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Catalytic Enantioselective Conversion of Epoxides to Thiiranes

Saihu Liao, Markus Leutzsch, Mattia Riccardo Monaco, and Benjamin List*

Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, 45470 Mülheim an der Ruhr, Germany

Supporting Information

ABSTRACT: A highly efficient and enantioselective Brønsted acid catalyzed conversion of epoxides to thiiranes has been developed. The reaction proceeds in a kinetic resolution, furnishing both epoxide and thiirane in high yields and enantiomeric purity. Heterodimer formation between the catalyst and sulfur donor affords an effective way to prevent catalyst decomposition and enables catalyst loadings as low as 0.01 mol %.

As a unique class of three-membered heterocyclic compounds, thiiranes are of significance in both synthetic and medicinal chemistry.[1] Due to their ring strain (ca. 18.6 kcal/mol),[1b] they can readily undergo various ring-opening reactions to yield useful sulfurous compounds.[2] Thiiranes can also polymerize or copolymerize with other monomers to produce sulfur-rich and high refractive index polymers (HRIP).[3] They are often prepared to compare their biological activity with that of the corresponding epoxides,[1,4] and several thiiranes have been successfully identified as potent A1 adenosine receptor agonists and selective gelatinase inhibitors.[4b,d] For the preparation of enantiopure thiiranes, known methods generally rely on stoichiometric amounts of enantioenriched starting materials, chiral reagents, or auxiliaries.[5] A catalytic enantioselective approach has remained elusive until today. Here we report a highly efficient and enantioselective **TRIP** catalyzed synthesis of thiiranes from epoxides via kinetic resolution using thiolactames as sulfur donors.[6]

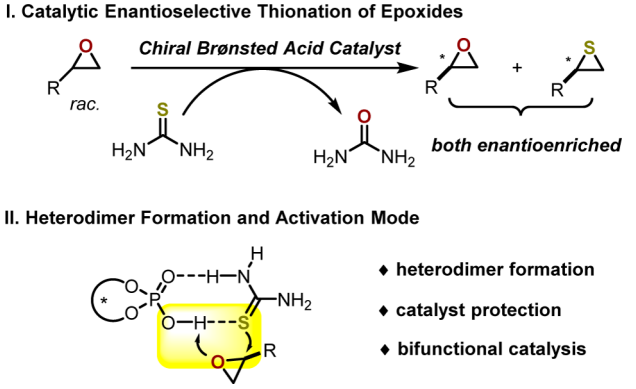
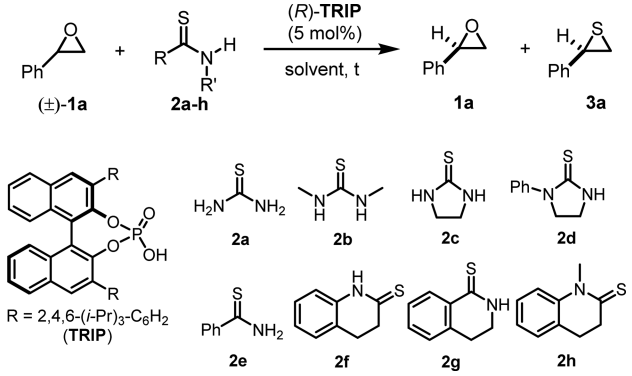


Figure 1. Reaction design.

The conversion of epoxides to thiiranes with appropriate thionating agents has been known for almost 80 years and remains one of the most common and convenient approaches for the synthesis of thiiranes.[1] The initial documentation can be dated back to a patent described in 1936 by Dachlauer and Jackel, in which thiourea and alkaline isocyanates were utilized as a sulfur donor.[7] Since then, toward increasing the reaction efficiency, this transformation has been extensively studied and a number of Lewis acid and Brønsted acid catalysts have been disclosed.[8,9] We hypothesized that this transformation may proceed enantioselectively in the presence of suitable chiral bifunctional Brønsted

Table 1. Reaction Optimization[a]



entry	2	solvent	T (°C)	time (h)	conv. (%)[b]	s[c]
1	**2a**	EtOAc	25	24	50	5
2[d]	**2a**	EtOAc	25	96	–	–
3	**2a**	EtOAc	0	48	20	7
4	**2b**	EtOAc	25	120	19	6
5	**2c**	EtOAc	25	6	55	10
6	**2d**	EtOAc	25	24	54	9
7	**2e**	EtOAc	25	8	55	9
8	**2f**	EtOAc	25	2	55	20
9[e]	**2f**	EtOAc	−20	12	46.5	25
10[e]	**2f**	THF	−20	12	50	37
11[e]	**2f**	CH_2Cl_2	−20	12	48	45
12[e]	**2f**	$CHCl_3$	−20	12	50.5	86
13[e]	**2g**	$CHCl_3$	−20	24	30	12
14[e]	**2h**	$CHCl_3$	−20	24	<1	–
15[e,f]	**2f**	$CHCl_3$	−20	12	50	85
16[e,g]	**2f**	$CHCl_3$	−20	48	50	85
17[e,h]	**2f**	$CHCl_3$	−20	96	47	48

[a]Reaction conditions: **1a** (0.1 mmol), **2** (0.55 equiv), (*R*)-**TRIP** (5 mol %), in 1.0 mL of solvent. [b]Calculated based on er values and in good agreement with NMR conversion. [c]The selectivity factor was calculated according $\ln(1 - C)(1 - ee_{SM})/(1 - C)(1 + ee_{SM})$. [d]Without catalyst. [e]**2f**: 0.05 equiv. [f]1 mol % of **TRIP**. [g]0.1 mol % of **TRIP**. [h]0.01 mol % of **TRIP**.

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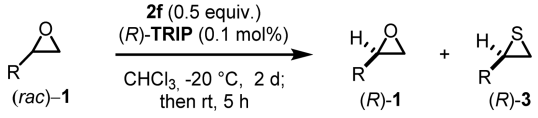
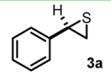
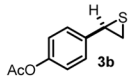
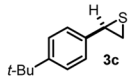
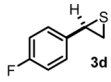
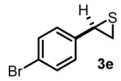
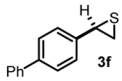
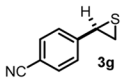
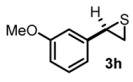
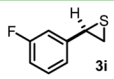
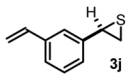
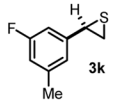
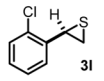
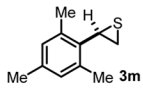
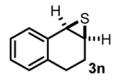
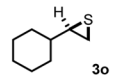
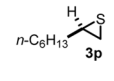
Table 2. Reaction Scope[a,d]



entry	product	conv.(yield) (%)[b]	er (**1**)[c]	er (**3**)[c]	s[d]
1	 **3a**	50.5 (47)	97:3	96:4	83
2	 **3b**	51.0 (46)	97.5:2.5	95.5:4.5	76
3	 **3c**	53.0 (48)	99.7:0.3	93.5:6.5	86
4	 **3d**	51.0 (48)	97:3	95:5	69
5	 **3e**	51.7 (51)	97.5:2.5	94.5:5.5	66
6	 **3f**	50.0 (50)	96:4	95.5:4.5	68
7[e]	 **3g**	49.0 (49)	94:6	95.5:4.5	62
8	 **3h**	49.3 (47)	96.5:3.5	97.5:2.5	145
9	 **3i**	49.5 (47)	94.5:5.5	95.5:4.5	61
10	 **3j**	49.5 (48)	96:4	97:3	107
11	 **3k**	49.0 (48)	94.5:5.5	96.5:3.5	80
12[e]	 **3l**	47.5 (47)	92:8	96.5:3.5	71
13[e]	 **3m**	48.0 (48)	92.5:7.5	96:4	69
14	 **3n**	50.8 (47)	92:8	90.5:9.5	24
15[f]	 **3o**	52.9 (49)	77:23	74:26	5
16[f]	 **3p**	47.2(47)	84:16	88:12	14

[a]Reaction conditions: epoxide (0.5 mmol), **2f** (0.5 equiv), (*R*)-**TRIP** (0.1 mol %), in 5.0 mL of dry $CHCl_3$, −20 °C. [b]Conversions were calculated based on er values and are in good agreement with NMR conversion; isolated yields of thiiranes **3** are given in parentheses. [c]Er was measured by chiral GC or HPLC analysis. [d]The selectivity factor was calculated according $\ln(1 - C)(1 - ee_{SM})/(1 - C)(1 + ee_{SM})$. [e]4 days. [f]1 mol % of **TRIP** was used, 3 days.

acid catalysts such as chiral phosphoric acids.[10] In principle, one enantiomer of the starting epoxide could be selectively converted into the corresponding thiirane, thus providing both the remaining epoxide and the thiirane in enantioenriched form (Figure 1, I).[11] However, the activation of epoxides in asymmetric Brønsted acid catalysis has been challenging. Due to their high reactivity, the acid catalysts are prone to be alkylated by the epoxides, leading to catalytically inactive species.[12] Recently, we introduced a novel activation strategy in asymmetric catalysis based on the heterodimeric self-assembly between chiral phosphoric acid catalysts and carboxylic acids.[13] Such an association was demonstrated to be an effective approach to protect the catalysts from the undesired catalyst alkylation. We envisioned that this strategy might also be applicable to the present transformation, as both thiourea and the produced urea can be expected to heterodimerize with the phosphoric acid, thus affording full protection to the catalyst throughout the reaction. Accordingly, the approaching epoxide could then disrupt the hydrogen-bonding of the heterodimer, leading to its nucleophilic opening with the S-nucleophile via bifunctional activation (Figure 1, II).

Initial studies were conducted by using thiourea (**2a**) as a sulfur donor and (*R*)-**TRIP** as the catalyst (Table 1). Indeed, this phosphoric acid did promote the reaction and the epoxide and thiirane products can both be obtained with a significant enantiomeric ratio (both 75:25 er, $s = 5$, entry 1). Importantly, while we have previously shown that **TRIP** is prone to be alkylated by epoxides, the catalyst remained intact, even after the thiourea was completely consumed.[13b] Without catalyst, no product could be detected after 4 days (entry 2). Lowering the temperature slightly increased the enantioselectivity, but the reaction became sluggish (entry 3). To increase both the reactivity and enantioselectivity, we turned our attention to other sulfur donors. While the reaction with alkylated thiourea **2b** was even slower than with thiourea (entry 4), cyclic derivative **2c** exhibited much better reactivity and selectivity (entry 5), and thiourea **2d** also gave similar selectivity (entry 6). This encouraged us to test the performance of a number of thioamides and thiolactams (e.g., **2e**−**2g**),[14] upon which **2f** was found to give quite promising results in terms of both reactivity and enantioselectivity (entry 8). By lowering the temperature to −20 °C, the selectivity factor could be further increased to 25 (entry 9). Different solvents were

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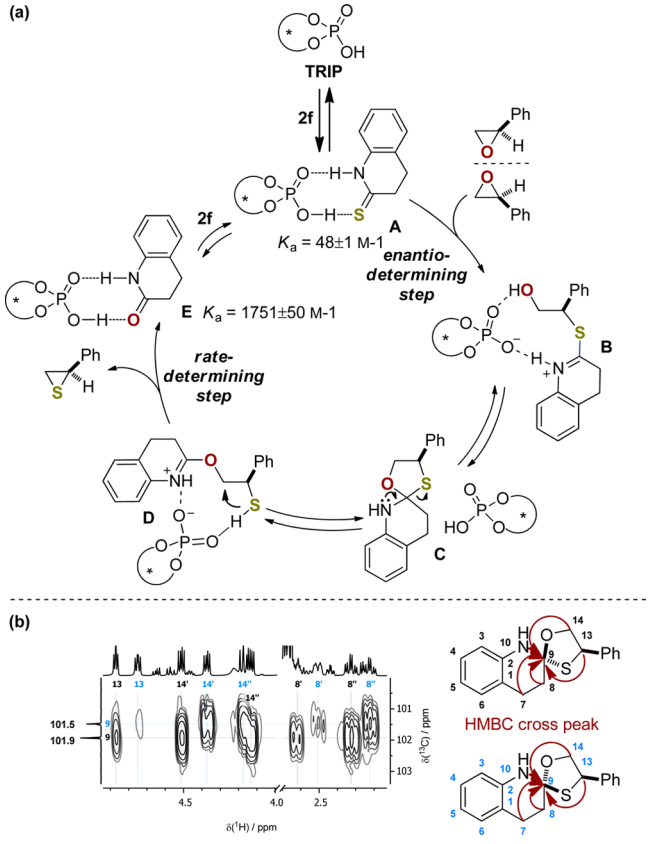
Scheme 1. Proposed Catalytic Cycle (a) and Relevant $^{1}H-^{13}C$-HMBC-Cross Peaks of Intermediates C (b)



examined at −20 °C (entries 9−12), and excellent selectivity was achieved in chloroform (s = 86, entry 12). In this case, both epoxide and thiirane were isolated with high enantioselectivity (97:3 and 96:4 er respectively). For comparison, thiolactam **2g** was much less efficient (entry 13). The use of the *N*-alkylated thiolactam **2h** resulted in a complete loss of reactivity and full degradation of the acid catalyst (entry 14), confirming the notion that the heterodimerization is important for reactivity and stereoselectivity. In fact, thiolactam **2f** is a very effective sulfur donor and the catalyst loading can be reduced to 0.1 mol % without affecting the enantioselectivity (entries 12, 15−16). Remarkably, even at a catalyst loading as low as 0.01 mol %, a good selectivity factor (s = 48) can still be observed, giving the thiirane product in 95:5 er (entry 17).

Under the optimized reaction conditions, the scope of this transformation was examined next (Table 2). The reaction was found to exhibit wide applicability and worked well with a variety of aryl epoxides, affording the corresponding thiiranes in high yields and enantioselectivity. Different functional groups, both electron-donating and -withdrawing, are well tolerated (entries 2−7), although higher reactivity was observed with the electron-rich substrates (e.g., entry 1 vs 7). Meta-substituted substrates are also suitable (entries 8−11), and an excellent selectivity factor was obtained with the 3-methoxy-substituted one (s = 145, entry 8). The reactions of ortho-substituted and 2,4,6-trimethyl substituted substrates were slower, but still highly enantioselective (entries 12 and 13). A 1,2-disubstituted epoxide, dihydronaphthalene oxide, also proved to be a suitable substrate (entry 14). Notably, aliphatic substrates also smoothly underwent this transformation albeit with lower enantioselectivity (entries 15 and 16). Interestingly, the reaction of the linear epoxide was found to be much more selective than that of the branched one (entry 16 vs 15).

By comparing optical rotations with literature values, the absolute configurations of the recovered epoxide **1a** and thiirane **3a** were both determined to be (*R*). This result is in agreement with a mechanism involving an S_N2 attack of the sulfur atom at the benzylic carbon, which thus leads to the inversion of this stereocenter.[1,8j,k] Based on this finding and our mechanistic investigations, a catalytic cycle is proposed (Scheme 1). Initially, the **TRIP** catalyst binds with the sulfur donor **2f** to form heterodimer **A** (TRIP·**2f**, $K_a = 48 \pm 1\ M^{-1}$).[15] Then, the catalyst directs the attack of the sulfur donor onto the benzylic carbon of the incoming styrene oxide, resulting in ring opened intermediate **B**, which will undergo a ring closure reaction to form spirocyclic intermediate **C**. The epoxide ring opening step is relatively fast, as an in situ ^{1}H NMR analysis at −20 °C showed ∼45% conv. of **1a** in 5 h. The epoxide ring opening is assumed to be the enantiodetermining step.[16] Intermediate **C** could be characterized as a 1:1 mixture of diastereomers by two-dimensional NMR methods. A cross peak in the $^{1}H-^{13}C$-HMBC connected the two rings via a quaternary carbon ($\delta(^{13}C)$ = 101.5 and 101.9 ppm, Scheme 1b).[17] Additionally a $^{1}H-^{15}N$-HMBC experiment showed the presence of a secondary amine ($\delta(^{15}N) = -285$ ppm, $^{1}J_{NH}$ = 89 Hz).[18] Interestingly we could observe a chemical exchange between intermediates **B** and **C** in EXSY-NMR-measurements (for further details, see Supporting Information). Opening of the oxathiolane ring generates intermediate **D**, as a result of a formal shift of the dihydroquinoline moiety from sulfur to oxygen (from **B** to **D**). The ratio between all the intermediates does not change over the reaction course in the NMR measurement suggesting that they are probably all in equilibrium. Subsequent ring closure releases the thiirane and the acid catalyst together with the lactam byproduct, which is expected to bind to the acid catalyst forming heterodimer **E** ($K_a = 1751 \pm 50\ M^{-1}$).[15] Replacing the lactam by reagent **2f** will regenerate the active heterodimer **A**. Therefore, both **A** and **E** equilibrate rapidly in solution and contribute to the catalyst protection. The full conversion to the product at lower temperatures takes longer than the formation of the intermediates, which leads to the conclusion that the reaction from **D** to **E** is the overall rate-determining step of the transformation. When the reaction is warmed up to rt, intermediates **B**, **C**, **D** are all quickly converted into product, almost reaching completion in 30 min.

In conclusion, a highly enantioselective catalytic transformation of epoxides to thiiranes has been disclosed. The reaction provides two useful products, epoxide and thiirane, both in high yield and high enantiomeric purity. This chiral phosphoric acid catalyzed reaction exhibits high reaction efficiency and proceeds well with catalyst loadings as low as 0.01 mol %, further illustrating that our heterodimerization strategy is an effective approach to protect the acid catalyst in certain labile systems.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b01960.

Experimental procedures, characterizations and analytical data of products, and spectra of NMR and HPLC (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: list@kofo.mpg.de.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Ditter, D. C.; Katritzky, A. R.; Rees, C. W. In *Thiiranes and Thiirenes in Comprehensive Heterocyclic Chemistry*; Pergamon: NewYork, 1984; Vol. 7, pp 132−182. (b) Sander, M. *Chem. Rev.* **1966**, *66*, 297. (c) Chew, W.; Harpp, D. N. *Sulfur Rep.* **1993**, *15*, 1.

(2) For examples, see: (a) Sauve, A. A.; Groves, J. T. *J. Am. Chem. Soc.* **2002**, *124*, 4770. (b) Huang, J.; Wang, F.; Du, D.-M.; Xu, J. *Synthesis* **2005**, 2122. (c) Reddy, M. S.; Surendra, K.; Krishnaveni, N. S.; Narender, M.; Rao, K. R. *Helv. Chim. Acta* **2007**, *90*, 337. (d) Rogers, E.; Araki, H.; Batory, L. A.; McInnis, C. E.; Njardarson, J. T. *J. Am. Chem. Soc.* **2007**, *129*, 2768. (e) Yu, H.; Cao, S.; Zhang, L.; Liu, G.; Xu, J. *Synthesis* **2009**, *2009*, 2205. (f) Tanini, D.; Degl'Innocenti, A.; Capperucci, A. *Eur. J. Org. Chem.* **2015**, *2015*, 357. (g) Pathipati, S. R.; Singh, V.; Eriksson, L.; Selander, N. *Org. Lett.* **2015**, *17*, 4506.

(3) For examples, see: (a) Kudo, H.; Makino, S.; Kameyama, A.; Nishikubo, T. *Macromolecules* **2005**, *38*, 5964. (b) Nakano, K.; Tatsumi, G.; Nozaki, K. *J. Am. Chem. Soc.* **2007**, *129*, 15116. (c) Vo, C. D.; Kilcher, G.; Tirelli, N. *Macromol. Rapid Commun.* **2009**, *30*, 299 (Review). (d) Liu, J.; Ueda, M. *J. Mater. Chem.* **2009**, *19*, 8907 (Review on HRIP).

(4) (a) Goeke, A. *Sulfur Rep.* **2002**, *23*, 243. (b) Hutchinson, S. A.; Baker, S. P.; Linden, J.; Scammells, P. J. *Bioorg. Med. Chem.* **2004**, *12*, 4877. (c) Cho, H. J.; Jung, M. J.; Kwon, Y.; Na, Y. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6766. (d) Testero, S. A.; Lee, M.; Staran, R. T.; Espahbodi, M.; Llarrull, L. I.; Toth, M.; Mobashery, S.; Chang, M. *ACS Med. Chem. Lett.* **2011**, *2*, 177. (e) Gao, M.; Nguyen, T. T.; Suckow, M. A.; Wolter, W. R.; Gooyit, M.; Mobashery, S.; Chang, M. *Proc. Natl. Acad. Sci. U. S. A.* **2015**, *112*, 15226.

(5) (a) Meyers, A. I.; Mihelich, E. D. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 270. (b) Meyers, A. I.; Ford, M. E. *J. Org. Chem.* **1976**, *41*, 1735. (c) Johnson, C. R.; Tanaka, K. *Synthesis* **1976**, *1976*, 413. (d) Soai, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3371. (e) Łukowska, E.; Plenkiewicz, J. *Tetrahedron: Asymmetry* **2007**, *18*, 493. (f) Cano, I.; Gómez-Bengoa, E.; Landa, A.; Maestro, M.; Mielgo, A.; Olaizola, I.; Oiarbide, M.; Palomo, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 10856.

(6) TRIP: 3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate (abbreviated as). For a review on TRIP, see: Adair, G.; Mukherjee, S.; List, B. *Aldrichimica Acta* **2008**, *41*, 31.

(7) Dachlauer, K.; Jackel, L. French Patent 797621, 1936.

(8) For recent studies, see: (a) Borujeni, K. P. *Synth. Commun.* **2005**, *35*, 2575. (b) Bandgar, B. P.; Patil, A. V.; Kamble, V. T.; Totre, J. V. *J. Mol. Catal. A: Chem.* **2007**, *273*, 114. (c) Firouzabadi, H.; Iranpoor, N.; Khoshnood, A. *J. Mol. Catal. A: Chem.* **2007**, *274*, 109. (d) Reddy, Ch. S.; Nagavani, S. *Heteroat. Chem.* **2008**, *19*, 97. (e) Taghavi, S. A.; Moghadam, M.; Mohammadpoor-Baltork, I.; Tangestaninejad, S.; Mirkhani, V.; Khosropour, A. R.; Ahmadi, V. *Polyhedron* **2011**, *30*, 2244. (f) Chen, H.-M.; Chen, P.-Y.; Wang, C.-F.; Tsai, J.-C.; Wang, E.-C. *ARKIVOC* **2012**, 157. For examples using enantioenriched epoxides, see: (g) Gao, Y.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*, 4114. (h) Iranpoor, N.; Kazemi, F. *Tetrahedron* **1997**, *53*, 11377. (i) Iranpoor, N.; Tammi, B.; Shekarriz, M. *Synth. Commun.* **1999**, *29*, 3313. (j) Malaschichin, S.; Fu, C.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **2005**, *88*, 3253. (k) Kleiner, C. M.; Horst, L.; Würtele, C.; Wende, R.; Schreiner, P. R. *Org. Biomol. Chem.* **2009**, *7*, 1397.

(9) Protic solvents and strong acid were typically employed for this transformation: (a) Bordwell, F. G.; Andersen, H. M. *J. Am. Chem. Soc.* **1953**, *75*, 4959. (b) Bouda, H.; Borredon, M. E.; Delmas, M.; Gaset, A. *Synth. Commun.* **1989**, *19*, 491.

(10) For reviews on phosphoric acid catalysis, see: (a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (b) Terada, M. *Chem. Commun.* **2008**, 4097. (c) You, S.-L.; Cai, Q.; Zeng, M. *Chem. Soc. Rev.* **2009**, *38*, 2190. (d) Kampen, D.; Reisinger, C. M.; List, B. *Top. Curr. Chem.* **2009**, *291*, 395. (e) Terada, M. *Synthesis* **2010**, *2010*, 1929. (f) Yu, J.; Shi, F.; Gong, L.-Z. *Acc. Chem. Res.* **2011**, *44*, 1156. (g) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047.

(11) For reviews on kinetic resolution of epoxides, see: (a) Nielsen, L. P. C.; Jacobsen, E. N. Catalytic Asymmetric Epoxide Ring-Opening Chemistry. In *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, Germany, 2006; Chapter 7, pp 229−269. (b) Pellissier, H. *Adv. Synth. Catal.* **2011**, *353*, 1613. (c) Huang, C.-Y.; Doyle, A. G. *Chem. Rev.* **2014**, *114*, 8153.

(12) Plettenburg, O.; Adelt, S.; Vogel, G.; Altenbach, H.-J. *Tetrahedron: Asymmetry* **2000**, *11*, 1057.

(13) (a) Monaco, M. R.; Poladura, B.; Diaz de los Bernardos Sanchez, M.; Leutzsch, M.; Goddard, R.; List, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 7063. (b) Monaco, M. R.; Prevost, S.; List, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 8142. (c) Monaco, M. R.; Prévost, S.; List, B. *J. Am. Chem. Soc.* **2014**, *136*, 16982. Also see: (d) Wang, Z.; Chen, Z.; Sun, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 6685. (e) Wang, Z.; Law, W.; Sun, J. *Org. Lett.* **2013**, *15*, 5964. (f) Wang, Z.; Sheong, F. K.; Sung, H. H. Y.; Williams, I. D.; Lin, Z.; Sun, J. *J. Am. Chem. Soc.* **2015**, *137*, 5895.

(14) For more details, please see the Supporting Information.

(15) For the determination of the association constants, please see the Supporting Information.

(16) When quenching the reaction at − 20 °C (24 h), the remaining epoxide was already enantioenriched (94:8 er, 47% conv.), but only a 15% yield of thiirane was formed at this time. In addition, the initial opening intermediate **B** could be trapped by isocyanate and its enantiopurity was measured to be 96.5:3.5 er, in good agreement with the er of the thiirane product. For details please see the Supporting Information.

(17) Belhadj, T.; Goekjian, P. G. *Tetrahedron Lett.* **2005**, *46*, 8117 (Compound **5** and **10**, similar ^{13}C shift 105 or 107 ppm).

(18) Martin, G. J.; Martin, M. L.; Gouesnard, J.-P. *^{15}N-NMR Spectroscopy*; Springer: Berlin, Heidelberg, 1981.

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