Design of Amphoteric Bifunctional Ligands: Application to the Enantioselective Simmons–Smith Cyclopropanation of Allylic Alcohols

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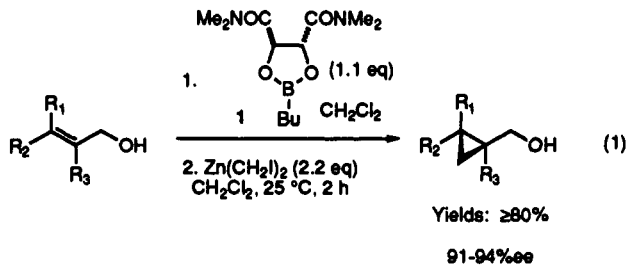
Received November 18, 1993

Although the Simmons–Smith cyclopropanation reaction is one of the most widely used methods to generate cyclopropanes,[2] an efficient chiral version (>90% ee) that avoids the use of covalently bonded chiral auxiliaries[3] has yet to appear in the literature.[4] We report herein that a simple amphoteric bifunctional ligand[5] derived from (*R,R*)-(+)-*N,N,N′,N′*-tetramethyltartaric acid diamide can be used as an efficient chiral controller for the Simmons–Smith cyclopropanation reaction of allylic alcohols to produce substituted cyclopropylmethanols in high enantiomeric excesses.

It was anticipated that a bifunctional, chiral, nonracemic ligand containing both an acidic and a basic site would allow simultaneous chelation of the acidic Simmons–Smith reagent[6] and the basic allylic alcohol or its corresponding metal alkoxide. If the topology of the ligand is carefully chosen, the subsequent pseudo intramolecular delivery should proceed with high enantioselectivity.

The most efficient chiral controller we have surveyed thus far is the dioxaborolane **1** prepared from commercially available

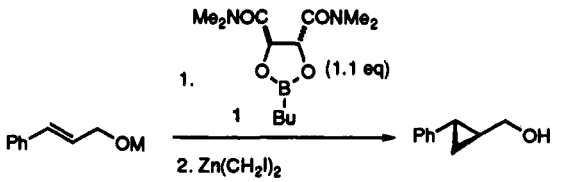


(1)

(*R,R*)-(+)-*N,N,N′,N′*-tetramethyltartaric acid diamide[7] and butylboronic acid (refluxing toluene, Dean–Stark) (eq 1). The effect of the nature of the metal alkoxide derived from cinnamyl alcohol on the yield and the enantioselectivity of the cyclopropane product is illustrated in Table 1. The yield of the desired product is good in all cases, and none of the methylated allyl alcohol was observed.[8] All the reactions were performed by adding a mixture of cinnamyl alcohol (or its corresponding metal alkoxide) and dioxaborolane **1** in CH_2Cl_2 to a preformed suspension of bis(iodomethyl)zinc at 0 °C (to room temperature). A number of metal alkoxides were surveyed, and potassium was found to be optimal (entry 3) [KH (1 equiv), ROH (1 equiv), Et_2O, followed by evaporation of Et_2O and addition of CH_2Cl_2)]. It was then established that adding a solution of the alcohol and dioxaborolane **1** to a preformed suspension of the reagent is as effective as using the potassium alkoxide and is much more convenient experimentally (entry 6). Although excellent results were obtained in a number of noncoordinating solvents, CH_2Cl_2 was found to be the most convenient and practical solvent (entries 6–11). It is also important to point out that quantitative yields were obtained in less than 2 h at room temperature. Lowering the reaction temperature had no effect on the level of stereochemical induction (entries 12, 13). The use of 2 equiv of the reagent appears to be optimal to obtain a quantitative yield of the cyclopropanation product (entry 14). Initial conversion of the alcohol into an (iodomethyl)zinc alkoxide seems to occur[9] since cyclopropanation of the methyl or triisopropylsilyl ether of cinnamyl alcohol in the presence of the chiral ligand afforded racemic material.

The dioxaborolane chiral ligand proved to be extremely effective with several types of substituted allylic alcohols. The scope of

Table 1. Effect of the Metal Alkoxide on the Enantioselectivity[a]



entry	M	$Zn(CH_2I)_2$ (eq)	solvent	enantioselectivity[b,c]
1	Li	5	CH_2Cl_2	17.1:1
2	Na	5	CH_2Cl_2	3.8:1
3	K	5	CH_2Cl_2	22:1
4	MgBr	5	CH_2Cl_2	2:1
5	ZnEt	5	CH_2Cl_2	12:1
6	H	5	CH_2Cl_2	26:1
7	H	5	toluene	26:1
8	H	5	$(ClCH_2)_2$	20:1
9	H	5	*t*-BuOMe	16.6:1
10	H	5	ether	7.8:1
11	H	5	DME	9.7:1
12	H	2.2	CH_2Cl_2	29:1
13	H	2.2	CH_2Cl_2 (0 °C)	26:1
14	H	1.0	CH_2Cl_2	29:1 (85%)[d]

[a] Unless otherwise noted, all the reactions were carried out at room temperature for 2 h. The reagent was formed at 0 °C and then warmed to room temperature after the addition of the substrate and ligand. See supplementary material for experimental details. [b] The enantioselectivity was determined by capillary gas chromatographic analysis of the crude reaction mixture after trifluoroacetylation (chiral column: Chiraldex G-TA, 110 °C). [c] Unless otherwise stated, the yields were >95%. [d] The remaining material was the unreacted starting material.

(1) NSERC (Canada) University Research Fellow, 1989–1998; Bio-Méga Young Investigator, 1991–1993.

(2) (a) Simmons, H. E.; Cairns, T. L.; Vladuchick, S. A.; Hoiness, C. M. *Org. React.* (N.Y.) **1973**, *20*, 1–131. (b) Zeller, K.-P.; Gugel, H. In *Houben-Weyl; Methoden der Organischen Chemie*; Regitz, M.; Ed.; Georg Thieme Verlag: Stuttgart, 1989; Band EXIXb, pp 195–212. (c) Denmark, S. E.; Edwards, J. P.; Wilson, S. R. *J. Am. Chem. Soc.* **1992**, *114*, 2592–2602.

(3) For chiral auxiliaries in asymmetric Simmons–Smith, see the following. Chiral acetals: (a) Charette, A. B.; Côté, B.; Marcoux, J.-F. *J. Am. Chem. Soc.* **1991**, *113*, 8166–8167. (b) Charette, A. B.; Marcoux, J.-F. *Tetrahedron Lett.* **1993**, *34*, 7157–7160. (c) Charette, A. B.; Turcotte, N.; Marcoux, J.-F. *Tetrahedron Lett.*, in press. (d) Mori, A.; Arai, I.; Yamamoto, H. *Tetrahedron* **1986**, *42*, 6447–6458. (e) Mash, E. A.; Hemperly, S. B.; Nelson, K. A.; Heidt, P. C.; Van Deusen, S. *J. Org. Chem.* **1990**, *55*, 2045–2055. Mash, E. A.; Hemperly, S. B. *J. Org. Chem.* **1990**, *55*, 2055–2060. (f) Mash, E. A.; Nelson, K. A. *Tetrahedron* **1987**, *43*, 679–692. (g) Arai, I.; Mori, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 8254–8256. (h) Mash, E. A.; Nelson, K. A. *J. Am. Chem. Soc.* **1985**, *107*, 8256–8258. Chiral diols: (i) Sugimura, T.; Yoshikawa, M.; Futagawa, T.; Tai, A. *Tetrahedron* **1990**, *46*, 5955–5966. (j) Sugimura, T.; Futagawa, T.; Yoshikawa, M.; Tai, A. *Tetrahedron Lett.* **1989**, *30*, 3807–3810. (k) Sugimura, T.; Futagawa, T.; Tai, A. *Tetrahedron Lett.* **1988**, *29*, 5775–5778. Chiral acyl iron complexes: (l) Ambler, P. W.; Davies, S. G. *Tetrahedron Lett.* **1988**, *29*, 6979–6982. (m) Ambler, P. W.; Davies, S. G. *Tetrahedron Lett.* **1988**, *29*, 6983–6984. Chiral boronic esters: (n) Imai, T.; Mineta, H.; Nishida, S. *J. Org. Chem.* **1990**, *55*, 4986–4988.

(4) For the use of chiral ligands in the Simmons–Smith cyclopropanation see: (a) Ukaji, Y.; Sada, K.; Inomata, K. *Chem. Lett.* **1993**, 1227–1230. (b) Ukaji, Y.; Nishimura, M.; Fujisawa, T. *Chem. Lett.* **1992**, 61–64. (c) Takahashi, H.; Yoshioka, M.; Ohno, M.; Kobayashi, S. *Tetrahedron Lett.* **1992**, *33*, 2575–2578. (d) Denmark, S. E.; Edwards, J. P. *Synlett* **1992**, 229–230.

(5) This concept has been used in the design of heterotopic host molecules: Reetz, M. T.; Niemeyer, C. M.; Harms, K. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1472–1474.

(6) For a review on directed Simmons–Smith cyclopropanation, see: (a) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370. (b) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860.

(7) Both enantiomers of the tartramide can easily be prepared using Seebach's procedure (580 g scale): Seebach, D.; Kalinowski, H.-O.; Langer, W.; Crass, G.; Wilka, E.-M. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, pp 41–50.

(8) For an improved procedure for the cyclopropanation of simple allylic alcohols, see: Denmark, S. E.; Edwards, J. P. *J. Org. Chem.* **1991**, *56*, 6974–6981.

(9) Rapid formation of CH_3I is observed by 400-MHz ^1H NMR when an alcohol is mixed with $Zn(CH_2I)_2$: Charette, A. B.; Côté, B. Unpublished results.

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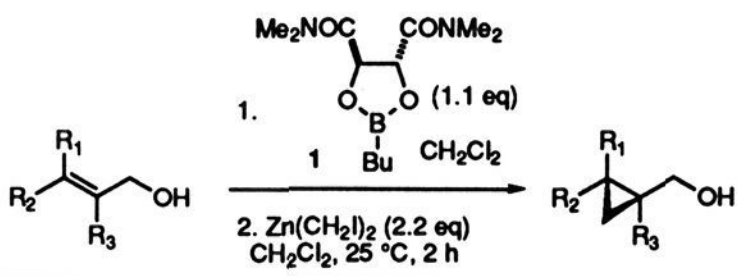
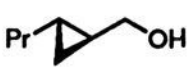
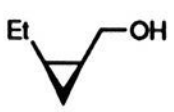
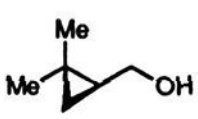
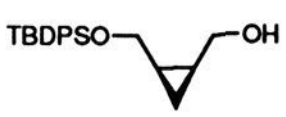
Table 2. Cyclopropanation of Substituted Allylic Alcohols



Entry	Product[a]	Yield[b]	Enantioselectivity
1		>98%	29 : 1 (93% ee)[c]
2		80%	27 : 1 (93% ee)[d]
3		90%	29 : 1 (93% ee)[e]
4		85%	32 : 1 (94% ee)[e]
5		80%	21 : 1 (91% ee)[e]

[a] The absolute stereochemistry was established for entries 1, 4, and 5 by comparing the sign of the optical rotation with literature data. [b] Isolated yields. Due to the volatility of the products of entries 3 and 4, the crude alcohols were converted into benzoates. [c] Determined by capillary GC analysis of the crude reaction mixture after trifluoroacetylation (chiral column: Chiraldex, G-TA, 110 °C). [d] Determined by ^{19}F NMR of Mosher's ester. [e] Determined by 400-MHz ^1H NMR of Mosher's ester.

the reaction is very broad, and high enantioselectivities are obtained with *trans*-substituted, *cis*-substituted, and trisubstituted olefins (Table 2). Furthermore, the chiral ligand can easily be removed and recovered (>80%) by a simple aqueous extraction of the organic layer after the reaction.

The presence of basic groups on the ligand is crucial for obtaining high enantioselectivities. The cyclopropanation of cinnamyl alcohol in the presence of the dioxaborolane derived from (*S*,*S*)-(–)-1,2-diphenyl-1,2-ethanediol led to racemic material. For stereoelectronic and steric reasons, it is postulated that the allylic alkoxide adopts the more stable pseudoaxial configuration[10] and that the cyclopropanation occurs via the formation of a bidentate chelate[2c] between the reagent and the substrate (Figure 1).[11] The complex is believed to involve the carbonyl oxygen of one of the amide groups (complexation *anti* to the C–NMe_2 amide bond) and the allylic oxygen. These two groups can efficiently direct the Simmons–Smith cyclopropanation reaction of olefins.[6,12]

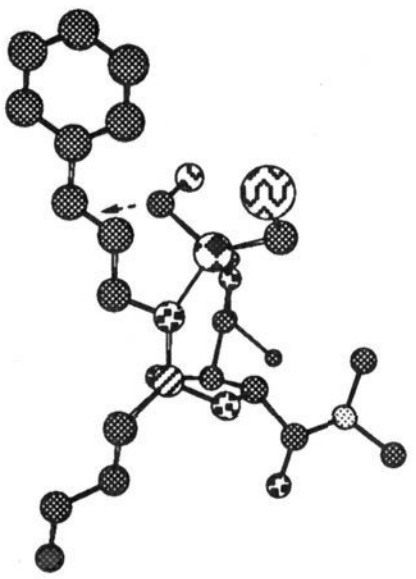


Figure 1.

In conclusion, dioxaborolane **1** is currently the most efficient chiral ligand for the enantioselective Simmons–Smith cyclopropanation reaction of substituted allylic alcohols. The application of this methodology to more complex allylic alcohols as well as mechanistic work are in progress and will be reported in due course.

Acknowledgment. This research was supported by the Natural Science and Engineering Research Council (NSERC) of Canada, FCAR (Québec), Merck Frosst Canada, Bio-Méga/Boehringer Ingelheim Recherche Inc., and the Université de Montréal. H.J. thanks the NSERC for a postgraduate fellowship.

Supplementary Material Available: Full details for the synthesis of **1**, the cyclopropanation reactions, the determination of the enantiomeric excesses, and the spectroscopic data of reaction products (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(10) For the X-ray structure determination of dioxaborolane complexes, see: (a) Reetz, M. T.; Niemeyer, C. M.; Harms, K. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1474–1476. (b) Paetzold, P.; Bohm, P.; Richter, A.; Scholl, E. *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **1976**, *31*, 754–764.

(11) A similar bidentate complex between the substrate and the $Zn(CH_2I)_2$ reagent[2c] is thought to be responsible for the high diastereoselection observed when the allylic alcohol is covalently linked to the carbohydrate- or to the cyclohexanediol-derived chiral auxiliary.[3a–c]

(12) Charette, A. B.; Prescott, S.; Marcoux, J.-F. Manuscript in preparation.