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 good yields. In addition, this squaramide-functionalised 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.
We began by synthesising \( \text{L1} \), using slight modifications of previously reported procedures.\(^{12}\) Then, \( \text{Sq}_\text{IRMOF-16} \) was synthesised by heating a mixture of \( \text{L1} \) and \( \text{Zn(NO}_3\text{)}_2 \) in \( \text{N,N-dimethylformamide (DMF)} \) at 85 °C for 7 days. After this period, yellow cubic crystals of \( \text{Sq}_\text{IRMOF-16} \) were harvested (yield = 53 %). As expected, the experimental powder X-ray diffraction (PXRD) pattern of \( \text{Sq}_\text{IRMOF-16} \) 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 minimisation to improve the geometry of the bonds within the framework using the Forcite tool of the Materials Studio software (Biovia),\(^{12}\) Therefore, analogously to IRMOF-16, \( \text{Sq}_\text{IRMOF-16} \) comprises a zinc-metal cluster \( (\text{Zn}_4\text{O}) \) bridged by six dicarboxylate linkers that form a network with pcu topology. The network is a three-dimensional mesopore system (pore size: \( \sim 17 \times 17 \times 17 \text{Å} \)) in which the squaramide moieties point towards the pores and therefore, are totally accessible in all three dimensions (Figure 1b).

For the catalytic experiments, we carefully dried \( \text{Sq}_\text{IRMOF-16} \) 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 \( \text{Sq}_\text{IRMOF-16} \) 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 \( \text{Sq}_\text{IRMOF-16} \) 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 \( \text{Sq}_\text{IRMOF-16} \) was not related to the degradation or leaching of molecular species under the reaction conditions.\(^{14}\)

As a first approach to studying the catalytic behaviour of \( \text{Sq}_\text{IRMOF-16} \), we monitored the kinetics of the reactions of each amine \( (1 \text{a}, \text{R}=\text{Me}, \text{or } 1 \text{b}, \text{R}=\text{t-Bu}) \) with each epoxide \( (2 \text{a}, \text{R}=\text{Et} \text{ or } 2 \text{b}, \text{R}=\text{C}_8\text{H}_17) \) at 60 °C (Figure 2b). We introduced to the reaction medium a 5 mol % content of catalytic centers, which are included in the structure of \( \text{Sq}_\text{IRMOF-16} \); that is, \( 2.9 \text{ mg of } \text{Sq}_\text{IRMOF-16} \) 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 para to the carboxylic group. Therefore, our design leads to a more acidic NH proton than in the meta case.

![Figure 1](image1.png)

**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 L, and of the structure of \( \text{Sq}_\text{IRMOF-16} \), in which the squaramide moieties have been highlighted in red. EWG refers to electron withdrawing groups. c) XRPD diffractogram of \( \text{Sq}_\text{IRMOF-16} \) (red) compared with the simulated powder pattern obtained from the structural model (black).

![Figure 2](image2.png)

**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 \( (2 \text{a} \text{ or } 2 \text{b}) \) by an amine \( (1 \text{a} \text{ or } 1 \text{b}) \), using either \( \text{MOF-Sq} \) (solid lines) or \( \text{C} \) (dashed lines) as catalyst (in both cases, 5 mol % of catalytic units). Reactions were run at 60 °C, using an excess of epoxide \( (200 \mu\text{l}) \) as solvent. Yield was measured by GC-MS and based on an internal standard.
performance of Sq\textsubscript{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\textsubscript{IRMOF-16} enhanced both kinetics and yields of these reactions. Moreover, when using Sq\textsubscript{IRMOF-16}, we observed that epoxide 2a (R\textsuperscript{2} = Et) appeared to react better than epoxide 2b (R\textsuperscript{2} = C\textsubscript{6}H\textsubscript{13}), 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\textsuperscript{1} = Me) typically reacted faster than amine 1b (R\textsuperscript{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 grey 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\textsubscript{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\textsubscript{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, homodisubstituted amino diols 4, began to form. Figure 3 shows a series of tandem reactions of the amines 1a-b and epoxides 2a-f to form the diols 4a-g catalysed by Sq\textsubscript{IRMOF-16} (5 mol\% to test its catalytic utility. Remarkably, this reaction tolerated many combinations of reagents. The times required to obtain optimised yields of a series of diols 4 correlated to the size (4a-4d; Figure 3, top row) and/or polarity (4e-4g; Figure 3, 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\textsuperscript{2} = C\textsubscript{6}H\textsubscript{13}) and 2c (R\textsuperscript{2} = C\textsubscript{8}H\textsubscript{17}), which could hamper the diffusion of each epoxide through the pores of Sq\textsubscript{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\textsubscript{2}OTBDMS group in epoxides 2f (R\textsuperscript{2} = CH\textsubscript{2}HNBoc) and 2g (R\textsuperscript{2} = CH\textsubscript{2}COEt) 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\textsubscript{IRMOF-16} to catalyse 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 (Figure 4).

We began by reacting para-methoxy aniline (1a) and epoxide (S)-2f in the presence of Sq\textsubscript{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 synthesised 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 catalyse multicomponent reactions, including diastereo-divergent ones.

In conclusion, we have synthesised a squaramide-functionalised 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 catalyse 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-functionalised 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.

Acknowledgements

This work was supported by the Spanish MINECO (projects PN MAT2015-65354-C2-1-R and CTQ2015-64561-R), the Catalan AGAUR (project 2014 SGR 80), the ERC under the EU FP7 (ERC-Co 615954 and ERC-CG 647550), and European Union’s Horizon 2020 research and innovation programme under grant agreement No 685727. It was also funded by the CERCA Programme/Generalitat de Catalunya. ICN2 acknowledges the support of the Spanish MINECO through the Severo Ochoa Centers of Excellence Program, under Grant SEV-2013-0295.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Metal-organic frameworks · H-bond catalysis · Tandem and multicomponent reactions · Squaramide