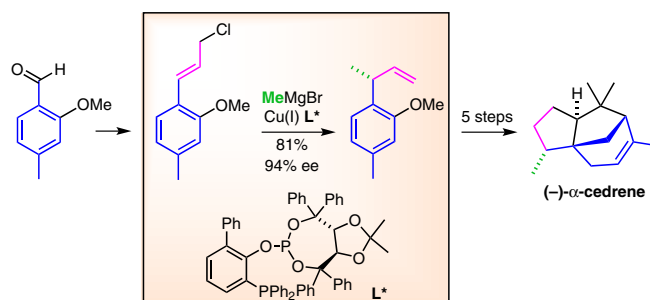J. Westphal et al.

The Wender Cedrene Synthesis Revisited: A Catalytic Enantioselective Entry to the Chiral Key Intermediate

Julia Westphal
Christian Eric Schumacher
Hans-Günther Schmalz*

Department für Chemie, Universität zu Köln,
Greinstrasse 4, 50939 Köln, Germany
schmalz@uni-koeln.de

Dedicated to Prof. Dr. Dieter Enders

Abstract The seminal synthesis of the sesquiterpene (±)-α-cedrene reported by Wender in 1981 offers a uniquely short and elegant access to the bridged-tricyclic target compound by exploiting an intramolecular arene-olefin photocycloaddition. However, the synthesis was performed only in the racemic series so far. This synthesis was now re-investigated and the catalytic methods for the enantioselective preparation of the chiral key intermediate were evaluated. It was found that Cu-catalyzed allylic substitution of a cinnamyl chloride with MeMgBr in the presence of a Taddol-derived chiral phosphine-phosphite ligand affords the corresponding (1-methylallyl)arene with high enantioselectivity (94% *ee*). Hydroboration and subsequent Suzuki coupling gave (*R*)-curcuphenol methyl ether from which (–)-α-cedrene was prepared along the route paved by Wender.

Figure 1 The sesquiterpenes α-cedrene (**1**), β-cedrene (**2**), cedrol (**3**), and cedrenol (**4**)

The sesquiterpene α-cedrene (**1**) is a natural product occurring in cedarwood oil together with its structural congeners β-cedrene (**2**), cedrol (**3**), and cedrenol (**4**) (Figure 1).[1] Besides their established uses in perfumery[2] and folk medicine[3] these natural products have recently also received attention as specific bioactive agents, for instance, as antimicrobial compounds,[4] or as selective inhibitors of certain cytochrome P450 enzymes.[5]

α-Cedrene (**1**) and its congeners all display the characteristic tricyclo[5.3.1.0^{1,5}]undecane skeleton with two quaternary carbon atoms and four chirality centers and have challenged organic chemists for more than six decades. Since the pioneering work of Stork,[6] several total syntheses of these molecules have been developed utilizing different cyclization or cycloaddition strategies to build up the tricycl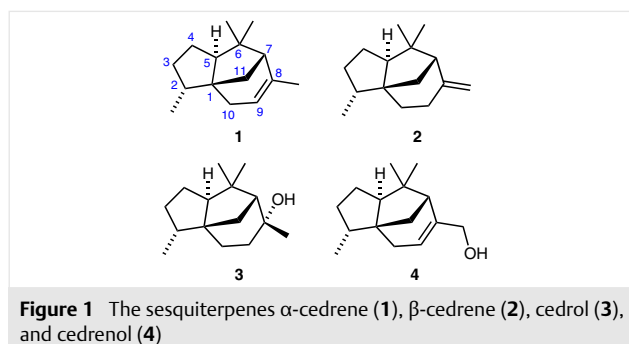ic ring system with the correct relative configuration of the bridgehead stereocenters.[7,8] Not surprisingly, stereocontrol at C2 proved to be a non-trivial task,[9] and only a few of the reported syntheses were conducted in the non-racemic series.[6,8k,q,r]

Among the all known routes toward the cedrenoids, the syntheses of (±)-α-cedrene (*rac*-**1**) disclosed by Wender in 1981 (Scheme 1)[7] stands out because of its exceptional brevity, overall efficiency, and conceptual elegance. This synthesis strategically exploits an intramolecular arene-olefin *meta*-photoaddition.[10]

More specifically, upon irradiation of curcuphenol methyl ether (*rac*-**7**), prepared from the *m*-cresol derivative **5** in a one-pot procedure, a mixture of regioisomeric photoproducts (*rac*-**8a** and *rac*-**8b**) is formed in a highly diastereoselective manner.[7,11] Treatment of this mixture with bromine and subsequently with HSnBu₃ then yields the ketone *rac*-**9**, from which (±)-α-cedrene (*rac*-**1**) is finally obtained by Wolff–Kishner reduction (Scheme 1).[12]

While the Wender cedrene synthesis has been appreciated as an (almost) 'ideal' synthesis[13] and as a beautiful example for a total synthesis with a photochemical key step,[14] one must be aware that it does not meet the requirements

Scheme 1 Total synthesis of (±)-α-cedrene (*rac*-**1**) according to Wender[7]
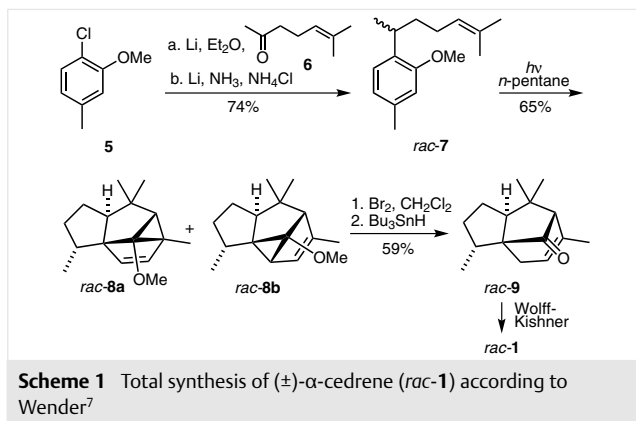
of modern natural product synthesis[15] as long as it only gives access to the racemic product. Notably, more than fifteen approaches towards the non-racemic cedrene precursor **7** or its O-demethylated derivative (i.e., curcuphenol) have been developed.[8r,16] However, a closer look reveals that most of these syntheses lack efficiency and/or practicability. Only recently, Feng et al. disclosed an apparently useful method for the conversion of citronellal into curcuphenol within six steps.[17]

Against this background, we asked ourselves whether the catalytic enantioselective methods recently developed in our laboratory for the preparation of benzylic chiral compounds (using modular Taddol-derived phosphine-phosphite ligands[18]) could be applied for the synthesis of (*R*)-curcuphenol methyl ether (**7**). Both the Co-catalyzed hydrovinylation of styrenes[19] and the Cu-catalyzed allylic alkylation of cinnamyl chlorides[20] lead to (1-methylallyl)benzenes and thus appeared to be possibly suitable for the preparation of olefin **10** from the achiral precursors **11** or **12**, respectively (Scheme 2). The conversion of **10** into **7** in
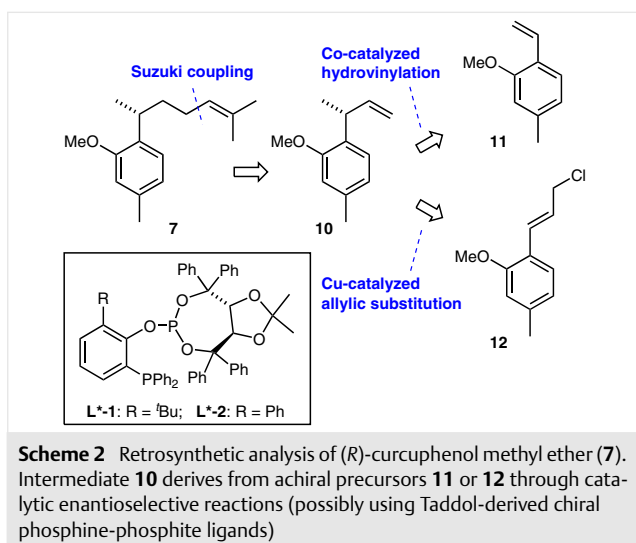
turn should be achievable by hydroboration and Suzuki coupling.[21]

The vinylbenzene derivative **11** was best prepared as shown in Scheme 3. Starting from *m*-cresol (**13**) MgCl₂/Et₃N-assisted *ortho*-formylation[22] with paraformaldehyde in THF and subsequent O-methylation (MeI, K₂CO₃, DMF) afforded an 86:14 mixture of regioisomers from which the pure main product **14** was isolated by chromatography in 81% yield.

Wittig methylenation of the aldehyde **14** under standard conditions then afforded **11** (93%). With this substrate the cobalt-catalyzed hydrovinylation was then tested, at first in the racemic series. Following our established protocol[19a] using PPh₃ as an achiral ligand the expected product *rac*-**10** was obtained in 92% yield (Scheme 3). However, despite extensive experimentation, we did not succeed in performing this transformation with satisfying levels of enantioselectivity. In the best case, employing ligand **L*-1**, the product **10** was formed with only 24% *ee*. Here, the limitation of our otherwise broadly applicable asymmetric hydrovinylation protocol in the case of certain *ortho*-substituted styrenes becomes apparent. Nevertheless, the prepared sample of *rac*-**10** at least provided a valuable racemic reference for analytical purposes.

Scheme 3 Preparation and Co-catalyzed hydrovinylation of the vinylarene **11**
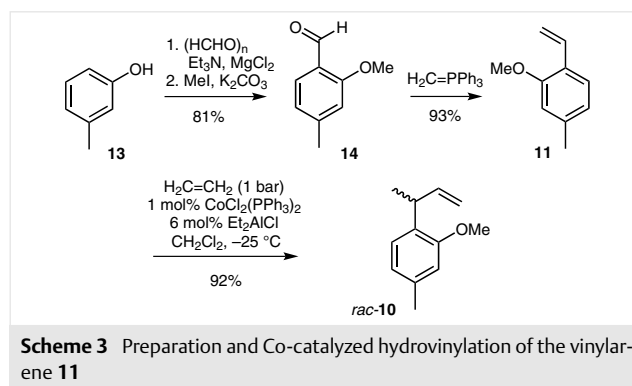
Next, we turned our attention to the asymmetric Cu-catalyzed allylic substitution as an alternative route towards non-racemic **10** (compare Scheme 2). The required substrate, that is, the cinnamyl chloride **12** was prepared by Grignard reaction of aldehyde **14** with vinylmagnesium bromide and treatment of the resulting alcohol (*rac*-**15**) with thionyl chloride in CH₂Cl₂. Noteworthy, compound **12** proved to be rather sensitive towards decomposition. For this reason, it was always freshly prepared and directly employed (as a crude product) in the Cu-catalyzed transformation.[20] Much to our satisfaction, the asymmetric allylic alkylation of **12** proceeded smoothly and with high regio- and enantioselectivity (Scheme 4). Using a catalyst generated in situ from CuBr·SMe₂ (2.5 mol%) and the Taddol-derived ligand **L*-2** (3 mol%), the reaction of **12** with MeMgBr in MTBE/CH₂Cl₂ cleanly afforded (*R*)-**10** in 80% yield after separating off minor amounts of the linear by-product by

Scheme 2 Retrosynthetic analysis of (*R*)-curcuphenol methyl ether (**7**). Intermediate **10** derives from achiral precursors **11** or **12** through catalytic enantioselective reactions (possibly using Taddol-derived chiral phosphine-phosphite ligands)

column chromatography. The enantiomeric purity of **10** was ≥94% *ee* (as determined by chiral GC and also confirmed at the stage of **7**). The expected[20a] *R*-configuration of the product was proven by its conversion into (–)-α-cedrene (**1**).
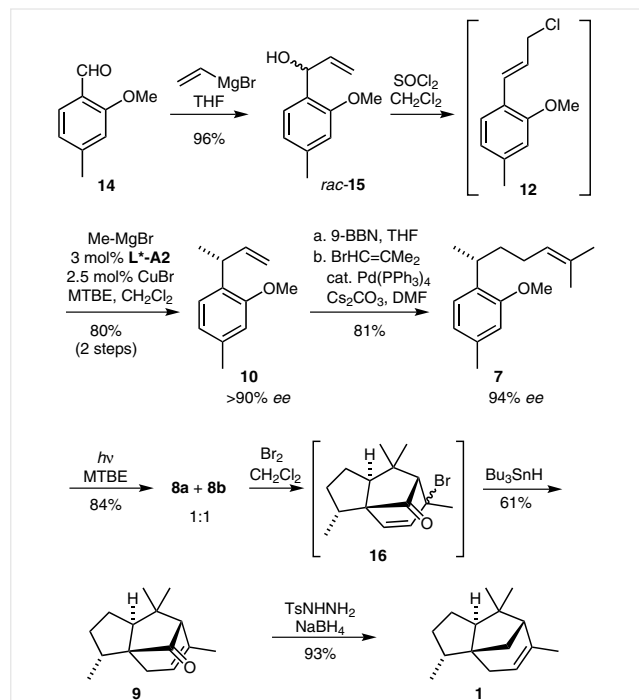
Scheme 4 Enantioselective synthesis of (*R*)-curcuphenol methyl ether (**7**) through Cu-catalyzed allylic substitution and Suzuki coupling and its conversion into (–)-α-cedrene (**1**)

Having prepared the key intermediate **7** in non-racemic form, we were curious whether the Wender protocols for its conversion into (–)-α-cedrene (**1**) could be reproduced in our hands. And indeed: Irradiation of a solution of **7** with UV light (254 nm) proceeded smoothly to afford a 1:1 mixture of the photoadducts **8a**/**8b** as reported. By changing the solvent from *n*-pentane to methyl *tert*-butyl ether (MTBE) the yield of **8a**/**8b** could even be improved to 84%.

The bromine-mediated cyclopropane opening (Br$_2$, CH$_2$Cl$_2$) and the subsequent reductive debromination step (HSnBu$_3$) proved to be a bit tricky. However, after some careful experimentation we were able to prepare pure cedrenone (**9**) in reproducible yields. To avoid the formation of 'cedradienone' as an elimination product, the sensitive (crude) mixture of bromides **16**, isolated by removal of all volatiles under reduced pressure, was immediately dissolved in *n*-pentane followed by addition of HSnBu$_3$ (1 equiv, 0.5 h, 0 °C). Purification by column chromatography then afforded **9** in 61–65% yield. Noteworthy, the final Wolff–Kishner reduction of cedrenone (**9**) was performed applying the TsNHNH$_2$/NaBH$_4$-based protocol introduced by Caglioti[23] to give (–)-α-cedrene (**1**) in greatly improved

yield of 92%.[12] The spectroscopic data[24] and the molecular rotation of the synthetic sample confirmed its identity with the natural product.

In conclusion, we have re-investigated the Wender route towards cedrene as one of the most prominent and conceptually stunning sesquiterpene syntheses. In this context, we developed a catalytic enantioselective entry to the chiral key intermediate (*R*)-curcuphenol methyl ether (**7**) exploiting an asymmetric Cu(I)-catalyzed allylic substitution as the chirogenic step. The further conversion of **7** into (–)-α-cedrene (**1**) was successfully performed according to Wender and improved in detail. The resulting synthesis (Scheme 4) of non-racemic **1** proceeds in eight steps (30% overall yield)

All reactions sensitive towards air or moisture were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. THF was freshly distilled from Na/benzophenone. NMR spectra were recorded in CDCl$_3$ on Bruker Avance II 300, Avance II 500, and Avance II 600 instruments. ^{13}C NMR spectra were recorded in the APT mode (attached proton test). Assignments were assisted by H,H-COSY, HMQC, and HMBC spectra. Enantiomeric analyses by GC were either performed on an Agilent (HP 7890B) instrument using a BGB 176SE capillary column [temperature program: 50 °C (10 min), 50–150 °C (1.0 °C/min), 150 °C (5 min)] or on an Agilent (HP 6890) instrument using a 6-TBDMS capillary column [50–100 °C (0.1 °C/min)] with H$_2$ as carrier gas (6 mL/min, 0.7 bar). Photoreactions were performed using a quartz exposure shaft in a Rayonet photoreactor of the type RPR-208 with eight lamps from Southern New England UV Company (P = 800 W, λ = 254 nm ± 25 nm).

2-Methoxy-4-methylbenzaldehyde (14)[25]

To a stirred solution of *m*-cresol (5.3 mL, 50 mmol, 1.0 equiv) and Et$_3$N (27 mL, 192 mmol, 3.8 equiv) in THF (250 mL) were added MgCl$_2$ (7.2 g, 75 mmol, 1.5 equiv) and paraformaldehyde (10.5 g, 338 mmol, 6.8 equiv) and the mixture was stirred for 18 h at 65 °C. After cooling to r.t., aq 1 M HCl (200 mL) was added, the phases were separated, and the aqueous phase was extracted with EtOAc (2 ×). After washing the combined organic layers with brine and drying (MgSO$_4$), the solvent was removed. The residue was filtered through a column of silica gel with *c*Hex/EtOAc (5:1) to give 6.59 g (48.5 mmol, 96%) of a 86:14 mixture of regioisomeric formylation products (as determined by NMR spectroscopy and GC-MS).

Under an atmosphere of argon, the above prepared aldehyde mixture (5.7 g, 41.9 mmol) was added to a stirred suspension of K$_2$CO$_3$ (12.6 g, 91 mmol, 2.2 equiv) in DMF (20 mL) followed by addition of MeI (5.8 mL, 92 mmol, 2.2 equiv). The mixture was stirred for 5 h at r.t. and then partitioned between Et$_2$O (150 mL) and H$_2$O (120 mL). The organic layer was washed with brine (5 × 50 mL) and dried (MgSO$_4$). Removal of all volatiles under reduced pressure and column chromatography with *c*Hex/EtOAc (10:1; R_f = 0.33) afforded 5.3 g (35.3 mmol, 84%) of the pure aldehyde **14** as a colorless solid; mp 40 °C.

IR (ATR): 3446 (br), 2936 (w), 2920 (w), 2862 (w), 2839 (w), 1673 (w), 1606 (m), 1514 (vs), 1465 (m), 1420 (m), 1364 (m), 1270 (vs), 1235 (s), 1207 (s), 1149 (s), 1122 (m), 1034 (s), 921 (m), 810 cm^{-1} (m).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 10.39 (s, 1 H, CHO), 7.71 (d, *J* = 7.9 Hz, 1 H, H6), 6.83 (d, *J* = 7.9 Hz, 1 H, H5), 6.78 (s, 1 H, H3), 3.90 (s, 3 H, OCH$_3$), 2.40 (s, 3 H, CH$_3$).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 189.6 (CHO), 162.0 (C2), 147.5 (C4), 128.7 (C6), 122.8 (C1), 121.8 (C5), 112.3 (C3), 55.7 (OCH$_3$), 22.5 (CH$_3$).

GC-MS (70 eV): m/z (%) = 150 (100, [M]$^+$), 133 (39), 107 (21), 91 (99).

2-Methoxy-4-methyl-1-vinylbenzene (11)

Under argon atmosphere, MePPh$_3$Br (2.02 g, 5.65 mmol, 1.2 equiv) was suspended in THF (40 mL) and cooled to 0 °C. Then, a n-BuLi solution (2.5 M in hexanes, 2.3 mL, 5.76 mmol, 1.2 equiv) was added and the mixture was stirred for 2 h at 0 °C. Afterwards, the aldehyde **14** (0.730 g, 4.89 mmol, 1.0 equiv) dissolved in THF (4 mL) was added dropwise and stirring was continued for 14 h at r.t. The solvent was removed under reduced pressure and the residue was purified by column chromatography (R_f = 0.72, cHex/EtOAc 10:1) to yield 0.647 g of vinylarene **11** as a yellow oil (4.55 mmol, 93%).

IR (ATR): 3005 (w), 2936 (w), 2253 (w), 1609 (w), 1502 (w), 1465 (w), 1412 (w), 1285 (w), 1266 (w), 1193 (w), 1161 (w), 1121 (w), 1042 (w), 998 (w), 904 (vs), 817 (w), 724 (vs), 650 cm^{-1} (m).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.38 (d, J = 7.8 Hz, 1 H, H6), 7.04 (dd, J = 17.8, 11.2 Hz, 1 H, =CH), 6.78 (d, J = 7.8 Hz, 1 H, H5), 6.72 (s, 1 H, H3), 5.72 (dd, J = 17.8, 1.6 Hz, 1 H, =CH$_2$), 5.24 (dd, J = 11.1, 1.6 Hz, 1 H, =CH$_2$), 3.86 (s, 3 H, OCH$_3$), 2.38 (s, 3 H, CH$_3$).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 156.8 (C2), 139.2 (C4), 131.7 (CH=), 126.5 (C6), 124.1 (C1), 121.5 (C5), 113.6 (C3), 111.9 (CH$_2$), 55.6 (OCH$_3$), 21.4 (CH$_3$).

GC-MS (70 eV): m/z (%) = 148 (63, [M]$^+$), 133 (67, [M – CH$_3$]$^+$), 105 (100).

1-(But-3-en-2-yl)-2-methoxy-4-methylbenzene (rac-10) through Hydrovinylation of 11

A Schlenk flask was charged with Co(PPh$_3$)$_2$Cl$_2$ (269 mg, 0.43 mmol, 1 mol%) under an argon atmosphere atmosphere, evacuated, and flooded with ethylene (1.2 bar) by connecting to an ethylene lecture bottle. The flask was immersed into an ice/water bath and anhyd CH$_2$Cl$_2$ (700 mL) was injected, followed by Et$_2$AlCl (2.48 mL, 2.51 mmol, 6 mol%) and the vinylarene **11** (6.20 g, 41.83 mmol, 1.0 equiv). The reaction mixture was stirred for 1 h at 0 °C before it was exposed to air and filtered through a pad of silica gel with n-pentane. After removal of all volatiles under reduced pressure 6.78 g (38.5 mmol, 92%) of virtually pure rac-**10** was obtained as a pale yellow oil (R_f = 0.77, cHex/EtOAc 10:1).

IR (ATR): 2960 (m), 2930 (m), 2869 (w), 2831 (w), 1612 (m), 1505 (vs), 1465 (s), 1409 (m), 1257 (vs), 1192 (m), 1156 (m), 1042 (vs), 908 (vs), 812 (vs), 731 cm^{-1} (vs).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.04 (d, J = 7.4 Hz, 1 H, H6), 6.74 (d, J = 7.4 Hz, 1 H, H5), 6.69 (s, 1 H, H3), 6.10–5.99 (m, 1 H, CH=), 5.07–5.00 (m, 2 H, =CH$_2$), 3.89 (t, J = 6.6 Hz, 1 H, H2′), 3.82 (s, 3 H, OCH$_3$), 2.33 (s, 3 H, ArCH$_3$), 1.30 (d, J = 7.0 Hz, 3 H, CH$_3$).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 156.1 (C2), 143.2 (C3′), 131.0 (C4), 127.3 (C6), 121.3 (C5), 112.7 (C3), 111.7 (C4′), 55.5 (OCH$_3$), 35.4 (C2′), 21.6 (ArCH$_3$), 19.7 (C1′).

GC-MS (70 eV): m/z (%) = 176 (49, [M]$^+$), 161 (100, [M – CH$_3$]$^+$).

1-(2-Methoxy-4-methylphenyl)prop-2-en-1-ol (rac-15)

A solution of aldehyde **14** (1.60 g, 10.7 mmol, 1.00 equiv) in THF (100 mL) was cooled to –78 °C and vinylmagnesium bromide (0.7 M in THF, 17.6 mL, 12.4 mmol, 1.15 equiv) was added over a period of 1.5 h. After stirring for 1.5 h at –78 °C, the reaction was stopped by addition of sat. aq NH$_4$Cl (20 mL) and MTBE (30 mL). After separation of the layers, the aqueous layer was extracted with MTBE (40 mL) and the com-

bined organic layers were dried (MgSO$_4$). The solvent was removed and the crude material purified by column chromatography with cHex/EtOAc 5:1 (R_f = 0.18) to afford 1.82 g (10.2 mmol, 96%) of rac-**15** as a colorless oil.

IR (ATR): 3402 (br), 3085 (w), 3003 (w), 2937 (w), 2864 (w), 2834 (w), 1612 (m), 1583 (m), 1505 (m), 1464 (m), 1409 (m), 1283 (s), 1255 (s), 1192 (m), 1155 (m), 1123 (m), 1102 (m), 1038 (vs), 989 (s), 918 (s), 805 cm^{-1} (vs).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.17 (d, J = 7.6 Hz, 1 H, H6′), 6.78 (d, J = 7.6 Hz, 1 H, H5′), 6.08–6.19 (m, 1 H, CH=), 5.37 (t, J = 5.8 Hz, 1 H, H1), 5.30 (dt, J = 17.2, 1.4 Hz, 1 H, =CH$_2$), 5.16 (dt, J = 10.4, 1.4 Hz, 1 H, =CH$_2$), 3.85 (s, 3 H, OCH$_3$), 2.76 (d, J = 6.2 Hz, 1 H, OH), 2.35 (s, 3 H, Ar-CH$_3$).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 156.8 (C2′), 139.8 (C2), 139.0 (C4′), 128.0 (C1′), 127.5 (C6′), 121.6 (C5′), 114.5 (C3′), 111.8 (=CH$_2$), 71.7 (C1), 55.5 (OCH$_3$), 21.7 (ArCH$_3$).

GC-MS (70 eV): m/z (%) = 178 (53, [M]$^+$), 163 (41), 149 (39), 135 (78), 122 (50), 115 (58), 105 (65), 91 (100), 77 (60), 65 (31), 51 (28).

(R)-1-(But-3-en-2-yl)-2-methoxy-4-methylbenzene (10) from rac-15 via Allylic Substitution of 12

Under inert conditions, rac-**15** (445 mg, 2.5 mmol, 1.00 equiv) was dissolved in CH$_2$Cl$_2$ (9 mL) and SOCl$_2$ (0.2 mL, 3.0 mmol, 1.23 equiv) was added. The resulting solution was stirred for 1 h at 0 °C. After partitioning between H$_2$O (10 mL) and Et$_2$O (10 mL), the layers were separated, the organic layer was dried (MgSO$_4$) and after filtration, the solvent was removed under reduced pressure to give the cinnamyl chloride **12** as a yellow oil.

Parallel to the preparation of **12**, ligand **L***-2** (prepared according to ref. 18b, 62 mg, 3 mol%) and CuBr·SMe$_2$ (12 mg, 2.5 mol%) were dissolved in MTBE (16 mL) under argon and stirred at r.t. for 30 min. Then, the cinnamyl chloride **12** was added via syringe and the mixture was stirred for further 10 min at r.t. After cooling the solution to –78 °C, MeMgBr (1.0 mL of a 3 M solution in Et$_2$O, 3.0 mmol, 1.22 equiv, diluted with 8 mL CH$_2$Cl$_2$) was slowly added by means of a syringe pump over a period of 10 h and the stirring was continued for 10 h at –55 °C. The reaction was then stopped by addition of aq 1 M HCl (30 mL), the layers were separated, and the aqueous layer was extracted with Et$_2$O (2 × 30 mL). The combined organic layers were washed with brine (30 mL) and dried (MgSO$_4$). The solvent was removed under reduced pressure and the crude product (containing the branched and the linear isomers in a 88:12 ratio according to GC analysis) was purified by column chromatography using n-pentane as eluent. The desired product **10** was obtained in a yield of 353 mg (2.0 mmol, 80%) as pale yellow oil (R_f = 0.49, cHex/EtOAc 50:1). The enantiomeric purity was >90% ee as determined by GC [BGB 176SE column, 50 °C (10 min), then 50 to 150 °C (1.0 °C/min); t_R = 49.9 min (main enantiomer), 50.7 min].

[α]$_λ^{20}$ +133 (365 nm), +77.5 (436 nm), +40.9 (546 nm), +35.4 (579 nm), +33.5 (589 nm) (c = 0.80 g/100 mL in CH$_2$Cl$_2$).

IR, ^{1}H NMR, ^{13}C NMR, and GC-MS data were identical to the sample of rac-**10** prepared through hydrovinylation (see above).

(R)-2-Methoxy-4-methyl-1-(6-methylhept-5-en-2-yl)benzene (7)

To a solution of olefin **10** (532 mg, 3.02 mmol, 1.0 equiv) in THF (40 mL) was added a 0.5 M solution of 9-BBN in THF (21.1 mL, 10.6 mmol, 3.5 equiv) and the mixture was stirred at r.t. for 5 h. In a second Schlenk flask, a suspension of Cs$_2$CO$_3$ (2.32 g, 6.2 mmol, 2 equiv) in DMF (25 mL) was stirred for 1 h at r.t. before 1-bromo-2-methylprop-1-ene (0.42 mL, 3.96 mmol, 1.3 equiv), Pd(PPh$_3$)$_4$ (0.18 g, 0.15 mmol,

5 mol%), and H_2O (2.8 mL, 157 mmol, 52 equiv) were added. After 3 h at r.t., the solution of the in situ generated alkylborane was added and stirring was continued at 85 °C for 16 h. Then, sat. aq NH_4Cl (150 mL) and MTBE (100 mL) were added and the layers were separated. The aqueous layer was extracted with MTBE (3 ×) and the combined organic layers were washed with H_2O (2 ×). After drying ($MgSO_4$), the solvent was evaporated under reduced pressure and the residue was purified by column chromatography (cHex/EtOAc 50:1) to afford **7** (650 mg, 2.80 mmol, 93%) as a colorless liquid (R_f = 0.72, cHex/EtOAc 10:1). The enantiomeric purity was 94% ee as determined by GC [BGB 6-TBDMS column, 50 to 100 °C (0.1 °C/min); t_R = 363 min, 367 min (main enantiomer)].

$[\alpha]_\lambda^{20}$ –23 (365 nm), –16.4 (436 nm), –9.8 (546 nm), –8.3 (579 nm), 7.9 (589 nm) (c = 0.79 g/100 mL in CH_2Cl_2).[3]

IR (ATR): 2958 (m), 2923 (m), 1611 (m), 1580 (m), 1506 (s), 1464 (s), 1455 (s), 1411 (m), 1286 (m), 1259 (vs), 1191 (m), 1157 (m), 1127 (m), 1098 (m), 1043 (vs), 927 (m), 845 (m), 809 cm⁻¹ (vs).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.10 (d, J = 7.7 Hz, 1 H, H6), 6.79 (d, J = 7.7 Hz, 1 H, H5), 6.72 (s, 1 H, H3), 5.17 (t, J = 7.0 Hz, 1 H, CH=), 3.85 (s, 3 H, OCH_3), 3.19 (sext, J = 7.0 Hz, 1 H, H2'), 2.38 (s, 3 H, ArCH_3), 1.97 (quint, J = 7.2 Hz, 2 H, H4'), 1.73 (s, 3 H, =CCH_3), 1.70–1.60 (m, 2 H, H3'), 1.59 (s, 3 H, =CCH_3), 1.23 (d, J = 7.0 Hz, 3 H, H1').

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.1 (C2), 136.3 (C4), 133.0 (C1), 131.2 (C6'), 126.7 (C6), 125.0 (C5'), 121.2 (C5), 111.6 (C3), 55.5 (OCH_3), 37.3 (C3'), 31.6 (C2'), 26.4 (C4'), 25.9 (vinyl-CH_3), 21.5 (ArCH_3), 21.2 (C1'), 17.7 (vinyl-CH_3).

GC-MS (70 eV): m/z (%) = 232 (27, [M]⁺), 217 (4, [M – CH_3]⁺), 201 (1, [M – OCH_3]⁺), 149 (100).

Photocyclization Products 8a and 8b

Compound **7** (200 mg, 0.86 mmol, 1.0 equiv) was dissolved in MTBE (40 mL, c = 0.02 M) and exposed to the light from a Rayonet photoreactor (254 nm, 250 W) for 6 h. Afterwards, the solvent was removed and the residue was subjected to column chromatography (cHex/EtOAc 50:1). Compound **8a** and **8b** were isolated in a combined yield of 168 mg (0.72 mmol, 84%) as a yellow oil. Analytically pure samples of both isomers were obtained from early and late fractions, respectively.

8a

R_f = 0.39 (cHex/EtOAc 50:1).

$[\alpha]_\lambda^{20}$ +36.8 (365 nm), +24.2 (436 nm), +11.0 (546 nm), +9.1 (579 nm), +8.1 (589 nm) (c = 0.65 g/100 ml in CH_2Cl_2).

IR (ATR): 2951 (vs), 2868 (m), 1458 (m), 1447 (m), 1375 (m), 1131 (m), 1038 (m), 751 cm⁻¹ (m).

^1H NMR (500 MHz, $CDCl_3$): δ = 5.57 (d, J = 5.6 Hz, 1 H, H10), 5.54 (d, J = 5.6 Hz, 1 H, H9), 3.35 (s, 3 H, OCH_3), 2.44–2.39 (m, 1 H, H2), 2.06–2.01 (m, 1 H, H3a), 1.87–1.84 (m, 1 H, H5), 1.62 (s, 1 H, H7), 1.55–1.49 (m, 2 H, H4), 1.32 (s, 3 H, CH_3 at C8), 1.11–1.08 (m, 1 H, H3b), 1.03 (d, J = 7.2 Hz, 3 H, CH_3 at C2), 1.00 (s, 3 H, CH_3 at C6), 0.99 (s, 3 H, CH_3 at C6).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 134.5 (C10), 131.7 (C9), 94.8 (C8), 72.9 (C11), 68.6 (C5), 57.7 (OCH_3), 56.1 (C7), 42.7 (C1), 40.8 (C6), 37.7 (C3), 32.5 (C2), 29.0 (2 × CH_3 at C6), 28.4 (C4), 18.7 (CH_3 at C2), 17.3 (CH_3 at C8).

GC-MS (70 eV): m/z (%) = 232 (7, [M]⁺), 217 (8, [M – CH_3]⁺), 149 (100), 133 (15), 115 (28), 91 (48).

8b

R_f = 0.46 (cHex/EtOAc 50:1).

$[\alpha]_\lambda^{20}$ +32.7 (365 nm), +20.0 (436 nm), +9.06 (546 nm), +7.5 (579 nm), +6.7 (589 nm) (c = 0.78 g/100 mL in CH_2Cl_2).

IR (ATR): 2951 (vs), 2900 (s), 2868 (m), 1470 (m), 1448 (s), 1399 (m), 1374 (m), 1363 (m), 1326 (m), 1266 (s), 1150 (m), 1114 (vs), 1024 (m), 1008 (s), 820 cm⁻¹ (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 5.37 (br s, 1 H, H9), 3.31 (s, 3 H, H15), 2.54 (s, 1 H, H7), 2.02–1.97 (m, 1 H, H2), 1.90–1.89 (m, 1 H, H5), 1.87–1.83 (m, 2 H, H3), 1.77 (s, 3 H, H14), 1.73–1.63 (m, 1 H, H10), 1.50–1.45 (m, 2 H, H4), 1.00 (s, 3 H, H12a), 0.89 (s, 3 H, H12b), 0.88 (d, J = 4.9 Hz, 3 H, H13).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.8 (C8), 124.3 (C9), 67.5 (C7), 58.3 (C11), 57.1 (C15), 53.9 (C1), 50.8 (C5), 36.5 (C3), 35.7 (C2), 31.8 (C10), 25.2 (C12a), 23.3 (C4), 22.8 (C12b), 19.1 (C13), 17.7 (C14).

GC-MS (70 eV): m/z (%) = 232 (10, [M]⁺), 217 (4, [M – CH_3]⁺), 200 (1), 175 (8), 149 (100), 115 (21), 91 (34).

Cedrenone (9)

To a stirred solution of the mixture **8a/8b** (200 mg, 0.86 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) under argon at 0 °C was added dropwise Br_2 (44 µL, 0.86 mmol, 1.0 equiv). After 0.5 h at 0 °C, all volatiles were removed under reduced pressure and the residue was diluted with n-pentane (5 mL). Then, $HSnBu_3$ (232 µL, 0.86 mmol, 1.0 equiv) was added. After 0.5 h at 0 °C, the whole mixture was directly subjected to column chromatography (n-pentane, ultra pure silica gel) to yield pure cedrenone **9** (115 mg, 0.53 mmol, 61%) as a colorless oil.

$[\alpha]_\lambda^{20}$ –29.4 (546 nm), –25.1 (579 nm), –24.6 (589 nm) (c = 0.37 g/100 mL in CH_2Cl_2).

IR (ATR): 2944 (s), 2866 (m), 1739 (vs), 1455 (m), 1377 (m), 1279 (m), 1217 (m), 1148 (m), 1035 (s), 981 (s), 944 (m), 846 (m), 678 cm⁻¹ (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 5.36 (dd, J = 2.6, 1.1 Hz, 1 H, H9), 2.53–2.36 (m, 2 H, H10), 2.32 (dd, J = 4.3, 2.1 Hz, 1 H, H2), 2.20 (dd, J = 8.6, 5.0 Hz, 1 H, H5), 2.07 (s, 1 H, H7), 1.72 (s, 3 H, CH_3 at C8), 1.65–1.59 (m, 2 H, H3, H4), 1.50–1.43 (m, 1 H, H4), 1.35–1.31 (m, 1 H, H3), 1.15 (s, 3 H, CH_3 at C6), 0.86 (s, 3 H, CH_3 at C6), 0.84 (d, J = 7.2 Hz, 3 H, CH_3 at C2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 219.3 (C11), 138.2 (C8), 120.6 (C9), 65.8 (C7), 60.2 (C1), 57.2 (C5), 42.3 (C6), 41.9 (C10), 36.1 (C3), 33.7 (C2), 25.9 (CH_3 at C6), 24.6 (C4 and CH_3 at C6), 24.3 (CH_3 at C8), 15.1 (CH_3 at C2).

(−)-(α)-Cedrene (1)

Cedrenone (**9**; 50 mg, 0.23 mmol, 1.0 equiv) and tosylhydrazine (53 mg, 0.26 mmol, 1.3 equiv) were dissolved in EtOH (2 mL) and refluxed for 2.5 h. The solvent was evaporated and the residue was dissolved in THF/H_2O (4:1, 5 mL). $NaBH_4$ (35 mg, 0.92 mmol, 4.0 equiv) was slowly added and the mixture was refluxed again for 2 h. After cooling down to r.t., the mixture was diluted with H_2O and n-pentane and the layers were separated. The aqueous layer was extracted with n-pentane (3 ×). The combined organic layers were washed first with sat. aq $NaHCO_3$, then with aq 1 N HCl and brine, and finally dried ($MgSO_4$). After evaporating the solvent, the residue was subjected to column chromatography (n-pentane) to yield (−)-α-cedrene (**1**) as a colorless liquid (43 mg, 0.22 mmol, 92%).

$[\alpha]_\lambda^{20}$ –330.5 (365 nm), –195.8 (436 nm), –109 (546 nm), –94.7 (579 nm), –91.2 (589 nm) (c = 0.57 g/100 mL in CH_2Cl_2).

IR (ATR): 2937 (vs), 2898 (s), 2869 (s), 2827 (m), 1469 (m), 1450 (s), 1374 (m), 1434 (s), 1362 (m), 1033 (m), 998 (m), 910 (m), 814 (m), 799 cm^{-1} (s).

^{1}H NMR (600 MHz, CDCl$_3$): δ = 5.23 (m, 1 H, H9), 2.18 (dp, J = 16.7, 2.4 Hz, 1 H, H10a), 1.90–1.83 (m, 1 H, H3a), 1.79 (m, J = 18.6, 3.7, 1.8 Hz, 3 H, H2, H7, H10b), 1.69 (s, 1 H, H5), 1.68 (q, J = 1.9 Hz, 3 H, CH$_3$ at C8), 1.67–1.64 (m, 1 H, 4a), 1.63–1.54 (m, 1 H, H11a), 1.43–1.34 (m, 3 H, H3b, H4b, H11b), 1.03 (s, 3 H, CH$_3$ at C6), 0.96 (s, 3 H, CH$_3$ at C6), 0.85 (d, J = 7.2 Hz, 3 H, H13).

^{13}C NMR (150 MHz, CDCl$_3$): δ = 140.7 (C8), 119.4 (C9), 59.1 (C5), 55.0 (C7), 54.0 (C1), 48.3 (C6), 41.6 (C2), 40.8 (C11), 39.0 (C10), 36.2 (C3), 27.8 (CH$_3$ at C6), 25.8 (CH$_3$ at C6), 25.0 (C4), 24.9 (CH$_3$ at C8), 15.6 (CH$_3$ at C2).

GC-MS (70 eV): m/z (%) = 204 (25, [M]$^+$), 189 (5), 161 (25), 119 (100), 93 (40), 77 (30), 56 (10), 41 (30).

HRMS (70 eV, EI): m/z calcd for C$_{15}$H$_{24}$: 204.1878; found: 204.1880.

Acknowledgment

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588602. NMR spectra and chromatograms are included.

References

(1) (a) Walter, P. *Justus Liebigs Ann. Chem.* **1841**, *39*, 247. (b) Walter, P. *Justus Liebigs Ann. Chem.* **1843**, *48*, 35.

(2) Ohloff, G.; Pickenhagen, W.; Kraft, P. *Scent and Chemistry. The Molecular World of Odors*; VHCA/Wiley-VCH: Zürich/Weinheim, **2012**, 296–300.

(3) Kim, T. H.; Yoo, S. D.; Lee, H. S.; Lee, K. M.; Seok, S. H.; Kim, M. G.; Jung, B. H.; Kim, M. G.; Shin, B. S. *Drug Metabol. Pharmacokinet.* **2015**, *30*, 168; and references cited therein.

(4) Johnston, W. H.; Karchesy, J. J.; Constantine, G. H.; Craig, A. M. *Phytother. Res.* **2001**, *15*, 586.

(5) Jeong, H. U.; Kwon, S. S.; Kong, T. Y.; Kim, J. H.; Lee, H. S. *J. Toxicol. Environ. Health, Part A* **2014**, *77*, 1522.

(6) (a) Stork, G.; Clark, F. H. *J. Am. Chem. Soc.* **1955**, *77*, 1072. (b) Stork, G.; Clark, F. H. *J. Am. Chem. Soc.* **1961**, *83*, 3114.

(7) Wender, P. A.; Howbert, J. J. *J. Am. Chem. Soc.* **1981**, *103*, 688.

(8) (a) Corey, E. J.; Girotra, N. N.; Mathew, C. T. *J. Am. Chem. Soc.* **1969**, *91*, 1557. (b) Crandall, T. G.; Lawton, R. G. *J. Am. Chem. Soc.* **1969**, *91*, 2127. (c) Demole, E.; Enggist, P.; Borer, C. *Helv. Chim. Acta* **1971**, *54*, 1845. (d) Anderson, N. H.; Syrdal, D. D. *Tetrahedron Lett.* **1972**, 2455. (e) Corey, E. J.; Balanson, R. D. *Tetrahedron Lett.* **1973**, 3153. (f) Lansbury, P. T.; Haddon, V. R.; Stewart, R. C. *J. Am. Chem. Soc.* **1974**, *96*, 896. (g) Breitholle, E. G.; Fallis, A. G. *J. J. Org. Chem.* **1978**, *43*, 1964. (h) Yates, P.; Stevens, K. E. *Tetrahedron* **1981**, *37*, 4401. (i) For a careful compilation of all syntheses published prior to 1983, see: *Synform*; Vol. 1; Quinkert, G., Ed.; Institut für Organische Chemie, University of Frankfurt: Frank-

furt/M, **1983**, 115. (j) Horton, M.; Pattenden, G. *Tetrahedron Lett.* **1983**, *24*, 2125. (k) Solas, D.; Wolinsky, J. *J. Org. Chem.* **1983**, *48*, 670. (l) Horton, M.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1984**, 811. (m) Chen, Y.-J.; Chen, C.-M.; Lin, W.-Y. *Tetrahedron Lett.* **1993**, *34*, 2961. (n) Rigby, J. H.; Kirova-Snover, M. *Tetrahedron Lett.* **1997**, *38*, 8153. (o) Lee, H.-Y.; Lee, S.; Kim, D.; Kim, B. K.; Bahn, J. S.; Kim, S. *Tetrahedron Lett.* **1998**, *39*, 7713. (p) Crawford, J. J.; Kerr, W. J.; McLaughlin, M.; Morrison, A. J.; Pauson, P. L.; Thurston, G. J. *Tetrahedron* **2006**, *62*, 11360. (q) Fürstner, A.; Schlecker, A. *Chem. Eur. J.* **2008**, *14*, 9181. (r) Green, J. C.; Pettus, T. R. R. *J. Am. Chem. Soc.* **2011**, *133*, 1603.

(9) (a) Naegeli, P.; Kaiser, R. *Tetrahedron Lett.* **1972**, 2013. (b) Büchi, G.; Hauser, A.; Limacher, J. *J. Org. Chem.* **1977**, *42*, 3323.

(10) For reviews, see: (a) Cornelisse, J. *Chem. Rev.* **1993**, *93*, 615. (b) Hoffmann, N. *Synthesis* **2004**, 481. (c) Streit, U.; Bochet, C. G. *Chimia* **2008**, *62*, 962. (d) Streit, U.; Bochet, C. G. *Beilstein J. Org. Chem.* **2011**, *7*, 525.

(11) The diastereoselectivity of the photochemical key step was rationalized by assuming one preferred photoreactive conformation (exciplex) of *rac*-**7** as shown in Scheme 5 (see also ref. 7).
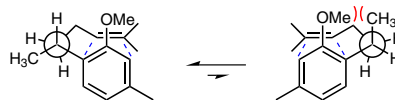
Scheme 5 Photoreactive conformations of *rac*-**7**

(12) While no yield is given in ref. 7 for the Wolff–Kishner reduction of *rac*-**9**, Pettus and co-workers (ref. 8r) reported a yield of 52% for this transformation [KOH, H$_2$NNH$_2$, O(CH$_2$CH$_2$OH)$_2$, 125–215 °C].

(13) (a) Wender, P. A. *Tetrahedron* **2013**, *69*, 7529. (b) Chappell, D.; Russell, T. *Org. Biomol. Chem.* **2006**, *4*, 4409. (c) Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167. (d) Hudlicky, T.; Reed, J. W. *The Way of Synthesis*; Wiley-VCH: Weinheim, **2007**.

(14) Bach, T.; Hehn, J. P. *Angew. Chem. Int. Ed.* **2011**, *50*, 1000.

(15) (a) Enders, D.; Hoffmann, R. W. *Chem. Unserer Zeit* **1985**, *19*, 177. (b) Noyori, R. *Angew. Chem. Int. Ed.* **2002**, *41*, 2008. (c) Federsel, H.-J. *Nat. Rev. Drug Disc.* **2005**, *4*, 685.

(16) (a) Fuganti, C.; Serra, S. *Synlett* **1998**, 1252. (b) Sugahara, T.; Ogasawara, K. *Tetrahedron: Asymmetry* **1998**, *9*, 2215. (c) Kimachi, T.; Takemoto, Y. *J. Org. Chem.* **2001**, *66*, 2700. (d) Ono, M.; Ogura, Y.; Hatogai, K.; Akita, H. *Chem. Pharm. Bull.* **2001**, *49*, 1581. (e) Hagiwara, H.; Okabe, T.; Ono, H.; Kamat, V. P.; Hoshi, T.; Suzuki, T.; Ando, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 895. (f) Harmata, M.; Hong, X.; Barnes, C. L. *Tetrahedron Lett.* **2003**, *44*, 7261. (g) Lu, J.; Xie, X.; Chen, B.; Shea, X.; Pan, X. *Tetrahedron: Asymmetry* **2005**, *16*, 1435. (h) Kim, S.-G.; Kim, J.; Jung, H. *Tetrahedron Lett.* **2005**, *46*, 2437. (i) Kamal, A.; Malik, M. S.; Shaik, A. A.; Azeeza, S. *Tetrahedron: Asymmetry* **2007**, *18*, 2547. (j) Green, J. C.; Jimenez-Alonso, S.; Brown, E. R.; Pettus, T. R. R. *Org. Lett.* **2011**, *13*, 5500. (k) Serra, S. *Tetrahedron: Asymmetry* **2011**, *22*, 619. (l) Soga, K.; Kanematsu, M.; Yoshida, M.; Shishido, K. *Synlett* **2011**, 1171. (m) Aggarwal, V. K.; Ball, L. T.; Carobene, S.; Connelly, R. L.; Hesse, M. J.; Partridge, B. M.; Roth, P.; Thomas, S. P.; Webster, M. P. *Chem. Commun.* **2012**, *48*, 9230. (n) Serra, S. *Tetrahedron: Asymmetry* **2014**, *25*, 1561. (o) Coffinier, R.; El Assal, M.; Peixoto, P. A.; Bosset, C.; Miqueu, K.; Sotiropoulos, J.-M.; Pouységur, L.; Quideau, S. *Org. Lett.* **2016**, *18*, 1120.

(17) Feng, J.; Zhu, G.; Liu, B.; Zhou, X. *Chin. J. Chem.* **2013**, *31*, 23.

(18) (a) Velder, J.; Robert, T.; Weidner, I.; Neudörfl, J.-M.; Lex, J.; Schmalz, H.-G. *Adv. Synth. Catal.* **2008**, *350*, 1309. (b) Dindaroglu, M.; Falk, A.; Schmalz, H.-G. *Synthesis* **2013**, *45*, 527. (c) Falk, A.; Göderz, A.-L.; Schmalz, H.-G. *Angew. Chem. Int. Ed.* **2013**, *52*, 1576. For a recent application of such a ligand in enantioselective 1,4-addition, see: (d) Cernijenko, A.; Risgaard, R.; Baran, P. S. *J. Am. Chem. Soc.* **2016**, *138*, 9425.

(19) (a) Movahhed, S.; Westphal, J.; Dindaroglu, M.; Falk, A.; Schmalz, H.-G. *Chem. Eur. J.* **2016**, *22*, 7381. For recent reviews on hydrovinylation, see: (b) Hilt, G. *Eur. J. Org. Chem.* **2012**, 4441. (c) RajanBabu, T. V.; Cox, G. A.; Lim, H. J.; Nomura, N.; Sharma, R. K.; Smith, C. R.; Zhang, A. In *Comprehensive Organic Synthesis II*; Vol. 5; Molander, G. A.; Knochel, P., Eds.; Elsevier: Amsterdam, **2014**, 2nd ed. 1582–1620.

(20) (a) Lölsberg, W.; Ye, S.; Schmalz, H.-G. *Adv. Synth. Catal.* **2010**, *352*, 2023. (b) Lölsberg, W.; Werle, S.; Neudörfl, J.-M.; Schmalz, H.-G. *Org. Lett.* **2012**, *14*, 5996. For reviews on asymmetric Cu-catalyzed allylic substitution using Grignard reagents, see:

(c) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796. (d) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824. For an early key publication, see also: (e) Tissot-Croset, K.; Alexakis, A. *Tetrahedron Lett.* **2004**, *45*, 7375.

(21) Zhang, A.; RajanBabu, T. V. *Org. Lett.* **2004**, *6*, 3159.

(22) Gharat, L. A.; Gajera, J. M.; Khairatkar-Joshi, N.; Kattije, V. G. PCT Int. Appl WO 2009081222 A1, **2009**.

(23) (a) Caglioti, L. *Org. Synth.* **1972**, *52*, 122. (b) Lesma, G.; Danieli, B.; Passarella, D.; Sacchetti, A.; Silvani, A. *Tetrahedron: Asymmetry* **2003**, *14*, 2453.

(24) For the complete assignment of all ^{1}H NMR signals of cedrene, see: Perez-Hernandez, N.; Gordillo-Roman, B.; Arrieta-Baez, D.; Cerda-Garcia-Rojas, C.-M.; Joseph-Nathan, P. *Magn. Reson. Chem.* **2015**, *53*, in press; DOI 10.1002/mrc.4246.

(25) The analytical data of **14** are in agreement with the literature: Glennon, R. A.; Raghupathi, R.; Bartyzel, P.; Teitlr, M.; Leonhardt, S. *J. Med. Chem.* **1992**, *35*, 734.