Rhodium and Palladium Catalysed Domino Reactions of Alkenyl Pyridines and Alkenyl Pyrazines

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science

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Domino catalysis is an ideal strategy in the synthesis of heterocyclic scaffolds, as multiple bonds can be formed under a single set of reaction conditions. In this work, we present the development of two novel domino processes which afford access to aza-analogues of the dihydrodibenzoxepine motif. Careful optimisation revealed that the Rh catalysed hydroarylation proceeds under mild conditions as compared to the C-O coupling. Furthermore, Pd was not required for the C-O bond formation when using alkenyl pyrazines as substrates. Variation of the substituents on both the heterocycle and on the boronic ester provided insight into the structural features required for successful domino reaction, and a stepwise protocol was developed for incompatible substrates. We have also developed the first multi-metal, multi-ligand domino reaction featuring both a chiral and achiral ligand in the same pot, still leading to an enantioenriched product.
Acknowledgments

I would first like to thank my supervisor, Prof. Dr. Mark Lautens, for his support, encouragement and advice throughout my time in the group. I'm grateful for the numerous opportunities that I've been afforded in the group, probably atypical of most Masters’ students at UofT.

I would not be where I am today without the support of my collaborators and mentors: Jackie, thank you for making me feel welcome my first summer in the group. We worked well together, and it was nice seeing you after meeting at RISE in 2009. Jane, you've imparted a great deal of wisdom in your time as my mentor. You were always willing to listen to any concerns that I had, and perhaps more importantly, you always believed in my skills. I continue to aspire to your level of work efficiency and chemical knowledge. Jenn, I'm grateful for your work on the asymmetric domino reaction, especially because my area of expertise is not asymmetric catalysis. I also enjoyed our conversations about everything non-chemistry and the introduction to the Friday Night Wines. Marie, I enjoyed working with you over the four months of your internship. Thank you for your contributions to my project, and for coming to the lab everyday with a smile. I hope you visit Toronto again!

Thank you to Dr. Darcy Burns in the NMR lab for his assistance with NMR experiments, Anna Liza for her assistance with administrative matters, and Prof. Dr. Mark Taylor for reviewing this thesis.

My labmates and friends have contributed to my well-being over the past two years, whether in discussions about chemistry, about life, or in sharing a laugh: Mo, thank you for sharing your insights on grad school and life experience with me. Harald, you were always helpful and willing to discuss chemistry, and despite what I might've said, you had an awesome music and YouTube collection. It was great to have company when I worked late, after Dave C and Jane had left. Lab 2 hasn't been the same without you. Chan, you were a great guy to talk to and I enjoyed your jokes. Richard, thank you for sharing a laugh, using that bombastic vocabulary, and discussing the latest events in
our lives. Julianne, thank you for Feuerzangenbowle! Dave P, I enjoyed our conversations about chemistry, life, and Seinfeld; whether at CSC, lunches or just day-to-day. Jordan, it was nice to have a late-night friend with whom to discuss chemistry, and to hear of your worldly experiences from Huntsville to Japan. Christine, thank you for sharing your ambitions over dinner that time at Tokyo Kitchen. You’ll make a great lecturer/professor, don’t give up on that dream! Sonja is lucky to have you. Thomas, you have a brilliant work schedule, and a calm and controlled method with which you excel. I enjoyed our talks about current events and politics. 4pm Phil Collins! Brendan, thank you for not giving up on me, no matter how many straight-laced conversations about chemistry/music I may have initiated. “Started from the bottom now I’m here”? Lei, I have always enjoyed our conversations about a multitude of topics, ranging from domino chemistry to Seinfeld to life’s true purpose, whether over lunch at Simon Sushi, (late night) dinners at Fran’s or Harbord House or just in the midst of the work day. And I’m sure you’ll make it, whether it is chemistry or venture capital or any other meaningful career. Theo, thank you for continuing the triazole legacy with Lei. You’ll have the (muffin) one on the right? To my friends outside the lab, whether from high school or Queen’s or UofT, including Yi-Min, Raymond, Carolyn, Mokit, Liz, Jessica, and any others, thank you for believing in me – I value you much more than you know.

My parents have been supportive throughout my university education, with a place to stay, with the financial backing so that I’ve graduated debt-free, and with emotional support in harder times. May my grandmother, Chiara Rayner, rest in peace knowing that her continued emphasis on my well-being and education will never be forgotten.

“and though
we are not now that strength which in old days
moved earth and heaven; that which we are, we are;
one equal temper of heroic hearts,
made weak by time and fate, but strong in will
to strive, to seek, to find, and not to yield.”
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List of Abbreviations

t-amyl 2-methyl-2-butyl
Ar aryl
BINAP 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BrettPhos 2-(Dicyclohexylphosphino)3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl
BSA bis(trimethylsilyl)acetamide
tBu tert-butyl
n-BuLi n-butyllithium
s-BuLi s-butyllithium
Bz benzoyl
cod 1,5-cyclooctadiene
Cy cyclohexyl
δ chemical shift, in parts per million
dba dibenzylideneacetone
DCM dichloromethane
dioxane 1,4-dioxane
DME dimethoxyethane
DMF dimethylformamide
DoM directed ortho metalation
dppb 1,4-bis(diphenylphosphino)butane
dppf 1,1′-bis(diphenylphosphino)ferrocene
dppp 1,3-bis(diphenylphosphino)propane
EAS electrophillic aromatic substitution
ee enantiomeric excess
EI electron impact
ESI electrospray ionisation
equiv. equivalents
EtOAc ethyl acetate
hr/s hour/s
HRMS high resolution mass spectrometry
IR infrared
Josiphos 1-[[Dicyclosethylphosphino)ethyl]-2-(diphenylphosphino)ferrocene
L generic ligand
M generic metal or molar concentration
Me methyl
MeCN acetonitrile
MeOH methanol
MHz megahertz
MOM methoxymethyl
mp melting point
Ms methanesulfonyl
nbd norbornadiene
NCS N-chlorosuccinimide
NMR nuclear magnetic resonance
o ortho
OAc acetate
p para
Ph phenyl
pin pinacolyl
R generic group
Q-Phos 1,2,3,4,5-Pentaphenyl-1'-di-tert-butylphosphino)ferrocene
rt room temperature
RuPhos 2-dicyclosethylphosphino-2',6'-disopropoxybiphenyl
sat. saturated
subl. sublimation point
TBS tert-butyldimethylsilyl
tBuOH tert-butanol
T temperature
THF tetrahydrofuran
TLC thin-layer chromatography
TMEDA N,N,N',N'-tetramethylethylenediamine
ToF-MS  time of flight mass spectrometry

tol  tolyl

X  generic halide or generic group

X-Phos  2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

Y  generic group
Chapter 1: Introduction

1.1 Domino Chemistry in Organic Synthesis

The use of domino processes in organic synthesis represent an ideal approach towards scaffolds of considerable intricacy, as multiple bonds are formed under a single set of reaction conditions. Beyond increased molecular complexity, time and cost-efficiencies resulting from the lack of purification of reaction intermediates make such protocols attractive. To this end, domino processes involving pericyclic, radical, photochemical, biochemical, and transition metal mediated reactions have been developed.¹

1.1.1 Catalysis in Domino Chemistry

Incorporation of catalysis in domino processes allows for a further increase in efficiency, due to the reduction in waste generated as compared to stoichiometric processes. Much recent study has been devoted to transition metal catalysed domino processes, due to the diverse range of transformations mediated by transition metals. Harnessing this reactivity, reactions pairing transition metal catalysis with organocatalysis,² biocatalysis (enzymes),³ Brönsted acid catalysis,⁴ or with other transition metals⁵ have all been demonstrated.

In 2002, Poli and co-workers developed a classification system for transition metal catalysed domino processes:⁶ “pure” domino processes utilise a single metal catalyst in the formation of multiple bonds as part of a single catalytic cycle, whereas “pseudo” domino processes (Type I or Type II) utilise one or more metals in the formation of multiple bonds as part of multiple (distinct) catalytic cycles, with the formation of discrete intermediates (Figure 1.1-1). As part of MacMillan and co-workers’ classification

---

A Type-II pseudo domino process involving two metals is equivalent to “cascade catalysis”.

![Diagram of domino catalysis](image)

**Figure 1.1-1 - Classification of Transition Metal Catalysis in Domino Reactions**

The development of efficient “pseudo” domino processes is inherently challenging, as the catalytic cycles comprising the overall transformation must be able to operate without interference. Especially in the case that different metals are used (Type II), there are a number of reasons that such transformations are problematic; for example, a functional group may react differently with each catalyst where selective reaction with one is required, or ligand exchange or redox processes may lead to deactivation of one or both catalysts. Despite these difficulties, examples of transition metals acting in

---

cascade towards a single product have been reported in the literature, and two examples are mentioned in detail.

An early report by Jeong and co-workers utilized the combination of a Pd catalyzed Tsuji-Trost allylation and a Rh catalyzed Pauson-Khand reaction. Optimisation demonstrated that the nature of the Rh catalyst was significant, as [Rh(CO)₂Cl]₂ and [Rh(CO)Cl(dppe)] shut down the allylation step, whereas [Rh(CO)Cl(dppp)]₂ and [Rh(CO)Cl(dppb)]₂ were compatible with the Pd-dppb catalyst. The inclusion of a silver additive to activate the Rh catalyst also had a deleterious effect. After considerable optimisation, fused cyclopentenones were formed in good to excellent yields (Equation 1.1-1).

\[
\text{XH} \quad \text{OAc} \quad \text{Pd-Catalyzed CHCl₃ (1.5 mol%), dppb (3 mol%)} \quad [\text{Rh(CO)Cl(dppp)}]₂ (7 mol%), BSA (1-2 equiv.)} \quad \text{Toluene, 90 ºC, 6 - 25 hrs} \quad \text{73-90%}
\]

\[
\text{X} = \text{NTs, (EtO₂)C} \quad \text{R} = \text{Ph, Me, H}
\]

**Equation 1.1-1 - Domino Formation of Fused Cyclopentenones**

Our group has also contributed to this field, wherein the combination of a Rh catalysed arylation ([Rh(cod)OH]₂/BINAP) and a Pd catalyzed C-N coupling (Pd(OAc)₂/X-Phos) led to dihydroquinolines (Equation 1.1-2). Ligand exchange effects were studied by NMR and it was determined that Rh did not bind to X-Phos to a measurable degree. However, since Pd-BINAP was inactive in the C-N coupling step, any ligand exchange of BINAP to Pd was deleterious. Increased loading of Pd-XPhos was also deleterious, due to the saturation of coordination sites at Pd or due to the formation of Suzuki products. As such, careful optimisation of reaction parameters, such as catalyst

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loadings and ratios, was required in order to achieve the desired bond formation sequence.

![Equation 1.1-2 - Domino Formation of Dihydroquinolines](image)

Evidently, careful optimisation of reaction parameters leads to successful domino reactions, limiting unwanted bond formation sequences. Due to our group’s continued interest in this field, we sought to extend our work in the use of Rh catalysed arylation and Pd catalyzed C-N or C-O coupling towards novel systems.
1.2 Rh Catalysed Addition to Activated Alkenes\textsuperscript{11}

Alkenes represent a versatile motif in organic synthesis as they may be further functionalised by addition, reduction and oxidation reactions. Despite classical methods effecting conjugate addition to activated alkenes, the discovery of a mild, high yielding protocol with excellent stereocontrol remained elusive into the 1990’s. Rh catalysed methodology, first reported by Miyaura in the reaction of organoboron reagents and enones, provides an ideal protocol to effect the transformation under mild conditions. Since the initial discovery, extension of the methodology to multiple substrate classes illustrates the synthetic utility of the reaction.

1.2.1 Addition to Enones

The Rh catalysed addition of boronic acids to enones was first reported by Miyaura and co-workers in 1997.\textsuperscript{12} Preliminary studies identified [Rh(acac)(CO)\textsubscript{2}] phosphine in an organic/aqueous co-solvent as optimal for the addition of phenylboronic acid to methyl vinyl ketone. Upon extension to other enones, the most general procedure was found to require [Rh(acac)(CO)\textsubscript{2}]/dppb in MeOH/H\textsubscript{2}O (6:1) (Equation 1.2-1). Yields decreased in the absence of water, and excess boronic acid was sometimes required in case of competitive protodeborylation. Competing 1,2-addition was not observed, highlighting the selectivity of the catalytic system.

\[
\begin{align*}
\text{Ph} & \quad \text{R}_2 \\
\text{R}_1 & \quad \text{R}_2 \\
\end{align*}
\]

\[
\begin{align*}
\text{MeOH/H}_2\text{O (6:1), 50 °C, 16 hrs} & \quad \text{52-90\%} \\
\end{align*}
\]

\text{R}_1 = \text{H, Me, Ph} \\
\text{R}_2 = \text{H, Me, nBu, Ph}

\textbf{Equation 1.2-1 - Miyaura’s Addition to Enones}

In 1998, Hayashi and Miyaura reported the asymmetric variant of this transformation.\textsuperscript{13} Cyclohexenone was chosen as the model substrate, and optimal conditions were


determined as [Rh(acac)(C₂H₄)]₂/BINAP in dioxane/H₂O (10:1) at 100 °C. The change in Rh precursor allowed for facile formation of the chiral Rh/BINAP complex, and the increased temperature was required for the addition to proceed. This protocol facilitated the addition of aryl and alkenylboronic acids to cyclic and acyclic enones, always with excellent enantiomeric control (Equation 1.2-2).

![Equation 1.2-2 - Hayashi-Miyaura Reaction](image)

These reports highlight the merit of this reaction as compared to other methods of asymmetric conjugate addition available at the time using organolithium, Grignard, and organozinc reagents in the presence of nickel, copper and zirconium catalysts. As compared to the usual organometallic nucleophiles, the organoboron coupling partners are relatively stable to air and moisture, a wider functional group tolerance is possible given the absence of less selective reagents, competing 1,2-addition is not observed, and enantioselectivities are excellent in all cases.

Mechanistic proposals in the seminal reports of Miyaura and Hayashi suggested a catalytic cycle consisting of transmetallation of the aryl group to Rh (A, Scheme 1.2-1), insertion into the enone (B), and protodemetalization (C). Hayashi later provided evidence in support of this mechanism via observation of reaction intermediates by NMR. The stereochemical configuration of the product was rationalized by approach of the si face of the enone to a free coordination site in a skewed M-BINAP complex.

---

Scheme 1.2-1 - Catalytic Cycle/Stereochemical Rationale for Hayashi-Miyaura Reaction

It has been shown that transmetallation is the rate determining step of the reaction,\textsuperscript{19} with the rate dependant on the nature of the rhodium precursor. For example, if [Rh(BINAP)OH]\textsubscript{2} is used in a reaction analogous to Equation 1.2-2, the addition reaction proceeds at 35 °C in 3 hrs in 96% yield and 99% ee.\textsuperscript{18} It was later determined that Rh-diene complexes were even more efficient in the transmetallation step,\textsuperscript{20} with additional base as the crucial additive. The additional base was proposed to assist in the generation of the hydroxyrhodium complex, as well as quaternise the boronic acid to facilitate transmetallation.\textsuperscript{21} With these rate enhancements, addition to enones occurred at room temperature or below (Scheme 1.2-2).\textsuperscript{22}

Scheme 1.2-2 - Addition to Enones with Diene/Base Combinations

With the discovery that achiral diene ligands like cod or nbd provided superior activity, Hayashi and co-workers developed a chiral diene to test asymmetric addition. In 2003, for the first time, a chiral Rh-diene complex effectively catalysed conjugate addition with comparable selectivity and yields to chiral Rh-phosphine complexes (Equation 1.2-3).23

Equation 1.2-3 - Use of Chiral Diene for Rh catalysed Addition to Enones

Following Hayashi’s initial success, much interest in the chiral diene scaffold has led to the development of new diene ligands24 for asymmetric addition, and has extended the methodology to a variety of α,β-unsaturated substrates, including esters, amides, phosphonates, and nitroalkenes (Figure 1.2-1).

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24 For a review on the use of chiral dienes in asymmetric synthesis, see C. Defieber, H. Grützmacher, E. M. Carreira, Angew. Chem. Int. Ed. 2008, 47, 4482-4502. For examples of reactivity made possible by diene (and other) ligands, see Ref. 11.
This extension to other α,β-unsaturated substrates has proved useful in the total syntheses of biologically active products. For example, Hayashi and co-workers used the addition to methylenecyanoacetates as the key step towards \((R)\)-tolterodine, a urinary incontinence drug, obtaining the product in 61% yield over five steps (Scheme 1.2-3).\(^{25}\) The mild conditions used in the key step illustrate the application of Rh catalysed addition methodology to densely functionalised starting materials.

\[ \text{Scheme 1.2-3 - Key Step in Synthesis of } (R)\text{-Tolterodine} \]

---

1.2.2 Addition to Vinyl Heterocycles and Carbocycles

Despite the application of Hayashi-Miyaura conditions to different substrate classes, the extension of methodology to more weakly activated alkenes has been less frequently studied. With precedent in the addition of boronic acids to strained alkenes via Rh catalysis, our group developed the Rh catalysed addition of aryl boronic acids to vinyl heterocycles and carbocycles (Scheme 1.2-4), a formal hydroarylation reaction. This protocol was conducted in (neat) water using a water soluble phosphine ligand and SDS as a phase transfer reagent. Interestingly, the final product obtained was a function of the starting material, such that carbocycles gave Heck-type products, whereas (nitrogenous) heterocycles gave addition products (Scheme 1.2-4).

Scheme 1.2-4 - Addition to Vinyl Heterocycles and Carbocycles

Mechanistic proposals were similar to those of the Hayashi-Miyaura reaction, with transmetallation and insertion as common steps in the reaction of both carbocycles and

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heterocycles (Scheme 1.2-5). In the reaction of styrenes, β-hydride elimination was proposed to generate the unsaturated product, with concomitant formation of a Rh-H species.\(^{30}\) Reaction with water was proposed to re-form the Rh-OH catalyst, generating hydrogen. In the case of vinyl pyridines and other nitrogenous heterocycles, protodemetalation of the aza-π-allylrhodium species formed after the insertion step gave the diarylethane addition product. Near quantitative deuterium incorporation at the α-position was observed when the reaction was conducted in D\(_2\)O, providing evidence for this final step.

\[ \text{Scheme 1.2-5 - Catalytic Cycles for Addition to Styrenes and Vinyl Pyridines} \]

Since this seminal report on the addition to vinyl heteroarenes, our group and others have attempted to extend addition methodology to a larger variety of weakly activated substrates and in an asymmetric fashion. For example, our group has demonstrated addition to allyl sulfones,\(^{31}\) allyl amines,\(^{32}\) and 2-alkynyl pyridines,\(^{33}\) proposing that Rh-heteroatom association facilitates the reaction. The extension to an asymmetric variant has been more challenging, presumably due to the reduced reactivity of substituted vinyl heteroarenes and the lack of commercially available diene ligands, in spite of their success in conjugate additions.

---

\(^{30}\) Reaction of 1,2-dihydronaphthalene gave no addition product, presumably due to the lack of \textit{syn} β-hydrogens, supporting this as the product-releasing step. See Amelie Roy, MSc. Thesis, 2002.


In 2010, Lam and co-workers reported the successful asymmetric addition of boronic acids to alkenylheteroarenes.$^{34}$ With 2-hexenylquinoline as the model substrate, a promising initial result was obtained with $[\text{Rh(cod)}\text{Cl}]_2/\text{KOH}$ in aqueous dioxane, which was optimised to the asymmetric variant using a chiral diene featuring an amide. A broad heterocyclic scope was demonstrated, with successful addition to quinoxalines, oxazoles, pyrimidines and others (Scheme 1.2-6). Mechanistically, it was proposed that the presence of structural features leading to the stabilization of the aza-$\pi$-allylrhodium intermediate allowed the reaction to proceed, due to the loss of aromaticity upon Rh insertion. These structural features included extended conjugation or the presence of another C=N moiety.

In a similar vein, Lam and co-workers later reported on the asymmetric addition to alkenylarenes.$^{35}$ The use of a para electron-withdrawing group was hypothesised to polarize the alkenyl arene, such that the addition product was obtained as opposed to the Heck-type product observed by our group. A large boronic acid scope was reported using substituted $p$-nitroalkenylarenes as the model system. Extending the concept to

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other electron-withdrawing groups was less successful, as \( p \)-acetyl, nitrile, or Ms groups failed to give any product, although a \( p \)-nitro-\( m \)-cyanophenyl substrate did undergo the addition reaction with a higher catalyst loading (Scheme 1.2-7).

The idea that a conjugated electron-withdrawing group would allow for more difficult additions to proceed is exemplified in the successful reaction of an alkenylpyridine. Under Lam’s previous conditions (Scheme 1.2-6), the reaction of an (unsubstituted) alkenylpyridine failed to provide more than 30% product, whereas reaction of a \( p \)-nitro variant proceeded in excellent yield and enantioselectivity, albeit with a more active catalyst (Equation 1.2-4).
1.3 Pd Catalysed C-N and C-O Coupling of Aryl Chlorides

Pd catalysis is a versatile method towards the construction of C-N and C-O bonds. As compared to classical methods such as reductive amination, Ullmann and Goldberg couplings, or $S_N$$Ar$ reactions, Pd catalysed methodology is often more functional group tolerant and utilises milder reaction conditions. From the discovery of C-N coupling reactivity by the Migita group in the 1980’s, to the development of tin-free methods and the seminal contributions of Buchwald and Hartwig in the mid-late 1990’s, early work has highlighted the role of specialized ligands on the success of the coupling process. Exemplified in the extension of methodology to the less reactive aryl chlorides, continued development of coupling methodology has led to its application in total syntheses and on industrial scale.

1.3.1 Seminal Reports of Coupling Methodology

The Pd catalysed C-N coupling of aryl halides was first reported by Migita and co-workers in 1983. The initial model system consisted of bromobenzene, a Pd/P(o-Tol)$_3$ catalyst, and an organostannane nucleophile, giving the desired coupling product in 81% yield. Other ligands, such as PPh$_3$ or P(o-ClPh)$_3$, were ineffective, as were aryl chlorides. Substituted bromobenzenes did react although in decreased yields (Equation 1.3-1).

\[
\text{Br} \quad \text{Et}_2\text{N-SnBu}_3 \quad \begin{array}{c}	ext{Pd[P(o-tolyl)$_3$]Cl$_2$ (1 mol\%)} \\ \text{Toluene, 100 °C, 3 hrs}
\end{array} \quad \text{NET}_2 \\
\]

81%, $R = H$
79%, $R = p$-$\text{OMe}$
16 - 61% $R = o$-$\text{Me}, m$-$\text{Me}$ $p$-$\text{NMe}_2, p$-$\text{Cl}, p$-$\text{Br}$

Equation 1.3-1 - Migita and co-workers’ Report of Pd Catalysed C-N Coupling

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39 Buchwald and co-workers later demonstrated that a higher catalyst loading and a longer reaction time led to efficient reaction of substituted bromobenzenes. A broader amine scope was tolerated upon the adoption of an in situ transamination protocol. See A. S. Guram, S. L. Buchwald, J. Am. Chem. Soc. 1994, 116, 7901-7902.
Despite this unprecedented reactivity observed by Migita and co-workers, ideal reaction conditions would preclude the use of tin reagents, due to toxicity and the difficulties encountered in the removal of reaction by-products. In concurrent reports, Buchwald and Hartwig demonstrated that free amines were viable coupling partners as long as reactions were conducted with strong base, i.e. NaOEtBu or LiHMDS. The base was required to effect deprotonation of the amine as part of the transmetallation step. A ligand screen confirmed P(o-Tol)₃ as the ligand of choice. The use of weaker bases, e.g. NaOMe, or other ligands, e.g. dppf or PPh₃, led to incomplete conversion of starting material or to the production of large amounts of the dehalogenation product. Under the reaction conditions, secondary cyclic amines were efficiently coupled with a variety of substituted aryl bromides, although acyclic amines proceeded in reduced yields, due to decomposition and competing β-hydride elimination/dehalogenation (Scheme 1.3-1).

Hartwig and co-workers:

\[
\begin{align*}
\text{PdCl}_2[P(o-Tol)_3]_2 & \quad \text{(5 mol%), LiHMDS (1.2 equiv)} \\
\text{Toluene, 100 °C, 2 hrs} & \\
R = p-\text{OMe}, p-\text{nBu} & \\
\end{align*}
\]

89-94%

\[
\begin{align*}
\text{PdCl}_2[P(o-Tol)_3]_2 & \quad \text{(5 mol%), LiHMDS (1.2 equiv)} \\
\text{Toluene, 55 °C, 24 hrs} & \\
\end{align*}
\]

26%

Buchwald and co-workers:

\[
\begin{align*}
\text{PdCl}_2[P(o-Tol)_3]_2 & \quad \text{(5 mol%), NaOEtBu (1.4 equiv)} \\
\text{Toluene, 100 °C, 3 hrs} & \\
\end{align*}
\]

89%

\[
\begin{align*}
\text{PdCl}_2[P(o-Tol)_3]_2 & \quad \text{(5 mol%), NaOEtBu (1.4 equiv)} \\
\text{Toluene, 100 °C, 3 hrs} & \\
\end{align*}
\]

72%

Scheme 1.3-1 - Buchwald and Hartwig Tin-Free C-N Coupling

While not proposed at the time, the requirement for a bulky, electron-rich ligand such as P(o-Tol)$_3$ hinted at the interplay necessary of catalyst sterics and electronics. For example, the use of dppf in Buchwald’s work led to consumption of the aryl bromide but only towards the dehalogenation product. This implied sufficient electron donation at Pd to favour oxidative addition, but insufficient steric encumbrance at Pd to favour reductive elimination over β-hydride elimination. Similar reactivity was observed when PPh$_3$ was used. These observations would be instrumental in the extension of methodology to a wider variety of coupling partners, including aryl chlorides, through the development of more reactive ligands.

1.3.2 Extension to Aryl Chlorides

The first examples of the C-N coupling of aryl chlorides were reported by Buchwald and co-workers, and Beller and co-workers, in the mid-late 1990’s. Despite the discovery of novel reactivity, methodology was limited to the reaction of activated substrates, such as trifluoromethyl-substituted aryl chlorides or chloropyridines. In order to extend methodology to a wider variety of substrates, Reddy and Tanaka proposed that electron-rich, sterically encumbered ligands should facilitate oxidative addition of less reactive starting materials. PCy$_3$ was identified as the ligand of choice, providing the coupling of aryl chlorides with secondary amines (Scheme 1.3-2). Similar to the work of Buchwald and Hartwig in the reaction of aryl bromides, acyclic secondary amines were ineffective reaction partners; competing β-hydride elimination led to dehalogenation, suggesting that a further increase in steric bulk might favour the reductive elimination pathway.

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Scheme 1.3-2 - Reddy and Tanaka's C-N Coupling using PCy₃

The development of sterically encumbered, chelating alkyl phosphine ligands by Hartwig and co-workers led to protocols tolerant of an increased variety of substrates, including amines featuring β-hydrogens. Lower reaction temperatures and shorter reaction times were also compatible, as was dioxane as a reaction solvent. This same class of ligands was applied to the synthesis of diaryl ethers, in the first reported examples of C-O coupling of aryl chlorides (Scheme 1.3-3). The increased catalytic activity observed arose from the synergistic combination of the electronic and steric properties of the ligands: the electron-donating effect and the steric hindrance of the alkyl groups favourably influenced the rate of both the oxidative addition and the reductive elimination steps. cis chelation of Hartwig's ligands to Pd also enforces geometry conducive to reductive elimination. These ferrocenyl ligands were the inspiration for the later development of the Josiphos and Q-Phos ligands by Hartwig and co-workers.

Concurrent to the Hartwig group, Buchwald and co-workers developed biaryl phosphine ligands for C-N coupling reactions. Although the ligands were compatible with the typical reaction conditions used at the time, requiring strong base and elevated reaction temperatures,\(^{47}\) later reports demonstrated that milder conditions could be used in certain cases.\(^{48}\) For example, room temperature amination of electron-rich and electron-poor aryl chlorides was achieved using strong base, whereas weaker bases, \(\text{e.g.}\) cesium carbonate or potassium phosphate, were sufficient for the amination of electron-poor aryl chlorides at elevated temperatures. Beyond the development of milder reaction conditions, the use of weaker bases expanded the scope of the methodology to substrates containing base-sensitive functionality. In the application of the Buchwald ligands to C-O coupling,\(^{49}\) weak bases were again sufficient for the reaction of electron-poor substrates, whereas sodium hydride was required for the reaction of electron-rich substrates.


substrates without ortho functionality.\textsuperscript{50} For some unactivated substrates, even these conditions were ineffective, leading to the development of increasingly reactive Buchwald ligands. These include the adamantyl variant shown in Scheme 1.3-4 or the subsequent development of X-Phos and BrettPhos. Increased catalytic activity due to the modification of ligand steric and electronic properties led to increased interest in computational and experimental investigations of the reaction mechanism.

![Scheme 1.3-4 - C-N and C-O Coupling Using Buchwald Ligands](image)

The catalytic cycle of C-N/C-O bond formation resembles that of other Pd catalysed processes, consisting of oxidative addition (Scheme 1.3-5, A), transmetallation (B), and reductive elimination (C) steps. Prior to oxidative addition of the aryl chloride, formation of the active catalyst occurs via dissociation of a bisphosphate complex.\textsuperscript{51} This process is promoted by the sterically hindered substituents on the ligand. If Pd(OAc)\textsubscript{2} is used as the Pd source, the pre-activation process involves in-situ reduction with amine coupling partner,\textsuperscript{52} phosphine ligand,\textsuperscript{53} or added water.\textsuperscript{54} Entering the catalytic cycle, oxidative

\textsuperscript{50} Presumably the ortho functionality assists in reductive elimination due to sterical crowding
addition of the aryl chloride can be rate limiting in the reaction of amines and amides,\textsuperscript{55} and may occur subsequent to base association with Pd (A → B vs. A’ → B’, Scheme 1.3-5).\textsuperscript{56} If the oxidative addition is not base-assisted, association of the coupling partner with Pd allows for deprotonation with weak bases, as pK\textsubscript{a}'s are lowered upon binding the metal. The Pd\textsuperscript{II} complexes arising from oxidative addition and transmetallation are stabilised by d-\pi metal-ligand orbital interactions when Buchwald ligands are used.\textsuperscript{57} Reductive elimination gives the desired coupling product and regenerates the Pd\textsuperscript{0} catalyst, although dehalogenation is a competing side reaction. In the case of C-O coupling, reductive elimination can be rate limiting, although studies specific to aryl chlorides have not been reported.\textsuperscript{58}

![Scheme 1.3-5 - Catalytic Cycle for C-N/C-O Coupling of Aryl Chlorides](image)

Currently, C-N/C-O coupling of aryl chlorides has a broad scope as mild conditions are applicable to a variety of substrates. For example, efficient reaction of functionalised

heterocycles has been demonstrated,\textsuperscript{59} highlighted in the use of C-N coupling as the key step towards Imatinib,\textsuperscript{60} an anti-cancer pharmaceutical (Equation 1.3-2). In our work, we envisioned the use of coupling methodology towards pyridyl and pyrazinyl analogues of the dihydrodibenzoxepine and dihydrodibenzazepine scaffold.

\textbf{Equation 1.3-2 - C-N Coupling as the Key Step Towards Imatinib}


1.4 Dihydropyridinobenzoepines and Dihydropyridinobenzazepines

The dihydropyridinobenzoepine and dihydropyridinobenzazepine scaffold is comprised of a saturated seven membered oxygen-containing ring annealed to two benzene rings. The structural core is found in several biologically active compounds (Figure 1.4-1).

![Figure 1.4-1 - Biologically Active Dihydropyridinobenzoepines and Dihydropyridinobenzazepines](image)

The dihydropyridinobenzazepine core is prominently featured in tricyclic anti-depressants (TCA’s), which were extensively used to treat psychiatric disorders in the latter half of the 20th century. Although largely replaced by modern therapies due to undesirable side effects, new uses for the TCA’s have been reported, suggesting further study of the scaffold is beneficial. Several natural products, such as the bauhiniolepins, the

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61 For a review on TCA use, see P. K. Gillman, *British Journal of Pharmacology* 2007, 151, 737-748.
bulbophylols,\textsuperscript{65} and the cularines\textsuperscript{66} have also been reported. The recent development of the pharmaceutical asenapine\textsuperscript{67} illustrates the continued relevance of the dihydrodibenzoazepine scaffold in spite of the discontinued use of TCA’s in psychotherapy. As such, studies towards the effective synthesis of dihydrodibenazepines and dihydrodibenzoazepines remain a worthwhile endeavour.

1.4.1 Synthetic Routes towards Dihydrodibenzoxepines and Dihydrodibenazepines\textsuperscript{68}

The synthesis of the dihydrodibenazepine core was first described in 1899 by Thiele and Holzinger, via the $S_N$Ar cyclisation of a diarylamine.\textsuperscript{69} Despite formation of the core in a single step in a moderate yield, harsh conditions were required (Equation 1.4-1).

\begin{equation*}
\begin{array}{c}
\text{NH}_2 \\
\text{H}_2\text{N}
\end{array}
\begin{array}{c}
\text{C}_6\text{H}_4\text{C}_6\text{H}_4
\end{array}
\xrightarrow{265 - 275^\circ\text{C}}
\begin{array}{c}
\text{H}
\end{array}
\begin{array}{c}
\text{C}_6\text{H}_4
\end{array}
\xrightarrow{26 - 30\text{ hrs}}
\begin{array}{c}
\text{H}
\end{array}
\begin{array}{c}
\text{C}_6\text{H}_4\text{N}
\end{array}
260\%
\end{equation*}

\textit{Equation 1.4-1 - Early Formation of Dihydrodibenazepine Core}

Another early approach by Bergmann and co-workers\textsuperscript{70} utilised a protected o-tolylamine. After formation of a dibromide \textit{via} benzylic bromination, cyclisation was effected with phenyllithium to give the dihydrodibenazepine in moderate yield over two-steps. This strategy was extended to the dihydrodibenzoazepine using o-tolylether as the starting material, albeit in poor yield (Equation 1.4-2).

\textsuperscript{68} For a review on the synthesis and reactions of dihydrodibenazepines and related ring systems see L. J. Kricka, A. Ledwith, \textit{Chem. Rev.} \textbf{1974}, 74, 101-123.
In the preparation of substituted products, Jørgensen and co-workers\textsuperscript{71} utilised a Goldberg reaction between anilines and aryl bromides as the key step, giving the desired dihydrodibenzazepine products in moderate to good yields after deprotection to the free amine (Equation 1.4-3). Although functionality was tolerated on the reaction partners, stoichiometric Cu was used.

Olivera and co-workers\textsuperscript{72} developed conditions to utilise either Cu or Pd to form pyrazole-fused dihydrodibenzoxepines. Although a strong base and excess metal were required, a protocol featuring Cu (Conditions A, Equation 1.4-4) gave good yields of the desired products in short reaction times, as compared to a catalytic Pd protocol (Conditions B, Equation 1.4-4). The Cu strategy was later applied as the key step in the total synthesis of Bulbophylol B.\textsuperscript{73}

25

Equation 1.4-4 - Formation of the Core via Pd or Cu Mediated C-O Coupling

More recently, Buchwald and co-workers\textsuperscript{74} reported a Pd catalysed C-O coupling of a diarylethene featuring an aryl bromide, giving the desired product in good yield with a low catalyst loading (Equation 1.4-5).

Equation 1.4-5 - C-O Coupling Towards Dihydrodibenzoxepine

1.4.2 Synthetic Routes towards Aza-Dihydrodibenzoxepines

A recent patent\textsuperscript{75} discloses the synthesis of pyrrolidine-fused aza-dihydrodibenzoxepines towards anti-depressant therapy, as selective norepinephrine and serotonin receptor blockers (Figure 1.4-2). Despite the synthesis of a novel heterocyclic scaffold, a seven step sequence was required to access the motif, giving poor overall yields of the desired products.

Figure 1.4-2 - aza-Dihydrodibenzoxepines Used as Anti-Depressants


\textsuperscript{75} M. Wang, J. Liu, F. Yang, A. Wang, J. Sun, Y. Wang, J. Cui, L. Ji, \textit{Noradrenaline and Selective 5-Hydroxytryptamine Receptor Blocker and Application} \textbf{2013}, CN102993208A.
For example, in the synthesis of a chloro-substituted variant, the following sequence was used: beginning from 3-bromo-2-methylpyridine, benzylic bromination and Wittig salt formation gave a phosphonium bromide, which was coupled with a substituted benzaldehyde in a Wittig reaction. Installation of the pyrrolidine ring followed by demethylation gave a diarylethane precursor, which underwent Cu catalysed C-O coupling to give the aza-dihydrobenzoxepine in 1.7% yield over six steps (Scheme 1.4-1).

\[
\begin{array}{c}
\text{Br} \\
\text{N} \\
\text{Me}
\end{array} \xrightarrow{1. \text{NBS (1.5 equiv.), } \text{Bz}_2\text{O}_2 (4 \text{ mol%})} \xrightarrow{\text{CCl}_4, \Delta, 48 \text{ hrs}} \xrightarrow{2. \text{PPh}_3 (1.2 \text{ equiv.}, \text{Toluene, } \Delta) \text{ K}_2\text{CO}_3 (2 \text{ equiv.}, \text{DMF, } 95^\circ\text{C)}} \\
\text{Br} \\
\text{N} \quad \text{PPh}_3
\end{array}
\]

Evidently, recent attention has been devoted to late-stage C-O and C-N coupling strategies in the formation of the oxepine and azepine rings. Although the diarylethane motif is a common precursor to the coupling step, lengthy synthetic sequences are required to access it. More efficient syntheses of the diarylethane intermediate, or the final product itself, should yield much interest due to the potential for biological activity.

### 1.4.3 Proposed Methodology

Previous work in the group has demonstrated the Rh catalysed arylation of vinylarenes and heteroarenes with arylboronic acids, as discussed in Section 1.2.2. We envisioned utilising this reaction as the key step towards an appropriately functionalised diarylethane, which could undergo a subsequent C-O coupling step to give an aza-dihydrodibenzoxepine or -dibenzazepine (Equation 1.4-6). This sequence would provide

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76 In fact the aza-analogue of Asenapine, see Figure 1.4-1.
a short route towards a scaffold of biological importance, and if the individual reactions were run under similar conditions, could be amenable to domino catalysis.

\[
\begin{align*}
  & \text{[Rh]} \quad & \text{[Pd]} \\
  & \begin{array}{c}
    \text{N} \\
    \text{X}
  \end{array} & \begin{array}{c}
    \text{Y} \\
    \text{B(OH)\textsubscript{2}}
  \end{array} & \quad & \begin{array}{c}
    \text{N} \quad \text{X} \quad \text{Y}
  \end{array} & \quad & \begin{array}{c}
    \text{N} \\
    \text{Y}
  \end{array}
\end{align*}
\]

\(X = \text{Cl}, \text{Br}\)  \(Y = \text{OH}, \text{NHR}\)

**Equation 1.4-6 - Proposed Methodology**
Chapter 2: Results and Discussion

2.1 Initial Reactivity of Vinyl Pyridines under Rh/Pd Catalysis

Following the report of the domino synthesis of dihydroquinolines, Jane Panteleev initiated an investigation into the reactivity of 2-vinylpyridines and 2-hydroxyphenylboronic acids under Rh and Pd catalysis, in conjunction with a visiting internship student, Vaizanne Huynh. They envisioned the arylation of 3-chloro-2-vinylpyridine (2.1) to produce an intermediate (2.2) that forms an aza-dihydrodibenzoxepine (2.3) after a C-O coupling (Equation 2.1-1). Their progress is summarized in this section in context of later studies undertaken by the author under the mentorship of, and in collaboration with, Jane Panteleev.\(^\text{77}\)

![Equation 2.1-1 - Formation of aza-Dihydrodibenzoxepine 2.3 by Rh/Pd Catalysis](image)

### 2.1.1 Synthesis of Vinyl Pyridine

The model system for methodology studies consisted of 2.1 and 2-hydroxyphenylboronic acid. Although the boronic acid is commercially available, the vinyl pyridine was synthesised in one step via Suzuki cross-coupling of a commercially available dihalopyridine. Several conditions were screened at the time of optimisation (Table 2.1.1, Entries 1 – 3), all giving 2.1 in good yield. Despite the higher catalyst loading, more practical conditions were later determined by the author, as the vinyl pyridine was produced in a shorter reaction time (Entry 4).\(^\text{78}\)

---


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Table 2.1.1 - Formation of Vinyl Pyridine 2.1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Boron Source</th>
<th>Conditions</th>
<th>Yield of 2.1 (%)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Boron Source" /></td>
<td>Pd(PPh(_3))(_4) (2.5 mol%), K(_2)CO(_3) (1 equiv.) THF/H(_2)O (3.5:1), 90 °C, 16 hrs</td>
<td>76(^b)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Boron Source" /></td>
<td>Pd(PPh(_3))(_4) (2.5 mol%), K(_2)CO(_3) (1 equiv.) THF/H(_2)O (3.5:1), 75 °C, 16 hrs</td>
<td>77(^b)</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Boron Source" /></td>
<td>Pd(dppf)Cl(_2)-DCM (2 mol%), tBuNH(_2) (3 equiv.) iPrOH/H(_2)O (2:1), 88 °C, 16 hrs</td>
<td>60(^b)</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Boron Source" /></td>
<td>Pd(PPh(_3))(_4) (5 mol%), K(_2)CO(_3) (4 equiv.) DME/H(_2)O (2:1), 100 °C, 5 hrs</td>
<td>72(^c)</td>
</tr>
</tbody>
</table>

\(^a\)Isolated yield. \(^b\)Performed by V. Huynh. \(^c\)Performed by the author

2.1.2 Optimisation of Arylation and C-O Coupling Steps

Optimisation of the Rh catalysed arylation was carried out using the Hayashi-Miyaura conditions\(^{13}\) and our previous domino conditions\(^{10}\) as a starting point (Table 2.1.2). Despite BINAP’s utility in previous reports, dppp was superior (Entries 2 and 4). Out of the bases screened, potassium carbonate was optimal (Entries 4 – 7). As protodemetalation is the final step of the arylation catalytic cycle, we screened several protic additives. Water was shown to be the best additive (Entries 4, 8-10), even though MeOH was used in our previous domino report. t-AmylOH was also competent (Entry 10). Under the optimised conditions, an excellent yield of the addition product (2.2, 94%) was obtained, with phenol as the only significant by-product observed. This by-product arises from deborylation of the boronic acid under the reaction conditions, and was separable from the product by chromatography.
Table 2.1.2 - Optimisation of Arylation of 2.1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand (mol%)</th>
<th>Base</th>
<th>Solvent</th>
<th>Time (hrs)</th>
<th>Yield (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>dppf (4)</td>
<td>K₂CO₃</td>
<td>Dioxane/H₂O (10:1)</td>
<td>16</td>
<td>10b</td>
</tr>
<tr>
<td>2</td>
<td>BINAP (4)</td>
<td>K₂CO₃</td>
<td>Dioxane/H₂O (10:1)</td>
<td>16</td>
<td>5b</td>
</tr>
<tr>
<td>3</td>
<td>PPh₃ (8)</td>
<td>K₂CO₃</td>
<td>Dioxane/H₂O (10:1)</td>
<td>16</td>
<td>52b</td>
</tr>
<tr>
<td>4</td>
<td>dppp (4)</td>
<td>K₂CO₃</td>
<td>Dioxane/H₂O (10:1)</td>
<td>5b, 16c</td>
<td>94b,d, 99c</td>
</tr>
<tr>
<td>5</td>
<td>dppp (4)</td>
<td>KOAc</td>
<td>Dioxane/H₂O (10:1)</td>
<td>16</td>
<td>23b</td>
</tr>
<tr>
<td>6</td>
<td>dppp (4)</td>
<td>NEt₃</td>
<td>Dioxane/H₂O (10:1)</td>
<td>5</td>
<td>67b</td>
</tr>
<tr>
<td>7</td>
<td>dppp (4)</td>
<td>CsCO₃</td>
<td>Dioxane/H₂O (10:1)</td>
<td>5</td>
<td>55b</td>
</tr>
<tr>
<td>8</td>
<td>dppp (4)</td>
<td>K₂CO₃</td>
<td>Dioxane/MeOH (10:1)</td>
<td>16</td>
<td>78c</td>
</tr>
<tr>
<td>9</td>
<td>dppp (4)</td>
<td>K₂CO₃</td>
<td>Dioxane/tBuOH (10:1)</td>
<td>16</td>
<td>79c</td>
</tr>
<tr>
<td>10</td>
<td>dppp (4)</td>
<td>K₂CO₃</td>
<td>Dioxane/t-amyloOH (10:1)</td>
<td>16</td>
<td>89c</td>
</tr>
<tr>
<td>11</td>
<td>dppp (4)</td>
<td>K₂CO₃</td>
<td>t-BuOH</td>
<td>16</td>
<td>15c</td>
</tr>
</tbody>
</table>

Reaction conditions: [Rh(cod)(OH)]₂ (2 mol%), ligand, base (2 equiv.) in dioxane pre-stirred for 10 minutes in sealable vial. Solution of vinyl pyridine and boronic acid (2 equiv.) added, vial sealed. Mixture heated to 60 °C for the indicated time. aYield obtained by NMR analysis of the crude reaction mixture, using 1,3,5-trimethoxybenzene as an internal standard. bPerformed by V. Huynh. cPerformed by the author. dIsolated yield.
Optimisation of the C-O coupling step was performed\textsuperscript{79} using our previous domino conditions as the starting point (Table 2.1.3). The key modification to the conditions was the use of tBuOH as a solvent,\textsuperscript{80} giving 2.3 in a good yield (Entry 3). Changing the base to potassium phosphate (Entry 4) or the use of a tBuOH/dioxane co-solvent (Entry 5) was inferior. The elevated temperature, 120 °C, was required, as reaction at 100 °C gave a poor yield (Entry 6).

\begin{table}[h]
\centering
\begin{tabular}{cccccc}
\hline
Entry & Base & Solvent & T (°C) & Time (hrs) & Yield (%)\textsuperscript{a} \\
\hline
1 & K\textsubscript{2}CO\textsubscript{3} & Dioxane (0.1M) & 120 & 24 & 32 \\
2 & K\textsubscript{2}CO\textsubscript{3} & Dioxane (0.2M) & 120 & 24 & 41 \\
3 & K\textsubscript{2}CO\textsubscript{3} & tBuOH (0.2M) & 120 & 24 & 84\textsuperscript{b} \\
4 & K\textsubscript{3}PO\textsubscript{4} & tBuOH (0.2M) & 120 & 24 & 45 \\
5 & K\textsubscript{2}CO\textsubscript{3} & Dioxane/tBuOH (1:1, 0.2M) & 120 & 36 & 33 \\
6 & K\textsubscript{2}CO\textsubscript{3} & tBuOH (0.2M) & 100 & 48 & 10 \\
\hline
\end{tabular}
\caption{Optimisation of C-O Coupling}
\end{table}

Reaction conditions: Pd(OAc)\textsubscript{2} (2 mol\%), X-Phos (4 mol\%), base (2 equiv.), and intermediate 2.2 added to a vial, purged with argon, dissolved in solvent and sealed. Mixture heated to the indicated temperature for the indicated time. \textsuperscript{b}Yield obtained by NMR analysis of the crude reaction mixture, using 1,3,5-trimethoxybenzene as an internal standard. \textsuperscript{a}Isolated yield.

Although considerable optimisation for the arylation and C-O coupling had been completed, combining the individual steps in a domino process had not yet been realised. Comparing the conditions for the individual steps illustrates several similarities along with one significant difference: while both steps involved weak bases, elevated temperatures and similar reaction times, the arylation proceeded in dioxane/water.

\textsuperscript{79} Performed by V. Huynh.
(Table 2.1.2, Entry 4), whereas the C-O coupling proceeded in \( t\text{BuOH} \) (Table 2.1.3, Entry 3).

Our initial attempts to use the same solvent for each step were met with poor yields of the desired products: application of \( t\text{BuOH} \) for the arylation gave only a 30% yield of 2.2 (Table 2.1.2, Entry 11), whereas the use of dioxane for the C-O coupling gave at best 41% yield of 2.3 (Table 2.1.3, Entry 2). For further optimisation, we chose to re-investigate the conditions for the C-O coupling step (Table 2.1.4).\(^81\) Although the use of Josiphos was unsuccessful,\(^82\) \( t\text{BuX-Phos} \) in conjunction with potassium phosphate in toluene\(^83\) gave 2.3 in good yield (Table 2.1.4, Entries 2 and 3). Substituting potassium carbonate, the base for the arylation step, for potassium phosphate was not effective (Entry 4). We were pleased to find that the \( t\text{BuX-Phos} \) catalyst system was compatible with dioxane, giving 2.3 in good yield (Entry 6). With comparable results to the \( t\text{BuOH} \) protocol (Table 2.1.3, Entry 3), these results indicate that a more active catalyst (Pd-\( t\text{BuX-Phos} \) vs. Pd-X-Phos) can overcome the difficulties imposed by the formation of an eight-membered palladacycle intermediate in a less polar solvent.

\begin{table}[h]
\centering
\begin{tabular}{llllll}
\hline
Entry & Ligand (mol\%) & Base (equiv.) & Solvent & T (ºC) & Time (hrs) & Yield (%)\(^a\) \\
\hline
1 & Josiphos (7) & NaOtBu (1.5) & DME (0.3M) & 100 & 15 & 0 \\
2 & \( t\text{BuX-Phos} \) (10) & K\textsubscript{3}PO\textsubscript{4} (2) & Toluene (0.3M) & 100 & 15 & 86 \\
3 & \( t\text{BuX-Phos} \) (10) & K\textsubscript{3}PO\textsubscript{4} (2) & Toluene (0.2M) & 100 & 5 & 89 \\
\hline
\end{tabular}
\caption{Further Optimisation of C-O Coupling Towards Domino Reactivity}
\end{table}

\(^{81}\) Performed by J. Panteleev.
<table>
<thead>
<tr>
<th></th>
<th>tBuX-Phos (10)</th>
<th>Base</th>
<th>Solvent</th>
<th>Temp</th>
<th>Time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td></td>
<td>K₂CO₃ (2)</td>
<td>Toluene (0.2M)</td>
<td>100</td>
<td>5</td>
<td>63</td>
</tr>
<tr>
<td>5</td>
<td>tBuX-Phos (10)</td>
<td>K₃PO₄ (2)</td>
<td>Dioxane (0.2M)</td>
<td>100</td>
<td>5</td>
<td>86</td>
</tr>
</tbody>
</table>

Reaction conditions: Pd(OAc)₂ (5 mol%), ligand, base, and intermediate 2.2 added to a vial. Contents purged with argon, dissolved in solvent and sealed. Mixture heated to the indicated temperature for the indicated time. Yield obtained by NMR analysis of the crude reaction mixture, using 1,3,5-trimethoxybenzene as an internal standard.
2.2 Towards Domino Reactivity and Stepwise Boronic Ester Scope

We envisioned two strategies towards the development of a domino protocol based on the arylation and C-O coupling described in Section 2.1. First, we considered the simple combination of both steps in one vessel, since reactions were conducted under similar conditions. Second, we devised a change in substrate electronics to facilitate the domino process, due to our initial results.

2.2.1 Initial Combination of Optimised Arylation and C-O Coupling Steps

Several of our initial attempts towards domino reactivity are featured in Table 2.2.1. While we were pleased to observe the formation of aza-dihydrodibenzoepine 2.3 even in preliminary experiments, the conversion of 2.2 to 2.3 via C-O coupling proved to be problematic. Our best result was the formation of 2.3 in 15% yield by NMR (Entry 2), even upon increasing the Pd/tBuX-Phos loading to push the Pd catalysed step to completion.

Table 2.2.1 - Preliminary Domino Attempts Towards 2.3

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equiv.)</th>
<th>Pd (mol%)</th>
<th>Ligand (mol%)</th>
<th>Yield of 2.2 (%)(^{a})</th>
<th>Yield of 2.3 (%)(^{a})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K(_2)CO(_3) (3)</td>
<td>Pd(OAc)(_2) (2)</td>
<td>tBuX-Phos (3)</td>
<td>60</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>K(_3)PO(_4) (3)</td>
<td>Pd(OAc)(_2) (2)</td>
<td>tBuX-Phos (3)</td>
<td>56</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>K(_3)PO(_4) (3)</td>
<td>Pd(OAc)(_2) (5)</td>
<td>tBuX-Phos (7)</td>
<td>63</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>K(_3)PO(_4) (3)</td>
<td>Pd(OAc)(_2) (10)</td>
<td>tBuX-Phos (14)</td>
<td>43</td>
<td>5</td>
</tr>
</tbody>
</table>

Reaction conditions: Vinyl pyridine, boronic acid (2 equiv.), base (3 equiv.) added to a vial and purged with argon. Pre-mixed catalyst solutions of [Rh] and [Pd] in dioxane added to reaction vials, water and additional dioxane added. Mixture sealed and heated to 100 °C for the indicated time. \(^{a}\)Yield obtained by NMR analysis of the crude reaction mixture, using 1,3,5-trimethoxy benzene as an internal standard.
Despite further optimisation, such as the use of stronger base (e.g. NaOtfBu) or the use of other bulky ligands (e.g. Me₄BuX-Phos, tBuBrettPhos), we always observed reaction stalled at the intermediate (2.2). As such, it became evident that favourable reaction conditions would be difficult to ascertain, and we turned towards an investigation of the substituents tolerated on the vinyl pyridine and the boronic acid. With a route towards vinyl pyridine 2.1 already in hand, we decided to pursue the reaction of differently substituted boronic acids in the two-pot, two-step process, before investigating the effect of substitution on the vinyl pyridine.

2.2.2 Synthesis of 2-Hydroxyphenylboronic Esters

Although 2-hydroxyphenylboronic acid was commercially available, its substituted analogs were unavailable or were prohibitively expensive. We instead used the commercially available 2-methoxy variants, obtaining the desired boronic acids in one step via demethylation. According to the literature, this has been readily accomplished using 3 equiv. BBr₃, although reports varied as to the required reaction temperature. In our hands, performing the reaction at -78 ºC led to the solidification of reaction mixtures, whereas performing the reaction at room temperature gave phenols, due to deborylation subsequent to demethylation. We therefore chose to conduct reactions at 0 ºC. Purification of the crude products proved difficult, as the boronic acids were unstable to silica and recrystallization was not trivial. We instead opted to protect the boronic acids as the pinacol esters, allowing for more facile purification via column chromatography. Using this protocol, we obtained several substituted 2-hydroxyphenylboronic esters in moderate to good yields, on gram scale (Table 2.2.2).

---

84 Generally $100/g or more, making these impractical to order for a scope of 5-10 different substituents
86 Excess (3 equiv.) BBr₃ allows for the reaction to proceed in the presence of other coordinating functional groups. In this case, the extra 2 equiv. sequester the hydroxy groups on the boronic acid. See J. F. W. McOmie, M. L. Watts, D. E. West, Tetrahedron 1968, 24, 2289-2292.
87 Adding only 1 equiv. of BBr₃ at 0 ºC and warming to room temperature gave poor conversion towards the desired 2-hydroxyphenylboronic acid, and deborylation of the product was observed by TLC.
In the synthesis of boronic esters containing methoxy functionality, we envisioned that selective demethylation of the o-methoxy group would be problematic. Because methoxy-substituted 2-halophenols were available, we instead opted for a lithium-halogen exchange protocol involving the formation of a dianion (Scheme 2.2-1). The major by-product of this protocol was the corresponding phenol, and we obtained low yields of the desired boronic esters (2.10 and 2.11). We attribute the low yields to product instability, as well as possible side reactions arising from the reaction procedure, such as reaction of n-butylbromide produced in-situ, or the quench of 2-lithiophenol produced in-situ with a mol of starting material, depending upon which anion had formed first.

---

88 2-bromo-4-methoxyphenol is commercially available, whereas 2-iodo-6-methoxyphenol was graciously synthesised by Dr. Harald Wein stabl
Scheme 2.2-1 - Formation of Methoxy-Substituted Boronic Esters

In the synthesis of a boronic ester featuring a naphthyl core, our attempts at demethylation using the procedure in Table 2.2.2 led to decomposition of starting material. In this case, adapting a DoM protocol of Snieckus using the MOM directing group,\(^\text{90}\) we obtained a good yield of the desired boronic ester, on gram scale (Equation 2.2-1).

\[ \text{Equation 2.2-1 - Synthesis of Naphthyl Boronic Ester 2.12} \]

In order to compare reactivity to the corresponding boronic acid, we also synthesised the pinacol protected variant of 2-hydroxyphenylboronic acid. Under Dean-Stark conditions, we obtained an excellent yield of boronic ester 2.13.

\[ \text{Equation 2.2-2 - Pinacol Protection Towards 2.13} \]

2.2.3 Boronic Ester Scope of Two-Step Protocol

Application of the substituted boronic esters proceeded smoothly using our previously optimised conditions. Our protocol consisted of a two-pot process, with chromatographic purification after both steps. Boronic esters featuring electron-donating (Entries 1 - 3) and electron-withdrawing (Entries 4 – 6) substituents were well tolerated, even if o-substituted (Entries 2 and 5). We observed better reactivity when performing the arylation step at 90 °C, likely due to the decreased reactivity of the pinacolyl derivatives.

Table 2.2.3 - Boronic Ester Scope of Two-step Protocol

<table>
<thead>
<tr>
<th>Entry</th>
<th>Boronic Ester</th>
<th>Product</th>
<th>Yield(%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>2.13</td>
<td>68</td>
</tr>
<tr>
<td>1</td>
<td>2.11</td>
<td>2.14</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>2.10</td>
<td>2.15</td>
<td>58b</td>
</tr>
</tbody>
</table>
When we used pinacol-protected 2.13 as the organoboron partner in the arylation step, we obtained a lower yield as compared to when we used 2-hydroxyphenylboronic acid (Scheme 2.2-2). Although the pinacol derivatives were easier to access, if a reproducible purification protocol for the boronic acids could be implemented, a more efficient process towards the aza-dihydrodibenzoepine motif could be developed.

![Scheme 2.2-2 - Arylation Using Boronic Acid and Boronic Ester](image)

When we used chloro-substituted 2.4 as the reaction partner in the arylation step, we obtained a good yield (Equation 2.2-3). However, when we subjected the product to the Pd catalysed C-O coupling step, we could only isolate an 80% pure mixture of the product and a decomposition product. This was likely due to insufficient electronic bias
towards oxidative addition of the pyridyl chloride, or due to oxidative addition into the product, leading to decomposition.

![Chemical Structures](image)

**Equation 2.2-3 - Arylation Using Chloro-Substituted Boronic Ester 2.4**

### 2.2.4 Modification of the Core: Bromo-Substituted Vinyl Pyridine

With the application of substituted boronic esters in our two-step protocol, we were able to access a variety of substitution patterns on the aryl ring of the azadihydrodibenzoepine motif. We were equally interested in modification of the pyridine fragment, especially if this would bias the electronics of the system towards a successful domino process. One of the first ideas that we tested involved the reaction of bromo-substituted vinyl pyridine 2.20. We reasoned that if the C-O coupling was in fact the problematic step (*vide supra*), then the more facile oxidative addition of a C-Br bond should make the C-O coupling more facile.\(^91\) We were able to synthesise bromo-substituted vinylpyridine 2.20 via the Suzuki coupling of 2,3-dibromopyridine, adapted from the literature.\(^92\)

![Chemical Structures](image)

**Equation 2.2-4 - Synthesis of Bromo-Substituted Vinyl Pyridine 2.20**

Application of 2.20 in our initial arylation procedure resulted in no observable product by crude NMR, leaving unreacted starting material. However, we did observe formation of two new spots by TLC, likely corresponding to phenol and the arylation product. This suggested that arylation was in fact occurring, but at a slow rate, likely due to the steric

---

\(^{91}\) This assumes that the oxidative addition is the rate-determining step in the reaction, which may not be the case.

bulk of the bromide substituent vs. the chloride, or oxidative addition into the C-Br bond by Rh,\textsuperscript{93} sequestering the catalyst.

$$\text{Br}$$

\[
\text{N} = \text{H}_2\text{O} \quad \text{[Rh(cod)OH]}_2 (2 \text{ mol\%}, \text{dppp} (4 \text{ mol\%})) \\
\text{K}_2\text{CO}_3 \text{ Dioxane/H}_2\text{O (10:1)} \\
60 \degree\text{C}, 5 \text{ hours} \rightarrow 90 \degree\text{C}, 16 \text{ hours}
\]

\[
\text{Br} \quad \text{OH}
\]

Equation 2.2-5 - Initial Attempt at the Arylation of 2.20

Although at the time we decided to pursue other options (\textit{vide infra}), we later reasoned that a more active Rh-diene catalyst might mitigate these problems.\textsuperscript{94} Using Lam’s diene as the ligand for Rh, we obtained a 22\% yield of the arylation product by NMR, in a comparable reaction time and catalyst loading to the Rh/dppp reaction (Equation 2.2-6). Further optimisation, such as an increased reaction time, a higher catalyst loading, or the use of microwave technology, should provide a working arylation procedure.

$$\text{Br}$$

\[
\text{CH}_2\text{OH} \quad \text{[Rh(cod)H]}_2 (2.5 \text{ mol\%}) \quad \text{Ligand (5 mol\%), K}_2\text{CO}_3 (2 \text{ equiv}) \\
\text{Dioxane/H}_2\text{O (10:1)}, 100 \degree\text{C}, 16 \text{ hours}
\]

\[
\text{Br} \quad \text{CH}_2\text{OH}
\]

Equation 2.2-6 - Arylation of 2.20 using Lam’s Diene

2.2.5 Modification of the Core: Trifluoromethyl-Substituted Vinyl Pyridine

In the development of a second strategy towards domino reactivity, we reasoned that an appropriately placed electron-withdrawing substituent should facilitate each or both of the arylation and C-O coupling steps, since the pyridine acts as the electrophile in both these reactions. As 2,3-dichloro-5-(trifluoromethyl)pyridine is readily available,\textsuperscript{95} we


\textsuperscript{94} See Section 1.2

\textsuperscript{95} <$1/g from several suppliers
decided to apply it to our methodology. Our first attempts towards the corresponding vinyl pyridine (2.22) used a Stille reaction protocol (Table 2.2.4).\(^{96}\)

**Table 2.2.4 - Optimisation of Stille Coupling Towards 2.22**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd</th>
<th>Additive (equiv.)</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Time (hrs)</th>
<th>Yield of SM (%)(^a)</th>
<th>Yield of 2.22 (%)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PPh(_3))Cl(_2)</td>
<td>None</td>
<td>Toluene</td>
<td>100</td>
<td>16</td>
<td>0</td>
<td>&lt;10</td>
</tr>
<tr>
<td>2</td>
<td>Pd(PPh(_3))Cl(_2)</td>
<td>LiCl (1.5)</td>
<td>Dioxane</td>
<td>100</td>
<td>16</td>
<td>0</td>
<td>&lt;10</td>
</tr>
<tr>
<td>3</td>
<td>Pd(PPh(_3))Cl(_2)</td>
<td>BHT (0.10)</td>
<td>Dioxane</td>
<td>100</td>
<td>16</td>
<td>0</td>
<td>&lt;10</td>
</tr>
<tr>
<td>4</td>
<td>Pd(PPh(_3))(_4)</td>
<td>None</td>
<td>Dioxane</td>
<td>100</td>
<td>16</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>Pd(PPh(_3))(_4)</td>
<td>None</td>
<td>Dioxane</td>
<td>100</td>
<td>2</td>
<td>31</td>
<td>26</td>
</tr>
<tr>
<td>6</td>
<td>Pd(PPh(_3))(_4)</td>
<td>LiCl (1.2)</td>
<td>Dioxane</td>
<td>100</td>
<td>2</td>
<td>39</td>
<td>38</td>
</tr>
<tr>
<td>7</td>
<td>Pd(PPh(_3))(_4)</td>
<td>LiCl (1.2)</td>
<td>Dioxane</td>
<td>100</td>
<td>2</td>
<td>50</td>
<td>23</td>
</tr>
<tr>
<td>8</td>
<td>Pd(PPh(_3))(_4)</td>
<td>BHT (0.05)</td>
<td>Dioxane</td>
<td>100</td>
<td>2</td>
<td>34</td>
<td>35</td>
</tr>
<tr>
<td>9</td>
<td>Pd(PPh(_3))(_4)</td>
<td>LiCl (1.2)</td>
<td>Dioxane</td>
<td>85</td>
<td>16</td>
<td>0</td>
<td>65(^b)</td>
</tr>
<tr>
<td>10</td>
<td>Pd(PPh(_3))(_4)</td>
<td>LiCl (1.2)</td>
<td>Dioxane</td>
<td>60</td>
<td>16</td>
<td>40</td>
<td>44</td>
</tr>
</tbody>
</table>

\(^{a}\)Yield obtained by NMR analysis of the crude reaction mixture, using 1,3,5-trimethoxybenzene as an internal standard. \(^{b}\)Isolated yield.

Our key realisation was the fact that 2.22 is unstable to prolonged heating. As such, early attempts at conducting the Stille reaction at reflux (\(\sim 100 \, ^{\circ}\)C) for a prolonged period were unsuccessful (Entries 1 - 4). We began to observe more of 2.22 when reducing the

\(^{96}\) Performed by J. Panteleev.
reaction time to 2 hrs (Entries 5 – 8). A longer reaction time was needed when the temperature was lowered to 85 °C (Entry 9), whereas a further reduction in temperature to 60 °C gave incomplete conversion to the product (Entry 10). Under our optimised conditions, we obtained a moderate yield of the desired vinylpyridine.

In the interest of scaling up the reaction for later optimisation studies, as well as the desire to avoid exposure to toxic tin reagents, we investigated the use of a Suzuki reaction towards 2.22. Our initial attempt proceeded via the formation of the 2-bromo-3-chloropyridine, although we later determined that the dichloropyridine was a suitable starting material (Scheme 2.2-3). The Suzuki protocol proceeded in a similar yield as the Stille protocol, but in a shorter reaction time.

Our initial application of 2.22 was in a stepwise procedure, providing our desired final product (2.24) in good yield over two-steps (Table 2.2.5, Entry 1). When we applied 2.22 in a domino transformation, we were pleased to observe full conversion to 2.24 by crude NMR, with none of vinyl pyridine 2.22 or arylated intermediate 2.23 detected (Table 2.2.5, Entry 2). Based upon our previous results, it seemed like the trifluoromethyl group had provided sufficient electronic bias for each reaction to proceed efficiently in the same pot, with similar yields to the stepwise protocol.

Scheme 2.2-3 - Synthesis of 2.22 via Suzuki Coupling

---

Table 2.2.5 - Comparison of Stepwise and Domino Processes Towards 2.24

<table>
<thead>
<tr>
<th>Entry</th>
<th>Protocol</th>
<th>Conditions</th>
<th>Yield of 2.24 (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
</table>
| 1     | Stepwise: Filter through silica between reactions | Arylation: 60 °C for 16 hrs  
C-O Coupling: 100 °C for 24 hrs | 62 |
| 2     | Domino: All components present from start, pre-mix catalyst solutions | 100 °C for 24 hr | 56<sup>b</sup>  
61<sup>c</sup> |

<sup>a</sup>Yield determined by NMR analysis of the crude reaction mixture, using p-nitroacetophenone as an internal standard. <sup>b</sup>Reaction performed using the boronic acid. <sup>c</sup>Reaction performed using the pinacol ester

---

98 Performed by J. Panteleev.
2.3 Domino Process Using Trifluomethyl-Substituted Vinyl Pyridine

With a promising initial hit in hand, we were anxious to investigate this new domino transformation of vinyl pyridines. We began with the optimisation of domino parameters, after which we looked into the order of events and mass balance of the combined transformation. After optimisation was complete, we tested the substituent scope on the boronic ester and on the vinyl pyridine. This work was conducted by the author in collaboration, and under the mentorship of, Jane Panteleev. Work was also conducted on an asymmetric variant of the domino reaction, first investigated by Jane Panteleev and later optimised by Jennifer Tsoung.

2.3.1 Initial Optimisation

We began our optimisation by looking at the effect of Pd/tBuX-Phos loading on the combined domino process (Table 2.3.1).\textsuperscript{99} We determined that there was little effect on the yield of 2.24 when varying the amount of Pd catalyst in the system, although the use of 10 mol% seemed to be inferior. In this case, by-product formation and decomposition seemed to make up the mass balance, as none of vinyl pyridine 2.22 or arylated intermediate 2.23 was observed by crude NMR. Suzuki products were not detected, suggesting that selectivity was possible under the reaction conditions.

Viewing the variation of Pd/tBuX-Phos loading as a change in the ratio of [Rh] to [Pd] present in the reaction, we concluded that higher loading of each catalyst did not interfere with the activity of the other. This result is opposite to what was observed in our domino synthesis of dihydroquinolines, as inhibition of the Pd catalyst was observed with increasing Rh/BINAP loading. Perhaps Rh binds dppp tighter than BINAP, or Pd-tBuX-Phos is of a higher catalytic activity, masking any inhibitory effects. It is also possible that tBuX-Phos does not bind Rh to an appreciable degree, as we observed for Rh/X-Phos binding in our previous domino study.

\textsuperscript{99} Performed by J. Panteleev.
Table 2.3.1 - Effect of Pd Loading on Domino Process

![Schema of the reaction](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd(OAc)₂ (mol%)</th>
<th>tBuX-Phos (mol%)</th>
<th>Yield of 2.24 (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.5</td>
<td>5</td>
<td>63</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>10</td>
<td>64</td>
</tr>
<tr>
<td>3</td>
<td>7.5</td>
<td>15</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>20</td>
<td>54</td>
</tr>
</tbody>
</table>

Reaction conditions: Vinyl pyridine, boronic acid (2 equiv.), base (3 equiv.) added to a vial and purged with argon. Pre-mixed catalyst solutions of [Rh] and [Pd] in dioxane added to reaction vial, water and additional dioxane added. Mixture sealed and heated to 100 °C for 16 hrs. <sup>a</sup>Yield obtained by NMR analysis of the crude reaction mixture, using p-nitroacetophenone as an internal standard.

We next examined the effect of individual ligand loading on the efficiency of the domino process (Table 2.3.2).<sup>100</sup> If conducted in the absence of tBuX-Phos, the domino reaction gave only arylated intermediate 2.23 (Entry 1). Removing the Pd source also gave 2.23, suggesting that the C-O coupling step does not proceed via an S<sub>N</sub>Ar mechanism (Entry 2). We observed that an increased amount of dppp led to a decreased yield of 2.24, whereas complete omission of dppp led to an increased yield of 2.24 (Entries 3 and 4). The decreased yield of 2.24 is ascribed to decomposition, as the vinyl pyridine or arylated intermediate were not observed by NMR. In this case, it is possible that Pd was sequestered by extraneous dppp, decreasing the efficiency of the C-O coupling step and allowing other processes to occur. The result obtained with the complete omission of dppp highlights the efficiency of diene ligands in the arylation process.

<sup>100</sup> Performed by J. Panteleev.
Table 2.3.2 - Effect of dppp and tBuX-Phos Loading

<table>
<thead>
<tr>
<th>Entry</th>
<th>dppp (mol%)</th>
<th>tBuX-Phos (mol%)</th>
<th>Yield of 2.23 (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield of 2.24 (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>0</td>
<td>77</td>
<td>0</td>
</tr>
<tr>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4</td>
<td>10</td>
<td>83</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>10</td>
<td>0</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td>73</td>
</tr>
</tbody>
</table>

Reaction conditions: Vinyl pyridine, boronic acid (2 equiv.), base (3 equiv.) added to a vial and purged with argon. Pre-mixed catalyst solutions of [Rh] and [Pd] in dioxane added to reaction vials, water and additional dioxane added. Mixture sealed and heated to 100 °C for 16 hrs. <sup>a</sup>Yield obtained by NMR analysis of the crude reaction mixture, using p-nitroacetophenone as an internal standard. <sup>b</sup>Reaction performed without Pd(OAc)<sub>2</sub>.

Our final round of optimisation involved an investigation into the pre-mixing requirement. Although we had performed each optimisation reaction using pre-mixed catalyst solutions, a more practical approach would involve combining all starting materials, catalysts, and bases in a single vessel. When we followed this approach, we observed similar reactivity to reaction conducted using pre-mixed catalyst solutions; these optimised conditions led to the desired domino product (2.24) in 67% yield.

Equation 2.3.1 - Optimised Domino Reaction
2.3.2 Order of Events and Further Optimisation

With optimised domino conditions in hand, we wondered if each catalyst combination was in fact operating in the same manner as in the stepwise process, such that Rh was performing the arylation and Pd was performing the C-O coupling. In addition, we wondered whether the removal of catalyst pre-mixing had an effect on the reactivity; whereas previously we had heated the reaction directly after adding catalyst solutions to the solution of starting materials and base, having all components present at the start and stirring at room temperature introduced a quasi “two-temperature” domino protocol.

When we took a TLC of the domino reaction mixture after the 10 minutes stirring period at room temperature, we, surprisingly, observed full conversion of vinyl pyridine 2.22 to arylated intermediate 2.23. Such reactivity was unexpected, as our previously established conditions for Rh catalysed arylation necessitated 60 °C or above heating for several hours (cf Table 2.1.2). However, in light of the efficiency of diene ligands in the Hayashi-Miyaura reaction, especially in allowing reaction at room temperature (cf Section 1.2.1), this reactivity was not unprecedented.

At this point, we compared the reactivity of each catalyst system under the room temperature reaction conditions (Table 2.3.3). Performing the domino reaction without Pd(OAc)$_2$ and tBuX-Phos led to 86% yield of 2.23 by NMR (Entry 1). Performing the domino reaction without [Rh(cod)OH]$_2$ led only to 10% of 2.23 by NMR, with the remainder being vinyl pyridine 2.22 (Entry 2). Since any Pd catalysed arylation had to have occurred via transmetallation of the aryl-boron species to Pd$^{II}$, we performed the domino reaction without [Rh(cod)OH]$_2$ but in the presence of Pd$_2$dba$_3$. In this case, 2.23 and 2.24 were not observed by NMR, leaving unreacted 2.22. However, the use of Pd$_2$dba$_3$ or other Pd$^0$ sources, such as Buchwald palladacycles, in the combined domino process did not lead to an increased yield of 2.24. Finally, if the domino reaction was allowed to stir overnight (18 hrs) at room temperature, 65% of 2.23 and 11% of 2.24 were observed by NMR (Entry 3).
Comparing our optimised domino conditions to our room temperature arylation conditions, we noticed a discrepancy in the conversion of intermediate 2.23 to final product 2.24; while the arylation gave 86% of 2.23 by NMR, we could only isolate 67% of 2.24 in the domino process. Closely investigating the crude domino reaction mixture by $^{19}$F NMR, we discovered that the spectrum contained two peaks. The major peak corresponded to the trifluoromethyl group of 2.24 as we expected, but one other by-product peak was also present.
ToF-MS of the crude suggested three possible structures that featured trifluoromethyl groups (Figure 2.3-1): A, the result of a C-O coupling of the arylated intermediate with phenol; B, the result of a Suzuki reaction of the arylated intermediate with boronic ester 2.13; C, the result of phenol formation from the chloride of the arylated intermediate.

Careful chromatography allowed us to isolate a sample of the by-product, identifying it as C in Figure 2.3-1. As the C-O coupling step of the domino process does not proceed via an $S_{N}Ar$ mechanism, we hypothesized that by-product 2.25 had formed via Pd catalysis. In fact, Buchwald and co-workers have demonstrated the Pd catalysed synthesis of phenols from aryl halides, using a Pd/tBuX-Phos catalyst system in aqueous basic dioxane. Using this protocol, we synthesised a larger quantity of by-product 2.25, allowing us to confirm its identity (Equation 2.3-3).

---

Equation 2.3-3 - Synthesis of 2.25

The fact that we still obtained 2.24 as the major product using Buchwald’s conditions suggests that the intramolecular C-O coupling outcompetes the attack of hydroxide (or the association/deprotonation of water) at Pd. Although we did not pursue this at the time, an investigation into the minimum amount of water required for the arylation may led to a higher yield of 2.24, suppressing the formation of 2.25. The use of t-amylOH may also be beneficial, as it performed well as a co-solvent in the arylation step.

2.3.4 Boronic Ester Scope

With optimisation complete and an overall picture of the order of events in hand, we proceeded to investigate the boronic ester scope of the domino process. Application of the boronic esters described previously led to the formation of the desired products in moderate to good yields (Table 2.3.4) with both electron-donating (Entries 2-4) and electron-withdrawing (Entries 5 – 7) substituents tolerated.

---

102 Despite the formation of an eight-membered palladacycle intermediate, the biphasic nature of the reaction medium likely favours the intramolecular process.

103 Buchwald and co-workers have shown that 1 equiv. of KOH is sufficient to effect full conversion of aryl halides to phenols, as the KOAr generated in situ deprotonates water bound to Pd. As our domino reaction utilises only K$_2$CO$_3$ and K$_3$PO$_4$, either these weaker bases deprotonate Pd-bound water, or the hydroxide generated in-situ associates with Pd. The use of less water should suppress both of these pathways.

104 See Section 2.1.2
Table 2.3.4 - Boronic Ester Scope of Domino Process

![Chemical Reaction Diagram]

- [Rh(cod)OH]$_2$ (2 mol%), Pd(OAc)$_2$ (5 mol%), iBuX-Phos (10 mol%)
- K$_2$CO$_3$ (2 equiv.), K$_2$PO$_4$ (2 equiv.)
- Dioxane/H$_2$O (10:1), 100 °C, 18 hrs

<table>
<thead>
<tr>
<th>Entry</th>
<th>Boronic Ester</th>
<th>Product</th>
<th>Yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.13</td>
<td>2.24</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>2.10</td>
<td>2.26</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>2.7</td>
<td>2.27</td>
<td>58$^b$</td>
</tr>
<tr>
<td>4</td>
<td>2.8</td>
<td>2.28</td>
<td>46$^c$</td>
</tr>
<tr>
<td>5</td>
<td>2.9</td>
<td>2.29</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>2.4</td>
<td>2.29(2.30, X = Cl, 2.30a, X = Morpholino, 82%)</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Yield of isolated product.

$^b$ Coupling yield.

$^c$ Coupling yield.

$^d$ Coupling yield.
For reaction conditions, see Equation 2.3-1. *Isolated yields. ²Reaction performed using Pd₂dba₃ (2.5 mol%) as the Pd source. ³Free hydroxyl group protected as silyl ether for more facile purification. Yield over 2 steps. ⁴Yield in parentheses refers to yield obtained in a stepwise process, involving purification of the arylation intermediate. ⁵Yield obtained by NMR analysis of the crude reaction mixture, using 1,3,5-trimethoxybenzene as an internal standard. A sample of 2.31 was isolated for identification by NMR and MS.

For two examples which proceeded in moderate yield (Entries 6 and 8), we attempted a two-pot protocol involving chromatographic purification between steps. We found that arylation reaction by-products of similar polarity to 2.30 and 2.32 were complicating purification of the domino reaction mixtures via column chromatography. In the stepwise process, we implemented a trituration step after chromatography of the intermediate in order to obtain pure material. Upon application of the intermediates in the C-O coupling step, more facile isolation of 2.30 and 2.32 led to increased overall yields in the combined process.

In the reaction of halogenated boronic esters, the formation of chloro-substituted 2.30 suggests preferential insertion into the pyridyl chloride after the arylation step,⁶ leaving the aryl chloride for further functionalisation; reaction of 2.30 via C-N coupling led to 2.30a in good yield, highlighting the utility of our products. Interestingly, the reaction of bromo-substituted boronic ester 2.5 only led to arylated intermediate 2.31. We

⁶When we synthesised 2.30 via the stepwise protocol, no decomposition or other products were observed by crude NMR after the C-O coupling step, confirming the selective nature of the reaction. This is opposed to the result obtained using a vinyl pyridine without the trifluoromethyl group. See Equation 2.2-3.
rationalise this via oxidative addition of Pd into one of the available aryl bromide bonds, sequestering the catalyst.\textsuperscript{106}

In an effort to circumvent this reactivity, we envisioned a domino process involving a third bond formation, such that oxidative addition into the aryl bromide of 2.31 would not lead to loss of catalytic activity. We proposed to intercept the oxidative addition intermediate via a C-N coupling reaction enroute to the aza-dihydrodibenzoxepine (Scheme 2.3-1).

![Scheme 2.3-1 - Domino Reaction of Intermediate Featuring an Aryl Bromide](image)

Our initial attempts at such reactivity are featured in Scheme 2.3-2. Addition of a secondary aniline to the domino process did not lead to C-N bond formation according to crude \textsuperscript{1}H NMR,\textsuperscript{107} producing 2.31 as the major product. Changing \textsuperscript{t}BuX-Phos to RuPhos, known to provide efficient C-N bond formation with secondary anilines,\textsuperscript{108} also led to 2.31. Although the yield of 2.31 was lower when using RuPhos, we could not observe any other arylated products in the crude NMR, suggesting that decomposition had occurred. In order to further investigate such reactivity, it would be beneficial to start from 2.31 as the model substrate, separating the catalytic steps. The use of a stronger base, e.g. NaOtBu, as precedented in the literature for C-N coupling reactions, or the

\textsuperscript{106} Although we could isolate a sample of 2.31, decomposition of a catalytic amount of this intermediate may not have been observed by crude NMR. Oxidative addition of the phenol by-product, 4-bromophenol, could also have occurred.

\textsuperscript{107} A better indicator would have been crude \textsuperscript{19}F NMR, although we did not try this at the time.

use of ligands known to provide reversible oxidative addition, such as PtBu$_3$ or Q-Phos,$^{109}$ would also be beneficial.

Scheme 2.3-2 - Three Component Domino Reaction

---

2.4 Domino Process Using Other Substituted Vinyl Pyridines

With the success of 5-trifluoromethyl-substituted 2.22 in our domino protocol, we were interested in determining whether the electronics of the 5-substituent had an effect on the success of the reaction. In addition, we were interested in extending our domino methodology towards an asymmetric variant, using a vinyl pyridine substituted at the β-position. We began our study in the synthesis of these vinyl pyridines, before applying them to our methodology.

2.4.1 Synthesis of Vinyl Pyridines and Precursors

Our strategy towards substituted vinyl pyridines began from appropriately substituted dihalopyridines, in the application of the cross-coupling strategy discussed previously. A variety of electron-donating and electron-withdrawing groups on the pyridine were compatible with the Stille or Suzuki protocols used. Pyridines featuring an electron-donating group required a higher reaction temperature in the Stille protocol (Table 2.4.1).

Table 2.4.1 - Synthesis of Substituted Vinyl Pyridines via Cross-Coupling

<table>
<thead>
<tr>
<th>Entry</th>
<th>Precursor</th>
<th>Product</th>
<th>Protocol</th>
<th>Yield (%)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.33</td>
<td>2.37</td>
<td>Suzuki - A</td>
<td>56</td>
</tr>
</tbody>
</table>

\[ R = \text{electron-donating group} \]

\[ R = \text{electron-withdrawing group} \]

**Table 2.4.1**

- A. Pd(PPh\(_3\))\(_4\) (5 mol%), K\(_2\)CO\(_3\) (4 equiv)
  DME/H\(_2\)O (2:1), 80 °C, 13 hrs
- B. Pd(dppf)Cl\(_2\)DCM (5 mol%), Na\(_2\)CO\(_3\) (3.3 equiv)
  Dioxane/H\(_2\)O (6:1), 85 °C, 16 - 17 hrs
Towards the synthesis of the dihalopyridines 2.33 and 2.35, we utilised a common
strategy involving late-stage introduction of one of the halides (Scheme 2.4-1). In the

isolation of cyano-substituted 2.33, we began from 2-amino-5-cyanopyridine, synthesizing
the product in a one pot transformation consisting of an EAS reaction and a
Sandmeyer\textsuperscript{110} reaction. In the case of methyl-substituted 2.35, the immediate precursor
to the Sandmeyer reaction was commercially available; application of this aminopyridine
gave the desired product (2.35) in a moderate yield.


\textsuperscript{Isolated yields.} \textsuperscript{Stille reaction performed at 100 °C for 3 hrs, using Cul (5 mol%) as an
additive.} \textsuperscript{Performed by J. Panteleev.} \textsuperscript{Performed by J. Tsoung.}
Our approach towards 2.34 and 2.36 involved functionalisation of a common starting material, 2,3-dichloro-5-bromopyridine (Scheme 2.4-2). This approach relied upon selective manipulation of the 5-bromo substituent (vs. the 2-chloro substituent), with a magnesiation occurring in the case of 2.34, and an oxidative addition occurring in the case of 2.36. We attribute the selectivity to the higher reactivity of the C-Br bond,\(^{111}\) as well as the steric influence of the 3-chloro substituent. Although the use of C-N coupling to install a morpholine group is well-precedented in the case of 2.36, the quench of a Grignard reagent with MsCl to install a sulfone, for 2.34, is not. We were fortunate to find precedence in the literature\(^ {112}\) for our conceived route, involving the direct installation of the sulfone moiety without the usual thioether oxidation protocol.

Scheme 2.4-2 - Synthesis of 2.34 and 2.36


2.4.2 Influence of Substituent Electronics on Domino Reaction

Application of vinyl pyridines 2.37 – 2.41 in our domino protocol provided an interesting observation: whereas the use of cyano-substituted 2.37, sulfone-substituted 2.38, or nitro-substituted 2.39 gave our desired domino products in good yields with none of the vinyl pyridine or arylated intermediate detected (Table 2.4.2, Entries 1 – 3), the use of methyl-substituted 2.40 or morpholine-substituted 2.41 gave mixtures of the arylated intermediate and the final products (Table 2.4.2, Entries 4 and 5). Re-subjecting vinyl pyridine 2.1 to the optimised domino conditions gave the same outcome (Entry 6).

Table 2.4.2 - Effect of Substituent Electronics on Domino Reactivity

<table>
<thead>
<tr>
<th>Entry</th>
<th>Vinyl Pyridine</th>
<th>Major Product/s</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NC</td>
<td>NC</td>
<td>61\textsuperscript{a}</td>
</tr>
<tr>
<td></td>
<td>2.37</td>
<td>2.44</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>OMe</td>
<td>OMe</td>
<td>56\textsuperscript{a}</td>
</tr>
<tr>
<td></td>
<td>2.38</td>
<td>2.45</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>O2N</td>
<td>O2N</td>
<td>50\textsuperscript{a,b}</td>
</tr>
<tr>
<td></td>
<td>2.39</td>
<td>2.46</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>Me</td>
<td>46\textsuperscript{c}</td>
</tr>
<tr>
<td></td>
<td>2.40</td>
<td>2.47</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.48</td>
<td>26\textsuperscript{c}</td>
</tr>
</tbody>
</table>
We envisioned two rationales as to why this reactivity was observed: first, that the electron-withdrawing group favourably increased the rate of the arylation step, such deleterious interactions or side reactions did not lead to pre-mature inactivation of the Pd catalyst; second, that the electron-withdrawing group facilitated the oxidative addition and/or the attack of the phenol nucleophile at Pd, giving full conversion in a reasonable reaction time.

In an attempt to determine the validity of our rationales, as well as develop methodology towards 2.48 and 2.50, we applied methyl-substituted vinyl pyridine 2.40 and morpholine-substituted vinyl pyridine 2.41 in a stepwise protocol. We were pleased to isolate our desired products in good yields over two-steps, although the C-O coupling towards morpholine-substituted 2.50 required a higher catalyst loading and a longer reaction time. As isolation of the steps of the domino process demonstrates that our catalytic system is compatible with electron-rich substrates, it is likely that some deleterious interaction led to the inactivation of the Pd catalyst before the C-O coupling.
was complete.\textsuperscript{113} Although we did not pursue this avenue of study, attempts towards a domino process involving electron-rich vinyl pyridines would require further control experiments on the C-O coupling step, as well as screening of more active catalyst systems.

![Scheme 2.4-3 - Stepwise Process Using Electron-rich Vinyl Pyridines](image)

\textbf{2.4.3 Asymmetric Domino Process}\textsuperscript{114}

Concurrent to our investigation into the scope of the domino process, we were interested in an asymmetric variant involving \(\beta\)-substituted vinyl pyridines. Despite the application of single metal/multi-ligand systems towards enantioenriched products,\textsuperscript{115} to the best of our knowledge, there had not been a report of a multi-metal/multi-ligand protocol towards an enatioenriched product.

\textsuperscript{113} A reaction conducted for 65 hrs using vinyl pyridine \textbf{2.40} gave a similar ratio of arylated intermediate and final product as in Table 2.4.2 suggesting that the issue is more complicated than just a slow reaction rate.

\textsuperscript{114} The majority of this work was conducted by Jennifer Tsoung in collaboration with the author. For preliminary reactivity of this system, see J. Panteleev, PhD Thesis, 2012.

We began our study with the application of alkenyl pyridine 2.42 in a stepwise, racemic process (Equation 2.4-1).\textsuperscript{116} Although the C-O coupling proceeded under identical conditions to those previously optimised, the arylation was significantly more difficult: whereas 2.22 required only 10 minutes at room temperature towards arylated intermediate 2.23, the reaction of 2.42 required an elevated reaction temperature, a higher catalyst loading, and a longer reaction time, likely due steric interactions of the β-substituent.\textsuperscript{117}

![Equation 2.4-1 - Racemic Stepwise Synthesis of 2.51](image)

We then screened\textsuperscript{118} several chiral ligands that have displayed excellent reactivity and enantioselectivity in conjugate additions of boronic acids, including dienes\textsuperscript{119} and phosphines\textsuperscript{120} (Table 2.4.3). While good enantiomeric induction was observed with many of the ligands tested, optimal results were obtained using Lam’s diene featuring a dibenzylamide (Entry 5, L5).

\textsuperscript{116} Performed by J. Tsoung.
\textsuperscript{117} We often observed starting material (alkenyl pyridine) remaining even when using these more forcing conditions, but we sought a compromise between reasonable reaction time and full conversion.
\textsuperscript{118} Performed by J. Tsoung.
Table 2.4.3 - Ligand Screen for Asymmetric Arylation

![Diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Yield of 2.51 (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
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</tr>
<tr>
<td>6</td>
<td><img src="image" alt="L6" /></td>
<td>14</td>
<td>ND</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yield of 2.51

<sup>b</sup> ee (%)

<sup>c</sup> Reaction conditions: [Rh(Cp2)Cl2] (6 mol%), L (10 mol%), K2CO3 (2 equiv), Dioxane/H2O (10:1), 80 °C, 16 hrs

<sup>d</sup> ee (%)

ND: Not determined
When we applied L5 in a domino transformation, we were pleased to isolate our desired product in satisfactory yield with no change in ee (Table 2.4.4, Entry 1). To the best of our knowledge, this is the first example of an asymmetric multi-component, multi-metal reaction with both a chiral diene and an achiral phosphine ligand present in one pot. A preliminary scope suggests that varying the substituents on the boronic ester (Entry 2) and on the pyridine (Entry 3) is possible, with similar yields and ee’s as 2.52.

---

121 For a previous attempt from our group that failed to maintain the ee in a one pot domino reaction with two metal catalysts/ligands present, see G. C. Tsui, J. Tsoung, P. Dougan, M. Lautens, Org. Lett. 2012, 14, 5542-5545.
Table 2.4.4 - Asymmetric Domino Reaction

![Chemical Structures](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkenyl Pyridine</th>
<th>Boronic Ester</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;c&lt;/sup&gt;</td>
<td><img src="image" alt="2.42" /></td>
<td><img src="image" alt="2.13" /></td>
<td><img src="image" alt="2.52" /></td>
<td>56</td>
<td>95</td>
</tr>
<tr>
<td>2&lt;sup&gt;c&lt;/sup&gt;</td>
<td><img src="image" alt="2.42" /></td>
<td><img src="image" alt="2.27" /></td>
<td><img src="image" alt="2.53" /></td>
<td>62</td>
<td>95</td>
</tr>
<tr>
<td>3&lt;sup&gt;d&lt;/sup&gt;</td>
<td><img src="image" alt="2.43" /></td>
<td><img src="image" alt="2.13" /></td>
<td><img src="image" alt="2.54" /></td>
<td>56</td>
<td>92</td>
</tr>
</tbody>
</table>

Reaction conditions: [Rh(C<sub>2</sub>H<sub>4</sub>)<sub>2</sub>Cl]<sub>2</sub> (5 mol%), L<sub>5</sub> (10 mol%), boronic ester (2 or 4 equiv.) in dioxane transferred to a solution of vinyl pyridine, K<sub>2</sub>CO<sub>3</sub> (2 equiv.), K<sub>3</sub>PO<sub>4</sub> (2 equiv.), Pd(OAc)<sub>2</sub> (5 mol%), and tBuX-Phos (10 mol%) in dioxane/water. Mixture was heated to 100 ºC for 16 – 18 hrs. <sup>a</sup>Isolated yield. <sup>b</sup>ee determined by HPLC analysis using a chiral stationary phase. <sup>c</sup>Performed by J. Tsoung. <sup>d</sup>Performed by the author.
2.5 Domino Reaction of Vinyl Pyrazines

With our success in the use of electron deficient vinyl pyridines in the domino process, we were interested in extending our methodology towards other vinylogous heterocycles. The vinyl pyrazine system was selected due to its ease of synthesis from commercially available starting materials. After synthesis of the vinyl pyrazine, we began our studies with the application of the vinyl pyridine domino conditions, after which we performed optimisation and investigated the scope of the new transformation. This work was conducted in collaboration with Marie Colmard, a visiting internship student, under the mentorship of the author.

2.5.1 Synthesis of Vinyl Pyrazine

Selecting 2-chloro-3-vinylpyrazine as our model substrate, we elected to synthesise the vinyl pyrazine via cross-coupling as described previously. We chose 2-chloro-3-iodopyrazine (2.55) as our substrate for cross-coupling, accessed via metalation reaction of 2-chloropyrazine.\(^{122}\) Suzuki reaction of this precursor with a trifluoroborate coupling partner proceeded in moderate yield\(^{123}\) (Scheme 2.5-1). Similar to vinyl pyridine 2.42, 2.56 was also unstable to prolonged heating.

\[
\begin{align*}
\text{2.55} & \quad 1. \text{LiTMP (1.3 equiv.), THF, \(-78^\circ C, 30\) mins} \\
& \quad 2. I_2 (2\) equiv.), THF, \(-78^\circ C, 2\) hrs} \\
& \quad \text{2.55, 78\%}
\end{align*}
\]

\[
\begin{align*}
\text{2.55} & \quad \text{BF}_3K \\
& \quad \text{Pd(dpdpfCl}_{2}\text{DCM (10 mol\%), Cs}_2\text{CO}_3 (3\) equiv.)} \\
& \quad \text{THF/H}_2\text{O (10:1), 85^\circ C, 16\) hrs} \\
& \quad \text{2.56, 55\%}
\end{align*}
\]

Scheme 2.5-1 - Synthesis of Vinyl Pyrazine 2.56 and Iodo-Precursor 2.55

We also explored other approaches towards 2.56. One strategy involved the synthesis of 3-chloropyrazine-2-carbaldehyde (2.57), such that Wittig reaction would give 2.56 without the use of transition metal catalysis. Formylation of 2-chloropyrazine under


Vilsmeier-Haack conditions failed to give any product, likely due to low nucleophilicity of the (electron deficient) pyrazine.\textsuperscript{124} However, we did obtain aldehyde 2.57 using metalation protocols previously reported\textsuperscript{125} (Scheme 2.5-2).

\begin{equation}
\text{POCl}_3 (2.1 \text{ equiv.}) \rightarrow \text{DMF, 0} ^\circ \text{C} \rightarrow 80 ^\circ \text{C, 22 hrs}
\end{equation}

\begin{equation}
\text{N} \begin{array}{c}
\text{Cl} \\
2.57
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
1. \text{LiTMP (1.3 equiv.), THF, -78} ^\circ \text{C, 30 mins} \\
2. \text{DMF (1.2 equiv.), THF, -78} ^\circ \text{C, 30 mins} \\
\rightarrow 0 ^\circ \text{C, 15 minutes}
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{N} \begin{array}{c}
\text{Cl} \\
2.57, 57%
\end{array}
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
1. \text{LiTMP (1.3 equiv.), THF, -78} ^\circ \text{C, 30 mins} \\
2. \text{Ethyl Formate (1.1 equiv.), THF, -78} ^\circ \text{C, 1.5 hrs}
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{N} \begin{array}{c}
\text{Cl} \\
2.57, 43%
\end{array}
\end{array}
\end{equation}

\textbf{Scheme 2.5-2 - Synthesis of Aldehyde 2.57}

Wittig reaction of aldehyde 2.57 proceeded in poor yield, due to difficulty in purification of the product and the product’s volatility, as opposed to incomplete conversion of starting materials (Equation 2.5-1).

\begin{equation}
\begin{array}{c}
\text{N} \begin{array}{c}
\text{Cl} \\
2.57
\end{array}
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{H}_2\text{C-PPPh}_3 \\
\text{NaOEtBu (1.3 equiv.)}
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{N} \begin{array}{c}
\text{Cl} \\
2.56, 20%
\end{array}
\end{array}
\end{equation}

\textbf{Equation 2.5-1 - Wittig Reaction Towards 2.56}

Our final approach involved a Suzuki coupling protocol beginning from a commercially available dichloropyrazine precursor (Equation 2.5-2).\textsuperscript{126} Compared to a 55% yield of 2.56 in the cross-coupling of iodopyrazine 2.55, here we obtained a 40% yield of 2.56, along with 13% of a divinylpyrazine product, using 1.2 equiv. of the trifluoroborate coupling partner. As the separation of the divinyl product from 2.56 was difficult by

\textsuperscript{124} Procedure originally used for amine-substituted pyrazines, see S. Sasaki, T. Kusumoto, I. Nomura, H. Maezaki, 	extit{PYRAZINOOXAZEPINE DERIVATIVES 2010, US 2010/0317651 A1.}


\textsuperscript{126} Performed by M. Colmard
column chromatography, we opted for our first cross-coupling approach for routine synthesis of 2.56.

\[
\text{Equation 2.5-2 - Synthesis of 2.56 from 2,3-Dichloropyrazine}
\]

2.5.2 Application of Previous Domino Protocol and Optimisation

With starting material in hand, we began our study of the vinyl pyrazine system via application of our previous domino conditions. Our initial attempt gave a mixture of two products by crude NMR. ToF-MS indicated that we had obtained a mixture of arylated intermediate and cyclised product, in an almost equal yield.

\[
\text{Equation 2.5-3 - Preliminary Domino Reaction of Vinyl Pyrazine 2.56}
\]

In order to determine why incomplete conversion to 2.59 was observed, we envisioned performing the transformation in a two-step, two-pot process. Exposing 2.56 to our arylation conditions still led to the formation of two products, one clearly the major product, along with a by-product in a low yield (Equation 2.5-4). We reasoned that the major product was the expected adduct 2.58, and the minor product, 2.59, arose from an S_NAr cyclisation of the intermediate under the reaction conditions, due to stabilisation from the imine-like nitrogen of the pyrazine.

\[
\text{Equation 2.5-4 - Preliminary Arylation of Vinyl Pyrazine 2.56}
\]
This result prompted us to investigate whether the choice and number of equivalents of base had an effect on the yield and ratio of 2.58 and 2.59 (Table 2.5.1). Although increased loading of potassium carbonate did lead to an increased yield of 2.59, this became impractical as even at 10 equiv. of base full conversion of 2.58 → 2.59 was not realised (Entries 1 – 3). Instead, we envisioned adding a second base to the reaction mixture, similar to our vinyl pyridine domino protocol, as we had hoped that a second (stronger) base would push the C-O bond formation to completion. Addition of KOtBu drastically increased the yield of 2.59 (Entry 5), whereas NaOMe suppressed almost all formation of 2.59 (Entry 9). Using only KOtBu as the base gave an improved yield of 2.59 (Entry 6), whereas using only NaOMe suppressed all formation of 2.59 (Entry 10). Increasing the number of equivalents of KOtBu to 3 equiv. (Entry 7) and raising the reaction temperature to 110 ºC (Entry 8) led to an excellent yield of 2.59 by NMR, albeit with a small amount of intermediate 2.58 remaining.

**Table 2.5.1 - Initial Optimisation for Pyrazine Domino Process**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equiv.)</th>
<th>T (ºC)</th>
<th>Yield of 2.58 (%)(^a)</th>
<th>Yield of 2.59 (%)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K₂CO₃ (2 equiv.)</td>
<td>90</td>
<td>85</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>K₂CO₃ (4 equiv.)</td>
<td>90</td>
<td>72</td>
<td>27</td>
</tr>
<tr>
<td>3</td>
<td>K₂CO₃ (10 equiv.)</td>
<td>90</td>
<td>50</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>K₂CO₃ (2 equiv.) KOtBu (2 equiv.)</td>
<td>90</td>
<td>5</td>
<td>77</td>
</tr>
<tr>
<td>6</td>
<td>KOtBu (2 equiv.)</td>
<td>90</td>
<td>22</td>
<td>67</td>
</tr>
<tr>
<td>7</td>
<td>KOtBu (3 equiv.)</td>
<td>90</td>
<td>4</td>
<td>85</td>
</tr>
</tbody>
</table>
Despite obtaining an excellent yield of 2.59, we were not able to optimise for full consumption of 2.58 using the current system, as there was always a small amount of intermediate 2.58 left (<5% by NMR) whenever we tried to reproduce our result. We first proposed running the reaction at a higher concentration (>0.1 M), but this led to incomplete consumption of the vinyl pyrazine (ca. 10% remaining by NMR). Realising that the KOtBu was being converted to KOH and tBuOH in situ due to the levelling effect, we hypothesised that the tBuOH was acting as an inferior proton source for the protodemetalation step of the arylation, which was exacerbated when the reaction was run at higher concentration.

In order to test these hypotheses, we performed the two-step domino transformation using tBuOH as the proton source, as well as KOH as the base.127 We determined that tBuOH was ineffective for both the arylation step and the S$_{N}$Ar step, leaving unreacted starting material and intermediate. The direct use of KOH was superior to the use of KOtBu, as we could isolate 88% of 2.59 without any of intermediate 2.58 detected by NMR (Table 2.5.2). This suggests that tBuOH was detrimental to our reaction, when produced in-situ.

---

127 Performed by M. Colmard. M. Colmard adopted a protocol wherein a solution of starting materials was added to a solution of catalyst and base, and the resulting mixture was stirred at room temperature for two minutes before heating the reaction.
Table 2.5.2 - Base/Solvent Optimisation of Pyrazine Domino Process

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Co-Solvent</th>
<th>Remaining 2.57 (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Remaining 2.58 (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield of 2.59 (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>KOtBu</td>
<td>H₂O</td>
<td>0</td>
<td>2</td>
<td>90</td>
</tr>
<tr>
<td>2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>KOtBu</td>
<td>tBuOH</td>
<td>31</td>
<td>13</td>
<td>53</td>
</tr>
<tr>
<td>3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>KOH</td>
<td>H₂O</td>
<td>0</td>
<td>0</td>
<td>88&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

For reaction conditions, see Table 2.5.1 for Entry 1, and Footnote 127 for Entries 2 and 3. <sup>a</sup>Yield obtained by NMR analysis of the crude reaction mixture, using 1,3,5-triethoxybenzene as an internal standard.<br><sup>b</sup>Performed by the author. <sup>c</sup>Performed by M. Colmard. <sup>d</sup>Isolated yield.

We next investigated the influence of reaction temperature on the yield and product distribution of 2.58 and 2.59 (Table 2.5.3).<sup>128</sup> We determined that higher temperatures were required to obtain full conversion to 2.59. Due to the slightly higher yield at 110 °C, we chose this as our optimal reaction temperature (Entry 8).

Table 2.5.3 - Temperature Optimisation for Vinyl Pyrazine Domino Process

<table>
<thead>
<tr>
<th>Entry</th>
<th>T (°C)</th>
<th>Yield of 2.58 (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield of 2.59 (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>45</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>38</td>
<td>61</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>27</td>
<td>59</td>
</tr>
</tbody>
</table>

<sup>128</sup> Performed by M. Colmard
For reaction conditions, see Footnote 127. *Yield obtained by NMR analysis of the crude reaction mixture, using 1,3,5-trimethoxybenzene as an internal standard.

With the optimal reaction temperature established, we focused on determining the required reaction time.\textsuperscript{129} We envisioned monitoring our domino reaction using NMR aliquots, such that every hour we could determine the relative amounts of starting material/intermediate/product present. Our results are presented in Table 2.5.4. Within 1 hour we observed full conversion of vinyl pyrazine 2.56 to arylated intermediate 2.58, with a significant amount of 2.59 already formed (Entry 1). Conversion of arylated intermediate 2.58 to cyclised product 2.59 became sluggish after 3 hours (Entry 3), with similar levels of conversion observed after five hours (Entries 3 - 5).\textsuperscript{130} As even after 14 hours we still observed remaining 2.58 (Entry 6), we chose our original 18 hour reaction time for further experiments.

### Table 2.5.4 - Reaction Time Optimisation for Pyrazine Domino Process

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (hrs)</th>
<th>Ratio of 2.58:2.59\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>23:77</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>12:88</td>
</tr>
</tbody>
</table>

\textsuperscript{129} Performed by M. Colmard

\textsuperscript{130} We were approaching the limit at which NMR integrals could provide an accurate portrayal of the intermediate:product ratio, as the intermediate peak had greatly diminished in intensity.
Despite considerable experimentation on the vinyl pyrazine domino process, we had not actually determined the conditions required for each individual step of the process. Our study towards the optimal domino reaction time (Table 2.5.3) and temperature (Table 2.5.4) gave us a reasonable starting point in this line of inquiry. Since the arylation of trifluoromethyl-substituted vinyl pyridine 2.22 had occurred at room temperature, we wondered if the same was true of vinyl pyrazine 2.56.

When we subjected vinyl pyrazine 2.56 to our domino conditions but without heating, we observed full conversion by TLC to intermediate 2.58 within 10 minutes. Although our domino protocol only involved a 2 minute pre-stirring step at room temperature before heating, it is conceivable that within this period the arylation was well underway, or was already completed. This suggests that the high reaction temperature is only necessary for the S\textsubscript{N}Ar-type cyclisation step. With all this information at hand, our optimised domino conditions are presented below (Equation 2.5-5):

\[
\text{Equation 2.5-5 - Optimised Vinyl Pyrazine Domino Conditions}
\]

\[
\begin{array}{ccc}
\text{N} & \text{Cl} & \text{N} \\
\text{2.56} & \text{2.13} & \text{2.58, 88%}
\end{array}
\]

\[
\text{Protocol:}
\]
\text{Add solution of pyrazine and boronic ester to solution of [Rh] and base}
\text{Stir for 2 minutes at rt before heating}
\text{Arylation complete within minutes at rt}

\[
131 \text{ See Footnote 127.}
\]
2.5.3 Boronic Ester Scope

With optimisation complete, we proceeded to investigate the boronic ester scope of the domino process (Table 2.5.5).\(^{132}\) We were pleased to observe excellent reactivity despite the differing functionality on the boronic esters, including electron-neutral (Entries 1 and 2), electron-donating (Entry 3), and electron-withdrawing (Entries 4 – 7) substituents. Scale-up of our model system proceeded in good yield when performed on 400 mg of 2.56.\(^{133}\) We were pleased to observe clean conversion to bromo-substituted 2.65 (Entry 7), compared to formation of arylated intermediate in the vinyl pyridine domino protocol (Table 2.3.4, Entry 7). Since the bromide is retained in the product, we envisioned developing a one-pot, three bond formation domino process in the future, wherein Pd reacts with the aryl bromide in another cross-coupling reaction. On-going work is devoted to the continued development of the boronic ester scope, modification of the vinyl pyrazine core towards pyrazine-substituted domino products, and subsequent modification of our oxepine products.

Table 2.5.5 - Boronic Ester Scope for Vinyl Pyrazine Domino Process

<table>
<thead>
<tr>
<th>Entry</th>
<th>Boronic Ester</th>
<th>Product</th>
<th>Yield (%)(^{a})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{C}<em>{2}H</em>{4}\text{OH})</td>
<td>(\text{N} \text{O} \text{C}<em>{2}H</em>{4})</td>
<td>88, 79(^b)</td>
</tr>
</tbody>
</table>

\(^{132}\) Performed by M. Colmard

\(^{133}\) We performed our optimisation on 0.2 mmol of 2.56, 28 mg, whereas we scaled up to 2.79 mmol of 2.56, 400 mg.
For reaction conditions, see Equation 2.5-5. Isolated yields. Reaction performed on 14× the usual scale, on 2.79 mmol/400 mg of 2.56. Performed by the author.
Chapter 3: Experimental Procedures

3.1 General Considerations

Unless otherwise stated, reactions were carried out under argon atmosphere in flame-dried round bottom flasks or in non flame-dried 2-dram vials or Biotage microwave vials. Air/water-sensitive liquids/solutions were transferred using standard syringe techniques. Reactions were monitored using thin layer chromatography (TLC) with Silicycle™ normal phase glass plates (0.25 mm, 60-Å pore size, 230-400 mesh), visualised by UV light and/or stained with potassium permanganate, anisaldehyde or vanillin stains. Column chromatography was performed using Silicycle™ Ultra-Pure 230-400 mesh silica gel. Yields quoted are isolated yields unless otherwise stated. Melting points are on materials obtained directly from column chromatography (and solvents used therein) unless otherwise stated.

Materials: All catalysts were purchased from Strem Chemicals and were used as received. All pyridines, boronic acids, and other reagents were purchased from Alfa Aesar, TCI, Combi-Blocks, or Sigma-Aldrich and were used as received. Anhydrous potassium carbonate, potassium hydroxide, and potassium phosphate (tribasic) were finely ground into powders and were stored in a dessicator. 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane (92.5%) was purchased from Frontier Scientific and was used as received, or was synthesised according to the literature and stored as a neat liquid under argon at -20 °C. Tributylvinyltin was synthesised according to the literature and stored at 5 °C. The reagent was transferred by syringe using the density of the commercial material. Triethylamine was added to column chromatography eluents in order to complex tin reaction by-products to the silica gel. Lithium chloride for Stille reactions was flame-dried under vacuum and stored in a dessicator.

Solvents: Tetrahydrofuran (THF) and dioxane were distilled from Na/benzophenone before use. Dimethoxyethane (DME), acetonitrile, and dichloromethane (DCM) were


distilled from calcium hydride before use. Methanesulfonylchloride (Mesyl chloride, MsCl) was distilled from phosphorus pentoxide before use. 2,2,6,6-tetramethylpiperidine (TMP) was distilled under reduced pressure from potassium hydroxide before use.

**Instrumentation:** $^1$H NMR, $^{13}$C NMR and $^{19}$F NMR spectra were recorded on a Varian Mercury 300, Varian Mercury 400, Varian VnmrS 400, Bruker Avance III 400, or Agilent DD2 600 at the specified field strengths. $^1$H NMR, $^{19}$F NMR, and $^{13}$C NMR spectra were recorded in CDCl$_3$ and CD$_2$Cl$_2$. For $^1$H NMR, residual chloroform served as the internal reference in CDCl$_3$, $\delta$$_H$ = 7.26, and CDHCl served as the internal reference in CD$_2$Cl$_2$, $\delta$$_H$ = 5.32. For $^{13}$C NMR, CDCl$_3$ served as the reference, $\delta$$_C$ = 77.16, and CD$_2$Cl$_2$ served as the reference, $\delta$$_C$ = 53.84. Resonances are given to the nearest 0.01 ppm. NMR signal multiplicities are as follows: s = singlet, d = doublet, t = triplet, m = multiplet, with combinations thereof as necessary, or as otherwise stated. Coupling constants (J) are quoted in Hz, to the nearest 0.1 Hz. For 2.25, $^1$H and $^{13}$C spectra were recorded on an Agilent DD2 500 MHz spectrometer with an Agilent HC 5-mm XSens cryogenically-cooled probe. We acknowledge the Canadian Foundation for Innovation, project number 19119, and the Ontario Research Fund for funding of the Centre for Spectroscopic Investigation of Complex Organic Molecules and Polymers. For the $^{13}$C NMR of 2.4 – 2.12, the resonance for the carbon attached to B is missing due to quadropolar relaxation. Infrared (IR) spectra were obtained using a Perkin-Elmer Spectrum 1000 FT-IR spectrometer as thin films from dichloromethane or chloroform. High resolution mass spectra (HRMS) were obtained on a JEOL AccuTOF JMS-T1000LC mass spectrometer equipped with an IONICS® Direct Analysis in Real Time (DART) ion source or an ABI/Sciex QStar mass spectrometer (ESI). The [M+H]$^+$ peak in positive ionisation mode was observed unless otherwise stated. Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected.
3.2 Synthesis of Compounds in Section 2.1

A non flame-dried 2-neck round bottom flask was charged with 2-bromo-3-chloropyridine (1.65 g, 8.57 mmol), potassium carbonate (4 equiv., 4.74 g, 34.3 mmol), and tetrakistriphenylphosphinepalladium(0) (5 mol%, 502 mg, 0.434 mmol). A reflux condenser was added and the setup was purged with argon. A mixture of DME/H$_2$O (50 mL/25 mL) was added (previously degassed by sparging under argon with sonication for 30 minutes), plus 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane (1.1 equiv., 1.65 mL, d = 0.88 g/mL, 92.5% in THF - FrontierSci, 9.43 mmol). This mixture was heated to 100 °C (reflux) for 5 hours, at which point a small aliquot of the organic layer was removed and analysed by $^1$H NMR, which showed complete consumption of starting material. Upon cooling to room temperature, the reaction was quenched with additional water, partitioned with diethyl ether, the organic layer separated and the aqueous layer extracted twice with diethyl ether. The combined organic layers were dried over magnesium sulphate and concentrated in vacuo to a yellow-orange oil. Silica flash column chromatography (25:1 Hexanes/Diethyl Ether) gave the product (863 mg, 72%) as a yellow oil. $^1$H-NMR (400 MHz, CDCl$_3$): δ/ppm = 8.48 (dd, J = 4.5, 1.3 Hz, 1H), 7.65 (dd, J = 8.1, 1.5 Hz, 1H), 7.31 – 7.20 (m, 1H), 7.13 (dd, J = 8.1, 4.6 Hz, 1H), 6.48 (dd, J = 17.0, 2.0 Hz, 1H), 5.59 (dd, J = 10.7, 2.0 Hz, 1H); $^{13}$C-NMR (101 MHz, CDCl$_3$): δ/ppm = 152.4, 147.7, 137.6, 131.7, 130.7, 123.6, 121.4; IR (film): v/cm$^{-1}$ = 3048, 2985, 2925, 2854, 1446, 1429, 1419, 1390, 1046, 788; HRMS (EI): m/z calculated for C$_7$H$_6$ClN (M$^+$): 139.0189, found 139.0192.

**Note:** this product is extremely volatile; the product was concentrated on a rotovap with the heating bath set no higher than 25 °C, at 30 – 40 mmHg; it was dried by passing a gentle stream of air over the mouth of the flask used to contain it (not via high vacuum); it was stored under argon in a -20 °C freezer, but was stable for several months in this way, darkening on storage.
A 2-dram vial was charged with 2.1 (40.9 mg, 0.293 mmol), potassium carbonate (2.1 equiv., 83 mg, 0.601), 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (2.1 equiv., 136 mg, 0.618 mmol), and purged with argon. Dioxane (2 mL) and water (300 µL) were added. A second vial was charged with hydroxy(cyclooctadiene)rhodium(I) dimer (4× 2 mol%, 10.5 mg, 0.0230 mmol), dppp (4× 8 mol%, 18.9 mg, 0.0458 mmol) and purged with argon. Dioxane (4 mL) was added and the solution was heated to 50 ºC for 15 minutes. Upon cooling to room temperature, catalyst solution (1 mL, containing 4 mol% [Rh]) was transferred to the reaction vial. The reaction mixture was then sealed and put into an oil-bath pre-heated at 90 ºC for 17 hours. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc), and concentrated in vacuo. Silica flash column chromatography (8:2 Hexanes/EtOAc) gave the product (55.9 mg, 81%), as an off-white solid, mp 113 – 114 ºC. ¹H-NMR (400 MHz, CDCl₃): δ/ppm = 10.41 (s, 1H), 8.45 (dd, J = 4.9, 1.5 Hz, 1H), 7.68 (dd, J = 8.0, 1.5 Hz, 1H), 7.22 – 7.16 (m, 2H), 7.11 (td, J = 8.1, 1.7 Hz, 1H), 6.91 (dd, J = 8.1, 1.3 Hz, 1H), 6.86 (td, J = 7.4, 1.3 Hz, 1H), 3.78 – 3.22 (m, 2H), 3.27 – 2.93 (m, 2H); ¹³C-NMR (101 MHz, CDCl₃): δ/ppm = 157.3, 155.3, 145.7, 137.7, 132.4, 130.8, 129.0, 127.9, 122.9, 120.4, 117.9, 36.8, 25.4; IR (film): ν/cm⁻¹ = 3360, 2360, 1570, 1460, 1421, 1240, 1122; HRMS (DART): m/z calculated for C₁₃H₁₃ClNO⁺ 234.0686, found 234.0690.

A microwave vial was charged with 2.2 (46.7 mg, 0.200 mmol), potassium carbonate (1.5 equiv., 42 mg, 0.304 mmol), palladium (II) acetate (2 mol%, 0.9 mg, 0.00400 mmol), X-Phos (4 mol%, 3.8 mg , 0.00797 mmol), and purged with argon. t-BuOH (1.0 mL) was added. The mixture was sealed with a crimp-top cap, and put into an oil-bath pre-heated at 120 ºC for 24 hours. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc), and concentrated in vacuo. Silica flash column chromatography (8:2 Hexanes/EtOAc) gave the product (33.0 mg, 84%), as a yellow oil. ¹H-NMR (400 MHz, CDCl₃): δ/ppm = 8.27 (dd, J = 4.6, 1.4 Hz, 1H), 7.48 (dd, J = 8.1, 1.4 Hz, 1H), 7.25 – 7.06 (m, 6H), 3.35 – 3.32 (m, 2H), 3.22 – 3.19 (m, 2H); ¹³C-NMR (101 MHz, CDCl₃): δ/ppm = 157.0, 153.6, 151.2, 144.0, 133.1, 130.1, 129.1, 127.8, 125.0, 122.5, 120.8, 35.2, 29.3; IR (film): ν/cm⁻¹ = 3384, 3061, 3024, 2926, 2855, 1588, 1569, 1489, 1456, 1447, 1423, 1419, 1268, 1237,
1158, 1094, 921, 803; **HRMS** (DART): $m/z$ calculated for $\text{C}_{13}\text{H}_{12}\text{N}_{1}\text{O}^{+}$ 198.0919, found 198.0914.
3.3 Synthesis of Compounds in Section 0

**Note:** Boron tribromide should be used in a well-ventilated hood using proper personal protective equipment. The quench of boron tribromide must be done slowly to avoid uncontrollable exotherm. Needles used to transfer boron tribromide were rinsed with DCM and the washing quenched with sodium thiosulphate solution.

A round bottom flask was charged with 5-chloro-2-methoxyphenylboronic acid (1.85 g, 9.92 mmol). DCM (25 mL) was added and the solution was cooled to 0 °C. Boron tribromide (3.0 equiv., 2.9 mL, d = 2.6 g/mL, 30.1 mmol) was added dropwise at this temperature and the reaction was stirred for 15 minutes at 0 °C, at which point TLC indicated complete consumption of starting material. The reaction was quenched by the dropwise addition of ice-water, transferred to another round bottom flask with a small amount of EtOAc, and the organic layer was concentrated *in vacuo*. The residue was taken up in EtOAc and the mixture was transferred to a separatory funnel. The organic layer was separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried over sodium sulphate and concentrated *in vacuo* to a white solid. The crude demethylated boronic acid was taken up in diethyl ether (50 mL) and transferred to a round bottom flask charged with pinacol (2 equiv., 2.33 g, 19.7 mmol). This mixture was stirred overnight at room temperature, concentrated *in vacuo*, and a small amount of toluene was added. No crystallisation occurred upon standing overnight in a -20 °C freezer, so the flask was submerged in a liquid nitrogen bath then warmed to room temperature. The white solid formed (716 mg) was filtered off, and the mother liquor was concentrated and subjected to silica flash column chromatography (9:1 Hexanes/EtOAc) to give an off-white solid (1.34 g). NMR analysis revealed both were pure product. Total yield: 2.06 g, 80%. **mp** 55 – 58 °C; **¹H-NMR** (400 MHz, CDCl₃): δ/ppm = 7.75 (s, 1H), 7.55 (d, J = 2.7 Hz, 1H), 7.29 (dd, J = 8.8, 2.7 Hz, 1H), 6.81 (d, J = 8.7 Hz, 1H), 1.37 (s, 12H); **¹³C-NMR** (75 MHz, CDCl₃): δ/ppm = 162.2, 134.9, 133.7, 124.7, 117.2, 85.0, 24.9; **IR** (film): ν/cm⁻¹ = 3443, 2982, 2934, 1616, 1572, 1471, 1429, 1418, 1389, 1342, 1301, 1273, 1213, 1141, 1100, 1064, 963, 914, 876, 849, 914, 876,
A round bottom flask was charged with 5-bromo-2-methoxyphenylboronic acid (2.00 g, 8.66 mmol). DCM (22 mL) was added and the solution was cooled to 0 °C. Boron tribromide (3.0 equiv, 2.5 mL, d = 2.6 g/mL) was added dropwise at this temperature. The mixture was stirred for 15 minutes at 0 °C, at which point TLC indicated full consumption of starting material. The reaction was quenched by the dropwise addition of ice-water, transferred to another round bottom flask with a small amount of EtOAc, and the organic layer was concentrated in vacuo. The residue was taken up in EtOAc, and the mixture was transferred to a separatory funnelly. The organic layer was separated, and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried over sodium sulphate and concentrated in vacuo. The crude demethylated boronic acid was taken up in diethyl ether (43 mL) and transferred to a round bottom flask charged with pinacol (2 equiv., 2.05 g, 17.3 mmol). This mixture was stirred overnight at room temperature and concentrated in vacuo to a yellow oil. Silica flash column chromatography (40:1 Hexanes/EtOAc) gave the product (1.83g, 71%), as an off-white solid, mp 58 – 60 °C.

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$/ppm = 7.76 (s, 1H), 7.69 (d, J = 2.6 Hz, 1H), 7.43 (dd, J = 8.7, 2.6 Hz, 1H), 6.77 (d, J = 8.8 Hz, 1H), 1.37 (s, 12H); $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$/ppm = 162.7, 137.9, 136.5, 117.7, 112.0, 85.0, 24.9; IR (film): $\nu$/cm$^{-1}$ = 3442, 2979, 2935, 1613, 1567, 1469, 1416, 1388, 1339, 1301, 1208, 1141, 1070, 961, 913, 867, 846, 824, 741, 678, 658, 625, 525; HRMS (DART, [M+NH$_4$]$^+$): m/z calculated for C$_{12}$H$_{20}$BBrNO$_3$ $^+$ 316.0720, found 316.0726.

A round bottom flask was charged with 2-fluoro-6-methoxyphenylboronic acid (2.66 g, 15.7 mmol). DCM (50 mL) was added and the solution was cooled to 0 °C. Some starting material precipitated out once cooled. Boron tribromide (3.0 equiv., 4.5 mL, d = 2.6 g/mL, 46.7 mmol) was added dropwise at this temperature, and an orange colour developed. After 10 minutes at 0 °C the reaction became homogenous and TLC indicated complete consumption of starting material. The reaction was quenched by the dropwise addition of ice-cold water (5 mL), and the
organic layer was concentrated in vacuo. The residue was taken up in EtOAc, and transferred to a separatory funnel. The organic layer was separated and the aqueous layer was extracted with EtOAc (3×). The combined organic layers were dried over sodium sulphate and concentrated in vacuo. The residue was taken up in diethyl ether (50 mL) and transferred to a round bottom flask charged with pinacol (1.2 equiv., 2.23 g, 18.9 mmol). The mixture was stirred overnight at room temperature and concentrated in vacuo to a yellow oil. Silica flash column chromatography (6:1 Hexanes/EtOAc) gave the product (2.51 g, 67%) as a white solid. The product was recrystallised (toluene) to give colourless crystals, mp 47 – 49 ºC. $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$/ppm = 8.35 (s, 1H), 7.30 (td, J = 8.3, 6.8 Hz, 1H), 6.67 (dd, J = 8.4, 0.8 Hz, 1H), 6.56 (ddd, J = 9.2, 8.2, 0.9 Hz, 1H), 1.39 (s, 12H); $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$/ppm = 167.9 (d, J = 251.6 Hz), 165.0 (d, J = 10.4 Hz), 134.6 (d, J = 11.5 Hz), 111.7 (d, J = 3.2 Hz), 106.5 (d, J = 23.9 Hz), 84.6, 24.9; $^{19}$F-NMR (282 MHz, CDCl$_3$): $\delta$/ppm = -100.84 (dd, J = 9.1, 6.8 Hz); IR (film): $\nu$/cm$^{-1}$ = 3404, 2891, 2934, 1633, 1582, 1567, 1460, 1392, 1346, 1318, 1274, 1207, 1141, 1091, 1051, 999, 962, 857, 794, 744, 656; HRMS (DART): m/z calculated for C$_{12}$H$_{17}$BFO$_3^+$ 239.1255, found 239.1262.

A round bottom flask was charged with 5-methyl-2-methoxyphenylboronic acid (2.94 mg, 17.8 mmol). DCM (44 mL) was added and the solution was cooled to 0 ºC. Boron tribromide (3.0 equiv., 5.1 mL, d = 2.6 g/mL, 52.9 mmol) was added dropwise to the reaction at this temperature. After 10 minutes at 0 ºC, TLC indicated complete consumption of starting material. The reaction was quenched by the careful dropwise addition of ice-cold water. The resulting heterogenous mixture was concentrated in vacuo to remove DCM. The residue was taken up in EtOAc and the mixture was transferred to a separatory funnel. The organic layer was separated and aqueous layer was extracted three times with EtOAc. The combined organic layers were dried over sodium sulphate and concentrated in vacuo to give the crude demethylated boronic acid, which was transferred to another round bottom flask charged with pinacol (2.0 equiv., 4.18 g, 35.4 mmol) and diethyl ether (88 mL). After stirring overnight at room temperature, the mixture was concentrated in vacuo. Silica flash column chromatography (49:1 → 20:1 Hexane/EtOAc) gave the product (2.69 g, 65%) as a yellow solid, mp 34 - 35 ºC. $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$/ppm = 7.63 (s, 1H), 7.41 (d, J
= 2.3 Hz, 1H), 7.18 (dd, J = 8.3, 2.4 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 2.26 (s, 3H), 1.37 (s, 12H). $^{13}$C-NMR (75 MHz, CDCl$_3$): δ/ppm = 161.6, 135.7, 134.7, 128.56, 115.4, 84.5, 24.9, 20.4; IR (film): ν/cm$^{-1}$ = 3457, 3021, 2979, 2932, 2868, 1625, 1590, 1487, 1399, 1391, 1349, 1303, 1277, 1243, 1211, 1168, 1066, 964, 903, 853, 826, 795, 752, 746, 677, 663, 537; HRMS (DART- $[\text{M+NH}_4]^+$): m/z calculated for C$_{13}$H$_{23}$BNO$_3^+$ 252.1771, found 252.1768.

A round bottom flask was charged with 2,5-dimethoxyphenylboronic acid (5.00 g, 27.5 mmol). DCM (69 mL) was added and the solution was cooled to 0 ºC. Boron tribromide (6 equiv., 15.9 mL, 2.6 g/mL, 165 mmol) was added dropwise at this temperature, and the mixture was stirred for 1 hour, at which point TLC indicated complete consumption of starting material. The reaction was quenched by the careful addition of ice-water, and the organic layer was concentrated in vacuo. The residue was taken up in EtoAc and transferred to a separatory funnel. The organic layer was separated and the aqueous layer was extracted three times with EtoAc. The combined organic layers were dried over magnesium sulphate and concentrated in vacuo to a brown solid. The crude demethylated boronic acid was taken up in diethyl ether (100 mL) and transferred to a round bottom flask charged with pinacol (1.3 equiv., 4.11 g, 34.8 mmol). This mixture was stirred at room temperature for 2 days, after which point the solvent was concentrated. The residue was taken up in EtOAc and transferred to a separatory funnel. The organic layer was washed twice with brine, dried over magnesium sulphate and concentrated in vacuo. Silica flash column chromatography (7:3 Hexanes/EtOAc) gave the product (3.11 g) as a tan solid. Additional product (1.12 g) was obtained by the recrystallisation (toluene) of the impure fractions from column chromatography. Total yield: 4.23 g, 65%. mp 138 – 140 ºC; $^1$H-NMR (400 MHz, CDCl$_3$): δ/ppm = 7.45 (s, 1H), 7.03 (d, J = 3.2 Hz, 1H), 6.89 (dd, J = 8.8, 3.2 Hz, 1H), 6.78 (d, J = 8.7 Hz, 1H), 4.45 (s, 1H), 1.36 (s, 12H); $^{13}$C-NMR (75 MHz, CDCl$_3$): δ/ppm = 157.6, 148.5, 121.6, 120.8, 116.6, 84.8, 24.9; IR (film): ν/cm$^{-1}$ = 3383, 3358, 3036, 2978, 2929, 1630, 1508, 1453, 1410, 1378, 1297, 1248, 1209, 1138, 1058, 967, 920, 914, 877, 853, 825, 794, 767, 741, 735, 666, 678, 624; HRMS (DART): m/z calculated for C$_{12}$H$_{18}$BO$_4^+$ 237.1298, found 237.1304.
A round bottom flask was charged with 5-fluoro-2-methoxyphenylboronic acid (954 mg, 5.61 mmol). DCM (20 mL) was added and the solution was cooled to 0 °C. Boron tribromide (3.1 equiv., 1.7 mL, d = 2.6 g/mL, 17.6 mmol) was added dropwise to the reaction at this temperature. After 15 minutes at 0 °C, TLC indicated complete consumption of starting material. The reaction was quenched by the dropwise addition of ice-cold water with the formation of a precipitate. The heterogeneous mixture was concentrated in vacuo to remove DCM, and the residue was taken up in EtOAc and transferred to a separatory funnel. The organic layer was separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried over magnesium sulphate and concentrated in vacuo to give the crude demethylated boronic acid. This was transferred to another round bottom flask charged with pinacol (2.1 equiv., 1.39 g, 11.8 mmol) and diethyl ether (43 mL). After stirring overnight at room temperature, the mixture was concentrated in vacuo. Silica flash column chromatography (9:1 Pentanes/EtOAc) and subsequent recrystallisation (toluene) gave the product (537 mg, 40%) as a white solid, mp 27 – 28 °C. 

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\begin{align*}
\text{H-NMR} & \quad (300 \text{ MHz, CDCl}_3): \delta/\text{ppm} = 7.63 (s, 1H), \quad 7.28 – 7.23 (m, 2H), \quad 7.05 (ddd, J = 9.0, 8.1, 3.2 \text{ Hz, } 1H), \quad 6.82 (dd, \quad J = 9.0, \quad 4.2 \text{ Hz, } 1H), \quad 1.37 (s, \quad 12H); \\
\text{C-NMR} & \quad (75 \text{ MHz, CDCl}_3): \delta/\text{ppm} = 159.7 (d, \quad J = 1.6 \text{ Hz}), \quad 156.4 (d, \quad J = 237.5 \text{ Hz}), \quad 120.8 (d, \quad J = 13.5 \text{ Hz}), \quad 120.5 (d, \quad J = 11.3 \text{ Hz}), \quad 116.8 (d, \quad J = 7.2 \text{ Hz}), \quad 84.9, \quad 24.9; \\
\text{F-NMR} & \quad (282 \text{ MHz, CDCl}_3): \delta/\text{ppm} = -126.03 (td, \quad J = 8.1, \quad 4.0 \text{ Hz}); \ IR (\text{film}): \nu/cm^{-1} = 3454, \quad 2982, \quad 2936, \quad 1632, \quad 1485, \quad 1449, \quad 1391, \quad 1344, \quad 1206, \quad 1273, \quad 1213, \quad 1196, \quad 1140, \quad 1056, \quad 965, \quad 915, \quad 853, \quad 827, \quad 758, \quad 744, \quad 676, \quad 664, \quad 542; \ HRMS (\text{DART}): \text{m/z calculated for C}_{12}\text{H}_{17}\text{BFO}_3^- 239.1255, \text{found 239.1252.} 
\end{align*}
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1H NMR was in accordance with a commercial sample kindly provided by CombiBlocks, PN-2701, batch L32680.

A round bottom flask was charged with 2-bromo-4-methoxyphenol (8.29 g, 40.8 mmol). THF (68 mL) was added and the solution was cooled to -78 °C. n-BuLi (2.2 equiv., 36 mL, 2.5 M, 90 mmol) was added dropwise over a 45 minute period by syringe-pump. The mixture was then brought to 0 °C and stirred for 30 minutes, at which point a yellow slurry had formed. TLC suggested complete dianion formation, comparing to 4-methoxyphenol. 2-Methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (OMeBpin, 3 equiv., 20.0 mL, 122 mmol) was added.
dropwise by syringe-pump to the reaction mixture at 0 °C. After complete addition of OMeBpin, the mixture was allowed to come to room temperature overnight, giving a heterogeneous yellow solution. The reaction was quenched at room temperature with 2.5 N HCl, the aqueous layer adjusted to pH 2 with additional HCl, and the mixture stirred for 30 minutes at which point it became homogenous. The mixture was transferred to a separatory funnel and partitioned with diethyl ether. The organic layer was separated and the aqueous layer was extracted three times with diethyl ether. The combined organic layers were dried over magnesium sulphate and concentrated in vacuo to an orange oil. Silica flash column chromatography (24:1 → 12:1 Hexanes/EtOAc) gave the product (3.20 g, 31%) as a yellow oil which solidified upon standing overnight in a freezer, mp 33 – 35 °C. \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta/\text{ppm} = 7.51\) (s, 1H), 7.08 (d, J = 3.1 Hz, 1H), 6.96 (dd, J = 8.9, 3.2 Hz, 1H), 6.82 (d, J = 8.8 Hz, 1H), 3.78 (s, 3H), 1.37 (s, 12H); \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)): \(\delta/\text{ppm} = 158.0, 152.7, 121.5, 118.2, 116.6, 84.7, 56.0, 24.9\); IR (film): \(\nu/\text{cm}^{-1} = 3462, 2981, 2938, 2834, 1623, 1592, 1489, 1449, 1436, 1415, 1389, 1303, 1274, 1211, 1179, 1169, 1141, 1061, 1039, 964, 914, 852, 827, 750, 743, 670\); HRMS (DART): m/z calculated for C\(_{13}\)H\(_{20}\)BO\(_4\)\(^+\) 251.1455, found 251.1460.

A round bottom flask was charged with 2-iodo-6-methoxyphenol (1.00 g, 4.00 mmol). THF (20 mL) was added and the solution was cooled to -78 °C. \(n\)-BuLi (2.2 equiv., 5.5 mL, 1.6 M, 8.80 mmol) was added dropwise at this temperature. The mixture was brought up to 0 °C and stirred for 40 minutes, at which point TLC suggested complete conversion to the dianion, comparing to 2-methoxyphenol. The reaction was cooled to -78 °C, and a solution of 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (OMeBpin, 4.0 equiv., 2.6 mL, d = 0.9642 g/mL, 15.9 mmol) in THF (4 mL, wash 2× 4 mL), was added dropwise to the reaction flask. After stirring for 1 hour at -78 °C, the mixture was allowed to warm to room temperature overnight. The reaction was quenched with 0.5 M HCl (< pH 6), creating a homogeneous solution, and partitioned with EtOAc. After transferring to a separatory funnel, the organic layer was separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over sodium sulphate, and concentrated in vacuo to a yellow oil. Silica flash column chromatography (9:1 Hexanes/EtOAc) gave the product (302 mg, 30%) as a yellow
solid. Recrystallization (acetonitrile) gave a colourless solid, mp 65 – 66 °C. $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$/ppm = 7.76 (d, J = 0.6 Hz, 1H), 7.21 (dd, J = 7.5, 1.6 Hz, 1H), 6.98 (dd, J = 8.0, 1.4 Hz, 1H), 6.88 – 6.72 (m, 1H), 3.88 (s, 3H), 1.37 (s, 12H). $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$/ppm = 153.1, 147.5, 127.1, 119.8, 115.6, 84.6, 56.1, 24.9; IR (film): $\nu$/cm$^{-1}$ = 3435, 2980, 2937, 2839, 1622, 1580, 1459, 1368, 1311, 1246, 1227, 1147, 1132, 1052, 965, 914, 851, 834, 744, 677; HRMS (DART): m/z calculated for C$_{13}$H$_{20}$BO$_4$ + 251.1455, found 251.1459.

A round bottom flask was charged with 1-naphthol (10.0 g, 69.4 mmol). DCM (139 mL) and DIPEA (3.0 equiv., 36 mL, 207 mmol, d = 0.742 g/mL) were added, and the solution was cooled to -78 °C. MOM-Cl (2.6 equiv., 15.5 mL, 92% technical grade, 178 mmol) was added dropwise at this temperature. The mixture was allowed to come to room temperature overnight. Water was added to quench the reaction, and the mixture was transferred to a separatory funnel. After separating the layers, the organic layer was washed with sat. sodium bicarbonate solution (2×) and brine (1×), dried over magnesium sulphate, and concentrated in vacuo to a red oil. Silica flash column chromatography (9:1 Hexanes:EtOAc) gave the product (10.42 g, 73%) as a yellow oil. $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$/ppm = 8.32 – 8.24 (m, 1H), 7.86 – 7.78 (m, 1H), 7.54 – 7.46 (m, 3H), 7.38 (dd, J = 8.3, 7.6 Hz, 1H), 7.11 (dd, J = 7.6, 1.0 Hz, 1H), 5.41 (s, 2H), 3.56 (s, 3H); $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$/ppm = 153.0, 134.7, 127.7, 126.4, 126.0, 126.0, 125.4, 122.0, 121.5, 107.9, 94.8, 56.3. IR (film): $\nu$/cm$^{-1}$ = 3054, 2998, 2955, 2900, 2854, 2825, 1629, 1596, 1582, 1510, 1464, 1441, 1411, 1389, 1240, 1208, 1175, 1149, 1104, 1088, 1073, 1055, 1018, 924, 794, 772, 713, 577, 564; HRMS (DART): m/z calculated for C$_{12}$H$_{13}$O$_2$ + 189.0916, found 189.0915.

A round bottom flask was charged with MOM-protected phenol (6.01 g, 31.9 mmol) and diethyl ether (80 mL). TMEDA (1.3 equiv., 6.2 mL, 41.4 mmol, d = 0.777 g/mL) was added in one portion. The mixture was cooled to -78 °C. s-BuLi (1.3 equiv., 30 mL, 42 mmol, 1.4M) was added dropwise over 12 minutes, such that the internal temperature did not rise above -70 °C. The mixture was stirred for 1.5 hrs at -78 °C, after which trimethyl borate (2 equiv., 7.1 mL, 63.7 mmol, d = 0.932 g/mL) was added dropwise over 10 minutes, such that the internal
temperature did not rise above -69 °C. After stirring for 1 hr at -78 °C, the mixture was warmed to 0 °C, and a solution of pinacol (4 equiv., 15.1 g, 128 mmol) in diethyl ether (80 mL) was added via cannula to the reaction flask, such that the internal temperature did not rise above 7 °C. This mixture was stirred at 0 °C for 1 hr and allowed to come to room temperature overnight. The reaction was quenched with 1M HCl (120 mL), forming two homogenous layers. After transferring to a separatory funnel, the layers were separated and the aqueous layer was extracted three times with diethyl ether. The combined organic layers were dried over magnesium sulphate and concentrated in vacuo to give the crude MOM-protected boronic ester. The residue was taken up in 1% HCl/MeOH (3 mL conc. HCl + 297 mL MeOH), and stirred at room temperature for 4 hrs, at which point TLC indicated complete removal of the MOM group. The reaction mixture was concentrated in vacuo, taken up in diethyl ether and brine, and transferred to a separatory funnel. After separating the layers, the organic layer was washed once with brine, dried over magnesium sulphate and concentrated in vacuo. Silica flash column chromatography (9:1 Hexanes/EtOAc) gave the product (6.19g, 72%) as a yellow solid, mp 48-50 °C. $^1$H-NMR (400 MHz, CDCl$_3$): δ/ppm = 8.61 (s, 1H), 8.31 (d, J = 8.3, 1.3 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 8.3 Hz, 1H), 7.52 (dd, J = 8.2, 6.8, 1.5 Hz, 1H), 7.46 (ddd, J = 8.2, 6.8, 1.4 Hz, 1H), 7.34 (d, J = 8.3 Hz, 1H), 1.41 (s, 12H); $^{13}$C-NMR (101 MHz, CDCl$_3$): δ/ppm = 161.7, 137.1, 130.4, 128.0, 127.5, 125.2, 124.3, 123.2, 119.1, 84.6, 25.0; IR (film): ν/cm$^{-1}$ = 3417, 3058, 2980, 2933, 1571, 1508, 1471, 1444, 1416, 1410, 1376, 1366, 1300, 1278, 1273, 125, 1203, 1141, 1075, 965, 850, 812, 750, 699, 576; HRMS (DART): m/z calculated for C$_{16}$H$_{20}$BO$_3$+ 271.1506, found 271.1507.

A round bottom flask with Dean-Stark apparatus and reflux condenser was charged with 2-hydroxyphenylboronic acid (1.97 g, 14.3 mmol), and pinacol (1.07 equiv., 1.79 g, 15.3 mmol). Toluene (48 mL) was added. The mixture was heated to reflux (130 °C) for 25 hours, then cooled to room temperature and concentrated. A small amount of hexanes was added to the residue and the mixture was allowed to stand overnight in a -20 °C freezer, during which the mixture solidified. Once warmed to room temperature, the majority of the solid melted but a white precipitate remained. This solid was filtered and the filtrate was concentrated and dried.
to give the product (2.91 g, 93%) as a yellow oil. $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$/ppm = 7.80 (s, 1H), 7.61 (dd, $J = 7.6$, 1.8 Hz, 1H), 7.37 (ddd, $J = 8.7, 7.4, 1.8$ Hz, 1H), 6.94 – 6.80 (m, 2H), 1.37 (s, 12H). $^1$H NMR was in accordance with a commercial sample kindly provided by CombiBlocks, PN-2519, batch L27675. This product is also available commercially from several other companies, including Sigma-Aldrich, TCI and Alfa-Aesar.

A 2-dram vial was charged with vinyl pyridine 2.1 (81.4 mg, 0.583 mmol), boronic ester 2.11 (2.0 equiv, 294 mg, 1.18 mmol), potassium carbonate (2 equiv., 164 mg, 1.19 mmol), and purged with argon. Dioxane (2 mL) and water (300 µL) were added.

Another vial was charged with hydroxy(cyclooctadiene)rhodium(I) dimer (3× 2 mol%, 15.8 mg, 0.0346 mmol), dppp (3× 4 mol%, 28.7 mg, 0.0696 mmol), and purged with argon. Dioxane (3 mL) was added, and the solution was heated to 50 ºC for 15 minutes. Upon cooling to room temperature, a portion of catalyst solution (1 mL, containing 4 mol% [Rh]) was transferred to the reaction vial. The reaction mixture was then sealed with a teflon cap and put into an oil-bath pre-heated at 90 ºC for 21 hours. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc), and concentrated in vacuo. Silica flash column chromatography (8:2 Hexanes/EtOAc) gave the product (130.0 mg, 85%), as a yellow solid, mp 95 - 97 ºC. $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$/ppm = 8.48 (dd, $J = 4.9$, 1.5 Hz, 1H), 8.12 (br s, 1H), 7.64 (d, $J = 8.0$, 1H), 7.13 (dd, $J = 8.0, 4.9$ Hz, 1H), 6.91 – 6.53 (m, 3H), 3.86 (s, 3H), 3.31 (t, $J = 7.0$ Hz, 2H), 3.13 (t, $J = 7.0$ Hz, 2H); $^{13}$C-NMR (101 MHz, CDCl$_3$): $\delta$/ppm = 158.1, 147.9, 146.6, 144.3, 137.2, 131.8, 128.4, 122.6, 122.5, 119.6, 109.3, 56.0, 36.1, 27.0; IR (film): v/cm$^{-1}$ = 3057, 2938, 2837, 1612, 1591, 1574, 1440, 1271, 1124, 1078; HRMS (DART): m/z calculated for C$_{14}$H$_{15}$ClNO$_2$+ 264.0791, found 264.0889.

A microwave vial was charged with 2.14-int (52.1 mg, 0.198 mmol), potassium carbonate (1.4 equiv., 39 mg, 0.282 mmol), palladium (II) acetate (2 mol%, 1.1 mg, 0.00490 mmol), X-Phos (4 mol%, 3.7 mg, 0.00776 mmol), and purged with argon. t-BuOH (930 µL) was added. The mixture was sealed with a crimp-top cap, and put into an oil-bath pre-heated at 120 ºC
for 22.5 hours. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc), and concentrated in vacuo. Silica flash column chromatography (8:2 Hexanes/EtOAc) gave the product (39.2 mg, 87%), as a yellow solid, mp 34-36 °C.  

\[ ^{1}H-\text{NMR} \ (400 \text{ MHz, CDCl}_3): \delta/\text{ppm} = 8.26 \ (\text{dd, J = 4.7, 1.5 Hz, 1H}), 7.58 \ (\text{dd, J = 8.1, 1.5 Hz, 1H}), 7.10 \ (\text{dd, J = 8.1, 4.7 Hz, 1H}), 7.03 \ (t, J = 7.9 \text{ Hz, 1H}), 6.83 - 6.79 \ (m, 2H), 3.87 \ (s, 3H), 3.32 - 3.26 \ (m, 2H), 3.24 - 3.19 \ (m, 2H); \]

\[ ^{13}C-\text{NMR} \ (101 \text{ MHz, CDCl}_3): \delta/\text{ppm} = 153.6, 151.5, 151.4, 146.6, 144.4, 135.7, 129.3, 125.1, 122.2, 121.1, 110.7, 56.2, 35.2, 28.7; \]

\[ \text{IR (film): } \nu/\text{cm}^{-1} = 3062, 3003, 2931, 2838, 1609, 1584, 1477, 1445, 1424, 1268, 1254, 1196, 1087, 1030, 948, 889, 833, 803, 784, 752, 729, 714, 678, 643, 591, 541; \]

\[ \text{HRMS (DART): } m/z \text{ calculated for C}_{14}\text{H}_{14}\text{NO}_2^+ 228.1025, \text{ found 228.1024.} \]

A microwave vial was charged with vinyl pyridine 2.1 (139.6 mg, 1.00 mmol), boronic ester 2.10 (1.5 equiv., 383 mg, 2.04 mmol), potassium carbonate (2 equiv., 279 mg, 2.02 mmol), and purged with argon. Dioxane (1 mL) and water (400 µL) were added. Another vial was charged with hydroxy(cyclooctadiene)rhodium(I) dimer (2 mol% 9.1 mg, 0.0199 mmol), dppp (2 mol%, 8.3 mg, 0.0201), and purged with argon. Dioxane (2 mL) was added, and the solution was heated to 50 °C for 15 minutes. Upon cooling to room temperature, the catalyst solution was transferred to the vial containing starting materials, washing with additional dioxane (2x 500 µL). The reaction mixture was then sealed with a crimp-top cap and put into an oil-bath pre-heated at 90 °C for 23 hours. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc), and concentrated in vacuo. Silica flash column chromatography (8:2 Hexanes/EtOAc) gave the product (200.0 mg, 76%), as an orange-pink solid, mp 122 – 124 °C.  

\[ ^{1}H-\text{NMR} \ (400 \text{ MHz, CDCl}_3): \delta/\text{ppm} = 8.48 \ (\text{dd, J = 4.9, 1.5 Hz, 1H}), 8.12 \ (\text{br s, 1H}), 7.64 \ (d, J = 8.0, 1H), 7.13 \ (\text{dd, J = 8.0, 4.9 Hz, 1H}), 6.91 - 6.53 \ (m, 3H), 3.86 \ (s, 3H), 3.31 \ (t, J = 7.0 \text{ Hz, 2H}); \]

\[ ^{13}C-\text{NMR} \ (101 \text{ MHz, CDCl}_3): \delta/\text{ppm} = 158.1, 147.9, 146.6, 144.3, 137.2, 131.8, 128.4, 122.6, 122.5, 119.6, 109.3, 56.0, 36.1, 27.0; \]

\[ \text{IR (film): } \nu/\text{cm}^{-1} = 3057, 2938, 2837, 1612, 1591, 1574, 1440, 1271, 1124, 1078; \]

\[ \text{HRMS (DART): } m/z \text{ calculated for C}_{14}\text{H}_{15}\text{ClNO}_2^+ 264.0791, \text{ found 264.0889.} \]
A microwave vial was charged with 2.15-int (76.1 mg, 0.289 mmol), potassium carbonate (1.3 equiv., 53 mg, 0.383 mmol), palladium (II) acetate (1.4 mg, 0.00624 mmol), X-Phos (4 mol%, 5.6 mg, 0.0117 mmol), and purged with argon. t-BuOH (1.4 mL) was added. The mixture was sealed with a crimp-top cap, and put into an oil-bath pre-heated at 120 °C for 23 hours. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc) and concentrated in vacuo. Silica flash column chromatography (7:3 Hexanes/EtOAc) gave the product (50.0 mg, 77%), as an off-white solid, mp 33-35 °C. 1H-NMR (400 MHz, CDCl3): δ/ppm = 8.25 (dd, J = 4.6, 1.5 Hz, 1H), 7.43 (dd, J = 8.1, 1.5 Hz, 1H), 7.11 – 7.05 (m, 2H), 6.73 (d, J = 3.1 Hz, 1H), 6.69 (dd, J = 8.7, 3.1 Hz, 1H), 3.76 (s, 3H), 3.33 – 3.28 (m, 2H), 3.19 – 3.13 (m, 2H); 13C-NMR (101 MHz, CDCl3): δ/ppm = 156.5, 153.8, 151.1, 151.1, 144.2, 134.3, 128.6, 122.3, 121.4, 114.8, 112.4, 55.7, 35.3, 29.3; IR (film): ν/cm⁻¹ = 3060, 3002, 2930, 2834, 2496, 1445, 1422, 1263, 1221, 1199, 1176, 1097, 1039, 932, 858, 825, 767, 751; HRMS (DART): m/z calculated for C14H14N1O2⁺ 228.1025, found 228.1022.

A 2-dram vial was charged with vinyl pyridine 2.1 (39.4 mg, 0.284 mmol), boronic ester 2.7 (1.5 equiv., 107 mg, 0.457 mmol), potassium carbonate (2 equiv., 80 mg, 0.578 mmol), and purged with argon. Dioxane (2 mL) and water (300 µL) were added. Another vial was charged with hydroxy(cyclooctadiene)rhodium(I) dimer (5× 2 mol%, 13.2 mg, 0.0289 mmol), dppp (5× 2 mol%, 12.0 mg, 0.0291 mmol), and purged with argon. Dioxane was added (5 mL), and the solution was heated to 50 °C for 15 minutes. Upon cooling to room temperature, a portion of catalyst solution (1 mL, containing 4 mol% [Rh]) was transferred to the reaction vial. The reaction mixture was then sealed with a teflon cap and put into an oil-bath pre-heated at 90 °C for 28.5 hours. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc), and concentrated in vacuo. Silica flash column chromatography (8:2 Hexanes/EtOAc) gave the product (51.2 mg, 72%), as an off-white solid, mp 135 – 137 °C. 1H-NMR (400 MHz, CDCl3): δ/ppm = 10.20 (br s, 1H), 8.45 (dd, J = 4.9, 1.5 Hz, 1H), 7.67 (dd, J = 8.0, 1.5 Hz, 1H), 7.17 (dd, J = 8.0, 4.9 Hz, 1H), 7.02 (d, J = 2.2 Hz, 1H), 6.92 (dd, J = 8.1, 2.2 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 3.39 – 3.34 (m, 2H), 3.19 – 3.11 (m, 2H), 2.27 (s, 3H); 13C-NMR (101 MHz, CDCl3):
A microwave vial was charged with 2.16-int (70.4 mg, 0.284 mmol), potassium carbonate (1.4 equiv., 53 mg, 0.383 mmol), palladium (II) acetate (5 mol%, 3.3 mg, 0.0146 mmol), X-Phos (10 mol%, 13.7 mg, 0.0287 mmol), and purged with argon. t-BuOH (1.4 mL) was added. The mixture was sealed with a crimp-top cap, and put into an oil-bath pre-heated at 120 °C for 22.5 hours. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc), and concentrated in vacuo. Silica flash column chromatography (8:2 Hexanes/EtOAc) gave the product (48.0 mg, 80%), as a yellow oil. 

1H-NMR (400 MHz, CDCl3): \( \delta /ppm = 8.26 \) (dd, \( J = 4.6, 1.5 \) Hz, 1H), \( 7.45 \) (dd, \( J = 8.2, 1.5 \) Hz, 1H), \( 7.10 \) (dd, \( J = 8.1, 4.6 \) Hz, 1H), \( 7.05 \) (d, \( J = 8.1 \) Hz, 1H), \( 7.02 – 6.94 \) (m, 2H), \( 3.34 – 3.28 \) (m, 2H), \( 3.18 – 3.12 \) (m, 2H), \( 2.30 \) (s, 3H); 13C-NMR (101 MHz, CDCl3): \( \delta /ppm = 155.0, 153.7, 151.4, 144.2, 134.3, 132.7, 130.5, 128.6, 128.1, 122.3, 120.4, 35.4, 29.2, 20.8 \); IR (film): \( \nu/cm^{-1} = 3059, 3010, 2924, 2858, 1586, 1570, 1494, 1450, 1446, 1441, 1349, 1274, 1267, 1255, 1222, 1199, 1176, 1160, 1097, 933, 857, 829, 810, 789, 759, 722, 713, 633, 572, 548 \); HRMS (DART): \( m/z \) calculated for C14H15ClNO+ 248.0842, found 248.0833.

A microwave vial was charged with vinyl pyridine 2.1 (140.0 mg, 1.00 mmol), boronic ester 2.9 (2 equiv., 485 mg, 2.04 mmol), potassium carbonate (2 equiv., 281 mg, 2.03 mmol), and purged with argon. Dioxane (1 mL) and water (400 \( \mu \)L) were added. Another vial was charged with hydroxy(cyclooctadiene)rhodium(I) dimer (2 mol%, 9.1 mg, 0.0199 mmol), dppp (2 mol%, 8.3 mg, 0.0201 mmol), and purged with argon. Dioxane (2 mL) was added, and the solution was heated to 50 °C for 15 minutes. Upon cooling to room temperature, the catalyst solution was transferred to the vial containing starting materials, washing with additional dioxane (2x 500 \( \mu \)L). The reaction mixture was then sealed with a crimp-top cap and put into an oil-bath pre-heated at 90 °C for 17.5 hours. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc), and concentrated in vacuo. Silica flash column chromatography (8:2
Hexanes/EtOAc) gave the product (225.0 mg, 89%), as a yellow solid, mp: 141 – 142 ºC. 

\[ ^1H\text{-NMR} \text{ (400 MHz, CDCl}_3\text{): } \delta/\text{ppm} = 10.30 \text{ (br s, 1H), } 8.44 \text{ (dd, } J = 4.9, 1.5 \text{ Hz, 1H), } 7.71 \text{ (dd, } J = 8.0, 1.5 \text{ Hz, 1H), } 7.21 \text{ (dd, } J = 8.0, 4.9 \text{ Hz, 1H), } 6.89 \text{ (dd, } J = 9.2, 2.9 \text{ Hz, 1H), } 6.85 - 6.74 \text{ (m, 2H), } 3.40 - 3.33 \text{ (m, 2H), } 3.18 - 3.11 \text{ (m, 2H); } ^{13}\text{C-NMR (101 MHz, CDCl}_3\text{): } \delta/\text{ppm} = 156.86 \text{ (d, } J = 237.1 \text{ Hz), } 156.83, 151.16 \text{ (d, } J = 1.9 \text{ Hz), } 145.57, 137.74, 132.35, 130.14 \text{ (d, } J = 7.0 \text{ Hz), } 122.92, 118.56 \text{ (d, } J = 8.2 \text{ Hz), } 116.45 \text{ (d, } J = 22.2 \text{ Hz), } 114.07 \text{ (d, } J = 22.7 \text{ Hz), } 36.48, 25.40 \text{ (d, } J = 1.4 \text{ Hz); } ^{19}\text{F-NMR (376 MHz, CDCl}_3\text{): } \delta/\text{ppm} = -125.86 \text{ (td, } J = 8.2 \text{ Hz, 5.4 Hz); IR (film): } \nu/cm^{-1} = 3100, 1512, 1371, 1256, 1192, 1047; HRMS (DART): m/z calculated for C$_{13}$H$_{12}$ClFNO$^+$ 252.0591, found 252.0589;

A microwave vial was charged with 2.17-int (74.8 mg, 0.297 mmol), potassium carbonate (1.4 equiv., 58 mg, 0.420 mmol), palladium (II) acetate (5 mol%, 3.4 mg, 0.0151 mmol), X-Phos (10 mol%, 14.3 mg, 0.0300 mmol), and purged with argon. t-BuOH (1.5 mL) was added. The mixture was sealed with a crimp-top cap, and put into an oil-bath pre-heated at 120 ºC for 24 hours. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc), and concentrated in vacuo. Silica flash column chromatography (8:2 Hexanes/EtOAc) gave the product (46.1 mg, 72%), as a yellow oil. 

\[ ^1H\text{-NMR (400 MHz, CDCl}_3\text{): } \delta/\text{ppm} = 8.27 \text{ (dd, } J = 4.5, 1.5 \text{ Hz, 1H), } 7.44 \text{ (dd, } J = 8.1, 1.5 \text{ Hz, 1H), } 7.14 - 7.07 \text{ (m, 2H), } 6.90 \text{ (dd, } J = 8.6, 3.1 \text{ Hz, 1H), } 6.84 \text{ (td, } J = 8.3, 3.1 \text{ Hz, 1H), } 3.33 - 3.28 \text{ (m, 2H), } 3.18 - 3.14 \text{ (m, 2H); } ^{13}\text{C-NMR (101 MHz, CDCl}_3\text{): } \delta/\text{ppm} = 159.40 \text{ (d, } J = 243.1 \text{ Hz), } 153.46, 153.16 \text{ (d, } J = 2.6 \text{ Hz), } 150.98, 144.52, 135.02 \text{ (d, } J = 7.8 \text{ Hz), } 128.64, 122.47, 121.99 \text{ (d, } J = 8.7 \text{ Hz), } 116.20 \text{ (d, } J = 23.1 \text{ Hz), } 113.99 \text{ (d, } J = 23.1 \text{ Hz), } 34.94, 29.15 \text{ (d, } J = 1.2 \text{ Hz); } ^{19}\text{F-NMR (376 MHz, CDCl}_3\text{): } \delta/\text{ppm} = -119.38 \text{ (td, } J = 8.3 \text{ Hz, 5.0 Hz); IR (film): } \nu/cm^{-1} = 3061, 2927, 2855, 1623, 1586, 1496, 1488, 1444, 1429, 1348, 1236, 1220, 1188, 1175, 1142, 1104, 987, 938, 868, 859 828, 809, 791, 765, 756, 713; HRMS (DART): m/z calculated for C$_{13}$H$_{11}$FNO$^+$ 216.0825, found 216.0832;
A microwave vial was charged with vinyl pyridine \(2.1\) (140.0 mg, 1.00 mmol), boronic ester \(2.6\) (2 equiv., 484 mg, 2.03 mmol), potassium carbonate (2 equiv., 278 mg, 2.01 mmol), and purged with argon. Dioxane (1 mL) and water (400 µL) were added. Another vial was charged with hydroxy(cyclooctadiene)rhodium(I) dimer (2 mol%, 9.1 mg, 0.0199 mmol), dppp (4 mol%, 16.6 mg, 0.0403 mmol), and purged with argon. Dioxane (2 mL) was added, and the solution was heated to 50 ºC for 15 minutes. Upon cooling to room temperature, the catalyst solution was transferred to the vial containing starting materials, washing with additional dioxane (2x 500 µL). The reaction mixture was then sealed with a crimp-top cap and put into an oil-bath pre-heated at 110 ºC for 21 hours. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc), and concentrated in vacuo. Silica flash column chromatography (6:1 Hexanes/EtOAc) gave the product (169.9 mg, 67%) as a white solid, \(\text{mp: 143-144 ºC.}\)

\(1^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)): \(\delta/\text{ppm} = 10.94\) (s, 1H), 8.44 (dd, \(J = 4.9, 1.5\) Hz, 1H), 7.71 (dd, \(J = 8.0, 1.5\) Hz, 1H), 7.21 (ddt, \(J = 8.0, 4.9, 0.9\) Hz, 1H), 7.05 (td, \(J = 8.2, 6.7\) Hz, 1H), 6.70 (dt, \(J = 8.2, 1.1\) Hz, 1H), 6.60 (dddd, \(J = 9.4, 8.2, 1.1\) Hz, 1H), 3.40 – 3.35 (m, 2H), 3.23 – 3.19 (m, 2H); \(1^3\text{C-NMR}\) (101 MHz, CDCl\(_3\)): \(\delta/\text{ppm} = 162.4\) (d, \(J = 243.7\) Hz), 157.2, 157.1 (d, \(J = 6.9\) Hz), 145.5, 137.9, 132.7, 127.9 (d, \(J = 10.9\) Hz), 123.0, 116.8 (d, \(J = 16.8\) Hz), 113.6 (d, \(J = 2.8\) Hz), 106.8 (d, \(J = 22.5\) Hz), 35.1, 18.4 (d, \(J = 4.0\) Hz); \(1^9\text{F-NMR}\) (376 MHz, CDCl\(_3\)): \(\delta/\text{ppm} = -118.27\) (t, \(J = 8.2\) Hz); \(\text{IR}\) (film): \(\nu/\text{cm}^{-1} = 3071, 2934, 2662, 1466, 1360, 1292, 1161, 1130, 1020, 936\); \(\text{HRMS}\) (DART): \(m/z\) calculated for \(\text{C}_{13}\text{H}_{12}\text{ClFNO}^+\) 252.0591, found 252.0593.

A microwave vial was charged with \(2.18\text{-int}\) (72.0 mg, 0.286 mmol), potassium carbonate (1.5 equiv., 60 mg, 0.434 mmol), palladium (II) acetate (5 mol%, 4.5 mg, 0.0156 mmol), X-Phos (10 mol%, 14.3 mg, 0.0300 mmol), and purged with argon. \(t\)-BuOH (1.5 mL) was added. The mixture was sealed with a crimp-top cap, and put into an oil-bath pre-heated at 120 ºC for 24 hours. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc), and concentrated in vacuo. Silica flash column chromatography (9:1 Hexanes/EtOAc) gave the product (46.2 mg, 75%), as a yellow oil. \(1^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)): \(\delta/\text{ppm} = 8.29\) (dd, \(J = 4.7, 1.5\) Hz, 1H), 7.45 (dd, \(J = 8.1, 1.5\) Hz, 1H), 7.16 –
A 2-dram vial was charged with vinyl pyridine 2.1 (82.0 mg, 0.587 mmol), boronic ester 2.4 (2.2 equiv., 324 mg, 1.27 mmol), potassium carbonate (2 equiv., 161 mg, 1.16 mmol), and purged with argon. Dioxane (2 mL) and water (300 µL) were added. Another vial was charged with hydroxy(cyclooctadiene)rhodium(I) dimer (3× 2 mol%, 15.8 mg, 0.0346 mmol), dppp (3× 4 mol%, 28.7 mg, 0.0696 mmol), and purged with argon. Dioxane (3 mL) was added and the solution was heated to 50 ºC for 15 minutes. Upon cooling to room temperature, a portion of catalyst solution (1 mL, containing 4 mol% [Rh]) was transferred to the reaction vial. The reaction mixture was then sealed with a teflon cap and put into an oil-bath pre-heated at 90 ºC for 21 hours. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc), and concentrated in vacuo. Silica flash column chromatography (8:2 Hexanes/EtOAc) gave the product (127.7 mg, 81%), as an off-white solid, mp 167 - 169 ºC. \(^1\)H-NMR (400 MHz, CDCl₃): δ/ppm = 10.62 (s, 1H), 8.43 (dd, J = 5.0, 1.5 Hz, 1H), 7.70 (dd, J = 8.0, 1.5 Hz, 1H), 7.20 (dd, J = 8.0, 5.0 Hz, 1H), 7.15 (d, J = 2.6 Hz, 1H), 7.04 (dd, J = 8.6, 2.6 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 3.50 – 3.21 (m, 2H), 3.21 – 2.80 (m, 2H); \(^{13}\)C-NMR (101 MHz, CDCl₃): δ/ppm = 156.9, 154.1, 145.6, 137.9, 132.5, 130.68, 130.3, 127.7, 124.8, 123.1, 119.3, 36.6, 25.4; IR (film): ν/cm\(^{-1}\) = 2939, 2650, 1599, 1580, 1492, 1442, 1431, 1419, 1361, 1271, 1237, 1174, 1129, 1086, 1049, 987, 882, 812; HRMS (DART): m/z calculated for C\(_{13}\)H\(_{12}\)Cl\(_2\)NO\(^+\) 268.0296, found 268.0298.
A sealable pressure flask was charged with 2,3-dibromopyridine (0.999 g, 4.22 mmol), [1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium(II)-dichloromethane complex (6 mol%, 209 mg, 0.256 mmol), potassium vinyltrifluoroborate (1.1 equiv., 624 mg, 4.66 mmol), and purged with argon. Anhydrous methanol (3.2 mL) was added, followed by triethylamine (1.1 equiv., 650 µL, 4.66 mmol, d = 0.726 g/mL). The flask was sealed and put into a pre-heated oil-bath at 100 ºC for 22 hrs. Upon cooling to room temperature, the reaction mixture was transferred to a round bottom flask (EtOAc) and concentrated in vacuo. Silica flash column chromatography (9:1 DCM/Pentanes) gave the product (388 mg, 50%) as a yellow oil.

**1H NMR** (300 MHz, CDCl$_3$): δ/ppm = 8.49 (dd, J = 4.5, 1.5 Hz, 1H), 7.82 (dd, J = 8.1, 1.5 Hz, 1H), 7.23 (dd, J = 16.9, 10.7 Hz, 1H), 7.02 (dd, J = 8.1, 4.6 Hz, 1H), 6.44 (dd, J = 16.9, 2.0 Hz, 1H), 5.55 (dd, J = 10.7, 2.0 Hz, 1H); **13C-NMR** (75 MHz, CDCl$_3$): δ/ppm = 153.2, 148.1, 140.8, 133.7, 123.7, 121.6, 120.8; **IR** (film): ν/cm$^{-1}$ = 3099, 3045, 2983, 1631, 1568, 1545, 1442, 1429, 1387, 1299, 1272, 1233, 1214, 1130, 1074, 1034, 1007, 9885, 939, 913, 787, 746, 743, 665, 588; **HRMS** (DART): m/z calculated for C$_7$H$_7$BrN$^+$ 183.9762; found 183.9760.

**Note:** this product is extremely volatile; the product was concentrated on a rotovap with the heating bath set no higher than 25 ºC, at 30 – 40 mmHg; it was dried by passing a gentle stream of air over the mouth of the flask used to contain it (not via high vacuum); it was stored under argon in a -20 ºC freezer, but was stable for several months in this way, darkening on storage.

**Stille Protocol:** A non flame-dried round bottom flask was charged with 2,3-dichloro-5-(trifluoromethyl)pyridine (1.00 g, 4.63 mmol), lithium chloride (1.2 equiv., 236 mg, 5.56 mmol), and tetrakis(triphenylphosphine)palladium (5 mol%, 385 mg, 0.23 mmol). The flask was fitted with a condenser and purged with argon. Dioxane (20 mL) was added, followed by tributylvinyltin (1.1 equiv, 1.5 ml, 5.1 mmol). The reaction was heated to 85 ºC for 16 hours, at which point an aliquot showed full consumption of starting material by **1H NMR.** Upon cooling to room temperature, the reaction was filtered through Celite and the solvent was concentrated in vacuo. Silica flash column chromatography (Hexanes/Triethylamine 98:2) gave the product (624 mg,
65%) as a yellow oil. $^1$H-NMR (400 MHz, CD$_2$Cl$_2$): $\delta$/ppm = 8.70 (d, J = 0.8 Hz, 1H), 7.91 (d, J = 1.4 Hz, 1H), 7.26 (dd, J = 16.9, 10.7 Hz, 1H), 6.60 (dd, J = 16.9, 1.9 Hz, 1H), 5.71 (dd, J = 10.7, 1.9 Hz, 1H); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$/ppm = 8.75 – 8.69 (m, 1H), 7.90 (dq, J = 2.1, 0.7 Hz, 1H), 7.27 (dd, J = 17.2, 10.7 Hz), 6.63 (dd, J = 16.9, 1.8 Hz, 1H), 5.74 (dd, J = 10.7, 1.8 Hz, 1H), NMR in CDCl$_3$ useful for reaction monitoring. $^{13}$C-NMR (101 MHz, CD$_2$Cl$_2$): $\delta$/ppm = 155.3 (q, J = 1.5 Hz), 144.3 (q, J = 4.0 Hz), 134.7 (q, J = 3.7 Hz), 130.6, 130.0, 126.0 (q, J = 33.5 Hz), 124.0, 123.0 (q, J = 272.5 Hz); $^{19}$F NMR (377 MHz, CD$_2$Cl$_2$): $\delta$/ppm = -63.7; IR (film): v/cm$^{-1}$ = 2955, 2916, 2849, 1599, 1323, 1163, 1138, 1094, 1055; HRMS (DART): m/z calculated for C$_8$H$_6$ClF$_3$N$^+$ 208.0141, found 208.0145.

Note: this product is extremely volatile and several precautions were taken to ensure the best possible yield: the product was concentrated on a rotovap with the heating bath set no higher than 25 °C, at 30 – 40 mmHg; it was dried by passing a gentle stream of air over the mouth of the flask used to contain it (not via high vacuum); it was stored under argon in a -20 °C freezer, but was stable only for several weeks when stored in this way, darkening upon storage; unusable samples are those which have darkened to black and/or have thickened to viscous gums. Multiple column purifications may be necessary to remove all the tin residues from the product. Due to the volatile nature of the product, the yield quoted will only be obtained if two column purifications are performed.

Suzuki Protocol: A non flame-dried sealable pressure flask was charged with 2,3-dichloro-5-trifluoromethylpyridine (947 mg, 4.38 mmol), potassium carbonate (4 equiv., 2.42g, 17.5 mmol), tetrakistriphenylphosphinepalladium (5 mol%, 253 mg, 0.219 mmol), 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane (1.1 equiv., 771 mg, 5.01 mmol), and purged with argon. DME (24 mL) and water (12 mL) were added. The flask was sealed and put into an oil-bath pre-heated at 100 ºC for 4 hours. At this point, a small aliquot of the organic layer was removed and analysed by $^1$H NMR, which showed complete consumption of starting material. Upon cooling to room temperature, the reaction was quenched with additional water, partitioned with diethyl ether, and transferred to a separatory funnel. The organic layer was separated and the
aqueous layer was extracted twice with diethyl ether. The combined organic layers were
dried over magnesium sulphate and concentrated in vacuo to a red oil. Silica flash
column chromatography (Hexanes → 99:1 Hexanes/Diethyl Ether) gave the product
(548 mg, 60%) as a yellow oil.
3.4 Synthesis of Compounds in Section 2.3

Note: In order to determine the identity of by-product 2.25, we also attempted the synthesis of compounds A and B in Figure 2.3-1 via silyl protection of 2.23 and a subsequent cross-coupling. Our isolated sample of 2.23 arose from incomplete silylation of 2.23 under our reaction conditions:

A 2-dram vial was charged with 2-hydroxyphenylboronic acid (2.1 equiv., 141 mg, 1.02 mmol), hydroxy(cyclooctadiene)rhodium(I) dimer (2 mol%, 4.4 mg, 0.0965 mmol), potassium carbonate (2.1 equiv., 144 mg, 1.04 mmol), vinyl pyridine 2.22 (102.8 mg, 0.495 mmol), and purged with argon. Dioxane (5 mL) and water (500 µL) were added. The mixture was stirred at room temperature for 10 minutes, at which point TLC indicated complete consumption of starting material. The mixture was passed through a silica plug (EtOAc), concentrated in vacuo, and the residue was taken up in anhydrous DMF (5 mL). TBS-Cl (excess, 2.3 equiv., 171 mg, 1.13 mmol) and imidazole (5.1 equiv., 172 mg, 2.53 mmol) were added, and the mixture was stirred at room temperature for 33 hours. An additional portion of TBS-Cl (1.1 equiv., 84 mg, 0.557 mmol) and imidazole (2.2 equiv., 74 mg, 1.09 mmol) were added after 16 hours. The reaction was quenched with sat. sodium bicarbonate solution, partitioned with diethyl ether, transferred to a separatory funnel, and the layers were separated. The organic layer was washed five times with water, and the combined aqueous washings were back-extracted twice with diethyl ether. The combined organic layers were dried over magnesium sulphate and concentrated in vacuo to a yellow oil. Silica flash column chromatography (20:1 Hexanes/EtOAc → 9:1 Hexanes/EtOAc) gave silyl-protected 2.23 (55.7 mg, 27%) as a colourless oil, and intermediate 2.23 as a white solid (67.8 mg, 45%).

\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta/\text{ppm} = 8.75 (s, 1\text{H}), 7.93 (d, J = 1.9 \text{ Hz}, 1\text{H}), 7.18 (dd, J = 7.5, 1.7 \text{ Hz}, 1\text{H}), 7.12 (\text{td, } J = 7.7, 1.7 \text{ Hz}, 1\text{H}), 6.94 – 6.81 (m, 2\text{H}), 3.43 (t, J = 6.2 \text{ Hz}, 2\text{H}), 3.24 – 3.15 (m, 2\text{H}); \)^13C-NMR (101 MHz, CDCl\(_3\)): \(\delta/\text{ppm} = 161.8 (m), 154.8, 142.9 (q, J = 4.1 \text{ Hz}), 134.5 (q, J = 3.4 \text{ Hz}), 132.7, 130.8, 128.1 (2), 126.4 (q, J = 34.1 \text{ Hz}), 122.6 (q, J = 272.8 \text{ Hz}), 120.8, 117.7, 37.0, 25.4; \)^19F-NMR (376 MHz, CDCl\(_3\)): \(\delta/\text{ppm} = -62.42; \) IR (film): \(\nu/\text{cm}^{-1} = 3426, 3065, 2952, 2934, 2863, 1608, 1504, 1459, 1399, 1325, 1297,
A 2-dram vial was charged with vinyl pyridine 2.22 (86.7 mg, 0.418 mmol), boronic ester 2.13 (2.0 equiv., 180 mg, 0.818 mmol), potassium carbonate (2.0 equiv., 113 mg, 0.818 mmol), potassium phosphate (1.9 equiv., 170 mg, 0.801 mmol), hydroxy(cyclooctadiene)rhodium(I) dimer (2 mol%, 3.7 mg, 0.00811 mmol), palladium (II) acetate (5 mol%, 4.6 mg, 0.0205 mmol), tBuX-Phos (10 mol%, 17.3 mg, 0.0407 mmol), and purged with argon. Dioxane (2 mL) and water (200 µL) were added, and the mixture was stirred at room temperature for 10 minutes. The mixture was then sealed with a Teflon cap, and put into an oil-bath pre-heated at 100 ºC for 19 hours. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc), and concentrated in vacuo. Silica flash column chromatography (25:1 Hexanes/EtOAc) gave the product (73.9 mg, 67%), as a yellow oil. $^1$H-NMR (400 MHz, CDCl$_3$): δ/ppm = 8.52 (d, J = 1.8 Hz, 1H), 7.70 (d, J = 2.0 Hz, 1H), 7.21 (td, J = 6.9, 1.8 Hz, 2H), 7.22 – 7.14 (m, 1H), 7.12 (td, J = 6.9, 1.9 Hz, 1H), 3.42 – 3.34 (m, 2H), 3.24 – 3.18 (m, 2H); $^{13}$C-NMR (101 MHz, CDCl$_3$): 156.6, 155.4 (d, J = 1.5 Hz), 152.9, 140.6 (q, J = 4.1 Hz), 132.8, 130.0, 128.0, 126.0 (q, J = 3.5 Hz), 125.7 (q, J = 33.3 Hz), 125.4, 123.2 (q, J = 272.5 Hz), 120.8, 35.7, 28.9; $^{19}$F-NMR (376 MHz, CDCl$_3$): δ/ppm = -62.07; IR (film): v/cm$^{-1}$ = 3065, 3040, 2930, 2859, 1616, 1607, 1564, 1489, 1451, 1431, 1410, 1335, 1267, 1238, 1204, 1173, 1128, 1100, 1084, 955, 912, 764, 748, 650; HRMS (DART): m/z calculated for C$_{14}$H$_{10}$F$_3$NO$^+$ 266.0793, found 266.0796.

Note: Mixed fractions containing phenol (the deborylation product) were concentrated separately, taken up in diethyl ether and transferred to a separatory funnel. The organic layer was washed 3× with a 1M KOH solution, dried over magnesium sulphate and concentrated, then combined with pure fractions to give the product.
A 2-dr vial was charged with tris(dibenzylideneacetone)dipalladium (4 mol%, 2.8 mg, 0.00306 mmol), tBuX-Phos (8 mol%, 0.0101 mmol), potassium hydroxide (4 equiv., 29 mg, 0.517 mmol) and purged with argon. A solution of arylated intermediate (38 mg, 0.126 mmol) in dioxane (400 µL, wash 3× 400 µL) was added, following by water (1600 µL). The reaction was sealed with a Teflon cap and put into a pre-heated oil-bath at 100 ºC for 19 hours. The following day, the reaction was cooled to room temperature and acidified to pH 2 with 5% H₂SO₄ solution. After transferring to a separatory funnel, the organic layer was separated and the aqueous layer was extracted 3× with EtOAc. The combined organic layers were dried over magnesium sulphate and concentrated in vacuo. Silica flash column chromatography (40:1 → 2:1 Hexanes/EtOAc) gave the domino product as a yellow oil (15 mg, 44%) and the phenol as an off-white solid (13 mg, 35%), isolated with an inseparable alkyl-based impurity, mp 138 – 143 ºC; ¹H-NMR (500 MHz, CDCl₃): δ/ppm = 8.32 (dd, J = 2.0, 1.0 Hz, 1H), 7.32 (d, J = 1.9 Hz, 1H), 7.18 (dd, J = 7.5, 1.7 Hz, 1H), 7.12 (ddd, J = 8.0, 7.3, 1.7 Hz, 1H), 6.91 – 6.85 (m, 2H), 3.30 (t, J = 6.5 Hz, 2H), 3.15 – 3.08 (m, 2H); ¹³C-NMR (126 MHz, CDCl₃): δ/ppm = 154.1, 152.8 (q, J = 1.3 Hz), 151.6, 135.5 (q, J = 4.4 Hz), 130.8, 128.7, 128.2, 126.5 (q, J = 33.4 Hz), 123.2 (q, J = 272.4 Hz), 121.2, 119.2 (q, J = 3.4 Hz), 117.5, 33.6, 26.2; ¹⁹F NMR (376 MHz, CDCl₃): δ/ppm = -62.42; IR (film): ν/cm⁻¹ = 2961, 2932, 2855, 1613, 1457, 1430, 1343, 1248, 1170, 1134, 1089, 949, 913, 749; HRMS: m/z calculated for C₁₄H₁₃F₃NO₂⁺ 284.0898, found 284.0905.

A 2-dram vial was charged with vinyl pyridine 2.22 (87.6 mg, 0.422 mmol), boronic ester 2.10 (1.9 equiv., 203 mg, 0.812 mmol), potassium carbonate (1.9 equiv., 112 mg, 0.810 mmol), potassium phosphate (2.0 equiv., 176 mg, 0.829 mmol), hydroxy(cyclooctadiene)rhodium(I) dimer (2 mol%, 3.8 mg, 0.00833 mmol), palladium (II) acetate (5 mol%, 4.6 mg, 0.0205 mmol), tBuX-Phos (10 mol%, 17.2 mg, 0.0422 mmol), and purged with argon. Dioxane (2 mL) and water (200 µL) were added, and the mixture was stirred at room temperature for 10 minutes. The mixture was then sealed with a Teflon cap, and put into an oil-bath pre-heated at 100 ºC for 18 hours. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc), and
concentrated in vacuo. The residue was taken up in diethyl ether, transferred to a separatory funnel, and the organic layer was washed 3× with a 1M KOH solution. The organic layer was dried over magnesium sulphate and concentrated in vacuo. Silica flash column chromatography (9:1 Hexanes/EtOAc) gave the product in vacuo. Silica flash column chromatography (9:1 Hexanes/EtOAc) gave the product (73.0 mg, 59%), as a tan solid, mp 36 – 38 ºC; ¹H-NMR (400 MHz, CDCl₃): δ/ppm = 8.52 – 8.49 (m, 2H), 7.67 (d, J = 1.9 Hz, 1H), 7.09 (d, J = 8.7 Hz, 1H), 6.75 (d, J = 3.0 Hz, 1H), 6.71 (dd, J = 8.7, 3.1 Hz, 1H), 3.78 (s, 3H), 3.38 – 3.33 (m, 2H), 3.20 – 3.14 (m, 2H); ¹³C-NMR (101 MHz, CDCl₃): 156.9, 155.2 (q, J = 1.4 Hz), 153.2, 150.7, 140.5 (q, J = 4.1 Hz), 134.1, 125.8 (q, J = 3.6 Hz), 125.6 (q, J = 33.1 Hz), 123.2 (q, J = 272.4 Hz), 121.5, 114.8, 112.6, 55.7, 35.7, 28.9; ¹⁹F-NMR (376 MHz, CDCl₃): δ/ppm = -62.07; IR (film) ν/cm⁻¹: 3067, 3004, 2938, 2844, 1607, 1564, 1496, 1469, 1428, 1411, 1339, 1287, 1264, 1224, 1202, 1187, 1129, 1085, 1042, 957, 913, 69, 851, 817, 794, 761, 747, 716, 687, 653; HRMS (DART): m/z calculated for C₁₅H₁₃F₃NO₂⁺ 296.0898, found 296.0900.

A 2-dram vial was charged with vinyl pyridine 2.22 (43.0 mg, 0.207 mmol), boronic ester 2.7 (2.0 equiv., 96 mg, 0.410 mmol), potassium carbonate (2.0 equiv., 56 mg, 0.405 mmol), potassium phosphate (2.0 equiv., 87 mg, 0.410 mmol), hydroxy(cyclooctadiene)rhodium(I) dimer (2 mol%, 1.9 mg, 0.00416 mmol), tris(dibenzylideneacetone)dipalladium(0) (2.5 mol%, 4.7 mg, 0.00513 mmol), tBuX-Phos (10 mol%, 8.6 mg, 0.0203 mmol), and purged with argon. Dioxane (2 mL) and water (200 µL) were added, and the mixture was stirred at room temperature for 10 minutes. The mixture was then sealed with a Teflon cap, and put into an oil-bath pre-heated at 100 ºC for 17 hours. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc), and concentrated in vacuo. Silica flash column chromatography (60:1 → 20:1 Hexanes/EtOAc) gave the product as a yellow solid, mp 36 – 38 ºC; ¹H-NMR (400 MHz, CDCl₃): δ/ppm = 8.51 (s, 1H), 7.68 (d, J = 1.9 Hz, 1H), 7.07 (d, J = 8.1 Hz, 1H), 7.03 (d, J = 2.0 Hz, 1H), 7.00 (dd, J = 8.0, 2.2 Hz, 1H), 3.39 – 3.34 (m, 2H), 3.19 – 3.15 (m, 2H), 2.31 (s, 3H); ¹³C-NMR (101 MHz, CDCl₃): 155.4 (t, J = 1.4 Hz), 140.5 (q, J = 4.1 Hz), 135.0, 132.4, 130.5, 128.4, 125.8 (q, J = 3.5 Hz), 125.7 (q, J = 33.2 Hz), 123.2 (q, J = 272.4 Hz), 120.5, 35.8, 28.8, 20.8; ¹⁹F-NMR (376 MHz, CDCl₃): δ/ppm = -63.13; IR (film) ν/cm⁻¹: 3028, 2931, 2862, 1497, 1431, 1408, 1334, 1265, 1247, 1221, 1201, 1168, 1137, 1110, 1084, 958,
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914, 824, 797, 773, 746; **HRMS** (DART): \( m/z \) calculated for \( \text{C}_{15}\text{H}_{13}\text{F}_{3}\text{NO} \) 280.0949, found 280.0951.

A 2-dram vial was charged with vinyl pyridine 2.22 (83.8 mg, 0.404 mmol), boronic ester 2.8 (2.0 equiv., 193 mg, 0.818 mmol), potassium carbonate (2.1 equiv., 116 mg, 0.839 mmol), potassium phosphate (2.1 equiv., 177 mg, 0.834 mmol), hydroxy(cyclooctadiene)rhodium(I) dimer (2 mol%, 3.8 mg, 0.00833 mmol), palladium (II) acetate (5 mol%, 4.6 mg, 0.0205 mmol), \( \text{tBuX-Phos} \) (7 mol%, 11.9 mg, 0.0280 mmol), and purged with argon. Dioxane (2 mL) and water (200 \( \mu \)L) were added, and the mixture was stirred at room temperature for 10 minutes. The mixture was then sealed with a Teflon cap, and put into an oil-bath pre-heated at 100 °C for 18 hours. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc), and concentrated *in vacuo*. The residue was taken up in DMF (4 mL) and purged with argon. Excess triethylamine (4 equiv., 220 \( \mu \)L, 1.58 mmol), and TBS-Cl (3 equiv., 181 mg, 1.20 mmol) were added, and the mixture was stirred at room temperature overnight. The following day, the reaction mixture was diluted with diethyl ether and transferred to a separatory funnel. The organic layer was washed 5× with water, and the combined aqueous washings were back-extracted twice with diethyl ether. The organic layer was dried over magnesium sulphate and concentrated *in vacuo*. Silica flash column chromatography (30:1 Hexanes/EtOAc) gave the product (73.7 mg, 46% over 2 steps), as an orange solid, \( \text{mp} \) 33 – 34 °C. \(^1\text{H-NMR} \) (300 MHz, CDCl\(_3\)): \( \delta/\text{ppm} = 8.51 \) (dd, \( J = 2.0, 1.0 \) Hz, 1H), 7.67 (d, \( J = 1.7 \) Hz, 1H), 7.03 (d, \( J = 8.6 \) Hz, 1H), 6.69 (d, \( J = 2.8 \) Hz, 1H), 6.65 (dd, \( J = 8.6, 2.9 \) Hz, 1H), 3.38 – 3.31 (m, 2H), 3.17 – 3.11 (m, 2H), 0.98 (s, 9H), 0.19 (s, 6H); \(^{13}\text{C-NMR} \) (101 MHz, CDCl\(_3\)): 155.3 (q, \( J = 1.3 \) Hz), 153.2, 152.9, 151.1, 140.5 (q, \( J = 4.1 \) Hz), 134.0, 125.8 (q, \( J = 3.7 \) Hz), 125.8 (q, \( J = 33.2 \) Hz), 123.2 (q, \( J = 272.4 \) Hz), 121.4, 120.9, 118.9, 35.8, 28.8, 25.8, 18.3, -4.3; \(^{19}\text{F-NMR} \) (282 MHz, CDCl\(_3\)): \( \delta/\text{ppm} = -62.10 \); \( \text{IR} \) (film) \( \nu/\text{cm}^{-1} \): 2957, 2931, 2898, 2860, 1617, 1607, 1591, 1490, 1473, 1408, 1334, 1296, 1261, 1221, 1194, 1165, 1136, 1102, 1084, 994, 960, 941, 913, 874, 852, 840, 804, 781; **HRMS** (DART): \( m/z \) calculated for \( \text{C}_{20}\text{H}_{25}\text{F}_{3}\text{NO}_{2}\text{Si}^+ \) 396.1607, found 396.1612.
A 2-dram vial was charged with vinyl pyridine 2.22 (83.0 mg, 0.400 mmol), boronic ester 2.9 (2.1 equiv., 198 mg, 0.832 mmol), potassium carbonate (2.1 equiv., 117 mg, 0.847 mmol), potassium phosphate (2.0 equiv., 174 mg, 0.820 mmol), hydroxy(cyclooctadiene)rhodium(I) dimer (2 mol%, 3.8 mg, 0.00833 mmol), palladium (II) acetate (5 mol%, 4.6 mg, 0.0205 mmol), tBuX-Phos (7 mol%, 12.0 mg, 0.0283 mmol), and purged with argon. Dioxane (2 mL) and water (200 µL) were added, and the mixture was stirred at room temperature for 10 minutes. The mixture was then sealed with a Teflon cap, and put into an oil-bath pre-heated at 100 ºC for 18 hours. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc), and concentrated in vacuo. The residue was taken up in diethyl ether, transferred to a separatory funnel, and the organic layer was washed 3× with a 1M KOH solution. The organic layer was dried over magnesium sulphate and concentrated in vacuo. Silica flash column chromatography (1:1 DCM/Hexanes) gave the product (67.8 mg, 60%), as a yellow oil which solidified upon standing overnight in a -20 ºC freezer, mp 27 – 28 ºC. 1H-NMR (400 MHz, CDCl3): δ/ppm = 8.53 (s, 1H), 7.69 (d, J = 1.9 Hz, 1H), 7.13 (dd, J = 8.8, 4.8 Hz, 1H), 6.93 (dd, J = 8.5, 3.0 Hz, 1H), 6.88 (td, J = 8.3, 3.1 Hz, 1H), 3.39 – 3.34 (m, 2H), 3.21 – 3.16 (m, 2H); 13C-NMR (101 MHz, CDCl3): 159.7 (d, J = 244.2 Hz), 155.0 (q, J = 1.4 Hz), 140.8 (q, J = 4.1 Hz), 134.8 (d, J = 7.8 Hz), 125.9 (q, J = 3.6 Hz), 125.8 (q, J = 33.3 Hz), 123.1 (q, J = 272.5 Hz), 122.1 (d, J = 8.7 Hz), 116.3 (d, J = 23.3 Hz), 114.4 (d, J = 23.1 Hz), 35.4, 28.8 (d, J = 1.2 Hz); 19F-NMR (376 MHz, CDCl3): δ/ppm = -63.11, -118.48 (td, J = 8.1, 4.8 Hz); IR (film): ν/cm⁻¹ = 2965, 2928, 1494, 1430, 1407, 1335, 1282, 1259, 1187, 1164, 1132, 1084, 960, 912, 867, 828, 798, 773, 750, 727, 689; HRMS (DART): m/z calculated for C₁₄H₁₀F₄NO₂⁺ 284.0699, found 284.0689.
for 10 minutes. The mixture was then sealed with a Teflon cap, and put into an oil-bath pre-heated at 100 °C for 18 hours. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc), and concentrated in vacuo. Silica flash column chromatography (25:1 Hexanes/EtOAc) gave the product (49.9 mg, 39%) as an off-white solid, mp 63 – 65 °C. \(^1H\)-NMR (400 MHz, CDCl\(_3\)): δ/ppm = 8.53 (d, J = 1.8 Hz, 1H), 7.68 (d, J = 1.9 Hz, 1H), 7.21 (d, J = 2.5 Hz, 1H), 7.16 (dd, J = 8.6, 2.5 Hz, 1H), 7.10 (d, J = 8.6 Hz, 1H), 3.38 – 3.33 (m, 2H), 3.19 – 3.14 (m, 2H); \(^{13}C\)-NMR (101 MHz, CDCl\(_3\)): 155.0, 154.8 (q, J = 1.4 Hz), 152.5, 140.8 (q, J = 4.1 Hz), 134.3, 130.2, 129.7, 127.8, 125.8 (q, J = 3.6 Hz), 125.8 (q, J = 33.4 Hz), 123.0 (q, J = 272.5 Hz), 122.1, 35.2, 28.6; \(^{19}F\)-NMR (376 MHz, CDCl\(_3\)): δ/ppm = -62.09; IR (film) v/cm\(^{-1}\): 3071, 2932, 2863, 1615, 1482, 1429, 1335, 1264, 1239, 1204, 1173, 1136, 1084, 955, 914, 876, 862, 772, 745; HRMS (DART): m/z calculated for C\(_{14}\)H\(_{10}\)ClF\(_3\)NO\(^+\) 300.0403, found 300.0401.

A 2-dram vial was charged with palladium (II) acetate (5 mol%, 1.0 mg, 0.00445 mmol), RuPhos (10 mol%, 4.3 mg, 0.00921 mmol), and sodium \(t\)-butoxide (2 equiv., 18 mg, 0188 mmol). The vial was purged with argon, and a solution of 2.30 (26.8 mg, 0.0894 mmol) in dioxane (500 µL, wash 3× 500 µL) was added, followed by morpholine (1.3 equiv., 10 µL, d = 0.996 g/mL, 0.114 mmol). The vial was then sealed with a Teflon cap and put into a pre-heated oil-bath at 100 °C for 21 hours. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc), and concentrated in vacuo. Silica flash column chromatography (6:4 Hexanes/EtOAc) gave the product (25.8 mg, 82%) as an off-white solid, mp: 74 – 76 °C. \(^1H\)-NMR (400 MHz, CDCl\(_3\)): δ/ppm = 8.50 (d, J = 1.8 Hz, 1H), 7.67 (d, J = 2.0 Hz, 1H), 7.10 (d, J = 8.5 Hz, 1H), 6.78 – 6.71 (m, 2H), 3.88 – 3.82 (m, 4H), 3.40 – 3.33 (m, 2H), 3.20 – 3.15 (m, 2H), 3.13 – 3.08 (m, 4H); \(^{13}C\)-NMR (101 MHz, CDCl\(_3\)): 155.2 (m), 153.3, 150.4, 149.00, 140.4 (q, J = 4.1 Hz), 133.5, 125.8 (q, J = 3.6 Hz), 125.6 (q, J = 132.0 Hz), 123.2 (q, J = 272.5 Hz), 121.3, 116.9, 115.1, 67.0, 50.0, 35.9, 29.2; \(^{19}F\)-NMR (376 MHz, CDCl\(_3\)): δ/ppm = -62.06; IR (film): v/cm\(^{-1}\) = 2962, 2856, 2823, 1502, 1409, 1263, 1232, 1209, 1167, 1138, 2224, 1084, 994, 959, 942, 913, 744; HRMS (DART): m/z calculated for C\(_{18}\)H\(_{18}\)F\(_3\)N\(_2\)O\(_2\)\(^+\) 351.1320, found 351.1321.
A 2-dram vial was charged with vinyl pyridine 2.22 (43.7 mg, 0.211 mmol), boronic ester 2.5 (1.9 equiv., 122 mg, 0.408 mmol), potassium carbonate (2.0 equiv., 58 mg, 0.420 mmol), potassium phosphate (1.9 equiv., 87 mg, 0.410 mmol), hydroxy(cyclooctadiene)rhodium(I) dimer (2 mol%, 2.0 mg, 0.00438 mmol), palladium (II) acetate (5 mol%, 2.4 mg, 0.0107 mmol), tBuX-Phos (7 mol%, 6.0 mg, 0.0141 mmol), and purged with argon. Dioxane (2 mL) and water (200 µL) were added, and the mixture was stirred at room temperature for 10 minutes. The mixture was then sealed with a Teflon cap, and put into an oil-bath pre-heated at 100 ºC for 18 hours. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc), and concentrated in vacuo. The residue was taken up in diethyl ether, transferred to a separatory funnel, and the organic layer was washed 3× with a 1M KOH solution. The organic layer was dried over magnesium sulphate and concentrated in vacuo.

Silica flash column chromatography (12:1 Hexanes/EtOAc) gave the product as a yellow solid.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$/ppm = 8.73 (dd, J = 2.0, 1.0 Hz, 1H), 7.95 (dd, J = 2.0, 0.7 Hz, 1H), 7.29 (d, J = 2.5 Hz, 1H), 7.19 (dd, J = 8.6, 2.5 Hz, 1H), 6.77 (d, J = 8.6 Hz, 1H), 3.45 – 3.38 (m, 2H), 3.17 – 3.11 (m, 2H); $^{13}$C-NMR (101 MHz, CDCl$_3$): $\delta$/ppm = 161.4 – 161.2 (m), 154.1, 142.8 (q, J = 4.1 Hz), 134.7 (q, J = 3.5 Hz), 133.2, 132.8, 130.9, 130.4, 126.6 (q, J = 34.2 Hz), 123.9 (q, J = 272.7 Hz), 119.6, 112.6, 36.8, 25.1; $^{19}$F-NMR (377 MHz, CDCl$_3$): $\delta$/ppm = -62.31; HRMS (DART): m/z calculated for C$_{14}$H$_{11}$BrClF$_3$NO$^+$ 379.9665, found 379.9662.
taken up in diethyl ether, transferred to a separatory funnel, and the organic layer was washed 3× with a 1M KOH solution. The organic layer was dried over magnesium sulphate and concentrated in vacuo. Silica flash column chromatography (40:1 Hexanes/EtOAc) gave the product (39.0 mg, 33%), as a yellow oil. $^1$H($^{19}$F)-NMR (400 MHz, CDCl$_3$): δ/ppm = 8.56 (d, J = 2.0 Hz, 1H), 7.69 (d, J = 2.0 Hz, 1H), 7.16 (t, J = 8.2 Hz, 1H), 7.01 (dd, J = 8.3, 1.1 Hz, 1H), 6.88 (dd, J = 8.3, 1.1 Hz, 1H), 3.43 – 3.38 (m, 2H), 3.23 – 3.17 (m, 2H); $^{13}$C-NMR (101 MHz, CDCl$_3$): 160.8 (d, J = 246.4 Hz), 157.1 (d, J = 6.2 Hz), 156.5 (d, J = 1.4 Hz), 153.0, 141.4 (q, J = 4.2 Hz), 127.8 (d, J = 10.3 Hz), 126.0 (q, J = 33.3 Hz), 125.8 (q, J = 3.5 Hz), 123.1 (q, J = 272.5 Hz), 120.0 (d, J = 18.7 Hz), 116.5 (d, J = 3.3 Hz), 111.9 (d, J = 22.8 Hz), 34.0, 21.1 (d, J = 5.0 Hz); $^{19}$F-NMR (376 MHz, CDCl$_3$): δ/ppm = -62.08, -115.36 (t, J = 7.5 Hz); IR (film): ν/cm$^{-1}$ = 3078, 2931, 2858, 1621, 1613, 1573, 1461, 1409, 1334, 1259, 1173, 1133, 1086, 1045, 1006, 928, 913, 791, 771, 748, 743; HRMS (DART): m/z calculated for C$_{14}$H$_{10}$F$_4$NO$^+$ 284.0699, found 284.0697.
3.5 Synthesis of Compounds in Section 2.4

A round bottom flask was charged with 2-amino-5-cyanopyridine (1.00 g, 8.40 mmol) and NCS (1.1 equiv, 1.24 g, 9.29 mmol). MeCN (20 mL) was added. The mixture was stirred at room temperature for 39 hours, at which point TLC showed incomplete consumption of starting material. The mixture was then heated to 60 ºC for 2 hours, at which point TLC showed complete consumption of starting material. Upon cooling to room temperature, copper (II) bromide (2 equiv., 3.75 g, 16.8 mmol) and isopentyl nitrite (2 equiv., 2.3 mL, d = 0.872 g/mL, 17.1 mmol) were added and the mixture was heated to 65 ºC for 2 hours. Upon cooling to room temperature, the reaction was quenched with sat. ammonium chloride solution, partitioned with DCM, and transferred to a separatory funnel. The organic layer was separated and the aqueous layer was extracted three times with DCM. The combined organic layers were dried over magnesium sulphate and concentrated in vacuo to a brown solid. Silica flash column chromatography (11:1 Hexanes/EtOAc) gave the product (635 mg, 35% over 2 steps) as a yellow solid, recrystallised (hexanes/DCM) to give white needles, mp 129 ºC, subl. \(^1\text{H-NMR}\) (300 MHz, CDCl\(_3\)): \(\delta/\text{ppm} = 8.55\) (d, \(J = 2.0\) Hz, 1H), 7.99 (d, \(J = 2.0\) Hz, 1H); \(^{13}\text{C-NMR}\) (75 MHz, CDCl\(_3\)): \(\delta/\text{ppm} = 149.7, 146.9, 140.2, 134.6, 114.6, 110.0\); \(\text{IR}\) (film): v/cm\(^{-1}\) = 3030, 2993, 2240, 1409, 1371, 1276, 1259, 1133, 1041, 914, 765, 750; \(\text{HRMS}\) (DART): m/z calculated for C\(_6\)H\(_2\)BrClN\(_2\)\(^+\) 216.9168, found 216.9165.

A round bottom flask was charged with 2,3-dichloro-5-bromopyridine (807 mg, 3.56 mmol). THF (6 mL) was added. The solution was cooled to 0 ºC and \(\text{iPrMgCl}\) (1.3 equiv., 2.3 mL, 2.0 M) was added dropwise at this temperature. The mixture was stirred for 50 minutes at 0 ºC, at which point TLC indicated complete magnesium-halogen exchange (comparing to 2,3-dichloropyridine). MsCl (2.0 equiv., 550 µL, 7.11 mmol) in THF (2 mL, wash 2× 1 mL) was added dropwise to the reaction at 0 ºC. The mixture was stirred at 0 ºC for 5 minutes, the ice bath was removed, and the mixture was allowed to come to room temperature overnight. TLC the next day indicated formation of the product, along with unquenched magnesium-exchanged staring material. The mixture was cooled back to 0
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°C and another portion of MsCl (1.0 equiv, 230 µL) in THF (1 mL, wash 2× 1 mL) was added dropwise. After complete addition, the mixture was allowed to come to room temperature and was stirred for 1.5 hours. TLC at this point indicated little change in consumption of unquenched Grignard. The reaction was quenched with sat. ammonium chloride solution, partitioned with diethyl ether, and transferred to a separatory funnel. The layers were separated, and the aqueous layer extracted twice with diethyl ether. The combined organic layers were dried over magnesium sulphate and concentrated in vacuo to a yellow solid. Silica flash column chromatography (8:2 → 7:3 Hexanes/EtOAc) gave the product (467 mg, 58%) as a white solid, mp 125 – 127 °C. \(^1\)H-NMR (400 MHz, CDCl\(_3\)): δ/ppm = 8.82 (d, J = 2.2 Hz, 1H), 8.29 (d, J = 2.2 Hz, 1H), 3.15 (s, 3H); \(^{13}\)C-NMR (101 MHz, CDCl\(_3\)): δ/ppm = 154.7, 146.1, 137.7, 136.8, 131.8, 45.0; IR (film): ν/cm\(^{-1}\) = 3050, 3023, 2934, 1557, 1405, 1370, 1360, 1150, 1103, 1044, 970, 914, 855, 748, 743, 664; HRMS (DART): m/z calculated for C\(_6\)H\(_5\)Cl\(_2\)NO\(_2\)S\(^+\) 225.9507, found. 225.9496.

A round bottom flask was charged with 3-amino-2-chloro-5-methylpyridine (1.01 g, 7.07 mmol). Conc. HCl (7 mL) was added, and the mixture was cooled to 0 °C. Sodium nitrite (1.2 equiv., 592 mg, 8.58 mmol) in water (7 mL) was added dropwise to the reaction mixture at this temperature. After 1 hour at 0 °C, CuCl (1.4 equiv., 972 mg, 9.82 mmol) was added slowly, in three portions. Vigorous gas evolution was observed and an orange precipitate began to form. The reaction was stirred for an additional hour at 0 °C, quenched by pouring onto a 1:1 mixture of conc. NH\(_4\)OH/H\(_2\)O (10 mL/10 mL) and partitioned with DCM. An additional portion of conc. NH\(_4\)OH (10 mL) was added to dissolve the remaining Cu salts. After transferring to a seperatory funnel, the layers were separated, and the aqueous layer was extracted twice with DCM. The combined organic layers were washed with brine, dried over magnesium sulphate and concentrated in vacuo to a red oil. Silica flash column chromatography (30:1 Hexanes/EtOAc) gave the product (596 mg, 52%) as a white solid, mp 38 – 40 °C. \(^1\)H-NMR (300 MHz, CDCl\(_3\)): δ/ppm = 8.12 (s, 1H), 7.60 (d, J = 2.0 Hz, 1H), 2.33 (s, 3H); \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)): δ/ppm = 147.7, 146.3, 139.4, 133.8, 123.0, 17.5; IR (film): ν/cm\(^{-1}\) = 3036, 2957, 2928, 1583, 1553, 1421, 1380, 1203, 1157,
A sealable pressure flask was charged with 2,3-dichloro-5-bromopyridine (674 mg, 2.97 mmol), bis(dibenzylideneacetone)palladium(0) (2.5 mol%, 43 mg, 0.0748 mmol), XantPhos (2.6 mol%, 44 mg, 0.0760 mmol), sodium t-butoxide (1.5 equiv., 427 mg, 4.44 mmol) and purged with argon. Toluene (15 mL) and morpholine (1.1 equiv., 280 µL, 3.20 mmol, d = 0.996 g/mL) were added. The flask was sealed with a screw-top cap, and put into a pre-heated oil-bath at 100 ºC. After 3 hours, TLC indicated complete consumption of starting material. Upon cooling to room temperature, the reaction was filtered through Celite (EtOAc) and concentrated in vacuo. Silica flash column chromatography (9:1 → 7:3 Hexanes/EtOAc) gave the product (606 mg, 88%) as an off-white solid, mp 96 – 98 ºC. 

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\text{H-NMR} \quad (300 \text{ MHz, CDCl}_3): \delta/\text{ppm} = 7.94 \text{ (d, J = 2.8 Hz, 1H), 7.26 \text{ (d, J = 2.7 Hz, 1H), 3.89 – 3.84 (m, 4H), 3.21 – 3.15 (m, 4H);} \\
\text{C-NMR} \quad (75 \text{ MHz, CDCl}_3): \delta/\text{ppm} = 146.8, 138.4, 134.7, 130.2, 124.5, 66.3, 48.1; \text{ IR (film): } \nu/\text{cm}^{-1} = 2972, 2959, 2815, 2876, 2849, 1582, 1559, 1447, 1398, 1261, 1233, 1169, 1126, 1020, 957, 874, 853, 801, 706, 664; \text{ HRMS (DART): m/z calculated for } C_9H_11Cl_2N_2O^+ 233.0248, \text{ found 233.0252.} 
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A non flame-dried 2-neck round bottom flask was charged with 2.33 (303 mg, 1.39 mmol), potassium carbonate (4 equiv., 763 mg, 5.53 mmol), and tetrakistriphenylphosphinepalladium (5 mol%, 80 mg, 0.0692 mmol). A reflux condenser was added and the setup was purged with argon. DME (8 mL) and water (4 mL) were added, followed by 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane (1.2 equiv., 254 mg, 1.65 mmol). The mixture was sealed and put into a pre-heated oil-bath at 80 ºC for 13 hours. At this point, a small aliquot of the organic layer was removed and analysed by \text{H NMR, which showed complete consumption of starting material. Upon cooling to room temperature, the reaction was quenched with additional water, partitioned with diethyl ether, and transferred to a separatory funnel. The organic layer was separated and the aqueous layer extracted three times with diethyl ether. The combined organic layers were dried over magnesium sulphate and concentrated in vacuo to a red oil. Silica flash column chromatography (40:1 → 30:1 Hexanes/EtOAc)
gave the product (131 mg, 58%) as a white solid, mp 87 – 89 °C. \(^1\text{H-NMR}\) (300 MHz, CDCl\(_3\)): \(\delta/\text{ppm} = 8.70\) (d, \(J = 1.9\) Hz, 1H), 7.92 (d, \(J = 1.9\) Hz, 1H), 7.24 (dd, \(J = 16.9, 10.7\) Hz, 1H), 6.66 (dd, \(J = 16.9, 1.8\) Hz, 1H), 5.80 (dd, \(J = 10.7, 1.8\) Hz, 1H); \(^{13}\text{C-NMR}\) (75 MHz, CDCl\(_3\)): \(\delta/\text{ppm} = 155.6, 149.8, 140.2, 130.4, 125.8, 115.7, 109.0\); IR (film): \(\nu/\text{cm}^{-1} = 3071, 3063, 2234, 1583, 1451, 1385, 1373, 1302, 1276, 1262, 1233, 1209, 1061, 988, 944, 915, 906, 791, 748, 744\); HRMS (DART): m/z calculated for \(\text{C}_8\text{H}_5\text{ClN}_2^+\) 165.0220, found 165.0219.

A microwave vial was charged with 2.34 (354 mg, 1.57 mmol), lithium chloride (1.4 equiv., 92 mg, 2.17 mmol), tetrakistriphenylphosphinepalladium (5 mol%, 97 mg, 0.0839 mmol), and purged with argon. Dioxane (8 mL) and tributylvinyl tin (1.3 equiv, 610 \(\mu\)L, 2.09 mmol) were added. The vial was sealed with a crimp-top cap, and put into a pre-heated oil-bath at 85 °C for 21 hours. At this point, an aliquot was removed and analysed by \(^1\text{H NMR}\), which revealed complete consumption of starting material. Upon cooling to room temperature, the reaction was filtered through Celite (EtOAc) and concentrated in vacuo to a red oil. Silica flash column chromatography (90:8:2 \(\rightarrow\) 70:25:5 \(\rightarrow\) 85:15:5 Hexanes/EtOAc/Triethylamine) gave the product (189 mg, 55%) as a yellow solid, mp 87 – 88 °C. \(^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)): \(\delta/\text{ppm} = 8.96\) (d, \(J = 2.1\) Hz, 1H), 8.18 (d, \(J = 2.1\) Hz, 1H), 7.29 (dd, \(J = 16.9, 10.6\) Hz, 1H), 6.70 (dd, \(J = 16.9, 1.8\) Hz, 1H), 5.81 (dd, \(J = 10.6, 1.8\) Hz, 1H), 3.13 (s, 3H); \(^{13}\text{C-NMR}\) (101 MHz, CDCl\(_3\)): \(\delta/\text{ppm} = 156.7, 146.0, 136.7, 136.0, 130.4, 125.9, 45.1\); IR (film): \(\nu/\text{cm}^{-1} = 3100, 3065, 2928, 1568, 1533, 1443, 1362, 1154, 1109, 1049, 974, 910, 789, 770, 743, 648\); HRMS (ESI): m/z calculated for \(\text{C}_9\text{H}_9\text{ClNO}_{2\text{S}}^+\) 218.0037, found 218.0046.

A non flame-dried round bottom flask was charged with 2,3-dichloro-5-nitropyridine (588 mg, 3.05 mmol), lithium chloride (1.2 equiv., 155 mg, 3.66 mmol), and tetrakistriphenylphosphinepalladium (5 mol%, 176 mg, 0.152 mmol). The flask was fitted with a reflux condenser and purged with argon. Dioxane (15 mL) and tributylvinyl tin (1.1 equiv, 1.09 ml, 3.70 mmol) were added. The reaction was heated to 100 °C for 3 hours, at which point an aliquot showed full consumption of starting material by \(^1\text{H NMR}\). Upon cooling to room temperature, the
reaction was filtered through Celite and concentrated in vacuo. Silica flash column chromatography (95:5 Hexanes/EtOAc) gave the product (124 mg, 25%) as a white solid, mp 34 – 36 °C. $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$/ppm = 9.27 (d, J = 2.3 Hz, 1H), 8.46 (d, J = 2.3 Hz, 1H), 7.29 (dd, J = 16.9, 10.6 Hz, 1H), 6.72 (dd, J = 16.9, 1.7 Hz, 1H), 5.85 (dd, J = 10.6, 1.7 Hz, 1H); $^{13}$C-NMR (101 MHz, CDCl$_3$): $\delta$/ppm = 157.3, 142.8, 142.7, 132.6, 130.3, 130.0, 126.7; IR (film): $\nu$/cm$^{-1}$ = 3080, 2916, 2849, 1645, 1587, 1570, 1520, 1348, 1294, 1275, 1223, 1049, 908, 743; HRMS (ESI): m/z calculated for C$_7$H$_6$ClN$_2$O$_2$+ 185.0118, found 185.0110;

**Note:** This product turns red upon prolonged storage at room temperature, and should be stored under argon at -20 °C.

A sealable pressure flask was charged with 2.35 (300 mg, 1.85 mmol), tetrakistriphenylphosphinepalladium (5 mol%, 109 mg, 0.0943 mmol), lithium chloride (1.2 equiv., 97 mg, 2.29 mmol) and purged with nitrogen. Dioxane (9 mL) and tributylvinyltin (1.1 equiv., 600 µL, 2.05 mmol) were added. The flask was sealed and put into a pre-heated oil-bath at 100 °C for 16 hours. At this point, an aliquot was removed and analysed by $^1$H NMR, which revealed complete consumption of starting material. Upon cooling to room temperature, the mixture was filtered through Celite (5% Triethylamine/EtOAc) and concentrated in vacuo. Silica flash column chromatography (30:1 Hexanes/EtOAc) gave the product, which by TLC still contained tin by-products. The residue was passed through a plug of Silica (~30:1:2 Hexanes/EtOAc/Triethylamine, 5 mL triethylamine + 100 mL 30:1 Hexanes/EtOAc) and concentrated to give the product (213 mg, 75%) as a yellow oil. $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$/ppm = 8.34 – 8.27 (m, 2H, unresolved dq), 7.48 (dq, J = 1.6, 0.8 Hz, 1H), 7.20 (dd, J = 17.1, 10.8 Hz, 1H), 6.41 (dd, J = 17.1, 2.0 Hz, 1H), 5.53 (dd, J = 10.7, 2.0 Hz, 1H), 2.33 (s, unresolved t, 3H); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$/ppm = 149.2, 147.9, 138.0, 133.8, 131.2, 130.0, 120.5, 17.9; IR (film): $\nu$/cm$^{-1}$ = 3004, 2926, 2864, 1456, 1375, 1055, 987, 913, 784, 749; HRMS (DART): m/z calculated for C$_8$H$_9$ClN$^+$ 154.0424, found 154.0419.
A sealable pressure flask was charged with **2.36** (500 mg, 2.15 mmol), tetrakistriphenylphosphinepalladium (5 mol%, 126 mg, 0.109 mmol), lithium chloride (1.2 equiv., 113 mg, 2.67 mmol), and purged with argon. Dioxane (8 mL) and tributylvinyltin (1.2 equiv., 750 µL, 2.57 mmol) were added. The flask was sealed and put into a pre-heated oil-bath at 100 ºC for 23 hours. At this point, an aliquot was removed and analysed by ¹H NMR, revealing complete consumption of starting material. Upon cooling to room temperature, the reaction was passed through a silica plug (5% Triethylamine/EtOAc) and concentrated in vacuo. Silica flash column chromatography (90:8:2 → 80:15:5 → 70:25:5 Hexanes/EtOAc/Triethylamine, then 9:1 → 7:3 Hexanes/EtOAc) gave the product (321 mg, 67%) as an off-white solid, mp 73 – 74 ºC, after 2 purifications. ¹H-NMR (300 MHz, CDCl₃): δ/ppm = δ 8.17 (d, J = 2.7 Hz, 1H), 7.11 (dd, J = 17.1, 10.8 Hz, 1H), 7.07 (d, J = 2.7 Hz, 1H), 6.24 (dd, J = 17.1, 2.0 Hz, 1H), 5.40 (dd, J = 10.8, 2.0 Hz, 1H), 3.94 – 3.75 (m, 4H), 3.26 – 3.08 (m, 4H); ¹³C-NMR (75 MHz, CDCl₃): δ/ppm = 146.7, 142.9, 136.0, 131.2, 130.5, 122.1, 117.8, 66.5 (2), 48.2 (2); IR (film): v/cm⁻¹ = 3090, 3065, 3032, 2953, 2916, 2849, 1589, 1472, 1449, 1396, 1357, 1313, 1261, 1250, 1069, 1014, 986, 905, 739, 696; HRMS (DART): m/z calculated for C₁₁H₁₄ClN₂O²⁺ 225.0795, found 225.0797.

A non flame-dried round bottom flask was charged with 2,3- dichloro-5-(trifluoromethyl)pyridine (648 mg, 3.00 mmol), (E)-pent-1-en-1-ylboronic acid (1.5 equiv., 513 mg, 4.5 mmol), 1,1′-bis(diphenylphosphino)ferrocene)dichloropalladium(II) dichloromethane complex (5 mol%, 123 mg, 0.151 mmol), and sodium carbonate (3.3 equiv., 1.05 g, 9.84 mmol). The flask was fitted with a reflux condenser, and purged with argon. Dioxane (30 mL) and water (5 mL) were added, and the mixture was heated at 85 ºC for 16 hours. Upon cooling to room temperature, the reaction was quenched with additional water, partitioned with EtOAc and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water, dried over magnesium sulphate and concentrated in vacuo. Silica flash column chromatography (96:4 Hexanes/DCM) gave the product (576 mg, 77%) as a colourless oil. ¹H-NMR (400 MHz, CDCl₃): δ/ppm = 8.66 (dd, J = 2.1, 1.0 Hz, 1H), 7.85 (dd, J = 1.9, 0.8 Hz, 1H), 7.17 (dt, J = 15.2, 7.1 Hz, 1H), 6.93 (dt, J = 15.3,
1.5 Hz, 1H), 2.33 (qd, J = 7.2, 1.5 Hz, 2H), 1.65 – 1.51 (m, 4H), 0.99 (t, J = 7.4 Hz, 3H);

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$/ppm = 156.95 – 154.03 (m, apparent q), 144.1 (q, J = 4.0 Hz), 142.9, 134.5 (q, J = 3.7 Hz), 125.2 (q, J = 33.5 Hz), 124.0, 123.0 (q, J = 272.4 Hz), 35.3, 22.1, 14.0; $^{19}$F NMR (564 MHz, CDCl$_3$): $\delta$/ppm = -62.21; IR (film): $\nu$/cm$^{-1}$ = 2963, 2931, 2875, 1610, 1502, 1318, 1280, 1134, 1089, 1052, 973, 913; HRMS (DART): m/z calculated for C$_{11}$H$_{11}$ClF$_3$N$^+$ 249.0532, found 249.0610.

A round bottom flask with reflux condenser was charged with 2.33 (297 mg, 1.37 mmol), [1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium(II) dichloromethane complex (5 mol%, 57 mg, 0.0698 mmol), sodium bicarbonate (3.3 equiv., 382 mg, 4.55 mmol), (E)-1-octenylboronic acid (1.0 equiv., 219 mg, 1.40 mmol), and purged with argon. Dioxane (14 mL) and water (3 mL) were added, and the reaction was heated to 85 ºC for 17 hours. At this point, a small aliquot was withdrawn and analysed by $^1$H NMR, revealing complete consumption of starting material. Upon cooling to room temperature, the reaction was quenched with additional water, partitioned with EtOAc and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried over magnesium sulphate and concentrated in vacuo. Silica flash column chromatography (60:1 → 20:1 Hexanes/EtOAc) gave the product (261 mg, 77%) as a tan solid, mp 34 – 35 ºC. $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$/ppm = 8.65 (dd, J = 2.0, 0.4 Hz, 1H), 7.87 (d, J = 2.0 Hz, 1H), 7.29 – 7.19 (m, 1H), 6.91 (dt, J = 15.2, 1.5 Hz, 1H), 2.35 (qd, J = 7.3, 1.6 Hz, 2H), 1.63 – 1.46 (m, apparent quintet, 2H), 1.42 – 1.22 (m, 6H), 0.97 – 0.76 (m, apparent t, 1H); $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$/ppm = 156.2, 149.7, 145.0, 140.0, 129.1, 123.7, 115.9, 107.8, 33.4, 13.8, 29.1, 28.7, 22.7, 14.2; IR (film): $\nu$/cm$^{-1}$ = 3065, 3054, 2956, 2927, 2869, 2853, 2230, 1642, 1578, 1450, 1387, 1375, 1286, 1269, 1226, 1123, 1113, 1059, 975, 929, 913, 845, 807, 747, 680, 596; HRMS (DART): m/z calculated for C$_{14}$H$_{18}$ClN$_2$+ 249.1153, found 249.1155.
A 2-dram vial was charged with **2.44** (33.4 mg, 0.203 mmol), boronic ester **2.13** (2.0 equiv., 89 mg, 0.404 mmol), potassium carbonate (2.1 equiv., 59 mg, 0.427 mmol), potassium phosphate (2.1 equiv., 91 mg, 0.429 mmol), hydroxy(cyclooctadiene)rhodium(I) dimer (2 mol%, 1.9 mg, 0.00416 mmol), palladium (II) acetate (5 mol%, 2.3 mg, 0.0102 mmol), tBuX-Phos (10 mol%, 8.6 mg, 0.0203 mmol), and purged with argon. Dioxane (2 mL) and water (200 µL) were added, and the mixture was stirred at room temperature for 10 minutes. The mixture was then sealed with a Teflon cap, and put into an oil-bath pre-heated at 100 ºC for 18 hours. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc), and concentrated in vacuo. Silica flash column chromatography (12:1 → 9:1 Hexanes/EtOAc, then 99:1 DCM/Diethyl Ether → 98:2 DCM/Diethyl Ether) gave the product (27.4 mg, 61%) as a white solid, after two purifications, mp 101 – 103 ºC. **1H-NMR** (400 MHz, CDCl₃): δ/ppm = 8.51 (d, J = 1.9 Hz, 1H), 7.73 (d, J = 1.9 Hz, 1H), 7.25 – 7.19 (m, 2H), 7.21 – 7.07 (m, 2H), 3.41 – 3.33 (m, 2H), 3.24 – 3.17 (m, 2H); **13C-NMR** (101 MHz, CDCl₃): δ/ppm = 156.4 (2), 152.8, 146.2, 132.7, 131.6, 130.0, 128.2, 125.6, 120.8, 116.1, 108.3, 36.1, 28.7; **IR** (film): ν/cm⁻¹ = 3061, 2957, 2928, 2855, 2233, 1596, 1547, 1490, 1459, 1399, 1286, 1278, 1236, 1222, 1199, 1181, 1128, 1099, 1033, 992, 939, 911, 835, 773, 745, 704, 644, 621, 589; **HRMS** (DART): m/z calculated for C₁₄H₁₁N₂O⁺ 223.0871, found 223.0873.

A 2-dram vial was charged with **2.38** (44.3 mg, 0.204 mmol), boronic ester **2.13** (2.0 equiv., 91 mg, 0.414 mmol), potassium carbonate (2.1 equiv., 58 mg, 0.420 mmol), potassium phosphate (2.1 equiv., 91 mg, 0.429 mmol), hydroxy(cyclooctadiene)rhodium(I) dimer (2 mol%, 2.0 mg, 0.00438 mmol), palladium (II) acetate (5 mol%, 2.4 mg, 0.0107 mmol), tBuX-Phos (9 mol%, 8.8 mg, 0.0193 mmol), and purged with argon. Dioxane (2 mL) and water (200 µL) were added, and the mixture was stirred at room temperature for 10 minutes. The mixture was then sealed with a Teflon cap, and put into an oil-bath pre-heated at 100 ºC for 19 hours. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc), and concentrated in vacuo. Silica flash column chromatography (2:1 Hexanes/EtOAc) gave two portions of product, one which was pure, another which co-eluted with pinacol residue from the boronic ester. The second portion was taken up in
DCM (4 mL) and transferred to a round bottom flask charged with sodium periodate (excess, 56 mg, 0.262 mmol), tetramethylammonium chloride (cat., spatula tip) and water (2 mL). The biphasic mixture was stirred overnight, and then transferred to a separatory funnel. The organic layer was separated and the aqueous layer was extracted twice with DCM. The combined organic layers were dried over magnesium sulphate, concentrated in vacuo and combined with the first portion of product to give a yellow solid (31.3 mg, 56%). $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$/ppm = 8.76 (d, $J = 2.1$ Hz, 1H), 7.98 (d, $J = 2.1$ Hz, 1H), 7.25 – 7.17 (m, 3H), 7.16 – 7.10 (m, 1H), 3.43 – 3.38 (m, 2H), 3.25 – 3.20 (m, 2H), 3.11 (s, 3H); $^{13}$C-NMR (101 MHz, CDCl$_3$): $\delta$/ppm = 157.5, 156.5, 153.1, 142.3, 135.6, 132.5, 130.1, 128.1, 127.7, 125.6, 120.9, 45.1, 36.0, 28.7; IR (film) $\nu$/cm$^{-1}$: 3062, 3010, 2927, 2863, 1490, 1457, 1395, 1316, 1274, 1268, 1235, 1201, 1177, 1152, 1137, 1098, 979, 948, 913, 834, 765, 751; HRMS (ESI$^+$): $m/z$ calculated for C$_{14}$H$_{14}$NO$_3$S$^+$ 276.0688, found 276.0690.

A 2-dram vial was charged with 2.46 (36.9 mg, 0.200 mmol), boronic ester 2.13 (2 equiv., 88 mg, 0.400 mmol), hydroxy(cyclooctadiene)rhodium(I) dimer (2 mol%, 1.8 mg, 0.00395 mmol), palladium (II) acetate (5 mol%, 2.2 mg, 0.00980 mmol), tBuX-Phos (10 mol%, 8.2 mg, 0.0193 mmol), potassium carbonate (2 equiv., 55 mg, 0.398 mmol), potassium phosphate (2 equiv., 85 mg, 0.400 mmol), and purged with argon. Dioxane (2 mL) and water (200 $\mu$L) were added, and the mixture was stirred at room temperature for 10 minutes. The vial was then sealed with a Teflon cap, and put into an oil-bath pre-heated at 100 $^\circ$C for 16 hours. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc), and concentrated in vacuo. Silica flash column chromatography (9:1 Hexanes/EtOAc) gave the product (24.1 mg, 50%) as an off-white solid, mp 98 – 101 $^\circ$C. $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$/ppm = 9.09 (d, $J = 2.0$ Hz, 1H), 8.25 (d, $J = 2.1$ Hz, 1H), 7.30 – 7.09 (m, 4H), 3.48 – 3.35 (m, 2H), 3.30 – 3.18 (m, 2H); $^{13}$C-NMR (101 MHz, CDCl$_3$): $\delta$/ppm = 158.3, 156.4, 152.9, 138.9, 132.6, 130.1, 128.2, 125.7, 123.7, 120.8, 36.2, 28.5; IR (film): $\nu$/cm$^{-1}$ = 3080, 2918, 2851, 1595, 1578, 1520, 1489, 1456, 1404, 1348, 1252, 1234, 1177; HRMS (DART) $m/z$ calculated for C$_{13}$H$_{11}$N$_2$O$_3$S$^+$ 243.0770, found 243.0773.
A 2-dram vial was charged with vinyl pyridine 2.40 (48.0 mg, 0.312 mmol), potassium carbonate (2 equiv., 87 mg, 0.629 mmol), boronic ester 2.13 (2 equiv., 135 mg, 0.613 mmol), and purged with argon. A round bottom flask was charged with hydroxy(cyclooctadiene)rhodium(I) dimer (3× 2 mol%, 8.2 mg, 0.0180 mmol) and purged with argon. Dioxane (3 mL) was added and the mixture was stirred at room temperature for 15 minutes. Catalyst solution (1 mL, containing 4 mol% [Rh]) was added to the reaction vial, followed by additional dioxane (2 mL). The vial was sealed with a Teflon cap and put into a pre-heated oil-bath at 90 °C for 14 hours. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc). Silica flash column chromatography (9:1 Hexanes/EtOAc) gave the product (65 mg, 88%) as a tan solid, mp 87 – 89 °C. \(^1\)H-NMR (400 MHz, CDCl\(_3\)): δ/ppm = 10.57 (s, 1H), 8.28 (s, 1H), 7.50 (s, 1H), 7.19 (dd, J = 7.5, 1.8 Hz, 1H), 7.11 (td, J = 7.6, 1.7 Hz, 1H), 6.90 (dd, J = 8.1, 1.3 Hz, 1H), 6.85 (td, J = 7.4, 1.3 Hz, 1H), 3.36 – 3.28 (m, 2H), 3.20 – 3.13 (m, 2H), 2.30 (s, 3H); \(^{13}\)C-NMR (101 MHz, CDCl\(_3\)): δ/ppm = 155.3, 154.0, 145.9, 138.3, 133.0, 131.8, 130.8, 129.1, 127.8, 120.3, 117.9, 36.3, 25.5, 17.7; IR (film): ν/cm\(^{-1}\) = 3322, 3144, 3066, 3010, 2928, 1594, 1584, 1488, 1456, 1421, 1387, 1241, 1141, 1096, 1067, 1041, 882, 752; HRMS (DART): m/z calculated for C\(_{14}\)H\(_{15}\)ClNO\(^+\) 248.0842, found 248.0842.

A 2-dram vial was charged with 2.47 (40.6 mg, 0.164 mmol), palladium (II) acetate (5 mol%, 2.0 mg, 0.00891 mmol), tBuX-Phos (10 mol%, 7.2 mg, 0.0170 mmol), potassium phosphate (2 equiv., 72 mg, 0.339 mmol) and purged with argon. Dioxane (820 µL) was added. The vial was sealed with a Teflon cap, and put into a pre-heated oil-bath at 100 °C for 24 hours. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc) and concentrated in vacuo. Silica flash column chromatography (8:2 Hexanes/EtOAc) gave the product (24.0 mg, 69%) as a yellow solid, mp 54 – 55 °C. \(^1\)H-NMR (400 MHz, CDCl\(_3\)): δ/ppm = 8.10 (s, 1H), 7.30 (s, 1H), 7.22 – 7.17 (m, 1H), 7.17 – 7.13 (m, 1H), 7.07 (td, J = 7.1, 1.9 Hz, 1H), 3.30 – 3.25 (m, 2H), 3.21 – 3.16 (m, 2H), 2.30 (s, 3H); \(^{13}\)C-NMR (101 MHz, CDCl\(_3\)): δ/ppm = 157.1, 153.1, 148.0, 144.7, 133.2, 132.4, 130.0, 129.2, 127.7, 124.8, 120.7, 34.9, 29.4, 17.8; IR (film): ν/cm\(^{-1}\) = 3014, 2923, 2865, 1559, 1490, 1465, 1457, 1448, 1398, 1288, 1278, 1236, 1201, 1177, 1127,
1099, 901, 883, 834, 771, 746; **HRMS** (DART): \(m/z\) calculated for \(\text{C}_{14}\text{H}_{14}\text{NO}^+\) 212.1075, found 212.1074.

A 2 dram vial was charged with vinyl pyridine **2.41** (67.7 mg, 0.301 mmol), potassium carbonate (2 equiv., 85 mg, 0.615 mmol), 2-hydroxyphenylboronic acid (5 equiv., 211 mg, 1.53 mmol), hydroxyl(cyclooctadiene)rhodium(I) dimer (2 mol%, 3.0 mg, 0.00658 mmol), and purged with argon. Dioxane (3 mL) and water (300 µL) were added. The vial was sealed with a Teflon cap, and put into a pre-heated oil-bath at 100 °C for 15 hours. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc) and concentrated *in vacuo*. Silica flash column chromatography (8:2 → 7:3 Hexanes/EtOAc) gave the product (87.1 mg, 91%) as an orange solid, **mp** 133 – 135 °C. **\(^1\)H-NMR** (400 MHz, CDCl₃): \(\delta/\text{ppm} = 10.65\) (s, 1H), 8.08 (d, J = 2.6 Hz, 1H), 7.21 (d, J = 2.6 Hz, 1H), 7.19 (dd, J = 7.5, 1.6 Hz, 1H), 7.13 – 7.07 (m, 1H), 6.88 (dd, J = 8.1, 1.1 Hz, 1H), 6.85 (ap td, J = 7.4, 1.2 Hz, 1H), 3.91 – 3.78 (m, 4H), 3.29 – 3.23 (m, 2H), 3.18 – 3.09 (m, 6H); **\(^{13}\)C-NMR** (101 MHz, CDCl₃): \(\delta/\text{ppm} = 155.4, 147.1, 146.6, 133.3, 132.3, 130.9, 129.4, 127.8, 124.1, 120.3, 117.9, 66.5\) (2), 48.4 (2), 35.7, 25.5; **IR** (film) ν/cm⁻¹: 3347, 2965, 2918, 2851, 1593, 1489, 1456, 1398, 1381, 1267, 1236, 1140, 1123, 1063, 1045, 959, 870, 756, 735; **HRMS** (DART): \(m/z\) calculated for \(\text{C}_{17}\text{H}_{20}\text{ClN}_2\text{O}_2^+\) 319.1208, found 319.1205.

A 2 dram vial was charged with **2.49** (36.7 mg, 0.115 mmol), palladium (II) acetate (10 mol%, 2.7 mg, 0.0120 mmol), tBuX-Phos (20 mol%, 9.9 mg, 0.0233 mmol), potassium phosphate (2 equiv., 54 mg, 0.254 mmol), and purged with argon. Dioxane (1 mL) was added. The vial was sealed with a Teflon cap, and put into a pre-heated oil-bath at 100 °C for 36 hours. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc) and concentrated *in vacuo*. Silica flash column chromatography (7:3 Hexanes/EtOAc → 3:7 Hexanes/EtOAc) gave the product (25.6 mg, 78%) as an off-white solid, **mp** 59 – 62 °C. **\(^1\)H-NMR** (400 MHz, CDCl₃): \(\delta/\text{ppm} = 7.98\) (d, J = 2.6 Hz, 1H), 7.20 (ddd, J = 7.7, 5.7, 1.8 Hz, 2H), 7.17 – 7.11 (m, 1H), 7.08 (td, J = 7.1, 1.7 Hz, 1H), 6.99 (d, J = 2.5 Hz, 1H), 3.90 – 3.83 (m, 4H), 3.25 – 3.20 (m, 2H), 3.19 – 3.14 (m, 7H); **\(^{13}\)C-NMR** (101 MHz, CDCl₃): \(\delta/\text{ppm} = 157.1, 153.4, 146.8, 141.4, 133.5, 132.7,
A 2-dram vial was charged with chlorobis(ethylen)rhodium dimer (5 mol%, 2.9 mg, 0.00746 mmol), **L5** (10 mol%, 5.8 mg, 0.015 mmol), potassium carbonate (42 mg, 0.304 mmol, 2 equiv), and was purged with argon. Dioxane (1 mL) and water (0.3 mL) were added, and the mixture was stirred at room temperature for 5 minutes. Another 2-dram vial was charged with vinyl pyridine **2.42** (37.5 mg, 0.150 mmol), boronic ester **2.13** (66 mg, 0.300 mmol, 2 equiv), and purged with argon. Dioxane (1 mL) was added. The solution of starting materials was transferred to the vial containing base and rhodium catalyst, rinsing with additional dioxane (1 mL). The reaction vial was sealed with a Teflon cap, and put into a pre-heated oil-bath at 80°C for 16 hrs. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc) and concentrated in vacuo. Silica flash column chromatography (9:1 Pentanes/EtOAc) gave the product (37 mg, 72%) as a colourless oil. **1H-NMR** (400 MHz, CDCl_3): δ/ppm = 8.70 (s, 1H), 8.68 (s, 1H), 7.89 (d, J = 2.1 Hz, 1H), 7.21 (dd, J = 7.6, 1.7 Hz, 1H), 7.11 – 7.05 (m, 1H), 6.94 – 6.86 (m, 2H), 3.77 (tdd, J = 9.1, 6.2, 4.5 Hz, 1H), 3.43 – 3.26 (m, 2H), 1.97 – 1.85 (m, 1H), 1.78 (ddt, J = 13.0, 9.2, 6.4 Hz, 1H), 1.35 – 1.16 (m, 2H), 0.90 (t, J = 7.3 Hz, 3H). **13C-NMR** (101 MHz, CDCl_3): δ/ppm = 161.8 – 161.7 (m), 154.7, 142.9 (q, J = 4.1 Hz), 134.4 (q, J = 3.5 Hz), 132.5, 131.9, 127.4, 126.9, 126.2 (q, J = 34.1 Hz), 122.6 (q, J = 272.8 Hz), 121.2, 118.0, 43.5, 38.6, 33.3, 20.9, 14.0; **19F NMR** (376 MHz, CDCl_3): δ/ppm = -62.35; **IR** (film) v/cm⁻¹: 3325, 2958, 2931, 2872, 1700, 1653, 1607, 1507, 1456, 1324, 1236, 1177, 1138, 1089, 1065, 753; **HRMS** (DART): m/z calculated for C_{17}H_{19}F_{3}NO⁺ 344.0951, found: 344.1029; [α]_D^{26.8} = +22.5 (c 1.00, CHCl_3) for 97.2:2.8 er, as measured by HPLC analysis (Chiralcel AD-H, isocratic 0.25% i-PrOH/hexane, 0.70 mL/min, 225 nm), t_R = 17.07 min (major), t_R = 17.85 min (minor).
**Stepwise:** A 2 dram vial was charged with palladium (II) acetate (5 mol%, 1.8 mg, 0.00802 mmol), tBuX-Phos (10 mol%, 6.8 mg, 0.0160 mmol), potassium phosphate (2 equiv., 68 mg, 0.320 mmol), and purged with argon. A solution of 2.51 (54.8 mg, 0.159 mmol) in dioxane (400 µL, wash 4× 400 µL) was added. The reaction vial was sealed with a Teflon cap, and put into a pre-heated oil-bath at 100 ºC for 19 hours. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc) and concentrated in vacuo. Silica flash column chromatography (50:1 → 20:1 Hexanes/EtOAc) gave the product (39.4 mg, 81%) as a colourless oil.

**Domino:** A 2 dram vial was charged with vinyl pyridine 2.42 (37.5 mg, 0.150 mmol), potassium carbonate (2 equiv, 42 mg, 0.304 mmol), potassium phosphate (2 equiv, 64 mg, 0.302 mmol), palladium (II) acetate (5 mol%, 1.8 mg, 0.00802 mmol), tBuX-Phos (10 mol%, 6.4 mg, 0.015 mmol), and purged with argon. Water (150 µL) was added. A second 2 dram vial was charged with chlorobis(ethylen)rhodium dimer (5 mol%, 2.9 mg, 0.00746 mmol), L5 (10 mol%, 5.8 mg, 0.015 mmol), boronic ester 2.13 (2 equiv., 66mg, 0.300 mmol) and purged with argon. Dioxane (500 µL) was added. The mixture was stirred at room temperature until the contents dissolved (typically 30 seconds or less), then transferred to the first vial, washing with additional dioxane (2× 500 µL). The reaction was sealed with a Teflon cap and put into a pre-heated oil-bath at 100 ºC for 16 hours. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc) and concentrated in vacuo. Silica flash column chromatography (95:5 Hexanes/Diethyl Ether) gave the product (25.8 mg, 56%) as a colourless oil. 

**1H-NMR** (400 MHz, CDCl3): δ/ppm = 8.53 (dt, J = 2.0, 0.9 Hz, 1H), 7.69 (d, J = 1.8 Hz, 1H), 7.25 – 7.11 (m, 4H), 3.50 (ddt, J = 16.5, 2.9, 1.2 Hz, 1H), 3.33 (qd, J = 7.4, 3.0 Hz, 1H), 3.25 (dd, J = 16.3, 7.5 Hz, 1H), 1.81 (dddd, J = 13.3, 9.8, 7.3, 5.7 Hz, 1H), 1.65 – 1.55 (m, 1H), 1.52 – 1.42 (m, 1H), 1.41 – 1.33 (m, 1H), 0.93 (t, J = 7.3 Hz, 3H). 

**13C-NMR** (101 MHz, CDCl3): δ/ppm = 155.8, 153.9 (d, J = 1.4 Hz), 152.3, 140.4 (q, J = 4.1 Hz), 135.8, 129.2, 127.9, 125.7 (q, J = 33.1 Hz), 125.5 (q, J = 3.4 Hz), 123.3 (q, J = 272.4 Hz), 41.1, 39.3, 35.9, 20.9, 14.2; 

**19F NMR** (377 MHz, CDCl3) δ/ppm = -62.10; 

**IR** (film): ν/cm⁻¹ = 2960, 2930, 2874, 2359, 2345, 1700, 1683, 1653, 1616, 1559, 1507, 1490, 1457, 1419,
1335, 1170, 1134, 1085, 956, 912, 757; **HRMS** (DART): m/z calculated for C_{17}H_{19}F_{3}NO^{+} 307.1184, found 307.1262; \([\alpha]_{D}^{26.8} = +22.5\) (c 1.00, CHCl\(_3\)) for 97.2:2.8 er, as measured by HPLC analysis (Chiralcel AD-H, isocratic 0.25% i-PrOH/hexane, 0.70 mL/min, 225 nm), \(t_R = 17.07\) min (major), \(t_R = 17.85\) min (minor).

A 2 dram vial was charged with vinyl pyridine 2.42 (37.5 mg, 0.150 mmol), potassium carbonate (2 equiv, 42 mg, 0.304 mmol), potassium phosphate (2 equiv, 64 mg, 0.302 mmol), palladium (II) acetate (5 mol\%, 1.8 mg, 0.00802 mmol), tBuX-Phos (10 mol\%, 6.4 mg, 0.015 mmol), and purged with argon. Water (150 \(\mu\)L) was added. A second 2 dram vial was charged with chlorobis(ethylene)rhodium dimer (5 mol\%, 2.9 mg, 0.00746 mmol), L5 (10 mol\%, 5.8 mg, 0.015 mmol), boronic ester 2.7 (4 equiv., 142 mg, 0.606 mmol), and purged with argon. Dioxane (500 \(\mu\)L) was added. The mixture stirred at room temperature until the contents dissolved (typically 30 seconds or less), then transferred to the first vial, washing with additional dioxane (2\(\times\) 500 \(\mu\)L). The reaction was sealed with a Teflon cap and put into a pre-heated oil-bath at 100 \(^\circ\)C for 16 hours. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc) and concentrated in vacuo. Silica flash column chromatography (9:1 Hexanes/EtOAc) gave the product (28.6 mg, 62%) as a colourless oil. ¹H-NMR (400 MHz, CDCl\(_3\)): \(\delta/\text{ppm} = 8.51\) (s, 1H), 7.66 (d, J = 1.9 Hz, 1H), 7.08 – 6.97 (m, 3H), 3.54 – 3.43 (m, 1H), 3.30 – 3.16 (m, 2H), 2.32 (s, 3H), 1.81 (dddd, J = 12.8, 9.7, 7.0, 5.6 Hz, 1H), 1.65 – 1.52 (m, 2H), 1.50 – 1.41 (m, 1H), 1.41 – 1.32 (m, 1H), 0.93 (t, J = 7.3 Hz, 3H); ¹³C-NMR (101 MHz, CDCl\(_3\)): \(\delta/\text{ppm} = 154.0\) (m, apparent q), 153.8, 152.4, 140.3 (q, J = 4.2 Hz), 135.4, 134.7, 129.7, 128.3, 125.7 (q, J = 33.0 Hz), 125.4 (q, J = 3.6 Hz), 123.3 (q, J = 273.1 Hz), 120.8, 41.2, 39.3, 35.8, 21.0, 21.0, 14.2; ¹⁹F NMR (377 MHz, CDCl\(_3\)) \(\delta/\text{ppm} = -62.05\); IR (film): v/cm\(^{-1}\) = 3304, 2959, 2932, 2873, 2359, 2344, 1705, 1559, 1495, 1457, 1410, 1335, 1201, 1169, 1157, 1085, 957, 911, 826, 668; **HRMS** (DART): m/z calculated for C_{18}H_{19}F_{3}NO^{+} 321.1340, found 321.1319; \([\alpha]_{D}^{25.3} = +100.6\) (c 0.50, CHCl\(_3\)) for 97.2:2.8 er, as measured by HPLC analysis (Chiralcel AD-H, isocratic 0.05% i-PrOH/hexane, 0.70 mL/min, 225 nm), \(t_R = 5.90\) min (major), \(t_R = 6.22\) min (minor).
**Note:** a racemic sample was prepared according to the previous stepwise protocol in order to provide a sample for HPLC determination of enantiomeric excess.

A 2 dram vial was charged with vinyl pyridine $2.43$ (49.9 mg, 0.201 mmol), potassium carbonate (2.1 equiv, 59 mg, 0.427 mmol), potassium phosphate (2.2 equiv, 93 mg, 0.438 mmol), palladium (II) acetate (6 mol%, 2.5 mg, 0.0111 mmol), tBuX-Phos (10 mol%, 6.4 mg, 0.0210 mmol), and purged with argon. Water (200 µL) was added. A second 2 dram vial was charged with chlorobis(ethylene)rhodium dimer (5 mol%, 3.9 mg, 0.0102 mmol), L5 (11 mol%, 8.9 mg, 0.0231 mmol), boronic ester $2.13$ (4 equiv., 177 mg, 0.805 mmol) and purged with argon. Dioxane (500 µL) was added. The mixture was stirred at room temperature until the contents dissolved (typically 30 seconds or less), then transferred to the first vial, washing with additional dioxane (3× 500 µL). The reaction was sealed with a Teflon cap and put into a pre-heated oil-bath at 100 ºC for 16 hours. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc) and concentrated *in vacuo*. Silica flash column chromatography (60:1 → 20:1 Hexanes/EtOAc) gave two fractions of product, one pure and the other containing the phenol by-product. The impure fractions were concentrated, taken up in diethyl ether, and transferred to a separatory funnel. The organic layer was washed three times with a 1M KOH solution, dried over magnesium sulphate, concentrated *in vacuo*, and combined with the pure fractions to give the product (34.3 mg, 56%) as a colourless oil.

$^{1}$H-NMR (400 MHz, CDCl$_3$): δ/ppm = δ 8.52 (d, J = 1.8 Hz, 1H), 7.71 (d, J = 1.8 Hz, 1H), 7.25 – 7.20 (m, 2H), 7.18 – 7.10 (m, 2H), 3.49 (dd, J = 16.3, 2.7 Hz, 1H), 3.33 – 3.19 (m, 2H), 1.87 – 1.74 (m, 1H), 1.66 – 1.51 (m, 1H), 1.48 – 1.18 (m, 5H), 0.90 – 0.82 (m, 3H); $^{13}$C-NMR (75 MHz, CDCl$_3$): δ/ppm = 155.6, 155.1, 152.2, 146.2, 135.6, 131.1, 129.2, 128.0, 125.4, 121.1, 116.2, 108.3, 41.5, 39.4, 33.6, 31.8, 29.3, 27.7, 22.7, 14.2; IR (film): ν/cm$^{-1}$ = 2955, 2928, 2857, 2233, 2595, 1547, 1486, 1457, 1402, 1279, 1219, 1199, 1132, 1095, 990, 914, 773; HRMS (DART): m/z calculated for C$_{20}$H$_{23}$N$_{2}$O$^{+}$ 307.1810, found 307.1807; [α]$_{D}^{27.0}$ = -8.4 (c 0.25, CHCl$_3$) for 95.9:4.1 er, as measured by HPLC analysis (Chiralcel AD-H, isocratic 0.05% i-PrOH/hexane, 0.70 mL/min, 235 nm), $t_R$ = 30.34 min (major), $t_R$ = 33.96 min (minor).
Note: a racemic sample was prepared according to the previous stepwise protocol in order to provide a sample for HPLC determination of enantiomeric excess.
3.6 Synthesis of Compounds in Section 2.5

A round bottom flask was charged with TMP (1.35 equiv., 4.6 mL, 27.3 mmol, \(d = 0.837 \text{ g/mL}\)). THF (60 mL) was added. The solution was cooled to \(-78 ^\circ\text{C}\), and \(n\)-BuLi (1.25 equiv, 11.5 mL, 2.2 M, 25.3 mmol) was added dropwise at this temperature. The mixture was warmed to \(0 ^\circ\text{C}\) and stirred for 30 minutes. This solution of LiTMP was cooled back to \(-78 ^\circ\text{C}\) and 2-chloropyrazine (1.8 mL, 20.2 mmol, \(d = 1.283 \text{ g/mL}\)) was added dropwise, such that the internal temperature did not rise above \(-70 ^\circ\text{C}\). The mixture was stirred for 30 mins at \(-78 ^\circ\text{C}\), developing a deep red colour, before iodine (2 equiv., 10.3 g, 40.6 mmol) in THF (15 mL) was added dropwise, such that the internal temperature did not rise above \(-68 ^\circ\text{C}\). The reaction was stirred for 2 hrs at \(-78 ^\circ\text{C}\), quenched by the addition of MeOH (5 mL) in one portion, and allowed to come to room temperature. The solvent was concentrated \textit{in vacuo}, the residue was taken up in DCM and sat. sodium thiosulphate solution, and the mixture was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted three times with DCM. The combined organic layers were dried over magnesium sulphate, and concentrated \textit{in vacuo} to a red-brown oil. Silica flash column chromatography (21:1 Hexanes/EtOAc) gave the product (3.79 g, 78%) as a yellow solid, \textit{mp} 65-67 \(^\circ\text{C}\). \(\textsuperscript{1}H\text{-NMR}\) (400 MHz, CDCl\(_3\)): \(\delta/\text{ppm} = 8.30 \text{ (d, J = 2.4 Hz, 1H)}, 8.28 \text{ (d, J = 2.4 Hz, 1H)}\); \(\textsuperscript{13}C\text{-NMR}\) (101 MHz, CDCl\(_3\)): \(\delta/\text{ppm} = 154.6, 142.7, 142.1, 119.7\); \textit{HRMS} (DART): m/z calculated for C\(_4\)H\(_3\)ClIN\(_2\)^+ 240.9029, found 240.9029.

\textbf{Suzuki Protocol:} A 2-neck round bottom flask was charged with iodopyrazine 2.55 (1.14 g, 4.74 mmol), potassium vinyl trifluoroborate (1.2 equiv., 760 mg, 5.67 mmol), cesium carbonate (3 equiv., 4.61 g, 14.1 mmol), and 1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium(II) dichloromethane complex (10 mol%, 389 mg, 0.476 mmol). A reflux condenser was attached and the setup was purged with argon. THF (47 mL) and water (5 mL) were added, and the mixture was heated to reflux (85 \(^\circ\text{C}\)) for 18 hours. At this point, an aliquot of the organic layer was withdrawn and analysed by \(\textsuperscript{1}H\) NMR, revealing full consumption of starting material. Upon cooling to room temperature, the reaction was quenched with additional water, partitioned with diethyl ether, and transferred to a separatory funnel. The layers were
separated, and the aqueous layer was extracted three times with diethyl ether. The combined organic layers were dried over magnesium sulphate and concentrated in vacuo. Silica flash column chromatography (30:1 Hexanes/EtOAc) gave the product (363 mg, 55%) as a yellow oil. $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$/ppm = 8.47 (dd, $J = 2.4$, 0.5 Hz, 1H), 8.25 (d, $J = 2.4$ Hz, 1H), 7.20 (ddd, $J = 16.9$, 10.7, 0.5 Hz, 1H), 6.57 (ddd, $J = 17.0$, 1.7, 0.2 Hz, 1H), 5.72 (ddd, $J = 10.8$, 1.7, 0.3 Hz, 1H); $^{13}$C-NMR (151 MHz, CDCl$_3$): $\delta$/ppm = 149.1, 147.5, 142.5, 142.5, 130.4, 124.0.; IR (film): $\nu$/cm$^{-1}$ = 3050, 1626, 1546, 1517, 1447, 1411, 1349, 1189, 1161, 1080, 1065, 985, 945, 857, 798, 688, 657; HRMS (DART): m/z calculated for C$_6$H$_6$ClN$_2$$^+$ 141.0220, found 141.0221.

Note: this product is extremely volatile and several precautions were taken to ensure the best possible yield: the product was concentrated on a rotovap with the heating bath set no higher than 25 °C, at 30 – 40 mmHg; it was dried by passing a gentle stream of air over the mouth of the flask used to contain it (not via high vacuum); it was stored under argon in a -20 °C freezer, but was stable only for several weeks when stored in this way, darkening upon storage; unusable samples are those which have darkened to black and/or have thickened to viscous gums.

**Wittig Protocol:** A round bottom flask was charged with sodium t-butoxide (1.5 equiv., 916 mg, 9.53 mmol). THF (16 mL), was added and the heterogeneous mixture was cooled to 0 °C. Methyl triphenylphosphonium bromide (1.5 equiv., 3.40 g, 9.53 mmol) was added in portions and the mixture was stirred at 0 °C for 30 mins. A solution of aldehyde 2.57 (905 mg, 6.35 mmol) in THF (10 mL, wash 2× 3 mL) was added dropwise at this temperature. After stirring for another 30 mins at 0 °C, TLC indicated complete consumption of starting material. The reaction was quenched with sat. ammonium chloride solution and allowed to come to room temperature. The mixture was filtered through Celite (Diethyl Ether) and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted twice with diethyl ether. The combined organic layers were dried over magnesium sulphate and concentrated in vacuo. Silica flash column chromatography (50:1 → 20:1 Hexanes/EtOAc) gave the product (181 mg, 20%) as a yellow oil.
A 2-dram vial was charged with hydroxy(cyclooctadiene)rhodium(I) dimer (2 mol%, 1.8 mg, 0.00395 mmol), potassium hydroxide (2.9 equiv., 34 mg, 0.606 mmol) and purged with argon. Another 2-dram vial was charged with boronic ester 2.13 (2 equiv., 88 mg, 0.400 mmol), vinyl pyrazine 2.56 (28.1 mg, 0.200 mmol) and purged with argon. Dioxane (1 mL) was added. The contents were transferred to the vial containing catalyst and base, rinsing with additional dioxane (2× 500 µL). Water (200 µL) was added to the reaction vial, and the mixture was stirred at room temperature for 2 minutes. The reaction was then sealed with a Teflon cap, and put into a pre-heated oil-bath at 110 ºC for 18 hrs. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc) and concentrated in vacuo. Silica flash column chromatography (9:1 → 7:3 Hexanes/EtOAc) gave the product (35.0 mg, 88%) as a yellow oil. 

**1H-NMR** (400 MHz, CDCl₃): δ/ppm = 8.26 (d, J = 2.5 Hz, 1H), 7.33 – 7.28 (m, 1H), 7.22 (td, J = 6.8, 1.8 Hz, 2H), 7.13 – 7.08 (m, 1H), 3.34 – 3.29 (m, 2H), 3.22 – 3.15 (m, 2H); 

**13C-NMR** (101 MHz, CDCl₃): δ/ppm = 158.2, 155.2, 146.7, 140.0, 139.5, 132.9, 129.6, 128.1, 125.5, 121.4, 5.7, 28.8; 

**IR** (film): ν/cm⁻¹ = 3055, 2930, 2857, 1586, 1536, 1488, 1456, 1429, 1394, 1354, 1266, 1223, 1183, 1166, 1136, 1102, 1075, 1033, 932, 858, 765, 736, 689; 

**HRMS (DART):** m/z calculated for C₁₂H₁₁N₂O⁺ 199.0871, found 199.0871.
1H), 7.81 (d, J = 8.1 Hz, 1H), 7.63 (d, J = 8.3 Hz, 1H), 7.58 (ddd, J = 8.3, 6.8, 1.3 Hz, 1H), 7.48 (ddd, J = 8.1, 6.7, 1.3 Hz, 1H), 7.32 (d, J = 8.3 Hz, 1H), 3.43 – 3.39 (m, 2H), 3.38 – 3.34 (m, 2H); \textbf{13C-NMR} (101 MHz, CDCl$_3$): $\delta$/ppm = 158.5, 150.5, 147.6, 140.1, 139.9, 133.7, 128.5, 127.6, 127.5, 126.8, 126.3, 125.2, 122.2, 35.4, 28.7; \textbf{IR} (film): $\nu$/cm$^{-1}$ = 3417, 3058, 2980, 2933, 1634, 1571, 1508, 1471, 1444, 1416, 1409, 1376, 1366, 1300, 1278, 1258, 1141, 1075, 965, 850, 812, 750, 699, 576; \textbf{HRMS} (DART): m/z calculated for $\text{C}_{16}\text{H}_{13}\text{N}_2\text{O}^+$ 249.1028, found 249,1033.

A 2-dram vial was charged with hydroxy(cyclooctadiene)rhodium(I) dimer (2 mol%, 2.1 mg, 0.00460 mmol), potassium hydroxide (2.9 equiv., 34 mg, 0.606 mmol) and purged with argon. Another 2-dram vial was charged with boronic ester 2.7 (2 equiv., 94 mg, 0.402 mmol), vinyl pyrazine 2.56 (28.1 mg, 0.200 mmol) and purged with argon. Dioxane (1 mL) was added. The contents were transferred to the vial containing catalyst and base, rinsing with additional dioxane (2× 500 $\mu$L). Water (200 $\mu$L) was added to the reaction vial, and the mixture was stirred at room temperature for 2 minutes. The reaction was then sealed with a Teflon cap, and put into a pre-heated oil-bath at 110 °C for 18 hrs. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc) and concentrated in vacuo. Silica flash column chromatography (9:1 → 7:3 Hexanes/EtOAc) gave the product (42.5 mg, 79%) as a yellow oil. \textbf{1H-NMR} (400 MHz, CDCl$_3$): $\delta$/ppm = 8.25 (d, J = 2.5 Hz, 1H), 8.11 (d, J = 2.4 Hz, 1H), 7.21 – 7.15 (m, 1H), 7.01 (d, J = 6.7 Hz, 2H), 3.34 – 3.27 (m, 2H), 3.17 – 3.10 (m, 2H), 2.30 (s, 3H); \textbf{13C-NMR} (75 MHz, CDCl$_3$): $\delta$/ppm = 158.3, 153.0, 146.7, 139.9, 139.4, 135.1, 132.5, 130.0, 128.5, 121.1, 35.8, 28.7, 20.8; \textbf{IR} (film): $\nu$/cm$^{-1}$ = 3052, 2921, 2858, 1494, 1430, 1396, 1348, 1267, 1235, 1222, 1206, 1159, 1138, 1113, 1075, 1500, 940, 891, 871, 855, 825, 805, 745, 700, 687; \textbf{HRMS} (DART): m/z calculated for $\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}^+$ 213.1022, found 213,1022.

A 2-dram vial was charged with hydroxy(cyclooctadiene)rhodium(I) dimer (3 mol%, 2.5 mg, 0.00548 mmol), potassium hydroxide (2.9 equiv., 34 mg, 0.606 mmol) and purged with argon. Another 2-dram vial was charged with boronic ester 2.4 (2 equiv., 103 mg, 0.405 mmol), vinyl pyrazine 2.56 (28.9 mg, 0.206 mmol) and purged with argon. Dioxane (1
mL) was added. The contents were transferred to the vial containing catalyst and base, rinsing with additional dioxane (2× 500 µL). Water (200 µL) was added to the reaction vial, and the mixture was stirred at room temperature for 2 minutes. The reaction was then sealed with a Teflon cap, and put into a pre-heated oil-bath at 110 ºC for 18 hrs. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc) and concentrated in vacuo. Silica flash column chromatography (9:1 → 1:1 Hexanes/EtOAc) gave the product (40.8 mg, 85%) as a yellow solid, mp 56-58 ºC. $^1$H-NMR (400 MHz, CDCl₃): δ/ppm = 8.29 (d, J = 2.5 Hz, 1H), 8.13 (d, J = 2.4 Hz, 1H), 7.25 – 7.20 (m, 2H), 7.18 (dd, J = 8.5, 2.6 Hz, 1H), 3.34 – 3.28 (m, 2H), 3.19 – 3.13 (m, 2H); $^{13}$C-NMR (75 MHz, CDCl₃): δ/ppm = 157.9, 153.7, 146.3, 140.2, 139.9, 134.5, 130.4, 129.4, 128.0, 122.9, 35.3, 28.7; IR (film): v/cm⁻¹ = 3057, 2952, 2927, 2854, 1750, 1700, 1601, 1570, 1525, 1478, 1432, 1393, 1350, 1266, 1235, 1221, 1179, 1164, 1142, 1137, 1112, 1085, 1043, 970, 925, 872, 861, 824, 800, 657; HRMS (DART): m/z calculated for C₁₂H₁₀ClN₂O²⁺ 233.0482, found 233.0484.

A 2-dram vial was charged with hydroxy(cyclooctadiene)rhodium(I) dimer (2 mol%, 1.9 mg, 0.00416 mmol), potassium hydroxide (3.2 equiv., 37 mg, 0.660 mmol) and purged with argon. Another 2-dram vial was charged with boronic ester 2.9 (2 equiv., 96 mg, 0.403 mmol), vinyl pyrazine 2.56 (28.8 mg, 0.205 mmol) and purged with argon. Dioxane (1 mL) was added. The contents were transferred to the vial containing catalyst and base, rinsing with additional dioxane (2× 500 µL). Water (200 µL) was added to the reaction vial, and the mixture was stirred at room temperature for 2 minutes. The reaction was then sealed with a Teflon cap, and put into a pre-heated oil-bath at 110 ºC for 18 hrs. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc) and concentrated in vacuo. Silica flash column chromatography (9:1 → 6:4 Hexanes/EtOAc) gave the product (37.5 mg, 85%) as a yellow-orange solid, mp 48-50 ºC. $^1$H-NMR (300 MHz, CDCl₃): δ/ppm = 8.29 (d, J = 2.5 Hz, 1H), 8.13 (d, J = 2.4 Hz, 1H), 6.99 – 6.84 (m, 2H), 3.36 – 3.29 (m, 2H), 3.20 – 3.14 (m, 2H). $^{13}$C-NMR (75 MHz, CDCl₃): δ/ppm = 159.7 (d, J = 244.4 Hz), 158.1, 151.2 (d, J = 2.7 Hz), 146.3, 140.1, 139.7, 134.9 (d, J = 8.0 Hz), 122.8 (d, J = 8.8 Hz), 115.9 (d, J = 23.3 Hz), 114.5 (d, J = 23.1 Hz), 35.2, 28.6 (d, J = 1.2 Hz); $^{19}$F NMR (564 MHz, CDCl₃): δ/ppm = -117.29 - -
117.37 (m); IR (film): v/cm\(^{-1}\) = 3059, 2927, 2854, 2358, 2333, 1700, 1595, 1488, 1429, 1394, 1350, 1279, 1262, 1250, 1252, 1194, 1164, 1144, 1134, 987, 945, 901, 868, 820, 730, 690, 550; HRMS (DART): m/z calculated for C\(_{12}H_{10}FN_2O^+\) 217.0778, found 217.0773.

**Note:** HQSC was used to assign splittings due to F in the \(^{13}\)C NMR.

A 2-dram vial was charged with hydroxy(cyclooctadiene)rhodium(I) dimer (2 mol%, 2.2 mg, 0.00482 mmol), potassium hydroxide (3 equiv., 36 mg, 0.642 mmol) and purged with argon. Another 2-dram vial was charged with boronic ester 2.9 (1.9 equiv., 96 mg, 0.403 mmol), vinyl pyrazine 2.56 (29.6 mg, 0.211 mmol) and purged with argon. Dioxane (1 mL) was added. The contents were transferred to the vial containing catalyst and base, rinsing with additional dioxane (2 \times 500 \mu L). Water (200 \mu L) was added to the reaction vial, and the mixture was stirred at room temperature for 2 minutes. The reaction was then sealed with a Teflon cap, and put into a pre-heated oil-bath at 110 °C for 18 hrs. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc) and concentrated in vacuo. Silica flash column chromatography (9:1 \rightarrow 7:3 Hexanes/EtOAc) gave the product (37.7 mg, 83%) as a yellow-orange solid, mp 51-53 °C. \(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta/\text{ppm} = 8.30 \ (d, \ J = 2.5 \text{ Hz}, 1\ H), \ 8.14 \ (d, \ J = 2.5 \text{ Hz}, 1\ H), \ 7.21 - 7.09 \ (m, 2\ H), \ 6.89 \ (\text{ddd}, \ J = 9.3, 7.5, 2.0 \text{ Hz}, 1\ H), \ 3.39 - 3.27 \ (m, 2\ H), \ 3.27 - 3.15 \ (m, 2\ H); \) \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)): \(\delta/\text{ppm} = 160.4 \ (d, \ J = 246.0 \text{ Hz}), \ 158.3, \ 155.9 \ (d, \ J = 6.2 \text{ Hz}), \ 147.4, \ 140.3, \ 140.1, \ 127.9 \ (d, \ J = 10.2 \text{ Hz}), \ 120.3 \ (d, \ J = 18.9 \text{ Hz}), \ 117.2 \ (d, \ J = 3.4 \text{ Hz}), \ 112.0 \ (d, \ J = 22.8 \text{ Hz}), \ 33.0 \ (d, \ J = 0.9 \text{ Hz}), \ 20.6 \ (d, \ J = 4.8 \text{ Hz}); \) \(^{19}\)F NMR (282 MHz, CDCl\(_3\)): \(\delta/\text{ppm} = -116.43 \ (dd, \ J = 9.2, 5.4 \text{ Hz}); \) IR (film): v/cm\(^{-1}\) = 3033, 2922, 2865, 2362, 2341, 1877, 1616, 1600, 1511, 1505, 1436, 1364, 1239, 1171, 1104, 1025, 815, 739, 650; HRMS (DART): m/z calculated for C\(_{12}H_{10}FN_2O^+\) 217.0778, found 217.0771.

**Note:** HQSC was used to assign splittings due to F in the \(^{13}\)C NMR.
A 2-dram vial was charged with boronic ester 2.5 (2 equiv., 176 mg, 0.885 mmol), potassium hydroxide (3.3 equiv., 54 mg, 0.962 mmol), hydroxy(cyclooctadiene)rhodium(I) dimer (2 mol%, 2.6 mg, 0.00570 mmol), vinyl pyrazine 2.56 (41.6 mg, 0.296 mmol), and purged with argon. Dioxane (3 mL) and water (300 µL) were added, and the mixture was stirred at room temperature (30 seconds) to dissolve all components. The reaction was then sealed with a Teflon cap, and put into an oil-bath pre-heated at 110 °C for 19 hours. Upon cooling to room temperature, the mixture was passed through a silica plug (EtOAc), and concentrated in vacuo. Silica flash column chromatography (20:1 → 7:3 Hexanes/EtOAc) gave the product (66.8 mg, 81%), as an orange solid, mp 76-78 °C. $^1$H-NMR (400 MHz, CDCl$_3$): 8.27 (d, $J = 2.4$ Hz, 1H), 8.12 (d, $J = 2.3$ Hz, 1H), 7.35 (d, $J = 2.4$ Hz, 1H), 7.32 (dd, $J = 8.5, 2.5$ Hz, 1H), 7.16 (d, $J = 8.5$ Hz, 1H), 3.32 – 3.28 (m, 2H), 3.16 – 3.12 (m, 2H); $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$/ppm = 157.8, 154.2, 146.3, 140.2, 139.9, 135.0, 132.4, 131.1, 123.3, 118.1, 35.3, 28.7; IR (film): v/cm$^{-1}$ = 3056, 2927, 2854, 1750, 1693, 1578, 1476, 1431, 1393, 1264, 1235, 1222, 1206, 1160, 1137, 1111, 1077, 1000, 960, 925, 900, 872, 852, 822, 785, 640, 550; HRMS (DART): m/z calculated for C$_{12}$H$_{10}$BrN$_2$O$^+$ 276.9977, found 276.9976.
Appendix 1: Spectra of Newly Synthesised Compounds
chem_Proton_Day CDCl3 /opt/data ariedma 59

chem_Carbon_Day CDCl3 /opt/data ariedma 59
chem_Fluorine CDCl3 /opt/data afriedma 57
chem_Fluorine CDC13 /opt/data afriedma 36
chem_Fluorine CDC3 /opt/data affilierna 23