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Asymmetric Acylation of *meso*-Diols with Benzoyl Halide in the Presence of a Chiral Diamine

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Abstract: Nonenzymatic desymmetrization of *cis*-1,2-cyclohexanediol by the asymmetric acylation with achiral benzoyl chloride in the presence of a chiral diamine derived from (*S*)-proline took place to give monobenzoate in high optical yield.

Asymmetric acylation is very important in synthetic organic chemistry and holds potential for preparation of small chiral compounds which are well suited for further manipulation. Although enzymatic acylation of racemic alcohols[1] has been extensively studied and established as a promising method for the preparation of chiral alcohol variants, development of nonenzymatic alternatives in this field[2] has been scattered. Very recently, some papers which are based on the catalytic asymmetric acylation of alcohols with achiral acylating agents have emerged in succession.[3] We have also succeeded in developing an expedient methodology for the asymmetric acylation of racemic secondary alcohols with achiral acyl halide combined with a chiral diamine derived from (*S*)-proline. In a previous communication,[4] we demonstrated the first example of highly enantioselective acylation of racemic alcohols by a convenient nonenzymatic procedure (*E*-value = 4.5 ~ > 100).

On the other hand, optically active diols and their derivatives play significant roles as versatile intermediates of complex natural products and biologically active compounds. Many synthetic methods for the preparation of optically active 1,2-diol variants have been established, e.g., asymmetric dihydroxylation,[5] enzymatic acylation of diols,[6] and others. From the synthetic viewpoint, it is very interesting to discriminate between enantiotopic groups of symmetrical 1,2-diols to afford synthetically useful chiral synthon by a simple procedure. Our previous investigation[4] suggested that combined use of benzoyl halide with a chiral diamine derived from (*S*)-proline would provide an efficient reagent system for the nonenzymatic asymmetric acylation of *meso*-diols.[7] We report here a novel and convenient asymmetric acylation of *meso*-1,2-diols.

First, we undertook to examine the reaction of *cis*-1,2-cyclohexanediol as a model substrate with benzoyl bromide (1.0 equiv.) under the influence of 0.3 equiv. of the chiral diamine in dichloromethane according to the procedure similar to that for the racemic alcohols reported in the previous paper.[4] After 24 h at -78°C, the

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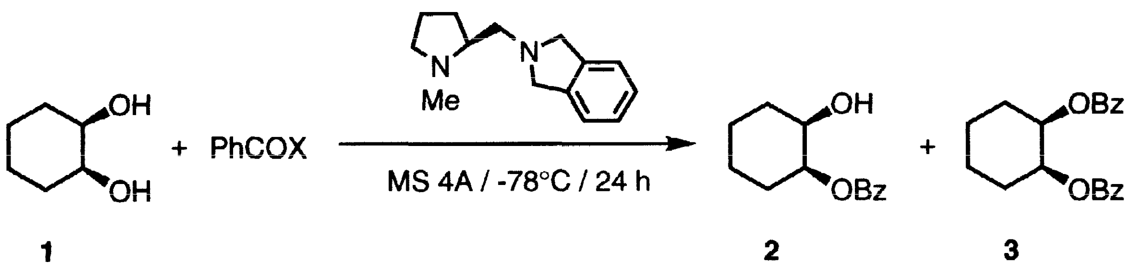
usual work-up of the reaction mixture gave the desired monobenzoate of diol, *cis*-2-benzoyloxycyclohexanol, in 6% yield with 81% ee (Table 1, Run 1). After various trials to improve both the chemical and optical yields, we found that $SnBr_2$ is not significantly effective[8] in this asymmetric acylation of *meso*-diol. Next, the solvent effect was examined in the reaction of *cis*-1,2-cyclohexanediol with 1.5 equiv. of benzoyl bromide, and dichloromethane gave the best enantioselectivity (91% ee, Runs 3, 4, and 5) among the tested solvents. Treatment of *meso*-diol with benzoyl chloride proved to be more effective in the enantioselectivity than benzoyl bromide (Runs 3 and 6). Higher yields of the monoacylation product were obtained by increasing the amount of the chiral diamine. Using a stoichiometric amount (1.0 equiv.) of the chiral diamine, the desired monoester of *meso*-diol was obtained in 62% yield (95% ee) (Run 8). However, the yield of a diester was also increased concomitant with increasing the amount of the chiral diamine (Runs 6, 7, and 8). So we have tentatively chosen a molar ratio of diol : diamine : benzoyl chloride = 1 : 1 : 1.5 as optimum conditions. We also found that propionitrile in place of dichloromethane gave monoester in 89% yield (93% ee)(Run 9).

Table 1. Asymmetric Acylation of *cis*-1,2-Cyclohexanediol



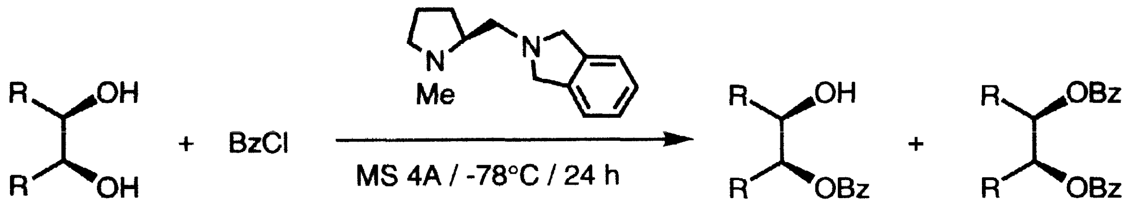
Run	X	PhCOX / equiv.	Diamine / equiv.	Solvent	**2** Yield[a] / %	**2** ee[b] / %	**3** Yield[a] / %
1	Br	1.0	0.3[c]	CH_2Cl_2	6	81	19
2	Br	1.0	0.3	CH_2Cl_2	15	94	13
3	Br	1.5	0.5	CH_2Cl_2	37	91	17
4	Br	1.5	0.5	EtCN	34	88	4
5	Br	1.5	0.5	Et_2O	34	84	4
6	Cl	1.5	0.5	CH_2Cl_2	38	94	3
7	Cl	1.5	0.7	CH_2Cl_2	49	93	6
8	Cl	1.5	1.0	CH_2Cl_2	62	95	12
9	Cl	1.5	1.0	EtCN	89	93	5
10	Cl	1.5	1.0	$PhCH_3$	22	88	29

a) Isolated yields of purified product. b) Determined by the analysis of the corresponding Mosher's ester.
c) Reaction was carried out in the presence of 0.3 equiv. of $SnBr_2$.

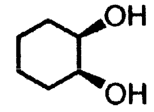
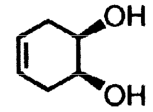
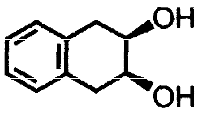
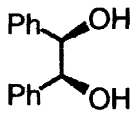
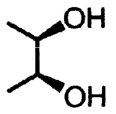
Preliminary screening of a series of chiral diamines validated the occurrence of face-selection, and (*S*)-1-methyl-2-[(dihydroisoindol-2-yl)methyl]pyrrolidine[9] was found to be the chiral diamine of choice. Although the role of MS 4A has not been clarified at present, the reactions are accelerated by its addition to the reaction mixture.

The optimal reaction conditions defined above for the asymmetric acylation were used for representative *meso*-diols including cyclic and acyclic ones, and the results are summarized in Table 2.[10] As can be seen, various monobenzoates were obtained with moderate to high enantioselectivities. Not only cyclic *meso*-diols but also acyclic ones can be acylated with synthetically useful levels of enantioselectivity.

Table 2. Asymmetric Acylation of Various *meso*-Diols[a)]



4 5 6

Run	*meso*-Diol	Solvent	5			6
			Yield[b)] / %	ee[c)] / %	$[\alpha]_D^{25}$ (c 1.0, $CHCl_3$)	Yield[b)] / %
1		EtCN	89	93	+15.5°	5
2		CH_2Cl_2	62	95 (93)[d)]	+15.7°	12
3		EtCN	76	91	+45.4°	13
4		CH_2Cl_2	78	96 (91)[d)]	+46.7°	1
5		EtCN	82	51	+12.1°	8
6		CH_2Cl_2	89	48		0
7		EtCN	62	55		1
8		CH_2Cl_2	68	64	−21.0°	4
9		EtCN	92	76	+11.0°	7
10		CH_2Cl_2	80	91 (95)[d)]	+12.9°	1

a) Molar ratio of diol : BzCl : chiral diamine = 1 : 1.5 : 1. b) Isolated yields of purified product.
c) Determined by the analysis of the corresponding Mosher's ester. d) Determined by chiral HPLC analysis.

In summary, the present asymmetric acylation of *meso*-diols demonstrates its rich synthetic utility as follows: 1) high enantioselectivities and 2) experimental convenience. Further investigations to broaden the scope and synthetic applications of this asymmetric acylation are underway in our laboratory.

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10. A typical experiment proceeded as follows: to molecular sieve 4A (46.1 mg) was added a solution of (*S*)-1-methyl-2-[(dihydroisoindol-2-yl)methyl] pyrrolidine (74.4 mg, 0.344 mmol) in CH_3CH_2CN (1.0 ml), a solution of *cis*-1,2-cyclohexanediol (40.0 mg, 0.344 mmol) in CH_3CH_2CN (2.5 ml) and a solution of benzoyl chloride (72.5 mg, 0.516 mmol) in CH_3CH_2CN (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 Et_2O and the combined extracts were dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by thin-layer chromatography on silica gel (AcOEt : hexane = 1 : 3) to yield 67.5 mg of *cis*-2-benzoyloxy-1-cyclohexanol (89%, $[\alpha]_D$+15.5° (c 0.92, $CHCl_3$) and 6.0 mg of *cis*-1,2-dibenzoyloxycyclohexane (5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07-8.04 (m, 2H), 7.58-7.54 (m, 1H), 7.46-7.42 (m, 2H), 5.23-5.20 (m, 1H), 3.97-3.94 (m, 1H), 2.26 (br, 1H), 2.05-1.98 (m, 1H), 1.88-1.64 (m, 5H), 1.47-1.38 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.20, 132.97, 130.34, 129.55, 128.32, 74.53, 69.53, 30.30, 27.36, 21.69, 21.53.