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Catalytic Asymmetric Synthesis of Dihydrofurans and Cyclopentenols with Tertiary Stereocenters

Zhongtao Wu,[a] Ashoka V. R. Madduri,[a] Syuzanna R. Harutyunyan,*[a] and Adriaan J. Minnaard*[a]

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A new asymmetric synthesis of dihydrofurans and cyclopentenols has been developed and is based on the copper-catalyzed 1,2-addition of Grignard reagents to enones in combination with Sonogashira coupling/cyclization or ring-closing metathesis. By this approach, dihydrofurans with an oxygen-containing tertiary stereocenter and chiral tertiary cyclopentenols are efficiently prepared. The absolute stereochemistry of the products has been established.

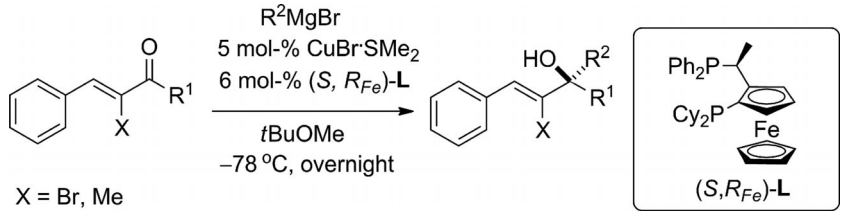
Introduction

Functionalized chiral five-membered cyclic ethers, for example, dihydro- and tetrahydrofuran derivatives, are ubiquitous structural units in natural products.[1] Also, owing to their wide-spread applications,[2] for example, as probe molecules for chemical reactions,[3] in complex pharmaceuticals, and in commodity chemicals,[2,4] the synthesis of compounds containing chiral (dihydro)furans has been intensively studied.[3,5]

The asymmetric synthesis of five-membered ring ethers in which the oxygen atom is connected to a secondary or tertiary stereocenter is of particular importance. Ring closing by face-selective attack of an oxygen nucleophile to an alkene is most commonly used. In this process, the alkene is activated either by a Lewis acid by protonation,[6] allylic substitution,[7] or conjugate addition[8] or alternatively by ring-opening of the corresponding epoxide[9] or halonium ion.[10] Alternatively, asymmetric ring-closing olefin metathesis has been applied.[11]

For cyclic ether formation by the alternative approach, that is, the alkylation of a chiral tertiary alcohol followed by a ring-closing reaction, the literature is particularly scarce. This is easily explained by the limited examples of effective methods for the enantioselective synthesis of the latter.

Recently, we reported the use of a copper/Josiphos-type catalyst system to accomplish the enantioselective 1,2-addition of Grignard reagents to α,β-unsaturated ketones (Scheme 1).[12] This leads to chiral enantioenriched tertiary allylic alcohols, although currently β-branched Grignard reagents are required for high enantioselectivity.[13] We realized that with the subsequent alkylation of the oxygen atom to provide the corresponding ethers, together with suitable ring-closing reactions, this strategy will provide a useful method for the synthesis of chiral five-membered cyclic ethers. As the tertiary stereocenter formed is clearly not prone to racemization and not involved in the ring-closing reaction, the latter process should not lead to erosion of *ee*. As an additional task, we planned to unambiguously establish the absolute configuration of the tertiary alcohols and ethers formed in this way, as reliable data on these compounds are practically absent.



Scheme 1. Asymmetric Cu-catalyzed 1,2-addition of Grignard reagents.

On the basis of the product of the enantioselective 1,2-Grignard addition reaction, several approaches for ring clo-

[a] Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 7, 9747 AG, Groningen, The Netherlands
E-mail: a.j.minnaard@rug.nl
s.harutyunyan@rug.nl
http://www.rug.nl/staff/departments/11680

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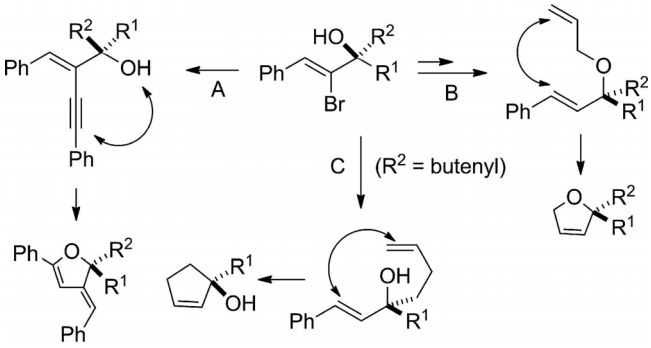
sure were selected (Scheme 2). When the X substituent is bromide, we have already shown that a Sonogashira reaction readily leads to the corresponding enyne.[12c] Base-induced intramolecular hydroalkoxylations by literature procedures[14] then lead directly to substituted dihydrofurans (route A).



Scheme 2. Strategies for the formation of chiral cyclic ethers.

Upon allylation of the hydroxy group in the addition product, formally 1,6-dienes are formed. These should be very suitable substrates for ring-closing olefin metathesis to form chiral dihydrofurans with a double bond at the 3,4-position (route B). In turn, these out-of-conjugation alkenes can be further functionalized to provide highly substituted tetrahydrofurans.

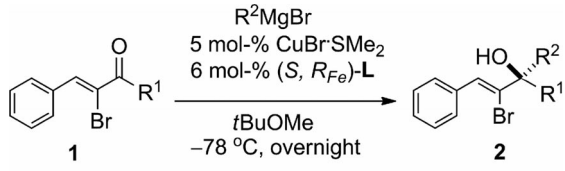
The use of butenylmagnesium bromide in the asymmetric addition reaction also gives direct access to 1,6-dienes (route C). Although the enantioselectivity of the addition reaction in this particular case is less satisfactory (the reaction requires branched Grignard reagents to reach excellent *ee* values), we wanted to pursue this approach, as subsequent ring closure by olefin metathesis leads to chiral allylic cyclopentenols. Formally, these originate from the addition of a carbon nucleophile to cyclopentenone,[15] but this reaction in an enantioselective fashion is not known. Alternatively, 1-methyl-2-cyclopentenol has been prepared from linalool by ring-closing metathesis.[16]

Results and Discussion

The study commenced with the preparation of the enantioenriched tertiary allylic alcohols by the catalytic asymmetric addition of Grignard reagents to the corresponding enones. These α-bromo enones **1**, in turn, are readily obtained by aldol condensation of benzaldehyde and the appropriate ketone, followed by dibromination/HBr elimination.[17]

Upon treatment of the α-bromo enones **1a** and **1b** with isobutylmagnesium bromide in the presence of $CuBr{\cdot}SMe_2$ (5 mol-%) and (S,R_{Fe})-**L** (6 mol-%) in methyl *tert*-butyl ether (MTBE) at –78 °C, the desired chiral tertiary alcohols **2a** and **2b** were obtained in good yields and good-to-excellent enantioselectivities (Table 1).[12] In addition, **1a** was used in the addition of (2-ethyl)butylmagnesium bromide and cyclohexylmethylmagnesium bromide to form the corresponding alcohols. As expected, the reactions could be performed on gram-scale without deterioration in yield or *ee* except for **2d**, for which a longer reaction time led to a slightly lower *ee*.

Table 1. Asymmetric 1,2-addition to α-bromo enones **1**.



R^1 (**1**)	R^2	**2**[a]	Yield (%)	*ee* (%)
Me (**1a**)	$(CH_3)_2CHCH_2$	**2a**	85	86
Ph (**1b**)	$(CH_3)_2CHCH_2$	**2b**	63	98
Me (**1a**)	Et_2CHCH_2	**2c**	82	94
Me (**1a**)	$CyCH_2$	**2d**	70	75

[a] The absolute configuration of **2** is *R*, vide infra.

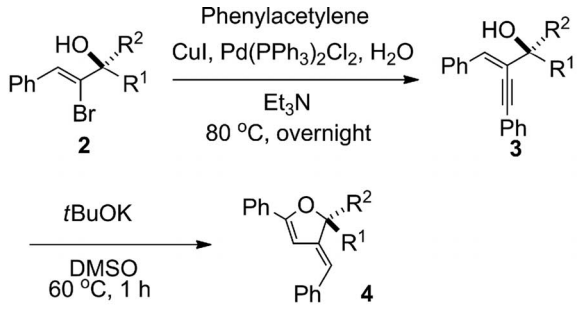
With the products **2** in hand, the Sonogashira reactions, as part of route A, were performed with 5 mol-% $Pd(PPh_3)_2Cl_2$ and 10 mol-% CuI as the catalysts in Et_3N. The corresponding enynes **3a**–**3d** were isolated in high yields (Table 2).[18] The subsequent treatment with *t*BuOK in dimethyl sulfoxide (DMSO) for 1 h at 60 °C afforded the desired cyclized products **4a**–**4d** in good yields.[14a] 3-Benzylidene-2,3-dihydrofurans are strongly fluorescent compounds.[19]

The synthesis of the 2,5-dihydrofurans **7** by route B also started from the chiral tertiary alcohols **2**. The allylation of the tertiary alcohols **2** was extremely sluggish, as was the subsequent metathesis step, so the debromination of **2** was performed first. The debromination with *t*BuLi in dry Et_2O at –78 °C for 0.5 h,[20] followed by aqueous workup, yielded the desired products **5a**–**5c** in good isolated yields (Table 3). The alkylation of the hydroxy groups in **5** was surprisingly difficult, and substituents other than allyl could not be introduced. However, under optimized conditions, namely, the use of 1.5 equiv. allyl bromide, 1.5 equiv. NaH, and 3.0 equiv. hexamethylphosphoramide (HMPA) in dry tetrahydrofuran (THF) at reflux,[21] **6a**–**6c** were prepared in high-to-excellent yield. Remarkably, **2d** refused to react under all conditions, presumably because of steric hindrance.

Compounds **6a**–**c** were subsequently transformed into the corresponding 2,5-dihydrofurans **7a**–**7c** by treatment with 5 mol-% Hoveyda–Grubbs second-generation catalyst in dichloromethane (Table 3).[22] The reactions was fully selective to complete conversion, and the high yields are probably only reduced because of the volatility of the products.

For the synthesis of cyclopentenols according to route C, butenylmagnesium bromide was added to **1a** and its α-methyl (instead of α-bromo) analogue **1c** (Scheme 3).[12] The enantioselectivities were modest, as expected. The subsequent debromination of **2e** by the procedure described earlier gave **5e** in 83% isolated yield. The subsequent ring-closing metathesis resulted in 1-methyl-2-cyclopentenol (**8a**)

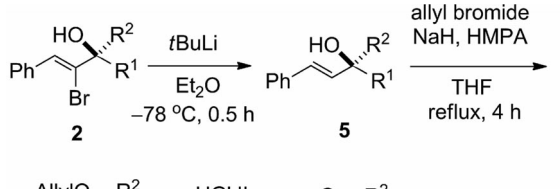
Table 2. Synthesis of 3-benzylidene-2,3-dihydrofurans **4**.



2	R^1	R^2	3	Yield (%)	4	Yield (%)
2a	Me	$(CH_3)_2CHCH_2$	**3a**	88	**4a**	80
2b	Ph	$(CH_3)_2CHCH_2$	**3b**	80	**4b**[a]	82
2c	Me	Et_2CHCH_2	**3c**	92	**4c**	91
2d	Me	$CyCH_2$	**3d**	84	**4d**	72

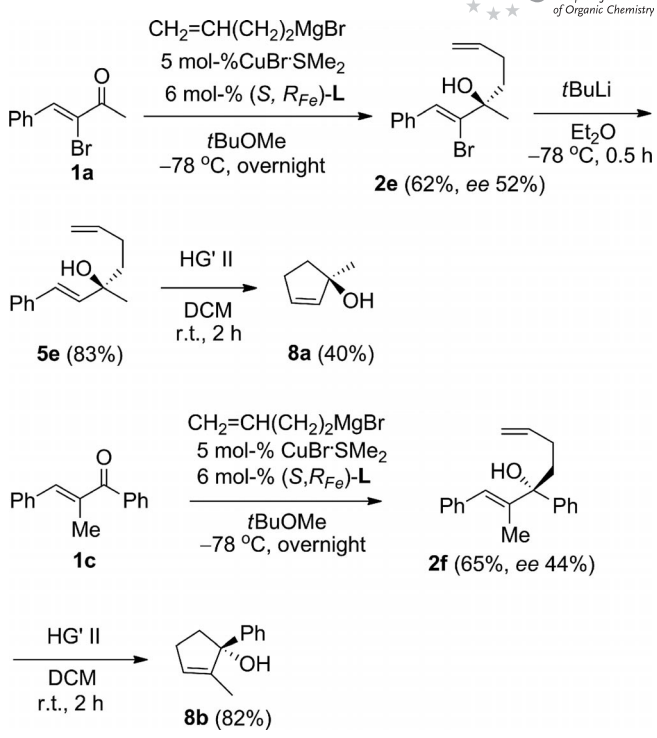
[a] *E*/*Z* = 5:1, determined by ^{1}H NMR spectroscopy.

Table 3. Synthesis of 2,5-dihydrofurans **7**.



2	R^1	R^2	5	Yield (%)	6	Yield (%)	7	Yield (%)
2a	Me	$(CH_3)_2CHCH_2$	**5a**	84	**6a**	93	**7a**	85
2b	Ph	$(CH_3)_2CHCH_2$	**5b**	87	**6b**	97	**7b**	90
2c	Me	Et_2CHCH_2	**5c**	82	**6c**	84	**7c**	82

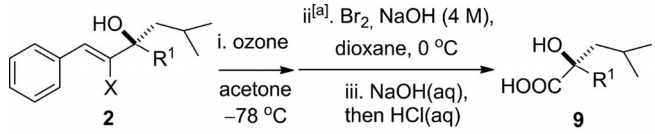
in 40% yield; the moderate yield is solely caused by its extreme volatility. The ring-closing metathesis of its congener **2f** gave **8b** in high yield.



Scheme 3. Synthesis of 2-cyclopenten-1-ols **8**.

To determine the absolute configuration of this class of tertiary alcohols and ethers, we decided to prepare the corresponding α-hydroxy acids **9a** and **9b** from **2a**, **2b**, and **2g** (Table 4). This would lead to known well-described compounds, and this approach might serve as an alternative route to chiral enantioenriched α,α-disubstituted acids, which are important building blocks in natural product synthesis and normally prepared from chiral pool precursors. Hydroxy acid **9a** and **9b** were obtained from **2a** and **2b** in good yield by ozonolysis in acetone. The sign of their optical rotation, in comparison with the literature data,

Table 4. Synthesis of α-hydroxy acids **9**.



R^1 / X (**2**)	**9**	Yield (%)	Config. (**2**)
Me / Br (**2a**)	**9a**	75	R
Ph / Br (**2b**)	**9b**	86	R
Ph / Me (**2g**)	**9b**	16	S

[a] Reaction (ii) is only for the synthesis of **9b** from **2g**.

showed unambiguously that the (S,R_{Fe}) enantiomer of ligand **L** produces the opposite stereochemistry for R^1 = Me than for R^1 = Ph, though both products are assigned the *R* configuration owing to the application of the Cahn–Ingold–Prelog (CIP) rules. For **2g**, the ozonolysis was followed by a bromoform reaction, which provided **9b** in low yield. For this substrate, it follows that the (S,R_{Fe}) enantiomer of **L** provides the same stereochemistry as for **2b** (in both cases R^1 is Ph), although the product is designated *S* by the CIP rules.[23]

Conclusions

We have developed a new approach for the enantioselective synthesis of chiral dihydrofurans with a tertiary oxygen-containing stereocenter and of tertiary cyclopentenols. By the catalytic asymmetric 1,2-addition of Grignard reagents, combined with a Sonogashira coupling/cyclization approach or an alkylation followed by ring-closing metathesis, different kinds of dihydrofurans were prepared efficiently. With their absolute stereochemistry established, the obtained compounds are versatile building blocks both for natural product synthesis and pharmaceuticals.

Experimental Section

General: ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded with $CDCl_3$ as solvent. Chemical shifts were determined relative to the residual solvent peaks ($CHCl_3$, δ = 7.26 ppm for ^{1}H NMR, δ = 77.0 ppm for ^{13}C NMR). The following abbreviations are used to indicate signal multiplicity: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. Enantiomeric excesses were determined by chiral HPLC in comparison with racemic products. Racemic products were obtained by the same procedure as used for the enantioselective 1,2-addition but with the ligand and CuBr·SMe_2 (5 mol-%) omitted and only the Grignard reagent (1.2 equiv.) at 0 °C in Et_2O used. Regioselectivities were determined by ^{1}H NMR spectroscopy. Optical rotations were measured with a 10 cm cell (*c* given in g/100 mL) at 20 °C. Thin-layer chromatography (TLC) was performed on TLC silica gel. Flash chromatography was performed on silica gel. Mass spectra were obtained from a high-resolution [ESI+ or atmospheric-pressure chemical ionization (APCI+)] mass spectrometer. All starting materials, copper salt, ligand (S,R_{Fe})-**L**, and *i*BuMgBr (2 M in Et_2O) were purchased and used without further purification. All Grignard reagents were prepared from the corresponding alkyl bromides and Mg activated with I_2 in Et_2O.

For the stereochemistry of α-bromo enones **1**, to our surprise, we could not find a rigorous proof of the stereochemistry of the so-obtained bromo enones in literature, although these compounds have been reported several times. In this study, the stereochemistry is determined unambiguously a posteriori; upon catalytic asymmetric 1,2 addition with the bromo enones as substrate, the products are identical to those obtained in the uncatalyzed addition with the same Grignard reagent used to prepare the racemic reference material, so isomerization during the Grignard addition can be excluded. After debromination of the resulting tertiary alcohols with *t*BuLi (vide infra), ^{1}H NMR spectroscopy clearly shows the presence of an *E* carbon–carbon double bond. This determines that the stereochemistry of the starting bromo enones is as shown.

1a–1c: The starting materials were prepared by following literature procedures.[17]

General Procedure for the Copper-Catalyzed 1,2-Addition of Grignard Reagents: A Schlenk tube equipped with a septum and stirring bar was charged with CuBr·SMe_2 (11.3 mg, 0.055 mmol, 5 mol-%) and ligand (S,R_{Fe})-**L** (39.2 mg, 0.066 mmol, 6 mol-%). Under nitrogen, dry *t*BuOMe (8 mL) was added, and the solution was stirred at room temperature for 15 min. Then, the corresponding enone (1.10 mmol, in 5 mL *t*BuOMe) was added, and the resulting solution was cooled to –78 °C. The corresponding Grignard reagent (1.32 mmol, 1.2 equiv. in Et_2O) was diluted with *t*BuOMe (2 mL) and added to the reaction mixture over 3 h. The mixture was left to stir overnight at –78 °C. The reaction was quenched by the addition of MeOH and saturated aqueous NH_4Cl, and the mixture was warmed to room temperature and diluted with Et_2O. The layers were then separated, and the aqueous layer was extracted with Et_2O. The combined organic phases were dried with anhydrous Na_2SO_4, filtered, and the solvents were evaporated in vacuo. The residue was purified by column chromatography on silica gel (pentane/Et_2O 20:1) to afford alcohol **2**.

(*R*)-(*Z*)-2-Bromo-3,5-dimethyl-1-phenyl-1-hexen-3-ol (2a): Light yellow oil (265 mg, 85%). 86%*ee* determined by HPLC (Chiral AS-H column, heptane/*i*PrOH 90:10, 40 °C, 210 nm). Retention time: t_{major} = 23.6 and t_{minor} = 22.5 min. $[\alpha]_D^{20}$ = +10.0 (*c* = 1.04, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.54 (m, 2 H), 7.39–7.35 (m, 2 H), 7.32–7.28 (m, 1 H), 7.24 (s, 1 H), 2.01 (br s, 1 H), 1.89 (dd, *J* = 14.0, 5.6 Hz, 1 H), 1.84–1.78 (m, 1 H), 1.65 (dd, *J* = 14.0, 6.0 Hz, 1 H), 1.58 (s, 3 H), 1.00 (2 × d, *J* = 6.4 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.2, 134.7, 129.0, 128.1, 127.7, 126.3, 77.6, 49.1, 28.8, 24.5, 24.2 ppm.

(*R*)-(*Z*)-2-Bromo-5-methyl-1,3-diphenyl-1-hexen-3-ol (2b): Light yellow oil (239 mg, 63%). 98%*ee* determined by HPLC (Chiral OD-H column, heptane/*i*PrOH 99:1, 40 °C, 230 nm). Retention time: t_{major} = 21.9 and t_{minor} = 20.8 min. $[\alpha]_D^{20}$ = –7.8 (*c* = 0.49, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 7.6 Hz, 2 H), 7.56 (d, *J* = 7.6 Hz, 2 H), 7.43–7.32 (m, 7 H), 2.60 (s, 1 H), 2.23 (dd, *J* = 14.4, 5.6 Hz, 1 H), 2.14–2.09 (m, 1 H), 1.91–1.84 (m, 1 H), 1.08 (d, *J* = 6.8 Hz, 3 H), 0.89 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.4, 135.9, 134.9, 129.2, 128.3, 128.2, 128.0, 127.5, 126.0, 81.0, 48.0, 24.7, 24.5 ppm. HRMS (APCI): calcd. for $C_{19}H_{20}Br$ $[M - OH]^+$ 327.0743; found 327.0740.

(*R*)-(*Z*)-2-Bromo-5-ethyl-3-methyl-1-phenyl-1-hepten-3-ol (2c): Light yellow oil (281 mg, 82%). 94%*ee* determined by HPLC (Chiral AS-H column, heptane/*i*PrOH 90:10, 40 °C, 210 nm). Retention time: t_{major} = 16.0 and t_{minor} = 17.6 min. $[\alpha]_D^{20}$ = +14.1 (*c* = 1.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (d, *J* = 7.2 Hz, 2 H), 7.39–7.35 (m, 2 H), 7.32–7.28 (m, 1 H), 7.22 (s, 1 H), 1.98 (br s, 1 H), 1.87–1.83 (m, 1 H), 1.69–1.64 (m, 1 H), 1.59 (s, 3 H), 1.46–1.35 (m, 5 H), 0.90–0.86 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.3, 135.0, 129.0, 128.1, 127.6, 126.3, 77.6, 43.8, 36.4, 28.6, 26.5, 10.8 ppm. HRMS (ESI): calcd. for $C_{16}H_{22}Br$ $[M - OH]^+$ 293.0905; found 293.0879.

(*R*)-(*Z*)-3-Bromo-1-cyclohexyl-2-methyl-4-phenyl-3-buten-2-ol (2d): Light yellow oil (249 mg, 70%). 75%*ee* determined by HPLC (Chiral AD-H column, heptane/*i*PrOH 98:2, 40 °C, 250 nm). Retention time: t_{major} = 25.1 and t_{minor} = 23.9 min. $[\alpha]_D^{20}$ = +12.2 (*c* = 0.64, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 7.2 Hz, 2 H), 7.41–7.38 (m, 2 H), 7.34–7.30 (m, 1 H), 7.27 (s, 1 H), 2.18 (s, 1 H), 1.91–1.83 (m, 3 H), 1.74–1.65 (m, 4 H), 1.61 (s, 3 H), 1.56–1.49 (m, 1 H), 1.35–1.17 (m, 3 H), 1.13–1.03 (m, 2 H) ppm. ^{13}C

NMR (100 MHz, $CDCl_3$): δ = 136.4, 134.9, 129.1, 128.1, 127.7, 126.3, 77.7, 48.0, 34.9, 34.7, 33.9, 28.8, 26.5, 26.3 ppm. HRMS (ESI): calcd. for $C_{17}H_{22}Br$ $[M - OH]^+$ 305.0899; found 305.0901.

(*R*)-(*Z*)-2-Bromo-3-methyl-1-phenyl-1,6-heptadien-3-ol (2e): Light yellow oil (191 mg, 62%). 52% *ee* determined by HPLC (Chiral AD-H column, heptane/*i*PrOH 98:2, 40 °C, 260 nm). Retention time: t_{major} = 15.9 and t_{minor} = 14.1 min. $[\alpha]_D^{20}$ = +4.8 (c = 0.58, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, J = 7.9 Hz, 2 H), 7.45–7.27 (m, 3 H), 7.21 (s, 1 H), 5.88 (m, 1 H), 5.19–4.83 (m, 2 H), 2.21–2.10 (m, 3 H), 2.10–1.98 (m, 1 H), 1.82 (m, 1 H), 1.57 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.4, 136.1, 133.7, 129.0, 128.1, 127.8, 126.8, 115.1, 77.3, 39.7, 28.4, 27.9 ppm. HRMS (ESI): calcd. for $C_{14}H_{16}Br$ $[M - OH]^+$ 263.0436; found 263.0431.

(*S*)-(*E*)-2-Methyl-1,3-diphenyl-1,6-heptadien-3-ol (2f): Light yellow oil (199 mg, 65%). 44% *ee* determined by HPLC (Chiral AD-H column, heptane/*i*PrOH 98:2, 40 °C, 250 nm). Retention time: t_{major} = 30.6 and t_{minor} = 27.8 min. $[\alpha]_D^{20}$ = –19.4 (c = 0.95, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, J = 7.6 Hz, 2 H), 7.38–7.22 (m, 8 H), 6.91 (s, 1 H), 5.97–5.87 (m, 1 H), 5.07 (d, J = 17.2 Hz, 1 H), 5.00 (d, J = 10.4 Hz, 1 H), 2.31–2.10 (m, 4 H), 1.97 (s, 1 H), 1.67 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.1, 141.7, 138.9, 138.1, 129.1, 128.2, 128.1, 127.1, 126.4, 125.9, 124.8, 114.8, 79.6, 38.0, 28.2, 15.1 ppm. HRMS (APCI): calcd. for $C_{20}H_{21}$ $[M - OH]^+$ 261.1638; found 261.1639.

(*S*)-(*E*)-2,5-Dimethyl-1,3-diphenyl-1-hexen-3-ol (2g): Light yellow oil (188 mg, 61%). 37% *ee* determined by HPLC (Chiral OD-H column, heptane/*i*PrOH 98:2, 40 °C, 250 nm). Retention time: t_{major} = 14.1 and t_{minor} = 14.5 min. $[\alpha]_D^{20}$ = –16.3 (c = 0.32, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.38 (m, 2 H), 7.25–7.08 (m, 8 H), 6.81 (s, 1 H), 2.03 (dd, J = 14.4, 5.6 Hz, 1 H), 1.93 (dd, J = 14.4, 5.6 Hz, 1 H), 1.75–1.70 (m, 2 H), 1.55 (d, J = 0.8 Hz, 3 H), 0.91 (d, J = 6.8 Hz, 3 H), 0.80 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.9, 142.4, 138.3, 129.1, 128.16, 128.11, 126.9, 126.3, 125.9, 124.4, 80.1, 47.2, 24.84, 24.83, 24.2, 15.4 ppm. HRMS (ESI): calcd. for $C_{20}H_{23}$ $[M - OH]^+$ 263.1794; found 263.1800.

General Procedure for the Pd-Catalyzed Synthesis of Enynes:[18] To a solution of **2** (0.50 mmol) in Et_3N (5 mL) was added $Pd(PPh_3)_2Cl_2$ (17.5 mg, 0.025 mmol, 5 mol-%), CuI (9.5 mg, 0.050 mmol, 10 mol-%), phenylacetylene (0.082 mL, 0.75 mmol, 1.5 equiv.), and H_2O (0.045 mL, 2.5 mmol, 5 equiv.), and the resulting mixture was stirred at 80 °C. The solvent was evaporated under reduced pressure after the starting material had been consumed, and the residue was diluted with Et_2O and washed with saturated aqueous NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried with Na_2SO_4, concentrated in vacuo, and the residue was purified by column chromatography on silica gel (pentane/Et_2O 12:1) to afford enyne **3**.

(*R*)-3-[(*E*)-Benzylidene]-4,6-dimethyl-1-phenyl-1-heptyn-4-ol (3a): Light brown oil (134 mg, 88%). $[\alpha]_D^{20}$ = +24.2 (c = 0.48, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 8.0 Hz, 2 H), 7.51–7.49 (m, 2 H), 7.42–7.37 (m, 5 H), 7.32–7.29 (m, 1 H), 7.10 (s, 1 H), 1.99 (dd, J = 14.0, 5.6 Hz, 1 H), 1.92–1.86 (m, 1 H), 1.81 (br s, 1 H), 1.74–1.69 (m, 1 H), 1.60 (s, 3 H), 1.04–1.00 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.5, 131.8, 131.3, 128.9, 128.5, 128.4, 128.2, 128.0, 126.3, 123.4, 97.5, 88.1, 76.5, 50.1, 29.6, 24.6, 24.52, 24.50 ppm. HRMS (ESI): calcd. for $C_{22}H_{23}$ $[M - OH]^+$ 287.1794; found 287.1795.

(*R*)-3-[(*E*)-Benzylidene]-6-methyl-1,4-diphenyl-1-heptyn-4-ol (3b): Light brown oil (147 mg, 80%). $[\alpha]_D^{20}$ = +28.0 (c = 1.18, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82–7.80 (m, 2 H), 7.55–7.52 (m, 2 H), 7.28–7.12 (m, 11 H), 7.05 (s, 1 H), 2.31 (dd, J = 14.4, 5.6 Hz, 1 H), 2.20 (br s, 1 H), 2.04 (dd, J = 14.4, 5.6 Hz, 1 H), 1.86–1.79 (m, 1 H), 0.96 (d, J = 6.8 Hz, 3 H), 0.86 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.9, 136.4, 132.9, 131.3, 129.0, 128.50, 128.46, 128.43, 128.22, 128.21, 128.1, 127.1, 125.9, 123.3, 98.1, 88.2, 79.5, 48.5, 24.9, 24.8, 24.5 ppm. HRMS (ESI): calcd. for $C_{27}H_{25}$ $[M - OH]^+$ 349.1951; found 349.1948.

(*R*)-3-[(*E*)-Benzylidene]-6-ethyl-4-methyl-1-phenyl-1-octyn-4-ol (3c):[12c] Light brown oil (152 mg, 92%). $[\alpha]_D^{20}$ = +51.6 (c = 1.80, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02–7.84 (m, 2 H), 7.59–7.26 (m, 8 H), 7.07 (s, 1 H), 2.06–1.88 (m, 2 H), 1.78 (s, 1 H), 1.60 (s, 3 H), 1.54–1.28 (m, 5 H), 0.88 (t, J = 7.2 Hz, 3 H), 0.72 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.6, 131.8, 131.3, 129.2, 128.9, 128.44, 128.37, 128.2, 128.1, 127.9, 123.4, 97.4, 88.2, 76.5, 44.7, 36.3, 29.3, 26.9, 10.8 ppm. HRMS (ESI): calcd. for $C_{24}H_{27}$ $[M - OH]^+$ 315.2113; found 315.2107.

(*R*)-3-[(*E*)-Benzylidene]-1-cyclohexyl-2-methyl-5-phenyl-4-pentyn-2-ol (3d): Light brown oil (145 mg, 84%). $[\alpha]_D^{20}$ = +37.6 (c = 1.20, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84–7.82 (m, 2 H), 7.40–7.38 (m, 2 H), 7.32–7.25 (m, 5 H), 7.23–7.22 (m, 1 H), 6.98 (s, 1 H), 1.88–1.83 (m, 1 H), 1.75 (d, J = 12.4 Hz, 2 H), 1.67 (s, 1 H), 1.62–1.56 (m, 3 H), 1.53 (d, J = 1.2 Hz, 1 H), 1.49 (s, 3 H), 1.18–1.08 (m, 3 H), 1.07–0.92 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.6, 131.7, 131.3, 129.2, 128.8, 128.43, 128.37, 128.2, 127.9, 123.4, 97.4, 88.1, 76.5, 48.9, 35.2, 34.8, 33.8, 29.5, 26.4, 26.3 ppm. HRMS (ESI): calcd. for $C_{25}H_{27}$ $[M - OH]^+$ 327.2107; found 327.2107.

General Procedure for the Cyclization of the Enyne:[14a,19] To a solution of **3** (0.25 mmol) in DMSO (4.0 mL) was added *t*BuOK (31 mg, 0.275 mmol, 1.1 equiv.), and the resulting mixture was stirred at 60 °C for 1 h. The mixture was poured into water (50 mL) and extracted with Et_2O. The combined organic phases were dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (pentane) to afford **4**.

(*R*)-3-[(*E*)-Benzylidene]-2-isobutyl-2-methyl-5-phenyl-2,3-dihydrofuran (4a): Yellow oil (61 mg, 80%). $[\alpha]_D^{20}$ = +27.6 (c = 2.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (dd, J = 8.4, 1.6 Hz, 2 H), 7.32–7.24 (m, 7 H), 7.10–7.05 (m, 1 H), 6.55 (s, 1 H), 5.62 (s, 1 H), 1.81–1.71 (m, 2 H), 1.62–1.57 (m, 1 H), 1.41 (s, 3 H), 0.86 (dd, J = 11.2, 6.4 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.0, 150.5, 139.1, 130.8, 129.3, 128.49, 128.45, 127.5, 125.7, 125.5, 111.6, 98.7, 91.9, 50.1, 28.2, 24.6, 24.5, 24.3 ppm. HRMS (APCI): calcd. for $C_{22}H_{25}O$ $[M + H]^+$ 305.1900; found 305.1905.

4b: Yellow oil (75 mg, 82%, *Z*/*E* = 5:1). $[\alpha]_D^{20}$ = +41.1 (c = 0.94, $CHCl_3$). HRMS (ESI): calcd. for $C_{27}H_{27}O$ $[M + H]^+$ 367.2056; found 367.2055. The NMR data of (*E*)-**4b** and (*Z*)-**4b** are given separately as the two groups of signals are clearly identified in the NMR spectrum of **4b**, although no separation was performed. **(*R*)-3-[(*E*)-Benzylidene]-2-isobutyl-1,5-diphenyl-2,3-dihydrofuran [(*E*)-4b]:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (dd, J = 7.2, 1.2 Hz, 2 H), 7.59–7.57 (m, 2 H), 7.49–7.37 (m, 10 H), 7.22–7.18 (m, 1 H), 6.73 (s, 1 H), 6.00 (s, 1 H), 2.39–2.34 (m, 1 H), 2.18–2.12 (m, 1 H), 2.02–1.96 (m, 1 H), 1.08–1.06 (m, 3 H), 1.02 (dd, J = 6.8, 1.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.2, 149.5, 144.3, 138.7, 130.4, 129.5, 128.6, 128.5, 128.4, 127.8, 127.3, 125.8, 125.5, 124.8, 114.3, 98.9, 94.1, 49.4, 29.8, 24.9, 24.6 ppm.

(*R*)-3-[(*Z*)-Benzylidene]-2-isobutyl-1,5-diphenyl-2,3-dihydrofuran [(*Z*)-4b]: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.68 (m, 0.40 H), 7.63–7.61 (m, 0.40 H), 7.49–7.37 (m, 0.20 H), 7.33–7.29 (m, 1.00 H), 7.12–7.11 (m, 0.60 H), 6.95–6.93 (m, 0.40 H), 6.61 (s, 0.20 H), 6.27 (s, 0.20 H), 2.39–2.34 (m, 0.40 H), 2.02–1.96 (m, 0.20 H), 1.08–1.02 (m, 1.20 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.0, 148.9, 143.6, 137.1, 130.5, 129.1, 128.5, 128.0, 127.8, 126.4, 125.9, 125.6, 117.2, 105.9, 93.5, 42.9, 29.4, 25.0, 24.9 ppm.

(*R*)-3-[(*E*)-Benzylidene]-2-(2-ethylbutyl)-2-methyl-5-phenyl-2,3-dihydrofuran (4c):[12c] Yellow oil (76 mg, 91%). $[\alpha]_D^{20}$ = +37.7 (c = 0.90, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82–7.65 (m, 2 H), 7.37 (m, 7 H), 7.17 (t, J = 7.1 Hz, 1 H), 6.64 (s, 1 H), 5.73 (s, 1 H), 1.76 (m, 2 H), 1.50 (s, 3 H), 1.42–1.24 (m, 5 H), 0.80 (t, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.0, 150.5, 139.1, 130.7, 129.3, 128.5, 128.4, 127.5, 125.7, 125.4, 111.6, 98.7, 92.0, 44.5, 36.4, 28.1, 26.8, 26.5, 10.9 ppm.

(*R*)-3-[(*E*)-Benzylidene]-2-cyclohexyl-2-methyl-5-phenyl-2,3-dihydrofuran (4d): Yellow oil (62 mg, 72%). $[\alpha]_D^{20}$ = +41.4 (c = 1.07, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, J = 6.8 Hz, 2 H), 7.32–7.24 (m, 7 H), 7.08 (t, J = 7.2 Hz, 1 H), 6.54 (s, 1 H), 5.62 (s, 1 H), 1.77–1.71 (m, 1 H), 1.68 (d, J = 5.6 Hz, 1 H), 1.65–1.60 (m, 1 H), 1.58–1.49 (m, 4 H), 1.40 (s, 3 H), 1.18–0.88 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.0, 150.7, 139.1, 130.8, 129.3, 128.50, 128.45, 127.5, 125.7, 125.5, 111.6, 98.6, 91.9, 48.8, 34.8, 34.7, 33.9, 28.1, 26.44, 26.39 ppm. HRMS (ESI): calcd. for $C_{25}H_{29}O$ $[M + H]^+$ 345.2213; found 345.2211.

General Procedure for the Preparation of α,β-Unsaturated Alcohols:[20] To a solution of **2** (0.55 mmol) in Et_2O (5.0 mL) was slowly added a solution of *t*BuLi (1.65 mmol, 3.0 equiv., 1.7 M in pentane) under nitrogen at –78 °C, and the resulting mixture was stirred at this temperature for 30 min. The reaction was then quenched with MeOH and saturated aqueous NH_4Cl, and the mixture was warmed to room temperature and diluted with Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic phase was dried with Na_2SO_4 and filtered, and the solvents were evaporated in vacuo. The residue was purified by column chromatography on silica gel (pentane/Et_2O 20:1) to afford alcohol **5**.

(*R*)-(*E*)-3,5-Dimethyl-1-phenyl-1-hexen-3-ol (5a): Light yellow oil (94 mg, 84%). $[\alpha]_D^{20}$ = +32.4 (c = 0.53, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, J = 7.6 Hz, 2 H), 7.35–7.31 (m, 2 H), 7.24 (t, J = 7.2 Hz, 1 H), 6.61 (d, J = 16.0 Hz, 1 H), 6.31 (d, J = 16.0 Hz, 1 H), 1.84–1.79 (m, 1 H), 1.62 (br s, 1 H), 1.59 (d, J = 6.0 Hz, 2 H), 1.40 (s, 3 H), 1.00–0.96 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.3, 137.2, 128.6, 127.3, 126.5, 126.4, 73.7, 51.6, 29.2, 24.63, 24.59, 24.45 ppm. HRMS (ESI): calcd. for $C_{14}H_{19}$ $[M – OH]^+$ 187.1481; found 187.1480.

(*S*)-(*E*)-5-Methyl-1,3-diphenyl-1-hexen-3-ol (5b): Light yellow oil (127 mg, 87%). $[\alpha]_D^{20}$ = +18.8 (c = 0.49, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (d, J = 7.6 Hz, 2 H), 7.44–7.25 (m, 8 H), 6.70 (d, J = 16.0 Hz, 1 H), 6.60 (d, J = 16.0 Hz, 1 H), 2.06–2.01 (m, 1 H), 2.01 (br s, 1 H), 1.95 (dd, J = 14.4, 6.0 Hz, 1 H), 1.84–1.78 (m, 1 H), 1.00 (d, J = 6.8 Hz, 3 H), 0.90 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.3, 137.0, 136.6, 128.6, 128.3, 127.5, 127.4, 126.8, 126.6, 125.5, 77.5, 51.3, 24.6, 24.3 ppm. HRMS (APCI): calcd. for $C_{19}H_{21}$ $[M – OH]^+$ 249.1638; found 249.1634.

(*R*)-(*E*)-5-Ethyl-3-methyl-1-phenyl-1-hepten-3-ol (5c): Light yellow oil (105 mg, 82%). $[\alpha]_D^{20}$ = +38.7 (c = 0.45, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (d, J = 7.2 Hz, 2 H), 7.35–7.31 (m, 2 H), 7.25–7.22 (m, 1 H), 6.60 (d, J = 16.0 Hz, 1 H), 6.30 (d, J = 16.0 Hz, 1 H), 1.61–1.58 (m, 3 H), 1.42 (s, 3 H), 1.42–1.34 (m, 5 H), 0.89–0.83 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.3, 137.2, 128.6, 127.3, 126.5, 126.4, 73.8, 46.3, 36.3, 29.0, 27.0, 26.9, 10.8 ppm. HRMS (ESI): calcd. for $C_{16}H_{23}$ $[M – OH]^+$ 215.1794; found 215.1793.

(*R*)-(*E*)-3-Methyl-1-phenyl-1,6-heptadien-3-ol (5e): Light yellow oil (92 mg, 83%). $[\alpha]_D^{20}$ = +9.1 (c = 1.95, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.22 (m, 5 H), 6.60 (d, J = 16.0 Hz, 1 H), 6.28 (d, J = 16.0 Hz, 1 H), 5.91–5.81 (m, 1 H), 5.05 (d, J = 17.6 Hz, 1 H), 4.97 (d, J = 10.4 Hz, 1 H), 2.20–2.14 (m, 2 H), 1.76–1.72 (m, 3 H), 1.41 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.8, 136.9, 136.4, 128.6, 127.4, 127.3, 126.4, 114.6, 73.3, 41.7, 28.6, 28.4 ppm. HRMS (ESI): calcd. for $C_{14}H_{17}$ $[M – OH]^+$ 185.1325; found 185.1322.

General Procedure for the Allylation of the α,β-Unsaturated Tertiary Alcohols:[21] To a solution of **5** (0.35 mmol) in dry THF (5.0 mL) was added NaH (21.0 mg, 0.53 mmol, 1.5 equiv., 60% oil dispersion) under nitrogen, and the resulting mixture was stirred under reflux for 2 h. Then, HMPA (0.18 mL, 1.05 mmol, 3.0 equiv.) was added to the mixture followed by allyl bromide (0.046 mL, 0.53 mmol, 1.5 equiv.). After the addition, the mixture was stirred under reflux for another 2 h. The reaction mixture was cooled to room temperature, quenched with 2 M aqueous HCl, and extracted with Et_2O. The combined organic phases were washed with saturated $NaHCO_3$ and brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (pentane/Et_2O 100:1) to afford diene **6**.

(*R*)-(*E*)-3-Allyloxy-3,5-dimethyl-1-phenyl-1-hexene (6a): Light yellow oil (80 mg, 93%). $[\alpha]_D^{20}$ = –15.4 (c = 0.50, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, J = 7.2 Hz, 2 H), 7.35–7.31 (m, 2 H), 7.26–7.22 (m, 1 H), 6.50 (d, J = 16.4 Hz, 1 H), 6.20 (d, J = 16.4 Hz, 1 H), 5.99–5.89 (m, 1 H), 5.33–5.28 (m, 1 H), 5.14–5.10 (m, 1 H), 3.91 (d, J = 5.2 Hz, 2 H), 1.87–1.80 (m, 1 H), 1.63–1.60 (m, 2 H), 1.41 (s, 3 H), 0.98–0.96 (2 × d, J = 2.2 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.1, 136.1, 135.5, 129.0, 128.6, 127.4, 126.4, 115.4, 78.0, 63.5, 49.7, 24.7, 24.6, 24.1, 22.9 ppm. HRMS (ESI): calcd. for $C_{14}H_{19}$ $[M – OAllyl]^+$ 187.1481; found 187.1480.

(*S*)-(*E*)-3-Allyloxy-5-methyl-1,3-diphenyl-1-hexene (6b): Light yellow oil (104 mg, 97%). $[\alpha]_D^{20}$ = –5.5 (c = 0.66, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (d, J = 7.2 Hz, 2 H), 7.46 (d, J = 7.6 Hz, 2 H), 7.41–7.35 (m, 4 H), 7.32–7.26 (m, 2 H), 6.75 (d, J = 16.4 Hz, 1 H), 6.42 (d, J = 16.4 Hz, 1 H), 6.09–5.97 (m, 1 H), 5.44 (dd, J = 17.2, 1.2 Hz, 1 H), 5.21 (d, J = 10.8 Hz, 1 H), 3.94–3.86 (m, 2 H), 2.13–2.02 (m, 2 H), 1.80–1.72 (m, 1 H), 0.91 (dd, J = 50.0, 6.4 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.9, 137.1, 135.6, 134.2, 129.5, 128.6, 128.1, 127.6, 126.9, 126.5, 115.3, 81.8, 63.9, 46.5, 24.5, 24.4, 23.8 ppm. HRMS (APCI): calcd. for $C_{19}H_{21}$ $[M – OAllyl]^+$ 249.1638; found 249.1639.

(*R*)-(*E*)-3-Allyloxy-5-ethyl-3-methyl-1-phenyl-1-heptene (6c): Light yellow oil (80 mg, 84%). $[\alpha]_D^{20}$ = –24.1 (c = 0.49, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (d, J = 7.2 Hz, 2 H), 7.36–7.33 (m, 2 H), 7.27–7.24 (m, 1 H), 6.50 (d, J = 16.4 Hz, 1 H), 6.21 (d, J = 16.4 Hz, 1 H), 5.99–5.92 (m, 1 H), 5.35–5.30 (m, 1 H), 5.14 (dd, J = 10.4, 1.6 Hz, 1 H), 3.93 (d, J = 5.2 Hz, 2 H), 1.64–1.62 (m, 2 H), 1.42 (s, 3 H), 1.42–1.36 (m, 4 H), 1.29 (s, 1 H), 0.89–0.83 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.1, 136.2, 135.4, 129.2, 128.6, 127.4, 126.4, 115.2, 78.3, 63.6, 45.0, 36.0, 26.9, 26.8, 22.5, 10.82, 10.76 ppm. HRMS (ESI): calcd. for $C_{16}H_{23}$ $[M – OAllyl]^+$ 215.1794; found 215.1795.

General Procedure for the Ring-Closing Metathesis of the Dienes:[22] To a solution of diene (0.29 mmol) in dichloromethane (5 mL) was added Hoveyda–Grubbs second-generation catalyst (9.4 mg, 0.015 mmol, 0.05 equiv.), and the resulting mixture was stirred under nitrogen at room temperature for 2 h. The mixture was then concentrated in vacuo, and the crude product was purified by column chromatography (pentane/Et_2O 200:1) to afford five-membered ring **7** or **8**.

(*R*)-2-Isobutyl-2-methyl-2,5-dihydrofuran (7a): Colorless oil (35 mg, 85%). $[\alpha]_D^{20}$ = –7.5 (*c* = 1.13, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.71 (d, *J* = 6.0 Hz, 1 H), 5.64–5.63 (m, 1 H), 4.58–4.51 (m, 2 H), 1.63–1.55 (m, 1 H), 1.50–1.37 (m, 2 H), 1.19 (s, 3 H), 0.84–0.81 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.4, 124.9, 90.4, 74.1, 49.4, 34.1, 24.6, 24.4, 24.3 ppm. HRMS (ESI): calcd. for $C_9H_{17}O$ $[M + H]^+$ 141.1274; found 141.1276.

(*S*)-2-Isobutyl-2-phenyl-2,5-dihydrofuran (7b): Colorless oil (53 mg, 90%). $[\alpha]_D^{20}$ = –94.0 (*c* = 1.08, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 7.6 Hz, 2 H), 7.35–7.32 (m, 2 H), 7.26–7.21 (m, 1 H), 6.04–6.02 (m, 1 H), 5.86 (d, *J* = 6.0 Hz, 1 H), 4.82–4.78 (m, 1 H), 4.73–4.69 (m, 1 H), 1.89 (dd, *J* = 14.4, 5.6 Hz, 1 H), 1.80 (dd, *J* = 14.4, 6.0 Hz, 1 H), 1.73–1.67 (m, 1 H), 0.94 (d, *J* = 6.8 Hz, 3 H), 0.88 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.5, 133.4, 128.2, 126.4, 125.2, 124.7, 93.8, 74.7, 50.1, 24.6, 24.32, 24.29 ppm. HRMS (APCI): calcd. for $C_{14}H_{19}O$ $[M + H]^+$ 203.1430; found 203.1427.

(*R*)-2-(2-Ethylbutyl)-2-methyl-2,5-dihydrofuran (7c): Colorless oil (40 mg, 82%). $[\alpha]_D^{20}$ = –5.7 (*c* = 0.53, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.78 (d, *J* = 6.4 Hz, 1 H), 5.69 (d, *J* = 6.4 Hz, 1 H), 4.64–4.57 (m, 2 H), 1.57–1.52 (m, 1 H), 1.45 (dd, *J* = 14.4, 4.8 Hz, 1 H), 1.39–1.25 (m, 5 H), 1.26 (s, 3 H), 0.85–0.79 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.4, 125.0, 90.5, 74.3, 44.0, 36.7, 27.1, 26.8, 26.7, 10.82, 10.80 ppm. HRMS (ESI): calcd. for $C_{11}H_{21}O$ $[M + H]^+$ 169.1587; found 169.1583.

(*R*)-1-Methyl-2-cyclopenten-1-ol (8a):[15] Colorless oil (11 mg, 40%)*. $[\alpha]_D^{20}$ = +16.8 (*c* = 0.25, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.83–5.81 (m, 1 H), 5.70–5.69 (m, 1 H), 2.51–2.45 (m, 1 H), 2.35–2.29 (m, 1 H), 1.98–1.89 (m, 2 H), 1.68 (br s, 1 H), 1.38 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.9, 132.7, 83.4, 39.7, 31.1, 27.4 ppm. HRMS (ESI): calcd. for C_6H_9 $[M – OH]^+$ 81.0699; found 81.0695.

*This reaction gave full conversion to the desired product, but the yield was diminished because of the volatility of the product.

(*S*)-2-Methyl-1-phenyl-2-cyclopenten-1-ol (8b): Colorless oil (44 mg, 87%). $[\alpha]_D^{20}$ = +33.2 (*c* = 0.85, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.24 (m, 4 H), 7.18–7.15 (m, 1 H), 5.63 (d, *J* = 1.6 Hz, 1 H), 2.44–2.37 (m, 1 H), 2.33–2.25 (m, 2 H), 2.20–2.12 (m, 1 H), 1.86 (s, 1 H), 1.48–1.47 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.0, 144.0, 128.7, 128.1, 126.5, 124.8, 87.9, 43.4, 29.4, 11.9 ppm. HRMS (ESI): calcd. for $C_{12}H_{13}$ $[M – OH]^+$ 157.1012; found 157.1008.

α-Hydroxy Acids 9: Compound **9a**–**b** and **S9c** were prepared from **2a**–**b** and **2g** by following the literature procedure,[24] and **S9c** afforded **9b** by following a literature procedure.[23c] The absolute configurations of **9a** and **9b** were assigned on the basis of specific rotations reported in literatures.[23a,23b]

(*R*)-3-Hydroxy-5-methyl-3-phenyl-2-hexanone (S9c): Colorless oil (46 mg, 79%). $[\alpha]_D^{20}$ = –16.9 (*c* = 0.43, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.39 (m, 2 H), 7.30–7.26 (m, 2 H), 7.23–7.19 (m, 1 H), 4.46 (s, 1 H), 2.13–2.06 (m, 2 H), 2.04 (s, 3 H), 1.79–1.72 (m, 1 H), 0.90–0.85 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.9, 141.7, 128.5, 127.8, 126.1, 82.8, 44.9, 24.6, 24.2, 23.8, 23.7 ppm. HRMS (ESI): calcd. for $C_{13}H_{17}O$ $[M – OH]^+$ 189.1274; found 189.1268.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra for all compounds.

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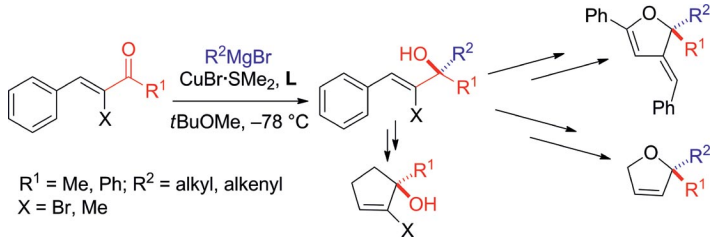

The copper-catalyzed 1,2-addition of Grignard reagents to enones, combined with Sonogashira coupling/cyclization or ring-closing metathesis, provides a new asymmetric synthesis of dihydrofurans and cyclopentenols. Two different kinds of dihydrofurans are obtained with medium-to-high enantioselectivities.

Keywords: Synthetic methods / Nucleophilic addition / Cyclization / Alcohols / Oxygen heterocycles

