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# Turning On Catalysis: Incorporation of a Hydrogen-Bond-Donating Squaramide Moiety into a Zr Metal–Organic Framework

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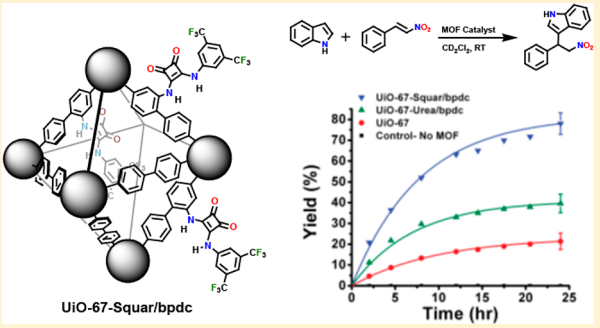
Supporting Information

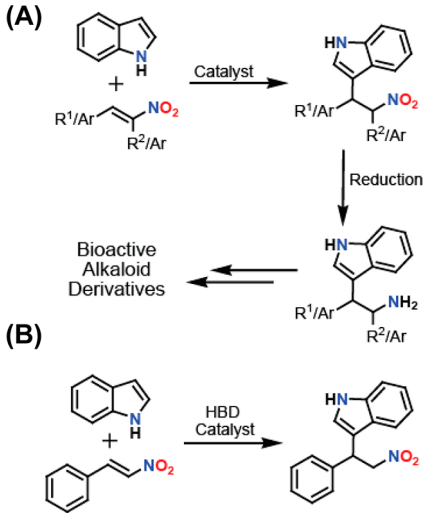
**ABSTRACT:** Herein, we demonstrate that the incorporation of an acidic hydrogen-bond-donating squaramide moiety into a porous UiO-67 metal–organic framework (MOF) derivative leads to dramatic acceleration of the biorelevant Friedel–Crafts reaction between indole and β-nitrostyrene. In comparison, it is shown that free squaramide derivatives, not incorporated into MOF architectures, have no catalytic activity. Additionally, using the UiO-67 template, we were able to perform a direct comparison of catalytic activity with that of the less acidic urea-based analogue. This is the first demonstration of the functionalization of a heterogeneous framework with an acidic squaramide derivative.




## INTRODUCTION

The Friedel–Crafts (F-C) reactions between indole and β-nitroalkenes, such as β-nitrostyrene, are of particular interest, as this reaction is currently the most widely used approach for the synthesis of tryptamine derivatives (Scheme 1A).[1] In contrast to F-C reactions between β-nitroalkenes and N-alkylated indole derivatives (e.g., 1-methylindole), reactions of unsubstituted indole with β-nitroalkenes are slow, due to the significantly lower nucleophilicity of indole.[2,3] Overcoming this synthetic barrier is critical, as tryptamine derivatives containing non-N-substituted indole backbones are critical precursors in the synthesis of targeted, biologically active alkaloids (Scheme 1A), such as the amino acid tryptophan,[4,5] neurotransmitters (e.g., serotonin),[6,7] anti-tumor drugs (e.g., lavendamycin),[8] and psychedelic compounds (e.g., psilocybin).[9] We thus desire to find a novel and robust catalyst toward this central transformation. One family of catalysts that have shown activity toward this pivotal reaction is hydrogen-bond-donating (HBD) organocatalysts.[3,10,11]

**Scheme 1. Friedel–Crafts Reactions (A) between Indole and β-Nitroalkenes for the Synthesis of Alkaloid Derivatives, and (B) between Indole and β-Nitrostyrene**




Hydrogen-bond-donating organocatalysts are a unique family of simple pseudo-Lewis-acidic organic compounds, which are able to activate electrophilic moieties (e.g., β-nitroalkenes) toward nucleophilic (e.g., indole) addition via cooperative hydrogen bonding.[12−14] This cooperative hydrogen bonding has been shown to lower the lowest unoccupied molecular orbital (LUMO) of the electrophile, thus lowering the activation barrier for nucleophilic attack.[12] Due to this effect, HBD organocatalysts have proven capable of catalyzing a huge array of bond-forming transformations, including Strecker reactions,[15] Diels–Alder reactions,[16] conjugate additions,[17] and F-C reactions (Scheme 1B).[18,19] In general, the activity of HBD organocatalysts toward such transformations increases as a function of acidity, due to the greater dipole moment across the HBD moiety (i.e., N–H bonds) and the greater ability to lower the LUMO of the electrophile (e.g., β-nitroalkene).[20,21] Squaramide-based HBD organocatalysts,

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recently developed by Rawal et al., have been shown to be approximately 6 orders of magnitude more acidic than their urea counterparts (Figure 1A).[20−22] This drastic difference is due to the potential for resonance stabilization of enhanced electron density by the partially aromatic squaramide ring.[23,24] Consequently, squaramide derivatives have been shown to greatly accelerate key bond-forming transformations relative to earlier HBD organocatalysts.[25] Although this improved acidity is a promising advancement in HBD organocatalysis, the strong hydrogen-bonding nature of the squaramide-based catalysts also drives catalytically detrimental self-association (Figure 1B);[26,27] a similar phenomenon occurs for their urea-based predecessors (see Supporting Information (SI), Figure S23).[28,29] Therefore, we hypothesized that immobilizing the very acidic HBD squaramide fragments onto the strut of a metal−organic framework (MOF) would prevent this self-association, promote hydrogen-bond-accepting substrate recognition, and improve catalytic activity (Figure 1C).

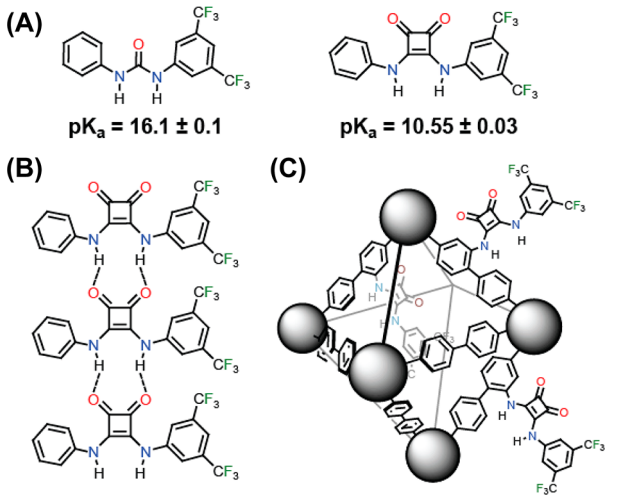
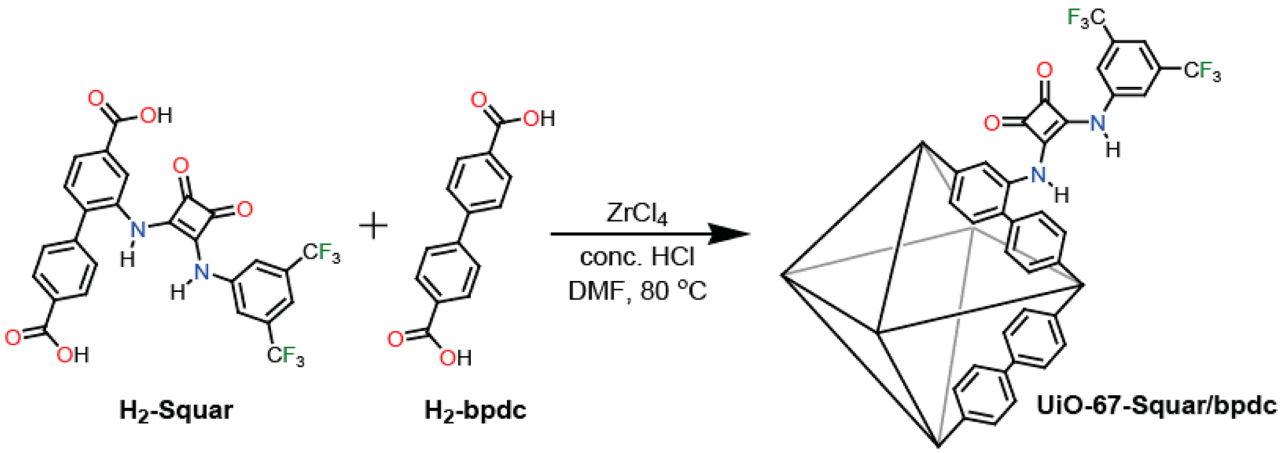



**Figure 1.** (A) Reported acidities of analogous urea and squaramide derivatives in DMSO. (B) Idealized self-association pattern of squaramide derivatives. (C) Idealized structure of squaramide-functionalized UiO-67 MOF derivative.

MOFs are a widely studied class of porous, crystalline materials that are composed of inorganic nodes connected by polytopic organic linkers.[30] The enormous potential combinations of different inorganic nodes and organic linkers have allowed for the synthesis of a diverse array of MOFs with applications in gas storage and separation,[31−33] biomedicine,[34] light harvesting,[35,36] and heterogeneous catalysis.[37] Due to the extended 3-D ordered structure of these porous crystalline structures, novel properties (e.g., lack of self-association) can be imparted to known organic and inorganic moieties by incorporation into coordinating struts.[38] In many such cases, these unique properties are either inaccessible or synthetically challenging in the homogeneous state. For example, Lin et al. have demonstrated the ability to increase the catalytic activity of an otherwise self-deactivating iridium−bipyridyl catalyst by 3 orders of magnitude via incorporation into the strut of a MOF.[39] Therefore, we hypothesized that by incorporation into a MOF system (Figure 1C), we could significantly improve the activity of a squaramide-based HBD organocatalyst, particularly toward the otherwise dormant F-C reaction between indole and *β*-nitrostyrene (Scheme 1B). Namely, by fixing the squaramide moiety in a 3-D porous framework, detrimental self-association (such as that shown schematically in Figure 1B) would be prevented by the ordered structure, thus catalytic activity would be "turned-on". To test our hypotheses, we have synthesized a mixed strut squaramide-functionalized UiO-67 derivative (UiO-67-Squar/bpdc) (Scheme 2), and studied the activity of this system toward the F-C reaction between indole and *β*-nitrostyrene to produce 3-(2-nitro-1-phenylethyl)-1*H*-indole (see Figure 4A, below). The UiO-67 family was chosen for this study due to their porosity and thermal and chemical stability.[40,41] Using this system, we were able to study the effects of heterogenization of the HBD organocatalyst into a porous MOF architecture, as well as how the superior acidity and unique structure of squaramide derivatives affects catalytic activity.[24] Specifically, by creating a motif in which we are able to systematically prevent self-association of HBD organocatalysts, we can directly probe and compare the relative activity of different catalysts, without the additional variable of self-association. Our results demonstrate that upon incorporation of a catalytically dormant HBD organic moiety into a porous MOF architecture, we are able to impose truly significant catalytic activity toward this pivotal organic transformation. Additionally, in the absence of self-association, the squaramide-based HBD organocatalyst produces substantially greater activity relative to a urea-derived counterpart. Therefore, it is clear that incorporation into a MOF structure is the ideal

**Scheme 2. Synthesis of 1:1 Mixed Strut MOF UiO-67-Squar/bpdc**



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approach to both improve and study the catalytic activity of a HBD squaramide moiety. To our knowledge, this is the first demonstration of the functionalization of a heterogeneous framework with a HBD squaramide motif.[42]

## RESULTS AND DISCUSSIONS

**Synthesis and Characterization.** Synthesis of the targeted HBD squaramide-functionalized strut ($H_2$-Squar, Scheme 2) was achieved by the Lewis-acid catalyzed condensation of dimethyl 2-aminobiphenyl-4,4′-dicarboxylate with 3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione to form $Me_2$-Squar (See SI for structures of precursors), followed by an acid-catalyzed saponification to cleanly produce $H_2$-Squar.[43,44] Single crystals of the protected precursor, $Me_2$-Squar, suitable for X-ray diffraction studies were grown via recrystallization from hot DMSO (Figure 2). Of note, in the solid-state the bis(trifluoromethyl)phenyl group is effectively coplanar with the squaramide moiety. This conformation is induced by hydrogen bonding between the squaramide carbonyl moiety and the ortho C−H bond on the phenyl substituent, and is known to lower the entropic cost of binding to a substrate.[22] $H_2$-Squar was subsequently incorporated into a zirconium-cluster-based UiO-67 MOF via a HCl-modulated preparation, utilizing $ZrCl_4$ as the zirconium source.[40] In order to accommodate the relatively sterically demanding squaramide motif, and maintain open pores, we utilized a 1:1 molar ratio mixed-strut approach to the solvothermal synthesis of our UiO-67 derivative, in which unfunctionalized 4,4′-biphenyldicarboxylate ($H_2$-bpdc) was used in addition to $H_2$-Squar (UiO-67-Squar/bpdc, Scheme 2).[45,46] After digestion of the MOF in $D_2SO_4$ and DMSO, the ratio of $H_2$-bpdc and $H_2$-Squar in UiO-67-Squar/bpdc was found to be 1:1 by $^1$H NMR spectroscopy (see SI). This ratio was found to be consistent throughout multiple synthesized batches. $^{13}C\{^1H\}$ NMR spectroscopy also confirmed the presence of $H_2$-Squar in the synthesized MOF (Figure S9). Additionally, elemental analysis and $^{35}$Cl NMR spectroscopy were used to determine that no detectable $Cl^-$ (from HCl) was present in the final structure indicating that the squaramide moiety is not an HCl adduct within the MOF. The formula of UiO-67-Squar/bpdc was determined by $^1$H NMR spectroscopy to be $Zr_6O_4(OH)_4(Squar)_2(bpdc)_2$ by digesting the MOF in the presence of an internal standard (Figure S7 and S8). Importantly, the idealized mixed strut UiO-67 formula is $Zr_6O_4(OH)_4(strutA)_3(strutB)_3$, therefore on average there are two strut vacancies per formula in UiO-67-Squar/bpdc. These vacancies can potentially aid in the diffusion of substrates and products in and out of the framework. Powder X-ray diffraction (PXRD) of UiO-67 and UiO-67-Squar/bpdc (Figure 3) indicates that the desired 3-D architecture is retained upon incorporation of the squaramide-functionalized linker. Additionally, $N_2$ isotherms of supercritical $CO_2$-dried samples show that the MOF materials are porous, having Brunauer−Emmett−Teller (BET) surface areas of 2500 $m^2/g$ (UiO-67) and 1700 $m^2/g$ (UiO-67-Squar/bpdc) (Figure S2).

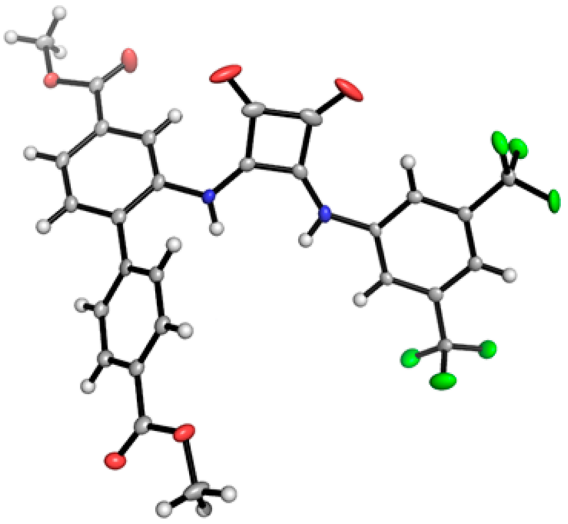

**Figure 2.** Solid-state X-ray structure of $Me_2$-Squar. Thermal ellipsoids are drawn to 50% probability. Solvent is omitted for clarity. C, gray; O, red; N, blue; F, green; H, white.

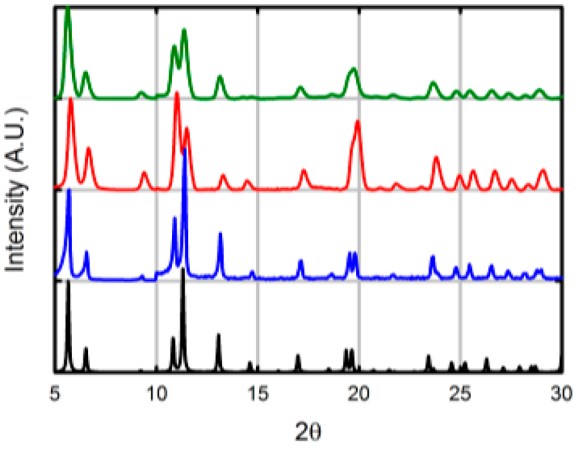


**Figure 3.** Powder X-ray diffractograms of simulated UiO-67 (black), UiO-67 (blue), UiO-67-Squar/bpdc (red), and post-catalysis UiO-67-Squar/bpdc (green). Peaks at $2\theta > 10$ have been enhanced by 10× for clarity. The PXRD patterns of the urea-containing derivatives have been reported elsewhere.[45]

**Catalysis Studies.** With the MOF in hand, we set out to study the catalytic activity of the squaramide moiety, as well as the effects of heterogenization into the porous MOF architecture. Unless otherwise noted, reactions were carried out at 23 °C in $CD_2Cl_2$ at 0.03 M indole and 0.02 M $\beta$-nitrostyrene, with 10 mol% loading of the determined $Zr_6O_4(OH)_4(Squar)_2(bpdc)_2$ formula. The reaction progress was monitored using $^1$H NMR spectroscopy. As seen in Figure 4B, UiO-67-Squar/bpdc is capable of achieving approximately 80% yield after 24 h. Conversely, no reaction products were observed in the absence of the MOF catalyst. Post-catalysis, UiO-67-Squar/bpdc was isolated via filtration, and PXRD was performed. Figure 3 (green) shows that the 3-D framework is preserved. To determine if any product was trapped in the MOF post-catalysis, a $^1$H NMR spectrum of thoroughly washed then digested UiO-67-Squar/bpdc was taken. No product was observed. Importantly, this post-catalysis $^1$H NMR spectrum shows that the squaramide moiety is still intact (Figure S20). Additionally, a recycling experiment was performed (Figure S19), which showed that UiO-67-Squar/bpdc maintains its catalytic activity through multiple cycles of catalysis and post-catalysis isolation. The catalytic activities of multiple different synthesized batches of UiO-67-Squar/bpdc were tested, and they demonstrated high consistency and reproducibility, with a narrow standard deviation after 24 h (Figure 4B).


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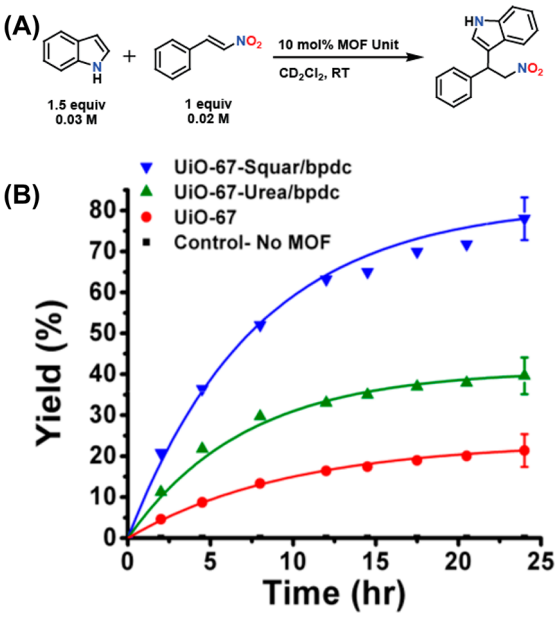


**Figure 4.** (A) Reaction conditions for F-C reaction between indole and $\beta$-nitrostyrene. (B) UiO-67-Squar/bpdc (blue) shows drastically improved catalytic activity over UiO-67-Urea/bpdc (green) and UiO-67 (red). The MOF-free control shows no detectable yield (black). Reaction progress was monitored by $^1$H NMR spectroscopy. Standard deviation at 24 h determined using multiple synthesized batches of respective MOFs. Product determined to be racemic by chiral HPLC (see SI).

In comparison to UiO-67-Squar/bpdc, when squaramide-free UiO-67 is utilized, only 22% conversion is observed (Figure 4B) over the 24 h period. Unsurprisingly, the Lewis-acidic zirconium clusters of the MOF are able to accelerate the transformation.[47] To probe the necessity of the mixed-strut MOF approach to create a viable catalytic system, UiO-67-Squar was synthesized, in which only the $H_2$-Squar strut was used. The $N_2$ isotherm of the supercritical $CO_2$-dried UiO-67-Squar gave a BET surface area (530 $m^2/g$) significantly lower than UiO-67 and UiO-67-Squar/bpdc. In the presence of UiO-67-Squar the yield decreased significantly (22% in 24 h) (Table 1, entry 4). This yield is attributed to the reactivity of the zirconium-based nodes. The drastic decrease in activity may be due to a combination of detrimental intermolecular hydrogen bonding of the squaramide moieties and/or the shrinking of pores of the MOF. Importantly, this result demonstrates that the mixed-strut approach is critical to the activity of the squaramide moiety. To activate the squaramide moiety to catalytic activity, the framework must both alleviate the detrimental self-associative hydrogen bonding, while also allowing substrates to access the catalyst. Indeed, the mixed-strut UiO-67-Squar/bpdc does just that. Additionally, filter tests performed with both UiO-67-Squar/bpdc and UiO-67 confirmed the heterogeneous nature of the catalysts (Figure S18). Therefore, by incorporating a HBD squaramide moiety into a mixed-strut UiO-67 derivative we have created an active catalytic system with high activity toward the pharmaceutically relevant F-C reaction between indole and $\beta$-nitrostyrene.[1]

To directly investigate how the alleviation of detrimental self-association events via the incorporation of the squaramide-based organocatalysts into a porous MOF architecture affects catalytic activity for the targeted transformation, the catalytic activities of MOF-free squaramide derivatives were also examined (Table 1). Using the same conditions as above, $Me_2$-Squar (insoluble in $CD_2Cl_2$) and the semi-soluble squaramide derivative 3-((3,5-bis(trifluoromethyl)phenyl)-amino)-4-((4-ethynylphenyl)amino)-3-ene-1,2-dione (Ethynyl-Squar) (See SI for structure) fail to produce any detectable product after 24 h (Table 1, entries 7, 8). These results confirm our hypothesis that incorporating squaramide-containing struts into a MOF architecture prevents catalytically detrimental self-association. Additionally, the catalytic dormancy of the free squaramide derivatives emphasizes that via incorporation into the organized, porous 3-D architecture we are able to "turn-on" the activity of the squaramide moiety. We further ruled out any cooperative effects between the UiO-67 framework and the HBD moieties by performing catalytic studies with mixtures of unfunctionalized UiO-67 and the free HBD squaramide catalysts; only the 20% conversion attributed to unfunctionalized UiO-67 was observed (Table 1, entries 10, 11).

**Table 1. Catalytic Studies for F-C Reaction of Indole and $\beta$-Nitrostyrene**

| entry | catalyst | solvent | temp (°C) | time (h) | yield (%) |
|---|---|---|---|---|---|
| 1 | none | DCM | RT | 24 | 0 |
| 2 | UiO-67-Squar/bpdc | DCM | RT | 24 | 78 |
| 3 | UiO-67-Urea/bpdc | DCM | RT | 24 | 38 |
| 4 | UiO-67-Squar | DCM | RT | 24 | 22 |
| 5 | UiO-67 | DCM | RT | 24 | 22 |
| 6 | UiO-66 | DCM | RT | 24 | 19 |
| 6 | UiO-67 (not SC dried)[a] | DCM | RT | 24 | 0 |
| 7 | $Me_2$-Squar | DCM | RT | 24 | 0 |
| 8 | Ethynyl-Squar[b] | DCM | RT | 24 | 0 |
| 9 | $Me_2$-Urea | DCM | RT | 24 | 0 |
| 10 | UiO-67 + $Me_2$-Squar[c] | DCM | RT | 24 | 21 |
| 11 | UiO-67 + Ethynyl-Squar[b,c] | DCM | RT | 24 | 22 |
| 12 | UiO-67 + $Me_2$-Urea[b] | DCM | RT | 24 | 20 |
| 13 | UiO-67 (not SC dried)[a] + $Me_2$-Squar[c] | DCM | RT | 24 | 0 |
| 14 | $ZrCl_4$ | DCM | RT | 24 | 0 |
| 15 | UiO-67-Squar/bpdc | 1,2-DCB | 50 | 5 | 74 |
| 16 | UiO-67-Squar/bpdc | 1,2-DCB | 50 | 24 | 93 |
| 17 | UiO-67-Squar/bpdc | toluene | 50 | 5 | 84 |
| 18 | UiO-67-Squar/bpdc[d] | toluene | 50 | 24 | 95 |
| 19 | UiO-67-Urea/bpdc | toluene | 50 | 5 | 50 |
| 20 | UiO-67-Urea/bpdc | toluene | 50 | 24 | 79 |
| 21 | UiO-67 | toluene | 50 | 5 | 33 |
| 22 | UiO-67 | toluene | 50 | 24 | 58 |
| 23 | $Me_2$-Squar | toluene | 50 | 24 | 7 |
| 24 | $Me_2$-Urea | toluene | 50 | 24 | 4 |
| 25 | none | toluene | 50 | 24 | 0 |
| 26 | UiO-67-Squar/bpdc | toluene | RT | 5 | 52 |
| 27 | UiO-67-Squar/bpdc | toluene | RT | 24 | 91 |
| 28 | none | toluene | RT | 24 | 0 |
| 29 | UiO-67-Squar/bpdc | ethanol | RT | 24 | 8 |
| 30 | none | ethanol | RT | 24 | 0 |
| 31 | UiO-67-Squar/bpdc | ethanol | 50 | 24 | 35 |
| 32 | none | ethanol | 50 | 24 | 2 |

Reactions carried out under conditions detailed in Figure 4A using deuterated solvents unless noted otherwise. [a]MOF not supercritically dried during synthesis. [b]See SI for structure. [c]10 mol% MOF and 10 mol% HBD moiety used. [d]Conditions used to scale up to isolate over 1 g of product. Reaction progress was monitored by $^1$H NMR spectroscopy.



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Having demonstrated the ability to prevent detrimental self-association via incorporation into a MOF architecture, we wanted to use this approach to directly compare the catalytic activity of two different HBD organocatalysts, namely squaramide and urea derivatives. In using our design principle, we are able to isolate the substrate activation ability of a HBD organocatalyst from its otherwise unavoidable self-associative behavior. Thus, we can directly probe how the structure of the catalyst affects activity, without the consideration of inter-homomolecular hydrogen bonding. Therefore, to probe these effects, the urea-functionalized strut, $H_2$-Urea, was synthesized, and then incorporated into the analogous mixed-strut UiO-67 derivative UiO-67-Urea/bpdc (Figure S1).[45] The structure was confirmed by PXRD, and the percent loading was determined by $^1$H NMR spectroscopy after digestion. UiO-67-Urea/bpdc was found to have a similar 1:1 strut ratio as its squaramide-containing counterpart, as well as a similar formula, $(Zr_6O_4(OH)_4(Urea)_2(bpdc)_2)$, which was used to calculate the loading of the MOF for catalysis experiments. Under the same reaction conditions reported above, UiO-67-Urea/bpdc only produced a 38% yield after 24 h, compared to the approximately 80% yield achieved by UiO-67-Squar/bpdc (Figure 4B). Clearly, the unique structure of the squaramide moiety imparts a greater ability to activate the electrophilic $\beta$-nitrosytrene toward nucleophilic attack by indole. Further controls, analogous to those run with the squaramide-derivatives, were performed with the urea-based catalysts. Even though soluble in $CD_2Cl_2$, strut precursor $Me_2$-Urea shows no detectable product after 24 h (Table 1, entry 9). Additionally, when the reaction was run in the presence of both UiO-67 and soluble $Me_2$-Urea, no increase relative to the unfunctionalized MOF was observed (20% yield) (Table 1, entry 12). Although soluble, the self-associative behavior of the urea-derivative likely prevents activity toward the F-C reaction of $\beta$-nitrosytrene and indole.

In general, the catalytic efficacy of HBD organocatalysts improves when catalysis is performed in low-polarity solvents (e.g., 1,2-dichlorobenzene and toluene) and at higher temperatures.[48] With low-polarity solvents, the propensity for disruptive interactions with the catalyst is decreased. Therefore, catalysis was performed with squaramide-functionalized UiO-67-Squar/bpdc in 1,2-dichlorobenzene-$d_4$ ($E^T_N$ = 0.225) and toluene-$d_8$ ($E^T_N$ = 0.099) at 50 °C ($E^T_N$ for $CD_2Cl_2$ = 0.309).[49] After 5 h, the reaction was 74% and 84% complete, respectively (TOF = 4.1 × $10^{-4}$ $s^{-1}$ and 4.6 × $10^{-4}$ $s^{-1}$), with nearly quantitative conversion after 24 h (Table 1, entries 15−18). Thus, under these conditions we are able to dramatically improve the catalytic efficacy of UiO-67-Squar/bpdc, allowing one to achieve nearly complete conversion of this otherwise sluggish reaction in just a few hours. Importantly, under these conditions we see that UiO-67-Squar/bpdc is still significantly more catalytically active than UiO-67-Urea/bpdc (50% yield after 5 h, Table 1, entry 19) and UiO-67 (33% yield after 5 h, Table 1, entry 21). For further comparison of reaction conditions, catalysis was performed in ethanol-$d_6$ at 50 °C. After 24 h in polar ethanol-$d_6$ ($E^T_N$ = 0.654) the reaction with UiO-67-Squar/bpdc was only 35% complete (Table 1, entry 31), demonstrating that competitive hydrogen bonding by the solvent with the catalyst deters activity.

To confirm that the difference in activity between UiO-67-Squar/bpdc, UiO-67-Urea/bpdc, and UiO-67 is not unique to the reaction of indole and $\beta$-nitrostyrene, we examined our catalysts' activity for the analogous F-C reaction between pyrrole and $\beta$-nitrostyrene (Figure 5). Indeed, under similar reaction conditions (room temperature (RT), $CD_2Cl_2$) as the first test reactions, we observe a parallel trend in activity (Table 2). After 24 h, UiO-67-Squar/bpdc gives a 51% yield, whereas UiO-67-Urea/bpdc and UiO-67 give 28% and 8% yields, respectively. Interestingly, although pyrrole is significantly smaller than indole, the electronic effects of the substrate seem to dictate the relative yield.

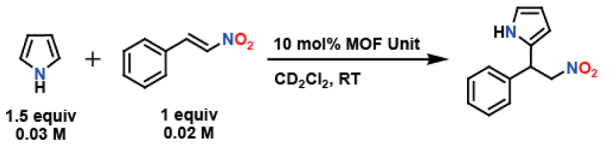


**Figure 5.** Reaction conditions for F-C reaction between pyrrole and $\beta$-nitrostyrene.

**Table 2. Catalytic Studies for F-C Reaction of Pyrrole and $\beta$-Nitrostyrene**[a]

| entry | catalyst | solvent | temp (°C) | time (h) | yield (%) |
|---|---|---|---|---|---|
| 1 | none | DCM | RT | 24 | 0 |
| 2 | UiO-67-Squar/bpdc | DCM | RT | 24 | 51 |
| 3 | UiO-67-Urea/bpdc | DCM | RT | 24 | 28 |
| 4 | UiO-67 | DCM | RT | 24 | 8 |

[a]All reactions carried out under conditions detailed in Figure 5 using $CD_2Cl_2$. Reaction progress monitored by $^1$H NMR spectroscopy.

## CONCLUSION

In summary, through the incorporation of a squaramide-based HBD organocatalyst into the framework of a mixed-strut UiO-67 derivative, we have created an efficient, and robust heterogeneous catalyst for F-C reactions between unsubstituted indole and a $\beta$-nitroalkenes. Importantly, we have demonstrated that via the incorporation of the self-associative HBD organocatalyst into a MOF, one can "turn on" novel catalytic activity not seen in the free organocatalyst. By preventing detrimental self-association, we are able to maintain the active state of the organocatalyst, thus promoting activity. This is noteworthy, as it allows for the exploration of HBD organocatalysis for many other reactions that are critical for the synthesis of targeted, bioactive molecules. Additionally, by creating a framework which occludes the self-association of a HBD organocatalyst, we were able to make a first of its kind direct comparison of the catalytic activity of different HBD moieties. Thus, we have shown that the greater acidity of squaramides promotes significant rate acceleration relative to the urea counterpart. Significantly, this first demonstration of the incorporation of an acidic squaramide derivative into a MOF will allow for the application of more catalytically active HBD MOFs to various important transformations. Additional implications of the incorporation of a strongly HBD motif into a MOF architecture are in anion sensing, substrate detection, and gas uptake and separation. For example, a targeted toxic substrate with electron-rich moieties may be selectively up-taken and sequestered by such HBD structures. Hence, we have developed a MOF construct, which demonstrates unique and significant functionality, as well as opens the doors for many future applications.


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## EXPERIMENTAL SECTION

**General Methods.** All reactions were carried out under a nitrogen atmosphere in oven-dried glassware with magnetic stirring unless otherwise stated. All solvents were purchased from Sigma-Aldrich, and were degassed with argon and dried using 3 or 4 Å sieves where appropriate. All reagents were purchased from Aldrich Chemical Co., and used as received unless otherwise stated. Dimethyl-2-amino-biphenyl-4,4′-dicarboxylate was prepared using a slight modification of the procedure previously reported.[43] $H_2$-Urea was prepared as previously reported.[45] 3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione was prepared as previously reported.[44] Deuterated solvents were purchased from Cambridge Isotope Laboratories. For recording $^1$H NMR spectra for characterization, the solvents were used as received. For catalysis experiments, the solvents were dried over 3 Å sieves. $^1$H NMR spectra were recorded on a Bruker Avance III 400 MHz spectrometer. $^1$H NMR spectra were referenced internally to residual protons in the deuterated solvents (dichloromethane-$d_2$ = $\delta$ 5.32 ppm, dimethyl sulfoxide-$d_6$ = $\delta$ 2.50 ppm). Data are reported as (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constant(s); integration). Electrospray ionization (ESI) mass spectra were recorded on a Bruker AmaZon SL LC-MS instrument in either positive or negative ion mode. Samples were sent to Intertek Pharmaceutical Services (Whitehouse, NJ) for elemental analysis.

Powder X-ray diffraction (PXRD) patterns were collected on a Bruker AXS APEX2 diffractometer equipped with a CCD detector and a Cu K$\alpha$ I$\mu$S mircrofocus source with MX optics. Samples were mounted in nylon cryoloops on a goniometer head. Data was collected with an area detector as rotation frames over 180° in $\varphi$ at 2$\theta$ values of 12°, 24°, 36°, and 48° and exposed for 10 min for each frame. At a distance of 150 mm, the detector area covers 24° in 2$\theta$. Powder pattern data were treated for amorphous background scatter (EVA 16, Copyright Bruker-AXS 1996−2010).

Supercritical $CO_2$ drying was performed using a Tousimis Samdri PVT-30 critical point dryer. $N_2$ adsorption and desorption isotherm measurements were performed on a Micromeritics Tristar II 3020 (Micromeritics, Norcross, GA) at 77 K.

**Synthesis.** *$Me_2$-Squar.* To an anhydrous mixture of toluene:dimethylformamide (19:1, 20 mL) were added 3-((3,5-bis-(trifluoromethyl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (1.08 g, 3.18 mmol) and zinc trifluoromethanesulfonate (230 mg, 0.63 mmol). The suspension was stirred vigorously for 10 min at RT. Dimethyl 2-aminobiphenyl-4,4′-dicarboxylate was added to the mixture at once (1.00 g, 3.50 mmol). The mixture was heated to 100 °C and stirred overnight. The reaction was cooled to −20 °C and filtered. The retentate was washed with toluene and hexanes. The solid was dried to give a yellow solid (980 mg, 52% yield). $^1$H NMR (400.16 MHz, 25 °C, DMSO-$d_6$): $\delta$ 10.19 (br s, 1H), 9.69 (br s, 1H) 8.05 (d, $J_{H-H}$ = 8 Hz, 2H), 7.94 (d, $J_{H-H}$ = 4 Hz, 2H), 7.86 (m, 2H), 7.71 (d, $J_{H-H}$ = 8 Hz, 2H), 7.68 (br s, 1H), 7.53 (d, $J_{H-H}$ = 8 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H). ESIMS ($m/z$): 592 $[M]^+$; found 593.

*$H_2$-Squar.* To 50 mL of acetic acid (99%) was added 800 mg (1.35 mmol) of $Me_2$-Squar, and the mixture was stirred for 5 min at RT. To the mixture was added 50 mL of $H_2SO_4$ (98%). With vigorous stirring, 10 mL of water was added dropwise, in order to maintain one homogeneous phase. The reaction was stirred at 50 °C for 48 h. The reaction was cooled to 0 °C, and ice water was added dropwise with vigorous stirring. Upon cooling, the mixture was filtered over a glass frit. The retentate was washed with water (3 × 200 mL). The solid retentate was dried under high vacuum to yield $H_2$-Squar as a yellow solid (343 mg, 45% yield). $^1$H NMR (400.16 MHz, 25 °C, DMSO-$d_6$): $\delta$ 10.21 (br s, 1H), 9.66 (br s, 1H), 8.04 (d, $J_{H-H}$ = 8 Hz, 2H), 7.84 (m, 2H), 7.68 (br s, 1H), 7.67 (d, $J_{H-H}$ = 8 Hz, 2H), 7.57 (d, $J_{H-H}$ = 8 Hz, 1H), 7.51 (d, $J_{H-H}$ = 8 Hz, 1H), 7.46 (d, $J_{H-H}$ = 8 Hz, 1H). $^{13}$C{$^1$H} NMR (100.6 MHz, 25 °C, DMSO-$d_6$): $\delta$ 185.3, 183.0, 167.5, 167.4, 167.1, 167.0, 142.4, 141.9, 137.2, 135.5, 131.5, 130.8, 130.5, 130.1, 129.9, 126.3, 125.6, 122.4, 119.4, 116.0. ESIMS ($m/z$): 582 $[M+H_2O]^+$; found 583.

*Ethynyl-Squar.* To an anhydrous mixture of toluene:dimethylformamide (6:1, 10 mL) were added 3-((3,5-bis(trifluoromethyl)phenyl)-amino)-4-methoxycyclobut-3-ene-1,2-dione (540 mg, 1.59 mmol) and zinc trifluoromethanesulfonate (115 mg, 0.32 mmol). The suspension was stirred vigorously for 10 min at RT. 4-Ethynylaniline was added to the mixture at once (146 mg, 1.25 mmol). The mixture was heated to 50 °C and stirred for 3 days. The reaction was cooled to RT and filtered. The retentate was washed with toluene and hexanes. The retentate was then recrystallized from DMSO. The resulting precipitate was filtered and washed with DMSO and diethyl ether. The solid was dried to give a pale yellow/white solid (318 mg, 60% yield). $^1$H NMR (400.16 MHz, 25 °C, DMSO-$d_6$): $\delta$ 10.37 (br s, 1H), 10.17 (br s, 1H), 8.05 (s, 2H), 7.75 (s, 1H), 7.49 (d, $J_{H-H}$ = 8 Hz, 2H), 7.43 (d, $J_{H-H}$ = 8 Hz, 2H), 4.15 (s, 1H). ESIMS ($m/z$): 424 $[M]^-$; found 423.

*General Procedure for Synthesis of UiO-67 and Derivatives.* All UiO-67 materials were synthesized using the following general procedure. An 8-dram vial was loaded with $ZrCl_4$ (67 mg, 0.29 mmol), which was purchased from Aldrich and kept in an Ar(g) glovebox, one-third of the DMF, and 0.5 mL of HCl before being sonicated for 20 min until fully dissolved. The mixture of ligands (Table S1) and the remainder of the DMF were then added, and the mixture was sonicated an additional 20 min before being heated at 80 °C overnight (bpdc was not completely soluble under these conditions). For UiO-67, the resulting solid was filtered and washed first with DMF (2 × 30 mL) and then with EtOH (2 × 30 mL). UiO-67 was subsequently heated at 90 °C under vacuum until a pressure of 100 mTorr was reached. The samples were then heated to 150 °C under vacuum for 24 h. For all the other samples, the reaction mixture was centrifuged and the solvent exchanged for DMF several times in order to remove any unreacted starting material. Subsequently, the MOF was soaked in EtOH for 3 days, replacing both at the beginning and end of the day to ensure complete solvent exchange. Samples were subsequently dried under supercritical $CO_2$.

*UiO-66.* The general procedure for synthesis of UiO-67 was followed, but replacing bpdc with terephthalic acid (see SI).

## ASSOCIATED CONTENT

### Supporting Information

Ligand structures, MOF synthesis table, porosity measurements, procedure for catalytic experiments, filter tests, $^1$H NMR spectra of digested MOFs for ratio study, $^1$H NMR spectra of digested MOFs with standards for formula and loading calculations, recycling experiment, filter tests, ORTEP diagrams and crystallographic data tables for single-crystal studies, CIF files, and diagrams of urea self-association. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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