Permethylated β-Cyclodextrin as Chiral Solvating Agent for the NMR Assignment of the Absolute Configuration of Chiral Trisubstituted Allenes

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Permethylated β-cyclodextrin is a convenient chiral solvating agent (CSA) for the determination by NMR of the enantiomeric purities of chiral trisubstituted allenes and of their absolute configuration. All the allene proton resonances are deshielded, and this effect is stronger for the (*S*)-enantiomer of the allene than for the (*R*)-enantiomer.

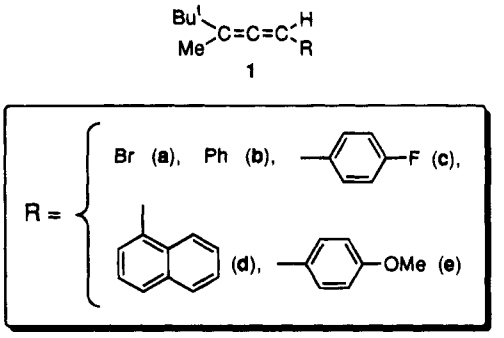
Introduction

The assignment of the absolute configuration of chiral allenes remains a difficult task. This problem has been solved by suitable chemical correlations of allenes with centrodissymmetric molecules of known absolute configuration[1,2] or developing semiempirical rules which relate the absolute configuration to the sign of the rotatory power or CD bands.[3,4]

An alternative approach to this problem is provided by the NMR spectroscopy. Separate NMR signals can be in principle obtained for stable or short-lived diastereoisomeric derivatives[5–8] of the enantiomeric mixtures, the intensities of which are correlated to the enantiomeric composition and their relative position to the absolute configuration. For this reason, great effort has been continously devoted to the development of new chiral auxiliaries for NMR spectroscopy, the majority of them being dedicated to the chiral assay of molecules having polar functional groups.[5–8]

Recently, we found that heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (permethylated β-cyclodextrin, TRIMEB) induced nonequivalence in the ^{1}H NMR spectra, in CD_3OD solutions, of enantiomeric mixtures of trisubstituted allenes devoid of polar functional groups, thus affording a simple and general way to their enantiomeric purity determinations.[9]

Chart 1



Now we report that a consistent correlation between the absolute configuration of the trisubstituted allenes **1a–e** (Chart 1) and the permethylated β-cyclodextrin induced shifts of their proton signals exists; therefore, the use of TRIMEB as chiral auxiliary for the rapid and reliable NMR determination of their absolute configuration can be proposed.

Results and Discussion

The chiral trisubstituted allenes **1** have been conveniently obtained in high enantiomeric purities and prefixed absolute configuration starting from the optically active propargyl alcohol (*S*)-**2** by the stereocontrolled routes **A** and **B**[1e,9,10] (Scheme 1). **2** was converted into the corresponding methanesulfonate **3**, whose reaction with a suspension of $LiCu_2Br_3$ in THF at −70 °C afforded the bromoallene **1a** with *anti* stereochemistry (reaction **I**).[1g,9] This last product was converted into the corresponding aryl-substituted allenes **1b–e** by the *anti* stereocontrolled reaction **II**,[9,10] with the appropriate Grignard reagent in the presence of a catalytic amount of anhydrous CuBr (5%). Alternatively, the aryl-substituted allenes **1b–e** have been obtained directly from **3** by using bromocuprates (reaction **III**, Scheme 1). This reaction too proceeds via a predominant *anti* stereochemistry.[1e] Therefore, the two enantiomers of each

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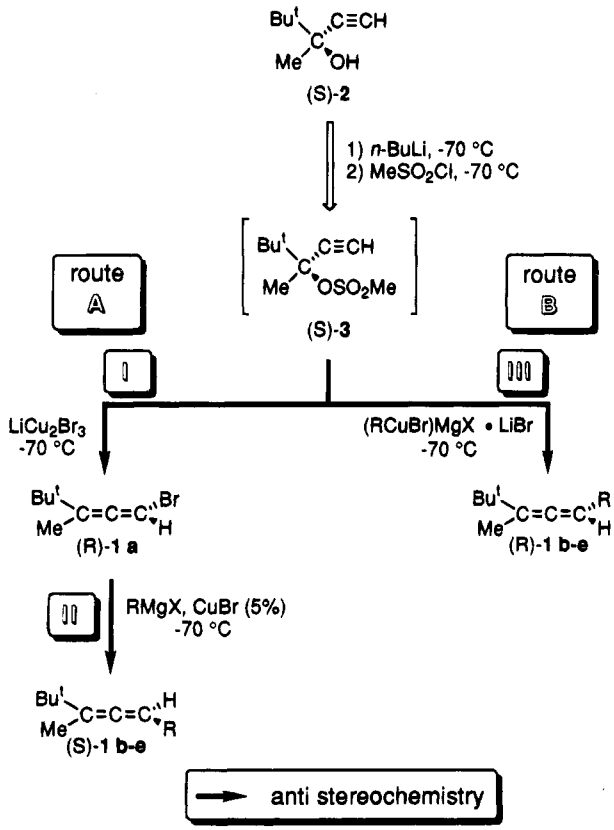
Scheme 1



allene **1b**–**e** can be obtained by the routes **A** and **B**, respectively, starting from the same chiral precursor (*S*)-**2**.

The enantiomeric purities of the samples obtained have been determined, as recently proposed,[9] by analyzing the ^{1}H NMR spectra of their mixtures with permethylated β-cyclodextrin (molar ratio TRIMEB/allene ranging from 1 to 2), in CD_3OD solutions, and in all cases TRIMEB discriminated between the two enantiomers of allenes **1a**–**e**. The corresponding spectral regions relative to the resonances of the allene protons of the substrates in the presence of the cyclodextrin are reported in Figure 1. The bromoallene (*R*)-**1a**, obtained from the (*S*)-alcohol (ee 89%) by following the chemical pathway **I**, showed the major signal at 6.10 ppm, at lower frequency with respect to the minor signal corresponding to the (*S*)-allene (6.14 ppm). Accordingly, for a sample of (*S*)-**1a** obtained from (*R*)-**2** (ee 64%), the major signal was the one centered at 6.14 ppm. The allenes **1b**–**e**, having (*S*)-absolute configuration, arising from the bromoallene **1a** by the pathway **II**, showed a major signal (at 6.12 ppm for **1b**, 6.13 ppm for **1c**, 7.02 ppm for **1d** and 6.09 ppm for **1e**) which was at higher frequency with respect to the minor signal due to the (*R*)-allene (at 6.09 ppm for **1b**–**c**, 6.95 ppm for **1d**, and 6.06 ppm for **1e**). Also in the cases of the (*R*)-allenes **1b**–**e**, obtained *via* the route **III** directly from (*S*)-**2**, it has been verified that the allene absorption of the (*R*)-enantiomer resonates at lower frequency with respect to the same signal of the (*S*)-enantiomer. It is noteworthy that the same kind of correlation between the sense of nonequivalence, i.e., the relative position of the absorption of one enantiomer with respect to the other, and the absolute configuration has been found for the alkyl protons: all the proton signals due to the (*S*)-enantiomer are high-frequency shifted with respect to the corresponding signals due to the (*R*)-enantiomer (Table 1).

Table 1. Complexation Shifts ($\Delta\delta$,[a] 300 MHz, CD_3OD) Induced by TRIMEB on the Two Enantiomers of Allenes 1a–e

	$\Delta\delta_S$			$\Delta\delta_R$				
allene	H	Me	Bu^t	H	Me	Bu^t	T (°C)	molar ratio
1a	9.88	3.48	3.30	7.69	2.38	2.93	25	1:1
	40.55	11.16	8.20	29.88	7.93	6.55	−20	1:1
1b	7.05	5.14	4.12	5.43	4.18	3.68	25	1:1
	23.83	12.52	10.27	15.59	9.22	7.89	−20	1:1
1c	4.86	1.72	1.62	2.21	0.47	0.59	25	1:1
	22.75	9.02	7.78	11.58	5.01	4.49	−20	1:1
1d	9.15	4.40	4.40	5.67	2.20	2.57	25	1:2
	67.41	21.70	25.35	42.05	10.99	14.55	−40	1:2
1e	8.23	4.03	3.66	3.94	1.83	1.47	25	1:1
	26.85	11.88	10.50	10.14	5.42	4.64	−20	1:1

[a] $\Delta\delta = \delta_{mixture} - \delta_{free}$, Hz.

The general trend observed suggests that the absolute configuration of an unknown trisubstituted allene can be simply determined by preparing, in CD_3OD as solvent, a mixture with TRIMEB (the molar ratio TRIMEB/allene can be 1 or greater) and by observing the relative positions of the NMR signals of the prevailing isomer with respect to the minor one: if the most intense absorption is found at lower frequency, the (*R*) absolute configuration can be assigned to the former; on the contrary, the (*S*)-enantiomer is the prevailing one if the most intense signal is observed at higher frequency. Of course, at least a minimum amount (>2%) of the minor enantiomer should be present.

It is worthy of note that the pioneering Pirkle's CSAs[11] and also many other classes of chiral auxiliaries,[6] provided with different kinds of polar functional groups, commonly produced in the proton nuclei of the substrates analyzed both high- and low-frequency shifts, which have been well explained as, respectively, due to the spatial proximity between groups of the selector having shielding or deshielding effects and groups of the selectand. Also in the case of underivatized cyclodextrins, the interaction with a substrate often produced opposite effects (deshielding or shielding) for groups which are located inside or outside the cavity.[12] Interestingly, the analysis of the complexation shifts for the two enantiomer of **1a**–**e**, i.e., the comparison of their proton chemical shifts in the presence of TRIMEB and in the free state (Table 1), showed that all the proton nuclei of the allenes felt a deshielding effect as a consequence of the interaction with TRIMEB. This behavior immediately awakened our interest, because any commonly employed CSA/substrate interaction model did not appear suitable for the system TRIMEB/allene and additional investigations seemed essential. For this reason we carried out an accurate ^{1}H NMR investigation in CD_3OD solution of the adducts formed starting from the two enantiomers of the bromoallene **1a** and TRIMEB.

Taking into account that only one signal can be observed for each enantiomer in the free state and in the presence of TRIMEB, the fast exchange conditions clearly hold and the measured chemical shifts (δ_{obs}) are the

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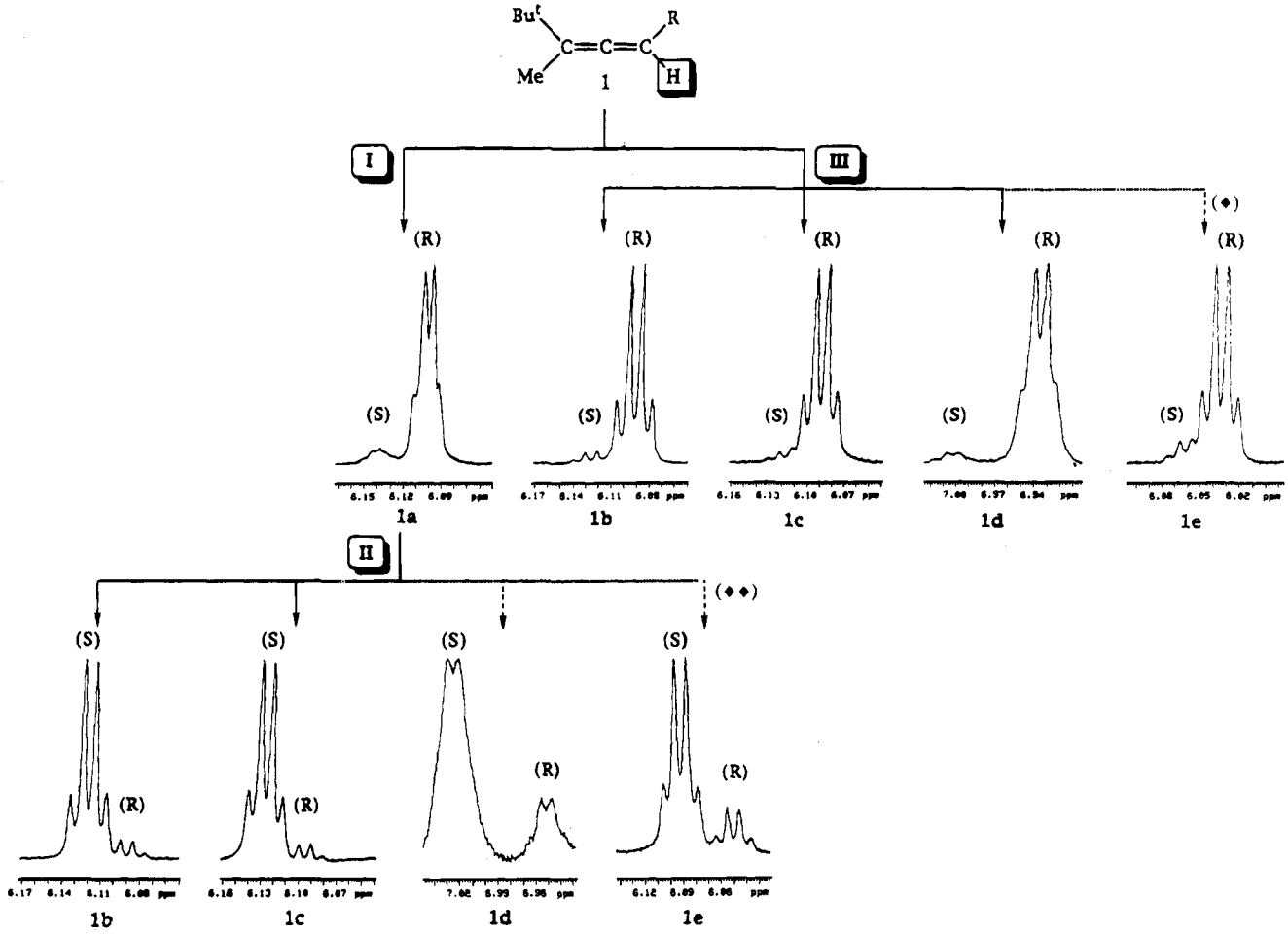

Figure 1. Analysis of the samples of allenes **1a**–**e** obtained starting from (*S*)-**2** (ee 89%): ^{1}H NMR (300 MHz, CD_3OD) spectral regions corresponding to the allene proton absorptions for mixtures TRIMEB/allene (molar ratio 1:1 for **1a**–**c, e** and 2:1 for **1d**) at −20 °C for **1a**–**c, e** and −40 °C for **1d**. (◆) (*R*)-**1e** was obtained starting from a sample of (*S*)-**2** with lower enantiomeric purity (81%). (◆◆) (*S*)-**1d**–**e** were obtained starting from a sample of **1a** with lower enantiomeric purity (64%).

weighted average of the corresponding chemical shifts in the free (δ_{free}) and bound states (δ_{bound}) (eq 1)

$$\delta_{obs} = X_{free}\delta_{free} + X_{bound}\delta_{bound} \quad (1)$$

where X_{free} and X_{bound} are, respectively, the molar fractions in the free and bound states. In these conditions, the stoichiometry of the complexes formed by each enantiomer of **1a** and the CSA can be simply determined by following the classical continuous variation Job's method[13] by analyzing the proton spectra of mixtures of allene/TRIMEB where the total concentration was kept constant (59.2 mM) and the initial molar fraction of **1a** was varied from 0 to 1. In Figure 2 the Job plot is reported for (*S*)-**1a** obtained by plotting the chemical shift of the allene proton, referred to its molar fraction, *versus* the molar fraction of the cyclodextrin. The symmetrical bell-shaped curve centered at a molar fraction of TRIMEB of 0.5 supports a well-defined one-to-one stoichiometry. The same result was obtained for (*R*)-**1a**. Hence, the interaction between the (*S*)- or (*R*)-allene and TRIMEB can be described by the equilibrium

$$\text{allene} + \text{TRIMEB} \rightleftarrows [\text{allene·TRIMEB}]$$

characterized by the association constant K_{assoc}, which,

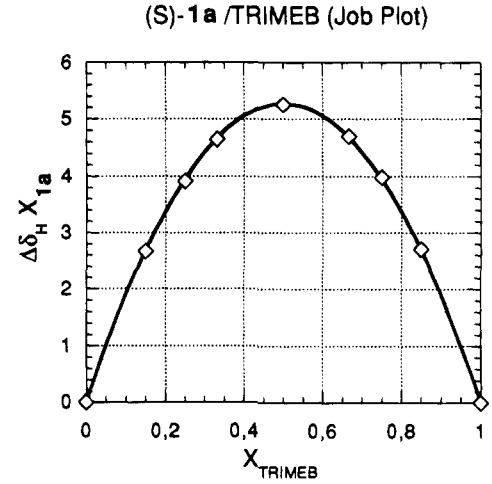

Figure 2. Continuous-variation plot (Job plot) for the allene proton of (*S*)-**1a** in TRIMEB/**1a** mixtures (total concentration, 59.2 mM); $\Delta\delta$ (Hz) is the difference between the chemical shift of the allene proton in the mixture and in the free state.

for an equimolar mixture, can be simply expressed in terms of the initial concentration of the substrates (C_0) and the measured chemical shifts as in eq 2:

$$C_0 = 1/K_{assoc}(\delta_{obs} - \delta_F)(\delta_B - \delta_F)/(\delta_B - \delta_{obs})^2 \quad (2)$$

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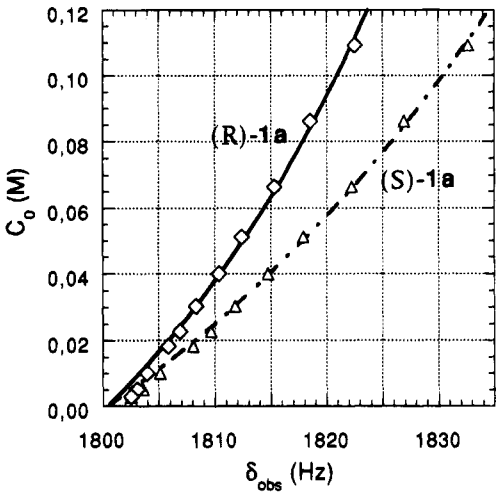

Figure 3. Plot of C_0 (M) against δ_{obs} (Hz) for the allene proton of (*S*)-**1a** and (*R*)-**1a** in equimolar mixtures with TRIMEB.

Table 2. Association Constants (K_{assoc}, M^{-1}) and Chemical Shifts in the Bound State (δ_B, Hz) for the Allene Protons of the Two Enantiomers of 1a in the Complex with TRIMEB

1a	δ_B	K_{assoc}
(*S*)-enantiomer	1990.4 ± 18.0	2.22 ± 0.23
(*R*)-enantiomer	1920.0 ± 16.8	2.48 ± 0.47

By measuring the chemical shift of the allene proton in two separate equimolar solutions (*S*)-allene/TRIMEB and (*R*)-allene/TRIMEB, progressively diluted (C_0 was ranged from 2.9 to 109.3 mM), the plot of C_0 against δ_{obs} afforded the lines of Figure 3. In this way the two constants for the association of the two enantiomers to TRIMEB and the two limiting values for the chemical shifts in the bound state have been obtained, and they are reported in Table 2. It can be observed that no significant differences between the two association constants have been detected (2.48 ± 0.47 M^{-1} for the (*R*)-enantiomer and 2.22 ± 0.23 M^{-1} for the (*S*)-one), whereas the limiting chemical shifts for the two enantiomers in the bound state are remarkably different, being 1990 Hz for the (*S*)-allene and 1920 Hz for the (*R*)-allene.

Therefore, it can be assessed that the observed nonequivalence, i.e., the differences of the chemical shifts of the two allene enantiomers in the presence of TRIMEB, originates from differences between the chemical shifts in the two complexed enantiomers rather than from differences in the association constants of the two complexes, which are very small. The weakness of the two diastereoisomeric complexes also explains the failure to observe differences in their stereochemistry by NOE experiments: only weak but reproducible intermolecular NOEs between the allene protons and the external cyclodextrin protons have been detected. On this basis it can be questioned if the enantiomeric substrates include to the cavity of the cyclodextrin or the enantioselective interaction takes place at the outer surface of the molecule. This kind of superficial interaction could be in keeping with the observed trend of the complexation shifts, which are positive for all the protons of the allenes: the deshielding effect of the unpaired lone pairs of the external ethereal oxygen atoms of the TRIMEB could be responsible for this behavior.

In conclusion, the most important result is that the use of permethylated cyclodextrin as chiral solvating agent for NMR spectroscopy not only affords a simple and practical way for the determination of the stereochemical purities of trisubstituted allenes but also allows us to simultaneously determine their absolute configuration. Indeed, TRIMEB induced only positive complexation shifts of all the allene protons, which are greater for the (*S*)-enantiomer with respect to the (*R*)-one, independently from the structure of the allene. This empirical correlation seems to be reliable since it has been satisfied by a large number of trisubstituted allenes.

The method is undoubtedly very attractive on a practical point of view: it only requires the acquisition of a routine NMR spectrum for the suitable allene/TRIMEB mixture.

Experimental Section

General Methods. The ^1H NMR measurements were performed at 300 MHz in CD_3OD; the temperature was controlled (accuracy ± 0.1 °C). The $^1H\{^1H\}$-NOE experiments were performed on degassed samples in the difference mode. The decoupler power used was the minimum required to saturate the spin of interest. A waiting time of 10 s was used to allow the system to reach the equilibrium. Each NOE experiment was repeated at least four times. All reactions were carried out under an inert atmosphere of dry argon. The enantiomeric purity of the trisubstituted allenes **1** was assayed[9] by analyzing the ^1H NMR (300 MHz, CD_3OD) spectra of the mixtures **1**/TRIMEB (molar ratio 1:1 and −20 °C for **1a−c,e**; 1:2 and −40 °C for **1d**).

Materials. Heptakis(2,3,6-tri-O-methyl)-β-cyclodextrin (TRIMEB) was obtained from Sigma. Tetrahydrofuran (THF) was distilled from $LiAlH_4$ prior to use. Grignard reagents were prepared in THF and standardized by titration methods. *n*-BuLi was purchased from Fluka A. G. Co., Buchs, as a 1.6 M solution in hexane. Commercial (Fluka) LiBr and CuBr were used without purification. Aryl heterocuprates were prepared according to literature methods.[14] 3,4,4-Trimethyl-1-pentyn-3-ol was obtained by a published procedure.[15]

Resolution of 3,4,4-Trimethyl-1-pentyn-3-ol (2).[16] The hydrogen phthalate of racemic **2** (140.7 g, 0.51 mol) and anhydrous brucine (0.51 mol) were dissolved in 4 L of boiling acetone. After the mixture was cooled to room temperature, the brucine salt was filtered off, recrystallized from acetone five times, and decomposed with dilute HCl (6 N). The obtained hydrogen phthalate (30.6 g; ee 90%, evaluated by NMR employing quinine as chiral solvating agent[17]) was treated with 10 M KOH solution (100 mL), and (*S*)-**2** was recovered by steam distillation (11.65 g, 83%, bp 50 °C/ 17 mmHg). The enantiomeric purity (89%) of (*S*)-**2** was determined by GLC (25 m, CYDEX-B (chiral) capillary column).

Analogously, by successive recristallizations (five) of the brucine salt obtained from the mother solution, (*R*)-**2** (5.73 g; ee 64%) was recovered.

(*R*)- and (*S*)-1-Bromo-3,4,4-trimethyl-1,2-pentadiene (1a).[9] (*R*)-**1a** was obtained from the optically active alcohol (*S*)-**2** (51.6 mmol) by reacting the corresponding methanesulfonate ester with $LiCu_2Br_3$ (67.1 mmol) in THF at −70 °C, according to ref 9. Fractional distillation yielded chemically pure (*R*)-**1a** (8.77 g, 90%) as a colorless liquid: bp 68 °C (17 mmHg); ee 87%; mass spectrum *m/e* 188 for ^{79}Br (M^+); ^1H NMR δ = 1.09 (9H), 1.82 (3H), 6.01 (1H); ^{13}C NMR δ = 14.6, 20.5, 34.0, 71.5, 120.1, 198.8.

According to the above procedure, from (*R*)-**2** was obtained (*S*)-**1a** (4 g, 89%; ee 63%).

General Procedure. Trisubstituted Allenes (*S*)-1b-e (Reaction II).[9] To a stirred suspension of CuBr (0.4 mmol) in dry THF (50 mL) was added (*R*)-**1a** (8.5 mmol) and, at −70

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°C, a THF solution of the appropriate arylmagnesium chloride (17 mmol). After being stirred for 3–5 min at −70 °C, the mixture was allowed to warm to room temperature, and stirring was continued for 2 h. The mixture was then treated with saturated NH_4Cl solution, and the organic materials were extracted with Et_2O. After the usual workup, fractional distillation (Fischer-Spaltrohr MMS 202 column) or chromatographic elution (SiO_2, *n*-pentane) yielded pure products (*S*)-**1b-e**.

(*S*)-1-Phenyl-3,4,4-trimethyl-1,2-pentadiene [(*S*)-1b]:[14] 94% yield; ee 84%; bp 98 °C (20 mmHg); mass spectrum *m/e* 186 (M^+, 4), 41 (100); ^1H NMR δ = 1.12 (9H), 1.80 (3H), 6.04 (1H), 7.04–7.68 (5H); ^{13}C NMR δ = 14.7, 29.1, 34.2, 94.1, 112.6, 126.2, 126.3, 128.5, 136.3, 201.8. Anal. Calcd for $C_{14}H_{18}$: C, 90.26; H, 9.74. Found: C, 90.09; H, 9.86.

(*S*)-1-(4-Fluorophenyl)-3,4,4-trimethyl-1,2-pentadiene [(*S*)-1c]: 94% yield; ee 83%; bp 94–95 °C (3 mmHg); mass spectrum *m/e* 204 (M^+, 1.5), 41 (100); ^1H NMR δ = 1.12 (9H), 1.80 (3H), 6.05 (1H), 6.98 (2H), 7.23 (2H); ^{13}C NMR δ = 14.9, 29.7, 35.1, 94.1, 113.9, 116.2, 128.7, 133.6, 163.0, 202.8. Anal. Calcd for $C_{14}H_{17}F$: C, 82.31; H, 8.39. Found: C, 82.25; H, 8.40.

(*S*)-**1d** and (*S*)-**1e** were obtained starting from a sample of (*R*)-**1a** having a lower enantiomeric purity (64%).

(*S*)-1-(1-Naphthyl)-3,4,4-trimethyl-1,2-pentadiene [(*S*)-1d]: 79% yield; ee 56%; mass spectrum *m/e* 236 (M^+, 4), 41 (100); ^1H NMR δ = 1.16 (9H), 1.88 (3H), 6.80 (1H), 7.30–7.60 (4H), 7.70 (1H), 7.84 (1H), 8.28 (1H); ^{13}C NMR δ = 15.1, 29.5, 35.0, 91.7, 112.2, 124.5, 125.6, 126.6, 126.7, 126.8, 127.9, 129.6, 132.2, 133.3, 135.5, 204.6. Anal. Calcd for $C_{18}H_{20}$: C, 91.47; H, 8.53. Found: C, 91.39; H, 8.58.

(*S*)-1-(4-Methoxyphenyl)-3,4,4-trimethyl-1,2-pentadiene [(*S*)-1e]: 85% yield; ee 63%; mass spectrum *m/e* 216 (M^+, 22), 159 (100); ^1H NMR δ = 1.12 (9H), 1.79 (3H), 3.76 (3H), 6.00 (1H), 6.82 (2H), 7.14 (2H); ^{13}C NMR δ = 14.7, 29.2, 34.2, 55.2, 93.5, 112.4, 114.1, 127.3, 128.7, 158.3, 201.1. Anal. Calcd for $C_{15}H_{20}O$: C, 83.29; H, 9.32. Found: C, 83.27; H, 9.30.

Trisubstituted Allenes (*R*)-1b-e (Reaction III).[18] A solution of (*S*)-**2** (11.1 mmol) in anhydrous THF (50 mL) was treated, at −70 °C, with a stoichiometric amount of *n*-BuLi 1.6 N in hexane. Subsequently, at the same temperature, was added $MeSO_2Cl$ (11.1 mmol). After 10 min the mixture was added, at −70 °C via cannula, to a well-stirred suspension of the appropriate bromocuprate (22.2 mmol) in THF (50 mL). Stirring was continued at −70 °C for 2 h, and then the mixture was hydrolyzed with aqueous NH_4Cl. After the usual workup, bulb-to-bulb distillation and chromatographic purification (SiO_2, pentane) gave chemically pure products (*R*)-**1b–e**.

(*R*)-1-Phenyl-3,4,4-trimethyl-1,2-pentadiene [(*R*)-1b]:[14] 89% yield; ee 89%.

(*R*)-1-(4-Fluorophenyl)-3,4,4-trimethyl-1,2-pentadiene [(*R*)-1c]: 90% yield; ee 88%.

(*R*)-1-(1-Naphthyl)-3,4,4-trimethyl-1,2-pentadiene [(*R*)-1d]: 78% yield; ee 89%.

(*R*)-1-(4-Methoxyphenyl)-3,4,4-trimethyl-1,2-pentadiene [(*R*)-1e]: 87% yield; ee 80% (this product was obtained starting from a sample of (*S*)-**2** with op 81%).

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