Squaramide-IRMOF-16 Analogue for Catalysis: Epoxide Ring-Opening Tandem and Multicomponent Reactions

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ABSTRACT: Tandem and multicomponent one-pot reactions are highly attractive because they enable synthesis of target molecules in a single reaction vessel. However, they are difficult to control, as they can lead to the formation of many undesired side-products. Herein we report the use of metal-organic framework (MOF) pores decorated with organocatalytic squaramide moieties to confine ring-opening epoxide reactions of diverse substrates. Controlled mono-addition or tandem reactions inside the pores yield 1,2-aminoalcohols or 1,2,2'-aminodialcohols, respectively. In addition, this squaramide-functionalized MOF enables catalysis of higher-complexity multicomponent reactions such as the catalytic ring-opening of two different epoxides by a single amine to afford 1,2,2'-aminodialcohols.

Tandem reactions are among the best strategies to achieve molecular complexity in a single process.[1] They comprise two or more consecutive independent reactions, which are catalysed by one or more catalysts. Each catalyst produces an intermediate that is further transformed by a second catalytic cycle to give the final product. This translates to lower requirements for solvent, time and energy and to less waste relative to traditional processes. Consequently, tandem reactions have peaked the interest of numerous industries,[2] especially in their solvent-free form.[3]

1,2-amino alcohols (**3**) and 1,2,2'-aminodialcohols (**4**) are structural subunits that are widespread in natural products of industrial relevance (see Figure 1a).[4] Some of these natural products include (*S*, *R*, *R*, *R*)-Nebivolol, which is a β1-adrenergic receptor blocker;[4e] Bestatin, which is an aminopeptidase inhibitor that exhibits immunomodulatory activity;[4d] Sphingosine, which is a a class of cell membrane lipids;[4d] and Cytoxazone, which is an immunomodulatory.[4d] They are also important synthetic intermediates for biologically active compounds,[4] stationary phases in HPLC,[5] and chiral ligands (*e.g.* Oxazaborolidine derivatives; Figure 1a)[6a] or auxiliaries in asymmetric reactions.[6] 1,2-aminoalcohols and 1,2,2'-aminodialcohols can each be readily prepared via ring-opening of epoxides by amines. However, controlling the reaction of the amine (*i.e.* mono- *vs.* di-addition) to the epoxide is difficult, leading to mixtures of the two types of compounds.

Herein we show that confining the aforementioned reaction to metal-organic framework (MOF)[7] pores decorated with organocatalytic squaramide moieties enables control over the formation of the mono- or di- addition products (see below). Furthermore, it also allows for the selective synthesis of heterogeneous double-addition products via multicomponent reactions in which two different epoxides are opened by a single amine (see below). Recently, Hupp, Farha, Mirkin *et al.*[8] and Cohen *et al.*[9] demonstrated that squaramide moieties can be incorporated into MOFs by post-synthetic modification of UiO-67 and by using a tetracarboxylate squaramide-based linker to produce a new Cu(II)-based MOF showing a pore diameter of ~ 8 Å x 8 Å. Both squaramide-functionalized MOFs[10] were successfully tested as catalysts for Friedel-Crafts reactions between indoles and β-nitroalkenes. For our targeted catalytic reactions, we constructed a squaramide-functionalized IRMOF-16 analogue (hereafter called **Sq_IRMOF-16**) because it shows a three-dimensional mesopore system in which the squaramide moieties are totally accessible in all three dimensions and are well separated to avoid any self-quenching phenomena. In addition, the pore diameter is ~ 17 Å x 17 Å, which is sufficiently large to host the intermediates produced during the tandem reactions. The linker (3,4-dioxocyclobut-1-ene-1,2-diyl)bis(azanedyil)-p-dibenzoic acid, hereafter called **L1**) was designed to resemble, both in topology and in length, to the *p,p'*-terphenyldicarboxylic acid (tpdc), which is the linker used to synthesize IRMOF-16 (Figure 1b).[11] Moreover, and in contrast to a previously reported linker[9] in which the squaramide moiety is in the meta position to the acid, in **L1** the squaramide moiety is para to the carboxylic group. Therefore, our design leads to a more acidic NH proton than in the meta case.

We began by synthesizing **L1**, using slight modifications of previously reported procedures.[12] Then, **Sq_IRMOF-16** was synthesized by heating a mixture of **L1** and $Zn(NO_3)_2$ in *N*,*N*-dimethylformamide (DMF) at 85 °C for 7 days. After this period, yellow cubic crystals of **Sq_IRMOF-16** were harvested (yield = 53%). As expected, the experimental powder X-ray diffraction (PXRD) pattern of **Sq_IRMOF-16** was in excellent agreement with the one calculated from the envisioned squaramide-based IRMOF-16 (Figure 1c, see also Supporting Information, Figure S1). The squaramide-based IRMOF-16 model was constructed from the experimental IRMOF-16 structure[11] by ligand replacement, respecting the symmetry of IRMOF-16 (Pm-3m space group). This step was followed by a molecular mechanics energy minimization to improve the geometry of the bonds within the framework using the Forcite tool of the Materials Studio software (Biovia).[13] Therefore, analogously to IRMOF-16, **Sq_IRMOF-16** comprises a zinc-metal cluster (Zn_4O) bridged by six dicarboxylate linkers that form a network with **pcu** topology. The network is a three-dimensional mesopore system (pore size: ~ 17 Å × 17 Å) in which the squaramide moieties point towards the pores and therefore, are totally accessible in all three dimensions (Figure 1b).

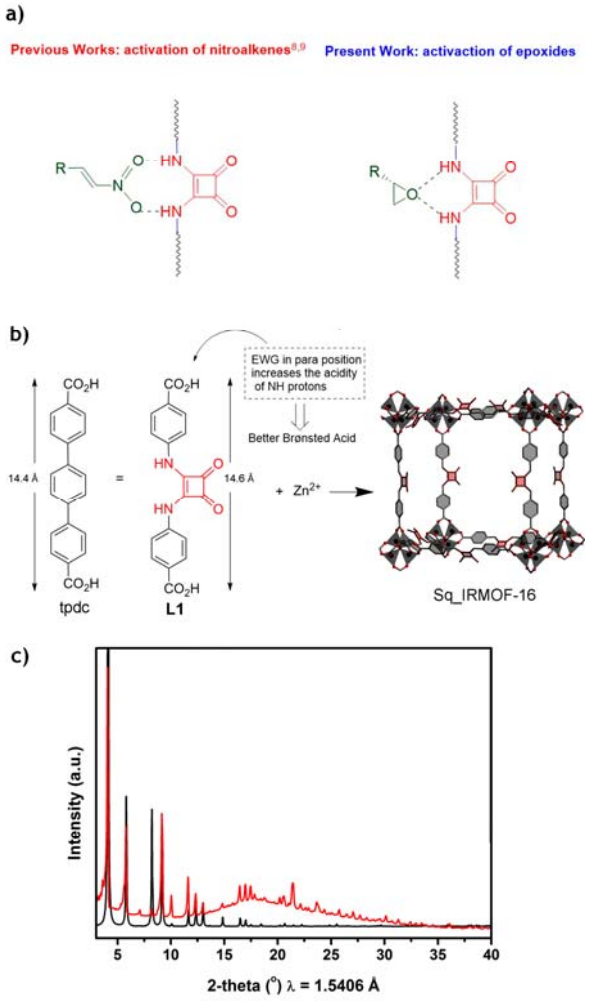


Figure 1. a) Schematic illustration of the introduction of squaramide moieties in MOFs for catalysing Friedel-Craft reactions with nitroalkanes (previous works) and simple, tandem and multicomponent epoxide ring-openings under solvent-free conditions (this work). b) Representation of the linkers tpdc and **L1**, and of the structure of **Sq_IRMOF-16**, in which the squaramide moieties have been highlighted in red. EWG refers to electron withdrawing groups. c) XRPD diffractogram of **Sq_IRMOF-16** (red), compared with the simulated powder pattern obtained from the structural model (black).

For the catalytic experiments, we carefully dried **Sq_IRMOF-16** dried under inert atmosphere and then, immediately mixed it with the other reagents (Supporting Information, Figure S2). It is worth to mention that this drying step was critical, as **Sq_IRMOF-16** tends to become amorphous upon exposure to vacuum, and to transform into an unknown crystalline phase upon contact with water (Supporting Information, Figure S3). In order to verify that **Sq_IRMOF-16** remained stable during the catalytic processes, it was recovered from the reaction media after the catalytic runs and its crystalline phase was confirmed by XRPD (Supporting Information, Figure S4). Additional experiments proved that the catalytic activity of **Sq_IRMOF-16** was not related to the degradation or leaching of molecular species under the reaction conditions.[14]

As a first approach to studying the catalytic behavior of **Sq_IRMOF-16**, we monitored the kinetics of the reactions of each amine (**1a**, R=Me, or **1b**, R= *t*-Bu) with each epoxide (**2a**, R= Et or **2b**, R= $C_{10}H_{21}$) at 60 ºC (Figure 2b). We introduced to the reaction medium a 5 mol% content of catalytic centers, which are included in the structure of **Sq_IRMOF-16**; that is, 2.9 mg of **Sq_IRMOF-16** that corresponds to 0.005 mmol of catalytic units were used to catalyze the reaction of 0.1 mmol of the corresponding aniline with an excess of epoxide. Figure 2c is a plot of the kinetics for each mono-addition product, which was the major species at 8 hours of reaction. Here, the performance of **Sq_IRMOF-16** was also compared with the molecular squaramide C as catalyst (Figure 2a). Using both catalysts, we studied the reaction of **1a** with **2a** (compare the blue dashed line with the blue solid one) and **2b** (compare the red dashed line with the red solid one). The reactions barely progressed when using **C**, probably due to the auto-self-aggregation and poor solubility of the catalyst. In quite contrast, the use of **Sq_IRMOF-16** enhanced both kinetics and yields of these reactions. Moreover, when using **Sq_IRMOF-16**, we observed that epoxide **2a** (R^2 = Et) appeared to react better than epoxide **2b** ($R^2 = C_{10}H_{21}$), as observed in Figure 2c (compare the solid blue line with the solid red one, or the solid grey line with the solid orange one). Likewise, amine **1a** (R^1 = Me) typically reacted faster than amine **1b** (R^1 = *t*-Bu), also evidenced in Figure 2c (compare the solid blue line to the solid grey one, or the solid red line to the solid orange one. Interestingly, in the case of the use of the smaller epoxide **2a** in their reaction with **1a** and **1b** (blue and greys lines), we also found a significant amount of the dialkylated products **4a** and **4b** (see Supporting Information). Altogether, these observations suggest that there is a size discrimination effect when **Sq_IRMOF-16** is used, which is probably due to the lower diffusion rates of the bulkier substrates. These differences confirm that the catalytic processes occur inside the pores of **Sq_IRMOF-16** rather than on its external crystal surfaces.

Interestingly, we observed that once the mono-addition products **3** were obtained, the bis-addition products, homo-disubstituted amino diols **4**, began to form. Scheme 1 shows a series of tandem reactions of the amines **1a-b** and epoxides **2a-f** to form

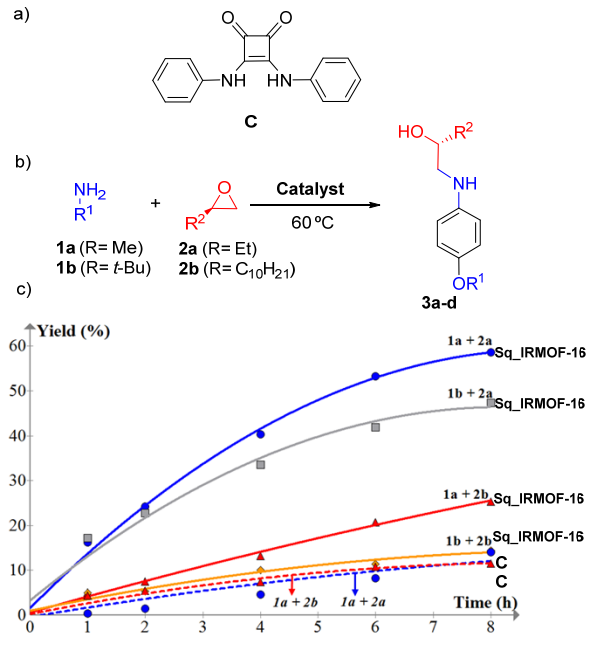
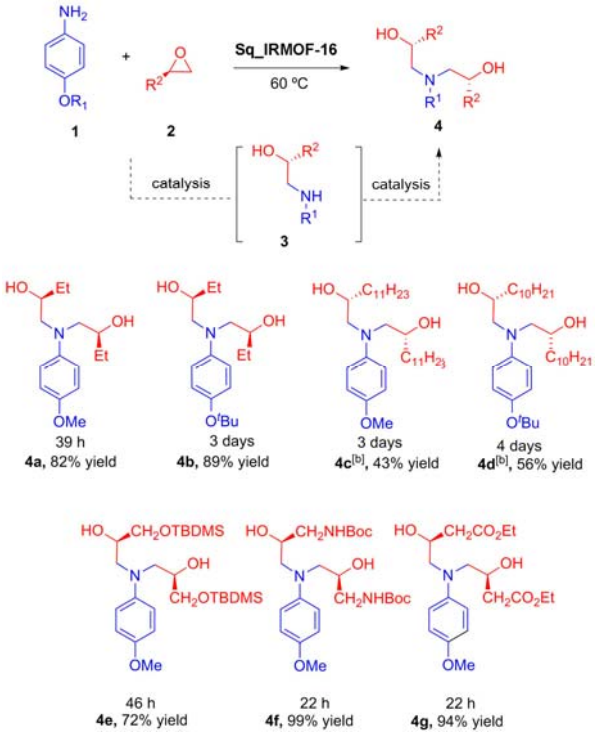


Figure 2. a) Representation of the molecular structure of catalyst **C**. b) Schematic representation of the epoxide ring-opening mono-addition reactions. c) Kinetics plots for ring-openings of an epoxide (**2a** or **2b**) by an amine (**1a** or **1b**), using either **MOF-Sq** (solid lines) or **C** (dashed lines) as catalyst (in both cases, 5 mol% of catalytic units). Reactions were run at 60 ºC, using an excess of epoxide (200 µL) as solvent. Yield was measured by GC-MS and based on an internal standard.

the diols **4a-g** catalyzed by **Sq_IRMOF-16** (5 mol%) to test its catalytic utility. Remarkably, this reaction tolerated many combinations of reagents. The times required to obtain optimized yields of a series of diols **4** correlated to the size (**4a-4d**; Scheme 1, top row) and/or polarity (**4e-4g**; Scheme 1, bottom row) of the substrates. For example, comparing the synthesis of **4a** with that of **4b** reveals that ethyl-epoxide (**2a**) reacted faster with para-methoxy aniline (**1a**) than with para-tert-butyl aniline (**1b**). Similarly to **4b**, the diols **4c** (from **1a** and **2b**) and **4d** (from **1b** and **2c**) required 3 days and 4 days, respectively, to reach moderate yields. We attributed these low reaction rates and moderate yields to the steric bulk and hydrophobicity of the alkyl chains in epoxides **2b** ($R^2 = C_{11}H_{23}$) and **2c** ($R^2 = C_{10}H_{21}$), which could hamper the diffusion of each epoxide through the pores of **Sq_IRMOF-16**.

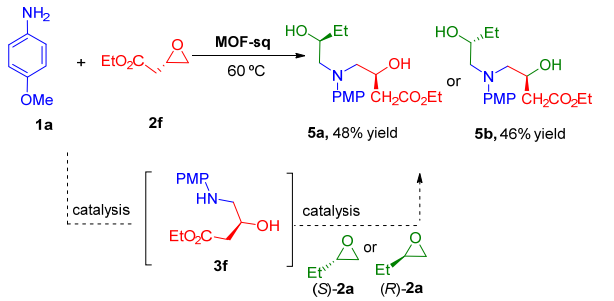
In the above reactions, we also found that the bulkier epoxide **2e** reacted at a similar reaction rate than did the smaller epoxide **2a**. We ascribed this fact to the greater polarity of the -CH_2OTBDMS group in **2e** relative to the -Et group in **2a**, which may help the diffusion of **2e** through the pores of **Sq_IRMOF-16**. Consistent with our hypothesis, the more polar epoxides **2f** (R^2 = CH_2HNBoc) and **2g** (R^2 = CH_2CO_2Et) gave near-total conversion (yields > 90%) to their corresponding diols **4f** and **4g**, respectively, after only 22 h.

We next evaluated the capacity of **Sq_IRMOF-16** to catalyze multicomponent reactions of higher complexity. To this end, we used three reagents (one amine reacted sequentially with two epoxides) to generate heterogeneous diols in one-pot multicomponent reactions. This approach typically requires less energy and generate less waste than step-reactions which needs multiple purification processes. However, a drawback of one-pot reactions for heterogeneous additions is that they demand strict control of the chemistry. In our case, to avoid the formation of undesired side-products, a single mono-addition intermediate **3** had to be generated first. Once **3** had been formed in the reaction media, via one pot process (*i.e.* without any purification), other epoxides can be added to obtain the desired hetero-disubstituted amino diols **5** (Scheme 2).



Scheme 1. Schematic representation of the epoxide ring-opening tandem reaction (top) and representation of the molecular structures of the synthesized homo-disubstituted amino diols **4** (bottom). All the reactions were performed on a 0.1 mmol of aniline **1** and 1.0 mmol of epoxide **2**. In the case of **2b**, **2c** and **2e** were used 0.4 mmol of epoxide under solvent free conditions. [b] The corresponding mono-addition products were also detected in the crude mixture.

We began by reacting para-methoxy aniline (**1a**) and epoxide (*S*)-**2f** in the presence of **Sq_IRMOF-16** for 8 hours to produce the non-isolated intermediate **3f**. Then, the enantiopure epoxide (*S*)-**2a** was added to the reaction medium to give the desired amino-diol (*S,S*)-**5a**. Similarly, we synthesized the amino-diol (*S,R*)-**5b** using the same conditions as for **5a**, except that instead of (*S*)-**2a**, we used (*R*)-**2a**. In both cases, we found a substantial amount of the homo-substituted product **4g** (~ 20%) in the crude mixture. These results indicate that **Sq_IRMOF-16** can indeed catalyze multicomponent reactions, including diastereo-divergent ones.



Scheme 2. Schematic representation of the epoxide ring-opening multicomponent reaction to form the amino diols 5. All the reactions were performed on 0.1 mmol of aniline **1a** and 0.1 mmol of **3f** for the first step, followed by 1.0 mmol of epoxide **2a** for the second step.

In conclusion, we have synthesized a squaramide-functionalized IRMOF-16 analogue, **Sq_IRMOF-16**, for use as a catalyst in the ring-opening of epoxides by nucleophilic amines. **Sq_IRMOF-16** does not undergo the self-aggregation phenomena usually observed for squaramides in solution; in fact, this heterogeneous catalyst is superior to its molecular squaramide analogue. The pores in **Sq_IRMOF-16** are sufficiently large to catalyze the ring-opening of diverse epoxides using different amines. We have demonstrated the catalytic activity of **Sq_IRMOF-16** in the synthesis of simple, tandem and multicomponent epoxide ring-openings under solvent-free conditions and in good yields. The evidences suggest that these reactions are confined to the squaramide-functionalized pores, as **Sq_IRMOF-16** shows size- and polarity-discrimination effects. Given that many organocatalytic moieties can be introduced into MOF pores, we are confident that MOF-based catalysts such as **Sq_IRMOF-16** should help to expand the scope of heterogeneous catalysis in one-pot reactions.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, material characterization and catalytic studies are included in Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org."

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Author Contributions

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(14) To investigate any possible leaching of molecular catalytic species from **Sq_IRMOF-16**, we allowed the mixture of **1a**, **2a** and **Sq_IRMOF-16** to react for 2 hours. The mixture was then filtered and the filtrate was left to react for 2 more hours. This experiment revealed that after filtration, the catalytic activity was stopped. Therefore, the catalytic activity that we observed in this study is derived from the presence of heterogeneous material **Sq_IRMOF-16**, excluding the possibility that homogeneous catalytically active species underwent any leaching.