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Nonenzymatic Kinetic Resolution of 1,2-Diols Catalyzed by an Organotin Compound

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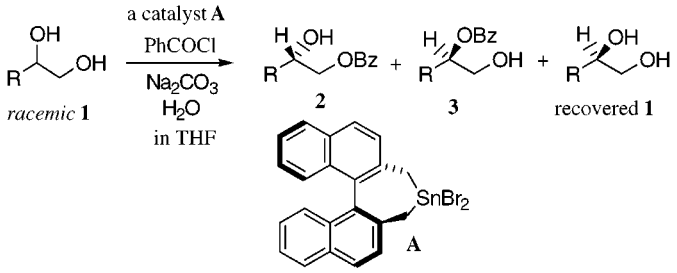
ABSTRACT

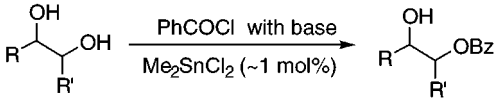


A new nonenzymatic kinetic resolution method of 1,2-diols 1 using chiral organotin catalyst A with benzoyl chloride was developed. A remarkable effect due to an inorganic base such as sodium carbonate and a small portion of water on the ee of the main products 2 was observed. The reaction showed high enantio- and chemoselectivities to 1,2-diols 1.

Nonenzymatic kinetic resolution is emerging as an important field of organic chemistry. Some effective catalysts for asymmetric acylation of racemic secondary alcohols[1] or desymmetrization of *meso* diols[2] have been reported for this purpose. On the other hand, there is no precedent for the kinetic resolution of racemic diols using chiral catalysts, except enzymatic methods,[3] despite its synthetic importance.

Recently, we reported a catalytic monobenzoylation of diols with benzoyl chloride where a catalytic amount (~1 mol %) of dimethyltin dichloride selectively worked to activate the diols, giving monobenzoylated products quantitatively (Scheme 1)[4] The successful result of the catalytic process prompted us to extend the reaction to an asymmetric version. We present herein the first chemoselective kinetic

Scheme 1. Selective Monobenzoylation of 1,2-Diols Catalyzed by Organotin Compounds



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(1) (a) Vedejs, E.; Daugulis, O.; Diver, S. T. *J. Org. Chem.* **1996**, *61*, 430. (b) Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 7230. (c) Oriyama, T.; Hori, Y.; Imai, K.; Sasaki, R. *Tetrahedron Lett.* **1996**, *37*, 8543. (d) Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492. (e) Kawabata, T.; Nagao, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc.* **1997**, *119*, 3169. (f) Copeland, G. T.; Jarvo, E. R.; Miller, S. J. *J. Org. Chem.* **1998**, *63*, 6784.

(2) (a) Oriyama, T.; Imai, K.; Hosoya, T.; Sano, T. *Tetrahedron Lett.* **1998**, *39*, 397. (b) Oriyama, T.; Imai, K.; Sano, T.; Hosoya, T. *Tetrahedron Lett.* **1998**, *39*, 3529. (c) Otera, J.; Sakamoto, K.; Tsukamoto, T.; Orita, A. *Tetrahedron Lett.* **1998**, *39*, 3201.

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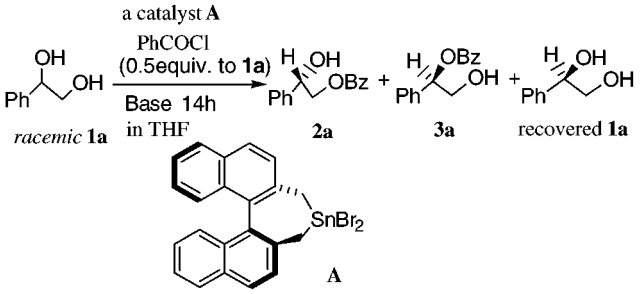
resolution of racemic 1,2-diols using a chiral organotin catalyst.

Racemic 1-phenyl-1,2-ethanediol (**1a**) was used as a representative example of 1,2-diols, and (*S*)-4,4-dibromo-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1′,2′-*e*]stannepin (**A**)[5] synthesized according to the reported method[6] was employed as a chiral organotin catalyst (Scheme 2).

Scheme 2. Kinetic Resolution of 1-Phenyl-1,2-ethanediol (**1a**) with Catalyst **A**



The reaction was carried out under a variety of conditions, and the results are summarized in Table 1. The main product was (*S*)-enantiomer-enriched 2-benzoyloxy-1-phenylethanol (**2a**), and its ee was determined by CSP HPLC analysis. The absolute configuration of **2a** was confirmed by alkaline hydrolysis followed by comparison of the specific rotation of the resulting **1a** with that[7] of an authentic sample. The recovered **1a** was enriched with the (*R*)-enantiomer in a 36−87% yield. A small amount of 1-benzoylated diol **3a** (0−10%)[8] was found, but no dibenzoylated product.

Table 1. Kinetic Resolution of Diol **1a** by Benzoylation with Catalyst **A**[a]

run	**A** (mol%)	H_2O (μL)	base (1.5 equiv.)	temp. (°C)	%ee[b,c] (yields %[d]) of **2a**[e]	selectivity s[f]
1	0	0	Et_3N	r.t.	~0 (40)	-
2	0	0	Na_2CO_3	r.t.	~0 (23)	-
3	0.25	0	Et_3N	-20	~0 (43)	-
4	0.25	0	Na_2CO_3	r.t.	(+) 32 (31)	2.2
5	0.25	100	Na_2CO_3	r.t.	(+) 58 (42)	5.6
6	0.25	1000	Na_2CO_3	r.t.	(+) 23 (16)	1.7
7	0.25	100	Et_3N	r.t.	(+) 13 (19)	1.3
8	0.25	100	Na_2CO_3	0	(+) 75 (54)	18.6
9	0.25	100	Na_2CO_3	-10	(+) 86 (38)	22.4
10	0.25	100	Na_2CO_3	-20	(+) 84 (41)	20.7
11	0.25	100	Na_2CO_3	-30	(+) 79 (28)	11.5
12	0.25	100	Na_2CO_3	-40	(+) 32 (10)	2.0

[a] Reaction conditions: **1a** (1.0 mmol), BzCl (0.5 mmol), THF (5 mL). [b] Determined by CSP HPLC analysis (for **2a**, Chiralcel OB column; 254 nm; *n*-hexane:*i*-PrOH = 9:1). [c] Corrected value based on the ee of used **A** (91%). [d] Isolated yield based on starting **1a**. [e] (+); (*S*)-isomer. [f] See ref 10.

The results showed the remarkable effects of chiral tin catalyst **A**, the type of base, and water on the ee of **2a**. Namely, the absence of **A** in the reaction system did not result in resolution of **1a** (runs 1 and 2), though **2a** was formed in moderate yields (theoretically, the maximum yield is 50% since the amount of benzoyl chloride was 0.5 equiv to **1a**). On the other hand, the presence of **A** afforded a result with a resolution of **1a** (runs 4−12). Although triethylamine gave an unsuccessful result with respect to the ee of **2a** (run 3), sodium carbonate as a suspended state[9] gave an appreciable degree of ee (32%) of **2a** (run 4), which was improved to 58% ee if a small amount of water was present (run 5). However, the ee decreased in the presence of a large amount of water (run 6), where sodium carbonate was completely dissolved to give a homogeneous solution. In contrast, with sodium carbonate, triethylamine was not effective even though water was present (run 7).

Although the selectivity (*s* value)[10] did not vary much in the temperature range of 0 to −30 °C (runs 8−11), the yield of **2a** dropped when the reaction was carried out at −30 °C (run 11). The reaction at −40 °C resulted in both low ee and low yield (run 12).[11] The best selectivity was obtained when the reaction was performed using sodium carbonate in the presence of a small amount of water at −10 °C (run 9).

The procedure for the best result (run 9) is as follows. Sodium carbonate (1.5 mmol) as a base was suspended in THF (5 mL) containing **1a** (1 mmol), water (100 μL, 5.5 mmol), and 0.25 mol % of **A**. Then into the suspension was added benzoyl chloride (0.5 mmol) at −10 °C, and the resulting solution was stirred at that temperature for 14 h. After the usual workup, a mixture of **2a** (86% ee, 38% yield) and recovered **1a** (46% ee, 58% yield) was obtained with a trace amount of **3a**.

On the basis of these results, we applied this method to various 1-substituted 1,2-ethanediols **1b**−**e**. The results are summarized in Table 2.

(3) (a) Chenault, H. K.; Chafin, L. F.; Liehr, S. *J. Org. Chem.* **1998**, *63*, 4039. (b) Egri, G.; Baitzz-Gács, E.; Poppe, L. *Tetrahedron: Asymmetry* **1996**, *7*, 1437. (c) Theil, F.; Weidner, J.; Ballschuh, S.; Kunath, A.; Schick, H. *J. Org. Chem.* **1994**, *59*, 388. (d) Weidner, J.; Theil, F.; Schick, H. *Tetrahedron: Asymmetry* **1994**, *5*, 751. (e) Theil, F.; Weidner, J.; Ballschuh, S.; Kunath, A.; Schick, H. *Tetrahedron Lett.* **1993**, *34*, 305. (f) Theil, F.; Ballschuh, S.; Kunath, A.; Schick H. *Tetrahedron: Asymmetry* **1991**, *2*, 1031.

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(7) Brown, J. M.; Murrer, B. A. *J. Chem. Soc., Perkin Trans. 2* **1982**, 489.

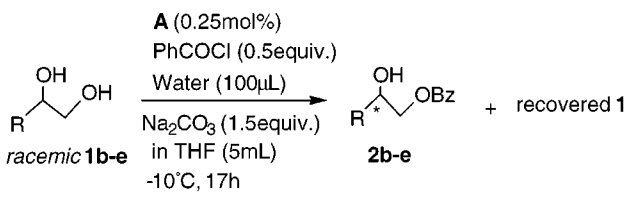
(8) (*R*)-Enantiomer-enriched **3a** with 0−59% ee was generated.

(9) Potassium carbonate was usable. Satisfactory results were obtained by using solid bases pulverized as small as possible.

(10) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.

(11) There has recently appeared an interesting temperature-dependent switching of enantioselectivity (<42.3% ee) in a desymmetric carbamoylation of 2-substituted 1,3-propanediol using catalyst **A**; see ref 2c. However, the enantioselectivity in **A**-catalyzed benzoylation of the 1,3-diol was 0% in our hand.

Table 2. Kinetic Resolution of Diols **1b**−**e** by Benzoylation with Catalyst **A**[a]



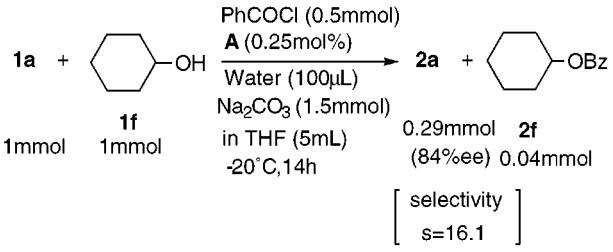
run	R	1	2	%ee[a] (yield %)[b]	selectivity[c] s
1		**1b**	**2b**	64 (25)	5.6
2		**1c**	**2c**	72 (41)	10.0
3	$CH_3(CH_2)_9$-	**1d**	**2d**	59 (35)	5.2
4	C_2H_5-	**1e**	**2e**	44 (35)	3.2

[a] Determined by CSP HPLC analysis. [b] Isolated yield. [c] See ref 10.

Moderate selectivities were also observed for the **A**-catalyzed benzoylation of **1b**−**e** in which the 2-benzoylated diols **2b**−**e** were enriched with (*S*)-enantiomer and 1-benzoylated products were found in trace amounts. Other 1,2-diols such as *trans*-1,2-cyclohexanediol afforded poor results under similar reaction conditions.

The other remarkable property of our method was its 1,2-diol selectivity. That is, **1a** was efficiently resolved even in the presence of an equimolar amount of cyclohexanol (**1f**) (Scheme 3). The ee of **2a** in the reaction was almost

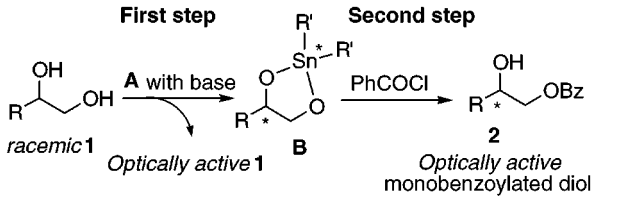
Scheme 3. Chemoselective Kinetic Resolution of **1a** in the Presence of Cyclohexanol (**1f**)



unaffected by the presence of **1f**, though a small amount of cyclohexyl benzoate (**2f**) was formed. This result suggests that the initiation step involves formation of stannylene acetal as an intermediate as described below.

The resolution reaction presented here may involve two crucial steps: formation of stannylene acetal **B** by the reaction of **1** with chiral tin catalyst **A** (first step) and benzoylation of **B** with benzoyl chloride (second step) (Scheme 4). The formation of **B** is supported by the high chemoselective formation of **2a** with a high ee from a mixture of **1a** and **1f** (Scheme 3).

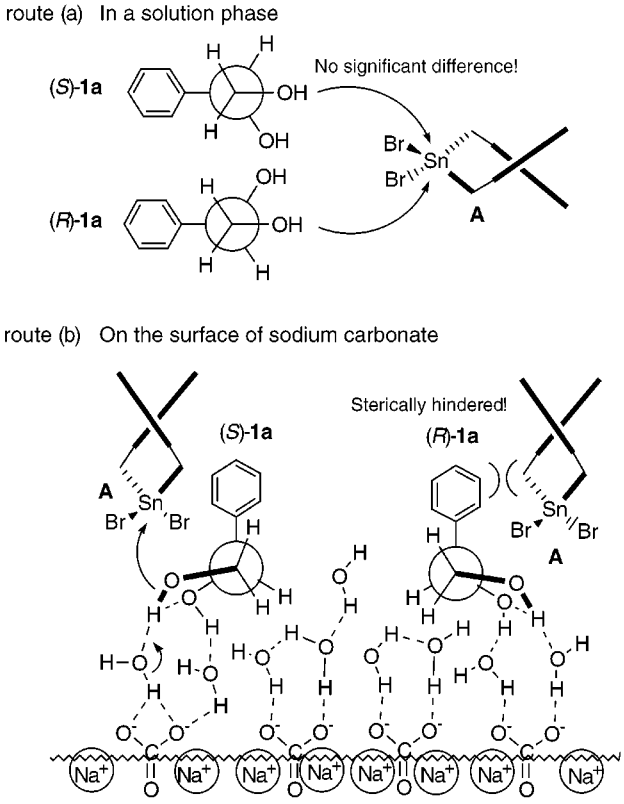
Scheme 4. Enantioselective Benzoylation of 1,2-Diol by a Chiral Organotin Catalyst



Since the observed ee was strongly dependent on the type of base (Table 1) and it has been well documented that stannylene acetals are easily acylated without bases by various acid chlorides,[12] the first step may be responsible for the enantiodiscrimination of racemic **1**, which may occur on the surface of sodium carbonate.

Thus, we propose a mechanism for the kinetic resolution of **1a** using **A** as depicted in Scheme 5. That is, when amine

Scheme 5. A Mechanism for Resolution of **1a** with Catalyst **A**



is used as a base, stannylene acetals **B** may be formed in a solution phase (THF) in which **A** approaches the primary hydroxyl group of **1a** from as far away as possible from a bulky phenyl group (route a in Scheme 5). According to this hypothesis, there seems to be no significant difference between the accessibility of **A** toward (*S*)-**1a** and (*R*)-**1a**.

On the contrary, when sodium carbonate is used as the base, the hydrophilic 1,2-diol moiety of **1a** may be adsorbed

on the surface of the sodium carbonate, directing the hydrophobic phenyl group toward the solution phase (THF) (route b in Scheme 5). In the presence of a small amount of water, a thin aqueous phase is formed on the surface of the sodium carbonate and, as the result, the adsorption of **1a** is assisted by hydrogen bonding as depicted in Scheme 5. Provided that this hypothesis is true, **A** should approach from the solution phase in a manner that allows the steric repulsion between **A** and the phenyl group to be as small as possible. Thus, the discrimination of (*S*)-**1a** from (*R*)-**1a** takes place since a steric repulsion between the methylene group of **A** and the phenyl group of (*S*)-**1a** is less than that between **A** and (*R*)-**1a**.

In conclusion, we report the first catalytic system for nonenzymatic kinetic resolution of 1,2-diols. Since the known acylating catalysts for 1,2-diols work by activating acylating reagents, further modification to recognize substrates is required. On the other hand, our method was based on the selective activation of 1,2-diols by a chiral organotin catalyst and therefore the process could *possess not only a high enantioselectivity but also a high chemoselectivity*.

Our report presents complementary information for the design of new artificial enzymes to allow for the recognition of both acylating reagents and substrates.

A detailed mechanistic study and development of new chiral organotin catalysts are under investigation.

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Supporting Information Available: Full experimental and analytical data for all new compounds; the conditions of HPLC analysis for **2b**−**e**; the specific rotations of **2b**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Acylation of dibutylstannylene acetals was well documented, for example: (a) Hanessian, S.; David, S. *Tetrahedron* **1985**, *41*, 643 and references therein. (b) Ricci, A.; Roelens, S.; Vannucchi, A. *J. Chem. Soc., Chem. Commun.* **1985**, 1457. (c) Roelens, S. *J. Chem. Soc., Perkin Trans 2* **1988**, 1617. (d) Reginato, G.; Ricci, A.; Roelens, S.; Scapecchi, S. *J. Org. Chem.* **1990**, *55*, 5132. (e) Roelens, S. *J. Org. Chem*. **1996**, *61*, 5257. (f) Hanessian, S.; Reinhold, U.; Gentile, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1881.