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Nonenzymatic Enantioselective Monoacetylation of Prochiral 2-Protectedamino-2-alkyl-1,3-propanediols Utilizing a Chiral Sulfonamide–Zn Complex Catalyst

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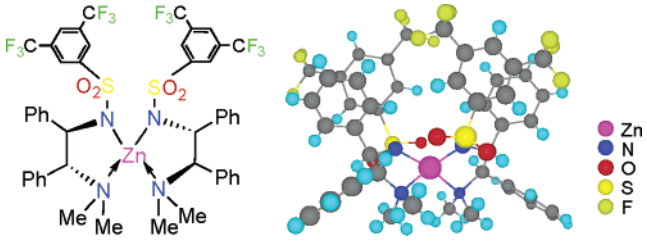
ABSTRACT



Treatment of a chiral sulfonamide with Et_2Zn gave quantitatively its Zn complex and then the structure was determined by X-ray crystallographic analysis. Reaction of prochiral *N*-Boc-2-amino-2-alkyl-1,3-propanediols with Ac_2O in the presence of 5 mol % of chiral sulfonamide–Zn complex catalyst afforded the corresponding chiral monoacetyl products in 70–92% yields with 70–88% ee values. The proposed mechanism for the catalytic monoacetylation of a prochiral 1,3-propanediol was presented on the basis of CSI-MS analysis.

In recent years, numerous nonenzymetic catalytic kinetic resolution methods for racemic alcohols have been disclosed by utilizing chiral analogues of trialkylphosphine,[1] diamine,[2] 4-(dimethylamino)pyridine,[3] peptide-based catalyst,[4] 1-alkylimidazole,[5] and dihydroimidazopyridine.[6] On the other hand, catalytic asymmetric desymmetrization procedures for prochiral and *meso* diols have been less investigated. Catalytic asymmetric desymmetrization methods for *meso* 1,2-diols have been reported with good yields and enantioselectivities.[7] However, similar desymmetrization methods for prochiral 1,3-diols are rare.[8,9] To obtain the high ee products in asymmetric acylation of prochiral 1,3-diols, the monoacylated product was subjected to further kinetic resolution forming

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the diester. Thereby, the utility should be limited from a viewpoint of their chemical yields.[8a,b] Recently, Trost and Mino reported a new fascinating method for catalytic and direct asymmetric monobenzoylation of prochiral 1,3-diols having a tertiary prochiral center by the use of a dinuclear zinc catalyst.[9] However, our target substrates, prochiral 2-protectedamino-2-alkyl-1,3-propanediols (PAAPs), having a quaternary-like prochiral center seemed to be very difficult compounds for asymmetric monoacylation. Although some enzymatic acylation methods for prochiral PAAPs (useful prochiral precursors for chiral α-substituted serines) have been described,[10] there has been no report of the nonenzymatic catalytic procedure to the best of our knowledge.[11] Herein, we describe a nonenzymatic enantioselective monoacetylation of prochiral 2-protectedamino-2-alkyl-1,3-propanediols in the presence of a novel chiral sulfonamide−Zn complex catalyst.

We tentatively carried out monobenzoylation of *N*-Z-2-amino-2-methyl-1,3-propanediol using the Trost's catalyst.[9] The benzoylation proceeded slightly to give a chiral monobenzoyl derivative in 12% yield with 10% ee. Thus, we designed a simple chiral Zn-bridging bis-sulfonamide catalyst **1**. Very recently, we developed catalytic enantioselective thiolysis of various prochiral dicarboxylic anhydrides using a chiral sulfonamide **2** based on our concerns about cysteine protease.[11,12] The key function of the Zn^{2+} cation in the reactive site of Zn peptidase involves the OH^- ion generated by abstraction of H^+ from H_2O with the neighboring basic group.[13] Hence, a chiral Zn catalyst seemed to exhibit Lewis acidic activity to the OH and carbonyl groups. A diuretic drug acetazolamide bearing the sulfonamide moiety coordinates to the Zn^{2+} cation in the molecule of carbonic anhydraze I or II.[14] Then, we tried to synthesize a Zn-contained catalyst using **2**. A new chiral sulfonamide−Zn complex **1** was quantitatively obtained by the reaction of sulfonamide **2** with Et_2Zn (0.55 equiv) in $CHCl_3$ at room temperature within 1 min (Scheme 1). The structure of crystalline compound **1** was determined by X-ray crystallographic analysis. Fortunately, compound **1** is remarkably stable and can be stored at room temperature for several months without any decomposition.

First, we examined enantioselective acetylation of **3a** with Ac_2O (1.5 equiv) in the presence of 2.5 mol % of **1** in THF at room temperature for 20 h. The reaction smoothly proceeded to afford the monoacetylated product **4a** in 82% yield with 63% ee (Table 1, entry 1). Diacetate compound of **3a** was formed in only 3% yield. The ee of **4a** should not be due to a kinetic resolution of the initial monoacetyl compound because of the very low yield of diacetate.

Scheme 1. Synthesis and X-ray Structure of **1**

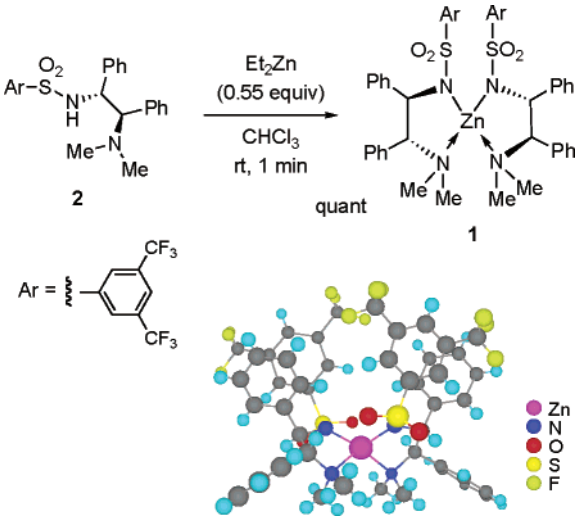
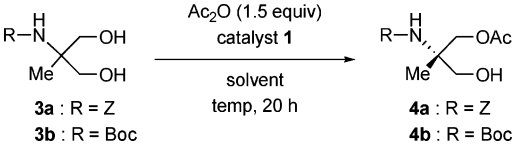


Table 1. Investigation of the Reaction Conditions for the Catalytic Enantioselective Monoacetylation of Prochiral 2-Protectedamino-2-methyl-1,3-propanediols



entry	1,3-diol	catalyst (mol %)	solvent	temp (°C)	yield,[a] %	ee,[b] %
1	**3a**	**1** (2.5)	THF	rt	82[c]	63
2	**3a**	**1** (2.5)	CH_2Cl_2	rt	51[c]	57
3	**3a**	**1** (2.5)	toluene	rt	31[c]	59
4	**3a**	**1** (2.5)	MeCN	rt	60[c]	32
5	**3a**	**1** (2.5)	Et_2O	rt	82[c]	70
6	**3b**	**1** (2.5)	Et_2O	rt	90[d]	77
7	**3b**	**1** (2.5)	*i*-Pr_2O	rt	91[d]	77
8	**3b**	**1** (2.5)	CPME	rt	87[d]	80
9	**3b**	**1** (2.5)	*t*-AmylOMe	rt	92[d]	83
10	**3b**	**1** (2.5)	*t*-BuOMe	rt	94[d]	83
11	**3b**	**1** (2.5)	*t*-BuOMe	4	77[d]	87
12	**3b**	**1** (2.5)	*t*-BuOMe	0	74[d]	88
13	**3b**	**1** (5)	*t*-BuOMe	0	92[d]	88
14	**3b**	**1** (5)	*t*-BuOMe	−5	80[d]	86
15	**3b**	**1** (5)	*t*-BuOMe	−15	65[d]	86

[a] Isolated yield. [b] Determined by HPLC analysis. [c] Yield of diacetate is less than 4%. [d] No production of diacetate. Z = benzyloxycarbonyl, Boc = *tert*-butoxycarbonyl, CPME = cyclopentyl methyl ether.

We investigated the similar catalytic enantioselective acetylation of **3a** employing several solvents such as CH_2Cl_2, toluene, MeCN, and Et_2O but the yield and the ee were

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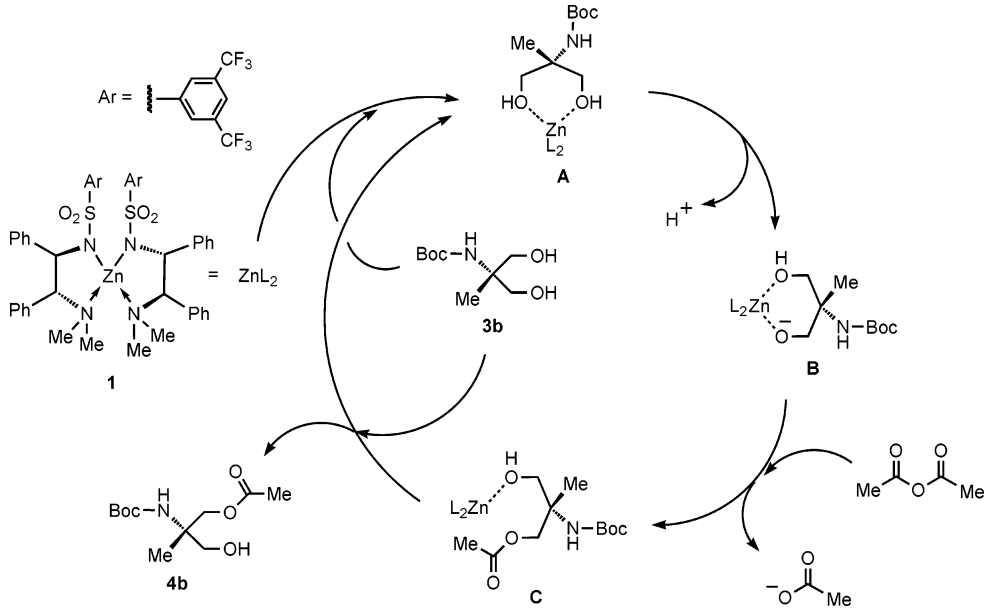


Figure 1. Proposed mechanism for catalytic monoacetylation of prochiral *N*-Boc-2-amino-2-methyl-1,3-propanediol **3b** with chiral sulfonamide−Zn complex catalyst **1**.

not remarkably improved (Table 1, entries 2−5). Subsequently, enantioselective acetylation of *N*-Boc-2-amino-2-methyl-1,3-propanediol **3b** was attempted as follows. Treatment of **3b** with Ac_2O (1.5 equiv) in the presence of 2.5 mol % of the Zn complex catalyst **1** in Et_2O at room temperature for 20 h afforded only monoacetylated product **4b** in 90% yield with 77% ee (Table 1, entry 6). This outcome prompted us to investigate the influence of the solvent and the possibility of increasing the enantioselectivity by lowering the reaction temperature for the catalytic enantioselective acetylation of **3b** (Table 1, entries 7−15). The best result was obtained when *t*-BuOMe was used as a solvent in the presence of 5 mol % of chiral catalyst **1** at 0 °C, thus giving **4b** in 92% yield with 88% ee (Table 1, entry 13). Tentative catalytic enantioselective acylation of **3a** or **3b** with 1.5 equiv of benzoic anhydride [$(PhCO)_2O$] in the presence of 2.5 mol % of the Zn complex catalyst **1** in Et_2O at room temperature gave the corresponding monobenzoylated *N*-Z-product (60% ee) or *N*-Boc-product (71% ee) in 60% or 66% yield, respectively.[15]

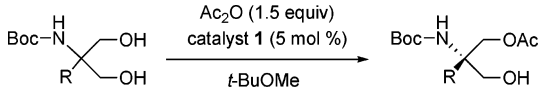
On the basis of the best reaction conditions (Table 1, entry 13), the catalytic enantioselective acetylation of various prochiral 1,3-propanediols **3b** and **5**−**8** were performed. The corresponding chiral monoacetyl products **4b** and **9**−**12** were obtained in 70−92% yields with 70−88% ee values (Table 2).

The absolute configuration of the newly formed chiral carbon atom in the monoacetyl product **4b**, **10**, **11**, and **12** was determined to be *S* by their chemical conversion into the corresponding known α-alkyl serine derivatives.[15] Stereochemistry of another monoacetyl product **9** seems to be *S* based on a similar reaction.

(15) See the Supporting Information.

Finally, we determined cold-spray ionization mass spectrometry (CSI-MS),[16] which allows facile and precise characterization of labile organic species bearing noncovalent bonding interactions in a solution. The CSI-MS spectrum for a 1:1 mixture of the Zn complex catalyst **1** [0.1 mM] and 1,3-diol **3b** [0.1 mM] in THF at room temperature showed the prominent ion peak of 1:1 complex [**1**-**3b**-Na]$^+$ at *m*/*z* 1322.3.[15] Thus, we consider that coordination of 1,3-propanediol **3b** to the Zn complex catalyst **1** may first generate an activated form **A** of the 1,3-diol. Then, enantioselective hydrogen abstraction of one of two enantiotopic hydroxy groups with one of two dimethylamino groups in **A** (i.e., the Zn complex catalyst **1**) would give an anionic intermediate **B**. Acetylation of **B** with Ac_2O would furnish a monoacetate **C** releasing an acetate ion. The desirable chiral monoacetate **4b** can be obtained by coordination of the 1,3-

Table 2. Catalytic Enantioselective Monoacetylation of Various Prochiral *N*-Boc-2-amino-2-alkyl-1,3-propanediols



3b, **5-8** → **4b**, **9-12**

entry	1,3-diol	product	yield,[a] %	ee,[b] %
1	**3b** (R = Me)	**4b** (R = Me)	92	88
2	**5** (R = Et)	**9** (R = Et)	87	86
3	**6** (R = allyl)	**10** (R = allyl)	70	82
4	**7** (R = *n*-hexyl)	**11** (R = *n*-hexyl)	84	83[c]
5	**8** (R = Bn)	**12** (R = Bn)	70	70

[a] Isolated yield. [b] Determined by HPLC analysis. [c] Determined by HPLC analysis after quantitative conversion of **11** to its (+)-MTPA ester.

propanediol **3b** to monool zincate **C** regenerating the 1,3-propanediol−Zn complex **A**, which would be utilized for further similar reactions in a catalytic cycle manner, as shown in Figure 1.

In conclusion, we have demonstrated, for the first time, nonenzymatic, catalytic, and enantioselective monoacetylation of prochiral 2-protectedamino-2-alkyl-1,3-propanediols utilizing the novel chiral sulfonamide−Zn complex catalyst **1**.

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Supporting Information Available: Experimental procedures, compound characterization, X-ray data (CIF), and CSI mass spectral chart. This material is available free of charge via the Internet at http://pubs.acs.org.

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