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A Catalytic Enantioselective Reaction Using a C_2-Symmetric Disulfonamide as a Chiral Ligand: Cyclopropanation of Allylic Alcohols by the Et_2Zn-CH_2I_2-Disulfonamide System

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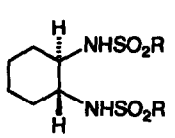
Key Words: cyclopropanation; Simmons-Smith reaction; chiral Lewis acid; enantioselective reaction; disulfonamide;

Abstract: *The first catalytic, enantioselective Simmons-Smith cyclopropanation of an allylic alcohol has been achieved by the reaction of an allylic alcohol with Et_2Zn and CH_2I_2 in the presence of a catalytic amount of chiral disulfonamide* ***1****.*

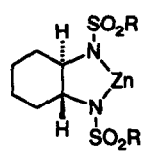
The development of catalytic, enantioselective reactions is at present one of the most important and challenging topics in organic synthesis. As one approach to solve this problem, we and Corey have independently demonstrated the potential utility of Lewis acid catalysts modified by electron-withdrawing chiral disulfonamides.[2] We now report the first catalytic, enantioselective Simmons-Smith cyclopropanation[3] of disubstituted allylic alcohols by the disulfonamide-Et_2Zn-CH_2I_2 system.

Among the various types of catalytic, enantioselective reaction investigated, cyclopropanation has attracted continued and increasing attention since the pioneering work by Nozaki in 1966,[4] and, indeed, reactions catalyzed by bis(oxazoline)copper complexes were reported recently by two groups.[5] However, the carben sources employed in previous studies have been limited to diazoacetate derivatives, and to our knowledge, there have been no examples using the Simmons-Smith type of reagent.[6] It is known that the Simmons-Smith reaction of an allylic alcohol or its ether derivative proceeds much faster than that of a simple olefin.[7] This enhancement of reactivity is attributed to the strong affinity between the organozinc reagent and the oxygen atom.[8] Further, it has also been reported that the addition of catalytic amounts of $TiCl_4$ facilitates the Simmons-Smith reaction.[9] Based on these facts, we became interested in examining the Simmons-Smith reaction of an allyl alcohol derivative in the presence of a sulfonamide-modified Lewis acid catalyst. The chiral Lewis acid catalysts used in the present study are the zinc complexes **2**, prepared *in situ* from chiral disulfonamides **1** and diethylzinc.

Scheme 1



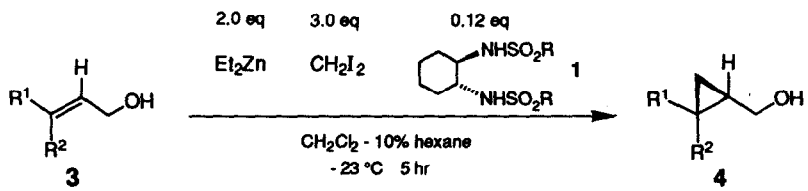
1: **a**: R = C_6H_5; **b**: R = *o*-O_2N-C_6H_4;
c: R = *m*-O_2N-C_6H_4; **d**: R = *p*-O_2N-C_6H_4



2

When cinnamyl alcohol **3a** was treated with Et_2Zn (2.0 equiv), CH_2I_2 (3.0 equiv), and disulfonamide **1a** (0.12 equiv) in CH_2Cl_2 at -23°C, the corresponding cyclopropane **4a** was isolated in 75% yield with 68% e.e. (entry 1). Enantiomeric excess was directly determined by HPLC analysis,[10] and the absolute stereochemistry of the major isomer was assigned as shown by comparison of specific rotation values with those in the literature.[11] It was also found that, under the same conditions, the cyclopropanation of **3a** proceeds faster using the *o*-nitro derivative **1b** affording **4a** in 92% yield with 75% e.e. (entry 2), and that the reaction is rather slow without any **1** (CH_2Cl_2, -23°C, 5hr, ~20% yield). Further, cyclopropanation did not proceed in ethereal solvents such as Et_2O or THF. These results clearly suggest that the chiral zinc complex **2** facilitates the reaction through its Lewis acid character, which, in turn, is attained through substitution with electron-withdrawing sulfonamide ligands.

Table 1



entry	allyl alcohol 3	R^1	R^2	disulfonamide 1	cyclopropane 4 yield(%)	e.e.(%)
1	**3a**	Ph	H	**1a**	75	68
2				**1b**	92	75
3				**1c**	72	33
4				**1d**	82	76
5	**3b**	H	Ph	**1b**	82	51
6				**1c**	71	31
7				**1d**	71	75
8	**3c**	$PhCH_2CH_2$	H	**1b**	82	80
9				**1d**	quant	82
10	**3d**	$BzlOCH_2$	H	**1d**	70	36
11	**3e**	$TrtOCH_2$	H	**1d**	86	80
12	**3f**	H	$BzlOCH_2$	**1d**	36*	13
13	**3g**	H	$TrtOCH_2$	**1d**	79	66

* The yield after 17 hr. **3f** was recovered in about 60% yield.

The reaction of allyl alcohols **3a~3c** with Et_2Zn and CH_2I_2 in the presence of differently substituted nitrobenzene sulfonamides, **1b~1d**, was then examined in detail. The corresponding cyclopropanes, **4a**, **4b**,[10,11] and **4c**,[10,12] were isolated in good to excellent yields (entry 2~9).[13] As can also be seen from the data in Table 1, a higher enantiomeric excess was obtained with the *p*-isomer **1d**. The *o*-isomer **1b** showed similar selectivity to **1d** in the case of *E*-olefins (entry 2 *vs* 4, and entry 8 *vs* 9), while low selectivity was observed with the *m*-isomer **1c**.

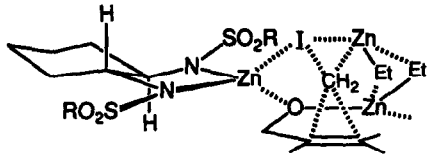
Another intriguing result is that while cinnamyl methyl ether also underwent cyclopropanation under similar conditions, it affords the corresponding cyclopropane as an almost racemic mixture. Therefore, the free hydroxyl group is necessary for producing an effective chiral environment probably through complexation as a zinc alkoxide. In this context, we were interested in examining the cyclopropanation of 2-butene-1,4-diol derivatives

3d~3g which contain both a hydroxyl group and an alkoxyl group at the allylic positions. As shown in Table 1 (entry 10~13[13]), higher enantioselectivity was obtained with the trityl derivative than the benzyl derivative. It may be that a competitive and less-selective ether-directed pathway is suppressed in the case of the trityl derivative due to steric interaction.

Further, it is also important to note that upon use of a given enantiomer of **1** the cyclopropanation occurs from the same enantioface of the olefin regardless of its geometry.

Although we do not have any experimental evidence as to how the chiral zinc complex **2** participates in the transition state, we assume that both the oxygen atom of a zinc alkoxide and iodine atom of iodometylzinc coordinate to the Lewis acid character possessing chiral zinc complex **2** as shown in Scheme 2.

Scheme 2



The formation of such a trinuclear complex might well accounts for the big difference in an enantioselectivity between the allylic alcohol and its methyl ether. Further, coordination between zinc atom of **2** and iodine atom might responsible for the remarkable rate acceleration[15] as well as an efficient catalytic turn over of the chiral catalyst **2**.

The representative procedure is as follows: To a solution of **1d** (354 mg, 0.73 mmol, 12 mol%) and *trans*-5-phenyl-2-penten-1-ol **3c** (988 mg, 6.1 mmol) in 200 mL of anhydrous CH_2Cl_2 was added a hexane solution of Et_2Zn (0.98 M, 12.4 mL, 12.2 mmol) and CH_2I_2 (4.89 g, 18.3 mmol) in 20 mL of CH_2Cl_2 at -23°C. The reaction mixture was stirred at that temperature for 5 h, then 40 mL of 2*N* NaOH solution was added, and the product was extracted with Et_2O. The organic phase was washed with sat.NaCl solution, dried over anhydrous Na_2SO_4, and condensed under reduced pressure. The residue was chromatographed on silica gel (AcOEt/n-hexane=1/4) to afford **4c** as a colorless oil (1.06 g, quant). The sulfonamide **1d** was recovered quantitatively from the combined aqueous solution after being acidified with HCl solution.

Extension of this new method to other allylic alcohols and efforts to improve the enantiomeric excesses, as well as a mechanistic study, are now under investigation.[16]

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10. Daicel chiral column OJ. Eluent systems: **4a** and **4b**; 2% *i*-PrOH in hexane. **4c**; 0.1% *i*-PrOH in hexane.
11. **4a**: $[\alpha]_D^{21}$ -56.2°(*c* 0.60, EtOH); lit., $[\alpha]_D^{?}$ -46.6°(*c* 2.64, EtOH) for **4a** with 75% e.e. Sugita, T.; Inoue, Y. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 1075-1076. **4b**: $[\alpha]_D^{23}$ -41.1°(*c* 1.42, $CHCl_3$); lit., $[\alpha]_D^{29}$ +39° (*c* 2.42, $CHCl_3$) for *ent*-**3b** with 50% e.e. Aratani, T.; Nakanishi, Y.; Nozaki, H. *Tetrahedron* **1970**, *26*, 1675-1684.
12. The absolute stereochemistry of **4c** was determined after transformation to the known (1*R*,2*R*)-1,2-bis-(hydroxymethyl)cyclopropane by the following sequence of reactions; (i) PhCOCl/pyridine, (ii) NBS, cat.AIBN/CCl_4, (iii) PhSeNa/EtOH, (iv) 30% H_2O_2/THF, (v) O_3/MeOH, then $NaBH_4$/MeOH. $[\alpha]_D^{26}$ -9.3°(*c* 0.78, EtOH): lit., $[\alpha]_D^{22}$ -3.2°(*c* 8.0, EtOH) as 9% e.e. Inoue, Y.; Sugita, T.; Walborsky, H. M. *Tetrahedron* **1964**, *20*, 1695-1699.
13. The enantiomeric excesses of **4d~4g** were determined by HPLC analysis. Chiral column and eluent systems used are as follows: **4d** and **4f**; Daicel OJ (2% *i*-PrOH in hexane). **4e** and **4g**; Daicel OD (2% *i*-PrOH in hexane). The absolute stereochemistry of **4d~4g** was determined as follows. **4e**, $[\alpha]_D^{25}$ -7.4° (*c* 1.57, $CHCl_3$) as 80% e.e., was correlated to (1*R*,2*R*)-1,2-bis(hydroxymethyl)cyclopropane[12], $[\alpha]_D^{25}$ -12.9°(*c* 1.37, EtOH), by detritylation (HCl/MeOH). **4g**, $[\alpha]_D^{25}$ -64.5°(*c* 0.93, $CHCl_3$) as 66% e.e., was correlated to *ent*-**4e**, $[\alpha]_D^{25}$ +9.6°(*c* 0.77, $CHCl_3$), by three steps; (i) PCC/CH_2Cl_2, (ii) NaOMe,[14] (iii) $NaBH_4$/EtOH. The absolute stereochemistry of **4d** was determined by comparing the $[\alpha]_D$ value, $[\alpha]_D^{25}$ -2.7°(*c* 0.53, $CHCl_3$) as 23% e.e., with that of an authentic sample, $[\alpha]_D^{25}$ -9.3°(*c* 0.70, $CHCl_3$), derived from stereochemically established **4e**, $[\alpha]_D^{25}$ -7.3°(*c* 2.52, $CHCl_3$) as 69% e.e.; (i) NaH, BzlBr/DMF, (ii) HCl/MeOH. The absolute stereochemistry of **4f** was determined by comparing the $[\alpha]_D$ value, $[\alpha]_D^{25}$ -4.0°(*c* 1.05, $CHCl_3$) as 13% e.e., with that of *ent*-**4f**, $[\alpha]_D^{25}$ +32.1°(*c* 1.02, $CHCl_3$) as 65% e.e., prepared from **4g**, $[\alpha]_D^{25}$ -67.0°(*c* 1.69, $CHCl_3$) as 65% e.e., by two steps; (i) NaH, BzlBr/DMF, (ii) HCl/MeOH.
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