

## ABSTRACT

GARIM YOU Structure-Reactivity Relationship Studies of Bifunctional (Benz)imidazolyl-Palladium Catalysts in Cross-Coupling Reactions. (Under the direction of Dr. Vincent Lindsay).

In the past few decades, N-heterocyclic carbenes (NHCs) have evolved as a prominent class of ligands in metal catalysis because of their structural simplicity and their electronic and steric tunability. The conventional di-*N*-substituted NHC complexes have been employed in a variety of cross-coupling and C–H functionalization reactions. However, studies regarding the use of *protic* NHC-metal complexes (*p*NHC complexes) in catalysis, where at least one nitrogen atom is left unfunctionalized, remain scarce. These complexes are considered ‘bifunctional’, where the free NH-functionality of the ligand can participate in the catalysis, acting as hydrogen bond donor. Herein, we report the synthesis and use of imidazolyl-palladium complexes, the deprotonated form of *p*NHC complexes, as highly efficient bifunctional catalysts in sustainable cross-coupling reactions under environmentally benign conditions. In this work, the Lewis basic imidazolyl nitrogen atom in the ligand acts as the second functionality, promoting transmetallation events in an intramolecular manner. Moreover, a structure-reactivity study of 2-imidazolyl palladium complexes with various electronics is reported and used to evaluate the effect of varying electron properties to further improve their catalytic properties.

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Structure-Reactivity Relationship Studies of Bifunctional (Benz)imidazolyl-Palladium Catalysts  
in Cross-Coupling Reactions

by  
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## BIOGRAPHY

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## LIST OF ABBREVIATIONS

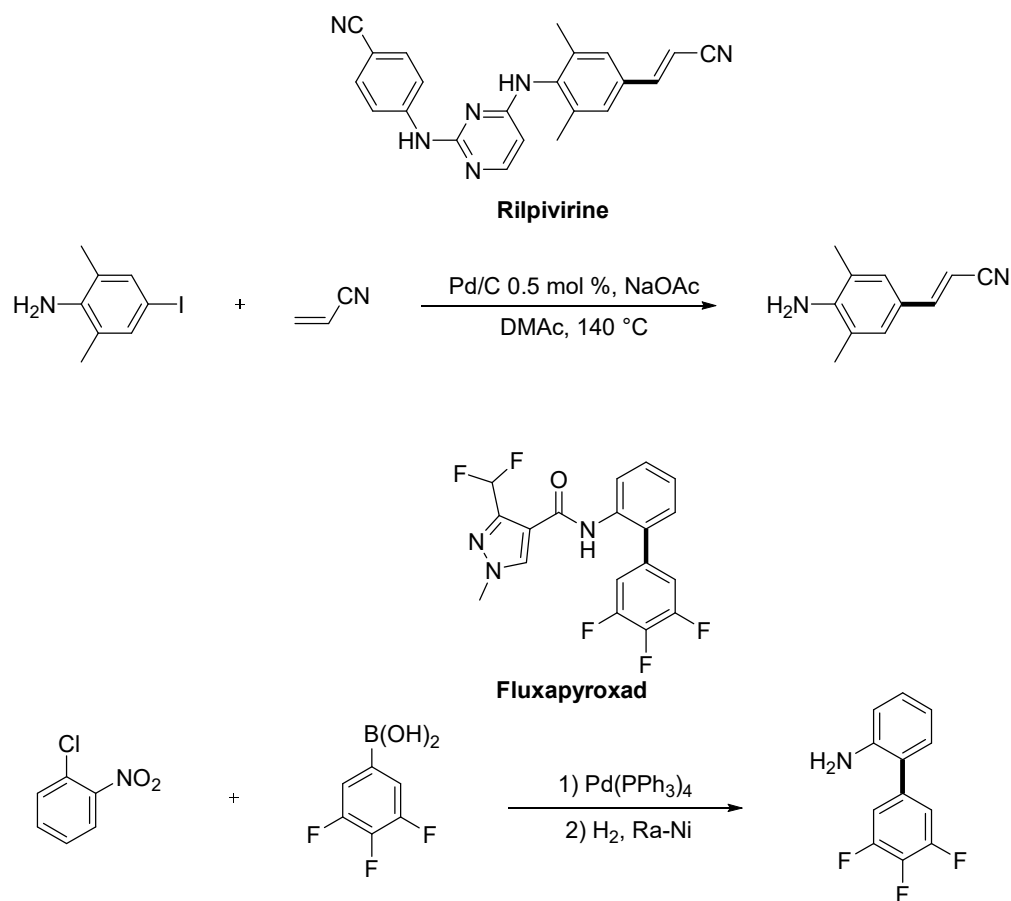
acac	Acetylacetone	HCl	Hydrochloric acid
AIBN	Azo(bis)isobutyronitrile	HRMS	High-resolution mass spectrometry
AgTFA	Silver trifluoroacetate		
AgOAc	Silver acetate	I <sub>2</sub>	Iodine
AgOPiv	Silver pivalate	K <sub>2</sub> CO <sub>3</sub>	Potassium carbonate
AgNTf <sub>2</sub>	Silver bis(Trifluoromethanesulfonyl)-imide	KMnO <sub>4</sub>	Potassium permanganate
		KOH	Potassium hydroxide
		LDA	Lithium diisopropylamide
AMLA	Ambiphilic metal ligand activation	Me	Methyl
		MeCN	Acetonitrile
BIES	Base-assisted intramolecular electrophilic-type substitution	MeI	Iodomethane
		MeLi	Methyl lithium
Bu	Butyl	MeOH	Methanol
<i>n</i> -BuLi	<i>n</i> -Butyllithium	min	Minutes
C <sub>2</sub> Cl <sub>6</sub>	Hexachloroethane	mmol	Millimoles
<sup>13</sup> C NMR	Carbon nuclear magnetic resonance	NaH	Sodium hydride
		NBS	<i>N</i> -Bromosuccinimide
CDCl <sub>3</sub>	Deuterated chloroform	NHC	<i>N</i> -heterocyclic carbene
CHCl <sub>3</sub>	Chloroform	NH <sub>4</sub> PF <sub>6</sub>	Ammonium hexafluorophosphate
CH <sub>2</sub> Cl <sub>2</sub>	Dichloromethane		
CMD	Concerted metalation-deprotonation	N.R.	No reaction
		OMe	Methoxy
CsF	Cesium fluoride	Pd	Palladium
DCE	1,2-Dichloroethane	Pd <sub>2</sub> (dba) <sub>3</sub>	Tris(dibenzylideneacetone)dipalladium(0)
DMF	<i>N,N</i> -Dimethylformamide		
DMSO	Dimethyl sulfoxide	Pd(OAc) <sub>2</sub>	Palladium(II) acetate
EDG	Electron-donating group	Ph	Phenyl
Et	Ethyl	<i>n</i> -Pr	Propyl
Et <sub>2</sub> O	Diethyl ether	rt	Room temperature
Et <sub>3</sub> N	Triethylamine	S.M.	Starting material
EtOH	Ethanol	TFA	Trifluoroacetic acid
Equiv	Equivalents	THF	Tetrahydrofuran
EWG	Electron-withdrawing group	TLC	Thin-layer chromatography
FG	Functional group	TMSCl	Trimethylsilyl chloride
FT-IR	Fourier-transform infrared		
<sup>1</sup> H NMR	Proton nuclear magnetic resonance		

## 1. General Introduction

### 1.1 Introduction to Green Methodologies for Cross-Coupling Reactions

Carbon-carbon bond-forming reactions constitute some of the most important processes in organic chemistry, as they serve as key steps in the elaboration of complex molecules from simple precursors.<sup>1</sup> Along with the dramatic developments of organometallic chemistry in the past few decades, many types of metal catalysts and ligands were developed and applied to the coupling of organic molecules, leading to a highly important research topic in chemical synthesis.<sup>2</sup> First identified in early 1970's, palladium-based catalysts have gained enormous significance in organic chemistry.<sup>3</sup> These types of transformations offer several advantages such as high reaction rate, high yield, total cost reduction, application in asymmetric catalysis, high atom economy, high tolerance to functional groups, low waste, and low reaction temperatures.<sup>4</sup> Because of all these advantages, several named reactions in this field such as the Suzuki-Miyaura,<sup>3</sup> Sonogahira-Hagihara,<sup>5</sup> and Heck-Mizoroki,<sup>6</sup> have been explored and broadly applied in industrial areas, thus furthering the development of pharmaceuticals, agrochemicals, and functional materials as well as greatly enlarging the scope of available transformations in organic synthesis.<sup>7</sup>

One relevant example is Rilpivirine, a potent non-nucleoside reverse transcriptase inhibitor used for the treatment of HIV (approved by the FDA in 2011). Its preparation on an industrial scale (about 1 ton per batch) has been developed by researchers at Johnson & Johnson and includes a Heck coupling of an aryl iodide substrate with acrylonitrile (**Figure 1**).<sup>8</sup> Another example is the fungicide Fluxapyroxad presented by BASF in 2012, a broad-spectrum pyrazole carboxamide fungicide, where a Suzuki coupling is used as one of the key synthetic steps.<sup>9</sup>



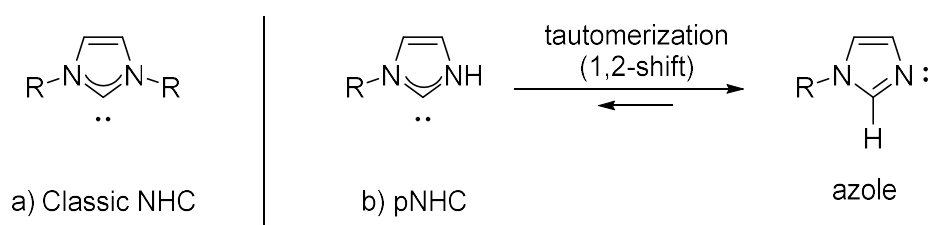
**Figure 1.** Examples of drugs and fungicides made via cross-coupling reactions

While cross-coupling has been a highly useful and versatile method for the development of modern drug discovery and in the synthesis of many natural products and polymers, the chemical industry is a major contributor to environmental pollution. Thus, research in green and sustainable organic chemistry is a quickly growing and nowadays constitutes a high impact research area. Due to the increasing concerns over the world's environment, green chemical reactions that diminish or remove the use of toxic chemicals and significantly reduce chemical waste are enforcing innovation in industry and academia.<sup>10</sup> Developing green chemistry methodologies is a challenge that may be viewed through the framework of the “Twelve Principles of Green Chemistry”.<sup>11</sup> These principles identify catalysis as one of the most valuable tools to

green chemistry as a development strategy (low metal catalyst loading, use of green solvent, ease of separation from the product, etc.). For the next few decades, this field will likely continue to be one of the main vehicles that takes the chemical enterprise into a sustainable future.

## 1.2 Introduction to Protic NHC-Metal Complexes and their Applications

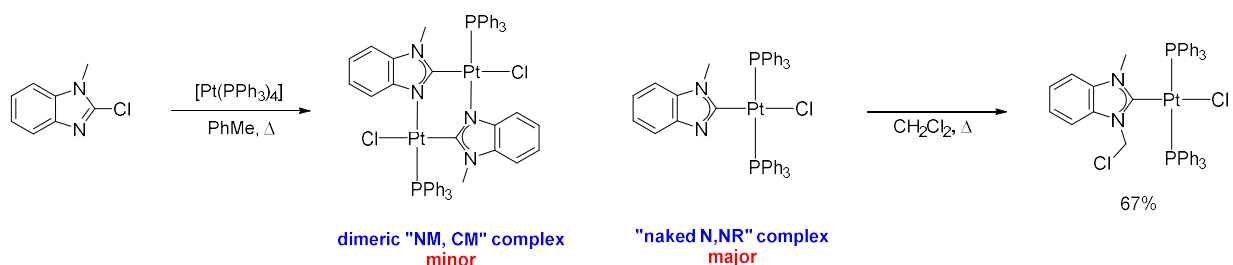
N-heterocyclic carbenes (NHCs) have been developed as a prominent class of efficient ligands in metal catalysis because of their structural simplicity and their electronic and steric tunability.<sup>12</sup> The conventional (classic) di-*N*-substituted NHC complexes have been employed in a variety of cross-coupling and C–H functionalization reactions (**Figure 2a**). Of importance is the ability of NHC ligands to enable difficult oxidative additions through strong  $\sigma$ -donation to a wide variety of metal centers. Furthermore, NHC ligands represent one of the most versatile ways to vary the steric environment around the metal by *N*-wingtip substitution and backbone modifications of the ligand.<sup>13</sup>



**Figure 2.** Comparison between non-protic and protic N-Heterocyclic Carbenes

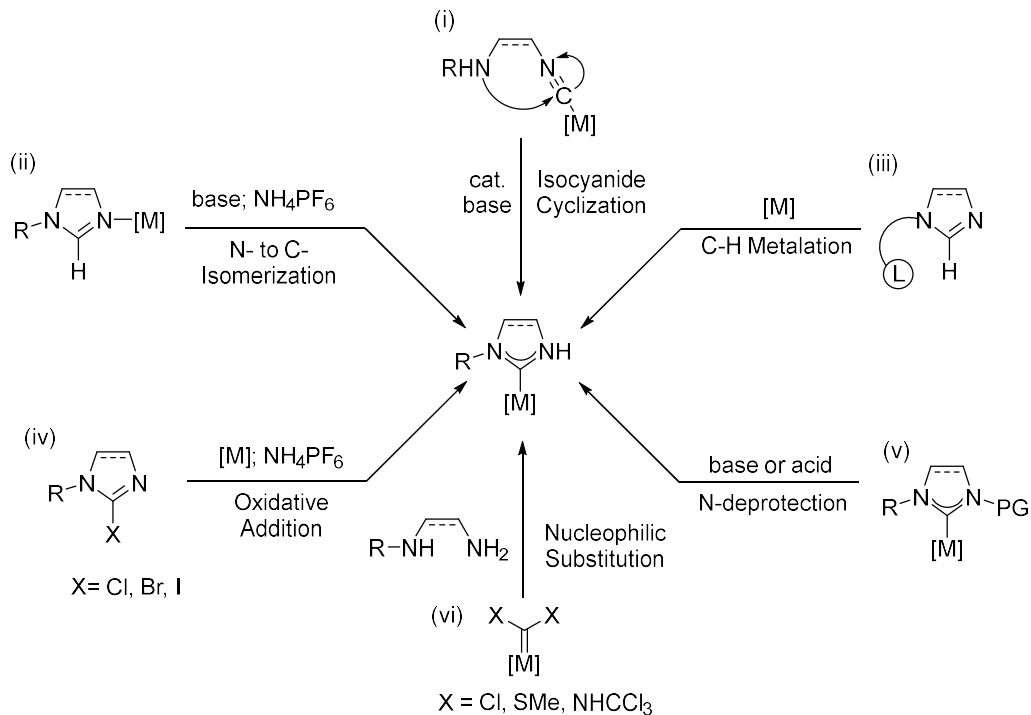
However, the protic version (**Figure 2b**) of these NHC ligands, where at least one side remains unsubstituted, has not been widely studied in catalysis.<sup>14</sup> Their deprotonated form is already known to be effective nucleophilic species at the free *N*-position. As a representative

example, this is supported by the research of Hahn et al illustrated in **Figure 3**.<sup>15</sup> The reaction of 2-chloro-*N*-methylbenzimidazole with  $[\text{Pt}(\text{PPh}_3)_4]$  gives a mixture of “naked N,NR” complex along with its dimerization product. Uniquely, this “naked N,NR” complex behaves as a strong *N*-nucleophile which attacks dichloromethane with formation of an *N*-alkylated complex, showing that the lone pair of N is nucleophilic enough to undergo alkylation. This also indicates that the basic *N*-functionality can potentially play significant role in catalytic cycles using these complexes as catalysts, facilitating, for example, a bond-breaking event. This type of *N*-functionalization via nucleophilic substitution has also been demonstrated with analogous palladium complexes.<sup>16</sup>



**Figure 3.** Example of the utilization the nucleophilicity of “naked N,NR” complex for alkylation

In the literature, a number of synthetic methods have already been disclosed to access protic NHCs, as summarized in **Figure 4**. These include: (i) cyclization of isocyanides and amines already bound to metal templates,<sup>17</sup> (ii) base/acid-promoted tautomerization of imidazole ligands,<sup>18-20</sup> (iii) chelation-assisted formal tautomerization of imidazoles,<sup>21</sup> (iv) oxidative addition of 2-haloimidazoles followed by *N*-protonation,<sup>22</sup> (v) deprotection of NH-masked NHC<sup>23,24</sup> and (vi) nucleophilic substitution of Fischer carbene complexes.<sup>25</sup> These established methods have thus been extremely useful for the formation of structurally diverse complexes for evaluation in catalysis during our studies.



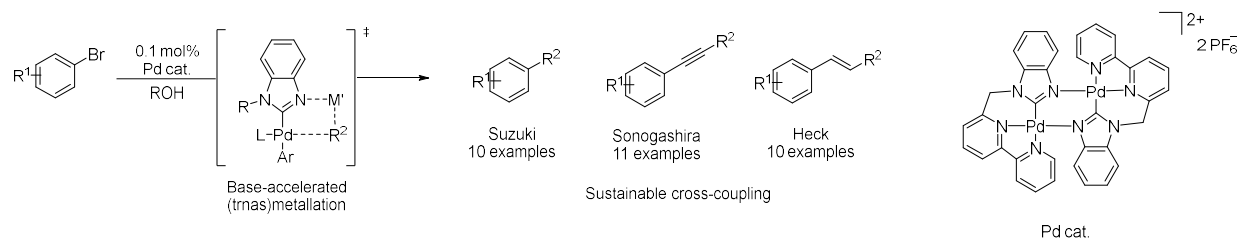
**Figure 4.** Representative synthetic strategies to access *p*NHC complexes

## 2. Design and Synthesis of 2-Benzimidazolyl-Palladium Complexes

### 2.1. Structure-reactivity Relationship of NHC-Metal Complexes and Applications: Properties, Preparation and Design

In our group, Jiancheng Zhu reported that dinuclear palladium complexes bearing 2-benzimidazolyl ligands were highly effective in diverse cross-coupling reactions and also noticed that the use of multidentate ligands increased the catalytic activity by decreasing the risk of decomposition via ligand decomplexation, since it is still chelated by bipyridine and has a chance to reattach back to the ligand if such an event occurred during the reaction (**Figure 5**).<sup>26</sup> Our group

has hypothesized that in the case of cross-coupling reactions, the ligand's free nitrogen acts as a second functionality to accelerate key (trans)metalation steps in the mechanism. Obtaining the desirable complex for optimal catalytic activity thus not only requires synthetic skills but also an understanding of all kinds of factors influencing the fundamental steps of cross-coupling reactions.

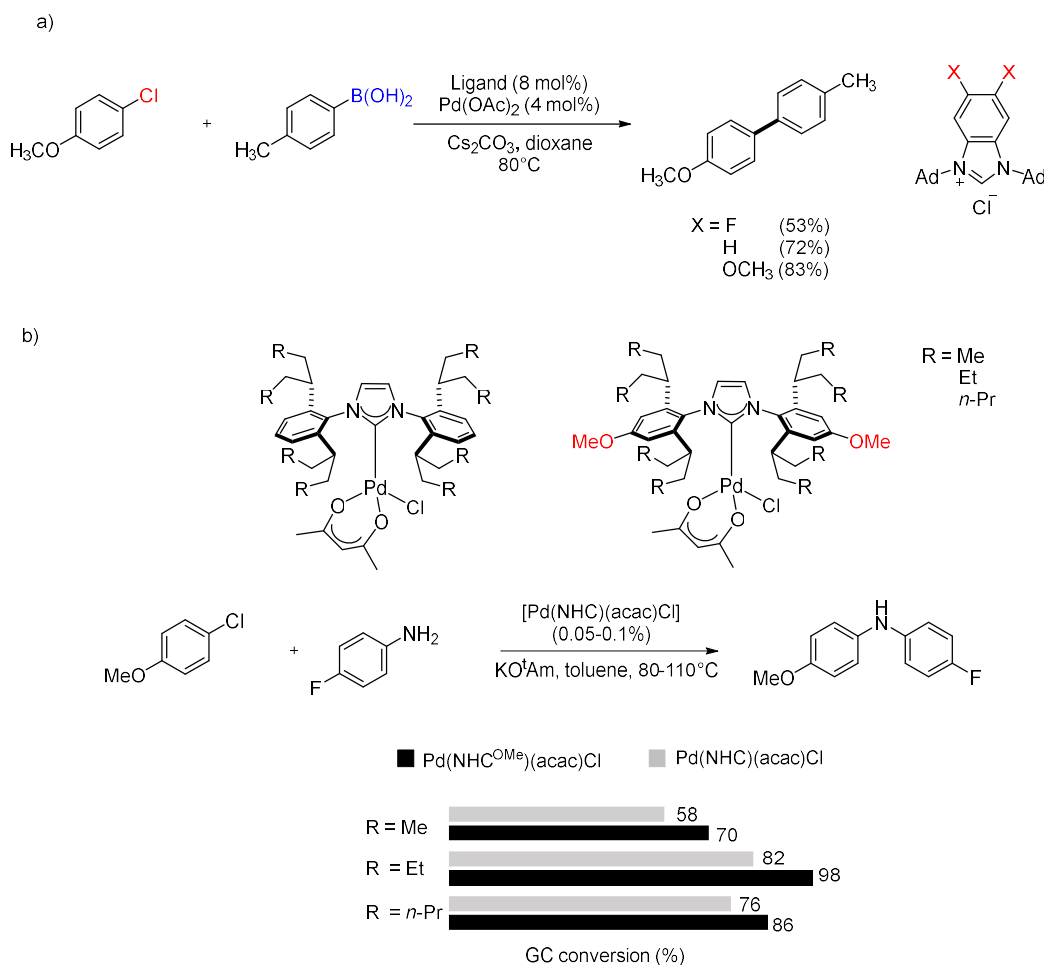


**Figure 5.** 2-(Benz)imidazolyl-metal complexes as sustainable cross-coupling catalysts

We then hypothesized that an optimal combination of bite angle and electronic properties of the ligands may further improve the performance of ligands in catalysis.<sup>27</sup> For example, the electronic nature of N-heterocyclic carbenes ligand has previously been shown in the literature to have an impact on many elementary steps of catalytic cycles.<sup>28</sup> For facile oxidative addition into the strong carbon-chlorine bond of aryl chlorides, an electron-rich ligand is needed and their strong  $\sigma$ -donor character plays a major role in their ability to perform in this regard.<sup>29</sup> First, one of the best way to change the electronic properties of an NHC is to alter the nature of the azole ring. In this respect, it is reasonable to assume that the electron-donating effect should increase in the order of benzimidazole < imidazole < imidazoline, which is in line with some previously reported computational data.<sup>30</sup> Second, appending an additional bipyridine side-arm can expand the tunability of the electronic properties of the ligands, as the substituents are not directly attached to the sensitive NHC heterocycle. In addition, such distal substitution does not lead to perturbation

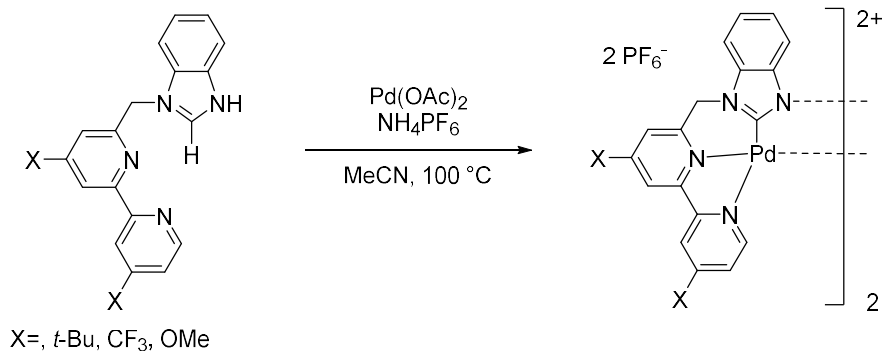
of the steric environment that the ligands create around the Pd center, if for example the substituents are added at the 4 and 4' positions of the bipyridine moiety.

As an example of the aforementioned strategies, the Organ group reported the electronic effects of the NHC ligand in the Suzuki-Miyaura coupling using the *N,N*-bis(adamantyl) derivatives (**Figure 6a**).



**Figure 6.** (a) Ligand activity *N,N'*-bis(adamantyl)benzimidazolium salt in the Suzuki-Miyaura coupling; (b) Comparison of [Pd(NHC<sup>OMe</sup>)(acac)Cl] and [Pd(NHC)(acac)Cl] precatalysts in aryl amination

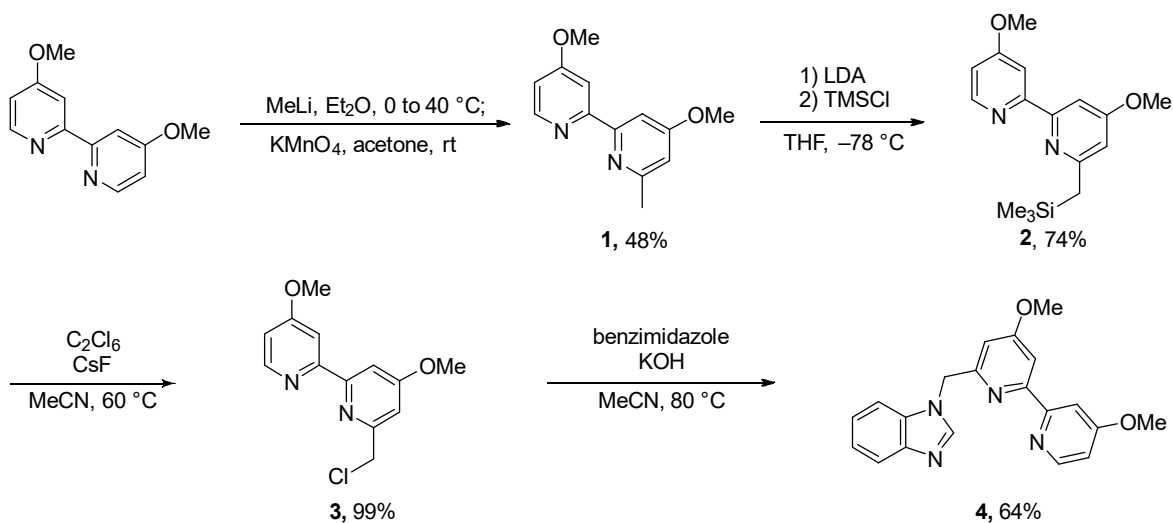
The reactions conducted with the electron-deficient ligand yielded the lowest amount of product, while the most electron-rich ligand was found to give the highest yield.<sup>31</sup> In another example, Nolan and co-workers demonstrated that [Pd(NHC<sup>OMe</sup>)(acac)Cl] exhibited excellent catalytic activity in Buchwald-Hartwig coupling reactions and it was superior to their less electron-rich [Pd(NHC)(acac)Cl] analogues. The extra  $\sigma$ -donor properties could offer greater stabilization of the NHC complex and these results suggest that oxidative addition is the rate-determining step of the process, the overall rate being increased by an electron-rich metal center. (**Figure 6b**).<sup>32</sup> Thus, we have focused on designing new NHC ligands with various electronic properties and aimed to use these ligands to identify cross-coupling reactivity trends to aid further ligand design. In order to modify the electronic nature of catalysts, Jiancheng introduced more electron-rich *tert*-butyl-substituted bipyridine moieties on the ligand (compared to unsubstituted bipyridine), and it afforded high conversion with very low catalyst loading (0.01%) for a model Suzuki reaction, providing the basis of a suitable structure reactivity study platform for tuning the electron density on the metal center (*not shown*). In this work, the systematic modification of the electronic properties of the aromatic rings, introduced by the presence of a *tert*-butyl, methoxy and trifluoromethyl groups will thus be used to evaluate the effect of electronic properties, ultimately affecting the electron density of the metal center and providing a deeper understanding of these novel complexes in catalysis (**Figure 7**). This will possibly allow the use of minute catalyst loading for the overall catalytic reactions to proceed, and possibly lead to a wider scope of substrates.



**Figure 7.** Structural modifications of catalyst for catalytic activity studies

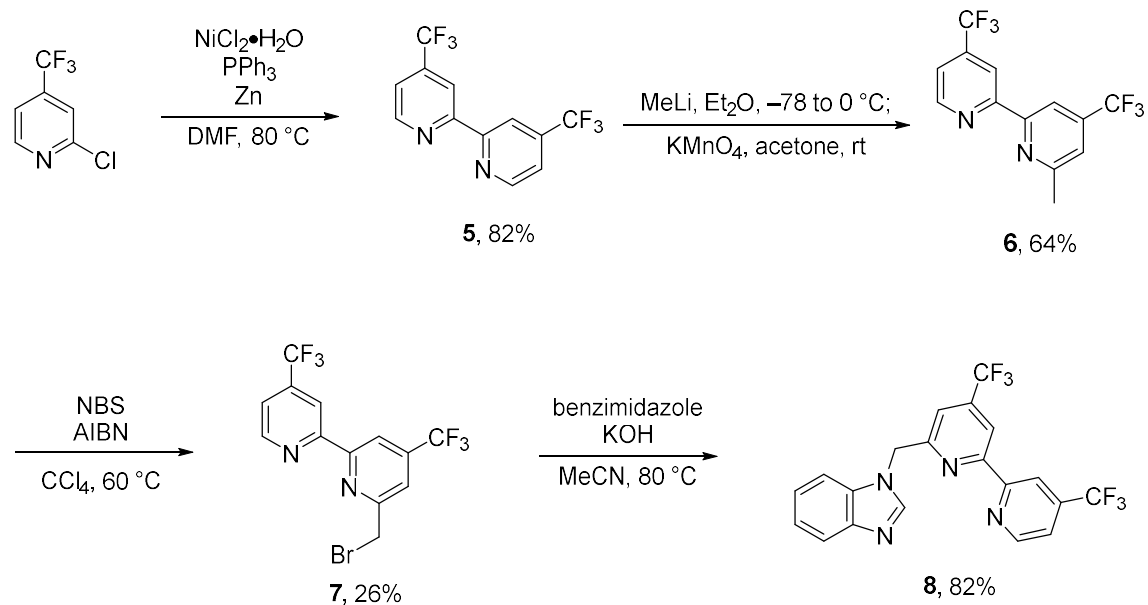
## 2.2 Syntheses of 2-Imidazolyl-Palladium Complexes

According to previous results obtained in our group, we hypothesized that the reactivity of the palladium catalysts could be fine-tuned by diversifying substituents on the bipyridine moiety. As a first target, we aimed to synthesize a (bis)methoxy-substituted ligand by following the procedure reported by Jiancheng. As shown in **Scheme 1**, 4,4'-dimethoxy-2,2'-bipyridine was treated with MeLi at 0 °C and then refluxed at 40 °C to methylate the 2-position in 48% yield. The methyl group was then lithiated at -78 °C and treated with TMSCl in THF to yield the trimethylsilyl-substituted intermediate **2** in 74% yield. Subsequent chlorination proceeded with hexachloroethane and CsF in MeCN at elevated temperature. Benzimidazole was deprotonated and underwent nucleophilic attack to compound **3**, thus delivering the desired tridentate ligand **4** in 64% yield.



**Scheme 1.** Synthetic route to tridentate ligand **4**.

In addition, an electron-poor ligand (**8**) was prepared with trifluoromethyl groups to compare its electronic effect on the catalytic activity. As shown in **Scheme 2**, trifluoromethyl-substituted bipyridine was accessed through nickel-catalyzed coupling of a 2-halopyridine. This was followed by our previous procedure for the methylation at the 2-position. Since the initial yield of this methylation was found to be less than ideal when performed in our previous conditions (25%, **Table 1**, entry 1), we performed a brief optimization in an attempt to improve it, which revealed that running the reaction at 0 °C for 15 minutes led to a better yield (64%, entry 6), likely due to a better control over undesired dimethylation. For the subsequent chlorination, the previously developed silylation was attempted first, but no positive result was obtained. As an alternative, substrate **6** was treated with NBS in the presence of AIBN to afford the monobrominated product in modest yield. The sequence was then completed via nucleophilic addition of deprotonated benzimidazole, generating a trifluoromethyl-substituted version of the ligand (**8**) in 82% yield.



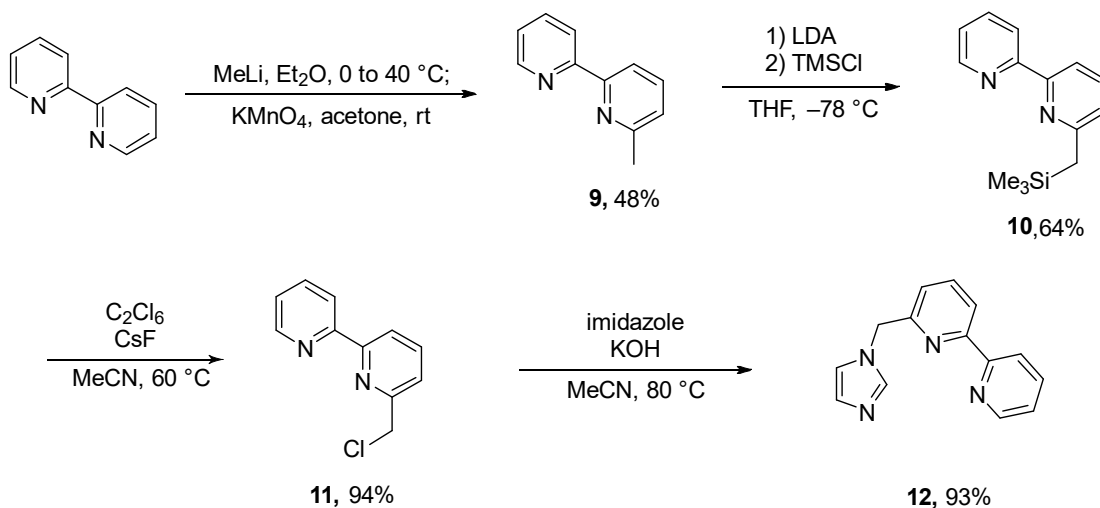
**Scheme 2.** Synthetic route to tridentate ligand **8**

**Table 1.** Optimization of the 2-methylation of 4,4'-bis(trifluoromethyl)-2,2'-bipyridine.

<i>Entry</i>	<i>Time &amp; Temp</i>	<i>Yield (%)</i>	<i>Starting Material Left (%)</i>
1	0 °C → 40 °C	25	-
2	-78 °C (2 h) → rt (1 h)	34	-
3	-78 °C (2h) → 0 °C	17	40
4	-78 °C (2 h) → 0 °C (1 h)	44	-
5	-78 °C (2h) → 0 °C (30 min)	52	-
<b>6</b>	<b>-78 °C (2h) → 0 °C (15 min)</b>	<b>64</b>	-

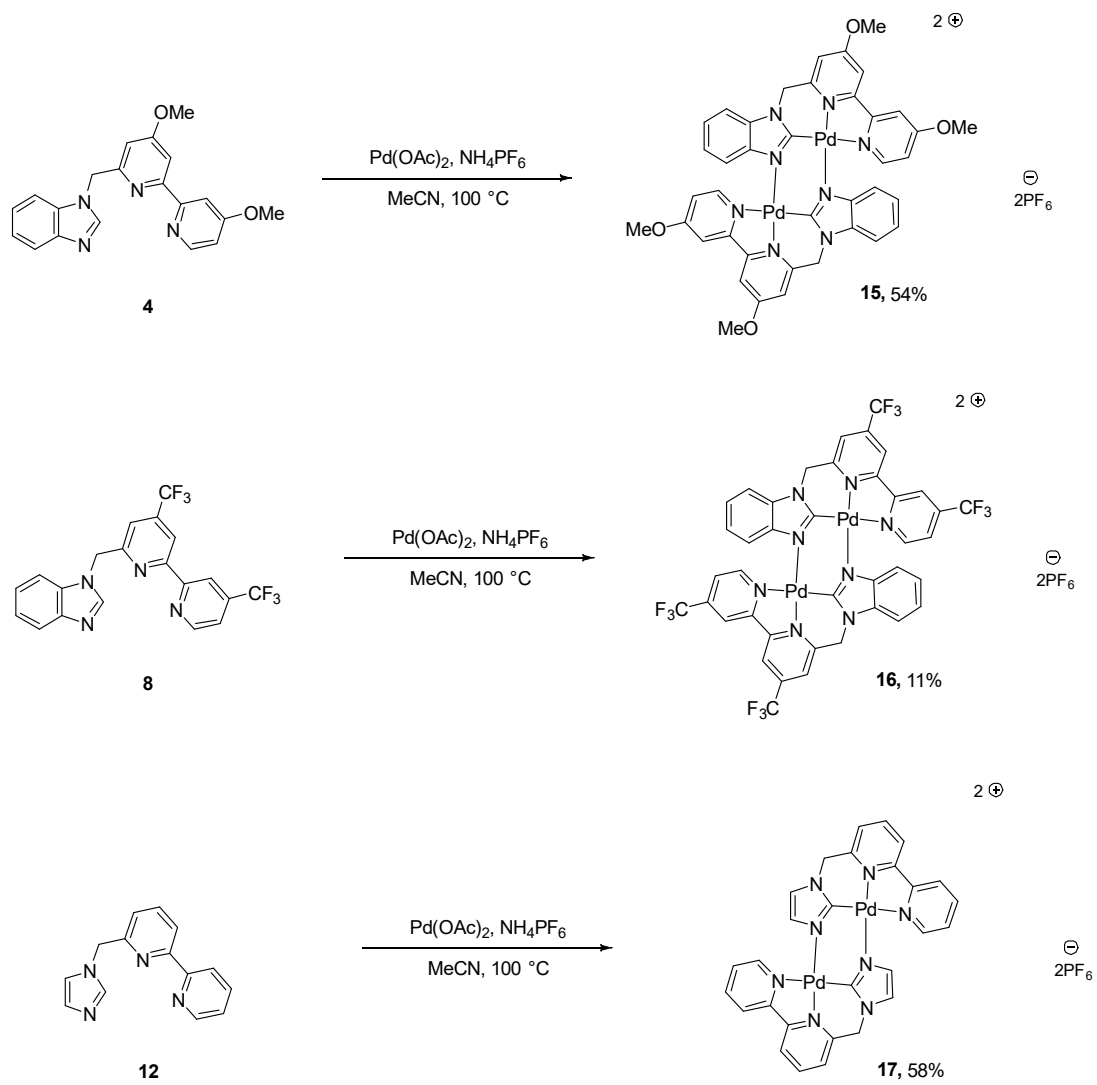
We also wanted to evaluate the steric and electronic effects of modifying the benzimidazole ring itself. To do so, one important derivative designed consists of replacing the benzimidazole moiety by an imidazole, which should be both more electron-donating to the metal and less

sterically crowded around the nitrogen atom acting as a second functionality in the final catalyst. As shown in **Scheme 3**, 2,2'-bipyridine was treated with MeLi at 0 °C and then refluxed at 40 °C to methylate at C(2) in 48% yield after oxidation with KMnO<sub>4</sub>. The methyl group was lithiated at -78 °C and treated with TMSCl in THF to yield the trimethylsilyl intermediate **10** in 64% yield. Subsequent chlorination proceeded in 94% yield using hexachloroethane and CsF in MeCN at elevated temperature. Using imidazole and KOH generated the nucleophile to react with **11** and thus delivered the desired tridentate ligand **12** in 93% yield.



**Scheme 3.** Synthetic route to tridentate ligand **12**

Complexation of the tridentate ligand **15**, **16**, and **17** prepared with Pd(OAc)<sub>2</sub> via bipyridine directed C–H activation delivered the dinuclear benzimidazolyl-Pd complexes (**Scheme 4**). As noticed here, the yield of C–H activation with electron-poor ligand **8** was significantly lower than usual (11%), likely due to the poor ability of such an electron-poor bipyridine to act as directing group via initial complexation of the palladium center.



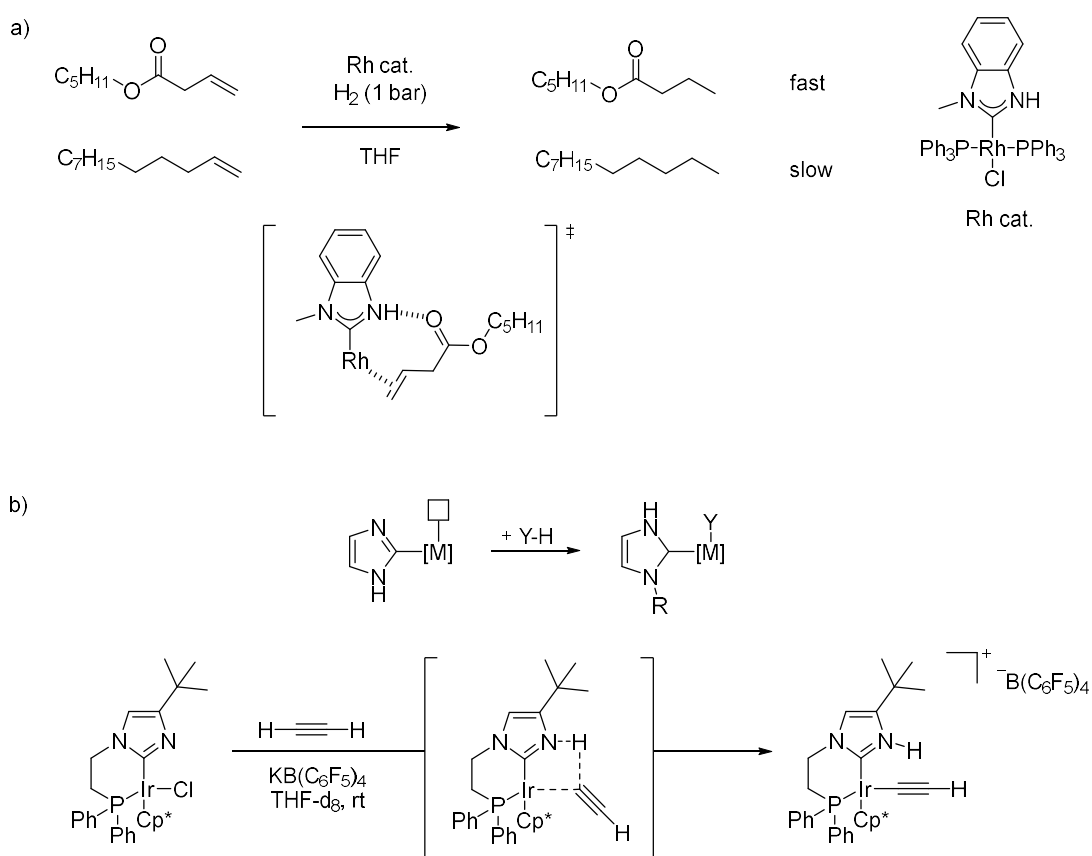
**Scheme 4.** Synthesis of complexes **15-17**

## 3. 2-Imidazolyl-Pd Complexes Catalyzed Cross-Couplings

### 3.1 Introduction to Cross-Coupling with New Perspectives

The general concept behind bifunctional catalysis is that two distinct types of active sites are present in the same catalyst framework, thus lowering the energy of the transition state of difficult mechanistic steps and increasing the rate of the overall process. However, a more sophisticated approach is often required for designing bifunctional catalysts, as these not only combine two complementary catalytic sites on the catalyst structure but also require for participation of these complementary catalytic sites at the same time for the activation of one or more substrates. In the literature, this concept has emerged as a powerful tool allowing some of the most difficult transformations to proceed under mild conditions. Bifunctional catalysts work by control of a catalytic process through multiple weak catalyst-substrate interactions, in which the Lewis acids and basic functionalities, for example, interact directly with the substrate binding, activation, and transformation by the catalyst. In a lot of cases, the acidic site is modeled by a metal center and the basic site by an electron-rich ligand functional group (FG). One of key aspects for our catalyst design was inspired from the study of in the Hahn and Waldvogel groups.<sup>33</sup> Their studies show that 3-butenic acid ester was reduced nearly two times faster than 1-dodecene with a rhodium-*p*NHC complex, suggesting that the NH group of the carbene ligand can function as H-bond donor in the substrate recognition (**Figure 8a**). Another example is the one from Grotjahn and co-workers, using imidazol-2-yl complexes with a vacant coordination site at the metal and a basic nitrogen in proximity, which could facilitate breaking a C–H bond in substrates like acetylene or H<sub>2</sub>, forming NHC complexes containing an free NH moiety (**Figure 8b**).<sup>34</sup> Protic N-heterocyclic carbene complexes have been known for a long time, yet they have rarely been used as bifunctional

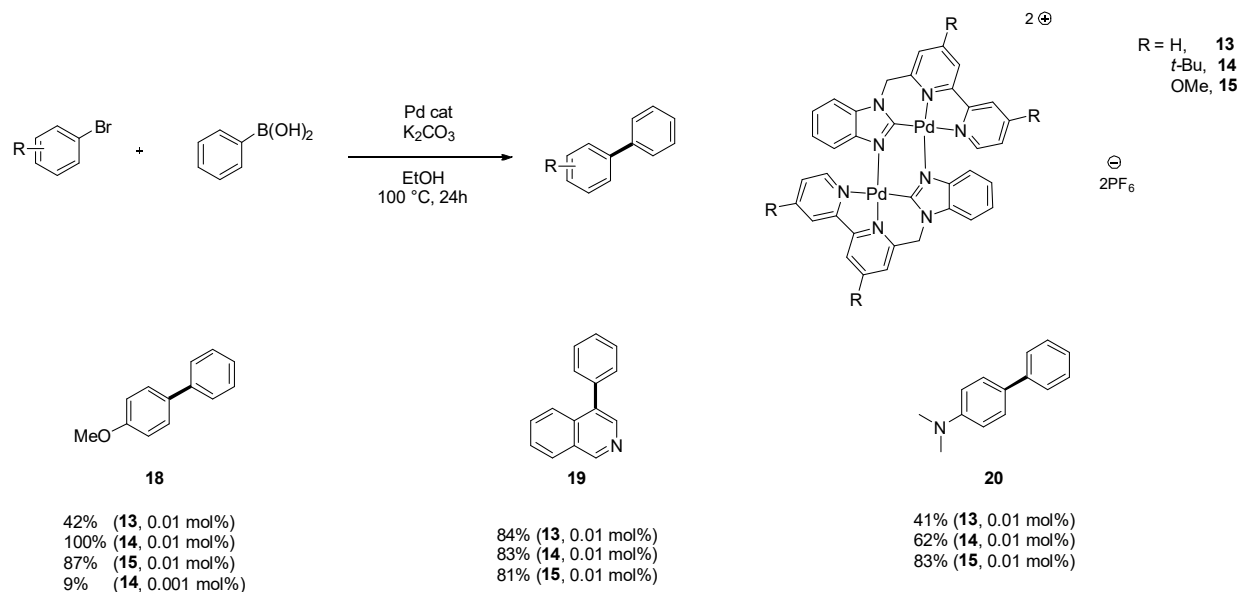
catalysts. In general, classic-di-N-substituted NHC metal complex had been applied on a variety of cross-couplings or C–H functionalization. On the other hand, in our catalytic system, the basic N-functionality of the ligand is proposed to coordinate to the FG of cross-coupling partners (e.g. B(OR)<sub>2</sub>) to accelerate key (trans)metalation steps, leading to a new mechanistic paradigm. Herein 2-imidazolyl-metal analogues were expected to catalyze traditional cross-coupling reactions with high efficiency.



**Figure 8.** (a) Competitive hydrogenation of alkenes with and without a carbonyl, catalyzed by a *p*NHC complex; (b) Metal–ligand bifunctional reactions of a *p*NHC-iridium complex

### 3.2 Evaluation of the 2-Imidazolyl-Palladium Complexes catalyzed Cross-Couplings.

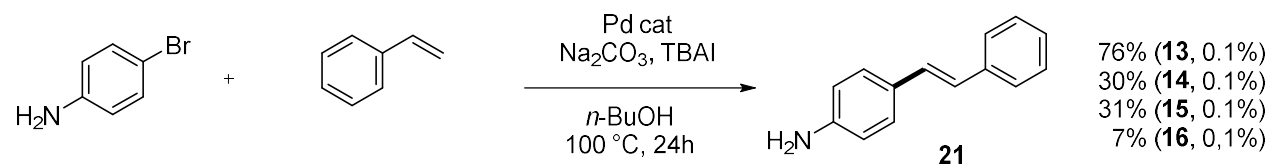
Using the previously developed optimal conditions for the Suzuki cross-coupling,<sup>26</sup> a variety of aryl bromides with different functional groups were used to evaluate the performance of the various 2-(benz)imidazolyl-metal complexes analogues prepared (**Figure 9**). As the model catalyst **13** was previously shown by Jiancheng to be efficient at 0.1 mol% catalyst loading (>99% yield) but not at 0.01 mol% (42% yield), this loading was used to observe an effect on the product yield. By comparing catalysts **13**, **14** and **15** under the same conditions, a significant difference in catalytic activity was revealed. When electron-rich catalysts **14** and **15** were used, significantly improved yields under the optimal conditions were observed with 4-bromoanisole (100% and 87%, respectively). In the case of the 4-bromo-*N,N*-dimethylaniline, the most electron-rich ligand (**15**) was found to give the highest yields, while 4-bromoisoquinoline offered similar results with all 3 catalysts. In the future, catalysts **16** and **17** will also be evaluated in various reactions in order to obtain a clearer structure-reactivity trend.



**Figure 9.** Evaluation of catalyst **13-15** as catalysts in Suzuki reactions

As these ligands of various electronic nature can be considered sterically similar, as the substituents reside away from the immediate metal coordination environment, the stronger  $\sigma$ -donor character of electron-donating substituent compared with unsubstituted complex (**13**) can presumably account for the difference in the catalytic performance observed. Extra  $\sigma$ -donation may help in the initial oxidative addition step, which in this case is believed to proceed from Pd(II) to Pd(IV).

Moreover, catalysts **13**, **14**, **15** and **16** were evaluated in Heck coupling reactions using 4-bromoaniline as substrate. Unlike the Suzuki-Miyaura reaction, the unsubstituted ligand (**13**) was found to give the highest yields, a result that cannot be explained at this time (**Figure 10**).



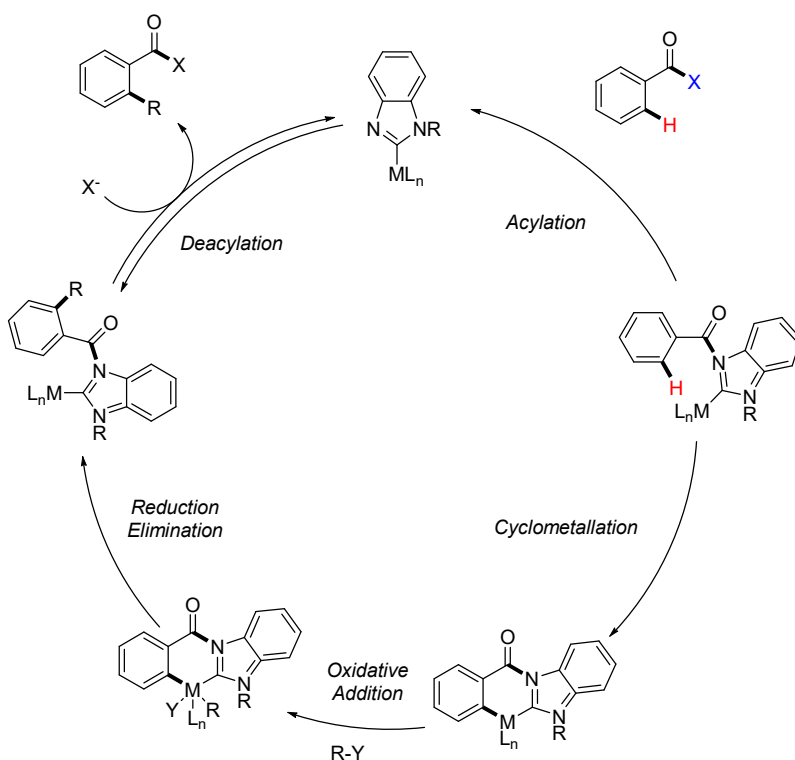
**Figure 10.** Evaluation of catalyst **13-16** as catalysts in Heck-Mizoroki reaction

## 4. Use of (Benz)imidazolyl-Metal Complexes as Catalytic Directing Groups in C–H Functionalization

### 4.1 Introduction to C–H Activation and *p*NHC-based Catalytic Cycle

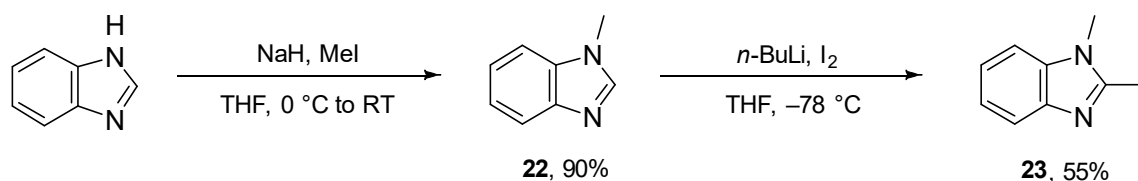
The possibility of direct introduction of a new functionality or a new C–C bond via direct C–H bond activation is a highly attractive strategy in organic synthesis. We propose that the use of our bifunctional catalysts, where the directing group is embedded in the catalyst template, could

serve as a new paradigm avoiding the use of stoichiometric directing group on the substrate to select for a desired C–H bond. The concept is to employ a 2-(benz)imidazolyl-metal as a catalytic directing site through reversible acylation with an acyl electrophile as substrate. In other words, the (benz)imidazolyl-ligand is reversibly bonding the substrates via its nucleophilic nitrogen functionality, while it is permanently attached to the metal center to activate a proximal C–H activation through a subsequent cyclometallation event. Subsequently, oxidative addition of a pseudo-electrophile such as an aryl halide leads to a palladium(IV) intermediate and reductive elimination produces an ortho-functionalized acyl electrophile product (**Scheme 5**).

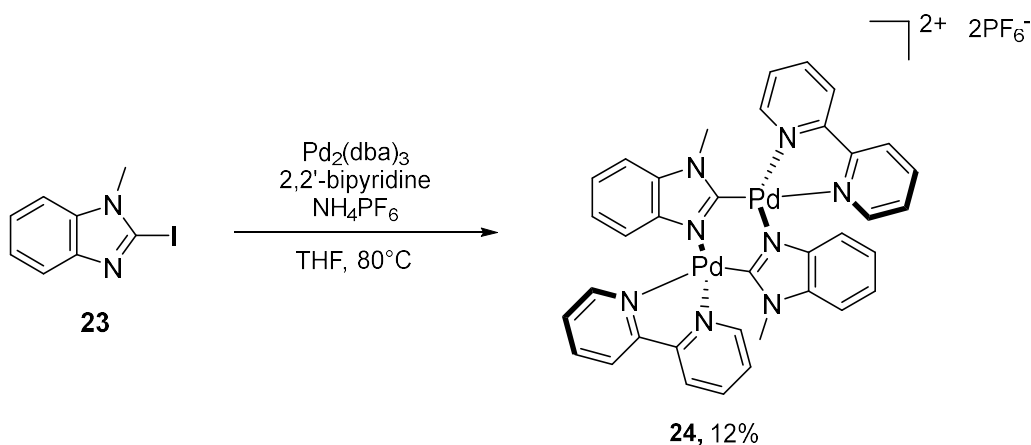


**Scheme 5.** Proposed mechanism for the use of 2-metalated (benz)imidazoles as catalytic directing groups in C–H activation

A monodentate catalyst analogue was prepared in view of such a C–H functionalization application, since significant rotational freedom is expected to be necessary throughout the catalytic cycle. To do so, we envisioned that oxidative addition of a Pd(0) species into a 2-benzimidazole-halogen bond would be appropriate, leading to an benzimidazolyl-Pd(II) catalyst. To introduce a halogen atom at the C(1) position of benzimidazole, 1-methylbenzimidazole was prepared by treating benzimidazole with NaH and MeI sequentially (**Scheme 6**). Then, *n*-BuLi was used to deprotonate the C(1) proton followed by iodination with I<sub>2</sub>. Reaction of Pd<sub>2</sub>(dba)<sub>3</sub> with 2-iodo-*N*-methylbenzimidazole **23** and 2,2'-bipyridine at 80 °C followed by treatment with NH<sub>4</sub>PF<sub>6</sub> provided complex **24** (**Scheme 7**).

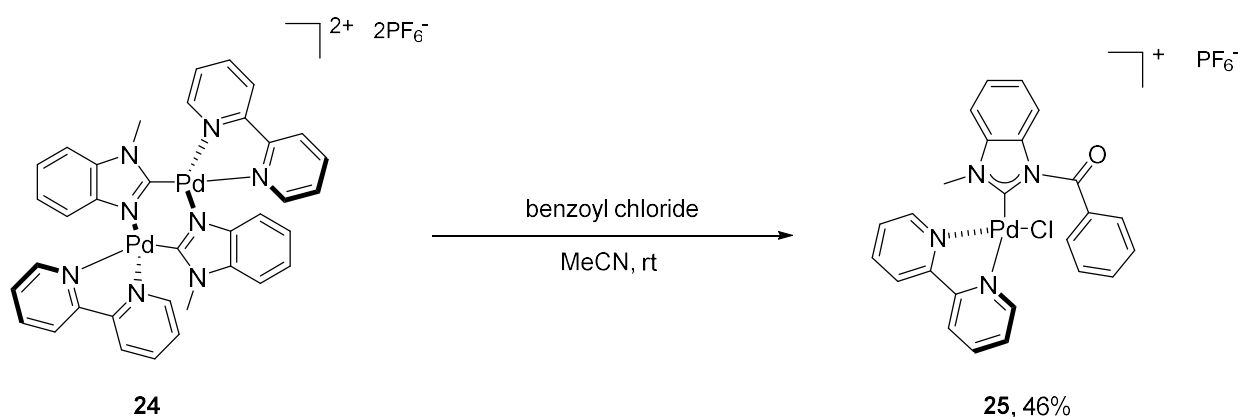


**Scheme 6.** Synthetic route to monodentate ligand **23**



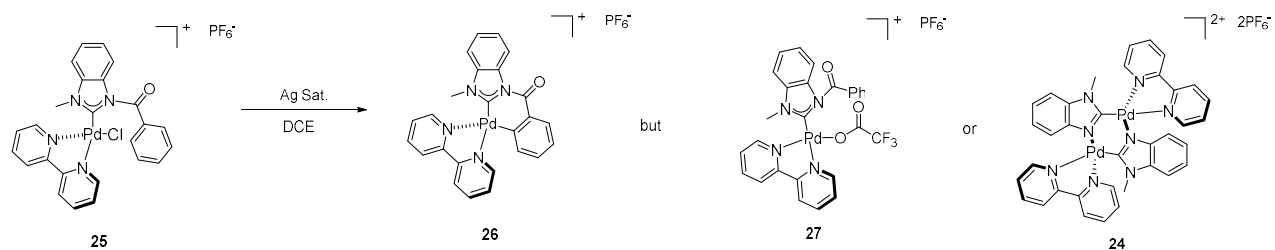
**Scheme 7.** Synthesis of complex **24**

With the monodentate benzimidazole-Pd complex in hand, we wanted to isolate and characterize the corresponding intermediates to examine the viability of our catalytic cycle of the individual step of the proposed mechanism (acylation, cyclometalation, etc.; see **Scheme 5**). The preparation and isolation of the *N*-acyl-NHC-Pd was performed with dinuclear complex **24** and benzoyl chloride in MeCN at the room temperature (**Scheme 8**). This showed that the lone pair acts as a good nucleophile even after the complexation with Pd, validating the first step of the mechanism.



**Scheme 8.** Isolation of the acylated benzimidazolyl-Pd complex intermediate **25**

To evaluate the viability of cyclometalation in our proposed catalytic cycle, we attempted C–H functionalization in the presence of different silver salts at room or elevated temperature via a CMD mechanism (**Scheme 9**).<sup>35</sup> However, we found that under most of the conditions the complexes were unreactive (**Table 2**). The complex would either simply exchange ligand with TFA or break down to the dimer Pd complex (**24**).

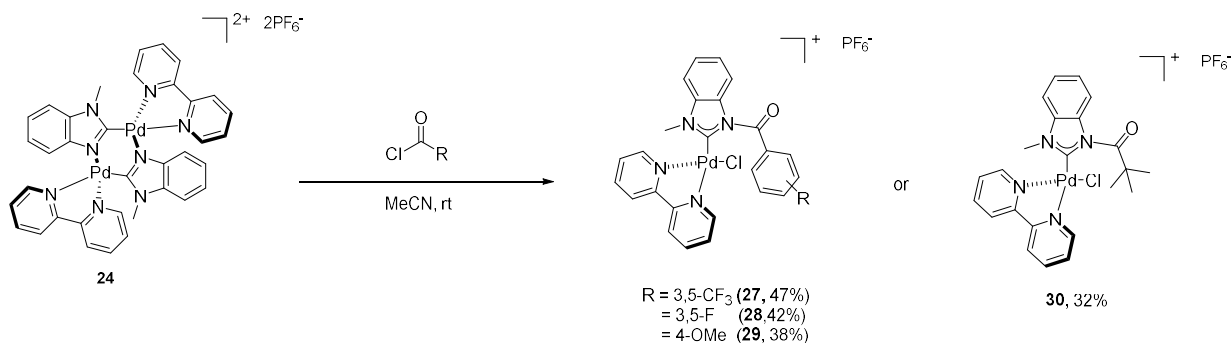


**Scheme 9.** Attempts at the isolation of cyclometalated intermediate **26**

**Table 2.** Evaluation of *N*-acyl-NHC-Pd complexes for cyclometalation

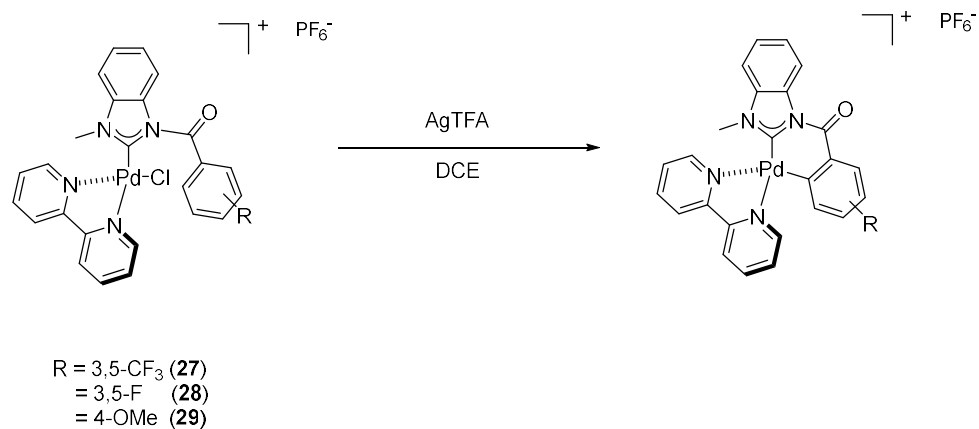
<i>Entry</i>	<i>Ag sat. (equiv.)</i>	<i>Time &amp; Temp</i>	<i>Solvent</i>	<i>Result</i>
1	AgTFA (2.0)	80 °C, 12 h	DCM	<b>24, 27</b>
2	AgTFA (1.0)	RT, 30 min	DCM	<b>24</b>
3	AgTFA (2.0)	RT, 30 min	DCM	<b>24, 27</b>
4	AgOAc (2.0)	60 °C, 12 h	DCM	<b>24</b>
5	AgTFA (2.0)	100 °C, 12 h	MeCN	<b>24</b>
6	AgTFA (2.0)	125 °C, 12 h	DCE	<b>24, 27</b>
7	AgOAc (2.0)	60 °C, 12 h	DCE	<b>24</b>
8	Ag <sub>2</sub> CO <sub>3</sub> (2.0)	60 °C, 12 h	DCE	<b>24</b>
9	AgOPiv (2.0)	125 °C, 12 h	DCE	<b>24</b>
10	AgNTf <sub>2</sub> (2.0)	125 °C, 12 h	DCE	<b>24</b>
11	Ag(1-AdCO <sub>2</sub> ) (2.0)	125 °C, 12 h	DCE	<b>24</b>

After the unsuccessful attempts at synthesizing organometallic intermediates, we proposed an alternative approach in order to enhance the propensity to undergo C–H activation by the presence of electron-donating and withdrawing substituents. Some examples in the literature indicate that C–H activation is preferred at more acidic C–H sites.<sup>36</sup> Also, several examples have been reported where electron-releasing substituents enhance the reaction efficiency,<sup>37,38</sup> and such observations have been taken as evidence for a BIES mechanism over AMLA/CMD.<sup>39</sup> Thus, a variety of acylated benzimidazole-Pd complexes **27-29** having different electronic properties were prepared with moderate yields (**Scheme 10**). Additionally, an aliphatic acyl electrophile as substrates was employed in view of a  $\beta$ -C–H functionalization of the *N*-acyl NHC complex intermediate **30**.



**Scheme 10.** Synthesis of various acylated benzimidazolyl-Pd complex intermediate

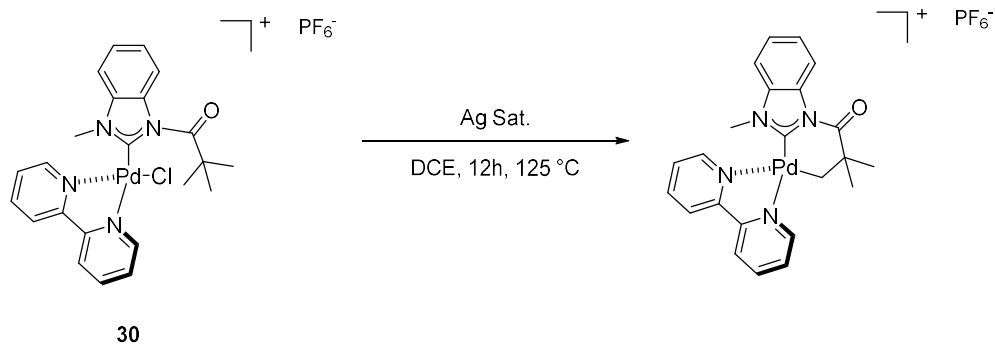
Unfortunately, cyclometalation attempts with various silver salts led only to de-acylation and break down to the dimer Pd complex (**24**) (**Scheme 11** and **Table 3**; **Scheme 12** and **Table 4**).



**Scheme 11.** Attempt at the isolation of cyclometalated intermediates of various acylated benzimidazolyl-Pd complexes

**Table 3.** Evaluation of electron-rich and poor *N*-acyl-NHC-Pd for cyclometalation

<i>Entry</i>	<i>R</i>	<i>Time &amp; Temp</i>	<i>Solvent</i>	<i>Result</i>
1	3,5-CF <sub>3</sub>	rt, 12 h	DCE	<b>24</b>
2	3,5-F	125 °C, 12 h	DCE	<b>24</b> , ligand exchange
3	4-OMe	125 °C, 12 h	DCE	<b>24</b>



**Scheme 12.** Isolation of cyclometalated intermediates of aliphatic acylated benzimidazolyl-Pd complexes

**Table 4.** Evaluation of aliphatic acyl-NHC-Pd for cyclometalation

<i>Entry</i>	<i>Ag sat. (equiv.)</i>	<i>Result</i>
1	AgTFA (2.0)	24
2	AgOAc (2.0)	24
3	AgOPiv (2.0)	24
4	AgNTf <sub>2</sub> (1.0)	24

In the future, more screening will be performed to access a C–H activated intermediate by cyclometalation reaction or by continuing to evaluate more active analogous transition-metal complexes.

## 5. Conclusion

In summary, we successfully synthesized methoxy-substituted (electron donating group), trifluoromethyl-substituted (electron withdrawing group) 2-benzimidazolyl palladium complexes and 2-imidazolyl palladium complexes as highly active bifunctional catalysts. Notably, evaluation of more electron-rich catalysts under our optimal Suzuki conditions indeed revealed that it is far superior catalyst to the unsubstituted version of the catalyst. When electron-rich catalyst was used with even lower catalyst loading (0.01 mol%), quantitative yields could be observed. This study provided further insight into the importance of electronic effects of substituents for this novel class of bifunctional catalysts. Moreover, a new strategy for the use of (benz)imidazolyl-metal species as catalytic directing groups for C–H functionalization was investigated, bringing to light the different challenges that will have to be addressed in the future to achieve success in this novel mechanistic paradigm.

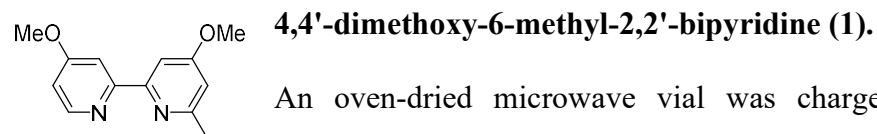
## 6. Experimental

### General Experimental Conditions

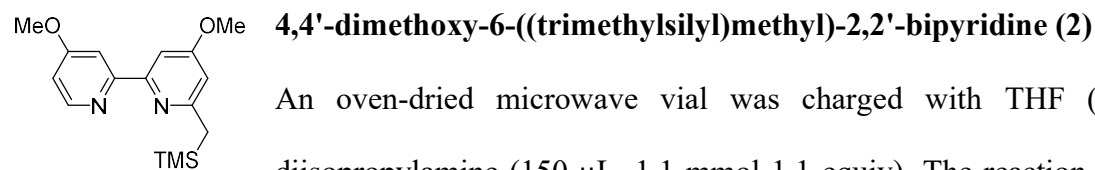
**General:** Unless stated otherwise, all non-aqueous reactions were performed in oven-dried glassware sealed with microwave caps or rubber septa under a nitrogen atmosphere and were stirred with Teflon-coated magnetic stir bars. Tetrahydrofuran (THF), diethyl ether (Et<sub>2</sub>O), dichloromethane (DCM) and acetonitrile (MeCN) were dried by passage over a column of activated alumina (JC Meyers Solvent System). Anhydrous N,N-dimethylformamide (DMF) and were obtained in Sure Seal bottles from Aldrich. Anhydrous 1,2-dichloroethane (DCE) and propylene carbonate were obtained in Sure Seal bottles from Acros Organics. 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 visualized by UV irradiation and anisaldehyde, potassium permanganate or iodine stain. Sorbent silica gel (particle size 40-63 μm) was used for flash chromatography in the indicated solvent system according to standard techniques. Flash chromatography was performed on a Biotage Isolera One. Nuclear magnetic resonance (NMR) spectra (<sup>1</sup>H, <sup>13</sup>C) were recorded on Varian or Bruker spectrometers operating at either 500 600 or 700 MHz for <sup>1</sup>H and 126 MHz for <sup>13</sup>C experiments. for <sup>1</sup>H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform, δ 7.26 ppm; DMSO-*d*<sub>6</sub>, δ 2.50 ppm; or CD<sub>3</sub>CN, δ 1.94 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 <sup>13</sup>C NMR spectra are recorded in parts per million from tetramethylsilane using the central peak of CDCl<sub>3</sub> (δ 77.16 ppm), DMSO-*d*<sub>6</sub> (δ 39.52 ppm) or CD<sub>3</sub>CN (1.32 ppm) as the internal standard. 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 ( $\text{cm}^{-1}$ ). Only selected IR frequencies are reported.

### Synthesis of ligands and complexes

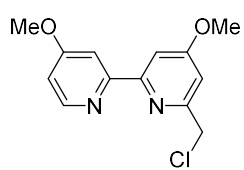


An oven-dried microwave vial was charged with 4,4'-dimethoxy-2,2'-bipyridine (1 g, 4.6 mmol, 1.0 equiv) and  $\text{Et}_2\text{O}$  (40 mL) under  $\text{N}_2$ . The reaction mixture was cooled to  $0^\circ\text{C}$  and a solution of  $\text{MeLi}$  (4 mL, 1.6 M in  $\text{Et}_2\text{O}$ , 4.6 mmol, 1.0 equiv) was added dropwise. The resulting black solution was heated up to  $40^\circ\text{C}$  and stirred for 4 h. the reaction was allowed to cool to room temperature and formed a biphasic yellow solution after water was added. The aqueous layer was separated from organic layer and extracted with  $\text{Et}_2\text{O}$ . The combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. A solution of  $\text{KMnO}_4$  in acetone (100 mL, sat.) was added in one portion to the resulting orange oil and a  $\text{MnO}_2$  precipitate was formed immediately. After the  $\text{MnO}_2$  was filtered on Celite eluting with acetone, the acetone was removed by rotary evaporation. The crude product was purified by flash chromatography ( $\text{SiO}_2$ , 10%  $\text{EtOAc}$ /hexanes) to afford **1** (511 mg, 48%) as a pale yellow oil. All analyses were consistent with previously reported data.<sup>40</sup>



An oven-dried microwave vial was charged with THF (4 mL) and diisopropylamine (150  $\mu\text{L}$ , 1.1 mmol 1.1 equiv). The reaction mixture was cooled to  $-78^\circ\text{C}$  and a solution of butyllithium (*n*-BuLi) (2.1 M in hexanes, 520  $\mu\text{L}$ , 2.4 mmol 1.1 equiv) was added. The solution was stirred at  $-78^\circ\text{C}$  for 10 min, warmed to  $0^\circ\text{C}$  and stirred for 10 min, then cooled back to  $-78^\circ\text{C}$ . A solution of **1** (224.3 mg, 0.97 mmol 1 equiv) in THF (5

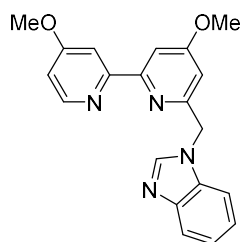
mL), prepared in an oven-dried microwave vial under a nitrogen atmosphere, was added via cannula to the cold lithium diisopropylamide (LDA) solution. The resulting black mixture was stirred at the same temperature for 1 hour. TMSCl (135  $\mu$ L, 1.1 mmol, 1.1 equiv) was then added rapidly, and the mixture was stirred vigorously for 20 seconds. The reaction was quenched by rapid addition of absolute EtOH (0.6 mL), and the cold mixture was poured into a separatory funnel containing aq. sat. NaHCO<sub>3</sub> and allowed to warm to room temperature. The solution was extracted three times with CH<sub>2</sub>Cl<sub>2</sub>, and the combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (10% EtOAc/hexanes) to afford **2** (217.5 mg, 74%) as a colorless oil. **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.46 (d,  $J$  = 5.7 Hz, 1H), 8.09 (s, 1H), 7.75 (s, 1H), 6.84 (dd,  $J$  = 5.5, 2.4 Hz, 1H), 6.54 (d,  $J$  = 2.1 Hz, 1H), 3.96 (s, 3H), 3.93 (s, 3H), 0.08 (s, 9H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  166.9, 166.6, 162.2, 158.6, 156.8, 150.1, 110.6, 109.1, 106.5, 102.3, 55.2, 55.2, 30.1, -1.4. **IR** (neat) 3007, 2953, 2898, 2840, 1582, 1561, 1297, 1263, 1036, 846, 808, 733, 697. **HRMS** (HESI) calcd for [C<sub>16</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>Si+H]<sup>+</sup>:  $m/z$  303.15233, found 303.15258.



**6-(chloromethyl)-4,4'-dimethoxy-2,2'-bipyridine (3)**

An oven-dried microwave vial equipped with a magnetic stirbar was charged with **2** (217.5 mg, 0.72 mmol, 1.0 equiv), hexachloroethane (680.1 mg, 2.88 mmol, 4.0 equiv), CsF (436.9 mg, 2.88 mmol, 4.0 equiv) and dry MeCN (15 mL). The resulting heterogeneous mixture was heated at 60 °C for 4 hours, allowed to cool to room temperature and then EtOAc and H<sub>2</sub>O were added. The layers were separated, and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (15%

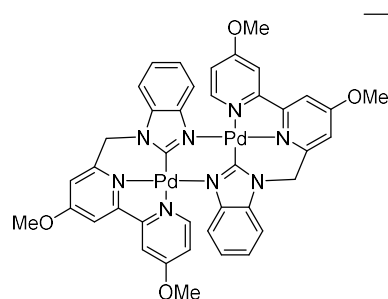
EtOAc/hexanes) to afford **3** (189.7 mg, 99%) as a colorless oil. **mp** 89-90 °C. **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 8.46 (d, *J* = 5.6 Hz, 1H), 7.98 (d, *J* = 2.5 Hz, 1H), 7.89 (d, *J* = 2.2 Hz, 1H), 7.02 (d, *J* = 2.2 Hz, 1H), 6.83 (dd, *J* = 5.6, 2.6 Hz, 1H), 4.69 (s, 2H), 3.94 (s, *J* = 6.1 Hz, 3H), 3.93 (s, 3H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 167.5, 166.7, 157.5, 157.5 157.4, 150.2, 110.8, 109.8, 106.8, 105.5, 55.5, 55.3, 46.9. **IR** (neat) 3100, 2970, 2922, 2843, 1581, 1561, 1422, 1295, 1242, 1042, 1025, 888, 800, 755, 717, 631, 573. **HRMS** (HESI) calcd for [C<sub>13</sub>H<sub>13</sub>ClN<sub>2</sub>O<sub>2</sub>+H]<sup>+</sup>: *m/z* 265.07383, found 265.07326.



**1-((4,4'-dimethoxy-[2,2'-bipyridin]-6-yl)methyl)-1H-benzo[d]imidazole**  
**(4)**

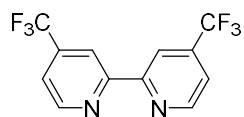
An oven-dried microwave vial equipped with a magnetic stirbar was charged with **3** (189.7 mg, 0.72 mmol, 1.0 equiv), benzimidazole (84.7 mg, 0.72 mmol, 1.0 equiv), KOH (48.2 mg, 0.86 mmol, 1.2 equiv) and dry MeCN (10 mL). The resulting white heterogeneous mixture was heated at 80 °C for 24 h. The resulting pale red solution was allowed to cool to room temperature and then CH<sub>2</sub>Cl<sub>2</sub> and aq. sat. NaHCO<sub>3</sub> were added. The layers were separated and the aqueous layer was extracted three times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (5% MeOH /CH<sub>2</sub>Cl<sub>2</sub>) to afford **4** (160.6 mg, 64%) as a white solid. **mp** 175-176 °C. **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 8.46 (d, *J* = 5.7 Hz, 1H), 8.12 (s, 1H), 7.90 (d, *J* = 2.2 Hz, 1H), 7.87 - 7.84 (m, 2H), 7.45 - 7.42 (m, 1H), 7.32 - 7.26 (m, 2H), 6.84 (dd, *J* = 5.7, 2.6 Hz, 1H), 6.56 (d, *J* = 2.2 Hz, 1H), 5.49 (s, 2H), 3.88 (s, 3H), 3.87 (s, 3H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 167.7, 166.7, 157.9, 157.3, 156.0, 150.2, 143.9, 143.7, 134.2, 123.2, 122.3, 120.4, 111.2, 110.2, 108.7, 106.6, 104.9, 55.6, 55.3, 50.3. **IR** (neat) 3096, 3073, 3000, 3017,

2976, 2943, 2837, 1587, 1567, 1424, 1307, 1279, 1264, 1251, 1038, 832, 812, 756, 449. **HRMS** (HESI) calcd for  $[C_{20}H_{18}N_4O_2+H]^+$ :  $m/z$  347.15025, found 347.14900.



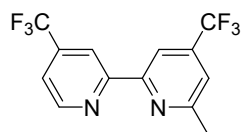
$2+$   $2PF_6^-$  **Palladium complex 15**

In an inert atmosphere glove-box, an oven-dried microwave vial equipped with a magnetic stirbar was charged with **4** (160.6 mg, 0.46 mmol, 1.0 equiv),  $Pd(OAc)_2$  (104.1 mg, 0.46 mmol, 1.0 equiv) and  $NH_4PF_6$  (83.1 mg, 0.51 mmol, 1.1 equiv). The vial was capped and taken out of the glove-box, dry MeCN (15 mL) was added and the reaction was heated at 90 °C for 24 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 crude product was purified by flash chromatography (5% MeOH /  $CH_2Cl_2$ ) to afford **15** (150.3 mg, 54%). **mp** 276 °C (decomposition).  **$^1H$  NMR** (500 MHz,  $DMSO-d_6$ )  $\delta$  8.41 (d,  $J = 2.4$  Hz, 1H), 8.37 (d,  $J = 2.6$  Hz, 1H), 7.92 (d,  $J = 8.3$  Hz, 1H), 7.84 (d,  $J = 2.4$  Hz, 1H), 7.81 (d,  $J = 8.2$  Hz, 1H), 7.58 (d,  $J = 6.6$  Hz, 1H), 7.47 (t,  $J = 7.7$  Hz, 1H), 7.33 (t,  $J = 7.6$  Hz, 1H), 7.14 (dd,  $J = 6.6, 2.6$  Hz, 1H), 6.31 (d,  $J = 16.6$  Hz, 1H), 5.74 (d,  $J = 16.4$  Hz, 1H), 4.17 (s, 3H), 3.98 (s, 3H).  **$^{13}C$  NMR** (126 MHz,  $CD_3CN$ )  $\delta$  170.1, 169.6, 163.4, 159.4, 156.9, 155.8, 152.1, 140.5, 134.9, 124.0, 123.4, 116.5, 112.7, 112.5, 111.5, 111.0, 110.7, 58.0, 57.4, 50.7. **IR** (neat) 3657, 3589, 3103, 2949, 2852, 1613, 1398, 1349, 1318 1065, 1040, 823, 740, 556. **HRMS** (HESI) calcd for  $[C_{40}H_{34}N_8O_4Pd_2]^{2+}$ :  $m/z$  451.03809, found 451.03794.



**4,4'-bis(trifluoromethyl)-2,2'-bipyridine (5)**

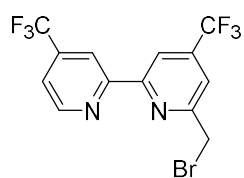
In an oven-dried microwave vial, NiCl<sub>2</sub>·6H<sub>2</sub>O, (1.1 g, 4.7 mmol, 1.0 equiv) and PPh<sub>3</sub>, (2.5 g, 9.5 mmol, 2.0 equiv) were dissolved in degassed DMF (10 mL). The resulting blue solution was sparged with argon for 30 min. Activated zinc dust (464.3 mg, 7.1 mmol) was added and 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 °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<sub>4</sub>, filtered, and evaporated. The crude product was purified on silica gel (4:1 hexane/CH<sub>2</sub>Cl<sub>2</sub>), giving 570.7 mg (82%) of **5** as a white solid. All analyses were consistent with previously reported data.<sup>41</sup>



**6-methyl-4,4'-bis(trifluoromethyl)-2,2'-bipyridine (6)**

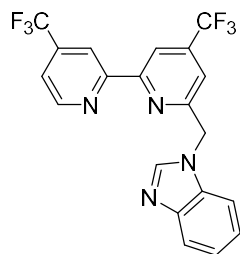
An oven-dried microwave vial was charged with 6-methyl-4,4'-bis(trifluoromethyl)-2,2'-bipyridine **5** (332.7 mg, 0.17 mmol, 1.0 equiv) and Et<sub>2</sub>O (2 mL) under N<sub>2</sub>. The reaction mixture was cooled to -78 °C and a solution of MeLi (4 mL, 1.6M in Et<sub>2</sub>O, 0.17 mmol, 1.0 equiv) was added dropwise to the solution. The resulting black solution was stirred for 2 h. The reaction was allowed to warm to 0 °C and formed a biphasic yellow solution after water was added. The aqueous layer was separated from the organic layer and extracted with Et<sub>2</sub>O. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. A solution of KMnO<sub>4</sub> in acetone (100 mL, sat.) was added in one portion to the resulting orange oil and a MnO<sub>2</sub> precipitate was formed immediately. After the MnO<sub>2</sub> was filtered on Celite eluting with acetone, the acetone was removed by rotary evaporation. The crude product was purified by flash chromatography (SiO<sub>2</sub>, 10% EtOAc/hexanes) to afford **6** (223.1 mg, 64%) as a

white solid. **mp** 70-72 °C. **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 8.86 (d, *J* = 5.0 Hz, 1H), 8.72 (s, 1H), 8.51 (s, 1H), 7.56 (d, *J* = 4.8 Hz, 1H), 7.43 (s, 1H), 2.73 (s, 3H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 159.8, 156.4, 155.4, 150.2, 139.8 (q, *J* = 33.8 Hz), 139.5 (q, *J* = 34.1 Hz), 123.0 (q, *J* = 273.3 Hz), 122.9 (q, *J* = 273.4 Hz), 119.7 (q, *J* = 3.4 Hz), 119.5 (q, *J* = 3.4 Hz), 117.1 (q, *J* = 3.6 Hz), 114.2 (q, *J* = 3.5 Hz), 24.6. **IR** (neat) 3105, 2925, 2852, 1605, 1577, 1321, 1163, 854, 670, 423. **HRMS** (HESI) calcd for [C<sub>13</sub>H<sub>8</sub>F<sub>6</sub>N<sub>2</sub>+H]<sup>+</sup>: *m/z* 307.06644, found 307.06563.



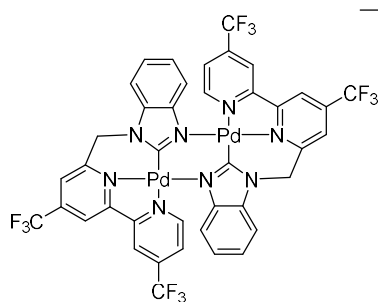
**6-(bromomethyl)-4,4'-bis(trifluoromethyl)-2,2'-bipyridine (7)**

An oven-dried microwave vial was charged with 6-methyl-4,4'-bis(trifluoromethyl)-2,2'-bipyridine **6** (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 carbon tetrachloride (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 Na<sub>2</sub>SO<sub>4</sub> filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (30% hexanes/CH<sub>2</sub>Cl<sub>2</sub>) to afford **7** as a white solid (45.0 mg, 26% yield), **mp** 85-88 °C. **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 8.88 (d, *J* = 5.0 Hz, 1H), 8.73 (s, 1H), 8.65 (s, 1H), 7.74 (s, 1H), 7.60 (d, *J* = 4.1 Hz, 1H), 4.70 (s, *J* = 5.0 Hz, 2H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 158.2, 155.9, 155.6, 150.3, 140.8 (q, *J* = 68.6, 34.3 Hz), 139.6 (q, *J* = 68.7, 34.4 Hz), 123.0 (q, *J* = 273.5 Hz), 122.8 (q, *J* = 273.2 Hz), 120.2 (q, *J* = 3.4 Hz), 119.9 (q, *J* = 3.4 Hz), 117.3 (q, *J* = 3.6 Hz), 116.5 (q, *J* = 3.4 Hz), 32.7. **IR** (neat) 3092, 2922, 2850, 1571, 1342, 1165, 1128, 1100, 854, 670, 624, 594, 420. **HRMS** (HESI) calcd for [C<sub>13</sub>H<sub>7</sub>BrF<sub>6</sub>N<sub>2</sub>+H]<sup>+</sup>: *m/z* 384.97696, found 384.97607.



**1-((4,4'-bis(trifluoromethyl)-[2,2'-bipyridin]-6-yl)methyl)-1H-benzo[d]imidazole (8)**

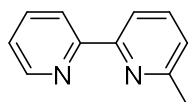
An oven-dried microwave vial equipped with a magnetic stirbar was charged with **7** (58.9 mg, 0.19 mmol, 1.0 equiv), benzimidazole (22.7 mg, 0.19 mmol, 1.0 equiv), KOH (13.0 mg, 0.23 mmol, 1.2 equiv) and dry MeCN (5 mL). The resulting white heterogeneous mixture was heated at 80 °C for 24 h. The resulting pale red solution was allowed to cool to room temperature and then CH<sub>2</sub>Cl<sub>2</sub> and aq. sat. NaHCO<sub>3</sub> were added. The layers were separated and the aqueous layer was extracted three times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (10% MeOH /CH<sub>2</sub>Cl<sub>2</sub>) to afford **8** (65.8 mg, 82%) as a white solid. **mp** 138-140 °C. **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) 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 (d, *J* = 4.9 Hz, 1H), 7.44 - 7.40 (m, 1H), 7.32 (dq, *J* = 5.8, 1.9 Hz, 2H), 7.29 (s, 1H), 5.65 (s, 2H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 156.8, 156.4, 155.4, 150.4, 143.9, 143.2, 141.0 (q, *J* = 34.2 Hz), 139.7 (q, *J* = 34.4 Hz), 133.8, 123.6, 122.7, 120.7, 122.8 (q, *J* = 273.5 Hz), 122.5 (q, *J* = 273.8 Hz), 120.2 (q, *J* = 3.2 Hz), 117.3 (q, *J* = 3.1 Hz), 117.2 (q, *J* = 3.4 Hz), 116.7 (q, *J* = 3.5 Hz), 50.2. **IR** (neat) 3096, 3044, 2924, 2851, 1616, 1567, 1500, 1322, 1284, 1172, 1139, 746, 669, 424. **HRMS** (HESI) calcd for [C<sub>20</sub>H<sub>12</sub>F<sub>6</sub>N<sub>4</sub>+H]<sup>+</sup>: *m/z* 423.10389, found 423.10245.



**Palladium complex 16**

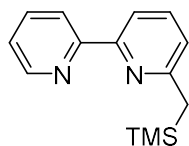
In an inert atmosphere glove-box, an oven-dried microwave vial equipped with a magnetic stirbar was charged with **8** (10 mg, 0.02 mmol, 1.0 equiv), Pd(OAc)<sub>2</sub>

(5.3 mg, 0.02 mmol, 1.0 equiv) and  $\text{NH}_4\text{PF}_6$  (4.2 mg, 0.03 mmol, 1.1 equiv). The vial was capped and taken out of the glove-box, dry MeCN (3 mL) was added and the reaction was heated at 100 °C for 2 hours to yield a black mixture. 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 solid was purified by recrystallization from diethyl ether/ $\text{CH}_2\text{Cl}_2$  to afford **16** (1.8 mg, 11%) as yellow solid.  $^1\text{H NMR}$  (700 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  8.89 (d,  $J = 15.1$  Hz, 4H), 8.45 (s,  $J = 63.9$  Hz, 2H), 8.04 (d,  $J = 5.8$  Hz, 2H), 7.86 (d,  $J = 8.3$  Hz, 2H), 7.82 (d,  $J = 8.1$  Hz, 2H), 7.76 (d,  $J = 5.4$  Hz, 2H), 7.52 (t,  $J = 7.7$  Hz, 2H), 7.37 (t,  $J = 7.6$  Hz, 2H), 6.23 (d,  $J = 17.2$  Hz, 2H), 5.77 (d,  $J = 17.1$  Hz, 2H).



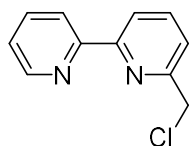
**6-methyl-2,2'-bipyridine (9)**

An oven-dried 100 mL round-bottom flask was charged with 2,2'-bipyridine (1.0 g, 6.4 mmol, 1.0 equiv) and dry  $\text{Et}_2\text{O}$  (40 mL) under  $\text{N}_2$ . The reaction mixture was cooled to 0 °C. A solution of MeLi (4.0 mL, 1.6 M in  $\text{Et}_2\text{O}$ , 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 formed biphasic yellow solution after water was added. The aqueous layer was separated from organic layer and extracted three times with  $\text{Et}_2\text{O}$ . The combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. A solution of  $\text{KMnO}_4$  in acetone (100 mL, sat.) was added at once to the resulting orange oil and a  $\text{MnO}_2$  precipitate formed immediately. After the  $\text{MnO}_2$  was filtered on Celite eluting with acetone, the acetone was removed by rotary evaporation. The crude product was purified by flash chromatography (10% EtOAc/hexanes) to afford **9** (525 mg, 48%) as a pale yellow oil. All analyses were consistent with previously reported data.<sup>42</sup>



### 6-((trimethylsilyl)methyl)-2,2'-bipyridine (10)

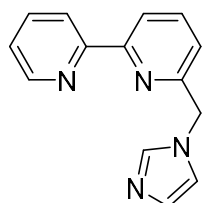
An oven-dried microwave vial was charged with THF (4 mL) and diisopropylamine (472  $\mu\text{L}$ , 2.7 mmol 1.25 equiv). The reaction mixture was cooled to  $-78^\circ\text{C}$  and a solution of butyllithium (*n*-BuLi) (2.5 M in hexanes, 953  $\mu\text{L}$ , 2.4 mmol 1.1 equiv) is added. The solution is stirred at  $-78^\circ\text{C}$  for 10 min, warmed to  $0^\circ\text{C}$  and stirred for 10 min, then cooled back to  $-78^\circ\text{C}$ . A solution of **1** (525 mg, 2.2 mmol 1 equiv) in THF (5 mL), prepared in an oven-dried microwave vial a under a nitrogen atmosphere, is added via cannula to the cold lithium diisopropylamide (LDA) solution. The resulting black mixture was stirred at the same temperature for 1 hour. TMSCl (302  $\mu\text{L}$ , 2.4 mmol, 1.1 equiv) was then added rapidly, and the mixture was stirred vigorously for 20 seconds. The reaction was quenched by rapid addition of absolute EtOH (1 mL), and the cold mixture was poured into a separatory funnel containing aq. sat.  $\text{NaHCO}_3$  and allowed to warm to room temperature. The solution was extracted three times with  $\text{CH}_2\text{Cl}_2$ , and the combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuo. The crude product was purified by flash chromatography (10% EtOAc/hexanes) to afford **10** (476 mg, 64%) as a colorless oil. All analyses were consistent with previously reported data.<sup>43</sup>



### 6-(chloromethyl)-2,2'-bipyridine (11)

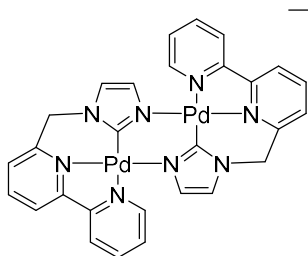
An oven-dried microwave vial was charged with **2** (476 mg, 2.0 mmol, 1.0 equiv), hexachloroethane (2.31 g, 7.9 mmol, 4.0 equiv), CsF (1.48 g, 7.9 mmol, 4.0 equiv) and dry MeCN (22 mL). The resulting heterogeneous mixture was heated at  $60^\circ\text{C}$  for 4 hours, allowed to cool to room temperature and then EtOAc and  $\text{H}_2\text{O}$  were added. The layers were separated, and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The crude product was purified

by flash chromatography (30% EtOAc/hexanes) to afford **11** (377.2 mg, 94%) as a colorless oil. All analyses were consistent with previously reported data.<sup>43</sup>



**6-((1*H*-imidazol-1-yl)methyl)-2,2'-bipyridine (**12**)**

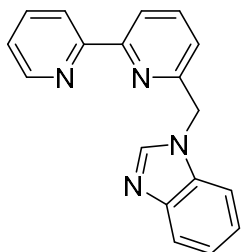
An oven-dried microwave vial equipped with a magnetic stirbar was charged with **3** (127.1 mg, 1.61 mmol, 1.0 equiv), imidazole (42.3 mg, 1.61 mmol, 1.0 equiv), KOH (41.8 mg, 1.93 mmol, 1.2 equiv) and dry MeCN (22 mL). The resulting white heterogeneous mixture was heated at 80 °C for 24 h. The resulting pale yellow solution was allowed to cool to room temperature and then CH<sub>2</sub>Cl<sub>2</sub> and aq. sat. NaHCO<sub>3</sub> were added. The layers were separated and the aqueous layer was extracted three times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (10% MeOH /CH<sub>2</sub>Cl<sub>2</sub>) to afford **12** (135.8 mg, 93%) as a white solid. **mp** 121-124 °C. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.68 (d, *J* = 4.7 Hz, 1H), 8.35 (t, *J* = 7.1 Hz, 2H), 7.86-7.77 (m, 3H), 7.36-7.30 (m, 1H), 7.16 (s, 1H), 7.08 (s, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 5.35 (s, 2H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 156.2, 155.5, 155.1, 149.3, 138.2, 137.0, 129.1, 129.1, 124.1, 121.2, 121.1, 120.4, 52.7. **IR** (neat) 3101, 2924, 2850, 1581, 1426, 1082, 756, 661, 618, 419. **HRMS** (HESI) calcd for [C<sub>14</sub>H<sub>12</sub>N<sub>4</sub>+H]<sup>+</sup>: *m/z* 237.11347, found 237.11253.



**Palladium complex 17**

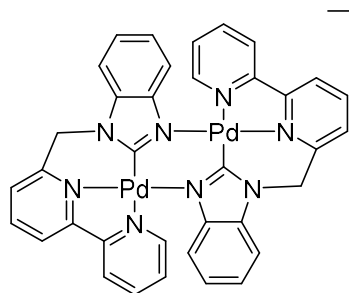
In an inert atmosphere glove-box, an oven-dried microwave vial equipped with a magnetic stirbar was charged with **12** (31.8 mg, 0.1 mmol, 1.0 equiv), Pd(OAc)<sub>2</sub> (30.2 mg, 0.1 mmol, 1.0

equiv) and  $\text{NH}_4\text{PF}_6$  (24.1 mg, 0.1 mmol, 1.1 equiv). The vial was capped and taken out of the glove-box, dry MeCN (3 mL) was added and the reaction was heated at 100 °C for 18 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 solid was purified by recrystallization from diethyl ether/MeCN to afford **17** (38.3 mg, 58%) as yellow solid. mp 256 °C (decomposition).  $^1\text{H NMR}$  (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  8.76 (t,  $J = 7.6$  Hz, 4H), 8.62 (s, 2H), 8.50 (t,  $J = 7.9$  Hz, 2H), 8.39 (t,  $J = 7.7$  Hz, 2H), 8.01 (d,  $J = 7.7$  Hz, 2H), 7.89 (d,  $J = 4.8$  Hz, 2H), 7.78 - 7.73 (m, 1H), 6.07 (s, 2H), 5.88 (d,  $J = 17.0$  Hz, 2H), 5.80 (d,  $J = 16.9$  Hz, 2H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  158.7, 155.2, 155.0, 149.7, 143.0, 142.1, 138.9, 133.9, 129.3, 128.7, 127.9, 124.7, 124.3, 54.8. IR (neat) 3657, 3588, 3131, 1603, 1524, 1482, 1460, 1437, 1109, 832, 767, 555.



**1-([2,2'-bipyridin]-6-ylmethyl)-1H-benzo[d]imidazole (**4**)**

An oven-dried microwave vial was charged with **3** (377.2 mg, 1.8 mmol, 1.0 equiv), benzimidazole (217.7 mg, 1.8 mmol, 1.0 equiv), KOH (124.1 mg, 2.2 mmol, 1.2 equiv) and dry MeCN (22 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  $\text{CH}_2\text{Cl}_2$  and aq. sat.  $\text{NaHCO}_3$  were added. The layers were separated, and the aqueous layer was extracted three times with  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (0-5% MeOH/ $\text{CH}_2\text{Cl}_2$  elution gradient) to afford **4** (446.9 mg, 85%) as a white solid. All analyses were consistent with previously reported data.<sup>26</sup>



$2+$   $2\text{PF}_6^-$  **Palladium complex 13**

In an inert atmosphere glove-box, an oven-dried microwave vial equipped with a magnetic stirbar was charged with **4** (30.0 mg, 0.10 mmol, 1.0 equiv), Pd(OAc)<sub>2</sub> (23.5 mg, 0.10 mmol, 1.0 equiv) and NH<sub>4</sub>PF<sub>6</sub> (18.8 mg, 0.12 mmol, 1.1 equiv). The vial was capped and taken out of the glove-box, dry MeCN (3 mL) was added and the reaction was heated at 100 °C for 24 hours to yield a green/black mixture. 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 solid was purified by recrystallization from diethyl ether/MeCN to afford **13** (47.2 mg, 84%) as yellow solid. All analyses were consistent with previously reported data.<sup>26</sup>

## 7. References

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