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Highly Efficient Catalytic Asymmetric Acylation of *meso*-1,2-Diols with Benzoyl Chloride in the Presence of a Chiral Diamine Combined with Et₃N

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Abstract: Catalytic asymmetric acylation of meso-1,2-diols has been successfully performed by the reaction with benzoyl chloride in the presence of 0.5 mol% of chiral diamine derived from (S)-proline combined with a stoichiometric amount of triethylamine to give the corresponding monobenzoate with good to excellent enantioselectivities. © 1998 Elsevier Science Ltd. All rights reserved.

Extensive methodology for asymmetric synthesis, including carbon-carbon bond formations and functional group transformations, has been explored.¹ Additionally, the catalytic version in asymmetric synthesis has been evaluated and various types of asymmetric reactions have reached high levels of enantioselectivity and efficiency. Recently, much attention has been focused on the nonenzymatic asymmetric acylation of racemic secondary alcohols² and *meso*-diols.³ We have also demonstrated asymmetric acylation of racemic secondary alcohols⁴ and *meso*-1,2-diols⁵ by the reaction with achiral benzoyl halide in the presence of a chiral diamine derived from (S)-proline. Furthermore, some papers which are based on the catalytic asymmetric acylation of alcohols with achiral acylating agents have emerged successively in recent years.⁶ However, neither methodology has been developed to such a level as to find widespread use in organic synthesis.

To date, we have focused our attention primarily on the enantioselectivity of asymmetric acylation of alcohols. In this communication, we establish that a chiral diamine derived from (S)-proline can function as a highly efficient catalyst for the catalytic asymmetrization of *meso*-1,2-diols.

First, we undertook to examine the reaction of cis-1,2-cyclohexanediol (1) as a model substrate with benzoyl chloride (1.5 equiv.) under the influence of the chiral 1,2-diamine⁷ (10 mol%) combined with achiral amine, triethylamine (1.5 equiv.), in dichloromethane. After 24 h at -78°C, the usual work-up of the reaction mixture gave the desired monobenzoate of diol, cis-2-benzoyloxycyclohexanol (2), in 60% yield with 94% ee (Table 1, Run 1). The preliminary result was found to be highly encouraging. In the case of using 1.5 equiv. of achiral tertiary amine, a significant amount of dibenzoate (3, 34%) was obtained. However, treatment of *meso*-diol with 1.5 equiv. of benzoyl chloride, 5 mol% of a chiral diamine, and 1 equiv. of triethylamine in dichloromethane at -78 °C cleanly affords a monobenzoate (2) in good yield without concomitant production of dibenzoate 3 (Run 2). After screening the achiral amine, we found that simple triethylamine gave the best result

among the tested amines (Runs 2-6). The reactions in the presence of MS 4A proceeded somewhat faster than in the absence of MS 4A (Runs 9 and 10). Surprisingly, even in the case of decreasing the molar ratio of the catalyst (0.5 mol%) in shorter reaction time (3 h), the asymmetric acylation proceeded smoothly to give a satisfactory result (Run 14). Judging from the efficiency and convenience, we have tentatively chosen the reaction conditions of Run 14 as optimum conditions.

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

\frown	ОН	1.5 equiv.	Me 1.0 equiv. N I + Amine Me Bn					+ OBz	
\smile	•он	DZOI		MS 4A			OBz		
1						2		3	
Run	Diamine / mol%	Amine	Solvent	Temp	Time / h	2 Yield ^{a)} / %	ee ^{b)} / %	3 Yield ^{a)} / %	
1	10	Et ₃ N ^{c)}	CH ₂ Cl ₂	-78°C	24	60	94	34	
2	5	Et ₃ N	CH_2Cl_2	-78°C	24	92	97	0	
3	5	'Pr ₂ NEt	CH_2Cl_2	-78°C	24	92	97	0	
4	5	TMEDA	CH_2Cl_2	-78°C	24	17	0	56	
5	5	FN:F Me	CH ₂ Cl ₂	-78°C	24	92	95	1	
6	5	(c-C6H11)2NEt	CH ₂ Cl ₂	-78°C	24	92	78	2	
7	5	Et ₃ N	PhCH ₃	-78°C	24	7	76	14	
8	5	Et ₃ N	EtCN	-78°C	24	87	93	3	
9	2	Et ₃ N	CH ₂ Cl ₂	-78°C	24	85	96	0	
10 ^{d)}	2	Et ₃ N	CH ₂ Cl ₂	-78°C	24	59	95	0	
11	2	Et ₃ N	CH ₂ Cl ₂	-20°C	24	91	89	2	
12	2	Et ₃ N	CH ₂ Cl ₂	0°C	24	80	83	1	
13	0.5	Et ₃ N	CH ₂ Cl ₂	-78°C	24	87	97	0	
14	0.5	Et ₃ N	CH ₂ Cl ₂	-78°C	3	83	96	0	

a) Isolated yields of purified product. b) Determined by chiral HPLC analysis.

c) 1.5 equiv. of Et₃N was used. d) In the absence of MS 4A.

The reaction of various *meso*-1,2-diols, including cyclic and acyclic ones, with benzoyl chloride was screened using 0.5 mol% of a chiral diamine. The successful results are tabulated in Table 2^8 and can be seen to be uniformly good to excellent in terms of both enantioselectivity and isolated yield.

Although the detailed reaction mechanism has not been clarified at present, the catalytic asymmetric process is exemplified in Scheme 1. Two nitrogens of the chiral diamine presumably coordinate to the carbonyl carbon of benzoyl chloride in a rigid and bidentate manner and play an important role in enantioselection.

Table 2. Catalytic Asymmetric Acylation of Various meso-Diols^{a)}

		0.5 mol%			
	+ BzCl		Me ; H ₂ Cl ₂	R OBz 5	+ R OBz R OBz 6
Run	meso-Diol	Yield ^{b)} / %	5 ee ^{c)} / %	[α] _D ²⁵ (c 1.0, CHCl ₃)	6 Yield ^{b)} / %
1	OH	83	96	+16.3°	0
2	СЧон	87 ^{d)}	97	+16.4°	0
3	ОН	81	90	+44.7°	1
4		99 0H	66	+16.9°	2
5	Ph OH Ph OH	80 ^{d)}	60	-19.1°	3
6	, он	85	94	+14.2°	0
7	BnO C	H 73 ^{d)} H	82 ^{e)}	+17.8°	0

a) Molar ratio of diol : BzCl : chiral diamine : $Et_3N = 1 : 1.5 : 0.005 : 1$.

b) Isolated yields of purified product. c) Determined by chiral HPLC analysis.

d) Reaction was carried out for 24 h. e) Determined by the ¹H NMR analysis of the corresponding MTPA ester.

In conclusion, we have succeeded in developing a highly efficient method for the enantioselective asymmetrization of *meso*-1,2-diols with benzoyl chloride. This catalytic asymmetric acylation is operationally straightforward to conduct, since a chiral diamine is very easy to be prepared and handled. This process demonstrates a significant advance in the area for the nonenzymatic enantioselective asymmetrization of *meso*-1,2-diols. Further studies to broaden the synthetic applications of this catalytic asymmetric acylation are under way in our laboratory.



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- 7. A screening of a series of chiral diamines validated the occurrence of face-selection, and (S)-1-methyl-2-[(benzylmethylamino)methyl]pyrrolidine was found to be the chiral diamine of choice.
- 8. A typical experiment proceeded as follows: to molecular sieve 4A (400 mg) was added a solution of (S)-1-methyl-2-[(benzylmethylamino)methyl]pyrrolidine (3.3 mg, 0.0151 mmol) in dichloromethane (2.5 ml), a solution of triethylamine (306 mg, 3.02 mmol) in dichloromethane (2.5 ml), a solution of *cis*-1,2-cyclohexanediol (351 mg, 3.02 mmol) in dichloromethane (20 ml) and a solution of benzoyl chloride (636 mg, 4.52 mmol) in dichloromethane (2.5 ml) sequentially at -78℃ under an argon atmosphere. The reaction was quenched after 3 h at -78℃ 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 554 mg of *cis*-2-benzoyloxy-1-cyclohexanol (83%, [α]_D+16.3°(*c* 1.0, CHCl₃)).