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Chiral Synthesis *via* Organoboranes. 37. Enantioselective Synthesis of Conjugated Acyclic α-Chiral (*E*)-Alkenones

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Abstract: A highly enantioselective synthesis of conjugated acyclic α-chiral (*E*)-alkenones has been achieved from representative prochiral alkenes. Enantiomerically pure (*E*)-1-alkenylalkylborinic esters, R*B(HC=CHR)OR', required for the synthesis of the (*E*)-alkenones, are obtained either by the reaction of enantiomerically pure boronic esters, R*B(OR)$_2$, with (*E*)-1-lithio-1-alkenes, followed by treatment with ethereal hydrogen chloride, or by the hydroboration of a terminal alkyne with an enantiomerically pure isopinocampheylalkylborane, IpcR*BH, followed by elimination of the Ipc group as α-pinene by treatment with an aldehyde. These (*E*)-1-alkenylalkylborinic esters react smoothly with α,α-dichloromethyl methyl ether (DCME) in the presence of a hindered base (the DCME reaction) to yield, after oxidation with hydrogen peroxide in pH 8 phosphate buffer, conjugated acyclic α-chiral (*E*)-alkenones. The alkenones retain the same stereo- and enantiomeric purity of the chiral borinic esters. To our knowledge, this is the first general synthesis of conjugated acyclic α-chiral (*E*)-alkenones in high enantiomeric purity (≥99% ee).

The successful asymmetric hydroboration of *cis*-2-butene by diisopinocampheylborane, Ipc$_2$BH, in 1961 marked a milestone in achieving asymmetric synthesis approaching 100% ee by a nonenzymatic process.[1] However, Ipc$_2$BH proved effective only for the asymmetric hydroboration of less hindered alkenes. To handle more hindered alkenes, we developed[2] monoisopinocampheylborane, IpcBH$_2$, a reagent of lower steric requirements than Ipc$_2$BH. The asymmetric hydroboration of *trans*- and trisubstituted alkenes with IpcBH$_2$ provided, after simple crystallization,[3] enantiomerically pure products. The asymmetric hydroboration of alkenes with Ipc$_2$BH or IpcBH$_2$ forms the corresponding intermediates, which, upon treatment with an appropriate aldehyde, liberate[4] the chiral auxiliary as α-pinene, readily recycled, to provide the corresponding enantiomerically pure boronic esters, R*B(OR)$_2$, for utilization. Optically pure boronic esters are elegantly suited for carbon-carbon bond forming reactions with elaboration to useful organic compounds. They have been converted into enantiomerically pure alcohols[5], aldehydes[6], acids[6], terminal and internal acetylenes[7], and homologated alcohols[6], as well as borohydrides[8], diols[9] and amines.[10] As part of our continuing research efforts to develop simple, practical methods for enantioselective synthesis via organoboranes, we were interested in developing a general, enantioselective synthesis of conjugated acyclic α-chiral (*E*)-alkenones.

Conjugated acyclic alkenones in general and optically active conjugated acyclic alkenones in particular are potentially interesting intermediates in organic synthesis.[11] The ability to functionalize selectively up to five carbons of an enone by conjugate addition, alkylation, Diels-Alder reaction, etc., enhances the versatility of these compounds and thus they have been utilized in the syntheses of many complex molecules both in racemic and optically pure forms.[11] Even though many methods are known for the synthesis of enantiomerically pure acyclic α-chiral ketones[12] and α-chiral α'-alkynylketones,[13] there is no general procedure in the literature to synthesize conjugated acyclic α-chiral (*E*)-alkenones in high enantiomeric excess. Previous syntheses of such enones have utilized optically active precursors.[14] This deficiency prompted us to undertake the development of a general, enantioselective synthesis of conjugated acyclic α-chiral alkenones.

Recently, we have reported a simple methodology for the synthesis of conjugated acyclic (*E*)-alkenones via organoboranes.[15] The methodology appeared promising also for extension to the asymmetric synthesis of conjugated acyclic α-chiral (*E*)-alkenones. In order to explore the full scope and establish the full generality of this methodology, we have now extended it to synthesize various representative conjugated acyclic α-chiral (*E*)-alkenones achieving consistently high enantiomeric excess.

Results and Discussion

Previously, we have achieved the synthesis of acyclic α-chiral ketones of high enantiomeric purity from enantiomerically pure dialkylborinic esters, R*RBOR, via the DCME reaction (eq 1).[16]

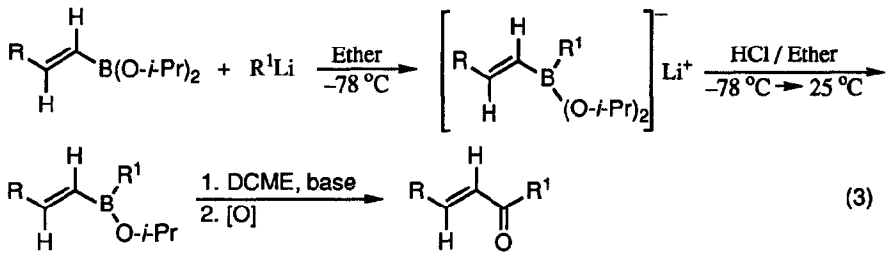
$$\text{R*RBOR'} \xrightarrow[\text{2) base}\\ \text{3) [O]}]{\text{1) DCME}} \text{R*COR} \qquad (1)$$

Later, the methodology was extended to synthesize optically active α-chiral acetylenic ketones from alkyl-alkynylborinic esters, (eq 2).[17]

$$\begin{matrix}\text{OR}\\ |\\ \text{R*BC}{\equiv}\text{CR'}\end{matrix} \xrightarrow[\text{2) base}\\ \text{3) [O]}]{\text{1) DCME}} \begin{matrix}\text{O}\\ \|\\ \text{R*CC}{\equiv}\text{CR'}\end{matrix} \qquad (2)$$

Our approach to the synthesis of conjugated acyclic α-chiral (*E*)-alkenones is based on the carbon-carbon bond forming reaction of stereodefined (*E*)-1-alkenylalkylborinic esters, R*B(HC=CHR)OR', with α,α-dichloromethyl methyl ether in the the presence of a hindered base (the DCME reaction). 1-Alkenylalkylborinic esters are attractive organoborane intermediates for carbon-carbon bond forming reactions. No loss of alkyl group occurs and such 1,2-migrations are known to proceed with complete retention of stereochemistry and configuration of the migrating carbon group. As part of our efforts to obtain organoboranes not available via hydroboration, we have recently developed a simple methodology for preparing isopropyl (*E*)-1-alkenylalkylborinates by the sequential treatment of diisopropyl (*E*)-1-

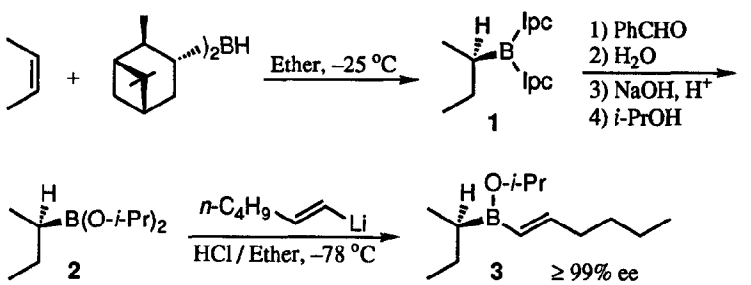
alkenylboronates with an alkyllithium and ethereal hydrogen chloride.[15] These (*E*)-1-alkenylalkylborinic esters were converted into the corresponding conjugated (*E*)-1-alkenones stereoselectively *via* the DCME reaction (eq 3).[15]



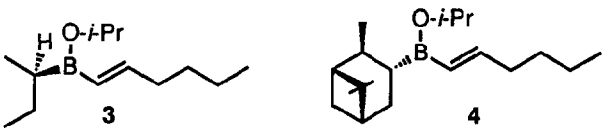
(3)

In order to extend this methodology to the synthesis of conjugated acyclic α-chiral (*E*)-alkenones, we needed to synthesize optically active (*E*)-1-alkenylalkylborinic esters. Enantiomerically pure (*E*)-1-alkenylalkylborinic esters were prepared by the displacement of an alkoxy group of an enantiomerically pure alkylboronic ester by sequential treatment with (*E*)-1-lithio-1-alkene and ethereal hydrogen chloride at –78 °C. In a typical experiment, *cis*-2-butene was hydroborated[18] with diisopinocampheylborane, $^{d}Ipc_2BH$, from (*R*)-(+)-α-pinene, to form (*R*)-*sec*-butyldiisopinocampheylborane (**1**). The trialkylborane **1** was treated with 1.9 equivalents of benzaldehyde[18] to form dibenzyl (*R*)-*sec*-butylboronate, which was hydrolyzed and then reesterified with 2-propanol to form diisopropyl (*R*)-*sec*-butylboronate (**2**). The boronate **2** was treated with (*E*)-1-lithio-1-hexene, generated from the reaction of (*E*)-1-iodo-1-hexene with 2 equivalents of *t*-butyllithium in *n*-pentane,[19] at –78 °C for 3 h. Addition of ethereal hydrogen chloride at –78 °C formed the corresponding enantiomerically pure borinate **3** (Scheme I).

Scheme I



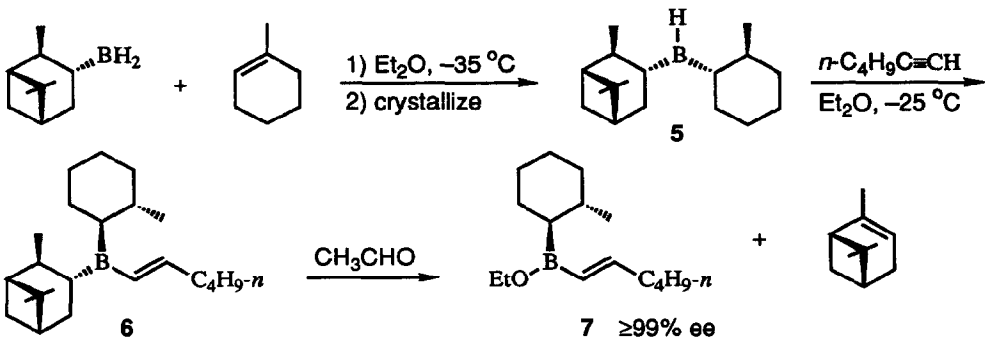
Utilizing the general procedure described above, a number of representative (*E*)-1-alkenylalkylborinic esters were prepared in high enantiomeric purity (≥99% ee).



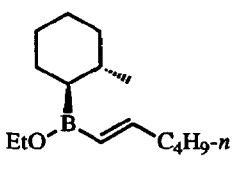
Diisopropyl isopinocampheylboronate, required for the synthesis of borinic ester (**4**), was prepared simply by the treatment of $^{d}IpcBH_2$ with 2-propanol in diethyl ether at 0 °C.

As pointed out earlier, Ipc_2BH and $IpcBH_2$ are complementary reagents for the asymmetric hydroboration of prochiral alkenes, the former being effective for less hindered alkenes and the latter for more hindered alkenes. In order for this methodology for the synthesis of chiral (*E*)-alkenones to be truly general, we also needed to convert the asymmetric hydroboration products, $^{d}IpcR^{*}BH$, of prochiral olefins with monoisopinocampheylborane into the corresponding (*E*)-1-alkenylalkylborinic esters, which could then be transformed into conjugated acyclic α-chiral alkenones. Recently, we have reported a direct synthesis of (*E*)-1-alkenylalkylborinic esters from $IpcR^{*}BH$ and utilized them in the synthesis of enantiomerically pure (*Z*)- and (*E*)-alkenes.[20] In a typical experiment, hydroboration of 1-methylcyclohexene with monoisopinocampheylborane, $^{d}IpcBH_2$, followed by crystallization[3] formed ≥99% enantiomerically pure isopinocampheyl-(1*S*,2*S*)-*trans*-2-methylcyclohexylborane (**5**). The dialkylborane readily hydroborates 1-hexyne at –25 °C to provide the desired trialkylborane **6**. Treatment of this trialkylborane **6** with acetaldehyde at 0 °C results in the selective, facile elimination of the chiral auxiliary, providing the corresponding enantiomerically pure borinate **7** (Scheme II).

Scheme II



Utilizing the general procedure described above the following representative (*E*)-1-alkenylalkylborinic esters were prepared in high enantiomeric purity (≥99% ee).



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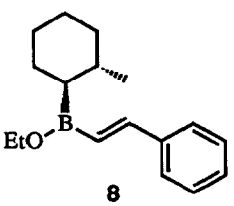

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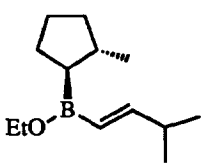

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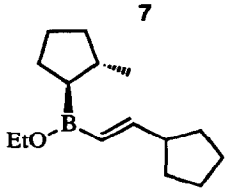

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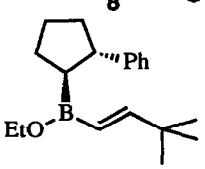

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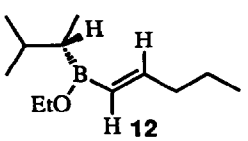

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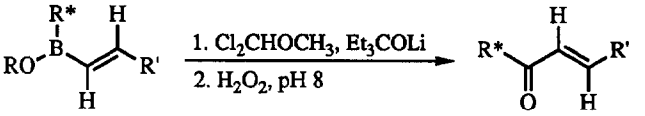
The enantiomeric excess of all these organoborane intermediates was determined by capillary GC analysis of the appropriate derivatives of the alcohols obtained following alkaline hydrogen peroxide oxidation.[6]

Next, we explored the DCME reaction[21] of these enantiomerically pure (*E*)-1-alkenylalkylborinic esters. It was gratifying to find that these enantiomerically pure (*E*)-1-alkenylalkylborinic esters smoothly undergo the DCME reaction,[21] followed by oxidation work-up using hydrogen peroxide in pH 8 phosphate buffer[6,16] to form conjugated acyclic α-chiral (*E*)-alkenones stereoselectively and in ≥99% enantiomeric purity (eq 4).



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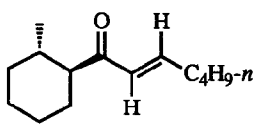
The general procedure described above provided the following representative conjugated acyclic α-chiral (*E*)-alkenones, indicating the generality of the procedure.



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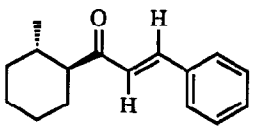

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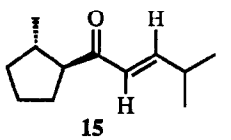

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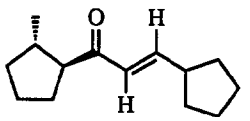

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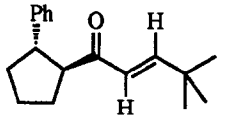

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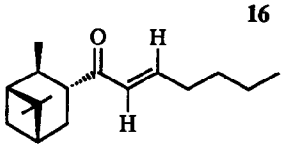

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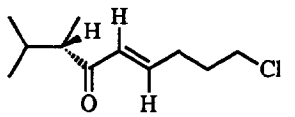

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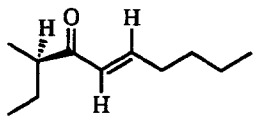

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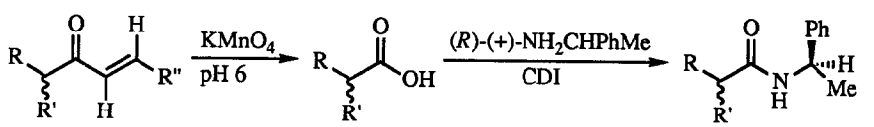
The enones retain the same stereo- and enantiomeric purity of the chiral borinic esters (Table I). The absolute configuration of the (*E*)-alkenones are determined in the asymmetric hydroboration step of the prochiral olefins.[22] The *trans* geometry of the alkenones was indicated by the IR (985 cm^{-1}) and ^1H NMR spectra.

In order to determine the enantiomeric purity of the alkenones, the double bond was cleaved with $KMnO_4$ to form the corresponding carboxylic acids.[17] The acids were then coupled to (*R*)-(+)-methylbenzylamine in the presence of 1,1'-carbonyldiimidazole (CDI) to yield the diastereomeric amides (eq 5).[13b]



(5)

Each pair of diastereomeric amides was readily resolved by capillary GC (SPB-5, 30 m). Racemic acids gave two peaks for the amides in a 1:1 ratio, thus assuring that no kinetic resolution had taken place.

Table I. Conjugated Ayclic α-Chiral (*E*)-Alkenones Obtained from Enantiomerically Pure (*E*)-1-Alkenylalkylborinic Esters

(*E*)-alkenylalkylborinic esters [a]	conjugated (*E*)-alkenones [b]	config of alkenones	yield, % (isolated) [c]	% ee[d]
3	3-methyldec-5-en-4-one (**20**)	3*R*	66	≥99
4	isopinocampheyl hex-1-enyl ketone (**18**)	1*R*,2*R*,3*R*,5*S*	63	≥99
7	*trans*-2-methylcyclohexyl hex-1-enyl ketone (**13**)	1*S*,2*S*	67	≥99
8	*trans*-2-methylcyclohexyl 2-phenyleth-1-enyl ketone (**14**)	1*S*,2*S*	69	≥99
9	*trans*-2-methylcyclopentyl 3-methylbut-1-enyl ketone (**15**)	1*S*,2*S*	71	≥99
10	*trans*-2-methylcyclopentyl 2-cyclopentyleth-1-enyl ketone (**16**)	1*S*,2*S*	69	≥99
11	*trans*-2-phenylcyclopentyl 3,3-dimethylbut-1-enyl ketone (**17**)	1*S*,2*S*	72	≥99
12	9-chloro-2,3-dimethylnon-5-en-4-one (**19**)	3*S*	67	≥99

[a] Not distilled. Volatiles removed in vacuo to give essentially quantitative yield of borinate ≥95% purity (^{11}B and ^{1}H NMR). [b] Geometric purity established by GC, IR and ^{1}H NMR data. [c] Yields based on alkenylalkylborinic esters. [d] Enantiomeric purity established by capillary GC.

In conclusion, the methodology presented here makes possible the facile preparation and isolation of a wide variety of conjugated acyclic α-chiral (*E*)-alkenones of uniformally high enantiomeric purity. Since the chiral auxiliary, α-pinene, is readily available in the both (+) and (–) form, providing both ^{d}IpcBH$_2$ and ^{l}IpcBH$_2$, we can now synthesize both (+) and (–) conjugated acyclic α-chiral (*E*)-alkenones of known absolute configuration and consistently high enantiomeric and geometric purity. Reactions which have been applied to conjugated (*E*)-alkenones should also be applicable to enantiomerically pure conjugated (*E*)-alkenones and thus these should be readily transformed by synthetic chemistry into many more complex molecules.

Experimental

All operations were carried out under nitrogen atmosphere with oven-dried glassware. The ^{11}B NMR spectra were recorded on a Varian FT-80A instrument, with the ^{11}B chemical shifts relative to BF_3·Et_2O. The ^{1}H NMR spectra were scanned on a Varian T-60 and Varian 200 MHz spectrometers, and the ^{13}C spectra were obtained on a Varian 200 MHz instrument. The chemical shifts are relative to Me_4Si for the ^{1}H and ^{13}C NMR spectra. IR and mass spectra were recorded on a Perkin-Elmer 137 and Finnegan GC/mass spectrometers respectively. Gas chromatography analyses were carried out with a Hewlett-Packard 5750 chromatograph

with a TC-detector. Optical rotations were measured on a Rudolph Polarimeter Autopol III. Capillary gas chromatographic analyses were carried out with a Hewlett-Packard 5890 chromatograph fitted with a 50-m methylsilicone, 15-m Supelcowax, or 30-m SPB-5 columns.

Materials. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Anhydrous diethyl ether (EE) was purchased from Mallinckrodt, Inc., and used directly. (–)-Menthyl chloroformate (MCF) was purchased from the Aldrich Chemical Company. (*R*)-MTPA was purchased from the Aldrich Chemical Company, converted[23] to the acid chloride, and distilled. The enantiomerically pure boronic esters, $R^*B(OR)_2$, and isopinocampheylalkylboranes, R*IpcBH, used in this study were prepared by procedures described previously[3,18] starting from (+)-α-pinene. Previous studies have shown that the same procedure can be used with (–)-α-pinene to give the pure opposite enantiomers.[24]

Preparation of Isopropyl (*E*)-1-Alkenylalkylborinates from Diisopropyl Alkylboronates. The following procedure for the preparation of isopropyl (*E*)-1-hexenyl-*sec*-butylborinate (**3**) is representative. A solution of (*E*)-1-iodo-1-hexene (17.5 mmol, 3.67 g) in diethyl ether (20 mL) was cooled to –78 °C and to it *t*-butyllithium in *n*-pentane (35 mmol, 23.33 mL, 1.5 M) was added dropwise. The reaction mixture was stirred at –78 C for 3 h. To the mixture diisopropyl *sec*-butylboronate (**2**) (17.5 mmol, 2.97 g) was added at –78 °C with stirring and the reaction was continued for another 3 h at –78 °C. HCl in diethyl ether (21 mmol, 8.4 mL, 2.5 M) was added dropwise and the mixture was allowed to warm up to room temperature. The clear ether layer was decanted and LiCl was washed with ether (3 x 10 mL). The solvent was removed under pressure to get isopropyl (*E*)-1-hexenyl-*sec*-butylborinate (**3**) (3.46 g). ^{11}B NMR (ether): δ +47.87; ^{1}H NMR ($CDCl_3$): 0.82-1.5 (m, 21H), 2.18 (m, 2H), 4.50 (m, 1H), 5.75 (d, 1H, *J*=18Hz), 6.55 (dt, 1H, *J*=18Hz, 7Hz). The borinate (**3**) was oxidized and worked-up following the literature procedure. 2-Butanol, thus obtained, was converted to its MTPA derivative and analyzed on capillary GC (SPB-5), which indicated it to be ≥99% ee.

Preparation of Ethyl (*E*)-1-Alkenylalkylborinates from Isopinocampheylalkylboranes. The following procedure for the preparation of ethyl (*E*)-(1*S*,2*S*)-*trans*-2-methylcyclohexyl-1-hexenylborinate (**7**) is representative. 1-Hexyne (2.75 mL, 22.5 mmol) was added to a suspension of isopinocampheyl-(1*S*,2*S*)-*trans*-2-methylcyclohexylborane (**5**) (4.96 g, 20.12 mmol) in EE (25 mL) at –25 °C. The reaction mixture was stirred for a period of 2 h at –25 °C. The disappearance of the solid (dialkylborane) and the formation of a clear homogeneous solution indicated completion of the hydroboration. An aliquot drawn from the reaction mixture showed a peak at δ +71.8 in the ^{11}B NMR, indicating the formation of the desired trialkylborane (**6**). The mixture was warmed up to 0 °C and acetaldehyde (2.79 mL, 50 mmol) was added slowly. The reaction mixture was stirred vigorously for a further period of 0.5 h. An aliquot drawn from the reaction mixture showed a peak at δ +46.3 in the ^{11}B NMR, indicating elimination of the chiral auxiliary and formation of the borinate (**7**). Excess acetaldehyde, α-pinene and solvent were pumped off at room temperature under vacuum (5.0 Torr) to yield ethyl (*E*)-(1*S*,2*S*)-*trans*-2-methylcyclohexyl-1-hexenylborinate (**7**) (4.72 g). ^{1}H NMR ($CDCl_3$): 0.7-1.9 (m, 23H), 2.21 (m, 2H), 4.02 (q, 2H), 5.75 (d, 1H, *J*=18 Hz), 6.61 (dt, 1H, *J*=18 Hz, 7 Hz). The borinate was oxidized and worked-up following the literature procedure.[6] (1*S*,2*S*)-*trans*-2-methyl-

cyclohexanol, thus obtained, was converted to its MCF derivative and analyzed on capillary GC (SPB-5), which indicated it to be ≥99% ee.

General Procedure for the Preparation of Conjugated Acyclic α-Chiral (*E*)-Alkenones from (*E*)-1-Alkenylalkylborinic Esters. The following procedure for the preparation of (*E*)-(1*S*,2*S*)-*trans*-2-methylcyclohexyl hex-1-enyl ketone (**13**) is representative. The borinate (**7**) (4.72 g, 20 mmol) was dissolved in EE (25 mL) and cooled to 0 °C. To it α,α-dichloromethyl methyl ether (2.71 mL, 30 mmol) was added followed by dropwise addition of Et_3COLi (40 mmol, the base was prepared from *n*-butyllithium and triethylcarbinol). The mixture was stirred at 0 °C for 0.5 h and then at 25 °C for 2 h, while LiCl precipitated out. The reaction mixture was cooled to 0 °C and pH 8 phosphate buffer solution (60 mmol, 24 mL) was added followed by 30% hydrogen peroxide (2.50 mL, 22.13 mmol). The ice-bath was removed and the two-phase system was stirred for 24 h. The organic layer was separated and the aqueous portion extracted with ether (3 x 10 mL). The combined ether extract was washed with water (3 x 15 mL), brine (15 mL) and dried over anhydrous $MgSO_4$. The solvent was removed and the residue on careful distillation gave 2.79 g (67%) of (*E*)-(1*S*,2*S*)-*trans*-2-methylcyclohexyl hex-1-enyl ketone (**13**), bp 100-102 °C (0.5 Torr); $[\alpha]^{23}_D$ +44.0 ± 0.01 (c 1.83, MeOH); IR (neat): 1688, 1664, 1624, 980 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.8 (d, 3H), 0.92 (t, 3H), 1.16-1.84 (m, 13H), 2.24 (m, 3H), 6.16 (d, 1H, *J*=16 Hz), 6.88 (dt, 1H, *J*=16Hz, 7 Hz); ^{13}C NMR (200 MHz, $CDCl_3$): δ 13.90, 20.77, 22.36, 25.93, 26.09, 30.12, 30.36, 32.32, 33.91, 34.77, 55.70, 130.25, 147.88, 204.88; MS, *m / e* (chemical ionization) 209 (100, M+H); MS, *m / e* (electron impact) 209 (1.8, M+H), 193 (1.8), 151 (32.4), 111 (43.2), 55 (100).

(*E*)-(1*S*,2*S*)-*trans*-2-Methylcyclohexyl 2-Phenyleth-1-enyl Ketone (14): The hydroboration of phenylacetylene with isopinocampheyl-(1*S*,2*S*)-*trans*-2-methylcyclohexylborane did not go to completion at –25 °C for 8 h. Therefore, the reaction mixture was stirred at 0 °C for 1 h, when the solution became homogeneous. A clean formation of the trialkylborane was indicated by the ^{11}B NMR (δ +72). The trialkylborane was then converted into the alkenone **14** by the general procedure described above. Yield 69%; bp 132-134 °C (0.4 Torr); $[\alpha]^{23}_D$ +55.7 ± 0.01 (c 1.69, MeOH); IR (neat): 1681, 1651, 1608, 1574, 980 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.85 (d, 3H), 0 .96-1.92 (m, 9H), 2.41 (m, 1H), 6.82 (d, 1H, *J*=16 Hz), 7.16-7.65 (m, 6H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 20.83, 25.92, 26.07, 30.10, 34.03, 34.76, 56.71, 126.11, 128.70, 129.29, 130.74, 135.14, 142.84, 204.57; MS, *m / e* (chemical ionization) 229 (100, M+H); MS, *m / e* (electron impact) 228 (5.5, M^+), 213 (2.4), 131 (100), 103 (25.3), 55 (55.2).

(*E*)-(1*S*,2*S*)-*trans*-2-Methylcyclopentyl 3-methylbut-1-enyl Ketone (15): Yield 71%; bp 70-72 °C(0.5 Torr); α^{23}_D +53.3 ± 0.01 (neat, l 1.0); IR (neat): 1688, 1664, 1624, 980 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.96-2.3 (m, 18H), 2.38-2.75 (m, 2H), 6.11 (d, 1H, *J*=16 Hz), 6.82 (dd, 1H, *J*=16 Hz, 7Hz); ^{13}C NMR (200 MHz, $CDCl_3$): δ 19.92, 21.48, 24.86, 30.33, 31.28, 35.19, 38.29, 57.15, 127.61, 153.84, 204.01; MS, *m / e* (chemical ionization) 181 (100, M+H); MS, *m / e* (electron impact) 181 (3.0, M+H), 165 (1.2), 137 (20.6), 97 (100), 55 (37).

(E)-(1*S*,2*S*)-*trans*-2-Methylcyclopenyl 2-cyclopentyleth-1-enyl Ketone (16): Yield 69%; bp 84-86 °C (1.0 Torr); $[\alpha]^{23}_D$ +56.4 ± 0.01 (c 1.95, MeOH); IR (neat): 1684, 1661, 1624, 983 cm^{-1}; ^1H NMR (200

MHz, $CDCl_3$): δ 1.02 (d, 3H), 1.17-2.32 (m, 15H), 2.64 (m, 2H), 6.15 (d, 1H, *J*=16 Hz), 6.83 (dd, 1H, *J*=16 Hz, 7Hz); ^{13}C NMR (200 MHz, $CDCl_3$): δ 19.94, 24.85, 25.40, 30.29, 32.70, 35.19, 38.30, 43.25, 57.15, 128.43, 151.96, 203.86; MS, *m / e* (chemical ionization) 207 (100, M+H); MS, *m / e* (electron impact) 206 (1.2, M^+), 165 (2.4), 123 (38.2), 83 (35.1), 55 (100).

(*E*)-(1*S*,2*S*)-*trans*-2-Phenylcyclopentyl 3,3-dimethylbut-1-enyl Ketone (17): Yield 72%; bp 88-90 °C (0.1 Torr); $[\alpha]^{23}_D$ +117.9 ± 0.01 (c 8.82, MeOH); IR (neat): 1688, 1661, 1621, 983 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.95 (s, 9H), 1.72-2.24 (m, 6H), 3.27 (m, 2H), 5.87 (d, 1H, *J*=16 Hz), 6.61 (d, 1H, *J*=16 Hz); 7.08-7.32 (m, 5H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 25.73, 28.63, 30.33, 33.62, 35.91, 49.54, 57.24, 125.64, 126.53, 127.74, 128.76, 145.15, 157.64, 203.04; MS, *m / e* (chemical ionization) 257 (100, M+H), 199 (2.7); MS, *m / e* (electron impact) 257 (1.8, M+H), 199 (78), 111 (100), 91 (68.5), 55 (42.5).

(*E*)-(1*R*,2*R*,3*R*,5*S*)-Isopinocampheyl Hex-1-enyl Ketone (18): Yield 63%; bp 108-110 °C (0.4 Torr); $[\alpha]^{23}_D$ −30.4 ± 0.01 (c 1.66, MeOH); IR (neat): 1691, 1668, 1624, 980 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.83-2.01 (m, 23H), 2.25 (m, 2H), 2.51 (m, 1H), 6.21 (d, 1H, *J*=16 Hz), 6.89 (dt, 1H, *J*=16 Hz, 7Hz); ^{13}C NMR (200 MHz, $CDCl_3$): δ 13.89, 22.28, 22.36, 23.02, 27.95, 30.39, 30.53, 32.30, 32.73, 36.79, 38.84, 41.12, 47.30, 47.47, 129.87, 147.76, 203.47; MS, *m / e* (chemical ionization) 249 (19.7, M+H), 203 (35.8), 137 (97.5), 117 (100), 81 (41.3); MS, *m / e* (electron impact) 248 (3.3, M^+), 193 (21.2), 111 (35.8), 81 (25.9), 55 (100).

(*E*)-(3*S*)-9-Chloro-2,3-dimethylnon-5-en-4-one (19): Yield 67%; bp 78-80 °C (0.4 Torr); $[\alpha]^{23}_D$ +50.3 ± 0.01 (c 10.0, MeOH); IR (neat): 1688, 1664, 1624, 977 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (2d, 6H), 1.04 (d, 3H), 1.96 (m, 3H), 2.32-2.59 (m, 3H), 3.56 (m, 2H), 6.24 (d, 1H, *J*=16 Hz), 6.82 (dt, 1H, *J*=16 Hz, 7Hz); ^{13}C NMR (200 MHz, $CDCl_3$): δ 12.95, 18.90, 21.43, 29.54, 30.34, 30.93, 44.16, 50.91, 130.52, 145.02, 204.35; MS, *m / e* (chemical ionization) 203 (100, M+H); MS, *m / e* (electron impact) 203 (1.2, M+H), 187 (1.2), 160 (17.2), 131 (100), 55 (24).

(*E*)-(3*R*)-3-Methyldec-5-en-4-one (20): Yield 66%; bp 90-92 °C (15 Torr); $[\alpha]^{23}_D$ −26.9 ± 0.01 (c 3.78, MeOH); IR (Neat): 1691, 1668, 1628, 980 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.82–0.96 (m, 6H), 1.08 (d, 3H), 1.24-1.81 (m, 6H), 2.23 (m, 2H), 2.68 (m, 1H), 6.17 (d, 1H, *J*=16 Hz), 6.88 (dt, 1H, *J*=16 Hz, 7 Hz); ^{13}C NMR (200 MHz, $CDCl_3$): δ 11.71, 13.84, 16.20, 22.34, 26.29, 30.38, 32.27, 45.43, 129.36, 147.70, 204.59; MS, *m / e* (chemical ionization) 169 (100, M+H); MS, *m / e* (electron impact) 168 (0.3, M^+), 140 (7.0), 111 (100), 83 (6.1), 55 (93.8).

General Procedure for the Determination of the Enantiomeric Purity of Alkenones. The alkenone was dissolved in acetone (10 mL/mmol) at 0 °C and then treated dropwise with an aqueous solution of $KMnO_4$ (300 mol%) in 15 mL of phosphate buffer, pH 6. The dark mixture was stirred at 25 °C for 24 h. Sodium bisulfite (solid) was added, in portions, until the mixture became colorless. The mixture was acidified with 3 M HCl and then diluted with EE. Aqueous and organic layers were separated. The aqueous portion was saturated with NaCl and then extracted three times with EE. The combined organic portion was washed with brine and dried over $MgSO_4$. The solvent was removed to get the residue, which was distilled under

reduced pressure to get the carboxylic acid. The acid (0.02 mmol) was coupled to (*R*)-(+)-methylbenzylamine (0.02 mmol) in the presence of 1,1'-carbonyldiimidazole (0.02 mmol) in ether to give the desired amide. The crude amide was taken up in EE and analyzed by capillary GC.

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