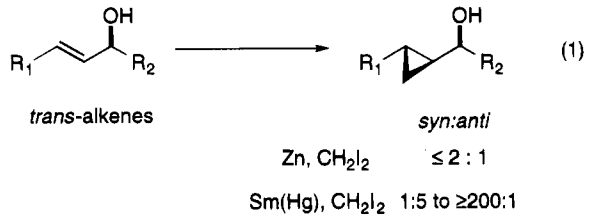
Diastereoselective Cyclopropanation of Chiral Allylic Alcohols: A More Efficient Reagent for the Relative Stereocontrol

André B. Charette* and Hélène Lebel

Département de Chimie, Université de Montréal, Québec, Canada H3C 3J7

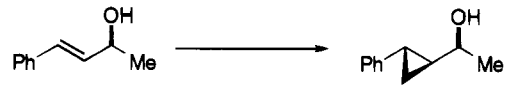
Received December 29, 1994

Since the recognition that acyclic stereocontrol was an efficient strategy for the generation of new stereogenic centers, high levels of stereochemical induction have been observed in a number of addition reactions to chiral allylic alcohols.[1] Conversely, a wide range of diastereoselectivities has been reported in the cyclopropanation reactions of chiral acyclic allylic alcohols. In 1978, Pereyre[2] reported that even though (*Z*)-substituted olefins gave high *syn*-selectivities (>200:1), those obtained with the corresponding (*E*)-substituted olefins were usually very modest (<2:1) (eq 1). In 1987, Molander[3] described that a samarium-derived reagent could slightly improve the diastereoselectivities in these systems. Again, (*Z*)-substituted allylic alcohols reacted with very high *syn*-selectivities, whereas (*E*)-olefins showed modest to good selectivities. Quite intriguingly, the sense of the stereochemical induction was shown to depend on the size of the substituent at the allylic position.[4] The occurrence of this chiral subunit in a number of natural products prompted us to develop an efficient methodology based on the diastereoselective cyclopropanation of chiral substrates. We report here that the cyclopropanation of a variety of chiral allylic alcohols using a (iodomethyl)zinc reagent proceeds with unprecedently high *syn*-selectivities.



In our project aiming at developing new chiral auxiliaries[5] and reagents[6] for the stereoselective cyclopropanation of allylic alcohols, we have observed that several factors had a strong influence on the level of the stereochemical induction observed in these zinc carbenoid-mediated reactions of allylic alcohols.[7] We have examined whether these factors could also be important in dictating the level of the diastereofacial control in the cyclopropanation of the related chiral allylic alcohols.

Table 1. Effect of the Nature of the Reagent



entry[a]	Et_2Zn (equiv)	CH_2I_2 (equiv)	yield,[b] %	ratio[c] *syn:anti*
2	1	75	6.6:1	
2	2	4	95	2.3:1
3	5	5	>95	7.0:1
4	5	10	>95	3.2:1
5	10	5	85	6.6:1
6[d]	2	4	90	2.7:1
7	5	5[e]	80	3.7:1

[a] All the reactions were conducted at 0 °C to rt in CH_2Cl_2. [b] Yields evaluated by ^1H NMR. [c] The ratios were determined by cap. GC analysis of the crude reaction mixture. [d] The allylic alcohol was added to the preformed reagent according to Denmark's procedure.[12] [e] In this case, chloroiodomethane was used instead of diiodomethane.

Surprisingly, very little work has been done on the diastereoselective cyclopropanation of chiral allylic alcohols using Furukawa's reagent.[8,9]

The diastereoselectivities observed in the cyclopropanation of a typical (*E*)-disubstituted olefin using different sets of reaction conditions and reagents are shown in Table 1. In addition, this substrate led to a 1:6 (*syn:anti*) ratio when $Sm(Hg)/CH_2I_2/THF$ was used and to a 1:1 diastereomeric mixture with $Zn/CH_2I_2/Et_2O$. Quite surprisingly, the $ZnEt_2/CH_2I_2$-derived reagent was not only superior, but it also led to the opposite stereoisomer.

These preliminary observations also clearly indicate that the stoichiometry of the reagent is extremely important to maximize the ratios. The reagent formed from a 1:1 mixture of $ZnEt_2$ and CH_2I_2 (tentatively assigned as $EtZnCH_2I$, entries 1, 3, and 5) appears to be much superior to the classic Simmons–Smith reagent [$Zn(CH_2I)_2 \cdot ZnI_2$] or to the analogous $Zn(CH_2I)_2$ reagent[11] (entries 2, 4, and 6). Five equivalents of $EtZnCH_2I$ were necessary to maximize the ratios and to obtain complete consumption of the olefin.

Several chiral allylic alcohols[12] were submitted to these optimized conditions and the observed diastereoselectivities were compared to those obtained with the corresponding $Sm(Hg)/CH_2I_2$ reaction (Table 2) (see supplementary material). In all the cases, the *syn* isomer was the major obtained and the level of diastereoselection was excellent.

This method is applicable to a variety of chiral allylic alcohols, and the level of induction shows little substrate

(1) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370. (b) Hoffman, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860.

(2) Ratier, M.; Castaing, M.; Godet, J.-Y.; Pereyre, M. *J. Chem. Res. (M)* **1978**, 2309–2318.

(3) (a) Molander, G. A.; Harring, L. S. *J. Org. Chem.* **1989**, *54*, 3525–3532. (b) Molander, G. A.; Etter, J. B. *J. Org. Chem.* **1987**, *52*, 3942–3944.

(4) See also: (a) Lautens, M.; Delanghe, P. H. M. *J. Am. Chem. Soc.* **1994**, *116*, 8526–8535. (b) Lautens, M.; Delanghe, P. H. M. *J. Org. Chem.* **1992**, *57*, 798–800.

(5) (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.* **1994**, *35*, 513–516.

(6) Charette, A. B.; Juteau, H. *J. Am. Chem. Soc.* **1994**, *116*, 2651–2652.

(7) Motherwell, W. B.; Nutley, C. J. *Contemporary Organic Synthesis* **1994**, *1*, 219–241.

(8) (a) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron Lett.* **1966**, *28*, 3353–3354. (b) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53–58.

(9) For other recent examples of diastereoselective cyclopropanation of allylic alcohols, see: (a) Groth, U.; Schöllkopf, U.; Tiller, T. *Liebigs Ann. Chem.* **1991**, 857–860. (b) Schöllkopf, U.; Tiller, T.; Bardenhagen, J. *Tetrahedron* **1988**, *44*, 5293–5305. (c) Zhao, Y.; Yang, T.-F.; Lee, M.; Chun, B. K.; Du, J.; Schinazi, R. F.; Lee, D.; Newton, M. G.; Chu, C. K. *Tetrahedron Lett.* **1994**, *35*, 5405–5408. (d) Mohamadi, F.; Still, W. C. *Tetrahedron Lett.* **1986**, *27*, 893–896.

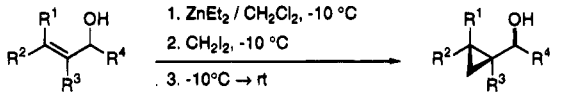
(10) Denmark, S. E.; Edwards, J. P. *J. Org. Chem.* **1991**, *56*, 6974–6981.

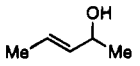
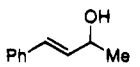
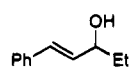
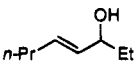
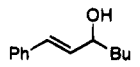
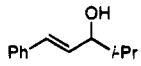
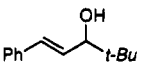
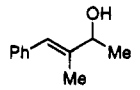
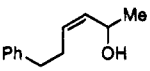
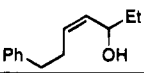
(11) (a) Denmark, S. E.; Edwards, J. P.; Wilson, S. R. *J. Am. Chem. Soc.* **1992**, *114*, 2592–2602. (b) Denmark, S. E.; Edwards, J. P.; Wilson, S. R. *J. Am. Chem. Soc.* **1991**, *113*, 723–725.

(12) Most of the chiral allylic alcohols are known or were prepared using literature procedures. Compounds and diastereomeric ratios obtained with $Sm(Hg)/CH_2I_2$ in entries 2 and 5–7 are described by Molander (ref 3). Compounds in entry 3, 4, and 8 were prepared by the addition of the appropriate Grignard reagent to the α,β-unsaturated aldehyde. Compounds in entries 9, and 10 were prepared from 3-phenyl-1-propanal in three steps (1. CBr_4, PPh_3; 2. BuLi; RCHO; 3. P-2 NiB, H_2).

0022-3263/95/1960-2966$09.00/0

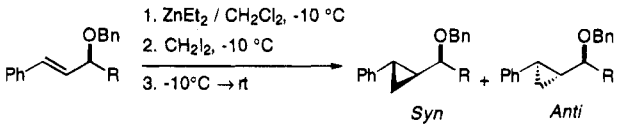
Table 2. Cyclopropanation of Chiral Allylic Alcohols



Entry	Allylic alcohol	Yield[a]	Ratio *syn* : *anti* Our Conditions[b]	Ratio *syn* : *anti* Sm(Hg) CH_2I_2
1		75%[c]	6 : 1[c]	1 : 3
2		86% (98%)[d]	7 : 1	1 : 6
3		97%	130 : 1	1 : 1
4		87%	110 : 1	2.6 : 1
5		98%	150 : 1	1 : 1.4
6		97%	>200 : 1	200 : 1
7		84%	>200 : 1	200 : 1
8		95%	33 : 1	1 : 1[e]
9		96%	>200 : 1	50 : 1
10		98%	>200 : 1	>200 : 1

[a] Isolated yield of chromatographically pure *syn*-isomer using the zinc reagent. [b] The diastereoselectivities were determined by cap. GC analysis of the crude reaction mixture. [c] The yield (mixture of isomers) and ratio were measured on the corresponding benzoate derivative. [d] The yield in parentheses is for the mixture of isomers. [e] $ClCH_2I$ was used instead of CH_2I_2.

Table 3. Diastereoselective Cyclopropanation of Allylic Ethers



entry	R	yield,[a] %	ratio[b] *syn/anti*
1	Me	94	1:9
2	Et	97	1:2
3	*i*-Pr	82[c]	19:1

[a] Yield of chromatographically pure mixture of isomers. [b] The diastereoselectivities were determined by cap. GC analysis of the crude reaction mixture. [c] Yield of the chromatographically pure *syn*-isomer.

dependency. Even the simplest substrates reacted to produce the *syn*-cyclopropylmethanol isomer with reasonably good selectivities (entries 1 and 2). Excellent ratios are observed with all the other types of olefins. It is quite remarkable to observe that the selectivities jump from 7 to >100:1 when going from Me to Et in entry 2 and 3. The new method is also very effective with trisubstituted olefins such as that in entry 8. These substrates have been known to produce very low diastereoselectivities with the samarium-derived reagents.

In order to gain some mechanistic insights about the (iodomethyl)zinc cyclopropanation and to explain the significant differences with the analogous Sm(Hg)-derived reaction, the cyclopropanation of allylic benzyl ethers under these newly developed conditions was also investigated.[13] The rather unexpected results are illustrated in Table 3. As the size of the alkyl group at the allylic position increases, the *anti* selectivity gradually decreases to eventually lead to a *syn*-selective reaction. This general trend for the (iodomethyl)zinc cyclopropanation of benzyl-protected alcohols appears to follow that of the corresponding samarium version on the free hydroxy group. Presumably, both reactions involve formation of a coordinative bond between the metal center and the oxygen directing group.

These results clearly indicate that the mechanism responsible for the stereochemical outcome of the reaction greatly differs whether a covalent or a coordinative bond is formed between the metal and the substrate. In the case of zinc alkoxide formation, the *syn* stereoisomer can result from the minimization of $A^{1,3}$ strain in the transition state. As initially postulated by Molander, Houk's model[14] can be invoked to explain the sense of induction with the benzyl protected substrates. A more exhaustive study is underway in our laboratories to explain the subtle differences between the two processes.

In conclusion, we have demonstrated that a number of structurally related iodomethylzinc reagents can produce significantly different results in a given reaction. The selection of the iodomethylzinc reagent is, therefore, essential for controlling the relative stereochemistry in the cyclopropanation of chiral allylic alcohols. Excellent diastereoselectivities are observed with a variety of olefins.

Acknowledgment. This research was supported by the Natural Science and Engineering Research Council (NSERC) of Canada, Merck Frosst Canada, Bio-Méga/Boehringer Ingelheim Research Inc., F.C.A.R. (Québec), Eli Lilly, Servier, and the Université de Montréal. H.L. thanks the NSERC for a Science 67 fellowship. We also thank a referee for very useful comments.

Supplementary Material Available: General procedure and copies of the ^1H and ^{13}C NMR spectra and characterization data for all compounds (39 pages).

JO942180Z

(13) There are only a few examples of Simmons–Smith cyclopropanation on allylic ethers, and the scope of these reactions has never been clearly established: (a) Morikawa, T.; Sasaki, H.; Hanai, R.; Shibuya, A.; Taguchi, T. *J. Org. Chem.* **1994**, *59*, 97–103. (b) Barrett, A. G. M.; Kasdorf, K.; Williams, D. J. *Chem. Commun.* **1994**, 1781–1782.

(14) (a) Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162–7166. (b) Houk, K. N.; Rondan, N. G.; Wu, Y.-D.; Metz, J. T.; Paddon-Row, M. N. *Tetrahedron* **1984**, *40*, 2257–2274. (c) Mareda, J.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1983**, *105*, 6997–6999.