A New Strategy for the Lewis Acid-Catalyzed Cyclopropanation of Allylic Alcohols

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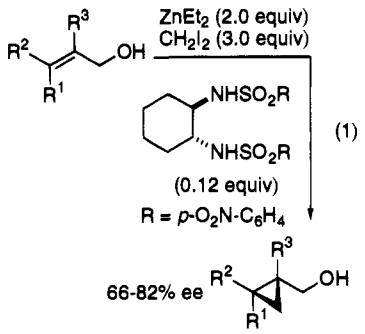
The efficient enantioselective synthesis of organic compounds using chiral catalysts is of great current interest.[1] The enantioselective (iodomethyl)zinc-mediated cyclopropanation of allylic alcohols has been the subject of relatively few investigations compared to most other carbon−carbon bond forming reactions. Kobayashi and co-workers recently found that good enantioselectivities were observed if a C_2-symmetric chiral disulfonamide was added in catalytic amounts to the (iodomethyl)zinc-mediated cyclopropanation of allylic alcohols (eq 1).[2,3]



One of the major drawbacks of this approach for obtaining high enantioselectivities is that the rate of the uncatalyzed reaction is not overwhelmingly different from that of the catalyzed process. For example, Kobayashi reported that a 20% yield of the cyclopropyl derivative was obtained in the absence of the chiral Lewis acid. In this communication, we unveil a new strategy for the Lewis acid-catalyzed cyclopropanation of allylic alcohols in which the rate of the uncatalyzed process is significantly slower than that of the catalyzed reaction.

The basis of the project lies on the fact that treatment of an allylic alcohol with 1 equiv of $Zn(CH_2I)_2$ should produce the (iodomethyl)zinc alkoxide and CH_3I (Scheme 1). Based on observations made during the course of studies directed toward the development of a chiral auxiliary for the cyclopropanation reaction,[4] we had evidence that these alkoxides do not undergo rapid cyclopropanation at low temperature (*vide infra*). We reasoned that the addition of a Lewis acid could trigger the subsequent cyclopropanation reaction by increasing the electrophilicity of the methylene group upon complexation. Subsequent formation of the halozinc alkoxide and regeneration of the Lewis acid would complete the catalytic cycle.

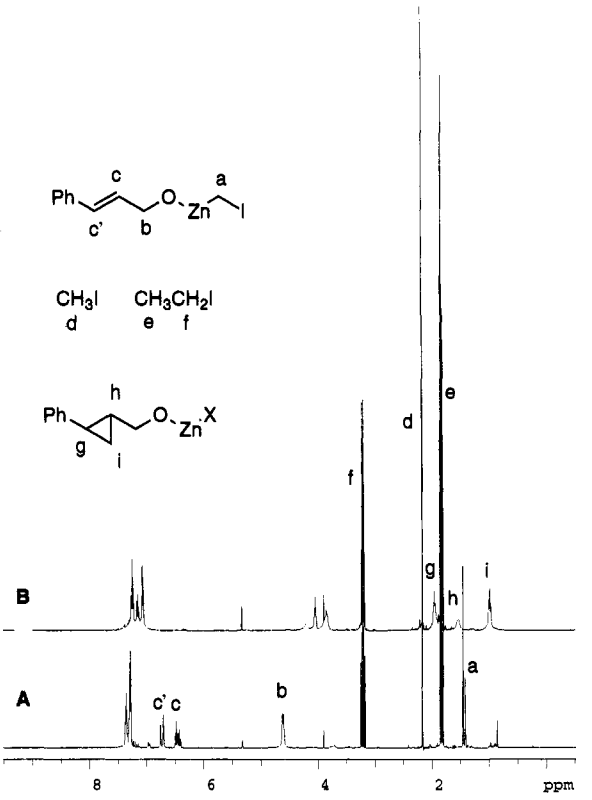
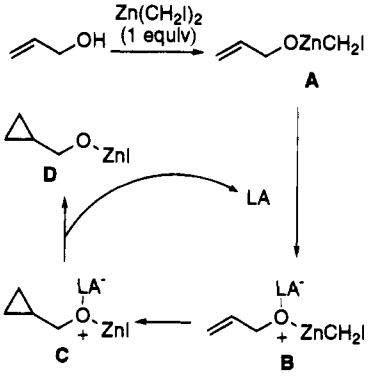


Figure 1. 400 MHz ^1H NMR of (A) ROH + $Zn(CH_2I)_2$ (1 equiv), CD_2Cl_2, −20 °C, 30 min, and (B) A + $TiCl_4$ (0.15 equiv), 2 h, −20 °C.

Scheme 1



Initially, several ^1H NMR control experiments were performed with cinnamyl alcohol and different (iodomethyl)zinc species. First, the treatment of cinnamyl alcohol with $ZnEt_2$ (1 equiv) in CD_2Cl_2 at 0 °C resulted in the rapid formation of the ethylzinc alkoxide (ROZnEt). Subsequent addition of CH_2I_2 (1 equiv) did not produce any cyclopropanes, the $ROZnCH_2I$ moiety, or EtI (2 h, 0 °C).[5] As expected, the addition of a second equivalent of $ZnEt_2$ and CH_2I_2 induced rapid cyclopropane formation.[6] Conversely, treatment of cinnamyl alcohol with the Simmons−Smith reagent,[7] $IZnCH_2I$[8] (1 equiv, −20 °C, CD_2Cl_2), resulted in the formation of the corresponding cyclopropane (~60%) and CH_3I (~40%).[5] The cyclopropanation is, therefore, competitive with the formation of the zinc

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(3) (a) Denmark, S. E.; Christenson, B. L.; Coe, D. M.; O'Connor, S. P. *Tetrahedron Lett.* **1995**, *36*, 2215−2218. (b) Denmark, S. E.; Christenson, B. L.; O'Connor, S. P. *Tetrahedron Lett.* **1995**, *36*, 2219−2222.

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(5) ^1H NMR spectra are provided in the supporting information.

(6) (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.

(7) Simmons, H. E.; Cairns, T. L.; Vladuchick, S. V.; Hoiness, C. M. *Org. React.* **1973**, *20*, 1−131.

(8) $IZnCH_2I$ was prepared by adding CH_2I_2 (1 equiv) to EtZnI·DME (1 equiv). For the spectroscopic characterization of this reagent, see: Charette, A. B.; Marcoux, J.-F. *J. Am. Chem. Soc.*, in press.

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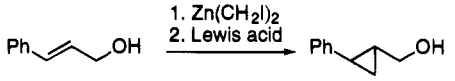
Table 1. Lewis Acid-Catalyzed Cyclopropanation[a]



		conversion (%)[b]		
entry	Lewis acid	0 °C	−20 °C	−40 °C
1	none	23[c]	<5[c]	<5[c]
2	BBr_3	93	90	60
3	$B(OMe)_3$	50	10	4
4	$TiCl_4$[d]	94[e]	90	60
5	$Ti(Oi\text{-}Pr)_4$	50	45	8
6	$TiCl_2(Oi\text{-}Pr)_2$	85	80	45
7	$SiCl_4$	90	88	58
8	$SnCl_4$	83	55	55
9	Et_2AlCl[d]	93[e]	87	70
10	$Zn(OTf)_2$	45	18	7
11	ZnI_2	50	14	9

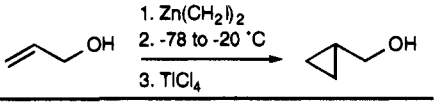
[a] All the reactions were carried out by adding 1 equiv of the alcohol to 1 equiv of $Zn(CH_2I)_2$ at −78 °C. The mixture was warmed to −40 °C, −20 °C or 0 °C, and, after 15 min, 0.15 equiv of the Lewis acid was added. The mixture was stirred for 6 h at that temperature and then quenched. [b] The conversion was evaluated by ^1H NMR. [c] Average value for six runs.[11] [d] In these cases, 0.05 equiv of the Lewis acid was sufficient to produce the rate acceleration. [e] These reactions were complete in less than 2 h.

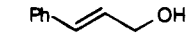
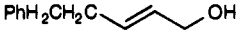
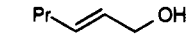
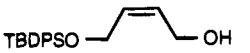
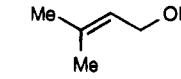
alkoxide when $IZnCH_2I$ is used. Finally, the addition of $Zn(CH_2I)_2$[9] (1 equiv, −40 °C, −20 °C, or 0 °C, CD_2Cl_2) to cinnamyl alcohol led to the quantitative formation of $ROZnCH_2I$ and CH_3I. More importantly, *cyclopropane formation from this species was not detected by ^1H NMR after 15 min* (Figure 1A).[10] Gratifyingly, addition of 0.15 equiv of $TiCl_4$ to this species induced near quantitative cyclopropane formation in less than 4 h at −20 °C (Figure 1B). Several Lewis acids proved to be quite efficient at catalyzing this process (Table 1). For comparison, the yields of the uncatalyzed process after 6 h at various temperature are also shown.

Several (*E*)- and (*Z*)-substituted allylic alcohols were then submitted to the optimal reaction conditions with $TiCl_4$. In all cases, excellent yields of the cyclopropane products were obtained, and the olefin substitution pattern had little effect on the efficiency of the process (Table 2).

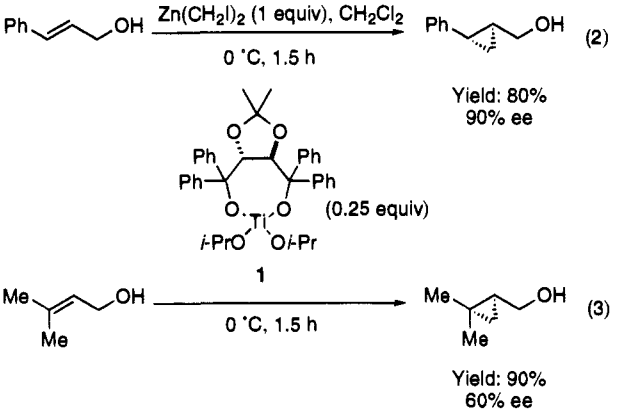
Preliminary results using chiral catalysts confirmed that the Lewis acid is involved in the transition state. Enantiomerically enriched cyclopropylmethanol moieties where obtained if the cyclopropanation reactions were carried out in the presence of the titanium catalyst **1** (eqs 2 and 3).[12,13] In these cases, optimal enantiomeric excesses were obtained using 0.25 equiv of the Lewis acid.

Table 2. $TiCl_4$-Catalyzed Cyclopropanation Reaction[a]



Entry	Allylic Alcohol	Yield (%)[b]
1		90
2		88
3		85
4		94
5		85
6		90

[a] Typical procedure: To a mixture of $Zn(CH_2I)_2$ (prepared from 1 mmol of $ZnEt_2$ and 2 mmol of CH_2I_2) in CH_2Cl_2 (8 mL) at −78 °C was added the allylic alcohol (1 mmol in 5 mL of CH_2Cl_2). After the mixture was stirred for 15 min at −20 °C, $TiCl_4$ (0.15 mmol) was added. The mixture was stirred at −20 °C for 2−7 h (see supporting information for further details). [b] Isolated yield of the cyclopropane.



The search for better chiral Lewis acids for the cyclopropanation reaction is actively being pursued and will be reported in due course.

Acknowledgment. This research was supported by the Natural Science and Engineering Research Council (NSERC) of Canada, the Petroleum Research Fund, administered by the American Chemical Society, Merck Frosst Canada, F.C.A.R. (Québec), Eli Lilly, Servier, and the Université de Montréal. C.B. would like to thank the F.C.A.R. for a fellowship.

Supporting Information Available: Experimental procedures and copies of spectra for the ^1H NMR experiments (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(10) We believe that the presence of two signals for $ROZnCH_2I$ (a, Figure 1A) indicates different aggregated forms of the zinc alkoxide. These two peaks are converted into a single broad signal over time without any noticeable cyclopropane formation (~4 h).

(11) Traces of oxygen appear to increase the yield of the uncatalyzed reaction. For a discussion of the effect of oxygen on the rate of the cyclopropanation reaction, see: (a) Miyano, S.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3665−3668. (b) Miyano, S.; Matsumoto, Y.; Hashimoto, H. *J. Chem. Soc., Chem. Commun.* **1975**, 364. (c) Miyano, S.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 892−897. (d) Miyano, S.; Hashimoto, H. *J. Chem. Soc., Chem. Commun.* **1971**, 1418.

(12) (a) Seebach, D.; Beck, A. K.; Imwinkelried, R.; Roggo, S.; Wonnacott, A. *Helv. Chim. Acta* **1987**, *70*, 954−974. (b) Narasaka, K.; Inoue, M.; Yamada, T. *Chem. Lett.* **1986**, 1967−1968.

(13) Consistently high enantiomeric excesses (the highest to date for a substoichiometric process) were obtained with *trans*-3-aryl-2-propen-1-ol, whereas lower ee's were obtained with alkyl-substituted allylic alcohols. A more extensive study of chiral catalysts will be presented in the full account of this work.