Communications

Asymmetric Catalysis

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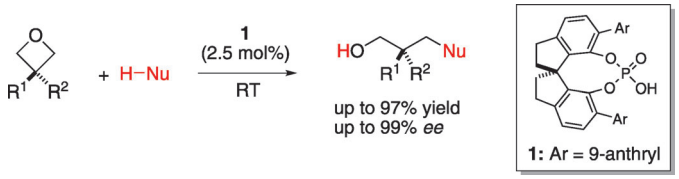
Catalytic Enantioselective Intermolecular Desymmetrization of 3-Substituted Oxetanes



Wring it out: The title reaction proceeds in the presence of chiral Brønsted acid catalysts. This efficient ring-opening process features low catalyst loading, mild reaction conditions, broad functional group compatibility, high enantioselectivity, and the capability to generate chiral quaternary centers. The highly functionalized desymmetrization products are versatile chiral building blocks in organic synthesis.

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DOI: 10.1002/anie.201300188

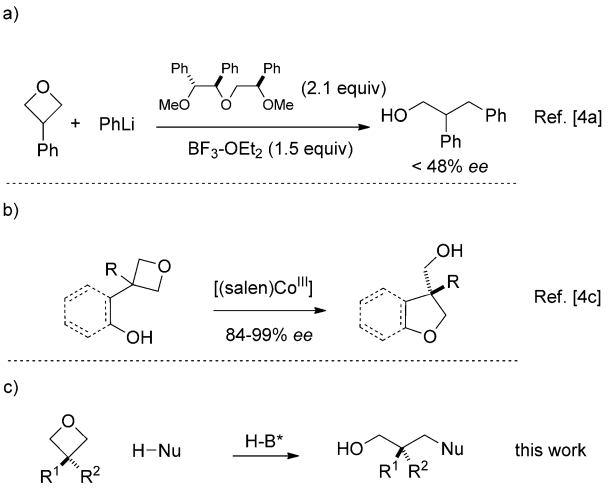
Catalytic Enantioselective Intermolecular Desymmetrization of 3-Substituted Oxetanes**

*Zhaobin Wang, Zhilong Chen, and Jianwei Sun**

Dedicated to Professor Gregory C. Fu on the occasion of his 50th birthday

Enantioselective desymmetrization represents a powerful method to access chiral building blocks.[1] For example, the enantioselective ring opening of *meso* epoxides has been a topic of intense investigations.[1,2] In contrast, oxetanes, the immediate homologue of epoxides, have been much less studied in terms of enantioselective ring openings,[3–5] although studies on their preparation[6] and application[7] have been well-documented. Oxetanes substituted at the 3-position are prochiral, and can lead to various useful three-carbon chiral building blocks upon enantioselective ring opening by nucleophiles. However, there have been only two reports to date. In 1996, Tomioka and co-workers reported the first (and only) example of intermolecular desymmetrization of 3-substituted oxetanes by organolithium reagents, but the reaction requires a stoichiometric amount of a chiral boron reagent and proceeds with low enantioselectivity (< 48 % *ee*; Scheme 1 a).[4a] Recently, Loy and Jacobsen reported an intramolecular desymmetrization catalyzed by [(salen)Co^{III}] complexes with good to excellent enantioselectivity (Scheme 1 b).[4c] However, the same catalytic system could not be extended to an intermolecular reaction.[4c] Herein we describe the first catalytic enantioselective intermolecular desymmetrization of 3-substituted oxetanes leading to the efficient synthesis of useful chiral building blocks, bearing tertiary or quaternary chiral centers, with high enantioselectivity (Scheme 1 c).

The limited success in the intermolecular enantioselective ring opening of oxetanes is partly due to the decreased ring strain relative to epoxides, as well as the increased difficulty in controlling chirality while maintaining good reactivity.[8] Therefore, realization of the process entails the proper choice of not only an excellent catalyst for both sufficient activation and excellent chiral induction, but also a suitable nucleophile. Intrigued by the superior basicity of oxetanes relative to epoxides and other ethers[9] and the recent success of chiral Brønsted acid catalysis,[10] we hypothesized that the use of a suitable chiral phosphoric acid may provide both good oxetane activation and an excellent chiral environment



Scheme 1. Enantioselective desymmetrization of 3-substituted oxetanes. a) First and only intermolecular example (noncatalytic, low *ee* values).[4a] b) First intramolecular example (catalytic, good *ee* values).[4c] c) First intermolecular catalytic example (good *ee* values).

for subsequent nucleophilic attack.[11] Meanwhile, in view of the relatively weak acidity of chiral phosphoric acids, we also anticipated a significant challenge in search for a suitable nucleophile.

We began to test our hypothesis with 3-phenyloxetane (**1a**). Initial evaluation of different types of nucleophiles, such as alcohols and amines, resulted in essentially no conversion, presumably because of either low nucleophilicity or competing binding with the catalyst.

After considerable effort, we were pleased to identify 2-mercaptobenzothiazole (**2**)[12] as a nucleophile of choice (Table 1), and other typical thiols, such as PhSH and BnSH, remain unreactive even at an elevated temperature. Thus, in the presence of 2.5 mol % of the catalyst (*R*)-**A1**, the reaction between **1a** and **2** in CH_2Cl_2 proceeds smoothly at room temperature to form the desired product **3a**, albeit with a disappointingly low enantioselectivity (entry 1). Further screening of phosphoric acids having different chiral backbones indicated that the spinol-derived catalyst (*R*)-**C2** exhibited superior catalytic capability regarding both product yield and enantioselectivity (entries 2–7).[13] Subsequent optimization suggested that the use of Et_2O as a solvent provides both excellent yield and enantioselectivity (entry 10).[14]

With the established standard reaction conditions, we next examined the scope of the desymmetrization reaction. As shown in Table 2, a wide array of oxetanes having different

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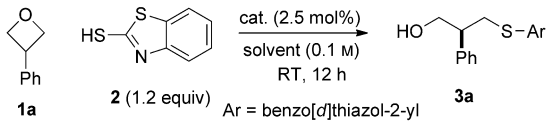
[**] Financial support was provided by the HKUST and Hong Kong RGC (GRF-604411).

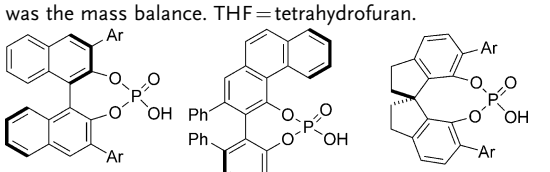
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201300188.

Table 1: Optimization of reaction parameters.



Entry	Catalyst	Solvent	Yield [%][a]	*ee* [%][b]
1	(*R*)-**A1**	CH_2Cl_2	51[c]	−8
2	(*R*)-**A2**	CH_2Cl_2	90	−44
3	(*R*)-**A3**	CH_2Cl_2	94	−55
4	(*R*)-**B**	CH_2Cl_2	92	18
5	(*R*)-**C1**	CH_2Cl_2	90	55
6	(*R*)-**C2**	CH_2Cl_2	97	88
7	(*R*)-**C3**	CH_2Cl_2	93	75
8	(*R*)-**C2**	toluene	92	88
9	(*R*)-**C2**	THF	9[c]	92
10	(*R*)-**C2**	Et_2O	92	93

[a] Determined by GC analysis with decane as an internal standard. [b] Determined by HPLC analysis using a chiral stationary phase. [c] **1a** was the mass balance. THF = tetrahydrofuran.

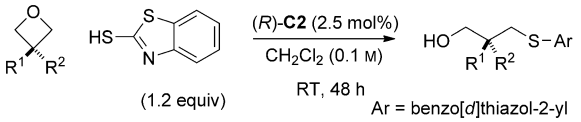


A1: Ar = Ph
A2: Ar = 9-anthryl
A3: Ar = 2,4,6-*i*Pr$_3$C$_6$H$_2$

C1: Ar = 2,4,6-*i*Pr$_3$C$_6$H$_2$
C2: Ar = 9-anthryl
C3: Ar = 9-phenanthryl

substituents in the 3-position all participate smoothly in the C–S bond-formation process, thus furnishing the corresponding alcohols **3** with high efficiency. The desymmetrization process is not limited to the formation of tertiary chiral centers. As shown in Table 3, chiral quaternary centers can also be efficiently formed with good to excellent enantioselectivity from the corresponding 3,3-disubstitued oxetanes.[15]

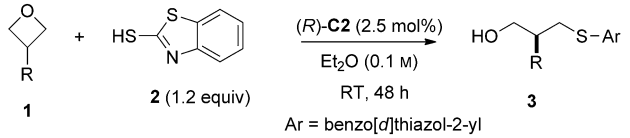
Table 3: Scope study for quaternary chiral center formation.

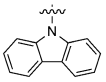
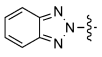


Entry	R^1	R^2	**4**	Yield [%][a]	*ee* [%]
1	Ph	OH	**4a**	91	97
2	2-BrC_6H_4	OH	**4b**	86	99
3	4-H_2C=CHC_6H_4	OH	**4c**	80	97
4	2-H_2C=CHC_6H_4	OH	**4d**	81	98
5	2-TMSC≡CC_6H_4	OH	**4e**	86	89
6	allyl	OH	**4f**	93	94
7	C≡CH	OH	**4g**	96	87
8	C≡CPh	OH	**4h**	93	97
9[c]	CF_3	OH	**4i**	93	97
10[c]	Ph	*t*BuSO_2NH	**4j**	82	78
11[d]	CH_2OTBS	Me	**4k**	94	71
12[c]	Ph	Me	**4l**	93	77

[a] Yield of purified product. [b] Run with Et_2O as the solvent. [c] Run at 40 °C with 5 mol% of (*R*)-**C2**. [d] Run at 40 °C with CPME as the solvent. CPME = cyclopentylmethyl ether, TMS = trimethylsilyl.

Table 2: Scope study for tertiary chiral center formation.



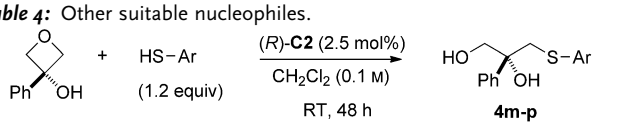
Entry	R		**3**	Yield [%][a]	*ee* [%]
1	Ph	**1a**	**3a**	91	92
2	4-MeC_6H_4	**1b**	**3b**	91	92
3	3-ClC_6H_4	**1c**	**3c**	90	92
4	3-BrC_6H_4	**1d**	**3d**	92	92
5	4-CNC_6H_4	**1e**	**3e**	96	90
6	3-$CF_3C_6H_4$	**1f**	**3f**	96	92
7	4-$CF_3OC_6H_4$	**1g**	**3g**	97	91
8		**1h**	**3h**	91	92
9	2-Np	**1i**	**3i**	91	92
10	OTBS	**1j**	**3j**	90	93
11	OBn	**1k**	**3k**	96	96
12	OTs	**1l**	**3l**	87	91
13	O$(CH_2)_2$OBn	**1m**	**3m**	87	96
14	O$(CH_2)_4$OBn	**1n**	**3n**	97	96
15[b]	O$(CH_2)_3$CHO	**1o**	**3o**	74	94
16	O(4-MeOC_6H_4)	**1p**	**3p**	94	96
17	O(3,4,5-$(MeO)_3C_6H_2$)	**1q**	**3q**	92	91
18	O(1-Np)	**1r**	**3r**	94	96
19	S(4-MeOC_6H_4)	**1s**	**3s**	94	92
20	S(2-Np)	**1t**	**3t**	86	92
21		**1u** (R′=H)	**3u**	94	96
22		**1v** (R'=2-Me)	**3v**	97	98
23		**1w** (R'=5-OMe)	**3w**	96	96
24		**1x** (R'=6-Br)	**3x**	96	96
25		**1y**	**3y**	93	97
26		**1z**	**3z**	85	92
27	*t*BuSO_2NH	**1aa**	**3aa**	73	77

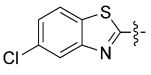
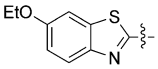
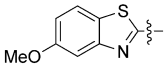
[a] Yield of purified product. [b] Run with CH_2Cl_2 as the solvent. Np = naphthyl, TBS = *tert*-butyldimethylsilyl, Ts = 4-toluenesulfonyl.

It is also noteworthy that the method is capable of generating all-carbon chiral quaternary centers (Table 3, entries 11 and 12), which is a well-known challenge in organic synthesis.[15c] Finally, the mild reaction conditions tolerate a diverse set of functional groups, including halides, ethers, silyl ethers, aldehydes, sulfonamides, sulfonates, free alcohols, alkenes, and alkynes.

We have also evaluated the effect of substituents on the nucleophile (Table 4). 2-Mercaptobenzothiazoles substituted with an electron-withdrawing or electron-donating group all participate smoothly in the efficient desymmetrization reactions, thus furnishing the corresponding alcohol products **4m**–**o** with both excellent yield and enantioselectivity. In addition, 1,3,4-thiadiazole-2-thiol is also a suitable nucleophile (**4p**). It is worth noting that the benzothiazole/thiadiazole thioether moiety in the desymmetrization products is not only an important structural unit found in many biologically active

Table 4: Other suitable nucleophiles.

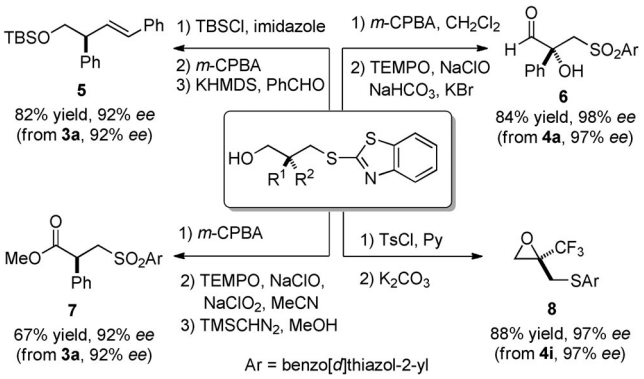


Entry	Ar	Product	Yield [%][a]	*ee* [%]
1		**4m**	97	99
2		**4n**	97	96
3		**4o**	96	>99
4		**4p**	73	90

[a] Yield of purified product.

molecules,[16] but also a versatile functional group which can be easily converted into other useful functionalities.[17]

The enantioenriched products obtained by our catalytic intermolecular desymmetrization reactions can be transformed into other useful compounds (Scheme 2). The benzothiazole thioether can be easily oxidized to the corresponding sulfone, which is widely used as a Julia olefination reagent (e.g., formation of **5**).[17] Moreover, the primary alcohols can also be oxidized to carbonyl compounds with an α-tertiary or quaternary chiral center (e.g., aldehyde **6** and ester **7**).[18] The conventional synthesis of these compounds through the catalytic enantioselective α arylation or α heterofunctionalization has been a long-standing topic in organic synthesis and some of these reactions are still challenging today.[19] Finally, enantioenriched 1,1-disubstituted epoxides (e.g., **8**) can be obtained from the corresponding 1,2-diols after two simple chemical steps. It is worth noting that 1,1-disubstituted terminal olefins are, in general, challenging substrates for asymmetric epoxidation.[20] It is also noteworthy that in all these transformations no erosion in product enantiopurity was observed, thus demonstrating that our present method is versatile and complementary to known strategies for the synthesis of useful chiral building blocks.



Scheme 2. Representative transformations of the desymmetrization products.

As shown in Figure 1, we have proposed possible transition states to rationalize the absolute stereochemical outcome of the intermolecular ring-opening process. We believe that the hydrogen bond between the catalyst OH and the oxetane oxygen atom is the primary substrate–catalyst interaction. Additional interactions vary with substrates. For oxetanes bearing a hydrogen-bond donor substituent (e.g., OH) at the 3-position, we propose a nine-membered cyclic transition state, which involves another hydrogen bond between the catalyst phosphoryl oxygen atom and the substituent (Figure 1a). In contrast, oxetanes lacking such a hydrogen-bond donor substituent may adopt a transition state with the larger substituent (R_L) oriented opposite to the catalyst pocket to minimize steric interactions (Figure 1b). In both cases, the nucleophile approaches the reactive center from the back side because the front side is blocked by the bulky anthryl group in the catalyst. These rationalizations are consistent with the absolute stereochemistry observed for the product.

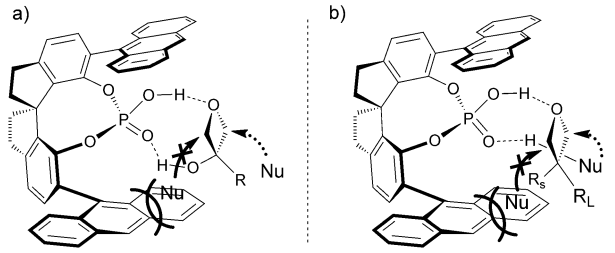


Figure 1. Plausible transition states for activation of oxetanes with (a) and without (b) a hydrogen-bond donor substituent.

Although attempts to obtain a substrate/catalyst cocrystal failed, we were able to observe an obvious substrate–catalyst interaction by NMR experiments. As shown in Figure 2, the addition of one equivalent of the catalyst **C2** to either the substrate **1a** or **1ab** results in dramatic shifts of all the proton signals in the oxetane ring towards high field. A higher catalyst/substrate ratio causes a larger shift, thus indicating a reversible interaction. In addition, more complicated peak splitting patterns of the oxetane signals were observed, thus suggesting that the interaction imposes a chiral environment around the prochiral oxetane ring. These observations fully agree with our proposed transition states.

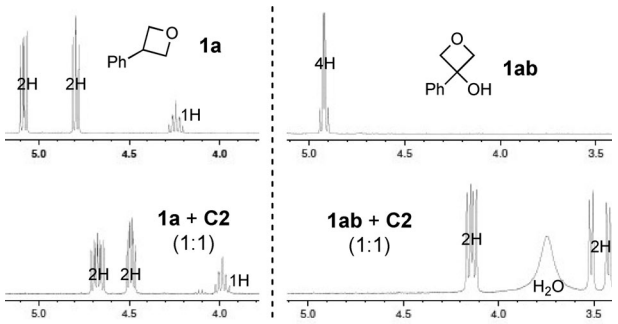


Figure 2. NMR observation of the substrate–catalyst interaction.[14] Values on the horizontal axes: $\delta(^1H)$ [ppm].

In summary, the first catalytic asymmetric intermolecular desymmetrization of 3-substituted oxetanes has been developed. It represents a new addition to the small family of asymmetric reactions of oxetanes. With the proper choice of the catalyst and nucleophile, a range of readily available oxetanes participate smoothly in the ring-opening process, thus furnishing a diverse set of highly functionalized chiral building blocks with remarkable efficiency and enantioselectivity. This mild process, featuring low catalyst loading and broad functional group compatibility, is also effective for the formation of quaternary chiral centers, including all-carbon quaternary stereocenters. Moreover, the enantioenriched desymmetrization products are versatile precursors to other useful chiral building blocks, thus suggesting that our present method provides an attractive alternative to other strategies in asymmetric synthesis. The development of other useful processes of oxetanes is underway.

Received: January 9, 2013
Published online: ■■ ■■, ■■■■

Keywords: asymmetric catalysis · nucleophilic addition · organocatalysis · strained molecules · sulfur

[1] a) E. García-Urdiales, I. Alfonso, V. Gotor, *Chem. Rev.* **2005**, *105*, 313 – 354; b) A. Studer, F. Schleth, *Synlett* **2005**, 3033 – 3041; c) S. Rendler, M. Oestreich, *Angew. Chem.* **2008**, *120*, 254 – 257; *Angew. Chem. Int. Ed.* **2008**, *47*, 248 – 250; d) V. S. Sajisha, S. Anas, J. John, K. V. Radhakrishnan, *Synlett* **2009**, 2885 – 2895; e) M. D. Díaz de Villegas, J. A. Gálvez, P. Etayo, R. Badorrey, P. López-Ram-de-Víu, *Chem. Soc. Rev.* **2011**, *40*, 5564 – 5578.

[2] a) D. M. Hodgson, A. R. Gibbs, G. P. Lee, *Tetrahedron* **1996**, *52*, 14361 – 14384; b) E. N. Jacobsen, *Acc. Chem. Res.* **2000**, *33*, 421 – 431; c) C. Schneider, *Synthesis* **2006**, 3919 – 3944.

[3] For leading reviews on oxetanes, see: a) J. A. Burkhard, G. Wuitschik, M. Rogers-Evans, K. Müller, E. M. Carreira, *Angew. Chem.* **2010**, *122*, 9236 – 9251; *Angew. Chem. Int. Ed.* **2010**, *49*, 9052 – 9067; b) G. Wuitschik, E. M. Carreira, B. Wagner, H. Fischer, I. Parrilla, F. Schuler, M. Rogers-Evans, K. Müller, *J. Med. Chem.* **2010**, *53*, 3227 – 3246.

[4] For pioneering studies on asymmetric opening of oxetanes, see: a) M. Mizuno, M. Kanai, A. Iida, K. Tomioka, *Tetrahedron: Asymmetry* **1996**, *7*, 2483 – 2484; b) M. Mizuno, M. Kanai, A. Iida, K. Tomioka, *Tetrahedron* **1997**, *53*, 10699 – 10708; c) R. N. Loy, E. N. Jacobsen, *J. Am. Chem. Soc.* **2009**, *131*, 2786 – 2787.

[5] For examples of asymmetric ring expansions of oxetanes, see: a) H. Nozaki, S. Moriuti, H. Takaya, R. Noyori, *Tetrahedron Lett.* **1966**, *7*, 5239 – 5244; b) H. Nozaki, H. Takaya, S. Moriuti, R. Noyori, *Tetrahedron* **1968**, *24*, 3655 – 3669; c) K. Ito, T. Katsuki, *Chem. Lett.* **1994**, 1857 – 1860; d) M. M.-C. Lo, G. C. Fu, *Tetrahedron* **2001**, *57*, 2621 – 2634; e) B. Guo, G. Schwarzwalder, J. T. Njardarson, *Angew. Chem.* **2012**, *124*, 5773 – 5776; *Angew. Chem. Int. Ed.* **2012**, *51*, 5675 – 5678.

[6] For selected examples: a) M. A. J. Duncton, M. A. Estiarte, D. Tan, C. Kaub, D. J. R. O'Mahony, R. J. Johnson, M. Cox, W. T. Edwards, M. Wan, J. Kincaid, M. G. Kelly, *Org. Lett.* **2008**, *10*, 3259 – 3262; b) T. Sone, G. Lu, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2009**, *121*, 1705 – 1708; *Angew. Chem. Int. Ed.* **2009**, *48*, 1677 – 1680; c) M. A. J. Duncton, M. A. Estiarte, R. J. Johnson, M. Cox, D. J. R. O'Mahony, W. T. Edwards, M. G. Kelly, *J. Org. Chem.* **2009**, *74*, 6354 – 6357; d) L. Ye, W. He, L. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 8550 – 8551; e) E. D. Butova, A. V. Barabash, A. A. Petrova, C. M. Kleiner, P. R. Schreiner, A. A. Fokin, *J. Org. Chem.* **2010**, *75*, 6229 – 6235; f) P. J. Hamzik, J. D. Brubaker, *Org. Lett.* **2010**, *12*, 1116 – 1119.

[7] a) Ref. [3]; b) G. Wuitschik, M. Rogers-Evans, K. Müller, H. Fischer, B. Wagner, F. Schuler, L. Polonchuk, E. M. Carreira, *Angew. Chem.* **2006**, *118*, 7900 – 7903; *Angew. Chem. Int. Ed.* **2006**, *45*, 7736 – 7739.

[8] T. Dudev, C. Lim, *J. Am. Chem. Soc.* **1998**, *120*, 4450 – 4458.

[9] M. Berthelot, F. Besseau, C. Laurence, *Eur. J. Org. Chem.* **1998**, 925 – 931.

[10] For leading reviews, see: a) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999 – 1010; b) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744 – 5758; c) M. Terada, *Chem. Commun.* **2008**, 4097 – 4112; d) G. Adair, S. Mukherjee, B. List, *Aldrichimica Acta* **2008**, *41*, 31 – 39; e) D. Kampen, C. M. Reisinger, B. List, *Top. Curr. Chem.* **2010**, *291*, 395 – 456; f) M. Terada, *Synthesis* **2010**, 1929 – 1982; g) M. Rueping, R. M. Koenigs, I. Atodiresei, *Chem. Eur. J.* **2010**, *16*, 9350 – 9365; h) J. Yu, F. Shi, L. Gong, *Acc. Chem. Res.* **2011**, *44*, 1156 – 1171; i) M. Rueping, A. Kuenkel, I. Atodiresei, *Chem. Soc. Rev.* **2011**, *40*, 4539 – 4549.

[11] Ref. [5e] reports the first chiral phosphoric acid catalyzed opening of an oxetane. For another recent example, which is our parallel study: Z. Chen, Z. Wang, J. Sun, *Angew. Chem.* **2013**, *125*, 2081 – 2085; *Angew. Chem. Int. Ed.* **2013**, *52*, 2027 – 2031.

[12] For a review on 2-mercaptobenzothiazole, see: F.-L. Lu, W. M. Hussein, B. P. Ross, R. P. McGeary, *Curr. Org. Chem.* **2012**, *16*, 1555 – 1580.

[13] The catalyst **C2** was first developed by List and co-workers: S. Müller, M. J. Webber, B. List, *J. Am. Chem. Soc.* **2011**, *133*, 18534 – 18537.

[14] See the Supporting Information for more details.

[15] For reviews on formation of quaternary chiral centers, see: a) E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, *110*, 2092 – 2118; *Angew. Chem. Int. Ed.* **1998**, *37*, 388 – 401; b) J. Christoffers, A. Mann, *Angew. Chem.* **2001**, *113*, 4725 – 4732; *Angew. Chem. Int. Ed.* **2001**, *40*, 4591 – 4597; c) C. J. Douglas, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363 – 5367.

[16] For examples of benzothiazole- and thiadiazole-containing bioactive compounds, see: a) J. Dumas, D. Brittelli, J. Chen, B. Dixon, H. Hatoum-Mokdad, G. König, R. Sibley, J. Witowsky, S. Wong, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2531 – 2536; b) A. Naya, K. Kobayashi, M. Ishikawa, K. Ohwaki, T. Saeki, K. Noguchi, N. Ohtake, *Chem. Pharm. Bull.* **2003**, *51*, 697 – 701; c) A. Thiry, C. T. Supuran, B. Masereel, J.-M. Dogne, *J. Med. Chem.* **2008**, *51*, 3051 – 3056.

[17] a) Ref. [12]; b) P. R. Blakemore, *J. Chem. Soc. Perkin Trans. 1* **2002**, 2563 – 2585.

[18] a) M. Zhao, J. Li, E. Mano, Z. Song, D. M. Tschaen, E. J. J. Grabowski, P. J. Reider, *J. Org. Chem.* **1999**, *64*, 2564 – 2566; b) M. Shibuya, M. Tomizawa, I. Suzuki, Y. Iwabuchi, *J. Am. Chem. Soc.* **2006**, *128*, 8412 – 8413.

[19] For reviews on asymmetric α-functionalization of carbonyl compounds, see: a) G. Guillena, D. J. Ramón, *Tetrahedron: Asymmetry* **2006**, *17*, 1465 – 1492; b) A. M. R. Smith, K. K. Hii, *Chem. Rev.* **2011**, *111*, 1637 – 1656; c) D. W. C. MacMillan, A. J. B. Watson in *Science of Synthesis Stereoselective Synthesis* (Eds.: J. G. De Vries, G. A. Molander, P. A. Evans), Thieme, Stuttgart, **2011**, p. 675 – 745.

[20] For an example, see: a) B. Wang, O. A. Wong, M.-X. Zhao, Y. Shi, *J. Org. Chem.* **2008**, *73*, 9539 – 9543. For reviews on asymmetric epoxidation, see: b) Q.-H. Xia, H.-Q. Ge, C.-P. Ye, Z.-M. Liu, K.-X. Su, *Chem. Rev.* **2005**, *105*, 1603 – 1662; c) O. A. Wong, Y. Shi, *Chem. Rev.* **2008**, *108*, 3958 – 3987; d) G. De Faveri, G. Ilyashenko, M. Watkinson, *Chem. Soc. Rev.* **2011**, *40*, 1722 – 1760.

