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Copper-Catalyzed Enantioselective Conjugate Addition of Organometallic Reagents to Acyclic Dienones

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Abstract: The enantioselective, copper/phosphoramidite-catalyzed 1,4-addition of dialkylzinc reagents to acyclic dienones is described. The products of this reaction, obtained with enantioselectivities of up to 95%, can be further functionalized by a second conjugate addition, or employed in an enolate trapping, ring-closing metathesis protocol.

Keywords: conjugate addition; copper; dialkylzinc reagents; dienones; enantioselectivity; phosphoramidites

Introduction

The conjugate addition of organometallic reagents to α,β-unsaturated systems is an important transformation in synthetic organic chemistry.[1] Major efforts have been devoted in the past decade to the development of enantioselective copper-catalyzed conjugate additions.[2] Copper complexes based on chiral phosphoramidite ligands were established as versatile catalysts for promoting enantioselective 1,4-additions of dialkylzinc reagents to a range of enones.[3,4] Although subsequently a variety of other chiral ligands was introduced for this C–C bond formation,[2,5,6] acyclic α,β-unsaturated systems constitute a considerable challenge in order to obtain high enantioselectivities. Only recently, several structurally diverse chiral ligands were reported to be suitable for a number of important acyclic substrates.[6] Much less effort has been devoted to dienones, although they offer very interesting possibilities for further functionalization as the products of the conjugate addition still contain an enone moiety. So far, only enantioselective catalytic additions of organozinc reagents to cyclic dienones were reported and shown to provide versatile chiral synthons for natural product synthesis.[7] Here we report the first enantioselective Cu/phosphoramidite-catalyzed conjugate addition of organometallic reagents to readily accessible symmetrical acyclic dienones to provide optically active multi-functional building blocks.

Results and Discussion

As an initial model substrate, *trans,trans*-dibenzylideneacetone **1a** was employed. The addition of diethylzinc was catalyzed by an *in situ* prepared copper-phosphoramidite complex.

Previously, phosphoramidite ligands **(*S*,*R*,*R*)-L1** and **(*S*)-L5** were found to afford 75% and 83% *ee*, respectively, in the copper catalyzed Et_2Zn addition to chalcone.[8]

This prompted us to test several structurally related ligands **L1**–**L5**[9] using 5 mol% of catalyst and 2.0 equivalents of Et_2Zn (Figure 1). Yields and enantioselectivities of the product from this initial screening are summarized in Table 1.

With these reaction conditions, ligand **(*S*,*R*,*R*)-L1** afforded the product **2a** in 80% isolated yield and 90% enantioselectivity (Table 1). A slightly lower *ee* of 86% was achieved using **(*S*,*R*)-L2** in which the steric hindrance of the amine moiety has been reduced and a stereogenic center removed. Ligand **(*S*,*R*,*R*)-L3**, where a phenyl ring has been replaced by a naphthyl substituent, afforded the product with 80% *ee*. In comparison with **L3**, the removal of a

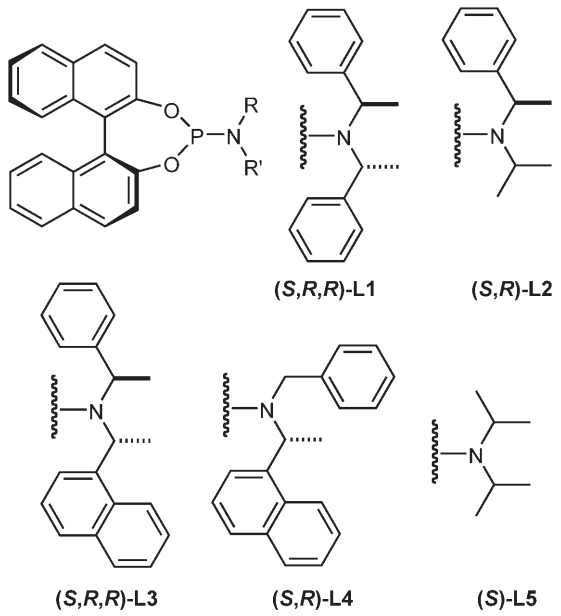
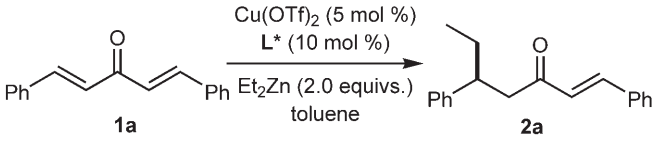


Figure 1. Phosphoramidite ligands.

Table 1. Ligand variation in the Cu-catalyzed conjugate addition of Et_2Zn to benzylideneacetone.[a]



Ligand	Isolated yield [%]	*ee* [%][b]
(*S*,*R*,*R*)-L1	80	90 (*S*)
(*S*,*R*)-L2	64	86 (*S*)
(*S*,*R*,*R*)-L3	69	80 (*S*)
(*S*,*R*)-L4	75	71 (*S*)
(*S*)-L5	60	84 (*S*)
(*R*,*R*,*R*)-L1	53	50 (*R*)

[a] *Reaction conditions:* dibenzylideneacetone (0.50 mmol), $Cu(OTf)_2$ (0.025 mmol), L (0.050 mmol), Et_2Zn (1.0 mmol), toluene (3 mL), −25 °C, 18 h.

[b] Enantioselectivities determined by HPLC on a Chiralpak AD column.

methyl group in ligand **(*S*,*R*)-L4** resulted in a further decrease in the enantioselecivity to 71%. Better results (84% *ee*) were achieved using ligand **(*S*)-L5** where the chirality is present only in the binaphthol part and the amine moiety is derived from diisopropylamine. The isolated product yields using the ligands **L2–L5** range between 60% and 75%. The use of the diastereoisomer **(*R*,*R*,*R*)-L1** afforded the product **2a** with low yield (53%) and enantioselectivity (50%) indicating a mismatch combination of the binaphthol and amine chiral moieties. Moreover, the formation of the opposite enantiomer of **2a** indicates that the binaphthol part determines the sign of the chiral induction.

Ligand **(*S*,*R*,*R*)-L1** proved to be the most efficient and the catalytic 1,4-addition based on this ligand was studied in further detail. The results are summarized in Table 2 and Table 3. Several dialkylzinc reagents were reacted with dibenzylideneacetone. The reaction with Me_2Zn turned out to be problematic due to the low reactivity of this reagent. Although the product was obtained with 95% *ee*, the yields were poor using several reaction conditions. It has been reported[10] that Me_3Al sometimes leads to higher yields than Me_2Zn, but in our case we could not improve the yield of the product **2b** significantly. A methyl substituent was successfully introduced, however, with MeMgBr using $CuBr{\cdot}SMe_2$ and *Josiphos* as chiral ligand using conditions recently published.[11] Addition of Et_2Zn and Bu_2Zn proceeded well and the corresponding products **2a** and **2d** were obtained in satisfactory yields and with high enantiomeric excess (Table 2). Addition of diisopropylzinc afforded product **2c** albeit with lower, 73%, *ee*.

It was possible to decrease the catalyst loading to 2 mol% and the amount of the organozinc reagent to 1.5 equivalents without affecting the enantioselectivity of the reaction, although a modest decrease of the isolated yield to 73% was observed (Table 3, entry 1). Similar results were obtained when the reaction was performed on a larger scale (Table 3, entry 2).

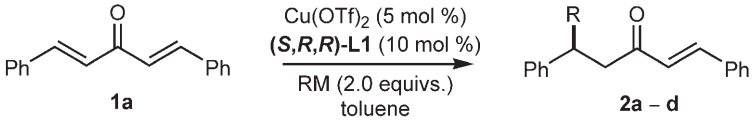
The scope of the reaction was explored further by performing the Et_2Zn addition on a series of substituted dienones **1b–h** (Table 3). The corresponding products **2e** and **2g**–l were obtained in good yields and with high enantiomeric excess.

The reaction of dienone **1b** with Et_2Zn affords product **2e** with a somewhat lower enantioselectivity of 77% (Table 3, entry 3), indicating the sensitivity to steric bulk near the β-carbon atom. The 34% *ee* obtained in the addition of *i*-Pr_2Zn to substrate **1b** is in agreement with these results.

Comparison of entries 5/6 and 7/8, where the dienones are substituted in *meta* and *para* positions, respectively, with electron-withdrawing and electron-donating groups, indicates that electronic effects do not play a major role. Slightly higher enantioselectivities were obtained with *para* substituted substrates. Good enantioselectivities were obtained with the dienones **1g** and **1h** (entries 9 and 10), although the corresponding products **2k** and **2l** were isolated in lower yields.

An interesting feature of this class of dienones is that the product of the conjugate addition reaction itself is an α,β-unsaturated system which allows one to perform a subsequent 1,4-addition reaction (Scheme 1). Enone **2a** (92% *ee*) was subjected to Et_2Zn addition under standard conditions. C_2-Sym-

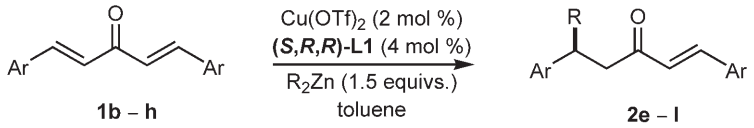
Table 2. Addition of organometallic reagents to dienone **1a** catalyzed by $Cu(OTf)_2$ and **(*S*,*R*,*R*)-L1**.



Entry	Dienone	RM	Product	Yield [%][a]	*ee* [%][b]
1	**1a**	Et_2Zn	**2a**	73	92 (*S*)
2	**1a**	Me_2Zn	**2b**	12	95 (*S*)
3	**1a**	Me_3Al[c]	**2b**	16	96 (*R*)
4	**1a**	MeMgBr[d]	**2b**	50	88 (*S*)
5	**1a**	*i*-Pr_2Zn	**2c**	60	73 (*S*)
6	**1a**	Bu_2Zn	**2d**	61	89 (*S*)

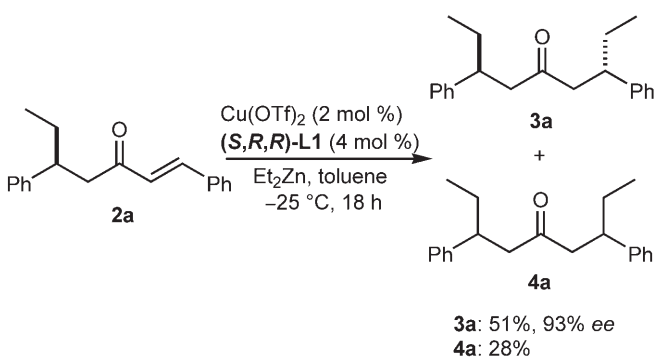
[a] Isolated yield of purified product.
[b] Determined by HPLC on a Chiralpak AD or a Chiralcel OD columns.
[c] Et_2O as solvent at −50 °C.
[d] $CuBr.SMe_2$ (5 mol %), (*R*,*S*)-Josiphos (6 mol %), MeMgBr (1.5 equivs.), BuOMe as solvent at −75 °C for 18 h.

Table 3. Addition of organozinc reagents to dienones **1b–h** catalyzed by $Cu(OTf)_2$ and **(*S*,*R*,*R*)-L1**.[a]



Entry	Dienone	Ar	R_2Zn	Product	Yield [%][b]	*ee* [%][c]
1	**1a**	C_6H_5	Et_2Zn	**2a**	73	92 (*S*)
2	**1a**[d]	C_6H_5	Et_2Zn	**2a**	75	92 (*S*)
3	**1b**	2-Cl-C_6H_4	Et_2Zn	**2e**	79	77 (*S*)
4	**1b**	2-Cl-C_6H_4	*i*-Pr_2Zn	**2f**	53	34 (*S*)
5	**1c**	3-Br-C_6H_4	Et_2Zn	**2g**	66	90 (*S*)
6	**1d**	3-Me-C_6H_4	Et_2Zn	**2h**	69	88 (*S*)
7	**1e**	4-Cl-C_6H_4	Et_2Zn	**2i**	71	95 (*S*)
8	**1f**	4-MeO-C_6H_4	Et_2Zn	**2j**	59	94 (*S*)
9	**1g**	2-thienyl	Et_2Zn	**2k**	48	87 (*S*)
10	**1h**	1-naphthyl	Et_2Zn	**2l**	53	93 (*S*)

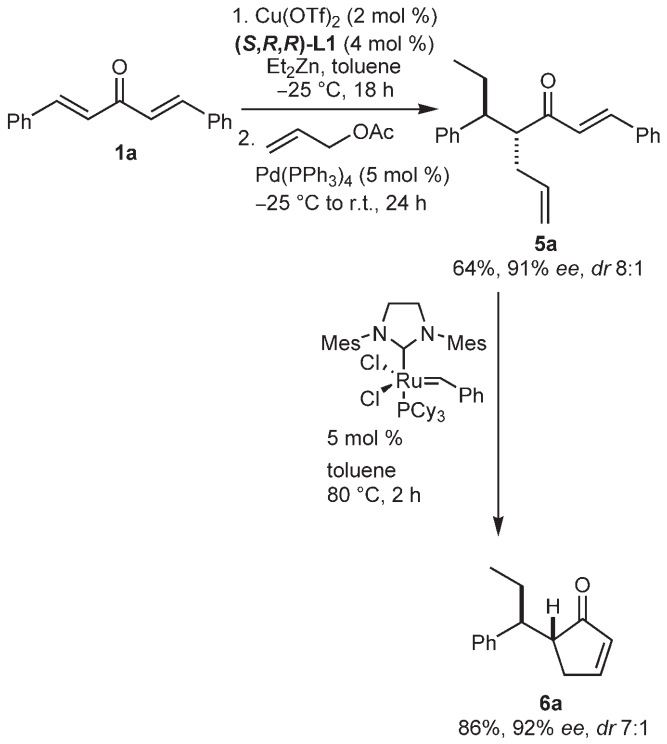
[a] Reaction conditions: dienone (0.50 mmol), $Cu(OTf)_2$ (0.010 mmol), **(*S*,*R*,*R*)-L1** (0.020 mmol), R_2Zn (0.75 mmol), toluene (3 mL), −25 °C, 18 h.
[b] Isolated yield of purified product.
[c] Enantioselectivities determined by HPLC on a Chiralpak AD column.
[d] Reaction carried out on a 4.27 mmol scale of dienone.



Scheme 1. Sequential conjugate addition.

metrical ketone **3a** was obtained with high enantiomeric excess (93 % *ee*). The diastereoselectivity of the reaction, however, was only modest because along with **3a** also 28 % of achiral *meso*-compound **4a** was obtained.

The fact that the initial products of the 1,4-addition of dialkylzinc reagents are zinc enolates and might be converted *in situ* in a tandem protocol, further broadens the possible scope and utility of the reaction. Accordingly, the enolate formed from Et_2Zn and dienone **1a** was trapped in a diastereoselective Pd-catalyzed allylation.[12] The resulting product **5a** was obtained with 91 % *ee* and high diastereoselectivity



Scheme 2. Tandem conjugate addition/allylation followed by RCM.

(*dr* = 8:1). The presence of two suitably located olefinic groups raised the possibility to apply a ring-closing metathesis (RCM). Indeed, with the second generation Grubbs' catalyst[13] a clean cyclization reaction was observed, affording cyclopentenone **6a** in 86% yield (Scheme 2).

Thus, a tandem 1,4-addition-allylation (Cu and Pd catalysis) followed by an RCM (Ru catalysis) gives access to optically active cyclopentenones with high diastereoselectivity and enantioselectivity.

Conclusions

In summary, we have demonstrated that the 1,4-addition of alkyl organometallic reagents to acyclic dienones proceeds in good yields and with high enantioselectivities. A subsequent conjugate addition is possible, albeit with modest diastereoselectivity. The potential of this class of substrates in conjugate additions is demonstrated with the combination of three sequential catalytic steps comprising tandem conjugate addition-allylation-RCM resulting in optically active cyclopentenones. This catalytic asymmetric C–C bond formation provides alternative opportunities in a concise route to cyclopentenoid natural products.

Experimental Section

General Methods

All reactions were performed in oven- or flame-dried glassware under inert atmosphere of N_2 or argon and conjugate additions were carried out using standard Schlenk techniques. Toluene, THF and ether were distilled from sodium. Dialkylzinc reagents: Me_2Zn (2 M in toluene), and *i*-Pr_2Zn (1 M in toluene) were purchased from Aldrich, Et_2Zn (1.1 M in toluene) and Bu_2Zn (1 M in heptane) were purchased from Fluka; MeMgBr (3 M in Et_2O) and Me_3Al (1 M in heptane) were purchased from Aldrich. *trans,trans*-Dibenzylideneacetone was purchased from Aldrich. Thin-layer chromatography (TLC) was performed on Merck silica gel 60 TLC-plates F254 and visualized using UV light or phosphomolybdic acid. Flash chromatography was carried out on silica gel (Aldrich, 230–400 mesh). ^{1}H NMR spectra were recorded at 300 or 400 MHz with $CDCl_3$ as solvent, ^{13}C NMR were obtained at 50, 75 or 100 MHz in $CDCl_3$ (Varian spectrometers). Chemical shifts were determined relative to the residual solvent peaks ($CHCl_3$, $\delta = 7.26$ ppm for hydrogen atoms, $\delta = 77.0$ for carbon atoms). Optical rotations were recorded on Schmidt-Haench Polartronic MH8 instrument at 589 nm. HPLC analyses were performed on Shimadzu LC-10 AD VP instrument equipped with 6 parallel normal phase chiral columns, using a diode array detector. Mass spectra were recorded on an AEI-MS-902 mass spectrometer. Absolute configurations were assigned on the basis of the facial selectivity observed with the same catalysts **(*S*,*R*,*R*)-L1** with chalcone.[8]

General Procedure for the Copper/Phosphoramidite Catalyzed Conjugate Addition of Dialkylzinc Reagents to Dienones

$Cu(OTf)_2$ (3.6 mg, 0.010 mmol) and ligand **(*S*,*R*,*R*)-L1** (10.8 mg, 0.020 mmol) were dissolved in anhydrous toluene (3 mL) and stirred for 40 min at room temperature. The substrate (0.50 mmol) was added to this solution and the mixture was cooled to −25 °C. A solution of a R_2Zn (0.75 mmol) was added dropwise and the reaction mixture was stirred for 18 h at −25 °C, then quenched with saturated aqueous NH_4Cl and extracted with AcOEt (3×). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography.

1,4-Additions Products

(*S*)-*E*-1,5-Diphenylhept-1-en-3-one (2a): The crude product was purified by flash chromatography (heptane/AcOEt = 97:3) to give pure **2a** in 73% yield as a white solid, mp 78–79 °C (lit.[14] mp 87 °C). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.81$ (t, $J = 7.3$ Hz, 3H), 1.58–1.77 (m, 2H); 2.95 (m, 2H), 3.14 (m, 1H), 6.65 (d, $J = 16.5$ Hz, 1H), 7.16–7.50 (m, 11H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 12.0$, 29.2, 43.3, 48.0, 126.3, 126.5, 127.6, 128.2, 128.4, 128.9, 130.4, 134.5, 142.5, 144.5, 199.3; HR-MS: calcd. for $C_{19}H_{20}O$: 264.1514, found: 264.1516; HPLC on Chiralpak AD column (heptane/propan-2-ol = 96:4, flow = 1.0 mL min^{-1}): t_R 7.56 min (minor), t_R 8.62 min (major); $[\alpha]_D$: +34.0 (*c* 0.50, $CHCl_3$),

90% *ee*; anal. calcd. for $C_{19}H_{20}O$: C 86.32, H 7.63; found: C 86.30, H 7.62.

(*S*)-*E*-1,5-Diphenylhex-1-en-3-one (2b): The crude product was purified by flash chromatography (heptane/AcOEt = 97:3) to give pure **2b** as a white solid, mp 66–68 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (d, *J* = 7.0 Hz, 3H), 2.85–3.03 (m, 2H), 3.43 (q, *J* = 7.3 Hz, 1H), 6.69 (d, *J* = 16.1 Hz, 1H), 7.18–7.53 (m, 11H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.8, 35.8, 49.3, 126.3, 126.4, 126.8, 128.2, 128.5, 128.9, 130.4, 134.5, 142.6, 146.4, 199.1; HR-MS: calcd. for $C_{18}H_{18}O$: 250.1358, found: 250.1368; HPLC on Chiralpak AD column (heptane/propan-2-ol = 96:4, flow = 1.0 mL min^{-1}): t_R 7.52 min (minor), t_R 8.37 min (major); $[\alpha]_D$: +20.5 (*c* 0.20, $CHCl_3$), 95% *ee*.

(*S*)-*E*-1,5-Diphenyl-6-methylhept-1-en-3-one (2c): The crude product, obtained by the general procedure, was purified by flash chromatography (heptane/AcOEt = 97:3) to give pure **2c** in 60% yield as a white solid, mp 97–98 °C (lit.[15] mp 95 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.80 (d, *J* = 6.6 Hz, 3H), 1.00 (d, *J* = 6.6 Hz, 3H), 1.93 (m, 1H), 3.07 (m, 3H), 6.64 (d, *J* = 16.1 Hz, 1H), 7.16–7.50 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3, 20.9, 33.3, 45.1, 48.2, 126.2, 126.3, 128.1, 128.2, 128.3, 128.9, 130.3, 134.5, 142.2, 143.4, 226.3; HR-MS: calcd. for $C_{20}H_{22}O$: 278.1671, found: 278.1673; HPLC on Chiralpak AD column (heptane/propan-2-ol = 96:4, flow = 1.0 mL min^{-1}): t_R 7.76 min (minor), t_R 8.66 min (major); $[\alpha]_D$: +13.2 (*c* 0.50, $CHCl_3$), 73% *ee*.

(*S*)-*E*-1,5-Diphenylnon-1-en-3-one (2d): The crude product was purified by flash chromatography (heptane/AcOEt = 97:3) to give pure **2d** in 61% yield as a white solid, mp 89–90 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 7.0 Hz, 3H), 1.10–1.31 (m, 4H), 1.62–1.71 (m, 2H), 2.94 (dd, *J* = 7.0, 2.9 Hz, 2H), 3.23 (m, 1H), 6.64 (d, *J* = 16.1 Hz, 1H), 7.18–7.50 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 22.6, 29.7, 36.0, 41.6, 48.4, 126.3, 126.5, 127.6, 128.2, 128.4, 128.9, 130.4, 134.5, 142.5, 144.8, 199.3; anal. calcd. for $C_{21}H_{24}O$ (292.4): C 86.26, H 8.27; found: C 85.90, H 8.30; HR-MS calcd. for $C_{21}H_{24}O$: 292.1827, found: 292.1819; HPLC on Chiralpak AD column (heptane/propan-2-ol = 96:4, flow = 1.0 mL min^{-1}): t_R 6.88 min (minor), t_R 7.55 min (major); $[\alpha]_D$: +15.7 (*c* 0.37, $CHCl_3$), 89% *ee*; anal. calcd for $C_{21}H_{24}O$: C 86.26, H 8.27; found: C 85.90, H 8.30.

(*S*)-*E*-1,5-Bis-(2-chlorophenyl)-hept-1-en-3-one (2e): The crude product was purified by flash chromatography (heptane/AcOEt = 97:3) to give pure **2e** in 76% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (t, *J* = 7.3 Hz, 3H), 1.77 (m, 2H), 3.00 (m, 2H), 3.80 (m, 1H), 6.66 (d, *J* = 16.1 Hz, 1H), 7.10–7.43 (m, 7H), 7.58 (m, 1H), 7.93 (d, *J* = 16.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.8, 28.0, 39.0, 46.5, 127.0, 127.1, 127.4, 127.5, 127.9, 128.6, 129.7, 130.2, 131.1, 132.8, 134.3, 135.2, 138.4, 141.4, 198.6; MS (EI): calcd. for $C_{19}H_{18}Cl_2O$: 332, found: 332 (it was not possible to obtain an exact mass); HPLC on Chiralpak AD column (heptane/propan-2-ol = 97:3, flow = 1.0 mL min^{-1}): t_R 7.22 min (minor), t_R 7.78 min (major); $[\alpha]_D$: +35.5 (*c* 0.80, $CHCl_3$), 78% *ee*.

(*S*)-*E*-1,5-Bis-(2-chlorophenyl)-6-methylhept-1-en-3-one (2f): The crude product was purified by flash chromatography (heptane/AcOEt = 97:3) to give pure **2f** in 53% yield as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.6 Hz, 3H), 1.03 (d, *J* = 6.6 Hz, 3H), 2.00 (m, 1H), 3.04 (m, 2H), 3.68 (m, 1H), 6.61 (d, *J* = 16.1 Hz, 1H), 7.07–7.57 (m, 8H), 7.87 (d, *J* = 16.1 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): d = 20.2, 20.7, 33.2, 43.9, 126.7, 127.0, 127.3, 127.5, 128.3, 128.6, 129.7, 130.1, 131.1, 132.8, 135.2, 138.2, 141.1, 198.9; MS (CI): calcd. for $C_{20}H_{21}Cl_2O$ (MH^+): 347, found 347; calcd. for ($M+NH_4^+$): 364, found: 364; (it was not possible to obtain an exact mass); HPLC on Chiralpak AD column (heptane/propan-2-ol = 96:4, flow = 1.0 mL min^{-1}): t_R 6.59 min (minor), t_R 6.99 min (major); $[\alpha]_D$: −6.2 (*c* 0.50, $CHCl_3$), 34% *ee*.

(*S*)-*E*-1,5-Bis-(3-bromophenyl)-hept-1-en-3-one (2g): The crude product was purified by flash chromatography (heptane/AcOEt = 97:3 → 95:5) to give pure **2g** in 66% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81 (t, *J* = 7.3 Hz, 3H), 1.60–1.74 (m, 2H), 2.93 (d, *J* = 7.0 Hz, 2H), 3.11 (m, 1H), 6.63 (d, *J* = 16.1 Hz, 1H), 7.15–7.64 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.0, 29.1, 42.8, 47.9, 123.0, 126.5, 126.9, 127.3, 127.9, 129.5, 130.0, 130.4, 130.5, 130.8, 133.2, 136.5, 140.8, 146.9, 198.2; HR-MS: calcd. for $C_{19}H_{18}Br_2O$: 419.9724, found: 419.9755; HPLC on Chiralcel OD column (heptane/propan-2-ol = 99:1, flow = 1.0 mL min^{-1}): t_R 23.0 min (minor), t_R 26.0 min (major); $[\alpha]_D$: +3.1 (*c* 0.32, $CHCl_3$), 90% *ee*.

(*S*)-*E*-1,5-Bis-(3-methylphenyl)-hept-1-en-3-one (2h): The crude product was purified by flash chromatography (heptane/AcOEt = 97:3 → 95:5) to give pure **2h** in 69% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): d = 0.80 (t, *J* = 7.3 Hz, 3H), 1.59–1.77 (m, 2H), 2.33 (s, 3H), 2.36 (s, 3H), 2.93 (d, *J* = 7.0 Hz, 2H), 3.11 (m, 1H), 6.64 (d, *J* = 16.5 Hz, 1H), 6.99–7.30 (m, 8H), 7.44 (d, *J* = 16.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.1, 21.3, 21.5, 29.1, 43.2, 48.0, 124.6, 125.4, 126.3, 127.0, 128.2, 128.4, 128.7, 128.8, 131.2, 134.4, 137.8, 138.5, 142.6, 144.5, 199.4; HR-MS: calcd. for $C_{21}H_{24}O$: 292.1827, found: 292.1823; HPLC on Chiralpak AD column (heptane/propan-2-ol = 98:2, flow = 1.0 mL min^{-1}): t_R 7.50 min (minor), t_R 7.98 min (major); $[\alpha]_D$: +31.3 (*c* 0.61, $CHCl_3$), 88% *ee*.

(*S*)-*E*-1,5-Bis-(4-chlorophenyl)-hept-1-en-3-one (2i): The crude product was purified by flash chromatography (heptane/AcOEt = 97:3) to give pure **2i** in 71% yield as a white solid, mp 76–77 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.80 (t, *J* = 7.3 Hz, 3H), 1.54–1.77 (m, 2H), 2.92 (d, *J* = 7.3 Hz, 2H), 3.13 (m, 1H), 6.60 (d, *J* = 16.1 Hz, 1H), 7.14 (d, *J* = 8.1 Hz, 2H), 7.24–7.43 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.0, 29.2, 42.5, 48.0, 126.6, 128.5, 129.0, 129.2, 129.4, 131.9, 132.9, 136.4, 141.1, 142.9, 198.5; anal. calcd. for $C_{19}H_{18}Cl_2O$ (333.3): C 68.48, H 5.44; found: C 68.40, H 5.52; HR-MS: calcd. for $C_{19}H_{18}Cl_2O$: 332.0735, found: 332.0729; HPLC on Chiralpak AD column (heptane/propan-2-ol = 95:5, flow = 1.0 mL min^{-1}): t_R 9.94 min (minor), t_R 13.71 min (major); $[\alpha]_D$: +33.9 (*c* 0.75, $CHCl_3$), 95% *ee*; anal. calcd. for $C_{19}H_{18}Cl_2O$: C 68.48, H 5.44; found: C 68.40, H 5.51.

(*S*)-*E*-1,5-Bis-(4-methoxyphenyl)-hept-1-en-3-one (2j): The crude product was purified by flash chromatography (heptane/AcOEt = 95:5 → 80:20) to give pure **2j** in 59% yield as a white solid, mp 84–86 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.79 (t, *J* = 7.3 Hz, 3H), 1.56–1.76 (m, 2H), 2.89 (d, *J* = 7.0 Hz, 2H), 3.09 (m, 1H), 3.77 (s, 3H), 3.84 (s, 3H), 6.53 (d, *J* = 16.1 Hz, 1H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 16.5 Hz, 1H), 7.44 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.0, 29.3, 42.6, 48.1, 55.1, 55.3, 113.7, 114.3, 124.3, 127.1,

128.5, 129.9, 136.6, 142.2, 157.9, 161.5, 199.4; HR-MS: calcd. for $C_{21}H_{24}O_3$: 324.1725, found: 324.1724; HPLC on Chiralpak AD column (heptane/propan-2-ol = 92:8, flow = 1.0 mL min^{-1}): t_R 12.26 min (minor), t_R 16.46 min (major); $[\alpha]_D$: +17.6 (*c* 0.50, $CHCl_3$), 94% *ee*; anal. calcd. for $C_{21}H_{24}O_3$: C 77.75, H 7.46; found: C 77.44, H 7.43.

(*S*)-*E*-1,5-Dithiophene-2-yl-hept-1-en-3-one (2k): The crude product was purified by flash chromatography (heptane/AcOEt = 97:3→95:5) to give pure **2k** in 48% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.80 (t, *J* = 7.3 Hz, 3H), 1.62–1.82 (m, 2H), 2.94 (m, 2H), 3.51 (m, 1H), 6.49 (d, *J* = 15.7 Hz, 1H), 6.83–7.07 (m, 3H), 7.13 (d, *J* = 5.1 Hz, 1H), 7.27 (m, 1H), 7.39 (d, *J* = 4.8 Hz, 1H), 7.62 (d, *J* = 15.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.9, 30.3, 38.5, 48.7, 122.9, 124.1, 125.0, 126.5, 128.2, 128.8, 131.7, 135.1, 139.8, 148.4, 198.1; HR-MS: calcd. for $C_{15}H_{16}OS_2$: 276.0643, found: 276.0659; HPLC on Chiralpak AD column (heptane/propan-2-ol = 96:4, flow = 1.0 mL min^{-1}): t_R 8.16 min (minor), t_R 9.32 min (major); $[\alpha]_D$: +5.6 (*c* 0.61, $CHCl_3$), 87% *ee*.

(*S*)-*E*-1,5-Dinaphthalene-1-yl-hept-1-en-3-one (2l): The crude product was purified by flash chromatography (heptane/AcOEt = 97:3→95:5) to give pure **2l** in 53% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.3 Hz, 3H), 1.97 (m, 2H), 3.18 (d, *J* = 6.6 Hz, 2H), 4.23 (m, 1H), 6.77 (d, *J* = 15.8 Hz, 1H), 7.43–8.34 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.0, 28.7, 48.0, 123.2, 123.3, 125.0, 125.35, 125.41, 126.0, 126.2, 126.75, 126.8, 128.7, 128.8, 128.9, 130.6, 131.5, 131.8, 132.0, 133.6, 134.0, 139.3, 140.7, 199.1; HR-MS: calcd. for $C_{27}H_{24}O$: 364.1827, found: 364.1831; HPLC on Chiralcel OD column (heptane/propan-2-ol = 95:5, flow = 1.0 mL min^{-1}): t_R 23.19 min (minor), t_R 26.30 min (major); $[\alpha]_D$: +90.6 (*c* 0.88, $CHCl_3$), 93% *ee*.

(*S,S*)-3,7-Diphenyl-nonan-5-one (3a/4a): The crude product was purified by flash chromatography (heptane/AcOEt = 98:2) to give pure **3** (the diastereoisomers could not be separated) in 51% yield as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) (signals for the *meso* compound **4a** are in italics): d = 0.71 (t, *J* = 7.3 Hz, 6H), *0.73* (t, *J* = 7.3 Hz), 1.45–1.57 (m, 4H), 2.48–2.66 (m, 4H), 2.97 (m, 2H), 7.09–7.30 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.9, *11.91*, 29.1, *42.55*, 42.6, *50.2*, 50.4,126.2, *127.46*, 127.5, 128.3, 144.4, 209.0; HR-MS: calcd. for $C_{21}H_{26}O$: 294.1984, found: 294.1987; HPLC on Chiralpak AD column (heptane/propan-2-ol = 99:1, flow = 1.0 mL min^{-1}): t_R 6.01 min (minor), t_R 6.72 min (*meso*), 8.53 min (major); $[\alpha]_D$: −40.1 (*c* 0.85, $CHCl_3$), 93% *ee*, **3a**/**4a** = 72:28.

(*4R,5S*)-1-Phenyl-4-(1-phenylpropyl)-hepta-1,6-dien-3-one (5a)

$Cu(OTf)_2$ (3.6 mg, 0.010 mmol) and **(*S,R,R*)-L1** (10.8 mg, 0.020 mmol) were dissolved in anhydrous toluene (3 mL) and stirred 40 min at room temperature. Dibenzylideneacetone (117 mg, 0.50 mmol) was added and the resulting yellow solution was cooled to −25 °C. Et_2Zn (1.1 M in toluene, 0.68 mL, 0.75 mmol) was added and the reaction mixture was stirred for 18 h at −25 °C. Subsequently a solution of $Pd(PPh_3)_4$ (87 mg, 0.075 mmol) and allyl acetate (0.16 mL, 150 mg, 1.5 mmol) in toluene (3 mL), was added and the mixture was stirred for 24 h allowing the temperature to rise gradually to room temperature. The reaction mixture was treated with saturated aqueous NH_4Cl solution and extracted with AcOEt (3×). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (heptane/AcOEt = 98:2) to give pure **5a** in 64% yield as a slightly yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): d = 0.65 (t, *J* = 7.3 Hz, 3H), 1.52–1.69 (m, 2H), 2.00 (m, 1H), 2.21 (m, 1H), 2.82 (dt, *J* = 10.6, 3.7 Hz, 1H), 3.17 (dt, *J* = 10.3, 4.0 Hz, 1H), 4.85 (m, 2H), 5.58 (m, 1H), 6.85 (d, *J* = 16.1 Hz, 1H), 7.12–7.65 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.2, 27.4, 35.7, 50.1, 56.2, 116.6, 126.5, 126.6, 128.2, 128.4, 128.7, 128.9, 130.5, 134.6, 135.3, 142.3, 142.7, 203.3; HR-MS: calcd. for $C_{22}H_{24}O$: 304.1827, found: 304.1833; HPLC on Chiralpak AD column (heptane/propan-2-ol = 98:2, flow = 1.0 mL min^{-1}): t_R 7.37 min (major), t_R 8.03 min (minor), 8.80 min (minor diastereoisomer); $[\alpha]_D$: +24.7 (*c* 0.76, $CHCl_3$), 91% *ee*, *dr* 8:1.

(*5R,1′S*)-5-(1-Phenylpropyl)-cyclopent-2-enone (6a)

Grubbs' 2nd generation catalyst[13] (17 mg, 0.020 mmol) was dissolved in toluene (5 mL) and to this solution diene **5a** (122 mg, 0.40 mmol) in toluene (5 mL) was added. The resulting red-brown solution was stirred for 2 h at 80 °C. After cooling, solvent was evaporated and the residue was purified by flash chromatography (heptane/AcOEt = 95:5) to afford 69 mg (86%) of pure **6a** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) (signals for the minor diastereoisomer are in italics): δ = *0.79* (t, *J* = 7.3 Hz), 0.85 (t, *J* = 7.3 Hz, 3H), 1.81 (m, 1H), 2.02 (m, 1H), 2.39 (m, 1H), 2.63 (m, 2H), 3.05 (m, 1H), *3.15* (m), 6.00 (m, 1H), *6.17* (m), 7.12–7.28 (m, 5H), 7.46 (m, 1H), *7.64* (m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1, *12.4*, *22.7*, 26.1, *32.1*, 32.5, 47.4, 49.3, *50.9*, 126.4, 128.0, 128.1, *128.4*, 128.6, 134.1, *134.6*, *141.2*, 163.6, *163.9*, 211.6; HR-MS: calcd. for $C_{14}H_{16}O$: 200.1201, found: 200.1210; HPLC on Chiralpak AD column (heptane/propan-2-ol = 99.5:0.5, flow = 1.0 mL min^{-1}): t_R 11.25 min (minor), t_R 13.90 min (major), 16.61 min (minor diastereoisomer). $[\alpha]_D$: −127.7 (*c* 0.73, $CHCl_3$), 92% *ee*, *dr* 7:1.

Supporting Information

Synthesis and NMR data of the starting materials are available as supporting information.

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