Highly Efficient and Enantioselective Method for the Synthesis of Chiral Building Blocks Derived from *meso*-1,3-Propanediols

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Highly efficient, direct, and enantioselective synthesis of useful chiral building blocks with excellent ee was performed by the catalytic asymmetric acylation of *meso*-1,3-propanediols. A structurally most simple *meso*-1,3-propanediol, 2-methyl-1,3-propanediol, was asymmetrized in 96% ee catalyzed by 0.5 mol% of chiral 1,2-diamine.

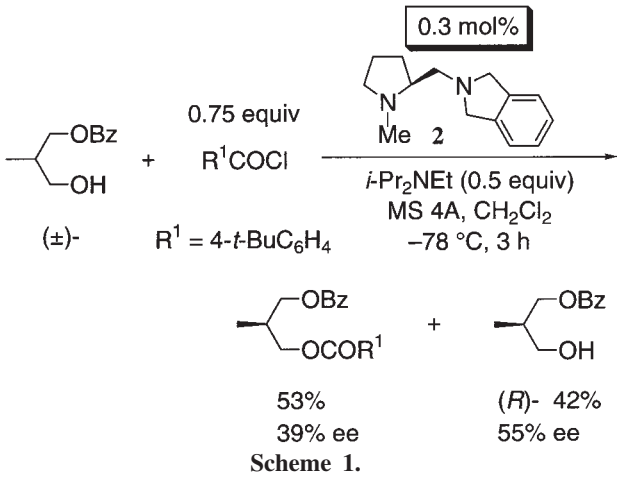
2-Methyl-1,3-propanediol (**1**) is a structurally most simple *meso*-1,3-diol and a very attractive substrate in view of its usefulness as a precursor to chiral building blocks, which have oxygen-containing functional groups.[1] Enantiotopic group differentiation of **1** is believed to be more difficult and challenging than that of *meso*-1,2-diols, because its two hydroxy groups are both primary and the prochiral carbon center is β-position to the hydroxy group. From this synthetic viewpoint, asymmetrization of 2-methyl-1,3-propanediol (**1**) is a very significant functional group transformation. However, most methods for this purpose are enzymatic procedures.[2,3]

On the other hand, we have developed novel and efficient non-enzymatic methods for the catalytic asymmetric acylation of racemic secondary alcohols[4] and *meso*-1,2-diols.[5] High enantioselectivities have been achieved by the reaction with benzoyl chloride as an achiral acylating agent catalyzed by a chiral 1,2-diamine such as **2** and **4** derived from (*S*)-proline. Asymmetric acylation of alcohols are divided into two types of reaction, that is, kinetic resolution of alcohols and asymmetrization of *meso*-diols. Although some outstanding methods for non-enzymatic asymmetric acylation of racemic *sec*-alcohols, especially aryl carbinols, have been reported,[6] few examples of asymmetrization of *meso*-diols have been developed. If our non-enzymatic methodology could be extended to *meso*-1,3-propanediol, the method would find application for the construction of more useful chiral building blocks.

Now we wish to report an efficient catalytic asymmetrization of *meso*-1,3-propanediols into highly enantiomerically enriched 3-acyloxy alcohols.

A screening of various reaction conditions based on the procedure described in the previous papers[4,5] revealed that asymmetric acylation of **1** with 4-*t*-butylbenzoyl chloride instead of benzoyl chloride in *n*-butyronitrile instead of dichloromethane afforded the corresponding monoacylated product **3** with the highest ee[7] (Table 1, Runs 1-3). The scope of this asymmetrization is very wide, and useful chiral building blocks were also obtained with excellent ee's by asymmetrization of *meso*-2-substituted-1,3-propanediols having an allyl group[8] (Run 6) and an oxirane ring[9] (Run 8).

These asymmetrizations presumably proceeded as follows. First, enantiotopic differentiation of two hydroxy groups of *meso*-1,3-diol has occurred in moderate enantioselectivity. Second, so obtained monoester was kinetically resolved as shown in Scheme 1 to give monoester with higher ee in matched fashion. Due to this two-step asymmetric induction, the lower (22–33%) chemical yields of asymmetrization product were observed in Table 1.[10] After these asymmetrizations, conversion of the diester to the starting materials, *meso*-1,3-diols, can be readily carried out by the methanolysis with sodium methoxide.



Scheme 1.

In summary, we have presented a promising catalyst for asymmetrization of symmetrical 1,3-propanediols. To the best of our knowledge, this is the first example for non-enzymatic catalytic asymmetrization of *meso*-1,3-propanediols.

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This paper is dedicated to Professor Teruaki Mukaiyama on the occasion of his 75th birthday, and for his outstanding contributions to synthetic organic chemistry.

References and Notes

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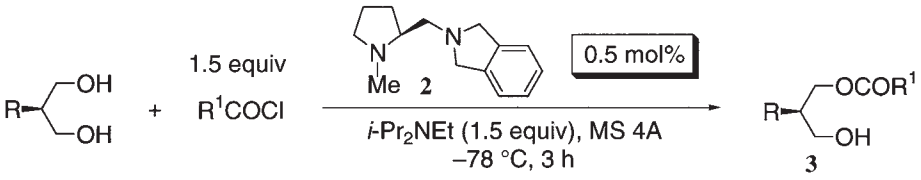
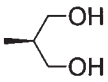
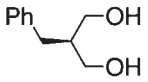
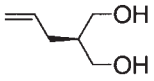
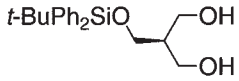
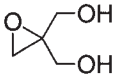
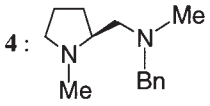
Table 1. Catalytic Asymmetric Acylation of *meso*-2-Substituted-1,3-propanediols



Run	*meso*-1,3-Diol	Solvent	R^1	3 Yield[a] / %	3 ee[b] / %
1		CH_2Cl_2	Ph	24	85
2	**1**	CH_2Cl_2	4-*t*-BuC_6H_4	26	90
3		*n*-PrCN	4-*t*-BuC_6H_4	33	96
4[c]		*n*-PrCN	4-*t*-BuC_6H_4	28	86
5		*n*-PrCN	4-*t*-BuC_6H_4	22	93
6		*n*-PrCN	4-*t*-BuC_6H_4	30	98
7		CH_2Cl_2	4-*t*-BuC_6H_4	24	89
8[d,e,f]		*n*-PrCN	Ph	31	96

[a]Isolated yield of purified product. The corresponding diester was also obtained in 50–67% yield. [b]Determined by chiral HPLC analysis. [c]The reaction was carried out at –40 °C. [d]Chiral diamine **4** was used instead of **2**. [e]Et_3N was used instead of *i*-Pr_2NEt. [f]1.7 equivalents of BzCl and Et_3N were used, respectively.



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7 The absolute configuration of **3** was assigned to be *R* by comparison with specific rotation after conversion to silyloxy alcohol.[2c]

8 a) T. Fukuyama, C.-L. J. Wang, and Y. Kishi, *J. Am. Chem. Soc.*, **101**, 260 (1979). b) K. Mori and N. Chiba, *Liebigs Ann. Chem.*, **1989**, 957. c) T. B. Sells and V. Nair, *Tetrahedron Lett.*, **33**, 7639 (1992). d) B. M. Trost and J. R. Corte, *Angew. Chem., Int. Ed.*, **38**, 3664 (1999).

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10 A typical experiment proceeded as follows: To molecular sieves 4A (600 mg) were added a solution of (*S*)-1-methyl-2-[(dihydroisoindol-2-yl)methyl]pyrrolidine (**2**) (21.6 mg, 0.1 mmol) in *n*-PrCN (3 ml), a solution of diisopropylethylamine (3.88 g, 30 mmol) in *n*-PrCN (5 ml), a solution of 2-methyl-1,3-propanediol (1.80 g, 20 mmol) in *n*-PrCN (5 ml) and a solution of 4-*tert*-butylbenzoyl chloride (5.90 g, 30 mmol) in *n*-PrCN (5 ml) sequentially at −78 °C under an argon atmosphere. The reaction was quenched after 3 h at −78 °C by the addition of a phosphate buffer (pH 7). The organic materials were extracted with ether and the combined extracts were dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (AcOEt : hexane = 1 : 15) to yield 1.63 g (33%) of (*R*)-3-(4-*tert*-butylbenzoyloxy)-2-methylpropan-1-ol ($[\alpha]_D$ + 2.03 ° (*c* 1.0, $CHCl_3$)).