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Nonenzymatic Enantioselective Acylation of Racemic Secondary Alcohols Catalyzed by a SnX_2-Chiral Diamine Complex

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Abstract: Kinetic resolution of racemic secondary alcohols has been achieved by the reaction with benzoyl halide in the presence of a SnX_2-chiral diamine complex to afford the corresponding benzoate in good to excellent enantioselectivities. Copyright © 1996 Elsevier Science Ltd

Enzymes hold great potential for asymmetric synthesis of small polyfunctional chiral compounds which are well suited for further manipulation and have been widely used in synthetic organic chemistry.[1] Many methods have been well documented for the enzymatic kinetic resolution of alcohols in organic media.[2] On the other hand, concerning the nonenzymatic procedures for the efficient synthesis of optically active alcohol variants from alcohols, several methods have been reported. Most of them were based on the enantioselective acylation with *chiral* acylating agents.[3,4] Scattered examples of nonenzymatic acylation of alcohols with *achiral* acylating agents are found in the literature; however, these reactions require further elaboration before they can become practical methods.[5,6]

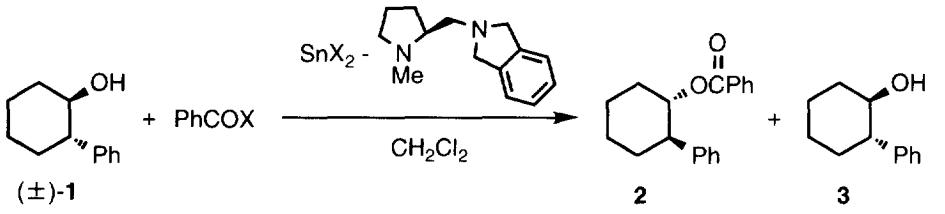
Herein we report the preliminary results of highly enantioselective acylation of racemic secondary alcohols with achiral acyl halides using chiral diamine derived from (*S*)-proline.

We recently developed a catalytic asymmetric ring-opening of cyclohexene oxide, meso epoxide, using benzoyl halides in the presence of a catalytic amount of chiral diamine derived from (*S*)-proline.[7] Our interest in creating readily chiral compounds from racemic alcohols has led us to consider an asymmetric acylation of racemic secondary alcohols with *achiral* acyl halides in the presence of chiral diamine.

First, treatment of *trans*-2-phenyl-1-cyclohexanol (**1**) with benzoyl bromide[8] in the presence of a catalytic amount of a $SnBr_2$-chiral diamine[9] complex induced asymmetric acylation providing optically active benzoate **2** and unreacted alcohol **3**. Screening various reaction conditions, we found that CH_2Cl_2 was the most suitable solvent and molecular sieve was a very effective additive. Other solvents such as Et_2O and CH_3CN provided lower levels of acyl transfer selectivity. Faster acylation occurred with benzoyl bromide as compared to benzoyl chloride, but lower enantioselectivities were obtained in the acylation of *trans*-2-phenyl-1-cyclohexanol (Table 1, Runs 3 *vs.* 5, and 6 *vs.* 8). However, in the case of benzoyl bromide, higher enantioselectivities

were obtained by lowering the reaction temperature (Runs 3 *vs.* 4, and 6 *vs.* 7). We, therefore, tentatively chose a combination of $SnBr_2$ and benzoyl bromide in the presence of MS 4A (molar ratio of alcohol : $SnBr_2$-chiral diamine : BzBr = 1 : 0.3 : 1).

Table 1. Asymmetric Acylation of *trans*-2-Phenyl-1-cyclohexanol



(±)-**1** **2** **3**

Run	X	PhCOX / equiv.	Catalyst / equiv.	Additive	Temp	Time / h	Ester **2** Yield[a] / %	Ester **2** ee[b] / %	Alcohol **3** Yield[a] / %	Alcohol **3** ee[c] / %
1	Br	1	0.1	none	r t	8	29	11	58	15
2	Br	1	0.2	none	r t	3	22	43	53	35
3	Br	1	0.2	MS 3A	r t	3	32	71	64	36
4	Br	1	0.2	MS 4A	-78°C	24	36	97	49	60
5	Cl	2	0.2	MS 4A	r t	24	34	87	52	46
6	Br	1	0.3	MS 4A	r t	3	47	75	45	71
7	Br	1	0.3	MS 4A	-78°C	24	44	97	49	84
8	Cl	2	0.3	MS 4A	r t	8	41	92	53	73
9	Cl	2	0.3	MS 4A	-78°C	24	35	96	46	59
10	Br	1	0.4	MS 4A	r t	0.25	42	86	48	74
11	Cl	2	0.4	MS 4A	r t	3	45	87	47	73

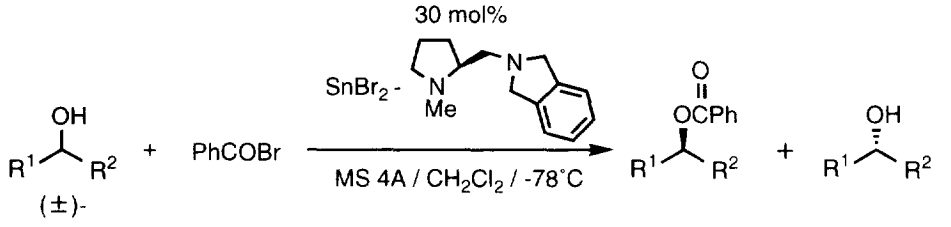
a) Isolated yields of purified product. b) Determined by the analysis of the derived Mosher's ester after reduction of ester **2**. c) Determined by the analysis of the corresponding Mosher's ester.

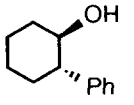
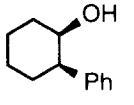
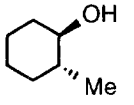
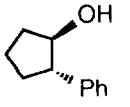
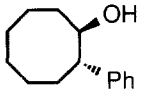
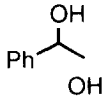
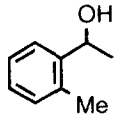
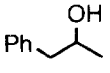
The asymmetric acylation was conducted with various racemic secondary alcohols including cyclic and acyclic alcohols under the optimum conditions and the successful results are summarized in Table 2. Excellent enantioselectivities were obtained with *trans*-2-phenyl-1-cyclohexanol and *cis*-2-phenyl-1-cyclohexanol (Runs 1 and 2). We found that *trans*-2-phenyl-1-cyclopentanol and *trans*-2-phenyl-1-cyclooctanol also undergo asymmetric acylation to give the corresponding benzoate derivatives with high enantioselectivities (Runs 4 and 5) The reaction was similarly effective with acyclic racemic secondary alcohols (Runs 6, 7, and 8).[10]

A typical experiment proceeded as follows: To anhydrous tin(II) bromide (25.1 mg, 0.0901 mmol) and molecular sieve 4A (40.7 mg) were added a solution of (*S*)-1-methyl-2-[(dihydroisoindol-2-yl)methyl]-pyrrolidine (21.4 mg, 0.0989 mmol) in CH_2Cl_2 (0.5 ml), a solution of *trans*-2-phenyl-1-cyclohexanol (52.6 mg, 0.298 mmol) in CH_2Cl_2 (0.5 ml) and a solution of benzoyl bromide (55.4 mg, 0.299 mmol) in CH_2Cl_2 (0.5 ml) sequentially at -78°C under an argon atmosphere. The reaction was quenched after 24 h at -78°C by the addition of a phosphate buffer (pH 7). The organic materials were extracted with CH_2Cl_2 and the combined

extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by thin layer chromatography on silica gel to yield 36.4 mg of *trans*-1-benzoyloxy-2-phenylcyclohexane (44%, $[\alpha]_D$+106.2° (c 1.0, MeOH)) and 25.8 mg of *trans*-2-phenyl-1-cyclohexanol (49%, $[\alpha]_D$-46.6° (c 1.0, MeOH)).

Table 2. Asymmetric Acylation of Various Secondary Alcohols with Benzoyl Bromide[a]



Run	Alcohol	Time / h	Ester Yield[b] / %	ee[c] / %	Alcohol Yield[b] / %	ee[d] / %	E[e]
1		24	44	97 (1*S*, 2*R*)[f]	49	84 (1*R*, 2*S*)	>100
2		24	40	94 (1*S*, 2*S*)[g]	45	87 (1*R*, 2*R*)	62
3		12	50	73 (1*S*, 2*S*)[h]	32	96 (1*R*, 2*R*)	14
4		24	44	86 (1*S*, 2*R*)[f]	46	86 (1*R*, 2*S*)	27
5		24	47	89	42	95	41
6		2.5	44	59 (*S*)[i]	43	61 (*R*)	6.0
7		4	38	77	40	79	12
8[j]		12	34	55 (*S*)[k]	42	51 (*R*)	4.5

a) Molar ratio of alcohol : PhCOBr : $SnBr_2$: chiral diamine = 1 : 1 : 0.3 : 0.3. b) Isolated yields of purified product. c) Determined by the analysis of the derived Mosher's ester after reduction of ester. d) Determined by the analysis of the corresponding Mosher's ester. e) Calculated from percent conversion (isolated yield) and acylation product ee. *J. Am. Chem. Soc.* **1982**, *104*, 7294-7299. f) *J. Org. Chem.* **1982**, *47*, 5074-5088. g) *J. Org. Chem.* **1968**, *33*, 4045-4049. h) *J. Am. Chem. Soc.* **1986**, *108*, 6761-6764. i) *Tetrahedron* **1965**, *21*, 1701-1709. j) 20 mol% of catalyst was used. k) *J. Chem. Soc.* **1914**, *105*, 1115-1131.

In brief, the salient features of the present nonenzymatic asymmetric acylation of racemic secondary alcohols include 1) the ease of operation, 2) ready availability of inexpensive reagents, 3) mild reaction conditions, and 4) high enantioselectivities, especially for cyclic alcohols. Further investigation to broaden the scope and synthetic application of this asymmetric acylation of alcohols and mechanistic study are underway in our laboratory.

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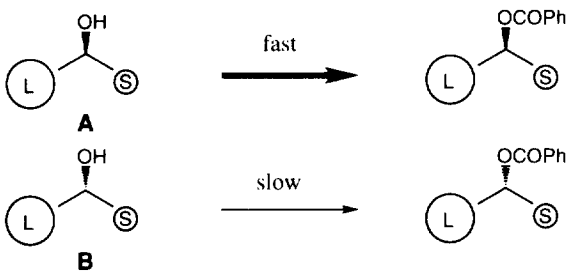
References and Notes

1. Burgess, K.; Jennings, L. D. *J. Am. Chem. Soc.* **1991**, *113*, 6129-6139.
2. Reviews: (a) Whitesides, G. M.; Wong, C.-H. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 617-638. (b) Chen, C.-S.; Sih, C. J. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 695-707. (c) Klibanov, A. M. *Acc. Chem. Res.* **1990**, *23*, 114-120. (d) Drueckhammer, D. G.; Hennen, W. J.; Pederson, R. L.; Barbas, C. F., III; Gautheron, C. M.; Krach, T.; Wong, C.-H. *Synthesis* **1991**, 499-525.
3. For asymmetric acylation of *meso*-diols with chiral acylating agents: (a) Mukaiyama, T.; Tomioka, I.; Shimizu, M. *Chem. Lett.* **1984**, 49-52. (b) Mukaiyama, T.; Tanabe, Y.; Shimizu, M. *Chem. Lett.* **1984**, 401-404. (c) Ishihara, K.; Kubota, M.; Yamamoto, H. *Synlett* **1994**, 611-614.
4. For asymmetric acylation of racemic alcohols with chiral acylating agents: (a) Chinchilla, R.; Nájera, C.; Yus, M.; Heumann, A. *Tetrahedron: Asymmetry* **1990**, *1*, 851-854. (b) Chinchilla, R.; Nájera, C.; Yus, M.; Heumann, A. *Tetrahedron: Asymmetry* **1991**, *2*, 101-104. (c) Mazón, A.; Nájera, C.; Yus, M.; Heumann, A. *Tetrahedron: Asymmetry* **1992**, *3*, 1455-1466. (d) Evans, D. A.; Anderson, J. C.; Taylor, M. K. *Tetrahedron Lett.* **1993**, *34*, 5563-5566.
5. (a) Bird, C. W. *Tetrahedron* **1962**, *18*, 1-5. (b) Stegmann, W.; Uebelhart, P.; Heimgartner, H.; Schmid, H. *Tetrahedron Lett.* **1978**, 3091-3092. (c) Ichikawa, J.; Asami, M.; Mukaiyama, T. *Chem. Lett.* **1984**, 949-952. (d) Duhamel, L.; Herman, T. *Tetrahedron Lett.* **1985**, *26*, 3099-3102.
6. Very recently, Vedejs reported some successful results of enantioselective acylations of *meso*- and racemic alcohols: (a) Vedejs, E.; Daugulis, O.; Diver, S. T. *J. Org. Chem.* **1996**, *61*, 430-431. (b) Vedejs, E.; Chen, X.; *J. Am. Chem. Soc.* **1996**, *118*, 1809-1810.
7. Oriyama, T.; Hori, Y.; Okada, C.; Nakayama, N.; Koga, G. unpublished results.
8. AcX-SnX_2 and BzX-SnX_2 are very efficient reagent systems for direct conversion of alkyl benzyl ethers and alkyl silyl ethers into the corresponding esters such as acetates and benzoates: (a) Oriyama, T.; Kimura, M.; Oda, M.; Koga, G. *Synlett* **1993**, 437-440. (b) Oriyama, T.; Oda, M.; Gono, J.; Koga, G. *Tetrahedron Lett.* **1994**, *35*, 2027-2030.
9. Some successful asymmetric synthesis using this type of diamine: (a) Kobayashi, S.; Horibe, M. *J. Am. Chem. Soc.* **1994**, *116*, 9805-9806. (b) Kobayashi, S.; Horibe, M. *Tetrahedron: Asymmetry* **1995**, *6*, 2565-2569.
10. The detailed reaction mechanism is not yet made clear; however, the stereochemical results were completely identical, that is, enantiomer A is acylated faster than enantiomer B as shown in Scheme 1.



Scheme 1

(*Received in Japan* 6 *September* 1996; *accepted* 7 *October* 1996)