Asymmetric Synthesis

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Highly Enantioselective Catalytic Thiolysis of Prochiral Cyclic Dicarboxylic Anhydrides Utilizing a Bifunctional Chiral Sulfonamide**

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Asymmetric differentiation between two identical carbonyl groups of prochiral σ-symmetric dicarboxylic acid derivatives by using an enzymatic or a nonenzymatic procedure is a rational and useful strategy for the asymmetric synthesis of biologically active compounds and medicines. The resultant chiral products can be subjected to further so-called "enantioconvergent" and "enantiodivergent" transformations on the basis of latent σ symmetry.[1] Previously, we disclosed remarkable nonenzymatic asymmetric induction methods for various prochiral σ-symmetric dicarboxylic acid derivatives based on highly diastereoselective aminolysis and Dieckmann-type cyclizations using functional heterocycles, such as the C4-chiral 1,3-thiazolidine-2-thiones.[2] Recent efforts in this field have been directed towards the development of methods for the catalytic desymmetrization of prochiral cyclic dicarboxylic anhydrides, such as enantioselective ring opening with methanol and carbon nucleophiles in the presence of a catalytic amount of chiral reagents.[3] We have focused on the development of simple and versatile chiral sulfonamides that are available for various catalytic asymmetric reactions. Very recently, Wang et al. reported highly enantioselective Michael addition reactions catalyzed by a chiral pyrrolidine sulfonamide[4] and Ishihara et al. disclosed an attractive method for the kinetic resolution of racemic alcohols that utilized an L-histidine sulfonamide derivative.[5] Ikariya and co-workers also carried out catalytic enantioselective Michael addition reactions that employed chiral Ru amido complexes.[6] However, to the best of our knowledge, there has been no report of a catalytic asymmetric desymmetrization of prochiral dicar-

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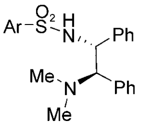

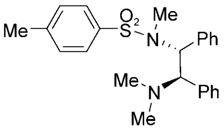

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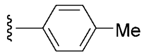

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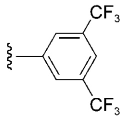

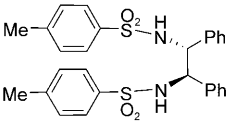

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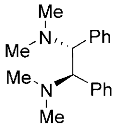

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boxylic anhydrides by sulfur nucleophiles. Herein, we describe the highly enantioselective thiolysis of prochiral cyclic dicarboxylic anhydrides with benzyl mercaptan (BnSH) in the presence of a catalytic amount of chiral bifunctional sulfonamide.

First, we inspected the molecular structure of two chiral sulfonamide catalysts **1** and **2** expecting to observe bifunctional catalytic effects, namely, both acid- and base-like properties. The nucleophilicity of the SH group can be enhanced by an amine base, and the electrophilicity of the carbonyl group may be activated by an acidic proton from the sulfonamide moiety.[4,5] On the basis of an X-ray crystallographic analysis of **2** (see below), we envisaged that chiral sulfonamides **1** and **2** would not only show acid- and base-like catalytic functions but may also provide suitable conditions for the enantioselective molecular recognition between a prochiral dicarboxylic anhydride and BnSH based on hydrogen-bonding interactions. Chiral sulfonamides **1** and **2** were readily synthesized as follows: The treatment of (1*R*,2*R*)-*N*,*N*-dimethyl-1,2-diphenyl-1,2-ethanediamine[7] with *p*-toluenesulfonyl chloride or 3,5-bis(trifluoromethyl)benzenesulfonyl chloride in the presence of Et_3N in CH_2Cl_2 afforded the desired products **1** and **2** (89 and 76% yields, respectively).[8] Figure 1 shows the X-ray crystal structure[9] of **2**, in which the three phenyl groups are positioned alongside each other, two of which are organized in a stacked manner,[13] whereas the third occupies a more open position. Thus, the acidic ($-SO_2NH-$) and basic (Me_2N-) bifunctional groups are located beside each other opposite the phenyl groups and may be suitable for trapping both reactants, namely, the anhydride and thiol moieties, through hydrogen-bonding interactions at the thiolysis site. To verify the bifunctionality of **1** and **2** based on the hypothesis described above, the related chiral compounds **3**–**5** were also synthesized from (1*R*,2*R*)-1,2-diphenyl-1,2-ethanediamine.[8,14]

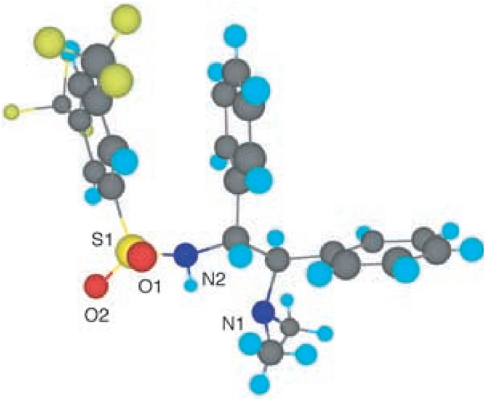
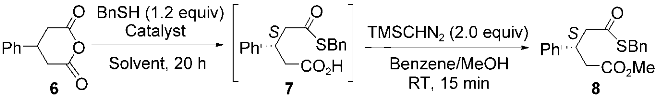


Figure 1. Computer-generated drawing derived from the X-ray coordinates of sulfonamide **2**.

Thus, the asymmetric thiolysis of 3-phenylglutaric anhydride **6** with BnSH (1.2 equiv) was examined in the presence of 10 mol% of chiral catalysts **1**–**5** in toluene at room temperature for 20 h. Then, the resultant crude *S*-benzyl thioester monocarboxylic acid **7** was converted into its methyl ester **8** without isolation of **7** for easy handling to determine the *ee* (Table 1). The desired catalytic asymmetric thiolysis of **6** with 1.2 equivalents of BnSH in the presence of 10 mol% of the bifunctional sulfonamides **1** and **2** smoothly proceeded to afford the chiral product **8** in 78 and 88% yields with 83 and 90% *ee*, respectively (Table 1, entries 1 and 2). However, the thiolysis of **6** with BnSH in the presence of *N*-methyl sulfonamide **3**, containing an *N*,*N*-dimethylamino basic functionality, or bisamino sulfonamide **4**, without an *N*,*N*-dimethylamino group, did not proceed at all (Table 1, entries 3 and 4). In the case of (1*R*,2*R*)-*N*,*N*,*N*′,*N*′-tetramethyl-1,2-diphenyl-1,2-ethanediamine (**5**), the thiolysis proceeded slightly to give **8** in 20% yield with 6% *ee* (Table 1, entry 5). On the basis of the experimental results (Table 1, entries 1–5), we conclude that both the acid catalysis resulting from the sulfonamide proton and the base catalysis resulting from the *N*,*N*-dimethylamino group in the exploitation of catalysts **1** and **2** were equally effected through this facile catalytic and enantioselective thiolysis of **6** with BnSH.

The reaction conditions were optimized with an investigation of the influence of the solvent, reaction temperature, and amount of catalyst **2** on the yield and enantioselectivity of the thiolysis of **6** with 1.2 equivalents of BnSH (Table 1,

Table 1: Investigation of the reaction conditions for the enantioselective thiolysis of 3-phenylglutaric anhydride **6** with benzyl mercaptan in the presence of chiral catalysts.



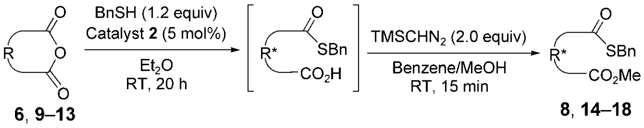
Entry	Catalyst (mol%)	Solvent	*T* [°C]	Yield [%][a]	*ee* [%][b]
1	**1** (10)	toluene	RT	78	83
2	**2** (10)	toluene	RT	88	90
3	**3** (10)	toluene	RT	NR[c]	–
4	**4** (10)	toluene	RT	NR[c]	–
5	**5** (10)	toluene	RT	20	6
6	**2** (10)	CH_2Cl_2	RT	61	83
7	**2** (10)	MeCN	RT	88	38
8	**2** (10)	THF	RT	87	84
9	**2** (10)	Et_2O	RT	94	92
10	**2** (10)	Et_2O	0	94	92
11	**2** (10)	Et_2O	−30	93	92
12	**2** (5)	Et_2O	RT	95	91
13	**2** (1)	Et_2O	RT	87	87

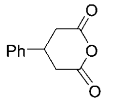
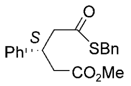
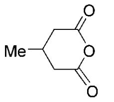
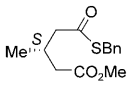
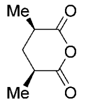
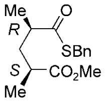
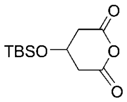
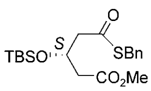
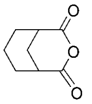
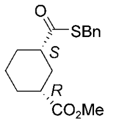
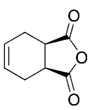
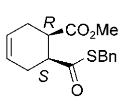
[a] Yield of isolated product. [b] Determined by HPLC analysis. [c] NR = no reaction. Bn = benzyl, TMS = trimethylsilyl.

entries 6–13). Among the solvents used (namely, toluene, CH_2Cl_2, MeCN, THF, and Et_2O), Et_2O at room temperature provided the best result, thus giving the chiral product **8** in 94% yield with 92% *ee* (Table 1, entries 2 and 6–9). At reaction temperatures lower than room temperature (0 and −30 °C), the enantioselective thiolysis was almost the same as at room temperature (Table 1, entries 9–11). Interestingly, this catalytic enantioselective thiolysis even proceeded in the presence of 5 and 1 mol% of **2** at room temperature to afford **8** in 95 and 87% yields with 91 and 87% *ee*, respectively (entries 12 and 13). Similar enantioselective thiolysis of **6** with 1.2 equivalents of ethanethiol or thiophenol in the presence of 5 mol% of **2** in Et_2O at room temperature followed by methylation with $TMSCHN_2$ gave the corresponding *S*-ethyl and *S*-phenyl thioesters in 61 and 90% yields with 78 and 16% *ee*, respectively.

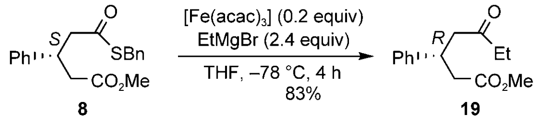
Thus, highly enantioselective thiolysis of prochiral dicarboxylic anhydrides **6** and **9–13** with 1.2 equivalents of BnSH was performed in the presence of 5 mol% of **2** in Et_2O at room temperature for 20 h followed by methylation of the resultant corresponding monocarboxylic acids with $TMSCHN_2$. The corresponding chiral monomethyl esters **8** and **14–18** were efficiently obtained in yields of 87–100% with *ee* values of 83–98% (Table 2). The absolute configuration of the newly formed chiral carbon atom(s) in **8** and **14–18** was determined by conversion[8] into known chiral compounds.[15] Although the detailed reaction mechanism of this catalytic and highly enantioselective thiolysis in the presence of chiral sulfonamides remains unclear, this quite simple catalytic desymmetrization procedure should be a fascinating method for the practical syntheses of chiral synthons (synthetic building blocks). Using the active monothioester character, **8** (91% *ee*) was tentatively treated with 0.2 equivalents of $[Fe(acac)_3]$ (acac = acetylacetonate) and 2.4 equivalents of EtMgBr in THF at −78 °C to give chemoselectively the desired chiral ketoester **19** in 83% yield with 91% *ee*.[16]

Table 2: Catalytic, enantioselective thiolysis of various prochiral cyclic dicarboxylic anhydrides.



Entry	Anhydride		Product		Yield [%][a]	ee [%][b]
1		**6**		**8**	95	91
2		**9**		**14**	87	91
3		**10**		**15**	100	90
4		**11**		**16**	88	93
5		**12**		**17**	90	98
6		**13**		**18**	90	83

[a] Yield of isolated product. [b] Determined by HPLC analysis. TBS = *tert*-butyldimethylsilyl.



8
91% *ee*

19
91% *ee*

The chiral monothioesters **8** and **14–18** will be exploited for the asymmetric synthesis of macrocyclic antibiotic drugs and biologically active natural products.[17] Newly designed bifunctional chiral sulfonamides, including **2**, seem to be promising for the development of various catalytic asymmetric induction methods.

Experimental Section

A typical procedure of the catalytic enantioselective thiolysis: Benzyl mercaptan (141 μL, 1.2 mmol) was added to a solution of 3-phenylglutaric anhydride **6** (190 mg, 1.0 mmol) and chiral sulfonamide **2** (25.8 mg, 0.05 mmol) in Et_2O (10 mL) at room temperature. The mixture was stirred at room temperature under Ar for 20 h and treated with 10% HCl followed by extraction with $CHCl_3$. The $CHCl_3$ extracts were dried over $MgSO_4$ and filtered. After evaporation of the filtrate in vacuo, the residue was dissolved in benzene/MeOH (7:2; 9 mL) and a solution of $TMSCHN_2$ in Et_2O (2.0 M, 1 mL, 2.0 mmol) was added. The mixture was stirred at room temperature for 15 min and then evaporated in vacuo to give an oily residue. Purification of the residue by column chromatography on silica gel with EtOAc/*n*-hexane (1:4) afforded compound **8** (312 mg, 95% yield, 91% *ee*) as a white solid (m.p. 34.5–35 °C).

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Keywords: anhydrides · asymmetric synthesis · homogeneous catalysis · sulfonamides · thiolysis

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[8] See Supporting Information.

[9] Crystallographic study for compound **2**: Intensity data were collected on a Rigaku RAXIS-RAPID imaging plate diffractometer with $\mathrm{Cu}_{K\alpha}$ radiation at a temperature of 93.2 K. The program of PROCESS-AUTO[10] was used during data collection. The structure was solved by direct methods with SIR97[11] and refined by least-squares methods with CRYSTALS.[12] **2**: crystallized from MeOH/$CHCl_3$, $C_{24}H_{22}F_6N_2O_2S$, $M_r = 516.50$, colorless block $0.30 \times 0.20 \times 0.10$ mm, monoclinic, $P2_1(4)$, $a = 11.6363(11)$, $b = 8.2929(9)$, $c = 12.4374(13)$ Å, $\beta = 96.404(6)°$, $V = 1192.7(2)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.438$ g cm^{-3}, 2θmax 136.5°, measured reflections = 12702, independent reflections = 4013 ($R_{int} = 0.029$), $R1 = 0.0307$ for 3797 reflections with $I > 2\sigma(I)$, $wR2 = 0.0812$ for all reflections with $I > 2\sigma(I)$, GOF = 1.054. The absolute configuration was determined based on the Flack parameter (0.004(14)) refined using 1684 Friedel pairs. CCDC-269460 (**2**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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