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Exploring palladium catalysis: From *N-tert*-prenylation to green chemistry

by

Ryan Van Zeeland

A dissertation submitted to the graduate faculty

in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Major: Organic Chemistry

Program of Study Committee:
Levi Stanley, Major Professor
Aaron Sadow
Jason Chen
Keith Woo
Wenyu Huang

Iowa State University

Ames, Iowa

2016

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ACKNOWLEDGEMENTS

There are many people I need to thank for their help, support, guidance and, of course, comic relief.

There isn't a better place to start than with the people who have known me longest. Mom, thank you for all you do for me. For as long as I can remember (and probably even before I can remember) you have always been there for me, ready to do whatever was necessary. That hasn't changed in grad school, whether it was letting me vent my frustrations, share my successes or I just needed a good ole fashion kick in the ass I always knew you were just a phone call away. And of course, I need to thank you for all the frozen, home-cooked lunches (or as it has more popularly been named "slop") it saved me an enormous amount of money, time, cooking and probably spared me from gaining another 25 pounds of fat from eating pizza. Dad, watching you get up at all hours of the day and night to go work twelve hour shifts for the last 27 years is an inspiration. Nobody knows how to push the right buttons to get me motivated quite the way you do. Whether it was hockey, school, work or making an ice cream cone you have always found a way to push me to not accept anything but my best effort. I know I wouldn't have made it this far without you. Brandon, we spent nearly every minute of our childhood together, you are my best friend, and the best brother I could ever ask for. You know me as well or better than I know myself sometimes. I could fill another thesis with all kinds of wild stories but no one wants to read that. Thanks for putting up with my shit. You rock.

I need to thank my wonderful girlfriend Jasmine. You have been there for me whenever I needed it these last two and half years. You made Iowa an almost bearable

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place to reside (is there a bigger compliment than that?). Coming home and seeing that smile on your face makes it easy to forget the struggles of the day and be happy. More importantly, thank you for dealing with the psychotic way I watch sports you deserve some type of global recognition for that. I love you so much and can't wait to see what our future holds.

The graduate students of the Stanley lab have also earned some serious recognition, Tony Gerten, Avipsa Ghosh, Kirsten Johnson, James Walker, Sagarika Weerasekara, Kevin Vickerman, Abhishek Kadam, Tanner Metz, and Brian Schumacher.

Tony, I don't think I've ever had, or will ever find, a more enigmatic friendship than ours. One week you'd drive me bananas the next everything would be peachy. The cow obsession, your personalized apartment security, the calendars, the absurd phrases, the puns, the cleanliness (or lack thereof), Jimmy John's Monday, Chipotle trips, the "150 plan", introducing you to Sherlock, Ron Swanson and whatever other shows on Netflix, the Superman onesie, eating a pound of bacon each for breakfast 4 times a year, and of course the 9-day trip to Hawaii for Pacifichem are just a few highlights of our time here together. Did you know some people say a cucumber tastes better than a pickle?

Avi, or I suppose more accurately, Pippy, being at "war" with you for the last three years or so has been great. I'll continue to be on the lookout for people trying to trip me. You'll never win.

Abhishek, it's weird to call to call you that. You are Milkshake. As you always say "we are bros for life…. and the afterlife." Hook 'em horns, let's go Texas (sorry Tanner)!

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Tanner and Mr. Brian Bizzle Schumacher. This probably isn't the platform to discuss most of our best memories. But the two of you have made the last two years of graduate school much more enjoyable. I really want to say more, but we'll save it for other times. ALLS I'm saying is, do yourselves a favor and quit being Packers fans. WHAT!?!?

Thank you to all my undergraduate chemistry professors at Ripon, Dr. Joe, Dr. Byron, Dr. Katahira, and especially Dr. Mas. Dr. Mas, I never even considered graduate school until you brought it up. Thank you for pushing me to follow this path, and for introducing me to "real organic chemistry". And more than anything, thank you for helping me believe in myself during tough times.

Thank you to all my committee members for their time and effort, Dr. Aaron Sadow, Dr. Jason Chen, Dr. Keith Woo, Dr. Wenyu Huang, Dr. Javier Vela and of course, my Ph.D advisor Dr. Levi Stanley.

Levi, I wish I knew a word for someone being "more patient than patient" because that's what you have been with me. Thank you for not giving up on me when I was struggling. All it takes is a quick glance at early presentations and the early stages of my notebook to realize how much I've learned. You have taught me so much, whether it is experimental design, or lab technique, or writing or just how to not be a hack, the list goes on. You have been a great boss by all accounts, which is astonishing considering you are a Mac user.

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ABSTRACT

In this thesis, various palladium-catalyzed reactions to form C-N and C-C are discussed. These reactions span *N-tert*-prenylation, conjugate addition of arylboronic acids to β,β-disubstituted enones and Suzuki-Miyaura cross-coupling of haloarenes and arylboronic acids.

Palladium-catalyzed conjugate addition of wide range of arylboronic acids to *β,β*-disubstituted enones occur to form ketone products bearing benzylic all-carbon quaternary centers. A simple catalyst prepared from palladium trifluoroacetate and 2,2′-bipyridine promotes these reactions. The use of aqueous sodium trifluoroacetate as the reaction medium significantly enhances reactivity and enables formation of challenging bis-benzylic and *ortho*-substituted benzylic all-carbon quaternary centers.

Palladium(II)-functionalized MOF-253 (MOF-253-Pd(OAc)$_2$) can be used as a recyclable catalyst to form all-carbon quaternary centers via conjugate additions of arylboronic acids to *β,β*-disubstituted enones in aqueous media. MOF-253-Pd(OAc)$_2$ can be reused 8 times to form ketone products in high yields and PXRD confirms the crystallinity remains intact. Additions of a range of stereoelectronically diverse arylboronic acids to a variety of *β,β*-disubstituted enones catalyzed by MOF-253-Pd(OAc)$_2$ occur in modest-to-high yields.

The electronic and steric effects of linker substitution on the activity of metalated MOFs have been investigated in the context of Suzuki–Miyaura cross-coupling reactions. m-6,6´-Me$_2$bpy-MOF-PdCl$_2$ (UiO-67-Pd-6,6´-dimethyl-bpydc$_{0.4}$/bpdc$_{0.6}$) exhibited a remarkable enhancement in the activity compared to non-functionalized m-bpy-MOF-PdCl$_2$ (UiO-67-Pd-bpydc$_{0.5}$/bpdc$_{0.5}$) and m-4,4´-Me$_2$bpy-MOF-PdCl$_2$(UiO-67-Pd-4,4´-

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dimethyl-bpydc$_{0.4}$/bpdc$_{0.6}$). This result clearly demonstrates that the stereoelectronic properties of metal-binding linker units are critical to the activity of single-site organometallic catalysts in MOFs.

Three distinct protocols are developed for the synthesis of *N*-*tert*-prenylindoles using indole, (η^6-indole)Cr(CO)$_3$, and indoline nucleophiles in the presence of the same catalyst generated from [Pd(η^3-prenyl)Cl]$_2$ and Xantphos. These reactions form *N*-*tert*-prenylindole products with a broad range of substitution and electronic character in high yields with high *tert*-prenyl-to-*n*-prenyl selectivity.

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CHAPTER 1: INTRODUCTION

General Introduction

Since the genesis of the principles of green chemistry,[1] synthetic chemists have made significant progress toward developing processes that improve atom and step economy,[2] reduce hazardous waste,[3] and use catalytic reagents.[4] In this thesis, these techniques will be applied in the context of palladium-catalyzed conjugate addition of arylboronic acids to enones to form all-carbon quaternary centers in aqueous media, the development of metalated MOFs as transition-metal catalysts and the palladium-catalyzed *N-tert*-prenylation of indoles.

Conjugate additions of arylboronic acids to β,β-disubstituted enones to form all-carbon quaternary centers in the presence of palladium(II) complexes of achiral[5] or chiral, non-racemic[6] bidentate nitrogen ligands are well established (Scheme 1a). However, palladium-catalyzed conjugate additions of *ortho*-substituted arylboronic acids to β,β-disubstituted enones and additions of arylboronic acids to β-aryl enones to generate bis-benzylic quaternary centers remain challenging and often result in little or no yield of the desired ketone product (Scheme 1b and 1c).

Recent studies by Stoltz demonstrate a clear enhancement in catalyst activity when the reaction occurs in the presence of water.[6e] Despite this observation, studies detailing palladium-catalyzed conjugate additions of arylboronic acids to β,β-disubstituted enones to form all-carbon quaternary centers in solely aqueous media do not exist.

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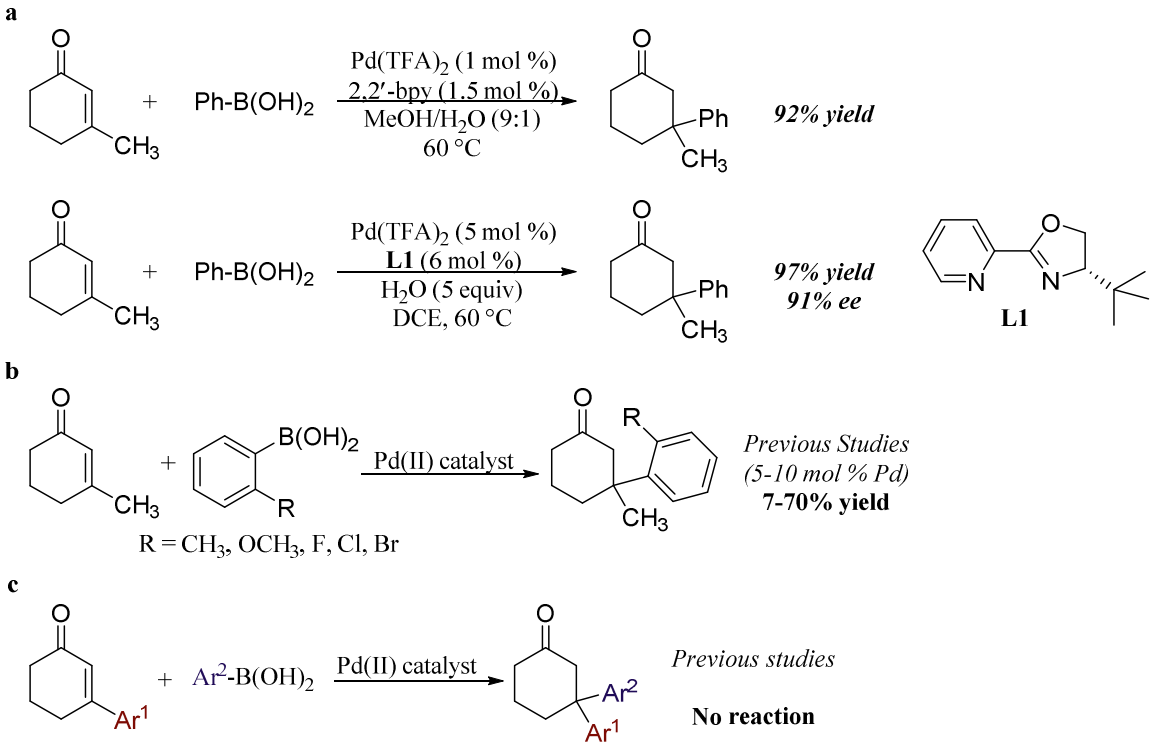
Scheme 1. Palladium-catalyzed conjugate additions of arylboronic acids to β,β-disubstituted enones



This thesis describes the development of a palladium(II) complex of 2,2′-bipyridine (bpy) as an active catalyst for conjugate addition of arylboronic acids to β,β-disubstituted enones in aqueous media. The observed increase in catalyst activity enables the addition of sterically encumbered *ortho*-substituted arylboronic and allows the formation of ketone products containing bis-benzylic quaternary centers in good yields. The value of the developed method is two-fold; environmentally hazardous organic solvents used in previous studies are replaced with the more environmentally benign aqueous media, and the observed increase in activity greatly expands the substrate scope of palladium-catalyzed conjugate additions of arylboronic acids to β,β-disubstituted enones. Further studies describe the ability of a palladium(II) bpy complex immobilized in a metal-organic frameworks (MOF) to act as a recyclable catalyst for the conjugate

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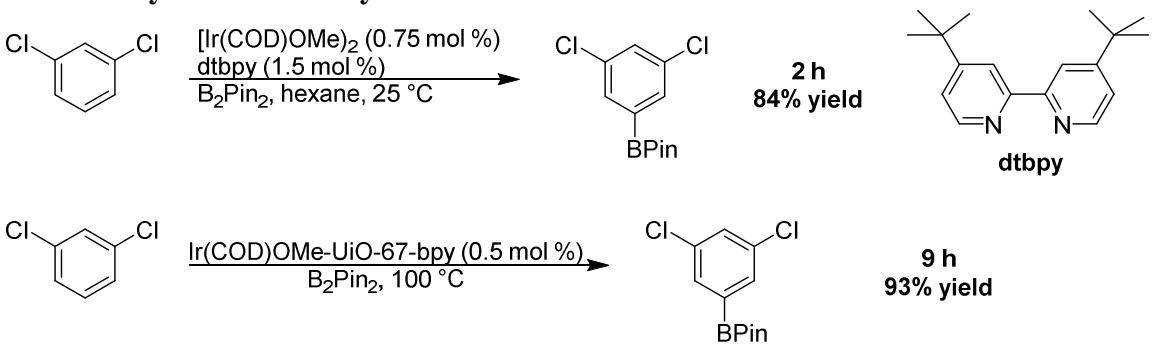
addition of arylboronic acids to β,β-disubstituted enones in aqueous media. However, this metalated MOF catalyst is a significantly less active catalyst for conjugate addition of arylboronic acids to β,β-disubstituted enones than its homogeneous counterpart.

In many reactions the activity of metalated MOFs is significantly lower than known homogeneous catalysts (Scheme 2).[7] For metalated MOFs to become more practical, widely used catalysts, the activity of these catalyst systems must be improved while maintaining the stability and recyclability.

Scheme 2. Comparison of homogeneous transition metal catalyst and metalated MOF catalyst for C-H borylation of arenes.



This thesis contributes to the development of metalated MOF catalysts by describing the design and synthesis of a series of stereoelectronically diverse bipyridyl linker units for the preparation of new metalated MOFs. These MOFs are studied in the context of Suzuki-coupling as a model reaction to observe the impact of steric and electronic properties on activity, selectivity, and stability of metalated MOFs containing 2,2′-bipyridyl units.

N-tert-prenylated indoles and analogs containing oxidized prenyl moieties show an array of medicinal properties.[8] Unfortunately, current synthetic routes to *N-tert*-prenylated indoles involve multiple nonstrategic redox steps[9] and the use of prefunctionalized starting materials.[10] The only direct method to generate *N-tert*-

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prenylated requires high loadings of palladium catalyst (20-40 mol %) and a silver co-oxidant (2.0-2.5 equiv).[11] This thesis contributes to the development of methods to form *N-tert*-prenylindoles by providing a direct method to generate a broad range of *N-tert*-prenylindole products. These reactions require significantly lower loadings of palladium catalyst and do not require metal co-oxidants.

Thesis Organization

This thesis contains six chapters composed of published journal papers and manuscripts in preparation for publication. Chapter one serves as a general introduction to the motivation behind the development of various catalytic transformations described in the thesis. Chapter two through five are journal articles of which chapters two and five contained published materials. Modifications have been made to each chapter to offer the reader a more coherent and complete research description. Each chapter beings with a review of the literature relevant to the topic to provide additional value and context to the original research discussed.

Chapter two is a modification of a paper published in *ACS Catalysis* in 2015 that describes conjugate additions of arylboronic acids to β,β-disubstituted enones in aqueous media catalyzed by Pd(II)-bpy compex. The author of this thesis is responsible for the entirety of the research discussed.

Chapter three is a modification of a manuscript submitted to *Green Chemistry* in 2016. This manuscript describes the metalation of bpy-UiO and MOF-253 with palladium. These metalated MOFs are recyclable catalysts for conjugate additions of arylboronic acids to β,β-disubstituted enones in aqueous media. This work was done in

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close collaboration with Xinle Li. The author of this thesis is responsible for the synthesis and characterization of the bpy linkers, performing all conjugate addition reactions described and characterization of all the resultant products. Xinle Li, was responsible for the preparation, metalation and characterization of bpy-UiO and MOF-253.

Chapter four is a modification of a manuscript submitted to *Angewandte Chemie International Edition*. This manuscript describes the synthesis of a series of stereoelectronically diverse 2,2′-bipyridyl linkers for the preparation of substituted, metalated bpy-UiO MOFs. The impact of the stereoelectronic properties of these metalated MOFs in Suzuki-coupling is investigated. This work was done in close collaboration with Xinle Li. The author of this thesis is responsible for the synthesis and characterization of new organic linkers. Xinle Li was responsible for MOF preparation, characterization and the Suzuki-coupling reactions.

Chapter 5 is a modification of a paper published in *Organic Letters*. This chapter describes three distinct methods for the synthesis of *N*-*tert*-prenyl indoles using indole, (η^6-indole)$Cr(CO)_3$, and indoline nucleophiles. The unique features of each method allow *N*-*tert*-prenylindoles with a broad range of substitution and electronic character to be accessed. This work was done in close collaboration with Kirsten F. Johnson. The author of this thesis is responsible for the synthesis, characterization and decomplexation of chromium containing compounds. Kirsten F. Johnson was responsible for all other synthesis and characterization.

Chapter six draws general conclusions from the work performed during the author's graduate studies.

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CHAPTER 2: PALLADIUM-CATALYZED CONJUGATE ADDITION OF ARYLBORONIC ACIDS TO *β*,*β*-DISUBSTITUED ENONES IN AQUEOUS MEDIA: FORMATION OF BIS-BENZYLIC AND *ORTHO*-SUBSTITUTED BENZYLIC QUATERNARY CENTERS

Modified from a paper published in *ACS Catalysis*

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Abstract

Palladium-catalyzed conjugate addition of arylboronic acids to *β*,*β*-disubstituted enones in aqueous media is reported. Additions of a wide range of arylboronic acids to *β*,*β*-disubstituted enones occur to form ketone products bearing benzylic all-carbon quaternary centers. A simple catalyst prepared from palladium trifluoroacetate and 2,2′-bipyridine promotes these reactions. The use of aqueous sodium trifluoroacetate as the reaction medium significantly enhances reactivity and enables formation of challenging bis-benzylic and *ortho*-substituted benzylic all-carbon quaternary centers.

Introduction

Transition metal-catalyzed conjugate addition of aryl nucleophiles to β,β-disubstituted enones is a valuable approach to construct benzylic all-carbon quaternary centers.[1] Nickel-catalyzed conjugate additions of arylaluminum reagents[2] and copper-catalyzed additions of arylaluminum,[3] arylmagnesium,[4] and arylzinc[5] reagents are established methods to generate benzylic all-carbon quaternary centers. These processes

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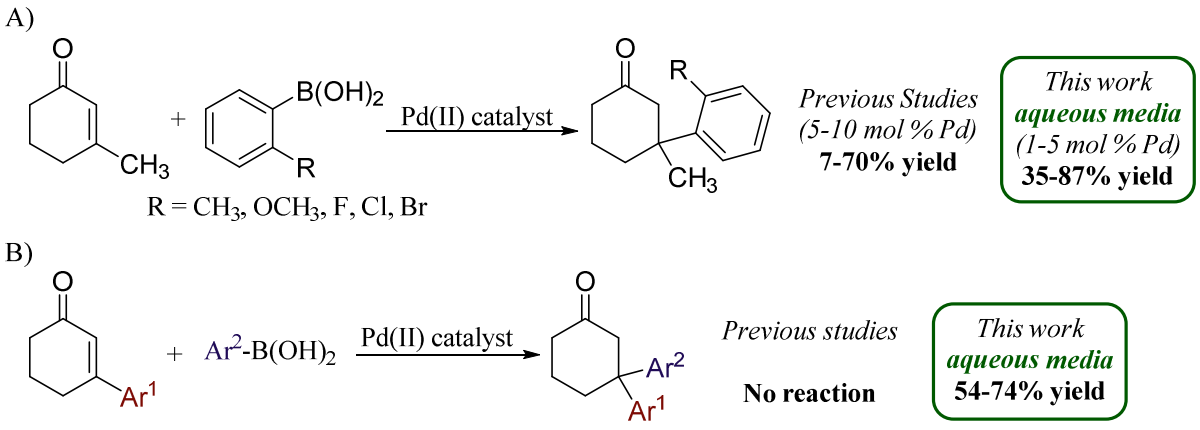
involve air- and/or moisture-sensitive organometallic nucleophiles and typically do not occur in aqueous media. In contrast, rhodium- and palladium-catalyzed conjugate additions of air- and moisture-stable tetraarylborates,[6] arylboroxines[7] and arylboronic acids[8,9] form the corresponding ketones containing benzylic quaternary carbon centers in high yields, and, in several cases, with high enantioselectivities.

In recent years, palladium-catalyzed conjugate additions of arylboronic acids to β,β-disubstituted enones have emerged as a primary target for further development due to the stability, functional group compatibility, and commercial availability of arylboronic acids.[9,10,11] Conjugate additions of a wide range of arylboronic acids to β,β-disubstituted enones occur in high yields when the reactions are conducted in the presence of readily accessible palladium(II) complexes of 2,2′-bipyridine (2,2′-bpy).[9] In addition, Stoltz and Minnaard have developed highly enantioselective variants of these reactions using palladium(II) complexes of chiral, non-racemic pyridinooxazoline (Pyox)[10] and bisoxazoline (Box)[11] ligands as catalysts.

Scheme 1. Challenges in Pd-Catalyzed Conjugate Addition of Arylboronic Acids to *β,β*-Disubstituted Enones



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Although current palladium catalysts promote conjugate additions of arylboronic acids to form ketones containing benzylic quaternary carbon centers, additions of *ortho*-substituted arylboronic acids to β,β-disubstituted enones and reactions to generate bis-benzylic quaternary centers remain challenging. (Scheme 1). Palladium-catalyzed conjugate additions of *ortho*-substituted arylboronic acids to β,β-disubstituted enones often result in low yields of the corresponding ketone products and require high loadings of the palladium catalyst (Scheme 1A).[10b, 10f, 11b] In addition, palladium-catalyzed conjugate additions of arylboronic acids to β-aryl β,β-disubstituted enones have not been reported to form bis-benzylic quaternary carbon centers (Scheme 1B). We initiated studies to identify a combination of palladium catalyst and aqueous reaction conditions to address these limitations and enable the formation of ketones containing sterically encumbered benzylic and bis-benzylic all-carbon quaternary centers.

Results and Discussion

At the outset of our studies, we noted a report by Stoltz indicating that the presence of water increases the overall rate of palladium-catalyzed conjugate additions to β,β-disubstituted enones.[10b] We hypothesized that the choice of aqueous reaction medium may also function to enhance the reactivity of palladium catalysts such that *ortho*-substituted benzylic and bis-benzylic all-carbon quaternary centers could be readily formed in these reactions. To test our hypothesis, we evaluated the Pd(II)-catalyzed addition of phenylboronic acid to 3-methylcyclohex-2-en-1-one **1a** in a variety of mixed organic/aqueous reaction media (Table 1).

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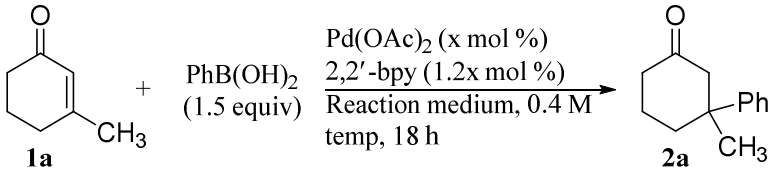
The reaction of **1a** with 1.5 equiv of phenylboronic acid in the presence of a catalyst prepared from $Pd(OAc)_2$ and 2,2´-bipyridine was initially evaluated in MeOH:H_2O mixtures ranging from 9:1 to 1:9 (table 1, entries 1-3). The ratio of MeOH to water has a modest impact on the yields of 3-methyl-3-phenylcyclohexan-1-one **2a** (49-65%). Increasing the ionic strength of the aqueous reaction medium further

Table 1. Identification of Reaction Conditions in Mixed Organic/Aqueous Medium[a]



Entry	Reaction Medium	$Pd(OAc)_2$	Temp (°C)	NMR Yield[b]
1	9:1 MeOH:H_2O	5.0 mol %	40	49%
2	1:1 MeOH:H_2O	5.0 mol %	40	65%
3	1:9 MeOH:H_2O	5.0 mol %	40	60%
4	1:9 MeOH: 50 mM NaOAc	5.0 mol %	40	68%
5	1:9 MeOH: 50 mM NaOAc	5.0 mol %	80	86%
6	1:9 MeOH: 50 mM NaOAc	1.0 mol %	80	47%

[a] Reaction conditions: **1a** (1.0 mmol), $PhB(OH)_2$ (1.5 mmol), $Pd(OAc)_2$ (x mmol), 2,2′-bpy (1.2x mmol), reaction medium (2.5 mL), 18 h. [b] Determined by ^1H NMR using dibromomethane as an internal standard.

increased the yield of **2a** to 68% (Table 1, entry 4). Changing the temperature of the reaction from 40 °C to 80 °C led to the formation of ketone **2a** in 86% yield (Table 1, entry 5). The reaction of **1a** with phenylboronic acid in the presence of only 1.0 mol % catalyst generated ketone **2a** in 47% yield.

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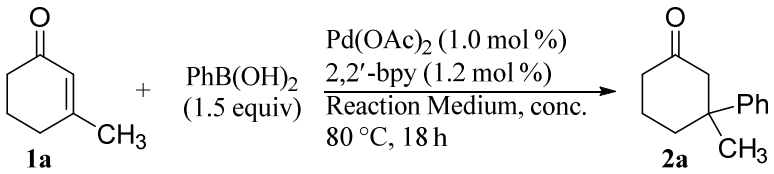
Table 2. Impact of Concentration on Pd-Catalyzed Addition of Phenylboronic Acid to 1a[a]



Entry	Reaction Medium	pH	Concentration of **1a**	NMR Yield[b]
1	1:9 MeOH: 50 mM NaOAc	7.0	0.4 M	47%
2	1:9 MeOH: 50 mM NaOAc	7.0	0.8 M	52%
3	1:9 MeOH: 50 mM NaOAc	7.0	1.6 M	55%
4	1:9 MeOH: 50 mM NaOAc	7.0	3.0 M	70%

[a] Reaction conditions: **1a** (1.0 mmol), $PhB(OH)_2$ (1.5 mmol), $Pd(OAc)_2$ (0.010 mmol), 2,2′-bpy (0.012 mmol), reaction medium (x mL), 18 h. [b] Determined by ^1H NMR using dibromomethane as an internal standard.

The reaction of **1a** with phenylboronic acid is largely influenced by the concentration of the reaction relative to enone **1a** (Table 2). Changing the concentration of the reaction relative to enone **1a** from 0.4 M to 3.0 M increased the yield of ketone **2a** from 47% to 70% (Table 2, entry 1 and 4).

The reaction temperature, pH of the aqueous reaction medium, and the identity of the Pd(II) salt also impact the efficiency of the Pd(II)-catalyzed addition of phenylboronic acid to **1a** (Table 3). The addition of phenylboronic acid to **1a** formed ketone **2a** in 85% yield when the reaction was run under completely aqueous reaction conditions. The reaction of **1a** with phenylboronic acid conducted in the presence of 50 mM aqueous NaTFA (pH = 7) generated ketone **2a** in 88% yield (Table 3, entry 3). Ketone **2a** is formed in 95-97% yield when the reaction is conducted in 50 mM aqueous NaTFA at 100

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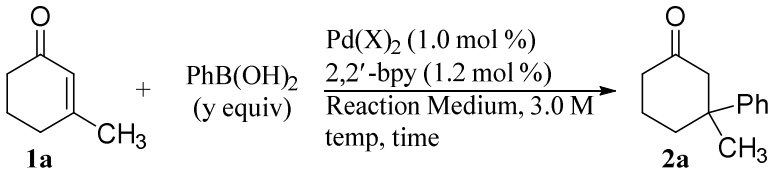
°C with catalysts generated from 2,2´-bipyridine and either $Pd(OAc)_2$ or $Pd(TFA)_2$ (Table 3, entries 4 and 5). The combination of a palladium catalyst generated from $Pd(TFA)_2$

Table 3. Identification of Reaction Conditions in Aqueous Media[a]



Entry	Reaction Medium	pH	X	$PhB(OH)_2$ (x equiv)	Temp (°C)	NMR Yield[b]
1	1:9 MeOH: 50 mM NaOAc	7.0	OAc	1.5 equiv	80	70%
2	50 mM NaOAc	7.0	OAc	1.5 equiv	80	85%
3	50 mM NaTFA	7.0	OAc	1.5 equiv	80	88%
4	50 mM NaTFA	7.0	OAc	1.5 equiv	100	95%
5	50 mM NaTFA	7.0	TFA	1.5 equiv	100	97%
6	50 mM NaTFA	7.0	TFA	1.2 equiv	100	91%
7	50 mM NaTFA	6.5	TFA	1.2 equiv	100	62%
8[c]	50 mM NaTFA	8.2	TFA	1.2 equiv	100	99%
9[d]	50 mM NaTFA	8.2	TFA	1.2 equiv	100	99%
10[e]	50 mM NaTFA	8.2	TFA	1.2 equiv	100	60%
11[c]	Keystone Light	----	TFA	1.2 equiv	100	93%

[a] Reaction conditions: **1a** (1.0 mmol), $PhB(OH)_2$ (y mmol), $Pd(X)_2$ (0.010 mmol), 2,2′-bpy (0.012 mmol), reaction medium (0.33 mL), 18 h. [b] Determined by ^1H NMR using dibromomethane as an internal standard. [c] Reactions run for 2 h. [d] Reaction run for 4 h in the presence of 0.5 mol % $Pd(TFA)_2$ and 0.6 mol % 2,2′-bpy. [e] Reaction run for 8 h in the presence of 0.25 mol % $Pd(TFA)_2$ and 0.3 mol % 2,2′-bpy.

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and a higher reaction temperature enabled us to lower the loading of phenylboronic acid to 1.2 equiv with only a modest decrease in the yield of **2a** (Table 3, entry 6). The pH of the reaction medium dramatically influences the efficiency of the model reaction (Table 3, entries 7 and 8). The addition of phenylboronic acid to **1a** under slightly acidic conditions leads to a significant decrease in the yield of **2a** (62% yield, Table 3, entry 7). In contrast, the model reaction forms **2a** in nearly quantitative yield when the reaction is conducted under basic conditions (99%, Table 3, entry 8). Under these reaction conditions, the loading of the palladium catalyst can be lowered to 0.5 mol % without impacting the yield of **2a**, but a decrease in reaction efficiency is observed upon lowering the catalyst loading to 0.25 mol % (Table 3, entries 9 and 10). The reaction of **1a** and phenylboronic acid performed with Keystone Light, a product of Coors Brewing Company, as the reaction medium formed ketone **2a** in 93% yield (Table 3, entry 11).

We chose to proceed with studies to evaluate additions of a variety of arylboronic acids to **1a** under the reaction conditions identified in entry 7 of Table 3. These results are summarized in Scheme 2. As noted above, the addition of phenylboronic acid to **1a** occurs to form **2a** in high yield. The addition of the related phenylboronic acid pinacol ester to **1a** occurs to form **2a** in 84% yield when the reaction is conducted with 2 mol % Pd catalyst. Additions of 4-substituted phenylboronic acids containing substituents ranging from strongly electron-donating to strongly electron-withdrawing form ketones **2b**-**2g** in 82-92% yield. Additions of a variety of 3-substituted and 3,5-disubstituted phenylboronic acids form the corresponding ketones **2h**-**2l** in high yields (81-90% yield).

Additions of 2-substituted phenylboronic acids to β,β-disubstituted enones often occur in low yields with previously developed palladium catalysts and reaction

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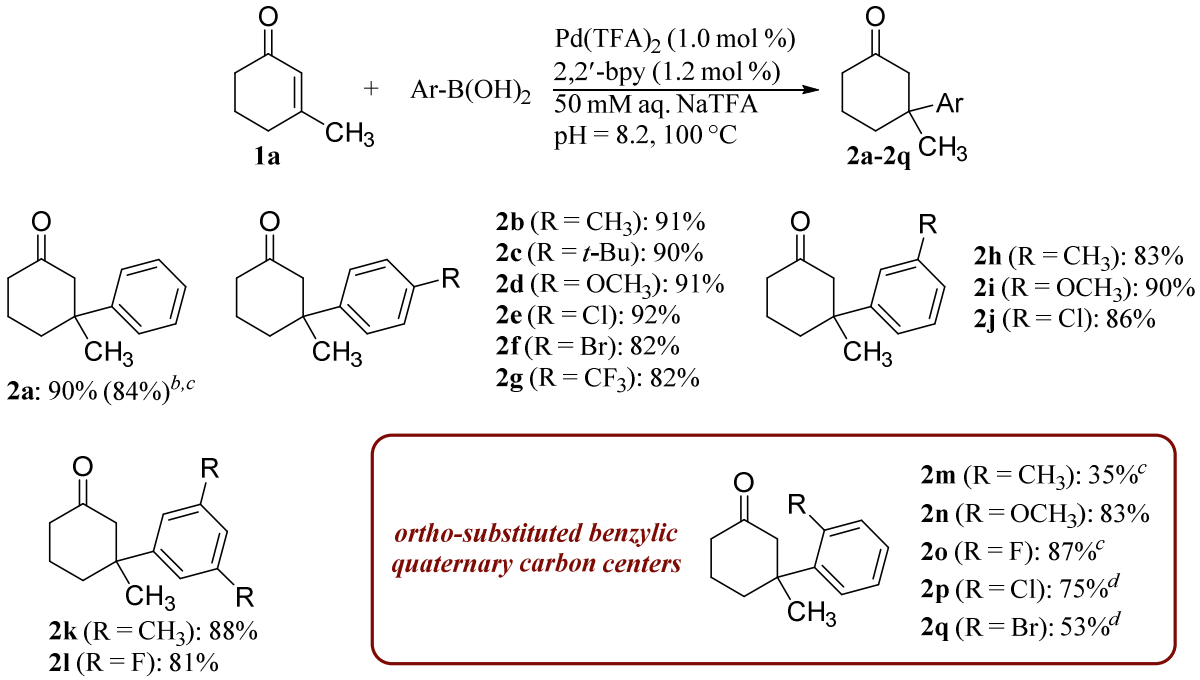
systems.[10b-c,11b] However, additions of a range 2-substituted phenylboronic acids to **1a** occur in the presence of 1-5 mol % catalyst when the reactions are conducted in aqueous NaTFA. These reactions form ketones **2m**-**2q** containing *ortho*-substituted benzylic

Scheme 2. Pd-Catalyzed Addition of Arylboronic Acids to 1a in Aqueous NaTFA[a]



[a] Reaction conditions: **1a** (1.0 mmol), arylboronic acid (1.2 mmol), palladium trifluoroacetate ($Pd(TFA)_2$), (0.010 mmol), 2,2′-bpy (0.012 mmol), 50 mM aq. NaTFA (0.33 mL, pH = 8.2), 100 °C, 2-24 h. Isolated yields are reported after purification by flash chromatography. [b] Reaction performed with 2.0 equiv PhBPin in place of $PhB(OH)_2$. [c]Reaction run in the presence of 2.0 mol % $Pd(TFA)_2$ and 2.4 mol % 2,2′-bpy with 2.0 equiv $ArB(OH)_2$. [d] Reaction run in the presence of 5 mol % $Pd(TFA)_2$ and 6 mol % 2,2′-bpy with 2.0 equiv $ArB(OH)_2$.

quaternary carbons in 35-87% yield. Additions of more challenging 2,6-dichloro-, 2,6-difluoro-, and 2,6-dimethoxyphenylboronic acids to enone **1a** did not form the corresponding ketone products in the presence of 5 mol % catalyst, even when reactions were run with 4.0 equivalents of the appropriate 2,6-disubstituted phenylboronic acid.

Additions of phenylboronic acid to a variety of 3-substituted enones also occur in good to excellent yields (Scheme 3). The additions of phenylboronic acid to 3-

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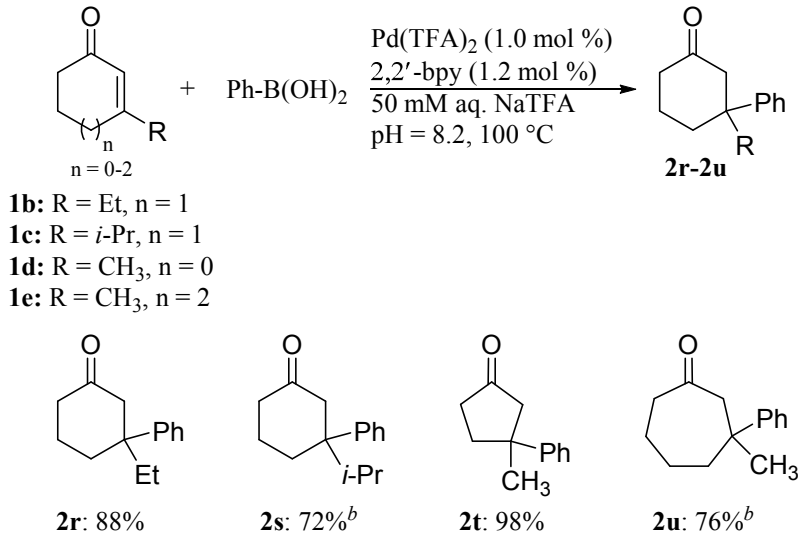
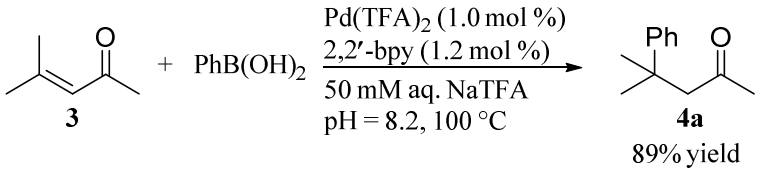
ethylcyclohexenone and 3-isopropylcyclohexenone form ketones **2r** (R = Et) and **2s** (R = *i*-Pr) in 88% and 72% yield. Additions of phenylboronic acid to 5- and 7-membered cyclic enones also occur to form ketones containing benzylic quaternary carbons. The addition of phenylboronic acid to 3-methylcyclopentenone forms ketone **2t** in 98% yield

Scheme 3. Pd-Catalyzed Addition of $PhB(OH)_2$ to Cyclic Enones 1b-1e[a]



[a] Reaction conditions: **1b-1e** (1.0 mmol), $PhB(OH)_2$ (1.2 mmol), $Pd(TFA)_2$, (0.010 mmol), 2,2′-bpy, (0.012 mmol), 50 mM aq. NaTFA (0.33 mL, pH = 8.2), 100 °C, 16-24 h. Isolated yields are reported after purification by flash column chromatography. [b] Reaction run in the presence of 2.0 mol % $Pd(TFA)_2$, and 2.4 mol % 2,2′-bpy with 2.0 equiv of $PhB(OH)_2$.

under our standard reaction conditions. The addition of phenylboronic acid to 3-methylcycloheptenone forms ketone **2u** in 76% yield. However, 3-methylcycloheptenone is less reactive than the corresponding 5- and 6-membered ketones, and 2 mol % catalyst is required to drive this reaction to completion.



(1)

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Our catalytic conditions also enable conjugate additions of arylboronic acids to acyclic β,β-disubstituted enones.[12] For example, the addition of phenylboronic acid to 4-methylpent-3-en-2-one **3** occurs under our standard reaction conditions to form ketone **4** in 89% yield (eq 1).

The ability to form challenging *ortho*-substituted benzylic quaternary carbons through Pd-catalyzed conjugate additions of arylboronic acids led us to investigate whether our reaction system would enable the formation of bis-benzylic quaternary carbon centers. Formation of this class of quaternary carbon center by conjugate addition of aryl nucleophiles to cyclic β-aryl enones typically requires air- and/or moisture-sensitive organometallic reagents.[3c,13] To our knowledge, Pd-catalyzed additions of air- and moisture-stable arylboronic acids to cyclic β-aryl enones have not been reported.[14]

Scheme 4 summarizes additions of a variety of arylboronic acids to cyclic β-aryl enones **1f**-**1h** to form bis-benzylic quaternary carbon centers in aqueous media. These reactions form the β,β-diaryl ketone products **2v**-**2ab** in moderate to good yields, but 5 mol % palladium catalyst and 4.0 equiv of the arylboronic acid are required. Additions of phenyl-, 4-chlorophenyl-, and 3-chlorophenylboronic acids to 3-phenylcyclohexenone **1f** form ketones **2v**-**2x** in 54-74% yield. In contrast, additions of electron-rich arylboronic acids to **1f** occur in low yields due to protodeboronation.[10e, 11b, 15] To address this issue, we incorporated the electron-rich aryl group (Ar^1 = 4-$(H_3C)C_6H_4$ (**1g**) and 4-$H_3COC_6H_4$ (**1h**)) into the 3-arylenone substrates. Additions of phenyl- and 4-chlorophenylboronic acid to enones **1g** and **1h** form the corresponding ketones **2y**-**2ab** containing bis-benzylic quaternary carbons in 66-74% yield. Attempts to construct bis-benzylic quaternary

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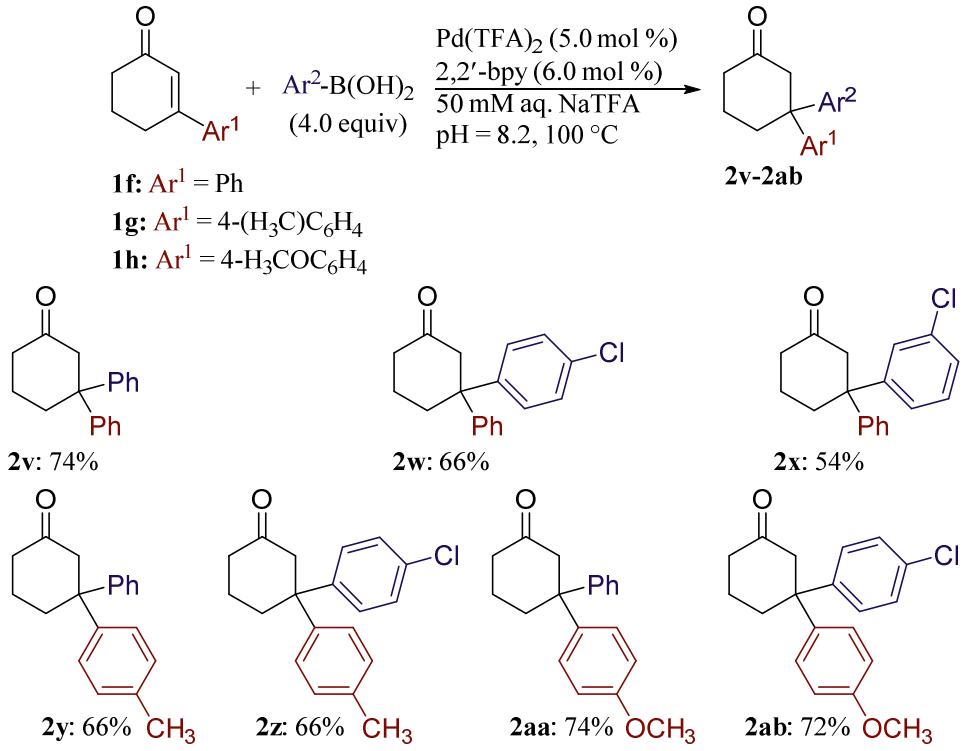
centers containing an *ortho*-substituted aryl group by addition of *ortho*-substituted arylboronic acids to enone **1f** led to low yields of the ketone products.[16]

Scheme 4. Pd-Catalyzed Addition of Arylboronic Acids to *β*-aryl Cyclohex-2-enones 1f-1h[a]



[a] Reaction conditions: **1f-1h** (0.50 mmol), $Ar^2B(OH)_2$ (2.0 mmol), $Pd(TFA)_2$ (0.025 mmol), 2,2′-bpy (0.030 mmol), 50 mM NaTFA (0.17 mL, pH = 8.2), 100 °C, 16-20 h. Isolated yields are reported after purification by column chromatography.

We investigated a small number of chiral, non-racemic catalysts generated from $Pd(TFA)_2$, and a pyridinooxazoline ligand (Pyox) **L1-L3** in the reaction of **1a** with phenylboronic acid. The addition of two equivalents of phenylboronic acid to enone **1a** catalyzed by 5 mol % of catalyst generated from $Pd(TFA)_2$ and **L1** generated enone **2a** in 91% yield and 72% ee. Modifying the chiral substituent in the 4-position of Pyox ligand to isopropyl (**L2**), or phenyl (**L3**) led to the formation of ketone product **2a** in 20% or

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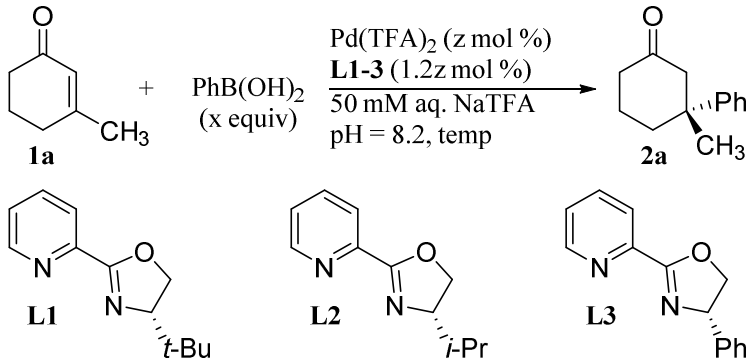
34% ee (Table 4, entries 2 and 3). Decreasing the reaction temperature, the catalyst loading, and the loading of phenylboronic acid had little impact on the yield or ee of **2a**

Table 4. Enantioselective Pd-Catalyzed Addition of Phenylboronic Acid to 1a in Aqueous NaTFA[a]



Entry	Ligand	$Pd(TFA)_2$	$PhB(OH)_2$	Temp (°C)	Yield	ee
1	L1	5.0 mol %	2.0 equiv	60	91%	72%
2	L2	5.0 mol %	2.0 equiv	60	71%	20%
3	L3	5.0 mol %	2.0 equiv	60	95%	34%
4	L1	5.0 mol %	2.0 equiv	40	90%	67%
5	L1	1.0 mol %	2.0 equiv	40	88%	70%
6	L1	1.0 mol %	1.2 equiv	40	86%	71%

[a] Reaction conditions: **1a** (0.5 mmol), arylboronic acid (x mmol), palladium trifluoroacetate ($Pd(TFA)_2$), (z mmol), **L1-3** (1.2z mmol), 50 mM aq. NaTFA (0.17 mL, pH = 8.2), temp, 16 h. Isolated yields are reported after purification by flash chromatography; enantiomeric excesses were determined by chiral HPLC analysis

when the reaction was run in the presence of a catalyst generated from $Pd(TFA)_2$ and **L1** (Table 4, entries 4-6). The conditions described in entry 6 demonstrate a catalytic, enantioselective addition of phenylboronic acid to enone **1a** occurs in 86% yield and 71% ee under our aqueous reaction conditions. To our knowledge, this reaction represents the

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first enantioselective example of conjugate addition to form a benzylic, all-carbon quaternary center under completely aqueous conditions.

Conclusion

We developed a set of catalytic reaction conditions for palladium-catalyzed conjugate addition of arylboronic acids to β,β-disubstituted enones in aqueous media. Additions of a wide range of arylboronic acids to β,β-disubstituted enones occur to form ketone products bearing benzylic all-carbon quaternary centers in moderate to high yields. The use of aqueous NaTFA as the reaction medium significantly enhances reactivity and enables the formation of challenging bis-benzylic and *ortho*-substituted benzylic quaternary centers. The addition of phenylboronic acid to enone **1a** in the presence of a catalyst generated from $Pd(TFA)_2$ and a pyridinooxazoline can form enantioenriched enone **2a** in high yields.

Experimental

General Experimental Details. All reactions were performed under air unless otherwise noted. Reactions involving air-sensitive reagents were conducted under inert atmospshere in a nitrogen-filled dry box or by standard Schlenk techniques. Glassware for moistures sensitive reactions was dried at 140 °C in an oven for at least one hour prior to use. Aqueous sodium acetate and sodium trifluoroacetate solutions were prepared by dissolving the appropriate sodium salt in deionized water. The aqueous solutions were adjusted to the appropriate pH by addition of concentrated HCl or sodium hydroxide pellets. Flash column chromatography was performed on Siliflash® P60 silica gel (230-

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400 mesh) using hexane/ethyl acetate mixtures as the eluent. Products were visualized on TLC by UV light and/or by staining with 2,4-dinitrophenylhydrazine.

HRMS (ESI) analysis was performed at the Iowa State Chemical Instrumentation Facility on an Agilent 6540 QTOF spectrometer. NMR spectra were acquired on Varian MR-400 and Bruker Avance III 600 spectrometers at the Iowa State Chemical Instrumentation Facility. Chemical shifts are reported relative to a residual solvent peak ($CDCl_3$ = 7.26 ppm for ^{1}H, and 77.10 ppm for ^{13}C) or an external standard ($F_3CC_6H_5$ = -63.72 ppm for ^{19}F). Coupling constants are reported in hertz.

Materials. 3-Methylcyclohex-2-en-1-one **1a,** 3-methylcyclopent-2-en-1-one **1d**, and 4-methylpent-3-en-2-one **3** were purchased from TCI and used without further purification. 3-Ethylcyclohex-2-en-1-one **1b**, 3-isopropylcyclohex-2-en-1-one **1c**, 3-phenylcyclohex-2-en-1-one **1f**, 3-(4-methylphenyl)cyclohex-2-en-1-one **1g**, and 3-(4-methylphenyl)cyclohex-2-en-1-one **1h** were synthesized according to a literature procedure.[17] 3-Methylcyclohept-2-en-1-one **1e** was synthesized according to a literature procedure.[18] 4-Methylphenylboronic acid, 2-methylphenylboronic acid, 2-fluorophenylboronic acid, and phenylboronic acid pinacol ester were purchased from Combi-Blocks and used without further purification. 3,5-Difluorophenylboronic acid, 4-trifluoromethylphenylboronic acid, 4-bromophenylboronic acid and 3-chlorophenylboronic acid were purchased from Frontier Scientific and used without further purification. 2-Methoxyphenylboronic acid, 3,5-dimethylphenylboronic acid, 4-chlorophenylboronic acid, palladium acetate, and palladium trifluoroacetate were purchased from Sigma-Aldrich and used with further purification. 3-Methylphenylboronic acid was purchased from ArkPharm Inc. and used without further

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purification. 3-Methoxyphenylboronic acid, 4-methoxyphenylboronic acid and 4-*tert*-butylphenylboronic acid were purchased from AK Scientific and used without further purification. 2,2´-Bipyridine was purchased from Fisher Scientific and used without further purification. (*S*)-4-*tert*-Butyl-2-(2-pyridyl)oxazoline **L1** was synthesized according to a literature procedure.[19]

General Procedure A: Pd-Catalyzed Conjugate Addition of Arylboronic Acids to Enones 1a-1b, 1d, and 3.

To a 1 dram vial was added the appropriate arylboronic acid (1.20 mmol, 1.20 equiv), $Pd(TFA)_2$ (3.3 mg, 0.010 mmol, 0.010 equiv), 2,2´-bipyridine (1.8 mg, 0.012 mmol, 0.012 equiv), enone **1a**, **1b**, **1d**, or **3** (1.00 mmol, 1.00 equiv) and 50 mM aqueous sodium trifluoroacetate solution (333 µL, pH = 8.2). The vial was sealed with a PFTE/silicone-lined septum cap. The reaction mixture was heated to 100 °C and allowed to stir at this temperature (2-18 h) until the reaction was judged to be complete by TLC analysis. The mixture was allowed to cool, diluted with EtOAc (3 mL), and filtered through a pad of silica gel. The silica gel was washed with EtOAc (3 x 10 mL). The resulting organic layer was washed with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was dissolved in $CDCl_3$ (0.70 mL) and CH_2Br_2 (35.1 µL, 0.500 mmol) was added as an internal standard. NMR yields were determined by ^1H NMR spectroscopy of the crude reaction mixture. The crude reaction mixture was purified by flash column chromatography on silica gel (hexane:EtOAc) to yield the desired ketones **2a**-**2l**, **2n**, **2r**, **2t**, and **4**.

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Characterization Data for Ketones 2a-2l, 2n, 2r, 2t, and 4

3-Methyl-3-phenylcyclohexan-1-one (2a):[9a] Prepared according to General Procedure A from 3-methylcyclohex-2-en-1-one **1a** (110 mg, 1.00 mmol) and phenylboronic acid (146 mg, 1.20 mmol) (reaction time = 2 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2a** (169 mg, 0.899 mmol, 90%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.33 (s, 3H), 1.64-1.71, (m, 1H), 1.85-1.95 (m, 2H), 2.17-2.21 (m, 1H), 2.32 (app t, *J* = 6.0 Hz, 2H), 2.44 (d, *J* = 14.4 Hz, 1H), 2.88 (d, *J* = 14.4 Hz, 1H) 7.19-7.22 (m, 1H), 7.33 (m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 22.1, 29.9, 38.0, 40.9, 42.9, 53.2, 125.7, 126.3, 128.6, 147.5, 211.5.

3-Methyl-3-(*p*-tolyl)cyclohexan-1-one (2b):[9a] Prepared according to General Procedure A from 3-methylcyclohex-2-en-1-one **1a** (110 mg, 1.00 mmol) and *p*-tolylboronic acid (163 mg, 1.20 mmol) (reaction time = 3 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2b** (184 mg, 0.911 mmol, 91%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.31 (s, 3H), 1.64-1.71 (m, 1H), 1.84-1.92 (m, 2H), 2.15-2.19 (m, 1H), 2.31 (app t, *J* = 6.6 Hz, 2H), 2.32 (s, 3H), 2.42 (d, *J* = 14.4 Hz, 1H), 2.86 (d, *J* = 14.4 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 2H), 7.21 (d, *J* = 7.8 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 20.9, 22.1, 29.9, 38.0, 40.9, 42.6, 53.3, 125.5, 129.3, 135.8, 144.5, 211.7.

3-Methyl-3-(4-*tert*-butylphenyl)cyclohexan-1-one (2c): Prepared according to General Procedure A from 3-methylcyclohex-2-en-1-one **1a** (110 mg, 1.00 mmol) and 4-*tert*-butylphenylboronic acid (214 mg, 1.20 mmol) (reaction time = 16 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2c** (221 mg, 0.906 mmol, 91%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.31 (s, 9H), 1.35 (s, 3H),

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1.67-1.73 (m, 1H), 1.84-1.93 (m, 2H), 2.15-2.19 (m, 1H), 2.31 (dd, *J* = 9.6, 6.6 Hz, 2H), 2.43 (d, *J* = 14.4 Hz, 1H), 2.87 (d, *J* = 14.4 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 22.2, 29.7, 30.8, 31.4, 34.4, 40.9, 42.5, 53.3, 125.2, 125.4, 144.5, 148.9, 211.8. HRMS (ESI) calcd. for $C_{17}H_{24}O^+$ $[M+H]^+$ 245.1900, found 245.1900.

3-(4-Methoxyphenyl)-3-methylcyclohexan-1-one (2d):[9a] Prepared according to General Procedure A from 3-methylcyclohex-2-en-1-one **1a** (110 mg, 1.00 mmol) and 4-methoxyphenylboronic acid (182 mg, 1.20 mmol) (reaction time = 2 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2d** (198 mg, 0.908 mmol, 91%) as a clear, yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.30 (s, 3H), 1.62-1.69 (m, 1H), 1.83-1.91 (m, 2H), 2.13-2.17 (m, 1H), 2.33 (dd, *J* = 6.6, 4.8 Hz, 2H), 2.41 (d, *J* = 14.4 Hz, 1H), 2.85 (d, *J* = 14.4 Hz, 1H), 3.78 (s, 3H), 6.85 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 22.1, 30.2, 38.1, 40.9, 42.4, 53.4, 55.3, 113.9, 126.7, 139.5, 157.8, 211.6.

3-(4-Chlorophenyl)-3-methylcyclohexan-1-one (2e):[7a] Prepared according to General Procedure A from 3-methylcyclohex-2-en-1-one **1a** (110 mg, 1.00 mmol) 4-chlorophenylboronic acid (188 mg, 1.20 mmol) (reaction time = 18 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2e** (205 mg, 0.919 mmol, 92%) as a colorless oil. ^{1}HNMR (600 MHz, $CDCl_3$): δ 1.30 (s, 3H), 1.61-1.68 (m, 1H), 1.84-1.93 (m, 2H), 2.13-2.18 (m, 1H), 2.31(app t, *J* = 6.6 Hz, 2H), 2.43 (d, *J* = 14.4 Hz, 1H), 2.83 (d, *J* = 14.4 Hz, 1H), 7.24-7.26 (m, 2H), 7.27-7.29 (m, 2H). ^{13}CNMR (150 MHz, $CDCl_3$): δ 22.0, 30.0, 38.0, 40.8, 42.7, 53.1, 127.2, 128.7, 132.1, 145.9, 211.0.

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3-(4-Bromophenyl)-3-methylcyclohexan-1-one (2f):[7a] Prepared according to General Procedure A from 3-methylcyclohex-2-en-1-one **1a** (110 mg, 1.00 mmol) and 4-bromophenylboronic acid (241 mg, 1.20 mmol) (reaction time = 18 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2f** (207 mg, 0.818 mmol, 82%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.30 (s, 3H), 1.60-1.67 (m, 1H), 1.84-1.93 (m, 2H), 2.13-2.17 (m, 1H), 2.29-2.34 (app t, *J* = 6.6 Hz, 2H), 2.42 (d, *J* = 14.4 Hz, 1H), 2.83 (d, *J* = 14.4 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 22.0, 30.0, 37.9, 40.8, 42.8, 53.0, 120.2, 127.6, 131.7, 146.5, 211.0.

3-Methyl-3-(4-(trifluoromethyl)phenyl)cyclohexan-1-one (2g):[20] Prepared according to General Procedure A from 3-methylcyclohex-2-en-1-one **1a** (110 mg, 1.00 mmol) 4-trifluoromethylphenylboronic acid (228 mg, 1.20 mmol) (reaction time = 16 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2g** (209 mg, 0.816 mmol, 82%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.34 (s, 3H), 1.61-1.66 (m, 1H), 1.88-1.97 (m, 2H), 2.19-2.23 (m, 1H), 2.30-2.34 (m, 2H), 2.47 (d, *J* = 14.4 Hz, 1H), 2.88 (d, *J* = 14.4 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 22.0, 29.9, 37.9, 40.8, 43.2, 52.9, 124.2 (q, *J* = 270 Hz), 125.6 (q, *J* = 3.0 Hz), 126.1, 128.63 (q, *J* = 33.0 Hz), 151.5, 210.8. ^{19}F NMR (376.05 MHz, $CDCl_3$): δ -64.8 (s, 3F).

3-Methyl-3-(*m*-tolyl)cyclohexan-1-one (2h):[20] Prepared according to General Procedure A from 3-methylcyclohex-2-en-1-one **1a** (110 mg, 1.00 mmol) and *m*-tolylboronic acid (146 mg, 1.20 mmol) (reaction time = 12 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2h** (168 mg, 0.832 mmol, 83%) as a

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colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.31 (s, 3H), 1.65-1.72 (m, 1H), 1.86-1.93 (m, 2H), 2.16-2.20 (m, 1H), 2.31 (t, *J* = 6.6 Hz, 2H), 2.35 (s, 3H), 2.42 (d, *J* = 14.4 Hz, 1H), 2.87 (d, *J* = 14.4 Hz, 1H), 7.03 (d, *J* = 7.2 Hz, 1H), 7.11-7.12 (m, 2H), 7.21 (t, *J* = 7.2 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.2, 22.1, 29.8, 38.0, 40.9, 42.8, 53.2, 122.7, 126.4, 127.0, 128.5, 138.1, 147.6, 211.6.

3-(3-Methoxyphenyl)-3-methylcyclohexan-1-one (2i):[20] Prepared according to General Procedure A from 3-methylcyclohex-2-en-1-one **1a** (110 mg, 1.00 mmol) and 3-methoxyphenylboronic acid (182 mg, 1.20 mmol) (reaction time = 12 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2i** (196 mg, 0.899 mmol, 90%) as a clear, yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.31 (s, 3H), 1.64-1.71 (m, 1H), 1.84-1.93 (m, 2H), 2.15-2.19 (m, 1H), 2.31 (t, *J* = 7.2 Hz, 2H), 2.43 (d, *J* = 14.4 Hz, 1H), 2.86 (d, *J* = 14.4 Hz, 1H), 3.80 (s, 3H), 6.75 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.87 (m, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 7.24 (dd, *J* = 8.4, 8.4 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 22.1, 29.8, 38.0, 40.9, 42.9, 53.2, 55.2, 111.0, 112.2, 118.1, 129.5, 149.3, 159.7, 211.4.

3-(3-Chlorophenyl)-3-methylcyclohexan-1-one (2j):[7a] Prepared according to General Procedure A from 3-methylcyclohex-2-en-1-one **1a** (110 mg, 1.00 mmol) and 3-chlorophenylboronic acid (188 mg, 1.20 mmol) (reaction time = 16 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2j** (191 mg, 0.857 mmol, 86%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.30 (s, 3H), 1.64-1.71 (m, 1H), 1.85-1.94 (m, 2H), 2.13-2.17 (m, 1H), 2.30-2.34 (m, 2H), 2.43 (d, *J* = 14.4 Hz, 1H), 2.82 (d, *J* = 14.4 Hz, 1H), 7.17-7.20 (m, 2H), 7.24 (d, *J* = 7.8, 1H), 7.30 (t, *J* = 2.4

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Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 22.0, 29.6, 37.8, 40.8, 42.9, 53.0, 123.9, 126.0, 126.5, 129.9, 134.6, 149.7, 210.8.

3-(3,5-Dimethylphenyl)-3-methylcyclohexan-1-one (2k): Prepared according to General Procedure A from 3-methylcyclohex-2-en-1-one **1a** (110 mg, 1.00 mmol) and 3,5-dimethylphenylboronic acid (180 mg, 1.20 mmol) (reaction time = 16 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2k** (191 mg, 0.884 mmol, 88%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.30 (s, 3H), 1.66-1.73 (m, 1H), 1.84-1.92 (m, 2H), 2.14-2.20 (m, 1H), 2.30-2.32 (m, 8H), 2.41 (d, *J* = 14.4 Hz, 1H), 2.86 (d, *J* = 14.4 Hz, 1H), 6.86 (s 1H), 6.93 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.6, 22.1, 29.7, 38.0, 40.9, 42.6, 53.3, 123.5, 127.9, 137.9, 147.6, 211.7. HRMS (ESI) calcd. for $C_{15}H_{20}O^+$ $[M+H]^+$ 217.1587, found 217.1589.

3-(3,5-Difluorophenyl)-3-methylcyclohexan-1-one (2l): Prepared according to General Procedure A from 3-methylcyclohex-2-en-1-one **1a** (110 mg, 1.00 mmol) and 3,5-difluorophenylboronic acid (190 mg, 1.20 mmol) (reaction time = 16 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2l** (181 mg, 0.808 mmol, 81%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.26 (s, 3H), 1.65 (m, 1H), 1.87 (m, 2H), 2.10 (m, 1H), 2.32 (t, *J* = 6.6 Hz, 2H), 2.40 (d, *J* = 14.4 Hz, 1H), 2.75 (d, *J* = 14.4 Hz, 1H), 6.64 (tt, *J* = 8.4, 1.8 Hz, 1H), 6.83 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 22.0, 29.5, 37.7, 40.7, 43.1, 52.8, 101.8 (t, *J* = 25.0 Hz), 108.9 (dd, *J* = 15.0, 6.0 Hz), 151.9 (t, *J* = 7.5 Hz), 163.2 (dd, *J* = 233.5, 13.5 Hz), 210.3. ^{19}F NMR (376.05 MHz, $CDCl_3$): δ -110.3 (t, *J* = 9.4 Hz, 2F). HRMS (ESI) calcd. for $C_{13}H_{14}F_2O^+$ $[M+H]^+$ 225.1085, found 225.1086.

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3-(2-Methoxyphenyl)-3-methylcyclohexan-1-one (2n):[11b] Prepared according to General Procedure A from 3-methylcyclohex-2-en-1-one **1a** (110 mg, 1.00 mmol) and 2-methoxyphenylboronic acid (182 mg, 1.20 mmol) (reaction time = 12 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2n** (139 mg, 0.637 mmol, 64%) as a clear, yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.40 (s, 3H), 1.62-1.69 (m, 1H), 1.81-1.91 (m, 2H), 2.31 (t, *J* = 7.2 Hz, 2H), 2.45 (d, *J* = 14.4 Hz, 1H), 2.55-2.59 (m, 1H), 2.99 (d, *J* = 14.4 Hz, 1H), 3.84 (s, 3H), 6.89-6.92 (m, 2H), 7.20-7.26 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 22.2, 26.4, 35.0, 41.0, 42.9, 53.5, 55.0, 111.8, 120.7, 127.5, 127.8, 134.9, 157.9, 212.5.

3-Ethyl-3-phenylcyclohexan-1-one (2r):[20] Prepared according to General Procedure A from 3-ethylcyclohex-2-en-1-one **1b** (124 mg, 1.00 mmol) and phenylboronic acid (146 mg, 1.20 mmol) (reaction time = 16 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2r** (178 mg, 0.881 mmol, 88%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.60 (t, *J* = 6.0 Hz, 3H), 1.55-1.86 (m, 4H), 1.96-2.01 (ddd, *J* = 12.0, 9.0, 3.0 Hz 1H), 2.15-2.20 (m, 1H), 2.28-2.31 (m, 2H), 2.41 (d, *J* = 14.4 Hz, 1H), 2.92 (d, *J* = 14.4 Hz, 1H), 7.19(tt, *J* = 7.8, 1.8 Hz, 1H), 7.25-7.26 (m, 2H), 7.30-7.33 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 8.0, 21.6, 35.8, 36.3, 41.1, 46.5, 50.6, 126.1, 126.6, 128.5, 144.9, 211.6.

3-Methyl-3-phenylcyclopentan-1-one (2t):[9a] Prepared according to General Procedure A from 3-methylcyclopent-2-en-1-one **1d** (96 mg, 1.0 mmol) and phenylboronic acid (146 mg, 1.20 mmol) (reaction time = 16 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2t** (171 mg, 0.983 mmol, 98%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.39 (s, 3H), 2.27-2.38 (m, 3H), 2.44 (dd, *J*

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= 8.4, 8.4 Hz, 1H), 2.48 (d, *J* = 17.4 Hz, 1H), 2.66 (d, *J* = 17.4 Hz, 1H), 7.22-7.25 (m, 1H), 7.29-7.31 (m, 2H), 7.34-7.36 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 29.5, 35.8, 36.8, 43.9, 52.3, 125.5, 126.4, 128.6, 148.5, 218.6.

4-Methyl-4-phenylpentan-2-one (4):[9a] Prepared according to General Procedure A from 4-methylpent-3-en-2-one **3** (98 mg, 1.0 mmol) and phenylboronic acid (146 mg, 1.20 mmol) (reaction time = 16 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **4** (157 mg, 0.892 mmol, 89%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.44 (s, 6H), 1.80 (s, 3H), 2.75 (s, 2H), 7.20 (tt, *J* = 7.2, 1.2 Hz, 1H), 7.31-7.34 (m, 2H), 7.37-7.39 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 29.0, 31.9, 37.4, 57.1, 125.6, 126.0, 128.4, 148.2, 208.2.

Pd-Catalyzed Conjugate Addition of Phenylboronic Acid Pinacol Ester to Enone 1a

To a 1 dram vial was added the phenylboronic acid pinacol ester (408 mg, 2.00 mmol, 2.00 equiv), $Pd(TFA)_2$ (6.6 mg, 0.020 mmol, 0.020 equiv), 2,2´-bipyridine (3.6 mg, 0.024 mmol, 0.024 equiv), enone **1a** (113 µL, 1.00 mmol, 1.00 equiv) and 50 mM aqueous sodium trifluoroacetate solution (333 µL, pH = 8.2). The vial was sealed with a PFTE/silicone-lined septum cap. The reaction mixture was heated to 100 °C and allowed to stir at this temperature (18 h) until the reaction was judged to be complete by TLC analysis. The mixture was allowed to cool, diluted with EtOAc (3 mL), and filtered through a pad of silica gel. The silica gel was washed with EtOAc (3 x 10 mL). The resulting organic layer was washed with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was dissolved in $CDCl_3$ (0.70 mL) and CH_2Br_2 (35.1 µL, 0.500 mmol) was added as an internal standard. NMR yields were determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

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The crude reaction mixture was purified by flash column chromatography on silica gel (hexane:EtOAc) to yield the ketone **2a**. Characterization data for ketone **2a** matches the data reported for **2a** derived from addition of phenylboronic acid to **1a**.

General Procedure B: Pd-Catalyzed Conjugate Addition of Arylboronic Acids to Enones 1a, 1c, and 1e

To a 1 dram vial was added the appropriate arylboronic acid (2.00 mmol, 2.00 equiv), $Pd(TFA)_2$ (6.6 mg, 0.020 mmol, 0.020 equiv), 2,2´-bipyridine (3.6 mg, 0.024 mmol, 0.024 equiv), enone **1a**, **1c**, or **1e** (1.00 mmol, 1.00 equiv) and 50 mM aqueous sodium trifluoroacetate solution (333 µL, pH = 8.2). The vial was sealed with a PFTE/silicone-lined septum cap. The reaction mixture was heated to 100 °C and allowed to stir at this temperature (16-24 h) until the reaction was judged to be complete by TLC analysis. The mixture was allowed to cool, diluted with EtOAc (3 mL), and filtered through a pad of silica gel. The silica gel was washed with EtOAc (3 x 10 mL). The resulting organic layer was washed with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was dissolved in $CDCl_3$ (0.70 mL) and CH_2Br_2 (35.1 µL, 0.500 mmol) was added as an internal standard. NMR yields were determined by ^1H NMR spectroscopy of the crude reaction mixture. The crude reaction mixture was purified by flash column chromatography on silica gel (hexane:EtOAc) to yield the desired ketones **2m**, **2o**, **2s**, and **2u**.

Characterization Data for Ketones 2m, 2o, 2s, and 2u

3-(*o*-tolyl)-3-methylcyclhexan-1-one (2m):[11b] Prepared according to General Procedure B from 3-methylcyclohex-2-en-1-one **1a** (110 mg, 1.00 mmol) and *o*-tolylboronic acid (272mg, 2.00 mmol) (reaction time = 24 h). The crude product was purified by flash

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chromatography (90:10 hexane: EtOAc) to yield **2m** (71.0 mg, 0.351 mmol, 35%) as a clear, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (s, 3H), 1.57-1.67 (m, 1H), 1.83-1.98 (m, 2H), 2.29 (t, *J* = 6.8 Hz, 2H), 2.46 (d, *J* = 16 Hz, 1H), 2.54 (s, 3H), 3.00 (d, *J* = 16.0 Hz, 1H), 7.14 (d, *J* = 4.8 Hz, 3H), 7.21-7.25 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 22.8, 26.8, 35.4, 40.2, 43.6, 54.5, 125.6, 126.0, 126.5, 133.9, 135.0, 144.3, 211.3.

3-(2-Fluorophenyl)-3-methylcyclohexan-1-one (2o):[10a] Prepared according to General Procedure B from 3-methylcyclohex-2-en-1-one **1a** (110 mg, 1.00 mmol) and 2-fluorophenylboronic acid (280 mg, 2.00 mmol) (reaction time = 16 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2o** (180 mg, 0.874 mmol, 87%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.41 (s, 3H), 1.59-1.66 (m, 1H), 1.84-1.97 (m, 2H), 2.32 (app t, *J* = 7.2 Hz, 2H), 2.43-2.45 (m, 2H), 2.94 (d, *J* = 14.4 Hz, 1H), 7.01 (ddd, *J* = 13.2, 7.8, 1.2 Hz, 1H), 7.07 (dt, *J* = 1.2, 7.2 Hz, 1H), 7.20-7.24 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 22.2, 27.2 (d, *J* = 3.6 Hz), 35.8 (d, *J* = 4.8 Hz), 41.0, 42.5 (d, *J* = 2.9 Hz), 53.3, 116.7 (d, *J* = 24.3 Hz), 124.2 (d, *J* = 2.9 Hz), 128.0 (d, *J* = 5.1 Hz), 128.4 (d, *J* = 9.0 Hz), 133.7 (d, *J* = 10.5 Hz), 161.3 (d, *J* = 246.0 Hz), 211.3.

3-Isopropyl-3-phenylcyclohexan-1-one (2s):[9a] Prepared according to General Procedure B, from 3-isopropylcyclohex-2-en-1-one **1c** (138 mg, 1.00 mmol) and phenylboronic acid (244 mg, 2.00 mmol) (reaction time = 16 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2s** (155 mg, 0.717 mmol, 72%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.64 (d, *J* = 7.2 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H), 1.39-1.42 (m, 1H), 1.80-1.83 (m, 1H), 1.89-1.93 (m, 1H), 2.02 (dt, *J* = 3.6, 12.7 Hz, 1H), 2.21-2.26 (m, 3H), 2.42 (d, *J* = 14.4 Hz, 1H), 2.96 (d, *J* = 14.4 Hz, 1H), 7.17-

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7.19 (t, *J* = 7.2 Hz, 1H), 7.24-7.25 (d, *J* = 7.2 Hz, 2H), 7.28-7.31 (app t, *J* = 7.2 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 17.4, 17.6, 21.6, 34.1, 38.5, 41.1, 46.4, 49.6, 126.1, 127.5, 128.2, 143.5, 212.1.

3-Methyl-3-phenylcycloheptan-1-one (2u):[20] Prepared according to General Procedure B, from 3-methylcyclohept-2-en-1-one **1e** (124 mg, 1.00 mmol) and phenylboronic acid (244 mg, 2.00 mmol) (reaction time = 16 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2u** (154 mg, 0.762 mmol, 76%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.27 (s, 3H), 1.71-1.82 (m, 5H), 2.17-2.20 (m, 1H), 2.37-2.43 (m, 2H), 2.71 (d, *J* = 14.4 Hz, 1H), 3.21 (d, *J* = 14.4 Hz, 1H), 7.18-7.21 (m, 1H), 7.32 (dd, *J* = 4.2, 1.8 Hz, 4H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 23.9, 25.8, 31.9, 39.9, 43.5, 44.2, 55.7, 125.6, 126.0, 128.6, 147.9, 213.9.

General Procedure C: Pd-Catalyzed Conjugate Addition of Arylboronic Acids to Enone 1a

To a 1 dram vial was added the appropriate arylboronic acid (1.00 mmol, 2.00 equiv), $Pd(TFA)_2$ (8.3 mg, 0.025 mmol, 0.050 equiv), 2,2´-bipyridine (4.5 mg, 0.030 mmol, 0.060 equiv), enone **1a** (57.0 µL, 0.500 mmol, 1.00 equiv) and 50 mM aqueous sodium trifluoroacetate solution (166 µL, pH = 8.2). The vial was sealed with a PFTE/silicone-lined septum cap. The reaction mixture was heated to 100 °C and allowed to stir at this temperature (16-18 h) until the reaction was judged to be complete by TLC analysis. The mixture was allowed to cool, diluted with EtOAc (3 mL), and filtered through a pad of silica gel. The silica gel was washed with EtOAc (3 x 10 mL). The resulting organic layer was washed with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was dissolved in $CDCl_3$ (0.70 mL) and CH_2Br_2 (17.6 µL, 0.250 mmol) was added as an internal standard. NMR yields were

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determined by ^{1}H NMR spectroscopy of the crude reaction mixture. The crude reaction mixture was purified by flash column chromatography on silica gel (hexane:EtOAc) to yield the desired ketones **2p** and **2q**.

Characterization Data for Ketones 2p and 2q

3-(2-chlorophenyl)-3-methylcyclohexan-1-one (2p):[11b] Prepared according to General Procedure C from 3-methylcyclohex-2-en-1-one **1a** (110 mg, 1.00 mmol) and 2-chlorophenylboronic acid (313 mg, 2.00 mmol) (reaction time = 16 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2p** (167 mg, 0.750 mmol, 75%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52 (s, 3H), 1.54-1.62 (m, 1H), 1.84-1.94 (m, 2H), 2.32 (t, *J* = 6.8 Hz, 2H), 2.48 (d, *J* = 14.4 Hz, 1H), 2.82-2.89 (m, 1H), 3.06 (d, *J* = 14.4 Hz, 1H), 7.15 (ddd, *J* = 7.6, 7.6, 1.6 Hz, 1H), 7.20 (ddd, *J* = 7.6, 7.6, 1.6 Hz, 1H), 7.32 (dd, *J* = 7.6, 2.4 Hz, 1H), 7.36 (dd, *J* = 7.6, 2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 26.2, 34.3, 41.0, 44.3, 54.0, 127.1, 128.0, 128.9, 132.6, 133.0, 142.9, 211.6.

3-(2-bromophenyl)-3-methylcyclohexan-1-one (2q): Prepared according to General Procedure C from 3-methylcyclohex-2-en-1-one **1a** (55.0 mg, 0.500 mmol) 2-bromophenylboronic acid (402 mg, 2.00 mmol) (reaction time = 18 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2q** (71.0 mg, 0.265 mmol, 53%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.55-1.63 (m, 4H), 1.85-1.95 (m, 2H), 2.31-2.35 (m, 2H), 2.50 (d, *J* = 16.0 Hz, 1H), 2.95-3.02 (m, 1H), 3.12 (d, *J* = 16.0 Hz, 1H), 7.05 (ddd, *J* = 8.0, 8.0, 1.6 Hz 1H), 7.25 (ddd, *J* = 8.0, 8.0, 1.6 Hz, 2H), 7.61 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 26.3,

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34.2, 40.9, 44.8, 54.2, 121.9, 127.7, 128.2, 129.2, 136.4, 144.0, 211.6. HRMS (ESI) calcd. for $C_{13}H_{15}BrO^+$ $[M+H]^+$ 267.0379, found 267.0380.

General Procedure D: Pd-Catalyzed Conjugate Addition of Arylboronic Acids to Enones 1f-1h

To a 1 dram vial was added the appropriate arylboronic acid (2.00 mmol, 4.00 equiv), $Pd(TFA)_2$ (8.3 mg, 0.025 mmol, 0.050 equiv), 2,2´-bipyridine (4.5 mg, 0.030 mmol, 0.060 equiv), enone **1f**, **1g**, or **1h** (0.500 mmol, 1.00 equiv) and 50 mM aqueous sodium trifluoroacetate solution (166 µL, pH = 8.2). The vial was sealed with a PFTE/silicone-lined septum cap. The reaction mixture was heated to 100 °C and allowed to stir at this temperature (16-20 h) until the reaction was judged to be complete by TLC analysis. The mixture was allowed to cool, diluted with EtOAc (3 mL), and filtered through a pad of silica gel. The silica gel was washed with EtOAc (3 x 10 mL). The resulting organic layer was washed with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was dissolved in $CDCl_3$ (0.70 mL) and CH_2Br_2 (17.6 µL, 0.250 mmol) was added as an internal standard. NMR yields were determined by ^1H NMR spectroscopy of the crude reaction mixture. The crude reaction mixture was purified by flash column chromatography on silica gel (hexane:EtOAc) to yield the desired ketones **2v**-**2ab**.

Characterization Data for Ketones 2v-2ab

3,3-Diphenylcyclohexan-1-one (2v):[13] Prepared according to General Procedure D, from 3-phenylcyclohex-2-en-1-one **1f** (86.1 mg, 0.500 mmol) and phenylboronic acid (244 mg, 2.00 mmol) (reaction time = 16 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2v** (93.0 mg, 0.371 mmol, 74%) as a white solid. ^1H NMR (600 MHz, $CDCl_3$): δ 1.67-1.71 (m, 2H), 2.36 (t, J = 6.6 Hz, 2H),

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2.59 (t, J = 6.0 Hz, 2H), 2.97 (s, 2H), 7.17-7.22 (m, 6H), 7.26-7.30 (m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.1, 35.8, 40.8, 50.4, 53.7, 126.3, 127.0, 128.5, 147.3, 210.7.

3-(4-Chlorophenyl)-3-phenylcyclohexan-1-one (2w): Prepared according to General Procedure D from 3-phenylcyclohex-2-en-1-one **1f** (86.1 mg, 0.500 mmol) and 4-chlorophenylboronic acid (312 mg, 2.00 mmol) (reaction time = 18 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2w** (94.0 mg, 0.330 mmol, 66%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.70-1.75 (m, 2H), 2.39 (t, J = 6.8 Hz, 2H), 2.58 (m, 2H), 2.95 (app s, 2H), 7.15-7.33 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 35.7, 40.7, 50.1, 53.7, 126.5, 126.9, 128.5, 128.6 (2C), 132.2, 145.9, 146.8, 210.4. HRMS (ESI) calcd. for $C_{18}H_{17}ClO^+$ $[M+H]^+$ 285.1041. found 285.1045.

3-(3-Chlorophenyl)-3-phenylcyclohexan-1-one (2x): Prepared according to General Procedure D, from 3-phenylcyclohex-2-en-1-one **1f** (86.1 mg, 0.500 mmol) and 3-chlorophenylboronic acid (312 mg, 2.00 mmol) (reaction time = 20 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2x** (76.0 mg, 0.270 mmol, 54%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.65-1.72 (m, 2H), 2.36 (t, J = 6.8 Hz, 2H), 2.56 (m, 2H), 2.90 (d, J = 16.0 Hz, 1H), 2.98 (d, J = 16.0 Hz, 1H), 7.08 (dd, J = 6.0, 1.6 Hz, 1H), 7.15-7.23 (m, 6H), 7.26-7.31 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 35.7, 40.7, 50.4, 55.3, 125.4, 126.6, 127.0, 127.1, 128.7 (2C), 129.8, 134.5, 146.4, 149.6, 210.3. HRMS (ESI) calcd. for $C_{18}H_{17}ClO^+$ $[M+H]^+$ 285.1041, found 285.1041.

3-(*p*-Tolyl)-3-phenylcyclohexan-1-one (2y): Prepared according to General Procedure D, from 3-(4-tolyl)cyclohex-2-en-1-one **1g** (93.1 mg, 0.500 mmol) and phenylboronic

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acid (244 mg, 2.00 mmol) (reaction time = 20 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2y** (87.0 mg, 0.330 mmol, 66%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.66-1.73 (m, 2H), 2.31 (s, 3H), 2.36 (t, *J* = 6.8 Hz, 2H), 2.58 (t, *J* = 5.6 Hz, 2H), 2.95 (s, 2H), 7.10 (s, 4H), 7.16-7.28 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.1, 21.2, 35.8, 40.8, 50.1, 53.8, 126.2, 126.9, 127.0, 128.5, 129.2, 135.9, 144.4, 147.6, 210.9. HRMS (ESI) calcd. for $C_{19}H_{20}O^+$ $[M+H]^+$ 264.1587, found 265.1584

3-(4-Chlorophenyl)-3-(*p*-tolyl)cyclohexan-1-one (2z): Prepared according to General Procedure D, from 3-(4-tolyl)cyclohex-2-en-1-one **1g** (93.1 mg, 0.500 mmol) 4-chlorophenylboronic acid (312 mg, 2.00 mmol) (reaction time = 20 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2z** (99.0mg, 0.330 mmol, 66%) as a colorless oil. ^{1}HNMR (400 MHz, $CDCl_3$): δ 1.65-1.72 (m, 2H), 2.30 (s, 3H), 2.35 (t, *J* = 6.8 Hz, 2H), 2.51-2.58 (m, 2H), 2.91 (d, *J* = 3.6 Hz, 2H), 7.05-7.14 (m, 6H), 7.23-7.25 (m, 2H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 21.0, 21.1, 35.7, 40.7, 49.8, 53.7, 126.8, 128.5, 128.6, 129.3, 132.1, 136.1, 143.8, 146.1, 210.5. HRMS (ESI) calcd. for $C_{19}H_{19}ClO^+$ $[M+Na]^+$ 321.1017, found 321.1015.

3-(4-Methoxyphenyl)-3-phenylcyclohexan-1-one (2aa):[13] Prepared according to General Procedure D, from 3-(4-methoxyphenyl)cyclohex-2-en-1-one **1h** (101 mg, 0.500 mmol) and phenylboronic acid (244 mg, 2.00 mmol) (reaction time = 20 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2aa** (103 mg, 0.370 mmol, 74%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.66-1.72 (m, 2H), 2.34 (t, *J* = 6.8 Hz, 2H), 2.53-2.56 (m, 2H), 2.93 (d, *J* = 3.2 Hz, 2H), 3.77 (s, 3H), 6.81 (d, *J* = 8.8 Hz, 2H), 7.10-7.20 (m, 5H), 7.25-7.29 (m, 2H). ^{13}C NMR (100 MHz,

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$CDCl_3$): δ 21.2, 35.9, 40.8, 50.0, 54.0, 55.2, 113.8, 126.2, 126.9, 128.1, 128.5, 139.3, 147.7, 157.8, 210.9.

3-(4-Chlorophenyl)-3-(4-methoxyphenyl)cyclohexan-1-one (2ab): Prepared according to General Procedure D, from 3-(4-methoxyphenyl)cyclohex-2-en-1-one **1h** (101 mg, 0.500 mmol) and 4-chlorophenylboronic acid (312 mg, 2.00 mmol) (reaction time = 20 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2ab** (113 mg, 0.360 mmol, 72%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.65-1.71 (m, 2H), 2.34 (t, *J* = 6.8 Hz, 2H), 2.50-2.53 (m, 2H), 2.89 (m, 2H), 3.77 (s, 3H), 6.81 (d, *J* = 8.8 Hz, 2H), 7.08 (d, *J* = 8.8 Hz, 2H), 7.12 (d, *J* = 8.8 Hz, 2H), 7.23 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 35.8, 40.7, 49.6, 53.8, 55.2, 113.9, 128.0, 128.4, 128.6, 132.1, 138.8, 146.3, 158.0, 210.5. HRMS (ESI) calcd. for $C_{19}H_{19}ClO_2^+$ $[M+H]^+$ 315.1146, found 315.1141.

Catalytic, Enantioselective Addition of Phenylboronic Acid to Enone 1a

To a 1 dram vial was added phenylboronic acid (146 mg, 1.20 mmol, 1.20 equiv), $Pd(TFA)_2$ (3.3 mg, 0.010 mmol, 0.010 equiv), (*S*)-4-*tert*-Butyl-2-(2-pyridyl)oxazoline **L1** (2.5 mg, 0.012 mmol, 0.012 equiv), enone **1a** (113 µL, 1.00 mmol, 1.00 equiv) and 50 mM aqueous sodium trifluoroacetate solution (666 µL, pH = 8.2). The vial was sealed with a PFTE/silicone-lined septum cap. The reaction mixture was heated to 40 °C and allowed to stir at this temperature (16 h) until the reaction was judged to be complete by TLC analysis. The mixture was allowed to cool, diluted with EtOAc (3 mL), and filtered through a pad of silica gel. The silica gel was washed with EtOAc (3 x 10 mL). The resulting organic layer was washed with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was dissolved in

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$CDCl_3$ (0.70 mL) and CH_2Br_2 (35.1 μL, 0.500 mmol) was added as an internal standard. NMR yields were determined by ^1H NMR spectroscopy of the crude reaction mixture. The crude reaction mixture was purified by flash column chromatography on silica gel (hexane:EtOAc) to yield the desired ketone **2a** (162 mg, 0.862 mmol, 86%) as a colorless oil. Spectral data for enantioenriched ketone **2a** matches the data reported above for racemic **2a**. The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 14.9 (*R*-**2a**, major); t_R 18.7 (*S*-**2a**, minor) [Chiralcel OJ-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 99:1, 1.0 mL/min] to be 71% ee.

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16. As an example, the additions of ortho-fluorophenylboronic acid to 3-phenylcyclohexenone occurs under the reaction conditions illustrated in Scheme 4 to form the corresponding ketone product in 27% yield by 1H NMR analysis

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CHAPTER 3: MOF-253-Pd(OAc)$_2$: A RECYCLABLE MOF FOR TRANSITION-METAL CATALYSIS IN WATER

Modified from a paper submitted to *ACS Catalysis*

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Abstract

We report palladium(II)-functionalized MOF-253 (MOF-253-Pd(OAc)$_2$) as a recyclable catalyst to form all-carbon quaternary centers via conjugate additions of arylboronic acids to β,β-disubstituted enones in aqueous media. We demonstrate MOF-253-Pd(OAc)$_2$ can be reused 8 times to form ketone products in yields above 75% while maintaining its crystallinity based on PXRD. Additions of a range of stereoelectronically diverse arylboronic acids to a variety of β,β-disubstituted enones catalyzed by MOF-253-Pd(OAc)$_2$ occur in modest-to-high yields (34-95%).

Introduction

Metal-organic frameworks (MOFs) have emerged as a promising platform for catalysis at the interface of traditional homogeneous and heterogeneous catalysis.[1] In recent years, MOFs containing 2,2´-bipyridyl linker units (bpy-MOFs) have been shown to be capable of supporting a variety of transition-metal complexes. The utility of these transition metal-functionalized bpy-MOF catalysts has been demonstrated in a wide variety of organic transformations including: cross-coupling reactions;[2] reductions of carbon dioxide[3] and alkenes;[4] oxidations of alcohols,[5] water,[3b, 6] arylboronic acids,[7] and

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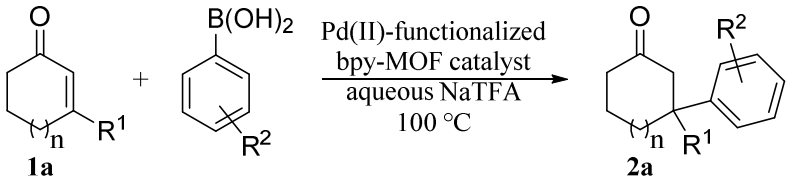
alkenes;[8] oxidative coupling of amines;[3b] C-H borylation and silylation of arenes;[4, 9] hydrosilylation of ketones;[9a] and hydroborations of alkenes, aldehydes and ketones.[4] These transformations are typically carried out in aprotic reaction media and the structures of the bpy-MOFs are known to be relatively stable even at high temperatures. Much less is understood about the structural stability of bpy-MOFs and metalated derivatives in polar, protic solvents, especially at elevated reaction temperatures.[10] As a result, the utility of metal-functionalized bpy-MOFs as catalysts of reactions typically run in polar, protic solvents remains underexplored.

We have reported palladium(II) complexes of 2,2′-bipyridine that catalyze conjugate additions of arylboronic acids to *β*,*β*-disubstituted enones in aqueous media.[11] During the course of the reaction, the molecular Pd(II) catalyst decomposes, and the catalyst cannot be reused. The ability of MOFs to support active metal complexes and prevent bimolecular deactivation processes[3b, 6, 12] prompted us to study palladium(II)-functionalized bpy-MOFs as potentially recyclable catalysts for these conjugate addition reactions and a platform for green catalysis in water. Herein, we report studies to develop palladium(II)-functionalized bpy-MOFs as recyclable catalysts to form all-carbon quaternary centers via conjugate additions of arylboronic acids to *β*,*β*-disubstituted enones in aqueous media (Scheme 1).

Scheme 1. Formation of All-Carbon Quaternary Centers via Conjugate Addition in Aqueous Media Catalyzed by Pd(II)-Functionalized bpy-MOFs



n = 0-1
R^1 = alkyl

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Results and Discussion

MOF-253 and bpy-UiO-67, two prototypical MOFs containing 2,2´-bipyridyl linkers, were synthesized via reported protocols from [2,2′-bipyridine]-5,5′-dicarboxylic acid and either $ZrCl_4$ or $AlCl_3 \cdot 6H_2O$.[13] Powder X-ray diffraction (PXRD) patterns and nitrogen sorption analyses of the bpy-MOFs are consistent with reported data (Figures 1-4).

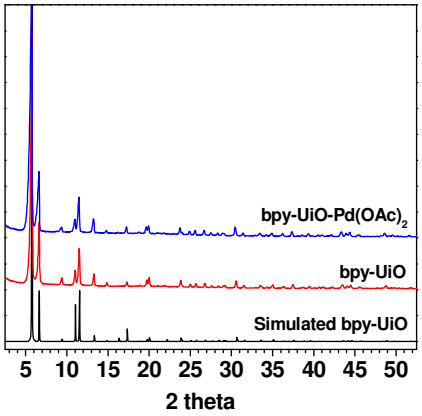

Figure 1. PXRD patterns of simulated bpy-UiO, pristine bpy-UiO and bpy-UiO-Pd(OAc)$_2$ **C1**.

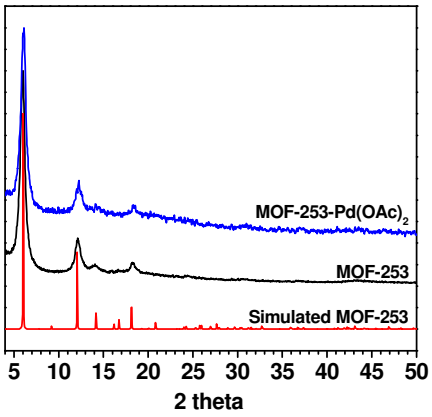

Figure 2. PXRD patterns of simulated MOF-253, pristine MOF-253 and MOF-253-Pd(OAc)$_2$ **C2**.

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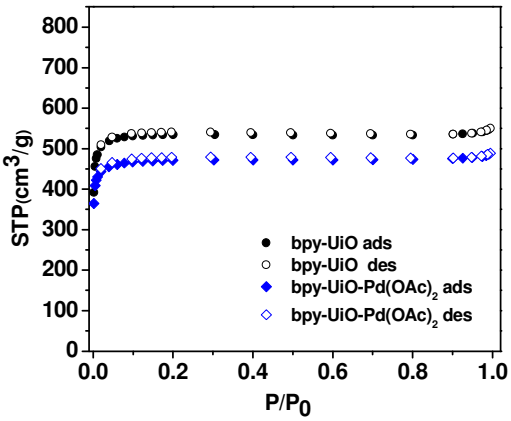

Figure 3. Nitrogen adsorption/desorption isotherms of the bpy-UiO (BET surface area 2209.0 ± 7.3 m^2/g) and bpy-UiO-Pd(OAc)$_2$ **C1** (BET surface area 1900.0 ± 3.7 m^2/g).

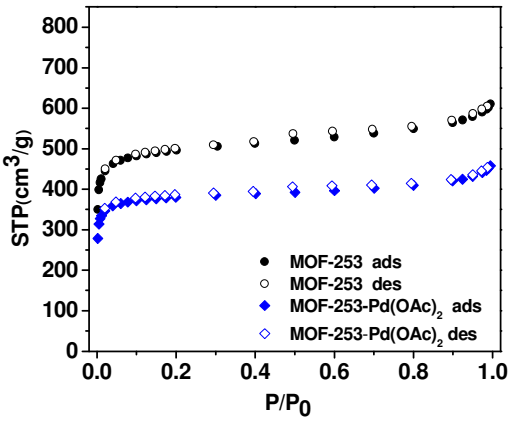

Figure 4. Nitrogen adsorption/desorption isotherms of the as-synthesized MOF-253 (BET surface area 1949.3 ± 10.0 m^2/g) and MOF-253-Pd(OAc)$_2$ **C2** (BET surface area 1515.0 ± 6.7 m^2/g).

The postsynthetic metalation of bpy-UiO-67 and MOF-253 was performed by treating the bpy-MOFs with Pd(OAc)$_2$ in acetone at ambient temperature to afford bpy-UiO-67-Pd(OAc)$_2$ (**C1**) and MOF-253-Pd(OAc)$_2$ (**C2**) (Figure 5). The integrity of the bpy-MOFs was maintained after metalation based on PXRD patterns (Figure 1 and 2). The palladium content of the catalysts was determined quantitatively by inductively coupled plasma-mass spectrometry (ICP-MS).

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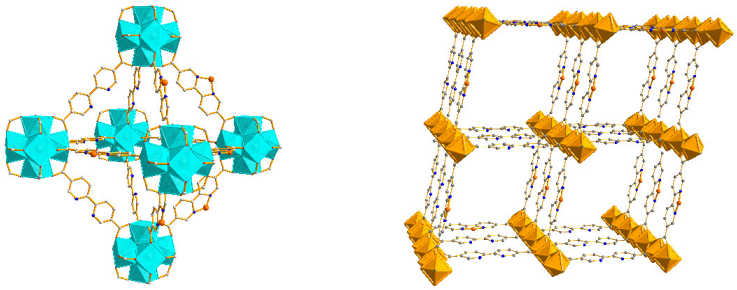

bpy-UiO-Pd(OAc)$_2$ (**C1**) MOF-253-Pd(OAc)$_2$ (**C2**)

Figure 5. Structures of bpy-UiO-Pd(OAc)$_2$ (**C1**) and MOF-253-Pd(OAc) (**C2**). Turquoise and yellow octahedral represent Zr and Al clusters, while brown, red, blue and gray spheres represent Pd(OAc)$_2$ species, O, N, and C atoms; H atoms are omitted for clarity.

With bpy-UiO-67-Pd(OAc)$_2$ and MOF-253-Pd(OAc)$_2$ in hand, we studied the model reaction of phenylboronic acid with 3-methylcyclohex-2-en-1-one **1a** to evaluate the utility of these Pd(II)-functionalized MOFs as catalysts in polar, protic media (Table 1). The reaction of enone **1a** with 1.2 equivalents of phenylboronic acid in the presence of bpy-UiO-67-Pd(OAc)$_2$ (**C1**) (1.5 mol % total palladium based on **1a**) did not form ketone **2a** at 60 °C and formed **2a** in 2% yield at 80 °C when the reactions were run in methanol (entries 1 and 2). Changing the reaction medium from methanol to 50 mM aqueous sodium trifluoroacetate (aq. NaTFA, pH = 8.2) led to the formation of ketone **2a** in 20% yield when the reaction was run at 80 °C (entry 3). Ketone **2a** was formed in 50% yield upon increasing the reaction temperature to 100 °C (entry 4).

We found that the total loading of palladium in the reaction, the number of equivalents of phenylboronic acid, and the weight % palladium present in the MOF significantly impact the yield of our model reaction (entries 5-7). Increasing the total

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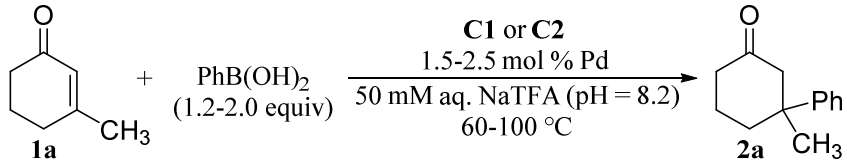
Table 1. Identification of Reaction Conditions[a]



Entry	Solvent	Catalyst (mol % Pd)	Wt. % Pd in MOF[b]	Temp (°C)	$PhB(OH)_2$ (equiv)	Yield (%)[c]
1	Methanol	**C1** (1.5)	5.0	60	1.2	0
2	Methanol	**C1** (1.5)	5.0	80	1.2	2
3	50 mm aq. NaTFA	**C1** (1.5)	5.0	80	1.2	20
4	50 mm aq. NaTFA	**C1** (1.5)	5.0	100	1.2	50
5	50 mm aq. NaTFA	**C1** (2.5)	5.0	100	1.2	74
6	50 mm aq. NaTFA	**C1** (2.5)	5.0	100	2.0	90
7[d]	50 mm aq. NaTFA	**C1** (2.5)	8.1	100	2.0	99
8[d]	50 mm aq. NaTFA	**C2** (2.5)	8.4	100	2.0	99
9[d]	50 mm aq. NaTFA	bpy-UiO (0.0)	0.0	100	2.0	0
10[d]	50 mm aq. NaTFA	UiO-67-$Pd(OAc)_2$ (2.5)	2.4	100	2.0	0

[a] Reaction conditions: **1a** (0.500 mmol), $PhB(OH)_2$ (0.600-1.00 mmol), MOF catalyst (0.008-0.0013 mmol), reaction medium (0.33 mL), 16 h. [b] Weight % Pd loaded in MOF determined by ICP-MS. [c] Determined by ^1H NMR spectroscopy using dibromomethane as an internal standard. [d] Reaction run for 2 hours.

palladium content of the reaction from 1.5 mol % to 2.5 mol % and the amount of phenylboronic acid from 1.2 equivalents to 2.0 equivalents led to the formation of **2a** in 90% yield (entry 6). When the weight % Pd loaded in the MOF was increased from 5.0% to 8.1%, the reaction was complete after two hours and generated **2a** in 99% yield (entry 7). The reaction of phenylboronic acid with **1a** catalyzed by MOF-253-$Pd(OAc)_2$ **C2** in place of **C1** also formed **2a** in 99% yield in two hours (entry 8). Reactions of **1a** with phenylboronic acid run in the presence of bpy-UiO-67 with no palladium and an analogous MOF without bipyridine sites, UiO-67-$Pd(OAc)_2$, did not occur to form the conjugate addition product **2a** (entries 9 and 10). These results are consistent with

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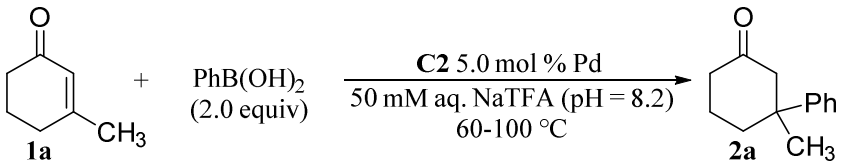
supported Pd(II)-bipyridine complexes as the active catalysts when MOFs **C1** and **C2** are used to promote the model reaction.

The palladium-functionalized MOFs bpy-UiO-67-Pd(OAc)$_2$ **C1** and MOF-253-Pd(OAc)$_2$ **C2** perform similarly as catalysts in the model reaction. Two features of MOF-253-Pd(OAc)$_2$ **C2** led us to select this material for additional catalytic studies. The larger pore size of MOF-253 compared to bpy-UiO-67[14] is attractive because the resulting larger pore volumes will be able to accommodate a wider array of enone and arylboronic acid substrates and will facilitate flux of reagents and products into and out of the pores. In addition, we found that MOF-253 could be consistently metalated with approximately 8 weight % Pd, while we observed significant batch-to-batch variations for metalation of bpy-UiO-67 with Pd(OAc)$_2$.

Scheme 2. Recycling of C2 in the Addition of PhB(OH)$_2$ to Enone 1a[a]



Run	1	2	3	4	5	6	7	8	9
Time (h)	2	2	2.5	2.5	4	4	8	8	16
Yield (%)[b]	99	92	76	80	96	90	99	99	99

[a] Reaction conditions: **1a** (1.50 mmol, 1.00 equiv), PhB(OH)$_2$ (3.00 mmol, 2.00 equiv), **C2** (0.075 mmol, 0.050 equiv) and aqueous 50 mM NaTFA (1.00 mL). [b] Determined by ^{1}H NMR spectroscopy using dibromomethane as an internal standard.

To gain insight into the stability of MOF-253-Pd(OAc)$_2$ **C2** under our aqueous reaction conditions, we evaluated the recyclability of **C2** in our model addition of phenylboronic acid to enone **1a** (Scheme 2). Consistent with our data in Table 1, the initial reaction with pristine **C2** as catalyst formed ketone **2a** in 99% yield in less than

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two hours. Upon recovery of the catalyst and exposure to additional enone **1a**, phenylboronic acid, and aqueous NaTFA, the yield of ketone **2a** dropped to 92% in run 2 and 76-80% in runs 3 and 4 after 2-2.5 hour reaction times. The yield of **2a** could be increased to 90-99% for runs 5-9 by extending the reaction times.

The results shown in Scheme 2 clearly demonstrate the ability to reuse MOF-253-$Pd(OAc)_2$ **C2** in conjugate additions of phenylboronic acid to enone **1a**. However, these results also show that, at minimum, partial degradation of the **C2** occurs over time. To verify that the solid MOF-supported 2,2′-bipyridine complex of $Pd(OAc)_2$ is the active catalyst in these reactions, we performed leaching tests to eliminate the possibility for MOF degradation into an active and homogeneous palladium species (see Supporting Information). Exposure of **C2** to the reagents and reaction conditions for two hours and analysis of the palladium content of the aqueous supernatant showed that 0.6% of the palladium had leached out of **C2**. However, the palladium found in the supernatant is not catalytically competent under our reaction conditions. Ketone **2a** is formed in 1% yield after two hours when the palladium contained in the supernatant is evaluated as a catalyst of the model reaction under the optimized reaction conditions.

To develop an understanding of the rate of catalyst deactivation under our reaction conditions, we conducted an additional recycling study where **C2** was reused and the yield of the conjugate addition reaction was determined after one-hour reaction times (Figure 6). As expected from our initial recycling experiment, a slow decline in the activity of the catalyst is observed during the initial recycling runs. By the fourth run, the activity of the catalyst is halved and ketone **2a** is formed in 29% yield compared to 60%

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in the first run. However, the activity of the catalyst remains consistent in runs 4-10 and **2a** is formed in 23-30% yield after one hour.

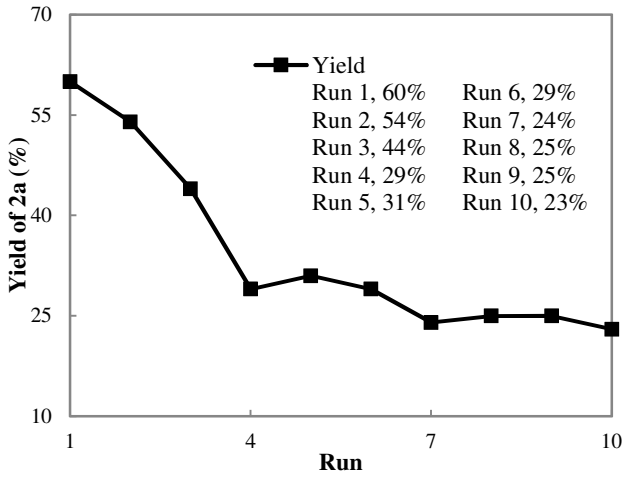

Figure 6. Low Conversion recycling experiments. Reaction conditions: **1a** (1.50 mmol, 1.00 equiv), $PhB(OH)_2$ (3.00 mmol, 2.00 equiv), **C2** (0.75 mmol, 0.050 equiv), and aqueous 50 mM NaTFA (1.0 mL, pH = 8.2), 1 h reaction time. Yields of **2a** were determined by ^1H NMR spectroscopy using dibromomethane as an internal standard.

The PXRD pattern of MOF-253-$Pd(OAc)_2$ **C2** after the 10^{th} run remained unchanged from that of **C2** before catalysis (Figure 7). More importantly, the used **C2** possesses comparably high surface area relative to freshly prepared **C2** (Figure 8). However, the decrease in activity of the catalyst after two hours (run 2 in Figure 6) is not consistent with the quantity of palladium lost to leaching over two hours. The combination of these results suggests additional pathways for deactivation of the palladium catalyst are operative.[9b]

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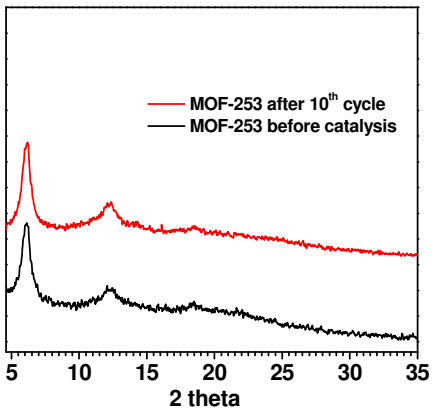

Figure 7. PXRD patterns of as-synthesized MOF-253-Pd(OAc)$_2$ **C2** and used MOF-253-Pd(OAc)$_2$ **C2** after 10 cycles.

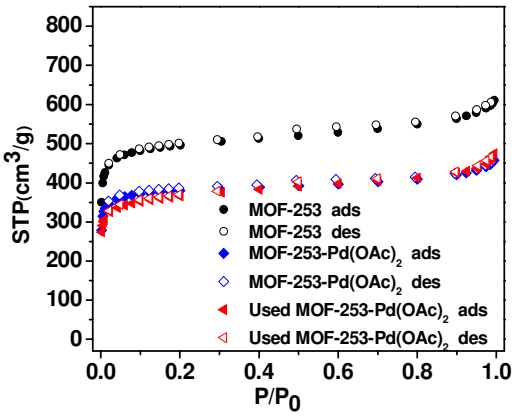

Figure 8. Nitrogen adsorption/desorption isotherms of the bare MOF-253 (BET surface area 1949.3 ± 10.0 m^2/g), as-synthesized MOF-253-Pd(OAc)$_2$ **C2** (BET surface area 1515.0 ± 6.7 m^2/g) and used MOF-253-Pd(OAc)$_2$ **C2** (BET surface area 1423.0 ± 2.3 m^2/g) after 10 cycles.

With a robust palladium-functionalized MOF for catalysis in water identified, we evaluated the scope of the conjugate addition reaction. Additions of a variety of arylboronic acids to a selection of enones **1a**-**c** catalyzed by MOF-253-Pd(OAc)$_2$ **C2** are summarized in Scheme 3. As demonstrated in our optimization studies, the addition of phenylboronic acid to 3-methylcyclohex-2-en-1-one **1a** occurs to form ketone **2a** in 90% yield. Additions of 4-substituted arylboronic acids containing electron-donating, electron-withdrawing, and halogen substituents to enone **1a** formed ketones **2b**-**d** in 80-

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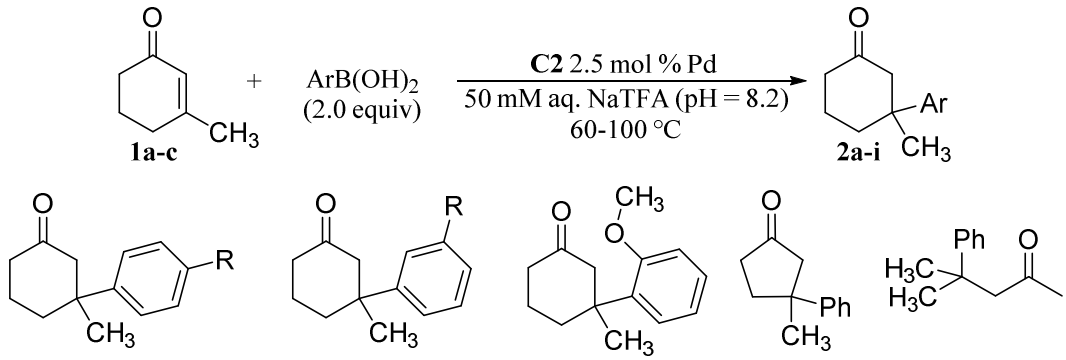
90%. 3-Substituted arylboronic acids are also suitable substrates for conjugate additions catalyzed by **C2**. Additions of 3-methoxy- and 3-chlorophenylboronic acids to enone **1a** generated ketones **2e** and **2f** in 91% yield. The addition of 2-methoxyphenylboronic acid to **1a** occurred to form ketone **2g** in 34% yield. However, additions of 2-substituted arylboronic acid lacking a strong electron-donating substituent did not occur. In these cases, protodeborylation of the 2-substituted arylboronic acid is the primary reaction pathway observed.[15]

Scheme 3. Conjugate Addition of Arylboronic Acids to Enones 1a-c Catalyzed by MOF-253-Pd(OAc)$_2$[a]



2a (R = H): 90%
2b (R = OCH_3): 80%
2c (R = Cl): 90%
2d (R = CF_3): 87%

2e (R = OCH_3): 91%
2f (R = Cl): 91%

2g: 34%

2h: 95%

2i: 83%

[a] Reaction conditions: **1a-c** (0.500 mmol), arylboronic acid (1.00 mmol), MOF-253-Pd(OAc)$_2$ **C2** (0.013 mmol of Pd), 50 mM aqueous NaTFA (0.33 mL, pH = 8.2), 100 °C, 2-18 h. Isolated yields are reported after purification by flash chromatography.

MOF-253-Pd(OAc)$_2$ **C2** also catalyzes conjugate additions of phenylboronic acid to additional cyclic and acyclic β,β-disubstituted enones. The addition of phenylboronic acid to 3-methylcyclopent-2-en-1-one **1b** forms ketone **2h** in 95% yield. The addition of phenylboronic acid to acyclic 4-methylpent-3-en-2-one **1c** generated ketone **2i** in 83%

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yield. However, additions of phenylboronic acid to 3-arylcyclohex-2-en-1-ones and 3-methylcyclohept-2-en-1-one occurred in <10% yield in the presence of MOF-253-$Pd(OAc)_2$ **C2**. The poor reactivity of these two enone substrates contrasts with analogous reactions carried out in aqueous media and catalyzed by a complex of 2,2′-bipyridine and palladium trifluoroacetate.[11] The low yields observed for additions of arylboronic acids to 3-arylcyclohex-2-en-1-ones and 3-methylcyclohept-2-en-1-one likely results from attenuated rates for reactions catalyzed by **C2** compared to reactions catalyzed by a complex of 2,2′-bipyridine and palladium trifluoroacetate. Attenuated rates for catalysis by **C2** in combination with rates of protodeborylation that remain consistent regardless of the identity of the catalyst can lead to arene formation through protodeborylation as the primary reaction pathway for these more challenging substrates classes.

Conclusion

In summary, we have established two palladium-functionalized bpy-MOFs, bpy-UiO-67-$Pd(OAc)_2$ and MOF-253-$Pd(OAc)_2$, as competent catalysts for conjugate additions of arylboronic acids to *β*,*β*-disubstituted enones in water. We have also demonstrated that MOF-253-$Pd(OAc)_2$ is a reusable catalyst system that promotes additions of a range of arylboronic acid to *β*,*β*-disubstituted enone reaction partners to form ketones containing quaternary carbon centers. The development of MOF-253-$Pd(OAc)_2$ as a reusable platform for transition-metal catalysis in water sets the stage for new applications of this and related catalyst systems in the areas of green catalysis and green chemical synthesis. Studies to improve the catalytic activities and stabilities of

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MOF-253-Pd(OAc)$_2$ and additional metalated derivatives for new catalytic transformations in aqueous environments are ongoing.

Experimental

General Experimental Details. Nitrogen physisorption isotherms were recorded in a Micromeritics 3Flex surface characterization analyzer at 77 K. MOF samples (ca. 100 mg) were degassed under vacuum (~5 × 10^{-5} torr) at 200 °C for 12 h prior to analysis. Powder X-ray diffraction (PXRD) patterns of the MOFs were obtained on a STOE Stadi P powder diffractometer using Cu Kα radiation (40 kV, 40 mA, λ = 0.1541 nm). MOFs were dried under vacuum (ca. 30 mTorr) at 150 °C for 12 h prior to PXRD analysis. Inductively coupled plasma-mass spectroscopy was performed on a Thermo Scientific X Series II ICP-MS to determine the palladium content in bpy-UiO-Pd(OAc)$_2$ and MOF-253-Pd(OAc)$_2$. Prior to ICP-MS measurements, bpy-UiO-Pd(OAc)$_2$ and MOF-253-Pd(OAc)$_2$ were dissolved in boiling aqua regia.

All reactions were performed under air unless otherwise noted. Reactions involving air-sensitive reagents were conducted under an inert atmosphere in a nitrogen-filled dry box or by standard Schlenk techniques. Glassware for moisture sensitive reactions was dried at 140 °C in an oven for at least one hour prior to use. Aqueous sodium trifluoroacetate solutions were prepared by dissolving the sodium trifluoroacetate in deionized water. The aqueous solutions were adjusted to pH 8.2 by addition of concentrated HCl. Flash column chromatography was performed on Siliflash® P60 silica gel (230-400 mesh) using hexane/ethyl acetate mixtures as the eluent. Products were visualized on TLC by UV light and/or by staining with 2,4-dinitrophenylhydrazine.

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NMR spectra were acquired on Varian MR-400 and Bruker Avance III 600 spectrometers at the Iowa State University Chemical Instrumentation Facility. Chemical shifts are reported in ppm relative to a residual solvent peak ($CDCl_3$ = 7.26 ppm for ^1H and 77.1 ppm for ^{13}C). ^{19}F NMR shifts are reported in ppm relative to trifluoroacetic acid as an external standard ($F_3CC_6H_5$ = -63.72 ppm). Coupling constants are reported in hertz.

Materials. 3-Methylcyclohex-2-en-1-one **1a,** 3-methylcyclopent-2-en-1-one **1b**, and 4-methylpent-3-en-2-one **1c** were purchased from TCI and used without further purification. 4-Methylphenylboronic acid, 4-trifluoromethylphenylboronic acid, and 3-chlorophenylboronic acid were purchased from Frontier Scientific and used without further purification. 2-Methoxyphenylboronic acid and palladium acetate were purchased from Sigma-Aldrich and used with further purification. Phenylboronic acid, 3-Methoxyphenylboronic acid, and 4-methoxyphenylboronic acid were purchased from AK Scientific and used without further purification. 2,2´-Bipyridine-5,5´-dicarboxylic acid was synthesized according to a literature procedure.[16] bpy-UiO and MOF-253 were synthesized according to a literature procedures.[13]

Synthesis and Metalation of Metal-Organic Frameworks

Synthesis of bpy-UiO MOF.

$ZrCl_4$ (300 mg, 1.28 mmol) and 2,2´-bipyridine-5,5´-dicarboxylic acid (300 mg,1.23 mmol) were dissolved in 120 mL of *N*,*N*´-dimethylformamide (DMF) by sonication in a 480 mL Teflon PFA wide mouth jar. Glacial acetic acid (5.6 mL) was added as a modulator. The jar was capped and placed in a pre-heated oven at 120 °C for 3 days. After cooling to ambient temperature, the solid bpy-UiO MOF was collected via

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centrifugation and washed with DMF (3x) and ethanol (3x) every 12 hours. Finally, bpy-UiO was activated at 150 ˚C under vacuum (30 mTorr) for 12 hours prior to experimental use (380 mg, 1.033 mmol, 84% yield).

Synthesis of MOF-253.

$AlCl_3 \cdot 6H_2O$ (151 mg, 0.625 mmol) and 2,2´-bipyridine-5,5´-dicarboxylic acid (153 mg, 0.625 mmol) were dissolved in 10 mL of *N*,*N*´-dimethylformamide (DMF) in a 20 mL scintillation vial. The vial was placed in a pre-heated oven at 130 ˚C for 24 hours. After cooling to ambient temperature, MOF-253 was collected as a white solid via centrifugation and thoroughly washed with DMF (3x) and methanol (3x) every 12 hours. Finally, MOF-253 was activated at 150 ˚C under vacuum (30 mTorr) for 12 hours prior to experimental use (150 mg, 0.531 mmol, 85% yield).

Metalation of bpy-UiO with $Pd(OAc)_2$.

Activated bpy-UiO (200 mg) was dispersed in acetone (6 mL) and was sonicated for 30 min to achieve a homogeneous dispersion. Palladium acetate (47 mg) in acetone (6 mL) was added dropwise to the dispersion of bpy-UiO with vigorous stirring (800 rpm). After 24 hours of stirring at ambient temperature, the as-prepared bpy-UiO-$Pd(OAc)_2$ was washed with acetone (3x) every 12 hours to completely remove the palladium salts not bound to the bipyridine linkers. Finally, the solid was dried at 50 °C, under vacuum to produce bpy-UiO-$Pd(OAc)_2$ **C1** (8.1 weight % Pd). An analogous procedure can be followed to produce **C1** (5.0 weight % Pd) by adding 23.5 mg of palladium acetate, rather than 47 mg of palladium acetate.

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Metalation of MOF-253 with $Pd(OAc)_2$.

Activated MOF-253 (200 mg) was dispersed in acetone (6 mL) and was sonicated for 30 min to achieve a homogenous dispersion. Palladium acetate (23.5 mg) in acetone (6 mL) was added dropwise to the dispersion of MOF with vigorous stirring (800 rpm). After 24 hours of stirring at ambient temperature, the as-prepared MOF-253-$Pd(OAc)_2$ was washed with acetone (3x) every 12 hours to completely remove the palladium salts not bound to the bipyridine linkers. Finally, the solid was dried at 50 °C under vacuum to produce MOF-253-$Pd(OAc)_2$ **C2** (8.4 weight % Pd).

General Procedure A: Conjugate Additions of Arylboronic Acids to Enones 1a-1c Catalyzed by MOF-253-$Pd(OAc)_2$ C2

To a 1 dram vial was added the appropriate arylboronic acid (1.00 mmol, 2.00 equiv), MOF-253-$Pd(OAc)_2$ **C2** (0.013 mmol, 0.025 equiv), enone **1a-c** (0.50 mmol, 1.00 equiv) and 50 mM aqueous sodium trifluoroacetate solution (333 µL, pH = 8.2). The vial was sealed with a PFTE/silicone-lined septum cap. The reaction mixture was heated to 100 °C and allowed to stir at this temperature (2-18 h) until the reaction was judged to be complete by TLC analysis. The mixture was allowed to cool to room temperature, diluted with EtOAc (3 mL), and filtered through a pad of silica gel. The silica gel was washed with EtOAc (3 x 10 mL). The resulting organic layer was washed with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was dissolved in $CDCl_3$ (0.70 mL) and CH_2Br_2 (17.6 µL, 0.250 mmol) was added as an internal standard. NMR yields were determined by ^1H NMR spectroscopy of the crude reaction mixture. The crude reaction mixture was purified by

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flash column chromatography on silica gel (hexane:EtOAc) to yield the desired ketones **2a**-**2i**.

Characterization Data for Ketones 2a-2i

3-Methyl-3-phenylcyclohexan-1-one (2a): Prepared according to General Procedure A from 3-methylcyclohex-2-en-1-one **1a** (55 mg, 0.50 mmol) and phenylboronic acid (122 mg, 1.00 mmol) (reaction time = 3 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2a** (85 mg, 0.452 mmol, 90%) as a colorless oil. Characterization data is consistent with previously reported data.[11] ^{1}HNMR (400 MHz, CDCl3): δ 1.33 (s, 3H), 1.64-1.71 (m, 1H), 1.85-1.95 (m, 2H), 2.17-2.21 (m, 1H), 2.32 (app t, *J* = 7.0 Hz, 2H), 2.44 (d, *J* = 14.0 Hz, 1H), 2.88 (d, *J* = 14.0 Hz, 1H), 7.19-7.22 (m, 1H), 7.22 (m, 4H). ^{13}C NMR (100 MHz, CDCl3): δ 22.1, 29.9, 38.0, 40.9, 42.9, 53.2, 125.7, 126.3, 128.6, 147.5, 211.5.

3-(4-Methoxyphenyl)-3-methylcyclohexan-1-one (2b): Prepared according to General Procedure A from 3-methylcyclohex-2-en-1-one **1a** (55 mg, 0.50 mmol) and 4-methoxyphenylboronic acid (152 mg, 1.00 mmol) (reaction time = 16 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2b** (87 mg, 0.399 mmol, 80%) as a clear, yellow oil. Characterization data is consistent with previously reported data.[11] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (s, 3H), 1.61-1.70 (m, 1H), 1.83-1.92 (m, 2H), 2.13-2.18 (m, 1H), 2.30 (app t, *J* = 6.8, 2H), 2.41 (d, *J* = 14.0 Hz, 1H), 2.85 (d, *J* = 14.0 Hz, 1H), 3.78 (s, 3H), 6.85 (d, *J* = 8.8 Hz, 2H), 7.23 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1, 30.2, 38.1, 40.9, 42.4, 53.4, 55.3, 113.9, 126.7, 139.5, 157.8, 211.6.

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3-(4-Chlorophenyl)-3-methylcyclohexan-1-one (2c): Prepared according to General Procedure A from 3-methylcyclohex-2-en-1-one **1a** (55 mg, 0.50 mmol) 4-chlorophenylboronic acid (156 mg, 1.00 mmol) (reaction time = 5 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2c** (100 mg, 0.450 mmol, 90%) as a colorless oil. Characterization data is consistent with previously reported data.[11] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (s, 3H), 1.59-1.68 (m, 1H), 1.83-1.94 (m, 2H), 2.12-2.18 (m, 1H), 2.31 (app t, *J* = 6.8 Hz, 2H), 2.43 (d, *J* = 14.0 Hz, 1H), 2.84 (d, *J* = 14.0 Hz, 1H), 7.23-7.29 (m, 4H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 22.0, 30.0, 38.0, 40.8, 42.7, 53.1, 127.2, 128.7, 132.1, 145.9, 211.0.

3-Methyl-3-(4-(trifluoromethyl)phenyl)cyclohexan-1-one (2d): Prepared according to General Procedure A from 3-methylcyclohex-2-en-1-one **1a** (55 mg, 0.50 mmol) 4-trifluoromethylphenylboronic acid (190mg, 1.00 mmol) (reaction time = 16 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2d** (111 mg, 0.434 mmol, 87%) as a colorless oil. Characterization data is consistent with previously reported data.[11] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (s, 3H), 1.58-1.68 (m, 1H), 1.85-1.99 (m, 2H), 2.18-2.23 (m, 1H), 2.31-2.35 (m, 2H), 2.47 (d, *J* = 14.4 Hz, 1H), 2.88 (d, *J* = 14.4 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 29.9, 37.9, 40.8, 43.2, 52.9, 124.2 (q, *J* = 270 Hz), 125.6 (q, *J* = 3.0 Hz), 126.1, 128.63 (q, *J* = 33.0 Hz), 151.5, 210.8. ^{19}F NMR (376.05 MHz, $CDCl_3$): δ -64.8 (s, 3F).

3-(3-Methoxyphenyl)-3-methylcyclohexan-1-one (2e): Prepared according to General Procedure A from 3-methylcyclohex-2-en-1-one **1a** (55 mg, 0.50 mmol) and 3-methoxyphenylboronic acid (152 mg, 1.00 mmol) (reaction time = 16 h). The crude

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product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2e** (99 mg, 0.454 mmol, 91%) as a clear, yellow oil. Characterization data is consistent with previously reported data.[11] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.64-1.72 (m, 1H), 1.83-1.94 (m, 2H), 2.14-2.20 (m, 1H), 2.31 (app t, *J* = 6.8 Hz, 2H), 2.43 (d, *J* = 14.0 Hz, 1H), 2.86 (d, *J* = 14.0 Hz, 1H), 3.80 (s, 3H), 6.75 (dd, *J* = 8.0, 2.4 Hz, 1H), 6.87 (m, 1H), 6.90 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.25 (dd, *J* = 8.0, 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1, 29.8, 38.0, 40.9, 42.9, 53.2, 55.2, 111.0, 112.2, 118.1, 129.5, 149.3, 159.7, 211.4.

3-(3-Chlorophenyl)-3-methylcyclohexan-1-one (2f): Prepared according to General Procedure A from 3-methylcyclohex-2-en-1-one **1a** (55 mg, 0.50 mmol) and 3-chlorophenylboronic acid (156 mg, 1.00 mmol) (reaction time = 16 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2f** (101 mg, 0.455 mmol, 91%) as a colorless oil. Characterization data is consistent with previously reported data.[11] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (s, 3H), 1.62-1.71 (m, 1H), 1.83-1.94 (m, 2H), 2.11-2.18 (m, 1H), 2.31 (app t, *J* = 6.8 Hz, 2H), 2.42 (d, *J* = 14.0 Hz, 1H), 2.82 (d, *J* = 14.0 Hz, 1H), 7.16-7.19 (m, 2H), 7.24 (d, *J* = 7.6, 1H), 7.29 (app t, *J* = 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 29.6, 37.8, 40.8, 42.9, 53.0, 123.9, 126.0, 126.5, 129.9, 134.6, 149.7, 210.8.

3-(2-Methoxyphenyl)-3-methylcyclohexan-1-one (2g): Prepared according to General Procedure A from 3-methylcyclohex-2-en-1-one **1a** (55 mg, 0.50 mmol) and 2-methoxyphenylboronic acid (152 mg, 1.00 mmol) (reaction time = 16 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2g** (37 mg, 0.339 mmol, 34%) as a clear, yellow oil. Characterization data is consistent with

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previously reported data.[11] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (s, 3H), 1.60-1.70 (m, 1H), 1.80-1.92 (m, 2H), 2.31 (app t, *J* = 6.8 Hz, 2H), 2.45 (d, *J* = 14.4 Hz, 1H), 2.54-2.61 (m, 1H), 2.99 (d, *J* = 14.4 Hz, 1H), 3.84 (s, 3H), 6.89 (app d, *J* = 8.0 Hz, 2H), 7.20 (app d, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.2, 26.4, 35.0, 41.0, 42.9, 53.5, 55.0, 111.8, 120.7, 127.5, 127.8, 134.9, 157.9, 212.5.

3-Methyl-3-phenylcyclopentan-1-one (2h): Prepared according to General Procedure A from 3-methylcyclopent-2-en-1-one **1b** (48 mg, 0.50 mmol) and phenylboronic acid (122 mg, 1.00 mmol) (reaction time = 16 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2h** (83 mg, 0.476 mmol, 95%) as a colorless oil. Characterization data is consistent with previously reported data.[11] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (s, 3H), 2.26-2.44 (m, 4H), 2.48 (d, *J* = 17.2 Hz, 1H), 2.66 (d, *J* = 17.2 Hz, 1H), 7.21-7.25 (m, 1H), 7.29-7.37 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.5, 35.8, 36.8, 43.9, 52.3, 125.5, 126.4, 128.6, 148.5, 218.6.

4-Methyl-4-phenylpentan-2-one (2i): Prepared according to General Procedure A from 4-methylpent-3-en-2-one **1c** (49 mg, 0.50 mmol) and phenylboronic acid (122 mg, 1.00 mmol) (reaction time = 16 h). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2i** (74 mg, 0.417 mmol, 83%) as a colorless oil. Characterization data is consistent with previously reported data.[11] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (s, 6H), 1.80 (s, 3H), 2.74 (s, 2H), 7.20 (tt, *J* = 7.2, 1.2 Hz, 1H), 7.31-7.34 (m, 2H), 7.37-7.39 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.0, 31.9, 37.4, 57.1, 125.6, 126.0, 128.4, 148.2, 208.2.

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Recycling Studies of C2 in Conjugate Addition Phenylboronic Acid to Enone 1a

To a 1 dram vial was added phenylboronic acid (3.00 mmol, 2.00 equiv), MOF-253-Pd(OAc)$_2$ **C2** (0.075 mmol, 0.050 equiv), enone **1a** (1.5 mmol, 1.00 equiv) and 50 mM aqueous sodium trifluoroacetate solution (1 mL, pH = 8.2). The vial was sealed with a PFTE/silicone-lined septum cap. The reaction mixture was heated to 100 °C and allowed to stir at this temperature (2-16 h). The mixture was allowed to cool to room temperature, diluted with EtOAc (3 mL), and the mixture was centrifuged at 5000 RPM for 5 minutes. The organic layer was separated from the aqueous layer, and the aqueous layer was extracted twice more with EtOAc (3 mL). The combined organics were washed with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was dissolved in $CDCl_3$ (0.70 mL) and CH_2Br_2 (52.8 μL, 0.750 mmol) was added as an internal standard. NMR yields were determined by ^{1}H NMR spectroscopy of the crude reaction mixture. Following the final extraction, the aqueous layer was removed from the vial, and fresh reagents and reaction medium were added to the MOF-253-Pd(OAc)$_2$ for the next cycle.

Low Conversion Recycling Studies for Conjugate Addition of Phenylboronic Acids to Enone 1a Catalyzed by MOF-253-Pd(OAc)$_2$ C2

To a 1 dram vial was added phenylboronic acid (3.00 mmol, 2.00 equiv), MOF-253-Pd(OAc)$_2$ **C2** (0.075 mmol, 0.050 equiv), enone **1a** (1.5 mmol, 1.00 equiv) and 50 mM aqueous sodium trifluoroacetate solution (1 mL, pH = 8.2). The vial was sealed with a PFTE/silicone-lined septum cap. The reaction mixture was heated to 100 °C and allowed to stir at this temperature for 1 hour. The mixture was allowed to cool to room temperature, diluted with EtOAc (3 mL), and the mixture was centrifuged at 5000 RPM

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for 5 minutes. The organic layer was separated from the aqueous layer, and the aqueous layer was extracted twice more with EtOAc (3 mL). The combined organics were washed with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was dissolved in $CDCl_3$ (0.70 mL) and CH_2Br_2 (52.8 µL, 0.750 mmol) was added as an internal standard. NMR yields were determined by ^1H NMR spectroscopy of the crude reaction mixture. Following the final extraction, the aqueous layer was removed from the vial, and fresh reagents were added to the MOF-253-Pd(OAc)$_2$ for the next cycle.

Leaching Test for Conjugate Addition of Phenylboronic Acid to Enone 1a Catalyzed by MOF-253-Pd(OAc)$_2$ C2

To a 1 dram vial was added phenylboronic acid (3.00 mmol, 2.00 equiv), MOF-253-Pd(OAc)$_2$ **C2** (0.075 mmol, 0.050 equiv), and 50 mM aqueous sodium trifluoroacetate solution (1 mL, pH = 8.2). The vial was sealed with a PFTE/silicone-lined septum cap. The reaction mixture was heated to 100 °C and allowed to stir at this temperature for 2 hours. The mixture was centrifuged at 5000 RPM for 1 minute and the aqueous layer was immediately removed from the reaction mixture and added to a new vial containing fresh phenylboronic acid (3.00 mmol, 2.00 equiv), and enone **1a** (1.50 mmol, 1.00 equiv). This vial was stirred at 100 °C for 2 hours. The mixture was allowed to cool, diluted with EtOAc (3 mL), and the mixture centrifuged at 5000 RPM for 5 minutes. The organic layer was separated from the aqueous layer, and the aqueous layer was extracted twice more with EtOAc (3 mL). The combined organics were washed with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was dissolved in $CDCl_3$ (0.70 mL) and CH_2Br_2

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(52.8 µL, 0.750 mmol) was added as an internal standard. The yield of ketone **2a** was determined to approximately 1% by ^{1}H NMR spectroscopy.

ICP-MS Leaching Test for Conjugate Addition of Phenylboronic Acids to Enone 1a Catalyzed by MOF-253-Pd(OAc)$_2$ C2

To a 1 dram vial was added phenylboronic acid (3.00 mmol, 2.00 equiv), MOF-253-Pd(OAc)$_2$ **C2** (0.075 mmol, 0.050 equiv), and 50 mM aqueous sodium trifluoroacetate solution (1 mL, pH = 8.2). The vial was sealed with a PFTE/silicone-lined septum cap. The reaction mixture was heated to 100 °C and allowed to stir at this temperature for 2 hours. The mixture was centrifuged at 5000 RPM for 1 minute and the aqueous layer was immediately removed from the mixture. ICP-MS analysis was performed to determine Pd content revealing 16 µg (0.6% of the original palladium content in the reaction) had leached into the aqueous supernatant.

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CHAPTER 4 – SYNTHESIS OF STEREOELECTRONICALLY DIVERSE MOFS FOR TRANSITION METAL CATALYSIS

Modified from a paper submitted to *ACS Catalysis*

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Abstract

A new series of isoreticular, mixed-linker metal-organic frameworks (MOFs) containing palladium chloride-bipyridine sites has been developed. The electronic and steric effects of linker substitution on the activity of metalated MOFs have been investigated in the context of Suzuki–Miyaura cross-coupling reactions. m-6,6´-Me_2bpy-MOF-$PdCl_2$ (UiO-67-Pd-6,6´-dimethyl-bpydc$_{0.4}$/bpdc$_{0.6}$) exhibited a remarkable enhancement in the activity compared to non-functionalized m-bpy-MOF-$PdCl_2$ (UiO-67-Pd-bpydc$_{0.5}$/bpdc$_{0.5}$) and m-4,4´-Me_2bpy-MOF-$PdCl_2$(UiO-67-Pd-4,4´-dimethyl-bpydc$_{0.4}$/bpdc$_{0.6}$). This result clearly demonstrates that the stereoelectronic properties of metal-binding linker units are critical to the activity of single-site organometallic catalysts in MOFs. Our studies also show that there was no leaching of active catalytic species during the reaction and the catalyst, m-6,6´-Me_2bpy-MOF-$PdCl_2$, can be reused up to three times without significant deactivation.

Introduction

In transition metal-catalyzed cross-coupling reactions, the steric and electronic properties of ancillary ligands bound to the metal center significantly impact the catalytic

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properties of transition metal complexes.[1] Previous studies detail how the steric and electronic properties of phosphine,[2] *N*-heterocyclic carbene,[3] and diamine ligands[4] impact reactions catalyzed by transition metal complexes. However, these studies are currently limited to homogeneous catalyst systems, and analogous studies on heterogeneous transition metal catalysts have not been reported. The lack of studies on the impact of ancillary ligands on heterogeneous transition metal catalysts likely results from a lack of catalyst supports that enable facile tuning of ligand structures at the atomic level.

Metal-organic frameworks (MOFs) have recently gained attention due to their high surface area and porosity, structural tunability, and applications in diverse areas such as catalysis, chemical sensors, drug delivery, gas storage and separation.[5] MOFs have been established as a versatile platform for the immobilization of homogeneous organometallic catalysts. These catalytic entities are attractive because they integrate the benefits of the well-defined stereoelectronic properties of homogeneous organometallic catalysts with the uniform active sites and recyclability of MOFs. Recent studies have greatly expanded the types of organometallic transformations catalyzed by metalated bipyridyl-MOFs.[6] However, there remains minimal understanding of how the steric and electronic properties of the bipyridyl linker unit impact the properties of these heterogeneous catalysts.

In comparison to conventional porous supports, MOFs feature the advantages of adjustable pore structures and broad synthetic diversity accessible through an array of structural building units. In addition, MOFs are well suited to establish clear structure-function relationships through rational functionalization of linkers in isoreticular MOFs.[7] Recent attention has been directed to studying how modified linker units in isoreticular

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MOFs impact heterogeneous catalysis.[8] Given that the steric and electronic properties of ancillary ligands are crucial to improving activity in transition metal-catalyzed reactions,[2b, 2c, 9] we envisioned that anchoring homogeneous transition metal catalysts in MOFs may allow the heterogeneous catalytic behavior to be fine-tuned in a similar fashion to ligand modification in homogeneous catalyst systems. To the best of our knowledge, studies to elucidate the effects of metal-binding linker units in MOFs on transition metal catalyzed reactions have not been conducted in a systematic manner.

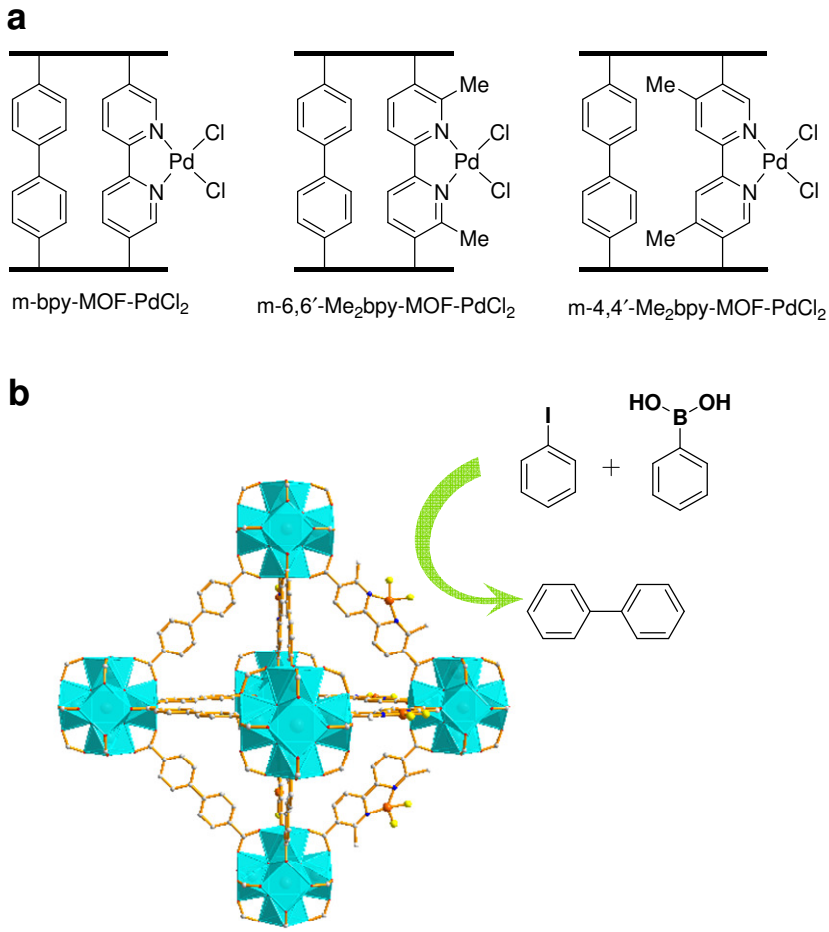

Figure 1. a) Schematic structures of m-MOF-$PdCl_2$ precatalysts. b) Idealized structure of m-6,6′-Me_2bpy-MOF-$PdCl_2$ as a precatalyst for the model Suzuki–Miyaura cross-coupling reaction.

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We report the synthesis and subsequent immobilization of palladium chloride within a series of bipyridyl-MOFs (m-bpy-MOF-$PdCl_2$, m-6,6´-Me_2bpy-MOF-$PdCl_2$ and m-4,4´-Me_2bpy-MOF-$PdCl_2$) synthesized via a mixed-linker approach to afford heterogeneous catalysts for Suzuki-Miyaura cross-coupling reactions (Figure 1). Mixed-ligand MOFs (m-MOFs) hold multiple advantages. They possess high surface areas and stability, the bipyridine sites are capable of coordinating palladium complexes[10] and the ligands without bipyridine sites ensure the separation of the active palladium centers in the individual cages of the MOFs, preventing deactivation of the palladium catalysts. These metalated isoreticular MOFs are crystalline, porous and robust. m-6,6´-Me_2bpy-MOF-$PdCl_2$ exhibited a remarkable enhancement in the activity compared to m-bpy-MOF-$PdCl_2$ and m-4,4´-Me_2bpy-MOF-$PdCl_2$. This work constitutes a rare example detailing the impact of ancillary ligand properties on reactions catalyzed by heterogeneous, metalated MOFs.

Results and Discussion

At the outset of our studies, we synthesized a series of 2,2´-bipyridine-5,5´-dicarboxylic acid derivatives. 2,2´-bipyridine-5,5´-dicarboxylic acid (H_2bdydc) was prepared according to a literature procedure.[11] Unique synthetic pathways were designed for 6,6´-dimethyl-[2,2´-bipyridine]-5,5´-dicarboxylic acid (H_2-6,6´-Me_2bpydc), 4,4´-dimethyl-[2,2´-bipyridine]-5,5´-dicarboxylic acid (H_2-4,4´-Me_2bpydc), and 4,4´-dimethoxy-[2,2´-bipyridine]-5,5´-dicarboxylic acid (H_2-4,4´-$(MeO)_2$bpydc) derivatives. These linkers were prepared by synthetic sequences summarized in Schemes 1-3.

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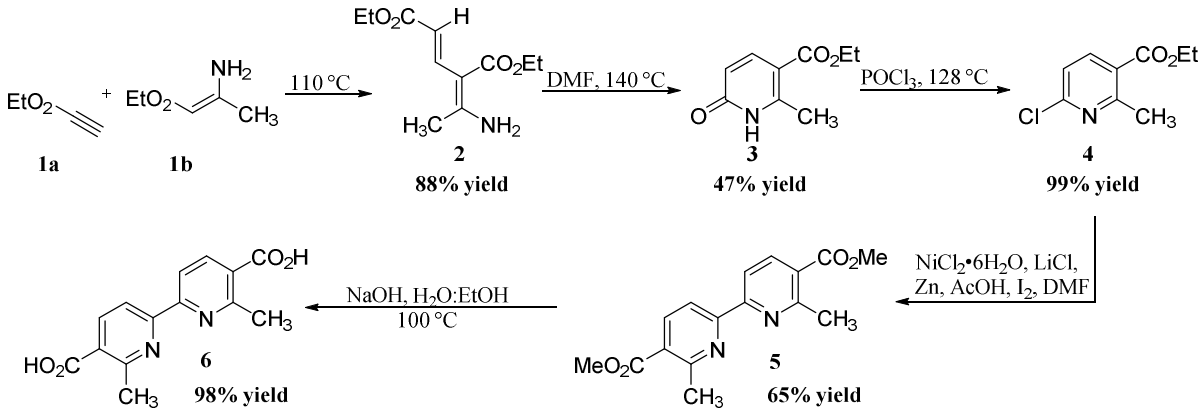
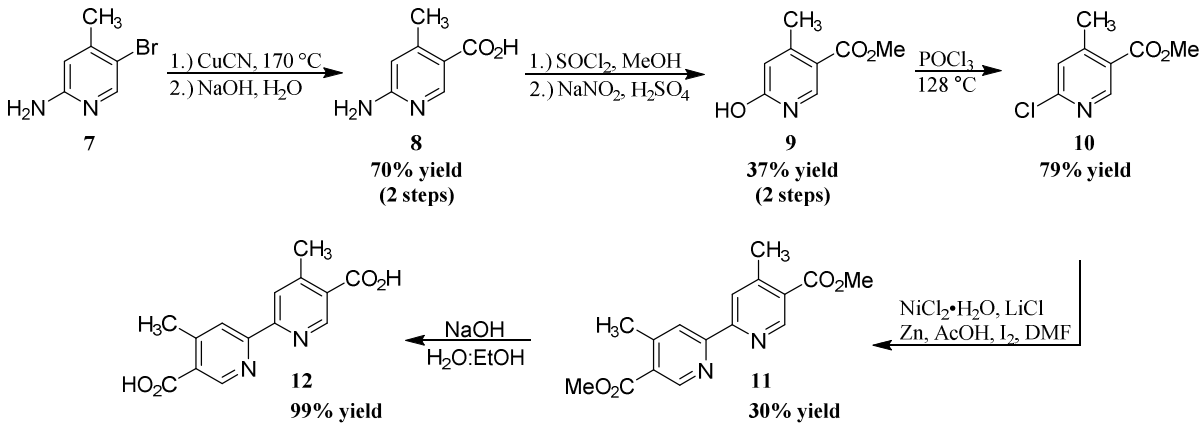
H_2-6,6′-Me_2bpydc **6** was synthesized in five steps in 26% overall yield (Scheme 1). This synthetic sequence is highlighted by the key nickel-catalyzed reductive homocoupling[12] of ethyl-6-chloro-2-methylnicotinate **4** to generate diethyl-6,6′-dimethyl-[2,2′-bipyridine]-5,5′-dicarboxylate **5** in 65% yield. The synthetic pathway described in **6** requires only one purification by flash chromatography and leads to the formation of the final product in significantly higher yields than previous reports.

Scheme 1. Synthesis of H_2-6,6´-Me_2bpydc (6).



Scheme 2. Synthesis of H_2-4,4´-Me_2bpydc (12).



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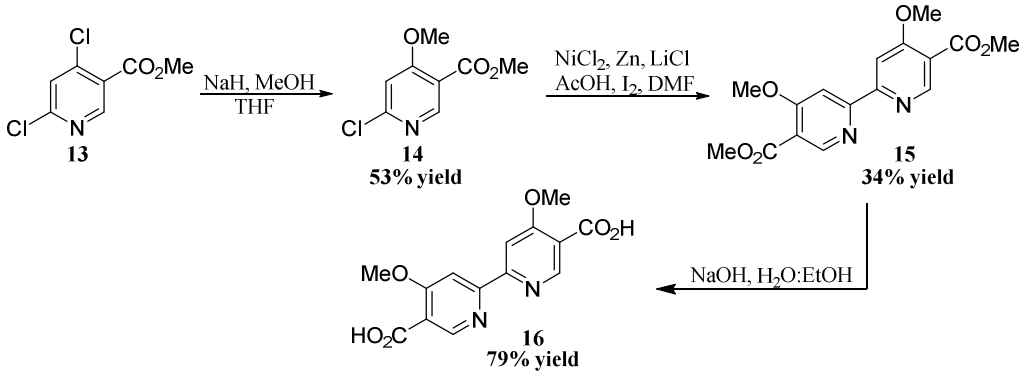
H_2-4,4′-Me_2bpydc **12** was synthesized in seven steps in 6% overall yield (Scheme 2). Cyanation of **7** followed by hydrolysis led to the formation of 6-amino-4-methylnicotinic acid **8** in 70% yield over two steps. The reaction of **8** with the thionyl chloride formed the corresponding methyl ester in 66% yield, which upon addition of $NaNO_2$ forms an aryl diazonium salt *in situ* that is converted to methyl 6-hydroxy-4-methylnicotinate **9** (56% yield) in the presence of dilute sulfuric acid. Addition of phosphoryl chloride to **9** led to the formation methyl 6-chloro-4-methylnicotinate **10** in 79% yield. This sequence is once again highlighted by a key homocoupling of methyl 6-chloro-4-methylnicotinate **10** which leads to the formation of dimethyl 4,4′-dimethyl-[2,2′-bipyridine]-5,5′-dicarboxylate **11** in 30% yield. Hydrolysis of **11** generated 4,4′-dimethyl-[2,2′-bipyridine]-5,5′-dicarboxylic acid **12** in 99% yield.

Scheme 3. Synthesis of H_2-4,4′-$(MeO)_2$bpydc (16).



H_2-4,4′-$(MeO)_2$bpydc **16** was synthesized in 14% overall yield in three steps. Methoxylation of methyl 4,6-dichloronicotinate **13** led to the formation of methyl 6-chloro-4-methoxynicotinate **14** in 53% yield. Homocoupling of **14** generated **15** in 34% yield, and a subsequent hydrolysis formed **16** in 79% yield.

Our approach to the synthesis of H_2-4,4′-$(CF_3)_2$bpydc **21** is summarized in Scheme 4. Synthesis of 2,5-dichloro-4-iodopyridine **18** by iodination of commercially

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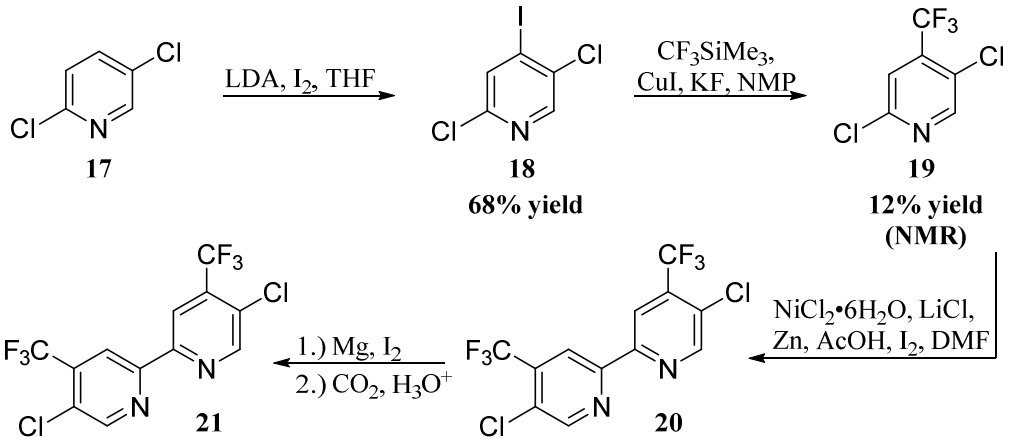
available 2,5-dichloropyridine **17** occurred in 68% yield. The trifluoromethylation of **18** with Ruppert's reagent formed 2,5-dichloro-4-trifluoromethylpyridine **19** in very low yields by NMR. Attempts to improve this result are ongoing. Nickel-catalyzed reductive coupling of **19** followed by grignard formation, addition of CO_2, and an acidic workup should lead to the formation of H_2-4,4′-$(CF_3)_2$bpydc **21**.

Scheme 4. Synthesis of H_2-4,4′-$(CF_3)_2$bpydc (21).



Using this series of bipyridyl linkers, we prepared mixed-linker MOFs (m-bpy-MOF, m-6,6´-Me_2bpy-MOF, and m-4,4´-Me_2bpy-MOF) from equimolar amounts of the bipyridyl and biphenyl linkers based on a reported protocol (Figure 2a).[13] Powder X-ray diffraction (PXRD) patterns of the MOFs are in good agreement with simulated patterns for UiO-67, indicating that these MOFs have isoreticular crystalline structures (Figure 2b). Linker ratios were quantified by ^{1}H NMR spectroscopy upon digestion of the MOF with HF in d_6-DMSO. m-bpy-MOF, m-6,6´-Me_2bpy-MOF, and m-4,4´-Me_2bpy-MOF contained 1:1, 1.5:1, and 1.5:1 ratios of the biphenyl and bipyridyl linkers (Table 1).

The m-MOF-$PdCl_2$ precatalysts were synthesized by post-synthetic metalation of the

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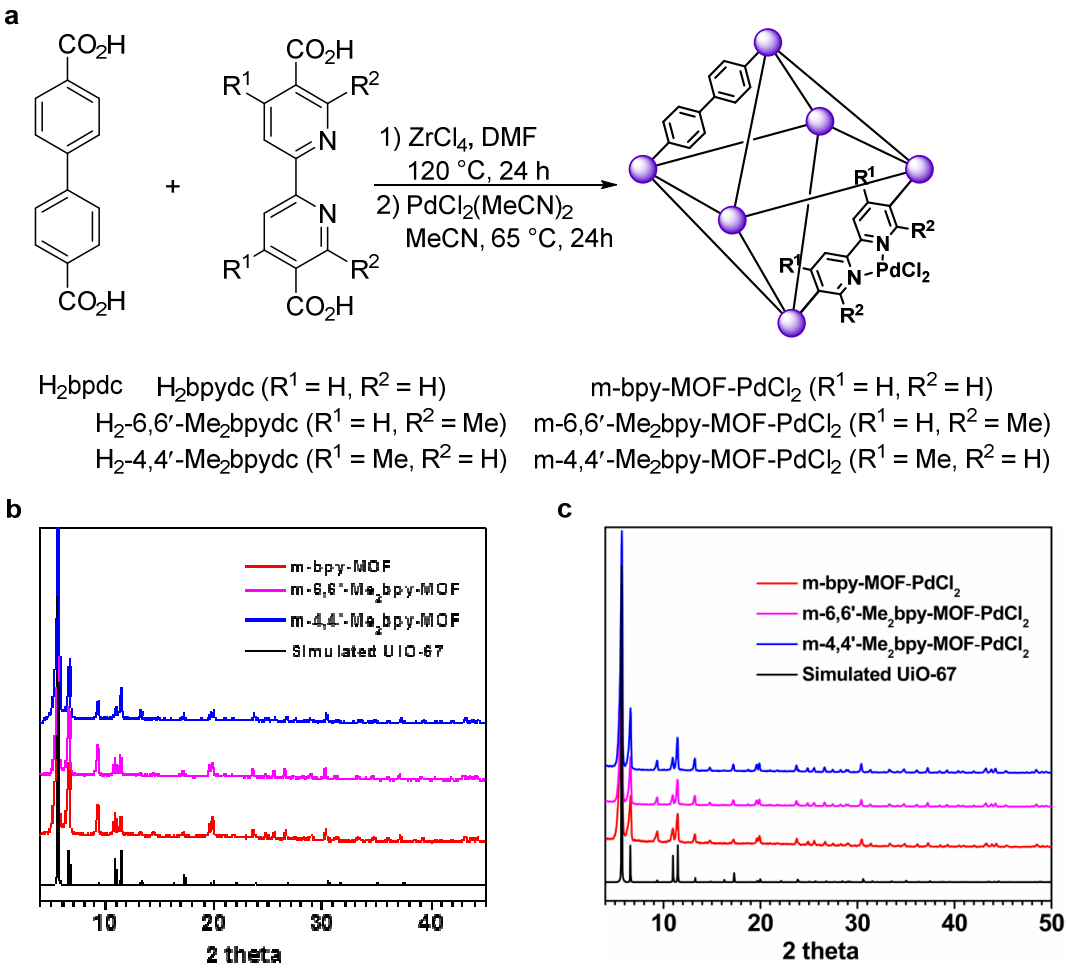

Figure 2. a) Hydrothermal synthesis of m-MOFs; b) PXRD of simulated UiO-67 and m-MOFs c) PXRD of simulated UiO-67 and m-MOFs-$PdCl_2$.

mixed-linker MOFs with $PdCl_2(CH_3CN)_2$ in acetonitrile (Figure 2a). PXRD analyses of the metalated MOFs show that the m-MOF-$PdCl_2$ complexes remain crystalline during the post-synthetic metalation (Figure 2c).

We determined the loading of palladium in the metalated MOFs by inductively coupled plasma-mass spectroscopy (ICP-MS). The palladium loadings are 2.8 wt.% for m-bpy-MOF-$PdCl_2$, 2.9 wt.% for m-6,6´-Me_2bpy-MOF-$PdCl_2$, and 3.0 wt.% for m-4,4´-Me_2bpy-MOF-$PdCl_2$. At these loadings, palladium could coordinate to 19.3%, 25.8% and

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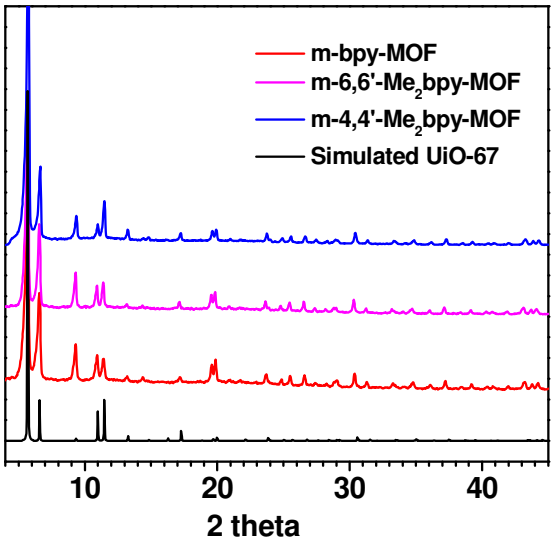

Figure 3. PXRD patterns of simulated UiO-67 and m-MOFs series.

Table 1. Linker ratio of m-MOFs (UiO-67-X-bpydc$_{0.5}$/bpdc$_{0.5}$) determined by ^{1}H NMR.

	X-H_2bpydc /H_2bpdc	
Sample	Target Ratio	Actual Ratio
m-bpy-MOF	0.5/0.5	**0.5/0.5**
m-6,6′-Me_2bpy-MOF	0.5/0.5	**0.4/0.6**
m-4,4′-Me_2bpy-MOF	0.5/0.5	**0.4/0.6**

26.7% of total bipyridyl linkers for m-bpy-MOF-$PdCl_2$, m-6,6´-Me_2bpy-MOF-$PdCl_2$, and m-4,4´-Me_2bpy-MOF-$PdCl_2$.

N_2 adsorption-desorption isotherm profiles of mixed-linker MOFs and m-MOF-$PdCl_2$ complexes all exhibit a type I curve, which is characteristic of microporous materials (Figure 4). The Brunauer–Emmett–Teller (BET) surface area and micropore volume of m-bpy-MOF are calculated to be 2526 m^2 g^{-1} and 0.91 cm^3 g^{-1}, which are in agreement with reported values (Table 2).

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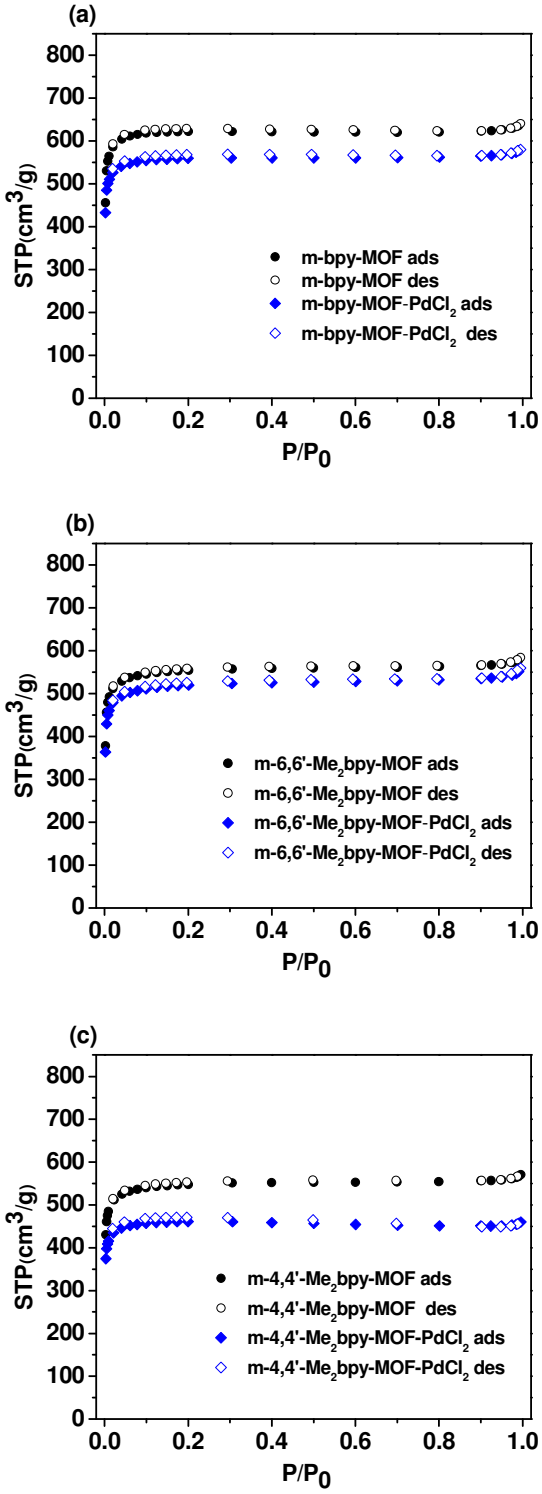

Figure 4. Nitrogen physisorption isotherms of (a) m-bpy-MOF and 2.8% m-bpy-MOF-$PdCl_2$; (b) m-6,6′-Me_2bpy-MOF, and 2.9% m-6,6′-Me_2bpy-MOF-$PdCl_2$; (c) m-4,4′-Me_2bpy-MOF, and 3.0% m-4,4′-Me_2bpy-MOF-$PdCl_2$.

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The introduction of methyl groups at the 4,4′ or 6,6′ positions of bipyridyl linker leads to a decrease in the BET surface areas of the corresponding mixed-linker MOFs. The surface areas of m-6,6′-Me_2bpy-MOF and m-4,4′-Me_2bpy-MOF are 2259 m^2g^{-1} and 2219 m^2g^{-1}. The BET surfaces areas of m-bpy-MOF-$PdCl_2$, m-6,6´-Me_2bpy-MOF-$PdCl_2$, and m-4,4´-Me_2bpy-MOF-$PdCl_2$ decrease to 2293 m^2g^{-1}, 2105 m^2g^{-1}, and 1900 m^2g^{-1} primarily due to incorporation of $PdCl_2$ into the cages of the MOFs.

Table 2. BET surface area and pore volume of m-MOFs and m-MOFs-$PdCl_2$. The Pd content in the metalated MOFs are measured by ICP-MS.

Sample	BET (m^2g^{-1})	Micropore volume (cm^3g^{-1})
m-bpy-MOF	2526.1 ± 9.6	0.91
2.8% m-bpy-MOF-$PdCl_2$	2292.9 ± 5.4	0.80
Used 2.8% m-bpy-MOF-$PdCl_2$	2126.2 ± 3.7	0.76
m-6,6′-Me_2bpy-MOF	2258.6 ± 2.8	0.76
2.9% m-6,6′-Me_2bpy-MOF -$PdCl_2$	2104.8 ± 3.7	0.71
Used 2.9% m-6,6′-Me_2bpy-MOF -$PdCl_2$	2036.7 ± 4.8	0.69
m-4,4′-Me_2bpy-MOF	2219.4 ± 3.1	0.76
3.0% m-4,4′-Me_2bpy-MOF-$PdCl_2$	1900.0 ± 3.7	0.68
Used 3.0% m-4,4′-Me_2bpy-MOF -$PdCl_2$	1817.6 ± 2.1	0.62

We chose the coupling of iodobenzene with phenylboronic acid as a model reaction to evaluate the effect of linker substitution in Suzuki-Miyaura reactions catalyzed by m-MOFs-$PdCl_2$ (Figure 5). During our initial identification of reaction conditions, a range of common solvent and base combinations for Suzuki-Miyaura reactions, including DMF/H_2O (1/1) + K_2CO_3, EtOH/H_2O (1/1) + K_2CO_3, toluene/H_2O (9/1) + K_2CO_3, EtOH + KF, EtOH/H_2O (1/1) + KF, were evaluated. However, the metalated MOFs collapsed within 3 hours in the presence of these polar, protic reaction media. Decomposition of the metalated MOFs is not observed when the model coupling

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reaction is run in toluene with K_2CO_3 as the base. m-bpy-MOF, m-4,4´-Me_2bpy-MOF, and m-6,6´-Me_2bpy-MOF exhibit dramatic differences in their catalytic activity in the coupling reaction. We calculated the rate constants of coupling reaction over m-bpy-MOF-$PdCl_2$, m-4,4´-Me_2bpy-MOF-$PdCl_2$ and m-6,6´-Me_2bpy-MOF-$PdCl_2$ as 0.24 min^{-1}, 0.053 min^{-1} and 26.3 min^{-1}. The m-6,6´-Me_2bpy-MOF-$PdCl_2$ exhibited a remarkable enhancement in the activity compared to non-functionalized m-bpy-MOF-$PdCl_2$ and m-4,4´-Me_2bpy-MOF-$PdCl_2$.

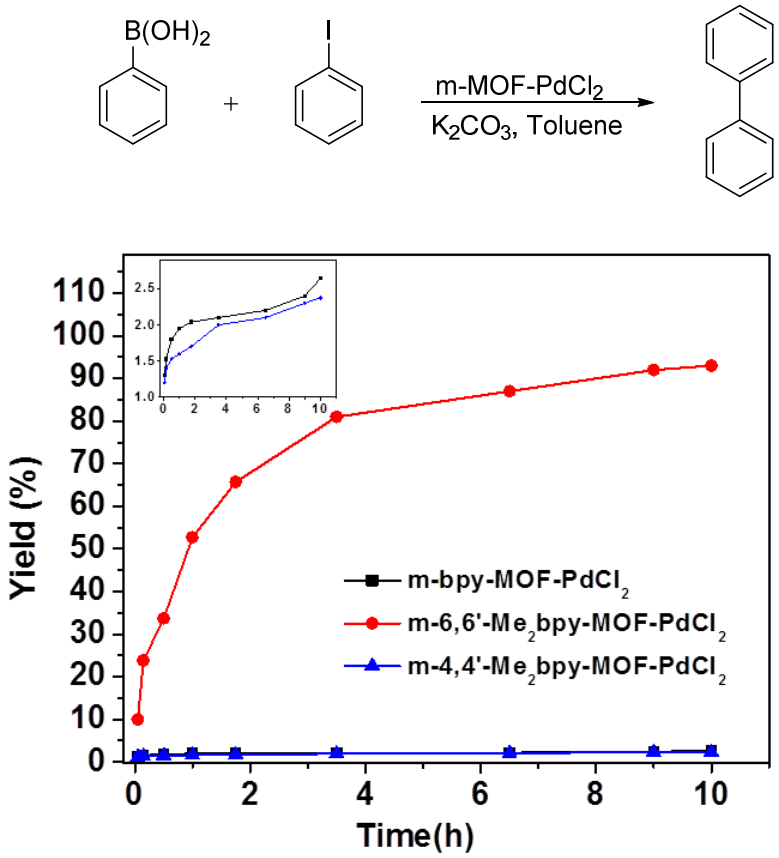

Figure 5 Suzuki-Miyaura cross-coupling reaction catalyzed by m-MOF-$PdCl_2$; Catalytic difference of m-MOF-$PdCl_2$. The inset shows the reaction yield by m-bpy-MOF-$PdCl_2$ and m-4,4´-Me_2bpy-MOF-$PdCl_2$. Reaction conditions: 4-iodobenzene (0.100 mmol), phenylboronic acid (0.150 mmol), K_2CO_3 (0.200 mmol), toluene (0.500 mL), m-MOF-$PdCl_2$ (0.001 mmol Pd), Ar atmosphere, 85 °C.

The m-MOFs without palladium were also catalytically inactive, confirming that the palladium center is the active site for the Suzuki coupling reaction (Table 3, entry 1).

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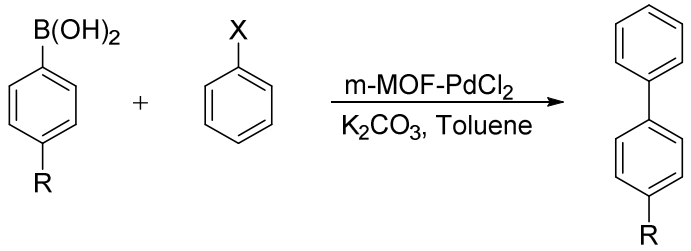
The Suzuki coupling of iodobenzene and 4-methylphenylboronic acid led to the formation 4-methyl-1,1′-biphenyl as the sole product (Table 3, entry 2), which suggests no homocoupling of arylboronic acid or iodobenzene occurs under the investigated conditions. The reaction of phenylboronic acid with iodobenzene in the presence of m-6,6´-Me_2bpy-MOF-$PdCl_2$ led to formation of biphenyl in 99% yield when 1.0 mol Pd % was used (Table 3, entry 3). When bromobenzene was used in place of iodobenzene the reaction reached 95% yield in 10 h under our standard reaction conditions (Table 3, entry 4).

Table 3. Suzuki-Miyaura cross-coupling reaction catalyzed by various m-MOFs. [a]



Entry	Catalysts	X	R	Pd	Time (h)	Yield (%)
1	m-6,6′-Me_2bpy-MOF	I	H	0 mol %	12	0%
2	m-6,6′-Me_2bpy-MOF-$PdCl_2$	I	Me	1 mol %	12	95%
3	m-6,6′-Me_2bpy-MOF-$PdCl_2$	I	H	1 mol %	12	99%
4	m-6,6′-Me_2bpy-MOF-$PdCl_2$	Br	H	1 mol %	10	92%

[a] Condition: iodobenzene (0.100 mmol), phenylboronic acid (0.110 mmol), m-MOF (0.001 mmol-0.005 mmol) K_2CO_3 (0.150 mmol), Toluene (0.5 mL), Ar atmosphere, 85 °C.

This sharply differing catalytic behavior prompted us to gain more insight into the relationship between linker substitution and the catalytic properties of the coordinated palladium centers in Suzuki-Miyaura coupling reactions. Compared to non-functionalized m-bpy-MOF-$PdCl_2$, m-6,6´-Me_2bpy-MOF-$PdCl_2$ contains a relatively hindered and electron-rich metal center and is a more active catalyst. We found the activity of m-4,4´-

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Me_2bpy-MOF-$PdCl_2$ to be slightly lower than non-functionalized m-bpy-MOF-$PdCl_2$ (Figure 5 inset), suggesting the electronic character of the new linker units has minimal impact on the activity of the metalated MOF catalysts. This data suggests reductive elimination, which is favored at sterically congested metal centers, is the turnover-limiting step of the catalytic cycle for Suzuki-Miyaura coupling reactions.

The heterogeneity of the active catalyst, m-6,6´-Me_2bpy-MOF-$PdCl_2$, was assessed by hot filtration of the catalyst. Upon removal of the solid catalyst, we did not observe further increase in the conversion of iodobenzene in the reaction mixture (Figure 6a). The palladium content in the reaction solution was determined by ICP-MS and only negligible Pd (< 0.1% of added Pd) was detected. These results suggest that the Suzuki-Miyaura cross-coupling reaction catalyzed by m-6,6´-Me_2bpy-MOF-$PdCl_2$ is indeed catalyzed by a heterogeneous palladium species.

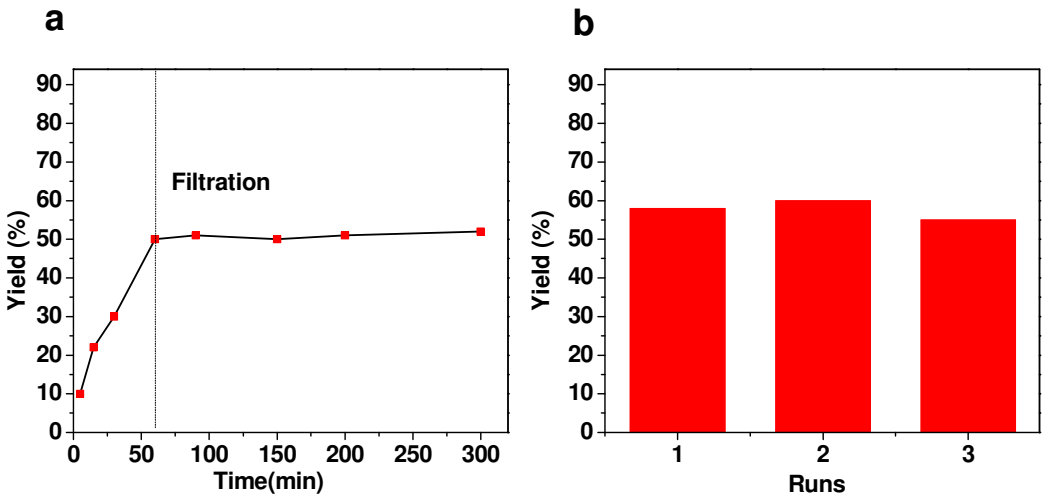

Figure 6. Leaching and recycle test of m-6,6´-Me_2bpy-MOF-$PdCl_2$ in the Suzuki-Miyaura cross-coupling reaction. Reaction conditions: 4-iodobenzene (0.1 mmol), phenylboronic acid (0.15 mmol), K_2CO_3 (0.2 mmol), Toluene (0.5 mL), m-6,6´-Me_2bpy-MOF-$PdCl_2$ (1.0 mol% Pd), Ar atmosphere, 85 °C for 1.5 hours.

The reusability of the m-6,6´-Me_2bpy-MOF-$PdCl_2$ catalyst was also examined. After an initial reaction for 1.5 hours, we separated the solid catalyst from the reaction

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medium by centrifugation and then reused the catalyst in successive runs under identical condition. The m-6,6´-Me_2bpy-MOF-$PdCl_2$ catalyst could be recycled at least three times without significant loss in yield (Figure 6b).

Conclusion

We developed a series of mixed-ligand bipyridyl MOF-supported palladium catalysts which were used to catalyze Suzuki-Miyaura cross-coupling reactions. We have shown for the first time that, the linker modification in m-MOFs can significantly impact the activity in the coupling reactions. We found that the reaction rate of a model Suzuki coupling reaction increases in the order m-6,6´-Me_2bpy-MOF-$PdCl_2$ > m-bpy-MOF-$PdCl_2$ > m-4,4´-Me_2bpy-MOF-$PdCl_2$. Our data is consistent with a hindered palladium center accounting for the high activity of m-6,6´-Me_2bpy-MOF-$PdCl_2$ system because similar electronic properties provided by m-4,4´-Me_2bpy-MOF-$PdCl_2$ lead to a catalyst with low activity. We confirmed that the coupling reaction catalyzed by m-6,6´-Me_2bpy-MOF-$PdCl_2$ is heterogeneous, excluded the possibility of homo-coupling under the investigated condition, and showed the catalyst can be recycled three times without obvious deactivation.

Experimental

Experimental details. Powder X-ray diffraction data was recorded on a STOE Stadi P powder diffractometer using Cu K_α radiation (40 kV, 40 mA, λ = 0.1541 nm). Surface area analysis of the catalysts was performed by nitrogen physisorption isotherms in a

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Micromeritics Tristar 3000 surface area analyzer at 77 K. m-MOF samples (ca. 50 mg) were degassed under vacuum (5 x 10^{-5} torr) at 200 °C for 12 hours prior to measurements. Inductively coupled plasma-mass spectroscopy (ICP-MS) analysis was performed on Optima 2100 DV. MOF-$PdCl_2$ was heated in a boiling aqua regia solution until the solid was completely dissolved prior to ICP-MS analysis.

All reactions were performed under air unless otherwise noted. Reactions involving air-sensitive reagents were conducted under inert atmosphere in a nitrogen-filled dry box or by standard Schlenk techniques. Glassware for moistures sensitive reactions was dried at 140 °C in an oven for at least one hour prior to use. Flash column chromatography was performed on Siliflash® P60 silica gel (230-400 mesh) using hexane/ethyl acetate or dichloromethane/methanol mixtures as the eluent. Products were visualized on TLC by UV light. NMR spectra were acquired on Varian MR-400, Bruker DRX 400 and Bruker Advance III 600 spectrometers at the Iowa State Chemical Instrumentation Facility. Chemical shifts are reported relative to a residual solvent peak ($CDCl_3$ = 7.26 ppm for ^1H, and 77.10 ppm for ^{13}C, d_6-DMSO = 2.50 ppm for ^1H and 39.5 ppm for ^{13}C). Coupling constants are reported in hertz.

Materials. Ethyl-3-amino crotonate **1a**, dimethylformamide, phosphorous oxychloride, nickel (II) chloride hexahydrate, zinc dust, copper (I) cyanide, thionyl chloride, phenylboronic acid and anhydrous methanol were purchased from Sigma-Aldrich and used without further purification. Ethyl propiolate **1b** and 5-bromo-4-methylpyridin-2-amine **6** were purchased from AK Scientific and used without further purification. Iodobenzene, lithium chloride, acetic acid, sodium hydroxide, potassium permanganate, acetonitrile and sodium nitrite were purchased from Fisher Scientific and used without

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further purification. 5,5′-dimethyl-2,2′-bipyridine was purchased from Alfa Aesar and used without further purification. Mesitylene and zirconium chloride were purchased from Acros Organics and used without further purification.

Synthesis of 6,6′-dimethyl-[2,2′-bipyridine]-5,5′-dicarboxylic acid

Diethyl(2E, 4Z)-4-(1-aminoethylidene)pent-2-enedioate (2)

Adapted from a literature procedure,[14] to a 250 mL round-bottom flask was added ethyl-3-amino crotonate **1a** (15.6 g, 120 mmol, 1.00 equiv) and ethyl propiolate **1b** (12.2 mL, 120 mmol, 1.00 equiv). This mixture was heated at 108 °C for 4 hours under N_2. After cooling, the resulting solid was recrystallized from methanol to give diethyl (2E, 4Z)-4-(1-aminoethylidene)pent-2-enedioate **2** (23.9 g, 105 mmol, 88% yield). Characterization data is consistent with previous studies.[15] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (t, *J* = 7.0 Hz, 3H), 1.36 (t, *J* = 7.0 Hz, 3H), 2.27 (s, 3H), 4.19 (q, *J* = 7.0 Hz, 2H), 4.26 (q, *J* = 7.0 Hz, 2H), 6.15 (d, *J* = 15.6 Hz, 1H), 7.65 (d, *J* = 15.6 Hz, 1H).

Ethyl-2-methyl-6-oxo5,6-dihydropyridine-3-carboxylate (3)

Adapted from a literature procedure,[14] a mixture of diethyl(2E, 4Z)-4-(1-aminoethylidene)pent-2-enedioate **2** (23.0 g, 100.8 mmol, 1.00 equiv) and DMF (114 mL) were heated to 140 °C for 14 hours under N_2. After cooling, the resulting solid was collected by vacuum filtration, washed with ice cold ether (3x) and dried to give ethyl-2-methyl-6-oxo5,6-dihydropyridine-3-carboxylate **3** (8.6 g, 47.5 mmol, 47% yield). Characterization data is consistent with previous studies.[14] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (t, *J* = 7.0 Hz, 3H), 2.73 (s, 3H), 4.29 (q, *J* = 7.0 Hz, 2H), 6.40 (d, *J* = 9.6 Hz, 1H), 8.03 (d, *J* = 9.6 Hz, 1H) 13.28 (br s, 1H).

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Ethyl-6-chloro-2-methylnicotinate (4)

Adapted from a literature procedure,[14] a mixture of ethyl-2-methyl-6-oxo5,6-dihydropyridine-3-carboxylate **3** (7.5 g, 41.4 mmol, 1.00 equiv) and phosphorous oxychloride (18.0 mL, 193 mmol, 4.66 equiv) was heated at 128 °C for 4 hours. The reaction was cooled to room temperature, then poured onto ice water, made basic with 8M NaOH and extracted three times with EtOAc (100 mL). The combined organics were washed with brine, dried over Na_2SO4, and concentrated under reduce pressure to give ethyl-6-chloro-2-methylnicotinate **4** (7.41 g, 41.3 mmol, 99% yield). Characterization data is consistent with previous studies.[14] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (t, *J* = 7.2 Hz, 3H), 2.82 (s, 3H), 4.38 (q, *J* = 7.2 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 1H), 8.16 (d, *J* = 8.0 Hz, 1H)

6,6′-dimethyl-[2,2′-bipyridine]-5,5′-dicarboxylic acid (6)

Adapted from a literature procedure,[12] a 250 mL round-bottom flask was charged with $NiCl_2{\cdot}6H_2O$ (0.475 g, 2.00 mmol, 0.100 equiv), and DMF (120 mL). The resulting solution was stirred and heated to 40 °C, and ethyl-6-chloro-2-methylnicotinate **4** (3.60 g, 20.0 mmol, 1.00 equiv), anhydrous LiCl, (0.848 g, 20.0 mmol, 1.00 equiv), and zinc dust (1.57 g, 24.0 mmol, 1.20 equiv) were added. When the temperature rose to 50 °C, a grain of iodine crystal and two drops of acetic acid were added to the mixture. The mixture was stirred at 60 °C for 16 hours. The reaction was cooled to room temperature and 10% HCl added (25 mL), the resulting mixture was made alkaline with 25% aqueous ammonia and extracted with DCM. The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by flash chromatography to give dimethyl 6,6′-dimethyl-[2,2′-bipyridine]-5,5′-

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dicarboxylate **5** (2.13 g, 6.5 mmol, 65% yield). Characterization data is consistent with previous studies.[16] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (t, *J* = 7.2 Hz, 6H), 2.74 (s, 6H), 4.30 (q, *J* = 7.2 Hz, 4H), 7.16 (d, *J* = 8.4 Hz, 2H), 8.08 (d, *J* = 8.4 Hz, 2H).

To a round-bottom flask was added dimethyl 6,6′-dimethyl-[2,2′-bipyridine]-5,5′-dicarboxylate **5** (2.0 g, 6.1 mmol, 1 equiv), KOH (3.43 g, 61.0 mmol, 10.0 equiv), water (70 mL) and EtOH (70 mL). The mixture was heated at 100 °C for 16 hours. The reaction was allowed to cool to room temperature and then made acidic with 1M HCl. The resultant precipitate was filtered and washed three times with ether (50 mL), and dried to give 6,6′-dimethyl-[2,2′-bipyridine]-5,5′-dicarboxylic acid **6** (1.61 g, 5.90 mmol, 98% yield). Characterization data is consistent with previous studies.[16] ^{1}H NMR (400 MHz, d_6-DMSO): δ 2.83 (s, 6H), 8.33-8.37 (m, 4H).

Synthesis of 4,4′-dimethyl-[2,2′-bipyridine]-5,5′-dicarboxylic acid

6-amino-4-methylnicotinic acid (8)

Prepared according to a literature procedure.[17] To a 250 mL round-bottom flask, Copper (I) cyanide (28.8 g, 321 mmol, 3.00 equiv) was added to a solution of 5-bromo-4-methylpyridin-2-amine **7** (20.0 g, 107 mmol, 1.00 equiv) in DMA 120 mL and the reaction was stirred under N_2, at 170 °C for 14 hours. After cooling to room temperature, the reaction mixture was added to a solution of ethylenediamine (60 mL) and water (240 mL) and stirred for 15 minutes. The mixture was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, filtered and concentrated to give 6-amino-4-methylnicotinonitrile (11.0 g, 82.6 mmol, 77% yield). The crude product was used in the next step. Characterization data is consistent with previous reports.[51] ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H), 4.99 (br s, 2H), 6.37, (s, 1H), 8.27 (s, 1H).

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In a 500 mL round-bottom flask, 6-amino-4-methylnicotinonitrile (11.0 g, 82.6 mmol, 1.00 equiv) was suspended in a 4M aqueous NaOH solution. The reaction mixture was heated to 100 °C for 6 hours. The mixture was cooled to room temperature and made acidic with 6M HCl. The precipitate was filtered and washed with water and dried to give 6-amino-4-methylnicotinic acid **8** (11.5 g, 75.6 mmol, 91% yield. Characterization data is consistent with previous reports.[51] ^{1}H NMR (400 MHz, d_6-DMSO): δ 2.37 (s, 3H), 6.25 (s, 1H), 6.59 (br s, 2H), 8.45 (s, 1H).

Methyl 6-hydroxy-4-methylnicotinate (9)

Prepared according to a literature procedure.[14] To a heterogeneous mixture of 6-amino-4-methylnicotinic acid **8** (12.7g, 83.5 mmol, 1.00 equiv) in methanol (250 mL) was added thionyl chloride (7.6 mL, 104 mmol, 1.25 equiv). The mixture was refluxed for 14 hours, cooled to room temperature, and the solvent was removed under reduced pressure. The resulting solid was dissolved in water and the pH adjusted to 13 with 1M aqueous NaOH the resulting solid was collected by vacuum filtration, rinsed with water and air dried to give methyl 6-amino-4-methylnicotinate (9.20g, 55.4 mmol, 66% yield). Characterization data is consistent with previous reports.[14] ^{1}H NMR (400 MHz, d_6-DMSO): δ 2.37 (s, 3H), 3.73 (s, 3H), 6.26 (s, 1H), 6.64 (br s, 2H), 8.45 (s, 1H).

Prepared according to a literature procedure.[14] To an ice cold 15% aqueous sulfuric acid (180 mL) was added methyl 6-amino-4-methylnicotinate (9.20 g, 55.4 mmol, 1.00 equiv) followed by portionwise addition of sodium nitrite (7.66 g, 111 mmol, 2.00 equiv). The reaction mixture was stirred at 0 °C for 2 hours and the resulting solid was collected by vacuum filtration, rinsed sequentially with water (100 mL) and diethyl ether (100 mL) and dried to give methyl 6-hydroxy-4-methylnicotinate **9** (5.21 g, 31.2

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mmol, 56% yield). Characterization data is consistent with previous reports.[14] ^{1}H NMR (400 MHz, d_6-DMSO): δ 2.35 (s, 3H), 3.73 (s, 3H), 6.21 (s, 1H), 8.00 (s, 1H).

Methyl 6-chloro-4-methylnicotinate (10)

Prepared according to a literature procedure.[14] To a suspension of methyl 6-hydroxy-4-methylnicotinate **9** (5.1 g, 30.5 mmol, 1.00 equiv) was added phosphorous oxychloride (20 mL). The mixture was heated 50 128 °C for 4 hours, cooled to room temperature and poured onto ice water. The mixture was neutralized with aqueous 3M NaOH, extracted with dichloromethane, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give methyl 6-chloro-4-methylnicotinate **10** (4.47 g, 24.1 mmol, 79% yield). Characterization data is consistent with previous reports.[14] ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.61 (s, 3H), 3.93 (s, 3H), 7.24 (s, 1H), 8.86 (s, 1H).

Dimethyl 4,4′-dimethyl-[2,2′-bipyridine]-5,5′-dicarboxylate (11)

Adapted from a literature procedure,[12] a 250 mL round-bottom flask was charged with $NiCl_2{\cdot}6H_2O$ (2.82 g, 11.9 mmol, 0.50 equiv), and DMF (48 mL). The resulting solution was stirred and heated to 40 °C, and methyl-6-chloro-4-methylnicotinate **10** (4.40 g, 23.7 mmol, 1.00 equiv), anhydrous LiCl, (1.00 g, 23.7 mmol, 1.00 equiv), and zinc dust (3.88 g, 59.3 mmol, 2.50 equiv) were added. When the temperature rose to 50 °C, a grain of iodine crystal and two drops of acetic acid were added to the mixture. The mixture was stirred at 60 °C for 16 hours. The reaction was cooled to room temperature and 10% HCl added (25 mL), the resulting mixture was made alkaline with 25% aqueous ammonia and extracted with DCM. The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by flash chromatography to give dimethyl 4,4′-dimethyl-[2,2′-bipyridine]-

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5,5′-dicarboxylate **11** (1.05 g, 3.5 mmol, 30% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.73 (s, 6H), 3.97 (s, 6H), 8.36 (s, 2H), 9.14 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.6, 157.2, 151.5, 150.8, 126.1, 124.4, 52.3, 21.6.

4,4′-dimethyl-[2,2′-bipyridine]-5,5′-dicarboxylic acid (12)

To a round-bottom flask was added dimethyl 4,4′-dimethyl-[2,2′-bipyridine]-5,5′-dicarboxylate **11** (1.05 g, 3.50 mmol, 1 equiv), NaOH (0.140 g, 35.0 mmol, 10.0 equiv), water (6 mL) and EtOH (6 mL). The mixture was heated at 100 °C for 16 hours. The reaction was allowed to cool to room temperature and then made acidic with 1M HCl. The resultant precipitate was filtered and washed with 50 mL ether (3x), and dried to give 4,4′-dimethyl-[2,2′-bipyridine]-5,5′-dicarboxylic acid **12** (0.952 g, 3.5 mmol, 99% yield). ^{1}H NMR (400 MHz, d_6-DMSO): δ 2.66 (s, 6H), 8.37 (s, 2H), 9.04 (s, 2H), 13.4 (s, 2H). ^{13}C NMR (150 MHz, d_6DMSO): δ 167.0, 156.0, 150.8, 149.7, 126.9, 123.4, 20.8.

Synthesis of 4,4′-dimethoxy-[2,2′-bipyridine]-5,5′-dicarboxylic acid (16)

methyl 6-chloro-4-methoxynicotinate (14)

To a suspension of NaH (2.14g, 53.4 mmol, 1.1 equiv) in THF (80 mL) was added MeOH (2.16 mL, 53.4 mmol, 1.1 equiv) at 0 °C under N_2 in 250 mL two-necked flask. After 20 minutes, methyl 4,6-dichloronicotinate **13** (10.0 g, 48.5 mmol, 1.0 equiv) in THF (20 mL) was added dropwise to the solution, and then the mixture was warmed to room temperature. After the mixture was stirred for 4 h, water was added. The mixture was extracted with CH_2Cl_2 three times and the combined organic layer was washed with brine and dried over $MgSO_4$. After removal of solvent under reduced pressure, the residue was purified by silica-gel chromatography to give methyl 6-chloro-4-methoxynicotinate **14** as a white solid (5.20 g, 25.7 mmol, 1.0 equiv). Characterization

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data is consistent with previous reports.[18] ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.90 (s, 3H), 3.97 (s, 3H), 6.92 (s, 1H), 8.71 (s, 1H).

Dimethyl 4,4′-dimethoxy-[2,2′-bipyridine]-5,5′-dicarboxylate (15)

Adapted from a literature procedure,[12] a 250 mL round-bottom flask was charged with $NiCl_2 \cdot 6H_2O$ (0.366 g, 1.54 mmol, 0.10 equiv), and DMF (92 mL). The resulting solution was stirred and heated to 40 °C, and methyl 6-chloro-4-methoxynicotinate **14** (3.11 g, 15.4 mmol, 1.00 equiv), anhydrous LiCl, (0.653 g, 15.4 mmol, 1.00 equiv), and zinc dust (1.21 g, 18.5 mmol, 1.2 equiv) were added. When the temperature rose to 50 °C, a grain of iodine crystal and two drops of acetic acid were added to the mixture. The mixture was stirred at 60 °C for 16 hours. The reaction was cooled to room temperature and 10% HCl added (25 mL), the resulting mixture was made alkaline with 25% aqueous ammonia and extracted with DCM. The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by flash chromatography to give dimethyl 4,4′-dimethoxy-[2,2′-bipyridine]-5,5′-dicarboxylate **15** (0.864 g, 2.6 mmol, 34% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.95 (s, 6H), 4.11 (s, 6H), 8.18 (s, 2H), 8.98 (s, 2H).

4,4′-dimethoxy-[2,2′-bipyridine]-5,5′-dicarboxylic acid (16)

To a round-bottom flask was added dimethyl 4,4′-dimethoxy-[2,2′-bipyridine]-5,5′-dicarboxylate **15** (0.930 g, 2.80 mmol, 1 equiv), KOH (1.57 g, 28.0 mmol, 10.0 equiv), water (33 mL) and EtOH (33 mL). The mixture was heated at 100 °C for 16 hours. The reaction was allowed to cool to room temperature and then made acidic with 1M HCl. The resultant precipitate was filtered and washed with 50 mL ether (3x), and dried to give 4,4′-dimethoxy-[2,2′-bipyridine]-5,5′-dicarboxylic acid **16** (0.672 g, 2.21

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mmol, 79% yield). ^{1}H NMR (400 MHz, d_6-DMSO): δ 3.35 (s, 6H), 8.15 (s, 2H), 8.85 (s, 2H).

Synthesis of 4,4′-bistrifluoromethyl-[2,2′-bipyridine]-5,5′-dicarboxylic acid (21)

2,5-dichloro-4-iodopyridine (18)

To a 500 mL round-bottom flask was added diisopropyl amine (10.5 mL, 74.3 mmol, 1.1 equiv) and THF (30 mL). This solution was cooled -78 °C for 15 minutes and n-butyl lithium was added (34 mL, 67.5 mmol, 1.0 equiv). The reaction was stirred at -78 °C for 30 minutes and a solution of 2,5-dichloropyridine **17** (10g, 67.5 mmol, 1.0 equiv) in THF (40 mL) was added over 5 minutes and the reaction stirred for 1 hour. A solution of iodine (18.9 g, 74.3 mmol, 1.1 equiv) in THF (80 mL) was added dropwise over the course of 30 minutes and the reaction stirred for 2 additional hours at -78 °C. The reaction mixture was quenched with water (40 mL) and extracted three times with dichloromethane. The combined organics were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography to give 2,5-dichloro-4-iodopyridine **18** as a white solid (12.6 g, 45.9 mmol, 68% yield). ^{1}H NMR (400 mHz, $CDCl_3$): δ 7.85 (s, 1H), 8.34 (s, 1H).

2,5-dichloropyridine-4-trifluoromethylpridine (19)

Prior to use in this reaction potassium fluoride and copper (I) iodide were flame dried under vacuum for 30 minutes and stored in an air- and moisture-free glovebox. To a 50 mL round-bottom flask, in a glove box, was added potassium fluoride (234 mg, 4.02 mmol, 1.1 equiv), copper (I) iodide (766 mg, 4.02 mmol, 1.1 equiv) and trifluoromethyl(trimethyl)silane (572 mg, 4.02 mmol, 1.1 equiv). The flask was removed from the glovebox, NMP (4 mL) was added, and the reaction stirred at 50 °C for 30

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minutes. A solution of 2,5-dichloro-4-iodopyridine **18** in NMP (4 mL) was added and the reaction stirred at 50 °C overnight. The reaction mixture was diluted with ethyl acetate (50 mL) washed with aqueous ammonia (10 mL), water (10 mL) and brine (10 mL). The volatile organics were removed under reduced pressure and the yield of the reaction was determined by ^{1}H NMR using dibromomethane as an internal standard. ^{1}H NMR (400 mHz, $CDCl_3$): δ 7.62 (s, 1H), 8.55 (s, 1H).

Synthesis of 2,2′-bipyridine-5,5′-dicarboxylic acid (22)

Prepared according to a literature procedure.[19] 5,5′-dimethyl-2,2′-bipyridine (5.75 g, 27.1 mmol, 1.00 equiv) and potassium permanganate (29.2 g, 185 mmol, 6.80 equiv) were added to 300 mL of water. The resulting mixture was heated to 100 °C with stirring for 18 hours. After the mixture cooled to room temperature, a brown precipitate was removed by filtration and the filtrate was extracted with 100 mL diethyl ether (3x). The resulting aqueous solution was acidified to pH = 2 with 1M HCl, which led to the formation of a white precipitate. The precipitate was collected by vacuum filtration, washed with diethyl ether (100 mL) and dried to give 2,2′-bipyridine-5,5′-dicarboxylic acid **22** (4.03 g, 19.0 mmol, 70%). Characterization data is consistent with previous reports.[19] ^{1}H NMR (600 MHz, d_6-DMSO): δ 8.45 (d, J = 8.4 Hz, 2H), 8.57 (d, J = 8.4 Hz, 2H), 9.20 (s, 2H).

General Procedure for the Synthesis of Mixed-Linker MOFs.

The m-MOFs were synthesized and purified according to a modified version of a procedure reported by Cohen et al.[6c] $ZrCl_4$ (24.5 mg, 0.105 mmol 2.0 equiv), glacial acetic acid (189 mg, 3.15 mmol, 60 equiv), biphenyl-4,4′-dicarboxylic acid (H_2bpdc) (0.053 mmol, 1.0 equiv), and H_2-bpydc, H_2-6,6′Me_2-bpydc, or H_2-4,4′Me_2-bpydc (0.053

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mmol, 1.0 equiv) were placed in a scintillation vial with 4 mL of *N*,*N*′-dimethylformamide. The reagents were dispersed via sonication for 10 min, followed by incubation in an oven at 120 °C for 24 hours. The solid MOFs were washed with DMF three times, followed by soaking in methanol for 3 days. The MOFs were collected via centrifugation and activated at 150 °C under vacuum (30 mTorr) for 12 hours.

General Procedure for the Synthesis of m-MOF-$PdCl_2$.

100 mg of m-MOFs was dispersed in 5 mL of acetonitrile. After sonication for 10 min, an acetonitrile solution of $PdCl_2(CH_3CN)_2$ (9.2 mg $PdCl_2(CH_3CN)_2$ in 3 mL CH_3CN) was added to the MOF solution, and mixture was incubated at 65 °C for 24 hours. After 24 hours, the solid was isolated by centrifugation and washed three times with acetonitrile (5 mL). The solids were suspended in methanol for 3 days, and the methanol (5 mL) was exchanged every 24 hours. After 3 days, the solids were collected via centrifugation and dried at 80 °C under vacuum for further use.

Quantitative analysis of linkers by ^{1}H NMR.

m-MOFs samples (10 mg) were dried under vacuum and digested with sonication in 570 μL DMSO-d_6 and 30 μL of 40% HF to perform ^{1}H NMR analysis of the linkers.

General Procedure for Suzuki-Miyaura Cross-Coupling of Iodobenzene and Phenylboronic Acid Catalyzed by m-MOF-$PdCl_2$.

The Suzuki-Miyaura cross-coupling was carried out in Argon atmosphere. Iodobenzene (20 mg, 0.100 mmol, 1.0 equiv), phenylboronic acid (13 mg, 0.110 mmol, 1.1 equiv), K_2CO_3 (21 mg, 0.150 mmol, 1.5 equiv), m-MOF-$PdCl_2$ (.002 mmol, 0.015 equiv) and mesitylene (8 mg, 0.067 mmol, 0.67 equiv) were added to a 20 mL vial containing 2 mL of toluene. The vial was incubated in an oil bath which was preheated to

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85 °C. Upon the completion of reaction, the product was separated from the m-MOF-$PdCl_2$ via centrifugation and the yield was determined using gas chromatography.

Suzuki-Miyaura Cross-Coupling of Iodobenzene and 4-methylphenylboronic Acid Catalyzed by m-6,6′-Me_2-bpy-MOF-$PdCl_2$.

The Suzuki-Miyaura cross-coupling was carried out in Argon atmosphere. Iodobenzene (20 mg, 0.100 mmol, 1.0 equiv), 4-methylphenylboronic acid (14 mg, 0.110 mmol, 1.1 equiv), K_2CO_3 (21 mg, 0.150 mmol, 1.5 equiv), m-6,6′-Me_2-bpy-MOF-$PdCl_2$ (.002 mmol, 0.015 equiv) and mesitylene (8 mg, 0.067 mmol, 0.67 equiv) were added to a 20 mL vial containing 2 mL of toluene. The vial was incubated in an oil bath which was preheated to 85 °C. Upon the completion of reaction (reaction time = 12 hours), the product was separated from the m-MOF-$PdCl_2$ via centrifugation and the yield was determined using gas chromatography, no homocoupling products were observed.

Recycling Studies for Suzuki-Miyaura Cross-Coupling Iodobenzene and Phenylboronic Acids Catalyzed by m-6,6′-Me_2-bpy-MOF-$PdCl_2$

The Suzuki-Miyaura cross-coupling was carried out in Argon atmosphere. Iodobenzene (20 mg, 0.100 mmol, 1.0 equiv), phenylboronic acid (13 mg, 0.110 mmol, 1.1 equiv), K_2CO_3 (21 mg, 0.150 mmol, 1.5 equiv), m-MOF-$PdCl_2$ (.002 mmol, 0.015 equiv) and mesitylene (8 mg, 0.067 mmol, 0.67 equiv) were added to a 20 mL vial containing 2 mL of toluene. The vial was incubated in an oil bath which was preheated to 85 °C. Upon the completion of reaction (reaction time = 6 hours), the product was separated from the m-MOF-$PdCl_2$ via centrifugation and the yield was determined using gas chromatography. The m-6,6′-Me_2bpy-MOF-$PdCl_2$ was washed with dilute HCl (pH =

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1) to remove the undissolved K_2CO_3 and then washed three times with methanol. Finally, the m-6,6′-Me_2bpy-MOF-$PdCl_2$ were dried in vacuum at 80 °C and reused under the identical reaction conditions in the next run.

Leaching Test for Suzuki-Miyaura Cross-Coupling of Iodobenzene and Phenylboronic Acid Catalyzed by m-6,6′-Me_2-bpy-MOF-$PdCl_2$

The Suzuki-Miyaura cross-coupling was carried out in Argon atmosphere. Iodobenzene (20 mg, 0.100 mmol, 1.0 equiv), phenylboronic acid (13 mg, 0.110 mmol, 1.1 equiv), K_2CO_3 (21 mg, 0.150 mmol, 1.5 equiv), m-MOF-$PdCl_2$ (.002 mmol, 0.015 equiv) and mesitylene (8 mg, 0.067 mmol, 0.67 equiv) were added to a 20 mL vial containing 2 mL of toluene. The vial was incubated in an oil bath which was preheated to 85 °C. After three hours the m-6,6′-Me_2bpy-MOF-$PdCl_2$ was separated from the hot solution. The reaction was continued with the filtrate in the absence of solid catalyst for an additional 4 hours. No further increase in the conversion of iodobenzene was observed, which indicates that the catalytically active sites for cross coupling reaction are contained in or on the solid catalyst.

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CHAPTER 5 – PALLADIUM-CATALYZED SYNTHESIS OF *N-TERT*-PRENYLINDOLES

Modified from a paper published in *Organic Letters*

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Abstract

We report three distinct protocols for the synthesis of *N-tert*-prenylindoles using indole, (η^6-indole)$Cr(CO)_3$, and indoline nucleophiles in the presence of the same palladium catalyst. These reactions form *N-tert*-prenylindole products with a broad range of substitution and electronic character in high yields (up to 94%) with high *tert*-prenyl-to-*n*-prenyl selectivity (up to 12:1).

Introduction

Prenylated indoles are found in structurally diverse fungal, plant and bacterial natural products[1] and have been the focus of many recent synthetic[2] and biosynthetic studies.[3] The diversity of these natural products stems from nature's ability to incorporate the prenyl group throughout the indole core as either an *n*-prenyl (prenyl) or *tert*-prenyl (reverse prenyl) moiety. Synthetic chemists have developed a variety of methods to prepare both prenylated and *tert*-prenylated indoles that exhibit promising medicinal properties.[1-3] Despite these efforts, the synthetic methodology necessary to access certain classes of *tert*-prenylated indoles remains underdeveloped.

N-tert-Prenylated indoles (Figure 1) are a class of prenylated indoles in which prenyl group is linked to the indole core through a carbon-nitrogen bond. *N-tert*-

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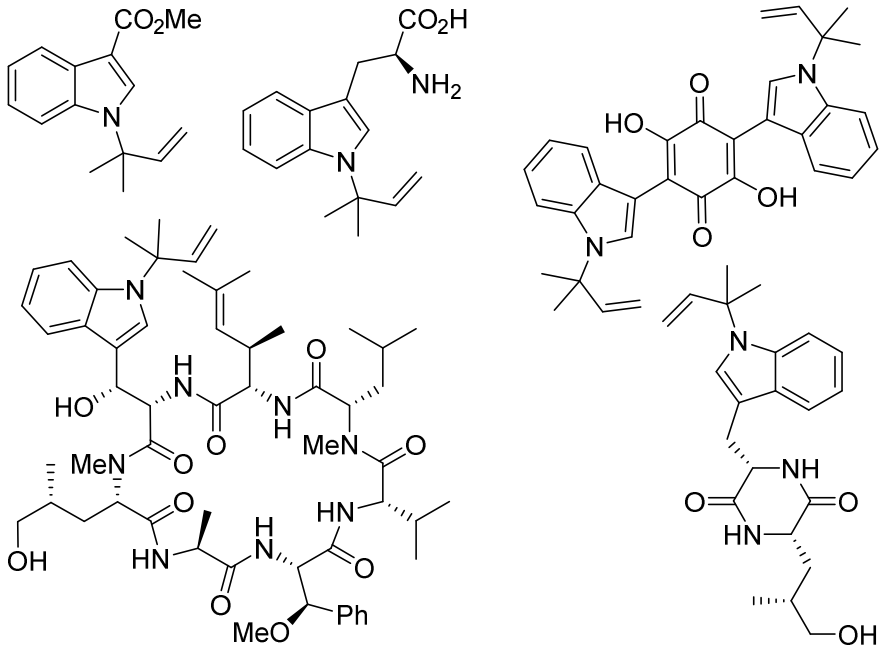
Prenylated indoles and analogs containing oxidized prenyl moieties exhibit an array of medicinal properties including activation of insulin receptors, cytotoxicity toward cancer cell lines, as we all as anti-inflammatory, antimycobacterial, and antifungal activities.[4]

Figure 1. Examples of *N-tert*-Prenylindole Natural Products



Current synthetic routes to *N-tert*-prenylated indoles involve 1) multiple non-strategic redox steps, 2) the use of pre-functionalized starting materials, or 3) high loadings of a precious metal catalyst and metal co-oxidants (Scheme 1). The traditional, four-step synthetic sequence to generate *N-tert*-prenylated indoles includes reduction of the indole to an indoline, Cu(I)-catalyzed propargylic substitution, partial reduction of the alkyne to an alkene, and oxidation of the *N-tert*-prenylated indoline to the corresponding indole (Route A).[5] In 2007, Willis and co-workers reported a tandem Pd-catalyzed synthesis of *N-tert*-prenylated indoles from 2-methyl-3-butene-2-amine and 2-bromo-β-chlorostyrenes by a sequence involving amination of an aryl bromide followed by amination of a vinyl chloride (Route B).[6] In 2011, Nishikawa and co-workers reported by

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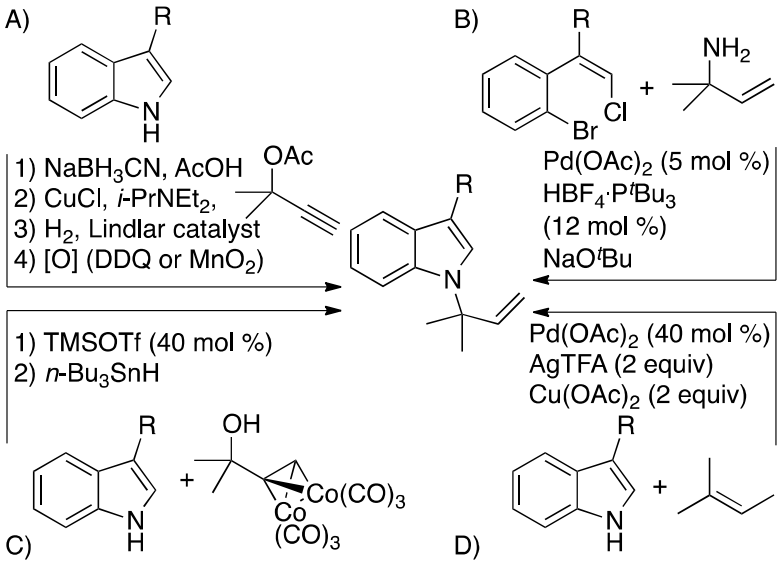
N-tert-prenylation of methyl indole-3-acetate by alkylation with the dicobalthexacarbonyl complex of 2-methyl-3-butyn-2-ol in the presence of TMSOTf, followed by reduction and decomplexation with *n*-Bu_3SnH (Route C).[7]

To date, only one direct *N-tert*-prenylation of indoles has been reported. In 2009, Baran and co-workers reported a direct synthesis of *N-tert*-prenylated indoles by Pd-mediated C-H functionalization of 2-methyl-2-butene with indoles (route D).[8] The direct C-H functionalization of 2-methyl-2-butene enables the synthesis of *N-tert*-prenylated indoles from a broad array of readily accessible indoles, but the synthetic utility and practicality of this strategy remains limited because high loadings of the palladium catalyst (20-40 mol %) and a silver co-oxidant (2.0-2.5 equiv) are required.

Scheme 1. Strategies to Form *N-tert*-Prenylated Indoles



At the outset of this project, we sought to develop strategies to form *N-tert*-prenylindoles with a range of electronic properties that minimize the number of non-strategic redox steps and employ practical loadings of catalyst precursors. We reported syntheses of *N-tert*-prenylated indoles by a palladium-catalyzed allylic alkylation

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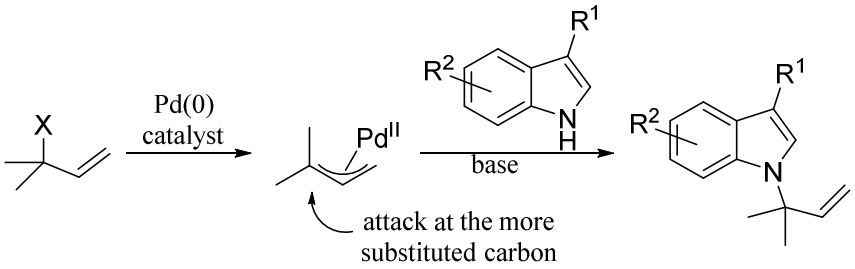
approach (eq 1).[9] Three distinct protocols for the synthesis of *N-tert*-prenylindoles are described, using indole, (η^6-indole)$Cr(CO)_3$, and indoline nucleophiles in the presence of the same palladium catalyst prepared *in situ* from readily available precursors. These reactions require loadings of the palladium catalyst that are up to ten times less than required for previously reported direct *N-tert*-prenylations of indoles.



(eq 1)

Results and Discussion

To establish the viability of our allylic substitution approach, we conducted reactions of *tert*-butyl (2-methylbut-3-en-2-yl) carbonate with indole-3-carboxaldehyde in the presence of Cs_2CO_3 and catalysts generated from a variety of Pd precursors, bisphosphine ligands and solvents. We found that palladium complexes of bisphosphine ligands with wide natural bite angles catalyze the *N*-prenylation of indole-3-carboxaldehyde **1a** with high *tert*-prenyl:*n*-prenyl selectivity (9:1 to 13:1) (Table 1, entries 1-5). Palladium complexes of Xantphos catalyzed the *N*-prenylation of indole-3-carboxaldehyde **1a** with the highest combination of yield and selectivity (68% yield, 13:1, Table 1, entry 5). The reaction of **1a** with *tert*-butyl (2-methylbut-3-en-2-yl) carbonate **2** in the presence of a catalyst generated from various palladium sources and Xantphos occurred with good yield and selectivity (Table 1, entries 5-7). Despite reactions using [Pd(η^3-allyl)Cl]$_2$ as the palladium source generating *N-tert*-prenylindole **3a** in the highest yield and selectivity (68% yield, 13:1, Table 1, entry 5), [Pd(η^3-

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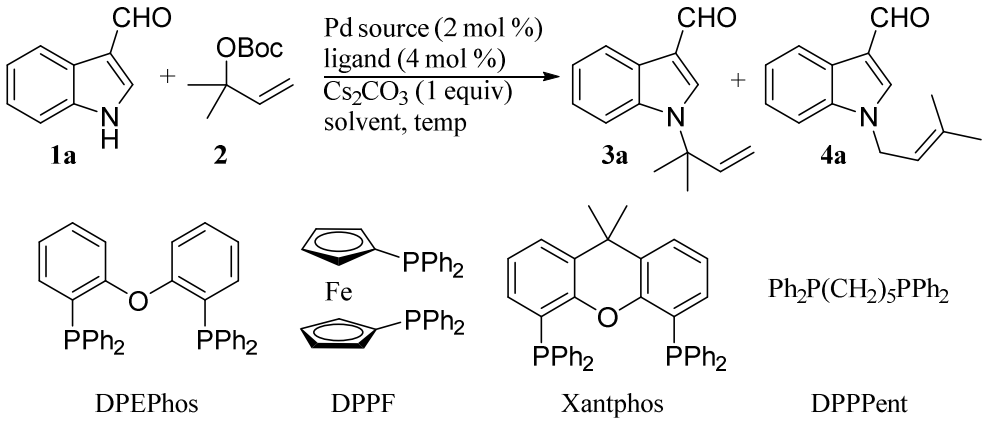
prenyl)Cl]$_2$ was chosen as the palladium source for further experiments as a practical means of avoiding a challenging separation of **3a** from the small amount of corresponding *N*-allylated product formed when [Pd(η^3-allyl)Cl]$_2$ was used as the palladium source (62% yield, 9:1, Table 1, entry 7). Reactions conducted in the presence of benzonitrile formed **3a** in slightly increased yield and selectivity (69% yield, 10:1, Table 1, Entry 8), however difficulty removing benzonitrile from the reaction mixture (b.p. = 189 °C)

Table 1. Study of reaction conditions for the *N-tert*-prenylation of 1a with 2.[a]



entry	equiv **2**	ligand	Pd source (mol %)	solvent	temp. (° C)	yield (%)[b]	**3a**:**4a**
1	1.00	DPPF	[Pd(η^3-allyl)Cl]$_2$ (2)	CH_2Cl_2	rt	59	9:1
2	1.00	DPEPhos	[Pd(η^3-allyl)Cl]$_2$ (2)	CH_2Cl_2	rt	53	10:1
3	1.00	DPPPent	[Pd(η^3-allyl)Cl]$_2$ (2)	CH_2Cl_2	rt	58	11:1
4	1.00	*rac*-BINAP	[Pd(η^3-allyl)Cl]$_2$ (2)	CH_2Cl_2	rt	52	9:1
5	1.00	Xantphos	[Pd(η^3-allyl)Cl]$_2$ (2)	CH_2Cl_2	rt	68	13:1
6	1.00	Xantphos	$Pd_2(dba)_3$ (2)	CH_2Cl_2	rt	58	8:1
7	1.00	Xantphos	[Pd(η^3-prenyl)Cl]$_2$ (2)	CH_2Cl_2	rt	62	9:1
8	1.00	Xantphos	[Pd(η^3-prenyl)Cl]$_2$ (2)	PhCN	rt	69	10:1
9	1.00	Xantphos	[Pd(η^3-prenyl)Cl]$_2$ (2)	MeCN	rt	61	8:1
10	1.50	Xantphos	[Pd(η^3-prenyl)Cl]$_2$ (2)	CH_2Cl_2	rt	88	10:1
11	2.00	Xantphos	[Pd(η^3-prenyl)Cl]$_2$ (2)	CH_2Cl_2	rt	99	10:1
12	2.00	Xantphos	[Pd(η^3-prenyl)Cl]$_2$ (2)	CH_2Cl_2	0	99 (76)[c]	12:1

[a] Reaction conditions: indole-3-carboxaldehyde **1a** (0.500 mmol), Cs_2CO_3 (0.500 mmol), ligand (0.020 mmol), Pd source (0.010 mmol), *tert*-butyl (2-methylbut-3-en-2-yl) carbonate **2** (0.500-1.00 mmol), solvent (2.5 mL). [b] Determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [c] Isolated yield of **3a**.

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made it impractical to use in further reactions. Performing theses reactions in acetonitrile led to yields and selectivities that were lower than observed when dichloromethane was used (61% yield, 8:1, compare Table 1, entries 7 and 9). Increasing the loading of **2** in the reaction mixture to two equivalents helped drive the reaction to completion (99% yield, 10:1, Table 1, Entry 11) and the selectivity could be further increased by lowering the reaction temperature from room temperature to 0 °C (99% yield, 12:1, Table 1, Entry 12).

We then evaluated these conditions for palladium-catalyzed *N*-*tert*-prenylation in reactions of a series of indoles containing electron-withdrawing groups at either the 3-position or the 5-position with carbonate **2**. The data from these experiments are summarized in Table 2. As shown in entries 1-4 in Table 2, 3-substituted indoles **1a**-**1d** (R^1 = CHO, C(O)Me, CO_2Me, or CN) reacted with carbonate **2** to form *N*-*tert*-prenylindoles **3a**-**3d** in good-to-excellent yield with 10:1 or greater regioselectivity (**3**:**4**). *N*-*tert*-Prenylindoles **3a** and **3b** were isolated in 76% and 65% yield as single constitutional isomers. In contrast, *N*-*tert*-prenylindoles **3c** and **3d** were not readily seperable from the *N*-*n*-prenyl isomers **4c** and **4d**. These products were isolated as 12:1 mixtures of the *N*-*tert*-prenylindole and *N*-*n*-prenyl isomers.

The presence of electron-withdrawing substitution at the 3-position of the indole core is not a strict requirement under our reaction conditions. Reactions of 5-cyanoindole **1e** and 5-nitroindole **1f** with carbonate **2** occurred to form mixtures of *N*-prenylindole products **3e**-**3f** and **4e**-**4f** in 40% and 62% yield with 7:1 *tert*-prenyl:*n*-prenyl selectivity (Table 2, entries 5 and 6). However, reactions of indoles lacking electron-withdrawing substituents and reactions of 2-substituted indoles did not form *N*-prenylindole products.

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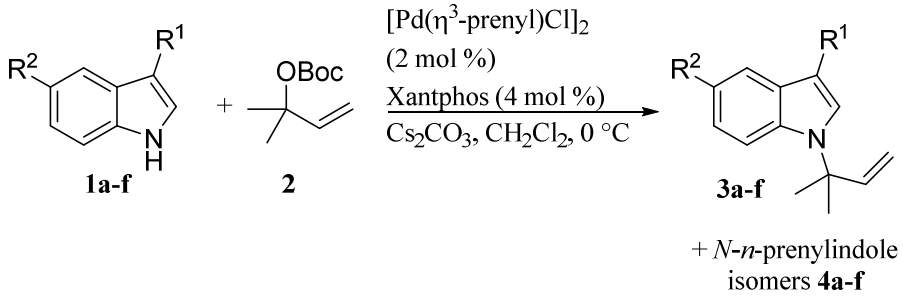
The disparate reactivity of indoles with and without electron-withdrawing susbstituents suggested that indolate anions of the electron-deficient indoles were primarily responsible for nucleophilic attack on a prenylpalladium(II) intermediate. Thus, the difference in relative acidity of the indole N-H is likely responsible for the difference in reactivity between more acidic, electron deficient indoles and less acidic, electron-rich indoles.[10] Since η^6-coordination of metal carbonyl complexes to arenes is known to increase the acidity of benzylic C-H bonds,[11] we hypothesized that η^6-coordination of a metal carbonyl complex to the indole core would similarly increase the acidity of the indole N-H bond by reducing the electron density in the indole π-system.

Table 2. Scope of Pd-Catalyzed *N-tert*-Prenylation of Indoles[a]



Entry	**1**	R^1	R^2	**3**	Yield **3** + **4** (%)[b]	**3**:**4**[c]
1	**1a**	CHO	H	**3a**	76[d]	12:1
2	**1b**	C(O)Me	H	**3b**	65[d]	10:1
3	**1c**	CO_2Me	H	**3c**	90	12:1
4	**1d**	CN	H	**3d**	94	12:1
5[e]	**1e**	H	CN	**3e**	40	7:1
6[e]	**1f**	H	NO_2	**3f**	62	7:1

[a] Reaction conditions: Indole **1a-f** (0.500 mmol), Cs_2CO_3 (0.500 mmol), Xantphos (0.020 mmol), [Pd(η^3-prenyl)Cl]$_2$ (0.010 mmol), *tert*-butyl (2-methylbut-3-en-2-yl) carbonate **2** (1.00 mmol), CH_2Cl_2 (2.5 mL), 0 °C, 2-6 h. [b] Isolated yields of **3** + **4**. [c] Determined by ^{1}H NMR spectroscopy. [d] Isolated yields of **3**. [e] Reactions run at room temperature

We prepared a series of (η^6-indole)Cr(CO)$_3$ complexes of electron-rich indoles and evaluated their reactivity as nucleophiles in Pd-catalyzed prenylation reactions. Reactions of (η^6-indole)Cr(CO)$_3$ complexes of indoles **5a**-**g** with carbonate **2** are

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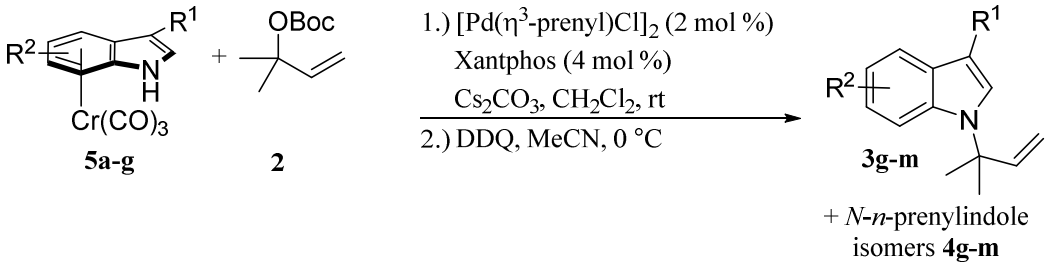
summarized in Table 3. As shown in entries 1-3 in Table 3, (η^6-indole)$Cr(CO)_3$ complexes prepared from indole, 3-methylindole and methylindole-3-acetate (**5a**-**c**) reacted with carbonate **2** to form *N*-*tert*-prenylindoles **3g**-**i** after oxidative decomplexation with DDQ. These one-pot, two-step transformations gave the *N*-*tert*-prenylindoles **3g**-**i** and *N*-*n*-prenylindoles **4g**-**i** in 62-86% yield with 6:1 to 9:1 *tert*-prenyl:*n*-prenyl selectivity. Reactions of (η^6-indole)$Cr(CO)_3$ complexes prepared from 4-MeO, 5-MeO and 6-MeO-indole also occurred in moderate to good yields with high *tert*-prenyl:*n*-prenyl selectivities (Table 3, entries 4-6). The reactions of (η^6-indole)$Cr(CO)_3$ complexes **5d**-**f** with **2** and subsequent decomplexation formed *N*-*tert*-prenylindoles **3j**-**l** and *N*-*n*-prenylindoles **4j**-**l** in 51-78% yield and 7-8:1 1 *tert*-prenyl:*n*-prenyl selectivity.

Table 3. Scope of Pd-Catalyzed *N*-*tert*-Prenylation of (η^6-indole)$Cr(CO)_3$ Complexes[a]



Entry	**5**	R^1	R^2	**3**	Yield **3** + **4** (%)[b]	**3**:**4**[c]
1	**5a**	H	H	**3g**	86	8:1
2	**5b**	Me	H	**3h**	75	8:1
3	**5c**	CH_2CO_2Me	H	**3i**	78	9:1
4	**5d**	H	4-MeO	**3j**	78	7:1
5	**5e**	H	5-MeO	**3k**	51	8:1
6	**5f**	H	6-MeO	**3l**	72	7:1
7	**5g**	H	7-MeO	**m**	46	<1:20

[a] Reaction conditions: 1) (η^6-indole)$Cr(CO)_3$ complex **5a**-**g** (0.250 mmol), Cs_2CO_3 (0.250 mmol), Xantphos (0.010 mmol) [Pd(η^3-prenyl)Cl]$_2$ (0.005 mmol), *tert*-butyl (2-methylbut-3-en-2-yl) carbonate **2** (0.500 mmol), CH_2Cl_2 (2.5 mL), room temperature, 2-6 h. 2) DDQ (0.750 mmol), CH_3CN (3 mL), 0 °C, 2-6 h. [b] Isolated yield of **3** + **4**. [c] Determined by ^{1}H NMR spectroscopy

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In contrast, the prenylation of (η^6-7-MeO-indole)$Cr(CO)_3$ **5g** with **2** occurred with >20:1 selectivity favoring the *N*-*n*-prenylindole isomer **4m** (entry 7).

The synthesis of *N*-*tert*-prenylindoles from electron-rich indole precursors is enabled by the markedly different electronic properties of the corresponding (η^6-indole)$Cr(CO)_3$ complexes. The utility of these complexes is, however, inherently limited by the need for stoichiometric quantities of chromium. In addition, the synthesis of (η^6-indole)$Cr(CO)_3$ complexes from indoles containing even weakly deactivating groups is challenging. For example, standard procedures for synthesis of (η^6-indole)$Cr(CO)_3$ complexes formed (η^6-5-bromoindole)$Cr(CO)_3$ in less than 5% yield.

We conducted the reactions of indolines with carbonate **2** under the assumption that the increased nucleophilicity of the indoline nitrogen would enable us to synthesize *N*-*tert*-prenylindoles with a greater range of electronic character after oxidation (Table 4).[12] Indoline, 3-methylindoline, methyl indoline-3-acetate, and 3-phenylindoline react with carbonate **2** to form **3g**-**i** and **3n** after oxidation of the intermediate *N*-*tert*-prenylindolines with MnO_2 (Table 4, entries 1-4). The reactions occur with 5-6:1 *tert*-prenyl:*n*-prenyl selectivity, and the *N*-*tert*-prenylindoles are readily separated. *N*-*tert*-prenylindoles **3g**-**i** and **3n** were isolated in 43-80% yield over two steps as single constitutional isomers. Reactions of 4-MeO-, 5-MeO-, and 6-MeO-indolines with **2** occurred with 2-4:1 selectivity and subsequent oxidation gave *N*-*tert*-prenylindoles **3j**-**l** in 25-60% yield (Table 4, entries 6-8) as single constitutional isomers.

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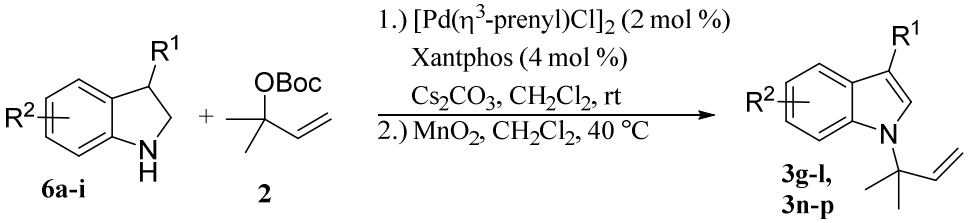
Table 4. Scope of Pd-Catalyzed *N-tert*-Prenylation of Indolines[a]



Entry	**6**	R^1	R^2	**3**	Yield **3** (%)[b]	*tert*-:*n*-prenyl[c]
1	**6a**	H	H	**3g**	80	6:1
2	**6b**	Me	H	**3h**	57	5:1
3	**6c**	CH_2CO_2Me	H	**3i**	43	5:1
4	**6d**	Ph	H	**3n**	47	5:1
5	**6e**	$(CH_2)_2NPhth$	H	**3o**	47	4:1
6	**6f**	H	4-MeO	**3j**	54	4:1
7	**6g**	H	5-MeO	**3k**	26	2:1
8	**6h**	H	6-MeO	**3l**	60	5:1
9	**6i**	H	5-Br	**3p**	64	5.5:1

[a] Reaction conditions: 1) Indoline **6a-g** (0.500 mmol), Cs_2CO_3 (0.500 mmol), Xantphos (0.020 mmol) $[Pd(\eta^3\text{-prenyl})Cl]_2$ (0.010 mmol), *tert*-butyl (2-methylbut-3-en-2-yl) carbonate **2** (1.00 mmol), CH_2Cl_2 (2.5 mL), room temperature, 2-6 h. 2) MnO_2 (5.00 equiv), CH_2Cl_2 (4 mL), 50 °C, 24-48 h. [b] Isolated yield of **3** over two steps. [c] Ratio of *N-tert*-prenylindoline:*N-n*-prenylindoline determined by ^1H NMR spectroscopy.

The sequence of *N*-prenylation of indolines followed by oxidation to the corresponding indoles allowed us to form *N-tert*-prenylindoles that were not accessible via the approaches shown in Tables 1 and 2. Reactions of protected tryptamine derivatives, 3-phenylindole, and 5-bromoindole with carbonate **2** either did not occur in high yields or the corresponding $(\eta^6\text{-indole})Cr(CO)_3$ complexes were difficult to isolate. However, reactions of 3-phenylindoline **6d**, indoline **6e** (R = $(CH_2)_2NPhth$), and 5-bromoindoline **6i** with **2** occurred with 4-5.5:1 *tert*-prenyl:*n*-prenyl selectivity (Table 4, entries 4, 5 and 9). The *N-tert*-prenylindoles **3n-p** were isolated in 47-64%.

Conclusion

We developed three strategies based on palladium-catalyzed allylic alkylation reactions to generate *N-tert*-prenylindoles. In the presence of the same palladium catalyst,

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good yields and high regioselectivity are observed for three distinct classes of nucleophiles. Direct *N-tert*-prenylations of electron-deficient indoles and indolines occur readily, while *N-tert*-prenylations of electron-rich indoles are facilitated by complexation with chromium. Straightforward procedures for oxidative decomplexation of the chromium carbonyl fragments from (η^6-*N-tert*-prenylindole)$Cr(CO)_3$ intermediates and oxidation of the *N-tert*-prenylindoles provide access to electron-rich *N-tert*-prenylindoles in moderate to good yields. Thus, *N-tert*-prenylindoles with a broad range of substitution and electronic character can be accessed through these complementary approaches.

Experimental

General Experimental Details. All air-sensitive procedures were conducted under inert atmosphere in a nitrogen-filled dry box or by standard Schlenk techniques. All reactions were performed under an atmosphere of nitrogen unless otherwise stated. All glassware for moisture sensitive reactions was dried at 140 °C in an oven. THF and CH_2Cl_2 were degassed by purging with argon for 45 minutes and dried with a solvent purification system by passing through a one-meter column of activated alumina. Anhydrous *n*-dibutylether, acetonitrile, benzonitrile, and dioxane were purchased from Aldrich. Flash column chromatography was performed on Fisher brand silica gel 60 (230-400 mesh) using hexanes/ethyl acetate, hexanes/ether, or hexanes/dichloromethane mixtures. Products were visualized on TLC by UV light or by staining with $KMnO_4$.

HRMS (ESI) analysis was performed at the Iowa State University Chemical Instrumentation Facility on an Agilent 6540 QTOF spectrometer. NMR spectra were acquired on Varian MR-400 and Bruker Avance III 600 spectrometers at the Iowa State

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University Chemical Instrumentation Facility. Chemical shifts are reported in ppm relative to a residual solvent peak ($CDCl_3$ = 7.26 ppm for ^1H and 77.36 ppm for ^{13}C; C_6D_6 = 7.16 for ^1H and 128.06 for ^{13}C). Coupling constants are reported in hertz.

Materials. Indole-3-carboxaldehyde **1a**, 3-acetylindole **1b**, methyl indole-3-carboxylate **1c**, 3-cyanoindole **1d**, indole, 3-methylindole, 3-indoleacetic acid, and tryptamine were purchased from Sigma-Aldrich and used with out further purification. 5-Cyanoindole **1e** and 5-nitroindole **1f** were purchased from TCI and used without further purification. 4-Methoxyindole, 5-methoxyindole, 6-methoxyindole, and 7-methoxyindole were purchased from AK Scientific and used without further purification. 5-Bromoindole was purchased from Frontier Scientific and used without further purification. Methyl indole-3-acetate was synthesized according to a literature procedure from 3-indoleacetic acid.[13] 3-Phenylindole was synthesized according to a literature procedure from 2-phenylacetaldehyde and phenylhydrazine[14] *N*-Phthalimidotryptamine was synthesized according to a literature procedure from tryptamine and phthalic anhydride.[4a] *tert*-Butyl (2-methylbut-3-en-2-yl) carbonate was prepared according to a literature procedure from 2-methylbut-3-en-2-ol and Boc_2O.[2g]

$[Pd(\eta^3\text{-allyl})Cl]_2$, $Pd_2(dba)_3$, and $PdCl_2$ were purchased from Strem and used without further purification. $[Pd(\eta^3\text{-prenyl})Cl]_2$ was synthesized from $PdCl_2$ and 1-chloro-3-methyl-2-butene according to a literature procedure. DPEPhos (oxydi-2,1-phenylene)bis(diphenylphosphine) and *rac*-BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthalene) were purchased from Strem and used without further purification. DPPPent (1,5-bis(diphenylphosphino)pentane), DPPF (1,1-bis(diphenylphosphino)ferrocene, Xantphos (4,5-bis(diphenylphosphino)-9,9-

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dimethylxanthene) and Cs_2CO_3 were purchased from Sigma-Aldrich and used without further purification.

Identification of Reaction Conditions for the *N-tert*-Prenylation of Indoles

In a nitrogen-filled dry-box, indole-3-carboxaldehyde **1a** (72.5 mg, 0.500 mmol, 1.00 equiv), Cs_2CO_3 (162 mg, 0.500 mmol, 1.00 equiv), ligand (0.020 mmol, 0.040 equiv), and the Pd source (0.010 mmol, 0.020 equiv.) were added to a 1-dram vial. *tert*-Butyl (2-methylbut-3-en-2-yl) carbonate **2** (0.500-1.00 mmol, 2.00 equiv) was added to a second 1-dram vial. Both vials were sealed with a PFTE/silicone-lined septum cap and removed from the dry-box. The mixture of **1a**, Cs_2CO_3, and catalyst precursors was suspended in CH_2Cl_2 (1.5 mL). Carbonate **2** was dissolved in CH_2Cl_2 (1 mL). The vials were allowed to stir for 5 minutes at the appropriate temperature. The solution of *tert*-butyl (2-methylbut-3-en-2-yl) carbonate **2** was then added to the suspension of **1a**, Cs_2CO_3, and catalyst precursors. The reaction mixture was allowed to stir at the reaction temperature (2-20 h) until the consumption of carbonate **2** was observed by TLC analysis. The reaction mixture was filtered through a pad of silica (eluting with Et_2O). The crude reaction mixture was concentrated under reduced pressure. $CDCl_3$ (0.5-0.7 mL) was added to dissolve the crude reaction mixture, and 1,3,5-trimethoxybenzene (28.6 mg, 0.170 mmol) was added as an internal standard. The ratio of *N-tert*-prenylindole **3a**:*N-n*-prenylindole **4a** and the combined yield of *N-tert*-prenylindole **3a** and *N-n*-prenylindole **4a** was then determined by ^1H NMR spectroscopy. For entry 14, the crude reaction mixture was purified by flash column chromatography (1:1 hexane:Et_2O) to yield **3a** (80.6 mg, 0.377 mmol).

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***N-tert*-Prenylation of Indoles 1a-f**

General Procedure A: In a nitrogen-filled dry-box, the appropriate indole **1** (0.500 mmol, 1.00 equiv), Cs_2CO_3 (163 mg, 0.500 mmol, 1.00 equiv), Xantphos (11.6 mg, 0.020 mmol, 0.040 equiv), and [Pd(η^3-prenyl)Cl]$_2$ (4.2 mg, 0.010 mmol, 0.020 equiv.) were added to a 1-dram vial. *tert*-Butyl (2-methylbut-3-en-2-yl) carbonate **2** (186 mg, 1.00 mmol, 2.00 equiv) was added to a second 1-dram vial. Both vials were sealed with a PFTE/silicone-lined septum cap and removed from the dry-box. The mixture of **1**, Cs_2CO_3, and catalyst precursors was suspended in CH_2Cl_2 (1.5 mL). Carbonate **2** was dissolved in CH_2Cl_2 (1 mL). The vials were cooled to 0 °C and allowed to stir for 5 minutes. The solution of *tert*-butyl (2-methylbut-3-en-2-yl) carbonate **2** was then added to the suspension of **1**, Cs_2CO_3, and catalyst precursors. The reaction mixture was allowed to stir at the reaction temperature (4-24 h) until the consumption of carbonate **2** was observed by TLC analysis. The reaction mixture was filtered through a pad of silica (eluting with EtOAc). The crude reaction mixture was concentrated under reduced pressure. $CDCl_3$ (0.5-0.7 mL) was added to dissolve the crude reaction mixture, and the ratio of *N-tert*-prenylindole **3**:*N-n*-prenylindole **4** was determined by ^{1}H NMR spectroscopy. The crude reaction mixture was purified by flash column silica gel chromatography (hexane:EtOAc or hexane:Et_2O) to yield **3a** and **3b** as single isomers and isomeric mixtures of **3c-f + 4c-f**.

1-(2-Methylbut-3-en-2-yl)-1H-indole-3-carbaldehyde[8] (3a): Prepared according to General Procedure A from indole-3-carboxaldehyde **1a** (72.5 mg, 0.500 mmol) (reaction time = 4 h). ^{1}H NMR spectroscopy showed a 12:1 *N-tert*-prenylindole **3a**:*N-n*-prenylindole **4b** ratio. The mixture was purified by flash column chromatography (1:1

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hexane:EtOAc) to yield **3a** (80.6 mg, 0.377 mmol, 76%) as an off-white amorphous solid. R_f 0.16 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (s, 1H), 8.31 (d, *J* = 7.2 Hz, 1H), 7.90 (s, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.29 - 7.18 (m, 2H), 6.10 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.27 (d, *J* = 10.8 Hz, 1H), 5.19 (d, *J* = 17.6 Hz, 1H), 1.79 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.9, 142.7, 136.8, 136.6, 126.9, 123.4, 122.8, 122.2, 117.7, 115.1, 114.8, 60.7, 28.1. HRMS (ESI) calcd. for $C_{14}H_{16}NO^+$ $[M+H]^+$ 214.1226, found 214.1226.

1-(1-(2-Methylbut-3-en-2-yl)-1*H*-indol-3-yl)ethanone (3b): Prepared according to General Procedure A from 3-acetylindole **1b** (79.6 mg, 0.500 mmol) (reaction time = 24 h). ^{1}H NMR spectroscopy showed a 10:1 *N-tert*-prenylindole **3b**:*N-n*-prenylindole **4b** ratio. The crude material was purified by flash column chromatography (1:1 hexane:EtOAc) to yield **3b** (73.7 mg, 0.324 mmol, 65%) as a off-white amorphous solid. R_f 0.19 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (d, *J* = 7.6 Hz, 1H), 7.94 (s, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.26 (dd, *J* = 8.4, 7.6 Hz, 1H), 7.20 (dd, *J* = 8.4, 7.6 Hz, 1H), 6.12 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.28 (d, *J* = 10.8 Hz, 1H), 5.20 (d, *J* = 17.6 Hz, 1H), 2.54 (s, 3H), 1.81 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.3, 143.0, 136.4, 132.7, 127.9, 122.73, 122.68, 122.4, 116.6, 114.9, 114.6, 60.4, 28.2, 28.0. HRMS (ESI) calcd. for $C_{15}H_{18}NO^+$ $[M+H]^+$ 228.1383, found 228.1383.

Methyl 1-(2-methylbut-3-en-2-yl)-1*H*-indole-3-carboxylate[8] (3c): Prepared according to General Procedure A from methyl indole-3-carboxylate **1c** (87.6 mg, 0.500 mmol) (reaction time = 22 h). ^{1}H NMR spectroscopy showed a 12:1 *N-tert*-prenylindole **3c**:*N-n*-prenylindole **4c** ratio. The mixture was purified by flash column chromatography (1:1 hexane:Et_2O) to yield a mixture of **3c** and **4c** (109.1 mg, 0.448 mmol, 90%) as a colorless

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oil. R_f 0.47 (1:1 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.0 Hz, 1H), 8.01 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.22 (dd, *J* = 8.0, 8.4 Hz, 1H), 7.16 (dd, *J* = 8.0. 8.4 Hz, 1H), 6.08 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.23 (d, *J* = 10.8 Hz, 1H), 5.15 (d, *J* = 17.6 Hz, 1H), 3.89 (s, 3H), 1.75 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 143.2, 136.1, 132.3, 128.2, 122.2, 121.9, 121.8, 114.7, 114.7, 106.5, 60.4, 51.2, 28.2. HRMS (ESI) calcd. for $C_{15}H_{18}NO_2^+$ $[M+H]^+$ 244.1332, found 244.1333.

1-(2-Methylbut-3-en-2-yl)-1*H*-indole-3-carbonitrile (3d): Prepared according to General Procedure A from 3-cyanoindole **1d** (71.1 mg, 0.500 mmol) (reaction time = 22 h). ^{1}H NMR spectroscopy showed a 12:1 *N-tert*-prenylindole **3d**:*N-n*-prenylindole **4d** ratio. The mixture was purified by flash column chromatography (1:1 hexane:Et_2O) to yield a mixture of **3d** and **4d** (99.6 mg, 0.474 mmol, 94%) as a colorless oil. R_f 0.41 (80:20 hexane:Et_2O) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (s, 1H), 7.42 - 7.35 (m, 1H), 7.25 - 7.17 (m, 1H), 6.94 - 6.85 (m, 2H), 5.74 (dd, *J* = 17.4, 10.6 Hz, 1H), 4.94 (d, *J* = 10.6 Hz, 1H), 4.83 (d, *J* = 17.4 Hz, 1H), 1.42 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.6, 134.9, 132.8, 129.4, 123.2, 122.1, 120.1, 116.4, 115.1, 110.9, 85.5, 60.9, 28.1. HRMS (ESI) calcd. for $C_{14}H_{15}N_2^+$ $[M+H]^+$ 211.1230, found 211.1229.

1-(2-Methylbut-3-en-2-yl)-1*H*-indole-5-carbonitrile (3e): Prepared according to General Procedure A from 5-cyanoindole **1e** (71.1 mg, 0.500 mmol) (reaction time = 22 h at room temperature). ^{1}H NMR spectroscopy showed a 7:1 *N-tert*-prenylindole **3e**:*N-n*-prenylindole **4e** ratio. The mixture was purified by flash column chromatography (1:1 hexane:Et_2O) to yield a mixture of **3e** and **4e** (41.6 mg, 0.198 mmol, 40%) as a colorless oil. R_f 0.47 (1:1 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.42 (d, *J* = 3.2 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 6.56 (d, *J* = 3.2 Hz, 1H),

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6.11 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.26 (d, *J* = 10.8 Hz, 1H), 5.16 (d, *J* = 17.6 Hz, 1H), 1.76 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5, 137.1, 129.9, 127.7, 126.7, 123.7, 121.1, 114.7, 114.5, 102.4, 102.0, 60.0, 28.2. HRMS (ESI) calcd. for $C_{14}H_{15}N_2^+$ $[M+H]^+$ 211.1230, found 211.1230.

1-(2-Methylbut-3-en-2-yl)-5-nitro-1*H*-indole (3f): Prepared according to General Procedure A from 5-nitroindole **1f** (81.1 mg, 0.500 mmol) (reaction time = 24 h at room temperature). ^{1}H NMR spectroscopy showed a 7:1 *N-tert*-prenylindole **3f**:*N-n*-prenylindole **4f** ratio. The mixture was purified by flash column chromatography (1:1 hexane:Et_2O) to yield a mixture of **3f** and **4f** (71.8 mg, 0.312 mmol, 62%) as a light yellow amorphous solid. R_f 0.59 (1:1 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, *J* = 1.2 1H), 7.98 (d, *J* = 9.2, 1.2 Hz, 1H), 7.53 (d, *J* = 9.2 Hz, 1H), 7.44 (d, *J* = 3.2 Hz, 1H), 6.64 (d, *J* = 3.2 Hz, 1H), 6.11 (dd, *J* = 17.2, 10.4 Hz, 1H), 5.27 (d, *J* = 10.4 Hz, 1H), 5.16 (d, *J* = 17.2 Hz, 1H), 1.76 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.4, 141.4, 138.4, 129.5, 128.7, 118.2, 116.4, 114.6, 113.7, 103.6, 60.2, 28.2. HRMS (ESI) calcd. for $C_{13}H_{15}N_2O_2^+$ $[M+H]^+$ 231.1128, found 231.1128.

Synthesis of (η^6-Indole)Cr(CO)$_3$ Complexes 5a-g

General Procedure B: In a nitrogen-filled dry-box, the appropriate indole **1g-m** (2.00-15.0 mmol), $Cr(CO)_6$ (1.42-1.78 equiv), *n*-dibutylether (40 mL) and THF (4 mL) were added to an oven-dried Schlenk flask (100 mL). The flask was sealed, removed from the dry-box, placed under a positive pressure of nitrogen and equipped with a reflux condenser. Positive pressure of nitrogen gas was maintained throughout the reaction by a nitrogen line equipped to the top of the condenser. The reaction mixture was heated at reflux (oil bath temperature = 145 °C) for 48 h. The resulting yellow/orange solution was

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allowed to cool to room temperature under nitrogen then filtered through a short plug of silica gel. The filtrate was concentrated under reduced pressure (70 °C water bath temp) to remove excess $Cr(CO)_6$ and *n*-dibutylether. The resulting yellow/orange solid was recrystallized from hexane:EtOAc to afford (η^6-indole)$Cr(CO)_3$ complexes **5a**-**g**.

(η^6-Indole)$Cr(CO)_3$[15] (5a): Prepared according to General Procedure B from indole (1.20 g, 10.2 mmol) and $Cr(CO)_6$ (3.20 g, 14.5 mmol, 1.42 equiv). The crude product was purified by recrystallization from hexane:EtOAc to yield **5a** (1.99 g, 7.84 mmol, 73%) as a yellow crystalline solid. Mp = 123-125 °C (decomposition). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (br s, 1H), 7.23 (app s, 1H), 6.41 (app s, 1H), 6.36 (d, *J* = 6.6 Hz, 1H), 6.12 (d, *J* = 6.6 Hz, 1H), 5.40 (t, *J* = 6.6 Hz, 1H), 5.12 (t, *J* = 6.6 Hz, 1H). ^{13}C NMR (150 MHz, C_6D_6) δ 235.0, 130.0, 115.5, 104.0, 100.6, 90.5, 88.6, 87.4, 78.4. IR: λ_{max} 1847, 1941, 2848, 2916, 3428. HRMS (ESI) calcd. for $C_{11}H_7CrNO_3^+$ $[M+H]^+$ 253.9904, found 253.9901.

(η^6-3-Methyl-1*H*-indole)$Cr(CO)_3$[16] (5b): Prepared according to General Procedure B from 3-methylindole (1.00 g, 7.62 mmol) and $Cr(CO)_3$ (3.00 g, 13.6 mmol, 1.78 equiv). The crude product was purified by recrystallization from hexane:EtOAc and to yield **5b** (1.44 g, 5.39 mmol, 73%) as a yellow crystalline solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59 (br s, 1H), 6.96 (s, 1H), 6.27 (d, *J* = 6.0 Hz, 1H), 6.09 (d, *J* = 6.0 Hz, 1H), 5.41 (t, *J* = 6.0 Hz, 1H), 5.11 (t, *J* = 6.0 Hz, 1H), 2.26 (s, 3H). Mp = 121-123 °C (decomposition). ^{1}H NMR (600 MHz, C_6D_6) δ 5.94 (app s, 1H), 5.82 (br s, 1H), 5.58 (d, *J* = 3.4, 1H), 5.24 (d, *J* = 3.4, 1H), 4.73 (app s, 1H), 4.41 (app s, 1H), 1.86 (s, 3H). ^{13}C NMR (150 MHz, C_6D_6) δ 235.4, 128.4, 126.9, 116.5, 113.6, 100.4, 90.8, 87.5, 87.0, 79.0, 9.1. IR: λ_{max}

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1848, 1933, 2849, 2917, 3428. HRMS (ESI) calcd. for $C_{12}H_9CrNO_3^+$ $[M+H]^+$ 268.0060, found 268.0061.

(η^6-Methyl 2-(1*H*-indol-3-yl)acetate)Cr(CO)$_3$ (5c): Prepared according to General Procedure B from methyl indole-3-acetate (0.380 g, 2.01 mmol) and $Cr(CO)_3$ (0.750 g, 3.41 mmol, 1.70 equiv). The crude product was purified by recrystallization from hexane:EtOAc and to yield **5c** (0.291 g, 0.895 mmol, 45%) as a yellow crystalline solid. Mp = 124-126 °C (decomposition). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (br s, 1H), 7.18 (s, 1H), 6.33 (app s, 1H), 6.08 (app s, 1H), 5.41 (app s, 1H), 5.11 (app s, 1H), 3.77 (s, 3H), 3.68 (s, 2H). ^{13}C NMR (150 MHz, C_6D_6) δ 234.9, 170.6, 128.34, 116.0, 110.1, 99.7, 90.6, 87.5, 87.0, 78.4, 51.7, 30.5. IR: λ_{max} 1721, 1849, 1943, 2848, 2916, 3416. HRMS (ESI) calcd. for $C_{14}H_{11}CrNO_5^+$ $[M+H]^+$ 326.0115, found 326.0122.

(η^6-4-Methoxy-1*H*-indole)Cr(CO)$_3$ (5d): Prepared according to General Procedure B from 4-methoxyindole (1.00 g, 2.92 mmol) and $Cr(CO)_3$ (1.70 g, 5.10 mmol, 1.75 equiv). The crude product was purified by recrystallization from hexane:EtOAc and to yield **5d** (0.256 g, 0.904 mmol, 31%) as a yellow crystalline solid. Mp = 132-134 °C (decomposition). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 (br s, 1H), 7.21 (app s, 1H), 6.63 (app s, 1H), 5.74 (app s, 1H), 5.46 (app s, 1H), 4.88 (app s, 1H), 3.97 (s, 3H). ^{1}H NMR (600 MHz, C_6D_6) δ 6.39 (app s, 1H), 6.14 (app s, 1H), 6.02 (br s, 1H), 4.92 (app s, 1H), 4.80 (app s, 1H), 4.08 (app s, 1H), 3.27 (s, 3H). ^{13}C NMR (150 MHz, C_6D_6) δ 235.4, 139.7, 129.2, 118.1, 102.8, 95.4, 90.1, 73.0, 69.6, 55.7. IR: λ_{max} 1815, 1841, 1929, 3437. HRMS (ESI) calcd. for $C_{12}H_9CrNO_4^+$ $[M+H]^+$ 284.0009, found 284.0009.

(η^6-5-Methoxy-1*H*-indole)Cr(CO)$_3$ (5e): Prepared according to General Procedure B from 5-methoxyindole (0.650 g, 4.42 mmol) and $Cr(CO)_3$ (1.46 g, 6.63 mmol, 1.50

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equiv). The crude product was purified by recrystallization from hexane:EtOAc and to yield **5e** (0.591 g, 2.09 mmol, 46%) as a yellow crystalline solid. Mp = 133-135 °C (decomposition). ^{1}HMR (600MHz, $CDCl_3$) δ 6.15 (s, 1H), 6.63 (app s, 1H), 5.74 (app s, 1H), 5.46 (app s, 1H), 4.88 (app s, 1H), 3.11 (s, 3H). ^{1}HMR (600MHz, C_6D_6) 6.15 (app s, 1H), 5.83 (app s, 1H), 5.72 (br s, 1H), 5.41 (app s, 1H), 5.30 (app s, 1H), 4.79 (app s, 1H), 3.11 (s, 3H). ^{13}C NMR (150 MHz, C_6D_6) δ 235.4, 138.7, 131.2, 109.5, 103.4, 102.1, 79.5, 79.2, 71.8, 55.6. IR: λ_{max} 1849, 1933, 2849, 2916, 2961, 3445. HRMS (ESI) calcd. for $C_{12}H_9CrNO_4^+$ $[M+H]^+$ 284.0009, found 284.0013.

(η^6-6-Methoxy-1*H*-indole)Cr(CO)$_3$ (5f): Prepared according to General Procedure B from 6-methoxyindole (0.500 g, 3.40 mmol) and $Cr(CO)_3$ (1.12 g, 5.09 mmol, 1.50 equiv). The crude product was purified by recrystallization from hexane:EtOAc and to yield **5f** (0.202 g, 0.713 mmol, 21%) as a yellow crystalline solid. Mp = 131-133 °C (decomposition). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (br s, 1H), 7.16 (s, 1H), 6.42 (d, *J* = 6.6 Hz, 1H), 6.31 (s, 1H), 5.95 (s, 1H), 5.04 (d, *J* = 6.6 Hz, 1H), 3.78 (s, 3H). ^{1}H NMR (600MHz, C_6D_6) δ 6.18 (s, 1H), 5.90 (br s, 1H), 5.77 (s, 1H), 5.76 (d, *J* = 6.6 Hz, 1H), 5.21 (s, 1H), 4.41 (d, *J* = 6.6 Hz, 1H), 3.17 (s, 1H). ^{13}C NMR (150 MHz, C_6D_6) δ 235.5, 141.2, 129.5, 117.7, 104.3, 95.4, 87.9, 75.6, 65.8, 55.4. IR: λ_{max} 1834, 1877, 1934, 3114, 3146, 3359, 3418. HRMS (ESI) calcd. for $C_{12}H_9CrNO_4^+$ $[M+H]^+$ 284.0009, found 284.0013.

(η^6-7-Methoxy-1*H*-indole)Cr(CO)$_3$ (5g): Prepared according to General Procedure B from 7-methoxyindole (0.500 g, 3.40 mmol) and $Cr(CO)_3$ (1.12 g, 5.09 mmol, 1.50 equiv). The crude product was purified by recrystallization from hexane:EtOAc and to yield **5g** (0.505 g, 1.78 mmol, 53 %) as a yellow crystalline solid. Mp = 116-118 °C

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(decomposition). ^{1}H NMR (400MHz, $CDCl_3$) δ 8.2 (br s, 1H), 7.32 (app s,1H), 6.49 (app s, 1H), 5.81 (d, *J* = 6.4 Hz, 1H), 5.23 (t, *J* = 6.4, 1H) 5.07 (d, *J* = 6.4, 1H), 3.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 235.1, 132.6, 131.3, 108.8, 104.3, 88.6, 82.5, 77.4, 72.2, 56.7. IR: λ_{max} 1825, 1936, 2848, 2916, 3405. HRMS (ESI) calcd. for $C_{12}H_9CrNO_4^+$ $[M+H]^+$ 284.0009, found 284.0011.

***N-tert*-Prenylation of (η^6-Indole)Cr(CO)$_3$ Complexes 5a-g**

General Procedure C: In a nitrogen-filled dry-box, the appropriate (η^6-indole)Cr(CO)$_3$ complex **5** (0.250 mmol, 1.00 equiv), Cs_2CO_3 (81.2 mg, 0.250 mmol, 1.00 equiv), Xantphos (5.79 mg, 0.010 mmol, 0.020 equiv), and [Pd(η^3-prenyl)Cl]$_2$ (2.11 mg, 0.005 mmol, 0.010 equiv.) were added to a 1-dram vial. *tert*-Butyl (2-methylbut-3-en-2-yl) carbonate **2** (93.1 mg, 0.500 mmol, 2.00 equiv) was added to a second 1-dram vial. Both vials were sealed with a PFTE/silicone-lined septum cap and removed from the dry-box. The mixture of **5**, Cs_2CO_3, and catalyst precursors was suspended in CH_2Cl_2 (1.5 mL). Carbonate **2** was dissolved in CH_2Cl_2 (1 mL). The vials were allowed to stir for 5 minutes. The solution of *tert*-butyl (2-methylbut-3-en-2-yl) carbonate **2** was then added to the suspension of **5**, Cs_2CO_3, and catalyst precursors. The reaction mixture was allowed to stir at room temperature (2-6 h) until the consumption of carbonate **2** was observed by TLC analysis. The solvent was removed under reduced pressure. The residue was taken up in CH_3CN (3 mL), cooled to 0 °C, and DDQ (85.0 mg, 0.750 mmol, 1.50 equiv) was added. The reaction mixture was allowed to stir at 0 °C for 2-6 h. The reaction progress was monitored by TLC analysis. When the reaction was judged to be complete, the solvent was removed under reduced pressure. The resulting residue was taken up in Et_2O, filtered through a short plug of silica gel (eluting with Et_2O), and concentrated

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under reduced pressure. $CDCl_3$ (0.5 - 0.7 mL) was added to dissolve the crude reaction mixture and the ratio of *N-tert*-prenylindole **3**:*N-n*-prenylindole **4** was determined by ^1H NMR spectroscopy. The crude reaction mixture was purified by flash column silica gel chromatography (hexane:EtOAc or hexane:Et_2O) to yield isomeric mixtures of **3g-m** + **4g-m**.

1-(2-Methylbut-3-en-2-yl)-1*H*-indole[5c] (3g): Prepared according to General Procedure C from (η^6-indole)$Cr(CO)_3$ (63.3 mg, 0.250 mmol) (reaction time = 3 h). ^1H NMR spectroscopy showed an 8:1 *N-tert*-prenylindole **3g**:*N-n*-prenylindole **4g** ratio. The crude material was purified by flash chromatography (95:5 hexane:Et_2O) to yield a mixture of **3g** and **4g** (39.9 mg, 0.215 mmol, 86%) as a colorless oil. R_f 0.64 (80:20 hexane:EtOAc) ^1H NMR (400 MHz, $CDCl_3$): δ 7.71 - 7.66 (m, 1H), 7.61 - 7.55 (m, 1H), 7.36 (d, *J* = 2.0 Hz, 1H), 7.22 - 7.10 (m, 2H), 6.55 (d, *J* = 2.6 Hz, 1H), 6.21 (dd, *J* = 17.2, 10.8 Hz, 1H), 5.28 (d, *J* = 10.8 Hz, 1H), 5.22 (d, *J* = 17.2 Hz, 1H), 1.81 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.5, 135.6, 130.3, 125.3, 121.2, 120.9, 119.4, 114.1, 113.8, 100.9, 59.3, 28.2 HRMS (ESI) calcd. for $C_{13}H_{16}N^+$ $[M+H]^+$186.1277, found 186.1279.

3-Methyl-1-(2-methylbut-3-en-2-yl)-1*H*-indole (3h): Prepared according to General Procedure C from (η^6-3-methyl-1*H*-indole)$Cr(CO)_3$ (70.6 mg, 0.250 mmol) (reaction time = 2 h). ^1H NMR spectroscopy showed an 8:1 *N-tert*-prenylindole **3h**:*N-n*-prenylindole **4h** ratio. The crude material was purified by flash chromatography (95:5 hexane:Et_2O) to yield a mixture of **3h** and **4h** (37.3 mg, 0.187 mmol, 75%) as a colorless oil. R_f 0.64 (80:20 hexane:EtOAc) ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 - 7.59 (m, 1H), 7.57 - 7.50 (m, 1H), 7.20 - 7.09 (m, 3H), 6.20 (dd, *J* = 18.0, 11.2 Hz, 1H), 5.25 (d, *J* = 11.2 Hz, 1H), 5.21 (d, *J* = 18.0 Hz, 1H), 2.38 (s, 3H), 1.78 (s, 6H). ^{13}C NMR (100 MHz,

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$CDCl_3$): δ 144.8, 135.9, 130.4, 123.1, 120.9, 119.2, 118.7, 113.9, 113.6, 109.7, 59.0, 28.2, 10.0. HRMS (ESI) calcd. for $C_{14}H_{18}N^+$ $[M+H]^+$ 200.1434, found 200.1435.

Methyl 2-(1-(2-methylbut-3-en-2-yl)-1*H*-indol-3-yl)acetate (3i): Prepared according to General Procedure C from (η^6-methyl 2-(1*H*-indol-3-yl)acetate)$Cr(CO)_3$ (85.1 mg, 0.250 mmol) (reaction time = 2 h). ^{1}H NMR spectroscopy showed a 9:1 *N-tert*-prenylindole **3i**:*N-n*-prenylindole **4i** ratio. The crude material was purified by flash chromatography (70:30 hexane:Et_2O) to yield a mixture of **3i** and **4i** (50.3 mg, 0.195 mmol, 78%) as a colorless oil. R_f 0.51 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (m, 1H), 7.52 (m, 1H), 7.30 (s, 1H), 7.18 - 7.08 (m, 2H), 6.16 (dd, *J* = 17.6, 11.0 Hz, 1H), 5.23 (d, *J* = 11.0, 1H), 5.20 (d, *J* = 17.8 Hz, 1H), 3.79 (s, 2H), 3.72 (s, 3H), 1.77 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 144.5, 135.8, 129.4, 124.4, 121.2, 119.31, 119.25, 114.1, 113.8, 106.5, 59.3, 52.2, 31.6, 28.2. HRMS (ESI) calcd, for $C_{16}H_{20}NO_2^+$ $[M+H]^+$ 258.1489, found 258.1491.

4-Methoxy-1-(2-methylbut-3-en-2-yl)-1*H*-indole (3j): Prepared according to General Procedure C from (η^6-4-methoxy-1*H*-indole)$Cr(CO)_3$ (74.6 mg, 0.250 mmol) (reaction times = 6 h). ^{1}H NMR spectroscopy showed a 7:1 *N-tert*-prenylindole **3j**:*N-n*-prenylindole **4j** ratio. The crude material was purified by flash chromatography (95:5 hexane:Et_2O) to yield a mixture of **3j** and **4j** (41.8 mg, 0.194 mmol, 78%) as a colorless oil. R_f 0.53 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 3.2 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.07 (app t, *J* = 8.0 Hz, 1H), 6.63 (d, *J* = 3.2 Hz, 1H), 6.53 (d, *J* = 8.0 Hz, 1H), 6.18 (dd, *J* = 17.6, 10.4 Hz, 1H), 5.24 (d, *J* = 10.4 Hz, 1H), 5.18 (d, *J* = 17.6 Hz, 1H), 3.98 (s, 3H), 1.78 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.6, 144.5,

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137.0, 123.9, 121.6, 120.9, 113.7, 107.7, 99.2, 98.0, 59.4, 55.6, 28.3. HRMS (ESI) calcd. for $C_{14}H_{18}NO^+$ $[M+H]^+$ 216.1383, found 216.1381.

5-Methoxy-1-(2-methylbut-3-en-2-yl)-1*H*-indole (3k): Prepared according to General Procedure C from (η^6-5-methoxy-1*H*-indole)$Cr(CO)_3$ (74.6 mg, 0.250 mmol) (reaction time = 5 h). ^{1}H NMR spectroscopy showed an 8:1 *N-tert*-prenylindole **3k**:*N-n*-prenylindole **4k** ratio. The crude material was purified by flash chromatography (95:5 hexane:Et_2O) to yield a mixture of **3k** and **4k** (27.4 mg, 0.127 mmol, 51%) as a colorless oil. R_f 0.35 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, *J* = 9.2 Hz, 1H), 7.30 (d, *J* = 2.4 Hz, 1H), 7.11 (d, *J* = 2.4 Hz, 1H), 6.82 (dd, *J* = 9.2, 2.8 Hz, 1H), 6.44 (d, *J* = 2.8 Hz, 1H), 6.16 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.24 (d, *J* = 10.8 Hz, 1H), 5.18 (d, *J* = 17.6 Hz, 1H), 3.87 (s, 3H), 1.76 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9, 144.5, 130.9, 130.7, 125.9, 114.7, 113.8, 111.3, 102.6, 100.5, 59.2, 56.0, 28.2. HRMS (ESI) calcd. for $C_{14}H_{18}NO^+$ $[M+H]^+$ 216.1383, found 216.1385.

6-Methoxy-1-(2-methylbut-3-en-2-yl)-1*H*-indole (3l): Prepared according to General Procedure C from (η^6-6-methoxy-1*H*-indole)$Cr(CO)_3$ (74.6 mg, 0.250 mmol) (reaction time = 5 h). ^{1}H NMR spectroscopy showed a 7:1 *N-tert*-prenylindole **3l**:*N-n*-prenylindole **4l** ratio. The crude material was purified by flash chromatography (95:5 hexane:Et_2O) to yield a mixture of **3l** and **4l** (39.0 mg, 0.181 mmol, 73%) as a colorless oil. R_f 0.54 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 8.4 Hz, 1H), 7.23 (d, *J* = 3.2 Hz, 1H), 7.07 (d, *J* = 1.6 Hz, 1H), 6.80 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.45 (d, *J* = 3.2 Hz, 1H), 6.18 (dd, *J* = 17.6, 10.4 Hz, 1H), 5.27 (d, *J* = 10.4 Hz, 1H), 5.22 (d, *J* = 17.6 Hz, 1H), 3.85 (s, 3H), 1.77 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.4, 144.5, 136.3,

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124.7, 124.3, 121.5, 113.7, 108.9, 100.8, 98.3, 59.2, 56.0, 28.0. HRMS (ESI) calcd. for $C_{14}H_{18}NO^+$ $[M+H]^+$ 216.1383, found 216.1379.

7-Methoxy-1-(3-methylbut-2-en-1-yl)-1*H*-indole (4m): Prepared according to General Procedure C from (η^6-7-methoxy-1*H*-indole)$Cr(CO)_3$ (74.6 mg, 0.250 mmol) (reaction time = 5 h). ^{1}H NMR spectroscopy showed a <1:20 *N-tert*-prenylindole **3m**:*N-n*-prenylindole **4m** ratio. The crude material was purified by flash chromatography (95:5 hexane:Et_2O) to yield the linear isomer **4m** (24.5 mg, 0.114 mmol, 46%) as a colorless oil. R_f 0.68 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 2.8 Hz, 1H), 6.99 (t, *J* = 8.0 Hz, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 6.45 (d, *J* = 2.8 Hz, 1H), 5.43 (t, *J* = 7.0 Hz, 1H), 5.04 (d, *J* = 7.0 Hz, 2H), 3.94 (s, 3H), 1.81 (s, 3H), 1.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.0, 135.0, 131.2, 128.5, 126.0, 122.4, 119.9, 114.1, 102.6, 101.7, 55.7, 47.0, 26.0, 18.3. HRMS (ESI) calcd. for $C_{14}H_{18}NO^+$ $[M+H]^+$ 216.1383, found 216.1383.

Synthesis of Indolines 6b-i

General Procedure D: To a stirred solution of indole **1h**, **1j-m** (2.38 – 6.79 mmol) in acetic acid (4–15 mL) was added $NaBH_3CN$ (5.96-17.0 mmol, 2.50 equiv). The reaction was let stir at room temperature and reaction progress was monitored by TLC analysis. The reaction mixture was diluted with H_2O, basified to pH ~9 using NaOH pellets and extracted using EtOAc (3x). The combined organic layers were washed with H_2O, saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexane:EtOAc) to yield products **6b** and **6f-i**.

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General Procedure E: To a stirred solution of indole **1i**, **1n-o** (1.38 – 2.64 mmol) in trifluoroacetic acid (3–6 mL) at 50 °C was added Et_3SiH (2.76-5.29 mmol, 2.00 equiv) and the reaction was heated for 48 h and reaction progress was monitored by TLC analysis. The reaction mixture was cooled to room temperature, diluted with H_2O, basified to pH ~9 using a saturated solution of $NaHCO_3$ and extracted using $CHCl_3$ (3x). The combined organic layers were washed dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexane:EtOAc) to yield products **6c**–**e**.

3-methyl-1*H*-indoline[17] (6b): Prepared according to General Procedure D from 3-methyl-1*H*-indole (0.500 g, 3.81 mmol), $NaBH_3CN$ (0.600 g, 9.53 mmol, 2.50 equiv) and 8 mL acetic acid (reaction time = 4.5 h) and monitored by TLC. The crude product was purified by flash column silica gel chromatography (80:20 hexane:EtOAc) to yield **6b** (0.394 g, 2.96 mmol, 78%) as a brown/red oil. R_f 0.40 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (app d, *J* = 7.6 Hz, 1H), 7.27 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 2H), 6.99 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 6.81 (app d, *J* = 7.6 Hz, 1H), 3.87 (br s, 1H), 3.82 (t, *J* = 8.8 Hz, 1H), 3.61 - 3.49 (m, 1H), 3.24 (t, *J* = 8.8 Hz, 1H), 1.54 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.3, 134.2, 127.1, 123.2,118.4, 109.3, 55.3, 36.5, 18.6. HRMS (ESI) calcd. for $C_9H_{12}N^+$ $[M+H]^+$ 134.0963, found 134.0965.

methyl 2-(indolin-3-yl)acetate[18] (6c): Prepared according to General Procedure E from methyl 2-(1*H*-indol-3-yl)acetate (0.50 g, 2.64 mmol), Et_3SiH (0.59 mL, 5.29 mmol, 2.00 equiv) and 4 mL trifluoroacetic acid (reaction time = 48 h at 50 °C). The crude product was dried on a vacuum line at 40 °C to remove unreacted Et_3SiH and yield **6c** (0.303 g, 1.58 mmol, 60%) as a brown oil. R_f 0.13 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz,

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$CDCl_3$): δ 7.11 - 7.02 (m, 2H), 6.72 (ddd, *J* = 7.6, 7.6,1.2 Hz, 1H), 6.65 (app d, *J* = 7.6 Hz, 1H), 3.79 (t, *J* = 8.8 Hz, 2H), 3.74 (s, 1H), 3.72 (s, 3H), 3.27 (dd, *J* = 8.8, 6.0 Hz, 1H), 2.78 (dd, *J* = 16.0, 6.0 Hz, 1H), 2.58 (dd, *J* = 16.0, 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 151.5, 131.5, 128.3, 124.2, 119.0, 110.0, 53.7, 52.0, 39.0, 38.8. HRMS (ESI) calcd. for $C_{11}H_{14}NO_2^+$ $[M+H]^+$ 192.1019, found 192.1019.

3-phenyl-1*H*-indoline[19] (6d): Prepared according to General Procedure E from 3-phenyl-1*H*-indole (0.500 g, 2.57 mmol), Et_3SiH (0.570 mL, 5.15 mmol, 2.00 equiv) and 6 mL trifluoroacetic acid (reaction time = 48 h). The crude product was dried on a vacuum line at 40 °C to remove unreacted Et_3SiH and yield **6d** (0.356 g, 1.82 mmol, 71%) as a light brown oil. R_f 0.37 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 - 7.18 (m, 5H), 7.09 - 7.02 (m, 1H), 6.89 (m, 1H), 6.69 (m, 2H), 4.46 (t, *J* = 9.2 Hz, 1H), 3.90 (t, *J* = 9.2 Hz, 1H), 3.89 (br s, 1H), 3.47 (t, *J* = 9.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.8, 143.8, 132.7, 128.9, 128.5, 128.1, 127.0, 125.3, 119.4, 110.1, 57.0, 49.0. HRMS (ESI) calcd. for $C_{14}H_{14}N^+$ $[M+H]^+$ 196.1121, found 196.1119.

2-(2-(indolin-3-yl)ethyl)isoindoline-1,3-dione (6e): Prepared according to General Procedure E from 2-(2-(1*H*-indol-3-yl)ethyl)isoindoline-1,3-dione (0.400 g, 1.38 mmol), Et_3SiH (0.310 mL, 2.76 mmol, 2.00 equiv) and 3 mL trifluoroacetic acid (reaction time = 48 h). The crude product was purified by flash column chromatography (60:40 hexane:EtOAc) to yield **6e** (0.281 g, 0.96 mmol, 70%) as a tan amorphous solid. R_f 0.31 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 - 7.80 (m, 2H), 7.75 - 7.67 (m, 2H), 7.15 (app d, *J* = 7.6 Hz, 1H), 7.01 (app t, *J* = 7.6 Hz, 1H), 6.70 (ddd, *J* = 7.6, 7.6, 0.8 Hz, 2H), 6.63 (app d, *J* = 7.6 Hz, 1H), 3.84 - 3.74 (m, 3H), 3.33 - 3.25 (m, 2H), 2.27 - 2.16 (m, 1H), 1.99 - 1.88 (m, 1H), 1.26 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ

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168.7, 151.5, 134.3, 132.4, 132.1, 128.0, 124.2, 123.6, 119.1, 110.0, 53.3, 40.0, 36.4, 33.0. HRMS (ESI) calcd. for $C_{18}H_{17}N_2O_2^+$ $[M+H]^+$ 293.1285, found 293.1286.

4-methoxy-1*H*-indoline[20] (6f): Prepared according to General Procedure D from 4-methoxy-1*H*-indole (0.500 g, 3.40 mmol), $NaBH_3CN$ (0.530 g, 8.49 mmol, 2.50 equiv) and 7 mL acetic acid (reaction time = 3 h). The crude product was purified by flash column chromatography (80:20 hexane:EtOAc) to yield **6f** (0.332 g, 2.22 mmol, 65%) as an opaque oil. R_f 0.28 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.01 (d, *J* = 8.0 Hz, 1H), 6.32 (d, *J* = 8.0 Hz, 2H), 3.97 (br s, 1H), 3.83 (s, 3H), 3.57 (t, *J* = 8.4 Hz, 2H), 3.00 (t, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.7, 153.4, 128.9, 116.1, 103.6, 102.0, 55.5, 47.7, 27.1. HRMS (ESI) calcd. for $C_9H_{12}NO^+$ $[M+H]^+$ 150.0913, found 150.0913.

5-methoxy-1*H*-indoline[21] (6g): Prepared according to General Procedure D from 5-methoxy-1*H*-indole (1.00 g, 6.79 mmol), $NaBH_3CN$ (1.07 g, 17.0 mmol, 2.50 equiv) and 14 mL acetic acid (reaction time = 2 h). The crude product was purified by flash column chromatography (80:20 hexane:EtOAc) to yield **6g** (0.766 g, 5.13 mmol, 76%) as a brown/red oil. R_f 0.16 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.78 (s, 1H), 6.65 - 6.55 (m, 2H), 3.75 (s, 3H), 3.52 (t, *J* = 8.4 Hz, 2H), 3.52 (br s, 1H), 3.01 (t, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.6, 145.6, 131.3, 112.3, 111.7, 110.2, 56.1, 48.0, 30.6. HRMS (ESI) calcd. for $C_9H_{12}NO^+$ $[M+H]^+$ 150.0913, found 150.0913.

6-methoxy-1*H*-indoline[22] (6h): Prepared according to General Procedure D from 6-methoxy-1*H*-indole (0.350 g, 2.38 mmol), $NaBH_3CN$ (0.370 g, 5.95 mmol, 2.50 equiv) and 5 mL acetic acid (reaction time = 2 h). The crude product was purified by flash column chromatography (80:20 hexane:EtOAc) to yield **6h** (0.326 g, 2.19 mmol,, 92%)

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as a brown/red oil. R_f 0.26 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (d, *J* = 8.0 Hz, 1H), 6.33 - 6.22 (m, 2H), 3.92 (br s, 1H), 3.77 (s, 3H), 3.55 (t, *J* = 8.2 Hz, 2H), 2.98 (t, *J* = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 153.1, 124.7, 121.7, 103.4, 96.4, 55.4, 48.0, 29.1. HRMS (ESI) calcd. for $C_9H_{12}NO^+$ $[M+H]^+$ 150.0913, found 150.0912.

5-bromo-1*H*-indoline (6i): Prepared according to General Procedure D from 5-bromo-1*H*-indole (0.500 g, 2.55 mmol), $NaBH_3CN$ (0.400 g, 6.38 mmol, 2.50 equiv) and 5 mL acetic acid (reaction time = 2 h). The crude product was purified by flash column chromatography (80:20 hexane:EtOAc) to yield **6i** (0.469 g, 3.14 mmol, 93%) as a brown/red oil. R_f 0.29 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.69 (d, *J* = 2.0 Hz, 1H), 6.59 (dd, *J* = 8.4, 2.0 Hz, 1H), 5.99 (d, *J* = 8.4 Hz, 1H), 3.16 (br s, 1H), 3.04 (t, *J* = 8.6 Hz, 2H), 2.50 (t, *J* = 8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.9, 132.1, 130.1, 127.8, 110.9, 110.4, 47.8, 30.0. HRMS (ESI) calcd. for $C_8H_9BrN^+$ $[M+H]^+$ 197.9913, observed 197.9914.

***N-tert*-Prenylation of Indolines 6a-i**

General Procedure F: In a nitrogen-filled dry-box, the appropriate indoline **6** (0.500 mmol, 1.00 equiv), Cs_2CO_3 (163 mg, 0.500 mmol, 1.00 equiv), Xantphos (11.6 mg, 0.020 mmol, 0.040 equiv), and $[Pd(\eta^3\text{-prenyl})Cl]_2$ (4.21 mg, 0.010 mmol, 0.020 equiv.) were added to a 1-dram vial. *tert*-Butyl (2-methylbut-3-en-2-yl) carbonate **2** (186 mg, 1.00 mmol, 2.00 equiv) was added to a second 1-dram vial. Both vials were sealed with a PFTE/silicone-lined septum cap and removed from the dry-box. The mixture of **1**, Cs_2CO_3, and catalyst precursors was suspended in CH_2Cl_2 (1.5 mL). Carbonate **2** was dissolved in CH_2Cl_2 (1 mL). The vials were cooled to 0 °C and allowed to stir for 5

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minutes. The solution of *tert*-butyl (2-methylbut-3-en-2-yl) carbonate **2** was then added to the suspension of **1**, Cs_2CO_3, and catalyst precursors. The reaction mixture was allowed to stir at the reaction temperature (1.5-2 h) until the consumption of carbonate **2** was observed by TLC analysis. The reaction mixture was filtered through a pad of silica (eluting with EtOAc) and the crude reaction mixture was concentrated under reduced pressure. $CDCl_3$ (0.5-0.7 mL) was added to dissolve the crude reaction mixture, and the ratio of *N*-*tert*-prenylindoline **S1a-i**:*N*-*n*-prenylindoline **S2a-i** was determined by ^{1}H NMR spectroscopy. The crude reaction mixture was purified by flash column chromatography (hexane:Et_2O) to yield **S1a-d** and **S1f-i** as single constitutional isomers and an isomeric mixture of **S1e + S2e**. *N*-*tert*-prenylindoline **S1a-i** (0.125-0.200 mmol, 1.00 equiv) was then added to a scintillation vial, dissolved in 4 mL CH_2Cl_2 and MnO_2 (5.00 equiv) was added. The reaction mixture was heated to 50 °C for 24 - 48 hours in the sealed vial. The reaction mixture was cooled to room temperature, filtered through a pad of celite (eluting with EtOAc) and concentrated under reduced pressure to yield products **3g-l** and **3n-p**.

1-(2-methylbut-3-en-2-yl)indoline[5c] (S1a): Prepared according to General Procedure F from 1*H*-indoline (59.6 mg, 0.500 mmol) (reaction time = 2 h). ^{1}H NMR spectroscopy showed a 6:1 *N*-*tert*-prenylindoline **S1a**:*N*-*n*-prenylindoline **S2a** ratio. The crude material was purified by flash chromatography (98:2 hexane:Et_2O) to yield **S1a** (77.5 mg, 0.414 mmol, 83%) as a colorless oil. R_f 0.42 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (d, *J* = 7.6 Hz, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 7.6 Hz, 1H), 6.68 (t, *J* = 7.6 Hz, 1H), 6.18 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.28 (d, *J* = 17.6 Hz, 1H), 5.18 (d, *J* = 10.8 Hz, 1H), 3.47 (t, *J* = 8.4 Hz, 2H), 2.95 (t, *J* = 8.4 Hz, 2H), 1.39 (s, 6H). ^{13}C NMR

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(100 MHz, $CDCl_3$): δ 151.0, 147.32, 131.7, 126.7, 124.5, 117.5, 112.4, 111.4, 57.6, 49.3, 28.4, 24.3. HRMS (ESI) calcd. for $C_{13}H_{18}N^+$ $[M+H]^+$ 188.1434, observed 188.1435.

1-(2-methylbut-3-en-2-yl)-1*H*-indole[5c] (3g): Prepared according to General Procedure F from **S1a** (37.5 mg, 0.200 mmol) and MnO_2 (87.0 mg, 1.00 mmol, 5.00 equiv) and heated for 24 h. Pure isomer **3g** was isolated as a colorless oil (36.1 mg, 0.195 mmol, 96%). Experimental data matches values for Table 2, entry 1.

3-methyl-1-(2-methylbut-3-en-2-yl)-1H-indoline (S1b): Prepared according to General Procedure F from **6b** (66.6 mg, 0.500 mmol) (reaction time = 2 h) ^{1}H NMR spectroscopy showed a 5:1 *N-tert*-prenylindoline **S1b**:*N-n*-prenylindoline **S2b**. The crude material was purified by flash chromatography (98:2 hexane:Et_2O) to yield **S1b** (59.6 mg, 0.296 mmol, 59%) as a colorless oil. R_f 0.65 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07 (app d, *J* = 7.2 Hz, 1H), 7.01 (app t, *J* = 8.8 Hz, 1H), 6.83 (app d, *J* = 8.0 Hz, 1H), 6.70 (ddd, *J* = 7.2, 7.2, 0.8 Hz, 1H), 6.17 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.27 (dd, *J* = 17.6, 1.2 Hz, 1H), 5.17 (dd, *J* = 10.8, 1.2 Hz, 1H), 3.66 (t, *J* = 8.4 Hz, 1H), 3.33 - 3.19 (m, 1H), 2.99 (t, *J* = 8.4 Hz, 1H), 1.40 (s, 3H), 1.37 – 1.32 (d, *J* = 6.8, 3H), 1.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.6, 147.3, 136.6, 126.9, 123.1, 117.5, 112.4, 111.4, 57.4, 34.7, 26.8, 22.0, 18.6. HRMS (ESI) calcd. for $C_{14}H_{20}N^+$ $[M+H]^+$ 202.1590, found 202.1591.

3-methyl-1-(2-methylbut-3-en-2-yl)-1H-indole (3h): Prepared according to General Procedure F from **S1b** (40.3 mg, 0.200 mmol) and MnO_2 (87.0 mg, 1.00 mmol, 5.00 equiv) and heated for 24 h. Pure isomer **3h** was isolated as a colorless oil (38.5 mg, 0.193 mmol, 97%). Experimental data matches values for Table 2, entry 2.

methyl 2-(1-(2-methylbut-3-en-2-yl)-1*H*-indolin-3-yl)acetate (S1c): Prepared according to General Procedure F from **6c** (95.6 mg, 0.500 mmol) (reaction time = 1.5 h). ^{1}H

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NMR spectroscopy showed a 5:1 *N-tert*-prenylindoline **S1c**:*N-n*-prenylindoline **S2c**. The crude material was purified by flash chromatography on silica gel (98:2 hexane:Et_2O) to yield **S1c** (73.2 mg, 0.282 mmol, 56%) as a colorless oil. R_f 0.51 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 -7.01 (app d, *J* = 7.2 Hz, 1 H), 7.00 - 6.96 (app t, *J* = 8.0, 1H), 6.79 (app d, *J* = 8.0 Hz, 1H), 6.64 (app t, *J* = 7.2 Hz, 1H), 6.10 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.22 (dd, *J* = 17.6, 1.0 Hz, 1H), 5.13 (d, *J* = 10.8, 1.0 Hz, 1H), 3.73 (s, 3H), 3.69 (t, *J* = 8.4 Hz, 1H), 3.63 - 3.52 (m, 1H), 3.15 (dd, *J* = 8.6, 6.0 Hz, 1H), 2.79 (dd, *J* = 16.4, 6.0 Hz, 1H), 2.58 (dd, *J* = 16.4, 8.6 Hz, 1H), 1.34 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 150.6, 147.0, 133.4, 127.6, 123.6, 117.5, 112.6, 111.7, 57.4, 55.4, 52.0, 38.9, 36.6, 24.8, 24.1. HRMS (ESI) calcd. for $C_{16}H_{22}NO_2^+$ $[M+H]^+$ 260.1645, found 260.1646.

methyl 2-(1-(2-methylbut-3-en-2-yl)-1*H*-indol-3-yl)acetate (3i): Prepared according to General Procedure F from **S1c** (51.9 mg, 0.200 mmol) and MnO_2 (87.0 mg, 1.00 mmol, 5.00 equiv) and heated for 48 h. Pure isomer **3i** was isolated as a colorless oil (39.6 mg, 0.154 mmol, 77%). Experimental data matches values for Table 2, entry 3.

1-(2-methylbut-3-en-2-yl)-3-phenyl-1*H*-indoline (S1d): Prepared according to General Procedure F from **6d** (97.6 mg, 0.500 mmol) (reaction time = 2 h). ^{1}H NMR spectroscopy showed a 5:1 *N-tert*-prenylindoline **S1d**:*N-n*-prenylindoline **S2d**. The crude material was purified by flash chromatography (98:2 hexane:Et_2O) to yield **S1d** (80.8 mg, 0.307 mmol, 61%) as a colorless oil. R_f 0.68 (80:20 hexane:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (m, 4H), 7.24 – 7.16 (m, 1H), 6.95 (app t, *J* = 8.0 Hz, 1H), 6.82 (app d, *J* = 8.0 Hz, 1H), 6.79 (app d, *J* = 8.0 Hz, 1H), 6.57 (app t, *J* = 8.0 Hz, 1H), 6.11 (dd, *J* = 17.6, 10.4 Hz, 1H), 5.21 (dd, *J* = 17.6, 0.8 Hz, 1H), 5.10 (dd, *J* = 10.4, 0.8 Hz, 1H), 4.29 (t, *J* = 8.8

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Hz, 1H), 3.80 (t, *J* = 8.8 Hz, 1H), 3.30 (t, *J* = 8.8 Hz, 1H), 1.31 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.0, 147.1, 144.0, 134.6, 128.8, 128.6, 127.3, 127.0, 124.9, 117.9, 112.6, 111.8, 58.7, 57.7, 47.0, 26.6, 22.4. HRMS (ESI) calcd. for $C_{19}H_{22}N^+$ $[M+H]^+$.264.1747, found 264.1745.

1-(2-methylbut-3-en-2-yl)-3-phenyl-1*H*-indole (3n): Prepared according to General Procedure F from **S1d** (52.7 mg, 0.200 mmol) and MnO_2 (87.0 mg, 1.00 mmol, 5.00 equiv) and heated for 24 h. Pure isomer **3n** was isolated as a colorless oil (48.3 mg, 0.185 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 - 7.72 (m, 1H), 7.47 (m, 2H), 7.42 - 7.35 (m, 1H), 7.28 - 7.20 (m, 3H), 7.14 - 7.04 (m, 1H), 7.00 - 6.92 (m, 2H), 5.99 (dd, *J* = 17.0, 10.2 Hz, 1H), 5.06 (dd, *J* = 10.2, 0.8 Hz, 1H), 5.02 (dd, *J* = 17.0, 0.8 Hz, 1H), 1.60 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3, 136.4, 136.2, 129.0, 128.0, 127.8, 126.0, 123.4, 121.4, 120.2, 120.0, 116.5, 114.4, 114.0, 59.6, 28.3. HRMS (ESI) calcd. for $C_{19}H_{20}N^+$ $[M+H]^+$ 262.1590, found 262.1591.

2-(2-(1-(2-methylbut-3-en-2-yl)indolin-3-yl)ethyl)isoindoline-1,3-dione (S1e): Prepared according to General Procedure F from **6e** (146 mg, 0.500 mmol) (reaction time = 3 h). ^{1}H NMR spectroscopy showed a 4:1 *N-tert*-prenylindoline **S1e**:*N-n*-prenylindoline **S2e**. The crude material was purified by flash chromatography (98:2 hexane:Et_2O) to yield **S1e** (89.5 mg, 0.248 mmol, 50%) as a colorless oil. R_f 0.43 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 - 7.82 (m, 2H), 7.76 - 7.68 (m, 2H), 7.13 - 7.03 (m, 2H), 6.95 (t, *J* = 7.7 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.64 (dt, *J* = 12.9, 7.4 Hz, 1H), 6.50 (d, *J* = 7.8 Hz, 1H), 6.10 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.20 (dd, 17.6, 0.8 Hz, 1H), 5.12 (dd, *J* = 10.8, 0.8 Hz, 1H), 3.84 – 3.78 (m, 2H), 3.72 - 3.66 (m, 1H), 3.24 - 3.01 (m, 2H), 2.29 - 2.18 (m, 1H), 1.96 - 1.85 (m, 1H), 1.35 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (100

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MHz, $CDCl_3$): δ 168.7, 150.6, 147.1, 134.3, 134.0, 132.5, 127.3, 123.6, 123.5, 117.6, 112.5, 111.6, 57.5, 55.1, 37.6,36.4, 32.9, 25.6, 23.4, HRMS (ESI) calcd, for $C_{23}H_{24}N_2O_2^+$ $[M+H]^+$ 361.1911, found 361.1917.

2-(2-(1-(2-methylbut-3-en-2-yl)-1*H*-indol-3-yl)ethyl)isoindoline-1,3-dione (3o): Prepared according to General Procedure F from **S1e** (45.7 mg, 0.125 mmol) and MnO_2 (87.0 mg, 1.00 mmol, 5.00 equiv) and heated for 24 h. Pure isomer **3o** was isolated as a yellow/orange oil (42.2 mg, 0.118 mmol, 94%). R_f 0.21 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 – 7.83 (m, 2H), 7.77 - 7.68 (m, 3H), 7.51 - 7.47 (m, 1H), 7.20 (s, 1H), 7.14 - 7.08 (m, 2H), 6.13 (dd, *J* = 17.2, 10.8 Hz, 1H), 5.21 (d, *J* = 10.8 Hz, 1H), 5.14 (d, *J* = 17.2 Hz, 1H), 4.01 (dd, *J* = 7.6 Hz, 7.4 Hz, 2H), 3.15 (dd, *J* = 7.6 Hz, 7.4 Hz, 2H), 1.72 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 144.5, 135.9, 134.1, 132.6, 129.5, 123.6, 123.4, 121.1, 119.3, 119.1, 114.0, 113.7, 110.4, 59.2, 38.9, 28.2, 24.8. HRMS (ESI) calcd. for $C_{23}H_{23}N_2O_2^+$ $[M+H]^+$ 359.1754, found 359.1757.

4-methoxy-1-(2-methylbut-3-en-2-yl)-1*H*-indoline (S1f): Prepared according to General Procedure F from **6f** (74.6 mg, 0.500 mmol) (reaction time = 2 h). ^{1}H NMR spectroscopy showed a 4:1 *N-tert*-prenylindoline **S1f**:*N-n*-prenylindoline **S2f**.. The crude material was purified by flash chromatography (98:2 hexane:Et_2O) to yield **S1f** (63.1 mg, 0.290 mmol, 58%) as a colorless oil. R_f 0.53 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.95 (t, *J* = 7.2 Hz, 1H), 6.52 (d, *J* = 7.2 Hz, 1H), 6.27 (d, *J* = 7.2 Hz, 1H), 6.14 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.23 (d, *J* = 17.6 Hz, 1H), 5.13 (d, *J* = 10.8 Hz, 1H), 3.82 (s, 3H), 3.47 (t, *J* = 8.4 Hz, 2H), 2.88 (t, *J* = 8.4 Hz, 2H), 1.35 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.1, 152.7, 147.5, 128.0, 112.3, 107.7, 105.5, 100.9, 57.7,

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55.5, 49.6, 25.1, 24.5. HRMS (ESI) calcd. for $C_{14}H_{20}NO^+$ $[M+H]^+$ 218.1539, found 218.1545.

4-methoxy-1-(2-methylbut-3-en-2-yl)-1*H*-indole (3j): Prepared according to General Procedure F from **S1f** (43.5 mg, 0.200 mmol) and MnO_2 (87.0 mg, 1.00 mmol, 5.00 equiv) and heated for 24 h. Pure isomer **3j** was isolated as a colorless oil (40.2 mg, 0.186 mmol, 93%). Experimental data matches values for Table 2, entry 4.

5-methoxy-1-(2-methylbut-3-en-2-yl)-1*H*-indoline (S1g): Prepared according to General Procedure F from **6g** (74.6 mg, 0.500 mmol) (reaction time = 2 h) ^{1}H NMR spectroscopy showed a 2:1 *N-tert*-prenylindoline **S1g**:*N-n*-prenylindoline **S2g**. The crude material was purified by flash chromatography (98:2 hexane:Et_2O) to yield **S1g** (28.4 mg, 0.131 mmol, 26%) as a colorless oil. R_f 0.32 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.72 (d, *J* = 8.8 Hz, 1H), 6.71 (s, 1H), 6.52 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.12 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.22 (d, *J* = 17.4 Hz, 1H), 5.12 (d, *J* = 10.8 Hz, 1H), 3.73 (s, 3H), 3.37 (t, *J* = 8.0 Hz, 2H), 2.88 (t, *J* = 8.0 Hz, 2H), 1.31 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7, 147.6, 145.2, 133.4, 112.4, 111.8 (2C), 111.2, 57.7, 56.1, 49.7, 28.8, 24.1. HRMS (ESI) calcd. for $C_{14}H_{20}NO^+$ $[M+H]^+$ 218.1539, found 218.1537.

5-methoxy-1-(2-methylbut-3-en-2-yl)-1*H*-indole (3k): Prepared according to General Procedure F from **S1g** (43.5 mg, 0.200 mmol) and MnO_2 (87.0 mg, 1.00 mmol, 5.00 equiv) and heated for 24 h. Pure isomer **3k** was isolated as a colorless oil (43.4 mg, 0.200 mmol, 99%). Experimental data matches values for Table 2, entry 5.

6-methoxy-1-(2-methylbut-3-en-2-yl)-1*H*-indoline (S1h): Prepared according to General Procedure F from **6h** (74.6 mg, 0.500 mmol) (reaction time = 2 h). ^{1}H NMR spectroscopy showed a 5:1 *N-tert*-prenylindoline **S1h**:*N-n*-prenylindoline **S2h**. The crude

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material was purified by flash chromatography (98:2 hexane:Et_2O) to yield **S1h** (66.2 mg, 0.305 mmol, 61%) as a colorless oil. R_f 0.54 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.95 (d, *J* = 8.0 Hz, 1H), 6.45 (s, 1H), 6.24 - 6.07 (m, 2H), 5.25 (d, *J* = 17.6 Hz, 1H), 5.16 (d, *J* = 10.8 Hz, 1H), 3.74 (s, 3H), 3.46 (t, *J* = 8.0 Hz, 2H), 2.86 (t, *J* = 8.0 Hz, 2H), 1.36 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 152.2, 147.3, 124.2, 113.7, 112.5, 101.1, 99.3, 55.6, 49.9, 27.9, 27.5, 24.3. HRMS (ESI) calcd. for $C_{14}H_{20}NO^+$ $[M+H]^+$ 218.1539, found 218.1539.

6-methoxy-1-(2-methylbut-3-en-2-yl)-1*H*-indole (3l): Prepared according to General Procedure F from **S1h** (43.5 mg, 0.200 mmol) and MnO_2 (87.0 mg, 1.00 mmol, 5.00 equiv) and heated for 24 h. Pure isomer **3l** was isolated as a colorless oil (42.3 mg, 0.196 mmol, 98%). Experimental data matches values for Table 2, entry 6.

5-bromo-1-(2-methylbut-3-en-2-yl)-1*H*-indoline (S1i): Prepared according to General Procedure F from **6i** (99.0 mg, 0.500 mmol) (reaction time = 1.5 h). ^{1}H NMR spectroscopy showed a 5.5:1 *N-tert*-prenylindoline **S1i**:*N-n*-prenylindoline **S2i**. The crude material was purified by flash chromatography (98:2 hexane:Et_2O) to yield **S1i** (98.0 mg, 0.368 mmol, 74%) as a colorless oil. R_f 0.59 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (app s, 1H), 7.03 (dd, *J* = 8.8, 2.0, Hz, 1H), 6.65 (d, *J* = 8.4 Hz, 1H), 6.08 (dd, *J* = 17.6, 11.6 Hz, 1H), 5.22 (d, *J* = 17.6 Hz, 1H), 5.15 (d, *J* = 11.6 Hz, 1H), 3.44 (t, *J* = 8.4 Hz, 2H), 2.89 (t, *J* = 8.4 Hz, 2H), 1.33 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.1, 146.7, 134.1, 129.3, 127.3, 112.8, 112.6, 109.2, 57.6, 49.5, 28.1, 24.3. HRMS (ESI) calcd. for $C_{13}H_{17}BrN^+$ $[M+H]^+$ 266.0539, found 266.0540.

5-bromo-1-(2-methylbut-3-en-2-yl)-1*H*-indole (3p): Prepared according to General Procedure G from **S1i** (53.2 mg, 0.200 mmol) and MnO_2 (87.0 mg, 1.00 mmol, 5.00

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equiv) and heated for 24 h. Pure isomer **3p** was isolated as a colorless oil (46.1 mg, 0.175 mmol, 87%). R_f 0.59 (80:20 hexane:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 1.6 Hz, 1H), 7.40 (app d, *J* = 8.8 Hz, 1H), 7.31 (d, *J* = 3.2 Hz, 1H), 7.20 (dd, *J* = 8.8, 1.6 Hz, 1H), 6.43 (dd, *J* = 3.2, 0.8 Hz, 1H), 6.12 (dd, *J* = 17.6, 11.2 Hz, 1H), 5.24 (d, *J* = 11.2 Hz, 1H), 5.15 (d, *J* = 17.6 Hz, 1H), 1.75 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 134.2, 132.0, 126.6, 123.7, 123.6, 115.4, 114.2, 112.9, 100.5, 59.6, 28.2. HRMS (ESI) calcd. for $C_{13}H_{15}BrN^+$ $[M+H]^+$ 264.0382, found 264.0379.

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CHAPTER 6: CONCLUSIONS

We have shown that a Pd(II)-bipyridine complex catalyzes additions of a wide range of arylboronic acids to β,β-disubstituted enones occur to form ketone products bearing benzylic all-carbon quaternary centers in moderate to high yields. The use of aqueous NaTFA as the reaction medium significantly enhances reactivity and enables the formation of challenging bis-benzylic and *ortho*-substituted benzylic quaternary centers.

We also established two palladium-functionalized bpy-MOFs, bpy-UiO-67-$Pd(OAc)_2$ and MOF-253-$Pd(OAc)_2$, as competent catalysts for conjugate additions of arylboronic acids to *β*,*β*-disubstituted enones in water. We have also demonstrated that MOF-253-$Pd(OAc)_2$ is a reusable catalyst system that promotes additions of a range of arylboronic acid to *β*,*β*-disubstituted enone reaction partners to form ketones containing quaternary carbon centers. However, MOF-253-$Pd(OAc)_2$ was a much less active catalyst than the homogeneous Pd(II)-bipyridine complex for the conjugate additions of phenylboronic acid to β,β-disubstituted enones.

We conducted studies to improve the catalytic activities and stabilities of metalated MOFs containing 2,2′-bipyridyl units. We developed a series of mixed-ligand bipyridyl MOF-supported palladium catalysts which were used to catalyze Suzuki-Miyaura cross-coupling reactions. We have shown for the first time that, the linker modification in m-MOFs can significantly impact the activity in the coupling reactions. We found that the reaction rate of a model Suzuki coupling reaction increases in the order m-6,6´-Me_2bpy-MOF-$PdCl_2$ > m-bpy-MOF-$PdCl_2$ > m-4,4´-Me_2bpy-MOF-$PdCl_2$. We demonstrated that the coupling reaction catalyzed by m-6,6´-Me_2bpy-MOF-$PdCl_2$ is

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heterogeneous and showed the catalyst can be recycled two times without obvious deactivation.

Finally, we developed three strategies based on palladium-catalyzed allylic alkylation reactions to generate *N-tert*-prenylindoles. In the presence of the same palladium catalyst, good yields and high regioselectivity are observed for three distinct classes of nucleophiles. Direct *N-tert*-prenylations of electron-deficient indoles and indolines occur readily, while *N-tert*-prenylations of electron-rich indoles are facilitated by complexation with chromium. Straightforward procedures for oxidative decomplexation of the chromium carbonyl fragments from (η^6-*N-tert*-prenylindole)$Cr(CO)_3$ intermediates and oxidation of the *N-tert*-prenylindoles provide access to electron-rich *N-tert*-prenylindoles in moderate to good yields. Thus, *N-tert*-prenylindoles with a broad range of substitution and electronic character can be accessed through these complementary approaches.

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