

Enzyme-inspired supramolecular catalysis with metal-organic frameworks as scaffolds

by

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B.S., University of Zimbabwe, 2016

M.S., University of Zimbabwe, 2018

AN ABSTRACT OF DISSERTATION

submitted in partial fulfillment of the requirements for the degree

DOCTOR OF PHILOSOPHY

Department of Chemistry  
College of Arts and Sciences

KANSAS STATE UNIVERSITY  
Manhattan, Kansas

2025

## Abstract

Metal-organic frameworks (MOFs) provide a versatile platform for constructing advanced catalysts due to their tunable structures and ability to incorporate diverse functionalities. To mimic the confined space of enzymes, uniform distribution of functional groups is crucial. A reliable strategy for obtaining uniformly multifunctionalized MOF materials is the independent post-synthetic modification (PSM) of MOFs containing multiple modifiable functional groups in well-defined locations.

This thesis describes how we leverage the covalent post-synthesis modification (PSM) of MOFs, to introduce catalytic functionalities into a well-defined Zn-based pillared MOF, **KSU-1**, which consists of amine-bearing (BDC-NH<sub>2</sub>) and hydroxyl-bearing (DPG) linkers. This modular system enables systematic tuning of catalytic properties. Reacting **KSU-1** with various isocyanates revealed an unexpected selectivity, where hydroxyl groups reacted preferentially over amines, contrary to expectations observed from its previous reactions with other electrophiles. This selective functionalization enabled systematic modification of the hydroxyl groups of **KSU-1** with hydrophobic isocyanates (isopropyl, *tert*-butyl, *n*-hexyl, and tetradecyl) while preserving the active amine group. We determined that systematically increasing the hydrophobicity of the pores results in a commensurate increase of catalyst efficiency for the amine-catalyzed Knoevenagel condensation.

Additionally, to demonstrate the versatility of PSM, we introduced catalytic urea groups by selectively modifying the amine sites of **KSU-1**, while modification at the hydroxyls imparted secondary functionality to once again modulate the pore environment. We initially conducted the Henry reaction of benzaldehyde and nitroalkane in the presence of base. However, this reaction only proceeds with just the base, so the background reaction made it difficult to evaluate catalytic

performance. We then shifted our focus towards the Friedel-Crafts alkylation of 3-methoxy dimethylamine with  $\beta$ -nitrostyrene, using a urea-based MOF **KSU-1<sub>MeU</sub>**, produced from the functionalization of the amine groups of **KSU-1**. As expected, **KSU-1** showed lower conversions of 14% compared to the 25% conversion observed for **KSU-1<sub>MeU</sub>** demonstrating the strength of urea's two-point H-bond activation. We subsequently functionalized the hydroxyl groups in **KSU-1<sub>MeU</sub>** with isocyanate of varying electronics, sterics and, chirality to study the effect of this pore modulation on the catalytic activity and selectivity.

Finally, to highlight the utility of post-synthetic modification in constructing catalysts with functional groups that are likely inaccessible via *de novo* synthesis (such as pendant carboxylic groups), while preserving independent and uniform functionalization, we developed a new PSM strategy. Previous methods for achieving independent functionalization have relied on the orthogonal reactivity of modifiable functionalities, or the significantly different reactivities of the modifying substrates. In a new strategy, we carefully selected reaction conditions and reagents in the functionalization of **KSU-1** with cyclic anhydrides which allowed us to achieve stability of the initial post-synthetic product from the reaction of the amines (**KSU-1<sub>Amide</sub>**), allowing us to obtain homobifunctionalized and well-defined heterobifunctionalized **KSU-1** derivatives for potential applications in catalysis.

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Finally, to highlight the utility of post-synthetic modification in constructing catalysts with functional groups that are likely inaccessible via *de novo* synthesis (such as pendant carboxylic groups), while preserving independent and uniform functionalization, we developed a new PSM strategy. Previous methods for achieving independent functionalization have relied on the orthogonal reactivity of modifiable functionalities, or the significantly different reactivities of the modifying substrates. In a new strategy, we carefully selected reaction conditions and reagents in the functionalization of **KSU-1** with cyclic anhydrides which allowed us to achieve stability of the initial post-synthetic product from the reaction of the amines (**KSU-1<sub>Amide</sub>**), allowing us to obtain homobifunctionalized and well-defined heterobifunctionalized **KSU-1** derivatives for potential applications in catalysis.

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## Acknowledgements

For the past five years of my PhD studies, I have met friends and colleagues and friends who have been instrumental in the successful completion of my dissertation. I would like to express my appreciation for their support and contributing in some way to my thesis.

Firstly, I am immensely grateful to my supervisor Dr. Tendai Gadzikwa for her excellent mentorship and support in every way throughout my PhD. Dr. T, I admire your creativity, the way you see a big picture on the results obtained and ability to translate that into good scientific stories. This thesis would not have been possible without your constant support and guidance. Words are simply not enough to express how grateful I am for your kindness and support.

To my committee members, Dr. Christer Aakeroy, Dr. Ryan Rafferty, and Dr. Placidius Amama, I am grateful for all your support and input in my success during these past my PhD studies. Thank you for being very nice to me whenever to come to you for help. I hope you are proud of how I have progressed as a scientist.

My gratitude also goes to Dr. Socrates Munoz for training me on how to use Supercritical fluid chromatography. I would also like to extend my gratitude to all SupraCatLab members past and present, Dr Mohammad S. Yazdanparast, Dr Donovan Mafukidze, Dr. Kanchana P. Samarakoon, Taylor Perkins, Amanda Currie, Astrid Armas, Udo P. Otuonye, Margret Pagare, Lahiru I. Pothupitiya, Terrell Campell and Lamontain Udube, for all your contribution to my research journey.

I would like to acknowledge friends, colleagues, faculty, and staff members in the Department of Chemistry at Kansas State for helping me and contributing to my success in some ways. Special thanks go to Michael Hinton for sharing all your teaching skills and making teaching CHM1 and CHM2 labs easy. Simon Sham and Tomohiro thank you for your help with NMR and

being there on time whenever there are issues with the instrument. Tobb Eggers I appreciate your help for fixing our hotplates and other instruments that I brought to you in a timely manner. Bart Bath, I appreciate your work of making sure we get chemicals in a timely manner. To my chemistry friends Dr. Rosa Chinheya, Dr Sandile Mtetwa-Umuthe, Patience Sibanda and Linda Maphosa thank you for your support and motivation throughout my studies, I needed all those life updates WhatsApp video calls we had 😊. Dr James Nyakuchena, you were always available to have chemistry discussions and practice presentations with me, truly my study buddie from my undergrad to PhD. I am grateful for your support. Sachithra Somachandra thanks for coming to K-State same time as me. I think every girl needs a friend like you in their PhD studies. I am grateful for our friendship. Dr. Samiksha Khadka, thank you for agreeing to be my thesis writing partner. I am grateful that our goals aligned during the most crucial phase of my dissertation, and your support made a significant difference in bringing this work to fruition. Dr. George Anaman aka “Uncle George” an economist who ended up understanding what metal-organic frameworks (MOFs) are - especially KSU-1, thank you for all your support.

To my family, especially my parents, Edmore Matseketsa and Ever Munetsi, thank you. Your unwavering support has been the foundation of my journey, and I truly wouldn't have made it this far without you. I'm deeply grateful for always being there whenever I needed you. To my siblings Nigrate, Tsitsi, Yemurai, Mary and Manasseh thank you for being my built-in-cheerleaders and my greatest source of motivation.

Finally, I would like to extend my sincere gratitude to everyone who contributed to my academic journey but is not mentioned by name. Your support, guidance, and encouragement have been invaluable in helping me complete this work, and I am deeply appreciative of all your efforts.

## **Dedication**

To my family, for whom this moment once seemed impossible. I dedicate this to being the first woman in our family to earn a PhD and to making sure I'm not the last.

# Chapter 1 - Introduction

## 1.1. Introduction to metal-organic frameworks MOFs

Metal organic frameworks are a class of porous crystalline materials made of organic linkers connected to a metal or metal clusters via coordination bonding (**Figure 1.1**).<sup>1</sup> They are highly porous and crystalline. By judicious choice of metal sources and linkers it is possible to generate MOFs with exceptional structural diversity and tunable chemical functionality.<sup>2,3</sup> The choice of the organic linker depends on the specific application, e.g., some applications require hydrophilicity or hydrophobicity in the MOF pore environments while others require specific pore volumes or pore window sizes. Therefore, several factors are considered during MOF synthesis.

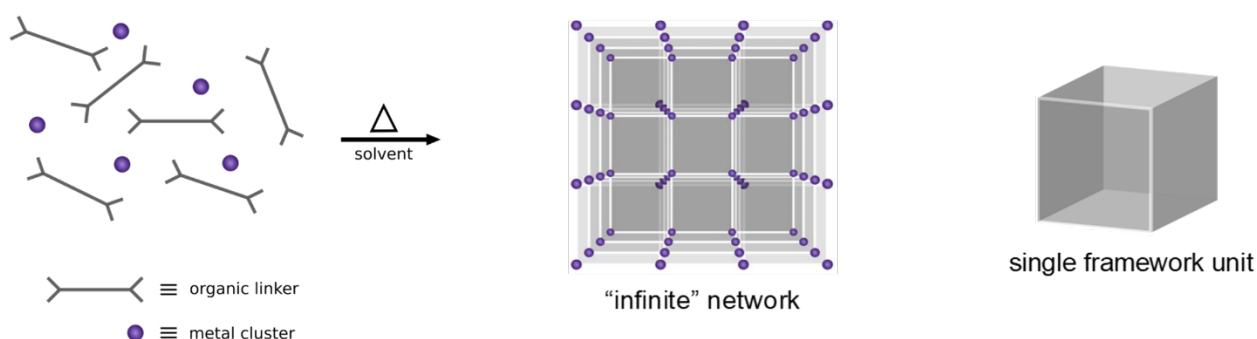


Figure 1.1. A general representation of MOF synthesis.

For applications such as catalysis or sensing, longer organic linkers or those possessing specific functional groups are desirable (**Figure 1.2**). The size and shape of these linkers can result in pore window that allow access to catalytic sites and/or facilitate the formation of large pores enabling easy diffusion of reactants and products. The pore size can also act as a criterion for substrate size selectivity. Additionally, metal nodes and clusters play a crucial role in determining the stability of the resulting MOFs. (**Figure 1.3**) shows a variety of MOFs with their corresponding lattice structures, organic linker, SBU metals.<sup>4</sup> However, in this thesis we use Zn-based paddlewheel MOF. Since Zn is not as hard as metals like Zr, it is capable of coordinating with

both carboxylate and pyridyl linkers provided other synthesis conditions such as temperature and concentrations of reactants are precisely controlled.

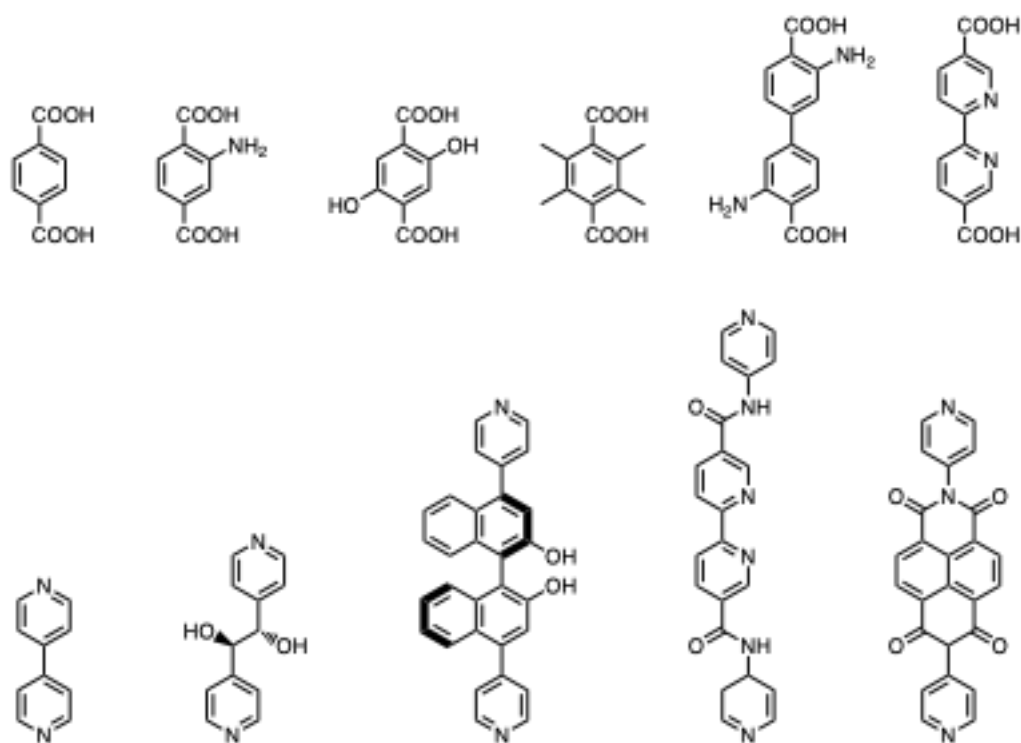


Figure 1.2. A representation of some linkers that are used for MOF synthesis. Top: Dicarboxylate linkers. Bottom: Dipyriddy pillars.

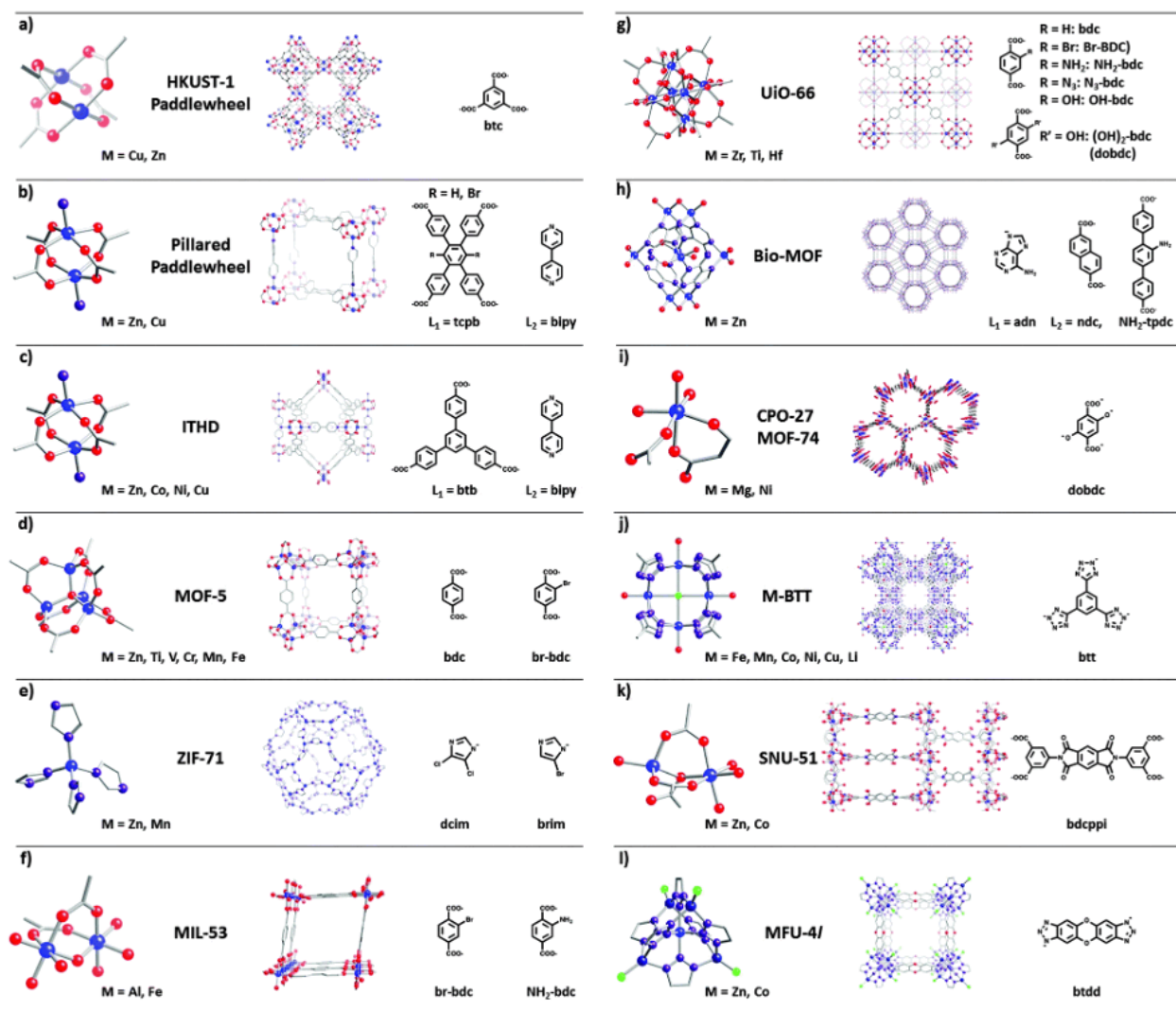


Figure 1.3. Lattice structures (middle) and corresponding SBUs (metal nodes (left), and organic linkers (right)) of some of the MOFs. Atom definition: blue – metal, red – oxygen, purple – nitrogen, grey – carbon, green – chlorine. Reproduced with permission from REF<sup>4</sup>.

## 1.2. Parallels between (MOFs) and enzymes

Enzymes are nature's highly efficient catalysts, capable of performing complex biochemical transformations with remarkable selectivity and efficiency. Their efficiency is largely attributed to their well-defined active sites, which are confined environments decorated with functional groups capable of secondary and/or cooperative interactions that fine-tune catalytic activity.<sup>5</sup> In recent years, MOFs have emerged as a class of synthetic materials that share several key characteristics with enzymes. MOFs are highly ordered and porous structures with (i) pore



sizes ranging from ~0.5- ~2.0 nm enabling built-in confinement similar to that observed in enzymes (ii) the ability to host catalytic sites through metal nodes or organic linkers, and (iii) a tunable chemical environment that facilitates the introduction of secondary functionality, making them promising candidates for enzyme-inspired applications.<sup>6,7</sup> The multiple secondary supramolecular interactions – including ion-pairing, hydrogen bonding, hydrophobic effects,  $\pi$ - $\pi$  interactions, cation- $\pi$  interactions, and anion- $\pi$  interactions – can significantly influence chemical reactions (**Figure 1.4**).

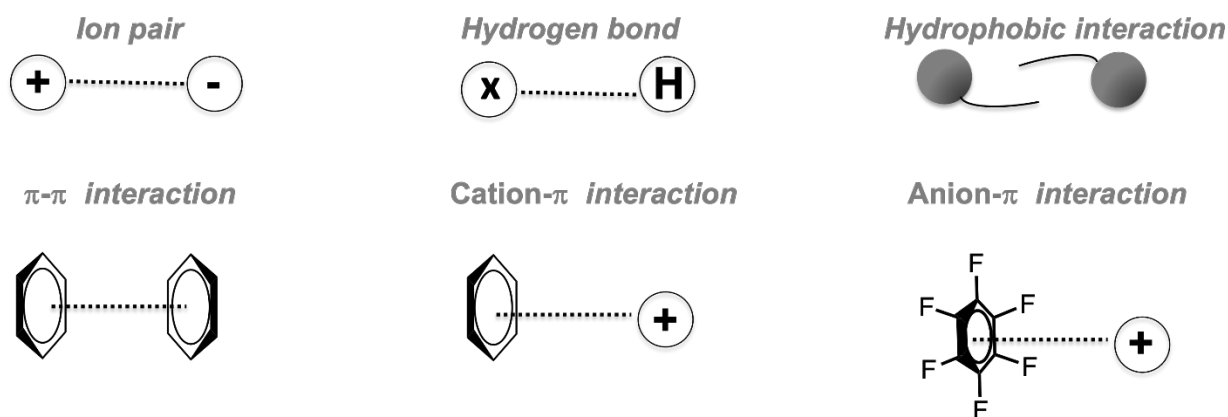


Figure 1.4. Representative examples of noncovalent supramolecular interactions.

By carefully designing MOF architectures by incorporating multiple functional groups through organic linkers and controlling metal cluster composition, researchers can create MOFs that not only mimic enzymes, but also surpass certain limitations of natural enzymes such as stability in extreme conditions.<sup>8-10</sup> Popular examples of enzyme-inspired catalysis are based on mimicking metalloenzymes by modifying the secondary sphere around the catalytic metal site or replacing the metal with one better suited for the desired catalytic activity (**Figure 1.5A**).<sup>11,12</sup> However, in our lab we are interested in mimicking the active sites and functional groups present in metal free enzymes such as TEV proteases (**Figure 1.5B**).

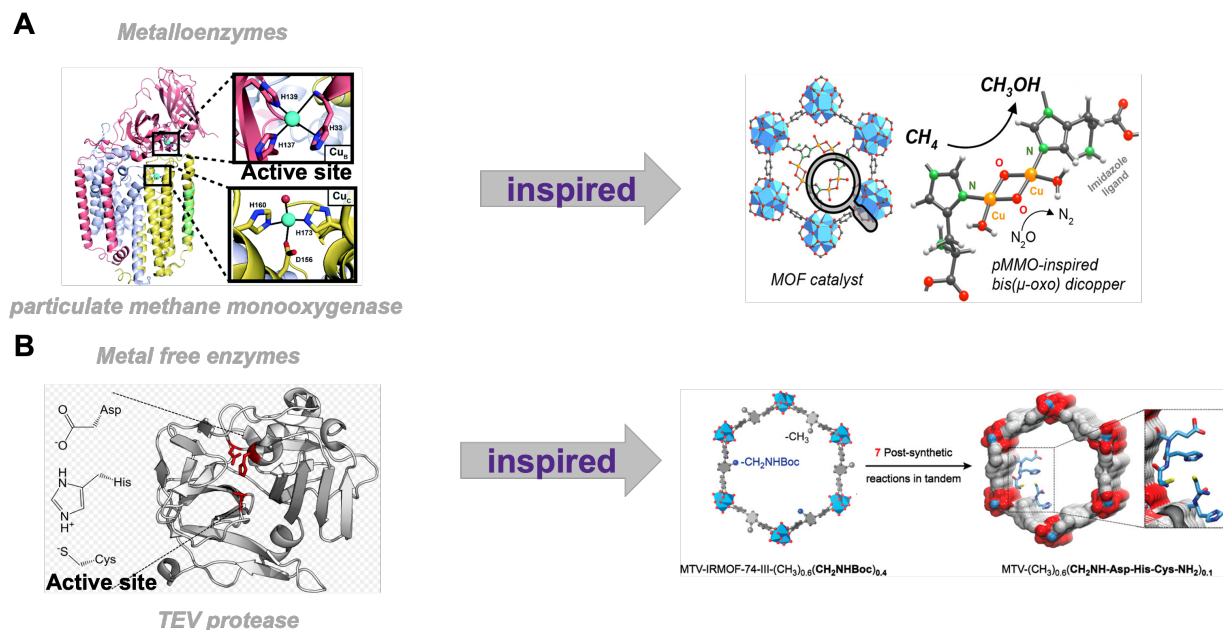


Figure 1.5. Representation of an enzyme active site inspiring MOF catalyst design. A: p-Methanemonooxygenase, whose catalytic activity is based on Cu metals and its MOF mimic B: TEV protease, featuring an active site is composed of three distinct amino acids that work cooperatively in catalysis and its mimic. Adapted from REF<sup>12–15</sup>.

### 1.3. Strategies for multifunctionalization of MOF for catalysis

As mentioned in the section above, MOFs already possess built-in confinement once they are synthesized. In some cases, the MOF maybe already have the necessary functional groups for catalysis. For example, a MOF constructed from a linker containing hydrogen bond donating urea groups was used directly for catalysis and shown to surpass the activity of its homogenous counterparts.<sup>16</sup> However, expanding the usefulness of MOFs in the context of enzyme-inspired catalysis can be challenging as key functional groups such as free carboxylic groups and hydroxyls are difficult to obtain via *de novo* synthesis. These groups tend to coordinate with metals during crystal formation,<sup>17</sup> making post-synthetic modification (PSM) the most effective strategy to introduce them. For instance, **MIL-53-(Al)-NH<sub>2</sub>** has been post synthetically modified with a series of cyclic anhydrides to obtain pendent carboxylic groups for an epoxide ring opening reaction.

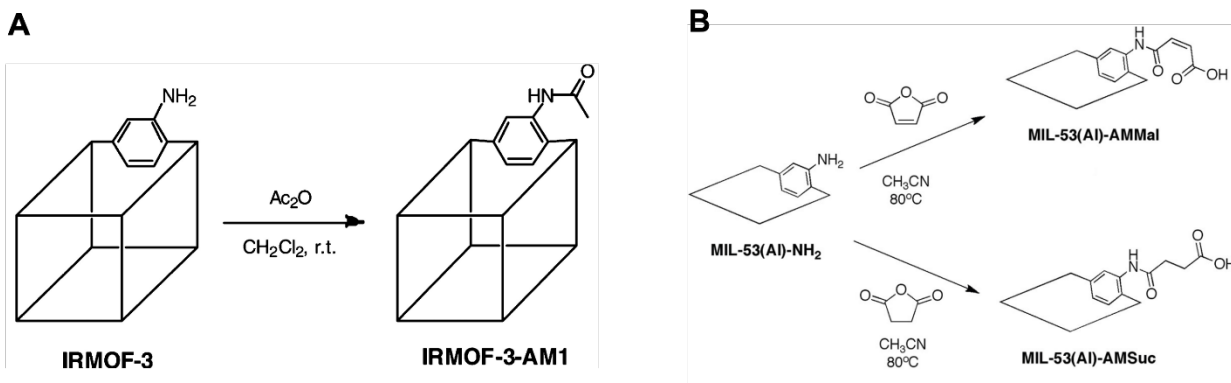


Figure 1.6. A representation of PSM in IRMOF-3 B: Introduction of functionality that would be difficult with PSM. Adapted from REF<sup>14,15</sup>.

While this represents a promising starting point, we know from enzymes that their exceptional catalytic performance arises from multiple functional groups working together to enhance selectivity and reactivity. To achieve multifunctionalization several strategies have been developed. The first strategy involves using a MOF with a single reactive functional group, which is subsequently reacted with different reagents to yield a non-uniformly multifunctionalized MOF, a so-called “multivariate” or MOF. For example, The amine-tagged **IRMOF-3** was previously functionalized with various reagents to introduce multiple functional groups (**Figure 1.7**).<sup>18</sup>

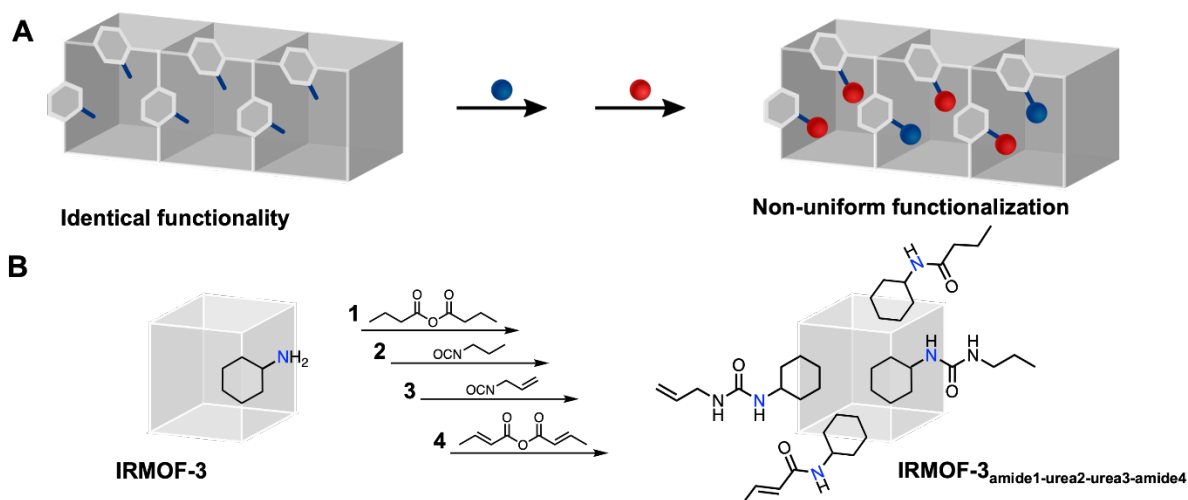


Figure 1.7. A strategy for obtaining multifunctionalization A: cartoon representation of PSM of a MOF with different reagent to achieve non uniform multifunctionalization. B: PSM of amine bearing IRMOF-3 with different reagents to obtain non uniformly functionalized IRMOF-3<sub>amide1-urea2-urea3-amide4</sub>.

Another common strategy involves the use of mixed-linker MOFs with functional groups that exhibit orthogonal reactivity. In most cases, these linkers have identical coordination chemistry, leading to their random distribution throughout the MOF during synthesis. Subsequent independent quantitative PSM with different reagents leads again to a multivariate (MTV) functionalized MOF (**Figure 1.8A**). This uneven distribution of active sites limits the selectivity of the resultant MOF catalyst. The lack of uniformity affects substrates interactions, leading to variations in the catalytic performance. These limitations are evident in the catalytic studies where such strategies have been employed. For instance, Fracaroli et al. performed seven post-synthetic amino acid coupling steps to introduce oligopeptides in **MTV-IRMOF-74**.<sup>13</sup> When evaluated for the  $\alpha$ -chlorination of butyraldehyde, the catalyst yielded a modest enantiomeric excess (ee) of 20 %. Similarly, multivariate zirconium-based MOF **UiO-68N<sub>3</sub>/C $\equiv$ C** was independently functionalized producing two different triazoles in the framework (**Figure 1.8B**). The resulting catalyst **UiO-68Ph(1)/Ph(2)-(B)** was tested in the reaction of cyclohexanone with 4-nitrobenzaldehyde, yielding the aldol product with a diastereomeric ratio (dr) of 35:65 (syn/anti).<sup>19</sup> We can speculate that if the active sites had been uniformly distributed, higher selectivity might have been achieved. Another limitation of these strategies is that it does not allow for structure/catalytic performance relationships to be systematically studied.

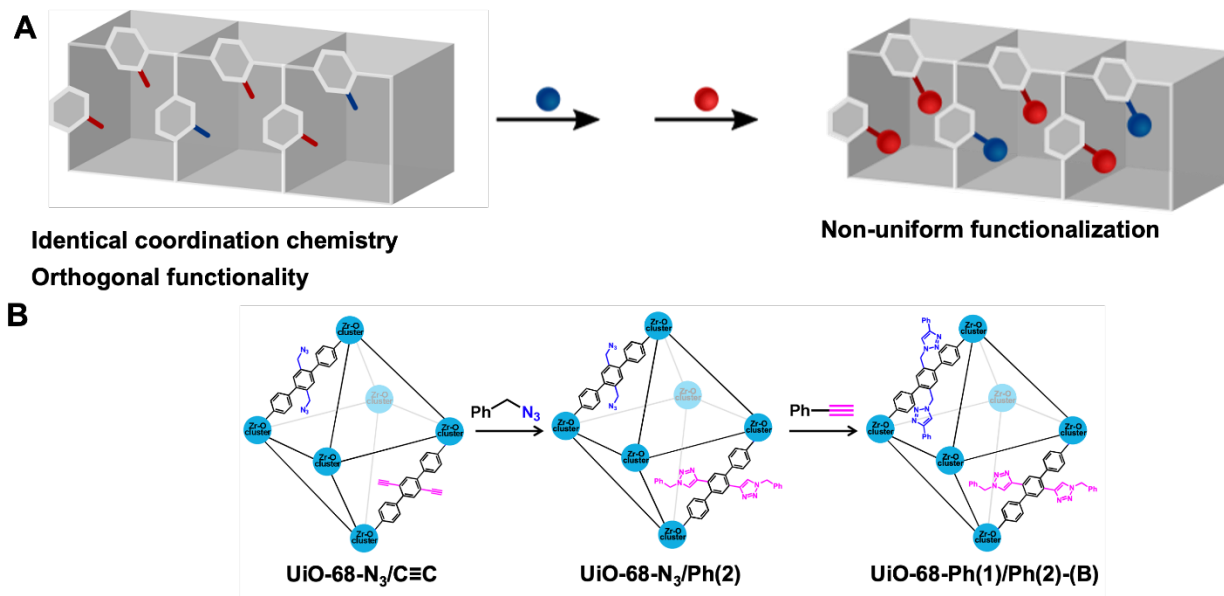


Figure 1.8. A strategy for obtaining multifunctionalization A: cartoon representation of PSM of a MOF with functional groups that have orthogonal reactivity to achieve non uniform multifunctionalization. B: PSM of UiO-68-N<sub>3</sub>/C≡C to obtain non uniformly functionalized UiO-68Ph(1)/Ph(2)-(B). Adapted from REF<sup>18</sup>.

To address these problems, our lab has developed strategies to uniformly multifunctionalize MOFs via covalent PSM. We have employed a pillared, mixed-linker approach which guarantees placement of the organic linkers in well-defined positions (**Figure 1.9A**). If interpenetration is prevented, pillared mixed-linker MOFs result in large pores suitable for catalysis which requires diffusion of reactants and products in and outside the pores. We also selected organic linkers with tags that can be functionalized independently post MOF synthesis. In this way we can introduce a desired catalytic active group in the MOF via functionalization of one linker, then tune the secondary environment around the catalyst by PSM of the auxiliary linker. As proof of concept our group published work to show the uniform multifunctionalization of the MOF **KSU-2 (Figure 1.9B)**.<sup>17</sup>

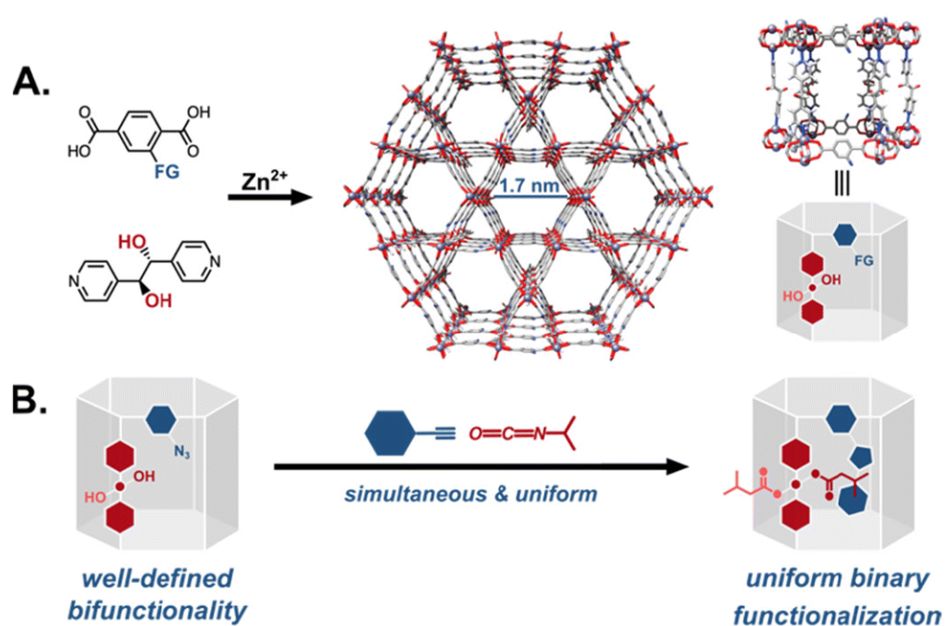


Figure 1.9. Uniform post-synthetic multifunctionalization of MOFs (A) well-defined, large-pore, pillared MOFs are constructed with two different linkers, each with independently reactive tags. For example, (B) a framework with orthogonally reactive tags yields a uniformly bifunctionalized MOF even in simultaneous reactions. Reproduced with permission from REF<sup>17</sup>.

#### 1.4. Significance of uniform PSM of MOFs in catalysis

MOFs provide unique microenvironments that can significantly alter the reactivity of encapsulated molecules and functional groups.<sup>20,21</sup> The previous section briefly discusses the importance of carrying out PSM to position the catalytic sites in a uniform and well-defined manner to ensure that all active sites are perfectly arranged throughout the framework to promote effective interactions among the functional groups. Our work is inspired by enzymes such as serine proteases whose active sites bear the famous enzyme catalytic triad of nucleophile, acid, and base – serine, aspartic acid, and histidine in the case of serine proteases – that are in proximity to each other. Mechanistic studies show that it is only when they are in a specific configuration where efficient proton transfer can occur during their catalysis of peptide bond cleavage. Thus, in our lab we believe by using pillared mixed linker MOFs with functionalizable handles we will be able to mimic such an active site by precisely and uniformly arranging the catalytic functionalities. Apart

from copying existing enzymes' active sites, we believe that our catalyst design allows us to systematically modulate the pore environment which may lead to the discovery of new catalysts with unprecedented properties. Compared to other well-defined systems that have been developed,<sup>8,22</sup>our system offers facile generation of multiple systematically modified catalysts. This also combines the advantages homogenous catalysts with those of heterogenous system.

## 1.5. Thesis overview

Chapter 2 of this thesis describes the discovery of unexpected reversal of reactivity in organic functionalities when they are immobilized together in a MOF and attempts to unravel its molecular origin. We also establish a method of independently functionalizing the MOF's pores by carefully selecting the reactants and reagents.

The next chapters demonstrate the versatility of using the post-synthetic mono- and bi-functionalization of one parent MOF to generate several daughter MOFs possessing distinct catalytic properties. In Chapter 3. we take advantage of the results obtained in Chapter 2 to hydrophobize the pores of an amine-based MOF catalyst to enhance its catalytic activity in the Knoevenagel reaction. In Chapter 4 we carry out independent covalent PSM to uniformly bifunctionalize a MOF with urea, a catalytic dual hydrogen-bond donor, and to modulate its secondary sphere in the catalytic Henry and Friedel-Crafts reactions. Finally, in Chapter 5 we independently functionalize the interior of the MOF with pendent carboxylic groups, generating several daughter MOFs that are unattainable via *de novo* synthesis.

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## **Chapter 2 - Unexpected reversal of reactivity in organic functionalities when immobilized together in a metal organic framework (MOF) material.**

Portions of this chapter appear in the following manuscript:

Matseketsa, P.; Mafukidze, D.; Pothupitiya, L.; Otuonye, U. P.; Mutlu, Y. Ç.; Averkiev, B. B.; Gadzikwa, T. Unexpected Reversal of Reactivity in Organic Functionalities When Immobilized Together in a Metal–Organic Framework (MOF). *Mol. Syst. Des. Eng.* **2024**, 5, 445-448  
<https://doi.org/10.1039/D3ME00185G>.

### **2.1. Confinement effects in MOFs**

The popularity of MOFs in catalysis is increasing due to their similarities with enzymes. Enzymes remain at the forefront as Nature’s best catalysts, owing to a variety of characteristics, including confined active sites in a well-defined environment, multiple functionalities, and flexibility.<sup>1</sup> These characteristics lead to substrates experiencing confinement effects where they are forced to orient in a specific way due to their size as well as the shape, proximity, and orientation of multiple functionalities in the cavity, all of which induce excellent activities and selectivity.<sup>1,2</sup>

As crystalline, multicomponent materials, metal–organic frameworks (MOFs) have properties that are a function of their metal clusters, organic linkers, and diverse topologies.<sup>3–5</sup> From this combination of attributes, the confined space of MOF pores arises as an additional structural feature of interest, particularly with respect to catalysis.<sup>6</sup> The confinement effects in MOFs arise from the unique topologies and functional groups present in their pores.<sup>7–9</sup> During MOF construction, different topologies can be achieved based on the choice of metal nodes and organic linkers, resulting in well-defined, porous, and crystalline frameworks. Additionally, functional groups on the organic linkers can be introduced through pre- or post-assembly

modifications, allowing for the tunability of the pore's chemical environment.<sup>6</sup> The tuning of MOF pore size and pore chemical environment is possible by judicious choice of organic linker, that can be made longer to increase pore window or bear functionalizable groups to allow for the introduction of additional functionality via post-synthesis modification (PSM).<sup>10,11</sup> MOFs and other molecular cage-based catalysts have proven that by merely confining the catalytic groups or altering the chemical environment in the MOF pores, the substrates can experience confinement effects leading to improved conversion and selectivity.<sup>12</sup> Zheng et al. showed that a chiral MOF made from  $[\text{Cu}_2(\text{carboxylate})_4]$  secondary building unit (SBU) and chiral 3,3',6,6'-tetrakis(4-benzoic acid)-1,1'-binaphthyl phosphate ligands yielded major enantiomers of opposite chirality to those obtained by the corresponding homogeneous catalyst.<sup>9</sup> Xiao et al. also showed that by altering the hydrophobic pore environment and pore diameter of their MOFs they obtained a 3-fold enhancement in the selectivity and increase in turnover number (**Figure 2.1**).<sup>13</sup>

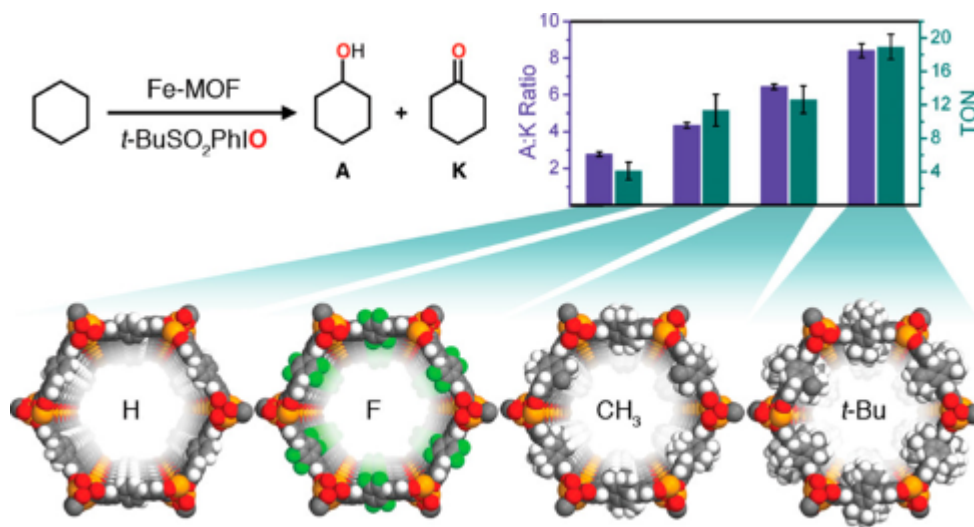


Figure 2.1. Modifying the framework pore diameter and introducing nonpolar functional groups near the iron site resulted in a threefold increase in alcohol-to-ketone (A:K) ratio and the order of magnitude enhancement in turnover number. Reproduced with permission from REF<sup>8</sup>.

These examples are proof that the confined pore environment plays a crucial role in determining catalyst efficiency and selectivity. What has received less consideration, however, is

the effect that this confinement has on the reactivities of the functional groups that decorate the frameworks themselves. In this chapter, we report how the presence of two different functional groups within a MOF material results in unexpected, and unique, changes in their relative reactivities.

## 2.2. Strategies for uniform multi-functionalization of MOFs

Generating uniformly *multifunctionalized* cavities remains a significant challenge in MOF chemistry. Most approaches that use post-synthesis modification (PSM) employ parent MOFs with either a single functionalizable group or multiple differently functionalizable linkers that assemble randomly in the MOF structure. The subsequent reaction of these linkers with various functionalities either simultaneously or sequentially results in MOFs that are non-uniformly functionalized.<sup>14,15</sup> The primary issue with these strategies is the uneven distribution of functional groups within the MOFs pores which renders the resulting multifunctional MOFs unsuitable for applications like catalysis and sensing. Thus, better alternatives are required to design MOF catalyst that closely resemble the well-defined active sites of enzymes. Our group has developed strategies to address this issue.

One example is demonstrated in the work by Samarakoon et al. that utilized **KSU-1**, a pillared mixed-ligand MOF containing Zn metal nodes, 2-amino terephthalic acid (BDC-NH<sub>2</sub>) and *meso*- $\alpha,\beta$ -di(4-pyridyl)glycol (DPG).<sup>16</sup> BDC-NH<sub>2</sub> and DPG are in well-defined positions throughout the framework and have functionalizable amine and hydroxyl groups respectively which act as nucleophiles during post synthetic modification. Due to their relative nucleophilicities, the choice of a less electrophilic anhydride allows for the independent functionalization of the more nucleophilic amine group, leaving the hydroxyl groups available for subsequent functionalization (**Figure 2.2**).

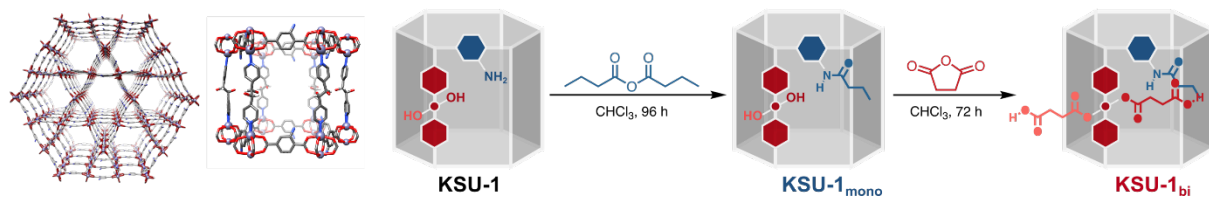


Figure 2.2. Representation **KSU-1** viewed down the c-axis and its network unit followed by sequential, independent functionalization of **KSU-1** with butyric anhydride followed by succinic anhydride. Reprinted with permission from REF<sup>11</sup>.

### 2.3. Unexpected reversal of reactivity

Given the overall goal of this thesis is the development of multifunctionalized MOF-based catalysts, we were interested in uniformly introducing catalytic urea functionality into **KSU-1**. To do so, we needed to obtain the independent reaction of the amine group with an isocyanate. Examining the relative reactivities of isocyanates (**Figure 2.3A**), we speculated that it would be possible to achieve independent functionalization of **KSU-1** amines by choosing a less reactive aliphatic isocyanate, leaving the hydroxyl for further PSM with a more activated isocyanate (**Figure 2.3B**). **KSU-1** was incubated in an acetonitrile solution of isopropyl isocyanate (*i*Pr-NCO) at 80 °C and stopped at 3 h with the intention of terminating the reaction after only the -NH<sub>2</sub> groups had reacted.

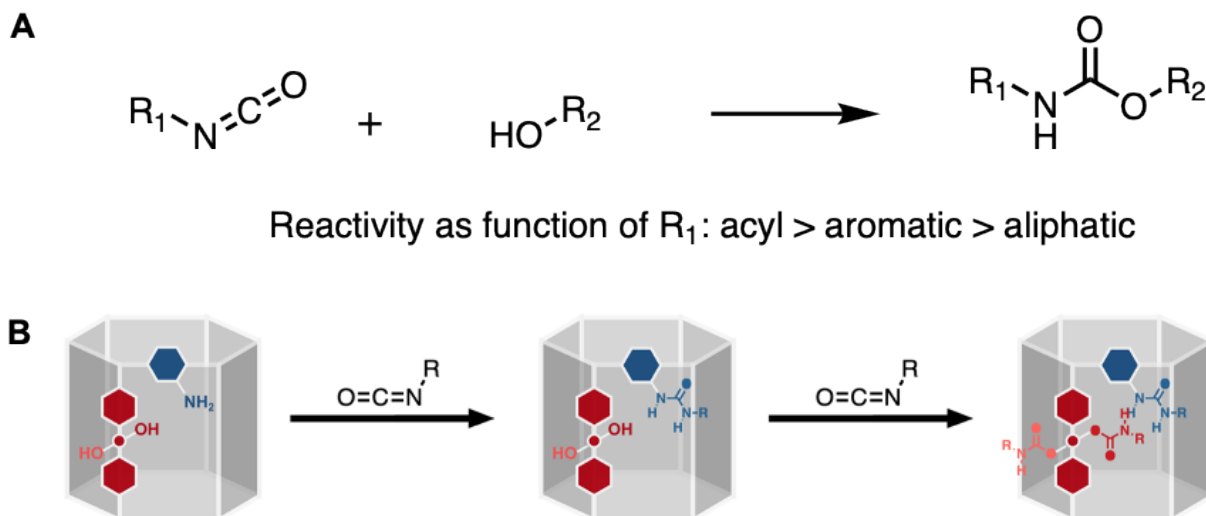


Figure 2.3. Relative reactivity of isocyanates B: Expected order of reactivity of isocyanates in KSU-1. Reprinted with permission from REF<sup>17</sup>.

To our surprise, after 3 h we found that the -OH groups had been almost quantitatively converted to carbamates while there was barely any reaction on the -NH<sub>2</sub> groups (**Figure 2.4A**). This result was observed by proton nuclear magnetic resonance (<sup>1</sup>H-NMR) spectroscopy of the MOF product digested in a solution of D<sub>2</sub>SO<sub>4</sub> in d<sub>6</sub>-DMSO. The spectrum showed also complete disappearance of DPG proton singlet at 4.98 ppm along with the appearance of the DPG dicarbamate product peak at 6.15 ppm. On the other hand, there was minimal reaction on BDC-NH<sub>2</sub> as shown by a nearly non-existence peak at 9.0 ppm corresponding to the aromatic proton that is ortho to the urea group (**Figure 2.4B**). Interestingly, when monitored over time we noticed that the reaction was almost complete at the hydroxyls before it started reacting at the amine, where it proceeded at a very slow rate (**Figure 2.4C**). Investigation of the reaction at room temperature showed that, while both reactions occurred at a much slower rate, conversion was still greater at the hydroxyl than at the amine (**Table 2.1**). Digesting the products of this reaction in 1,4-diazobicyclo[2.2.2]octane (DABCO) and running the sample on high resolution mass spectrometry also confirmed the functionalized products (**Figure 2.5**).

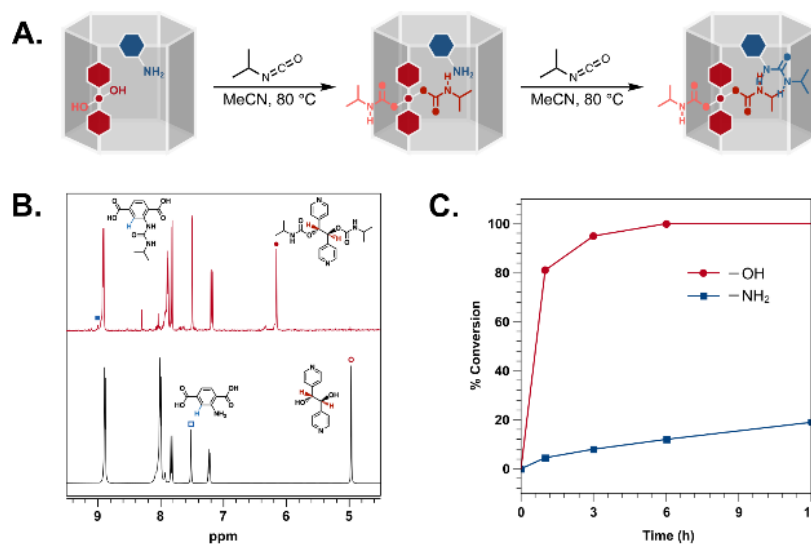


Figure 2.4. Observed order of reaction of the functional groups in KSU-1 with *i*Pr-NCO. B:  $^1\text{H}$ -NMR spectra of KSU-1 before (bottom), and after (top) incubation with *i*Pr-NCO (MeCN, 3 h, 80 °C). Open symbols represent unreacted linkers; filled symbols represent the urea and carbamate products. C: Conversions of KSU-1-NH<sub>2</sub> and OH over 12 h. Reproduced with permission from REF<sup>13</sup>.

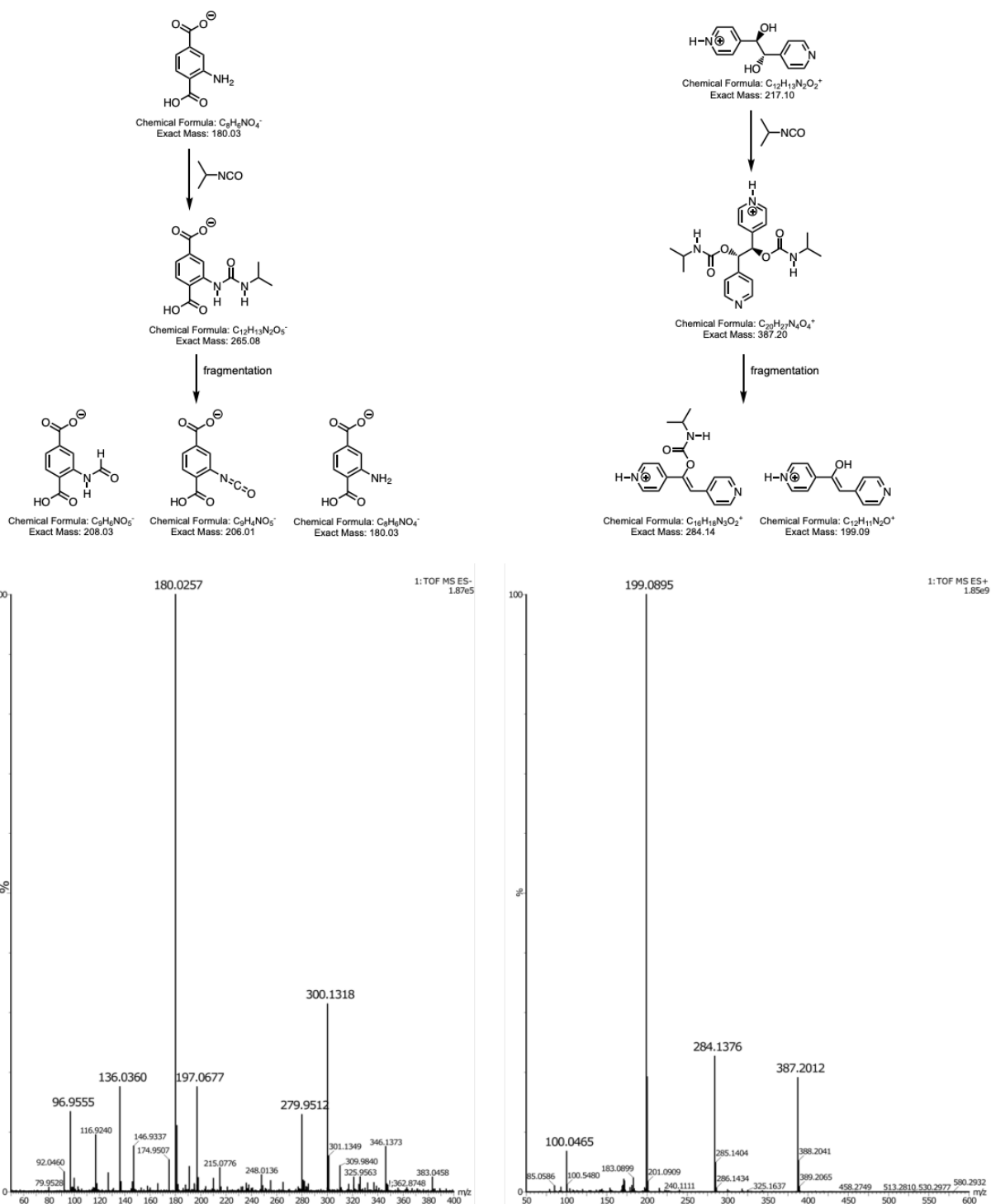


Figure 2.5. HRMS of **KSU-1** after reacting with *i*Pr-NCO (2 h). Left: the negative mode has no indication of the BDC urea product, though the  $[BDC-NH_2-H^+]$  starting material peak could also be a fragmentation product. Right: the positive mode has  $m/z$  peaks corresponding to DPG dicarbamate and its fragments, with no indication of starting DPG.



## 2.4. Investigation of possible causes of the unexpected reversal

Initially, we thought the reversal in the expected reactivity between the organic linkers was due to protonation of amine group which could slow down the addition of the isocyanate. However, when we used (1,8-bis(dimethylamino)naphthalene), ‘Proton Sponge’, a bulky base which does not catalyze the reaction, we found no change in the order of reactivity (**Table 2.1**; Entry 2).

Table 2.1. Reactions of **KSU-1** -NH<sub>2</sub> and -OH with isopropyl isocyanate under different conditions.

| Entry | Temp. °C | Additive (0.2 M)  | % Conversion 3 h (stdev) |         | % Conversion 24 h (stdev) |     |
|-------|----------|-------------------|--------------------------|---------|---------------------------|-----|
|       |          |                   | -NH <sub>2</sub>         | -OH     | -NH <sub>2</sub>          | -OH |
| 1     | 80       | -                 |                          |         |                           |     |
| 2     | 25       | -                 | 1                        | 4       | 3                         | 32  |
| 3     | 80       | Proton Sponge     | 8 (6)                    | 96 (4)  | -                         | -   |
| 4     | 80       | Et <sub>3</sub> N | 38 (11)                  | 82 (15) | -                         | -   |

0.2 M in acetonitrile.

We then considered that steric hindrance due to the position of the amine functional group in the corners of the MOF, versus the more accessible hydroxyl group, was slowing down the amine reaction. However, when reacted with linear isocyanates (ethyl, propyl, and ally), a similar trend in reactivity was observed (**Table 2.2**; Entries 2-4). Investigating more reactive isocyanates,<sup>18</sup> we observed that with phenyl isocyanate, even though the hydroxyl were still more reactive than the amine, the reaction on the amine had significantly increased (**Table 2.2**; Entry 5). With the most reactive isocyanates (4-iodophenyl and 3-pyridyl), we observed a switch with the amine groups reacting faster than the hydroxyls (**Table 2.2**; Entries 6-7).

Table 2.2. Comparison of reactivity of **KSU-1**-NH<sub>2</sub> and -OH with different isocyanates.

| Entry | Isocyanate       | % Conversion (stdev) |        |
|-------|------------------|----------------------|--------|
|       |                  | -NH <sub>2</sub>     | -OH    |
| 1     | Isopropyl        | 7 (5)                | 97 (6) |
| 2     | Ethyl            | 10 (1)               | 68 (7) |
| 3     | <i>n</i> -Propyl | 12 (3)               | 81 (6) |
| 4     | Allyl            | 18 (1)               | 82 (3) |
| 5     | Phenyl           | 60 (4)               | 92 (3) |
| 6     | 4-Iodophenyl     | 89 (1)               | 72 (4) |
| 7     | 3-Pyridyl        | 80 (12)              | 20 (4) |

0.2 M in acetonitrile, 3 h, 80 °C.

These findings indicated that the preference for one functionality to react over the other depended on the electrophilicity of the isocyanate, i.e., less electrophilic isocyanates reacted at the hydroxyl to a greater extent while more reactive isocyanates reacted more with the amine. We then reacted **KSU-1** with *i*Pr-NCO in the presence of triethylamine, a base that catalyzes the reaction by activating isocyanates.<sup>19</sup> Under these conditions, the reaction on the amine did increase but it was still slow on the hydroxyls (**Table 2.2**; Entry 4). Considering that less electrophilic isocyanates were reacting preferentially at the hydroxyl, we hypothesized that, for less activated isocyanates, the amine groups somehow promote the reaction at hydroxyls, with the hydroxyls unable to return the favour. To verify this theory, we attempted to compare the reactivities of the linkers in solution, but comparisons were difficult to make since DPG and its dimethylated salt, were both insoluble in all applicable solvents. To address this challenge, we synthesized MOFs in which the amine and hydroxyl groups are immobilized separately. **KSU-1000** is a MOF composed of BDC-NH<sub>2</sub> and 4,4-dipyridyl (**Figure 2.6A**) and **KSU-3** is similar to **KSU-1** except BDC-NH<sub>2</sub> is replaced with

benzene 1,4 dicarboxylic acid (BDC; **Figure 2.6B**). It should be noted that, like **KSU-1**, neither **KSU-1000** and **KSU-3** are permanently microporous, both experiencing pore collapse and loss of crystallinity with evacuation (**Figure 22** and **Figure 23**). While **KSU-1000** recovers crystallinity after resolution, **KSU-1** and **KSU-3** do not.

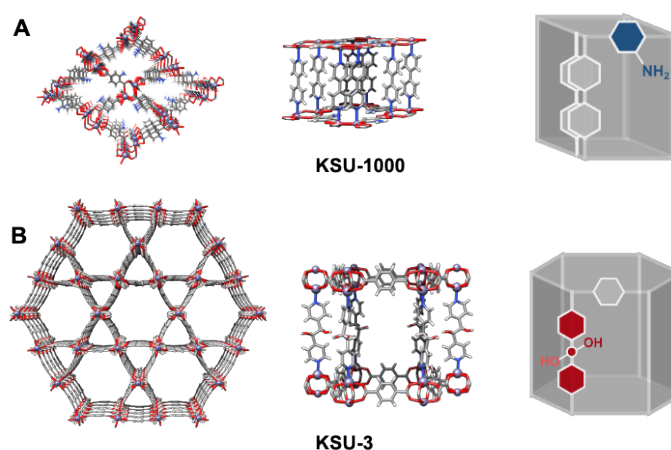


Figure 2.6. **KSU-1000**; MOF functionalized with -NH<sub>2</sub> only. B: **KSU-3**; MOF functionalized with -OH only. Reproduced with permission from REF<sup>13</sup>.

We compared the functional group reactivities in **KSU-1**, **KSU-1000**, and **KSU-3** by incubating the MOFs in various isocyanates under the same conditions as previous experiments except we quantified the conversions after only 1 h, which is before most of the reactions would have reached completion. At 1 h, **KSU-1** displayed similar reactivity as before with aliphatic isocyanates reacting preferentially at the hydroxyl while more reactive isocyanates reacted more on the amines (**Table 2.3**).<sup>20</sup> In **KSU-1000**, the amine group reacted according to the expected literature trend<sup>21</sup> with less electrophilic aliphatic isocyanates reacting poorly and more electrophilic isocyanates giving high conversions (**Table 2.3**). Additionally, the conversions were consistently higher in **KSU-1000** compared to the amines of **KSU-1** regardless of **KSU-1** having larger channels than **KSU-1000** (17 Å vs 9 Å). In **KSU-3**, the hydroxyls were converted to a much lower extent than the hydroxyls of **KSU-1** for all isocyanates, with the exception of 3-pyridyl isocyanate (**Table 2.3**). Furthermore, when compared to the amine groups in **KSU-1000**, the

conversions at the hydroxyls were lower than at the amines in all cases, despite **KSU-3** having larger channels than **KSU-1000**.

Table 2.3. The reactivity of different isocyanates with **KSU-1**, **KSU-1000**, and **KSU-3**.

| Entry | Isocyanate   | % Conversion (stdev)            |          |        |
|-------|--------------|---------------------------------|----------|--------|
|       |              | KSU-1<br>-NH <sub>2</sub> : -OH | KSU-1000 | KSU-3  |
| 1     | Isopropyl    | 4 (1): 64 (3)                   | 10 (1)   | 3 (1)  |
| 2     | Ethyl        | 8 (2): 38 (8)                   | 13 (6)   | 6 (2)  |
| 3     | n-Propyl     | 5 (2): 52 (6)                   | 12 (4)   | 2 (1)  |
| 4     | Allyl        | 10 (2): 41 (2)                  | 16 (7)   | 5 (1)  |
| 5     | Phenyl       | 36 (1): 75 (8)                  | 80 (1)   | 8 (2)  |
| 6     | 4-Iodophenyl | 70 (3): 54 (2)                  | 100 (0)  | 31 (1) |
| 7     | 3-Pyridyl    | 78 (1): 21 (2)                  | 100 (0)  | 66 (9) |

0.2M in acetonitrile, 1 h, 80 °C.

Based on these results, we see that when the MOFs are monofunctional, they follow the expected order of reactivity with the amine groups reacting faster than the hydroxyls. When both the amine and the hydroxyl groups are present together in the MOF, however, the reaction at the hydroxyls is accelerated at the expense of the amine reaction. However, it is only when the electrophiles are less activated that the hydroxyls react prior to the amines. This implies that in cases where both reactions are slow, rather than reacting themselves, the amines somehow promote the reaction on the hydroxyls. Considering the large distance between the -OH and -NH<sub>2</sub> groups in the MOF (6 Å), it is unlikely that the promotion of the hydroxyl reaction is via a direct amine⋯isocyanate⋯hydroxyl interaction. Another possibility is that the amines interact with the isocyanates through amine⋯(H<sub>2</sub>O)<sub>n</sub>⋯isocyanate⋯hydroxyl chains.<sup>22,23</sup> The elevated temperature

at which the reaction is conducted makes the formation of such chains with adventitious water unlikely,<sup>24</sup> however we have not discounted the possibility.

Table 2.4. Comparison of the reactivity of **KSU-1** -NH<sub>2</sub> and -OH in different solvents.

| Entry    | Solvent           | % Conversion (stdev) |              |                 |        |
|----------|-------------------|----------------------|--------------|-----------------|--------|
|          |                   | <b>KSU-1000</b>      | <b>KSU-3</b> | <b>KSU-1</b>    |        |
|          |                   | NH <sub>2</sub>      | OH           | NH <sub>2</sub> | OH     |
| <b>1</b> | MeCN              | 13 (3)               | 19 (3)       | 7(5)            | 97 (6) |
| <b>2</b> | Toluene           | 16 (3)               | 32 (8)       | 39 (6)          | 85 (5) |
| <b>3</b> | CHCl <sub>3</sub> | 27 (8)               | 42 (1)       | 60 (8)          | 78 (9) |

0.2 M *i*Pr-NCO, 3 h, 80 °C.

Finally, to gain more insights into the reactivity of **KSU-1**, we investigated the reaction of the three MOFs with *i*Pr-NCO in different solvents. Matzger and co-workers previously reported that the reactivities of a BDC-NH<sub>2</sub> based MOF with different isocyanates are affected by solvent choice with the influence of the solvent also depending on the identity of the isocyanate.<sup>18</sup> Comparing *i*Pr-NCO reactions in acetonitrile, toluene and chloroform, we found that the reactions of the -NH<sub>2</sub> groups in **KSU-1000** and -OH groups in **KSU-3** were both slowest in acetonitrile and fastest in chloroform (**Table 2.4**). For **KSU-1** the hydroxyls were still more reactive than the amine in all the three solvents, but the extent of the -NH<sub>2</sub> conversion increased significantly in toluene and chloroform (**Table 2.4**; Entries 2-3). These results support the observation that the reversal in reactivity in the bifunctional MOF is more marked under conditions where the reactions are slowest for the isolated functionalities.

## 2.5. Conclusion

Based on the results we have obtained, we conclude that the reaction of the -OH groups with isocyanates is promoted, in preference to the reaction of the -NH<sub>2</sub> groups by the confinement

of the two functional groups together in the pores. We also note that the effect is greatest when the reaction would have been slowest for both functionalities. While the origin of this unexpected reversal in reactivity is yet to be determined, it does offer tantalizing preview of the confinement effects that can be realized in the pores of multifunctional MOFs. It also lends credence to the parallel that is often drawn between MOFs and enzymes, as there are several examples of perturbation of the properties of chemical functionalities because of mutual confinement with other functional groups in the enzyme cavities.<sup>25–27</sup> Thus, this result has exciting implications for MOF applications, such as catalysis and sensing, that will rely on the action of multiple functionalities.

## 2.6. Experimental

### 2.6.1. Materials

All chemicals were used as received from commercial sources unless otherwise noted. Isopropyl isocyanate (98%), ethyl isocyanate (98%), *n*-propyl isocyanate (99%), allyl isocyanate (98%), phenyl isocyanate ( $\geq 98\%$ ), 2-aminoterephthalic acid (**BDC-NH<sub>2</sub>**, 99%), terephthalic acid (benzene dicarboxylic acid, **BDC**, 98%), and chloroform were purchased from Sigma Aldrich. *Meso- $\alpha,\beta$* -di(4-pyridyl) glycol (**DPG**, 98.0+%), 4,4'-bipyridine (**BIPY**, 98%), 3,5-bis(trifluoromethyl)phenyl isocyanate (98.0+%), triethylamine (99%), and diisopropylethylamine (99%) were purchased from TCI. Sulfuric acid-*d*<sub>2</sub> (D<sub>2</sub>SO<sub>4</sub>, 98 wt.% in D<sub>2</sub>O, 99.5+% atom D) was purchased from Acros Organics. *N,N*-dimethylformamide (DMF), acetonitrile, chloroform, and toluene were purchased from Fisher Scientific (ACS certified). Zinc nitrate hexahydrate was purchased from Strem Chemicals, and 3-isocyanatopyridyl (95%) from Enamine. 1,4-Diazabicyclo[2.2.2]octane (DABCO) (95%) was purchased from Oakwood Products. Dimethyl sulfoxide-*d*<sub>6</sub> (*d*<sub>6</sub>-DMSO, 99.9 atom % D) was purchased from Cambridge Isotopes Laboratories.

## 2.6.2. Synthesis Procedures

### 2.6.2.1. Synthesis of KSU-1000

Zn(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O (940 mg; 3.16 mmol), **BIPY** (624 mg; 4.00 mmol), and DMF (100 mL) were combined in a 500 mL Florence flask. A solution of **BDC-NH<sub>2</sub>** (181 mg, 1.00 mmol) in DMF (20 mL) was added, and the flask incubated at 60 °C. After 1 h, the flask was removed from the heating block and left at room temperature for a month. Yellow-orange crystals (135 mg, 27 % yield) of the product were collected by filtration after several ~30 min washings with DMF.

### 2.6.2.2. Synthesis of KSU-3

Zn(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O (223 mg; 0.75 mmol), **DPG** (182 mg; 0.84 mmol), deionized water (2 mL) and DMF (180 mL) were combined in a 500 mL Florence flask. The flask was heated at 60 °C in an oven until all solids dissolved and the solution became clear. A solution of **BDC** (140 mg; 0.84 mmol) in DMF (20 mL) was added, and the flask incubated at 60 °C. After 24 h, the flask was removed from the oven and left at room temperature for 48 h. Colorless transparent crystals (142 mg, 28 % yield) of the product were collected by filtration and washed several times with warm DMF (~60 °C).

### 2.6.2.3. General procedure for the reaction of MOF materials with isocyanates

At least three replicates were performed for all experiments. In a typical experiment, the as-synthesized MOF in DMF was filtered and ~15 mg was transferred to a 1-dram vial containing fresh acetonitrile and mixed for ~30 min. The supernatant was exchanged with fresh acetonitrile and mixed for ~30 min, 3 more times. After the final rinsing, 2 mL of a 0.2 M solution of the isocyanate (0.4 mmol) in acetonitrile were added to the vial. The reaction was left at 80 °C with continuous mixing on a Corning LSE Low Speed Orbital Shaker. Samples of the reacted MOF were taken at appropriate intervals, filtered, and digested for analysis.

Table 2.5. Approximate amounts of MOF in reactions with isocyanate solutions.

| MOF             | Weight | Moles  | -OH    | -NH <sub>2</sub> |
|-----------------|--------|--------|--------|------------------|
|                 | (mg)   | (mmol) | (mmol) | (mmol)           |
| <b>KSU-1</b>    | 15     | 0.021  | 0.043  | 0.043            |
| <b>KSU-1000</b> | 15     | 0.037  | -      | 0.037            |
| <b>KSU-3</b>    | 15     | 0.022  | 0.044  | -                |

0.2 M, 2 mL, MeCN.

### 2.6.3. Characterization

#### 2.6.3.1. High-resolution mass spectrometry (HRMS)

MOF samples (~5 mg) were placed in a solution of DABCO (10 mg) and 0.25 ml of DMSO in a 2-dram vial. The vial was sonicated for ~ 1 min then heated at 80 °C overnight. A small amount of residue was filtered out and the resulting solution was analyzed using a Xevo G2-XS QToF quadrupole time-of-flight mass spectrometer coupled with an ACQUITY M-class UPLC and a NanoLockSpray dual electrospray ion source. Mass spectra were acquired in “eXtreme Resolution” mode.

#### 2.6.3.2. Proton nuclear magnetic resonance (<sup>1</sup>H-NMR)

Spectra were recorded on a Bruker Avance NEO spectrometer (400 MHz for <sup>1</sup>H, Bruker BioSpin, Billerica, MA, USA). NMR chemical shifts are reported in ppm against a residual solvent resonance as the internal standard ( $\delta(d_6\text{-DMSO}) = 2.5$  ppm). In a typical analysis, MOF materials stored in DMF were solvent exchanged with CHCl<sub>3</sub>, isolated by vacuum filtration, and then evacuated in a vacuum oven at 80 °C overnight. Evacuated MOF samples (5-6 mg) were transferred into an NMR tube and *d*<sub>6</sub>-DMSO (0.55 mL) was added. Subsequently, D<sub>2</sub>SO<sub>4</sub> (0.09 mL, 98% w/w in D<sub>2</sub>O) was also added. The tubes were capped and sonicated until all the solid was dissolved (~ 1 min).



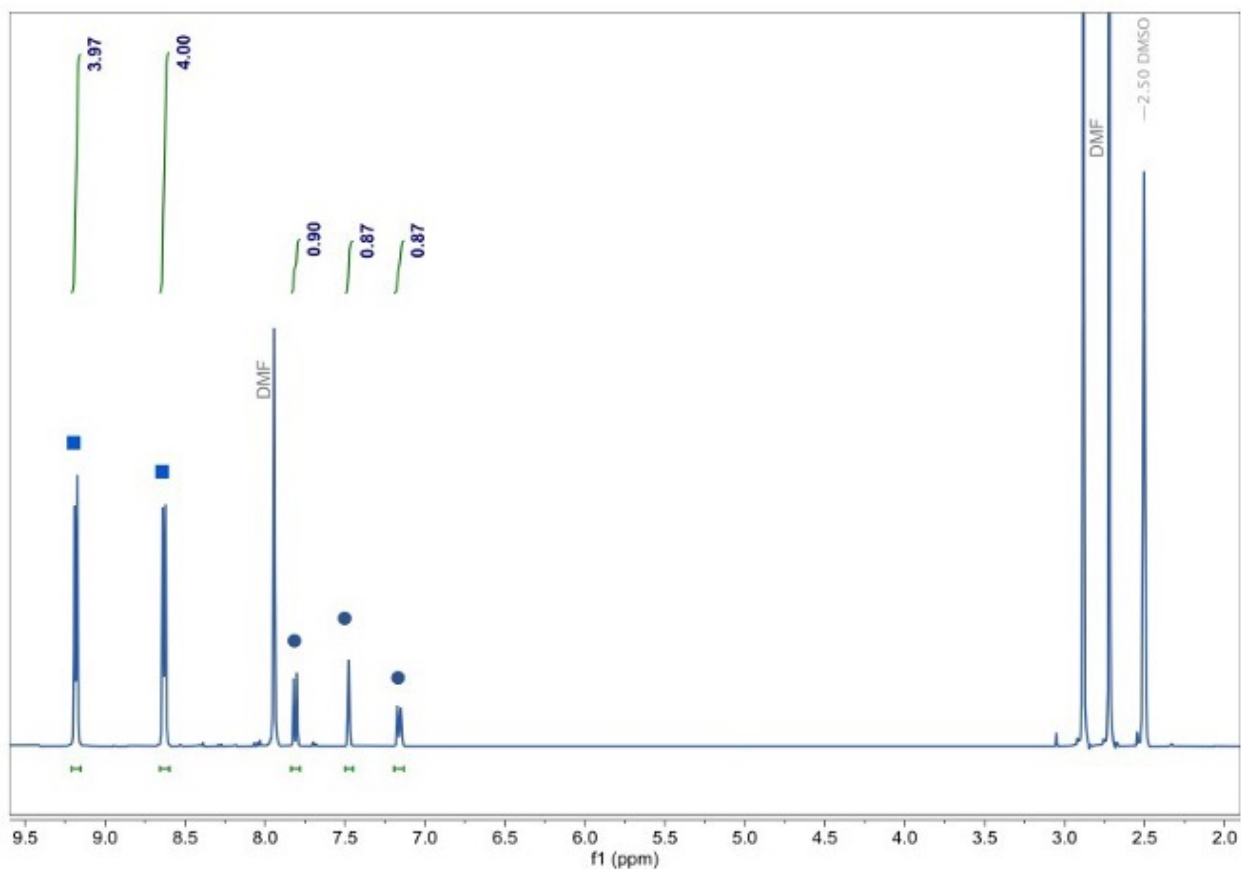


Figure 2.7.  $^1\text{H}$ -NMR (400MHz,  $d_6$ -DMSO/ $\text{D}_2\text{SO}_4$ ) spectrum of **KSU-1000**. Circles represent 2 molecules of BDC- $\text{NH}_2$  [ $\delta$  7.81 (d, 2H,  $J = 8$  Hz, ArH),  $\delta$  7.48 (s, 2H, ArH),  $\delta$  7.16 (d, 2H,  $J = 8$  Hz, ArH)]. Squares represent one molecule of BIPY [ $\delta$  9.82 (d, 4H,  $J = 6.5$  Hz, ArH),  $\delta$  8.63 (d, 4H,  $J = 6.5$  Hz, ArH)].

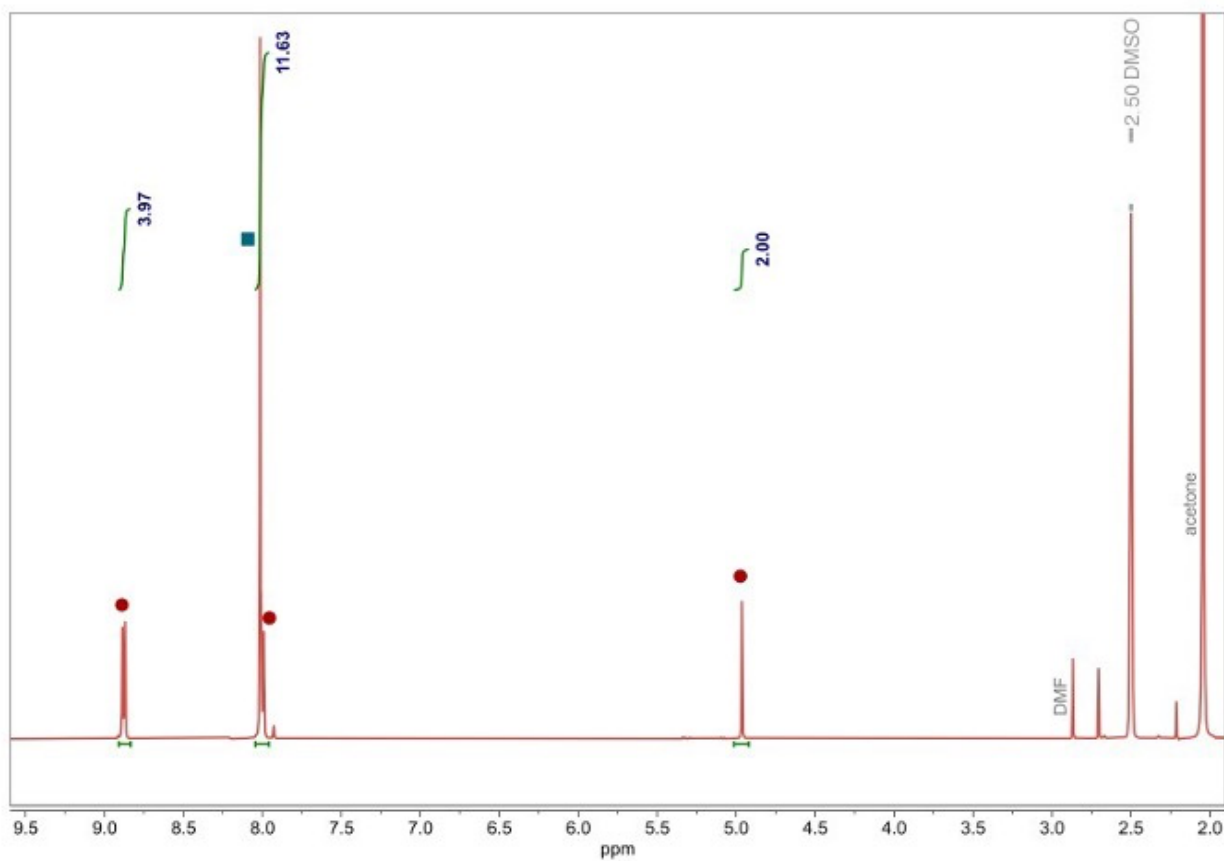


Figure 2.8. <sup>1</sup>H-NMR (400 MHz, *d*<sub>6</sub>-DMSO/D<sub>2</sub>SO<sub>4</sub>) spectrum of **KSU-3**. Circles represent 1 molecule of DPG [ $\delta$  8.88 (d, 4H, *J* = 6.5 Hz, ArH),  $\delta$  8.00 (s, 4H, *J* = 6.5 Hz, ArH),  $\delta$  4.96 (s, 2H, -CHOH)]. Square represents two molecules of BDC [ $\delta$  8.02 (s, 8H, ArH)].

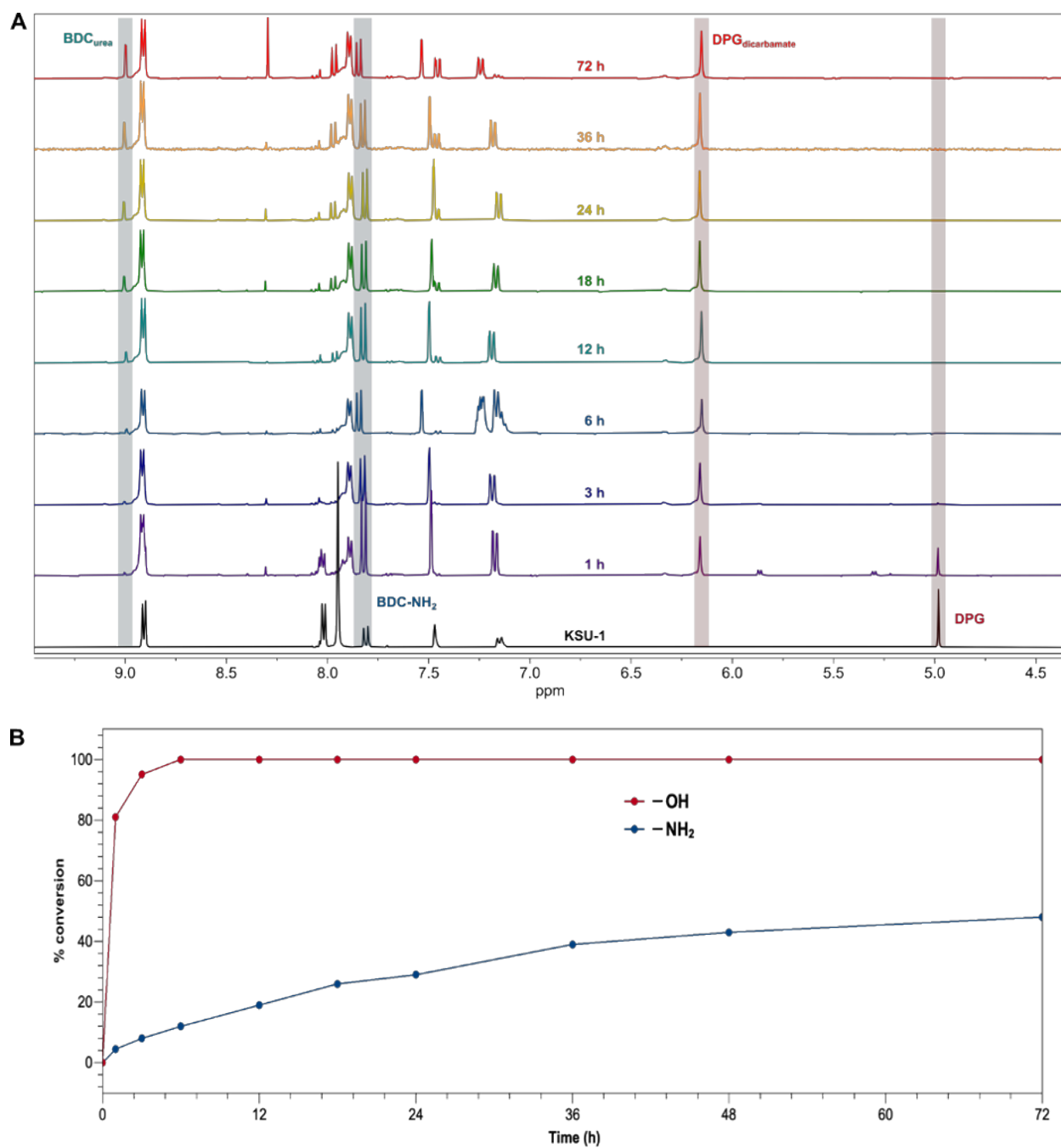


Figure 2.9. A: Representative  $^1\text{H}$ -NMR spectra of reactions of **KSU-1** with isopropyl isocyanate over a 72 h period. B: Plot of conversions over time.

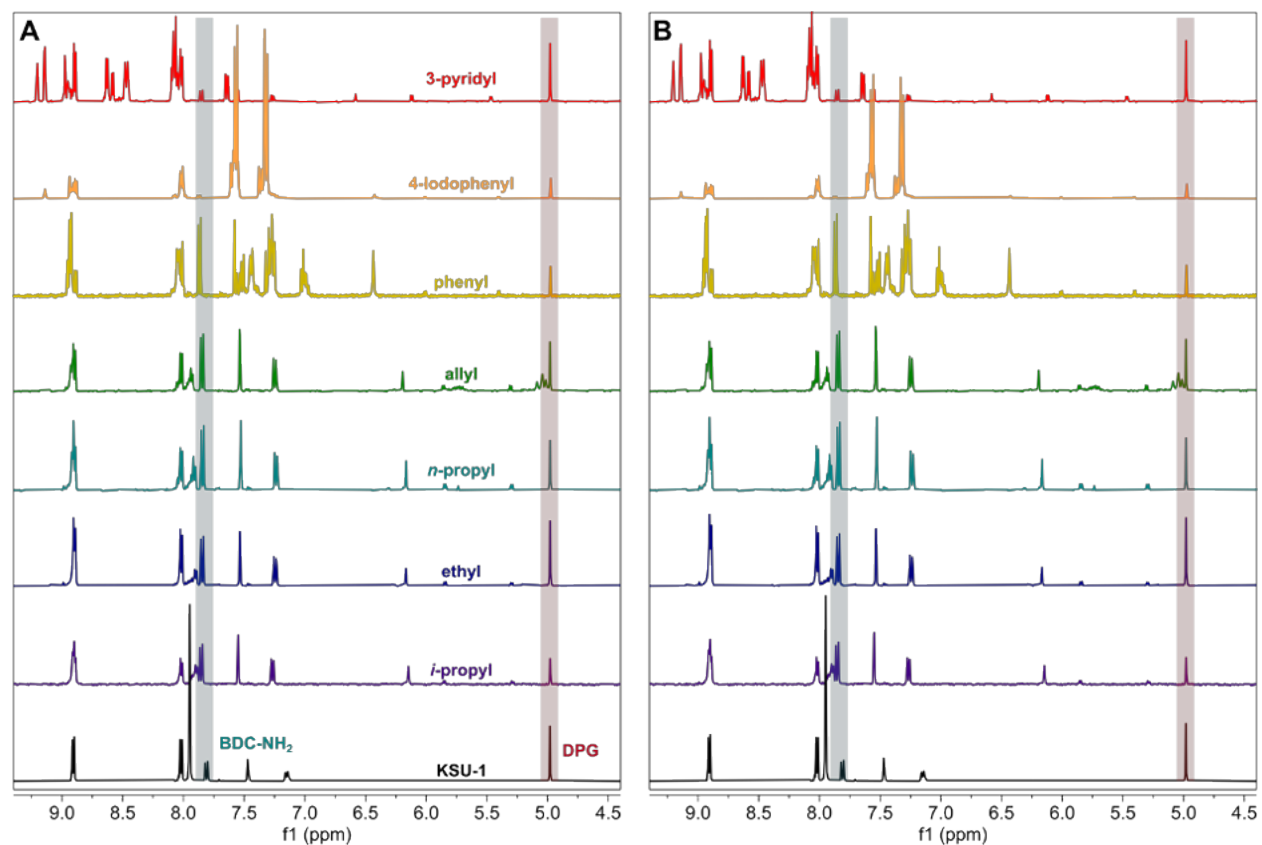


Figure 2.10. Representative  $^1\text{H}$ -NMR spectra of reactions of **KSU-1** with different isocyanates. A: Analyzed at 1 h. B: Analyzed at 3 h.

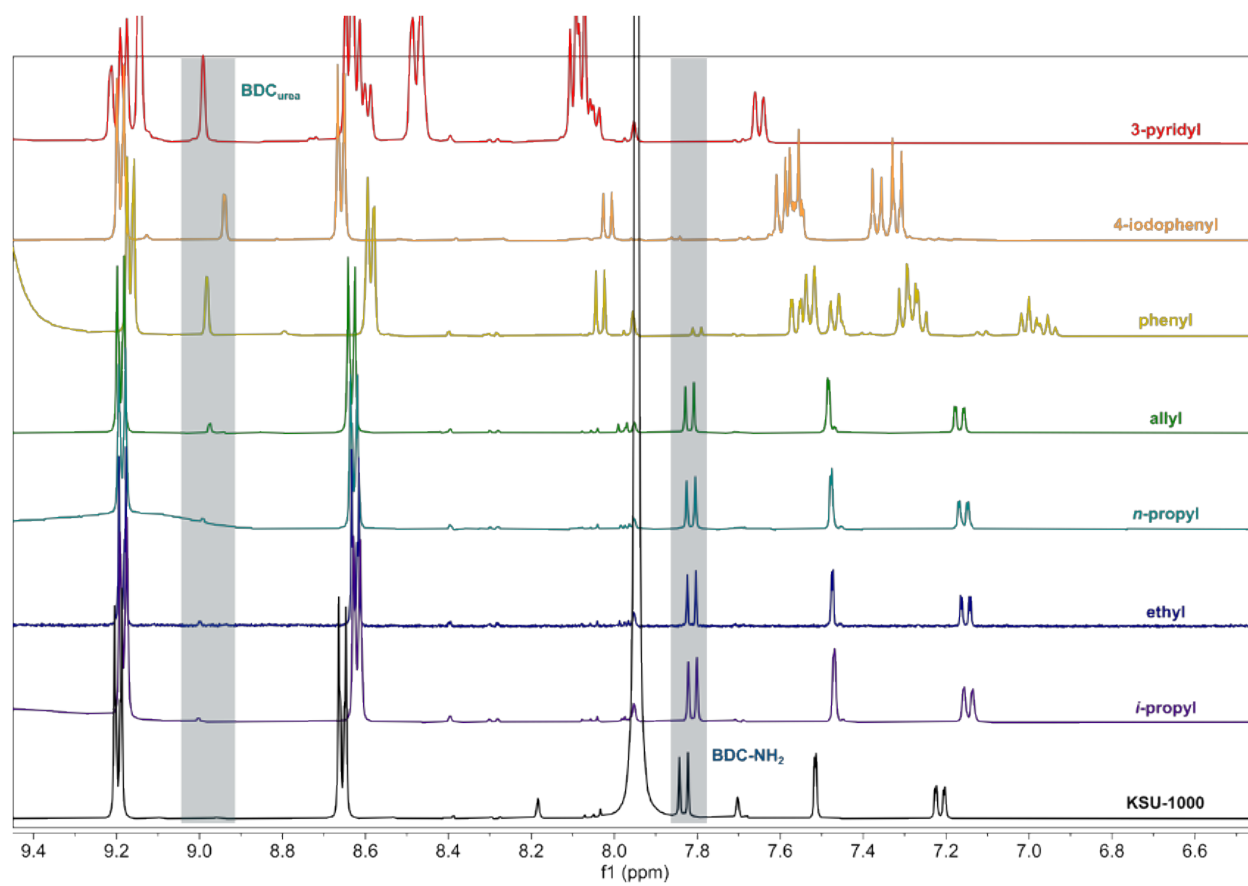


Figure 2.11. Representative  $^1\text{H}$ -NMR spectra of reactions of **KSU-1000** with different isocyanates 1 h.

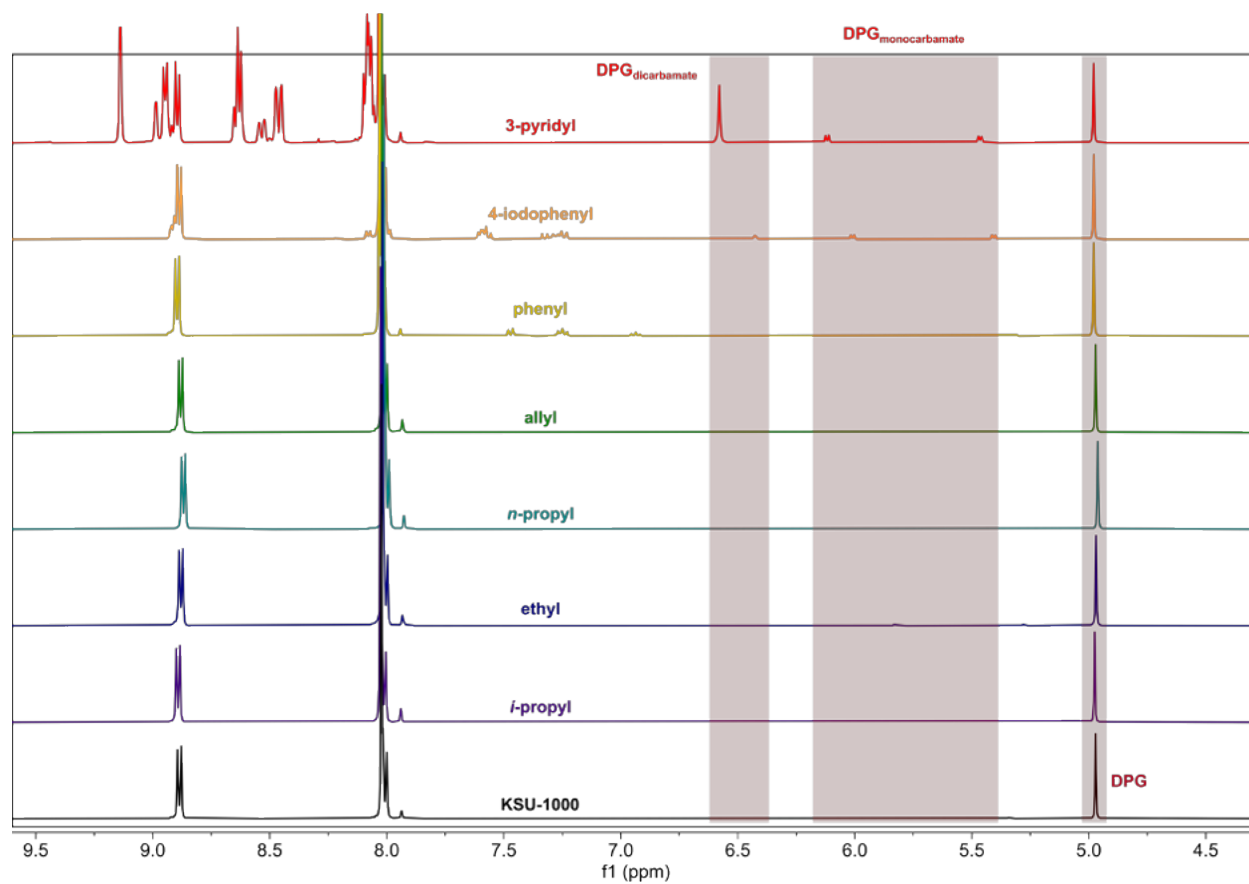


Figure 2.12. Representative  $^1\text{H}$ -NMR spectra of reactions of **KSU-3** with different isocyanates 1 h.

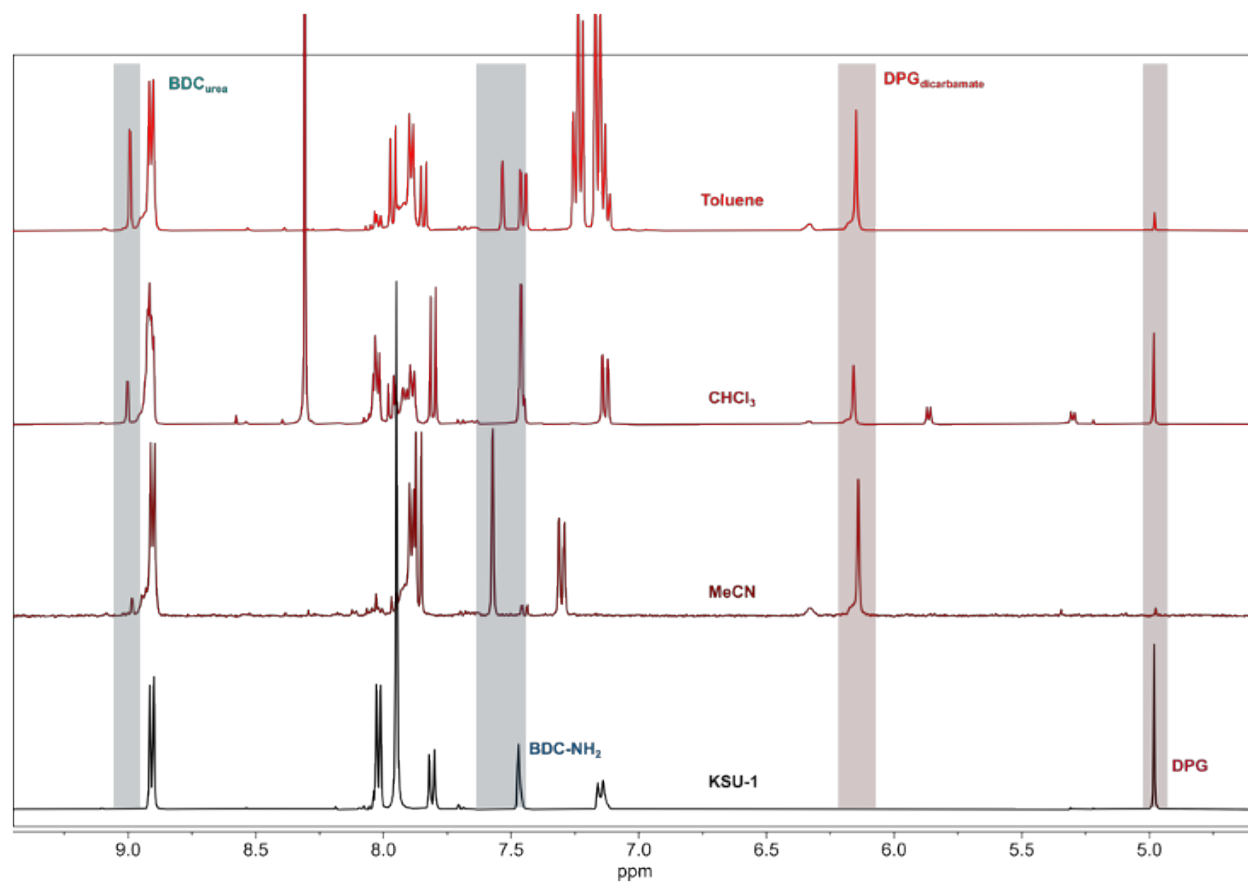


Figure 2.13. Representative  $^1\text{H}$ -NMR spectra of reactions of **KSU-1** with isopropyl isocyanate in different solvents 3 h.

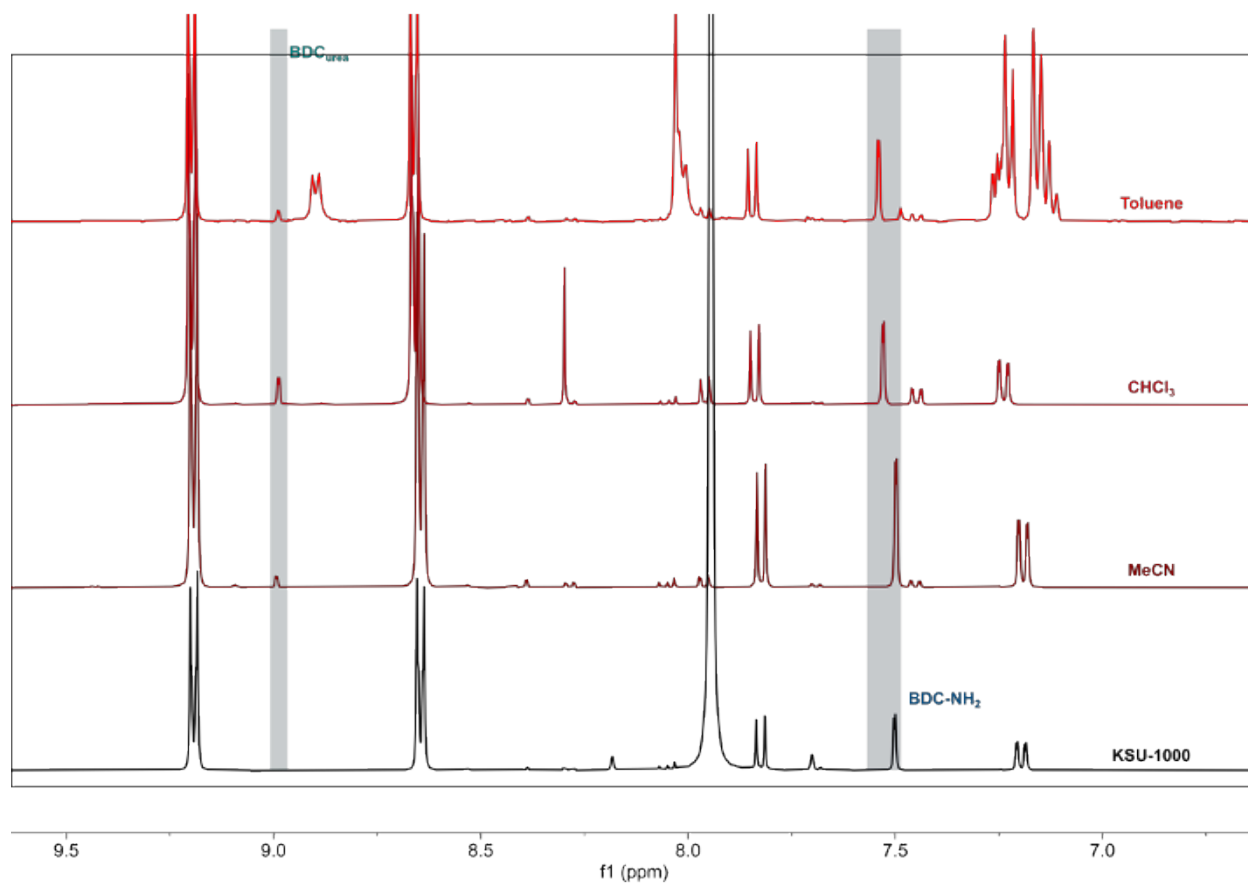


Figure 2.14. Representative  $^1\text{H}$ -NMR spectra of reactions of **KSU-1000** with isopropyl isocyanate in different solvents 3 h.



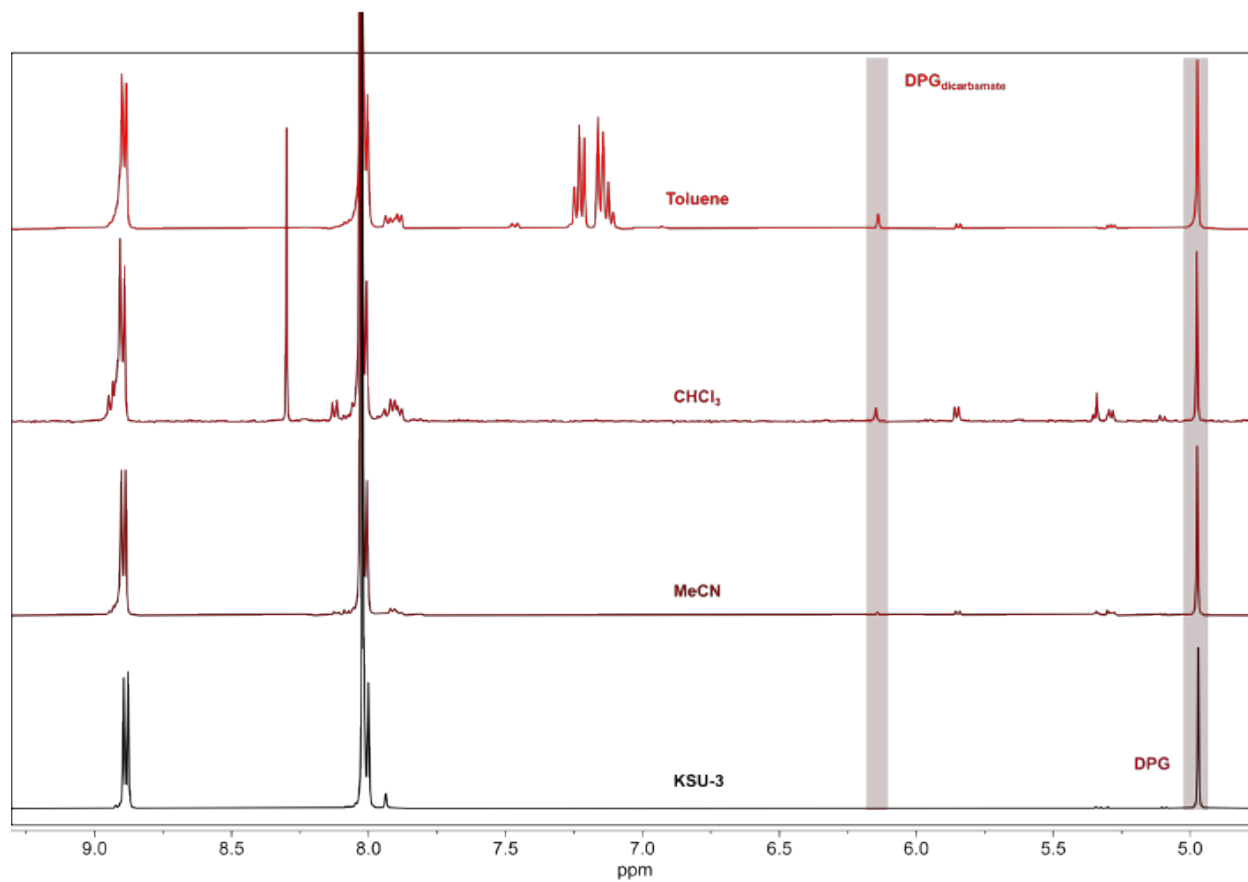


Figure 2.15. Representative  $^1\text{H}$ -NMR spectra of reactions of **KSU-3** with isopropyl isocyanate in different solvents 3 h.

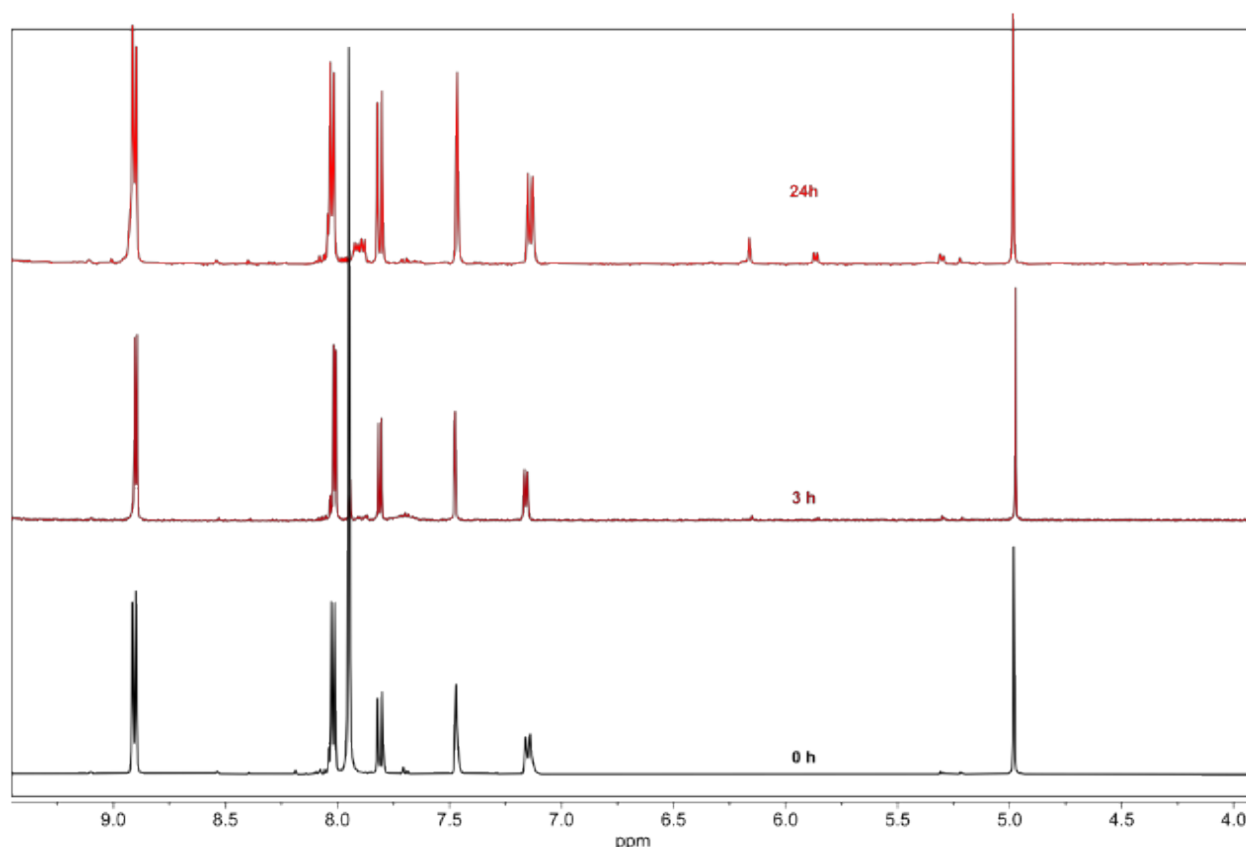


Figure 2.16.  $^1\text{H}$ -NMR spectra of room temperature reaction of **KSU-1** with isopropyl isocyanate.

### 2.6.3.3. Single crystal X-ray diffraction (SXRD)

Single crystal X-ray diffraction data for compounds **KSU-1000** and **KSU-3** were collected using a Rigaku XtaLAB Synergy-S diffractometer equipped with a HyPix-6000HE Hybrid Photon Counting (HPC) detector and Cu microfocus sealed X-ray source ( $\lambda = 1.54184 \text{ \AA}$ ). Data collection strategy was calculated within CrysAlisPro<sup>28</sup> to ensure desired data redundancy and percent completeness. Unit cell determination, initial indexing, data collection, frame integration, Lorentz-polarization corrections and final cell parameter calculations were carried out using CrysAlisPro. An absorption correction was performed using the SCALE<sup>29</sup> ABSPACK scaling algorithm embedded within CrysAlisPro. The structures were solved using ShelXT<sup>30</sup> structure solution program using Intrinsic Phasing and refined by Least Squares using ShelXL<sup>31</sup> program. All non-hydrogen atoms were refined anisotropically. The solvent mask function of Olex2<sup>32</sup> was used to

calculate and account for the electron density within the solvent accessible voids. Hydrogen atom positions were calculated geometrically and refined using the riding model. Olex2, was used for the preparation of the publication materials.

Table 2.6. Crystal and Refinement Data **KSU-1000** and **KSU-3**.

|                          | <b>KSU-1000</b>                                                                                                  | <b>KSU-3</b>                                                                                                          |
|--------------------------|------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|
| <b>Empirical formula</b> | C <sub>36</sub> H <sub>26</sub> N <sub>6</sub> O <sub>8</sub> Zn <sub>2</sub> *6C <sub>3</sub> H <sub>7</sub> NO | C <sub>28</sub> H <sub>20</sub> N <sub>2</sub> O <sub>10</sub> Zn <sub>2</sub> *9.667C <sub>3</sub> H <sub>7</sub> NO |
| <b>Formula weight</b>    | 1239.94                                                                                                          | 1239.94                                                                                                               |
| <b>Temperature</b>       | 140K                                                                                                             | 120K                                                                                                                  |
| <b>Crystal system</b>    | Monoclinic                                                                                                       | Trigonal                                                                                                              |
| <b>Space group</b>       | P2 <sub>1</sub>                                                                                                  | P312                                                                                                                  |
| <b>a</b>                 | 11.4068(2) Å                                                                                                     | 21.4634(7) Å                                                                                                          |
| <b>b</b>                 | 20.0205(3) Å                                                                                                     | 21.4634(7) Å                                                                                                          |
| <b>c</b>                 | 15.0036(3) Å                                                                                                     | 16.1290(7) Å                                                                                                          |
| <b><i>α</i></b>          | 90.00°                                                                                                           | 90.00°                                                                                                                |
| <b><i>β</i></b>          | 93.119(2)°                                                                                                       | 90.00°                                                                                                                |
| <b><i>γ</i></b>          | 90.00°                                                                                                           | 120.00°                                                                                                               |
| <b>Volume</b>            | 3421.29(10) Å <sup>3</sup>                                                                                       | 6517.9(3) Å <sup>3</sup>                                                                                              |
| <b>Density</b>           | 1.204 g/cm <sup>3</sup>                                                                                          | 1.070 g/cm <sup>3</sup>                                                                                               |
| <b>Z</b>                 | 2                                                                                                                | 3                                                                                                                     |

|                                         |                                                   |                                                   |
|-----------------------------------------|---------------------------------------------------|---------------------------------------------------|
| <b>Absorption coefficient</b>           | 1.392 mm <sup>-1</sup>                            | 1.201 mm <sup>-1</sup>                            |
| <b>Crystal size</b>                     | 0.28 x 0.23 x 0.19 mm <sup>3</sup>                | 0.44 x 0.27 x 0.22 mm <sup>3</sup>                |
| <b>Theta range</b>                      | 2.95 to 77.85°                                    | 2.37 to 77.76°                                    |
| <b>Reflections collected</b>            | 103778                                            | 34564                                             |
| <b>Independent reflections</b>          | 14292 [R <sub>int</sub> = 0.1243]                 | 8137 [R <sub>int</sub> = 0.0622]                  |
| <b>Completeness to q = 67.68°</b>       | 99.70%                                            | 99.50%                                            |
| <b>Data restraints</b>                  | / 14292 / 8 / 480                                 | 8137 / 55 / 236                                   |
| <b>parameters</b>                       |                                                   |                                                   |
| <b>Goodness-of-fit on F<sup>2</sup></b> | 1.019                                             | 0.963                                             |
| <b>Final R indices [I&gt;2s(I)]</b>     | R <sub>1</sub> = 0.0509, wR <sub>2</sub> = 0.1395 | R <sub>1</sub> = 0.0843, wR <sub>2</sub> = 0.2344 |
| <b>R indices (all data)</b>             | R <sub>1</sub> = 0.0557, wR <sub>2</sub> = 0.1478 | R <sub>1</sub> = 0.1112, wR <sub>2</sub> = 0.2631 |
| <b>Largest diff. peak and hole</b>      | 1.00 and -0.52 e <sup>-</sup> / Å <sup>3</sup>    | 1.92 and -0.66 e <sup>-</sup> / Å <sup>3</sup>    |

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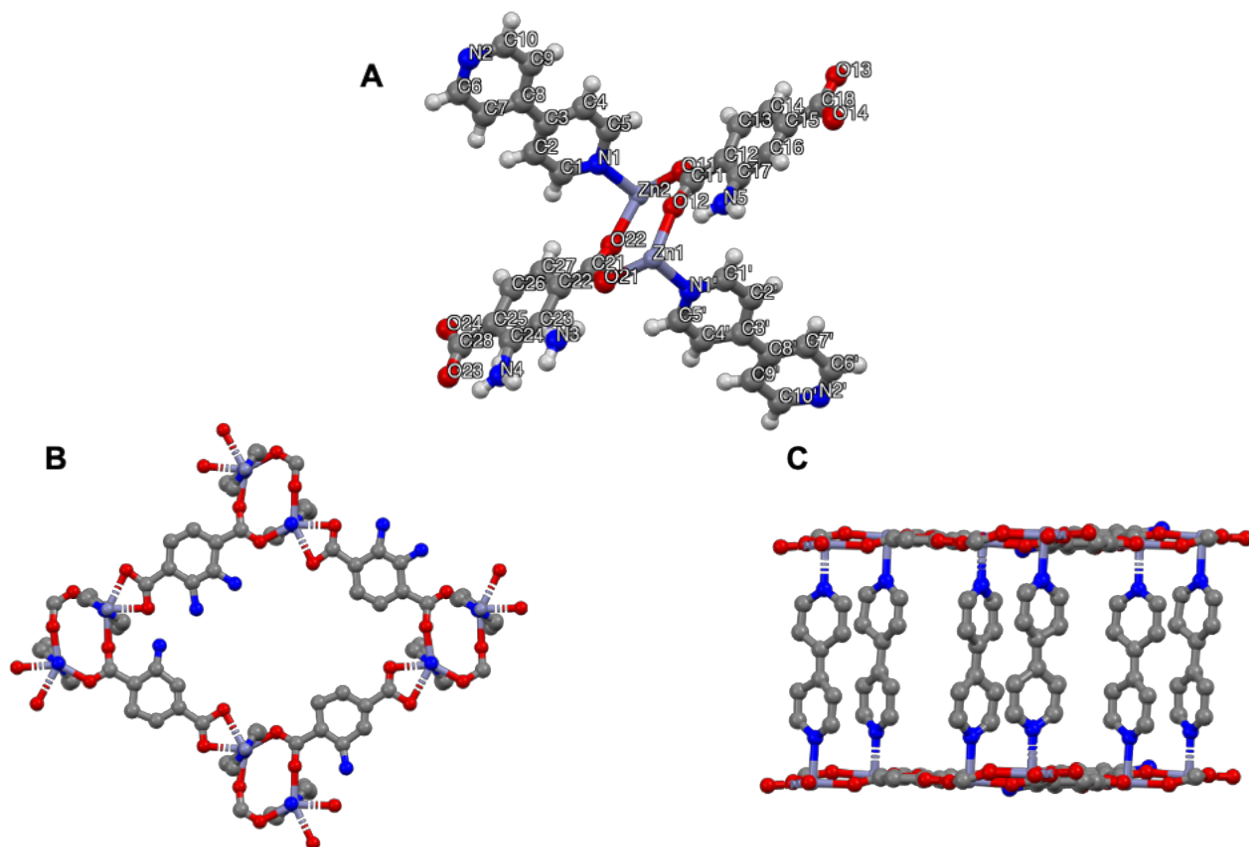


Figure 2.17. The crystal structure of **KSU-1000**. A) Moieté formula unit [-solvent] with atom labels. B) Framework unit viewed down the a-axis. C) Framework unit viewed down the b-axis.

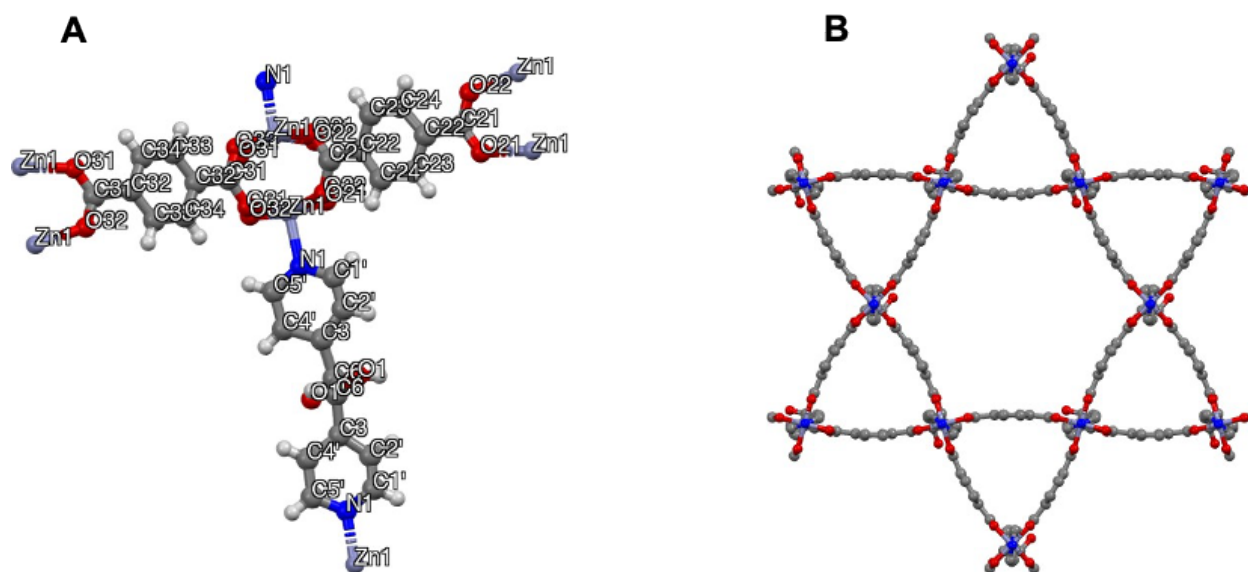


Figure 2.18. The crystal structure of **KSU-3**. A) Moieté formula unit [-solvent] with atom labels. Only one set of disordered DPG atoms are shown for clarity. B) Framework viewed down the c-axis.

#### 2.6.3.4. Powder X-ray diffraction (PXRD)

Powder X-ray diffraction patterns were recorded on a Bruker AXS D8 Advance Phaser diffractometer (Bruker AXS, Karlsruhe, Germany) with Cu K $\alpha$  radiation ( $\lambda = 1.5418 \text{ \AA}$ ) over a range of  $4^\circ < 2\theta < 40^\circ$  in  $0.02^\circ$  steps with a 0.5 s counting time per step. Samples were collected from the bottom of the reaction vial as a thick suspension in DMF and spread on a Si-Einkristalle plate immediately before PXRD measurements.

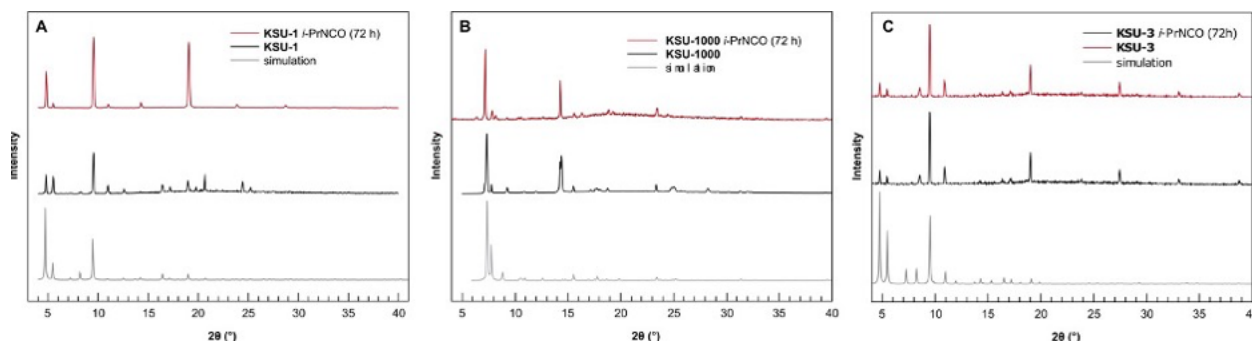


Figure 2.19. The PXRD patterns of the simulated parent MOF, the experimental parent MOF, and the MOF after reacting with isopropyl isocyanate at  $80^\circ\text{C}$  for 72 h. A: **KSU-1**, B: **KSU-1000**, and C: **KSU-3**.

#### 2.6.3.5. Fourier-transform infrared spectrometry (FTIR)

Spectra were collected on MOF samples ( $\sim 1 \text{ mg}$ ) which were placed directly on the sample holder.

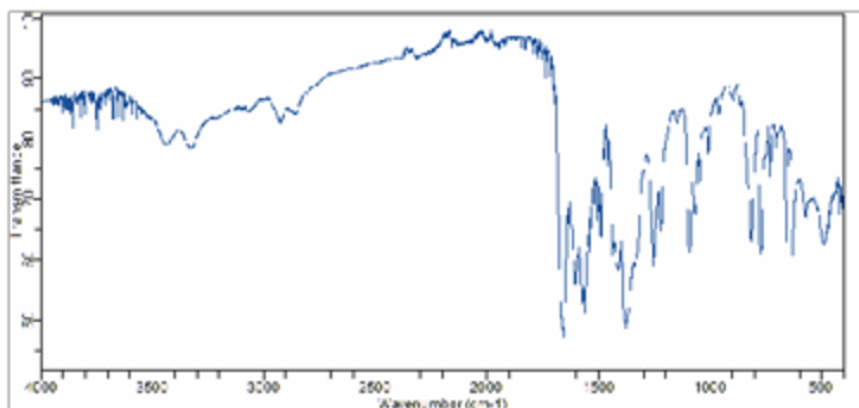


Figure 2.20. IR for **KSU-1000**. The peaks in the  $3300\text{--}3500 \text{ cm}^{-1}$  correspond to the N-H stretches of BDC-NH $_2$ .

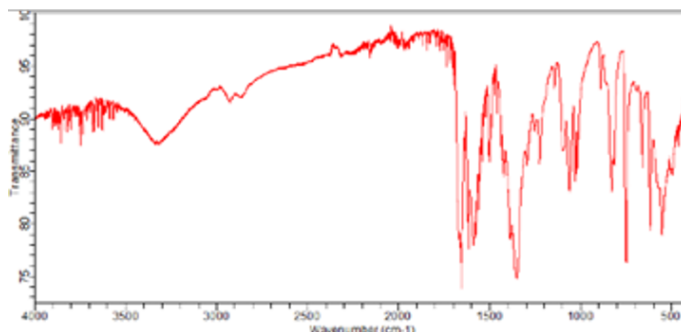


Figure 2.21. IR for **KSU-3**. The broad peaks at  $3400\text{ cm}^{-1}$  corresponds to the O-H stretch of DPG.

#### 2.6.3.6. Nitrogen gas adsorption/desorption

Measurements for **KSU-1000** were performed on a Micromeritics Tristar II 3020 (Micromeritics, Norcross, GA) at 77 K on samples that underwent supercritical  $\text{CO}_2$  drying. Supercritical  $\text{CO}_2$  drying was performed using Tousimis Samdri PVT-30 critical point dryer (Tousimis, Rockville, MD, USA). Supercritically dried samples were prepared in the following manner: MOF materials that had undergone DMF to hexanes solvent exchanges were again solvent exchanged with ethanol by two quick washes. The ethanol-dispersed samples were transferred into the sample holder with a glass pipet and allowed to settle down. Excess EtOH was pipetted out and the sample holder was placed into a Tousimis Samdri-PVT-3D supercritical  $\text{CO}_2$  dryer. The temperature was lowered to  $0\text{ }^\circ\text{C}$ , and the chamber was filled with liquid  $\text{CO}_2$  (ultrahigh grade  $\text{CO}_2$  with a siphon from Air-Gas Inc). The samples were soaked for 8 hours total, venting for five minutes every two hours. The chamber was then heated to  $30\text{ }^\circ\text{C}$ , and the supercritical  $\text{CO}_2$  was bled off at a rate of  $0.25\text{ mL/min}$  until the chamber reached ambient pressure (typically overnight). The chamber was opened and the sample was quickly transferred into a pre-weighed glass sample tube which was sealed and quickly transferred to a system providing  $10^{-4}$  torr dynamic vacuum, Measurements for **KSU-3** were performed on an Autosorb iQ MP (Quantachrome Instruments, Anton Paar USA, Ashland VA) at 77 K. Samples were prepared in the following manner: **KSU-3** underwent DMF-to-hexanes solvent exchange followed by two quick  $\text{CHCl}_3$  washes then dried at

60 °C overnight under vacuum (<10<sup>-3</sup> torr). Using the “outgas” function of the surface analyzer, the sample was dried again for 360 mins at 80 °C to remove all residual solvent.

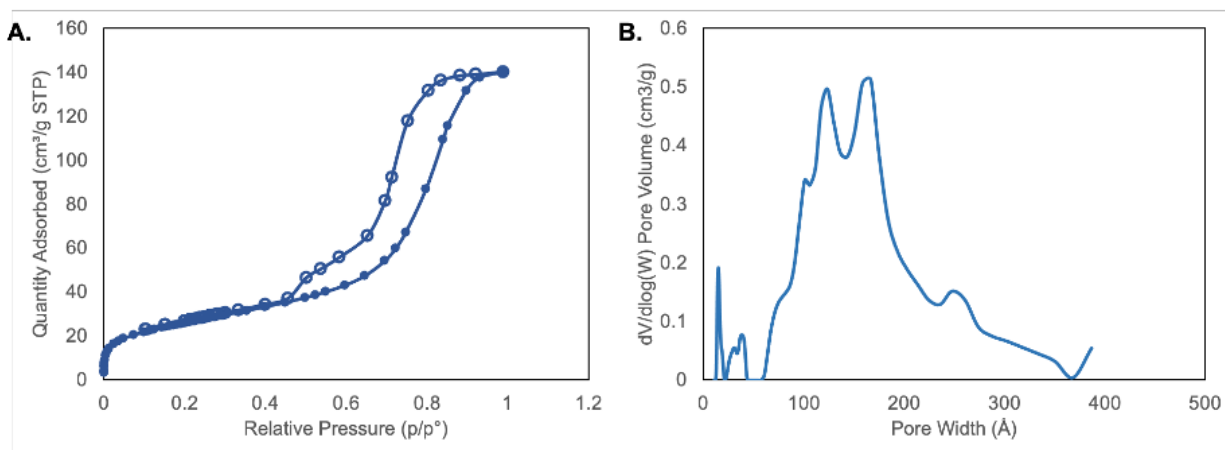


Figure 2.22. A: N<sub>2</sub> gas adsorption measurement for **KSU-1000** (closed circles, adsorption; open circles, desorption). The calculated Brunauer-Emmett-Teller (BET) area is 93 m<sup>2</sup>/g. B: Pore-size distribution (PSD) of **KSU-1000**. The material showed hierarchical porosity composed of various sizes of micro- and mesopores, however, dominant micropores (1.5 nm), mesopores (3.1 and 3.9 nm), and (12.2 and 16.3 nm) are clearly visible from the PSD plot.

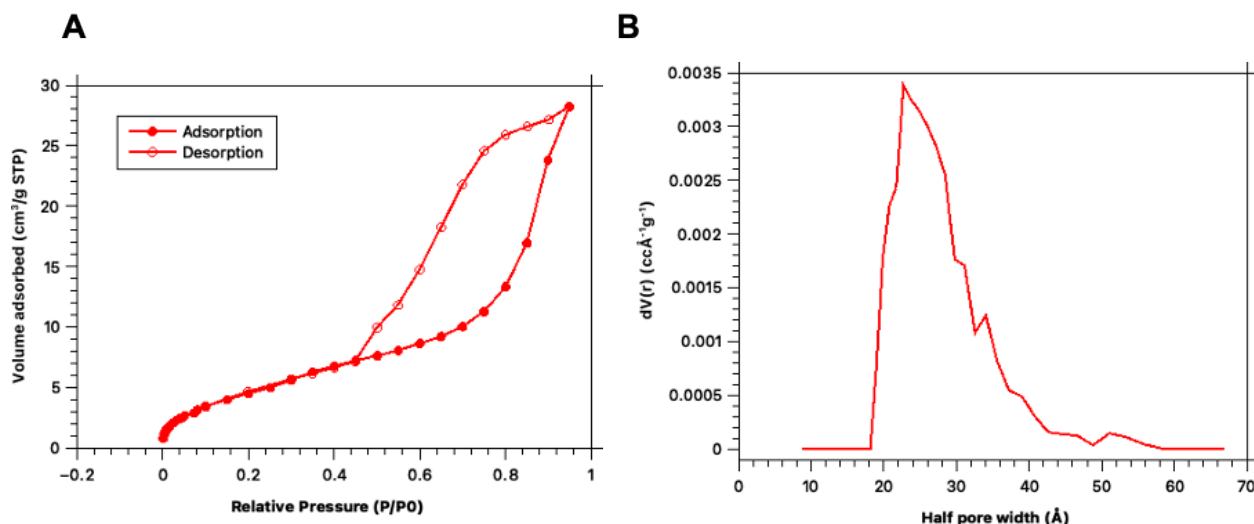


Figure 2.23. A: N<sub>2</sub> gas adsorption measurement for **KSU-3** (closed circles, adsorption; open circles, desorption). The calculated BET area is 10 m<sup>2</sup>/g. B: Pore-size distribution of **KSU-3**. The material displayed predominant mesoporosity, with a mode half pore width of 2.8 nm.

#### 2.6.3.7. Thermogravimetric analysis (TGA)

Thermogravimetric analysis was performed on a TGA 8000 (PerkinElmer Inc., Waltham, MA, USA) interfaced with a PC using Pyris software. Samples were heated at a rate of 10 °C/min



under a nitrogen atmosphere. All samples were extensively solvent exchanged with fresh DMF prior to analysis.

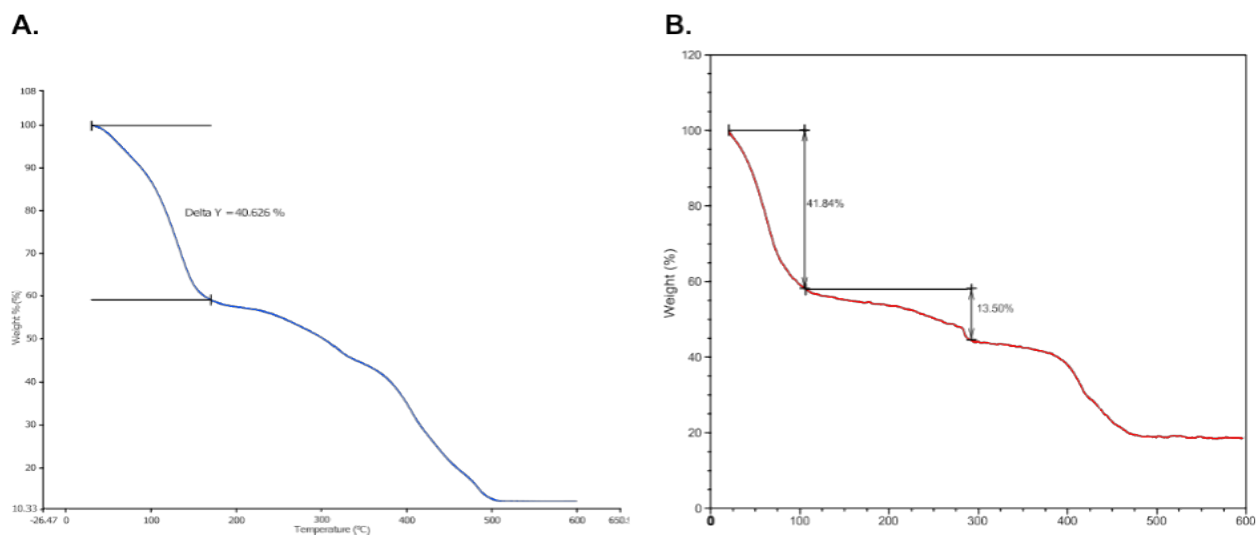


Figure 2.24. TGA traces for as-synthesized MOFs. A: **KSU-1000**. Calculated solvent loss for  $C_{36}H_{25}N_6O_8Zn_2 \cdot 6[C_3H_7NO]$ : 35.3 %; found: 40.6 %. B: **KSU-3**. Calculated solvent loss for  $C_{28}H_{20}N_2O_{10}Zn_2 \cdot 9\frac{2}{3}[C_3H_7NO]$ : 51.4 %; found: 55.3 %.

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## Chapter 3 - Systematic pore hydrophobization to enhance the efficiency of an amine-based MOF catalyst

Portions of this chapter appear in the following preprint:

Matseketsa, P.; Gadzikwa, T. "Systematic Pore Hydrophobization to Enhance the Efficiency of an Amine-Based MOF Catalyst" *Beilstein Arch.* **2025**, 20252. DOI:

10.3762/bxiv.2025.2.v1

### 3.1. Enzyme-inspired catalysis

The primary focus of our lab is to develop modular catalytic systems that mimic enzymes in their catalytic performance, leveraging supramolecular interactions. Enzymes are remarkable due to their (i) confined active site, (ii) multiple functional groups, (iii) flexibility, and (iv) well-defined pore environment.<sup>1</sup> We aim to construct catalytic systems with these characteristics, believing they may compete or surpass natural enzymes in efficiency and selectivity.

Most enzymatic catalysis occurs in multifunctional cavities in which multiple amino acid residues work cooperatively to orient and activate reactants.<sup>2-4</sup> These residues can also enhance covalent and/or acid-base catalysis via non-covalent interactions (hydrogen bonding,  $\pi$ - $\pi$  stacking, hydrophobic interactions, etc.).<sup>5-7</sup> To mimic nature's most efficient catalysts, chemists have long endeavored to synthesize catalytic materials in which multiple functional groups are isolated in confined space.<sup>2-4</sup> In the solid-state, the generation of such multifunctional cavities has been pursued upon the scaffold of nanoporous solids that include polymers of intrinsic microporosity (PIMs),<sup>5-8</sup> mesoporous silica materials (MSMs),<sup>9-12</sup> and metal-organic-frameworks (MOFs), among others (**Figure 3.1**).<sup>9-21</sup> Within this group of porous materials, MOFs boast the advantages of their crystallinity, the uniformity of their pores that are typically in the microporous range (5 – 20 Å), and the ability to fine-tune their pore chemical environment.<sup>13,14</sup> These attributes allow us

to construct active sites with cavities that are of the same size range as small molecules and whose walls are decorated with precisely located functional groups that we can rationally replace to modulate catalytic performance or to systematically investigate the influence of a particular chemical or structural property on reactivity.<sup>15</sup>

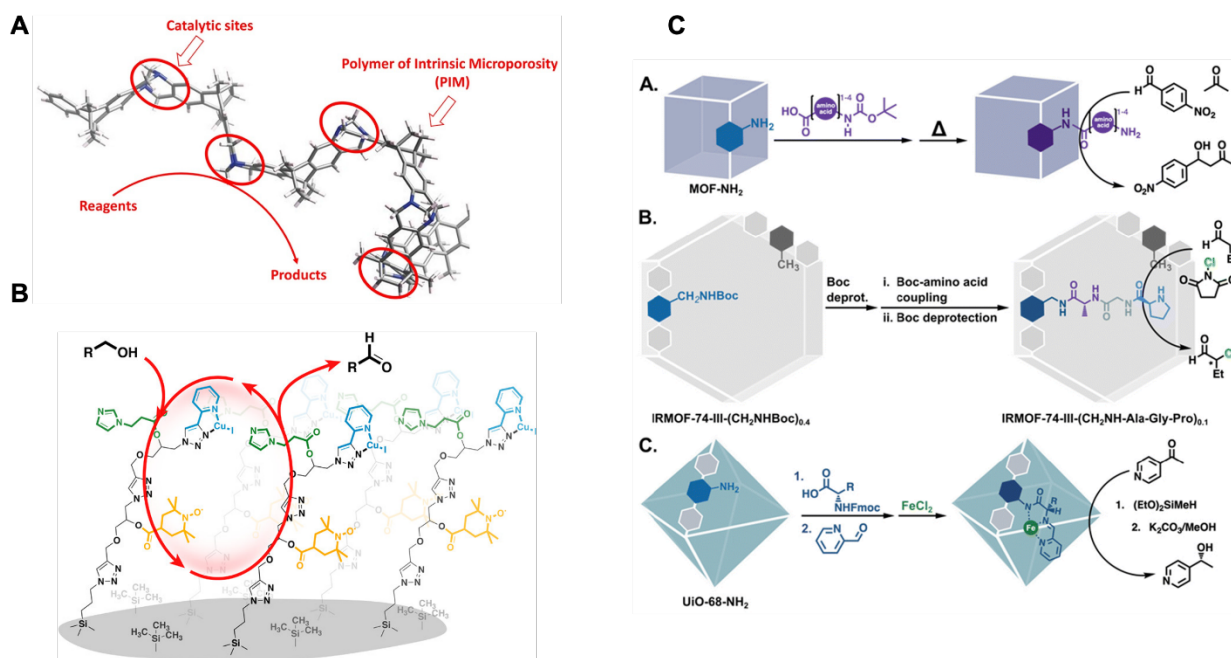


Figure 3.1. Showing examples of nanoporous solid materials used in catalysis. A: The use of polymers of intrinsic porosity (PIMs) for catalysis B: The grafting of sequence-defined oligomers on the surfaces of mesoporous silica materials MSMs for cooperative catalysis. C: The versatility of MOFs in catalysis by introducing the catalytic groups via post-synthesis modification (PSM). Adapted from REF<sup>16–18</sup>.

For an example of tailoring the pore environment in MOF-based catalysts to modulate catalytic performance, we can refer to the elegant work of Telfer and co-workers. In two separate reports, they synthesized well-defined MOFs composed of three different linkers: the proline-functionalized linker functioned as the catalytic unit, while the auxiliary linkers were varied to alter catalyst activity and enantioselectivity,<sup>19</sup> or product-selectivity.<sup>20</sup> In those works the researchers tailored their catalyst via the *de novo* solvothermal synthesis of their MOFs using differently-substituted auxiliary linkers, a non-trivial effort which involves the synthesis of new organic linkers and their assembly into completely new frameworks (**Figure 3.2A**). In this report

we describe how a similar tailoring of a MOF's pore environment with consequent activity modulation can be realized more efficiently using covalent post-synthetic modification (PSM) strategies.<sup>21,22</sup> Starting with a single MOF material with both catalytic linkers and auxiliary linkers that bear reactive "tags", we can graft additional functionalities onto the auxiliaries that adjust the steric and electronic environment of the catalytic units (**Figure 3.2B**).

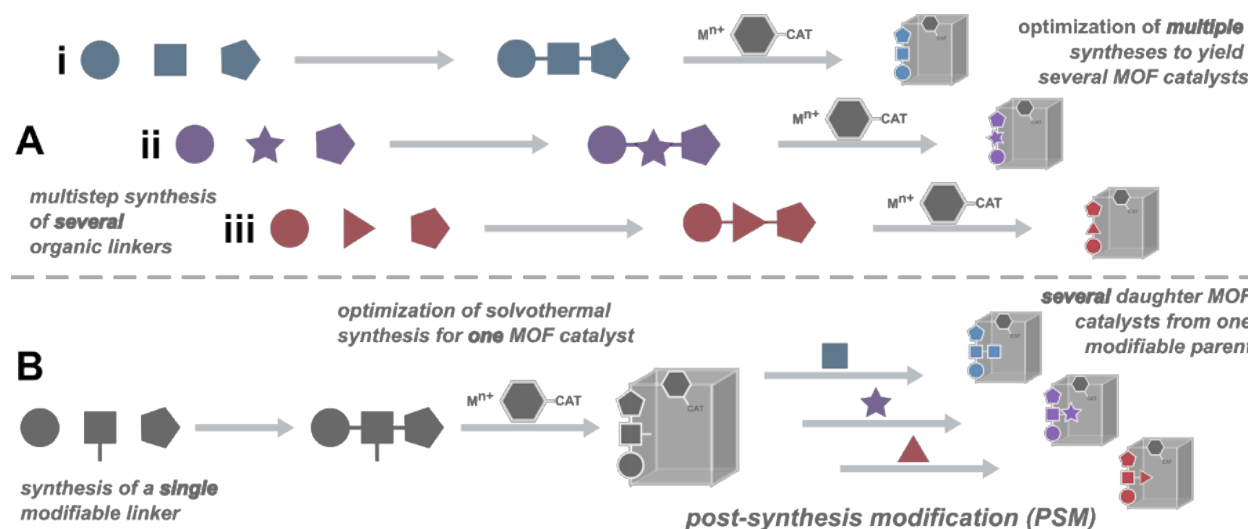


Figure 3.2. Schematic representation of the modulation of MOF pore environments. A: *De novo* synthesis of several MOFs requiring the multistep synthesis of different organic linkers. B: Synthesis of several frameworks from a single parent MOF using post-synthesis modification (PSM).

### 3.2. PSM to obtain hydrophobic MOFs

As mentioned above, one of the strategies to design unique and excellent catalysts using MOFs is via post-synthetic modification (PSM) of the parent MOFs.<sup>23,24</sup> PSM offers a predictable way of obtaining MOFs with known topologies and possessing the required chemical functionalities, which is not easy to obtain using *de novo* synthesis. In that case, it is a very attractive strategy to enhance and/or alter the parent MOF properties to suit a specific application.

The advantages of PSM as a strategy for generating MOF-based catalysts are that we can efficiently generate several daughter catalytic MOFs from a single parent framework, and we can introduce new functionality into a MOF without changing the framework topology, minimizing

the number of variables to consider as we study the influence of a particular property on catalytic performance. Perhaps more importantly for enzyme-inspired materials, PSM allows us to incorporate catalytically interesting functionalities that would normally interfere with MOF assembly, e.g., hydrogen bonding groups like  $\text{-OH}$  and  $\text{-COOH}$  that are difficult to obtain as free uncoordinated moieties within MOF pores.<sup>25,26</sup> Given these benefits, it is no surprise that PSM is a prevalent method for synthesizing MOF-based catalysts.<sup>18</sup>

In particular, hydrophobic MOFs are of significant interest in this work as they benefit from PSM. For instance, Li and coworkers utilized open metal sites in MIL-101(Cr) to coordinate hydrophobic groups via PSM to improve water stability.<sup>27</sup> However, to avoid problems like leaching of the hydrophobic functional groups, a better alternative would be covalent PSM. Cohen and coworkers have worked on improving the moisture resistance of a MOF by carrying out PSM on an amine-bearing MOF to introduce alkyl hydrophobic groups in a MOF (**Figure 3.3**).<sup>28</sup> Similarly, Yan et al. introduced trifluoromethyl groups into MIL-101(Fe)- $\text{NH}_2$  to improve its aqueous stability for water purification.<sup>29</sup> Li et al. utilized covalent PSM to improve the corrosion resistance of five MOFs (ZrTz-68, UiO-66, CYCU-3, HKUST-1, and ZIF-8) using different functional groups to improve hydrophobicity.

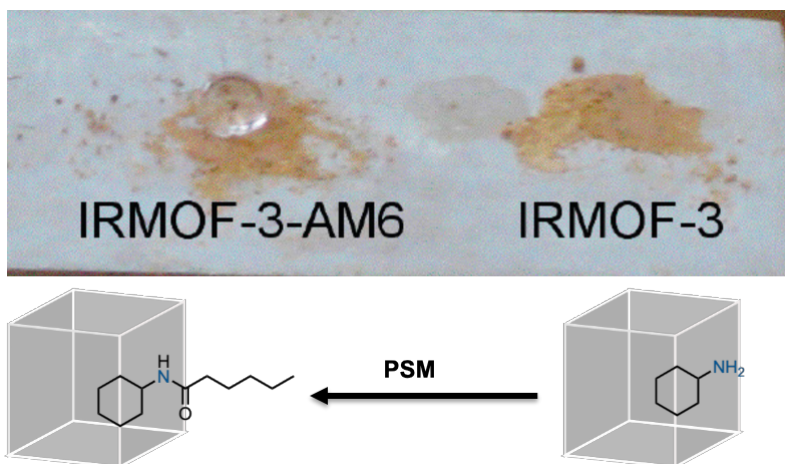


Figure 3.3. Water-resistance after post-synthetic modification with alkyl groups. Adapted from REF<sup>28</sup>.



### 3.3. Knoevenagel reaction in MOFs

Our current work was inspired by Canivet et al., who previously reported the hydrophobization of a catalytic MOF material by grafting long alkyl chains to the *external* surfaces of its crystals (**Figure 3.4**). The active sites are believed to be coordinatively unsaturated zincs at the MOF surfaces, and their hydrophobization resulted in a greater than ten-fold increase in the initial rate of the reaction.<sup>30</sup> The promotion of this reaction was attributed to the repulsion of the water byproduct by the hydrophobic surface, thereby preventing its interference with the Lewis acidic catalyst surface sites. Thus, we wondered if a similar reaction acceleration of a condensation reaction could be achieved by the hydrophobization of the *internal* surfaces of an amine-based MOF catalyst.

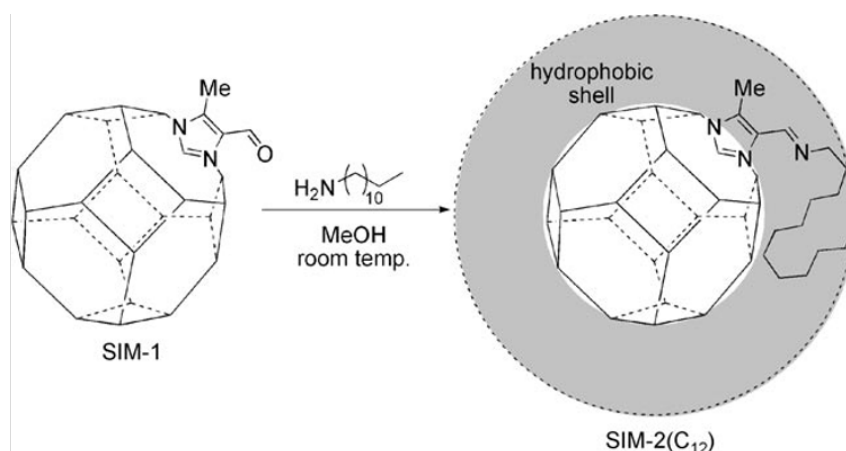


Figure 3.4. Surface hydrophobization of a  $\text{Zn}^{2+}$  based MOF catalyst's external surface to accelerate Knoevenagel reaction. Reproduced from REF<sup>30</sup>.

Most studies on hydrophobic MOFs in catalysis have focused on hydrophobization to prevent catalyst deactivation by water, with only a few investigating how hydrophobic pores surfaces can increase catalyst efficiency,<sup>31,32</sup> despite enzymes employing such a strategy. The hydrophobicity of enzyme active sites tends to improve reaction rates by increasing the binding affinity for the hydrophobic reactants and by decreasing the energy required to desolvate acid/base

amino acid catalysts.<sup>33,34</sup> Thus, in this work, we investigate the influence of pore hydrophobicity on the amine-catalyzed Knoevenagel condensation.

The Knoevenagel condensation reaction is a vital organic reaction involving the condensation of carbonyl compounds, such as aldehydes or ketones, with active methylene compounds.<sup>35</sup> The resulting  $\alpha,\beta$ -unsaturated carbonyl products can then be further elaborated to form natural products, therapeutic agents, polymers, pesticides, and insecticides,<sup>36</sup> which have important applications in the pharmaceutical and agrochemical industries.<sup>36,37</sup> Various types of catalysts are used to enhance the efficiency and selectivity of the Knoevenagel reaction, including Lewis acids, ureas/thioureas, amino acids, and bases such as alkali metal hydroxides, alkali metal alkoxide, amines, etc.<sup>35,38–41</sup> The following section describes our catalyst of choice and how we strategically synthesized it.

### 3.4. Strategy to develop bifunctional amine-based hydrophobic catalyst

We opted for amine-based catalysis using our modifiable framework **KSU-1**, a pillared paddlewheel MOF assembled using zinc, 2-aminobenzene-1,4-dicarboxylic acid (BDC-NH<sub>2</sub>), and *meso*- $\alpha,\beta$ -di(4-pyridyl) glycol (DPG), as our parent MOF (**Figure 3.5A**). As this is a well-defined mixed-linker MOF with molecular formula Zn<sub>2</sub>(BDC-NH<sub>2</sub>)<sub>2</sub>(DPG), each unit cell has a 2:1 ratio of dicarboxylate to dipyridyl, and therefore in a 1:1 ratio of amine (-NH<sub>2</sub>) to hydroxyl (-OH) groups and large triangular and hexagonal pore sizes of 10 and 17 Å respectively. The Zn atoms in the paddlewheel metal sites are coordinatively saturated,<sup>42</sup> thus we anticipated that only the amine group would function as the catalytic unit for the Knoevenagel reaction, while the hydroxyl group would serve as the handle through which we would tune the hydrophobicity of the catalyst.

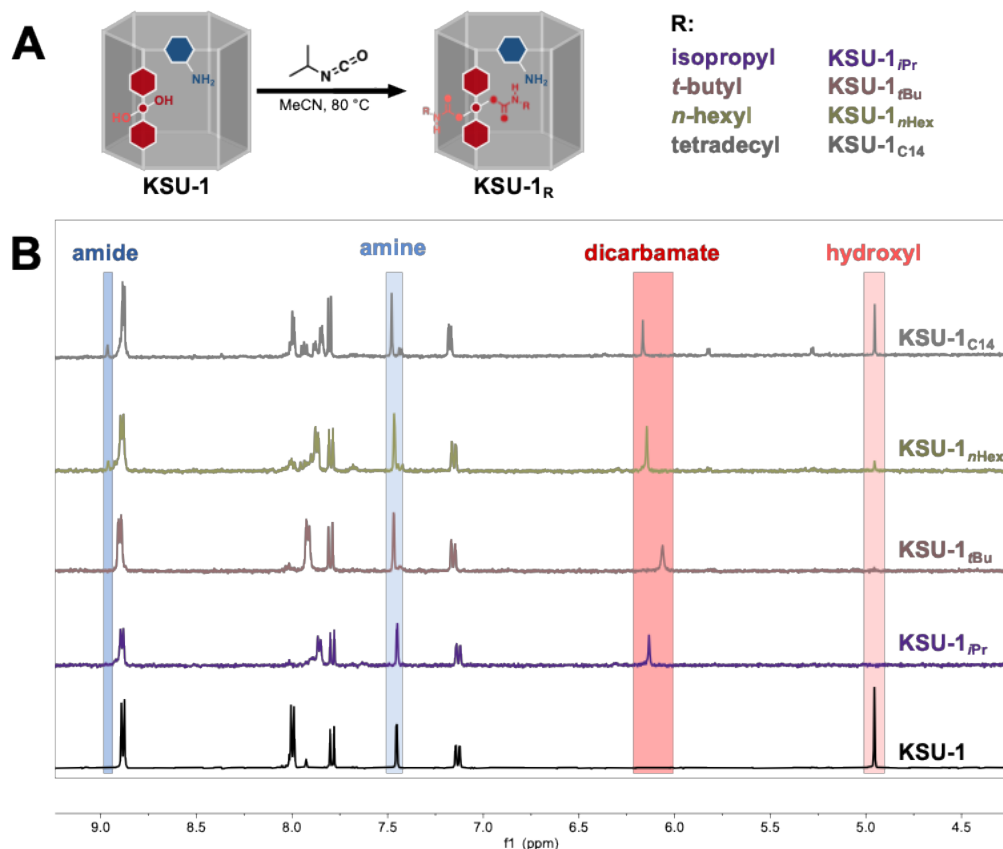


Figure 3.5. Schematic representation of the selective reaction of **KSU-1** with aliphatic isocyanates. B: The corresponding  $^1H$ -NMRs of the MOF reaction products digested in a solution of  $D_2SO_4$  in  $d_6$ -DMSO.

Recently, we found that isopropyl isocyanate reacts preferentially at the DPG hydroxyls of **KSU-1**,<sup>43</sup> despite an earlier demonstration of the superior nucleophilicity of BDC- $NH_2$  (*vide infra*).<sup>44</sup> Interestingly, this apparent reversal in reactivity is most significant with aliphatic isocyanates, with the reactivity reverting to what is expected with the use of more activated isocyanates. Subsequently, we determined that, when incubated with secondary or tertiary isocyanates, **KSU-1** reacts exclusively at the hydroxyls of the DPG linker before proceeding to react at the amines of BDC- $NH_2$  (**Table 3.1**; Entries 1-2). Thus, we had a method to generate a series of amine-based MOFs whose pores are uniformly decorated with different hydrophobic groups, all from a single MOF (**Figure 3.5A**). Using this strategy, we quantitatively functionalized the  $-\text{OH}$  groups of **KSU-1** with isopropyl and *tert*-butyl isocyanate. While primary isocyanates

were less selective, starting to react at the amines before the hydroxyl reaction was complete, we reacted **KSU-1** with *n*-hexyl and tetradecyl isocyanate as well (**Table 3.1**; Entries 3-4) because we wanted to use longer alkyl chains to further increase the hydrophobicity.

Table 3.1. Conversion of -OH and -NH<sub>2</sub> in the isocyanate reactions of **KSU-1**.<sup>a</sup>

| Entry | Isocyanate              | -OH % conversion (stdev) | -NH <sub>2</sub> % conversion (stdev) |
|-------|-------------------------|--------------------------|---------------------------------------|
| 1     | Isopropyl <sup>b</sup>  | 100 (0)                  | 0                                     |
| 2     | Tert-butyl <sup>c</sup> | 94 (5)                   | 0                                     |
| 3     | Hexyl <sup>d</sup>      | 73 (2)                   | 11 (3)                                |
| 4     | Tetradecyl <sup>d</sup> | 64 (5)                   | 8 (3)                                 |

<sup>a</sup>0.2 M in acetonitrile, 80 °C; <sup>b</sup>3 h; <sup>c</sup>4 h; <sup>d</sup>2 h.

To obtain our bifunctional amine-based **KSU-1** MOF catalysts, we incubated **KSU-1** in a 0.2M solution of the respective isocyanate in acetonitrile at 80 °C; **KSU-1** reacted with isopropyl, *tert*-butyl, *n*-hexyl and tetradecyl isocyanate to generate **KSU-1<sub>iPr</sub>** and **KSU-1<sub>tBu</sub>**, **KSU-1<sub>nHex</sub>**, and **KSU-1<sub>C14</sub>** respectively. Successful post synthetic reaction was observed by proton nuclear magnetic resonance (<sup>1</sup>H-NMR) spectroscopy of the MOF product digested in D<sub>2</sub>SO<sub>4</sub>/*d*<sub>6</sub>-DMSO (**Figure 3.5B**). We observed that the reactions with isopropyl isocyanate and *tert*-butyl isocyanate required 3 and 4 hours, respectively, to achieve complete conversion at the hydroxyl without any amine reaction. With *n*-hexyl isocyanate and tetradecyl isocyanate, the reaction at the amine reaction was noticed after just an hour, before incomplete conversion at the hydroxyl. To prevent excessive reaction at the amine, both reactions were stopped at 2 hours.

Aside from <sup>1</sup>H-NMR, the independent functionalization of **KSU-1** with isocyanates was also confirmed by conducting electrospray ionization mass spectrometry (ESI-MS) on samples of the MOF products digested by 1,4-diazabicyclo[2.2.2]octane (DABCO) (**Figures 3.9-3.12**). For

**KSU-1<sub>Pr</sub>** and **KSU-1<sub>tBu</sub>**, the mass spectra in negative mode had  $[M-H^+]$  peaks corresponding to deprotonated BDC-NH<sub>2</sub>, while in the positive mode, the  $[M+H^+]$  peaks indicated the presence of the protonated DPG dicarbamates, along with their various fragmentation products. The mass spectra for **KSU-1<sub>nHex</sub>** and **KSU-1<sub>C14</sub>** show evidence of urea products in negative mode and protonated DPG carbamates along with their fragmentation products in positive mode (**Figures 3.9-3.12**). Powder X-ray diffraction (PXRD) confirmed that crystallinity was preserved even after complete functionalization of DPG (**Figure 3.13**).

### 3.5. Catalysis experiments

To test the catalytic behavior of our amine-based hydrophobic MOF catalysts, we chose the Knoevenagel reaction between benzaldehyde and malononitrile to form benzylidenemalononitrile (BMN, **Figure 3.6A**). In the initial trial, 12 mol% of the MOF catalyst was added to a vial containing benzaldehyde, malononitrile, toluene solvent, and dodecane internal standard, and the reaction was shaken at 50 °C. Aliquots were collected at 30 minutes and diluted in CDCl<sub>3</sub> and conversions were determined by analyzing the <sup>1</sup>H-NMRs of the samples (**Figure 3.6B**).

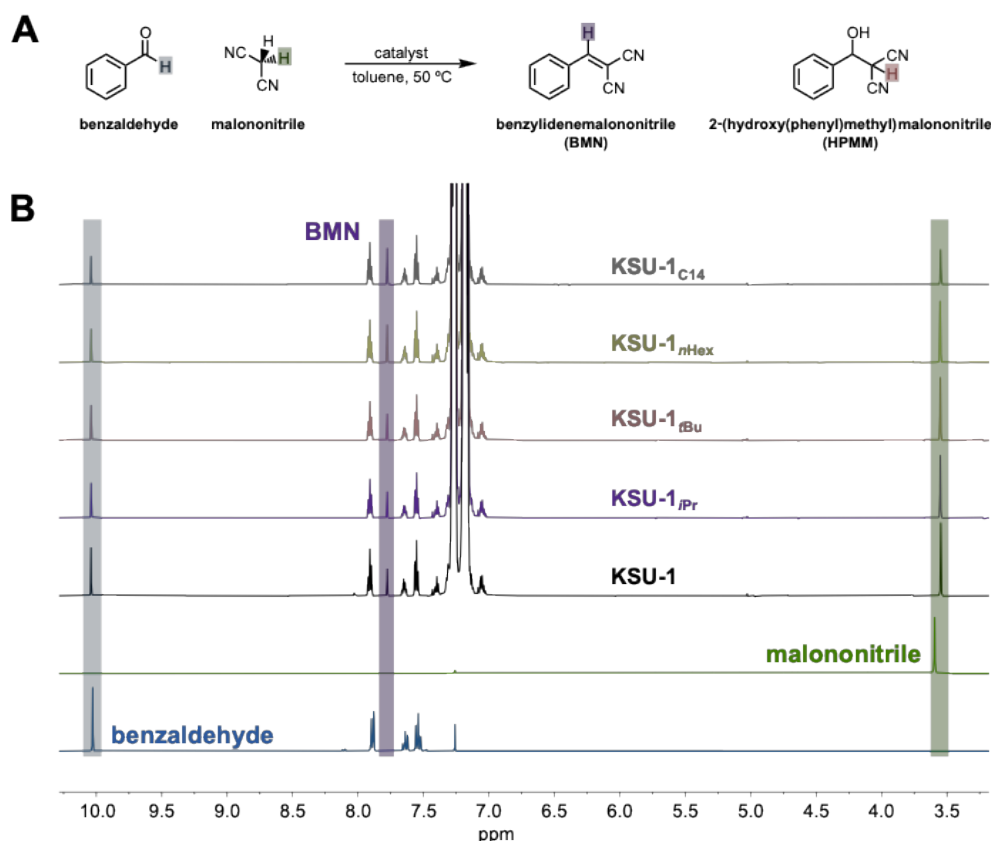


Figure 3.6. A: Schematic representation of the reaction between benzaldehyde and malononitrile to form benzylidenemalononitrile (BMN). B: Representative  $^1\text{H-NMR}$  for the reaction of benzaldehyde and malononitrile in toluene with dodecane as an internal standard, analyzed after 30 minutes.

The results showed a general increase in catalysis efficiency as we increased the hydrophobicity of the MOF pores. However, the observed differences in conversion between the hydrophobized catalysts were marginal, with a variation of  $\sim 8\%$  (**Table 3.2A**). We were concerned that dodecane, our aliphatic internal standard, was negatively affecting our results by decreasing the difference in hydrophobicity between the MOF pores and the extra-MOF solution. Comparing the conversions we obtained using the dodecane calibration curve with those determined by directly comparing the integrations of the benzaldehyde and BMN protons in the  $^1\text{H-NMR}$  spectra, we found little difference (**Table 3.4**), thus, we decided to discontinue the addition of internal standard to our catalysis reactions.

Table 3.2. Comparison of Knoevenagel catalysis results under different conditions. <sup>a</sup>

| Entry | Catalyst              | % Conversion (stdev.)            |                         |                         |                      |
|-------|-----------------------|----------------------------------|-------------------------|-------------------------|----------------------|
|       |                       | A. Toluene+dodecane <sup>b</sup> | B. Toluene <sup>c</sup> | C. Toluene <sup>d</sup> | D. Neat <sup>e</sup> |
| 1     | KSU-1                 | 36 (2)                           | 8 (1)                   | 3 (0)                   | 43 (2)               |
| 2     | KSU-1 <sub>iPr</sub>  | 48 (1)                           | 19 (2)                  | 3 (0.5)                 | 56 (3)               |
| 3     | KSU-1 <sub>tBu</sub>  | 51 (1)                           | 23 (4)                  | 2.5 (0.5)               | 65 (5)               |
| 4     | KSU-1 <sub>nHex</sub> | 51 (1)                           | 15 (3)                  | 5 (1)                   | 67 (5)               |
| 5     | KSU-1 <sub>C14</sub>  | 56 (3)                           | 16 (5)                  | 8 (0)                   | 77 (5)               |

<sup>a</sup>0.0625 mmol benzaldehyde, 0.068 mmol malononitrile, 50 °C; <sup>b</sup>12 mol% catalyst, 0.083 mmol dodecane, 250  $\mu$ L toluene; <sup>c</sup>12 mol% catalyst, 250  $\mu$ L toluene; <sup>d</sup>1.5 mol% catalyst, 250  $\mu$ L toluene; <sup>e</sup>1.5 mol% catalyst.

Performing the reaction without dodecane revealed significantly lower conversions, and our anticipated trend in catalyst efficiency, i.e., increasing conversions with the increasing hydrophobicity of the carbamate substituents, was not consistently followed (**Table 3.2B**). While conversions increased going from no substitution to isopropyl, then *tert*-butyl, subsequent increases in hydrophobicity with *n*-hexyl and tetradecyl resulted in decreased conversions at 30 minutes, a trend that can be more clearly perceived in (**Figure 3.7A**). This result led us to speculate that using hydrophobic toluene as our solvent likely also decreased the difference in relative hydrophobicity between the interior and exterior of the MOF pores. Thus, we thought we would run the Knoevenagel reaction under neat conditions. However, because solvents improve the solubility of the reactants and products, making it easier for the reagents to reach the active sites, we were concerned that performing the reaction neat would be detrimental: malononitrile is solid, *and* the rapid formation of solid product BMN often results in a thick sludge that hinders the flow of the reaction solution.

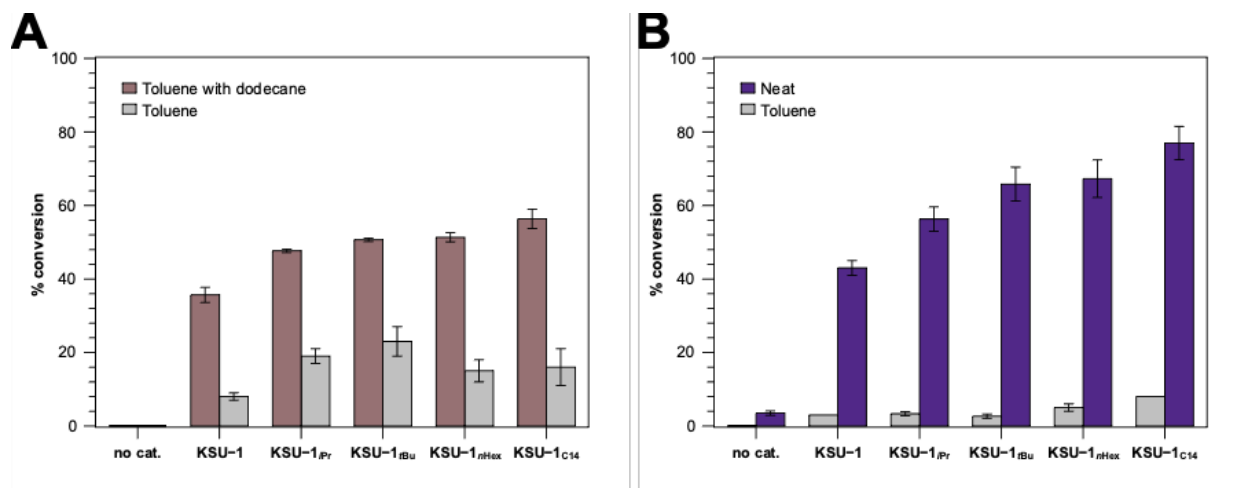


Figure 3.7. Graphical representation of Knoevenagel catalysis results. A: Comparison of the reaction in toluene with and without internal standard using 12 mol% catalyst. B: Catalysis performed under neat conditions and in toluene using 1.5 mol% catalyst.

To ensure that the MOFs were completely submerged in the reaction mixture, we reduced the catalyst amount to 1.5 mol%. Interestingly, the reaction conversions were higher than those in toluene with 12 mol% catalyst, and significantly so (ca. 10-fold) with a more appropriate comparison at the same catalyst loading of 1.5 mol% (Table 3.2C-D). Further to our delight, **KSU-1<sub>C14</sub>** was the most active catalyst, achieving 77 % conversion vs 43 % for **KSU-1** after 30 mins. In addition, a remarkably clear and gradual increase in the rate of reaction was observed from **KSU-1** < **KSU-1<sub>iPr</sub>** < **KSU-1<sub>tBu</sub>** < **KSU-1<sub>nHex</sub>** < **KSU-1<sub>C14</sub>** (Figure 3.7B) even though roughly 10% of the -NH<sub>2</sub> groups in both **KSU-1<sub>nHex</sub>** and **KSU-1<sub>C14</sub>** had been converted to the less catalytically active alkyl ureas.<sup>45</sup> We should also point out that, although the introduction of large alkyl substituents in a MOF is associated with a reduction in pore accessibility, the lower percentage of alkyl grafting for both **KSU-1<sub>nHex</sub>** and **KSU-1<sub>C14</sub>** results in similar solvent accessible volumes for all the modified MOFs, as shown by thermogravimetric analysis (TGA; Figure 3.14). Thus, our results indicate that catalytic efficiency improves with the increasing hydrophobicity of the alkyl chains, which is a result of the increase in surface area of the alkyl groups.<sup>46</sup>



Finally, we emphasize that our study was not geared toward obtaining particular conversions with our catalysts, but rather at investigating the effect that systematic pore environment modulation has on catalyst reactivity; specifically, how hydrophobization affects a condensation process like the Knoevenagel reaction. As such, it was also interesting to observe differences in the relative amount of reaction intermediate depending on the hydrophobicity of the pores. Under solvent-free conditions, we observed the formation of 2-(hydroxy(phenyl)methyl)malononitrile (HPMM, **Figure 3.8**), an intermediate which is subsequently dehydrated to yield the main product (BMN) as the reaction progresses.<sup>47</sup> Looking at the ratio of final product to intermediate (BMN: HPMM), we saw that relatively more of the hydroxyl intermediate was observed with the unfunctionalized **KSU-1** catalyst (**Table 3.3, Entry 2**) compared to the hydrophobicized catalysts, with the amount of HPMM decreasing with increasing aliphatic chain surface area. This trend suggests that the hydrophobic surfaces may destabilize hydrophilic intermediates, promoting faster conversion of HPMM to BMN, like the ground state destabilization of polar substrates observed in enzymes with hydrophobic pockets.<sup>48,49</sup>

Table 3.3. Ratio of BMN: HPMM product.

| Entry | Catalyst                    | BMN: HPMM |
|-------|-----------------------------|-----------|
| 1     | no catalyst                 | 0.3:1     |
| 2     | <b>KSU-1</b>                | 4.3:1     |
| 3     | <b>KSU-1<sub>iPr</sub></b>  | 10:01     |
| 4     | <b>KSU-1<sub>tBu</sub></b>  | 15:01     |
| 5     | <b>KSU-1<sub>nHex</sub></b> | 17:01     |
| 6     | <b>KSU-1<sub>C14</sub></b>  | 23:01     |

<sup>a</sup>Neat, 50 °C, 1.5 mol% catalyst.

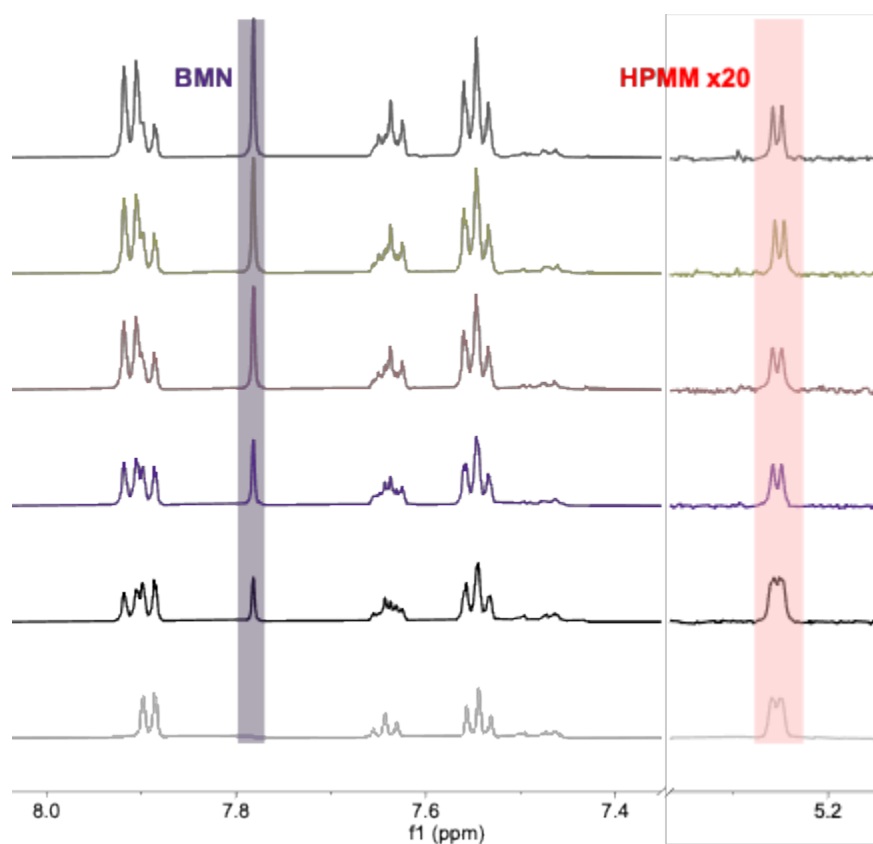


Figure 3.8. Comparison of BMN and HPMM protons in <sup>1</sup>H-NMR.

### 3.6. Conclusion

By employing a covalent post synthesis modification strategy that selectively introduces hydrophobic functionality into MOFs, we confined catalytically active amines within MOF pores of systematically increasing hydrophobicity. Our results reveal a clear correlation between increased pore hydrophobicity and enhanced catalytic activity. Additionally, increasing hydrophobicity resulted in congruent changes in the distribution of intermediate versus product during the reaction. Both these behaviors, increased efficiency and different intermediate product distributions, call to mind the effect of hydrophobic pockets in enzyme catalysis, and offer a view to the possibilities that can be achieved in enzyme-inspired catalysis via the rational functionalization of MOF pores.

### 3.7. Experimental

#### 3.7.1. Materials

All chemicals were used as received from commercial sources unless otherwise noted. Isopropyl isocyanate (98%), *tert*-butyl isocyanate (97%) and tetradecyl isocyanate (97%) were purchased from Sigma Aldrich. Hexyl isocyanate (99%) and 2-aminoterephthalic acid (BDC-NH<sub>2</sub>) (99%) were purchased from Thermo Scientific. Meso- $\alpha,\beta$ -di(4-pyridyl) glycol (>98%) (DPG) and malononitrile (97%) were purchased from TCI. Sulfuric acid-*d*<sub>2</sub> (D<sub>2</sub>SO<sub>4</sub>, 98 wt.% in D<sub>2</sub>O, 99.5+ % atom D) was purchased from Acros Organics. *N,N*-dimethylformamide (DMF), toluene, acetonitrile and benzaldehyde were purchased from Fisher Scientific (ACS certified). Zinc nitrate hexahydrate from Strem Chemicals and 1,4-Diazabicyclo[2.2.2]octane (DABCO) (95%) was purchased from Oakwood Products. Dimethyl sulfoxide-*d*<sub>6</sub> (*d*<sub>6</sub>-DMSO, 99.9 atom% D) was purchased from Cambridge Isotopes Laboratories.

### 3.7.2. Synthetic Procedures

**KSU-1** was synthesized according to the literature procedure.<sup>58</sup>

#### 3.7.2.1. General procedure for the reaction of MOF materials with isocyanates

In a typical experiment, ~ 10 mg of **KSU-1** (0.012 mmol) (-OH (0.025 mmol) and -NH<sub>2</sub> (0.025 mmol)) as-synthesized in DMF was transferred to a 1-dram vial. Then, 2 mL of a 0.2 M solution of the isocyanate (0.4 mmol) in acetonitrile were added to the vial. The reaction was left at 80 °C with continuous mixing on a Corning LSE Low Speed Orbital Shaker. Samples of the reacted MOF were taken at 3 h, washed in acetonitrile 3 times, filtered, and digested for analysis.

#### 3.7.2.2. General procedure for catalysis

MOF material (0.0075 mmol) was introduced into a 0.10 mL glass vial. Benzaldehyde (0.5 mmol; 50.8 uL) and malononitrile (0.55 mmol; 36.5 mg) were then added and the vial was sealed. The resultant suspension was allowed to react at 50 °C for 30 min. After quenching by cooling to room temperature, the product dissolved with CHCl<sub>3</sub> to separate the solid catalyst. The supernatant was analyzed by <sup>1</sup>H-NMR and the yield determined by integration of signals using disappearance of the starting material to appearance of product.

### 3.7.3. Characterization

#### 3.7.3.1. High-resolution mass spectrometry (HRMS)

MOF samples (~5 mg) were placed in a solution of DABCO (10 mg) and 0.25 mL of DMSO in a 2-dram vial. The vial was sonicated for ~ 1 min then heated at 80 °C overnight. A small amount of residue was filtered out and the resulting solution was analyzed using a Xevo G2-XS QT of quadrupole time-of-flight mass spectrometer coupled with an ACQUITY M-class UPLC and a NanoLockSpray dual electrospray ion source. Mass spectra were acquired in "eXtreme Resolution" mode.

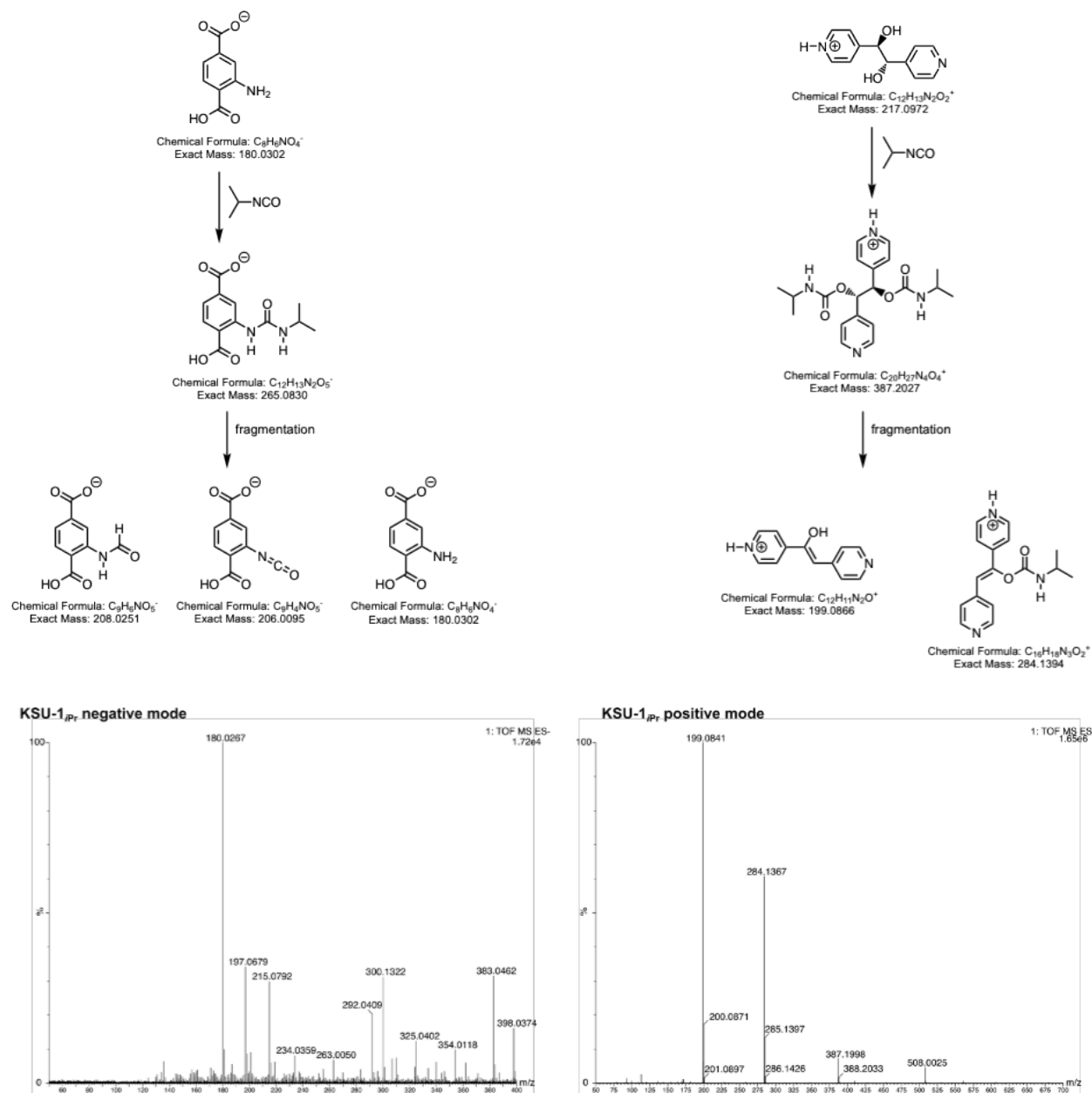


Figure 3.9. HRMS of **KSU-1** after reacting with isopropyl isocyanate to form **KSU-1<sub>IPr</sub>**. Left: the negative mode has no indication of the BDC urea product, though the [BDC-NH<sub>2</sub>-H<sup>+</sup>] starting material peak could also be a fragmentation product. Right: the positive mode has  $m/z$  peaks corresponding to [DPG<sub>dicarbamate</sub>+H<sup>+</sup>] and its various fragmentation products.

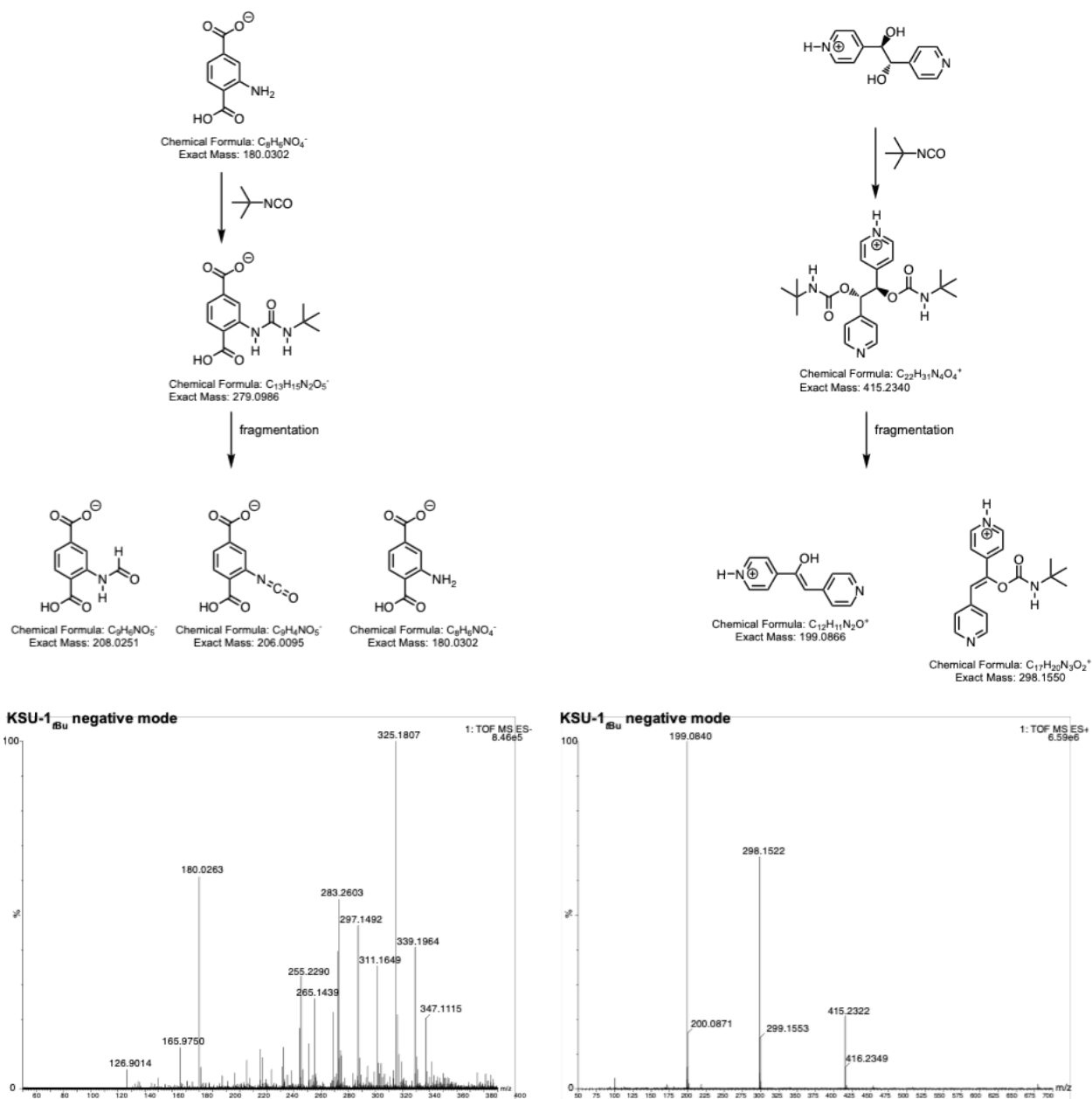


Figure 3.10. HRMS of **KSU-1** after reacting with tert-butyl isocyanate to form **KSU-1<sub>Bu</sub>**. Left: the negative mode has no indication of the BDC urea product ( $m/z = 279.0986$ ), though the  $[BDC-NH_2-H^+]$  starting material peak could also be a fragmentation product (note the presence of an unidentified mass at  $m/z = 339.1964$  that appears to lose successive numbers of  $-CH_2$  groups). Right: the positive mode has  $m/z$  peaks corresponding to  $[DPG_{dicarbamate}+H^+]$  ( $m/z = 415.2322$ ) and its various fragmentation products.

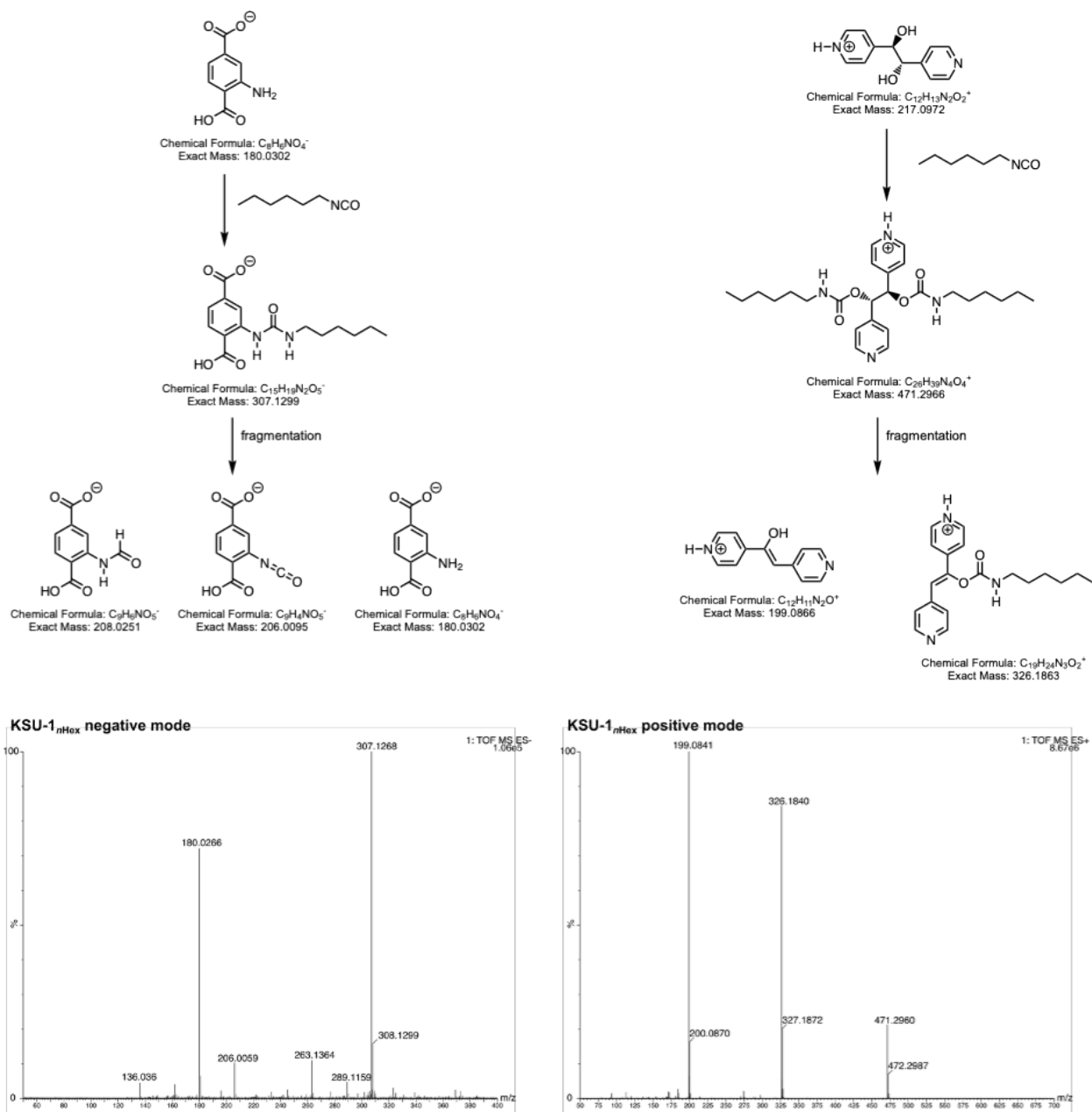


Figure 3.11. HRMS of **KSU-1** after reacting with *n*-hexyl isocyanate to form **KSU-1<sub>nHex</sub>**. Left: the negative mode shows indication of the BDC urea product, and the [BDC-NH<sub>2</sub>-H<sup>+</sup>] starting material peak could also be a fragmentation product. Right: the positive mode has m/z peaks corresponding to [DPGdicarbamate+H<sup>+</sup>] and its various fragmentation products.

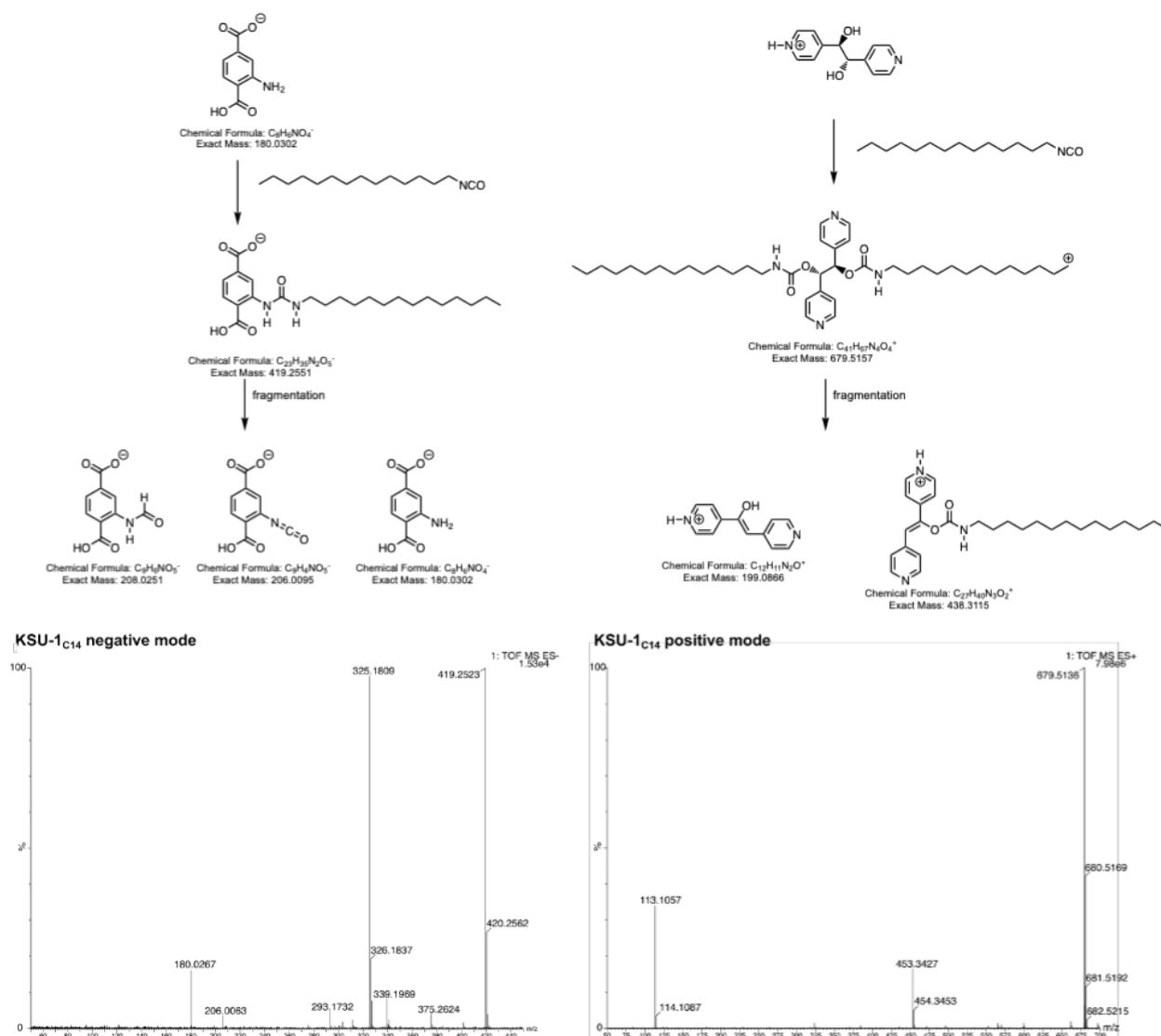


Figure 3.12. HRMS of **KSU-1** after reacting with tetradecyl isocyanate to form **KSU-1<sub>C14</sub>**. Left: the negative mode indicates the presence of the BDC urea product ( $m/z = 419.2523$ ), and the [BDC-NH<sub>2</sub>-H<sup>+</sup>] starting material peak could also be a fragmentation product. Right: the positive mode has  $m/z$  peaks corresponding to [DPG<sub>dicarbamate</sub>-CH<sub>3</sub>]<sup>+</sup> ( $m/z = 679.5136$ ).

### 3.7.3.2. Powder X-ray diffraction (PXRD)

Powders were recorded on a Bruker AXS D8 Advance Phaser diffractometer (Bruker AXS, Karlsruhe, Germany) with Cu K $\alpha$  radiation ( $\lambda = 1.5418 \text{ \AA}$ ) over a range of  $4^\circ < 2\theta < 40^\circ$  in  $0.02^\circ$  steps with a 0.5 s counting time per step. Samples were collected from the bottom of the reaction vial as a thick suspension in DMF and spread on a Si-Einkristalle plate immediately before PXRD measurements.



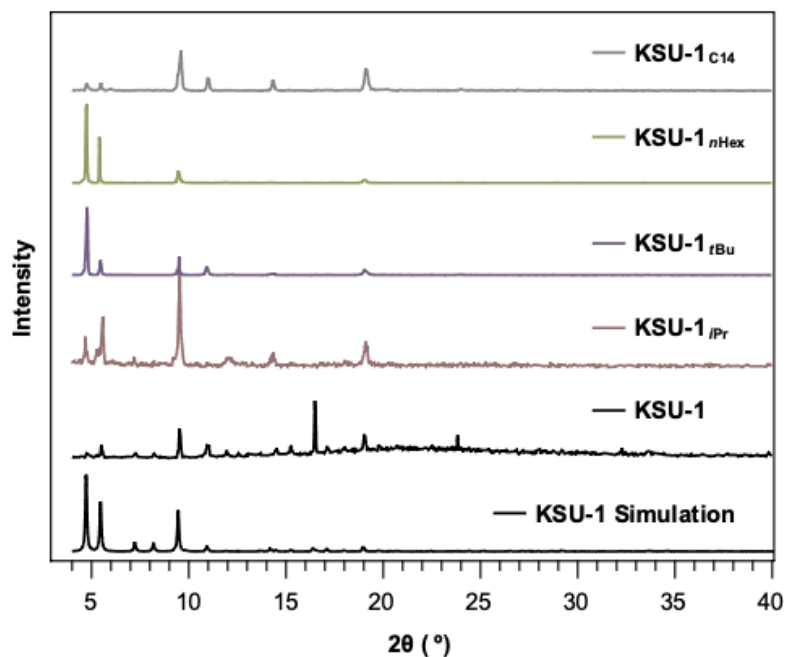


Figure 3.13. The PXRD patterns of the simulated **KSU-1**, the experimental **KSU-1**, and the **KSU-1** after reacting with the alkyl isocyanates **KSU-1<sub>iPr</sub>** and **KSU-1<sub>tBu</sub>**, **KSU-1<sub>nHex</sub>**, and **KSU-1<sub>C14</sub>** respectively.

### 3.7.3.3. Thermogravimetric analysis (TGA)

Thermogravimetric analysis was performed on a TGA 8000 (PerkinElmer Inc., Waltham, MA, USA) interfaced with a PC using Pyris software. Samples were heated at a rate of 10 °C/min under a nitrogen atmosphere. All samples were extensively solvent exchanged with fresh toluene prior to analysis.

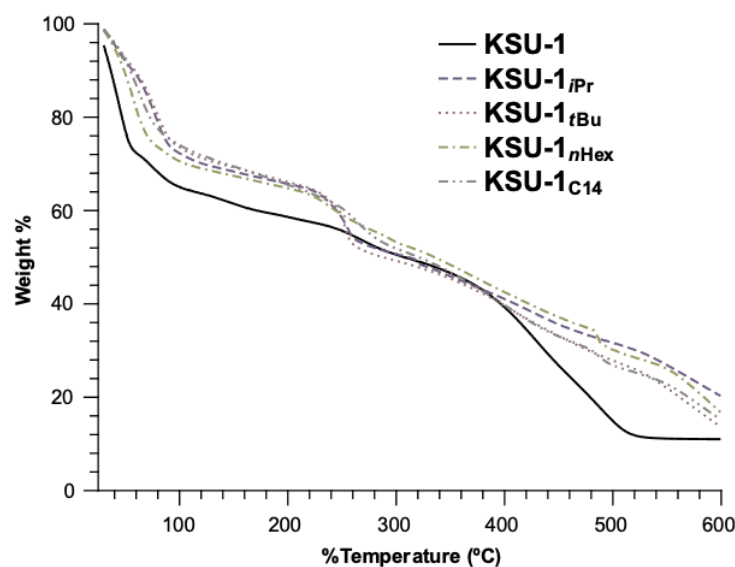


Figure 3.14. TGA data for as-synthesized **KSU-1**, **KSU-1<sub>iPr</sub>** and **KSU-1<sub>tBu</sub>**, **KSU-1<sub>nHex</sub>**, and **KSU-1<sub>C14</sub>** exchanged with toluene.

#### 3.7.3.4. Proton nuclear magnetic resonance (<sup>1</sup>H-NMR)

Spectra were recorded on a Bruker Avance NEO spectrometer (400 MHz for <sup>1</sup>H, Bruker BioSpin, Billerica, MA, USA). NMR chemical shifts are reported in ppm against a residual solvent resonance as the internal standard ( $\delta(d_6\text{-DMSO}) = 2.5$  ppm). In a typical analysis, MOF materials stored in DMF were solvent exchanged with CHCl<sub>3</sub>, isolated by vacuum filtration, and then evacuated in a vacuum oven at 80 °C overnight. Evacuated MOF samples (5-6 mg) were transferred into an NMR tube and *d*<sub>6</sub>-DMSO (0.55 mL) was added. Subsequently, D<sub>2</sub>SO<sub>4</sub> (0.09 mL, 98% w/w in D<sub>2</sub>O) was also added. The tubes were capped and sonicated until all the solid was dissolved (~ 1 min).

#### 3.7.3.6. Dodecane calibration curve

Benzaldehyde (0.5 mmol; 50.8  $\mu$ L) and dodecane (0.5 mmol; 113.6  $\mu$ L) were then added into two separate half vials followed by 2.00 mL of toluene in each vial to make a 0.50 M solution. These solutions were then diluted to make 0.250 M, 0.200 M, 0.150 M, 0.100 M and 0.0500 M solution. Aliquots for each solution were analyzed by <sup>1</sup>H-NMR and the ratio of benzaldehyde and

dodecane in each standard was determined by integration of dodecane signal at 0.89ppm vs benzaldehyde signal at 10.03ppm.

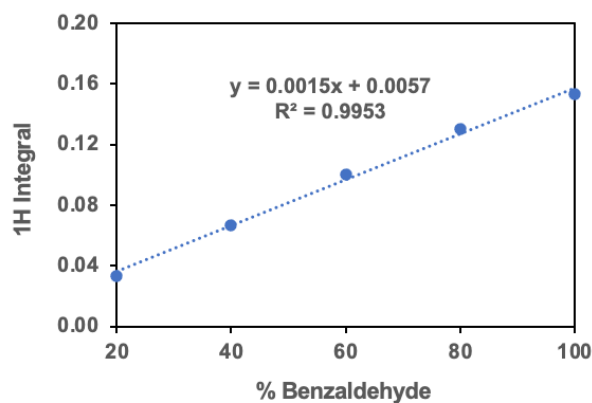


Figure 3.15. Calibration curve of the benzylidenemalononitrile proton with dodecane internal standard.

Table 3.4. Comparison of conversions obtained comparing the integral of the benzylidenemalononitrile proton to that of the dodecane internal standard (I.S.) vs comparing to the benzaldehyde (BA) proton.<sup>a</sup>

| Entry | Catalyst                     | % Conversion   |              |            |          |            |          |
|-------|------------------------------|----------------|--------------|------------|----------|------------|----------|
|       |                              | 30 min. (I.S.) | 30 min. (BA) | 3 h (I.S.) | 3 h (BA) | 6 h (I.S.) | 6 h (BA) |
| 1     | no catalyst                  | 0              | 0            | 0          | 0        | 0          | 0        |
| 2     | KSU-1                        | 37             | 37           | 75         | 77       | 90         | 97       |
| 3     | KSU-1 <sub><i>i</i>Pr</sub>  | 37             | 37           | 87         | 90       | 96         | 97       |
| 4     | KSU-1 <sub><i>t</i>Bu</sub>  | 42             | 44           | 90         | 90       | 96         | 100      |
| 5     | KSU-1 <sub><i>n</i>Hex</sub> | 54             | 57           | 89         | 90       | 96         | 97       |
| 6     | KSU-1 <sub>C14</sub>         | 58             | 64           | 92         | 90       | 97         | 100      |

<sup>a</sup>0.0625 mmol benzaldehyde, 0.068 mmol malononitrile, 0.083 mmol dodecane, 250  $\mu$ L toluene, 12 mol% catalyst, 50  $^{\circ}$ C.

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## Chapter 4 - Bifunctional urea MOF catalysts: Synthesis via PSM and catalytic evaluation

### 4.1. Cooperative catalysis

Catalysis is fundamentally a kinetic process, lowering the activation energy barrier required for the transformation and facilitating the conversion of starting materials into products, as illustrated in the potential energy diagram (**Figure 4.1**).<sup>1</sup> However, the most sought-after catalysts are not only those that enhance reaction rates but also those that exhibit high selectivity. This is particularly crucial in pharmaceutical synthesis, where the stereochemistry of a compound directly influences its medicinal properties.<sup>2</sup> By enabling a more direct way to desired products, selective catalysts help minimize waste, reduce costs, and lower energy input, making them essential for sustainable chemical processes. Therefore, the core objective of catalyst design and discovery is to accelerate the reactions and selectivity towards desired products. Chapter 3 detailed the design, synthesis, and characterization of amine-based hydrophobized MOF catalysts for the catalysis of the Knoevenagel reaction. The study established a parallel between enzyme hydrophobic pockets and synthetic enzyme-inspired catalysts generated from our mixed linker MOF, **KSU-1**, through post-synthetic modification (PSM). Again, drawing inspiration from enzymes, Nature's best catalyst, and employing strategies outlined in Chapter 3, we aim to develop bifunctional urea-based catalysts.

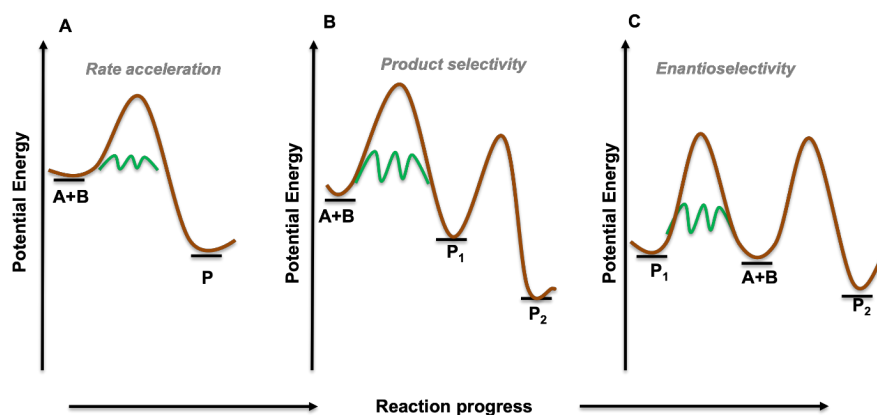


Figure 4.1. Representation of the effect of catalyst on reactions. A: Reaction rate acceleration by lowering the activation energy. B: Selective catalysis, lowers the activation energy barrier to a desired intermediate to produce one product without accelerating subsequent steps C: Demonstrates selectivity between two main primary products where the selective catalyst lowers the barrier to favor one product for example enantioselective catalysis.



## 4.2. Confinement effects

Enzyme active sites are confined within environments of specific size and shape. This confinement significantly enhances catalytic performance by influencing reaction pathways, improving selectivity, and suppressing undesired side reactions.<sup>3</sup> To emulate these effects, various materials, such as molecular capsules, molecular cages, cavitands, boxes, MOFs, etc., have been explored for catalysis. By restricting active centers in these confined spaces, these materials have demonstrated superior activity and selectivity compared to non-confined counterparts.<sup>4,5</sup>

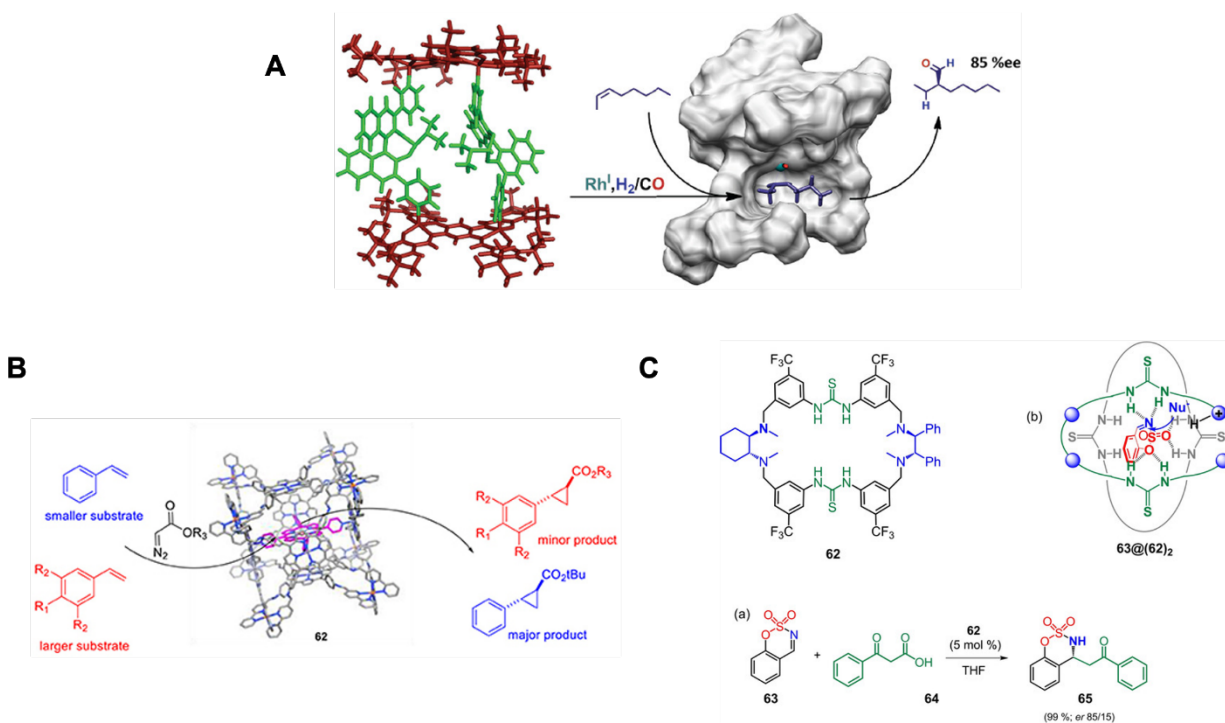


Figure 4.2. Mimicking of confinement and cooperativity in enzymes A: Confinement of Rh based catalyst in a chiral supramolecular box led to high ee for hydroformylation of unfunctionalized internal alkene B: Size-selectivity in cyclopropanation reactions by an encapsulated cobalt-porphyrin catalyst C: Substrate induced microcycle 62 catalyzes the Michael reaction between 63 and 64 to give 65 via induced dimerization assembly  $63@(\text{62})_2$  cooperative H-bonding interactions. Adapted from REF<sup>3-5</sup>.

A study by Gadzikwa et al.; demonstrated that encapsulation of  $\text{Rh}(\text{acac})(\text{CO})_2$  within a chiral supramolecular box constructed using  $\text{bis}[\text{Zn}^{\text{II}}(\text{salphen})]$  as a template and a chiral phosphorus-based ligand as the dipyrindyl pillar produced a chiral catalyst capable of achieving extraordinary enantioselectivities in hydroformylation of unfunctionalized internal alkenes, particularly for challenging substrates such as *cis*-2-olefins (**Figure 4.2A**).<sup>5</sup> In another study, De Bruin and coworkers encapsulated a single catalytically active cobalt(II)-tetra pyridyl porphyrin within a cubic  $\text{M}_8\text{L}_6$  cage (62). The resulting cobalt catalysts were tested for cyclopropanation

reaction and exhibited excellent activity and demonstrated size selectivity for smaller styrene analogs (**Figure 4.2B**).<sup>3</sup> Confinement of these metal sites offers several advantages, including enhanced stereo control by restricting their spatial positioning and preventing deactivation via metal cluster or bimetallic species formation. Another approach is the confinement of homogenous catalysts such as urea and thioureas. Beyond the inherent benefits of confinement, encapsulating these catalysts enhances their efficiency by minimizing deactivation, which often arises due to hydrogen bonding. Wang and coworkers (**Figure 4.2.C**) demonstrated that, in the presence of the substrate (**63**), a macrocycle dimerizes **63**@(**62**)<sub>2</sub> forming a sandwich-like structure stabilized by a hydrogen-bonding network.<sup>4</sup> This study provided a rare example of substrate-induced chiral catalyst assembly, mimicking the induced-fit mechanism of enzymes and achieving high enantioselectivity. Among these confinement-based catalytic materials, MOFs stand out as particularly promising materials. They not only provide confinement but also offer versatility in tuning the pore size, shape, and chemical environment of the pores. The next section will discuss how ureas and thioureas have been incorporated in MOFs for catalysis and explore strategies for further improving these systems.

### 4.3. Urea-based MOF catalysts

The objective of this chapter is to make MOF-based urea bifunctional catalysts. Several urea functionalized MOF catalysts have been synthesized either by *de novo* synthesis or post synthetic modification (PSM). For example, **TMU-18** and **TMU-19** made from *de novo* synthesis have been used for catalyzing the methanolysis reaction via hydrogen-bonding activation of the epoxide (**Figure 4.3A and B**).<sup>6-8</sup> Inductively Coupled Plasma (ICP) analysis confirm that ~99% of zinc metal centers remained intact without leaching into the reaction mixture under the methanolysis conditions. This result indicates that catalysis occurs exclusively through hydrogen bonding rather than Lewis acidic activation by zinc metal sites (**Figure 4.3B**). A more efficient approach to developing urea-based catalysts is through covalent post-synthetic modification (PSM) which enables the transformation of a parent MOF into multiple daughter MOFs. This allows systematic modification of pore environments without significantly altering variables such as pore size or shape, which could otherwise affect catalytic properties. Dong and coworkers applied this strategy to modify **Cr-MIL-101-NH<sub>2</sub>** to three distinct urea-based catalysts (**Figure 4.4A**).<sup>9</sup> Their study demonstrated that the catalytic performance in the Michael addition followed a trend: **Cr-MIL-101-R1**<**Cr-MIL-101-R2**<**Cr-MIL-101-R3** (**Figure 4.4B**). This increase in

activity was attributed to the enhanced hydrogen bond donation of the MOF catalysts, driven by increasing the electron-withdrawing capacity of the substituents attached to the urea groups.

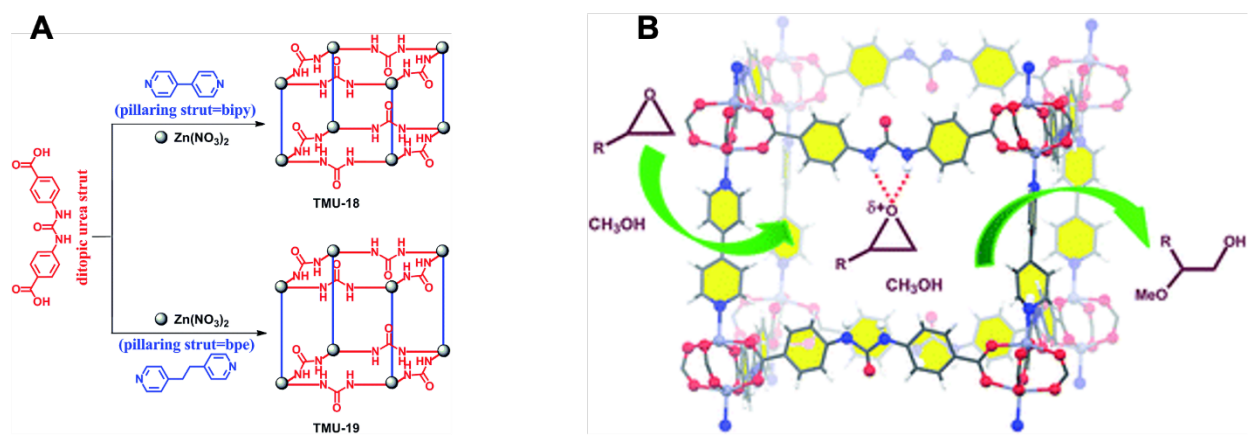


Figure 4.3. A: *De novo* synthesis of urea-based MOF catalyst. B: Application of the urea-based MOFs for methanolysis reaction. Adapted from REF<sup>6,8</sup>.

Regardless of which method is used to generate urea-based MOF catalysts, both strategies have tackled major challenges of homogenous catalysts, including self-quenching, functional group incompatibility, and difficulty in catalyst recovery and separation. Immobilization of the catalytic urea groups within the MOF pores ensures spatial separation and prevents self-quenching, while heterogenization facilitates easy catalyst separation and recyclability.<sup>8,10</sup>

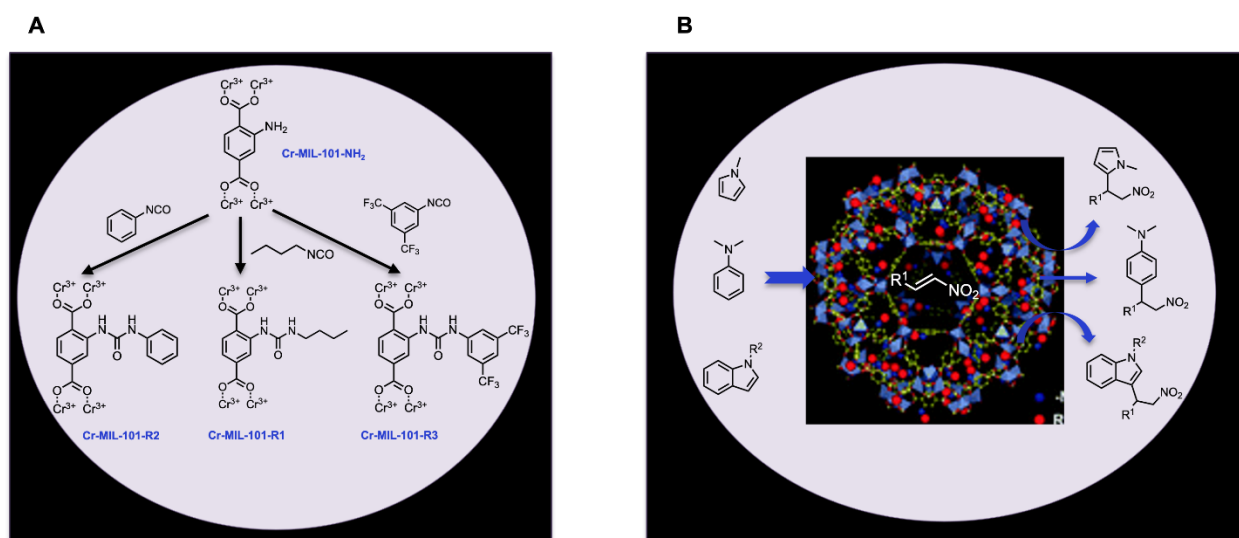


Figure 4.4. A: PSM of  $\text{Cr-MIL-101-NH}_2$  with isocyanates to  $\text{Cr-MIL-101-R1}$ ,  $\text{Cr-MIL-101-R2}$  and  $\text{Cr-MIL-101-R3}$ . B: The urea catalyst showed excellent catalytic activity over a broad scope of substrates. Adapted from REF<sup>9</sup>.

## 4.4. Bifunctional catalysts

For enhanced catalytic efficiency, multifunctional catalysts have significant potential. Their appeal lies in their ability to activate multiple substrates or stabilize transition-state molecules, a mechanism reminiscent of enzyme function. In enzymes, various functional groups surrounding the active site work together to activate, orient, or stabilize substrates, thereby improving efficiencies and selectivity in catalytic transformations. Multifunctional catalysts can be classified into several categories including bifunctional, cascade, double activation, and synergistic catalysts.<sup>11</sup>

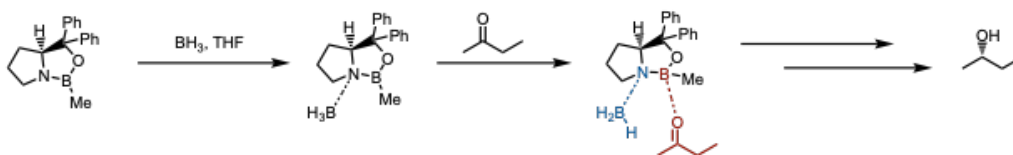


Figure 4.5. Bifunctional catalyst containing basic amine and Lewis acidic boron. Adapted from REF<sup>11</sup>.

One example is the Corey-Bakshi-Shibata catalyst, which operates as a bifunctional catalyst. It contains a basic amine, that activates the borane and a Lewis acidic boron, that activates the carbonyl. The proximity of these catalytic functionalities enables stereo control by precisely orienting substrates (**Figure 4.5**). However, a major drawback of bifunctional catalysts is the complexity of their synthesis. Even minor modifications to the catalyst require a complete resynthesis, making their development challenging. In contrast, synergistic catalysis involves two distinct catalysts working together in solution to activate both the electrophile and nucleophile, facilitating a single chemical transformation (**Figure 4.6**).<sup>12</sup>

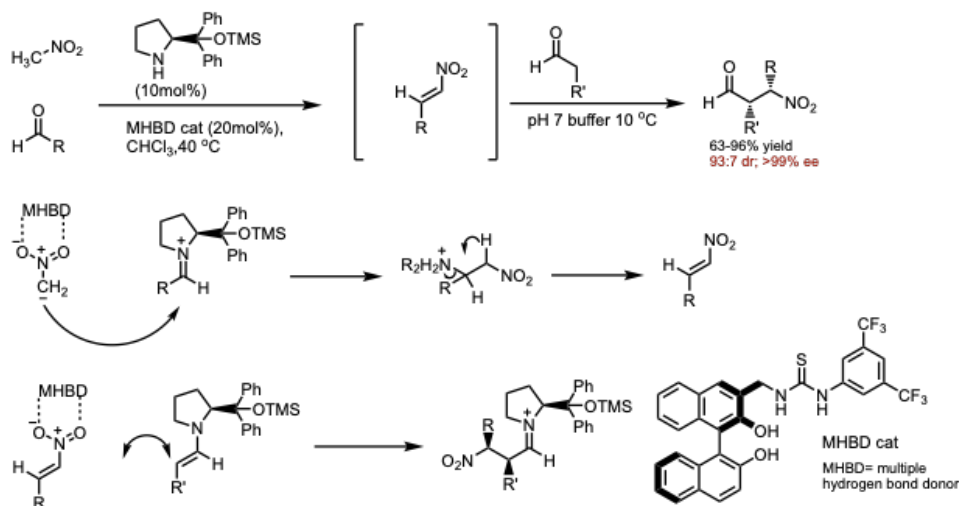


Figure 4.6. Enantioselective three-component reaction via synergistic hydrogen bond donation and enamine catalysis. Adapted from REF<sup>12</sup>.

However, synergist catalysts often suffer from catalyst deactivation if the catalytic components interact. Moreover, the mobility of the components relative to each other in solution limits enantioselectivity unless the individual catalysts are inherently stereoselective. To address these limitations, we propose designing a bifunctional urea-based MOF catalyst that combines the advantages of both synergistic catalysts and bifunctional catalysts while mitigating their drawbacks. Our MOF-based urea catalyst will offer (i) modular synthesis, (ii) improved efficiency, and (iii) improved selectivity.<sup>13–18</sup> Specifically, we aim to utilize a Zn pillared MOF, **KSU-1**, which consists of two functionalizable linkers, 2-aminobenzene 1,4-dicarboxylic acid (BDC-NH<sub>2</sub>) and hydroxyl-bearing linker *meso-α,β*-di(4-pyridyl) glycol (DPG) (**Figure 4.7**). This design enables the incorporation of the urea catalytic functionality via PSM of the amine functional group. This can then be followed by modular addition of additional functional groups through PSM of the hydroxyl group.

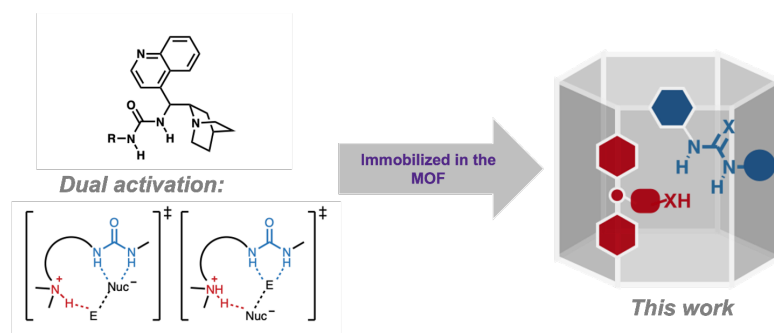


Figure 4.7. Cooperative catalysis in urea-based catalysts.

#### 4.5. Strategies to develop bifunctional urea-based MOF catalyst

**KSU-1**, a Zn-based pillared MOF composed of amine-bearing (BDC-NH<sub>2</sub>) and hydroxyl-bearing (DPG) linkers, serves as our modular platform for generating bifunctional catalysts. Its unit cell consists of two Zn metal atoms in a paddlewheel secondary building unit (SBU) coordinated to two BDC-NH<sub>2</sub> and one DPG to form a Kagome lattice. The MOF features triangular (1 nm) and hexagonal (1.7 nm) channels along the c-axis, with functional groups positioned within the hexagonal channels, ensuring sufficient space for reactant diffusion during PSM and catalysis. To achieve uniform bifunctionalization, each reaction step must proceed quantitatively before advancing to the next step. While previous studies from our group demonstrated the superior nucleophilicity of -NH<sub>2</sub>,<sup>19</sup> we recently discovered that when both the amine and hydroxyl functional groups are immobilized together in the **KSU-1**, the -OH preferentially reacts with linear

and or branched isocyanates.<sup>20</sup> Leveraging this reactivity, we synthesized multiple well-defined bifunctional urea-based MOF catalysts (**Figure 4.8**).

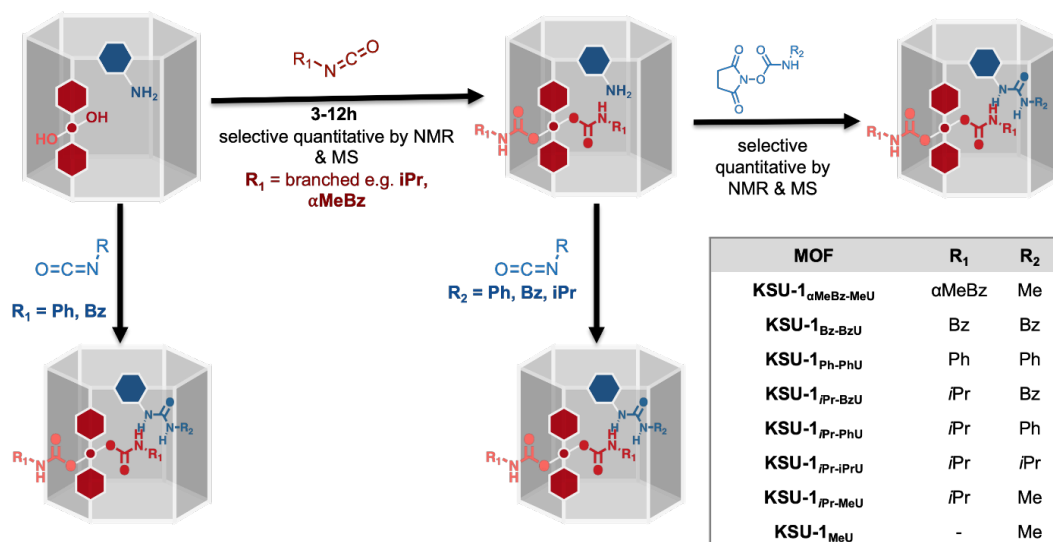


Figure 4.8. Facile post synthesis modulation of KSU-1 into several well-defined urea-based catalysts.

To synthesize **KSU-1**<sub>carbamate</sub>, we incubated **KSU-1** in a 0.2 M solution of the respective isocyanate in acetonitrile at 80 °C. **KSU-1** reacted with isopropyl-, R-methyl benzyl- and S-methyl benzyl-isocyanates to generate **KSU-1**<sub>iPr</sub>, **KSU-1**<sub>R-MeBz</sub> and **KSU-1**<sub>S-MeBz</sub> respectively (**Figure 4.9A**). Successful post synthetic reaction was confirmed by proton nuclear magnetic resonance (<sup>1</sup>H-NMR) spectroscopy of the digested MOF product in D<sub>2</sub>SO<sub>4</sub>/*d*<sub>6</sub>-DMSO (**Figure 4.9B**).

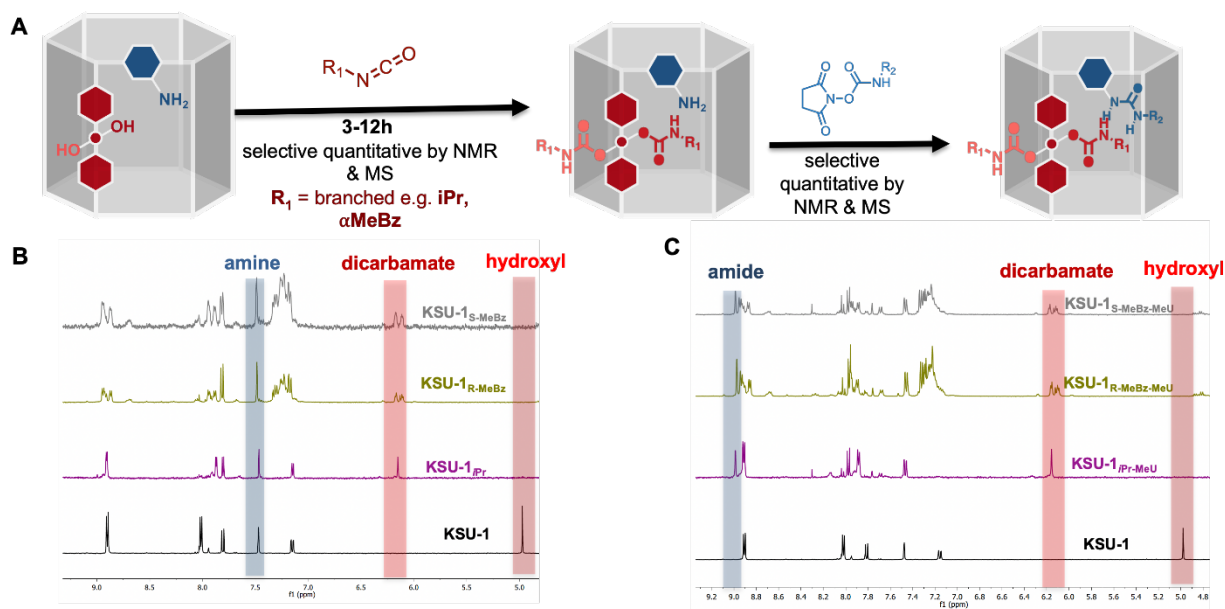


Figure 4.9. Schematic of synthesis of **KSU-1**<sub>carbamate-MeU</sub>. B: The corresponding <sup>1</sup>H-NMRs of the MOF-carbamate products. C: The corresponding <sup>1</sup>H-NMRs of the MOF-carbamate-MeU products digested in a solution of D<sub>2</sub>SO<sub>4</sub> in *d*<sub>6</sub>-DMSO.

To introduce the urea catalyst, **KSU-1<sub>iPr</sub>**, **KSU-1<sub>R-MeBz</sub>** and **KSU-1<sub>S-MeBz</sub>** carbamates were reacted with 2.0 M solution of N succinimidyl N methyl carbamate at 60 °C for 24 h, yielding bifunctionalized **KSU-1<sub>iPr-MeU</sub>**, **KSU-1<sub>R-MeBz-MeU</sub>** and **KSU-1<sub>S-MeBz-MeU</sub>** (**Figure 4.9C**). Successful post synthetic bifunctionalization of the reaction was confirmed by proton nuclear magnetic resonance (<sup>1</sup>H-NMR) spectroscopy of the MOF product digested in D<sub>2</sub>SO<sub>4</sub>/d<sub>6</sub>-DMSO (**Figure 4.9C**). Further characterization to confirm independent functionalization of the hydroxyl and amine was conducted using electrospray ionization mass spectrometry (HR-MS) on MOF samples digested with 1,4-diazabicyclo [2.2.2] octane (DABCO) (**Figure 4.26**).

To modulate the sterics and electronics of the pore environment while maintaining uniformity, **KSU-1<sub>iPr</sub>** was reacted with isopropyl, phenyl, and benzyl isocyanates, respectively (**Figure 4.10**). Notably, the second reaction step with isopropyl isocyanate proceeded more efficiently in CHCl<sub>3</sub> than acetonitrile, whereas acetonitrile was suitable for phenyl and benzyl isocyanates.

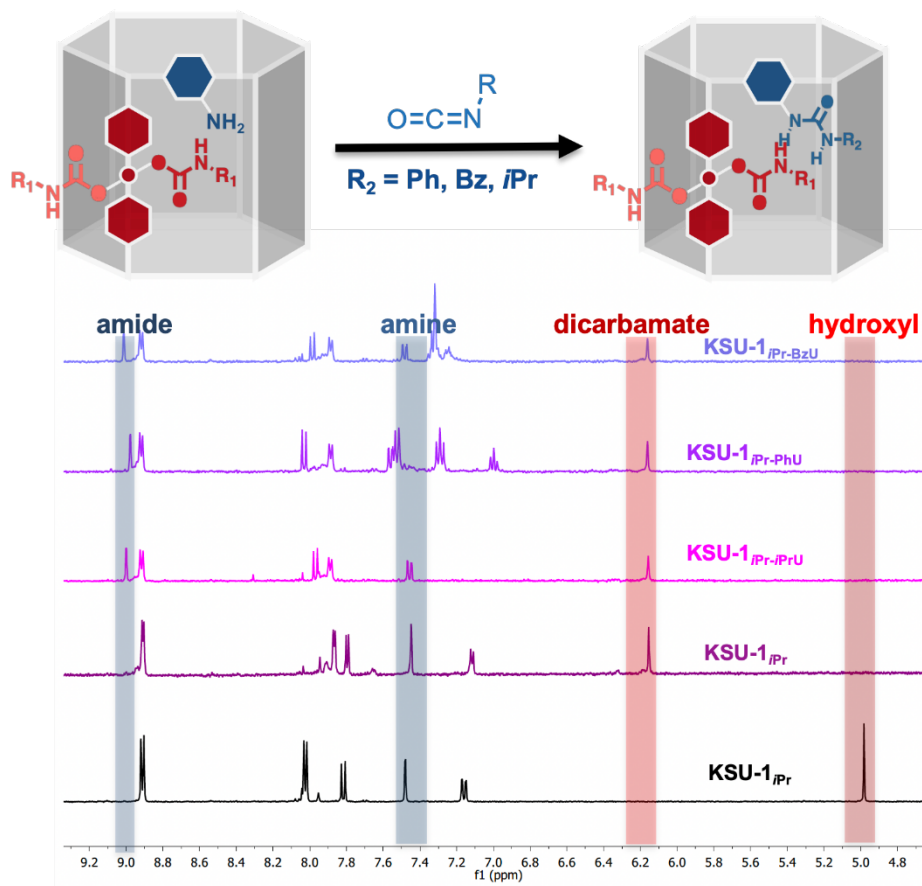


Figure 4.10. Synthesis and <sup>1</sup>H-NMR representation of **KSU-1<sub>iPr-iPr</sub>**, **KSU-1<sub>iPr-Ph</sub>** and **KSU-1<sub>iPr-Bz</sub>** from **KSU-1<sub>iPr</sub>**.



Another set of bifunctionalized catalysts was synthesized by incubating **KSU-1** in a 0.2 M solution of the respective isocyanate in acetonitrile at 80 °C. The reactions with phenyl, benzyl, R-methyl benzyl, and S-methyl benzyl isocyanates yielded **KSU-1<sub>Ph-Ph</sub>**, **KSU-1<sub>Bz-Bz</sub>**, **KSU-1<sub>R-MeBz-R-MeBz</sub>** and **KSU-1<sub>S-MeBz-S-MeBz</sub>**, respectively. Successful post synthetic modification was observed by proton nuclear resonance (<sup>1</sup>H-NMR) of the MOF products digested in D<sub>2</sub>SO<sub>4</sub>/d<sub>6</sub>-DMSO (**Figure 4.11**). Additionally, MOF catalysts version of **KSU-1<sub>R-MeBz-S-MeBz</sub>** and **KSU-1<sub>R-MeBz-S-MeBz</sub>** were synthesized by first modifying the hydroxyl groups of **KSU-1** with R-methyl benzyl and S-methyl benzyl isocyanates, respectively, followed by the functionalization of the amine. Electrospray ionization mass spectrometry (ESI-MS) was performed on all the bifunctionalized MOF catalysts. Powder X-ray diffraction (PXRD) confirmed that crystallinity was preserved even after complete bifunctionalization of **KSU-1**(**Figure 4.29**).

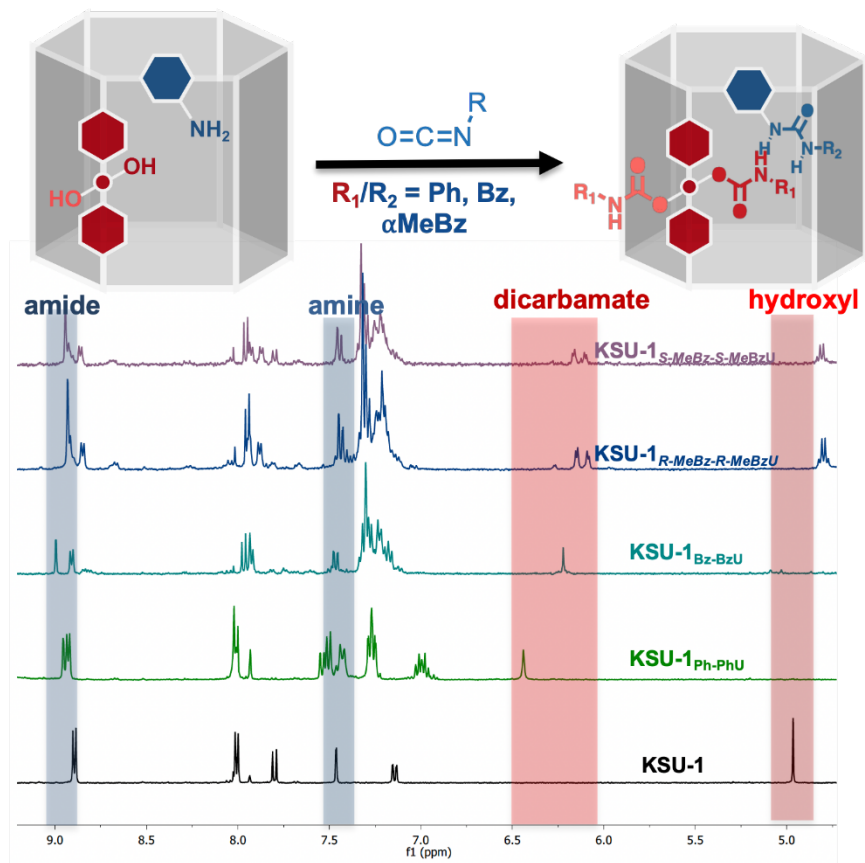


Figure 4.11. Synthesis and <sup>1</sup>H-NMR of uniformly bifunctionalized **KSU-1** urea-based catalyst using the same isocyanate.



## 4.6. The Henry Reaction

We chose to evaluate our urea-based catalyst using the Henry reaction between benzaldehyde and nitromethane. This reaction is commonly used to investigate the hydrogen bond donor ability of urea-based organocatalysts in the presence of organic bases such as *N,N*-diisopropylethylamine (DIPEA).<sup>21</sup> In the catalytic reaction we expected benzaldehyde to be activated via hydrogen bonding to make the carbonyl carbon more electrophilic while the nitromethane was also activated by urea to promote the abstraction of the proton by the base to form the enol (**Figure 4.12**). In addition, we expected to observe enantioselectivity after performing catalysis with our catalyst functionalized with chiral substituents on the hydroxyl.

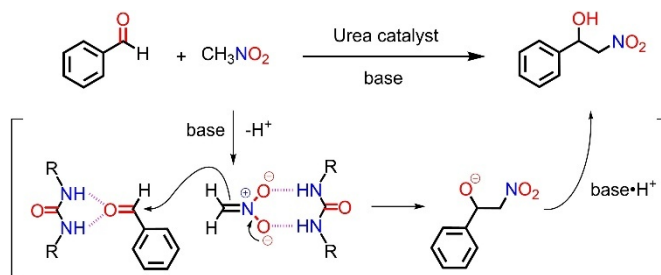


Figure 4.12. Henry reaction mechanism catalyzed by urea catalysts. Reproduced from REF<sup>22</sup>.

## 4.7. Catalysis experiments for Henry reaction

In the initial trial, 10 mol% of the MOF catalyst was added to a vial containing benzaldehyde, nitromethane, diisopropylethylamine (DIPEA), and THF solvent. The reaction was shaken at room temperature and aliquots were collected at the 3 h mark, diluted in CDCl<sub>3</sub>, and analyzed using <sup>1</sup>H-NMR to determine conversions (**Figure 4.13B**). In the control experiment, which contained DIPEA and no catalyst, a conversion of 4.5% was observed (**Table 4.1**; Entry 1). When **KSU-1** and **KSU-1<sub>MeU</sub>** were used, the conversions were 4% and 20%, respectively (**Table 4.1**; Entries 2 and 3). We attribute the increase in conversion with **KSU-1<sub>MeU</sub>** to the strong dual hydrogen bond donor ability of methyl urea compared to the amine in **KSU-1**. To investigate whether the chiral groups grafted to the hydroxyls could work cooperatively with the urea group, we performed catalysis using **KSU-1<sub>R-MeBz-MeU</sub>** and **KSU-1<sub>S-MeBz-MeU</sub>**. We anticipated that the chiral catalyst would exhibit selectivity between the enantiomers of the product. However, no conversion was observed after 3 h (**Table 4.1**; Entries 4 and 5). Extending the reaction time to 6 h resulted in very low conversion of 3.5% and 2.5% for **KSU-1<sub>R-MeBz-MeU</sub>** and **KSU-1<sub>S-MeBz-MeU</sub>** respectively. We believe this reduction in conversion is due to the decrease in pore size upon bifunctionalization

of the MOF catalyst (**Figure 4.30**) which likely limits the accessibility of the urea active site. This also meant the reaction is potentially happening on the surface with DIPEA catalyzing the reaction. After performing enantioselective separation with SFC, we observed no ee. We conducted another control experiment using **KSU-1** but without DIPEA, and no conversion was observed within 24 h. This confirms that the reaction does not proceed without a base, consistent with most urea-based catalysts reported in the literature.<sup>23–25</sup> We are currently exploring strategies to functionalize the MOF pores with a base, thereby promoting the reaction within the framework. Since the reaction only proceeds in the presence of a base, we anticipate that anchoring the base to the MOF will drive the reaction to occur in the pores. This should increase interactions with the chiral functionality, compared to having the base in solution (e.g., DIPEA).

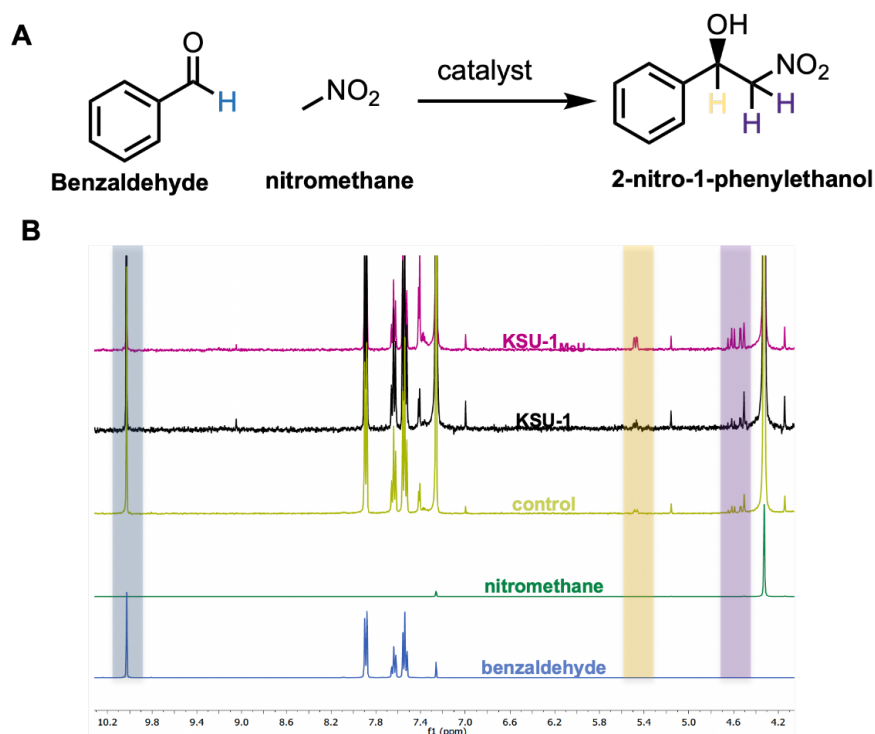


Figure 4.13. A schematic representation of the reaction between benzaldehyde and nitromethane to form 2-nitro-1-phenylethanol B: Representative <sup>1</sup>H-NMR for the reaction of benzaldehyde and nitromethane in CHCl<sub>3</sub> analyzed after 3 h using 10 mol % catalyst. The control experiment contains DIPEA without any catalyst.

Table 4.1. Conversions observed for Henry reaction at different times.

| Entry | Catalyst                          | % Conversion |         |
|-------|-----------------------------------|--------------|---------|
|       |                                   | 3 h          | 6 h     |
| 1     | no catalyst                       | 4.5 (2)      | 8 (0)   |
| 2     | <b>KSU-1</b>                      | 4 (0)        | 11 (0)  |
| 3     | <b>KSU-1<sub>MeU</sub></b>        | 20 (0)       | 28 (8)  |
| 4     | <b>KSU-1<sub>R-MeBz-MeU</sub></b> | 0 (0)        | 3.5 (1) |
| 5     | <b>KSU-1<sub>S-MeBz-MeU</sub></b> | 0 (0)        | 2.5 (1) |

0.5 mmol benzaldehyde, 5.0 mmol nitromethane, 23 °C; 10 mol% catalyst, 0.05 mmol DIPEA, 100  $\mu$ L THF.

While nitropropane is less reactive than nitromethane due to steric hinderance,<sup>26</sup> we chose to test it for catalysis because it can produce diastereomers that are easily detectable by <sup>1</sup>H-NMR (**Figure 4.14**). Using the same conditions as for nitromethane, we stopped the reaction after 24 h and the conversions and diastereomeric ratios (d.r.s) were determined by <sup>1</sup>H-NMR (**Figure 4.14B**).

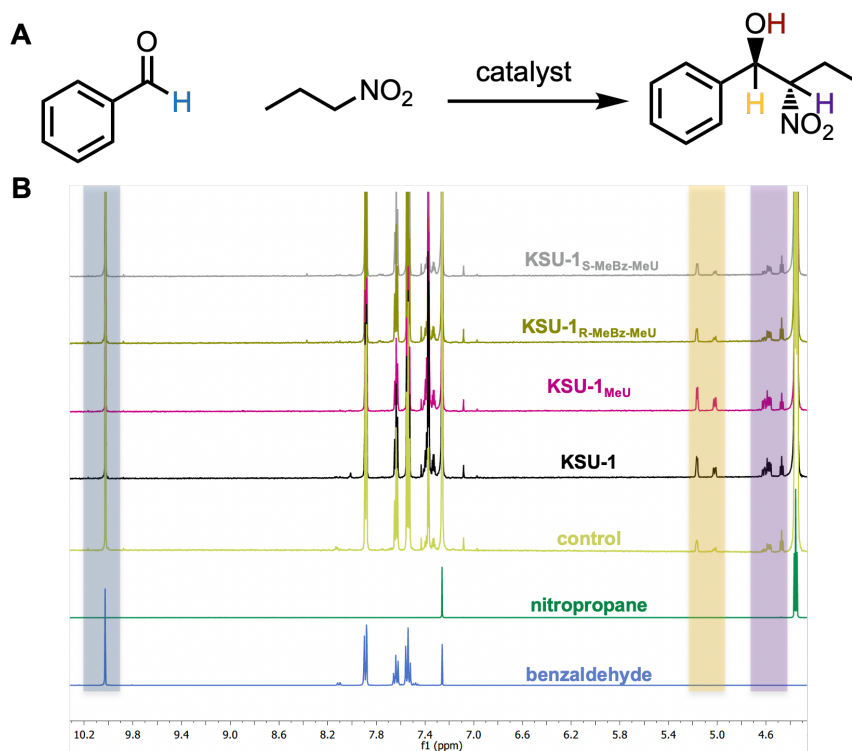


Figure 4.14. A schematic representation of the reaction between benzaldehyde and nitropropane to form 2-nitro-1-phenylbutanol B: Representative <sup>1</sup>H-NMR for the reaction of benzaldehyde and nitromethane in

CHCl<sub>3</sub> analyzed after 3 h using 10 mol % catalyst. The control experiment contains DIPEA without any catalyst.

The conversion without catalyst was 8%, with (d.r.) of 67:33 (**Table 4.2**; Entry 2). When **KSU-1** was used the yield increased to 31% with dr of 88/12% (**Table 4.2**; Entry 2), likely due to confinement effects. Using **KSU-1**<sub>MeU</sub>, the yield increased slightly to 36 % with dr of 52/48 % (**Table 4.2**; Entry 3) possibly due to more reaction happening on the surface as the pore size decreases upon functionalization. Similarly, the conversion decreased to 17% and 12% with dr of 53/47% and 58/42% for **KSU-1**<sub>R-MeBz-MeU</sub> and **KSU-1**<sub>S-MeBz-MeU</sub> respectively (**Table 4.2**; Entries 4 and 5). This decrease could be attributed to limited access to the catalytic site due to reduced pore sizes. While we attempted to troubleshoot these problems, we decided to explore the Friedel Crafts alkylation reaction with same system.

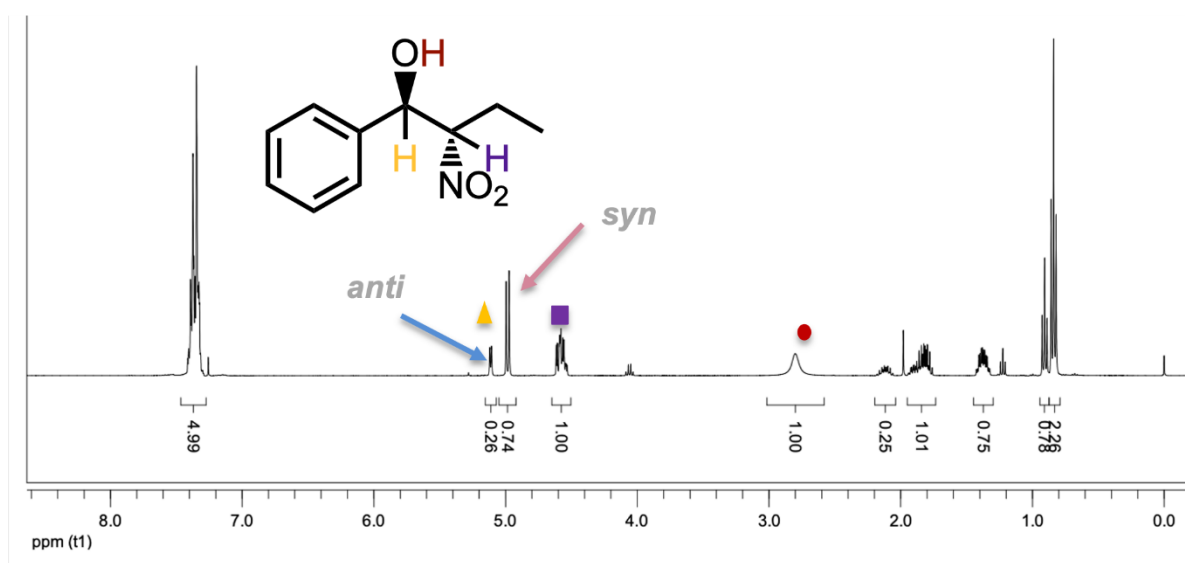


Figure 4.15. <sup>1</sup>H-NMR for 2-Nitro-1-phenylbutan-1-ol. Adapted from REF<sup>27</sup>.

Table 4.2. Conversion and dr ratios for the reaction of nitropropane and benzaldehyde.

| Entry | Catalyst                           | % Conversion | anti/ syn (%) |
|-------|------------------------------------|--------------|---------------|
| 1     | no catalyst                        | 8            | 67/33         |
| 2     | <b>KSU-1</b>                       | 31           | 88/12         |
| 3     | <b>KSU-1</b> <sub>MeU</sub>        | 36           | 52/48         |
| 4     | <b>KSU-1</b> <sub>R-MeBz-MeU</sub> | 17           | 53/47         |
| 5     | <b>KSU-1</b> <sub>S-MeBz-MeU</sub> | 12           | 58/42         |

0.5 mmol benzaldehyde, 5.0 mmol nitropropane, 23 °C; 10 mol% catalyst, 0.05 mmol DIPEA, 100 μL THF.

## 4.8. Friedel Crafts Alkylation reaction.

Friedel Crafts alkylation is an important C-C bond-formation reaction widely used in organic chemistry, particularly in fine chemical synthesis.<sup>28,29</sup> A variety of nucleophiles, including arene derivative substituted anilines, phenols, naphthols, and heteroarenes such as indole, dihydroindole, and pyrrole have been used in the Friedel Crafts reaction. On the other hand, unsaturated electrophiles such as enals, enones, chalcones, nitroalkenes etc., have been extensively applied for the Friedel crafts alkylation. Most reactions in this area have focused on relatively more reactive derivatives, such as indole or pyrrole. To demonstrate the catalytic properties of our bifunctional MOF-based urea catalysts, we chose to explore the Friedel Crafts alkylation reaction between nitrostyrene and 3-methoxydimethyl aniline (**Figure 4.16**). The major reason we chose this reaction is that it does not proceed without a catalyst; thus, background reactions are eliminated.

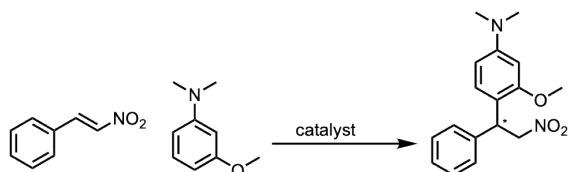


Figure 4.16. Reaction between nitrostyrene and 3 methoxydimethyl aniline.

This reaction has been traditionally catalyzed by metals acting as Lewis acid-based catalysts e.g. Cu, Zn, Yb(OTf)<sub>3</sub>·3H<sub>2</sub>O, Sc(OTf)<sub>3</sub> or Bi(OTf)<sub>3</sub> by coordinating with the lone pairs of Lewis bases e.g. the nitro group in nitrostyrene thus activating the electrophile. However, there has been a shift towards metal-free organocatalysts, which utilize hydrogen bonding donor groups such as ureas, thioureas, silanediol, etc., to activate electrophiles, thus offering sustainable, milder and more efficient catalytic approaches. The most important of these organocatalysts are the ones that are capable of dual activation, thus improving efficiency or selectivity. However, they still suffer from difficult synthesis procedures, catalyst deactivation, and or difficulty in separating them from reaction mixtures. We believe our bifunctional urea-based MOF catalyst can address these problems (**Figure 4.17**).

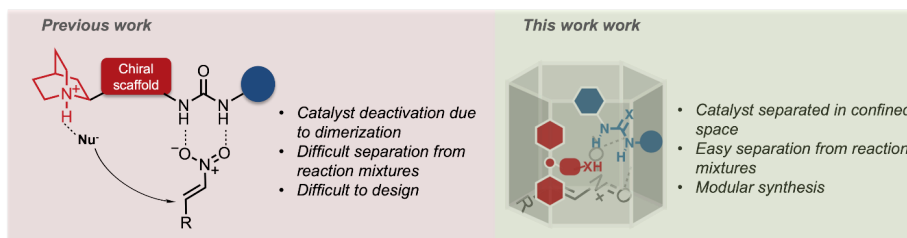


Figure 4.17. Activation of nitrostyrene by dual hydrogen bonding catalysis.

## 4.10. Kinetic studies catalysis experiments

To evaluate the catalytic behavior of our urea-based MOF catalysts, we selected the Friedel crafts alkylation between nitrostyrene and 3-methoxyl dimethyl aniline to form 3-methoxy-*N,N*-dimethyl-4-(2-nitro-1-phenylethyl)aniline (DMNPA) (**Figure 4.18A**). In the initial trial, 10 mol % of the MOF catalyst was added to a vial containing nitrostyrene and 3-methoxyl dimethyl aniline,  $\text{CHCl}_3$  solvent, and mesitylene internal standard. The reaction was shaken at 60 °C. Aliquots were collected at 24 h, diluted in  $\text{CDCl}_3$ , and analyzed using  $^1\text{H}$ -NMR to determine conversion rates (**Figure 4.18B**).

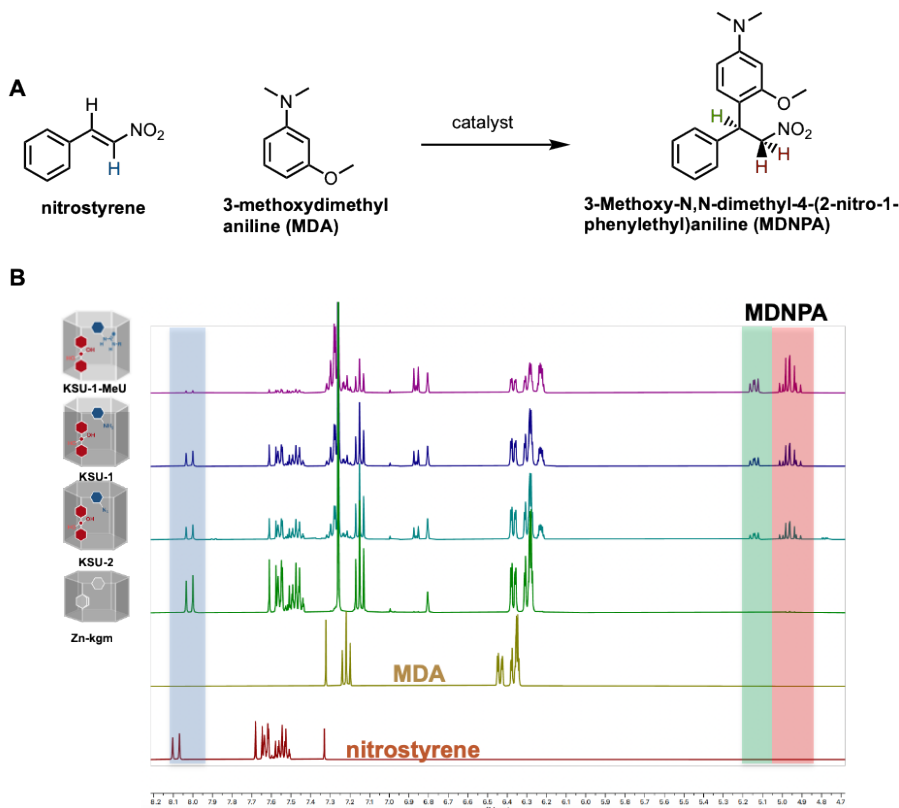


Figure 4.18. A schematic representation of the reaction between nitrostyrene and 3-methoxyl dimethyl aniline to form MDNPA B: Representative  $^1\text{H}$ -NMR for the reaction of nitrostyrene and 3-methoxy dimethyl aniline in  $\text{CHCl}_3$  using mesitylene as internal standard analyzed after 24 h using 10 mol % catalyst.

Control experiments confirmed that the reaction does not proceed in the absence of a catalyst, eliminating the possibility of a background reaction. When **Zn-kgm**, a MOF with a topology similar to **KSU-1** but lacking pore decoration with functional groups, was used, we observed 0 % conversion. This result confirms that Zn nodes are fully saturated and do not participate in catalyzing the reaction as Lewis acids. When **KSU-1** was used, a conversion of ~55 % was observed, which was expected, as the amine group is capable of hydrogen bonding, thereby activating nitrostyrene and accelerating the reaction. Interestingly, **KSU-2**, a MOF containing both azide and hydroxyl functionality, performed equally as well as **KSU-1**. Although the exact mechanism remains unclear, we think the azide may be participating in the reaction catalysis somehow since **KSU-3**, a MOF containing hydroxyl functional groups immobilized in the MOF alone give lower conversions. Notably, **KSU-1<sub>MeU</sub>** catalyzed the reaction to ~100 % conversion, demonstrating the efficiency of dual hydrogen bond donation in catalysis. The conversion values we obtained using internal standards were consistent with those determined by comparing the integrations of the disappearing nitrostyrene proton vs the appearing MDNPA protons in the <sup>1</sup>H-NMR spectra. As a result, we decided to discontinue the use of the internal standard.

Given the high efficiency of **KSU-1<sub>MeU</sub>** in catalyzing the reaction, we sought to explore the effect of secondary functionality on the reaction kinetics between nitrostyrene and 3-methoxy dimethyl aniline. Our objective was to investigate how each additional functional group influences catalytic activity within the confined spaces of the MOF. Following the procedures outlined above, we synthesized **KSU-1<sub>iPr-MeU</sub>**, **KSU-1<sub>iPr-iPrU</sub>**, **KSU-1<sub>iPr-PhU</sub>**, **KSU-1<sub>iPr-BzU</sub>**, **KSU-1<sub>Ph-PhU</sub>**, **KSU-1<sub>Bz-BzU</sub>**. For our control experiments, we selected **Zn-kgm**, **KSU-3**, and **KSU-1000** (Figure 4.19). We replaced **KSU-2** with **KSU-3** as a suitable control to assess the effect of the hydroxyl functional group in the catalysis. **KSU-3** is a *kgm* MOF that has benzene dicarboxylic acid (BDC) and *meso*- $\alpha,\beta$ -di(4-pyridyl) glycol (DPG) as organic linkers, while **KSU-1000** is made of 2-aminobenzene-1,4-dicarboxylic acid (BDC-NH<sub>2</sub>) and 4,4 bipyridine.

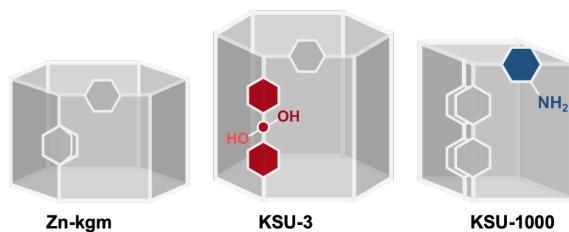


Figure 4.19. Schematic representation of **Zn-kgm**, **KSU-3**, and **KSU-1000** MOFs used as controls in the catalysis.

For the remaining experiments, we reduced the catalyst loading to 5 mol % since our initial results demonstrated good catalytic performance with **KSU-1<sub>MeU</sub>** at 10 mol%. Conversions were measured after 6 hours. The control MOF catalysts **Zn-kgm**, **KSU-1000**, **KSU-3**, and **KSU-1** gave conversions of 0%, 5%, 6%, and 14%, respectively. As expected, **Zn-kgm** had no conversion since it lacks functional groups. **KSU-3** had slightly higher conversion than **KSU-1000** despite the fact amine is better at hydrogen bonding than hydroxyl. We attribute this to the larger pore size of **KSU-3** (1.7 nm) compared to **KSU-1000** (0.9 nm), which likely facilitates better substrate diffusion and slightly enhances the reaction rate. **KSU-1** exhibited higher conversion, likely due to the combined catalytic effect of both amine and hydroxyl functionalities. **KSU-1<sub>MeU</sub>** gave a 25% conversion, demonstrating the efficiency of two-point H-bond activation. The functionalized MOF catalysts **KSU-1<sub>iPr-MeU</sub>**, **KSU-1<sub>iPr-iPrU</sub>**, **KSU-1<sub>iPr-PhU</sub>**, **KSU-1<sub>iPr-BzU</sub>**, **KSU-1<sub>Ph-PhU</sub>**, **KSU-1<sub>Bz-BzU</sub>** exhibited average conversion of 24%, 29%, 35%, 54%, 47% and 63% respectively (**Figure 4.20**). The values used to calculate average conversion were selected from a pool of data, ensuring consistency by only including closely matched results. The drop in conversion from **KSU-1<sub>MeU</sub>** to **KSU-1<sub>iPr-MeU</sub>** could be attributed to the substitution of a catalytic hydroxyl group with a non-catalytic carbamate.

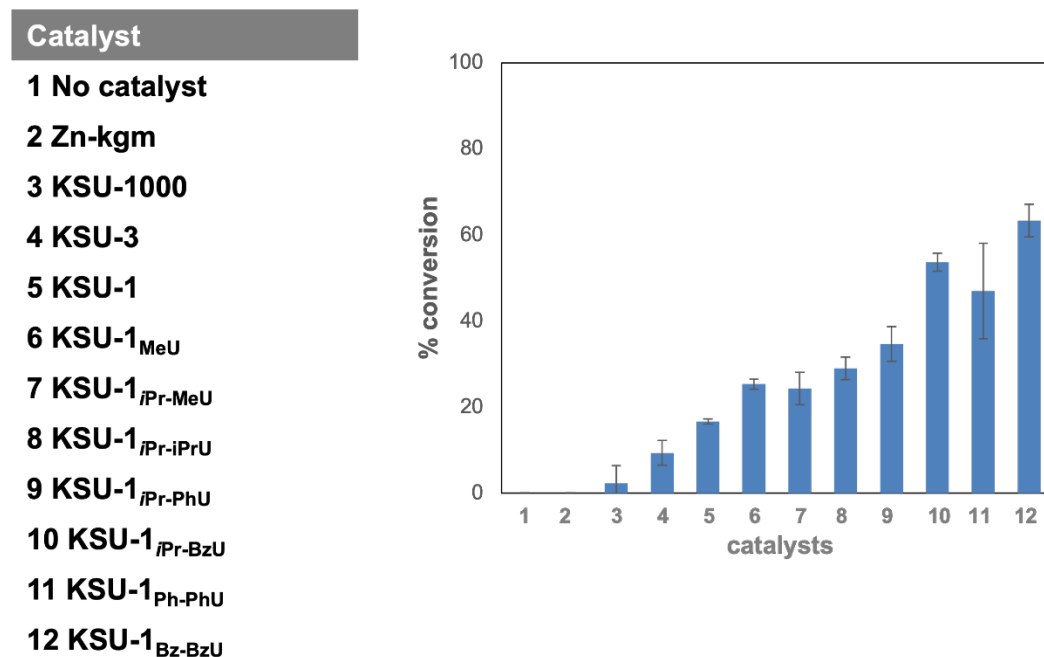


Figure 4.20. Graphical representation of the selected Friedel crafts alkylation catalysis results using different bifunctional catalysts at 5 mol% catalyst loading.



We observed that conversion generally increased with bulkier or more flexible substituents, suggesting that the reaction predominantly occurs on the MOF surface where substrate accessibility is improved. Conversely, more rigid aryl substituents hindered substrate interaction, leading to lower conversions. Notably, **KSU-1<sub>MeBz-MeU</sub>** derivatives consistently reached 100% conversion within 6 hours, confirming that surface reactivity drives the catalytic performance. To gain a clearer understanding of the overall data distribution, a box plot was plotted (**Figure 4.21**). As shown in the plot, the observed range of values for each catalyst is relatively large, making it difficult to make a definitive trend in the catalyst activity.

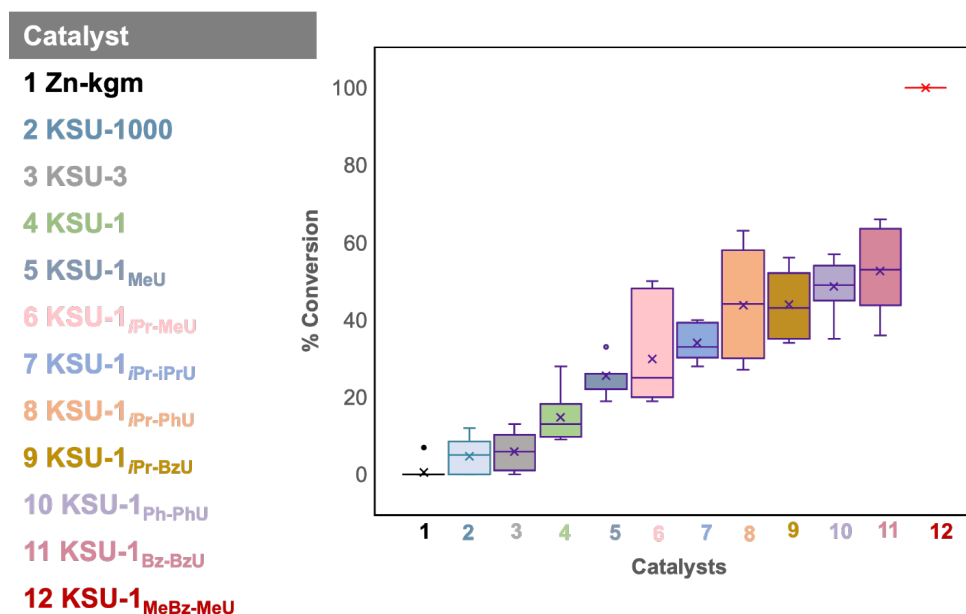


Figure 4.21. Box plot representation of the selected Friedel crafts alkylation catalysis results using different bifunctional catalysts at 5 mol% catalyst loading.

At one point, we hypothesized that the difference in catalyst particle sizes might be influencing the reaction outcomes. To address this, we ground all the MOF catalysts before catalysis, however, this did not result in any significant changes in performance. Additionally, thermogravimetric analysis (TGA) revealed a reduction in pore-accessible volume due to bifunctionalization of our catalyst (**Figure 4.30**). This observation led us to speculate that the gradual increase in the catalyst's performance was likely due to reactions occurring on the surface of the MOF rather than within confined pores. Given these challenges, we decided to shift our focus toward asymmetric catalysis, as this approach prioritizes selectivity over reaction rate.

## 4.11. Attempts for asymmetric catalysis

Apart from modifying the steric and electronic environments in the urea-based **KSU-1** catalysts to influence reaction rates, we were also interested in investigating the effect of incorporating chiral groups to enhance the enantioselectivity of the catalysts. Literature reports have demonstrated numerous cases where enantioselectivity was improved by coordinating the active catalytic metal with chiral ligands or encapsulating it within chiral supramolecular cavities.<sup>5,30</sup> Following this approach, we hypothesized that functionalizing the hydroxyl of **KSU-1<sub>MeU</sub>** with (R)-(+)- $\alpha$ -methyl benzyl isocyanate and (S)-(-)- $\alpha$ -methyl benzyl isocyanate to yield **KSU-1<sub>R-MeBz-MeU</sub>** and **KSU-1<sub>S-MeBz-MeU</sub>**, respectively, would allow us to modulate enantioselectivity.

To begin, we conducted an experiment using  $\text{ZnCl}_2$  as a catalyst, following the procedure outlined in the experimental section. The product was characterized by dissolving it in  $\text{CDCl}_3$  and analyzing it using  $^1\text{H-NMR}$ . Additionally, GC-MS analysis was performed to confirm the purity of MDNPA (**Figure 4.24**). Supercritical fluid chromatography (SFC) was employed (**Figure 4.22**) to determine the enantiomeric composition, which confirmed the 1:1 ratio. Next, we carried out Friedel Crafts alkylation using our chiral catalysts **KSU-1<sub>R-MeBz-MeU</sub>** and **KSU-1<sub>S-MeBz-MeU</sub>**. The conversion rates were assessed by comparing the integrations of disappearing protons of nitrostyrene with the appearance of new MDNPA protons using  $^1\text{H-NMR}$  spectra. To obtain a purified sample, 10  $\mu\text{L}$  from the reaction mixture, diluted in isopropyl alcohol, was loaded onto a TLC plate and placed in a developing chamber for approximately 30 minutes. The product was separated from the starting materials using a 1:4 EtOAc: hexane solvent mixture. The isolated product spot was scrapped off and filtered for SFC analysis.

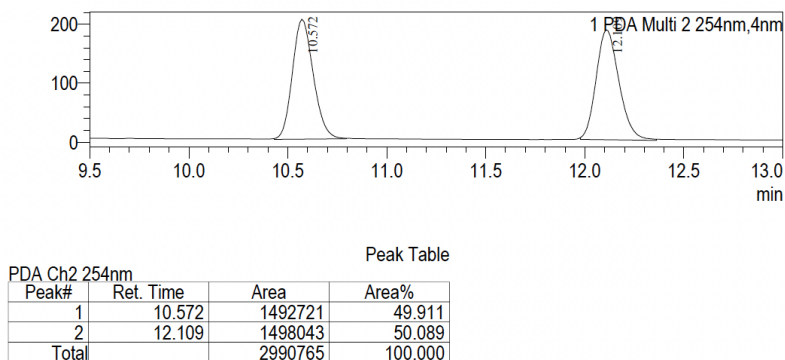


Figure 4.22. SFC spectra for the elution of racemic mixture of (DMNPA).

When **KSU-1<sub>R-MeBz-MeU</sub>** and **KSU-1<sub>S-MeBz-MeU</sub>** were used, higher conversions were observed compared to **KSU-1<sub>MeU</sub>** (**Table 4.3**; Entries 1- 4). However, no enantiomeric excess (ee) was detected in the SFC analysis. Since reaction conditions such as temperature are known to affect enantioselectivities,<sup>31,32</sup> we decided to lower the reaction temperature. Under these conditions, the reaction rate significantly dropped, but no improvement in enantioselectivity was observed (**Table 4.3**; Entries 5 & 6). We then attempted to functionalize the hydroxyl with S-(-)-acetoxy succinic anhydride to synthesize **KSU-1<sub>S-acetoxy-MeU</sub>**, hoping that hydrogen bonding with the carboxylic group would enforce enantioselectivity (**Table 4.3**; Entry 7). However, no ee was observed. Similarly, using ethanol as a solvent – chosen for its hydrogen bonding capability – led to an increase to 9 % conversion, but still without any enantioselectivity (**Table 4.3**; Entry 8). This could be due to ethanol catalyzing the reaction itself through nitrostyrene activation. Speculating that there may be weak interactions between the reactants and the carbamates decorating the DPG ligand, we functionalized the amine with (R)-(-)- $\alpha$ -methylbenzyl isocyanate and (S)-(-)- $\alpha$ -methylbenzyl isocyanate to make **KSU-1<sub>R-MeBz-R-MeBzU</sub>** and **KSU-1<sub>S-MeBz-S-MeBzU</sub>** respectively. We hope that such interactions with the auxiliary chiral functionality would contribute to stereoselectivity, however, no enantioselectivity was observed at room temperature (**Table 4.3**; Entries 9 & 10).

As highlighted in the kinetics experiments, catalysis likely occurs on the surface of the MOF catalysts. We realized that this surface reactivity might be preventing enantioselectivity, as achieving enantioselectivity requires the reaction to take place within the confined chiral MOF catalyst pores. To address this, we attempted to manipulate solvent miscibility to drive the reaction onto the MOF pores.<sup>33</sup> The reactants were dissolved in CH<sub>3</sub>CN and mixed with hexane. Since hexane is nonpolar it would occupy the surface and inhibit surface reactions (**Table 4.3**; Entries 11 & 12). However, no enantioselectivity was observed.

Table 4.3. The reaction conditions tried for bifunctional urea-chiral functional MOF catalyst.

|    | Solvent                       | Cat               |                        | Temp.<br>(°C) | Time<br>(h) | Conversion<br>(%) | ee |
|----|-------------------------------|-------------------|------------------------|---------------|-------------|-------------------|----|
|    |                               | Urea              | Carbamate              |               |             |                   |    |
| 1  | CHCl <sub>3</sub>             | Me                | R- $\alpha$ -MeBz      | 60            | 3           | 91                | 0  |
| 2  | CHCl <sub>3</sub>             | Me                | S- $\alpha$ -MeBz      | 60            | 3           | 75                | 0  |
| 3  | CHCl <sub>3</sub>             | Me                | R- $\alpha$ -MeBz      | 60            | 6           | 100               | 0  |
| 4  | CHCl <sub>3</sub>             | Me                | S- $\alpha$ -MeBz      | 60            | 6           | 100               | 0  |
| 5  | CHCl <sub>3</sub>             | Me                | R- $\alpha$ -MeBz      | rt            | 24          | 1                 | 0  |
| 6  | CHCl <sub>3</sub>             | Me                | S- $\alpha$ -MeBz      | rt            | 24          | 1                 | 0  |
| 7  | CHCl <sub>3</sub>             | Me                | S-acetoxysuccinic acid | 60            | 24          | 3                 | 0  |
| 8  | EtOH                          | Me                | R- $\alpha$ -MeBz      | rt            | 12          | 9                 | 0  |
| 9  | CHCl <sub>3</sub>             | R- $\alpha$ -MeBz | R- $\alpha$ -MeBz      | rt            | 12          | 8                 | 0  |
| 10 | CHCl <sub>3</sub>             | S- $\alpha$ -MeBz | S- $\alpha$ -MeBz      | rt            | 12          | 13                | 0  |
| 11 | Hexane/<br>CH <sub>3</sub> CN | R- $\alpha$ -MeBz | R- $\alpha$ -MeBz      | rt            | 12          | 6                 | 0  |
| 12 | Hexane/<br>CH <sub>3</sub> CN | S- $\alpha$ -MeBz | S- $\alpha$ -MeBz      | rt            | 12          | 3                 | 0  |

An alternative approach to ensure the reaction occurs within the confined MOF pores was to surface functionalize our chiral catalyst using hexanoic anhydride. We hypothesized that covering the surface with non-catalytic alkyl amide would prevent the reaction from happening on the surface thereby forcing the reaction to take place within the confined space. Catalysts surface functionalized with hexanoic anhydride were designated ‘sur-hex’ in their name. As expected, we observed a decrease in rate (**Table 4.4**; Entries 1 & 2). In our initial trial, we observed enantioselectivity of +9 % ee and -7 % ee with **KSU-1<sub>sur-hex-R-MeBz-MeU</sub>** and **KSU-1<sub>sur-hex-S-MeBz-MeU</sub>** catalyst, respectively, after 24 h at 60 °C (**Figure 4.23**). Given the slow reaction rates, we extended the reaction time to 48 h but observed a decrease in the enantioselectivity to 5 % for both catalysts (**Table 4.4**; Entries 3 & 4). Multiple repeated trials failed to reproduce enantioselectivity (**Table 4.7**). Upon careful analysis of our experiment in which we had observed enantioselectivity, we

detected extra peaks corresponding to 2-propanol in the catalysts (**Figure 4.25**). This led us to hypothesize that 2-propanol might have contributed to the selectivity by catalyzing through hydrogen bonding. To test this, we conducted an experiment in which we spiked the reaction with 5  $\mu\text{L}$  of  $\text{H}_2\text{O}$  or 2-propanol (**Table 4.4**; Entries 5-8). While we were able to achieve enantioselectivity under these conditions, subsequent experiments failed to reproduce the result consistently. We are currently investigating the validity of the enantioselectivity values obtained and exploring the potential reaction mechanism responsible for these observations.

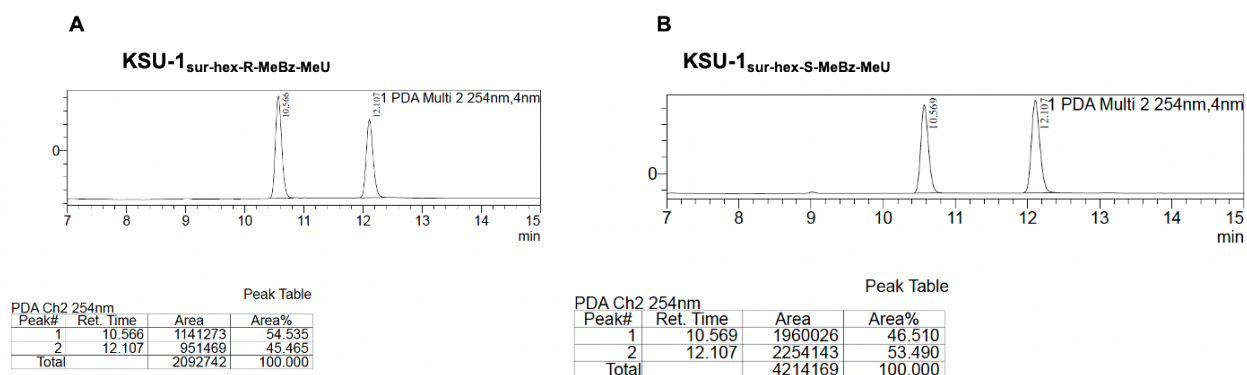


Figure 4.23. Enantioselectivity  $\sim 9\%$  observed when **KSU-1<sub>sur-hex-R-MeBz-MeU</sub>** reversal  $\sim 7\%$  when **KSU-1<sub>sur-hex-S-MeBz-MeU</sub>** was used.

Table 4.4. Reaction conditions tried for surface functionalized urea-chiral catalyst.

| Entry | Solvent                                                       | Cat  |                   | Temperature (°C) | Time (h) | Conversion % | % ee     |
|-------|---------------------------------------------------------------|------|-------------------|------------------|----------|--------------|----------|
|       |                                                               | Urea | Carbamate         |                  |          |              |          |
| 1     | $\text{CHCl}_3$                                               | Me   | R- $\alpha$ -MeBz | 60               | 24       | 16           | 9        |
| 2     | $\text{CHCl}_3$                                               | Me   | S- $\alpha$ -MeBz | 60               | 24       | 17           | 7        |
| 3     | $\text{CHCl}_3$                                               | Me   | R- $\alpha$ -MeBz | 60               | 48       | 34           | 5        |
| 4     | $\text{CHCl}_3$                                               | Me   | S- $\alpha$ -MeBz | 60               | 48       | 46           | 5        |
| 5     | Anh $\text{CHCl}_3$<br>+ 5 $\mu\text{L}$ $\text{H}_2\text{O}$ | Me   | R- $\alpha$ -MeBz | 60               | 24       | 31           | 4        |
| 6     | Anh $\text{CHCl}_3$<br>+ 5 $\mu\text{L}$ $\text{H}_2\text{O}$ | Me   | S- $\alpha$ -MeBz | 60               | 24       | 17           | 9        |
| 7     | Anh $\text{CHCl}_3$<br>+ 5 $\mu\text{L}$ IPA                  | Me   | R- $\alpha$ -MeBz | 60               | 24       | 17           | $\sim 3$ |
| 8     | Anh $\text{CHCl}_3$<br>+ 5 $\mu\text{L}$ IPA                  | Me   | S- $\alpha$ -MeBz | 60               | 24       | 24           | $\sim 3$ |
| 9     | Anh $\text{CHCl}_3$<br>+ 5 $\mu\text{L}$ $\text{H}_2\text{O}$ | Me   | R- $\alpha$ -MeBz | 60               | 24       | 31           | $\sim 3$ |

## 4.12. Conclusion

In summary, we have successfully demonstrated the use of covalent post synthesis modification strategies as a facial method to develop a myriad of well-defined urea-based catalytic daughter MOFs. Our first catalytic study shows that catalysis is mostly happening on the surface of MOF. We have studied the effect of changing steric and electronic in the MOF pores. However, our results were not conclusive as they are not consistent in addition to catalysis happening on the surface. Asymmetric catalysis with surface functionalized MOFs gave promising results with opposite ee of 9% and 7% when **KSU-1<sub>R-MeBz-MeU</sub>** and **KSU-1<sub>S-MeBz-MeU</sub>**, respectively. We thought the selectivity was assisted by the presence of a hydrogen bonding group 2-isopropanol. Further, the reactions are underway to solidify our claim.

## 4.13. Experimental

### 4.13.1. Materials

All chemicals were used as received from commercial sources unless otherwise noted. Isopropyl isocyanate (98%), phenyl isocyanate (98+%), 3-methoxy-N, N-dimethylalniline (98%) and trans- $\beta$ -nitrostyrene were purchased from Sigma Aldrich. N-succinimidyl N-methylcarbamate (97%) and 2-amino terephthalic acid (BDC-NH<sub>2</sub>) (99%) were purchased from Thermo Scientific. Meso- $\alpha,\beta$ -di(4-pyridyl) glycol (>98%) (DPG), 4,4 bipyridine (98 %), terephthalic acid (BDC) (> 99 %), (R)-(+)- $\alpha$ -methyl benzyl isocyanate (98%), (S)-(+)- $\alpha$ -methyl benzyl isocyanate (98%) were purchased from TCI. Benzyl isocyanate (99+ %), zinc chloride (97+%) and sulfuric acid-*d*<sub>2</sub> (D<sub>2</sub>SO<sub>4</sub>, 98 wt.% in D<sub>2</sub>O, 99.5+% atom D) were purchased from Acros Organics. *N, N*-dimethylformamide (DMF), hexanes, ethanol, chloroform, ethyl acetate and acetonitrile were purchased from Fisher Scientific (ACS certified). Zinc nitrate hexahydrate from Strem Chemicals and 1,4-Diazabicyclo [2.2.2] octane (DABCO) (95%) was purchased from Oakwood Products. SiliaPlate™ TLC Plates, Glass-Backed Silica Hard Layer, 250  $\mu$ m, 20 x 20 cm, F254 were purchased from Silicycle. Dimethyl sulfoxide-*d*<sub>6</sub> (*d*<sub>6</sub>-DMSO, 99.9 atom % D) was purchased from Cambridge Isotopes Laboratories.

### 4.13.2. Synthetic Procedures

**KSU-1** was synthesized according to the procedure in the literature.<sup>19</sup> **KSU-3** and **KSU-1000** were synthesized according to the procedure in the literature.<sup>20</sup> **Zn-kgm** was synthesized according to the procedure in the literature.<sup>34</sup>

#### 4.13.2.1 Synthesis of **KSU-1<sub>iPr</sub>**, **KSU-1<sub>RMeBz</sub>**, **KSU-1<sub>SMeBz</sub>**, **KSU-1<sub>sur-hex-R-MeBz</sub>** and **KSU-1<sub>sur-hex-S-MeBz</sub>**

In a typical experiment, the as-synthesized MOF in DMF ~15 mg was transferred to a 1-dram vial containing 2 mL of 0.2 M solution of the isocyanate (0.4 mmol) in acetonitrile. The reaction was left at 80 °C with continuous mixing on a Corning LSE Low-Speed Orbital Shaker. The reaction MOF with isopropyl isocyanate was stopped after 3 h, while reactions with R or S-methyl benzyl isocyanate were left for 7 h before halting the reaction. Samples of the reacted MOF were taken, filtered, and digested for analysis.

#### 4.13.2.2. Synthesis of **KSU-1<sub>S-acetoxy</sub>**

In a typical experiment, the as-synthesized MOF in DMF ~15 mg was transferred to a 1-dram vial containing 2 mL of 0.25 M solution of the S-acetoxy succinic anhydride (0.5 mmol) in chloroform. The reaction was left at 80 °C with continuous mixing on a Corning LSE Low-Speed Orbital Shaker. Samples of the reacted MOF were taken at 24 h, washed in acetonitrile 3 times, filtered, and digested for analysis.

#### 4.13.2.3. Synthesis of **KSU-1<sub>MeU</sub>**, **KSU-1<sub>iPr-MeU</sub>**, **KSU-1<sub>R-MeBz-MeU</sub>**, **KSU-1<sub>S-MeBz-MeU</sub>**, **KSU-1<sub>S-acetoxy-MeU</sub>**, **KSU-1<sub>sur-hex-R-MeBz-MeU</sub>** and **KSU-1<sub>sur-hex-S-MeBz-MeU</sub>**

MOF material in DMF ~15 mg was transferred to a 1-dram vial containing 3 mL of 2.0 M solution of the N succinimidyl N- methyl carbamate (0.8 mmol) in acetonitrile. The reaction was left at 60 °C with continuous mixing on a Corning LSE Low-Speed Orbital Shaker. Samples of the reacted MOF were taken at 24 h, washed in acetonitrile 3 times, filtered, and digested for analysis.

#### 4.13.2.4. Synthesis of **KSU-1<sub>sur-hex-R-MeBz-MeU</sub>** and **KSU-1<sub>sur-hex-S-MeBz-MeU</sub>**

MOF material in DMF ~50 mg was transferred to a 1-dram vial containing 10 mL of 0.05 M solution of the hexanoic anhydride (0.5 mmol) in 1:1 acetonitrile:hexane. The reaction was left for 2 h with continuous mixing on a Corning LSE Low-Speed Orbital Shaker and room temperature.

Samples of the reacted MOF were taken, washed in acetonitrile 3 times, filtered, and digested for analysis.

#### 4.13.2.5. General procedure for catalysis

MOF material (0.006 mmol) was introduced into a 0.10 mL glass vial. Nitrostyrene (0.06 mmol; 8.95 mg) and 3-methoxydimethyl aniline (0.12 mmol; 18  $\mu$ L) in 125  $\mu$ L of  $\text{CHCl}_3$  were then added, and the vial was sealed. The resultant suspension was allowed to react at 60  $^\circ\text{C}$  for a certain amount of time. After quenching by cooling to room temperature, aliquots from the reaction were analyzed by  $^1\text{H}$ -NMR, and the yield was determined by integration of signals using the disappearance of the starting material to the appearance of the product.

#### 4.13.2.6. Synthesis of racemic product

Zinc chloride ( $\text{ZnCl}_2$ ) catalyst (0.90 mmol) was introduced into a 20 mL scintillation vial. Nitrostyrene (1.01 mmol; 150 mg; 1.34 M) and 3-Methoxy-*N,N*-dimethylaniline (2.02 mmol; 296  $\mu$ L) in 1.5 mL Chloroform were added, and the vial was sealed. The resultant suspension was allowed to react at 60  $^\circ\text{C}$  overnight. The progress of the reaction was monitored by TLC. Once the reaction was complete, the product was separated from the remaining using 3-methoxy-*N,N*-dimethylaniline, and catalyst using 1:4 EtOAc: hexane with column chromatography. The product was analyzed by  $^1\text{H}$ -NMR.

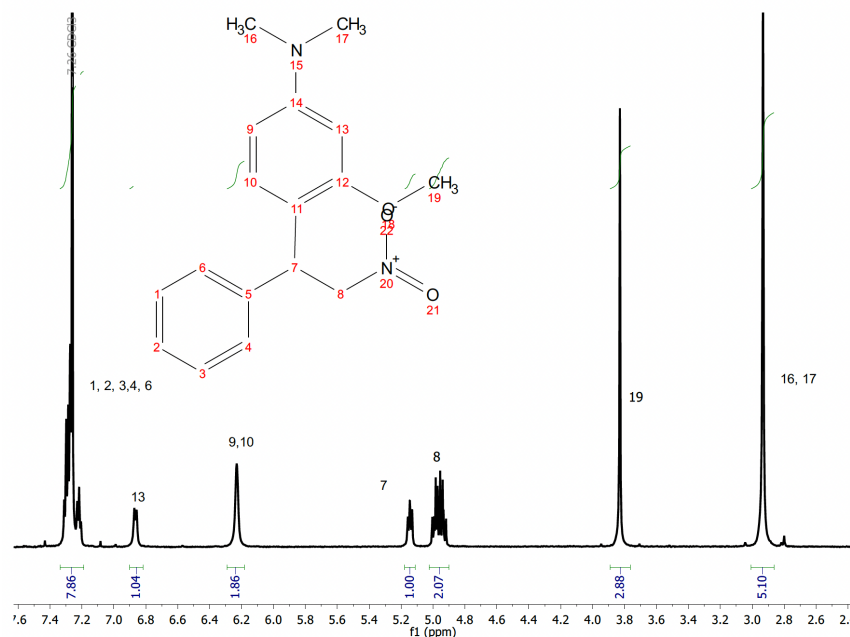


Figure 4.24.  $^1\text{H}$ -NMR of the pure racemic product of the reaction between nitrostyrene and 3 methoxy dimethyl aniline.



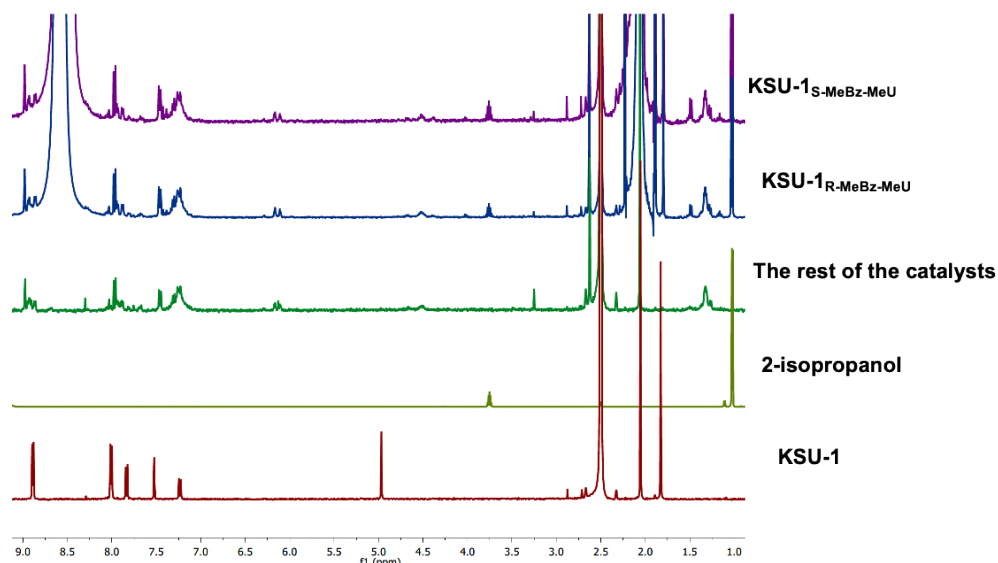


Figure 4.25. Comparison of the  $^1\text{H}$ -NMR spectra of the catalysts when we obtained enantioselectivity showing the presence of 2-isopropanol versus  $^1\text{H}$ NMR of the rest of the catalysts without 2-isopropanol.

### 4.13.3. Characterization

#### 4.13.3.1. High-resolution mass spectrometry (HRMS)

MOF samples (~5 mg) were placed in a solution of DABCO (10 mg) and 0.25 mL of DMSO in a 2-dram vial. The vial was sonicated for ~ 1 min, then heated at 80 °C overnight. A small amount of residue was filtered out, and the resulting solution was analyzed using a Xevo G2-XS QToF quadrupole time-of-flight mass spectrometer coupled with an ACQUITY M-class UPLC and a NanoLockSpray dual electrospray ion source. Mass spectra were acquired in "eXtreme Resolution" mode.

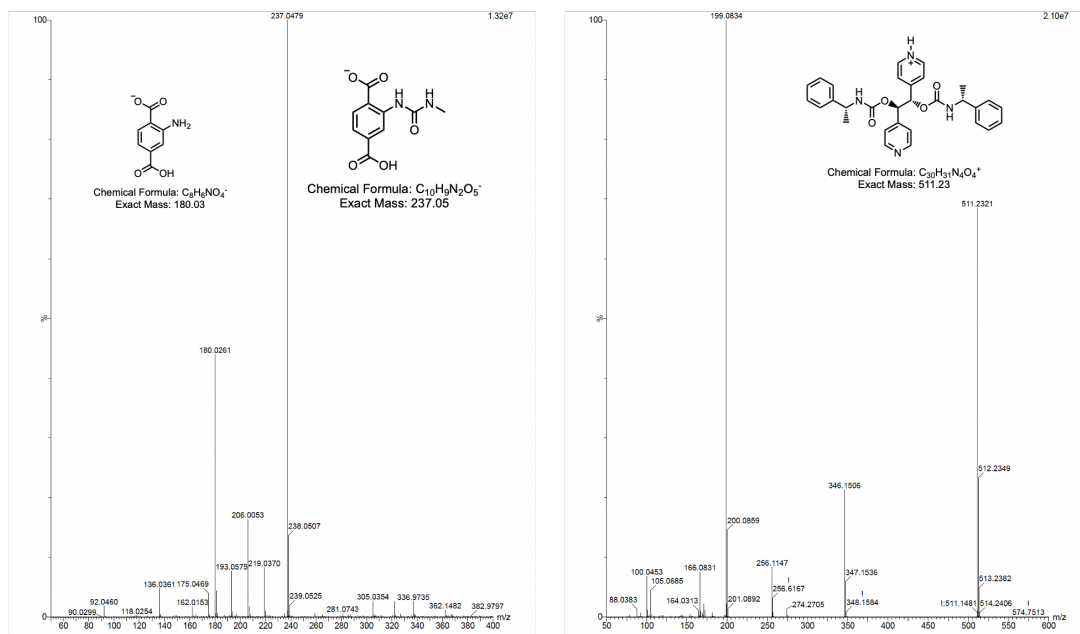


Figure 4.26. HRMS of **KSU-1** after reacting with R or S methyl benzyl isocyanate and N succinimidyl N methylcarbamate to form **KSU-1<sub>RMeBz-MeU</sub>**. Left: the negative mode has indication of the BDC urea product ( $m/z$  = 237.05), though the  $[BDC-NH_2-H^+]$  starting material peak could also be a fragmentation product. Right: the positive mode has  $m/z$  peaks corresponding to  $[DPG_{dicarbamate}+H^+]$  ( $m/z$  = 511.2321) and its various fragmentation products.

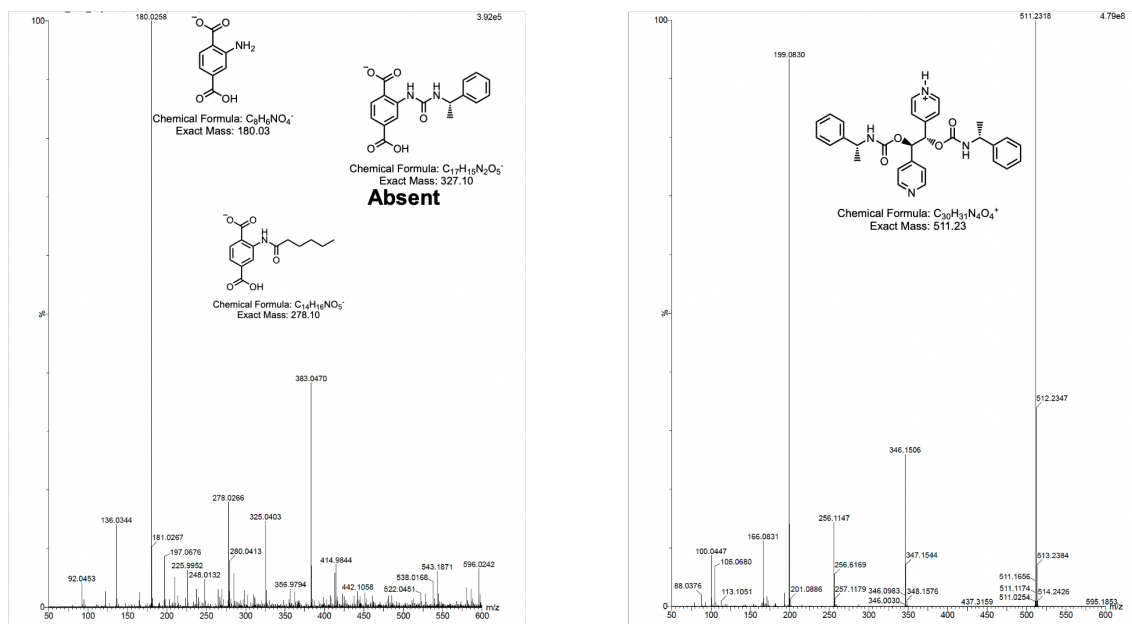


Figure 4.27. HRMS of **KSU-1** after reacting with hexanoic anhydride and R or S methyl benzyl isocyanate to form **KSU-1<sub>sur-hex-RMeBz</sub>**. Left: the negative mode has indication of the BDC amide product ( $m/z$  = 278.10), though the  $[BDC-NH_2-H^+]$  starting material peak could also be a fragmentation product. Right: the positive mode has  $m/z$  peaks corresponding to  $[DPG_{dicarbamate}+H^+]$  ( $m/z$  = 511.2321) and its various fragmentation products.

#### 4.13.3.2. Powder X-ray diffraction (PXRD)

Powder was recorded on a Bruker AXS D8 Advance Phaser diffractometer (Bruker AXS, Karlsruhe, Germany) with Cu K $\alpha$  radiation ( $\lambda = 1.5418 \text{ \AA}$ ) over a range of  $4^\circ < 2\theta < 40^\circ$  in  $0.02^\circ$  steps with a 0.5 s counting time per step. Samples were collected from the bottom of the reaction vial as a thick suspension in DMF and spread on a Si-Einkristalle plate immediately before PXRD measurements.

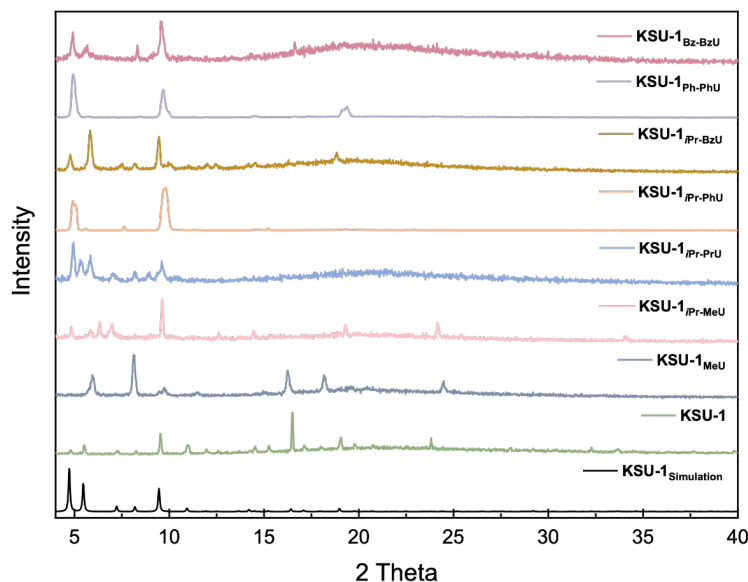


Figure 4.28. The PXRD patterns of the simulated **KSU-1**, the experimental **KSU-1**, and the **KSU-1** post synthetic modification to form **KSU-1<sub>MeU</sub>** and **KSU-1<sub>iPr-MeU</sub>**, **KSU-1<sub>iPr-iPrU</sub>**, **KSU-1<sub>iPr-PhU</sub>**, **KSU-1<sub>iPr-BzU</sub>**, **KSU-1<sub>Ph-PhU</sub>** and **KSU-1<sub>Bz-BzU</sub>**.

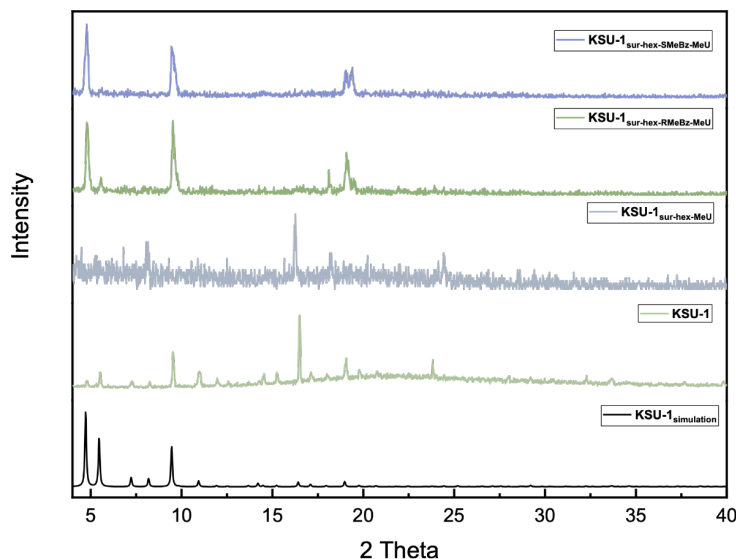


Figure 4.29. The PXRD patterns of the simulated **KSU-1**, the experimental **KSU-1**, and the **KSU-1** post synthetic modification to form **KSU-1<sub>sur-hex-MeU</sub>**, **KSU-1<sub>sur-hex-RMeBz-MeU</sub>** and **KSU-1<sub>sur-hex-SMeBz-MeU</sub>**.

#### 4.13.3.3. Thermogravimetric analysis (TGA)

Thermogravimetric analysis was performed on a TGA 8000 (PerkinElmer Inc., Waltham, MA, USA) interfaced with a PC using Pyris software. Samples were heated at a rate of 10 °C/min under a nitrogen atmosphere. All samples were extensively solvent exchanged with fresh toluene prior to analysis.

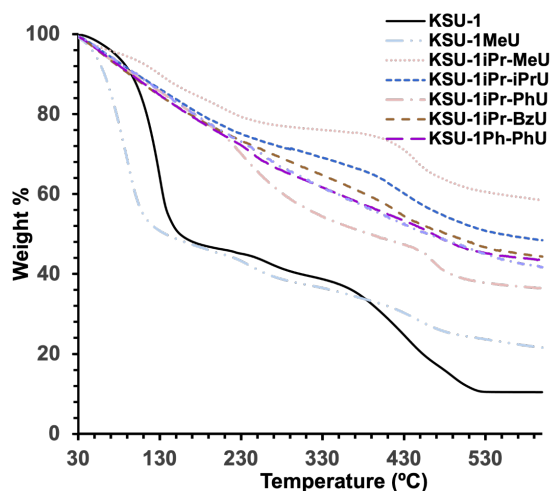


Figure 4.30. TGA data for as-synthesized **KSU-1**, **KSU-1<sub>MeU</sub>**, **KSU-1<sub>iPr-MeU</sub>**, **KSU-1<sub>iPr-iPrU</sub>**, **KSU-1<sub>iPr-PhU</sub>**, **KSU-1<sub>iPr-BzU</sub>**, **KSU-1<sub>Ph-PhU</sub>**, **KSU-1<sub>Bz-BzU</sub>** exchanged with DMF.

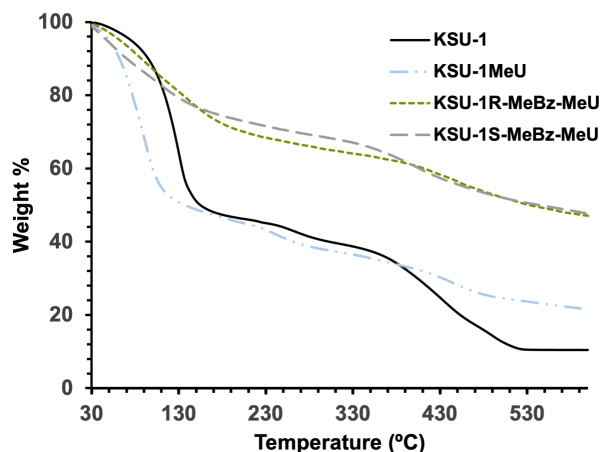


Figure 4.31. TGA data for as-synthesized **KSU-1**, **KSU-1<sub>MeU</sub>**, **KSU-1<sub>RMeBz-MeU</sub>** and **KSU-1<sub>SMeBz-MeU</sub>** exchanged with DMF.

#### 4.12.3.4. Proton nuclear magnetic resonance (<sup>1</sup>H-NMR)

Spectra were recorded on a Bruker Avance NEO spectrometer (400 MHz for <sup>1</sup>H, Bruker BioSpin, Billerica, MA, USA). NMR chemical shifts are reported in ppm against a residual solvent resonance as the internal standard ( $\delta(d_6\text{-DMSO}) = 2.5$  ppm). In a typical analysis, MOF materials

stored in DMF were solvent exchanged with  $\text{CHCl}_3$ , isolated by vacuum filtration, and then evacuated in a vacuum oven at 80 °C overnight. Evacuated MOF samples (5-6 mg) were transferred into an NMR tube, and  $d_6$ -DMSO (0.55 mL) was added. Subsequently,  $\text{D}_2\text{SO}_4$  (0.09 mL, 98 % w/w in  $\text{D}_2\text{O}$ ) was also added. The tubes were capped and sonicated until all the solid was dissolved (~ 1 min).

#### 4.12.3.5. Reaction of nitrostyrene and 3-methoxy N,N dimethyl aniline or indole in different solvents.

Using the general catalysis procedure without catalyst, nitrostyrene (0.06 mmol; 8.95 mg) and 3-methoxydimethyl aniline (0.12 mmol; 18  $\mu\text{L}$ ) or indole (0.12 mmol; 14.10  $\mu\text{L}$ ) in 125  $\mu\text{L}$  of solvent were then added and the vial was sealed. The resultant suspension was allowed to react at 60 °C for a certain amount of time. After quenching by cooling to room temperature, aliquots from the reaction were analyzed by  $^1\text{H}$ -NMR, and the yield was determined by integration of signals using the disappearance of the starting material to the appearance of the product. We established that the best reaction would be in  $\text{CHCl}_3$  as there would be insignificant background reaction and clean NMR spectra to check our conversions.

Table 4.5. Reaction of nitrostyrene with 3 methoxy N,N dimethyl aniline or indole without catalyst.

| Entry | Solvent                  | Relative Polarity | Boiling Point (°C) | % Conv 24 h Aniline | % Conv 24 h Indole |
|-------|--------------------------|-------------------|--------------------|---------------------|--------------------|
| 1     | $\text{CCl}_4$           | unknown           | 76.72              | 1                   | 81                 |
| 2     | $\text{CHCl}_3$          | 0.259             | 61.2               | 2                   | 58                 |
| 3     | $\text{CH}_2\text{Cl}_2$ | 0.309             | 40                 | 3                   | 63                 |
| 4     | $\text{CH}_3\text{NO}_2$ | 0.481             | 101                | 42                  | 0                  |
| 5     | $\text{CH}_3\text{CN}$   | 0.46              | 81                 | 2                   | 2                  |
| 6     | $\text{CH}_3\text{OH}$   | 0.762             | 64.6               | 100                 | 100                |
| 7     | Benzene                  | 0.111             | 78.12              | 1                   | 10                 |
| 8     | Toluene                  | 0.099             | 110.6              | 0                   | 3                  |
| 9     | P-xylene                 | 0.074             | 138.3              | 0                   | 1                  |
| 10    | Chlorobenzene            | 0.188             | 132                | 0                   | 20                 |
| 11    | Cyclohexane              | 0.006             | 80.7               | 1                   | 91                 |
| 12    | THF                      | 0.207             | 66                 | 0                   | 18                 |

#### 4.13.3.6. Mesitylene calibration curve

Solution A containing nitrostyrene (0.6 mmol; 89.5 mg) was dissolved in 1.0 mL of  $\text{CHCl}_3$  to make a 0.6 M solution, while solution B containing mesitylene (0.05 mmol; 6.95  $\mu\text{L}$ ) was diluted with 118.5  $\mu\text{L}$  of  $\text{CHCl}_3$  to make a 0.4 M solution. The standards were diluted such that each contained 0.48 M, 0.384 M, 0.288 M, 0.192 M, and 0.096 M concentrations of nitrostyrene with a constant amount of 0.08 M mesitylene. Aliquots from each solution were analyzed by  $^1\text{H}$ -NMR, and the ratio of nitrostyrene and mesitylene in each standard was determined by integration of the mesitylene signal at 6.80 ppm vs nitrostyrene signal at 8.00 ppm.

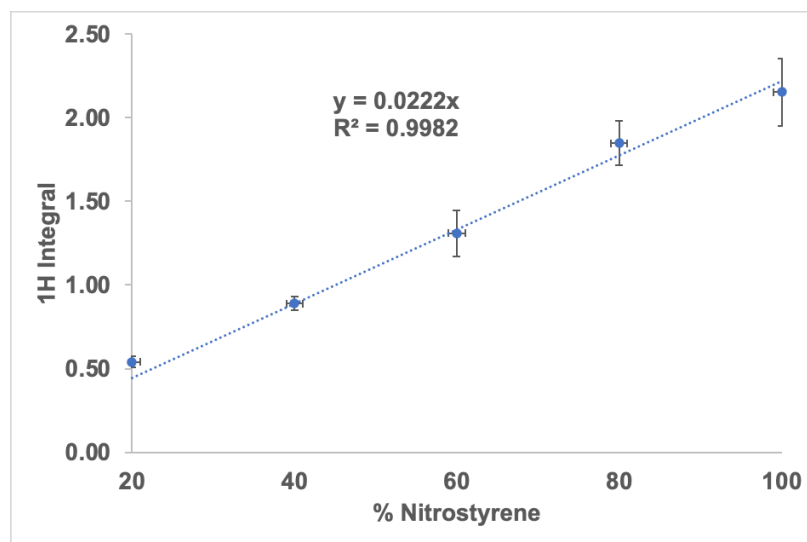


Figure 4.32. Calibration curve of the MDNPA proton with mesitylene internal standard.

#### 4.13.3.7. GC Conditions

3 mg into 1 mL ethyl acetate, then diluted: 0.2 mL into 1 mL. Run at 25  $^{\circ}\text{C}/\text{min}$  from 50 – 250  $^{\circ}\text{C}$ .

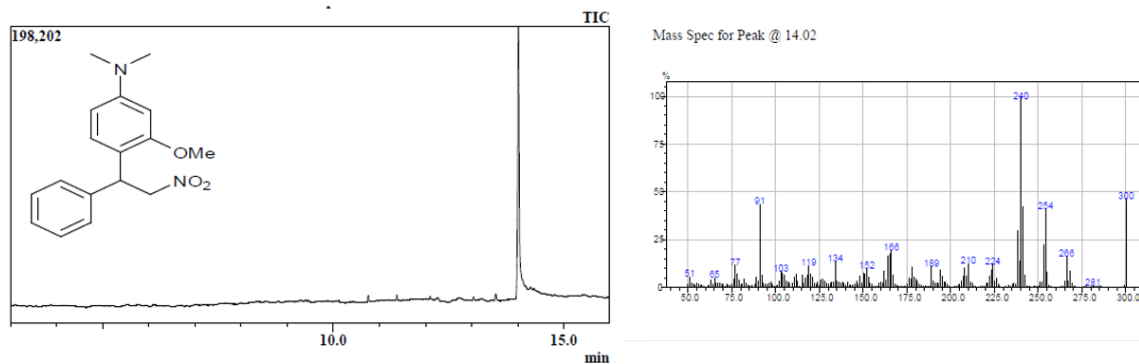


Figure 4.33. GC-MS of 3-Methoxy-N,N-dimethyl-4-(2-nitro-1-phenylethyl)aniline (DMNPA). The Left shows its elution profile and the right shows m/z 300 peaks corresponding to DMNPA.

#### 4.13.3.8. Supercritical fluid chromatography (SFC)

SFC analyses were carried out on a Shimadzu SFC-30A model with a CHIRALPAK®IBN5 column (4.6 x 250 mm, particle size 5  $\mu$ m; gradient 5-30 % IPA in supercritical CO<sub>2</sub>, 1.0 mL/min). The outlet pressure was set at 11.5 MPa, the oven temperature was 35 °C, and the injection volume was 10  $\mu$ L for all the experiments. The ee's were determined via SFC after purification by thin-layer chromatography.

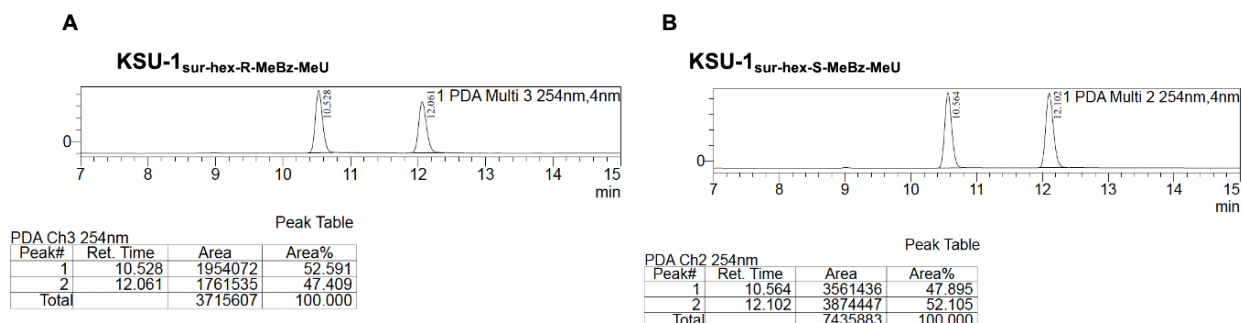


Figure 4.34. Enantioselectivity ~5% observed when KSU-1<sub>sur-hex-R-MeBz-MeU</sub> reversal ~5 % when KSU-1<sub>sur-hex-S-MeBz-MeU</sub> was used.

Table 4.6. List of different conditions tried for enantioselective catalysis

| Entry | Solvent           | Catalyst               | Temp (°C) | Time | % Conv. | % ee |
|-------|-------------------|------------------------|-----------|------|---------|------|
| 1     | CHCl <sub>3</sub> | sur-hex-R              | 60        | 24 h | 13      | 0    |
| 2     | CHCl <sub>3</sub> | sur-hex-S              | 60        | 24 h | 26      | 0    |
| 3     | CHCl <sub>3</sub> | sur-hex-RNAPHTHYL      | 60        | 24 h | 9       | 0    |
| 4     | CHCl <sub>3</sub> | sur-hex-SNAPHTHYL      | 60        | 48 h | 4       | 0    |
| 5     | Toluene           | sur-hex-R              | 60        | 24 h | 19      | 0    |
| 6     | Toluene           | sur-hex-iPr-RU         | rt        | 10 d | 17      | 0    |
| 7     | Toluene           | sur-hex-iPr-SU         | rt        | 10 d | 7       | 0    |
| 8     | Toluene           | sur-hex-iPr-RNaphthylU | rt        | 10 d | 0       | 0    |
| 9     | Toluene           | sur-hex-iPr-SNaphthylU | rt        | 10 d | 0       | 0    |
| 10    | CHCl <sub>3</sub> | sur-hex-R              | 60        | 5 d  | 73      | 0    |

|    |                                                    |                |    |      |    |    |
|----|----------------------------------------------------|----------------|----|------|----|----|
| 11 | CHCl <sub>3</sub>                                  | sur-hex-S      | 60 | 5 d  | 65 | 0  |
| 12 | CHCl <sub>3</sub>                                  | sur-hex-R      | rt | 4 d  | 8  | 0  |
| 13 | CHCl <sub>3</sub>                                  | sur-hex-S      | rt | 4 d  | 7  | 0  |
| 14 | CHCl <sub>3</sub>                                  | sur-hex-iPr-RU | 60 | 5 d  | 25 | 0  |
| 15 | CHCl <sub>3</sub>                                  | sur-hex-iPr-SU | 60 | 5 d  | 18 | 0  |
| 16 | CHCl <sub>3</sub>                                  | sur-hex-iPr-RU | rt | 4 d  | 8  | 0  |
| 17 | CHCl <sub>3</sub>                                  | sur-hex-iPr-SU | rt | 4 d  | 7  | 0  |
| 18 | Anh CHCl <sub>3</sub>                              | sur-hex-R      | 60 | 24 h | 40 | 0  |
| 19 | Anh CHCl <sub>3</sub>                              | sur-hex-S      | 60 | 24 h | 43 | 0  |
| 20 | Anh CHCl <sub>3</sub> + 5 $\mu$ L H <sub>2</sub> O | sur-hex-R      | 60 | 24 h | 31 | 4  |
| 21 | Anh CHCl <sub>3</sub> + 5 $\mu$ L H <sub>2</sub> O | sur-hex-S      | 60 | 24 h | 17 | 9  |
| 22 | Anh CHCl <sub>3</sub> + 5 $\mu$ L iPA              | sur-hex-R      | 60 | 24   | 17 | ~3 |
| 23 | Anh CHCl <sub>3</sub> + 5 $\mu$ L iPA              | sur-hex-S      | 60 | 24 h | 24 | ~3 |
| 24 | Anh CHCl <sub>3</sub> + 5 $\mu$ L H <sub>2</sub> O | sur-hex-R      | 60 | 24   | 31 | ~3 |
| 25 | Anh CHCl <sub>3</sub> + 5 $\mu$ L H <sub>2</sub> O | sur-hex-S      | 60 | 24 h | 17 | 0  |
| 26 | Anh CHCl <sub>3</sub> + 5 $\mu$ L H <sub>2</sub> O | sur-hex-R      | 60 | 24 h | 22 | 0  |
| 27 | Anh CHCl <sub>3</sub> + 5 $\mu$ L H <sub>2</sub> O | sur-hex-S      | 60 | 24 h | 36 | 0  |
| 28 | Anh CHCl <sub>3</sub> + 5 $\mu$ L H <sub>2</sub> O | sur-hex-R      | rt | 24 h | 7  | 0  |
| 29 | Anh CHCl <sub>3</sub> + 5 $\mu$ L H <sub>2</sub> O | sur-hex-S      | rt | 24 h | 4  | 0  |
| 30 | Toluene + 5 $\mu$ L H <sub>2</sub> O               | sur-hex-R      | 60 | 24 h | 31 | 0  |
| 31 | Toluene + 5 $\mu$ L H <sub>2</sub> O               | sur-hex-S      | 60 | 24 h | 28 | 0  |



|           |                                         |                       |    |      |    |   |
|-----------|-----------------------------------------|-----------------------|----|------|----|---|
| <b>32</b> | Toluene + 5 $\mu$ L<br>H <sub>2</sub> O | sur-hex-R             | rt | 24 h | 2  | 0 |
| <b>33</b> | Toluene + 5 $\mu$ L<br>H <sub>2</sub> O | sur-hex-S             | rt | 24 h | 1  | 0 |
| <b>34</b> | CHCl <sub>3</sub>                       | sur-hex-R 20<br>mol%  | rt | 48 h | 1  | 0 |
| <b>35</b> | CHCl <sub>3</sub>                       | sur-hex-S 20<br>mol%  | rt | 48 h | 1  | 0 |
| <b>36</b> | CHCl <sub>3</sub>                       | sur-hex-R<br>100 mol% | 60 | 2 h  | 38 | 0 |
| <b>37</b> | CHCl <sub>3</sub>                       | sur-hex-S<br>100 mol% | 60 | 2 h  | 41 | 0 |
| <b>38</b> | CHCl <sub>3</sub>                       | sur-hex-R<br>100 mol% | rt | 18 h | 4  | 0 |
| <b>39</b> | CHCl <sub>3</sub>                       | sur-hex-S<br>100 mol% | rt | 18 h | 6  | 0 |

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## Chapter 5 - Reagent and condition control for the selective post-synthetic modification of a metal-organic framework with different carboxylic acids.

### 5.1. Carboxylic acid containing enzymes

Once again, nature inspires us: many enzymes feature carboxylic acids in their active sites.<sup>1,2</sup> In particular, aspartic proteases are noteworthy because their active sites contain aspartic acid residues that catalyze peptide bond cleavage through water-mediated hydrogen bonding (**Figure 5.1**). Beyond their role in peptide bond catalysis, carboxylic acids contribute to various applications such as catalysis and sensing by exploiting carboxylate-based supramolecular interactions.<sup>3,4</sup> These examples underscore the importance of carboxylic groups. In this chapter, we will develop a new strategy to independently and uniformly functionalize **KSU-1** via PSM.

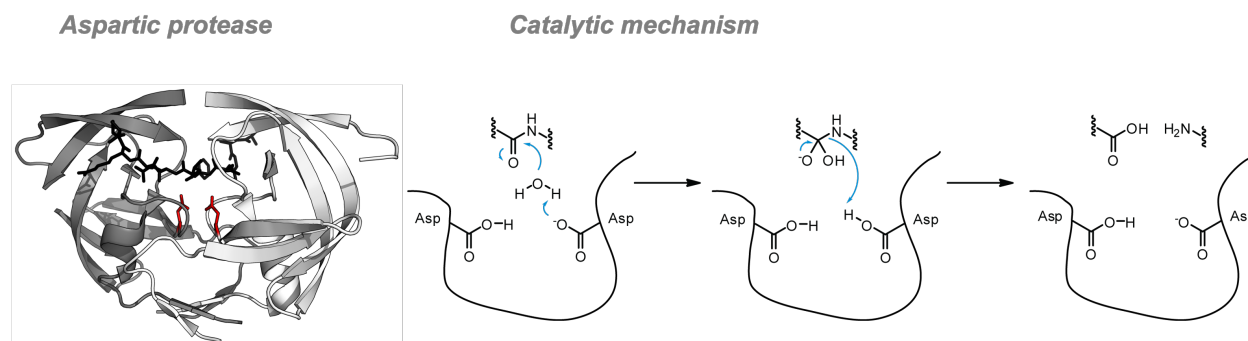


Figure 5.1. Aspartic acid and its proposed mode of action. Adapted from REF<sup>5</sup>.

### 5.2. Chemoselectivity and dual PSM in MOFs

The post-synthetic modification (PSM) of metal-organic framework (MOF) materials is an efficient strategy by which chemists can tailor the chemical pore environment of the frameworks.<sup>6–8</sup> With the judicious implementation of different techniques, PSM is a predictable method of obtaining MOFs with known topology and possessing desired chemical functionality, something which is nearly impossible in the traditional solvothermal syntheses of MOFs.<sup>9</sup> Within PSM there is a subclass of post-synthetic functionalization which involves pore decoration and within that class there is covalent and coordinative functionalization.<sup>10</sup> By decorating the pores of a parent MOF with different chemical functional groups post-assembly, it is possible to rationally generate

a series of daughter materials with different functionality,<sup>11–13</sup> and thus, different potential applications.<sup>14–17</sup> Within the area of covalent MOF pore functionalization, our lab has demonstrated the concept of uniform, independent dual functionalization, in which two different moieties are grafted onto the interior surfaces of a framework in well-defined locations throughout the material.<sup>18,19</sup> With this strategy, we can increase the complexity of MOF cavities while retaining control over the location and identity of each functionality in a pore.

In our work, we have employed strategies that use Zn-based pillared frameworks in which two different linkers that are located in well-defined positions throughout the materials each bearing a different reactive handle.<sup>20–22</sup> The uniformity of the dual functionalization approach relies on the chemoselectivity of reactions used, i.e. the preferential reaction of a reactant with one functional group out of a number of possible functionalities.<sup>23</sup> Chemoselectivity is a major pursuit of synthetic chemists as it allows them to construct complex molecules via the precise modification of highly functionalized synthetic intermediates.<sup>24</sup> In our quest to generate increasingly complex, but well-defined confined spaces, we too have focused on developing different methods for achieving chemoselectivity in the multifunctionalization of MOFs.

### 5.3. Strategies for independent bifunctionalization

Inspired by others working in the area of MOF covalent modification,<sup>25–27</sup> we previously employed an orthogonal functionalization strategy, where the two reactive handles of the framework have completely divergent reactivity, resulting in independent functionalization (**Figure 5.2A**). That work relied on the lack of overlap in the reactivity of azide ( $-\text{N}_3$ ) and hydroxyl ( $-\text{OH}$ ) groups in their reactions with terminal alkynes and isocyanates, respectively.<sup>19</sup> Another approach we took was to use reactive MOF functionalities that have similar *modes* of reaction, but have different *extents* of reaction with different substrates. Using a **KSU-1**, MOF bearing amine ( $-\text{NH}_2$ ) and  $-\text{OH}$  groups, which both react as nucleophiles, we took advantage of the greater nucleophilicity of the amine groups that allowed their selective reaction with linear anhydrides, while the  $-\text{OH}$  groups required the more reactive cyclic anhydrides to react (**Figure 5.2.B**).<sup>18</sup> When we attempted to use the same strategy with isocyanates we discovered unexpected reactivity with the  $-\text{OH}$  groups reacting to a greater extent than the  $-\text{NH}_2$  groups. As discussed in **Chapter 2**, we do not yet know the molecular origin of this reversal of reactivity, but initial results show that altering the nature of the isocyanate and reaction conditions such as solvent and catalyst changes the extent of this reversal of reactivity. In this chapter, we introduce a third strategy for achieving

selective functionalization, specifically, where the synthetic handles have similar modes of reaction, but they react independently with the *same* reactants (**Figure 5.2C**). Here, the use of different reaction conditions and the careful selection of the reactant for the first functionalization step controls the chemoselectivity of the reactions and enables the uniform bifunctionalization of the MOF material.

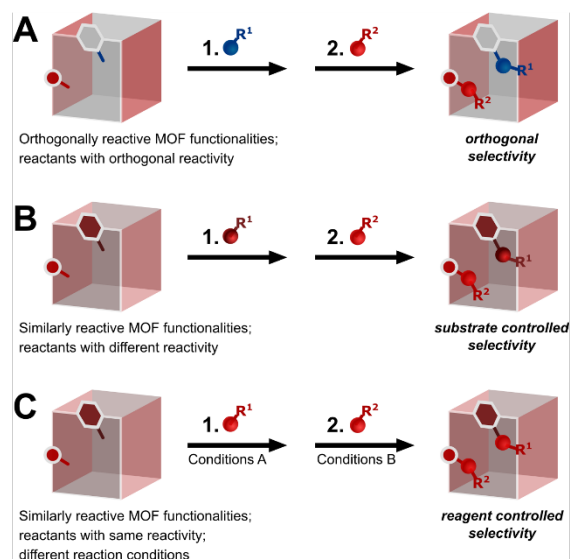


Figure 5.2. (A) Functionalization of orthogonally reactive linkers yields uniformly multifunctional MOF (B) Functionalization of regularly positioned, with controlled substrate yields uniformly multifunctional MOF (C) Functionalization of regularly positioned, with controlled reagents and reaction conditions yields uniformly multifunctional MOF.

In all previous examples, the amine and the hydroxyl linkers existed individually, and our example will be unique in demonstrating their coexistence. We anticipated three challenges in independently functionalizing **KSU-1** to achieve uniform bifunctionalization. Firstly, to achieve uniform functionalization, we require selective and quantitative reactions at each step. However, the functionalization of BDC-NH<sub>2</sub> linkers with aliphatic cyclic anhydrides in the Zn-based MOF **IRMOF-3** is known to result in the loss of MOF crystallinity at high conversions.<sup>28</sup> It is presumed to be due to the proximity of the resulting flexible carboxylic acids to the metal corners, which leads to metal ion abstraction. To our knowledge, there are no examples of functionalizing BDC-NH<sub>2</sub> linkers in MOFs with cyclic anhydrides that have achieved high conversions. Secondly, DPG also reacts with succinic anhydride,<sup>18,29</sup> thus careful choice of reaction conditions is required to obtain independent reaction of the cyclic anhydrides at the -NH<sub>2</sub> vs. -OH groups. The final concern is the potential hydrolysis of the amide bonds formed in the first step, during the second

functionalization. Therefore, the cyclic anhydride that reacts with KSU-1 first should be stable otherwise we will end up with non-uniformly functionalized MOF.

### 5.3. Elaboration of KSU-1 with cyclic anhydrides - first step

The MOF **KSU-1** is a pillared MOF that is composed of the linkers 2-aminobenzene-1,4-dicarboxylic acid (BDC-NH<sub>2</sub>) and *meso*- $\alpha,\beta$ -di(4-pyridyl) glycol (DPG) (**Figure 5.3A**). The nucleophilic -NH<sub>2</sub> and -OH groups are in well-defined locations throughout the framework (**Figure 5.3B**) and both linkers have been shown to react with cyclic anhydrides in MOFs, producing amides<sup>30–34</sup> and esters respectively.<sup>18,29</sup>

We selected four cyclic anhydrides namely maleic, succinic, itaconic and glutaric anhydride to elaborate the MOF pores. The nucleophilic ring-opening of cyclic anhydrides is an efficient strategy for introducing free carboxylic acids in MOF pores.<sup>28</sup> Considering the reaction conversions reported in the literature for IRMOF-3 with maleic anhydride and succinic anhydride (~49% after 1 day) and for MIL-53-NH<sub>2</sub> (~39% and ~34% after 1 day with maleic and succinic anhydride, respectively),<sup>35,36</sup> we opted for more rigorous conditions to achieve quantitative conversion. KSU-1 was incubated in a toluene solution of cyclic anhydrides and DIPEA as a base at 50 °C, with the reaction halted after 30 minutes to selectively target the -NH<sub>2</sub> groups. However, both amine and hydroxyl groups reacted simultaneously with maleic, succinic, and glutaric anhydrides (**Figure 5.11 and Table 5.1**). Gratifyingly, under milder conditions, i.e., without the base, the reaction selectively targeted the amine groups and reached completion within 1 hour at 50 °C. Further, when the reaction was performed at room temperature, we still achieved quantitative conversion for all the cyclic anhydrides within 5 hours (**Figure 5.3C**). Independent functionalization was confirmed by conducting electrospray ionization mass spectrometry (ESI-MS) of samples of the MOF products digested by 1,4-diazabicyclo[2.2.2]octane (DABCO) (**Figures 5.5-5.11**). The mass spectra in negative mode had [M-H<sup>+</sup>] peaks corresponding to the BDC-amides, while in positive mode, the [M+H<sup>+</sup>] peaks indicated the presence of unreacted DPG. Powder X-ray diffraction (PXRD) confirmed that crystallinity was preserved even after complete functionalization of BDC-NH<sub>2</sub> (**Figure 5.14**).



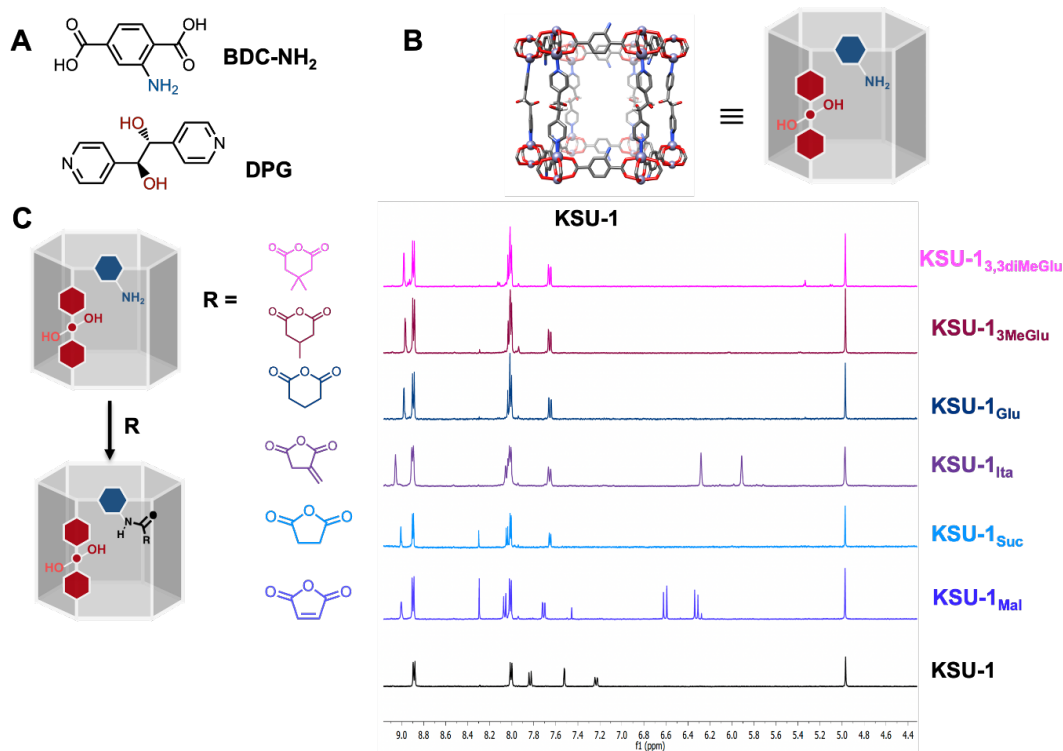


Figure 5.3. (A) Reactive linkers in KSU-1 B: Network unit of KSU-1 and schematic presentation C: Schematic representation of the selective reaction of KSU-1 with cyclic anhydrides and the corresponding <sup>1</sup>H-NMRs of the MOF reaction products digested in a solution of D<sub>2</sub>SO<sub>4</sub> in DMSO-d<sub>6</sub>.

#### 5.4. Elaboration of KSU-1 with cyclic anhydrides – the second step

In this work, the free carboxylic acids are grafted to the MOF linkers by amide and ester bonds which are susceptible to hydrolysis. Therefore, the stability of the initial PSM product is crucial to obtain a uniformly bifunctionalized MOF. At room temperature without base, the conversion for the PSM of DPG with cyclic anhydrides in the second step ranged from 10 % to 50 % after leaving the reaction for 1 week. Since our main goal was to show the possibility of uniform bifunctionalization we resorted to more rigorous conditions, i.e., toluene at 50 °C, with DIPEA as an added base. Since, amide bonds are prone to hydrolysis under strongly acidic or basic conditions, we thought adding DIPEA would neutralize the reaction environment. In addition, these conditions favored more conversion at the hydroxyls. According to pK<sub>a</sub> values, the order of stability of the selected cyclic anhydrides is glutaric amide > succinic amide > itaconic amide > maleic amide. Maleic amides tend to be least stable under acidic environments due to the cis configuration which brings carboxylate oxygen near the amide group. The carboxylate oxygen then attacks the amide leading to the reformation of the amine and maleic anhydride (**Figure 5.4**).<sup>37</sup>

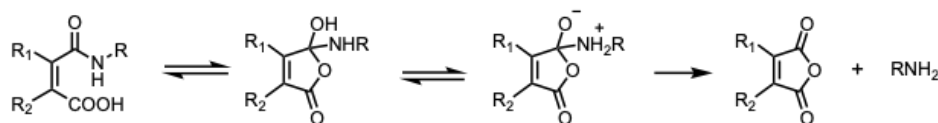


Figure 5.4. The mechanism of the hydrolysis of maleic amide.

When **KSU-1<sub>mal</sub>** was incubated with succinic anhydride for bifunctionalization, we observed the substitution of maleic amide. We believed that it could be due to hydrolysis of the maleic amide bond. These results were confirmed with <sup>1</sup>H-NMR (**Figure 5.14**) and by HRMS (**Figure 5.12**) which showed the complete absence of the peak corresponding to the BDC maleic amide. To obtain a well-defined bifunctionalized **KSU-1<sub>Amide-Ester</sub>**, we hypothesized that the less acidic anhydrides (glutaric and succinic) would form the most stable amides and thus we reacted them first and anticipated to obtain six uniformly bifunctional MOF bearing pendant -COOH groups (**Figure 5.5B**). The second functionalizations of **KSU-1<sub>Glut-amide</sub>** and **KSU-1<sub>Suc-amide</sub>** with succinic, glutaric and maleic anhydrides gave conversions ranging from ~51 % to ~90 % after 24h. These conversions were recorded by observing the disappearance of singlet at 4.9 and appearance of one at ~6.0 ppm. We were surprised that the peaks corresponding to the diesters of DPG were visible despite the expected hydrolysis of the ester bond during MOF digestion by D<sub>2</sub>SO<sub>4</sub> in preparation for <sup>1</sup>H-NMR analysis. It is assumed that the presence of DIPEA in the MOF pores prevents the hydrolysis, but more investigation is required. We admit that it is possible that some hydrolysis does take place, making our determination of the conversions of the bifunctionalization unreliable.

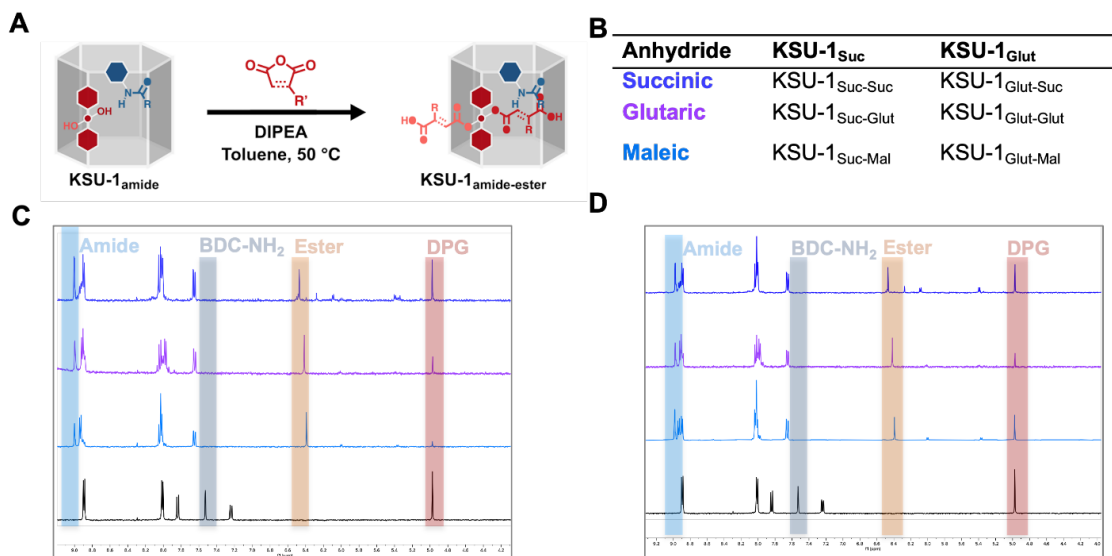


Figure 5.5. A: Schematic representation of the functionalization of the hydroxyls in **KSU-1<sub>Amide</sub>** with various cyclic anhydrides. B: Summary table of the bifunctionalization of the monofunctionalized **KSU-1<sub>Amide</sub>**

MOFs. C:  $^1\text{H}$ -NMR spectra showing the starting materials and products of the functionalization of KSU-1<sub>Suc</sub> and D: KSU-1<sub>Glut</sub> digested in a solution of  $\text{D}_2\text{SO}_4$  in  $\text{DMSO-d}_6$ .

Attempts of bifunctionalization with itaconic anhydride showed no conversion after 24 h. This is not surprising as itaconic anhydride is less reactive than glutaric, succinic, and maleic anhydrides,<sup>38</sup> which have similar reactivity with each other.<sup>39</sup> Conversions were determined by  $^1\text{H}$ -NMR analysis of the acid-digested MOF products (**Figure 5.5C and 5.5D**). This second functionalization was also confirmed by HRMS (**Figure 5.13**). The products retained their crystallinity which was evidenced by their PXRD patterns (**Figure 5.15B**).

## 5.5. Conclusion

In this work, we demonstrated that the same functional group, with or without different substituents, can be used to independently functionalize a MOF under varying reaction conditions. Where, previously, careful consideration had to be taken in the selection of differently activated reaction partners to functionalize the modifiable handles in the MOF, we now are afforded more freedom in choosing potential reactants with which to elaborate our MOF pores. With conversion on the second step reaching conversion of ~51 % 90 % we were close to achieving uniformity in the MOFs. However, these results are impressive since these are the highest conversions reached so far is PSM with cyclic anhydrides without the MOFs losing their crystallinity. Therefore, the control of reagent and reaction conditions is a valuable addition to achieving chemoselectivity in the uniform multifunctionalization of MOFs toolbox as it widens the landscape for possible reaction partners. This, in turn, increases the potential number and complexity of the well-defined multifunctionalized MOF products, which has direct influence on the potential applications of the resultant uniformly multifunctionalized MOFs.

## 5.6. Experimental

### 5.6.1. Materials

All chemicals were used as received from commercial sources unless otherwise noted. Succinic anhydride ( $\geq 99\%$ ), itaconic anhydride (95%), 3-methylglutaric anhydride (98%), 3,3-dimethylglutaric anhydride (99%), 2-aminoterephthalic acid (**BDC-NH<sub>2</sub>**, 99%) and chloroform were purchased from Sigma Aldrich. *Meso- $\alpha,\beta$ -di(4-pyridyl) glycol* (**DPG**, 98.0+ %), , triethylamine (99%), maleic anhydride ( >99%) and glutaric anhydride (>98%) were purchased from TCI. Sulfuric acid- $d_2$  ( $\text{D}_2\text{SO}_4$ , 98 wt.% in  $\text{D}_2\text{O}$ , 99.5+ % atom D) was purchased from Acros

Organics. *N,N*-dimethylformamide (DMF), chloroform, hexanes and toluene were purchased from Fisher Scientific (ACS certified). Zinc nitrate hexahydrate was purchased from Strem Chemicals. 1,4-Diazabicyclo[2.2.2]octane (DABCO) (95 %) was purchased from Oakwood Products. Dimethyl sulfoxide-*d*<sub>6</sub> (*d*<sub>6</sub>-DMSO, 99.9 atom % D) was purchased from Cambridge Isotopes Laboratories.

### 5.6.2. Synthesis Procedures

#### 5.6.2.1. Synthesis of KSU-1

**KSU-1** was synthesized according to literature procedure.<sup>40</sup>

#### 5.6.2.2. Synthesis of KSU-1<sub>Amides</sub>

In a typical experiment, ~ 10 mg of **KSU-1** (0.012 mmol) (-OH (0.025 mmol) and -NH<sub>2</sub> (0.025 mmol)) as-synthesized in DMF was transferred to a 1-dram vial. Then, 4 mL of a 0.2 M solution of the cyclic anhydride (0.8 mmol) in chloroform were added to the vial. The reaction was left at room temperature with continuous mixing on a Corning LSE Low Speed Orbital Shaker. Samples of the reacted MOF were taken at 3-18 h, washed in chloroform 3 times filtered, and digested for analysis.

#### 5.6.2.2. Synthesis of KSU-1<sub>Amides-Ester</sub>

In a typical experiment, ~ 10 mg of **KSU-1<sub>Amide</sub>** (0.012 mmol) (-OH (0.025 mmol) and -NH<sub>2</sub> (0.025 mmol)) as-synthesized in DMF was transferred to a 1-dram vial. Then, 4 mL of a 0.2 M solution of the cyclic anhydride (0.8 mmol) in Toluene and (0...mmol) DIPEA were added to the vial. The reaction was left at 50 °C with continuous mixing on a Corning LSE Low Speed Orbital Shaker. Samples of the reacted MOF were taken at 24 h, washed in chloroform 3 times filtered, and digested for analysis.

### 5.6.3. Characterization

#### 5.6.3.1. High-resolution mass spectrometry (HRMS)

MOF samples (~5 mg) were placed in a solution of DABCO (10 mg) and 0.25 mL of DMSO in a 2-dram vial. The vial was sonicated for ~ 1 min then heated at 80 °C overnight. A small amount of residue was filtered out and the resulting solution was analyzed using a Xevo G2-XS QToF quadrupole time-of-flight mass spectrometer coupled with an ACQUITY M-class UPLC

and a NanoLockSpray dual electrospray ion source. Mass spectra were acquired in “eXtreme Resolution” mode.

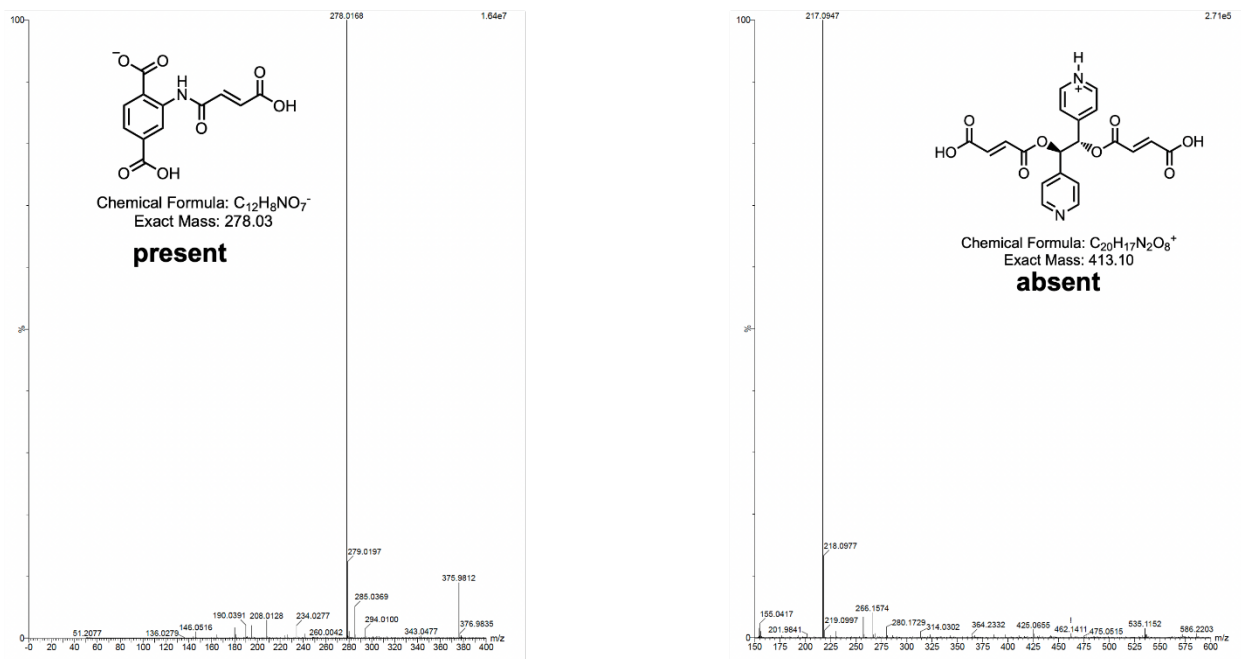


Figure 5.6. HRMS of KSU-1 after reacting with maleic anhydride (3 h). Left: the negative mode has  $m/z$  peak corresponding to the BDC amide product. Right: the positive mode peaks correspond to  $m/z$  of starting DPG, and has no indication of  $m/z$  peaks corresponding to DPG ester and its fragments, with starting DPG.

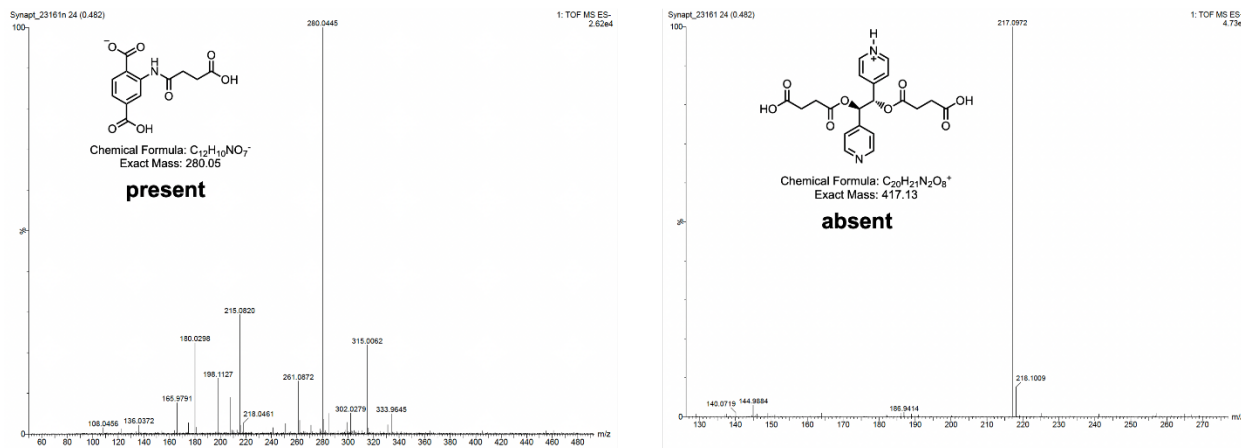


Figure 5.7. HRMS of KSU-1 after reacting with succinic anhydride (4 h). Left: the negative mode has  $m/z$  peak corresponding to the BDC amide product and BDC-NH<sub>2</sub> is form fragmentation. Right: the positive mode peaks correspond to  $m/z$  of starting DPG and has no indication of  $m/z$  peaks corresponding to DPG ester and its fragments, with starting DPG.

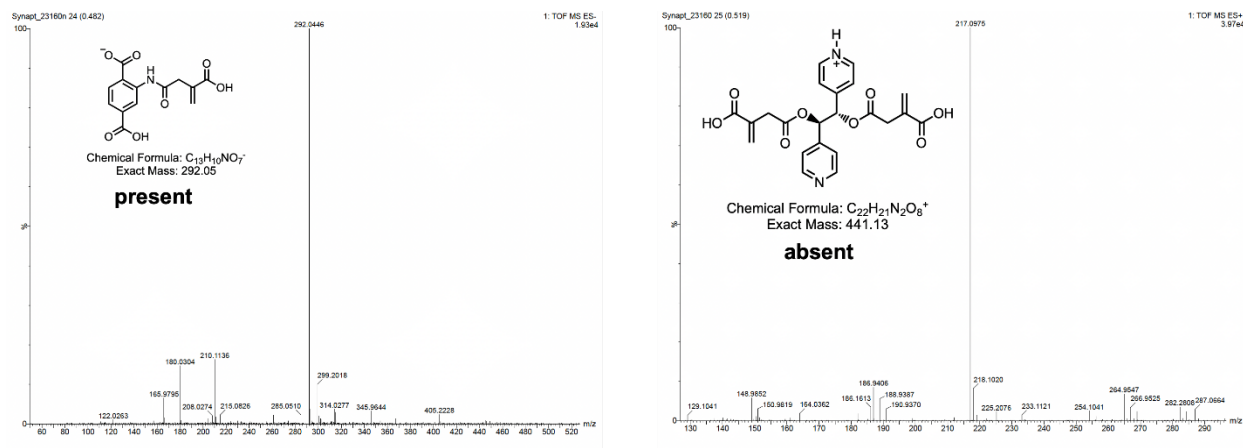


Figure 5.8. HRMS of KSU-1 after reacting with itaconic anhydride (4 h). Left: the negative mode has  $m/z$  peak corresponding to the BDC amide product and BDC-NH<sub>2</sub> is form fragmentation. Right: the positive mode peaks correspond to  $m/z$  of starting DPG and has no indication of  $m/z$  peaks corresponding to DPG ester and its fragments, with starting DPG.

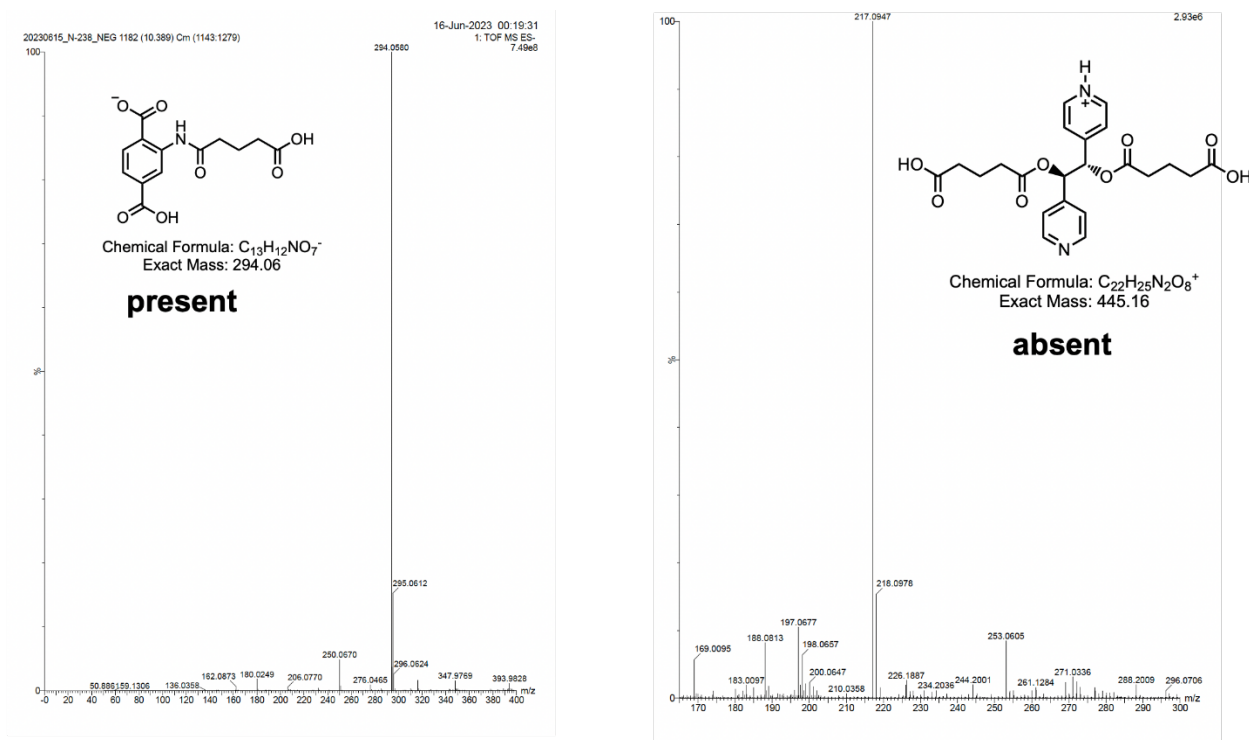


Figure 5.9. HRMS of KSU-1 after reacting with glutaric anhydride (4 h). Left: the negative mode has  $m/z$  peak corresponding to the BDC amide product and BDC-NH<sub>2</sub> is form fragmentation. Right: the positive mode peaks correspond to  $m/z$  of starting DPG and has no indication of  $m/z$  peaks corresponding to DPG ester and its fragments, with starting DPG.



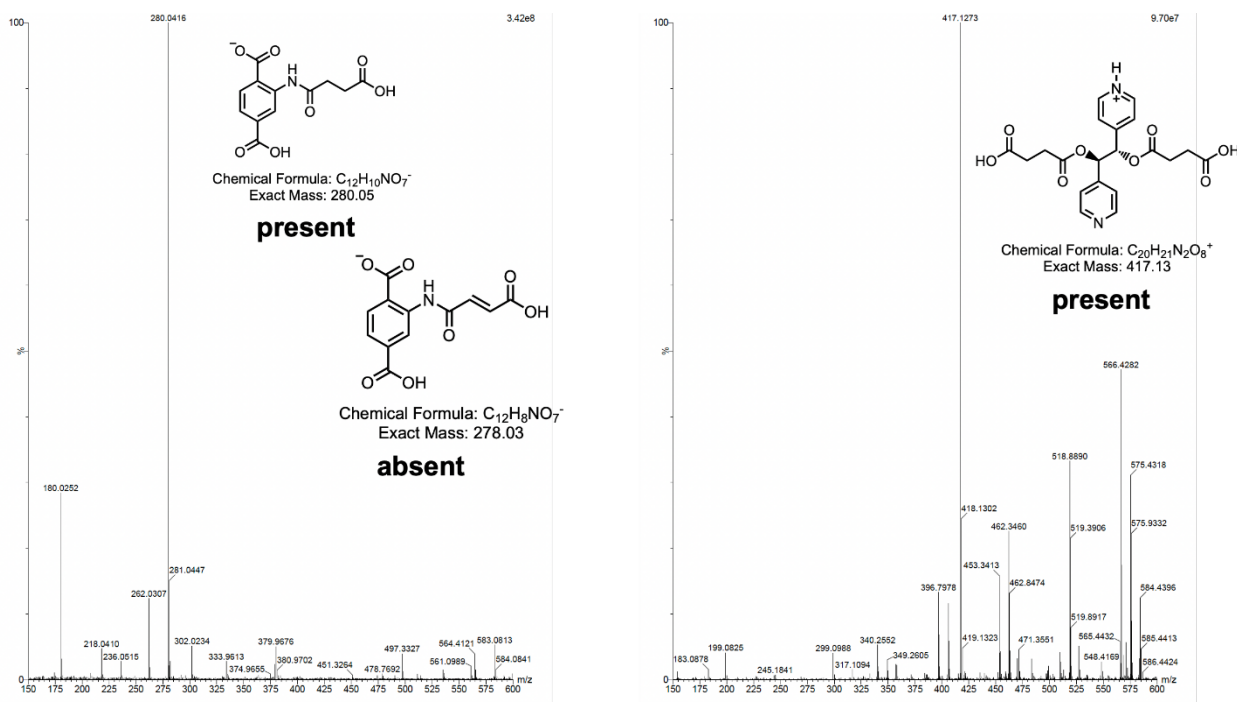


Figure 5.10. HRMS of KSU-1<sub>mal</sub> after reacting with succinic anhydride (24 h). Left: the negative mode has m/z peak corresponding to the BDC succinic amide product with no indication of and BDC maleic amide and BDC-NH<sub>2</sub> is form fragmentation. Right: the positive mode peaks corresponding to m/z of DPG succinic ester indication.

### 5.6.3.2. Proton nuclear magnetic resonance (<sup>1</sup>H-NMR)

Spectra were recorded on a Bruker Avance NEO spectrometer (400 MHz for <sup>1</sup>H, Bruker BioSpin, Billerica, MA, USA). NMR chemical shifts are reported in ppm against a residual solvent resonance as the internal standard ( $\delta(d_6\text{-DMSO}) = 2.5$  ppm). In a typical analysis, MOF materials stored in DMF were solvent exchanged with CHCl<sub>3</sub>, isolated by vacuum filtration, and then evacuated in a vacuum oven at 80 °C overnight. Evacuated MOF samples (5-6 mg) were transferred into an NMR tube and *d*<sub>6</sub>-DMSO (0.55 mL) was added. Subsequently, D<sub>2</sub>SO<sub>4</sub> (0.09 mL, 98 % w/w in D<sub>2</sub>O) was also added. The tubes were capped and sonicated until all the solid was dissolved (~ 1 min).

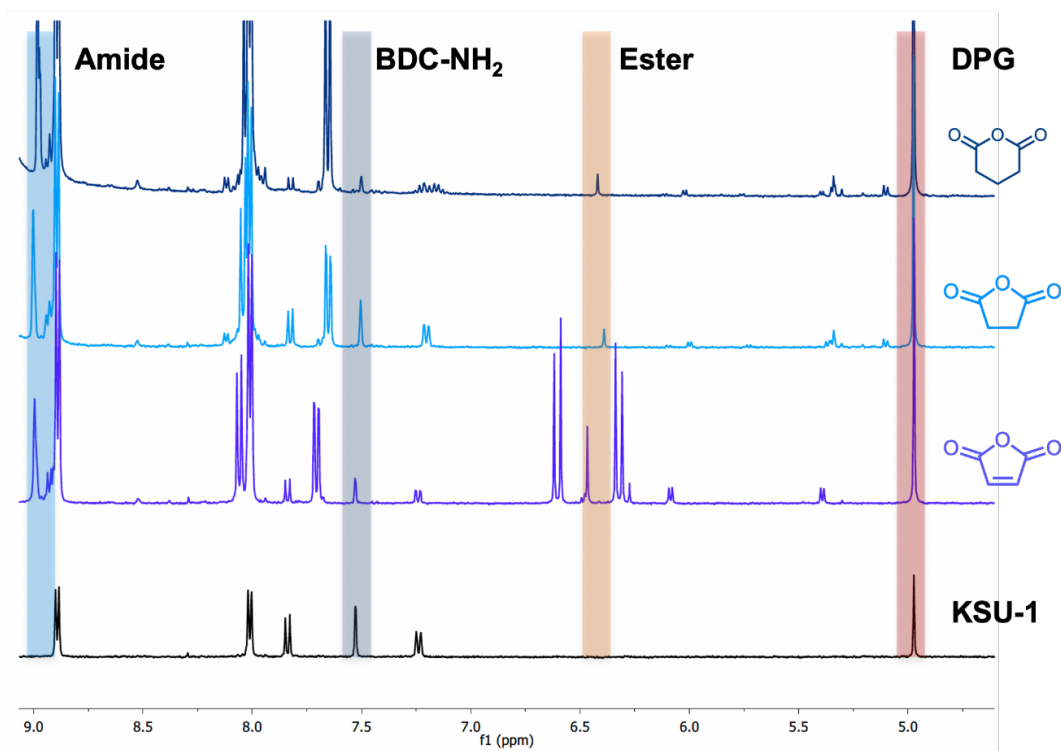


Figure 5.11. Representative  $^1\text{H}$ -NMR spectra of reactions of KSU-1 with different cyclic anhydrides in toluene at 50 °C analyzed at 30 minutes.

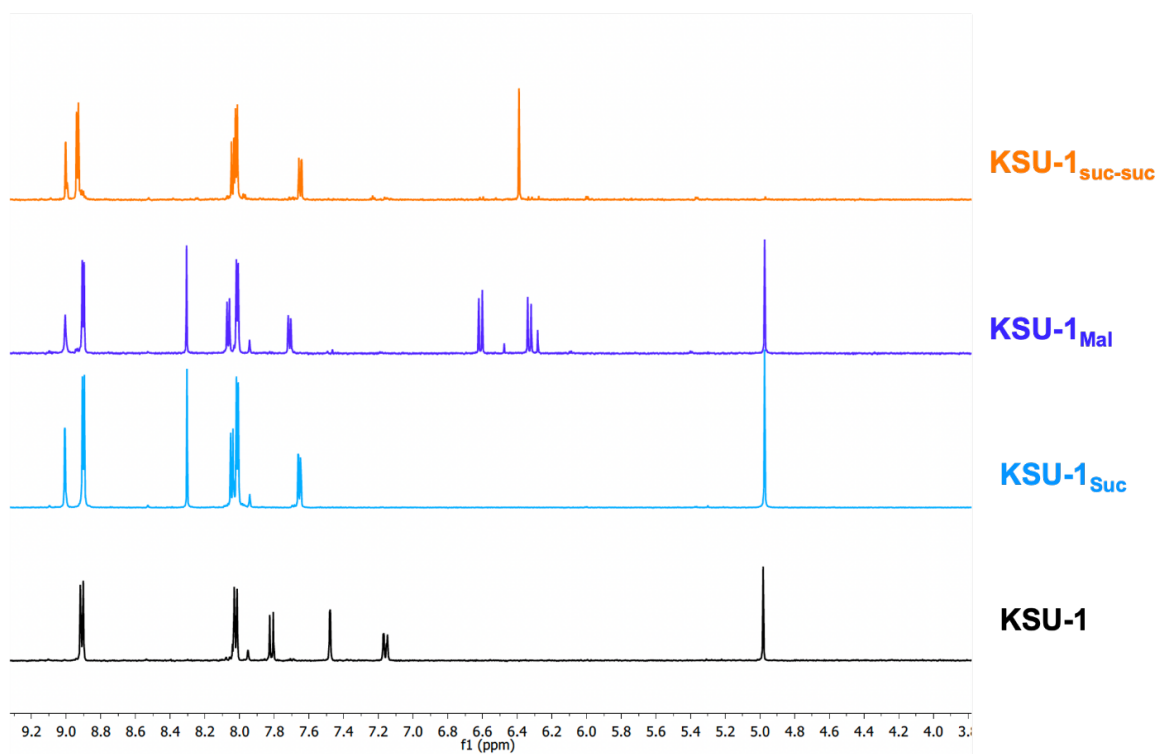


Figure 5.12. Representative  $^1\text{H}$ -NMR spectra of reactions of KSU-1<sub>mal</sub> with succinic anhydrides in toluene at 50 °C resulting in KSU-1<sub>suc-suc</sub> analyzed at 24h.



Table 5.1. Simultaneous reaction on KSU-1-NH<sub>2</sub> and -OH with different cyclic anhydrides.

| Entry | Cyclic anhydride | % conv.          |     |
|-------|------------------|------------------|-----|
|       |                  | -NH <sub>2</sub> | -OH |
| 1     | Maleic           | 87               | 32  |
| 2     | Succinic         | 76               | 21  |
| 4     | Glutaric         | 90               | 22  |

0.2M in Toluene, 30min, 50 °C

### 5.6.3.3. Powder X-ray diffraction (PXRD)

Powder X-ray diffraction patterns were recorded on a Bruker AXS D8 Advance Phaser diffractometer (Bruker AXS, Karlsruhe, Germany) with Cu K $\alpha$  radiation ( $\lambda = 1.5418 \text{ \AA}$ ) over a range of  $4^\circ < 2\theta < 40^\circ$  in  $0.02^\circ$  steps with a 0.5 s counting time per step. Samples were collected from the bottom of the reaction vial as a thick suspension in DMF and spread on a Si-Einkristalle plate immediately before PXRD measurements.

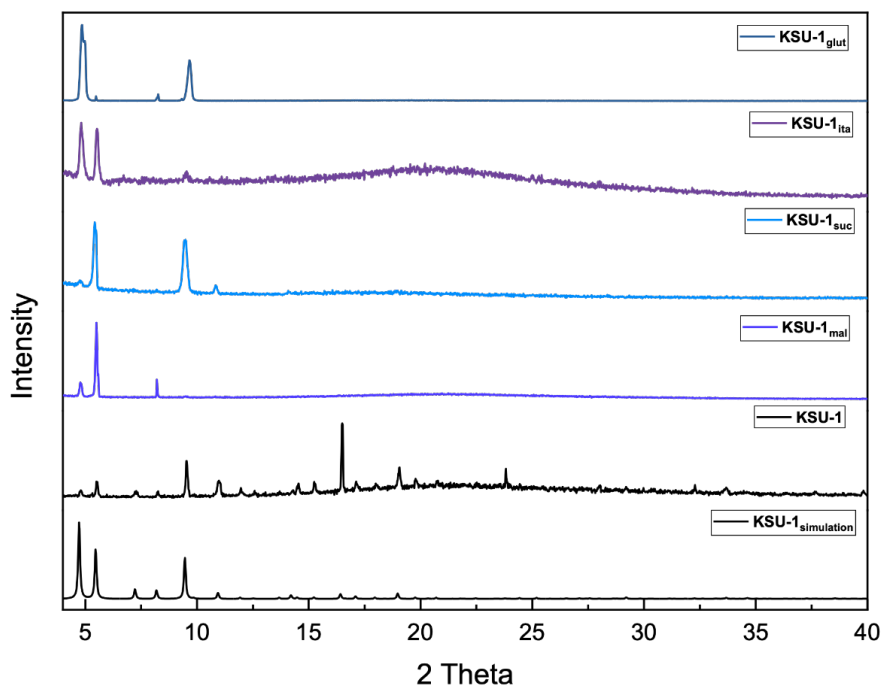


Figure 5.13. The PXRD patterns of the simulated KSU-1, the experimental KSU-1, and the KSU-1 after reacting with the cyclic anhydrides to form KSU-1<sub>Mal</sub> and KSU-1<sub>Suc</sub>, KSU-1<sub>Ita</sub> and KSU-1<sub>Glut</sub> respectively.

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## Chapter 6 - Epilogue

Based on the findings of this thesis, several promising directions for future research emerge. In Chapter 2 we observed unexpected reversal in reactivity when organic functionalities were immobilized together in a MOF. This observation indicates that chemical functionalities can alter their chemical behavior when immobilized in confined spaces much like in enzyme active sites. Consequently, when multiple functionalities work together in such confined spaces, they can generate new, useful properties for applications reliant on supramolecular interactions such as catalysis and sensing. To fully harness these emerging properties, it is crucial to elucidate the molecular origin of this reversal, which can further guide design of innovative materials. As such, future research should focus on unravelling the mechanisms behind these unexpected reversal of reactivities within confined spaces, ultimately informing the development of next-generation materials.

### 6.1. Study of origin of confinement effects with uniformly functionalized multifunctional MOFs

From Chapter 2, we identified following two major conclusions that require further investigation:

- (i) there was possibly activation of the hydroxyl via adventitious solvent mediated hydrogen bonding through  $\text{-NH}_2 \rightarrow \text{solvent} \rightarrow \text{-OH}$  under conditions where both functionalities reacted slowest.
- (ii) the reversal of reactivity depended to the electrophilicity of the isocyanates.

To probe the origin of unexpected reversal, particularly the first conclusion, we propose the synthesis of *kgm* multifunctional MOFs using BDC derivatives where the amine is replaced with various functional groups such as H,  $\text{-OCF}_3$ ,  $\text{-OH}$  and  $\text{-SH}$  with varying nucleophilicities and hydrogen bond donor or acceptor abilities (Figure 6.1).<sup>1</sup>

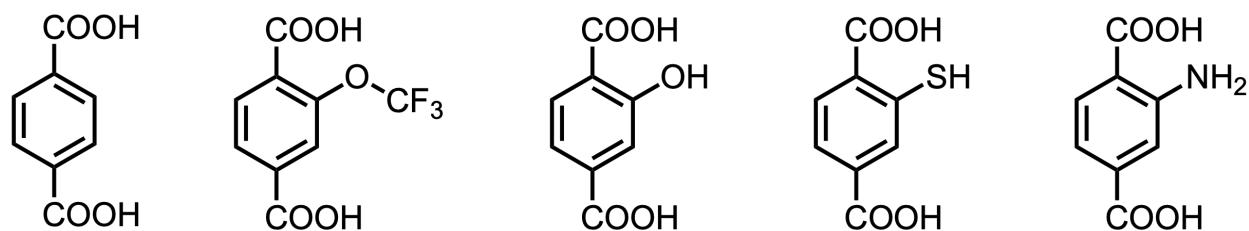


Figure 6.1. Possible BDC derivatives that can be used for construction of kgm **KSU** versions to study the contribution of the amine in influencing the unexpected reversal of reactivity.

By varying these electronic properties, we aim to determine whether the amine is essential for activation of the hydroxyl or whether other functional groups can similarly promote or impede the reactivity on the hydroxyl site. We anticipate the challenge of predicting the resulting MOF framework topology, but if different topologies are obtained, we can still explore their reactions with isocyanates. Such studies would offer valuable insights into how distances or positioning of functional groups influence the observed unexpected reactivity reversal.

A more reliable way to establish whether hydrogen bond acceptor or hydrogen donor ability promotes the reaction is to modify the amine via PSM by introducing alkyl or carboxylic substituents and observe their reactivity with isopropyl isocyanate. Both PSM approaches have been successfully demonstrated in our group, as discussed in Chapter 5 and published work by Samarakoon et. al (**Figure 6.2**).<sup>2</sup>

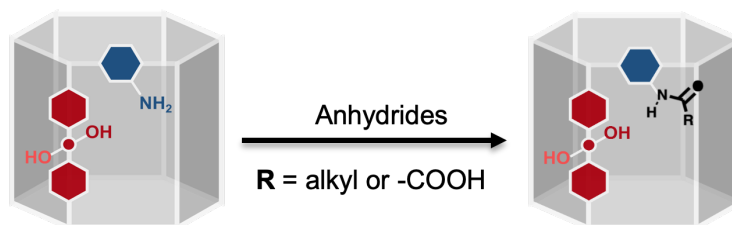


Figure 6.2. Modification of amine group to tune the hydrogen bond acceptor or donor ability of the MOF pore environment.

Lastly, the effects of solvents properties such as polarity, hydrogen bond acceptor ability should be investigated. In particular, using dry solvents and systematically adding of water molecules will allow us to explore solvent-mediated hydrogen bond activation of the hydroxyl.

This approach will test the hypothesis that the amine activates the hydroxyl via solvent-mediated hydrogen bonding. Moreover, since solvents are known to affect selectivity, a range of isocyanates (alkyl, cyclic, and activated) can be evaluated to further understand these interactions. The findings from this work will not only provide insights into the molecular origin of the unexpected reactivity but also open new avenues for the rational design of well-defined, multifunctionalized MOFs.

## 6.2. Efficient and selective catalysis in confined MOF pores

As observed in Chapter 4, a major drawback of modifying framework pores is the reduction in accessible volume, which can lead to diminished reactivity if the reaction occurs within the pores. This is due to impaired diffusion of reactants and products, ultimately reducing the overall reaction rate.<sup>3</sup> Alternatively, the reaction may occur on the external surface of the MOF catalyst, making it challenging to observe the confinement effect—an effect central to our lab’s development of enzyme-inspired catalysts. To accurately study confinement, it is essential that the MOF’s surface be rendered non-catalytic so that reactions occur exclusively within the pores. To achieve this, we proposed the surface functionalization of all catalysts used in kinetic studies (**Figure 6.3**).

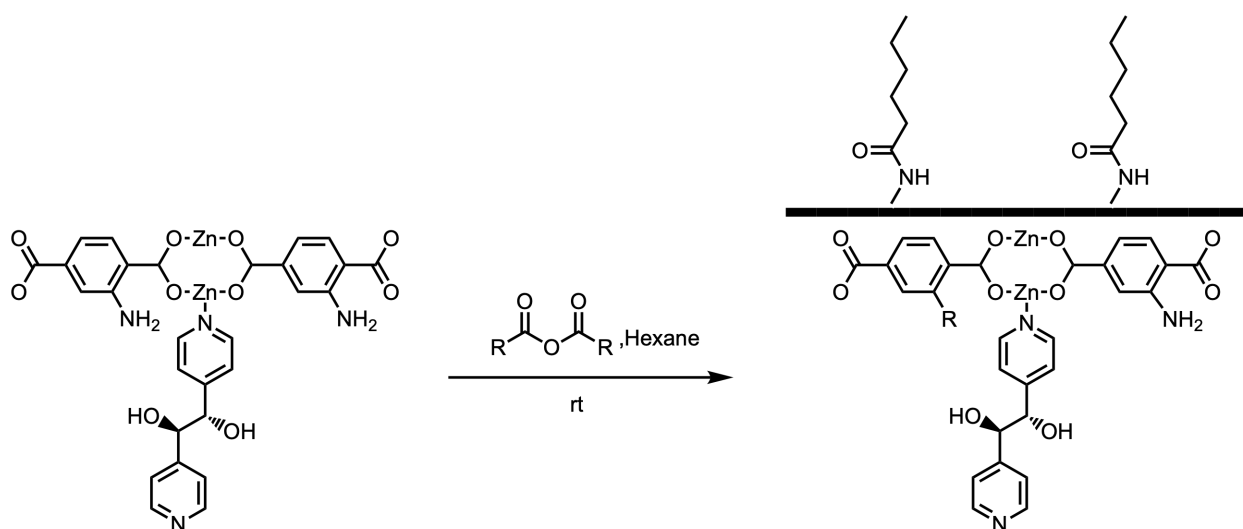


Figure 6.3. Illustration of surface functionalization.

An alternative is to construct catalytic **MOF@MOF** (**Figure 1.4**). Since both **KSU-1** and **KSU-3** share a *kgm* structure with the same parameters, it is feasible to build **KSU-3** which is non-catalytic on top of the bifunctional catalysts. This design would confine the reaction exclusively to the pores.

Another challenge emerged in catalysis of the Henry reaction—it is catalyzed by a base. Due to the reduced pore accessible volume, the reaction occurs on the external surface of the MOF. To address this, we propose incorporating a strong base directly into the MOF framework. Considering our past PSM procedures, selecting a basic isocyanate made sense, however these compounds are costly, ~ \$1000 per mg and difficult to synthesize. Instead, we suggest a two-step PSM strategy: first, reacting the amine with a diisocyanate, and then reacting with L-serine to introduce a basic amine (**Figure 1.5**). While this product may exist as a zwitterion, a proton sponge can be employed during catalysis to efficiently abstract protons. Furthermore, given that diffusion issues due to reduced pore volume after PSM can affect reactivity, utilizing smaller aldehydes, such as isovaleraldehyde, may provide a better probe of the confinement effect in MOF catalysis

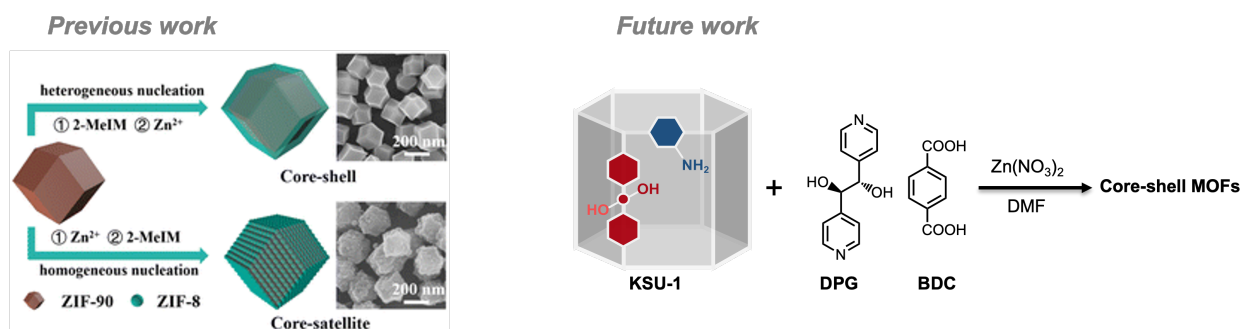


Figure 6.4. Left: Schematic illustration of the synthesis of **ZIF-90@ZIF-8**, Right: proposed synthesis of **KSU-1@KSU-3**. Adapted from REF<sup>4</sup>.



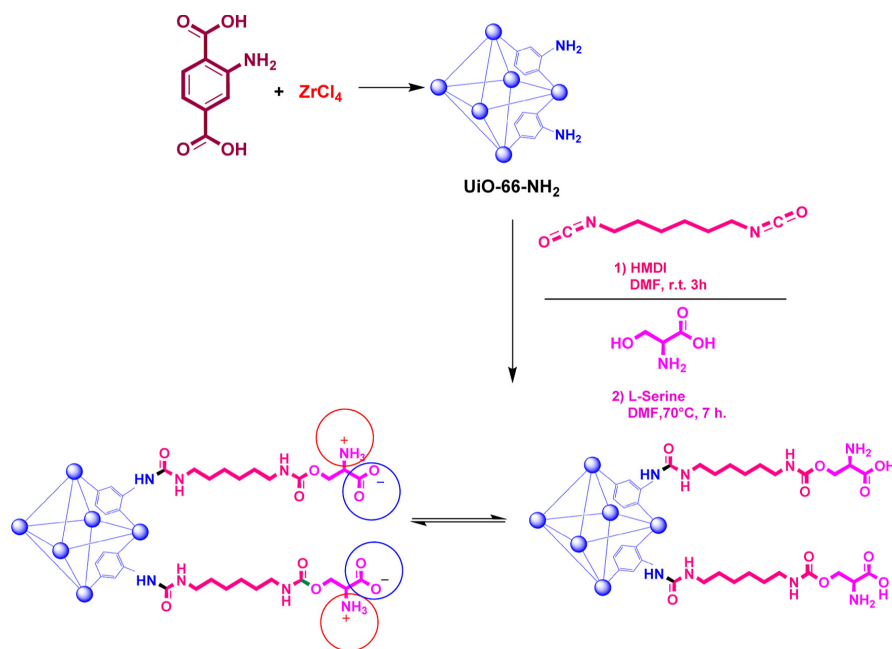


Figure 6.5. Stepwise grafting of a basic amine into MOF pores that can be adopted for chiral **KSU-1** catalysts. Reproduced with permission from REF<sup>5</sup>.

### 6.3. Utilization of uniformly bifunctionalized MOFs bearing pendent carboxylic groups

In Chapter 5, we demonstrated the potential of uniformly functionalizing MOF pores with various acids. However, the reactions need to be optimized to obtain 100% conversion on the second step. This versatile synthetic strategy can be used to systematically tune catalyst performance—whether by enhancing efficiency or selectivity—in Brønsted acid-catalyzed reactions such as methanolysis. In particular, enantioselectivity could be achieved using chiral acyclic anhydrides, for example, *S*-acetoxy succinic anhydride for post-synthetic modification. Additionally, 3-methyl glutaric anhydride may be employed, as it becomes chiral once attached to the MOF. Beyond catalysis, these chiral-functionalized KSU-1 MOFs hold promise for enantioselective separation.<sup>6</sup>

## 6.4. References

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