DOI: 10.1002/adsc.200800761

A Novel Cost-Effective Thiourea Bifunctional Organocatalyst for Highly Enantioselective Alcoholysis of *meso*-Cyclic Anhydrides: Enhanced Enantioselectivity by Configuration Inversion

Su-Xi Wang[a] and Fen-Er Chen[a,*]

[a] Fudan-DSM Joint Lab for Synthetic Method and Chiral Technology, Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, People's Republic of China
Fax: (+86)-21-65643811; e-mail: rfchen@fudan.edu.cn

Received: December 9, 2008; Published online: March 5, 2009

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200800761.

Abstract: A novel inexpensive thiourea bifunctional organocatalyst which can promote the highly enantioselective (up to 95% *ee*) alcoholysis of *meso*-cyclic anhydrides has been developed. Computational studies on the catalytic process as well as a synthetic application of this new catalyst are also presented.

Keywords: alcoholysis; asymmetric catalysis; bifunctional organocatalyst; *meso*-cyclic anhydrides; thioureas

Peptide-like bifunctional catalysts with high activity and broad substrate applicability have emerged as powerful reagents in organic synthesis over the past few decades.[1] The combination of two active sites within an asymmetric space in a catalyst leads to synergistic activation of both electrophilic and nucleophilic substrates, providing extremely high enantioselectivity. Recent efforts toward the development of chiral thiourea-based bifunctional organocatalysts have produced outstanding efficiency in a wide variety of asymmetric transformations.[2]

The stereoselective alcoholysis of *meso*-cyclic anhydrides is a proven strategy to conveniently access optically active hemiesters as valuable building blocks for many natural products and biologically active substances.[3] Since the first non-enzymatic and metal-free catalytic process reported by Oda and co-workers,[4a,b] impressive progress has been made in the opening of anhydrides by chiral Lewis bases,[4] as demonstrated by *Cinchona* alkaloids and their derivatives. Those protocols, however, are limited by the requirements for high catalyst loading, low temperatures, and long reaction periods. Until quite recently, a remarkable breakthrough has been achieved by Connon et al.[5] and Song et al.[6], who independently observed the highly stereoselective methanolysis of cyclic anhydrides catalyzed by *Cinchona*-derived amine-thiourea bifunctional organocatalyst **1** (Figure 1) at room temperature, with ≤ 10 mol% catalyst loading.

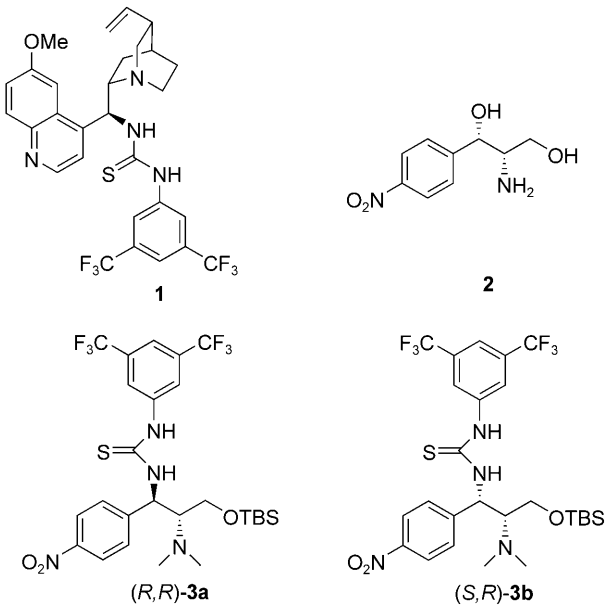


Figure 1. Structures of chiral organocatalysts.

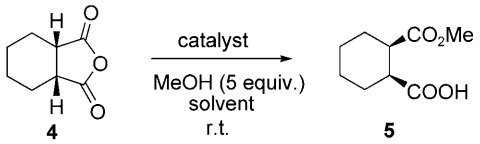
Despite the numerous advances in thiourea-based bifunctional catalysis, the structures of these organocatalysts are limited, and some are even unfavorable for commercial applications. This problem prompted us to initiate an exploration of novel organocatalysts with easy accessibility and high efficiency. Previously,

our laboratory employed the derivative of the inexpensive (*1S, 2S*)-2-amino-1-(*p*-nitrophenyl)propane-1,3-diol **(2)**, a by-product in the industrial production of chloramphenicol, as a ligand in the asymmetric synthesis of (+)-biotin.[7] Later, the distinct potency of this chiral scaffold in transferring stereochemical information was further demonstrated in the enantioselective alkynylation of various substrates.[8] In our design for new catalysts, some appealing features of this amino alcohol aroused our attention. First, both its enantiomers are readily available and much cheaper than *Cinchona* alkaloids. Second, the convenient modification at the nitrogen atom and amino functionality at C-1 could easily form a chiral 1,2-diamine scaffold, which appears to be the most prevalent structure for the introduction of a thiourea moiety. Third, the opportunity for inversion of configuration at C-1 of this chiral scaffold is an attractive advantage for catalyst optimization. Finally, the substituent at the terminal hydroxy is readily tunable, permitting adjustment of the steric hindrance of the skeleton. With the above features in mind, we envisaged that the chiral amino alcohol **2** would be the starting material of choice to generate a new class of cost-effective and powerful bifunctional organocatalysts. In this paper, we report the synthesis of novel chiral amine-thioureas **3a** and **b** (Figure 1) and their first applications for the highly enantionselective alcoholysis of *meso*-cyclic anhydrides. We also present computational studies on the catalytic process.

Catalysts **3a** and **b** were prepared from (*1S, 2S*)-2-amino-1-(*p*-nitrophenyl)propane-1,3-diol **(2)** *via* experimentally conventional four- and five-step protocols, respectively.[9]

The results of our preliminary evaluation of the novel organocatalysts **3a** and **b** by methanolysis of cyclic anhydride **4** and the optimization of reaction conditions are presented in Table 1. Initially, different solvents were screened with 10 mol% **3a** and 5 equivalents of methanol at room temperature (Table 1,entries 1–5). The reaction proceeded best in methyl *tert*-butyl ether with a yield of 94% and an *ee* of 82%. Encouraged by the promising results obtained with catalyst (*R,R*)-**3a**, we next examined the effectiveness of its isomer (*S,R*)-**3b**. We were delighted to observe an even higher *ee* of 89%, furnished with no loss of chemical yield (Table 1, entry 6). Interestingly, the hemiester was formed in the same configuration as that induced by catalyst **3a**. An even more satisfactory *ee* of 93% was obtained by diluting the reaction mixture from 0.05 M to 0.0125 M (Table 1, entry 8). We also investigated the effect of catalyst loading (entries 9–12) and found that 5 mol% catalyst was sufficient to maintain the high chemical yield (93%) and *ee* (95%) with a satisfactory reaction rate. A further decrease in the catalyst loading resulted in relatively lower yield and longer reaction time. Notably, a slight deterioration in enantiomeric excess was observed when the reaction was run at 0 °C (Table 1, entry 13).

Table 1. Catalyst evaluation and optimization of reaction conditions.

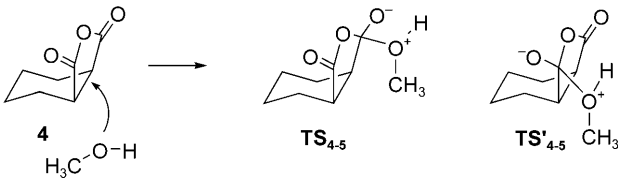


4 **5**

Entry	Catalyst (equiv.)	Solvent	Concentration [M][a]	*t* [h]	Yield [%][b]	*ee* [%][c,d]
1	**3a** (0.1)	Toluene	0.05	24	94	56
2	**3a** (0.1)	CH_2Cl_2	0.05	24	89	63
3	**3a** (0.1)	MTBE	0.05	24	94	82
4	**3a** (0.1)	THF	0.05	24	85	77
5	**3a** (0.1)	Dioxane	0.05	24	94	80
6	**3b** (0.1)	MTBE	0.05	24	96	89
7	**3b** (0.1)	MTBE	0.025	24	95	91
8	**3b** (0.1)	MTBE	0.0125	24	94	93
9	**3b** (0.2)	MTBE	0.0125	12	95	94
10	**3b** (0.05)	MTBE	0.0125	30	93	95
11	**3b** (0.02)	MTBE	0.0125	48	85	95
12	**3b** (0.01)	MTBE	0.0125	72	81	92
13[e]	**3b** (0.05)	MTBE	0.0125	60	88	91

[a] Refers to the concertration of the anhydride in the solvent.
[b] Yield of isolated product.
[c] Determined by HPLC (see Supporting Information).
[d] Absolute configuration was determined by comparing the sign of the optical rotation of the major enantiomer with known data.[5]
[e] Reaction was performed at 0 °C.

To provide a theoretical explanation for both the predominant configuration of the product and the superior enantioselectivity of catalyst **3b**, we have thus initiated quantum chemical calculations in the catalytic methanolysis of **4**. As proposed by Song et al.,[6] the complexes of catalysts **3a** and **b** and the transition state analogues of the uncatalyzed methanolysis reaction (**TS$_{4\text{-}5}$** and **TS′$_{4\text{-}5}$**, Scheme 1) could be regarded as transition state analogues for the catalytic process. The structures of these complexes, which involve two complementary hydrogen bonding interactions, were optimized by molecular mechanics computation performed at the B3LYP/6-31G* level (Figure 2). The calculations show that **3a**-**TS$_{4\text{-}5}$** complex is



Scheme 1. Transition state analogues of uncatalyzed methanolysis of **4.**

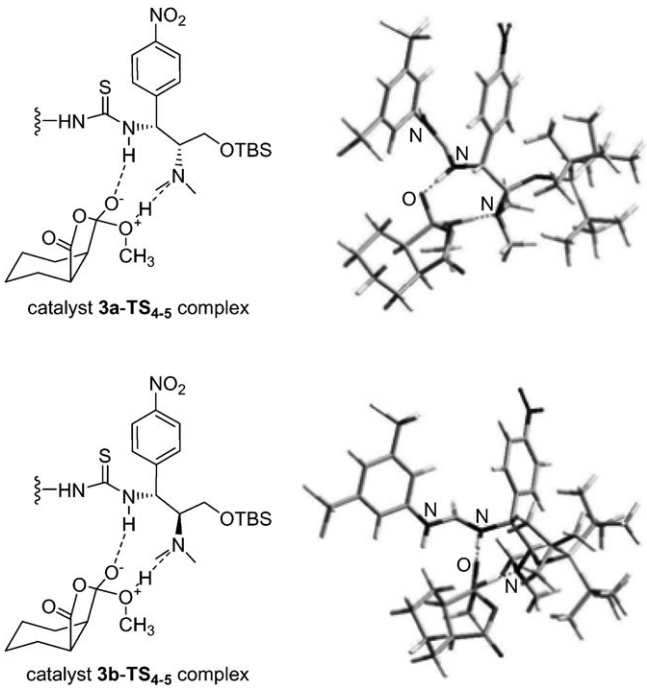


Figure 2. Optimized structures of transition state analogues yielding hemiester **5**.

5.2 kcal mol^{-1} more stable than **3a**-**TS′$_{4\text{-}5}$** and, similarly, **3b**-**TS$_{4\text{-}5}$** is likewise found to be 7.0 kcal mol^{-1} more favored than its counterpart. Moreover, the optimized structure of **3b**-**TS$_{4\text{-}5}$** complex is 1.5 kcal mol^{-1} more stable in comparison with **3a**-**TS$_{4\text{-}5}$**. These energy differences explain the generation of the same isomer **5** from catalysts **3a** and **3b** which have two different configurations, and also indicate the higher selectivity of catalyst **3b** which is in qualitative agreement with experimental findings.

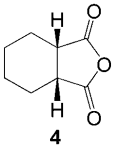
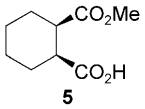
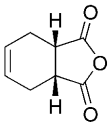
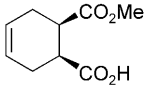
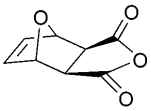
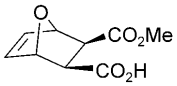
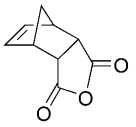
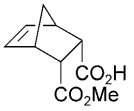
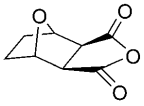
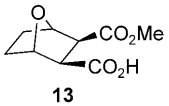
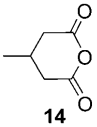
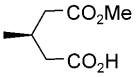
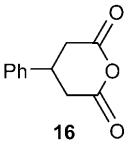
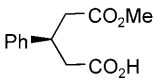
With the optimal catalyst and reaction conditions established, we next examined the scope and limitations of the methodology by surveying a series of *meso*-cyclic anhydrides in the methanolysis reaction (Table 2). In general, the bi- and tricyclic succinic anhydrides were readily desymmetrized to give the corresponding hemiesters in good yields and with excellent enantioselectivities (90–95% *ee*). The reaction was most effective for bicyclic substrates (Table 2, entries 1 and 2), which underwent rapid methanolysis with low catalyst loading (5 mol%). In contrast, longer reaction periods (72–96 h) were required for complete conversion of the more sterically hindered tricyclic substrates (Table 2, entries 3, 4 and 5). Notably, for the anhydrides bearing multiple polar functionalities (**8** and **12**), the use of an increased catalyst loading (20 mol%) was needed to generate comparable results. The methanolytic desymmetrization of monocyclic glutaric anhydrides was also attempted (Table 2, entries 6 and 7), and while nearly quantitative yields were obtained, the *ee* values decreased, which could be ascribed to the lack of rigidity of the substrates.

Subsequently, different alcohols were examined as nucleophiles in the desymmetrization of the model substrate **10** under the optimized conditions (Table 3). The steric hindrance of the alcohol had a limited impact on enantioseletivity since excellent *ee* values were furnished with alcohols more sterically bulky than methanol, such as ethanol, 1-propanol, and even 2-propanol. These results are at odds with the observations made by Bolm et al.[4l] in the quinidine-catalyzed alcoholysis of cyclic anhydride **10**. With respect to unsaturated alcohols, propargyl alcohol still led to a good selectivity (91% *ee*, Table 3, entry 6); however, considerably lower *ee* values were obtained with allyl alcohol (35% *ee*, Table 3, entry 5) and *trans*-cinnamyl alcohol (75% *ee*, Table 3, entry 8).

We have demonstrated a practical use of the current study by the conversion of cyclic anhydride **25** into (3a*S*,6a*R*)-lactone **27**, the key chiral building block for asymmetric total synthesis of (+)-biotin (Scheme 2).[4i,10] Due to the bulky size and the presence of multiple polar functionalities, a catalyst loading of 30 mol% was needed for desymmetrization of **25** with propargyl alcohol at room temperature, generating the (4*S*,5*R*)-hemiester **26** in 96% yield and 82% *ee*. After a single recrystallization, **26** was subjected to reductive ring closure[10] to yield (3a*S*,6a*R*)-lactone **27** in 97% *ee*, which was previously converted to (+)-biotin *via* four steps.[4i,10] It is worth mentioning that the catalyst used in the alcoholysis of **25** could be easily separated and quantitatively recovered by basification of the reaction mixture.[9]

In conclusion, we have successfully developed a novel series of readily available amine-thiourea bifunctional organocatalysts, which exhibit catalytic activity that is readily enhanced by changing the configuration of the chiral scaffold. Quantum chemical calculations provided the theoretical explanation for the observed stereoinduction of the catalysts. In the presence of a catalytic amount of **3b**, asymmetric methanolysis of various *meso*-cyclic anhydrides proceeded smoothly to afford the corresponding hemiesters in high yields and with good to excellent enantioselectivities. Alcohols other than methanol were effective nucleophiles in the desymmerization reaction and also provided excellent enantiomeric excesses. Furthermore, a synthetic utility of this catalyst was demonstrated in the asymmetric synthesis of (+)-biotin. Investigations on the full scope of this new catalyst in asymmetric transformations are currently in progress and will be reported in due course.

Table 2. Enantioselective methanolysis of various *meso*-cyclic anhydrides by catalyst **3b**.[a]

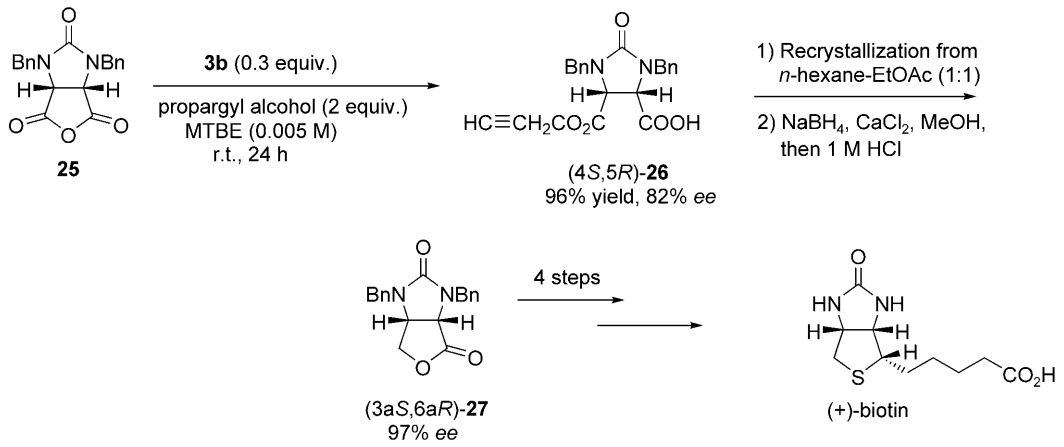
Entry	Anhydride	Product[b]	*t* [h]	Yield [%][c]	*ee* [%][d]
1	 **4**	 **5**	30	93	95
2	 **6**	 **7**	30	94	95
3[e]	 **8**	 **9**	96	89	90
4	 **10**	 **11**	72	90	95
5[e]	 **12**	 **13**	96	88	90
6	 **14**	 **15**	18	97	82
7	 **16**	 **17**	24	95	85

[a] Unless otherwise noted, all reactions were carried out with anhydride (0.5 mmol), MeOH (2.5 mmol) and **3b** (0.025 mmol) in MTBE (40 mL) at room temperature.
[b] Absolute configurations were determined by comparing the sign of the optical rotation of the major enantiomer with known data.[4h,5]
[c] Yield of isolated product.
[d] Determined by HPLC or ^{1}H NMR (see Supporting Information).
[e] Reaction performed with **3b** (0.1 mmol) in MTBE (80 mL).

Experimental Section

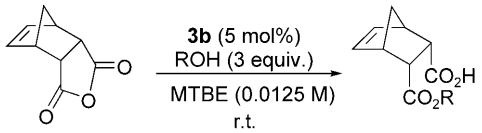
Typical Procedure for the Asymmetric Alcoholysis of *meso*-Cyclic Anhydrides using Catalyst 3b

The following procedure for the methanolysis of *cis*-cyclohexane-1,2-dicarboxylic acid anhydride (**4**) using catalyst **3b** is representative. Methanol (80 mg, 2.5 mmol) was added dropwise to a stirred solution of the anhydride **4** (77 mg, 0.5 mmol) and **3b** (15.6 mg, 0.025 mmol) in MTBE (40 mL) at room temperature under nitrogen. When TLC analysis indicated complete consumption of the anhydride, the solvent was evaporated under vacuum and the residue was dissolved in CH_2Cl_2 (10 mL). The solution was washed with saturated Na_2CO_3 (2×5 mL) and the combined aqueous layers were acidified with excess 2 N HCl, followed by extraction with EtOAc (3×20 mL). The combined organic layers were dried over Na_2SO_4 and concertrated to afford the hemiester **5** (yield: 86 mg, 93%) as a white solid without further purification by chromatography. HPLC analysis of the corresponding amide-ester[9] of hemiester **5** (Chiralcel OD-H, hexane/2-propanol 93/7, flow rate = 0.5 mL min^{-1}, λ = 220 nm): retention time t_r (major) = 38.6 min, t_r (minor) = 54.4 min; mp 68.2–69.1 °C; $[\alpha]_D^{25}$: 3.7 (*c* 2.0, $CHCl_3$); ^{1}H NMR (400 MHz,



Scheme 2. Synthetic application of **3b** in the total synthesis of (+)-biotin.

Table 3. Asymmetric alcoholysis of cyclic anhydride **10** with different alcohols.[a]



Entry	ROH	Hemiester	Yield[b] [%]	*ee*[c] [%]
1	Methanol	**11**	94	95
2	Ethanol	**18**	93	92
3	1-Propanol	**19**	89	95
4	2-Propanol	**20**	87	91
5	Allyl alcohol	**21**	83	35
6	Propargyl alcohol	**22**	92	91
7	Benzyl alcohol	**23**	88	89
8	*trans*-Cinnamyl alcohol	**24**	89	75

[a] Reactions were carried out with **10** (0.5 mmol), ROH (1.5 mmol) and **3b** (0.025 mmol) in MTBE (40 mL) at room temperature.
[b] Yield of isolated product.
[c] Determined by HPLC (see Supporting Information).

$CDCl_3$): $\delta = 3.68$ (s, 3H), 2.91–2.80 (m, 2H), 2.10–1.96 (m, 2H), 1.84–1.73 (m, 2H), 1.61–1.37 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 179.3$, 173.5, 51.2, 42.1, 41.8, 25.8, 25.4, 23.3, 23.1.

References

[1] For reviews on bifunctional catalysis, see: a) S. J. Connon, *Chem. Commun.* **2008**, 2499–2510; b) M. Kanai, N. Kato, E. Ichikawa, M. Shibasaki, *Synlett* **2005**, 1491–1508; 2006, 45, 1–5; c) P. I. Dalko, L. Moison, *Angew. Chem.* **2004**, *116*, 5248–5286; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175; d) J.-A. Ma, D. Cahard, *Angew. Chem.* **2004**, *116*, 4666–4683; *Angew. Chem. Int. Ed.* **2004**, *43*, 4566–4583; e) P. M. Pihko, *Angew. Chem.* **2004**, *116*, 2110–2113; *Angew. Chem. Int. Ed.* **2004**, *43*, 2062–2064; f) M. Shibasaki, N. Yoshikawa, *Chem. Rev.* **2002**, *102*, 2187–2209; g) H. Groger, *Chem. Eur. J.* **2001**, *7*, 5246–5251.

[2] For selected examples using chiral thiourea-based bifunctional catalysts in asymmetric transformations, see: a) J. M. Andres, R. Manzano, R. Pedrosa, *Chem. Eur. J.* **2008**, *14*, 5116–5119; b) X. Tian, K. Jiang, J. Peng, W. Du, Y.-C. Chen, *Org. Lett.* **2008**, *10*, 3583–3586; c) M. P. Sibi, K. Itoh, *J. Am. Chem. Soc.* **2007**, *129*, 8064–8065; d) Y.-L. Shi, M. Shi, *Adv. Synth. Catal.* **2007**, *349*, 2129–2135; e) K. Liu, H.-F. Cui, J. Nie, K.-Y. Dong, X.-J. Li, J.-A. Ma, *Org. Lett.* **2007**, *9*, 923–925; f) Y.-Q. Wang, J. Song, R. Hong, H. Li, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 8156–8157; g) Y.-J. Cao, H.-H. Lu, Y.-Y. Lai, L.-Q. Lu, W.-J. Xiao, *Synthesis* **2006**, 3795–3800; h) C.-L. Cao, M.-C. Ye, X.-L. Sun, Y. Tang, *Org. Lett.* **2006**, *8*, 2901–2904; i) D. A. Yalalov, S. B. Tsogoeva, S. Schmatz, *Adv. Synth. Catal.* **2006**, *348*, 826–832; j) S. H. McCooey, S. J. Connon, *Angew. Chem.* **2005**, *117*, 6525–6528; *Angew. Chem. Int. Ed.* **2005**, *44*, 6367–6370; k) S. B. Tsogoeva, D. A. Yalalov, M. J. Hateley, C. weckbecker, K. Huthmacher, *Eur. J. Org. Chem.* **2005**, 4995–5000; l) J. Wang, H. Li, X.-H. Yu, L.-S. Zu, W. Wang, *Org. Lett.* **2005**, *7*, 4293–4296; m) J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481–4482; n) B. Vakulya, S. Varga, A. Csampai, T. Soos, *Org. Lett.* **2005**, *7*, 1967–1969; o) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.

[3] For reviews on asymmetric alcoholysis of cyclic anhydrides, see: a) I. Atodiresei, I. Schiffers, C. Bolm, *Chem. Rev.* **2007**, *107*, 5683–5712; b) Y.-G. Chen, P. McDaid, L. Deng, *Chem. Rev.* **2003**, *103*, 2965–2983; c) A. C. Spivey, B. I. Andrews, *Angew. Chem.* **2001**, *113*, 3227–3230; *Angew. Chem. Int. Ed.* **2001**, *40*, 3131–3134.

[4] a) J. Hiratake, Y. Yamamoto, J. Oda, *J. Chem. Soc. Chem. Commun.* **1985**, 1717–1719; b) J. Hiratake, M. Inagaki, Y. Yamamoto, J. Oda, *J. Chem. Soc. Perkin Trans. 1* 1987, 1053–1058; c) R. A. Aitken, J. Gopal, J. A. Hirst, *J. Chem. Soc. Chem. Commun.* **1988**, 632–634; d) R. A. Aitken, J. Gopal, *Tetrahedron: Asymme-*

try **1990**, *1*, 517–520; e) C. Bolm, A. Gerlach, C. L. Dinter, *Synlett* **1999**, 195–196; f) C. Bolm, C. L. Dinter, A. Seger, H. Hoecker, J. Brozio, *J. Org. Chem.* **1999**, *64*, 5730–5731; g) C. Bolm, I. Schiffers, C. L. Dinter, A. Gerlach, *J. Org. Chem.* **2000**, *65*, 6984–6991; h) Y.-G. Chen, S.-K. Tian, L. Deng, *J. Am. Chem. Soc.* **2000**, *122*, 9542–9543; i) C. Choi, S.-K. Tian, L. Deng, *Synthesis* **2001**, 1737–1741; j) Y. Uozumi, K. Yasoshima, T. Miyachi, S.-i. Nagai. *Tetrohedron Lett.* **2001**, *42*, 411–414; k) J. Woltinger, H.-P. Krimmer, K. Drauz, *Tetrohedron Lett.* **2002**, *43*, 8531–8533; l) C. Bolm, I. Schiffers, I. Atodiresei, C. P. R. Hackenberger, *Tetrahedron: Asymmetry* **2003**, *14*, 3455–3467; m) Y.-M. Song, J. S. Choi, J. W. Yang, H. Han, *Tetrahedron Lett.* **2004**, *45*, 3301–3304; n) B. Rodriguez, T. Rantanen, C. Bolm, *Angew. Chem.* **2006**, *118*, 7078–7080; *Angew. Chem. Int. Ed.* **2006**, *45*, 6924–6926.

[5] A. Peschiulli, Y. Gun′ko, S. J. Connon, *J. Org. Chem.* **2008**, *73*, 2454–2457.

[6] H. S. Rho, S. H. Oh, J. W. Lee, J. Y. Lee, J. Chin, C. E. Song, *Chem. Commun.* **2008**, 1208–1210.

[7] F.-E. Chen, H.-F. Dai, Y.-Y. Kuang, H.-Q. Jia, *Tetrahedron: Asymmetry* **2003**, *14*, 3667–3672.

[8] a) B. Jiang, Z.-L. Chen, W.-N. Xiong, *Chem. Commun.* **2002**, 1524–1525; b) B. Jiang, Z.-L. Chen, X.-X. Tang, *Org. Lett.* **2002**, *4*, 3451–3453; c) Z.-L. Chen, W.-N. Xiong, B. Jiang, *Chem. Commun.* **2002**, 2098–2099; d) B. Jiang, Y.-G. Si, *Angew. Chem.* **2004**, *116*, 218–220; *Angew. Chem. Int. Ed.* **2004**, *43*, 216–218; e) B. Jiang, Y.-G. Si, *Adv. Synth. Catal.* **2004**, *346*, 669–674; f) B. Jiang, Z.-L. Chen, H. Huang, *Lett. Org. Chem.* **2005**, *2*, 319–322.

[9] For details see Supporting Information.

[10] J. Huang, F. Xiong, F.-E. Chen, *Tetrahedron: Asymmetry* **2008**, *19*, 1436–1443.

