# Towards Enantioselective Rhodium-Catalysed Addition of Alkenylboron Species to Azinium Salts

University of Nottingham

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Thesis submitted in accordance with the requirement of the University of Nottingham for the degree of Chemistry (MRes)

By

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Supervisor: Professor Hon Wai Lam

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## Declaration

I hereby declare that, except for where specific reference is made to other sources, the work contained within this thesis is the original work of my own research since the registration of my MRes degree in October 2019, and any collaboration is clearly indicated. This thesis has been composed by myself and has not been submitted, in whole or part, for any other degree diploma or other qualification. I confirm that the work submitted is my own except work which has formed part of jointly-authored publications. The contributions of myself and other authors to this work have been specifically indicated where relevant. I confirm that appropriate credit has been given within the thesis where references have been made to the work of others.

## Acknowledgements

Firstly, I would like to thank my supervisor Professor Hon Wai Lam for giving me the opportunity to work in the Lam group for the last year. His feedback and guidance has been extremely useful and greatly appreciated.

Secondly, I would like to thank Simone Gillbard, Luke O'Brien, Shivanee Borpatra Gohain and Dr. Alistair Groves for their supervision over the year. I really appreciate the help and guidance you have all given to me.

Finally, I would like to thank my family and friends for all the support they have provided over the year.

**Contents**

**Abbreviations**

| | |
|---|---|
| Acac | acetylacetonate |
| Ar | aryl |
| BCat | boronic acid catechol ester |
| Boc | di-*tert*-butyl carbonate |
| BPin | boronic acid pinacol ester |
| $B_2Pin_2$ | bis(pinacolato)diboron |
| cod | cyclooctadiene |
| Cy | tricyclohexylphosphine |
| d | doublet |
| DCE | dichloroethane |
| dd | doublet of doublets |
| DMA | *N*,*N*-dimethylacetamide |
| DME | dimethoxyethane |
| *ee* | enantiomeric excess |
| equiv | equivalents |
| ESI | electrospray ionisation |
| EWG | electron withdrawing group |
| HBCat | catecholborane |
| HPLC | high performance liquid chromatography |
| HRMS | high resolution mass spectrometry |
| *i* | ipso |
| IR | infrared |
| m | multiplet |
| MIDA | *N*-methyliminodiacetic acid |
| mmol | millimol |
| MeO-mop | 2-(diphenylphosphino)-2'-methoxy-1,1'-binaphthyl |
| m.p. | melting point |
| NMR | nuclear magnetic resonance |
| Ns | Nosyl |

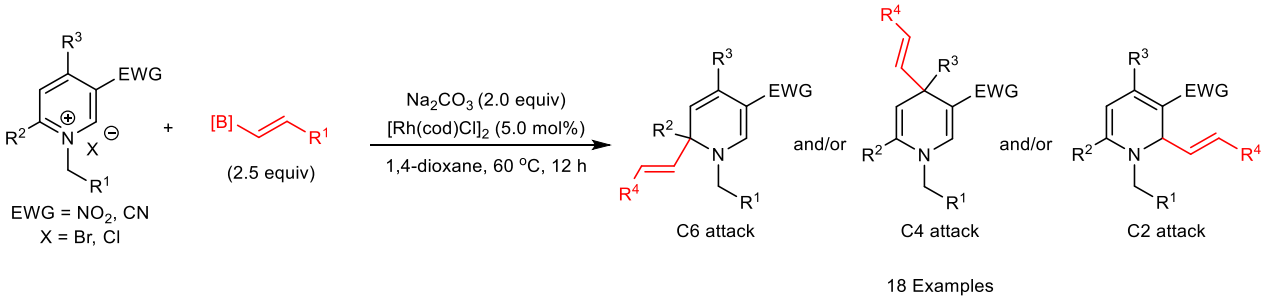
| | |
|---|---|
| *p* | para |
| pin | pinacol |
| PMB | paramethoxybenzyl |
| PMP | paramethoxyphenyl |
| Py | pyridyl |
| $R_f$ | retention factor |
| s | singlet |
| t | triplet |
| TMS | trimethylsilane |
| *t*- | *tert* |
| THF | tetrahydrofuran |
| Ts | tosyl |

**Abstract**

Described is the rhodium-catalysed addition of alkenylboron species to azinium salts. Previous work has demonstrated this addition is limited to azinium salts with an ester electron-withdrawing group (EWG) at the C3 position or when quinolinium salts are used. This work plans to expand the scope of the azinium salts to include alternative EWGs, such as the nitro and cyano group, at the C3 position.

It is important to note, azinium salts with an EWG at the C3 position can be attacked at three different carbon centres: C6, C4 and C2. Therefore, poor regioselectivity is expected as addition will lead to multiple products. Within the literature, selective addition at C6 is recorded with residual addition at C4 or C2, this work reports selective C2 and C6 addition.

Investigations into the scope of the alkenylboron reagent and azinium salt are performed to understand their effect on regioselectivity and yield. Furthermore, the reaction conditions are optimised towards a highly yielding and regioselective addition.



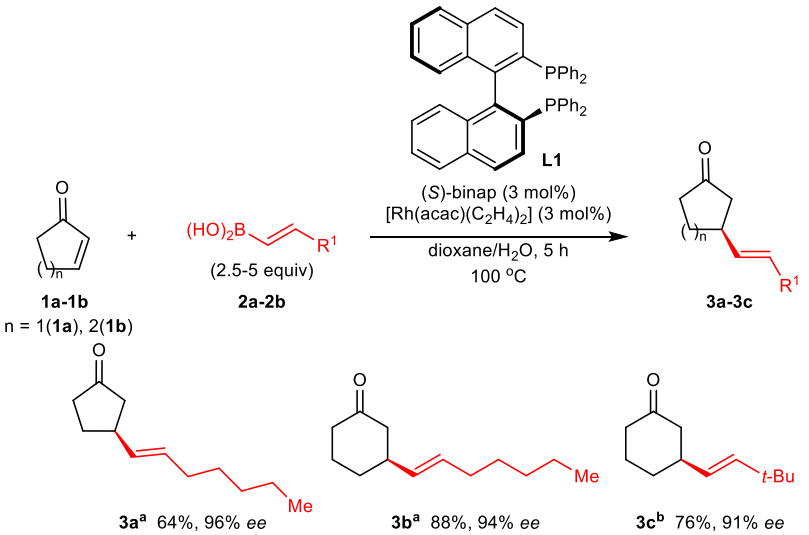

Finally, this work includes investigations into an enantioselective variant of this addition by evaluating a range of chiral ligands.

## 1.Introduction

The enantioselective transition metal catalysed formation of C-C bonds is integral to the construction of molecules.[1, 2] Among these, the transition metal catalysed addition of organoboron species is prevalent. The use of rhodium to perform this transformation has had substantial development and is proving to be effective.[3, 4]

Within the literature, the rhodium-catalysed addition of arylboron species has been well developed.[5] In comparison, the development for the rhodium-catalysed addition of alkenylboron species has been limited, stemming from the alkenylrhodium species being less stable than their aryl counterparts.[6, 7] The difference in stability results in side reactions, such as protodeboronation, becoming more competitive with the addition of the alkenylboron reagent. Methods to mitigate these side reactions use a more stable boron reagent than the commonly used boronic acid, such as *N*-methyliminodiacetic acid (MIDA), boronate esters and organotrifluoro borates.[8, 9] The rhodium-catalysed addition of an alkenylboron reagent to an acceptor can provide a useful alkene functional group handle for further functionalisation. The mechanism of this addition, when concerning azinium salts, is discussed in section 1.2.4.

The seminal report in this area was published in 1998 by Miyaura and Hayashi, who reported the first enantioselective rhodium-catalysed addition of alkenylboronic acids to cyclic enones (Scheme 1).[10] $[Rh(acac)(C_2H_4)_2]$ and (*S*)-binap (**L1**) catalysed the reaction in a 3 mol% loading using a dioxane/$H_2O$ mixture and heating the reaction at 100 °C for 5 h. The addition achieved good yields and exceptional enantioselectivity, this work led to further expansion of this addition.

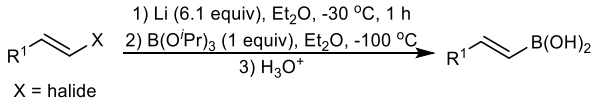



**Scheme 1**: Rh-catalysed addition of alkenylboronic acids to enones by the Miyaura and Hayashi group.[10] [a] Used 2.5 equivalents of the boron reagent. [b] Used 5 equivalents of the boron reagent.

Over the next few years, the seminal report was expanded to include improved alkenylboron scope and a more diverse range of acceptors. Included within this report is discussion of the different types of acceptors and boron reagents that are used for this rhodium-catalysed addition.

### 1.1. The Synthesis and Stability of Alkenylboron Reagents

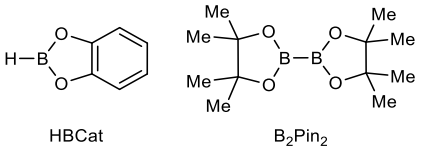
Boronic acids are widely used within cross coupling reactions due to their low toxicity and simple synthesis. Common methods to synthesise boronic acids produce the boronate ester equivalent followed by hydrolysis. This is demonstrated by Krauss who performed the transmetallation of a vinyl halide to generate the boronate ester followed by hydrolysis to generate the boronic acid (Scheme 2).[11]




**Scheme 2**: Synthesis of alkenylboronic acids via transmetallation.[11]

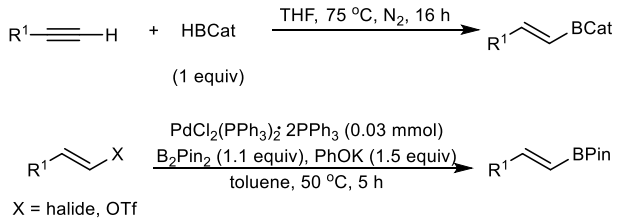
Unfortunately, boronic acids suffer from limited stability, due to the vacant orbital on boron, which lead to unwanted side reactions such as protodeboronation and oxidation. Important surrogates have been developed to stabilise the boron species towards these unwanted side reactions by exchanging the hydroxyl groups for other ligands.[12] Examples of this protection include boronate esters, potassium trifluoroborates and *N*-coordinated boronates, which are discussed below.

Boronate esters are simple to synthesise and are more stable towards unwanted side reactions than their boronic acid equivalents. The most common reagents used to form boronate esters are catecholborane (HBCat) and bis(pinacolato)diboron ($B_2Pin_2$) (Scheme 3).




**Scheme 3**: Common molecules used to form boronate esters.

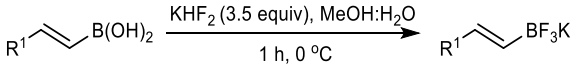
A common method used to synthesise boronate esters is transmetallation, as described above by Krauss (Scheme 2).[11] In addition, the boronate ester can be formed via hydroboration, as demonstrated by Hayashi,[13] or by performing a Miyaura borylation to generate the boronate ester species via cross coupling with vinyl halides (Scheme 4).[14]




**Scheme 4**: Examples of the synthesis of alkenylboronates esters.

In terms of stability, boronate esters are more stable than boronic acids as the hydroxyl groups have been replaced with ligands that are more electron donating. This decreases the Lewis acidity of the boron centre and stabilises it towards nucleophilic attack.[12] In spite of this increased stability, boronate esters readily form the boronic acid equivalent following hydrolysis, as previously discussed in the synthesis of boronic acids (Scheme 2).

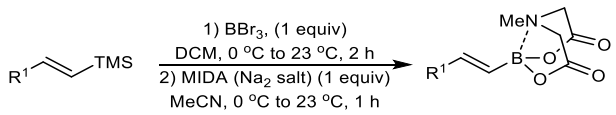
Another stable boron species commonly used in cross coupling reactions are potassium trifluoroborates ($BF_3K$). These boron species show excellent stability towards nucleophilic attack as well as air and moisture whilst also achieving excellent reactivity.[15] These species can be synthesised by reacting the boronic acid equivalent with $KHF_2$ (3.5 equiv) in a MeOH:$H_2O$ mixture at 0 °C for 1 h (Scheme 5).[9]




**Scheme 5**: The synthesis of alkenyl potassium trifluoroborate species from boronic acids. [9]

Unlike boronic acids, potassium trifluoroborates are tetrahedral in geometry and not lewis acidic, as another ligand is attached to the boron centre. However, similar to boronate esters, potassium trifluoroborates are not stable towards hydrolysis.[16]

The final type of boron species that will be discussed are the *N*-coordinated boronates, which are species that include a nitrogen atom within a cyclic boronate ester backbone. A commonly used ligand to form *N*-coordinated boronates is MIDA. BMIDA can be synthesised via transmetallation between trimethylsilane (TMS) and $BBr_3$ followed by trapping with the bis-sodium salt of MIDA (Scheme 6).[17]




**Scheme 6**: The synthesis of alkenyl BMIDA species. [17]

The nitrogen coordinates to the boron converting it from $sp^2$ to $sp^3$ hybridisation, forcing the boron centre to take a tetrahedral geometry. BMIDA is more stable towards hydrolysis than the other boron species and is also stable towards air and chromatography.[17] This increased stability towards hydrolysis allows for the controlled in-situ release of boronic acids, which results in increased reactivitiy.[8]

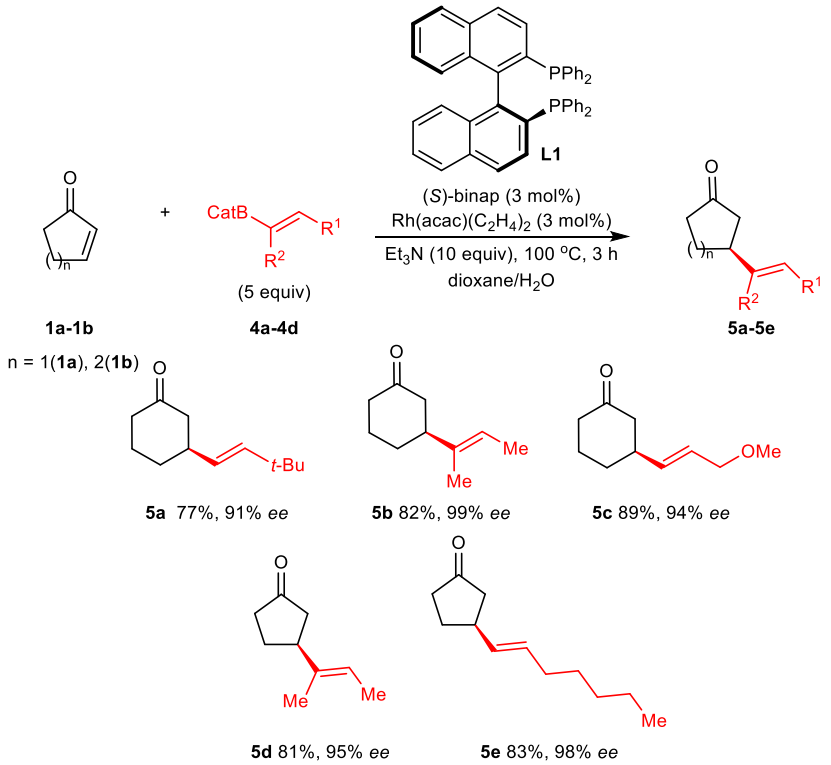
Overall, a range of boron species can be used within cross coupling reactions which provide benefits in terms of stability and synthesis. These important surrogates for boronic acids allow for the wider use of boron reagents within synthetic methods. Discussed in the remainder of the report are their uses within the enantioselective rhodium-catalysed addition.

## 1.2. Enantioselective Rhodium-Catalysed Addition of Alkenylboron Reagents

### 1.2.1. Additions of Alkenylboron Species to Electron-Deficient Alkenes

The enantioselective rhodium-catalysed addition of alkenylboron species to electron-deficient alkenes has been well developed.[18] These reactions provide a simple method to produce β-substituted products, such as carbonyl, sulfonyl and nitro compounds, with an alkene functional group handle that can be used for further functionalisation.

As described in scheme 1, the seminal report for the enantioselective rhodium-catalysed addition of alkenylboron species to acceptors was performed by Hayashi in 1998, using boronic acids and cyclic enones as acceptors.[10] Later that year, Hayashi expanded upon the work within this seminal report to include sterically bulky alkenes and optimised reaction conditions (Scheme 7).[13] The reaction proceeded using similar conditions to the seminal report but used a shorter reaction time of 3 h, a boronic acid catechol ester (BCat) reagent and $NEt_3$ (10 equiv).

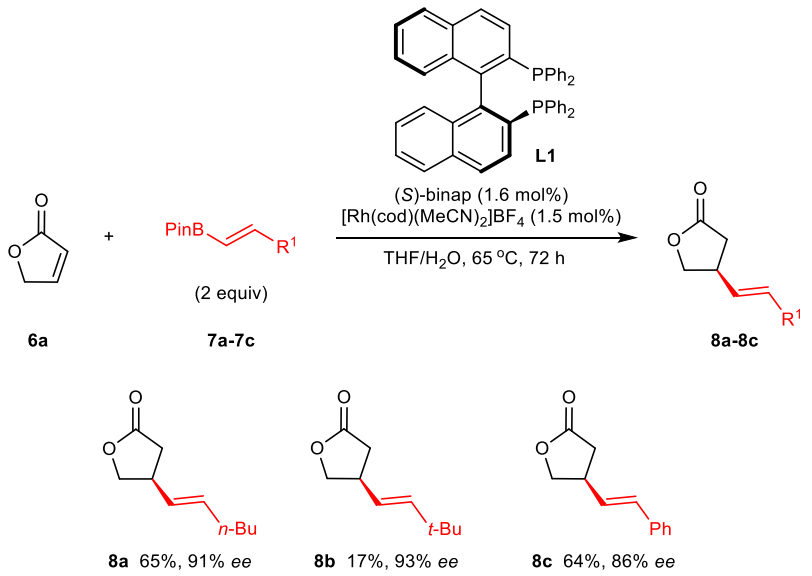



**Scheme 7**: Rh-catalysed addition of alkenylboronic acid catechol ester reagents to enones by the Hayashi group.[13]

Sterically bulky alkenes (**5b** and **5d**) and heteroatom functionality (**5c**) are tolerated, producing the corresponding products in high yields. The alkyl substituted alkenes led to **5a** and **5e** in 77% and 83% yields respectively. Notably, all additions within this report achieved exceptional enantioselectivity using the (*S*)-binap (**L1**) ligand. Improved yields are observed,

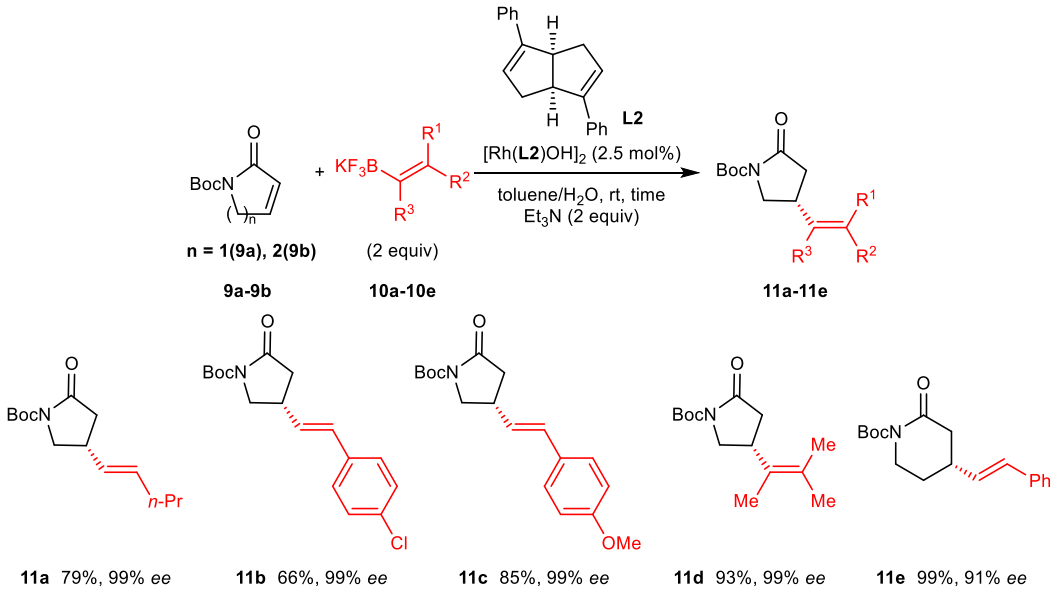
compared to the seminal report, as the more stable BCat boron reagent was used instead of a boronic acid.

Expansion of this work to improve the enone scope followed in 2010 where the 1,4 addition to α,β-unsaturated esters was reported.[19] The enantioselective rhodium-catalysed addition of alkenylboronic acid pinacol esters (BPin) to α,β-unsaturated esters was reported by Furstner in the total synthesis of ecklonialactones (Scheme 8). 1.5 mol% of $[Rh(cod)(MeCN)_2]BF_4$ and 1.6 mol% of (*S*)-binap (**L1**) catalysed the reaction in a THF/$H_2O$ solvent whilst being heated at 65 °C for 72 h. The addition was tolerant to alkyl (**8a** and **8b**) and aryl (**8c**) substituents, although poor to moderate yields are recorded. Notably, the (*S*)-binap ligand led to exceptional enantioselectivity in all additions. Compared to the above cases, a reduced catalyst loading and temperature were used but a longer reaction time was required.



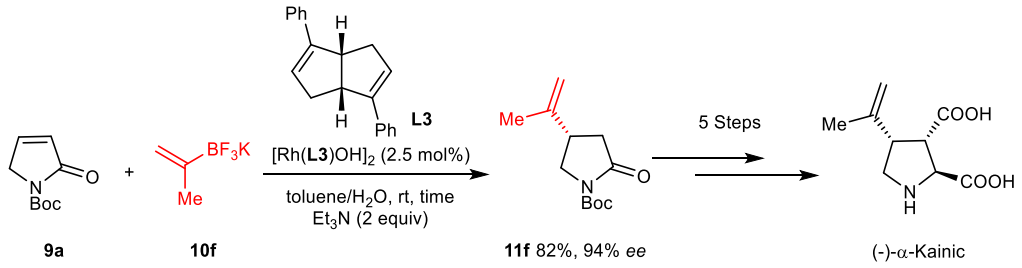

**Scheme 8**: Rh-catalysed addition of alkenylboronic acid pinacol esters to α,β-unsaturated esters by the Furstner group.[19]

In 2012, Feng and Lin reported the first case of the enantioselective rhodium-catalysed addition of alkenyl $BF_3K$ species to α,β-unsaturated amides (Scheme 9).[20] This reaction proved to be highly enantioselective, with enantiomeric excess (*ee*) >91%, alongside yields ranging from 66-99%. Notably, the reaction was catalysed using 2.5 mol% of $[Rh(\mathbf{L2})OH]_2$, where **L2** is a diene ligand, with $Et_3N$ (2.0 equiv) in toluene/$H_2O$ at room temperature.




**Scheme 9**: Rh-catalysed addition of alkenyl $BF_3K$ species to α,β-unsaturated amides by the Feng and Lin group.[20]

Electron-deficient (**11b**) and electron-rich (**11c**) aryl functionality was tolerated, the electron-rich substituent led to greater yields. A sterically bulky alkene (**11d**) and an alkyl substituent (**11a**) were also tolerated resulting in yields of 93% and 79% respectively. Notably, addition to both 5-membered and 6-membered rings were reported. The synthesis of (-)-α-kainic acid (Scheme 10), a naturally occurring molecule used in neuropharmacology, was demonstrated using this addition. The vinyl addition led to the corresponding product (**11f**) in an 82% yield and 94% *ee*. Following the addition, five further steps were taken in order to synthesise the (-)-α-kainic acid.

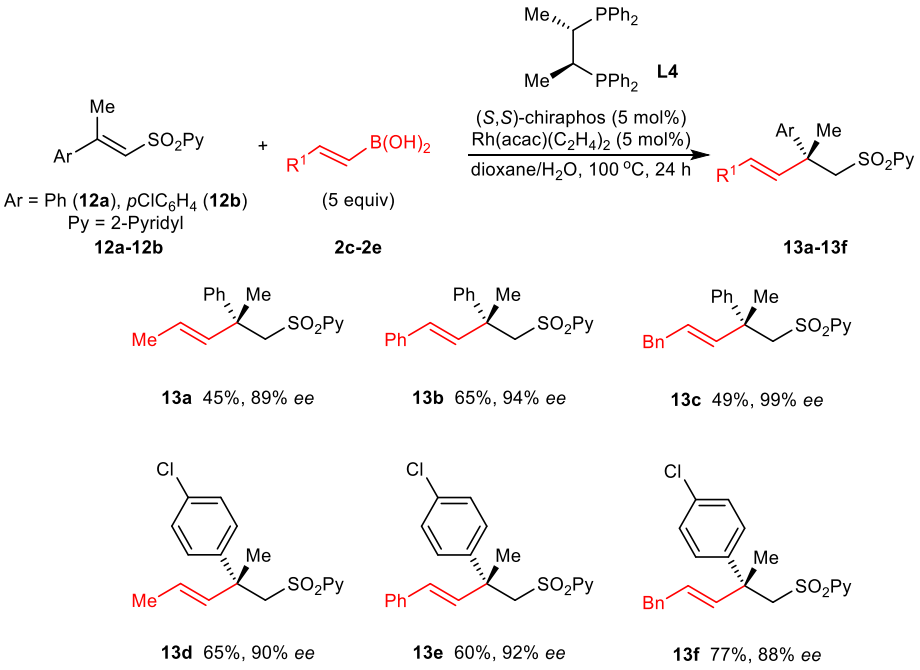



**Scheme 10**: (-)-α-Kainic acid synthesised using rhodium-catalysed addition by the Feng and Lin group.[20]

The enantioselective rhodium-catalysed addition of alkenylboron species to electron-deficient alkenes is not limited to additions to α,β-unsaturated carbonyls. Other electron withdrawing functionality, such as sulfonyl and nitro groups, are reported within the literature.

The enantioselective rhodium-catalysed addition of alkenylboronic acids to alkenylsulfones was reported by Carretero in 2005 which produced quaternary centres (Scheme

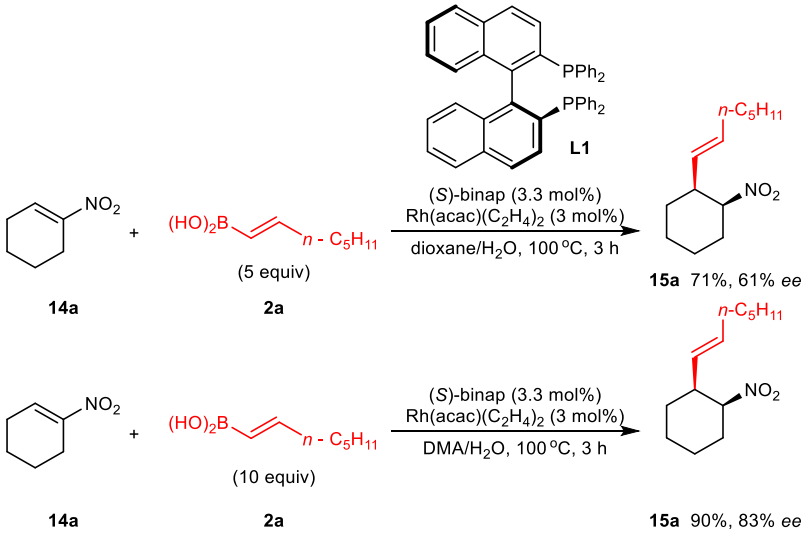
11).[21] The reaction used similar conditions to those previously described by Hayashi in the seminal report but used an (*S*,*S*)-chiraphos ligand (**L4**), a reaction time of 24 h and an increased catalyst loading of 5 mol%.




**Scheme 11**: Rh-catalysed addition of alkenylboronic acids to alkenylsulfones by the Carretero group.[21]

Both alkyl and aryl substituted alkenes were tolerated giving **13a**-**13f** in 45-77% yields and >88% *ee*. Exchanging Ph for a more electron-deficient aryl group (**13d**, **13e** and **13f**) led to improved yields in most cases. Notably, conversion of the sulfonyl to alternative functional groups, such as an electron-deficient aryl and a carbonyl, was performed in an attempt to demonstrate the versatile reactivity of the sulfonyl. Overall, although this rhodium-catalysed addition is promising, the scope is limited to three alkenyboronic acids and only moderate yields are achieved when the Ph alkenylsulfonyl substituent is present (**13a**,**13b** and **13c**).

In addition to alkenylsulfones, the enantioselective rhodium-catalysed addition of alkenylboron species has been developed to include nitroalkenes. Nitro groups have versatile reactivity and can be converted to other useful functional groups, such as amines, nitriles or carbonyls. Thus, nitro compounds are effective building blocks in the synthesis of a variety of products. The first case of the enantioselective rhodium-catalysed addition of alkenylboron species to nitroalkenes was reported by Hayashi in 2000 using boronic acids (Scheme 12).[22] 3 mol% of [Rh(acac)($C_2H_4$)$_2$] and 3.3 mol% of (*S*)-binap (**L1**) catalysed the reaction in dioxane/$H_2O$ at 100 °C for 3 h.



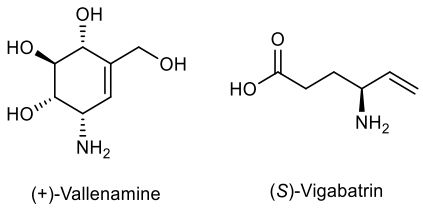

**Scheme 12**: Rh-catalysed addition of alkenylboronic acid reagents to nitroalkenes by the Hayashi group.[22]

The addition of an alkyl substituted alkenylboronic acid species achieved a moderate yield of 71% and *ee* of 61% (**15a**), this is the only example of an addition of this fashion in this report. However, exchanging the solvent for *N*,*N*-dimethylacetamide (DMA) and increasing the boronic acid equivalents resulted in an increase to both the yield and *ee* to 90% and 83% respectively. The addition proved to be effective, but further work to understand the scope of the alkenylboron species and nitroalkene is required.

To summarise, the enantioselective rhodium-catalysed addition of alkenylboron species to electron-deficient alkenes is diverse and can lead to a range of optically active products. However, some additions are limited in development and report poor yields, further work to improve the scope and reaction conditions are required. The enantioselective rhodium-catalysed addition of alkenylboron species is not limited to the use of electron-deficient alkenes. Examples of the addition to electron-deficient imines have also been reported, which will be discussed in the next section.

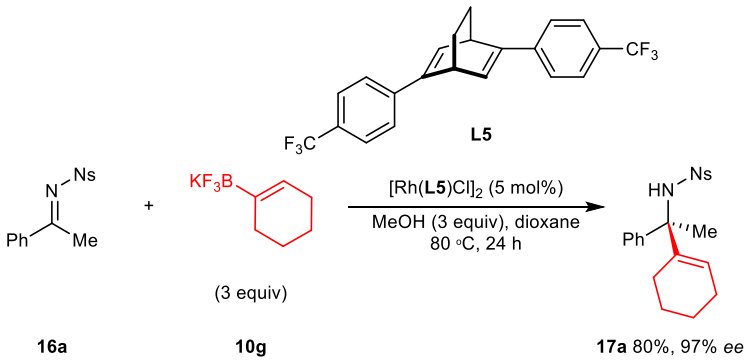
### 1.2.2. Additions of Alkenylboron Species to Imines

The enantioselective rhodium-catalysed addition of alkenylboron species to imines produce chiral allylic amines, which are common motifs in biologically active species such as (+)-Vallenamine and (*S*)-Vigabatrin (Scheme 13).[23, 24] These reactions have been well developed to include a broad scope as well as exceptional yields and *ee*.




**Scheme 13**: Examples of allylic amine in biologically active molecules

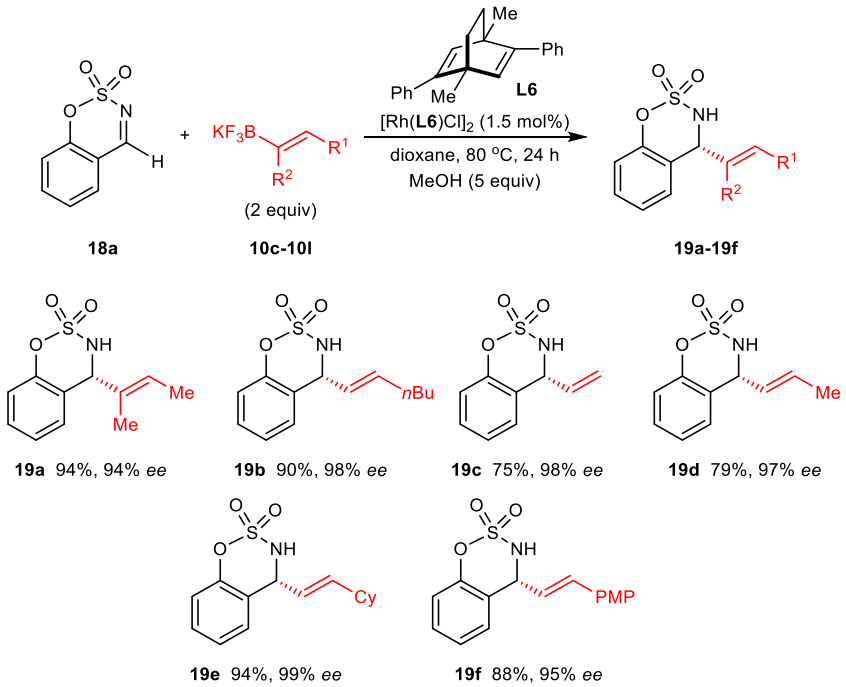
The seminal case for this addition was reported by Hayashi and Shintani in 2011, where a single addition of an alkenyl $BF_3K$ species was recorded (Scheme 14).[25] The reaction was catalysed using 5 mol% [Rh(**L5**)Cl]$_2$, where **L5** is a diene ligand, with MeOH (3.0 equiv) in dioxane whilst heating at 80 °C for 24 h.




**Scheme 14**: Rh-catalysed addition of alkenyl $BF_3K$ reagents to imines by the Hayashi and Shintani group.[25]

The addition of a cyclohexene $BF_3K$ reagent (**10g**) to a highly substituted imine is reported, producing the allylic amine (**17a**) in an 80% yield and 97% *ee*. This report demonstrates the effectiveness of chiral diene ligands as exceptional *ee* is recorded, all subsequent cases of the addition to imines use this type of ligand. Although this report is limited to only a single example, its success meant that further expansion would soon follow.

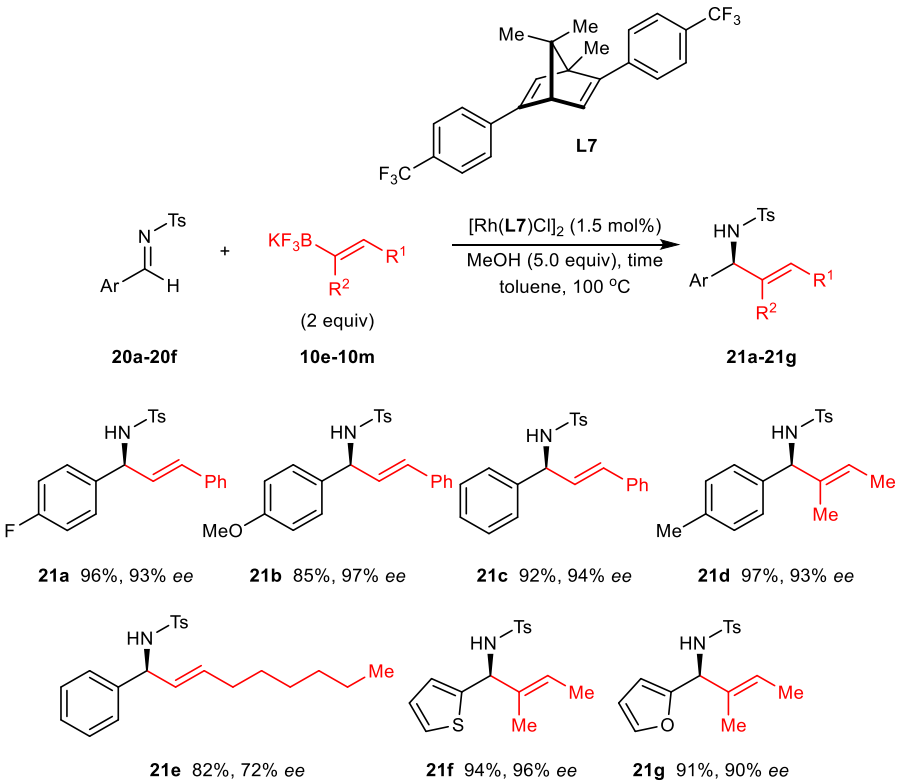
In 2012, Lam reported the enantioselective rhodium-catalysed addition of alkenyl $BF_3K$ species to cyclic imines (Scheme 15).[6] Similar conditions to those previously described by Hayashi and Shintani were used but a reduced catalyst loading, an increased MeOH equivalence and diene ligand **L6** was used.




**Scheme 15**: Rh-catalysed addition of alkenyl $BF_3K$ reagents to imines by the Lam group.[6]

The addition of butyl (**19b**) and methyl (**19d**) substituted alkenyl $BF_3K$ reagents resulted in exceptional yields and *ee*, electron-rich aryl functionality (**19f**) is also tolerated achieving a yield of 88% and an *ee* of 95%. Notably, the addition of a vinyl $BF_3K$ reagent was recorded (**19c**) achieving a yield of 75% alongside an *ee* of 98%. Improved yields were recorded, compared to the above case by Hayashi and Shintani and exceptional enantioselectivity is reported in all cases.

Finally, Wu reported the enantioselective rhodium-catalysed addition of alkenyl $BF_3K$ species to tosylimines (Scheme 16).[26] The reaction used similar conditions to those demonstrated by Lam but used an increased temperature of 100 °C, chiral diene ligand **L7** and a range of reaction times.



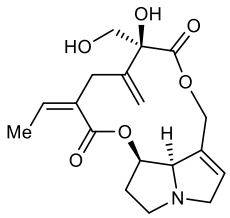

**Scheme 16**: Rh-catalysed addition of alkenyl $BF_3K$ reagents to imines by the Wu group.[26]

This report demonstrates that alkyl (**21e**) and aryl (**21a**,**21b** and **21c**) alkenylboron substituents are tolerated, achieving yields of >82% and *ee* of >72%. The aldimine was tolerant to electron-deficient (**21a**) and electron-rich (**21b**) aryl functionality, improved yields were recorded in the electron-deficient case. Notably, thiophene (**21f**) and furan (**21g**) aldimine substituents were tolerated achieving 94% and 91% yields respectively. A hexyl substituted alkene (**21e**) resulted in a slight reduction to the *ee*, but exceptional enantioselectivity is reported in all other cases. Unfortunately, the addition requires a high temperature and in some cases large reaction times.

In summary, the enantioselective rhodium-catalysed addition of alkenylboron species to imines is an effective tool to synthesise chiral allylic amines in a high yield and *ee*. This addition has been well developed to include a broad scope for both the alkenylboron reagent and the imine. The enantioselective rhodium-catalysed 1,2-addition of an alkenylboron species to an acceptor is not limited to the use of an imine, the addition to carbonyls has also been reported within the literature.

### 1.2.3. Additions of Alkenylboron Species to Carbonyls

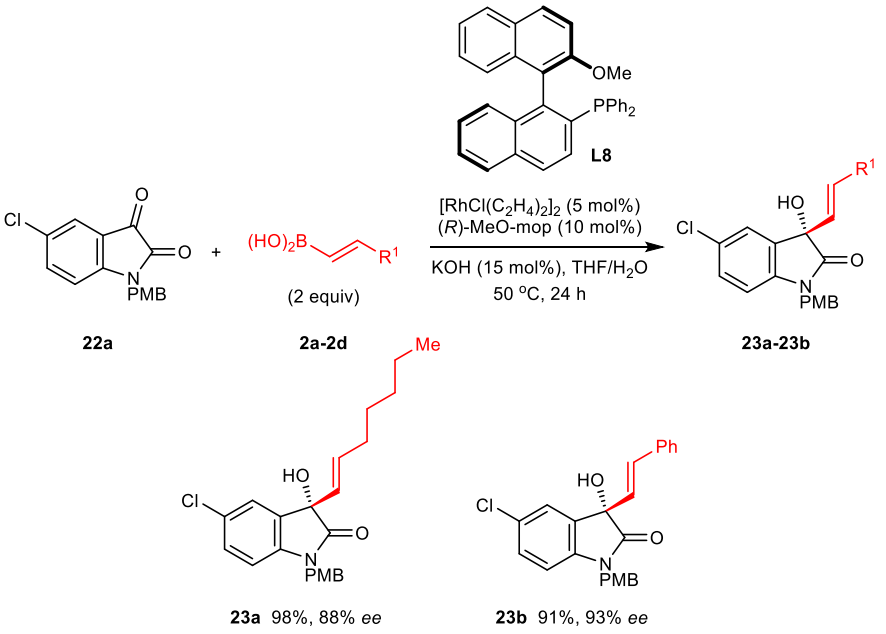
The enantioselective rhodium-catalysed addition of alkenylboron species to carbonyls has been underdeveloped. These reactions are limited to the use of 1,2-dicarbonyls, which can be converted to α-hydroxy carbonyl compounds following an addition. α-Hydroxy carbonyl molecules are important structural motifs found in naturally occurring molecules, such as Riddelliine (Scheme 17).[27]




Riddelliine

**Scheme 17**: Example of an α-hydroxy carbonyl molecule

The seminal report for this addition was recorded by Hayashi in 2006, the use of alkenylboronic acids and isatin as an acceptor is demonstrated (Scheme 18).[28] The reaction required 5 mol% $[RhCl(C_2H_4)_2]_2$ and 10 mol% (*R*)-MeO-mop (**L8**) with 15 mol% KOH in $THF/H_2O$ whilst heating at 50 °C for 24 h.

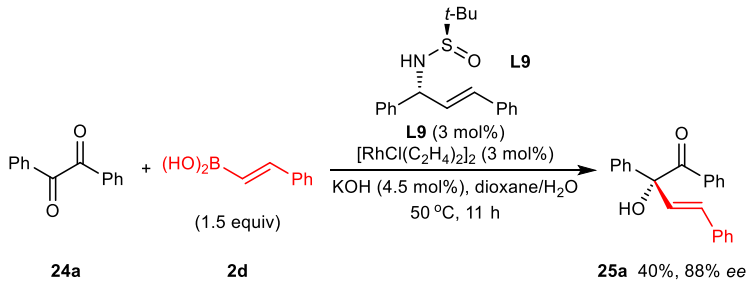



**Scheme 18**: Rh-catalysed addition of alkenylboronic acids to carbonyls by the Hayashi group.[28]

The addition of an alkyl (**23a**) and aryl (**23b**) substituted alkene was reported, both achieving exceptional yields and *ee*. Addition to an isatin in this fashion produces oxindoles, which are important structural motifs in biologically active molecules.[29, 30] Although the report

demonstrates the addition of a variety of arylboron reagents, the addition of alkenylboron species to isatins is limited to these two examples. Further work to expand upon the alkenylboron scope is required.

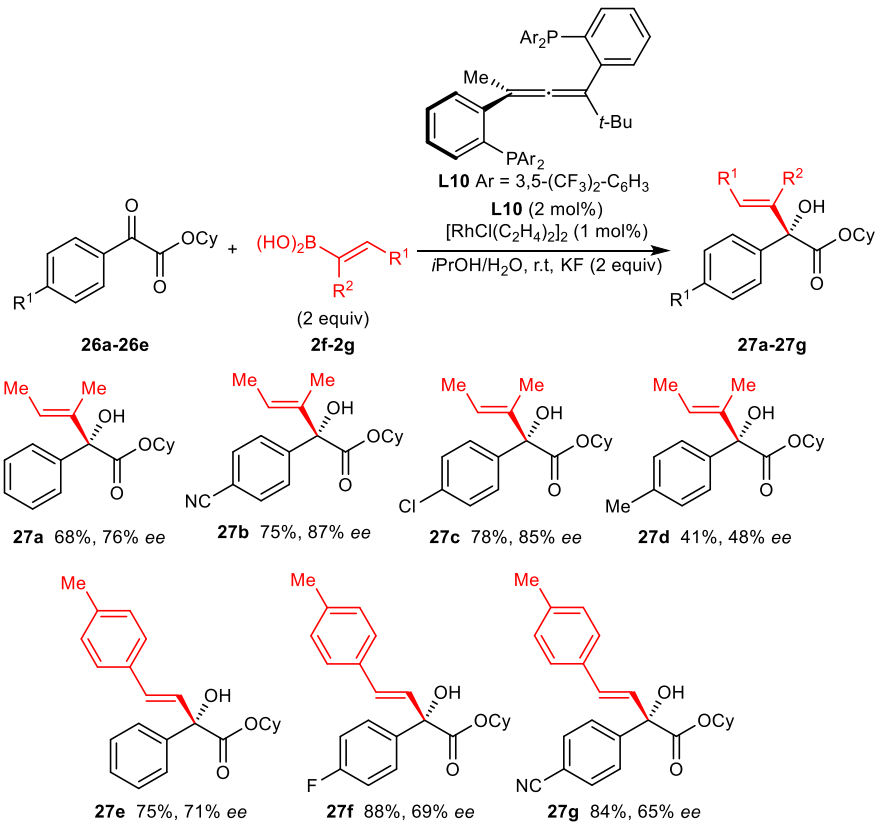
Du and Yang reported the enantioselective rhodium-catalysed addition of (*E*)-styryl boronic acid to an α-diketone in 2011 (Scheme 19).[31] The reaction was catalysed by $[RhCl(C_2H_4)_2]_2$ and the sulfur-alkene hybrid ligand (**L9**) in a 3 mol% catalyst loading with 4.5 mol% of KOH in dioxane/$H_2O$ at 50 °C for 11 h.




**Scheme 19**: Rh-catalysed addition of alkenylboronic acids to a carbonyl by the Du and Yang group.[31]

The addition produced the α-hydroxy carbonyl (**25a**) in a 40% yield and 88% *ee*. The poor yield may be due to the use of the boronic acid instead of a more stable boron reagent. Notably, the reaction took only 11 h to complete, compared to the 24 h required by Hayashi above. However, only a single alkenylboron addition was recorded within this report, further expansion of this work to include a broader range of alkenylboron reagents is required.

Finally, the addition of alkenylboronic acids to α-ketoesters was recorded by Ready in 2011 using an allene containing phosphine ligand (Scheme 20).[32] The reaction was catalysed using 1 mol% of $[RhCl(C_2H_4)_2]_2$ and 2 mol% of the allene containing phosphine ligand (**L10**) with KF (2.0 equiv) in *i*PrOH/$H_2O$ at room temperature.




**Scheme 20**: Rh-catalysed addition of alkenylboronic acids to a carbonyl by the Ready group.[32]

The addition was tolerant to both alkyl (**27a**,**27b**,**27c** and **27d**) and aryl (**27e**, **27f** and **27g**) alkenylboronic acid substituents, most achieving good yields and moderate *ee*. Improved yields occurred when a more electron-deficient substituent is adjacent to the carbonyl (**27b**, **27c, 27f** and **27g**). Notably, the reaction time varied from 2 h to 72 h. Overall, this report demonstrated a highly yielding and enantioselective addition, further work to expand the scope and optimise the reaction conditions is required.

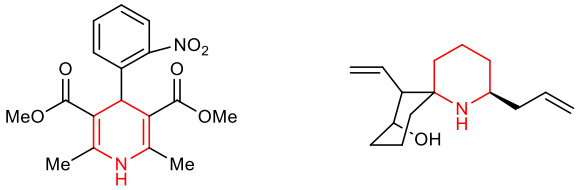
To summarise, the enantioselective rhodium-catalysed addition of alkenylboron species to carbonyls is an effective method to synthesise chiral allylic alcohols in high *ee*, although poor yields are recorded in most cases. Unfortunately, this addition is currently limited to the addition to dicarbonyls, expansion of this scope to include carbonyls in different environments is required.

Finally, the enantioselective rhodium-catalysed addition of alkenylboron species has been developed to include azinium salts. Similar to carbonyls, this acceptor has been underdeveloped within the literature and is focused on the addition of arylboron species.

### 1.2.4. Additions of Alkenylboron Species to Azinium Salts

The rhodium-catalysed addition of an alkenylboron species to an azinium salt can be used in the synthesis of highly desirable heterocycles such as dihydropyridines. These are common motifs found in drug molecules such as nifedipine.[33] Dihydropyridines can then be converted to piperidines, following a hydrogenation, which are also highly desirable and are common motifs in natural products such as HTX 235A (Scheme 21).[34] The addition of the alkenylboron species can install a stereocenter on the heterocycle, providing a streamlined approach to optically active piperidine or dihydropyridine containing products.

Examples of pharmaceuticals and natural products with piperidine/dihydropyridine cores



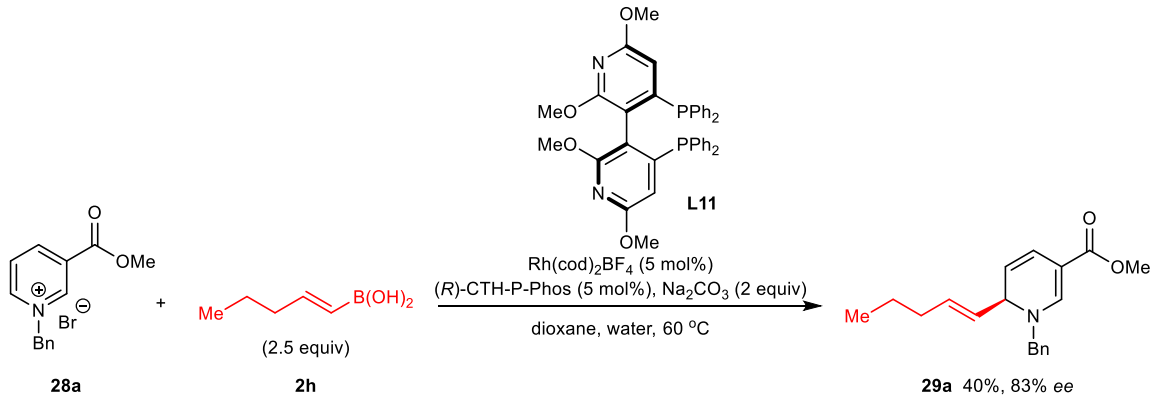

Nifedipine HTX 235A

**Scheme 21**: Examples of dihydropyridine and piperidine in drug molecules and natural products.

Despite the fact that this addition could lead to highly desirable products, the enantioselective rhodium-catalysed addition of alkenylboron reagents to azinium salts has been underdeveloped. The work within the literature focuses on the addition of arylboron reagents whilst exploring few examples of alkenylboron reagents.

The first case of this addition was reported by Nadeau in 2011 where the addition of an alkyl substituted alkenylboronic acid to an azinium salt is demonstrated (Scheme 22).[35] The reaction is catalysed by $[Rh(cod)_2BF_4]$ and (*R*)-CTH-P-Phos (**L11**) in a 5 mol% catalyst loading with $Na_2CO_3$ (2.0 equiv) in dioxane/$H_2O$ at 60 $^{O}$C.

It should be noted, azinium salts with an EWG at the C3 position can be attacked at C2, C4 and C6, the literature demonstrates selective C6 attack whilst C4 or C2 addition occur in trace amounts. Positions C6 and C2 are adjacent to the electron withdrawing nitrogen atom; thus they are the most activated towards attack. As C2 is the most sterically hindered position, C6 attack is the major product, selective addition at C2 or C4 is not recorded within the literature.



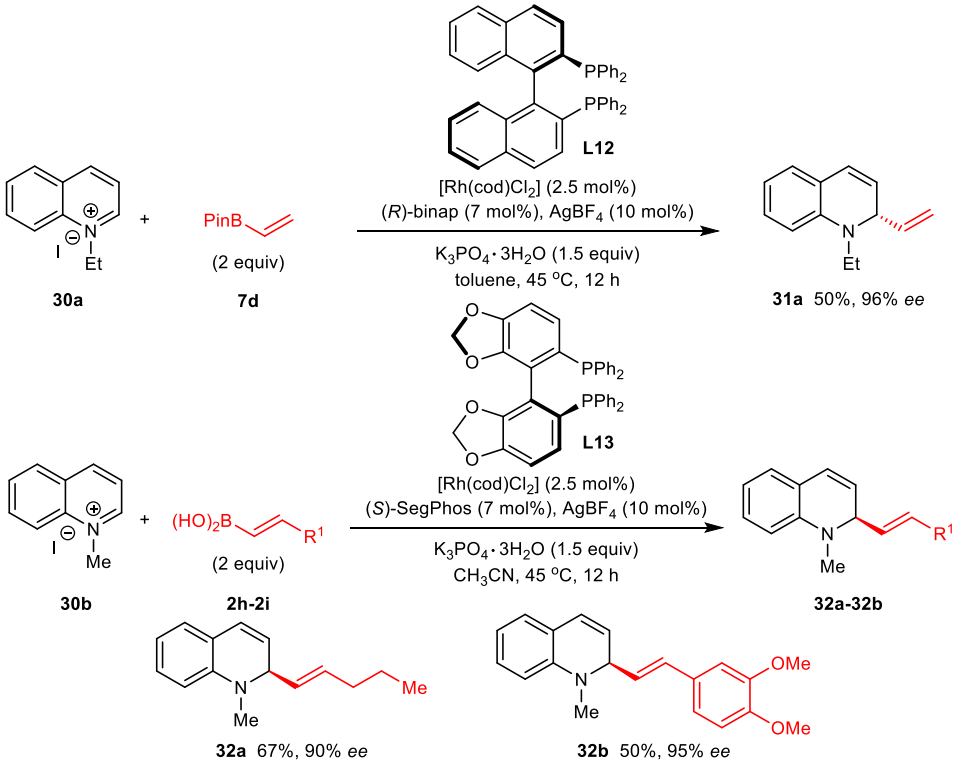

**28a** **2h** **29a** 40%, 83% *ee*

**Scheme 22**: Rh-catalysed addition of alkenylboronic acids to azinium salts by the Nadeau group.[35]

The addition of the alkyl substituted alkenylboronic acid gave the product (**29a**) in a yield of 40% alongside an *ee* of 83%. Although the yield is poor, the reaction proved to be highly enantio- and regioselective. The reduced yield can be attributed to the use of a boronic acid, a more stable boron reagent may have improved the yields by mitigating the side reactions. Notably, trace amounts of C4 addition were recorded with no addition at C2.

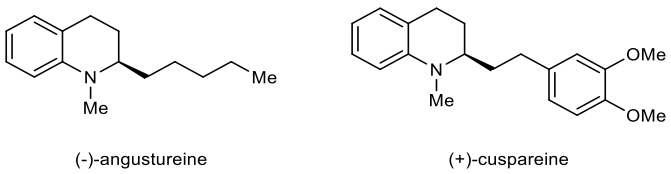
In 2016, Wang and Wei reported the enantioselective rhodium-catalysed addition of alkenylboron species to quinolinium salts (Scheme 23).[36] The reaction is catalysed using 2.5 mol% of [Rh(cod)$Cl_2$] and 7 mol% of (*R*)-binap (**L12**) with 10 mol% of $AgBF_4$ and $K_3PO_4 \cdot 3H_2O$ (1.5 equiv) in toluene whilst heating at 45 °C for 12 h. Notably, this addition uses a BPin boron reagent. The addition of an alkyl and an electron-rich aryl substituted alkenylboron reagent was also reported but used the corresponding boronic acids, an (*S*)-SegPhos (**L13**) ligand and a $CH_3CN$ solvent.

In contrast to the selectivity observed for azinium salts, quinolinium salts can only be attacked at positions C2 and C4. No addition is observed for the adjacent benzene ring as the pyridine ring is more electron deficient. The C2 position is adjacent to the electron-withdrawing nitrogen atom; therefore, C2 is more activated towards attack compared to C4.



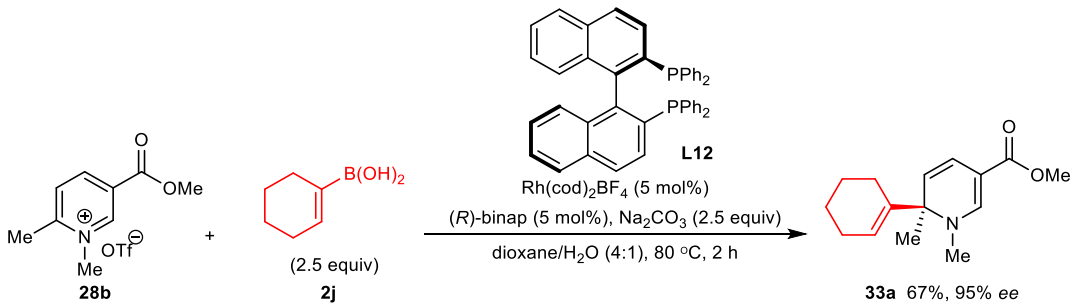

**Scheme 23**: Rh-catalysed addition of alkenylboron reagents to azinium salts by the Wang and Wei group.[36]

Reported was the addition of a vinyl BPin reagent to a quinolinium salt (**31a**) achieving a 50% yield and 96% *ee*. The addition of alkyl (**32a**) and electron-rich aryl (**32b**) substituted alkenylboronic acids resulted in good yields and exceptional *ee*. Notably, the addition used a reduced temperature and catalyst loading, compared to the case above by Nadeau. Significant boron reagent decomposition was recorded in the synthesis of products **32a** and **32b**. The report then demonstrates the synthesis of naturally occurring alkaloids (-)-angustureine and (+)-cuspareine from products **32a** and **32b** respectively following a hydrogenation (Scheme 24).




**Scheme 24**: (-)-angustureine and (+)-cuspareine demonstrated by the Wang *and Wei group*.[36]

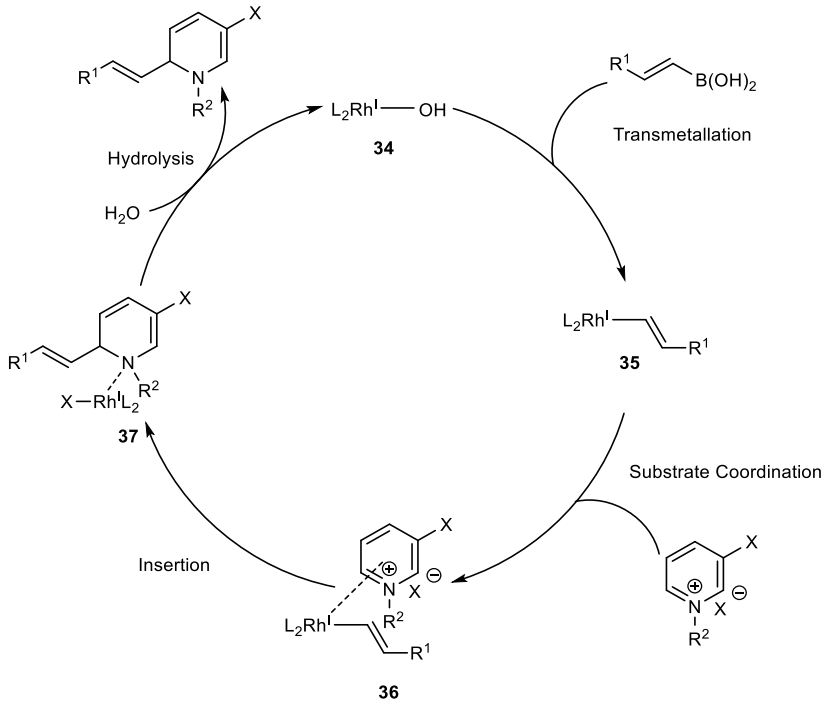
In a final example of the enantioselective rhodium-catalysed addition of alkenylboron reagents to azinium salts , Karimov reported the addition of a cyclic alkenylboronic acid (Scheme 25).[37] The reaction uses similar conditions to those described by Nadeau but uses (*R*)-binap (**L12**), an increased temperature of 80 °C and an increased $Na_2CO_3$ equivalence.




**Scheme 25**: The Rh-catalysed addition of an alkenylboronic acid to an azinium salt by the Karimov group.[37]

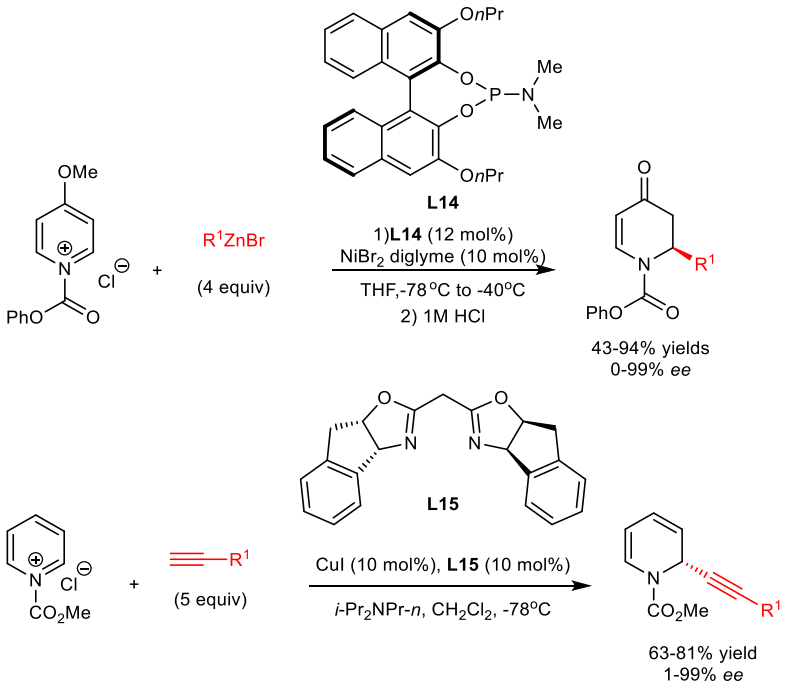
The addition, producing **33a**, was successful achieving a 67% yield and 95% *ee*, using a short reaction time of 2 h. Surprisingly, the addition selectively formed a quaternary centre at C6 with trace addition at C2, no C4 addition occurred. Karimov stated that this addition is limited to the use of an ester EWG, as alternative EWGs, such as cyano, nitro and ketone, did not lead to the desired product.

The proposed catalytic cycle for the rhodium-catalysed addition of alkenylboron reagents to azinium salts is assumed to be the same as those proposed for the aryl boron species (Scheme 26).[37] The cycle begins with transmetallation of the alkenylboron species and the rhodium species (**34**). The alkenylrhodium species (**35**) then coordinates to the azinium salt to give intermediate **36**. Insertion of the C=N bond into the Rh-C bond follows to produce **37**. Hydrolysis then regenerates the catalyst (**34**) and releases the alkenylation product.




**Scheme 26**: Postulated catalytic cycle.

Finally, it is important to compare rhodium to other transition metals that have been used in this fashion. The addition to azinium salts is not limited to the use of a rhodium complex alongside a boron species. There have been reports of nickel,[38] copper[39] and organocatalysts[40, 41] being used in the addition to azinium salts (Scheme 27). The yields achieved in these additions are comparable to the examples above. However, the enantioselectivity is much more inconsistent.




**Scheme 27**: General scheme for Ni and Cu catalysed additions to azinium salts

Overall, the enantioselective rhodium-catalysed addition of alkenylboron species to azinium salts is an effective method to install an alkene on an *N*-heterocycle core enantioselectively. However, this area of research has been under developed and focuses primarily on arylboron species. Expansion of the azinium salt and alkenylboron species scope is required.

### 1.3. Summary on Enantioselective Rhodium-Catalysed Addition of Alkenylboron Species

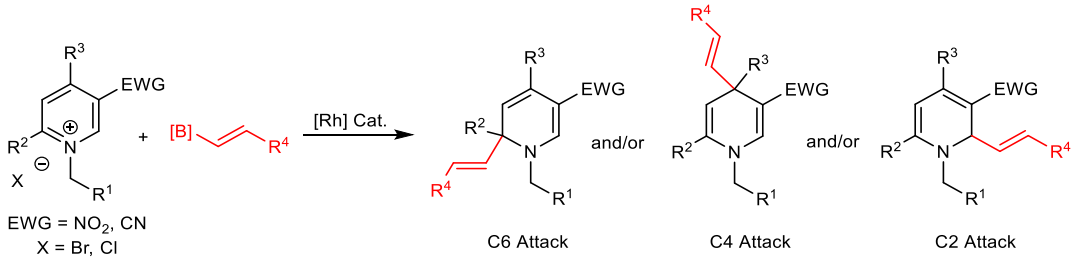
In summary, the enantioselective rhodium-catalysed addition of alkenylboron species is a prevailing tool for synthetic chemists. The addition installs an alkene onto acceptors, most common of which are electron-deficient alkenes and imines. Further functionalisation of the alkene can lead to the synthesis of a variety of highly desirable optically active products.

The enantioselective rhodium-catalysed addition of alkenylboron species to azinium salts has been underdeveloped. The addition is limited to an ester EWG at the C3 position and selective C6 addition. A broader range of EWGs and selective addition at C2 or C4 would be useful in the synthesis of a wider range of optically active piperidine or dihydropyridine containing products. Incorporation of switchable reactivity to this addition would also be useful to improve the scope as selective addition to C2, C4 and C6 could be performed by altering the reaction conditions.

## 2. Results and Discussion

### 2.1. Aims and Objectives

The enantioselective rhodium-catalysed addition of alkenylboron species to azinium salts has been described by the Nadeau group,[35] the Wang and Wei group[36] and the Karimov group.[37] These works report that an ester EWG at the C3 position or a quinolinium salt is required for the addition's success. This work plans to expand the scope to include alternative EWGs, such as the nitro and cyano group (Scheme 28).

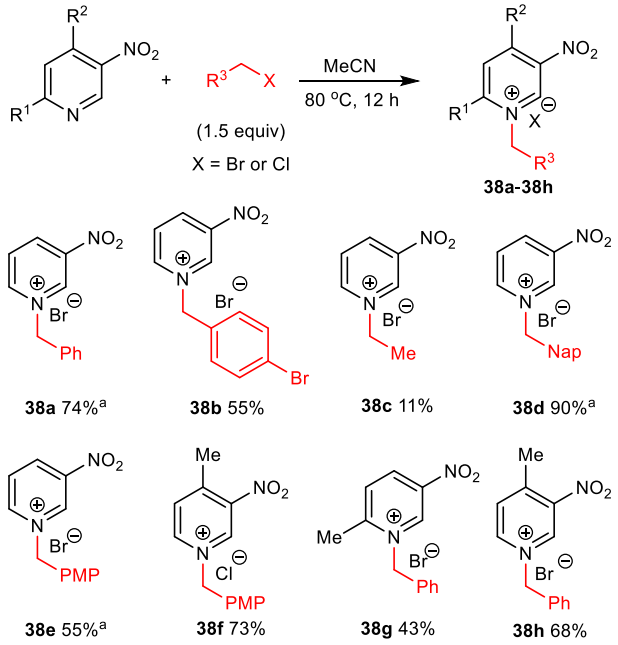



**Scheme 28**: Proposed reaction

Investigations into the scope of the alkenylboron reagent are included which will attempt to expand the alkenylboron scope to include more aryl substituted and sterically bulky alkenylboron substituents. In addition to this, this work will investigate the effects of substituents upon the azinium salt. This work also includes reaction optimisation to improve the yields and selectivity. Finally, this work will also attempt to develop an enantioselective variant of this addition.

## 2.2. Reaction Optimisation

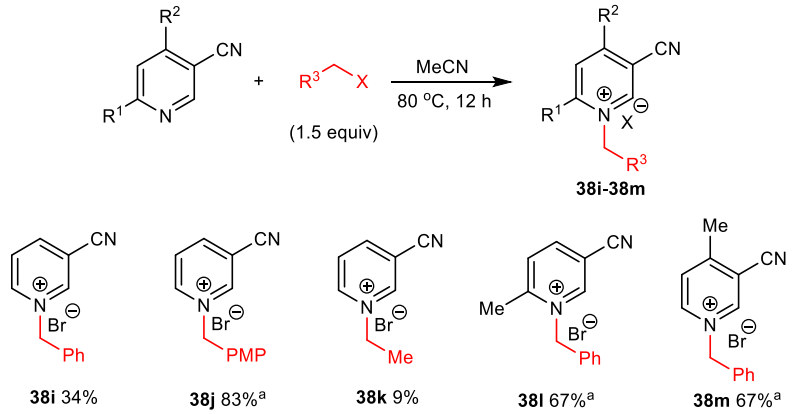
The azinium salts were synthesised by alkylating pyridine using a method previously described by Bertuzzi.[42] In order to attain a variety of substrates, azinium salts **38a** – **38m** were synthesised. Initially, the nitro azinium salts (**38a** – **38h**) were synthesised (Scheme 29).




**Scheme 29**: Azinium salt formation reactions. [a] Salts synthesised by Shivanee Borpatra Gohain and are used in later experiments'.

The benzyl substituted nitro pyridine (**38a**) was synthesised in an adequate yield of 74%. Including a halogen within the system (**38b**) is tolerated leading to a yield of 55%. Using ethyl bromide reduced the yield of the azinium salt to 11% (**38c**). Protecting the nitrogen with paramethoxyphenyl (PMP) (**38e** and **38f**) led to the corresponding azinium salts in good yields of 55% and 73% respectively. Incorporation of a methyl to the C6 position (**38g**) led to a yield of 43% whilst a methyl at the C4 position (**38h**) led to a yield of 68%.

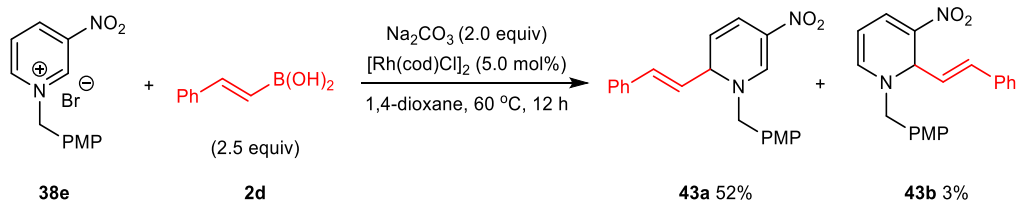
With a collection of nitro substituted azinium salts in hand, focus turned to the synthesis of cyano substituted azinium salts (Scheme 30).




**Scheme 30**: Azinium salt formation reactions. [a] Salts synthesised previously by Shivanee Borpatra Gohain and are used in later experiments'.

The benzyl substituted cyano pyridine (**38i**) was synthesised in a 34% yield. Exchanging the Ph for PMP led to the synthesis of the corresponding azinium salt (**38j**) in an 83% yield. The use of ethyl bromide led to the azinium salt (**38k**) in a poor yield of 9%. Finally, incorporation of a methyl to the C6 and C2 position (**38l** and **38m**) gave the corresponding azinium salts in 67% yields.

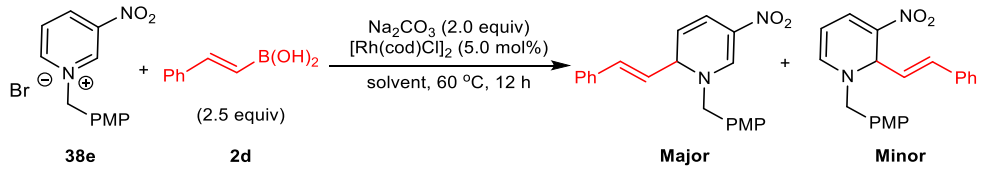
With these azinium salts in hand, focus turned to finding optimal reaction conditions for the rhodium-catalysed addition of alkenylboron species to azinium salts. The required transformation was found to occur using conditions previously developed by Nadeau.[22] By heating a mixture of the azinium salt (**38e**), (*E*)-styryl boronic acid (**2d**) (2.5 equiv) and $Na_2CO_3$ (2.0 equiv) in the presence of 5 mol% $[Rh(cod)Cl]_2$ in 1,4-dioxane at 60 °C for 12 h the desired product formed. The addition proved to be moderately yielding with 52% addition at C6 (**43a**) and 3% addition at C2 (**43b**) (Scheme 31)[a].




**Scheme 31**: [a] Reactions were performed with 0.30 mmol of the azinium salt in 1,4-dioxane (5 mL). Yields are of isolated products.

With these conditions in hand, focus shifted to reaction optimisation. The objective of this process was to improve the yields as well as selectivity. Initially, the solvent system was investigated (Table 1).

**Table 1** Solvent Screening [a]




| Entry | Solvent | Major | Minor |
|---|---|---|---|
| 1 | 1,4-dioxane | 26 | - |
| 2 | THF | 45 | 10 |
| 3 | Toluene | 18 | 5 |
| 4 | 1,4-dioxane:$H_2O$ (9:1) | 15 | Trace |
| 5 | THF:$H_2O$ (9:1) | 7 | Trace |
| 6 | DCE | 18 | - |
| 7 | DME | 7 | - |
| 8 | THF:$^t$AmylOH (9:1) | 32 | 6 |
| 9 | MeOH | - | - |
| 10 | DCM | 5 | - |

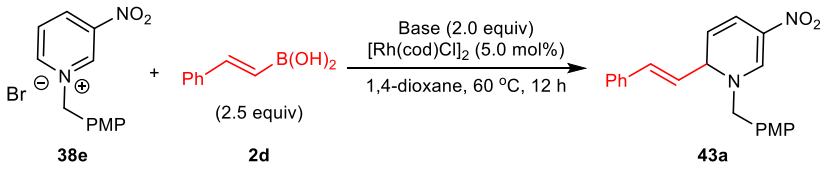
[a] Reactions were performed with 0.05 mmol of the azinium salt in 1,4-dioxane (1 mL). Yields determined by $^1$H NMR analysis using 1,3,5 trimethoxybenzene as an internal standard.

The initial discovery (Scheme 31) was repeated on a smaller scale, from 0.3 mmol to 0.05 mmol (Entry 1). Unfortunately, a reduction in the yield occurred alongside no C2 addition. Following this discovery that the scale affects the yield, the screening process continued on the 0.05 mmol scale. Entry 1 was used as a standard to understand the effects of changing the solvent and base.

Tetrahydrofuran (THF) (Entry 2) resulted in the highest yield of the major product with a 45% yield but significant minor product was also recorded. Toluene (Entry 3) gave a reduced yield of 18% for the major product and also saw poor selectivity. The addition of water to the solvent system (Entry 4 + Entry 5) resulted in reduced yields. Dichloroethane (DCE) and dimethoxyethane (DME) (Entry 6 + Entry 7) led to poor yields for the major product. A THF and $^t$AmylOH (Entry 8) mixture produced 32% of the major product and 6% of the minor. Unfortunately, the reaction did not proceed in the presence of MeOH (Entry 9) and dichloromethane (DCM) (Entry 10) led to a poor yield of 5% for the major product.

The base screening process then began (Table 2).

**Table 2** Base Screening[a]




| Entry | Variable | **43a** |
|---|---|---|
| 1 | $Na_2CO_3$ | 26 |
| 2 | NaOAc | 6 |
| 3 | $NEt_3$ | Trace |

[a] Reactions were performed with 0.05 mmol of the azinium salt in 1,4-dioxane (1 mL). Yields determined by $^1H$ NMR analysis using 1,3,5 trimethoxybenzene as an internal standard.

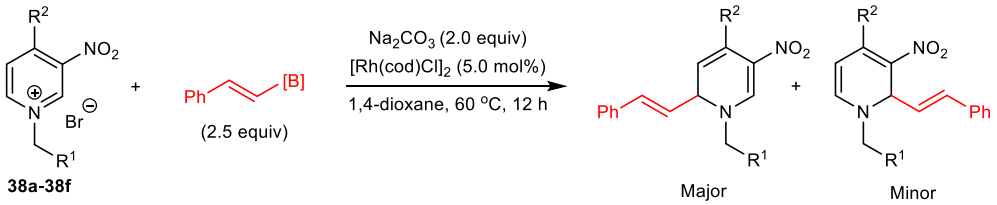
It should be noted that selective addition to C6 was observed in all cases. $Na_2CO_3$ led to a 26% yield on the smaller scale (Entry 1). Exchanging the base for NaOAc (Entry 2) saw a significant reduction to the yield to 6% and $NEt_3$ led to trace addition (Entry 3).

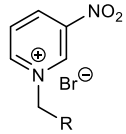
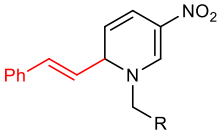
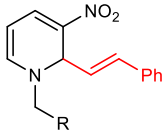
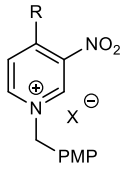
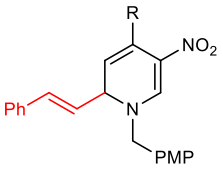
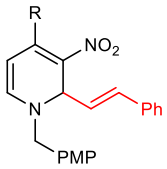
Therefore, 1,4-dioxane and a $Na_2CO_3$ base were used as a moderate yield with excellent selectivity was recorded on the small scale. Unfortunately, exchanging the solvent and the base had little effect on the selectivity of this addition as C6 addition was the major product in all cases.

### 2.3. Reaction Scope

Using a mixture of the azinium salt, the boron reagent (2.5 equiv) and $Na_2CO_3$ (2.0 equiv) in the presence of 5 mol% $[Rh(cod)Cl]_2$ in 1,4 dioxane at 60 °C for 12 h, the scope of the rhodium-catalysed addition of alkenylboron reagents to azinium salts was investigated (Table 3). It should be note, most cases led to significant amounts of unreacted azinium salt following the addition. The investigation began using the nitro azinium salts made previously and (*E*)-styryl boron reagents. It should be noted, all additions within the reaction scope were performed on the 0.3 mmol scale.

**Table 3** Reaction Scope [a]



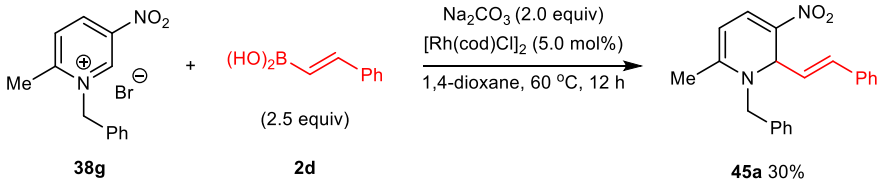

| entry | substrate | | [B] | Major | Major yield (%) | | Minor | Minor yield (%) | |
|---|---|---|---|---|---|---|---|---|---|
| 1 |  | R = Ph **38a** | $B(OH)_2$ |  | **39a** | 38 |  | - | - |
| 2 | | R = *p*-$C_6H_5Br$ **38b** | $B(OH)_2$ | | **40a** | 32 | | - | - |
| 3 | | R = Me **38c** | $B(OH)_2$ | | **41a** | 27 | | **41b** | 6 |
| 4 | | R = Nap **38d** | $B(OH)_2$ | | **42a** | 29 | | - | - |
| 5 | | R = PMP **38e** | $B(OH)_2$ | | **43a** | 52 | | **43b** | 3 |
| 6 |  | R = H **38e** | $BF_3K$ |  | **43a** | 63 |  | **43b** | 9 |
| 7 | | R = Me **38f** | $BF_3K$ | | **44a** | 10 | | **44b** | 16 |

[a] Reactions were performed with 0.30 mmol of the azinium salt in 1,4-dioxane (5 mL). Yields are of isolated products.

The benzyl substituted nitro pyridine (**38a**) led to the alkenylation product (**39a**) selectively in a 38% yield (Entry 1). Using this as a standard, investigations into the nitrogen substituent began using boronic acids. A halogenated benzyl protecting group on nitrogen was tolerated (Entry 2) resulting in selective addition to C6 in a 32% yield (**40a**). Using an ethyl substituted nitrogen (Entry 3) led to C6 addition in a 27% yield (**41a**) alongside trace amounts of C2 addition (**41b**). The naphthyl substituted nitrogen (**38d**) (Entry 4) resulted in selective addition to C6 in a reduced yield of 29% (**42a**). Finally, the PMP protected nitrogen (**38e**) (Entry 5) led to C6 addition in a 52% yield (**43a**) and C2 addition in a 3% yield (**43b**), which was the initial discovery.

To summarise, electron-rich nitrogen substituents (**43a**) led to an improved yield when compared to electron-deficient substituents (**40a**). Steric bulk had little effect on the yield as the large naphthyl substituent (**42a**) led to a similar yield to the methyl substituent (**41a**).

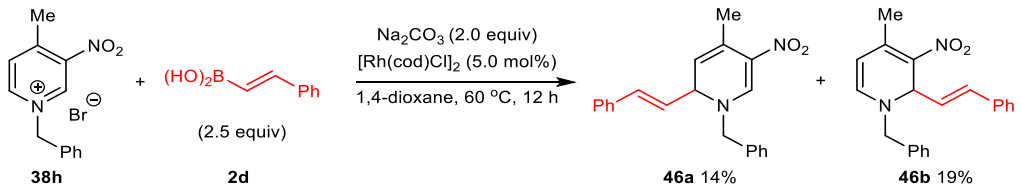
The focus then turned to understanding the effect of the boron reagent on yield and selectivity. Repeating the initial discovery (Entry 5) using a $BF_3K$ reagent, rather than a boronic acid, led to increased yields for both the major and minor product alongside poorer selectivity (Entry 6). Still using the $BF_3K$ boron reagent, incorporation of a methyl to the C4 position led to poor yields, although a 1:1 selectivity is also observed resulting in the largest proportion of C2 addition recorded within this study (Entry 7). It should be noted that C4 addition was not recorded in any of these additions. Variation of the substituents on the pyridine core was then investigated beginning with incorporation of Me to the C6 position (Scheme 32).




**Scheme 32**: [a] Reaction was performed with 0.30 mmol of the azinium salt in 1,4-dioxane (5 mL). Yield is of isolated product.

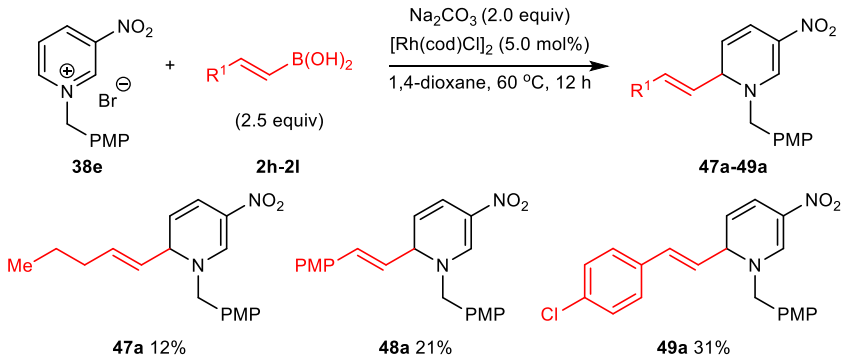
Within the literature, Karimov found that addition with a methyl at the C6 position led to the formation of a quaternary centre (Scheme 25).[37] This study attempted a similar addition and saw instead a switch in reactivity to selectively attack the C2 position in a 30% yield (**45a**), this is in contrast to the selective C6 addition observed in the production of product **39a** when a methyl is not present. The steric bulk introduced by the methyl means the C2 position is the least sterically hindered carbon adjacent to the electron withdrawing nitrogen atom. Thus, the C2 carbon becomes the most desirable carbon of attack.

Introduction of a methyl to the C4 position led to major C2 addition in a 19% yield (**46b**) alongside C6 addition in a 14% yield (**46a**) (Scheme 33). This may indicate that steric bulk at C6 or C4 is enough to switch reactivity to favour the more electron deficient C2 position.



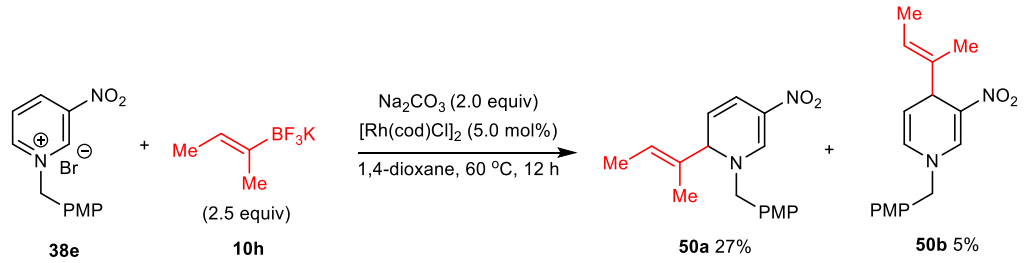

**Scheme 33**: [a] Reaction was performed with 0.30 mmol of the azinium salt in 1,4-dioxane (5 mL). Yields are of isolated products.

Next, focus shifted to the use of substituents on the alkenylboronic acid, all additions used azinium salt **38e** (Scheme 34). An alkyl substituted alkene (**47a**) was successful resulting in a yield of 12%. Both electron-rich (**48a**) and electron-deficient (**49a**) aryl functionality was also tolerated resulting in a yield of 21% and 31% respectively.



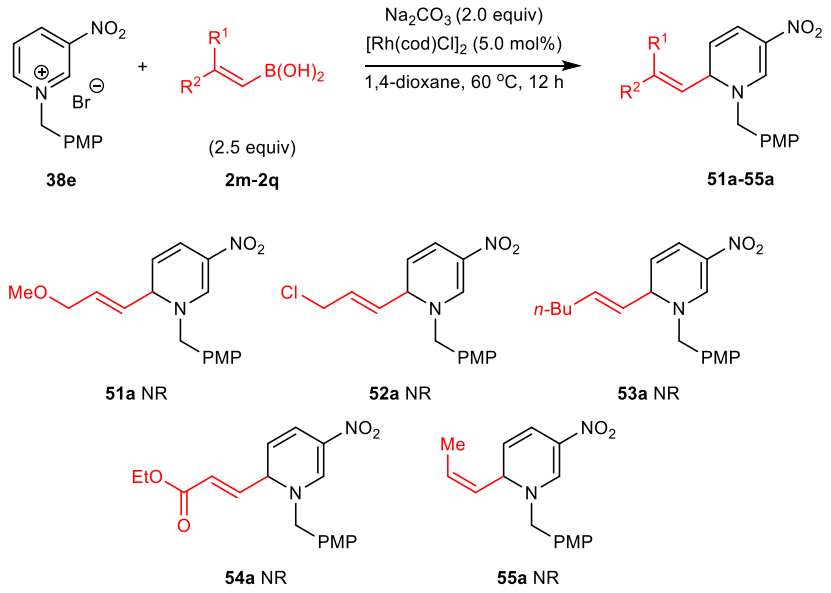

**Scheme 34**: [a] Reaction was performed with 0.30 mmol of the azinium salt in 1,4-dioxane (5 mL). Yields are of isolated products.

Interestingly, using a sterically bulky alkenyl $BF_3K$ reagent (**10h**) led to selective C6 addition in a 27% yield (**50a**) with addition at C4 in 5% yield (**50b**) (Scheme 35). It should be noted, a $BF_3K$ boron reagent was used for this addition.




**Scheme 35**: [a] Reaction was performed with 0.30 mmol of the azinium salt in 1,4-dioxane (5 mL). Yields are of isolated products.

This is the only case of C4 addition recorded in this work. It is theorised that the α-methyl introduces enough steric hindrance that attack at C4 is preferred compared to the more sterically hindered C2 position. Following these successful examples of alkenylboron variants, it is important to acknowledge those additions that were unsuccessful (Scheme 36). All of these unsuccessful examples used the corresponding boronic acid.

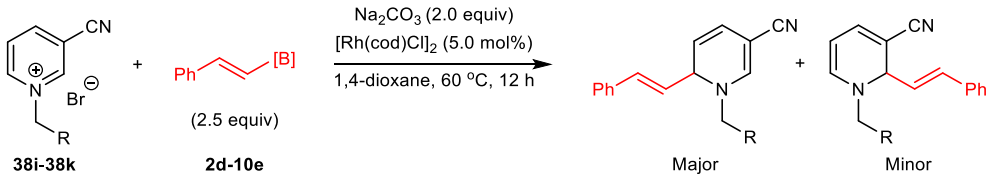


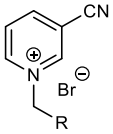
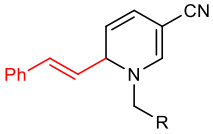
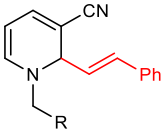

**Scheme 36**: [a] Reaction was performed with 0.30 mmol of the azinium salt in 1,4-dioxane (5 mL).

Although electron-rich and electron-deficient aryl functionality is tolerated, the corresponding alkyl examples (**51a** and **52a**) both led to no addition. The use of ester functionality was not tolerated (**54a**) and a cis propeneyl boronic acid also led to no addition (**55a**).

Finally, the scope of the cyano azinium salts was investigated using a (*E*)-styryl boron reagent. This investigation began by exchanging the nitrogen substituent (Table 4).

**Table 4** Cyano Reaction Scope[a]



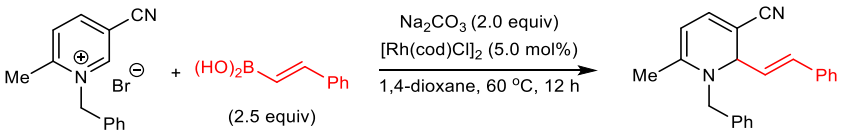

| entry | substrate | | [B] | Major | Major yield (%) | Minor | Minor yield (%) |
|---|---|---|---|---|---|---|---|
| 1 |  | R = Ph **38i** | $BF_3K$ |  | **56a** 44 |  | - - |
| 2 | | R = PMP **38j** | $BF_3K$ | | **57a** 23 | | **57b** 7 |
| 3 | | R = Me **38k** | $B(OH)_2$ | | **58a** 11 | | - - |

[a] Reaction was performed with 0.30 mmol of the azinium salt in 1,4-dioxane (5 mL). Yields are of isolated products.

Initially, the benzyl substituted cyano pyridine salt was used (Entry 1), resulting in selective addition to C6 in a 44% yield (**56a**). On exchanging the Ph for PMP (Entry 2), a reduced yield of 23% of C6 addition (**57a**) was recorded alongside minor addition to C4 (**57b**) in a 7% yield. Finally, addition of (*E*)-styryl boronic acid to the alkyl substituted pyridine (Entry 3) led to selective

addition to the C6 position in a reduced yield of 11% (**58a**). It should be noted entry 1 and 2 use the $BF_3K$ boron reagent whilst entry 3 uses the boronic acid equivalent.

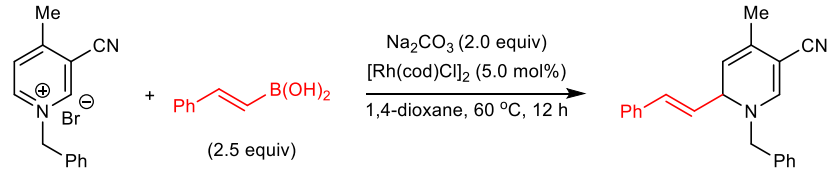
Investigations into the effects of substitutions on the pyridine core were then investigated. The incorporation of a methyl to the C6 position led to a diminished yield forming the product (**59a**) in a 17% yield (Scheme 36). But, similar to the nitro case (Scheme 32), reactivity switched from selective C6 addition (**56a**) to selective C2 addition (**59a**).




**38l** **2d** **59a** 17%

**Scheme 36**: [a] Reaction was performed with 0.30 mmol of the azinium salt in 1,4-dioxane (5 mL). Yields are of isolated products.

The incorporation of a methyl to the C4 position saw selective addition at C6 in a 36% yield (**60a**) (Scheme 37). This is in contrast to the poor selectivity observed in the nitro case (Scheme 33). This switch in reactivity, compared to the nitro case, may be because the nitro group is a stronger EWG than the cyano group and therefore makes the C2 position more electron deficient.



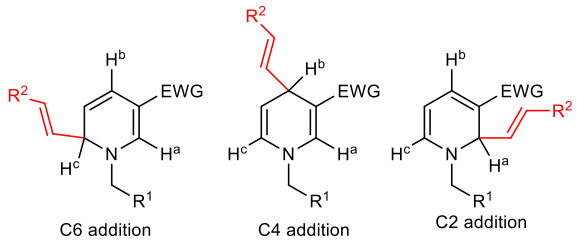

**38m** **2d** **60a** 36%

**Scheme 37**: [a] Reaction was performed with 0.30 mmol of the azinium salt in 1,4-dioxane (5 mL). Yields are of isolated products.

Overall, the rhodium-catalysed addition of alkenylboron reagents to azinium salts proved to be effective and is tolerant to a range of functional groups. Unfortunately, the yields recorded were mostly poor, further optimisation of the reaction conditions should improve the yields recorded as well as the selectivity in some cases.

## 2.5. Identifying Regioisomers

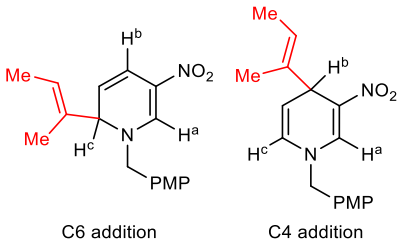
Azinium salts with an EWG at the C3 position can be attacked at three different carbon centres: C6, C4 and C2 (Scheme 38). Therefore, regioisomers must be assigned after the rhodium-catalysed addition of an alkenylboron species to an azinium salt. Following the identification that addition had occurred, the 2D NMR techniques, COSY and HSQC, as well as the coupling constants from the $^{1}$H NMR were used to understand the relationship of the product peaks.




**Scheme 38**: Significant hydrogens in the rhodium-catalysed addition of alkenylboron species to azinium salts

C2 addition can be distinguished from addition to the other positions as C6 and C4 addition lead to a high singlet for $H^a$, the absence of this singlet indicates C2 addition. To distinguish between C4 and C6 addition, protons $H^b$ and $H^c$ were investigated further. One of these protons are on a newly formed $sp^3$ hybridised carbon, this proton can be identified within the NMR spectrum using coupling constants and chemical shift. Once this proton is identified, it must be assigned as $H^b$ in C4 addition or $H^c$ in C6 addition, the difference in chemical shift of these protons should be considered. $H^c$ would lead to a greater chemical shift in C6 addition compared to $H^b$ in C4 addition. This is due to the electron-withdrawing nitrogen atom directly attached to the $sp^3$ hybridised carbon in C6 addition.

To demonstrate this, products **50a** and **50b** will be examined further (Scheme 39). Addition of the sterically bulky alkene (**10h**) to azinium salt **38e** led to the formation of two regioisomers. Both of these regioisomers gave rise to a high singlet peak, therefore these products were the result of addition to C6 and C4.




**Scheme 39**: Protons of interest in the rhodium-catalysed addition of an alkenylboron reagent to an azinium salt

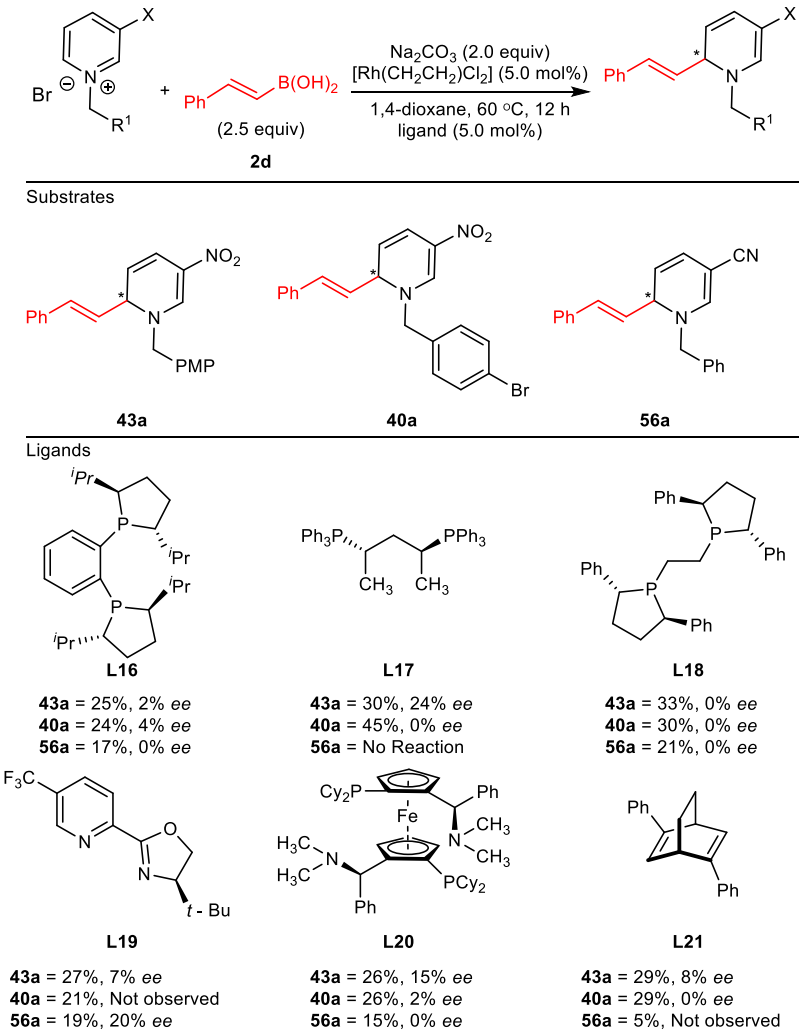
To distinguish between C6 and C4 addition, the chemical shift of the proton on the newly formed $sp^3$ hybridised carbon was found within the $^1H$ NMR. One product gave rise to a chemical shift of 4.56 ppm for this proton, the other product led to a chemical shift of 4.29 ppm. The product giving rise to the peak at 4.56 ppm was the result of C6 addition and the product that gave rise to the 4.29 ppm peak is the result of C4 addition.

The majority of additions within this report led to major C6 addition, alongside minor C2 addition. These products were assigned using the chemical shift of the proton on the newly formed $sp^3$ hybridised carbon. For most major additions, a chemical shift of around 4.7 ppm was recorded. This relatively high chemical shift indicates C6 addition had taken place instead of C4 addition. Using this information alongside coupling constants and the 2D NMR techniques, the remaining protons were assigned.

## 2.5. Enantioselective Variant

An enantioselective variant of the rhodium-catalysed addition of alkenylboron reagents to azinium salts was investigated. Within the literature, the enantioselective rhodium-catalysed addition of alkenylboron species to azinium salts use diphosphine ligands. Therefore, a variety of ligands were screened with a specific attention to diphosphine ligands (Table 5). It should be noted; these reactions were performed on the 0.05 mmol scale. Therefore, reduced yields to those observed on the 0.3 mmol scale are expected, as previously discussed.

**Table 5** Ligand Screening [ab]




[a] Reactions were performed with 0.05 mmol of the azinium salt in 1,4-dioxane (1 mL). Yields determined by $^1$H NMR analysis using 1,3,5 trimethoxybenzene as an internal standard. [b] Enantiomeric excess determined by HPLC analysis on a chiral stationary phase.

Initially, product **43a** was used to investigate the possibility of an enantioselective variant of this addition. **L16** led to a yield of 25% whilst introducing an *ee* of 2%. Ligand **L17** proved to be effective and increased the yield and *ee* to 30% and 24% respectively. **L18** increased the yield to 33% but

introduced no enantioselectivity. The nitrogen ligand (**L19**) led to the corresponding product in a 7% *ee*. The phosphorous-nitrogen ligand (**L20**) introduced an *ee* of 15% and the diene ligand (**L21**) led to an *ee* of 8%.

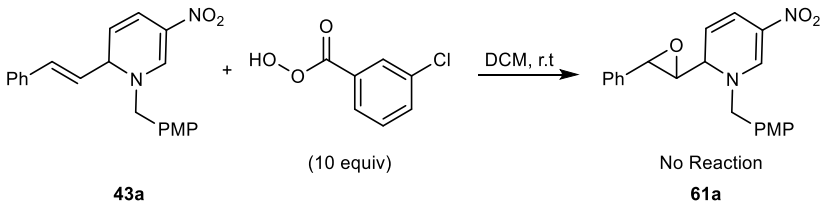
The halogen containing product (**40a**) was subjected to the same conditions. **L16** led to the corresponding product in a 24% yield and 4% *ee*. Satisfyingly, a yield of 45% was recorded when ligand **L17** was used, but no enantioselectivity was introduced. The final diphosphine ligand (**L18**) led to the corresponding product in a poor yield of 21% and introduced no enantioselectiivty. Unfortunately, the use of the nitrogen ligand (**L19**) led to a reduced yield of 21%. The phosphorous-nitrogen ligand (**L20**) led to the corresponding product in a yield of 26% alongside an *ee* of 2%. Finally, the diene ligand (**L21**) led to a yield of 29% and introduced no enantioselectivity.

Finally, an enantioselective variant for the production of **56a** was investigated. **L16** led to a poor yield of 17% and introduced no enantioselectivity. Notably, the use of ligand **L17** led to no addition being recorded. The final diphosphine ligand (**L18**) led to a reduced yield of 21% alongside no enantioselectivity. The nitrogen ligand (**L19**) led to an *ee* of 20%, but a reduced yield of 19% was also recorded. The phosphorous-nitrogen ligand (**L20**) led to a reduced yield of 15% and no enantioselectivity and the diene ligand (**L21**) led to only trace addition.

Further work is required in the development of an enantioselective variant of this addition. More work to screen a larger variety of ligands is required as well as further attempts to optimise the reaction conditions to increase the *ee*.

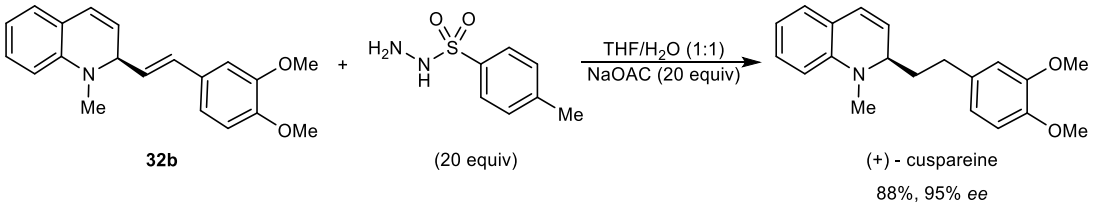
## 2.6. Reaction Derivatisation

An attempt was made to demonstrate the reactivity of the alkene after being installed on to the heterocycle using the rhodium-catalysed addition of an alkenylboron reagent. Initially an epoxidation was attempted. (Scheme 40).



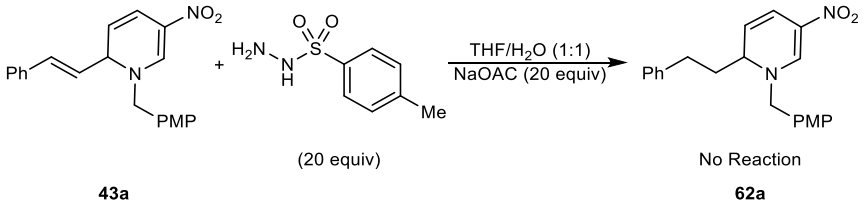

**Scheme 40**: Derivatisation of the alkenylation product via an epoxidation.[30]

Unfortunately, these reaction conditions led to no formation of the desired epoxide (**61a**).[43] Following this, an attempt was made to perform a hydrogenation using conditions previously demonstrated by Wang and Wei in the conversion of product **32b** (Scheme 23) into (+)-cuspareine (Scheme 41).[36]




**Scheme 41**: Hydrogenation of **32b** to afford (+) – cuspareine by the Wang and Wei group.[23]

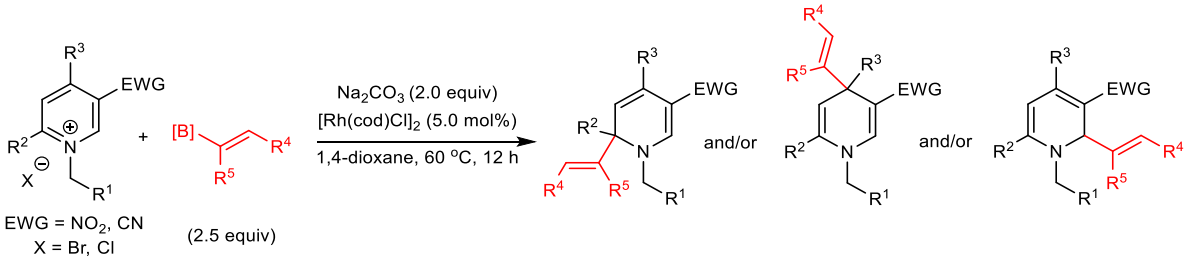
Unfortunately, the required transformation did not occur and none of the desired product (**62a**) formed (Scheme 42). Further work to expand this work to include a larger variety of reactions is required.




**Scheme 42**: Derivatisation of the alkenylation product via a hydrogenation.

## 2.7. Conclusion and Future Work

In summary, the scope for the rhodium-catalysed addition of alkenylboron reagents to azinium salts has been expanded (Scheme 43). This work has successfully included the nitro and cyano EWGs within the scope of this addition. This study has also included electron-rich and electron-deficient aryl alkenylboron substituents as well as substitutions to the pyridine core to the scope. Notably, this study demonstrated selective C2 addition, which has not been recorded within the literature.




**Scheme 43**: Rhodium-catalysed addition of alkenylboron reagents to azinium salts

Unfortunately, this reaction generates the products in poor yields and in some cases poor selectivity, further optimisation of the reaction conditions is required. In addition to this, further work should be performed to improve the scope of the azinium salt and alkenylboron reagent. This could be done by expanding the tolerated EWGs at the C3 position to other electron withdrawing functionality, such as halogens or ketones. Expansion of the alkenylboron scope could include meta/ortho substituted aryl functionality or cyclic alkenes, as these have precedent within the literature. Investigations into switchable reactivity could be performed, by altering the ligand or reaction conditions selective addition to C6, C4 and C2 could be achieved allowing the synthesis of a wider range of dihydropyridine or piperidine containing products.

This study was unable to develop an enantioselective variant of this addition, but demonstrated the potential of the reaction to become enantioselective. Further optimisation of the reaction conditions and the ligand choice is required to improve the *ee*.

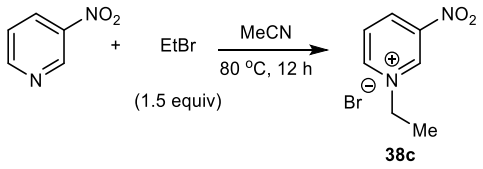
# 3. Experimental

### 3.1 General Information

All air-sensitive reactions were carried out under an inert atmosphere using oven-dried apparatus. Anhydrous 1,4-dioxane was purchased from Acros Organics and deoxygenated before use, using a stream of argon gas (30 min). All commercially available reagents were used as received unless otherwise stated. Petroleum ether refers to Sigma-Aldrich product 24587 (petroleum ether boiling point 40-60 °C). Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien 60F254 0.2 mm precoated plates. Compounds were visualized by exposure to UV light or by dipping the plates into solutions of potassium permanganate or vanillin followed by gentle heating. Flash column chromatography was carried out using silica gel (Fisher Scientific 60 Å particle size 35-70 micron or Fluorochem 60 Å particle size 40-63 micron). Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. The solvent of recrystallization is reported in parentheses. Infrared (IR) spectra were recorded on Bruker platinum alpha FTIR spectrometer on the neat compound using the attenuated total refraction technique. NMR spectra were acquired on Bruker AV500, Bruker AV500(III)HD, Bruker AV400, Bruker AV(III)400HD, or Bruker DPX400 spectrometers. $^{1}H$ and $^{13}C$ NMR spectra were referenced to external tetramethylsilane via the residual protonated solvent ($^{1}H$) or the solvent itself ($^{13}C$). All chemical shifts are reported in parts per million (ppm). For $CDCl_3$, the shifts are referenced to 7.26 ppm for $^{1}H$ NMR spectroscopy and 77.16 ppm for $^{13}C$ NMR spectroscopy. For $(CD_3)SO$, the shifts are referenced to 2.5 ppm for $^{1}H$ NMR spectroscopy and 39.52 ppm for $^{13}C$ NMR spectroscopy. Coupling constants (*J*) are quoted to the nearest 0.1 Hz. High-resolution mass spectra were recorded using electrospray ionization (ESI) techniques. Chiral HPLC analysis was performed on an Agilent 1290 series or Agilent 1260 series instrument using 4.6 x 250 mm columns.

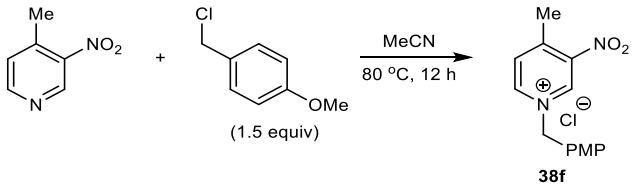
### 3.2. Preparation of Azinium Salts

#### 1-Ethyl-3-nitropyridin-1-ium (38c)




An oven dried vial was charged with 3-nitropyridine (0.99 g, 8.00 mmol) and ethyl bromide (0.9 mL, 12 mmol) which was then dissolved in acetonitrile (10 mL). The mixture was heated under reflux at 80 °C for 18 h. The mixture was then cooled to 0 °C and precipitated with $Et_2O$. The resulting precipitate was then collected by filtration and washed with $Et_2O$ and dried *in vacuo* which yielded a white solid **38c** (191 mg, 11%) m.p. 161-162 °C ($Et_2O$); IR (ATR) 3006, 2930, 1647, 1601, 1504 (N-O), 1181, 985, 893, 832, 671 $cm^{-1}$; $^1H$ NMR (400 MHz, $(CD_3)_2SO$) δ 10.20–10.18 (1H, m, NC**H**), 9.48 (1H, d, *J* = 6.1 Hz, NCHCHC**H**), 9.35-9.32 (1H, m, NC**H**CHCH), 8.44 (1H, t, *J* = 8.6, 6.1 Hz, NCHC**H**CH), 4.82 (2H, q, *J* = 7.3 Hz, C**H**$_2$), 1.59 (3H, t, *J* = 7.3 Hz, C**H**$_3$); $^{13}C$ NMR (101 MHz, $(CD_3)_2SO$) 155.2 (C), 144.6 (CH), 140.4 (CH), 131.6 (CH), 128.7 (CH), 57.5 ($CH_2$), 16.3 ($CH_3$); HRMS (ESI) Exact mass calculated for $[C_7H_9N_2O_2][M^+]$: 153.0659, found: 153.0657.

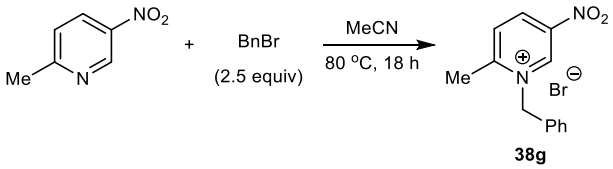
#### 1-(4-Methoxybenzyl)-4-methyl-3-nitropyridin-1-ium chloride (38f)




An oven dried microwave vial was charged with 4-methyl-3-nitropyridine (0.79 mL, 7.00 mmol) and 4-methoxybenzyl chloride (1.42 mL, 10.5 mmol) which was then dissolved in acetonitrile (10 mL). The mixture was heated under reflux at 80 °C for 18 h. The mixture was then cooled to 0 °C and precipitated with $Et_2O$. The resulting precipitate was then collected by filtration and washed with $Et_2O$ and dried *in vacuo* which yielded a brown solid **38f** (1.33 g, 73%). m.p. 168–169 °C ($Et_2O$); IR (ATR) 3062, 1652, 1600, 1503 (N-O), 1312, 1191, 929, 804, 742, 577 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 10.03–9.97 (2H, m, Ar**H**), 8.16 (1H, d, *J* = 5.8 Hz, NCHC**H**), 7.68 (2H, d, *J* = 8.4 Hz, Ar**H**), 6.91 (2H, d, *J* = 8.4 Hz, Ar**H**), 6.39 (2H, s, C**H**$_2$), 3.79 (3H, s, OC**H**$_3$), 2.87 (3H, s, CC**H**$_3$); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 161.1 (C), 154.0 (C), 147.9 (CH), 141.7 (CH), 132.2 (CH), 132.1 (2 x CH), 124.0 (C),

115.4 (2 x CH), 64.6 ($CH_2$), 55.6 ($OCH_3$), 29.8 (C), 21.6 ($CCH_3$); HRMS (ESI) Exact mass calculated for [$C_{14}H_{15}N_2O_3^+$] $[M]^+$ : 259.1082, found: 259.1075.

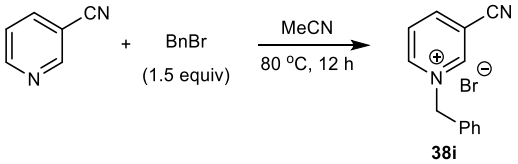
**1-Benzyl-2-methyl-5-nitropyridin-1-ium bromide (38g)**[42]



**38g**

An oven dried microwave vial was charged with 6-methoxy-3-nitropyridine (1.11 g, 8.00 mmol) and benzyl bromide (2.05 g, 12.0 mmol) which was then dissolved in acetonitrile (10 mL). The mixture was heated under reflux at 80 °C for 18 h. The mixture was then cooled to 0 °C and precipitated with $Et_2O$. The resulting precipitate was then collected by filtration and washed with $Et_2O$ and dried *in vacuo* which yielded a brown solid **38g** (0.78 g, 43%). m.p. 171–172 °C ($Et_2O$); IR (ATR) 2966, 1644, 1514 (N-O), 1353, 1150, 953, 779, 733, 693, 559 $cm^{-1}$; $^1H$ NMR (400 MHz, $(CD_3)_2SO$) δ 10.24 (1H, d, *J* = 2.4 Hz, NC**H**), 9.33 (1H, dd, *J* = 8.8, 2.4 Hz, C($CH_3$)CHC**H**), 8.36 (1H, d, *J* = 8.8 Hz, C($CH_3$)C**H**CH), 7.49–7.32 (5H, m, Ar**H**), 6.11 (2H, s, C**H**$_2$), 2.84 (3H, s, C**H**$_3$); $^{13}C$ NMR (101MHz, $(CD_3)_2SO$) δ 161.4 (C), 145.2 (C), 143.7 (CH), 139.5 (CH), 132.3 (C), 131.0 (CH), 129.2 (2 x CH), 129.0 (CH), 127.7 (2 x CH), 61.4 ($CH_2$), 20.4 ($CH_3$); HRMS (ESI) Exact mass calculated for $[C_{13}H_{13}N_2O_2]^+[M^+]$: 229.0972, found: 229.0972.

**1-Benzyl-3-cyanopyridin-1-ium (38i)**[42]

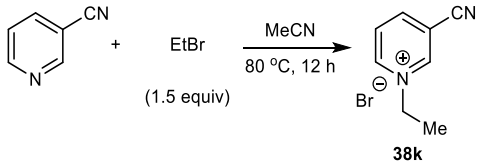


**38i**

An oven dried vial was charged with 3-cyanopyridine (833 mg, 8.00 mmol) and benzyl bromide (1.43 mL, 12.0 mmol) which was then dissolved in acetonitrile (10 mL). The mixture was heated under reflux at 80 °C for 18 h. The mixture was then cooled to 0 °C and precipitated with $Et_2O$. The resulting precipitate was then collected by filtration and washed with $Et_2O$ and dried *in vacuo* which yielded a white solid **38i** (536 mg, 34%). m.p. 157-158 °C ($Et_2O$); IR (ATR) 3040, 2900, 2246 (C≡N), 1439, 1307, 1159, 1144, 840, 678, 547 $cm^{-1}$; $^1H$ NMR (400 MHz, $(CD_3)_2SO$) δ 10.06 (1H, s,

NC**H**), 9.48 (1H, d, *J* = 6.2 Hz, NCHCHC**H**), 9.16–9.11 (1H, m, NC**H**CHCH), 8.42–8.34 (1H, m, NCHC**H**CH), 7.66–7.58 (2H, m, Ar**H**), 7.51–7.41 (3H, m, Ar**H**), 5.91 (2H, s, C**H**$_2$); $^{13}$C NMR (101 MHz, $(CD_3)_2SO$) δ 149.1 (CH), 149.0 (CH), 148.1 (CH), 133.4 (C), 129.6 (CH), 129.2 (2 x CH), 129.2 (2 x CH), 128.9 (CH), 113.9 (C), 113.3 (C), 63.9 ($CH_2$); HRMS (ESI) Exact mass calculated for $[C_{13}H_{11}N_2][M]^+$: 195.0917, found: 195.0911.

**3-Cyano-1-ethylpyridin-1-ium bromide (38k)**

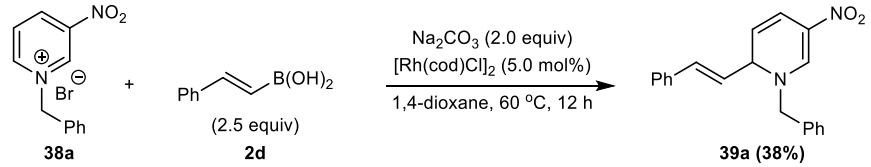


**38k**

An oven dried vial was charged with 3-cyanopyridine (833 mg, 8.00 mmol) and ethyl bromide (0.9 mL, 12 mmol) which was then dissolved in acetonitrile (10 mL). The mixture was heated under reflux at 80 °C for 18 h. The mixture was then cooled to 0 °C and precipitated with $Et_2O$. The resulting precipitate was then collected by filtration and washed with $Et_2O$ and dried *in vacuo* which yielded a white solid **38k** (155.7 mg, 9%). m.p. 252-253 °C ($Et_2O$); IR (ATR) 3081, 2919, 2245 (C≡N), 1417, 1234, 1095, 983, 834, 678, 473 cm$^{-1}$; $^1$H NMR (400 MHz, $(CD_3)_2SO$) δ 9.84 (1H, s, NC**H**), 9.39 (1H, d, *J* = 6.2 Hz, NCHCHC**H**), 9.12–9.08 (1H, m, NC**H**CHCH), 8.37 (1H, dd, *J* = 8.1, 6.2 Hz, NCHC**H**CH), 4.68 (2H, q, *J* = 7.3 Hz, C**H**$_2$), 1.58 (3H, t, *J* = 7.3 Hz, C**H**$_3$);$^{13}$C NMR (101 MHz, $(CD_3)_2SO$) 148.9 (CH), 148.3 (CH), 148.1 (CH), 128.4 (CH), 114.0 (C), 112.7 (C), 57.4 ($CH_2$), 15.8 ($CH_3$); HRMS (ESI) Exact mass calculated for $[C_8H_9N_2][M^+]$: 133.0760, found: 133.0757.

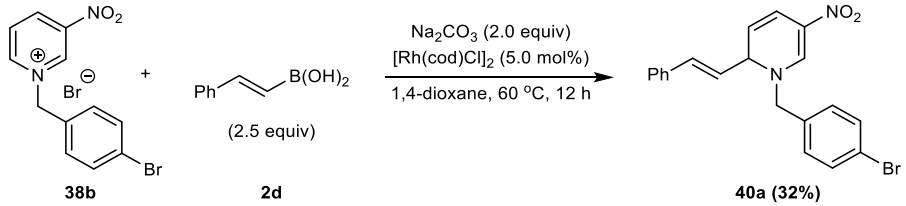
### 3.3. Racemic Rhodium-Catalysed Addition of Alkenylboron Species to Azinium Salts

**(*E*)-1-Benzyl-5-nitro-2-styryl-1,2-dihydropyridine (39a)**




An oven dried microwave vial was charged with **38a** (88.5 mg, 0.30 mmol), $[Rh(cod)Cl]_2$ (7.4 mg, 0.015 mmol), trans-2-phenylvinylboronic acid (111 mg, 0.75 mmol) and $Na_2CO_3$ (63.6 mg, 0.60 mmol). The vial was then purged with argon for 30 min. Freshly degassed (purged with argon for 30 mins) 1,4-dioxane (3 mL) was added. The resulting solution was stirred at 60 °C for 12 h. The resulting mixture was filtered through a plug of silica using EtOAc as an eluent and concentrated *in vacuo.* Purification by column chromatography (40% $Et_2O$/pentane) gave the product **39a** as a red oil (36.3 mg, 38%). $R_f$ = 0.28 (40% $Et_2O$/pentane); IR (ATR) 3205, 2922, 1619, 1492 (N-O), 1339, 1271, 1183, 992, 749, 493 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.22–8.18 (1H, m, NC**H**), 7.47–7.25 (10H, m, Ar**H**), 6.86–6.80 (1H, m, NCHCHC**H**), 6.45 (1H, d, *J* = 15.7 Hz, PhC**H**CH), 6.19 (1H, dd, *J* = 15.7 Hz, 8.5 Hz, PhCHC**H**), 5.08 (1H, dd, *J* = 10.3, 4.6 Hz, NCHC**H**CH), 4.73–4.67 (1H, *J* = 8.5,4.5 Hz, NC**H**CHCH), 4.57 (1H, d, *J* = 14.8 Hz, C**H**$_a$H$_b$), 4.47 (1H, d, *J* = 14.8 Hz, CH$_a$**H**$_b$); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 166.9 (C), 146.2 (CH), 135.5 (C), 133.5 (C), 133.2 (CH), 129.5 (2 x CH), 129.1 (CH), 128.9 (2 x CH), 128.9 (CH), 128.3 (2 x CH), 127.0 (2 x CH), 125.0 (CH), 118.5 (CH), 113.7 (CH), 60.8 (CH), 58.5 ($CH_2$); HRMS (ESI) Exact mass calculated for$[C_{20}H_{18}N_2O_2]$ $[M+H^+]$: 319.1441, found: 319.1441.

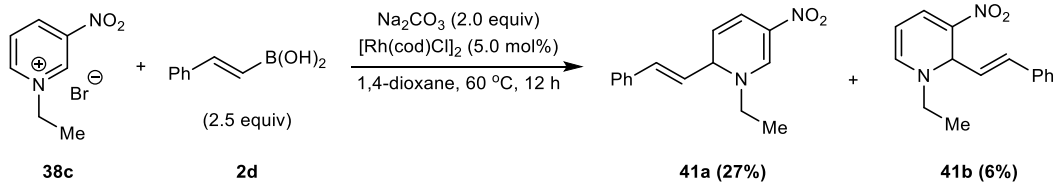
**(*E*)-1-(4-Bromobenzyl)-5-nitro-2-styryl-1,2-dihydropyridine (40a)**



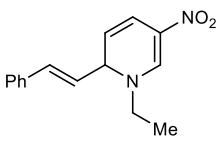

An oven dried microwave vial was charged with **38b** (88.2 mg, 0.3 mmol), $[Rh(cod)Cl]_2$ (7.4 mg, 0.015 mmol), trans-2-phenylvinylboronic acid (111 mg, 0.75 mmol) and $Na_2CO_3$ (63.6 mg, 0.6 mmol). The vial was then purged with argon for 30 min. Freshly degassed (purged with argon for 30 mins) 1,4-dioxane (5 mL) was added. The resulting solution was stirred at 60 °C for 12 h. The resulting mixture was filtered through a plug of silica using EtOAc as an eluent and concentrated

*in vacuo.* Purification by column chromatography (40% $Et_2O$/pentane) gave the product **40a** as a red oil (37.9 mg, 32%). $R_f$ = 0.49 (40% $Et_2O$/pentane); IR (ATR) 3055, 2921, 1632, 1487 (N-O), 1196, 890, 775, 691, 546, 476 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.16 (1H, s, NC**H**), 7.56 (2H, d, *J* = 8.2 Hz, Ar**H**), 7.41–7.28 (5H, m, Ar**H**), 7.17 (2H, d, *J* = 8.2 Hz, Ar**H**), 6.82 (1H, d, *J* = 10.3 Hz, NCHCHC**H**), 6.42 (1H, d, *J* = 15.7 Hz, PhC**H**CH), 6.16 (1H, dd, *J* = 15.7 Hz, 8.5 Hz, PhCHC**H**), 5.07 (1H, dd, *J* = 10.3 Hz, 4.5 Hz, NCHC**H**CH), 4.66 (1H, dd, *J* = 8.6 Hz, 4.5 Hz, NC**H**CHCH), 4.53 (1H, d, *J* = 14.9 Hz, C**H**$_a$H$_b$), 4.41 (1H, d, *J* = 15.0, CH$_a$**H**$_b$); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 145.9 (CH), 135.3 (C), 133.2 (CH), 132.7 (2 x CH), 132.7 (C), 129.9 (2 x CH), 129.0 (CH), 129.0 (2 x CH), 127.0 (2 x CH), 124.8 (CH), 123.2 (C), 123.1 (C), 118.5 (CH), 113.8 (CH), 60.7 (CH), 57.8 ($CH_2$); HRMS (ESI) Exact mass calculated for [$C_{20}H_{17}N_2O_2Br$] [M+$Na^+$]: 419.0366, found: 419.0355.

**(*E*)-1-Ethyl-5-nitro-2-styryl-1,2-dihydropyridine (41a) and (*E*)-1-ethyl-3-nitro-2-styryl-1,2-dihydropyridine (41b)**

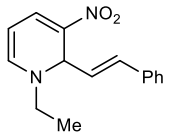



An oven dried microwave vial was charged with **38c** (69.6 mg, 0.3 mmol), $[Rh(cod)Cl]_2$ (7.4 mg, 0.015 mmol), trans-2-phenylvinylboronic acid (111 mg, 0.75 mmol) and $Na_2CO_3$ (63.6 mg, 0.6 mmol). The vial was then purged with argon for 30 min. Freshly degassed (purged with argon for 30 mins) 1,4-dioxane (5 mL) was added. The resulting solution was stirred at 60 °C for 12 h. The resulting mixture was filtered through a plug of silica using EtOAc as an eluent and concentrated *in vacuo.* Purification by column chromatography (40% EtOAc/PE) gave the product **41a** as a red oil (29.5 mg, 27%) and the product **41b** as a brown oil (4.1 mg, 6%).



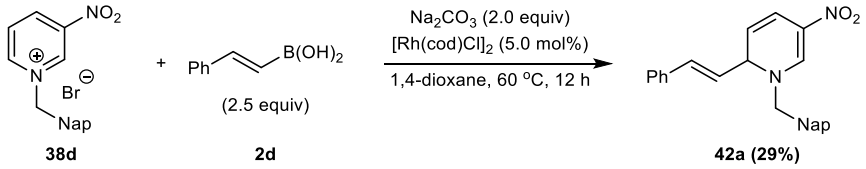

**(*E*)-1-Ethyl-5-nitro-2-styryl-1,2-dihydropyridine (41a).** $R_f$ = 0.33 (40% EtOAc/PE); IR (ATR) 3060, 2930, 1731, 1574, 1492 (N-O), 1178, 1129, 967, 749, 691 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.12 (1H, s, NC**H**), 7.42–7.25 (5H, m, Ar**H**), 6.81 (1H, d, *J* = 10.1 Hz, NCHCHC**H**), 6.53 (1H, d, *J* = 15.7 Hz, PhC**H**CH), 6.16 (1H, dd, *J* = 15.8 Hz, 8.4 Hz, PhCHC**H**), 5.10 (1H, dd, *J* = 10.7 Hz, 4.5 Hz, NCHC**H**CH), 4.83 (1H, dd, *J* = 8.5 Hz, 4.5 Hz, NC**H**CHCH), 3.46 (1H, m, C**H**$_a$H$_b$), 3.36 (1H, m, CH$_a$**H**$_b$), 1.34 (3H, t, *J* = 7.2 Hz, C**H**$_3$); $^{13}C$ NMR (101 MHz, $CDCl_3$) 145.5 (CH), 135.4 (C), 132.6 (CH), 128.9 (2 x CH), 128.8 (CH), 127.0 (2 x CH), 125.4

(CH), 122.3 (C), 118.6 (CH), 113.3 (CH), 61.7 (CH), 49.3 ($CH_2$), 13.7 ($CH_3$); HRMS (ESI) Exact mass calculated for [$C_{15}H_{16}N_2O_2$][M+$H^+$]: 257.1285, found: 257.1278.



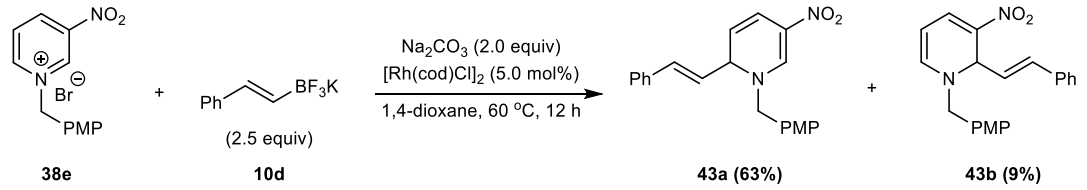

**(*E*)-1-Ethyl-3-nitro-2-styryl-1,2-dihydropyridine (41b).** $R_f$ = 0.55 (40% $Et_2O$/pentane); IR (ATR) 2924, 1613, 1510 (N-O), 1287, 1247, 1186, 1114, 937, 742, 693 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.68 (1H, d, *J* = 7.4 Hz, NCHCHC**H**), 7.40–7.23 (5H, m, Ar**H**), 6.90–6.82 (1H, m, NC**H**CHCH), 6.60 (1H, d, *J* = 15.8 Hz, CHCH=C**H**Ph), 6.22 (1H, dd, *J* = 15.8, 7.1 Hz, CHC**H**=CHPh), 5.74 (1H, d, *J* = 7.1 Hz, C**H**CH=CHPh), 4.95 (1H, t, *J* = 6.8 Hz, NCHC**H**CH), 3.57–3.46 (1H, m, C**H**$_a$H$_b$), 3.46–3.34 (1H, m, CH$_a$**H**$_b$), 1.37–1.32 (3H, m, C**H**$_3$); HRMS (ESI) Exact mass calculated for [$C_{15}H_{16}N_2O_2$][M+$H^+$]: 257.1285 found: 257.1278. Insufficient material for $^{13}C$ NMR, available spectroscopic data is consistent with the other 2-alkenylation product that has been isolated (**41a**).

**(*E*)-1-(Naphthalen-2-ylmethyl)-5-nitro-2-styryl-1,2-dihydropyridine (42a)**

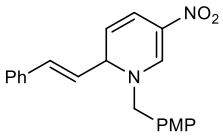



An oven dried microwave vial was charged with **38d** (103.47 mg, 0.30 mmol), $[Rh(cod)Cl]_2$ (7.4 mg, 0.015 mmol), trans-2-phenylvinylboronic acid (111 mg, 0.75 mmol) and $Na_2CO_3$ (63.6 mg, 0.60 mmol). The vial was then purged with argon for 30 min. Freshly degassed (purged with argon for 30 mins) 1,4-dioxane (5 mL) was added. The resulting solution was stirred at 60 °C for 12 h. The resulting mixture was filtered through a plug of silica using EtOAc as an eluent and concentrated *in vacuo.* Purification by column chromatography (60% $Et_2O$/pentane) gave the product **42a** as a red oil (8.7 mg, 29%). $R_f$ = 0.33 (60% $Et_2O$/pentane); IR (ATR) 3054, 1491 (N-O), 1282, 1196, 1176, 857, 748, 726, 524, 443 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.27 (1H, s, NC**H**), 7.96–7.23 (12H, m, Ar**H**), 6.87-6.82 (1H, m, NCHCHC**H**), 6.46 (1H, d, *J* = 15.7 Hz, PhC**H**CH), 6.22 (1H, dd, *J* = 15.7, 8.5 Hz, PhCHC**H**), 5.06 (1H, dd, *J* = 10.3, 4.5 Hz, NCHC**H**CH), 4.76–4.69 (1H, m, NC**H**CHCH), 4.76–4.68 (1H, m, C**H**$_a$H$_b$), 4.63 (1H, *J* = 14.8 Hz, CH$_a$**H**$_b$); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 146.2 (CH), 135.5 (C), 133.5 (C), 133.4 (C), 133.3 (CH), 130.8 (C), 129.7 (CH), 129.0 (2 x CH), 128.9 (CH), 128.0 (2 x CH), 127.9 (CH), 127.1 (CH), 127.0 (2 x CH), 127.0 (CH), 125.3 (CH), 125.0 (CH), 122.9 (C), 118.5 (CH), 113.8 (CH), 60.7 (CH), 58.7 ($CH_2$); HRMS (ESI) Exact mass calculated for [$C_{24}H_{20}N_2O_2$][M+$Na^+$]: 391.1417, found: 391.1419.

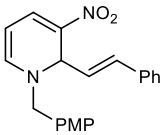
**(*E*)-1-(4-Methoxybenzyl)-5-nitro-2-styryl-1,2-dihydropyridine (43a) and (*E*)-1-(4-methoxybenzyl)-3-nitro-2-styryl-1,2-dihydropyridine (43b)**




An oven dried microwave vial was charged with **38e** (97.5 mg, 0.30 mmol), $[Rh(cod)Cl]_2$ (7.4 mg, 0.015 mmol), potassium (*E*)-trifluoro(styryl)borate (157 mg, 0.75 mmol) and $Na_2CO_3$ (63.6 mg, 0.60 mmol). The vial was then purged with argon for 30 min. Freshly degassed (purged with argon for 30 mins) 1,4-dioxane (3 mL) was added. The resulting solution was stirred at 60 °C for 12 h. The resulting mixture was filtered through a plug of silica using EtOAc as an eluent and concentrated *in vacuo.* Purification by column chromatography (40% $Et_2O$/pentane) gave the product **43a** as a red oil (66.1 mg, 63%) and the product **43b** as a brown oil (9.4 mg, 9%).

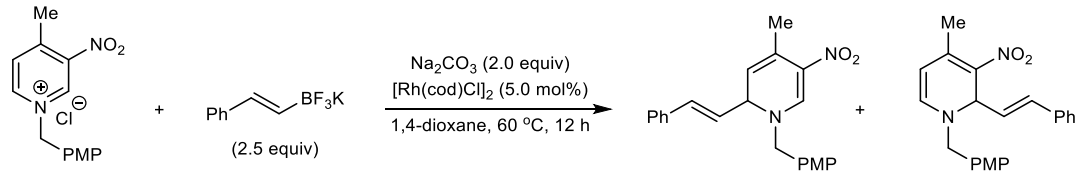


**(*E*)-1-(4-Methoxybenzyl)-5-nitro-2-styryl-1,2-dihydropyridine (43a).** $R_f$ = 0.27 (50% $Et_2O$/pentane); IR (ATR) 2930, 1610, 1512 (N-O), 1284, 1170, 1029, 908, 728, 692, 529 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.19–8.16 (1H, m, NC**H**), 7.42-7.28 (5H, m, Ar**H**), 7.23–7.18 (2H, m, Ar**H**), 6.97–6.92 (2H, m, Ar**H**), 6.84–6.79 (1H, m, NCHCHC**H**), 6.45 (1H, d, *J* = 15.7 Hz, PhC**H**CH), 6.17 (1H, dd, *J* = 15.7 Hz, 8.6 Hz, PhCHC**H**), 5.05 (1H, dd, *J* = 10.2 Hz, 4.5 Hz, NCHC**H**CH), 4.72–4.67 (1H, m, NC**H**CHCH), 4.48 (1H, d, *J* = 14.5 Hz, C**H**$_a$H$_b$), 4.41 (1H, d, *J* = 14.6 Hz, CH$_a$**H**$_b$), 3.83 (3H, s, C**H**$_3$); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 160.3 (C), 146.0 (CH), 135.5 (C), 133.0 (CH), 129.9 (2 x CH), 128.9 (2 x CH), 128.9 (CH), 127.0 (2 x CH), 125.1 (C), 125.1 (CH), 122.6 (C), 118.5 (CH), 114.8 (2 x CH), 113.6 (CH), 60.6 (CH), 58.0 ($CH_2$), 55.5 ($CH_3$); HRMS (ESI) Exact mass calculated for$[C_{21}H_{20}N_2O_3]$ $[M+H^+]$: 349.1547, found: 349.1549.

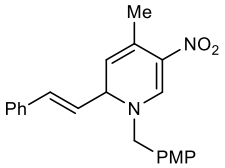


**(*E*)-1-(4-Methoxybenzyl)-3-nitro-2-styryl-1,2-dihydropyridine (43b).** $R_f$ = 0.29 (50% $Et_2O$/pentane); IR (ATR) 2923, 1610, 1511 (N-O), 1437, 1284, 1151, 963, 738, 691, 506 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.69–7.65 (1H, m, NCHCHC**H**), 7.40-7.17 (5H, m, Ar**H**), 7.24–7.21 (2H, m, Ar**H**), 6.94–6.89 (2H, m, Ar**H**), 6.86–6.82 (1H, d, *J* = 6.5 Hz, NC**H**CHCH), 6.58 (1H, d, *J* = 15.9 Hz, CHCH=C**H**Ph), 6.22 (1H, dd, *J* = 15.8, 7.4 Hz, CHC**H**=CHPh), 5.64–5.60 (1H, m, C**H**CH=CHPh), 4.95 (1H, dd, *J* = 7.3, 6.3 Hz, NCHC**H**CH), 4.53–4.40 (2H, m, C**H**$_2$), 3.83–3.80 (3H, m, C**H**$_3$); HRMS (ESI) Exact mass calculated for $[C_{21}H_{20}N_2O_3]$ $[M+H^+]$: 349.1547 found: 349.1552. Insufficent material for $^{13}C$ NMR, available spectroscopic data is consistent with the other 2-alkenylation product that has been isolated (**8a**).

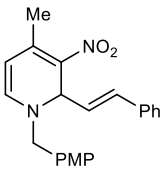
**(*E*)-1-(4-Methoxybenzyl)-4-methyl-3-nitro-2-styryl-1,2-dihydropyridine (44a) and (*E*)-1-(4-methoxybenzyl)-4-methyl-5-nitro-2-styryl-1,2-dihydropyridine (44b)**




An oven dried microwave vial was charged with **38f** (77.8 mg, 0.30 mmol), $[Rh(cod)Cl]_2$ (7.4 mg, 0.015 mmol), potassium (*E*)-trifluoro(styryl)borate (157 mg, 0.75 mmol) and $Na_2CO_3$ (63.6 mg, 0.60 mmol). The vial was then purged with argon for 30 min. Freshly degassed (purged with argon for 30 mins) 1,4-dioxane (3 mL) was added. The resulting solution was stirred at 60 °C for 12 h. The resulting mixture was filtered through a plug of silica using EtOAc as an eluent and concentrated *in vacuo.* Purification by column chromatography (40% $Et_2O$/pentane) gave the product **44a** as a red oil (11.3 mg, 10%) and the product **44b** as an orange oil (17.4 mg, 16%).



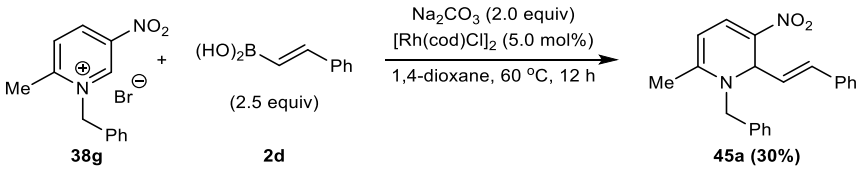

**(*E*)-1-(4-Methoxybenzyl)-4-methyl-5-nitro-2-styryl-1,2-dihydropyridine (44a).** $R_f$ = 0.22 (40% $Et_2O$/pentane); IR (ATR) 2930, 1735, 1484 (N-O), 1390, 1271, 1218, 1148, 959, 851, 695 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.32 (1H, s, NC**H**), 7.41–7.29 (5H, m, Ar**H**), 7.22–7.18 (2H, m, Ar**H**), 6.96–6.91 (2H, m, Ar**H**), 6.40 (1H, d, *J* = 15.7 Hz, PhC**H**CH), 6.15 (1H, dd, *J* = 15.7, 8.5 Hz, PhCHC**H**), 4.77–4.73 (1H, m, NCHC**H**), 4.62–4.56 (1H, m, NC**H**CH), 4.47 (1H, d, *J* = 14.6 Hz, C**H**$_a$H$_b$), 4.42 (1H, d, *J* = 14.6 Hz, CH$_a$**H**$_b$), 3.83 (3H, s, OC**H**$_3$), 2.23–2.20 (3H, m, CC**H**$_3$); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 160.2 (C), 147.8 (CH), 135.6 (C), 132.5 (CH), 129.9 (2 x CH), 129.7 (C), 128.9 (2 x CH), 128.7 (2 x CH), 128.4 (C), 127.0 (CH), 125.4 (CH), 125.3 (C), 114.8 (2 x CH), 111.9 (CH), 60.9 (CH), 57.8 ($CH_2$), 55.5 ($CH_3$), 21.5 ($CH_3$); HRMS (ESI) Exact mass calculated for [$C_{22}H_{22}NO_3$] [M+H$^+$]: 363.1703, found: 363.1700.




**(*E*)-1-(4-Methoxybenzyl)-4-methyl-3-nitro-2-styryl-1,2-dihydropyridine (44b).** $R_f$ = 0.27 (40% $Et_2O$/pentane); IR (ATR) 2922, 1600, 1480 (N-O), 1389, 1247 , 1149, 1149, 960, 820, 741 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.46–7.24 (7H, m, Ar**H**), 7.00–6.95 (2H, m, Ar**H**), 6.78–6.75 (1H, m, NC**H**CH), 6.62 (1H, d, *J* = 15.9 Hz, CHCH=C**H**Ph), 6.30 (1H, dd, *J* = 15.9 Hz, 7.2 Hz, CHC**H**=CHPh), 5.75–5.71 (1H, m, C**H**CH=CHPh), 4.92 (1H, d, *J* = 6.4 Hz, NCHC**H**), 4.56 (1H, d, *J* = 14.6 Hz, C**H**$_a$H$_b$), 4.50 (1H, d, *J* = 14.6 Hz, CH$_a$**H**$_b$), 3.87 (3H, s, OC**H**$_3$), 2.51 (3H, s, CC**H**$_3$); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 160.0 (C), 148.3 (C), 145.3 (CH), 136.2 (C), 132.3 (CH), 129.7 (2 x CH), 128.7 (2 x CH), 128.2 (CH), 127.1 (2 x CH), 126.9 (C), 126.6

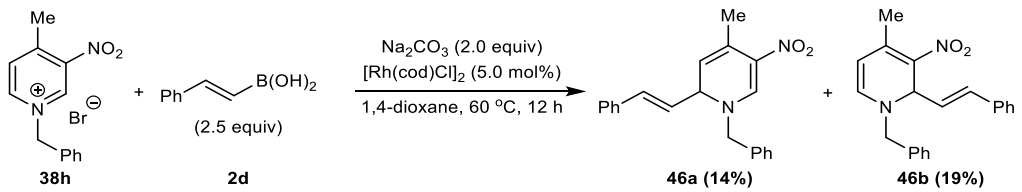
(C), 123.4 (CH), 114.7 (2 x CH), 99.8 (CH), 58.7 (CH), 57.5 ($CH_2$), 55.5 ($CH_3$), 22.8 ($CH_3$); HRMS (ESI) Exact mass calculated for [$C_{22}H_{22}NO_3$] [M+H$^+$]: 363.1703, found: 363.1698.

**(*E*)-1-Benzyl-6-methyl-3-nitro-2-styryl-1,2-dihydropyridine (45a)**

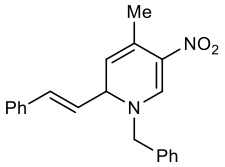



An oven dried microwave vial was charged with **38g** (92.4 mg, 0.30 mmol), $[Rh(cod)Cl]_2$ (7.4 mg, 0.015 mmol), trans-2-phenylvinylboronic acid (111 mg, 0.75 mmol) and $Na_2CO_3$ (63.6 mg, 0.60 mmol). The vial was then purged with argon for 30 min. Freshly degassed (purged with argon for 30 mins) 1,4-dioxane (5 mL) was added. The resulting solution was stirred at 60 °C for 12 h. The resulting mixture was filtered through a plug of silica using EtOAc as an eluent and concentrated *in vacuo.* Purification by column chromatography (40% EtOAc/PE) gave the product **45a** as a brown oil (34.3 mg, 30%). $R_f$ = 0.34 (40% $Et_2O$/pentane); IR (ATR) 3027, 2924, 1732, 1598, 1493 (N-O), 1430, 1237, 1168, 913, 731 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.66 (1H, d, *J* = 7.4 Hz, C($CH_3$)CHC**H**), 7.42–7.19 (10H, m, Ar**H**), 6.52 (1H, d, *J* = 6.55 Hz, CHCH=C**H**Ph), 6.22 (1H, dd, *J* = 15.8, 7.0 Hz, CHC**H**=CHPh), 5.66 (1H, d, *J* = 7.0 Hz, C**H**CH=CHPh), 5.00 (1H, d, *J* = 7.4 Hz, C($CH_3$)C**H**CH), 4.81 (1H, d, *J* = 16.4 Hz, C**H**$_a$H$_b$), 4.54 (1H, d, *J* = 16.4 Hz, CH$_a$**H**$_b$), 2.15 (3H, s, C**H**$_3$); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 157.1 (C), 136.0 (C), 135.4 (C), 134.1 (CH), 132.5 (CH), 129.4 (2 x CH), 128.7 (2 x CH), 128.4 (2 x CH), 127.0 (2 x CH), 126.5 (2 x CH), 124.6 (C), 121.5 (CH), 96.6 (CH), 60.4 (CH), 53.8 ($CH_2$), 20.7 ($CH_3$); HRMS (ESI) Exact mass calculated for [$C_{21}H_{20}N_2O_2$][M+H$^+$]: 333.1598, found: 333.1597.

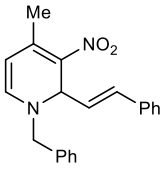
**(*E*)-1-Benzyl-4-methyl-5-nitro-2-styryl-1,2-dihydropyridine (46a) and (*E*)-1-benzyl-4-methyl-3-nitro-2-styryl-1,2-dihydropyridine (46b)**



An oven dried microwave vial was charged with **38h** (92.8 mg, 0.3 mmol), $[Rh(cod)Cl]_2$ (7.4 mg, 0.015 mmol), trans-2-phenylvinylboronic acid (111 mg, 0.75 mmol) and $Na_2CO_3$ (63.6 mg, 0.6 mmol). The vial was then purged with argon for 30 min. Freshly degassed (purged with argon for 30 mins) 1,4-dioxane (5 mL) was added. The resulting solution was stirred at 60 °C for 12 h. The resulting mixture was filtered through a plug of silica using EtOAc as an eluent and concentrated *in vacuo.* Purification by column chromatography (40% $Et_2O$/pentane) gave the product **46a** as a red oil (20.7 mg, 14%) and the product **46b** as a brown oil (11.7 mg, 19%).

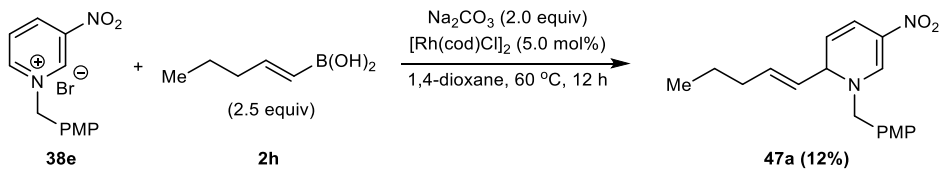



**(*E*)-1-Benzyl-4-methyl-5-nitro-2-styryl-1,2-dihydropyridine (46a).** $R_f$ = 0.29 (40% $Et_2O$/pentane); IR (ATR) 2924, 1524, 1492 (N-O) 1349, 1204, 1167, 912, 732, 694, 561 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.33 (1H, s, NC**H**), 7.46-7.24 (10H, m, Ar**H**), 6.40 (1H, d, *J* = 15.7 Hz, PhC**H**CH), 6.16 (1H, dd, J = 15.7 Hz, 8.5 Hz, PhCHC**H**) 4.79–4.75 (1H, m, NCHC**H**), 4.58-4.45 (1H, m, NC**H**CH), 4.60-4.54 (1H, m, C**H**$_a$H$_b$), 4.52 (1H, d, *J* = 14.8 Hz, CH$_a$**H$_b$**), 2.22 (3H, s, C**H$_3$**); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 171.3 (C), 148.1 (CH), 146.0 (C), 135.6 (C), 133.7 (C), 132.6 (CH), 129.4 (2 x CH), 129.0 (CH), 128.9 (2 x CH), 128.8 (CH), 128.2 (2 x CH), 127.0 (2 x CH), 125.2 (CH), 112.0 (CH), 61.7 (CH), 58.2 ($CH_2$), 21.5 ($CH_3$); HRMS (ESI) Exact mass calculated for $[C_{21}H_{20}N_2O_2][M+H^+]$: 333.1598, found: 333.1595.




**(*E*)-1-Benzyl-4-methyl-3-nitro-2-styryl-1,2-dihydropyridine (46b).** $R_f$ = 0.43 (40% $Et_2O$/pentane); IR (ATR) 2922, 1601, 1479 (N-O) 1430, 1073, 1010, 932, 729, 689, 458 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.43–7.23 (10H, m, Ar**H**), 6.71 (1H, d, *J* = 6.4 Hz, NC**H**CH), 6.56 (1H, d, *J* = 15.8 Hz, CHCH=C**H**Ph), 6.24 (1H, dd, *J* = 15.8, 7.2 Hz, CHC**H**=CHPh), 5.65 (1H, d, *J* = 7.1 Hz, C**H**CH=CHPh), 4.87 (1H, d, *J* = 6.4 Hz, NCHC**H**), 4.56 (1H, d, *J* = 14.9 Hz, C**H**$_a$H$_b$), 4.47 (1H, d, *J* = 14.9 Hz, CH$_a$**H$_b$**), 2.44 (3H, s, C**H$_3$**); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 148.1 (C), 145.4 (CH), 136.2 (C), 134.9 (C), 132.4 (CH), 129.4 (2 x CH), 128.8 (CH), 128.7 (2 x CH), 128.3 (CH), 128.1 (2 x CH), 127.0 (2 x CH), 123.8 (C), 121.4 (CH), 99.9 (CH), 59.0 (CH), 57.9 ($CH_2$), 22.7 ($CH_3$); HRMS (ESI) Exact mass calculated for $[C_{20}H_{20}N_2O_2]$ $[M+H^+]$: 333.1598, found: 333.1595.

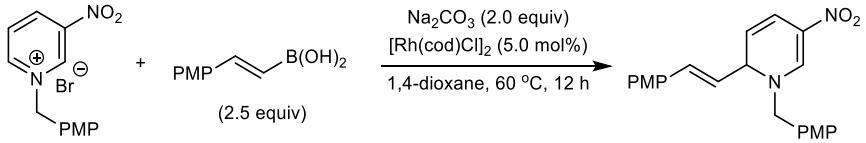
**(*E*)-1-(4-Methoxybenzyl)-5-nitro-2-(pent-1-en-1-yl)-1,2-dihydropyridine (47a)**




An oven dried microwave vial was charged with **38e** (97.3 mg, 0.30 mmol), $[Rh(cod)Cl]_2$ (7.4 mg, 0.015 mmol), (*E*)-pent-1-en-ylboronic acid (85.5 mg, 0.75 mmol) and $Na_2CO_3$ (63.6 mg, 0.60

mmol). The vial was then purged with argon for 30 min. Freshly degassed (purged with argon for 30 mins) 1,4-dioxane (5 mL) was added. The resulting solution was stirred at 60 °C for 12 h. The resulting mixture was filtered through a plug of silica using EtOAc as an eluent and concentrated *in vacuo.* Purification by column chromatography (40% EtOAc/PE) gave the product **47a** as a red oil (13.7 mg, 12%). $R_f$ = 0.45 (40% $Et_2O$/pentane); IR (ATR) 2927, 1612, 1494 (N-O), 1312, 1247, 1170, 1031, 820, 727, 527 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.13 (1H, s, NC**H**), 7.20–7.14 (2H, m, Ar**H**), 6.95–6.90 (2H, m, Ar**H**), 6.74 (1H, d, *J* = 10.3 Hz, NCHCHC**H**), 5.63–5.57 (1H, m, $(CH_2)$C**H**CH), 5.51–5.44 (1H, m, $(CH_2)$CHC**H**), 4.98 (1H, dd, *J* = 10.3, 4.4 Hz, NCHC**H**CH), 4.48 (1H, dd, *J* = 8.5, 4.5 Hz, NC**H**CHCH), 4.43 (1H, d, *J* = 14.5 Hz, C**H**$_a$H$_b$), 4.39–4.33 (1H, m, CH$_a$**H**$_b$), 3.82 (3H, s, OC**H**$_3$), 2.08–2.02 (2H, m, $CH_3CH_2$C**H**$_2$), 1.46–1.39 (2H, m, $CH_3$C**H**$_2CH_2$), 0.93 (3H, t, *J* = 7.4 Hz, C**H**$_3CH_2CH_2$); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 160.2 (C), 146.2 (CH), 135.3 (CH), 129.9 (2 x CH), 126.7 (CH), 125.2 (C), 118.0 (CH), 114.8 (2 x CH), 114.5 (CH), 60.6 (CH), 57.7 ($CH_2$), 55.5 ($CH_3$), 34.1 ($CH_2$), 29.8 (C), 22.2 ($CH_2$), 13.8 ($CH_3$); HRMS (ESI) Exact mass calculated for [$C_{18}H_{22}N_2O_3$][M+H$^+$]: 315.1703, found:315.1696.

**(*E*)-1-(4-Methoxybenzyl)-2-(4-methoxystyryl)-5-nitro-1,2-dihydropyridine (48a)**

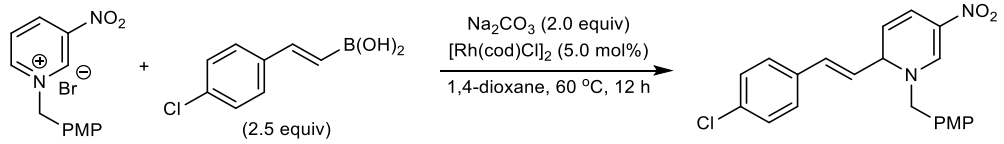



**38e** **2k** **48a (21%)**

An oven dried microwave vial was charged with **38e** (97.3 mg, 0.30 mmol), $[Rh(cod)Cl]_2$ (7.4 mg, 0.015 mmol), (*E*)-(4-methoxystyryl)boronic acid (133.5 mg, 0.75 mmol) and $Na_2CO_3$ (63.6 mg, 0.60 mmol). The vial was then purged with argon for 30 min. Freshly degassed (purged with argon for 30 mins) 1,4-dioxane (5 mL) was added. The resulting solution was stirred at 60 °C for 12 h. The resulting mixture was filtered through a plug of silica using EtOAc as an eluent and concentrated *in vacuo.* Purification by column chromatography (40% $Et_2O$/pentane) gave the product **48a** as a red oil (27.9 mg, 21%). $R_f$ = 0.52 (40% $Et_2O$/pentane); IR (ATR) 2933, 1732, 1574, 1510 (N-O), 1283, 1170, 1029, 816, 751, 552 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.17 (1H, s, NC**H**), 7.35–7.31 (2H, m, Ar**H**), 7.22–7.18 (2H, m, Ar**H**), 6.96–6.91 (2H, m, Ar**H**), 6.90–6.86 (2H, m, Ar**H**), 6.80 (1H, d, *J* = 10.0 Hz, $(NO_2)$C**H**CH), 6.39 (1H, d, *J* = 15.7 Hz, C**H**CHCHN), 6.02 (1H, dd, *J* = 15.7, 8.6 Hz, CHC**H**CHN), 5.04 (1H, dd, *J* = 10.2, 4.5 Hz, $(NO_2)$CCHC**H**), 4.65 (1H, dd, *J* = 8.6, 4.5 Hz, CHCHC**H**N), 4.49 (1H, d, *J* = 14.6 Hz, C**H**$_a$H$_b$), 4.40 (1H, d, *J* = 14.5 Hz, CH$_a$**H**$_b$), 3.84–3.79 (6H, m, C**H**$_3$); $^{13}C$ NMR (101 MHz,

$CDCl_3$) δ 160.2 (C), 146.0 (CH), 132.7 (CH), 129.9 (2 x CH), 128.8 (C), 128.3 (2 x CH), 128.1 (C), 125.2 (C), 122.8 (CH), 122.5 (C), 118.3 (CH), 114.8 (2 x CH), 114.3 (2 x CH), 113.9 (CH), 60.8 (CH), 57.9 ($CH_2$), 55.5 ($CH_3$), 55.5 ($CH_3$); HRMS (ESI) Exact mass calculated for [$C_{22}H_{22}N_2O_4$][M+$Na^+$]: 401.1472, found: 401.1468.

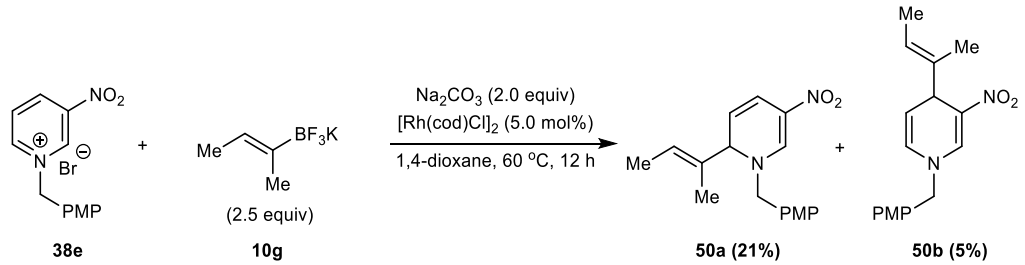
**(*E*)-2-(4-Chlorostyryl)-1-(4-methoxybenzyl)-5-nitro-1,2-dihydropyridine (49a)**



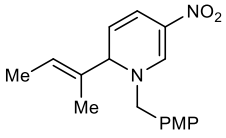

**38e** **2l** **49a (33%)**

An oven dried microwave vial was charged with **38e** (97.3 mg, 0.30 mmol), $[Rh(cod)Cl]_2$ (7.4 mg, 0.015 mmol), (*E*)-(4-chlorostyryl)boronic acid (136.8 mg, 0.75 mmol) and $Na_2CO_3$ (63.6 mg, 0.60 mmol). The vial was then purged with argon for 30 min. Freshly degassed (purged with argon for 30 mins) 1,4-dioxane (5 mL) was added. The resulting solution was stirred at 60 °C for 12 h. The resulting mixture was filtered through a plug of silica using EtOAc as an eluent and concentrated *in vacuo.* Purification by column chromatography (40% $Et_2O$/pentane) gave the product **49a** as a red oil (3.3 mg, 33%). $R_f$ = 0.56 (40% $Et_2O$/pentane); IR (ATR) 2930, 1633, 1573, 1490 (N-O), 1305, 1246, 1169, 967, 807, 697 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.17 (1H, d, *J* = 1.7 Hz, NC**H**), 7.39–7.23 (4H, m, Ar**H**), 7.22–7.18 (2H, m, Ar**H**), 6.96–6.92 (2H, m, Ar**H**), 6.84-6.81 (1H, m, $(NO_2)$CC**H**CH), 6.40 (1H, d, *J* = 15.7 Hz, C**H**CHCHN), 6.13 (1H, dd, *J* = 15.7, 8.4 Hz, CHC**H**CHN), 5.04 (1H, dd, *J* = 10.2, 4.6 Hz, $(NO_2)$CHC**H**), 4.72–4.67 (1H, m, CHCHC**H**N), 4.49–4.34 (1H, m, C$\mathbf{H}_a$$H_b$), 4.41 (1H, d, *J* = 14.6 Hz, $CH_a$$\mathbf{H}_b$), 3.85 (3H, s, C$\mathbf{H}_3$); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 160.3 (C), 145.8 (CH), 134.6 (C), 134.0 (C), 131.7 (CH), 129.9 (2 x CH), 129.1 (2 x CH), 128.2 (2 x CH), 127.5 (C), 125.7 (CH), 125.1 (C), 118.8 (CH), 114.9 (2 x CH), 113.3 (CH), 60.5 (CH), 58.2 ($CH_2$), 55.5 ($CH_3$); HRMS (ESI) Exact mass calculated for [$C_{21}H_{19}N_2O_3Cl$][M+$H^+$]: 383.1157, found: 383.1154.

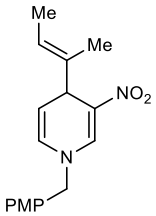
**(*E*)-2-(But-2-en-2-yl)-1-(4-methoxybenzyl)-5-nitro-1,2-dihydropyridine (50a) and (*E*)-2-(but-2-en-2-yl)-1-(4-methoxybenzyl)-3-nitro-1,2-dihydropyridine (50b)**




An oven dried microwave vial was charged with **38e** (97.3 mg, 0.30 mmol), $[Rh(cod)Cl]_2$ (7.4 mg, 0.015 mmol), (*Z*)-but-2-en-2-yltrifluoro-l4-borane potassium salt (121.5 mg, 0.75 mmol) and $Na_2CO_3$ (63.6 mg, 0.60 mmol). The vial was then purged with argon for 30 min. Freshly degassed (purged with argon for 30 mins) 1,4-dioxane (5 mL) was added. The resulting solution was stirred at 60 °C for 12 h. The resulting mixture was filtered through a plug of silica using EtOAc as an eluent and concentrated *in vacuo.* Purification by column chromatography (40% $Et_2O$/pentane) gave the product **50a** as a red oil (27.9 mg, 21%) and product **50b** as a brown oil (6 mg, 5%).

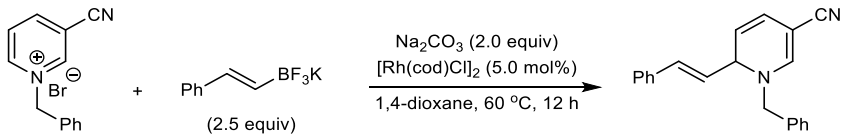



**(*E*)-2-(But-2-en-2-yl)-1-(4-methoxybenzyl)-3-nitro-1,2-dihydropyridine (50a).** $R_f$ = 0.61 (40% $Et_2O$/pentane); IR (ATR) 2917, 1636, 1576, 1513 (N-O), 1248, 1210, 1171, 1031, 820, 752 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.26–8.23 (1H, m, NC**H**), 7.18–7.12 (2H, m, Ar**H**), 6.94–6.89 (2H, m, Ar**H**), 6.79–6.74 (1H, m, NCHCHC**H**), 5.43–5.37 (1H, m, $(CH_3)$C**H**), 4.90 (1H, dd, *J* = 10.4, 4.2 Hz, NCHC**H**CH), 4.56 (1H, d, *J* = 4.2 Hz, NC**H**CHCH), 4.28 (1H, d, *J* = 14.5 Hz, C**H**$_a$H$_b$), 4.24 (1H, d, *J* = 14.4 Hz, CH$_a$**H**$_b$), 3.82 (3H, s, O(C**H**$_3$)), 1.70–1.65 (6H, m, C**H**$_3$); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 160.2 (C), 147.1 (CH), 133.0 (C), 129.9 (2 x CH), 125.0 (C), 124.4 (CH), 121.8 (C), 118.8 (CH), 115.1 (CH), 114.7 (2 x CH), 66.7 (CH), 57.5 ($CH_2$), 55.5 ($CH_3$), 13.5 ($CH_3$), 11.0 ($CH_3$); HRMS (ESI) Exact mass calculated for $[C_{17}H_{20}N_2O_3][M+H^+]$: 301.1547, found: 301.1539.




**(*E*)-2-(But-2-en-2-yl)-1-(4-methoxybenzyl)-3-nitro-1,2-dihydropyridine (50b).** $R_f$ = 0.51 (40% EtOAc/PE); IR (ATR) 2921, 1664, 1584, 1512 (N-O), 1382, 1249, 1171, 1030, 745, 728 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.01 (1H, s, NC**H**), 7.18–7.13 (2H, m, Ar**H**), 6.93–6.89 (2H, m, Ar**H**), 5.89–5.85 (1H, m, NC**H**CHCH), 5.43–5.34 (1H, m, $(CH_3)$C**H**), 5.07 (1H, dd, *J* = 7.5, 5.0 Hz, NCHC**H**CH), 4.42 (2H, s, C**H**$_2$), 4.29 (1H, d, *J* = 5.1 Hz, NCHCHC**H**), 3.83–3.79 (3H, m, OC**H**$_3$), 1.61–1.57 (6H, m, C**H**$_3$); HRMS (ESI) Exact mass calculated for $[C_{17}H_{20}N_2O_3][M+H^+]$: 301.1547 found: 301.1534. Insufficient material for $^{13}C$ NMR, available spectroscopic data is consistent with the other 6-alkenylation product that has been isolated (**50a**).

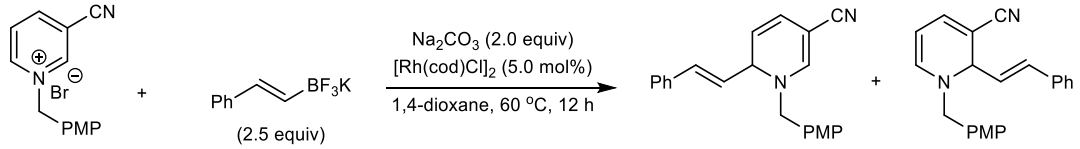
**(*E*)-1-Benzyl-6-styryl-1,6-dihydropyridine-3-carbonitrile (56a)**




**38i** **10d** **56a (44%)**

An oven dried microwave vial was charged with **38i** (82.5 mg, 0.30 mmol), $[Rh(cod)Cl]_2$ (7.4 mg, 0.015 mmol), potassium (*E*)-trifluoro(styryl)borate (157 mg, 0.75 mmol) and $Na_2CO_3$ (63.6 mg, 0.60 mmol). The vial was then purged with argon for 30 min. Freshly degassed (purged with argon for 30 mins) 1,4-dioxane (3 mL) was added. The resulting solution was stirred at 60 °C for 12 h. The resulting mixture was filtered through a plug of silica using EtOAc as an eluent and concentrated *in vacuo.* Purification by column chromatography (40% $Et_2O$/pentane) gave the product **56a** as a yellow oil (39.1 mg, 44%). $R_f$ = 0.17 (40% $Et_2O$/pentane); IR (ATR) 3027, 2919, 2192 (C≡N), 1634, 1568, 1494, 1434, 1357, 956, 694 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.45-7.24 (10H, m, Ar**H**), 6.92–6.87 (1H, m, NC**H**), 6.38 (1H, d, *J* = 15.8 Hz, PhC**H**CH), 6.26 (1H, dd, *J* = 15.8 , 8.1 Hz, PhCHC**H**), 5.95–5.90 (1H, m, NCHCHC**H**), 5.01–4.95 (1H, m, NCHC**H**CH), 4.63 (1H, dd, *J* = 8.1, 4.9 Hz, NC**H**CHCH), 4.38 (1H, d, *J* = 15.0 Hz, C**H**$_a$H$_b$), 4.27 (1H, d, *J* = 15.0 Hz, CH$_a$**H**$_b$); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 147.6 (CH), 135.9 (C), 135.0 (C), 131.4 (CH), 129.2 (2 x CH), 128.8 (2 x CH), 128.6 (CH), 128.5 (CH), 128.1 (2 x CH), 127.0 (2 x CH), 126.0 (CH), 121.1 (CH), 113.6 (CH), 67.2 (2 x C), 59.3 (CH), 57.4 ($CH_2$); HRMS (ESI) Exact mass calculated for [$C_{21}H_{18}N_2$] [M+H$^+$]: 299.1543, found: 299.1537.

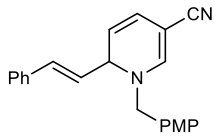
**(*E*)-1-(4-Methoxybenzyl)-6-styryl-1,6-dihydropyridine-3-carbonitrile (57a) and(*E*)-1-(4-methoxybenzyl)-2-styryl-1,2-dihydropyridine-3-carbonitrile (57b)**



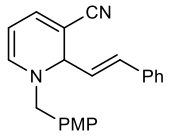

**38j** **10d** **57a (23%)** **57b (7%)**

An oven dried microwave vial was charged with **38j** (67.6 mg, 0.30 mmol), $[Rh(cod)Cl]_2$ (7.4 mg, 0.015 mmol), potassium (*E*)-trifluoro(styryl)borate (157 mg, 0.75 mmol) and $Na_2CO_3$ (63.6 mg, 0.60 mmol). The vial was then purged with argon for 30 min. Freshly degassed (purged with argon for 30 mins) 1,4-dioxane (3 mL) was added. The resulting solution was stirred at 60 °C for 12 h. The resulting mixture was filtered through a plug of silica using EtOAc as an eluent and

concentrated *in vacuo.* Purification by column chromatography (40% $Et_2O$/pentane) gave the product **57a** as a red oil (22.8 mg, 23%) and the product **57b** as a brown oil (7.3 mg, 7%).

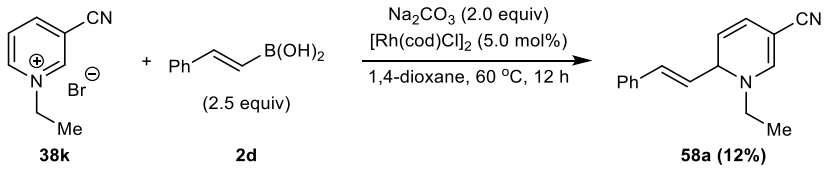



**(*E*)-1-(4-Methoxybenzyl)-6-styryl-1,6-dihydropyridine-3-carbonitrile (57a)**. $R_f$ = 0.36 (40% $Et_2O$/pentane); IR (ATR) 2923, 2853, 1738, 1464, 1375, 1244 (C-O), 1212, 1022, 793, 416 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.42-7.27 (5H, m, Ar**H**), 7.21–7.16 (2H, m, Ar**H**), 6.94–6.90 (2H, m, Ar**H**), 6.88 (1H, s, NC**H**), 6.38 (1H, d, *J* = 15.8 Hz, PhC**H**CH), 6.24 (1H, dd, *J* = 15.8 Hz, 8.2 Hz, PhCHC**H**), 5.94–5.89 (1H, m, NCHCHC**H**), 4.95 (1H, dd, *J* = 9.7, 4.8 Hz, NCHC**H**CH), 4.62 (1H, dd, *J* = 8.2, 4.8 Hz, NC**H**CHCH), 4.29 (1H, d, *J* = 14.7 Hz, C**H**$_a$H$_b$), 4.21 (1H, d, *J* = 14.7 Hz, CH$_a$**H**$_b$), 3.82 (3H, s, C**H**$_3$); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 159.9 (C), 147.4 (CH), 136.0 (C), 131.3 (CH), 129.6 (2 x CH), 128.8 (2 x CH), 128.5 (CH), 126.9 (2 x CH), 126.7 (C), 126.1 (CH),121.6 (C) 120.1 (CH), 114.6 (2 x CH), 113.4 (CH), 59.1 (CH), 56.9 ($CH_2$), 55.5 ($CH_3$); HRMS (ESI) Exact mass calculated for [$C_{23}H_{20}N_2O$] [M+H$^+$]: 329.1648, found: 329.1653.




**(*E*)-1-(4-Methoxybenzyl)-2-styryl-1,2-dihydropyridine-3-carbonitrile (57b)**. $R_f$ = 0.16 (40% $Et_2O$/pentane); IR (ATR) 2925, 2192 (C≡N), 1609, 1511, 1449, 1246 , 1174, 1028, 814, 692 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.44-7.12 (7H, m, Ar**H**), 6.94–6.89 (2H, m, Ar**H**), 6.69–6.66 (1H, m, NCHCHC**H**), 6.51–6.49 (1H, m, NC**H**CHCH), 6.46 (1H, d, *J* = 15.8 Hz, CHCH=C**H**Ph), 6.34 (1H, dd, *J* = 15.8 Hz, 7.5 Hz, CHC**H**=CHPh), 4.81 (1H, d, *J* = 6.6 Hz, NCHC**H**CH), 4.62 (1H, d, *J* = 7.5 Hz, C**H**CH=CHPh), 4.33 (1H, d, *J* = 14.7 Hz, C**H**$_a$H$_b$), 4.24 (1H, d, *J* = 14.7 Hz, CH$_a$**H**$_b$), 3.83–3.79 (3H, m, C**H**$_3$); HRMS (ESI) Exact mass calculated for [$C_{23}H_{20}N_2O$] [M+H$^+$]: 329.1648, found: 329.1651. Insufficent material for $^{13}C$ NMR, available spectroscopic data is consistent with the other 2-alkenylation product that has been isolated (**57a**).

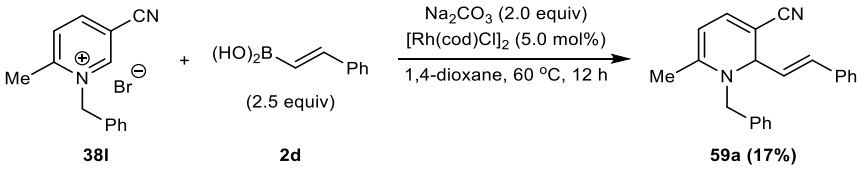
**(*E*)-1-Ethyl-6-styryl-1,6-dihydropyridine-3-carbonitrile (58a)**




An oven dried microwave vial was charged with **38k** (63.6 mg, 0.30 mmol), $[Rh(cod)Cl]_2$ (7.4 mg, 0.015 mmol), trans-2-phenylvinylboronic acid (111 mg, 0.75 mmol) and $Na_2CO_3$ (63.6 mg, 0.60 mmol). The vial was then purged with argon for 30 min. Freshly degassed (purged with argon for 30 mins) 1,4-dioxane (5 mL) was added. The resulting solution was stirred at 60 °C for 12 h. The

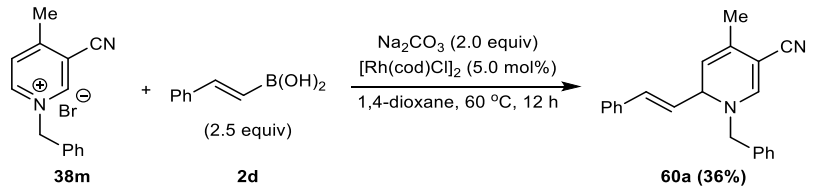
resulting mixture was filtered through a plug of silica using EtOAc as an eluent and concentrated *in vacuo.* Purification by column chromatography (40% EtOAc/PE) gave the product **58a** as a red oil (5.1 mg, 12%). $R_f$ = 0.34 (40% EtOAc/PE); IR (ATR) 2975, 2190 (C≡N), 1618, 1573, 1372, 1240, 1044, 1003, 750, 696; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.43–7.24 (5H, m, Ar**H**), 6.82 (1H, s, NC**H**), 6.44 (1H, d, *J* = 15.8 Hz, PhC**H**CH), 6.24 (1H, dd, *J* = 15.8, 8.2 Hz, PhCHC**H**), 5.91 (1H, d, *J* = 9.6 Hz, NCHCHC**H**), 4.99 (1H, dd, *J* = 9.6, 4.9 Hz, NCHC**H**CH), 4.74 (1H, dd, *J* = 8.2 Hz, 4.9 Hz, NC**H**CHCH), 3.34–3.23 (1H, m, C**H**$_a$H$_b$), 3.18–3.07 (1H, m, CH$_a$**H**$_b$), 1.24 (3H, t, *J* = 7.1 Hz, C**H**$_3$); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 146.7 (CH), 136.0 (C), 130.7 (CH), 128.9 (2 x CH), 128.5 (CH), 126.9 (2 x CH), 126.7 (CH), 121.8 (C), 121.3 (CH), 115.9 (CH), 112.9 (C), 59.8 (CH), 48.4 ($CH_2$), 13.9 ($CH_3$); HRMS (ESI) Exact mass calculated for [$C_{16}H_{16}N_2$][M+H$^+$]: 237.1386, found: 237.1386.

**(*E*)-1-Benzyl-6-methyl-2-styryl-1,2-dihydropyridine-3-carbonitrile (59a)**



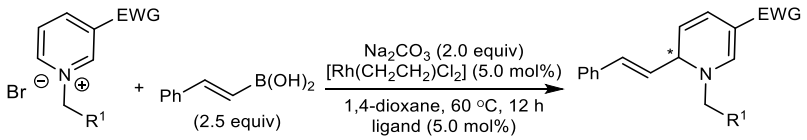

An oven dried microwave vial was charged with **38l** (86.8 mg, 0.30 mmol), $[Rh(cod)Cl]_2$ (7.4 mg, 0.015 mmol), trans-2-phenylvinylboronic acid (111 mg, 0.75 mmol) and $Na_2CO_3$ (63.6 mg, 0.6 mmol). The vial was then purged with argon for 30 min. Freshly degassed (purged with argon for 30 mins) 1,4-dioxane (5 mL) was added. The resulting solution was stirred at 60 °C for 12 h. The resulting mixture was filtered through a plug of silica using EtOAc as an eluent and concentrated *in vacuo.* Purification by column chromatography (40% $Et_2O$/pentane) gave the product **59a** as a brown oil (15.1 mg, 17%). $R_f$ = 0.48 (40% $Et_2O$/pentane); IR (ATR) 3026, 2185 (C≡N), 1604, 1516, 1429, 1286, 1108, 963, 730, 485 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.43–7.23 (10H, m, Ar**H**), 6.68 (1H, d, *J* = 6.4 Hz, C($CH_3$)CHC**H**), 6.42 (1H, d, *J* = 15.8 Hz, CHCH=C**H**Ph), 6.31 (1H, dd, *J* = 15.8 Hz, 7.1 Hz, CHC**H**=CHPh), 4.84 (1H, d, *J* = 6.5 Hz, C($CH_3$)C**H**CH), 4.73 (1H, d, *J* = 16.4 Hz, C**H**$_a$H$_b$), 4.61 (1H, d, *J* = 7.1 Hz, C**H**CH=CHPh), 4.33 (1H, d, *J* = 16.4 Hz, CH$_a$**H**$_b$), 2.01 (3H, s, C**H**$_3$); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 150.1 (C), 139.3 (CH), 137.0 (C), 136.2 (C), 131.1 (CH), 129.2 (2 x CH), 128.7 (2 x CH), 128.3 (CH), 128.0 (CH), 127.0 (2 x CH), 126.7 (2 x CH), 123.6 (CH), 120.1 (C), 96.4 (CH), 86.8 (C), 60.9 (CH), 52.6 ($CH_2$), 20.5 ($CH_3$); HRMS (ESI) Exact mass calculated for [$C_{22}H_{20}N_2$][M+Na$^+$]: 335.1519, found: 335.1510.

**(*E*)-1-Benzyl-3-carbonitrile-4-methyl-6-styryl-1,6-dihydropyridine (60a)**




An oven dried microwave vial was charged with **38m** (86.4 mg, 0.30 mmol), $[Rh(cod)Cl]_2$ (7.4 mg, 0.015 mmol), trans-2-phenylvinylboronic acid (111 mg, 0.75 mmol) and $Na_2CO_3$ (63.6 mg, 0.60 mmol). The vial was then purged with argon for 30 min. Freshly degassed (purged with argon for 30 mins) 1,4-dioxane (5 mL) was added. The resulting solution was stirred at 60 °C for 12 h. The resulting mixture was filtered through a plug of silica using EtOAc as an eluent and concentrated *in vacuo.* Purification by column chromatography (40% EtOAc/PE) gave the product **60a** as a red oil (26.1 mg, 36%). $R_f$ = 0.30 (40% EtOAc/PE); IR (ATR) 2916, 2188 (C≡N), 1711, 1574, 1694, 1321, 1208, 965, 732, 693 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.45–7.22 (10H, m, Ar**H**), 6.91 (1H, s, NC**H**), 6.33 (1H, d, *J* = 15.8 Hz, PhC**H**CH), 6.23 (1H, dd, *J* = 15.8, 8.1 Hz, PhCHC**H**), 4.77–4.70 (1H, m, NCHC**H**), 4.57 (1H, dd, *J* = 8.0, 4.9 Hz, NC**H**CH), 4.36 (1H, d, *J* = 14.9 Hz, C**H**$_a$H$_b$), 4.26 (1H, d, *J* = 15.0 Hz, CH$_a$**H**$_b$), 1.86 (3H, s, C**H**$_3$); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 147.7 (CH), 136.1 (C), 135.1 (C), 131.0 (CH), 129.2 (2 x CH), 128.8 (2 x CH), 128.5 (CH), 128.4 (CH), 128.1 (2 x CH), 127.9 (C), 126.9 (2 x CH), 126.8 (C), 126.5 (CH), 121.1 (C), 109.9 (CH), 60.1 (CH), 57.2 ($CH_2$), 19.4 ($CH_3$); HRMS (ESI) Exact mass calculated for $[C_{22}H_{20}N_2][M+H^+]$: 313.1691, found: 313.1699.

### 3.4. General Procedure for Ligand Screening




An oven-dried microwave vial was charged with $[Rh(CH_2CH_2)Cl_2]$ (0.005 mmol, 5.0 mol%) and the specified ligand (0.005 mmol, 5.0 mol%) and purged with argon for 30 mins. Freshly degassed (purged with argon for 30 mins) 1,4-dioxane (0.5 mL) was added and the mixture was stirred for 30 mins. In a separate oven-dried microwave vial, the azinium salt (0.30 mmol, 1.0 equiv), trans-2-phenylvinylboronic acid (0.13 mmol, 2.5 equiv) and $Na_2CO_3$ (0.10 mmol, 2.0 equiv) were added. The vial was then purged with argon for 30 mins. A solution of freshly degassed (purged with argon for 30 mins) 1,4-dioxane (0.5 mL) was added. The catalyst solution was then added and the mixture stirred at 60 $^oC$ for 12 h. The resulting mixture was filtered through a plug of silica using EtOAc as an eluent and concentrated *in vacuo.* Purification by preparative TLC (40% $Et_2O$/pentane) gave the resulting product. This procedure was used to isolate enantioenriched products for HPLC analysis.

**4. References**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