Tandem reactions are among the best strategies to achieve molecular complexity in a single process. 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, especially in their solvent-free form.

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). Some of these natural products include (S, R, R, R)-Nebivolol, which is a β1-adrenergic receptor blocker,4d Bestatin, which is an aminopeptidase inhibitor that exhibits immunomodulatory activity;4d Sphingosine, which is a class of cell membrane lipids;4d and Cytoxazone, which is an immunomodulatory.4d They are also important synthetic intermediates for biologically active compounds,4e stationery phases in HPLC,4e and chiral ligands (e.g. Oxazaborolidine derivatives; Figure 1a)4f or auxiliaries in asymmetric reactions.4f 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 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.
We began by synthesizing L1, using slight modifications of previously reported procedures. Then, Sq_IRMOF-16 was synthesized by heating a mixture of L1 and Zn(NO3)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 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 Forge tool of the Materials Studio software (Biovia). Therefore, analogously to IRMOF-16, Sq_IRMOF-16 comprises a zinc-metal cluster (ZnO) 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).

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.

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= C10H21) 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 (R2 = Et) appeared to react better than epoxide 2b (R2 = C10H21), 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 (R1 = Me) typically reacted faster than amine 1b (R1 = 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_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 1](image-url). 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).
the diols 4a-g catalyzed by \textit{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 2e) 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 (R2 = C11H23) and 2c (R2 = C10H21), which could hamper the diffusion of each epoxide through the pores of \textit{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 \(-\text{CH2OTBDMS}\) group in 2e relative to the -Et group in 2a, which may help the diffusion of 2e through the pores of \textit{Sq\_IRMOF-16}. Consistent with this hypothesis, the more polar epoxides 2f (R2 = \text{CH2HNBOc}) and 2g (R2 = \text{CH2CO2Et}) gave near-total conversion (yields > 90\%) to their corresponding diols 4f and 4g, respectively, after only 22 h.

We next evaluated the capacity of \textit{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).

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 °C, using an excess of epoxide (200 \(\mu\text{L}\)) as solvent. Yield was measured by GC-MS and based on an internal standard.

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 \textit{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 \textit{Sq\_IRMOF-16} can indeed catalyze multicomponent reactions, including diastereo-divergent ones.
Enantioselective Direct Aldol Reaction

Jiang, Y-Z.; Wu, Y-D. Novel Small Organic Molecules for a Highly Efficient Catalysis

REFERENCES


