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Enantioselective Construction of Cyclopropane Rings *via* Asymmetric Simmons-Smith Reaction of Allylic Alcohols

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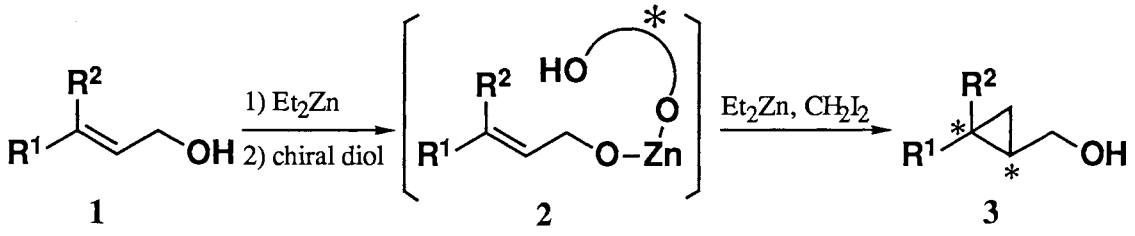
The Simmons-Smith reaction starting from allylic alcohols using (*R,R*)-diethyl tartrate as a chiral auxiliary was found to proceed enantioselectively; *i.e.*, the treatment of allylic alcohols with diethylzinc and diethyl tartrate, followed by the reaction with diethylzinc and diiodomethane, afforded the corresponding cyclopropylmethyl alcohols in optically active form.

The cyclopropane structural unit is found as a basic structural element in a wide range of naturally occurring substances in plants and microorganism, both fungal and bacterial, and the formation of the cyclopropane ring in optically active form has been strongly required for more detailed biological and biochemical investigations.[1] Recently, useful methods for preparing optically active cyclopropanes have been reported. The Simmons-Smith reactions[2] of olefins possessing chiral auxiliaries were reported to give cyclopropanes with high stereoselectivity, but it was still necessary to introduce and remove chiral auxiliaries.[3] The reactions between diazoacetic acid esters and olefins in the presence of chiral metal-catalysts are also efficient methods to produce optically active cyclopropanes. Although these methods provide *trans*-cyclopropanes with high enantioselectivity, it is difficult to synthesize *cis*-cyclopropanes stereoselectively.[4,5] In this paper, we would like to describe an enantioselective construction of cyclopropane rings by the asymmetric Simmons-Smith reaction starting from achiral allylic alcohols.

The present asymmetric cyclopropanation of allylic alcohol was studied based on the following hypothesis. When diethylzinc is treated with allylic alcohol **1** followed by a chiral diol as a chiral auxiliary, the zinc-bridging intermediate **2** would be formed. By the subsequent treatment with diethylzinc and diiodomethane, cyclopropanation would be expected to proceed in a stereoselective manner directed by the hydroxyl group in the chiral diol[6] to furnish the corresponding cyclopropylmethyl alcohol **3** in optically active form. By the above hypothesis, the asymmetric Simmons-Smith reaction was investigated utilizing the chiral diol with a C_2 symmetry axis.



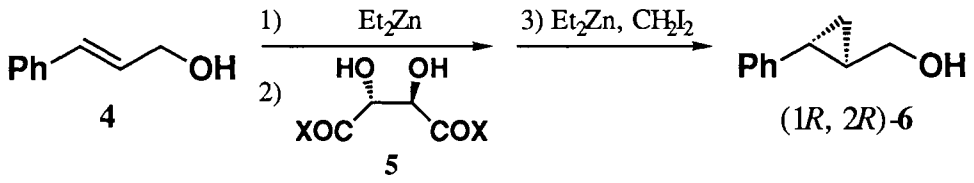
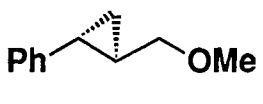


Table 1. The Simmons-Smith reaction of *trans*-3-phenyl-2-propen-1-ol (**4**) using (*R,R*)-tartaric acid derivatives **5**

Entry	X in **5**	Solvent	Temp/°C	Yield/%	$[\alpha]_D^{23}$ a)	Optical yield/% ee
1	OEt	DME	0 - rt	39	-13°	15b)
2		$PhCH_3$	0 - rt	55	-35°	39b)
3		CH_2Cl_2	0 - rt	22	-46°	50b)
4		CCl_4	0 - rt	28	-45°	49b)
5		$ClCH_2CH_2Cl$	0 - rt	13	-60°	66b) 64c)
6		$ClCH_2CH_2Cl$	-12	54	-72°	79b) 71c)
7	OMe	CH_2Cl_2	0 - rt	12	-58°	64b)
8		$ClCH_2CH_2Cl$	0 - rt	52	-21°	23b)
9	O^iPr	CH_2Cl_2	0 - rt	24	-24°	27b)
10	O^nBu	CH_2Cl_2	0 - rt	17	-52°	58b)
11	1-pyrrolidinyl	CH_2Cl_2	0 - rt	69	+12°	13b,d)

a) $[\alpha]_D^{23}$ was measured in EtOH (c 0.4 - 2.1). b) Optical yield was calculated based on $[\alpha]_D^{23}$ in comparison with the datum of Ref. 7. c) Optical yield was determined by the conversion to the MTPA ester followed by ^1H NMR analysis in the presence of $Eu(fod)_3$. d) (*1S,2S*)-**6** was mainly obtained.

Firstly (*R,R*)-tartaric acid derivatives **5** were chosen as chiral auxiliaries[8] and the cyclopropanation of *trans*-3-phenyl-2-propen-1-ol (**4**) in several solvents was examined. As listed in the Table 1, when (+)-(*R,R*)-diethyl tartrate ((+)-DET) was used, DME and toluene were not so effective for this reaction (entries 1 and 2). Switching to halogenated solvents, especially 1,2-dichloroethane, was found to improve the selectivity (entries 3-5). Among the esters of (*R,R*)-tartaric acid such as methyl, ethyl, isopropyl, and butyl esters, ethyl ester gave (*1R,2R*)-**6** in higher optical yields (entries 3-5, 7-10). It was noted that, using tartramide derived from pyrrolidine, the opposite enantiomer (*1S,2S*)-**6** was mainly obtained (entry 11). In the reaction of the allylic alcohol **4** using (+)-DET in 1,2-dichloroethane (entry 5), the corresponding methyl ether **7** ($[\alpha]_D^{23}$ -62° (c 0.6, EtOH)) (21%) and a formaldehyde acetal **8** ($[\alpha]_D^{23}$ -71° (c 1.1, EtOH)) (34%) were obtained in addition to cyclopropylmethyl alcohol **6**. From their specific rotations,[9] it was found that cyclopropanation itself



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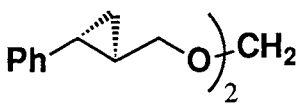

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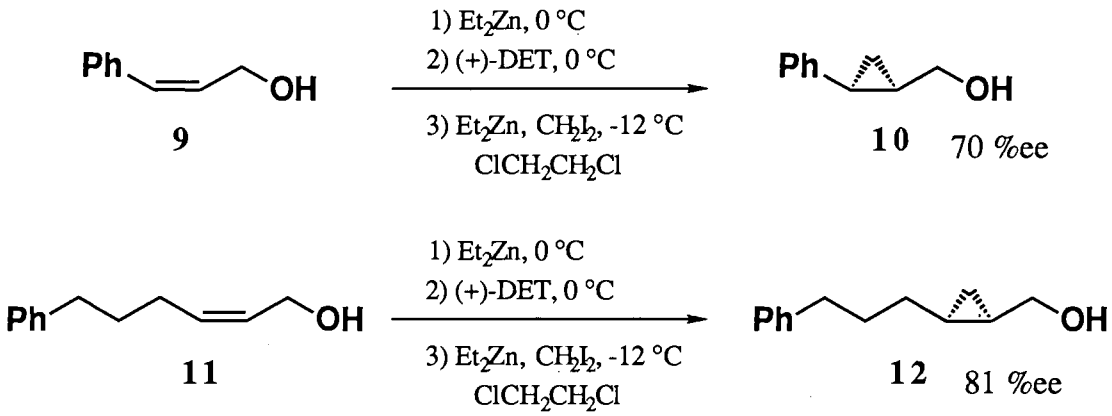
proceeded enantioselectively. In order to suppress the side reactions and enhance the stereoselectivity, the reaction was carried out at lower temperature. As shown in entry 6, when the reaction was conducted at -12 °C, (*1R,2R*)-cyclopropylmethyl alcohol **6** was obtained in enhanced yield and higher optical yield was achieved.

Next, this enantioselective Simmons-Smith reaction was applied to acyclic *cis*-allylic alcohols in order to synthesize optically active *cis*-cyclopropanes, which are difficult to be obtained by other methods. The cyclopropanation reaction of *cis*-3-phenyl-2-propen-1-ol (**9**) using (+)-DET at -12 °C gave the *cis*-cyclopropane **10** ($[\alpha]_D^{23}$ -52° (c 1.3, EtOH)) (60%, 70% ee[10]). Furthermore, the reaction of *cis*-6-phenyl-2-hexen-1-ol (**11**) proceeded in a highly stereoselective manner to afford the corresponding *cis*-cyclopropane **12** ($[\alpha]_D^{23}$ +19° (c 0.7, EtOH)) (46%, 81% ee[10]).

The absolute configuration of **6** was determined by the comparison of its specific rotation value with that reported.[7] *cis*-Cyclopropane **10**, obtained as described above, was converted to the corresponding carboxylic acid methyl ester [1) $KMnO_4$,[11] 2) CH_2N_2] and its absolute configuration was determined to be *1R,2S* form by its specific rotation ($[\alpha]_D^{23}$ -40° (c 0.2, 95% EtOH), lit.[12] (*1R,2S*); $[\alpha]_D^{25}$ -51.0° (c 1.74, 95% EtOH)).



The representative procedure for the enantioselective Simmons-Smith reaction is as follows: To a 1,2-dichloroethane (3 ml) solution of *cis*-6-phenyl-2-hexen-1-ol (91 mg, 0.51 mmol) was added diethylzinc (0.57 mmol, 0.25 ml in hexane) at 0 °C under an argon atmosphere, and the mixture was stirred for 15 min. To the solution, a 1,2-dichloroethane (3 ml) solution of (+)-DET (119 mg, 0.57 mmol) was added and the mixture was stirred for 1 h. After the solution was cooled to -12 °C, diethylzinc (1.03 mmol, 0.51 ml in hexane), followed by diiodomethane (0.17 ml, 2.06 mmol) after 10 min, was added and the reaction mixture was stirred for 43 h. The reaction was quenched with sat. aq NH_4Cl. Extraction with CH_2Cl_2 and evaporation of the solvent gave the crude product containing (+)-DET and a small amount of unreacted allylic alcohol, which made it difficult to purify the product. In order to make purification much easier, the conversion of unreacted allylic alcohol to the corresponding epoxide by *m*-chloroperbenzoic acid (185 mg) in CH_2Cl_2 for 3 h, extraction, evaporation, and the successive saponification of (+)-DET with 2 mol dm^{-3} NaOH were performed. After the extraction with CH_2Cl_2 and the evaporation of the solvent, purification by TLC on silica gel finally afforded *cis*-1-hydroxymethyl-2-(3-phenyl-propyl)cyclopropane (45 mg, 46%) in 81% ee.

As mentioned above, the enantioselective construction of cyclopropane rings was developed starting from achiral allylic alcohols. This method has some merits to be commented; 1) introduction of the chiral auxiliary to the substrate and its removal were not necessary; 2) both *trans*- and *cis*-cyclopropane rings could be prepared starting from *trans*- and *cis*-allylic alcohols, respectively; 3) because of easy availability of (*R,R*)- and (*S,S*)-

diethyl tartrates, both enantiomers of cyclopropylmethyl alcohols could be synthesized. Thus, this method provides one of the useful examples to prepare optically active cyclopropanes.

References

1) a) C. J. Suckling, *Angew. Chem., Int. Ed. Engl.*, **27**, 537 (1988); b) H. N. C. Wong, M.-Y. Hon, C.-W. Tse, Y.-C. Yip, J. Tanko, and T. Hudlicky, *Chem. Rev.*, **89**, 165 (1989); c) J. Salaün, *ibid.*, **89**, 1247 (1989).

2) a) H. E. Simmons, T. L. Cairns, S. A. Vladuchick, and C. M. Hoiness, *Org. React.*, **20**, 1 (1973); b) J. Furukawa, N. Kawabata, and J. Nishimura, *Tetrahedron*, **24**, 53 (1968); c) S. E. Denmark, J. P. Edwards, and S. R. Wilson, *J. Am. Chem. Soc.*, **113**, 723 (1991).

3) a) A. Mori, I. Arai, and H. Yamamoto, *Tetrahedron*, **42**, 6447 (1986); b) E. A. Mash, and D. S. Torok, *J. Org. Chem.*, **54**, 250 (1989); c) T. Imai, H. Mineta, and S. Nishida, *ibid.*, **55**, 4986 (1990); d) T. Sugimura, M. Yoshikawa, T. Futagawa, and A. Tai, *Tetrahedron*, **46**, 5955 (1990); e) M. P. Frutos, M. D. Fernández, E. F.-Alvarez, and M. Bernabé, *Tetrahedron Lett.*, **32**, 541 (1991).

4) H. Nozaki, H. Takaya, S. Moriuti, and R. Noyori, *Tetrahedron*, **24**, 3655 (1968); A. Nakamura, A. Konishi, Y. Tatsuno, and S. Otsuka, *J. Am. Chem. Soc.*, **100**, 3443 (1978); T. Aratani, *Pure Appl. Chem.*, **57**, 1839 (1985); R. E. Lowenthal, A. Abiko, and S. Masamune, *Tetrahedron Lett.*, **31**, 6005 (1990); D. A. Evans, K. A. Woerpel, M. M. Hinman, and M. M. Faul, *J. Am. Chem. Soc.*, **113**, 726 (1991); D. Müller, G. Umbricht, B. Weber, and A. Pfaltz, *Helv. Chim. Acta*, **74**, 232 (1991) and references cited therein.

5) Other methods to prepare optically active cyclopropanes; C. R. Johnson and M. R. Barbachyn, *J. Am. Chem. Soc.*, **104**, 4290 (1982); G. Quinkert, H.-G. Schmalz, E. M. Dzierzynski, G. Dürner, and J. W. Batz, *Angew. Chem., Int. Ed. Engl.*, **25**, 992 (1986); Y. Gao and K. B. Sharpless, *J. Am. Chem. Soc.*, **110**, 7538 (1988); D. Romo, J. L. Romine, W. Midura, and A. I. Meyers, *Tetrahedron*, **46**, 4951 (1990); M. Brookhart, Y. Liu, E. W. Goldman, D. A. Timmers, and G. D. Williams, *J. Am. Chem. Soc.*, **113**, 927 (1991) and see also Ref. 1c.

6) Cyclopropanations directed by the hydroxyl group were reported: C. D. Poulter, E. C. Friedrich, and S. Winstein, *J. Am. Chem. Soc.*, **91**, 6892 (1969); G. A. Molander and L. S. Harring, *J. Org. Chem.*, **54**, 3525 (1989) and see also Refs. 2a and 3d.

7) The reduction of methyl (*1R,2R*)-2-phenylcyclopropanecarboxylate (51.3% ee) with $LiAlH_4$ was reported to give (-)-**6** ($[\alpha]_D^{12}$ -46.6° (c 2.640, EtOH)); T. Sugita and Y. Inouye, *Bull. Chem. Soc. Jpn.*, **39**, 1075 (1966).

8) The asymmetric oxidation of allylic alcohols using diethyl tartrate was known as Sharpless oxidation: M. G. Finn and K. B. Sharpless, "Asymmetric Synthesis," ed by J. D. Morrison, Academic Press, New York (1985), Vol. 5, pp. 247-348.

9) The etherification of the alcohol **6** ($[\alpha]_D^{23}$ -35° (c 1.8, EtOH)) by NaH and MeI gave the corresponding methyl ether **7** ($[\alpha]_D^{23}$ -40° (c 1.6, EtOH)).

10) Optical yield was determined by the conversion to the MTPA ester followed by ^{1}HNMR analysis in the presence of $Eu(fod)_3$.

11) H. E. Zimmerman and J. English, Jr., *J. Am. Chem. Soc.*, **76**, 2285 (1954).

12) P. E. Krieger and J. A. Landgrebe, *J. Org. Chem.*, **43**, 4447 (1978).

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