

ABSTRACT

PENN, KYLE ROBERT. Controlled α -Halogenation of Alkyl Sulfonamides and Development of Highly Active Bifunctional (benz)imidazolyl-Palladium Catalysts for Application in Sustainable Cross-Coupling Reactions. (Under the direction of Dr. Vincent N. G. Lindsay).

Transition-metal-catalyzed cross-coupling reactions are some of the most valuable and synthetically productive steps in the formation of organic compounds and materials relevant to an array of chemical industries. The Suzuki-Miyaura Coupling (SMC) specifically, is the single most commonly used carbon-carbon bond forming reaction in the pharmaceutical industry. Historically, improvements in Suzuki-Miyaura coupling reactions have often been accomplished by increasing the reactivity and stability of the metal catalysts by use of increasingly more effective ligands. In this work, a family of air- and moisture-stable dinuclear 2-benzimidazolylpalladium complexes, known to act as highly active bifunctional catalysts for sustainable cross-coupling reactions, is expanded upon and structure-activity relationships are studied and defined with respect to the catalysts' performance in Suzuki-Miyaura Coupling (SMC) reactions. New understanding of structure-activity trends is leveraged to develop a more active catalyst capable of catalyzing the Suzuki coupling of aryl bromides as well as aryl chlorides efficiently and with good functional group compatibility in alcohol solvents at catalyst loadings of 0.003 mol% (60 ppm Pd) for aryl bromides and as low as 0.1 mol% (2000 ppm Pd) for aryl chlorides.

Bis(azolium)dichloride salts constitute stable and convenient precursors for metal bis(carbenes) as ligands for a wide range of metal-catalyzed processes. However, the synthesis of such salts is often inefficient in part due to the low reactivity of dichloroalkanes in nucleophilic substitution reactions. New reaction kinetics and mechanistic studies in the literature on pyridine derivatives have inspired us to develop a novel method for the improved synthesis of bis(azolium)

chloride salts in excellent yields, applicable to a wide scope of heterocyclic cores. This method can also be applied to the direct synthesis of bis(NHC)-metal complexes in a one-pot reaction from imidazole derivatives.

The sulfonamide functional group has many unique factors that can be leveraged for drug design, and some biologically relevant sulfonamide-containing compounds have been accessed from α -halogenated sulfonamide derivatives. However, synthesis of such derivatives is often difficult due to unselective polyhalogenation, often creating inseparable mixtures of product when base-mediated halogenation is attempted. In this work we developed new methods to selectively access these α -halogenated derivatives directly from alkyl sulfonamides.

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Controlled α -Halogenation of Alkyl Sulfonamides and Development of Highly Active
Bifunctional (benz)imidazolyl-Palladium Catalysts for Application in Sustainable Cross-
Coupling Reactions

by
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DEDICATION

I would like to dedicate this work to my parents. Without their lifelong support, I would never have reached this goal.

BIOGRAPHY

Kyle was born and raised in Wilmington, North Carolina. He received his B.S. in Chemistry in 2018 from NC State University, where he started working in the Lindsay lab in February 2017 on the development of novel synthetic methods toward the efficient elaboration of bidentate ligands. During the summers, he worked at Alcami corporation in Wilmington, NC. He joined the Lindsay lab as a graduate student in October 2018, working on the development of selective halogenation methodologies and the design of new sustainable catalysts.

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LIST OF ABBREVIATIONS

Ag ₂ O	Silver(I) Oxide	NaH	Sodium Hydride
AIBN	Azobisisobutyronitrile	NaI	Sodium Iodide
Br ₂	Bromine	NaOH	Sodium hydroxide
BuN ⁺ ·HSO ₄ ⁻	Tetrabutylammonium Hydrogen Sulfate	Na ₂ SO ₃	Sodium Sulfite
CBr ₄	Carbon Tetrabromide	Na ₂ SO ₄	Sodium Sulfate
Cl ₄	Carbon tetraiodide	<i>n</i> -BuLi	<i>n</i> -butyllithium
CuI	Copper(I) Iodide	<i>n</i> -BuOAc	<i>n</i> -butylacetate
CsF	Cesium Fluoride	<i>t</i> -BuOMe	<i>tert</i> -Butyl methyl ether
CyH	Cyclohexane	NBS	<i>N</i> -Bromosuccinimide
DBDMH	1,3-Dibromo-5,5- dimethylhydantoin	NIS	<i>N</i> -Iodosuccinimide
DCM	Dichloromethane	NHC	<i>N</i> -Heterocyclic Carbene
DIH	1,3-Diiodo-5,5- dimethylhydantoin	NH ₄ PF ₆	Ammonium Hexafluorophosphate
DMSO	Dimethylsulfoxide	NMR	Nuclear Magnetic Resonance
DMA	Dimethylacetamide	<i>n</i> -PrOH	<i>n</i> -propyl alcohol
DMAP	4-Dimethylaminopyridine	PCl ₅	Phosphorous Pentachloride
DME	Dimethoxyethane	Pd(OAc) ₂	Palladium(II) Acetate
DMF	Dimethylformamide	PEG	Polyethylene Glycol
Et ₃ N	Triethylamine	PhH	Benzene
Et ₂ O	Diethyl Ether	PhMe	Toluene
FeCl ₃	Iron(III) Chloride	pNHC	Protic <i>N</i> -heterocyclic Carbene
GPa	Gigapascal	Py·Br ₃	Pyridinium Tribromide
HBr	Hydrobromic acid	SAR	Structure-Activity Relationship
I ₂	Iodine	<i>s</i> -BuLi	<i>sec</i> -butyllithium
<i>i</i> -PrOH	Isopropyl Alcohol	S _N 2	Nucleophilic substitution of second order
<i>i</i> -Pr ₂ O	Diisopropyl Ether	S _N Ar	Nucleophilic aromatic substitution
KAuCl ₄	Potassium Gold(III) Chloride	SMC	Suzuki-Miyaura Coupling
KF	Potassium Fluoride	TBAB	Tetrabutylammonium bromide
KHMDS	Potassium bis(trimethylsilyl)amide	TBDMS	<i>tert</i> -butyldimethylsilyl
LDA	Lithium diisopropylamide	TBDPS	<i>tert</i> -butyldiphenylsilyl
LiHMDS	Lithium bis(trimethylsilyl)amide	<i>t</i> -BuOH	<i>tert</i> -butyl alcohol
LiOAc	Lithium Acetate	<i>t</i> -BuOK	Potassium <i>tert</i> -butoxide
LiTMP	Lithium Tetramethylpiperidide	TESCl	Chlorotriethylsilane
MeCN	Acetonitrile	TFA	Trifluoroacetic acid
MeOH	Methanol	THF	Tetrahydrofuran
MHz	Megahertz	TMSCl	Chlorotrimethylsilane
MgSO ₄	Magnesium Sulfate		

CHAPTER 1

Development of Highly Active Bifunctional Benzimidazolyl-Palladium Catalysts for Application in Sustainable Cross-Coupling Reactions

1.1 Introduction to pNHC and 2-Benzimidazolyl-Metal Catalysts

N-Heterocyclic carbenes (NHCs) are used as σ -donating ligands in a wide variety of transition-metal catalyzed reactions, often valued for their electronic and steric tunability and the robust nature of the NHC-metal complexes. Within the realm of NHC-metal catalysis, traditional *N,N'*-disubstituted NHC-metal complexes have been widely employed in various reactions, whereas use of protic NHC-metal complexes (pNHCs) or their deprotonated 2-imidazolyl-metal analogues as catalysts, with one or both nitrogen atoms left unsubstituted (Figure 1.1),¹ remains scarce. Utilization of pNHC- or 2-imidazolyl-metal complexes for catalysis is perhaps rare due to the fact that, unlike *N,N*-disubstituted NHC-metal complexes, these complexes are known to exhibit tautomerization between their *C*-bound and *N*-bound metal-azole isomers (Figure 1.2). This observation, first reported by the Crabtree group in 2002,² could pose problems for catalytic systems employing pNHC-metal catalysts where the complex could lose the σ -donation granted by the *C*-bound form and furthermore, be prone to decomplexation of the imidazole ligand when in the *N*-bound form, resulting in decomposition of the catalyst.

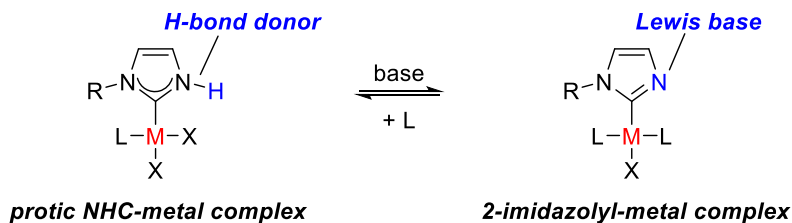


Figure 1.1 Base-mediated equilibrium between protic NHC- and 2-imidazolyl-metal complexes

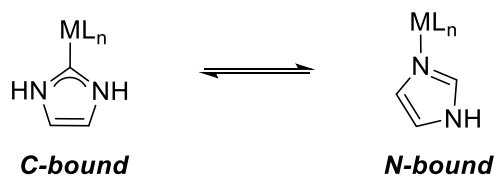


Figure 1.2 Tautomerization of pNHC-metal complexes

While examples of pNHC-metal catalysis are scarce, pNHC-rhodium and ruthenium complexes have been found to show bifunctional character via H-bond donation with carbonyl-containing substrates to achieve catalytic efficiency in specific hydrogenation reactions.^{1c,3} Furthermore, Grotjahn and co-workers showed an example of a 2-imidazolyl-iridium complex activating acetylene via a Brønsted base interaction to assist in forming the corresponding acetylide carbene complex (Figure 1.3).⁴ It should also be noted that 2-imidazolyl-metal complexes are also known to be effective nucleophilic species and Lewis bases at the free N-position.⁵

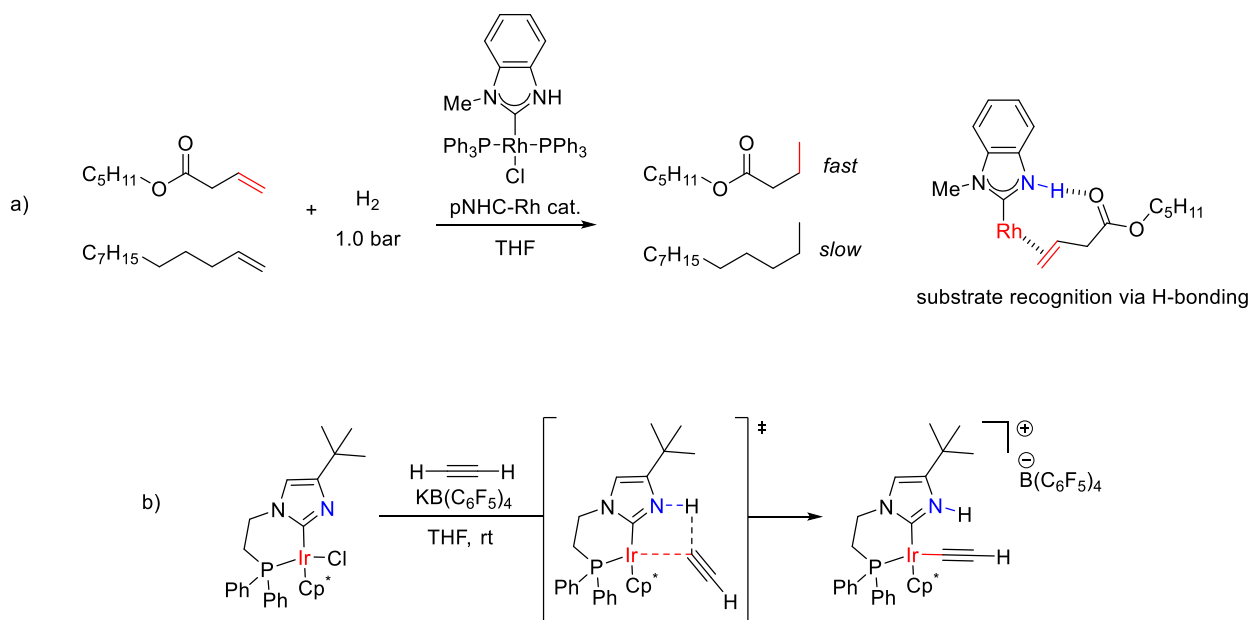


Figure 1.3 Reactivity of protic NHC- and imidazolyl-metal complexes as bifunctional catalysts

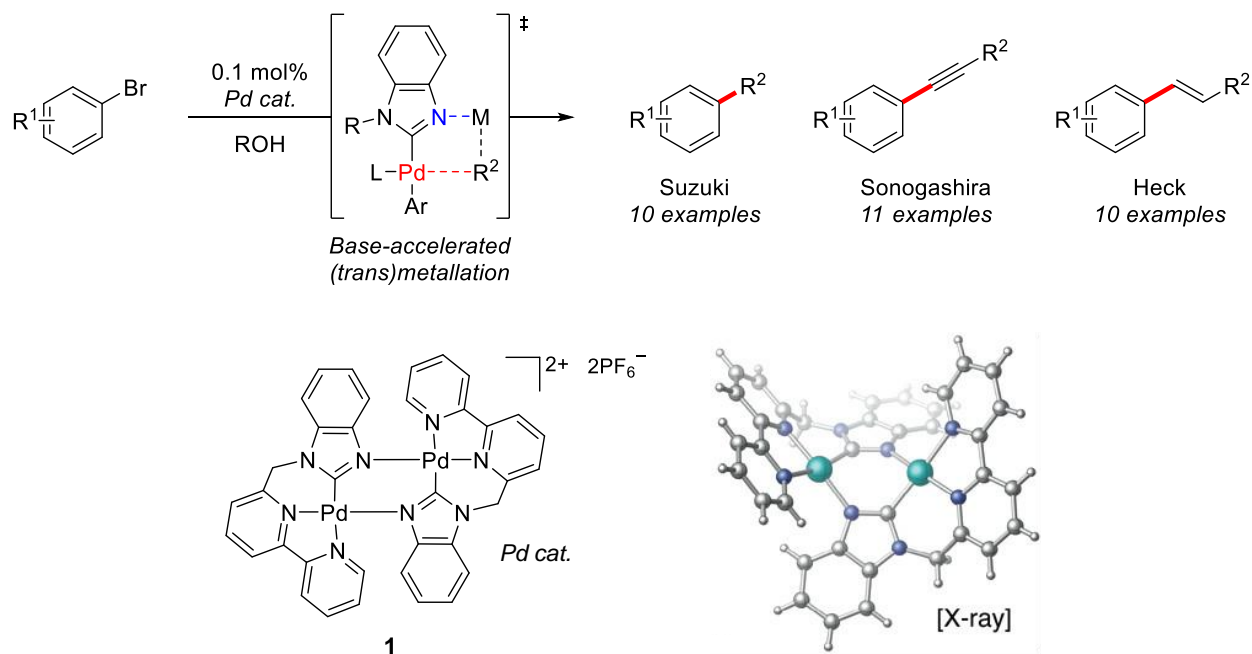


Figure 1.4 2-Benzimidazolyl-palladium catalysts as bifunctional catalysts in sustainable cross-couplings (Work of Jiancheng Zhu)

In a previous report by our lab, it was shown that 2-benzimidazolyl-palladium complexes could also exhibit bifunctional character in the catalysis of cross-coupling reactions (Figure 1.4, work of Jiancheng Zhu).⁶ Application of these novel catalysts was demonstrated in sustainable Suzuki, Sonogashira, and Heck reactions in which the unsubstituted nitrogen atom of the 2-benzimidazolyl ligand is proposed to accelerate the (trans)metallation step via intramolecular assistance. More specifically, it is proposed that the transmetalation step of the Suzuki-Miyaura coupling is assisted via a Lewis acid/base interaction between the free *N*-functionality of the imidazole and the boronic acid coupling partner, while the metalation step of the Sonogashira coupling is assisted via a Brønsted base interaction between the free *N*-functionality and the

alkyne coupling partner (Figure 1.5). Not only were the catalysts able to catalyze Suzuki, Sonogashira, and Heck cross-coupling reactions at 0.1 mol% catalyst loading, but they were shown to do so in environmentally benign solvents such as ethanol and water and the catalysts themselves are air- and moisture-stable.

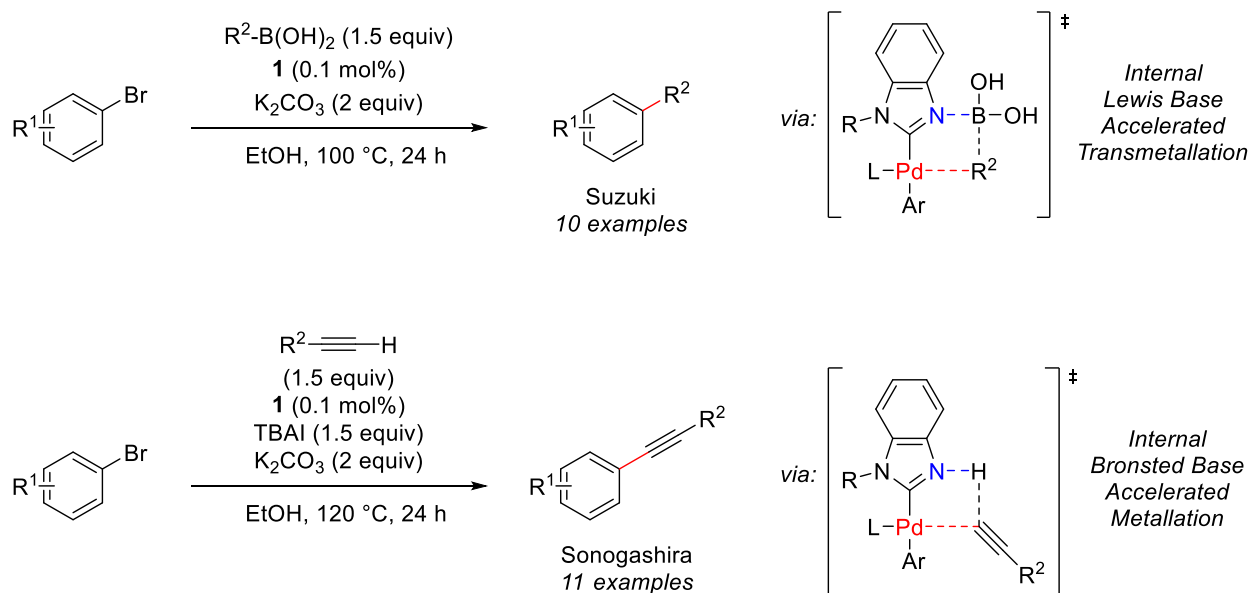


Figure 1.5 Proposed mechanism for base assisted (trans)metalation in Suzuki and Sonogashira couplings

1.1.1 Demand for Sustainable Cross-Couplings in Industrial Processes

Transition-metal-catalyzed cross-coupling reactions constitute some of the most valuable and synthetically productive steps in the formation of organic compounds and materials relevant to an array of chemical industries.^{7,8} The Suzuki-Miyaura coupling (SMC) specifically, is one of the most powerful carbon-carbon bond-forming transformations available to synthetic organic chemists and is the single most commonly used carbon-carbon bond forming reaction in the pharmaceutical industry.^{9a} Its popularity in industry is due to its ability to perform a wide variety of C(sp²)-C(sp²) couplings, allowing the expedient generation of a broad range of biaryl motifs

with a high level of functional group tolerance. Historically, improvements in Suzuki-Miyaura coupling reactions have often been accomplished by increasing the reactivity and stability of the metal catalysts by use of increasingly more effective ligands.¹⁰

While significant limitations have been overcome in terms of functional group compatibility and ease of access to the substrates and metal catalyst, the applicability of these reactions to the large-scale production of fine chemicals and pharmaceuticals still faces sustainability challenges. Therefore, it is critically important to find systems using minute amounts of transition-metal and sustainable replacements for expensive, toxic and environmentally damaging organic solvents.¹¹ The demand for SMC reactions with low catalyst loadings is not only due to concerns of cost and sustainability but also to minimize the required effort in removal of palladium from the final product which can be immense when performing cross-couplings on a large scale.¹² The tremendous amount of energy invested by pharmaceutical and fine chemical industries to solve these issues and minimize the toxic waste generated from these processes serves to highlight the great synthetic value of these reactions.¹³

1.2 Development of Highly Active Benzimidazolyl-Pd catalysts and Structure-Activity-Relationship Studies

In order to study structure-activity relationships for this new class of catalysts, and develop even more active catalysts, we synthesized seven new 2-(benz)imidazolyl-Pd complexes which exhibited modifications to the electronics and flexibility of the ligand. To evaluate the catalytic activity of catalysts **1-8**, we selected the Suzuki-Miyaura coupling of 4-bromoanisole and phenylboronic acid in EtOH as a model reaction and ran reactions at 1.0, 0.1, 0.01, and 0.003 mol% to thoroughly judge the activity.

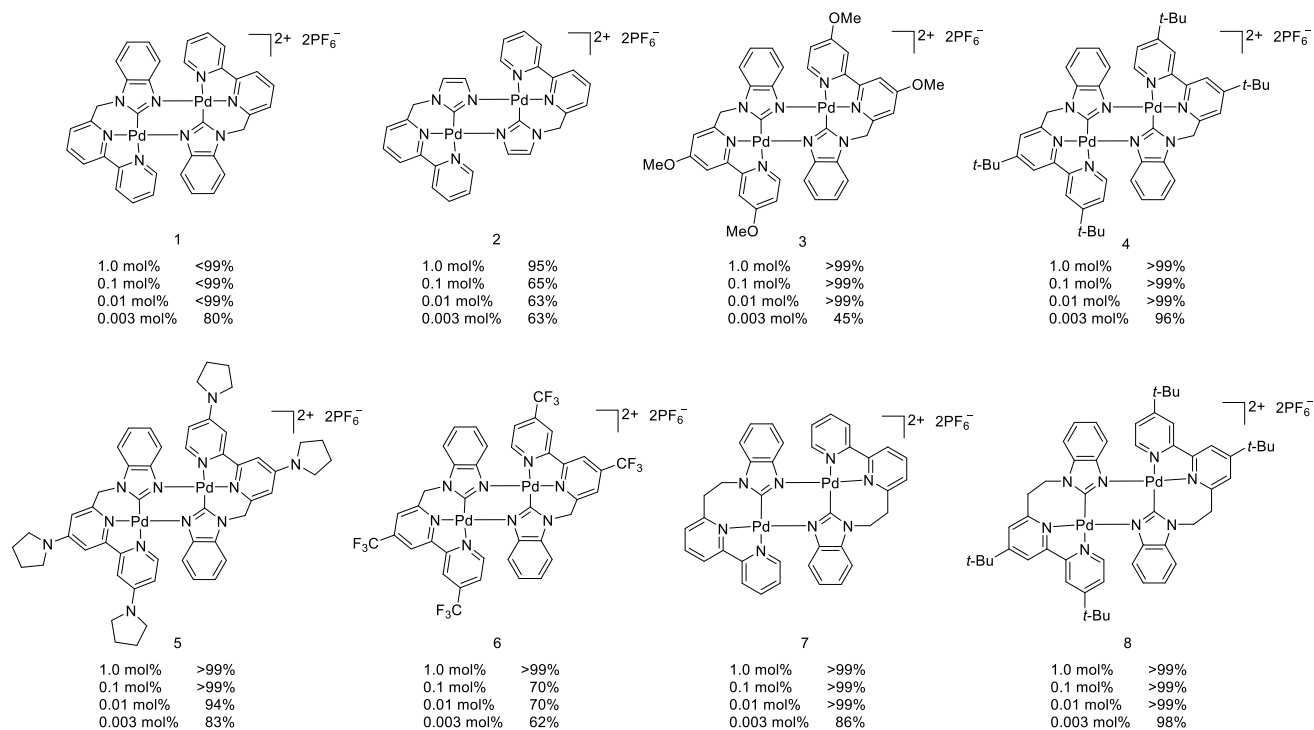
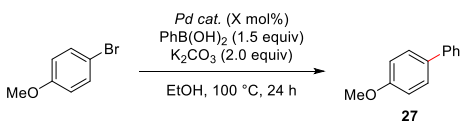


Figure 1.6 Comparison of catalysts **1-8** in the SMC of 4-bromoanisole

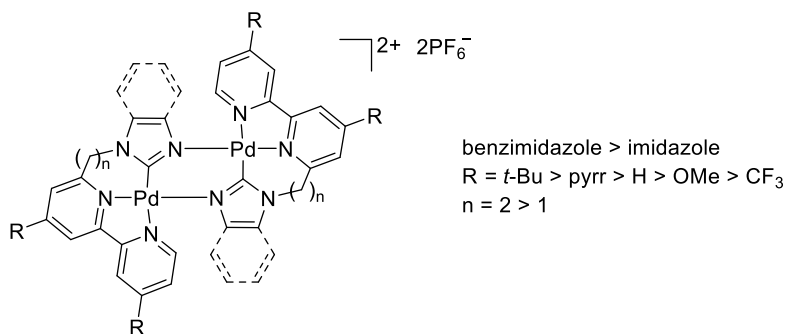


Figure 1.7 Summary of structure-activity relationships

Early studies showed that using imidazole as in **2** as opposed to the benzimidazole in **1** had a deleterious effect on the activity. Moving forward, we thought to probe the ligands' electronics by modifying the functional groups at the 4,4'-positions of the bipyridine moiety. In doing so, we

found that the di-*tert*-butyl catalyst **4** exhibited higher activity, while the 4,4'-CF₃ version of the catalyst had worse activity. The poor performance of -OMe substituted catalyst **3** compared to unsubstituted **1**, may at first look like a deviation from the trend. However, we think this can be attributed to the known decomposition of the *p*-methoxy pyridine to *N*-methylpyridone at high temperatures.¹⁴ Similarly, while the *N*-pyrrolidino substituted **5** may in theory make for a more active catalyst since the *N*-pyrrolidino substituent is more electron donating than the *tert*-butyl group,¹⁵ we postulate that the higher activity of **8** could be attributed its superior stability. Having observed in our previous studies that the flexible nature of the imidazole-bipyridine tether has a significant effect on the activity,⁶ we sought to make a more flexible catalyst by installing an ethylene tether in **7**. Having observed greater activity with the ethylene tethered **7** and electron-rich **4**, we combined these two aspects to make **8** which showed an improved overall performance, catalyzing our model reaction at 98% yield using only 0.003 mol% or 60 ppm of palladium.

1.2.1 Synthesis of 2-Benzimidazolyl-Pd Catalysts

The synthesis of catalysts **1** and **4** were performed by Jiancheng Zhu while **2** and **3** were synthesized by Garim You. Each of these four syntheses utilized the same general route that Jiancheng used to obtain **1** (Figure 1.8) in which the commercially available bipyridine was first methylated with MeLi¹⁶ before base-mediated silylation and subsequent chlorination¹⁷ could yield the 6-(chloromethyl)-bipyridine to which the imidazole could then be installed via nucleophilic substitution to furnish the ligand. Furthermore, all eight ligands prepared could undergo metalation via carboxylate-assisted C—H activation with palladium(II) acetate in MeCN to grant the 2-(benz)imidazolyl-Pd complex.

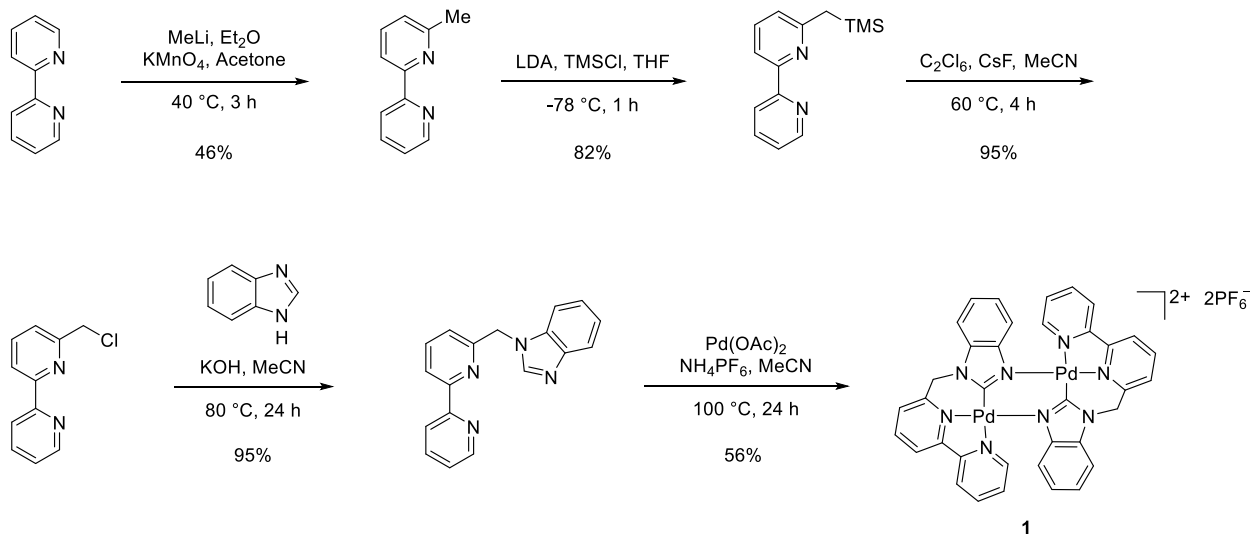


Figure 1.8 Synthesis of palladium complex **1** (Work of Jiancheng Zhu)

As shown in Figure 1.9, palladium complex **5** could be synthesized in seven steps starting from commercially available 2-bromo-4-fluoro-pyridine. First, S_NAr with pyrrolidine in refluxing ethanol could afford **10** in 93% yield. The homocoupling of 2-bromo-4-pyrrolidinopyridine **10** had not been reported in the literature and initial attempts to apply known conditions for the homocoupling of electron-rich 2-halopyridines were not successful. Fortunately, collaboration and discussions with Prof. Daniel Comins led to the identification of conditions employing palladium on carbon and K_3PO_4 in water and methanol to achieve the homocoupling of 4,4'-dipyrrolidino-bipyridine **11** in 55% yield. The subsequent methylation step could proceed with the same conditions preceded to methylate other electron-rich bipyridines,^{18,19} with the exception of using 1,4-dioxane as a solvent which seemed to overcome the issue of **11** exhibiting extremely poor solubility in Et_2O . Next, silylation to obtain **13** was performed using TESC1 which was selected instead of TMSCl in an attempt to overcome issues in isolating the pure 4,4'-dipyrrolidino-6-((trimethylsilyl)methyl)-2,2'-bipyridine. Subsequent chlorination proceeded in 49% yield of **14** using hexachloroethane and CsF in MeCN.¹⁷ Nucleophilic substitution with

benzimidazole was then performed at 30 °C for 24 h, affording 59% yield of the ligand **15**, which could then undergo C—H activation with palladium acetate to yield 56% catalyst **5**.

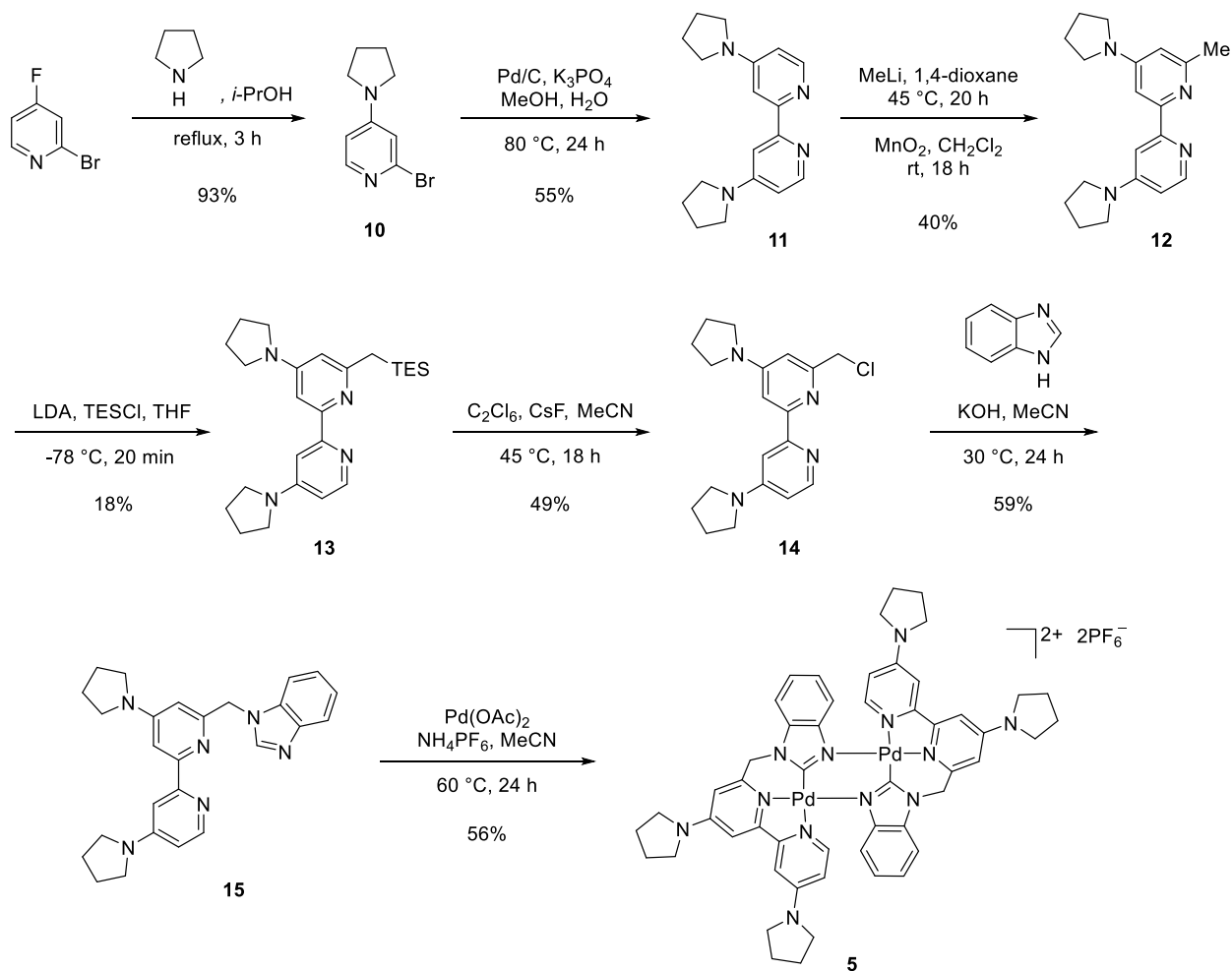


Figure 1.9 Synthesis of palladium complex **5**

Trifluoromethane-substituted catalyst **6** was prepared in five steps starting from commercially available 2-chloro-4-(trifluoromethyl)pyridine. As shown in Figure 1.10, 4,4'-(trifluoromethyl)-2,2'-bipyridine **16** was accessed through nickel-catalyzed homocoupling of 2-chloro-4-(trifluoromethyl)pyridine which proceeded in 58% yield.²⁰ Conditions optimized by Garim You

allowed for methylation of the 2-position to obtain **17** in 64% yield. In place of the silylation and chlorination steps used for other methylene-tethered ligands, 6-methyl-4,4'-(trifluoromethyl)-2,2'-bipyridine could undergo direct bromination with NBS in the presence of AIBN to afford the monobrominated product **18** in 26% yield. Nucleophilic substitution with benzimidazole was then performed at 100 °C to afford the ligand **19** in 82% yield. Because the catalyst **6** seemed to decompose when running the C—H activation reaction at 100 °C for 24 hours, the temperature and time were lowered to 75 °C for 2 hours. While yields were still quite low with these conditions, 11% yield of pure catalyst **6** could be isolated via recrystallization in CH₂Cl₂.

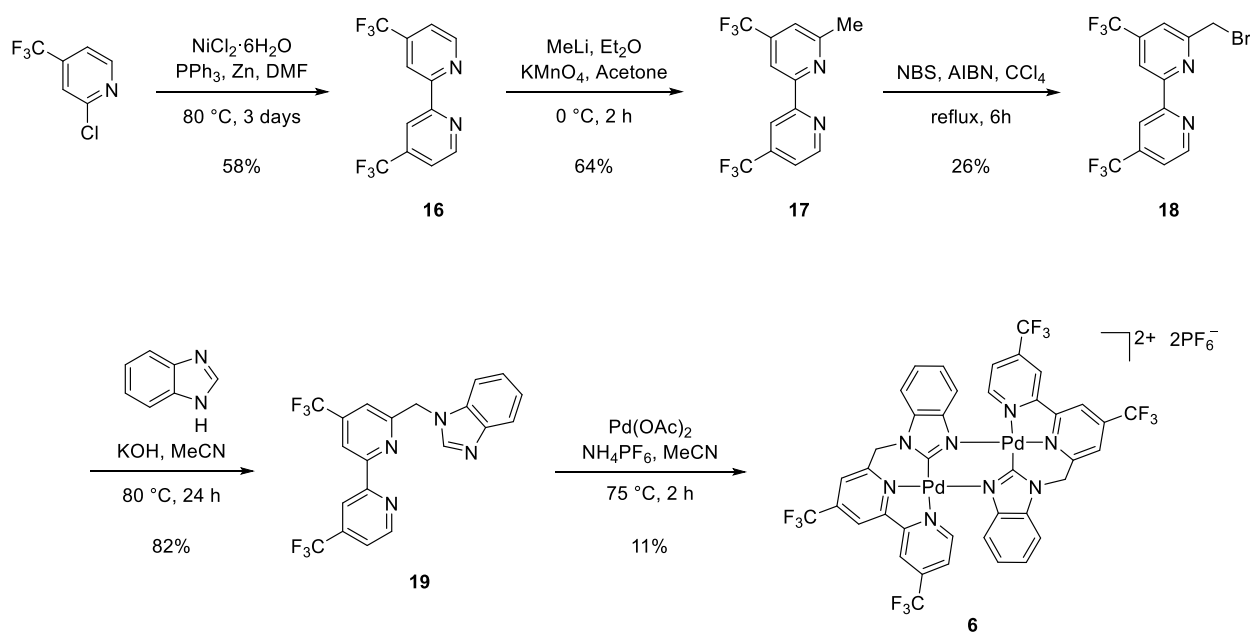


Figure 1.10 Synthesis of palladium complex **6** (work performed with Garim You)

Our first attempt at synthesizing a catalyst with enhanced flexibility, in which the benzimidazole moiety is attached to the bipyridine via an ethylene tether rather than the previously reported methylene tether, started with the synthesis of catalyst **7** (Figure 1.11). **7** could be synthesized in five steps from 2,2'-bipyridine, first starting with methylation via MeLi

and subsequent treatment with KMnO_4 to obtain **20** in 46% yield.¹⁶ This was then followed by deprotonation with LDA and treatment with paraformaldehyde to grant the 6-(2-hydroxyethyl)-2,2'-bipyridine **21** in 23% yield.²¹ The alcohol was then stirred in 33% HBr/acetic acid at 100 °C to afford compound **22** in 77% yield.²¹ Initial attempts at performing the nucleophilic substitution on **22** with benzimidazole using hydroxide bases resulted in low yields due to formation of the undesired elimination product, but the use of catalytic NaI in THF and toluene resulted in 37% yield of the ligand **23**. Catalyst **7** could then be formed via carboxylate-assisted C—H activation using palladium acetate and then recrystallized in $\text{Et}_2\text{O}/\text{MeCN}$ in the same manner as **1** albeit in slightly lower yield (45%).

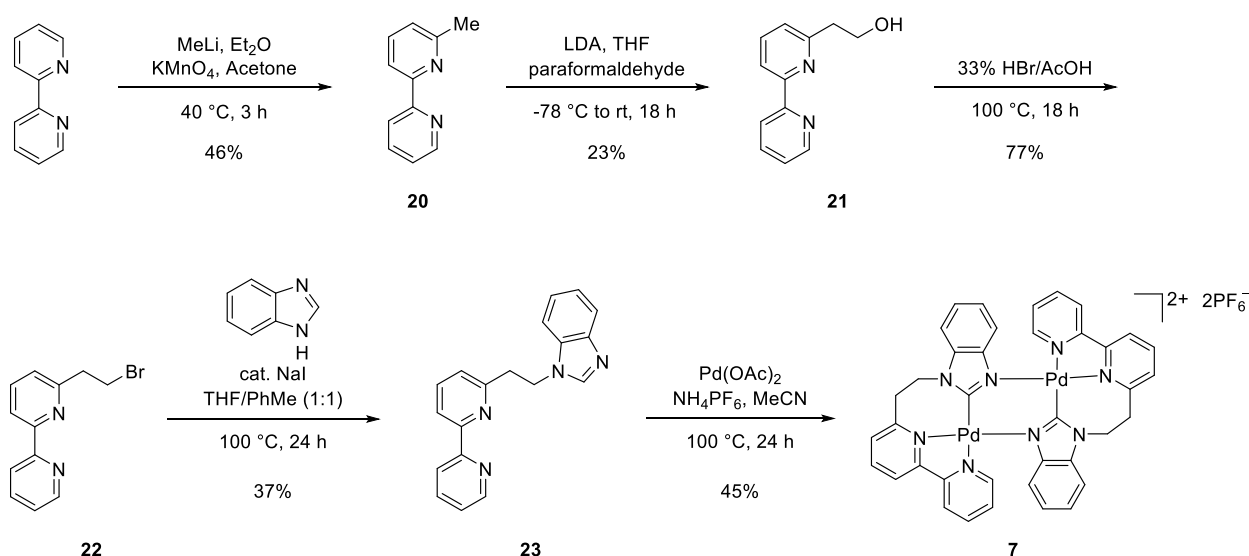


Figure 1.11 Synthesis of palladium complex **7**

The synthetic route to catalyst **8** is shown in Figure 1.12. The ligand can be synthesized in three steps using commercially available reagents. First, commercially available 4,4'-di-*tert*-butyl-2,2'-bipyridine can be chlorinated with POCl₃ after first forming the pyridine-*N*-oxide to access **24** in 58% overall yield.²² A Stille coupling with tributyl(vinyl)tin, catalyzed by

tetrakis(triphenylphosphine)palladium(0) was then used to obtain 4,4'-di-*tert*-butyl-6-vinyl-2,2'-bipyridine **25**. This intermediate could then undergo an iron-catalyzed anti-Markovnikov hydroamination to furnish the ligand **26**.²³ Finally, metalation to afford complex **8** was achieved with Pd(OAc)₂ via carboxylate-assisted C–H activation and the catalyst could easily be purified by recrystallization in MeOH in 65% yield overall.

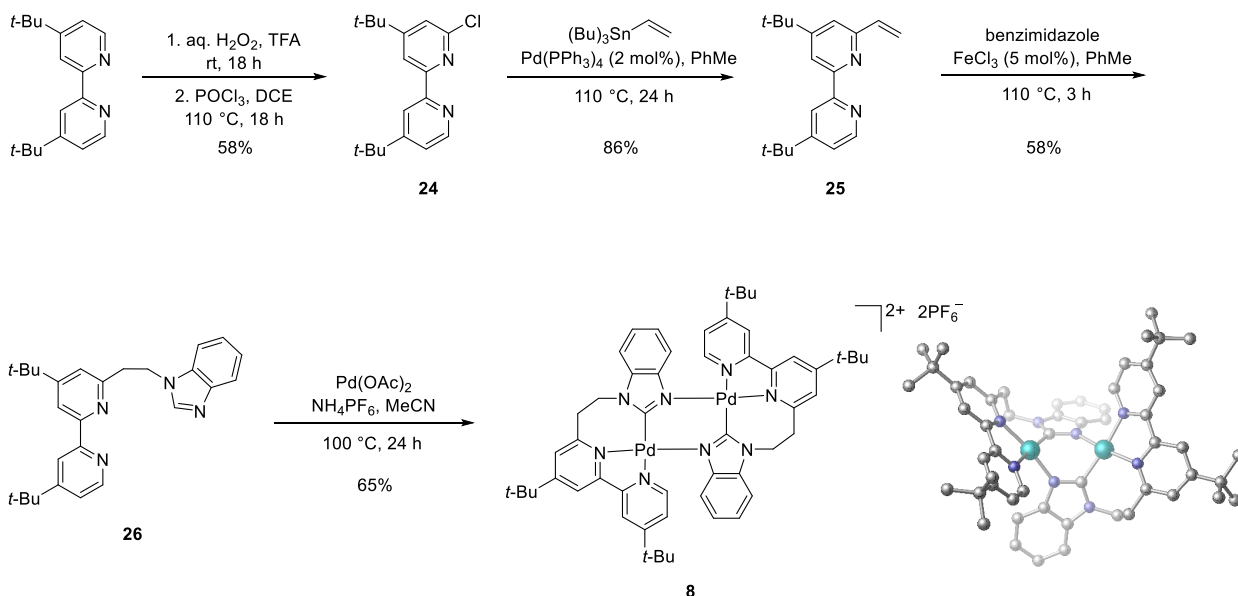


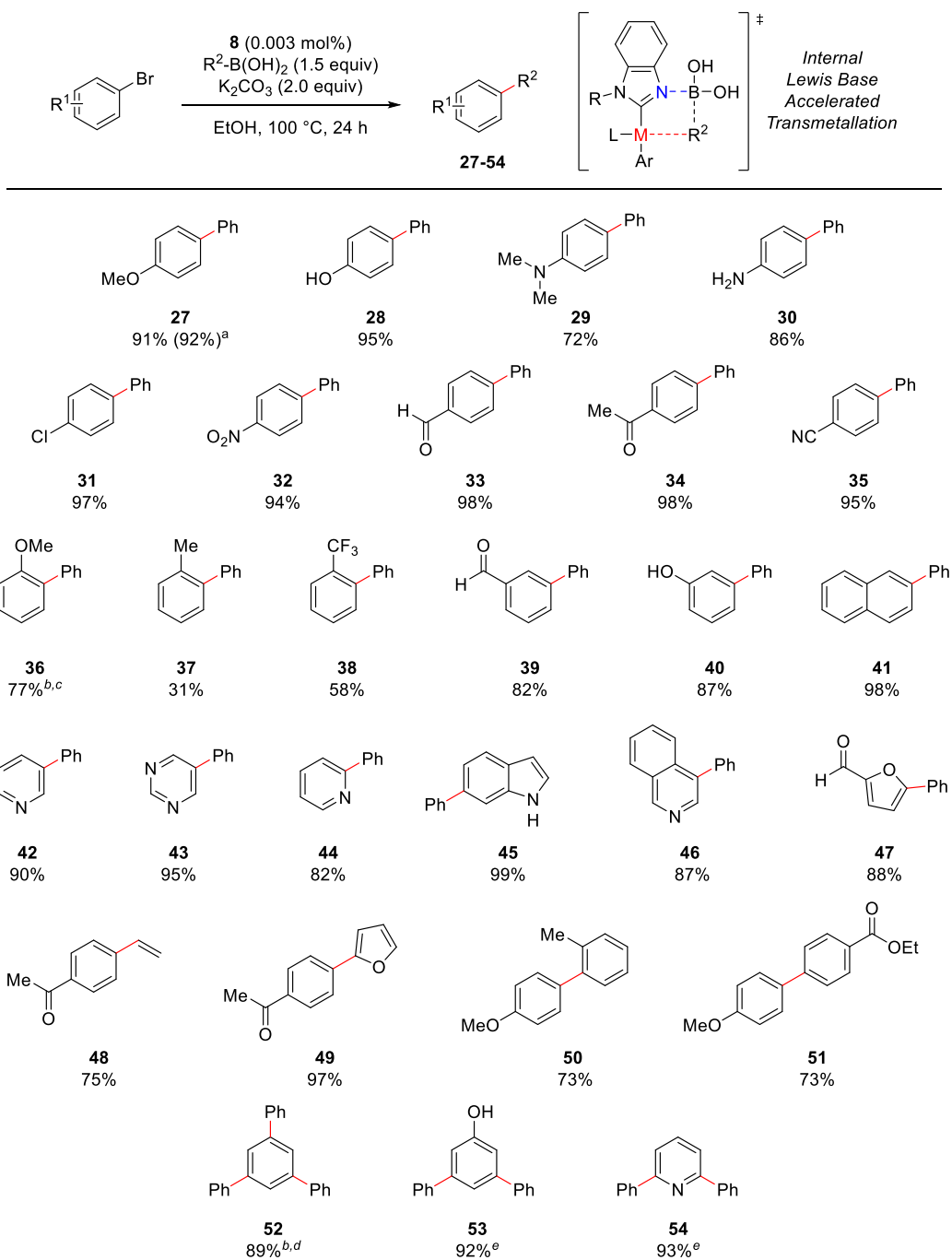
Figure 1.12 Synthesis of palladium complex **8**

Comparing the X-ray crystallographic data of **8** and **1** we can see **8** has the same general bimetallic structure as **1** in which the benzimidazolyl group is pseudo-coplanar with the bipyridine moiety. However, **8** has a greater C(1)–Pd–N(2)–C(1') dihedral angle than **1** measuring 51° and 40°, respectively. Considering the improved activity of **8** versus **1**, these observations seem to support our previous hypothesis that having increased flexibility of the benzimidazolyl moiety in the ligand is important to help stabilize intermediates of the cross-

coupling mechanism. Note, however, that too much freedom of the benzimidazolyl moiety could allow decomposition to the *N*-bound form.²

1.2.2 Scope of Suzuki-Miyaura coupling reactions

Having an improved catalyst in hand, we sought to explore the scope of its efficiency by evaluating different aryl bromides with various functional groups and substitution patterns in the SMC reaction. Considering that electron-withdrawing groups on the aryl halide facilitate oxidative addition while electron donating groups make it more challenging,²⁴ we were delighted to find that good to excellent yields could be achieved with both electron-rich and -poor aryl groups. Our catalyst seemed to work better with less sterically hindered 4- and 3-substituted aryl bromides than with 2-substituted compounds (see **36-38**). Still the SMC of 2-bromoanisole and phenylboronic could still be successful in 77% yield (**36**) when using 0.01 mol% catalyst at 90 °C. As for functional group tolerance, our catalytic system is not only tolerant of free alcohols, amines, aldehydes, and nitro groups but also could handle heterocyclic substrates, such as pyridine, isoquinoline, pyrimidine, indole, and furan. This distinction is particularly important for potential application of this catalytic system to the production of biologically relevant compounds.



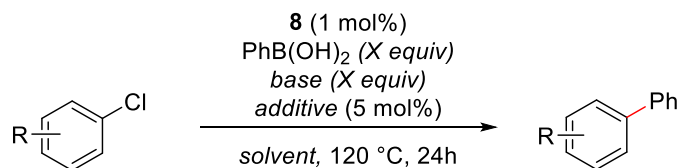
^aReaction performed on gram scale (26.7 mmol). ^bReaction ran at 0.01 mol% catalyst loading. ^cReaction ran at 90 °C. ^d4.5 equiv phenylboronic acid used. ^e3.0 equiv phenylboronic acid used.

Figure 1.13 Scope of SMC products accessible from aryl bromides catalyzed by **8**

Another important aspect for considering the viability of a SMC system in an industrial setting, for example to generate libraries of different biaryl compounds, is the compatibility with a range of boronic acids. We tested different boronic acids/boronate esters (see **48-51**) and found vinylboronic acid pinacol ester to be a viable coupling partner, giving styrene derivative **48**. Such cross-coupling processes installing vinyl groups are known to be difficult processes (likely due to subsequent Heck coupling on the product), often requiring the use of trifluoroborates or other aryl-metal species altogether.²⁵ Moreover, 2-furanboronic acid, the more sterically hindered 2-tolylboronic acid, and electron deficient 4-ethoxycarbonylphenylboronic acid could all be employed, still achieving good to excellent yields for **49-51**. Lastly, polyarylation could be achieved to form *m*-terpene compounds **52**, **53** and 2,6-diphenyl pyridine **54**.

1.2.3 Suzuki Coupling of Aryl Chlorides with Catalyst **8**

We also wanted to expand the scope of catalyst **8** to perform the SMC reaction with aryl chlorides, which are generally the most challenging aryl halide species to use in the SMC due to their slower oxidative addition to palladium compared to aryl bromides, iodides, and triflates.³ Despite being challenging substrates, they are often the most preferred substrate in industrial scale cross-coupling reactions over aryl bromides and iodides due to their increased availability and low cost.³

Table 1.1 Optimization of SMC of aryl chlorides with palladium complex **8**

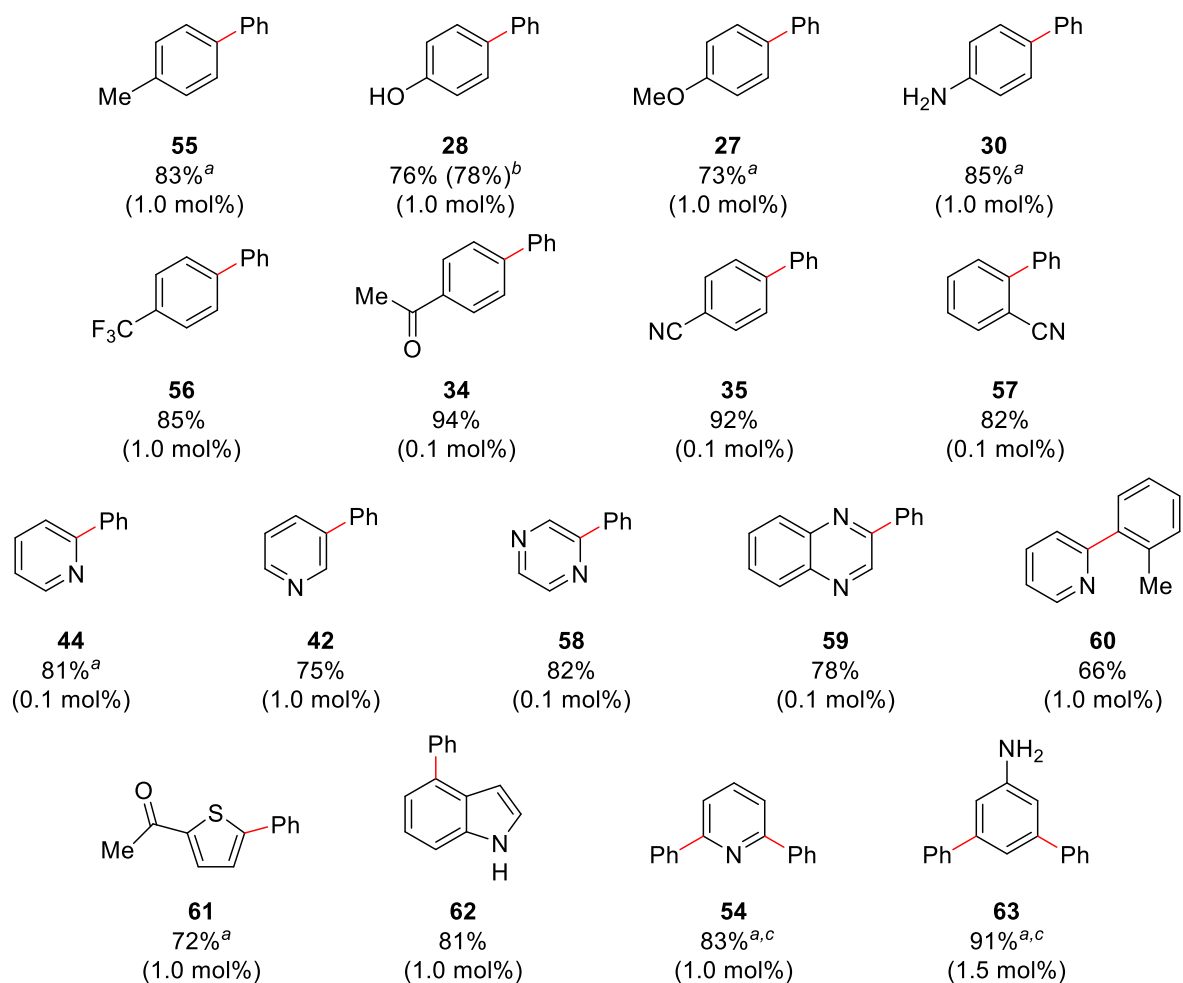
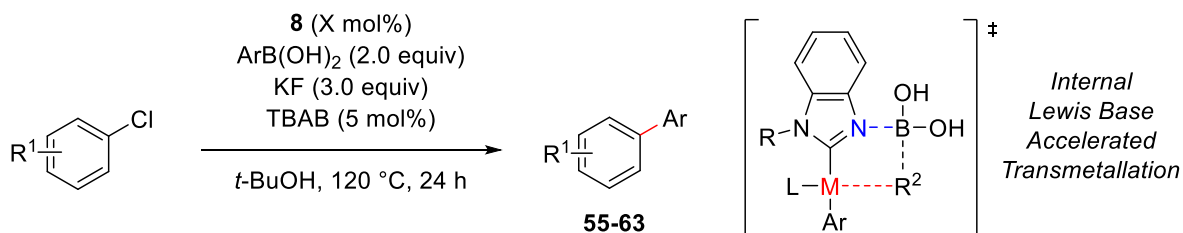
Entry	Ar-Cl	Base	PhB(OH) ₂ equiv	Solvent	Additive	Conc (M)	Setup	Temp (°C)	Yield ^a (%)	Note
1	4-Chlorobenzonitrile	K ₂ CO ₃ (2.0)	1.5	EtOH	-	0.12	air	120	26	-
2	4-Chlorobenzonitrile	KOt-Bu (2.0)	1.5	EtOH	-	0.12	air	120	<5	-
3	4-Chlorobenzonitrile	KF (3.0)	1.5	EtOH	-	0.12	air	120	45	-
4	4-Chlorobenzonitrile	KF (3.0)	1.5	<i>t</i> -BuOH	-	0.12	air	120	81	-
5	4-Chlorobenzonitrile	KF (3.0)	1.5	<i>t</i> -BuOH	-	0.12	air	120	0	no cat.
6	4-Chlorotoluene	KF (3.0)	1.5	<i>t</i> -BuOH	-	0.12	air	120	0	-
7	4-Chlorotoluene	K ₂ CO ₃ (3.0)	1.5	<i>t</i> -BuOH	-	0.12	air	120	9	-
8	4-Chlorotoluene	NaOH (3.0)	1.5	<i>t</i> -BuOH	-	0.12	air	120	0	-
9	4-Chlorotoluene	K ₃ PO ₄ (3.0)	1.5	<i>t</i> -BuOH	-	0.12	air	120	10 (3)	-
10	4-Chlorotoluene	K ₃ PO ₄ (3.0)	1.5	<i>t</i> -BuOH	-	0.12	air	140	8	-
11	4-Chlorotoluene	K ₃ PO ₄ (3.0)	1.5	<i>t</i> -BuOH	-	0.12	air	100	3	-
12	4-Chlorotoluene	K ₃ PO ₄ (3.0)	1.5	H ₂ O/Dioxane	-	0.12	air	120	0	-
13	4-Chlorotoluene	K ₃ PO ₄ (3.0)	1.5	PhMe	-	0.12	air	120	7	-
14	4-Chlorotoluene	K ₃ PO ₄ (3.0)	1.5	<i>t</i> -BuOH	TBAB	0.12	air	120	13	-
15	4-Chlorotoluene	K ₃ PO ₄ (3.0)	2.0	<i>t</i> -BuOH	TBAB	0.5	gb	120	13	-
16	4-Chlorotoluene	KF (3.0)	2.0	<i>t</i> -BuOH	TBAB	0.5	gb	120	80 (71)	-
17	4-Chlorotoluene	KF (3.0)	2.0	<i>t</i> -BuOH	TBAB	0.5	gb	120	87 (83)	Solvent dried/degassed
18	4-Chlorotoluene	KF (3.0)	2.0	<i>t</i> -BuOH	TBAB	1.0	gb	120	80	Solvent dried/degassed

^aYields determined by NMR using 1,3,5-trimethoxybenzene as internal standard

When we first attempted to use catalyst **8** for the SMC of aryl chlorides, using our conditions optimized for aryl bromides, it was only possible to get results with activated aryl chlorides such as 4-chlorobenzonitrile. Even with 1 mol% of catalyst, only 26% yield could be achieved at first

(Table 1.1, entry 1). When evaluating different bases, we found KF seemed to be the most promising, and further improvement could be seen when using *t*-BuOH as the solvent. We then switched to an unactivated substrate, 4-chlorotoluene for further optimization and found no yield at first (entry 6). Having been aware that the first reports of using KF in aryl chloride SMC systems by Fu used higher concentrations and were set up in the glovebox,²⁶ we adapted these conditions while also opting to use 2.0 equivalents of boronic acid. Use of 5 mol% tetrabutylammonium bromide as an additive also seemed to benefit the reaction yield (entries 9 and 14) and with these conditions we were able to achieve 80% yield (entry 16). Drying the reagent grade *t*-BuOH that we had been using served to increase the yield to 87% NMR yield (entry 17).

In exploring the reaction scope of aryl chloride SMCs with our newly defined conditions we were delighted to find that tolerance for free alcohol and unprotected aniline groups was maintained and heterocycles such as pyridine, pyrazine, quinoxaline, indole, and even thiophene could be tolerated as well. Furthermore, the catalyst loading could be reduced to 0.1 mol% for activated aryl chlorides (**34**, **35**, **57**, **44**, **58**, **59**).



^aSolvent dried and degassed. ^bReaction performed on gram scale (7.8 mmol). ^c4.0 equiv phenylboronic acid used.

Figure 1.14 Scope of SMC products accessible from aryl chlorides catalyzed by **8**

A notable feature of these SMC reactions is their compatibility with unprotected aniline functional groups and in the case of the aryl bromides SMC, compatibility with an aryl chloride substituent (**31**). This aspect can be synthetically advantageous because sequential orthogonal

SMC couplings, or in the case of unprotected aniline products like **30** and **63**, SMC followed by Buchwald-Hartwig amination conditions can potentially be achieved. To exemplify the orthogonal use of each of our procedures in sequence, we started with a SMC on 1-bromo-4-chlorobenzene followed by an SMC on the aryl chloride **31** to make **64** (Figure 1.15).

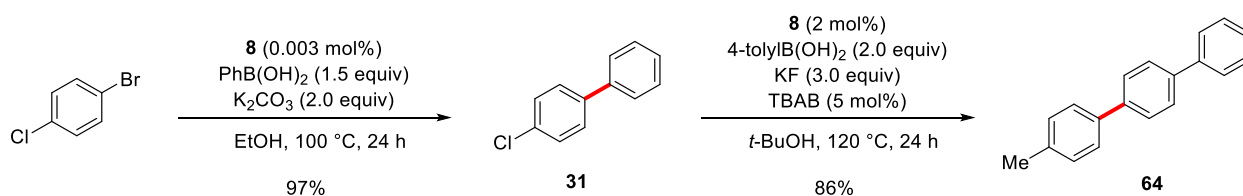


Figure 1.15 Sequential orthogonal SMC reactions catalyzed by **8** to synthesize **64**

1.2.4 Comparison of Catalysts **8** and **1**

To further measure the difference in activity and scope between catalyst **8** and **1**, we ran tandem reactions with both the SMC aryl chlorides and bromides (Tables 1.2 and 1.3). For some activated substrates, both catalysts achieved yields in the excellent range. However, **8** generally proved to be significantly better than **1** and interestingly, the margin of difference in activity observed between **8** and **1** is larger for the SMC of aryl chlorides versus aryl bromides. Reactions involving the coupling of 2-tolylboronic acid (Table 1.3) seemed to display a relatively larger margin which might suggest that catalyst **8** is particularly more effective in coupling more hindered boronic acids compared to **1**, potentially due to increased flexibility in the ligand tether.

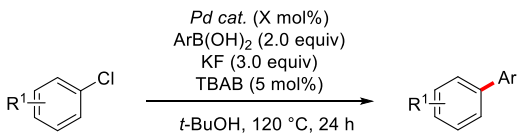
Table 1.2 Comparison of catalysts **8** and **1** in the SMC of aryl bromides

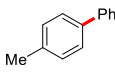
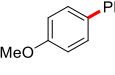
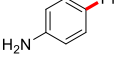
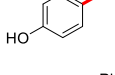
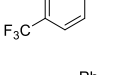
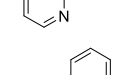
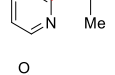
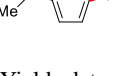
$\text{R}^1\text{-C}_6\text{H}_4\text{-Br} \xrightarrow[\text{EtOH, 100 }^\circ\text{C, 24 h}]{\text{Pd cat. (X mol\%), R}^2\text{-B(OH)}_2 \text{ (1.5 equiv), K}_2\text{CO}_3 \text{ (2.0 equiv)}} \text{R}^1\text{-C}_6\text{H}_4\text{-R}^2$

	product	mol %	8 (product yield, %) ^a	1 (product yield, %) ^a
	27	0.003	98	80
	36	0.01	73	45
	38	0.003	66	47
	39	0.003	87	71
	28	0.003	>99	>99
	40	0.003	94	80
	44	0.003	87	47
	45	0.003	>99	85
	47	0.003	>99	94
	50	0.003	79	49
	65	0.1	59	18
	46	0.003	>99	>99
	42	0.003	>99	>99
	43	0.003	>99	>99
	31	0.003	>99	>99
	32	0.003	>99	>99

^aYields determined by NMR using 1,3,5-trimethoxybenzene as internal standard

Table 1.3 Comparison of catalysts **8** and **1** in the SMC of aryl chlorides



	product	mol %	8 (product yield, %) ^a	1 (product yield, %) ^a
	55	1.0	87	41
	27	1.0	76	60
	30	1.0	93	40
	28	1.0	79	37
	56	1.0	94	65
	44	0.1	89	33
	60	1.0	72	26
	61	1.0	77	43

^aYields determined by NMR using 1,3,5-trimethoxybenzene as internal standard

1.3 Conclusions

A family of air- and moisture-stable dinuclear 2-benzimidazolylpalladium complexes, known to act as highly active bifunctional catalysts for sustainable cross coupling reactions, was expanded upon structure-activity relationship studies and defined with respect to the catalysts' performance in Suzuki-Miyaura cross-coupling reactions. New understanding of structure-activity trends was leveraged to develop a more active catalyst via modification of the ligand's structural rigidity and electronic character. The newly developed 2-benzimidazolyl-Pd catalyst **8** shows significantly enhanced activity than our previously reported catalyst **1**, particularly when

comparing their activity in the SMC of aryl chlorides. Under optimal conditions, SMC of aryl bromides and aryl chlorides can be performed efficiently with good functional group compatibility in alcohol solvents at catalyst loadings of 0.003 mol% (60 ppm Pd) for aryl bromides and as low as 0.1 mol% (2000 ppm Pd) for aryl chlorides. Sequential orthogonal reactions as well as reactions on a gram scale were also performed to further demonstrate the synthetic viability of this catalytic system.

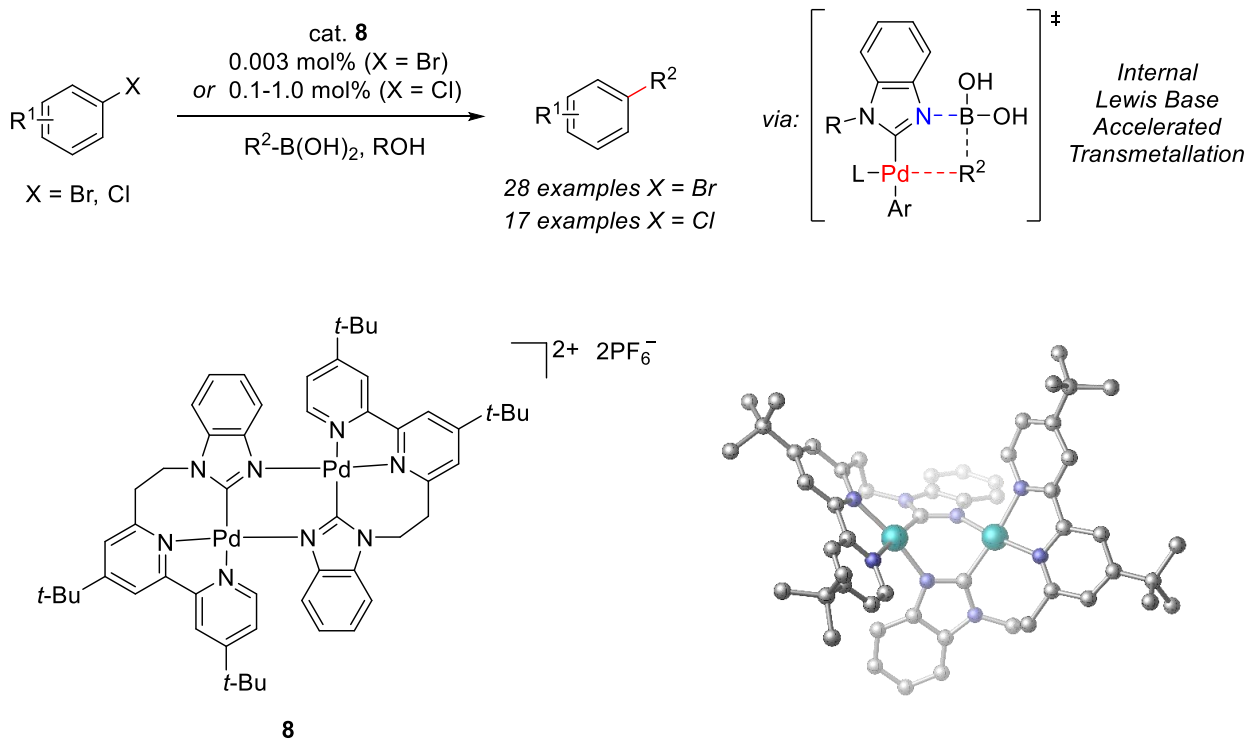


Figure 1.16 Highly active bifunctional 2-benzimidazolyl-Pd catalyst **8**

1.4 Experimental

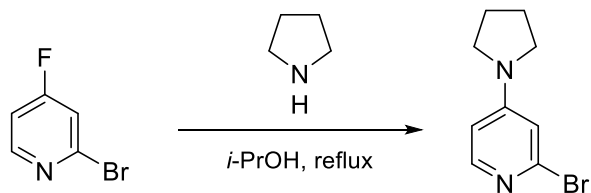
General: Unless stated otherwise, all non-aqueous reactions were performed in oven-dried glassware sealed with microwave caps or rubber septa under a nitrogen atmosphere, and were stirred with Teflon-coated magnetic stir bars.²⁷ Liquid reagents and solvents were transferred by syringe using standard Schlenk techniques. Tetrahydrofuran (THF), diethyl ether (Et₂O), dichloromethane (CH₂Cl₂), toluene (PhMe), acetonitrile (MeCN), and methanol (MeOH) were dried by passage over a column of activated alumina (JC Meyers Solvent System). Anhydrous dimethyl sulfoxide (DMSO) and *N,N*-dimethylformamide (DMF) were obtained in Sure Seal bottles from Aldrich and used as received. All other solvents and reagents were used as received unless otherwise noted. Thin layer chromatography was performed using Silicycle silica gel 60 F-254 precoated plates (0.25 mm) and visualised by UV irradiation and anisaldehyde, CAM, potassium permanganate, or iodine stain. Sorbent silica gel (particle size 40-63 μm) was used for flash chromatography of the indicated solvent system according to standard techniques.²⁸ Flash chromatography was performed on a Biotage Isolera One. Nuclear magnetic resonance (NMR) spectra (¹H, ¹³C) were recorded on Varian or Bruker spectrometers operating at either 300, 400, 500, 600 or 700 MHz for ¹H and 75, 100, 125, 150 or 175 MHz for ¹³C experiments. Chemical shifts (δ) for ¹H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform, δ 7.26 ppm, DMSO, δ 2.50 ppm, or MeCN, δ 1.93 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet and br = broad), coupling constant in Hz, and integration. Chemical shifts for ¹³C NMR spectra are recorded in parts per million from tetramethylsilane using the central peak of deuteriochloroform (δ 77.16 ppm), acetonitrile-*d*₃ (δ 118.26 ppm) or DMSO-*d*₆ (δ 39.52 ppm)

as the internal standard. All spectra were obtained with complete proton decoupling. Only select ^1H and ^{13}C spectra are reported. Infrared (IR) spectra were collected on a Thermo Scientific Nicolet iS5 FTIR instrument using attenuated total reflectance (ATR) mode and signals are reported in reciprocal centimeters (cm^{-1}). Only selected IR frequencies are reported. High-resolution mass spectral data were obtained from the NC State University Mass Spectrum Facility, using a Thermo Fisher Scientific Exactive Plus for ESI.

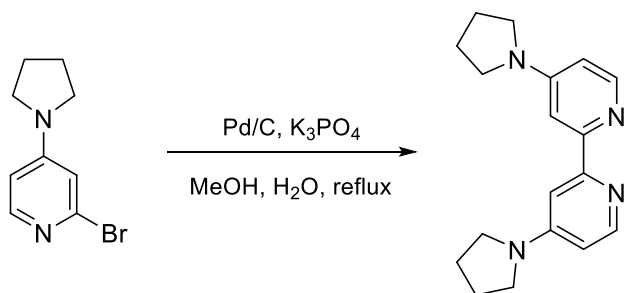
Reagents: benzimidazole, pyrrolidine, paraformaldehyde, palladium on carbon (Pd/C), ammonium hexafluorophosphate (NH_4PF_6), potassium hydroxide (KOH), palladium(II) acetate ($\text{Pd}(\text{OAc})_2$), methyl lithium (MeLi), potassium permanganate (KMnO_4), manganese dioxide (MnO_2), lithium diisopropylamide (LDA), nickel(II)chloride hexahydrate ($\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$), N-bromosuccinimide (NBS),) azobisisobutyronitrile (AIBN), chlorotrimethylsilane (TMSCl), chlorotriethylsilane (TESCl), hexachloroethane ($\text{Cl}_3\text{C}-\text{CCl}_3$), potassium carbonate (K_2CO_3), tetrabutylammonium bromide (TBAB), cesium fluoride (CsF), potassium fluoride (KF), (vinyl)tributyl tin, iron(III) chloride (FeCl_3), palladium(0)tetrakis(triphenyl)phosphine ($\text{Pd}(\text{PPh}_3)_4$), potassium phosphate tribasic (K_3PO_4), phenylboronic acid ($\text{PhB}(\text{OH})_2$), vinylboronic acid pinacol ester, 2-furanylboronic acid, ethylbenzoateboronic acid, and all aryl halides were purchased from commercial sources and used without further purification.

Synthesis of palladium complexes

Synthesis of palladium complex 5

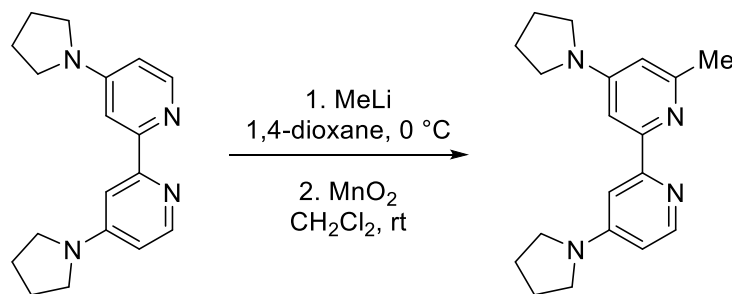


2-bromo-4-(pyrrolidin-1-yl)pyridine (10). To a roundbottom flask equipped with a stir bar was added 2-bromo-4-fluoropyridine (5.0 g, 28.4 mmol, 1.0 equiv), pyrrolidine (11.64 mL, 142.0 mmol, 5.0 equiv), *i*-PrOH (170 mL) and the reaction was refluxed for 3 h. The reaction was then allowed to cool to room temperature before K_2CO_3 (25.0 g) was added and solution stirred for 1 h. 200 mL CH_2Cl_2 was then added and solution was sonicated and filtered on celite. The crude was then concentrated under reduced pressure and purified on a silica plug eluting with acetone to yield **10** (5.96 g, 93%) as a white solid. All analyses were consistent with previously reported data.²⁹



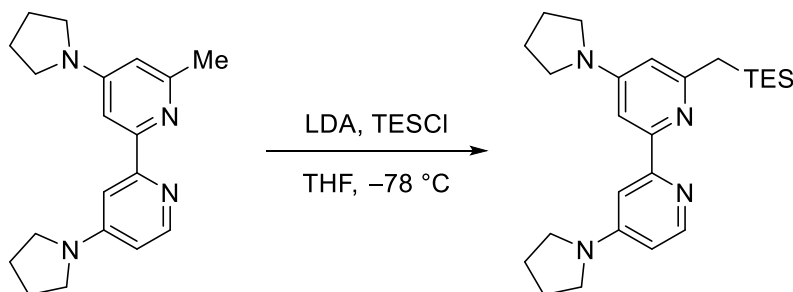
4,4'-di(pyrrolidin-1-yl)-2,2'-bipyridine (11). To a roundbottom flask equipped with a stir bar was added **10** (5.96 g, 26.2 mmol, 1.0 equiv), K_3PO_4 (267 mg, 1.26 mmol, 2.0 equiv), and Pd/C (839 mg, 2.62 mmol, 0.1 equiv). MeOH (252 mL) and H_2O (9.7 mL) were then added and the reaction was stirred at reflux for 24 h. After cooling to room temperature, $CHCl_3$ was added and the mixture was stirred for 15 minutes before filtering on celite. The crude was then concentrated

under reduced pressure and purified by recrystallization in hot propionitrile to yield **11** (2.14 g, 55%) as a white solid. All analyses were consistent with previously reported data.³⁰



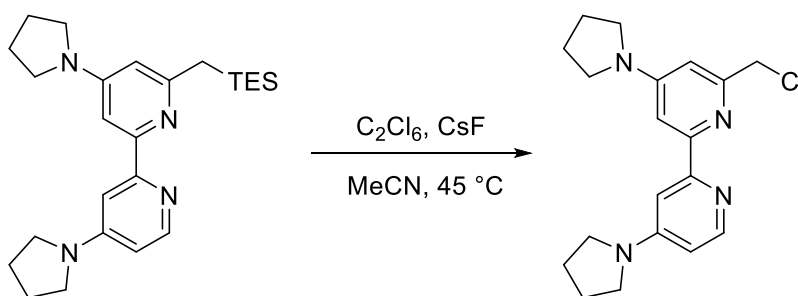
6-methyl-4,4'-di(pyrrolidin-1-yl)-2,2'-bipyridine (12). An oven-dried 100 mL round-bottom flask equipped with a magnetic stirbar was charged with **11** (1.875 g, 6.37 mmol, 1.0 equiv) and dry 1,4-dioxane (30 mL) and the resulting solution was cooled to 0 °C. A solution of MeLi (8.76 mL, 1.6 M in Et₂O, 14.0 mmol, 2.2 equiv) was added dropwise, and the resulting solution was heated to 45 °C for 20 h. The reaction was allowed to cool to room temperature and H₂O was added. The layers were separated and the aqueous layer was extracted three times with Et₂O. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo to afford the crude as an orange oil. MnO₂ (2.21 g, 25.48 mmol, 4.0 equiv) and 22 mL dry CH₂Cl₂ was then added and stirred at room temperature for 18 hours, after which the mixture was filtered on Celite eluting with CH₂Cl₂. Solvents were evaporated in vacuo and the crude product was purified by flash chromatography on silica gel (80% EtOAc/1% TEA/hexanes) to afford pure **12** (792 mg, 40%) as a white solid. **mp** 184 °C (decomposition). **¹H NMR** (600 MHz, CDCl₃) δ 8.26 (d, *J* = 5.7 Hz, 1H), 7.53 (d, *J* = 2.6 Hz, 1H), 7.34 (d, *J* = 2.4 Hz, 1H), 6.37 (dd, *J* = 5.9, 2.6 Hz, 1H), 6.26 (d, *J* = 2.4 Hz, 1H), 3.43 (m, 8H), 2.52 (s, 2H), 2.02 (m, 8H). **¹³C NMR** (150 MHz, CDCl₃) δ 157.6, 157.3, 156.7, 153.2, 152.7, 149.0, 106.6, 105.8, 104.7, 102.3, 47.2 (2C), 25.5, 25.4, 25.0. **IR** (neat, cm⁻¹) 2963, 2917, 2833, 1586, 1538, 1477, 1184, 1163, 1008,

975, 849, 809, 660, 552, 446. **HRMS** (HESI) calcd for $[C_{19}H_{24}N_4+H]^+$: m/z 309.20737, found 309.20758.



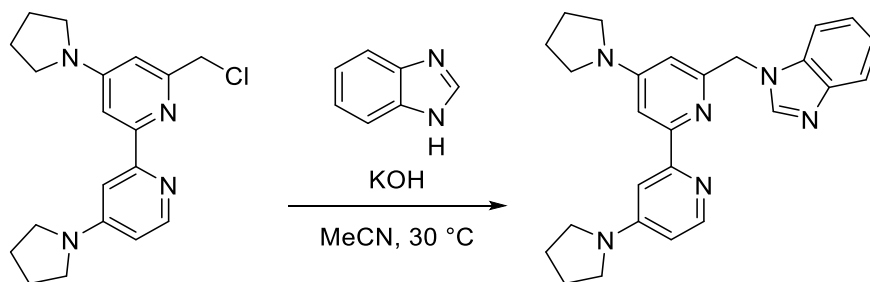
4,4'-di(pyrrolidin-1-yl)-6-((triethylsilyl)methyl)-2,2'-bipyridine (13). To an oven-dried microwave vial was added diisopropylamine (20.2 mg, 0.20 mmol 1.0 equiv) and THF (0.5 mL). The reaction mixture was cooled to -78 °C and a solution of *n*-BuLi (1.92 M in hexanes, 104 μ L, 0.20 mmol 1.0 equiv) was added. The solution was stirred at -78 °C for 10 min, and then allowed to warm to room temperature. In another flame-dried microwave vial, **12** (62 mg, 0.20 mmol, 1.0 equiv) was stirred in THF (0.5 mL) at -78 °C, resulting in a white suspension to which the previous solution was added dropwise via syringe. The resulting dark mixture was stirred at the same temperature for 20 minutes. TESC1 (25 μ L, 0.20 mmol, 1.0 equiv) was then added rapidly, and the mixture was stirred vigorously for 20 seconds. The reaction was quenched by rapid addition of absolute EtOH (0.05 mL), and the cold mixture was poured into a separatory funnel containing aq. sat. $NaHCO_3$ and allowed to warm to room temperature. The solution was extracted three times with CH_2Cl_2 , and the combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (65-80% EtOAc/5% Et_3N /hexanes) to afford **13** (15.5 mg, 18%) as a white solid. **mp** 196.9 °C (decomposition). **1H NMR** (500 MHz, $CDCl_3$) δ 8.26 (d, $J = 6.1$ Hz, 1H), 7.65 (d, $J = 2.7$ Hz, 1H), 7.31 (m, 1H), 6.36 (dd, $J = 6.0, 2.7$ Hz, 1H), 6.10 (m, 1H), 3.40 (m,

8H), 2.30 (s, 2H), 2.06 – 1.97 (m, 8H), 0.98 (t, $J = 7.9$ Hz, 9H), 0.62 (q, $J = 7.9$ Hz, 6H). ^{13}C NMR (150 MHz, CDCl_3) δ 160.4, 153.1, 152.7, 148.9, 148.8, 106.5, 105.0, 104.9, 101.0, 47.3, 47.2, 25.6, 25.5, 7.6, 3.6. IR (neat, cm^{-1}) 2948, 2905, 2869, 1582, 1537, 1452, 1375, 1349, 1238, 1148, 1008, 978, 814, 728, 572. HRMS (HESI) calcd for $[\text{C}_{25}\text{H}_{38}\text{N}_4\text{Si}+\text{H}]^+$: m/z 423.29385, found 423.29335.

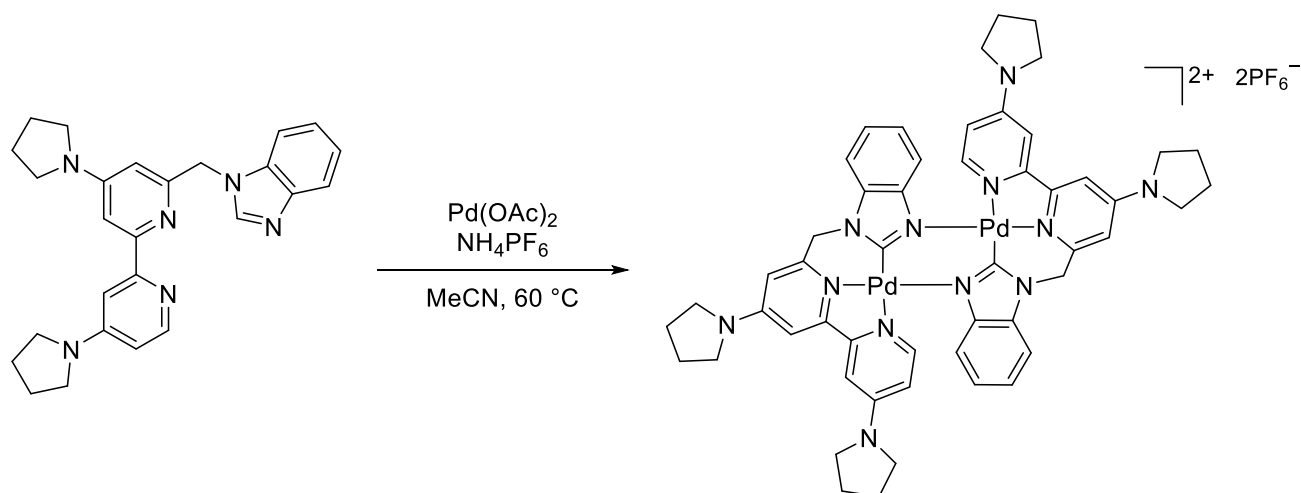


6-(chloromethyl)-4,4'-di(pyrrolidin-1-yl)-2,2'-bipyridine (14). An oven-dried microwave vial equipped with a magnetic stirbar was charged with **13** (19.5 mg, 0.046 mmol, 1.0 equiv), hexachloroethane (43.7 mg, 0.184 mmol, 4.0 equiv), CsF (28.0 mg, 0.184 mmol, 4.0 equiv) and dry MeCN (0.4 mL). The resulting heterogeneous mixture was heated at 45 °C for 18 hours, allowed to cool to room temperature and then CH_2Cl_2 and H_2O were added. The layers were separated and the aqueous layer was extracted three times with CH_2Cl_2 . The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (65-80% EtOAc/5% Et_3N /hexanes) to afford **14** (7.8 mg, 49%) as a white solid. mp 257 °C (decomposition). ^1H NMR (600 MHz, CDCl_3) δ 8.26 (d, $J = 5.8$ Hz, 1H), 7.54 (d, $J = 2.5$ Hz, 1H), 7.45 (m, 1H), 6.58 (d, $J = 2.3$ Hz, 1H), 6.39 (dd, $J = 5.9, 2.6$ Hz, 1H), 4.66 (s, 2H), 3.44 (m, 8H), 2.04 (m, 8H). ^{13}C NMR (150 MHz, CDCl_3) 156.5, 156.1, 153.6, 152.8, 148.8, 106.8, 105.4, 104.8, 103.9, 48.0, 47.4, 47.3, 25.5 IR (neat, cm^{-1}) 2962, 2909, 2850, 1585, 1538, 1474, 1455, 1381, 1350, 1007, 976, 809, 748,

713, 659, 623, 580, 447. **HRMS** (HESI) calcd for $[C_{19}H_{23}ClN_4+H]^+$: m/z 343.16840, found 343.16795.

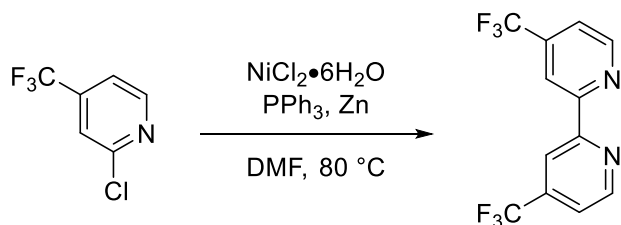


1-((4,4'-di(pyrrolidin-1-yl)-[2,2'-bipyridin]-6-yl)methyl)-1H-benzimidazole (15). An oven-dried microwave vial equipped with a magnetic stirbar was charged with **14** (356.5 mg, 1.13 mmol, 1.0 equiv), benzimidazole (132.9 mg, 1.13 mmol, 1.0 equiv), KOH (76.0 mg, 1.35 mmol, 1.2 equiv) and dry MeCN (11 mL). The resulting mixture was stirred at 30 °C for 24 h. The reaction was then cooled to room temperature and CH_2Cl_2 and aq. sat. $NaHCO_3$ were added. The layers were separated and the aqueous layer was extracted three times with CH_2Cl_2 . The combined organic layers were dried over Na_2SO_4 , filtered and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (0-5% MeOH/1% Et_3N/CH_2Cl_2 elution gradient) to afford **15** (68 mg, 59%) as a white solid. **mp** 257 °C (decomposition). **1H NMR** (600 MHz, $CDCl_3$) δ 8.24 (d, $J = 5.9$ Hz, 1H), 8.10 (s, 1H), 7.82 (m, 1H), 7.49 – 7.44 (m, 2H), 7.39 (d, $J = 2.7$ Hz, 1H), 7.27 – 7.24 (m, 3H), 6.37 (dd, $J = 6.0, 2.6$ Hz, 1H), 6.08 (d, $J = 2.3$ Hz, 1H), 5.42 (s, 2H), 3.36 (m, 4H), 3.31 (m, 4H), 2.05 (m, 4H), 1.96 (m, 4H). **^{13}C NMR** (150 MHz, $CDCl_3$) 154.7, 153.6, 153.0, 144.0, 134.5, 123.0, 122.1, 121.5, 121.4, 121.2, 120.3, 110.5, 106.8, 104.8, 103.9 (2C), 103.8, 51.0, 47.5, 47.4, 25.5, 25.4. **IR** (neat, cm^{-1}) 3066, 2960, 2915, 2851, 1586, 1539, 1454, 1382, 1351, 1171, 1008, 978, 807, 745, 659, 624, 429. **HRMS** (HESI) calcd for $[C_{26}H_{28}N_6+H]^+$: m/z 425.24482, found 425.24374.

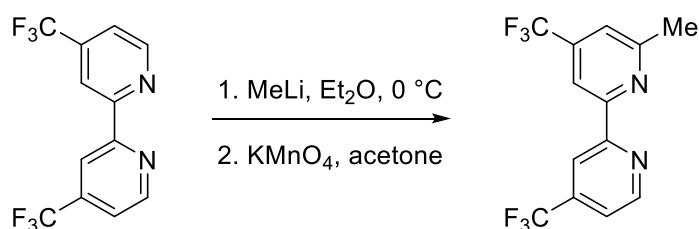


Palladium Complex 5. In an inert atmosphere glove-box, an oven-dried microwave vial equipped with a magnetic stirbar was charged with **15** (63.0 mg, 0.148 mmol, 1.0 equiv), Pd(OAc)₂ (33.3 mg, 0.148 mmol, 1.0 equiv) and NH₄PF₆ (26.6 mg, 0.162 mmol, 1.1 equiv). The vial was capped and taken out of the glove-box, dry MeCN (1.5 mL) was added and the reaction was heated at 60 °C for 24 hours. The reaction was allowed to cool to room temperature and then filtered on Celite eluting with MeCN. The solvent was then removed under reduced pressure, and product was purified by flash chromatography on alumina (0-10% MeCN/CH₂Cl₂ elution gradient) affording **5** (56 mg, 56%) as a white solid. **mp** 279 °C (decomposition). **¹H NMR** (700 MHz, CD₃CN) δ 7.74 (d, *J* = 8.1 Hz, 2H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.22 (t, *J* = 7.6 Hz, 2H), 7.20 – 7.17 (m, 6H), 6.90 (d, *J* = 2.6 Hz, 1H), 6.20 (dd, *J* = 6.8, 2.4 Hz, 2H), 5.63 (d, *J* = 15.8 Hz, 2H), 5.34 (d, *J* = 16.0 Hz, 2H), 3.67 – 3.41 (m, 12H), 3.34 – 3.17 (m, 4H), 2.14 – 2.04 (m, 8H), 2.02 – 1.96 (m, 8H). **¹³C NMR** (150 MHz, CD₃CN) δ 166.2, 158.5, 156.2, 154.5, 154.0, 152.5, 149.4, 141.2, 135.2, 123.8, 123.2, 117.0, 111.0, 108.7, 108.3, 106.2, 105.7, 51.1, 49.1, 48.7, 25.9, 25.8 **IR** (neat, cm⁻¹) 3657, 2951, 2872, 1615, 1523, 1458, 1396, 1279, 1025, 823, 735, 582, 434. **HRMS** (HESI) calcd for [C₅₂H₅₄N₁₂Pd₂]²⁺ : *m/z* 529.13265, found 529.13505.

Synthesis of palladium complex **6**

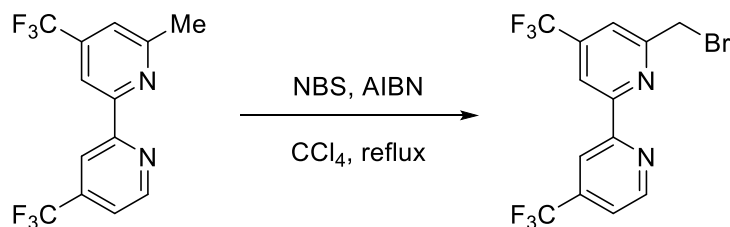


4,4'-bis(trifluoromethyl)-2,2'-bipyridine (16). In an oven-dried microwave vial, $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$, (1.1 g, 4.7 mmol, 1.0 equiv) and PPh_3 , (2.5 g, 9.5 mmol, 2.0 equiv) were dissolved in degassed DMF (10 mL). The resulting blue solution was sparged with argon for 30 min. Activated zinc dust (464.3 mg, 7.1 mmol) was added and the mixture was stirred with argon sparging for 1 h. To the resulting red-brown slurry, 2-chloro-4-(trifluoromethyl)pyridine (859.3 mg, 4.7 mmol) was added and heated in an $80\text{ }^\circ\text{C}$ oil bath for 72 h. The reaction mixture was then poured into a beaker containing 10 mL ammonia (24% aq) and 100 g of ice. The mixture was extracted with diethyl ether. The diethyl ether phase was dried over MgSO_4 , filtered, and evaporated. The crude product was purified on silica gel (20% CH_2Cl_2 /hexanes), giving **16** (570.7 mg, 82%) as a white solid. All analyses were consistent with previously reported data.²⁰



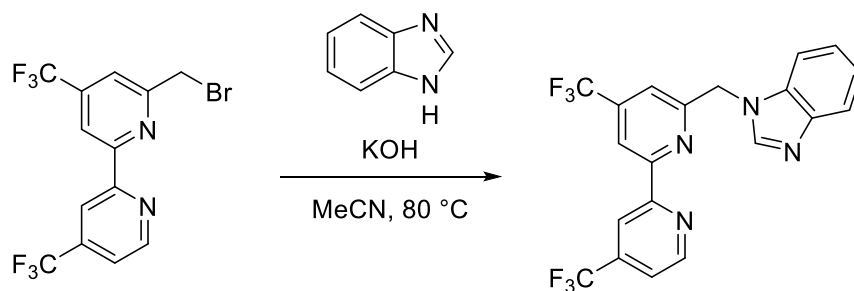
4,4'-bis(trifluoromethyl)-6-methyl-2,2'-bipyridine (17). An oven-dried microwave vial was charged with **16** (332.7 mg, 0.17 mmol, 1.0 equiv) and Et_2O (2 mL) under N_2 . The reaction mixture was cooled to $-78\text{ }^\circ\text{C}$ and a solution of MeLi (4 mL, 1.6M in Et_2O , 0.17 mmol, 1.0 equiv) was added dropwise to the solution resulting in a black solution which was stirred for 2 h. The reaction was allowed to warm to $0\text{ }^\circ\text{C}$ and then stirred for another 15 minutes before water

was added, forming a biphasic yellow solution. The aqueous layer was separated from the organic layer and extracted with Et₂O. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. A solution of KMnO₄ in acetone (100 mL, sat.) was added in one portion to the resulting orange oil and a MnO₂ precipitate was formed immediately. After the MnO₂ was filtered on Celite eluting with acetone, the acetone was removed by rotary evaporation. The crude product was purified by flash chromatography (SiO₂, 10% EtOAc/hexanes) to afford **17** (223.1 mg, 64%) as a white solid. **mp** 70-72 °C. **¹H NMR** (500 MHz, CDCl₃) δ 8.85 (d, *J* = 5.0 Hz, 1H), 8.72 (m, 1H), 8.50 (s, 1H), 7.55 (dd, *J* = 5.1, 2.1 Hz, 1H), 7.42 (s, 1H), 2.73 (s, 3H). **¹³C NMR** (175 MHz, CDCl₃) δ 159.9, 156.6, 155.6, 150.3, 139.9 (q, *J* = 33.7 Hz), 139.6 (q, *J* = 33.7 Hz), 123.2 (q, *J* = 272.8 Hz), 123.1 (q, *J* = 272.8 Hz), 119.8 (q, *J* = 3.2 Hz), 119.6 (q, *J* = 3.2 Hz), 117.2 (q, *J* = 3.5 Hz), 114.4 (q, *J* = 3.8 Hz), 24.8. **IR** (neat, cm⁻¹) 3105, 2925, 2852, 1605, 1577, 1321, 1163, 854, 670, 423. **HRMS** (HESI) calcd for [C₁₃H₈F₆N₂+H]⁺: *m/z* 307.06644, found 307.06563.



6-(bromomethyl)-4,4'-bis(trifluoromethyl)-2,2'-bipyridine (18). An oven-dried microwave vial was charged with **17** (173.1 mg, 0.57 mmol, 1.0 equiv), *N*-bromosuccinimide (100.6 mg, 0.57 mmol, 1.0 equiv), 2,2 -azobis(isobutyronitrile) (9.3 mg, 0.057 mmol, 0.1 equiv) and CCl₄ (7 mL) under nitrogen atmosphere. The mixture was stirred at reflux for 6 h. The solvent was removed under vacuum and the residue was dissolved in chloroform. The resulting solution was washed with water and brine, dried over Na₂SO₄ filtered and concentrated *in vacuo*. The crude

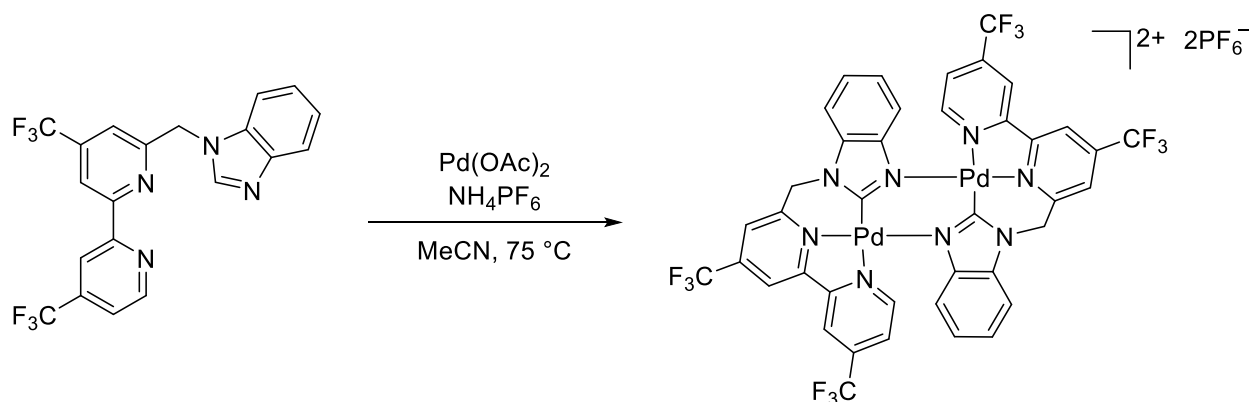
product was purified by flash chromatography (30% hexanes/CH₂Cl₂) to afford **18** as a white solid (45.0 mg, 26% yield), **mp** 85-88 °C. **¹H NMR** (500 MHz, CDCl₃) δ 8.88 (d, *J* = 5.0 Hz, 1H), 8.73 (s, 1H), 8.65 (s, 1H), 7.74 (s, 1H), 7.60 (s, 1H), 4.70 (s, 2H). **¹³C NMR** (125 MHz, CDCl₃) δ 158.3, 156.0, 155.8, 150.4, 140.9 (q, *J* = 34.3 Hz), 139.8 (q, *J* = 34.2 Hz), 123.0 (q, *J* = 273.4 Hz), 122.8 (q, *J* = 273.2 Hz), 120.2 (q, *J* = 3.7 Hz), 119.9 (q, *J* = 3.7 Hz), 117.4 (q, *J* = 3.6 Hz), 116.6 (q, *J* = 3.6 Hz), 32.8. **IR** (neat, cm⁻¹) 3092, 2922, 2850, 1571, 1342, 1165, 1128, 1100, 854, 670, 624, 594, 420. **HRMS** (HESI) calcd for [C₁₃H₇BrF₆N₂+H]⁺: *m/z* 384.97696, found 384.97607.



1-((4,4'-bis(trifluoromethyl)-[2,2'-bipyridin]-6-yl)methyl)-1H-benzo[d]imidazole (19).

An oven-dried microwave vial equipped with a magnetic stirbar was charged with **18** (58.9 mg, 0.19 mmol, 1.0 equiv), benzimidazole (22.7 mg, 0.19 mmol, 1.0 equiv), KOH (13.0 mg, 0.23 mmol, 1.2 equiv) and dry MeCN (5 mL). The resulting white heterogeneous mixture was heated at 80 °C for 24 h. The resulting pale red solution was allowed to cool to room temperature and then CH₂Cl₂ and aq. sat. NaHCO₃ were added. The layers were separated and the aqueous layer was extracted three times with CH₂Cl₂. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (10% MeOH /CH₂Cl₂) to afford **19** (65.8 mg, 82%) as a white solid. **mp** 138-140 °C. **¹H NMR** (500 MHz, CDCl₃) δ 8.86 (d, *J* = 5.0 Hz, 1H), 8.66 (s, 1H), 8.56 (s, 1H), 8.13 (s, 1H), 7.94 - 7.81 (m, 1H), 7.58 (m, 1H), 7.44 - 7.40 (m, 1H), 7.32 (m, 2H), 7.29 (s, 1H), 5.65

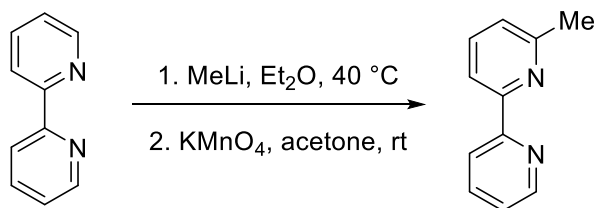
(s, 2H). ^{13}C NMR (125 MHz, CDCl_3) δ 156.9, 156.5, 155.5, 150.5, 144.0, 143.3, 141.1 (q, $J = 34.4$ Hz), 139.8 (q, $J = 34.2$ Hz), 133.9, 123.7, 122.9 (q, $J = 273.4$ Hz) 122.8, 122.6 (q, $J = 273.5$ Hz), 120.8, 120.3 (q, $J = 3.7$ Hz), 117.4 (q, $J = 3.2$ Hz), 117.3 (q, $J = 3.4$ Hz), 116.8 (q, $J = 3.5$ Hz), 50.3. **IR** (neat, cm^{-1}) 3096, 3044, 2924, 2851, 1616, 1567, 1500, 1322, 1284, 1172, 1139, 746, 669, 424. **HRMS** (HESI) calcd for $[\text{C}_{20}\text{H}_{12}\text{F}_6\text{N}_4+\text{H}]^+$: m/z 423.10389, found 423.10245.



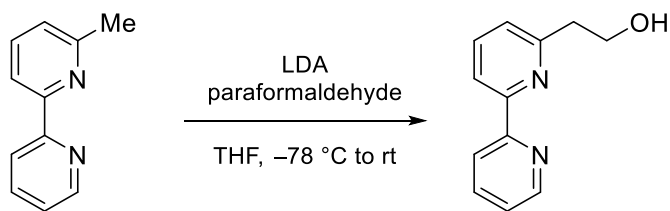
Palladium complex 6. In an inert atmosphere glove-box, an oven-dried microwave vial equipped with a magnetic stirbar was charged with **19** (50 mg, 0.12 mmol, 1.0 equiv), $\text{Pd}(\text{OAc})_2$ (26.5 mg, 0.12 mmol, 1.0 equiv) and NH_4PF_6 (21.2 mg, 0.13 mmol, 1.1 equiv). The vial was capped and taken out of the glove-box, dry MeCN (1.2 mL) was added and the reaction was heated at 75 °C for 2 hours. The reaction was allowed to cool to room temperature and then passed through a pad of celite, eluting with MeCN. After evaporation of the solvent under reduced pressure, the resulting crude was purified by recrystallization from warm CH_2Cl_2 to afford **6** (8.0 mg, 11%) as a yellow solid. **mp** 217 °C. (decomposition) ^1H NMR (500 MHz, CD_3CN) δ 8.90 (s, 2H), 8.88 (s, 2H), 8.45 (m, 2H), 8.04 (d, $J = 5.8$ Hz, 2H), 7.86 (d, $J = 8.2$ Hz, 2H), 7.82 (d, $J = 8.1$ Hz, 2H), 7.79 – 7.74 (m, 2H), 7.52 (t, $J = 8.2$ Hz, 2H), 7.37 (t, $J = 8.2$ Hz, 2H), 6.23 (d, $J = 17.2$ Hz, 2H), 5.78 (d, $J = 17.1$ Hz, 2H). ^{13}C NMR (125 MHz, CD_3CN) 161.5, 159.1, 157.4, 156.3, 152.9, 143.0 (m, 2C), 140.8, 135.3, 125.1 (m), 124.6 (m, 2C), 122.5 (m), 121.9 (m),

121.8, 116.8, 112.0, 51.5. **IR** (neat, cm^{-1}) 3657 3092, 2962, 1629, 1577, 1398, 1326, 1272, 1139, 823, 739, 682, 555, 431. **HRMS** (HESI) calcd for $[\text{C}_{40}\text{H}_{22}\text{F}_{12}\text{N}_8\text{Pd}_2]^{2+}$: m/z 526.99173, found 526.99316.

Synthesis of palladium complex **7**

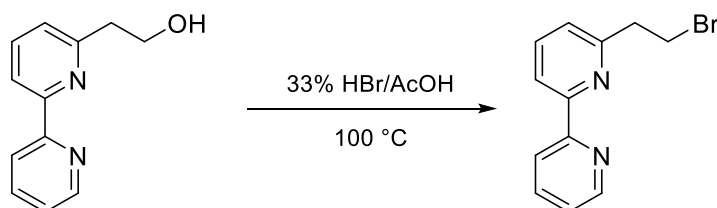


6-methyl-2,2'-bipyridine (20). An oven-dried 100 mL round-bottom flask equipped with a magnetic stirbar was charged with 2,2'-bipyridine (1.0 g, 6.4 mmol, 1.0 equiv) and dry Et₂O (40 mL) and the resulting solution was cooled to 0 °C. A solution of MeLi (4.0 mL, 1.6 M in Et₂O, 6.4 mmol, 1.0 equiv) was added dropwise, and the resulting black solution was heated to 40 °C for 3 h. The reaction was allowed to cool to room temperature and H₂O was added. The layers were separated and the aqueous layer was extracted three times with Et₂O. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford the crude **S1** an orange oil. A saturated solution of KMnO₄ in acetone (100 mL) was added, stirred for a few seconds and the mixture was filtered on Celite eluting with acetone to remove the MnO₂ precipitate. Solvents were evaporated *in vacuo* and the crude product was purified by flash chromatography (10% EtOAc/hexanes) to afford pure **S1** (503 mg, 46%) as a pale yellow oil. All analyses were consistent with previously reported data.¹⁶

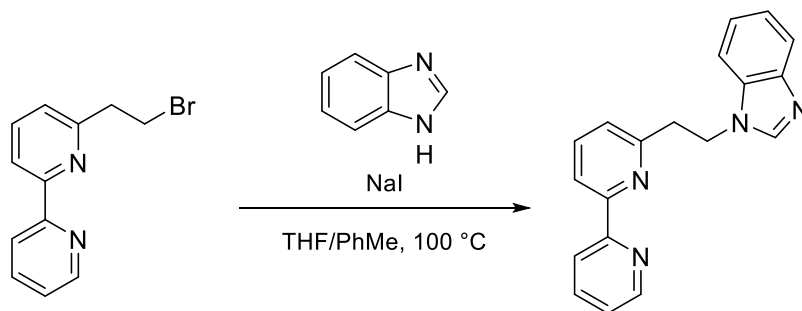


6-(2-Hydroxyethyl)-2,2'-bipyridine (21). *n*-BuLi, (2.3 M in hexanes, 3.37 mL, 7.75 mmol, 1.1 equiv), was added dropwise to a solution of diisopropylamine (784 mg, 7.75 mmol, 1.1 equiv) in THF (9 mL) at -78 °C. After 20 min a solution of **20** (1.2 g, 7.05 mmol, 1.0 equiv) in THF (15 mL)

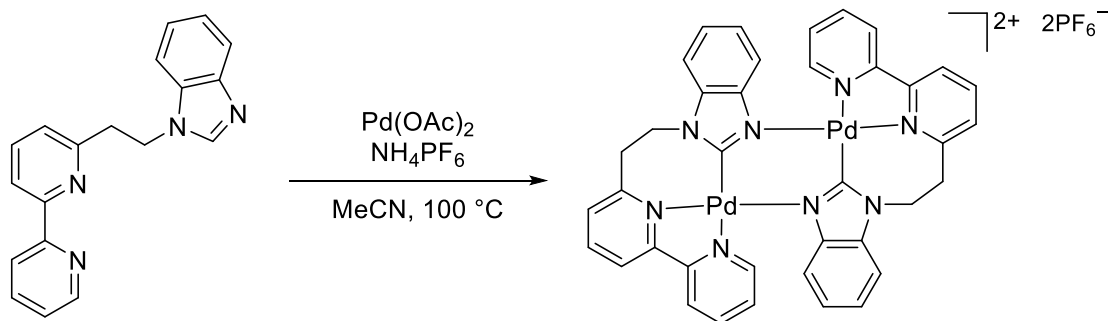
was added dropwise and the reaction stirred at -78°C for 2 hours. Anhydrous paraformaldehyde (910 mg, 30.3 mmol, 4.3 equiv) was then added as a solid and, after stirring for 1 h at -78°C , the temperature was allowed to rise to room temperature and the reaction stirred overnight. The solution was quenched with 0.5 mL saturated NH_4Cl before removing the solvent under reduced pressure. The crude product was purified by flash chromatography (1:1 CH_2Cl_2 :hexanes, then 0-5% $\text{MeOH}/\text{CH}_2\text{Cl}_2$ elution gradient) on alumina to afford **21** (330 mg, 23%) as a colorless oil. All analyses were consistent with previously reported data.²¹



6-(2-Bromoethyl)-2,2'-bipyridine (22). In a 50 mL roundbottom flask equipped with a magnetic stirbar, **21** (330 mg, 1.65 mmol) was treated with 33% HBr in AcOH (3.5 mL) and stirred at 100°C for 18 h. The reaction mixture was then allowed to cool to room temperature before adding H_2O (10 mL) and the resultant solution was then neutralised with aqueous NaOH (1.0 M) solution. The yellow solution obtained was then extracted with CH_2Cl_2 (3×10 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 . The crude compound was purified by flash chromatography (0-30% $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$ elution gradient) on silica gel to obtain **22** (332 mg, 77%) as a colorless oil. All analyses were consistent with previously reported data.²¹

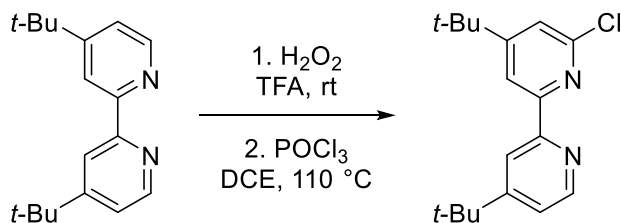


1-([2,2'-bipyridin]-6-ylmethyl)-1H-benzo[d]imidazole (23). An oven-dried roundbottom flask equipped with a magnetic stirbar was charged with **22** (1.0 g, 3.8 mmol, 1.0 equiv), benzimidazole (272.4 mg, 5.7 mmol, 1.5 equiv), NaI (57 mg, 0.38 mmol, 0.1 equiv). Dry THF (14 mL) and toluene (14 mL) were then added and the mixture was heated at 100 °C for 16 h. The reaction mixture was then allowed to cool to room temperature after which the solvent was removed under reduced pressure and crude was redissolved in CH₂Cl₂, washed with sat. NaHCO₃, dried with Na₂SO₄, and concentrated in vacuo. The crude product was purified by flash chromatography (30% EA/CH₂Cl₂ followed by 0-5% MeOH/1% Et₃N/CH₂Cl₂ elution gradient) on silica gel to afford **23** (422 mg, 37%) as a white solid. **mp** 153.7-156.2 °C. **¹H NMR** (500 MHz, CDCl₃) δ 8.70 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 8.40 (dt, *J* = 8.1, 1.1 Hz, 1H), 8.26 (d, *J* = 7.9 Hz, 1H), 7.84 (td, *J* = 7.6, 1.8 Hz, 1H), 7.80 – 7.75 (m, 2H), 7.66 (t, *J* = 7.7 Hz, 1H), 7.44 (m, 1H), 7.33 (ddd, *J* = 7.5, 4.7, 1.2 Hz, 1H), 7.30 – 7.25 (m, 3H), 6.94 (d, *J* = 7.6 Hz, 1H), 4.76 (t, *J* = 6.9 Hz, 2H), 3.40 (t, *J* = 6.9 Hz, 2H). **¹³C NMR** (150 MHz, CDCl₃) δ 156.8, 156.2, 156.1, 149.4, 144.0, 143.3, 137.7, 137.1, 133.8, 124.0, 123.7, 123.0, 122.2, 121.2, 120.6, 119.5, 109.7, 44.4, 38.1 **IR** (neat, cm⁻¹) 3059, 2919, 2850, 1726, 1583, 1560, 1457, 1419, 1281, 1145, 991, 771, 740, 634, 478, 431. **HRMS** (HESI) calcd for [C₁₉H₁₆N₄+H]⁺ : *m/z* 301.14477, found 301.14493.



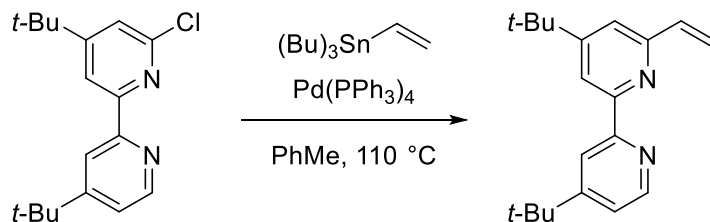
Palladium complex 7. In an inert atmosphere glove-box, an oven-dried microwave vial equipped with a magnetic stirbar was charged with **23** (70 mg, 0.23 mmol, 1.0 equiv), $\text{Pd}(\text{OAc})_2$ (51.5 mg, 0.23 mmol, 1.0 equiv) and NH_4PF_6 (41.7 mg, 0.26 mmol, 1.1 equiv). The vial was capped and taken out of the glove-box, dry MeCN (2.3 mL) was added and the reaction was heated at $100\text{ }^\circ\text{C}$ for 24 hours to yield a dark brown mixture. The reaction was allowed to cool to room temperature and then passed through a pad of celite, eluting with MeCN . The solvent was then removed under reduced pressure, and product was purified by recrystallization in $\text{Et}_2\text{O}/\text{MeCN}$ affording **7** (113 mg, 45%) as a white solid. **mp** $294\text{ }^\circ\text{C}$ (decomposition). **$^1\text{H NMR}$** (500 MHz, CD_3CN) δ 8.37 (d, $J = 8.0\text{ Hz}$, 2H), 8.34 (d, $J = 8.0\text{ Hz}$, 2H), 8.22 – 8.11 (m, 4H), 7.79 (d, $J = 8.1\text{ Hz}$, 2H), 7.72 (m, 2H), 7.65 – 7.58 (m, 4H), 7.33 (m, 4H), 7.25 (t, $J = 7.7\text{ Hz}$, 2H), 5.17 (dd, $J = 15.4, 8.5\text{ Hz}$, 2H), 4.78 (dd, $J = 15.0, 7.8\text{ Hz}$, 2H), 3.85 (dd, $J = 18.5, 7.4\text{ Hz}$, 2H), 3.26 (dd, $J = 18.7, 8.9\text{ Hz}$, 2H). **$^{13}\text{C NMR}$** (150 MHz, CD_3CN) δ 166.6, 163.0, 158.8, 156.6, 150.5, 142.5, 141.9 (2C), 135.1, 132.0, 127.8, 124.7, 123.9, 123.8, 123.7, 116.4, 111.3, 41.6, 40.5. **IR** (neat, cm^{-1}) 3651, 3441, 3097, 2924, 1603, 1575, 1454, 1395, 1323, 1170, 827, 772, 555, 435, 438. **HRMS** (HESI) calcd for $[\text{C}_{38}\text{H}_{30}\text{N}_8\text{Pd}_2]^{2+}$: m/z 405.03261, found 405.03364.

Synthesis of palladium complex 8

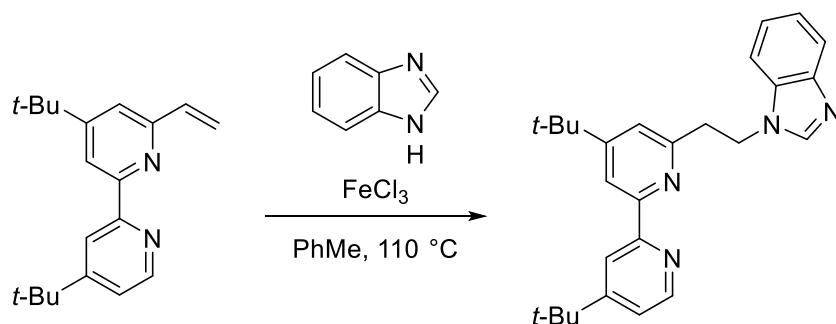


4,4'-di-tert-butyl-6-chloro-2,2'-bipyridine (24). To a solution of 4,4'-di-tert-butyl-2,2'-bipyridine (7.50 g, 28.0 mmol, 1.0 equiv) in TFA (22.5 mL) was added aq. H₂O₂ (30%, 3.3 mL) at room temperature. After stirring for 8 h at the same temperature, additional aq. H₂O₂ (30%, 3.3 mL) was then added, and the resulting solution was stirred overnight. The reaction mixture was cooled with an ice bath, neutralized with aq. saturated KOH until the solid precipitated (pH = 11), and water (45 mL) was then added (more solid precipitated). After filtration, the obtained solid was dissolved in ethyl acetate (75 mL), dried over Na₂SO₄, and concentrated in vacuo to give the 4,4'-di-tert-butyl-[2,2'-bipyridine] 1-oxide as a white solid which was used directly in the next step without further purification.

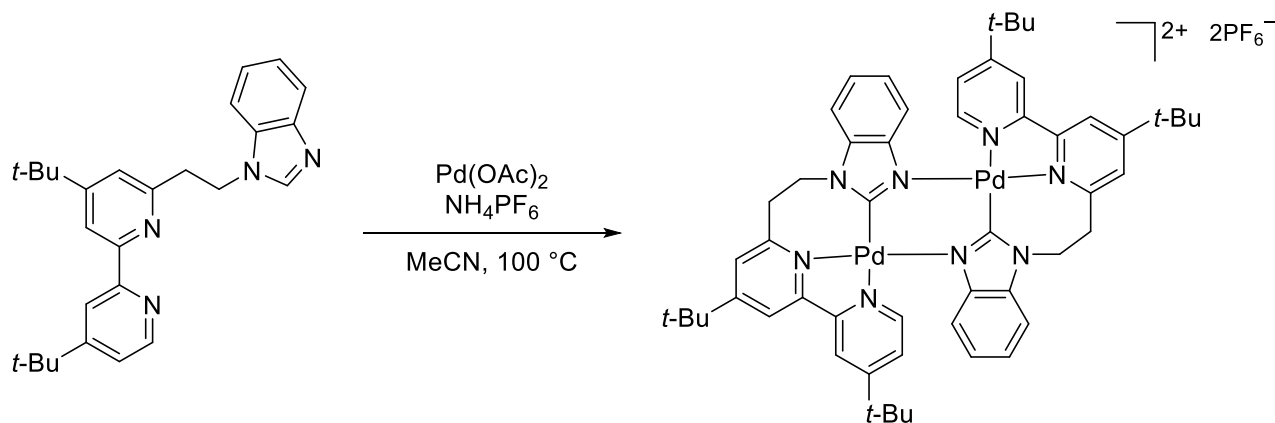
To a solution of the aforementioned 4,4'-di-tert-butyl-[2,2'-bipyridine] 1-oxide in DCE (30 mL) was added POCl₃ (4.92 mL) dropwise at 0 °C. The resulting mixture was stirred at 110 °C for 18 hours. The reaction mixture was cooled to 0 °C and neutralized by slow addition of aq. saturated Na₂CO₃. The mixture was extracted with CHCl₃ (30 mL x 3), and the combined organic layers were dried over Na₂SO₄. Crude was concentrated in vacuo and product purified by column chromatography on silica gel (0-10% EtOAc/Hexanes elution gradient) to yield **24** (4.95 g, 58%) as a white solid. All analyses were consistent with previously reported data.²²



4,4'-di-tert-butyl-6-vinyl-2,2'-bipyridine (25). In an inert atmosphere glove-box, an oven-dried microwave vial equipped with a magnetic stirbar was charged with **24** (4.95 g, 16.34 mmol, 1.0 equiv), tributyl(vinyl)tin (5.34 g, 4.94 ml, 16.83 mmol, 1.03 equiv) and tetrakis(triphenylphosphine)palladium(0) (47.2 mg, 0.408 mmol, 2.5 mol%) in toluene (23.2 mL) was refluxed for 24 h. After the reaction was cooled to room temperature, aqueous potassium fluoride was added, then resulting insoluble matter was removed by filtration. The filtrate was extracted three times with ethyl acetate, and the combined organic phases washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The product was purified by column chromatography on silica gel (0-10% EtOAc/Hexanes elution gradient) to yield **25** (4.16 g, 86%) as a white solid. **mp** 81.9 – 85.0 °C. **¹H NMR** (500 MHz, CDCl₃) δ 8.59 (dd, *J* = 5.3, 0.8 Hz, 1H), 8.53 (d, *J* = 2.1 Hz, 1H), 8.31 (d, *J* = 1.8 Hz, 1H), 7.33 (d, *J* = 1.7 Hz, 1H), 7.30 (dd, *J* = 5.3, 2.1 Hz, 1H), 6.92 (dd, *J* = 17.4, 10.8 Hz, 1H), 6.39 (dd, *J* = 17.4, 1.3 Hz, 1H), 5.51 (dd, *J* = 10.7, 1.3 Hz, 1H), 1.39 (s, 18H). **¹³C NMR** (150 MHz, CDCl₃) 161.6, 160.9, 156.7, 156.1, 154.9, 149.0, 137.5, 120.9, 118.7, 118.6, 117.8, 117.4, 35.1 (2C), 30.8, 30.7. **IR** (neat, cm⁻¹) 3095, 3014, 2963, 2902, 2867, 1585, 1542, 1475, 1374, 1270, 1201, 1142, 1001, 926, 888, 847, 727, 602, 535, 442. **HRMS** (HESI) calcd for [C₂₀H₂₆N₂+H]⁺ : *m/z* 295.21688, found 295.21694.



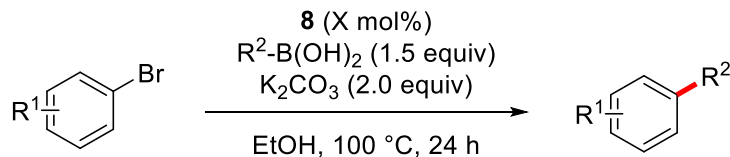
1-(2-(4,4'-di-tert-butyl-[2,2'-bipyridin]-6-yl)ethyl)-1H-benzo[d]imidazole (26). To an oven-dried microwave vial equipped with a magnetic stirbar was added benzimidazole (1.11 g, 9.42 mmol, 1.0 equiv), **25** (4.16 mmol, 14.1 mmol, 1.5 equiv), FeCl₃ (75.6 mg, 0.47 mmol, 5 mol %) and dry toluene (9.45 mL) were added and the reaction was stirred at 110 °C for 3 h. The reaction was then allowed to cool to room temperature and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (0-5% MeOH/1% Et₃N/CH₂Cl₂ elution gradient) to afford **26** (2.27 g, 58%) as a white solid. **mp** 182.4 – 183.5 °C (decomposition). **¹H NMR** (500 MHz, CDCl₃) δ 8.61 (dd, *J* = 5.2, 0.8 Hz, 1H), 8.45 (d, *J* = 1.7 Hz, 1H), 8.25 (d, *J* = 1.8 Hz, 1H), 7.83 (s, 1H), 7.80 – 7.76 (m, 1H), 7.43 – 7.39 (m, 1H), 7.33 (dd, *J* = 5.3, 1.9 Hz, 1H), 7.29 – 7.24 (m, 2H), 6.84 (d, *J* = 1.7 Hz, 1H), 4.76 (t, *J* = 6.9 Hz, 2H), 3.40 (t, *J* = 6.9 Hz, 2H), 1.41 (s, 9H), 1.24 (s, 9H). **¹³C NMR** (125 MHz, CDCl₃) δ 161.9, 161.1, 156.6, 156.5, 156.4, 149.2, 143.8, 143.2, 133.9, 123.0, 122.2, 121.0, 120.7, 120.5, 118.3, 116.8, 109.8, 44.6, 38.4, 35.1, 35.0, 30.8, 30.6. **IR** (neat, cm⁻¹) 3053, 2962, 2866, 1586, 1547, 1494, 1375, 1281, 1249, 1167, 936, 841, 751, 625, 535, 430. **HRMS** (HESI) calcd for [C₂₇H₃₂N₄+H]⁺ : *m/z* 413.26997, found 413.26970.



Palladium Complex 8. In an inert atmosphere glove-box, an oven-dried microwave vial equipped with a magnetic stirbar was charged with **26** (80 mg, 0.19 mmol, 1.0 equiv), Pd(OAc)₂ (43.5 mg, 0.19 mmol, 1.0 equiv) and NH₄PF₆ (34.8 mg, 0.21 mmol, 1.1 equiv). The vial was capped and taken out of the glove-box, dry MeCN (2.7 mL) was added and the reaction was heated at 100 °C for 24 hours to yield a dark brown mixture. The reaction was allowed to cool to room temperature and then passed through a pad of celite, eluting with MeCN. The solvent was then removed under reduced pressure, and product was purified by recrystallization in hot MeOH affording **8** (83.1 mg, 65%) as a white solid. Colorless crystals suitable for X-ray crystallography were obtained by allowing a concentrated solution of **8** in MeOH to slowly evaporate to open atmosphere at room temperature. **mp** 284 °C (decomposition). **¹H NMR** (500 MHz, CD₃CN) δ 8.31 (d, *J* = 2.0 Hz, 2H), 8.27 (d, *J* = 2.1 Hz, 2H), 7.79 (d, *J* = 8.1 Hz, 2H), 7.64 – 7.58 (m, 6H), 7.36 – 7.28 (m, 4H), 7.25 (t, *J* = 7.6 Hz 2H), 5.16 (dd, *J* = 15.1, 8.4 Hz, 1H), 4.77 (dd, *J* = 15.2, 7.4 Hz, 1H), 3.84 (dd, *J* = 18.3, 7.6 Hz, 1H), 3.20 (dd, *J* = 18.5, 9.0 Hz, 1H), 1.44 (s, 18H), 1.35 (s, 18H). **¹³C NMR** (125 MHz, CD₃CN) δ 167.1, 166.3, 166.0, 163.8, 158.7, 156.5, 150.0, 141.9, 135.1, 128.9, 124.7, 123.8, 123.6, 121.9, 121.3, 116.3, 111.2, 41.6, 40.6, 36.6, 36.5, 30.2, 30.1. **IR** (neat, cm⁻¹) 2960, 2909, 2872, 1612, 1551, 1455, 1397, 1367, 1255, 1015, 829, 735, 556, 432. **HRMS** (HESI) calcd for [C₅₄H₆₂N₈Pd₂]²⁺ : *m/z* 517.15781, found 517.15922.

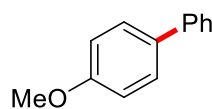
Cross-coupling reactions catalyzed by palladium complex **8**

GENERAL PROCEDURE A: Suzuki cross-coupling catalyzed by palladium complex **8**



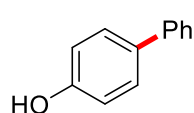
An oven-dried 5 mL microwave vial equipped with a magnetic stirbar was charged with catalyst **8** which was measured using a 2.05×10^{-4} M stock solution in MeCN. After removing the MeCN under reduced pressure, the vial was charged with the aryl bromide, then put in a nitrogen-filled glovebox where K_2CO_3 (2.0 equiv) and the boronic acid (1.5 equiv) were weighed. The vial was capped and removed from the glovebox and absolute EtOH [0.12M] was added via syringe before stirring the reaction at 100 °C for 24 hours. The reaction was allowed to cool to room temperature, Et_2O and H_2O were added, and the layers were separated. The aqueous layer was extracted three times with Et_2O , the combined organic layers were dried over Na_2SO_4 , filtered and concentrated *in vacuo* to afford the crude product, which was purified by flash chromatography (see specific procedures for individual purification conditions).

Specific procedures and characterization data for Suzuki cross-coupling products 27-54

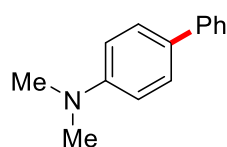


4-methoxy-1,1'-biphenyl (27). General procedure A was followed, using 4-bromoanisole (38.3 mg, 0.21 mmol, 1.0 equiv), K_2CO_3 (57.0 mg, 0.41 mmol, 2.0 equiv), phenylboronic acid (37.5 mg, 0.31 mmol, 1.5 equiv), **8** (0.008 mg, 6.1×10^{-6} mmol, 0.003 mol%) and absolute EtOH (1.7 mL), affording **27** (34.2 mg, 91%) as a white powder after purification by flash chromatography (0-5% EtOAc/Hexanes elution gradient).

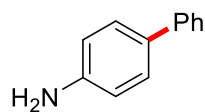
On gram scale: General procedure A was followed, using 4-bromoanisole (5.0 g, 26.7 mmol, 1.0 equiv), K_2CO_3 (7.39 g, 53.5 mmol, 2.0 equiv), phenylboronic acid (4.89 g, 40.1 mmol, 1.5 equiv), **8** (1.06 mg, 8.0×10^{-4} mmol, 0.003 mol%) and absolute EtOH (222 mL), affording **27** (4.543 g, 92%) as a white powder after purification by flash chromatography (0-5% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31a,b,c,d}



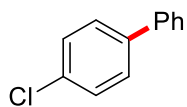
[1,1'-biphenyl]-4-ol (28). General procedure A was followed, using 4-bromophenol (35.5 mg, 0.21 mmol, 1.0 equiv), K_2CO_3 (57.0 mg, 0.41 mmol, 2.0 equiv), phenylboronic acid (37.5 mg, 0.31 mmol, 1.5 equiv), **8** (0.008 mg, 6.1×10^{-6} mmol, 0.003 mol%) and absolute EtOH (1.7 mL), affording **28** (33.1 mg, 95%) as a white powder after purification by flash chromatography (0-10% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31c,e,f}



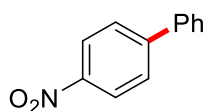
N,N-dimethyl-[1,1'-biphenyl]-4-amine (29). General procedure A was followed, using 4-bromo-N,N-dimethylaniline (41.0 mg, 0.21 mmol, 1.0 equiv), K_2CO_3 (57.0 mg, 0.41 mmol, 2.0 equiv), phenylboronic acid (37.5 mg, 0.31 mmol, 1.5 equiv), **8** (0.008 mg, 6.1×10^{-6} mmol, 0.003 mol%) and absolute EtOH (1.7 mL), affording **29** (29.1 mg, 72%) as a white powder after purification by flash chromatography (0-5% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31b}



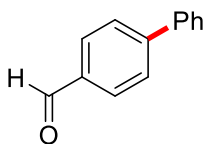
[1,1'-biphenyl]-4-amine (30). General procedure A was followed, using 4-bromoaniline (35.3 mg, 0.21 mmol, 1.0 equiv), K_2CO_3 (57.0 mg, 0.41 mmol, 2.0 equiv), phenylboronic acid (37.5 mg, 0.31 mmol, 1.5 equiv), **8** (0.008 mg, 6.1×10^{-6} mmol, 0.003 mol%) and absolute EtOH (1.7 mL), affording **30** (29.8 mg, 86%) as a white powder after purification by flash chromatography (10-20% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31c}



4-chloro-1,1'-biphenyl (31). General procedure A was followed, using 1-bromo-4-chlorobenzene (39.3 mg, 0.21 mmol, 1.0 equiv), K_2CO_3 (57.0 mg, 0.41 mmol, 2.0 equiv), phenylboronic acid (37.5 mg, 0.31 mmol, 1.5 equiv), **8** (0.008 mg, 6.1×10^{-6} mmol, 0.003 mol%) and absolute EtOH (1.7 mL), affording **31** (37.4 mg, 97%) as a white powder after purification by flash chromatography (0-5% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31c,e}

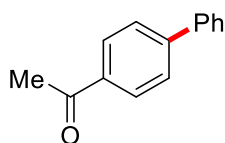


4-nitro-1,1'-biphenyl (32). General procedure A was followed, using 1-bromo-4-nitrobenzene (41.4 mg, 0.21 mmol, 1.0 equiv), K_2CO_3 (57.0 mg, 0.41 mmol, 2.0 equiv), phenylboronic acid (37.5 mg, 0.31 mmol, 1.5 equiv), **8** (0.008 mg, 6.1×10^{-6} mmol, 0.003 mol%) and absolute EtOH (1.7 mL), affording **32** (38.5 mg, 94%) as a yellow powder after purification by flash chromatography (0-5% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31e,f}

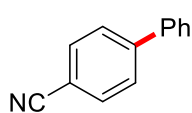


[1,1'-biphenyl]-4-carbaldehyde (33). General procedure A was followed, using 4-bromobenzaldehyde (37.9 mg, 0.21 mmol, 1.0 equiv), K_2CO_3 (57.0 mg, 0.41 mmol, 2.0 equiv), phenylboronic acid (37.5 mg, 0.31 mmol, 1.5 equiv), **8**

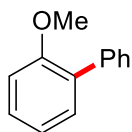
(0.008 mg, 6.1×10^{-6} mmol, 0.003 mol%) and absolute EtOH (1.7 mL), affording **33** (36.7 mg, 98%) as a white powder after purification by flash chromatography (0-5% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31d}



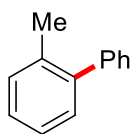
1-([1,1'-biphenyl]-4-yl)ethan-1-one (34). General procedure A was followed, using 4-bromoacetophenone (40.8 mg, 0.21 mmol, 1.0 equiv), K_2CO_3 (57.0 mg, 0.41 mmol, 2.0 equiv), phenylboronic acid (37.5 mg, 0.31 mmol, 1.5 equiv), **8** (0.008 mg, 6.1×10^{-6} mmol, 0.003 mol%) and absolute EtOH (1.7 mL), affording **34** (39.3 mg, 98%) as a white powder after purification by flash chromatography (0-5% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31c,d,e,g}



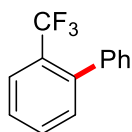
[1,1'-biphenyl]-4-carbonitrile (35). General procedure A was followed, using 4-bromobenzonitrile (37.3 mg, 0.21 mmol, 1.0 equiv), K_2CO_3 (57.0 mg, 0.41 mmol, 2.0 equiv), phenylboronic acid (37.5 mg, 0.31 mmol, 1.5 equiv), **8** (0.008 mg, 6.1×10^{-6} mmol, 0.003 mol%) and absolute EtOH (1.7 mL), affording **35** (35.0 mg, 95%) as a white powder after purification by flash chromatography (0-5% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31a,e,f}



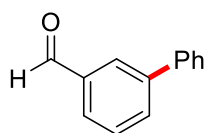
2-methoxy-1,1'-biphenyl (36). General procedure A was followed using 2-bromoanisole (38.3 mg, 0.21 mmol, 1.0 equiv), K_2CO_3 (57.0 mg, 0.41 mmol, 2.0 equiv), phenylboronic acid (37.5 mg, 0.31 mmol, 1.5 equiv), **8** (0.027 mg, 2.1×10^{-5} mmol, 0.01 mol%) and absolute EtOH (1.7 mL), and stirring the reaction at 90 °C, affording **36** (28.9 mg, 77%) as a white powder after purification by flash chromatography (0-5% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31g}



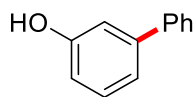
2-methyl-1,1'-biphenyl (37). General procedure A was followed, using 2-bromotoluene (35.1 mg, 0.21 mmol, 1.0 equiv), K₂CO₃ (57.0 mg, 0.41 mmol, 2.0 equiv), phenylboronic acid (37.5 mg, 0.31 mmol, 1.5 equiv), **8** (0.008 mg, 6.1 × 10⁻⁶ mmol, 0.003 mol%) and absolute EtOH (1.7 mL), affording **37** (10.9 mg, 31%) as a colorless oil after purification by flash chromatography (0-1% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31g}



2-(trifluoromethyl)-1,1'-biphenyl (38). General procedure A was followed, using 1-bromo-2-(trifluoromethyl)benzene (46.1 mg, 0.21 mmol, 1.0 equiv), K₂CO₃ (57.0 mg, 0.41 mmol, 2.0 equiv), phenylboronic acid (37.5 mg, 0.31 mmol, 1.5 equiv), **8** (0.008 mg, 6.1 × 10⁻⁶ mmol, 0.003 mol%) and absolute EtOH (1.7 mL), affording **38** (26.6 mg, 58%) as a colorless oil after purification by flash chromatography (0-1% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31h}

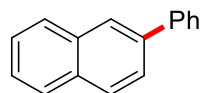


[1,1'-biphenyl]-3-carbaldehyde (39). General procedure A was followed, using 3-bromobenzaldehyde (37.9 mg, 0.21 mmol, 1.0 equiv), K₂CO₃ (57.0 mg, 0.41 mmol, 2.0 equiv), phenylboronic acid (37.5 mg, 0.31 mmol, 1.5 equiv), **8** (0.008 mg, 6.1 × 10⁻⁶ mmol, 0.003 mol%) and absolute EtOH (1.7 mL), affording **39** (30.7 mg, 87%) as a white powder after purification by flash chromatography (0-5% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31f,i}

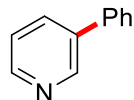


[1,1'-biphenyl]-3-ol (40). General procedure A was followed, using 3-bromophenol (35.5 mg, 0.21 mmol, 1.0 equiv), K₂CO₃ (57.0 mg, 0.41 mmol, 2.0 equiv), phenylboronic acid (37.5 mg, 0.31 mmol, 1.5 equiv), **8** (0.008 mg, 6.1 × 10⁻⁶ mmol, 0.003 mol%) and absolute EtOH (1.7 mL), affording **40** (30.3 mg, 87%) as a white powder after

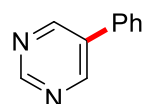
purification by flash chromatography (0-10% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31i,j}



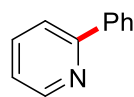
2-phenylnaphthalene (41). General procedure A was followed, using 2-bromonaphthalene (42.4 mg, 0.21 mmol, 1.0 equiv), K₂CO₃ (57.0 mg, 0.41 mmol, 2.0 equiv), phenylboronic acid (37.5 mg, 0.31 mmol, 1.5 equiv), **8** (0.008 mg, 6.1 × 10⁻⁶ mmol, 0.003 mol%) and absolute EtOH (1.7 mL), affording **41** (41.1 mg, 87%) as a white powder after purification by flash chromatography (0-1% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31f,k}



3-phenylpyridine (42). General procedure A was followed, using 3-bromopyridine (32.4 mg, 0.21 mmol, 1.0 equiv), K₂CO₃ (57.0 mg, 0.41 mmol, 2.0 equiv), phenylboronic acid (37.5 mg, 0.31 mmol, 1.5 equiv), **8** (0.008 mg, 6.1 × 10⁻⁶ mmol, 0.003 mol%) and absolute EtOH (1.7 mL), affording **42** (28.5 mg, 90%) as a white powder after purification by flash chromatography (10-20% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31g}

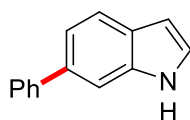


5-phenylpyrimidine (43). General procedure A was followed, using 5-bromopyrimidine (32.6 mg, 0.21 mmol, 1.0 equiv), K₂CO₃ (57.0 mg, 0.41 mmol, 2.0 equiv), phenylboronic acid (37.5 mg, 0.31 mmol, 1.5 equiv), **8** (0.008 mg, 6.1 × 10⁻⁶ mmol, 0.003 mol%) and absolute EtOH (1.7 mL), affording **43** (30.5 mg, 95%) as a white powder after purification by flash chromatography (0-25% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31a,i}

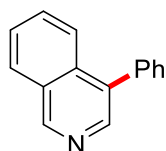


2-phenylpyridine (44). General procedure A was followed, using 2-bromopyridine (32.4 mg, 0.21 mmol, 1.0 equiv), K₂CO₃ (57.0 mg, 0.41 mmol, 2.0 equiv),

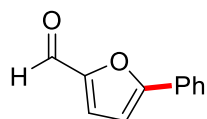
phenylboronic acid (37.5 mg, 0.31 mmol, 1.5 equiv), **8** (0.008 mg, 6.1×10^{-6} mmol, 0.003 mol%) and absolute EtOH (1.7 mL), affording **44** (26.1 mg, 82%) as a white powder after purification by flash chromatography (10-20% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31a,g}



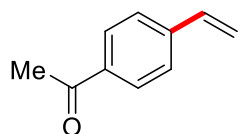
6-phenylindole (45). General procedure A was followed, using 6-bromoindole (40.2 mg, 0.21 mmol, 1.0 equiv), K_2CO_3 (57.0 mg, 0.41 mmol, 2.0 equiv), phenylboronic acid (37.5 mg, 0.31 mmol, 1.5 equiv), **8** (0.008 mg, 6.1×10^{-6} mmol, 0.003 mol%) and absolute EtOH (1.7 mL), affording **45** (39.2 mg, 99%) as a white powder after purification by flash chromatography (5-20% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31k}



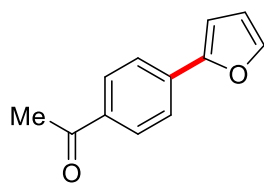
4-phenylisoquinoline (46). General procedure A was followed, using 4-bromoisoquinoline (42.6 mg, 0.21 mmol, 1.0 equiv), K_2CO_3 (57.0 mg, 0.41 mmol, 2.0 equiv), phenylboronic acid (37.5 mg, 0.31 mmol, 1.5 equiv), **8** (0.008 mg, 6.1×10^{-6} mmol, 0.003 mol%) and absolute EtOH (1.7 mL), affording **46** (36.8 mg, 87%) as a white powder after purification by flash chromatography (5-15% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31a}



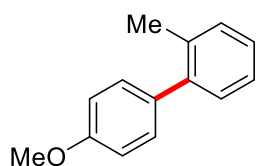
5-phenylfuran-2-carbaldehyde (47). General procedure A was followed, using 5-bromo-2-furaldehyde (35.9 mg, 0.21 mmol, 1.0 equiv), K_2CO_3 (57.0 mg, 0.41 mmol, 2.0 equiv), phenylboronic acid (37.5 mg, 0.31 mmol, 1.5 equiv), **8** (0.008 mg, 6.1×10^{-6} mmol, 0.003 mol%) and absolute EtOH (1.7 mL), affording **47** (31.0 mg, 88%) as a white powder after purification by flash chromatography (0-5% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31a,i}



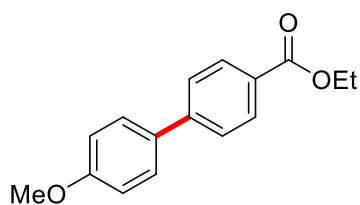
1-(4-vinylphenyl)ethan-1-one (48). General procedure A was followed, using 4-bromoacetophenone (40.8 mg, 0.21 mmol, 1.0 equiv), K_2CO_3 (57.0 mg, 0.41 mmol, 2.0 equiv), vinylboronic acid pinacol ester (47.3 mg, 0.31 mmol, 1.5 equiv), **8** (0.008 mg, 6.1×10^{-6} mmol, 0.003 mol%) and absolute EtOH (1.7 mL), affording **48** (22.3 mg, 75%) as a colorless oil after purification by flash chromatography (0-5% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31l}



1-(4-(furan-2-yl)phenyl)ethan-1-one (49). General procedure A was followed, using 4-bromoacetophenone (40.8 mg, 0.21 mmol, 1.0 equiv), K_2CO_3 (57.0 mg, 0.41 mmol, 2.0 equiv), 2-furanylboronic acid (34.4 mg, 0.31 mmol, 1.5 equiv), **8** (0.008 mg, 6.1×10^{-6} mmol, 0.003 mol%) and absolute EtOH (1.7 mL), affording **49** (37.0 mg, 97%) as a white powder after purification by flash chromatography (0-10% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31m}

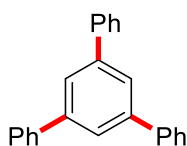


4'-methoxy-2-methyl-1,1'-biphenyl (50). General procedure A was followed, using 4-bromoanisole (38.3 mg, 0.21 mmol, 1.0 equiv), K_2CO_3 (57.0 mg, 0.41 mmol, 2.0 equiv), 2-tolylboronic acid (41.7 mg, 0.31 mmol, 1.5 equiv), **8** (0.008 mg, 6.1×10^{-6} mmol, 0.003 mol%) and absolute EtOH (1.7 mL), affording **50** (29.7 mg, 73%) as a white powder after purification by flash chromatography (0-3% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31c}

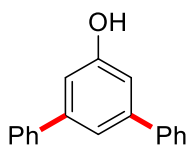


ethyl 4'-methoxy-[1,1'-biphenyl]-4-carboxylate (51). General procedure A was followed, using 4-bromoanisole (38.3 mg, 0.21 mmol, 1.0 equiv), K_2CO_3 (57.0 mg, 0.41 mmol, 2.0 equiv), 4-ethoxycarbonylphenylboronic acid (59.6 mg, 0.31 mmol, 1.5 equiv), **8** (0.008 mg, 6.1×10^{-6} mmol, 0.003 mol%) and absolute EtOH (1.7 mL), affording **51** (38.3 mg, 73%) as a white

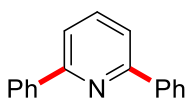
powder after purification by flash chromatography (0-5% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31f}



1,3,5-triphenylbenzene (52). General procedure A was followed, using 1,3,5-tribromobenzene (64.5 mg, 0.21 mmol, 1.0 equiv), K₂CO₃ (57.0 mg, 0.41 mmol, 2.0 equiv), phenylboronic acid (112.5 mg, 0.92 mmol, 4.5 equiv), **8** (0.027 mg, 2.1×10^{-5} mmol, 0.01 mol%) and absolute EtOH (1.7 mL), affording **52** (56.0 mg, 89%) as a white powder after purification by flash chromatography (0-1% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.³¹ⁿ

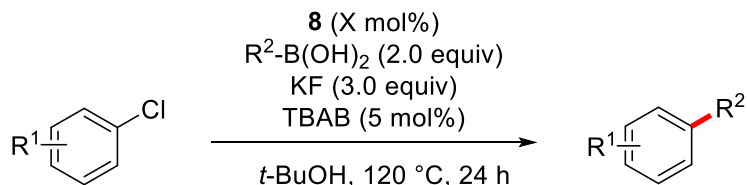


3,5-diphenylphenol (53). General procedure A was followed, using 3,5-dibromophenol (51.6 mg, 0.21 mmol, 1.0 equiv), K₂CO₃ (57.0 mg, 0.41 mmol, 2.0 equiv), phenylboronic acid (75.0 mg, 0.61 mmol, 3.0 equiv), **8** (0.008 mg, 6.1×10^{-6} mmol, 0.003 mol%) and absolute EtOH (1.7 mL), affording **53** (46.7 mg, 92%) as a white powder after purification by flash chromatography (0-15% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31j}

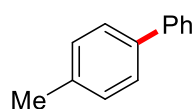


2,6-diphenylpyridine (54). General procedure A was followed, using 2,6-dibromopyridine (48.6 mg, 0.21 mmol, 1.0 equiv), K₂CO₃ (57.0 mg, 0.41 mmol, 2.0 equiv), phenylboronic acid (75.0 mg, 0.61 mmol, 3.0 equiv), **8** (0.008 mg, 6.1×10^{-6} mmol, 0.003 mol%) and absolute EtOH (1.7 mL), affording **54** (44.0 mg, 93%) as a white powder after purification by flash chromatography (0-1% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.³¹ⁿ

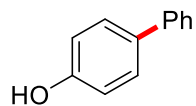
GENERAL PROCEDURE B: Suzuki cross-coupling catalyzed by palladium complex **8**



An oven-dried 5 mL microwave vial equipped with a magnetic stirbar was charged with catalyst **8** which was measured using a 2.1×10^{-3} M stock solution in MeCN. After removing the MeCN under reduced pressure, the vial was charged with the aryl chloride, then put in a nitrogen-filled glovebox where KF (3.0 equiv), the boronic acid (2.0 equiv), and TBAB (5 mol%) were weighed. The vial was capped and removed from the glovebox and *t*-BuOH [0.5M] was added via syringe before stirring the reaction at 120 °C for 24 hours. The reaction was allowed to cool to room temperature, Et₂O and H₂O were added, and the layers were separated. The aqueous layer was extracted three times with Et₂O, the combined organic layers were dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford the crude product, which was purified by flash chromatography (see specific procedures for individual purification conditions).

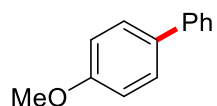


4-methyl-1,1'-biphenyl (55). General procedure B was followed, using 4-chlorotoluene (25.9 mg, 0.21 mmol, 1.0 equiv), KF (35.7 mg, 0.61 mmol, 3.0 equiv), phenylboronic acid (50.0 mg, 0.41 mmol, 2.0 equiv), TBAB (3.3 mg, 0.01 mmol, 5 mol%), **8** (2.7 mg, 2.1×10^{-3} mmol, 1.0 mol%) and absolute *t*-BuOH (0.41 mL), affording **55** (28.8 mg, 83%) as a white powder after purification by flash chromatography (100% Hexanes). All analyses were consistent with previously reported data.^{31c}

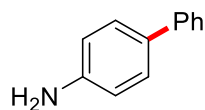


[1,1'-biphenyl]-4-ol (28). General procedure B was followed, using 4-chlorophenol (26.3 mg, 0.21 mmol, 1.0 equiv), KF (35.7 mg, 0.61 mmol, 3.0 equiv), phenylboronic acid (50.0 mg, 0.41 mmol, 2.0 equiv), TBAB (3.3 mg, 0.01 mmol, 5 mol%), **8** (2.7 mg, 2.1×10^{-3} mmol, 1.0 mol%) and absolute *t*-BuOH (0.41 mL), affording **28** (26.5 mg, 76%) as a white powder after purification by flash chromatography (0-10% EtOAc/Hexanes elution gradient).

On gram scale: General procedure B was followed, using 4-chlorophenol (1.0 g, 7.78 mmol, 1.0 equiv), KF (1.35 g, 23.3 mmol, 3.0 equiv), phenylboronic acid (1.9 g, 15.6 mmol, 2.0 equiv), TBAB (125 mg, 0.39 mmol, 5 mol%), **8** (103 mg, 7.8×10^{-2} mmol, 1.0 mol%) and absolute *t*-BuOH (15.6 mL), affording **28** (1.03 g, 78%) as a white powder after purification by flash chromatography (0-10% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31c,e}

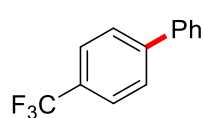


4-methoxy-1,1'-biphenyl (27). General procedure B was followed, using 4-chloroanisole (29.2 mg, 0.21 mmol, 1.0 equiv), KF (35.7 mg, 0.61 mmol, 3.0 equiv), phenylboronic acid (50.0 mg, 0.41 mmol, 2.0 equiv), TBAB (3.3 mg, 0.01 mmol, 5 mol%), **8** (2.7 mg, 2.1×10^{-3} mmol, 1.0 mol%) and absolute *t*-BuOH (0.41 mL), affording **27** (27.5 mg, 73%) as a white powder after purification by flash chromatography (0-5% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31a,b,c,d}

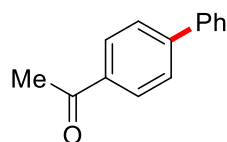


[1,1'-biphenyl]-4-amine (30). General procedure B was followed, using 4-chloroaniline (26.1 mg, 0.21 mmol, 1.0 equiv), KF (35.7 mg, 0.61 mmol, 3.0 equiv), phenylboronic acid (50.0 mg, 0.41 mmol, 2.0 equiv), TBAB (3.3 mg, 0.01 mmol, 5 mol%), **8** (2.7 mg, 2.1×10^{-3} mmol, 1.0 mol%) and absolute *t*-BuOH (0.41 mL),

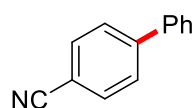
affording **30** (29.4 mg, 85%) as a white powder after purification by flash chromatography (10-20% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31c}



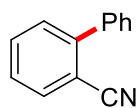
4-(trifluoromethyl)-1,1'-biphenyl (56). General procedure B was followed, using 4-chlorobenzotrifluoride (37.0 mg, 0.21 mmol, 1.0 equiv), KF (35.7 mg, 0.61 mmol, 3.0 equiv), phenylboronic acid (50.0 mg, 0.41 mmol, 2.0 equiv), TBAB (3.3 mg, 0.01 mmol, 5 mol%), **8** (2.7 mg, 2.1×10^{-3} mmol, 1.0 mol%) and absolute *t*-BuOH (0.41 mL), affording **56** (38.7 mg, 85%) as a white powder after purification by flash chromatography (0-1% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31g}



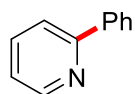
1-([1,1'-biphenyl]-4-yl)ethan-1-one (34). General procedure B was followed, using 4-chloroacetophenone (31.7 mg, 0.21 mmol, 1.0 equiv), KF (35.7 mg, 0.61 mmol, 3.0 equiv), phenylboronic acid (50.0 mg, 0.41 mmol, 2.0 equiv), TBAB (3.3 mg, 0.01 mmol, 5 mol%), **8** (0.27 mg, 2.1×10^{-4} mmol, 0.1 mol%) and absolute *t*-BuOH (0.41 mL), affording **34** (38.0 mg, 94%) as a white powder after purification by flash chromatography (0-5% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31c,d,g}



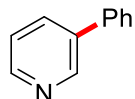
[1,1'-biphenyl]-4-carbonitrile (35). General procedure B was followed, using 4-chlorobenzonitrile (28.2 mg, 0.21 mmol, 1.0 equiv), KF (35.7 mg, 0.61 mmol, 3.0 equiv), phenylboronic acid (50.0 mg, 0.41 mmol, 2.0 equiv), TBAB (3.3 mg, 0.01 mmol, 5 mol%), **8** (0.27 mg, 2.1×10^{-4} mmol, 0.1 mol%) and absolute *t*-BuOH (0.41 mL), affording **35** (33.8 mg, 94%) as a white powder after purification by flash chromatography (0-5% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31a,c}



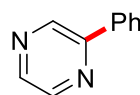
[1,1'-biphenyl]-2-carbonitrile (57). General procedure B was followed, using 4-chlorobenzonitrile (28.2 mg, 0.21 mmol, 1.0 equiv), KF (35.7 mg, 0.61 mmol, 3.0 equiv), phenylboronic acid (50.0 mg, 0.41 mmol, 2.0 equiv), TBAB (3.3 mg, 0.01 mmol, 5 mol%), **8** (0.27 mg, 2.1×10^{-4} mmol, 0.1 mol%) and absolute *t*-BuOH (0.41 mL), affording **57** (30.4 mg, 82%) as a white powder after purification by flash chromatography (0-5% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31o}



2-phenylpyridine (44). General procedure B was followed, using 2-chlorobenzene (23.3 mg, 0.21 mmol, 1.0 equiv), KF (35.7 mg, 0.61 mmol, 3.0 equiv), phenylboronic acid (50.0 mg, 0.41 mmol, 2.0 equiv), TBAB (3.3 mg, 0.01 mmol, 5 mol%), **8** (0.27 mg, 2.1×10^{-4} mmol, 0.1 mol%) and absolute *t*-BuOH (0.41 mL), affording **44** (25.8 mg, 81%) as a white powder after purification by flash chromatography (10-20% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31a,g}

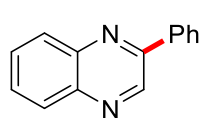


3-phenylpyridine (42). General procedure B was followed, using 3-chloropyridine (23.3 mg, 0.21 mmol, 1.0 equiv), KF (35.7 mg, 0.61 mmol, 3.0 equiv), phenylboronic acid (50.0 mg, 0.41 mmol, 2.0 equiv), TBAB (3.3 mg, 0.01 mmol, 5 mol%), and absolute *t*-BuOH (0.41 mL), **8** (2.7 mg, 2.1×10^{-3} mmol, 1.0 mol%) affording **42** (23.9 mg, 75%) as a white powder after purification by flash chromatography (10-20% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31a,g}

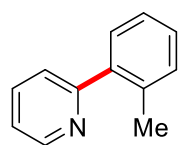


2-phenylpyrazine (58). General procedure B was followed, using 2-chloropyrazine (23.5 mg, 0.21 mmol, 1.0 equiv), KF (35.7 mg, 0.61 mmol, 3.0 equiv), phenylboronic acid (50.0 mg, 0.41 mmol, 2.0 equiv), TBAB (3.3 mg, 0.01 mmol, 5 mol%), **8** (0.27 mg, 2.1×10^{-4} mmol, 0.1 mol%) and absolute *t*-BuOH (0.41 mL), affording **58** (26.1 mg,

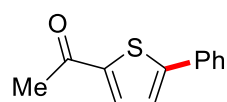
82%) as a white powder after purification by flash chromatography (0-20% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31p}



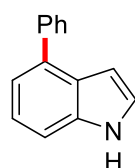
2-phenylquinoxaline (59). General procedure B was followed, using 2-chloroquinoxaline (33.7 mg, 0.21 mmol, 1.0 equiv), KF (35.7 mg, 0.61 mmol, 3.0 equiv), phenylboronic acid (50.0 mg, 0.41 mmol, 2.0 equiv), TBAB (3.3 mg, 0.01 mmol, 5 mol%), **8** (0.27 mg, 2.1×10^{-4} mmol, 0.1 mol%) and absolute *t*-BuOH (0.41 mL), affording **59** (33.1 mg, 78%) as a white powder after purification by flash chromatography (0-15% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31p}



2-(*o*-tolyl)pyridine (60). General procedure B was followed, using 2-chloropyridine (23.3 mg, 0.21 mmol, 1.0 equiv), KF (35.7 mg, 0.61 mmol, 3.0 equiv), 2-tolylboronic acid (55.7 mg, 0.41 mmol, 2.0 equiv), TBAB (3.3 mg, 0.01 mmol, 5 mol%), and absolute *t*-BuOH (0.41 mL), **8** (2.7 mg, 2.1×10^{-3} mmol, 1.0 mol%) affording **60** (22.9 mg, 66%) as a white powder after purification by flash chromatography (0-25% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{13c}

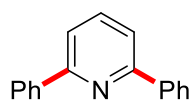


2-acetyl-5-phenylthiophene (61). General procedure B was followed, using 2-acetyl-5-chlorothiophene (32.9 mg, 0.21 mmol, 1.0 equiv), KF (35.7 mg, 0.61 mmol, 3.0 equiv), phenylboronic acid (50.0 mg, 0.41 mmol, 2.0 equiv), TBAB (3.3 mg, 0.01 mmol, 5 mol%), and absolute *t*-BuOH (0.41 mL), **8** (2.7 mg, 2.1×10^{-3} mmol, 1.0 mol%) affording **61** (29.7 mg, 72%) as a yellow powder after purification by flash chromatography (0-5% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31e}

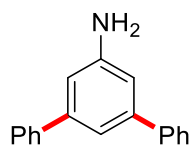


4-phenylindole (62). General procedure B was followed, using 4-chloroindole (31.1 mg, 0.21 mmol, 1.0 equiv), KF (35.7 mg, 0.61 mmol, 3.0 equiv), phenylboronic acid

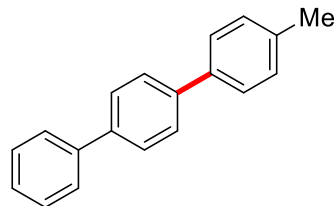
(50.0 mg, 0.41 mmol, 2.0 equiv), TBAB (3.3 mg, 0.01 mmol, 5 mol%), and absolute *t*-BuOH (0.41 mL), **8** (2.7 mg, 2.1×10^{-3} mmol, 1.0 mol%) affording **62** (32.0 mg, 81%) as a white powder after purification by flash chromatography (5-20% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31q}



2,6-diphenylpyridine (54). General procedure B was followed, using 2,6-dichloropyridine (30.3 mg, 0.21 mmol, 1.0 equiv), KF (35.7 mg, 0.61 mmol, 3.0 equiv), phenylboronic acid (100.0 mg, 0.82 mmol, 4.0 equiv), TBAB (3.3 mg, 0.01 mmol, 5 mol%), and absolute *t*-BuOH (0.41 mL), **8** (2.7 mg, 2.1×10^{-3} mmol, 1.0 mol%) affording **54** (39.4 mg, 83%) as a white powder after purification by flash chromatography (0-1% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.³¹ⁿ



3,5-diphenylaniline (63). General procedure B was followed, using 3,5-dichloroaniline (33.2 mg, 0.21 mmol, 1.0 equiv), KF (35.7 mg, 0.61 mmol, 3.0 equiv), phenylboronic acid (100.0 mg, 0.82 mmol, 4.0 equiv), TBAB (3.3 mg, 0.01 mmol, 5 mol%), and absolute *t*-BuOH (0.41 mL), **8** (4.1 mg, 3.1×10^{-3} mmol, 1.5 mol%) affording **63** (46.0 mg, 91%) as a white powder after purification by flash chromatography (0-15% EtOAc/Hexanes elution gradient). All analyses were consistent with previously reported data.^{31r}



4-(4-Methylphenyl)biphenyl (64). General procedure B was followed, using **31** (37.3 mg, 0.20 mmol, 1.0 equiv), KF (34.5 mg, 0.60 mmol, 3.0 equiv), 4-tolylboronic acid (53.7 mg, 0.40 mmol, 2.0 equiv), TBAB (3.3 mg, 0.01 mmol, 5 mol%), and absolute *t*-BuOH (0.40 mL), **8** (5.2 mg, 4.0×10^{-3} mmol, 2.0 mol%) affording **64** (41.7 mg, 86%) as a white powder after purification by flash chromatography (100% Hexanes). All analyses were consistent with previously reported data.^{31s}

CHAPTER 2

Expedient Synthesis of Bis(imidazolium) Dichloride Salts and Bis(NHC) Complexes from Imidazoles Using DMSO as a Key Polar Additive

Penn, K. R.; Anders, E. J.; Lindsay, V. N. G. *Organometallics* **2021**, *40*, 3871-3875.

2.1 Introduction to Bis(azolium) Salts and Bis(NHC) Metal Complexes

N-Heterocyclic Carbenes (NHCs) are commonly used as a superior alternative to phosphine ligands for metal catalysis as they are able to bind to most transition metals and exhibit characteristics similar to other strong σ -donating ligands in metal coordination chemistry. NHC ligands are often employed in metal-catalyzed reactions due to their high stability and tolerance for harsh reaction conditions such as high temperatures and the presence of moisture.³² The Nolan group concluded that NHCs “behave as better donors than the best phosphine ligands with the exception of sterically demanding (e.g. adamantyl) carbenes”.³³ While there are many well-studied examples of monodentate NHCs, the use of alkane-bridged chelating bis(carbenes) as ligands in catalysis has only more recently been reported, demonstrating impressive stability and activity in metal catalysis. These bis(NHC)-metal complexes are thought to be even more stable than monodentate NHC complexes due to their conformationally restrictive structure, which impedes reductive elimination and subsequent decomposition of the carbene.³² Figure 2.1 depicts a representative family of palladium-bound bis(azolium)dichloride NHC.

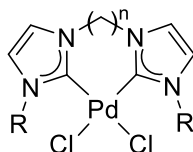


Figure 2.1 General structure of palladium-bis(NHC) complexes

Bis(azolium)dichloride salts constitute stable and convenient precursors for metal bis(carbene) catalysts useful for a wide range of reactions including C–H functionalization, C–C, C–N, and C–O bond formation.^{32,34} Furthermore, bis(NHC) complexes of gold have been used as halide sensors³⁵ and iridium(III)-bis(NHC) complexes have been studied for their anticancer activity.³⁶ Bis(azolium) salts have also been employed as ionic liquids³⁷ and as thermochromic and photoluminescent materials,³⁸ often accessed from the bis(azolium) dichloride derivatives via anion exchange. Despite the broad utility of bis(azolium) dichloride salts, their current syntheses suffer from low yields and often exhibit a limited scope.^{32,39} Analogous dihalide salts such as bis(azolium)dibromides and diiodides can be accessed in higher yields, but their utility is limited by the lower stability of their corresponding metal complexes.⁴⁰ With these factors in mind, straightforward and high-yielding methods for the synthesis of bis(azolium) dichloride salts are expected to be highly valuable and useful to chemists in a variety of research fields.

2.2 Problems in the Synthesis of Bis(azolium)dichloride Salts

Currently, one method for synthesizing bis(azolium)dichloride salts from imidazoles and dichloromethane seeks to overcome the energy barrier of the difficult S_N2 reaction by heating to high temperatures in PEG 200 as solvent.³² While this synthetic route does work with a variety of imidazoles when other dichloroalkanes (e.g. dichloroethane) are used, notable problems exist in the efficiency of this reaction with CH₂Cl₂, evidenced by moderate yields such as 65% for **66**. The use of high temperatures for a prolonged period of time in combination with the use of

volatile reactants such as CH_2Cl_2 can potentially result in the loss of reagent and thereby lead to lower yields and scalability issues. More recently, Harwood showed that the reaction could be accelerated by applying ultra-high pressure and achieved quantitative yield for **66** (Figure 2.2b).³⁹ This approach, however, is not general as yields decrease significantly with a larger alkyl substituent at the *N*-position. In addition, the need for an ultra-high pressure apparatus renders this route less practical and may pose scalability issues.

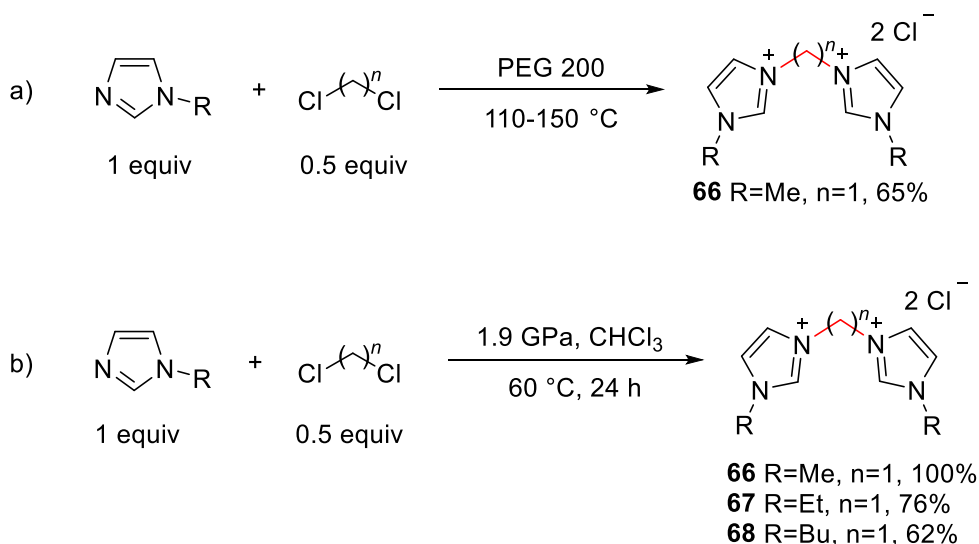


Figure 2.2 Current methods for accessing bis(azolium)dichloride salts

The aforementioned methods use exactly 1 equivalent of the imidazole derivative such as 1-methylimidazole and 0.5 equivalent of dichloroalkane, perhaps in fear that the reaction would get stuck at the mono-bisazolium intermediate if using an excess of dichloroalkane (Figure 2.3). While the risk of the reaction stopping at a mono(azolium) intermediate had been suggested as a limitation of the reaction in previous studies, Wamser showed that for an analogous transformation, the reaction of dichloromethane and pyridine derivatives to form bis(pyridinium) dichloride salts, the mono-substituted pyridinium intermediate is never detected (Figure 2.4).⁴¹ This was explained by the fact that, in the reaction of 4-(dimethylamino)pyridine and CH_2Cl_2 ,

the second substitution (k_2) is significantly faster than the first (k_1), having second-order rate constants of $4.29(\pm 0.01) \times 10^{-4}$ and $2.56(\pm 0.06) \times 10^{-8} \text{ M}^{-1} \text{ s}^{-1}$, respectively.⁴¹ Because pyridine ($N=12.0$) and 1-methylimidazole ($N=11.9$) have very comparable nucleophilicities,⁴² we hypothesized that using an excess CH_2Cl_2 in the formation of bis(azolium) chloride salts from imidazoles should proceed without formation of the undesired monosubstituted intermediate and that this approach could eventually lead to a more efficient and high-yielding route to these compounds.

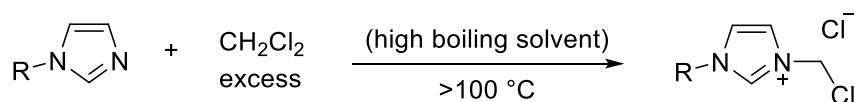


Figure 2.3 Proposed undesired monosubstituted product using excess CH_2Cl_2 as reagent

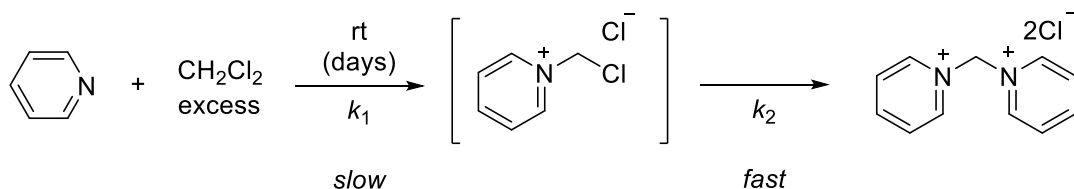
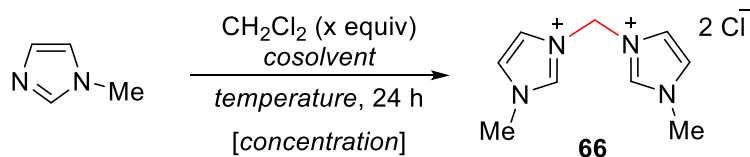


Figure 2.4 Literature reaction kinetic studies of pyridine and excess CH_2Cl_2

2.3 Optimization of Bis(azolium) Dichloride Salt Synthesis

Initial reaction optimization began with 1-methylimidazole and a large excess of CH_2Cl_2 stirring at $70 \text{ } ^\circ\text{C}$ for 24 hours in a sealed microwave vial (Table 2.1, entries 1-19). We first evaluated a range of different co-solvents and found that DMSO was the most effective in accelerating the reaction (entry 19), presumably due to its high polarity, allowing improved stabilization of the $\text{S}_{\text{N}}2$ transition state. Next, the concentration and temperature were adjusted

(entries 20-24) until we observed near-quantitative NMR yield and measured an isolated yield of 94% using three equivalents of CH_2Cl_2 at a concentration of 4.0M (entry 24).

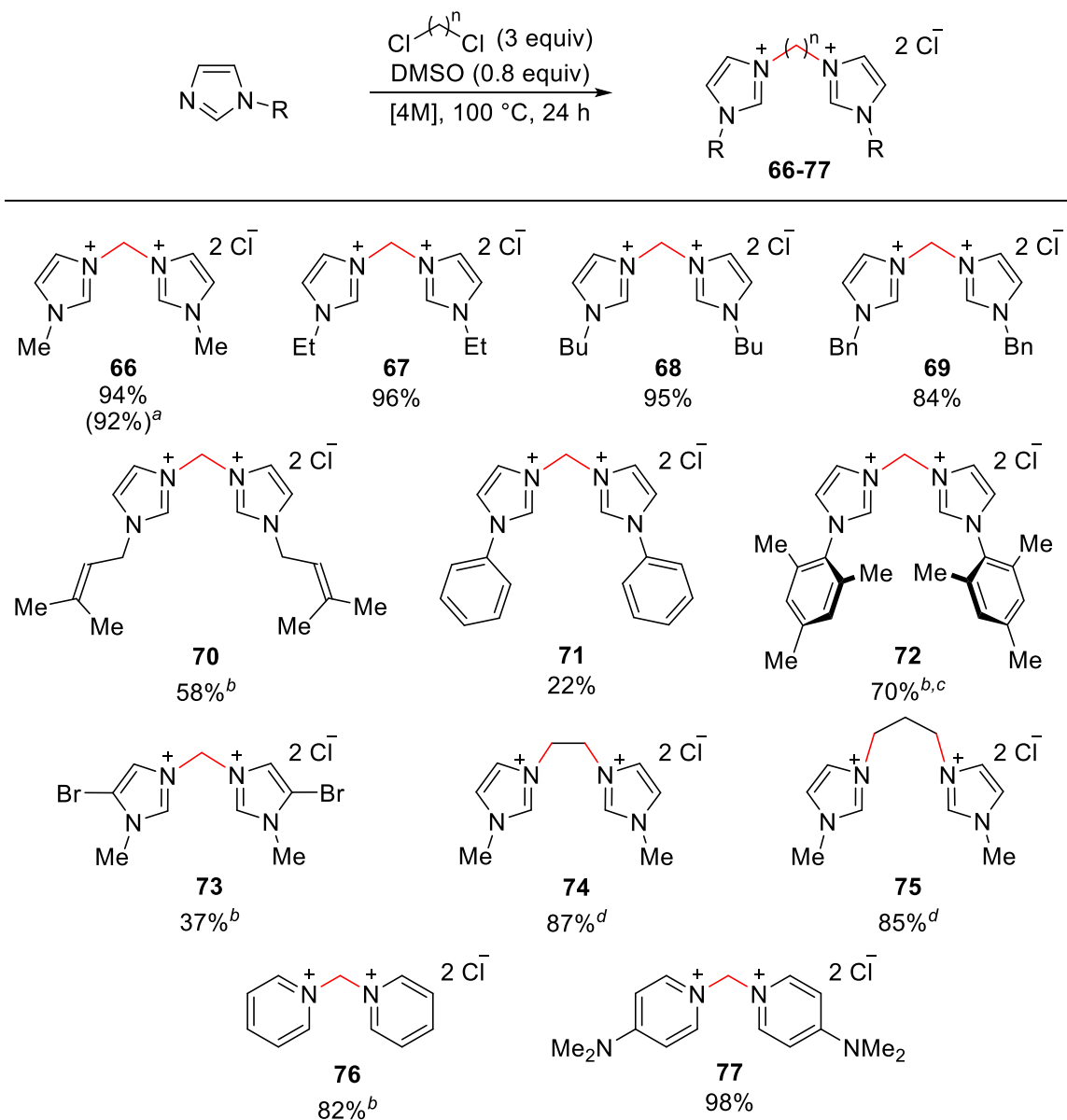
Table 2.1 Optimization of the formation of bis(imidazolium) dichloride **66**

Entry	Cosolvent	Conc. (M)	Temp. (°C)	Yield 66 ^a (%)
1	-	2.0	70	7
2	MeCN	2.0	70	5
3	PhMe	2.0	70	2
4	MeOH	2.0	70	2
5	THF	2.0	70	2
6	Et ₂ O	2.0	70	4
7	DMF	2.0	70	7
9	iPrOH	2.0	70	3
10	<i>n</i> -BuOAc	2.0	70	2
11	H ₂ O	2.0	70	1
12	PhH	2.0	70	3
13	1,4-dioxane	2.0	70	3
14	<i>n</i> -PrOH	2.0	70	0
15	CyH	2.0	70	8
16	tBuOH	2.0	70	3
17	DME	2.0	70	13
19	DMSO	2.0	70	16
20	DMSO	2.0	90	55
21	DMSO	3.0	90	76
22	DMSO	4.0	90	84
23	DMSO	4.0	100	98
24	DMSO	4.0	100	94 ^b

^a NMR yield determined using 1,3,5-trimethoxybenzene as internal standard. ^b Isolated yield.

2.4 Scope Expansion of Bis(azolium) Dichloride Salts

After developing an improved methodology for the synthesis of the model bis(imidazolium) dichloride salt **66**, we applied the optimized conditions to other imidazoles and pyridine derivatives, as well as longer dichloroalkanes. Good to excellent yields were achieved with various alkyl-functionalized imidazoles (**66-69**) and other *N*-heterocycles (Figure 2.5). The bis(phenylimidazole) product **71** was produced in a low 22% yield, even after attempts to push the reaction by increasing the reaction time and temperature, presumably due to the lower nucleophilicity of the 1-phenylimidazole substrate. In addition to bis(imidazolium) derivatives, bis(pyridinium) dichloride salts **76** and **77** were produced in good to excellent yields. With longer dichloroalkanes such as dichloroethane and dichloropropane, an excess of dichloroalkane was not necessary so 0.5 equivalents were used in both cases to reach yields over 80% for **74** and **75**.



^aIsolated yield on a 20 mmol (1.64 g) scale of N-methylimidazole. ^bReaction was performed for 48 h. ^cReaction was performed at 110 °C. ^d0.5 equiv of dichloroalkane was used.

Figure 2.5 Scope of bis(azolium)dichloride salts (completed with Evan Anders)

2.5 One-pot Synthesis of Metal-bis(NHC) Complexes

After finding our method to have great utility in accessing various bis(azolium)dichloride salt complexes, we then demonstrated how this method can be utilized to form metal-NHC

complexes in one-pot by applying known conditions from previous literature reports to unisolated **66** (Figure 2.6). Using our telescoped or one-pot, method we were able to make complexes of palladium, silver, and gold directly from 1-methylimidazole. The Pd(II) complex **78** is an effective catalyst for cross-coupling reactions^{34b,c} and C—H activation of alkanes.^{32,34i} The dinuclear Ag(I) complex **79** is commonly used as a precursor to synthesize other metal complexes as the carbene ligands can easily be transferred to another metal center.^{36,43}

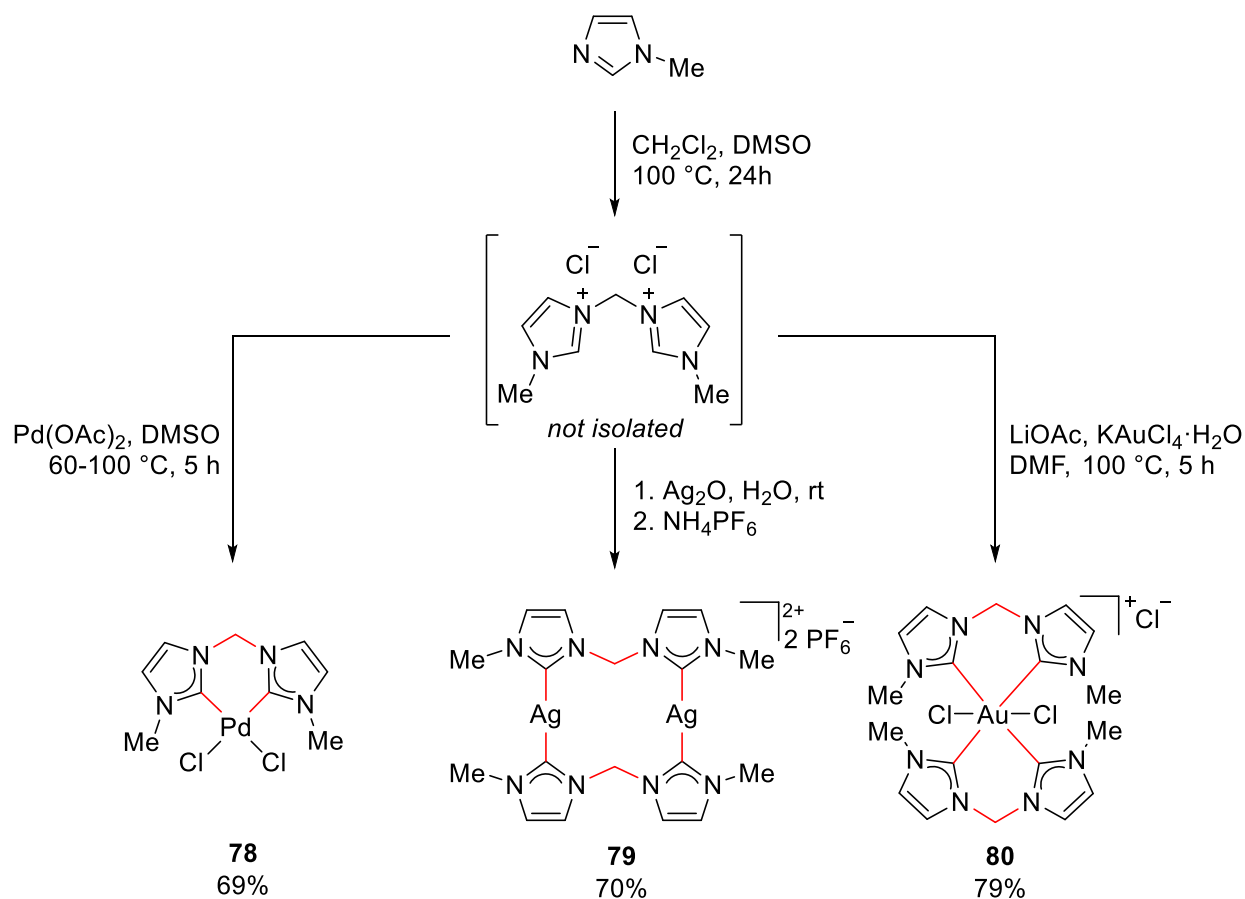


Figure 2.6 Telescoped synthesis of bis(NHC) metal complexes directly from imidazole

2.6 Conclusions

An improved and convenient methodology for the synthesis of bis(azolium) salts from imidazoles and dichloroalkanes is reported and shown to be a high-yielding, general, and practical method for accessing these compounds. Known limitations of the reaction, specifically in accessing methylene-bridged bis(azolium) salts, were addressed by using an excess of CH_2Cl_2 and a cosolvent, DMSO, which improves conversion presumably by stabilizing the $\text{S}_{\text{N}}2$ transition state. The method was also shown to be effective in accessing bis(NHC) metal complexes in a telescoped manner, exemplified by forming bis(NHC) complexes of palladium, silver, and gold.

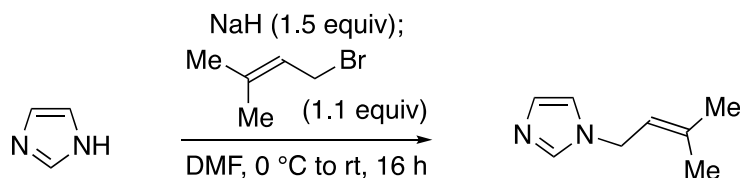
2.7 Experimental

General: Unless stated otherwise, all non-aqueous reactions were performed in oven-dried glassware sealed with microwave caps or rubber septa under a nitrogen atmosphere, and were stirred with Teflon-coated magnetic stir bars.²⁷ Liquid reagents and solvents were transferred via syringe using standard Schlenk techniques. Tetrahydrofuran (THF), toluene (PhMe), acetonitrile (MeCN), dichloromethane (CH₂Cl₂), diethyl ether (Et₂O) and methanol (MeOH) were dried by passage over a column of activated alumina (JC Meyers Solvent System). Anhydrous dimethylformamide (DMF), 1,2-dichloroethane (DCE) and dimethyl sulfoxide (DMSO) were purchased in sealed bottles and used as received. All other solvents were used as received unless otherwise noted. Thin layer chromatography (TLC) was performed using Silicycle silica gel 60 F-254 precoated plates (0.25 mm) and visualized by UV irradiation and anisaldehyde, CAM, potassium permanganate or iodine stain. Sorbent silica gel (particle size 40-63 μm) was used for flash chromatography of the indicated solvent system according to standard techniques.²⁸ Flash chromatography was performed on a Biotage Isolera One. Nuclear magnetic resonance (NMR) spectra (¹H, ¹³C) were recorded on Bruker spectrometers operating at either 500, 600, or 700 MHz for ¹H and 125, 150 or 175 MHz for ¹³C experiments. Chemical shifts (δ) for ¹H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (dimethylsulfoxide-*d*₆, δ 2.50 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet and br = broad), coupling constant in Hz, and integration. Chemical shifts for ¹³C NMR spectra are recorded in parts per million from tetramethylsilane using the central peak of dimethylsulfoxide-*d*₆ (δ 39.52 ppm) or sodium trimethylsilylpropanesulfonate (DSS) (δ 0.00 ppm) as the internal standard. All spectra were obtained with complete proton decoupling. Only select ¹H and ¹³C

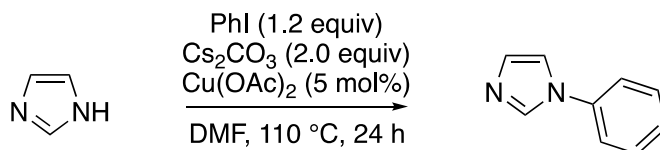
spectra are reported. Infrared (IR) spectra were collected on a Thermo Scientific Nicolet iS5 FTIR instrument using attenuated total reflectance (ATR) mode and signals are reported in reciprocal centimeters (cm^{-1}) and rounded to 1 cm^{-1} . Only selected IR frequencies are reported. Melting points were collected on Mettler Toledo MP50 melting point system. High-resolution mass spectral data (HRMS) were obtained from the NC State University Molecular Education, Technology and Research Innovation Center (METRIC), on a Thermo Fisher Scientific Exactive Plus (ion trap mass analyzer, Orbitrap™) using EI or HESI.

Reagents: *N*-methylimidazole, *N*-ethylimidazole, *N*-butylimidazole, *N*-benzylimidazole, 5-bromo-1-methylimidazole, imidazole, pyridine, 4-dimethylaminopyridine (DMAP), sodium hydride (60% w/w in mineral oil), 3,3-dimethylallyl bromide, iodobenzene, potassium phosphate tribasic, copper(I) iodide, formaldehyde (37% w/w in H_2O), glyoxal (40% w/w in H_2O), ammonium acetate and 1,3-dichloropropane were purchased from commercial sources and used without further purification.

Specific procedures and characterization data for *N*-substituted imidazoles 81-83

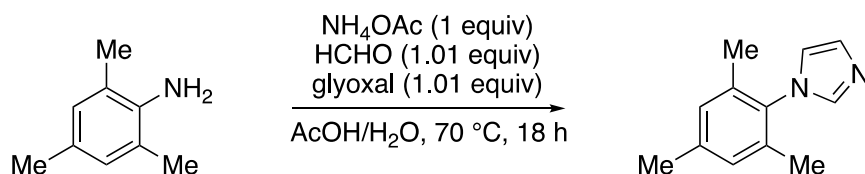


1-(3-methylbut-2-en-1-yl)-1H-imidazole (81). An oven-dried 50 mL round bottom flask equipped with a magnetic stirbar was charged with sodium hydride (60% w/w in mineral oil, 438 mg, 10.9 mmol, 1.5 equiv) and flushed with nitrogen. A solution of imidazole (0.5 g, 7.34 mmol, 1.0 equiv) in anhydrous DMF (15 mL) was added and the resulting mixture was stirred for 30 minutes at room temperature, then cooled to 0 °C. 3,3-Dimethylallyl bromide (0.93 mL, 8.05 mmol, 1.1 equiv) was added at 0 °C and the resulting solution was left to slowly warm to room temperature and stirred for 16 hours. After this time, the reaction was quenched by slow addition of aq. sat. NaHCO₃ and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried with MgSO₄, and concentrated under vacuum to afford the pure imidazole **81** (781 mg, 78%) as a colorless oil after purification by flash chromatography, eluting with 0-10% MeOH in CH₂Cl₂ (elution gradient). All analyses were consistent with the previously reported data.⁴⁴



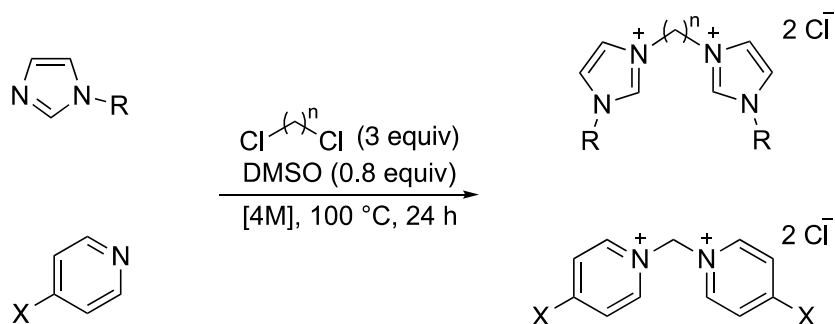
1-phenyl-1H-imidazole (82). An oven-dried 20 mL microwave vial equipped with a magnetic stirbar was charged with Cu(OAc)₂ (45.4 mg, 0.25 mmol, 0.05 equiv), iodobenzene (670 μL, 6.0 mmol, 1.2 equiv), imidazole (340 mg, 5.0 mmol, 1.0 equiv) and Cs₂CO₃ (3.26 g, 10.0 mmol, 2.0

equiv), the vial was capped and flushed with nitrogen and anhydrous DMF (10 mL) was added. The resulting mixture was heated to 110 °C for 24 hours, then cooled to room temperature, diluted with H₂O and extracted with EtOAc. The combined organic layers were washed four times with brine, dried over MgSO₄ and concentrated under vacuum. The resulting crude product was purified by flash chromatography, eluting with 1-10% MeOH in CH₂Cl₂ (elution gradient), affording the pure imidazole **82** (612 mg, 85%) as a pale yellow oil. All analyses were consistent with the previously reported data.⁴⁵



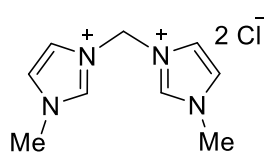
1-mesityl-1H-imidazole (83). To a 100 mL round bottom flask equipped with a magnetic stirbar was added formaldehyde (37% w/w in H₂O, 3.0 mL, 40.4 mmol, 1.01 equiv), glyoxal (40% w/w in H₂O, 4.6 mL, 40.4 mmol, 1.01 equiv), and glacial acetic acid (10 mL) and the resulting solution was heated to 70 °C. In a 25 mL flask was prepared a solution of 2,4,6-trimethylaniline (5.41 g, 40.0 mmol, 1.0 equiv) and ammonium acetate (3.08 g, 40.0 mmol, 1.0 equiv) in H₂O (2 mL) and glacial acetic acid (10 mL) and added dropwise to the reaction mixture at 70 °C and kept at that temperature for 18 hours. After this time, the reaction was cooled to room temperature and the resulting brown heterogenous mixture was poured very slowly to a stirred 1.2 M aqueous NaHCO₃ solution, causing the precipitation of the crude product as a brown solid. The brown precipitate was filtered off and dried under vacuum, then purified by flash chromatography using 1-15% MeOH in CH₂Cl₂ (elution gradient), affording the pure imidazole **83** as a pale brown solid (4.64 g, 62%). All analyses were consistent with the previously reported data.⁴⁶

General procedure for the synthesis of bis(imidazolium) and bis(pyridinium) dichloride salts 66-77



An oven-dried 5 mL microwave vial equipped with a magnetic stirbar was charged with the imidazole or pyridine substrate (4.0 mmol, 1.0 equiv), capped and flushed with N₂. The anhydrous dichloroalkane (12.0 mmol, 3.0 equiv) and DMSO (0.23 mL, 3.2 mmol, 0.8 equiv) were added and the resulting homogenous solution was stirred at 100 °C for 24 hours. The resulting white heterogenous mixture was allowed to cool to room temperature, anhydrous Et₂O (5 mL) was added and the mixture was stirred at room temperature for 5 minutes to break the clumps of solid product (sonicate if necessary). The resulting white suspension was then filtered over a pad of Celite, rinsing with Et₂O (3 x 25 mL) to remove the excess dichloroalkane, trace remaining substrate and DMSO cosolvent. The filtrate was discarded and the receiving flask was replaced. The filter funnel containing a mixture of the product and Celite was then rinsed thoroughly with MeOH (3 x 35 mL) to dissolve and extract the product. The resulting clear MeOH solution of product was concentrated under vacuum to afford the pure bis(imidazolium) or bis(pyridinium) dichloride salt as a white solid.

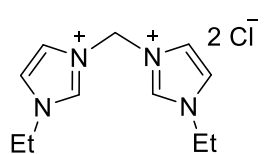
Specific procedures and characterization data for bis(imidazolium) and bis(pyridinium) salts 66-77



3,3'-methylenebis(1-methyl-1*H*-imidazol-3-ium) dichloride (66).

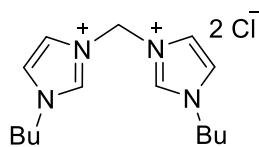
General procedure for the synthesis of bis(imidazolium) and bis(pyridinium) dichloride salts was followed, starting with 1-methylimidazole (0.320 mL, 4.0 mmol, 1.0 equiv), CH₂Cl₂ (0.770 mL, 12.0 mmol, 3.0 equiv) and DMSO (0.230 mL, 3.2 mmol, 0.8 equiv) at 100 °C for 24 hours, affording salt **66** (468 mg, 94% yield) as a white solid.

On a gram scale: Modified general procedure for the synthesis of bis(imidazolium) and bis(pyridinium) dichloride salts was followed, starting with 1-methylimidazole (1.60 mL, 20.0 mmol, 1.0 equiv), CH₂Cl₂ (3.85 mL, 60.0 mmol, 3.0 equiv) and DMSO (1.15 mL, 16.0 mmol, 0.8 equiv) in a 20 mL oven-dried microwave vial at 100 °C for 24 hours, affording salt **66** (2.30 g, 92% yield) as a white solid. All analyses were consistent with previously reported data.³²



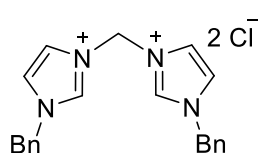
3,3'-methylenebis(1-ethyl-1*H*-imidazol-3-ium) dichloride (67).

General procedure for the synthesis of bis(imidazolium) and bis(pyridinium) dichloride salts was followed, starting with 1-ethylimidazole (0.386 mL, 4.0 mmol, 1.0 equiv), CH₂Cl₂ (0.770 mL, 12.0 mmol, 3.0 equiv), DMSO (0.230 mL, 3.2 mmol, 0.8 equiv) at 100 °C for 24 hours, affording salt **67** (534 mg, 96% yield) as a white solid. **mp** 242-247 °C. **¹H NMR** (700 MHz, DMSO-*d*₆) δ 9.96 (s, 2H), 8.26 (s, 2H), 7.92 (s, 2H), 6.84 (s, 2H), 4.24 (q, *J* = 7.3 Hz, 4H), 1.44 (t, *J* = 7.3 Hz, 6H). **¹³C NMR** (175 MHz, DMSO-*d*₆) δ 137.4, 122.7, 122.3, 57.9, 44.7, 14.7. **IR** (neat) 3051, 1581, 1352, 1215, 764, 647, 623. **HRMS** (EI⁺) *m/z*: [M]²⁺ Calcd for C₁₁H₁₈N₄ 103.07602; found 103.07586. All other analyses were consistent with previously reported data.³⁶



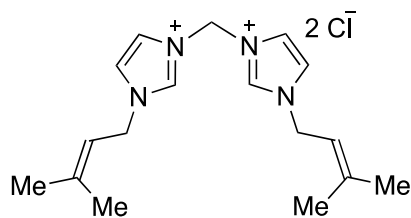
3,3'-methylenebis(1-butyl-1*H*-imidazol-3-ium) dichloride (68). General

procedure for the synthesis of bis(imidazolium) and bis(pyridinium) dichloride salts was followed, starting with 1-butylimidazole (0.530 mL, 4.0 mmol, 1.0 equiv), CH₂Cl₂ (0.770 mL, 12.0 mmol, 3.0 equiv), DMSO (0.230 mL, 3.2 mmol, 0.8 equiv) at 100 °C for 24 hours, affording salt **68** (632 mg, 95% yield) as a white solid. **mp** 252-253 °C. **¹H NMR** (700 MHz, DMSO-*d*₆) δ 10.02 (s, 2H), 8.30 (s, 2H), 7.91 (s, 2H), 6.86 (s, 2H), 4.22 (t, *J* = 7.3 Hz, 4H), 1.81-1.77 (m, 4H), 1.31-1.26 (m, 4H), 0.90 (t, *J* = 7.4 Hz, 6H). **¹³C NMR** (175 MHz, DMSO-*d*₆) δ 137.7, 123.0, 122.3, 57.8, 49.0, 31.1, 18.8, 13.3. **IR** (neat) 3053, 2958, 1579, 1211, 767, 637. **HRMS** (EI⁺) *m/z*: [M]²⁺ Calcd for C₁₅H₂₆N₄ 131.10732; found 131.10728. All other analyses were consistent with previously reported data.³⁶



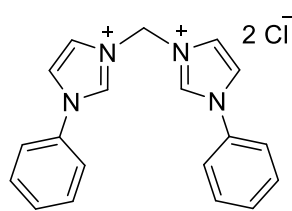
3,3'-methylenebis(1-benzyl-1*H*-imidazol-3-ium) dichloride (69). General

procedure for the synthesis of bis(imidazolium) and bis(pyridinium) dichloride salts was followed, starting with 1-benzylimidazole (633 mg, 4.0 mmol, 1.0 equiv), CH₂Cl₂ (0.770 mL, 12.0 mmol, 3.0 equiv), DMSO (0.230 mL, 3.2 mmol, 0.8 equiv) at 100 °C for 24 hours, affording salt **69** (676 mg, 84% yield) as a white solid. **mp** 168 °C. **¹H NMR** (700 MHz, DMSO-*d*₆) δ 9.94 (s, 2H), 8.24 (s, 2H), 7.91 (s, 2H), 7.48-7.40 (m, 10H), 6.81 (s, 2H), 5.51 (s, 4H). **¹³C NMR** (175 MHz, DMSO-*d*₆) δ 137.8, 134.2, 129.0, 128.9, 128.6, 123.2, 122.7, 58.3, 52.3. **IR** (neat) 3026, 1977, 1589, 1497, 1457, 1321, 1163, 709. **HRMS** (EI⁺) *m/z*: [M]²⁺ Calcd for C₂₁H₂₂N₄ 165.09167; found 165.09158.



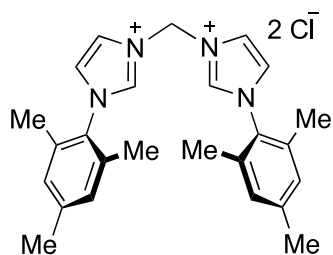
3,3'-methylenebis(1-(3-methylbut-2-en-1-yl)-1H-imidazol-3-ium) di-chloride (70).

Modified general procedure for the synthesis of bis(imidazolium) and bis(pyridinium) dichloride salts was followed, starting with 1-(3-methylbut-2-en-1-yl)-1H-imidazole (**81**) (545 mg, 4.0 mmol, 1.0 equiv), CH₂Cl₂ (0.770 mL, 12.0 mmol, 3.0 equiv) and DMSO (0.230 mL, 3.2 mmol, 0.8 equiv) at 100 °C for 48 hours, affording salt **70** (413 mg, 58% yield) as a white solid. **mp** 225 °C. **¹H NMR** (700 MHz, DMSO-*d*₆) δ 9.75 (s, 2H), 8.18 (s, 2H), 7.80 (s, 2H), 6.76 (s, 2H), 5.41 (s(br), 2H), 4.84 (d, *J* = 7.5 Hz, 4H), 1.78 (s, 12H). **¹³C NMR** (175 MHz, DMSO-*d*₆) δ 141.1, 137.3, 122.9, 122.3, 116.5, 57.9, 47.0, 25.4, 18.0. **IR** (neat) 3038, 2968, 1547, 1439, 1162, 862, 777, 617. **HRMS** (HESI) *m/z*: [M]²⁺ Calcd for C₁₇H₂₆N₄ 143.10733; found 143.10668.



3,3'-methylenebis(1-phenyl-1H-imidazol-3-ium) di-chloride (71).

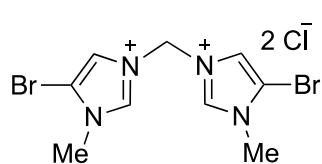
General procedure for the synthesis of bis(imidazolium) and bis(pyridinium) dichloride salts was followed, starting with 1-phenyl-1H-imidazole (**82**) (433 mg, 3.0 mmol, 1.0 equiv), CH₂Cl₂ (0.580 mL, 9.0 mmol, 3.0 equiv) and DMSO (0.170 mL, 2.4 mmol, 0.8 equiv) at 100 °C for 24 hours, affording salt **71** (122 mg, 22% yield) as a white solid. All analyses were consistent with previously reported data.³⁶



1,1'-(1-(2,4,6-trimethylphenyl))-3,3'-methylenediimidazolium

di-chloride (70). Modified general procedure for the synthesis of bis(imidazolium) and bis(pyridinium) dichloride salts was followed, starting with 1-mesityl-1H-imidazole (**83**) (745 mg, 4.0 mmol, 1.0 equiv), CH₂Cl₂ (0.77 mL, 12.0 mmol, 3.0 equiv) and DMSO (0.23 mL, 3.2 mmol, 0.8 equiv) at

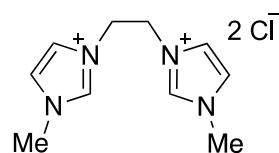
110 °C for 48 hours, where anhydrous THF was used instead of Et₂O for the wash over Celite, affording salt **70** (642 mg, 70%). All analyses were consistent with previously reported data.⁴⁷



3,3'-methylenebis(5-bromo-1-methyl-1*H*-imidazol-3-ium)

dichloride (73). Modified general procedure for the synthesis of bis(imidazolium) and bis(pyridinium) dichloride salts was followed,

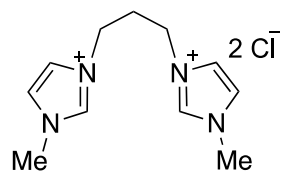
starting with 5-bromo-1-methylimidazole (644 mg, 4.00 mmol, 1.0 equiv), CH₂Cl₂ (0.77 mL, 12.0 mmol, 3.0 equiv) and DMSO (0.23 mL, 3.2 mmol, 0.8 equiv) at 100 °C for 48 hours, affording a crude product which was purified directly by recrystallization in hot MeOH without performing the Et₂O wash over Celite, affording the pure salt **73** (301 mg, 37% yield) as a white solid. **mp** 252 °C (decomp.). **¹H NMR** (600 MHz, DMSO-*d*₆) δ 9.78 (s, 2H), 8.38 (s, 2H), 6.80 (s, 2H), 3.84 (s, 6H). **¹³C NMR** (175 MHz, D₂O) δ 140.9, 124.8, 113.7, 62.0, 38.4 (standard peaks: 57.1, 21.8, 17.8, 0.0). **IR** (neat) 3007, 1563, 1025, 776, 614. **HRMS** (HESI) *m/z*: [M]²⁺ Calcd for C₉H₁₂Br₂N₄ 166.97089; found 166.97070.



3,3'-(ethane-1,2-diyl)bis(1-methyl-1*H*-imidazol-3-ium) dichloride (74).

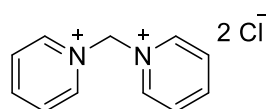
Modified general procedure for the synthesis of bis(imidazolium) and bis(pyridinium) dichloride salts was followed, starting with 1-

methylimidazole (0.320 mL, 4.0 mmol, 1.0 equiv), 1,2-dichloroethane (0.160 mL, 2.0 mmol, 0.5 equiv) and DMSO (0.840 mL, 11.8 mmol, 3.0 equiv) at 100 °C for 24 hours, affording salt **74** (457 mg, 87% yield) as a white solid. All analyses were consistent with previously reported data.³²



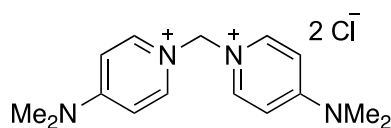
3,3'-(propane-1,3-diyl)bis(1-methyl-1*H*-imidazol-3-ium) dichloride

(75). Modified general procedure for the synthesis of bis(imidazolium) and bis(pyridinium) dichloride salts was followed, starting with 1-methylimidazole (0.320 mL, 4.0 mmol, 1.0 equiv), 1,3-dichloropropane (0.190 mL, 2.0 mmol, 0.5 equiv) and DMSO (0.810 mL, 11.4 mmol, 2.9 equiv) at 100 °C for 24 hours, affording salt **75** (471 mg, 85% yield) as a white solid. All analyses were consistent with previously reported data.³²



1,1'-methylenebis(pyridin-1-ium) dichloride (76).

Modified general procedure for the synthesis of bis(imidazolium) and bis(pyridinium) dichloride salts was followed, starting with pyridine (0.322 mL, 4.0 mmol, 1.0 equiv), CH₂Cl₂ (0.77 mL, 12.0 mmol, 3.0 equiv) and DMSO (0.23 mL, 3.2 mmol, 0.8 equiv) at 100 °C for 48 hours, where the filtration on Celite was not performed. After cooling to room temperature, the heterogenous mixture was dissolved in MeOH (20 mL) and concentrated under vacuum, directly affording pure salt **76** (399 mg, 82% yield). All analyses were consistent with previously reported data.⁴¹

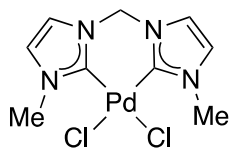


1,1'-methylenebis(4-(dimethylamino)pyridin-1-ium)

dichloride (77). Modified general procedure for the synthesis of bis(imidazolium) and bis(pyridinium) dichloride salts was followed, starting with 4-dimethylaminopyridine (489 mg, 4.0 mmol, 1.0 equiv), CH₂Cl₂ (0.77 mL, 12.0 mmol, 3.0 equiv), DMSO (0.23 mL, 3.2 mmol, 0.8 equiv) at 100 °C for 24 hours, where the filtration on Celite was not performed. After cooling to room temperature, the heterogenous mixture was dissolved in MeOH (20 mL) and concentrated under vacuum, directly affording pure salt **77** (648 mg, 98% yield) as a white solid. ¹H NMR (700 MHz, DMSO-*d*₆) δ

8.89-8.83 (m, 4H), 7.18-7.12 (m, 4H), 6.64 (s, 2H), 3.22 (s, 12H). ^{13}C NMR (175 MHz, DMSO- d_6) δ 156.5, 141.4, 108.2, 71.3, 40.1. IR (neat) 3362, 2982, 1635, 1574, 1245, 809, 563. HRMS (EI $^+$) m/z : $[\text{M}]^{2+}$ Calcd for $\text{C}_{15}\text{H}_{22}\text{N}_4$ 129.09167; found 129.09158. All other analyses were consistent with previously reported data.⁴¹

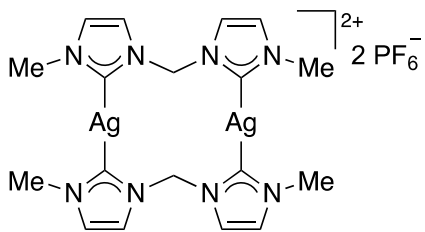
Specific procedures and characterization data of metal-bis(NHC) complexes 3a-3c



1,1-Dimethyl-3,3-methylenediimidazoline-2,2-diylidenepalladium(II)

dichloride (78). Modified general procedure for the synthesis of bis(imidazolium) and bis(pyridinium) dichloride salts was followed, starting

with 1-methylimidazole (0.32 mL, 4.0 mmol, 1.0 equiv), CH₂Cl₂ (0.77 mL, 12.0 mmol, 3.0 equiv) and DMSO (0.230 mL, 3.2 mmol, 0.8 equiv) at 100 °C for 24 hours, where the filtration on Celite was not performed. After cooling to room temperature, a solution of Pd(OAc)₂ (449 mg, 2.0 mmol, 0.5 equiv) in anhydrous DMSO (3 mL) was added to the reaction and the resulting mixture was heated at 60 °C for 2 hours, then at 80 °C for 2 hours, then at 100 °C for 2 hours. The reaction was cooled to room temperature, concentrated under vacuum and the crude product was washed with anhydrous MeOH (2 x 4 mL) and filtered on a Büchner funnel, affording the pure complex **78** (488 mg, 69% yield over two steps) as a white solid. All analyses were consistent with previously reported data.³²

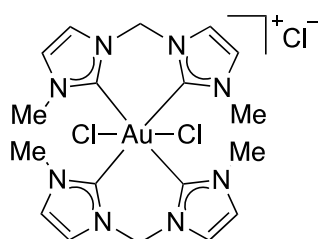


Bis(1,1'-dimethyl-3,3'-methylenediimidazolin-2,2'-

diylidene) disilver(I) dihexafluorophosphate (79). Modified general procedure for the synthesis of bis(imidazolium) and bis(pyridinium) dichloride salts was followed, starting with 1-

methylimidazole (0.160 mL, 2.0 mmol, 1.0 equiv), CH₂Cl₂ (0.383 mL, 6.0 mmol, 3.0 equiv) and DMSO (0.114 mL, 1.6 mmol, 0.8 equiv) at 100 °C for 24 hours, where the filtration on Celite was not performed. After cooling to room temperature, H₂O (5 mL) was added followed by Ag₂O (579 mg, 2.5 mmol, 1.25 equiv), and the reaction was stirred at room temperature for 15 minutes. The solution was then filtered through Celite and to the filtrate was added NH₄PF₆ (163 mg, 1.0 mmol, 1.0 equiv) causing the precipitation of a white powder which was filtered on a

Büchner funnel and dried under vacuum to afford the pure complex **79** (300 mg, 70% yield over 2 steps) as a white solid. All analyses were consistent with previously reported data.⁴³



Bis[methylenebis(3-methyl-1H-imidazol-1-yl-2(3H)-

ylidene)]gold(III) chloride (80). Modified general procedure for the synthesis of bis(imidazolium) and bis(pyridinium) dichloride salts was

followed, starting with 1-methylimidazole (0.160 mL, 2.0 mmol, 1.0

equiv), CH₂Cl₂ (0.383 mL, 6.0 mmol, 3.0 equiv) and DMSO (0.114 mL, 1.6 mmol, 0.8 equiv) at 100 °C for 24 hours, where the filtration on Celite was not performed. The reaction mixture was allowed to cool to room temperature and transferred to a 100 mL round-bottomed flask containing a solution of KAuCl₄•H₂O (198 mg, 0.5 mmol, 0.25 equiv) in anhydrous DMF (10 mL), by rinsing with 3 x 5 mL DMF (overall 25 mL DMF). The resulting solution was warmed to 80 °C and a solution of LiOAc (198 mg, 3.0 mmol, 1.5 equiv) in anhydrous DMF (12.5 mL) was immediately added. The reaction mixture was heated to 100 °C for 5 hours, causing the precipitation of a white solid. The precipitate was collected by filtration and washed successively with anhydrous DMF (5 mL), acetone (5 mL) and Et₂O (5 mL), affording the pure complex **80** (259 mg, 79% yield over 2 steps) as a white solid. All analyses were consistent with previously reported data.⁴⁸

CHAPTER 3

Controlled α -Mono- and α,α -Di-Halogenation of Alkyl Sulfonamides

3.1 Introduction to α -Halosulfonamides

The sulfonamide functional group has several key characteristics that can be leveraged for drug discovery. One characteristic of the sulfonamide functional group is a high topological polar surface area which can have a significant effect on the blood-brain barrier permeability and overall toxicity of a drug molecule.^{49,50} Compared to amides, the sulfonamide functional group exhibits a distinct 90° turn in its conformation⁵¹ as well as a relatively high pKa due to the fact that, unlike amides and other carbonyl functional groups, sulfonamides do not participate in resonance stabilization of their corresponding α -carbanions.⁵² For these reasons, it is important to have the ability to incorporate the sulfonamide group in pharmaceuticals and to functionalize existing alkyl sulfonamide drug scaffolds (Figure 3.1). Examples of drug molecules bearing the alkylsulfonamide functional group include Dronedarone and Dofetilide, which are used to treat heart conditions, as well as Dasabuvir which can be used to treat Hepatitis C.

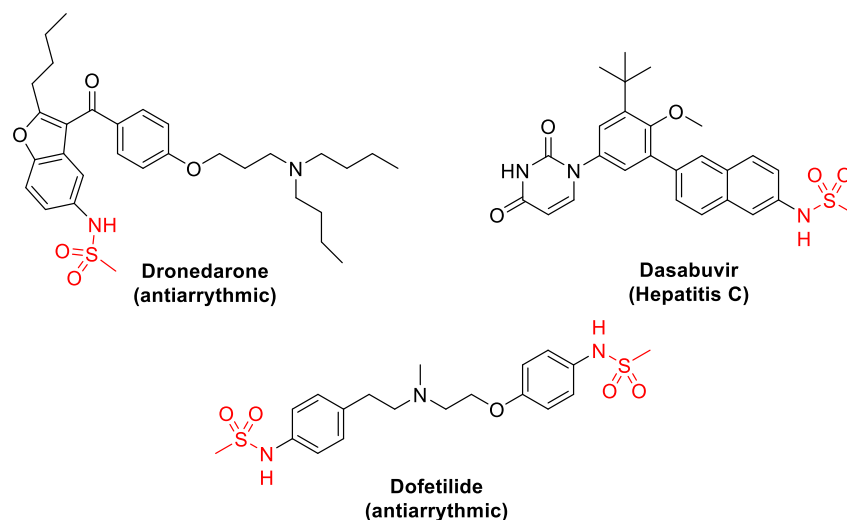


Figure 3.1 Pharmaceuticals containing alkyl sulfonamides

As shown in Figure 3.2, α -halogenated sulfonamide derivatives can serve as key intermediates in the synthesis of biologically relevant molecules. Sulfonamide-containing compounds can be accessed from α -halogenated sulfonamide derivatives via substitution chemistry, as shown in Figure 3.2a which allowed the synthesis of a tetrahydroisoquinoline derivative shown to exhibit BET bromodomain inhibitory activity.⁵³ Furthermore, a nickel-catalyzed enantioconvergent hydroalkylation (Figure 3.2b) allows for the introduction of a sulfonylmorpholine functionality to generate a chiral indomethacin derivative.⁵⁴ Example C also shows the ability to produce chiral epoxides via Darzens reactions of α -bromosulfonamides;⁵⁵ such chiral epoxides were shown to exhibit antifilarial activity.

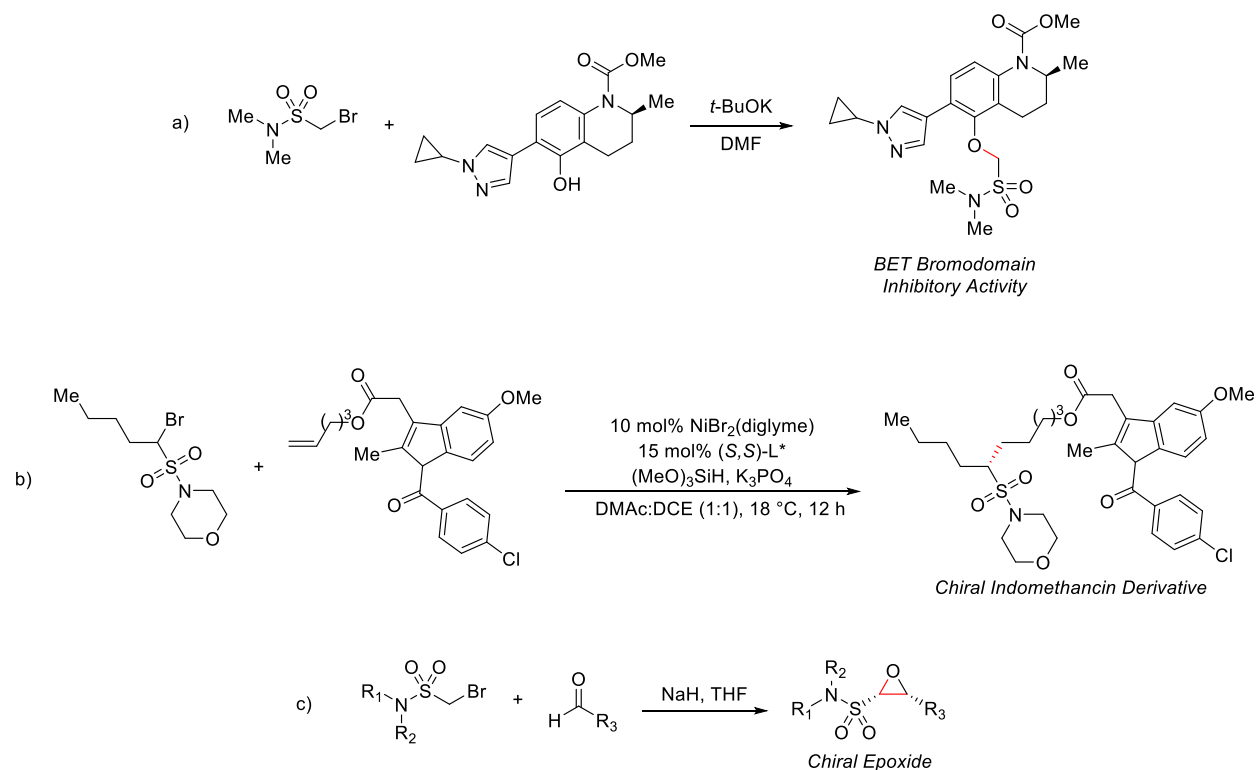


Figure 3.2 Examples of α -bromosulfonamides used in pharmaceutical chemistry

3.1.1 Inherent Problems in Base-Mediated α -Halogenation of Sulfonamides

While the direct base-mediated halogenation of alkyl sulfonamides constitutes the most straightforward route to these compounds, it is rarely used as it typically suffers from poor selectivity due to the increased acidity of the α -mono-halogenated product as compared with the starting sulfonamide, leading to inseparable mixtures of halogenated sulfonamides (Figure 3.3). In the case of carbonyl compounds, this lack of control can usually be circumvented through the use of acidic conditions, effectively leading to halogenation via an enol intermediate. Sulfonamides, however, do not tautomerize in this way and require strongly basic conditions for the formation of an α -carbanion prior to halogenation. In this work, we have developed an

efficient and selective α -halogenation of sulfonamides to produce either mono- or di-halogenated derivatives with complete selectivity.

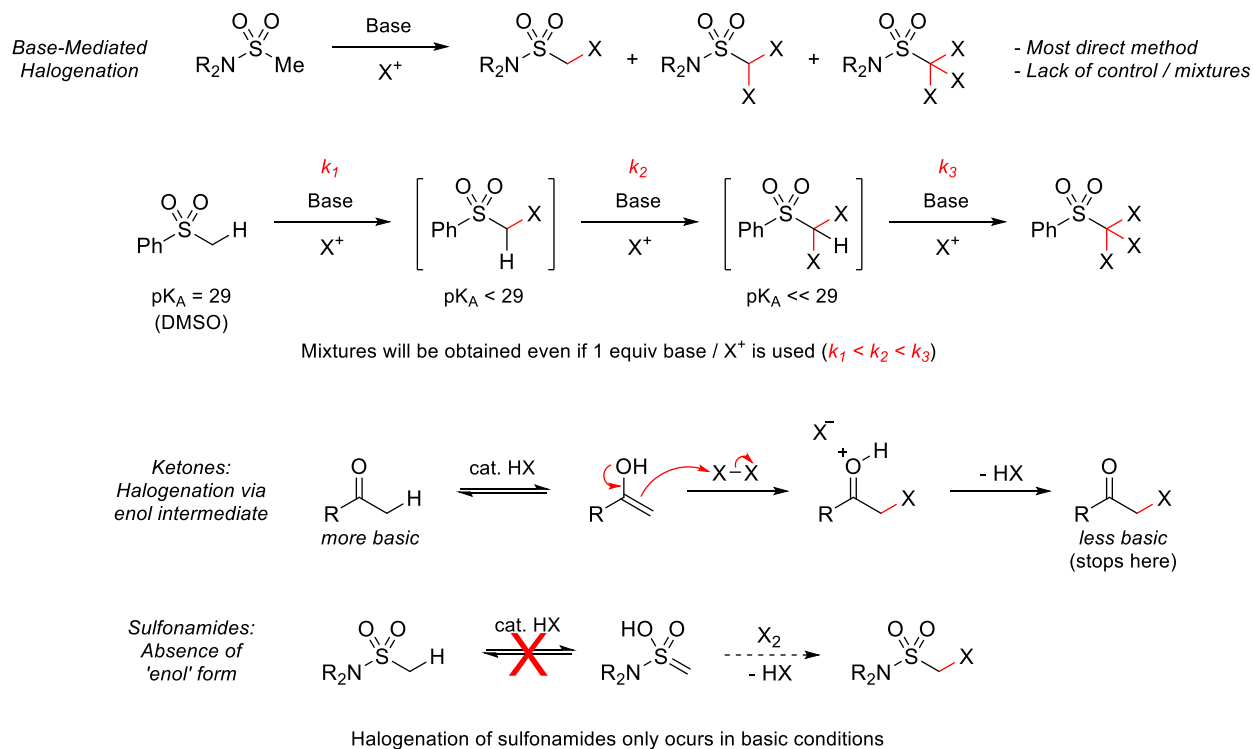


Figure 3.3 Inherent problems with base-mediated halogenation of sulfonamides

3.2 Controlled α -Mono- and α,α -Di-Halogenation of Alkyl Sulfonamides

3.2.1 Current Limitations in the Selective Halogenation of Alkyl Sulfonamides

Currently, a common route to mono-brominated sulfonamide intermediates involves the use of tetrabutylammonium hydrogen sulfate, sodium sulfite, and phosphorous pentachloride to form bromomethanesulfonyl chloride in 2 steps followed by substitution with an amine (Figure 3.4).⁵⁴⁻

⁵⁶ This method requires multiple steps and would not allow for late-stage modification at the α -position of an existing alkylsulfonamide molecule, which would be desired for studying the SAR

of modifications on pre-existing sulfonamide drug scaffolds. Generally, mixtures of polyhalogenated alkylsulfonamides are not easily separable by typical chromatographic methods. Figure 3.5 shows the bromination of *N*-protected β -sultams at the 4-position resulting in a mixture of products that could be purified by column chromatography if the protecting group was TBDPS or a cyclohexyl substituent.⁵⁷ Protection with TBDMS instead did not yield separable mixtures. While such protecting group chemistry method could possibly be used to overcome the problem in yielding inseparable mixtures of polyhalogenated products, the need for *N*-protection/deprotection would severely limit the scope of potential sulfonamide substrates, and renders this a poor approach with regards to step- and atom economy.

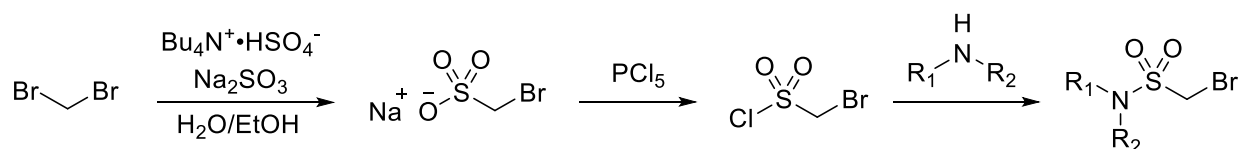


Figure 3.4 Multi-step method for accessing α -halogenated sulfonamides

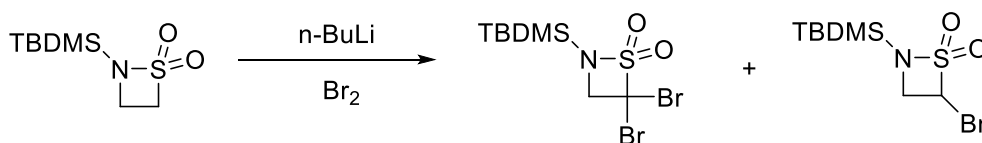
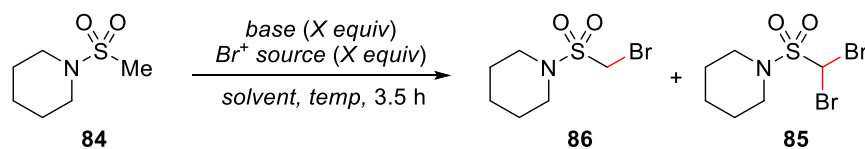


Figure 3.5 Literature method for accessing 4-bromo- β -sultams

3.2.2 Optimization of the α,α -Dibromination of Sulfonamides

Having already established conditions in our group for the controlled α,α -di-halogenation of alkyl sulfones from the work of graduate student Chris Poteat,⁵⁸ we first applied similar conditions to our alkyl sulfonamide model substrate, methanesulfonylpiperidine **84** (Table 3.1).

We were initially met with promising results for the α,α -di-bromination reaction using LDA, CBr_4 and Et_2O , observing selective formation of 43% α,α -dibrominated product **85** (entry 5), which could be improved to 59% when adding 1.4 equiv water, an effect that was previously observed in our group when it was noticed that CBr_4 reagent containing water had performed better in the dibromination of methylsulfones than that of dry CBr_4 .⁵⁸ After evaluating different solvents in the same reaction (entries 7-20), it was found *i*- Pr_2O and *t*-BuOMe showed increased yields over Et_2O . Furthermore, it was found that running the reaction in *i*- Pr_2O along with 1.4 equivalents of water offered an NMR yield of 65% with complete selectivity for dibrominated **85** (entry 20). In effort to further increase the yield while maintaining selectivity, the concentration and temperature were adjusted and different bases were evaluated (entries 21-29). However, no further increase in the yield was observed, and attempts to expand the scope beyond our model substrate were not selective (Figure 3.6).

Table 3.1 Optimization of the α,α -dibromination reaction

Entry	Base	Br ⁺ Source	Solvent	Temp.	Conc. [M]	Yield ^a 86 (%)	Yield ^a 85 (%)
1	LDA (2.2)	Br ₂ (3.0)	Et ₂ O	rt	0.043	26	13
2	LDA (2.2)	NBS (3.0)	Et ₂ O	rt	0.043	11	2
3	LDA (2.2)	DBDMH (3.0)	Et ₂ O	rt	0.043	10	5
4	LDA (2.2)	Pyr·Br ₃ (3.0)	Et ₂ O	rt	0.043	9	8
5	LDA (2.2)	CBr ₄ (3.0)	Et ₂ O	rt	0.043	1	43
6 ^b	LDA (2.2)	CBr ₄ (3.0)	Et ₂ O	rt	0.043	3	59
7	LDA (2.2)	CBr ₄ (3.0)	THF	rt	0.043	1	36
8	LDA (2.2)	CBr ₄ (3.0)	PhMe	rt	0.043	3	50
9	LDA (2.2)	CBr ₄ (3.0)	DMF	rt	0.043	3	0
10	LDA (2.2)	CBr ₄ (3.0)	1,4-dioxane	rt	0.043	44	0
11	LDA (2.2)	CBr ₄ (3.0)	PhH	rt	0.043	5	41
12	LDA (2.2)	CBr ₄ (3.0)	Hexane	rt	0.043	2	40
13	LDA (2.2)	CBr ₄ (3.0)	DMSO	rt	0.043	12	0
14	LDA (2.2)	CBr ₄ (3.0)	DME	rt	0.043	34	19
15	LDA (2.2)	CBr ₄ (3.0)	<i>t</i> -BuOMe	rt	0.043	3	54
16 ^c	LDA (2.2)	CBr ₄ (3.0)	<i>t</i> -BuOMe	rt	0.043	2	57
17 ^b	LDA (2.2)	CBr ₄ (3.0)	<i>t</i> -BuOMe	rt	0.043	5	54
18	LDA (2.2)	CBr ₄ (3.0)	<i>i</i> -Pr ₂ O	rt	0.043	2	50
19 ^c	LDA (2.2)	CBr ₄ (3.0)	<i>i</i> -Pr ₂ O	rt	0.043	1	62
20^b	LDA (2.2)	CBr₄ (3.0)	<i>i</i>-Pr₂O	rt	0.043	0	65 (60)^d
21 ^b	LDA (2.2)	CBr ₄ (3.0)	<i>i</i> -Pr ₂ O	0 °C	0.043	0	58
22 ^b	LDA (2.2)	CBr ₄ (3.0)	<i>i</i> -Pr ₂ O	50 °C	0.043	8	38
23 ^b	LDA (2.2)	CBr ₄ (3.0)	<i>i</i> -Pr ₂ O	rt	0.085	2	56
24 ^b	LDA (2.2)	CBr ₄ (3.0)	<i>i</i> -Pr ₂ O	rt	0.021	14	42
25	LiHMDS (2.2)	CBr ₄ (3.0)	<i>i</i> -Pr ₂ O	rt	0.043	0	40
26	<i>n</i> -BuLi (2.2)	CBr ₄ (3.0)	<i>i</i> -Pr ₂ O	rt	0.043	3	45
27	LiTMP (2.2)	CBr ₄ (3.0)	<i>i</i> -Pr ₂ O	rt	0.043	4	45
28	KHMDS (2.2)	CBr ₄ (3.0)	<i>i</i> -Pr ₂ O	rt	0.043	2	25
29	<i>s</i> -BuLi (2.2)	CBr ₄ (3.0)	<i>i</i> -Pr ₂ O	rt	0.043	14	43

^aNMR yield determined using 1,3,5-trimethoxybenzene as internal standard. ^b1.4 equiv H₂O was added. ^c1.0 equiv H₂O was added. ^dIsolated yield in parentheses.

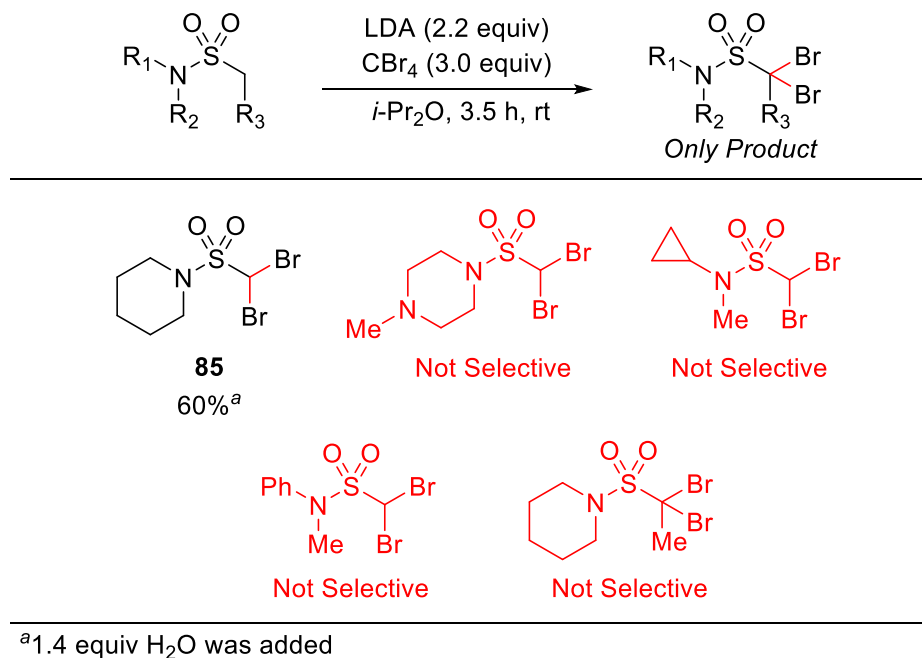
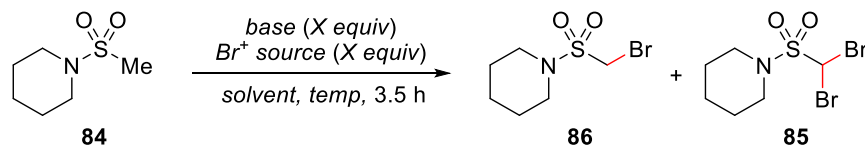


Figure 3.6 Attempts to expand scope of α,α -dibromination

3.2.3 Optimization of the α -Monobromination of Sulfonamides

While initial attempts at the selective α,α -dibromination of sulfonamides were promising, treating our model substrate with LiHMDS and Br₂ in 1,4-dioxane, the optimal conditions for the monobromination of alkyl sulfones,⁵⁸ resulted in both poor yield and no selectivity for the α -monobrominated product **86** (Table 3.2, entry 1). Using *n*-BuLi as the base was found to give higher yields but still without the desired selectivity for the α -monobrominated product (entry 2). The selectivity issue was resolved after screening electrophilic bromine sources (entries 3-7), with DBDMH offering 51% yield of **86** with complete selectivity. Other bases and solvents were then screened (entries 8-18) and it was found that only DME gives the same full selectivity as 1,4-dioxane, however at a lower yield (entry 17).

Table 3.2 Optimization of the α -monobromination reaction

Entry	Base	Br ⁺ Source	Solvent	Temp.	Yield ^a 86 (%)	Yield ^a 85 (%)
1	LiHMDS (1.1)	Br ₂ (1.5)	1,4-dioxane	rt	22	16
2	<i>n</i> -BuLi (1.1)	Br ₂ (1.5)	1,4-dioxane/Et ₂ O	-40 °C	53	13
3	<i>n</i> -BuLi (1.1)	Br ₂ (1.5)	1,4-dioxane	rt	32	6
4	<i>n</i> -BuLi (1.1)	Py·Br ₃ (1.5)	1,4-dioxane	rt	22	0
5	<i>n</i> -BuLi (1.1)	NBS (1.5)	1,4-dioxane	rt	40	0
6	<i>n</i> -BuLi (1.1)	CBr ₄ (1.5)	1,4-dioxane	rt	34	0
7	<i>n</i>-BuLi (1.1)	DBDMH (1.5)	1,4-dioxane	rt	51 (45)^b	0
8	LiHMDS (1.1)	DBDMH (1.5)	1,4-dioxane	rt	27	0
9	LDA (1.1)	DBDMH (1.5)	1,4-dioxane	rt	23	15
10	<i>n</i> -BuLi (1.1)	DBDMH (1.5)	THF	rt	5	0
11	<i>n</i> -BuLi (1.1)	DBDMH (1.5)	PhMe	rt	47	31
12	<i>n</i> -BuLi (1.1)	DBDMH (1.5)	<i>i</i> -Pr ₂ O	rt	35	15
13	<i>n</i> -BuLi (1.1)	DBDMH (1.5)	Et ₂ O	rt	50	11
14	<i>n</i> -BuLi (1.1)	DBDMH (1.5)	DMF	rt	33	1
15	<i>n</i> -BuLi (1.1)	DBDMH (1.5)	<i>t</i> -BuOMe	rt	32	30
16	<i>n</i> -BuLi (1.1)	DBDMH (1.5)	PhH	rt	33	25
17	<i>n</i> -BuLi (1.1)	DBDMH (1.5)	DME	rt	26	0
18	LDA (2.2)	DBDMH (3.0)	Et ₂ O	rt	10	5

^aNMR yield determined using 1,3,5-trimethoxybenzene as internal standard. ^bIsolated yield in parentheses.

3.2.4 Scope of Accessible α -Monobromosulfonamides

We applied our optimal conditions to five alkyl sulfonamide substrates in addition to **84**, chosen with the intent of showing compatibility with functional groups that are common in

sulfonamide drugs. Compounds **87** and **89** could be synthesized in yields similar to that of the model reaction while the other examples proceeded with rather low yield (Figure 3.7). Successful monobromination of ethanesulfonamide **91** shows that the method is not limited to only methanesulfonamides.

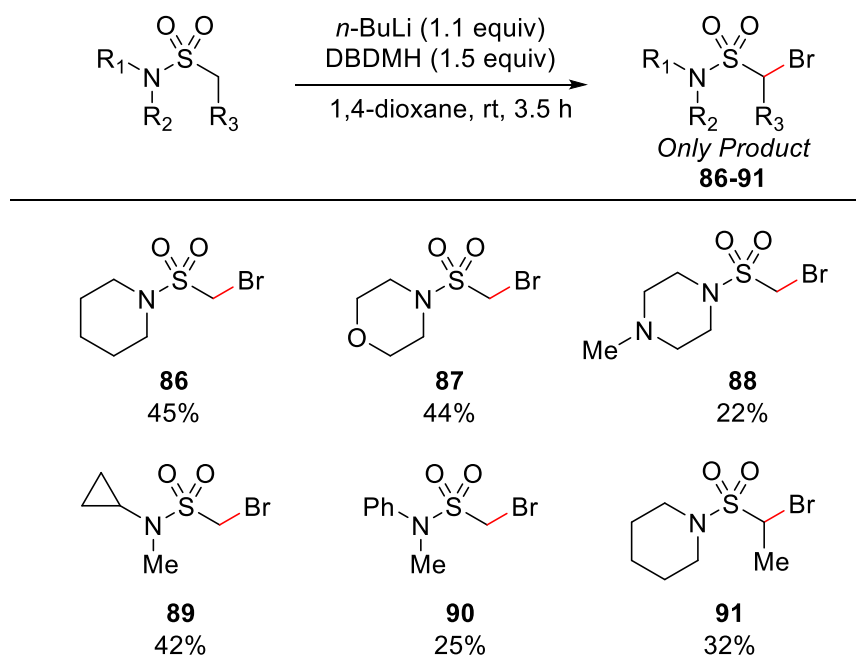
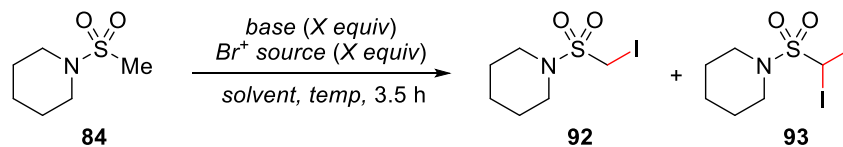


Figure 3.7 Scope of α -monobromosulfonamides

3.2.5 Optimization of the α -Monoiodination of Sulfonamides

Conditions for the α -monoiodination were discovered during attempts to find conditions for selective α,α -diiodination (Table 3.3). In initial reactions aimed at α,α -diiodination, it was found that LDA and NIS in *i*-Pr₂O gave 39% di- and 14% monoiodinated product (entry 7). While these conditions were not selective, we moved forward with testing LDA and NIS in different solvents in hopes of finding conditions for selective α,α -diiodination. While no solvent helped

achieve selectivity for diiodination, it was found that performing the reaction in 1,4-dioxane led to a 67% NMR yield of monoiodinated **92** with full selectivity (entry 16).

Table 3.3 Optimization of the α -monoiodination reaction

Entry	Base	I ⁺ Source	Solvent	Temp.	92 ^a (%)	93 ^a (%)	SM
1	LDA (2.2)	Cl ₄ (3.0)	Et ₂ O	rt	4	30	8
2	LDA (2.2)	Cl ₄ (3.0)	<i>i</i> -Pr ₂ O	rt	17	18	18
3 ^b	LDA (2.2)	Cl ₄ (3.0)	Et ₂ O	rt	25	18	13
4	LDA (2.2)	I ₂ (3.0)	Et ₂ O	rt	26	37	14
5 ^b	LDA (2.2)	I ₂ (3.0)	Et ₂ O	rt	48	21	22
6	LDA (2.2)	NIS (3.0)	Et ₂ O	rt	15	28	20
7	LDA (2.2)	NIS (3.0)	<i>i</i> -Pr ₂ O	rt	14	39	30
8	LDA (4.0)	NIS (6.0)	<i>i</i> -Pr ₂ O	rt	16	39	22
9	LDA (2.2)	NIS (3.0)	THF	rt	34	18	20
10	LDA (2.2)	NIS (3.0)	PhMe	rt	20	44	13
11	LDA (2.2)	NIS (3.0)	DME	rt	45	0	26
12	LDA (2.2)	NIS (3.0)	2-MeTHF	rt	16	44	8
13	LDA (2.2)	NIS (3.0)	<i>t</i> BuOMe	rt	13	34	5
14	LDA (2.2)	NIS (3.0)	CCl ₄	rt	0	0	60
15	LDA (2.2)	NIS (3.0)	<i>i</i> -Pr ₂ O/CCl ₄	rt	4	6	13
16	LDA (2.2)	NIS (3.0)	1,4-dioxane	rt	67	0	16
17	LDA (2.2)	NIS (1.5)	1,4-dioxane	rt	55	0	23
18	LDA (1.1)	NIS (1.5)	1,4-dioxane	rt	40	0	53
19	LDA (2.2)	DIH (3.0)	1,4-dioxane	rt	26	56	15
20	LDA (1.1)	DIH (1.5)	1,4-dioxane	rt	18	31	54
21	LDA (2.2)	I ₂ (3.0)	1,4-dioxane	rt	21	48	22

^aNMR yield determined using 1,3,5-trimethoxybenzene as internal standard. ^b0.9 equiv H₂O was added. ^c1.4 equiv. H₂O added. ^dIsolated yield.

3.2.6 Scope of Accessible α -Monoiodosulfonamides

We applied our optimal conditions for the α -monoiodination to the same set of substrates used in the α -monobromination scope (Figure 3.8). Somewhat similar trends were observed in the yields among the monoiododinated sulfonamides as were observed for the monobrominated products. That is, yields were lower for **95** and **97**. Still, the scope exemplifies the ability to selectively iodinate alkyl sulfonamides bearing functional groups commonly found in pharmaceuticals, as well as ethanesulfonamides such as **97**.

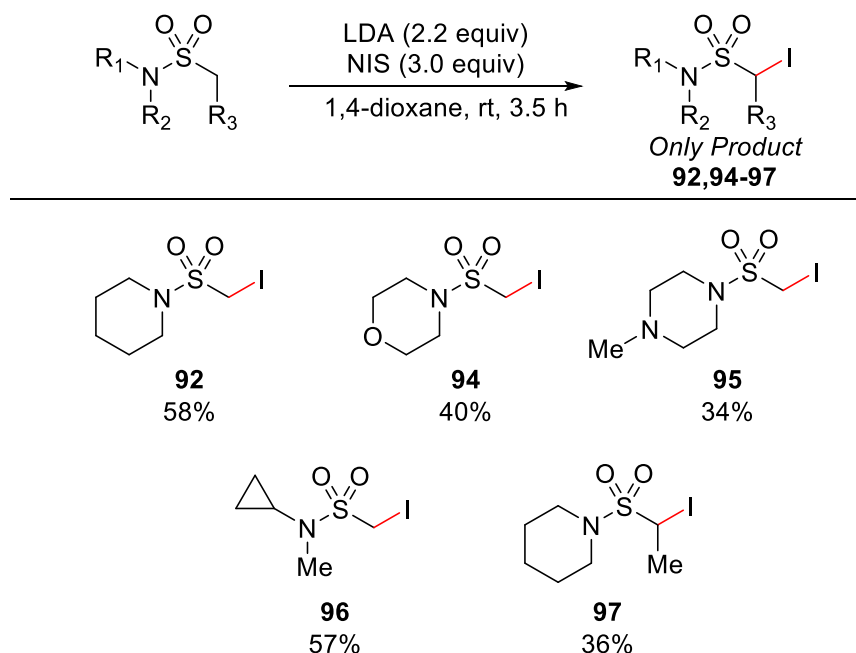


Figure 3.8 Scope of α -monoiodosulfonamides

3.3 Conclusions

In summary, we have successfully developed a method for the direct and selective α -mono- and α,α -dibromination of alkyl sulfonamides. The reaction could be extended to the selective α -iodination of sulfonamides, and the use of CBr_4 in *i*- Pr_2O as reagent-solvent combination enabled the development of the first direct and selective α,α -dibromination of an alkyl sulfonamide.

Products formed are shown in the literature to be useful synthetic intermediates in various transformations, notably in medicinal chemistry.

3.4 Experimental

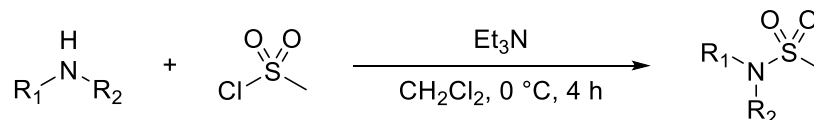
General: Unless stated otherwise, all non-aqueous reactions were performed in oven-dried glassware sealed with microwave caps or rubber septa under a nitrogen atmosphere, and were stirred with Teflon-coated magnetic stir bars.¹ Liquid reagents and solvents were transferred by syringe using standard Schlenk techniques. Tetrahydrofuran (THF), diethyl ether (Et₂O), dichloromethane (CH₂Cl₂), toluene (PhMe), acetonitrile (MeCN), and methanol (MeOH) were dried by passage over a column of activated alumina (JC Meyers Solvent System). Anhydrous 1,4-dioxane and diisopropyl ether (i-Pr₂O) were obtained in Sure Seal bottles from Aldrich and used as received. Anhydrous 1,2-dichloroethane (DCE) and 1,2-dimethoxyethane (DME) were obtained in Sure Seal bottles from Acros Organics and used as received. All other solvents and reagents were used as received unless otherwise noted. Thin layer chromatography was performed using Silicycle silica gel 60 F-254 precoated plates (0.25 mm) and visualised by UV irradiation and anisaldehyde, CAM, potassium permanganate, or iodine stain. Sorbent silica gel (particle size 40-63 μm) was used for flash chromatography of the indicated solvent system according to standard techniques.² Flash chromatography was performed on a Biotage Isolera One. Nuclear magnetic resonance (NMR) spectra (¹H, ¹³C) were recorded on Varian or Bruker spectrometers operating at either 500 or 600 MHz for ¹H and 125, 150, or 175 MHz for ¹³C experiments. Chemical shifts (δ) for ¹H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform, δ 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet and br = broad), coupling constant in Hz, and integration. Chemical shifts for ¹³C NMR spectra are recorded in parts per million from tetramethylsilane using the central peak of deuteriochloroform (δ 77.16 ppm) as the internal standard. All spectra

were obtained with complete proton decoupling. Only select ^1H and ^{13}C spectra are reported. Infrared (IR) spectra were collected on a Thermo Scientific Nicolet iS5 FTIR instrument using attenuated total reflectance (ATR) mode and signals are reported in reciprocal centimeters (cm^{-1}). Only selected IR frequencies are reported. High-resolution mass spectral data were obtained from the NC State University Mass Spectrum Facility, using a Thermo Fisher Scientific Exactive Plus for ESI.

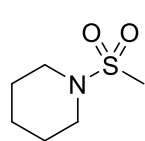
Reagents: 1,3-Dibromo-5,5-dimethylhydantoin, and bromotrichloromethane were purchased from commercial sources and used without further purification. Carbon tetrabromide was purchased from Acros Organics. *n*-BuLi (2.0 M in THF/hexanes) was purchased from Sigma-Aldrich and LDA (2.0 M in THF/*n*-heptane/ethylbenzene) was purchased from Acros Organics.

Synthesis of alkyl sulfonamides 84,98-103

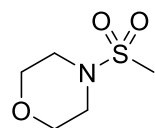
GENERAL PROCEDURE A: Synthesis of Alkyl Sulfonamides 84, 98-103



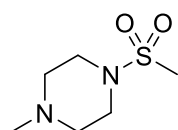
To a 250 mL flame-dried round bottom flask was added a secondary amine (30.0 mmol, 1.0 equiv) and CH₂Cl₂ (80 mL), and cooled to 0 °C. Next, methanesulfonyl chloride (30.0 mmol, 1.0 equiv) and Et₃N (33.0 mmol, 1.1 equiv) were added and the reaction was stirred for 4 hours at 0 °C. After this time the reaction was quenched with brine and extracted three times with CH₂Cl₂. The combined extracts were dried with Na₂SO₄ and passed through a silica plug before concentrating under vacuum.



Methanesulfonylpiperidine (84). General Procedure A was followed using piperidine (2.96 mL, 30.0 mmol, 1.0 equiv), methanesulfonyl chloride (2.32 mL, 30.0 mmol, 1.0 equiv) and Et₃N (33.0 mmol, 1.1 equiv) to obtain **84** (4.32 g, 88%). All analyses were consistent with the previously reported data.^{59,60}

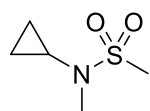


Methanesulfonylmorpholine (98). General Procedure A was followed using morpholine (2.59 mL, 30.0 mmol, 1.0 equiv), methanesulfonyl chloride (2.32 mL, 30.0 mmol, 1.0 equiv) and Et₃N (33.0 mmol, 1.1 equiv) to obtain **98** (4.52 g, 90%). All analyses were consistent with the previously reported data.⁵⁹

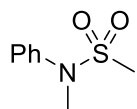


Methanesulfonyl-4-methylpiperazine (99). General Procedure A was followed using 4-methylpiperazine (4.44 mL, 40.0 mmol, 1.0 equiv), methanesulfonyl chloride (3.09 mL, 40.0 mmol, 1.0 equiv) and Et₃N (6.13 mL, 44.0 mmol, 1.1

equiv) to obtain **99** (5.48 g, 77%). **mp** 94-96 °C. **¹H NMR** (600 MHz, CDCl₃) δ 3.25 (t, J = 5.0 Hz, 4H), 2.77 (s, 3H), 2.51 (t, J = 4.9 Hz, 4H), 2.33 (s, 3H). **¹³C NMR** (125 MHz, CDCl₃) δ 54.4, 45.9, 45.8, 34.4. **IR** (neat) 2984, 2949, 2853, 2801, 2772, 2453, 1322, 1282, 1134, 962, 942, 785, 592, 518, 498. **HRMS** (HESI) calcd for [C₆H₁₅N₂O₂S+H]⁺: *m/z*, 179.08487 found 179.08471.

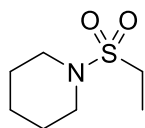


Methanesulfonyl-N-methyl-cyclopropylamine (100). Compound **103** (2.28 mg, 16.8 mmol, 1.0 equiv) was dissolved in CH₂Cl₂ and cooled to 0 °C before adding NaH (505 mg, 21.0 mmol, 1.25 equiv). After stirring for 1 h, MeI (1.57 mL, 25.2 mmol, 1.5 equiv) was added slowly and the reaction was then stirred at room temperature for 16 h. After this time the reaction was quenched with water, extracted with ethyl acetate, and dried with Na₂SO₄. The solution was then passed through a silica plug and concentrated under vacuum to yield **100** (894 mg, 36% yield). **mp** 57-59 °C. **¹H NMR** (500 MHz, CDCl₃) δ 2.88 (s, 3H), 2.87 (s, 3H), 2.25 (tt, J = 6.8, 3.6 Hz, 1H), 0.89–0.83 (m, 2H), 0.81–0.70 (m, 2H). **¹³C NMR** (125 MHz, CDCl₃) δ 37.2, 34.5, 32.1, 7.8. **IR** (neat). 3099, 3019, 3007, 2933, 1458, 1367, 1317, 1243, 1156, 1139, 1081, 1024, 972, 956, 934, 852, 822, 783, 762, 662, 525, 511. **HRMS** (HESI) calcd for [C₅H₁₂NO₂S+H]⁺: *m/z*, 150.05833 found 150.05798.



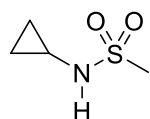
Methanesulfonyl-N-methylaniline (101). General Procedure A was followed using N-methylaniline (3.21 g, 30.0 mmol, 1.0 equiv), methanesulfonyl chloride (2.32 mL, 30.0 mmol, 1.0 equiv) and Et₃N (2.32 mL, 33.0 mmol, 1.1 equiv) to obtain **101** (1.69 g, 30%).

All analyses were consistent with the previously reported data.⁵⁹



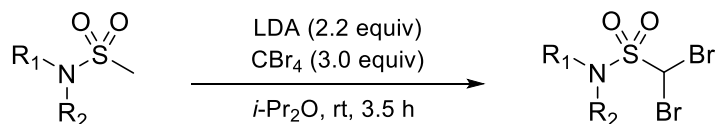
Ethanesulfonylpiperidine (102) A mixture of ethanesulfonic acid (3.3 g, 30.0 mmol, 1.0 equiv), SOCl₂ (4.28 g, 36.0 mmol, 1.2 equiv), DMF (20 mL), and DCM (200 mL) was refluxed for 4 h. After this time, the reaction was allowed to cool to room

temperature and concentrated to yield an orange oil. The crude oil was then dissolved in 75 mL CH₂Cl₂ and cooled to 0 °C before adding piperidine (2.55 g, 30.0 mmol, 1.0 equiv) and Et₃N (3.34 g, 33.0 mmol, 1.1 equiv) and stirring for 4 h. The reaction was then quenched with brine and extracted with CH₂Cl₂. The combined organic fractions were washed with brine, dried with Na₂SO₄, and concentrated under vacuum to afford **102** (1.27 g, 24% over 2 steps) after purification by flash chromatography, eluting with 0-30% EA in hexanes (elution gradient). All analyses were consistent with the previously reported data.⁶⁰

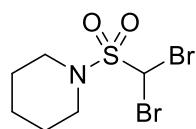


Methanesulfonylcyclopropylamine (103). General Procedure A was followed using cyclopropylamine (2.28 g, 40.0 mmol, 1.0 equiv), methanesulfonyl chloride (3.09 mL, 40.0 mmol, 1.0 equiv) and Et₃N (6.13 mL, 44.0 mmol, 1.1 equiv) to obtain **103** (2.28 g, 42%). All analyses were consistent with the previously reported data.⁶¹

GENERAL PROCEDURE B: Synthesis of α,α -dibromosulfonamide 85

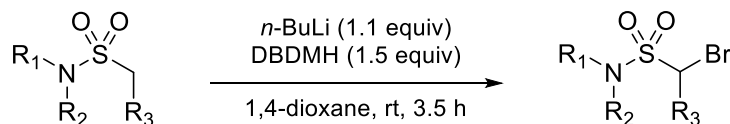


An oven-dried microwave vial equipped with a magnetic stirbar was charged with alkyl sulfonamide (1.0 mmol, 1.0 equiv), capped and flushed with N_2 . Anhydrous $i\text{-Pr}_2\text{O}$ (7.5 mL) was added and to the resulting solution was added LDA (2.0 M in THF/n-heptane/ethylbenzene, 1.1 mL, 2.2 mmol, 2.2 equiv) and stirred for 1.5 hours. After this time, the deprotonated sulfonamide solution was transferred via syringe to a separate microwave vial containing CBr_4 (995 mg, 3.0 mmol, 3.0 equiv) in $i\text{-Pr}_2\text{O}$ (15 mL). The reaction mixture was stirred for 2 h and then quenched by slow addition of aqueous sat. Na_2SO_3 (15 mL) and extracted with CH_2Cl_2 (2 x 80 mL). The combined organic fractions were washed with aqueous sat. Na_2SO_3 (3 x 80 mL), dried over Na_2SO_4 , and concentrated under vacuum to give the crude α,α -dibrominated sulfonamide, which was purified by flash chromatography to afford the pure product.



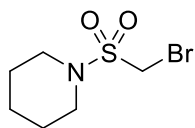
1-((1-Bromomethyl)sulfonyl)piperidine (85). General procedure B was followed, starting with 1-(methylsulfonyl)piperidine (**84**) (163 mg, 1.0 mmol, 1.0 equiv), LDA (2.0 M in THF/n-heptane/ethylbenzene, 1.1 mL, 2.2 mmol, 2.2 equiv), and CBr₄ (995 mg, 3.0 mmol, 3.0 equiv) in *i*-Pr₂O (15 mL), affording **85** (194 mg, 60% yield) as a white solid after purification by flash chromatography, eluting with 0-50% EA in hexanes (elution gradient). **mp** 50-52 °C. **¹H NMR** (600 MHz, CDCl₃) δ 6.23 (s, 1H), 3.53 (m, 4H), 1.72 – 1.66 (m, 4H), 1.64 (dd, J = 8.9, 4.0 Hz, 2H). **¹³C NMR** (150 MHz, CDCl₃) δ 49.2, 47.6, 26.2, 23.8. **IR** (neat) 3021, 2980, 2951, 2922, 2864, 2850, 1450, 1366, 1333, 1166, 1139, 1022, 956, 680, 752. **HRMS** (HESI) calcd for [C₆H₁₁Br₂NO₂S+Na]⁺: *m/z*, 341.87695 found 341.87624.

GENERAL PROCEDURE C: Synthesis of α -monobromosulfonamides 86-91

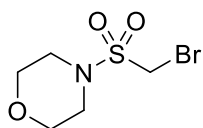


An oven-dried microwave vial equipped with a magnetic stirbar was charged with the alkyl sulfonamide (1.0 mmol, 1.0 equiv), capped and flushed with N_2 . Anhydrous dioxane (7.5 mL) was added and to the resulting solution was added n -BuLi (2.0 M in THF/hexanes, 0.55 mL, 1.1 mmol, 1.1 equiv) and stirred for 1.5 hours. After this time, the deprotonated sulfonamide solution was transferred via syringe to a separate oven-dried microwave vial containing DBDMH (429 mg, 1.5 mmol, 1.5 equiv) in 1,4-dioxane (15 mL). The reaction mixture was stirred for 2 h and then quenched by slow addition of aqueous sat. Na_2SO_3 (15 mL) and extracted with CH_2Cl_2 (3 x 80 mL). The combined organic fractions were washed with aqueous sat. Na_2SO_3 (2 x 80 mL), dried over Na_2SO_4 , and concentrated under vacuum to give the crude α -brominated sulfonamide, which was purified by flash chromatography to afford the pure product. **Important note:** Using wet dioxane will result in lower yields and loss of selectivity.

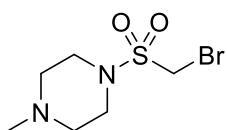
Specific procedures and characterization data of 86-91



1-((1-Bromomethyl)sulfonyl)piperidine (86). General procedure C was followed, starting with 1-(methylsulfonyl)piperidine (**84**) (163 mg, 1.0 mmol, 1.0 equiv), *n*-BuLi (2.0 M in THF/hexanes, 0.55 mL, 1.1 mmol, 1.1 equiv), and DBDMH (429 mg, 1.5 mmol, 1.5 equiv) in dioxane for 3.5 h, affording **86** (109 mg, 45% yield) as a white solid after purification by flash chromatography, eluting with 0-40% Et₂O in hexanes (elution gradient). **mp** 99-101 °C. **¹H NMR** (600 MHz, CDCl₃) δ 4.38 (s, 2H), 3.42 (m, 4H), 1.66 (m, 4H), 1.62 (m, 2H). **¹³C NMR** (150 MHz, CDCl₃) δ 47.7, 40.1, 26.0, 23.8. **IR** (neat) 3021, 2953, 2936, 1449, 1372, 1331, 1249, 1162, 1140, 1100, 1078, 958, 934, 855, 829, 751, 682, 608. **HRMS** (HESI) calcd for [C₆H₁₂BrNO₂S+Na]⁺: *m/z*, 263.96643 found 263.96594.

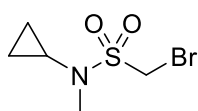


1-((1-Bromomethyl)sulfonyl)morpholine (87). General procedure C was followed, starting with 1-(methylsulfonyl)morpholine (**98**) (165 mg, 1.0 mmol, 1.0 equiv), *n*-BuLi (2.0 M in THF/hexanes, 0.55 mL, 1.1 mmol, 1.1 equiv), and DBDMH (429 mg, 1.5 mmol, 1.5 equiv) in dioxane for 3.5 h, affording **87** (107 mg, 44% yield) as a white solid after purification by flash chromatography, eluting with 0-5% MeOH in DCM (elution gradient). **mp** 134-135 °C. **¹H NMR** (500 MHz, CDCl₃) δ 4.42 (s, 2H), 3.79 – 3.72 (m, 4H), 3.60 – 3.22 (m, 4H). **¹³C NMR** (125 MHz, CDCl₃) δ 66.9, 46.9, 39.8. **IR** (neat). 3022 3038, 3022, 2967, 2953, 2920, 2856, 1448, 1372, 1323, 1255, 1182, 1161, 1139, 1077, 956, 846, 829, 791, 774, 750, 668, 604, 526, 490. **HRMS** (HESI) calcd for [C₅H₁₀BrNO₃S+Na]⁺: *m/z*, 265.94570 found 265.94541.



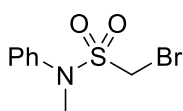
1-((1-Bromomethyl)sulfonyl)-4-methylpiperazine (88). General procedure A was followed, starting with 1-(methylsulfonyl)-4-methylpiperazine (**99**) (178 mg, 1.0 mmol, 1.0 equiv), *n*-BuLi (2.0 M in THF/hexanes, 0.55 mL, 1.1 mmol, 1.1 equiv),

and DBDMH (429 mg, 1.5 mmol, 1.5 equiv) in dioxane for 3.5 h, affording **88** (56 mg, 22% yield) as a white solid after purification by flash chromatography, eluting with 0-5% MeOH in DCM (elution gradient). **mp** 153-155 °C **¹H NMR** (500 MHz, CDCl₃) δ 4.40 (s, 2H), 3.48 (t, J = 5.0 Hz, 4H), 2.48 (t, J = 5.0 Hz, 4H), 2.32 (s, 3H). **¹³C NMR** (150 MHz, CDCl₃) δ 54.8, 46.7, 46.1, 40.0. **IR** (neat) 3032, 2967, 2915, 2854, 1443, 1364, 1320, 1256, 1198, 1151, 1104, 1073, 951, 921, 841, 771, 708, 524, 492. **HRMS** (HESI) calcd for [C₆H₁₄N₂O₂BrS+H]⁺: *m/z*, 256.99539 found 227.99477.



1-((1-Bromomethyl)sulfonyl)-N-methyl-cyclopropylamine (89). General

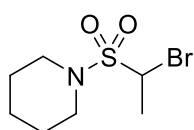
procedure C was followed, starting with (methylsulfonyl)-*N*-methyl-cyclopropylamine (**100**) (149 mg, 1.0 mmol, 1.0 equiv), *n*-BuLi (2.0 M in THF/hexanes, 0.55 mL, 1.1 mmol, 1.1 equiv), and DBDMH (429 mg, 1.5 mmol, 1.5 equiv) in dioxane for 3.5 h, affording **89** (96 mg, 42% yield) as a white solid after purification by flash chromatography, eluting with 50-80% Et₂O in hexanes (elution gradient). **mp** 46-48 °C. **¹H NMR** (500 MHz, CDCl₃) δ 4.50 (s, 2H), 3.05 (s, 3H), 2.58 (tt, J = 6.9, 3.6 Hz, 1H), 0.93–0.87 (m, 2H), 0.84–0.77 (m, 2H). **¹³C NMR** (125 MHz, CDCl₃) δ 39.3, 38.5, 32.0, 7.8. **IR** (neat) 3041, 2970, 1451, 1371, 1337, 1254, 1204, 1167, 1141, 1080, 1054, 1023, 958, 937, 856, 827, 773, 755, 685, 657, 530, 502. **HRMS** (HESI) calcd for [C₅H₁₁BrNO₂S+H]⁺: *m/z*, 227.96884 found 227.96851.



1-((1-Bromomethyl)sulfonyl)-N-methylaniline (90). General procedure C was

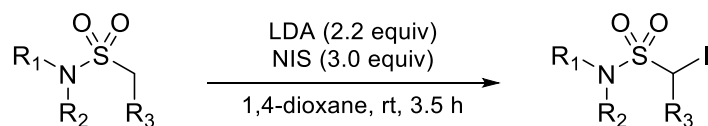
followed, starting with (methylsulfonyl)-*N*-methylaniline (**101**) (185 mg, 1.0 mmol, 1.0 equiv), *n*-BuLi (2.0 M in THF/hexanes, 0.55 mL, 1.1 mmol, 1.1 equiv), and DBDMH (429 mg, 1.5 mmol, 1.5 equiv) in dioxane for 3.5 h, affording **90** (66 mg, 25% yield) as a colorless oil after purification by flash chromatography, eluting with 0-40% EA in hexanes (elution gradient). **¹H NMR** (500 MHz, CDCl₃) δ 7.51–7.45 (m, 2H), 7.42 (dd, J = 8.7, 6.8 Hz,

2H), 7.39–7.31 (m, 1H), 4.41 (s, 2H), 3.52 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 140.5, 129.8, 128.3, 127.2, 41.4, 39.7. **IR** (neat) 3061, 3042, 2955, 2924, 2852, 1595, 1492, 1453, 1349, 1268, 1182, 1143, 1066, 1026, 889, 828, 771, 697, 658, 574, 538. **HRMS** (HESI) calcd for $[\text{C}_8\text{H}_{10}\text{BrNO}_2\text{S}+\text{Na}]^+$: m/z , 285.95078 found 285.95022.



1-((1-Bromoethyl)sulfonyl)piperidine (91). General procedure C was followed, starting with 1-(ethylsulfonyl)piperidine **102** (177 mg, 1.0 mmol, 1.0 equiv), *n*-BuLi (2.0 M in THF/hexanes, 0.55 mL, 1.1 mmol, 1.1 equiv), and DBDMH (429 mg, 1.5 mmol, 1.5 equiv) in dioxane for 3.5 h, affording **91** (81 mg, 32%) as a colorless oil after purification by flash chromatography, eluting with 15–40% EA in hexanes (elution gradient). ^1H NMR (500 MHz, CDCl_3) δ 4.86 (q, $J = 6.9$ Hz, 1H), 3.42 (d, $J = 5.7$ Hz, 3H), 2.00 (d, $J = 6.9$ Hz, 4H), 1.65 (m, 4H), 1.62–1.60 (m, 2H). ^{13}C NMR (125 MHz, CDCl_3) δ 57.1, 48.2, 26.2, 23.9, 21.2. **IR** (neat) 2935, 2854, 1443, 1333, 1279, 1165, 1141, 1054, 1042, 948, 853, 834, 743, 623, 575, 552, 533, 493. **HRMS** (HESI) calcd for $[\text{C}_7\text{H}_{14}\text{BrNO}_2\text{S}+\text{Na}]^+$: m/z , 277.98208 found 277.98163.

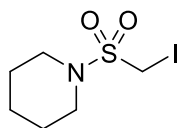
GENERAL PROCEDURE D: Synthesis of α -monoiodosulfonamides 92,94-97



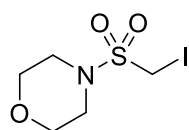
An oven-dried microwave vial equipped with a magnetic stirbar was charged with the alkyl sulfonamide (1.0 mmol, 1.0 equiv), capped and flushed with N_2 . Anhydrous dioxane (7.5 mL) was added and to the resulting solution was added LDA (2.0 M in THF/n-heptane/ethylbenzene, 1.1 mL, 2.2 mmol, 2.2 equiv) and stirred for 1.5 hours. After this time, the deprotonated sulfonamide solution was transferred via syringe to a separate oven-dried microwave vial containing NIS (675 mg, 3.0 mmol, 3.0 equiv) in 1,4-dioxane (15 mL). The reaction mixture was stirred for 2 h and then quenched by slow addition of aqueous sat. Na_2SO_3 (15 mL) and extracted with CH_2Cl_2 (3 x 80 mL). The combined organic fractions were washed with aqueous sat. Na_2SO_3 (2 x 80 mL), dried over Na_2SO_4 , and concentrated under vacuum to give the crude α -iodinated sulfonamide, which was purified by flash chromatography to afford the pure product.

Important note: Using wet dioxane will result in lower yields and loss of selectivity.

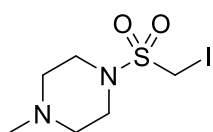
Specific procedures and characterization data of 92,94-97



1-((1-Iodomethyl)sulfonyl)piperidine (92). General procedure D was followed, starting with 1-(methylsulfonyl)piperidine (**84**) (163 mg, 1.0 mmol, 1.0 equiv), LDA (2.0 M in THF/n-heptane/ethylbenzene, 1.1 mL, 2.2 mmol, 2.2 equiv), and NIS (675 mg, 3.0 mmol, 3.0 equiv) in dioxane for 3.5 h, affording **92** (168 mg, 58% yield) as a white solid after purification by flash chromatography, eluting with 0-40% Et₂O in hexanes (elution gradient). **mp** 50-51 °C. **¹H NMR** (600 MHz, CDCl₃) δ 4.33 (s, 2H), 3.38 (t, J = 5.2 Hz, 4H), 1.67 (m, 4H), 1.61 (m, 2H). **¹³C NMR** (150 MHz, CDCl₃) δ 47.8, 25.9, 23.9, 9.9. **IR** (neat). 3032, 2947, 2926, 2913, 2854, 1447, 1321, 1278, 1255, 1160, 1139, 1100, 1053, 1024, 933, 852, 830, 792, 751, 702, 546, 528, 513. **HRMS** (HESI) calcd for [C₆H₁₂INO₂S+Na]⁺: *m/z*, 311.95256 found 311.95172.

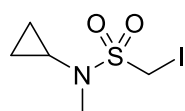


1-((1-Iodomethyl)sulfonyl)morpholine (94). General procedure D was followed, starting with 1-(methylsulfonyl)morpholine (**98**) (165 mg, 1.0 mmol, 1.0 equiv), LDA (2.0 M in THF/n-heptane/ethylbenzene, 1.1 mL, 2.2 mmol, 2.2 equiv), and NIS (675 mg, 3.0 mmol, 3.0 equiv) in dioxane for 3.5 h, affording **94** (116 mg, 40% yield) as a white solid after purification by flash chromatography, eluting with 0-20% Et₂O in DCM (elution gradient). **mp** 189-197 °C. **¹H NMR** (500 MHz, CDCl₃) δ 4.36 (s, 2H), 3.94 – 3.64 (m, 4H), 3.50 – 3.29 (m, 4H). **¹³C NMR** (125 MHz, CDCl₃) δ 66.8, 47.0, 9.1. **IR** (neat) 3032, 2967, 2915, 2890, 2854, 1444, 1364, 1320, 1256, 1151, 1121, 1104, 1073, 951, 921, 771, 708, 631, 524, 492. **HRMS** (HESI) calcd for [C₅H₁₀INO₃S+Na]⁺: *m/z*, 313.93183 found 313.93100.



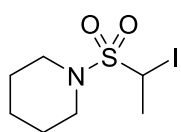
1-((1-Iodomethyl)sulfonyl)-4-methylpiperazine (95). General procedure D was followed, starting with 1-(methylsulfonyl)-4-methylpiperazine (**99**) (178

mg, 1.0 mmol, 1.0 equiv), LDA (2.0 M in THF/n-heptane/ethylbenzene, 1.1 mL, 2.2 mmol, 2.2 equiv), and NIS (675 mg, 3.0 mmol, 3.0 equiv) in dioxane for 3.5 h, affording **95** (103 mg, 34% yield) as a white solid after purification by flash chromatography, eluting with 0-5% MeOH in DCM (elution gradient). **mp** 100-104 °C. **¹H NMR** (500 MHz, CDCl₃) δ 4.34 (s, 2H), 3.44 (t, J = 5.0 Hz, 4H), 2.48 (t, J = 5.0 Hz, 4H), 2.32 (s, 3H). **¹³C NMR** (125 MHz, CDCl₃) δ 54.7, 46.7, 46.0, 9.5. **IR** (neat) 3027, 2921, 2786, 2161, 1445, 1334, 1320, 1286, 1162, 1143, 1143, 1088, 1067, 947, 762, 553, 524, 488. **HRMS** (HESI) calcd for [C₆H₁₄IN₂O₂S+H]⁺: *m/z*, 304.98152 found 304.98093.



1-((1-Iodomethyl)sulfonyl)-N-methyl-cyclopropylamine (96). General procedure D was followed, starting with (methylsulfonyl)-N-methyl-

cyclopropylamine (**100**) (149 mg, 1.0 mmol, 1.0 equiv), LDA (2.0 M in THF/n-heptane/ethylbenzene, 1.1 mL, 2.2 mmol, 2.2 equiv), and NIS (675 mg, 3.0 mmol, 3.0 equiv) in dioxane for 3.5 h, affording **96** (157 mg, 57% yield) as a white solid after purification by flash chromatography, eluting with 0-40% EA in hexanes (elution gradient). **mp** 79-82 °C **¹H NMR** (500 MHz, CDCl₃) δ 4.45 (s, 2H), 3.02 (s, 3H), 2.52 (tt, J = 6.9, 3.6 Hz, 1H), 0.90 (m, 2H), 0.82 (m, 2H). **¹³C NMR** (125 MHz, CDCl₃) δ 38.5, 32.2, 8.9, 7.9. **IR** (neat) 3022, 2953, 1741, 1450, 1372, 1332, 1248, 1165, 1138, 1077, 1022, 957, 935, 853, 827, 781, 749, 679, 605. **HRMS** (HESI) calcd for [C₅H₁₀INO₂S+Na]⁺: *m/z*, 297.93691 found 297.93636.



1-((1-Iodoethyl)sulfonyl)piperidine (97). General procedure D was followed, starting with 1-(ethylsulfonyl)piperidine (**102**) (177 mg, 1.0 mmol, 1.0 equiv),

LDA (2.0 M in THF/n-heptane/ethylbenzene, 1.1 mL, 2.2 mmol, 2.2 equiv), and NIS (675 mg, 3.0 mmol, 3.0 equiv) in dioxane for 3.5 h, affording **97** (110 mg, 36% yield) as a white solid after purification by flash chromatography, eluting with 0-25% EA in hexanes (elution gradient). **mp**

53-55 °C. **¹H NMR** (500 MHz, CDCl₃) δ 5.00 (q, J = 7.0 Hz, 1H), 3.41 (t, J = 5.2 Hz, 4H), 2.18 (d, J = 7.0 Hz, 3H), 1.65 (m, 4H), 1.62 (m, 2H). **¹³C NMR** (125 MHz, CDCl₃) δ 48.5 31.4, 26.3, 24.0, 23.8. **IR** (neat). 2960, 2937, 2858, 1442, 1329, 1319, 1282, 1211, 1160, 1141, 1108, 1053, 1043, 944, 906, 852, 731, 575, 540, 532, 490. **HRMS** (HESI) calcd for [C₇H₁₅INO₂S+H]⁺: *m/z*, 303.98627 found 303.98569.

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