil (67.5 mg, 85%)

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.61−7.48 (m, 2 H, Ar*H*$_{(o\text{-alkene})}$), 7.46−7.34 (m, 3 H, Ar*H*$_{(m\text{-alkene})}$ and Ar*H*$_{(p\text{-alkene})}$), 7.06 (d, *J* = 1.5 Hz, 1 H, Ph(CH$_3$)C=C*H*), 5.24 (d, *J* = 2.5 Hz, 1 H, C=CH$_a$*H*$_b$), 4.50 (d, *J* = 2.5 Hz, 1 H, C=C*H*$_a$H$_b$), 3.85 (q, *J* = 7.0 Hz, 2 H, OC*H*$_2$CH$_3$), 2.57 (d, *J* = 1.5 Hz, 3 H, Ph(C*H*$_3$)C=CH), and 1.41 ppm (t, *J* = 7.0 Hz, 3 H, OCH$_2$C*H*$_3$); **^{13}C NMR** (*chloroform-d*, 126 MHz): δ = 187.6, 159.2, 156.2, 143.0, 129.1, 128.5, 126.6, 120.4, 91.1, 63.8, 18.9, and 14.4 ppm; **HRMS** (ESI$^+$) Calculated for $C_{14}H_{16}O_2$. $[M+H]^+$ requires 217.1223; found 217.1233 (Δ = −4.6 ppm); **FTIR** ν_{max} (thin film): 1673, 1593, 1573, 1446, 1378, 1295, 1257, 1099, 1059, 972, 885, 848, and 695 cm^{-1}

(E)-5-(1-Hydroxybut-2-en-1-yl)-3-methylfuran-2(5H)-one (421)



The synthesis of furanone ***421*** *was adapted from a reported literature procedure that was used for the preparation of related compounds*[191]

Furan ***423*** (200 mg, 1.18 mmol) was added *via* syringe to a 25 mL round-bottom flask sealed with a rubber septum and fitted with a magnetic follower. Dichloromethane (4.70 mL, 0.251 M) and crotonaldehyde (***422***) (82.7 mg, 1.18 mmol) were sequentially added *via* syringe. The reaction mixture was cooled to −78 °C. Boron trifluoride diethyl etherate (0.146 mL, 1.18 mmol) was added drop-wise *via* syringe. The reaction mixture was warmed to 0 °C and stirred at this temperature for 2 h. On completion, the reaction mixture was quenched with sodium bicarbonate (aq., sat.) and warmed to room temperature. The reaction mixture was extracted with dichloromethane (×3). The combined organic phases were dried over magnesium sulphate, filtered, and concentrated *in vacuo*.

The crude material was purified by flash-column chromatography [silicon dioxide, 10% to 20% diethyl ether in dichloromethane] to afford *furanone* ***421*** as a colourless oil and an inseparable 3:1 mixture (by ^{1}H NMR analysis) of diastereoisomers (117 mg, 59%).

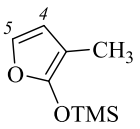
Data for both diastereoisomers are reported simultaneously

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.12−7.06 (m, 0.75 H, C*H*=CCH$_3$, major), 7.04−6.96 (m, 0.25 C*H*=CCH$_3$, minor), 5.92−5.80 (m, 1 H, CH=C*H*CH$_3$, major and minor), 5.55−5.46 (m, 1 H, C*H*=CHCH$_3$, major and minor), 4.88−4.80 (m, 1 H, C*H*^{5}, major and minor), 4.34 (t, *J* = 5.5 Hz, 0.75 H, C*H*OH, major), 4.09 (t, *J* = 7.0 Hz, 0.25 H, C*H*OH, minor), 1.96−1.91 (m, 4 H, CH=CC*H*$_3$ and CHO*H*, major and minor), and 1.74 ppm (d, *J* = 6.5 Hz, 3 H, C*H*$_3$CH, major and minor); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 174.2 (major), 173.9 (minor), 145.7 (minor), 145.5 (major), 131.6 (major), 131.5 (minor), 131.4 (minor), 130.5 (major), 127.7 (major), 127.6 (minor), 83.9 (minor), 83.5 (major), 73.9 (minor), 72.3 (major), 17.9 (major), and 10.8 ppm (2) (major and minor); **HRMS** (ESI^{+}) Calculated for $C_9H_{12}O_3$. $[M+Na]^{+}$ requires 191.0679; found 191.0675 (Δ = +2.1 ppm); **FTIR** ν_{max} (thin film): 3428, 2924, 1735, 1657, 1448, 1380, 1344, 1205, 1090, 1061, 996, 968, 928, 870, 791, 737, 668, and 611 cm^{-1}

Only 17 signals (signal overlap) observed in ^{13}C NMR (18 signals should be observed including major and minor diastereoisomers; minor (×1) missing)

NMR assignments for furanone ***421*** *were aided by COSY and HSQC based NMR experiments*

Trimethyl((3-methylfuran-2-yl)oxy)silane (423)



The synthesis of furan ***423*** *followed a reported literature procedure*[188]

Furanone ***427*** (4.20 g, 42.9 mmol) was added *via* syringe to a 250 mL round-bottom flask sealed with a rubber septum and fitted with a magnetic follower. Dichloromethane (85.0 mL, 0.505 M) was added directly from the activated alumina purification column. Triethylamine (7.15 mL, 51.4 mmol) was added *via* syringe. The reaction mixture was cooled to 0 °C. Trimethylsilyl trifluoromethanesulfonate (7.76 mL, 42.9 mmol) was added drop-wise *via* syringe. The reaction

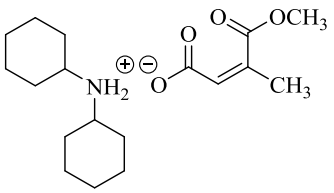
mixture stirred at this temperature for 1.5 h. The reaction mixture was warmed room temperature and stirred at this temperature for 1.5 h. On completion, the reaction mixture was diluted with pentane. The organic phase was washed with pH 7 buffer (potassium phosphate monobasic/potassium phosphate dibasic), copper (II) sulphate (×2), and brine (×2). The combined organic phases were dried over sodium sulphate, filtered, and concentrated *in vacuo* (water bath temperature did not exceed 20 °C, vacuum no lower than 150 mmHg). The crude material was purified by vacuum distillation [90 °C, 68 mmHg] to afford *furan* ***423*** as a colourless oil (5.13 g, 70%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 6.77 (d, *J* = 2.0 Hz, 1 H, Ar$\underline{H}^{5}$), 6.11 (d, *J* = 2.0 Hz, 1 H, Ar$\underline{H}^{4}$), 1.83 (s, 3 H, C$\underline{H}_3$), and 0.29 ppm (s, 9 H, Si(C$\underline{H}_3$)$_3$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 152.6, 131.2, 113.4, 92.2, 8.3, and 0.0 ppm

Spectroscopic data are consistent with those reported in the literature for furan ***423***[215]

NMR assignments for furan ***423*** *were aided by COSY and HSQC based NMR experiments*

Dicyclohexylammonium (Z)-4-methoxy-3-methyl-4-oxobut-2-enoate (425)



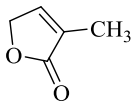
The synthesis of carboxylate salt ***425*** *followed a reported literature procedure*[189]

Citraconic anhydride (***424***) (75.0 g, 669 mmol) was added *via* syringe to a 2-necked 2000 mL round-bottom flask fitted with a magnetic follower, pressure-equalising dropping funnel, and sealed with a rubber septum. Methanol (670 mL, 1.00 M) was added directly from the activated alumina purification column. The reaction mixture was cooled to −15 °C. Dicyclohexylamine (147 mL, 735 mmol) was added drop-wise *via* pressure-equalising dropping funnel. The reaction mixture was warmed to room temperature and stirred at this temperature for 1 h. On completion, the reaction mixture was transferred to a 2000 mL round-bottom flask and concentrated *in vacuo* (water bath temperature did not exceed 25 °C) to afford *carboxylate salt* ***425*** as a colourless crystalline solid (170 g, 78%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 9.26 (br. s, 2 H, $^+$N$\underline{H}_2$Cy$_2$), 6.02 (d, *J* = 1.5 Hz, 1 H, C$\underline{H}$=COO$^-$), 3.68 (s, 3 H, OC$\underline{H}_3$), 2.94 (tt, *J* = 11.5, 3.5 Hz, 2 H, $^+$NH$_2$(C$\underline{H}$)$_2$), 2.08−1.95 (m, 4 H, C$\underline{H}$), 1.90 (d, *J* = 1.5 Hz, 3 H, C$\underline{H}_3$), 1.81−1.71 (m, 4 H, C$\underline{H}$), 1.65−1.56 (m, 2 H, C$\underline{H}$), 1.54−1.40 (m, 4 H, C$\underline{H}$), and 1.31−1.10 ppm (m, 6 H, C$\underline{H}$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 171.2, 169.9, 133.0, 132.7, 52.5, 51.4, 28.9, 25.1, 24.9, and 19.7 ppm; **HRMS** (ESI$^+$) Calculated for $C_{12}H_{24}N$. $[M]^+$ requires 182.1903; found 182.1902 (Δ = +0.55 ppm); **HRMS** (ESI$^-$) Calculated for $C_6H_7O_4$. $[M]^-$ requires 143.0350; found 143.0344 (Δ = +4.2 ppm); **FTIR** ν_{max} (thin film): 2931, 2857, 1727, 1656, 1618, 1559, 1447, 1390, 1330, 1210, 1120, 1065, 981, 951, 872, 773, 736, and 696 cm^{-1}; **MP** 121−123 °C (dichloromethane/petrol)

*Spectroscopic data are consistent with those reported in the literature for carboxylate salt **425***[189]

3-Methylfuran-2(5H)-one (427)



*The synthesis of furanone **427** followed a reported literature procedure*[189]

Step 1

*Carboxylate salt **425*** (50.0 g, 154 mmol) was added to a 2-necked 500 mL round-bottom flask fitted with a magnetic follower and a pressure-equalising dropping funnel. The round-bottom flask was sealed with a rubber septum. Dichloromethane (150 mL, 1.03 M) was added directly from the activated alumina purification column. The reaction mixture was cooled to −10 °C. Isobutyl chloroformate (22.1 mL, 169 mmol) was added drop-wise *via* pressure-equalising dropping funnel. The reaction mixture was stirred at this temperature for 1.5 h. Tetrahydrofuran (150 mL, 1.03 M) was added and the reaction mixture was left to stir for 10 mins. On completion, the reaction mixture was filtered (filtrate kept at 0 °C) to afford *carbonate **426***.

Step 2

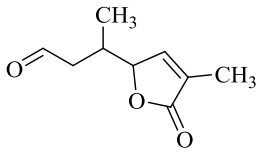
*Carbonate **426*** was added to a 2-necked 500 mL round-bottom flask fitted with a magnetic follower and a pressure-equalising dropping funnel. The round-bottom flask was sealed with a rubber septum. The reaction mixture was cooled to 0 °C. Sodium borohydride (11.7 g, 308 mmol) in water

(20.0 mL) was added drop-wise *via* pressure-equalising dropping funnel. The reaction mixture was stirred at this temperature for 1 h. On completion, the reaction mixture was filtered and the filtrate was concentrated *in vacuo* (water bath did not exceed 30 °C). Diisopropyl ether was added and the crude material was dried over magnesium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by vacuum distillation [82 °C, 1.5 mmHg] to afford *furanone **427*** as a colourless oil (10.2 g, 68% over two steps).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.21−7.06 (m, 1 H, C*H*=CCH$_3$), 4.77−4.64 (m, 2 H, C*H*$_2$O), and 1.93−1.79 ppm (m, 3 H, C*H*$_3$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 174.9, 145.3, 129.5, 70.1, and 10.6 ppm

*Spectroscopic data are consistent with those reported in the literature for furanone **427***[190]

3-(4-Methyl-5-oxo-2,5-dihydrofuran-2-yl)butanal (428)



*The synthesis of furanone **428** was adapted from a reported literature procedure that was used for the preparation of related compounds*[191]

*Furan **423*** (100 mg, 0.588 mmol) was added *via* syringe to a 25 mL round-bottom flask sealed with a rubber septum and fitted with a magnetic follower. Dichloromethane (2.40 mL, 0.245 M) and crotonaldehyde (***422***) (41.2 mg, 0.588 mmol) were sequentially added *via* syringe. The reaction mixture was cooled to −78 °C. Zinc bromide (132 mg, 0.588 mmol) was added in a single portion. The reaction mixture was stirred at this temperature for 2 h. On completion, the reaction mixture was quenched with sodium bicarbonate (aq., sat.) and warmed to room temperature. The reaction mixture was extracted with dichloromethane (×3). The combined organic phases were dried over magnesium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 40% ethyl acetate in petrol] to afford *furanone **428*** as a colourless oil and an inseparable 4:1 mixture (by ^{1}H NMR analysis) of diastereoisomers (43.6 mg, 45%).

*Furanone **428** was contaminated with 20% inseparable impurities (by ^{1}H NMR analysis)*

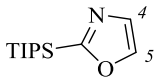
Data for both diastereoisomers are reported simultaneously

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 9.81−9.78 (m, 0.2 H, C*H*O, minor), 9.76−9.73 (m, 0.8 H, C*H*O, major), 7.08−7.03 (m, 0.8 H, C*H*=CCH$_3$, major), 6.98−7.01 (m, 0.2 H, C*H*=CCH$_3$, minor), 4.83−4.70 (m, 1 H, C*H*OCO, major and minor), 2.75−2.33 (m, 3 H, C*H*CH$_3$ and C*H*$_2$CHO, major and minor), 1.95−1.91 (m, 3 H, CH=CC*H*$_3$, major and minor), 1.14−1.07 (d, *J* = 7.0 Hz, 2.4 H, CHC*H*$_3$, major), and 0.91−0.87 ppm (d, *J* = 7.0 Hz, 0.6 H, CHC*H*$_3$, minor); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 200.7 (minor), 200.5 (major), 173.8 (major), 147.0 (major), 146.8 (minor), 131.1 (major), 84.0 (major), 83.1 (minor), 46.8 (minor), 45.7 (major), 31.5 (major), 30.2 (minor), 16.6 (major), 13.8, (minor), and 10.7 ppm (2) (major and minor); **HRMS** (ESI$^+$) Calculated for $C_9H_{12}O_3$. $[M+Na]^+$ requires 191.0679; found 191.0680 (Δ = −0.52 ppm); **FTIR** ν_{max} (thin film): 2974, 1778, 1747, 1457, 1409, 1382, 1298, 1187, 1141, 1100, 1036, 974, 927, 897, 828, 733, and 702 cm^{-1}

Only 16 signals (signal overlap) observed in ^{13}C NMR (18 signals should be observed including major and minor diastereoisomers; minor (×2) missing)

*NMR assignments for furanone **428** were aided by COSY and HSQC based NMR experiments*

2-(Triisopropylsilyl)oxazole (430)



*The synthesis of oxazole **430** followed a reported literature procedure*[193]

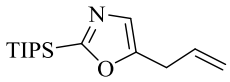
Oxazole (***429***) (1.00 g, 14.5 mmol) was added *via* syringe to a 100 mL round-bottom flask sealed with a rubber septum and fitted with a magnetic follower. Tetrahydrofuran (44.0 mL, 0.330 M) was added *via* syringe and the reaction mixture was cooled to −35 °C. *n*-Butyllithium (1.60 M in hexanes) (9.94 mL, 15.9 mmol) was added drop-wise *via* syringe. The reaction mixture was stirred at this temperature for 15 mins. The reaction mixture was warmed to −15 °C and triisopropylsilyl trifluoromethanesulfonate (4.29 mL, 15.9 mmol) was added drop-wise *via* syringe. The reaction mixture was warmed to room temperature and stirred at this temperature for 1.5 h. On completion, the reaction mixture was quenched with water and extracted with diethyl ether (×3). The combined organic phases were washed with brine (sat.), dried over magnesium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon

dioxide, 33% to 60% dichloromethane in petrol] to afford *oxazole* ***430*** as a colourless oil (3.10 g, 95%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.81 (s, 1 H, Ar$\underline{H}^{5}$), 7.20 (s, 1 H, Ar$\underline{H}^{4}$), 1.40 (spt, *J* = 7.5 Hz, 3 H, SiC$\underline{H}$(CH$_3$)$_2$), and 1.12 ppm (d, *J* = 7.5 Hz, 18 H, SiCH(C$\underline{H}_3$)$_2$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 168.6, 140.5, 126.6, 18.3, and 11.0 ppm

Spectroscopic data are consistent with those reported in the literature for oxazole ***430***[193]

5-Allyl-2-(triisopropylsilyl)oxazole (431)



Procedure 1

The synthesis of oxazole ***431*** *followed a reported literature procedure*[194]

Oxazole ***430*** (3.00 g, 13.3 mmol) was added *via* syringe to a 100 mL round-bottom flask sealed with a rubber septum and fitted with a magnetic follower. Tetrahydrofuran (44.0 mL, 0.302 M) was added directly from the activated alumina purification column and the reaction mixture was cooled to −35 °C. *n*-Butyllithium (1.60 M in hexanes) (9.13 mL, 14.6 mmol) was added drop-wise *via* syringe. The reaction mixture was stirred at this temperature for 15 mins. The reaction mixture was warmed to −15 °C and allyl bromide (filtered through potassium carbonate) (2.32 mL, 26.6 mmol) was added drop-wise *via* syringe. The reaction mixture was warmed to room temperature and stirred at this temperature for 1 h. On completion, the reaction mixture was quenched with water and extracted with diethyl ether (×3). The combined organic phases were washed with brine (sat.), dried over magnesium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 5% diethyl ether in petrol] to afford *oxazole* ***431*** as a colourless oil and an inseparable 4.0:1.0 mixture (by ^{1}H NMR analysis) of *oxazole* ***431***/*oxazole* ***430*** (3.02 g, 86%).

Mixtures of oxazole ***431****/oxazole* ***430*** *vary from 2.0:1.0 to 5.0:1.0 and have been employed in subsequent reactions as stated*

Procedure 2

The synthesis of oxazole ***431*** *was adapted from a procedure developed by a co-worker; this procedure was based upon optimisation of a reported literature procedure that was used for the preparation of related compounds*[216]

Step 1

Oxazole ***430*** (200 mg, 0.889 mmol) was added *via* syringe to a 10 mL round-bottom flask sealed with a rubber septum and fitted with a magnetic follower. Tetrahydrofuran (3.00 mL, 0.296 M) was added *via* syringe and the reaction mixture was cooled to −78 °C. *tert*-Butyllithium (1.70 M in pentane) (0.575 mL, 0.978 mmol) was added drop-wise *via* syringe. The reaction mixture was stirred at this temperature for 15 mins to afford the *organolithium* reagent.

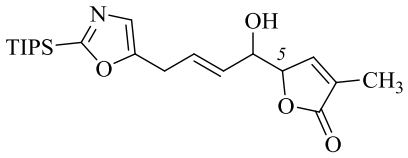
Step 2

Lithium chloride (41.5 mg, 0.978 mmol) and copper (I) cyanide (43.8 mg, 0.489 mmol) were added to a 25 mL round-bottom flask fitted with a magnetic follower. The round-bottom flask was sealed with a rubber septum. Tetrahydrofuran (3.00 mL, 0.296 M) was added *via* syringe and the reaction mixture was cooled to −78 °C. The reaction mixture was stirred at this temperature for 30 mins. The *organolithium* reagent was added drop-wise *via* syringe. The reaction mixture was stirred at this temperature for 30 min. Allyl bromide (filtered through potassium carbonate) (0.155 mL, 1.78 mmol) was added drop-wise *via* syringe. The reaction mixture was warmed to room temperature and stirred at this temperature for 1 h. On completion, the reaction mixture was quenched with water and extracted with diethyl ether (×3). The combined organic phases were washed with brine (sat.), dried over magnesium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 5% diethyl ether in petrol] to afford *oxazole* ***431*** as a colourless oil and an inseparable 18.0:1.0 mixture (by ^{1}H NMR analysis) of *oxazole* ***431***/*oxazole* ***430*** (144 mg, 61%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 6.84 (t, *J* = 1.0 Hz, 1 H, Ar*H*), 5.99−5.85 (m, 1 H, $CH_2C\underline{H}=CH_2$) 5.16−5.09 (m, 2 H, $CH_2CH=C\underline{H_2}$), 3.45 (dq, *J* = 6.5, 1.5 Hz, 2 H, $C\underline{H_2}CH=CH_2$), 1.36 (spt, *J* = 7.5 Hz, 3 H, $SiC\underline{H}(CH_3)_2$), and 1.12 ppm (d, *J* = 7.5 Hz, 18 H, $SiCH(C\underline{H_3})_2$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 167.8, 152.4, 132.9, 122.8, 117.4, 30.1, 18.4, and 11.0 ppm

*Spectroscopic data are consistent with those reported in the literature for oxazole **431***[194]

(E)-5-(1-Hydroxy-4-(2-(triisopropylsilyl)oxazol-5-yl)but-2-en-1-yl)-3-methylfuran-2(5H)-one (432)



*The synthesis of oxazole **432** was adapted from a reported literature procedure that was used for the preparation of related compounds*

Hoveyda-Grubbs 2nd generation catalyst (***132***)[111,112] (9.32 mg, 14.9 μmol) was added to a microwave vial fitted with a magnetic follower. The microwave vial was sealed with a crimped microwave lid with a septum. Dichloromethane (1.20 mL, 0.248 M), *furanone **421*** (3.5:1.0 diastereomeric ratio) (50.0 mg, 0.298 mmol), and *oxazole **431*** (4.0:1.0 *mixture of oxazole **431**/oxazole **430***) (158 mg (198 mg of mixture), 0.596 mmol) were sequentially added *via* syringe. The reaction mixture was heated to 40 °C and stirred at this temperature for 16 h. On completion, the reaction mixture was cooled to room temperature. The crude material was purified by flash-column chromatography [silicon dioxide, 30% to 50% ethyl acetate in petrol) to afford *oxazole **432*** as a brown oil and an inseparable 4.0:1.0 mixture (by ^{1}H NMR analysis) of diastereoisomers (42.0 mg, 36%).

Data for both diastereoisomers are reported simultaneously

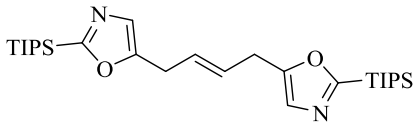
^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.09−7.06 (m, 0.8 H, C*H*=CCH$_3$, major), 7.03−6.99 (m, 0.2H, C*H*=CCH$_3$, minor), 6.84 (s, 1 H, Ar*H*, major and minor), 5.97−5.87 (m, 1 H, CH$_2$C*H*=CH, major and minor), 5.60 (dd, *J* = 15.5, 5.5 Hz, 1 H, CH$_2$CH=C*H*, major and minor), 4.88−4.80 (m, 1 H, C*H*^{5}, major and minor), 4.44−4.38 (m, 0.8 H, C*H*OH, major), 4.24−4.14 (m, 0.2 H, C*H*OH, minor), 3.50 (d, *J* = 6.5 Hz, 2 H, C*H*$_2$CH=CH, major and minor), 3.15 (br. s, 1 H, CHO*H*, major and minor), 1.94−1.91 (m, 3 H, CH=CC*H*$_3$, major and minor), 1.39 (spt, *J* = 7.5 Hz, 3 H, SiC*H*(CH$_3$)$_2$, major and minor), and 1.12 ppm (d, *J* = 7.5 Hz, 18 H, SiCH(C*H*$_3$)$_2$, major and minor); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 174.0 (major), 168.1 (major), 152.0 (major), 151.8 (minor), 145.3 (2) (major and minor), 131.7 (2) (major and minor), 130.0 (major), 129.9 (minor), 128.7 (major), 123.0 (2) (major and minor), 83.7 (minor), 83.2 (major), 73.3 (minor), 71.6 (major), 28.6 (major), 18.4

(major), 10.9 (major), and 10.8 ppm (major); **HRMS** (ESI^+) Calculated for $C_{21}H_{33}NO_4Si$. $[M+Na]^+$ requires 414.2071; found 414.2078 ($\Delta = -1.7$ ppm); **FTIR** ν_{max} (thin film): 3429, 2926, 2866, 1737, 1448, 1090, 1061, 968, 883, 792, 676, 648, and 610 cm^{-1}

Only 21 signals (signal overlap) observed in ^{13}C NMR (28 signals should be observed including major and minor diastereoisomers; minor (×7) missing)

*NMR assignments for oxazole **432** were aided by COSY and HSQC based NMR experiments*

(E)-1,4-Bis(2-(triisopropylsilyl)oxazol-5-yl)but-2-ene (433)



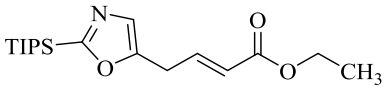
*Oxazole dimer **433** was isolated as a side-product from the synthesis of oxazole **432***

Hoveyda-Grubbs 2nd generation catalyst (***132***)[111,112] (9.32 mg, 14.9 μmol) was added to a microwave vial fitted with a magnetic follower. The microwave vial was sealed with a crimped microwave lid with a septum. Dichloromethane (1.20 mL, 0.248 M), *furanone **421*** (50.0 mg, 0.298 mmol), and *oxazole **431*** (4.0:1.0 *mixture of oxazole **431**/oxazole **430***) (158 mg (198 mg of mixture), 0.595 mmol) were sequentially added *via* syringe. The reaction mixture was heated to 40 °C and stirred at this temperature for 16 h. On completion, the reaction mixture was cooled to room temperature. The crude material was purified by flash-column chromatography [silicon dioxide, 30% to 50% ethyl acetate in petrol) to afford *oxazole dimer **433*** as a brown oil and as a 5:1 mixture (by ^1H NMR analysis) of geometric isomers (*E*:*Z*) (40.0 mg, 27%).

^1H NMR (*chloroform-d*, 400 MHz): δ = 6.86−6.79 (m, 2 H, Ar*H*), 5.80−5.63 (m, 2 H, C*H*CH_2), 3.59−3.39 (m, 4 H, CHC*H*$_2$), 1.49−1.27 (m, 6 H, SiC*H*$(CH_3)_2$), and 1.12 ppm (d, J = 6.5 Hz, 36 H, SiCH(C*H*$_3)_2$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 127.5, 122.7, 28.9, 18.4, and 11.0 ppm; **HRMS** (ESI^+) Calculated for $C_{28}H_{50}N_2O_2Si_2$. $[M+Na]^+$ requires 525.3303; found 525.3296 (Δ = +3.2 ppm); **FTIR** ν_{max} (thin film): 2944, 2868, 1643, 1593, 1465, 1385, 1073, 986, 919, 884, 825, 760, 676, and 657 cm^{-1}

Only 5 signals observed in ^{13}C NMR (7 signals should be observed, 167.8 ppm and 152.4 ppm obtained from ^{13}C NMR performed by a co-worker)

Ethyl (E)-4-(2-(triisopropylsilyl)oxazol-5-yl)but-2-enoate (435)

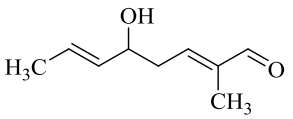


*The synthesis of oxazole **435** was adapted from a reported literature procedure that was used for the preparation of related compounds*[121]

Hoveyda-Grubbs 2nd generation catalyst (***132***)[111,112] (7.09 mg, 11.3 μmol) was added to a microwave vial fitted with a magnetic follower. The microwave vial was sealed with a crimped microwave lid with a septum. Dichloromethane (0.750 mL, 0.252 M), and ethyl acrylate (***306***) (31.7 mg, 0.377 mmol), and *oxazole **431*** (5.0:1.0 *mixture of oxazole **431**/oxazole **430*** (50.0 mg (60.0 mg of mixture), 0.189 mmol) were sequentially added *via* syringe. The reaction mixture was left at room temperature and stirred at this temperature for 15 h. On completion, the reaction mixture was concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide 10% ethyl acetate in petrol) to afford *oxazole **435*** as a brown oil (47.0 mg, 78%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 7.06−6.96 (m, 1 H, $CH_2C\underline{H}$=CH), 6.94−6.86 (d, 1 H, Ar$\underline{H}$), 5.87 (dd, *J* = 15.5, 1.0 Hz, 1 H, CH_2CH=C$\underline{H}$), 4.24−4.16 (m, 2 H, OC$\underline{H_2}CH_3$), 3.61 (d, *J* = 6.0 Hz, 2 H, C$\underline{H_2}$CH=CH), 1.46−1.33 (m, 3 H, Si C$\underline{H}(CH_3)_2$), 1.31−1.26 (m, 3 H, $OCH_2C\underline{H_3}$), and 1.13 ppm (d, *J* = 7.5 Hz, 18 H, SiCH(C$\underline{H_3}$)$_2$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 168.5, 166.1, 150.1, 142.4, 123.8, 123.7, 60.4, 28.4, 18.4, 14.2, and 11.0 ppm; **HRMS** (ESI^+) Calculated for $C_{18}H_{31}NO_3Si$. $[M+Na]^+$ requires 360.1965; found 360.1964 (Δ = +0.28 ppm); **FTIR** ν_{max} (thin film): 2945, 2868, 2361, 1723, 1658, 1465, 1368, 1270, 1178, 1042, 978, 921, 884, 827, and 657 cm^{-1}

(2E,6E)-5-Hydroxy-2-methylocta-2,6-dienal (439)

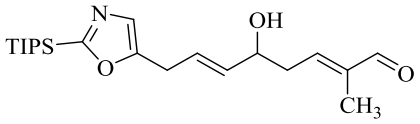


*The synthesis of enal **439** was adapted from a procedure developed by a co-worker; this procedure was based upon optimisation of a reported literature procedure that was used for the preparation of related compounds*[217]

Enol ether ***445*** (3.34 g, 21.4 mmol) was added *via* syringe to a 500 mL round-bottom flask sealed with a rubber septum and fitted with a magnetic follower. Dichloromethane (190 mL, 0.112 M) and diethyl ether (20.0 mL, 1.06 M) were added directly from the activated alumina purification columns. Crotonaldehyde (***422***) (1.00 g, 14.3 mmol) was added *via* syringe. The reaction mixture was cooled to −78 °C. Boron trifluoride diethyl etherate (4.40 mL, 35.7 mmol) was added drop-wise *via* syringe. The reaction mixture stirred at this temperature for 1.5 h. On completion, the reaction mixture was quenched with a 5.0:1.0:0.4 mixture of tetrahydrofuran, water and hydrochloric acid (aq., 1.00 M). The reaction mixture was warmed to room temperature. The reaction mixture was diluted with sodium bicarbonate (aq., sat.) and extracted with dichloromethane (×3). The combined organic phases were dried over sodium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 5% diethyl ether in dichloromethane] to afford *enal* ***439*** as a colourless oil (1.36 g, 63%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 9.40 (s, 1 H, C*H*O), 6.57 (td, *J* = 7.0, 1.5 Hz, 1 H, C*H*=C(CH$_3$)CHO), 5.80−5.65 (m, 1 H, CH$_3$C*H*=CH), 5.60−5.47 (m, 1 H, CH$_3$CH=C*H*), 4.26 (q, *J* = 6.5 Hz, 1 H, C*H*OH), 2.66−2.50 (m, 2 H, C*H*$_2$CHOH), 2.04 (br. s, 1 H, CHO*H*), and 1.77−1.67 ppm (m, 6 H, C*H*$_3$ ×2); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 195.3, 150.2, 140.8, 133.0, 128.0, 71.7, 36.7, 17.7, and 9.5 ppm; **HRMS** (ESI$^+$) Calculated for $C_9H_{14}O_2$. $[M+Na]^+$ requires 177.0886; found 177.0891 (Δ = −2.8 ppm); **FTIR** ν_{max} (thin film): 3420, 2919, 1683, 1643, 1406, 1034, and 967 cm^{-1}

(2E,6E)-5-Hydroxy-2-methyl-8-(2-(triisopropylsilyl)oxazol-5-yl)octa-2,6-dienal (440)



Procedure 1

The synthesis of oxazole ***440*** *was adapted from a procedure developed by a co-worker; this procedure was based upon optimisation of a reported literature procedure that was used for the preparation of related compounds*[121]

Hoveyda-Grubbs 2nd generation catalyst (***132***)[111,112] (13.5 mg, 21.5 μmol) was added to a microwave vial fitted with a magnetic follower. The microwave vial was sealed with a crimped microwave lid with a septum. Dichloromethane (0.230 mL, 1.56 M) and *enal* ***439*** (110 mg, 0.716 mmol) were sequentially added *via* syringe. *Oxazole* ***431*** (5.0:1.0 *mixture of oxazole* ***431****/oxazole* ***430***) (95.0 mg (114 mg of mixture), 0.358 mmol) was added over 3 h *via* syringe pump. The reaction mixture was left at room temperature and stirred at this temperature for 24 h. On completion, the reaction mixture was concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 20% to 30% ethyl acetate in petrol) to afford *oxazole* ***440*** as a brown oil (44.6 mg, 27%).

Procedure 2

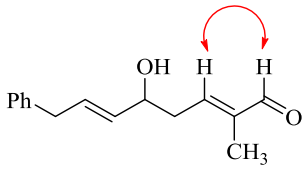
The synthesis of oxazole ***440*** *was adapted from a reported literature procedure used for the preparation of related compounds*[121]

Hoveyda-Grubbs 2nd generation catalyst (***132***)[111,112] (17.7 mg, 28.2 μmol) was added to a microwave vial fitted with a magnetic follower. The microwave vial was sealed with a crimped microwave lid with a septum. Dichloromethane (1.50 mL, 0.253 M), *enal* ***452*** (157 mg, 0.754 mmol), and *oxazole* ***431*** (18.0:1.0 *mixture of oxazole* ***431****/oxazole* ***430***) (100 mg (106 mg of mixture), 0.377 mmol) were sequentially added *via* syringe. The reaction mixture was heated to 40 ºC and stirred at this temperature for 19 h. On completion, the reaction mixture was concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 25% to 40% ethyl acetate in petrol) to afford *oxazole* ***440*** as a brown oil (47.0 mg, 33%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 9.42 (s, 1 H, C*H*O), 6.84 (s, 1 H, Ar*H*), 6.58 (td, *J* = 7.5, 1.0 Hz, 1 H, CH_2CH=CCH_3), 5.86 (dtd, *J* = 15.5, 6.5, 1.0 Hz, 1 H, CH_2CH=CH), 5.66 (ddt, *J* = 15.5, 6.5, 1.5 Hz, 1 H, CH_2CH=C*H*), 4.35 (d, *J* = 6.5 Hz, 1 H, C*H*OH), 3.47 (d, *J* = 6.5 Hz, 2 H, CH_2CH=CH), 2.63−2.57 (m, 2 H, CH_2CH=CCH_3), 2.02 (br. s, 1 H, CHO*H*), 1.76 (d, *J* = 1.0 Hz, 3 H, CH_2CH=CCH_3), 1.39 (spt, *J* = 7.5 Hz, 3 H, SiC*H*$(CH_3)_2$), and 1.13 ppm (d, *J* = 7.5 Hz, 18 H, SiCH$(CH_3)_2$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 195.0, 168.1, 152.0, 149.4, 141.1, 134.7, 126.9, 122.9, 71.2, 36.6, 28.5, 18.4, 11.0, and 9.5 ppm; **HRMS** (ESI^+) Calculated for $C_{21}H_{35}NO_3Si$.

$[M+Na]^+$ requires 400.2278; found 400.2285 ($\Delta = -1.7$ ppm); **FTIR** ν_{max} (thin film): 3386, 2945, 2868, 1687, 1465, 1261, 972, 883, and 657 cm^{-1}

(2E,6E)-5-Hydroxy-2-methyl-8-phenylocta-2,6-dienal (442)



Procedure 1

The synthesis of enal ***442*** *was adapted from a reported literature procedure that was used for the preparation of related compounds*[121]

Hoveyda-Grubbs 2nd generation catalyst (***132***)[111,112] (15.8 mg, 25.2 µmol) was added to a microwave vial fitted with a magnetic follower. The microwave vial was sealed with a crimped microwave lid with a septum. Dichloromethane (1.70 mL, 0.247 M), *enal* ***439*** (131 mg, 0.847 mmol), and allyl benzene (***441***) (50.0 mg, 0.424 mmol) were sequentially added *via* syringe. The reaction mixture was left at room temperature and stirred at this temperature for 48 h. On completion, the reaction mixture was concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 25% to 30% ethyl acetate in petrol) to afford *enal* ***442*** as a brown oil (31.2 mg, 32%).

Procedure 2

The synthesis of enal ***442*** *was adapted from a reported literature procedure that was used for the preparation of related compounds*[121]

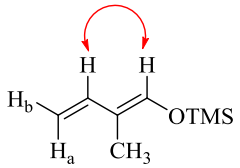
Hoveyda-Grubbs 2nd generation catalyst (***132***)[111,112] (17.9 mg, 28.6 µmol) was added to a microwave vial fitted with a magnetic follower. The microwave vial was sealed with a crimped microwave lid with a septum. Dichloromethane (1.50 mL, 0.254 M), *enal* ***452*** (158 mg, 0.762 mmol), and allyl benzene (***441***) (45.0 mg, 0.381 mmol) were sequentially added *via* syringe. The reaction mixture was left at room temperature and stirred at this temperature for 16 h. On completion, the reaction mixture was concentrated *in vacuo*. The crude material was purified by flash-column

chromatography [silicon dioxide, 30% ethyl acetate in petrol) to afford *enal* ***442*** as a brown oil (35.2 mg, 40%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 9.43 (s, 1 H, C*H*O), 7.43−7.14 (m, 5 H, Ar*H*), 6.59 (td, *J* = 7.0, 1.0 Hz, 1 H, CH_2CH=CCH_3), 5.98−5.85 (m, 1 H, CH_2CH=CH), 5.61 (dd, *J* = 15.5, 7.0 Hz, 1 H, CH_2CH=C*H*), 4.36 (q, *J* = 6.5 Hz, 1 H, C*H*OH), 3.41 (d, *J* = 7.0 Hz, 2 H, CH_2CH=CH), 2.67−2.61 (m, 2 H, CH_2CH=CCH_3), 1.91 (br. s, 1 H, CHO*H*), and 1.78 ppm (s, 3 H, CH_3); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 195.2, 149.9, 140.9, 139.6, 133.0, 131.7, 128.6, 128.5, 126.3, 71.5, 38.6, 36.7, and 9.5 ppm; **HRMS** (ESI^+) Calculated for $C_{15}H_{18}O_2$. $[M+Na]^+$ requires 253.1199; found 253.1198 (Δ = +0.40 ppm); **FTIR** ν_{max} (thin film): 3429, 3028, 1683, 1495, 1453, 1030, 973, 750, and 700 cm^{-1}

Red arrows indicate a significant nOe enhancement as observed by a 1D nOe based NMR experiment. This nOe based NMR experiment was performed by a co-worker.

(E)-Trimethyl((2-methylbuta-1,3-dien-1-yl)oxy)silane (445)



The synthesis of enol ether ***445*** *was adapted from a reported literature procedure*[218]

Tiglic aldehyde (***444***) (5.40 g, 64.2 mmol) was added *via* syringe to a 250 mL round-bottom flask sealed with a rubber septum and fitted with a magnetic follower. Dichloromethane (92.0 mL, 0.698 M) was added directly from the activated alumina purification column and the reaction mixture was cooled to 0 °C. Triethylamine (13.4 mL, 96.3 mmol) was added drop-wise *via* syringe. The reaction mixture was stirred at this temperature for 15 min. Trimethylsilyl trifluoromethanesulfonate (12.8 mL, 70.7 mmol) was added drop-wise *via* syringe. The reaction mixture was stirred at this temperature for 1 h. On completion, the reaction mixture was quenched with sodium bicarbonate (aq., sat.). The organic phase was washed with hydrochloric acid (aq., 1.00 M), and sodium bicarbonate (aq., sat.). The organic phase was dried over sodium sulphate, filtered, and concentrated *in vacuo*. The crude material (8.35 g total, 650 mg of crude material used

for reaction studies) was purified by vacuum distillation [60 °C, 11 mmHg] to afford *enol ether* ***445*** as a colourless oil (7.13 g, 71%).

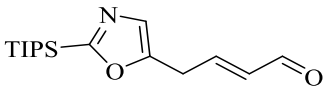
^{1}H NMR (*chloroform-d*, 400 MHz): δ = 6.41 (s, 1 H, C*H*OSi(C*H*$_3$)$_3$), 6.31 (dd, *J* = 17.0, 11.0 Hz, 1 H, C*H*=CH$_a$H$_b$), 5.01 (d, *J* = 17.0 Hz, 1 H, CH=C*H*$_a$H$_b$), 4.85 (dd, *J* = 11.0, 1.0 Hz, 1 H, CH=CH$_a$*H*$_b$), 1.73 (d, *J* = 1.0 Hz, 3 H, C*H*$_3$), and 0.22 ppm (s, 9 H, Si(C*H*$_3$)$_3$)

^{13}C NMR (*chloroform-d*, 101 MHz): δ = 141.7, 137.5, 119.4, 108.8, 9.2, and 0.0 ppm

Spectroscopic data are consistent with those reported in the literature for enol ether ***445***[218]

Red arrows indicate a significant nOe enhancement as observed by a 1D nOe based NMR experiment. This nOe based NMR experiment was performed by a co-worker.

(E)-4-(2-(Triisopropylsilyl)oxazol-5-yl)but-2-enal (446)

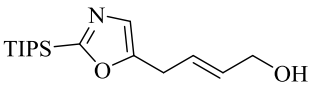


Dess-Martin periodinane (108 mg, 0.254 mmol) and sodium bicarbonate (35.6 mg, 0.424 mmol) were added to a 25 mL round-bottom flask fitted with a magnetic follower. The round-bottom flask was sealed with a rubber septum. Dichloromethane (1.70 mL, 0.100 M) was added *via* syringe and the reaction mixture was cooled to 0 °C. *Oxazole* ***448*** (50.0 mg, 0.169 mmol) was added *via* syringe. The reaction mixture was stirred at this temperature for 1 h. On completion, the reaction mixture was warmed to room temperature. The reaction mixture was quenched with sodium bicarbonate (aq., sat.) and extracted with ethyl acetate (×3). The combined organic phases were washed with brine (sat.), dried over sodium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 30% ethyl acetate in petrol] to afford *oxazole* ***446*** as a colourless oil (25.0 mg, 50%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 9.57 (d, *J* = 8.0 Hz, 1 H, CHO), 6.95 (t, *J* = 1.0 Hz, 1 H, Ar*H*), 6.89 (dt, *J* = 15.5, 6.5 Hz, 1 H, CH$_2$C*H*=CH), 6.15 (ddt, *J* = 15.5, 8.0, 1.5 Hz, 1 H, CH$_2$CH=C*H*), 3.75 (dq, *J* = 6.5, 1.0 Hz, 2 H, C*H*$_2$CH=CH), 1.48−1.29 (m, 3 H, SiC*H*(CH$_3$)$_2$), and 1.12 ppm (d, *J* = 7.0 Hz, 18 H, SiCH(C*H*$_3$)$_2$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 193.3, 168.9, 151.2, 149.4, 134.5, 123.8, 28.9, 18.3, and 10.9 ppm; **HRMS** (ESI$^+$) Calculated for $C_{16}H_{27}NO_2Si$.

$[M+Na]^+$ requires 316.1703; found 316.1702 (Δ = +0.32 ppm); **FTIR** ν_{max} (thin film): 2945, 2868, 1696, 1465, 1386, 1122, 976, 884, and 657 cm^{-1}

(E)-4-(2-(Triisopropylsilyl)oxazol-5-yl)but-2-en-1-ol (448)



Procedure 1

*The synthesis of oxazole **448** was adapted from a reported literature procedure that was used for the preparation of related compounds*[121]

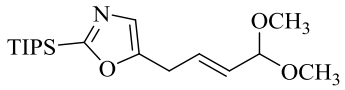
Hoveyda-Grubbs 2nd generation catalyst (***132***)[111,112] (88.8 mg, 0.142 mmol) was added to a microwave vial fitted with a magnetic follower. The microwave vial was sealed with a crimped microwave lid with a septum. Dichloromethane (7.60 mL, 0.249 M), and allyl alcohol (***447***) (328 mg, 5.66 mmol), and *oxazole **431*** (19.0:1.0 *mixture of oxazole **431**/oxazole **430***) (500 mg (526 mg of mixture), 1.89 mmol) were sequentially added *via* syringe. The reaction mixture was left at room temperature and stirred at this temperature for 15 h. On completion, the reaction mixture was concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide 30% ethyl acetate in petrol) to afford *oxazole **448*** as a brown oil (198 mg, 36%).

Procedure 2

*Oxazole **435*** (100 mg, 0.297 mmol) was added *via* syringe to a 25 mL round-bottom flask sealed with a rubber septum and fitted with a magnetic follower. Tetrahydrofuran (3.00 mL, 0.099 M) was added *via* syringe and the reaction mixture was cooled to −78 °C. Diisobutylaluminium hydride (1.00 M in tetrahydrofuran) (0.593 mL, 0.593 mmol) was added drop-wise *via* syringe. The reaction mixture was stirred at this temperature for 2 h. On completion, the reaction mixture was warmed to room temperature. The reaction mixture was quenched with hydrochloric acid (aq., 1.00 M) and extracted with ethyl acetate (×3). The combined organic phases were washed with brine (sat.), dried over sodium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 30% ethyl acetate in petrol] to afford *oxazole **448*** as a colourless oil (64.0 mg, 73%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 6.85−6.80 (m, 1 H, Ar*H*), 5.88−5.68 (m, 2 H, CH_2CH=C*H*), 4.19−4.10 (m, 2 H, CH_2OH), 3.46 (d, *J* = 6.0 Hz, 2 H, CH_2CH=CH), 1.92 (br. s, 1 H, CH_2OH), 1.38 (sxt, *J* = 7.5 Hz, 3 H, $SiCH(CH_3)_2$), and 1.12 ppm (d, *J* = 7.5 Hz, 18 H, $SiCH(CH_3)_2$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 167.9, 152.5, 132.2, 126.4, 122.7, 63.1, 28.6, 18.4, and 11.0 ppm; **HRMS** (ESI^+) Calculated for $C_{16}H_{29}NO_2Si$. $[M+H]^+$ requires 296.2040; found 296.2039 (Δ = +0.34 ppm); **FTIR** ν_{max} (thin film): 3332, 2944, 2867, 1697, 1465, 1386, 1074, 970, 921, 883, 825, 677, and 657 cm^{-1}

(E)-5-(4,4-Dimethoxybut-2-en-1-yl)-2-(triisopropylsilyl)oxazole (450)



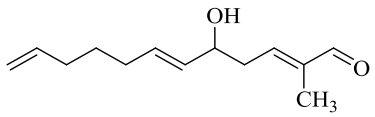
*The synthesis of oxazole **450** was adapted from a reported literature procedure that was used for the preparation of related compounds*[121]

Hoveyda-Grubbs 2nd generation catalyst (***132***)[111,112] (5.92 mg, 9.45 μmol) was added to a microwave vial fitted with a magnetic follower. The microwave vial was sealed with a crimped microwave lid with a septum. Dichloromethane (1.00 mL, 0.189 M), and acrolein dimethyl acetal (***449***) (96.5 mg, 0.945 mmol), and *oxazole **431*** (4.5:1.0 *mixture of oxazole **431**/oxazole **430***) (50.0 mg (61.1 mg of mixture), 0.189 mmol) were sequentially added *via* syringe. The reaction mixture was heated to 40 °C and stirred at this temperature for 22 h. On completion, the reaction mixture was cooled to room temperature and concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide (pH 7 buffered, potassium phosphate monobasic/potassium phosphate dibasic), 10% to 20% ethyl acetate in petrol) to afford *oxazole **450*** as a brown oil (46.0 mg, 72%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 6.86 (s, 1 H, Ar*H*), 5.95 (dtd, *J* = 15.5, 6.5, 1.0 Hz, 1 H, CH_2CH=CH), 5.57 (ddt, *J* = 15.5, 5.0, 1.5 Hz, 1 H, CH_2CH=C*H*), 4.78 (d, *J* = 5.0 Hz, 1 H, $CH(OCH_3)_2$), 3.49 (d, *J* = 6.5 Hz, 2 H, CH_2CH=CH), 3.31 (s, 6 H, OCH_3), 1.49−1.26 (m, 3 H, $SiCH(CH_3)_2$), and 1.14 ppm (d, *J* = 7.0 Hz, 18 H, $SiCH(CH_3)_2$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 168.0, 151.9, 129.6, 129.5, 123.0, 102.5, 52.7, 28.5, 18.4, and 11.0 ppm; **HRMS**

(ESI$^+$) Calculated for $C_{18}H_{33}NO_3Si$. $[M+H]^+$ requires 340.2302; found 340.2298 (Δ = +1.2 ppm); **FTIR** ν_{max} (thin film): 2945, 2868, 1697, 1465, 1367, 1193, 1129, 1057, 976, 921, 883, 827, 677, and 657 cm^{-1}

(2E,6E)-5-Hydroxy-2-methyldodeca-2,6,11-trienal (452)

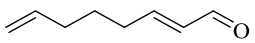


*The synthesis of enal **452** was adapted from a reported literature procedure*[217]

*Enol ether **445*** (200 mg, 1.28 mmol) was added *via* syringe to a 25 mL round-bottom flask sealed with a rubber septum and fitted with a magnetic follower. Dichloromethane (9.00 mL, 0.142 M) and diethyl ether (3.00 mL, 0.427 M) were sequentially added *via* syringe. *Enal **458*** (318 mg, 2.56 mmol) was added *via* syringe. The reaction mixture was cooled to −78 °C. Boron trifluoride diethyl etherate (0.396 mL, 3.21 mmol) was added drop-wise *via* syringe. The reaction mixture stirred at this temperature for 1.5 h. On completion, the reaction mixture was quenched with a 6.0:1.0 mixture of tetrahydrofuran and hydrochloric acid (aq., 1.00 M). The reaction mixture was warmed to room temperature. The reaction mixture was diluted with sodium bicarbonate (aq., sat.) and extracted with dichloromethane (×3). The combined organic phases were dried over sodium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 20% ethyl acetate in petrol] to afford *enal **452*** as a colourless oil (196 mg, 74%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 9.39 (s, 1 H, C$\underline{H}$O), 6.57 (td, *J* = 7.0, 1.5 Hz, 1 H, C$\underline{H}$=C(CH$_3$)CHO), 5.83−5.63 (m, 2 H, C$\underline{H}$=CHCHOH and CH$_2$=C$\underline{H}$), 5.50 (ddt, *J* = 15.5, 7.0, 1.5 Hz, 1 H, CH=C$\underline{H}$CHOH), 5.03−4.90 (m, 2 H, C$\underline{H}_2$=CH), 4.27 (q, *J* = 6.5 Hz, 1 H, C$\underline{H}$OH), 2.62−2.55 (m, 2 H, C$\underline{H}_2$CHOH), 2.42 (br. s, 1 H, CHO$\underline{H}$), 2.08−2.01 (m, 4 H, C$\underline{H}_2$CH$_2$C$\underline{H}_2$), 1.74 (s, 3 H, C$\underline{H}_3$), and 1.46 ppm (quin, *J* = 7.5 Hz, 2 H, CH$_2$C$\underline{H}_2$CH$_2$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 195.3, 150.2, 140.8, 138.4, 132.8, 132.0, 114.8, 71.7, 36.7, 33.1, 31.5, 28.2, and 9.5 ppm; **HRMS** (ESI$^+$) Calculated for $C_{13}H_{20}O_2$. $[M+Na]^+$ requires 231.1356; found 231.1358 (Δ = −0.87 ppm); **FTIR** ν_{max} (thin film): 3423, 2927, 1685, 1642, 1406, 970, and 961 cm^{-1}

(E)-Octa-2,7-dienal (458)



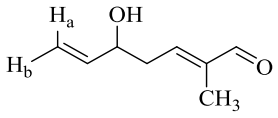
*The synthesis of enal **458** followed a reported literature procedure*[199]

Pyridinium chlorochromate (16.2 g, 75.0 mmol) and celite (50.0 g) were added to a 100 mL round-bottom flask fitted with a magnetic follower. The round-bottom flask was sealed with a rubber septum and dichloromethane (250.0 mL, 0.200 M) was added directly from the activated alumina purification column. (*E*)-2,7-Octadien-1-ol (***457***) (6.31 g, 50.0 mmol) was added *via* syringe. The reaction mixture was left at room temperature and stirred at this temperature for 2.5 h. On completion, the reaction mixture was filtered [silicon dioxide, 100% diethyl ether]. The fractions that contained *enal **458*** were combined and concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 20% ethyl acetate in petrol] to afford *enal **458*** as a colourless oil (4.62 g, 74%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 9.49 (d, *J* = 8.0 Hz, 1 H, C*H*O), 6.84 (dt, *J* = 15.5, 7.0 Hz, 1 H, C*H*=CHCHO), 6.11 (dd, *J* = 15.5, 8.0 Hz, 1 H, CH=C*H*CHO), 5.87−5.70 (m, 1 H, $CH_2C\underline{H}=CH_2$), 5.09−4.91 (m, 2 H, $CH_2CH=C\underline{H}_2$), 2.34 (q, *J* = 7.0 Hz, 2 H, $C\underline{H}_2CH=CHCHO$), 2.10 (q, *J* = 7.5 Hz, 2 H, $C\underline{H}_2CH=CH_2$), and 1.60 ppm (quin, *J* = 7.5 Hz, 2 H, $CH_2C\underline{H}_2CH_2$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 194.1, 158.5, 137.7, 133.1, 115.4, 33.0, 32.0, and 26.9 ppm

*Spectroscopic data are consistent with those reported in the literature for enal **458***[199]

(E)-5-Hydroxy-2-methylhepta-2,6-dienal (461)



*Enal **461** was isolated as a side-product in the synthesis of oxazole **440***

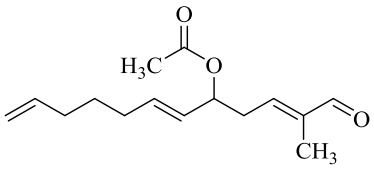
Hoveyda-Grubbs 2nd generation catalyst (***132***)[111,112] (5.32 mg, 8.49 μmol) was added to a microwave vial fitted with a magnetic follower. The microwave vial was sealed with a crimped microwave lid with a septum. Dichloromethane (0.450 mL, 0.251 M), and *enal **452*** (47.1 mg, 0.226 mmol), and *oxazole **431*** (18:1 *mixture of oxazole **431**/oxazole **430***) (30.0 mg (31.7 mg of mixture), 0.113 mmol)

were sequentially added *via* syringe. The reaction mixture was heated to 40 °C and stirred at this temperature for 19 h. On completion, the reaction mixture was cooled to room temperature and concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 25% ethyl acetate in petrol) to afford *enal* ***461*** as a brown oil (7.00 mg, 22%).

Enal ***461*** *was contaminated by inseparable grease-like impurities*

^{1}H NMR (*chloroform-d*, 500 MHz): δ = 9.45 (s, 1 H, C*H*O), 6.59 (td, *J* = 7.0, 1.5 Hz, 1 H, C*H*=C(CH$_3$)CHO), 5.93 (ddd, *J* = 17.0, 10.5, 6.0 Hz, 1 H, CH$_a$H$_b$=C*H*), 5.32 (dt, *J* = 17.5, 1.0 Hz, 1 H, C*H*$_a$H$_b$=CH), 5.21 (dt, *J* = 10.5, 1.0 Hz, 1 H, CH$_a$*H*$_b$=CH), 4.36 (q, *J* = 6.5 Hz, 1 H, C*H*OH), 2.63 (t, *J* = 6.5 Hz, 2 H, C*H*$_2$CHOH), and 1.78 ppm (s, 3 H, C*H*$_3$); **^{13}C NMR** (*chloroform-d*, 126 MHz): δ = 195.0, 149.3, 141.1, 139.8, 115.9, 71.8, 36.3, and 9.5 ppm; **HRMS** (ESI$^+$) Calculated for $C_8H_{12}NO_2$. $[M+Na]^+$ requires 163.0730; found 163.0726 (Δ = +2.5 ppm); **FTIR** ν_{max} (thin film): 3420, 2921, 2852, 1739, 1685, 1466, 1260, 1021, and 801 cm^{-1}

(2E,6E)-2-Methyl-1-oxododeca-2,6,11-trien-5-yl acetate (464)

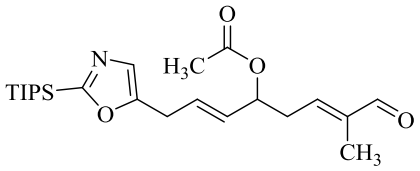


4-Dimethylaminopyridine (71.0 mg, 0.576 mmol) was added to a 50 mL round-bottom flask fitted with a magnetic follower. The round-bottom flask was sealed with a rubber septum. Dichloromethane (19.2 mL, 0.100 M), *enal* ***452*** (400 mg, 1.92 mmol), triethylamine (0.537 mL, 3.85 mmol), and acetic anhydride (0.363 mL, 3.85 mmol) were sequentially added *via* syringe. The reaction mixture was left at room temperature and stirred at this temperature for 16 h. On completion, the reaction mixture was concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 20% to 30% ethyl acetate in petrol) to afford *enal* ***464*** as a colourless oil (358 mg, 75%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 9.40 (s, 1 H, C*H*O), 6.44 (td, *J* = 7.0, 1.0 Hz, 1 H, C*H*=C(CH$_3$)CHO), 5.87−5.68 (m, 2 H, C*H*=CHCHOCO and CH$_2$=C*H*), 5.50−5.31 (m, 2 H, CH=C*H*CHOCO and C*H*OCO), 5.04−4.89 (m, 2 H, C*H*$_2$=CH), 2.77−2.58 (m, 2 H, C*H*$_2$CHOCO),

2.09−1.99 (m, 7 H, C<u>*H*</u>$_2$CH$_2$C<u>*H*</u>$_2$ and C<u>*H*</u>$_3$COO), 1.75 (d, *J* = 1.0 Hz, 3 H, CH=CC<u>*H*</u>$_3$), and 1.46 ppm (quin, *J* = 7.5 Hz, 2 H, CH$_2$C<u>*H*</u>$_2$CH$_2$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 194.9, 170.2, 148.3, 141.3, 138.3, 135.2, 127.3, 114.8, 73.0, 34.1, 33.1, 31.5, 28.0, 21.2, and 9.5 ppm; **HRMS** (ESI$^+$) Calculated for $C_{15}H_{22}O_3$. $[M+Na]^+$ requires 273.1461; found 273.1461 (Δ = 0.0 ppm); **FTIR** ν_{max} (thin film): 2929, 1738, 1688, 1642, 1371, 1233, 1020, 968, and 912 cm^{-1}

(2E,6E)-7-Methyl-8-oxo-1-(2-(triisopropylsilyl)oxazol-5-yl)octa-2,6-dien-4-yl acetate (465)



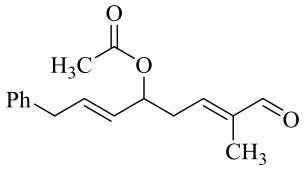
*The synthesis of oxazole **465** was adapted from a reported literature procedure that was used for the preparation of related compounds*[121]

Hoveyda-Grubbs 2nd generation catalyst (***132***)[111,112] (2.93 mg, 4.67 μmol) was added to a microwave vial fitted with a magnetic follower. The microwave vial was sealed with a crimped microwave lid with a septum. Dichloromethane (0.250 mL, 0.249 M), *enal **464*** (31.1 mg, 0.125 mmol), and *oxazole **431*** (18.0:1.0 *mixture of oxazole **431**/oxazole **430***) (16.5 mg (17.4 mg of mixture), 62.3 μmol) were sequentially added *via* syringe. The reaction mixture was left at room temperature and stirred at this temperature for 18 h. On completion, the reaction mixture was concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 30% ethyl acetate in petrol) to afford *oxazole **465*** as a brown oil (8.10 mg, 31%).

^{1}H NMR (*chloroform-d*, 400 MHz): δ = 9.41 (s, 1 H, C<u>*H*</u>O), 6.85 (s, 1 H, Ar<u>*H*</u>), 6.43 (td, *J* = 7.0, 1.5 Hz, 1 H, CH$_2$C<u>*H*</u>=CCH$_3$), 5.89 (dtd, *J* = 15.0, 6.5, 0.5 Hz, 1 H, CH$_2$C<u>*H*</u>=CH), 5.54 (ddt, *J* = 15.0, 7.0, 1.5 Hz, 1 H, CH$_2$CH=C<u>*H*</u>), 5.43 (q, *J* = 6.5 Hz, 1 H, C<u>*H*</u>OCO), 3.46 (d, *J* = 6.5 Hz, 2 H, C<u>*H*</u>$_2$CH=CH), 2.76−2.60 (m, 2 H, C<u>*H*</u>$_2$CH=CCH$_3$), 2.05 (s, 3 H, C<u>*H*</u>$_3$COO), 1.75 (s, 3 H, CH$_2$CH=CC<u>*H*</u>$_3$), 1.44−1.34 (m, 3 H, SiC<u>*H*</u>(CH$_3$)$_2$), and 1.13 ppm (d, *J* = 7.5 Hz, 18 H, SiCH(C<u>*H*</u>$_3$)$_2$); **^{13}C NMR** (*chloroform-d*, 101 MHz): δ = 194.7, 170.0, 168.1, 151.6, 147.6, 141.5, 130.0, 129.2, 123.2, 72.3, 33.9, 28.4, 21.1, 18.4, 11.0, and 9.5 ppm; **HRMS** (ESI$^+$) Calculated for $C_{23}H_{37}NO_4Si$.

$[M+Na]^+$ requires 442.2384; found 442.2387 ($\Delta = -0.67$ ppm); **FTIR** ν_{max} (thin film): 2943, 2866, 1738, 1687, 1464, 1371, 1232, 1020, 966, 883, 834, 676, and 648 cm^{-1}

(2E,6E)-7-Methyl-8-oxo-1-phenylocta-2,6-dien-4-yl acetate (466)



*The synthesis of enal **466** was adapted from a reported literature procedure that was used for the preparation of related compounds*[121]

Hoveyda-Grubbs 2nd generation catalyst (***132***)[111,112] (11.9 mg, 19.1 μmol) was added to a microwave vial fitted with a magnetic follower. The microwave vial was sealed with a crimped microwave lid with a septum. Dichloromethane (1.00 mL, 0.254 M), *enal **464*** (128 mg, 0.508 mmol), and allyl benzene (***441***) (30.0 mg, 0.254 mmol) were sequentially added *via* syringe. The reaction mixture was left at room temperature and stirred at this temperature for 16 h. On completion, the reaction mixture was concentrated *in vacuo*. The crude material was purified by flash-column chromatography [silicon dioxide, 30% ethyl acetate in petrol) to afford *enal **466*** as a brown oil (25.4 mg, 40%).

^{1}H NMR (*chloroform-d*, 400 MHz): $\delta = 9.40$ (s, 1 H, C*H*O), 7.34−7.12 (m, 5 H, Ar*H*), 6.44 (td, $J = 7.5$, 1.5 Hz, 1 H, CH_2CH=CCH_3), 6.00−5.88 (m, 1 H, CH_2CH=CH), 5.56−5.40 (m, 2 H, CH_2CH=C*H* and C*H*OCO), 3.39 (d, $J = 6.5$ Hz, 2 H, CH_2CH=CH), 2.80−2.62 (m, 2 H, CH_2CH=CCH_3), 2.07 (s, 3 H, CH_3COO), and 1.76 ppm (s, 3 H, CH_2CH=CCH_3); **^{13}C NMR** (*chloroform-d*, 101 MHz): $\delta = 194.8$, 170.1, 148.0, 141.4, 139.3, 133.6, 128.6, 128.5, 128.4, 126.3, 72.7, 38.5, 34.1, 21.2, and 9.5 ppm; **HRMS** (ESI^+) Calculated for $C_{17}H_{20}O_3$. $[M+Na]^+$ requires 295.1305; found 295.1299 ($\Delta = +2.0$ ppm); **FTIR** ν_{max} (thin film): 1737, 1688, 1495, 1371, 1232, 1020, 971, 750, and 700 cm^{-1}

Appendix 1

X-ray crystallography data

for pyridine 175

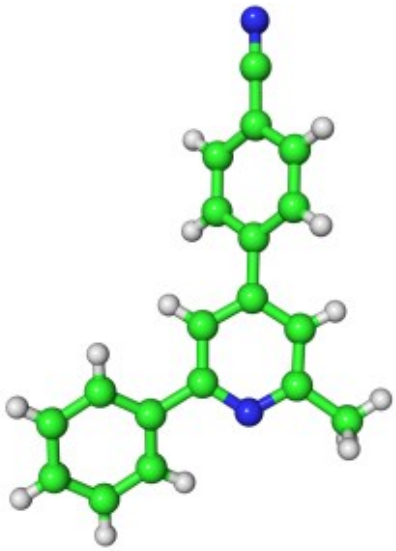


Figure A1.1** Crystal structure of pyridine **175

Single crystal diffraction data were collected at 150 K[204] using a Nonius Kappa CCD Diffractometer ($\lambda = 0.71073$Å). Data were reduced using DENZO/SCALEPACK.[205] The structure was solved with SuperFlip[206] and refined by full-matrix least squares on F^2 using CRYSTALS.[207] Non-hydrogen atoms were refined with anisotropic displacement parameters and hydrogen atoms were treated in the usual manner.[208] A summary of crystallographic data are given below (***Table A1.1***, ***Table A1.2***, and ***Table A1.3***), as well as full lists of fractional atomic coordinates and isotropic/equivalent isotropic displacement parameters (***Table A1.4***), atomic displacement parameters (***Table A1.5***), bond lengths (***Table A1.6***), and bond angles (***Table A1.7***).

Data collection	
Diffractometer	Nonius KappaCCD diffractometer
Absorption correction	Multi-scan *DENZO*/*SCALEPACK*
T_{min}, T_{max}	0.95, 1.00
No. of measured, independent and observed [I > 2.0σ(I)] reflections	11611, 3194, 2659
R_{int}	0.019
$(\sin\theta/\lambda)_{max}$ ($Å^{-1}$)	0.651

Table A1.1** Crystal data collection information for pyridine **175

Crystal data	
Chemical formula	$C_{19}H_{14}N_2$
M_r	270.33
Crystal system, space group	Triclinic, $P\bar{1}$
Temperature (K)	150
a, b, c (Å)	8.0582 (2), 9.9181 (3), 9.9557 (3)
α, β, γ (°)	62.2103 (15), 85.9715 (14), 87.9363 (12)
V (Å^3)	702.17 (4)
Z	2
Radiation type	Mo *K*α
μ (mm^{-1})	0.08
Crystal size (mm)	0.25 × 0.15 × 0.04

Table A1.2 *Crystal data for pyridine* ***175***

Refinement	
R[F^2 > 2σ(F^2)], wR(F^2), S	0.043, 0.122, 0.94
No. of reflections	3194
No. of parameters	190
Δρ$_{max}$, Δρ$_{min}$ (e Å^{-3})	0.29, −0.22

Table A1.3 *Crystal refinement details for pyridine* ***175***

Atom	*x* (Å^2)	*y* (Å^2)	*z* (Å^2)	U_{iso}*/U_{eq} (Å^2)
N1	1.16420 (13)	0.32468 (12)	0.49906 (11)	0.0259
C2	1.07467 (15)	0.19553 (14)	0.56561 (14)	0.0262
C3	0.93130 (16)	0.17766 (14)	0.50525 (14)	0.0274
C4	0.87867 (15)	0.29590 (14)	0.36964 (14)	0.0257
C5	0.97270 (15)	0.42915 (14)	0.30023 (14)	0.0263
C6	1.11339 (15)	0.43986 (13)	0.36854 (13)	0.0243
C7	1.21833 (15)	0.57958 (14)	0.30007 (13)	0.0253
C8	1.38238 (16)	0.57046 (15)	0.34038 (14)	0.0294
C9	1.48190 (17)	0.69979 (16)	0.28101 (15)	0.0335
C10	1.41749 (18)	0.84044 (15)	0.18101 (14)	0.0336
C11	1.25553 (18)	0.85043 (14)	0.13805 (14)	0.0318
C12	1.15666 (16)	0.72105 (14)	0.19616 (14)	0.0281
C13	0.72747 (15)	0.28122 (13)	0.30037 (14)	0.0252
C14	0.58540 (16)	0.20855 (15)	0.39149 (14)	0.0290
C15	0.44374 (16)	0.19637 (15)	0.32664 (15)	0.0297
C16	0.44302 (15)	0.25617 (14)	0.16914 (15)	0.0277
C17	0.58487 (16)	0.32661 (14)	0.07675 (14)	0.0285
C18	0.72594 (15)	0.33873 (14)	0.14286 (14)	0.0277
C19	0.29424 (17)	0.24823 (15)	0.10084 (16)	0.0335
N20	0.17500 (17)	0.24367 (16)	0.04588 (16)	0.0461
C21	1.13939 (17)	0.06978 (15)	0.70888 (15)	0.0333
H31	0.8702	0.0836	0.5567	0.0330*
H51	0.9377	0.5136	0.2061	0.0315*
H81	1.4263	0.4741	0.4081	0.0345*
H91	1.5944	0.6919	0.3099	0.0399*
H101	1.4841	0.9308	0.1401	0.0406*
H111	1.2114	0.9464	0.0683	0.0385*
H121	1.0457	0.7310	0.1653	0.0332*
H141	0.5862	0.1682	0.4986	0.0354*
H151	0.3464	0.1488	0.3912	0.0369*
H171	0.5862	0.3657	−0.0308	0.0341*
H181	0.8233	0.3852	0.0789	0.0353*
H212	1.0627	−0.0156	0.7581	0.0502*
H211	1.1558	0.1078	0.7819	0.0498*
H213	1.2466	0.0315	0.6883	0.0509*

Table A1.4 *Fractional atomic coordinates and isotropic/equivalent isotropic displacement parameters*

Atom	U^{11}(Å^2)	U^{22}(Å^2)	U^{33}(Å^2)	U^{12}(Å^2)	U^{13}(Å^2)	U^{23}(Å^2)
N1	0.0268 (5)	0.0249 (5)	0.0244 (5)	−0.0005 (4)	−0.0016 (4)	−0.0102 (4)
C2	0.0272 (6)	0.0242 (6)	0.0257 (6)	0.0004 (4)	−0.0001 (4)	−0.0106 (5)
C3	0.0298 (6)	0.0241 (6)	0.0269 (6)	−0.0031 (4)	0.0001 (5)	−0.0108 (5)
C4	0.0268 (6)	0.0268 (6)	0.0255 (6)	−0.0021 (4)	−0.0011 (4)	−0.0137 (5)
C5	0.0299 (6)	0.0238 (6)	0.0241 (6)	−0.0004 (4)	−0.0040 (4)	−0.0099 (5)
C6	0.0266 (6)	0.0231 (5)	0.0226 (5)	−0.0012 (4)	−0.0014 (4)	−0.0101 (4)
C7	0.0296 (6)	0.0250 (6)	0.0217 (5)	−0.0034 (5)	−0.0020 (4)	−0.0108 (5)
C8	0.0324 (6)	0.0283 (6)	0.0242 (6)	−0.0035 (5)	−0.0073 (5)	−0.0084 (5)
C9	0.0343 (7)	0.0358 (7)	0.0271 (6)	−0.0097 (5)	−0.0065 (5)	−0.0107 (5)
C10	0.0437 (7)	0.0299 (6)	0.0247 (6)	−0.0126 (5)	−0.0012 (5)	−0.0098 (5)
C11	0.0420 (7)	0.0236 (6)	0.0264 (6)	−0.0020 (5)	−0.0041 (5)	−0.0083 (5)
C12	0.0316 (6)	0.0258 (6)	0.0254 (6)	−0.0003 (5)	−0.0037 (5)	−0.0103 (5)
C13	0.0276 (6)	0.0227 (5)	0.0269 (6)	−0.0013 (4)	−0.0025 (4)	−0.0126 (5)
C14	0.0309 (6)	0.0298 (6)	0.0262 (6)	−0.0033 (5)	0.0013 (5)	−0.0130 (5)
C15	0.0270 (6)	0.0290 (6)	0.0322 (6)	−0.0037 (5)	0.0026 (5)	−0.0138 (5)
C16	0.0270 (6)	0.0248 (6)	0.0337 (6)	−0.0012 (4)	−0.0041 (5)	−0.0154 (5)
C17	0.0310 (6)	0.0291 (6)	0.0266 (6)	−0.0032 (5)	−0.0022 (5)	−0.0138 (5)
C18	0.0280 (6)	0.0289 (6)	0.0269 (6)	−0.0048 (5)	0.0002 (5)	−0.0134 (5)
C19	0.0318 (7)	0.0294 (6)	0.0374 (7)	−0.0021 (5)	−0.0052 (5)	−0.0134 (5)
N20	0.0380 (7)	0.0408 (7)	0.0528 (8)	−0.0066 (5)	−0.0134 (6)	−0.0143 (6)
C21	0.0335 (7)	0.0271 (6)	0.0306 (6)	0.0005 (5)	−0.0037 (5)	−0.0060 (5)

Table A1.5 *Atomic displacement parameters*

Bond	*Length (Å²)*	*Bond*	*Length (Å²)*
N1–C2	1.3447 (15)	*C11–C12*	1.3902 (17)
N1–C6	1.3483 (15)	*C11–H111*	0.953
C2–C3	1.3925 (17)	*C12–H121*	0.953
C2–C21	1.5035 (17)	*C13–C14*	1.3989 (17)
C3–C4	1.3951 (17)	*C13–C18*	1.3974 (17)
C3–H31	0.963	*C14–C15*	1.3859 (18)
C4–C5	1.3947 (17)	*C14–H141*	0.949
C4–C13	1.4852 (16)	*C15–C16*	1.3944 (18)
C5–C6	1.3941 (16)	*C15–H151*	0.962
C5–H51	0.974	*C16–C17*	1.3969 (17)
C6–C7	1.4908 (16)	*C16–C19*	1.4412 (18)
C7–C8	1.3960 (17)	*C17–C18*	1.3888 (17)
C7–C12	1.3981 (17)	*C17–H171*	0.953
C8–C9	1.3923 (17)	*C18–H181*	0.957
C8–H81	0.950	*C19–N20*	1.1510 (19)
C9–C10	1.390 (2)	*C21–H212*	0.973
C9–H91	0.959	*C21–H211*	0.979
C10–C11	1.388 (2)	*C21–H213*	0.978
C10–H101	0.960		

Table A1.6 *Bond lengths*

Bond	*Angle (°)*	*Bond*	*Angle (°)*
C2–N1–C6	118.46 (11)	*C12–C11–H111*	119.6
N1–C2–C3	122.32 (11)	*C7–C12–C11*	120.46 (12)
N1–C2–C21	116.10 (11)	*C7–C12–H121*	120.8
C3–C2–C21	121.57 (11)	*C11–C12–H121*	118.8
C2–C3–C4	119.54 (11)	*C4–C13–C14*	120.67 (11)
C2–C3–H31	119.8	*C4–C13–C18*	120.28 (11)
C4–C3–H31	120.6	*C14–C13–C18*	119.05 (11)
C3–C4–C5	117.96 (11)	*C13–C14–C15*	120.63 (12)
C3–C4–C13	121.37 (11)	*C13–C14–H141*	119.4
C5–C4–C13	120.67 (11)	*C15–C14–H141*	119.9
C4–C5–C6	119.32 (11)	*C14–C15–C16*	119.74 (11)
C4–C5–H51	119.4	*C14–C15–H151*	119.2
C6–C5–H51	121.2	*C16–C15–H151*	121.0
C5–C6–N1	122.38 (11)	*C15–C16–C17*	120.33 (12)
C5–C6–C7	121.76 (11)	*C15–C16–C19*	119.93 (12)
N1–C6–C7	115.86 (10)	*C17–C16–C19*	119.72 (12)
C6–C7–C8	119.69 (11)	*C16–C17–C18*	119.45 (12)
C6–C7–C12	121.70 (11)	*C16–C17–H171*	120.8
C8–C7–C12	118.61 (11)	*C18–C17–H171*	119.7
C7–C8–C9	120.90 (12)	*C13–C18–C17*	120.77 (11)
C7–C8–H81	119.1	*C13–C18–H181*	120.3
C9–C8–H81	120.0	*C17–C18–H181*	118.9
C8–C9–C10	119.86 (12)	*C16–C19–N20*	179.18 (15)
C8–C9–H91	120.0	*C2–C21–H212*	112.2
C10–C9–H91	120.1	*C2–C21–H211*	110.0
C9–C10–C11	119.74 (12)	*H212–C21–H211*	107.4
C9–C10–H101	120.8	*C2–C21–H213*	111.2
C11–C10–H101	119.4	*H212–C21–H213*	108.2
C10–C11–C12	120.40 (12)	*H211–C21–H213*	107.6
C10–C11–H111	120.0		

Table A1.7 *Bond angles*

Appendix 2

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