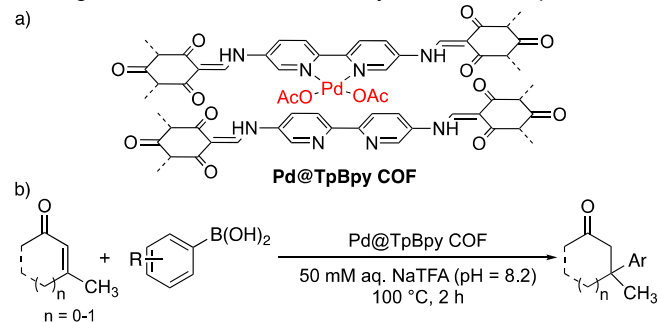


A Pd(II)-Functionalized Covalent Organic Framework for Catalytic Conjugate Additions of Arylboronic Acids to β,β -Disubstituted Enones

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Abstract: A palladium(II)-functionalized covalent organic framework (Pd@TpBpy COF) constructed from 1,3,5-triformylphloroglucinol (Tp) and [2,2'-bipyridine]-5,5'-diamine (Bpy) is reported as a recyclable catalyst for conjugate additions in aqueous media. Additions of an array of stereoelectronically diverse arylboronic acid nucleophiles to β,β -disubstituted enones form a variety of ketones containing benzylic all-carbon quaternary centers in up to 92% isolated yield. Studies on the recyclability of Pd@TpBpy COF show this catalyst remains active through at least 7 cycles and shows superior stability to related MOF catalysts with bipyridine linker units.

Covalent organic frameworks (COFs) have recently emerged as promising platforms for heterogeneous catalysis^[1] that encompass transition-metal catalysis of important organic transformations, including Heck^[2], Suzuki-Miyaura^[3], and epoxidation^[4], CO oxidation^[5], and hydroformylation.^[6] The majority of these catalysts are derived from COFs synthesized by reversible imine condensation of a variety of aldehyde and amine building blocks.^[7] Of the transition metal-functionalized COFs constructed from imine bonds, two metal-binding modes are common. Initial reports of these catalysts propose coordination of the transition-metal center between imine nitrogens within the layered covalent organic framework.^[3a] More recently, COFs with transition metals coordinated to metal binding units (bipyridine, salen, porphyrin) contained within the aldehyde or amine building blocks have been reported (Scheme 1a).^[5, 8] The ability to functionalize COFs by using different metal-binding units and loading different transition metals provides the potential to generate heterogeneous structures with a wide range of potential catalytic activity.^[6, 9] Previous reports on metal-functionalized COFs begin to demonstrate the utility of COFs in heterogeneous transition metal catalysis, but the scope of reactions catalysed by these structures remains limited.



Scheme 1. a) Binding of Pd(II) in Pd@TpBpy COF. b) Conjugate Additions to Form Benzylic All-Carbon Quaternary Centers Catalyzed by Pd@TpBpy COF.

Our group has previously developed conjugate additions of arylboronic acids to β,β -disubstituted enones catalysed by metal-organic frameworks (MOFs) containing palladium(II) complexes of the 2,2'-bipyridine-5,5'-dicarboxylate linkers.^[10] These catalysts display excellent activity in aqueous reaction media. However, the MOF catalysts are prone to degradation in aqueous media over time, which leads to loss of activity in recycling studies. To address this limitation of palladium-functionalized MOFs, we turned our attention to COFs as a platform for heterogeneous catalysis based on the emerging literature demonstrating their superior stability in aqueous media.^[7b, 11] We were drawn to COFs prepared from 1,3,5-triformylphloroglucinol and diamine linkers because tautomerization of the initially formed imine bond to an enamine produces a robust framework that is resistant to hydrolysis even under forcing reaction conditions.^[11c] Herein, we report the application of Pd@TpBpy COF as a recyclable catalyst for the formation of quaternary carbon centers via conjugate additions of arylboronic acids to β,β -disubstituted enones in aqueous media (Scheme 1b).

TpBpy COF and its corresponding linkers, 1,3,5-triformylphloroglucinol (Tp) and [2,2'-bipyridine]-5,5'-diamine (Bpy) were synthesized following reported protocols.^[12] The characterization data for the TpBpy COF, powder X-ray diffraction (PXRD) and Brunauer Emmett Teller (BET) analysis, were in agreement with previously reported data. TpBpy COF was post synthetically metalated with Pd(OAc)₂ in dichloromethane at room temperature to provide Pd@TpBpy COF. The framework

maintained crystallinity after metalation based on PXRD analysis (Figure S1). Inductively coupled plasma-mass spectrometry (ICP-MS) was used to quantitatively determine the weight percent palladium content to be 5.8%.

The conjugate addition of phenylboronic acid to 3-methylcyclohex-2-en-1-one **1a** was selected as a model reaction to establish the activity of the Pd@TpBpy COF catalyst (Table 1). The model reaction forms ketone product **2a** in 99% yield when the reaction is performed in aqueous NaTFA at 100 °C (entry 1). This reaction was conducted in the presence of 5 mol % Pd based on a 5.8 wt. % Pd in Pd@TpBpy COF. We conducted additional reactions to further evaluate the impact of palladium loading, reaction time, and equivalents of phenylboronic acid on the model reaction. Lowering the catalyst loading from 5 mol % to 1 mol % did not impact the yield of ketone **2a** (entries 1-3). Reducing the reaction time from 16 h to 2 h still led to the formation of ketone **2a** in 98-99% yield (entries 3-6). Further attempts to decrease the reaction time, catalyst loading, and equivalents of phenylboronic acid did not lead to complete conversion of the β,β -disubstituted enone **1a** to ketone **2a** (entries 7-9). In addition, running the model reaction with a Pd-functionalized COF lacking a bipyridine unit (biphenyl linker in place of the bipyridine linker) did not occur with competitive rates (entry 10). This result suggests that even though coordination to the imine nitrogens is possible, the active catalyst for this reaction is a palladium complex of the bipyridine linker.

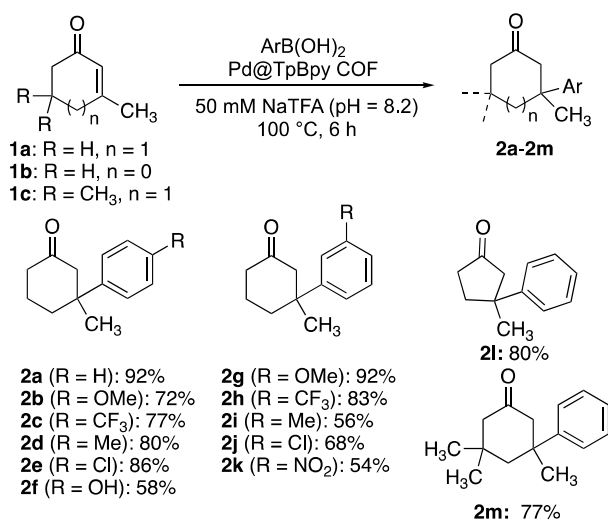
Table 1. Identification of Reaction Conditions.^a

Entry	mol % Pd	Time (h)	Yield (%) ^b
1	5	16	99
2	2	16	99
3	1	16	99
4	1	8	99
5	1	4	99
6	1	2	98
7	1	0.5	47
8	0.5	2	65
9 ^c	1	2	87
10 ^d	1	2	18

^a) Reaction conditions: **1a** (0.5 mmol), PhB(OH)₂ (1 mmol), Pd@TpBpy COF (0.0025-0.025 mmol Pd), 50 mM NaTFA (pH = 8.2) (0.33 mL) (NaTFA tuned to pH = 8.2), 100 °C. ^b) Determined by ¹H NMR using dibromomethane as internal standard. ^c) 1.2 mmol PhB(OH)₂ used. ^d) COF containing biphenyl instead of bipyridine used (TpBiph COF)

We chose to evaluate the scope of the reaction using 1 mol% Pd and 2.0 equivalents of arylboronic acid for 6 h to account for potential differences in reactivity of the arylboronic acid nucleophiles. Using Pd@TpBpy COF as the catalyst, an array of arylboronic acids were added to a selection of enones **1a-c** (Scheme 2). The parent reaction of 3-methylcyclohex-2-en-1-one **1a** with phenylboronic acid generated **2a** in 92% isolated yield. Additions of *para*-substituted arylboronic acid with electron-donating groups (MeO, Me, and OH) occur to form ketones **2b-2d** in 58-80%. In addition, reactions of *para*-substituted arylboronic acid containing halogen and electron-withdrawing groups are also well tolerated and lead to the formation of ketones **2e** and **2f** in 86% and 77% yield.

3-Substituted arylboronic acids are also competent nucleophiles for the Pd@TpBpy-catalyzed conjugate addition reactions. Electron-donating, electron-withdrawing, and halogenated 3-substituted arylboronic acids react with **1a** to produce ketones **2g-k** in moderate-to-good yields (54-92%). Additions of *ortho*-substituted arylboronic acids to enone **1a** did not occur to form the corresponding ketone products in high yields. However, reactions of phenylboronic acid with additional cyclic enone electrophiles occur in high yields. The additions of phenylboronic acid to 3-methylcyclopent-2-en-1-one **1b** and to 3,5,5-trimethylcyclohex-2-en-1-one **1c** generated ketones **2l** and **2m** in 80% and 77% yield, respectively.



Scheme 2. Substrate scope. Reaction conditions: **1a-c** (0.5 mmol), PhB(OH)₂ (1 mmol), Pd@TpBpy COF (0.010 mmol Pd), 50 mM NaTFA (pH = 8.2) (0.33 mL) (NaTFA tuned to pH = 8.2). Isolated yields are reported.

To determine the stability of Pd@TpBpy COF, the recyclability in the conjugate addition of phenylboronic acid to **1a** was evaluated (Figure 1). As expected, the pristine Pd@TpBpy COF catalyzed the formation of ketone product **2a** in 99% yield over six hours. After recovering and washing the catalyst, additional enone **1a**, phenylboronic acid, and aqueous NaTFA were added. The activity of the catalyst remains high in runs 2-4, and the ketone product **2a** is formed in high yields (95-98%). However, significant loss of catalyst activity is observed in runs 5 and 6 with the yield of **2a** decreasing to 38% after run 6. Increasing the reaction time to 11 h for run 7 led to an increase in yield (56%) of **2a**. When testing the recyclability with the optimal conditions determined for our model reaction, we observed more consistent yields with a modest decrease in activity between runs, maintaining yields of 79-99% over 7 runs. Although we observe a decrease in catalyst activity over time, the Pd@TpBpy COF catalyst is significantly more stable and outperforms related MOF catalysts reported by our group^[10].

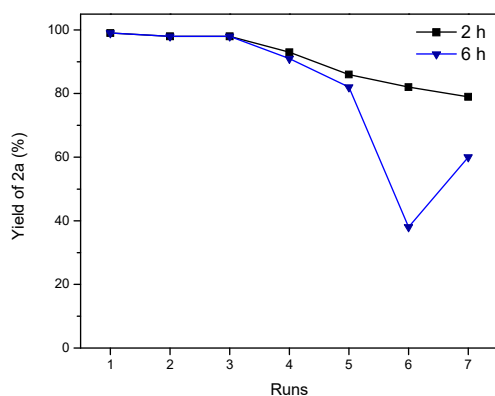
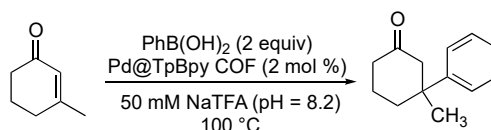


Figure 1. Two/six-hour recycling experiments. Reaction conditions: **1a** (1.5 mmol), PhB(OH)₂ (3.0 mmol), Pd@TpBpy COF (0.03 mmol Pd), 50 mM NaTFA (pH = 8.2) (1.0 mL). Yield determined by ¹H NMR using dibromomethane as internal standard.

To test for leaching of palladium species, we performed ICP-MS on the post-reaction supernatant. After six hours of reaction time, 4.0% of the originally added palladium content in the reaction was detected in the post-reaction supernatant. To test the catalytic activity of the leached palladium species, Pd@TpBpy was removed from the reaction by filtration at 30 minutes and formed ketone **2a** in 47% yield (via ^1H NMR) after this initial time. After removing the Pd@TpBpy catalyst from the reaction mixture, the remaining reagents were allowed to react for the remainder of the reaction time (6h), and the yield of ketone **2a** only increased to 49% after this time (Figure 2). This result suggests that palladium species leached from the COF are not competitive catalysts of the conjugate addition reaction. To further probe this hypothesis, we heated Pd@TpBpy in aqueous NaTFA for 6 h at 100 °C in the absence of reactants. The Pd@TpBpy catalyst was then removed by filtration and reactants added to the resulting supernatant. Ketone product **2a** was not observed after heating the mixture for 2 h at 100 °C. This result further suggests that any leached palladium species are not active catalysts of the conjugate addition reaction.

To examine the loss of reactivity of the catalyst over time, the impact of the catalytic reaction conditions on the crystallinity of the Pd@TpBpy COF was evaluated. After recycling the catalyst six times (run 7, 79% yield), the PXRD of the recovered Pd@TpBpy COF shows a slight decrease in intensity and broadening of the first peak at $\sim 3.5^\circ$ (Figure 3a). This difference is consistent with the decrease of BET surface area from 578 m^2/g for fresh Pd@TpBpy COF to 390 m^2/g for the one recycled for 7 times (Figure 3b and S2). This observation suggests that over time the COF framework is becoming less ordered allowing for less accessibility to active sites which could account for the decrease in yield observed.

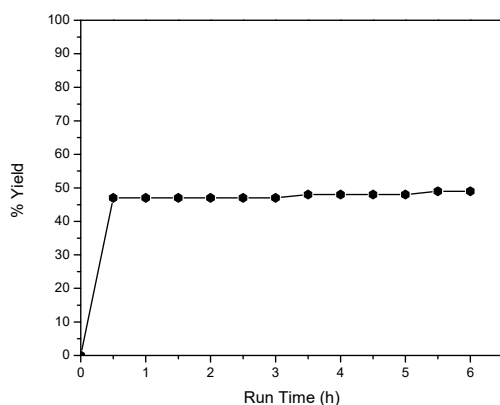


Figure 2: Leaching experiments. Reaction conditions: **1a** (1.5 mmol), PhB(OH)₂ (3.0 mmol), Pd@TpBpy COF (0.03 mmol Pd), 50 mM NaTFA (pH = 8.2) (1.0 mL). Catalyst was filtered off after 30 min. Yield determined by ^1H NMR using dibromomethane as internal standard.

Transmission electron microscopy (TEM) was performed before and after exposure of the Pd@TpBpy COF to reaction conditions to determine if the formation of palladium nanoparticles occurs over the course of the reaction. A low density of palladium nanoparticles can be observed on the as-synthesized Pd@TpBpy COF (Figure 4a). After seven catalytic cycles, an increased density of palladium nanoparticles is observed in the TEM image of the used Pd@TpBpy COF (Figure 4b). To confirm the formation of additional metallic palladium nanoparticles,

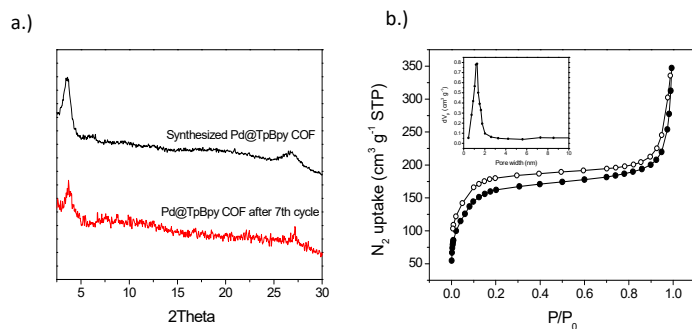


Figure 3: a.) XRD of Pd@TpBpy COF before and after catalysis b.) N₂ adsorption isotherm of Pd@TpBpy COF (right) and pore size distribution (inlet).

X-ray photoelectron spectroscopy (XPS) analyses were performed to provide insight on the oxidation state of the palladium species present in Pd@TpBpy COF. Upon loading of palladium to the fresh COF, the Pd3d core level shows the presence of one dominant peak at the binding energy of 337.9 eV corresponding to a Pd^{II} oxidation state (Figure 4c). We also observed a small peak at 335.0 eV corresponding to Pd⁰,^[3a] which agrees with the presence of Pd NPs in the TEM image in Figure 4a. The Pd^{II} accounts for 93.3 % of total Pd species on the surface of the Pd@TpBpy COF. The XPS analyses of the Pd@TpBpy COF catalyst after 7 recycles shows an increased intensity of the peak at the lower binding energy (335.1 eV) corresponding to higher percentage (11%) of the Pd⁰ species (Figure 4d).^[3b] Through these analyses, we conclude that the Pd^{II} species are the dominant species in the fresh and recycled Pd@TpBpy COF (see Figure S3 for a proposed catalytic cycle). The slight reduction of Pd^{II} to Pd⁰ over subsequent cycles could explain the loss of activity over time.

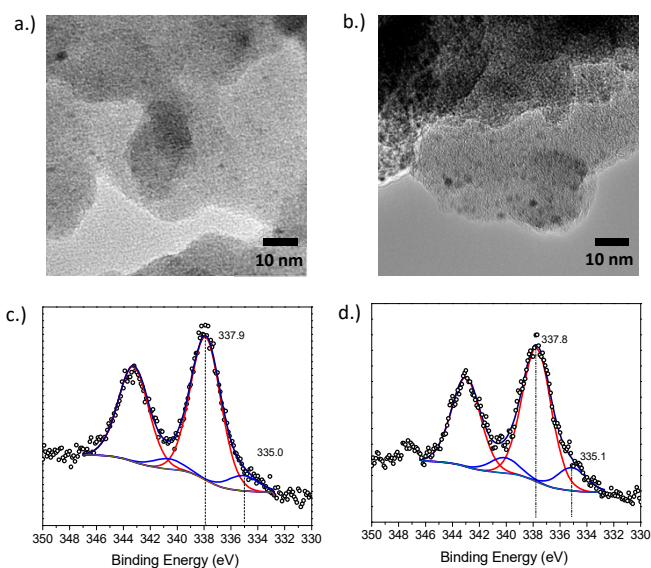


Figure 4: a.) TEM of Pd@TpBpy COF before catalysis b.) TEM of Pd@TpBpy COF after 7 catalytic cycles c.) Pd3d XPS of Pd@TpBpy COF as prepared d.) Pd3d XPS of Pd@TpBpy COF after 7 catalytic cycles.

In summary, we have shown Pd@TpBpy COF to be a robust heterogeneous catalyst for conjugate addition of arylboronic acids to β,β -disubstituted enones in aqueous media. Pd@TpBpy COF is a recyclable catalyst that promotes additions of a wide range of arylboronic acids to cyclic enones to generate quaternary, all-carbon stereogenic centers. This study begins to demonstrate the potential of COFs as a platform for transition-metal catalysis with a range of potential applications in green chemical processes. Further studies to explore the utility of transition metal-functionalized COFs in new catalytic reactions are ongoing.

Acknowledgements

We thank Iowa State University, the Iowa State University Center for Catalysis, and the Ames Laboratory for supporting this work. The Ames Laboratory is operated for the U.S. Department of Energy by Iowa State University under contract number DE-AC02-07CH11358.

Keywords: covalent organic framework (COF), conjugate addition, palladium, quaternary centers, heterogeneous catalysis

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