

# Enantioselective ring-opening of *meso*-epoxides by aromatic amines catalyzed by a homochiral metal–organic framework†

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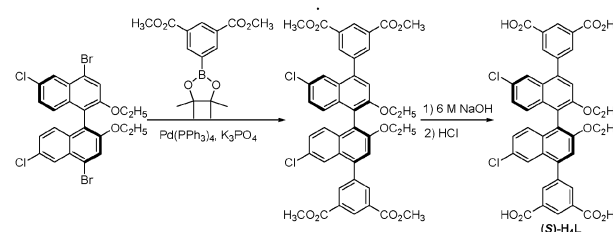
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The enantioselective ring-opening of *meso*-epoxides by aromatic amines was achieved by using a new chiral metal–organic framework **UTSA-32a**. The corresponding  $\alpha$ -hydroxyamines were obtained with good yields and ee values (up to 89% ee).

Porous metal–organic frameworks (MOFs) have emerged as multifunctional materials in the past two decades. The rapid progress has even led to the use of some MOF materials for their potential industrial applications in gas storage and separation.<sup>1,2</sup> Although porous MOFs have also been extensively explored for their heterogeneous catalysis,<sup>3,4</sup> their catalytic properties are typically not as good as other porous solid catalysts such as zeolites. The power to tune the pores and introduce chiral pore spaces into the homochiral MOFs through the interplay of metal ions/clusters and chiral organic linkers should theoretically produce homochiral MOFs whose catalytic properties might surpass those of well-developed asymmetric heterogeneous catalysts; however, such a promise has been rarely fulfilled. In fact, since the discovery of the first two homochiral MOF catalysts during 2000–2001,<sup>5</sup> only a few dozens of homochiral MOFs have been realized for their asymmetric catalysis,<sup>6–8</sup> underlining the big challenge of targeting MOF asymmetric catalysts. Herein we report the synthesis and structure of a new homochiral MOF  $\text{Zn}_2(\text{L})(\text{H}_2\text{O})_2 \cdot (\text{DMA})_4$  (**UTSA-32**, **UTSA** = University of Texas at San Antonio;  $\text{H}_4\text{L}$  = (*S*)-6,6'-dichloro-2,2'-diethoxyl-1,1'-binaphthyl-4,4'-bis(5-isophthalic acid); **DMA** = *N,N'*-dimethylacetamide) constructed using a chiral organic linker  $\text{H}_4\text{L}$  (Scheme 1), and its heterogeneous enantioselective ring-opening of *meso*-epoxides by aromatic amines for the production of chiral 1,2-aminols.



**Scheme 1** Synthetic route to the organic linker (*S*)- $\text{H}_4\text{L}$ .

The enantiopure organic linker  $\text{H}_4\text{L}$  was synthesized by a Pd-catalyzed Suzuki cross-coupling reaction between (*S*)-6,6'-dichloro-4,4'-dibromo-2,2'-diethoxyl-1,1'-binaphthyl and dimethyl 5-(pinacolboronyl)isophthalate followed by hydrolysis and acidification.<sup>9</sup> **UTSA-32** was obtained by the solvothermal reaction of  $\text{H}_4\text{L}$  and  $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$  in a DMA–EtOH mixture at 110 °C for 2 days. The structure was characterized by single-crystal X-ray diffraction studies, and the phase purity of the bulk material was confirmed by powder X-ray diffraction (PXRD) (Fig. S1, ESI†). **UTSA-32** can be formulated as  $\text{Zn}_2(\text{L})(\text{H}_2\text{O})_2 \cdot (\text{DMA})_4$  on the basis of single-crystal X-ray structure determination, thermogravimetric analysis (TGA, Fig. S2, ESI†) and microanalysis.‡

Single-crystal X-ray diffraction analysis reveals that **UTSA-32** crystallizes in the chiral space group  $P2_1$  because of the incorporation of the chiral organic linker **L**. The binuclear  $\text{Zn}_2$  clusters are bridged by the organic linkers **L** to form a three-dimensional framework in which there exist one-dimensional irregular pores of about  $3.2 \times 10.0$  Å along the *a* axis (Fig. 1a). Topologically, each binuclear  $\text{Zn}_2$  cluster and organic linker **L** can be considered as the 4-coordinated nodes which are connected with each other to form the rare lonsdaleite (point symbol 6<sup>6</sup>) network (Fig. 1b). The void volume comprises 53.5% of the total crystal volume as estimated using PLATON.<sup>10</sup> The permanent porosity has been established by  $\text{CO}_2$  sorption isotherm at 196 K, indicating that it has a BET surface area of  $289.1 \text{ m}^2 \text{ g}^{-1}$  (Fig. S3, ESI†).

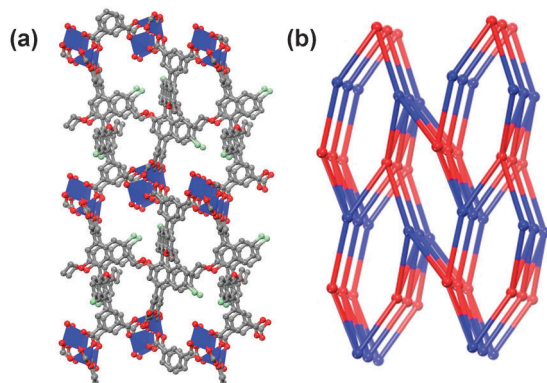
Using *cis*-stilbene epoxide (**1a**) and aniline (**2a**) as the model substrates, we first evaluated whether **UTSA-32a** could be used as a catalyst for the enantioselective ring-opening reaction.<sup>8</sup> The results are summarized in Table 1. As the data in Table 1

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† Electronic supplementary information (ESI) available: Experimental procedures, characterization data of all compounds, and copy of NMR spectra. CCDC 713157. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc45988h

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**Fig. 1** Single-crystal X-ray structure of **UTSA-32** showing (a) a three-dimensional framework structure and one-dimensional irregular micropores of about  $3.2 \times 10.0$  Å along *a* axis and (b) the rare lonsdaleite (point symbol  $6^6$ ) framework topology.

**Table 1** Optimization of the reaction conditions<sup>a</sup>

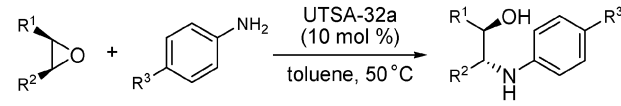
Entry	1a/2a <sup>b</sup>	Solvent	<i>T</i> (°C)	Time (h)	Yield <sup>c</sup> (%)	ee <sup>d</sup>
1	1/1.2	Toluene	rt	27	15	87
2	1/1.2	—	rt	27	21	0
3	5/1	Toluene	rt	24	25 <sup>e</sup>	86
4	1/5	Toluene	rt	24	27	86
5	1/1.2	Toluene	80	14	27	87
6	1/5	Toluene	80	14	89	69
7	1/5	Toluene	50	15	91	69
8	1/2.5	Toluene	50	15	91	85
9	1/2.5	Toluene	rt	40	30	77
10	1/2.5	Benzene	50	17	82	52
11	1/2.5	CH <sub>2</sub> Cl <sub>2</sub>	50	17	78	11
12	1/2.5	THF	50	17	51	26
13	1/2.5	CH <sub>3</sub> CN	50	17	82	29
14	1/2.5	DMSO	50	17	0	—

<sup>a</sup> Unless otherwise specified, all reactions were carried out using *cis*-stilbene epoxide (**1a**, 0.10 mmol) and aniline **2a** (amount see column 2), and **UTSA-32a** (0.010 mmol, 10 mol%) in the indicated solvent (0.5 mL) at the specified temperature. <sup>b</sup> Molar ratios. <sup>c</sup> Yield of the isolated product after column chromatography. <sup>d</sup> Determined using HPLC analysis on a ChiralCel AD-H column. <sup>e</sup> Yield in this case was based on the limiting reagent **2a**.

show, when 1.2 equivalents of **2a** and 10 mmol% **UTSA-32a** were used in toluene at rt for 27 h, the desired ring-opened aminol **3a** was obtained in 15% yield with an ee value of 87% (entry 1). Although the yield is low, the ee value of the product is very promising. Encouraged by these results, we tried to optimize the reaction conditions to improve the yield of this reaction. We then carried out the reaction under neat conditions. Surprisingly, a racemic product was obtained in 21% yield (entry 2). The increase of the molar ratio of *cis*-stilbene epoxide (**1a**) to **2a** to 5 : 1 only increased the yield slightly to 25%, without affecting the product ee value (entry 3). Similarly, the use of a molar ratio of 1 : 5 of **1a/2a** did not help to increase the yield (entry 4). Since the loading of the starting materials have almost no influence on the yield, we went back to our original conditions (entry 1), but increased the reaction temperature to 80 °C (entry 5). We found

the reaction to be faster; however, the product yield was not much improved. Interestingly, when the loading of **2a** was increased to 5 equivalents under these new conditions, a high yield of 89% was obtained for **3a**, although the ee value dropped significantly to 69% (entry 6). We then tried to lower the reaction temperature to 50 °C; a similarly high yield was obtained, but there was no improvement in the ee value at all (entry 7). Gratifyingly, when the loading of **2a** was reduced to 2.5 equivalents, product **3a** was obtained in 91% yield and with a high ee value of 85% (entry 8). Using this new ratio, a similar reaction at room temperature led to a very slow reaction that produced a 40% yield in 40 h and a lower ee value of 77% for **3a** (entry 9). These results indicate that the reaction temperature and the loading of **2a** have major effects on the reactivity and the enantioselectivity of this reaction, while the loading of epoxide **1a** has only some minor effects. From these data, it is evident that the **UTSA-32a**-catalysed reaction is very sensitive toward temperature. The reactivity of the MOF catalyst was dramatically improved when the temperature was 50 °C or above. Next, we screened some common organic solvents, such as benzene, methylene chloride, THF, acetonitrile, and DMSO (entries 10–14), under the optimized conditions (entry 8), and it was found none of these solvents were better than toluene in terms of reactivity and enantioselectivity. It is interesting to note that no product was obtained when the very polar solvent DMSO was used (entry 14). Thus, this screening identified toluene as the best solvent for this reaction. Since much lower ee values were obtained in benzene (entry 10) and methylene chloride (entry 11), which should not interfere with the coordination between the substrates and the MOF metal center, we speculated that the desired high enantioselective ring-opening reaction might occur inside the pores of the MOF, whereas the reaction on the catalyst surface is less enantioselective. The major solvent effects observed can then be explained by the fact that some of these solvents can prevent epoxide **1a** from entering the pores to some extent and lead to lower product ee values due to the low enantioselective reaction on the catalyst surface. Large loading of **2a** (entries 2, 6, and 7) probably has similar effects as solvents. DMSO can even interfere with the reaction on the surface of the MOF catalyst because it can disrupt the coordination between the substrates and the catalyst and, therefore, no reaction is observed.

Once the reaction conditions were optimized, the scope of this reaction was evaluated, and the results are collected in Table 2. In the beginning the scope of aniline was evaluated with *cis*-stilbene epoxide (**1a**). As is evident from the data in Table 2, besides aniline (Table 2, entry 1), 4-substituted anilines can also be applied in this reaction. Use of the electron-donating methyl group leads to a lower yield (78%) and ee value (75% ee) of the product **3b** (entry 2). 4-Methoxyaniline provided an even lower yield (70%) and ee value (62% ee) for the product **3c** (entry 3). In contrast, when an electron-withdrawing fluoro group is at the *para*-position of aniline, the corresponding product **3d** was obtained in the highest yield of 95% and with the highest ee value of 89% (entry 4). Nevertheless, the yields and ee values of the ring-opening products dropped significantly when the substituent was changed from fluoro- to chloro- (58% ee, entry 5) and bromo- (31% ee, entry 6). Thus, aniline (entry 1) and 4-fluoroaniline (entry 4) yield the best results in terms of both reactivity and selectivity, which

**Table 2** Substrate scope of the epoxide ring-opening catalyzed by **UTSA-32a**<sup>a</sup>


Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Time (h)	3/Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	Ph	Ph	H	15	a/91	85
2	Ph	Ph	Me	70	b/78	75
3	Ph	Ph	MeO	63	c/70	62
4	Ph	Ph	F	63	d/95	89
5	Ph	Ph	Cl	63	e/70	58
6	Ph	Ph	Br	63	f/72	31
7	4-ClC <sub>6</sub> H <sub>4</sub>	4-ClC <sub>6</sub> H <sub>4</sub>	H	64	g/86	34
8	4-MeC <sub>6</sub> H <sub>4</sub>	4-MeC <sub>6</sub> H <sub>4</sub>	H	39	h/81	17
9	2-Nap	2-Nap	H	75	i/78	32
10	-(CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> )		H	47	j/69	12
11	-(CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> )		H	42	k/78	15

<sup>a</sup> Unless otherwise specified, all reactions were carried out with the *meso*-epoxide **1** (0.10 mmol) and the aniline derivative **2** (0.25 mmol, 2.5 equiv.), and **UTSA-32a** (0.010 mmol, 10 mol%) as the catalyst in toluene (0.5 mL) at 50 °C. <sup>b</sup> Yield of the isolated product **3** after column chromatography.

<sup>c</sup> Determined using HPLC analyses using chiral columns.

most likely is due to the size effects instead of the electronic effects. The results obtained with these substituted anilines also suggest that the ring-opening reaction happens inside the pores of the MOF. We then evaluated the epoxide scope using aniline (**2a**). Both *cis*-4,4'-dichlorostilbene epoxide (entry 7) and *cis*-4,4'-dimethylstilbene epoxide (entry 8) gave much lower ee values for the corresponding ring-opened aminol products than *cis*-stilbene epoxide (entry 1). Also *cis*-2,3-di(naphthalen-2-yl)oxirane yielded a low ee value of the desired aminol **3i** (32% ee, entry 9). Cyclopentene oxide (entry 10) and cyclohexene oxide (entry 11) were also studied. However, none of these cyclic aliphatic substrates are good substrates for this reaction and poor ee values of the ring-opened aminol products were obtained. The heterogeneous asymmetric MOF catalyst can be easily recovered. After five cycles, the used MOF catalyst basically keeps the same catalytic activity and selectivity as the original one.

In summary, we have demonstrated that **UTSA-32a** a new chiral MOF based on the binaphthyl scaffold is a very good catalyst for the aminolysis of *meso*-epoxides. The corresponding ring-opened aminol products may be obtained in good to excellent yields with mediocre to excellent ee values (up 89% ee). Enantio-enriched 1,2-aminols are very useful building blocks for the preparation of complex molecules, chiral catalysts and ligands, and auxiliaries in organic synthesis.<sup>11</sup> Catalytic asymmetric ring-opening of *meso*-epoxides using amine nucleophiles is a powerful strategy for the synthesis of these molecules. The enantioselectivity of this reaction was found to be highly sensitive toward the epoxide and aniline structures.

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## Notes and references

§ Crystal data for **UTSA-32**: C<sub>40</sub>H<sub>23</sub>Cl<sub>2</sub>O<sub>12</sub>Zn<sub>2</sub>, *M* = 897.22, monoclinic, space group *P*2<sub>1</sub>, *a* = 10.1889(13) Å, *b* = 16.651(2) Å, *c* = 19.730(3) Å, β = 101.825(2)°, *V* = 3276.4(7) Å<sup>3</sup>, *Z* = 2, *D*<sub>c</sub> = 0.909 g cm<sup>-3</sup>, μ(Mo-Kα,

λ = 0.71073 Å) = 0.851 mm<sup>-1</sup>, *F*(000) = 906, 2θ<sub>max</sub> = 50.1, 17 147 reflections collected, 9823 independent reflections (*R*<sub>int</sub> = 0.0702), which were used in all the calculations, final *R*<sub>1</sub> = 0.0893 for *I* > 2σ(*I*), *wR*<sub>2</sub> = 0.2404 for all data, GOF = 0.943, Flack parameter = 0.10(3). CCDC 713157.

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