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Desymmetrization of acid anhydride with asymmetric esterification catalyzed by chiral phosphoric acid

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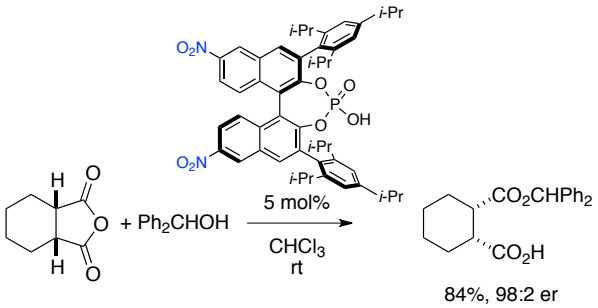

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Desymmetrization of acid anhydride with asymmetric esterification catalyzed by chiral phosphoric acid

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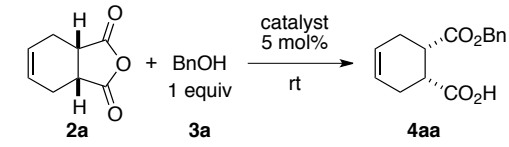
ABSTRACT

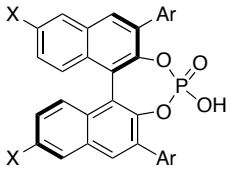
Asymmetric desymmetrization of σ-symmetric acid anhydrides was achieved with chiral phosphoric acid as a Brønsted acid catalyst. The key of success was finding of benzhydrol and 2,2-diphenylethanol as the nucleophiles of choice. The corresponding half esters were obtained in good yields with high selectivity.

Brønsted acid catalysis is one of the most important and fundamental activation modes in organic chemistry.[1] Recently, we reported kinetic resolution of chiral secondary alcohols[2] and asymmetric intramolecular S_N2' reaction[3] using chiral phosphoric acid as a Brønsted acid catalyst.[4,5] In the former report,[2] we demonstrated that chiral phosphoric acid enabled to enhance the electrophilicity of acid anhydrides and to selectively activate one enantiomer of secondary alcohol at the same time. As a continuing study, we investigated desymmetrization of prochiral σ-symmetric acid anhydrides by selective recognition of one of the carbonyl groups. Desymmetrization of acid anhydrides is a powerful strategy to obtain chiral starting materials for natural product syntheses[6] and has been extensively studied.[7,8] Chiral phosphoric acids, however, have never been successfully utilized as a catalyst for this purpose, yet.[9] Herein, we report desymmetrization of acid anhydrides using asymmetric esterification catalyzed by chiral phosphoric acid.

First, we screened (*R*)-binaphthyl-based chiral phosphoric acids **1** with acid anhydride **2a** using benzyl alcohol (**3a**) as a nucleophile (Table 1). A solution of **2a** (0.1 mmol), **3a** (0.1 mmol), and phosphoric acid **1a**, bearing 9-anthryl groups at the 3,3'-positions, (5 mol %) in chloroform (0.25 mL) was stirred at room temperature (entry 2). After 4 h, the reaction completed, and half ester **4aa** was obtained in 93% yield in completely racemic form. When **1b**, bearing 4-nitrophenyl groups, was used in place of **1a**, **4aa** was produced with a slight excess of the (1*R*,6*S*)-

Table 1. Screening of Catalyst and Solvent.





1a X = H, Ar = 9-anthryl
1b X = H, Ar = 4-$NO_2C_6H_4$
1c X = H, Ar = 3,5-$(CF_3)_2C_6H_3$
1d X = H, Ar = 2,4,6-*i*-$Pr_3C_6H_2$
1e X = NO_2, Ar = 2,4,6-*i*-$Pr_3C_6H_2$

entry	catalyst	solvent	time (h)	% yield[a]	er[b]
1	-	$CHCl_3$	12	7	50:50
2	**1a**	$CHCl_3$	4	93[c]	50:50
3	**1b**	$CHCl_3$	4	91	57:43
4	**1c**	$CHCl_3$	4	91	69:31
5[d]	**1d**	$CHCl_3$	4	96	75:25
6[e]	**1e**	$CHCl_3$	4	91	77:23
7[e]	**1e**	Et_2O	4	quant	76:24
8[e]	**1e**	toluene	4	quant	75:25
9[e]	**1e**	MeCN	12	31	75:25

[a]Based on ^{1}H NMR of the crude mixture. [b]Determined by chiral stationary phase HPLC. [c]Isolated yield. [d]Using 1.5 equiv of **3a**. [e]Using 1.2 equiv of **3a**.

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enantiomer[10] (entry 3). The product was obtained in much better enantiomer ratio (69:31 er) when **1c**, bearing 3,5-bis(trifluoromethyl)pheny groups, was employed in the reaction (entry 4).

The electron-deficiency of the 3,3'-substituents of **1b** and **1c** was not an important factor for the enantioselectivity because the enantiomer ratio of the product was improved to 75:25 with TRIP (**1d**) as a catalyst (entry 5). Finally, the use of our nitro-TRIP,[2] bearing 2,4,6-triisopropylphenyl and nitro groups at the 3,3'- and 6,6'-positions, respectively, was beneficial to further increase the selectivity, affording **4aa** with 77:23 er (entry 6). Importantly, the phosphoric acids dramatically accelerated the reaction; in the absence of the catalysts, the reaction of **2a** and **3a** produced **4aa** in only 7% yield after 12 h along with 3% of *cis*-4-cyclohexene-1,2-dicarboxylic acid, which probably resulted from hydrolysis of **2a** (entry 1).

Solvent effects were also investigated. When chloroform, diethyl ether, or toluene was used as a solvent, almost the same results were obtained (entries 6–8). The reaction was, however, much slower in acetonitrile (entry 9). This observation indicates the importance of hydrogen bonding in the rate-determining step.

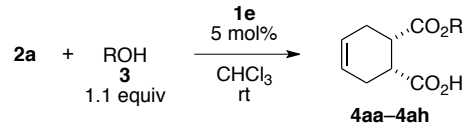
The structure of the utilized alcohol significantly affected the enantioselectivity as well as the rate of the reaction (Table 2). Comparing the reaction using methanol (**3b**), benzyl alcohol (**3a**), and isopropanol (**3c**) (entries 1–3), the enantioselectivity was increased from 53:47 to 85:15 er as the bulkiness of the alcohols increased, although the reaction failed to proceed with *tert*-butanol (**3d**) (entry 4).

Then, benzyl alcohols bearing a sterically hindered substituent were tested in the reaction. As expected, the use of 2-methylbenzyl alcohol (**3e**) improved the selectivity to 86:14 er (entry 5); however, mesitylmethanol (**3f**), bearing substituents at the *o,o*'-positions, were unexpectedly not helpful for improving selectivity, giving **4af** with 77:23 er (entry 6). To our delight, the reaction with benzhydrol (**3g**) provided **4ag** with high selectivity (98:2 er) at the cost of the reaction rate (entry 7). 2,2-Diphenylethanol (**3h**) showed a good balance of the reactivity and the selectivity to give **4ah** with 93:7 er in 94% yield after 6 h (entry 8).

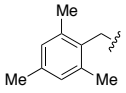
The reaction was applied to other acid anhydrides using benzhydrol (**3g**) or diphenylethanol (**3h**) as a nucleophile (Table 3). Although the reaction of **2a** with **3g** was slow (Table 2, entry 7), **4ag** was produced in 78% yield when the reaction time was extended to 74 h (Table 3, entry 1). The reaction of **2b** with **3g** proceeded more smoothly at room temperature, and **4bg** with 98:2 er was obtained in 84% yield after 48 h (entry 2). The reaction with **2c** gave **4cg** with almost perfect enantioselectivity (entry 3). Although the reaction of **2d** with **3g** gave **4dg** in only 21% yield after 48 h (entry 4), **4dh** with 92:8 er was obtained in 91% yield after 12 h when **3h** was used in place of **3g** (entry 5). Thus, **3h** was a useful alternative nucleophile when the reaction was sluggish with **3g**.

Because the reaction with 6-membered acid anhydrides **2e**–**g** was much slower than those with 5-membered ones **2a**–**d**, **3h** was used as a nucleophile. With **2e**, having α,α'-substituents, **4eh** was produced with 89:11 er in 84% yield after 15 h (entry 6). As expected, recognition of stereochemical information at a β-position was a more difficult task for the chiral catalyst than that at α,α'-positions. The reaction of **2f** with a phenyl group at the β-

Table 2. Screening of Alcohol.

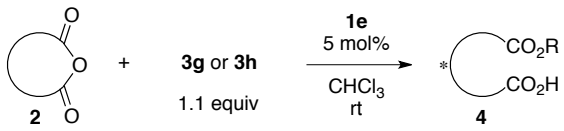


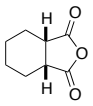
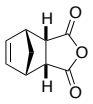
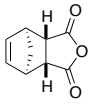
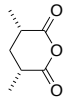
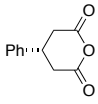
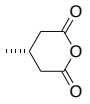
4aa–4ah

entry	R	3	time (h)	4	% yield[a]	er[b]
1	Bn	**3a**	3	**4aa**	98	77:23
2	Me	**3b**	2	**4ab**	98	53:47
3	*i*-Pr	**3c**	8	**4ac**	84	85:15
4	*t*-Bu	**3d**	24	**4ad**	trace	-
5		**3e**	5	**4ae**	96	86:14
6		**3f**	5	**4af**	93	77:23
7		**3g**	24	**4ag**	51[c]	98:2
8		**3h**	6	**4ah**	94	93:7

[a]Based on ^{1}H NMR of the crude mixture. [b]Determined by chiral stationary phase HPLC. [c]Isolated yield after methyl esterification with $TMSCHN_2$.

Table 3. Desymmetrization of Acid Anhydrides.

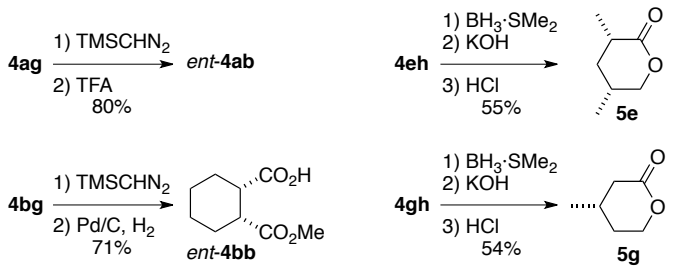


entry	2	3	time (h)	4	% yield[a]	er[b]
1	**2a**	**3g**	74	**4ag**	78[c]	98:2
2	 **2b**	**3g**	48	**4bg**	84	98:2
3	 **2c**	**3g**	72	**4cg**	72	99:1
4	 **2d**	**3g**	48	**4dg**	21	-[d]
5	**2d**	**3h**	12	**4dh**	91	92:8
6	 **2e**	**3h**	15	**4eh**	84	89:11
7	 **2f**	**3g**	24	**4fg**	8	89:11
8	**2f**	**3h**	16	**4fh**	83	85:15
9[e]	 **2g**	**3g**	24	**4gg**	39	77:23
10	**2g**	**3h**	6	**4gh**	95	82:18

[a]Isolated yield. [b]Determined by chiral stationary phase HPLC. [c]Isolated yield after methyl esterification with $TMSCHN_2$. [d]Undetermined. [e]Conducted at 40 °C.

position exhibited lower enantioselectivity than those with α,α'-substituents, giving **4fh** with 85:15 er in 83% yield after 16 h (entry 8). Bulkiness of the β-substituent was not so important for the enantioselectivity that the reaction of **2g**, bearing a methyl group at the β-position, provided **4gh** with comparable er (82:18) to that of **4fh**, bearing a phenyl group, in 95% yield after 6 h (entry 10). Using **3g** as a nucleophile, the reactions of **2f** and **2g** were much slower than those using **3h**, giving the corresponding half esters **4fg** and **4gg** in much lower yields (8% and 39%) after longer reaction time (24 h), respectively (entries 7 vs 8 and 9 vs 10).

The absolute configuration of the products was established by converting into known compounds as shown in Scheme 1. Treatment of **4ag** and **4bg** with trimethylsilyldiazomethane and the following debenzhydrylation with TFA and hydrogenolysis gave known half methyl esters *ent*-**4ab**[11] and *ent*-**4bb**[12] in 80% and 71% yields, respectively. The carboxylic acid moieties of acyclic products **4eh** and **4gh** were reduced into alcohols by a borane dimethyl sulfide complex. The basic hydrolysis of the diphenylethyl ester moieties followed by the treatment with hydrochloric acid produced lactones **5e**[13] and **5g**[14] in 55% and 54% yields, respectively. Comparing the specific rotation with the literature data determined the absolute configuration of these compounds as depicted. The absolute configuration of the other products was tentatively assigned by analogy.



Scheme 1. Determination of the Absolute Configuration

In conclusion, we have developed the first successful desymmetrization of acid anhydride using esterification catalyzed by chiral phosphoric acid. The use of a bulky alcohol improved the enantioselectivity at the cost of the reaction rate. Benzhydrol was the best nucleophile to realize high enantioselectivity, while 2,2-diphenylethanol was an alternative in case that the reaction with benzhydrol is too slow. Further investigation, including clarification of the mechanism, is underway in this laboratory.

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Supplementary Material

Experimental details, HPLC traces, and NMR spectra of the new compounds are available.

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