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SHORT COMMUNICATION

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Highly Enantioselective Thiolysis of Prochiral Cyclic Anhydrides Catalyzed by Amino Alcohol Bifunctional Organocatalysts and Its Application to the Synthesis of Pregabalin

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Asymmetric thiolysis of prochiral cyclic anhydrides was achieved with our developed chiral sulfonamide and squaramide bifunctional organocatalysts based on amino alcohol scaffolds. The corresponding thioesters were obtained in high yields with excellent enantioselectivities. The usefulness of this methodology was demonstrated in the enantioselective synthesis of pregabalin.

Introduction

Asymmetric ring opening of prochiral cyclic anhydrides by various nucleophiles is a powerful tool to construct one or multiple stereogenic centers for organic synthesis.[1] The enantiopure ring-opening products are extremely versatile chiral building blocks that can undergo valuable transformations in organic synthetic chemistry.[2] The organocatalytic enantioselective desymmetrization of cyclic anhydrides represents a straightforward and convenient approach towards such useful, optically active, ring-opening products.[1c,1d] Among the desymmetrization reactions reported to date, considerable effort has been directed to the development of the alcoholysis of prochiral cyclic anhydrides by applying various organocatalysts. To our surprise, although thiols have proved to be efficient nucleophiles in many asymmetric catalytic reactions,[3] there are only four reports of the asymmetric thiolysis of achiral cyclic anhydrides.[4] The asymmetric anhydride thiolysis pioneered by Nagao et al.[4a] provides chiral thioesters in good yields with high enantioselectivities by using sulfonamide catalysts **1** (Figure 1), but only phenylmethanethiol was used as the nucleophile. The tandem kinetic resolution of secondary thiols through the asymmetric thiolysis of prochiral anhydrides was developed by the Connon group, and this reaction afforded chiral hemithioesters and thiols simultaneously in the presence of a catalytic amount of cinchona alkaloid thiourea **2** or sulfonamide **3**; however, high enantioselectivity was achieved if secondary thiols were used for this transformation.[4b] Bolm's work on asymmetric anhydride thiolysis furnished the corresponding thioesters in moderate to good yields with moderate to good enantioselectivities through the use of low-molecular-weight organocatalyst **4**, but the scope of the reaction was limited to certain anhydrides.[4d] Therefore, the development of a general and highly enantioselective protocol for the thiolysis of prochiral cyclic anhydrides still remains a challenging goal in asymmetric catalysis.

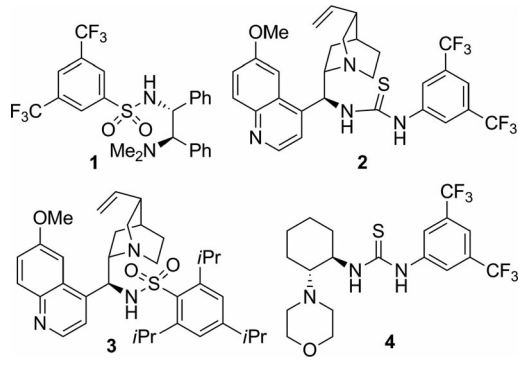

Figure 1. Structures of various organocatalysts.

In recent years, our laboratory has developed various enantioselective alcoholysis reactions that are based on hydrogen-bonding catalysts such as quinine,[5] quinine derivatives,[6] chiral amino alcohols,[7] amino alcohol–thioureas,[8] and amino alcohol–sulfonamides and their squaramides.[9] Encouraged by these studies, we envisioned the extension of our asymmetric anhydride alcoholysis strategy to asymmetric anhydride thiolysis, and herein we wish to report a highly enantioselective desymmetrization of prochiral cyclic anhydrides with thiols by utilizing our recently developed bifunctional sulfonamide and squaramide cata-

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lysts **5** and **6**[9] (Figure 2). We also report the application of this methodology to the asymmetric synthesis of pregabalin.

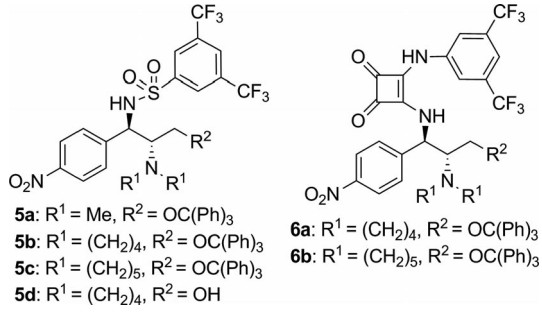
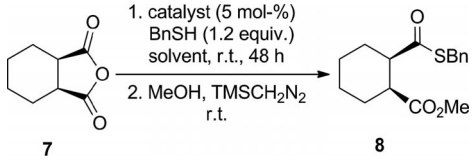


Figure 2. Structure of chiral catalysts.

Results and Discussion

To evaluate the ability of catalysts **5** and **6**, initial experiments were performed for the reaction between phenylmethanethiol and (3a*R*,7a*S*)-hexahydroisobenzofuran-1,3-dione (**7**) in methyl *tert*-butyl ether (MTBE) followed by the addition of $TMSCH_2N_2$ and methanol to generate the thioester in situ. Bifunctional squaramide and sulfonamide catalysts **5** and **6** were screened. As shown in Table 1, all catalysts smoothly promoted the reaction at room temperature. Sulfonamide **5a** was identified as the best catalyst, as it afforded desired thioester **8** in 87% yield with 78% enantiomeric excess (*ee*) (Table 1, Entry 1). Subsequently, various solvents were then examined to determine their effects on the yield and enantioselectivity (Table 1). If an arene solvent was used instead of MTBE, the enantioselectivity decreased slightly (Table 1, Entry 7). Poor enantioselectivity was observed for both CH_2Cl_2 and acetonitrile (Table 1, Entries 8 and 9). In addition, similar results were gained for other ether solvents (Table 1, Entries 10–12).

Table 1. Catalyst and solvent screening. Bn = benzyl.

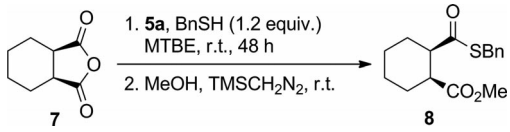


Entry	Catalyst	Solvent	Yield[a] [%]	*ee*[b,c] [%]
1	**5a**	MTBE	87	78
2	**5b**	MTBE	94	72
3	**5c**	MTBE	90	50
4	**5d**	MTBE	89	64
5	**6a**	MTBE	84	50
6	**6b**	MTBE	87	32
7	**5a**	PhMe	88	60
8	**5a**	MeCN	85	10
9	**5a**	CH_2Cl_2	89	34
10	**5a**	Et_2O	90	76
11	**5a**	THF	90	77
12	**5a**	dioxane	89	77

[a] Yield of isolated product. [b] Determined by HPLC. [c] Absolute configuration was determined by comparing the sign of the optical rotation of the major enantiomer with the known data.

Next, we tested the effect of catalyst loading and concentration of the substrates (Table 2). An even more satisfactory enantioselectivity was obtained by raising the catalyst loading from 5 to 20 mol-% (Table 2, Entries 1–5). When reducing the concentration of the substrates from 0.5 to 0.1 M in the presence of 20 mol-% of the catalyst, the enantioselectivity was gradually enhanced (Table 2, Entries 5–7). A further decrease in the concentration of the substrate resulted in lower enantioselectivity (Table 2, Entries 8 and 9). In addition, the *ee* value of the thioester could be enhanced through lowering of the temperature (Table 2, Entry 10).

Table 2. Survey of the reaction conditions.



Entry	Substrate concentration [M]	Catalyst loading [mol-%]	Yield[a] [%]	*ee*[b] [%]
1	0.1	1	89	64
2	0.1	2	90	68
3	0.1	5	87	78
4	0.1	10	87	80
5	0.1	20	88	86
6	0.5	20	87	60
7	0.2	20	82	84
8	0.05	20	80	68
9	0.025	20	81	34
10[c]	0.1	20	93	90

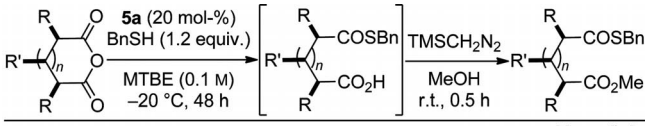
[a] Yield of isolated product. [b] Determined by HPLC. [c] The reaction was conducted at –20 °C.

With the optimized reaction conditions in hand, the scope and limitations of the sulfonamide **5a** promoted asymmetric thiolysis were explored (Table 3). A series of prochiral cyclic anhydrides were treated with phenylmethanethiol in the presence of the catalyst (20 mol-%) followed by the addition of $TMSCH_2N_2$ and methanol to give the corresponding thioester in good yield with high enantioselectivity. Notably, aliphatic groups or hetero-substituted glutaric anhydrides could also be successfully employed to afford the desired products in good yields with excellent enantioselectivities (Table 3, Entries 4, 5, 10).

Subsequently, different thiols were examined as nucleophiles in the ring opening of model substrate **11** under the standard conditions. As summarized in Table 4, aromatic methanethiols bearing electron-withdrawing or -donating groups still provided good yields with excellent enantioselectivities, as did heteroaromatic thiols (Table 4, Entries 1–4). In contrast, longer reaction periods were required for complete conversion of less reactive aliphatic thiols (Table 4, Entries 5 and 6).

To demonstrate the synthetic utility of this methodology, a short synthesis of pregabalin (**37**), an anticonvulsant drug used for neuropathic pain treatment, was developed. As shown in Scheme 1, thiolysis of 3-isobutylglutaric an-

Table 3. Asymmetric thiolysis of prochiral cyclic anhydrides with catalyst **5a**.

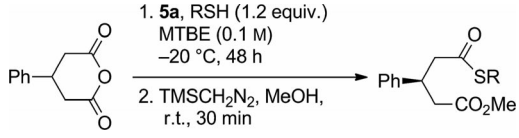


Entry	Anhydride	Product	Yield[a] [%]	*ee*[b,c] [%]
1	**7**	**8**	93	90
2	**9**	**10**	92	81
3	**11**	**12**	91	92
4	**13**	**14**	94	90
5	**15**	**16**	93	89
6	**17**	**18**	84	89
7	**19**	**20**	89	87
8	**21**	**22**	86	86
9	**23**	**24**	88	89
10[d]	**25**	**26**	85	87

[a] Yield of isolated product. [b] Determined by HPLC. [c] Absolute configurations were determined by comparing the sign of the optical rotation of the major enantiomer with known data. [d] TBS = *tert*-butyldimethylsilyl.

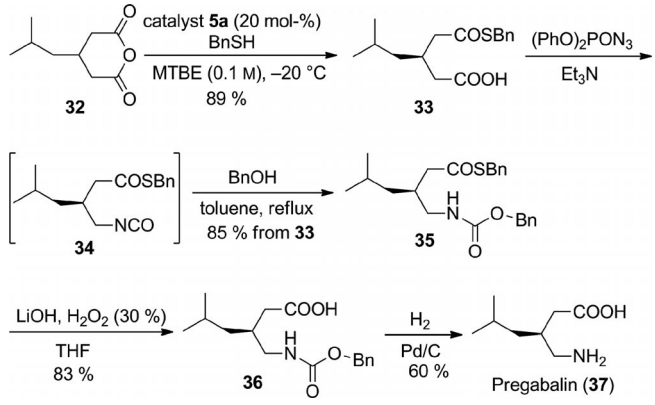
hydride (**32**) performed in the presence of **5a** (20 mol-%) at –20 °C gave the corresponding hemithioester **33** in 89% yield with 94%*ee*. Amino thioester **35** was generated in 85% yield over two steps involving first Curtius rearrangement of **33** with phenyl benzylphosphonazidate in the presence of Et_3N and second the addition of phenylmethanol. Hydrolysis of the thioester was achieved in the presence of LiOH and H_2O_2 to afford benzyl carbamate **36**. Pregabalin was furnished by hydrogenation of **36** with 98%*ee*.[10]

Table 4. Asymmetric thiolysis of prochiral cyclic anhydrides with various thiols.



Entry	R	Product	Yield[a] [%]	*ee*[b] [%]
1	Bn	**12**	91	92
2	4-$ClC_6H_4CH_2$	**27**	93	90
3	4-*t*$BuC_6H_4CH_2$	**28**	92	87
4	furfuryl	**29**	85	88
5[c]	cyclopentyl	**30**	82	92
6[c]	*i*Pr	**31**	78	82

[a] Yield of isolated product. [b] Determined by HPLC. [c] All reactions were carried out in the presence of the thiols (5.0 equiv.) for 96 h.



Scheme 1. Asymmetric synthesis of Pregabalin.

Conclusions

We have developed a highly enantioselective thiolysis of prochiral cyclic anhydrides in good yields by using amino alcohol derivatives as organocatalysts. Thiols other than phenylmethanethiol were also effective nucleophiles in the desymmetrization reaction and gave excellent enantioselectivities. In addition, a novel strategy for the synthesis of γ-amino acids was demonstrated through a synthetic application of our methodology to the asymmetric synthesis of pregabalin. This class of sulfonamides and squaramides are good bifunctional organocatalysts, and further investigations are underway to broaden their application in asymmetric catalysis.

Experimental Section

Typical Procedure for the Enantioselective Thiolysis of Prochiral Cyclic Anhydrides with Catalyst 5a: Phenylmethanethiol (30 μL, 0.24 mmol) was added to a stirred solution of **5a** (30 mg, 0.04 mmol) and **7** (31 mg, 0.20 mmol) in MTBE (2.0 mL) at –20 °C under nitrogen. When TLC analysis indicated complete consumption of the anhydride, $TMSCH_2N_2$ (0.40 mmol) and methanol (200 μL) were consecutively added. The solution was stirred at room temperature for 30 min and then concentrated under vacuum to give a crude product. Purification of the crude product by column chromatography (silica gel; petroleum ether/EtOAc, 8:1) furnished thioester **8** (52 mg, 93%). HPLC (Chiralcel OD-H, hexane/*i*PrOH = 80:20, flow rate = 0.50 mL min^{-1}, T = 30 °C, λ = 254 nm): t_R = 11.2 (major), 10.2 min (minor). $[a]_D^{25}$ = –3.3 (c = 0.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 (d, J = 6.4 Hz, 3 H), 2.26 (dd, J = 15.2, 7.2 Hz, 1 H), 2.41 (dd, J = 15.2, 5.2 Hz, 1 H), 2.49–2.69 (m, 3 H), 3.68 (s, 3 H), 7.25–7.33 ppm (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.97, 28.44, 33.57, 40.82, 50.15, 51.83, 127.56, 128.93, 129.10, 137.87, 172.88, 197.78 ppm.

Supporting Information (see footnote on the first page of this article): Experimental details and characterization data for all compounds.

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