# <u>Organic</u> LETTERS

# Unravelling a New Class of Chiral Organocatalyst for Asymmetric Ring-Opening Reaction of *Meso* Epoxides with Anilines

Manish Kumar,<sup>†,‡</sup> Rukhsana I. Kureshy,<sup>\*,†,‡</sup> S. Saravanan,<sup>†,‡</sup> Shailesh Verma,<sup>†,‡</sup> Ajay Jakhar,<sup>†,‡</sup> Noor-ul H. Khan,<sup>†,‡</sup> Sayed H. R. Abdi,<sup>†,‡</sup> and Hari C. Bajaj<sup>†,‡</sup>

<sup>†</sup>Discipline of Inorganic Materials and Catalysis and <sup>‡</sup>Academy of Scientific and Innovative Research, Central Salt and Marine Chemicals Research Institute (CSMCRI), Council of Scientific & Industrial Research (CSIR), G. B. Marg, Bhavnagar 364 002 Gujarat, India

**Supporting Information** 

**ABSTRACT:** Chiral sulfinamide based organocatalyst **11** was synthesized from readily available starting materials and used for the asymmetric ring-opening (ARO) reaction of *meso* epoxides with anilines. A high yield (up to 95%) of chiral  $\beta$ -amino alcohols with excellent enantioselectivity (ee up to 99%) was achieved in 24–30 h at rt under optimized reaction conditions. A probable mechanism for the catalytic ARO reaction is envisaged by <sup>1</sup>H and <sup>13</sup>C NMR experiments.

n the field of asymmetric catalysis over the past 15–20 years, organocatalysts<sup>1</sup> or metal-free catalysts have attracted great deal of attention because of their notable advantages such as their environmentally benign and nontoxic nature, low cost, and the most significantly easy structural modifications to suit specific requirement. Various types of organocatalysts viz. phosphorenes,<sup>2</sup> sulfones,<sup>3</sup> Jacobsen's urea and thiourea derivatives,<sup>4</sup> Feng's N-oxides,<sup>5</sup> amino acids,<sup>6</sup> and alkaloids<sup>7</sup> were explored for different organic transformations<sup>8</sup> where the catalysts work via their ability to interact with substrates through hydrogen bonding. Asymmetric ring-opening (ARO) reaction of epoxides with amines<sup>9</sup> is an efficient and effective method for the synthesis of highly valuable chiral  $\beta$ -amino alcohols.<sup>10–12</sup> This class of compounds has direct application in pharmaceuticals, fine chemicals, flavors, fragrances, and chiral auxiliaries. Many efficient catalytic methods have been reported for the ARO of meso-epoxides with alkyl/aryl amines by using metal based catalysts<sup>13–21</sup> to provide  $\beta$ -amino alcohols in excellent yield and enantioselectivity. Although organocatalyzed dynamic kinetic resolution (DKR) of racemic aryloxy epoxide with secondary amine is reported by Rama Rao et al.,<sup>22</sup> to the best of our knowledge there are no reports for the desymmetrization of meso epoxides with amines using organocatalysts, although organocatalyzed ARO of meso epoxides with carbon<sup>23</sup> and chlorine<sup>24</sup> as nucleophile have been reported widely by many groups. In our quest to develop a new and efficient metal-free catalytic system for the ARO of meso epoxides with amines, here we are reporting for the first time the use of an organocatalyst derived from easily available starting materials (Figure 1) for ARO of various meso epoxides with anilines for the synthesis of enantiopure  $\beta$ -amino alcohols. The preceding works on the organocatalyst in different organic transformation revealed that the presence of key factors such as the ability to act as hydrogen bond donor or one or more suitable chiral centers with requisite steric and electronic environment are necessary to affect the reaction rate and the stereo induction.







With this backdrop, our initial study begins with commercially available amino acids and alkaloids such as L-proline, Boc-Lproline, Boc-L-phenylalanine, cinchonidine, and quinidine to examine their catalytic property for ARO of meso epoxides with aniline. The model reaction was carried out with organocatalysts 1-3 (10 mol %), using cyclohexene oxide 1b as a substrate and aniline 2a as a nucleophile in DCM at room temperature (rt), but these otherwise well-known catalysts were found to be unsuitable for ARO of epoxides by giving the desired product, i.e.,  $\beta$ -amino alcohols in low yield and enantioselectivity (Table 1, entries 1– 3) even after very long reaction time (60 h). Then, attempts were made to conduct the same reaction with alkaloid based organocatalysts such as cinchonidine 4 and quinidine 5; however, only trace amounts of  $\beta$ -amino alcohols were detected even on prolonged reaction time (Table 1, entries 4 and 5). Recently, chiral sulfinyl motif (R-S(O)-) based organocatalysts have shown promising results for many organic transformations; thus, we have screened chiral R- and S-forms of tert-butylsulfinamide 6 and 7 (10 mol %) for this reaction in DCM at rt where 35% of yield and 15% of enantioselectivity of  $\beta$ -amino alcohol was obtained (Table 1, entry 6). Though the results obtained were inferior, it encouraged us to develop a catalyst derived from a sulfinamide group. In a logical maneuver, we incorporated carbonyl amide to introduce more acidic sites in the catalyst and

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# Table 1. Screening of the Catalysts<sup>a</sup>



<sup>*a*</sup>Conditions: epoxide **1b** (0.2 mmol), PhNH<sub>2</sub> **2a** (0.22 mmol), chiral organocatalyst **1–15** (0.02 mmol) in CH<sub>2</sub>Cl<sub>2</sub>. <sup>*b*</sup>Isolated yield after flash chromatography. <sup>*c*</sup>ee were determined by HPLC using Chiralcel OD column. <sup>*d*</sup>Not determined.





as a result the organocatalyst **8** was synthesized<sup>25</sup> that gave, as expected, improved yield and ee of the  $\beta$ -amino alcohol (Table 1, entry 8). Further, we have changed the *tert*-butyl group to  $\alpha$ methylbenzyl amine (Scheme 1) and varied all the possible configurations of (S(O)–NH) and (C(O)–NH) motifs and synthesized organocatalysts **9–12** reported by our group.<sup>25</sup> These organocatalysts **9–12** (10 mol %) were screened for this model ARO reaction under the same reaction conditions.

#### Table 2. Optimization of the Reaction Conditions<sup>a</sup>

e

	Ni           1b         2a           0.2 mmol         0.22	H <sub>2</sub> catalyst 11 solvent, rt 2 mmol		"ОН <sup>s)</sup> N	
ntry	cat. loading (mol %)	solvent	time (h)	yield <sup><math>b</math></sup> (%)	$ee^{c}(\%)$
1	10	DCM	46	88	85
2	5	DCM	33	55	80
3	15	DCM	25	90	82
4	20	DCM	24	95	89
5	25	DCM	18	96	85
6	20	toluene	28	65	52
7	20	THF	16	96	40
8	20	ACN	30	71	68
9	20	CHCl <sub>3</sub>	26	85	79
10	20	DCE	26	82	82
11	20	$(bmim)PF_6$	60	trace	$\mathrm{nd}^d$

<sup>*a*</sup>Conditions: epoxide **1b** (0.2 mmol), PhNH<sub>2</sub> **2a** (0.22 mmol), chiral organocatalyst **11** in CH<sub>2</sub>Cl<sub>2</sub>. <sup>*b*</sup>Isolated yield after flash chromatography. <sup>*c*</sup>ee were determined by HPLC using Chiralcel OD column. <sup>*d*</sup>Not determined.

Excellent yield (88%) and enantioselectivity (85%) were achieved in the case of organocatalyst 11 having the (S,S)configuration for both the stereogenic centers in 30 h (Table 1, entry 11). Further, to check the utility of the phenyl ring of (S)- $\alpha$ methylbenzyl amine, we have prepared organocatalyst 13 with a naphthyl moiety, but it detrimentally affected both yield (64%) as well as enantioselectivity (45%). Moreover, to confirm the role of the (S(O)-NH) group in this reaction, we have replaced it with another  $\alpha$ -methylbenzylamine and synthesized the organocatalyst 14, but here again the results obtained were inferior (yield 32% and ee 15%) (Table 1, entry 14). We subsequently checked this reaction with  $C_2$ -symmetric organocatalyst<sup>26</sup> possessing both carbonyl and sulfonyl amide for its catalytic activity under the identical reaction conditions; however, results were not promising in terms of yield and enantioselectivity (yield 78% and ee 20%) of  $\beta$ -amino alcohols (Table 1, entry 15).

Having identified compound 11 as the catalyst of choice, the optimization of reaction conditions such as catalyst loading and choice of solvents were investigated for the model reaction as these parameters are known to influence the yield and enantioselectivity of the products. First, we varied the catalyst loading from 5 to 25 mol % (Table 2, entries 1-5) and found that 20 mol % of the catalyst is sufficient to give 95% yield with 89% enantioselectivity in chiral  $\beta$ -amino alcohol. Different solvents explored for this ARO reaction of epoxides were dichloromethane, toluene, tetrahydrofuran, acetonitrile, dichloroethane, and chloroform (Table 2, entries 6-10). However, none of these could match the performance (yield 95% and ee 89%) of DCM (Table 2, entry 4). We have also used ionic liquids as a reaction media for this reaction, but only a trace amount of the desired product was obtained (entry 11). With the optimum reaction conditions (Table 2, entry 4), the scope of the organocatalyst 11 was extended for the ARO of various meso epoxides, viz. cyclopentene oxide 1a, cyclohexene oxide 1b, cycloheptene oxide 1c, cyclooctene oxide 1d, cis-butene oxide 1e, and cisstilbene oxide 1f and also with trans epoxides such as transbutene oxide 1g and trans-stilbene oxide 1h with aniline 2a (Table 3). We got excellent results in term of product yields (80–95%), and enantioselectivities (ee up to >99%) with meso epoxides. However, cyclooctene oxide 1d and trans epoxides, viz.

Table 3. Generality of the organocatalyst 11<sup>a</sup>



<sup>*a*</sup>Conditions: epoxide 1a-h (0.2 mmol), PhNH<sub>2</sub> 2a (0.22 mmol), chiral organo catalyst 11 (0.04 mmol) in CH<sub>2</sub>Cl<sub>2</sub>. <sup>*b*</sup>Isolated yield after flash chromatography. <sup>*c*</sup>ee were determined by HPLC using a Chiralcel OD/OJ/AD/IC column. <sup>*d*</sup>Not determined.

trans-butene oxide 1g and trans-stilbene oxide 1h failed to react with aniline 2a. To understand the reasons behind the inability of these epoxide to react with aniline 2a, a conformational search was performed by using semiempirical AM1 method employing the Monte Carlo search method to examine the conformations of all the used epoxides (details are given in the Supporting Information). From DFT calculations,  $^{27-30}$  we found that in the case of cyclooctene oxide the distance between the epoxide carbons and neighboring methylene group is minimum in comparison to the rest of the cycloalkane epoxides, which possibly caused steric and hydrophobic repulsion and does not allowing the organocatalyst to activate the oxirane ring of cyclooctene oxide 1d. Similarly, trans epoxides 1g and 1h have not undergone this reaction possibly due to the unfavorable positioning of methyl/phenyl group on the respective epoxides that prevent the accessibility of the catalyst to promote the ARO reaction. In this way, these results strongly support the involvement of acidic protons on the catalyst in the proposed mechanism. Further, various substituted anilines viz., 2-MeO- 2b, 4-MeO- 2c, 4-Me- 2d, 2-Cl- 2e, 4-Cl 2f, 4-NO2-anilines 2g, and aliphatic amines viz., propylamine 2h, pyrrolidine 2i, and morpholine 2j were also used as nucleophile with meso-stilbene oxide 1f as model substrates under the above optimized conditions with catalyst 11 in order to understand the effect of nucleophilicity in the ARO reaction.

The corresponding  $\beta$ -amino alcohols were achieved with anilines **2b**, **2c**, **2d**, and **2e** in moderate to good yields (70–86%) and up to 95–99% ee in 30–48 h (Scheme 2), but only a trace amount and no product was obtained with 4-chloroaniline **2f** and 4-nitroaniline **2g**, respectively (Scheme 2), possibly due to their poor nucleophilicity. No ARO products could be obtained with aliphatic amine as well, where high basicity of these amines may possibly block the acid sites of the catalyst leaving behind the epoxide unactivated.<sup>31</sup>

In order to develop a useful understanding to ascertain the precise role of catalyst 11 in the ARO reaction, we conducted a series of  ${}^{1}$ H and  ${}^{13}$ C NMR experiments in CDCl<sub>3</sub>, where we

Scheme 2. Variation of Amines



<sup>*a*</sup>Conditions: epoxide 1f (0.2 mmol), R-NH<sub>2</sub> 2b-j (0.22 mmol), chiral organo catalyst 11 (0.04 mmol) in CH<sub>2</sub>Cl<sub>2</sub>. <sup>*b*</sup>Isolated yield after flash chromatography. <sup>*c*</sup>ee were determined by HPLC using Chiralcel OD/ IC column. <sup>*d*</sup>Not determined.



**Figure 2.** <sup>1</sup>H NMR spectra recorded in CDCl<sub>3</sub>: (a) spectra represent sulfonyl *N*-H (3.749 ppm) and carbonyl *N*-H (6.837 ppm) of catalyst **11**; (b) catalyst **11** after interaction with epoxide; (c) catalyst **11** after interaction with epoxide and aniline.

looked for the interaction of catalyst with the substrate (Figure 2). When we mixed the catalyst 11 with cyclohexene oxide, the N-H protons of the carbonyl (6.837 ppm) as well as sulfonyl (3.749 ppm) moieties of the catalyst shifted upfield in the <sup>1</sup>H NMR spectrum in 1 h. A similar trend was also observed in <sup>13</sup>C NMR of the catalyst as well as NMR spectra of the epoxide (Supporting Information), which clearly indicates interaction between the catalyst and epoxide (Figure 2a,b). Upon addition of aniline to the above mixture the above-mentioned N-H peaks were downfield shifted. Interestingly N-H peak belonging to -(CO)NH came to nearly same positions as in the original catalyst while the N-H peak belonging to the sulfonyl group was shifted even more downfield ( $\delta$  3.766 ppm) (Figure 2c). Simultaneously, the N-H peak of aniline is upfield shifted (Supporting Information). These shifts indicate an intermediate (Figure 3) proposed in the mechanism. (See the Supporting Information for the NMR spectra of individual reactants and their various permutations and combinations).



Figure 3. Probable catalytic cycle.

In the present study, we have given a proof of concept that chiral sulfinamide derivatives can be used as an efficient organocatalyst in ARO of various *meso*-epoxides with anilines to give corresponding enantioenriched  $\beta$ -amino alcohols (ee up to >99%) with high yield (up to 95%). Based on the experimental results with structural variation in the catalyst it was observed that the chirality of sulfur determines the configuration of the product.

### ASSOCIATED CONTENT

#### **Supporting Information**

<sup>1</sup>H and <sup>13</sup>C NMR spectra of products and reaction intermediates and HPLC profiles of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

#### AUTHOR INFORMATION

#### **Corresponding Author**

\*E-mail: rukhsana93@yahoo.co.in.

#### Notes

The authors declare no competing financial interest.

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