Rhodium and Palladium Catalysis in the Synthesis of Carbo- and Heterocycles

by

Jane Panteleev

A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
Department of Chemistry
University of Toronto

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Jane Panteleev

Doctor of Philosophy, Department of Chemistry
University of Toronto, 2012

Abstract

This thesis describes the development of transition metal catalyzed transformations towards the synthesis of stereochemically rich motifs and heterocycles. The main themes present throughout this thesis are rhodium-catalysis in reactions of boronic acids with alkenes and alkynes, the use of alkynes as a key motif in the synthesis of heterocycles, and the use of domino and one-pot processes to effect high efficiency in multistep transformations.

In Chapter 1, a rhodium-catalyzed desymmetrization of diazabicyclic alkenes with boronic acids is discussed. In this work a chemodivergent and enantioselective process for the synthesis of substituted cyclopentenes and cyclopentanes is developed. Both the chemo- and the enantioselectivity of the reaction are shown to be highly dependent on the phosphine ligand structure. The observed reactivity of rhodium is further applied to a domino reaction to synthesize highly substituted benzofuranones.

In Chapter 2, the reactivity of boronic acids and alkynes under rhodium catalysis is exploited as a key step to access polycyclic motifs. In the first part of this chapter the development of a domino process using both rhodium and palladium catalysis is described. Detailed mechanistic investigations allow some insight into the interactions between two catalysts. In the last part of this chapter, preliminary experiments in the application of multimetallic catalysis in the synthesis of azadibenzoxepines are discussed.
Chapter 3 summarizes work on the arylation of propargylic alcohols with boronic acids under rhodium catalysis. This reaction is shown to proceed with high regioselectivity and can be conducted under mild conditions. The resulting allylic alcohols are shown to be versatile motifs and are applied in a synthesis of indenes and quinolines.

In the final chapter of this thesis, iodontriazoles are explored as key intermediates in the synthesis of fused triazole-containing heterocycles. Palladium-catalyzed cyclization, either through C-H functionalization or through Heck coupling, is achieved. Furthermore, it is shown that the copper-catalyzed azide-alkyne cycloaddition and palladium-catalyzed C-H arylation can be combined into a one-pot process.
Acknowledgments

First and foremost I would like to thank my supervisor, Professor Mark Lautens, who made this thesis and the work leading up to it possible. I feel that my experience in this group has made it possible for me to succeed and solve any problems I encounter in the future. I especially appreciate the freedom and independence we experience when it comes to research, and the opportunities to mentor students. I would also like to thank the members of my PhD committee, professors Andrei Yudin, Rob Batey and Mark Taylor for their patience and advice throughout my degree. I am thankful to Professor Gary Molander for agreeing to serve as my external examiner.

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<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tbody>
<tr>
<td>Ar</td>
<td>aromatic group</td>
</tr>
<tr>
<td>atm</td>
<td>atmosphere</td>
</tr>
<tr>
<td>d. r.</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>E or E⁺</td>
<td>electrophile</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>e. r.</td>
<td>enantiomeric ratio</td>
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<tr>
<td>equiv</td>
<td>equivalents</td>
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<td>h</td>
<td>hour</td>
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<td>HetAr</td>
<td>heteroaromatic group</td>
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<tr>
<td>KIE</td>
<td>kinetic isotope effect</td>
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<tr>
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<td>intermediate</td>
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<td>LA</td>
<td>Lewis acid</td>
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<td>Nu or NuH</td>
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**Chemical abbreviations**

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<tr>
<td>Bmim</td>
<td>1-butyl-3-methylimidazolium hexafluorophosphate</td>
</tr>
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<tr>
<td>NHC</td>
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<td>tetra-n-butylammonium fluoride</td>
</tr>
<tr>
<td>TBABr</td>
<td>tetra-n-butylammonium bromide</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TIPS</td>
<td>tri-isopropylsilyl</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethyrsulfonate</td>
</tr>
<tr>
<td>triflates</td>
<td></td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>o-Tol</td>
<td>ortho-tolyl</td>
</tr>
<tr>
<td>p-Tol</td>
<td>para-tolyl</td>
</tr>
<tr>
<td>TPPTS</td>
<td>3,3',3''-phosphinidynetris (benzenesulfonic acid)</td>
</tr>
<tr>
<td>Ts</td>
<td>para-toluenesulfonate</td>
</tr>
<tr>
<td>TIPS</td>
<td>triisopropylsilyl</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethysulfonate</td>
</tr>
<tr>
<td>TBD</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetra-n-butylammonium fluoride</td>
</tr>
</tbody>
</table>
Chapter 1

Chemoselective Desymmetrization of Bicyclic Hydrazines
1 Chemoselective Desymmetrization of Bicyclic Hydrazines

1.1 Introduction

The ability to synthesize molecules enantioselectively is vital to the pharmaceutical industry since different enantiomers of a molecule can have completely different biological properties. Oftentimes in synthesis, enantiomeric excess is introduced by using chiral pool reagents as substrates or by utilizing stoichiometric auxiliaries, and conducting subsequent chemistry diastereoselectively. These methods, however, can be limiting if unnatural enantiomers are required or if the desired product differs significantly from any available chiral reagents. The use of stoichiometric amounts of enantiopure chiral reagents can also be problematic because of high costs. Alternatively, racemic compounds can be separated using chromatography, which results in a loss of half of the material. Asymmetric transition metal catalysis provides an excellent alternative for the introduction of asymmetry into prochiral intermediates. More often than not, the chiral environment is created through the use of chiral ancillary ligands.

1.1.1 Desymmetrization Reactions

The development of new catalytic enantioselective reactions can be a formidable challenge in synthetic chemistry. Desymmetrization of prochiral meso compounds is an efficient strategy for generating chiral building blocks with one or more stereocenters. In the Lautens group, a number of such methods have been developed. The most noteworthy are the desymmetrizations of bicyclic alkenes such as I and II (Figure 1.1). Under transition metal catalysis these substrates

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can yield stereochemically rich scaffolds and synthons. The key discovery during the study of desymmetrization of I and II was that a rhodium and a bisphosphine ligand, t-Bu-Josiphos, afforded excellent enantioselectivity. Oxygen, nitrogen, and carbon-based nucleophiles could be added successfully (Eqn 1.1).

![Figure 1.1: Bicyclic heterocyclic alkenes studied by the Lautens group.](image)

Related systems, such as bicyclic hydrazine III, have received considerably less attention. Our previous success in ring-opening reactions prompted us to investigate the desymmetrization of III, ultimately leading to the development of two enantioselective transformations described in this chapter.

### 1.1.2 Reactions of Bicyclic Hydrazines

Bicyclic hydrazines predominantly react at the olefin, which is more reactive than acyclic alkenes because of strain released during reduction or ring opening. Most functionalizations of this alkene can be divided into either ring opening reactions, wherein the bicyclic structure is broken to generate substituted cyclopentenes, or alternatively through reductive means, where the bicyclic structure remains intact but the alkene is either reduced or reductively

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5 For reviews on reactivity of bicyclic hydrazines see: Bournaud, C.; Chung, F.; Luna, A. P.; Pasco, M.; Errasti, G.; Lecourt, T. Micouin, L. Synthesis 2009, 869.
functionalized. A few isolated reports of non-ring opening reactions of the alkene in predictable hydrogenations,⁶ Pauson-Khand reactions⁷ or ring opening metathesis reactions⁸ can be found. A considerable number of contributions from the Micouin group demonstrated that bicyclic hydrazines can undergo enantioselective hydroboration or hydroformylation reactions without ring opening.⁹ The same group also reported that the epoxides of III can undergo rearrangement reactions.¹⁰

**Addition of aryl halides.** The first thorough studies of the reactivity of bicyclic hydrazines under transition metal catalysts were reported by Kaufmann. In 2001, he described that bicyclic hydrazines can react with aryl and vinyl halides under palladium catalysis to generate hydroarylation products A (Eqn 1.2).¹¹ Remarkably, it was possible to substitute the formic acid with phenylacetylene, and a trimolecular coupling product C could be generated (Eqn 1.3). The reaction proceeded through oxidative addition followed by carbopalladation of the alkene. At this stage formic acid functioned as a hydride source to give the final product. Formation of byproduct B, where the N-N bond was cleaved and the olefin remained intact was explained by competitive addition of arylpalladium(II) species to the N-N single bond followed by reductive cleavage.

![Diagram](image-url)

---

In a separate report, Kaufmann showed that it was possible to obtain ring-opened compounds as major products under similar conditions, but using a fluoride salt additive. The fluoride was proposed to be instrumental in an anti-nitrogen elimination leading to the final product (Scheme 1.1). The use of formic acid was essential in these reactions to reduce palladium(II) and regenerate the palladium(0) catalyst.

More recently, Radhakrishnan reported the use of ortho-functionalized aryl iodides in a ring opening reaction of III (Scheme 1.2). This domino reaction was thought to proceed through a similar carbopalladation mechanism, as described by Kaufmann, but the reaction of the ortho hydroxy or amino group with the palladium center facilitated the anti-nitrogen elimination. A subsequent nitro- or oxypalladation of the resulting alkene furnishes the final products. Interestingly, in the absence of the tetrabutylammonium chloride salt the reaction yielded the ring-opened product, which could then be cyclized in a separate reaction.

\[ \text{Scheme 1.1 Palladium-catalyzed ring opening of bicyclic hydrazines.} \]

\[ (a) \text{John, J.; U, I.; Suresh, E.; Radhakrishnan, K. V. J. Am. Chem. Soc. 2009, 131, 5042} \]
Addition of carbon-based nucleophiles. The addition of carbon-based nucleophiles to bicyclic hydrazines has also been reported. The first instance of this reactivity was described by Pineschi in 2005.\textsuperscript{13} He observed that bicyclic hydrazines could be opened by adding dialkylzinc or trialkylaluminum reagents using a copper catalyst (Eqn 1.4). With a phosphoramidite ligand an enantiomeric excess of 86% could be achieved. Interestingly the chirality of the amine of the phosphoramidite played the more important role than the binaphthol chirality, and reversal of the amine stereochemistry ($R,S,S$ versus $R,R,R$ (pictured) led to the product with opposite stereochemistry. With trialkylaluminum reagents the enantioselectivity was highly dependent on the nature of the nucleophilic alkyl groups, with more sterically hindered reagents giving lower and even reversed enantiomeric ratio. Overall the method furnished the products in high yields, but the enantioselectivity was variable.

\textsuperscript{13} Pineschi, M; Del Moro, F.; Crotti, P.; Macchia, F. Org. Lett. \textbf{2005}, \textit{7}, 3605.
Following this work, the same group reported a rhodium-catalyzed ring-opening of these bicyclic motifs using boronic acids as nucleophiles (Eqn 1.5).\textsuperscript{14a} This report utilized considerably milder conditions. A chiral binap ligand was found to give some enantioselectivity (up to 70%), but the enantiomeric excess was exceedingly variable with respect to the substitution pattern on the arylboronic acid, and no clear trends were observed. This work was soon followed up by a report using alkynylboronic acids as nucleophiles, achieving similar moderate yields and enantioselectivities.\textsuperscript{14b}

\[ \text{[Rh(C_2H_4)Cl}_2 \text{Ligand (6 mol\%)} \]

\[ \text{CaF (2 equiv)} \]

\[ \text{MeOH, 65 °C} \]

\[ \text{35 – 90\% yield up to 70\% ee} \]

The Alexakis and Micouin groups reported an enantioselective addition of alkylaluminum reagents under copper catalysis (Scheme 1.3).\textsuperscript{15} Using a SimplePhos phosphoramidite ligands up to 95\% of enantiomeric excess could be generated. It was proposed that the reaction proceeded through formation of a $\sigma$-allylcopper species $\text{II}$, which then reductively eliminated to generate the product.

\[ \text{CuTC = copper(I)-thiophene-2-carboxylate} \]

**Scheme 1.3** Addition of trialkylaluminum reagents to bicyclic hydrazines.


In addition to the examples described above, several reports from Radhakrishnan and coworkers described the non-asymmetric addition of various organometallic reagents across bicyclic hydrazines.\(^{16}\) It was found that palladium could be used to catalyze these reactions in the presence of a Lewis acid, such as iodine or scandium and ytterbium triflates. A considerable portion of the group’s work utilized alkyl or arylstannanes (Eqn 1.6), but reactions of boronic acids and \textit{in situ}-formed alkylindium reagents were also reported.

\[
\begin{align*}
\text{NCO}_2\text{Et} & \quad \text{NCO}_2\text{Et} \quad + \\
\text{SnBu}_3 & \quad \text{I}_2 \quad \text{PhMe, 75 °C, 24 h} \\
\text{[Pd(allyl)Cl]_2 (5 mol\%)} & \quad \text{dppe (10 mol\%)} \\
\end{align*}
\]

(1.6)

An interesting example of a carbonylative ring opening of bicyclic hydrazines was reported by the Lautens group in 2007.\(^{17}\) It was found that in the presence of a carbon monoxide atmosphere, products of addition of acyl anion equivalents were observed (Eqn 1.7). This transformation was quite remarkable, considering that in the absence of CO good yields of the ring-opened product were obtained. In the presence of carbon monoxide, migratory insertion of CO into the arylrhodium bond was significantly faster than the carborhodation of the alkene. Unfortunately, attempts to render this reaction enantioselective have not been met with success.

\[
\begin{align*}
\text{NCO}_2\text{R} & \quad \text{NCO}_2\text{R} \quad + \\
\text{Ar-B(OH)}_2 & \quad \text{[Rh(CO)]_3acac (10 mol\%)} \quad \text{BINAP (12 mol\%)} \\
\text{PhMeH}_2\text{O (10:1), r. t., 24 h} & \quad \text{CO (atm)} \\
\end{align*}
\]

(1.7)

**Addition of ‘soft’ nucleophiles.** Even though there are a number of examples where carbon-based nucleophiles are used to open bicyclic hydrazines, there are very few reports of oxygen or nitrogen nucleophiles partaking in this reaction.


In 2003, Micouin reported that an intermolecular ring-opening with alcohol or malonate nucleophiles could take place in the presence of a palladium catalyst (Eqn 1.8). A moderate level of enantioselectivity could be achieved by using a PHOX ligand. The reaction was thought to proceed through the formation of a palladium-allyl species which was then trapped by the external nucleophile. The end result was the relative syn geometry of the cyclopentene substituents.

\[
\begin{align*}
\text{N-CO}_2\text{Bn} & \quad \text{Pd}_2(\text{dba})_3 (5 \text{ mol\%}) \\
& \quad (R)-\text{PHOX} (17 \text{ mol\%}) \\
\text{PhOH} & \quad \text{THF, 2 h} \\
\rightarrow & \quad \text{PhO} \\
\text{N-CO}_2\text{Bn} & \quad (R)-\text{PHOX} \\
\text{NHCO}_2\text{Bn} & \quad 80\% \\
& \quad 58\% \text{ ee}
\end{align*}
\]

In the same report it was noted that the bicyclic alkene rearranged upon exposure to acids through an intramolecular ring opening. (Eqn 1.9). This tendency of bicyclic hydrazines to rearrange has been reported much earlier by Mackay. The earliest reports of this reactivity, however, utilized different N-protecting groups, and the products obtained did not undergo an elimination reaction (Eqn 1.10).

\[
\begin{align*}
\text{H}_2\text{SO}_4 & \quad \text{CF}_3\text{CH}_2\text{OH, 20 min} \\
\rightarrow & \quad \text{HO} \\
\text{OMe} & \quad \text{NH}_2
\end{align*}
\]

In a more recent report from the Lautens group, the structure of the rearranged product observed by Micouin (Eqn 1.9) was revised based on X-ray crystallography data (Eqn 1.11). Instead of containing a six-membered ring the rearranged product was found to result from the addition of the other protecting group, furnishing an isomeric five-membered ring product (Scheme 1.4). In

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this report a one-pot reaction of bicyclic hydrazines, featuring the rearrangement and a copper-catalyzed C-N coupling reaction was described (Eqn 1.11). Despite considerable efforts, an enantioselective version of this rearrangement has not been developed.\textsuperscript{21}

\[ \text{Scheme 1.4 Mechanism of acid-catalyzed rearrangement of bicyclic hydrazines.} \]

Shortly thereafter, a report from Pineschi and coworkers supported the formation of the 5,5 fused bicycle.\textsuperscript{22} In their work, the authors utilized the rearranged product in an allylic substitution with Grignard reagents (Eqn 1.12). The outcome of this addition reaction was different than that of rhodium- and copper-catalyzed additions of nucleophiles, as the 1,4-products were predominantly obtained instead of the 1,2-substituted cyclopentenes.

Addition of boronic acids to electrophiles is still a highly valuable transformation because of the mildness of the reaction conditions. We were interested in further examining the transition-metal

catalyzed reaction of boronic acids with bicyclic hydrazines. More so, because of our expertise in enantioselective desymmetrization of oxa- and azabicycles, we were intrigued at the prospect of developing a highly enantioselective ring-opening of these molecules. As outlined above, the reports of this reactivity to date usually report either moderate enantioselectivity or use highly reactive organometallic reagents as nucleophiles.

In the following chapter of this thesis a chemodivergent, ligand-controlled transformation of 1.1 is described (Scheme 1.5). It was found that compound 1.1 could undergo ring-opening to yield cyclopentene 1.2 in a highly enantioselective reaction, particularly when ortho-substituted boronic acids were used. Alternatively, when appropriate ligands were used, nucleophiles could be added reductively to 1.1 to give bicycles 1.3. A 1,4-migration/C-H insertion mechanism was proposed based on deuterium labeling experiments. This process differs substantially from the reductive arylations under palladium catalysis, and thus opens the possibilities for new reaction development. Reduction and deprotection of compounds 1.2 and 1.3 could yield 1.4 and 1.5, respectively, with retention of relative stereochemistry. Substituted chiral scaffolds such as these are common in biologically significant molecules, and their stereoselective synthesis is a worthwhile goal (Figure 1.2). To the best of our knowledge, an enantioselective reaction to access 1.3 has not been reported.

---

23 In previous work, we observed that organoboron reagents add to the alkene of diazabicycle without ring-opening: (a) Lautens, M.; Mancuso, J. J. Org. Chem. 2004, 69, 3478; (b) Tseng, N.-W.; Mancuso, J. J.; Lautens, M. J. Am. Chem. Soc. 2006, 128, 5338.
Scheme 1.5 Divergent pathways in the desymmetrization of bicyclic hydrazines.

Figure 1.2: Biologically active compounds containing a substituted aminocyclopentane core.

The following work originated from studies of Dr. Fred Menard and resulted in a collaboration. Dr. Menard’s contributions are acknowledged where appropriate.

1.2 Rhodium-Catalyzed Chemoselective Desymmetrization of Bicyclic Hydrazines

Ring opening of bicyclic hydrazines could generate chiral amines, and the development of such enantioselective desymmetrizing reactions is quite important. Since the examples presented in the introduction generate the products in moderate ee, there was room for improvement. Initially, an enantioselective ring opening of bicyclic hydrazines was developed, but during this study a secondary process giving formal hydroarylation products was observed. The mechanistic investigations of this strategy led to studies into domino processes using this new reactivity.

27 Then a senior Ph.D. student in the Lautens group. Present location: PostDoctoral Fellow, Stanford University, Stanford, CA, USA.
We elected to examine the desymmetrization of 1.1 using rhodium catalysis and boronic acids as nucleophiles.

### 1.2.1 Substrate Synthesis

The bicyclic hydrazines were synthesized through Diels-Alder cycloaddition of cyclopentadiene and appropriately protected diazenes (Eqn 1.13). With a tert-butyl carboxylate protecting group, the reaction proceeded cleanly, and the final product 1.1a was recrystallized from the reaction crude as a colorless solid.

\[
\]

### 1.2.2 Development of Ring Opening Reaction

Our previous conditions for desymmetrizing meso allylic bicarbonates provided a starting point for the enantioselective ring-opening of 1.1b. Preliminary results were promising (Scheme 1.6). Xylyl-P-Phos (L9) generated moderate enantioselectivity (87% ee) and t-Bu-Josiphos (L1) led to high conversion (72% yield, Figure 1.3). A strong dependence of the ligand on the reactivity was observed (Table 1).

\[
\text{Scheme 1.6 Preliminary findings in the enantioselective ring-opening reaction.}
\]

A range of ligands was examined using phenylboronic acid as a nucleophile (Figure 1.3, Table 1.1). Good levels of enantioselectivity could be obtained with a subset of ligands, such as P-Phos and DifluorPhos\(^{32}\) (entries 1-4, Table 1). BINAP and its derivatives showed slightly lower selectivity, but marginally superior conversion (entries 5-8). Additionally, ferrocenyl phosphine ligand L1 \((t\text{-Bu-Josiphos})\) showed high conversion and modest enantioselectivity (entries 10-12). Additional reaction parameters needed to be optimized since we were unable to attain both high conversion and enantioselectivity with any of the ligands studied. Importantly, a byproduct was observed during ligand screening when a more electron deficient ligand L4 was used, and was later identified as the reductive arylation product 1.3 (entry 13).

---

Table 1.1 Ligand screening for rhodium-catalyzed ring-opening of diazabicycles.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>T (°C)</th>
<th>Yield (%)(^b)</th>
<th>ee (%)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^d)</td>
<td>Xylyl-P-phos</td>
<td>L9</td>
<td>60</td>
<td>18</td>
</tr>
<tr>
<td>2(^d)</td>
<td>Xylyl-P-phos</td>
<td>L9</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>3(^d)</td>
<td>P-phos</td>
<td>L8</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>4(^d)</td>
<td>DifluorPhos</td>
<td>L15</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>5(^d)</td>
<td>BINAP</td>
<td>L10</td>
<td>60</td>
<td>15</td>
</tr>
<tr>
<td>6(^d)</td>
<td>BINAP</td>
<td>L10</td>
<td>25</td>
<td>6</td>
</tr>
<tr>
<td>7(^d)</td>
<td>Tolyl-BINAP</td>
<td>L12</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>8(^d)</td>
<td>Xylyl-BINAP</td>
<td>L11</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>9(^d)</td>
<td>SegPhos</td>
<td>L14</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>10(^d)</td>
<td>t-Bu-Josiphos</td>
<td>L1</td>
<td>25</td>
<td>n.d.</td>
</tr>
<tr>
<td>11(^d)</td>
<td>t-Bu-Josiphos</td>
<td>L1</td>
<td>0</td>
<td>80</td>
</tr>
<tr>
<td>12(^e,)</td>
<td>Josiphos</td>
<td>L2</td>
<td>25</td>
<td>84</td>
</tr>
<tr>
<td>13(^e,)</td>
<td>Josiphos</td>
<td>L4</td>
<td>25</td>
<td>10</td>
</tr>
</tbody>
</table>

\(^a\) Conditions: [Rh]\(^2\) (5 mol%), ligand (12 mol%) and base (2 equiv) were premixed in THF/water (50:1). Solution of 1.1b and PhB(OH)\(_2\) (2 equiv) was added. \(^b\) Yields of isolated products. \(^c\) Enantiomeric excess determined by chiral HPLC. \(^d\) Experiments performed by F. Menard. \(^e\) Reaction performed using 1.1a. \(^f\) See Figure 1.3 for ligand structure. \(^g\) Product 1.23 was a major side product (see Scheme 1.8).

When the influence of the solvent was examined, THF and toluene proved to be the most successful (Table 1.2). A preliminary screen of boronic acids showed that t-Bu-Josiphos (L1) afforded excellent stereoinduction with \textit{ortho}-substituted boronic acids. Unfortunately, although DifluorPhos afforded the highest ee, the reaction proceeded with very low conversion (entries 18-20). Neither changes in concentration, nor temperature, influenced the product distribution significantly. Below 0 °C the reaction was sluggish, giving partial conversion when bicyclic hydrazine 1.1a was used (entry 12, Table 1.2).

Water was required in the reaction, with lower yields being observed under anhydrous conditions (entry 11, Table 1.2). It is presumed that water is essential for regeneration of the catalyst. The rhodium chloride complex did not give product without base and water, suggesting \textit{in situ} formation of [Rh(cod)OH]\(_2\) (entries 16 and 17). Although the reaction proceeded with excellent
conversion in ethereal solvents, higher yield of 1.2b could be obtained in toluene and water (entries 9 and 10, Table 1.2).

**Table 1.2** Influence of solvent on the ring-opening reaction with selected ligands.\(^ a \)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>T (°C)</th>
<th>Solvent</th>
<th>Yield (%) ( b )</th>
<th>ee (%) ( c )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ( d, e )</td>
<td>BINAP</td>
<td>L10</td>
<td>0</td>
<td>THF</td>
<td>6</td>
</tr>
<tr>
<td>2 ( e )</td>
<td>BINAP</td>
<td>L10</td>
<td>25</td>
<td>THF</td>
<td>16</td>
</tr>
<tr>
<td>3 ( e )</td>
<td>BINAP</td>
<td>L10</td>
<td>25</td>
<td>Dioxane</td>
<td>35</td>
</tr>
<tr>
<td>4 ( e )</td>
<td>BINAP</td>
<td>L10</td>
<td>25</td>
<td>Chloroform</td>
<td>38</td>
</tr>
<tr>
<td>5 ( e )</td>
<td>BINAP</td>
<td>L10</td>
<td>25</td>
<td>DCE</td>
<td>6</td>
</tr>
<tr>
<td>6 ( e )</td>
<td>BINAP</td>
<td>L10</td>
<td>25</td>
<td>Benzene</td>
<td>70</td>
</tr>
<tr>
<td>7 ( e )</td>
<td>BINAP</td>
<td>L10</td>
<td>25</td>
<td>Toluene</td>
<td>57</td>
</tr>
<tr>
<td>8 ( e )</td>
<td>BINAP</td>
<td>L10</td>
<td>0</td>
<td>Toluene</td>
<td>91</td>
</tr>
<tr>
<td>9 ( e )</td>
<td>t-Bu-Josiphos</td>
<td>L1</td>
<td>0</td>
<td>Toluene</td>
<td>93</td>
</tr>
<tr>
<td>10 ( e )</td>
<td>t-Bu-Josiphos</td>
<td>L1</td>
<td>0</td>
<td>THF</td>
<td>80</td>
</tr>
<tr>
<td>11 ( e, f )</td>
<td>t-Bu-Josiphos</td>
<td>L1</td>
<td>25</td>
<td>THF</td>
<td>29</td>
</tr>
<tr>
<td>12 ( e, f )</td>
<td>t-Bu-Josiphos</td>
<td>L1</td>
<td>0</td>
<td>THF</td>
<td>55</td>
</tr>
<tr>
<td>13 ( e, f )</td>
<td>t-Bu-Josiphos</td>
<td>L1</td>
<td>50</td>
<td>THF</td>
<td>79</td>
</tr>
<tr>
<td>14 ( e )</td>
<td>t-Bu-Josiphos</td>
<td>L1</td>
<td>25</td>
<td>Dioxane</td>
<td>69</td>
</tr>
<tr>
<td>15 ( e )</td>
<td>t-Bu-Josiphos</td>
<td>L1</td>
<td>25</td>
<td>DME</td>
<td>Trace</td>
</tr>
<tr>
<td>16 ( e, g, h )</td>
<td>t-Bu-Josiphos</td>
<td>L1</td>
<td>25</td>
<td>THF</td>
<td>0</td>
</tr>
<tr>
<td>17 ( e, h )</td>
<td>t-Bu-Josiphos</td>
<td>L1</td>
<td>25</td>
<td>THF</td>
<td>65</td>
</tr>
<tr>
<td>18 ( d, e )</td>
<td>DifluorPhos</td>
<td>L15</td>
<td>25</td>
<td>THF</td>
<td>Trace</td>
</tr>
<tr>
<td>19 ( e )</td>
<td>DifluorPhos</td>
<td>L15</td>
<td>25</td>
<td>THF</td>
<td>Trace</td>
</tr>
<tr>
<td>20 ( e )</td>
<td>DifluorPhos</td>
<td>L15</td>
<td>25</td>
<td>Toluene</td>
<td>Trace</td>
</tr>
</tbody>
</table>

\( a \) Conditions as in Table 1.1. \( b \) Yield of isolated products. \( c \) Enantiomeric excess determined by chiral HPLC. \( d \) Reaction performed without addition of water. \( e \) Reaction performed by F. Menard. \( f \) Starting material 1.1a used to give product 1.2a (Boc protecting group). \( g \) No base used. \( h \) Reaction performed using [Rh(cod)Cl] \( 2 \) as rhodium source.

The nature of the protecting group on the bicyclic hydrazine influenced the yield and selectivity of the reaction (Table 1.3). The enantioselectivity was highest with Cbz-substituted derivative 1.1c (entry 4). Phthalazine derivative 1.1d afforded 1.2d in higher yield and moderate selectivity (entry 5). The increase in yield suggests that the more electron deficient protecting group may improve the leaving group ability of the hydrazide, thereby increasing the yield and preventing a
competing 1,4-migration from taking place (*vide infra*). With a Boc-protected derivative **1.1a**, the enantioselectivity and yield were marginally lower (entry 6), but because **1.1a** is a highly crystalline solid, and is readily soluble in THF, this substrate was used for a large fraction of the experiments.

In an attempt to extend the reaction to alternative organometallic nucleophiles, phenylmagnesium bromide and phenylzinc bromide were tested (entries 7 and 8, Table 1.3). Intriguingly, even though comparable yields were obtained, the enantiomeric excess of the products was very low. Clearly, the increased reactivity of the nucleophile or the presence of metal halide salts was responsible for this dramatic difference.

In addition to rhodium catalysts, we tested palladium under conditions previously developed for ring-opening of bicyclic compounds (entries 9 and 10, Table 1.3). The reaction proceeded to give yields similar to rhodium (entry 10), however, the ee was much lower.

**Table 1.3** Influence of protecting group, nucleophile and catalyst.³³

<table>
<thead>
<tr>
<th>Entry</th>
<th><strong>1.1</strong></th>
<th>X</th>
<th>Ph-M</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1³³</td>
<td><strong>1.1b</strong></td>
<td>CO₂Et</td>
<td>Ph-B(OH)₂</td>
<td>80</td>
<td>77</td>
</tr>
<tr>
<td>2³³</td>
<td><strong>1.1b</strong></td>
<td>CO₂Et</td>
<td>Ph-B(OH)₂</td>
<td>96</td>
<td>71</td>
</tr>
<tr>
<td>3³³</td>
<td><strong>1.1b</strong></td>
<td>CO₂Et</td>
<td>Ph-B(OH)₂</td>
<td>72</td>
<td>75</td>
</tr>
<tr>
<td>4³³</td>
<td><strong>1.1c</strong></td>
<td>CO₂Bn</td>
<td>Ph-B(OH)₂</td>
<td>72</td>
<td>80</td>
</tr>
<tr>
<td>5³³</td>
<td><strong>1.1d</strong></td>
<td>Phthalyl</td>
<td>Ph-B(OH)₂</td>
<td>99</td>
<td>70</td>
</tr>
<tr>
<td>6³³</td>
<td><strong>1.1a</strong></td>
<td>CO₂t-Bu</td>
<td>Ph-B(OH)₂</td>
<td>85</td>
<td>66</td>
</tr>
<tr>
<td>7³³</td>
<td><strong>1.1a</strong></td>
<td>CO₂t-Bu</td>
<td>Ph-MgBr</td>
<td>65</td>
<td>12</td>
</tr>
<tr>
<td>8³³</td>
<td><strong>1.1a</strong></td>
<td>CO₂t-Bu</td>
<td>Ph-ZnBr</td>
<td>63</td>
<td>22</td>
</tr>
<tr>
<td>9³³</td>
<td><strong>1.1a</strong></td>
<td>CO₂t-Bu</td>
<td>Ph-B(OH)₂</td>
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<td>42</td>
</tr>
<tr>
<td>10³³</td>
<td><strong>1.1a</strong></td>
<td>CO₂t-Bu</td>
<td>Ph-B(OH)₂</td>
<td>84</td>
<td>0</td>
</tr>
</tbody>
</table>

³³ Reaction conditions as described in Table 1.1. ³³ Yield of isolated products. ³³ Enantiomeric excess determined by chiral HPLC. ³³ Experiment performed by F. Menard; ³³ Degassed solvents used. ³³ No base used. ³³ Reaction performed under anhydrous conditions. ³³ Reaction conditions: 10 mol% Pd(CH₃CN)₂Cl₂ and 11 mol% p-tol-BINAP (L12) in MeOH. ³³ Reaction conditions: 10 mol% Pd(CH₃CN)₂Cl₂ and 11 mol% L1 in MeOH.

³³ Conditions for Pd catalyzed reaction were derived from Lautens, M.; Dockendorff, C. *Org. Lett.* 2003, 5, 3695.
1.2.3 Scope of Boronic Acids in Ring-Opening of 1.1a

The ring-opening reaction was shown to proceed with high conversion with a variety of arylboronic acids (Table 1.4). The yield depended largely on the electronic changes in the nucleophile, where electron rich boronic acids gave the highest yields (entries 5-7, 9, 10, 13 and 14). The decreased yield of ring-opening product may have been caused by competing reductive arylation leading to 1.3 by a mechanism that appears to be more facile with electron deficient arylboronic acids (entries 1-4, 8, 11, 12, *vide infra*). The product ratio could be influenced to favor ring-opening by performing the reaction in a toluene/THF solvent system (entry 5 vs. 6).

*Ortho*-substituted boronic acids were ideal nucleophiles for this transformation, giving products with excellent enantioselectivity (entries 1, 4-10). The nature of the *ortho* substituent could be varied extensively, giving good yields with electron rich or neutral groups. It was apparent that steric bulk is important for generating good ee. Reaction conditions were mild and compatible with various functional groups (entries 10, 12 and 14). Styryl boronic acid reacted quantitatively, although the selectivity was moderate (entry 15).

The stereochemical assignment of the substituted cyclopentenes 1.2a was difficult because of the presence of rotamers by NMR analysis. Fortunately, the relative stereochemistry could be determined for phthalazine 1.2d, through X-ray crystallography. The absolute and relative stereochemistry of Boc-protected 1.2a was determined by reduction of the N–N bond, deprotection to the free amine, and comparison of the optical rotation to literature values.

---

34 In cases where the boronic acid was insoluble in toluene, a few drops (~0.05 mL) of THF were added to the reaction until it became homogeneous. It should be noted that the reaction mixture was biphasic after addition of water.

35 CCDC 661282 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data request/cif.

Table 1.4 Ring-opening of diazabicycle 1.1a with substituted boronic acids.\(^a\)

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Ar</th>
<th>Yield (%)(^b)</th>
<th>ee (%)(^c)</th>
<th>Entry</th>
<th>Product</th>
<th>Ar</th>
<th>Yield (%)(^b)</th>
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<td>96</td>
</tr>
<tr>
<td>2</td>
<td>1.7</td>
<td><img src="image" alt="Structure" /></td>
<td>66</td>
<td>51</td>
<td>11(^{de})</td>
<td>1.14</td>
<td><img src="image" alt="Structure" /></td>
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<td>84</td>
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<tr>
<td>3(^f)</td>
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<td><img src="image" alt="Structure" /></td>
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<td>82</td>
<td>12(^{e})</td>
<td>1.15</td>
<td><img src="image" alt="Structure" /></td>
<td>58</td>
<td>86</td>
</tr>
<tr>
<td>4(^d)</td>
<td>1.9</td>
<td><img src="image" alt="Structure" /></td>
<td>40</td>
<td>99</td>
<td>13(^{e})</td>
<td>1.16</td>
<td><img src="image" alt="Structure" /></td>
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<td>50</td>
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<td>5(^{e})</td>
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<td><img src="image" alt="Structure" /></td>
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<td>97</td>
<td>14(^{e})</td>
<td>1.17</td>
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<td>15(^{e})</td>
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<tr>
<td>7(^{e})</td>
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<td>99</td>
<td>16(^{e})</td>
<td></td>
<td><img src="image" alt="Structure" /></td>
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<td></td>
</tr>
</tbody>
</table>

\(^{a}\) Reaction conditions as described in Table 1.1. \(^b\) Yield of isolated products. \(^c\) Enantiomeric excess determined by chiral HPLC. \(^d\) Reductive arylation product observed. \(^e\) Reaction performed by F. Menard. \(^f\) Reaction performed using Walphos L5 as ligand. \(^g\) Reaction performed in Toluene/THF/H\(_2\)O mixture (1:1:0.1).

### 1.2.4 Chemoselectivity between Ring-Opening and Hydroarylation

During the course of the study we observed the ratio of 1.2 and 1.3 varied as a function of the nucleophile and solvent. While 1.3 was initially a minor byproduct, we discovered that its formation occurred through sequential addition/C--H activation, which was intriguing and potentially applicable to more sophisticated reactions.
We observed that a substantial amount of 1.3 formed with heteroaromatic and electron deficient boronic acids (entries 1, 4, 11, Table 1.4). Upon further investigation of the reaction with pyrimidine derivative 1.19 in the presence of D2O, we observed deuterium incorporation at the ortho aromatic position in 1.20 (Scheme 1.7). This ortho deuteration was observed with other boronic acids in products 1.21 and 1.22. Formation of these products was hypothesized to occur via a 1,4-rhodium migration, which is a known process in rhodium catalysis. We speculated that electron deficient boronic acids favored reductive arylation because of increased acidity of the ortho C–H bond, which may facilitate oxidative insertion of rhodium(I). In accord with this reasoning, nearly exclusive 1,4-migration was observed with thienylboronic acid to give 1.22 in 87% yield.

![Scheme 1.7 Initial observations of deuterium incorporation.](image)

Since product 1.3 was initially observed during ligand screening, we examined the influence of ligand on the 1.2:1.3 product ratio. A trend was detected between this ratio and the electronic density of the phosphines in the ligand (Table 1.5). Josiphos ligands bearing electron-poor aromatic phosphines produced more reductive arylation product 1.3a (L3 and L4, entries 3 and 5). On the other hand, electron rich ligands gave mainly ring-opened product 1.2a (L1 and L2, entries 1 and 2). Upon examination of a related Walphos family of ligands, multiple 1,4-migrations were observed with L5 to give the byproduct 1.23 (entry 6, Table 1.5, Scheme 1.8). Formation of 1.23 can be explained by carborhodation / 1,4-migration followed by a reaction with a second equivalent of 1.1a, akin to the “merry-go-round” reactivity observed with norbornene under similar conditions.

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37 It should be noted that similar reactivity may have been occurring in the studies of Pineschi and coworkers, but it appears it was not investigated. See Bertolini, F.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* 2006, 47, 9173.

38 For a review on rhodium and palladium 1,4-shifts see: Ma, S.; Gu, Z. *Angew. Chem. Int. Ed.* 2005, 44, 7512; See section 1.3.1 for examples of this reactivity.

The chemoselectivity of the reaction was somewhat influenced by the solvent. Whereas the reductive arylation product was readily observed in THF, it either disappeared or diminished significantly in reactions run in a THF/toluene mixture (Table 1.4). Such an outcome suggested that coordinating solvents may favor rhodium C–H insertion by stabilizing a Rh(III) complex, while non-coordinating solvents favor ring-opening.

Formation of other disubstituted compounds, 1.24 and 1.25, occurred with 3-furylboronic acid and with Boc-protected 3-pyrrolylboronic acid. 1.24 formed through a 1.4-migration followed by ring-opening of a second equivalent of bicycle 1.1a. Formation of 1.23 could be decreased by slow addition of 1.1a (entry 7, Table 1.5). Overall, Walphos ligands were superior to Josiphos ligands at inducing 1,4-migration (entries 2 and 4, Table 1.5). This observation suggested that the bite angle, along with electronics, is an important factor in the observed chemoselectivity.

### Table 1.5 Chemodivergence between ring-opening and reductive arylation with variation in ligand structure.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>R</th>
<th>R’</th>
<th>Yield 1.2 (%)</th>
<th>Yield 1.3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L2</td>
<td>Cy</td>
<td>t-Bu</td>
<td>84</td>
<td>Trace</td>
</tr>
<tr>
<td>2</td>
<td>L1</td>
<td></td>
<td>t-Bu</td>
<td>70</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>L3</td>
<td></td>
<td>t-Bu</td>
<td>45</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td>L7</td>
<td></td>
<td>Cy</td>
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</tr>
<tr>
<td>8</td>
<td>L6</td>
<td></td>
<td></td>
<td>trace</td>
<td>51</td>
</tr>
</tbody>
</table>

* Reaction conditions as described in Table 1.1. All yields are isolated. 48% yield of 1.23. 61% yield of 1.23. PhB(OH)2 and diazabicycle 1.1a were added via syringe pump over 1 h.
Scheme 1.8 Polysubstituted compounds derived from repeated carborhodation of substrate. 1.24 was formed using L1. 1.23 and 1.25 were formed using L5.

A number of reductive arylation products could be synthesized (Table 1.6). Under the developed conditions, the yields and enantioselectivity were variable. With Walphos ligands, the enantioselectivity was not as high for ortho-substituted boronic acids as with L1. The use of a Josiphos ligand L1 still furnished moderate to good yields of products if electron withdrawing substituents were present.

Table 1.6 Enantioselective reductive arylation of diazabicycle 1.1a with substituted boronic acids.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Ar</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
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<td>1.3a</td>
<td>69</td>
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</tr>
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<td>L1</td>
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<td>L1</td>
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<td>65</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>L6</td>
<td>1.29a</td>
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<td>78</td>
<td></td>
</tr>
<tr>
<td>6&lt;sup&gt;d&lt;/sup&gt;</td>
<td>L1</td>
<td>1.20</td>
<td>66</td>
<td>99</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions as in Table 1.1. <sup>b</sup> All yields are isolated. <sup>c</sup> Enantioselectivity was determined by chiral HPLC. <sup>d</sup> Reaction performed by F. Menard.
As exclusive C–H insertion was observed with both 3-thienylboronic acid and 3-furylboronic acid, we anticipated that 3-pyrrolylboronic acid would be an appropriate candidate to study the electronic and steric influence of the aryl moiety by varying the nitrogen protecting group. In this case, boronic pinacol esters had to be used instead of boronic acids owing to the inherent instability of pyrrolylboronic acids.\(^{40}\) Surprisingly, unlike the other 5-membered heterocycles, pyrroles afforded considerably less reductive arylation product (Table 1.7). With the unprotected pyrrole 1.27a, the reaction proceeded with poor conversion (20% combined yield, entry 1).

**Table 1.7** Selectivity between ring-opening and reductive arylation with pyrrolylboronic esters bearing different protecting groups.*

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>(1.28) Yield (%)(^b)</th>
<th>(1.28) ee (%)(^c)</th>
<th>(1.29) Yield (%)(^b)</th>
<th>(1.29) ee (%)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H (a)</td>
<td>15</td>
<td>12</td>
<td>5</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>Me (b)</td>
<td>80</td>
<td>10</td>
<td>trace</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>TIPS (c)</td>
<td>87</td>
<td>30</td>
<td>11</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>Ac (d)</td>
<td>65</td>
<td>46</td>
<td>22</td>
<td>86</td>
</tr>
<tr>
<td>5</td>
<td>Boc (e)</td>
<td>68</td>
<td>37</td>
<td>30</td>
<td>80</td>
</tr>
</tbody>
</table>

* Reaction conditions as described in Table 1.1. \(^b\) Yield of isolated products. \(^c\) Enantiomeric excess determined by chiral HPLC.

The electron withdrawing or donating ability of the N-protecting group had a moderate influence on chemoselectivity. Overall, rhodium migration was faster in pyrroles with electron deficient protecting groups 1.27d and 1.27e. Thus more reductive arylation occurred with acylated and Boc-protected pyrrolylboronic esters, but in all cases the ring opened product 1.28 was favored with t-Bu-Josiphos (entries 4 and 5, Table 1.7).

A telling influence of steric effects was seen during deuterium quench experiments (Scheme 1.9). The reaction was performed in a THF/D\(_2\)O mixture, and deuterium incorporation was quantified in the reductive arylation products of the unprotected and the Boc-protected pyrroles

\(^{40}\) When the 3-pyrrolylboronic acid was prepared from N-TIPS-3-bromopyrrole, the colorless crystalline solid decomposed under vacuum to give a brown liquid.
(1.29a and 1.29e, respectively). In the case of the Boc protected 1.29e, deuteration occurred only at the β position, whereas in the unprotected example, 1.29a, deuterium was observed only at the α position. This strong steric effect may explain the lack of reductive arylation in pyrroles in comparison to other heterocycles. Although the α position carries the more activated C–H bond, the rhodium insertion is hindered by steric bulk of the protecting group. In the reaction with Boc-protected 1.27e, Josiphos (L1) led to deuterium incorporation exclusively at the β position, while with Walphos (L5) some deuteration was seen at the α position as well. This discrepancy demonstrated that, although similar, the two ligands have distinctly different steric demands.

**Scheme 1.9** Deuterium quench experiments conducted with pyrolyl- and N-Boc-pyrrolylboronic esters.

### 1.2.5 Mechanistic Considerations

The proposed mechanism for the reaction is illustrated in Scheme 1.10. Initially, transmetallation with the boronic acid gives rise to an arylrhodium species that coordinates to the alkene. The subsequent carborhodation is presumed to be irreversible and leads to formation of C. Complex C can ring-open to give product 1.2 or undergo a 1,4-rhodium migration to give arylrhodium intermediate E, which protodemeta
tates to yield 1.3. Similar 1,4-migration of rhodium has been reported previously.41

Chemodivergence arises following formation of complex C. Thereafter, the ring-opening and C–H activation are in competition. Our results show that outside of ligand control, rhodium 1,4-migration can be favored by: 1) using electron rich protecting groups on the hydrazine to reduce β-nitrogen elimination (Table 1.3); 2) using coordinating solvents to stabilize Rh(III) intermediate D (Table 1.2 and 1.4); and 3) utilizing σ-withdrawing groups on the aryl moiety to facilitate C–H insertion (Table 1.4). The formation of hydridorhodium intermediate D is supported by the observation of deuterium transfer between the aromatic position and the

---

41 See section 1.3.1 for examples of this reactivity.
bicyclic hydrazine when deuterated phenylboronic acid was used (Scheme 1.11). Moreover, deuterium experiments confirmed the validity of intermediate E. Conducting the reaction in a THF:D$_2$O mixture afforded ortho-deuterated products. These results were found to be consistent for several boronic acids (Scheme 1.7).

**Scheme 1.10** Proposed mechanism accounting for the formation of 1.2 and 1.3.

An intriguing observation was made in the pyrrolylboronic ester study. The enantioselectivities of 1.28 and 1.29 were not the same even though the two products likely form via a common intermediate C (Table 1.7). In fact, with these boronic acids, the minor reductive arylation product consistently had higher enantiomeric excess. This observation was perplexing, because it suggested that after formation of the diastereomeric intermediate C, the different diastereomers of the complex proceeded through ring-opening and migration at different rates.

**Scheme 1.11** Deuterium transfer experiment.
1.3 Development of Domino Reactions Featuring 1,4-Rhodium Migration

The observation of a 1,4-migration in the diazabicyclic products 1.3 has led us to question whether or not it is possible to use this C-H activation in a productive manner. We were initially intrigued by the prospect of developing a trimolecular coupling reaction, where the arylrhodium species is trapped by an external electrophile to give a product akin to 1.30 (Scheme 1.12). After considerable study of this reactivity, however, we found that this proposal was flawed, and only products such as 1.23 and 1.31 could be detected. To stack the odds in our favor we modified the strategy and looked into boronic acids with a general structure 1.32 containing an appended electrophile (Scheme 1.13).

![Scheme 1.12 Proposed trimolecular coupling reaction.](image)

![Scheme 1.13 Proposed domino reaction with intramolecular electrophile trapping.](image)

Although we were the first group to describe this 1,4-rhodium migration in bicyclic molecules capable of ring opening, there were previous reports of this reactivity in other rhodium and palladium catalyzed reactions.42

---

1.3.1 Prior Observations of Rhodium 1,4-Migration

In the last decade, a number of reports have described this type of reactivity and migration in rhodium and palladium species has been reviewed.\textsuperscript{43} The first report of a 1,4-migration of a rhodium species was reported Miura.\textsuperscript{44} He observed that if phenylboronic acid was subjected to rhodium catalysis in the presence of norbornene, the reaction furnished products of several carborhodation/migration steps (Eqn 1.14). In fact it was nearly impossible to obtain any mono-substituted product.

Soon thereafter, similar reactivity was observed by Hayashi in reactions of arylboronic acids and alkynes.\textsuperscript{45} After formation of a vinylrhodium species, the rhodium migrated to the ortho aromatic position, and the arylrhodium intermediate could be trapped with deuterium. In the presence of excess alkyne, products featuring 1,4-migration and addition to a second equivalent of alkyne could be isolated (Scheme 1.14). Since this report, a number of examples describing similar alkenyl to aryl migrations, in rhodium intermediates, have been reported.\textsuperscript{46}

![Scheme 1.14 First observation of vinyl to aryl migration.](image-url)

Since these initial reports, a number of interesting applications of this migration have been reported. In 2005, the Hayashi and Iwasawa groups independently reported the synthesis of indanones from arylpropargylic alcohols (Scheme 1.15).47 A noteworthy feature in both reports was the use of a monodentate ligand. Previous reports of rhodium 1,4-migrations required the bidentate ligands to obtain high yields. Different versions of this reaction featuring β-carbon eliminations or using chiral ligands to give enantiomerically enriched products were reported soon thereafter.48

![Scheme 1.15](https://example.com/scheme115.png)

**Scheme 1.15** Synthesis of indanones through vinyl to aryl 1,4-migration.

Murakami reported a synthesis of dihydronaphthalenones through an addition of tetraphenylborate sodium salts across alkynes (Scheme 1.16). A subsequent 1,4-migration yielded an arylrhodium intermediate, which reacted with a pendant ester group to give the final product.49

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In 2009, two independent reports from the Cramer and Murakami groups described a productive trapping following a 1,4-migration from an alkyl to an aryl position (Scheme 1.17). The reactions relied on strain to facilitate a β-carbon elimination which led to an alkylrhodium species A. This intermediate underwent a 1,4-rhodium shift giving an arylrhodium intermediate B capable of reacting with an appended ketone moiety. This 1,2-addition could be rendered enantioselective if an appropriate Josiphos ligand was used.

In most of the above examples the mechanism of 1,4-migration was proposed to proceed through oxidative insertion and reductive elimination, which was usually supported through deuterium transfer. Recently, Hayashi and Kantchev reported a computational study of a 1,4-migration.

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from an alkenyl to an aryl position in styrylboronic acids (Eqn 1.15). These studies supported the proposed mechanism of C-H insertion. The arylrhodium species was calculated to be 3 kcal/mol lower in energy than the corresponding vinylrhodium species. The calculations also suggested that, in this specific system, the 1,4-migration was reversible.

\[
\begin{align*}
\text{[Rh(bod)Cl]_2} (2.5 \text{ mol\%}) & \quad \text{Cs_2CO_3} (1.5 \text{ equiv}) \\
\text{dioxane/H_2O (20:1)} & \quad 70^\circ\text{C}, 4 \text{ h} \\
\text{A} & \quad \text{B} \\
\text{bod = (1S,4S)-bicyclo[2.2.2]octa-2,5-diene} \\
\end{align*}
\]

98% yield
A:B >99:1

1.3.2 Reaction Development

Over the course of our studies, we synthesized several different boronic acids of general structure 1.32 (Scheme 1.13). The most successful analogue 1.36 contained an α,β-unsaturated alkene as the electrophilic acceptor. This boronic acid was synthesized in several steps from substituted aromatic compound 1.33 (Scheme 1.18). The optimal way to install the boronic ester was through lithium-halogen exchange followed by trapping with triisopropoxyborate. The use of the TBS protecting group was instrumental in this reaction, and attempts of conducting protecting group-free syntheses furnished very low yields. After deprotection, compound 1.35 was acylated with an appropriate acyl chloride. A challenging aspect of synthesizing 1.36 was its instability on silica, and purification through crystallization was preferred.

\[
\begin{align*}
\text{OTBS} & \quad \text{a) n-BuLi (1.2 equiv)} \\
& \quad \text{B(Oi-Pr)_3 (1.2 equiv)} \\
\text{THF/PhMe, \text{–78 °C},} & \quad \text{b) HCl(\text{aq})} \\
& \quad \text{c) pinacol, DCM} \\
\text{OMe} & \quad \text{R = TBS} \\
\text{OMe} & \quad \text{R = H} \\
\text{1.33} & \quad \text{1.34} \\
\text{HCl (1%) in MeOH} & \quad \text{1.35 up to 60\% over 2 steps} \\
\text{} & \quad \text{methacryloyl} \\
& \quad \text{chloride (1.2 equiv)} \\
& \quad \text{NEt}_3 (1.2 \text{ equiv}) \\
& \quad \text{DCM, 0 °C} \\
\text{1.36} & \quad \text{80\%}
\end{align*}
\]

Scheme 1.18 Substrate synthesis

Next, we examined the reactivity of 1.36 with bicyclic hydrazine 1.1a (Scheme 1.19). A mixture of products was observed, and we detected both a ring-opened and a bicyclic product in the reaction mixture. To simplify the system and eliminate the possibility of competitive ring opening, we subjected 1.36 to a reaction with norbornene instead of 1.1a. To our gratification, the desired domino product 1.38 was isolated as the major product in good yield. The exo addition was noteworthy; to date there are no examples featuring a rhodium-catalyzed addition akin to this.$^{52}$

![Scheme 1.19 Reactions of 1.36 with bicyclic alkenes.](image)

With this promising result in hand, we spent considerable time examining the scope of the transformation. We found, however, that the results were poor when we modified any portion of the substrate structure. The major problems encountered in this transformation were the competitive protodemetalations of arylrhodium species either before addition to norbornene or before addition to the alkene moiety, giving products 1.39 and 1.40 (Scheme 1.20). Limiting the amount of water was important to suppress the formation of these products, but conducting the reaction in the absence of water led to incomplete conversion.

---

When we examined the reaction of substrate 1.41 with norbornadiene, we found that the reaction worked in moderate yields, giving a diastereomeric mixture of products 1.42a and 1.42b (Scheme 1.21). The use of norbornadiene was essential to allow estimation of yields and diastereomeric ratios by NMR, using the characteristic alkene peaks for analysis.

We opted to examine the effect that the ligand has on the diastereoselectivity and enantioselectivity of the transformation (Table 1.8). Despite considerable screening, the reaction proceeded in only moderate yields, and the diastereoselectivity was always low. Using t-Bu-Josiphos (L1), the two products could be obtained in high enantiomeric excess (entry 3). Based on our work on reactions of ortho-substituted boronic acids with bicyclic alkenes, it is likely that L1 facilitates selective addition to norbornadiene. In reaction of 1.41 it is probable that the enantiocontrol of addition to the pendant alkene is low. Our attempts at cleaving norbornadiene through a retro-Diels Alder reaction to give a product with a single stereocenter furnished exceedingly low yields of a racemic product.

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53 The relative stereochemistry of the two diastereomeric products was not assigned and they were numbered arbitrarily.
Table 1.8 Diastereoselectivity and enantioselectivity in reactions of $\text{1.41}^a$.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Yield (%) $^b$</th>
<th>d.r. $^c$</th>
<th>ee (%) $^d$</th>
<th>ee (%) $^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(+/-) BINAP</td>
<td>48</td>
<td>1.9 : 1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>(S)-BINAP</td>
<td>50</td>
<td>2.2 : 1</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>t-Bu-Josiphos</td>
<td>56</td>
<td>2.5 : 1</td>
<td>98</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>MeO-Biphep</td>
<td>54</td>
<td>2.5 : 1</td>
<td>83</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>P-Phos</td>
<td>61</td>
<td>2.3 : 1</td>
<td>83</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>Segphos</td>
<td>52</td>
<td>2.2 : 1</td>
<td>86</td>
<td>84</td>
</tr>
<tr>
<td>7</td>
<td>Walphos</td>
<td>35</td>
<td>1.8 : 1</td>
<td>32</td>
<td>40</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: A stock solution of $[\text{Rh(cod)OH}]_2$ and ligand (1.2 equiv to $[\text{Rh}]$) was premixed at 50 °C for 15 minutes in THF. This solution (5 mol% $[\text{Rh}]_2$) was added to a vial containing 1.41 and norbornadiene in THF. The reaction was heated at 60 °C for 5 h. $^b$ Determined from crude NMR using 4-nitroacetophenone as internal standard. $^c$ Determined from crude NMR using alkene protons in 1.42. $^d$ Determined using chiral HPLC.

We successfully proved that it is possible to exploit the 1,4-migration of rhodium in a productive manner. However, the scope of the transformation remains limited. Further efforts in studying this reaction may expand this method to give more useful products.

1.4 Conclusions

In summary, a rhodium catalyzed chemodivergent desymmetrization of diazabicycles with boronic acids was developed. Ring-opening gave access to substituted cyclopentenes, while reductive arylation accessed precursors to trisubstituted cyclopentanes. Significantly, the ring-opening proceeded in high yield and ee with electron rich, ortho-substituted boronic acids. Reductive arylation products could be isolated in moderate to high yields, with electron deficient boronic acids. Ligand control over the two competing reaction pathways was observed, and electron deficient Walphos-type ligands favored the 1,4-migration, leading to the reductive arylation product.

It was found that the 1,4-migration of rhodium, which involved an aromatic C-H activation, could be applied in a domino reaction, where after migration, the arylrhodium species could be trapped intramolecularly with an electrophilic alkene. Even though an extensive scope of this transformation was not achieved, it serves as a “proof-of-concept” of this idea.

More detailed tuning of the ligand structure could lead to the development of Josiphos ligands specialized for additions of meta, para and unsubstituted boronic acids. Considering that this
transformation gives products with high stereochemical complexity, it should be possible to apply this reactivity to target synthesis.
1.5 Experimental Section

**General Experimental Procedures.** Unless otherwise noted, reactions were carried out under argon atmosphere, in flame-dried, single-neck, round bottom flasks fitted with a rubber septum, with magnetic stirring. Air- or water-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Where necessary (so noted), solutions were deoxygenated by successive freeze-pump-thaw cycles (≥ three iterations). Organic solutions were concentrated by rotary evaporation at 23–40 °C under 40 Torr (house vacuum). Analytical thin layer chromatography (TLC) was performed with Silicycle™ normal phase glass plates (0.25 mm, 60-A pore size, 230-400 mesh). Visualization was done under a 254 nm UV light source and generally by immersion in acidic aqueous-ethanolic vanillin solution, or in potassium permanganate (KMnO₄), followed by heating using a heat gun. Purification of reaction products was generally done by flash chromatography with Silicycle™ Ultra-Pure 230-400 mesh silica gel, as described by Still et al.⁵⁴

**Materials.** Unless otherwise indicated, starting materials and catalysts were obtained from Aldrich, Strem or VWR and used without further purification. Tetrahydrofuran, 1,4-dioxane and toluene were purified by distillation under N₂ from Na/benzophenone immediately prior to use.

**Instrumentation.** Proton nuclear magnetic resonance spectra (¹H NMR) and carbon nuclear magnetic resonance spectra (¹³C NMR) were recorded at 23 °C with a Bruker Avance III 400 (400 MHz/100 MHz) NMR spectrometer equipped with a ATM BBOF probe, a Varian Mercury 400 (400 MHz/100 MHz) NMR spectrometer equipped with a Nalorac4N-400 probe, a Varian Unity 500 (500 MHz/125 MHz) NMR spectrometer equipped with a Nalorac3-500 probe, or a Varian 400 (400 MHz/100 MHz) NMR spectrometer equipped with ATB8123-400 probe. Recorded shifts for protons are reported in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvents (CHCl₃: δ 7.26, CHDCI₂: δ 5.29, C₆HD₅: δ 7.15, CD₂HOD: δ 3.30). Chemical shifts for carbon resonances are reported in parts per million (δ scale) downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent (CDCl₃: δ 77.0, CH₃Cl: δ 53.8, C₆D₆: δ 128.0, CD₃OD: δ 49.2). Data are represented as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintuplet, sx = sextet, sp = septuplet, dd = doublet of doublets, m = multiplet, br = broad), and coupling constant (J, Hz). Infrared (IR) spectra were obtained using a Perkin-Elmer Spectrum 1000 FT-IR spectrometer as a neat film on a NaCl plate. Data is presented as follows: frequency of absorption (cm⁻¹). High resolution mass spectra were obtained from a SI2 Micromass 70S-250 mass spectrometer (EI) or an ABI/Sciex Qstar mass spectrometer (ESI). Melting points were taken on a Fisher-Johns melting point apparatus and are

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uncorrected. Optical rotations were measured in a 10.0 cm cell with a Rudolph Autopol IV polarimeter digital polarimeter equipped with a sodium lamp source (589 nm), and are reported as follows: $[\alpha]_D^{T \circ C} \ (c = g/100 \ mL, \ solvent)$.

**Determination of the Enantiomeric Excesses by HPLC Analysis.** The enantiomeric excess (ee) of the ring-opened and reductive arylation products was determined by HPLC analysis after chromatographic purification on silica-gel (see following section for details). Unless otherwise noted, enantiomeric excesses of the bis-protected hydrazine products were determined using analytical chiral columns from Daicel Chemical Industries Ltd, (fitted with a matching 5.0 cm guard column), at 25 ºC with 4.0 µL injections of sample solution of approximately 2 mg/mL. The HPLC system was a HP 1100 Series modular system from Agilent, operated by a ChemStation LC 3D software, v. 10.02.

**1.5.1 Characterization Data and Experimental Procedures**

**Procedure 1.1:** General procedure for the desymmetrization of diazabicyclo[2.2.1]heptenes (1.1) by rhodium-catalyzed allylic substitution with organoboron nucleophiles.

In a representative example: to a 10 mL round-bottom flask equipped with a magnetic stir bar was added $[\text{Rh} \text{cod} \text{OH}]_2$ (3.1 mg, 0.0067 mmol), tert-Bu-Josiphos (L1) (8.8 mg, 0.016 mmol). The vial was flushed with argon (balloon) and distilled THF (1.0 mL) and $\text{H}_2\text{O}$ (0.2 mL) were added. The clear orange solution was stirred at room temperature for 15-20 min. Diazabicyclo[2.2.1]heptene dicarbamate 1.1a (40 mg, 0.135 mmol) and the arylboronic acid (0.20–0.27 mmol, 1.5–2.0 equiv) were added together as a solution in distilled THF (0.80 mL of a freshly prepared stock solution) and the darkening reaction mixture allowed to react at r.t. (or 0 ºC). After 16 h, TLC showed full consumption of 1.1a (20% EtOAc/Hex; acidic vanillin stain). The reaction mixture was filtered on a short silica gel pad (~2 g), washing with four portions of EtOAc. The filtrate was concentrated under reduced pressure, then was applied to the top of a column of silica gel and purified by column chromatography (5-10-20% EtOAc/hexane as elution gradient). The ring-opened hydrazine 1.2a (Note 3) was recovered as a colorless oil, 43 mg (85%). The enantiomeric excess was determined on the purified product (*vide infra*).

**Note 1:** NMR analysis displayed very broad peaks for all ring-opened and reductively arylated products due to: (i) rotamers of the bis-carbamate hydrazine moiety, (ii) conformers equilibrium for some products, and (iii) atropisomers for some compounds bearing aromatic ortho-substituents. Resolution for both $^1H$ and $^{13}C$ NMR spectra did not improve significantly when temperature was varied; most likely due to differential coalescence temperature of the multiple

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55 The reaction vessel must remain unopened, as the active catalyst in solution appears sensitive to oxygen traces.
conformers. Doubling of signals was often observed: the word ‘and’ is used specifically to signify extra peaks arising from rotamers in the spectra.

Note 2: Alternatively, the reaction was performed in a 1 or 2 dram screw-cap vial equipped with a stirring bar (flea) and fitted with a septum or a screw cap with a Teflon septum.

Note 3: The same protocol was used to obtain the reductive arylation products akin to 1.3a, only different ligands were utilized.

Characterization Data

Diazabicyclo[2.2.1]hept-5-ene-dicarbamates 1.1a, 1.1b, 1.1c and 1.1d were prepared in quantitative yields by Diels-Alder reactions between freshly distilled cyclopentadiene and the corresponding azadicarbamates at r.t. according to literature procedures and characterization data were fully consistent with that previously reported. Full characterization data and traces for compounds 1.6, 1.9-1.16, 1.20-1.22 are available. All compounds were prepared according to the general procedure described above unless stated otherwise. The assignment of relative and absolute stereochemistry for compounds synthesized with L1 ligand is determined by analogy. Compound 1.2a was deprotected and reduced and the optical rotation of the resultant cyclopentylamine was compared with literature.

Di-tert-butyl 5-phenyl-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (1.3a)

\[
\text{NBoc} \quad \text{NBoc}
\]

In a 10 mL round bottom flask, a solution of [Rh(cod)OH]₂ (2.3 mg, 0.005 mM) and (R,R)-Walphos (L5) (11.2 mg, 0.012 mM) in THF (2 ml) and H₂O (0.5 ml) was stirred for 15 minutes. A solution of phenylboronic acid (24.4 mg, 0.2 mM) and 1.1a (29.6 mg, 0.1 mM) in THF (1 ml) was added to the reaction mixture using a syringe pump over the course of 1 hour. The solution was further stirred for 3 hours, after which the reaction mixture was extracted with ethyl acetate (2x) and concentrated. Flash column chromatography (pentanes:EtOAc - 9:1) yielded the titled compound in 69% yield (26 mg) as a colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 7.27-7.18 (m, 2H), 7.18-7.07 (m, 3H), 4.74-4.18 (m, 2H), 3.47-3.09 (m, 1H), 2.27-1.96 (m, 1H), 1.77-1.54 (m, 1H), 1.53-1.32 (m, 20H); ¹³C NMR (126 MHz, CDCl₃) δ 156.34 (m, 2), 141.8 and 140.9(rotamers), 128.4 (2), 126.7 (2), 126.3, 81.1 (2), 66.0 and 64.9 (m, rotamers), 60.9 and 60.1 (m, rotamers), 45.9 and 44.6 (m, rotamers), 36.0 (m), 34.2 and 32.4 (rotamers), 28.0 (6); IR (NaCl, neat): 3002, 2972, 1723, 1690, 1473, 1452, 1370, 1347, 1318, 1256, 1158, 1120, 1106, 853, 755 cm⁻¹. HRMS (ESI): calc'd for

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C$_{21}$H$_{31}$N$_2$O$_4$ (M+H)$^+$: 375.2278; found: 375.2296; $[\alpha]_D^{27.8} = +5.98$ (c 1.64, CHCl$_3$) for 83:17 er, as determined by HPLC analysis: (Chiralcel AD, isocratic 6% i-PrOH/hexane, 0.80 mL/min, 225 nm); $t_R = 8.8$ min (minor), $t_R = 11.3$ min (major).

**Di-tert-butyl 1-((2,6-difluorophenyl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (1.7)**

The compound was prepared using the general procedure. Using ($R,R$)-Walphos (L5) as chiral ligand, and a mixture of THF/water (10:1) as solvent, the bis-protected hydrazine was obtained as a colorless oil in 86% yield (35 mg). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.15 (1H, q, $J = 6.8$ Hz), 6.83 (2H, t, $J = 8.0$), 6.23 and 5.98 (1H, coalescing br.s), 5.79 (1H, m), 5.68 (1H, m), 5.03 (1H, br.s), 4.28 (1H, br.m), 2.65 (2H, m), 1.48 (9H, s), 1.25 (9H, br.s); $^13$C NMR (100 MHz, CDCl$_3$): $\delta$ 162.1 (d, $J = 61.5$ Hz), 162.0 (d, $J = 61.2$ Hz), 156.1, 155.0, 130.8, 129.3, 128.2, 118.2, 111.7, 111.5, 81.4 (2), 65.5 and 64.4 (br, rotamers), 42.6, 34.9, 28.4 (3), 28.1 (3); IR (NaCl, neat): 3302, 2977, 2930, 1747, 1711, 1465, 1369, 1163 cm$^{-1}$; HRMS (ESI): calcd for C$_{21}$H$_{28}$N$_2$O$_4$F$_2$: 433.1909; found: 433.1915; $[\alpha]_D^{29.2} = +115.7$ (c 1.17, CHCl$_3$) for 91.0:9.0 er, as determined by HPLC analysis: (Chiralcel AD, isocratic 15% i-PrOH/hexane, 0.8 mL/min, 225 nm); $t_R = 14.15$ min (major), $t_R = 30.5$ min (minor).

**Di-tert-butyl 1-((2-chlorophenyl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (1.8)**

Using ($R$,S)-tert-Bu-Josiphos (L1) as chiral ligand, and a mixture of THF/water (10:1) as solvent, the bis-protected hydrazine was obtained as a colorless oil in 40% yield (16 mg). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.31 (1H, d, $J = 7.6$ Hz), 7.24 (2H, m), 7.15 (1H, m), 6.31 (1H, br. s), 5.90 (1H, m), 5.60 (1H, s), 4.71 (1H, m), 4.42 (1H, m), 2.64 (2H, m), 1.49 (9H, s), 1.25 (9H, coalescing doublet, $J = 103$ Hz); $^13$C NMR (100 MHz, CDCl$_3$): $\delta$ 156.3, 155.0, 141.2, 133.8, 131.5, 131.3, 129.2, 128.6, 127.8, 127.3, 81.2 (2), 68.4 and 66.0 (br, rotamers), 49.2, 35.2, 28.2 (3), 27.8 (3); IR (NaCl, neat): 3271, 2977, 2930, 1742, 1708, 13909, 1365, 1155 cm$^{-1}$; HRMS (ESI): calcd for C$_{21}$H$_{29}$N$_2$O$_4$F$_2$Na (M+Na)$^+$: 433.1909; found: 433.1915; $[\alpha]_D^{29.2} = +115.7$ (c 1.17, CHCl$_3$) for 91.0:9.0 er, as determined by HPLC analysis: (Chiralpak AD, isocratic 10% i-PrOH/hexane, 0.8 mL/min, 225 nm); $t_R = 14.0$ min (major), $t_R = 18.1$ min (minor).

**2,3-Di-tert-butyl 5,5'-(1,2-phenylene)bis(2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate) (1.23)**

Using ($R,R$)-Walphos (L5) as chiral ligand, and a mixture of THF/water (10:1) as solvent, the hydrazine was obtained as a colorless oil in 61% yield (21 mg). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.17 (m, 2H), 7.08 (m, 2H), 4.57 (m, 4H), 3.41 (m, 2H), 2.42 (m, 2H), 1.93 (m, 2H), 1.75 (m, 2H), 1.60 (m, 2H), 1.46 (s, 9H), 1.43 (m, 9H); $^13$C NMR (126 MHz, CDCl$_3$) $\delta$ 156.0 (m, 4), 141.2 (2),
126.5 (2), 125.2 (2), 81.3 (br, 4), 64.0 (2), 41.2 (m, 2), 37.3 (m, 4), 28.2 (6), 27.9 (6); IR (NaCl, neat): 3002, 2971, 1744, 1731, 1716, 1700, 1473, 1345, 1318, 1256, 1158, 1129, 850, 755 cm⁻¹; HRMS (ESI): calcd for C_{36}H_{55}N_{4}O_{8} (M+H)^+: 671.4014; found: 671.4033; [α]_{D}^{27.8} = +5.85 (c 1.504, CHCl₃).

2,3-Di-tert-butyl 5,5’-(1,2-phenylene)bis(2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate) (d⁵-1.23)

Using (R,R)-Walphos (L₅) as chiral ligand, and a mixture of THF/H₂O (10:1) as solvent, bishydrazine was obtained as a colorless oil in 64% yield (22 mg). In order to quantify the extent of deuteration at the aromatic positions the hydrazines were deprotected.

1,2-di(2,3-diazabicyclo[2.2.1]heptan-5-yl)benzene (d⁵-1.23b)

Compound d⁵-1.23 (21 mg) was dissolved in DCM (0.15 M) and cooled to 0°C. Trifluoroacetic acid (0.15M, 214 μl) was added dropwise and the mixture was stirred for 30 minutes. TLC revealed full consumption of starting material. After evaporation of the liquids, the mixture was quenched with NaHCO₃ and extracted with EtOAc. The organic phase yielded the titled product as a colorless oil in 36% yield (5 mg). 

Di-tert-butyl 5-(2-(5-(1,2-bis(tert-butoxycarbonyl)hydrazinyl)cyclopent-2-enyl)furan-3-yl)-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (1.24)

Using (R,S)-tert-Bu-Josiphos (L₁) as chiral ligand, and a mixture of THF/water (10:1) as solvent, the hydrazine was obtained as a colorless oil in 68% yield (23 mg) as a mixture of 2 diastereomers (1: 0.44). ^1H NMR indicated the presence of 2 diastereomers in a ratio of 1:0.75. ^1H NMR (400 MHz, CDCl₃): δ 7.20 and 7.18 (s, 1H), 5.30 and 5.27 (br. s, 2H), 5.19 and 5.18 (br. s, 2H), 2.54 and 2.41 (d, J = 9.1 Hz, 2H), 1.69 – 1.62 (m, 2H), 1.60 – 1.50 (m, 2H), 1.46 – 1.36 (m, 2H).
2,3-Di-tert-butyl 5,5’-(1-(tert-butoxycarbonyl)-1H-pyrrole-3,4-diyl)bis(2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate) (1.25)

Using (R,R)-Walphos (L5) as chiral ligand, and a mixture of THF/water (10:1) as solvent, the protected hydrazine was obtained as a colorless oil in 74% yield (28 mg). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.85 (br. s, 2H), 4.72-4.30 (m, 4H), 3.30-2.86 (m, 2H), 2.56-2.15 (m, 2H), 1.88-1.65 (m, 2H), 1.56 (br. s, 13H), 1.46 (br. s, 36H); $^{13}$C NMR (126 MHz, CDCl$_3$)$\delta$ 157.7-155.2 (m, 2), 148.5, 128.6 (br), 115.4 (br), 83.9, 81.7-80.9 (m, 4), 63.7 (br. 2), 60.5 (br. 2), 38.3-33.9 (m, 6), 28.2 (br. 6), 28.1 (br. 6), 27.9 (3); IR (NaCl, neat): 3002, 2972, 1734, 1695, 1475, 1449, 1375, 1346, 1279, 1256, 1158, 755 cm$^{-1}$; HRMS (ESI): calcd for C$_{39}$H$_{62}$N$_5$O$_{10}$ (M+H)$^+$: 760.4491; found: 760.4522; $[\alpha]_D^{27.8} = -4.23$ (c 1.14, CHCl$_3$).

Di-tert-butyl 5-(2-chlorophenyl)-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (1.26)

Using (R,S)-tert-Bu-Josiphos (L1) as chiral ligand, and a mixture of THF/water (10:1) as solvent, the bis-protected hydrazine was obtained as a colorless oil in 47% yield (19 mg). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.38 (1H, d, $J = 7.62$ Hz), 7.18 (3H, m), 4.88-4.41 (2H, m), 3.59 (1H, m), 2.49 (1H, m), 1.79 (2H, br. s), 1.52 (10H, s), 1.49 (9H, s); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 167.6, 155.9 (2), 130.4, 120.3, 115.6, 113.4, 81.7 and 81.4 (2, rotamers), 65.2 and 64.5 (br, rotamers), 60.9 and 60.3 (rotamers), 39.4 and 38.2 (rotamers), 35.4 and 34.8 (rotamers), 28.4 (6); IR (NaCl, neat): 2977, 2930, 1734, 1716, 1698, 1367, 1341, 1155 cm$^{-1}$; HRMS (ESI): calcd for C$_{21}$H$_{29}$N$_2$O$_4$Na (M+Na)$^+$: 431.1708; found: 431.1712; $[\alpha]_D^{27.1} = +36.4$ (c 0.885, CHCl$_3$) for >99.4:0.6 er, as determined by HPLC analysis: (Chiralcel AD, isocratic 4% $i$-PrOH/hexane, 0.8 mL/min, 230 nm); $t_R = 11.83$ min (minor), $t_R = 23.32$ min (major).

1-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole (1.27b)

Pyrrolylboronic pinacol ester 1.27a (1.6 mM, 300 mg) and methyl iodide (2.4 mM, 150 μL) were dissolved in THF (1 M) and added dropwise using a syringe pump to a suspension of NaH (2.15 mM, 54 mg) in THF (0.5 M) at 0 °C. The mixture was stirred at 0 °C for 10 min, then warmed to room temperature and stirred for another 1.5 hours. The reaction was quenched with aqueous NH$_4$Cl, extracted with ethyl acetate, washed with brine and dried with Na$_2$SO$_4$. After evaporation under reduced pressure, flash column chromatography (95:5 Pentanes:EtOAc) yielded the titled compound as a colorless solid in 67% yield (223 mg). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.05 (1H, s), 6.63 (1H, t, $J = 2$ Hz), 6.47 (1H, t, $J = 1.6$ Hz), 3.65 (3H, s), 1.30 (12H, s); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 131.1, 123.1, 114.5, 83.0, 36.2, 25.0; IR (NaCl, neat): 2977, 2930, 1543, 1289, 1253, 1142 cm$^{-1}$; M.p. 55-58 °C; HRMS (EI): calcd for C$_{11}$H$_{18}$BNO$_2$ (M$^+$): 207.1431; found: 207.1422.
A solution of pyrrolylboronic pinacol ester 1.27a (1.5 mM, 290 mg) in THF (1 M) was added dropwise to a suspension of NaH (2.25 mM, 57 mg) in THF (0.5 M) at 0 °C. After 30 minutes, acetyl chloride (3.5 mM) was added. The mixture was allowed to warm to room temperature and stirred for 1 hour. The reaction was quenched with saturated NH₄Cl, extracted with ethyl acetate, and dried with Na₂SO₄. After removal of the solvent under reduced pressure, flash chromatography (9:1 Pentanes:EtOAc) yielded the product as a colorless oil in 25% yield (88 mg). ¹H NMR (400 MHz, CDCl₃): δ 7.65 (1H, s), 7.36 (1H, s), 6.53 (1H, dd, J = 1.4, 3.1 Hz)), 2.54 (3H,s), 1.32 (12H, s); ¹³C NMR (126 MHz, CDCl₃): δ 167.7, 128.2, 119.9, 117.3, 83.5, 24.9, 22.6; IR (NaCl, neat): 2977, 2930, 1721, 1563, 1488, 1375, 1308, 1277, 1142 cm⁻¹; HRMS (ESI): calcd for C₁₂H₁₉BNO₃ (M+H)⁺: 236.1452; found: 236.1462.

Di-tert-butyl 1-(2-(1H-pyrrol-3-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (1.28a)

Using (R,S)-tert-Bu-Josiphos (L1) as chiral ligand, and a mixture of THF/water (10:1) as solvent, the bis-protected hydrazine was obtained as a colorless oil in 15% yield (4 mg). For characterization purposes, 1.28a, was prepared through deprotection of 1.28c (TBAF (1.05 equiv) in THF (0.25 M) quantitative yield). The ¹H NMR data was consistent between the two compounds. ¹H NMR (400 MHz, CDCl₃): δ 8.47 (1H, br.s), 6.70 (1H, q, J = 2Hz), 6.65 (1H, br.s), 6.37 and 6.24 (1H, coalescing br.s), 6.10 (1H, s), 5.72 (2H, m), 4.75 (1H, m), 3.88 (1H, m), 2.56 (2H, m), 1.47 (9H, s), 1.38 (9H, m); ¹³C NMR (100 MHz, CDCl₃): δ 155.9, 155.3, 134.0, 128.5, 125.4, 118.2, 115.0, 107.4, 81.2 (2), 67.8 and 65.0 (br, rotamers), 46.1, 35.2, 28.4 (3), 28.3 (3); IR (NaCl, neat): 3354, 2982, 2925, 1726, 1690, 1475, 1452, 1372, 1349, 1315, 1163, 1132, 755 cm⁻¹; HRMS (ESI): calcd for C₁₉H₃₀N₃O₄ (M+H)⁺: 364.2230; found: 364.2249; [α]D²⁷.⁷ = −8.76 (c 0.55, CHCl₃) for 56.0:42.0 er, as determined by HPLC analysis: (Chiralcel AD, isocratic 35% i-PrOH/hexane, 0.80 mL/min, 230 nm); tₐ = 14.23 min (major), tᵣ = 22.40 min (minor).

Di-tert-butyl 1-(2-(1-methyl-1H-pyrrol-3-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (1.28b)

Using (R,S)-tert-Bu-Josiphos (L1) as chiral ligand, and a mixture of THF/water (10:1) as solvent, the bis-protected hydrazine was obtained as a colorless oil in 80% yield (31 mg). ¹H NMR (400 MHz, CDCl₃): δ 6.48 (2H, m), 6.26 and 6.1 (1H, coalescing br. s), 6.00 (1H, br. s), 5.71 (1H, m), 4.88-4.53 (1H, m), 4.05-3.7 (1H, m), 3.57 (3H, s), 2.60 (1H, m), 2.50 (1H, m), 1.47 (9H, s), 1.40 (9H, br.s); ¹³C NMR (100 MHz, CDCl₃): δ 155.8, 155.0, 133.9, 128.3, 125.9, 121.9, 119.0, 107.5, 81.3 (2), 67.7 and 65.2 (br, rotamers), 46.2, 36.2, 35.3, 28.4 (3), 28.3 (3); IR (NaCl, neat): 3314, 2987, 2971, 2920, 1724, 1695, 1475, 1385, 1250, 1158, 756 cm⁻¹; HRMS (EI): calcd for C₂₀H₃₁N₅O₄
(M)$^+$: 377.2315; found: 377.2314; $[\alpha]_D^{25.6} = +7.27$ (c 1.05, CHCl$_3$) for 54.5:45.5 er, as determined by HPLC analysis: (Chiralcel AD, isocratic 20% i-PrOH/hexane, 0.8 mL/min, 225 nm); $t_R = 13.8$ min (major), $t_R = 18.6$ min (minor).

**Di-tert-butyl 1-(2-(1-(triisopropylsilyl)-1H-pyrrol-3-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (1.28c)**

Using $(R,S)$-tert-Bu-Josiphos (L1) as chiral ligand, and a mixture of THF/water (10:1) as solvent, the bis-protected hydrazine was obtained as a colorless oil in 86% yield (260 mg). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.68 (1H, t, $J = 2.3$Hz), 6.58 (1H, br. s), 6.26 (1H, br. s), 6.17 (1H, m), 5.72 (2H, m), 4.76 (1H, m), 3.87 (1H, m), 2.58 (1H, m), 2.48 (1H, m), 1.47 (9H, s), 1.38 (10H, m), 1.07 (12H, d, $J = 7.5$Hz); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 156.2 and 155.8 (2, rotamers), 154.9, 134.0, 128.3, 127.6, 124.4, 120.8, 110.1, 81.5 and 80.9 (br. rotamers), 67.6 and 64.7 (br. rotamers), 46.1, 35.2, 28.3, 18.1, 11.8; IR (NaCl, neat): 2946, 2863, 1737, 1697, 1367, 1336, 1157, 1104 cm$^{-1}$; HRMS (ESI): calcd for C$_{28}$H$_{50}$N$_3$O$_4$Si (M+H)$^+$: 520.3565; found: 520.3587; $[\alpha]_D^{26.3} = -25.9$ (c 1.20, CHCl$_3$) for 63.0:37.0 er, as determined by HPLC analysis: (Chiralcel AD, isocratic 5% i-PrOH/hexane, 0.8 mL/min, 220 nm); $t_R = 11.6$ min (major), $t_R = 16.6$ min (minor).

**Di-tert-butyl 1-(2-(1-acetyl-1H-pyrrol-3-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (1.28d)**

Using $(R,S)$-tert-Bu-Josiphos (L1) as chiral ligand, and a mixture of THF/water (10:1) as solvent, the bis-protected hydrazine was obtained as a colorless oil in 65% yield (27 mg). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.17 (1H, m), 7.08 (1H, m), 6.42 (1H, br. s), 6.21 (1H, m), 5.71 (1H, br. s), 5.62 (1H, br. s), 4.69 (1H, br. s), 3.80 (1H, m), 2.53 (1H, m), 2.47 (1H, m), 2.41 (3H, s), 1.41 (9H, s), 1.34 (9H, br. s); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 167.8, 155.8, 155.0, 132.3, 130.9, 129.6, 119.7, 116.0, 113.6, 81.3 and 81.1 (2, rotamers), 66.3 and 64.6 (br, rotamers), 46.0, 35.2, 28.3 (3), 30.4 (3), 22.3; IR (NaCl, neat): 3307, 2977, 2930, 1742, 1706, 1331, 1158 cm$^{-1}$; HRMS (ESI): calcd for C$_{21}$H$_{31}$N$_3$O$_5$Na (M+Na)$^+$: 428.2155; found: 428.2154; $[\alpha]_D^{26.3} = +62.5$ (c 0.97, CHCl$_3$) for 75.0:25.0 er, as determined by HPLC analysis: (Chiralcel AD, isocratic 5% i-PrOH/hexane, 0.8 mL/min, 225 nm); $t_R = 17.4$ min (minor), $t_R = 23.5$ min (major).

**Di-tert-butyl 1-(2-(1-(tert-butoxycarbonyl)-1H-pyrrol-3-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (1.28e)**

Using $(R,S)$-tert-Bu-Josiphos (L1) as chiral ligand, and a mixture of THF/water (10:1) as solvent, the bis-protected hydrazine was obtained as a colorless oil in 68% yield (31 mg). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.16 (1H, m), 7.02 (1H, s), 6.21 (1H, m), 6.16 (1H, m), 5.75 (1H, m), 5.68 (1H, m), 4.71 (1H, m), 3.83 (1H,
m), 2.56 (2H, m), 1.56 (9H, s), 1.47 (9H, s), 1.39 (9H, s); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 155.9, 154.8, 149.2, 132.6, 129.4, 120.4, 116.5, 112.1, 83.3, 81.3, 81.0, 66.6 and 65.0 (rotamers), 46.2, 35.2, 28.3(3), 28.2(6); IR (NaCl, neat): 3318, 2972, 2930, 1739, 1705, 1367, 1344 cm$^{-1}$; HRMS (ESI): calcd for C$_{24}$H$_{38}$N$_3$O$_6$ (M+H)$^+$: 464.2755; found: 464.2756; [α]$_D$ = +52.3 (c 1.20, CHCl$_3$) for 68.0:32.0 er, as determined by HPLC analysis: (Chiralcel AD, isocratic 15% i-PrOH/hexane, 0.8 mL/min, 235 nm); t$_R$ = 11.6 min (minor), t$_R$ = 29.8 min (major).

**Di-tert-butyl 5-(1H-pyrrol-3-yl)-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (1.29a)**

Using Walphos (L5) as chiral ligand, and a mixture of THF/water (10:1) as solvent, the bis-protected hydrazine was obtained as a colorless oil in 45% yield (16 mg). When L1 was used a yield of 5% was obtained. $^1$H NMR (400 MHz, $CDCl_3$): δ 8.09 (1H, br.s), 6.68(1H, m), 6.51 (1H, m), 6.02 (1H, m), 4.41 (2H, m), 3.21 (1H, m), 2.19 (1H, m), 1.71 (2H, d, J = 10.0 Hz), 1.43 (19H, m); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 156.8 (2), 125.3, 118.6, 115.0, 107.5, 81.6, 81.3, 66.6 and 65.5 (br, rotamers), 61.0 and 60.5 (br, rotamers), 39.7, 38.1, 34.9, 28.4 (6); IR (NaCl, neat): 3348, 2977, 2925, 1726, 1687, 1475, 1396, 1284, 1248, 1158, 752 cm$^{-1}$; HRMS (ESI): calcd for C$_{19}$H$_{30}$N$_3$O$_4$ (M+H)$^+$: 364.2230; found: 364.2244; [α]$_D$ = +20.6 (c 0.713, CHCl$_3$) for 89.0:11.0 er, as determined by HPLC analysis: (Chiralcel AD, isocratic 10% i-PrOH/hexane, 0.8 mL/min, 220 nm); t$_R$ = 10.4 min (minor), t$_R$ = 18.9 min (major).

**Di-tert-butyl 5-(1-(triisopropylsilyl)-1H-pyrrol-3-yl)-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (1.29c)**

Using (R,S)-tert-Bu-Josiphos (L1) as chiral ligand, and a mixture of THF/water (10:1) as solvent, the bis-protected hydrazine was obtained as a colorless oil in 11% yield (33 mg). $^1$H NMR (400 MHz, $CDCl_3$): δ 6.71 (1H, s), 6.50 (1H, m), 6.13 (1H, m), 4.47 (2H,m), 3.27 (1H, m), 2.55 (1H, m), 2.23 (1H, m), 1.75 (2H, m), 1.50 (18H, br. s), 1.41 (1H, hept, J = 6.9Hz), 1.07 (12H, d, J = 7.6Hz); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 157.1 (2), 127.5, 124.8, 120.9, 109.8, 81.4 and 81.1 (2, rotamers), 66.5 and 65.6 (br, rotamers), 61.0 and 60.5 (br, rotamers), 39.8 and 38.4 (br, rotamers), 35.4 and 34.8 (br, rotamers), 28.4 (2), 18.0 (6), 11.85 (6); IR (NaCl, neat): 2946, 2863, 1737, 1697, 1367, 1336, 1284, 1248, 1158, 752 cm$^{-1}$; HRMS (ESI): calcd for C$_{28}$H$_{50}$N$_3$O$_4$Si (M+H)$^+$: 520.3565; found: 520.3587; [α]$_D$ = +16.9 (c 0.793, CHCl$_3$) for 87.5:12.5 er, as determined after desilylation through the same method as 1.29a.

**Di-tert-butyl 5-(1-acetyl-1H-pyrrol-3-yl)-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (1.29d)**

Using (R,S)-tert-Bu-Josiphos (L1) as chiral ligand, and a mixture of THF/water (10:1) as solvent, the bis-protected hydrazine was obtained as a colorless oil in
22% yield (9 mg). $^1$H NMR (400 MHz, CDCl$_3$): δ 7.18 (1H, br. s) 7.05 (1H, m), 6.15 (1H, m), 4.72-4.20 (2H, m), 3.35-3.02 (1H, m), 2.24 (3H, s), 1.68 (2H, m), 1.46 (18H, br.s); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 167.6, 155.9 (2), 130.4, 120.3, 115.6, 113.4, 81.7 (2), 65.2 and 64.5 (br, rotamers), 60.9 and 60.3 (rotamers), 39.4 and 38.2 (br. rotamers), 34.8 and 35.4 (rotamers), 28.4 (6), 22.3; IR (NaCl, neat): 2977, 2930, 1718, 1695, 1367, 1321, 1139 cm$^{-1}$; HRMS (EI): calc for C$_{21}$H$_{31}$N$_3$O$_5$ (M$^+$): 405.2264; found: 405.2263; $[\alpha]_D^{28}=+31.8$ (c 0.553, CHCl$_3$) for 93.0:7.0 er, as determined by HPLC analysis: (Chiralpak AD, isocratic 3% i-PrOH/hexane, 0.8 mL/min, 225 nm); $t_R=20.1$ min (minor), $t_R=22.0$ min (major).

Di-tert-butyl 5-(1-(tert-butoxycarbonyl)-1H-pyrrol-3-yl)-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (1.29e)

Using (R,S)-tert-Bu-Josiphos (L1) as chiral ligand, and a mixture of THF/water (10:1) as solvent, the bis-protected hydrazine was obtained as a colorless oil in 30% yield (14 mg). $^1$H NMR (400 MHz, CDCl$_3$): δ 7.17 (1H, s), 6.97 (1H, br.s), 6.09 (1H, br. s), 4.48 (2H, m), 3.18 (1H, m), 2.24 (1H, m), 1.71 (2H, d, $J=10.4$ Hz), 1.58 (10H, br. s), 1.5 (18 H, br. s); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 156.7, 149.0, 129.0, 120.9, 116.4, 111.9, 83.9, 81.6, 81.3, 65.5 and 64.7 (br, rotamers), 61.0 and 60.4 (rotamers), 39.5 and 38.3 (rotamers), 35.3 and 34.9 (rotamers), 28.4(3), 28.2(6); IR (NaCl, neat): 2976, 2925, 1742, 1695, 1367, 1158 cm$^{-1}$; HRMS (ESI): calc for C$_{24}$H$_{38}$N$_3$O$_6$ (M+H)$^+$: 464.2755; found: 464.2771; $[\alpha]_D^{27.1}=+25.8$ (c 0.83, CHCl$_3$) for 90.0:10.0 er, as determined by HPLC analysis: (Chiralpak AD, isocratic 3% i-PrOH/hexane, 0.8 mL/min, 225 nm); $t_R=10.4$ min (minor), $t_R=16.4$ min (major).

4-Methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (1.35)

Into an oven-dried roundbottom flask fitted with a stirring bar was weighed out (3-bromo-4-methoxyphenoxy)(tert-butyl)dimethylsilane (2.46 g, 7.75 mmol). The flask was purged with argon, and toluene (12 ml) and THF (3.1 ml) were added. The reaction was cooled to -78 °C in an acetone-dry ice bath. Triisopropoxyborane (2.15 ml, 9.3 mmol, 1.2 equiv) was added. $n$-Butyllithium (1.6M, 5.81 ml, 9.3 mmol, 1.2 equiv) was added dropwise using a syringe pump. After completion of the addition, the reaction was allowed to warm to 0 °C, at which time aqueous HCl (1 M) was added. After warming to room temperature, the reaction was extracted with EtOAc, and washed with water and brine. The solvents were removed under reduced pressure. The crude was dissolved in DCM and pinacol (2.2 g, 9.3 mmol, 1.2 equiv) was added. The reaction was allowed to stand for ~10 minutes and the solvent was removed under reduced pressure. The crude was then suspended in HCl (1% in MeOH, 20 ml), was stirred and monitored by TLC. After consumption of the TBS-protected compound, the reaction was carefully quenched with saturated aqueous NaHCO$_3$, and extracted with ethyl acetate. The product crystallized out of the crude, and could be recrystallized from toluene. Colorless solid, 61% yield (1.18 g); $^1$H NMR
(400 MHz, CD$_2$Cl$_2$) $\delta$ 7.13 (d, $J = 3.1$ Hz, 2H), 6.88 (dd, $J = 8.8, 3.2$ Hz, 2H), 6.74 (d, $J = 8.8$ Hz, 2H), 3.72 (s, 8H), 1.31 (s, 27H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 158.5, 149.4, 123.1, 119.2, 112.4, 83.8, 56.6, 24.9; IR (NaCl, neat): 3429, 2999, 2980, 2966, 2940, 1587, 1495, 1435, 1383, 1354, 1296, 1142, 1067, 1030, 966, 922, 856, 818, 741 cm$^{-1}$; M. p.: sublimes at $>150$ °C; HRMS (ESI): calcd for C$_{13}$H$_{20}$BO$_4$ (M+H)$^+$: 251.1455; found: 251.1457.

4-Methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl methacrylate (1.36)

Into a flame-dried roundbottom flask fitted with a stirring bar was weighed out 1.35 (1 g, 4 mmol). The flask was purged with argon and DCM (20 ml) and triethylamine (670 $\mu$l, 4.8 mmol, 1.2 equiv) were added. The reaction was cooled to 0 °C and methacryloyl chloride (480 $\mu$l, 4.8 mmol, 1.2 equiv) was added dropwise. Upon completion of this addition the reaction was allowed to warm to room temperature. In ~20 minutes, TLC indicated full consumption of starting material and the reaction was quenched with aqueous NH$_4$Cl. The crude was extracted with DCM and washed with brine and dried over Mg$_2$SO$_4$. After removal of the solvents, the crude was purified through column chromatography (hexane:EtOAc 9:1) to give the titled compound as a colorless solid in 80% yield (1.02 g); $^1$H NMR (400 MHz, CD$_2$Cl$_2$) $\delta$ 7.35 (d, $J = 3.0$ Hz, 1H), 7.12 (dd, $J = 8.9, 3.0$ Hz, 1H), 6.87 (d, $J = 8.9$ Hz, 1H), 6.31 – 6.23 (m, 1H), 5.72 (p, $J = 1.5$ Hz, 1H), 3.80 (s, 3H), 2.02 (dd, $J = 1.4, 1.0$ Hz, 3H), 1.31 (s, 13H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 166.3, 162.0, 144.1, 136.1, 129.4, 127.0, 125.4, 111.5, 83.8 (2), 56.5, 24.9 (4), 18.5; IR (NaCl, neat): 2978, 2932, 2837, 1732, 1635, 1609, 1464, 1424, 1373, 1344, 1317, 1267, 1190, 1126, 1067, 1030, 966, 951, 912, 856, 810 cm$^{-1}$; M. p.: 70-74 °C; HRMS (ESI): calcd for C$_{17}$H$_{24}$BO$_5$ (M+H)$^+$: 319.1717; found: 319.1726.

4-(Bicyclo[2.2.1]heptan-2-yl)-5-methoxy-3,3-dimethylbenzofuran-2(3H)-one (1.38)

Into a vial were weighed: [Rh(cod)OH]$_2$ (2.3 mg, 0.005 mmol, 5 mol%), BINAP (6.8 mg, 0.011 mmol, 11 mol%), Cs$_2$CO$_3$ (36 mg, 0.11 mmol, 1.1 equiv) and the starting material (32 mg, 0.1 mmol). The reaction vial was purged with argon, and THF (2 ml) was added. After stirring at room temperature for 10 minutes, the reaction was heated at 60 °C for 16 hours. Upon completion, the crude was filtered through a silica plug and concentrated. The pure material was obtained using column chromatography (hexane:EtOAc 95:5) as a colorless solid in 82% yield (23 mg); $^1$H NMR (400 MHz, CD$_2$Cl$_2$) $\delta$ 6.90 (d, $J = 8.7$ Hz, 1H), 6.75 (d, $J = 8.7$ Hz, 1H), 3.75 (s, 3H), 2.74 (t, $J = 8.4$ Hz, 1H), 2.38 (t, $J = 4.0$ Hz, 1H), 2.29 (dp, $J = 9.3, 1.9$ Hz, 1H), 2.19 (br. s, 1H), 2.08 – 1.97 (m, 1H), 1.71 – 1.49 (m, 3H), 1.60 (s, 3H), 1.59 (s, 3H), 1.35 (m, $J = 10.0, 2.5$ Hz, 1H), 1.31 – 1.22 (m, 1H), 1.17 (br. d, $J = 9.3$ Hz, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 181.9, 155.6, 146.2, 132.7, 132.0, 111.4, 108.6, 55.5, 44.8, 43.1, 42.6, 38.5, 37.8, 37.4, 33.3, 28.1, 25.4, 25.0; IR (NaCl, neat): 2953, 2870, 2837, 1800, 1614, 1465, 1365, 1265, 1244, 1201, 1101, 1042, 1017 cm$^{-1}$; M. p.: 115-120 °C; HRMS (ESI): calcd for C$_{18}$H$_{23}$O$_3$ (M+H)$^+$: 287.1641; found: 287.1631.
Chapter 2

*Rhodium and Palladium Catalysis in Domino Synthesis of Heterocycles*
2 Rhodium and Palladium Catalysis in Domino Synthesis of Heterocycles

2.1 Introduction

2.1.1 Domino Chemistry

The use of organic synthesis on industrial scale has changed the lives of people around the world profoundly by making a plethora of synthetic materials readily available. A major downside of industrial chemistry is the sheer amount of waste produced, disposal of which requires enormous resources and contributes to our carbon footprint on Earth. To limit the waste production in large scale synthesis, significant efforts are being put forth to increase the efficiency of synthetic strategies. The study of ‘green chemistry’ or ‘sustainable chemistry’ examines this idea of increasing efficiency and decreasing waste in synthetic sequences.¹ One way of improving the productivity of a synthetic sequence is to utilize reactions which achieve multiple bond-forming events under a single set of conditions. In this way, complexity is generated more rapidly, allowing conservation of time and materials. This concept, in a way, mimics how synthesis is accomplished in Nature.

Production of metabolites by cells is an exceptionally efficient example of multistep synthesis. In a highly complex environment, multiple enzymes carry out multistep reaction sequences with nearly perfect selectivity and excellent yields. Organic synthesis is very distant from being able to replicate such productivity, but an important advantage of synthesis is the ability to use reagents and catalysts inaccessible to or incompatible with cellular organisms. For instance, utilization of transition metal catalysis can facilitate transformations which are difficult or impossible to achieve through the use of purely organic systems.

In effort to mimic enzyme-mediated cascade reactions, methods utilizing domino or one-pot reactivity are being developed.² Such methods for carrying out multiple reactions are usually

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superior to stepwise approaches since no isolation of intermediates is required (Figure 2.1). The resulting syntheses are more time and cost-efficient. In domino reactions two or more synthetic steps occur in a single reaction vessel under a constant set of reaction conditions (Eqn 3). Alternatively, in a one-pot process the reaction conditions can be modified throughout the reaction sequence, but workup and purification is only necessary after the final step of the sequence (Eqn 2). A requirement of a domino sequence is that the first reaction leads to an intermediate, which can only then participate in the subsequent step, and so forth. Tandem reactivity also makes use of two or more transformation in a single reaction, but unlike domino reactions, the multiple synthetic transformations are independent of one another.

**Sequential Stepwise Reactivity**

\[
\text{SM} \xrightarrow{\text{Conditions 1}} \text{I}^1 \xrightarrow{\text{Work Up Purification}} \text{Conditions 2} \xrightarrow{\text{I}^2} \xrightarrow{\text{etc.}} \xrightarrow{\text{Conditions X}} \text{I}^{1-1} \xrightarrow{\text{Work Up Purification}} \text{P} \quad (1)
\]

**One-Pot Reactivity**

\[
\text{SM} \xrightarrow{\text{Conditions 1}} \left[ \text{I}^1 \right] \xrightarrow{\text{Conditions 2}} \left[ \text{I}^2 \right] \xrightarrow{\text{etc.}} \xrightarrow{\text{Conditions X}} \left[ \text{I}^{1-1} \right] \xrightarrow{\text{Work Up Purification}} \text{P} \quad (2)
\]

**Domino Reactivity**

\[
\text{SM} \xrightarrow{\text{Conditions 1 to X}} \left[ \text{I}^1 \right] \xrightarrow{\text{I}^2} \xrightarrow{\text{etc.}} \xrightarrow{\text{Work Up Purification}} \text{P} \quad (3)
\]

**Figure 2.1:** Different ways of carrying out synthetic sequences.

### 2.1.2 Catalysis in Domino Reactions

Domino reactivity has been studied for some time, and a large number of examples making use of this concept can be found. To further increase the efficiency of these processes, recent attention has been focused on developing domino sequences featuring catalytic reactions. Catalytic processes are less wasteful than stoichiometric ones, and through the use of transition metal (TM) catalysts very diverse and unusual transformations can be accomplished.
In 2002, Poli offered a classification system for the use of catalytic reactions in domino transformations (Figure 2.2). He proposed distinguishing between a *pure* domino catalytic process and a *pseudo* domino catalytic process. In the former, a single catalyst is used to carry out a domino sequence of events occurring in a single catalytic cycle (Eqn 1). In the alternative *pseudo* domino catalytic process either a single catalyst or multiple catalysts are utilized, which carry out two or more transformations in separate catalytic cycles (Eqn 2 and 3). This combination of multiple catalytic cycles into a single domino process is especially challenging. Compatibility of the two catalytic systems in terms of reaction rates and catalyst longevity is essential for success, and it is this concept which is examined throughout this chapter.

![Diagram of domino transition metal catalysis](image)

**Figure 2.2**: Types of catalysis in domino reactions.

Recent work can be used to exemplify the difference between *pure* and *pseudo* domino catalysis. In 2011, a report from the Lautens group describes a domino palladium-catalyzed reaction

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cascade, which can be regarded as “pure” domino TM catalysis (Eqn 2.1). Palladium-Q-Phos catalyst reacts with the aryl bromide substrate and then carries out a sequence of additions to double bonds before terminating in a reductive elimination event. The entire sequence proceeds without formation of isolable intermediates.

\[
\begin{align*}
\text{[Pd]Ph} & \rightarrow \text{[Pd]N} \\
\text{[Pd]N} & \rightarrow \text{[Pd]} \\
\text{[Pd]} & \rightarrow \text{[Pd]} \\
\text{[Pd]} & \rightarrow \text{[Pd]} \\
\text{[Pd]} & \rightarrow \text{[Pd]N} \\
\end{align*}
\]

An example of a “pseudo” domino Type I reaction, wherein the same catalyst performs two independent transformations can be found in the work of Tietze and coworkers (Eqn 2.2). In this sequence, Tsuji-Trost reaction occurs first and the intermediate of this reaction could be isolated if lower reaction temperatures are used. Under the described conditions this intermediate undergoes Heck coupling and the entire sequence proceeds to completion in good yield.

Considering that the use of two different catalysts in situ is significantly more difficult than having a single catalyst, “pseudo” domino Type II reactions are by far more challenging to develop. To date a significant number of scientists carry out research in this field, and examples

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of combinations of organocatalysts\textsuperscript{7} or biocatalysts\textsuperscript{8} with transition metal catalysts into domino sequences can be found.\textsuperscript{9}

2.1.2.1 The Use of Multiple Transition Metal Catalysts in Domino Reactions

There are very few examples available wherein two transition metal catalysts function independently in a domino fashion (Eqn 1, Figure 2.3). Examples featuring one-pot reactivity, where a second catalytic system is added to the reaction upon completion of the first reaction step, are more common. Alternatively, in many other examples utilizing multiple catalytic metals, the two catalysts participate in cooperating catalytic cycles carrying out a single transformation (Eqn 2, Figure 2.3). In such cases the presence of a second metal can be essential, or can accelerate the rate of the reaction. This reactivity, which resembles the recently termed contemporaneous catalysis,\textsuperscript{10} is not a domino process in itself, but can be used to carry out domino transformations.

The use of multiple metal catalysts in domino transformations can be problematic for a number of reasons. Oftentimes, different transition metals can react differently with similar reactive functional groups, presenting problems in selectivity in a domino process. Redox or ligand exchange processes between two or more different catalysts can be complex and potentially deleterious. Spectator ligands, which are often instrumental for selectivity and reactivity, can be labile and can swap between different transition metals, leading to deactivation of one or both of the catalysts. Regardless of this, a number of successful applications of this concept can be found. These processes often share some key features which go a long way in preventing deleterious catalyst interactions. The use of ligands forming very stable complexes, such as NHC or tridentate ligands, can limit any ligand interchange. Alternatively selecting two catalytic


\textsuperscript{10} Trost, B. M.; Luan, X. \textit{J. Am. Chem. Soc.} \textbf{2011}, \textit{133}, 1706
transformations utilizing the same or very similar ligands (i.e., dppp and dppb), or using ligand free catalysts can result in success.

**Domino catalysis**

\[ \text{Substrate} \xrightarrow{\text{Cat 1}} \text{Intermediate} \xrightarrow{\text{Cat 2}} \text{Product} \quad (1) \]

**Contemporaneous catalysis**

\[ \text{Substrate 1} \xrightarrow{\text{Cat 1}} \text{Substrate 1 - Cat 1} \xrightarrow{\text{Cat 2}} \text{Product} \quad (2) \]

**Figure 2.3:** Distinction between domino and contemporaneous or co-catalysis.

The following section outlines the available examples where two transition metal complexes are used *in situ* to conduct two discrete transformations. In all of these cases, if only the first catalytic system was used, the intermediate of the reaction could be isolated and subjected to the second step. Primarily, homogeneous catalytic systems are examined.

**Reactions featuring hydroformylation.** One of the earliest examples using two transition metal catalysts in a single reaction was reported by Herwig and Beller. They described a two-metal catalytic system comprised of rhodium and iridium, where the former catalyzed a hydroformylation reaction followed by a reductive amination with ammonia under iridium catalysis (Eqn 2.3).\(^\text{11}\) This biphasic reaction required the use of a water-soluble ligand (TPPTS), which is compatible with both catalytic cycles.

\[
\text{[Rh(cod)Cl]_2 (0.026 mol\%)} \\
\text{[Ir(cod)Cl]_2 (0.21 mol\%)} \\
\text{TPPTS (11 mol\%)} \\
\text{NH_3 (aq, 25\%) (8 equiv)} \\
\text{MTBE, CO}_2 \text{H} (1:5, 78 bar) \\
\text{130 °C, 10 h} \\
\xrightarrow{\text{[Ir]}} \\
\xrightarrow{72\%} \\
\text{primary:secondary \(86:14\)}}
\]

In 2010, Nozaki reported a domino hydroformylation/hydrogenation of terminal olefins (Eqn 2.4). The initial step was a rhodium-catalyzed hydroformylation reaction, followed by a ruthenium-catalyzed hydrogenation of the resulting aldehyde. A number of important observations were made regarding the reactivity of the two catalysts. Hydrogenation of the starting olefin could occur under both rhodium and ruthenium catalysis, leading to alkane byproduct. Olefin isomerization also occurred under ruthenium catalysis, giving internal alkenes, but an optimal Rh:Ru ratio reduced this side reaction. It was observed that the hydroformylation reaction was faster than the subsequent hydrogenation.

Reactions featuring allylic or propargylic substitution. One of the first examples of a combination of a palladium and rhodium catalyst was reported by Jeong and coworkers (Eqn 2.5). The reaction relied on the use of a [Pd(dppb)] catalyst in an allylic substitution reaction followed by a rhodium catalyzed Pauson – Khand reaction (PKR). The transformation was found to be highly sensitive to the nature of the rhodium catalysts used: complexes such as [RhCl(CO)\(_2\)]\(_2\) and [RhCl(CO)dppe] blocked the allylation reaction, while [RhCl(CO)(dppp)]\(_2\) and [RhCl(CO)(dppb)]\(_2\) were compatible with the [Pd(dppb)] catalyst. Interestingly [Pd(dppe)] was an efficient catalyst for the transformation, which shows that ligand interchange is not what shuts down the reaction when the [Rh(dppe)] complex is used. The [Rh] to [Pd] ratio was optimized at 3 – 4.6 to 1, and while the palladium-catalyzed allylation typically took 2 hours to complete, the second reaction had a slower rate, requiring up to 20 hours. Phosphorus NMR

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studies suggested that when the two catalyst solutions were combined, new species were formed, implying possible interactions between the rhodium and palladium catalyst.

Soon thereafter, Chung demonstrated that this transformation is possible using palladium and cobalt nanoparticles as catalysts (Eqn 2.6). This was the first example where heterobimetallic nanoparticles were used to catalyze two independent transformations. It was found that significant palladium leaching occurred during the reaction, and as a result the reusability of the catalysts was limited.

The Nishibayashi, Hidai, and Uemura group reported a number of examples combining ruthenium-catalyzed propargylic substitution with a subsequent cycloisomerization reaction (Scheme 2.1). Their initial attempts to synthesize oxazoles using a gold catalyzed cycloisomerization were met with some success, but much higher yields were obtained in a one-pot process (88% vs. 51%, Eqn 1). Following this, an investigation into the synthesis of furans using a platinum catalyst resulted in a high yielding domino process (Eqn 2). A very similar catalyst system could also be applied to an intramolecular cyclization to yield fused polycyclic compounds (Eqn 3). In all cases the reaction sequence initiated through a ruthenium catalyzed activation of the propargylic alcohol, forming an allenylidene complex, which underwent an addition reaction or an ene reaction, subsequently regenerating the alkyne. This intermediate can be isolated in the absence of platinum, but in a domino sequence it is converted to the final

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product through gold or platinum catalyzed cycloisomerization reaction. In both domino examples the initial ruthenium-catalyzed transformation is rapid, quickly generating a pool of the intermediate alkyne which further reacts.

Scheme 2.1 Synthesis of heterocycles through propargylic substitution and isomerization.

Reactions featuring metathesis reaction. In 2008, Prestat and Poli reported a domino reaction combining two catalytic steps – a palladium catalyzed allylation of allylmalonate and a ruthenium catalyzed ring-closing metathesis (RCM) (Eqn 2.7). The nature of the phosphine ligand was important, and when hindered ligands were used, such as PCy₃, the conversion of the RCM reaction was affected. The catalyst ratio was also important, with the reaction stalling at the intermediate when the ruthenium loading was decreased. It is noteworthy that in the absence of palladium the Grubbs II catalyst promoted the allylation reaction to some extent, but in turn displayed no RCM activity.

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An interesting example was reported by the Cossey group, involving a three-step domino process, which features a ruthenium catalyzed cross-metathesis and a platinum-catalyzed hydrogenation (Eqn. 2.8). This domino reaction demonstrates the importance of rate compatibility in multicatalytic systems. The starting allylic and homoallylic alcohols undergo a cross metathesis reaction forming \textit{trans-}alkene intermediates, which then undergo hydrogenation. The resulting hydroxy acids spontaneously lactonize. In the cases where sterically hindered alcohols were utilized, the hydrogenation was faster than cross metathesis, and the saturated alcohol byproducts were obtained in significant amounts.

Goldman and Brookhart published a report in 2006 on a homogeneous two-metal system for alkane metathesis (Eqn 2.9). An iridium pincer complex was used to dehydrogenate \( n \)-hexane, which subsequently underwent cross-metathesis with a Schrock-type molybdenum catalyst. In practice, because of olefin isomerization during the reaction, a disproportionation of hexane was observed to yield a mixture of \( n \)-alkanes in the range of \( C_2 \) to \( C_5 \) and \( C_7 \) to \( C_{10} \). A noteworthy feature of this reaction is the fact that the dehydrogenation activity of the iridium catalyst is highly prone to product inhibition, and conducting this reaction in a domino sense, where the

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alkene is quickly consumed, is essential to achieve reasonable conversion. It was noted that Grubbs-type catalysts reacted with and deactivated the iridium complex.

**Multiple transition metals in polymerization reactions.** In addition to the examples discussed above, the use of multiple catalysts in single vessel processes can be useful in polymer synthesis. In such processes, typically the first catalyst is used to oligomerize ethylene to give \( \alpha \)-olefins of a certain size, and a second catalyst incorporates these \( \alpha \)-olefins into a growing polymer chain. The two catalysts can be based on two different transition metals or the same transition metal with different ligands. The overall effect of using such catalyst systems is the formation of low-density polyethylene, which is less brittle and easier to process than the non-branched high-density polyethylene. In a notable example, Bazan has reported on the combinations of three catalysts in ethylene polymerization (Figure 2.4). Two of the catalysts, B and C, polymerize ethylene to generate differently sized \( \alpha \)-olefins, while the third catalyst, A, incorporates these olefins into a growing polymer chain. The end result is a low density polymer with incorporation of sidechains of varying lengths.

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2.1.2.2 Domino Reactions Using a Transition Metal Catalyst and a Transition Metal Co-catalyst

"Contemporaneous Catalysis" versus Multicatalytic Domino Reactions. A considerable number of domino reactions using multiple transition metal catalysts use the two metals as co-catalysts. Unlike in previous examples, where isolable intermediates were usually obtained, in these examples the two catalysts are involved in interconnecting catalytic cycles with little or no temporal separation. Occasionally, such reactions can be difficult to classify as multicatalytic or contemporaneous catalytic domino reactions. The difference lies in whether an intermediate of the first reaction dissociates from the first catalyst before undergoing a second reaction or reacts as a catalyst-metal complex in the second step (Figure 2.5).

In a representative example, Chang and coworkers reported a two-metal reaction featuring formate decarbonylation and alkoxy carbonylation of aryl halides (Eqn 2.10).\(^\text{23}\) Ruthenium promotes decarbonylation of the 2-pyridylmethyl formate yielding pyridylmethanol, which is believed to react with CO and iodobenzene under palladium catalysis. In the absence of ruthenium, the reaction still proceeds, albeit at a slower rate, yielding only 33% of the benzoate.

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product. The authors propose a cooperative catalysis mechanism during which the ruthenium facilitates the initial decarbonylation and also the transfer of CO and 2-pyridinemethanol unto the palladium center.

\[
\text{[Ru]} \quad \begin{array}{c}
\text{Ph}_2\text{I} + \text{HO-Ph-N} \\
\text{PdCl}_2 (2 \text{ mol%}) \\
\text{Ru}_3(\text{CO})_{12} (3 \text{ mol%}) \\
\text{NaHCO}_3 (1.5 \text{ equiv}) \\
\text{DMF, } 135 \degree \text{C} \\
\end{array} \quad \text{PhO-Ph-N} \\
94\% \\
\]

A recent report from the Chiba group exemplifies the difficulty in classification of some reactions, especially if the mechanism is not well understood. In this work, rhodium and copper catalysts are combined in a synthesis of isoquinolines (Eqn 2.11). The vinyl azide substrates react with a copper catalyst to generate a proposed iminyl copper species. This intermediate can then undergo a rhodium catalyzed C-H activation and insertion reaction. This sequence of events is supported by the production of acetophenone when only a copper catalyst is utilized. It is unclear however, whether the iminium copper species enters the rhodium catalytic cycle directly or if copper dissociates prior to this. It is this difference in mechanism that is a distinguishing feature between cooperative catalysis (or “contemporaneous catalysis”) and two-metal domino catalysis (or “Pseudo domino catalysis – Type II”).

\[
\text{[Rh(Cp*)Cl]_2 (2.5 \text{ mol%})} \\
\text{CuOAc (20 \text{ mol%})} \\
\text{AcOH (1 equiv)} \\
\text{1,2-diptylylethene} \\
\text{DMF, } 90 \degree \text{C, } 30 \text{ min} \\
\quad \begin{array}{c}
\text{PhN} \\
\text{or} \\
\text{PhN[Cu]} \\
\text{[Cu]} \\
\end{array} \quad \text{PhN} \\
84\% \\
\]

---

2.1.2.3 Domino Reactions Using a Transition Metal and Second Non-Transition Metal Catalyst

Combinations of two transition metal catalysts in domino processes are somewhat uncommon, but some combinations of non-TM catalysts with transition metal catalysis have received more attention and warrant some discussion.

**Domino reactions using a transition metal and other catalysts.** The use of transition metal catalyzed processes in conjunction with different organocatalysts has received considerable interest over the last two decades. The majority of the available examples either feature imine/enamine or Bronsted and Lewis acid catalysis. When considered from a mechanistic standpoint, many of these examples are better described as co-catalytic, since the organocatalysts function by forming a complex with one of the substrates, which then undergoes a TM-catalyzed transformation. There are however, an ample number of cases where both catalysts function independently. A recent report from Lambert provides an example of such reactivity (Eqn 2.12). In their work, the authors disclose a combination of palladium catalyzed aminochlorocarbonylation followed by an indium catalyzed Friedel-Crafts acylation reaction.25 Both of the reactions were developed separately, and the intermediate acyl chloride can be isolated or trapped with alcohols.

![Chemical Reaction Equation](image)

**Domino reactions using a transition metal and biocatalysis.** Work on the use of enzymes and transition metal catalysts is highly significant with respect to dynamic kinetic resolution chemistry.26 Contributions from the Backvall group went a long way to develop the ruthenium

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and lipase-catalyzed resolution of racemic alcohols.\textsuperscript{27} Pioneering work from the Williamson,\textsuperscript{28} Kim and Park\textsuperscript{29} groups, who utilized palladium racemization catalysts in conjunction with lipases, should also be acknowledged. In a state of the art example, diastereomeric mixtures of racemic diols were subjected to a resolution by a lipase in the presence of a ruthenium racemization catalyst (Eqn 2.13).\textsuperscript{30} When this reaction was carried out without a ruthenium catalyst, a mixture of three enantiopure products was formed: the diacetate, monoacetate, and diol in a 1:2:1 ratio. In the presence of ruthenium, C\textsubscript{2} asymmetric diacetate products were isolated in very high ee and yields.

\begin{equation}
\text{Ru Catalyst (5 mol\%)} \\
\text{t-BuOK (5 mol\%)} \\
\text{CALB (12.5 mg/mmol)} \\
\text{isopropenyl acetate (4 equiv)} \\
\text{Na}_2\text{CO}_3 (1 equiv) \\
\text{PhMe, 50 °C}
\end{equation}

\textbf{2.1.2.4 One-Pot Catalysis}

The above sections cover strictly the examples using domino reactivity, meaning that after combination of the catalysts and substrates, the reaction conditions remain constant until completion of the reaction. In terms of practicality, one-pot transformations offer most of the same benefits as domino transformations, requiring only an interruption between the two reaction steps, usually in the form of addition of a second catalyst or reagent. The combination of multiple catalytic steps into one-pot processes is significantly less challenging since the sensitivity of the first catalyst is not an issue. A plethora of such examples can be found in literature and are summarized in excellent reviews.\textsuperscript{31} Notably, some transformations are very

similar to true domino processes and require only a temperature or atmosphere change as the alteration of conditions with both catalysts present from the beginning of the reaction.\(^\text{32}\)

### 2.1.2.5 Summary

It is evident that to date, there are rather few examples of true domino processes where two transition metal mediated transformations are combined. A few trends can be observed from the available examples. Notably, highly robust reactions with a generous scope and mild reaction conditions are usually used (i.e., metathesis, allylic substitution, hydroformylation). More often than not, the first reaction is kinetically facile, quickly generating a pool of the intermediate, which then reacts at a slower rate with the second catalyst. The ligands used, if any, are either very similar in both catalyst complexes or are very strongly binding.

We were intrigued by the prospect of developing reactions using multiple metals in a domino process. Building on our work on arylation of alkynes, we proposed a synthesis of heterocycles (Scheme 2.2). If we used appropriately substituted alkynes bearing an electrophilic substituent and a nucleophilic substituent, the syn-arylation would place the two groups into a cis configuration making a cyclization event possible. Before the discussion of results, a brief introduction into the pertinent rhodium-catalyzed alkyne arylation and palladium-catalyzed C-N and C-O coupling is warranted.

![Scheme 2.2 Proposed synthesis of heterocycles through rhodium and palladium catalysis.](image)

### 2.1.3 Rhodium-Catalyzed Arylation of Alkynes with Boronic Acids

Alkynes comprise a highly useful motif in organic synthesis, since they can be converted to a number of useful synthons through one or more reductive functionalization events. A variety of transition metal catalysts can react with alkynes to give di-, tri- and tetrasubstituted alkene

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Rhodium catalyzed arylation of alkynes with boronic acids is a highly useful example of this reactivity. Typical reaction conditions are very mild, utilizing weak carbonate bases and tolerating water. The use of boronic acids in this transformation is noteworthy, since these “hard” carbon nucleophiles are air and moisture stable and show excellent compatibility with other functional groups.

The initial report of rhodium catalyzed alkyne arylation emerged from the Hayashi group (Scheme 2.3). Reacting symmetrical alkynes with arylboronic acids or boroxines with [Rh(acac)(C₂H₅)₂] and dppb as catalyst system led to alkene products in high yields and excellent E/Z ratio (>97%). High loading of boronic acids was necessary because of competitive hydrolysis under the reaction conditions. In the cases with non-symmetrical alkynes the regioselectivity depended on the nature of the substituents. With 1-phenyl-1-propyne a 3:1 regioisomeric ratio was observed, favoring addition to the carbon β to the phenyl group. When alkynoates were utilized a single regioisomer was detected.

Scheme 2.3 Hayashi’s rhodium-catalyzed arylation of alkynes.

The mechanism of the reaction is proposed to involve a syn carborhodation (Scheme 2.4). Rhodium(I) hydroxide or alkoxide complexes have a tendency to dimerize, and during an arylation reaction the initial formation of the active rhodium monomer (II) is required. This species can then undergo transmetallation with a boronic acid and a subsequent carborhodation of an alkyne to give a vinylrhodium intermediate IV. If the alkyne substituent α to the rhodium can stabilize a negative charge (i.e., an ester) a rhodium enolate forms. Alternatively protonation of the vinylrhodium specie can occur. With addition of most arylboronic acids, however, a 1,4-rhodium migration to the ortho aromatic position follows, to give an arylrhodium species V. At this stage protonolysis occurs to give the final product and regenerate the catalyst. Typically, protic additives, such as water or alcohol, are required to facilitate a complete reaction.

![Scheme 2.4](https://example.com/scheme24.png)

**Scheme 2.4** Proposed catalytic cycle of alkyne arylation.

Although Hayashi’s report of this reaction described a very efficient method in terms of yields and stereocontrol, the issue of regioselectivity in additions to non-symmetrical alkenes still needed to be addressed. Over the years following this report a number of publications described applications of this reactivity in the synthesis of carbo- and heterocyclic motifs. In most of the

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cases the regioselectivity was good provided that the alkyne was appropriately substituted. Aside from using alkynoates, alkynes bearing highly sterically hindered substituents, such as SiMe₃ or tert-butyl, give excellent regiocontrol. Arylalkynes give intermediate results, but oftentimes higher selectivity is reported compared to Hayashi’s original report, especially when ortho-substituted boronic acids are used.

To remedy some of these regioselectivity issues, the Lautens group studied alkyne substrates capable of chelation to the catalyst. In 2002, a report describing arylation of pyridinyl alkynes was disclosed (Eqn 2.14). The reaction proceeded with excellent regiocontrol, giving a single product. It was proposed that coordination of the pyridine nitrogen was important for high selectivity of addition (Scheme 2.5). Alternatively, formation of a dienylamide-rhodium species B is also possible. Stabilization of a vinyl-rhodium species A was also suggested in deuterium trapping experiments. While Hayashi reported incorporation of deuterium at the ortho aromatic position, suggesting a 1,4-rhodium migration, in pyridinylalkynes deuterium incorporation was only observed at the vinyl position.

Scheme 2.5 Stabilization of vinylrhodium species.


Achieving good selectivity with less electronically biased substrates, for instance dialkyl alkynes, is considerably more challenging, and the main avenues for generating any selectivity rely on steric differentiation (i.e., t-Bu or TMS versus Me) or through conducting the reaction in an intramolecular manner. In 2010, the Lautens group reported that the sulfone group can influence the regioselectivity of addition to such alkynes (Eqn 2.15). 38 It was proposed that coordination of the sulfone oxygens to the rhodium center influenced the regiocontrol (B). Based on this work we were intrigued by the prospect of studying other alkynes with heteroatom substitution.

2.1.4 Palladium-Catalyzed C-N/C-O Coupling of Aryl Chlorides

The palladium-catalyzed amination and alkoxylation reaction of aryl halides has been extensively studied over the last decade, and a considerable number of reviews summarize this reactivity. 39 Largely based on the work of Buchwald and Hartwig, 40 C-N coupling has been shown to be applicable to large scale synthesis. 41 The original methods were only viable for aryl bromide and aryl iodide substrates, but since 1998, significant breakthroughs were made in applying aryl chlorides to coupling reactions. 42 Development of specialized ligands played a key role in these advancements. Considering the availability and stability of aryl and heteroaryl

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chlorides and their compatibility with a large scope of reactions makes them more versatile than corresponding aryl bromide and aryl iodide electrophiles.

The mechanism of aryl halide amination consists of three main steps: oxidative addition into the aryl halide bond, transmetallation with the amine, and subsequent reductive elimination giving the final product (Scheme 2.6). In practice, a number of factors determine the mechanism. The formation of the active catalyst generally occurs through reduction of a Pd$^{II}$ salt and complexation to the phosphine ligands to generate a Pd$^{0}$($PR_3$)$_2$ species. With sterically hindered ligand formation of the reactive monophosphine complex Pd$^{0}$PR$_3$ needs to occur, and in the presence of excess ligand the reaction rate is inverse first order with respect to the ligand.$^{43}$ With coupling of aryl chlorides, the monophosphine is in equilibrium with the diphosphine complex, and the oxidative addition can be rate determining.$^{44}$ The transmetallation proceeds under different mechanisms depending on the nature of the base and ligand used: either through an anionic mechanism (where the alkoxide base associated with palladium prior to oxidative addition), a neutral mechanism (shown), or a mixture of the two.$^{45}$ The final step of reductive elimination is promoted by sterically hindered, electron poor ligands. The most reactive complexes, necessary for coupling of aryl chlorides, utilize ligands which are both electron rich (to promote oxidative addition) and very sterically hindered (to promote reductive elimination).

In the early days of aryl chloride amination, very harsh conditions were required, often leading to decomposition and significant byproduct formation. The first successful aminations of aryl chlorides relied on coupling of activated substrates, such as 2-chloropyridines and 2-chloroimidazoles (Scheme 2.7a).$^{46}$ Standard conditions using Pd/BINAP or Pd/dppf, and sodium tert-butoxide as a base could be applied successfully. The first coupling of a non-hetero-aryl chlorides was reported by Beller (Scheme 2.7b).$^{47}$ This method utilized a palladacyclic catalyst, and an electron withdrawing group was still necessary.

---

Following this work, studies from numerous groups indicated that highly electron rich and sterically demanding ligands were crucial to ensure successful oxidative addition to the unreactive C-Cl bond (Figure 2.6). The major ligand classes found to be successful were monodentate phosphines, including hindered trialkylphosphines (PCy₃, Pt-Bu₃), dialkylferrocenyl derivatives (i.e., Q-Phos⁴⁸), MOP-type ligands,⁴⁹ CataCXium-type ligands,⁵⁰ and dialkylbiaryl ligands (i.e., DavePhos, X-Phos, BrettPhos).⁵¹ Some NHCs⁵² and bidentate

---

ligands (i.e., Josiphos\textsuperscript{53}) were also found to be applicable. Typical reaction conditions involved the use of bases, such as NaOt-Bu or NaHMDS, or less often, weaker bases such as Cs\textsubscript{2}CO\textsubscript{3}, K\textsubscript{2}CO\textsubscript{3}, and K\textsubscript{3}PO\textsubscript{4}. As solvents, toluene and dioxane were common, but tert-butanol was often utilized with more challenging reactions.

\textbf{Figure 2.6:} Common ligands for amination and alkoxylation of aryl chlorides.

Currently, C-N coupling of aryl chlorides has a very broad scope and very mild conditions can be applied to many substrates. This fact is further emphasized in the following section of this thesis, where intramolecular C-N coupling of aryl chlorides and sulfonamide is accomplished in a multicatalytic domino reaction.

2.2 Rhodium and Palladium Catalyzed Domino Synthesis of Dihydroquinolines

The following part of this thesis describes the development of a domino reaction sequence to access dihydroquinolines. This project was carried out in collaboration with a fellow graduate student, Lei Zhang. The majority of the experimental work described below was conducted by the author, and the experiments conducted by L. Zhang are labeled as such.

2.2.1 Preliminary Work

Building on our work with vinyl- and alkynylpyridines, we devised a synthesis of nitrogen-containing heterocycles using rhodium-catalyzed alkyne arylation and C-N bond formation (Scheme 2.8). Considering that both of these reactions can proceed under very mild conditions, we saw potential in combining these two transformations into a domino process.

![Scheme 2.8 Proposed synthesis of dihyronaphthyridines.](image)

Early on, work with the pyridinyl system proved to be challenging, both in terms of substrate synthesis and alkyne arylation, and the parent aryl alkyne was studied instead (Scheme 2.9a). Considering that at the beginning of this work no examples of arylations of propargylic amine or ortho-halogenated aryl alkynes was reported, the model alkyne 2.1 was examined. Gratifyingly, the arylation proceeded efficiently, giving good yields of the alkene 2.2a and 2.2b with high regiocontrol. Around this time, a report by Marinelli and coworkers further demonstrated that propargylic benzyamines are good substrates for this reaction, albeit under different reaction conditions (Scheme 2.9b).

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54 For a communication of this work see: (a) Panteleev, J.; Zhang, L.; Lautens, M. Angew. Chem. Int. Ed. 2011, 133, 14200; (b) Zhang, L.; Panteleev, J.; Lautens, M. manuscript in preparation.
55 L. Zhang was a 1-2nd year PhD student throughout this project. Current location: PhD student, University of Toronto.
With these promising results in hand, the ortho-halogenated derivatives were examined (Scheme 2.10). We initially examined the brominated derivative 2.3a, to facilitate the subsequent C-N coupling reaction. However, it became evident that this substrate was unreactive under the reaction conditions. It was possible that the catalyst was deactivated either through complexation or oxidative addition into the substrate. Reactions with the chlorinated analogue 2.3b gave more promising results, furnishing a 62% yield of the alkene product 2.4b.

Since we could access this key intermediate early on, we tested the C-N coupling reaction (Scheme 2.11). Gratifyingly, when using standard ligands for aryl chloride coupling, we

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58 For an example of rhodium oxidative additions into aryl bromide bonds see: Harada, Y.; Nakanishi, J.; Fujihara, H.; Tobisu, M.; Fukumoto, U.; Chatani, N. J. Am. Chem. Soc. 2007, 129, 5766
observed formation of the cyclized product 2.5, despite the low nucleophilicity of the sulfonamide.\(^{59}\)

\[
\begin{array}{cccc}
\text{Ph} & \text{Cl} & \text{NHTs} & \text{Ph} \\
2.4b & & & \\
\text{Pd(OAc)}_2 & (2 \text{ mol} \%) & \text{Ligand} (X \text{ mol} \%) & \\
\text{Cs}_2\text{CO}_3 (1.4 \text{ equiv}) & \text{dioxane, } 90^\circ\text{C, 16 h} & & \\
2.5 & \text{Ts} & & \\
\end{array}
\]

**Scheme 2.11** Preliminary C-N coupling results.

These preliminary results were very promising since mild conditions could be used in both of the key steps of the reaction. At this stage, however, the overall yield for the two step process was low (43%) and significant optimization of both reactions was carried out.

### 2.2.2 Substrate Synthesis

The Sonogashira reaction between propargylic amines and aryl bromides or aryl iodides provided the most efficient access point to the substrates for this project (Table 2.1).\(^{60}\) We found that it was necessary to modify the reaction conditions depending on the protecting group present on the propargylamine. Because of low solubility of methanesulfonyl and \(p\)-toluenesulfonyl protected propargylamines, the reaction gave a better outcome when using a 1:1 mixture of acetonitrile and diisopropylamine. With aryl iodide substrates the reaction proceeded at room temperature over the course of 4 – 5 hours using triethylamine as a solvent and base. With aryl bromide substrates, the reactions were performed at reflux for 5 – 16 hours.

A much cleaner reaction profile was observed with Boc-protected propargylamine as a coupling partner. To access differently protected substrates for scope studies, large scale synthesis of the Boc protected derivative 2.3d was carried out, followed by deprotection with HCl in ethyl acetate. After removal of solvents, this salt was protected under typical conditions. Using this protocol the more challenging substrates, such as 2.11, could be prepared (Scheme 2.12).

---

\(^{59}\) For examples of sulfonamide coupling: (a) Burton, G.; Cao, P.; Li, G.; Rivero, R. *Org. Lett.* 2003, 5, 4373; (b) Alcaraz, L.; Bennion, C.; Morris, J.; Meghani, P.; Thom, S. M. *Org. Lett.* 2004, 6, 2705.

Table 2.1 Synthesis of substrates through Sonogashira coupling.

R\[Cl (X = Br or I)] + \[\text{Alkyne} \rightarrow \text{Pd(PPh}_3\text{)}_2\text{Cl}_2 \text{ (2 mol%)} + \text{Cul (4 mol%)} \rightarrow \text{Solvent / Base} \rightarrow \text{Product}

Table 2.2 Synthesis of substrates through protecting group exchange.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>PG</th>
<th>Yield (%)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.3e</td>
<td>SO(_2)Ph</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>2.3f</td>
<td>SO(_2)(p-MeO-C(_6)H(_4))</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>2.3g</td>
<td>SO(_2)(p-O(_2)N-C(_6)H(_4))</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>2.3h</td>
<td>SO(_2)(2,4,6-Me(_3)-C(_6)H(_2))</td>
<td>60</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yields.

Scheme 2.12 Synthesis of pyridine substrate 2.11.

\[\text{Br (Cl)} \rightarrow \text{Pd(PPh}_3\text{)}_2\text{Cl}_2 \text{ (2 mol%)} + \text{Cul (4 mol%)} \rightarrow \text{Solvent / Base} \rightarrow \text{Product} \rightarrow \text{1) HCl (3 M) EtoAc, r.t.} \rightarrow \text{2) MsCl (1.1 equiv) NEt}_3 \text{ (2.2 equiv) DCM, 0 \text{°C to r. t.}} \rightarrow \text{Product 2.11} \rightarrow 39\% \text{ over three steps} \]
2.2.3 Optimization Studies

**Alkyne Arylation.** To obtain good yields in a domino process such as this, we optimized the yields of both reactions separately. We carried out significant optimization of the rhodium-catalyzed arylation reaction (Table 2.3 and 2.4). Racemic BINAP (L7) was found to be the optimal ligand for alkyne arylation of 2.3b, yielding the product in 63% yield (entries 1-6, Table 2.3). The regioselectivity was generally good, but was dependent on the temperature of the reaction, the base, and the ligand used. Addition of methanol instead of water improved the reaction outcome, increasing the yield and giving higher regioisomeric ratio (entry 19).

**Table 2.3** Optimization of reaction conditions in rhodium-catalyzed alkyne arylation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>L</th>
<th>Base</th>
<th>Solvent/Additive</th>
<th>T (°C)</th>
<th>2.4b (%)</th>
<th>r. r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>dppp</td>
<td>L1</td>
<td>K₂CO₃</td>
<td>dioxane/H₂O</td>
<td>60</td>
<td>(24)</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>dppf</td>
<td>L2</td>
<td>K₂CO₃</td>
<td>dioxane/H₂O</td>
<td>60</td>
<td>(27)</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>P(4-FC₆H₄)₃</td>
<td>L3</td>
<td>K₂CO₃</td>
<td>dioxane/H₂O</td>
<td>60</td>
<td>(54)</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>PPh₃</td>
<td>L4</td>
<td>K₂CO₃</td>
<td>dioxane/H₂O</td>
<td>60</td>
<td>(&lt;5)</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>P(4-MeOC₆H₄)₃</td>
<td>L5</td>
<td>K₂CO₃</td>
<td>dioxane/H₂O</td>
<td>60</td>
<td>(&lt;5)</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>P(C₆F₅)₃</td>
<td>L6</td>
<td>K₂CO₃</td>
<td>dioxane/H₂O</td>
<td>60</td>
<td>0⁵</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>cod</td>
<td>K₂CO₃</td>
<td>dioxane/H₂O</td>
<td>60</td>
<td>0⁵</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>BINAP</td>
<td>L7</td>
<td>K₂CO₃</td>
<td>dioxane/H₂O</td>
<td>80</td>
<td>47</td>
<td>7.5:1</td>
</tr>
<tr>
<td>9</td>
<td>BINAP</td>
<td>L7</td>
<td>K₂CO₃</td>
<td>dioxane/H₂O</td>
<td>60</td>
<td>56</td>
<td>10:1</td>
</tr>
<tr>
<td>10ᵉ</td>
<td>BINAP</td>
<td>L7</td>
<td>K₂CO₃</td>
<td>dioxane/H₂O</td>
<td>r.t.</td>
<td>63</td>
<td>13:1</td>
</tr>
<tr>
<td>11</td>
<td>BINAP</td>
<td>L7</td>
<td>-</td>
<td>dioxane/H₂O</td>
<td>60</td>
<td>(18)</td>
<td>7:1</td>
</tr>
<tr>
<td>12</td>
<td>BINAP</td>
<td>L7</td>
<td>Cs₂CO₃</td>
<td>dioxane/H₂O</td>
<td>60</td>
<td>(40)</td>
<td>12:1</td>
</tr>
<tr>
<td>13</td>
<td>BINAP</td>
<td>L7</td>
<td>Na₂CO₃</td>
<td>dioxane/H₂O</td>
<td>60</td>
<td>(36)</td>
<td>8:1</td>
</tr>
<tr>
<td>14</td>
<td>BINAP</td>
<td>L7</td>
<td>K₃PO₄</td>
<td>dioxane/H₂O</td>
<td>60</td>
<td>(32)</td>
<td>10:1</td>
</tr>
<tr>
<td>15</td>
<td>BINAP</td>
<td>L7</td>
<td>KOAc</td>
<td>dioxane/H₂O</td>
<td>60</td>
<td>(53)</td>
<td>20:1</td>
</tr>
<tr>
<td>16</td>
<td>BINAP</td>
<td>L7</td>
<td>NEt₃</td>
<td>dioxane/H₂O</td>
<td>60</td>
<td>(49)</td>
<td>9:1</td>
</tr>
<tr>
<td>17</td>
<td>BINAP</td>
<td>L7</td>
<td>K₂CO₃</td>
<td>THF/H₂O</td>
<td>60</td>
<td>(51)</td>
<td>12:1</td>
</tr>
<tr>
<td>18</td>
<td>BINAP</td>
<td>L7</td>
<td>K₂CO₃</td>
<td>toluene/H₂O</td>
<td>60</td>
<td>(50)</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>19</td>
<td>BINAP</td>
<td>L7</td>
<td>K₂CO₃</td>
<td>dioxane/MeOH</td>
<td>60</td>
<td>67</td>
<td>&gt;20:1</td>
</tr>
</tbody>
</table>

a [Rh] and ligand and base were weighed into a vial, which was then purged with argon. Dioxane and additive were added and catalyst solution was stirred for 10 minutes at r.t.; Solution of alkyne and boronic acid was added and the vial was sealed with a Teflon-lined septum and stirred at the indicated temperature for 16 hours. b Isolated yields, yields in parentheses indicate NMR yields. c Measured from crude NMR. d Decomposition was observed. e 48 hour reaction time.
When we examined the effect of the protecting group on the propargylamine, it became apparent that the nature of this substituent was very important (entries 1-10, Table 2.4). Sulfonate based protecting groups gave the best outcome, with carbamate and amide derivatives giving lower conversion. A variety of boronic acid derivatives were also examined, and similar outcomes were observed with boronic acids, esters, and boroxine (entries 14-17). Somewhat higher regioisomeric purity was noted when boronic esters were used.

**Table 2.4** Effect of protecting group and boronic acid derivative on yield.a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>PG</th>
<th>PhB(OR)₂</th>
<th>Solvent/Additive</th>
<th>Product</th>
<th>2.4 (%)b</th>
<th>r. r.c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>CO₂Et</td>
<td>PhB(OH)₂</td>
<td>dioxane/H₂O</td>
<td>-</td>
<td>(&lt;50)</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>2.3d</td>
<td>CO₂t-Bu</td>
<td>PhB(OH)₂</td>
<td>dioxane/H₂O</td>
<td>2.4d</td>
<td>(&lt;5)</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>COMe</td>
<td>PhB(OH)₂</td>
<td>dioxane/H₂O</td>
<td>-</td>
<td>(30)</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>2.3c</td>
<td>Ms</td>
<td>PhB(OH)₂</td>
<td>dioxane/H₂O</td>
<td>2.4c</td>
<td>71</td>
<td>12:1</td>
</tr>
<tr>
<td>5</td>
<td>2.3c</td>
<td>Ms</td>
<td>PhB(OH)₂</td>
<td>dioxane/MeOH</td>
<td>2.4c</td>
<td>77</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>6</td>
<td>2.3e</td>
<td>SO₂Ph</td>
<td>PhB(OH)₂</td>
<td>dioxane/H₂O</td>
<td>2.4e</td>
<td>70</td>
<td>9:1</td>
</tr>
<tr>
<td>7</td>
<td>2.3i</td>
<td>Tf</td>
<td>PhB(OH)₂</td>
<td>dioxane/H₂O</td>
<td>2.4i</td>
<td>(40)</td>
<td>14:1</td>
</tr>
<tr>
<td>8</td>
<td>2.3j</td>
<td>COPh</td>
<td>PhB(OH)₂</td>
<td>dioxane/H₂O</td>
<td>2.4j</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>2.3k</td>
<td>CO₂Ph</td>
<td>PhB(OH)₂</td>
<td>dioxane/H₂O</td>
<td>2.4k</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>2.3l</td>
<td>PO₃Ph₂</td>
<td>PhB(OH)₂</td>
<td>dioxane/H₂O</td>
<td>2.4l</td>
<td>33</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>2.3b</td>
<td>Ts</td>
<td>PhB(OH)₂</td>
<td>dioxane/H₂O</td>
<td>2.4b</td>
<td>62</td>
<td>9:1</td>
</tr>
<tr>
<td>12</td>
<td>2.3b</td>
<td>Ts</td>
<td>PhB(OH)₂</td>
<td>dioxane/MeOH</td>
<td>2.4b</td>
<td>70</td>
<td>19:1</td>
</tr>
<tr>
<td>13d</td>
<td>2.3b</td>
<td>Ts</td>
<td>PhB(OH)₂</td>
<td>dioxane/MeOH</td>
<td>2.4b</td>
<td>66</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>14</td>
<td>2.3b</td>
<td>Ts</td>
<td>PhBF₃K</td>
<td>dioxane/MeOH</td>
<td>2.4b</td>
<td>63</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>15</td>
<td>2.3b</td>
<td>Ts</td>
<td>Phbin</td>
<td>dioxane/MeOH</td>
<td>2.4b</td>
<td>63</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>16</td>
<td>2.3b</td>
<td>Ts</td>
<td>(PhBO)₃</td>
<td>dioxane/MeOH</td>
<td>2.4b</td>
<td>67</td>
<td>15:1</td>
</tr>
<tr>
<td>17</td>
<td>2.3b</td>
<td>Ts</td>
<td>PhBO₂C₂H₆</td>
<td>dioxane/MeOH</td>
<td>2.4b</td>
<td>58</td>
<td>&gt;20:1</td>
</tr>
</tbody>
</table>

*a* See Table 2.3 for conditions. *b* Isolated yields, yields in parentheses indicate NMR yields using 1,3,5-trimethoxybenzene as an internal standard. *c* Measured from crude NMR using the alkenyl proton resonance. *d* Using Cs₂CO₃ as base.

Following the optimization of the rhodium-catalyzed arylation, it was found that the best conditions utilized dioxane and methanol as solvent and K₂CO₃ as base. Methanesulfonylamine group was superior to other protecting groups. We screened a number of boronic acids in this transformation (Table 2.5). The key observations showed that the electronics of the boronic acid
had little influence on the yield of the reaction (entries 3-5). The alcohol derivatives of these alkynes were also examined, and the desired alkenes could be isolated, albeit in lower yields (Scheme 2.13).

**Table 2.5** Effect of boronic acid substitution on yield of arylation.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>PG</th>
<th>Ar</th>
<th>Yield (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.3b</td>
<td>2.4b</td>
<td>Ts</td>
<td>Ph</td>
<td>73</td>
</tr>
<tr>
<td>2(^c)</td>
<td>2.3c</td>
<td>2.4c</td>
<td>Ms</td>
<td>Ph</td>
<td>77</td>
</tr>
<tr>
<td>3(^d)</td>
<td>2.3b</td>
<td>2.12</td>
<td>Ts</td>
<td>4-F(_3)CC(_6)H(_4)</td>
<td>69</td>
</tr>
<tr>
<td>4(^d)</td>
<td>2.3b</td>
<td>2.13</td>
<td>Ts</td>
<td>4-MeC(_6)H(_4)</td>
<td>64</td>
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<tr>
<td>5(^d)</td>
<td>2.3b</td>
<td>2.14</td>
<td>Ts</td>
<td>4-MeOC(_6)H(_4)</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>2.3b</td>
<td>2.15</td>
<td>Ts</td>
<td>3-thiophenyl</td>
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<td>2.3c</td>
<td>2.16</td>
<td>Ms</td>
<td>3-thiophenyl</td>
<td>77</td>
</tr>
</tbody>
</table>

\(^a\) See Table 2.3 for conditions. \(^b\) Isolated yields. \(^c\) Reaction conducted at 60 °C. \(^d\) Performed by L. Zhang.

**Scheme 2.13** Arylation of propargylic and homopropargylic alcohols.\(^61\)

**C-N coupling.** Our preliminary experiments on the C-N coupling reaction were very promising, and minimal optimization was necessary (Table 2.6). X-Phos (L_2-10) was found to be the optimal ligand for this transformation.\(^62\) When alcohol additives were examined, it became apparent that methanol and tert-butanol improved both the rate and the yield of the reaction.

---

\(^{61}\) Experiments performed by L. Zhang.

The coupling also proceeded in higher yield with methanesulfonylamine substrate 2.4c compared to the toluenesulfonylamine substrate 2.4b (92% vs. 83%, entries 4 and 5).

Table 2.6 Optimization of C-N coupling.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>PG</th>
<th>Ligand</th>
<th>Base (equiv)</th>
<th>Additive (mL)</th>
<th>Product</th>
<th>T (°C)</th>
<th>2.5 (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Ts</td>
<td>Xantphos\textsuperscript{c}</td>
<td>L8</td>
<td>Cs₂CO₃ (1.4)</td>
<td>-</td>
<td>2.5b</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>Ts</td>
<td>Davephos</td>
<td>L9</td>
<td>Cs₂CO₃ (1.4)</td>
<td>-</td>
<td>2.5b</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>Ts</td>
<td>X-Phos</td>
<td>L10</td>
<td>Cs₂CO₃ (1.4)</td>
<td>-</td>
<td>2.5b</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>Ts</td>
<td>X-Phos</td>
<td>L10</td>
<td>K₂CO₃ (1.4)</td>
<td>MeOH (0.1)</td>
<td>2.5b</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>Ms</td>
<td>X-Phos</td>
<td>L10</td>
<td>K₂CO₃ (1.4)</td>
<td>MeOH (0.1)</td>
<td>2.5c</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>Ts</td>
<td>X-Phos</td>
<td>L10</td>
<td>Cs₂CO₃ (1.4)</td>
<td>MeOH (0.1)</td>
<td>2.5b</td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td>Ts</td>
<td>X-Phos</td>
<td>L10</td>
<td>Cs₂CO₃ (1.4)</td>
<td>MeOH (0.1)</td>
<td>2.5b</td>
<td>70</td>
</tr>
<tr>
<td>8</td>
<td>Ts</td>
<td>X-Phos</td>
<td>L10</td>
<td>Cs₂CO₃ (1.4)</td>
<td>MeOH (0.1)</td>
<td>2.5b</td>
<td>70</td>
</tr>
<tr>
<td>9</td>
<td>Ts</td>
<td>X-Phos</td>
<td>L10</td>
<td>Cs₂CO₃ (1.4)</td>
<td>MeOH (0.1) + t-BuOH (0.1)</td>
<td>2.5b</td>
<td>70</td>
</tr>
<tr>
<td>10</td>
<td>Ts</td>
<td>X-Phos</td>
<td>L10</td>
<td>Cs₂CO₃ (1.4)</td>
<td>MeOH (0.1) + t-BuOH (0.5)</td>
<td>2.5b</td>
<td>70</td>
</tr>
</tbody>
</table>

\textsuperscript{a} [Pd] and ligand (and base) were weighed into a vial, which was then purged with argon. Dioxane and additive were added and the catalyst solution was stirred for 10 minutes at r. t. Solution of substrate was added. Vial was sealed and heated for 16 hours. \[\textsuperscript{b}\] Isolated yields, yields in parentheses indicate NMR yields using 1,3,5-trimethoxybenzene as an internal standard. \[\textsuperscript{c}\] 3 mol% of ligand were used.

We were interested in combining the two steps into a single reaction vessel (Scheme 2.14). To prevent incorrect catalyst complex formation, the ligand-metal solutions were prepared separately prior to addition of the substrates.\textsuperscript{63} Gratifyingly, the overall transformation proceeded in a combined yield similar to the two reaction steps done independently (69% vs. 71%). Examples of domino reactions catalyzed by two different transition metals are rare, thus we elected to investigate the interactions between the two catalyst systems further.

2.2.4 Mechanistic Studies

An interesting feature of this catalytic system is that both transition metal complexes are bound to structurally different phosphine ligands, which could potentially dissociate and exchange between the two metals. In turn, these alternative metal-ligand combinations can have dramatically different reactivity with the components of the reaction.

Control experiments. To survey the reactivity of the possible metal-ligand combinations we carried out several control experiments on each step (Table 2.7). Phosphine-free [Rh(cod)OH]$_2$ led primarily to decomposition of 2.3c (entry 2). The arylation reaction using X-Phos as a ligand gave low yields of 2.4c (5%) and a significant amount of decomposition (40%, entry 3). Subjecting the substrate 2.3c to [Pd(BINAP)] gave only starting material (entry 4)$^{64}$ and using [Pd(X-Phos)] instead led to byproduct formation.

Upon closer examination we found that [Pd(X-Phos)] furnished the Suzuki cross-coupling product 2.19 in good yield (76%, Eqn 2.16).$^{65}$ The reaction of 2.4c with [Pd(BINAP)] yielded only trace amounts of 2.5c, showing that this was not an effective catalyst for C-N coupling of this aryl chloride.

---


Table 2.7 Reaction of 2.3c with different catalyst-ligand combinations.\(^a\)

![image of reaction](attachment:image.png)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>(mol%)</th>
<th>Ligand</th>
<th>(mol%)</th>
<th>2.3c (%)(^b)</th>
<th>2.4c (%)(^b)</th>
<th>2.5c (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Rh(cod)OH](_2)</td>
<td>2.5</td>
<td>BINAP</td>
<td>5.2</td>
<td>0</td>
<td>77(^c)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>[Rh(cod)OH](_2)</td>
<td>2.5</td>
<td>-</td>
<td>-</td>
<td>0(^d)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>[Rh(cod)OH](_2)</td>
<td>2.5</td>
<td>X-Phos</td>
<td>10</td>
<td>56</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)(_2)</td>
<td>2</td>
<td>BINAP</td>
<td>2</td>
<td>96</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)(_2)</td>
<td>2</td>
<td>X-Phos</td>
<td>4</td>
<td>6(^e)</td>
<td>0</td>
<td>9</td>
</tr>
</tbody>
</table>

\(^a\) Conditions: Catalyst, ligand and base were weighed into a vial, which was purged with argon. Half of dioxane and methanol were added, and the catalyst mixtures were premixed for 15 minutes. Solution of substrates was added and the reaction was stirred at 90 °C for 16 hours. \(^b\) NMR yields obtained using 1,3,5-trimethoxybenzene as internal standard. \(^c\) Isolated yield. \(^d\) Decomposition observed. \(^e\) Formation of byproduct 2.19 observed.

From these control experiments it became apparent that [Rh(BINAP)] yielded the desired product and phosphine-free rhodium lead to decomposition of 2.3c. The formation of [Pd(X-Phos)] was equally important since [Pd(BINAP)] was catalytically inactive in C–N coupling.

The formation of compound 2.19 is significant. Unlike some other examples of domino catalysis, in this system the placement of the second catalyst into the domino system expands the available scope of reactivity. This possibility for Suzuki coupling further complicates the reaction, and necessitates compatibility of the rates of the three available processes. It is thus remarkable that the domino reaction occurs in such a high efficiency in comparison to the two-step process.

**31P NMR experiments.** Both reactions utilize specialized phosphine ligands, which have the potential to exchange between the metal centers. We observed that Pd(OAc)\(_2\) forms discrete complexes with both BINAP and X-Phos.\(^{66}\) While rhodium is known to bind BINAP,\(^{63}\) no complexation of rhodium and X-Phos was seen by 31P NMR.\(^{67}\) These NMR experiments suggested that palladium could bind both phosphine ligands, however rhodium could only complex BINAP.

---

\(^{66}\) See Experimental Section for 31PNMR spectra of these complexes.  
\(^{67}\) Hydrogenation of cod with H\(_2\) \textit{in situ} did not yield any observable rhodium X-Phos complexation
Catalyst inhibition in alkyne arylation. We further examined the effect of Pd(OAc)₂ or X-Phos addition on the conversion of the alkyne arylation reaction (Figure 2.7). When the reaction was run with X-Phos present in the catalyst solution, minimal effect on the reaction was observed (entry 2 vs. 1). In contrast, addition of 5 mol% of Pd(OAc)₂ led to only trace formation of 2.4c (5%, entry 3), while with the addition of 5 mol% of [Pd(X-Phos)] solution to the reaction mixture, the conversion of 2.3c returned to >70% (entry 4). With higher [Pd(X-Phos)] loading the Suzuki product 2.19 was formed in substantial amounts (entry 5). Interestingly, no Suzuki products containing the hydroarylated alkene, such as 2.20, were ever observed in the optimized reaction, indicating that even though an excess of the arylboronic acid is used, the Suzuki coupling is slower than intramolecular C–N coupling with compound 2.4c.

---

Reactions were carried out with premixing of Rh-BINAP and Pd-X-Phos catalyst solution separately for 15 minutes at 50 °C. All yields are based on crude NMR using 1,3,5-trimethoxybenzene as internal standard. See Table 2.8 for conditions.
Catalyst inhibition in C-N coupling. Similarly, we examined the C–N coupling step (Figure 2.8). While 92% yield of product 2.5c was achieved using [Pd(X-Phos)], only 4% of product was obtained when [Pd(BINAP)] was utilized (entry 4, Table 2.7). This observation had significant implications on the domino process, considering that any ligand interchange between rhodium and palladium could be deleterious to the C–N bond formation. In fact, when the reaction was carried out using a premixed [Pd(X-Phos)] catalyst solution and an added 5 mol% of BINAP, the yield plummeted from 92% to 3% (entry 2, Figure 2.8). When we looked at the reaction of 2.4c with added 5 mol% of [Rh(BINAP)OH]₂ the yield returned to 91% (entry 4). With higher rhodium loading (10 mol%, entry 5) a decrease in conversion was observed, possibly resulting from catalyst inhibition by trace binap in solution. Addition of [Rh(cod)OH]₂ had no noticeable effects on the reaction outcome (entry 3).

![Diagram of reaction](image)

**Figure 2.8:** Effect of alkyne arylation components on the yield of C-N coupling.

We can observe the direct dependence of the conversion of 2.4c to product 2.5c with respect to BINAP loading (Figure 2.9a). The reaction was stopped at partial conversion (70% at 40 min at 90 °C), to probe the effect BINAP has on the rate of the reaction. It becomes evident that with
over 2 mol% of BINAP, significant inhibition is observed. Considering that Suzuki reaction of 2.3c was a competing process, we opted to see whether the boronic acid interfered in the C-N coupling reaction. When the reaction was carried out in the presence of phenylboronic acid, no deleterious effects on the yield of the reaction were observed (Figure 2.9b) nor were any products resembling 2.20 detected.

![Figure 2.9](image-url)  
*Figure 2.9: a) Effect of BINAP addition on conversion of 2.4c to 2.5c; b) Effect of PhB(OH)₂ on yield of C-N coupling of 2.4c.*

Ligand interference was further confirmed when examining the Rh/Pd ratio in the domino reaction (Figure 2.10). When increasing the loading of the [Rh(BINAP)] catalyst, progressively less product 2.5c was formed, and the reaction stalled at the intermediate stage. Adding free BINAP had a much more prominent deleterious effect (entry 5, Figure 2.10a).

Varying the ligand equivalents showed similar trends (Table 2.8). With BINAP loading exceeding 5.5 mol%, the reaction stalled at the intermediate stage (entries 1-4). Addition of excess X-Phos did not remedy this effect; in fact using excess of X-Phos lowered the yield (entries 4-6). While counterintuitive at first, this is consistent with an inverse rate dependence
often observed with bulky phosphine ligands, which is caused by saturation of the coordination sites on palladium.$^{69}$

The experiments described above gave us some insight into the mechanism of the reaction (Scheme 2.15). It appears that the two catalytic cycles occur independently, and no direct interactions between the two active metal complexes exist. Initially, the substrate 2.3c reacts rapidly under rhodium catalysis to yield 2.4c, which can then cyclize through a palladium-catalyzed C–N coupling to yield the product 2.5c. An alternative reaction pathway occurs where 2.3c undergoes Suzuki cross-coupling to give 2.19, but with optimized catalyst ratios this pathway is suppressed. Additionally, inhibition of the C–N coupling by BINAP is observed. We propose that [Rh(BINAP)OH]$_2$ solution is a source of trace amounts of free BINAP, but Rh-BINAP binding largely remedies the inhibitory effect of the free ligand.

---

Table 2.8 Effect of ligand loading on the domino reaction.\textsuperscript{a}

\begin{center}
\begin{tabular}{|c|c|c|c|c|c|}
\hline
Entry & BINAP (mol\%) & X-Phos (mol\%) & 2.4c (%)\textsuperscript{b} & 2.5c (%)\textsuperscript{b} & 2.4c:2.5c \\
\hline
1 & 5.2 & 4 & 6 & 69 & 1:11 \\
2 & 5.5 & 4 & 22 & 47 & 1:2.1 \\
3 & 7.5 & 4 & 38 & 33 & 1:2.1 \\
4 & 10 & 4 & 55 & 27 & 2:1 \\
5 & 10 & 2 & 47 & 36 & 1:3.1 \\
6 & 10 & 6 & 61 & 21 & 2.9:1 \\
7 & 10 & 8 & 75 & 6 & 12.5:1 \\
\hline
\end{tabular}
\end{center}

\textsuperscript{a} Conditions: Stock solutions of Rh/BINAP and Pd/X-Phos were prepared by premixing in dioxane at 50 °C. Alkyne, boronic acid base and extra additives were weighed into a vial, which was purged with argon. Catalyst solutions were added via syringe, vial was sealed and heated to 90 °C for 16 h.\textsuperscript{b} NMR yields using 1,3,5-trimethoxybenzene as an internal standard.

Scheme 2.15 a) The proposed mechanism of the domino dihydroquinoline synthesis; b) Mode of catalyst inhibition.
2.2.5 Scope Studies

The domino reaction proceeded in an overall yield of 69%, in comparison to the two-step combined yield of 72%. However isolation of the intermediate in good yield and purity was often problematic because of the presence of minor by-products. We examined the effect of the nitrogen protecting group and it was found that electron neutral groups were optimal (Table 2.9). The sterically encumbered mesitylsulfonate group inhibited the C-N coupling (entry 6).

Table 2.9 Scope of the N-protecting group in the domino reaction.a

<table>
<thead>
<tr>
<th>Entry</th>
<th>PG</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ts</td>
<td>2.5b</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>Ms</td>
<td>2.5c</td>
<td>69</td>
</tr>
<tr>
<td>3</td>
<td>SO2Ph</td>
<td>2.5e</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>SO2(4-MeOC6H4)</td>
<td>2.5f</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>SO2(4-O2NC6H4)</td>
<td>2.5g</td>
<td>36</td>
</tr>
<tr>
<td>6</td>
<td>SO2(2,4,6-Me3C6H3)</td>
<td>2.5h</td>
<td>(&lt;15)</td>
</tr>
</tbody>
</table>

a See Table 2.10 for conditions. b Isolated yields for domino process, NMR yields in brackets.

Investigations of the scope of boronic acids showed that electron rich and electron poor aryl and heteroarylboronic acids could be used in moderate to good overall yields (Table 2.10). We observed significantly higher yields when using 3-thienylboronic acid as the nucleophile (entries 3 vs. 1). A competition experiment indicated that this boronic acid is approximately five times more reactive than phenylboronic acid (Scheme 2.16). In general higher yields were obtained for methanesulfonyl substituted substrates than their p-toluenesulfonyl protected counterparts.

The reaction also tolerated a number of different substituents on the propargylamine substrates (Table 2.11). The presence of electron withdrawing substituents improved the reaction outcome, which is consistent with more favorable electronic properties of these alkynes. With the CF3 substituted compound, performing the reaction in two-stage heating (60 °C for 1.5 h then 90 °C) had a very subtle beneficial effect (81% versus 78%, entries 5 and 6). An interesting example derived from alkynyl pyridine 2.10 also furnished the desired 1,5-naphthyridine derivative 2.40, albeit in moderate yield.
Table 2.10 Scope of boronic acids in the domino reaction.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>PG</th>
<th>Yield (%)\textsuperscript{b}</th>
<th>Entry</th>
<th>Product</th>
<th>PG</th>
<th>Yield (%)\textsuperscript{b}</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>Ms</td>
<td>2.5c</td>
<td>13</td>
<td></td>
<td>Ms</td>
<td>2.27</td>
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<tr>
<td>2</td>
<td></td>
<td>Ts</td>
<td>2.5b</td>
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<td>2.28</td>
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<td>Ts</td>
<td>2.23b</td>
<td>20</td>
<td></td>
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<td>2.33c</td>
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<tr>
<td>9\textsuperscript{c}</td>
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<td>10</td>
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<td>Ms</td>
<td>2.25c</td>
<td></td>
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<td>11\textsuperscript{c}</td>
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<tr>
<td>12\textsuperscript{c}</td>
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<td>Ts</td>
<td>2.26</td>
<td></td>
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</tr>
</tbody>
</table>

\textsuperscript{a} Stock catalyst solutions ([Rh\textsubscript{2}(0.005 M) with BINAP (1.05 equiv to [Rh] and Pd(OAc)\textsubscript{2} (0.008 M) with X-Phos (2 equiv to [Pd])), were mixed separately in dioxane at 50 °C for 15 min. 0.5 ml of each solution was added to a vial containing the alkyne (0.2 mmol, 49 mg), boronic acid (0.4 mmol, 49 mg), K\textsubscript{2}CO\textsubscript{3} (61 mg) and 100μl MeOH in 1 ml of dioxane. The mixture was stirred at 90 °C for 16 h.\textsuperscript{b} Isolated yields for domino process.\textsuperscript{c} Performed by L. Zhang. |
Scheme 2.16 Competition experiment between phenylboronic acid and 3-thienylboronic acid.

Table 2.11 Scope of the domino reaction.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield (%)\textsuperscript{b}</th>
<th>Entry</th>
<th>Product</th>
<th>Yield (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{c}</td>
<td>MeO\textsubscript{2}N</td>
<td>2.34</td>
<td>54</td>
<td>6\textsuperscript{c}</td>
<td>F \textsubscript{2}N</td>
</tr>
<tr>
<td>2</td>
<td>F\textsubscript{3}C</td>
<td>2.35</td>
<td>78</td>
<td>7\textsuperscript{c}</td>
<td>F \textsubscript{2}N</td>
</tr>
<tr>
<td>3\textsuperscript{d}</td>
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</tr>
<tr>
<td>4</td>
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<td>70</td>
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</tr>
<tr>
<td>5</td>
<td></td>
<td>2.37</td>
<td>63</td>
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<td></td>
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</tbody>
</table>

\textsuperscript{a} See Table 2.10 for conditions. \textsuperscript{b} Isolated yields for domino process. \textsuperscript{c} Performed by L. Zhang. \textsuperscript{d} Reaction carried out at 60 °C over 1.5 h then heated to 90 °C for 14.5 h.

It was also possible to use this method to synthesize 2\textit{H}-chromene products (Scheme 2.17). These products were obtained in lower yields under the standard conditions, mostly because of
lower conversion of the intermediate to product, and a mixture of intermediate and product was often isolated. It was crucial to have a sufficiently active catalyst for the second reaction in the domino sequence, since combining multiple catalysts in our studies, seemed to further slow down the C-N/C-O cross coupling rate. We could obtain moderate yields if using a different palladium source ([Pd(allyl)Cl]₂) and toluene as a solvent.

![Scheme 2.17 Domino synthesis of 2H-chromenes.](image)

### 2.2.6 Product Derivatization

The obtained dihydroquinolines are interesting structural motifs and substituted quinolines are common in biologically active molecules and natural products. The 1,2-dihydroquinolines could be easily converted into quinoline **2.44** in high yields through an elimination reaction (Scheme 2.18).

![Scheme 2.18 Synthesis of quinolines through elimination of the protecting group.](image)

Experiments performed by L. Zhang using conditions described in Table 2.10.
In addition to this, we also demonstrated that the chromene products can be enantioselectively dihydroxylated to give the diol 2.45 (Scheme 2.19). The alkene in these products could also be hydrogenated according to literature precedent.  

![Scheme 2.19 Dihydroxylation of chromene product.](image)

### 2.2.7 Conclusions

Our work on reductive arylation of alkynes has led to a domino synthesis of dihydroquinolines through a combination of rhodium and palladium catalysis. We found that the transformation occurred with nearly identical yields when carried out in domino or stepwise manner. The two catalytic systems appeared to function independently. Some inhibition of palladium-catalyzed C–N coupling by the rhodium arylation ligand was observed. Our work provides a rare example of a system where two transition metal complexes with different phosphine ligands capable of dissociation, function along a desired pathway, even when other reaction pathways are available.

Having realized a domino multicatalytic synthesis of dihydroquinolines, we were excited by the prospect of developing other transformations using this reactivity. The following section illustrates that this is achievable. We applied this rhodium and palladium catalyst combination to a synthesis of aza-dibenzoaxepines, a very useful heterocyclic motif in biological chemistry.

### 2.3 Rhodium and Palladium Catalysis in the Synthesis of Aza-Dibenzoaxepines

#### 2.3.1 Dibenazepines and Dibenzoaxepines

Dibenzoaxepines and dibenazepines are compounds comprised of a seven-membered oxygen or nitrogen-containing ring annealed to two benzene rings (Figure 2.11). These motifs are present in a variety of biologically active molecules.

---

The N-alkylated azepines are particularly interesting since they comprise a large portion of tricyclic antidepressants (TCAs), which have been used to treat major depressive disorders. Although currently largely replaced by newer antidepressants with more favorable side-effect profiles, compounds containing the dibenzazepine core still gather a lot of interest. In addition to antidepressant properties, dibenzazepine derivatives have been shown to have antiallergic, spasmolytic, serotonin antagonistic, antiemetic, antiepileptic, antiinflammatory, sedative, and fungicidal activities.

Dibenzoxepines are also found in some pharmaceutical agents, for instance Bermoprofen and Asenapine. This motif is also common in natural products with varied and often strong biological activities. Notable examples are bulbophylols, atrocarpols, bauhinoxepins, and cularine alkaloids.

2.3.2 Synthetic Methods to Access Dibenzoazepines and Dibenzoxepines

Although the backbone structure of these tricyclic motifs is readily available, analogous compounds with substitution on the aryl rings are more difficult to access. Recent studies show that differently substituted analogues can have significantly more interesting biological properties. The synthesis of substituted analogues is often accomplished by substituting the core structure, usually through reactions based on electrophilic aromatic substitution. These classical reactions often proceed in low yields and give regioisomeric mixtures of products with limited control over site selectivity. Occasionally, lithiation chemistry can be used to access substitution at the 4 and 6 positions.

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72 For a review on TCA use see Gillman, P. K. J Pharmacol. 2007, 151, 737.
73 Such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).
There are a number of de-novo syntheses of these tricyclic motifs. The earliest methods to access the dibenzazepine backbone was reported by Thiele and Holzinger and was later utilized to synthesize symmetrical frameworks (Eqn 2.17). Although diamine synthesis was straightforward the key cyclization proceeded in very low yields.

Figure 2.11: Dibenzoxepine and dibenzazepine structural motif in biologically active compounds.

\[
\begin{align*}
\text{dibenzo}[(b,f)]\text{oxepin-10(11H)-one} & & 10,11\text{-dihydrodibenzo}[(b,f)]\text{oxepine} \\
& & \text{"dibenzoaxepin"} \\
\text{10,11\text{-dihydro-5H-dibenzo}[(b,f)]\text{azepine}} & & \text{"dibenzazepin"}
\end{align*}
\]

*Pharmaceutical agents*

- **Quinupramine**
  - TCA
  - R = Me; X = Cl: Clomipramine
  - R = Me; X = H: Imipramine
  - R = X = H: Desipramine
  - X = H; R = CH₂C(O)(4-ClC₆H₄): Lofepramine TCA

- **Metapramine**
  - TCA
  - R = Me; X = H: Metipramine

- **Opipramol**
  - TCA
  - R = Me; X = H: Desipramine

- **Bermoprofen**
  - Nonsteroidal antiinflammatory drug

*Natural products*

- **Bauhinaxepin D**
  - Cytoxic
  - R¹ = H; R² = OMe: Cularine
  - R¹ = OMe; R² = H: Sarcocapnine

- **Atrocarp A**
  - Antiinflammatory agent

- **Bulbophylo B**
  - Antitumour properties

---

\[ 81 \text{ (a) Thiele, J.; Holzinger, O. Liebig's Ann. Chem.} \textbf{1899}, \textit{305}, 100. \]
This strategy was later adapted to access non-symmetric products, but required lengthy substrate synthesis featuring the Horner-Wadsworth-Emmons olefination (Eqn 2.18).

\[
\begin{align*}
\text{NO}_2 \quad \text{Me} & \xrightarrow[1) \text{Halogenation}]{2) \text{Substitution}} \text{NO}_2 \quad \text{P}(O)\text{OE}_2 \quad \text{R}^1 \quad \text{R}^2 \\
\text{H} \quad \text{O} \quad \text{NO}_2 & \xrightarrow[1) \text{Horner-Wadsworth-Emmons olefination}]{2) \text{Reduction}} \text{NH}_2 \quad \text{NH}_2 \quad \text{R}^2
\end{align*}
\] (2.18)

Other strategies to form the 7-membered ring were reported by Bergman\(^8^2\) featuring an intramolecular coupling of a dibromide A (Eqn 2.19). Alternatively, the N-aryl bond could be formed through C-N coupling of B using Goldberg conditions with copper powder as a catalyst.\(^8^3\) Although these methods were higher yielding, the former required quite harsh reaction conditions, and the latter utilized a lengthy linear substrate synthesis (akin to Eqn 2.18).

The dibenzoxepine motifs are commonly accessed from dibenzo[b,f]oxepin-10(11\(H\))-one through reduction (Eqn 2.20). This precursor is most often synthesized through a Friedel-Crafts type cyclization of the appropriately substituted biaryl ether C.\(^8^4\) This classic chemistry often furnishes the products in moderate to good yields, but regioselectivity is an issue with meta substituted nucleophilic aryl groups.

\[
\begin{align*}
\text{O} \quad \text{R} \quad \text{C} & \xrightarrow[\text{AlCl}_3 \text{ or Polyposphoric acid}
\text{70 – 100 °C}]
\text{O} \quad \text{O} \quad \text{C} \quad \text{R}^1 \quad \text{R}^2 \\
\text{reduction} & \xrightarrow[50 - 75\%]{}
\text{O} \quad \text{O} \quad \text{C} \quad \text{R}^1 \quad \text{R}^2
\end{align*}
\] (2.20)

---


\(^{8^4}\) For an examples see: Paduraru, M. P.; Wilson, P. D. *Org. Lett.* **2003**, *5*, 4911.
A recent example from the Buchwald group showed that the dibenzoepine can be synthesized through C-O coupling of the corresponding aryl bromide (Eqn 2.21).\textsuperscript{85} Reports of copper-catalyzed C-O coupling of similar intermediates can also be found.\textsuperscript{86}

Clearly, appropriately substituted diarylethanes comprise a common starting point for constructing the azepine and oxepine ring. Earlier work in the Lautens group demonstrated that vinylpyridines could be used as substrates in rhodium-catalyzed arylation reactions to give 2- and 4-phenethylpyridines (Eqn 2.22).\textsuperscript{87} We proposed that this reaction could be used as a key step in a synthesis of aza-analogues of dibenzoepines and dibenazapines (Eqn 2.23). These motifs have never been synthesized before and could have interesting biological properties. Furthermore, the reactions utilized in this sequence are both robust and could be run under similar conditions, possibly making this process amenable to domino catalysis.


Portions of the following section were carried out by Vaizanne Huynh\textsuperscript{88} and Adam Friedman,\textsuperscript{89} under the mentorship of the author. The project was conceived and initiated by the author; then V. Huynh and A. Friedman further investigated the scope of the transformation. V. Huynh’s and A. Friedman’s contributions are acknowledged where appropriate. This work was ongoing during the writing of this thesis and a complete set of results will be published in due course.

2.3.3 Reactions of Vinylpyridines

Earlier work from the Lautens group demonstrates that vinylpyridines behave significantly differently than their styrene counterparts under rhodium catalysis. In the 2001 report, it was described that in reactions of (het)aryl olefins with boronic acids, an unsaturated Heck-type product was obtained with styrenes, and a formal hydroarylation product was observed with the nitrogen-containing heterocycles (Eqn 2.22). This work was followed shortly thereafter by a report from the Michelet and Genet group reporting similar reactivity.\textsuperscript{90} The difference in reactivity of vinylpyridines and styrenes under rhodium catalysis can be attributed to stabilization of a benzylic rhodium intermediate through nitrogen coordination, which could inhibit $\beta$-hydride elimination (I, Figure 2.12). An alternative explanation is that an aza-$\pi$-allylrhodium complex II is formed, which is susceptible to protonation by water to give the saturated product.

![Figure 2.12: Proposed stabilization of alkylrhodium intermediate.](image)

Recently, Lam reported an enantioselective variant of this reaction using diene ligands and dioxane/water solvent combination (Eqn 2.24).\textsuperscript{91} This reaction gave high yields and good

\textsuperscript{88} V. H. was a visiting summer student from Paris, France, who contributed to the optimization of this reaction.

\textsuperscript{89} A. F. was a Master’s student at the time of this publication, who contributed to the scope of this transformation.


selectivity with quinoline, quinoxaline, pyrimidine and oxazole derivatives, but vinylpyridine was not reactive under the reaction conditions.

Similar reactivity is also possible under ruthenium catalysis, as reported by Kochi and Kakiuchi (Eqn 2.25). In this example it is proposed that elimination of methanol from pyridylethyl ethers yields vinylpyridines, which then react with arylboroxines. The intermediacy of vinylpyridine was confirmed by $^1$H NMR. 2-Methyl-4-vinylpyridine furnished the highest yields, with 2-vinylpyridine giving the product in 60% yield.

2-Phenethylpyridines can also be accessed from 2-vinylpyridines through a Heck addition/hydrogenation sequence, superacid promoted addition of benzene, or hydroboration followed by cross-coupling. More often than not, the vinylpyridines behave similar to styrenes, and a number of examples of Heck additions, metathesis reactions, or hydroformylations of

---

vinylpyridines have been reported. Soft nucleophiles such as malonates can also be added to vinylpyridines, although the reversibility of these reactions can be problematic.\textsuperscript{99} The position β to pyridine can also be functionalized directly through C-H functionalization, wherein the pyridine nitrogen functions as a directing group to facilitate C-H activation.\textsuperscript{100}

### 2.3.4 Substrate Synthesis

The vinylpyridine substrates could be accessed in 1-2 steps from commercially available materials. Although not always high yielding, the methods we used relied on transition metal catalysis and were by far more direct than other approaches. The vinylpyridine compound 2.46 could be accessed through either Suzuki or Stille coupling of 2-bromo- or 2-chloropyridines. The Suzuki reaction was optimal for pyridyl bromide substrates and avoided the use of toxic tin reagents (Table 2.12).

For the dichloropyridine substrates the more robust Stille coupling was necessary. Electron neutral, rich and some electron-poor substrates could be synthesized in high yields (Table 2.13). We encountered some difficulty in accessing CF₃ and NO₂ substituted compounds 2.47 and 2.48, as well as the quinoxaline derivative 2.52 (Eqn 2.26). In these cases, because of product decomposition and side reactions, the coupling reactions had to be carefully monitored in terms of reaction time and temperature. Nevertheless, a useful amount of material could be obtained for these substrates.

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Table 2.12 Synthesis of substrates through Suzuki cross-coupling.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>B(OR)\textsubscript{2}</th>
<th>Conditions</th>
<th>Yield (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{BF}_4K )</td>
<td>Pd(PPh\textsubscript{3}) \textsubscript{4} (2.5 mol%), K\textsubscript{2}CO\textsubscript{3} (1 equiv) THF/H\textsubscript{2}O (3.5:1), 90 °C, 16 h</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>( \text{BF}_4K )</td>
<td>Pd(PPh\textsubscript{3}) \textsubscript{4} (2.5 mol%), K\textsubscript{2}CO\textsubscript{3} (1 equiv) THF/H\textsubscript{2}O (3.5:1), 75 °C, 16 h</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>( \text{BF}_4K )</td>
<td>Pd(PPh\textsubscript{3}) \textsubscript{4} (2.5 mol%), K\textsubscript{2}CO\textsubscript{3} (1 equiv) THF/H\textsubscript{2}O (3.5:1), 70 °C, 16 h</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>( \text{BF}_4K )</td>
<td>Pd(dppe)\textsubscript{Cl}\textsubscript{2}CH\textsubscript{2}Cl\textsubscript{2} (2 mol%), t-BuNH\textsubscript{2} (3 equiv) i-PrOH/H\textsubscript{2}O (2:1), 88 °C, 16 h</td>
<td>60</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reaction conditions: [Pd], base and solid starting materials were weighed into a flask. Reaction was purged with argon, solvents and liquid starting materials were added as solution. Reaction was heated to the indicated temperature for 16 h. \textsuperscript{b} Isolated yields.

Table 2.13 Synthesis of substrates using Stille cross-coupling.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>Product</th>
<th>Yield (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CF\textsubscript{3}</td>
<td>80</td>
<td>16</td>
<td>2.47</td>
<td>65</td>
</tr>
<tr>
<td>2\textsuperscript{c}</td>
<td>NO\textsubscript{2}</td>
<td>100</td>
<td>3</td>
<td>2.48</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>Morpholine</td>
<td>100</td>
<td>16</td>
<td>2.49</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>CO\textsubscript{2}Me</td>
<td>85</td>
<td>16</td>
<td>2.50</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>CONHBn</td>
<td>80</td>
<td>16</td>
<td>2.51</td>
<td>74</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reaction conditions: [Pd], LiCl and dichloropyridine were weighed into a flask. Reaction was purged with argon, solvent and tributylvinyltin were added. Reaction was heated to the indicated temperature and time. \textsuperscript{b} Isolated yields. \textsuperscript{c} Cul (5 mol%) was used as an additive as well as LiCl.
Synthesizing electron deficient vinylpyridines with a substituent at the terminal end of the alkene, such as 2.53, was less problematic since these compounds were significantly more stable. Suzuki coupling conditions were used to access these motifs (Eqn 2.27).

$$\text{F}_3\text{C} \text{Cl} \text{N} \text{Cl} + (\text{HO})\text{B} \text{Cl} \text{n-Hex} \xrightarrow{\text{Pd(dppf)Cl}_2\text{-DCM} (5 \text{ mol\%})} \text{F}_3\text{C} \text{Cl} \text{N} \text{Cl} \text{n-Hex} \quad 2.53 \quad 87\%$$

2.3.5 Optimization Studies

In the early stages of this project we carried out some optimization studies (Table 2.14). A good starting point was the set of conditions established for arylation in our synthesis of dihydroquinolines. Early on it was observed that BINAP was not the optimal ligand and much higher yields were obtained using dppp (entries 1-4). Methanol was also not necessary for the reaction and water was used as an additive instead. The reaction did not work in $t$-BuOH as a solvent. Under the optimized conditions the reaction was very clean and high yields were obtained.

Table 2.14 Optimization of arylation of 3-chloro-2-vinylpyridine.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand (mol%)</th>
<th>Base</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Conversion (%)(^b)</th>
<th>Yield (%)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^d)</td>
<td>dppf (4)</td>
<td>$\text{K}_2\text{CO}_3$</td>
<td>dioxane/$\text{H}_2\text{O}$ (10:1)</td>
<td>16</td>
<td>15</td>
<td>(10)</td>
</tr>
<tr>
<td>2(^d)</td>
<td>BINAP (4)</td>
<td>$\text{K}_2\text{CO}_3$</td>
<td>dioxane/$\text{H}_2\text{O}$ (10:1)</td>
<td>16</td>
<td>33</td>
<td>(5)</td>
</tr>
<tr>
<td>3(^d)</td>
<td>dppp (4)</td>
<td>$\text{K}_2\text{CO}_3$</td>
<td>dioxane/$\text{H}_2\text{O}$ (10:1)</td>
<td>5</td>
<td>100</td>
<td>94</td>
</tr>
<tr>
<td>4(^d)</td>
<td>PPh$_3$ (8)</td>
<td>$\text{K}_2\text{CO}_3$</td>
<td>dioxane/$\text{H}_2\text{O}$ (10:1)</td>
<td>16</td>
<td>60</td>
<td>(52)</td>
</tr>
<tr>
<td>5(^d)</td>
<td>dppp (4)</td>
<td>KOAc</td>
<td>dioxane/$\text{H}_2\text{O}$ (10:1)</td>
<td>16</td>
<td>40</td>
<td>(23)</td>
</tr>
<tr>
<td>6(^d)</td>
<td>dppp (4)</td>
<td>NEt$_3$</td>
<td>dioxane/$\text{H}_2\text{O}$ (10:1)</td>
<td>5</td>
<td>95</td>
<td>(67)</td>
</tr>
<tr>
<td>7(^d)</td>
<td>dppp (4)</td>
<td>Cs$_2\text{CO}_3$</td>
<td>dioxane/$\text{H}_2\text{O}$ (10:1)</td>
<td>5</td>
<td>96</td>
<td>(55)</td>
</tr>
<tr>
<td>8(^d)</td>
<td>dppp (4)</td>
<td>$\text{K}_2\text{CO}_3$</td>
<td>$t$-BuOH</td>
<td>16</td>
<td>33</td>
<td>(15)</td>
</tr>
<tr>
<td>9(^d)</td>
<td>dppp (4)</td>
<td>$\text{K}_2\text{CO}_3$</td>
<td>dioxane/MeOH (1:1)</td>
<td>16</td>
<td>89</td>
<td>(37)</td>
</tr>
</tbody>
</table>

\(^a\)Rhodium, ligand, and base presterred for 10 minutes. Solution of starting materials was added to the reaction, which was then sealed and heated at 60 °C for the indicated time. \(^b\)Determined from crude NMR using 1,3,5-trimethoxybenzene as internal standard. \(^c\)Isolated yields, yields in parentheses indicate NMR yields determined using 1,3,5-trimethoxybenzene as internal standard. \(^d\)Performed by V. Huynh.
The C-O coupling was somewhat more challenging and the conditions we used previously for C-N coupling gave only 30% yield of the cyclized product 2.55, even at 120 °C (entry 1, Table 2.15). In order to improve this reaction a number of variables were examined. tert-Butanol is known to accelerate C-N/C-O coupling reactions by increasing the basicity of the medium, and when we used this solvent, full conversion was observed and the product could be obtained in 84% yield (entry 3). The more reactive palladacycle worked well in the reaction, giving good yields of the product at 100 °C (entry 7). We examined other conditions, more often used for C-O coupling. Ullman coupling conditions using copper and phenanthroline resulted in very low conversion (entry 8). Hartwig’s Josiphos ligand did not give the desired product and byproduct formation was observed (entry 9). Slightly modified Buchwald conditions using t-Bu-X-Phos as a ligand and K₃PO₄ as a base in toluene furnished the product in high yields (entry 10). Using these conditions we reexamined X-Phos and K₂CO₃ and found that this ligand and base were inferior. Reaction in dioxane, however, gave high yields as long as t-Bu-X-Phos and K₃PO₄ combination was used (entry 14). With the reaction giving full conversion under milder conditions we could consider developing a domino process.

Our first attempts at combining the arylation of 2.46 and C–O coupling of 2.54 into a domino process were not successful. The first reaction in the sequence proceeded very efficiently but almost no cyclization to give the final product 2.55 occurred. This finding was not surprising since we found the C–O coupling to form 2.55 to be more challenging than the C–N coupling in dihydroquinoline synthesis (vide infra). In the latter case we also observed that the rate of the C–N coupling decreased in the domino process. We attempted to carry out this reaction using even bulkier ligands (i.e., t-BuBrettPhos), stronger base (NaOt-Bu), and more polar solvent additives (t-BuOH), but to no avail; the reaction always stalled at the intermediate or generated alternative products. It became clear that options for more favorable reaction conditions were limited, and the reaction would be dependent on substrate electronics. Nevertheless, this two-step method still provided interesting motifs very efficiently and we worked on developing the scope of the reaction.

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### Table 2.15 Optimization of C-N coupling.\(^a\)

![Diagram](image_url)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Ligand (mol%)</th>
<th>Base (equiv)</th>
<th>Solvent (M)</th>
<th>T(°C) / t (h)</th>
<th>Conversion (%)(^b)</th>
<th>Yield (%)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^d)</td>
<td>Pd(OAc)(_2) (2)</td>
<td>X-Phos (4)</td>
<td>K(_2)CO(_3) (1.5)</td>
<td>Dioxane (0.1)</td>
<td>120 / 24</td>
<td>33 (32)</td>
<td></td>
</tr>
<tr>
<td>2(^d)</td>
<td>Pd(OAc)(_2) (2)</td>
<td>X-Phos (4)</td>
<td>K(_2)CO(_3) (1.5)</td>
<td>Dioxane/t-BuOH (1:1, 0.2)</td>
<td>120 / 36</td>
<td>34 (33)</td>
<td></td>
</tr>
<tr>
<td>3(^d)</td>
<td>Pd(OAc)(_2) (2)</td>
<td>X-Phos (4)</td>
<td>K(_2)CO(_3) (1.5)</td>
<td>t-BuOH (0.2)</td>
<td>120 / 24</td>
<td>100 (84)</td>
<td></td>
</tr>
<tr>
<td>4(^d)</td>
<td>Pd(OAc)(_2) (2)</td>
<td>X-Phos (4)</td>
<td>K(_3)PO(_4) (1.5)</td>
<td>t-BuOH (0.2)</td>
<td>120 / 24</td>
<td>49 (45)</td>
<td></td>
</tr>
<tr>
<td>5(^d)</td>
<td>Pd(OAc)(_2) (2)</td>
<td>X-Phos (4)</td>
<td>K(_3)PO(_4) (1.5)</td>
<td>Dioxane (0.2)</td>
<td>120 / 24</td>
<td>52 (41)</td>
<td></td>
</tr>
<tr>
<td>6(^d)</td>
<td>Pd(OAc)(_2) (2)</td>
<td>X-Phos (4)</td>
<td>K(_2)CO(_3) (1.5)</td>
<td>t-BuOH (0.2)</td>
<td>100 / 48</td>
<td>47 (10)</td>
<td></td>
</tr>
<tr>
<td>7(^d)</td>
<td>Pd(OAc)(_2) (2)</td>
<td>-</td>
<td>K(_2)CO(_3) (1.5)</td>
<td>t-BuOH (0.2)</td>
<td>100 / 16</td>
<td>87 (71)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Cul (5)</td>
<td>1,10-phenanthroline (10)</td>
<td>Cs(_2)CO(_3) (1.5)</td>
<td>PhMe (0.1)</td>
<td>100 / 16</td>
<td>&lt;5</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>Pd(OAc)(_2) (5)</td>
<td>Josiphos(^e)</td>
<td>NaOt-Bu (1.5)</td>
<td>DME (0.3)</td>
<td>100 / 16</td>
<td>30 (0)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Pd(OAc)(_2) (5)</td>
<td>t-Bu-X-Phos (7)</td>
<td>K(_3)PO(_4) (2)</td>
<td>PhMe (0.3)</td>
<td>100 / 16</td>
<td>100 (87)</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Pd(OAc)(_2) (5)</td>
<td>t-Bu-X-Phos (7)</td>
<td>K(_3)PO(_4) (2)</td>
<td>PhMe (0.2)</td>
<td>100 / 5</td>
<td>100 (89)</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Pd(OAc)(_2) (5)</td>
<td>X-Phos (7)</td>
<td>K(_3)PO(_4) (2)</td>
<td>PhMe (0.2)</td>
<td>100 / 5</td>
<td>33 (23)</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Pd(OAc)(_2) (5)</td>
<td>t-Bu-X-Phos (7)</td>
<td>K(_2)CO(_3) (2)</td>
<td>PhMe (0.2)</td>
<td>100 / 5</td>
<td>77 (63)</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Pd(OAc)(_2) (5)</td>
<td>t-Bu-X-Phos (7)</td>
<td>K(_3)PO(_4) (2)</td>
<td>Dioxane (0.2)</td>
<td>100 / 5</td>
<td>100 (87)</td>
<td></td>
</tr>
</tbody>
</table>

\(a\) Catalyst, ligand, and base were weighed into a vial, which was then purged with argon. Solvent(s) were added and the catalyst mixture was prestirred for 10 minutes. Solution of starting materials was added to the reaction, which was then sealed and heated at the indicated temperature and time. \(b\) Determined from crude NMR using 1,3,5-trimethoxybenzene as internal standard. \(c\) Isolated yields, yields in parentheses indicate NMR yields determined using 1,3,5-trimethoxybenzene as internal standard. \(d\) Performed by V. Huynh. \(e\) Josiphos = (R)-1-[(SP)-2-(Dicyclohexylphosphino)ferrocenyl]ethyldi-tert-butylphosphine.

### 2.3.6 Substrate Scope for Hydroarylation

Initially a variety of different ortho-hydroxyphenylboronic acids were examined (Table 2.16). The notable features of this investigation were that substitution at any position of the benzene ring could be accessed through this method. Even 2,6-disubstituted boronic ester furnished the product 2.58 in good yield. Both electron rich and electron poor substituents were well tolerated, and it was observed that higher yields were obtained with boronic acids instead of esters at lower
reaction temperatures. In practice, accessing the ester substrates was significantly easier. The cyclization of these structures is ongoing and will be reported in due time.

**Table 2.16** Scope of arylation of vinylpyridine.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.46</td>
<td>[Rh(cod)OH]₂ (2 mol%) dppp (4 mol%)</td>
<td>95%³⁵</td>
</tr>
<tr>
<td>2.54</td>
<td>Boronic acid used instead of ester, reaction run at 60 °C</td>
<td>93%³⁵</td>
</tr>
<tr>
<td>2.56</td>
<td>Boronic acid used instead of ester, reaction run at 60 °C</td>
<td>93%³⁵</td>
</tr>
<tr>
<td>2.57</td>
<td>Boronic acid used instead of ester, reaction run at 60 °C</td>
<td>93%³⁵</td>
</tr>
<tr>
<td>2.58</td>
<td>Boronic acid used instead of ester, reaction run at 60 °C</td>
<td>93%³⁵</td>
</tr>
<tr>
<td>2.59</td>
<td>Boronic acid used instead of ester, reaction run at 60 °C</td>
<td>93%³⁵</td>
</tr>
<tr>
<td>2.60</td>
<td>Boronic acid used instead of ester, reaction run at 60 °C</td>
<td>93%³⁵</td>
</tr>
<tr>
<td>2.61</td>
<td>Boronic acid used instead of ester, reaction run at 60 °C</td>
<td>93%³⁵</td>
</tr>
<tr>
<td>2.62</td>
<td>Boronic acid used instead of ester, reaction run at 60 °C</td>
<td>93%³⁵</td>
</tr>
<tr>
<td>2.63</td>
<td>Boronic acid used instead of ester, reaction run at 60 °C</td>
<td>93%³⁵</td>
</tr>
</tbody>
</table>

³ Conditions: Rhodium, ligand and base were weighed into a vial, purged with argon. Solvent and water was added and the catalyst solution was stirred at r.t. for 15 min. Solution of substrates was added, the reaction was heated for 16 h. ³ Boronic acid used instead of ester, reaction run at 60 °C. ³ Performed by V. Huynh. ³ Performed by A. Friedman. ³ 2 mol% of dppp used.

### 2.3.7 Development and Optimization of the Domino Reaction

Through the synthesis of substituted boronic acids we could access a variety of substitution patterns on the aryl group of the azadibenzoxepine products. We were equally interested in modifying the pyridine fragment. Although Suzuki cross coupling gave very low yields when 2,3-dichloropyridines were used as substrates, we observed they could be functionalized under Stille coupling conditions. One of the first derivatives that we studied was the 5-trifluoromethylvinyl pyridine 2.47. We viewed that by adding electron withdrawing substituents on the pyridine ring both of the transformations would be favorably affected since this fragment functions as an electrophile in both the rhodium-catalyzed arylation and palladium-catalyzed C-O coupling. We attempted to carry out the two reactions in a stepwise, one-pot, and domino sequence, and were pleased to find that the reaction sequence proceeded to completion, giving the azadibenzoxepines 2.64 as a major product with no starting material or intermediate 2.63 detected by TLC or ¹H NMR (Table 2.17). We observed a higher overall yield in a one-pot process then a stepwise reaction, where the crude from the first reaction was filtered through
silica and concentrated before being subjected to the second set of conditions. The domino reaction proceeded in moderate yield, but this preliminary result was promising, and we opted to carry out further optimization of the domino sequence.

Table 2.17 Comparison of different protocols for synthesis of 2.64. a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Protocol</th>
<th>T / t</th>
<th>SM (%) b</th>
<th>I (%) b</th>
<th>P (%) b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>One-pot: Pd, t-Bu-X-Phos, and K3PO4 added as a solid after completion of Step 1.</td>
<td>100 °C for 16 h; then 100 °C for 24 h</td>
<td>0</td>
<td>0</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>Stepwise: Filtered through silica plug between reactions</td>
<td>60 °C for 16 h; then 100 °C, for 24 h</td>
<td>0</td>
<td>0</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>Domino: All components present from the start of reaction</td>
<td>100 °C for 16 h.</td>
<td>0</td>
<td>0</td>
<td>56</td>
</tr>
</tbody>
</table>

a Catalyst-ligand solutions were premixed prior to substrate and base addition. Reactions were done under argon atmosphere. b NMR yields using 1,3,5-trimethoxybenzene as internal standard.

We found that the reaction was more reproducible when the pinacol ester was used instead of the free boronic acid, largely because the ester could be obtained in higher purity and there was less variation in purity between different batches of this substrate. We first examined the effect that the ratio of rhodium to palladium would have on this transformation (Table 2.18). Surprisingly, no effects on yield were observed when we increased or decreased the amount of palladium catalyst in the system. This indicated that Suzuki cross-coupling was not a competitive process in this reaction. Additionally, at lower palladium loading we did not observe any difference in product / intermediate ratio of the reaction. Unlike with dihydroquinolines, higher relative dppp loading in reactions with low palladium/X-Phos loading did not interfere in the C-O coupling. This outcome likely occurred either because of better complexation of dppp to rhodium, or because the reactivity of palladium-t-Bu-X-Phos catalyst was sufficiently high to mask any inhibitory effects in the experiments we examined.
Table 2.18  Effect of Rh:Pd ratio on reaction of 2.64.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd (mol%)</th>
<th>t-Bu-X-Phos (mol%)</th>
<th>2.47 (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>2.63 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>2.64 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.5</td>
<td>3.5</td>
<td>0</td>
<td>0</td>
<td>63</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>64</td>
</tr>
<tr>
<td>3</td>
<td>7.5</td>
<td>10.5</td>
<td>0</td>
<td>0</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>64</td>
</tr>
</tbody>
</table>

<sup>a</sup> Catalyst-ligand solutions were premixed prior to substrate and base addition. Reactions were done under argon atmosphere. <sup>b</sup> NMR yields using 1,3,5-trimethoxybenzene as internal standard.

With this information in hand we examined the effect of ligand loading on the transformation (Table 2.19). When we varied the dppp loading in the reaction, we were surprised to observe that a significantly higher yield of 2.64 was obtained in the absence of this ligand (entry 1-3). Evidently, the 1,5-cyclooctadiene served as a better ligand than the bisphosphine. A larger excess of dppp further lowered the yield of the transformation (entry 3). This effect was not caused by inhibition of C-O coupling, since no intermediate was observed in any of these reactions. Instead, byproduct formation accounted for the decreasing mass balance. Increasing t-Bu-X-Phos loading had little effect on the reaction (entry 6), but conducting the reaction in the absence of this ligand gave only intermediate 2.63 (entry 4). This result shows that t-Bu-X-Phos is absolutely necessary for oxidative addition into the C-Cl bond. It should be noted that in the absence of Pd(OAc)2 only the arylation reaction occurred, suggesting that the reaction most likely did not proceed through an S<sub>N</sub>Ar type of mechanism (entry 7).

<sup>102</sup> Diene ligands are known to be effective in this transformation ; See Pattison, G.; Piraux, G.; Lam, H. W. *J. Am. Chem. Soc.* 2010, 132, 14373.
Table 2.19 Effect of ligand loading on reaction.\textsuperscript{a}

\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
Entry & dppp (mol\%) & t-Bu-\text{X}Phos (mol\%) & 2.47 (\%)\textsuperscript{b} & 2.63 (\%)\textsuperscript{b} & 2.64 (\%)\textsuperscript{b} \\
\hline
1 & 0 & 7 & 0 & 0 & 73 \\
2 & 4 & 7 & 0 & 0 & 57 \\
3 & 8 & 7 & 0 & 0 & 45 \\
4 & 4 & 0 & 0 & 77 & 0 \\
5 & 4 & 7 & 0 & 0 & 57 \\
6 & 4 & 14 & 0 & 0 & 54 \\
7\textsuperscript{c} & 0 & 7 & 0 & 83 & 0 \\
\hline
\end{tabular}

\textsuperscript{a} Catalyst-ligand solutions were premixed prior to substrate and base addition. Reactions were done under argon atmosphere. \textsuperscript{b} NMR yields using 1,3,5-trimethoxybenzene as internal standard. \textsuperscript{c} Reaction performed in the absence of Pd(OAc)\textsubscript{2}.

Interestingly, if the vinylpyridine substrate was subjected to the reaction conditions in the presence of only the palladium catalyst system, significant amount of hydroarylation occurred, but no C-O coupling product was detected (Eqn 2.28). Palladium-catalyzed additions of boronic acids to \(\alpha,\beta\)-unsaturated ketones and esters is known,\textsuperscript{103} but there are no reports of this reactivity with vinylpyridines.\textsuperscript{104}

We examined other substrates bearing electron withdrawing substituents (Table 2.20). In addition to the CF\textsubscript{3} group, CO\textsubscript{2}Me and NO\textsubscript{2} groups sufficiently biased the electronics to allow a domino process to occur. Although 2.48 gave only 49% yield of 2.66, no starting material or product was observed in the reaction, and from previous work it is known that nitro substituted


\textsuperscript{104} The most relevant example of similar hydroarylation features an intramolecular Heck-type of addition to a styrene alkene, followed by migration to form a palladium enolate, which is protonated: Gagnier, S. V.; Larock, R. C. \textit{J. Am. Chem. Soc.} \textbf{2003}, \textit{125}, 4804.
compounds are prone to decomposition in rhodium-catalyzed arylation reactions.\textsuperscript{105} When we examined a vinylpyridine 2.51 bearing an amide only the intermediate phenol 2.80 could be isolated. It was apparent that the pyridine moiety had to be sufficiently electron-poor in order to allow this domino reaction to take place. This could result from palladium catalyst inhibition or decomposition during the reaction.

Table 2.20  Aza-dibenzoxepines obtained from domino reaction.\textsuperscript{a}

\[
\begin{array}{ccc}
\text{R}^1 \text{Cl} + \text{R}^{\text{OH}} \text{B(pin)} & \overset{[\text{Rh(cod)OH}]_2 (2 \text{ mol})}{\text{Pd(OAc)}_2 (5 \text{ mol})}; \text{t-Bu-XPhos} (7 \text{ mol})} & \text{K}_2\text{CO}_3 (2 \text{ equiv}); \text{K}_3\text{PO}_4 (2 \text{ equiv}) \\
(2 \text{ equiv}) & \text{Dioxane/H}_2\text{O} (10:1) & \text{R}^1 \text{O} = \text{R}^2
\end{array}
\]

\[
\begin{array}{ccc}
\text{F}_3\text{C} & \text{MeO}_2\text{C} & \text{O}_2\text{N} \\
\text{N} & \text{N} & \text{N}
\end{array}
\]

\[
\begin{array}{ccc}
2.64 & 2.65 & 2.66 \\
71\% & 72\% & 49\%
\end{array}
\]

\textsuperscript{a} Conditions: All of the substrates, catalysts, ligands, and bases were weighed into a single vial, which was purged with argon. Solvents were added and the reaction was stirred at r.t. for 10 minutes before being heated at 100 °C for 16 h.

As expected, when we examined substrates bearing electron neutral or electron donating groups on the pyridine ring, only the hydroarylation proceeded under the domino conditions, with minimal C-O coupling occurring (Table 2.21). An electron rich morpholinovinylpyridine 2.49 required higher temperature and boronic ester loading to obtain full conversion and higher yields of 2.68. It was apparent that in this case the hydrolysis of the boronic ester became competitive with alkene arylation.\textsuperscript{106} Furthermore we confirmed that the arylation of vinyl pyridines is very selective for the vinyl group ortho to the nitrogen. Substrates bearing a vinyl group in a meta position (2.71) did not give any product under the reaction conditions of the first step. Similarly, a divinyl pyridine led to formation of 2.70 selectively.

\textsuperscript{105} We also observed this in reactions of 4-nitrophenylalkynes with boronic acids.

\textsuperscript{106} Hydrolysis of boronic acids and esters in protic conditions is facile at high reaction temperatures, and high boronic acid loading is often necessary; see original report: Hayashi, T.; Inoue, K.; Tamiguchi, N.; Ogasawara, M. J. Am. Chem. Soc. \textbf{2001}, 123, 9918.
Table 2.21 Stepwise reactions of more electron rich aza-dibenzoxepines.\textsuperscript{a}

\begin{equation*}
\begin{array}{c}
\text{R} \quad \text{Cl} \\
\text{N} \quad \text{O} \\
\end{array}
\quad \begin{array}{c}
\text{R} \quad \text{Cl} \\
\text{N} \quad \text{O} \\
\end{array}
\quad \begin{array}{c}
\text{R} \quad \text{Cl} \\
\text{N} \quad \text{O} \\
\end{array}
\end{equation*}

\begin{equation*}
\text{BnHNOC} \\
\text{Intermediate 2.67: 90\%} \\
\end{equation*}

\begin{equation*}
\text{O} \quad \text{N} \\
\text{Intermediate 2.68: 78\%} \\
\text{Product 2.69: 60\%} \\
\end{equation*}

\begin{equation*}
\text{\textit{no reaction}} \\
\text{Intermediate 2.70: 60\%} \\
\end{equation*}

\textsuperscript{a} See Table 2.14 and 2.15 for reaction conditions, no dppp used. \textsuperscript{b} Using 5 equiv of boronic ester at 100 °C. \textsuperscript{c} Yield of intermediate obtained from a domino reaction.

2.3.8 Development of an Enantioselective Domino Reaction

In 2010, Lam and coworkers showed that when using chiral diene ligands it is possible to add boronic acids to vinylpyridines with substituents on the alkene.\textsuperscript{91} Since we found that [Rh(cod)OH]\textsubscript{2} complex was highly effective in the reaction of 3-chloro-2-vinylpyridine 2.47 it could be imagined that chiral azadibenzoxepines could be accessed. To our gratification, subjecting the substituted vinylpyridine 2.53 to the typical reaction conditions using [Rh(cod)OH]\textsubscript{2} yielded the desired phenol 2.72 in good yield (Scheme 2.20). This compound cyclized very efficiently to give the racemic product 2.73 in an overall yield of 65\%.

\begin{equation*}
\begin{array}{c}
\text{F}_3\text{C} \quad \text{Cl} \\
\text{N} \quad \text{O} \\
\text{n-Hex} \\
\end{array}
\quad \begin{array}{c}
\text{F}_3\text{C} \quad \text{Cl} \\
\text{N} \quad \text{O} \\
\text{n-Hex} \\
\end{array}
\quad \begin{array}{c}
\text{F}_3\text{C} \quad \text{Cl} \\
\text{N} \quad \text{O} \\
\text{n-Hex} \\
\end{array}
\end{equation*}

\begin{equation*}
\text{2.53} \\
\text{2.72} \\
\text{2.73} \\
\end{equation*}

\begin{equation*}
\text{81 \%} \\
\text{80 \%} \\
\end{equation*}

\textbf{Scheme 2.20 Synthesis of racemic 2.88.}

We screened several diene ligands, including ligands developed by Carreira (L\textsubscript{11}), Genet (L\textsubscript{12}) and Hayashi (L\textsubscript{13}, Table 2.22). The hydroarylation proceeded with good enantiomeric control. The e.r. values that we observed were similar to the reported values, and neither the ortho-chloro nor the ortho-hydroxy substituent impacted the stereochemical outcome significantly.
Table 2.22  Survey of chiral dienes for an enantioselective arylation of 2.53.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>L</th>
<th>[Rh]</th>
<th>T</th>
<th>2.53 (%)(^b)</th>
<th>2.72 (%)(^b)</th>
<th>e.r.(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td></td>
<td>[Rh(cod)OH](_2)</td>
<td>60</td>
<td>0</td>
<td>80</td>
<td>50:50</td>
</tr>
<tr>
<td>3</td>
<td>L11</td>
<td></td>
<td>[Rh(C(_2)H(_4))(_2)OH]_2</td>
<td>80</td>
<td>32</td>
<td>35</td>
<td>10:90</td>
</tr>
<tr>
<td>4</td>
<td>L12</td>
<td></td>
<td>[Rh(C(_2)H(_4))(_2)OH]_2</td>
<td>80</td>
<td>6</td>
<td>64</td>
<td>88:12</td>
</tr>
<tr>
<td>5</td>
<td>L13</td>
<td></td>
<td>-</td>
<td>80</td>
<td>26</td>
<td>47</td>
<td>95:5</td>
</tr>
</tbody>
</table>

\(^a\) Conditions: [Rh]\(_2\), base and substrates were weighed into vial, purged with argon. Solvents were added and reaction was heated to indicated temperature for 16h. With L11 and L12 [Rh]\(_2\) and ligand are premixed at room temperature for 20 minutes. \(^b\) NMR yields. \(^c\) Determined using chiral HPLC of the crude reaction mixture.

The highest enantiomeric excess (90\%) was obtained using a rhodium complex based on the Hayashi ligand L13. We tested this catalyst in a domino transformation and were pleased to find that the final product 2.73 could be isolated in moderate yield with high enantiomeric excess (Eqn 2.29). With this result in hand, ongoing work is dedicated to exploring this reaction in more detail to improve the yield and expand the scope.

2.3.9  Further Work toward Azadibenbazepine Synthesis

Dibenbazepines are significantly more represented in biological literature than dibenzoepines, and we were very interested in adapting our method to their synthesis. In practice, we encountered several difficulties in achieving this goal. Accessing N-alkyl substituted ortho-
aminoarylboronic esters was challenging, and when we did attempt a reaction using 2.75 or unsubstituted 2.74, the hydroarylation reaction failed (Scheme 2.21). Using the more readily available N-methanesulfonyl substituted compound 2.76 was more effective, and the aniline product 2.79 could be isolated in 67% yield. When we attempted to cyclize this compound through C-N coupling we were again met with failure. Only small amounts of the desired azadibenzoazepine could be observed by NMR.

At this stage we modified our strategy, and examined the reaction of ortho-halogenated boronic acids 2.80a and 2.80b with vinylpyridine 2.47 (Scheme 2.22). Both bromide and chloride substitution was tolerated and the dihalogenated products 2.81a and 2.81b could be obtained in good yields. It is foreseeable that these compounds could be functionalized in a number of ways to yield interesting heterocycles.

Although the investigation of the reactivity of 2.81a and 2.81b is ongoing, we have preliminary results on the C-N coupling reaction (Eqn 2.30). When 2.81a and 2.81b were subjected to the standard coupling conditions in the presence of 3-phenyl-1-propylamine, the major products obtained in both reactions were different, but isomeric by mass spectrometry. At this stage it is
apparent that a single C-N coupling event with the more reactive C-X bond takes place in both cases, generating two uncyclized isomers 2.82a and 2.82b.

Current work in our group is focused on exploring these results further and potentially developing a trimolecular coupling reaction to generate tricyclic products such as 2.83 (Eqn 2.31). It is possible that the double C-N coupling reaction will require more reactive catalyst-ligand combination, or a two ligand combination adapted for coupling of both primary and secondary amines.107

2.4 Conclusions

Domino reactions attempt to address the need for less wasteful and more time- and cost-efficient synthetic pathways. At this time, the use of multiple transition-metal catalyzed transformations in domino processes is rare. The above chapter discusses domino multienzyme syntheses of dihydroquinolines and dibenzoxepines, wherein rhodium-catalyzed arylations products were cyclized via palladium-promoted C–N or C–O coupling (Eqn 2.32 and 2.33).

107 An example of this strategy is described by Buchwald: (a) Fors, B. P.; Buchwald, S. L. J. Am. Chem. Soc. 2010, 132, 15914; the use of multiple ligands with a single catalysts have also been reported by Cole-Hamilton: (b) Boogaerts, I. I. F.; White, D. F. S.; Cole-Hamilton, D. J. Chem. Commun. 2010, 46, 2194.
We undertook detailed mechanistic investigations of the dihydroquinolines system in order to gain some insight into the nature of the interactions between the two catalytic systems. What we observed was that the two catalytic cycles appeared to function independently of one another, although we detected some inhibition of palladium-catalyzed C–N coupling by traces of free ligand used in the rhodium catalyzed step. Nevertheless, the domino reaction proceeded in equivalent yields to the sequential reaction protocol. This dihydroquinoline synthesis provides an example of a system where two transition metal complexes with different phosphine ligands capable of dissociation, function along a desired pathway, even when other reaction pathways are available. It is remarkable that even though competitive Suzuki coupling is possible, selective formation of dihydroquinolines occurs. In this particular sequence, the rates of the individual reactions are compatible and can further be adjusted through catalyst ratio optimization. In both of the discussed transformations, the first reaction occurred rapidly under the given conditions, and was followed by slower conversion to the final product. This difference in reactivity of the two catalyst systems is necessary to ensure correct sequence of events, and is a shared trait among a number of other examples featuring multicatalytic reactivity.

In the synthesis of dibenzoepines there appeared to be minimal interactions between the ligands and catalysts of the two transformations. It should be noted, however, that the reactivity of the palladium-catalyzed C–O coupling was somewhat tempered in a domino process. This difficult coupling necessitated the use of electronically biased substrates. Notably, we demonstrated a proof of concept that asymmetry can also be introduced in a selective multicatalytic domino reaction.

Ongoing work in the group is focused on developing other reactions featuring this multicatalytic mode of reactivity, while utilizing a more diverse scope of reactions available to rhodium and palladium catalysis.
2.5 Experimental Section

General Experimental Procedures. Unless otherwise noted, reactions were carried out under argon atmosphere, in flame-dried, single-neck, round bottom flasks fitted with a rubber septum, with magnetic stirring. Air- or water-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Where necessary (so noted), solutions were deoxygenated by successive freeze-pump-thaw cycles (≥ three iterations). Organic solutions were concentrated by rotary evaporation at 23–40 °C under 40 Torr (house vacuum). Analytical thin layer chromatography (TLC) was performed with Silicycle™ normal phase glass plates (0.25 mm, 60-A pore size, 230-400 mesh). Visualization was done under a 254 nm UV light source and generally by immersion in acidic aqueous-ethanolic vanillin solution, or in potassium permanganate (KMnO₄), followed by heating using a heat gun. Purification of reaction products was generally done by flash chromatography with Silicycle™ Ultra-Pure 230-400 mesh silica gel, as described by Still et al.108

Materials. Unless otherwise indicated, starting materials and catalysts were obtained from Aldrich, Strem or VWR and used without further purification. Tetrahydrofuran, 1,4-dioxane and toluene were purified by distillation under N₂ from Na/benzophenone immediately prior to use.

Instrumentation. Proton nuclear magnetic resonance spectra (¹H NMR) and carbon nuclear magnetic resonance spectra (¹³C NMR) were recorded at 23 °C with a Bruker Avance III 400 (400 MHz/100 MHz) NMR spectrometer equipped with a ATM BB0F probe, a Varian Mercury 400 (400 MHz/100 MHz) NMR spectrometer equipped with a Nalorac4N-400 probe, a Varian Unity 500 (500 MHz/125 MHz) NMR spectrometer equipped with a Nalorac3-500 probe, or a Varian 400 (400 MHz/100 MHz) NMR spectrometer equipped with ATB8123-400 probe. Recorded shifts for protons are reported in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvents (CHCl₃: δ 7.26, CHDCI₃: δ 5.29, C₆H₄D₂: δ 7.15, CD₂HOD: δ 3.30). Chemical shifts for carbon resonances are reported in parts per million (δ scale) downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent (CDCl₃: δ 77.0, CH₂Cl₂: δ 53.8, C₆D₆: δ 128.0, CD₃OD: δ 49.2). Data are represented as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintuplet, sx = sextet, sp = septuplet, dd = doublet of doublets, m = multiplet, br = broad), and coupling constant (J, Hz); ap t (apparent triplet) and ap td or ap dt (apparent doublet of triplets) imply a doublet of doublets with identical coupling constant instead of a true triplet. Infrared (IR) spectra were obtained using a Perkin-Elmer Spectrum 1000 FT-IR spectrometer as a neat film on a NaCl plate. Data is presented as follows: frequency of absorption (cm⁻¹). High resolution mass spectra were obtained from a S12

Micromass 70S-250 mass spectrometer (EI) or an ABI/Sciex Qstar mass spectrometer (ESI). Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected.

2.5.1 Characterization Data for Section 2.2

\( N-(3-(2\text{-Chlorophenyl})\text{prop-2-yn-1-yl})\text{-4-methylbenzenesulfonamide (2.3b)} \)

This compound was prepared by L. Zhang. A round-bottom flask containing \( \text{Pd(PPh}_3\text{)}_2\text{Cl}_2 \) (71 mg, 1 mol\%) and \( \text{CuI} \) (38 mg, 2 mol\%) was purged with argon. \( \text{N,N-dimethylformamide (50 ml, 0.2M)} \) and \( \text{triethylamine (13.9 ml, 10 equiv)} \) were added, followed by the 2-chloro-1-iodobenzene (1.34 ml, 1.1 equiv.) was added, followed by \( N-(\text{prop-2-ynyl})\text{toluene sulfonamide (2.09 g, 10 mmol, 1 equiv)} \) and the flask was stirred at r.t. for 16 hours. The reaction mixture was diluted with \( \text{EtOAc} \) and partitioned with water. The organic phase was separated and washed with water 2x and brine, dried over \( \text{Na}_2\text{SO}_4 \), filtered and concentrated under vacuum. Column chromatography (pentane:EtOAc 7:3) yielded the titled compound as an off-white solid in 70% yield (2.24 g). The spectral data was consistent with literature. \( ^1\text{H NMR (400 MHz, CDCl}_3 \) δ 7.81 (d, \( J = 8.3 \) Hz, 2H), 7.33 (d, \( J = 8.0 \) Hz, 1H), 7.30 – 7.18 (m, 3H), 7.15 (d, \( J = 4.2 \) Hz, 2H), 4.72 (s, 1H), 4.14 (d, \( J = 6.1 \) Hz, 2H), 2.32 (s, 3H); \( ^{13}\text{C NMR (100 MHz, CDCl}_3 \): δ 143.93, 136.88, 135.90, 133.51, 129.85, 129.73, 129.32, 127.60, 126.42, 122.15, 88.55, 81.65, 34.00, 21.57; IR (NaCl, neat): 3256, 2862, 1596, 1472, 1431, 1332, 1293, 1140, 1092, 1066, 963, 837, 819 cm\(^{-1}\); M. p.: 134-136 °C; HRMS (ESI): calcd for \( \text{C}_{16}\text{H}_{15}\text{ClNO}_2\text{S (M+H)}^+ \): 320.0506; found: 320.0499.

\( N-(3-(2\text{-Chlorophenyl})\text{prop-2-ynyl})\text{methanesulfonamide (2.3c)} \)

A round-bottom flask containing \( \text{Pd(PPh}_3\text{)}_2\text{Cl}_2 \) (100 mg, 2 mol\%) and \( \text{CuI} \) (60 mg, 4 mol\%) was purged with argon. Acetonitrile (30 ml, 0.2M) and triethylamine (30 ml, 0.2M) were added, followed by the 2-chloro-1-iodobenzene (926 \( \mu \)l, 1.1 equiv.) was added, followed by \( N-(\text{prop-2-ynyl})\text{toluene sulfonamide (918 mg, 6.9 mmol, 1 equiv} \) and the flask was stirred at 40 °C for 4 hours when no starting material remained on TLC. The reaction crude was filtered through a Celite plug and concentrated under vacuum. Column chromatography (pentane:EtOAc 7:3) yielded the titled compound as an off-white solid in 75% yield (1.26 g). \( ^1\text{H NMR (400 MHz, CDCl}_3 \): δ 7.45 (dd, \( J = 7.5, \) 1.8 Hz, 1H), 7.40 (dd, \( J = 8.0, \) 1.2 Hz, 1H), 7.29 (ap td, \( J = 7.8, \) 1.8 Hz, 1H), 7.23 (ap td, \( J = 7.5, \) 1.4 Hz, 1H), 4.70 (t, \( J = 5.6 \) Hz, 1H), 4.27 (d, \( J = 6.2 \) Hz, 2H), 3.17 (s, 3H); \( ^{13}\text{C NMR (100 MHz, CDCl}_3 \): δ 143.93, 136.88, 135.90, 133.51, 129.85, 129.73, 129.32, 127.60, 126.42, 122.15, 88.55, 81.65, 34.00, 21.57; IR (NaCl, neat): 3280, 3016, 2961, 2930, 2879, 1472, 1431, 1332, 1293, 1140, 1092, 1066, 963, 837, 819 cm\(^{-1}\); M. p.: 65-67 °C; HRMS (EI): calcd for \( \text{C}_{16}\text{H}_{10}\text{ClNO}_2\text{S (M)}^+ \): 243.0121; found: 243.0117.
**tert-Butyl 3-(2-chlorophenyl)prop-2-ynylcarbamate (2.3d)**

A round-bottom flask containing Pd(PPh₃)₂Cl₂ (354 mg, 1 mol%), Cul (192 mg, 2 mol%), and a stirring bar was purged with argon. Triethylamine (170 ml, 0.3 M) was added. Following this, 2-chloro-1-iodobenzene (6.15 ml, 1.01 equiv) was added, followed by tert-butyl prop-2-yn-1-ylcarbamate (7.76 g, 50 mmol, 1 equiv), and the reaction was allowed to stir at room temperature for 4 hours, at which point no starting material could be observed by TLC. The reaction crude was filtered through a Celite plug and concentrated under vacuum. Column chromatography (pentane:EtOAc 9:1) yielded the titled compound as a colorless solid in 95% yield (12.6 g).

**1H NMR** (400 MHz, CDCl₃): δ 7.42 (dd, J = 7.4, 1.8 Hz, 1H), 7.35 (dd, J = 7.9, 1.2 Hz, 1H), 7.21 (aptd, J = 7.7, 1.9 Hz, 1H), 7.16 (aptd, J = 7.5, 1.4 Hz, 1H), 4.93 (s, 1H), 4.19 (d, J = 3.3 Hz, 2H), 1.45 (s, 9H);

**13C NMR** (101 MHz, CDCl₃): δ 155.4, 136.0, 133.5, 129.4, 129.3, 126.5, 122.7, 90.9, 80.1, 79.9, 31.4, 28.4;

**IR** (NaCl, neat): 3343, 2979, 2933, 1712, 1679, 1505, 1475, 1368, 1274, 1249, 1168, 1064, 1049, 1033, 859, 755 cm⁻¹;

**M. p.**: 58-60 °C;

**HRMS** (ESI): calcd for C₁₄H₁₇ClNO₂ (M+H)+: 266.0948; found: 266.0941.

**Procedure 2.1:** Protocol for synthesis of protected propargylamines:

A round bottom flask was charged with a stirring bar and tert-butyl 3-(2-chlorophenyl)prop-2-ynylcarbamate 2.3d (11.93 g, 45 mmol, 1 equiv) and cooled to 0 °C in an ice bath. A solution of HCl (aq) in EtOAc (3M, 30 ml) was added to this flask. The reaction was allowed to stir at room temperature, until no starting material was observed by TLC (~2 h). The liquids were removed under reduced pressure, leaving an orange flaky solid (prop-2-yn-1-aminium chloride, 8.54 g, 42.2 mmol), which was used without further purification. In order to synthesize the protected propargylamines, the prop-2-yn-1-aminium chloride was treated with base (triethylamine, 2.2 equiv) and the appropriate electrophile (1.1 equiv) in dichloromethane as described in each specific case.

**N-(3-(2-Chlorophenyl)prop-2-ynyl)benzenesulfonamide (2.3e)**

According to the general procedure 2.1, prop-2-yn-1-aminium chloride (500 mg, 2.474 mmol, 1 equiv) was placed into an oven-dried round bottom flask with a stirring bar; dichloromethane (10 ml, 0.25 M) and triethylamine (753 μl, 2.2 equiv) were added. The reaction was cooled to 0 °C in an ice bath. Benzenesulfonyl chloride (350 μl, 1.1 equiv) was added dropwise over ~3 minutes, and the reaction was allowed to warm to room temperature. When the reaction was complete, as observed by TLC (<1 h), the mixture was quenched with saturated NH₄Cl (aq), extracted with dichloromethane, washed with brine, and dried over MgSO₄. Afterwards, the solvent was removed under reduced pressure, and the crude was purified using column chromatography (pentane:EtOAc 9:1 to 8:2) yielding the title compound in 74% yield (560 mg) as a colorless
solid. \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.97 – 7.92 (m, 2H), 7.56 – 7.44 (m, 3H), 7.36 – 7.30 (m, 1H), 7.22 (ddd, \(J = 8.0, 6.6, 2.5\) Hz, 1H), 7.18 – 7.11 (m, 2H), 4.87 (t, \(J = 5.8\) Hz, 1H), 4.16 (d, \(J = 6.1\) Hz, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): δ 139.9, 135.9, 133.5, 133.0, 129.8, 129.3, 129.3 (2), 127.5 (2), 126.4, 122.0, 88.4, 81.7, 34.0; IR (NaCl, neat): 3282, 3059, 2931, 2854, 1475, 1448, 1334, 1266, 1164, 1091, 1072, 1032, 967, 947, 844, 730 cm\(^{-1}\); M. p.: 84-85 °C; HRMS (EI): calcd for C\(_{15}\)H\(_{12}\)ClNO\(_2\)S (M\(^+\)): 305.0277; found: 305.0279.

**N-(3-(2-Chlorophenyl)prop-2-ynyl)-4-methoxybenzenesulfonamide (2.3f)**

According to the general procedure 2.1, prop-2-yn-1-aminium chloride (303 mg, 1.5 mmol, 1 equiv) was placed into an oven-dried round bottom flask with a stirring bar; dichloromethane (5 ml, 0.3 M) and triethylamine (237 μl, 2.2 equiv) were added. The reaction was cooled to 0 °C in an ice bath. 4-Methoxybenzene-1-sulfonyl chloride (341 mg, 1.1 equiv) in dichloromethane (1 ml) was added dropwise over ~3 minutes, and the reaction was allowed to warm to room temperature. When the reaction was complete, as observed by TLC (<1 h), the mixture was quenched with saturated NH\(_4\)Cl\(_{aq}\), extracted with dichloromethane, washed with brine, and dried over MgSO\(_4\). Afterwards, the solvent was removed under reduced pressure, and the crude was purified using column chromatography (pentane:EtOAc 7:3 to 6:4) yielding the title compound in 70% yield (352 mg) as a colorless solid.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.85 (d, \(J = 8.9\) Hz, 2H), 7.31 (d, \(J = 7.9\) Hz, 1H), 7.20 (ddd, \(J = 2.4, 6.8, 8.0\) Hz, 1H), 7.17 – 7.08 (m, 2H), 6.89 (d, \(J = 8.9\) Hz, 2H), 5.05 (t, \(J = 6.0\) Hz, 1H), 4.11 (d, \(J = 6.1\) Hz, 2H), 3.73 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): δ 163.1, 135.8, 133.5, 133.0, 129.7 (2), 129.6, 129.2, 126.4, 122.2, 114.3 (2), 88.8, 81.5, 55.6, 33.9; IR (NaCl, neat): 3268, 3094, 3023, 2981, 2854, 1595, 1575, 1472, 1432, 1326, 1310, 1302, 1265, 1152 1073, 1022, 832, 763 cm\(^{-1}\); M. p.: 105-107 °C; HRMS (ESI): calcd for C\(_{16}\)H\(_{15}\)ClNO\(_3\)S (M+H\(^+\)): 336.0461; found: 336.0449.

**N-(3-(2-Chlorophenyl)prop-2-ynyl)-4-nitrobenzenesulfonamide (2.3g)**

According to the general procedure 2.1, prop-2-yn-1-aminium chloride (303 mg, 1.5 mmol, 1 equiv) was placed into an oven-dried round bottom flask with a stirring bar; dichloromethane (5 ml, 0.3 M) and triethylamine (237 μl, 2.2 equiv) were added. The reaction was cooled to 0 °C in an ice bath. 4-Nitrobenzene-1-sulfonyl chloride (366 mg, 1.1 equiv) in dichloromethane (1 ml) was added dropwise over ~3 minutes, and the reaction was allowed to warm to room temperature. When the reaction was complete, as observed by TLC (<1 h), the mixture was quenched with saturated NH\(_4\)Cl\(_{aq}\), extracted with dichloromethane, washed with brine, and dried over MgSO\(_4\). Afterwards, the solvent was removed under reduced pressure, and the crude was purified using column chromatography (pentane:DCM:MeOH 47.5:47.5:5) yielding the title compound in 75% yield (385 mg) as a colorless solid. \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 8.24 (ap dt, \(J = 2, 9.2\) Hz, 2H), 8.12 (ap dt, \(J = 2, 8.8\) Hz, 2H), 7.31 (dd, \(J = 8.1, 0.8\) Hz, 1H), 7.18 – 7.08 (m, 2H), 6.89 (d, \(J = 8.9\) Hz, 2H), 5.05 (t, \(J = 6.0\) Hz, 1H), 4.11 (d, \(J = 6.1\) Hz, 2H), 3.73 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): δ 163.1, 135.8, 133.5, 133.0, 129.7 (2), 129.6, 129.2, 126.4, 122.2, 114.3 (2), 88.8, 81.5, 55.6, 33.9; IR (NaCl, neat): 3268, 3094, 3023, 2981, 2854, 1595, 1575, 1472, 1432, 1326, 1310, 1302, 1265, 1152 1073, 1022, 832, 763 cm\(^{-1}\); M. p.: 105-107 °C; HRMS (ESI): calcd for C\(_{16}\)H\(_{15}\)ClNO\(_3\)S (M+H\(^+\)): 336.0461; found: 336.0449.
N-(3-(2-Chlorophenyl)prop-2-ynyl)-2,4,6-trimethylbenzenesulfonamide (2.3h)

According to the general procedure 2.1, prop-2-yn-1-aminium chloride (303 mg, 1.5 mmol, 1 equiv) was placed into an oven-dried round bottom flask with a stirring bar; dichloromethane (5 ml, 0.3 M) and triethylamine (237 μl, 2.2 equiv) were added. The reaction was cooled to 0 °C in an ice bath. 4-2,4,6-Trimethylbenzene-1-sulfonyl chloride (361 mg, 1.1 equiv) in dichloromethane (1 ml) was added dropwise over ~3 minutes, and the reaction was allowed to warm to room temperature. When the reaction was complete, as observed by TLC (<1 h), the mixture was quenched with saturated NH₄Cl (aq), extracted with dichloromethane, washed with brine, and dried over MgSO₄. Afterwards, the solvent was removed under reduced pressure, and the crude was purified using column chromatography (pentane:EtOAc 95:5 to 9:1) yielding the title compound in 60% yield (313 mg) as an orange oil which solidifies over time.

**1H NMR (400 MHz, CDCl₃):** δ 7.32 (d, J = 7.7 Hz, 1H), 7.21 (ddd, J = 8.1, 6.7, 2.4 Hz, 1H), 7.16 – 7.09 (m, 2H), 6.88 (s, 2H), 4.89 (t, J = 6.1 Hz, 1H), 4.10 (d, J = 6.2 Hz, 2H), 2.68 (s, 6H), 2.15 (s, 3H); **13C NMR (101 MHz, CDCl₃):** δ 142.6, 139.3 (2), 135.9, 133.9, 133.5, 132.1(2), 129.6, 129.2, 126.4, 122.2, 88.3, 81.2, 77.5, 77.2, 76.8, 33.4, 23.2 (2), 20.9; **IR (NaCl, neat):** 3313, 2977, 2939, 2854, 1605, 1566, 1472, 1429, 1324, 1154, 1061, 1033, 852, 757, 657 cm⁻¹; **M. p.:** 52-54 °C; **HRMS (ESI):** calcd for C₁₈H₂₂ClN₂O₂S (M+NH₄)⁺: 365.1090; found: 365.1081.

N-(3-(2-Chlorophenyl)prop-2-ynyl)-1,1,1-trifluoromethanesulfonamide (2.3i)

According to the general procedure 2.1, prop-2-yn-1-aminium chloride (500 mg, 2.47 mmol, 1 equiv) was placed into an oven-dried round bottom flask with a stirring bar; dichloromethane (10 ml, 0.25 M) and triethylamine (753 μl, 2.2 equiv) were added. The reaction was cooled to 0 °C in an ice bath. Trifluoromethanesulfonyl chloride (458 μl, 1.1 equiv) was added dropwise over ~3 minutes, and the reaction was allowed to warm to room temperature. When the reaction was complete, as observed by TLC (<1 h), the mixture was quenched with saturated NH₄Cl (aq), extracted with dichloromethane, washed with brine, and dried over MgSO₄. Afterwards, the solvent was removed under reduced pressure, and the crude was purified using column chromatography (pentane:EtOAc 95:5) yielding the titled compound as an orange oil in 57% yield (420 mg). **1H NMR (400 MHz, CDCl₃):** δ 7.46 (dd, J = 7.6, 1.7 Hz, 1H), 7.40 (dd, J = 8.0, 1.1 Hz, 1H), 7.29 (ap td, J = 7.8, 1.8 Hz, 1H), 7.23 (ap td, J = 7.5, 1.3 Hz, 1H), 5.31 (bs, 1H),
4.38 (s, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 136.1, 133.6, 130.2, 129.4, 126.6, 121.6, 119.5 (q, $J = 320.9$ Hz), 86.8, 82.6, 34.9; $^{19}$F NMR (377 MHz, CDCl$_3$) δ -78.0; IR (NaCl, neat): 3322, 3071, 2927, 2239, 1475, 1429, 1373, 1231, 1198, 1144, 1058, 848, 755, 668, 612 cm$^{-1}$; HRMS (ESI): calcd for C$_{10}$H$_8$ClF$_3$NO$_2$S (M+H)$^+$: 297.9916; found: 297.9920.

**N-(3-(2-Chlorophenyl)prop-2-ynyl)benzamide (2.3j)**

According to the general procedure 2.1, prop-2-yn-1-aminium chloride (500 mg, 2.47 mmol, 1 equiv) was placed into an oven-dried round bottom flask with a stirring bar; dichloromethane (10 ml, 0.25 M) and triethylamine (753 μl, 2.2 equiv) were added. The reaction was cooled to 0 °C in an ice bath. Benzoyl chloride (320 μl, 1.1 equiv) was added dropwise over ~3 minutes, and the reaction was allowed to warm to room temperature. When the reaction was complete, as observed by TLC (<1 h), the mixture was quenched with saturated NH$_4$Cl(aq), extracted with dichloromethane, washed with brine, and dried over MgSO$_4$. Afterwards, the solvent was removed under reduced pressure, and the crude was purified using column chromatography (pentane:EtOAc 8:2) yielding the title compound in 70% yield (407 mg) as a colorless solid.

$^1$H NMR (399 MHz, CDCl$_3$): δ 7.87 – 7.78 (m, 2H), 7.55 – 7.35 (m, 5H), 7.25 (ap td, $J = 7.7$, 1.9 Hz, 1H), 7.20 (ap td, $J = 7.5$, 1.4 Hz, 1H), 6.48 (bs, 1H), 4.55 (d, $J = 5.2$ Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 167.2, 136.1, 134.0, 133.7, 131.9, 129.7, 129.4, 128.8 (2), 127.2 (2), 126.6, 122.5, 90.2, 80.6, 30.9; IR (NaCl, neat): 3312, 3063, 3030, 2918, 1666, 1649, 1532, 1489, 1436, 1354, 1295, 1159, 1129, 1066, 1033, 756 cm$^{-1}$; M. p.: 81-84 °C; HRMS (ESI): calcd for C$_{15}$H$_{13}$ClNO (M+H)$^+$: 270.0686; found: 270.0680.

**Phenyl 3-(2-chlorophenyl)prop-2-ynylcarbamate (2.3k)**

According to the general procedure 2.1, prop-2-yn-1-aminium chloride (500 mg, 2.47 mmol, 1 equiv) was placed into an oven-dried round bottom flask with a stirring bar; dichloromethane (10 ml, 0.25 M) and triethylamine (753 μl, 2.2 equiv) were added. The reaction was cooled to 0 °C in an ice bath. Phenyl chloroformate (345 μl, 1.1 equiv) was added dropwise over ~3 minutes, and the reaction was allowed to warm to room temperature. When the reaction was complete, as observed by TLC (<1 h), the mixture was quenched with saturated NH$_4$Cl(aq), extracted with dichloromethane, washed with brine, and dried over MgSO$_4$. Afterwards, the solvent was removed under reduced pressure, and the crude was purified using column chromatography (pentane:EtOAc 9:1) yielding the title compound in 78% yield (484 mg) as an off-white solid.

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.47 (dd, $J = 7.5$, 1.7 Hz, 1H), 7.44 – 7.31 (m, 3H), 7.30 – 7.12 (m, 5H), 5.39 (s, 1H), 4.35 (d, $J = 5.5$ Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 154.3, 151.0, 136.1, 134.0, 133.7, 131.9, 129.7, 129.4, 128.8 (2), 127.2 (2), 126.6, 122.5, 90.2, 80.6, 30.9; IR (NaCl, neat): 3328, 3066, 3036, 2922, 2861, 1727, 1532, 1477, 1432, 1354, 1206, 1063, 1033, 919, 893 cm$^{-1}$; M. p.: 85-87 °C; HRMS (ESI): calcd for C$_{16}$H$_{13}$ClNO$_2$ (M+H)$^+$: 286.0635; found: 286.0636.
Diphenyl 3-(2-chlorophenyl)prop-2-ynylphosphoramidate (2.3l)

According to the general procedure 2.1, prop-2-yn-1-aminium chloride (500 mg, 2.47 mmol, 1 equiv) was placed into an oven-dried round bottom flask with a stirring bar; dichloromethane (10 ml, 0.25 M) and triethylamine (753 μl, 2.2 equiv) were added. The reaction was cooled to 0 °C in an ice bath. Diphenyl phosphonyl chloride (570 μl, 1.1 equiv) was added dropwise over ~3 minutes, and the reaction was allowed to warm to room temperature. When the reaction was complete, as observed by TLC (<1 h), the mixture was quenched with saturated NH₄Cl(aq), extracted with dichloromethane, washed with brine, and dried over MgSO₄. Afterwards, the solvent was removed under reduced pressure, and the crude was purified using column chromatography (pentane:EtOAc 8:2) yielding the title compound in 85% yield (763 mg) as a colorless, highly crystalline solid.

**1H NMR** (399 MHz, CDCl₃): δ 7.38 (dd, J = 8.0, 1.2 Hz, 1H), 7.36–7.28 (m, 9H), 7.25 (ap td, J = 7.7, 1.8 Hz, 1H), 7.20–7.13 (m, 3H), 4.18 (dd, J = 11.6, 6.7 Hz, 2H), 3.46 (dd, J = 12.6, 6.4 Hz, 1H);

**13C NMR** (100 MHz, CDCl₃): δ 150.8 (d, J = 6.7 Hz, 2C), 136.0, 133.6, 129.9 (d, J = 0.5 Hz, 4C), 129.7, 129.4, 126.5, 125.2 (d, J = 1.2 Hz, 2C), 122.5, 120.5 (d, J = 4.7 Hz, 4C), 91.0 (d, J = 7.0 Hz), 80.8, 32.5;

**IR** (NaCl, neat): 3203, 2918, 2850, 1589, 1489, 1473, 1266, 1240, 1191, 1162, 1104, 938, 756, 689, 668 cm⁻¹; **M. p.**: 122–124 °C; **HRMS** (ESI): calcd for C₂₁H₁₈ClNO₃P (M+H)⁺: 398.0713; found: 398.0710.

N-(3-(2-Chloro-4-(trifluoromethyl)phenyl)prop-2-ynyl)methanesulfonamide (2.6)

This compound was prepared by L. Zhang: A round-bottom flask containing Pd(PPh₃)₂Cl₂ (72 mg, 2 mol%) and CuI (44 mg, 4 mol%) was purged with argon. Acetonitrile (25 ml, 0.2M) and triethylamine (25 ml, 0.2M) were added, followed by 2-chloro-1-ido-4-(trifluoromethyl)benzene (1.53 g, 5 mmol, 1 equiv) was added, followed by N-(prop-2-ynyl)methanesulfonamide (732 mg, 5.5 mmol, 1.1 equiv) and the flask was stirred at 40 °C for 5 hours when no starting material remained on TLC. The reaction crude was filtered through a Celite plug and concentrated under vacuum. Column chromatography (hexane:EtOAc 9:1 to 8:2) yielded the title compound as a pale yellow solid in 63% yield (0.98 g).

**1H NMR** (300MHz, CDCl₃): δ 7.68 (s, 1H), 7.57 (d, J = 8.2 Hz, 1H), 7.38 (d, J = 8.1 Hz, 1H), 4.75 (br s, 1H), 4.29 (d, J = 6.2 Hz, 2H), 3.16 (s, 3H);

**13C NMR** (75MHz, CDCl₃): δ 136.6, 133.9, 131.8 (q, J = 34Hz), 126.5 (q, J = 4 Hz), 125.7, 123.0 (q, J = 273 Hz), 92.0, 80.6, 41.7, 33.6; **19F NMR** (282 MHz, CDCl₃) δ -63.5; **IR** (NaCl, neat): 3281, 1391, 1320, 1141, 1082, 834, 723 cm⁻¹; **M. p.**: 73-75 °C; **HRMS** (ESI): calcd for C₁₁H₁₈ClF₃NO₂S: 312.0073 (M+H)⁺; found: 312.0074.

N-(3-(2-Chloro-5-fluorophenyl)prop-2-ynyl)methanesulfonamide (2.7)

A round-bottom flask containing Pd(PPh₃)₄ (58 mg, 5 mol%), Cul (19 mg, 10 mol%), 2-bromo-1-chloro-4-fluorobenzene (210 mg, 1 mmol) and N-
(prop-2-ynyl)methanesulfonamide (160 mg, 1.2 mmol, 1.2 equiv) was purged with argon. Acetonitrile (5 ml, 0.2 M) and diisopropylamine (5 ml, 0.2 M) were added. The reaction was sealed and stirred at 90 °C for 16 hours. The reaction crude was filtered through a Celite plug and concentrated under vacuum. Column chromatography (hexane:EtOAc 9:1 to 8:2) yielded the titled compound as a colorless solid in 63% yield (165 mg).

**1H NMR** (300MHz, CDCl₃): δ 7.36 (dd, J = 8.9, 5.1 Hz, 1H), 7.16 (dd, J = 8.5, 3.0 Hz, 1H), 7.02 (ddd, J = 8.9, 7.9, 3.0 Hz, 1H), 4.72 (s, 1H), 4.27 (d, J = 6.2 Hz, 2H), 3.16 (s, 3H); **13C NMR** (75MHz, CDCl₃): δ 161.0 (d, J = 248.0 Hz), 131.5 (d, J = 4.0 Hz), 131.0 (d, J = 9.0 Hz), 123.6 (d, J = 10.0 Hz), 120.4 (d, J = 25.0 Hz), 117.8 (d, J = 23.0 Hz), 90.6, 81.1 (d, J = 3 Hz), 42.0, 33.8; **19F NMR** (282 MHz, CDCl₃) δ -115.3 (td, J = 8.1, 5.1 Hz); **IR** (NaCl, neat): 3281, 1602, 1577, 1469, 1405, 1320, 1154, 1120, 1000, 874, 817, 649 cm⁻¹; **M. p.:** 74-76 °C; **HRMS** (ESI): calcd for C₁₀H₁₀ClFNO₂S (M+H)⁺: 262.0104; found: 262.0105.

### N-(3-(2-Chloro-3-fluorophenyl)prop-2-ynyl)methanesulfonamide (2.8)

A round-bottom flask containing Pd(PPh₃)₄ (58 mg, 5 mol%), CuI (19 mg, 10 mol%), 1-bromo-2-chloro-3-fluorobenzene (210 mg, 1 mmol) and N-(prop-2-ynyl)methanesulfonamide (160 mg, 1.2 mmol, 1.2 equiv) was purged with argon. Acetonitrile (5 ml, 0.2 M) and diisopropylamine (5 ml, 0.2 M) were added. The reaction was sealed and stirred at 90 °C for 16 hours. The reaction crude was filtered through a Celite plug and concentrated under vacuum. Column chromatography (hexane:EtOAc 9:1 to 8:2) yielded the titled compound as a colorless solid in 63% yield (165 mg). **1H NMR** (400MHz, CDCl₃): δ 7.26 (d, J = 7.7 Hz, 1H), 7.20 (ap dt, J = 8.2, 5.1 Hz, 1H), 7.14 (ap dt, J = 8.6, 1.8 Hz, 1H), 5.11 (t, J = 6.0 Hz, 1H), 4.27 (d, J = 6.2 Hz, 2H), 3.17 (s, 3H); **13C NMR** (100MHz, CDCl₃): δ 158.5 (d, J = 250 Hz), 129.0 (d, J = 3 Hz), 127.8 (d, J = 8 Hz), 123.4 (d, J = 18 Hz), 124.2, 117.3 (d, J = 21 Hz), 90.5, 80.8 (d, J = 4 Hz), 41.8, 33.7; **19F NMR** (282 MHz, CDCl₃) δ -113.0 (d, J = 8.4, 5.2 Hz); **IR** (NaCl, neat): 3285, 1569, 1468, 1440, 1320, 1247, 1153, 1076, 1036, 787 cm⁻¹; **M. p.:** 100-103 °C; **HRMS** (ESI): calcd for C₁₀H₁₀ClFNO₂S (M+H)⁺: 262.0105; found: 262.0106.

### N-(3-Chloro-4-(3-(methylsulfonamidomethyl)prop-1-ynyl)phenyl)acetamide (2.9)

A round-bottom flask containing Pd(PPh₃)₂Cl₂ (58 mg, 5 mol%) and CuI (19 mg, 10 mol%) was purged with argon. Acetonitrile (5 ml, 0.2M) and diisopropylamine (5 ml, 0.2M) were added, following this N-(4-bromo-3-chlorophenyl)acetamide (249 mg, 1 mmol, 1 equiv) was added, followed by N-(prop-2-ynyl)methanesulfonamide (173 mg, 1.3 equiv). The reaction was allowed to stir at 90 °C for 16 hours. The reaction crude was filtered through a Celite plug and concentrated under vacuum. Column chromatography (pentane:EtOAc 1:1) yielded the titled compound as a colorless solid, with low solubility in most solvents, in 50% yield (150 mg). **1H NMR** (400 MHz, DMSO) δ 10.26 (bs, 1H), 7.89 (s, 1H), 7.66 (ap t, J = 5.3 Hz, 1H), 7.49 (d, J = 8.5 Hz, 1H), 7.44 (d, J = 8.4
N-(3-(3-Chloropyridin-2-yl)prop-2-ynyl)methanesulfonamide (2.10)

A round-bottom flask containing Pd(PPh₃)₂Cl₂ (35 mg, 5 mol%), CuI (19 mg, 10 mol%), 3-chloro-2-bromopyridine (193 mg, 1 mmol) and N-(prop-2-ynyl)methanesulfonamide (160 mg, 1.2 mmol, 1.2 equiv) was purged with argon. Acetonitrile (5 ml, 0.2 M) and diisopropylamine (5 ml, 0.2 M) were added. The reaction was stirred at 50 °C for 16 hours at which point no starting material remained on TLC. The reaction crude was filtered through a Celite plug and concentrated under vacuum. Column chromatography (pentane:EtOAc 3:7 to 2:8) yielded the titled compound as a colorless solid which developed a dark green color over time in 73% yield (177 mg).

¹H NMR (400 MHz, CDCl₃): δ 8.49 (d, J = 3.8 Hz, 1H), 7.75 (dd, J = 8.2, 1.1 Hz, 1H), 7.25 (dd, J = 8.9, 3.9 Hz, 1H), 5.14 (t, J = 5.1 Hz, 1H), 4.31 (d, J = 6.2 Hz, 2H), 3.17 (s, 3H);

¹³C NMR (100 MHz, CDCl₃): δ 148.1, 140.9, 137.1, 134.4, 124.4, 89.7, 81.4, 41.8, 33.6;

IR (NaCl, neat): 3083, 2916, 2849, 2229, 1438, 1424, 1323, 1153, 1142, 1086, 1073,1042, 813, 776, 752 cm⁻¹; M. p.: 120-122 °C; HRMS (ESI): calcd for C₃H₁₀ClN₂O₂S (M+H)⁺: 245.0252; found: 245.0158.

N-(3-(2-Chloropyridin-3-yl)prop-2-ynyl)methanesulfonamide (2.11)

A round-bottom flask containing Pd(PPh₃)₄ (347 mg, 3 mol%) was purged with argon. Diisopropylamine (25 ml, 0.4M) and 3-bromo-2-chloropyridine (1.924 g, 10 mmol, 1 equiv) were added, followed by tert-butyl prop-2-ynylcarbamate (1.86 g, 1.2 equiv). The flask was stirred at 100 °C for 16 hours. The reaction crude was filtered through a Celite plug and concentrated under vacuum. Column chromatography (pentane:EtOAc 7:3) yielded tert-butyl(3-(2-chloropyridin-3-yl)prop-2-ynyl)carbamate in 67% yield as a brown solid. This material was then placed in a round bottom flask, cooled to 0 °C in an ice bath, and was treated with HCl(aq) in EtOAc (3 M, 30 ml). The reaction was monitored by TLC. Upon completion, the liquids were removed under vacuum to give a crystalline solid (3-(2-chloropyridin-3-yl)prop-2-ynyl-1-aminium chloride). This material (500 mg, 2.47 mmol, 1 equiv) was placed into a flame-dried round bottom flask. Dichloromethane (12 ml, 0.2M) and triethylamine (860 mg, 2.5 equiv) were added. Upon cooling to 0 °C in an ice bath, methanesulfonylchloride (230 μl, 1.2 equiv) was added dropwise over ~3 minutes. The reaction was allowed to warm to room temperature and monitored by TLC. Upon completion, the mixture was quenched with saturated NH₄Cl(aq), extracted with dichloromethane, washed with brine, and dried over MgSO₄. Afterwards, the solvent was removed under reduced pressure, and the crude was purified using column chromatography.
(pentane:EtOAc 1:1) yielding the title compound in 58% yield (351 mg, 39% overall) as a colorless solid. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 8.36\) (dd, \(J = 4.4, 1.2\) Hz, 1H), 7.77 (dd, \(J = 7.6, 4.9\) Hz, 1H), 4.86 (t, \(J = 5.3\) Hz, 1H), 4.28 (d, \(J = 6.2\) Hz, 2H), 3.16 (s, 3H); \(^1^3\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 152.4, 149.1, 141.9, 122.1, 119.4, 91.9, 33.7\); \(\text{IR (NaCl, neat): } 3269, 2918, 2850, 1395, 1318, 1152, 1092, 1070, 808 \text{ cm}^{-1}\); \(\text{M. p. } 113-114 ^\circ\text{C}; \text{HRMS (ESI): } \text{calcd for C}_{9}\text{H}_{10}\text{ClN}_{2}\text{O}_{2}\text{S (M+H)}^+: 245.0151; \text{found: 245.0147.}

**Procedure 2.2: Protocol for Rh-catalyzed alkyne arylation: (Z)-N-(3-(2-Chlorophenyl)-2-phenylallyl) methanesulfonamide (2.4c)**

[Rh(cod)OH]\(_2\) (11.4 mg, 2.5 mol\% (5 mol\% [Rh])) and BINAP (32.4 mg, 5.2 mol\%) were weighed into a 2-dram vial, which was fitted with a cap with a septum and purged with argon for 5 minutes. Dioxane (2 ml) was added to the vial and the solution was allowed to stir for 15 minutes at 50 °C (Note 1). Substrate 2.3c (1 mmol, 244 mg), phenylboronic acid (1.5 equiv, 183 mg), K\(_2\)CO\(_3\) (1.2 equiv, 166 mg) were weighed into a 25 ml round-bottom flask, which was fitted with a septum and purged with argon. 1,4-Dioxane (8 ml) and MeOH (0.5 ml) were added to the reaction. The catalyst solution was added to this reaction flask via syringe. The reaction was heated to 50 °C overnight (16 h), after which TLC showed complete consumption of 2.3c. The reaction mixture was cooled to room temperature, filtered through a plug of silica (washing with EtOAc), and the solvent was removed under vacuum. The crude was purified using column chromatography (loading with toluene, pentane:EtOAc 8:2 to 75:25) to yield a thick yellow oil which slowly solidified upon standing in 74% yield (slightly higher yield (77%) was isolated on 0.2 mmol scale). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.57 – 7.51\) (m, 2H), 7.48 – 7.27 (m, 7H), 6.97 (s, 1H), 4.32 – 4.23 (m, 3H), 2.72 (s, 3H); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 139.0, 138.4, 134.9, 134.0, 130.4, 129.9, 129.4, 129.2 (2), 128.8, 127.1, 127.0 (2), 42.5, 40.5; \text{IR (NaCl, neat): } 3282, 3058, 3023, 2963, 2932, 1496, 1471, 1445, 1428, 1409, 1318, 1264, 1153, 1067, 1052, 1034, 967, 883, 862, 836, 763, 699 \text{ cm}^{-1}\); \(\text{M. p.: } 77-78 ^\circ\text{C}; \text{HRMS (ESI): } \text{calcd for C}_{16}\text{H}_{20}\text{ClN}_{2}\text{O}_{2}\text{S (M+NH}_4^+: 339.0934; \text{found: 339.0938.}

Note 1: Premixing [Rh(cod)OH]\(_2\) and BINAP was not crucial for the single step procedure and similar yields (70-77%) were obtained if the catalyst and ligand were weighed as solids together with base and substrates.

**(Z)-N-(3-(2-Chlorophenyl)-2-phenylallyl)-4-methylbenzenesulfonamide (2.4b)**

This compound was prepared by L. Zhang according to procedure 2.2. The product was purified by flash chromatography (EtOAc/hexanes 1:9) to provide the title compound as an off white solid in 73% yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.51\) (d, \(J = 8.2\) Hz, 2H), 7.31 (d, \(J = 7.7\) Hz, 1H), 7.21 – 7.13 (m, 4H), 7.13 – 7.06 (m, 1H), 6.83 (s, 1H), 4.44 (s, 1H), 4.02 (d, \(J = 5.6\) Hz, 2H), 2.38 (s, 3H); \(^1^3\)C
NMR (101 MHz, CDCl₃) δ 143.5, 138.7, 137.3, 136.2, 134.8, 134.0, 130.2, 129.7, 129.6, 129.2, 129.0, 128.9, 128.5, 127.3, 126.8, 126.7, 42.4, 21.7; IR (NaCl, neat): 3266, 3057, 1660, 1599, 1471, 1445, 1404, 1327, 1163, 1094, 1067, 1053, 887, 814, 760, 698, 667 cm⁻¹; M.p.: 127-129 °C; HRMS (ESI): calcd for C₂₂H₂₁NO₂SCl (M+H)⁺: 398.0976; found: 398.0985.

(Z)-tert-Butyl 3-(2-chlorophenyl)-2-phenyl allylcarbamate (2.4d)

The titled compound was synthesized using procedure 2.2 using [Rh(cod)OH]₂ (2.3 mg, 2.5 mol%), BINAP (6.23 mg, 5 mol%), substrate 2.3d (53.15 mg, 0.2 mmol, 1 equiv), phenylboronic acid (49 mg, 2 equiv) and K₂CO₃ (31 mg, 1.1 equiv). The product was isolated through column chromatography (pentane:EtOAc 95:5) as a colorless solid in 45% yield; ¹H NMR (400 MHz, CDCl₃): δ 7.56 (d, J = 7.4 Hz, 2H), 7.45 – 7.31 (m, 5H), 7.31 – 7.21 (m, 2H), 6.95 (s, 1H), 4.40 (s, 1H), 4.32 (d, J = 4.6 Hz, 2H), 1.37 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ 155.6, 139.6, 139.4, 135.3, 134.0, 132.8, 129.7, 129.5, 128.8, 128.7, 128.1, 128.0, 126.9, 126.7, 79.4, 39.7, 28.3 (3); IR (NaCl, neat): 3335, 3059, 3003, 2978, 2932, 1709, 1674, 1593, 1506, 1392, 1367, 1269, 1246, 1165, 1065, 1034, 860, 754 cm⁻¹; M. p.: 84-88 °C; HRMS (ESI): calcd for C₂₀H₂₃ClNO₂ (M+H)⁺: 344.1417; found: 344.1428.

(Z)-N-(3-(2-Chlorophenyl)-2-phenylallyl)benzenesulfonamide (2.4e)

The titled compound was synthesized using procedure 2.2 using [Rh(cod)OH]₂ (2.3 mg, 2.5 mol%), BINAP (6.23 mg, 5 mol%), substrate 2.3e (61.2 mg, 0.2 mmol, 1 equiv), phenylboronic acid (49 mg, 2 equiv) and K₂CO₃ (31 mg, 1.1 equiv). The product was isolated through column chromatography (pentane:EtOAc 9:1) as a pale yellow solid in 70% yield (48.6 mg). ¹H NMR (400 MHz, CDCl₃): δ 7.56 (d, J = 7.4 Hz, 2H), 7.45 – 7.31 (m, 5H), 7.31 – 7.21 (m, 2H), 6.95 (s, 1H), 4.40 (s, 1H), 4.32 (d, J = 4.6 Hz, 2H), 1.37 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ 139.2, 138.6, 137.2, 134.8, 134.0, 132.8, 130.3, 129.7, 129.3, 129.2 (2), 129.0 (2), 128.5, 127.3 (2), 126.9, 126.7 (2), 42.4; IR (NaCl, neat): 3260, 3061, 3023, 2917, 2849, 1471, 1447, 1321, 1166, 1095, 1066, 1049, 757, 721, 689 cm⁻¹; M. p.: 131-134 °C; HRMS (ESI): calcd for C₂₁H₁₉ClNO₂S (M+H)⁺: 384.0825; found: 384.0829.

(Z)-N-(3-(2-Chlorophenyl)-2-phenylallyl)-1,1,1-trifluoromethanesulfonamide (2.4i)

The titled compound was synthesized using procedure 2.2 using [Rh(cod)OH]₂ (2.3 mg, 2.5 mol%), BINAP (6.23 mg, 5 mol%), substrate 2.3i (59.5 mg, 0.2 mmol, 1 equiv), phenylboronic acid (49 mg, 2 equiv) and K₂CO₃ (31 mg, 1.1 equiv). The product was isolated through column chromatography (pentane:EtOAc 9:1) as a pale orange oil in 39% yield (27 mg); ¹H NMR (400 MHz, CDCl₃): ¹H
NMR (400 MHz, CDCl$_3$) δ 7.55 – 7.37 (m, 6H), 7.37 – 7.28 (m, 3H), 7.01 (s, 1H), 4.73 (s, 1H), 4.43 (d, J = 5.2 Hz, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 138.0, 136.8, 134.5, 134.0, 130.4, 130.2, 129.9, 129.6, 129.3 (2), 129.0, 127.1, 126.9 (2), 119.6 (q, J = 321.4 Hz), 43.6; $^{19}$F NMR (377 MHz, CDCl$_3$) δ -78.0; IR (NaCl, neat): 3312, 3061, 3027, 2917, 2850, 1471, 1427, 1373, 1232, 1197, 1146, 1053, 880, 758, 699 cm$^{-1}$; HRMS (ESI): calcd for C$_{16}$H$_{17}$ClF$_3$N$_2$O$_2$S (M+NH$_4^+$): 393.0651; found: 393.0654.

(Z)-N-(3-(2-Chlorophenyl)-2-phenylallyl)benzamide (2.4j)

The titled compound was synthesized using procedure 2.2 using [Rh(cod)OH]$_2$ (2.3 mg, 2.5 mol%), BINAP (6.23 mg, 5 mol%), substrate 2.3j (47.1 mg, 0.2 mmol, 1 equiv), phenylboronic acid (49 mg, 2 equiv) and K$_2$CO$_3$ (31 mg, 1.1 equiv). The product was isolated through column chromatography (pentane:EtOAc 9:1 to 8:2) as a colorless solid in 10% yield. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.61 (d, J = 7.2 Hz, 2H), 7.54 (d, J = 7.1 Hz, 2H), 7.47 – 7.27 (m, 10H), 7.06 (s, 1H), 5.94 (s, 1H), 4.65 (d, J = 5.1 Hz, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 167.4, 139.3, 139.2, 135.4, 134.5, 134.1, 131.6, 130.6, 129.7, 129.1, 129.0 (2), 128.7 (3), 128.5, 127.0, 126.9 (2), 126.9 (2), 39.5; IR (NaCl, neat): 3294, 3059, 2926, 2853, 1713, 1634, 1537, 1489, 1472, 1296, 1204, 1053, 1034 cm$^{-1}$; M. p.: 146-149 °C; HRMS (ESI): calcd for C$_{22}$H$_{19}$ClNO (M+H): 348.1155; found: 348.1157.

(Z)-Diphenyl 3-(2-chlorophenyl)-2-phenylallylphosphoramidate (2.4l)

The titled compound was synthesized using procedure 2.2 using [Rh(cod)OH]$_2$ (2.3 mg, 2.5 mol%), BINAP (6.23 mg, 5 mol%), substrate 2.3l (72.7 mg, 0.2 mmol, 1 equiv), phenylboronic acid (49 mg, 2 equiv) and K$_2$CO$_3$ (31 mg, 1.1 equiv). The product was isolated through column chromatography (pentane:EtOAc 8:2) as a colorless solid in 33% yield. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.49 – 7.40 (m, 3H), 7.40 – 7.23 (m, 10H), 7.23 – 7.07 (m, 6H), 6.91 (s, 1H), 4.26 (t, J = 6.4 Hz, 2H), 3.02 (dt, J = 11.9, 5.8 Hz, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 150.8 (d, J = 6.7 Hz, 2C), 139.7 (d, J = 8.9 Hz), 139.1, 135.2, 134.3, 130.4, 129.8 (d, J = 0.5 Hz, 4C), 129.7, 129.0, 129.0 (2), 128.4, 128.2, 127.0 (2), 126.9, 125.1 (d, J = 1.1 Hz, 2C), 120.3 (d, J = 5.0 Hz, 4C), 40.9; IR (NaCl, neat): 3204, 3059, 2928, 2872, 1589, 1485, 1472, 1257, 1192, 1163, 1099, 1026, 933 cm$^{-1}$; M. p.: 117-120 °C; HRMS (ESI): calcd for C$_{27}$H$_{24}$ClNO$_3$P (M+H): 476.1182; found: 476.1193.

(Z)-N-(3-(2-Chlorophenyl)-2-(4-(trifluoromethyl)phenyl)allyl)-4-methylbenzenesulfonamide (2.12)

This compound was prepared by L. Zhang according to procedure 2.2. The product was purified by flash chromatography (EtOAc/hexanes 0 to 1:9) to
provide the title compound as an off white solid 69%. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.53 (d, $J = 8.2$ Hz, 3H), 7.43 (d, $J = 8.1$ Hz, 2H), 7.38 (d, $J = 7.9$ Hz, 1H), 7.28 – 7.13 (m, 5H), 6.93 (s, 1H), 4.61 (s, 1H), 4.07 (d, $J = 5.8$ Hz, 2H), 2.43 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 143.7, 142.5, 136.6, 136.2, 134.3, 134.0, 131.2, 130.1, 129.8, 129.7, 129.4, 127.2, 127.2, 126.9, 125.7 (q, $J = 3.8$ Hz), 42.4, 21.6; $^{19}$F NMR (377 MHz, CDCl$_3$): δ 63.0 (s); IR (NaCl, neat): 3264, 1616, 1435, 1323, 1161, 1123, 1072, 748 cm$^{-1}$; M. p.: 129-131°C; HRMS (ESI): calc'd for C$_{23}$H$_{20}$NO$_2$F$_3$SCl (M+H)$^+$: 466.0849; found: 466.0835.

(Z)-N-(3-(2-Chlorophenyl)-2-(p-tolyl)allyl)-4-methylbenzenesulfonamide (2.13)

This compound was prepared by L. Zhang according to procedure 2.2. The product was purified by flash chromatography (EtOAc/hexanes 0:1 to 1:9) to provide the title compound as an off white solid 64%. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.57 (d, $J = 8.3$ Hz, 2H), 7.35 (d, $J = 7.7$ Hz, 1H), 7.26 – 7.08 (m, 9H), 6.85 (s, 1H), 4.39 (s, 1H), 4.05 (d, $J = 5.6$ Hz, 2H), 2.43 (s, 3H), 2.36 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 143.6, 138.5, 137.1, 136.2, 135.7, 134.9, 134.1, 130.2, 129.7, 129.7, 129.6, 129.0, 128.4, 127.4, 126.8, 126.6, 77.5, 77.2, 76.8, 42.4, 21.7, 21.3; IR (NaCl, CDCl$_3$): 3244, 1435, 1316, 1165, 1096, 1065, 810, 748, 706 cm$^{-1}$; M. p.: 122-125°C; HRMS (ESI): calc'd for C$_{23}$H$_{23}$NO$_2$SCl (M+H)$^+$: 412.1132; found: 412.1142.

(Z)-N-(3-(2-Chlorophenyl)-2-(4-methoxyphenyl)allyl)-4-methylbenzenesulfonamide (2.14)

This compound was prepared by L. Zhang according to procedure 2.2. The product was purified by flash chromatography (EtOAc/hexanes 0 to 1:9) to provide the title compound as an off white solid 70%. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.58 (d, $J = 8.3$ Hz, 2H), 7.36 (dd, $J = 7.8$, 1.0 Hz, 1H), 7.28 – 7.11 (m, 7H), 6.89 – 6.78 (m, 3H), 4.28 (t, $J = 5.5$ Hz, 1H), 4.04 (d, $J = 5.6$ Hz, 2H), 3.84 (s, 3H), 2.44 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 159.9, 143.5, 136.5, 136.1, 134.9, 134.0, 130.8, 130.1, 129.7, 129.5, 128.8, 127.8, 127.6, 127.3, 114.3, 55.4, 42.3, 21.6; IR (NaCl, CDCl$_3$): 3264, 1616, 1435, 1323, 1161, 1123, 1072, 748 cm$^{-1}$; M. p.: 129-131°C; HRMS (ESI): calc'd for C$_{23}$H$_{23}$NO$_2$F$_3$SCl (M+H)$^+$: 466.0849; found: 466.0835.

(Z)-N-(3-(2-Chlorophenyl)-2-(6-chloropyridin-3-yl)allyl)-4-methylbenzenesulfonamide (2.15)

The titled compound was synthesized using procedure 2.2 using [Rh(cod)OH]$_2$ (2.3 mg, 2.5 mol%), BINAP (6.23 mg, 5 mol%), substrate 2.3b (64 mg, 0.2 mmol, 1 equiv), (6-chloropyridin-3-yl)boronic acid (63 mg, 2 equiv) and K$_2$CO$_3$ (61 mg, 2.2 equiv). The product was isolated through column chromatography (pentane:EtOAc 8:2) as a yellow solid in 77% yield (67 mg). $^1$H NMR (300 MHz, CDCl$_3$): δ 8.34 (d, $J = 2.4$ Hz, 1H), 7.64 (dd, $J = 8.3$, 2.5 Hz, 1H), 7.54 (d, $J = 8.2$
Hz, 2H), 7.38 (d, J = 7.8 Hz, 1H), 7.32 – 7.07 (m, 6H), 6.89 (s, 1H), 5.16 (t, J = 5.8 Hz, 1H), 4.02 (d, J = 5.8 Hz, 2H), 2.44 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 150.9, 147.9, 143.8, 137.0, 136.1, 134.0, 133.9, 131.3, 130.1, 129.8 (2), 129.7, 129.5, 127.1 (2), 126.9, 124.0, 42.2, 21.7; IR (NaCl, neat): 3265, 3062, 2922, 2852, 1582, 1469, 1377, 1326, 1160, 1109, 1094, 1067, 756 cm$^{-1}$; M. p.: 143-147 °C; HRMS (ESI): calcd for C$_{21}$H$_{19}$ClN$_2$O$_2$S (M+H)$^+$: 433.0538; found: 433.0552.

(Z)-N-(3-(2-Chlorophenyl)-2-(thiophen-3-yl)allyl)methanesulfonamide (2.16)

The titled compound was synthesized using procedure 2.2 using [Rh(cod)OH]$_2$ (2.3 mg, 2.5 mol%), BINAP (6.5 mg, 5.2 mol%), substrate 2.3c (48 mg, 0.2 mmol, 1 equiv), 3-thienylboronic acid (51 mg, 2 equiv) and K$_2$CO$_3$ (31 mg, 1.1 equiv). The product was isolated as a colorless thick oil in 73% yield (48 mg). $^1$H NMR (399 MHz, CDCl$_3$) δ 7.50 (dd, J = 2.8, 1.4 Hz, 1H), 7.48 – 7.42 (m, 1H), 7.41 – 7.25 (m, 5H), 7.10 (s, 1H), 4.53 (t, J = 5.6 Hz, 1H), 4.20 (d, J = 5.8 Hz, 2H), 2.79 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 140.3, 134.8, 134.0, 132.7, 130.4, 129.8, 129.4, 128.0, 127.0, 126.8, 125.8, 122.5, 42.8, 40.3; IR (NaCl, neat): 3286, 3108, 2959, 2917, 2850, 1468, 1428, 1403, 1321, 1152, 1066, 1053, 1033, 963, 912, 785, 759, 739 cm$^{-1}$; HRMS (ESI): calcd for C$_{14}$H$_{15}$ClNO$_2$S: 328.0233 (M+H)$^+$; found: 328.0228.

4-(2-Chlorophenyl)but-3-yn-1-ol (2.17b)

A round-bottom flask containing Pd(PPh$_3$)$_2$Cl$_2$ (70 mg, 0.5 mol%), Cul (38 mg, 1 mol%), and a stirring bar was purged with argon. Triethylamine (40 ml, 0.5 M) was added. Following this, 2-chloro-1-iodobenzene (2.69 ml, 1.1 equiv) was added, followed by 3-butyn-1-ol (1.51 ml, 20 mmol, 1 equiv), and the reaction mixture was degassed with argon. The mixture was stirred at room temperature for 16 hours. The reaction crude was filtered through a Celite plug and concentrated under vacuum. Column chromatography (pentane:EtOAc 9:1) yielded the titled compound as yellow oil in 79% yield. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.49 – 7.41 (m, 1H), 7.41 – 7.35 (m, 1H), 7.28 – 7.14 (m, 2H), 3.84 (t, J = 6.2 Hz, 2H), 2.74 (t, J = 6.2 Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 140.3, 134.8, 134.0, 132.7, 130.4, 129.8, 129.4, 128.0, 127.0, 126.8, 125.8, 122.5, 42.8, 40.3; IR (NaCl, neat): 3335, 2943, 2888, 2234, 1476, 1431, 1065, 1045, 1034, 754 cm$^{-1}$; HRMS (ESI+): calcd for C$_{10}$H$_{10}$ClO: 181.0420, Found: 181.0419.

(Z)-3-(2-Chlorophenyl)-2-phenylprop-2-en-1-ol (2.18a)

This compound was prepared by L. Zhang: The product was purified by flash chromatography (EtOAc/hexanes 0 to 10%) to provide the title compound as an off white solid 51%. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.62 (d, J = 7.1 Hz, 2H), 7.47 (dd, J = 7.3, 1.9 Hz, 1H), 7.41 (ap t, J = 7.3 Hz, 3H), 7.34 (t, J = 7.3 Hz, 1H), 7.26 (ap td, J
= 7.2, 1.7 Hz, 2H), 7.00 (s, 1H), 4.60 (s, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 141.5, 140.0, 135.5, 134.2, 130.8, 129.6, 128.9, 128.2, 128.1, 126.9, 126.8, 77.5, 77.2, 76.8, 60.5; IR (NaCl, neat): 3363, 3057, 2924, 1495, 1470, 1435, 1053, 1032, 1017, 758, 696 cm$^{-1}$; M. p.: 69-70 °C; HRMS (ESI): calc'd for C$_{15}$H$_{17}$ClNO (M+NH$_4^+$): 262.0999; found: 262.0998.

$(E)$-4-(2-Chlorophenyl)-3-phenylbut-3-en-1-ol (2.18b)

This compound was prepared by L. Zhang: The product was purified by flash chromatography (EtOAc/hexanes 0 to 10%) to provide the title compound as a white solid 51%. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.55–7.19 (m, 10H), 6.86 (s, 1H), 3.63 (t, J = 6.7 Hz, 2H), 2.91 (t, J = 6.6 Hz, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 141.6, 140.3, 136.3, 134.3, 130.7, 129.6, 128.7, 128.5, 128.4, 127.9, 126.9, 126.7, 77.5, 77.2, 76.8, 61.2, 33.6; IR (NaCl, neat): 3354, 3057, 3023, 2961, 2883, 1495, 1468, 1442, 1035, 758, 698 cm$^{-1}$; M. p.: 75-76 °C; HRMS (ESI): calc'd for C$_{16}$H$_{19}$ClNO (M+NH$_4^+$): 276.1155; found: 276.1148.

Procedure 2.3: C-N coupling - 1-(Methylsulfonyl)-3-phenyl-1,2-dihydroquinoline (2.5c)

(Z)-N-(3-(2-chlorophenyl)-2-phenylallyl)methanesulfonamide (2.4c) (64.4 mg, 0.2 mmol), K$_2$CO$_3$ (39 mg, 1.4 equiv), Pd(OAc)$_2$ (0.9 mg, 2 mol%, Note 1) and X-Phos (2.8 mg, 4 mol%, Note 1) were weighed into a 2 dram vial, which was fitted with a screw-cap with a septum and purged with argon. Dioxane was added (2 ml) and the septum was replaced with a Teflon-lined screw-cap (Note 2). The reaction was heated to 90 °C for 16 h, upon which the crude was filtered through a silica plug and concentrated. Column chromatography (pentane:EtOAc 9:1) yielded the titled compound in 91% yield as a colorless solid (all dihydropyridine compounds were highly fluorescent under UV light).

Note 1: Oftentimes Pd-Xphos was added as a stock solution prepared by stirring the Pd(OAc)$_2$ and X-Phos for 10-15 minutes (or until homogeneous) at room temperature or 50 °C.

Note 2: Alternatively, the argon inlet was removed and the vial septum was wrapped with parafilm.

Procedure 2.4: Domino synthesis of 3-aryl-1,2-dihydroquinolines from aryl propargyl alkynes.

The alkyne (0.2 mmol, 1 equiv), arylboronic acid (1.1-2 equiv) (Note 1) and K$_2$CO$_3$ (2.2 equiv) were weighed into a 2-dram vial (Note 2) equipped with a stirring bar and fitted with a septum. The reaction vessel was purged with argon and then 1,4-dioxane (1 ml, 0.2 M) and MeOH (0.1 ml, 2 M) were added. The catalyst solutions (0.5 ml of each, Note 3) were added to this reaction vessel. The septum was exchanged with a Teflon-lined screw cap and the reaction was heated at
90 °C for 16 h. The crude was filtered though at plug of silica, concentrated under reduced pressure and purified through column chromatography.

Note 1: 1.5 equiv of arylboronic acid was used for the majority of arylboronic acids (similar results were seen with 1.1 equiv or 2 equiv). Two equivalents of heteroaromatic boronic acids were used due to more facile protodemetalation reaction.

Note 2: Microwave vials could be used instead of screw-cap vials with similar results.

Note 3: The catalyst solutions were prepared as follows:

\([\text{Rh(cod)OH}]_2\) (2.5 mol%; 5 mol% [Rh]) and BINAP (5.2 mol%) were weighed into a screw-cap vial. Pd(OAc)$_2$ (2 mol%) and X-Phos (4 mol%) were weighed into a screw cap vial. Both vials were equipped with a septum and purged with argon. Dioxane (0.5 ml, 0.01 M for [Rh]$_2$ (0.005 M for [Rh]), 0.008 M for [Pd]) was added to both vials and the catalyst solutions were stirred at 50 °C for 15 minutes after which these solutions were added to the reaction flask. More conveniently, stock solutions of known concentration (usually: 0.01 mmol/ml for [Rh]$_2$ and 0.008 mmol/ml for [Pd]) were prepared and used in several parallel reactions. Sometimes a colorless precipitate (excess BINAP) was observed in the rhodium catalyst mixture. In this case the precipitate was allowed to settle (∼5 min), and only the supernatant was transferred to the reaction vessel.

1-(Methylsulfonyl)-3-phenyl-1,2-dihydroquinoline (2.5c)

According to the general procedure 2.4, substrate 2.3c (49 mg, 0.2 mmol) and phenylboronic acid (36.6 mg, 1.5 equiv) were reacted using \([\text{Rh(cod)OH}]_2\) (2.3 mg, 2.5 mol%), BINAP (6.5 mg, 5.2 mol%), Pd(OAc)$_2$ (0.9 mg, 2 mol%), X-Phos (3.8 mg, 4 mol%) and K$_2$CO$_3$ (61 mg, 2.2 equiv.). The product was isolated using column chromatography (pentane:EtOAc 9:1) in 69% yield (39.5 mg) as a colorless solid. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.69 – 7.63 (m, 1H), 7.59 – 7.53 (m, 2H), 7.47 – 7.40 (m, 2H), 7.40 – 7.33 (m, 1H), 7.34 – 7.26 (m, 3H), 6.94 (s, 1H), 4.78 (d, $J$ = 1.0 Hz, 2H), 2.64 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 137.2, 135.9, 134.6, 123.0, 129.2 (2), 128.8, 128.5, 127.3, 126.5, 125.5 (2), 122.0, 47.5, 37.7.; IR (NaCl, neat): 3070, 3031, 2930, 2891, 2853, 1589, 1496, 1484, 1455, 1344, 1321, 1203, 1154, 1083, 1037, 959, 912, 882, 845, 831, 761, 731, 693 cm$^{-1}$; M. p.: 119-121 °C; HRMS (EI): calcd for C$_{16}$H$_{15}$NO$_2$S (M)$^+$: 285.0824; found: 285.0816.

3-Phenyl-1-tosyl-1,2-dihydroquinoline (2.5b)

This compound was prepared by L. Zhang using procedure 2.4. Substrate 2.3b (64 mg, 0.2 mmol) and phenylboronic acid (49 mg, 2 equiv) were reacted using \([\text{Rh(cod)OH}]_2\) (2.3 mg, 2.5 mol%), BINAP (6.23 mg, 5 mol%), Pd(OAc)$_2$ (0.9
mg, 2 mol%), X-Phos (3.8 mg, 4 mol%) and K$_2$CO$_3$ (61 mg, 2.2 equiv) in dioxane:MeOH (2 ml : 0.1 ml). The product was isolated using column chromatography (pentane:EtOAc 9:1) in 65% yield (47 mg) as a white solid.$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.77 (d, $J = 7.9$ Hz), 7.43 – 7.18 (m), 7.16 (d, $J = 8.4$ Hz), 7.03 (dd, $J = 7.5$, 1.5 Hz), 6.91 (d, $J = 8.5$ Hz), 6.30 (s), 4.80 (d, $J = 1.1$ Hz), 2.28 (s); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 143.5, 137.5, 135.7, 134.6, 134.3, 130.6, 129.0, 128.8, 128.4, 128.0, 127.2, 127.1, 126.9, 125.3, 121.4, 77.5, 77.2, 76.8, 47.7, 21.6; IR (NaCl, neat): 2361, 1597, 1481, 1346, 1165, 1088, 810, 760 cm$^{-1}$; M. p.: 177-179 °C; HRMS (ESI): calcd for C$_{22}$H$_{19}$NO$_2$NaS (M+Na)$^+$: 384.1028; found: 384.1031.

$^N$-(3-(Biphenyl-2-yl)prop-2-ynyl)methanesulfonamide (2.19)

The substrate 2.3c was reacted according to procedure 2.4. 2.3c (49 mg, 0.2 mmol), phenylboronic acid (36.6 mg, 1.5 equiv), Pd(OAc)$_2$ (0.9 mg, 2 mol%), X-Phos (3.8 mg, 4 mol%) and K$_2$CO$_3$ (61 mg, 2.2 equiv) were combined in a 2 dram vial equipped with a stirring bar and a septum. After purging with argon, dioxane (2 ml, 0.1 M) and methanol (0.05 ml) was added. The reaction was stirred at 90 °C for 1 hour, then was allowed to cool, filtered through a silica plug and concentrated. Column chromatography (hexane:EtOAc 7:3) gave the titled compound in 76% yield (44 mg) as a pale yellow oil.$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.54 – 7.29 (m, 9H), 4.49 (t, $J = 5.9$ Hz, 1H), 4.07 (d, $J = 6.2$ Hz, 2H), 2.66 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 144.3, 140.6, 133.1, 129.7, 129.3, 129.2, 128.3, 127.9, 127.3, 120.5, 86.8, 84.8, 77.4, 77.2, 76.7, 40.9, 33.7; IR (NaCl, neat): 3287, 3061, 3024, 2931, 2853, 1589, 1476, 1432, 1415, 1322, 1153, 1071, 1009, 996, 960, 912, 831, 762, 738, 701 cm$^{-1}$; HRMS (ESI): calcd for C$_{16}$H$_{19}$N$_2$O$_2$S (M+NH$_4^+$): 303.1167; found: 303.1158.

3-Phenyl-1-(phenylsulfonyl)-1,2-dihydroquinoline (2.5e)

According to the general procedure 2.4, substrate 2.3e (61.1 mg, 0.2 mmol) and phenylboronic acid (49 mg, 2 equiv) were reacted using [Rh(cod)OH]$_2$ (2.3 mg, 2.5 mol%), BINAP (6.23 mg, 5 mol%), Pd(OAc)$_2$ (0.9 mg, 2 mol%), X-Phos (3.8 mg, 4 mol%) and K$_2$CO$_3$ (61 mg, 2.2 equiv.) in dioxane:MeOH (2 ml : 0.1 ml). The product was isolated using column chromatography (pentane:EtOAc 8:2) in 54% yield (37.4 mg) as a colorless solid.$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.78 (d, $J = 7.9$ Hz, 1H), 7.42 – 7.18 (m, 10H), 7.13 (t, $J = 7.9$ Hz, 2H), 7.02 (dd, $J = 7.5$, 1.1 Hz, 1H), 6.27 (s, 1H), 4.81 (d, $J = 0.5$ Hz, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 138.6, 137.4, 134.7, 134.2, 132.8, 130.6, 128.8 (2), 128.4, 128.3 (2), 128.1, 127.2, 127.2 (2), 127.1, 127.0, 125.2 (2), 47.7; IR (NaCl, neat): 3062, 3035, 2919, 2850, 1484, 1447, 1350, 1168, 1091, 1072, 757 cm$^{-1}$; M. p.: 135-138 °C; HRMS (ESI): calcd for C$_{21}$H$_{18}$NO$_2$S (M+H)$^+$: 348.1058; found: 348.1064.
1-(4-Methoxyphenylsulfonyl)-3-phenyl-1,2-dihydroquinoline (2.5f)

According to the general procedure 2.4, substrate 2.3f (67.2 mg, 0.2 mmol) and phenylboronic acid (49 mg, 2 equiv) were reacted using [Rh(cod)OH]2 (2.3 mg, 2.5 mol%), BINAP (6.23 mg, 5 mol%), Pd(OAc)2 (0.9 mg, 2 mol%), X-Phos (3.8 mg, 4 mol%) and K2CO3 (61 mg, 2.2 equiv.) in dioxane:MeOH (2 ml : 0.1 ml). The product was isolated using column chromatography (pentane:EtOAc 8:2) in 35% yield (26 mg) as a colorless oil. 

1H NMR (400 MHz, CDCl3): 7.77 (d, J = 8.0 Hz, 1H), 7.43 – 7.27 (m, 6H), 7.22 (dt, J = 7.6, 1.2 Hz, 1H), 7.20 (d, J = 8.9 Hz, 2H), 7.03 (dd, J = 7.5, 1.3 Hz, 1H), 6.59 (d, J = 8.9 Hz, 2H), 6.34 (s, 1H), 4.80 (s, 2H), 3.74 (s, 3H); 13C NMR (101 MHz, CDCl3): δ 163.0, 137.5, 134.7, 134.5, 130.6, 130.6, 129.3 (2), 128.8 (2), 128.4, 128.0, 127.1, 127.1, 125.3 (2), 121.3, 113.5 (2), 55.6, 47.7; IR (NaCl, neat): 3063, 2966, 2839, 1595, 1580, 1497, 1348, 1304, 1260, 1157, 1026 cm⁻¹; HRMS (ESI): calcd for C22H20N1O3S (M+H)+: 378.1164; found: 378.1169.

1-(4-Nitrophenylsulfonyl)-3-phenyl-1,2-dihydroquinoline (2.5g)

According to the general procedure 2.4, substrate 2.3g (70.2 mg, 0.2 mmol) and phenylboronic acid (49 mg, 2 equiv) were reacted using [Rh(cod)OH]2 (2.3 mg, 2.5 mol%), BINAP (6.23 mg, 5 mol%), Pd(OAc)2 (0.9 mg, 2 mol%), X-Phos (3.8 mg, 4 mol%) and K2CO3 (61 mg, 2.2 equiv.) in dioxane:MeOH (2 ml : 0.1 ml). The product was isolated using column chromatography (pentane:EtOAc 9:1) in 36% yield (28 mg) as a yellow solid. 

1H NMR (400 MHz, CDCl3): δ 7.96 (ap dt, J = 8.9, 2.2 Hz, 2H), 7.79 (d, J = 7.9 Hz, 1H), 7.45 – 7.33 (m, 6H), 7.31 – 7.22 (m, 3H), 7.06 (dd, J = 7.5, 1.4 Hz, 1H), 6.31 (s, 1H), 4.83 (d, J = 0.5 Hz, 2H); 13C NMR (100 MHz, CDCl3): δ 150.1, 144.0, 136.9, 134.5, 133.5, 130.5, 129.2 (2), 128.9, 128.5, 128.4 (2), 127.9, 127.5, 127.0, 125.0 (2), 123.5 (2), 121.3, 47.8; IR (NaCl, neat): 3063, 2966, 2839, 1595, 1580, 1497, 1348, 1304, 1260, 1157, 1026 cm⁻¹; M. p.: 190-192 °C; HRMS (ESI): calcd for C22H20N3O4S (M+H)+: 410.1175; found: 410.1187.

1-(Mesitylsulfonyl)-3-phenyl-1,2-dihydroquinoline (2.5h)

According to the general procedure 2.4, substrate 2.3h (67.2 mg, 0.2 mmol) and phenylboronic acid (49 mg, 2 equiv) were reacted using [Rh(cod)OH]2 (2.3 mg, 2.5 mol%), BINAP (6.23 mg, 5 mol%), Pd(OAc)2 (0.9 mg, 2 mol%), X-Phos (3.8 mg, 4 mol%) and K2CO3 (61 mg, 2.2 equiv.) in dioxane:MeOH (2 ml : 0.1 ml). The product was isolated using column chromatography (pentane:EtOAc 95:5) in ~15% yield (11.5 mg) as a colorless oil; 1H NMR (400 MHz, CDCl3): δ 7.39 – 7.27 (m, 6H), 7.17 – 7.13 (m, 3H), 6.81 (s, 2H), 6.67 (s, 1H), 4.76 (d, J = 1.1 Hz, 2H), 2.37 (s, 6H), 2.25 (s, 3H); HRMS (ESI): calcd for
C$_{24}$H$_{24}$NO$_2$S (M+H)$^+$: 390.1528; Found: 390.1540. This compound was not fully characterized because of difficulties in purification and low yield.

3-(Thiophen-3-yl)-1-tosyl-1,2-dihydroquinoline (2.21b)

According to the general procedure 2.4, substrate 2.3b (64 mg, 0.2 mmol) and thiophen-3-ylboronic acid (51 mg, 2 equiv) were reacted using [Rh(cod)OH]$_2$ (2.3 mg, 2.5 mol%), BINAP (6.23 mg, 5 mol%), Pd(OAc)$_2$ (0.9 mg, 2 mol%), X-Phos (3.8 mg, 4 mol%) and K$_2$CO$_3$ (61 mg, 2.2 equiv.) in dioxane:MeOH (2 ml : 0.1 ml). The product was isolated using column chromatography (pentane:EtOAc 9:1) in 46% yield (33.7 mg) as a pale yellow solid. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.76 (d, $J$ = 7.8 Hz, 1H), 7.35 – 7.12 (m, 6H), 7.07 (dd, $J$ = 5.0, 1.4 Hz, 1H), 7.01 (dd, $J$ = 7.4, 1.5 Hz, 1H), 6.89 (d, $J$ = 8.1 Hz, 2H), 6.27 (s, 1H), 4.74 (d, $J$ = 0.9 Hz, 2H), 2.27 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 143.5, 139.2, 135.6, 134.3, 130.4, 129.8, 128.9 (2), 127.8, 127.1 (2), 127.1, 126.9, 126.5, 124.6, 121.1, 120.0, 47.5, 21.6; IR (NaCl, neat): 3110, 3070, 3037, 2921, 2851, 1596, 1480, 1456, 1343, 1162, 1078, 769, 707, 694 cm$^{-1}$; M. p.: 175-177 °C; HRMS (ESI): calcd for C$_{20}$H$_{17}$NO$_2$S Na (M+Na)$^+$: 390.0592; found: 390.0603.

1-(Methylsulfonyl)-3-(thiophen-3-yl)-1,2-dihydroquinoline (2.21c)

According to the general procedure 2.4, substrate 2.3c (49 mg, 0.2 mmol) and thiophen-3-ylboronic acid (51 mg, 2 equiv) were reacted using [Rh(cod)OH]$_2$ (2.3 mg, 2.5 mol%), BINAP (6.5 mg, 5.2 mol%), Pd(OAc)$_2$ (0.9 mg, 2 mol%), X-Phos (3.8 mg, 4 mol%) and K$_2$CO$_3$ (61 mg, 2.2 equiv.). The product was isolated using column chromatography (pentane:EtOAc 85:15) in 78% yield (45.5 mg) as a colorless solid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.67 – 7.61 (m, 1H), 7.44 – 7.36 (m, 3H), 7.30 – 7.22 (m, 3H), 6.90 (s, 1H), 4.71 (s, 2H), 2.62 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 138.7, 134.4, 130.9, 129.8, 128.2, 127.3, 127.2, 126.5, 124.6, 121.8, 120.6, 47.3, 37.6; IR (NaCl, neat): 3105, 3066, 3018, 2929, 2853, 1625, 1599, 1482, 1455, 1409, 1342, 1222, 1203, 1155, 1118, 1078, 1036, 959, 909, 877, 819, 773, 760, 731 cm$^{-1}$; M. p.: 101-103 °C; HRMS (ESI): calcd for C$_{14}$H$_{17}$N$_2$O$_2$S$_2$ (M+NaH$_4$)$^+$: 309.0731; found: 309.0726.

3-(Furan-3-yl)-1-tosyl-1,2-dihydroquinoline (2.22b)

According to the general procedure 2.4, substrate 2.3b (64 mg, 0.2 mmol) and furan-3-ylboronic acid (45 mg, 2 equiv) were reacted using [Rh(cod)OH]$_2$ (2.3 mg, 2.5 mol%), BINAP (6.23 mg, 5 mol%), Pd(OAc)$_2$ (0.9 mg, 2 mol%), X-Phos (3.8 mg, 4 mol%) and K$_2$CO$_3$ (61 mg, 2.2 equiv.) in dioxane:MeOH (2 ml : 0.1 ml). The product was isolated using column chromatography (pentane:EtOAc 9:1) in 42% yield (29.4 mg) as a pale yellow solid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.75 (d, $J$ = 7.9 Hz, 1H), 7.60 (s, 1H), 7.42 (ap t, $J$ = 1.6 Hz, 1H), 7.27 (ap td, $J$ = 7.7, 1.6 Hz, 1H), 7.21 (dd, $J$ = 7.5, 1.3 Hz, 1H); 3.81 (s, 3H); IR (NaCl, neat): 3110, 3070, 3037, 2929, 2853, 1625, 1599, 1482, 1455, 1409, 1342, 1222, 1203, 1155, 1118, 1078, 1036, 959, 909, 877, 819, 773, 760, 731 cm$^{-1}$; M. p.: 101-103 °C; HRMS (ESI): calcd for C$_{14}$H$_{17}$N$_2$O$_2$S$_2$ (M+NaH$_4$)$^+$: 309.0731; found: 309.0726.
Hz, 1H), 7.17 (d, J = 8.3 Hz, 2H), 6.98 (dd, J = 7.5, 1.4 Hz, 1H), 6.93 (d, J = 8.1 Hz, 2H), 6.38 (dd, J = 1.8, 0.7 Hz, 1H), 6.12 (s, 1H), 4.59 (d, J = 0.9 Hz, 2H), 2.28 (s, 3H); 13C NMR (100 MHz, CDCl₃): δ 144.2, 143.5, 139.5, 135.5, 134.3, 130.3, 128.9 (2), 127.6, 127.1 (2), 127.1, 127.0, 126.7, 126.7, 124.3, 119.3, 107.1, 47.2, 21.6; IR (NaCl, neat): 3067, 2921, 2850, 1761, 1597, 1492, 1451, 1348, 1224, 1164, 1122, 1033, 1010, 815, 735, 682 cm⁻¹; M. p. (decomp): 138-148 °C; HRMS (EI): calcd for C₂₀H₁₇NO₃S (M⁺): 351.0929; found: 351.0931.

3-(Furan-3-yl)-1-(methylsulfonyl)-1,2-dihydroquinoline (2.22c)

According to the general procedure 2.4, substrate 2.3c (48.7 mg, 0.2 mmol) and furan-3-ylboronic acid (45 mg, 2 equiv) were reacted using [Rh(cod)OH]₂ (2.3 mg, 2.5 mol%), BINAP (6.23 mg, 5 mol%), Pd(OAc)₂ (0.9 mg, 2 mol%), X-Phos (3.8 mg, 4 mol%) and K₂CO₃ (61 mg, 2.2 equiv.) in dioxane:MeOH (2 ml : 0.1 ml). The product was isolated using column chromatography (pentane:EtOAc 85:15) in 51% yield (28.3 mg) as a pale yellow solid. ¹H NMR (399 MHz, CDCl₃): δ 7.68 (s, 1H), 7.66–7.60 (m, 1H), 7.49 (ap t, J = 2 Hz, 1H), 7.30–7.19 (m, 3H), 6.76 (s, 1H), 6.67 (dd, J = 1.8, 0.8 Hz, 1H), 4.57 (d, J = 1.0 Hz, 2H), 2.63 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 144.6, 139.9, 134.4, 129.7, 128.1, 127.7, 127.3, 127.1, 126.3, 126.9, 119.8, 107.2, 47.0, 37.6; M. p.: 163–167 °C; HRMS (ESI): calcd for C₁₄H₁₄NO₃S (M⁺H): 276.0694; found: 276.0685.

4-(1-Tosyl-1,2-dihydroquinolin-3-yl)benzonitrile (2.23b)

According to the general procedure 2.4, substrate 2.3b (64 mg, 0.2 mmol) and 4-(cyanophenyl)boronic acid (59 mg, 2 equiv) were reacted using [Rh(cod)OH]₂ (2.3 mg, 2.5 mol%), BINAP (6.23 mg, 5 mol%), Pd(OAc)₂ (0.9 mg, 2 mol%), X-Phos (3.8 mg, 4 mol%) and K₂CO₃ (61 mg, 2.2 equiv.) in dioxane:MeOH (2 ml : 0.1 ml). The product was isolated using column chromatography (pentane:EtOAc 95:5 to 9:1) in 56% yield (41 mg) as a colorless solid. ¹H NMR (400 MHz, CDCl₃): δ 7.78 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 8.4 Hz, 2H), 7.40–7.30 (m, 3H), 7.25 (ap dt, J = 1.2, 7.2 Hz, 1H), 7.13 (d, J = 8.3 Hz, 2H), 7.07 (dd, J = 7.5, 1.1 Hz, 1H), 6.93 (d, J = 8.1 Hz, 2H), 6.43 (s, 1H), 4.79 (s, 2H), 2.30 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 143.8, 141.8, 135.8, 134.8, 132.7 (2), 132.5, 129.7, 129.1, 129.1 (2), 127.7, 127.3, 127.1 (2), 127.0, 125.7 (2), 124.3, 118.7, 111.7, 47.2, 21.6; IR (NaCl, neat): 3040, 2960, 2855, 1484, 1363, 1323, 1151, 1079, 1035, 967, 958, 872, 889, 820, 786, 767 cm⁻¹; M. p.: 220-222 °C; HRMS (ESI): calcd for C₂₃H₁₉N₂O₂S (M⁺H): 387.1167; found: 387.1167.
According to the general procedure 2.4, substrate 2.3c (49 mg, 0.2 mmol) and 4-cyanophenylboronic acid (44.1 mg, 1.5 equiv) were reacted using [Rh(cod)OH]$_2$ (2.3 mg, 2.5 mol%), BINAP (6.5 mg, 5.2 mol%), Pd(OAc)$_2$ (0.9 mg, 2 mol%), X-Phos (3.8 mg, 4 mol%) and K$_2$CO$_3$ (61 mg, 2.2 equiv.). The product was isolated using column chromatography (pentane:EtOAc 7:3) in 68% yield (42 mg) as a pale yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.73 (d, $J$ = 8.3 Hz, 2H), 7.70 – 7.62 (m, 3H), 7.39 – 7.26 (m, 3H), 7.06 (s, 1H), 4.78 (s, 2H), 2.65 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 141.4, 134.8, 133.6, 132.9 (2H), 129.5, 129.1, 128.1, 127.3, 126.2, 125.9 (2H), 124.9, 118.6, 112.0, 47.0, 37.9; IR (NaCl, neat): 3070, 3041, 2931, 2853, 2227, 1603, 1495, 1482, 1455, 1415, 1344, 1203, 1155, 1082, 960, 912, 845, 831, 773, 762, 731 cm$^{-1}$; HRMS (ESI): calcd for C$_{17}$H$_{18}$N$_3$O$_2$S (M+NH$_4$)$^+$: 328.1120; found: 328.1114.

This compound was prepared by L. Zhang according to procedure 2.4. The product was purified by flash chromatography (EtOAc/hexanes 0 - 5%) to provide the title compound as an off white solid 59%. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.76 (d, $J$ = 7.9 Hz, 1H), 7.33 – 7.10 (m, 6H), 7.09 – 6.98 (m, 3H), 6.92 (d, $J$ = 8.1 Hz, 2H), 6.29 (s, 1H), 4.79 (d, $J$ = 0.8 Hz, 2H), 2.38 (s, 3H), 2.29 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 143.3, 138.3, 137.5, 135.7, 134.3, 134.3, 130.5, 129.0, 128.9, 128.6, 127.8, 127.1, 126.9, 126.8, 125.9, 122.3, 121.1, 47.7, 21.6, 21.5; IR (NaCl, neat): 1348, 1200, 1163, 1090, 1074, 1032, 785, 762, 711, 694, 671, 650, 584, 557 cm$^{-1}$; M. p.: 167-168 °C; HRMS (ESI): calcd for C$_{23}$H$_{22}$NO$_3$S (M+H)$^+$: 376.1371; found: 376.1381.

This compound was prepared by L. Zhang according to procedure 2.4. The product was purified by flash chromatography (Et$_2$O/hexanes 0-10%) to provide the title compound as a white solid in 40% yield. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.75 (d, $J$ = 7.9 Hz, 1H), 7.30 – 7.16 (m, 4H), 7.15 (d, $J$ = 8.3 Hz, 2H), 6.99 (dd, $J$ = 7.5, 1.5 Hz, 1H), 6.94 – 6.85 (m, 4H), 6.21 (s, 1H), 4.75 (s, 2H), 3.84 (s, 3H), 2.27 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 159.8, 143.4, 135.8, 134.2, 134.1, 130.8, 130.1, 128.9, 127.6, 127.2, 127.0, 126.9, 126.8, 126.5, 119.6, 114.2, 55.5, 47.6, 21.6; IR (NaCl, neat): 1609, 1516, 1456, 1348, 1290, 1252, 1182, 1165, 1120, 1032, 1008, 831, 816, 756, 682, 667, 567 cm$^{-1}$; M. p.: 109-110 °C; HRMS (ESI): calcd for C$_{23}$H$_{22}$NO$_3$S (M+H)$^+$: 392.1320; found: 392.1331.
3-(4-Methoxyphenyl)-1-(methylsulfonyl)-1,2-dihydroquinoline (2.25c)

This compound was prepared by L. Zhang according to procedure 2.4. The product was purified by flash chromatography (Et$_2$O/hexanes 0-20%) to provide the title compound as a white solid in 49% yield. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.69 – 7.59 (m, 1H), 7.51 (d, J = 9.0 Hz, 2H), 7.32 – 7.23 (m, 2H), 6.96 (d, J = 9.0 Hz, 2H), 6.85 (d, J = 0.6 Hz, 1H), 4.74 (d, J = 1.2 Hz, 2H), 3.85 (s, 3H), 2.62 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 160.2, 135.4, 134.3, 130.3, 129.6, 128.0, 127.2, 127.2, 126.8, 126.5, 120.2, 114.6, 77.6, 77.2, 76.7, 6.56, 47.4, 37.7; IR (NaCl, neat): 2359, 2342, 1684, 1653, 1607, 1562, 1516, 1506, 1481, 1456, 1344, 1249, 1182, 1155, 1080, 1034, 957, 827, 770 cm$^{-1}$; M.p.: 127-130 °C; HRMS (ESI): calcd for C$_{17}$H$_{21}$N$_2$O$_3$S (M+NH$_4$)$^+$: 333.1273; found: 333.1278.

1-(4-(1-Tosyl-1,2-dihydroquinolin-3-yl)phenyl)ethanone (2.26)

This compound was prepared by L. Zhang according to procedure 2.4. The product was purified by flash chromatography with (Et$_2$O/hexanes 0-20%) to provide the title compound as a white solid 63%. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.96 (d, J = 8.5 Hz, 2H), 7.78 (d, J = 7.9 Hz, 1H), 7.37 – 7.31 (m, 3H), 7.24 (ap td, J = 7.5, 1.1 Hz, 1H), 7.13 (d, J = 8.3 Hz, 2H), 7.07 (dd, J = 7.5, 1.3 Hz, 1H), 6.91 (d, J = 8.1 Hz, 2H), 6.43 (s, 1H), 4.82 (s, 2H), 2.63 (s, J = 6.7 Hz, 3H), 2.29 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 197.4, 143.5, 141.7, 136.4, 135.6, 134.6, 133.1, 129.9, 128.9, 128.8, 128.6, 127.4, 127.1, 127.0, 126.9, 125.1, 123.3, 47.3, 26.6, 21.5; IR (NaCl, neat): 1680, 1599, 1483, 1450, 1412, 1349, 1269, 1165, 1090, 1074, 810, 762, 716 cm$^{-1}$; M. p.: 179-180 °C; HRMS (ESI): calcd for C$_{24}$H$_{22}$NO$_3$S (M+H)$^+$: 404.1320; found: 404.1336.

3-(3,4-Dimethoxyphenyl)-1-(methylsulfonyl)-1,2-dihydroquinoline (2.27)

According to the general procedure 2.4, substrate 2.3c (48.7 mg, 0.2 mmol) and (3,4-dimethoxyphenyl)boronic acid (73 mg, 2 equiv) were reacted using [Rh(cod)OH]$_2$ (2.3 mg, 2.5 mol%), BINAP (6.23 mg, 5 mol%), Pd(OAc)$_2$ (0.9 mg, 2 mol%), X-Phos (3.8 mg, 4 mol%) and K$_2$CO$_3$ (61 mg, 2.2 equiv.) in dioxane:MeOH (2 ml : 0.1 ml). The product was isolated using column chromatography (pentane:EtOAc 8:2) in 50% yield (34.7 mg) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.68 – 7.61 (m, 1H), 7.31 – 7.23 (m, 3H), 7.13 (dd, J = 8.3, 2.2 Hz, 1H), 7.08 (d, J = 2.1 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.86 (s, 1H), 4.74 (d, J = 0.9 Hz, 2H), 3.97 (s, 3H), 3.93 (s, 3H), 2.63 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 150.0, 149.6, 135.6, 134.4, 130.2, 129.9, 128.2, 127.3, 127.2, 126.5, 120.4, 118.4, 111.5, 108.5, 56.2, 56.2, 47.5, 37.7; IR (NaCl, neat): 3061, 3003, 2957, 2928, 2852, 1601, 1516, 1456, 1342, 1252, 1155, 1080, 1024, 959, 763 cm$^{-1}$; HRMS (ESI): calcd for C$_{18}$H$_{23}$N$_2$O$_3$S (M+NH$_4$)$^+$: 363.1379; found: 363.1392.
3-(2-Fluorophenyl)-1-tosyl-1,2-dihydroquinoline (2.28)

According to the general procedure 2.4, substrate 2.3b (64 mg, 0.2 mmol) and 2-fluorophenylboronic acid (56 mg, 2 equiv) were reacted using [Rh(cod)OH]₂ (2.3 mg, 2.5 mol%), BINAP (6.23 mg, 5 mol%), Pd(OAc)₂ (0.9 mg, 2 mol%), X-Phos (3.8 mg, 4 mol%) and K₂CO₃ (61 mg, 2.2 equiv.) in dioxane:MeOH (2 ml : 0.1 ml). The product was isolated using column chromatography (pentane:EtOAc 95:5 to 9:1) in 39% yield (27.8 mg) as an orange oil. 

**¹H NMR (400 MHz, CDCl₃); δ 7.78 (d, J = 8.0 Hz, 1H), 7.37 – 7.20 (m, 3H), 7.18 (d, J = 8.2 Hz, 2H), 7.14 – 7.01 (m, 3H), 6.98 (d, J = 8.1 Hz, 2H), 6.92 (ap td, J = 7.7, 1.6 Hz, 1H), 6.31 (s, 1H), 4.78 (s, 2H), 2.34 (s, 3H); 

**¹³C NMR (101 MHz, CDCl₃); δ 160.3 (d, J = 249.6 Hz), 144.6, 144.5, 143.9, 137.7 (d, J = 2.5 Hz), 130.1, 129.8 (d, J = 8.4 Hz), 129.1 (2), 128.4, 128.3 (d, J = 4.2 Hz), 127.3 (2), 127.2, 127.0, 127.0, 126.0 (d, J = 13.6 Hz), 124.9 (d, J = 4.3 Hz), 124.3 (d, J = 3.4 Hz), 116.2 (d, J = 22.4 Hz), 48.2 (d, J = 7.2 Hz), 21.6; 

**¹⁹F NMR (377 MHz, CDCl₃) δ -111.3 – -111.4 (m); 

**IR (NaCl, neat): 3063, 2957, 2921, 2850, 1598, 1580, 1496, 1451, 1348, 1220, 1165, 1122, 1032, 1008, 815, 761, 679, 614 cm⁻¹; 

**HRMS (EI): calcd for C₂₂H₁₈NO₂FS (M⁺): 379.1042; found: 379.1040.

3-(6-Fluoropyridin-3-yl)-1-tosyl-1,2-dihydroquinoline (2.29)

This compound was prepared by L. Zhang according to procedure 2.4: Substrate 2.3b (64 mg, 0.2 mmol) and 2-fluorophenylboronic acid (56 mg, 2 equiv) were reacted using [Rh(cod)OH]₂ (2.3 mg, 2.5 mol%), BINAP (6.23 mg, 5 mol%), Pd(OAc)₂ (0.9 mg, 2 mol%), X-Phos (3.8 mg, 4 mol%) and K₂CO₃ (61 mg, 2.2 equiv.) in dioxane:MeOH (2 ml : 0.1 ml). The product was isolated using column chromatography (pentane:EtOAc 9:1) as an yellow solid in 47% yield. 

**¹H NMR (400 MHz, CDCl₃) δ 7.98 (s, 1H), 7.69 (d, J = 7.9 Hz, 1H), 7.60 (ap t, J = 8.0 Hz, 1H), 7.27 (ap t, J = 7.3 Hz, 1H), 7.18 (ap t, J = 7.3 Hz, 1H), 7.06 (d, J = 8.1 Hz, 2H), 6.99 (d, J = 7.3 Hz, 1H), 6.88 (d, J = 8.1 Hz, 3H), 6.24 (s, 1H), 4.67 (s, 2H), 2.23 (s, 3H); 

**¹³C NMR (101 MHz, CDCl₃) δ 163.3 (d, J = 241.2 Hz), 144.6, 144.5, 143.9, 137.7 (d, J = 8.0 Hz), 135.7, 134.5, 131.5 (d, J = 4.9 Hz), 130.2, 129.7, 129.1, 128.8, 127.3 (d, J = 6.3 Hz), 127.1, 122.9 (d, J = 1.4 Hz), 109.7 (d, J = 37.6 Hz), 47.2, 21.6; 

**¹⁹F NMR (377 MHz, CDCl₃) δ -67.33; 

**IR (NaCl, CDCl₃): 1582, 1485, 1472, 1346, 1258, 1167, 1020, 833, 762, 712, 664 cm⁻¹; 

**M. p.: 114-115 °C; 

**HRMS (ESI): calcd for C₂₁H₁₈N₂O₂FS (M⁺): 381.1073; found: 381.1074.

3-(6-Ethoxypyridin-3-yl)-1-tosyl-1,2-dihydroquinoline (2.30b)

According to the general procedure 2.4, substrate 2.3b (64 mg, 0.2 mmol) and (6-ethoxypyridin-3-yl)boronic acid (67 mg, 2 equiv) were reacted using [Rh(cod)OH]₂ (2.3 mg, 2.5 mol%), BINAP (6.23 mg, 5 mol%), Pd(OAc)₂ (0.9 mg, 2 mol%), X-Phos (3.8 mg, 4 mol%) and K₂CO₃ (61 mg, 2.2 equiv.) in dioxane:MeOH (2 ml : 0.1 ml). The product was isolated using column...
chromatography (pentane:EtOAc 9:1) in 47% yield (38.5 mg) as an orange solid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.07 (d, $J$ = 2.4 Hz, 1H), 7.75 (d, $J$ = 7.9 Hz, 1H), 7.45 (dd, $J$ = 8.7, 2.6 Hz, 1H), 7.29 (ap td, $J$ = 7.8, 1.4 Hz, 1H), 7.21 (ap td, $J$ = 7.5, 1.0 Hz, 1H), 7.15 (d, $J$ = 8.2 Hz, 2H), 7.01 (dd, $J$ = 7.4, 1.1 Hz, 1H), 6.93 (d, $J$ = 8.1 Hz, 2H), 6.72 (d, $J$ = 8.7 Hz, 1H), 6.21 (s, 1H), 4.73 (s, 2H), 4.38 (q, $J$ = 7.1 Hz, 2H), 2.28 (s, 3H), 1.42 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 163.8, 143.8, 143.6, 135.7, 135.4, 134.2, 131.6, 130.4, 129.0 (2), 128.0, 127.1 (3), 126.99, 126.98, 126.5, 120.5, 111.1, 62.2, 47.3, 21.6, 14.8; IR (NaCl, neat): 3059, 2981, 2926, 2870, 1605, 1498, 1475, 1383, 1346, 1293, 1245, 1164, 1122, 1091, 1033, 1009, 925, 816, 735, 681 cm$^{-1}$; M. p.: 92-95 °C; HRMS (ESI): calcd for C$_{23}$H$_{23}$N$_2$O$_3$S (M+H)$^+$: 407.1429; found: 407.1439.

3-(6-Ethoxypyridin-3-yl)-1-(methylsulfonyl)-1,2-dihydroquinoline (2.30c)

According to the general procedure 2.4, substrate 2.3c (49 mg, 0.2 mmol) and 6-ethoxypyridin-3-ylboronic acid (67 mg, 2 equiv) were reacted using [Rh(cod)OH]$_2$ (2.3 mg, 2.5 mol%), BINAP (6.5 mg, 5.2 mol%), Pd(OAc)$_2$ (0.9 mg, 2 mol%), X-Phos (3.8 mg, 4 mol%) and K$_2$CO$_3$ (61 mg, 2.2 equiv.). The product was isolated using column chromatography (pentane:EtOAc 7:3) in 66% yield (44 mg) as a yellow solid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.36 (d, $J$ = 2.4 Hz, 1H), 7.76 (dd, $J$ = 8.7, 2.6 Hz, 1H), 7.67–7.61 (m, 1H), 7.33–7.23 (m, 3H), 6.86 (s, 1H), 6.79 (dd, $J$ = 8.53, 0.34 Hz, 1H), 4.73 (d, $J$ = 1.1 Hz, 2H), 4.40 (q, $J$ = 7.1 Hz, 2H), 2.64 (s, 3H), 1.42 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 164.1, 144.1, 135.6, 134.4, 132.8, 129.8, 128.4, 127.3, 127.3, 126.4, 120.5, 111.1, 62.2, 47.1, 37.7, 14.7; IR (NaCl, neat): 3070, 3053, 3025, 2975, 2932, 2896, 2861, 1602, 1569, 1501, 1481, 1454, 1401, 1380, 1342, 1292, 1268, 1155, 1083, 1040, 956, 925, 842, 816, 771, 544 cm$^{-1}$; M. p.: 137-140 °C; HRMS (ESI): calcd for C$_{17}$H$_{19}$N$_2$O$_3$S (M+H)$^+$: 331.1116; found: 331.1113.

3-(3-Nitrophenyl)-1-tosyl-1,2-dihydroquinoline (2.31)

This compound was prepared by L. Zhang according to procedure 2.4. The product was purified by flash chromatography (Et$_2$O/hexanes 0-10%) to provide the title compound as a yellow solid 49%. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.20–8.12 (m, 1H), 7.95 (s, 1H), 7.79 (d, $J$ = 8.0 Hz, 1H), 7.61–7.53 (m, 2H), 7.37 (ap td, $J$ = 7.8, 1.5 Hz, 1H), 7.28 (ap td, $J$ = 7.4, 1.7 Hz, 1H), 7.16–7.03 (m, 3H), 6.95 (d, $J$ = 8.1 Hz, 2H), 6.43 (s, 1H), 4.80 (s, 2H), 2.32 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 148.6, 143.9, 139.3, 135.6, 134.6, 131.9, 130.7, 129.8, 129.6, 129.1, 128.9, 127.5, 127.2, 127.1, 127.0, 123.9, 122.7, 120.1, 77.4, 77.0, 76.7, 47.3, 21.5; IR (NaCl, neat): 1597, 1526, 1483, 1348, 1163, 1090, 880, 808, 762, 735 cm$^{-1}$; M. p.: 196-197 °C; HRMS (ESI): calcd for C$_{22}$H$_{22}$N$_3$O$_4$S (M+H)$^+$: 424.1331; found: 424.1327.
1-Tosyl-3-(4-(trifluoromethyl)phenyl)-1,2-dihydroquinoline (2.32)

This compound was prepared by L. Zhang according to general procedure 2.4. The product was purified by flash chromatography (Et<sub>2</sub>O/hexanes 0-5%) to provide the title compound as a white solid 64%. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.78 (d, J = 8.0 Hz, 1H), 7.61 (ap t, J = 8.6 Hz, 2H), 7.41 – 7.29 (m, 3H), 7.24 (ap td, J = 7.5, 1.1 Hz, 1H), 7.14 (d, J = 8.3 Hz, 2H), 7.06 (dd, J = 7.5, 1.2 Hz, 1H), 6.93 (d, J = 8.1 Hz, 2H), 6.39 (s, 1H), 4.80 (s, 2H), 2.29 (s, 3H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 143.7, 140.9, 135.8, 134.6, 133.1, 130.0, 129.1, 128.7, 127.5, 127.2, 127.2, 127.0, 125.8 (q, J = 3.8 Hz), 125.4, 123.4, 47.5, 21.6; <sup>19</sup>F NMR (377 MHz, CDCl<sub>3</sub>): δ 63.6 (s); IR (NaCl, neat): 1614, 1599, 1483, 1450, 1412, 1325, 1165, 1117, 1090, 1071, 831, 810, 762, 716, 679, 654 cm<sup>-1</sup>; M. p.: 152-155 °C; HRMS (ESI): calc for C<sub>23</sub>H<sub>19</sub>F<sub>3</sub>NO<sub>2</sub>S (M+H)<sup>+</sup>: 430.1089; found: 430.1084.

1-Tosyl-3-(3-(trifluoromethyl)phenyl)-1,2-dihydroquinoline (2.33b)

According to the general procedure 2.4, substrate 2.3b (64 mg, 0.2 mmol) and 3-(trifluoromethyl)phenylboronic acid (76 mg, 2 equiv) were reacted using [Rh(cod)OH]<sub>2</sub> (2.3 mg, 2.5 mol%), BINAP (6.23 mg, 5 mol%), Pd(OAc)<sub>2</sub> (0.9 mg, 2 mol%), X-Phos (3.8 mg, 4 mol%) and K<sub>2</sub>CO<sub>3</sub> (61 mg, 2.2 equiv.) in dioxane:MeOH (2 ml : 0.1 ml). The product was isolated using column chromatography (pentane:EtOAc 9:1) in 63% yield (54 mg) as a pale yellow solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.78 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 7.7 Hz, 1H), 7.51 (ap t, J = 7.7 Hz, 1H), 7.44 (d, J = 7.8 Hz, 1H), 7.35 (ap td, J = 7.8, 1.5 Hz, 1H), 7.31 (s, 1H), 7.26 (ap td, J = 7.5, 1.2 Hz, 1H), 7.13 (d, J = 8.3 Hz, 2H), 7.08 (dd, J = 7.5, 1.3 Hz, 1H), 6.94 (d, J = 8.1 Hz, 2H), 4.79 (d, J = 0.7 Hz, 2H), 2.31 (s, 3H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 143.8, 138.5, 135.8, 134.6, 132.9, 131.2 (q, J = 32.3 Hz), 123.0, 129.4, 129.1 (2), 128.6, 128.3 (q, J = 1.2 Hz), 127.4, 127.3, 127.2, 127.1 (2), 124.8 (q, J = 3.8 Hz), 124.1 (q, J = 273.7 Hz) 123.0, 122.1 (q, J = 3.8 Hz), 47.5, 21.5; <sup>19</sup>F NMR (377 MHz, CDCl<sub>3</sub>): δ -61.8; IR (NaCl, neat): 3066, 2960, 2922, 2850, 1647, 1598, 1489, 1453, 1336, 1241, 1160, 1122, 1032, 1009, 895, 815, 738, 701, 682 cm<sup>-1</sup>; M. p.: 97-100 °C; HRMS (EI): calc for C<sub>23</sub>H<sub>18</sub>F<sub>3</sub>NO<sub>2</sub>S (M)<sup>+</sup>: 429.1010; found: 429.1017.

1-(Methylsulfonyl)-3-(3-(trifluoromethyl)phenyl)-1,2-dihydroquinoline (2.33c)

According to the general procedure 2.4, substrate 2.3c (48.7 mg, 0.2 mmol) and 3-(trifluoromethyl)phenylboronic acid (57 mg, 2 equiv) were reacted using [Rh(cod)OH]<sub>2</sub> (2.3 mg, 2.5 mol%), BINAP (6.23 mg, 5 mol%), Pd(OAc)<sub>2</sub> (0.9 mg, 2 mol%), X-Phos (3.8 mg, 4 mol%) and K<sub>2</sub>CO<sub>3</sub> (61 mg, 2.2 equiv.) in dioxane:MeOH (2 ml : 0.1 ml). The product was isolated using column chromatography (pentane:EtOAc 85:15) in 55% yield (39 mg) as a pale yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.79 (s, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.67 (d, J = 7.1 Hz, 1H), 7.62 (d, J =
7.6 Hz, 1H), 7.57 (ap t, J = 7.7 Hz, 1H), 7.37 – 7.27 (m, 3H), 7.01 (s, 1H), 4.79 (s, 2H), 2.65 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): δ 138.0, 134.7, 134.2, 131.7 (q, J = 32.4 Hz), 129.8, 129.4, 129.1, 128.6 (q, J = 1.1 Hz), 127.8, 127.3, 126.3, 125.3 (q, J = 3.7 Hz), 124.2 (q, J = 310 Hz) 123.6, 122.1 (q, J = 3.8 Hz), 47.3, 37.8; \(^{19}\)F NMR (377 MHz, CDCl\(_3\)): δ -63.7; IR (NaCl, neat): 3070, 3037, 2930, 2854, 1593, 1484, 1451, 1432, 1343, 1332, 1278, 1268, 1156, 1126, 1076, 959 cm\(^{-1}\); HRMS (ESI): calcd for C\(_{17}\)H\(_{18}\)F\(_3\)N\(_2\)O\(_2\)S (M+NH\(_4^+\)): 371.1041; found: 371.1040.

7-Methoxy-1-(methylsulfonyl)-3-phenyl-1,2-dihydroquinoline (2.34)

This compound was prepared by L. Zhang according to procedure 2.4. The product was purified by flash chromatography (Et\(_2\)O/hexanes 0-10%) to provide the title compound as a white solid 54%. \(^{1}\)H NMR (400 MHz, CDCl\(_3\)): δ 7.53 (d, J = 7.3 Hz, 2H), 7.42 (ap t, J = 7.6 Hz, 2H), 7.34 (ap t, J = 7.3 Hz, 1H), 7.25 (d, J = 2.5 Hz, 1H), 7.19 (d, J = 8.5 Hz, 1H), 6.89 (s, 1H), 6.84 (dd, J = 8.4, 2.6 Hz, 1H), 4.75 (d, J = 0.8 Hz, 2H), 3.86 (s, 3H), 2.64 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): δ 159.7, 137.4, 136.0, 132.6, 129.2, 128.4, 128.4, 125.3, 123.1, 121.7, 113.9, 111.5, 77.5, 77.2, 76.8, 55.8, 47.3, 37.8; IR (NaCl, neat): 3101, 3011, 2362, 1616, 1600, 1496, 1328, 1270, 1213, 1155, 1039, 761, 554 cm\(^{-1}\); M. p.: 119-187 °C; HRMS (ESI): calcd for C\(_{17}\)H\(_{17}\)NO\(_3\)S (M+Na): 338.0821; found: 338.0823.

1-(Methylsulfanyl)-3-(thiophen-3-yl)-7-(trifluoromethyl)-1,2-dihydroquinoline (2.35)

According to the general procedure 2.4, the alkyne substrate (62.3 mg, 0.2 mmol) and 3-thienylboronic acid (51 mg, 2 equiv) were reacted using [Rh(cod)OH]\(_2\) (2.3 mg, 2.5 mol%), BINAP (6.5 mg, 5.2 mol%), Pd(OAc)\(_2\) (0.9 mg, 2 mol%), X-Phos (3.8 mg, 4 mol%) and K\(_2\)CO\(_3\) (61 mg, 2.2 equiv.). The product was isolated using column chromatography (pentane:EtOAc 8:2) in 78% yield (56 mg) as a pale yellow solid. Alternatively, this compound was synthesized by the above procedure, heating at 60 °C for 1.5 h then to 90 °C for 14.5 h to give 81% yield (58.3 mg). \(^{1}\)H NMR (400 MHz, CDCl\(_3\)): δ 7.93 – 7.86 (m, 1H), 7.53 – 7.47 (m, 2H), 7.44 (dd, J = 5.1, 2.8 Hz, 1H), 7.41 (dd, J = 5.1, 1.4 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 6.94 (s, 1H), 4.75 (d, J = 0.9 Hz, 2H), 2.66 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): δ 138.1, 134.6, 133.4, 129.9 (q, J = 32.8 Hz), 127.6, 127.5, 124.6, 123.9 (q, J = 3.8 Hz), 123.8 (q, J = 272.2 Hz), 123.5 (q, J = 4.0 Hz), 122.9, 119.3, 47.2, 38.0 (d, J = 2.0 Hz); \(^{19}\)F NMR (282 MHz, CDCl\(_3\)): δ -62.8 (s); IR (NaCl, neat): 3106, 3051, 3014, 2932, 2896, 2852, 1614, 1569, 1502, 1346, 1330, 1297, 1270, 1253, 1225, 1158, 1125, 1071, 1032, 960, 916, 875, 847, 828, 778.763, 740, 663, 633, 556, 536 cm\(^{-1}\); M. p.: 122-123 °C; HRMS (ESI): calcd for C\(_{18}\)H\(_{16}\)F\(_3\)N\(_2\)O\(_2\): 377.0605; found: 377.0594.
6-Fluoro-1-(methylsulfonyl)-3-(thiophen-3-yl)-1,2-dihydroquinoline (2.36)

According to the general procedure 2.4, alkyne substrate (52.4 mg, 0.2 mmol) and 3-thienylboronic acid (51 mg, 2 equiv.) were reacted using [Rh(cod)OH]2 (2.3 mg, 2.5 mol%), BINAP (6.5 mg, 5.2 mol%), Pd(OAc)2 (0.9 mg, 2 mol%), X-Phos (3.8 mg, 4 mol%) and K2CO3 (61 mg, 2.2 equiv.). The product was isolated using column chromatography (pentane:EtOAc 9:1) in 70% yield (43.3 mg) as an off-white solid.

**1H NMR** (300 MHz, CDCl3): δ 7.60 (dd, J = 9.9, 5.1 Hz), 7.50 – 7.34 (m), 7.03 – 6.91 (m), 6.85 (s), 4.71 (d, J = 1.1 Hz), 2.61 (s); **13C NMR** (75 MHz, CDCl3): δ 161.5 (d, J = 246 Hz), 138.3, 132.3, 131.6 (d, J = 9 Hz), 130.2 (d, J = 3 Hz), 128.5 (d, J = 9 Hz), 128.5 (d, J = 9 Hz), 127.5, 124.6, 122.5 (d, J = 8.3 Hz, 1H), 7.54 (d, J = 7.2 Hz, 2H), 7.44 (t, J = 7.2 Hz, 1H), 7.38 (t, J = 7.2 Hz, 1H), 7.29 (d, J = 5.0 Hz, 1H), 7.27 (d, J = 8.3 Hz, 1H), 7.10 (s, 1H), 4.63 (s, 2H), 2.72 (s, 3H), 2.05 (s, 3H); **19F NMR** (282 MHz, CDCl3) δ -115.1 (td, J = 8.4, 5.1 Hz); **IR** (NaCl, neat): 3091, 1485, 1338, 1156, 1076, 964, 827, 806, 769, 558 cm⁻¹; **M. p.**: 185-187 °C; **HRMS** (ESI): calcd for C14H13FNO2S2 (M+)': 310.0360; found: 310.0372.

8-Fluoro-1-(methylsulfonyl)-3-phenyl-1,2-dihydroquinoline (2.38)

This compound was prepared by L. Zhang according to procedure 2.4. The product was purified by flash chromatography (Et2O/hexanes 0-5%) to provide the title compound as a white solid.

**1H NMR** (400 MHz, CDCl3): δ 7.56 (d, J = 7.2 Hz, 2H), 7.44 (t, J = 7.4 Hz, 2H), 7.38 (t, J = 7.2 Hz, 1H), 7.29 – 7.21 (m, 1H), 7.11 – 7.04 (m, 2H), 6.93 (s, 1H), 4.69 (s, 2H), 2.94 (s, 3H); **13C NMR** (100 MHz, CDCl3): δ 158.3, 155.8, 138.5, 136.9, 132.8 (d, J = 1.6 Hz), 129.1, 128.9, 128.1 (d, J = 8.5 Hz), 125.6, 122.7 (d, J = 3.2 Hz), 122.5 (d, J = 12.3 Hz), 121.6 (d, J = 3.4 Hz), 116.0 (d, J = 21.1 Hz), 47.7, 39.6 (d, J = 3.7 Hz); **19F NMR** (377 MHz, CDCl3) δ -118.9 (dd, J = 10.1, 4.8 Hz); **IR** (NaCl, neat): 3063, 3030, 2934, 1615, 1574, 1476, 1343, 1155, 1080, 1042, 968, 872, 835, 746,
696 cm⁻¹; M. p.: 58-60 °C; HRMS (EI): calcd for C₁₆H₁₄FNO₂S (M⁺): 303.0729; found: 303.0728.

8-Fluoro-1-(methylsulfonyl)-3-(thiophen-3-yl)-1,2-dihydroquinoline (2.39)

According to the general procedure 2.4, alkyne substrate (52.4 mg, 0.2 mmol) and 3-thienylboronic acid (51 mg, 2 equiv) were reacted using [Rh(cod)OH]₂ (2.3 mg, 2.5 mol%), BINAP (6.5 mg, 5.2 mol%), Pd(OAc)₂ (0.9 mg, 2 mol%), X-Phos (3.8 mg, 4 mol%) and K₂CO₃ (61 mg, 2.2 equiv.). The product was isolated using column chromatography (pentane:EtOAc 8:2) in 73% yield (45 mg) as a colorless oil. ¹H NMR (399 MHz, CDCl₃) δ 7.44 (dd, J = 2.7, 1.3 Hz, 1H), 7.40 (dd, J = 5.1, 2.8 Hz, 1H), 7.37 (dd, J = 5.1, 1.4 Hz, 1H), 7.23 (dd, J = 12.7, 7.2, 3.2 Hz, 1H), 7.09 – 7.00 (m, 2H), 6.91 (d, J = 1.0 Hz, 1H), 4.63 (d, J = 1.0 Hz, 2H), 2.91 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 157.2 (d, J = 252.4 Hz), 138.4, 133.4, 132.8 (d, J = 1.7 Hz), 128.2 (d, J = 8.5 Hz), 127.2, 124.8, 122.62 (d, J = 3.2 Hz), 122.34 (d, J = 12.5 Hz), 122.2, 120.2 (d, J = 3.4 Hz), 115.9 (d, J = 21.1 Hz), 47.6, 39.5 (d, J = 3.7 Hz); ¹⁹F NMR (282 MHz, CDCl₃) δ -118.2 (dd, J = 10.0, 4.7 Hz); IR (NaCl, neat): 3104, 3025, 2930, 2896, 2850, 1611, 1572, 1471, 1342, 1296, 1271, 1220, 1156, 1079, 1006, 961, 909, 863, 836, 794, 730 cm⁻¹; HRMS (EI): calcd for C₁₆H₁₄FNO₂S₂ (M⁺): 309.0294; found: 309.0291.

1-(Methylsulfonyl)-3-(thiophen-3-yl)-1,2-dihydro-1,5-napthyridine (2.40)

According to the general procedure 2.4, alkyne substrate (49 mg, 0.2 mmol) and 3-thienylboronic acid (51 mg, 2 equiv) were reacted using [Rh(cod)OH]₂ (2.3 mg, 2.5 mol%), BINAP (6.5 mg, 5.2 mol%), Pd(OAc)₂ (0.9 mg, 2 mol%), X-Phos (3.8 mg, 4 mol%) and K₂CO₃ (61 mg, 2.2 equiv.). The product was isolated using column chromatography (pentane:EtOAc 1:1) in 45% yield (26 mg) as a colorless solid which turned dark green upon standing. ¹H NMR (399 MHz, CDCl₃) δ 8.46 (dd, J = 4.8, 1.5 Hz, 1H), 7.91 (ddd, J = 8.1, 1.5, 0.7 Hz, 1H), 7.53 – 7.49 (m, 1H), 7.45 – 7.41 (m, 2H), 7.19 (dd, J = 8.1, 4.8 Hz, 1H), 7.10 (s, 1H), 4.78 (d, J = 1.2 Hz, 2H), 2.68 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 148.9, 148.1, 138.0, 135.3, 133.4, 131.3, 127.6, 124.9, 123.1, 122.5, 121.7, 47.0, 38.0; IR (NaCl, neat): 3105, 3007, 2927, 2850, 1620, 1580, 1435, 1188, 1157, 960, 910, 875, 820, 776, 730 cm⁻¹; M. p.: 128-130 °C; HRMS (EI): calcd for C₁₃H₁₂N₂O₂S₂ (M⁺): 292.0340; found: 292.0347.

3-Phenyl-2H-chromene (2.41)

This compound was prepared by L. Zhang according to the general procedure 2.4, but using [Pd(allyl)Cl]₂ as the palladium source. The product was purified by flash chromatography (Et₂O/hexanes 0-3%) to provide the title compound as a yellow solid 59%. ¹H NMR (300 MHz, CDCl₃) δ 7.46 – 7.26 (m, 5H), 7.17 –
7.04 (m, 2H), 6.95 – 6.82 (m, 2H), 6.80 (s, 1H), 5.16 (d, J = 1.4 Hz, 2H); Spectral data is in accordance with literature.\(^\text{109}\)

4-(2H-Chromen-3-yl)benzonitrile (2.42)

This compound was prepared by L. Zhang according to the general procedure 2.4 using [Pd(allyl)Cl\(_2\)] as palladium source. The product was purified by flash chromatography (Et\(_2\)O/hexanes 0-3%) to provide the title compound as a yellow solid 27%. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.73 – 7.63 (m, 2H), 7.55 – 7.48 (m, 2H), 7.19 (s, 1H, J = 7.9, 1.6 Hz, 1H), 7.13 (dd, J = 7.5, 1.5 Hz, 1H), 6.98 – 6.91 (m, 2H), 6.88 (d, J = 8.1 Hz, 1H), 5.15 (d, J = 1.3 Hz, 2H); \(^1\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 153.7, 141.2, 132.7, 130.3, 129.8, 127.8, 125.3, 123.5, 122.4, 122.1, 118.9, 115.9, 111.3, 77.5, 77.2, 76.8, 66.7; IR (NaCl, neat): 2224, 1614, 1599, 1483, 1451, 1412, 1348, 1215, 1090, 1074, 831, 762, 716, 660 cm\(^{-1}\); M. p.: 104-105 °C; HRMS (EI): calc for C\(_{16}\)H\(_{10}\)NO (M)\(^{+}\): 232.0762; found: 232.0760.

Methyl 4-(2H-chromen-3-yl)benzoate (2.43)

This compound was prepared by L. Zhang according to the general procedure 2.4 using [Pd(allyl)Cl\(_2\)] as palladium source. The product was purified by flash chromatography (Et\(_2\)O/hexanes 0-3%) to provide the title compound as a yellow solid 50%. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.05 (d, J = 8.7 Hz, 2H), 7.49 (d, J = 8.7 Hz, 2H), 7.19 – 7.13 (m, 1H), 7.11 (dd, J = 7.5, 1.6 Hz, 1H), 6.93 (ddd, J = 7.4, 6.7, 1.1 Hz, 2H), 6.87 (d, J = 8.0 Hz, 1H), 5.18 (s, 2H), 3.93 (s, 3H); \(^1\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 166.8, 153.6, 141.4, 130.7, 130.2, 129.9, 129.5, 127.6, 124.75, 122.7, 122.4, 121.9, 115.8, 67.0, 52.3; IR (NaCl, neat): 2359, 2340, 1724, 1487, 1456, 1431, 1415, 1321, 1279, 1211, 1192, 1107, 1015, 934, 853, 769, 746, 737, 696, 667 cm\(^{-1}\); M. p.: 129-132 °C; HRMS (ESI): calc for C\(_{17}\)H\(_{15}\)O\(_3\) (M+NH\(_4\))^+: 267.1021; found: 267.1018.

3-(Phenyl)quinoline (2.44a)

This compound was synthesized by reacting dihydroquinolines 2.5b or 2.5c (0.1 mmol) with KOrBu (1.1 equiv) in dioxane at room temperature or with heating. The product was purified by flash chromatography (Et\(_2\)O/hexanes 0-10%) to provide the title compound as a white solid 93%. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.21 (d, J = 2.3 Hz, 1H), 8.29 (d, J = 2.1 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.86 (dd, J = 8.1, 1.4 Hz, 1H), 7.70 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H), 7.67 (dd, J = 2.9, 1.4 Hz, 1H), 7.57 (ddd, J = 8.1, 6.9, 1.2

Hz, 1H), 7.54 (dd, \( J = 5.0, 1.4 \) Hz, 1H), 7.50 (dd, \( J = 5.0, 2.9 \) Hz, 1H); Spectral data is in accordance with literature.  

3-(Thiophen-3-yl)quinoline (2.44b)

This compound was prepared by L. Zhang according to the same procedure as 2.44a. The product was purified by flash chromatography (Et2O/hexanes 1:9) to provide the title compound as a white solid 93%.  

\[ \text{^{1}H NMR (400 MHz, CDCl}_3 \delta 9.21 (d, J = 2.3 \text{ Hz}, 1H), 8.29 (d, J = 2.1 \text{ Hz}, 1H), 8.12 (d, J = 8.0 \text{ Hz}, 1H), 7.86 (dd, J = 8.1, 1.4 \text{ Hz}, 1H), 7.70 (ddd, J = 8.4, 6.9, 1.5 \text{ Hz}, 1H), 7.67 (dd, J = 2.9, 1.4 \text{ Hz}, 1H), 7.57 (ddd, J = 8.1, 6.9, 1.2 \text{ Hz}, 1H), 7.54 (dd, J = 5.0, 1.4 \text{ Hz}, 1H), 7.50 (dd, J = 5.0, 2.9 \text{ Hz}, 1H)}; \]

Spectral data is in accordance with literature.

(3S,4R)-3-Phenylchroman-3,4-diol (2.45)

This compound was prepared by L. Zhang: The starting alkene 2.41 was reacted with AD-mix-\( \alpha \) at room temperature in t-BuOH/H\(_2\)O as a solvent. At 72 hour reaction time no starting material remained by TLC. The product was purified by flash chromatography (EtOAc/hexanes 1:9) to provide the title compound as a white solid 78%.  

\[ \text{^{1}H NMR (400 MHz, CDCl}_3 \delta 7.57 - 7.47 (m, J = 8.9, 3.7 \text{ Hz}, 3H), 7.40 (t, J = 7.4 \text{ Hz}, 2H), 7.33 (t, J = 7.3 \text{ Hz}, 1H), 7.24 (ap t, J = 7.8 \text{ Hz}, 1H), 7.01 (ap t, J = 7.5 \text{ Hz}, 1H), 6.90 (d, J = 8.2 \text{ Hz}, 1H), 5.08 (s, J = 5.4 \text{ Hz}, 1H), 4.22 (d, J = 11.9 \text{ Hz}, 1H), 4.14 (d, J = 11.9 \text{ Hz}, 1H), 2.99 (s, 1H), 2.48 (s, 1H); ^{13}C NMR (100 MHz, CDCl}_3 \delta 153.3, 140.6, 129.5, 129.3, 128.8, 128.2, 125.8, 123.8, 121.7, 116.6, 71.7, 71.0, 70.3. \]

IR (NaCl, neat): 3408, 1611, 1586, 1489, 1460, 1447, 1229, 1200, 1045, 1026, 964, 910, 787, 756, 733, 700, 607 cm\(^{-1}\); M.p.: 76-77 °C; HRMS (ESI) calcd for C\(_{15}\)H\(_{18}\)NO\(_3\) (M+NH\(_4^+\)): 260.1288; found: 260.1287.

2.5.2 \(^{31}\)PNMR Spectra

Formation of Palladium(II)-Ligand Complexes Observed by \(^{31}\)P NMR.

\[ \text{Pd(OAc)}_2 + \text{BINAP} \rightleftharpoons [\text{Pd(BINAP)(OAc)}_2] \]

**Spectrum 1:** Pd(OAc)\(_2\) (4.5 mg, 0.02 mmol) and BINAP (12.45 mg, 0.02 mmol) were weighed into a 2 dram vial, which was equipped with a stirring bar and fitted with a septum. Dioxane (2 ml) was added and the mixture was stirred at room temperature for 30 minutes. An NMR tube was equipped with a sealed tube of H\(_3\)PO\(_4\) in D\(_2\)O (1:5, reference), fitted with a septum and purged with argon. An aliquot of the catalyst solution (0.5 ml) was transferred via syringe into

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the NMR tube. $^{31}$P NMR data was obtained using a Varian 400 (400 MHz/100 MHz) NMR spectrometer equipped with ATB8123-400 probe.

$$\text{Pd(OAc)}_2 + 2 \text{X-Phos} \rightarrow [\text{Pd(X-Phos)}_2\text{OAc}_2]$$

**Spectrum 2:** Pd(OAc)$_2$ (4.5 mg, 0.02 mmol) and X-Phos (19.07 mg, 0.04 mmol) were weighed into a 2 dram vial, which was equipped with a stirring bar and fitted with a septum. Dioxane (2 ml) was added and the mixture was stirred at room temperature for 30 minutes. An NMR tube was equipped with a sealed tube of H$_3$PO$_4$ in D$_2$O (1:5, reference), fitted with a septum and purged with argon. An aliquot of the catalyst solution (0.5 ml) was transferred via syringe into the NMR tube.

**Spectrum 1**
2.5.3 Characterization Data for Section 2.3

3-Chloro-2-vinylpyridine (2.46)

To a round bottom flask containing a stirring bar, 2-bromo-3-chloropyridine (1.924 g, 10 mmol) and Pd(PPh$_3$)$_4$ (0.289 g, 0.25 mmol, 2.5 mol%) were added. The flask was fitted with a reflux condenser and purged with nitrogen. THF (140 mL, 0.071 M) and water (40 mL, 0.25 M) were added and the reaction was stirred for 10 minutes at room temperature. The mixture became yellow. To the solution, 2,4,6-trivinyltricycloboroxane (2.12 g, 12 mmol, 1.2 equiv) and potassium carbonate (1.38 g, 10 mmol, 1 equiv) were added and the reaction was stirred at 90 °C for 16 hours. After cooling to room temperature, the solution was extracted with EtOAc, washing with H$_2$O. After drying over Mg$_2$SO$_4$, the solution was filtered and evaporated under reduced pressure. The resulting yellow oil was purified using flash chromatography (pentane/Et$_2$O, 95:5) to give the titled compound in 76% yield (1.06 g) as a colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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 (75 MHz, CDCl$_3$) $\delta$ 152.4, 147.7, 137.6, 131.7, 130.7, 123.6, 121.4; IR (NaCl, neat): 3047.63, 2984.94, 2925.15, 2853.78, 1445.70, 1429.30, 1418.69,
Procedure 2.6: Stille coupling reaction to access 2-vinyl-3-chloropyridines - 3-Chloro-5-(trifluoromethyl)-2-vinylpyridine (2.47)

The titled compound was prepared using a Stille coupling reaction: 2,3-dichloro-5-(trifluoromethyl)pyridine (1 g, 4.63 mmol), lithium chloride (236 mg, 5.56 mmol, 1.2 equiv), and Pd(PPh₃)₄ (385 mg, 0.23 mmol, 5 mol%) were weighed into a round bottom flask. The flask was fitted with a condenser and purged with argon (10 min). Dioxane (20 ml) was added, followed by tributylvinyltin (1.5 ml, 5.1 mmol, 1.1 equiv). The reaction was heated to 85 °C for 16 h, at which point, under argon flow, an aliquot (0.15 ml) was taken, filtered through a silica plug and examined by NMR, which showed full consumption of starting material. The reaction was filtered through celite and the solvent was removed under reduced pressure. The crude was purified by column chromatography (hexane:triethylamine 98:2) to yield the product in 65% yield as a pale yellow oil, which turns orange over time. The compound is stored in the freezer and used within a week. ¹H NMR (400 MHz, CD₂Cl₂) δ 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); ¹³C NMR (101 MHz, CD₂Cl₂) δ 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 = 16.9, 1.9 Hz, 1H), 124.0, 123.0 (q, J = 27.2 Hz); ¹⁹F NMR (377 MHz, CD₂Cl₂) δ -63.7; IR (NaCl, neat): 2955, 2916, 2849, 1599, 1323, 1163, 1138, 1094, 1055 cm⁻¹; HRMS (ESI): calcd for C₈H₆ClF₃N (M+H)⁺: 208.0141; found: 208.0145.

3-Chloro-5-nitro-2-vinylpyridine (2.48)

The titled compound is prepared using procedure 2.6, utilizing 2,3-dichloro-5-nitropyridine (588 mg, 3.045 mmol), tributylvinyltin (1.09 ml, 3.35 mmol, 1.1 equiv), Pd(PPh₃)₄ (176 mg, 5 mol%), lithium chloride (155 mg, 1.2 equiv) and copper iodide (29 mg, 5 mol%) in dioxane (15 ml, 0.2 M). Reaction was run for 3 hours at 100 °C, at which point no starting material was seen by HNMR. The product was isolated using flash column chromatography (95:5 Hexane:EtOAc) to give the titled compound in 25% yield (143 mg) as a colorless solid which turns red quickly. The product is prone to decomposition at room temperature, is stored in freezer and used as soon as possible. ¹H NMR (400 MHz, CDCl₃) δ 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); ¹³C NMR (101 MHz, CDCl₃) δ 157.3, 142.8, 142.7, 132.6, 130.3, 130.0, 126.7; M. p.: 34 – 36 °C; IR (NaCl, neat) 3080, 2916, 2849, 1645, 1587, 1570, 1520, 1348, 1294, 1275, 1223, 1049, 908, 743 cm⁻¹; HRMS (ESI): calcd for C₇H₆ClN₂O₂ (M+H)⁺: 185.0118; found: 185.0110.
**4-(5-Chloro-6-vinylpyridin-3-yl)morpholine (2.49)**

The titled compound is prepared using procedure 2.6, utilizing 4-(5,6-dichloropyridin-3-yl)morpholine (350 mg, 1.5 mmol), tributylvinyltin (500 μl, 1.65 mmol, 1.1 equiv), Pd(PPh₃)₄ (87 mg, 5 mol%), lithium chloride (76 mg, 1.2 equiv) in dioxane (7 ml, 0.2M). Reaction was run for 16 hours, at which point no starting material was seen by HNMR. The product was isolated using flash column chromatography (100 - 85:5 Hexane:EtOAc with 2 mol% NEt₃) to give the titled compound in 84% yield (282 mg) as a colorless solid. **¹H NMR** (400 MHz, CDCl₃) 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** (101 MHz, CDCl₃) δ 146.7, 142.9, 136.0, 131.2, 130.5, 122.1, 117.8, 66.5 (2), 48.2 (2); M. p.: 74 – 74 oC; IR (NaCl, neat): 3090, 3065, 3032, 2953, 2916, 2849, 1589, 1472, 1449, 1396, 1313, 1261, 1250, 1069, 1014, 986, 905, 739, 696 cm⁻¹; HRMS (ESI): calcd for C₁₁H₁₄ClN₂O(M+H)⁺: 225.0795; found: 225.0797.

**Methyl 5-chloro-6-vinylnicotinate (2.50)**

The titled compound is prepared using procedure 2.6, utilizing methyl 5,6-dichloronicotinate (330 mg, 1.6 mmol), tributylvinyltin (702 μl, 1.5 equiv), Pd(PPh₃)₄ (185 mg, 10 mol%), lithium chloride (82 mg, 1.2 equiv) in dioxane (8 ml, 0.2M). Reaction was run for 16 hours at 85 °C, at which point no starting material was seen by HNMR. The product was isolated using flash column chromatography (97.5:2.5 Hexane:EtOAc with 2 mol% NEt₃) to give the titled compound in 75% yield (238 mg) as a colorless solid. **¹H NMR** (400 MHz, CDCl₃) δ 9.03 (d, J = 1.8 Hz, 1H), 8.25 (d, J = 1.9 Hz, 1H), 7.27 (dd, J = 17.0, 10.7 Hz, 1H), 6.62 (dd, J = 17.0, 1.9 Hz, 1H), 5.72 (dd, J = 10.7, 1.9 Hz, 1H), 3.95 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 164.8, 155.6, 148.5, 138.5, 131.1, 130.1, 125.8, 124.2, 52.7; M. p.: 63 – 64 °C; IR (NaCl, neat): 3078, 3030, 2953, 2916, 2849, 1589, 1472, 1449, 1396, 1313, 1261, 1250, 1069, 1014, 986, 905, 739, 696 cm⁻¹; HRMS (ESI): calcd for C₉H₉ClNO₂(M+H)⁺: 198.0322; found. 198.0324.

**N-Benzyl-5-chloro-6-vinylnicotinamide (2.51)**

The titled compound is prepared using procedure 2.6, utilizing N-benzyl-5,6-dichloronicotinamide (140.6 mg, 0.5 mmol), tributylvinyltin (162 μl, 1.1 equiv), Pd(PPh₃)₄ (28.8 mg, 5 mol%), lithium chloride (26 mg, 1.2 equiv) in dioxane (3 ml, 0.2M). Reaction was run for 40 hours at 85 °C, at which point no starting material was seen by HNMR. The product was isolated using flash column chromatography (80:20 Hexane:EtOAc with 2 mol% NEt₃) to give the titled compound in 74% yield (101 mg) as a colorless solid. **¹H NMR** (400 MHz, CDCl₃/MeOD) δ 8.78 (d, J = 1.7 Hz, 1H), 8.08 (d, J = 1.8 Hz, 1H), 7.27 – 7.06 (m, 6H), 6.39 (dd, J = 17.0, 1.4 Hz, 1H), 5.57 (dd, J = 10.8, 1.4 Hz, 1H), 3.82 (d, J = 2.7 Hz, 3H), 3.29 (d, J = 2.7 Hz, 3H), 2.48 (m, 4H), 2.37 (m, 4H).
4.47 (s, 1H, NH), 4.46 (s, 2H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)/MeOD) \(\delta\) 164.6, 153.7, 145.8, 137.7, 136.5, 130.5, 129.8, 129.5, 128.1 (2), 127.2 (2), 126.9, 122.7, 43.4. M. p.: 128 – 130 °C; IR (neat): 3261, 3060, 3029, 2923, 1633, 1585, 1539, 1497, 1453, 1365, 1316, 1295, 1227, 1194, 1156, 1065, 1049, 1030, 979, 947, 922, 906, 789 cm\(^{-1}\); HRMS (ESI): calcd for C\(_{15}\)H\(_{14}\)ClN\(_2\)O (M+H\(^+\)): 273.0795; found: 273.0791.

3-Chloro-2,5-divinylpyridine

The titled compound is prepared using procedure 2.6, utilizing 5-bromo-2,3-dichloropyridine (691 mg, 3.045 mmol), tributylvinyltin (2.18 ml, 7.31 mmol, 2.4 equiv), Pd(PPh\(_3\))\(_4\) (176 mg, 5 mol%), lithium chloride (155 mg, 1.2 equiv) and copper iodide (29 mg, 5 mol%) in dioxane (15 ml, 0.2M). Reaction was run for 16 hours. The product was isolated using flash column chromatography (95:5 Hexane:EtOAc) to give the titled compound in 25% yield (143 mg) as an orange oil. The product is stored in freezer (-20 °C).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.47 (d, \(J = 1.9\) Hz, 1H), 7.68 (d, \(J = 1.9\) Hz, 1H), 7.22 (dd, \(J = 17.0, 10.7\) Hz, 1H), 6.65 (dd, \(J = 17.6, 11.0\) Hz, 1H), 6.46 (dd, \(J = 17.0, 2.0\) Hz, 1H), 5.83 (d, \(J = 17.6\) Hz, 1H), 5.57 (dd, \(J = 10.7, 2.0\) Hz, 1H), 5.41 (d, \(J = 11.0\) Hz, 1H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 151.0, 146.1, 133.8, 133.4, 132.2, 131.4, 130.4, 121.1, 117.3; IR (NaCl, neat): 3092, 3013, 2986, 1957, 2930, 2872, 2859, 1622, 1582, 1456, 1365, 1240, 1053, 986, 903, 787 cm\(^{-1}\); HRMS (ESI): calcd for C\(_9\)H\(_9\)ClN (M+H\(^+\)): 166.0423; found: 166.0419.

2-Chloro-3-vinylquinoxaline (2.52)

The titled compound is prepared using procedure 2.6, utilizing 2,3-dichloroquinoxaline (606 mg, 3.045 mmol), tributylvinyltin (1.09 ml, 3.35 mmol, 1.1 equiv), Pd(PPh\(_3\))\(_4\) (176 mg, 5 mol%), lithium chloride (155 mg, 1.2 equiv) and copper iodide (29 mg, 5 mol%) in dioxane (15 ml, 0.2M). Reaction was run for 1.5 hours at 100 °C. The product was isolated using flash column chromatography (9:1 Hexane:CH\(_2\)Cl\(_2\)) to give the titled compound in 31% yield (179 mg) as yellow solid. The product turns dark brown if stored at room temperature for a prolonged time. Stored in freezer (-20 °C).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.13 – 8.02 (m, 1H), 8.02 – 7.92 (m, 1H), 7.80 – 7.69 (m, 2H), 7.40 (dd, \(J = 17.0, 10.7\) Hz, 1H), 6.72 (dd, \(J = 17.6, 1.7\) Hz, 1H), 5.80 (dd, \(J = 10.7, 1.7\) Hz, 1H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 151.0, 146.1, 133.8, 133.4, 132.2, 131.4, 130.4, 121.1, 117.3; IR (NaCl, neat): 3057, 2955, 2916, 1849, 1719, 1674, 1628, 1601, 1559, 1481, 1464, 1269, 1182, 1121, 1044, 1020, 764, 739 cm\(^{-1}\); HRMS (ESI): calcd for C\(_8\)H\(_6\)ClF\(_3\)N (M+H\(^+\)): 191.0376; found: 191.0374.

(E)-3-Chloro-2-(oct-1-en-1-yl)-5-(trifluoromethyl)pyridine (2.53)

The titled compound was prepared using Suzuki cross coupling: 2,3-dichloro-5-(trifluoromethyl)pyridine (648 mg, 3 mmol), (E)-oct-1-en-1-
ylboronic acid (702 mg, 4.5 mmol, 1.5 equiv), Pd(dppf)Cl$_2$-DCM (123 mg, 0.15 mmol, 5 mol%), Na$_2$CO$_3$ (1.05 g, 9.84 mmol, 3.28 equiv) were weighed into a 100 ml round bottom flask with a stirring bar. The flask was fitted with a condenser, and purged with argon. Dioxane (30 ml, 0.1M) and water (4.92 ml, 4 M) were added. The reaction was stirred at 85 °C for 16h. Upon completion, the reaction mixture was extracted with EtOAc, washing with water. After concentration, the product was isolated using flash chromatography (Hexane:EtOAc 99:1) to give the titled compound in 87% yield (583 mg) as a colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.65 (d, $J$ = 0.8 Hz, 1H), 7.88 – 7.81 (m, 1H), 7.18 (dt, $J$ = 15.2, 7.2 Hz, 1H), 6.92 (dt, $J$ = 15.3, 1.4 Hz, 1H), 2.34 (qd, $J$ = 7.4, 1.3 Hz, 2H), 1.54 (quin, $J$ = 7.6 Hz, 2H), 1.42 – 1.25 (dd, $J$ = 6.7, 3.7 Hz, 6H), 0.89 (t, $J$ = 6.9 Hz, 3H);

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 156.0 (q, $J$ = 1.3 Hz), 144.1 (q, $J$ = 4.0 Hz), 143.2, 134.5 (q, $J$ = 3.7 Hz), 129.1, 125.1 (q, $J$ = 35.5 Hz), 123.8, 123.1 (q, $J$ = 272.4 Hz), 33.3, 31.8, 29.1, 28.8, 22.8, 14.2; $^{19}$F NMR (376 MHz, CDCl$_3$) δ -62.6; IR (NaCl, neat): 2959, 2930, 2874, 2859, 1647, 1456, 1395, 1319, 1281, 1159, 1138, 1089, 1053, 970, 912, 716 cm$^{-1}$; HRMS (ESI): calcd for C$_{14}$H$_{18}$ClF$_3$N (M+H)$^+$: 292.1080; found: 292.1082.

Procedure 2.7: Rhodium-catalyzed reductive arylation of vinylpyridines - 2-(2-(3-Chloropyridin-2-yl)ethyl)phenol (2.54)

To a 5 ml microwave tube (or 2 dram vial), were added [Rh(cod)OH]$_2$ (2.8 mg, 0.006 mmol, 2 mol%), dppp (4.95 mg, 0.012 mmol, 4 mol%) and K$_2$CO$_3$ (82.93 mg, 0.6 mmol, 2 equiv). The vial was purged with nitrogen, then, 1 ml of dioxane and 0.3 ml of water were added and the mixture was stirred at room temperature for 15 minutes. A solution of the 3-chlorovinylpyridine (43.3 mg, 0.3 mmol) and 2-hydroxyphenylboronic acid (83 mg, 0.6 mmol, 2 equiv) in 1 ml dioxane was added to the catalyst solution, rinsing with an extra 1 ml of dioxane. The reaction was heated at 60°C for 5h. At this point complete conversion was observed by TLC. The mixture was filtered through a silica plug with EtOAc and the solvent was removed under vacuum. The crude product was purified by silica gel chromatography (eluting with Hexane: EtOAc 8:2) to afford a yellow solid (66 mg, 94% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 10.47 (s, 1H), 8.45 (dd, $J$ = 4.9, 1.2 Hz, 1H), 7.69 (dd, $J$ = 8.0, 1.4 Hz, 1H), 7.20 (dd, $J$ = 10.6, 4.9 Hz, 2H), 7.14 – 7.08 (m, 1H), 6.87 (dd, $J$ = 9.8, 8.4, 4.5 Hz, 2H), 3.47 – 3.32 (m, 2H), 3.18 (dd, $J$ = 6.8, 4.9 Hz, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 157.6, 155.4, 145.9, 137.7, 132.5, 130.8, 129.0, 127.9, 122.9, 120.5, 117.9, 36.7, 25.7; IR (NaCl, neat): 3360, 2360, 1570, 1460, 1421, 1240, 1122 cm$^{-1}$; HRMS (ESI): calcd for C$_{13}$H$_{13}$ClF$_3$N (M+H)$^+$: 292.1080; found: 292.1082.

10,11-Dihydrobenzo[6,7]oxepino[3,2-b]pyridine (2.55)

To a 2.5 ml microwave tube (or 1 dram vial) were added 2-ethylphenol-3-chloropyridine (46.74 mg, 0.2 mmol), Pd(OAc)$_2$ (0.9 mg, 0.004 mmol, 2 mol%), X-Phos (3.81 mg, 0.008 mmol, 4 mol%) and K$_2$CO$_3$ (41.46 mg, 0.3 mmol, 1.5 equiv). The vial was purged with nitrogen. 1 ml of t-BuOH was added and the reaction mixture
was heated at 120 °C for 16 hours. The crude was filtered through a silica plug with EtOAc and the solvent was removed under vacuum. The crude product was purified by silica gel chromatography (eluting with Hexane: EtOAc 9:1) to afford a yellow oil (33 mg, 84%); \( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 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, 5H), 3.34 (dd, \( J = 7.5, 4.8 \) Hz, 2H), 3.21 (dd, \( J = 7.6, 4.8 \) Hz, 2H); \( ^{13}C \) NMR (101 MHz, CDCl\(_3\)) \( \delta \) 157.0, 154.5, 153.6, 151.3, 144.0, 133.0, 130.1, 129.1, 127.8, 125.0, 122.5, 120.8, 35.2, 29.3; IR (NaCl, neat): 3384.22, 3061.13, 3024.48, 2926.11, 2854.54, 1588.43, 1569.14, 1489.10, 1456.30, 1446.60, 1423.51, 1418.69, 1268.24, 1237.38, 1158.29, 1093.67, 921.04, 803.35 cm\(^{-1}\); HRMS (ESI): calcd for C\(_{13}\)H\(_{12}\)NO (M+H): 198.0919; found 198.0914.

\( \text{2-(2-(3-Chloropyridin-2-yl)ethyl)-5-fluorophenol (2.56)} \)

This compound was synthesized by V. Huynh according to procedure 2.7: using 3-chloro-2-vinylpyridine (83.75 mg, 0.6 mmol) 4-fluoro-2-hydroxyphenylboronic acid (187.1 mg, 1.2 mmol, 2 equiv), [Rh(cod)OH\(_2\)] (5.5 mg, 0.012 mmol, 2 mol%), dppp (9.9 mg, 0.024 mmol, 4 mol%) and K\(_2\)CO\(_3\) (166 mg, 1.2 mmol, 2 equiv). The product was obtained in 95% yield (144 mg) as a colorless solid. \( ^1H \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 8.45 (dd, \( J = 5.0, 1.4 \) Hz, 2H), 7.75 (dd, \( J = 8.0, 1.4 \) Hz, 2H), 7.28 – 7.20 (m, 5H), 7.10 (dd, \( J = 8.3, 6.7 \) Hz, 2H), 6.69 – 6.44 (m, 4H), 3.44 – 3.23 (m, 5H), 3.13 (dd, \( J = 6.9, 4.8 \) Hz, 5H); \( ^{13}C \) NMR (101 MHz, CDCl\(_3\)) \( \delta \) 162.5 (d, \( J = 243.4 \) Hz), 156.9, 156.5, 145.2, 138.1, 132.6, 131.3 (d, \( J = 9.9 \) Hz), 124.5, 123.0, 107.1 (d, \( J = 21.4 \) Hz), 105.1 (d, \( J = 23.1 \) Hz), 36.5, 24.9; IR (NaCl, neat): 3387.11, 2950.22, 2917.43, 2358.06, 2323.34, 1615, 1422.55, 1415.80, 1284.63, 1144.79, 1126.47, 1070.53, 1049.31, 913.32 cm\(^{-1}\); HRMS (ESI): calcd for C\(_{13}\)H\(_{12}\)FNOCl (M+H): 252.0594; found 252.0591.

\( \text{2-(2-(3-Chloropyridin-2-yl)ethyl)-4-fluorophenol (2.57)} \)

This compound was synthesized by A. Friedman according to procedure 2.7: 2-vinyl-3-chloropyridine (140.0 mg, 1.00 mmol), 4-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (485 mg, 2.04 mmol, 2 equiv), and potassium carbonate (281 mg, 2.03 mmol, 2 equiv) were weighed into a microwave vial and purged with argon. Dioxane (1 mL), and water (400 μL) were added. A premixed solution of [Rh(cod)OH\(_2\)] (9.1 mg, 0.0199 mmol, 2 mol%), dppp (8.3 mg, 0.0201 mmol, 2 mol%) was added. The reaction mixture was reacted at 90 °C for 17.5 hours. Silica flash column chromatography (8:2 Hexanes: EtOAc) gave the product (225.0 mg, 67%), as a yellow solid. \( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 10.30 (br s, 1H), 8.44 (dd, \( J = 4.9, 1.5 \) Hz, 1H), 7.71 (dd, \( J = 8.0, 1.5 \) Hz, 1H), 7.21 (dd, \( J = 8.0, 4.9 \) Hz, 1H), 6.89 (dd, \( J = 9.2, 2.9 \) Hz, 1H), 6.85 – 6.74 (m, 2H), 3.40 – 3.33 (m, 2H), 3.18 – 3.11 (m, 2H); \( ^{13}C \) NMR (101 MHz, CDCl\(_3\)) \( \delta \) 156.9 (d, \( J = 237.1 \) Hz), 156.8, 151.2 (d, \( J = 1.9 \) Hz), 145.6, 137.7, 132.4, 130.1 (d, \( J = 7.0 \) Hz), 122.9, 118.6 (d, \( J = 8.2 \) Hz), 116.5 (d, \( J = 22.2 \) Hz), 114.1 (d, \( J = 22.7 \) Hz), 36.5, 25.4 (d, \( J = 1.4 \) Hz); \( ^{19}F \) NMR (376 MHz, CDCl\(_3\)) \( \delta \) -125.9 (td, \( J = 8.2 \) Hz, 5.4 Hz); IR (NaCl, neat) 3100, 1512, 1371, 1256, 1192,
1047 cm⁻¹; M. p.: 141 – 142 ºC; HRMS (ESI): calcd for C₁₃H₁₂ClFNO (M+H)⁺: 252.0591; found: 252.0589.

2-(2-(3-Chloropyridin-2-yl)ethyl)-3-fluorophenol (2.58)

This compound was synthesized by A. Friedman according to procedure 2.7: 2-vinyl-3-chloropyridine (140 mg, 1.00 mmol), 3-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (484 mg, 2.03 mmol, 2 equiv) and potassium carbonate (278 mg, 2.01 mmol, 2 equiv) were weighed into a microwave vial and purged with argon. Dioxane (1 mL), and water (400 μL) were added. A premixed solution of [Rh(cod)OH]₂ (9.1 mg, 0.0199 mmol, 2 mol%), dppp (8.3 mg, 0.0201 mmol, 2 mol%) was added. The reaction mixture was reacted at 110 ºC for 21 hours. Silica flash column chromatography (6:1 Hexanes: EtOAc) gave the product (169.9 mg, 67%), as a white solid. ¹H NMR (400MHz, CDCl₃): δ 10.94 (br s, 1H), 8.44 (dd, J = 4.9, 1.5 Hz, 1H), 7.71 (dd, J = 8.0, 1.5 Hz, 1H), 7.21 (dd, J = 8.0, 4.9 Hz, 1H), 7.05 (ap td, J = 8.2, 6.7 Hz, 1H), 6.70 (d, J = 8.2 Hz, 1H), 6.60 (ddd, J = 9.4, 8.2, 1.1 Hz, 1H), 3.42 – 3.31 (m, 2H), 3.25 – 3.17 (m, 2H); ¹³C NMR (101MHz, CDCl₃): δ 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); ¹⁹F NMR (376 MHz, CDCl₃): δ -118.3 (t, J = 8.2 Hz); IR (NaCl, neat) 3071, 2934, 2662, 1466, 1360, 1292, 1161, 1130, 1020, 936 cm⁻¹; M. p.: 143 – 144 ºC; HRMS (ESI): calcd for C₁₃H₁₂ClFNO (M+H)⁺: 252.0591; found: 252.0593.

2-(2-(3-Chloropyridin-2-yl)ethyl)-4-methylphenol (2.59)

This compound was synthesized by A. Friedman according to procedure 2.7: 2-vinyl-3-chloropyridine (39.4 mg, 0.284 mmol), 4-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (107 mg, 0.457 mmol, 1.5 equiv) and potassium carbonate (80 mg, 0.58 mmol, 2 equiv) were weighed into a microwave vial and purged with argon. Dioxane (2 mL), and water (300 μL) were added. A premixed solution of [Rh(cod)OH]₂ (2 mol%), dpp (2 mol%) was added. The reaction mixture was reacted at 90 ºC for 28 hours. Silica flash column chromatography (8:2 Hexanes: EtOAc) gave the product (51.2 mg, 72%), as an off-white solid. ¹H NMR (400MHz, CDCl₃): δ 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 (101MHz, CDCl₃): δ 157.3, 152.9, 145.7, 137.6, 132.4, 131.3, 129.4, 128.7, 128.4, 122.8, 117.7, 77.5, 77.2, 76.8, 36.8, 25.3, 20.6; IR (NaCl, neat) 3134, 2934, 2662, 1580, 1501, 1269, 1132, 1105, 1073, 1047 cm⁻¹; M. p.: 135 – 137 ºC; HRMS (ESI): calcd for C₁₄H₁₃ClNO (M+H)⁺: 248.0842; found: 252.0833;
2-(2-(3-Chloropyridin-2-yl)ethyl)-4-methoxyphenol (2.60)

This compound was synthesized by A. Friedman according to procedure 2.7: 2-vinyl-3-chloropyridine (139.6 mg, 1.00 mmol), 4-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (383 mg, 2.04 mmol, 1.5 equiv) and potassium carbonate (279 mg, 2.02 mmol, 2 equiv) were weighed into a microwave vial and purged with argon. Dioxane (1 mL), and water (400 μL) were added. A premixed solution of [Rh(cod)OH]₂ (2 mol%), dppp (2 mol%) was added. The reaction mixture was reacted at 90 °C for 23 hours. Silica flash column chromatography (8:2 Hexanes: EtOAc) gave the product (200 mg, 76%), as an orange solid. ¹H NMR (400MHz, CDCl₃): δ 9.97 (br s, 1H), 8.43 (dd, J = 4.9, 1.5 Hz, 1H), 7.66 (dd, J = 8.0, 1.5 Hz, 1H), 6.76 (d, J = 3.1 Hz, 1H), 3.75 (s, 3H), 3.38 – 3.33 (m, 2H), 3.20 – 2.91 (m, 2H); ¹³C NMR (101MHz, CDCl₃): δ 157.1, 153.5, 149.0, 145.7, 137.7, 132.4, 129.8, 118.4, 115.9, 113.1, 35.8, 36.8, 25.5; IR (NaCl, neat): 3069, 2940, 1501, 1427, 1150, 1051, 1040 cm⁻¹; M. p.: 122 – 124 ºC; HRMS (ESI): calcd for C₁₄H₁₅ClNO₂(M+H)⁺: 264.0791; found: 264.0795.

4-Chloro-2-(2-(3-chloropyridin-2-yl)ethyl)phenol (2.61)

This compound was synthesized by A. Friedman according to procedure 2.7: 2-vinyl-3-chloropyridine (82.0 mg, 0.587 mmol), 4-chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (324 mg, 1.27 mmol, 2.2 equiv) and potassium carbonate (161 mg, 1.16 mmol, 2 equiv) were weighed into a microwave vial and purged with argon. Dioxane (2 mL), and water (300 μL) were added. A premixed solution of [Rh(cod)OH]₂ (2 mol%), dppp (4 mol%) was added. The reaction mixture was reacted at 90 °C for 21 hours. Silica flash column chromatography (8:2 Hexanes: EtOAc) gave the product (128 mg, 81%), as an off-white solid. ¹H NMR (400MHz, CDCl₃): δ 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); ¹³C NMR (101MHz, CDCl₃): δ 156.9, 154.1, 145.6, 137.9, 132.5, 130.7, 130.3, 127.7, 124.8, 123.1, 119.3, 36.6, 25.4; IR (NaCl, neat): 2939, 2650, 1599, 1580, 1492, 1442, 1431, 1419, 1361, 1271, 1237, 1174, 1129, 1086, 1049, 987, 882, 812 cm⁻¹; M. p.: 167 - 169 ºC; HRMS (ESI): calcd for C₁₃H₁₂ClNO (M+H)⁺: 268.0296; found: 268.0298.

2-(2-(3-Chloropyridin-2-yl)ethyl)-6-methoxyphenol (2.62)

This compound was synthesized by A. Friedman according to procedure 2.7: 2-vinyl-3-chloropyridine (81.4 mg, 0.583 mmol), 2-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (294 mg, 1.18 mmol, 2.0 equiv) and potassium carbonate (164 mg, 1.19 mmol, 2 equiv) were weighed into a microwave vial and purged with argon. Dioxane (2 mL), and water (300 μL) were added. A
premixed solution of [Rh(cod)OH]$_2$ (2 mol%), dppp (4 mol%) was added. The reaction mixture was reacted at 90 °C for 21 hours. Silica flash column chromatography (8:2 Hexanes: EtOAc) gave the product (130 mg, 85%), as a yellow solid. $^1$H NMR (400MHz, CDCl$_3$): δ 8.48 (dd, J = 4.9, 1.5 Hz, 1H), 8.12 (br s, 1H), 7.64 (d, J = 8.0, 1H), 7.12 (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 (101MHz, CDCl$_3$): δ 158.1, 147.9, 146.6, 144.4, 137.2, 131.8, 128.4, 122.6, 122.5, 119.6, 109.3, 56.0, 36.1, 27.0; IR (neat) 3057, 2938, 2837, 1612, 1591, 1574, 1440, 1271, 1124, 1078 cm$^{-1}$; M. p.: 95 - 97 ºC; HRMS (ESI): calcd for C$_{14}$H$_{15}$ClNO$_2$ (M+H)$^+$: 264.0791; found: 264.0889.

3-(Trifluoromethyl)-10,11-dihydrobenzo[6,7]oxepino[3,2-b]pyridine (2.64)

**One pot protocol:** To a 2 dram vial fitted with a stirring bar were added [Rh(cod)OH]$_2$ (1.84 mg, 0.004 mmol, 2 mol%), potassium carbonate (55.2 mg, 0.4 mmol, 2 equiv), 3-chloro-5-(trifluoromethyl)-2-vinylpyridine (41.5 mg, 0.2 mmol, 1 equiv) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (88 mg, 0.4 mmol, 2 equiv). This vial was purged with argon and dioxane (2 ml) and water (0.2 ml) were added. The reaction vial was heated at 60 ºC for 16 h, upon which Pd(OAc)$_2$ (2.24 mg, 0.01 mmol, 5 mol%), t-buty1-X-Phos (8.24 mg, 0.014 mmol, 7 mol%), and K$_3$PO$_4$ (85 mg, 0.4 mmol, 2 equiv) were added to the reaction as a solid, under a stream of argon. The reaction vial was fitted with a Teflon-lined cap and placed into a 100 ºC oil bath for 20 h. Upon completion the reaction crude was filtered through a silica plug (washing with EtOAc) and concentrated. NMR yield was determined using 1,3,5-trimethoxybenzene as an internal standard. The product could be isolated using column chromatography (hexane:EtOAc 9:1) to yield a colorless oil.

**Procedure 2.8: Domino protocol:** To a 2 dram vial fitted with a stirring bar was added [Rh(cod)OH]$_2$ (1.84 mg, 0.004 mmol, 2 mol%), Pd(OAc)$_2$ (2.24 mg, 0.01 mmol, 5 mol%) and t-buty1-X-Phos (8.24 mg, 0.014 mmol, 7 mol%), 3-chloro-5-(trifluoromethyl)-2-vinylpyridine (41.5 mg, 0.2 mmol, 1 equiv), 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (88 mg, 0.4 mmol, 2 equiv) and potassium carbonate (55.2 mg, 0.4 mmol, 2 equiv). The vial was purged with argon and dioxane (2 ml) and water (0.2 ml) were added and the vial was sealed with a Teflon-lined cap. The mixture was stirred at room temperature for 5 minutes and then placed into an oil bath at 100 ºC for 16h. At this time TLC indicated full consumption of starting material and intermediate. The reaction crude was filtered through a silica plug (washing with EtOAc) and concentrated. NMR yield was determined using 1,3,5-trimethoxybenzene as an internal standard. The product could be isolated using column chromatography (hexane:EtOAc 9:1) to yield a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.52 (d, J = 0.9 Hz, 1H), 7.71 (d, J = 1.7 Hz, 1H), 7.25 – 7.16 (m, 3H), 7.12 (ddd, J = 1.6, 6.4, 7.6 Hz, 1H), 3.44 – 3.33 (m, 2H), 3.27 – 3.17 (m, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 156.7, 155.4 (q, J = 1.3 Hz), 153.0, 140.6 (q, J = 4.1 Hz), 132.8, 130.1, 128.0, 126.0 (q, J = 3.5 Hz), 125.8 (q, J =33.3 Hz), 125.4, 123.2 (q, J = 272.4 Hz), 120.8, 35.8, 28.9; $^{19}$F NMR (377 MHz, CDCl$_3$) δ -
63.1; IR (NaCl, neat): 3065, 3040, 2930, 2859, 1616, 1564, 1489, 1450, 1431, 1410, 1335, 1267, 1238, 1203, 1173, 1128, 1099, 1084, 954, 912, 764, 748 cm\(^{-1}\); HRMS (ESI): calcd for C\(_{14}\)H\(_{11}\)F\(_3\)NO (M+H): 266.0793; found. 266.0796.

**Methyl 10,11-dihydrobenzo[6,7]oxepino[3,2-b]pyridine-3-carboxylate (2.65)**

This compound was prepared using procedure 2.8 using methyl 5-chloro-6-vinylnicotinate (39.5 mg, 0.2 mmol), 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (88 mg, 0.4 mmol, 2 equiv), [Rh(cod)OH]\(_2\) (1.84 mg, 0.004 mmol, 2 mol%), Pd(OAc)\(_2\) (2.24 mg, 0.01 mmol, 5 mol%), t-Bu-X-Phos (8.24 mg, 0.014 mmol, 7 mol%), K\(_2\)CO\(_3\) (55.4 mg, 0.4 mmol, 2 equiv) and K\(_3\)PO\(_4\) (85 mg, 0.4 mmol, 2 equiv). The product was isolated using flash column chromatography (hexane:EtOAc 85:15) to give the titled compound in 72% yield (37 mg) as a colorless solid. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.77 (d, \(J = 1.7\) Hz, 1H), 7.98 (d, \(J = 1.7\) Hz, 1H), 7.21 – 7.07 (m, 3H), 7.07 – 6.97 (m, 1H), 3.87 (s, 3H), 3.36 – 3.24 (m, 2H), 3.21 – 3.08 (m, 2H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 165.5, 156.8, 156.0, 153.1, 145.1, 132.9, 130.0, 129.7, 127.9, 125.3, 125.2, 120.8, 52.5, 35.7, 28.8; IR (NaCl, neat): 3065, 3028, 3001, 2951, 2926, 2849, 1732, 1717, 1599, 1558, 1489, 1435, 1394, 1296, 1263, 1234, 1197, 1177, 1142, 1099, 1005, 939, 924, 800, 773 cm\(^{-1}\); M. p.: 57-59 °C; HRMS (ESI): calcd for C\(_{15}\)H\(_{14}\)NO (M+H): 256.0974; found. 256.0972.

**3-Nitro-10,11-dihydrobenzo[6,7]oxepino[3,2-b]pyridine (2.66)**

This compound was prepared using procedure 2.8 using 3-chloro-5-nitro-2-vinylpyridine (36.9 mg, 0.2 mmol), 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (88 mg, 0.4 mmol, 2 equiv), [Rh(cod)OH]\(_2\) (1.84 mg, 0.004 mmol, 2 mol%), Pd(OAc)\(_2\) (2.24 mg, 0.01 mmol, 5 mol%), t-Bu-X-Phos (8.24 mg, 0.014 mmol, 7 mol%), K\(_2\)CO\(_3\) (55.4 mg, 0.4 mmol, 2 equiv) and K\(_3\)PO\(_4\) (85 mg, 0.4 mmol, 2 equiv). The product was isolated using flash column chromatography (hexane:EtOAc 9:1) to give the titled compound in 49% yield (24.1 mg) as an off-white solid. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 158.3, 156.4, 152.9, 138.9, 132.6, 131.0, 128.2, 125.4, 123.7, 120.8, 36.2, 28.5; IR (NaCl, neat): 3065, 3028, 3001, 2951, 2926, 2849, 1732, 1717, 1599, 1558, 1489, 1435, 1394, 1296, 1263, 1234, 1197, 1177, 1142, 1099, 1005, 939, 924, 800, 773 cm\(^{-1}\); M. p.: 98–101 °C; HRMS (ESI): calcd for C\(_{13}\)H\(_{11}\)N\(_2\)O\(_3\) (M+H): 243.0770; found. 243.0773.

**N-Benzyl-5-chloro-6-(2-hydroxyphenethyl)nicotinamide (2.67)**

This compound was prepared using procedure 2.7, using N-benzyl-5-chloro-6-vinylnicotinamide (47 mg, 0.2 mmol), 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (88 mg, 0.4 mmol, 2 equiv), [Rh(cod)OH]\(_2\) (1.84 mg, 0.004 mmol, 2 mol%) and K\(_2\)CO\(_3\) (55.4 mg).
The product was isolated using flash column chromatography (hexane:EtOAc 65:35) to give the titled compound in 90% yield (as calculated by NMR) as a highly insoluble, colorless solid. Isolation of the compound was difficult because of its low solubility; $^1$H NMR (300 MHz, CDCl$_3$) δ 9.68 (s, 1H), 8.78 (d, $J = 1.8$ Hz, 1H), 8.16 (d, $J = 1.9$ Hz, 1H), 7.43 – 7.28 (m, 5H), 7.18 (dd, $J = 7.8$, 1.6 Hz, 1H), 7.14 – 7.05 (m, 1H), 6.91 – 6.80 (m, 2H), 6.44 (t, $J = 5.1$ Hz, 1H), 4.63 (d, $J = 5.6$ Hz, 2H), 3.45 – 3.33 (m, 2H), 3.23 – 3.11 (m, 2H); 13C NMR (100 MHz, CDCl$_3$) δ 163.7, 160.5, 154.9, 143.5, 137.4, 136.9, 132.9, 130.8, 129.8, 129.1, 128.5, 128.2, 128.1, 120.7, 117.9, 44.6, 37.0, 25.1; IR (neat): 3296, 3057, 3030, 2938, 1635, 1594, 1537, 1455, 1388, 1368, 1318, 1266, 1244, 1138, 1095, 1067, 1043, 912, 846, 776 cm$^{-1}$; M. p.: 165 – 167; HRMS (ESI): calcd for C$_{22}$H$_{20}$ClN$_2$O$_2$ (M+H)$^+$: 367.1213; found. 367.1214.

2-(2-(3-Chloro-5-morpholinopyridin-2-yl)ethyl)phenol (2.68)

This compound was prepared using procedure 2.7 using 4-(5-chloro-6-vinylpyridin-3-yl)morpholine (45 mg, 0.2 mmol), 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (88 mg, 0.4 mmol, 2 equiv), [Rh(cod)OH]$$_2$$ (1.84 mg, 0.004 mmol, 2 mol%) and K$_2$CO$_3$ (55.4 mg). The product was isolated using flash column chromatography (hexane:EtOAc 65:35) to give the titled compound in 78% yield (50 mg) as a pale yellow solid. Some difficulty was encountered in separation of the product from pinacol. $^1$H NMR (400 MHz, CDCl$_3$) δ 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 – 3.81 (m, 4H), 3.29 – 3.23 (m, 2H), 3.18 – 3.09 (m, 6H); 13C NMR (101 MHz, CDCl$_3$) δ 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 (NaCl, neat): 3347, 2965, 2918, 2851, 1593, 1489, 1456, 1398, 1267, 1236, 1140, 1123, 1063, 1045, 959, 870, 756, 735 cm$^{-1}$; M. p.: 140-143 ºC; HRMS (ESI) Calcd for C$_{17}$H$_{20}$ClN$_2$O$_2$ (M+H)$^+$: 319.1208; found. 319.1205.

3-Morpholino-10,11-dihydrobenzo[6,7]oxepino[3,2-b]pyridine (2.69)

The intermediate 2.68 (23 mg, 0.071 mmol) was weighed into a vial with Pd(OAc)$_2$ (1 mg, 0.0035 mmol, 5 mol%), t-Bu-X-Phos (3 mg, 0.005 mmol, 7 mol%), and K$_3$PO$_4$ (31 mg, 0.142 mmol, 2 equiv). The vial was purged with argon and t-BuOH (1 ml) was added. The reaction was sealed with a Teflon-lined cap and placed into an oil bath at 100 ºC. After the reaction was complete (16 h) the crude was filtered through a silica plug and the solvent was removed. The crude was purified using column chromatography (hexane:EtOAc 7:3) to give the titled compound in 60% yield (12 mg) as a colorless solid. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.99 (d, $J = 2.2$ Hz, 1H), 7.24 – 7.12 (m, 3H), 7.09 (ap td, $J = 7.2$, 1.6 Hz, 1H), 7.00 (d, $J = 2.5$ Hz, 1H), 3.93 – 3.81 (m, 4H), 3.27 – 3.21 (m, 2H), 3.21 – 3.13 (m, 6H); 13C NMR (101 MHz, CDCl$_3$) δ 157.1, 153.4, 146.8, 141.4, 133.5, 132.7, 130.0, 127.7, 124.9, 120.7, 115.0, 66.8 (2), 48.9 (2), 34.6, 29.5. IR (NaCl,
neat): 2959, 2920, 2853, 1597, 1553, 1489, 1449, 1412, 1267, 1230, 1199, 1169, 1123, 1051, 999, 887 cm⁻¹; **HRMS** (ESI) Calcd for C₁₇H₁₉N₂O₂ (M+H)⁺: 283.1446; found. 283.1443.

2-(2-(3-Chloro-5-vinylpyridin-2-yl)ethyl)phenol (2.70)

![Chemical structure](image)

This compound was prepared using procedure 2.8, using o 3-chloro-2,5-divinylpyridine (33.2 mg, 0.2 mmol) 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (88 mg, 0.4 mmol, 2 equiv), [Rh(cod)OH]₂ (1.84 mg, 0.004 mmol, 2 mol%), Pd(OAc)₂ (2.24 mg, 0.01 mmol, 5 mol%), t-Bu-X-Phos (8.24 mg, 0.014 mmol, 7 mol%), K₂CO₃ (55.4 mg, 0.4 mmol, 2 equiv) and K₃PO₄ (85 mg, 0.4 mmol, 2 equiv). The product was isolated using flash column chromatography (hexane:EtOAc 92.5:7.5) to give the titled compound in 60% yield (31 mg) as an off-white solid. No cyclized product was detected. **¹H NMR** (300 MHz, CDCl₃) δ 10.34 (s, 1H), 8.44 (d, J = 1.6 Hz, 1H), 7.73 (d, J = 1.7 Hz, 1H), 7.19 (dd, J = 7.5, 1.3 Hz, 1H), 7.11 (ap td, J = 8.1, 1.6 Hz, 1H), 6.95 – 6.77 (m, 2H), 6.62 (dd, J = 17.6, 11.0 Hz, 1H), 5.81 (d, J = 11.0 Hz, 1H), 5.43 (d, J = 11.0 Hz, 1H), 3.40 – 3.28 (m, 2H), 3.23 – 3.10 (m, 2H); **¹³C NMR** (75 MHz, CDCl₃) δ 156.1, 155.3, 144.0, 134.2, 133.1, 132.4, 131.6, 130.9, 129.0, 127.9, 120.4, 118.0, 117.8, 36.6, 25.4; **IR** (NaCl, neat): 3346, 3065, 2955, 2918, 2849, 1593, 1489, 1456, 1420, 1381, 1248, 1207, 1151, 1138, 1096, 1063, 1042, 986, 920, 754 cm⁻¹; **M. p.**: 78–81 °C; **HRMS** (ESI): calcd for C₁₅H₁₅ClNO (M+H)⁺: 260.0842; found: 260.0835.

2-(Benzyloxy)-3-chloro-5-vinylpyridine (2.71)

![Chemical structure](image)

The titled compound is prepared using standard Stille coupling conditions, utilizing 5-(benzyloxy)-2,3-dichloropyridine (381 mg, 1.5 mmol), tributylvinyltin (500 μl, 1.65 mmol, 1.1 equiv), Pd(PPh₃)₄ (87 mg, 5 mol%), lithium chloride (76 mg, 1.2 equiv) in dioxane (7 ml, 0.2M). Reaction was run for 16 hours, at which point no starting material was seen by HNMR. The product was isolated using flash column chromatography (100 – 97.5:2.5 Hexane:EtOAc with 2 mol% NEt₃) to give the titled compound in 78% yield (286 mg) as a colorless oil. **¹H NMR** (400 MHz, CDCl₃) δ 8.02 (d, J = 2.1 Hz, 1H), 7.77 (d, J = 2.1 Hz, 1H), 7.49 (d, J = 7.3 Hz, 2H), 7.38 (t, J = 7.3 Hz, 2H), 7.32 (t, J = 7.3 Hz, 1H), 6.61 (dd, J = 17.6, 11.0 Hz, 1H), 5.66 (d, J = 17.6 Hz, 1H), 5.48 (s, 2H), 5.28 (d, J = 11.0 Hz, 1H); **¹³C NMR** (101 MHz, CDCl₃) δ 158.5, 143.2, 137.0, 135.1, 132.1, 128.6 (2), 128.3, 128.0, 127.7 (2), 118.8, 114.7, 68.5; **IR** (NaCl, neat): 3053, 2961, 2961, 2849, 1582, 1489, 1456, 1420, 1381, 1248, 1207, 1151, 1138, 1096, 1063, 1042, 986, 920, 754 cm⁻¹; **HRMS** (ESI): calcd for C₁₄H₁₃ClNO (M+H)⁺: 246.0842; found. 260.0835.

2-(1-(3-Chloro-5-(trifluoromethyl)pyridin-2-yl)octan-2-yl)phenol (2.72)

![Chemical structure](image)

This compound was prepared using procedure 2.7, using (E)-3-chloro-2-(oct-1-en-1-yl)-5-(trifluoromethyl)pyridine (45 mg, 0.2 mmol), 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (88 mg, 0.4 mmol,
2 equiv), [Rh(cod)OH]$_2$ (1.84 mg, 0.004 mmol, 2 mol%), and K$_2$CO$_3$ (55.4 mg, 0.4 mmol, 2 equiv). The product was isolated using flash column chromatography (hexane:EtOAc 97.5:2.5) to give the titled compound in 78% yield (63 mg) as a pale yellow solid. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.70 (d, $J$ = 0.6 Hz, 1H), 8.66 (s, 1H), 7.88 (d, $J$ = 1.5 Hz, 1H), 7.20 (dd, $J$ = 7.6, 1.4 Hz, 1H), 7.08 (ap td, $J$ = 7.7, 1.6 Hz, 1H), 6.94 – 6.85 (m, 2H), 3.80 – 3.63 (m, 1H), 3.42 – 3.22 (m, 2H), 1.99 – 1.70 (m, 2H), 1.41 – 1.08 (m, 8H), 0.85 (t, $J$ = 6.7 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 161.8, 154.6, 142.9 (q, $J$ = 4.2 Hz), 134.4 (q, $J$ = 3.4 Hz), 132.5, 132.0, 127.4, 126.8, 126.2 (q, $J$ = 34.0 Hz), 122.7 (q, $J$ = 272.8 Hz), 121.2, 118.0, 43.5, 36.5, 33.5, 31.8, 29.3, 27.7, 22.7, 14.2; $^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ -62.4; IR (NaCl, neat) 3366, 2957, 2926, 2857, 1606, 1456, 1325, 1229, 1173, 1138, 1092, 1067, 912, 878,752 cm$^{-1}$; HRMS (ESI): calcd for C$_{20}$H$_{24}$ClF$_3$NO (M+H)$^+$: 386.1499; found. 386.1508; $[\alpha]$$_D^{25.8}$ = +15.07 (c 1.69, CHCl$_3$) for 95:5 er, as measured by HPLC analysis: (Chiralcel OJ-RH, gradient 65:25 (H$_2$O:MeCN) to 60:40 over 25 minutes, 1.0 mL/min, 275 nm); $t_R$ = 17.7 min (major), $t_R$ = 18.8 min (minor).

10-Hexyl-3-(trifluoromethyl)-10,11-dihydrobenzo[6,7]oxepino[3,2-b]pyridine (2.73)

The intermediate phenol 2.72 was combined with Pd(OAc)$_2$ (5 mol%), t-Bu-X-Phos (7 mol%) and K$_2$PO$_4$ (2 equiv) in a vial, which was subsequently purged with argon. t-Butylalcohol (2 ml) was added and the reaction vial was sealed with a Teflon-lined cap and placed into an oil bath at 100 °C for 16 hours. Upon completion the reaction crude was filtered through a silica plug and concentrated. The product was obtained through column chromatography (hexane:EtOAc 97.5:2.5) as a colorless solid in 80% yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.52 (d, $J$ = 0.5 Hz, 1H), 7.69 (d, $J$ = 1.4 Hz, 1H), 7.25 – 7.09 (m, 4H), 3.50 (d, $J$ = 14.8 Hz, 1H), 3.36 – 3.19 (m, 2H), 1.90 – 1.75 (m, 1H), 1.68 – 1.53 (m, 1H), 1.52 – 1.38 (m, 1H), 1.38 – 1.18 (m, 7H), 0.86 (t, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 155.9, 154.0, 142.9 (q, $J$ = 3.6 Hz), 134.4, 135.9, 129.2, 128.0, 125.8 (q, $J$ = 33.2 Hz), 125.5 (q, $J$ = 3.6 Hz), 125.2, 123.3 (q, $J$ = 272.5 Hz), 121.1, 121.1, 39.5, 33.7, 31.8, 29.4, 27.7, 22.7, 14.2; $^{19}$F NMR (377 MHz, CDCl$_3$) $\delta$ -63.1; IR (NaCl, neat): 2957, 2930, 2859, 1487, 1427, 1410, 1335, 1242, 1207, 1171, 1134, 1086, 951, 912, 756 cm$^{-1}$; HRMS (ESI): calcd for C$_{20}$H$_{23}$F$_3$NO (M+H)$^+$: 350.1720; found. 350.1723; $[\alpha]$$_D^{25.8}$ = –19.94 (c 0.94, CHCl$_3$) for 95:5 er, as measured by HPLC analysis: (Chiralcel AD-H, isocratic 0.25% i-PrOH/hexane, 0.70 mL/min, 225 nm); $t_R$ = 10.86 min (major), $t_R$ = 12.65 min (minor).

N-(2-(2-(3-Chloropyridin-2-yl)ethyl)phenyl)methanesulfonamide (2.79)

This compound was prepared according to procedure 2.7: 2-vinyl-3-chloropyridine (45 mg, 0.2 mmol), N-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanesulfonamide (103 mg, 0.3 mmol, 1.5 equiv) and potassium carbonate (83 mg, 0.4 mmol, 2 equiv) were weighed into a vial and purged with argon. Dioxane (1 mL), and water (200 μL) were added. A premixed solution of [Rh(cod)OH]$_2$ (2 mol%), dppp (4 mol%) was added. The reaction mixture was reacted at 60 °C for 16 hours. Silica
flash column chromatography (6:4 Hexanes: EtOAc) gave the product (42 mg, 67%), as colorless solid. $^1$H NMR (400MHz, CDC$_3$I): $\delta$ 10.68 (br s, 1H), 8.57 (dd, $J$ = 4.9, 1.4 Hz, 1H), 7.66 (dd, $J$ = 8.0, 1.5 Hz, 1H), 7.53 (dd, $J$ = 8.0, 1.3 Hz, 1H), 7.31 (dd, $J$ = 7.5, 1.7 Hz, 1H), 7.23 – 7.15 (m, 2H), 7.12 (ap td, $J$ = 7.5, 1.3 Hz, 1H), 3.39 – 3.29 (m, 2H), 3.26 – 3.14 (m, 2H), 3.00 (s, 3H); $^{13}$C NMR (101MHz, CDC$_3$I): $\delta$ 156.6, 146.4, 137.6, 135.8, 134.0, 131.9, 131.0, 127.7, 125.4, 123.0, 122.6, 39.8, 36.5, 26.8; IR (NaCl, neat) 3254, 3069, 3022, 2930, 1581, 1492, 1327, 1152, 1047, 972 cm$^{-1}$; M. p.: 112 – 114 ºC. HRMS (ESI): calcd for C$_{14}$H$_{16}$ClN$_2$O$_2$S (M+H)$^+$: 311.0621; found: 311.0629.

**3-Chloro-2-(2-chlorophenethyl)-5-(trifluoromethyl)pyridine (2.81a)**

![Chemical structure image]

The titled compound was prepared using procedure 2.7 using 3-chloro-5-(trifluoromethyl)-2-vinylpyridine (148.4 mg, 0.715 mmol), 2-chlorophenylboronic acid (168 mg, 1.07 mmol, 1.5 equiv), [Rh(cod)OH]$_2$ (6.52 mg, 0.014 mmol, 2 mol%), and K$_2$CO$_3$ (197 mg, 1.43 mmol, 2 equiv). The product was isolated using flash column chromatography (hexane:EtO 98:2) to give the titled compound in 81% yield (186 mg) as a colorless oil. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.63 (s, 1H), 7.78 (s, 1H), 7.36 – 7.21 (m, 1H), 7.20 – 6.98 (m, 3H), 3.33 – 3.18 (m, 2H), 3.18 – 3.02 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 162.4, 144.0 (q, $J$ = 4.0 Hz), 138.6, 134.3, 133.9 (q, $J$ = 3.6 Hz), 131.6, 130.6, 129.7, 127.9, 127.0, 125.8 (q, $J$ = 33.7 Hz), 123.0 (q, $J$ = 272.7 Hz), 35.5, 31.9; $^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ -62.2; IR (NaCl, neat): 3071, 3019, 2936, 2862, 1605, 1559, 1476, 1445, 1397, 1323, 1171, 1136, 1090, 1059, 1053, 912 cm$^{-1}$; HRMS (ESI): calcd for C$_{14}$H$_{11}$ClF$_3$N (M+H)$^+$: 320.0221; found: 320.0224.

**2-(2-Bromophenethyl)-3-chloro-5-(trifluoromethyl)pyridine (2.81b)**

![Chemical structure image]

The titled compound was prepared using procedure 2.7 using 3-chloro-5-(trifluoromethyl)-2-vinylpyridine (42 mg, 0.2 mmol), 2-bromophenylboronic acid (80.3 mg, 0.4 mmol, 2 equiv), [Rh(cod)OH]$_2$ (1.84 mg, 0.004 mmol, 2 mol%), and K$_2$CO$_3$ (55 mg, 0.4 mmol, 2 equiv). The product was isolated using flash column chromatography (hexane:EtO 97.5:2.5) to give the titled compound in 79% yield (58 mg) as a colorless oil. $^1$H NMR (300 MHz, CCl$_3$) $\delta$ 8.73 (d, $J$ = 0.8 Hz, 1H), 7.88 (d, $J$ = 1.4 Hz, 1H), 7.56 (d, $J$ = 7.8 Hz, 1H), 7.23 (d, $J$ = 4.1 Hz, 2H), 7.09 (dd, $J$ = 8.1, 4.6 Hz, 1H), 3.40 – 3.27 (m, 2H), 3.28 – 3.17 (m, 2H); $^{13}$C NMR (101 MHz, CCl$_3$) $\delta$ 162.3 (q, $J$ = 1.3 Hz), 144.1 (q, $J$ = 4.0 Hz), 140.3, 133.9 (q, $J$ = 3.6 Hz), 133.1, 131.6, 130.6, 128.2, 127.7, 125.8 (q, $J$ = 33.5 Hz), 124.7, 123.0 (q, $J$ = 272.8 Hz), 35.6, 34.4; $^{19}$F NMR (282 MHz, CCl$_3$) $\delta$ -62.2; IR (NaCl, neat): 3068, 3015, 2936, 2851, 1605, 1472, 1439, 1395, 1323, 1169, 1134, 1090, 1059, 1026, 912, 752 cm$^{-1}$; HRMS (ESI): calcd for C$_{14}$H$_{11}$BrClF$_3$N (M+H)$^+$: 363.9716; found: 363.9719.
2-(2-Chlorophenethyl)-N-(3-phenylpropyl)-5-(trifluoromethyl)pyridin-3-amine (2.82a) and 2-(2-(3-Chloro-5-(trifluoromethyl)pyridin-2-yl)ethyl)-N-(3-phenylpropylaniline (2.82b).

The dihalogenated compounds 2.81a and 2.81b were subjected to the standard C-N coupling conditions. For 2.82a, in a vial were combined: 2.81a (46 mg, 0.144 mmol), Pd(OAc)$_2$ (1.61 mg, 0.0072 mmol, 5 mol%), t-Bu-X-Phos (5.9 mg, 0.01 mmol, 7 mol%) and K$_2$PO$_4$ (61 mg, 0.29 mmol, 2 equiv), and, after purging with argon, t-BuOH (1.5 ml). The reaction vial was sealed with a Teflon-lined cap and placed into an oil bath at 100 °C for 16 hours. After filtering and concentrating, the crude was purified by column chromatography (hexane:EtOAc 9:1) to yield small amounts of 2.82a (NMR analysis showed >90% starting material remaining and ~8% product). For 2.82b, in a vial were combined: 2.81b (56.6 mg, 0.155 mmol), Pd(OAc)$_2$ (1.74 mg, 0.0078, 5 mol%), t-Bu-X-Phos (6.4 mg, 0.011 mmol, 7 mol%) and K$_2$PO$_4$ (66 mg, 0.31 mmol, 2 equiv) in a vial, which was subsequently purged with argon. t-Butylalcohol (1.6 ml) was added and the reaction vial was sealed with a Teflon-lined cap and placed into an oil bath at 100 °C for 16 hours. At this time, the reaction crude was filtered through a silica plug and concentrated. The major product could be obtained through column chromatography (hexane:EtOAc 95:5) as colorless oil. NMR analysis of the crude showed 81% of the starting material remaining and 12% product. Because of low yields it was difficult to obtain these products in high purity. Only partial characterization was obtained at the time: 2.82a: $^1$H NMR (300 MHz, CDCl$_3$) δ 8.16 (s, 1H), 7.40 – 7.12 (m, 9H), 6.89 (d, J = 1.3 Hz, 1H), 3.97 (s, 1H), 3.18 – 3.03 (m, 4H), 3.00 – 2.84 (m, 2H), 2.76 (t, J = 7.4 Hz, 2H), 2.07 – 1.90 (m, 2H); HRMS (ESI): calcd for C$_{23}$H$_{23}$ClF$_3$N$_2$ (M+H)$^+$: 419.1502; found. 419.1504. 2.82b: $^1$H NMR (300 MHz, CDCl$_3$) δ 8.72 (d, J = 1.8 Hz, 1H), 7.89 (d, J = 1.9 Hz, 1H), 7.33 – 7.07 (m, 7H), 6.69 (ap dt, J = 8.5, 4.2 Hz, 1H), 6.63 (d, J = 8.1 Hz, 1H), 4.02 (s, 1H), 3.34 – 3.26 (m, 2H), 3.21 (t, J = 7.0 Hz, 2H), 2.94 – 2.85 (m, 2H), 2.83 – 2.75 (m, 2H), 2.10 – 1.95 (m, 2H); HRMS (ESI): calcd for C$_{23}$H$_{23}$ClF$_3$N$_2$ (M+H)$^+$: 419.1502; found. 419.1500.
Chapter 3

*Arylation of 3-Aryl-1-Propargyl Alcohols*
3 Arylation of 3-Aryl-1-Propargyl Alcohols

3.1 Introduction

The ability to synthesize polysubstituted olefins with high regio- and stereoselectivity remains an important goal. Following up on our success in using the rhodium-catalyzed arylation of alkynes en route to dihydroquinolines and 2H-chromenes, we became interested in establishing a general strategy for regio- and stereoselective synthesis of allylic alcohols. A number of methods exist to access these motifs through addition reactions with alkynes, but the rhodium-catalyzed arylation has not yet been studied. Considering that the conditions used in rhodium-catalyzed arylations are very mild and compatible with most functional groups, this investigation was undertaken. In the following section of this thesis a rhodium-catalyzed arylation of aryl-substituted propargylic alcohols is described, which takes place in high yields, regio- and stereoselectivity. Furthermore, the resulting allylic alcohols are used in a one-step synthesis of indenes and as an access point to quinolines, both of which are useful classes of molecules. Parts of the following section were carried out by two undergraduate students, Richard Huang and Erica Lui, under the mentorship of the author. R. Huang’s and E. Lui’s contributions are acknowledged where appropriate.

3.1.1 Metal Mediated Synthesis of Allylic Alcohols from Propargyl Alcohols

Carbometallation of alkynes is a convenient way to access highly substituted alkenes, and a variety of methods exist to affect this transformation with high regio- and stereocontrol. Development of such carbometallations of alkynes bearing reactive substituents such as amines or alcohols is quite useful, since the resulting allylic alcohols and amines are very handy building blocks for indene synthesis.

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3 R. H. was a 5th year undergraduate student from the University of Toronto, and contributed to determining the scope and application to indene synthesis.

4 E. L. was a 2nd year undergraduate summer student from the University of Toronto, who contributed to the development of this reaction.

blocks in organic synthesis. The presence of a heteroatom adds value to the olefin products, which can be further functionalized and contains a useful handle to facilitate further reactivity, which may benefit from chelation. In many examples of carbometallations of heteroatom containing alkynes the heteroatom is even necessary to effect stereo- or regiocontrol through chelation to a reagent or catalyst (i.e., Eqn 3.1). The downside of the majority of these protocols is the use of highly reactive organometallic reagents, such as alkylthium, -zinc and -magnesium reagents or reducing agents (i.e., HSiR₃), which are incompatible with more sensitive functional groups. More recently, some examples of catalytic reactions using more benign nucleophiles, (i.e., boronic acids) or electrophilic reagents (i.e., aryl halides) have been reported.

A few palladium-catalyzed addition reactions have been used to access allylic alcohols without the use of protecting groups. Cacchi and coworkers have reported the use of propargylic alcohol substrates in their palladium-catalyzed hydrovinylation and -arylation of alkynes with vinyl triflates and aryl halides (Eqn 3.2). They utilized this reactivity in a number of syntheses of heterocycles from appropriately substituted alkynes with electrophilic and nucleophilic functional groups. The presence of geminal substituents in the substrates is essential, likely to prevent isomerization of the alkene and/or elimination of water. The mechanism of the transformation is thought to proceed through oxidative addition of palladium into vinyltriflate, followed by carbopalladation. The vinylpalladium species subsequently reacts with formate and

---


generates a palladium hydride intermediate, which reductively eliminates to give the final product. The regioselectivity is thought to depend on the sterics of substituents and not the polarization of the alkyne.

\[
\begin{align*}
\text{(1.2 equiv)} + \text{Pd(OAc)}_2 (5 \text{ mol\%}) & \xrightarrow{\text{HCO}_2\text{K (2 equiv)}} \text{DMF, 40 °C} \rightarrow \\
\text{HO} & \rightarrow \\
\text{OMe} & \rightarrow \\
\text{Ph} & \rightarrow \\
\text{HO} & \rightarrow \\
\text{MeO}_2\text{C} & \rightarrow \\
\text{Ph} & \rightarrow \\
\text{HO} & \rightarrow \\
\text{Ph} & \rightarrow \\
\text{HO} & \rightarrow \\
\text{Pr} & \rightarrow \\
\end{align*}
\]

(3.2)

74%

In 2003, Oh and co-workers reported the palladium-catalyzed hydroarylation of alkynes using boronic acids and acetic acid, which proceeded in high yield with propargylic alcohol substrates (Eqn 3.3). Although high yielding, this transformation proceeded with poor regiocontrol when disubstituted alkynes were used, even those with a strong electronic bias. The mechanism is thought to proceed through an initial \textit{syn}-addition of a palladium-hydride species across the alkyne, followed by transmetallation and reductive elimination to give the final product.

\[
\begin{align*}
\text{COH} & \rightarrow \\
\text{Me} & \rightarrow \\
\text{Me} & \rightarrow \\
\text{B(OH)}_2 & \rightarrow \\
\text{Pd} & \rightarrow \\
\text{Pr} & \rightarrow \\
\text{HO} & \rightarrow \\
\text{Me} & \rightarrow \\
\text{Me} & \rightarrow \\
\text{HO} & \rightarrow \\
\text{Me} & \rightarrow \\
\end{align*}
\]

(3.3)

96%

Rhodium-catalyzed arylation of alkynes with boronic acids proceeds under very mild conditions, and we were interested in applying unprotected propargylic alcohol substrates in this transformation to generate allylic alcohols.

### 3.2 Rhodium-Catalyzed Arylation of Propargyl Alcohols

#### 3.2.1 Synthesis of Substrates

The majority of 3-aryl propargyl alcohol substrates were synthesized through Sonogashira coupling of the corresponding aryl halides and propargyl alcohols (Table 3.1). Coupling of aryl halides with propargylic alcohols proceeds under very mild conditions, and we were interested in applying unprotected propargylic alcohol substrates in this transformation to generate allylic alcohols.

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11 See Section 2.1.3 for a summary of this reaction.

iodide furnished the products in quantitative yields after 5 hours at room temperature (entries 1-2,7,11,13). Cross-coupling of aryl bromides required heating at reflux, and the yields were more variable. To couple 4-dimethylaminoaryl bromide, a more active catalyst was necessary (entry 6). To access substrates with variation of the alkyl group, the appropriately substituted alkynes were coupled. If unavailable, phenylacetylene could be added to aldehydes (Eqn 3.4). Overall a good scope of electron rich, neutral and poor substrates could be accessed, including heteroaryl motifs 3.8, 3.9 and 3.14.

Table 3.1 Synthesis of substrates through Sonogashira coupling. a

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Ar</th>
<th>R</th>
<th>Product</th>
<th>Pd (mol%)</th>
<th>T (°C)</th>
<th>T (h)</th>
<th>Yield (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I</td>
<td>C₆H₅</td>
<td>H</td>
<td>3.1</td>
<td>1</td>
<td>r. t.</td>
<td>5</td>
<td>&gt;95</td>
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<tr>
<td>2</td>
<td>I</td>
<td>C₆H₅</td>
<td>Me</td>
<td>3.2</td>
<td>1</td>
<td>r. t.</td>
<td>5</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>I</td>
<td>4-MeOC₆H₄</td>
<td>Me</td>
<td>3.3</td>
<td>1</td>
<td>r. t.</td>
<td>16</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>Br</td>
<td>4-F₃C₆H₄</td>
<td>Me</td>
<td>3.4</td>
<td>1</td>
<td>80</td>
<td>16</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td>I</td>
<td>3,5-(MeO)₂C₆H₃</td>
<td>Me</td>
<td>3.5</td>
<td>2</td>
<td>75</td>
<td>6.5</td>
<td>71</td>
</tr>
<tr>
<td>6</td>
<td>Br</td>
<td>4-(Me₂N)C₆H₄</td>
<td>Me</td>
<td>3.6</td>
<td>3</td>
<td>30</td>
<td>4 d</td>
<td>50</td>
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<tr>
<td>7</td>
<td>I</td>
<td>3,5-Me₂C₆H₃</td>
<td>Me</td>
<td>3.7</td>
<td>1</td>
<td>r. t.</td>
<td>4 h</td>
<td>&gt;95</td>
</tr>
<tr>
<td>8</td>
<td>Br</td>
<td></td>
<td>Me</td>
<td>3.8</td>
<td>0.5</td>
<td>45</td>
<td>20 h</td>
<td>67</td>
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<tr>
<td>9</td>
<td>Br</td>
<td></td>
<td>Me</td>
<td>3.9</td>
<td>1.5</td>
<td>90</td>
<td>36 h</td>
<td>41</td>
</tr>
<tr>
<td>10</td>
<td>Br</td>
<td>2-MeOC₆H₄</td>
<td>Me</td>
<td>3.10</td>
<td>1</td>
<td>90</td>
<td>4 d</td>
<td>6</td>
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<tr>
<td>11</td>
<td>I</td>
<td>4-MeC₆H₄</td>
<td>Me</td>
<td>3.11</td>
<td>1</td>
<td>r. t.</td>
<td>5.5 h</td>
<td>&gt;95</td>
</tr>
<tr>
<td>12</td>
<td>Br</td>
<td>4-F₃C₆H₄</td>
<td>H</td>
<td>3.12</td>
<td>1</td>
<td>60</td>
<td>17</td>
<td>88</td>
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<tr>
<td>13</td>
<td>I</td>
<td>4-AcC₆H₄</td>
<td>H</td>
<td>3.13</td>
<td>1</td>
<td>r. t.</td>
<td>1.5</td>
<td>95</td>
</tr>
<tr>
<td>14</td>
<td>Br</td>
<td></td>
<td>Me</td>
<td>3.14</td>
<td>1</td>
<td>50</td>
<td>17 h</td>
<td>&gt;95</td>
</tr>
</tbody>
</table>

a Conditions: [Pd] and CuI weighed into a flask, which is then purged with argon. Triethylamine is added followed by the aryl halide. After stirring for ~3 minutes solution of alkyne is added. Reaction is heated at the appropriate temperature for the indicated time. b Yields of isolated material. c Performed by E. Lui. d Performed by R. Huang. e Pd(OAc)₂ and P(Ph)₃ used instead of Pd(PPh₃)₂Cl₂.

3.2.2 Optimization of the Propargyl Alcohol Arylation

With a number of substrates in hand, we examined the arylation reaction. Our initial experiments using substrate 3.2 showed that \([\text{Rh(cod)}\text{OH}]_2\) and BINAP in the presence of \(\text{K}_2\text{CO}_3\) and dioxane/water furnished the desired product 3.16, in moderate yield (Eqn 3.5). Based on crude NMR, only one regioisomer was observed, without any \(\alpha\)-addition product 3.17 detected. Closer examination of minor byproducts in the reaction mixture, however, has led to the discovery of compound 3.18, which could be formed from the minor isomer after alkene isomerization. It is also possible that this byproduct originated from a rearrangement of the starting alkyne to \(\alpha,\beta\)-unsaturated ketone 3.19, and subsequent 1,4-addition of the boronic acid (Eqn 3.6).\(^{14}\) Since in the original report of this reactivity a cationic rhodium catalyst was absolutely necessary for this rearrangement to occur, it is more probable that the former mechanism takes place. As a result of this finding, the regioisomeric ratio was measured between the desired \(\beta\)-addition product, 3.16, and the sum of the \(\alpha\)-addition product 3.17 and ketone 3.18.

\(^{14}\)This reactivity is described by Tanaka: Tanaka, K.; Shoji, T. Org. Lett. 2005, 7, 3561.
Some optimization revealed that BINAP was the optimal ligand, when compared to other bidentate ligands such as dppp and dppf (Table 3.2). Although the yields were comparable, cleaner reaction and higher regioisomeric ratios were observed. The use of other bases and methanol as an additive did not improve the reaction outcome. Notably, when the reaction was run on larger scale, a better outcome was observed in terms of yield. The reaction was usually complete within three hours at 60 °C. These conditions are milder than Hayashi’s original report, and we could decrease the boronic acid loading to 2 equivalents or less.

### Table 3.2 Optimization of reaction conditions.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Scale (mmol)</th>
<th>Yield (%)(^b)</th>
<th>r. r.(^c)</th>
<th>3.20 : 3.21 : 3.22(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^d)</td>
<td>dppp</td>
<td>0.25</td>
<td>(63)</td>
<td>3.7:1</td>
<td>81:12:10</td>
</tr>
<tr>
<td>2(^d)</td>
<td>dppb</td>
<td>0.25</td>
<td>(46)</td>
<td>3.2:1</td>
<td>76:6:18</td>
</tr>
<tr>
<td>3(^d)</td>
<td>dppf</td>
<td>0.25</td>
<td>(67)</td>
<td>4.6:1</td>
<td>82:2:16</td>
</tr>
<tr>
<td>4(^d)</td>
<td>BINAP</td>
<td>0.25</td>
<td>(53)</td>
<td>8.1:1</td>
<td>89:0:11</td>
</tr>
<tr>
<td>5(^d,e)</td>
<td>BINAP</td>
<td>0.5</td>
<td>64</td>
<td>9:1</td>
<td>90:4:6</td>
</tr>
<tr>
<td>6(^d,e)</td>
<td>BINAP</td>
<td>1</td>
<td>80</td>
<td>10:1</td>
<td>91:3:6</td>
</tr>
<tr>
<td>7(^d,e)</td>
<td>BINAP</td>
<td>2</td>
<td>76</td>
<td>10:1</td>
<td>91:4:5</td>
</tr>
</tbody>
</table>

\(^a\) [Rh]2, ligand and base are premixed at 50 °C for 15 minutes, then substrates are added and reaction is heated at 60 °C for 3 hours. \(^b\) Yields of isolated material, NMR yields in parentheses. \(^c\) r.r. is determined from crude NMR. \(^d\) Performed by R. Huang. \(^e\) 4-ClC6H4B(OH)2 used as nucleophile.

The observation that the reaction was complete within 3 hours at 60 °C was somewhat surprising. In order to examine whether the free alcohol played a role in this rate enhancement, we looked at substrates 3.2b, 3.23 and 3.25 (Scheme 2.21). The standard substrate 3.2 was completely consumed in 3 hours. The methylated substrate 3.2b, gave partial conversion and considerable formation of unidentified byproducts, showing that the free hydroxyl group was important for the reaction. The homologated substrate 3.23 gave the product in lower yield, but complete consumption of starting material was observed. An alkyl-substituted alkyne 3.25 did not react, and the starting material could be reisolated. These control experiments indicated that the free alcohol improves the rate of the reaction considerably. The nature of this effect is not established at this point, but coordination of the heteroatom with the rhodium center is a possibility.
3.2.3 Scope Studies

During the investigation of the scope of this reaction, we found that a variety of substituents were tolerated on the aromatic ring of the propargylic substrate (Table 3.3). No strong effects of electronics on the regioselectivity were observed (entries 1, 4 and 5); however, substrates with a smaller R² substituent reacted with higher regioselectivity (entries 1, 12, 13). Notably, at reduced catalyst loading (0.5 mol% [Rh]₂) the reaction proceeded in comparable yields and slightly higher selectivity (entry 3).

A number of different arylboronic acids could be utilized giving products in high yields (Table 3.4). More electron-rich boronic acids reacted faster, but electron neutral and electron poor substituents also gave the product in high yield. Ortho-substitution was not well-tolerated, furnishing products 3.47 and 3.48 in lower yields (entries 10 and 11). With heptenylboronic acid as the nucleophile, a mixture of two isomers 3.49a and 3.49b was obtained (entry 12). An interesting feature of rhodium-catalyzed arylation of alkynes was the incompatibility with ortho-halogenated arylboronic acids 3.50 (Eqn 3.7). The presence of the aryl or heteroaryl group was essential for a clean reaction, and when we utilized 2-pentyne-1-ol as a substrate a complex mixture of products was observed and only a 35% yield of regioisomeric products could be isolated (r. r. of 1:1.8).

---

We also observe this in arylation of propargylamine substrates.
Table 3.3 Effect of propargylic alcohol structure on arylation reaction.\(^a\)

\[
\begin{align*}
\text{Ar}^1 & \text{R}^2 & \text{Product} & \text{Time (h)} & \text{Yield (%)} & \text{r. r.}^c \\
1 & \text{C}_6\text{H}_5 & \text{H} & 3.27 & 3 & 70 & 20:1 \\
2 & \text{C}_6\text{H}_5 & \text{Me} & 3.16 & 3 & 84 & 9:1 \\
3^{d} & \text{C}_6\text{H}_5 & \text{Me} & 3.16 & 16 & 73 & 14:1 \\
4 & 4\text{-MeOC}_6\text{H}_4 & \text{Me} & 3.28 & 3 & 91 & 10:1 \\
5 & 4\text{-F}_3\text{CC}_6\text{H}_4 & \text{Me} & 3.29 & 3 & 87 & 12:1 \\
6^{e} & 3,5\text{-MeO}_2\text{C}_6\text{H}_3 & \text{Me} & 3.30 & 3 & 93 & 16:1 \\
7^{e} & 4\text{-Me}_2\text{NC}_6\text{H}_4 & \text{Me} & 3.31 & 3 & 70 & 10:1 \\
8^{e} & 3,5\text{-Me}_2\text{C}_6\text{H}_3 & \text{Me} & 3.32 & 3 & 83 & 19:1 \\
9^{e,f} & \text{Me} & 3.33 & 3 & 73 & 7:1 \\
10^{e,f} & \text{Me} & 3.34 & 3 & 76 & 7:1 \\
11^{e} & 2\text{-MeOC}_6\text{H}_4 & \text{Me} & 3.35 & 3 & 74 & \text{>20:1} \\
12^{e} & 4\text{-F}_3\text{CC}_6\text{H}_4 & \text{H} & 3.36 & 19 & 71 & \text{>20:1} \\
13^{e} & 4\text{-Ac}_6\text{H}_4 & \text{H} & 3.37 & 7.5 & 75 & \text{>20:1} \\
14^{e} & 3,5\text{-MeO}_2\text{C}_6\text{H}_3 & \iPr & 3.38 & 3 & 73 & 10:1 \\
\end{align*}
\]

\(^a\) See Table 3.2 for reaction conditions. \(^b\) Isolated yield of major regioisomer. \(^c\) r.r. determined from crude NMR; r.r = β product/(α product + ketoene). \(^d\) Reaction conditions: [Rh]_2 (0.5 mol%), BINAP (1 mol%), K_2CO_3 (1.1 equiv) were mixed at 50 °C for 15 minutes. Alkyne and boronic acid (1.5 equiv) were added and the reaction was heated to 60 °C for 16 hours. 0.5 M concentration. \(^e\) Performed by R. Huang. \(^f\) Reactions run at 75 °C.

\[\text{Ar}^1 \text{R}^2 + \text{Ph-}B(\text{OH})_2 \xrightarrow{[\text{Rh}(\text{cod})\text{OH}]_2 (2 \text{ mol}\%)} \text{BINAP (4 \text{ mol}\%)} \xrightarrow{\text{K}_2\text{CO}_3 (1.1 \text{ equiv})} \text{Ph} \]

\[\text{Ar}^1 \text{R}^2 \text{OH} + \text{X} \xrightarrow{[\text{Rh}(\text{COD})\text{OH}]_2 (2 \text{ mol}\%)} \text{BINAP (4 \text{ mol}\%)} \xrightarrow{\text{K}_2\text{CO}_3 (1.1 \text{ equiv})} \text{Ph} \]

\[\text{X} = \text{Cl}, \text{Br} \]

\[\text{3.1} + \text{3.50} \rightarrow \text{3.51} \]
Table 3.4  Effect of boronic acid variation on arylation reaction.\textsuperscript{a}

\[
\begin{array}{cccc}
\text{Entry} & \text{R}^1 & \text{Ar}^2 & \text{Product} & \text{Yield (\%)}^b & \text{r. r.}^c \\
1 & \text{H} & 4\text{-Me-3-MeOC}_6\text{H}_3 & \text{3.39} & 84 & 7.5:1 \\
2^d & \text{4-Me} & 3,4\text{-MeO}_2\text{C}_6\text{H}_3 & \text{3.40} & 73 & 8:1 \\
3 & \text{4-MeO} & 3,4\text{-MeO}_2\text{C}_6\text{H}_3 & \text{3.41} & 91 & 10:1 \\
4^e & \text{3,5-MeO}_2 & 4\text{-TBSOC}_6\text{H}_4 & \text{3.42} & 81 & 17:1 \\
5 & \text{3-MeO} & \text{3-thiophenyl} & \text{3.43} & 70 & >20:1 \\
6 & \text{H} & 4\text{-ClC}_6\text{H}_4 & \text{3.44} & 87 & 13:1 \\
7 & \text{4-Me} & 4\text{-ClC}_6\text{H}_4 & \text{3.45} & 80 & 10:1 \\
8 & \text{H} & 3\text{-O}_2\text{NC}_6\text{H}_4 & \text{3.46} & 83 & 16:1 \\
9 & \text{H} & 2\text{-FC}_6\text{H}_4 & \text{3.47} & 77 & >20:1 \\
10^e & \text{H} & 2\text{-MeC}_6\text{H}_4 & \text{3.48} & 60 & 13:1 \\
11 & \text{H} & \text{E-CH=CHC}_5\text{H}_11 & \text{3.49ab} & 66^g & 1.8:1 \\
\end{array}
\]

\textsuperscript{a} See Table 3.2 for reaction conditions. \textsuperscript{b} Isolated yield of major regioisomer. \textsuperscript{c} r.r. determined from crude NMR, r.r = \(\beta\) product:(\(\alpha\) product+ketone). \textsuperscript{d} see Table 3.3 subscript \(d\) for reaction conditions. \textsuperscript{e} Performed by R. Huang. \textsuperscript{f} \(\text{R}^2 = \text{H}\), reactions run at 80 \(^\circ\text{C}\). \textsuperscript{g} Combined yield for two regioisomers.

3.3 Applications to the Syntheses of Indenes

With a convenient, stereo- and regioselective synthesis of substituted allylic alcohols in hand, we envisioned that the appended alcohol moiety could react in a 4\(\pi\) electrocyclization (or an intramolecular Friedel-Crafts alkylation) under acidic conditions to give indenes (Eqn 3.8).\textsuperscript{16} The vast majority of related literature examples utilize benzylic or doubly benzylic alcohols to facilitate carboxylation formation and unsubstituted or alkyl-substituted allylic alcohols generally

give poor results. Furthermore, typically only very electron rich aryl groups react in these cyclizations.

\[
\begin{array}{c}
\text{R}^2 \text{Ar} \quad \text{H}^+ \text{ or Lewis acid} \quad \text{R}^1 \\
3.52 \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad 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\quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad 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3.3.1 Optimization and Scope Studies

In order to effect this transformation, we screened several Bronsted and Lewis acids in catalytic and stoichiometric amounts. Some of these acids have been used for related cyclizations.\textsuperscript{16} With
substrate 3.45 we found that most strong acids led to formation of an inseparable mixture of products, including the desired indene 3.54 and an elimination byproduct 3.55. The highest NMR yield we were able to obtain was 23%, but the compound could not be isolated in high purity.

Table 3.5 Optimization of the 4π electrocyclization reaction.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Solvent</th>
<th>Time</th>
<th>(3.54^b)</th>
<th>(3.55^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{H}_3\text{PO}_4) (2.2 equiv)</td>
<td>DCM</td>
<td>72 h</td>
<td>No reaction</td>
<td></td>
</tr>
<tr>
<td>2(^c)</td>
<td>(p)-TsOH (10 mol%)</td>
<td>MeCN</td>
<td>72 h</td>
<td>0%</td>
<td>58%</td>
</tr>
<tr>
<td>3(^c)</td>
<td>TFOH (10 mol%)</td>
<td>DCM</td>
<td>1 h</td>
<td>0%</td>
<td>41%</td>
</tr>
<tr>
<td>4(^c)</td>
<td>BF(_3).Et(_2)O (50 mol%)</td>
<td>DCM</td>
<td>3 h</td>
<td>11%</td>
<td>1.2%</td>
</tr>
<tr>
<td>5(^c)</td>
<td>BF(_3).Et(_2)O (2 equiv)</td>
<td>DCM</td>
<td>1 h</td>
<td>20%</td>
<td>0%</td>
</tr>
<tr>
<td>6(^c,d)</td>
<td>BF(_3).Et(_2)O (4 equiv)</td>
<td>DCM</td>
<td>5 min</td>
<td>23%</td>
<td>0%</td>
</tr>
</tbody>
</table>

\(^a\) Substrate was weighed into a vial, solvent was added, acid was added. Reaction was stirred under air for the indicated time. \(^b\) NMR yields based on 1,3,5-trimethoxybenzene as internal standard. \(^c\) Performed by R. Huang. \(^d\) Reaction carried out at 0 °C.

In order to further stack the odds in our favor, we selected a more electron rich substrate 3.41 (Eqn 3.9). We found that phosphoric acid, which did not afford any conversion in the prior example, gave a clean reaction, albeit over a very long reaction time.

When we looked at several other substrates, we found that higher yields could be obtained in a shorter reaction time if the solvent was switched to 1,2-dichloroethane, and the reaction was conducted at 80 °C (Table 3.6). Remarkably, the transformation remained selective even at elevated temperatures. As expected, electron rich compounds cyclized faster; however, substrates with electron neutral substituents or unsubstituted substrates still reacted in high yield under these conditions (entries 9, 10, 11). The presence of electron donating groups on either aromatic ring improved the reaction rate (entries 7 and 8). Notably, the reaction still furnished
the desired product 3.68 with a nitro substituent (entry 12). A substrate bearing a primary alcohol cyclized very efficiently to give 3.67 under these conditions (entry 11). A phenolic TBS group was tolerated in 3.59, even though acidic conditions are commonly used to cleave this protecting group (entry 2), demonstrating the relatively mild nature of these biphasic conditions.

### 3.4 Applications to the Synthesis of Quinolines

Considering the importance of nitrogen-containing heterocycles in the pharmaceutical industry we were also interested in converting our allylic alcohol products to quinolines. To effect this annulation an O-acetyloxime group was installed after oxidation of the alcohols to the ketones to yield 3.70 (Eqn 3.10).

\[
\begin{align*}
\text{MePhO}H & \quad \text{Ar} \quad \text{DMP or MnO}_2 \quad \text{79 - 84\%} \quad \text{MePhO}C \quad \text{Ar} \\
\text{MePhO}C & \quad \text{Ar} \quad \text{NH}_2\text{OH}+\text{HCl (4 equiv)} \quad \text{NaOAc (4 equiv), MeOH} \quad \text{MePhO}N \quad \text{Ar} \\
\text{MePhO}N & \quad \text{Ar} \quad \text{AcCl, NEt}_3, \text{DCM} \quad \text{45 - 93\%} \quad \text{MePhO}N \quad \text{Ar} \\
\end{align*}
\]

(3.10)

We initially examined palladium-catalyzed cyclizations of 3.70 based on a report by Hartwig. However, we observed that the formation of quinoline occurred in the absence of palladium, under thermal conditions. Heating the O-acetyloximes in either toluene or dioxane at 150 °C afforded the desired quinoline products 3.71. 6π-Electrocyclizations of methyl and acetyl-oximes are known to occur under irradiation, although most examples feature cyclic substrates to force the substrates into an s-cis configuration, which facilitates the cyclization. Since the arylation reaction provides products with defined stereochemistry at the alkene, irradiation is not necessary for alkene isomerization, and the electrocyclization can occur under thermal conditions (Table 3.7). We found that electron neutral and electron poor substrates provided the highest yields, but product was also obtained with an electron rich substrate in modest yield.

---


Table 3.6: Scope of indene products

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Product</th>
<th>T (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;&lt;sup&gt;d&lt;/sup&gt;</td>
<td><img src="image1" alt="Product Image" /></td>
<td>3.58</td>
<td>r.t.</td>
<td>240</td>
<td>91</td>
</tr>
<tr>
<td>2&lt;sup&gt;d&lt;/sup&gt;</td>
<td><img src="image2" alt="Product Image" /></td>
<td>3.58</td>
<td>80</td>
<td>16</td>
<td>90</td>
</tr>
<tr>
<td>3&lt;sup&gt;d&lt;/sup&gt;</td>
<td><img src="image3" alt="Product Image" /></td>
<td>3.59</td>
<td>80</td>
<td>22</td>
<td>78</td>
</tr>
<tr>
<td>4&lt;sup&gt;e&lt;/sup&gt;&lt;sup&gt;d&lt;/sup&gt;</td>
<td><img src="image4" alt="Product Image" /></td>
<td>3.60</td>
<td>r.t.</td>
<td>17</td>
<td>69</td>
</tr>
<tr>
<td>5&lt;sup&gt;d&lt;/sup&gt;</td>
<td><img src="image5" alt="Product Image" /></td>
<td>3.61</td>
<td>80</td>
<td>15</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6" alt="Product Image" /></td>
<td>3.62</td>
<td>80</td>
<td>15</td>
<td>82</td>
</tr>
<tr>
<td>7&lt;sup&gt;d&lt;/sup&gt;</td>
<td><img src="image7" alt="Product Image" /></td>
<td>3.63</td>
<td>80</td>
<td>50</td>
<td>87</td>
</tr>
<tr>
<td>8&lt;sup&gt;d&lt;/sup&gt;</td>
<td><img src="image8" alt="Product Image" /></td>
<td>3.64</td>
<td>80</td>
<td>16</td>
<td>82</td>
</tr>
<tr>
<td>9&lt;sup&gt;e&lt;/sup&gt;</td>
<td><img src="image9" alt="Product Image" /></td>
<td>3.56</td>
<td>r.t.</td>
<td>80</td>
<td>66</td>
</tr>
<tr>
<td>10&lt;sup&gt;d&lt;/sup&gt;</td>
<td><img src="image10" alt="Product Image" /></td>
<td>3.65</td>
<td>80</td>
<td>40</td>
<td>80</td>
</tr>
<tr>
<td>11&lt;sup&gt;d&lt;/sup&gt;</td>
<td><img src="image11" alt="Product Image" /></td>
<td>3.66</td>
<td>80</td>
<td>40</td>
<td>74</td>
</tr>
<tr>
<td>12&lt;sup&gt;e&lt;/sup&gt;</td>
<td><img src="image12" alt="Product Image" /></td>
<td>3.67</td>
<td>80</td>
<td>44</td>
<td>88</td>
</tr>
<tr>
<td>13&lt;sup&gt;d&lt;/sup&gt;</td>
<td><img src="image13" alt="Product Image" /></td>
<td>3.68</td>
<td>80</td>
<td>44</td>
<td>65</td>
</tr>
</tbody>
</table>

<sup>a</sup> Conditions: H<sub>3</sub>PO<sub>4</sub> (85%) was added to a solution of alcohol in 1,2-dichloroethane. The reaction was monitored by TLC. <sup>b</sup> Isolated yields. <sup>c</sup> Dichloromethane used as a solvent. <sup>d</sup> Performed by R. Huang.
Table 3.7: Synthesis of quinolines

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.70</td>
<td>3.71</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PhMe, 150 °C</td>
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<tr>
<td>3.71a</td>
<td>68%</td>
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<tr>
<td>3.71b</td>
<td>55%</td>
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<tr>
<td>3.71c</td>
<td>79%</td>
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<tr>
<td>3.71d</td>
<td>73%</td>
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</table>

*Conditions: Starting material (0.1 mmol) was placed in a microwave tube, toluene was added (1 ml). The vial was sealed with a Teflon lined septum and placed in a 150 °C oil bath. Isolated yields.*

3.5 Conclusions

The preceding chapter described the development of a rhodium-catalyzed arylation of unprotected aryl propargyl alcohols. The utility of these synthons was showcased in a quick synthesis of indenes and a 3-step construction of quinolines. Both of these motifs are privileged, and are present in a variety of natural products, pharmaceuticals, and useful reagents. Synthetic strategies that forego the use of protecting groups are extremely valuable since the number of synthetic steps is reduced by two. To establish such reactions, very mild and robust reagents and catalysts need to be utilized. Rhodium-catalyzed reactions fit these requirements. Further efforts in our group are dedicated to exploring the potential of rhodium catalysis in a synthesis of other functionalized building blocks.
3.6 Experimental Section

General Experimental Procedures. Unless otherwise noted, reactions were carried out under argon atmosphere, in flame-dried, single-neck, round bottom flasks fitted with a rubber septum, with magnetic stirring. Air- or water-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Where necessary (so noted), solutions were deoxygenated by successive freeze-pump-thaw cycles (≥ three iterations). Organic solutions were concentrated by rotary evaporation at 23–40 °C under 40 Torr (house vacuum). Analytical thin layer chromatography (TLC) was performed with Silicycle™ normal phase glass plates (0.25 mm, 60-A pore size, 230-400 mesh). Visualization was done under a 254 nm UV light source and generally by immersion in acidic aqueous-ethanolic vanillin solution, or in potassium permanganate (KMnO₄), followed by heating using a heat gun. Purification of reaction products was generally done by flash chromatography with Silicycle™ Ultra-Pure 230-400 mesh silica gel, as described by Still et al.²⁰

Materials. Unless otherwise indicated, starting materials and catalysts were obtained from Aldrich, Strem or VWR and used without further purification. Tetrahydrofuran, 1,4-dioxane and toluene were purified by distillation under N₂ from Na/benzophenone immediately prior to use.

Instrumentation. Proton nuclear magnetic resonance spectra (¹H NMR) and carbon nuclear magnetic resonance spectra (¹³C NMR) were recorded at 23 °C with a Bruker Avance III 400 (400 MHz/100 MHz) NMR spectrometer equipped with a ATM BBOF probe, a Varian Mercury 400 (400 MHz/100 MHz) NMR spectrometer equipped with a Nalorac4N-400 probe, a Varian Unity 500 (500 MHz/125 MHz) NMR spectrometer equipped with a Nalorac3-500 probe, or a Varian 400 (400 MHz/100 MHz) NMR spectrometer equipped with ATB8123-400 probe. Recorded shifts for protons are reported in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvents (CHCl₃: δ 7.26, CHDCI₂: δ 5.29, C₆HD₅: δ 7.15, CD₃HOD: δ 3.30). Chemical shifts for carbon resonances are reported in parts per million (δ scale) downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent (CDCl₃: δ 77.0, CH₂Cl₂: δ 53.8, C₆D₆: δ 128.0, CD₃OD: δ 49.2). Data are represented as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintuplet, sx = sextet, sp = septuplet, dd = doublet of doublets, m = multiplet, br = broad), and coupling constant (J, Hz); ap t (apparent triplet) and ap td or ap dt (apparent doublet of triplets) imply a doublet of doublets with identical coupling constant instead of a true triplet. Infrared (IR) spectra were obtained using a Perkin-Elmer Spectrum 1000 FT-IR spectrometer as a neat film on a NaCl plate. Data is presented as follows: frequency of absorption (cm⁻¹). High resolution mass spectra were obtained from a SI2

Micromass 70S-250 mass spectrometer (EI) or an ABI/Sciex Qstar mass spectrometer (ESI). Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected.

3.6.1 Characterization Data

**1-Iodo-3,5-dimethoxybenzene**

The titled compound was synthesized via a modified literature procedure.\(^{21}\) A suspension of 3,5-dimethoxyaniline (4.69 g, 30 mmol) in distilled \(\text{H}_2\text{O}\) (50 mL) was cooled in an ice-salt bath, and a thermal probe inserted to monitor internal temperature. To this suspension was slowly added 98% sulfuric acid (4.5 mL, 8.11 g, 82.7 mmol, 2.76 equiv). A solution of \(\text{NaNO}_2\) (2.43 g, 35.2 mmol, 1.17 equiv) in 10 mL \(\text{H}_2\text{O}\) was added slowly via syringe over a period of 15 minutes. The deep red solution was stirred at –3 to –5 °C for 30 minutes, then 25 mL of \(\text{Et}_2\text{O}\) was added. A solution of KI (15.09 g, 90.9 mmol, 3.03 equiv) in 15 mL \(\text{H}_2\text{O}\) was added via syringe over 30 minutes at such a rate that kept internal temperature around 1-2 °C. Following complete addition, the reaction mixture was stirred for a further 3 hours at 0 °C. The crude was then poured into a separatory funnel, washed with saturated \(\text{Na}_2\text{S}_2\text{O}_3\) solution, and the aqueous washings extracted with EtOAc (3 x 100 mL). The organics were pooled, washed successively with saturated \(\text{Na}_2\text{S}_2\text{O}_3\) solution and brine, dried over \(\text{MgSO}_4\), and concentrated under reduced pressure. Purification by flash chromatography (hexanes:EtOAc 15:1) gave the title compound as a white flaky solid (7.149 g, 90% yield). The characterization data is consistent with literature.\(^{1}\) \(\text{M.p.}\) 73-74 °C; \(^1\text{H NMR}\) (400 MHz, \(\text{CDCl}_3\)) \(\delta\) 6.86 (d, \(J = 2.3\) Hz, 2H), 6.41 (t, \(J = 2.2\) Hz, 1H), 3.76 (s, 6H); \(^{13}\text{C NMR}\) (100 MHz, \(\text{CDCl}_3\)) \(\delta\) 161.2, 115.9, 100.8, 94.2, 55.6.

**Procedure 3.1: Sonogashira coupling of propargyl alcohols:** To a round bottom flask was added \(\text{Pd(PPh}_3\text{)}_2\text{Cl}_2\) and CuI. The flask was purged with \(\text{N}_2\) for 5 minutes, and \(\text{Et}_3\text{N}\) was transferred via cannula under \(\text{N}_2\). The aryl halide was then added, followed by the alkyne. The reaction mixture was stirred at room temperature or heated as necessary, and the reaction progress monitored by TLC. Upon completion, the crude mixture was filtered through a medium frit, the solid residue washed with \(\text{Et}_3\text{N}\), and the combined organics were concentrated under reduced pressure. Purification via flash column chromatography yielded the desired aryl propargyl alcohols.

**3-Phenylprop-2-yn-1-ol (3.1)**

According to the general procedure, \(\text{Pd(PPh}_3\text{)}_2\text{Cl}_2\) (280.8 mg, 0.4 mmol, 1 mol%) and CuI (152.4 mg, 0.8 mmol, 2 mol%) were suspended in \(\text{Et}_3\text{N}\) (160

mL) under N₂. Iodobenzene (4.55 mL, 8.16 g, 40 mmol) was added, followed by propargyl alcohol (2.63 mL, 2.47 g, 44 mmol, 1.1 equiv), and the reaction was stirred at room temperature for 5 hours. Subsequent workup and column chromatography (hexanes:EtOAc 7:3) yielded the title compound as an orange oil in quantitative yield. The characterization data is consistent with literature.

\[ ^1H \text{ NMR} (400 \text{ MHz, } CDCl_3) \delta 7.46 - 7.42 \text{ (m, 2H)}, 7.33 - 7.28 \text{ (m, 3H)}, 4.50 \text{ (s, 2H)}, 2.21 \text{ (br s, OH);} \]

\[ ^13C \text{ NMR} (100 \text{ MHz, } CDCl_3) \delta 131.8, 128.6, 128.4, 122.6, 87.4, 85.8, 51.7. \]

**4-Phenylbut-3-yn-2-ol (3.2)**

According to the general procedure 3.1, Pd(PPh₃)₂Cl₂ (0.2 mmol, 1 mol%) and CuI (0.4 mmol, 2 mol%) were suspended in Et₃N (160 mL) under N₂. Iodobenzene (4.08 g, 20 mmol) was added, followed by propargyl alcohol (1.24 g, 22 mmol, 1.1 equiv), and the reaction was stirred at room temperature for 5 hours. Subsequent workup and column chromatography (hexanes:EtOAc 7:3) yielded the title compound as an orange oil in 97% yield. The analytical data was consistent with literature.

\[ ^1H \text{ NMR} (400 \text{ MHz, } CDCl_3) \delta 7.48 - 7.37 \text{ (m, 2H), 7.30 (m, 3H), 4.76 (q, } J = 6.6 \text{ Hz, 1H), 2.02 (s, 1H), 1.56 (d, } J = 6.6 \text{ Hz, 3H).} \]

**3-(3-Methoxybut-1-ynyl)benzene (3.2b)**

Sodium hydride (205 mg, 1.5 equiv) was suspended in THF (5 ml) at 0 °C. A solution of 3.2 (500 mg, 3.42 mmol) in THF (5 ml) was added dropwise. The reaction was stirred for 30 minutes at 0 °C, then iodomethane (1.5 equiv, 5.13 mmol) was added dropwise. The reaction was allowed to warm to room temperature and was monitored by TLC. Upon full conversion the reaction was quenched with water, and extracted with ethyl acetate, washing with water and brine. The reaction crude was purified via column chromatography (95:5 pentane:EtOAc) to yield the titled compound as a colorless oil in 87% yield. The analytical data was consistent with literature.

\[ ^1H \text{ NMR} (400 \text{ MHz, } CDCl_3) \delta 7.48 - 7.40 \text{ (m, 2H), 7.31 (m, 3H), 4.31 (q, } J = 6.6 \text{ Hz, 1H), 3.47 (s, 3H), 1.52 (d, } J = 6.6 \text{ Hz, 3H).} \]

**4-(4-Methoxyphenyl)but-3-yn-2-ol (3.3)**

According to the general procedure 3.1, Pd(PPh₃)₂Cl₂ (0.2 mmol, 1 mol%) and CuI (0.4 mmol, 2 mol%) were suspended in Et₃N (160 mL) under N₂. 1-Iodo-4-methoxybenzene (4.68 g, 20 mmol) was added, followed by propargyl alcohol (1.24 g, 22 mmol, 1.1 equiv), and the reaction was stirred at room temperature for 5 hours. Workup of the reaction mixture and column chromatography (pentane:EtOAc 5:1) yielded the title compound as an orange oil in quantitative yield. The characterization data is consistent with literature.

\[ ^1H \text{ NMR} (400 \text{ MHz, } CDCl_3) \delta 7.46 - 7.37 \text{ (m, 2H), 7.30 (m, 3H), 4.50 (s, 2H), 2.21 (br s, OH);} \]

\[ ^13C \text{ NMR} (100 \text{ MHz, } CDCl_3) \delta 131.8, 128.6, 128.4, 122.6, 87.4, 85.8, 51.7. \]

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temperature for 16 hours. Subsequent workup and column chromatography (hexanes:EtOAc 7:3) yielded the title compound as a yellow oil in 80% yield. The analytical data was consistent with literature.\(^{25}\) \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) δ 7.36 (d, \(J = 8.8\) Hz, 2H), 6.82 (d, \(J = 8.8\) Hz, 2H), 4.74 (q, \(J = 6.4\) Hz, 1H), 3.80 (s, 3H), 2.10 (s, 1H), 1.54 (d, \(J = 6.6\) Hz, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) δ 159.9, 133.3, 114.9, 114.1, 89.8, 84.1, 59.1, 55.5, 24.7.

4-(4-(Trifluoromethyl)phenyl)but-3-yn-2-ol (3.4)

According to the general procedure 3.1, Pd(PPh\(_3\))\(_2\)Cl\(_2\) (0.2 mmol, 1 mol%) and CuI (0.4 mmol, 2 mol%) were suspended in Et\(_3\)N (160 mL) under N\(_2\). 1-Bromo-4-(trifluoromethyl)benzene (2.76 ml, 20 mmol) was added, followed by propargyl alcohol (1.24 g, 22 mmol, 1.1 equiv), and the reaction was stirred at 80 °C for 16 hours. Subsequent workup and column chromatography (hexanes:EtOAc 8:2) yielded the title compound as an orange oil in 84% yield. \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) δ 7.56 (d, \(J = 8.2\) Hz, 2H), 7.52 (d, \(J = 8.5\) Hz, 2H), 4.77 (q, \(J = 6.6\) Hz, 1H), 1.99 (m, 1H), 1.57 (d, \(J = 6.6\) Hz, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) δ 132.0 (2C), 130.3 (q, \(J = 32.7\) Hz), 126.6 (q, \(J = 1.01\) Hz), 125.4 (q, \(J = 3.9\) Hz, 2C), 124.0 (q, \(J = 273.7\) Hz), 93.5, 82.9, 58.9, 24.4; \(^{19}\)F NMR (377 MHz, CDCl\(_3\)) δ -63.9; IR (NaCl, neat): 3345, 2986, 2936, 2878, 1615, 1404, 1373, 1324, 1169, 1128, 1105, 1068, 1037, 1017, 935, 842 cm\(^{-1}\); HRMS (EI): calcd for C\(_{11}\)H\(_9\)O\(_3\)F\(_3\) (M\(^+\)): 214.0605; found: 214.0603.

4-(3,5-Dimethoxyphenyl)but-3-yn-2-ol (3.5)

This compound was synthesized by R. Huang according to the general procedure 3.1, Pd(PPh\(_3\))\(_2\)Cl\(_2\) (140.4 mg, 0.2 mmol, 1 mol%) and CuI (76.2 mg, 0.4 mmol, 2 mol%) were suspended in Et\(_3\)N (80 mL) under N\(_2\). 1-iodo-3,5-dimethoxybenzene (5.28 g, 20 mmol) was added, followed by 3-butyn-2-ol (1.72 mL, 1.54 g, 22 mmol, 1.1 equiv), and the reaction was heated to 70 °C. After 4.5 hours, additional Pd(PPh\(_3\))\(_2\)Cl\(_2\) (140.4 mg, 0.2 mmol, 1 mol%), CuI (76.2 mg, 0.4 mmol, 2 mol%), and 3-butyn-2-ol (0.32 mL, 0.286 g, 4 mmol, 0.2 equiv) was added under N\(_2\), and the temperature increased to 80 °C. The reaction was worked up after an additional 2 hours at 80 °C. Purification via column chromatography (hexanes:EtOAc 6:4) yielded the title compound as a red-orange oil (2.93 g, 71% yield). \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) δ 6.58 (d, \(J = 2.3\) Hz, 2H), 6.43 (t, \(J = 2.3\) Hz, 1H), 4.78 – 4.71 (m, 1H), 3.76 (s, 6H), 2.15 (d, \(J = 5.2\) Hz, OH), 1.55 (d, \(J = 6.6\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 160.6, 124.0, 109.6, 102.0, 90.7, 84.1, 58.9, 55.5, 24.5; IR (NaCl, neat): 3383, 2980, 2934, 2910, 2875, 2839, 2226, 1597, 1448, 1419, 1320, 1300, 1251, 1207, 1175, 1156, 1106, 1064, 1035, 990, 978, 928, 894, 834, 787, 682 cm\(^{-1}\); HRMS (EI): calcd for C\(_{12}\)H\(_{14}\)O\(_3\) (M\(^+\)): 206.0943; found: 206.0941.

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4-(4-(Dimethylamino)phenyl)but-3-yn-2-ol (3.6)

The title compound was synthesized via a modified procedure.\textsuperscript{26} To a round bottom flask was successively added Pd(OAc)\textsubscript{2} (33.7 mg, 0.15 mmol, 3 mol%), CuI (19 mg, 0.1 mmol, 2 mol%), dicyclohexylamine (1.2 mL, 1.092 g, 6 mmol, 1.2 equiv), and THF (5 mL). P(\(t\)-Bu)\textsubscript{3}HBF\textsubscript{4} (87 mg, 0.3 mmol, 6 mol%) was then added, the flask purged with N\textsubscript{2} for 10 minutes, and stirred at 30 °C for 40 minutes. 4-bromo-\(N_2\),\(N\)-dimethylaniline (1 g, 5 mmol) and 3-butyn-2-ol (0.47 mL, 0.42 g, 6 mmol, 1.2 equiv) were added, and the reaction mixture was stirred at 30 °C. The mixture solidified into a paste overnight, and additional THF (10 mL) was added to redissolve the paste. After stirring at 30 °C for 4 days, the reaction was diluted with EtOAc, then successively washed with saturated NH\textsubscript{4}Cl solution and brine. The aqueous layer was extracted with EtOAc x 2, the organics were combined, washed with brine, dried over MgSO\textsubscript{4}, and concentrated under reduced pressure. Purification by way of column chromatography (hexanes:EtOAc 7:3) yielded the title compound as a dark orange solid (474.2 mg, 50% yield). M.p. 55-56 °C; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.30 (d, \(J = 9.0\) Hz, 2H), 6.61 (d, \(J = 9.0\) Hz, 2H), 4.78 – 4.72 (m, 1H), 2.97 (s, 6H), 1.86 (d, \(J = 5.1\) Hz, OH), 1.54 (d, \(J = 6.6\) Hz, 3H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 150.3, 132.9, 111.9, 109.5, 88.9, 85.1, 59.2, 40.4, 24.8; IR (NaCl, neat): 3341, 2924, 2855, 2808, 2222, 1609, 1520, 1443, 1358, 1227, 1188, 1099, 945, 930, 814 cm\textsuperscript{-1}; HRMS (ESI): calcd for C\textsubscript{12}H\textsubscript{16}NO (M+H\textsuperscript{+}): 190.1226; found: 190.1228.

4-(3,5-Dimethylphenyl)but-3-yn-2-ol (3.7)

This compound was synthesized by R. Huang according to the general procedure 3.1, Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2} (143 mg, 0.2044 mmol, 1 mol%) and CuI (77.6 mg, 0.408 mmol, 2 mol%) were suspended in Et\textsubscript{3}N (80 mL) under N\textsubscript{2}. 5-iodo-\textit{m}-xylene (3 mL, 4.73 g, 20.37 mmol) was added, followed by 3-butyn-2-ol (1.76 mL, 1.573 g, 22.41 mmol, 1.1 equiv) and the reaction was stirred at room temperature for 4 hours. Subsequent workup and column chromatography (hexanes:EtOAc 8:2) yielded the title compound as a clear yellow oil in quantitative yield. The characterization data is consistent with literature.\textsuperscript{27} \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.06 (s, 2H), 6.95 (s, 1H), 4.78 – 4.71 (m, 1H), 2.28 (s, 6H), 1.95 (d, \(J = 4.9\) Hz, OH), 1.54 (d, \(J = 6.6\) Hz, 3H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 138.0, 130.4, 129.5, 122.3, 90.4, 84.4, 59.0, 24.6, 21.2.

\textsuperscript{26} Shin, M.; Hideyuiki, I. Int. App. PCT/JP2004/017628, 2004
4-(Thiophen-2-yl)but-3-yn-2-ol (3.8)

This compound was synthesized by R. Huang according to the general procedure 3.1, Pd(PPh₃)2Cl₂ (70.2 mg, 0.1 mmol, 0.5 mol%) and CuI (38.1 mg, 0.2 mmol, 1 mol%) were suspended in Et₃N (80 mL) under N₂. 2-bromothiophene (1.98 mL, 3.268 g, 20 mmol) was added, followed by 3-butyn-2-ol (1.65 mL, 1.475 g, 21 mmol, 1.05 equiv), and the reaction heated to 45 °C for 20 hours. Subsequent workup and column chromatography (hexanes:EtOAc 8:2) yielded the title compound as a yellow-orange oil (2.038 g, 67% yield). The characterization data is consistent with literature.

1H NMR (400 MHz, CDCl₃) δ 7.24 (dd, J = 5.2, 1.1 Hz, 1H), 7.19 (dd, J = 3.6, 1.0 Hz, 1H), 6.96 (dd, J = 5.1, 3.6 Hz, 1H), 4.76 (q, J = 6.6 Hz, 1H), 2.18 (br s, OH), 1.54 (d, J = 6.6 Hz, 3H); 13C NMR (100 MHz, CDCl₃) δ 132.3, 127.4, 127.1, 122.6, 94.9, 77.5, 59.1, 24.3.

4-(Thiophen-3-yl)but-3-yn-2-ol (3.9)

This compound was synthesized by R. Huang according to the general procedure 3.1, Pd(PPh₃)2Cl₂ (140.4 mg, 0.2 mmol, 1 mol%) and CuI (76.2 mg, 0.4 mmol, 2 mol%) were suspended in Et₃N (85 mL) under N₂. 3-bromothiophene (1.95 mL, 3.255 g, 20 mmol) was added, followed by 3-butyn-2-ol (1.65 mL, 1.475 g, 21 mmol, 1.05 equiv). A reflux condenser was attached, and the reaction was refluxed at 90 °C. After 24 hours, additional Pd(PPh₃)2Cl₂ (70.2 mg, 0.1 mmol, 0.5 mol%) and CuI (38.1 mg, 0.2 mmol, 1 mol%) were added. The reaction was worked up after 36 hours. Purification by column chromatography (hexanes:EtOAc 8:2) gave the title compound as a red oil (1.234 g, 41% yield). 1H NMR (400 MHz, CDCl₃) δ 7.43 (dd, J = 3.0, 1.1 Hz, 1H), 7.26 (dd, J = 5.0, 3.0 Hz, 1H), 7.10 (dd, J = 5.0, 1.1 Hz, 1H), 4.77 – 4.71 (m, 1H), 1.97 (d, J = 5.3 Hz, OH), 1.54 (d, J = 6.6 Hz, 3H); 13C NMR (100 MHz, CDCl₃) δ 130.0, 129.0, 125.5, 121.7, 90.7, 79.4, 59.0, 24.5; IR (NaCl, neat): 3333, 3105, 2982, 2931, 2874, 2234, 1519, 1358, 1327, 1180, 1103, 1076, 1038, 964, 972, 868, 841, 625 cm⁻¹; HRMS (EI): calcd for C₈H₈OS (M⁺): 152.0296; found: 152.0290.

4-(2-Methoxyphenyl)but-3-yn-2-ol (3.10)

This compound was synthesized by R. Huang according to the general procedure 3.1, Pd(PPh₃)2Cl₂ (140.4 mg, 0.2 mmol, 2 mol%) and CuI (76.2 mg, 0.4 mmol, 4 mol%) were suspended in Et₃N (40 mL) under N₂. 2-Iodoanisole (1.33 mL, 2.34 g, 10 mmol) was added, followed by 3-butyn-2-ol (0.86 mL, 0.769 g, 11 mmol, 1.1 equiv). The reaction was heated to 70 °C for 17 hours. Subsequent workup and column chromatography (hexanes:EtOAc 7:3) yielded the title compound as a red-brown oil (1.127 g, 64% yield). 1H NMR (400 MHz, CDCl₃) δ 7.39 (dd, J = 7.6, 1.7 Hz, 1H), 7.28 (ddd, J = 8.5, 7.6, 6.8 Hz, 3H), 6.83 (t, J = 7.6 Hz, 1H), 3.83 (s, OCH₃), 2.18 (br s, OH), 1.52 (d, J = 6.8 Hz, 3H).

1.8 Hz, 1H), 6.90 (dd, J = 7.5, 1.0 Hz, 1H), 6.86 (d, J = 8.3 Hz, 1H), 4.84 – 4.78 (m, 1H), 3.87 (s, 3H), 2.22 (d, J = 5.1 Hz, 1H), 1.57 (d, J = 6.6 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 160.0, 133.9, 130.0, 120.6, 111.9, 110.8, 95.3, 80.4, 59.1, 55.9, 24.5; IR (NaCl, neat): 3372, 3075, 2982, 2936, 2874, 2839, 2230, 1597, 1574, 1497, 1466, 1435, 1369, 1330, 1261, 1234, 1180, 1161, 1123, 1099, 1076, 1049, 934, 787, 752, 694 cm⁻¹; HRMS (EI): calcd for C11H12O2: 176.0837 (M)⁺; found: 176.0842.

3-(4-(Trifluoromethyl)phenyl)prop-2-yn-1-ol (3.12)

This compound was synthesized by R. Huang according to the general procedure 3.1, Pd(PPh3)2Cl2 (74.5 mg, 0.106 mmol, 1 mol%) and CuI (40.4 mg, 0.212 mmol, 2 mol%) were suspended in Et3N (40 mL) under N2. 4-bromobenzotrifluoride (1.5 mL, 2.39 g, 10.6 mmol) was added, followed by propargyl alcohol (0.69 mL, 0.66 g, 11.7 mmol, 1.1 equiv). The reaction was heated to 60 °C for 17 hours. Subsequent workup and column chromatography (hexanes:EtOAc 7:3) yielded the title compound as waxy yellow crystals (1.8777 g, 88% yield). The characterization data is consistent with literature. M.p. 35-36 °C; 1H NMR (400 MHz, CDCl3) δ 7.56 (d, J = 8.5 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 4.52 (d, J = 5.9 Hz, 2H), 1.97 (t, J = 6.0 Hz, 1H); 13C NMR (100 MHz, CDCl3) δ 132.0, 130.4 (q, J = 32.7 Hz), 126.5 (q, J = 1.4 Hz), 125.4 (q, J = 3.8 Hz). 124.0 (q, J = 271 Hz), 89.8, 84.5, 51.7; 19F NMR (377 MHz, CDCl3) δ -63.9 (s).

1-(4-(3-Hydroxyprop-1-ynyl)phenyl)ethanone (3.13)

This compound was synthesized by R. Huang according to the general procedure 3.1, Pd(PPh3)2Cl2 (84.3 mg, 0.12 mmol, 1 mol%) and CuI (45.7 mg, 0.24 mmol, 2 mol%) were suspended in Et3N (40 mL) under N2. 4-iodoacetophenone (3.013 g, 12 mmol) was added, followed by propargyl alcohol (0.78 mL, 0.751 g, 13.2 mmol, 1.1 equiv). The reaction was stirred at room temperature for 20 minutes, by which point it became a thick paste. Additional Et3N (20 mL) was added to resuspend the paste, and the reaction was stirred for another 70 minutes at room temperature. Subsequent workup and column chromatography (hexanes:EtOAc 6:4) yielded the title compound as an off-white solid (1.983 g, 95% yield). The characterization data is consistent with literature. M.p. 76-77 °C; 1H NMR (400 MHz, CDCl3) δ 7.86 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 4.51 (s, 2H), 2.58 (s, 3H), 2.52 (br s, OH); 13C NMR (100 MHz, CDCl3) δ 197.8, 136.4, 131.9, 128.3, 127.6, 90.9, 84.8, 51.6, 26.7.

1-(3,5-Dimethoxyphenyl)-4-methylpent-1-yn-3-ol (3.15)

A flame-dried round bottom flask was charged, under N\textsubscript{2}, 1-ethynyl-3,5-dimethoxybenzene (0.94 g, 5.8 mmol) and dry THF (20 mL). After cooling to –78 °C, a solution of n-BuLi (1.53 M in hexanes) (4.17 mL, 6.38 mmol, 1.1 equiv) was added dropwise via syringe pump over 30 minutes. The solution turned maroon upon complete addition, and was stirred for a further 30 minutes at -78 °C. Then, a solution of freshly distilled isobutyraldehyde (0.58 mL, 6.38 mmol, 1.1 equiv) in dry THF (10 mL) was added over 30 minutes via syringe pump. The mixture was warmed to room temperature and stirred for 17 hours. The crude was then quenched with saturated NH\textsubscript{4}Cl solution (20 mL), and extracted with Et\textsubscript{2}O (2 x 40 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO\textsubscript{4}, and concentrated under reduced pressure. Purification by column chromatography (hexanes:EtOAc 4:1) yielded the title compound as a thick, pale-yellow oil. (0.9369 g, 69% yield).

\textit{1H NMR} (400 MHz, CDCl\textsubscript{3}) \(\delta 6.58 \text{ (d, } J = 2.3 \text{ Hz, } 2\text{H}), 6.44 \text{ (t, } J = 2.3 \text{ Hz, } 1\text{H}), 4.38 \text{ (t, } J = 5.6 \text{ Hz, } 1\text{H}), 3.77 \text{ (s, } 6\text{H}), 2.03 \text{ – } 1.91 \text{ (m, } 2\text{H}), 1.08 \text{ – } 1.04 \text{ (m, } 6\text{H}); \textit{13C NMR} (100 MHz, CDCl\textsubscript{3}) \(\delta 160.6, 124.2, 109.7, 101.9, 88.7, 85.7, 68.5, 55.5, 34.8, 18.3, 17.7; \textit{IR} (NaCl, neat): 3420, 2962, 2939, 2873, 2839, 1597, 1589, 1456, 1422, 1345, 1332, 1207, 1196, 1170, 1156, 1065, 1032, 846, 833, 682 cm\textsuperscript{-1}; \textit{HRMS} (ESI): calcd for C\textsubscript{14}H\textsubscript{19}O\textsubscript{3} (M+H)\textsuperscript{+}: 235.1334; found: 235.1345.

4-p-Tolylbut-3-yn-2-ol (3.11)

According to the general procedure 3.1, Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2} (170 mg, 0.241 mmol, 1 mol%) and CuI (92 mg, 0.482 mmol, 2 mol%) were suspended in Et\textsubscript{3}N (96 mL) under N\textsubscript{2}. 4-Iodotoluene (5.26 g, 24.1 mmol) was added, followed by 3-butyn-2-ol (2.1 mL, 1.877 g, 26.8 mmol, 1.1 equiv), and the reaction was stirred at room temperature for 5.5 hours. Subsequent workup and column chromatography (hexanes:EtOAc 8:2) yielded the title compound as a yellow oil in quantitative yield. The oil solidified upon storing at –20 °C overnight to give an off-white solid. The characterization data is consistent with literature. \textbf{M.p.} 33-34 °C; \textit{1H NMR} (400 MHz, CDCl\textsubscript{3}) \(\delta 7.32 \text{ (d, } J = 8.1 \text{ Hz, } 2\text{H}), 7.11 \text{ (d, } J = 7.8 \text{ Hz, } 2\text{H}), 4.78 \text{ – } 4.72 \text{ (m, } 1\text{H}), 2.34 \text{ (s, } 3\text{H}), 2.17 \text{ (d, } J = 5.1 \text{ Hz, } \text{OH}), 1.55 \text{ (d, } J = 6.6 \text{ Hz, } 3\text{H}); \textit{13C NMR} (100 MHz, CDCl\textsubscript{3}) \(\delta 138.6, 131.7, 129.2, 119.6, 90.4, 84.3, 59.1, 24.6, 21.6.

Synthesis of Pinacol ester tert-butyl(dimethyl(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)silane

To a solution of 4-hydroxyphenylboronic acid (1.126 g, 8 mmol) in DCM (24 mL) was added imidazole (1.36 g, 20 mmol, 2.5 equiv) and t-butyldimethylsilyl chloride (1.45 g, 9.6 mmol, 1.2 equiv) in one portion. The reaction was stirred at room temperature for one hour, then additional imidazole (1.36 g, 20 mmol, 2.5 equiv), t-
butyldimethylsilyl chloride (2.17 g, 14.4 mmol, 1.8 equiv) and DCM (24 mL) were added. The reaction was stirred for another hour, then quenched with brine. The layers separated, and the aqueous layer extracted with DCM. The organics were combined, dried over MgSO₄, and purified by column chromatography (hexanes:EtOAc 40:1 to 100% EtOAc) to give a red-brown oil. The oil was redissolved in DCM (25 mL), and pinacol (1 g, 8.46 mmol) was added. The reaction was stirred at room temperature for 10 minutes, then concentrated under reduced pressure. The crude material was subject to column chromatography (hexanes:EtOAc 25:1) to give the title compound as white solid. (1.5875 g, 59% yield).

**Procedure 3.2: Protocol for Alkyne Arylation of Aryl Propargyl Alcohols**

To a vial or round bottom flask was added [Rh(cod)OH]₂ (0.02 equiv, 4 mol% Rh), BINAP (0.04 equiv, 4 mol%), and K₂CO₃ (1.1 equiv). The vessel was purged with N₂ for 5 minutes, 1,4-dioxane and distilled H₂O were added, and the solution was stirred at room temperature for 15 minutes, during which it a red-orange color developed. A solution of the propargyl alcohol (1 equiv) and boronic acid (2 equiv) in dioxane was then transferred via syringe into the reaction vessel. The mixture was heated to 60 °C, 75 °C, or 80 °C depending on the substrate. Reaction progress was monitored by TLC; the reaction was usually complete within 3 hours. The crude mixture was filtered through a short plug of silica, concentrated under reduced pressure, and purified by flash chromatography.

(Z)-3,4-Diphenylbut-3-en-2-ol (3.16)

According to the general procedure 3.2, [Rh(cod)OH]₂ (31 mg, 2 mol%), BINAP (85 mg, 4 mol%), K₂CO₃ (530 mg, 1.1 equiv) was dissolved in 1,4-dioxane (17 mL), followed by addition of distilled H₂O (2 mL). A solution of phenylboronic acid (834 mg, 6.84 mmol, 2 equiv) in dioxane was then transferred via syringe. The reaction mixture was heated to 60 °C for 3 hours. Subsequent workup and column chromatography (hexanes:EtOAc 9:1) yielded the title compound as a pale yellow oil (644 mg, 84% yield). The characterization data was consistent with literature.³⁰ In a separate experiment, this compound can be synthesized on the same scale (0.5 g) using 0.5 mol% of [Rh(cod)OH]₂ and 1 mol% of BINAP at 0.4 M concentration yielding the product in 73%. ¹H NMR (400 MHz, CDCl₃) δ 7.60 – 7.48 (m, 2H), 7.46 – 7.21 (m, 8H),

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6.66 (s, 1H), 5.14 (q, J = 6.4 Hz, 1H), 1.66 (s, 1H), 1.31 (d, J = 6.6 Hz, 3H); \(^{13}\)C NMR (101 MHz, \(CDCl_3\)) \(\delta\) 145.5, 140.6, 137.1, 131.4, 129.2, 129.0, 128.6, 128.3, 127.5, 127.4, 66.3, 22.6.

**4-Phenylbut-3-yn-1-ol (3.23)**

According to the general procedure 3.1, Pd(PPh\(_3\))\(_2\)Cl\(_2\) (0.074 mmol, 1 mol%) and CuI (0.15 mmol, 2 mol%) were suspended in Et\(_3\)N (30 mL) under N\(_2\). Iodobenzene (7.4 mmol) was added, followed by homopropargyl alcohol (7.7 mmol, 1.05 equiv), and the reaction was stirred at room temperature for 10 hours. Subsequent workup and column chromatography (hexanes:EtOAc 7:3) yielded the title compound as a yellow oil in 95% yield. The analytical data was consistent with literature. \(^{1}\)H NMR (400 MHz, \(CDCl_3\)) \(\delta\) 7.33 (d, \(J\) = 2.8 Hz, 2H), 7.24 – 7.19 (m, 3H), 3.74 (t, \(J\) = 5.6 Hz, 2H), 2.62 (t, \(J\) = 6.3 Hz, 2H), 1.88 (br s, 1H).

**\((E)\)-3,4-Diphenylbut-3-en-1-ol (3.24)**

According to the general procedure 3.2, [Rh(cod)OH]\(_2\) (9.2 mg, 0.02 mmol, 2 mol%), BINAP (24.9 mg, 0.04 mmol, 4 mol%), K\(_2\)CO\(_3\) (152 mg, 1.1 mmol, 1.1 equiv) was dissolved in 1,4-dioxane (2 mL), followed by addition of distilled H\(_2\)O (0.5 mL). A solution of phenylboronic acid (247 mg, 2 mmol, 2 equiv) and 3.23 (146 mg, 1 mmol) in 1,4-dioxane (3 mL) was then added via syringe. The reaction mixture was heated to 60 °C for 3 hours. Subsequent workup and column chromatography (hexanes:EtOAc 85:15) yielded the title compound as a colorless solid (135 mg, 60% yield). M.p. 71-72 °C; \(^{1}\)H NMR (400 MHz, \(CDCl_3\)) \(\delta\) 7.48 (dd, \(J\) = 8.3, 1.2 Hz, 2H), 7.44 – 7.35 (m, 6H), 7.35 – 7.24 (m, 2H), 6.86 (s, 1H), 3.71 (t, \(J\) = 6.9 Hz, 2H), 3.04 (t, \(J\) = 6.8 Hz, 2H), 1.39 (s, 1H). \(^{13}\)C NMR (101 MHz, \(CDCl_3\)) \(\delta\) 142.6, 139.1, 137.9, 131.2, 129.1, 128.8, 128.6, 127.8, 127.1, 126.8, 61.5, 33.6; IR (NaCl, neat) 3372, 3296, 3018, 2967, 2896, 1595, 1486, 1444, 1363, 1345, 1042, 1024 cm\(^{-1}\); HRMS (ESI): calcd for C\(_{16}\)H\(_{20}\)NO (M+NH\(_4\))\(^{+}\): 242.1545; found: 242.1551.

**\((Z)\)-2,3-Diphenylprop-2-en-1-ol (3.27)**

According to the general procedure 3.2, [Rh(cod)OH]\(_2\) (9.2 mg, 0.02 mmol, 2 mol%), BINAP (24.9 mg, 0.04 mmol, 4 mol%), K\(_2\)CO\(_3\) (152 mg, 1.1 mmol, 1.1 equiv) was dissolved in 1,4-dioxane (2 mL), followed by addition of distilled H\(_2\)O (0.5 mL). A solution of phenylboronic acid (247 mg, 2 mmol, 2 equiv) and 3.1 (132.2 mg, 1 mmol) in 1,4-dioxane (3 mL) was then added via syringe. The reaction mixture was heated to 60 °C for 3 hours. Subsequent workup and column chromatography (hexanes:EtOAc 85:15) yielded

the title compound as a pale yellow solid (147.7 mg, 70% yield). The characterization data is consistent with literature.\textsuperscript{32} \textbf{M.p.} 73-74 °C; \textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl$_3$) $\delta$ 7.62 – 7.59 (m, 2H), 7.45 – 7.29 (m, 8H), 6.99 (s, 1H), 4.72 (d, $J = 5.6$ Hz, 2H), 1.56 (t, $J = 5.6$ Hz, 1H); \textbf{\textsuperscript{13}C NMR} (100 MHz, CDCl$_3$) $\delta$ 140.7, 140.3, 137.1, 131.4, 129.1, 128.8, 128.5, 127.9, 127.5, 126.7, 60.5.

\textbf{(Z)-4-(4-Methoxyphenyl)-3-phenylbut-3-en-2-ol (3.28)}

\[
\text{MeO} \quad \text{Me} \quad \text{OH}
\]

According to the general procedure 3.2, [Rh(cod)OH]$_2$ (26 mg, 2 mol%), BINAP (71 mg, 4 mol%), K$_2$CO$_3$ (432 mg, 1.1 equiv) was dissolved in 1,4-dioxane (14 mL), followed by addition of distilled H$_2$O (2 mL). A solution of phenylboronic acid (834 mg, 6.84 mmol, 2 equiv) and 3.3 (500 mg, 2.84 mmol) in 1,4-dioxane (3 mL) was then added via syringe. The reaction mixture was heated to 60 °C for 3 hours. Subsequent workup and column chromatography (hexanes:EtOAc 85:15) yielded the title compound as a pale yellow oil (644 mg, 91% yield). \textbf{M.p.} 65-67 °C; \textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl$_3$) $\delta$ 7.48 – 7.40 (m, 2H), 7.33 – 7.14 (m, 5H), 6.84 (d, $J = 8.7$ Hz, 2H), 6.51 (s, 1H), 5.08 (q, $J = 6.5$ Hz, 1H), 3.75 (s, 3H), 1.62 (s, 1H), 1.23 (d, $J = 6.5$ Hz, 3H); \textbf{\textsuperscript{13}C NMR} (100 MHz, CDCl$_3$) $\delta$ 159.0, 144.2, 140.9, 130.8, 130.5, 129.5, 129.0, 128.2, 127.4, 114.0, 66.3, 55.5, 22.6; \textbf{IR} (NaCl, neat): 3479, 3055, 2969, 2934, 2836, 1606, 1511, 1443, 1299, 1250, 1177, 1103, 1032 cm$^{-1}$; \textbf{HRMS} calcd for C$_{17}$H$_{22}$NO$_2$ (M+NH$_4^+$): 272.1669; found: 272.1663.

\textbf{(Z)-3-Phenyl-4-(4-(trifluoromethyl)phenyl)but-3-en-2-ol (3.29)}

\[
\text{F}_3\text{C} \quad \text{MeO} \quad \text{Me} \quad \text{OH}
\]

According to the general procedure 3.2, [Rh(cod)OH]$_2$ (26.4 mg, 0.058 mmol, 2.5 mol%), BINAP (87.2 mg, 0.14 mmol, 6 mol%), K$_2$CO$_3$ (353.8 mg, 2.56 mmol, 1.1 equiv) was dissolved in 1,4-dioxane (5.8 mL), followed by addition of distilled H$_2$O (0.8 mL). A solution of phenylboronic acid (568.2 mg, 4.66 mmol, 2 equiv) and 3.4 (500 mg, 2.33 mmol) in 1,4-dioxane (5.8 mL) and distilled H$_2$O (0.8 mL) was then added via syringe. The reaction mixture was heated to 60 °C for 2 hours. Subsequent workup and column chromatography (hexanes:EtOAc 9:1) yielded the title compound as a pale yellow oil (592.4 mg, 87% yield). \textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl$_3$) $\delta$ 7.64 (d, $J = 8.1$ Hz, 2H), 7.54 (dd, $J = 8.0$, 1.6 Hz, 2H), 7.47 (d, $J = 8.0$ Hz, 2H), 7.42 – 7.34 (m, 3H), 6.65 (s, 1H), 5.08 – 5.02 (m, 1H), 1.67 (d, $J = 4.4$ Hz, OH), 1.32 (d, $J = 6.5$ Hz, 3H); \textbf{\textsuperscript{13}C NMR} (100 MHz, CDCl$_3$) $\delta$ 159.0, 144.2, 140.9, 130.8, 130.5, 129.5, 129.0, 128.2, 127.4, 114.0, 66.3, 55.5, 22.6; \textbf{IR} (NaCl, neat): 3479, 3055, 2969, 2934, 2836, 1606, 1511, 1443, 1299, 1250, 1177, 1103, 1032 cm$^{-1}$; \textbf{HRMS} (ESI) calcd for C$_{17}$H$_{19}$F$_3$NO (M+NH$_4^+$): 310.1419; found: 310.1409.

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(Z)-4-(3,5-Dimethoxyphenyl)-3-phenylbut-3-en-2-ol (3.30)

This compound was synthesized by R. Huang according to the general procedure 3.2, [Rh(cod)OH]$_2$ (27.4 mg, 0.06 mmol, 2 mol%), BINAP (74.7 mg, 0.12 mmol, 4 mol%), K$_2$CO$_3$ (456.1 mg, 3.3 mmol, 1.1 equiv) was dissolved in 1,4-dioxane (7 mL), followed by addition of distilled H$_2$O (1.5 mL). A solution of phenylboronic acid (739 mg, 6 mmol, 2 equiv) and 3.5 (618.7 mg, 3 mmol) in 1,4-dioxane (8 mL) was then added via syringe. The reaction mixture was heated to 60 °C for 3 hours. Subsequent workup and column chromatography (gradient hexanes:EtOAc 10:1 to hexanes:EtOAc 8:2) yielded the title compound as a pale yellow syrup (797.3 mg, 93% yield).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.55 – 7.52 (m, 2H), 7.40 – 7.30 (m, 3H), 6.60 (s, 1H), 6.50 (dd, $J$ = 2.2, 0.4 Hz, 2H), 6.42 (t, $J$ = 2.2 Hz, 1H), 5.16 (q, $J$ = 6.5 Hz, 1H), 3.82 (s, 6H), 1.69 (br s, OH), 1.31 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 160.8, 145.8, 140.4, 139.0, 130.9, 128.9, 128.2, 127.5, 107.1, 99.4, 66.3, 55.5, 22.6; IR (NaCl, neat): 3441, 3080, 3053, 2968, 2936, 2837, 1591, 1493, 1456, 1423, 1327, 1294, 1206, 1152, 1105, 1061, 993, 926, 887, 833, 768, 704 cm$^{-1}$; HRMS (EI): calcd for C$_{18}$H$_{20}$O$_3$ (M)$^+$: 284.1412; found: 284.1417.

(Z)-4-(4-(Dimethylamino)phenyl)-3-phenylbut-3-en-2-ol (3.31)

This compound was synthesized by R. Huang according to the general procedure 3.2, [Rh(cod)OH]$_2$ (4.6 mg, 0.01 mmol, 2 mol%), BINAP (12.5 mg, 0.02 mmol, 4 mol%), K$_2$CO$_3$ (76 mg, 0.55 mmol, 1.1 equiv) was dissolved in 1,4-dioxane (1 mL), followed by addition of distilled H$_2$O (0.2 mL). A solution of phenylboronic acid (122 mg, 1 mmol, 2 equiv) and 3.6 (94.4 mg, 0.5 mmol) in 1,4-dioxane (1 mL) was then added via syringe. The reaction mixture was heated to 60 °C for 3 hours. Subsequent workup and column chromatography (hexanes:EtOAc 8:2) yielded the title compound as a pale yellow syrup (797.3 mg, 93% yield). M.p. 89-90 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.53 – 7.51 (m, 2H), 7.35 – 7.21 (m, 5H), 6.72 (d, $J$ = 8.8 Hz, 2H), 6.56 (s, 1H), 5.23 (q, $J$ = 6.5 Hz, 1H), 2.96 (s, 6H), 1.78 (br s, OH), 1.31 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 149.7, 142.5, 141.2, 131.3, 130.2, 128.9, 128.0, 127.0, 124.9, 112.3, 66.3, 40.6, 22.4; IR (NaCl, neat): 3545, 3410, 3078, 3051, 2974, 2928, 2899, 2855, 1609, 1520, 1481, 1443, 1358, 1192, 1165, 1103, 1053, 961, 945, 887, 814, 768, 702 cm$^{-1}$; HRMS (EI): calcd for C$_{18}$H$_{21}$NO (M)$^+$: 267.1623; found: 267.1617.

(Z)-4-(3,5-Dimethylphenyl)-3-phenylbut-3-en-2-ol (3.32)

This compound was synthesized by R. Huang according to the general procedure 3.2, [Rh(cod)OH]$_2$ (9.2 mg, 0.02 mmol, 2 mol%), BINAP (24.9 mg, 0.04 mmol, 4 mol%), K$_2$CO$_3$ (152 mg, 1.1 mmol, 1.1 equiv) was dissolved in 1,4-dioxane (2 mL), followed by addition of distilled H$_2$O (0.5 mL). A solution of phenylboronic acid (247 mg, 2 mmol, 2 equiv) and 3.7
(174.2 mg, 1 mmol) in 1,4-dioxane (3 mL) was then added via syringe. The reaction mixture was heated to 60 °C for 3 hours. Subsequent workup and column chromatography (hexanes:EtOAc 10:1) yielded the title compound as a golden yellow syrup (209.1 mg, 83% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.59 – 7.56 (m, 2H), 7.42 – 7.35 (m, 3H), 6.99 (s, 2H), 6.97 (s, 1H), 6.64 (s, 1H), 5.21 – 5.16 (m, 1H), 2.38 (s, 6H), 1.76 (d, $J$ = 3.2 Hz, OH), 1.33 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 145.0, 140.6, 137.9, 136.9, 131.2, 128.9, 128.9, 128.1, 127.3, 126.8, 66.2, 22.5, 21.5; IR (NaCl, neat): 3570, 3403, 3053, 3019, 2972, 2919, 2864, 2864, 1599, 1486, 1443, 1373, 1104, 1054, 967, 950, 927, 904, 881, 845, 767, 701 cm$^{-1}$; HRMS (EI): calcd for C$_{18}$H$_{20}$O (M$^+$): 252.1514; found: 252.1519.

(Z)-3-Phenyl-4-(thiophen-2-yl)but-3-en-2-ol (3.33)

This compound was synthesized by R. Huang according to the general procedure 3.2, [Rh(cod)OH]$_2$ (18.3 mg, 0.04 mmol, 2 mol%), BINAP (49.8 mg, 0.08 mmol, 4 mol%), K$_2$CO$_3$ (304 mg, 2.2 mmol, 1.1 equiv) was dissolved in 1,4-dioxane (4 mL), followed by addition of distilled H$_2$O (1 mL). A solution of phenylboronic acid (493 mg, 4 mmol, 2 equiv) and 3.8 (304.4 mg, 2 mmol) in 1,4-dioxane (6 mL) was then added via syringe. The reaction mixture was heated to 75 °C for 3 hours. Subsequent workup and column chromatography (hexanes:EtOAc 9:1) yielded the title compound as an orange oil (336.8 mg, 73% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.52 – 7.49 (m, 2H), 7.40 – 7.33 (m, 4H), 7.09 – 7.05 (m, 2H), 6.68 (s, 1H), 5.52 – 5.46 (m, 1H), 1.83 (d, $J$ = 4.6 Hz, OH), 1.44 (d, $J$ = 6.6 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 144.2, 140.3, 139.0, 128.7, 128.2, 127.5, 127.3, 126.2, 123.0, 66.6, 22.3; IR (NaCl, neat): 3557, 3387, 3105, 3078, 3059, 3021, 2974, 2928, 1597, 1489, 1442, 1427, 1369, 1248, 1207, 1103, 1053, 1030, 956, 883, 852, 775, 760, 698 cm$^{-1}$; HRMS (EI): calcd for C$_{12}$H$_{14}$S (M-H$_2$O)$^+$: 212.0660; found: 212.0655.

(Z)-3-Phenyl-4-(thiophen-3-yl)but-3-en-2-ol (3.34)

This compound was synthesized by R. Huang according to the general procedure 3.2, [Rh(cod)OH]$_2$ (18.3 mg, 0.04 mmol, 2 mol%), BINAP (49.8 mg, 0.08 mmol, 4 mol%), K$_2$CO$_3$ (304 mg, 2.2 mmol, 1.1 equiv) was dissolved in 1,4-dioxane (4 mL), followed by addition of distilled H$_2$O (1 mL). A solution of phenylboronic acid (493 mg, 4 mmol, 2 equiv) and 3.9 (304.4 mg, 2 mmol) in 1,4-dioxane (6 mL) was then added via syringe. The reaction mixture was heated to 75 °C for 3 hours. Subsequent workup and column chromatography (hexanes:EtOAc 9:1) yielded the title compound as an orange oil (351.8 mg, 76% yield). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.52 – 7.49 (m, 2H), 7.40 – 7.33 (m, 4H), 7.29 – 7.28 (m, 1H), 7.16 (dd, $J$ = 4.9, 1.3 Hz, 1H), 6.55 (s, 1H), 5.30 – 5.24 (m, 1H), 1.76 (d, $J$ = 3.7 Hz, OH), 1.37 (d, $J$ = 6.6 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 145.0, 140.5, 137.6, 129.0, 128.7, 128.2, 127.4, 125.6, 125.0, 123.7, 66.5, 22.5; IR (NaCl, neat): 3566, 3372, 3102, 3055, 3021, 2974, 2928, 1597, 1574, 1489, 1443, 1416, 1103,
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1080, 1049, 1030, 964, 929, 887, 837, 783, 702 cm⁻¹; HRMS (EI): calcd for C₁₂H₁₄S (M-H₂O)⁺: 212.0660; found: 212.0655.

(Z)-4-(2-Methoxyphenyl)-3-phenylbut-3-en-2-ol (3.35)

This compound was synthesized by R. Huang according to the general procedure 3.2, [Rh(cod)OH]₂ (9.2 mg, 0.02 mmol. 2 mol%), BINAP (24.9 mg, 0.04 mmol, 4 mol%), K₂CO₃ (152 mg, 1.1 mmol, 1.1 equiv) was dissolved in 1,4-dioxane (2 mL), followed by addition of distilled H₂O (0.5 mL). A solution of phenylboronic acid (247 mg, 2 mmol, 2 equiv) and 3.10 (176.2 mg, 1 mmol) in 1,4-dioxane (3 mL) was then added via syringe. The reaction mixture was heated to 60 °C for 3 hours. Subsequent workup and column chromatography (hexanes:EtOAc 7:1) yielded the title compound as a yellow syrup (187.7 mg, 74% yield).

1H NMR (400 MHz, CDCl₃) δ 7.62 – 7.59 (m, 2H), 7.37 – 7.23 (m, 5H), 6.97 (td, J = 7.5, 0.5 Hz, 1H), 6.91 (d, J = 8.2 Hz, 1H), 4.95 (qd, J = 6.4, 2.4 Hz, 1H), 3.82 (s, 3H), 2.25 (d, J = 2.5 Hz, 1H), 1.23 (d, J = 6.5 Hz, 3H); 13C NMR (100 MHz, CDCl₃) δ 157.1, 145.6, 140.7, 130.5, 128.8, 128.0, 127.2, 126.7, 126.1, 120.6, 111.0, 66.8, 55.7, 21.6; IR (NaCl, neat): 3414, 3055, 3021, 2970, 2931, 2835, 1597, 1493, 1462, 1435, 1288, 1246, 1111, 1049, 1026, 887, 752, 702 cm⁻¹; HRMS (EI): calcd for C₁₇H₁₈O₂ (M)⁺: 254.1307; found: 254.1311.

(Z)-2-Phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-ol (3.36)

This compound was synthesized by R. Huang according to the general procedure 3.2, [Rh(cod)OH]₂ (18.3 mg, 0.04 mmol. 2 mol%), BINAP (49.8 mg, 0.08 mmol, 4 mol%), K₂CO₃ (304 mg, 2.2 mmol, 1.1 equiv) was dissolved in 1,4-dioxane (4 mL), followed by addition of distilled H₂O (1 mL). A solution of phenylboronic acid (493 mg, 4 mmol, 2 equiv) and 3.12 (400.3 mg, 2 mmol) in 1,4-dioxane (6 mL) was then added via syringe. The reaction mixture was heated to 60 °C for 19 hours. Subsequent workup and column chromatography (hexanes:EtOAc 9:1) yielded the title compound as yellow crystals (395 mg, 71% yield). M.p. 72-74 °C; 1H NMR (400 MHz, CDCl₃) δ 7.65 (d, J = 8.2 Hz, 2H), 7.62 – 7.57 (m, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.47 – 7.40 (m, 2H), 7.40 – 7.34 (m, 1H), 6.97 (s, 1H), 4.68 (d, J = 5.0 Hz, 2H), 1.62 (t, J = 5.3 Hz, 1H); 13C NMR (100 MHz, CDCl₃) δ 142.2, 140.6, 140.2, 130.0, 129.5 (q, J = 32.3 Hz), 129.3, 129.0, 128.3, 126.8, 125.5 (q, J = 3.8 Hz), 124.3 (q, J = 270 Hz), 60.4; 19F NMR (377 MHz, CDCl₃) δ -63.5 (s); IR (NaCl, neat): 3278, 1614, 1484, 1411, 1324, 1164, 1112, 1069, 1062, 1017, 891, 828, 763, 755, 695, 600 cm⁻¹; HRMS (ESI): calcd for C₁₆H₁₇F₃NO (M+NH₄)⁺: 296.1262; found: 296.1268.
(Z)-1-(4-(3-Hydroxy-2-phenylprop-1-enyl)phenyl)ethanone (3.37)

This compound was synthesized by R. Huang according to the general procedure 3.2, [Rh(cod)OH]$_2$ (18.3 mg, 0.04 mmol, 2 mol%), BINAP (49.8 mg, 0.08 mmol, 4 mol%), K$_2$CO$_3$ (304 mg, 2.2 mmol, 1.1 equiv) was dissolved in 1,4-dioxane (4 mL), followed by addition of distilled H$_2$O (1 mL). A solution of phenylboronic acid (493 mg, 4 mmol, 2 equiv) and 3.13 (348.4 mg, 2 mmol) in 1,4-dioxane (6 mL) was then added via syringe. The reaction mixture was heated to 60 °C for 7.5 hours. Subsequent workup and column chromatography (hexanes:EtOAc 65:35) yielded the title compound as a yellow solid (380.2 mg, 75% yield). The characterization data is consistent with literature.$^{33}$ M.p. 88-90 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.98 (d, $J = 8.3$ Hz, 2H), 7.60 (d, $J = 7.2$ Hz, 2H), 7.52 (d, $J = 8.1$ Hz, 2H), 7.42 (t, $J = 7.3$ Hz, 1H), 6.97 (s, 1H), 4.70 (d, $J = 5.3$ Hz, 2H), 2.62 (s, 3H), 1.78 (t, $J = 5.4$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 197.8, 142.2, 141.9, 140.4, 135.9, 130.3, 129.3, 128.9, 128.6, 126.8, 126.8, 60.4, 26.8.

(Z)-1-(3,5-Dimethoxyphenyl)-4-methyl-2-phenylpent-1-en-3-ol (3.38)

This compound was synthesized by R. Huang according to the general procedure 3.2, [Rh(cod)OH]$_2$ (9.2 mg, 0.02 mmol, 2 mol%), BINAP (24.9 mg, 0.04 mmol, 4 mol%), K$_2$CO$_3$ (152 mg, 1.1 mmol, 1.1 equiv) was dissolved in 1,4-dioxane (2 mL), followed by addition of distilled H$_2$O (0.5 mL). A solution of phenylboronic acid (247 mg, 2 mmol, 2 equiv) and 3.15 (234.3 mg, 1 mmol) in 1,4-dioxane (3 mL) was then added via syringe. The reaction mixture was heated to 60 °C for 3 hours. Subsequent workup and column chromatography (hexanes:EtOAc 10:1) yielded the title compound as a pale yellow syrup (227.1 mg, 73% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.64 (dd, $J = 8.1$, 1.5 Hz, 2H), 7.40 – 7.28 (m, 3H), 6.74 (d, $J = 6.5$ Hz, 3H), 6.51 (dd, $J = 2.3$, 0.7 Hz, 2H), 6.42 (t, $J = 2.2$ Hz, 1H), 4.46 (dd, $J = 9.9$, 3.8 Hz, 1H), 3.82 (s, 6H), 1.83 (d, $J = 4.0$ Hz, 1H), 1.81 – 1.71 (m, 1H), 0.99 (d, $J = 6.5$ Hz, 3H), 0.72 (d, $J = 6.7$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 160.8, 144.3, 141.0, 139.3, 133.2, 128.6, 128.1, 127.4, 107.1, 99.3, 76.5, 55.5, 31.7, 19.4, 19.2; IR (NaCl, neat): 3512, 3080, 3053, 2998, 2958, 2937, 2870, 2837, 1599, 1589, 1493, 1456, 1442, 1424, 1349, 1327, 1316, 1291, 1205, 1153, 1062, 1045, 1025, 1014, 928, 833, 769, 703, 678 cm$^{-1}$; HRMS (ESI): calcd for C$_{20}$H$_{23}$O$_2$ (M-H$_2$O)$^+$: 295.1698; found: 295.1689.

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(Z)-3-(3-Methoxy-4-methylphenyl)-4-phenylbut-3-en-2-ol (3.39)

According to the general procedure 3.2, [Rh(cod)OH]₂ (30 mg, 0.066 mmol, 2 mol%), BINAP (81 mg, 0.13 mmol, 4 mol%), K₂CO₃ (500 mg, 3.6 mmol, 1.1 equiv) was dissolved in 1,4-dioxane (12 mL), followed by addition of distilled H₂O (1.6 mL). A solution of 4-methyl-3-methoxyphenylboronic acid (1.1 g, 6.6 mmol, 2 equiv) and 3.2 (500 mg, 3.4 mmol) in 1,4-dioxane (4 mL) was then added via syringe. The reaction mixture was heated to 60 °C for 3 hours. Subsequent workup and column chromatography (hexanes:EtOAc 9:1) yielded the title compound as a pale yellow oil in 84% yield. In a separate experiment, this compound can be synthesized on the same scale (0.5 g) using 0.5 mol% of [Rh(cod)OH]₂ and 1 mol% of BINAP at 0.4 M concentration yielding the product in 83%. ¹H NMR (399 MHz, CDCl₃) δ 7.30 (m, 7H), 6.76 (d, J = 8.3 Hz, 1H), 6.58 (s, 1H), 5.09 (q, J = 6.5 Hz, 1H), 3.78 (s, 3H), 2.24 (s, 3H), 2.05 (s, 1H), 1.28 (d, J = 6.5 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 157.3, 145.1, 137.2, 132.5, 131.2, 130.0, 129.0, 128.4, 127.2, 127.0, 126.1, 109.5, 66.1, 55.4, 22.5, 16.5; IR (NaCl, neat): 3410, 2970, 2928, 1604, 1505, 1443, 1292, 1138, 1034 cm⁻¹; HRMS (EI): calcd for C₁₈H₂₀O₂ (M)⁺: 268.1463; found: 268.1467.

(Z)-3-(3,4-Dimethoxyphenyl)-4-(4-methoxyphenyl)but-3-en-2-ol (3.40)

According to the general procedure 3.2, [Rh(cod)OH]₂ (16.4 mg, 0.036 mmol, 2 mol%), BINAP (47 mg, 0.076 mmol, 4 mol%), K₂CO₃ (274 mg, 1.98 mmol, 1.1 equiv) was dissolved in 1,4-dioxane (6 mL), followed by addition of distilled H₂O (0.9 mL). A solution of 3,4-dimethoxyphenylboronic acid (670 mg, 3.6 mmol, 2 equiv) and 3.3 (323 mg, 1.8 mmol) in 1,4-dioxane (3 mL) was then added via syringe. The reaction mixture was heated to 60 °C for 3 hours. Subsequent workup and column chromatography (hexanes:EtOAc 9:1) yielded the title compound as an orange oil (414 mg, 73% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.30 – 7.22 (m, 2H), 7.14 (d, J = 2.0 Hz, 1H), 7.08 (dd, J = 8.2, 2.0 Hz, 1H), 6.89 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.3 Hz, 1H), 6.59 (s, 1H), 5.15 (q, J = 6.5 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.81 (s, 3H), 1.98 (br s, 1H), 1.32 (d, J = 6.5 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 157.3, 145.1, 137.2, 132.5, 131.2, 130.0, 129.0, 128.4, 127.2, 127.0, 126.1, 109.5, 55.4, 22.5, 16.5; IR (NaCl, neat): 3508, 2961, 2932, 2835, 1607, 1520, 1505, 1464, 1438, 133.6, 130.3, 129.5, 121.2, 113.9, 112.3, 110.9, 66.2, 56.0, 56.0, 55.4, 22.5; HRMS (ESI): calcd for C₁₉H₂₆NO₄ (M+NH₄)⁺: 332.1862; found: 332.1876.

(Z)-3-(3,4-Dimethoxyphenyl)-4-p-tolylbut-3-en-2-ol (3.41)

According to the general procedure 3.2, [Rh(cod)OH]₂ (9.2 mg, 0.02 mmol, 2 mol%), BINAP (47 mg, 0.076 mmol, 4 mol%), K₂CO₃ (152 mg, 1.1 mmol, 1.1 equiv) was dissolved in 1,4-dioxane (2 mL), followed by addition of distilled H₂O (0.5 mL). A solution of 3,4-dimethoxyphenylboronic acid (375.3 mg, 2 mmol, 2 equiv) and 3.11 (160.2 mg, 1 mmol) in 1,4-
dioxane (3 mL) was then added via syringe. The reaction mixture was heated to 60 °C for 3 hours. Subsequent workup and column chromatography (hexanes:EtOAc 3:1) yielded the title compound as a pale yellow syrup (273.5 mg, 91% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.22 (d, $J = 8.1$ Hz, 2H), 7.19 (d, $J = 8.2$ Hz, 2H), 7.15 (d, $J = 2.0$ Hz, 1H), 7.09 (dd, $J = 8.2$, 2.0 Hz, 1H), 6.87 (d, $J = 8.3$ Hz, 1H), 6.63 (s, 1H), 5.16 (dd, $J = 6.3$, 2.5 Hz, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 2.37 (s, 3H), 1.64 (d, $J = 3.3$ Hz, 1H), 1.32 (d, $J = 6.5$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 148.5, 148.5, 144.4, 137.0, 134.1, 133.4, 130.4, 129.2, 129.0, 121.2, 112.3, 110.9, 66.3, 56.1, 56.0, 22.5, 21.3; IR (NaCl, neat): 3502, 2966, 2932, 2835, 1601, 1578, 1504, 1466, 1508, 1369, 1242, 1169, 1142, 1103, 1057, 1026, 978, 907, 880, 814, 768, 721 cm$^{-1}$; HRMS (EI): calcd for C$_{19}$H$_{22}$O$_3$: 298.1569; found: 298.1576.

(Z)-3-(4-(tert-Butyldimethylsilyloxy)phenyl)-4-(3,5-dimethoxyphenyl)but-3-en-2-ol (3.42)

![Z)-3-(4-(tert-Butyldimethylsilyloxy)phenyl)-4-(3,5-dimethoxyphenyl)but-3-en-2-ol](image)

This compound was synthesized by R. Huang according to the general procedure 3.2, [Rh(cod)OH]$_2$ (9.2 mg, 0.02 mmol. 2 mol%), BINAP (24.9 mg, 0.04 mmol, 4 mol%), K$_2$CO$_3$ (152 mg, 1.1 mmol, 1.1 equiv) was dissolved in 1,4-dioxane (2 mL), followed by addition of distilled H$_2$O (0.5 mL). A solution of pinacol ester (668.7 mg, 2 mmol, 2 equiv) and 3.5 (206.2 mg, 1 mmol) in 1,4-dioxane (3 mL) was then added via syringe. The reaction mixture was heated to 60 °C for 3 hours. Subsequent workup and column chromatography (hexanes:EtOAc 20:1 to hexanes:EtOAc 8:2) yielded the title compound as a golden-yellow syrup (337.7 mg, 81% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.41 (d, $J = 8.6$ Hz, 2H), 6.83 (d, $J = 8.6$ Hz, 2H), 6.57 (s, 1H), 6.47 (d, $J = 1.9$ Hz, 2H), 6.40 (t, $J = 2.2$ Hz, 1H), 5.17 – 5.10 (m, 1H), 3.81 (s, 6H), 1.63 (d, $J = 4.7$ Hz, 1H), 1.30 (d, $J = 6.5$ Hz, 3H), 1.00 (s, 9H), 0.22 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 161.0, 155.4, 145.7, 139.4, 133.4, 130.1, 130.0, 119.7, 107.4, 99.6, 66.6, 55.6, 25.9, 22.7, 18.4, -4.2; IR (NaCl, neat): 3453, 2997, 2956, 2930, 2896, 2887, 2858, 1601, 1591, 1506, 1461, 1424, 1257, 1205, 1152, 1102, 1062, 914, 840, 807, 781, 677 cm$^{-1}$; HRMS (EI): calcd for C$_{24}$H$_{34}$O$_4$Si (M)$^+$: 414.2226; found: 414.2226.

(Z)-3-(Thiophen-3-yl)-4-p-tolylbut-3-en-2-ol (3.43)

![Z)-3-(Thiophen-3-yl)-4-p-tolylbut-3-en-2-ol](image)

This compound was synthesized by R. Huang according to the general procedure 3.2, [Rh(cod)OH]$_2$ (9.2 mg, 0.02 mmol. 2 mol%), BINAP (24.9 mg, 0.04 mmol, 4 mol%), K$_2$CO$_3$ (152 mg, 1.1 mmol, 1.1 equiv) was dissolved in 1,4-dioxane (2 mL), followed by addition of distilled H$_2$O (0.5 mL). A solution of 3-thienylboronic acid (262 mg, 2 mmol, 2 equiv) and 3.11 (160.2 mg, 1 mmol) in 1,4-dioxane (3 mL) was then added via syringe. The reaction mixture was heated to 60 °C for 3 hours. Subsequent workup and column chromatography (hexanes:EtOAc 85:15) yielded the title compound as an orange syrup (171.2 mg, 70% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.57 (dd, $J = 3.0$, 1.3 Hz, 1H), 7.36 (dd, $J = 5.0$, 1.3 Hz, 1H), 7.31 (dd, $J = 5.0$, 3.0 Hz, 1H), 7.20 – 7.16 (m, 4H), 6.83 (s, 1H), 5.21 (q, $J = 6.5$ Hz, 1H), 2.38 (s, 3H), 1.69 (br s, OH) 1.42 (d, $J =
6.6 Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl$_3$) $\delta$ 140.2, 139.7, 137.1, 134.0, 129.3, 129.2, 129.0, 128.2, 125.0, 122.7, 66.1, 22.3, 21.4; IR (NaCl, neat): 3549, 3364, 3105, 3082, 3020, 2974, 2924, 2866, 1608, 1566, 1508, 1446, 1408, 1369, 1346, 1053, 972, 945, 883, 864, 841, 814, 787,756, 717 cm$^{-1}$; HRMS (EI) calcd for C$_{15}$H$_{16}$OS$^+$: 244.0922; found: 244.0920.

(Z)-3-(4-Chlorophenyl)-4-phenylbut-3-en-2-ol (3.44)

![Chemical Structure](image)

According to the general procedure 3.2, [Rh(cod)OH]$_2$ (30 mg, 0.066 mmol, 2 mol%), BINAP (81 mg, 0.13 mmol, 4 mol%), K$_2$CO$_3$ (500 mg, 3.6 mmol, 1.1 equiv) was dissolved in 1,4-dioxane (12 mL), followed by addition of distilled H$_2$O (1.6 mL). A solution of 4-methyl-3-methoxyphenylboronic acid (1.1 g, 6.6 mmol, 2 equiv) and 3.2 (500 mg, 3.4 mmol) in 1,4-dioxane (4 mL) was then added via syringe. The reaction mixture was heated to 60 $^\circ$C for 3 hours. Subsequent workup and column chromatography (hexanes:EtOAc 9:1) yielded the title compound as a pale yellow oil in 87% yield. $^1$H NMR (399 MHz, CDCl$_3$) $\delta$ 7.59 – 7.51 (m, 2H), 7.46 – 7.29 (m, 7H), 6.68 (s, 1H), 5.18 (q, $J$ = 6.5 Hz, 1H), 2.27 (s, 1H), 1.30 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 144.1, 139.0, 136.6, 133.3, 131.3, 130.2, 129.0, 128.5, 128.2, 127.4, 65.8; IR (NaCl, neat): 3379, 3032, 2974, 1485, 1447, 1369, 1092, 837 cm$^{-1}$; HRMS (EI) calcd for C$_{16}$H$_{15}$ClO$^+$: 258.0811; found: 258.0817.

(Z)-3-(4-Chlorophenyl)-4-p-tolylbut-3-en-2-ol (3.45)

![Chemical Structure](image)

According to the general procedure 3.2, [Rh(cod)OH]$_2$ (9.2 mg, 0.02 mmol, 2 mol%), BINAP (24.9 mg, 0.04 mmol, 4 mol%), K$_2$CO$_3$ (152 mg, 1.1 mmol, 1.1 equiv) was dissolved in 1,4-dioxane (2 mL), followed by addition of distilled H$_2$O (0.5 mL). A solution of 4-chlorophenylboronic acid (319.2 mg, 2 mmol, 2 equiv) and 3.11 (160.2 mg, 1 mmol) in 1,4-dioxane (3 mL) was then added via syringe. The reaction mixture was heated to 60 $^\circ$C for 3 hours. Subsequent workup and column chromatography (gradient hexanes:EtOAc 19:1 to hexanes:EtOAc 9:1) yielded the title compound as a yellow-orange syrup (219.5 mg, 80% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.49 (d, $J$ = 8.5 Hz, 2H), 7.32 (d, $J$ = 8.5 Hz, 2H), 7.21 (d, $J$ = 8.3 Hz, 2H), 7.18 (d, $J$ = 8.3 Hz, 2H), 6.61 (s, 1H), 5.15 (q, $J$ = 6.2 Hz, 1H), 2.37 (s, 3H), 1.69 (br s, 1H), 1.27 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 143.6, 139.1, 137.3, 133.7, 133.3, 131.5, 130.2, 129.2, 129.0, 128.3, 66.0, 22.3, 21.3; IR (NaCl, neat): 3564, 3372, 3078, 3024, 2974, 2924, 2866, 1612, 1593, 1489, 1446, 1393, 1369, 1092, 1049, 1015, 961, 941, 887, 829, 768, 725 cm$^{-1}$; HRMS (EI) calcd for C$_{17}$H$_{17}$ClO$^+$: 272.0968; found: 272.0969.
(Z)-3-(3-Nitrophenyl)-4-phenylbut-3-en-2-ol (3.46)

According to the general procedure 3.2, [Rh(cod)OH]₂ (30 mg, 0.066 mmol, 2 mol%), BINAP (81 mg, 0.13 mmol, 4 mol%), K₂CO₃ (500 mg, 3.6 mmol, 1.1 equiv) was dissolved in 1,4-dioxane (12 mL), followed by addition of distilled H₂O (1.6 mL). A solution of 3-nitrophenylboronic acid (1.1 g, 6.6 mmol, 2 equiv) and 3.2 (500 mg, 3.4 mmol) in 1,4-dioxane (4 mL) was then added via syringe. The reaction mixture was heated to 60 °C for 3 hours. Subsequent workup and column chromatography (hexanes:EtOAc 9:1) yielded the title compound as a pale yellow oil in 83% yield.

**1H NMR** (400 MHz, CDCl₃) δ 8.46 (ap t, J = 1.9 Hz, 1H), 8.18 (ddd, J = 8.2, 2.3, 1.0 Hz, 1H), 8.01 – 7.93 (m, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.41 (dd, J = 7.8, 6.9 Hz, 2H), 7.34 (d, J = 7.7 Hz, 3H), 6.75 (s, 1H), 5.21 (q, J = 6.5 Hz, 1H), 1.79 (s, 1H), 1.30 (d, J = 6.5 Hz, 3H); **13C NMR** (101 MHz, CDCl₃) δ 148.3, 143.3, 142.4, 136.2, 135.2, 133.0, 129.1, 129.1, 128.7, 127.9, 123.9, 122.4, 65.9, 22.5; **IR** (NaCl, neat): 3410, 3082, 2974 2928, 2870, 1528, 1346, 1095, 1080, 1053, 806, 764, 741 cm⁻¹; **HRMS** (ESI): calcd for C₁₆H₁₉N₂O₃ (M+Na⁺): 287.1402; found: 287.1396.

(Z)-2-(2-Fluorophenyl)-3-phenylprop-2-en-1-ol (3.47)

This compound was synthesized by R. Huang according to the general procedure 3.2, [Rh(cod)OH]₂ (9.2 mg, 0.02 mmol, 2 mol%), BINAP (24.9 mg, 0.04 mmol, 4 mol%), K₂CO₃ (152 mg, 1.1 mmol, 1.1 equiv) was dissolved in 1,4-dioxane (2 mL), followed by addition of distilled H₂O (0.5 mL). A solution of 2-fluorophenylboronic acid (285.5 mg, 2 mmol, 2 equiv) and 3.1 (132.2 mg, 1 mmol) in 1,4-dioxane (3 mL) was then added via syringe. The reaction mixture was heated to 80 °C for 3 hours. Subsequent workup and column chromatography (hexanes:EtOAc 85:15) yielded the title compound as a light orange oil (175.8 mg, 77% yield).

**1H NMR** (400 MHz, CDCl₃) δ 7.49 – 7.39 (m, 5H), 7.35 – 7.29 (m, 2H), 7.19 (td, J = 7.5, 1.3 Hz, 1H), 7.12 (ddd, J = 11.1, 8.2, 1.2 Hz, 1H), 6.86 (s, 1H), 4.67 (s, 2H), 1.85 (br s, OH); **13C NMR** (100 MHz, CDCl₃) δ 160.3 (d, J = 245.9 Hz), 137.2 (d, J = 1.9 Hz), 136.5, 134.1 (d, J = 2.0 Hz), 130.8 (d, J = 4.2 Hz), 129.5 (d, J = 14.4 Hz), 129.3 (d, J = 8.4 Hz), 129.2, 128.5, 127.7, 124.5 (d, J = 3.5 Hz), 115.9 (d, J = 23.0 Hz), 61.3 (d, J = 3.5 Hz); **19F NMR** (376 MHz, CDCl₃) δ -115.1 – -115.2 (m); **IR** (NaCl, neat): 3580, 3374, 3059, 3024, 2937, 2894, 1599, 1574, 1486, 1451, 1215, 1106, 1030, 966, 924, 839, 823, 759, 718, 699 cm⁻¹; **HRMS** (EI): calcd for C₁₆H₁₅OF (M⁺): 287.0950; found: 287.0954.

(Z)-3-Phenyl-2-o-tolylprop-2-en-1-ol (3.48)

This compound was synthesized by R. Huang according to the general procedure 3.2, [Rh(cod)OH]₂ (9.2 mg, 0.02 mmol, 2 mol%), BINAP (24.9 mg, 0.04 mmol, 4 mol%), K₂CO₃ (152 mg, 1.1 mmol, 1.1 equiv) was dissolved in 1,4-dioxane (2 mL), followed by addition of distilled H₂O (0.5 mL). A solution
of 2-methylphenylboronic acid (277.6 mg, 2 mmol, 2 equiv) and 3.1 (132.2 mg, 1 mmol) in 1,4-dioxane (3 mL) was then added via syringe. The reaction mixture was heated to 80 °C for 3 hours. Subsequent workup and column chromatography (hexanes:EtOAc 85:15) yielded the title compound as a light orange syrup (133.5 mg, 60% yield). \( ^1H\) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.44 – 7.33 (m, 4H), 7.33 – 7.14 (m, 5H), 6.53 (s, 1H), 4.56 (d, \( J = 3.4 \) Hz, 2H), 2.37 (s, 3H), 1.47 (br s, OH); \( ^{13}C\) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 141.6, 141.2, 136.8, 136.1, 132.1, 130.5, 129.3, 129.0, 128.5, 127.6, 127.4, 125.9, 62.0, 20.2; IR (NaCl, neat): 3557, 3379, 3059, 3021, 2951, 2924, 2878, 1601, 1574, 1493, 1447, 1381, 1157, 1119, 1076, 1034, 1011, 964, 922, 880, 767, 729, 698 cm\(^{-1}\); HRMS (EI): calcd for C\(_{16}\)H\(_{16}\)O (M\(^+\)): 224.1201; found: 224.1201.

\((2Z,3E)-2\)-Benzyldienenon-3-en-1-ol (3.49a)

This compound was synthesized by R. Huang according to the general procedure 3.2, [Rh(cod)OH]\(_2\) (9.2 mg, 0.02 mmol, 2 mol%), BINAP (24.9 mg, 0.04 mmol, 4 mol%), K\(_2\)CO\(_3\) (152 mg, 1.1 mmol, 1.1 equiv) was dissolved in 1,4-dioxane (2 mL), followed by addition of distilled H\(_2\)O (0.5 mL). A solution of E-hepten-1-ylboronic acid (293 mg, 2 mmol, 2 equiv) and 3.1 (132.2 mg, 1 mmol) in 1,4-dioxane (3 mL) was then added via syringe. The reaction mixture was heated to 60 °C for 19 hours. Subsequent workup and column chromatography (gradient hexanes:EtOAc 9:1 to hexanes:EtOAc 7:3) yielded the title compound as an orange solid (101.8 mg, 44% yield). M.p. 44–46 °C; \( ^1H\) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.38 – 7.32 (m, 4H), 7.28 – 7.23 (m, 1H), 6.59 (s, 1H), 6.16 (dd, \( J = 15.9, 0.7 \) Hz, 1H), 6.02 (dt, \( J = 15.8, 6.8 \) Hz, 1H), 4.45 (d, \( J = 5.1 \) Hz, 2H), 2.18 (td, \( J = 7.7, 0.9 \) Hz, 2H), 1.52 – 1.42 (m, 3H), 1.37 – 1.27 (m, 4H), 0.91 (t, \( J = 7.0 \) Hz, 3H); \( ^{13}C\) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 138.1, 137.0, 132.2, 132.1, 131.7, 129.1, 128.5, 127.3, 58.4, 33.3, 31.7, 29.3, 22.7, 14.2; IR (NaCl, neat): 3268, 2952, 2923, 2870, 2856, 2852, 1489, 1467, 1445, 1421, 1078, 1015, 1004, 996, 962, 922, 875, 750, 697 cm\(^{-1}\); HRMS (ESI): calcd for C\(_{16}\)H\(_{26}\)NO (M+NH\(_4\))\(^+\): 248.2018; found: 248.2014.

\((2Z,4E)-3\)-Phenyldeca-2,4-dien-1-ol (3.49b)

Isolated as the minor isomer from the synthesis of \((2Z,3E)-2\)-benzyldienenon-3-en-1-ol. Pale yellow oil (51 mg, 22% yield). \( ^1H\) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.38 – 7.28 (m, 3H), 7.13 – 7.10 (m, 2H), 6.25 (d, \( J = 15.5 \) Hz, 1H), 5.77 (t, \( J = 7.0 \) Hz, 1H), 5.32 – 5.25 (m, 1H), 4.00 (d, \( J = 5.5 \) Hz, 2H), 2.05 (q, \( J = 6.8 \) Hz, 2H), 1.36 – 1.18 (m, 7H), 0.87 (t, \( J = 7.0 \) Hz, 3H); \( ^{13}C\) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 143.7, 137.7, 135.2, 133.4, 129.4, 128.2, 128.1, 127.3, 60.4, 33.0, 31.6, 29.0, 22.6, 14.2; IR (NaCl, neat): 3330, 3079, 3056, 3022, 2956, 2926, 2871, 2856, 1495, 1460, 1442, 1378, 1086, 1073, 1028, 1005, 998, 969, 778, 703 cm\(^{-1}\); HRMS (EI): calcd for C\(_{16}\)H\(_{22}\)O (M\(^+\)): 230.1671; found: 230.1676.
4,4-Diphenylbutan-2-one (3.22)

This product could be isolated in very small amounts (<5%) from the alkyne arylation reaction of 3.2 with phenylboronic acid after column chromatography (Pentane:DCM:EtOAc 85:10:5). The analytical data is consistent with literature.\(^{34}\)

\(^{1}\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\) 7.28 – 7.03 (m, 10H), 4.51 (t, \(J = 7.6\) Hz, 1H), 3.10 (d, \(J = 7.6\) Hz, 2H), 2.00 (s, 3H); \(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)) \(\delta\) 207.1, 144.1, 128.8 (4), 127.9 (4), 126.7 (2), 49.9, 46.3, 30.9; \text{HRMS} (ESI): calcd for C\(_{16}\)H\(_{20}\)NO (M+NH\(_4\))\(^+\): 242.1545; found: 242.1547.

**Procedure 3.3: 4π Electrocyclization for the Synthesis of Indenes:** To a vial was added the appropriate alcohol, dry dichloromethane (DCM) or 1,2-dichloroethane (DCE), and 85% H\(_3\)PO\(_4\). The reactions were stirred at room temperature or heated to the indicated temperature, and progress monitored by TLC. Upon completion, the reaction was quenched with saturated NaHCO\(_3\) solution, and diluted with EtOAc. The aqueous layer was extracted with EtOAc twice, the organics were pooled, dried over MgSO\(_4\), concentrated under reduced pressure, and purified by flash chromatography.

5,7-Dimethoxy-1-methyl-2-phenyl-1H-indene (3.58)

This compound was synthesized by R. Huang according to the general procedure 3.3, \((Z)-4-(3.5\text{-dimethoxyphenyl})\)-3-phenylbut-3-en-2-ol (57 mg, 0.2 mmol) was dissolved in dry DCE (1 mL). 85% H\(_3\)PO\(_4\) (68.4 \(\mu\)L, 98 mg, 1 mmol, 5 equiv) was added, and the reaction was heated to 80°C for 16 hours. Subsequent workup and column chromatography (hexanes:EtOAc 10:1) yielded the title compound as colorless crystals (48 mg, 90% yield). \text{M.p.} 82-83 °C; \(^{1}\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\) 7.56 (dd, \(J = 8.1, 1.0\) Hz, 2H), 7.42 (t, \(J = 7.7\) Hz, 2H), 7.30 (t, \(J = 7.3\) Hz, 1H), 7.00 (d, \(J = 0.9\) Hz, 1H), 6.62 (d, \(J = 2.0\) Hz, 1H), 6.39 (d, \(J = 2.0\) Hz, 1H), 4.02 (qd, \(J = 7.3, 0.9\) Hz, 1H), 3.91 (s, 3H), 3.87 (s, 3H); \(^{13}\text{C NMR}\) (100 MHz, CDCl\(_3\)) \(\delta\) 160.9, 156.1, 154.4, 145.7, 135.4, 128.7, 128.5, 127.5, 127.0, 125.5, 98.5, 96.1, 55.7, 55.4, 42.7, 15.9; \text{IR} (NaCl, neat): 3059, 2995, 2963, 2936, 2870, 2835, 1599, 1479, 1339, 1316, 1245, 1207, 1144, 1105, 1044, 978, 933, 869, 822, 761, 732, 693 cm\(^{-1}\); \text{HRMS} (ESI): calcd for C\(_{18}\)H\(_{19}\)O\(_2\) (M+H\(^+\)): 267.1385; found: 267.1385.

tert-Butyl(4-(5,7-dimethoxy-1-methyl-1H-inden-2-yl)phenoxy)dimethylsilane (3.59)

This compound was synthesized by R. Huang according to the general procedure 3.3, \((Z)-3-(4\text{-tert-butyl}3\text{methyl}silyloxy)phenyl)-

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4-(3,5-dimethoxyphenyl)but-3-en-2-ol (83 mg, 0.2 mmol) was dissolved in dry DCE (1 mL). 85% H₃PO₄ (68.4 μL, 98 mg, 1 mmol, 5 equiv) was added, and the reaction was heated to 80 °C for 22 h. Subsequent workup and purification by column chromatography (hexanes:EtOAc 20:1) yielded the title compound as a thick clear syrup, which solidified into an off-white solid upon storing at –20 °C overnight (62 mg, 78% yield). M.p. 71-72 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.41 (d, J = 8.6 Hz, 2H), 6.88 – 6.86 (m, 3H), 6.58 (d, J = 1.9 Hz, 1H), 6.34 (d, J = 1.9 Hz, 1H), 3.93 (q, J = 7.4 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 1.34 (d, J = 7.4 Hz, 3H), 1.01 (s, 9H), 0.23 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 160.9, 156.0, 155.4, 154.3, 146.0, 128.7, 128.2, 128.1, 123.8, 120.3, 98.3, 95.7, 55.7, 55.4, 42.7, 25.8, 18.4, 16.1, -4.2, -4.2; IR (NaCl, neat): 3035, 2956, 2930, 2858, 2836, 1599, 1597, 1507, 1480, 1273, 1463, 1454, 1438, 1428, 1338, 1313, 1262, 1207, 1171, 1144, 1105, 1057, 1044, 913, 838, 823, 809, 780 cm⁻¹; HRMS (ESI): calcd for C₂₄H₃₃O₅Si (M+H⁺): 397.2199; found: 397.2181.

6-Methyl-5-phenyl-6H-cyclopenta[b]thiophene (3.60)

This compound was synthesized by R. Huang according to the general procedure 3.3, (Z)-3-phenyl-4-(thiophen-3-yl)but-3-en-2-ol (115.2 mg, 0.5 mmol) was dissolved in dry DCM (2.5 mL). 85% H₃PO₄ (0.171 mL, 0.245 g, 2.5 mmol, 5 equiv) was added, and the reaction stirred at room temperature for 17 hours. Subsequent workup and column chromatography (gradient hexanes:Et₂O 200:1 to hexanes:Et₂O 100:1) yielded the title compound as a light yellow solid (73.7 mg, 69% yield). M.p. 55-56 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.45 (d, J = 7.9 Hz, 2H), 7.37 (t, J = 7.6 Hz, 2H), 7.28 – 7.22 (m, 2H), 7.02 (s, 1H), 7.00 (d, J = 4.8 Hz, 1H), 3.96 (q, J = 7.5 Hz, 1H), 1.36 (d, J = 7.5 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 154.7, 149.6, 147.3, 135.9, 128.8, 127.5, 126.9, 126.3, 122.0, 119.5, 42.6, 18.8; IR (NaCl, neat): 3102, 3028, 2969, 2927, 2868, 1099, 1496, 1452, 1380, 1387, 1092, 1071, 1048, 1031, 826, 759, 733, 713, 691, 652 cm⁻¹; HRMS (ESI): calcd for C₁₄H₁₃S (M+H⁺): 213.0738; found: 213.0745.

4-Methoxy-1-methyl-2-phenyl-1H-indene (3.61)

This compound was synthesized by R. Huang according to the general procedure 3.3, (Z)-4-(2-methoxyphenyl)-3-phenylbut-3-en-2-ol (127.2 mg, 0.5 mmol) was dissolved in dry DCE (2.5 mL). 85% H₃PO₄ (171 μL, 245 mg, 2.5 mmol, 5 equiv) was added, and the reaction was heated to 80 °C for 15 h. Subsequent workup and purification by column chromatography (hexanes:Et₂O 80:1) yielded the title compound as a white solid (100.8 mg, 85% yield). M.p. 106-108 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.54 (d, J = 7.3 Hz, 2H), 7.38 (t, J = 7.7 Hz, 2H), 7.28 – 7.22 (m, 2H), 7.18 (t, J = 7.7 Hz, 1H), 7.09 (d, J = 7.4 Hz, 1H), 6.80 (d, J = 8.1 Hz, 1H), 3.96 – 3.91 (m, 4H), 1.34 (d, J = 7.5 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 153.3, 151.7, 150.9, 135.7, 132.2, 128.8, 127.2, 126.9, 126.4, 122.1, 116.0, 108.8, 55.6, 44.7, 17.5; IR (NaCl, neat): 3062, 3030, 2999, 2964, 2933, 2900, 2869, 2834, 1591, 1559, 1493, 1478, 1464, 1454, 1355, 1290, 1275, 1261,
1259, 1095, 1050, 1014, 867, 777, 759, 740, 693, 668 cm⁻¹; **HRMS** (ESI): calcd for C₁₇H₁₇O (M+H)⁺: 237.1279; found: 237.1288.

6-Methoxy-1-methyl-2-phenyl-1H-indene (3.62)

This compound was synthesized by R. Huang according to the general procedure 3.3, (Z)-4-(4-methoxyphenyl)-3-phenylbut-3-en-2-ol (127.2 mg, 0.5 mmol) was dissolved in dry DCE (2.5 mL). 85% H₃PO₄ (171 μL, 245 mg, 2.5 mmol, 5 equiv) was added, and the reaction was heated to 80 °C for 15 h. Subsequent workup and purification by column chromatography (hexanes:EtOAc 20:1) yielded the title compound as an off-white solid (96.3 mg, 82% yield). **M.p.** 69-70 °C; **¹H NMR** (400 MHz, CDCl₃) δ 7.53 (ap dt, J = 8.2, 1.6 Hz, 2H), 7.40 (t, J = 7.7 Hz, 2H), 7.31 – 7.25 (m, 2H), 7.06 (d, J = 2.1 Hz, 1H), 7.04 (s, 1H), 6.84 (dd, J = 8.2, 2.4 Hz, 1H), 3.91 (q, J = 7.6 Hz, 1H), 3.87 (s, 3H), 1.36 (d, J = 7.5 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 158.2, 151.6, 150.6, 136.8, 135.8, 128.8, 127.1, 126.7, 125.6, 121.5, 112.2, 109.9, 55.7, 44.3, 17.7; **IR** (NaCl, neat): 3080, 3055, 3026, 2996, 2964, 2930, 2867, 2833, 1595, 1559, 1492, 1481, 1473, 1465, 1452, 1430, 1357, 1290, 1257, 1240, 1141, 1122, 1105, 1053, 1032, 914, 867, 815, 762, 748, 726, 693 cm⁻¹; **HRMS** (ESI): calcd for C₁₇H₁₇O (M+H)⁺: 237.1279; found: 237.1280.

1-Isopropyl-5,7-dimethoxy-2-phenyl-1H-indene (3.63)

This compound was synthesized by R. Huang according to the general procedure 3.3, (Z)-1-(3,5-dimethoxyphenyl)-4-methyl-2-phenylpent-1-en-3-ol (93.7 mg, 0.3 mmol) was dissolved in dry DCE (1.5 mL). 85% H₃PO₄ (102.6 μL, 147 mg, 1.5 mmol, 5 equiv) was added, and the reaction was heated to 80 °C for 50 h. Subsequent workup and purification by column chromatography (hexanes:EtOAc 20:1) yielded the title compound as a clear, viscous syrup, which solidified upon standing to a waxy white solid. (76.7 mg, 87% yield). **M.p.** 66-67 °C; **¹H NMR** (400 MHz, CDCl₃) δ 7.49 (d, J = 7.1 Hz, 2H), 7.38 (t, J = 7.6 Hz, 2H), 7.28 (t, J = 7.3 Hz, 1H), 6.87 (d, J = 1.0 Hz, 1H), 6.58 (d, J = 2.0 Hz, 1H), 6.36 (d, J = 2.0 Hz, 1H), 4.09 (dd, J = 2.3, 1.1 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 2.48 (d hept, J = 6.9, 2.3 Hz, 1H), 0.96 (d, J = 7.0 Hz, 3H), 0.55 (d, J = 7.0 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 160.7, 156.2, 153.3, 147.2, 137.3, 128.6, 127.8, 127.5, 127.4, 125.8, 98.4, 95.9, 55.7, 55.2, 54.4, 29.4, 20.5, 18.9; **IR** (NaCl, neat): 3058, 2956, 2935, 2869, 2835, 1598, 1580, 1495, 1478, 1464, 1451, 1436, 1428, 1340, 1317, 1245, 1207, 1167, 1142, 1110, 1048, 936, 867, 822, 759, 728, 695 cm⁻¹; **HRMS** (ESI): calcd for C₂₀H₂₃O₂ (M+H)⁺: 295.1698; found: 295.1685.

3-(1,6-Dimethyl-1H-inden-2-yl)thiophene (3.64)

This compound was synthesized by R. Huang according to the general procedure 3.3, (Z)-3-(thiophen-3-yl)-4-p-tolylbut-3-en-2-ol (48.9 mg, 0.2
mmol) was dissolved in dry DCE (1 mL). 85% H$_3$PO$_4$ (68.4 μL, 98 mg, 1 mmol, 5 equiv) was added, and the reaction was heated to 80 °C for 16 h. Subsequent workup and purification by column chromatography (hexanes:Et$_2$O 80:1) yielded the title compound as a light orange solid (37 mg, 82% yield). **M.p.** 67-69 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.36 – 7.33 (m, 2H), 7.26 – 7.24 (m, 3H), 7.09 – 7.06 (m, 1H), 6.93 (q, J = 7.5 Hz, 1H), 2.41 (s, 3H), 1.41 (d, J = 7.5 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 149.7, 146.7, 141.0, 137.7, 134.7, 127.6, 126.6, 125.9, 125.3, 123.9, 120.8, 120.6, 44.9, 21.8, 18.1; IR (NaCl, neat): 3102, 2004, 2968, 2926, 2865, 1477, 1452, 1369, 1287, 1130, 1086, 1053, 861, 810, 756 cm$^{-1}$; HRMS (EI): calcd for C$_{15}$H$_{14}$S (M)$^+$: 226.0816; found: 226.0818.

2-(3,4-Dimethoxyphenyl)-1,6-dimethyl-1H-indene (3.56)

According to the general procedure 3.3, (Z)-3-(3,4-dimethoxyphenyl)-4-p-tolylbut-3-en-2-ol (89.5 mg, 0.3 mmol) was dissolved in dry DCM (1.5 mL). 85% H$_3$PO$_4$ (82.1 μL, 117.6 mg, 1.2 mmol, 4 equiv) was added, and the reaction was stirred at room temperature for 3.5 days. Subsequent workup and purification by column chromatography (hexanes:EtOAc 9:1) yielded the title compound as an off-white solid (55.1 mg, 66% yield). **M.p.** 108-110 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.26 – 7.24 (m, 2H), 7.08 – 7.03 (m, 3H), 6.95 (s, 1H), 3.94 (s, 3H), 3.90 (s, 3H), 3.83 (q, J = 7.5 Hz, 1H), 2.41 (s, 3H), 1.34 (d, J = 7.5 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 151.5, 149.7, 149.2, 148.7, 141.1, 134.4, 128.9, 127.6, 124.4, 123.9, 120.5, 119.6, 111.4, 109.9, 56.1, 56.0, 44.1, 21.7, 17.8; IR (NaCl, neat): 3052, 3001, 2962, 2930, 2865, 2834, 1601, 1583, 1559, 1506, 1165, 1144, 1026, 913, 851, 763, 731 cm$^{-1}$; HRMS (ESI): calcd for C$_{19}$H$_{21}$O$_2$ (M+H)$^+$: 281.1542; found: 281.1532.

1,5,7-Trimethyl-2-phenyl-1H-indene (3.65)

This compound was synthesized by R. Huang according to the general procedure 3.3, (Z)-4-(3,5-dimethylphenyl)-3-phenylbut-3-en-2-ol (50.5 mg, 0.2 mmol) was dissolved in dry DCE (1 mL). 85% H$_3$PO$_4$ (68.4 μL, 98 mg, 1 mmol, 5 equiv) was added, and the reaction was heated to 80 °C for 40 h. Subsequent workup and column chromatography (hexanes:Et$_2$O 80:1) yielded the title compound as a white solid (37.3 mg, 80% yield). **M.p.** 64-65 °C; $^1$H NMR (400 MHz, CDCl$_3$) 7.58 (ap dt, J = 8.1, 1.6 Hz, 2H), 7.43 (t, J = 7.7 Hz, 2H), 7.31 (ap tt, J = 7.2, 1.6 Hz, 1H), 7.09 (s, 1H), 7.05 (d, J = 0.9 Hz, 1H), 6.86 (s, 1H), 3.97 (q, J = 7.3 Hz, 1H), 2.47 (s, 3H), 2.39 (s, 3H), 1.36 (d, J = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 152.9, 144.8, 144.0, 136.7, 135.6, 132.7, 128.8, 127.7, 127.4, 127.0, 125.8, 119.8, 43.4, 21.5, 18.8, 16.0; IR (NaCl, neat): 3056, 2970, 2931, 2870, 1613, 1600, 1494, 1456, 1445, 1075, 1051, 1031, 884, 863, 842, 759, 733, 693 cm$^{-1}$; HRMS (ESI): calcd for C$_{18}$H$_{19}$ (M+H)$^+$: 235.1487; found: 235.1497.
2-(4-Chlorophenyl)-1,6-dimethyl-1H-indene (3.66)

This compound was synthesized by R. Huang according to the general procedure 3.3, (Z)-3-(4-chlorophenyl)-4-p-tolylbut-3-en-2-ol (54.6 mg, 0.2 mmol) was dissolved in dry DCE (1 mL). 85% H₃PO₄ (68.4 μL, 98 mg, 1 mmol, 5 equiv) was added, and the reaction was heated to 80 °C for 40 h. Subsequent workup and column chromatography (hexanes:EtOAc 80:1) yielded the title compound as a golden-yellow solid (37.5 mg, 74% yield). M.p. 88–89 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.44 (d, J = 8.6 Hz, 2H), 7.35 (d, J = 8.6 Hz, 2H), 7.26 (t, J = 7.2 Hz, 2H), 7.09 (d, J = 8.1 Hz, 1H), 7.04 (s, 1H), 3.84 (q, J = 7.5 Hz, 1H), 2.42 (s, 3H), 1.32 (d, J = 7.5 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 150.3, 149.9, 140.8, 135.1, 134.3, 132.9, 128.9, 128.0, 127.7, 126.5, 124.0, 121.0, 44.1, 21.8, 17.4; IR (NaCl, neat): 3052, 3006, 2968, 2927, 2866, 1571, 1488, 1476, 1453, 1403, 1103, 1092, 1012, 828, 715; HRMS (ESI): calcd for C₁₇H₁₆Cl (M+H)⁺: 255.0940; found: 255.0941.

2-o-Tolyl-1H-indene (3.67)

This compound was synthesized by R. Huang according to the general procedure 3.3, (Z)-3-phenyl-2-o-tolylprop-2-en-1-ol (112.2 mg, 0.5 mmol) was dissolved in dry DCE (2.5 mL). 85% H₃PO₄ (171 μL, 245 mg, 2.5 mmol, 5 equiv) was added, and the reaction was heated to 80 °C for 44 h. Subsequent workup and purification by column chromatography (hexanes:EtO 80:1) yielded the title compound as a light-orange solid (91.2 mg, 88% yield). M.p. 44–45 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.49 (d, J = 7.4 Hz, 1H), 7.41 (ap t, J = 8.9 Hz, 2H), 7.32 – 7.18 (m, 5H), 6.95 (s, 1H), 3.80 (s, 2H), 2.50 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 147.3, 145.7, 143.3, 137.0, 136.0, 131.2, 130.6, 129.0, 127.4, 126.7, 126.1, 124.8, 123.7, 121.1, 42.4, 22.0; IR (NaCl, neat): 3068, 3054, 3018, 2952, 2927, 2866, 1571, 1488, 1476, 1453, 1403, 1103, 1092, 1012, 828, 715; HRMS (ESI): calcd for C₁₆H₁₅(M+H)⁺: 207.1174; found: 207.1171.

1-Methyl-2-(3-nitrophenyl)-1H-indene (3.68)

This compound was synthesized by R. Huang according to the general procedure 3.3, (Z)-3-(3-nitrophenyl)-4-phenylbut-3-en-2-ol (54 mg, 0.2 mmol) was dissolved in dry DCE (1 mL). 85% H₃PO₄ (68.4 μL, 98 mg, 1 mmol, 5 equiv) was added, and the reaction was heated to 80 °C for 44 h. Subsequent workup and purification by column chromatography (hexanes:EtOAc 10:1) yielded the title compound as a thick yellow-orange syrup (32.9 mg, 65% yield). ¹H NMR (400 MHz, CDCl₃) δ 8.37 (ap t, J = 1.9 Hz, 1H), 8.13 (ddd, J = 8.2, 2.2, 0.9 Hz, 1H), 7.85 (ddd, J = 7.8, 1.6, 1.1 Hz, 1H), 7.57 (ap t, J = 8.0 Hz, 1H), 7.49 (d, J = 7.1 Hz, 1H), 7.45 (dd, J = 6.6, 1.1 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.26 (s, 1H), 3.97 (q, J = 7.5 Hz, 1H), 1.37 (d, J = 7.5 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 149.9, 149.6, 142.8, 137.3, 134.1, 132.5, 129.7, 128.8, 127.2, 126.0, 123.2, 121.9, 121.9, 121.5,
(Z)-3,4-Diphenylbut-3-en-2-one (3.69a)

To a solution of 3.16 (350 mg, 1.56 mmol) in dichloromethane (0.25 M) was added Dess-Martin periodinane (1.1 equiv, 730 mg, 1.72 mmol) as a solid (a slight exotherm is observed). After 10 minutes at room temperature TLC (9:1 pentane EtOAc) shows full consumption of starting material. The reaction is quenched with a mixture of aqueous NaHCO₃ and H₂S₂O₃ and allowed to stir for 30 minutes. The reaction mixture is extracted with DCM and washed with NaHCO₃ and brine. After concentration, the crude is purified by flash column chromatography (95:5 pentane:EtOAc) to yield the titled compound as colorless oil (84% yield, 290 mg).

1H NMR (400 MHz, CDCl₃) δ 7.41 – 7.36 (m, 2H), 7.36 – 7.19 (m, 8H), 6.93 (s, 1H), 2.19 (s, 3H); 13C NMR (101 MHz, CDCl₃) δ 207.4, 143.9, 137.2, 135.8, 129.4, 128.9, 128.8, 128.7, 128.4, 126.7, 31.7; IR (NaCl, neat): 3081, 3057, 3025, 1700, 1695, 1599, 1494, 1449, 1350, 1276, 1206, 1158, 1078, 1035, 933, 765, 695, 529 cm⁻¹; HRMS (ESI): calcd for C₁₆H₁₄NO₂ (M+H)+: 252.1025; found: 252.1017.

(Z)-3-(3-Methoxy-4-methylphenyl)-4-phenylbut-3-en-2-one (3.69b)

To a solution of 3.39 (671 mg, 2.5 mmol) in dichloromethane (0.25 M) was added Dess-Martin periodinane (1.1 equiv, 1.17 g, 2.75 mmol) as a solid (a slight exotherm is observed). After 10 minutes at room temperature TLC (9:1 pentane EtOAc) shows full consumption of starting material. The reaction is quenched with a mixture of aqueous NaHCO₃ and H₂S₂O₃ and allowed to stir for 30 minutes. The reaction mixture is extracted with DCM and washed with NaHCO₃ and brine. After concentration, the crude is purified by flash column chromatography (85:15 pentane:EtOAc) to yield the titled compound as a yellow oil (82% yield, 514 mg).

1H NMR (400 MHz, CDCl₃) δ 7.38 – 7.25 (m, 5H), 7.21 (dd, J = 4.2, 2.0 Hz, 2H), 6.88 (s, 1H), 6.82 (d, J = 9.1 Hz, 1H), 3.85 (s, 3H), 2.241 (s, 3H), 2.237 (s, 3H); 13C NMR (101 MHz, CDCl₃) δ 208.1, 158.3, 143.9, 136.2, 129.3, 129.1, 128.9, 128.7, 128.2, 127.5, 127.4, 125.5, 110.3, 55.7, 31.8, 16.6. IR (NaCl, neat): 3055, 3001, 2951, 2835, 1693, 1604, 1508, 1447, 1350, 1296, 1250, 1134, 1030 cm⁻¹; HRMS (ESI): calcd for C₁₈H₁₈O₂ (M)^+: 266.1307; found: 266.1302.

(Z)-3-(3-Nitropheny1)-4-phenylbut-3-en-2-one (3.69c)

To a solution of 3.46 (673 mg, 2.5 mmol) in dichloromethane (0.25 M) was added Dess-Martin periodinane (1.1 equiv, 1.17 g, 2.75 mmol) as a solid (a slight exotherm is observed). After 10 minutes at room temperature TLC
(9:1 pentane EtOAc) shows full consumption of starting material. The reaction is quenched with a mixture of aqueous NaHCO₃ and H₂S₂O₃ and allowed to stir for 30 minutes. The reaction mixture is extracted with DCM and washed with NaHCO₃ and brine. After concentration, the crude is purified by flash column chromatography (9:1 hexane:EtOAc) to yield the titled compound as a yellow solid (79% yield, 528 mg). M. p. 65–68 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.33 (ap t, J = 2.0 Hz, 1H), 8.20 (ddd, J = 8.2, 2.2, 0.9 Hz, 1H), 7.75 (ddd, J = 7.8, 1.6, 1.0 Hz, 1H), 7.56 (t, J = 8.0 Hz, 1H), 7.45–7.33 (m, 5H), 7.16 (s, 1H), 2.24 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 206.3, 148.8, 141.6, 139.2, 135.2, 133.0, 132.9, 129.9, 129.4, 129.1, 129.0, 123.1, 121.9, 31.9; IR (NaCl, neat): 3082, 3024, 1701. 1693, 1528, 1380, 1161, 764 cm⁻¹; HRMS (EI): calcd for C₁₆H₁₃NO₃ (M)⁺: 267.0895; found: 267.0899.

(Z)-3-[(4-Chlorophenyl)-4-phenylbut-3-en-2-one (3.69d)

To a solution of 3.44 (647 mg, 2.5 mmol) in dichloromethane (0.25 M) was added Dess–Martin periodinane (1.1 equiv, 1.17 g, 2.75 mmol) as a solid (a slight exotherm is observed). After 10 minutes at room temperature TLC (9:1 pentane EtOAc) shows full consumption of starting material. The reaction is quenched with a mixture of aqueous NaHCO₃ and H₂S₂O₃ and allowed to stir for 30 minutes. The reaction mixture is extracted with DCM and washed with NaHCO₃ and brine. After concentration, the crude is purified by flash column chromatography (95:5 hexane:EtOAc) to yield the titled compound as a colorless solid (78% yield, 500 mg). M. p. 78–81 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.41 – 7.29 (m, 9H), 6.98 (s, 1H), 2.23 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 207.1, 142.9, 135.8, 135.6, 134.6, 130.3, 129.2, 129.0, 128.9, 128.2, 31.8; IR (NaCl, neat): 3059, 3028, 1693, 1589, 1489, 1354, 1157, 1092, 822, 760 cm⁻¹; HRMS (EI): calcd for C₁₆H₁₃ClO (M)⁺: 256.0655; found: 256.0652.

Procedure 3.4: Protocol for O-acetyl oxime synthesis: (3Z)-3,4-Diphenylbut-3-en-2-one O-acetyl oxime (3.70a)

The compound was synthesized using a procedure adapted from literature.³⁵ The ketone 3.69a (1 mmol, 222 mg), hydroxylamine hydrochloride (5 equiv, 347 mg) and sodium acetate (5 equiv, 410 mg) were dissolved in methanol (5 ml) and stirred at room temperature until no 3.69a remained, monitoring by TLC (pentane:EtOAc 9:1). Upon completion, the methanol was evaporated off under reduced pressure and the reaction mixture was suspended in ethyl acetate and filtered through a short silica plug. After concentration, a stirring bar and DCM (6 ml) were added to the flask, and the reaction was cooled to 0 °C. Triethylamine (1.2 equiv, 170 μl) was added, followed by a dropwise addition of acetyl chloride (1.2 equiv, 86 μl). The reaction was warmed to room

temperature and allowed to stir overnight. After ~16 h, the reaction was quenched with water and extracted with DCM, drying with Na₂SO₄. After concentration, column chromatography (Pentane: EtOAc 95:5 to 9:1) yielded the final product as a colorless oil (72% yield of major isomer, overall 93% yield 5:1 d.r.). Note: 8a and the corresponding oxime coelute on TLC and the acylation reaction can only be monitored by NMR. ¹H NMR (400 MHz, CDCl₃) δ 7.52 – 7.44 (m, 2H), 7.43 – 7.30 (m, 7H), 7.30 – 7.23 (m, 1H), 7.03 (s, 1H), 2.19 (s, 3H), 2.11 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 169.5, 164.7, 138.7, 137.0, 136.2, 131.5, 129.1, 128.9, 128.7, 128.5, 128.2, 127.0, 20.1, 17.8; IR (NaCl, neat): 3056, 3025, 2935, 1756, 1495, 1447, 1366, 1223, 1202, 993, 919 cm⁻¹; HRMS (ESI): calcd for C₁₈H₁₈NO₂ (M+H)⁺: 280.1338; found: 280.1342.

(3Z)-3-(3-Methoxy-4-methylphenyl)-4-phenylbut-3-en-2-one O-acetyl oxime (3.70b)

The titled compound was prepared by a general procedure 3.4, on 1 mmol scale yielding a pale yellow oil (63% of 5:1 mixture of isomers, major isomer characterized); ¹H NMR (400 MHz, CDCl₃) δ 7.40 – 7.20 (m, 7H), 6.92 (s, 1H), 6.82 (d, J = 9.1 Hz, 1H), 3.85 (s, 3H), 2.25 (s, 3H), 2.19 (s, 3H), 2.11 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 169.7, 164.8, 158.3, 136.7, 136.5, 130.7, 129.6, 129.3, 129.0, 128.7, 127.8, 127.1, 125.8, 110.1, 55.6, 20.1, 17.8, 16.6; IR (NaCl, neat): 3024, 3003, 2950, 2925, 2837, 1770, 1761, 1606, 1505, 1497, 1362, 1301, 1250, 1195, 1136 cm⁻¹; HRMS (ESI): calcd for C₂₀H₂₂NO₃ (M+H)⁺: 324.1600; found: 324.1605.

(3Z)-3-(3-Nitrophenyl)-4-phenylbut-3-en-2-one O-acetyl oxime (3.70c)

The titled compound was prepared by a general procedure 3.4, on 1 mmol scale yielding a yellow solid (65% yield, 4:1 d.r., major isomer characterized). M.p. 107-111 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.34 (ap t, J = 2.0 Hz, 1H), 8.18 (ddd, J = 8.2, 2.2, 0.9 Hz, 1H), 7.81 (ddd, J = 7.8, 1.7, 1.0 Hz, 1H), 7.56 (t, J = 8.0 Hz, 1H), 7.37 (m, 5H), 7.15 (s, 1H), 2.22 (s, 3H), 2.11 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 168.8, 164.3, 148.8, 140.9, 135.3, 134.9, 134.2, 133.0, 129.9, 123.1, 121.9, 20.0, 17.9; IR (NaCl, neat): 3088, 2924, 2855, 1759, 1629, 1369, 1239, 1202 cm⁻¹; HRMS (ESI): calcd for C₁₈H₂₀N₃O₄ (M+NH₄)⁺: 342.1454; found: 342.1456.

(3Z)-3-(4-Chlorophenyl)-4-phenylbut-3-en-2-one O-acetyl oxime (3.70d)

The titled compound was prepared by general procedure 3.4, on 1 mmol scale yielding a colorless solid (45% yield, 4:1 d.r., major isomer characterized). M.p. 105-105 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.28 (m, 9H), 6.92 (s, 1H), 2.11 (s, 3H), 2.01 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ
200

169.2, 164.5, 137.3, 135.8, 135.8, 132.0, 129.1, 129.1, 128.7, 128.4, 128.3, 20.0, 17.8

IR (NaCl, neat): 3084, 3055, 3027, 2923, 1771, 1756, 1496, 1447, 1362, 1203, 1174, 1092, 1013, 921 cm⁻¹; HRMS (ESI): calcd for C₁₈H₁₇ClNO₂ (M+H)⁺: 314.0948; found: 314.0950.

Procedure 3.5: Standard procedure for electrocyclization: 2-methyl-3-phenylquinoline (3.71a)

Compound 3.70a (0.2 mmol, 56 mg) was dissolved in toluene (2 ml) in a 5 ml microwave vial with a stirring bar. The vial was fitted with a Teflon-lined septum and placed in a 150 °C oil bath for 16 h. In the morning, the TLC indicated full starting material consumption. The reaction mixture could be concentrated or loaded on a column directly (pentane to 95:5 pentane:EtOAc). The titled compound is obtained in 68% yield (30 mg) as a colorless solid which turns dark overtime. The analytical data is consistent with literature.³⁶ ¹H NMR (400 MHz, CDCl₃) δ 8.10 (d, J = 8.5 Hz, 1H), 7.98 (s, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.76 – 7.65 (m, 1H), 7.55 – 7.35 (m, 6H), 2.69 (s, 3H).

2-Methyl-3-(3-methoxy-4-methylphenyl)quinoline (3.71b)

According to the general procedure 3.5, the titled compound can be synthesized in 55% yield (29 mg) as a yellow solid. M. p. 131-135 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.06 (d, J = 8.4 Hz, 1H), 7.93 (s, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.67 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.53 – 7.45 (m, 1H), 7.23 – 7.14 (m, 2H), 6.91 (d, J = 8.0 Hz, 1H), 3.90 (s, 3H), 2.69 (s, 3H), 2.30 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 158.0, 157.6, 147.1, 136.2, 135.9, 132.0, 131.8, 129.3, 128.6, 127.9, 127.6, 127.2, 126.9, 126.1, 110.0, 55.6, 24.9, 16.5; IR (NaCl, neat): 2994, 2955, 2913, 2832, 1558, 1504, 1419, 263.1310; HRMS (EI): calcd for C₁₈H₁₇NO (M)⁺: 263.1316; found: 263.1316.

2-Methyl-3-(3-nitrophenyl)quinoline (3.71c)

According to the general procedure 3.5, on 0.12 mmol scale the titled compound can be synthesized in 79% yield (25 mg) as a yellow-brown solid. M. p. 117-120 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.32 – 8.26 (m, 2H), 8.08 (d, J = 8.5 Hz, 1H), 8.00 (s, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.78 – 7.71 (m, 2H), 7.67 (dd, J = 8.9, 7.6 Hz, 1H), 7.55 (dd, J = 11.0, 4.0 Hz, 1H), 2.67 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 156.6, 148.6, 147.7, 141.8, 136.8, 135.5, 133.4, 130.3, 129.8, 128.8, 127.8, 126.8, 126.8, 124.4, 122.9, 24.7; IR (NaCl, neat): 2963, 2924, 2858, 1531, 1489, 1322, 1099, 1084 741 cm⁻¹; HRMS (EI): calcd for C₁₈H₁₂N₂O₂ (M)⁺: 264.0899; found: 264.0894.

2-Methyl-3-(4-chlorophenyl)quinoline (3.71d)

According to the general procedure 3.5, the titled compound can be synthesized in 73% yield (37 mg) as a yellow solid. 

**M. p.** 71-73 °C; **$^1$H NMR** (400 MHz, CDCl$_3$) $\delta$ 8.06 (d, $J = 8.5$ Hz, 1H), 7.92 (s, 1H), 7.78 (d, $J = 8.1$ Hz, 1H), 7.70 (ddd, $J = 8.4, 6.9, 1.4$ Hz, 1H), 7.54 – 7.47 (m, 1H), 7.47 – 7.41 (m, 2H), 7.37 – 7.29 (m, 2H), 2.65 (s, 3H). **$^{13}$C NMR** (101 MHz, CDCl$_3$) $\delta$ 157.2, 147.4, 138.5, 136.4, 134.7, 134.0, 130.8, 129.8, 128.9, 128.7, 127.7, 126.9, 126.4, 24.7; **IR** (NaCl, neat): 3055, 2970, 2920, 1558, 1489, 1419, 1092, 1014, 837, 752 cm$^{-1}$; **HRMS** (EI): calcd for C$_{16}$H$_{12}$NCl (M)$^+$: 253.0658; found: 253.0652.
Chapter 4

*Synthesis of Fused Heterocycles with a 1,2,3-Triazole Core*
4 Synthesis of Fused Heterocycles with a 1,2,3-Triazole Core

4.1 Introduction

Heterocyclic motifs containing nitrogen find use in a variety of different fields, and their presence in many pharmaceuticals and agrochemicals further promotes research into the synthesis of new analogues. In the following chapter synthetic strategies to access fused triazoles are discussed. This work presents a new access point to such motifs through the copper-catalyzed azide alkyne cycloaddition (CCAAC) of iodinated alkynes and a subsequent palladium-catalyzed direct arylation. The presented method is advantageous in the synthesis of these motifs for a number of reasons. Namely, the two reactions used are based on sustainable principles, such as atom economy, and the sequence can be conducted in a one-pot protocol without isolation of intermediates. Triazoles have received considerable attention since the development of the copper catalyzed reaction, and both fused and linear triazoles are commonly found in pharmaceutically relevant targets (Figure 4.1).

4.1.1 Copper-Catalyzed Azide Alkyne Cycloaddition

Huisgen first discovered the reaction between azides and alkynes in 1963. The preliminary reaction proceeded with heating, giving a mixture of 1,4- and 1,5-substituted isomeric products (Eqn 4.1). This transformation found little use, until the development of a copper catalyzed variant from the Sharpless and Meldal groups (Scheme 4.1). This catalytic reaction, often regarded as the best representation of a “click reaction,” proceeded in exceptionally high yields,

\[ \text{Huisgen R. Angew. Chem. 1963, 75, 604-637.} \]

regioisomeric ratios and at low reaction temperature.\(^4\) The 1,4-isomer could be formed exclusively. This reaction was extremely robust, and as a result found a lot of applications in the chemical community. Aside from synthesizing triazole containing small molecules, this cycloaddition is often utilized in conjugation of macromolecules, such as enzymes and polymers.\(^5\)

![Chemical structures](image)

**Figure 4.1**: Triazole-containing molecules with significant biological activity.

Despite the robustness of this reaction, until recently, the copper-catalyzed cycloaddition had a downside of only being applicable to terminal alkynes. Additionally, until recently, 1,5-substituted-1,2,3-triazoles were accessible primarily through intramolecular cycloaddition reactions\(^6\) or directed lithiation of monosubstituted triazoles.\(^7\) In 2005, Jia and Fokin groups

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reported the use of ruthenium catalysts in this cycloaddition to obtain the 1,5-isomer selectively (Scheme 4.1).\(^8\)

\[
\begin{align*}
R &= \text{Ruthenium catalyst} \\
\text{N}_3 &= \text{Azide} \\
N &= \text{Triazole}
\end{align*}
\]

Scheme 4.1 First examples of 1,4- and 1,5-selective azide alkyne cycloaddition.

The mechanism of the catalytic cycloaddition was thought to proceed through the formation of a copper-acetylide species \(\text{II} \) (Figure 4.2). DFT calculations and the observed second order kinetics with respect to copper suggest a dimeric or polymeric copper catalyst.\(^9\) Intermediates akin to \(\text{IIIa} \) and \(\text{IIIb} \) have been proposed, wherein the azide and the alkyne are activated by different copper centers. These intermediates then react to give a species akin to \(\text{IV} \), which then undergoes a ring contraction to yield copper-triazole species \(\text{V} \), which can be protonated. Some intermediate copper(I) triazolide species similar to \(\text{V} \) have been isolated and characterized by using sterically hindered NHC ligands.\(^{10}\)

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The above mechanism is very different from the thermal process, which occurs through a concerted (2+3) cycloaddition without any precoordination. It is this coordination of the azide to copper and formation of a cyclic structure IV that ensures high selectivity in the reaction. It should be noted that other metal-acetylidest are known to react with triazoles, but often furnish the opposite regioisomer. It is proposed that with bromomagnesium- and lithium acetylides a nucleophilic addition to the azide occurs as a first step instead of a concerted cycloaddition (Scheme 4.2). The requisite formation of a metalloacetylide complex II in copper mediated reactions of alkynes and azides precludes the use of internal alkynes. As a result, fully substituted triazoles can be challenging to synthesize, but over the years a number of creative strategies have been discovered.

4.1.1.1 Synthesis of Trisubstituted 1,2,3-Triazoles

Through trapping of metallotriazole intermediates. In metal-mediated reactions a metallotriazole intermediate formed after the cycloaddition reaction can often be trapped with electrophilic reagents to yield fully substituted triazoles. A few recent reports from the Wu, Zhang, and Dzyuba groups show that the cuprate intermediate V can be converted to 5-
halogenated triazole products (Eqn 4.2). To date this is only achievable through the use of stoichiometric copper. The use of such 5-iodotriazoles in classic cross coupling reactions yields fully substituted triazoles in good yields.

Reactions of preformed bromomagnesium acetylides with azides, in the absence of copper, yield similar organometallic species with the opposite regioselectivity (Scheme 4.2). Krasinski showed that the obtained magnesium triazolides could be trapped by a variety of electrophilic reagents. The difference in selectivity is proposed to emerge from a change in mechanism. It is suggested that instead of a concerted cycloaddition, the Grignard reagents adds to the azide first, with the cyclization occurring thereafter (Scheme 4.2)

Scheme 4.2 Proposed reactivity of azides with alkynyl Grignard reagents.

Through the use of TMS-protected acetylenes. The uncatalyzed cycloaddition has been reported to proceed with internal alkynes, but because of the lack of regioselectivity, this reactivity has been primarily applied to symmetrical alkynes (Scheme 4.3). An exception to this trend are TMS substituted alkynes, which react to give a single regioisomer in the thermal

\[ \text{R}^2-\text{N}_3 + \text{EtMgBr} \rightarrow \text{EtMgBr} \]


cycloaddition, albeit in moderate yields. Presumably, the selectivity resulted from steric factors, and the products were TMS substituted at the 4 position. The TMS protected acetylenes have also been used in one-pot Sonogashira/Cu-catalyzed cycloaddition sequences, but the removal of TMS in situ was essential. The TMS group could further be functionalized, or removed to yield 1,5-substituted triazoles.

**Scheme 4.3** Reaction of internal alkynes under thermal cycloaddition conditions.

A more recent report from the Harrity group described a thermal cycloaddition of alkynylboronates and azides (Scheme 4.4). This example is noteworthy, since selective parallel functionalization of the ensuing 1,4,5-trisubstituted triazole was possible through cross-coupling chemistry. The B(pin) group alone had little influence on the regioselectivity of the reaction. More recent reports mirror these findings showing that a variety of other TMS protected acetylenes undergo this cycloaddition reaction.

**Scheme 4.4** Reaction of internal alkynes.

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Through reactions of halogenated acetylenes. In 2005, a report from the Rutjes group described the copper-catalyzed cycloaddition of brominated alkynes (Eqn 4.3). This transformation utilized two catalytic copper catalysts, and the final 5-bromo triazoles could be obtained in good yields.

![Chemical structure](4.3)

During the development of the chemistry discussed in this chapter, a report from the Fokin group described the CCAAC reaction of iodoalkynes (Eqn 4.4). The authors found that the nature of the amine ligand is very important for the reaction outcome, and the optimal ligands were the tris(propargyl)amine derived triazolo ligands, TBTA and TTTA. This work also described a convenient method of iodination of terminal alkynes, which was used throughout the work described in this chapter. The products of the reaction were also shown to be useful substrates in a Suzuki reaction in a one-pot process.

![Chemical structure](4.4)

A couple of mechanistic postulates were proposed for the cycloaddition of these iodoalkynes (Figure 4.3). The reaction could proceed through a similar mechanism to non-halogenated alkynes, through formation of an intermediate copper-acetylide I (cycle a). After cycloaddition the copper-triazole intermediate III is turned over through a σ-bond metathesis, regenerating

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species I. An alternative to this mechanism is activation of acetylene through formation of a π-complex IV, which then reacts with the azide (cycle b). In the latter mechanism, the carbon-iodine bond is never broken, and the authors prefer this mechanism, since no protonated triazole could be detected when the reaction was conducted in protic media.

![Diagram of possible mechanisms for the copper-catalyzed cycloaddition of iodoalkynes.](image)

**Figure 4.3:** Possible mechanisms for the copper-catalyzed cycloaddition of iodoalkynes.

**Through reaction of aluminum acetylides.** An interesting example from the Micouin group described a copper-catalyzed cycloaddition of aluminum acetylides with azides.\(^{21}\) The reaction proceeded in excellent regioselectivities, favoring the 1,4-isomers after protonation, and good yield. Importantly, the aluminum triazole species could be reacted with a number of electrophiles in a one-pot procedure to give trisubstituted products. The proposed mechanism did not involve formation of copper acetylide and was similar to cycle b (where I = AlR\(_3\), Figure 4.3).

**Through direct arylation.** Considering the limitations in the reaction of internal alkynes and the recent advancements in direct functionalization chemistry, C-H functionalizing reactions provide a useful alternative to synthesize fully substituted triazoles. Recently, a number of studies featuring direct functionalization of 1,4-triazoles have been reported. In 2007, the Gevorgyan group reported the direct arylation of triazoles using palladium catalysis (Eqn 4.5).\(^{22}\) They observed that in N-monosubstituted triazoles the arylation favored formation of the 1,5-

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substituted product, and further direct arylation to give 1,4,5-trisubstituted products was sluggish. This, along with the lack of a kinetic isotope effect, suggested an electrophilic palladation mechanism. Following this publication, a number of reports described this reactivity utilizing various aryl halides.\(^{23}\)

In 2008, Ackermann reported that it is possible to perform this transformation using a copper catalyst (Eqn 4.6).\(^{24}\) The use of copper was noteworthy, since the cycloaddition and direct arylation could be performed as a one-pot process using a single batch of copper iodide catalyst.

Another interesting report from the same group described a palladium-catalyzed dehydrogenative intramolecular coupling of triazoles (Eqn 4.7).\(^{25}\) The reaction was quite general, although high temperatures were required. A limitation was that ortho-blocking groups were necessary in the synthesis of phenanthrotriazoles. Pivalic acid was necessary for the reaction, but the preferential arylation of less acidic hydrogens did not support a base-assisted metallation mechanism.


4.1.2 Palladium-Catalyzed C-H Arylation of Aromatic Compounds

Over the last two decades, direct functionalization of aromatic C-H bonds has become a popular approach in synthesis. In these reactions, instead of utilizing prefunctionalized substrates, substitution is introduced directly to replace a C-H bond. The end result is a less wasteful synthesis in terms of steps and reagents used.\(^{26}\) Using this strategy ensures more concise syntheses by foregoing the steps required to activate the starting materials necessary for conventional cross-coupling reactions. Direct arylation can be accomplished by a variety of different metal catalysts, but palladium catalyzed methods are by far the most common.\(^{26}\) The direct arylation of heteroaromatic compounds is widespread, but on the other hand, the use of halogenated heterocycles as electrophiles in C-H functionalizing reactions is less common.\(^{27}\)

The mechanism of palladium-catalyzed C-H functionalization has been the subject of debate over the last decade. It is apparent that several different mechanisms are possible, and the exact mode of C-H insertion is highly dependent on the structure of the reactant and the conditions used (Figure 4.3). In early arylations of heterocycles the Heck-type mechanism was typically proposed (b, Figure 4.3). This mechanism involved either an anti β-hydride elimination or an isomerization of the palladium complex to allow for syn β-hydride elimination.\(^{28}\) Although there is little mechanistic support for this mechanism in arylation of electron rich or neutral aromatic compounds, it is still proposed when highly electron deficient motifs possessing extended conjugated systems are arylated.

The electrophilic metallation mechanism is one of the more commonly accepted modes of C-H activation, especially in reactions with electron rich heterocycles (b, Figure 4.4). Extensive work


from the Sames and the Gevorgyan groups has supported this mechanism in arylations of indole and azole systems.\textsuperscript{29} The observations suggesting this mechanism included: 1) secondary KIE observed at the 3-position of indole, 2) negative slope in the Hammett plot, 3) inability to trap any intermediates of Heck-type carbopalladation with appended alkenes, and 4) correlation of relative reaction rates with Friedel-Crafts acylation of substituted azoles.

The concerted metallation/deprotonation mechanism has gained a lot of popularity in recent years (c, Figure 4.4). The most significant advocate of this mode of C-H activation has been Fagnou, reporting a number of mechanistic studies, including computational studies to support this mechanism. DFT calculations of this mechanism show that the site selectivity of heterocycle arylation can be accurately predicted.\textsuperscript{30} Either the carboxylate base, or common additives, such as pivalic acid derivatives, are thought to act as proton shuttles in the reaction, assisting in the deprotonation step.\textsuperscript{31}

\textsuperscript{29} (a) Lane, B. S.; Brown, M. A.; Sames, D. J. Am. Chem. Soc. 2005, 127, 8050; (b) Lane, B. S.; Sames, D. Org. Lett. 2004, 6, 2897; (c) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. Org. Lett. 2004, 6, 1159.
\textsuperscript{31} For review of carboxylate assisted C-H functionalizations see: Ackermann, L. Chem. Rev. 2011, 111, 1315.
The other mechanisms, the anionic cross-coupling and direct C-H insertion, have gained little support (d and e, Figure 4.4). The former mechanism would require a significantly stronger base than the ones usually used in direct arylation reactions. This mechanism is still proposed for reactions with motifs bearing highly acidic C-H bonds, such as imidazoles. There exists little evidence for direct C-H insertions, although it is still sometimes proposed when strong coordinating groups are present. Notably, in direct arylations no KIE is often observed, which is inconsistent with direct C-H insertion, and this mechanism is further disfavored by computational studies.32

4.1.2.1 Intramolecular Direct Annulation in the Synthesis of Heterocycles

In 2004, the Fagnou group disclosed one of the first highly efficient methods for the synthesis of benzochromene derivatives through direct arylation of aryl groups with appended aryl halides (Eqn 4.8).33 The reaction scope was extensively studied and it was found that 5, 6, and 7-membered rings could be formed using this reaction. In addition to aryl bromides, it was possible to utilize aryl chlorides and iodides, with the former, PCy3 was used as a ligand, and with the latter, silver salt additives were necessary to prevent catalyst inhibition. The reaction conditions were superior to previous reports of similar reactions in terms of efficiency and tolerance for different substitution patterns.34 The authors noted a primary kinetic isotope effect of 4.25, which suggested that the C-H functionalization was not occurring through an electrophilic palladation, and that a concerted metallation/deprotonation or σ-bond metathesis mechanism was more likely.

![Reaction Scheme](image)


In addition to Fagnou, the Harayama group has reported similar transformations, albeit typically using very high palladium loading.\textsuperscript{35} Since these reports, considerable work has expanded the scope of this reaction, and currently many applications of domino reactions using intramolecular direct arylation have been developed.\textsuperscript{36}

The Lautens group recently reported the synthesis of nitrogen-containing heterocycles through the use of such direct arylation reactions. In 2007, we reported the reaction of aryl halides across bicyclic systems, akin to norbornene (Eqn 4.9).\textsuperscript{37} This was followed by direct annulation to form a new six-membered ring. When norbornadiene was used, a retro-Diels Alder cycloaddition furnished the final pyrroloquinoline products. Shortly thereafter, the reaction of dibromoolefins was reported. This transformation formed a similar intermediate, which underwent direct arylation to give products of a similar structure (Eqn 4.10).\textsuperscript{38}

Our work on these systems has led us to examine similar annulations of other heterocycles. Because of their presence in biologically active agents (\textit{vide infra}), we were interested in developing methods to access fused 1,2,3-triazoles, such as 4.3 (Scheme 4.5). We envisioned a method to synthesize these motifs by applying direct arylation conditions to the Huisgen

\begin{itemize}
  \item \textsuperscript{37} Hulcoop, D. G.; Lautens, M. \textit{Org. Lett.} \textbf{2007}, \textit{9}, 1761.
  \item \textsuperscript{38} Chai, D.; Lautens, M. \textit{J. Org. Chem.} \textbf{2009}, \textit{74}, 3054
\end{itemize}
cycloadducts of iodoalkynes 4.1 and azides. Notably, 5-halotriazoles have not been used in direct arylation prior to this report, and this strategy would complement the earlier work in this field by giving access to products with different electronics and substitution patterns. Motifs such as 4.3 constitute a class of structurally unique heterocycles, and the work described in this chapter accesses them in high yields.39

![Scheme 4.5 Proposed synthesis of fused heterocycles.](image)

The work in the following section was conducted in collaboration with other researchers. The initial idea behind this project was conceived by Mr. Letian Wang.40 Some preliminary results were obtained by a postdoctoral fellow, Dr. Angelica Aguilar-Aguilar.41 A considerable portion of the scope and the establishment of the strategy used to access the substrates were developed by a postdoctoral fellow, Dr. Karolin Geyer.42 The work of Dr. Geyer is labeled as such.

4.2 One-Pot Synthesis of Triazole-Containing Heterocycles

4.2.1 Substrate Synthesis

At the onset of this project compounds with the structures akin to 4.7 were investigated. The initial route toward these motifs involved the use of ortho-aminobenzoic acids 4.4 in a Paal-Knorr pyrrole synthesis (Scheme 4.6). A subsequent adjustment of the oxidation state led to the aldehyde 4.6. This intermediate was reacted in a Ramirez olefination to give a dibromoolefin.

---


40 Letian Wang was a senior PhD student in the Lautens group, who examined systems resembling this work. His contributions are not discussed in this thesis.

41 Dr. Angelica Aguilar-Aguilar was postdoctoral fellow from Mexico. Her work included development of a different route to substrate synthesis and study of reactions of bromoalkynes.

42 Dr. Karolin Geyer was a postdoctoral fellow from the Seeberger group, ETH. Current location – BASF, Mulheim, Germany.
which could be easily converted to the bromoalkyne 4.7. Although successful, this sequence was quite lengthy, furnishing the final bromoalkynes in low yields. Sufficient material was accessed to examine the key cycloaddition and direct arylation reaction.

![Scheme 4.6 Synthesis of substrates from benzoic acids.](image)

When the reaction was examined in more detail it was found that iodoalkynes were more practical in the key transformation. Therefore a more modular route to the substrates was developed, in which the halogen was introduced in the final steps. The final route for pyrrolyl substituted substrates is depicted in Scheme 4.7. Ortho-bromoanilines were the commercial starting materials, and the pyrrole moiety was introduced through the Paal-Knorr reaction. The alkyne was introduced through Sonogashira cross coupling, and subsequent deprotection and iodination furnished the desired substrates.

![Scheme 4.7 Synthesis of substrates from ortho-bromoanilines.](image)

The Paal-Knorr pyrrole synthesis was quite efficient for substrates 4.8, and a typical protocol in DCE and water gave the products in near quantitative yields (Table 4.1). The coupling of electron deficient anilines was more challenging and required more forcing conditions. In these cases reflux in neat acetic acid was necessary (4.15 and 4.16).

---


44 This synthetic sequence was developed by Dr. Aguilar-Aguilar.

45 This synthetic sequence was developed by Dr. Karolin Geyer.
To synthesize an analogue 4.18, bearing an indole moiety, the indole was introduced through Ullmann coupling (Eqn 4.11). Using copper powder to promote this reaction the product could be isolated in good yield.

The Sonogashira reaction was also efficient for most of the substrates studied (Table 4.2). In the synthesis of compound 4.25 and 4.27 the yield was quite low, but a useable amount of material could be isolated. Other methods employing room temperature conditions gave considerably lower yields. In certain cases the purification of the Sonogashira product was difficult. In this case the crude or impure material was carried through the next step and purified thereafter.

---


Table 4.2 Sonogashira coupling reaction of ortho-pyrroloaryl bromides.

\[
\begin{align*}
\text{Br} & \quad \text{TMS} \\
\text{Me} & \quad \text{Cl} \\
\text{F} & \quad \text{F} \\
\text{O}_2\text{N} & \quad \text{CO}_2\text{Me} \\
\text{NO}_2 & \quad \text{Me} \\
\end{align*}
\]

\[
\text{Pd(PPh}_3)_2\text{Cl}_2 (5 \text{ mol\%}) \\
\text{CuI (10 mol\%)} \\
\text{NEt}_3 (\text{neat}) \\
\text{reflux, 16 h}
\]

In addition to compounds with N-containing heterocycle motifs, a few examples with other heterocyclic nucleophiles, such as furan and thiophene, were also synthesized. In these cases the heterocycle was connected to the aryl halide through a C-C bond. Because of extensive developments in Suzuki cross coupling of sterically hindered aryl halides, the sequence of events was different in the synthesis of these compounds (Scheme 4.8).

We found that starting with ortho-iodobromobenzene 4.17 a single Sonogashira cross coupling gave the alkyne 4.28 in near quantitative yield. A Suzuki reaction using a Buchwald ligand, S-Phos, gave the desired products in high yields.

---

In order to deprotect the TMS alkynes, a few different protocols were examined. The typical conditions utilizing potassium carbonate in methanol furnished the products in moderate but highly variable yields. The reaction using TBAF for desilylation gave much higher yields reproducibly (Table 4.3). In the case of 4.41 a low yield was observed because of challenging Sonogashira coupling in the preceding step.

**Table 4.3** Deprotection of TMS-protected alkynes.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.32</td>
<td>80%</td>
</tr>
<tr>
<td>4.33</td>
<td>76%</td>
</tr>
<tr>
<td>4.34</td>
<td>93%</td>
</tr>
<tr>
<td>4.35</td>
<td>90%</td>
</tr>
<tr>
<td>4.36</td>
<td>45%</td>
</tr>
<tr>
<td>4.37</td>
<td>86%</td>
</tr>
<tr>
<td>4.38</td>
<td>90%</td>
</tr>
<tr>
<td>4.39</td>
<td>90%</td>
</tr>
<tr>
<td>4.40</td>
<td>86%</td>
</tr>
<tr>
<td>4.41</td>
<td>25%</td>
</tr>
<tr>
<td>4.42</td>
<td>88%</td>
</tr>
<tr>
<td>4.43</td>
<td>85%</td>
</tr>
<tr>
<td>4.44</td>
<td>84%</td>
</tr>
</tbody>
</table>

*Experiments performed by K. Geyer. *Yields over two steps.*
To iodinate the resulting terminal alkynes conditions developed in the Fokin and Sharpless group were utilized.\textsuperscript{19} \textit{N}-Iodomorpholine proved to be a superior ‘I’ source in these reactions.\textsuperscript{50} The protocol using catalytic CuI was ideal, giving full conversion and high yields (Table 4.4). Very electron deficient compounds furnished products 4.50 and 4.52 in moderate yields because of byproduct formation. Other procedures utilizing \( n \)-butyllithium resulted in lower yields.

\textbf{Table 4.4} Iodination of terminal alkynes.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.45</td>
<td>82%</td>
</tr>
<tr>
<td>4.46*</td>
<td>76%</td>
</tr>
<tr>
<td>4.47*</td>
<td>80%</td>
</tr>
<tr>
<td>4.48*</td>
<td>83%</td>
</tr>
<tr>
<td>4.49*</td>
<td>96%</td>
</tr>
<tr>
<td>4.50*</td>
<td>41%</td>
</tr>
<tr>
<td>4.51*</td>
<td>98%</td>
</tr>
<tr>
<td>4.52*</td>
<td>50%</td>
</tr>
<tr>
<td>4.53*</td>
<td>95%</td>
</tr>
<tr>
<td>4.54</td>
<td>87%</td>
</tr>
<tr>
<td>4.55</td>
<td>92%</td>
</tr>
<tr>
<td>4.56</td>
<td>78%</td>
</tr>
<tr>
<td>4.57</td>
<td>92%</td>
</tr>
</tbody>
</table>

\* Performed by K. Geyer.

\textbf{4.2.2 Optimization of Reaction}

We initially examined the reactivity of bromoalkyne 4.7a (Scheme 4.9). The cycloaddition with benzyl azide under conditions developed by the Rutjes group, proceeded in modest yield to give 4.58.\textsuperscript{18} After some optimization of the direct arylation reaction, we observed formation of the desired product 4.59 in good yield under palladium/PPh\textsubscript{3} catalysis. However, high temperature and prolonged reaction time were required to complete the reaction. At this time, a report by

\textsuperscript{50} This reagent was easily prepared from morpholine and iodine. See reference 19.
Fokin and coworkers on the synthesis and cycloaddition of iodoalkynes prompted us to examine the iodinated substrate 4.45.\textsuperscript{19} Reaction of 4.45, using catalytic CuI and tris((1-benzyl-1H-1,2,3-triazolyl)methyl)amine (TBTA) ligand, furnished the triazole intermediate 4.60 in excellent yield. Notably, the direct arylation now proceeded to give a higher yield of 4.61 at 80 °C in THF. These milder annulation conditions were more promising in our goal of developing a one-pot protocol for these two transformations. To our gratification, after the completion of the [3+2] cycloaddition, it was possible to add Pd(OAc)$_2$, PPh$_3$, base and tetrabutylammonium bromide as solids and allow the annulation to proceed. The yields for the one-pot process were comparable or better than the two step procedure.

**Scheme 4.9** Preliminary experiments on cycloaddition and direct annulation.

### 4.2.3 Scope Studies

With a set of optimal conditions in hand, we examined the scope of this one-pot cycloaddition/annulation reaction (Table 4.5). A variety of different azides were examined, and good yields were obtained with benzyl and alkyl azides (entries 1-5). More sterically encumbered aryl- and TMS-azides failed to yield any cycloaddition product. Notably, the
palladium loading could be reduced to 1 mol% with the reaction still giving synthetically useful yields (entry 2). Both electron poor and electron neutral alkyne substrates reacted efficiently. Halogenated compounds could be synthesized in good yield (entries 8-10). Ester and nitro substituents were well tolerated (entries 11, 12), whereas the substrate bearing a cyano group gave a moderate yield (entry 13).

**Table 4.5** Effects of substitution pattern on reactivity in a one-pot reaction.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield (%)(^b)</th>
<th>Entry</th>
<th>Product</th>
<th>Yield (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Product 1" /></td>
<td>4.61</td>
<td>94</td>
<td>11(^a)</td>
<td><img src="image2.png" alt="Product 11" /></td>
</tr>
<tr>
<td>2</td>
<td>(R_2 = \text{Bn})</td>
<td>4.61</td>
<td>70(^c)</td>
<td>3</td>
<td>(R_2 = \text{PMB})</td>
</tr>
<tr>
<td>4</td>
<td>(R_2 = \text{PNB})</td>
<td>4.61(^c)</td>
<td>86</td>
<td>5</td>
<td>(R_2 = \text{Hex})</td>
</tr>
<tr>
<td>6</td>
<td>(R_2 = \text{TMS})</td>
<td>-</td>
<td>12(^a)</td>
<td><img src="image3.png" alt="Product 12" /></td>
<td>4.66</td>
</tr>
<tr>
<td>7</td>
<td>(R_2 = \text{PMP})</td>
<td>-</td>
<td>13(^a)</td>
<td><img src="image4.png" alt="Product 13" /></td>
<td>4.67</td>
</tr>
<tr>
<td>8(^a)</td>
<td><img src="image5.png" alt="Product 8" /></td>
<td>4.62</td>
<td>85</td>
<td>9(^a)</td>
<td><img src="image6.png" alt="Product 9" /></td>
</tr>
<tr>
<td>10(^a)</td>
<td><img src="image7.png" alt="Product 10" /></td>
<td>4.64</td>
<td>75</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: iodoalkyne (0.1 mmol), azide (0.1 mmol), \([\text{Cu}]\) (5 mol%), and TBTA (5 mol%) were stirred in THF at room temperature until full conversion was indicated (TLC). \([\text{Pd}]\) (10 mol%), \(\text{PPh}_3\) (20 mol%), \(\text{Bu}_4\text{NBr}\) (0.1 mmol) and \(\text{K}_2\text{CO}_3\) (0.1 mmol) were added as a solid. \(^b\) Isolated yields. \(^c\) Reaction performed using 1 mol% \(\text{Pd(OAc)}_2\) and 2 mol% \(\text{PPh}_3\). \(^d\) An additional 5 mol% of \(\text{CuI}\) and TBTA were added to the reaction after 24 h. \(^e\) Reactions performed by K. Geyer. PMB: \(p\)-methoxy benzyl. PNB: \(p\)-nitrobenzyl. PMP: \(p\)-methoxyphenyl.
We observed that several compounds containing heterocyclic nucleophiles other than pyrrole performed well in the reaction, giving good yields (Table 4.6). Notably, a single isomer was observed for the 3-thiophenyl substituted compound (4.70, entry 2). A product with a phenanthroline backbone 4.72 could also be accessed in high yield, illustrating that non-heterocyclic nucleophiles can participate in this reaction (entry 4). We observed a sluggish cycloaddition with certain substrates. However, addition of an extra 5 mol% of CuI and TBTA afforded full conversion, and the overall sequence still proceeded in excellent yields (entries 2-4).

Table 4.6 Effect of the heteroaromatic and aromatic nucleophile on reactivity.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield (%)(^b)</th>
<th>Entry</th>
<th>Product</th>
<th>Yield (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Product 1" /> 4.69</td>
<td>62</td>
<td>3</td>
<td><img src="image3.png" alt="Product 3" /> 4.71</td>
<td>80(^c)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Product 2" /> 4.70</td>
<td>92(^c,d)</td>
<td>4(^e)</td>
<td><img src="image4.png" alt="Product 4" /> 4.72</td>
<td>97(^e)</td>
</tr>
</tbody>
</table>

\(^a\) See Table 4.5 for representative procedure. \(^b\) Isolated yields. \(^c\) An additional 5 mol% of CuI and TBTA were added to the reaction after 24 h. \(^d\) A single regioisomer is observed. \(^e\) A control experiment shows no formation of 4.72 in the absence of Pd(OAc)\(_2\).  

During evaluation of this work an alternative access point to some of the above products was suggested by a referee. In theory, a 6-\(\pi\) electrocyclization/oxidation of non-halogenated triazoles could furnish some of these products. To compare our route with this strategy we subjected the non-halogenated triazole 4.73 to several representative reaction conditions (Scheme 4.10). Although most thermal/oxidative conditions did not show any starting material consumption,
some product could be obtained upon irradiation of 4.73 in the presence of iodine.\textsuperscript{51,52} While this approach is feasible, our work on the direct arylation of iodontriazoles provides a high-yielding method toward these targets, and is an uncommon example of direct arylation of heterocyclic electrophiles.

\begin{equation}
\text{Scheme 4.10 Experiments on 6π-electrocyclization/oxidation.}
\end{equation}

4.2.4 Further Work

The above synthesis is noteworthy because of the modularity of this approach. Cross-coupling chemistry was instrumental for the design of this synthetic sequence since it allowed using small functionalized motifs and combining them in a convergent fashion. Upon completion of this work it appeared that the annulation of 5-iodotriazoles was quite a general and high-yielding reaction. We posed that a variety of other polycyclic motifs could be accessed from this key intermediate. The remainder of this chapter describes the stepwise synthesis of such heterocycles.

4.3 Two-Step Synthesis of Triazole-Containing Heterocycles

The work in the following section was performed in collaboration with Jacqueline M. Schulman\textsuperscript{53} and Adam Friedman.\textsuperscript{54} Their contributions are labeled as such. The author of this


\textsuperscript{52} Other unsuccessful conditions examined: (a) DDQ (1 equiv) CH\textsubscript{2}Cl\textsubscript{2}:MeSO\textsubscript{4}H; (b) FeCl\textsubscript{3} (3 equiv), MeNO\textsubscript{2}, CH\textsubscript{2}Cl\textsubscript{2}.

\textsuperscript{53} Jacqueline M. Schulman was a Masters student in the Lautens group (2010-2011). Current location: Toronto Research Chemicals, Toronto.
thesis provided the guidance and direction for the project, contributed to the scope, and assisted J. Schulman and A. Friedman with interpretation of experimental and analytical data.

4.3.1 Synthesis of Fused Heterocycles through Direct Arylation

To expand the scope of the developed transformation, we decided to examine a class of substrates with an aliphatic linker between the triazole and the aromatic nucleophile (Scheme 4.11). These substrates possess substantially more freedom of rotation, and it was anticipated that direct annulation could be more difficult. In fact, previously developed conditions for the reaction of 4.45 were completely ineffective. During the study of substrates such as 4.74 we discovered that it was possible to furnish products from cyclization onto the azide substituent.

![Scheme 4.11 Modification of the original strategy.](image)

4.3.1.1 Synthesis of Substrates

The synthesis of the reactants for this part of the project was rather straightforward. Initially, the terminal acetylene compounds were prepared through alkylation of substituted phenols with propargyl bromide (Table 4.7). Subsequently, the same protocol for iodination of the terminal alkynes was applied, using catalytic CuI and N-iodomorpholine as the iodinating reagent. In some cases, purification of the iodoalkyne was challenging, and the material was subjected to the next reaction directly without purification (entry 9).

---

54 Adam Friedman was a fourth year undergraduate NSERC-USRA student. Current location: MSc student, University of Toronto.
Table 4.7 Synthesis of substrates.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Compound</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Entry</th>
<th>Compound</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4-MeOC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>4.76</td>
<td>71</td>
<td>7&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.82</td>
<td>90</td>
</tr>
<tr>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4-t-BuC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>4.77</td>
<td>93</td>
<td>8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.83</td>
<td>96</td>
</tr>
<tr>
<td>3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3,5-(MeO)&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;3&lt;/sub&gt;</td>
<td>4.78</td>
<td>99</td>
<td>9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.84</td>
<td>-&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>4.79</td>
<td>64</td>
<td>10&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.85</td>
<td>99</td>
</tr>
<tr>
<td>5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3-F&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>4.80</td>
<td>60</td>
<td>11&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.86</td>
<td>89</td>
</tr>
<tr>
<td>6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2-ClC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>4.81</td>
<td>88</td>
<td>12&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.87</td>
<td>99</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated Yields. <sup>b</sup>Performed by A. Friedman. <sup>c</sup>Isolated after subsequent cycloaddition reaction.

The triazole motif was introduced in the same manner as previously in good yields (Table 4.8). The only exceptions were compounds 4.88 and 4.94, which furnished the product in only moderate yields. With these iodotriazoles in hand, conditions for the cyclization were developed.

Table 4.8 Copper-catalyzed cycloaddition with iodoalkynes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4-MeOC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;O</td>
<td>(4-MeOC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;)CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>4.88</td>
<td>50</td>
</tr>
<tr>
<td>2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4-MeOC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;O</td>
<td>n-Hex</td>
<td>4.89</td>
<td>78</td>
</tr>
<tr>
<td>3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4-t-BuC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;O</td>
<td>n-Hex</td>
<td>4.90</td>
<td>77</td>
</tr>
<tr>
<td>4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3,5-(MeO)&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;O</td>
<td>n-Hex</td>
<td>4.91</td>
<td>59&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;O</td>
<td>n-Hex</td>
<td>4.92</td>
<td>81</td>
</tr>
<tr>
<td>6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3-F&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;O</td>
<td>n-Hex</td>
<td>4.93</td>
<td>72</td>
</tr>
<tr>
<td>7&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2-ClC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;O</td>
<td>n-Hex</td>
<td>4.94</td>
<td>67</td>
</tr>
<tr>
<td>8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>n-Pr</td>
<td>4-MeOC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>4.95</td>
<td>87</td>
</tr>
<tr>
<td>9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>n-Pr</td>
<td>4-MeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>4.96</td>
<td>82</td>
</tr>
<tr>
<td>10&lt;sup&gt;b&lt;/sup&gt;</td>
<td>n-Pr</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>4.97</td>
<td>85</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yields. <sup>b</sup>Performed by J. M. Schulman. <sup>c</sup>Performed by A. Friedman. <sup>d</sup>Yield over two steps.
4.3.1.2 Studies of Direct Annulation

The first substrate examined was compound 4.88. Upon subjecting this material to ligand-free Jeffery conditions we observed the formation of a mixture of compounds. Upon closer examination it appeared that two major isomeric products were formed. It became evident that cyclization onto both PMP groups was occurring (Scheme 4.12). The prospect of synthesizing e-fused triazoles such as 4.99 intrigued us, but in order to overcome the selectivity issue N-hexyl substituted compound 4.89 was examined.

Substrate 4.89 gave only partial conversion under the above conditions, and a variety of other protocols more tailored to this direct annulation were screened. The reaction conditions developed by the Fagnou group, which utilized sub-stoichiometric amounts of pivalic acid, yielded the product 4.100 in modest yield, but the reaction was very clean.\(^{55}\) By increasing the temperature and time it was possible to obtain the products in high yields with full conversion of starting materials.\(^{56}\) Pivalic acid was necessary for the reaction, and lower yields were seen in its absence (entry 2, Table 4.9). A number of substrates were examined, and it was observed that the reaction worked quite well with electron rich substrates (Table 4.9). The electron poor 4.93 furnished the product 4.104 in moderate yield.

Upon establishing the conditions discussed above, the cyclization unto the N-sidechain was examined. Substrate 4.95, bearing an n-butyl substituent at the 4-position was studied. After considerable optimization, reaction conditions utilizing CsOPiv as a base were found to give

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\(^{55}\) For original conditions see: Lafrance, M.; Lapointe, D.; Fagnou, K. *Tetrahedron* 2008, 64, 6015.

\(^{56}\) For complete optimization data see J. M. Schulman, Synthesis of 1,2,3-Triazole-Fused Heterocycles via Palladium Catalyzed Annulation of 5-Iodotriazoles M.Sc. Thesis, University of Toronto, 2011.
good yields of the final products. Several substituted compounds were screened, but the scope was found to be limited to electron rich and electron neutral aromatic substituents (Scheme 4.13).

Table 4.9 Scope of intramolecular direct arylation of 5-iodotriazoles.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield (%)(^b)</th>
<th>Entry</th>
<th>Product</th>
<th>Yield (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^c)</td>
<td><img src="4.100" alt="Image" /></td>
<td>88</td>
<td>5(^c)</td>
<td><img src="4.103" alt="Image" /></td>
<td>68</td>
</tr>
<tr>
<td>2(^c)</td>
<td><img src="4.100" alt="Image" /></td>
<td>25(^a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3(^c)</td>
<td><img src="4.101" alt="Image" /></td>
<td>93</td>
<td>6(^c)</td>
<td><img src="4.104" alt="Image" /></td>
<td>51</td>
</tr>
<tr>
<td>4(^c)</td>
<td><img src="4.102" alt="Image" /></td>
<td>75</td>
<td>7(^c)</td>
<td><img src="4.105" alt="Image" /></td>
<td>79</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: 5-iodo-1,2,3-triazole (1 equiv), PdCl\(_2\)(MeCN)\(_2\) (5 mol%), P(\(\rho\)-FC\(_6\)H\(_4\))\(_3\) (5 mol%), K\(_2\)CO\(_3\) (3 equiv) and PivOH (30 mol%) were dissolved in solvent (0.26 M) and heated to 130 °C. \(^b\) Isolated yields. \(^c\) Performed by A. Friedman. \(^d\) Reaction performed in the absence of PivOH.
4.3.2 Synthesis of Fused Triazoles via Heck Coupling

During the study of direct arylation of aromatic compounds we were also examining compounds capable of undergoing a Heck reaction. This strategy would yield even simpler fused heterocycles with exocyclic alkenes akin to 4.110 (Scheme 4.14).

4.3.2.1 Synthesis of Substrates

In order to examine this strategy substrates derived from allyl bromides were synthesized. The synthesis of these motifs was very straightforward and included an iodination and alkylation of propargyl alcohols and amines (Scheme 4.15, 4.16). It was necessary to iodinate propargyl alcohols prior to the introduction of the alkene substituent, and this process was accomplished by treating propargyl alcohol with KOH and iodine in a methanolic solution, or through sequential lithiation and iodination sequence.

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57 Experiments performed by J. Schulman
The subsequent allylation reaction was performed under typical alkylation conditions to give compounds 4.113 and 4.114 in good yields (Scheme 4.16). The obtained iodoalkynes were subjected to the cycloaddition conditions used throughout this chapter (Table 4.10).

Table 4.10 Synthesis of iodo triazoles for Heck coupling.

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>R</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>O</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH=CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>n-Hex</td>
<td>4.115</td>
<td>79</td>
</tr>
<tr>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NTs</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH=CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>n-Hex</td>
<td>4.116</td>
<td>84</td>
</tr>
<tr>
<td>3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>O</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH=CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>4-MeOC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>4.117</td>
<td>60</td>
</tr>
<tr>
<td>4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>O</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH=CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>4-MeOC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>4.118</td>
<td>56</td>
</tr>
<tr>
<td>6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>O</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH=CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>4.119</td>
<td>54</td>
</tr>
<tr>
<td>5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>O</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH=CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>4-O&lt;sub&gt;2&lt;/sub&gt;NCS&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>4.120</td>
<td>60</td>
</tr>
<tr>
<td>8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>O</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH=CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>3-thienyl</td>
<td>4.121</td>
<td>55</td>
</tr>
<tr>
<td>7&lt;sup&gt;b&lt;/sup&gt;</td>
<td>O</td>
<td>n-Bu</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH=CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>4.122</td>
<td>86</td>
</tr>
<tr>
<td>9</td>
<td>O</td>
<td>H</td>
<td>n-Hex</td>
<td>4.123</td>
<td>99</td>
</tr>
<tr>
<td>10&lt;sup&gt;b&lt;/sup&gt;</td>
<td>O</td>
<td>E-CH&lt;sub&gt;2&lt;/sub&gt;CH=CHCO&lt;sub&gt;2&lt;/sub&gt;Me</td>
<td>4-MeOC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>4.124</td>
<td>30</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yields. <sup>b</sup> Performed by J. M. Schulman.
To access compound 4.126 a slightly different protocol was utilized (Scheme 4.17). Compound 4.123 was used as a key intermediate. This alcohol could be alkylated or acylated to yield a variety of different motifs. Through mesylation and a subsequent nucleophilic displacement with malonate the intermediate 4.125 could be isolated. This material was allylated to give the desired iodo-triazole 4.126. With a variety of iodo-triazoles in hand the scope of the Heck addition could be examined.

![Scheme 4.17 Synthesis of carbocyclic substrates.](image)

### 4.3.2.2 Studies of Heck Addition of 5-Iodotriazoles

The examination of typical Heck coupling conditions revealed that the protocol developed by Larock furnished the desired product in good yields (85%).\(^\text{58}\) In these conditions, Pd-dppm catalyst was used in the presence of CsOPiv as a base. Significant optimization of the reaction conditions led to marginally higher yields (Table 4.11).\(^\text{56}\) The scope studies of the transformation showed that the reaction was general with regard to the azide and the linker used. Cyclization onto the azide substituent could also be achieved in excellent yield to give 4.135. When we examined substrates bearing disubstituted alkenes, a mixture of isomeric products was observed.

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\(^{58}\) Zhao, J.; Larock, R. C. *Org. Lett.* 2005, 7, 701
Table 4.11 Scope of intramolecular Heck reaction of 5-iodotriazoles.\(^a\)

\[
\begin{array}{ccc}
\text{Entry} & \text{Product} & \text{Yield (\%)}^b \\
1 & \text{4.127} & 92 \\
2^c & \text{4.128} & 99 \\
3 & \text{4.129} & 89 \\
4^c & \text{4.130} & 92 \\
5^c & \text{4.131} & 99 \\
6^c & \text{4.132} & 99 \\
7^c & \text{4.133} & 61 \\
8^c & \text{4.134} & 84 \\
9^c & \text{4.135} & 99 \\
\end{array}
\]

\(^a\) Reaction conditions: 5-iodo-1,2,3-triazole (1 equiv), PdCl\(_2\)(MeCN)\(_2\) (5 mol\%), PPh\(_3\) (10 mol\%), and CsOPiv (2 equiv) were dissolved in solvent (0.0625 M) and heated to 100 °C. \(^b\) Isolated yields. \(^c\) Reaction performed by J. M. Schulman.

4.4 Conclusions

In summary, this chapter described a series of reactions developed for the synthesis of fused heterocyclic motifs containing the 1,2,3-triazole core. The synthetic sequences use three to five steps to access the final products. The use of cross coupling chemistry enables a modular approach for the synthesis of compound libraries.

Section 4.2 described a protocol for conducting both copper-catalyzed cycloaddition and direct annulation in a one-pot process. This work complements the available methods for the synthesis of similar heterocycles in terms of reaction scope. For instance phenanthrotriazoles could be accessed without the need to block the ortho aromatic position, which was necessary in previous
reports. In Section 4.3 the development of different heterocyclic motifs is explored through a stepwise synthesis.
4.5 Experimental Section

General Experimental Procedures. Unless otherwise noted, reactions were carried out under argon atmosphere, in flame-dried, single-neck, round bottom flasks fitted with a rubber septum, with magnetic stirring. Air- or water-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Where necessary (so noted), solutions were deoxygenated by successive freeze-pump-thaw cycles (≥ three iterations). Organic solutions were concentrated by rotary evaporation at 23–40 °C under 40 Torr (house vacuum). Analytical thin layer chromatography (TLC) was performed with Silicycle™ normal phase glass plates (0.25 mm, 60-A pore size, 230-400 mesh). Visualization was done under a 254 nm UV light source and generally by immersion in acidic aqueous-ethanolic vanillin solution, or in potassium permanganate (KMnO₄), followed by heating using a heat gun. Purification of reaction products was generally done by flash chromatography with Silicycle™ Ultra-Pure 230-400 mesh silica gel, as described by Still et al.⁵⁹

Materials. Unless otherwise indicated, starting materials and catalysts were obtained from Aldrich, Strem or VWR and used without further purification. Tetrahydrofuran, 1,4-dioxane and toluene were purified by distillation under N₂ from Na/benzophenone immediately prior to use.

Instrumentation. Proton nuclear magnetic resonance spectra (^1H NMR) and carbon nuclear magnetic resonance spectra (^13C NMR) were recorded at 23 °C with a Bruker Avance III 400 (400 MHz/100 MHz) NMR spectrometer equipped with a ATM BBOF probe, a Varian Mercury 400 (400 MHz/100 MHz) NMR spectrometer equipped with a Nalorac4N-400 probe, a Varian Unity 500 (500 MHz/125 MHz) NMR spectrometer equipped with a Nalorac3-500 probe, or a Varian 400 (400 MHz/100 MHz) NMR spectrometer equipped with ATB8123-400 probe. Recorded shifts for protons are reported in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvents (CHCl₃: δ 7.26, CHDCl₂: δ 5.29, C₆H₄D₂: δ 7.15, CD₂HOD: δ 3.30). Chemical shifts for carbon resonances are reported in parts per million (δ scale) downfield from the carbon resonances of the solvent (CDCl₃: δ 77.0, CH₂Cl₂: δ 53.8, C₆D₆: δ 128.0, CD₃OD: δ 49.2). Data are represented as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintuplet, sx = sextet, sp = septuplet, dd = doublet of doublets, m = multiplet, br = broad), and coupling constant (J, Hz); ap t (apparent triplet) and ap td or ap dt (apparent doublet of triplets) imply a doublet of triplets instead of a true triplet. Infrared (IR) spectra were obtained using a Perkin-Elmer Spectrum 1000 FT-IR spectrometer as a neat film on a NaCl plate. Data is presented as follows: frequency of absorption (cm⁻¹). High resolution mass spectra were obtained from a SI2

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Micromass 70S-250 mass spectrometer (EI) or an ABI/Sciex Qstar mass spectrometer (ESI). Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected.

### 4.5.1 Characterization Data

General procedures for Paal-Knorr synthesis of bromo-pyrroles

**Procedure 4.1:** The aniline was dissolved in DCE, H₂O and AcOH were added and the reaction mixture was heated to 80 °C. 2,5-dimethoxytetrahydrofuran was added and the reaction mixture was stirred at 80 °C overnight. After cooling down to room temperature, the remainder was poured into an aqueous NaHCO₃ solution (100 mL), extracted with Et₂O (3 x 20 mL), the combined organic phases were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. Subsequent flash column chromatography with the indicated solvents yielded the target molecules.

**Procedure 4.2:** The aniline was mixed with 2,5-dimethoxytetrahydrofuran and glacial HOAc and stirred under reflux for 2h. After cooling down to room temperature, the residue was diluted with H₂O (40 mL), extracted with Et₂O (3 x 30 mL), the combined organic phases were washed with aqueous KOH (1M, 2 x 10 mL), H₂O and brine, dried over MgSO₄ and concentrated under reduced pressure. Subsequent flash column chromatography with the indicated solvents yielded the target molecules.

The aniline starting materials were purchased from Aldrich and Combiblocks and used without further purification. Compound 4.9 and 4.11 were synthesized by P. Thansandote according to procedure 4.1.⁶⁰

**1-(2-Bromo-4-chlorophenyl)-1H-pyrrole (4.12)**

This compound was prepared by Dr. K. Geyer according to the general procedure 4.1, the corresponding aniline (1.89 g, 9.6 mmol) and 2,5-dimethoxytetrahydrofuran (1.31 mL, 1.33 g, 10 mmol, 1.05 equiv) were reacted in DCE (1.96 mL), H₂O (1.12 mL) and AcOH (0.07 mL) at 80 °C overnight. Subsequent workup and flash column chromatography (pentane:CH₂Cl₂ 10:1) yielded 4.12 in 96% yield. Spectral data were consistent with the literature.⁶¹

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1-(2-Bromo-4,6-difluorophenyl)-1H-pyrrole (4.13)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.1, the corresponding aniline (2.00 g, 9.6 mmol) and 2,5-dimethoxytetrahydrofuran (1.31 mL, 1.33 g, 10 mmol, 1.05 equiv) were reacted in DCE (1.96 mL), H₂O (1.12 mL) and AcOH (0.07 mL) at 80 °C overnight. Subsequent workup and flash column chromatography (pentane:CH₂Cl₂ 3:1) yielded 4.13 as a colorless solid in 92% yield. 

\(^1\)H NMR (400 MHz, CDCl₃): δ 7.28-7.25 (m, 1H), 6.97 (ddd, 1H, J = 9.2, 8.2, 2.8 Hz), 6.73-6.72 (m, 2H), 6.38 (ap t, 2H, J = 2.1 Hz); \(^13\)C NMR (101 MHz, CDCl₃): δ 161.3 (dd, J = 254.0, 12.7 Hz), 158.6 (dd, J = 256.0, 13.5 Hz), 126.2 (dd, J = 15.1, 5.1 Hz), 123.5 (dd, J = 11.9, 1.5 Hz), 122.4 (2), 116.3 (dd, J = 25.1, 4.0 Hz), 109.6 (2), 104.3 (dd, J = 25.9, 25.0 Hz); IR (NaCl, neat): 3070, 1590, 1511, 1428, 1282, 1126, 1019, 863, 841, 733 cm⁻¹; M. p.: 78-81 °C; HRMS (EI): calcd for C₁₀H₉N₂Br (M⁺): 256.9652; found: 256.9646.

1-(2-Bromo-5-fluorophenyl)-1H-pyrrole (4.14)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.1, the corresponding aniline (1.82 g, 9.6 mmol) and 2,5-dimethoxytetrahydrofuran (1.31 mL, 1.33 g, 10 mmol, 1.05 equiv) were reacted in DCE (1.96 mL), H₂O (1.12 mL) and AcOH (0.07 mL) at 80 °C overnight. Subsequent workup and flash column chromatography (pentane:CH₂Cl₂ 5:1) yielded 4.14 as an orange oil in quantitative yield. 

\(^1\)H NMR (400 MHz, CDCl₃): δ 7.65 (dd, J = 8.9, 5.7 Hz, 1H), 7.09 (dd, J = 8.8, 3.0 Hz, 1H), 6.99 (ddd, J = 8.9, 7.6, 3.0 Hz, 1H), 6.89 (ap t, J = 2.0 Hz, 2H), 6.36 (ap t, J = 2.0 Hz, 2H); \(^13\)C NMR (100 MHz, CDCl₃): δ 161.8 (d, J = 249.4 Hz), 141.4 (d, J = 10.0 Hz), 134.7 (d, J = 8.7 Hz), 122.0 (2), 115.9 (d, J = 20.6 Hz), 115.7 (d, J = 22.5 Hz), 113.8 (d, J = 3.9 Hz), 109.7 (2); \(^19\)F NMR (376 MHz, CDCl₃): δ -112.9 (td, J = 7.5, 7.5 Hz); IR (NaCl, neat): 3092, 2917, 1591, 1484, 1320, 1236, 1198, 1087, 1061, 954, 863, 725 cm⁻¹; HRMS (ESI): calcd for C₁₀H₈BrF (M+H⁺): 238.9746; found: 238.9748.

3-Bromo-5-nitro-2-(1H-pyrrol-1-yl)benzonitrile (4.15)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.2, the corresponding aniline (125 mg, 0.52 mmol) and 2,5-dimethoxytetrahydrofuran (0.08 mL, 83.2 mg, 0.63 mmol, 1.22 equiv) were reacted in glacial AcOH (2 mL) under reflux for 2 h. Subsequent workup and flash column chromatography (pentane:EtOAc 20:1) yielded 4.15 as yellow solid in 94% yield (based on recovered starting material). 

\(^1\)H NMR (400 MHz, CDCl₃): δ 8.77 (d, J = 2.5 Hz, 1H), 8.56 (d, J = 2.5 Hz, 1H), 6.88 (ap t, J = 2.0 Hz, 2H), 6.49 (ap t, J = 2.0 Hz, 2H); \(^13\)C NMR (75 MHz, CDCl₃): δ 147.5, 146.3, 132.9, 127.6, 123.5, 121.7 (2), 114.11, 113.45, 111.80 (2C); IR (NaCl, neat): 3070, 2921, 2351, 1586, 1532, 1482, 1346, 1079, 1024, 903, 821, 738 cm⁻¹; M. p.: 148-152 °C; HRMS (EI): calcd for C₁₁H₈BrN₃O₂ (M⁺): 290.9643; found: 290.9649.
1-(2-Bromo-4-methyl-6-nitrophenyl)-1H-pyrrole (4.16)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.2, the corresponding aniline (115.5 mg, 0.52 mmol) and 2,5-dimethoxytetrahydrofuran (0.08 mL, 80.6 mg, 0.61 mmol, 1.22 equiv) were reacted in glacial AcOH (2 mL) under reflux for 2 h. Subsequent workup and flash column chromatography (pentane:CH₂Cl₂ 20:1) yielded 4.16 as red solid in quantitative yield. ¹H NMR (400 MHz, CDCl₃): δ 7.64 (s, 1H), 7.50 (s, 1H), 6.59 (ap t, J = 2.0 Hz, 2H), 6.26 (ap t, J = 2.1 Hz, 2H), 2.38 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 148.6, 140.9, 137.2, 131.0, 124.4, 123.6, 122.3 (2), 110.1 (2), 20.8; IR (NaCl, neat): 3119, 2919, 2351, 1521, 1344, 1265, 1078, 808, 724 cm⁻¹; M. p.: 85-91 °C; HRMS (ESI): calcd for C₁₁H₁₀BrN₂O₂ (M+H)⁺: 280.9920; found: 280.9913.

1-(2-Bromophenyl)-1H-indole (4.18)

The titled compound was prepared by a modified Ullmann-type coupling procedure.⁶² Aryl iodide (0.77 ml, 6 mmol, 1.2 equiv), indole (600 mg, 5 mmol), copper metal (64 mg, 1 mmol, 20 mol%) and K₃PO₄ (2.12 g, 10 mmol, 2 equiv) were weighed into a thick walled screw-top flask. MeCN (6.5 ml, 0.8 M) was added and the flask was purged with argon, sealed and placed into a 130 °C oil bath. After 24 hours almost full conversion of indole is observed. The reaction was filtered through a fritted funnel washing with ethyl acetate, and concentrated under reduced pressure. Flash chromatography (100% pentane to 95:5 pentane:EtOAc) yielded the titled compound in 80% yield as a pale yellow oil. The characterization data is consistent with literature.⁶³ ¹H NMR (400 MHz, CDCl₃) δ 7.76 (dd, J = 12.1, 4.5 Hz, 1H), 7.71-7.66 (m, 1H), 7.45-7.40 (m, 2H), 7.31 (ddd, J = 8.1, 5.9, 3.3 Hz, 1H), 7.23 (d, J = 3.2 Hz, 1H), 7.20-7.15 (m, 2H), 7.12-7.06 (m, 1H), 6.69 (dd, J = 3.2, 0.6 Hz, 1H).

Procedure 4.3: General procedure for Sonogashira coupling for the synthesis of TMS-alkynes.

The aryl bromide, CuI and Pd(PPh₃)₂Cl₂ were weighed into an oven dried flask which was purged with argon. NEt₃ and TMS-acetylene were added and the reaction mixture was stirred at 90 °C overnight. After cooling down to room temperature, the reaction mixture was filtered through celite, the solid residue was washed with EtOAc and the combined organic phases were concentrated under reduced pressure. Flash column chromatography using the stated solvent mixtures yielded the desired products.

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According to the general procedure 4.3, aryl bromide 4.9 (500 mg, 2.25 mmol) was mixed with CuI (5.1 mg, 0.027 mmol, 1.2 mol%) and Pd(PPh₃)₂Cl₂ (77.2 mg, 0.11 mmol, 5 mol%) under argon, NEt₃ (11.25 mL) and TMS-acetylene (481 µL, 331.7 mg, 3.37 mmol, 1.5 eqv) were added and the reaction mixture was stirred at 90 °C overnight. Subsequent workup and flash column chromatography (gradient pentane 100% to pentane:CH₂Cl₂ 50:1) yielded 4.10 in quantitative yield as an orange oil. ¹H NMR (400 MHz, CDCl₃): δ 7.57 (dd, J = 7.7, 1.5 Hz, 1H), 7.36 (aptd, J = 7.8, 1.4 Hz, 1H), 7.29 (dd, J = 8.1, 1.2 Hz, 1H), 7.22 (aptd, J = 7.5, 1.3 Hz, 1H), 7.13 (ap t, J = 2.2 Hz, 2H), 6.30 (t, J = 2.2 Hz, 2H), 0.19 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 142.4, 134.1, 129.5, 124.6, 121.5 (2C), 117.6, 109.1 (2C), 101.8, 99.7, -0.4 (3C); IR (NaCl, neat): 2957, 2154, 1559, 1491, 1322, 1253, 1085, 1027, 855, 739 cm⁻¹; HRMS (EI): calcd for C₁₅H₁₇NSi: 239.1130 (M)⁺; found: 239.1134.

1-(4-Methyl-2-((trimethylsilyl)ethynyl)phenyl)-1H-pyrrole (4.19)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.3, aryl bromide 4.11 (2.3 g, 9.6 mmol) was mixed with CuI (22 mg, 0.12 mmol, 1.2 mol%) and Pd(PPh₃)₂Cl₂ (337 mg, 0.48 mmol, 5 mol%) under argon, NEt₃ (50 mL) and TMS-acetylene (2.2 mL, 1.41 g, 14.4 mmol, 1.5 equiv) were added and the reaction mixture was stirred at 90 °C overnight. Subsequent workup and flash column chromatography (gradient pentane:CH₂Cl₂ 200:1 to pentane:CH₂Cl₂ 20:1) yielded 4.19 as an orange oil in 87% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.38 (s, 1H), 7.18 - 7.15 (m, 2H), 7.08 (ap t, J = 2.2 Hz, 2H), 6.28 (ap t, J = 2.2 Hz, 2H), 2.34 (s, 3H), 0.18 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 140.5, 136.2, 134.8, 130.6, 124.9, 121.9, 117.7, 109.2, 102.4, 99.6, 21.0, -0.01; IR (NaCl, neat): 3428, 2959, 2156, 1647, 1499, 1321, 1252, 1087, 955, 848 cm⁻¹; HRMS (EI): calcd for C₁₆H₂₀NSi (M)⁺: 253.1287; found: 253.1292.

1-(4-Chloro-2-((trimethylsilyl)ethynyl)phenyl)-1H-pyrrole (4.20)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.3, aryl bromide 4.12 (992 mg, 3.87 mmol) was mixed with CuI (8.8 mg, 0.046 mmol, 1.2 mol%) and Pd(PPh₃)₂Cl₂ (135.8 mg, 0.19 mmol, 5 mol%) under argon, NEt₃ (20 mL) and TMS-acetylene (830 µL, 570.9 mg, 5.81 mmol, 1.5 equiv) were added and the reaction mixture was stirred at 90 °C overnight. Subsequent workup and flash column chromatography (gradient pentane 100% to pentane:CH₂Cl₂ 10:1) yielded 4.20, a yellow oil, in 88% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.54 (d, J = 2.4 Hz, 1H), 7.33 (dd, J = 8.6, 2.5 Hz, 1H), 7.22 (d, J = 8.6 Hz, 1H), 7.09 (ap t, J = 2.2 Hz, 2H), 6.30 (ap t, J = 2.2 Hz, 2H), 0.19 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 140.9, 133.6, 131.4, 129.5, 125.7, 121.4 (2C), 119.1, 109.5 (2C), 101.2, 100.3, -0.5 (3C); IR (NaCl,
neat): 2959, 2157, 1491, 1321, 1116, 1078, 842, 719 cm⁻¹; HRMS (ESI): calcd for C₁₅H₁₇ClNSi (M)⁺: 274.0813; found: 274.0823.

1-(2,4-Difluoro-6-((trimethylsilyl)ethynyl)phenyl)-1H-pyrrole (4.21)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.3, aryl bromide 4.13 (200 mg, 0.78 mmol) was mixed with CuI (1.7 mg, 0.009 mmol, 1.2 mol%) and Pd(PPh₃)₂Cl₂ (27.2 mg, 0.039 mmol, 5 mol%) under argon, NEt₃ (3.9 mL) and TMS-acetylene (165 μL, 114.2 mg, 1.16 mmol, 1.5 equiv) were added and the reaction mixture was stirred at 90 °C overnight. Subsequent workup and flash column chromatography (gradient pentane 100% to pentane:CH₂Cl₂ 10:1) yielded 4.21 as an orange oil in 88% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.06 (ddd, J = 8.5, 2.8, 1.7 Hz, 1H), 6.94 (ddd, J = 9.8, 2.8, 2.8 Hz, 1H), 6.86 (dd, J = 3.7, 2.1 Hz, 2H), 6.31 (ap t, J = 2.2 Hz, 2H), 0.14 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ 160.3 (dd, J = 249.7, 12.7 Hz), 157.1 (dd, J = 252.5, 13.3 Hz), 127.8 (dd, J = 13.2, 4.2 Hz), 123.4 (dd, J = 11.6, 3.1 Hz), 122.3 (d, J = 1.6 Hz, 2C), 115.3 (dd, J = 23.7, 3.9 Hz), 109.1 (2), 105.5 (dd, J = 26.3, 25.0 Hz), 100.1, 98.9 (dd, J = 4.6, 3.2 Hz), -0.7 (3); ¹⁹F NMR (376 MHz, CDCl₃): δ -110.9 (q, J = 8.0 Hz), -118.0 (t, J = 8.5 Hz); IR (NaCl, neat): 3426, 2960, 2157, 1605, 1506, 1449, 1299, 1258, 1121, 1010, 851 cm⁻¹; HRMS (EI): calcd for C₁₅H₁₅F₂NSi (M)⁺: 275.0942; found: 275.0942.

1-(5-Fluoro-2-((trimethylsilyl)ethynyl)phenyl)-1H-pyrrole (4.22)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.3, aryl bromide 4.14 (1900 mg, 7.91 mmol) was mixed with CuI (18.1 mg, 0.095 mmol, 1.2 mol%) and Pd(PPh₃)₂Cl₂ (278 mg, 0.40 mmol, 5 mol%) under argon, NEt₃ (40 mL) and TMS-acetylene (1.82 mL, 1.17 g, 11.87 mmol, 1.5 equiv) were added and the reaction mixture was stirred at 90 °C overnight. Subsequent workup and flash column chromatography (gradient pentane 100% to pentane:CH₂Cl₂ 10:1) yielded 4.22 as due to major purification difficulties the compound was carried on to the next step and fully characterized after desilylation. ¹H NMR (400 MHz, CDCl₃): δ 7.54 (dd, J = 8.7, 6.2 Hz, 1H), 7.15 (ap t, J = 2.2 Hz, 2H), 7.01 (dd, J = 9.6, 2.5 Hz, 2H), 6.93 (dd, J = 8.6, 7.9, 2.6 Hz, 1H), 6.30 (ap t, J = 2.2 Hz, 1H), 0.19 (s, 9H).

1-(5-Nitro-2-((trimethylsilyl)ethynyl)phenyl)-1H-pyrrole (4.23)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.3, aryl bromide (600 mg, 2.25 mmol) was mixed with CuI (5.0 mg, 0.027 mmol, 1.2 mol%) and Pd(PPh₃)₂Cl₂ (80.0 mg, 0.11 mmol, 5 mol%) under argon, NEt₃ (12 mL) and TMS-acetylene (520 μL, 330.9 mg, 3.37 mmol, 1.5 equiv) were added and the reaction mixture was stirred at 90 °C overnight.
Subsequent workup and flash column chromatography (gradient pentane 100% to pentane:EtOAc 20:1) yielded 4.23 as an orange oil in 83% yield. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.20 (d, $J = 2.1$ Hz, 1H), 8.10 (dd, $J = 8.6, 2.2$ Hz, 1H), 7.74 (d, $J = 8.6$ Hz, 1H), 7.21 (ap t, $J = 2.0$ Hz, 2H), 6.39 (ap t, $J = 2.0$ Hz, 2H), 0.25 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 147.6, 142.9, 135.1, 123.6, 121.4 (2C), 120.3, 119.5, 110.4 (2C), 106.0, 100.0, -0.66 (3C); IR (NaCl, neat): 2959, 2919, 2853, 2361, 2337, 2159, 1581, 1526, 1494, 1347, 1252, 1091, 1068, 1025, 946, 850, 725 cm$^{-1}$; HRMS (ESI): calcd for C$_{15}$H$_{17}$N$_2$O$_2$Si (M+H)$^+$: 285.1053; found: 285.1049.

Ethyl 4-(1H-pyrrol-1-yl)-3-((trimethylsilyl)ethynyl)benzoate (4.24)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.3, aryl bromide (1980 mg, 7.07 mmol) was mixed with CuI (16.2 mg, 0.085 mmol, 1.2 mol%) and Pd(PPh$_3$)$_2$Cl$_2$ (248.1 mg, 0.35 mmol, 5 mol%) under argon, NEt$_3$ (35 mL) and TMS-acetylene (1630 $\mu$L, 1041 mg, 10.6 mmol, 1.5 equiv) were added and the reaction mixture was stirred at 90 °C overnight. Subsequent workup and flash column chromatography (gradient pentane 100% to pentane:EtOAc 10:1) yielded 4.24 as an orange oil in quantitative yield. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.25 (d, $J = 1.9$ Hz, 1H), 8.01 (dd, $J = 8.5, 2.0$ Hz, 1H), 7.34 (d, $J = 8.5$ Hz, 1H), 7.23 (ap t, $J = 2.1$ Hz, 2H), 6.33 (ap t, $J = 2.1$ Hz, 2H), 3.93 (s, 3H), 0.21 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 165.7, 145.3, 136.1, 130.6, 127.4, 124.0, 121.3 (2C), 116.9, 110.0 (2C), 101.1, 100.9, 52.3, -0.49 (3C); IR (NaCl, neat): 2955, 2899, 2158, 1725, 1605, 1505, 1474, 1333, 1296, 1250, 1203, 1119, 988, 848, 796, 767, 726 cm$^{-1}$; HRMS (ESI): calcd for C$_{17}$H$_{20}$NO$_2$Si (M+H)$^+$: 298.1257; found: 298.1260.

5-Nitro-2-(1H-pyrrol-1-yl)-3-((trimethylsilyl)ethynyl)benzonitrile (4.25)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.3, aryl bromide 4.15 (1.02 g, 3.49 mmol) was mixed with CuI (16.2 mg, 0.085 mmol, 1.2 mol%) and Pd(PPh$_3$)$_2$Cl$_2$ (122.5 mg, 0.17 mmol, 5 mol%) under argon, NEt$_3$ (18 mL) and TMS-acetylene (804 $\mu$L, 514.4 mg, 5.24 mmol, 1.5 equiv) were added and the reaction mixture was stirred at 90 °C overnight. Subsequent workup and flash column chromatography (gradient pentane 100% to pentane:EtOAc 30:1) yielded 4.25 as yellow solid in 28% yield. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.57 (d, $J = 2.6$ Hz, 1H), 8.51 (d, $J = 2.6$ Hz, 1H), 7.09 (ap t, $J = 2.3$ Hz, 2H), 6.43 (ap t, $J = 2.3$ Hz, 2H), 0.19 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 165.7, 145.3, 136.1, 130.6, 127.4, 124.0, 121.3 (2C), 116.9, 110.0 (2C), 101.1, 100.9, 52.3, -0.49 (3C); IR (NaCl, neat): 3423, 2918, 2158, 1725, 1605, 1505, 1474, 1333, 1296, 1250, 1203, 1119, 988, 848, 796, 767, 726 cm$^{-1}$; HRMS (ESI): calcd for C$_{16}$H$_{18}$N$_3$O$_2$Si: 309.0934; found: 309.0939.
1-(4-Methyl-2-nitro-6-((trimethylsilyl)ethynyl)phenyl)-1H-pyrrole (4.26)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.3, aryl bromide 4.16 (970 mg, 3.45 mmol) was mixed with Cul (7.9 mg, 0.04 mmol, 0.012 eq.) and Pd(PPh$_3$)$_2$Cl$_2$ (121 mg, 0.17 mmol, 0.05 eq.) under argon, NEt$_3$ (18 mL) and TMS-acetylene (795 μL, 508.3 mg, 5.17 mmol, 1.5 eq.) were added and the reaction mixture was stirred at 90°C overnight. Subsequent workup and flash column chromatography (gradient pentane 100% to pentane:CH$_2$Cl$_2$ 10:1) yielded 4.26 as an orange oil in 87% yield. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.55 (bs, 2H), 6.73 (ap t, J = 2.4 Hz, 2H), 6.30 (ap t, J = 2.4 Hz, 2H), 2.44 (s, 3H), 0.12 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 147.2, 138.6, 136.8, 133.5, 124.4, 124.0, 122.0 (2C), 109.9 (2C), 101.9, 98.7, 20.8, -0.63 (3C); IR (NaCl, neat): 3108, 2955, 2353, 2161, 1633, 1357, 1255, 1072, 1012, 851, 727 cm$^{-1}$; HRMS (EI): calcd for C$_{16}$H$_{18}$N$_2$O$_2$Si: 298.1138; found: 298.1147.

1-(2-((Trimethylsilyl)ethynyl)phenyl)-1H-indole (4.27)

According to the general procedure 4.3, aryl bromide 4.18 (8.8 mmol) was mixed with Cul (20.1 mg, 0.106 mmol, 1.2 mol%) and Pd(PPh$_3$)$_2$Cl$_2$ (309 mg, 0.44 mmol, 5 mol%) under argon, NEt$_3$ (44 mL) and TMS-acetylene (1.49 mL, 10.6 mmol, 1.5 equiv) were added and the reaction mixture was stirred at 90 °C overnight. Subsequent workup and flash column chromatography (gradient pentane 100% to pentane:CH$_2$Cl$_2$ 10:1) yielded 4.27 as a mixture of starting material and product. The compound was carried over the next step and the yield and characterization information was obtained for the desilylated compound 4.41 (vide supra).

**General procedure for Suzuki-Miyaura coupling for the synthesis of TMS-alkynes 6m-6o**

The procedure was adapted from literature. An oven dried round-bottom flask with a stirring bar was cooled under argon. Pd$_2$(dba)$_3$ (0.5 mol%), S-Phos (2 mol%), K$_3$PO$_4$ (3 equiv) and the boronic acid (2 equiv) are transferred into the flask. The flask was fitted with a condenser and was purged with argon for ~15 minutes. Toluene (1M) is added to the flask, then the aryl bromide is added via syringe and more toluene (1M) is used to rinse the aryl bromide vial and the condenser. The reaction is heated to 100 °C and the reaction is monitored by TLC. Usually complete reaction was observed at 5-6 h. The crude mixture is filtered through a plug of celite, concentrated under reduced pressure, and purified by flash chromatography.

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Trimethyl(2-(thiophen-3-yl)phenyl)ethynyl)silane (4.29)

According to the general procedure 4.3, aryl bromide 4.28 (1.27 g, 5 mmol) was added to a solution of Pd₂dba₃ (22.9 mg, 0.5 mol%), S-Phos (41 mg, 2 mol%), K₃PO₄ (3.18 g, 2 equiv) and 3-thiénylboronic acid (1.28 g, 10 mmol, 2 equiv) in a toluene (total volume of 10 ml). The reaction mixture was stirred at 100 °C for 5 hours. Subsequent workup and flash column chromatography (95:5 pentane:toluene) yielded 4.29 as a pale yellow oil; 1.09 g (85% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.69 (dd, J = 3.0, 1.2 Hz, 1H), 7.56 (dd, J = 7.7, 1.1 Hz, 1H), 7.48 (dd, J = 5.0, 1.2 Hz, 1H), 7.45 (dd, J = 7.8, 0.9 Hz, 1H), 7.37-7.31 (m, 2H), 7.23 (ap dt, J = 7.6, 1.3 Hz, 1H), 0.21 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 140.6, 138.4, 133.7, 128.8, 128.6, 126.7, 124.4, 123.7, 120.9, 105.1, 98.0, -0.27 (3C); IR (NaCl, neat) 3105, 3059, 2959, 2897, 2156, 1474, 1443, 1250, 1211; HRMS (EI): cålcd for C₁₅H₁₆SSi: 256.0742 (+); found: 256.0743.

((2-(Furan-2-yl)phenyl)ethynyl)trimethylsilane (4.30)

According to the general procedure 4.3, aryl bromide 4.28 (1.27 g, 5 mmol) was added to a solution of Pd₂dba₃ (22.9 mg, 0.5 mol%), S-Phos (41 mg, 2 mol%), K₃PO₄ (3.18 g, 2 equiv) and 2-furylboronic acid (1.12 g, 10 mmol, 2 equiv) in a toluene (total volume of 10 ml). The reaction mixture was stirred at 100 °C for 5 hours. Subsequent workup and flash column chromatography (100% pentane to 9:1 pentane:toluene) yielded 4.30 as a colorless oil; 0.833 g (69% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.84 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 7.7 Hz, 1H), 7.48 (d, J = 1.4 Hz, 1H), 7.42 (d, J = 3.4 Hz, 1H), 7.35 (ap t, J = 7.7 Hz, 1H), 7.18 (ap dt, J = 7.7, 0.9 Hz, 1H), 6.51 (dd, J = 3.4, 1.8 Hz, 1H), 0.30 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 151.8, 141.7, 134.2, 131.9, 128.7, 126.4, 125.2, 117.9, 111.4, 109.6, 105.1, 99.4, -0.13 (3); IR (NaCl, neat) 3105, 2959, 2897, 2156, 1481, 1250, 1007, 860; HRMS (ESI): Calcd for C₁₅H₁₆OSi (M+H)⁺: 240.0970; found: 240.0971.

((4'-Methoxybiphenyl-2-yl)ethynyl)trimethylsilane (4.31)

According to the general procedure 4.3, aryl bromide 4.28 (1.27 g, 5 mmol) was added to a solution of Pd₂dba₃ (22.9 mg, 0.5 mol%), S-Phos (41 mg, 2 mol%), K₃PO₄ (3.18 g, 2 equiv) and 4-methoxyphenylboronic acid (1.52 g, 10 mmol, 2 equiv) in a toluene (total volume of 10 ml). The reaction mixture was stirred at 100 °C for 6 hours. Subsequent workup and flash column chromatography (100% pentane to 9:1 pentane:toluene) yielded 4.31 as a colorless oil; 1.5 g (90% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.60-7.52 (m, 3H), 7.37-7.31 (m, 2H), 7.23 (ddd, J = 8.7, 6.9, 3.7 Hz, 1H), 6.94 (d, J = 8.8 Hz, 3H), 6.84 (s, 3H), 0.15 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 159.0, 143.7, 133.3, 132.7, 130.4 (2C), 129.1, 128.6, 126.4, 121.1, 113.1 (2C), 105.0, 97.3, 55.2, -0.25 (3C); IR (NaCl, neat) 3059, 3001, 2959, 2901, 2835, 2156, 1613, 1578, 1519,
1463, 1439, 1296, 1243, 1176, 1038; HRMS (EI): calcd for C_{18}H_{20}OSi (M)^+: 280.1283; found: 280.1283.

Procedure 4.4: General procedure for desilylation of the TMS-alkynes to yield terminal alkynes.

The TMS-alkyne was dissolved in THF, the reaction mixture was cooled to 0 °C, TBAF (hydrate or 1 M in THF) was added and the reaction was stirred at 0 °C then room temperature. After TLC analysis had shown complete conversion of the starting materials, aq. NH₄Cl (10 mL) was added, the mixture was extracted with EtOAc (3 x 15 mL), the combined organic layers were washed with H₂O and brine, dried over MgSO₄ and concentrated under reduced pressure. Flash column chromatography using the stated solvent mixtures yielded the desired products.

1-(2-Ethynylphenyl)-1H-pyrrole (4.32)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.4, TMS-alkyne 4.10 (500 mg, 2.09 mmol) reacted with TBAF (2.5 mL, 2.51 mmol, 1.2 equiv) in THF (15 mL) at 0 °C. Subsequent workup and flash column chromatography (gradient pentane 100% to pentane:CH₂Cl₂ 10:1) yielded 4.32 in 80% yield. Spectral data were consistent with the literature.⁶⁵

1-(2-ethyl-4-methylphenyl)-1H-pyrrole (4.33)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.4, TMS-alkyne 4.19 (1.0 g, 3.94 mmol) reacted with TBAF (4.75 mL, 4.74 mmol, 1.2 equiv) in THF (30 mL) at 0 °C. Subsequent workup and flash column chromatography (gradient pentane 100% to pentane:CH₂Cl₂ 50:1) yielded 4.33 as an orange oil in 76% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.42 (s, 1H), 7.21 - 7.15 (m, 2H), 7.06 (ap t, J = 2.1 Hz, 2H), 6.31 (ap t, J = 2.0 Hz, 2H), 3.13 (s, 1H), 2.36 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 136.3, 134.9, 130.7, 125.0, 122.9, 121.7, 116.8, 109.2, 81.5, 80.6, 20.7; IR (NaCl, neat) 3286, 2919, 1499, 1321.00, 1085, 1061, 828, 723 cm⁻¹; HRMS (ESI) calcd for C_{13}H_{12}N (M+H)^+: 192.0964; found: 192.0966.

1-(4-Chloro-2-ethylphenyl)-1H-pyrrole (4.34)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.4, TMS-alkyne 4.20 (298.2 mg, 1.09 mmol) reacted with TBAF (1.3 mL, 1.31 mmol, 1.2 equiv) in THF (8 mL) at 0 °C. Subsequent workup and flash column chromatography (gradient pentane 100% to pentane:CH₂Cl₂ 5:1) yielded 4.34 as

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yellow-brown solid in 93% yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.59 (d, \(J = 2.3\) Hz, 1H), 7.38 (dd, \(J = 8.6, 2.4\) Hz, 1H), 7.24 (d, \(J = 8.5\) Hz, 1H), 7.06 (ap t, \(J = 2.0\) Hz, 2H), 6.33 (ap t, \(J = 2.0, 2H\)), 3.22 (s, 1H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta\) 141.1, 134.1, 131.8, 130.0, 126.2, 121.6 (2C), 118.3, 109.8 (2C), 83.1, 79.2; IR (NaCl, neat): 3287, 1490, 1321, 1259, 1195, 1081, 862, 725 cm\(^{-1}\); M. p.: 35-37 °C; HRMS (ESI): calcd for C\(_{12}\)H\(_9\)ClN: 202.0418; found: 202.0418.

1-(2-Ethynyl-4,6-difluorophenyl)-1H-pyrrole (4.35)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.4, TMS-alkyne 4.21 (300 mg, 1.09 mmol) reacted with TBAF (1.3 mL, 1.31 mmol, 1.2 equiv) in THF (8 mL) at 0 °C. Subsequent workup and flash column chromatography (gradient pentane 100% to pentane:CH\(_2\)Cl\(_2\) 3:1) yielded 4.35 as yellow-brown solid in 90% yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.13 (dd, \(J = 8.3, 2.5, 1.9\) Hz, 1H), 6.99 (dd, \(J = 9.9, 8.3, 2.8\) Hz, 1H), 6.89 - 6.86 (m, 2H), 6.36 (ap t, \(J = 2.1\) Hz, 2H), 3.19 (s, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 160.5 (dd, \(J = 248, 12.5\) Hz), 157.3 (dd, \(J = 252, 13.0\) Hz), 127.9 (dd, \(J = 13.7, 4.3\) Hz), 122.4 (d, \(J = 1.5\) Hz, 2C), 122.3 (dd, \(J = 11.8, 3.2\) Hz), 116.1 (dd, \(J = 24.0, 4.0\) Hz), 109.3 (2), 106.0 (dd, \(J = 26.0\) Hz), 83.7, 78.0; \(^{19}\)F NMR (376 MHz, CDCl\(_3\)): \(\delta\) -109.3 (q, \(J = 7.7\) Hz), -116.7 (t, \(J = 8.0\) Hz); IR (NaCl, neat): 3248, 3072, 2119, 1709, 1594, 1505, 1443, 1309, 1120, 1059, 995, 863, 730 cm\(^{-1}\); M. p.: 74-79 °C; HRMS (ESI): calcd for C\(_{12}\)H\(_8\)F\(_2\)N (M+H): 204.0619; found: 204.0610.

1-(2-Ethynyl-5-fluorophenyl)-1H-pyrrole (4.36)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.4, TMS-alkyne 4.22 (170 mg, 0.66 mmol) reacted with TBAF (0.8 mL, 0.79 mmol, 1.2 equiv) in THF (5 mL) at 0 °C. Subsequent workup and flash column chromatography (gradient pentane 100% to pentane:CH\(_2\)Cl\(_2\) 10:1) yielded 4.36 in 85% yield as an orange oil (or 45% yield over two steps from 4.14). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.58 (dd, \(J = 8.6, 6.2\) Hz, 1H), 7.12 (ap t, \(J = 2.2\) Hz, 2H), 7.03 (dd, \(J = 9.4, 2.6\) Hz, 1H), 6.98 (ap td, \(J = 8.4, 2.4\) Hz, 1H), 6.34 (ap t, \(J = 2.2\) Hz, 2H), 3.16 (s, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 162.7 (d, \(J = 250.3\) Hz), 144.0 (d, \(J = 10.0\) Hz), 136.3 (d, \(J = 10.0\) Hz), 121.4 (2), 113.5 (q, \(J = 22.0\) Hz), 112.6 (d, \(J = 3.5\) Hz), 112.3 (d, \(J = 25.0\) Hz), 110.0 (2), 81.7, 79.7; \(^{19}\)F NMR (376 MHz, CDCl\(_3\)): \(\delta\) -108.1 (dt, \(J = 7.8\) Hz); IR (NaCl, neat): 3425, 3291, 2920, 2350, 1597, 1490, 1321, 1259, 1195, 1081, 862, 725 cm\(^{-1}\); HRMS (EI): calcd for C\(_{12}\)H\(_8\)F\(_2\)N: 185.0641 (M\(^+\)); found: 185.0649.

1-(2-Ethynyl-5-nitrophenyl)-1H-pyrrole (4.37)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.4, TMS-alkyne 4.23 (520 mg, 1.83 mmol) reacted with TBAF (2.2 mL, 2.2 mmol, 1.2 equiv) in THF (14 mL) at 0 °C. Subsequent workup and flash column
chromatography (gradient pentane 100% to pentane:EtOAc 10:1) yielded 4.37 as a yellow-brown solid in 86% yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.18 (d, \(J = 2.2\) Hz, 1H), 8.10 (dd, \(J = 8.5, 2.2\) Hz, 1H), 7.77 (d, \(J = 8.5\) Hz, 1H), 7.17 (ap t, \(J = 2.1\) Hz, 2H), 6.39 (ap t, \(J = 2.1\) Hz, 2H), 3.48 (s, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 147.8, 143.0, 135.6, 122.6, 121.3 (2C), 120.4, 119.7, 110.7 (2C), 86.9, 79.0; IR (NaCl, neat) 3279, 2109, 1525, 1494, 1347, 1287, 1068, 1020, 945, 898, 861, 783, 731 cm\(^{-1}\); M. p.: 84-95 °C; HRMS (ESI): calcld for C\(_{12}\)H\(_9\)N\(_2\)O\(_2\): 212.0586 (M+H)\(^+\); Found: 212.0589.

Methyl 3-ethynyl-4-(1H-pyrrol-1-yl)benzoate (4.38)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.4, TMS-alkyne 4.24 (2.1 mg, 7.07 mmol) reacted with TBAF (8.5 mL, 8.5 mmol, 1.2 equiv) in THF (50 mL) at 0 °C. Subsequent workup and flash column chromatography (gradient pentane 100% to pentane:EtOAc 10:1) yielded 4.38 as a yellow solid in 90% yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.30 (d, \(J = 1.8\) Hz, 1H), 8.06 (dd, \(J = 8.4, 1.9\) Hz, 1H), 7.36 (d, \(J = 8.4\) Hz, 1H), 7.19 (ap t, \(J = 2.1\) Hz, 2H), 6.36 (ap t, \(J = 2.1\) Hz, 2H), 3.94 (s, 3H), 3.26 (s, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 165.6, 145.6, 136.6, 131.0, 127.8, 124.5, 121.5 (2), 116.2, 110.3 (2), 82.9, 79.9, 52.4; IR (NaCl, neat): 3264, 2951, 2361, 1724, 1604, 1505, 1333, 1296, 1244, 1196, 1122, 766, 727 cm\(^{-1}\); M. p.: 62-64 °C; HRMS (ESI): calcld for C\(_{14}\)H\(_{12}\)NO\(_2\) (M+H)\(^+\): 226.0862; found: 226.0862.

3-Ethynyl-5-nitro-2-(1H-pyrrol-1-yl)benzonitrile (4.39)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.4, TMS-alkyne 4.25 (275.0 mg, 0.89 mmol) reacted with TBAF (1.06 mL, 1.06 mmol, 1.2 equiv) in THF (8 mL) at 0 °C. Subsequent workup and flash column chromatography (gradient pentane 100% to pentane:EtOAc 10:1) yielded 4.39 as yellow solid in 90% yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.64 (d, \(J = 2.5\) Hz, 1H), 8.56 (d, \(J = 2.6\) Hz, 1H), 7.10 (ap t, \(J = 2.0\) Hz, 2H), 6.47 (ap t, \(J = 2.0\) Hz, 2H), 3.41 (s, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 148.8, 145.2, 133.2, 129.1, 121.9 (2), 121.8, 114.2, 111.9 (2), 111.5, 86.7, 30.9; IR (NaCl, neat): 3277, 3083, 2919, 2232, 2108, 1589, 1533, 1478, 1353, 1085, 915, 732 cm\(^{-1}\); M. p.: 158 °C; HRMS (EI): calcld for C\(_{13}\)H\(_7\)N\(_3\)O\(_2\) (M): 237.0538; found: 237.0538.

1-(2-Ethynyl-4-methyl-6-nitrophenyl)-1H-pyrrole (4.40)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.4, TMS-alkyne 4.26 (839.1 mg, 2.80 mmol) reacted with TBAF (3.35 mL, 3.35 mmol, 1.2 equiv) in THF (21 mL) at 0 °C. Subsequent workup and flash column chromatography (gradient pentane 100% to pentane:EtOAc 10:1) yielded 4.40 as yellow solid in 86% yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.60 (bs, 2H), 6.76 (ap
t, J = 2.1 Hz, 2H), 6.34 (ap t, J = 2.0 Hz, 2H), 3.14 (s, 1H), 2.46 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 147.3, 138.9, 137.6, 133.4, 124.9, 122.9, 122.1 (2C), 110.1 (2C), 83.4, 77.9, 20.8; IR (NaCl, neat): 3264, 3131, 2918, 2120, 1527, 1358, 1080, 1059, 1024, 881, 744 cm$^{-1}$; M. p.: 96-99 °C; HRMS (ESI): calcd for C$_{13}$H$_{11}$N$_2$O$_2$: 227.0815; found: 227.0815.

1-(2-Ethynylphenyl)-1H-indole (4.41)

The impure TMS-alkyne 4.27 was reacted with TBAF-H$_2$O (1.2 equiv) in THF (0.1 M) at 0 °C. Subsequent workup and flash column chromatography (gradient pentane 100% to pentane:DCM 10:1) yielded 4.41 as yellow oil in 25% yield from 4.18. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.66 (m, 2H), 7.46-7.37 (m, 3H), 7.32 (m, 2H), 7.22-7.07 (m, 2H), 6.66 (d, J = 3.1 Hz, 1H), 2.98 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 141.1, 136.4, 134.4, 129.6, 128.9, 128.7, 127.1, 127.0, 122.0, 120.8, 120.2, 119.5, 110.7, 102.9, 82.2, 80.0; IR (NaCl, neat): 3287, 3051, 1597, 1566, 1490, 1458, 1330, 1307, 1234, 1138, 1014; HRMS (EI): calcd for C$_{16}$H$_{11}$N (M)$^+$: 217.0891; found: 217.0890.

3-(2-Ethynylphenyl)thiophene (4.42)

According to the general procedure 4.4, TMS-alkyne 4.29 (1.09 g, 4.24 mmol) reacted with TBAF-H$_2$O (1.33 g, 5.08 mmol, 1.2 equiv) in THF (33 ml, 0.13 M) at 0 °C. Subsequent workup and flash column chromatography (gradient pentane 100% to pentane:DCM 95:5) yielded 4.42 as yellow oil in 88% yield. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.65 (dd, J = 2.9, 1.1 Hz, 1H), 7.59 (dd, J = 7.7, 1.0 Hz, 1H), 7.47-7.43 (m, 2H), 7.39-7.32 (m, 2H), 7.25 (dt, J = 7.6, 1.1 Hz, 1H), 3.16 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 140.4, 138.5, 134.1, 129.0, 128.4, 126.8, 124.8, 123.6, 119.9, 83.4, 80.6; IR (neat) 3287, 3051, 1597, 1566, 1490, 1458, 1330, 1307, 1234, 1138, 1014; HRMS (EI): Calcd for C$_{12}$H$_{8}$S (M)$^+$: 184.0347. Found: 184.0345.

2-(2-Ethynylphenyl)furan (4.43)

According to the general procedure 4.4, TMS-alkyne 4.30 (0.832 g, 3.46 mmol) reacted with TBAF-H$_2$O (1.086 g, 4.15 mmol, 1.2 equiv) in THF (26 ml, 0.13 M) at 0 °C. Subsequent workup and flash column chromatography (gradient pentane 100% to pentane:DCM 95:5) yielded 4.43 as orange/red oil in 85% yield. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.84 (dd, J = 8.1, 0.5 Hz, 1H), 7.58 (dd, J = 7.7, 1.0 Hz, 1H), 7.49 (d, J = 1.6 Hz, 1H), 7.44-7.35 (m, 2H), 7.21 (ap dt, J = 7.6, 1.1 Hz, 1H), 6.51 (dd, J = 3.4, 1.8 Hz, 1H), 3.40 (s, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 151.6, 142.0, 134.6, 132.3, 129.1 (2), 126.6, 125.5, 117.0, 111.6, 109.7, 83.6, 82.0 (Overlapping resonances at 129.1); IR (neat) 3287, 3148, 3121, 3067, 2102, 1601, 1481, 1431, 1215, 1161; HRMS (EI) calcd for C$_{12}$H$_8$O (M)$^+$: 168.0575; found: 168.0573.
2-Ethynyl-4’-methoxybiphenyl (4.44)

According to the general procedure 4.4, TMS-alkyne 4.31 (1.5 g, 5.34 mmol) reacted with TBAF-H₂O (1.67 g, 6.41 mmol, 1.2 equiv) in THF (41 ml, 0.13 M) at 0 °C. Subsequent workup and flash column chromatography (gradient pentane 100% to pentane:DCM 95:5) yielded 4.44 as yellow oil in 84% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.58 (d, J = 7.6 Hz, 1H), 7.52 (d, J = 8.7 Hz, 2H), 7.37-7.30 (m, 2H), 7.26-7.20 (m, 1H), 6.94 (d, J = 8.7 Hz, 2H), 3.80 (s, 3H), 3.03 (s, 1H); ¹³C NMR (101 MHz, CDCl₃): δ 143.9, 133.8, 132.6, 130.3 (2C), 129.4, 128.9, 126.5, 113.4 (2C), 83.3, 80.0, 55.1; IR (neat): 3283, 3059, 3001, 2959, 2835, 1612, 1516, 1465, 1246, 1180; HRMS (EI): calcd for C₁₅H₁₂O (M)⁺: 208.0888; found: 208.0888.

1-(2-(Bromoethynyl)phenyl)-1H-pyrrole (4.7a)

Terminal alkyne 4.32 (25 mg, 0.15 mmol) was dissolved in THF (0.25 mL), the reaction mixture was cooled to -78 °C and n-BuLi (1.03 M in hexane, 144 μL, 0.15 mmol) was added. After stirring at -78°C for 30 min, NBS (26.5 mg, 0.15 mmol) in THF (0.25 mL) was added and the reaction was stirred for additional 15 min at -78°C. After warming to -10 °C, NH₄Cl(aq) solution (2 mL) was added, the reaction mixture was extracted with Et₂O (3 x 5 mL), the combined organic phases were washed with H₂O, dried over MgSO₄ and concentrated under reduced pressure. Flash column chromatography (gradient pentane 100% to pentane:CH₂Cl₂ 10:1) yielded 4.7a in 37%. The spectral data were consistent with the literature.⁶⁶

Procedure 4.5: General procedure for synthesis of iodoalkynes

The terminal alkyne, CuI and N-iodomorpholine were mixed, THF and 4 Å MS (4 to 6 pieces) were added and the reaction was stirred in the dark at room temperature. After TLC analysis had shown complete conversion of the starting materials, NH₄Cl(aq) (10 mL) was added, the mixture was extracted with Et₂O (3 x 15 mL), the combined organic layers were washed with H₂O, Na₂S₂O₃(aq) solution and brine, dried over MgSO₄ and concentrated under reduced pressure. Flash column chromatography using the stated solvent mixtures yielded the desired products.

1-(2-(Iodoethynyl)phenyl)-1H-pyrrole (4.45)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.5, terminal alkyne 4.32 (160 mg, 0.96 mmol), CuI (9.1 mg, 0.05 mmol, 5 mol%) and N-iodomorpholine (391 mg, 1.15 mmol, 1.2 equiv) were reacted in

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the presence of 4 Å MS in THF (18 mL) in the dark at room temperature. Subsequent workup and flash column chromatography (gradient pentane 100% to pentane:CH₂Cl₂ 10:1) yielded **4.45** as an orange oil in 82%. **¹H NMR** (400 MHz, CDCl₃): δ 7.62 (dd, J = 7.8, 1.4 Hz, 1H), 7.42 (ddd, J = 8.1, 1.5 Hz, 1H), 7.31 (dd, J = 8.1, 0.9 Hz, 1H), 7.25 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.12 (ap t, J = 2.2 Hz, 2H), 6.36 (ap t, J = 2.2 Hz, 2H); **¹³C NMR** (100 MHz, CDCl₃): δ 135.1, 130.3, 126.1, 124.7, 121.5 (2), 116.1, 109.8 (2), 105.0, 79.4, 1.0; **IR** (neat): 3395, 2921, 1638, 1488, 1324, 1265, 1083, 808 cm⁻¹; **HRMS** (EI): calcd for C₁₂H₇N (M)⁺: 292.9701; found: 292.9706.

1-(2-(iodoethynyl)-4-methylphenyl)-1H-pyrrole (4.46)

![Image of 1-(2-(iodoethynyl)-4-methylphenyl)-1H-pyrrole](image1)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.5, terminal alkyne **4.33** (13.6 mg, 0.08 mmol), Cul (0.7 mg, 0.003 mmol, 5 mol%) and N-iodomorpholine (30.7 mg, 0.09 mmol, 1.2 equiv) were reacted in the presence of 4 Å MS in THF (1 mL) in the dark at room temperature. Subsequent workup and flash column chromatography (gradient pentane 100% to pentane:Et₂O 50:1) yielded **4.46** as an orange oil in 75%. **¹H NMR** (400 MHz, CDCl₃): δ 7.36 (s, 1H), 7.18-7.16 (m, 2H), 7.06 (ap t, J = 2.2 Hz, 2H), 6.31 (ap t, J = 2.2 Hz, 2H), 2.34 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ 135.9, 135.1, 130.6, 124.5, 122.9, 121.6, 117.5, 109.3, 91.1, 81.5, 20.7; **IR** (NaCl, neat) 2919, 2852, 2361, 2341, 1508, 1478, 1329, 1103, 1069, 819, 725 cm⁻¹; **HRMS** (ESI): calcd for C₁₃H₁₁ICN (M+H)⁺: 307.9917; found: 307.9930.

1-(4-Chloro-2-(iodoethynyl)phenyl)-1H-pyrrole (4.47)

![Image of 1-(4-Chloro-2-(iodoethynyl)phenyl)-1H-pyrrole](image2)

This compound was prepared by Dr. K. Geyer according to the general procedure, terminal alkyne **4.34** (31 mg, 0.15 mmol), Cul (1.5 mg, 0.007 mmol, 5 mol%) and N-iodomorpholine (62.9 mg, 0.18 mmol, 1.2 equiv) were reacted in the presence of 4 Å MS in THF (2 mL) in the dark at room temperature. Subsequent workup and flash column chromatography (gradient pentane 100% to pentane:Et₂O 50:1) yielded **4.47** as an orange oil in 80%. **¹H NMR** (400 MHz, CDCl₃): δ 7.52 (d, J = 2.4 Hz, 1H), 7.34 (dd, J = 8.6, 2.4 Hz, 1H), 7.21 (d, J = 8.6 Hz, 1H), 7.05 (ap t, J = 2.2 Hz, 2H), 6.33 (ap t, J = 2.1, 2H); **¹³C NMR** (100 MHz, CDCl₃): δ 141.3, 134.3, 131.4, 129.9, 125.7, 121.4 (2), 119.0, 110.0 (2), 89.6, 13.9; **IR** (NaCl, neat): 3448, 2921, 1495, 1391, 1329, 1132, 1069, 819, 725 cm⁻¹; **HRMS** (ESI): calcd for C₁₃H₁₁IClN (M+H)⁺: 326.9312; found: 326.9318.

1-(2,4-Difluoro-6-(iodoethynyl)phenyl)-1H-pyrrole (4.48)

![Image of 1-(2,4-Difluoro-6-(iodoethynyl)phenyl)-1H-pyrrole](image3)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.5, terminal alkyne **4.35** (40.5 mg, 0.20 mmol), Cul (1.9 mg, 0.01 mmol, 5 mol%) and N-iodomorpholine (81.5 mg, 0.24 mmol, 1.2 equiv) were reacted in the presence of 4 Å MS in THF (3 mL) in the dark at room temperature.
Subsequent workup and flash column chromatography (gradient pentane 100% to pentane:CH₂Cl₂ 1:1) yielded 4.48 as a yellow solid in 83%. ^1H NMR (400 MHz, CDCl₃): δ 7.05 (ddd, J = 8.3, 2.6, 1.9 Hz, 1H), 6.94 (ddd, J = 10.0, 8.2, 2.8 Hz, 1H), 6.86 (ddd, J = 1.8 Hz, 2H), 6.33 (ap t, J = 2.0 Hz, 2H); ^13C NMR (100 MHz, CDCl₃): δ 160.2 (dd, J = 245.0, 12.8 Hz), 157.0 (dd, J = 253.0, 13.3 Hz), 128.3 (dd, J = 13.4, 4.0 Hz), 123.0 (dd, J = 11.7, 3.0 Hz), 122.5 (d, J = 1.5 Hz, 2C), 116.4 (dd, J = 23.8, 3.9 Hz), 109.4 (2C), 106.1 (dd, J = 26.3, 25.0 Hz), 88.6 (dd, J = 4.9, 3.5 Hz), 15.3; ^19F NMR (376 MHz, CDCl₃): δ -109.5 (q, J = 8.0 Hz); IR (NaCl, neat): 3409, 2162, 1584, 1510, 1432, 1345, 1307, 1128, 1066, 1012, 873, 845, 734 cm⁻¹; M. p.: 128 °C; HRMS (EI): calcd for C₁₂H₁₆F₂IN: 328.9513; found: 328.9510.

1-(5-Fluoro-2-(iodoethynyl)phenyl)-1H-pyrrole (4.49)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.5, terminal alkyne 4.36 (120 mg, 0.65 mmol), CuI (6.2 mg, 0.03 mmol, 5 mol%) and N-iodomorpholine (265 mg, 0.78 mmol, 1.2 equiv) were reacted in the presence of 4 Å MS in THF (12 mL) in the dark at room temperature. Subsequent workup and flash column chromatography (gradient pentane 100% to pentane:CH₂Cl₂ 10:1) yielded 4.49 as an orange oil in 96%. ^1H NMR (400 MHz, CDCl₃): δ 7.52 (dd, J = 8.7, 6.1 Hz, 1H), 7.11 (ap t, J = 2.2 Hz, 2H), 7.01 (dd, J = 9.5, 2.6 Hz, 1H), 6.94 (ddd, J = 8.7, 7.8, 2.6 Hz, 2H), 6.34 (ap t, J = 2.2 Hz, 2H); ^13C NMR (101 MHz, CDCl₃) δ 162.7 (d, J = 252.1 Hz), 144.2 (d, J = 10.3 Hz), 136.5 (d, J = 9.4 Hz), 121.3 (2), 113.5 (d, J = 3.5 Hz), 113.3 (d, J = 22.0 Hz), 111.9 (d, J = 24.9 Hz), 110.1 (2), 90.0, 11.5 (d, J = 2.1 Hz); ^19F NMR (376 MHz, CDCl₃): δ -108.1 (ddd, J = 9.4, 7.7, 6.2 Hz); IR (NaCl, neat): 3432, 3106, 2922, 2170, 1604, 1495, 1432, 1330, 1216, 1187, 1094, 1025, 958, 864, 819, 729, 629 cm⁻¹; HRMS (ESI): calcd for C₁₂H₁₆F₂IN (M+H)⁺: 311.9665; found: 311.9680.

1-(2-(Iodoethynyl)-5-nitrophenyl)-1H-pyrrole (4.50)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.5, terminal alkyne 4.37 (152 mg, 0.72 mmol), CuI (6.8 mg, 0.04 mmol, 5 mol%) and N-iodomorpholine (293 mg, 0.86 mmol, 1.2 equiv) were reacted in the presence of 4 Å MS in THF (11 mL) in the dark at room temperature. Subsequent workup and flash column chromatography (gradient pentane 100% to pentane:EtOAc 10:1) yielded 4.50 as red solid in 41%. ^1H NMR (400 MHz, CDCl₃): δ 8.17 (d, J = 2.2 Hz, 1H), 8.07 (dd, J = 8.6, 2.3 Hz, 1H), 7.71 (d, J = 8.6 Hz, 1H), 7.16 (ap t, J = 2.2 Hz, 2H), 6.39 (ap t, J = 2.2 Hz, 2H); ^13C NMR (100 MHz, CDCl₃): δ 147.8, 143.4, 135.9, 123.5, 121.3 (2), 120.3, 119.5, 110.9 (2C), 89.7, 19.4; IR (NaCl, neat): 2921, 2361, 2164, 1579, 1518, 1341, 1067, 900, 865, 833, 729 cm⁻¹; M. p.: 168 °C; HR MS (EI): calcd for C₁₂H₇IN₂O₂ (M)⁺: 337.9552; found: 337.9564.
Methyl 3-(iodoethynyl)-4-(1H-pyrrol-1-yl)benzoate (4.51)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.5, terminal alkyne 4.38 (300 mg, 1.33 mmol), Cul (12.7 mg, 0.07 mmol, 5 mol%) and N-iodomorpholine (545 mg, 1.60 mmol, 1.2 equiv) were reacted in the presence of 4 Å MS in THF (22 mL) in the dark at room temperature. Subsequent workup and flash column chromatography (gradient pentane 100% to pentane:EtOAc 10:3) yielded 4.51 as yellow solid in 98%. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.24 (d, \(J = 1.9\) Hz, 1H), 8.02 (dd, \(J = 8.5, 1.9\) Hz, 1H), 7.35 (d, \(J = 8.5\) Hz, 1H), 7.18 (ap t, \(J = 2.1\) Hz, 2H), 6.36 (ap t, \(J = 2.1\) Hz, 2H), 3.93 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 165.5, 145.7, 136.8, 130.9, 127.5, 124.0, 121.3, 117.0, 110.4, 90.2, 52.4, 13.4; IR (neat): 2951, 2361, 1720, 1603, 1503, 1438, 1332, 1298, 1236, 1118, 1068, 985, 912, 765, 730 cm\(^{-1}\); M. p.: 148-151 °C; HRMS (ESI): calcd for C\(_{14}\)H\(_{11}\)INO\(_2\) (M+H): 351.9829; found: 351.9817.

3-(Iodoethyl)-5-nitro-2-(1H-pyrrol-1-yl)benzonitrile (4.52)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.5, terminal alkyne 4.39 (97.6 mg, 0.28 mmol), Cul (2.6 mg, 0.014 mmol, 5 mol%) and N-iodomorpholine (115 mg, 0.34 mmol, 1.2 equiv) were reacted in the presence of 4 Å MS in THF (5 mL) in the dark at room temperature. Subsequent workup and flash column chromatography (gradient pentane 100% to pentane:EtOAc 10:3) yielded 4.52 as yellow solid in 50%. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.57 (d, \(J = 2.5\) Hz, 1H), 8.52 (d, \(J = 2.5\) Hz, 1H), 7.09 (ap t, \(J = 2.1\) Hz, 2H), 6.46 (ap t, \(J = 2.1\) Hz, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 149.0, 145.0, 133.4, 128.8, 122.6, 121.9, 114.3, 111.9, 111.0, 87.4, 20.4; IR (neat): 3082, 2918, 2361, 2237, 2167, 1578, 1538, 1528, 1483, 1348, 1318, 1096, 1057, 1011, 983, 907, 780, 730 cm\(^{-1}\); M. p.: 155-160 °C (decomp); HRMS (ESI): calcd for C\(_{13}\)H\(_{11}\)INO\(_2\) (M+H): 363.9577; found: 363.9563.

1-(2-(Iodoethyl)-4-methyl-6-nitrophenyl)-1H-pyrrole (4.53)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.5, terminal alkyne 4.40 (100 mg, 0.44 mmol), Cul (4.2 mg, 0.022 mmol, 5 mol%) and N-iodomorpholine (180.8 mg, 0.53 mmol, 1.2 equiv) were reacted in the presence of 4 Å MS in THF (8.5 mL) in the dark at room temperature. Subsequent workup and flash column chromatography (gradient pentane 100% to pentane:EtOAc 1:1) yielded 4.53 as red solid in 95%. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.60 (d, \(J = 4.1\) Hz, 2H), 6.74 (ap t, \(J = 2.0\) Hz, 2H), 6.36 (ap t, \(J = 2.0\) Hz, 2H), 2.45 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 147.1, 138.8, 137.9, 133.9, 125.6, 122.1, 122.0 (2), 110.6 (2), 78.6, 77.6, 20.8; IR (NaCl, neat): 2922, 2854, 2361, 2337, 1725, 1537, 1503, 1363, 1070, 1014, 870, 764, 727, 660 cm\(^{-1}\); M. p.: 200 °C (decomp); HRMS (ESI): calcd for C\(_{20}\)H\(_{14}\)N\(_4\)O\(_4\) (M+H): 451.1401; found: 451.1391.
1-(2-(Iodoethynyl)phenyl)-1H-indole (4.54)

According to the general procedure 4.5, terminal alkyne 4.41 (111 mg, 0.513 mmol), CuI (4.87 mg, 0.0256 mmol, 5 mol%) and N-iodomorpholine (209 mg, 0.615 mmol, 1.2 equiv) were reacted in the presence of 4 Å MS in THF (5 mL, 0.1 M) in the dark at room temperature. Subsequent workup and flash column chromatography (pentane:DCM 93:7) yielded 4.54 as red oil in 87% yield. \( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.68 (dd, \( J = 7.0, 1.5 \) Hz, 1H), 7.62 (dd, \( J = 7.7, 1.1 \) Hz, 1H), 7.48-7.43 (m, 2H), 7.42 (d, \( J = 3.3 \) Hz, 1H), 7.36-7.30 (m, 2H), 7.23-7.14 (m, 2H), 6.68 (d, \( J = 3.2 \) Hz, 1H); \( ^{13}C \) NMR (101 MHz, CDCl\(_3\)) \( \delta \) 141.6, 136.3, 134.6, 129.6, 129.0, 128.9, 126.8, 126.7, 122.1, 120.9, 120.3, 120.3, 110.8, 103.1, 90.6, 12.2; IR (neat) 3105, 3051, 3028, 2168, 1566, 1516, 1489, 1458, 1439, 1330, 1308, 1234, 1211, 1138; HRMS (ESI): calcd for C\(_{16}\)H\(_{10}\)NI (M+H)\(^+\): 342.9858; found: 342.9868.

3-(2-(Iodoethynyl)phenyl)thiophene (4.55)

According to the general procedure 4.5, terminal alkyne 4.42 (92.13 mg, 0.5 mmol), CuI (4.76 mg, 0.025 mmol, 5 mol%) and N-iodomorpholine (204 mg, 0.6 mmol, 1.2 equiv) were reacted in the presence of 4 Å MS in THF (5 mL) in the dark at room temperature. Subsequent workup and flash column chromatography (pentane:DCM 92:8) yielded 4.55 as yellow oil in 92% yield. \( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.62 (dd, \( J = 2.9, 1.0 \) Hz, 1H), 7.53 (dd, \( J = 7.6, 0.6 \) Hz, 1H), 7.48-7.41 (m, 2H), 7.38-7.30 (m, 2H), 7.23 (ap dt, \( J = 7.6, 0.7 \) Hz, 1H); \( ^{13}C \) NMR (101 MHz, CDCl\(_3\)) \( \delta \) 140.2, 138.8, 134.3, 129.0, 128.8, 128.3, 126.7, 124.9, 123.6, 121.0, 93.9, 9.8; IR (neat) 3105, 3051, 3028, 2168, 1593, 1562, 1474, 1439, 1362, 1192; HRMS (EI) calcd for C\(_{12}\)H\(_7\)SI (M)\(^+\): 309.9313; found: 309.9323.

2-(2-(Iodoethynyl)phenyl)furan (4.56)

According to the general procedure 4.5, terminal alkyne 4.43 (84.1 mg, 0.5 mmol), CuI (4.76 mg, 0.025 mmol, 5 mol%) and N-iodomorpholine (204 mg, 0.6 mmol, 1.2 equiv) were reacted in the presence of 4 Å MS in THF (5 mL) in the dark at room temperature. Subsequent workup and flash column chromatography (pentane:DCM 95:5) yielded 4.56 as red oil in 78% yield. \( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.83 (d, \( J = 8.0 \) Hz, 1H), 7.51 (d, \( J = 7.9 \) Hz, 1H), 7.49 (d, \( J = 1.6 \) Hz, 1H), 7.37 (ap dt, \( J = 7.8, 1.2 \) Hz, 1H), 7.26-7.14 (m, 1H), 6.53 (dd, \( J = 3.4, 1.8 \) Hz, 1H); \( ^{13}C \) NMR (101 MHz, CDCl\(_3\)) \( \delta \) 151.5, 142.0, 134.7, 132.7, 129.0, 126.5, 125.3, 118.2, 111.8, 109.6, 93.9, 11.2; IR (neat) 3287, 3144, 3120, 3063, 2168, 1682, 1597, 1497, 1481, 1431, 1030, 1007; HRMS (EI) calcd for C\(_{12}\)H\(_7\)OI (M)\(^+\): 293.9542; found: 293.9541.
2-(Iodoethynyl)-4'-methoxybiphenyl (4.57)

According to the general procedure 4.5, terminal alkyne 4.44 (104 mg, 0.5 mmol), Cul (4.76 mg, 0.025 mmol, 5 mol%) and N-iodomorpholine (204 mg, 0.6 mmol, 1.2 equiv) were reacted in the presence of 4 Å MS in THF (5 mL) in the dark at room temperature. Subsequent workup and flash column chromatography (pentane:DCM 9:1) yielded 4.57 as colorless oil in 92%.

\[ \text{IR (neat)} \text{ 3059, 3001, 2955, 2932, 2835, 1612, 1516, 1462, 1439, 1246, 1176} \]

HRMS (EI): calcd for C\(_{15}\)H\(_{11}\)OI (M): 333.9855; found: 333.9861.

Synthesis of 5-iodo-1,2,3-triazoles

4-(2-(1H-pyrrol-1-yl)phenyl)-1-benzyl-5-iodo-1H-1,2,3-triazole (4.60)

This compound was prepared by Dr. K. Geyer: Cul (1.0 mg, 0.005 mmol, 5 mol%) and TBTA (2.8 mg, 0.005 mmol, 5 mol%) were mixed in THF and stirred at room temperature until a clear solution was formed. The iodoalkyne 4.45 (31 mg, 0.011 mmol) and BnN\(_3\) (14.1 mg 0.11 mmol) were dissolved in THF were added and the reaction was stirred at room temperature in the dark. After TLC analysis showed complete conversion of the starting materials, aq. KOH (1M) was added, the mixture was extracted with EtOAc (3 x 5 mL), the combined organic layers were washed with brine, dried over MgSO\(_4\) and concentrated under reduced pressure. Flash column chromatography (gradient pentane 100% to EtOAc 100%) yielded 5-iodo-1,2,3-triazole 4.60 in quantitative yield as an orange oil.

\[ \text{IR (neat)} \text{ 3421, 3065, 3033, 2926, 2854, 2360, 2242, 1724, 1496, 1358, 1331, 1246, 1218, 1127, 1097, 1071, 909, 765, 735 \text{ cm}^{-1} \]

HRMS (ESI) calcd for C\(_{19}\)H\(_{16}\)IN\(_4\)(M+H): 427.0414; found: 427.0399.

Synthesis of fused 1,2,3-triazoles

Procedure 4.6 (separate steps): In a microwave seal tube, 5-iodo-1,2,3-triazole was dissolved in THF, Pd(OAc)\(_2\), PPh\(_3\), Bu\(_4\)NBr and K\(_2\)CO\(_3\) were added, the vial was purged with argon, sealed and the reaction was stirred at 80°C. After TLC analysis had shown complete conversion of the starting materials, the reaction mixture was cooled down to room temperature and concentrated under reduced pressure. Flash column chromatography using the stated solvent mixtures yielded the desired target structures.
Procedure 4.7 (one-pot procedure): In a microwave seal tube, CuI and TBTA were mixed in THF and stirred at room temperature until a clear solution was formed. The iodoalkyne and BnN₃ dissolved in THF were added and the reaction was stirred at room temperature in the dark. After TLC analysis had shown complete conversion of the starting materials, Pd(OAc)$_2$, PPh$_3$, Bu$_4$NBr and K$_2$CO$_3$ were added, the vial was purged with argon, sealed and the reaction was stirred at 80°C. After TLC analysis had shown complete conversion of the starting materials, the reaction mixture was cooled down to room temperature and concentrated under reduced pressure. Flash column chromatography using the stated solvent mixtures yielded the desired target structures.

3-Benzyl-3H-pyrrolo[1,2-a][1,2,3]triazolo[4,5-c]quinoline (4.61)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.6. 5-iodo-1,2,3-triazole 4.60 (13.4 mg, 0.03 mmol) was reacted with Pd(OAc)$_2$ (0.7 mg, 0.003 mmol, 10 mol%), PPh$_3$ (1.65 mg, 0.006 mmol, 20 mol%), Bu$_4$NBr (9.7 mg, 0.03 mmol) and K$_2$CO$_3$ (8.3 mg, 0.06 mmol, 2 equiv) in THF (1 mL). Subsequent workup and flash column chromatography (gradient pentane 100% to pentane:EtOAc 4:1) yielded fused 1,2,3-triazole 4.61 in 87% yield.

According to the general procedure 4.7, iodoalkyne 4.45 (29.3 mg, 0.1 mmol), BnN₃ (13.3 mg, 0.1 mmol), CuI (0.95 mg, 0.005 mmol, 5 mol%) and TBTA (2.65 mg, 0.005 mmol, 5 mol%) were reacted in THF (2.5 mL, 0.04 M). After full conversion of 4.45 to 4.60 (24 h), Pd(OAc)$_2$ (2.25 mg, 0.01 mmol, 10 mol%), PPh$_3$ (5.25 mg, 0.02 mmol, 20 mol%), Bu$_4$NBr (32.2 mg, 0.1 mmol) and K$_2$CO$_3$ (13.8 mg, 0.1 mmol) were added and the reaction was stirred at 80°C. Subsequent flash column chromatography (gradient pentane 100% to pentane:EtOAc 4:1) yielded fused 1,2,3-triazole 4.61 as yellow-orange solid in 94% yield.

$^1$H NMR (400 MHz, CDCl$_3$): δ 8.55 (dd, $J = 7.8$, 1.0 Hz, 1H), 7.90 - 7.85 (m, 2H), 7.56 (ap t, $J = 7.4$ Hz, 1H), 7.37 - 7.23 (m, 5H), 6.69 (ap t, $J = 3.4$ Hz, 1H), 6.62 (dd, $J = 3.7$, 2.1 Hz, 1H), 6.0 (s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 137.6, 134.7, 132.0, 129.1 (2), 128.3, 128.2, 126.92 (2), 125.6, 124.8, 123.7, 119.1, 117.0, 115.0, 114.9, 112.6, 103.6, 52.9; IR (neat): 2922, 2853, 1634, 1491, 1433, 1382, 1336, 1255, 1229, 1101, 1034, 909, 757, 702 cm$^{-1}$; M. p.: 154-158°C; HRMS (ESI): calcd for C$_{19}$H$_{15}$N$_4$ (M+H)$^+$: 299.1289; found: 299.1291.

3-(4-Methoxybenzyl)-3H-pyrrolo[1,2-a][1,2,3]triazolo[4,5-c]quinoline (4.61b)

According to the general procedure 4.7, iodoalkyne 4.45 (29.3 mg, 0.1 mmol), p-methoxybenzylazide (16.3 mg, 0.1 mmol), CuI (0.95 mg, 0.005 mmol, 5 mol%) and TBTA (2.65 mg, 0.005 mmol, 5 mol%) were reacted in THF (2.5 mL, 0.04 M). After 24 h TLC showed 4.45 remaining; an additional 5 mol% of CuI and TBTA is added. Full conversion of 4.45 to the iodotriazole is observed (24+16 h), Pd(OAc)$_2$ (2.25 mg, 0.01 mmol, 10 mol%), PPh$_3$ (5.25
mg, 0.02 mmol, 20 mol%), Bu₄NBr (32.2 mg, 0.1 mmol) and K₂CO₃ (13.8 mg, 0.1 mmol) were added and the reaction was stirred at 80 °C for 24 h. Subsequent flash column chromatography (pentane:EtOAc:NEt₃ 8:2:0.5) yielded fused 1,2,3-triazole 4.61b as a pale yellow solid in 94% yield. ¹H NMR (400 MHz, CDCl₃) δ 8.52 (dd, J = 7.8, 1.5 Hz, 1H), 7.84 (m, 2H), 7.53 (ap td, J = 7.4, 1.4 Hz, 1H), 7.46 (ap t, J = 7.4 Hz, 1H), 7.22 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 6.69 (dd, J = 4.3, 2.9 Hz, 1H), 6.64 (dd, J = 3.7, 1.2 Hz, 1H), 5.87 (s, 2H), 3.75 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 159.5, 137.5, 131.9, 128.4 (2), 128.1, 126.7, 125.4, 124.7, 123.6, 119.1, 116.9, 114.9, 114.8, 114.4 (2C), 112.5, 103.6, 55.2 (2), 52.4; IR (neat) 3153, 3066, 3009, 2939, 2840, 1635, 1612, 1513, 1460, 1432, 1336, 1253, 1176, 1024; M. p.: 179-181 °C; HRMS (ESI): Calcd for C₂₀H₁₇N₄O (M+H)⁺: 329.1396; found: 329.1405.

3-(4-Nitrobenzyl)-3H-pyrrolo[1,2-a][1,2,3]triazolo[4,5-c]quinoline (4.61c)

According to the general procedure 4.7, iodoalkyne 4.45 (29.3 mg, 0.1 mmol), p-nitrobenzylazide (17.8 mg, 0.1 mmol), CuI (0.95 mg, 0.005 mmol, 5 mol%) and TBTA (2.65 mg, 0.005 mmol, 5 mol%) were reacted in THF (2.5 mL, 0.04 M). After full conversion of 4.45 to the iodotriazole (20h), Pd(OAc)₂ (2.25 mg, 0.01 mmol, 10 mol%), PPh₃ (5.25 mg, 0.02 mmol, 20 mol%), Bu₄NBr (32.2 mg, 0.1 mmol) and K₂CO₃ (13.8 mg, 0.1 mmol) were added and the reaction was stirred at 80 °C. Subsequent flash column chromatography (pentane:EtOAc 8:2) yielded fused 1,2,3-triazole 4.61c as yellow solid in 86% yield. ¹H NMR (400 MHz, CDCl₃) δ 8.54 (dd, J = 7.8, 1.4 Hz, 1H), 8.20 (d, J = 8.8 Hz, 2H), 7.94-7.83 (m, 2H), 7.58 (ddd, J = 8.5, 7.3, 1.6 Hz, 1H), 7.50 (ap dt, J = 7.6, 1.0 Hz, 1H), 7.40 (d, J = 8.8 Hz, 2H), 6.69 (dd, J = 3.8, 3.1 Hz, 1H), 6.52 (dd, J = 3.9, 1.2 Hz, 1H), 6.05 (s, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 147.8, 141.6, 137.6, 131.9, 128.5, 127.7 (2C), 125.5, 125.0, 124.3 (2C), 123.7, 118.5, 116.6, 115.4, 112.7, 103.3, 52.1; IR (neat) 3147, 3079, 2931, 2853, 1634, 1601, 1521, 1427, 1343, 1336, 1228; M. p.: 179-181 °C; HRMS (EI) calcd for C₁₉H₁₃N₅O₂ (M⁺): 343.1069; found: 343.1063.

3-Hexyl-3H-pyrrolo[1,2-a][1,2,3]triazolo[4,5-c]quinoline (4.61d)

According to the general procedure 4.7, iodoalkyne 4.45 (29.3 mg, 0.1 mmol), n-hexylazide (12.7 mg, 0.1 mmol), CuI (0.95 mg, 0.005 mmol, 5 mol%) and TBTA (2.65 mg, 0.005 mmol, 5 mol%) were reacted in THF (2.5 mL, 0.04 M). After 24 h TLC shows 4.45 remaining; an additional 5 mol% of CuI and TBTA is added. Full conversion of 4.45 to the iodotriazole is observed (24+16 h), Pd(OAc)₂ (2.25 mg, 0.01 mmol, 10 mol%), PPh₃ (5.25 mg, 0.02 mmol, 20 mol%), Bu₄NBr (32.2 mg, 0.1 mmol) and K₂CO₃ (13.8 mg, 0.1 mmol) were added and the reaction was stirred at 80 °C for 16 h. Subsequent flash column chromatography (pentane:EtOAc 95:5) yielded fused 1,2,3-triazole 4.61d as colorless oil (turns dark green over time) in 95% yield. ¹H NMR (400 MHz, CDCl₃) δ
8.50 (dd, $J = 7.8, 1.4$ Hz, 1H), 7.89 (dd, $J = 3.0, 1.5$ Hz, 1H), 7.87 (d, $J = 8.3$ Hz, 1H), 7.57-7.49 (m, 1H), 7.45 (ap dt, $J = 7.7, 1.0$ Hz, 1H), 6.81-6.73 (m, 2H), 4.71 (t, $J = 7.4$ Hz, 2H), 2.10-1.97 (m, 2H), 1.39-1.24 (m, 4H), 0.88 (t, $J = 7.1, 1.1$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 137.1, 131.8, 127.9, 125.1, 124.7, 123.5, 119.3, 117.0, 114.9, 114.8, 112.4, 102.8, 49.5, 31.2, 29.4, 26.1, 22.4, 13.9; IR (NaCl, neat) 3136, 3109, 2955, 2928, 2858, 1635, 1508, 1489, 1465, 1431, 1384, 1339; HRMS (EI) calcd for C$_{18}$H$_{20}$N$_4$: 292.1688; found: 292.1695.

3-Benzyl-10-chloro-3H-pyrrolo[1,2-a][1,2,3]triazolo[4,5-c]quinoline (4.62)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.7, iodoalkyne 4.47 (22.0 mg, 0.07 mmol), BnN$_3$ (9.0 mg, 0.07 mmol), CuI (0.6 mg, 0.003 mmol, 5 mol%) and TBTA (1.8 mg, 0.003 mmol, 5 mol%) were reacted in THF (2 mL). Afterwards, Pd(OAc)$_2$ (1.5 mg, 0.006 mmol, 10 mol%), PPh$_3$ (3.5 mg, 0.01 mmol, 20 mol%), Bu$_4$NBr (21.6 mg, 0.07 mmol) and K$_2$CO$_3$ (9.3 mg, 0.07 mmol) were added and the reaction was stirred at 80 °C. Subsequent flash column chromatography (gradient pentane 100% to pentane:EtOAc 3:1) yielded fused 1,2,3-triazole 4.62 as yellow-orange solid in 85% yield. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.50 (d, $J = 2.2$ Hz, 1H), 7.80 (d, $J = 2.5$ Hz, 1H), 7.77 (d, $J = 9.0$ Hz, 1H), 7.48 (dd, $J = 8.9, 2.2$ Hz, 1H), 7.37 - 7.23 (m, 5H), 6.69 (ap t, $J = 3.4$ Hz, 1H), 6.61 (d, $J = 3.8$ Hz, 1H), 5.94 (s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 136.6, 134.5, 130.5, 130.5, 129.1 (2), 128.5, 128.2, 127.0 (2), 126.1, 123.3, 119.0, 118.3, 116.4, 115.2, 112.9, 104.1, 53.0; IR (neat): 2919, 2852, 2361, 1629, 1534, 1461, 1404, 1331, 1218, 1108, 940, 867, 808., 725 cm$^{-1}$; M. p.: 230-235 °C (decomp); HRMS (ESI): calcd for C$_{19}$H$_{14}$ClN$_4$(M+H)$^+$: 333.0901; found: 333.0915.

3-Benzyl-8,10-difluoro-3H-pyrrolo[1,2-a][1,2,3]triazolo[4,5-c]quinoline (4.63)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.7, iodoalkyne 4.48 (41.0 mg, 0.13 mmol), BnN$_3$ (16.6 mg, 0.13 mmol), CuI (1.2 mg, 0.006 mmol, 5 mol%) and TBTA (3.3 mg, 0.006 mmol, 5 mol%) were reacted in THF (4 mL). Afterwards, Pd(OAc)$_2$ (2.3 mg, 0.01 mmol, 10 mol%), PPh$_3$ (6.5 mg, 0.02 mmol, 20 mol%), Bu$_4$NBr (40.3 mg, 0.13 mmol) and K$_2$CO$_3$ (17.2, 0.13 mmol) were added and the reaction was stirred at 80 °C. Subsequent flash column chromatography (gradient pentane 100% to pentane:EtOAc 3:1) yielded fused 1,2,3-triazole 4.63 as slight yellow solid in 82% yield. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.25 (d, $J = 1.8$ Hz, 1H), 8.06 (ddd, $J = 8.4, 2.4, 1.6$ Hz, 1H), 7.39 - 7.26 (m, 5H), 7.10 (ddd, $J = 13.6, 8.2, 2.7$ Hz, 1H), 6.72 - 6.64 (m, 2H), 5.95 (s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 158.6 $^{67}$, 153.0 $^{67}$, 134.9, 134.4.

$^{67}$ The carbon atoms directly attached to fluorines could not be resolved. A 2D $^{13}$C/$^{19}$F measurements were preformed to determine the shift.
129.4, 129.1 (2), 129.0, 128.5, 126.9 (2), 126.5, 120.8 (d, J = 23.7 Hz), 118.9, 112.7 (d, J = 4.5 Hz), 105.1 (dd, J = 23.8, 3.9 Hz), 104.0 (dd, J = 27.4, 26.2 Hz), 103.7 (d, J = 1.5 Hz), 53.0; $^{19}$F NMR (376 MHz, CDC13): δ -113.7 (q, J = 7.6 Hz), -116.5 (dd, J = 13.5, 6.6 Hz); IR (neat): 2919, 2852, 2361, 1636, 1576, 1468, 1386, 1257, 1119, 1027, 854, 718 cm⁻¹; M. p.: 156-158 °C; HRMS (EI): calcd for C₁₅H₁₃F₄N₂(M⁺): 334.1030; found: 334.1031.

3-Benzyl-9-fluoro-3H-pyrrolo[1,2-a][1,2,3]triazolo[4,5-c]quinoline (4.64)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.7, iodoalkyne 4.49 (24.0 mg, 0.08 mmol), BnN₃ (10.3 mg, 0.08 mmol), Cul (0.7 mg, 0.004 mmol, 5 mol%) and TBTA (2.0 mg, 0.004 mmol, 5 mol%) were reacted in THF (2 mL). Afterwards, Pd(OAc)₂ (1.7 mg, 0.008 mmol, 10 mol%), PPh₃ (4.0 mg, 0.015 mmol, 20 mol%), Bu₄NBr (24.8 mg, 0.08 mmol) and K₂CO₃ (10.6, 0.08 mmol) were added and the reaction was stirred at 80 °C. Subsequent flash column chromatography (gradient pentane 100% to pentane:EtOAc 4:1) yielded fused 1,2,3-triazole 4.64 as yellow-brown solid in 75% yield. $^1$H NMR (400 MHz, CDCl₃): δ 8.49 (dd, J = 8.8, 6.1 Hz, 1H), 7.70 (dd, J = 3.0, 1.2 Hz, 1H), 7.51 (dd, J = 10.3, 2.3 Hz, 1H), 7.38 - 7.23 (m, 5H), 7.19 (ap dt, J = 8.5, 2.3 Hz, 1H), 6.68 (dd, J = 3.7, 3.2 Hz, 1H), 6.59 (dd, J = 3.9, 1.2 Hz, 1H), 5.93 (s, 2H); $^{13}$C NMR (100 MHz, CDCl₃): δ 162.6 (d, J = 246.0 Hz), 137.4, 134.8, 133.2 (d, J = 10.4 Hz), 129.3 (2), 128.6, 127.1 (2), 125.8 (d, J = 10.1 Hz), 125.3, 119.5, 115.4, 113.6 (d, J = 3.0 Hz), 113.3, 112.9 (d, J = 22.1 Hz), 104.2, 102.5 (d, J = 26.0 Hz), 53.2; $^{19}$F NMR (376 MHz, CDCl₃): δ -110.6 (dd, J = 16.6, 7.9 Hz); IR (neat): 3414, 3135, 2920, 2853, 1630, 1552, 1490, 1429, 1383, 1331, 1250, 1196, 1090, 1031, 846, 729, 701 cm⁻¹; M. p.: 194-196 °C (decomp); HRMS (ESI): calcd for C₁₅H₁₄F₄N₄(M+H)⁺: 317.1197; found: 317.1192.

3-Benzyl-9-nitro-3H-pyrrolo[1,2-a][1,2,3]triazolo[4,5-c]quinoline (4.65)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.7, iodoalkyne 4.50 (23.0 mg, 0.07 mmol), BnN₃ (9.0 mg, 0.07 mmol), Cul (0.7 mg, 0.003 mmol, 5 mol%) and TBTA (1.8 mg, 0.003 mmol, 5 mol%) were reacted in THF (2 mL). Afterwards, Pd(OAc)₂ (1.5 mg, 0.007 mmol, 10 mol%), PPh₃ (3.6 mg, 0.014 mmol, 20 mol%), Bu₄NBr (21.9 mg, 0.07 mmol) and K₂CO₃ (9.3, 0.07 mmol) were added and the reaction was stirred at 80 °C. Subsequent flash column chromatography (gradient pentane 100% to pentane:EtOAc 1:2) yielded fused 1,2,3-triazole 4.65 as yellow-orange solid in 91% yield. $^1$H NMR (400 MHz, CDCl₃): δ 8.78 (d, J = 2.0 Hz, 1H), 8.67 (d, J = 8.7 Hz, 1H), 8.33 (dd, J = 8.7, 2.1 Hz, 1H), 7.98 (dd, J = 3.0, 1.1 Hz, 1H), 7.39 - 7.27 (m, 5H), 6.78 (dd, J = 3.8, 3.2 Hz, 1H), 6.70 (dd, J = 3.9, 1.1 Hz, 1H), 5.97 (s, 2H); $^{13}$C NMR (100 MHz, CDCl₃): δ 146.8, 136.3, 134.2, 131.7, 129.2 (2), 128.6, 127.2, 127.0 (2), 124.5, 122.3, 119.5, 119.1, 116.2, 113.8, 111.0, 105.3, 53.1; IR (neat): 3123, 3067, 2921, 2853, 2361, 1725, 1629, 1575, 1516, 1428, 1341, 1224, 1113, 1032, 892, 829,
Methyl 3-benzyl-3H-pyrrolo[1,2-a][1,2,3]triazolo[4,5-c]quinoline-10-carboxylate (4.66)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.7, iodoalkyne 4.51 (29.5 mg, 0.08 mmol), BnN₃ (11.2 mg, 0.08 mmol), CuI (0.8 mg, 0.004 mmol, 0.05 equiv) and TBTA (2.2 mg, 0.004 mmol, 0.05 eq.) were reacted in THF (2 mL). Afterwards, Pd(OAc)₂ (1.9 mg, 0.008 mmol, 0.1 eq.), PPh₃ (4.4 mg, 0.017 mmol, 0.2 eq.), Bu₄NBr (27.1 mg, 0.08 mmol) and K₂CO₃ (11.6, 0.08 mmol) were added and the reaction was stirred at 80°C. Subsequent flash column chromatography (gradient pentane 100% to pentane:EtOAc 10:3) yielded fused 1,2,3-triazole 4.66 as red-brown solid in 85% yield. ¹H NMR (400 MHz, CDCl₃): δ 9.19 (s, 1H), 8.18 (d, J = 8.7 Hz, 1H), 7.87 - 7.83 (m, 2H), 7.38 - 7.20 (m, 5H), 6.71 (ap t, J = 3.3 Hz, 1H), 6.62 (d, J = 3.6 Hz, 1H), 5.94 (s, 2H), 3.99 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 166.3, 137.2, 134.6, 134.5, 129.2, 129.1 (2), 128.5, 127.0 (2), 126.5, 125.8, 125.6, 119.4, 116.8, 115.6, 115.0, 113.5, 104.5, 53.0, 52.3; IR (neat): 2920, 2853, 1717, 1629, 1434, 1409, 1334, 1280, 1236, 1120, 1026, 973, 759, 718 cm⁻¹; M. p.: 205-206 °C (decomp); HRMS (ESI): calcd for C₁₉H₁₄FN₂O₂ (M+H)⁺: 344.1142; found: 344.1125.

3-Benzyl-10-nitro-3H-pyrrolo[1,2-a][1,2,3]triazolo[4,5-c]quinoline-8-carbonitrile (4.67)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.7, iodoalkyne 4.52 (13.5 mg, 0.04 mmol), BnN₃ (5.0 mg, 0.04 mmol), CuI (0.5 mg, 0.002 mmol, 5 mol%) and TBTA (1.0 mg, 0.002 mmol, 5 mol%) were reacted in THF (1.5 mL). Afterwards, Pd(OAc)₂ (0.8 mg, 0.004 mmol, 10 mol%), PPh₃ (1.9 mg, 0.007 mmol, 20 mol%), Bu₄NBr (11.9 mg, 0.04 mmol) and K₂CO₃ (5.1 mg, 0.04 mmol) were added and the reaction was stirred at 80 °C. Subsequent flash column chromatography (gradient pentane 100% to pentane:EtOAc 5:1) yielded fused 1,2,3-triazole 4.67 as bright yellow solid in 62% yield. ¹H NMR (400 MHz, CDCl₃): δ 9.63 (d, J = 2.6 Hz, 1H), 9.13 (d, J = 3.1 Hz, 1H), 8.72 (d, J = 2.6 Hz, 1H), 7.41 - 7.31 (m, 5H), 6.88 (ap t, J = 3.6 Hz, 1H), 6.79 (ap t, J = 3.9 Hz, 1H), 5.99 (s, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 143.0, 135.6, 134.8, 133.8, 129.4, 129.3 (2), 128.8, 126.9 (2), 126.3, 123.4, 120.5, 120.0, 119.3, 117.4, 115.3, 106.5, 100.9, 53.3; IR (neat): 2919, 2853, 2361, 1580, 1536, 1461, 1340, 1259, 1102, 915, 796 cm⁻¹; M. p.: 205-206 °C (decomp); HRMS (ESI): calcd for C₂₁H₁₇N₄O₂: 357.1346; found: 357.1349.
3-Benzyl-10-methyl-8-nitro-3H-pyrrolo[1,2-a][1,2,3]triazolo[4,5-c]quinoline (4.68)

This compound was prepared by Dr. K. Geyer according to the general procedure 4.7, iodoalkyne 4.53 (28.0 mg, 0.08 mmol), BnN₃ (10.6 mg, 0.08 mmol), CuI (0.8 mg, 0.004 mmol, 5 mol%) and TBTA (2.1 mg, 0.004 mmol, 5 mol%) were reacted in THF (2 mL). Afterwards, Pd(OAc)₂ (1.8 mg, 0.008 mmol, 10 mol%), PPh₃ (4.2 mg, 0.008 mmol, 20 mol%), Bu₄NBr (25.8 mg, 0.08 mmol) and K₂CO₃ (11.1, 0.08 mmol) were added and the reaction was stirred at 80 °C. Subsequent flash column chromatography (gradient pentane 100% to pentane:EtOAc 5:1) yielded fused 1,2,3-triazole 4.68 as orange-brown solid in 92% yield. ¹H NMR (400 MHz, CDCl₃): δ 8.53 (d, J = 0.8 Hz, 1H), 7.48 (d, J = 1.3 Hz, 1H), 7.37 - 7.22 (m, 6H), 6.68 - 6.61 (m, 2H), 5.95 (s, 2H), 2.56 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 140.9, 136.1, 134.9, 134.2, 129.1 (2), 128.5, 126.9 (2), 126.7, 125.9, 124.1, 120.6, 119.8, 119.7, 118.7, 113.6, 104.5, 53.0, 20.6; IR (neat): 2922, 2361, 1637, 1527, 1462, 1407, 1359, 1317, 1283, 1028, 935, 909, 877, 787, 736 cm⁻¹; M. p.: 181-185 °C (decomp); HRMS (ESI): calcd for C₂₀H₁₆N₅O₂ (M+H)⁺: 358.1298; found: 358.1298.

7-Benzyl-7H-indolo[1,2-a][1,2,3]triazolo[4,5-c]quinoline (4.69)

According to the general procedure 4.7, iodoalkyne 4.54 (34.3 mg, 0.1 mmol), BnN₃ (13.3 mg, 0.1 mmol), CuI (0.95 mg, 0.005 mmol, 5 mol%) and TBTA (2.65 mg, 0.005 mmol, 5 mol%) were reacted in THF (2.5 mL, 0.04 M). After full conversion of 4.54 to the iodotriazole (16 h), Pd(OAc)₂ (2.25 mg, 0.01 mmol, 10 mol%), PPh₃ (5.25 mg, 0.02 mmol, 20 mol%), Bu₄NBr (32.2 mg, 0.1 mmol) and K₂CO₃ (13.8 mg, 0.1 mmol) were added and the reaction was stirred at 80 °C for 12 h. Subsequent flash column chromatography (pentane:EtOAc 5:1) yielded fused 1,2,3-triazole 4.69 as pale yellow solid in 62% yield. ¹H NMR (400 MHz, CDCl₃): δ 8.60 (d, J = 8.6 Hz, 1H), 8.44 (d, J = 8.6 Hz, 1H), 7.79 (d, J = 7.8 Hz, 1H), 7.64 (ddd, J = 8.6, 7.4, 1.3 Hz, 1H), 7.50-7.43 (m, 1H), 7.39-7.25 (m, 1H), 6.92 (s, 1H), 6.04 (s, 1H); ¹³C NMR (101 MHz, CDCl₃): δ 135.1, 134.4, 133.9, 129.8, 129.1 (2C), 128.6, 128.4, 126.7 (2C), 124.6, 123.9, 123.7, 123.5, 122.2, 121.6, 117.2, 116.3, 114.2, 97.9, 53.1 (2 resonances overlap); IR (neat) 3063, 3032, 2924, 2851, 1651, 1624, 1454, 1435, 1339; M. p.: 203-205 °C; HRMS (ESI) Calcd for C₂₃H₁₇N₅O (M+H)⁺: 349.1447; found: 349.1445.

3-Benzyl-3,4-dihydrobenzo[e][1,2,3]triazole[4,5-g]benzo[b]thiophene (4.70)

According to the general procedure 4.7, iodoalkyne 4.55 (31 mg, 0.1 mmol), BnN₃ (13.3 mg, 0.1 mmol), CuI (0.95 mg, 0.005 mmol, 5 mol%) and TBTA (2.65 mg, 0.005 mmol, 5 mol%) were reacted in THF (2.5 mL, 0.04 M). After 24 h TLC shows 1m remaining; an additional 5 mol% of CuI and TBTA is added. Full conversion of 4.55 to the iodotriazole is observed (24+16 h), Pd(OAc)₂ (2.25 mg,
0.01 mmol, 10 mol%), PPh₃ (5.25 mg, 0.02 mmol, 20 mol%), Bu₄NBr (32.2 mg, 0.1 mmol) and K₂CO₃ (13.8 mg, 0.1 mmol) were added and the reaction was stirred at 80 °C for 16 h. Subsequent flash column chromatography (pentane:EtOAc 95:5) yielded fused 1,2,3-triazole **4.70** as a yellow solid in 92% yield. **H NMR** (400 MHz, CDCl₃) δ 8.87 (dd, J = 8.0, 0.8 Hz, 1H), 8.31 (d, J = 7.8 Hz, 1H), 8.00 (d, J = 5.3 Hz, 1H), 7.73 (ddd, J = 8.1, 7.1, 1.3 Hz, 1H), 7.66 (ddd, J = 8.4, 7.2, 1.4 Hz, 1H), 7.61 (ap t, J = 5.1 Hz, 1H), 7.29 (m, 5H), 6.08 (s, 2H); **13C NMR** (101 MHz, CDCl₃) δ 141.4, 137.5, 134.7, 128.9 (2), 128.4, 127.7, 127.3 (2), 127.2, 127.2, 126.7, 126.4, 124.2, 123.9, 123.1, 123.0, 120.2, 52.9; **IR** (neat): 3108, 3055, 2923, 2850, 1582, 1541, 1495, 1454, 1434, 1384, 1215, 1103; **M. p.**: 126-129 °C; **HRMS** (EI) calcd for C₁₉H₁₃N₃S (M): 315.0830; found: 315.0822.

3-Benzy1-3,6-dihydrobenzo[g][1,2,3]triazole[4,5-e]benzofuran (4.71)

According to the general procedure 4.7, iodoalkyne **4.56** (29.4 mg, 0.1 mmol), BnN₃ (13.3 mg, 0.1 mmol), CuI (0.95 mg, 0.005 mmol, 5 mol%) and TBTA (2.65 mg, 0.005 mmol, 5 mol%) were reacted in THF (2.5 mL, 0.04 M). After 24 h TLC shows **4.56** remaining; an additional 5 mol% of CuI and TBTA is added. Full conversion of **4.56** is observed (24+16 h). Pd(OAc)₂ (2.25 mg, 0.01 mmol, 10 mol%), PPh₃ (5.25 mg, 0.02 mmol, 20 mol%), Bu₄NBr (32.2 mg, 0.1 mmol) and K₂CO₃ (13.8 mg, 0.1 mmol) were added and the reaction was stirred at 80 °C overnight. Subsequent flash column chromatography (pentane:EtOAc:NEt₃ 8:2:0.5) yielded fused 1,2,3-triazole **4.71** as a colorless solid in 80% yield. **H NMR** (400 MHz, CDCl₃) δ 8.84 (ddd, J = 7.9, 1.3, 0.6 Hz, 1H), 8.30 (ddd, J = 7.9, 1.2, 0.6 Hz, 1H), 7.74-7.68 (m, 2H), 7.66 (ddd, J = 8.4, 7.2, 1.4 Hz, 1H), 7.35-7.20 (m, 5H), 6.74 (d, J = 2.1 Hz, 1H), 6.03 (s, 2H); **13C NMR** (101 MHz, CDCl₃) δ 151.1, 144.6, 140.4, 135.0, 129.0 (2), 128.3, 127.2, 126.7 (2), 126.6, 126.2, 123.1, 122.8, 120.8, 120.0, 108.2, 105.1, 52.9; **IR** (neat) 3147, 3113, 3063, 3032, 2928, 2851, 1613, 1497, 1454, 1377, 1296, 1231, 1150; **M. p.**: 114-115 °C; **HRMS** (EI) calcd for C₁₉H₁₃N₃O (M): 299.1053; found: 299.1053.

1-Benzyl-10-methoxy-1H-phenanthro[9,10-d][1,2,3]triazole (4.72)

According to the general procedure 4.7, iodoalkyne **4.57** (33.4 mg, 0.1 mmol), BnN₃ (13.3 mg, 0.1 mmol), CuI (0.95 mg, 0.005 mmol, 5 mol%) and TBTA (2.65 mg, 0.005 mmol, 5 mol%) were reacted in THF (2.5 mL, 0.04 M). After 24 h TLC shows **4.57** remaining; an additional 5 mol% of CuI and TBTA is added. Full conversion of **4.57** is observed (24+24 h). Pd(OAc)₂ (2.25 mg, 0.01 mmol, 10 mol%), PPh₃ (5.25 mg, 0.02 mmol, 20 mol%), Bu₄NBr (32.2 mg, 0.1 mmol) and K₂CO₃ (13.8 mg, 0.1 mmol) were added and the reaction was stirred at 80 °C overnight. Subsequent flash column chromatography (pentane:EtOAc:NEt₃ 8:2:0.5) yielded fused 1,2,3-triazole **4.72** as a colorless solid in 97% yield. **H NMR** (400 MHz, CDCl₃) δ 8.80 (dd, J = 7.8, 1.3 Hz, 1H), 8.48
(d, J = 9.2 Hz, 1H), 8.43 (d, J = 8.1 Hz, 1H), 7.68 (ap dt, J = 7.7, 1.2 Hz, 1H), 7.63 (ddd, J = 8.6, 7.1, 1.6 Hz, 1H), 7.34-7.22 (m, 4H), 7.20-7.07 (m, 3H), 6.19 (s, 2H), 3.65 (s, 3H); \(^{13}\text{C}\) NMR (101 MHz, CDCl\(_3\)) \(\delta\) 158.5, 142.8, 135.1, 129.1 (2), 128.9, 128.0, 127.0 (2), 125.9 (2), 125.6, 124.5, 123.8, 122.8, 122.6, 121.1, 116.6, 105.3, 55.3, 54.0 (overlapping \(^{13}\text{C}\) resonances at 127.0); IR (neat) 2996, 2923, 2851, 1622, 1532, 1455, 1306, 1252, 1214, 1180, 1051, 1028; M.p.: 184-189 °C; HRMS (El): calcd for C\(_{22}\)H\(_{17}\)N\(_3\)O (M): 339.1372; found: 339.1377.

Experiments on electrocyclization/oxidation pathway

1-Benzyl-4-(4'-methoxybiphenyl-2-yl)-1H-1,2,3-triazole (4.73)

Sodium ascorbate (9.9 mg, 5 mol%) was dissolved in methanol (10 ml), To this solution was added benzylazide (133 mg, 1 mmol), 2-ethynyl-4'-methoxybiphenyl (4.44, 208 mg, 1 mmol) and copper acetate monohydrate (10 mg, 5 mol%). The solution was stirred at 45 °C overnight. In the morning TLC shows complete conversion of starting material. The reaction mixture was concentrated under reduced pressure, diluted in DCM and extracted with NH\(_4\)OH (aq, 3 x 5 ml). After concentration under reduced pressure the crude was purified by flash column chromatography (pentane:EtOAc, 8:2) to yield the titled compound as a colorless solid (273 mg, 80% yield). \(^1\text{H}\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.09 (dd, J = 7.7, 1.2 Hz, 1H), 7.43 (ap td, J = 7.6, 1.5 Hz, 1H), 7.36 (ap td, J = 7.5, 1.5 Hz, 1H), 7.34 – 7.30 (m, 3H), 7.28 (dd, J = 7.6, 1.3 Hz, 1H), 7.13-7.04 (m, J = 8.7 Hz, 4H), 6.78 (d, J = 8.7 Hz, 2H), 6.42 (s, 1H), 5.37 (s, 2H), 3.81 (s, 3H); \(^{13}\text{C}\) NMR (101 MHz, CDCl\(_3\)) \(\delta\) 158.8, 146.9, 139.9, 134.6, 133.9, 130.3 (2), 130.2, 129.3, 128.9 (2), 128.6, 128.5, 128.0, 127.8 (2), 127.6, 122.4, 113.7 (2), 55.2, 53.8; IR (neat, NaCl): 3128, 3059, 3032, 2936, 2835, 1612, 1516, 1477, 1454, 1246, 1176; M. p.: 100-102 °C; HRMS (El): calcd for C\(_{22}\)H\(_{19}\)N\(_3\)O (M): 341.1528; found: 341.1530.
Table 4.12 Reactions with 4.73.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield of 4.72</th>
<th>Starting material(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>150 °C, PhMe, air (atm), 20 h</td>
<td>-</td>
<td>4.73 observed</td>
</tr>
<tr>
<td>2</td>
<td>80 °C, THF, O(_2) (atm), 20 h</td>
<td>-</td>
<td>4.73 (93%)</td>
</tr>
<tr>
<td>3</td>
<td>FeCl(_3) (3 equiv), MeNO(_2) (0.044 M), DCM (0.03 M), Ar (bubbled through solution), 0 °C to 24 °C, 72 h (^68)</td>
<td>-</td>
<td>4.73 (75%)</td>
</tr>
<tr>
<td>4</td>
<td>DDQ (1 equiv), DCM:MeSO(_4)H (9:1, 0.01 M), 0 °C to 24 °C, 72 h (^69)</td>
<td>-</td>
<td>4.73 (57%)</td>
</tr>
<tr>
<td>5</td>
<td>(hv) (254 nm), I(_2) (1.5 equiv), PhMe/THF, 24 °C, 24 h</td>
<td>28%</td>
<td>4.73 (45%)</td>
</tr>
</tbody>
</table>

\(^a\)Reactions are carried out on 0.1 mmol scale. \(^b\)NMR yield using 1,3,5-trimethoxybenzene as an internal standard.

Experimental procedures

Entry 1: The substrate 4.73 (0.1 mmol) was weighed into a 10 ml microwave vial, toluene was added (1 ml). The vial was sealed and placed into a 150 °C oil bath for 20 h. The solvent was evaporated off to yield the crude.

Entry 2: The substrate was weighed into a 2 dram vial and fitted with a septum. THF was added and the vial was purged with O\(_2\), sealed and heated at 80 °C overnight (20 h). The solvent was removed under reduced pressure to yield the crude.

Entry 3: See reference for procedure.\(^8\)

Entry 4: See reference for procedure.\(^9\)

Entry 5: Procedure derived from reference.\(^70\) The substrate and iodine (1.5 equiv) were dissolved in toluene (5 ml) and THF (0.14 ml) in a photochemical reactor (using a low pressure mercury lamp (5.5W, 254 nm)). At 24 hours, the reaction mixture was extracted with Na\(_2\)S\(_2\)O\(_3\), washed with brine, dried over Mg\(_2\)SO\(_4\), and concentrated.

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Compounds 4.76-4.122 were synthesized by J. M. Schulman and A. Friedman. For characterization data see J. M. Schulman Masters thesis.\(^7\)

(1-Hexyl-5-iodo-1H-1,2,3-triazol-4-yl)methanol (4.123)

\[
\text{Cul (140 mg, 2.2 mol\%)} \text{ and TBTA (400 mg, 2.22 mol\%)} \text{ were mixed in THF and stirred at room temperature until a clear solution was formed. 3-Iodoprop-2-yn-1-ol (5.9 g, 32.6 mmol), } n\text{-hexylazide (5.0 g, 38 mmol)} \text{ were dissolved in THF were added and the reaction was stirred at room temperature. TLC analysis indicated complete conversion after 16 hours. The reaction was quenched with a solution of NH}_4\text{Cl (10\% aq). And extracted with EtOAc (3 x 5 mL), the combined organic layers were washed with brine, dried over Mg}_2\text{SO}_4 \text{ and concentrated under reduced pressure. Flash column chromatography (pentane:EtOAc 6:4 to 1:1) yielded the titled compound as an off-white solid (9.2 g, 84\%).} \]

\[
\text{1H NMR (400 MHz, CDCl}_3) \delta 4.73 (s, 4H), 4.37 (t, J = 7.3 Hz, 2H), 1.95 – 1.82 (m, 3H), 1.42 – 1.25 (m, 6H), 0.89 (t, J = 6.9 Hz, 3H); 13C NMR (101 MHz, CDCl}_3) \delta 150.9, 78.7, 56.4, 50.9, 31.2, 29.9, 26.1, 22.5, 14.0; \text{ IR (NaCl, neat): 3249, 2953, 2929, 2858, 1469, 1447, 1224, 1208, 1114, 1079, 1070, 1020 cm}^{-1}; \text{ M. p.: 74 – 76 °C; HRMS (ESI): calcd for C}_{9}H_{17}N_{3}OI (M+H): 310.0410; found: 310.0414.}
\]

Diethyl 2-((1-hexyl-5-iodo-1H-1,2,3-triazol-4-yl)methyl)malonate (4.125)

\[
\text{A solution of (1-hexyl-5-iodo-1H-1,2,3-triazol-4-yl)methanol (1.24 g, 4 mmol) and triethylamine (560 μl, 4 mmol) in THF (7 ml) was cooled to 0 °C in an ice bath. Methanesulfonyl chloride (310 μl, 4 mmol) was added dropwise to the solution, which was allowed to warm up to room temperature thereafter. After 30 minutes at room temperature the reaction mixture was filtered through celite, washing with THF (6 ml) and was added to a solution of sodium diethyl malonate (4.4 mmol) at 0 °C (Note 1). The reaction was allowed to warm to room temperature and reacted for 16 hours. The reaction was quenched with NH}_4\text{Cl (aq), extracted with ethyl acetate and dried over Mg}_2\text{SO}_4. The crude mixture was purified using flash column chromatography (pentane:EtOAc 9:1 to 8:2) to yield the titled compound as a colorless oil (902 mg, 50% yield). Note 1: Sodium malonate solution was prepared as follows: To a solution of diethyl malonate (671 μl, 4.4 mmol) in THF (7 ml) at 0 °C was added sodium hydride (220 mg, 5.5 mmol) in batches over 5 minutes. 1H NMR (400 MHz, CDCl}_3) \delta 4.30 (t, J = 7.4 Hz, 2H), 4.24 – 4.08 (m, 4H), 4.00 (t, J = 7.7 Hz, 1H), 3.21 (d, J = 7.7 Hz, 2H), 1.94 – 1.76 (m, 2H), 1.34 – 1.26 (m, 6H), 1.22 (t, J = 7.1 Hz, 6H), 0.86 (t, J = 6.6 Hz, 3H); 13C NMR (101 MHz, CDCl}_3) \delta 168.7, 148.2, 78.9, 61.7, 50.9, 31.2, 29.9, 26.1, 25.4, 22.5, 14.1, 14.0; IR (NaCl, neat): 2956, 2918, 2871, 2857, 1750, 1739, 1722, 1448, 1437, 1370, 1332, 1231, 71}
\]

\(^{71}\) For the full data see: (a) Schulman, J. M.; Friedman, A; Panteleev, J; Lautens, M. Chem. Commun. 2012, 48, 55; (b) J. M. Schulman, Master’s Thesis, University of Toronto, 2011.
1155, 1097, 1053, 1034 cm⁻¹; **HRMS (ESI):** calcd for C₁₆H₂₇I₃N₄O₄ (M+H)⁺: 452.1046; found: 452.1050.

**Diethyl 2-allyl-2-((1-hexyl-5-iodo-1H-1,2,3-triazol-4-yl)methyl)malonate (4.126)**

A solution of diethyl 2-((1-hexyl-5-iodo-1H-1,2,3-triazol-4-yl)methyl)malonate (226 mg, 0.5 mmol) in THF (5 ml) was cooled to 0 °C in an ice bath. Sodium hydride (50 mg, 2 equiv) was added in a single portion. After stirring at 0 °C for 20 minutes, allyl bromide (65 μl, 1.5 equiv) was added and the reaction was allowed to warm to room temperature and stirred overnight. The mixture was quenched with NH₄Cl(aq), extracted with ethyl acetate and dried over MgSO₄. The crude mixture was purified using flash column chromatography (pentane:EtOAc 9:1) to yield the titled compound as a colorless oil (180 mg, 73% yield). **¹H NMR (400 MHz, CDCl₃)** δ 5.80 (dq, J = 9.8, 7.4 Hz, 1H), 5.10 (d, J = 11.1 Hz, 1H), 5.06 (d, J = 3.7 Hz, 1H), 4.28 (t, J = 7.3 Hz, 2H), 2.68 (d, J = 7.4 Hz, 2H), 1.89 – 1.75 (m, 2H), 1.32 – 1.24 (m, 6H), 1.21 (t, J = 7.1 Hz, 6H), 0.83 (t, J = 6.5 Hz, 3H); **¹³C NMR (101 MHz, CDCl₃)** δ 170.4, 147.0, 132.7, 119.4, 80.4, 61.5, 57.7, 50.8, 36.4, 31.1, 29.8, 28.4, 26.0, 22.4, 14.1, 13.9; **IR (NaCl, neat):** 3078, 2979, 2956, 2919, 2871, 2858, 1747, 1732, 1720, 1641, 1464, 1445, 1367, 1287, 1190, 1065, 1037, 1011, 922, 862 cm⁻¹; **HRMS (ESI):** calcd for C₁₉H₃₁I₃N₃O₄ (M+H)⁺: 492.1359; found: 492.1366.

**Diethyl 1-hexyl-7-methylene-6,7-dihydro-1H-benzo[d][1,2,3]triazole-5,5(4H)-dicarboxylate (4.129)**

To a microwave vial fitted with a stirring bar, 5-iodo-1,2,3-triazole (98.3 mg, 0.2 mmol), Pd(PPh₃)₂Cl₂ (7.02 mg, 0.01 mmol) and CsOPiv (47 mg, 0.2 mmol) were added. The reaction vessel was purged with nitrogen, and MeCN (2 mL) was added. The reaction was allowed to stir at 100 °C for 16 hours. After cooling, the crude was filtered through a silica plug and purified through flash column chromatography (pentane:EtOAc 8:2) yielding the product as a colorless oil (65 mg, 89%). **¹H NMR (400 MHz, CDCl₃)** δ 5.30 (s, 1H), 5.25 (s, 1H), 4.38 (t, J = 7.4 Hz, 2H), 4.22 – 4.04 (m, 4H), 3.36 (s, 2H), 2.99 (s, 2H), 1.92 – 1.73 (m, 2H), 1.38 – 1.21 (m, 6H), 1.17 (t, J = 7.1 Hz, 6H), 0.83 (t, J = 6.5 Hz, 3H); **¹³C NMR (101 MHz, CDCl₃)** δ 169.9, 143.4, 129.1, 128.9, 112.4, 61.9, 55.0, 50.1, 39.1, 31.2, 29.0, 28.6, 26.1, 22.5, 14.0, 13.9; **IR (NaCl, neat):** 2977, 2958, 2933, 2871, 2858, 1747, 1732, 1720, 1641, 1464, 1445, 1367, 1287, 1190, 1065, 1037, 1011, 922, 862 cm⁻¹; **HRMS (ESI):** calcd for C₁₉H₃₀N₃O₄ (M+H)⁺: 364.2236; found: 364.2242.
Chapter 5: Conclusion

The development of new methods for the synthesis of different motifs is one of the most important contributions of academic chemistry. Today, new advances in method development go a long way in enabling transformation previously thought impossible. In this thesis both the synthesis of complex heterocycles and small stereochemically enriched synthons is described. The different rhodium and palladium catalyzed reactions developed over the course of this thesis make use of sustainable principles, such as C-H functionalization and domino catalysis. Study of such conservative modes of reactivity may have the potential to be applied to large scale synthesis and lead to cost reductions.

Chapter 1 described the development of a chemodivergent desymmetrization of bicyclic hydrazines. The method gave access to highly stereochemically rich cyclopentanes and cyclopentenes from very simple and easily accessible substrates. The work described in this chapter outlined the reaction features which could be modified to give a predictable reaction outcome. As such, this method could potentially be applied to target synthesis.

In Chapter 2, a domino synthesis of dihydroquinolines, applying a multimetallic catalytic system was discussed. This work provided a rare example of a combination of two late-transition metal catalysts in a single reaction. The interesting features of this reactivity proved to be: 1) the inhibition of one catalytic system by ligand interchange, and 2) selective reactivity in spite of the expansion of possible reaction pathways to include Suzuki cross-coupling. This work should promote further study of domino catalysis, which may eventually lead to the development of new avenues for reaction set up in large scale synthesis. In the latter portion of this chapter, an application of this multimetallic reactivity in a different system, furnishing azadibenzoxepines is disclosed. This new development showcases that combination of multiple catalysts can be viable in a variety of synthetic systems.

Chapter 3 outlines our work on extension of scope of rhodium-catalyzed arylation of alkynes with boronic acids. It is demonstrated that highly substituted allylic alcohols can be accessed using this reaction in a highly stereo- and regioselective manner. It is shown that the alcohol motif is not just a spectator, but is involved in enhancing the reactivity of the substrates. The utility of the obtained allylic alcohols is showcased in a one-step synthesis of indenes through a
4π electrocyclization. Alternatively, these motifs can be used to access quinolines through a three-step synthetic sequence, terminating in an electrocyclization.

In the final chapter of this thesis, a highly modular synthesis of 1,2,3-triazole containing heterocycles is disclosed. The developed method provides access to a large variety of different analogues through a high-yielding synthetic sequence. The final two steps of the synthesis: a copper-catalyzed alkyne azide cycloaddition and a palladium-catalyzed C-H functionalization can be conducted as a one-pot procedure in very good yields.

**Figure 5.1:** Reactions examined in this thesis.
Even though the methods developed throughout this thesis are distinct, overlapping concepts of rhodium-catalyzed arylation of alkenes and palladium-catalyzed coupling reaction are found throughout. This thesis exemplifies that transition metal catalysis is currently at the forefront of new reaction development and the use of such catalysts in synthesis can provide facile synthetic routes to small molecule targets.
Appendix 1: Spectra for New Compounds in Chapter 1
Di-tert-butyl 5-phenyl-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (1.3a)
Di-tert-butyl 1-(2-(2,6-difluorophenyl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (1.7)
Di-tert-butyl 1-(2-(2-chlorophenyl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (1.8)
2,3-di-tert-butyl 5,5'-(1,2-phenylene)bis(2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate)
(1.23)
Di-tert-butyl 5-(2-(5-(1,2-bis(tert-butoxycarbonyl)hydrazinyl)cyclopent-2-enyl)furan-3-yl)-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (1.24)
2,3-di-tert-butyl 5,5’-(1-(tert-butoxycarbonyl)-1H-pyrrole-3,4-diyl)bis(2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate) (1.25)
Di-tert-butyl 5-(2-chlorophenyl)-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (1.26)
1-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole (1.27b)
Di-tert-butyl 1-(2-(1H-pyrrol-3-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (1.28a)
Di-tert-butyl 1-(2-(1-methyl-1H-pyrrol-3-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (1.28b)
Di-tert-butyl 1-(2-(1-(triisopropylsilyl)-1H-pyrrol-3-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (1.28c)
Di-tert-butyl 1-(2-(1-acetyl-1H-pyrrol-3-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (1.28d)
Di-tert-butyl 1-(2-(1-(tert-butoxycarbonyl)-1H-pyrrol-3-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (1.28a)
Di-tert-butyl 5-(1H-pyrrol-3-yl)-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (1.29a)
Di-tert-butyl 5-(1-(triisopropylsilyl)-1H-pyrrolo-3-yl)-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (1.29c)
Di-tert-butyl 5-(1-acetyl-1H-pyrrol-3-yl)-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (1.29d)
Di-tert-butyl 5-(1-(tert-butoxycarbonyl)-1H-pyrrol-3-yl)-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (1.29e)
4-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (1.35)
4-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl methacrylate (1.36)
4-(bicyclo[2.2.1]heptan-2-yl)-5-methoxy-3,3-dimethylbenzofuran-2(3H)-one (1.38)
Appendix 2: Spectra of New Compounds in Chapter 2
$N$-(3-(2-Chlorophenyl)prop-2-yn-1-yl)-4-methylbenzenesulfonamide (2.3b)
$N$-(3-(2-Chlorophenyl)prop-2-ynyl)methanesulfonamide (2.3c)
tert-Butyl 3-(2-chlorophenyl)prop-2-ynylcarbamate (2.3d)
N-(3-(2-Chlorophenyl)prop-2-ynyl)benzenesulfonamide (2.3e)
N-(3-(2-Chlorophenyl)prop-2-ynyl)-4-methoxybenzenesulfonamide (2.3f)
N-(3-(2-Chlorophenyl)prop-2-ynyl)-4-nitrobenzenesulfonamide (2.3g)
$N$-(3-(2-Chlorophenyl)prop-2-ynyl)-2,4,6-trimethylbenzenesulfonamide (2.3h)
$N$-(3-(2-Chlorophenyl)prop-2-ynyl)-1,1,1-trifluoromethanesulfonamide (2.3i)
$N$-(3-(2-Chlorophenyl)prop-2-ynyl)benzamide (2.3j)
Phenyl 3-(2-chlorophenyl)prop-2-ynylcarbamate (2.3k)
Diphenyl 3-(2-chlorophenyl)prop-2-ynylphosphoramide (2.3l)
$N$-(3-(2-Chloro-4-(trifluoromethyl)phenyl)prop-2-ynyl)methanesulfonamide (2.6)
$N$-(3-(2-Chloro-5-fluorophenyl)prop-2-ynyl)methanesulfonamide (2.7)
N-(3-(2-Chloro-3-fluorophenyl)prop-2-ynyl)methanesulfonamide (2.8)
N-(3-Chloro-4-(3-(methylsulfonamido)prop-1-ynyl)phenyl)acetamide (2.9)
$N$-(3-(3-Chloropyridin-2-yl)prop-2-ynyl)methanesulfonamide (2.10)
$N$-(3-(2-Chloropyridin-3-yl)prop-2-ynyl)methanesulfonamide (2.11)
(Z)-N-(3-(2-Chlorophenyl)-2-phenylallyl) methanesulfonamide (2.4c)
(Z)-N-(3-(2-Chlorophenyl)-2-phenylallyl)-4-methylbenzenesulfonamide (2.4b)
(Z)-tert-Butyl 3-(2-chlorophenyl)-2-phenylallylcarbamate (2.4d)
(Z)-N-(3-(2-Chlorophenyl)-2-phenylallyl)benzenesulfonamide (2.4e)
(Z)-N-(3-(2-Chlorophenyl)-2-phenylallyl)-1,1,1-trifluoromethanesulfonamide (2.4i)
(Z)-N-(3-(2-Chlorophenyl)-2-phenylallyl)benzamide (2.4j)
(Z)-Diphenyl 3-(2-chlorophenyl)-2-phenylallylphosphoramidate (2.4l)
(Z)-N-(3-(2-Chlorophenyl)-2-(4-(trifluoromethyl)phenyl)allyl)-4-methylbenzenesulfonamide

(2.12)
(Z)-N-(3-(2-Chlorophenyl)-2-(p-tolyl)allyl)-4-methylbenzenesulfonamide (2.13)
(Z)-N-(3-(2-Chlorophenyl)-2-(4-methoxyphenyl)allyl)-4-methylbenzenesulfonamide (2.14)
(Z)-N-(3-(2-Chlorophenyl)-2-(6-chloropyridin-3-yl)allyl)-4-methylbenzenesulfonamide (2.15)
(Z)-N-(3-(2-Chlorophenyl)-2-(thiophen-3-yl)allyl)methanesulfonamide (2.16)
4-(2-Chlorophenyl)but-3-yn-1-ol (2.17b)
(Z)-3-(2-Chlorophenyl)-2-phenylprop-2-en-1-ol (2.18a)
(E)-4-(2-Chlorophenyl)-3-phenylbut-3-en-1-ol (2.18b)
1-(Methylsulfonyl)-3-phenyl-1,2-dihydroquinoline (2.5c)
3-Phenyl-1-tosyl-1,2-dihydroquinoline (2.5b)
N-(3-(Biphenyl-2-yl)prop-2-ynyl)methanesulfonamide (2.19)
3-Phenyl-1-(phenylsulfonyl)-1,2-dihydroquinoline (2.5e)
1-(4-Methoxyphenylsulfonyl)-3-phenyl-1,2-dihydroquinoline (2.5f)
1-(4-Nitrophenylsulfonyl)-3-phenyl-1,2-dihydroquinoline (2.5g)
3-(Thiophen-3-yl)-1-tosyl-1,2-dihydroquinoline (2.21b)
1-(Methylsulfonyl)-3-(thiophen-3-yl)-1,2-dihydroquinoline (2.21c)
3-(Furan-3-yl)-1-tosyl-1,2-dihydroquinoline (2.22b)
3-(Furan-3-yl)-1-(methylsulfonyl)-1,2-dihydroquinoline (2.22c)
4-(1-Tosyl-1,2-dihydroquinolin-3-yl)benzonitrile (2.23b)
4-(1-(Methylsulfonyl)-1,2-dihydroquinolin-3-yl)benzonitrile (2.23c)
3-(m-Tolyl)-1-tosyl-1,2-dihydroquinoline (2.24)
3-(4-Methoxyphenyl)-1-tosyl-1,2-dihydroquinoline (2.25b)
3-(4-Methoxyphenyl)-1-(methylsulfonyl)-1,2-dihydroquinoline (2.25c)
3-(3,4-Dimethoxyphenyl)-1-(methylsulfonyl)-1,2-dihydroquinoline (2.27)
3-(2-Fluorophenyl)-1-tosyl-1,2-dihydroquinoline (2.28)
3-(6-Fluoropyridin-3-yl)-1-tosyl-1,2-dihydroquinoline (2.29)
3-(6-Ethoxypyridin-3-yl)-1-tosyl-1,2-dihydroquinoline (2.30b)
3-(6-Ethoxypyridin-3-yl)-1-(methylsulfonyl)-1,2-dihydroquinoline (2.30c)
3-(3-Nitrophenyl)-1-tosyl-1,2-dihydroquinoline (2.31)
1-Tosyl-3-(4-(trifluoromethyl)phenyl)-1,2-dihydroquinoline (2.32)
1-Tosyl-3-(3-(trifluoromethyl)phenyl)-1,2-dihydroquinoline (2.33b)
1-(Methylsulfonyl)-3-(3-(trifluoromethyl)phenyl)-1,2-dihydroquinoline (2.33c)
7-Methoxy-1-(methylsulfonyl)-3-phenyl-1,2-dihydroquinoline (2.34)
1-(Methylsulfonyl)-3-(thiophen-3-yl)-7-(trifluoromethyl)-1,2-dihydroquinoline (2.35)
6-Fluoro-1-(methylsulfonyl)-3-(thiophen-3-yl)-1,2-dihydroquinoline (2.36)
$N$-(1-(Methylsulfonyl)-3-(thiophen-3-yl)-1,2-dihydroquinolin-7-yl)acetamide (2.37)
8-Fluoro-1-(methylsulfonyl)-3-phenyl-1,2-dihydroquinoline (2.38)
8-Fluoro-1-(methylsulfonyl)-3-(thiophen-3-yl)-1,2-dihydroquinoline (2.39)
1-(Methylsulfonyl)-3-(thiophen-3-yl)-1,2-dihydro-1,5-naphthyridine (2.40)
3-Phenyl-2H-chromene (2.41)
4-(2H-Chromen-3-yl)benzonitrile (2.42)
Methyl 4-(2H-chromen-3-yl)benzoate (2.43)
(3S,4R)-3-Phenylchroman-3,4-diol (2.45)
3-Chloro-2-vinylpyridine (2.46)
3-Chloro-5-(trifluoromethyl)-2-vinylpyridine (2.47)
3-Chloro-5-nitro-2-vinylpyridine (2.48)
4-(5-Chloro-6-vinylpyridin-3-yl)morpholine (2.49)
Methyl 5-chloro-6-vinylnicotinate (2.50)
$N$-Benzyl-5-chloro-6-vinylnicotinamide (2.51)
3-Chloro-2,5-divinylpyridine
2-Chloro-3-vinylquinoxaline (2.52)
(E)-3-Chloro-2-(oct-1-en-1-yl)-5-(trifluoromethyl)pyridine (2.53)
2-(2-(3-Chloropyridin-2-yl)ethyl)phenol (2.54)
10,11-Dihydrobenzo[6,7]oxepino[3,2-b]pyridine (2.55)
2-(2-(3-Chloropyridin-2-yl)ethyl)-5-fluorophenol (2.56)
2-(2-(3-Chloropyridin-2-yl)ethyl)-4-fluorophenol (2.57)
2-(2-(3-Chloropyridin-2-yl)ethyl)-3-fluorophenol (2.58)
2-(2-(3-Chloropyridin-2-yl)ethyl)-4-methylphenol (2.59)
2-(2-(3-Chloropyridin-2-yl)ethyl)-4-methoxyphenol (2.60)
4-Chloro-2-(2-(3-chloropyridin-2-yl)ethyl)phenol (2.61)
2-(2-(3-Chloropyridin-2-yl)ethyl)-6-methoxyphenol (2.62)
3-(Trifluoromethyl)-10,11-dihydrobenzo[6,7]oxepino[3,2-b]pyridine (2.64)
Methyl 10,11-dihydrobenzo[6,7]oxepino[3,2-b]pyridine-3-carboxylate (2.65)
3-Nitro-10,11-dihydrobenzo[6,7]oxepino[3,2-b]pyridine (2.66)
N-Benzyl-5-chloro-6-(2-hydroxyphenethyl)nicotinamide (2.67)
2-(2-(3-Chloro-5-morpholinopyridin-2-yl)ethyl)phenol (2.68)
3-Morpholino-10,11-dihydrobenzo[6,7]oxepino[3,2-b]pyridine (2.69)
2-(2-(3-Chloro-5-vinylpyridin-2-yl)ethyl)phenol (2.70)
2-(Benzyloxy)-3-chloro-5-vinylpyridine (2.71)
2-(1-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)octan-2-yl)phenol (2.72)
10-Hexyl-3-(trifluoromethyl)-10,11-dihydrobenzo[6,7]oxepino[3,2-b]pyridine (2.73)
N-(2-(2-(3-Chloropyridin-2-yl)ethyl)phenyl)methanesulfonamide (2.79)
3-Chloro-2-(2-chlorophenethyl)-5-(trifluoromethyl)pyridine (2.81a)
2-(2-Bromophenethyl)-3-chloro-5-(trifluoromethyl)pyridine (2.81b)
(3-Chloro-5-(trifluoromethyl)pyridin-2-yl)ethyl)-N-(3-phenylpropyl)aniline (2.82b)
Appendix 3: Spectra of New Compounds in Chapter 3
1-Iodo-3,5-dimethoxybenzene
3-Phenylprop-2-yn-1-ol (3.1)
4-Phenylbut-3-yn-2-ol (3.2)

(3-Methoxybut-1-ynyl)benzene (3.2b)
(3-Methoxybut-1-ynyl)benzene (3.2b)
4-(4-(Trifluoromethyl)phenyl)but-3-yn-2-ol (3.4)
4-(3,5-Dimethoxyphenyl)but-3-yn-2-ol (3.5)
4-(4-(Dimethylamino)phenyl)but-3-yn-2-ol (3.6)
4-(3,5-Dimethylphenyl)but-3-yn-2-ol (3.7)
4-(Thiophen-2-yl)but-3-yn-2-ol (3.8)
4-(Thiophen-3-yl)but-3-yn-2-ol (3.9)
4-(2-Methoxyphenyl)but-3-yn-2-ol (3.10)
3-(4-(Trifluoromethyl)phenyl)prop-2-yn-1-ol (3.12)
1-(4-(3-Hydroxyprop-1-ynyl)phenyl)ethanone (3.13)
1-(3,5-Dimethoxyphenyl)-4-methylpent-1-yn-3-ol (3.15)
4-p-Tolylbut-3-yn-2-ol (3.11)
*tert*-Butyldimethyl(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)silane
(Z)-3,4-Diphenylbut-3-en-2-ol (3.16)
4-Phenylbut-3-yn-1-ol (3.23)
(E)-3,4-Diphenylbut-3-en-1-ol (3.24)
(Z)-2,3-Diphenylprop-2-en-1-ol (3.27)
(Z)-4-(4-Methoxyphenyl)-3-phenylbut-3-en-2-ol (3.28)
(Z)-3-Phenyl-4-(4-(trifluoromethyl)phenyl)but-3-en-2-ol (3.29)
(Z)-4-(3,5-Dimethoxyphenyl)-3-phenylbut-3-en-2-ol (3.30)
(Z)-4-(4-(Dimethylamino)phenyl)-3-phenylbut-3-en-2-ol (3.31)
(Z)-4-(3,5-Dimethylphenyl)-3-phenylbut-3-en-2-ol (3.32)
(Z)-3-Phenyl-4-(thiophen-2yl)but-3-en-2-ol (3.33)
(Z)-3-Phenyl-4-(thiophen-3-yl)but-3-en-2-ol (3.34)
(Z)-4-(2-Methoxyphenyl)-3-phenylbut-3-en-2-ol (3.35)
(Z)-2-Phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-ol (3.36)
(Z)-1-(4-(3-Hydroxy-2-phenylprop-1-enyl)phenyl)ethanone (3.37)
(Z)-1-(3,5-Dimethoxyphenyl)-4-methyl-2-phenylpent-1-en-3-ol (3.38)
(Z)-3-(3-Methoxy-4-methylphenyl)-4-phenylbut-3-en-2-ol (3.39)
(Z)-3-(3,4-Dimethoxyphenyl)-4-(4-methoxyphenyl)but-3-en-2-ol (3.40)
(Z)-3-(3,4-Dimethoxyphenyl)-4-p-tolylbut-3-en-2-ol (3.41)
(Z)-3-((tert-Butyldimethylsilyloxy)phenyl)-4-(3,5-dimethoxyphenyl)but-3-en-2-ol (3.42)
(Z)-3-(Thiophen-3-yl)-4-p-tolylbut-3-en-2-ol (3.43)
(Z)-3-(4-Chlorophenyl)-4-phenylbut-3-en-2-ol (3.44)
(Z)-3-(4-Chlorophenyl)-4-p-tolylbut-3-en-2-ol (3.45)
(Z)-3-(3-Nitrophenyl)-4-phenylbut-3-en-2-ol (3.46)
(Z)-2-(2-Fluorophenyl)-3-phenylprop-2-en-1-ol (3.47)
(Z)-3-Phenyl-2-o-tolylprop-2-en-1-ol (3.48)
(2Z,3E)-2-Benzylidenenon-3-en-1-ol (3.49a)
(2Z,4E)-3-Phenyldeca-2,4-dien-1-ol (3.49b)
4,4-Diphenylbutan-2-one (3.22)
5,7-Dimethoxy-1-methyl-2-phenyl-1H-indene (3.58)
tert-Butyl(4-(5,7-dimethoxy-1-methyl-1H-inden-2-yl)phenoxy)dimethyldisilane (3.59)
6-Methyl-5-phenyl-6H-cyclopenta[b]thiophene (3.60)
4-Methoxy-1-methyl-2-phenyl-1H-indene (3.61)
6-Methoxy-1-methyl-2-phenyl-1H-indene (3.62)
1-Isopropyl-5,7-dimethoxy-2-phenyl-1H-indene (3.63)
3-(1,6-Dimethyl-1H-inden-2-yl)thiophene (3.64)
2-(3,4-Dimethoxyphenyl)-1,6-dimethyl-1H-indene (3.56)
1,5,7-Trimethyl-2-phenyl-1H-indene (3.65)
2-(4-Chlorophenyl)-1,6-dimethyl-1H-indene (3.66)
2-o-Tolyl-1H-indene (3.67)
1-Methyl-2-(3-nitrophenyl)-1H-indene (3.68)
(Z)-3,4-Diphenylbut-3-en-2-one (3.69a)
(Z)-3-(3-Methoxy-4-methylphenyl)-4-phenylbut-3-en-2-one (3.69b)
(Z)-3-(3-Nitrophenyl)-4-phenylbut-3-en-2-one (3.69c)
(Z)-3-(4-Chlorophenyl)-4-phenylbut-3-en-2-one (3.69d)
(3Z)-3,4-Diphenylbut-3-en-2-one O-acetyl oxime (3.70a)
(3Z)-3-(3-Methoxy-4-methylphenyl)-4-phenylbut-3-en-2-one O-acetyl oxime (3.70b)
(3Z)-3-(3-Nitrophenyl)-4-phenylbut-3-en-2-one O-acetyl oxime (3.70c)
(3Z)-3-(4-Chlorophenyl)-4-phenylbut-3-en-2-one O-acetyl oxime (3.70d)
2-methyl-3-phenylquinoline (3.71a)
2-Methyl-3-(3-methoxy-4-methylphenyl)quinoline (3.71b)
2-Methyl-3-(3-nitrophenyl)quinoline (3.71c)
2-Methyl-3-(4-chlorophenyl)quinoline (3.71d)
Appendix 4: Spectra of New Compounds in Chapter 4
1-(2-Bromo-4,6-difluorophenyl)-1H-pyrrole (4.13)
1-(2-Bromo-5-fluorophenyl)-1H-pyrrole (4.14)
3-Bromo-5-nitro-2-(1H-pyrrol-1-yl)benzonitrile (4.15)
1-(2-Bromo-4-methyl-6-nitrophenyl)-1H-pyrrole (4.16)
1-(2-Bromophenyl)-1H-indole (4.18)
1-(2-((Trimethylsilyl)ethynyl)phenyl)-1H-pyrrole (4.10)
1-(4-Chloro-2-((trimethylsilyl)ethynyl)phenyl)-1H-pyrrole (4.20)
1-(2,4-Difluoro-6-(((trimethylsilyl)ethynyl)phenyl)-1H-pyrrole (4.21)
1-(5-Fluoro-2-((trimethylsilyl)ethynyl)phenyl)-1H-pyrrole (4.22)
1-(5-Nitro-2-((trimethylsilyl)ethynyl)phenyl)-1H-pyrrole (4.23)
Ethyl 4-(1H-pyrrol-1-yl)-3-((trimethylsilyl)ethynyl)benzoate (4.24)
5-Nitro-2-(1H-pyrrol-1-yl)-3-((trimethylsilyl)ethynyl)benzonitrile (4.25)
1-(4-Methyl-2-nitro-6-((trimethylsilyl)ethynyl)phenyl)-1H-pyrrole (4.26)
Trimethyl((2-(thiophen-3-yl)phenyl)ethynyl)silane (4.29)
((2-(Furan-2-yl)phenyl)ethynyl)trimethylsilane (4.30)
((4'-Methoxybiphenyl-2-yl)ethynyl)trimethylsilane (4.31)
1-(4-Chloro-2-ethynylphenyl)-1H-pyrrole (4.34)
1-(2-Ethynyl-4,6-difluorophenyl)-1H-pyrrole (4.35)
1-(2-Ethynyl-5-fluorophenyl)-1H-pyrrole (4.36)
1-(2-Ethynyl-5-nitrophenyl)-1H-pyrrole (4.37)
Methyl 3-ethynyl-4-(1H-pyrrol-1-yl)benzoate (4.38)

\[
\text{\text{CO}_2\text{Me}}
\]

[Chart of chemical structure and NMR spectrum]
3-Ethynyl-5-nitro-2-(1H-pyrrol-1-yl)benzonitrile (4.39)
1-(2-Ethynyl-4-methyl-6-nitrophenyl)-1H-pyrrole (4.40)
1-(2-Ethynylphenyl)-1H-indole (4.41)
3-(2-Ethynylphenyl)thiophene (4.42)
2-(2-Ethynylphenyl)furan (4.43)
2-Ethynyl-4'-methoxybiphenyl (4.44)

![Chemical Structure]

ppm (f1)
1-(2-(Iodoethynyl)phenyl)-1H-pyrrole (4.45)
1-(4-Chloro-2-(iodoethynyl)phenyl)-1H-pyrrole (4.47)
1-(2,4-Difluoro-6-(iodoethynyl)phenyl)-1H-pyrrole (4.48)
1-(5-Fluoro-2-(iodoethynyl)phenyl)-1H-pyrrole (4.49)

N  F  I

ppm (f1)

ppm (f1)
1-(2-(Iodoethynyl)-5-nitrophenyl)-1H-pyrrole (4.50)
Methyl 3-(iodoethynyl)-4-(1H-pyrrol-1-yl)benzoate (4.51)
3-(Iodoethynyl)-5-nitro-2-(1H-pyrrol-1-yl)benzonitrile (4.52)

\[ \text{Structure Image} \]

\[ \text{Spectral Image} \]
1-(2-(Iodoethynyl)-4-methyl-6-nitrophenyl)-1H-pyrrole (4.53)
1-(2-(Iodoethynyl)phenyl)-1H-indole (4.54)
3-(2-(Iodoethynyl)phenyl)thiophene (4.55)
2-(2-(Iodoethynyl)phenyl)furan (4.56)
2-(Iodoethynyl)-4'-methoxybiphenyl (4.57)
4-(2-(1H-pyrrol-1-yl)phenyl)-1-benzyl-5-iodo-1H-1,2,3-triazole (4.60)
3-Benzyl-3H-pyrrolo[1,2-a][1,2,3]triazolo[4,5-c]quinoline (4.61)
3-(4-Methoxybenzyl)-3\textit{H}-pyrrolo[1,2-a][1,2,3]triazole[4,5-c]quinoline (4.61b)
3-(4-Nitrobenzyl)-3H-pyrrolo[1,2-a][1,2,3]triazolo[4,5-c]quinoline (4.61c)
3-Hexyl-3H-pyrrolo[1,2-a][1,2,3]triazolo[4,5-c]quinoline (4.61d)
3-Benzyl-10-chloro-3H-pyrrolo[1,2-a][1,2,3]triazolo[4,5-c]quinoline (4.62)
3-Benzyl-8,10-difluoro-3H-pyrrolo[1,2-a][1,2,3]triazolo[4,5-c]quinoline (4.63)
3-Benzy1-9-fluoro-3H-pyrrolo[1,2-a][1,2,3]triazolo[4,5-c]quinoline (4.64)
3-Benzyl-9-nitro-3\textit{H}-pyrrolo[1,2-\textit{a}][1,2,3]triazolo[4,5-\textit{c}]quinoline (4.65)
Methyl 3-benzyl-3H-pyrrolo[1,2-a][1,2,3]triazolo[4,5-c]quinoline-10-carboxylate (4.66)
3-Benzyl-10-nitro-3H-pyrrolo[1,2-a][1,2,3]triazolo[4,5-c]quinoline-8-carbonitrile (4.67)
3-Benzyl-10-methyl-8-nitro-3H-pyrrolo[1,2-a][1,2,3]triazolo[4,5-c]quinoline (4.68)

\[
\begin{array}{c}
\text{N} \quad \text{N} \\
\text{N} \quad \text{N} \\
\text{Bn} \\
\text{O}_2\text{N}
\end{array}
\]

\[\text{ppm (f1)}\]

\begin{align*}
8.54 & \quad 8.53 \\
7.49 & \quad 7.48 \\
7.34 & \quad 7.33 \\
7.30 & \quad 7.28 \\
6.66 & \quad 5.95 \\
5.01 & \quad 0.84 \\
10.0 & \quad 0.92 \\
150.0 & \quad 6.01 \\
3000.0 & \quad 1.85 \\
5000.0 & \quad 2.00 \\
7000.0 & \quad 3.08
\end{align*}

\[\text{ppm (f1)}\]

\begin{align*}
140.87 & \quad 136.14 \\
134.95 & \quad 129.13 \\
128.49 & \quad 126.87 \\
126.67 & \quad 126.67 \\
125.92 & \quad 125.92 \\
124.15 & \quad 124.15 \\
120.64 & \quad 120.64 \\
119.84 & \quad 119.84 \\
119.69 & \quad 119.69 \\
118.67 & \quad 118.67 \\
113.63 & \quad 113.63 \\
104.52 & \quad 53.04 \\
53.04 & \quad 20.60
\end{align*}
7-Benzyl-7H-indolo[1,2-a][1,2,3]triazolo[4,5-c]quinoline (4.69)
3-Benzyl-3,4-dihydrobenzo[e][1,2,3]triazole[4,5-g]benzo[b]thiophene (4.70)
3-Benzyl-3,6-dihydrobenzo[\textit{g}]\{1,2,3\}triazole[4,5-e]benzofuran (4.71)

\[
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{N} \\
\text{Bn} \\
\text{O}
\end{array}
\]
1-Benzyl-10-methoxy-1H-phenanthro[9,10-d][1,2,3]triazole (4.72)
1-Benzyl-4-(4'-methoxybiphenyl-2-yl)-1H-1,2,3-triazole (4.73)
(1-Hexyl-5-iodo-1H-1,2,3-triazol-4-yl)methanol (4.123)
Diethyl 2-((1-hexyl-5-iodo-1H-1,2,3-triazol-4-yl)methyl)malonate (4.125)
Diethyl 2-allyl-2-((1-hexyl-5-iodo-1H-1,2,3-triazol-4-yl)methyl)malonate (4.126)
Diethyl 1-hexyl-7-methylene-6,7-dihydro-1H-benzod[1,2,3]triazole-5,5(4H)-dicarboxylate (4.129)