Asymmetric alcoholytic kinetic resolution of styrene oxide catalysed by chiral metal–organic framework crystals†

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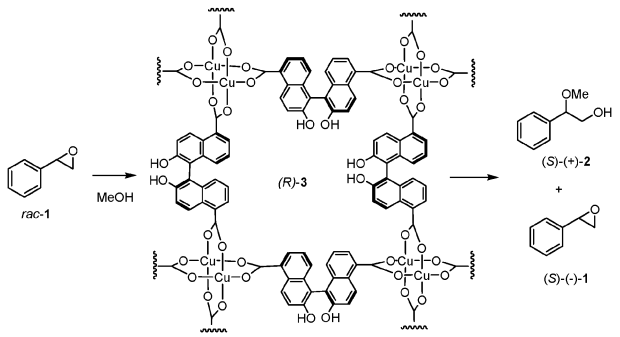
The methanolytic kinetic resolution of styrene oxide catalyzed by chiral metal–organic framework crystals afforded both 2-methoxy-2-phenylethanol and unreacted styrene oxide in good enantiomeric excesses.

The field of metal–organic frameworks (MOFs) has grown explosively in recent years[1] and numerous studies have been reported owing to their potential applications in gas storage,[2] separation,[3] luminescent materials[4] and heterogeneous catalysis.[5] While a large number of MOF are being discovered so far, only a few examples of chiral MOF for enantioselective separations or heterogeneous asymmetric catalysis have been investigated.[6] Recently, we have reported the synthesis of a novel chiral porous metal–organic framework (*R*)-**3** and its application to the asymmetric catalyst for asymmetric ring opening reaction of epoxide with amine under heterogeneous conditions.[7] Here we wish to report the alcoholytic kinetic resolution of styrene oxide **1** in the presence of chiral metal–organic framework crystals (*R*)-**3**.



The chiral MOF (*R*)-**3** was prepared according to our previously reported method[7] and dried in vacuum at 80 °C for 3 h prior to the reaction. For the alcoholysis reaction, styrene oxide and the catalyst (*R*)-**3** were stirred in alcohol under the conditions shown in Table 1. The products were identified by GC-MS and the yield was determined by ^{1}H-NMR analysis. The enantiomeric excess was determined by HPLC using Chiralpak IA and AS (Daicel). In a typical experiment, a solution of styrene oxide *rac*-**1** (0.5 mmol) in MeOH (0.5 mL) in the presence of (*R*)-**3** (20 mg, 0.046 mmol based on the formula unit) was stirred at 25 °C for 24 h, 2-methoxy-2-phenylethanol (*S*)-**2** of 81% ee and unreacted (*S*)-**1** of 5% ee were obtained in 5% and 83% yields, respectively (Table 1, entry 1). No reaction occurred without the catalyst under these conditions. When the reactions were carried out at higher temperatures (40 and 60 °C), the ee of unreacted **1** became higher and the ee of product **2** became lower, and the highest ee (98%) of recovered **1** was obtained in the reaction performed at 60 °C (Table 1, entry 2 and 3). Next, we performed the reactions using (*R*)- and (*S*)-**1** as substrate, (*S*)-**2** of >99% ee and (*R*)-**2** of >99% ee were obtained in 48% and 5% yields, respectively (Table 1, entries 4 and 5). This means styrene oxide (*R*)-**1** reacts with MeOH about two times faster than (*S*)-**1** in the presence of (*R*)-**3**.

It is interesting to note that the reaction is very sensitive to the structure of alcohol. In the case of the reactions between styrene oxide **1** with more bulky alcohols such as EtOH, *i*-PrOH and *t*-BuOH under the same conditions, the conversion as well as the enantioselectivity dropped dramatically (Table 1, entries 6–8). This may be due to the hindered diffusion of bulky alcohols inside the pores of the MOF catalyst.

To confirm the heterogeneity of this reaction, we filtered the catalyst after the reaction of entry 1. The reaction was continued with the filtrate for another 12 h, but no further conversion was observed. The reusability of (*R*)-**3** was also investigated in the reaction. The crystals of (*R*)-**3** were almost recovered by simple filtration and reused in the next cycles of the reaction without appreciable loss of both reactivity and enantioselectivity.

To further study the kinetic resolution of styrene oxide **1** in the presence of (*R*)-**3**, the relationship between the conversion of the reaction and the ee of that of the recovered **1** as well as that of the product **2** has been determined (Fig. 1). The results show that the ee of unreacted **1** increase with conversion, while the ee of product **2** decreases with conversion. After 50% conversion of **1**, the ee of recovered **1** increase markedly and the highest ee was obtained after 90% conversion. In parallel, the ee of the product **2** decrease from about 60% to 10% during this conversion.

The mechanism of the kinetic resolution of styrene oxide *rac*-**1** catalysed by (*R*)-**3** could be inferred from the methanolysis of styrene oxide since the methoxy group was incorporated at α-carbon to afford the product **2** exclusively. The reaction may proceed as follows. Firstly, (*R*)-**2** coordinates to Lewis acidic Cu site of (*R*)-**3** to form an adduct predominantly due to the steric reason. Next, methanol would attack the α-carbon atom of (*R*)-**1** from the backside position to give (*S*)-**2** with inversion of stereochemistry (Scheme 1).

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Table 1 Kinetic resolution of styrene oxide in the presence of (*R*)-**3**[a]

				Unreacted **1**		Product **2**	
Entry	Epoxide	Alcohol	Temp/°C	Yield (%)	ee[b] (%)	Yield (%)	ee[b] (%)
1	*rac*-**1**	MeOH	25	83	5 (*S*)	5	81 (*S*)
2	*rac*-**1**	MeOH	40	64	19 (*S*)	20	62 (*S*)
3	*rac*-**1**	MeOH	60	29	98 (*S*)	66	37 (*S*)
4	(*R*)-**1**	MeOH	40	50	>99 (*R*)	48	>99 (*S*)
5	(*S*)-**1**	MeOH	40	92	>99 (*S*)	5	>99 (*R*)
6	*rac*-**1**	EtOH	40	81	0.4[c]	3	12[c]
7	*rac*-**1**	*i*-PrOH	40	84	0.3[c]	2	4[c]
8	*rac*-**1**	*t*-BuOH	40	86	0.3[c]	0	—

[a] Reactions were carried out for 24 h. [b] Determined by HPLC. [c] Determined by GC.

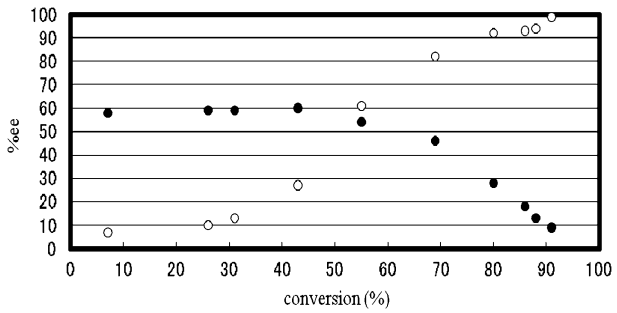
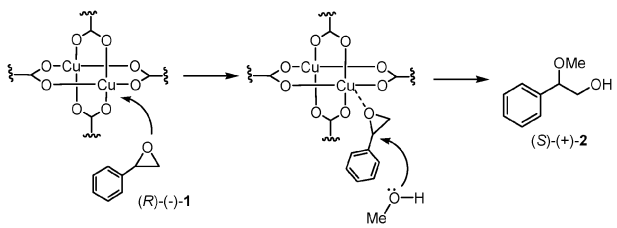
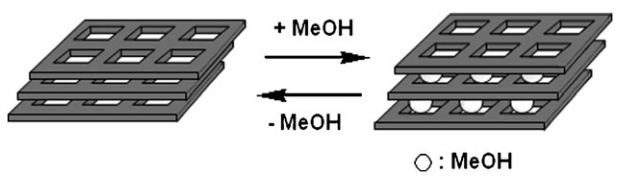


Fig. 1 Plot of enantiomeric excess of product **2** (●) and recovered **1** (○) as a function of conversion in methanolytic kinetic resolution of *rac*-**1** at 60 °C.



Scheme 1 A plausible mechanism of kinetic ring opening reaction.

The excellent catalytic properties of (*R*)-**3** in the methanolysis of styrene oxide may be due to the following reasons. The evacuated dense MOF is transformed to 2D sheets with open structure in the presence of MeOH[7] (Scheme 2), in which the substrate is accessible to the Cu active site through diffusion. The transformation is accompanied by pronounced color changes from black to green in MeOH. However, no color changes were observed in bulkier alcohols *i*-PrOH and *t*-BuOH. The adsorption experiment by mixing the evacuated MOF and styrene oxide for 24 h at room temperature resulted in no detectable inclusion of styrene oxide in the MOF crystals.



Scheme 2 Reversible intercalation of MeOH in the MOF (*R*)-**3**.

In summary, we have developed the first example of chiral MOF catalysed methanolytic kinetic resolution of styrene oxide. This raises the interesting possibility for applying this methodology to the catalytic asymmetric synthesis of various compounds. Further investigation of the scope and limitations of this reaction is now underway.

Experimental

Representative kinetic resolution of rac-**1**: (*R*)-**3** is desolvated at 80 °C for 3 h prior to reaction. The resultant solid catalyst is suspended in a MeOH (0.5 mL) solution of styrene oxide (0.06 g, 0.5 mmol) and stirred for 24 h. Then, the solid catalyst was collected by filtration, washed with MeOH. All MeOH portions are combined and evaporated under reduced pressure, and the yield is determined by NMR. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.25–7.39 (m, Ph, 5H), 4.31 (dd, J = 4.4 Hz, 1H), 3.56–3.72 (m, CH_2OH, 2H), 3.30 (s, OMe, 3H), 2.74 (br s, OH, 1H). The optical purity of 2-methoxy-2-phenylethanol **2** was determined by HPLC using Chiralpak IA (Daicel) column (hexane/2-PrOH: 97/3, flow rate 0.3 ml min^{-1}, t_r 37 min (*S*), 45 min (*R*)). The optical purity of styrene oxide **1** was determined by HPLC using Chiralpak AS (Daicel) column (hexane/2-PrOH: 99/1, flow rate 0.3 ml min^{-1}, t_r 26 min (*R*), 29 min (*S*)).

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