Catalytic Asymmetric Acylation of Racemic Secondary Alcohols with Benzoyl Chloride in the Presence of a Chiral Diamine

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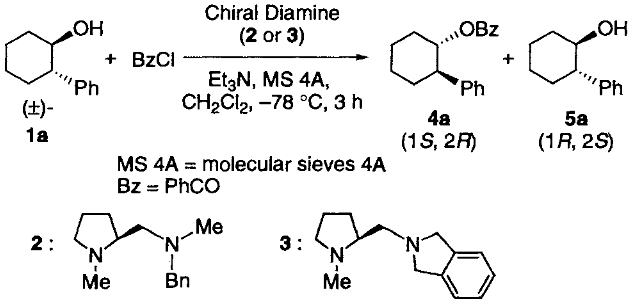
Nonenzymatic kinetic resolution of racemic secondary alcohols is an efficient synthetic method to obtain optically active compounds in organic chemistry. Catalytic asymmetric acylation of racemic secondary alcohols has been successfully performed with achiral benzoyl chloride in the presence of only 0.3 mol% of chiral diamine (**3**) derived from (*S*)-proline, combined with 0.5 equivalent of triethylamine. This asymmetric acylation of various racemic cyclic secondary alcohols, 5, 6, or 8 membered cycloalkanols (**1a–1c**), hydroxyesters (**1d** and **1e**), and bromohydrins (**1f** and **1g**) gave the corresponding optically active benzoates (84–97% ee) and unreacted alcohols (79–95% ee). Racemic acyclic secondary alcohols (**1h–1j**) were also acylated in moderate enantioselectivity.

Kinetic resolution of racemic secondary alcohols is a general efficient synthetic method to obtain optically active alcohols and their variants, and has been widely used for the synthesis of complex natural products and their derivatives.[1] Most methods involved the enzymatic acylation of alcohols;[2] therefore, a nonenzymatic procedure for the synthesis of optically active alcohol variants has been a challenging issue in synthetic organic chemistry. Although some nonenzymatic methods have been reported in recent years, most of them included the use of chiral acylating agents.[3] Very recently, some papers which are based on the catalytic asymmetric acylation of alcohols with achiral acylating agents have emerged in succession.[4] We have also reported that asymmetric acylation of racemic secondary alcohols[5] and of *meso*-1,2-diols[6] could be achieved when they were treated with achiral benzoyl halide in the presence of a chiral diamine derived from (*S*)-proline. Furthermore, we have demonstrated a catalytic asymmetric acylation of *meso*-1,2-diols with benzoyl chloride in the presence of a catalytic amount (0.5 mol%) of the chiral diamine combined with triethylamine.[7] Given that chiral diamines derived from (*S*)-proline are remarkably effective catalysts for the enantioselective asymmetrization of *meso*-1,2-diols, we considered whether similar systems could be extended to asymmetric acylation of racemic secondary alcohols.

Here, we describe a conceptually distinct approach which employs a catalytic amount of a chiral diamine derived from (*S*)-proline in combination with a stoichiometric amount of achiral triethylamine.

First, we undertook to examine the reaction of racemic *trans*-2-phenylcyclohexanol (**1a**) as a model substrate, with benzoyl chloride (0.75 equiv.) in the presence of a catalytic amount (5 mol%) of a chiral 1,2-diamine **2**[8] having benzylmethylamino skeleton, which is the most effective for asymmetric acylation of *meso*-1,2-diols, combined with triethylamine (0.5 equiv.) at −78 °C in dichloromethane. After 3 h the usual work-up of the reaction mixture gave the corresponding benzoate, *trans*-1-benzoyloxy-2-phenylcyclohexane (**4a**) in 48% yield with 97% ee and unreacted alcohol, *trans*-2-phenylcyclohexanol (**5a**) in 49% yield with 97% ee (Table 1, Entry 1). We were encouraged by this excellent result. However, when the amount of the chiral diamine **2** was decreased to 1 mol%, the acylation proceeded slowly to give the benzoate **4a** in low yield (Entry 2). On the other hand, treatment of **1a** with 5 mol% of a chiral diamine **3**[8,9] having dihydroisoindoline skeleton also showed satisfactory result (Entry 3). Surprisingly, the use of only 0.3 mol% of **3** smoothly gave **4a** with excellent enantioselectivity (Entry 4). When benzoyl bromide was used as an acylating agent in place of benzoyl chloride, **4a** was obtained in only 12% yield (Entry 5). We have tentatively chosen the reaction conditions of Entry 4 as optimal reaction conditions.

Table 1. Catalytic asymmetric acylation of racemic *trans*-2-phenylcyclohexanol[a]

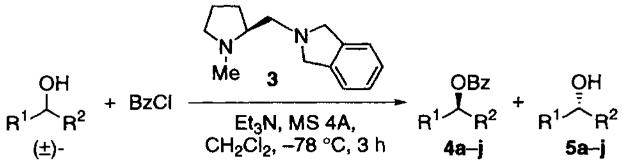


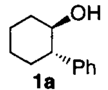
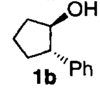
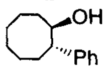
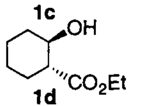
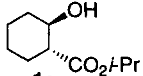
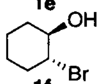
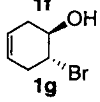
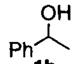
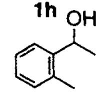
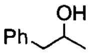
Entry	Chiral Diamine / mol%	4a Yield[b] / %	4a ee[c] / %	5a Yield[b] / %	5a ee[c] / %	*s*[d]
1	**2** (5)	48	97	49	97	200
2	**2** (1)	39	98	49	70	190
3	**3** (5)	50	95	49	>99	150
4	**3** (0.3)	49	96	48	95	160
5[e]	**3** (0.3)	12	97	78	14	75

[a] Molar ratio of **1a** : BzCl : Et_3N = 1 : 0.75 : 0.5. [b] Isolated yield of purified products. [c] Determined by chiral HPLC analysis (CHIRALPAK AD or CHIRACEL OD). [d] Calculated from the conversion (isolated yield) and ee of the acylated product: C. -S. Chen, Y. Fujimoto, G. Girdaukas, and C. J. Sih, *J. Am. Chem. Soc.*, **104**, 7294 (1982). [e] BzBr was used in place of BzCl.

The reaction was conducted with various racemic secondary alcohols under the optimal reaction conditions; the results are summarized in Table 2[10] and can be seen to be uniformly good to excellent in terms of both isolated yield and enantiomeric excess. The acylation of cyclic alcohols (Entries 1, 2, and 3), hydroxyesters (Entries 4 and 5), and bromohydrins[11] (Entries 6 and 7), successfully proceeded and the corresponding benzoates (**4a–g**)

Table 2. Catalytic asymmetric acylation of various racemic secondary alcohols[a]



Entry	Racemic Alcohol	**4** Yield[b] / %	**4** ee[c] / %	**5** Yield[b] / %	**5** ee[c] / %	*s*
1	 **1a**	49	96 (1*S*, 2*R*)	48	95 (1*R*, 2*S*)[d]	160
2	 **1b**	45	89 (1*S*, 2*R*)	42	88 (1*R*, 2*S*)[e]	37
3[f]	 **1c**	44	95	47	79	88
4	 **1d**	46	85	46	81	27
5	 **1e**	48	84	46	90	27
6[g]	 **1f**	47	96 (1*S*, 2*S*)	39	95 (1*R*, 2*R*)[h]	130
7[g]	 **1g**	46	97 (1*S*, 2*S*)	43	91 (1*R*, 2*R*)[h]	170
8	 **1h**	43	69 (*S*)	41	67 (*R*)[i]	9
9	 **1i**	45	82	49	78	20
10	 **1j**	49	46 (*S*)	39	51 (*R*)[j]	4

[a] Molar ratio of racemic alcohol : BzCl : Et_3N : chiral diamine = 1 : 0.75 : 0.5 : 0.003. [b] Isolated yield of purified products. [c] Determined by chiral HPLC analysis (CHIRALPAK AD or CHIRALCEL OD). [d] The optical rotation of unreacted **5a** was compared with **5a** purchased from Aldrich Chemical Co., Inc.. [e] H. C. Brown, P. K. Jadhav, and A. K. Mandal, *J. Org. Chem.*, **47**, 5074 (1982). [f] Reaction was performed for 24 h. [g] *i*-Pr_2NEt was used instead of Et_3N. [h] N. N. Joshi, M. Srebnik, and H. C. Brown, *J. Am. Chem. Soc.*, **110**, 6246 (1988). [i] I. K. Youn, S. W. Lee, and C. S. Pak, *Tetrahedron Lett.*, **29**, 4453 (1988). [j] M. P. DeNinno, R. J. Perner, and L. Lijewski, *Tetrahedron Lett.*, **31**, 7415 (1990).

and the unreacted alcohols (**5a**–**g**) were obtained in good to excellent optical yields, respectively. And the acyclic alcohols (**1h**–**j**) were acylated in moderate enantioselectivities (Entries 8, 9, and 10).

In summary, the present nonenzymatic asymmetric acylation of racemic secondary alcohols has the following synthetic advantages: 1) good to excellent enantioselectivities, 2) high efficiency (0.3 mol% of chiral diamine), and 3) experimental convenience. Further investigations to broaden the scope and synthetic applications of this asymmetric acylation are under way in our laboratory.

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10 A typical experiment proceeded as follows: To molecular sieves 4A (400 mg) was added a solution of (*S*)-1-methyl-2-[(dihydroisoindol-2-yl)methyl]pyrrolidine (**3**) (2.2 mg, 0.0102 mmol) in dichloromethane (5 ml), a solution of triethylamine (179.5 mg, 1.774 mmol) in dichloromethane (5 ml), and a solution of racemic *trans*-2-phenylcyclohexanol (**1a**) (598.2 mg, 3.394 mmol) in dichloromethane (5 ml) sequentially at room temperature and a solution of benzoyl chloride (350.2 mg, 2.491 mmol) in dichloromethane (5 ml) at –78 °C under argon atmosphere. After stirring for 3 h at –78 °C the reaction mixture was quenched with a phosphate buffer (pH 7) and the organic material was extracted with dichloromethane. The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel to yield 470.7 mg of *trans*-1-benzoyloxy-2-phenylcyclohexane (**4a**) (49%, 96% ee, $[\alpha]_D$ +122.5° (*c* 1.0, $CHCl_3$)) and 288.4 mg of *trans*-2-phenylcyclohexanol (**5a**) (48%, 95% ee, $[\alpha]_D$ –53.8° (*c* 1.0, MeOH)).

11 *i*-Pr_2NEt was used instead of Et_3N. In the case of the reactions performed in the presence of Et_3N, unreacted halohydrins were obtained in the lower optical yields. **1f** gave **4f** in 46% with 97% ee and **5f** in 45% with 85% ee, and **1g** gave **4g** in 45% with 97% ee and **5g** in 39% with 84% ee.