A Chiral Bifunctional Sulfonamide as an Organocatalyst: Alcoholysis of σ-Symmetric Cyclic Dicarboxylic Anhydrides

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Abstract: Enantioselective alcoholysis of σ-symmetric cyclic dicarboxylic anhydrides with benzyl alcohol catalyzed by a chiral bifunctional sulfonamide was achieved in up to 98% ee at 5 mol% loading.

Key words: anhydrides, asymmetric synthesis, homogeneous catalysis, sulfonamides, alcoholysis

Enzymes efficiently catalyze various organic reactions under mild conditions in nature.[1] Thus the development of artificial organocatalysts that mimic enzyme activity is of interest from the perspective of asymmetric synthesis.[2] On the other hand, desymmetrization of σ-symmetric dicarboxylic anhydrides is one of the most important strategies in organic synthesis.[3] Based on the structure of cinchona alkaloid, Song[4] and Connon[5] developed a bifunctional organocatalyst, which efficiently catalyzed enantioselective methanolysis of σ-symmetric dicarboxylic anhydrides. A cost-effective thiourea bifunctional organocatalyst for methanolysis of similar cyclic anhydrides has also been reported by Chen and co-workers.[6] We recently described enantioselective thiolysis of σ-symmetric dicarboxylic anhydrides with benzyl mercaptan utilizing a catalytic amount of chiral bifunctional sulfonamide **1** as an organocatalyst mimicking the organization of functional groups at the active site of the cysteine protease.[7] Here, we explore the enantioselective alcoholysis of σ-symmetric dicarboxylic anhydrides with benzyl alcohol, utilizing chiral sulfonamide **1** as an organocatalyst. The reaction is based on the hydrolysis of amide bonds catalyzed by serine proteases such as α-chymotrypsin (Figure 1).[8]

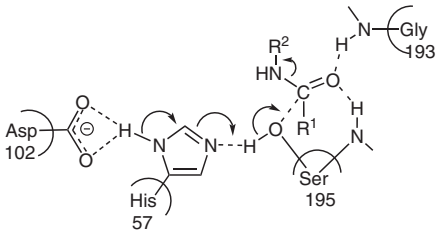
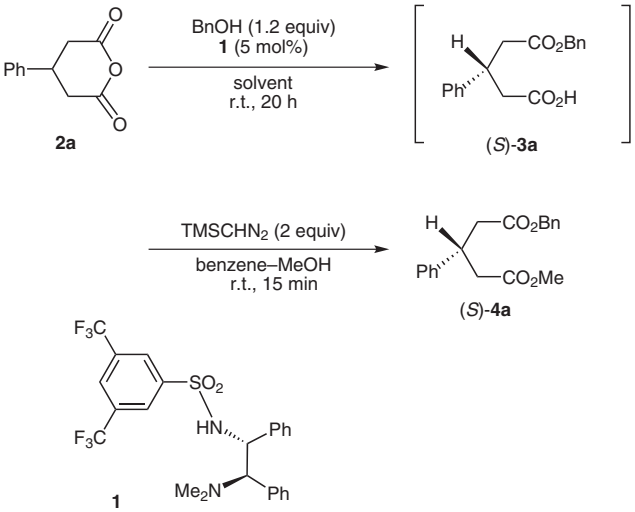


Figure 1 Hydrolysis of amide bonds catalyzed by α-chymotrypsin

Our investigation started with the reaction of 3-phenylglutaric anhydride (**2a**) with benzyl alcohol in the presence of a catalytic amount of sulfonamide **1**, which was readily synthesized from (1*R*,2*R*)-*N*,*N*-dimethyl-1,2-diphenyl-1,2-ethanediamine.[7] The ee (%) of the resultant benzyl ester monocarboxylic acid **3a** was determined by HPLC analysis with chiral stationary phase (CSP) after methylation with (trimethylsilyl)diazomethane ($TMSCHN_2$), as shown in Table 1. Methyl ester **4a** was obtained in 92% yield and 87% ee when diethyl ether was employed as a solvent in this reaction (Table 1, entry 1).[9] Both the yields and the enantioselectivities were not as high as those obtained when using diethyl ether (Table 1, entries 2–5).

Table 1 Enantioselective Alcoholysis of Cyclic Dicarboxylic Anhydride **2a** Catalyzed by Chiral Sulfonamide **1**



Entry	Solvent	Yield (%)[a]	ee (%)[b]
1	Et_2O	92	87
2	CH_2Cl_2	50	77
3	MeCN	53	83
4	THF	8	89
5	PhMe	87	81

[a] Isolated yield of **4a**.
[b] Determined by HPLC analysis (Chiralpak AD-H, *n*-hexane–2-PrOH).

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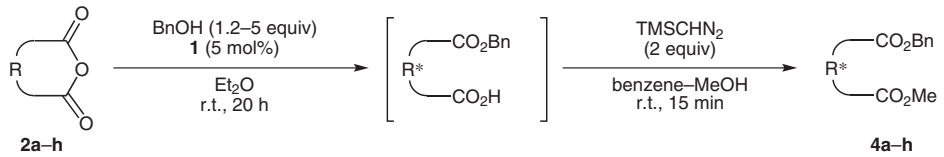
Once the optimized conditions for the alcoholysis of anhydride **2a** were established, we evaluated a wide range of cyclic anhydrides to determine the scope of the reaction. The results are summarized in Table 2. Monocyclic dicarboxylic anhydrides **2a–c** enantioselectively provided the corresponding methyl esters **4a–c** in acceptable yields (86–92%). In addition, the alcoholysis of bicyclic and tricyclic dicarboxylic anhydrides **2d–h** afforded methyl esters **4d–h** in satisfactory yields (89–99%) and enantioselectivities (97–98% ee). Thus far, tricyclic anhydrides **2g**,**h** are not accessible through enzymatic hydrolysis because of their steric bulkiness.[10] In particular, it is notable that the enantioselectivity in alcoholysis (98% ee) is superior to that in thiolysis (83% ee) of **2e** employing catalyst **1**. The absolute configuration of methyl esters **4a–h** was determined by their chemical conversion into the known chiral compounds.[11]

Table 2 Enantioselective Alcoholysis of Cyclic Dicarboxylic Anhydrides **2a–h** Catalyzed by Chiral Sulfonamide **1**



2a–h **4a–h**

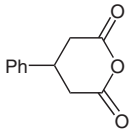
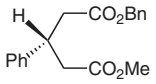
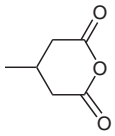
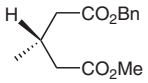
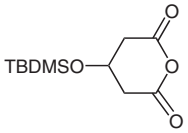
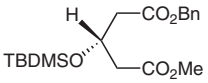
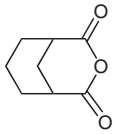
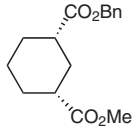
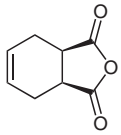
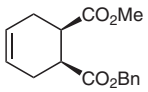
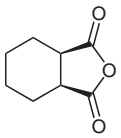
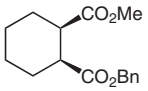
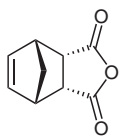
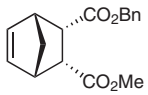
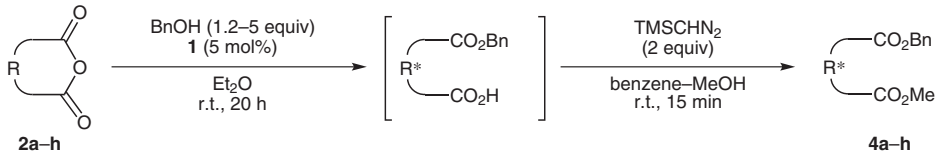
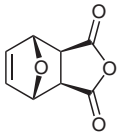
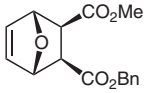
Entry	Anhydride	BnOH (equiv)	Product	Yield (%)[a]	ee (%)[b]
1	 **2a**	1.2	 (*S*)-**4a**	92	87
2	 **2b**	5	 (*S*)-**4b**	86	83
3	 **2c**	5	 (*S*)-**4c**	80	91[c]
4	 **2d**	3	 (1*S*,3*R*)-**4d**	90	98[c]
5	 **2e**	5	 (1*S*,2*R*)-**4e**	95	98
6	 **2f**	5	 (1*S*,2*R*)-**4f**	99	97
7[d]	 **2g**	5	 (1*R*,2*S*,3*R*,4*S*)-**4g**	91	98[c]

Table 2 Enantioselective Alcoholysis of Cyclic Dicarboxylic Anhydrides **2a–h** Catalyzed by Chiral Sulfonamide **1** (continued)



Entry	Anhydride	BnOH (equiv)	Product	Yield (%)[a]	ee (%)[b]
8	 **2h**	5	 (1*S*,2*R*,3*S*,4*R*)-**4h**	89	97

[a] Isolated yields of **4a–h**.
[b] Determined by HPLC analysis.
[c] Determined by HPLC analysis after conversion to a known compound.
[d] 10 mol% of **1** was used.

Finally, we used cold-spray ionization mass spectrometry (CSI-MS)[12] to analyze a 1:1 mixture of organocatalyst **1** (0.1 mM) and anhydride **2a** (0.1 mM) in THF at a spray temperature of –20 °C. The resulting CSI-MS spectrum showed a prominent ion peak corresponding to a 1:1 complex of organocatalyst **1** and anhydride **2a** at *m/z* = 706.4.[11] Thus, the dual activation of anhydride **2a** and benzyl alcohol by organocatalyst **1** may have been a cause of the enantioselective alcoholysis, similar to the hydrolysis of serine protease (Figure 2).[13]

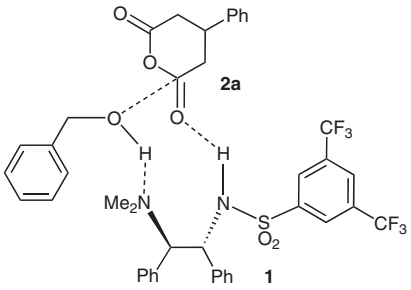


Figure 2 Plausible dual activation manner of anhydride **2a** and benzyl alcohol by organocatalyst **1**

In summary, chiral bifunctional sulfonamide **1** has been shown to promote highly efficient desymmetrization of σ-symmetric cyclic dicarboxylic anhydrides **2a–h** with benzyl alcohol. Further studies are under way to investigate the stereodifferentiating mechanism of the reaction.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

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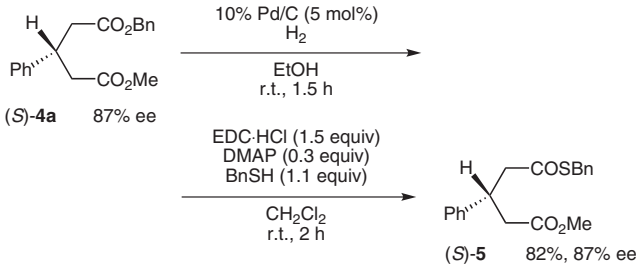
(9) **General Experimental Procedure for Chiral Sulfonamide 1 Catalyzed Alcoholysis of Cyclic Dicarboxylic Anhydrides**
To a solution of 3-phenylglutaric anhydride (**2a**, 190 mg, 1.0 mmol) and chiral sulfonamide **1** (25.8 mg, 0.05 mmol) in Et_2O (10 mL) was added BnOH (125 μL, 1.2 mmol) at r.t. After stirring at r.t. for 20 h, the reaction mixture was treated with 10% HCl followed by extraction with $CHCl_3$. The extract was dried over anhyd $MgSO_4$, filtered, and concentrated in vacuo. To a solution of the residue in benzene–MeOH (7:2, 9 mL) was added a solution of $TMSCHN_2$ (2.0 M in Et_2O, 1 mL, 2.0 mmol). After being stirred at r.t. for 15 min, the reaction mixture was evaporated in vacuo. The oily residue was purified by silica gel column chromatography [EtOAc–*n*-hexane (1:4)] to afford methyl ester (*S*)-**4a** (286 mg, 92% yield, 87% ee) as a colorless oil.
The ee (%) of (*S*)-**4a** was determined on a Chiralpak AD-H column [Daicel, eluent: *n*-hexane–2-PrOH (15:1), flow rate: 1 mL/min, detection: 254 nm]. The retention times were 12.5 min [minor isomer, (*R*)-**4a**] and 13.8 min [major isomer, (*S*)-**4a**], respectively. The absolute configuration of (*S*)-**4a** was explicitly determined by its chemical conversion to thioester (*S*)-**5** (Scheme 1).[7]



Scheme1

(10) Zhu, L.-M.; Tedford, M. C. *Tetrahedron* **1990**, *46*, 6587.
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