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Design and application of porous organic frameworks for recyclable, heterogeneous, transition-metal catalysis

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Design and application of porous organic frameworks for recyclable, heterogeneous, transition-metal catalysis

by

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Levi Stanley, Major Professor
Wenyu Huang
Brett VanVeller

The student author, whose presentation of the scholarship herein was approved by the program of study committee, is solely responsible for the content of this thesis. The Graduate College will ensure this thesis is globally accessible and will not permit alterations after a degree is conferred.

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ABSTRACT

In this thesis, heterogeneous frameworks are explored and examined for their use in recyclable catalysis. Specifically, metal-organic-frameworks (MOFs) and covalent-organic-frameworks (COFs) containing bidentate nitrogen ligands are pursued for their use in transition metal catalysis.

Palladium(II)-functionalized COF (Pd@TpBpy COF) is demonstrated as a recyclable, heterogeneous catalyst for palladium-catalyzed conjugate addition of arylboronic acids to *β*,*β*-disubstituted enones to form ketone products containing all-carbon quaternary centers in aqueous 50 mM NaTFA as the reaction medium. A wide range of arylboronic acids are added to various *β*,*β*-disubstituted enones in moderate-to-high yields.

Pyridine oxazoline derivatives are designed and synthesized for incorporation into MOFs through varying methods including amide coupling, amine coupling, and solvent-assisted ligand incorporation (SALI). Preliminary data shows potential for palladium-catalyzed, enantioselective conjugate addition of phenylboronic acid to *β*,*β*-disubstituted enones to form ketone products.

CHAPTER 1. INTRODUCTION

General Introduction

The importance of green chemistry has grown significantly in recent decades.[1-2] In pursuit of efficient and eco-friendly chemical syntheses and reactivities, chemists have aimed to develop processes that increase atom economy and decrease the need of hazardous chemicals.[3] One approach that is sought after is the replacement of organic solvents with aqueous media to decrease the amount of hazardous waste.[4]

Another route towards sustainable chemistry is the development of heterogeneous catalysts that can overcome the difficulties associated with the recyclability of homogeneous systems.[5] A variety of heterogeneous systems have been developed, with metal-organic frameworks (MOFs) and covalent-organic frameworks (COFs) drawing interest for applications in transition metal catalysis.

MOFs are stable, tunable, and recyclable materials composed of inorganic metal centers called nodes and organic linkers that bridge node to node. They possess large surface areas and highly ordered crystalline structures to allow for single site catalysis to occur.[6] The first report for catalysis from Fujita et al. in 1994 broke ground into a field that continuous to grow significantly.[7]

A key aspect of MOFs is their ability to maintain crystallinity during catalysis, making them significantly more recyclable catalytic systems than traditional homogeneous catalysts. The organic linkers can be designed to tune pore size, shape, chirality, and electronic properties of MOFs to suit the application. For catalysis, this often means the inclusion of modified ligands such as bipyridine, phenanthroline, BINAP, and BINOL type ligands (Figure 1).[8-13]

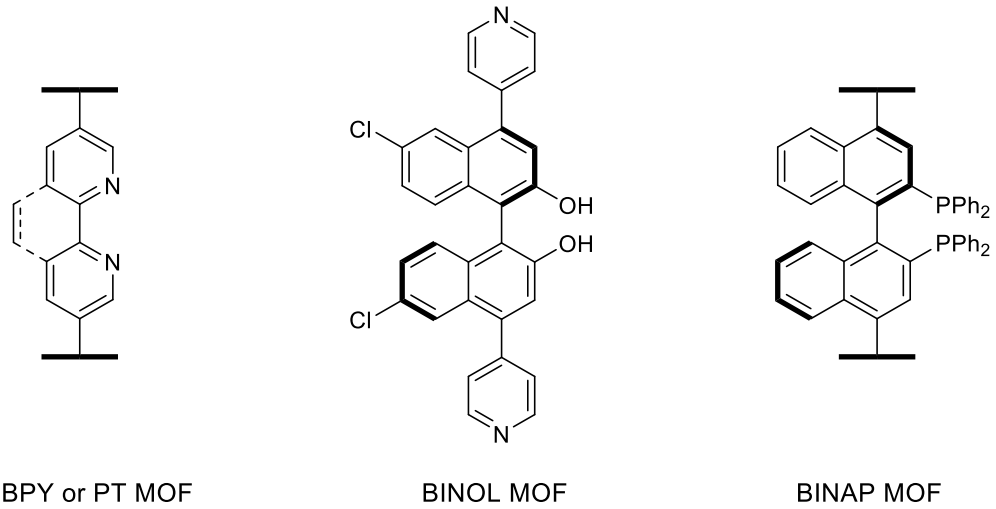

Figure 1. Examples of ligands being built into the organic linkers of MOFs for use in recyclable, transition-metal catalysis.

In addition to changing the linker's core structure, studies have emerged that are able to bind ligands to the linker backbone through pre-synthetic or post-synthetic modification. A report from Wenbin Lin details the use of chiral dienes pre-synthetically tethered to the linker through an amide bond coupling for asymmetric catalysis (Figure 2).[14]

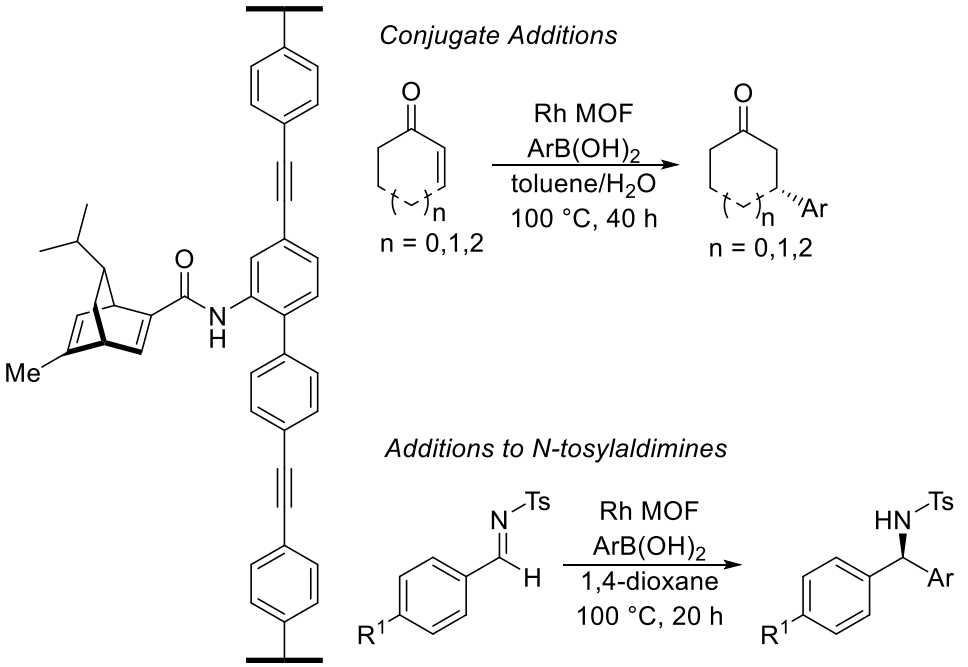

Figure 2. Use of amide bond coupling to attach a chiral diene ligand for asymmetric MOF catalysis.

A third method of ligand inclusion, solvent assisted ligand incorporation (SALI) makes use of the metal nodes for direct linker coordination.[15] Installing carboxylic acid moieties on common ligands allows for coordination to open sites on the metal clusters. At this point, the only transition-metal catalysis performed with SALI MOFs is gas-phase dimerization of ethylene.[16]

This thesis describes work towards inclusion of substituted pyridine oxazoline (PyOx) type ligands for use in asymmetric catalysis. PyOx ligands have been developed for use in a variety of transformations.[17-22] Studies by our group and Stoltz's group have demonstrated the viability of PyOx ligands for palladium-catalyzed, homogeneous, enantioselective conjugate additions of arylboronic acids to α,β-unsaturated ketones (Figure 3).[19-21] Additional studies by our group have led to the development of racemic conjugate addition reactions in aqueous sodium trifluoroacetate catalyzed by palladium(II)-bipyridine complexes for both homogeneous and MOF systems.[23-24]

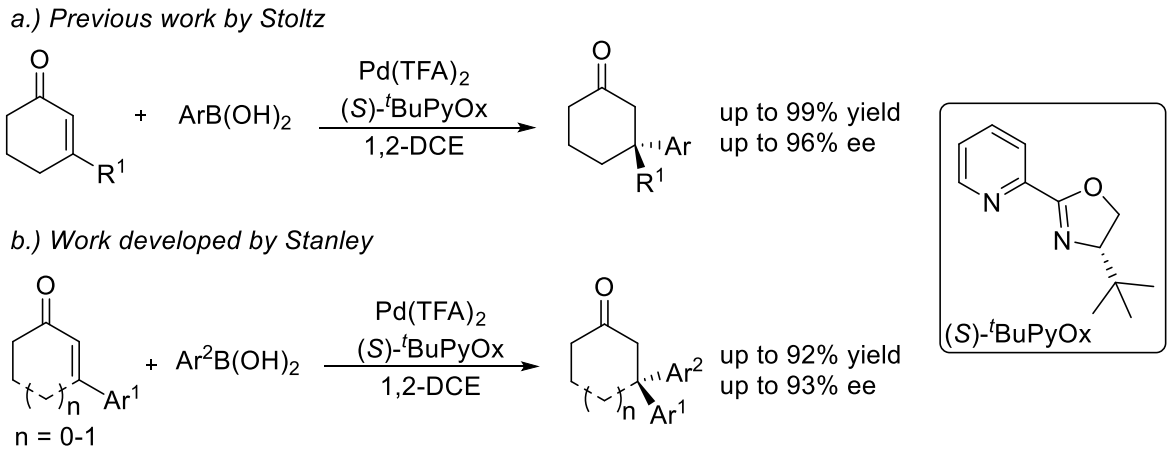

Figure 3. Homogeneous development of PyOx ligands for conjugate addition reactions.

This thesis details the application of a palladium(II)-bipyridine covalent organic framework for racemic conjugate additions of arylboronic acids to α,β-unsaturated ketones in aqueous media. COFs have recently emerged as promising heterogeneous catalytic systems for

both organocataylsis[6, 25-26] and transition-metal catalysis.[15, 27-31] Similarly to MOFs, covalent organic frameworks possess pores and high surface areas to provide single site catalysts of organic transformations. They differ from MOFs in the lack of metal nodes for coordination. Instead of nodes, COFs are composed of multiple organic linkers that are joined together in various topographies by either boronic ester, triazine, imide, and most commonly, imine formation.[26, 32] The majority of COFs make use of two-dimensional π-π stacking to provide stability for the heterogeneous structure. With the growth of recyclable and green catalysis, it is crucial to expand the utility and reactivities of both COF and MOF systems.

Thesis Organization

This thesis contains three chapters composed of a manuscript in preparation for publication and general progress on a project. Chapter one is a general introduction to the development of heterogeneous catalysts and the potential applications of such materials for conjugate addition reactions. Chapters two and three discuss the studies performed by the author of this thesis.

Chapter two is a modification of a manuscript in preparation detailing the studies on palladium-loaded TpBpy COF and its use as a recyclable catalyst for the conjugate addition of arylboronic acids to *β*,*β*-disubstituted enones in aqueous media. This work was done in close collaboration with Patrick Heintz. The author of this thesis is responsible for performing the conjugate addition reactions described and characterization of their products. Patrick Heintz was responsible for the synthesis, preparation, metalation, and characterization of TpBpy and its linker precursors.

Chapter three details the design and synthesis of pyridine oxazoline ligands for incorporation in MOFs for potential enantioselective catalysis. It also discusses initial results

for inclusion of the ligands in MOFs. This work was done in collaboration with Kevin Dolge. The author of this thesis is responsible for the synthesis of all ligands, linkers, and their corresponding characterization. Kevin Dolge was responsible for solvent assisted ligand insertion of the ligand onto the MOF NU-1000.

Chapter four draws general conclusions for the research completed during the author's graduate studies.

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CHAPTER 2. PD@TPBPY: A RECYLABLE COF FOR PALLADIUM-CATALYZED CONJUGATE ADDITIONS IN AQUEOUS MEDIA

Modified from a manuscript in preparation

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Abstract

A palladium(II)-functionalized covalent organic framework constructed from 1,3,5-triformylphloroglucinol and [2,2'-bipyridine]-5,5'-diamine (Pd@TpBpy COF) is evaluated as a recyclable catalyst for conjugate additions in aqueous media. Addition of an array of stereoelectronically diverse arylboronic acid nucleophiles have been applied to a selection of *β*,*β*-disubstituted enones to form a variety of ketones containing benzylic all-carbon quaternary centers in low-to-high yields (20-92%) has been studied. Pd@TpBpy remains active through 7 cycles.

Introduction

Covalent organic frameworks (COFs) have recently emerged as promising heterogeneous catalytic platforms for organo- and transition metal-catalysis[1]. COFs synthesized via reversible imine condensations have been most commonly reported as active catalytic systems[2]. Via coordination of transition metals to imine and pyridyl nitrogen atoms, COFs have been proven as viable catalysts for a handful of transition metal-catalyzed organic transformations including: cross-coupling reactions (Heck[3], Suzuki-Miyaura[4-5], and silane to aryl iodide[6]), CO oxidation,[7] and hydroformylation.[8] These reports provide a foundation for

COFs in catalysis, allowing future studies to progress towards expanding the scope of reactions and advancement of their use in green chemistry.

Our group has recently developed aqueous reaction conditions for the conjugate addition of arylboronic acids to *β*,*β*-disubstituted enones catalyzed by palladium(II) complexes of 2,2'-bipyridine for both homogeneous and MOF catalyst systems.[9-10] We were prompted to extend the system to COFs to expand the reactivities and robustness of the emerging frameworks as heterogeneous catalysts. Herein, we report the application of Pd@TpBpy COF as a recyclable catalyst for the conjugate additions of aryl-boronic acids to *β*,*β*-disubstituted enones in aqueous media.

Results and Discussion

TpBpy COF and its corresponding linkers, 1,3,5-triformylphloroglucinol and [2,2'-bipyridine]-5,5'-diamine were synthesized following reported protocols, making use of rapid COF synthesis via salt-mediated crystallization.[11] Powder X-ray diffraction (PXRD) patterns (Figure 1) and nitrogen physisorption analyses of TpBpy COF (Figure 2) agree with previously reported data. BET surface area was calculated to be 582 m^2/g. TpBpy COF was then post synthetically metallated with $Pd(OAc)_2$ in dichloromethane at room temperature to provide Pd@TpBpy COF. The framework maintained crystallinity after metalation based on PXRD. Inductively coupled plasma-mass spectrometry (ICP-MS) was used to quantitatively determine the weight percent palladium content to be 5.78%.

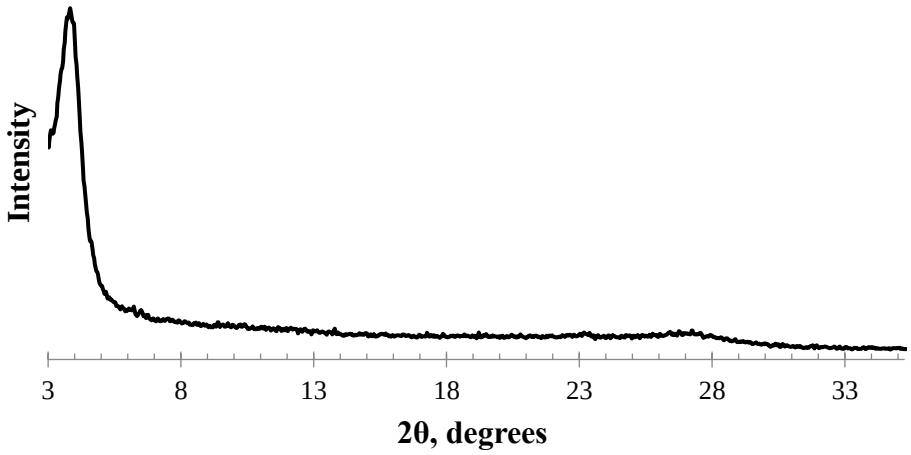


Figure 1. PXRD pattern of synthesized TpBpy COF.

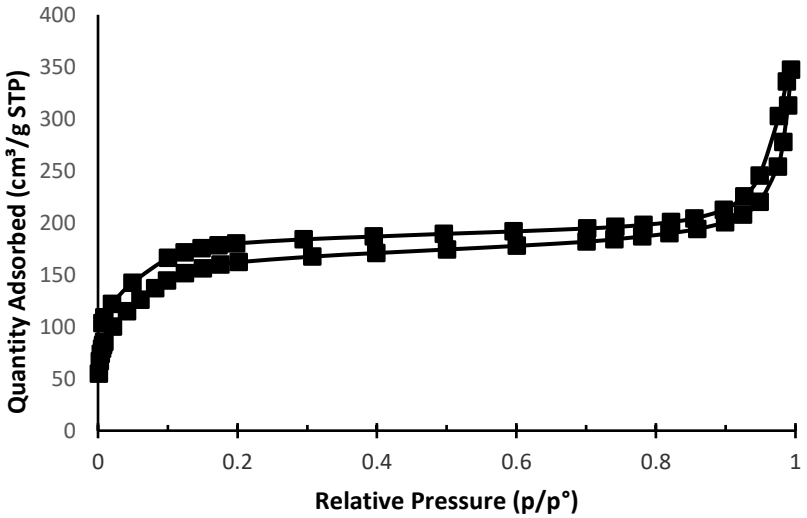
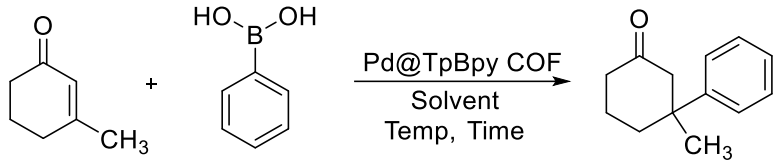


Figure 2. Nitrogen adsorption/desorption isotherms of TpBpy COF (BET surface area calculated to be 582 m^2/g).

After characterization of Pd@TpBpy COF, the model reaction of the conjugate addition of phenylboronic acid to 3-methylcyclohex-2-en-1-one **1a** was optimized to determine the reactivity of the COF (Table 1). Testing the reaction using standard homogeneous conditions[12] (mol % Pd based on total amount of Pd in reaction from 5.78% w/w% Pd@TpBpy COF) provided the ketone product **2a** in 68% after 16 hours (entry 1). Changing reaction media

to the 50 mM aqueous sodium trifluoroacetate (aq. NaTFA, pH = 8.2) and increasing the reaction temperature to 100 °C afforded **2a** in 99% yield using 5 mol % palladium (entry 2).

Table 1. Identification of Reaction Conditions [a]



Entry	Solvent	mol % Pd	Temp (°C)	Time (h)	Yield (%)[b]
1	1,2 DCE	10	60	16	68
2	NaTFA	5.0	100	16	99
3	NaTFA	2.0	100	16	99
4	NaTFA	1.0	100	16	99
5	NaTFA	1.0	100	8.0	99
6	NaTFA	1.0	100	6.0	99
7	NaTFA	1.0	100	4.0	99
8	NaTFA	1.0	100	2.0	98
9	NaTFA	1.0	100	0.5	47
10[c]	NaTFA	0.5	100	2.0	65
11[d]	NaTFA	1.0	100	2.0	87

[a] Reaction conditions: **1a** (0.5 mmol), $PhB(OH)_2$ (1 mmol), Pd@TpBpy COF (0.005-0.010 mmol Pd), solvent (0.33 mL) (NaTFA tuned to pH = 8.2). [b] Determined by ^1H NMR spectroscopy using dibromomethane as internal standard. [c] Reaction ran with 1 mmol **1a**, 2 mmol $PhB(OH)_2$, and 0.67 mL aq. NaTFA. [d] Reaction run with 1.2 equivalents of $PhB(OH)_2$.

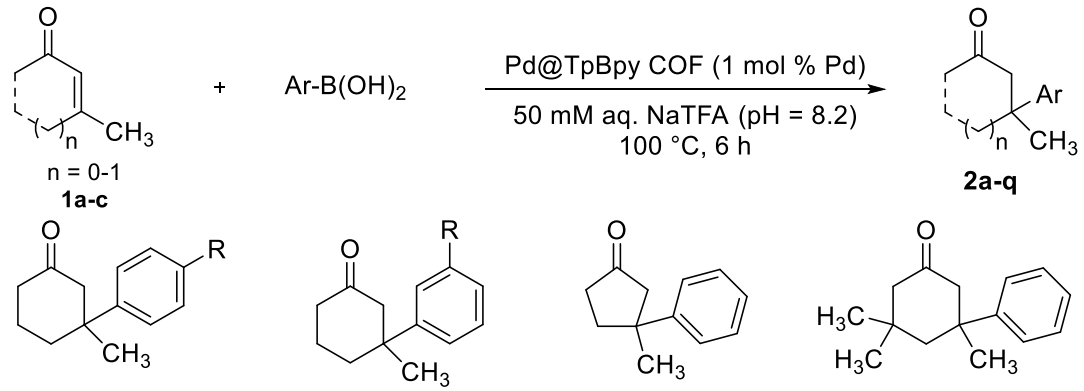
In further optimization, we analyzed the palladium loading, reaction time, and equivalents of phenylboronic acid. We found 1 mol% palladium was sufficient to catalyze the reaction over 16 hours to afford **2a** in 99% yield (entries 3-4). We then studied the reaction time and found the reaction proceeded to 98% yield in 2 hours (entries 5-7). To further screen the reactivity, we further decreased both the time (entry 8) and the palladium loading (entry 9) obtaining decreased yields of 55% and 65% respectively. Lastly, we attempted the reaction

with 1.2 equivalents of phenylboronic acid, observing a yield of 87% (entry 10). Keeping in mind the reactivity differences of arylboronic acids, we continued studies using 1 mol% Pd and 2.0 equivalents of arylboronic acid for six hours.

With practical reaction conditions identified, we set out to evaluate the scope of the conjugate addition reaction. Using Pd@TpBpy COF as the catalyst, an array of arylboronic acids were added to a selection of enones **1a-c** (Scheme 1). The parent reaction of 3-methylcyclohex-2-en-1-one, **1a**, with phenylboronic acid yields **2a** in 92% isolated yield. The conjugate addition of 4-substitued arylboronic acids proceeds well. Electron rich 4-methoxyphenyl boronic acid reacts with **1a** to produce ketone **2b** in 72% yield. Electron deficient 4-trifluoromethylphenylboronic acid is also tolerated, generating **2c** in 77% yield. The reaction with 4-tolylboronic acid proceeds well to yield 80% of the desired ketone **2d**. The addition of 4-chlorophenylboronic acid is well tolerated, leading to 86% yield of ketone **2e**. We are also able to perform the addition of arylboronic acids containing a free hydroxyl group, although in lower yield (**2f**, 58%).

3-Substituted arylboronic acids were also found to be reactive substrates for Pd@TpBpy-catalyzed conjugate additions. Electron-donating, electron-withdrawing, and halogen 3-substituted arylboronic acids reacted with **1a** to produce ketones **2g-k** in moderate-to-good yields (54-92%). We also evaluated other enones, finding the additions of phenylboronic acid to 3-methylcyclopent-2-en-1-one **1b** and to 3,5,5-trimethylcyclohex-2-en-1-one **1c** to yield 80% and 77% of products **2l** and **2m**.

Scheme 1. Pd@TpBpy COF Catalyzed Conjugate Addition of Arylboronic Acids to Enones 1a-c in Aqueous Media [a]



2a (R = H): 92%
2b (R = OMe): 72%
2c (R = CF_3): 77%
2d (R = Me): 80%
2e (R = Cl): 86%
2f (R = OH): 58%

2g (R = OMe): 92%
2h (R = CF_3): 83%
2i (R = Me): 56%
2j (R = Cl): 68%
2k (R = NO_2): 54%

2l: 80%

2m: 77%

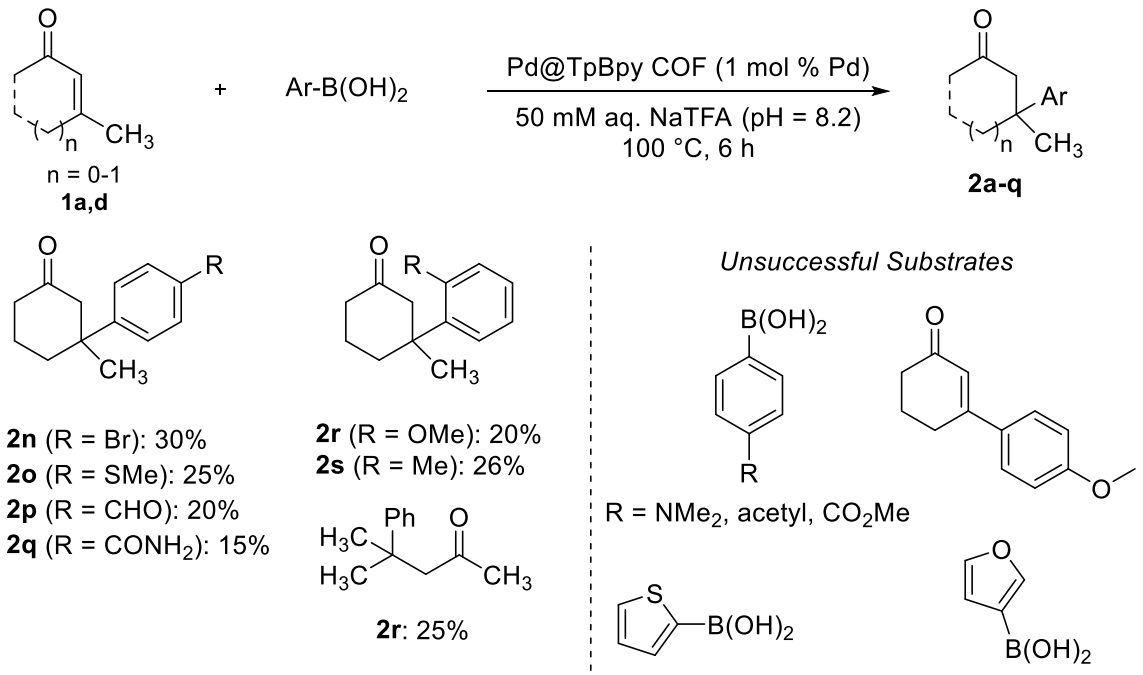
[a] Reaction Conditions: Enone **1a-c** (0.5 mmol), arylboronic acid (2.0 mmol), Pd@TpBpy COF (0.01 mmol Pd), 50 mM aqueous NaTFA (0.33 mL, pH = 8.2), 100 °C, 6 h. Isolated yields reported after purification by flash column chromatography.

To further examine the scope of the conjugate addition reactions, we screened a variety of more functionalized and less reactive (hetero)arylboronic acids and an acyclic enone (Scheme 2). Probing additional functional group tolerance, we found lower reactivities for bromo-, sulfane-, formyl-, and benzamide-substituted phenylboronic acids that generated ketones **2n-q** in 15-30% yields.

We also screened 2-substituted arylboronic acids, finding 2-methoxyphenylboronic acid reacting to form ketone **2r** in 20% yield and 2-methylphenylboronic acid generating 26% of ketone **2s**. It is known that 2-substituted arylboronic acids are likely to undergo protodeborylation,[13-16] leading to lower yields of the desired products. 4-Methylpent-3-en-2-

one **1d** was also examined as a suitable enone starting material, producing 25% of acyclic ketone **2r**. We also probed dimethyl-amino, acetyl, and methyl benzoate substituted arylboronic acids but observed no product. Heteroarylboronic acids also did not produce ketone products. Additionally, the addition of phenylboronic acid to 4'-methoxy-5,6-dihydro-[1,1'-biphenyl]-3(4H)-one was unsuccessful.

Scheme 2. Pd@TpBpy COF Catalyzed Conjugate Addition of Less Reactive Arylboronic Acids to Enones 1a,d in Aqueous Media [a]

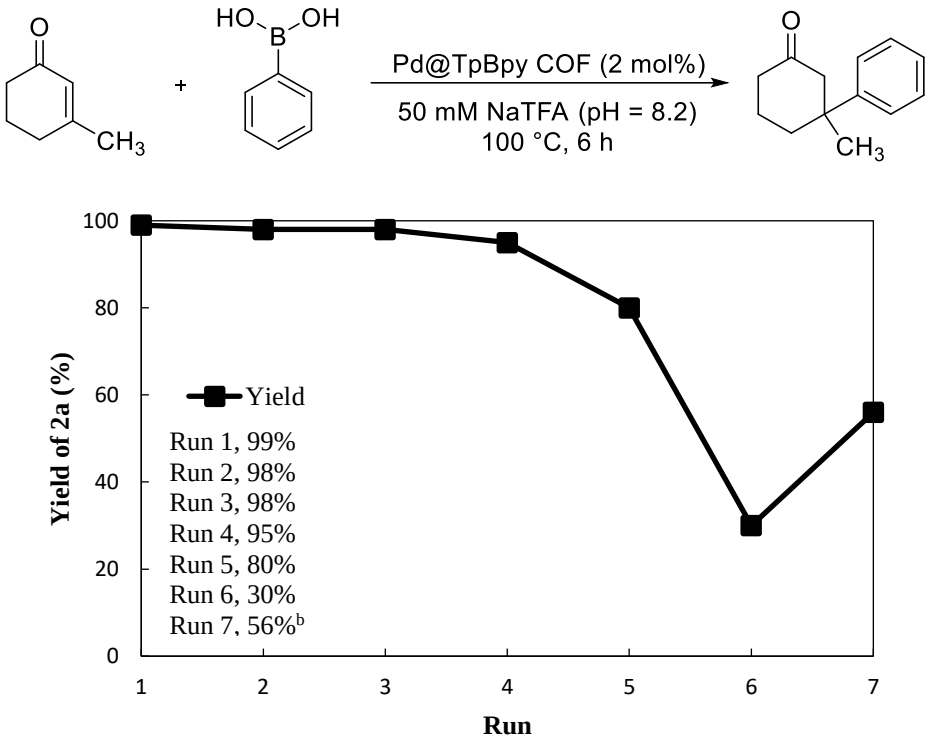


[a] Reaction Conditions: Enone **1a-c** (0.5 mmol), arylboronic acid (2.0 mmol), Pd@TpBpy COF (0.01 mmol Pd), 50 mM aqueous NaTFA (0.33 mL, pH = 8.2), 100 °C, 6 h. ^{1}H NMR yields with dibromomethane as standard are reported.

To determine the stability of Pd@TpBpy COF, we tested the recyclability in the conjugate addition of phenylboronic acid to **1a** (Scheme 3). As expected, fresh material formed ketone product **2a** in 99% yield over six hours. After recovering and washing the catalyst, additional **1a**, phenylboronic acid, and aqueous NaTFA were added. Runs 2-4 maintained high yields (95-98%). A significant decrease to 80% yield was observed in run 5, potentially due to

deterioration of the heterogeneous catalyst. An even larger decrease to 30% yield was observed after run 6. Allowing the reaction to run for 11 h for run 7 yielded 56% of the desired product.

Scheme 3. Six Hour Recycling Studies[a]



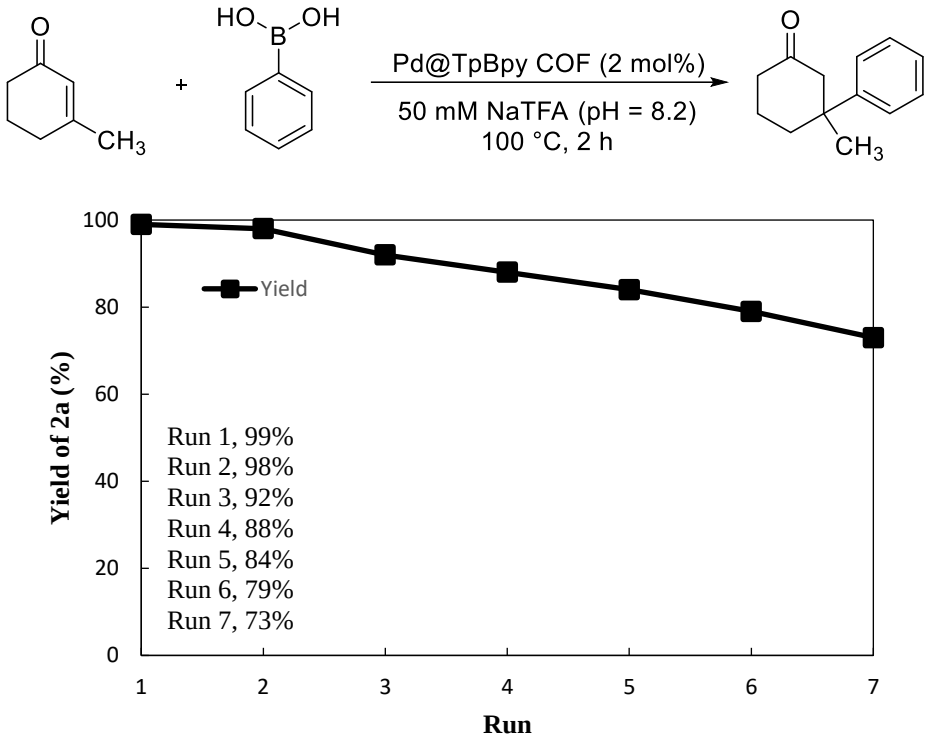
[a] Reaction conditions: **1a** (1.50 mmol, 1.00 equiv), $PhB(OH)_2$ (3.00 mmol, 2.00 equiv), Pd@TpBpy (0.030 mmol, 0.020 equiv) and aqueous 50 mM NaTFA (1.00 mL). Yields determined by ^1H NMR spectroscopy using dibromomethane as an internal standard. [b] Reaction ran for 11 hours.

To test for leaching of palladium species, ICP-MS of post-reaction supernatant and Pd@TpBpy was conducted. After 6 hours, the supernatant contained 126 µg Pd (3.97% original palladium content in the reaction). Analysis of used Pd@TpBpy that had been reacted for 48 hours, found 1.28 mg Pd (40% of original palladium content in the COF). To determine if the leached palladium was catalytically active, we set up a reaction in which Pd@TpBpy was removed from the reaction at 30 minutes and the remaining reagents were heated until six hours of total reaction time. This yielded 48% (via ^1H NMR) of ketone product **2a**. This data shows any palladium species that may be leaching is effectively inactive as a catalyst when

compared to Table 1, Entry 9, in which the reaction yielded ketone **2a** in 47% over a 30-minute reaction time.

With knowledge that palladium leaches out of the COF over time, we decided to run additional recycling studies in which the reaction was performed for two hours in hopes of maintaining higher yields between runs. We observed more consistent yields with lower decrease in activity between runs, maintaining yields of 73% or higher through 7 runs.

Scheme 4. Two Hour Recycling Studies[a]



[a] Reaction conditions: **1a** (1.50 mmol, 1.00 equiv), $PhB(OH)_2$ (3.00 mmol, 2.00 equiv), Pd@TpBpy (0.030 mmol, 0.020 equiv) and aqueous 50 mM NaTFA (1.00 mL). Yields determined by ^1H NMR spectroscopy using dibromomethane as an internal standard.

Conclusion

To summarize, we have shown Pd@TpBpy COF to be a recyclable, heterogeneous catalyst for conjugate addition of arylboronic acids to β,β-disubstituted enones in aqueous media. It is a reusable catalyst that tolerates a wide variety of arylboronic acid functionalities

and a selection of enone derivatives. Establishing Pd@TpBpy as a recyclable, water-stable catalyst expands the scope and potential for COFs and their use in green catalysis.

Experimental

General Experimental Details. Nitrogen physisorption isotherms were recorded in a Micrometrics 3Flex surface characterization analyzer at 77 K. COF samples (ca. 100 mg) were degassed under vacuum (~5 x 10^{-5} torr) at 200 °C for 12 h prior to analysis. Powder X-ray diffraction (PXRD) patterns of the COF samples were obtained on a STOE Stadi P powder diffractometer using Cu Kα radiation (40 kV, 40 mA, λ = 0.1541 nm). COFs 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 on Pd@TpBpy COF. Prior to ICP-MS measurements, Pd@TpBpy COF was 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 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.

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 based on indirect reference to $CDCl_3$.[17] Coupling constants are reported in hertz.

Materials.

3-Methylcyclohex-2-en-1-one, 3-methycyclopent-2-en-1-one, 4-methylpen-3-en-2-one, and 3,5,5-trimethylcyclohex-2-en-1-one were purchased from Tokyo Chemical Industry and used without further purification. 4-Methylphenylboronic acid, 4-trifluoromethylphenylboronic acid, 2-methoxyphenylboronic acid, 2-methylphenylboronic acid, 3-nitrophenylboronic acid, 4-bromophenylboronic acid, 4-methylthiophenylboronic acid, 4-formylphenylboronic acid, 4-carbamoylphenylboronic acid, 4-methoxycarbonylphenylboronic acid, furan-3-ylboronic acid, and 3-chlorophenylboronic acid were purchased from Frontier Scientific and used without further purification. 4-Methoxyphenylboronic acid, 4-acetylphenylboronic acid, 3-methoxyphenylboronic acid, and 3-trifluoromethylphenylboronic acid were purchased from AK Scientific and used without further purification. 4-Dimethylaminophenylboronic acid was purchased from Sigma Aldrich and used without further purification. 4-chlorophenylboronic acid was purchased from Combi-Blocks and used without further purification. 3-Methylphenylboronic acid was purchased from Ark Pharm and used without further purification. 4-Hydroxyphenylboronic acid was purchased from Alfa Aesar and used without further purification. Thiophen-2-ylboronic acid was purchased from Matrix Scientific and used without further purification. TpBpy COF, 1,3,5-Triformylphloroglucinol and [2,2'-bipyridine]-5,5'-diamine were synthesized according to reported procedures.[11]

General Procedure for the Metalation of TpBpy COF

$Pd(OAc)_2$ (60 mg), amount determined based on target loading, was weighed and charged into a 20ml vial. The powder was dissolved in 3mL of anhydrous dichloromethane. TpBpy COF (50 mg) was then suspended in the solution and allowed to stir at room temperature for 24 h. Following completion, the mixture was centrifuged down, the organic layer was removed, and the remaining solid was washed subsequently with dichloromethane (3 x 50mL) and dried under reduced pressure.

General Procedure A: Pd@TpBpy COF Catalyzed Conjugate Additions of Arylboronic Acids to Enones 1a-1d

In a 1-dram vial, Pd@TpBpy COF (0.005 mmol, 0.01 equiv), the appropriate arylboronic acid (1.00 mmol, 2.00 equiv), enone **1a-d**, and 50 mM aqueous sodium trifluoroacetate solution (333 µL, pH = 8.2) were added. The vial was sealed with a PFTE/silicone-lined septum cap. The reaction mixture was heated to and stirred at 100 ºC for 6 hours. The mixture was cooled to room temperature and diluted with EtOAc (3 mL), and filtered through a pad of silica gel. The pad was washed with EtOAc (3 x 10 mL). The resulting solution was washed with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was dissolved in $CDCl_3$ and CH_2Br_2 (17.6 µL, 0.250 mmol) was added as an internal standard. ^1H NMR spectroscopy was used to determine NMR yields 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-2m**.

Characterization Data for Ketones 2a-2m

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). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to

yield **2a** (86 mg, 0.456 mmol, 92%) as a colorless oil. Characterization is consistent with previously reported data.[18] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (s, 3H), 1.62-1.71 (m, 1H), 1.85-1.95 (m, 2H), 2.16-2.22 (m, 1H), 2.31 (app t, *J* = 7.0 Hz, 2H), 2.44 (d, *J* = 14.2 Hz, 1H), 2.88 (d, *J* = 14.2 Hz, 1H), 7.19-7.22 (m, 1H), 7.31-7.33 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.3, 30.1, 38.2, 41.1, 43.1, 53.4, 125.8, 126.5, 128.8, 147.7, 211.7.

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). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2b** (79 mg, 0.361 mmol, 72%) as a clear, yellow oil. Characterization is consistent with previously reported data.[18] ^{1}H NMR (600 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 Hz, 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 22.3, 30.4, 28.4, 41.1, 42.6, 53.6, 55.5, 114.1, 126.9, 139.8, 158.1, 211.8.

3-methyl-3-(4-(trifluoromethyl)phenyl)cyclohexan-1-one (2c): Prepared according to General Procedure A from 3-methylcyclohex-2-en-1-one **1a** (55 mg, 0.50 mmol) and 4-trifluoromethylphenylboronic acid (190 mg, 1.00 mmol). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2c** (99 mg, 0.387 mmol, 77%) as a colorless oil. Characterization is consistent with previously reported data.[19] ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.34 (s, 3H), 1.60-1.67 (m, 1H), 1.87-1.98 (m, 2H), 2.18-2.23 (m, 1H), 2.29-2.37 (m, 2H), 2.47 (d, *J* = 14.2 Hz, 1H), 2.88 (d, *J* = 14.2 Hz, 1H), 7.44 (d, *J* = 8.2, 2H), 7.58 (d, *J* = 8.2, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.2, 30.1, 38.1, 41.0, 43.4, 53.1, 124.5 (q, *J*

= 270 Hz), 125.8, 126.4, 128.8 (q, *J* = 32 Hz), 151.8, 210.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.5 (s, 3F)

3-methyl-3-(p-tolyl)cyclohexan-1-one (2d): Prepared according to General Procedure A from 3-methylcyclohex-2-en-1-one **1a** (55 mg, 0.50 mmol) and 4-tolylphenylboronic acid (136 mg, 1.00 mmol). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2d** (81 mg, 0.400 mmol, 80%) as a colorless oil. Characterization is consistent with previously reported data.[18] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (s, 3H), 1.64-1.73 (m, 1H), 1.82-1.94 (m, 2H), 2.14-2.21 (m, 1H), 2.27-2.35 (m, 5H), 2.42 (d, *J* = 14.2 Hz, 1H), 2.87 (d, *J* = 14.2 Hz, 1H), 7.14 (br d, *J* = 8 Hz, 2H), 7.21 (br d, *J* = 8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 21.2, 22.3, 30.2, 38.2, 41.1, 42.8, 53.5, 125.8, 129.5, 136.0, 144.8, 211.8.

3-(4-chlorophenyl)-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 4-chlorophenylboronic acid (156 mg, 1.00 mmol). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2e** (96 mg, 0.429 mmol, 86%) as a colorless oil. Characterization is consistent with previously reported data.[20] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (s, 3H), 1.58-1.68 (m, 1H), 1.82-1.93 (m, 2H), 2.11-2.18 (m, 1H), 2.30 (app t, *J* = 7.0 Hz, 2H), 2.42 (d, *J* = 14.2 Hz, 1H), 2.83 (d, *J* = 14.2 Hz, 1H), 7.22-7.29 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.3, 30.3, 38.2, 41.0, 43.0, 53.3, 127.4, 128.9, 132.3, 146.2, 211.3.

3-(4-hydroxyphenyl)-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 4-hydroxyphenylboronic acid (138 mg, 1.00 mmol). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2f** (60 mg, 0.292 mmol, 58%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (s, 3H), 1.56-1.67 (m, 1H), 1.81-1.91 (m, 2H), 2.15-

2.21 (m, 1H), 2.31 (app t, *J* = 6.4 Hz, 2H), 2.42 (d, *J* = 14.2 Hz, 1H), 2.90 (d, *J* = 14.2 Hz, 1H), 5.95 (s, 1H), 6.77 (d, *J* = 8.6, 2H), 7.15 (d, *J* = 8.6, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.4, 31.2, 38.3, 41.1, 43.0, 53.5, 115.7, 127.2, 138.8, 154.6, 214.0.

3-(3-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 3-methoxyphenylboronic acid (152 mg, 1.00 mmol). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2g** (100 mg, 0.458 mmol, 92%) as a clear, yellow oil. Characterization is consistent with previously reported data.[19] ^{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 (app t, *J* = 7.0 Hz, 2H), 2.43 (d, *J* = 14.2 Hz, 1H), 2.86 (d, *J* = 14.2 Hz, 1H), 3.80 (s, 3H), 6.75 (dd, *J* = 8, 2 Hz, 1H), 6.87 (app t, *J* = 2 Hz, 1H), 6.91 (ddd, *J* = 8, 2, 1 Hz, 1H), 7.25 (t, *J* = 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.3, 30.0, 38.2, 41.1, 43.1, 53.4, 55.4, 111.2, 112.5, 118.3, 129.8, 149.5, 160.0, 211.6.

3-methyl-3-(3-(trifluoromethyl)phenyl)cyclohexan-1-one (2h): Prepared according to General Procedure A from 3-methylcyclohex-2-en-1-one **1a** (55 mg, 0.50 mmol) and 3-trifluoromethylphenylboronic acid (190 mg, 1.00 mmol). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2h** (106 mg, 0.414 mmol, 83%) as a colorless oil. Characterization is consistent with previously reported data.[19] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (s, 3H), 1.63-1.73 (m, 1H), 1.86-2.00 (m, 2H), 2.15-2.22 (m, 1H), 2.27-2.39 (m, 2H), 2.48 (d, *J* = 14.2 Hz, 1H), 2.86 (d, *J* = 14.2 Hz, 1H), 7.41-7.52(m, 3H), 7.57 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.3, 29.7, 38.0, 41.0, 43.3, 53.2, 122.6, 123.5, 124.5 (q, *J* = 271 Hz), 129.3, 129.4, 131.2 (q, *J* = 32 Hz), 148.9, 211.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.5 (s, 3F)

3-methyl-3-(m-tolyl)cyclohexan-1-one (2i): Prepared according to General Procedure A from 3-methylcyclohex-2-en-1-one **1a** (55 mg, 0.50 mmol) and 3-tolylphenylboronic acid (136 mg, 1.00 mmol). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2i** (57 mg, 0.282 mmol, 56%) as a colorless oil. Characterization is consistent with previously reported data.[19] ^{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 (100 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-chlorophenyl)-3-methylcyclohexan-1-one (2j): 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). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2j** (76 mg, 0.339 mmol, 68%) as a colorless oil. Characterization is consistent with previously reported data.[20] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (s, 3H), 1.62-1.73 (m, 1H), 1.84-1.94 (m, 2H), 2.11-2.18 (m, 1H), 2.31 (app t, *J* = 7.0 Hz, 2H), 2.42 (d, *J* = 14.2 Hz, 1H), 2.82 (d, *J* = 14.2 Hz, 1H), 7.16-7.26 (m, 3H), 7.29 (br t, *J* = 2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.3, 29.8, 38.1, 41.0, 43.2, 53.2, 124.2, 126.3, 126.8, 130.1, 134.8, 150.0, 211.1

3-methyl-3-(3-nitrophenyl)cyclohexan-1-one (2k): Prepared according to General Procedure A from 3-methylcyclohex-2-en-1-one **1a** (55 mg, 0.50 mmol) and 3-nitrophenylboronic acid (167 mg, 1.00 mmol). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2k** (63 mg, 0.268 mmol, 54%) as a yellow oil. Characterization is consistent with previously reported data. ^{1}H NMR (400 MHz, $CDCl_3$):

δ 1.36 (s, 3H), 1.64-1.74 (m, 1H), 1.89-2.01 (m, 2H), 2.19-2.26 (m, 1H), 2.32-2.38 (m, 2H), 2.52 (d, *J* = 14 Hz, 1H), 2.88 (d, *J* = 14 Hz, 1H), 7.50 (t, *J* = 8 Hz, 1H), 7.66 (br d, *J* = 8 Hz, 1H), 8.08 (br d, *J* = 8 Hz, 1H), 8.22 (t, *J* = 2, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.3, 29.7, 38.0, 41.0, 43.5, 53.1, 121.1, 121.7, 129.9, 132.2, 148.9, 150.1, 210.4.

3-methyl-3-phenylcyclopentan-1-one (2l): 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). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2l** (70 mg, 0.402 mmol, 80%) as a colorless oil. Characterization is consistent with previously reported data.[18] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (s, 3H), 2.26-2.32 (m, 2H), 2.34-2.50 (m, 3H), 2.66 (d, *J* = 17.6 Hz, 1H), 7.21-7.26 (m, 1H), 7.28-7.40 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.7, 36.1, 37.1, 44.1, 53.5, 125.7, 126.6, 128.9, 148.8, 218.8.

3,3,5-trimethyl-5-phenylcyclohexan-1-one (2m): Prepared according to General Procedure A from 3,5,5-trimethylcyclohex-2-en-1-one **1c** (69 mg, 0.50 mmol) and phenylboronic acid (122 mg, 1.00 mmol). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to yield **2m** (83 mg, 0.386 mmol, 77%) as a colorless oil. Characterization is consistent with previously reported data.[21] ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.39 (s, 3H), 1.04 (s, 3H), 1.37 (s, 3H), 1.91 (d, *J* = 14.2, 1H), 2.10 (dt, *J* = 13.6, 2 Hz, 1H), 2.20-2.29 (m, 2H), 2.39 (dd, *J* = 14, 1 Hz, 1H), 7.16 (tt, *J* = 6.6, 1 Hz, 1H), 7.25-7.30 (m, 2H), 7.35-7.38 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.8, 33.4, 37.0, 43.0, 51.7, 51.9, 55.0, 126.2, 126.3, 128.6, 148.2, 211.9.

Six Hour Recycling Studies of Pd@TpBpy for the Conjugate Addition of Phenylboronic Acid to Enone 1a

Pd@TpBpy (0.030 mmol, 0.02 equiv Pd), phenylboronic acid (3.00 mmol, 2.00 equiv), enone **1a** (1.5 mmol, 1.00 equiv), and 50 mM aqueous sodium trifluoroacetate solution (1 mL,

pH = 8.2) were added to a 1 dram vial. The vial was sealed with a PFTE/silicone-lined septum cap. The reaction mixture was then heated and stirred at 100 ºC for 6 or 11 hours. The mixture was cooled to room temperature and diluted with EtOAc (3 mL). The diluted mixture was centrifuged at 5000 RPM for 5 minutes. The organic layer was separated from the aqueous layer and the aqueous layer was extracted four more times in a similar fashion. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was then dissolved in $CDCl_3$ (0.70 mL) and CH_2Br_2 (52.8 µL, 0.750 mmol) was added as internal standard. Yield was determined by ^1H NMR spectroscopy of the crude reaction mixture. After the final extraction, the aqueous layer was removed from the vial and fresh starting materials and aqueous media were added to the remaining Pd@TpBpy for the next run.

Six Hour Recycling Studies of Pd@TpBpy for the Conjugate Addition of Phenylboronic Acid to Enone 1a

Pd@TpBpy (0.030 mmol, 0.02 equiv Pd), phenylboronic acid (3.00 mmol, 2.00 equiv), enone **1a** (1.5 mmol, 1.00 equiv), and 50 mM aqueous sodium trifluoroacetate solution (1 mL, pH = 8.2) were added to a 1 dram vial. The vial was sealed with a PFTE/silicone-lined septum cap. The reaction mixture was then heated and stirred at 100 ºC for 2 hours. The crude solution was extracted via syringe filter. The vial was washed with EtOAc (3 x 4 mL) and then deionized water (3 x 4 mL). The combined organic and aqueous layers were filtered through a fritted filter to remove any remaining Pd@TpBpy. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was then dissolved in $CDCl_3$ (0.70 mL) and CH_2Br_2 (52.8 µL, 0.750 mmol) was added as internal standard. Yield was determined by ^1H NMR spectroscopy of the crude reaction mixture. After

the final washing, fresh reagents and reaction media were added to the remaining Pd@TpBpy for the next run.

ICP-MS Leaching Test for the Pd@TpBpy Catalyzed Conjugate Addition of Phenylboronic Acid to Enone 1a

Pd@TpBpy (0.030 mmol, 0.02 equiv Pd, 55.2 mg COF, 5.78 w/w% Pd), phenylboronic acid (3.00 mmol, 2.00 equiv), enone **1a** (1.5 mmol, 1.00 equiv), and 50 mM aqueous sodium trifluoroacetate solution (1 mL, pH = 8.2) were added to a 1 dram vial. The vial was sealed with a PFTE/silicone-lined septum cap. The reaction mixture was then heated and stirred at 100 ºC for 6 hours. The mixture was cooled to room temperature and diluted with EtOAc (3 mL). The diluted mixture was centrifuged at 5000 RPM for 5 minutes. The organic layer was separated from the aqueous layer and the aqueous layer was extracted four more times in a similar fashion. The remaining aqueous layer was removed and analyzed for palladium content using ICP-MS to find 1.28 mg Pd (40% of original palladium content of the pristine COF) had leached into the aqueous supernatant.

Leaching Test for the Pd@TpBpy Catalyzed Conjugate Addition of Phenylboronic Acid to Enone 1a

Pd@TpBpy (0.005 mmol, 0.01 equiv Pd), phenylboronic acid (1.50 mmol, 2.00 equiv), enone **1a** (0.5 mmol, 1.00 equiv), and 50 mM aqueous sodium trifluoroacetate solution (333 µL mL, pH = 8.2) were added to a 1 dram vial. The vial was sealed with a PFTE/silicone-lined septum cap. The reaction mixture was then heated and stirred at 100 ºC for 30 minutes. The solution was extracted from Pd@TpBpy COF via syringe filter and added to a fresh vial and heated and stirred at 100 ºC for an additional 5.5 hours. The mixture was cooled to room temperature and diluted with EtOAc (30 mL). The reaction mixture was washed with brine,

dried over Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was then dissolved in $CDCl_3$ (0.70 mL) and CH_2Br_2 (17.6 µL, 0.250 mmol) was added as internal standard. Yield was determined by ^1H NMR spectroscopy of the crude reaction mixture and compared to the parent reaction yield at 30 minutes (Table 1, entry 9).

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CHAPTER 3. DESIGN, SYNTHESIS, AND INCORPORATION OF PYRIDINE OXAZOLINE LIGANDS IN MOFS

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Abstract

Multiple routes towards the inclusion of (*S*)-4-*(tert*-butyl)-2-(pyridin-2-yl)-4,5-dihydrooxazole ((*S*)-^{t}BuPyOx) in metal organic frameworks (MOFs) for potential use in recyclable, enantioselective, transition metal-catalyzed organic transformations are reported. PyOx derivatives functionalized at the 5-position of the pyridine ring have been synthesized and tested for inclusion in MOFs via amide and amine couplings, and solvent assisted ligand incorporation (SALI).

Introduction

MOFs are widely studied materials for their potential applications in gas storage and separation, solar chemistry, chemical sensing, and catalysis. By mimicking traditional homogeneous catalyst sites within their pores while retaining heterogeneous crystallinity overall, MOFs have climbed to the interface of homogeneous and heterogeneous catalysis. Chiral, non-racemic MOFs for enantioselective transition-metal catalysis have been developed through chiral ligand inclusion in the backbone[1-3] and as a pendant[4] of the organic linkers.

Due to challenges in functionalizing many chiral ligands, fewer asymmetric MOF catalysts have been developed. A well-studied homogeneous ligand, (*S*)-4-(*tert*-butyl)-2-(pyridin-2-yl)-4,5-dihydrooxazole ((*S*)-^{t}BuPyOx)[5-13], was viewed as a promising ligand to incorporate into a MOF due to with the ability to functionalize the pyridine ring[5, 11]. (*S*)-

^{t}BuPyOx has been shown as an active ligand for conjugate additions of arylboronic acids to enones with high enantioselectivies.[9-10] The ability to perform conjugate additions in a recyclable manner is desirable for the synthesis of various natural products and pharmaceuticals that contain *β*-aryl ketones.

This thesis details efforts towards incorporating (*S*)-^{t}BuPyOx into MOFs through three different methods (Figure 1). The first is amide bond formation by coupling (*S*)-6-(4-(*tert*-butyl)-4,5-dihydrooxazol-2-yl)nicotinic acid (Nic-PyOx) with linkers containing amines. The second route aims to perform amine coupling between halogen substituted (*S*)-^{t}BuPyOx derivatives. Lastly, work has been done towards including (*S*)-^{t}BuPyOx via solvent assisted ligand incorporation (SALI)[14] with Nic-PyOx.

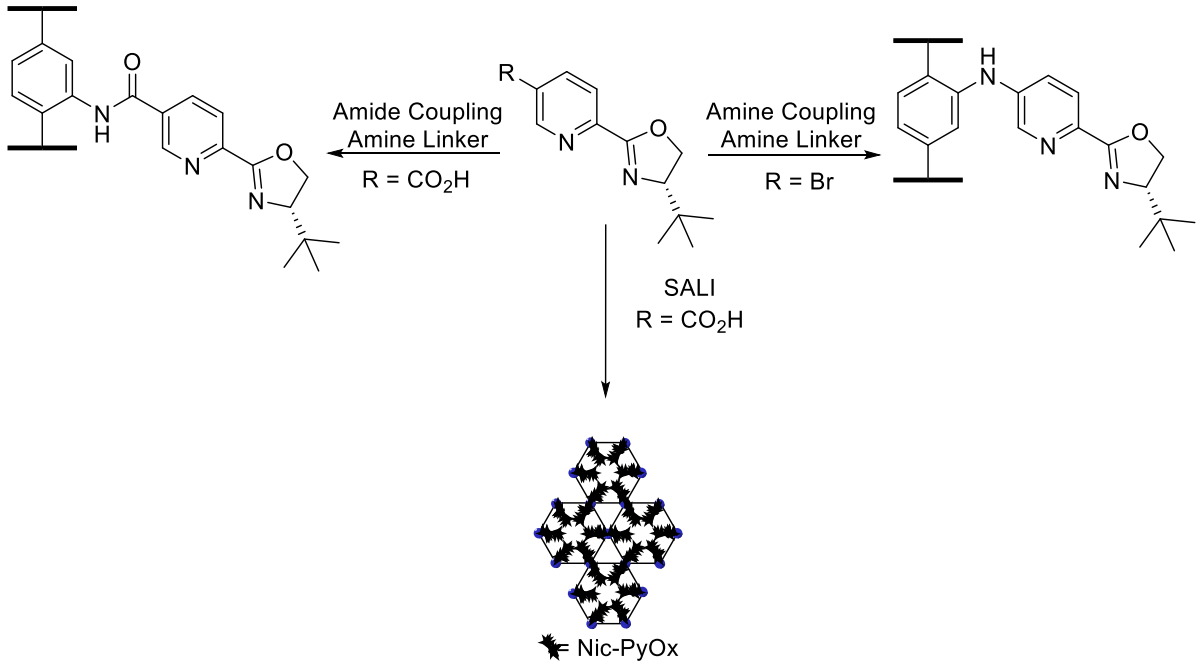


Figure 1. Methods of (*S*)-^{t}BuPyOx inclusion.

Results and Discussion

Nic-PyOx was the first derivative sought after for its use in both the amide coupling and SALI routes. By merging routes developed for other PyOx derivatives, compound **6** was synthesized (Figure 2).

The synthesis begins with commercially available pyridine-2,5-dicarboxylic acid (**1**) which can be esterified to form diethyl pyridine-2,5-dicarboxylate **2** in 72% yield on large scale. Compound **2** can undergo a regioselective hydrolysis reported by Schiffner et al. to produce 5-(ethoxycarbonyl)picolinic acid (**3**) in 74% yield.[11] A two-step amide coupling with (*S*)-*tert*-butyl leucinol produces amide alcohol **4** in 70% yield. Compound **4** undergoes a cyclization followed by hydrolysis to yield Nic-PyOx in 65% yield over the two steps (**6**).

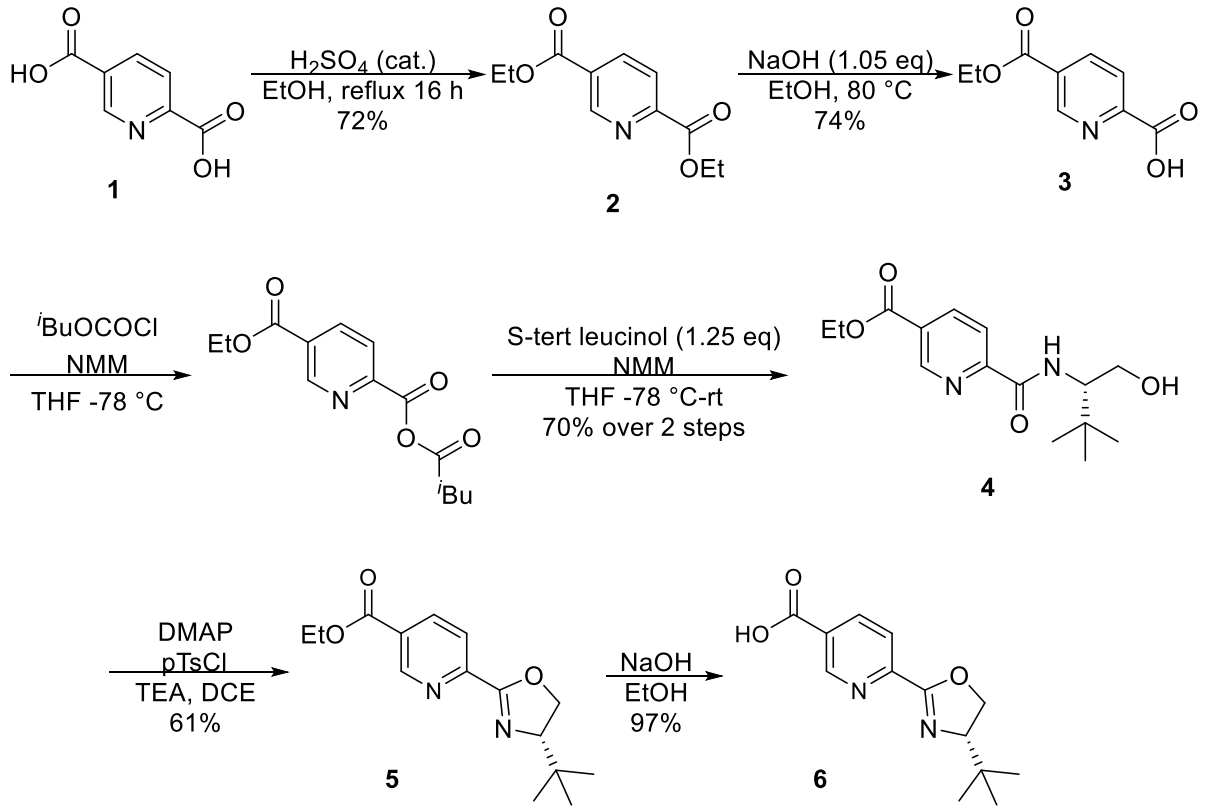


Figure 2. The synthesis of Nic-PyOx (**6**).

As a preliminary test towards forming the amide bond, Nic-PyOx was coupled to aniline (Figure 3) in 45% yield. We also wanted to establish that the change in electronics would still allow for enantioselective reactions to occur. Compounds **5** and **7** were used as homogeneous ligands for a Pd(II) salt in the conjugate addition of phenylboronic acid to 3-methylcyclohex-2-en-1-one using standard homogeneous conditions developed by Stoltz

(Equations 1 and 2).[10] Both showed the desired reactivity and selectivity, though lower than the unsubstituted (*S*)-^{t}BuPyOx.

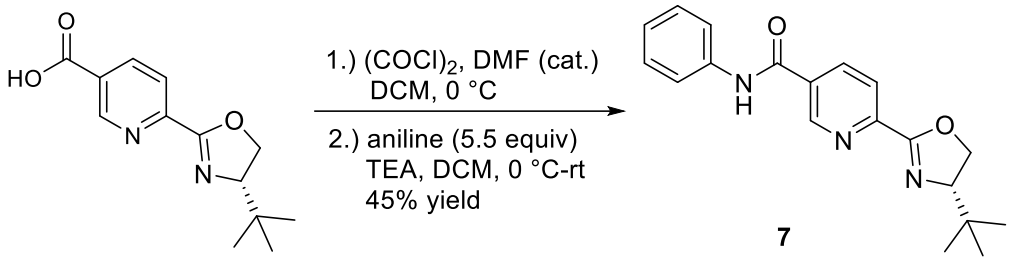
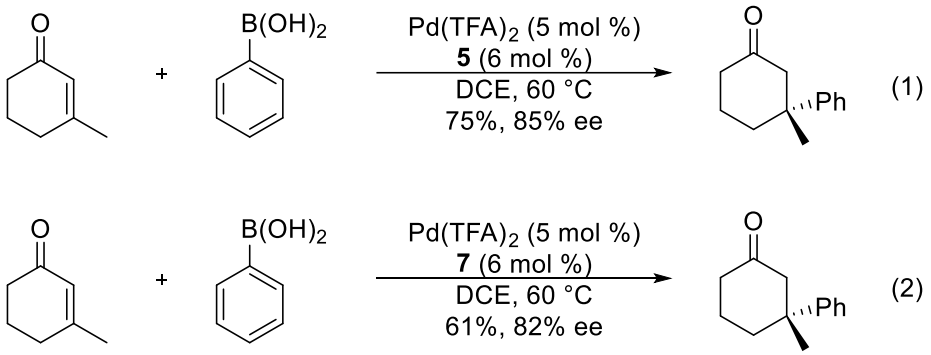


Figure 3. Preliminary coupling of Nic-PyOx with aniline to produce compound **7**.



With preliminary activity established, a selection of amine containing linkers were pursued as possible coupling partners. Weighing the ease of synthesis and pore size influence, we chose to synthesize reported linkers 4,4'-dimethyl-[1,1'-biphenyl]-2-amine bis(4-ethynylbenzoate) (**L1**) (Figure 4),[4] 2'-amino-[1,1':4',1''-terphenyl]-4,4''-dicarboxylic acid (**L2**) (Figure 5).[15]

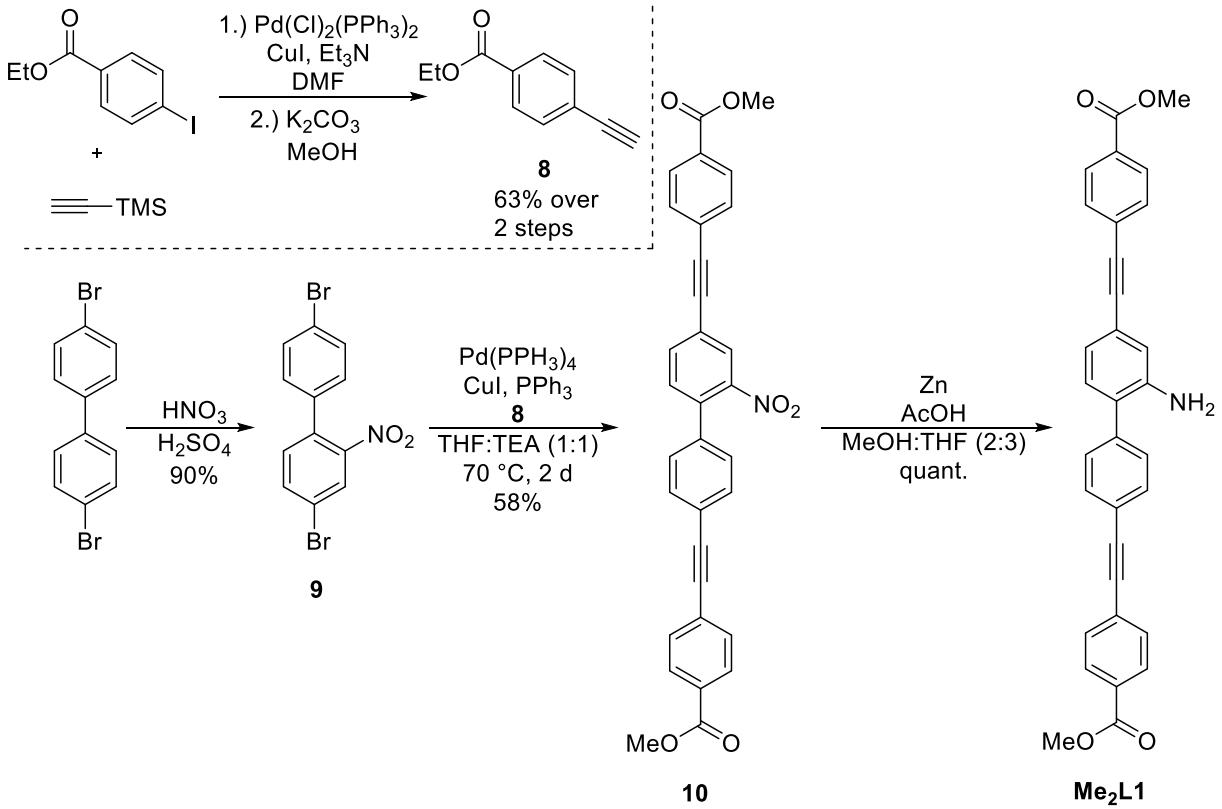


Figure 4. Synthesis of **Me$_2$L1** coupling partner.

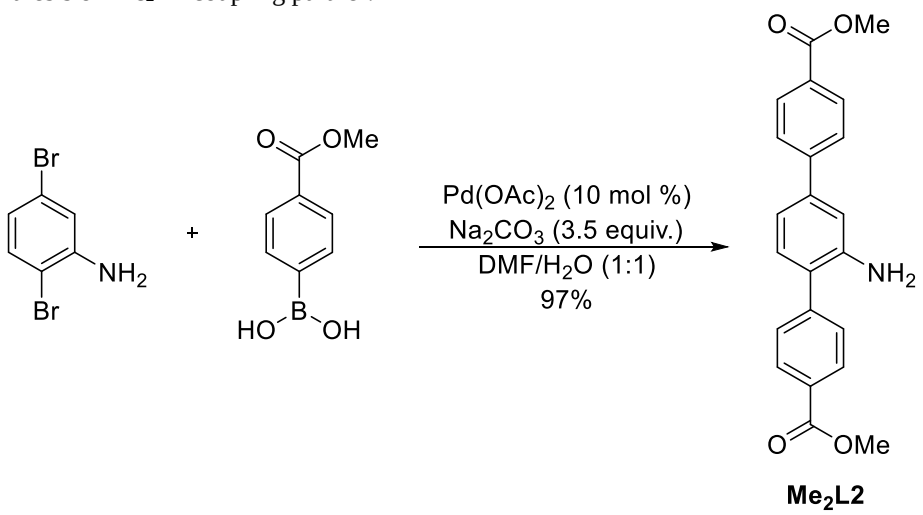
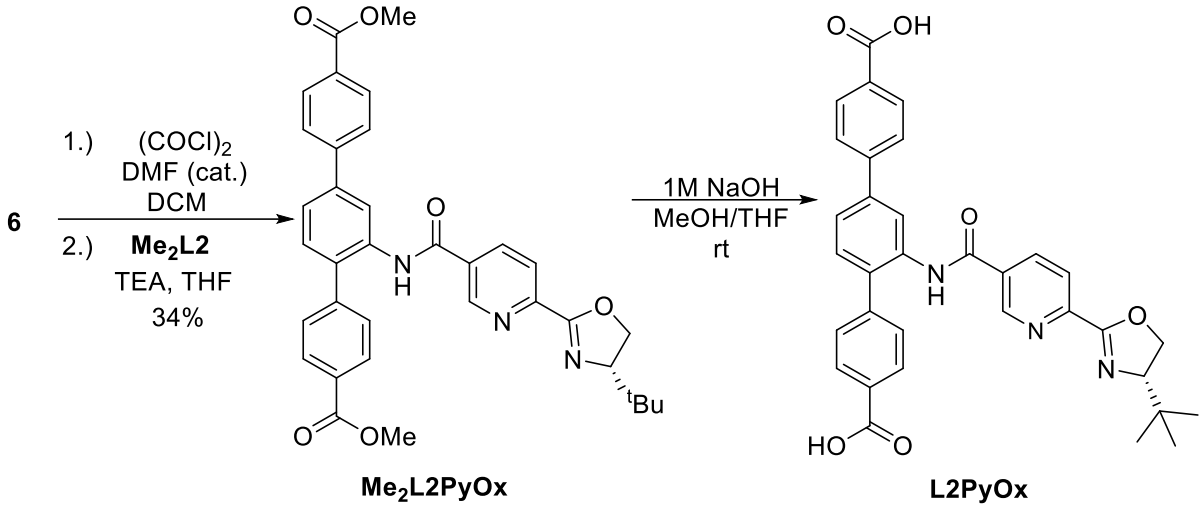


Figure 5. Synthesis of **Me$_2$L2** coupling partner.

After synthesizing the three desired linkers, we sought to couple Nic-PyOx to the amines. We chose to analyze with **Me$_2$L2** for its facile synthesis and the moderately sized pores it leads to in UiO-type MOFs. After screening a variety of coupling methods, we found that generating the acid chloride with oxalyl chloride and a catalytic amount of *N*,*N*-

dimethylformamide in dichloromethane followed by amide formation with **Me$_2$L2** and triethylamine in tetrahydrofuran forms **Me$_2$L2PyOx** in 34% overall yield. The product was subjected to hydrolysis conditions to generate the desired final linker, **L2PyOx**. This yielded a mixture of starting material, desired product, Nic-PyOx, and **Me$_2$L2** (Scheme 1). After extensive attempts at purification without success, we decided to direct focus towards other inclusion methods.

Scheme 1. Synthesis of **L2PyOx** via amide bond coupling and following hydrolysis.



With the amine linkers in hand, we envisioned an inclusion method via amine coupling reactions (Figure 6). The coupling of arylamines with haloarenes is well established in literature through Ullman-type and Buchwald-Hartwig type couplings. Modifying (*S*)-^{t}BuPyOx through the installation of a bromine substitution on the 5-position of the pyridine ring would provide a potential coupling partner for both coupling types.

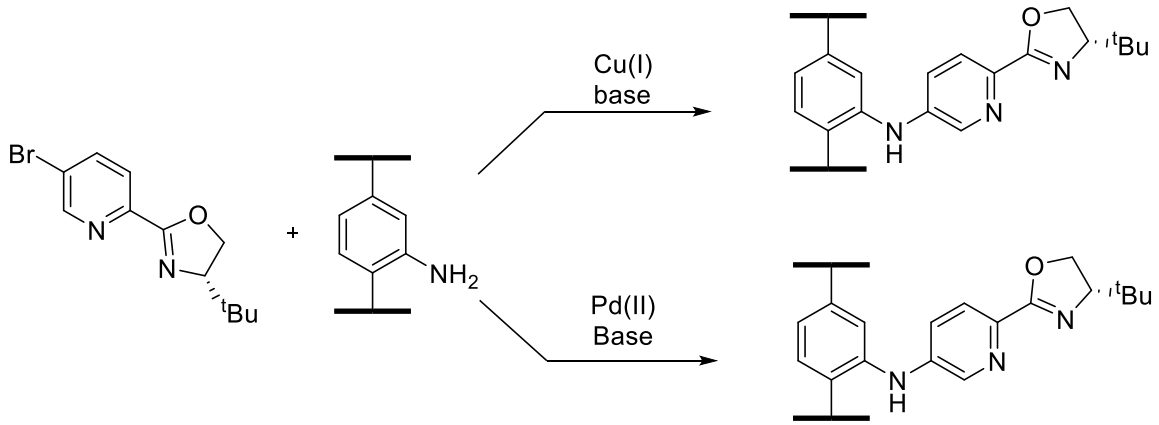


Figure 6. Designed inclusion of (*S*)-^{t}BuPyOx following Ullman-type (top) or Buchwald-Hartwig type (bottom) amine couplings.

Commercially available 5-bromopicolinic acid was coupled to (*S*)-*tert*-butyl leucinol to produce amide-alcohol **12** in 64% yield. After purification, **12** was cyclized to form the desired (*S*)-2-(5-bromopyridin-2-yl)-4-(*tert*-butyl)-4,5-dihydrooxazole (**13**) in 65% yield (Figure 7).

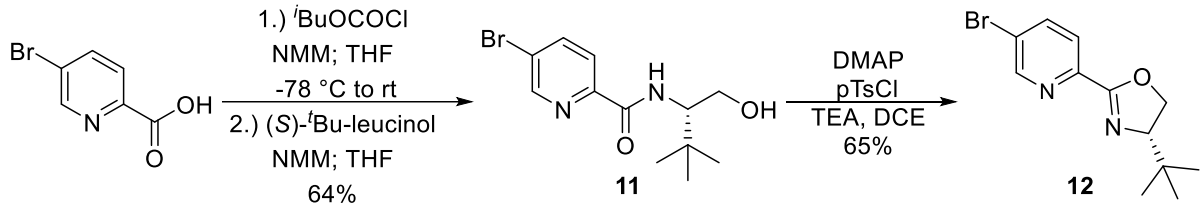


Figure 7. Synthesis of (*S*)-2-(5-bromopyridin-2-yl)-4-(*tert*-butyl)-4,5-dihydrooxazole (**13**).

We are also investigating the inclusion of Nic-PyOx through SALI with the NU-1000 MOF. After synthesis of the MOF and its corresponding linkers following literature protocols, we have successfully included Nic-PyOx in the framework (Figure 7).

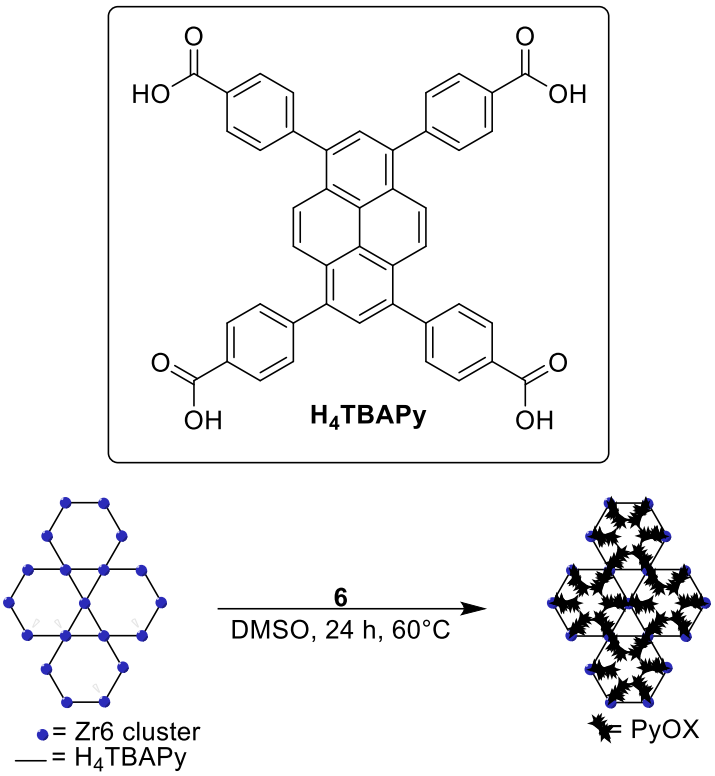


Figure 7. An illustration of PyOx inclusion in NU-1000 through SALI.

After loading with $Pd(TFA)_2$, the PyOx-NU-1000 was subjected to standard conjugate addition conditions for the addition of phenylboronic acid to 3-methylcyclohex-2-en-1-one. After 24 hours, 77% ketone product was observed, but with only 7% enantioselectivity. To test whether the palladium was coordinated to the PyOx or the open coordination sites, $Pd(TFA)_2$ was loaded in NU-1000 and tested for the same reactivity. After 24 hours, 71% yield of racemic ketone was observed, indicating the palladium was loaded on the coordination sites rather than the PyOx. Studies are under way to further understand this system and promote formation of the palladium(II)-PyOx complex.

Conclusions

Three routes are being investigated for the inclusion of (*S*)-^{t}BuPyOx into metal organic frameworks: amide bond coupling, amine coupling, and SALI. Preliminary results suggest the

amide could be active and selective ligands for conjugate addition reactions. While SALI has successfully included (*S*)-^{t}BuPyOx in the MOF, work must be done to ensure proper location of the loaded palladium centers.

Experimental

General Experimental Details. 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 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

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 ^{1}H and 77.1 ppm for ^{13}C) or DMSO-d^6 (2.50 ppm for ^{1}H). ^{19}F NMR shifts are reported in ppm based on indirect reference to $CDCl_3$. Coupling constants are reported in hertz.

Materials.

Pyridine-2,5,dicarboxylic acid, 4-(methoxycaronyl)phenyl)boronic acid, phenylboronic acid, 2,5-dibromoaniline, 5-bromopicolinic acid, ethyl-4-iodobenzoate, and 4,4'-Dibromo-1,1'-biphenyl were purchased from AK Scientific and used without further purification. L-tert-Leucine was purchased from Oakwood Chemical and used without further purification. TMS-Acetylene was purchased from Oakwood Chemical and distilled prior to

use. NU-1000 and its corresponding linker, 4,4',4",4"'-(pyrene-1,3,6,8-tetrayl)tetrabenzoic acid were synthesized according to literature procedures.[14]

Synthesis of (S)-6-(4-(tert-butyl)-4,5-dihydrooxazol-2-yl)nicotinic acid (6)

Diethyl pyridine-2,5-dicarboxylate (2)

In a 500 mL round bottom flask, pyridine-2,5-dicarboxylic acid (15g, 89.8 mmol) was dissolved in EtOH (150 mL) and catalytic amounts of concentrated sulfuric acid (2 mL). The reaction was heated to reflux and stirred at that temperature for 24 hours. The reaction was allowed to cool to room temperature and was diluted with dichloromethane (150 mL). The mixture was washed with a saturated aq. $NaHCO_3$ solution and then extracted with dichloromethane (100 mL x 3). The organic fractions were dried over Na_2SO_4 and concentrated to yield **2** in 72% yield as a yellow solid (14.35g, 64.3 mmol). The product was used without further purification. Characterization matches previous literature reports.[11] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (t, *J* = 7.0 Hz, 3H), 1.45 (t, *J* = 7.2 Hz, 3H), 4.43 (q, *J* = 7.0 Hz, 2H), 4.49 (q, *J* = 7.2 Hz, 2H), 8.19 (dd, *J* = 8.1, 0.8 Hz, 1H), 8.42 (dd, *J* = 8.1, 2.2 Hz, 1H), 9.30 (dd, *J* = 2.2, 0.8 Hz, 1H).

5-(Ethoxycarbonyl)picolinic acid (3)

Compound **2** was suspended in EtOH (0.5 M) and sodium hydroxide pellets (1.05 equiv.) were added. The mixture was heated at reflux for 8 h. While warm, the reaction was quenched with the dropwise addition of 2M HCl (0.7 mL/mmol **2**). The mixture was cooled to 0 ºC and a precipitate was formed. After 30 minutes, the precipitate was filtered off and washed with twice with cold EtOH and once with cold water to afford the monoester **3** in 74% yield as a white solid. The product was used without further purification. Characterization matches

previous reports.[11] ^{1}H NMR (400 MHz, DMSO-d^6): δ 1.35 (t, *J* = 7.0 Hz, 3H), 4.38 (q, *J* = 7.0 Hz, 2H), 8.16 (d, *J* = 8.2 Hz, 1H), 8.45 (dd, *J* = 8.2, 2.0 Hz, 1H), 9.16 (d, *J* = 2.0 Hz, 1H).

Ethyl (S)-6-((1-hydroxy-3,3-dimethylbutan-2-yl)carbamoyl)nicotinate (4)

Compound **3** (3.00g, 15.4 mmol) was added to an oven dried, N_2 filled round bottom flask containing anhydrous THF (40 mL). *N*-Methylmorpholine (2.56 mL, 23.2 mmol) was added. The solution was cooled to -78 °C in a dry-ice/acetone bath and isobutyl chloroformate (2.30 mL, 17.8 mmol) was added slowly via needle and syringe. The mixture was stirred for 2 h and brought to -40 ºC. A mixture of *N*-Methylmorpholine (2.04 mL, 18.5 mmol), (*S*)-*tert*-leucinol (2.27g, 19.3 mmol), and anhydrous THF (30 mL) was added slowly. After addition, the solution was brought to room temperature and stirred for 4 h. The reaction mixture was quenched with saturated aq. NH_4Cl and extracted with dichloromethane three times. The organics were dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified via flash column chromatography on silica gel (2:1 EtOAc:Hexanes). This yielded **4** in 70% yield (3.21g, 10.9 mmol) as a white solid. Characterization agrees with reported data.[11] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.04 (s, 9H), 1.42 (t, *J* = 7.0 Hz, 3H), 3.66-3.74 (m, 1H), 4.00 (m, 2H), 4.44 (q, *J* = 7.0 Hz, 2H), 8.25 (dd, *J* = 8.0, 1.0 Hz, 1H), 8.31 (br d, *J* = 9.2 Hz, 1H) 8.43 (dd, *J* = 8.0, 2.0 Hz, 1H), 9.15 (dd, *J* = 2.0, 1.0 Hz, 1H).

Ethyl (S)-6-(4-(tert-butyl)-4,5-dihydrooxazol-2-yl)nicotinate (5)

Amide **4** (1.00g, 3.40 mmol) and DMAP (83 mg, 0.68 mmol) were added to an oven dried, N_2-filled flask containing anhydrous 1,2-dichloroethane (40 mL) and TEA (1.90 mL, 13.59 mmol). *P*-TsCl (0.982g, 3.74 mmol) was added to the flask and the reaction was heated to reflux for 16 hours. The solution was cooled to room temperature, diluted with dichloromethane (80 mL), and washed with saturated aq. $NaHCO_3$ (3x) and Brine (3x). The

organics were dried over Na_2SO_4 and then concentrated under reduced pressure. The crude product was purified via flash column chromatography on silica gel (2:1 EtOAc:Hexanes) to afford **5** as an off-white solid (61%, 0.574g, 2.07 mmol). Characterization is consistent with previously reported data.[11] ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (s, 9H), 1.42 (t, *J* = 7.0 Hz, 3H), 4.16 (m, 1H), 4.34 (t, *J* = 8.6 Hz, 1H), 4.45 (m, 3H), 8.16 (dd, *J* = 8.0, 1.0 Hz, 1H), 8.37 (dd, *J* = 8.0, 2.0 Hz, 1H), 9.27 (dd, *J* = 2.0, 1.0 Hz, 1H).

(S)-6-(4-(tert-butyl)-4,5-dihydrooxazol-2-yl)nicotinic acid (6)

Compound **5** (1.00g, 3.62 mmol) and sodium hydroxide pellets (0.217g, 5.43 mmol) were added to a flask containing EtOH (10 mL) and refluxed for 16 h. The reaction mixture was allowed to cool and brought to pH = 6 by addition of 2M HCl. Solvent was removed under heat and reduced pressure to yield a crude solid. The crude product was dissolved in minimal amounts of water and acidified to pH = 4 by addition of 2M HCl. The solution was cooled at 0 °C until a precipitate was formed. The precipitate was filtered and washed with cold water to yield **6** in 97% yield (0.872g, 3.51 mmol). ^{1}H DMSO (400 MHz, DMSO-d^6): δ 1.07 (s, 9H), 3.34 (m, 1H), 4.44 (dd, *J* = 12.2, 7.8 Hz, 1H), 4.63 (dd, *J* = 12.2, 3.3 Hz, 1H), 8.38 (dd, *J* = 8.0, 1.0 Hz, 1H), 8.47 (dd, *J* = 8.0, 2.0 Hz, 1H), 9.19 (dd, *J* = 2.0, 1.0 Hz, 1H).

Synthesis of (S)-6-(4-(tert-butyl)-4,5-dihydrooxazol-2-yl)-N-phenylnicotinamide (7)

Compund **6** (75 mg, 0.30 mmol) was added to an oven-dried, N_2-filled flask containing anhydrous dichloromethane (0.5 mL). The suspension was cooled to 0 ºC and oxalyl chloride (0.30 mL, 0.60 mmol) was added through a septum. *N*,*N*-Dimethylformamide (1 drop) was added. The reaction was stirred for 30 minutes and concentrated under reduced pressure to a crude residue to remove excess oxalyl chloride. The residue was dissolved in anhydrous dichloromethane (1 mL) and a solution of aniline (34 µL, 0.38 mmol) and TEA (0.23 mL, 1.66

mL) in anhydrous dichloromethane (1 mL) was added dropwise. After the addition, the mixture was stirred at room temperature for 2 hours. The mixture was diluted with aq. NH_4Cl (10 mL) and extracted with dichloromethane (3 x 15 mL). The organic fractions were dried with Na_2SO_4 and concentrated under reduced pressure. The product was purified via flash column chromatography on silica gel (2:1 EtOAc:Hexanes).

Synthesis of dimethyl 4,4'-((2-amino-[1,1'-biphenyl]-4,4'-diyl)bis(ethyne-2,1-diyl))dibenzoate (Me_2L1)[4]

Methyl 4-ethynylbenzoate (8)

In a N_2 glovebox, bis(triphenylphosphine)palladium(II) dichloride (0.1404g, 0.20 mmol) and copper(I) iodide (766 mg, 0.40 mmol) were added to a round bottom flask. The flask was sealed and removed from the glovebox. A solution of ethyl 4-iodobenzoate (1.68 mL, 10.00 mmol), 2-(trimethlsilyl)ethyn-1-ylium (2.14 mL, 15.00 mmol) and TEA (2.79 mL, 20 mmol) in anhydrous THF (28 mL) were added via syringe. The reaction was stirred for 3 hours at room temperature and then concentrated under reduced pressure to a crude residue.

The residue was dissolved in a solution of K_2CO_3 (4.182 g, 30.26 mmol) in MeOH (10 mL). The reaction solution was stirred 16 h at room temperature and then concentrated under reduced pressure. The residue was dissolved in dichloromethane and washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to yield **8** in 63% yield (0.985 g, 6.15 mmol). Characterization is consistent with previously reported literature.[4]

4,4'-dibromo-2-nitro-1,1'-biphenyl (9)

4,4'-dibromo-1,1'-biphenyl (10.0 g, 32 mmol) was dissolved in glacial acetic acid (150 mL). The mixture was stirred and heated to 110 ºC. Fuming concentrated nitric acid (95%, 40

mL) was added dropwise via addition funnel to form a precipitate. The reaction continued until the precipitate redissolved, at which point it was brought to room temperature. The solid that precipitated over cooling was collected via filtration and recrystallized from EtOH to obtain **9** as a yellow solid (10.3 g, 28.9 mmol, 90% yield). Characterization was consistent with previously reported data.[16]

4,4'-((2-amino-[1,1'-biphenyl]-4,4'-diyl)bis(ethyne-2,1-diyl))dibenzoate (10)

In a N_2 glovebox, tetrakis(triphenylphosphine)palladium(0) (240 mg, 0.21 mmol), copper(I) iodide (80 mg, 0.42 mmol), triphenylphosphine (66 mg, 0.25 mmol) were added into an oven-dried flask. The flask was sealed and brought out of the glovebox. Anhydrous THF (5.3 mL) and TEA (5.3 mL) were added as solvent. 4,4'-dibromo-2-nitrobiphenyl (743 mg, 2.08 mmol) and methyl 4-ethynylbenzoate (1.00 g, 6. 20mmol) were added to the mixture and the reaction was stirred under N_2 at 70 °C for 2 d. The solution was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in water and chloroform and extracted with chloroform. The organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified via flash column chromatography on silica gel ($CHCl_3$) to produce **10** in 58% yield (622 mg, 1.21 mmol). Characterization is consistent with previously reported data.[4]

4,4'-((2-amino-[1,1'-biphenyl]-4,4'-diyl)bis(ethyne-2,1-diyl))dibenzoate (Me_2L1)

Compound **10** (172 mg, 0.33 mmol) and zinc dust (435 mg, 6.7 mmol) were dissolved in glacial acetic acid (1.1 mL), MeOH (6.7 mL), and THF (10.1 mL). The reaction mixture was stirred for 3 hours, at which point it was cooled to 0 ºC and saturated aq. $NaHCO_3$. The mixture was extracted with $CHCl_3$ and then the organic extracts were dried over Na_2SO_4 and

concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (19:1 Hexanes:EtOAc) to yield **Me_2L1**.

Synthesis of dimethyl 2'-amino-[1,1':4',1''-terphenyl]-4,4''-dicarboxylate (Me_2L2)

2,5-Dibromoaniline (2.30 g, 9.2 mmol), 4-(methoxycaronyl)phenyl)boronic acid (8.20 g, 45.8 mmol), Na_2CO_3 (3.40 g, 32.1 mmol), and $Pd(OAc)_2$ (21 mg, 0.09 mmol) were added to a mixture of DMF (25 mL) and H_2O (25 mL). The reaction was stirred and heated at 60 °C for 24 h. The reaction was cooled to room temperature and water (150 mL) was poured into the mixture. The solution was extracted with CH_2Cl_2 (50 mL x 3). The organic extract was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was recrystallized from EtOH to give **Me_2L2** as an off yellow solid (3.22 g, 8.91 mmol, 97% yield). Characterization is consistent with previous literature data.[15]

Coupling Ni-PyOx to Me_2L2 to form (S)-2'-(6-(4-(tert-butyl)-4,5-dihydrooxazol-2-yl)nicotinamido)-[1,1':4',1''-terphenyl]-4,4''-dicarboxylic acid (Me_2L2PyOx)

In an oven dried flask, Compound **6** (300 mg, 1.2 mmol) was added to dichloromethane (4 mL). 2M Oxalyl chloride in dichloromethane (0.75 mL, 1.5 mmol) was added, followed by the addition of catalytic DMF (1 drop). The reaction was stirred for 1 h at room temperature then concentrated under reduced pressure. The crude residue was dissolved in 5 mL of dichloromethane and TEA (0.5 mL, 1.2 mmol) was added. A solution of **Me_2L2** (440 mg, 1.2 mmol) and THF (5 mL) was added dropwise and the reaction was stirred for 16 h. The reaction was diluted with dichloromethane and washed with saturated aq. NH_4Cl. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified via flash column chromatography on silica gel (2:1 EtOAc:Hexanes) to afford **Me_2L2PyOx** (245 mg, 0.414 mmol, 34% yield).

Hydrolysis of Me_2L2PyOx to (S)-2'-(6-(4-(tert-butyl)-4,5-dihydrooxazol-2-yl)nicotinamido)-[1,1':4',1''-terphenyl]-4,4''-dicarboxylic acid (L2PyOx)

Me_2L2PyOx (129 mg, 0.22 mmol) was dissolved in 1M NaOH (11.2 mL), MeOH (11.2 mL), and THF (11.2 mL) and stirred at room temperature for 24 h. The reaction was acidified with 2M HCl and concentrated to a solid under reduced pressure. The solid was analyzed with ^{1}H NMR and UPLC-MS to reveal the presence of **L2PyOx**. Attempts at purification include recrystallization and flash column chromatography with normal and reverse phase silica gel but no attempts afforded pure product.

Synthesis of (S)-2-(5-bromopyridin-2-yl)-4-(tert-butyl)-4,5-dihydrooxazole (12)

(S)-5-bromo-N-(1-hydroxy-3,3-dimethylbutan-2-yl)picolinamide (11)

A flask was charged with 5-bromopicolinic acid (3.03 g, 15 mmol), *N*-methylmorpholine (2.47 mL, 22.5 mmol), and THF (40 mL). The solution was cooled to -78 ºC and isobutyl chloroformate (2.24 mL, 17.25 mmol) was added dropwise. The mixture was stirred for 2 h and brought to -40 ºC. A mixture of *N*-Methylmorpholine (1.68 mL, 18 mmol), (*S*)-*tert*-leucinol (2.20g, 18.75 mmol), and anhydrous THF (30 mL) was added slowly. After addition, the solution was brought to room temperature and stirred for 4 h. The reaction mixture was quenched with saturated aq. NH_4Cl and extracted with dichloromethane three times. The organics were dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified via flash column chromatography on silica gel (2:1 EtOAc:Hexanes) to afford **11** (2.90 g, 9.63 mmol, 64% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.04 (s, 9H), 3.66-3.72 (m ,1H), 3.95-4.01 (m, 2H), 8.00 (dd, *J* = 8.4, 2.2 Hz, 1H), 8.10 (d, *J* = 8.2 Hz, 1H), 8.15 (br d, *J* = 9 Hz, 1H), 8.62 (app s, 1H).

(S)-2-(5-bromopyridin-2-yl)-4-(tert-butyl)-4,5-dihydrooxazole (12)

Compound **11** (2.90 g, 9.30 mmol) was added to a solution of 1,2-dichloroethane (110 mL), 4-dimethylaminopyridine (227 mg, 1.86 mmol), and TEA (5.20 mL, 37.19 mmol). After **11** was dissolved, *p*-TsCl (2.70 g, 10.23 mmol) was added to the reaction vessel. The reaction was refluxed for 16 h. The reaction solution was cooled to room temperature and diluted with dichloromethane (100 mL). The solution was washed with $NaHCO_3$ (x3) and brine (x3). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified via flash column chromatography (2:1 EtOAc:Hexanes) to afford **12** as a white solid (1.68 g, 6.08 mmol, 65% yield).

General Procedure for Screening Conjugate Addition of Phenylboronic Acid to 3-methylcyclohex-2-en-1-one

Pd@PyOx-NU-1000 (0.05 equiv. of Pd) or Pd-NU-1000 (0.05 equiv. of Pd), 3-methylcyclohex-2-en-1-one (1.00 equiv.), and phenylboronic acid (2.00 equiv) were added to a vial and 1,2-dichloroethane (0.5M) was added. The vial was capped and heated at 60 ºC for 24 hours. The reaction was cooled to room temperature and diluted with EtOAc (15 mL), then washed with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. ^1H NMR with CH_2Br_2 as internal standard was utilized for determining yield. Enantiomeric excess was determined by HPLC analysis (220 nm, 25 ºC) [Chiralcel OJ-H (0.46 cm x 25 cm) (from Daicel Chemical IND., Ltd.) hexane/*i*-PrOH, 99:1, 1.0 mL/min].

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CHAPTER 4. GENERAL CONCLUSIONS

General Conclusions

We have developed Pd@TpBpy COF as a heterogeneous catalyst for conjugate additions of a wide range arylboronic acids to *β*,*β*-disubstituted enones in aqueous NaTFA. The ketone products are formed in moderate to high yields and contain all-carbon quaternary centers. We have shown Pd@TpBpy COF as a recyclable catalyst. The reactivity and recyclability helps extend covalent organic frameworks as useful catalytic systems for organic transformations.

Additionally, we have pursued a variety of routes to insert (*S*)-^{t}BuPyOx in metal organic frameworks. These routes include preliminary data towards inclusion via amide coupling, amine coupling, and SALI. Work remains to develop an active asymmetric MOF catalyst containing (*S*)-^{t}BuPyOx.