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Asymmetric Rearrangement of Racemic Epoxides Catalyzed by Chiral Brønsted Acids[†]

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This paper describes a chiral Brønsted acid catalyzed asymmetric 1,2-rearrangement of racemic epoxides via a hydrogen-shift process for the synthesis of chiral aldehydes, and followed by a reduction, a variety of optically active 10 alcohols can be furnished in moderate yields with up to 50% ee. Especially, a facile one pot synthesis of chiral alcohols directly from simple alkenes by a sequential epoxidation, rearrangement, and reduction, has also been realized.

Chiral aldehydes are important chemicals for the straightforward 15 synthesis of optically active amines, imines, alcohols, acids and so on. Accordingly, their asymmetric synthesis attracts broad interest, and significant progress has been made in this area.^{1,2} Epoxides are versatile functional groups in synthetic chemistry, and the asymmetric 1,2-rearrangement of epoxides via either a 20 semi-pinacol or Meinwald rearrangement process also provides an elegant approach to chiral aldehydes.^{3,4} Various Lewis acids have been reported to promote the substrate-controlled asymmetric rearrangement of chiral epoxides to produce optically active aldehydes.⁵ For example, in 1989, Yamamoto and 25 coworkers reported an organoaluminum-promoted rearrangement of chiral epoxy silvl ethers to siloxy aldehydes.^{5a} In 2004, the Suda group successfully employed a chromium-porphyrin complex for the same transformation.^{5c} Very recently, the Schreiner group accomplished a challenging stereospecific 1,2-30 rearrangement reaction of readily accessible enantioenriched trisubstituted epoxides to quaternary aromatic carbaldehydes under the catalysis of silicon-thiourea Lewis acids.^{5g} However, to the best of our knowledge, chiral catalyst controlled asymmetric 1,2rearrangement of racemic epoxides has rarely been reported and

³⁵ still remains as a challenge.
 Chiral Brønsted-acid catalysis has witnessed a rapid growth in

recent years,⁶ and has also been successfully applied to several types of asymmetric rearrangement reactions.⁷ In contrast to the wide usage of Lewis acids for the 1,2-rearrangement of ⁴⁰ epoxides,⁵ Brønsted acids have seldom been employed for this transformation. To realize the challengeable of chiral Brønsted acid catalyzed 1,2-rearrangement of racemic epoxides, we envision that 1,1-disubstituted epoxides **1** may be suitable substrates which will ensure the regiospecific generation of cation ⁴⁵ immediate **2** and exclude the competition between H-shift and alkyl-shift for tri-substituted epoxides to furnish the desired

efforts on this subject.

enantioenriched aldehydes 3 (Scheme 1). Herein, we report our

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Scheme 1. Strategy for Brønsted Acid catalyzed Asymmetric H-Shift of Epoxides







Initially, α -methylstyrene epoxide (1a) was chosen as a substrate for the chiral Brønsted acid catalyzed asymmetric 1,2rearrangement, and due to its instability, the obtained aldehyde 3a 60 was directly converted to the corresponding alcohol 4a (Scheme 2). With the use of BINOL-derived phosphoric acid 5a, the rearrangement of epoxide 1a can occur at 40 °C, but gave a racemic product. Several *N*-triflyl phosphoramides 5b-e with a stronger acidity were then synthesized in order to improve the complete rearrangement of epoxide 1a can be realized within 15 minutes to give the desired product with 26% ee under the catalysis of 10 mol % of phosphoramides **5d** (Scheme 2). A controlled experiment with enantioenriched **1a** (40% ee)⁹ as substrate also gave 26% ee, which suggests this reaction was s controlled by catalysts instead of substrates. Prolonged the reaction time from 15 min to 8 h, no changes for the enantioselectivity were observed, which can partially exclude the racemization possibility for the generated chiral aldehydes under

the reaction condition. Moreover, phosphoramide **5e** containing a ¹⁰ chiral spirobiindane scaffold¹⁰ can also promote this reaction with a relatively lower ee.

The reaction condition was next optimized for the rearrangement of epoxide 1a under the catalysis of phosphoramides 5d and 5e. It was found that solvents had 15 obvious impacts on the enantioselectivity (Table S1, Supporting Information). Although phosphoramide 5d was a better catalyst than 5e in toluene (Scheme 1), phosphoramide 5e was more sensitive for solvents. For example, CH2Cl2 gave a higher reactivity (>99% conv, 14% ee), but tetrahydrofuran (THF) gave 20 a better ee value (21% conv, 32% ee). A mixture of THF and CH₂Cl₂ (1/1 in volume) as solvent was therefore tested for this transformation, and product 4a can be afforded in >99% conv with 54% ee (Scheme 1). When the amount of phosphoramide 5e was reduced to 5 mol %, the asymmetric H-shift of epoxide 1a 25 can still proceed efficiently with only a slight loss of enantioselectivity (>99% conv, 48% ee) (Table S1, Supporting Information).

Table 1 Chiral Brønsted Acid Catalyzed Rearrangement of Epoxides^a

| | R ¹ 1. 5e (5 r CH ₂ Cl ₂ /7 2. NaBH ₄ | nol %) ⁻ HF (1/1) , CH ₃ OH | | н | |
|---------------------------------|--|---|--|------------------------|--|
| | 1a-m: R' = Me 1n: R' = Et | | 4a-m : R' = Me 4n : R' = Et | | |
| entry | product 4 | time (h) | yield (%) ^b | ee (%) ^c | |
| $1^{d,e}$ | 4a : R = H | 3 | 68 | 48 | |
| 2 | 4b : R = 4-F | 5 | 65 | 33 | |
| 3 ^{<i>e</i>, <i>f</i>} | 4c : $R = 4$ -Cl | 12 | 61 | 41 | |
| 4^{f} | 4d : R = 4-Br | 5 | 59 | 33 | |
| 5^e | 4e : R = 4-Me | 4 | 62 | 33 | |
| 6 | 4f : $R = 4^{-n}Bu$ | 5 | 48 | 33 | |
| 7 | $4\mathbf{g}: \mathbf{R} = 4 - {^i}\mathbf{P}\mathbf{r}$ | 5 | 59 | 35 | |
| 8 | 4h : R = 4-Ph | 4.5 | 53 | 33 | |
| 9 ^{<i>f</i>} | 4i : R = 3-F | 18 | 67 | 38 | |
| 10 | 4j : R = 3-Me | 5 | 67 | 35 | |
| 11 | 4k : R = 3-OMe | 9 | 61 | 37 | |
| 12 | 41 : R = 3-Ph | 5 | 65 | 42 | |
| 13 ^g | 4m : R = 2-Ph | 3 | 74 | 19 | |
| $14^{e, f}$ | 4n : R = H | 12 | 68 | 20 | |

^{*a*}All reactions were carried out with epoxide **1** (0.40 mmol), phosphoramide **5e** (0.02 mmol), and THF/CH₂Cl₂ (v/v = 1/1) (1.0 mL) at -78 °C until complete conversion of epoxide indicated by TLC. ^{*b*} Isolated yield for two steps. ^{*c*} The ee was determined by chiral HPLC. ^{*d*} The ee was determined by chiral GC. ^{*e*} The absolute configuration was assigned as *R* by comparing the optical rotation with the reported one. ^{*f*} The reaction was run at -60 °C. ^{*g*} The reaction was run at -20 °C.

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Subsequently, we examined the scope of epoxides for the asymmetric 1,2-rearrangement reaction with the use of 5.0 mol % of phosphoramide **5e** as catalyst. As shown in Table ^{View Article Online ³⁵ of epoxides derived from substituted α -methylstyrenes were well tolerated to give the desired products **4** in 48-74% yield¹¹ with 19-48% ee's (entries 1-13). When using epoxide **1n** derived from α -ethylstyrene as substrate, the reaction can also proceed efficiently to give the desired product **4n** in 68% yield with 20% ⁴⁰ ee (Table 1, entry 14).}

Since the 1,2-rearrangement of trisubstituted epoxides is a more challenging transformation,^{5g} epoxide **6** has also been subjected as a substrate under the current condition. Disappointingly, no reaction was observed to occur. When ⁴⁵ increasing the temperature from -78 °C to room temperature, allylic alcohol **7** was obtained in 84% yield instead of the expected aldehydes or ketones generated by either alkyl-shift or H-shift (Scheme 3).¹¹

50 Scheme 3. Brønsted Acid Catalyzed Reaction of Trisubstituted Epoxide

Interestingly, a facile one-pot direct transformation of α methylstyrene (8) to chiral alcohol was successfully realized to ⁵⁵ give the desired product 4a in 54% yield with 50% ee by sequential oxidation with *m*-CPBA, asymmetric 1,2-arrangement with chiral Brønsted acid 5e, and reduction with NaBH₄ (Scheme 4).

Scheme 4. One Pot Synthesis of Chiral Alcohol from Alkene

$$\begin{array}{c|c} & 1. m\text{-}\mathsf{CPBA} \\ & & 1. m\text{-}\mathsf{CPBA} \\ & & \mathsf{CH}_2\mathsf{Cl}_2, \text{ rt}, 1 \text{ h} \\ & & \mathsf{CH}_2\mathsf{Cl}_2/\mathsf{THF} (1/1) \\ & & \mathsf{-78}\ ^\circ\mathsf{C}, 3 \text{ h} \\ & & \mathsf{OH} \\ & & \mathsf{OH}$$

Conclusion

P

In summary, a chiral Brønsted acid catalyzed asymmetric 1,2rearrangement of readily accessible racemic epoxides to chiral ⁶⁵ aldehydes has been successfully realized, followed by a further reduction, a variety of optically active alcohols can be obtained in moderate yield with up to 50% ee. Significantly, chiral alcohols can also be furnished by a one pot sequential transformation of alkenes via epoxidation, rearrangement, and reduction. Although 70 the enantioselectivity and the substrate scope are still not satisfactory, this work represents the first example of catalystcontrolled rearrangement of racemic epoxides and provides an alternative approach for the synthesis of chiral aldehydes from simple starting materials.

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Notes and references

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