Catalytic Asymmetric Cyclopropanation of Allylic Alcohols with Titanium-TADDOLate: Scope of the Cyclopropanation Reaction

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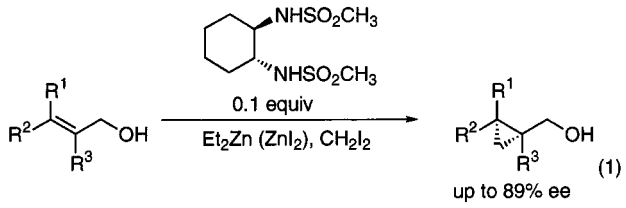
Abstract: A substoichiometric amount of titanium-TADDOLate complex was effective at catalyzing the cyclopropanation reaction of allylic alcohols in the presence 1 equiv of bis(iodomethyl)zinc. After initial optimization of the catalyst structure, excellent yields and enantiomeric ratios were obtained for 3-aryl- or 3-heteroaryl-substituted allylic alcohols (up to 97:3). Alkyl-substituted allylic alcohols gave modest yields and enantiomeric ratios (up to 87:13) but these compare favorably with those observed with other substoichiometric chiral ligands. The full synthetic scope of the reaction is presented in this paper.

Introduction

The [2+1] cycloaddition of a carbene or carbenoid (CH_2 or metal-associated carbene, M = CH_2 or MCH_2I) unit to an alkene is one of the most important reactions for accessing cyclopropanes. The palladium-catalyzed decomposition of diazomethane and the related transition metal-catalyzed decomposion of α-diazoesters are very good reactions for generating racemic cyclopropane derivatives. Although numerous chiral catalysts for the α-diazoesters decomposition are highly effective, all the efforts to find a suitable chiral palladium catalyst to develop an enantioselective version of this reaction have failed.[1] Conversely, the Simmons−Smith cyclopropanation reaction involving the use of halomethylzinc halides or other related reagents is one of the most widely used reactions in the organic chemist's arsenal for the conversion of olefins into cyclopropanes.[2] Enantioselective versions of the cyclopropanation of allylic alcohols, which involves stoichiometric chiral additives, are available and have been used extensively in natural product synthesis.[3] The assumption that catalytic amounts of Lewis acids can accelerate the cyclopropanation reaction of alkenes with haloalkylmetal reagents has been contemplated for many years,[4] but effective catalysts have been disclosed only recently. Kobayashi[5] and Denmark[6] have reported that chiral bis(sulfonamide) ligands could be used in substoichiometric amounts in the cyclopropanation of allylic alcohols to generate the cyclopropane in good to excellent enantioselectivities (eq 1).[7,8]



(1)

We recently reported an alternative method for the Lewis acid-catalyzed cyclopropanation reaction of allylic alcohols, in

(1) For selected contributions and reviews see: (a) Nozaki, H.; Moriuti, S.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1966**, 5239−5244. (b) Nozaki, H.; Moriuti, S.; Takaya, H.; Noyori, R. *Tetrahedron* **1968**, 3655−3669. (c) Aratani, T. *Pure Appl. Chem.* **1985**, *57*, 1839−1844. (d) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919−939. (e) Lowenthai, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005−6008. (f) Müller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232−240. (g) Evans, D. A.; Woerple, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726−727. (h) Doyle, M. P. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 305−316. (i) Lowenthal, R. E.; Masamune, S. *Tetrahedron Lett.* **1991**, *32*, 7373−7376. (j) Leutenegger, U.; Umbricht, G.; Fahrni, C.; von Matt, P.; Pfaltz, A.; *Tetrahedron* **1992**, *48*, 2143-2156. (k) Ito, K.; Katsuki, T. *Tetrahedron Lett.* **1993**, *34*, 2661−2664. (l) Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339−345. (m) Davies, H. M. L.; Hutcheson, D. K. *Tetrahedron Lett.* **1993**, *34*, 7243−7246. (n) Nishiyama, H.; Itoh, Y.; Matsumoto, H.; Park, S.-B.; Itoh, K. *J. Am. Chem. Soc.* **1994**, *116*, 2223−2224. (o) Ito, K.; Katsuki, T. *Chem. Lett.* **1994**, 1857−1860. (p) Martin, S. F.; Spaller, M. R.; Liras, S.; Hartmann, B. *J. Am. Chem. Soc.* **1994**, *116*, 4493−4494. (q) Furuda, T.; Katsuki, T. *Synlett* **1995**, 825−826. (r) Doyle, M. P.; Zhou, Q.-L.; Charnsangavej, C.; Longoria, M. A. *Tetrahedron Lett.* **1996**, *37*, 4129−4132. (s) Reissig, H.-U. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 971−973. (t) Singh, V. K.; DattaGupta, A.; Sekar, G. *Synthesis* **1997**, 137−149. (u) Galardon, E.; Le Maux P.; Simmonneaux, G. *Chem. Commun.* **1997**, 927−928. (v) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vols. I−III, p 1483. (w) Pfaltz, A. Cyclopropanation and C−H insertion with Cu. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. II, pp 513−538. (x) Lydon, K. M.; McKervey, M. A. Cyclopropanation and C−H insertion with Rh. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. II, pp 540−580. (y) Charette, A. B.; Lebel, H. Cyclopropanation and C−H insertion with Metals other than Cu and Rh. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. II, pp 581−603. (z) *Comprehensive Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH Inc.: New York, 2000; p 864.

(2) Furukawa, J.; Kawabata, N. *Adv. Organomet. Chem.* **1974**, *12*, 83−134.

(3) (a) Denmark, S. E.; Edwards, J. P. *Synlett* **1992**, 229−230. (b) Ukaji, Y.; Nishimura, M.; Fujisawa, T. *Chem. Lett.* **1992**, 61−64. (c) Ukaji, Y.; Sada, K.; Inomata, K. *Chem Lett* **1993**, 1227−1230. (d) Charette, A. B.; Juteau, H. *J. Am. Chem. Soc.* **1994**, *116*, 2651−2652. (e) Charette, A. B.; Prescott, S.; Brochu, C. *J. Org. Chem.* **1995**, *60*, 1081−1083. (f) Kitajima, H.; Aoki, Y.; Ito, K.; Katsuki, T. *Chem. Lett.* **1995**, 1113−1114. (g) Charette, A. B.; Juteau, H.; Lebel, H.; Deschênes, D. *Tetrahedron Lett.* **1996**, *37*, 7925−7928. (h) Charette, A. B.; Lemay, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1090−1092. (i) Kasdorf, K.; Liotta, D. C. *Chemtracts-Org. Chem.* **1997**, *10*, 533−535. (j) Kitajima, H.; Ito, K.; Aoki, Y.; Katsuki, T. *Bull. Chem. Soc. Jpn* **1997**, *70*, 207−217. (k) Turnbull, M. D. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1241−1247. (l) Charette, A. B.; Lebel, H. *Org. Synth.* **1998**, *76*, 86−100. (m) Charette, A. B.; Juteau, H.; Lebel, H.; Molinaro, C. *J. Am. Chem. Soc.* **1998**, *120*, 11943−11952.

(4) Friedrich, E. C.; Lunetta, S. E.; Lewis, E. J. *J. Org. Chem.* **1989**, *54*, 2388−2390.

(5) (a) Takahashi, H,.; Yoshioka, M.; Ohno, M.; Kobayashi, S. *Tetrahedron Lett.* **1992**, *33*, 2575−2578. (b) Imai, N.; Takahashi, H.; Kobayashi, S. *Chem. Lett.* **1994**, 177−180. (c) Imai, N.; Sakamoto, K.; Takahashi, H.; Kobayashi, S. *Tetrahedron Lett.* **1994**, *35*, 7045−7048. (d) Takahashi, H.; Yoshioka, M.; Shibasaki, M.; Ohno, M.; Imai, N.; Kobayashi, S. *Tetrahedron* **1995**, *51*, 12013−12026.

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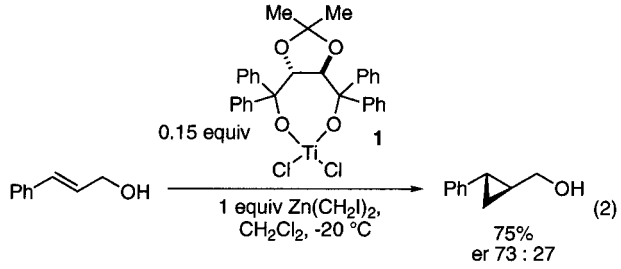
which the uncatalyzed process is minimized.[9] The addition of $Zn(CH_2I)_2$ (1 equiv) to an allylic alcohol (1 equiv) produced the iodomethylzinc alkoxide, which was shown to be a relatively stable species.[9b] Methylene transfer is then triggered by the addition of a Lewis acid in catalytic amounts. Several achiral Lewis acids were very effective in inducing the cyclopropanation process. Subsequent studies showed that the use a titanium derived chiral of a chiral Lewis acid **1** [derived from TADDOL and $Cl_2Ti(O\textit{i}\text{-}Pr)_2$] converts allylic alcohols into cyclopropanes with high enantioselectivity (eq 2). In this paper, we wish to report our full account of the synthetic scope of this work and we will highlight the importance of all the components present in the reaction.[9]



Results and Discussion

Survey of Chiral Lewis Acids.[10] The discovery that achiral Lewis acids can effectively catalyze the cyclopropanation reaction of halomethylzinc alkoxides prompted us to extend this concept toward an enantioselective version of this reaction.[9] The cyclopropanation of cinnamyl alcohol was used as the test reaction to optimize the conditions and the procedure for this enantioselective process. Thus, although a large variety of chiral Lewis acids from various metal complexes derived from ligands such as bis(oxazoline),[11] pyridine(bisoxazoline),[11] diethyl tartrate, dimethyltartramide, binaphthol, substituted binaphthols, and other diols were tested, they produced relatively low enantiomeric ratios (<65:35). However, the first promising result for this process was observed with the titanium TADDOLate complex[12] obtained by mixing TADDOL and $Cl_2Ti(O\textit{i}\text{-}Pr)_2$[13] (TADDOL-$TiCl_2$), which offered a 75% yield and some level of enantioselectivity (er 73:27) (eq 2). Quite interestingly, titanium bis(sulfonamides), which are highly effective catalysts in the Kobayashi/Denmark protocol,[5,6] were found to be poor catalysts for this process.

Optimization of TADDOLate Structure and Reaction Procedure:[10] **Solvent Effect.** The effect of the nature of the solvent on the yield and on the enantiomeric ratios with TADDOL-$TiCl_2$ was studied for this transformation and the survey revealed that etheral solvents such as diethyl ether, dimethoxyethane, and *tert*-butyl methyl ether led to much lower enantiomeric ratios and yields compared to CH_2Cl_2. The inferior results obtained with these solvents suggest that complexation of the zinc alkoxide and/or of the catalyst by the solvent appears to be detrimental.[14] Although comparable results were obtained with noncoordinating solvents such as benzene or toluene, CH_2Cl_2 was selected as the best solvent for this reaction since it is relatively easy to remove in the presence of more volatile allylic alcohols or cyclopropylmethanols.

Titanium TADDOLate: Study of the Titanium Ligands (TADDOL-TiX_2).[10] Dihalogenated (X = I, Br, Cl) as well as dialkoxy/diphenoxy titanium derived ligands (X = O*i*-Pr, OEt, O*t*-Bu, OPh)[15] generally gave enantiomeric ratios over 90:10. The only exception is the related oxo[16,17] complex (TADDOL-Ti=O) obtained from the controlled hydrolysis of $Ti(O\textit{i}\text{-}Pr)_4$, which led to racemic cyclopropane.[18] We chose to further pursue our optimization studies with TADDOL-$Ti(O\textit{i}\text{-}Pr)_2$ (**2**) since it is more conveniently prepared from commercially available starting materials and since the enantiomeric ratio observed is very high (96:4). Although in this case the yield of the reaction remained very modest at −20 °C, at 0 °C it considerably improved (from 55 to 85%) while high enantio-discrimination was maintained.

Titanium TADDOLate: Study of the TADDOL Structure.[10,19] The monitoring of structural changes on the TADDOL ligand revealed that, in our system, very little effect in the enantiomeric ratios was observed when the substituents on the

(6) (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. (c) Denmark, S. E.; Christenson, B. L.; O'Connor, S. P.; Noriaki, M. *Pure Appl. Chem.* **1996**, *68*, 23−27. (d) Denmark, S. E.; O'Connor, S. P. *J. Org. Chem.* **1997**, *62*, 584−594. (e) Denmark, S. E.; O'Connor, S. P. *J. Org. Chem.* **1997**, *62*, 3390−3401. (f) Denmark, S. E.; O'Connor, S. P.; Wilson, S. R. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1149−1151.

(7) For the asymmetric cyclopropanation of olefins in the absence of hydroxy groups with (halomethyl)zinc reagents see: (a) Sawada, S.; Oda, J.; Inouye Y. *J. Org. Chem.* **1968**, *33*, 2141−2143. (b) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron Lett.* **1968**, 3495−3498. (c) Yang, Z.; Lorenz, J. C.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 8621−8624. (d) Charette, A. B.; Francoeur, S.; Martel, J.; Wilb, N. *Angew. Chem., Int. Ed.* **2000**, *39*, 4539−4542.

(8) Other systems include disulfonamides derived from α-amino acids (Imai, N.; Sakamoto, K.; Maeda, M.; Kouge, K.; Yoshizane, K.; Nokami, J. *Tetrahedron Lett.* **1997**, *38*, 1423−1426) and sulfonamide/Schiff base ligands (Balsells J.; Walsh, P. J. *J. Org. Chem.* **2000**, *65*, 5005−5008).

(9) (a) Charette, A. B.; Brochu, C. *J. Am. Chem. Soc.* **1995**, *117*, 11367−11368. (b) A full account for the proof of principle is reported separately: Charette, A. B.; Molinaro, C.; Brochu, C. *J. Am. Chem. Soc.* **2001**, *123*, 12160−12167.

(10) See Supporting Information for tubulated examples.

(11) (a) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686−699 and references therein. (b) See also ref 1.

(12) (a) Seebach, D.; Weidmann, B.; Widler, L. In *Modern Synthetic Methods*; Scheffold, R., Ed.; John Wiley & Sons: Chichester, 1983; Vol. 3, pp 217−353. (b) Seebach, D.; Marti, R. E.; Hintermann, T. *Helv. Chim. Acta* **1996**, *79*, 1710−1740. (c) Beck, A. K.; Gysi, P.; La Vecchia, L.; Seebach, D. *Org. Synth.* **1999**, *76*, 12−22. (d) Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 92−138.

(13) For the preparation of $Ti(O\textit{i}\text{-}Pr)_2Cl_2$: (a) Dijkgraaf, C.; Rousseau, J. P. G. *Spectrochim. Acta* **1968**, *24A*, 1213−1217. (b) Mikami, K.; Terada, M.; Narisawa, S.; Nakai, T. *Org. Synth.* **1993**, *71*, 14−21.

(14) Ether and THF have been shown to be detrimental in other systems: Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340−5345.

(15) (a) Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340−5345. (b) Ito, Y. N.; Ariza, X.; Beck, A. K.; Bohac, A.; Ganter, C.; Gawley, R. E.; Kuhnle, F. N. M.; Tuleja, J.; Wang, Y. M.; Seebach, D. *Helv. Chim. Acta* **1994**, *77*, 2071−2110.

(16) For the controlled hydrolysis of $Ti(OiPr)_4$ see: Bradley, D. C.; Gaze, R.; Wardlaw, W. J. *J. Chem. Soc.* **1955**, 721−726.

(17) Mukaiyama, T.; Inubushi, A.; Suda, S.; Hara, R.; Kobayashi, S. *Chem. Lett.* **1990**, 1015−1018.

(18) For a discussion on the dynamic exchange of the sterically hindered titanium-TADDOLates and their applications see: (a) Narasaka, K.; Kanai, F.; Okudo, M.; Miyoshi, N. *Chem. Lett.* **1989**, 1187−1190. (b) Duthaler, R. O.; Hafner, A.; Alsters, P. L.; Rothe-Streit, P.; Rihs, G. *Pure Appl. Chem.* **1992**, *64*, 1897−1910. (c) Seebach, D.; Beck, A. K.; Schmidt, B.; Wang, Y. M. *Tetrahedron* **1994**, *50*, 4363−4384. (d) Seebach, D.; Jaeschke, G.; Wang, Y. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2395−2396. (e) Jaquith, J. B.; Guan, J.; Wang, S.; Collins, S. *Organometallics* **1995**, *14*, 1079−1081. (f) Gau, H.-M.; Lee, C.-S.; Lin, C.-C.; Jiang, M.-K.; Ho, Y.-C.; Kuo, C.-N. *J. Am. Chem. Soc.* **1996**, *118*, 2936−2941. (g) Ramon, D. J.; Guillena, G.; Seebach, D. *Helv. Chim. Acta* **1996**, *79*, 875−894. (h) Seebach, D.; Jaeschke, G.; Gottwald, K.; Matsuda, K.; Formisano, R.; Chaplin, D. A.; Brarning, M.; Bringmann, G. *Tetrahedron Lett.* **1997**, *53*, 7539−7556. (i) Jaeschke, G.; Seebach, D. *J. Org. Chem.* **1998**, *63*, 1190−1197.

(19) For the preparation of the TADDOL ligands see the Supporting Information.

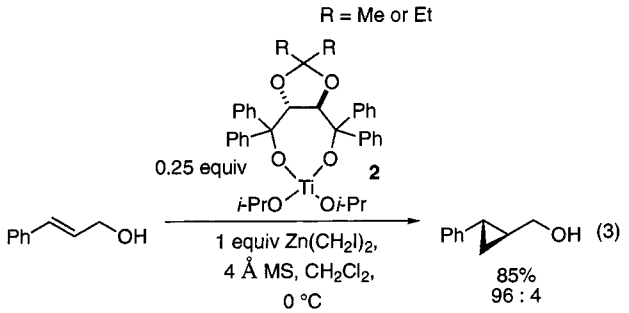
five-membered acetal moiety where changed (er between 93:7 and 96:4).[20] Even a TADDOL[21] having an unsymmetrical acetal at the 2-position of the dioxolane ring (H, Ph), which may produce several diastereomerically distinct complexes upon reaction with the allylic alcohol (or the zinc alkoxide), afforded acceptable enantiomeric ratios (93:7).

Replacing the phenyl groups of the titanium acetal relay by other aromatic substituents such as sterically more hindered β-naphthyl or 3,5-dimethylphenyl analogues provided comparable enantiomeric ratios (94:6 and 96:4). However, replacing these groups with nonaromatic groups such as H, Me, cyclohexyl, or benzyl resulted in a drastic decrease of the rate of the reaction (yields are typically <58%) but more importantly racemic cyclopropylmethanol was obtained. These results indicate that bulky/aromatic groups on the acetal relay are important for the catalytic efficiency, presumably because of their ability to form π-stacking with the substrate[22] and to favor a dynamic alkoxy exchange[18] in the reaction media. The pentafluoro-Ph analogue, which should have improved π-stacking interactions with electron-rich aromatic allylic alcohols, was found to be inactive probably due to the electron-withdrawing effect of fluoride.

Several other TADDOL-derived catalysts were also screened;[10] however, they afforded less effective systems. Moreover, the replacement of the titanium Lewis acid by zirconium did not lead to any improvements.

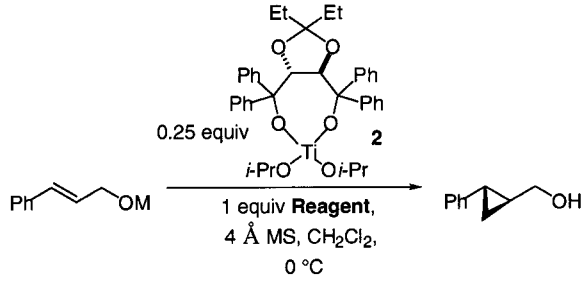
The full optimization of the catalyst structure presented above indicates that several catalysts are as effective as TADDOLate catalyst **2**; however, we chose this C_2-symmetric catalyst because its components are commercially available and easily accessible.

Optimization of the Enantioselective Cyclopropanation of Allylic Alcohols with TADDOLate 2: Preparation of the Catalyst. The C_2-symmetric TADDOL ligand (R = Me, eq 3)



is commercially available or readily prepared according to literature procedure from the corresponding tartrate ester acetal and PhMgBr in a 82% yield.[23] The titanium TADDOLate complex was prepared by mixing 1.2 equiv of TADDOL[24] and 1.0 equiv of titanium(IV) isopropoxide in the presence of 4 Å molecular sieves and the mixture was stirred for 2 h. This suspension was concentrated under reduced pressure and left under vacuum (0.4 mmHg) for 2 h and then used directly. The TADDOL ligand is very stable under the zinc-mediated cyclopropanation reaction and to the following acidic workup, and it could be quantitatively recovered after the cyclopropanation reaction. Subsequent recycling of the ligand indicated that neither the yield nor the enantiomeric ratio of the subsequent reaction was affected.

Table 1. Effect of Metal Alkoxides and Additives on the Enantiomeric Ratios[a]



entry	m	reagent (1 equiv)	er[b]
1	Li	$Zn(CH_2I)_2$	58:42
2	Na	$Zn(CH_2I)_2$	63:37
3	K	$Zn(CH_2I)_2$	57:43
4	ZnEt	$Zn(CH_2I)_2$	67:33
5[c]	$ZnCH_2Cl$		92:8
6[d]	$ZnCH_2I$		96:4 → 97:3[e]
7	Bn	$Zn(CH_2I)_2$	50:50[f]
8	H	$Zn(CH_2I)_2$	96:4

[a] Unless otherwise stated the reaction was carried out by adding the allylic alkoxide, alcohol, or ether to a preformed suspension of the chiral catalyst **2**, 4 Å MS, and $Zn(CH_2I)_2$ at −40 °C. The mixture was warmed to 0 °C and quenched after 1.5 h. [b] The enantiomeric ratio was determined by GC on the chiral stationary phase. [c] The reaction was carried out by adding a suspension of the chiral catalyst **2** and 4 Å MS to the preformed allylic alkoxide generated from $Zn(CH_2Cl)_2$ and the allylic alcohol, at −40 °C. The mixture was warmed to 0 °C and quenched after 1.5 h. [d] The reaction was carried out by adding a suspension of the chiral catalyst **2** and 4 Å MS to the preformed allylic alkoxide generated from $Zn(CH_2I)_2$ and the allylic alcohol, at −40 °C. The mixture was warmed to 0 °C and quenched after 1.5 h. [e] 68% conversion. [f] The enantiomeric ratio was determined by HPLC on the chiral stationary phase

Effect of the Nature of the Metal Alkoxides. All the reactions to optimize the substoichiometric enantioselective cyclopropanation of allylic alcohols with the titanium-TADDOLate complex **2** were conducted on cinnamyl alcohol by using the following procedure for Table 1. Unless otherwise stated the allylic alkoxide, alcohol, or ether was added to a preformed suspension of the catalyst **2** (0.25 equiv) and $Zn(CH_2I)_2$ (1 equiv) at −40 °C; the reaction mixture was then warmed to 0 °C and quenched after 1.5 h. The conversions were usually very high (>75%) in all the cases. Initial investigations were carried out

(20) The conformation of the five-membered acetal moiety has been shown to influence that of the seven-membered ring containing titanium: (a) Seebach, D.; Hayakawa, M.; Sakaki, J. I.; Schweizer, W. B. *Tetrahedron* **1993**, *49*, 1711−1724. (b) Sakaki, J. I.; Schweizer, W. B.; Seebach, D. *Helv. Chim. Acta* **1993**, *76*, 2654−2665. (c) Ito, Y. N.; Ariza, X.; Beck, A. K.; Bohac, A.; Ganter, C.; Gawley, R. E.; Kuhnle, F. N. M.; Tuleja, J.; Wang, Y. M.; Seebach, D. *Helv. Chim. Acta* **1994**, *77*, 2071−2110. (d) Jaquith, J. B.; Guan, J.; Wang, S.; Collins, S. *Organometallics* **1995**, *14*, 1079−1081. (e) Seebach, D.; Dahinden, R.; Marti, R. E.; Beck, A. K.; Plattner, D. A.; Kuhnle, F. N. M. *J. Org. Chem.* **1995**, *60*, 1788−1799. (f) Seebach, D.; Beck, A. K.; Dahinden, R.; Hoffmann, M.; Kuhnle, F. N. M. *Croat. Chem. Acta* **1996**, *69*, 459−484. (g) Seebach, D.; Beck, A. K. *Chimia* **1997**, *51*, 293−297.

(21) For a discussion and examples of C_1 symmetric TADDOL derived catalysts see: (a) Narasaka, K. *Synthesis* **1991**, 1−11. (b) See: ref 20c.

(22) (a) Jaquith, J. B.; Guan, J.; Wang, S.; Collins. S. *Organometallics* **1995**, *14*, 1079−1081. (b) Haase, C.; Sarko, C. R.; DiMare, M. *J. Org. Chem.* **1995**, *60*, 1777−1787. (c) Garcia, J. I.; Martinez-Merino, V.; Mayoral, J. A. *J. Org. Chem.* **1998**, *63*, 2321−2324.

(23) (a) Seebach, D.; Weidmann, B.; Widler, L. In *Modern Synthetic Methods*; Scheffold, R., Ed.; John Wiley & Sons: Chichester, 1983; Vol. 3, pp 217−353. (b) Seebach, D.; Beck, A. K.; Imwinkelried, R.; Roggo, S.; Wonnacott, A. *Helv. Chim. Acta* **1987**, *70*, 954−974. (c) Beck, A. K.; Bastani, B.; Plattner, D. A.; Petter, W.; Seebach, D.; Braunschweiger, H.; Gysi, P.; La Vecchia, L. *Chimia* **1991**, *45*, 238−244. (d) Seebach, D.; Dahinden, R.; Marti, R. E.; Beck, A. K.; Plattner, D. A.; Kühnle, F. N. *J. Org. Chem.* **1995**, *60*, 1788−1799. (e) Beck, A. K.; Gysi, P.; La Vecchia, L.; Seebach, D. *Org. Synth*. **1999**, *76*, 12−22.

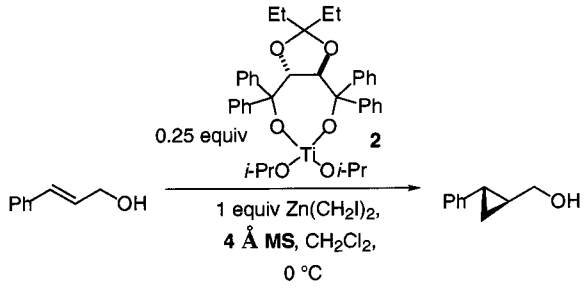
(24) Dahinden, R.; Beck, A. K.; Seebach, D. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L., Ed.; J. Wiley & Sons: Chichester, 1995; Vol. 3, pp 2167−2170.

by using various preformed metal alkoxides (entries 1−6, Table 1). Thus, the corresponding Li, Na, K, and ZnEt alkoxides gave inferior enantiomeric ratios compared to the corresponding allylic alcohol (entries 1−4 vs 8, Table 1). In these cases, we believe that the exchange with $Zn(CH_2I)_2$ is not occurring as rapidly and the uncatalyzed reaction becomes competitive.[25] Greater enantiomeric ratios were obtained when the preformed halomethylzinc alkoxides[9b] were generated (entries 5 and 6, Table 1). Thus, although the chloromethylzinc alkoxide gave excellent enantiomeric ratios (entry 5, Table 1), the best ones were obtained with the iodomethylzinc alkoxide analogue (entry 6, Table 1) albeit lower yields were observed in this case (68%). The enantioselective cyclopropanation of the benzyl protected allylic alcohol resulted in racemic material (entry 7, Table 1), which is an indication that the interaction between the alkoxide generated in the reaction media and the catalyst are important to achieve high selectivities. The results in Table 1 indicate that although the iodomethylzinc alkoxide gave the best results in terms of enantiomeric ratios, the optimal reaction conditions constitute the direct use of the alcohol giving both excellent yields (85%) and enantiomeric ratios (96:4).

Importance of Molecular Sieves.[26] Narasaka has reported that the presence of molecular sieves (zeolites) such as 3 Å, 4 Å, or 5 Å in the reaction mixture can have a significant impact on the level of enantioselectivities of the adduct in the asymmetric Diels−Alder reaction where a similar TADDOL catalyst was used.[27] On the basis of these observations, we also tested several types of molecular sieves to see if they had similar effects on the efficiency of the cyclopropanation reaction. Among those tested (3 Å, 4 Å, 5 Å, and 10 Å), only 3 Å and 4 Å produced a significant enhanced level of enantioselectivity.[28] A survey on the importance of molecular sieves in the formation of the catalyst and in the cyclopropanation reaction indicated that they where necessary in both instances to achieve high yields and enantiomeric ratios (Table 2). Although we are still uncertain of the exact role of the molecular sieves, it is clear that their ability to scavenge H_2O and perhaps *i*PrOH is important.[29] However, a combination of several hypotheses such as their dehydrating ability, their implication in the dynamic alkoxide exchange, and the possibility of a surface interaction[30] with the catalyst, are considered to be at least partially responsible for the catalytic reaction.

Optimizing the Cyclopropanation Reaction. The formation of the cyclopropanating reagent ($Zn(CH_2I)_2$[31,32]) at −10 °C may contain up to 20% of $IZnCH_2I$ resulting from a temperature-dependent decomposition of $Zn(CH_2I)_2$. The generation of $Zn(CH_2I)_2$ at −40 °C instead of −10 °C under the standard asymmetric cyclopropanating conditions resulted in slightly lower enantiomeric ratios (entry 1 Table 4 vs 1 Table 3) indicating that the quantity of $IZnCH_2I$ or ZnI_2 present in the reaction media may be important for high enantioselective induction.[6a,c]

Table 2. Importance of Molecular Sieves in the Cyclopropanation Reaction



entry	catalyst[a]	reaction[b]	yield (%)	er[c]
1	yes	yes	85	96:4
2	yes	no	61	75:25
3	no	yes	82	95:5
4	no	no	49	65:35

[a] Presence of 1.7 g/mmol of 4 Å MS during the formation of the catalyst. [b] Presence of 1.7 g/mmol of 4 Å MS during the cyclopropanation reaction. [c] The enantiomeric ratio was determined by GC on the chiral stationary phase.

To simplify the reaction protocol and decrease the overall reaction time we explored the possibility of not removing 2-propanol under vacuum prior to the cyclopropanation reaction.[33] The addition of ZnI_2 during the formation of $Zn(CH_2I)_2$ (to indirectly generate different quantities of $IZnCH_2I$)[6e] improved the enantiomeric ratios from 89:11 when no ZnI_2 was used up to 94:6 when 1 or 2 equiv of ZnI_2 were used (entries 2 vs 3−6, Table 3). However, the use of 2 equiv[34] of pure $IZnCH_2I$ or its THF complex[31c] generated from I_2, Et_2Zn, and

(25) Cheng, D.; Kreethadumrongdat, T.; Cohen, T. *Org. Lett.* **2001**, *3*, 2121−2123.

(26) For leading references on molecular sieves: (a) Breck, D. W. *Zeolite Molecular Sieves*; John Wiley: New York, 1974. (b) Davis, M. E. *Acc. Chem. Res.* **1993**, *26*, 111−115. (c) Thomas, J. *Chem. Rev.* **1993**, *93*, 301−320.

(27) (a) Narasaka, K.; Inoue, M.; Yamada, T. *Chem. Lett.* **1986**, 1967−1968. (b) Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340−5345.

(28) Enantiomeric ratios for cinnamyl alcohol under standard asymmetric cyclopropanating procedures with different molecular sieves: 3 Å (er 95:5), 4 Å (er 96:4), 5 Å (er 88:12) and 10 Å (er 80:20).

(29) The deliberate addition of as little as 0.0125 equiv of water to the catalyst before the reaction resulted in a drop in selectivity from 96:4 to 90:10.

(30) For a dicussion on the dynamic alkoxi exchange on the sterically hindered titanium-TADDOLates and the possible interaction of catalyst with the surface of zeolites see ref 18 and the following: (a) Narasaka, K.; Inoue, M.; Yamada, T.; Sugimori, J.; Iwasawa, N. *Chem. Lett.* **1987**, 2409−2412. (b) Iwasawa, N.; Hayashi, Y.; Sakurai, H.; Narasaka, K. *Chem. Lett.* **1989**, 1581−1584. (c) Ketter, A.; Glahsl, G.; Herrman, R. *J. Chem. Res. (S)* **1990**, 278−279. (d) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949−3954. (e) Narasaka, K.; Tanaka, H.; Kanai, F. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 387−391. (f) Seebach, D.; Plattner, D. A.; Beck, A. K.; Wang, Y. M.; Hunziker, D. *Helv. Chim. Acta* **1992**, *75*, 2171−2209. (g) Mikami, K.; Motoyama, Y.; Terada, M. *J. Am. Chem. Soc.* **1994**, *116*, 2812−2820. (h) Posner, G. H.; Dai, H.; Bull, D. S.; Lee, J.-K.; Eydoux, F.; Ishihara, Y.; Welsh, W.; Pryor, N.; Petr, S., Jr. *J. Org. Chem.* **1996**, *61*, 671−676. (i) Posner, G. H.; Dai, H.; Bull, D. S.; Lee, J.-K.; Eydoux, F.; Ishihara, Y.; Welsh, W.; Pryor, N.; Petr, S., Jr. *J. Org. Chem.* **1996**, *61*, 671−676. (j) Seebach, D.; Jaeschke, G.; Gottwald, K.; Matsuda, K.; Formisano, R.; Chaplin, D. A.; Brarning, M.; Bringmann, G. *Tetrahedron Lett.* **1997**, *53*, 7539−7556. (k) Jaeschke, G.; Seebach, D. *J. Org. Chem.* **1998**, *63*, 1190−1197. (l) Moharram, S. M.; Hirai, G.; Koyama, K.; Oguri, H.; Hirama, M. *Tetrahedron Lett.* **2000**, *41*, 6669−6673.

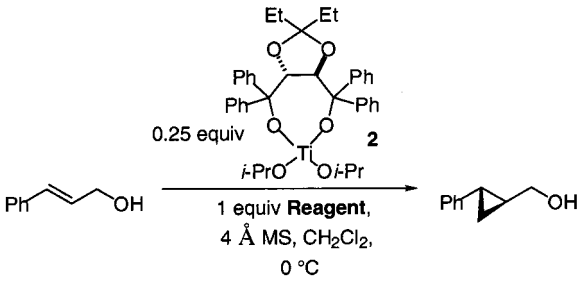
(31) For NMR and X-ray structures of this reagents as well as theoretical studies see: (a) Denmark, S. E.; Edwards, J. P.; Wilson, S. R. *J. Am. Chem. Soc.* **1991**, *113*, 723−725. (b) Denmark, S. E.; Edwards, J. P.; Wilson, S. R. *J. Am. Chem. Soc.* **1992**, *114*, 2592−2602. (c) Charette, A. B.; Marcoux, J.-F. *J. Am. Chem. Soc.* **1996**, *118*, 4539−4549. (d) Charette, A. B.; Marcoux, J.-F.; Bélanger-Gariépy, F. *J. Am. Chem. Soc.* **1996**, *118*, 6792−6793. (e) Dargel, T. K.; Koch, W. *J. Chem. Soc., Perkin Trans 2* **1996**, 877−881. (f) Bernardi, F.; Bottoni, A.; Miscione, G. P. *J. Am. Chem. Soc.* **1997**, *119*, 12300−12305. (g) Hirai, A.; Nakamura, M.; Nakamura, E. *Chem. Lett.* **1998**, 927−928. (h) Nakamura, E.; Hirai, A.; Nakamura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5844−5845. (i) Charette, A. B.; Marcoux, J.-F.; Molinaro, C.; Beauchemin, A.; Brochu, C.; Isabel, É. *J. Am. Chem. Soc.* **2000**, *122*, 4508−4509. (j) Hermann, H.; Lohrenz, J. C. W.; Kühn, A.; Boche, G. *Tetrahedron* **2000**, *56*, 4109−4115. (k) Bernardi, F.; Bottoni, A.; Miscione, G. P. *Organometallics* **2000**, *19*, 5529−5532. (l) Boche, G.; Lohrenz, J. C. W. *Chem. Rev.* **2001**, *101*, 697−756.

(32) (a) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron Lett.* **1966**, 3353−3354. (b) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53−58. (c) Nishimura, J. Furukawa, J.; Kawabata, N.; Kitayama, M. *Tetrahedron* **1971**, *27*, 1799−1806.

(33) See Experimental Section.

(34) The first equivalent deprotonates the alcohol to form the zinc alkoxide (ROZnI) and the second one will cyclopropanate the double bond.

Table 3. Effect of the Cyclopropanating Reagents on the Enantiomeric Ratios



entry	reagent	ZnI_2 (equiv)	conv.[a] (%)	er[b]
1[c]	$Zn(CH_2I)_2$ (−40 °C)		83	95:5
2[d]	$Zn(CH_2I)_2$ (−40 °C)		77	89:11
3[d]	$Zn(CH_2I)_2$ (−40 °C)	0.17	78	93:7
4[d]	$Zn(CH_2I)_2$ (−40 °C)	0.52	72	94:6
5[d]	$Zn(CH_2I)_2$ (−40 °C)	1	74	94:6
6[d]	$Zn(CH_2I)_2$ (−40 °C)	2	76	94:6
7[e,f]	$Zn(CH_2I)_2$ (−40 °C)	1	65	71:29
8[d]	$IZnCH_2I$		85	67:33
9[d]	$IZnCH_2I$·THF		90	89:11
10[d]	$EtZnCH_2I$[g]		43	81:19
11[c]	*i*-PrOZnCH_2I		74	87:13
12[h]	bipy·$Zn(CH_2I)_2$	2	75	88:12
13[h]	bipy·$Zn(CH_2Cl)_2$	1.5	70	88:12

[a] Conversions were evaluated by 400 MHz ^{1}H NMR. [b] The er were determined by GC on the chiral stationary phase. [c] The reaction was carried out by adding the allylic alcohol to a premixed suspension of the chiral catalyst **2**, 4 Å MS, and $Zn(CH_2I)_2$ at −40 °C. The mixture was warmed to 0 °C and quenched after 1.5 h. [d] The catalyst was not left under vacuum for 2 h before the cyclopropanation reaction. [e] The catalyst was pumped for 2 h under high vacuum at 80 °C. [f] No molecular sieves were used. [g] 1 equiv of $EtZnCH_2I$ was generated at −40 °C, from 1 equiv of Et_2Zn and 1 equiv of CH_2I_2. [h] 2 equiv of the reagent was used.

CH_2I_2 resulted in lower enantiomeric ratios than the corresponding example with $Zn(CH_2I)_2$ and 1 or 2 equiv of ZnI_2 (entries 8 and 9 vs 5 or 6, Table 3). Thus $IZnCH_2I$ does not seem to be the reagent that will give high enantiomeric ratios for this reaction. However, if one wishes to reduce the overall reaction times of this reaction and still maintain a certain level of selectivity, the protocol that uses $Zn(CH_2I)_2$ generated at −40 °C in the presence of ZnI_2 may be used.

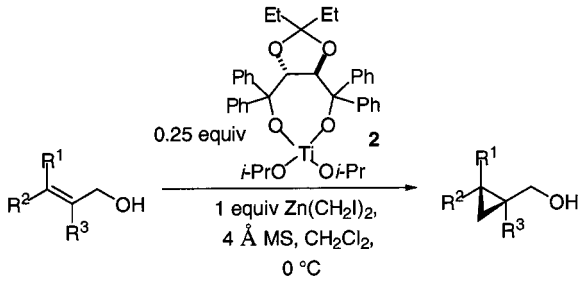
Another example which reinforces the idea that molecular sieves is not simply a *i*PrOH scavenger is represented in entry 7 of Table 3.

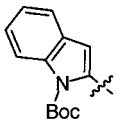
Noteworthy is that other zinc reagents never tested before for an asymmetric cyclopropanation such as $EtZnCH_2I$, *i*-PrOZnCH_2I, bipy·$Zn(CH_2I)_2$,[31i] and bipy·$Zn(CH_2Cl)_2$[31i] all showed quite interesting results with the titanium TADDOLate catalyst (entries 10−13, Table 3).

Finally, all the results compiled in Table 3 indicate that the important factors of this reaction are the procedure used for the preparation of the catalyst (it must be prepared in the presence of molecular sieves and left 2 h before use under vacuum) and that although many different types of cyclopropanating reagents can be used for this process the most effective one is $Zn(CH_2I)_2$.

Catalyst Loading vs Conversions and Enantiomeric Ratios. To determine the optimum catalyst loading for the enantioselective cyclopropanation of allylic alcohols, we studied the corresponding cyclopropanation of cinnamyl alcohol at various catalyst **2** loadings. The highest enantiomeric ratios were observed when the catalyst loading was between 0.25 and 0.45 equiv. Below or above that amount significantly lower enantiomeric ratios or conversions were observed. In the latter, this is probably due to the increase amount of residual 2-propanol that could eventually destroy the active methylene species. Therefore it was concluded that the optimal catalyst loading was 0.25 equiv of the Ti-TADDOLate complex and these reaction conditions were employed throughout the rest of our studies.[35]

Table 4. Enantioselective Cyclopropanation of Allylic Alcohols



Entry	R^1	R^2	R^3	Yield[a] (%)	er	er K-D[h]
1[g]	H	Ph	H	85	96 : 4 to 97 : 3[b]	---
2[g]	H	Ph	H	83	4 : 96[b,f]	5 : 95
3[h]	Ph	H	H	62	86 : 14[b]	9 : 91
4[g]	Me	Ph	H	80	94 : 6[b]	13 : 87
5[h]	H	Ph	Me	80	75 : 25[b]	47 : 53
6[g]	H	3,5-Me_2-Ph	H	86	96 : 4[b]	---
7[g]	H	2-napht	H	81	96 : 4[c]	---
8[h]	H	1-napht	H	80	92 : 8[c]	---
9[i]	H	*p*-Me-OPh	H	90	96 : 4[b]	---
10[g]	H	*p*-Cl-Ph	H	56	91 : 9[c]	---
11[h]	H	*p*-Cl-Ph	H	81	91 : 9[c]	---
12[h]	H	Pr	H	68	87 : 13[d]	---
13[h]	Pr	H	H	87	74 : 26[e]	---
14[h]	H	$PhCH_2CH_2$	H	63	80 : 20[c]	5 : 95
15[h]	H	Cyclohexyl	H	60	83 : 17[d]	---
16[h]	Me	Me	H	89	86 : 14[e]	---
17[g]	H		H	73	94 : 6[b]	---
18[g]	H		H	86	92 : 8[c]	---
19[g]	H		H	75	92 : 8[c]	---

[a] Isolated yield. [b] The er was determined by GC on the chiral stationary phase. [c] The er was determined by HPLC on the chiral stationary phase. [d] The er was determined by ^{19}F NMR of the corresponding Mosher ester. [e] The er was determined by ^{1}H NMR of the corresponding Mosher ester. [f] The other antipode of the catalyst was used. [g] Reaction time 1.5 h. [h] Reaction time 3 h. [i] Reaction time 75 min. [j] Comparison to the Kobayashi/Denmark system.

Conversions and Enantioselectivities as a Function of Time. Subsequently, a study of the enantioselectivities of the cyclopropanated product as a function of time was conducted to make sure that the Ti-TADDOLate complex was still the active catalyst throughout the reaction. This aspect is especially important in the cyclopropanation reaction since as the reaction proceeds several more acidic species are formed (such as ZnI_2 and ROZnI). Since our system is sensitive to air and water these reactions were carried out at −10 °C in a glovebox. Different aliquots of a single reaction taken at different times were analyzed. We were quite pleased to observe that the level of

(35) Similar results were observed when a Ti-TADDOLate catalyst obtained from $Ti(Oi\text{-}Pr)_2Cl_2$ and TADDOL was used instead of **1**.

enantioselectivity remained relatively constant throughout the reaction. It appears that the generation of ZnI_2 or the iodozinc alkoxides did not affect the enantioselective process.[36]

Scope of the Cyclopropanation Reaction. We finally examined the scope of the Ti-TADDOLate enantioselective cyclopropanation with a wide variety of allylic alcohols. The cyclopropanation reaction involved the addition of a preformed suspension of 0.25 equiv of Ti-TADDOLate (**2**) and 4 Å molecular sieves to 1 equiv of $Zn(CH_2I)_2$ followed by the allylic alcohol. The results are shown in Table 4. For comparison, the enantiomeric ratios under optimal conditions with the Kobayashi/Denmark chiral disulfonamide system (eq 1) are also provided. Ti-TADDOLate was quite an effective substoichiometric additive for generating enantiomerically enriched cyclopropylmethanols and gave excellent yields and enantiomeric ratios with 3-aryl-substituted allylic alcohols (entries 1, 2, and 6−11, Table 4). Generally, higher selectivities were obtained with *E*-allylic alcohols rather than with their corresponding *Z*-isomer (entries 1 vs 3 and 12 vs 13, Table 4). Acid-sensitive 3-furyl- and 3-indolyl-substituted allylic alcohols were also successfully converted into their corresponding cyclopropanes with excellent enantiomeric ratios (entries 17 and 18, Table 4). 2,3-Disubstituted and 3,3-disubstituted allylic alcohols were converted into their corresponding cyclopropane derivatives with modest and excellent enantiomeric ratios, respectively (entries 4 vs 5, Table 4). The cyclopropanation of alkyl-substituted allylic alcohols gave moderate enantiomeric ratios usually ranging from 74:26 to 87:13 depending on the substrate (entries 12−16, Table 4). Also, longer reaction times were usually required with these substrates. Quite interestingly, the cyclopropanation of a substituted 2,4-pentadien-1-ol produced the monocyclopropane with excellent chemo- and enantioselectivity (entry 19, Table 4).[37]

Conclusion. In conclusion, a very effective substoichiometric chiral ligand has been developed for the cyclopropanation of allylic alcohols. Our extensive studies indicate that 0.25 equiv of TADDOL-Ti(O*i*-Pr)$_2$ complex was optimal to get the highest enantiomeric ratios. Excellent yields and enantioselectivities were obtained for 3-aryl or 3-heteroaryl-substituted allylic alcohols. Alkyl-substituted allylic alcohols gave modest yields and enantioselectivities, but these compare favorably with those observed with other substoichiometric chiral ligands. Further studies are in progress to develop more effective catalysts for the alkyl-substituted allylic alcohols.

Experimental Section[38]

General Procedure for the Enantioselective Cyclopropanation: (+)-(1*S*,2*S*)-2-Phenylcyclopropylmethanol (entry 1, Table 4). Preparation of the catalyst: To a mixture of (4*R*,5*R*)-2,2-diethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol (144.6 mg, 0.29 mmol) and 4 Å molecular sieves (1.7 g) in anhydrous CH_2Cl_2 (5 mL) was added titanium (IV) isopropoxide (69.7 mg, 0.24 mmol). After the mixture was stirred at room temperature for 2 h the solvent was removed by a nitrogen or argon flow and the residue was left under high vacuum for 2 h. **Cyclopropanation:** To a stirred solution of diethylzinc (100 μL, 0.98 mmol) in anhydrous CH_2Cl_2 (3 mL) at −10 °C was added dropwise diiodomethane (160 μL, 1.99 mmol). The resulting solution was stirred at that temperature for 15 min and a white precipitate was formed. The solution was cooled at −40 °C for 5 min and the catalyst in anhydrous CH_2Cl_2 was added via cannula. The flask was rinsed with anhydrous CH_2Cl_2 (1 mL). The solution was stirred for 5 min and a solution of cinnamyl alcohol (131 mg, 0.976 mmol) in anhydrous CH_2Cl_2 (1 mL) was added. After another 5 min the solution was warmed to 0 °C. The resulting mixture was stirred at that temperature for 1.5 h. The solution was cooled at −40 °C and quickly transferred into an aqueous solution of 10% HCl and vigorously stirred. The biphasic solution was extracted 3 times with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$, saturated aqueous Na_2SO_3, and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was osmylated[39] (OsO_4 (catalyst), NMO (2 equiv), acetone/water (4:1)) and purified by flash chromatography on silica gel (10% EtOAc/Hexanes) to produce 123 mg (85%) of the desired cyclopropylmethanol: R_f 0.22 (20% EtOAc/Hexanes); $[\alpha]_D$ +74.7 (*c* 2.3, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.25 (m, 2H), 7.20−7.15 (m, 1H), 7.10−7.07 (m, 2H), 3.67−3.59 (m, 2H), 1.86−1.82 (m, 1H), 1.75 (s (br), 1H), 1.51−1.43 (m, 1H), 1.01−0.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 128.5, 125.3, 124.6, 66.0, 24.2, 21.4, 13.5; HRMS calcd for $C_{10}H_{12}O_1$ (M) 148.0888, found 148.0880. The enantiomeric ratio was determined by GC of the TFAA derivative (cyclodex-G-TA, 110 °C, 0.32 mm × 30 m, 25 psi) T_r(minor) 11.5 min, T_r(major) 12.0 min (er 96:4).

(−)-(1*R*,2*R*)-2-Phenylcyclopropylmethanol (entry 2, Table 4). The cyclopropanation of cinnamyl alcohol (131 mg, 0.98 mmol) was performed according to the previously described procedure (reaction time 1.5 h) but here the other antipode of the catalyst was used. The residue was purified by flash chromatography on silica gel (10% EtOAc/Hexanes) to produce the desired cyclopropylmethanol (120 mg, 83%): $[\alpha]_D$ −66.4 (*c* 2.0, $CHCl_3$). The enantiomeric ratio was determined by GC of the TFAA derivative (cyclodex-G-TA, 110 °C, 0.32 mm × 30 m, 25 psi) T_r(major) 11.5 min, T_r(minor) 12.0 min (er 4:96).

(+)-(1*S*,2*R*)-2-Phenylcyclopropylmethanol (entry 3, Table 4). The cyclopropanation of (*Z*)-3-phenyl-2-propenol (121 mg, 0.903 mmol) was performed according to the previously described procedure (reaction time 3 h). The residue was purified by flash chromatography on silica gel (20% EtOAc/Hexanes) to produce the desired cyclopropylmethanol (83 mg, 62%): R_f 0.30 (20% EtOAc/Hexanes); $[\alpha]_D$ +38.4 (*c* 3.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.25 (m, 4H), 7.22−7.18 (m, 1H), 3.49 (dd, J = 11.7, 6.3 Hz, 1H), 3.27 (dd, J = 11.7, 8.5 Hz, 1H), 2.31 (td, J = 8.4, 6.2 Hz, 1H), 1.56−1.46 (m, 1H), 1.08 (s (br), 1H), 1.05 (td, J = 8.4, 5.3 Hz, 1H), 0.89 (dd, J = 11.4, 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 128.7, 128.1, 126.0, 62.6, 20.7, 20.5, 7.5; HRMS calcd for $C_{10}H_{12}O_1$ (M) 148.0883, found 148.0888. The enantiomeric ratio was determined by GC of the TFAA derivative (cyclodex-G-TA, 90 °C, 0.32 mm × 30 m, 25 psi) T_r(minor) 10.5 min, T_r(major) 11.6 min (er 86:14).

(+)-(1*S*,2*S*)-2-Methyl-2-phenylcyclopropylmethanol (entry 4, Table 4). The cyclopropanation of (*E*)-3-phenyl-2-butenol (148 mg, 1.00 mmol) was performed according to the previously described procedure (reaction time 1.5 h). The residue was purified by flash chromatography on silica gel (25% EtOAc/Hexanes) to produce the desired cyclopropylmethanol (130 mg, 80%): R_f 0.29 (25% EtOAc/Hexanes); $[\alpha]_D$ +45.0 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.29 (m, 4H), 7.29−7.17 (m, 1H), 3.92 (dd, J = 11, 6 Hz, 1H), 3.71 (dd, J = 11, 8 Hz, 1H), 1.69 (s (br), 1H), 1.48 (s, 3H), 1.46−1.41

(36) A linear effect was observed when catalyst **2** solutions prepared from 1 equiv of TADDOL of the indicated enantiomeric excess and 1 equiv of Ti(O*i*-Pr)$_4$ were tested on cinnamyl alcohol: 31.5% ee TADDOL, 28% ee cyclopropylmethanol; 51.2% ee TADDOL, 48% ee cyclopropylmethanol; 75.2% ee TADDOL, 74% ee cyclopropylmethanol; 100% ee TADDOL, 92% ee cyclopropylmethanol. For a discussion on nonlinear effects in asymmetric catalysis see: (a) Guillaneux, D.; Zhao, S.-H.; Samuel, D.; Kagan, H. B. *J. Am. Chem. Soc.* **1994**, *116*, 9430−9439. (b) Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C. *Tetrahedron: Asymmetry* **1997**, *8*, 2997−3017. (c) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2922−2959. (d) Luukas, T. O.; Girard, C.; Fenwick, D. R.; Kagan, H. B. *J. Am. Chem. Soc.* **1999**, *121*, 9299−9306. (e) Mikami, K.; Terada, M.; Korenaga, T.; Matsumoto, Y.; ueki, M.; Angelaud, R. *Angew. Chem., Int. Ed.* **2000**, *39*, 3532−3556. (f) Blackmond, D. G. *J. Am. Chem. Soc.* **2001**, *123*, 545−553.

(37) The enantioselective cyclopropanation of cinnamyl alcohol with Zn(CHICH$_3$)$_2$, catalyst **2**, and 4 Å MS gave (1*S*,2*R*,3*S*)-(2-methyl-3-phenyl)-cyclopropylmethanol in 72% de and er for the major 60:40 and er for minor 55:45. The cyclopropanation of homoallylic alcohols or chiral secondary allylic alcohols gave low ee or de.

(38) See Supporting Information for general information.

(39) When a quantitative conversion to the cyclopropane was not achieved (and when both the alkene and the cyclopropane were not separable by chromatography), the crude product was treated with osmium tetroxide, O_3, or $KMnO_4$ to destroy any residual alkene and to facilitate the purification.

(m, 1H), 1.15 (dd, $J = 9$, 5 Hz, 1H), 0.61 (t, $J = 5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 128.2, 127.1, 125.7, 63.4, 27.7, 24.7, 20.4, 18.6; HRMS calcd for $C_{11}H_{14}O_1$ (M) 162.1045, found 162.1033. The enantiomeric ratio was determined by GC of the TFAA derivative (cyclodex-G-TA, 100 °C, 0.32 mm × 30 m, 25 psi) T_r(minor) 10.8 min, T_r(major) 11.2 min (er 94:6).

(+)-(1*S*,2*S*)-1-Methyl-2-phenylcyclopropylmethanol (entry 5, Table 4). The cyclopropanation of (*E*)-2-methyl-3-phenyl-2-propenol (148 mg, 1.00 mmol) was performed according to the previously described procedure (reaction time 3 h). The residue was purified by flash chromatography on silica gel (30% EtOAc/Hexanes) to produce the desired cyclopropylmethanol (130 mg, 80%): R_f 0.14 (20% EtOAc/Hexanes); $[\alpha]_D$ +13.9 (*c* 1.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.26 (m, 2H), 7.22−7.17 (m, 3H), 3.57 (d, $J = 11$ Hz, 1H), 3.53 (d, $J = 11$ Hz, 1H), 2.06 (dd, $J = 9$, 6 Hz, 1H), 1.57 (s (br), 1H), 0.94 (dd, $J = 9$, 5 Hz, 1H), 0.89 (s, 3H), 0.87 (t, $J = 5$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 129.0, 127.9, 125.8, 71.6, 26.6, 25.0, 15.6, 15.0; HRMS calcd for $C_{11}H_{14}O_1$ (M) 162.1045, found 162.1047. The enantiomeric ratio was determined by GC of TFAA derivative (cyclodex-G-TA, 110 °C, 0.32 mm × 30 m, 25 psi) T_r(minor) 8.6 min, T_r(major) 8.8 min (er 75:25).

(+)-(1*S*,2*S*)-2-(3,5-Dimethylphenyl)cyclopropylmethanol (entry 6, Table 4). The cyclopropanation of (*E*)-3-(3,5-dimethylphenyl)-2-propenol (162 mg, 0.996 mmol) was performed according to the previously described procedure (reaction time 1.5 h). The residue was purified by flash chromatography on silica gel (25% EtOAc/Hexanes) to produce the desired cyclopropylmethanol (151 mg, 86%): R_f 0.20 (20% EtOAc/Hexanes); $[\alpha]_D$ +67.6 (*c* 0.94, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (s, 1H), 6.71 (s, 2H), 3.63 (d, $J = 2$ Hz, 1H), 3.61 (d, $J = 2$ Hz, 1H), 2.30 (s, 6H), 1.80−1.74 (m, 1H), 1.76 (s (br), 1H), 1.50−1.42 (m, 1H), 1.00−0.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 137.8, 127.3, 123.6, 66.6, 25.0, 21.2, 21.17, 21.06, 13.5; HRMS calcd for $C_{12}H_{17}O_1$ (M + H) 177.1279, found 177.1275. The enantiomeric ratio was determined by GC of the TFAA derivative (cyclodex-G-TA, 110 °C, 0.32 mm × 30 m, 25 psi) T_r(minor) 20.2 min, T_r(major) 21.5 min (er 96:4).

(+)-(1*S*,2*S*)-2-Naphthylcyclopropylmethanol (entry 7, Table 4). The cyclopropanation of (*E*)-3-(2-naphthyl)-2-propenol (183 mg, 0.995 mmol) was performed according to the previously described procedure (reaction time 1.5 h). The residue was purified by flash chromatography on silica gel (25% EtOAc/Hexanes) to produce the desired cyclopropylmethanol (160 mg, 81%): R_f 0.28 (25% EtOAc/Hexanes); $[\alpha]_D$ +62.4 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82−7.75 (m, 3H), 7.55−7.40 (m, 3H), 7.20 (dd, $J = 8$, 2 Hz, 1H), 3.68−3.66 (m, 2H), 2.02−1.97 (m, 1H), 1.83 (s (br), 1H), 1.59−1.54 (m, 1H), 1.11−1.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 133.4, 131.9, 127.9, 127.5, 127.2, 126.0, 125.0, 124.6, 124.0, 66.4, 25.2, 21.4, 13.7; HRMS calcd for $C_{14}H_{14}O_1$ (M: 198.1044, found 198.1039. The enantiomeric ratio was determined by HPLC (chiralcel-OD: 4% *i*PrOH/Hexanes) T_r(major) 32.3 min, T_r(minor) 43.1 min (er 96:4).

(+)-(1*S*,2*S*)-1-Naphthylcyclopropylmethanol (entry 8, Table 4). The cyclopropanation of (*E*)-3-(1-naphthyl)-2-propenol (184 mg, 0.996 mmol) was performed according to the previously described procedure (reaction time 3 h). The residue was purified by flash chromatography on silica gel (25% EtOAc/Hexanes) to produce the desired cyclopropylmethanol (158 mg, 80%): R_f 0.35 (40% EtOAc/Hexanes); $[\alpha]_D$ +13.9 (*c* 2.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (dd, $J = 7$, 1 Hz, 1H), 7.88 (dd, $J = 7$, 1 Hz, 1H), 7.75 (d, $J = 8$ Hz, 1H), 7.60−7.52 (m, 2H), 7.41 (t, $J = 8$ Hz, 1H), 7.30 (m, 1H), 3.84 (d, $J = 3$ Hz, 1H), 3.81 (d, $J = 3$ Hz, 1H), 2.38−2.27 (m, 1H), 1.93 (s, 1H), 1.57−1.46 (m, 1H), 1.10−0.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 133.5, 133.2, 128.5, 126.8, 125.8, 125.6, 125.4, 124.2, 123.9, 66.7, 22.8, 19.1, 11.2; HRMS calcd for $C_{14}H_{14}O_1$ (M) 198.1044, found 198.1050. The enantiomeric ratio was determined by HPLC (chiralcel-OD: 4% *i*PrOH/Hexanes) T_r(major) 28.5 min, T_r(minor) 33.7 min (er 92:8).

(+)-(1*S*,2*S*)-2-(*p*-Methoxyphenyl)cyclopropylmethanol (entry 9, Table 4). The cyclopropanation of (*E*)-3-(*p*-methylphenyl)-2-propenol (164 mg, 0.997 mmol) was performed according to the previously described procedure (reaction time 1.25 h). The residue was purified by flash chromatography on silica gel (35% EtOAc/Hexanes) to produce the desired cyclopropylmethanol (160 mg, 90%): mp 47−49 °C; R_f 0.24 (30% EtOAc/Hexanes); $[\alpha]_D$ +71.9 (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03−6.99 (m, 2H), 6.83−6.79 (m, 2H), 3.78 (s, 3H), 3.64 (dd, $J = 11$, 7 Hz, 1H), 3.59 (dd, $J = 11$, 7 Hz, 1H), 1.47 (s (br), 1H), 1.49−1.35 (m, 1H), 0.93−0.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 134.2, 126.8, 113.7, 66.6, 55.2, 24.6, 20.4, 13.2; HRMS calcd for $C_{11}H_{14}O_2$ (M) 178.0994, found 178.0999. The enantiomeric ratio was determined by GC of the TFAA derivative (cyclodex-G-TA, 117 °C, 0.32 mm × 30 m, 25 psi) T_r(minor) 25.3 min, T_r(major) 26.2 min (er 96:4).

(+)-(1*S*,2*S*)-2-(*p*-Chlorophenyl)cyclopropylmethanol (entry 10, Table 4). The cyclopropanation of (*E*)-3-(*p*-chlorophenyl)-2-propenol (141 mg, 0.836 mmol) was performed according to the previously described procedure (reaction time 1.5 h). The residue was purified by flash chromatography on silica gel (35% EtOAc/Hexanes) to produce the desired cyclopropylmethanol (86 mg, 56%): R_f 0.21 (30% EtOAc/Hexanes); $[\alpha]_D$ +69.8 (*c* 3.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.21 (m, 2H), 7.03−6.98 (m, 2H), 3.63 (d, $J = 7$ Hz, 2H), 1.84−1.78 (m, 1H), 1.51 (s (br), 1H), 1.48−1.37 (m, 1H), 0.99−0.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 131.1, 128.3, 127.1, 66.1, 25.2, 20.7, 13.8; HRMS calcd for $C_{10}H_{11}O_1Cl_1$ (M) 182.0498, found 182.0501. The enantiomeric ratio was determined by HPLC (chiralcel-OD: 2% *i*PrOH/Hexanes) T_r(major) 20.9 min, T_r(minor) 23.3 min (er 91:9).

(+)-(1*S*,2*S*)-2-(*para*-Chlorophenyl)cyclopropylmethanol (entry 11, Table 4). The cyclopropanation of (*E*)-3-(*p*-chlorophenyl)-2-propenol (135 mg, 0.801 mmol) was performed according to the previously described procedure (reaction time 3 h). The residue was purified by flash chromatography on silica gel (35% EtOAc/Hexanes) to produce the desired cyclopropylmethanol (118 mg, 81%): $[\alpha]_D$ +72.4 (*c* 3.0, $CHCl_3$). The enantiomeric ratio was determined by HPLC (chiralcel-OD: 2% *i*PrOH/Hexanes) T_r(major) 20.9 min, T_r(minor) 23.3 min (er 91:9).

(+)-(1*S*,2*S*)-2-Propylcyclopropylmethanol (entry 12, Table 4). The cyclopropanation of (*E*)-2-hexenol (99 mg, 0.992 mmol) was performed according to the previously described procedure (reaction time 3 h). The residue was purified by flash chromatography on silica gel (25% EtOAc/Hexanes) to produce the desired cyclopropylmethanol (77 mg, 68%): R_f 0.18 (20% EtOAc/Hexanes); $[\alpha]_D$ +25.6 (*c* 3.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.50−3.39 (m, 2H), 1.44−1.35 (m, 2H), 1.30−1.20 (m, 3H), 0.92 (t, $J = 7$ Hz, 3H), 0.90−0.80 (m, 1H), 0.68−0.58 (m, 1H), 0.40−0.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 66.9, 35.8, 22.5, 19.9, 16.7, 13.8, 9.6. The enantiomeric ratio was determined by ^{19}F NMR of the Mosher ester derivative: −73.15 ppm (major), −73.19 ppm (minor) (er 87:13).

(+)-(1*S*,2*R*)-2-Propylcyclopropylmethanol (entry 13, Table 4). The cyclopropanation of (*Z*)-hexenol (76 mg, 0.759 mmol) was performed according to the previously described procedure (reaction time 3 h). The residue was purified by flash chromatography on silica gel (25% EtOAc/Hexanes) to produce the desired cyclopropylmethanol (75 mg, 87%): R_f 0.25 (20% EtOAc/Hexanes); $[\alpha]_D$ +17.0 (*c* 2.0, $CHCl_3$);^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (dd, $J = 11$, 7 Hz, 1H), 3.58 (dd, $J = 11$, 8 Hz, 1H), 1.49−1.37 (m, 3H), 1.32−1.18 (m, 2H), 1.15−1.05 (m, 1H), 0.94 (t, $J = 7$ Hz, 3H), 0.98−0.83 (m, 1H), 0.71 (td, $J = 8$, 5 Hz, 1H), −0.03 (dd, $J = 10$, 5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 63.3, 30.6, 23.1, 18.0, 15.8, 13.9, 9.3; HRMS calcd for $C_7H_{14}O_1$ (M) 114.1045, found 114.1038. The enantiomeric ratio was estimated by ^{1}H NMR of Mosher ester derivative: 4.44 ppm (major), 4.49 ppm (minor) (er 74:26).

(+)-(1*S*,2*S*)-2-(2-Phenylethyl)cyclopropylmethanol (entry 14, Table 4). The cyclopropanation of (*E*)-5-phenyl-2-pentenol (162 mg, 1.00 mmol) was performed according to the previously described procedure (reaction time: 3 h). The residue was purified by flash chromatography on silica gel (25% EtOAc/Hexanes) to produce the desired cyclopropylmethanol (111 mg, 63%): R_f 0.28 (20% EtOAc/Hexanes); $[\alpha]_D$ +14.8 (*c* 2.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.17 (m, 5H), 3.47−30.32 (m, 2H), 2.77−2.64 (m, 2H), 1.70−1.48 (m, 2H), 1.16 (s (br), 1H), 0.88−0.80 (m, 1H), 0.67−0.59 (m, 1H), 0.41−0.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 128.4, 128.2, 125.7, 66.9, 35.8, 35.3, 21.3, 16.8, 9.7; HRMS calcd for $C_{12}H_{15}$ (M − OH) 159.1174, found 159.1169. The enantiomeric ratio was determined

by HPLC (chiralcel-OD: 1% *i*PrOH/Hexanes) T_r(major) 24.3 min, T_r(minor) 31.1 min (er 80:20).

(+)-(1*S*,2*S*)-2-Cyclohexylcyclopropylmethanol (entry 15, Table 4). The cyclopropanation of (*E*)-3-cyclohexyl-2-propenol (139 mg, 0.994 mmol) was performed according to the previously described procedure (reaction time 3 h). The residue was purified by flash chromatography on silica gel (23% EtOAc/Hexanes) to produce the desired cyclopropylmethanol (92 mg, 60%): R_f 0.22 (20% EtOAc/Hexanes); $[\alpha]_D$ +26.0 (*c* 2.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.44 (dd, J = 11, 7 Hz, 1H), 3.39 (dd, J = 11, 7 Hz, 1H), 1.78−1.68 (m, 4H), 1.63−1.62 (m, 1H), 1.30 (s (br), 1H), 1.20−1.01 (m, 5H), 0.91−0.83 (m, 1H), 0.61−0.52 (m, 1H), 0.42 (sept, 1H), 0.37−0.31 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 67.1, 41.8, 33.0, 32.7, 26.4, 26.1, 23.9, 19.9, 8.6; HRMS calcd for $C_{10}H_{16}$ (M − H_2O) 136.1252, found 136.1247. The enantiomeric ratio was determined by ^{19}F NMR of the Mosher ester derivative: −73.08 ppm (major), −73.12 ppm (minor) (er 83:17).

(+)-(1*S*)-2,2-Dimethylcyclopropylmethanol (entry 16, Table 4). The cyclopropanation of 3-methyl-2-butenol (87 mg, 1.00 mmol) was performed according to the previously described procedure (reaction time 3 h). The residue was purified by flash chromatography on silica gel (25% EtOAc/Hexanes) to produce the desired cyclopropylmethanol (90 mg, 89%): R_f 0.20 (20% EtOAc/Hexanes); $[\alpha]_D$ −1.65 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (dd, J = 11, 7 Hz, 1H), 3.53 (dd, J = 11, 8 Hz, 1H), 1.12 (s, 3H), 1.08 (s, 3H), 0.96−0.87 (m, 1H), 0.49 (dd, J = 8, 4 Hz, 1H), 0.12 (t, J = 8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 63.8, 27.1, 26.5, 19.6, 18.1, 15.9. The enantiomeric ratio was estimated by ^{1}H NMR of Mosher ester derivative: 4.53 ppm (major), 4.58 ppm (minor) (er 86:15).

(+)-(1*S*,2*S*)-2-(Furan-2-yl)cyclopropylmethanol (entry 17, Table 4). The cyclopropanation of (*E*)-2-(prop-1-en-3-ol)furane (117 mg, 0.94 mmol) was performed according to the previously described procedure (reaction time 1.5 h). The residue was purified by flash chromatography on silica gel (15% EtOAc/Hexanes) to produce the desired cyclopropylmethanol (95 mg, 73%): R_f 0.14 (30% EtOAc/Hexanes); $[\alpha]_D$ +73.5 (*c* 2.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, J = 2, 1 Hz, 1H), 6.27 (dd, J = 3, 2 Hz, 1H), 5.97 (dt, J = 3, 1 Hz, 1H), 3.61 (dd, J = 11, 7 Hz, 1H), 3.59 (dd, J = 11, 7 Hz, 1H), 1.87−1.82 (m, 1H), 1.57−1.49 (m, 2H), 1.04 (dt, J = 9, 5 Hz, 1H), 0.88−0.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 140.4, 110.2, 103.6, 65.6, 22.6, 14.3, 11.2; HRMS calcd for $C_8H_{10}O_2$ (M) 138.0680, found 138.0676. Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.48; H, 7.29. The enantiomeric ratio was determined by GC of the TFAA derivative (cyclodex-G-TA, 105 °C, 0.32 mm × 30 m, 25 psi) T_r(minor) 40.3 min, T_r(major) 40.9 min (er 94:6).

(+)-(1*S*,2*S*)-2-(*tert*-Butylcarbonylindole)cyclopropylmethanol (entry 18, Table 4). The cyclopropanation of 1-*tert*-butylcarbonyl-3-(prop-1-en-3-ol)indole (90 mg, 0.33 mmol) was performed according to the previously described procedure (reaction time 1.5 h). The residue was purified by flash chromatography on silica gel (5% Et_3N/15% EtOAc/80% Hexanes) to produce the desired cyclopropylmethanol (81 mg, 86%): R_f 0.21 (30% EtOAc/Hexanes); $[\alpha]_D$ +21.5 (*c* 1.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.67 (d, J = 7 Hz, 1H), 7.34−7.23 (m, 3H), 3.71 (dd, J = 11, 7 Hz, 1H), 3.66 (dd, J = 11, 7 Hz, 1H), 1.85−1.80 (m, 1H), 1.66 (s, 9H), 1.66 (s, 1H), 1.47−1.40 (m, 1H), 1.00−0.95 (m, 1H), 0.93−0.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 130.8, 124.3, 122.3, 122.0, 121.3, 118.9, 115.1, 83.3, 66.5, 28.1, 22.6, 11.7, 11.1; HRMS calcd for $C_{17}H_{21}N_1O_3$ 287.1521, found 287.1511. The enantiomeric ratio was determined by HPLC (chiralcel-OD: 1% *i*PrOH/Hexanes) T_r(major) 37.5 min, T_r(minor) 43.6 min (er 92:8).

(+)-(1*S*,2*S*)-2-(2-Phenylethenyl)cyclopropylmethanol (entry 19, Table 4). The cyclopropanation of (2*E*,4*E*)-5-phenyl-2,4-pentadienol (161 mg, 1.00 mmol) was performed according to the previously described procedure (reaction time 1.5 h). The residue was purified by flash chromatography on silica gel (20% EtOAc/Hexanes) to produce the desired cyclopropylmethanol (131 mg, 75%): R_f 0.29 (20% EtOAc/Hexanes); $[\alpha]_D$ +51.2 (*c* 1.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.17 (m, 5H), 6.47 (d, J = 16 Hz, 1H), 5.80 (dd, J = 16, 8 Hz, 1H), 3.57 (d, J = 7 Hz, 2H), 1.65 (s (br), 1H), 1.55−1.47 (m, 1H), 1.32−1.25 (m, 1H), 0.80 (t, J = 7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 132.7, 128.4, 128.0, 126.7, 125.6, 66.2, 23.4, 20.3, 12.0; HRMS calcd for $C_{12}H_{14}O_1$ (M) 157.1017, found 157.1019. The enantiomeric ratio was determined by HPLC after hydrogenation (chiralcel-OD: 1% *i*PrOH/Hexanes) T_r(major) 24.3 min, T_r(minor) 31.1 min (er 92:8).

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Supporting Information Available: Experimental procedures and characterization data for all the tabulated examples and experimental procedures for the synthesis of starting materials (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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