Enantioselective Cyclopropanation of Allylic Alcohols with Dioxaborolane Ligands: Scope and Synthetic Applications

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Abstract: A very effective chiral controller has been found for the conversion of allylic alcohols into the corresponding enantiomerically enriched cyclopropanes using bis(iodomethyl)zinc. A variety of chiral, nonracemic cyclopropylmethanols could be obtained according to this method. This methodology was extended with success to the cyclopropanation of unconjugated and conjugated polyenes and homoallylic alcohols. The cyclopropanation of allylic carbamates has also been investigated with this system, but it was found that enantioenriched cyclopropylmethylamines are best prepared from enantioenriched cyclopropylmethanols.

Introduction

The chiral cyclopropane subunit is found in a wide range of natural and unnatural products possessing important biological properties.[1] Recently, many efforts have focused on the development of stereoselective methods to facilitate access to enantioenriched cyclopropanes. The stereoselective versions involving the haloalkylzinc reagents[2] are among the most successful methods to generate chiral, nonracemic cyclopropanes.[3] These methods have been particularly effective in generating oxygen-containing cyclopropanes. Several covalently bound chiral auxiliaries have been developed for the cyclopropanation of allylic alcohols using zinc reagents, but three steps are required to make one transformation.[4] Early examples using chiral modifiers in the Simmons−Smith cyclopropanation reaction gave very low selectivities.[5] In 1992, Fujisawa reported moderate levels of enantioselection when a stoichiometric amount of diethyl tartrate was added to a mixture of allylic alcohol, diethylzinc, and diiodomethane.[6] Two substoichiometric chiral systems have been described, but limited success has been achieved thus far. In 1992, Kobayashi reported relatively good enantioselectivities when a C_2-symmetric chiral disulfonamide ligand was added in a catalytic amount to the zinc-mediated cyclopropanation of allylic alco-

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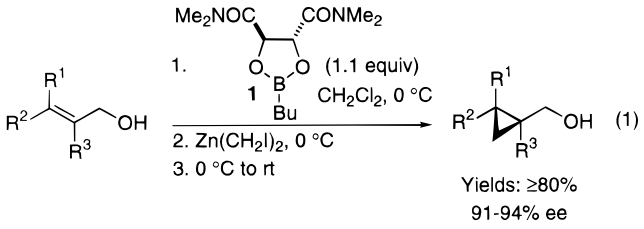
hols.[7] Recently, we reported that the addition of titanium TADDOLate in substoichiometric amounts allowed the conversion of 3-aryl-substituted allylic alcohols to the corresponding cyclopropane derivatives in enantiomeric excesses as high as 91%.[8] However, both systems show limitations as they are very capricious and highly substrate dependent.

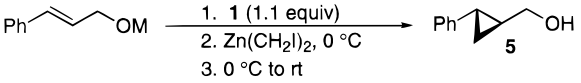
Recently, we reported that a new, amphoteric, bifunctional, chiral, dioxaborolane ligand derived from (*R*,*R*)-(+)-*N*,*N*,*N*′,*N*′-tetramethyltartaric acid diamide (**1**) was an efficient chiral controller for the enantioselective conversion of allylic alcohols to substituted cyclopropylmethanols in both high yields and enantiomeric excesses (eq 1).[9,10] The design of the dioxaborolane **1** relied on the presence of an acidic (boron) and a basic (amide) site that allowed the simultaneous complexation of the acidic halomethylzinc reagent and the basic allylic metal alkoxide. In this paper, we report a detailed study of this ligand for the enantioselective generation of cyclopropanes as well as a detailed investigation of reaction parameters along with a survey of the synthetic applications.



Results and Discussion

Chiral Dioxaborolane Synthesis. The chiral dioxaborolane **1** was originally prepared from butylboronic acid (**2**) and (*R*,*R*)-(+)-*N*,*N*,*N*′,*N*′-tetramethyltartaric acid diamide (**3**) under dehydrating conditions. Both precursors are readily available. Hence, diamide **3** and its enantiomer are commercially available or can easily be prepared using Seebach's procedure[11] and butylboronic acid is produced in a relatively good yield by the addition of butylmagnesium bromide to trimethylborate followed by an acidic hydrolysis. It is known, however, that alkylboronic acids are relatively unstable.[12] Thus, when dehydrated, butylboronic acid is transformed into tributylboroxine (a colorless oil) which is readily oxidized by air to *n*-butanol and boric acid. Alternatively, direct oxidation of butylboronic acid leads eventually to the same products. To avoid these complications, we developed an alternative procedure which involves the quick transformation of the unstable butylboronic acid into its air-stable and more robust diethanolamine derivative **4** (Scheme 1). This diethanolamine complex **4**, when treated with a slight excess of diamide in a biphasic medium, reacted to give the desired chiral dioxaborolane ligand **1** in a 93% yield. This sequence significantly simplified the synthesis of dioxaborolane **1** which could now be prepared on a multigram scale in high purity and shorter reaction times.[13]

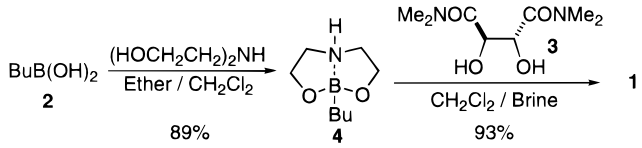
Table 1. Effect of the Metal Alkoxides and Solvents on Enantioselectivity[a]



entry	M	equiv	solvent	ee,[b,c] %
1	Li	5.0	CH_2Cl_2	88
2	Na	5.0	CH_2Cl_2	58
3	K	5.0	CH_2Cl_2	91
4	MgBr	5.0	CH_2Cl_2	33
5	ZnEt	5.0	CH_2Cl_2	85
6	H	5.0	CH_2Cl_2	93
7	H	2.2	CH_2Cl_2	93
8[d]	H	1.0	CH_2Cl_2	93
9	H	5.0	toluene	93
10	H	5.0	$(ClCH_2)_2$	90
11	H	5.0	*t*-BuOMe	89
12	H	5.0	ether	77
13	H	5.0	DMF	81

[a] The zinc reagent was preformed at 0 °C and, after the addition of the substrate and ligand, warmed to rt. [b] The enantioselectivities were determined by chiral GC. [c] Unless otherwise noted, conversions were >95%. [d] 85% conversion based on unreacted starting material.

Scheme 1



Methodology Improvements. The optimization of the cyclopropanation reaction using the dioxaborolane ligand **1** was done on cinnamyl alcohol. Initial investigations were carried out using preformed metal alkoxides of the cinnamyl alcohol in the presence of an excess of bis(iodomethyl)zinc ($Zn(CH_2I)_2$) and a stoichiometric amount of the dioxaborolane **1** (Table 1).[9] The conversions to the corresponding cyclopropylmethanol were excellent in most cases (>95%), and the enantioselectivities were found to be quite dependent on the nature of the metal alkoxide (entries 1−5, Table 1) with potassium alkoxide giving the highest ee's (91%). It was later established that the preformation of the metal alkoxide was not mandatory and adding a solution of the alcohol and dioxaborolane **1** to a preformed suspension of $Zn(CH_2I)_2$ led to the desired product in both high conversion and enantiomeric excess (entry 6, Table 1). Also, a significant decrease in the enantioselectivity was observed when the reaction was carried out in coordinating solvents such as ethers (entries 11−13, Table 1). Further studies on the effects of solvent and number of equivalents of $Zn(CH_2I)_2$ (entries 6−13, Table 1) revealed that 2 equiv of the zinc reagent in dichloromethane (entry 7, Table 1) constituted the optimal

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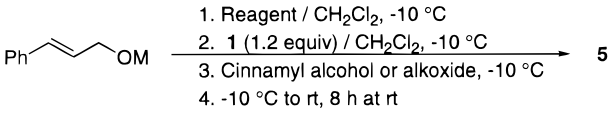
Table 2. Optimization of the Cyclopropanation with $RZnCH_2I$ ($R = CH_2I$, I)[a]



entry	M	reagent (*x* equiv)	conv,[b] %	ee,[c] %
1	H	$Zn(CH_2I)_2$·DME (5.0)[d]	≥98	90
2	H	$Zn(CH_2I)_2$·DME (2.0)[d]	≥98	90
3	H	$Zn(CH_2I)_2$·DME (2.0)	≥98	94
4	H	$Zn(CH_2I)_2$·DME (1.5)	90−95	94
5	ZnEt[e]	$Zn(CH_2I)_2$·DME (2.0)	≥98	93
6[f]	ZnEt[e]	$Zn(CH_2I)_2$·DME (2.0)	70	88
7	ZnI·THF[g]	$Zn(CH_2I)_2$·DME (2.0)	≥98	93
8	H	$Zn(CH_2I)_2$·THF (2.0)	≥98	93
9	H	$IZn(CH_2I)_2$·THF (4.0)	≥98	91
10	H	$IZn(CH_2I)_2$·THF (3.0)	≥98	93
11	ZnEt[e]	$IZn(CH_2I)_2$·THF (2.0)	≥98	92
12	ZnI·THF[g]	$IZn(CH_2I)_2$·THF (2.0)	≥98	94
13[f]	ZnI·THF[g]	$IZn(CH_2I)_2$·THF (2.0)	80	78

[a] Unless otherwise noted, all the reactions were carried out by mixing the preformed zinc reagent with **1** at −10 °C, then adding cinnamyl alcohol (or its metal alkoxide) at −10 °C, and finally warming the reaction mixture to rt. [b] Determined by ^{1}H NMR and based on unreacted starting material. [c] Determined by chiral GC. [d] Only 1.1 equiv of the dioxaborolane **1** was used. [e] Prepared from 1 equiv of Et_2Zn and 1 equiv of cinnamyl alcohol in CH_2Cl_2 at −10 °C. [f] The reaction was started and stirred 8 h at −30 °C. [g] Prepared from 1 equiv of EtZnI·THF and 1 equiv of cinnamyl alcohol in CH_2Cl_2 at −10 °C.

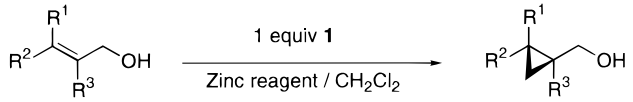
conditions for obtaining the highest conversion and ee's of the cyclopropanation adduct.

This original procedure was suitable for the preparation of a wide range of cyclopropylmethanol derivatives in high enantioselectivities on a *<1.0 mmol scale* only. *On a larger scale (8 mmol), this procedure sometimes led to violent explosions, due to the exothermicity of the formation of $Zn(CH_2I)_2$ or of the zinc alkoxide without a complexing additive.*[14] The potentially numerous applications of this methodology prompted us to report a safer procedure for large scale reactions using a homogeneous solution of $Zn(CH_2I)_2$·DME in dichloromethane.[15]

The optimization of this procedure is shown in Table 2. The allylic alcohol was added to a mixture of dioxaborolane **1** and a soluble version of the zinc reagent ($Zn(CH_2I)_2$·DME)[16] in CH_2Cl_2 at −10 °C. The homogeneous mixture was then warmed to room temperature and stirred for 8 h. It was shown that the reaction did not go to completion when less than 2 equiv of $Zn(CH_2I)_2$·DME was used (entry 4, Table 2). Furthermore, the enantioselectivities were slightly lower when 1.1 equiv of the dioxaborolane **1** was used (entries 1 and 2, Table 2). The preformation of the zinc alkoxide or running the reaction at a lower temperature gave no noticeable advantage (entries 5−7, Table 2). The best results were found when 2 equiv of $Zn(CH_2I)_2$·DME was used with 1.2 equiv of the dioxaborolane **1** in CH_2Cl_2 at −10 °C; under these conditions, the corresponding cyclopropylmethanol **5** was obtained in high conversion and 94% enantiomeric excess (entry 3, Table 2). This new procedure is safer and applicable to the preparation of a wide range of cyclopropylmethanols on a larger scale (>0.1 mol) (vide infra).

It should be pointed out that $IZnCH_2I$·DME is formed in small amounts when $Zn(CH_2I)_2$·DME is prepared from Et_2Zn (2 equiv), CH_2I_2 (4 equiv), and DME (2 equiv) at −10 °C.[16] This reagent ($IZnCH_2I$) is also a byproduct of the cyclopropanation with $Zn(CH_2I)_2$. For these reasons, we have also explored the cyclopropanation of cinnamyl alcohol with the dioxaborolane **1** using $IZnCH_2I$·THF as the source of methylene.[17] The results obtained with 2 equiv of $Zn(CH_2I)_2$·THF are similar to those obtained with 3 equiv of $IZnCH_2I$·THF (entries 8 and 10, Table 2). Finally, the enantioselectivities were not significantly improved when the preformed zinc alkoxides were used in the presence of $IZnCH_2I$·THF (entries 11 and 12, Table 2) or when the reaction was carried out at −30 °C (entry 13, Table 2). In conclusion, $IZnCH_2I$ is as efficient as $Zn(CH_2I)_2$ for the enantioselective cyclopropanation with the chiral ligand **1**. We also developed a special workup procedure in order to separate and recover the two major components of the reaction mixture which are the (*R,R*)-(+)-*N,N,N′,N′*-tetramethyltartaric acid diamide **3** and the cyclopropylmethanol **5** (see Experimental Section).[18]

Table 3. Enantioselective Cyclopropanation of Substituted Allylic Alcohols



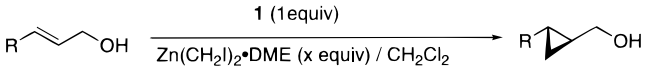
entry	R_1	R_2	R_3	proc[a]	yield,[b] % (**cpd**)	ee,[c] %
1	H	Ph	H	A	>98 (**5**)	93[d]
				B	95 (**5**)	94[d]
2	H	3-MeOPh	H	B	>98 (**6**)	93[d]
3	H	Pr	H	A	80 (**7**)	93[e]
4	H	$PhCH_2CH_2$	H	B	90 (**8**)	94[f]
5	H	$BnOCH_2$	H	B	87 (**9**)	94[f]
6	H	Bu_3Sn	H	A	82 (**10**)	ca. 90[g]
				B	88 (**10**)	ca. 90[g]
7	H	I	H	C	83 (**11**)	90[h]
8	Bu_3Sn	H	H	B	73 (**12**)	ca. 90[g]
9	I	H	H	C	71 (**13**)	83[e]
10	CH_3CH_2	H	H	A	90 (**14**)	93[h]
				D	>98[i] (**14**)	ca. 87[g]
11	$TBDPSOCH_2$	H	H	A	80 (**15**)	91[h]
12	$BnOCH_2$	H	H	A	93 (**16**)	91[f]
				B	92 (**16**)	91[f]
13	CH_3	CH_3	H	A	85 (**17**)	94[h]
14	H	Ph	CH_3	A	96 (**18**)	85[d]
				B	80 (**18**)	82[d]
15	H	CH_3CH_2	CH_2OTIPS	B	>98 (**19**)	89[e]
16	CH_3	CH_3	CH_2OTIPS	B	85 (**20**)	88[h]
17	H	$-CH_2CH_2CH_2CH_2-$		B	84 (**21**)	60[h]

[a] Procedure A (*with <1.0 mmol*): 2 equiv of $Zn(CH_2I_2)$ at 0 °C, then rt for 2 h. Procedure B (*with <1.0 mmol*): 2 equiv of $Zn(CH_2I)_2$·DME at −10 °C, then rt for 8 h. Procedure C (*with <1.0 mmol*): 5 × 2 equiv of $Zn(CH_2I)_2$·DME at −10 °C. Procedure D: dioxaborolane **22** was used instead of **1**. [b] Unless otherwise noted, these are isolated yields. Due to the volatility of the products of entries 3, 10, and 13, the crude alcohols were converted into benzoates. [c] The absolute stereochemistry was established for entries 1, 4−6, 8, 11−13, and 15 by comparing the sign of the optical rotation with literature data. [d] Determined by chiral GC. [e] Determined by ^{19}F NMR of the corresponding Mosher ester. [f] Determined by chiral HPLC. [g] Evaluated by comparing the optical rotation with literature data. [h] Determined by ^{1}H NMR of the corresponding Mosher ester. [i] Conversion evaluated by ^{1}H NMR.

Allylic Alcohols. We next studied the scope of this asymmetric cyclopropanation with a wide range of allylic alcohols. The different cyclopropylmethanols were prepared following the two previous procedures (Table 3). The original procedure

(14) Charette, A. B. *C&EN* **1995**, *73*, February 6, 2.
(15) Charette, A. B.; Prescott, S.; Brochu, C. *J. Org. Chem.* **1995**, *60*, 1081−1083.
(16) It should be pointed out that this reagent might contain up to 20% of $IZnCH_2I$ resulting from the temperature dependent decomposition of $Zn(CH_2I)_2$.
(17) For the preparation of this zinc reagent, see: Charette, A. B.; Marcoux, J.-F. *J. Am. Chem. Soc.* **1996**, *118*, 4539−4549.

Table 4. Chemo- and Enantioselective Cyclopropanation of Polyenes



entry	allylic alcohol (**cpd**)	*x* equiv	yield,[a] % (**cpd**)	ratio[b] mono:bis	selectivities
1	geraniol (**24**)	1.6	87 (**25**)	>20:1	93% ee[c]
2	farnesol (**26**)	1.6	84 (**27**)	>20:1	93% ee[c]
3[d]	(5*E*,9*E*)-11-hydroxy-6,10-dimethylundecadien-2-one (**28**)	4.2	>95 (**29**)	>20:1	88% ee[c]
4	(*S*)-(−)-perillyl alcohol ((−)-**30**)	2.5	70[e] (**31**)	19:1	65% de[f]
5	(*R*)-(+)-perillyl alcohol ((+)-**30**)	3.0	65[e] (**32**)	19:1	65% de[f]

[a] Unless otherwise noted, these are isolated yields of the cyclopropanated product at the allylic position. [b] Determined by ^{1}H NMR. [c] The enantioselectivities were determined by ^{1}H and ^{19}F NMR of the corresponding Mosher esters. [d] The *S*,*S* enantiomer of the dioxoborolane **1** was used. [e] Conversions evaluated by ^{1}H NMR. [f] The diastereoselectivities were determined by ^{1}H NMR.

(procedure A) involving the rapid addition of a CH_2Cl_2 solution of the allylic alcohol and the dioxaborolane **1** to the preformed zinc reagent (2 equiv of $Zn(CH_2I)_2$) at 0 °C was used for small scale preparations (<1.0 mmol). For the cyclopropanations on larger scales (>1.0 mmol), the dioxaborolane **1** was first added to a preformed complexed zinc reagent (2 equiv of $Zn(CH_2I)_2$•DME) in dichloromethane at −10 °C followed immediately by the allylic alcohol (procedure B).[19]

These two procedures are very effective for the enantioselective cyclopropanation of *trans*- and *cis*-substituted olefins (entries 1−5 and 10−12, Table 3). More specifically, the asymmetric cyclopropanation is compatible with various functional groups such as methyl, benzyl, or silyl ethers. Although this method is very effective in preparing cyclopropylstannanes (entries 6 and 8, Table 3) and cyclopropyl iodides (entries 7 and 9, Table 3) in good enantiomeric excesses, the latter required a larger excess of the reagent.[20] These compounds are useful precursors for palladium-catalyzed cross-coupling reactions.[21]

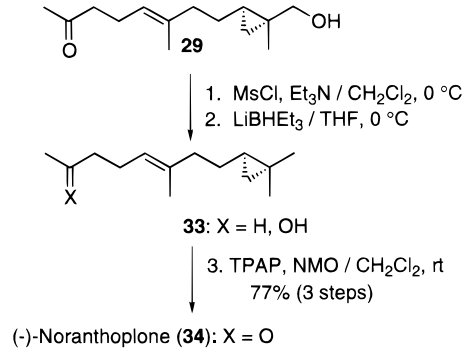
In cases where volatile cyclopropylmethanol derivatives are obtained, it is better to use dioxaborolane **22** since the byproduct derived from the oxidative workup (MeOH) is more easily separated from the desired product (see entry 10, Table 3; procedure D). The dioxaborolane **22** is prepared by condensing the commercially available trimethylboroxine (**23**) and the (*R*,*R*)-(+)-*N*,*N*,*N*′,*N*′-tetramethyltartaric acid diamide (**3**).

Equally high enantioselectivities were also observed with polysubstituted allylic alcohols. Accordingly, 3,3-trisubstituted allylic alcohols gave excellent ee's (entry 13, Table 3). Slightly lower enantioselectivities were obtained for the cyclopropanation of 2,3-trisubstituted allylic alcohols and 2,3,3-tetrasubstituted allylic alcohols (entries 14, 15, and 16, Table 3). The most striking example is 1-cyclohexenemethanol, which provided the corresponding cyclopropylmethanol with much lower ee's (entry 17, Table 3). In the latter case, the increased steric hindrance at the C_2-position on the double bond seems to affect the selectivities (vide infra).

Polyenes. The occurrence of natural products containing both an olefin and a cyclopropane ring prompted us to investigate the chemo- and enantioselective cyclopropanation of substrates containing more than one double bond. We found that the double bond of the allylic alcohol could be efficiently cyclopropanated in the presence of other olefinic sites. As shown in Table 4, high chemo- and enantioselectivities were obtained for a variety of polyenes using the chiral dioxaborolane **1**.[22]

We have also found that the use of the less reactive $Zn(CH_2I)_2$•DME complex was mandatory in these cases because irreproducible results were observed when the zinc reagent ($Zn(CH_2I)_2$) was used in the absence of DME. Hence, the typical procedure involved the addition of a solution of $Zn(CH_2I)_2$•DME in CH_2Cl_2 at 0 °C to a mixture of the allylic alcohol and dioxaborolane **1**. The optimized number of equivalents of the zinc reagent was found to be substrate dependent. Therefore, the corresponding monocyclopropanes produced from simple polyenes such as geraniol (**24**) and farnesol (**26**) could be obtained in high chemo- and enantioselectivities with 1.6 equiv of $Zn(CH_2I)_2$•DME (entries 1 and 2, Table 4). A larger excess of the zinc reagent was needed to produce monocyclopropane **29** in a quantitative yield and 88% ee (entry 3, Table 4). In this case, the presence of an additional basic groups on allylic alcohol **28**[23] (which can also complex the zinc reagent) is probably responsible for this requirement. The synthesis of (−)-noranthoplone (**34**),[24] a natural product which has antitumoral activity, could be easily achieved from cyclopropane **29** (Scheme 2) in 77% yield for the three-step process. Mesylation (MsCl, Et_3N, CH_2Cl_2, 0 °C) followed by reduction of the corresponding

Scheme 2



(18) The previously reported protocol to recover butylboronic acid and (*R*,*R*)-(+)-*N*,*N*,*N*′,*N*′-tetramethyltartaric acid diamide (see ref 15) could not be used with this new procedure. The number of equivalents of the zinc reagent and the reaction time seem to have a profound impact on the separation of the ligand components.

(19) Similar results (yield and enantioselectivities) were obtained if procedure B was used on a smaller scale.

(20) The use of chloroiodomethane was not effective in this case: Denmark, S. E.; Edwards, J. P. *J. Org. Chem.* **1991**, *56*, 6974−6981.

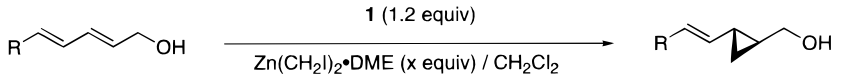
(21) (a) Charette, A. B.; Pereira De Freitas-Gil, R. *Tetrahedron Lett.* **1997**, *38*, 2809−2812. (b) Charette, A. B.; Giroux, A. *J. Org. Chem.* **1996**, *61*, 8718−8719. (c) Piers, E.; Coish, P. D. *Synthesis* **1994**, 47−55. (d) Piers, E.; Jean, M.; Marrs, P. S. *Tetrahedron Lett.* **1987**, *28*, 5075−5078. (e) Falck, J. R.; Mekonnen, B.; Yu, J.; Lai, J.-Y. *J. Am. Chem. Soc.* **1996**, *118*, 6096−6097.

(22) (a) Charette, A. B.; Juteau, H.; Lebel, H.; Deschênes, D. *Tetrahedron Lett.* **1996**, *37*, 7925−7928. (b) Barrett, A. G. M.; Kasdorf, K. *J. Chem. Soc., Chem. Commun.* **1996**, 325−326. (c) Barrett, A. G. M.; Hamprecht, D.; White, A. J. P.; Williams, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 8608−8615.

(23) The allylic alcohol was prepared from geranylacetone by allylic oxidation, see: McMurry, J. E.; Dushin, R. G. *J. Am. Chem. Soc.* **1990**, *112*, 6942−6949.

(24) Zheng, G.-C.; Hatano, M.; Ishitsuka, M. O.; Kusumi, T.; Kakisawa, H. *Tetrahedron Lett.* **1990**, *31*, 2617−2618.

Table 5. Enantioselective Cyclopropanation of Dienic Alcohols



Entry	R	Diene (**cpd#**)	x equiv	Yield[a] (**cpd#**)	Ratio[b] mono : bis	Selectivities
1	Ph	(**35**)	3.0	84% (**36**)	>20 : 1	91% ee[c]
2	BnO	(**37**)	2.5	78% (**38**)	8 : 1	>90% de[d]
3	TPSO	(**39**)	2.5	85%[e] (**40**)	8 : 1	>90% de[d]
4	TPSO(CH2)5	(**41**)	3.0	81% (**42**)	9 : 1	>90% de[d]

[a] Isolated yields. [b] Determined by ^{1}H NMR. [c] After hydrogenation of the product, the enantioselectivity was determined by chiral HPLC. [d] The diastereoselectivities were evaluated by ^{13}C NMR. [e] This yield includes ca.10% mixture of inseparable starting material and tricyclopropane.

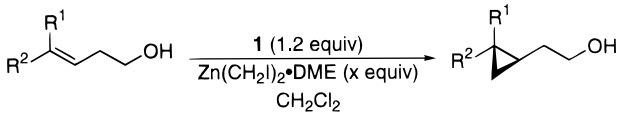
mesylate (Super Hydride, THF, 0 °C) and oxidation of the resulting secondary alcohol **33** with tetrapropylammonium perruthenate[25] (TPAP, NMO, CH_2Cl_2, rt) produced (−)-noranthoplone (**34**) ([α]$_D$ −8.80° (*c* 1.80, $CHCl_3$)) that was identical in all respects (IR, ^{1}H NMR, ^{13}C NMR, and HRMS) to the natural product.

The cyclopropanation of the (*S*)- and (*R*)-perillyl alcohols **30** with the dioxaborolane **1** was then investigated (entries 4 and 5, Table 4). The two opposite diastereoisomers of the corresponding monocyclopropane **31** and **32** were observed depending on the chirality of the starting material. However, the cyclopropanation of perillyl alcohols was problematic. In each case, we found that the cyclopropanation of the terminal double bond was competitive with that of the allylic alcohol. Furthermore, the corresponding cyclopropylmethanol was produced in low diastereomeric excess. This observation is not too surprising since perillyl alcohol has the same basic structural pattern as cyclohexenemethanol, which also gave a low enantiomeric excess (entry 17, Table 3; see mechanistic considerations).

2,4-Dien-1-ols. After studying the cyclopropanation of polyenic allylic alcohols, we next explored the cyclopropanation of 2,4-dien-1-ol with dioxaborolane **1** using the zinc complex ($Zn(CH_2I)_2$•DME) in CH_2Cl_2 (Table 5). The desired dienols were prepared from the corresponding aldehydes by a sequence involving a standard Horner−Emmons olefination followed by reduction.[26] The number of equivalents of the zinc reagent, as in the case of polyenes, was substrate dependent. With aromatic dienol **35**, 3 equiv of the $Zn(CH_2I)_2$•DME reagent was necessary to provide the vinylcyclopropane **36** in 84% yield and 91% ee (entry 1, Table 5). The remaining double bond was fairly unreactive, and it tolerated the slight excess of the zinc reagent. On the other hand, even though the cyclopropanation of 5-cyclopropyl-2,4-dien-1-ol derivatives **37**, **39**, and **41** proceeded well to give the corresponding *trans*-1,2-dicyclopropylolefins, relatively larger amounts of the biscyclopropanation-derived products were observed (entries 2−4, Table 5). These undesired products could usually be separated by flash chromatography (entries 2 and 4, Table 5). In all cases, the diastereoselectivities were excellent (>90% de).

Homoallylic Alcohols. To see if remote hydroxymethyl groups can still assist in the methylene-directed delivery on the double bond, we next investigated the enantioselective cyclopropanation of homoallylic alcohols with dioxaborolane **1** (Table 6). Quite interestingly, the corresponding cyclopropanes could be isolated in high yields and high ee (around 80%) when the cyclopropanation was carried out in the presence of an excess of the $Zn(CH_2I)_2$•DME complex in CH_2Cl_2. The cyclopropanation of *E*- and *Z*-aromatic olefins as well as *Z*-aliphatic olefins proceeded with similar levels of enantioselection (entries 1−3, Table 6). To the best of our knowledge, this is the first example of an enantioselective cyclopropanation of homoallylic alcohols that provides good enantioselectivities.[27]

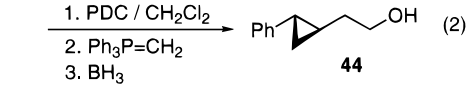
Table 6. Enantioselective Cyclopropanation of Homoallylic Alcohols



entry	R_1	R_2	*x* equiv	yield,[a] % (**cpd**)	ee, %
1	CH_3CH_2	H	2.0	90 (**43**)	82[b]
2	H	Ph	3.0	90 (**44**)	82[c]
3	Ph	H	4.0	86 (**45**)	81[c]

[a] Isolated yields. [b] Determined by ^{13}C NMR of the corresponding Mosher ester. [c] Determined by chiral HPLC.

The absolute configuration of the cyclopropane ring in product **44** was determined by comparison with the material obtained by the homologation of the cyclopropane derived from cinnamyl alcohol (eq 2). Thus, PDC oxidation of cyclopropylmethanol **5** followed by Wittig olefination and hydroboration gave cyclopropylmethanol **14**. HPLC analysis and comparison of the sign of the optical rotations revealed that the facial selectivity observed in this case was the same as that obtained for the cyclopropanation of allylic alcohols with the same antipode of chiral ligand **1**. The sense of induction in the other cyclopropanation reactions was assumed to be the same, and the absolute stereochemistry was not unambiguously determined.



(2)

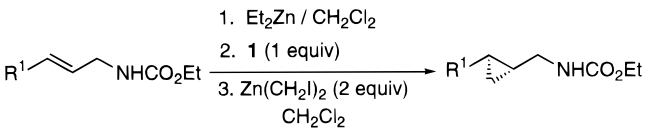
Allylic Amines. Finally, we examined the enantioselective Simmons−Smith cyclopropanation of protected allylic carbamates[28] (Table 7). Cyclopropylmethylamines are important derivatives, but their use has been mostly restricted to the

(25) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun*. **1987**, 1625−1627.

(26) See Supporting Information for experimental details.

(27) For example, the disulfonamide of Kobayashi/Denmark gave 5% ee with homoallylic alcohol **44**: see ref 7f.

Table 7. Enantioselective Cyclopropanation of Allylic Carbamates

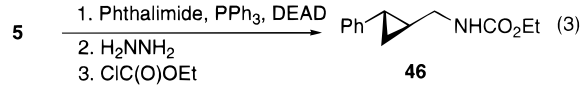


entry	R_1	yield,[a] % (**cpd**)	ee,[b] %
1	Ph	21 (**46**)	53
2	$PhCH_2CH_2$	25 (**47**)	~55

[a] Isolated yields. [b] Determined by chiral HPLC.

simplest achiral derivatives.[29] The cyclopropanation of allylic carbamates with bis(iodomethyl)zinc in dichloromethane in the absence of the chiral ligand proceeded extremely well to provide the corresponding cyclopropane in good yield. However, we found that the reaction did not produce any of the desired cyclopropane when it was carried out in the presence of the chiral ligand **1**. After many attempts, we eventually found that the prior formation of the zinc amide (by premixing the allylic carbamate with 1 equiv of diethylzinc) followed by the addition of the dioxaborolane and bis(iodomethyl)zinc led to cyclopropylcarbamate in low yield and ee (Table 7). In this case, the methylation of the amine group by the reagent competed with the cyclopropanation. These poor results clearly showed the critical importance of the hydroxymethyl group on the substrate. Furthermore, the absolute configuration of the cyclopropane ring in these cases was found to be opposite to that observed with allylic alcohols.

However, substituted cyclopropylamines are readily accessible by a Mitsunobu reaction of the corresponding cyclopropylmethanol with phthalimide followed by hydrazinolysis and carbamate formation. An example using cyclopropylmethanol **5** is given in eq 3.



(3)

Mechanistic Considerations. The proposed transition state for the enantioselective cyclopropanation of cinnamyl alcohol in the presence of dioxaborolane **1** is shown in Figure 1. It is postulated that the zinc alkoxide derived from cinnamyl alcohol reacted with the dioxaborolane to produce the ate complex. It is reasonable to assume that the bulkier butyl substituent on the dioxaborolane adopts the less congested pseudoequtorial position and the allylic alkoxide the more stable pseudoaxial position. This allows the complex to act as a bidentate ligand. The zinc reagent should then be complexed simultaneously by both the highly basic carbonyl amide of the dioxaborolane ligand and the oxygen atom of the allylic alkoxide. The most suitable conformation for the methylene delivery is that in which the allylic chain is in its most stable conformation. This model correctly predicts the absolute configuration for the cyclopropanation of all the allylic alcohols shown in Table 3.

The above analysis is also consistent with the α-substituent effect observed in the case of cyclohexenemethanol and (*R*)- or (*S*)-perillyl alcohol. Examination of the transition state for the cyclopropanation of cyclohexenemethanol shows severe

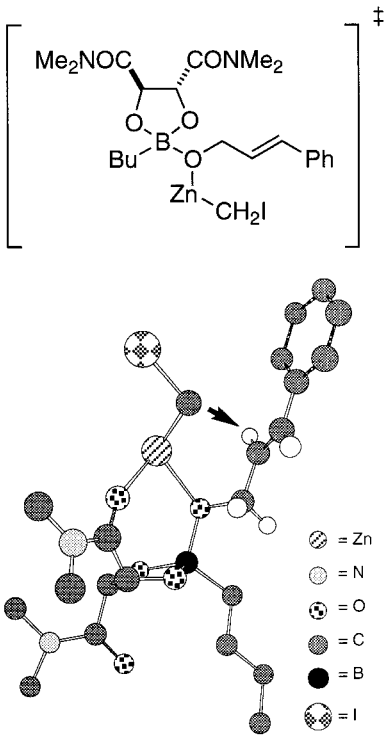


Figure 1. Chem 3D representation of the proposed transition state for the enantioselective cyclopropanation of allylic alcohols (cinnamyl alcohol).

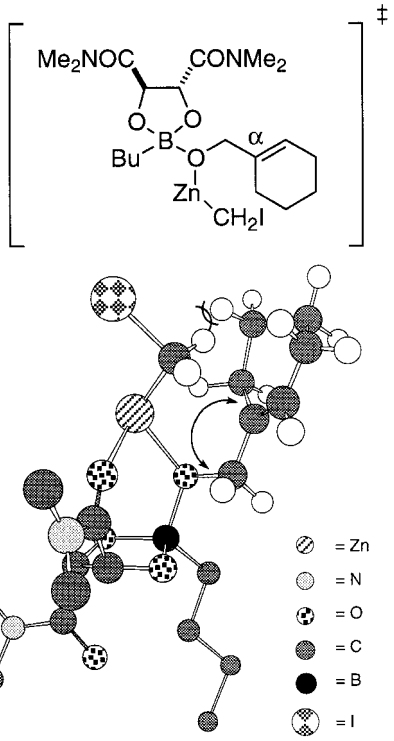


Figure 2. Chem 3D representation of the proposed transition state for the enantioselective cyclopropanation of 1-cyclohexenemethanol, (*S*)- and (*R*)-perillyl alcohols (1-cyclohexenemethanol).

interactions between the zinc reagent and the C_2-substituent (Figure 2). Furthermore, an $A^{1,2}$ strain is present between the C_2-substituent and the C−O in the reactive conformer.

The relatively lower level of enantioselectivity observed in the cyclopropanation of the homoallylic alcohols is a clear indication of the importance of the proximity of the hydroxy group. In this case, the addition of a methylene group between

(28) For examples of cyclopropanation of allylic amines with zinc reagent, see: (a) de Frutos, P.; Fernandez, D.; Fernandez-Alvarez, E.; Bernabé, M. *Tetrahedron Lett.* **1991**, *32*, 541−542. (b) Russ, P.; Ezzitouni, A.; Marquez, V. E. *Tetrahedron Lett.* **1997**, *38*, 723−726.

(29) For example, see: (a) Kubota, H.; Rice, K. C. *Tetrahedron Lett.* **1998**, 39, 2907−2910. (b) Lu, X.; Yang, S.; Silverman, R. B. *J. Org. Chem.* **1996**, *61*, 8961−8966.

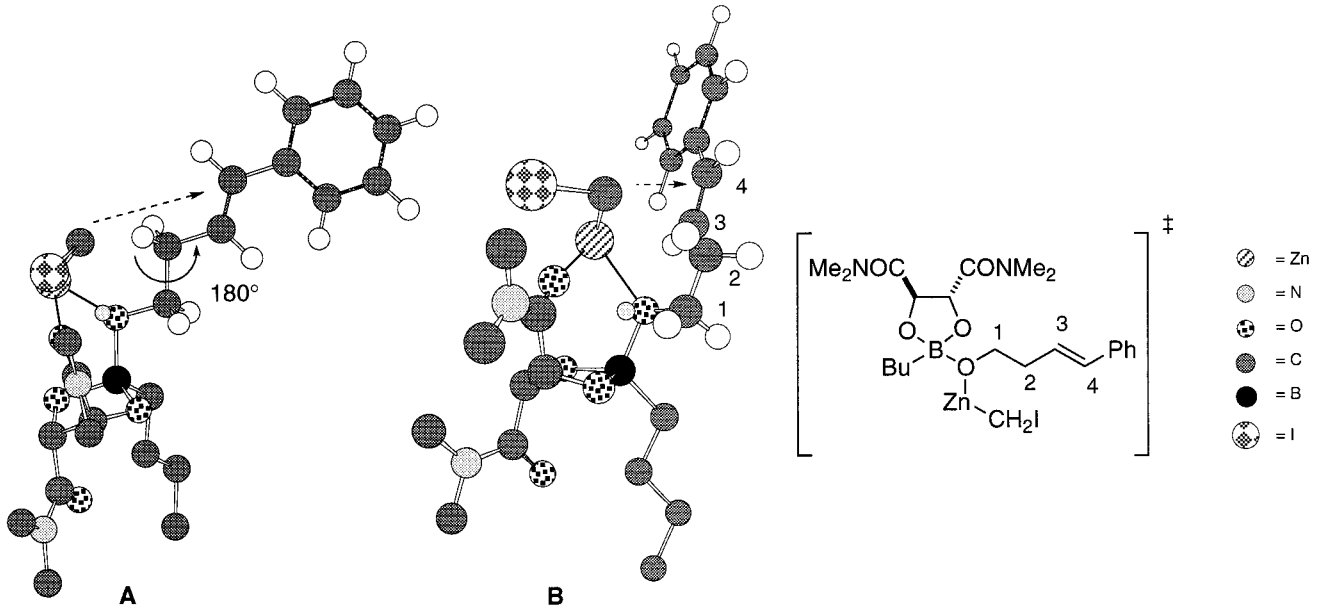


Figure 3. Chem 3D representation of the proposed transition state for the enantioselective cyclopropanation of homoallylic alcohols ((*E*)-4-phenyl-3-butenol).

the point of attachment (hydroxy group) and the reactive site (olefin) reduces the ee's from 93% to 80%. Although the enantioselectivities are slightly lower, they are still reasonably high both with *trans*- and *cis*-olefins. Quite surprisingly, the absolute stereochemistry observed was the same as that obtained with allylic alcohols. This is in sharp contrast to what is observed in the Sharpless epoxidation of allylic and homoallylic alcohols.[30] These observations suggest that the dioxaborolane-assisted cyclopropanation can only proceed by the transition state where the $O-C_1-C_2-C_3$ adopts a staggered conformation (model **B**) instead of the *anti* conformation (model **A**) as with allylic alcohols (Figure 3).

In conclusion, a very effective chiral controller has been found for the conversion of allylic alcohols into the corresponding enantiomerically enriched cyclopropanes using the Simmons−Smith zinc reagent. A variety of chiral, nonracemic cyclopropylmethanols could be obtained according to this method. This methodology was also extended with success to the cyclopropanation of unconjugated and conjugated polyenes and homoallylic alcohols. The cyclopropanation of the allylic carbamates have also been investigated with this system, but it was found that enantioenriched cyclopropylmethylamines are best prepared from enantioenriched cyclopropylmethanols.

Experimental Section

Unless otherwise noted, all nonaqueous reactions were performed under an oxygen-free atmosphere of nitrogen or argon with rigid exclusion of moisture from reagents and glassware. Analytical thin-layer chromatography (TLC) was performed using EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by UV absorbance, aqueous cerium molybdate, ethanolic phosphomolybdic acid, or aqueous potassium permanganate. Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle Silica Gel (230−400 mesh).[31] ^{1}H and ^{13}C NMR spectra were recorded in deuteriochloroform ($CDCl_3$), unless otherwise noted, at 300.16, 400.13, or 600 MHz. Chemical shifts of ^{1}H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, and br = broad), coupling constant in hertz (Hz), integration, and assignment. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (76.9 ppm) on the δ scale. ^{19}F NMR spectra were recorded at 376 MHz (9.4 T), and the chemical shifts are reported in ppm relative to $BF_3{\cdot}OEt_2$. Optical rotations were determined at 20 °C at 589 nm. Data are reported as follows: $[\alpha]_\lambda$, concentration (*c* g/100 mL), and solvent. Combustion analyses were performed by the Laboratoire d'analyse élémentaire of the Université de Montréal. High-resolution mass spectra (HMRS) (FAB, CI, EI) were obtained from the Centre régional de Spectrométrie de Masse of the Université de Montréal. Analytical gas chromatography (GLC) was carried out on a gas chromatograph equipped with a split mode capillary injector and a flame ionization detector. Unless otherwise noted, injector and detector temperatures were 250 °C. Data are reported as follows: column type, oven temperature, carrier pressure, and retention time (T_r). The following general procedure was used when the alcohol had to be derivatized into its trifluoroacetate ester: To a solution of the crude alcohol (10 mg) in pyridine (0.75 mL) was added trifluoroacetic anhydride (0.25 mL). After 30 min of stirring at room temperature, an additional portion of trifluoroacetic anhydride (0.25 mL) was added. After 30 min, the reaction mixture was diluted with ether (5 mL) and the resulting homogenious solution was analyzed by GC. All solvents were dried using standard methods prior to use. The following general procedure was used for the Moshers ester synthesis:[32] To a solution of crude alcohol (1 equiv), 4-(dimethylamino)-pyridine (1 equiv), and triethylamine (5 equiv) in dichloromethane was added (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (1.05 equiv). The reaction mixture was monitored by TLC to ensure complete reaction, quenched by the addition of 3-(dimethylamino)propylamine (3 equiv), and concentrated under reduced pressure. The residue was filtered through a short plug of silica gel in order to remove polar impurities (20% EtOAc/hexanes), concentrated under reduced pressure, and analyzed by NMR.

(+)-(1*S*,2*S*)-2-Phenylcyclopropylmethanol (5) (Procedure A). To a stirred solution of diethylzinc (50 μL, 0.49 mmol) in anhydrous CH_2Cl_2 (1.0 mL) at 0 °C was added diiodomethane (80 μL, 0.98 mmol). The mixture was stirred at 0 °C for 10 min (white precipitate is formed), and a preformed solution of dioxaborolane **1** (68 mg, 0.25 mmol) and cinnamyl alcohol (30 mg, 0.22 mmol) in anhydrous CH_2Cl_2 (1.5 mL)

(30) Rossiter, B. E.; Sharpless, K. B. *J. Org. Chem.* **1984**, *49*, 3707−3711.

(31) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.

(32) (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−2549. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamumne, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780.

was rapidly added via cannula. The resulting mixture was stirred at room temperature for 2 h and then cooled to 0 °C. Saturated aqueous NH_4Cl (5 mL) was added, and the mixture was washed with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (20% EtOAc/hexanes) to produce the desired cyclopropylmethanol **5** (32.5 mg, 100%): R_f 0.23 (20% EtOAc/hexanes); $[\alpha]_D$ +70 (*c* 1.9, EtOH) [lit.[33] (1*R*,2*R*)-2-phenylcyclopropylmethanol >99% ee: $[\alpha]_D$ −92 (*c* 1.23, 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, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 128.3, 125.8, 125.6, 66.3, 25.2, 21.2, 13.8; HRMS calcd for $C_{10}H_{12}O$ 148.0888, found: 148.0880. The enantiomeric excess (93% ee) was determined by GC analysis of the trifluoroacetate ester derived from (1*S*,2*S*)-2-phenylcyclopropylmethanol. Column: Cyclodex G-TA, 0.32 mm × 30 m. Pressure 25 psi. Isotherm: 110 °C. T_r(minor) 11.5 min, T_r(major) 12.0 min.

(+)-(1*S*,2*S*)-2-Phenylcyclopropylmethanol (5) (Procedure B). To a solution of dry DME (1.60 mL, 14.0 mmol) in anhydrous dichloromethane (45 mL) cooled at −10 °C (internal temperature) was added diethylzinc (1.50 mL, 14.9 mmol). Then, to this stirred solution was added diiodomethane (2.40 mL, 29.8 mmol) over a 15−20 min period while maintaining the internal temperature between −8 and −12 °C. After completion of the addition, the resulting clear solution was stirred for an additional 10 min at −10 °C. A solution of the dioxaborolane ligand **1** (2.41 g, 8.94 mmol) in anhydrous dichloromethane (10 mL) was then added via cannula under argon over a 5−6 min period immediately followed by a solution of cinnamyl alcohol (1.00 g, 7.45 mmol) in anhydrous dichloromethane (10 mL) added via cannula under argon over a 5−6 min period while maintaining the internal temperature under −5 °C at all times. The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature and was stirred for 8 h at that temperature.

(a) Standard Workup (Oxidative Workup). The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and 10% aqueous HCl (40 mL). The mixture was then diluted with ether (60 mL) and transferred into a separatory funnel. The reaction flask was rinsed with ether (15 mL) and 10% aqueous HCl (10 mL), and both solutions were transferred into the separatory funnel. The two layers were separated, and the aqueous layer was washed with ether (20 mL). The combined organic layers were transferred into an Erlenmeyer flask, and a solution containing 60 mL of 2 N aqueous NaOH and 10 mL of 30% aqueous H_2O_2 was added in one portion. The resulting biphasic solution was vigorously stirred for 5 min. The two layers were then separated, and the organic layer was successively washed with 10% aqueous HCl (50 mL), saturated aqueous Na_2SO_3 (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was left under vacuum (0.2 mmHg) overnight (12−16 h) to remove the *n*-butanol produced in this oxidative workup (this last step in not necessary if the product is purified by flash chromatography). The product was purified by a Kugelrohr distillation (90 °C, 0.8 mmHg) to afford the (2*S*,3*S*)-(+)-(3-phenylcyclopropyl)methanol **5** (1.05 g, 95%) as a colorless oil: bp 90 °C (0.8 mmHg); R_f 0.31 (30% EtOAc/hexanes); $[\alpha]_D$ +82 (*c* 1.74, EtOH) [lit.[33] $[\alpha]_D$ −92 (*c* 1.23, EtOH) for (−)-**5**]; ^{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, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 128.3, 125.8, 125.6, 66.3, 25.2, 21.2, 13.8. Anal. Calcd for $C_{10}H_{12}O$: C, 81.04 H, 8.16. Found: C, 81.15; H, 8.30. The enantiomeric excess (94% ee) was determined by GC analysis of the trifluoroacetate ester derived from (1*S*,2*S*)-2-phenylcyclopropylmethanol: Column: Cyclodex G-TA, 0.32 mm × 30 m. Pressure 25 psi. Isotherm: 110 °C. T_r(minor) 11.5 min, T_r(major) 12.0 min.

(b) Workup with Recovery of (*R*,*R*)-(+)-*N*,*N*,*N*′,*N*′-Tetramethyltartaric Acid Diamide. The mixture was quenched with saturated aqueous NH_4Cl (80 mL), and the resulting biphasic mixture was stirred for 5 min. The two clear layers were separated, and the aqueous layer was washed with dichloromethane (20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residual oil was then dissolved in ether (75 mL) and water (50 mL). The resulting biphasic mixture was stirred for 1 h. The layers were separated, and the aqueous layer was washed with ether (20 mL). This aqueous layer was kept for the tetramethyltartaric acid diamide recovery (see recovery of (*R*,*R*)-(+)-*N*,*N*,*N*′,*N*′-tetramethyltartaric acid diamide). The combined organic layers were treated with a solution of 2 N aqueous NaOH (60 mL) and 30% aqueous H_2O_2 (10 mL). The resulting biphasic mixture was stirred for 5 min. The two layers were then separated, and the organic layer was successively washed with 10% aqueous HCl (50 mL), saturated aqueous Na_2SO_3 (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was left under vacuum (0.2 mmHg) overnight (12−16 h) to remove *n*-butanol produced in this oxidative workup (this last step in not necessary if the product is purified by flash chromatography). The product was purified by a Kugelrohr distillation (90 °C, 0.8 mmHg) to afford (2*S*,3*S*)-(+)-(3-phenylcyclopropyl)methanol (1.02 g, 93%) as a colorless oil.

(c) Recovery of (*R*,*R*)-(+)-*N*,*N*,*N*′,*N*′-Tetramethyltartaric Acid Diamide. The aqueous layer from the above extraction was concentrated under reduced pressure, and the crude product was recrystallized by an initial dissolution in hot dichloromethane (5 mL) followed by the addition of ethyl acetate (10 mL) to afford (*R*,*R*)-(+)-*N*,*N*,*N*′,*N*′-tetramethyltartaric acid diamide (**3**) (600−750 mg, 33−41% yield). An additional 10−15% of the diol could be recovered from the first saturated aqueous ammonium chloride extract: the layer was concentrated on a rotatory evaporator and the white solid was then triturated with cold methanol (30 mL), the mixture was filtered on a Büchner funnel, and the solid washed with cold methanol (20 mL). The filtrate was concentrated to ca. 25 mL and treated with Na_2S (2.5 g). The resulting mixture was stirred for 30 min and then filtered on Celite (6 g, 1 cm × 4 cm). The filtrate was concentrated by rotatory evaporation and the residue purified by flash chromatography on silica gel (75 g, 3.5 cm × 14.5 cm) by dissolving it into 10 mL of 10% methanol in chloroform and eluting with 10% methanol in chloroform. A recrystallization with dichloromethane and ethyl acetate gave pure material.

(d) Nonoxidative Workup. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and 10% aqueous HCl (40 mL). The two layers were separated, and the aqueous layer was washed with dichloromethane (50 mL). The combined organic layers were transferred into an Erlenmeyer flask, and a solution of 5 M aqueous KOH (200 mL) was added. The resulting biphasic solution was stirred vigorously for 4 h. The two layers were then separated, and the organic layer was successively washed with saturated aqueous NH_4Cl (3 × 50 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product was purified by Kugelrohr distillation (90 °C, 0.8 mmHg) to afford the (2*S*,3*S*)-(+)-(3-phenylcyclopropyl)methanol (**5**) (1.05 g, 95%) as a colorless oil.

(+)-(1*R*,2*S*)-2-Iodocyclopropylmethanol (11) (Procedure C). To a solution of diethylzinc (130 μL, 1.24 mmol) and anhydrous DME (130 μL, 1.24 mmol) in anhydrous dichloromethane (3 mL) at −10 °C (internal temperature) was added diiodomethane (200 μL, 2.48 mmol) over 10 min. After completion of the addition, the resulting clear solution was stirred for an additional 10 min at −10 °C. A solution of the dioxaborolane ligand **1** (202 mg, 0.746 mmol) in anhydrous dichloromethane (1 mL) was then added immediately followed by a solution of (*E*)-3-iodo-2-propenol (114 mg, 0.619 mmol) in anhydrous dichloromethane (1 mL). The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature. The mixture was stirred for 4 h at that temperature, and another 2 equiv of the Zn$(CH_2I)_2$·DME in CH_2Cl_2 was added (preparation of Zn$(CH_2I)_2$·DME in CH_2Cl_2 as described above). After 4 h of stirring at −10 °C, another 2 equiv of the Zn$(CH_2I)_2$·DME in CH_2Cl_2 was added, and then the resulting mixture was stirred overnight at room temperature. The next morning, two other additions of 2 equiv of the Zn$(CH_2I)_2$·DME in CH_2Cl_2 were done at 4 h intervals (5 × 2 equiv of the Zn$(CH_2I)_2$·DME in CH_2Cl_2 were needed for this substrate). After an additional 4 h of stirring, the reaction was quenched with saturated aqueous NH_4Cl (10

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mL). The two layers were separated, and the aqueous layer was extracted with ether (2 × 10 mL). The combined organic layers were washed with 10% aqueous HCl (10 mL) and then transferred into an Erlenmeyer flask. A solution containing 30 mL of 2.5 M aqueous NaOH and 3 mL of 30% aqueous H_2O_2 was added in one portion, and the resulting biphasic solution was vigorously stirred for 30 min. The two layers were then separated, and the organic layer was successively washed with 10% aqueous HCl (10 mL), saturated aqueous Na_2SO_3 (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (5% EtOAc/hexanes) to afford the desired cyclopropylmethanol **11** (98.1 mg, 83%) as a pale yellow liquid: R_f 0.15 (20% EtOAc/hexanes); $[\alpha]_D$ +63.7 (*c* 1.92, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.61 (dd, J = 12, 6 Hz, 1H), 3.53 (dd, J = 12, 7 Hz, 1H), 2.30−2.24 (m, 1H), 1.59−1.48 (m, 2H), 1.06−0.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 64.7, 25.3, 14.4, −18.2; HRMS calcd for C_4H_7OI 197.95416, found 197.95352. The enantiomeric excess (90% ee) was evaluated by ^{1}H NMR (400 MHz, $CDCl_3$) by the relative integration of the multiplets at 4.36 ppm (major) and 4.28 ppm (minor) of the corresponding Mosher ester.

(-)-(1*S*,2*R*)-2-Ethylcyclopropylmethanol (14) (Procedure D). The cyclopropanation of (*Z*)-2-pentenol (38 mg, 0.44 mmol) was performed according to procedure B with a standard workup but, here, dioxaborolane ligand **22** was used instead of **1**. ^{1}H NMR analysis of the crude showed >98% conversion, and the residue was purified by flash chromatography on silica gel (5−10% EtOAc/hexanes) to produce the desired cyclopropylmethanol **14** (30 mg, 60%) (87% ee) (higher yields were obtained if the volatile alcohol was converted into its corresponding benzoate derivative, see below): R_f 0.18 (20% EtOAc/hexanes); $[\alpha]_D$ −27.9 (*c* 0.62, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (dd, J = 11, 7 Hz, 1H), 3.59 (dd, J = 11, 7 Hz, 1H), 1.50−1.24 (m, 3H), 1.15−1.07 (m, 1H), 1.02 (t, J = 7 Hz, 3H), 0.90−0.80 (m, 1H), 0.71 (td, J = 8, 5 Hz), −0.03 (dd, J = 10, 5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.8, 21.6, 18.0, 17.8, 14.2, 9.03.

The cyclopropanation of (*Z*)-2-pentenol (38 mg, 0.44 mmol) was also performed according to procedure A. The crude cyclopropylmethanol was directly converted to the corresponding benzoate ester: the cyclopropylmethanol was diluted in dichloromethane (5 mL), and then pyridine (50 μL, 0.60 mmol) and benzoyl chloride (60 μL, 0.55 mmol) were added. The mixture was stirred for 8 h and diluted with ethyl acetate (10 mL). The organic layer was successively washed with 10% aqueous HCl (5 mL), saturated aqueous $NaHCO_3$ (5 mL), and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (20% EtOAc/hexanes) to produce the desired cyclopropylmethyl ester derivative (82 mg, 90%): $[\alpha]_D$ −29.8° (*c* 1.56, $CHCl_3$). The enantiomeric excess (93%) was evaluated by ^{1}H NMR (400 MHz, $CDCl_3$) by the relative integration of the multiplets at 4.45 ppm (major) and 4.50 ppm (minor) of the corresponding Mosher ester.

(+)-(1*S*,2*R*)-2-Methyl-2-(4-methyl-3(*E*)-pentenyl)cyclopropyl]-methanol (25). To a solution of diethylzinc (100 μL, 0.98 mmol) in anhydrous dichloromethane (1.6 mL) and dry DME (100 μL, 0.98 mmol) at 0 °C was added dropwise diiodomethane (160 μL, 1.95 mmol) over 2 min. The resulting clear mixture was stirred for 15 min at 0 °C and then added to solution containing geraniol **24** (100 mg, 0.61 mmol) and dioxaborolane **1** (193 mg, 0.71 mmol) in anhydrous CH_2Cl_2 (1.2 mL). The clear solution was stirred for 15 min at that temperature and then warmed to room temperature and stirred for 2 h. Saturated aqueous NH_4Cl (5 mL) was added, and the mixture was washed with ethyl acetate (3 × 20 mL). The combined organic layers were successively washed with 10% aqueous HCl (15 mL), 2.5M aqueous NaOH (2 × 15 mL), and brine (15 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (20% EtOAc/hexanes) to afford the desired cyclopropylmethanol **22** (95 mg, 87%) as a colorless oil: R_f 0.15 (20% EtOAc/hexanes); $[\alpha]_D$ +2.16 (*c* 5.83, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.15−5.09 (m, 1H), 3.69 (dd, J = 11, 7 Hz, 1H), 3.46 (dd, J = 11, 8 Hz, 1H), 2.15−2.06 (m, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.42−1.35 (m, 1H), 1.18−1.11 (m, 1H), 1.07 (s, 3H), 0.95−0.87 (m, 1H), 0.50 (dd, J = 9, 5 Hz, 1H), 0.13 (t, J = 5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.4, 124.7, 64.0, 41.1, 26.3, 25.7, 25.5, 20.0, 17.73, 17.68, 17.1. The enantiomeric excess (93%) was evaluated by relative integration of the signals at −73.60 ppm (major) and −73.65 ppm (minor) of ^{19}F NMR of the corresponding Mosher ester.

8-[(1*R*,2*R*)-2,2-dimethylcyclopropyl]-6-methyl-5(*E*)-octen-2-ol (33). To a solution of alcohol **(−)-29** (155 mg, 0.69 mmol) in anhydrous dichloromethane (7 mL) at 0 °C was added fresly distilled triethylamine (200 μL, 1.38 mmol), followed by fresly distilled methanesulfonyl chloride (96 μL, 1.24 mmol). The resulting mixture was stirred for 90 min at 0 °C. Then ether (20 mL) was added, and the organic layer was washed with saturated aqueous $NaHCO_3$ (15 mL), water (15 mL) and brine (15 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude mesylate was used without any purification in the next step.

To a solution of the mesylate (209 mg, 0.69 mmol) in dry THF (25 mL) at 0 °C was slowly added a solution of 1.0 M in THF of Super Hydride (6.9 mL, 6.9 mmol) over a 15 min period. The resulting mixture was stirred at 0 °C for 2 h. The reaction was quenched with water (10 mL); then 2.5 M aqueous NaOH (10 mL) was added followed by 30% aqueous H_2O_2 (10 mL). The mixture was washed with ethyl acetate (2 × 30 mL), and the combined organic layers were succesively washed with saturated aqueous $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10% EtOAc/hexanes) to produce the title product **33** (112 mg, 77%): R_f 0.31 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.20−5.07 (m, 1H), 3.80 (sextuplet, J = 6 Hz, 1H), 2.12−1.99 (m, 4H), 1.61 (s, 3H), 1.53−1.40 (m, 2H), 1.37−1.31 (m, 2H), 1.18 (d, J = 6 Hz, 3H), 1.02 (s, 3H), 1.00 (s, 3H), 0.48−0.32 (m, 2H), −0.14 (t, J = 5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 123.6, 67.8, 40.1, 39.10, 39.05, 28.4, 27.5, 24.3, 23.3, 19.8, 19.5, 15.9, 15.2; HRMS calcd for $C_{14}H_{27}O$ 211.2062, found 211.2052.

(−)-8-[(1*R*,2*R*)-2,2-Dimethylcyclopropyl]-6-methyl-5(*E*)-octen-2-one or (−)-Noranthoplone (34). To a solution of alcohol **33** (70 mg, 0.33 mmol) in anhydrous dichloromethane (0.66 mL) was added NMO (60 mg, 0.50 mmol), followed by TPAP (6 mg, 0.017 mmol). The resulting mixture was stirred for 30 min at room temperature and then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10% EtOAc/hexanes) to produce (−)-noranthoplone (**34**) (69 mg, >99%): R_f 0.63 (20% EtOAc/hexanes); $[\alpha]_D$ −8.80 (*c* 1.80, $CHCl_3$) [lit.[24] $[\alpha]_D$ −10.5 (*c* 0.56, $CHCl_3$)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.20−5.07 (m, 1H), 2.44 (t, J = 8 Hz, 2H), 2.25 (q, J = 8 Hz, 2H), 2.10 (s, 3H), 2.01 (t, J = 8 Hz, 2H), 1.60 (s, 3H), 1.42−1.32 (m, 2H), 1.02 (s, 3H), 1.00 (s, 3H), 0.45−0.38 (m, 1H), 0.33 (dd, J = 9, 5 Hz, 1H), −0.15 (t, J = 5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.6, 136.6, 122.2, 43.6, 40.0, 29.7, 28.3, 27.5, 24.3, 22.3, 19.8, 19.5, 15.9, 15.2; HRMS calcd for $C_{14}H_{25}O$ 209.1905, found 209.1899.

(+)-(*E*)-1-[(1*S*,2*S*)-2-Hydroxymethylcyclopropyl]-2-phenylethene (36). To a solution of diethylzinc (190 μL, 1.87 mmol) in anhydrous dichloromethane (4 mL) and dry DME (195 μL, 1.87 mmol) at −10 °C was added dropwise diiodomethane (300 μL, 3.76 mmol) over 2 min. This clear colorless solution was stirred 10 min at −10 °C. Then a solution of the dioxaborolane **1** (202 mg, 0.75 mmol) in anhydrous dichloromethane (1 mL) was added, followed by a solution of the dienic alcohol **35** (100 mg, 0.624 mmol) in anhydrous dichloromethane (1 mL). The clear solution was stirred for 2 h at that temperature. Saturated aqueous NH_4Cl (2 mL) was slowly added followed by 10% aqueous HCl (5 mL). The mixture was diluted with ether (20 mL) and extracted. The organic layer was successively washed with saturated aqueous Na_2SO_3, 2 M aqueous NaOH containing 30% aqueous H_2O_2, saturated aqueous NH_4Cl, and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (20% EtOAc/hexanes) to afford the desired cyclopropylmethanol **36** (91.5 mg, 84%) as a colorless oil: R_f 0.33 (20% EtOAc/hexanes); $[\alpha]_D$ +99.3 (*c* 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.25 (m, 4H) 7.22−7.16 (m, 1H), 6.47 (d, J = 16 Hz, 1H), 5.80 (dd, J = 16, 9 Hz, 1H), 3.57 (d, J = 7 Hz, 2H), 1.65 (s (br), 1H), 1.55−1.49 (m, 1H), 1.33−1.26 (m, 1H), 0.79 (t, J = 7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.4, 132.9, 128.5, 127.9, 126.7, 125.6, 66.0, 23.3, 20.3, 12.1; The

enantiomeric excess (91%) was determined by HPLC analysis of the hydrogenated product on a chiral stationary phase. Conditions: column, Chiracel OD. Solvent system: 98:2 hexanes:*i*-PrOH. Mobile phase flow rate: 1 mL/min. UV detector: 254 nm. T_r(major) 22.4 min, T_r(minor) 28.3 min.

(*E*)-1-[(1*S*,2*S*)-2-Triisopropylsilyloxymethylcyclopropyl]-2-[(1*S*,2*S*)-2-hydroxymethylcyclopropyl]ethene (40). A $Zn(CH_2I)_2$·DME complex solution in CH_2Cl_2 was first prepared: To a solution of diethylzinc (100 μL, 0.976 mmol) in anhydrous dichloromethane (2 mL) and dry DME (100 μL, 0.976 mmol) at 0 °C was added dropwise diiodomethane (160 μL, 1.95 mmol) over 2 min. This clear colorless solution was used directly in the cyclopropantion reaction. To a solution of dienic alcohol **39**[26] (48.5 mg, 0.156 mmol) and dioxaborolane **1** (50.6 mg, 0.187 mmol) in anhydrous dichloromethane (1.6 mL) at −10 °C was added dropwise the solution of $Zn(CH_2I)_2$·DME in CH_2Cl_2 (800 μL, 0.39 mmol). The clear solution was stirred for 2 h at that temperature. Saturated aqueous NH_4Cl (2 mL) was slowly added followed by 10% aqueous HCl (2 mL). The mixture was extracted with ether (20 mL), and the organic layer was successively washed with saturated aqueous Na_2SO_3 (5 mL), 2 M aqueous NaOH (10 mL) containing 30% aqueous H_2O_2 (1 mL), saturated aqueous NH_4Cl (2 × 5 mL), and saturated aqueous NaCl (5 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (20% EtOAc/hexanes) to afford the desired cyclopropylmethanol **40** (43 mg, 85%) as a colorless oil, contamined with 5% of starting material and 5% of tricyclopropylmethanol: R_f 0.30 (20% EtOAc/hexanes); $[\alpha]_D$ +67.0 (*c* 0.96, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17−5.06 (m, 2H), 3.70 (dd, J = 10, 5 Hz, 1H), 3.58 (dd, J = 10, 6 Hz, 1H), 3.53−3.44 (m, 2H), 1.30−1.26 (m, 3H), 1.12−0.97 (m, 23H), 0.70−0.65 (m, 1H), 0.63−0.56 (m, 2H), 0.54−0.50 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.2, 129.8, 66.3, 65.3, 22.61, 22.55, 19.4, 18.5, 17.9, 11.9, 11.3, 10.9.

(−)-(2*S*,3*S*)-Ethyl *N*-(3-Phenyl-2-cyclopropylpropane)carbamate (46). To a stirred solution of (*E*)-ethyl *N*-(3-phenyl-2-propene)carbamate[26] (123 mg, 0.60 mmol) in anhydrous dichloromethane (1 mL) cooled at 0 °C was added a solution of diethylzinc (0.59 mL, 0.60 mmol) 1.01 M in CH_2Cl_2. Once the evolution of ethane has ceased, the dioxaborolane ligand **1** (166 mg, 0.62 mmol) was added.

To a stirred solution of diethylzinc (1.2 mL, 1.21 mmol), 1.01 M in CH_2Cl_2 at 0 °C, was added diiodomethane (0.20 mL, 2.48 mmol) over a 5 min period. The solution was stirred for an additional 20 min at that temperature, and the dioxaborolane−carbamate complex was added. The reaction mixture was warmed to room temperature and stirred for 6 h. The reaction was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The two layers were separated, and the organic layer was succesively washed with 10% aqueous HCl, 2.5 M aqueous NaOH, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (5−8% EtOAc/hexanes), dihydroxylated (OsO_4, NMO, acetone/water), and repurified by flash chromatography on silica gel (5−8% EtOAc/hexanes) to afford the desired cyclopropane **46** (27.8 mg, 21%) as a pale yellow liquid: R_f 0.40 (20% EtOAc/hexanes); $[\alpha]_D$ −33.6 (*c* 1.93, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.25 (m, 2H), 7.19−7.13 (m, 1H), 7.06−7.04 (m, 2H), 4.78 (s(br), 1H), 4.12 (q, J = 7 Hz, 2H), 3.27−3.14 (m, 2H), 1.85−1.78 (m, 1H), 1.36−1.26 (m, 1H), 1.25 (t, J = 7 Hz, 3H), 0.97−0.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 142.3, 128.8, 125.7, 125.5, 60.7, 45.0, 22.9, 21.8, 14.6, 14.3. HRMS calcd for $C_{13}H_{18}O_2N$ 220.13376, found 220.13300. The enantiomeric excess (53%) was determined by HPLC analysis of the crude reaction mixture on a chiral stationary phase. Conditions: column, Chiracel OD. Solvent system: 98:2 hexanes:*i*-PrOH. Mobile phase flow rate: 1 mL/min. UV detector: 254 nm. T_r(minor) 27.8 min, T_r(major) 31.5 min.

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Supporting Information Available: Experimental procedures and characterization data for all the tabulated examples; experimental procedures for the synthesis of starting materials (18 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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