Synthesis E. Rideau et al. Special Topic

Asymmetric Conjugate Addition of Alkylzirconocenes to Cyclopent-4-ene-1,3-dione Monoacetals

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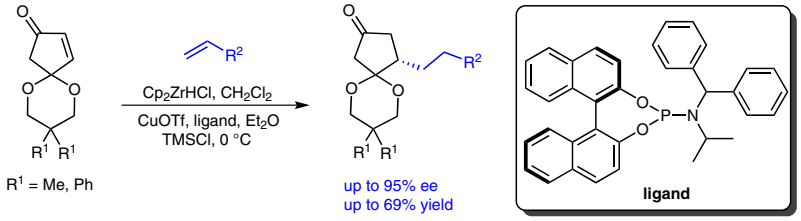

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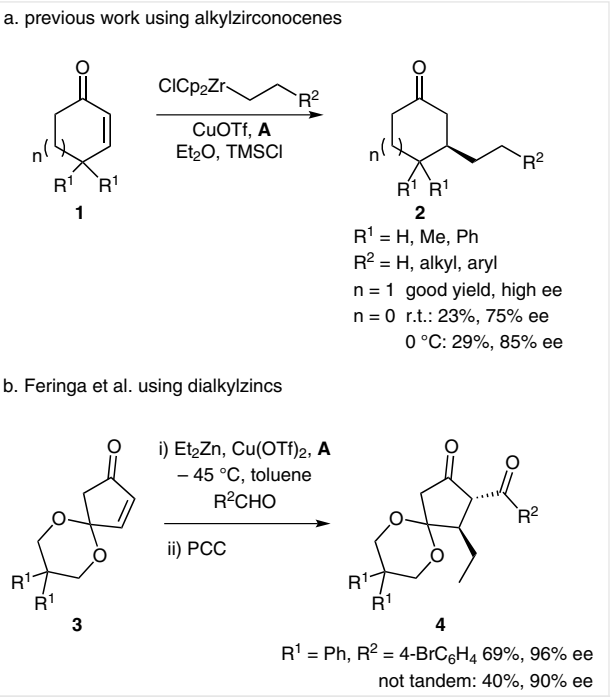
Abstract Copper-catalyzed asymmetric conjugate additions are powerful reactions that allow the formation of single-enantiomer building blocks in a few steps. However, highly enantioselective conjugate addition to five-membered-ring substrates is more challenging and is often neglected. Here, we report catalytic asymmetric 1,4-addition of alkylzirconocenes, formed in situ from readily available alkenes, to cyclopent-4-ene-1,3-dione monoacetals. Good to high enantioselectivities are observed and the procedure tolerates various functional groups.

Key words addition reactions, copper, asymmetric catalysis, organometallic reagents, acetals

The asymmetric conjugate addition of organometallic nucleophiles is a useful reaction for forming new C–C bonds enantioselectively.[1] Many methods have been developed, and these are finding use in a variety of applications.[1] However, cyclopent-2-en-1-one is a notoriously difficult substrate, and methods for its use in asymmetric addition are underdeveloped. Typically, methods that permit successful additions to cyclohex-2-en-1-one or cyclohept-2-en-1-one fail to give acceptable yields and enantioselectivities with cyclopent-2-en-1-one.[2] This observation has been attributed to the high reactivity and relative flatness of cyclopent-2-en-1-ones.[1e,3] Nevertheless, the asymmetric conjugate addition of cyclopent-2-en-1-ones is desirable and is a key step in several syntheses of natural products or biologically active molecules.[4]

We have previously developed methods that use alkylzirconium reagents as nucleophiles in asymmetric conjugate additions and allylic alkylation reactions.[5] Asymmetric conjugate additions to six-membered rings **1** (n = 1) give good yields and high enantioselectivities (Scheme 1, a).[5a,b] However, cyclopent-2-en-1-ones **1** (n = 0) are problematic substrates and give both lower yields and enantiomeric excesses. In the formation of ketone **2** (R^1 = H; R^2 = CH_2CH_2Ph; n = 0), only a 23% yield and 75% ee were obtained, and the results were only slightly improved on performing the reaction at 0 °C.



Scheme 1 Previous work

Feringa and co-workers reported asymmetric conjugate additions of dialkylzinc reagents to cyclopent-4-ene-1,3-dione monoacetals **3** (Scheme 1, b).[4d,6] A moderate yields and high enantiomeric excess of **4** (R^1 = Ph; R^2 = 4-BrC_6H_4) were obtained at –45 °C, but the yield was significantly improved (to 69%) when the enolate that formed was trapped in situ with an aldehyde. This trapping procedure prevents nucleophilic attack by the intermediate enolate on the unreacted enone starting material **3**, which would otherwise lower

the yield of the reaction, and it allows the formation of three stereogenic centers in one step. Because a mixture of isomers was obtained at the center bearing the hydroxy group, pyridinium chlorochromate was used to oxidize the aldol product to give the diketone **4**.

We had previously observed that asymmetric conjugate addition to sterically bulky derivatives of cyclohex-2-en-1-one gave higher isolated yields than additions to cyclohex-2-en-1-one itself[5a] and, inspired by the work described above,[4d,6] we decided to examine Feringa's cyclopent-4-ene-1,3-dione monoacetals with our method. The presence of the acetal alters the steric properties of the cyclopentenone and provides extensive opportunities for further derivatization of the products for applications in synthesis.

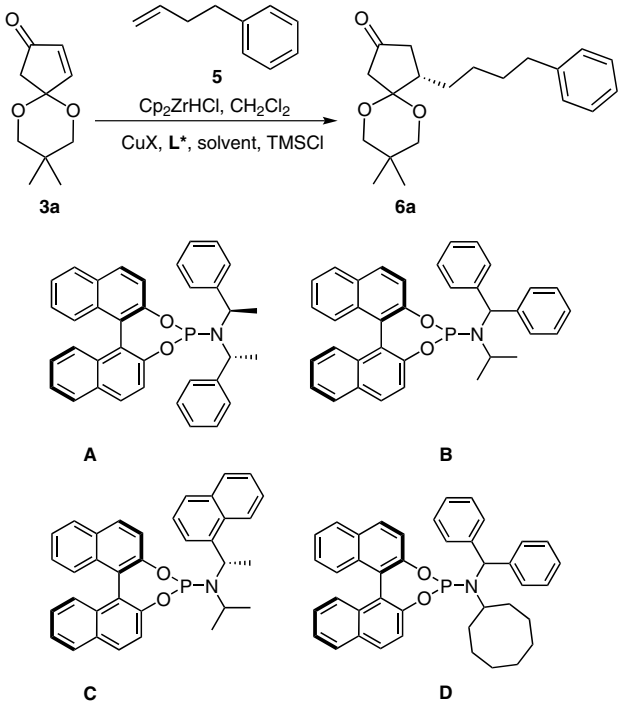
First, we examined the in situ hydrometalation and asymmetric conjugate addition of but-3-en-1-ylbenzene (**5**) to enone **3a** (Table 1). Subtle variations in the amine moiety of the phosphoramidite ligand proved important. Structural isomers **A** and **B** gave similar results (80% and 84% ee, respectively; Table 1, entries 1 and 2a). On the other hand, **C** and **D**, which are close relatives of **A** and **B**, gave poorer enantioselectivities (54% and 68% ee, respectively; entries 3 and 4). At this stage, lowering the temperature lowered the resulting ee (78% ee; entry 2b).

When we explored various counterions to the copper (Table 1, entries 5–7), it became clear that the initial triflate salt [from $(CuOTf)_2$·PhH] gave the highest enantiomeric excess and yield. Increasing the catalyst loading to 20% improved the enantioselectivity to 87% ee. As a solvent, diethyl ether gave the best results. Other solvents (entries 9–12) were detrimental to yields, although good enantiomeric excesses were obtained in dichloromethane, methyl *tert*-butyl ether, or toluene (81%, 85%, and 94% ee, respectively). The role of trimethylsilyl chloride is unclear, but it increases the enantioselectivity in these reactions (compare entries 8a to 8b and 10a to 10b), especially in diethyl ether (87% versus 33% ee), but it did not affect the yield.

These studies allowed us to achieve a good enantioselectivity (87% ee), but the yield was poor. We therefore went on to examine more subtle differences in the system that might lead to improved yields (Table 2). Conducting the reaction on cyclopent-4-ene-1,3-dione monoacetal **3b** (Table 2, entry 2) improved the ee to 90%, but gave a similar yield (43%). Increasing the amount of zirconocene nucleophile used (entries 3 and 4) improved the yield moderately (46%), and the ee remained unchanged. At this stage, a slight excess of ligand over copper (entry 3b) lowered both the ee and yield.

Interestingly, the use of a pre-prepared copper complex[5c] gave better results. A procedure involving mixing the copper and ligand in situ gave a lower yield (34%), while the ee was almost unchanged (85% ee; Table 2, entry 3c). This finding raised questions on the effect of isolating the copper complex and the difficulties associated with handling bis(copper(I) trifluoromethanesulfonate) benzene complex in air.[5a] Our self-prepared bis(acetonitrile)copper(I) trifluoromethanesulfonate complex as well as copper(I) triflate generated by metathesis of commercial copper(I) chloride and silver triflate were tested. The use of bis(acetoni-

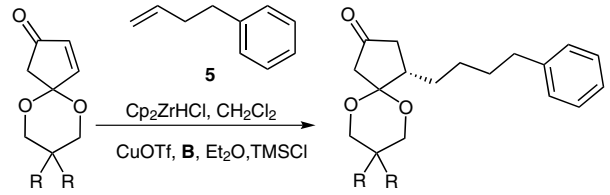
Table 1 Initial Screening[a]



Entry	Catalyst	Amount (mol%)	Ligand	Solvent	Yield[b] (%)	ee[c] (%)
1	$(CuOTf)_2$·PhH	10	**A**	Et_2O	41	80
2a	$(CuOTf)_2$·PhH	10	**B**	Et_2O	31	84
2b[d]					–	78
3	$(CuOTf)_2$·PhH	10	**C**	Et_2O	–	54
4	$(CuOTf)_2$·PhH	10	**D**	Et_2O	–	68
5	$CuNTf_2$ (Ag)	10	**B**	Et_2O	7	65
6	$CuClO_4$ (Ag)	10	**B**	Et_2O	28	73
7	$Cu(OTf)_2$	20	**B**	Et_2O	25	60
8a	$(CuOTf)_2$·PhH	20	**B**	Et_2O	~40	87
8b[e]					~40	33
9	$(CuOTf)_2$·PhH	20	**B**	CH_2Cl_2	~20	81
10a	$(CuOTf)_2$·PhH	20	**B**	MTBE	~20	85
10b[e]					~20	70
11	$(CuOTf)_2$·PhH	20	**B**	THF	–	–
12	$(CuOTf)_2$·PhH	20	**B**	toluene	traces	94

[a] Reaction conditions: but-3-en-1-ylbenzene (2.5 equiv), Cp_2ZrHCl (2.0 equiv), CH_2Cl_2 (0.2 mL), 8,8-dimethyl-6,10-dioxaspiro[4.5]dec-3-en-2-one (1.0 equiv), Cu**L*** complex, TMSCl (5.0 equiv), solvent (2.0 mL), r.t.,
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] The reaction was performed at 0 °C.
[e] The reaction was performed without TMSCl. For detailed information on the procedures, see the Supporting Information.

Table 2 Improving the Yield[a]



3a R = Me
3b R = Ph

6a R = Me
7a R = Ph

Entry	R	Cu	Zr (equiv)	**B** (equiv)	Yield[b] (%)	ee[c] (%)
1	Me	$(CuOTf)_2$·PhH[d]	2.0	0.20	~40	87
2	Ph	$(CuOTf)_2$·PhH[d]	2.0	0.20	43	90
3a	Me	$(CuOTf)_2$·PhH[d]	3.0	0.20	46	87
3b				0.22	42	83
3c[e]				0.20	34	85
4	Ph	$(CuOTf)_2$·PhH[d]	3.0	0.20	–	90
5	Me	$Cu(MeCN)_2OTf$[d]	3.0	0.22	53	73
6a	Me	CuOTf[f]	3.0	0.20	41	88
6b		CuOTf[f,g]			27	86
6c		CuOTf[f,h]			29	86
7	Me	CuOTf[f]	3.0	0.22	48	86
8	Me	CuOTf[f]	3.0	0.30	49	86
9	Me	CuOTf[f]	3.0	0.40	47	86
10a[i]	Ph	CuOTf[f]	3.0	0.22	50	87
10b[j]					37	87
10c[k]					54	90
10d[k,l]					61	92

[a] Reaction conditions: but-3-en-1-ylbenzene (**5**; 2.5 or 3.5 equiv), Cp_2ZrHCl, CH_2Cl_2 (0.2 mL), cyclopent-4-en-1,3-dione monoacetal **3** (1.0 equiv), Cu (20 mol%), ligand **B**, TMSCl (5.0 equiv), Et_2O (2.2 mL), r.t.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] Reaction performed using a preprepared Cu**L*** complex.
[e] Reaction performed using Cu**L*** prepared in situ.
[f] Reaction performed using Cu**L*** prepared in situ from CuCl (20 mol%), AgOTf (20 mol%), and **B**, and filtered.
[g] As above, without filtration.
[h] Reaction performed by using CH_2Cl_2 to prepare Cu**L***, with subsequent filtration, solvent removal, and addition of Et_2O.
[i] Reaction performed in Et_2O (2 mL).
[j] Reaction performed in Et_2O (1 mL).
[k] Reaction performed in Et_2O (3 mL).
[l] Reaction performed at 0 °C. For more information on the procedures see the Supporting Information.

trile)copper(I) triflate with an excess of ligand (entry 5) improved the yield (53%), but at the expense of enantioselectivity, which fell to 73% ee. The use of copper(I) triflate prepared from silver triflate gave the same results as bis(copper(I) trifluoromethanesulfonate) benzene complex, but the former system was operationally more convenient and gave more-reproducible results, so further experiments were carried out by using this procedure. When copper(I) triflate was synthesized in this way, the silver chloride was removed by filtration. We considered that this procedure might also remove some of the catalyst complex. However, not removing the silver chloride by filtration or changing the solvent, lowered the yield (27% and 29%, respectively, entries 7b and 7c) without affecting the ee. We found that the use of a slight excess of ligand over copper (1.1:1) improved the yield to ~48% (entry 7) but further additional ligand did not lead to any improvement (entries 7–9). The yields and ee obtained from cyclopent-4-en-1,3-dione monoacetal **3b** (entry 10a) were similar to those obtained with monoacetal **3a**. Finally, we examined the effect of the concentration. Increasing the concentration lowered the yield (37%, entry 10b), whereas diluting the mixture improved the enantioselectivity to 90% ee (entry 10c). At this concentration, lowering the temperature to 0 °C improved the results (61% yield, 92% ee).

We next examined the addition of various alkylzirconocene species to Feringa's cyclopentenone derivative **3b** at both room temperature and 0 °C (Figure 1). Nonfunctionalized and functionalized alkenes both gave moderate to

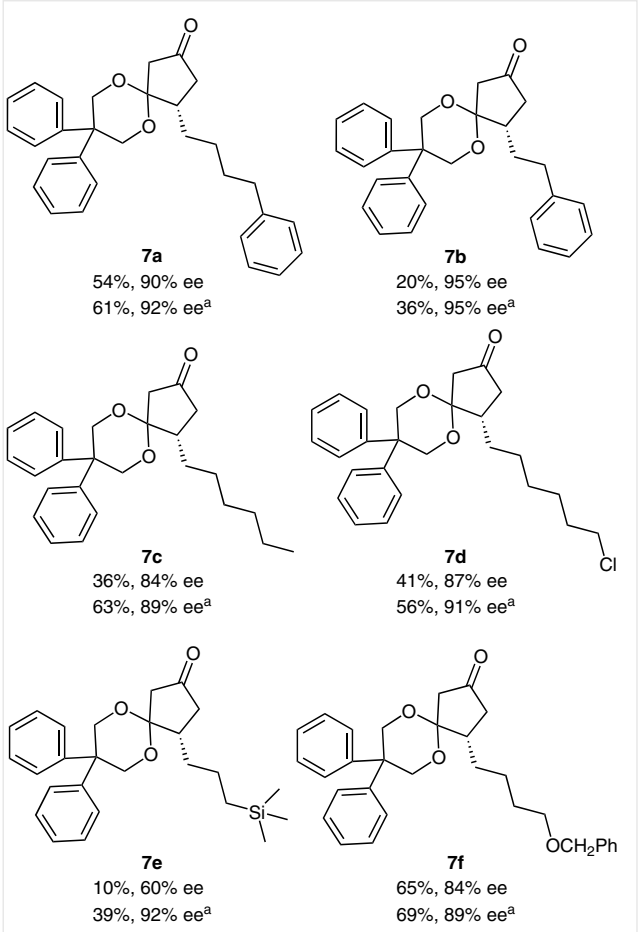


Figure 1 Scope of nucleophiles. *Reagents and conditions*: alkene (3.5 equiv), Cp_2ZrHCl (3.0 equiv), cyclopentenone **3b** (1.0 equiv), CuCl (20 mol%), ligand **B** (22 mol%), AgOTf (20 mol%), TMSCl (5.0 equiv), Et_2O (3.0 mL), r.t. Isolated yield and ee values determined by chiral HPLC are reported.
[a] Reaction performed at 0 °C. For more information on the procedures, see the Supporting Information.

good yields and high enantiomeric excesses, especially at 0 °C, showing that the reaction is quite tolerant to changes in the alkene coupling partner. The use of electron-rich styrene or allyl(trimethyl)silane in asymmetric hydrometalation and 1,4-addition procedures is often challenging, but here they gave high enantioselectivities (95% ee and 92% ee, respectively) and moderate yields (36% and 39%, respectively) at 0 °C.

We have demonstrated that, despite some problems, highly functionalized enantioenriched cyclopentanone derivatives can be successfully prepared by asymmetric conjugate addition reactions of alkylzirconocene species. Good yields and high levels of enantioselectivity are observed. Further experiments are ongoing.

All reactions involving oxygen/moisture sensitive reagents were performed with anhydrous solvents in flame-dried glassware under a positive pressure of anhydrous argon, using standard Schlenk techniques. Cooling of reaction mixtures to –78 °C was effected using an acetone/dry ice bath; to 0 °C using an ice/water bath; to other temperatures using a Julabo FT902 immersion cooler. Heating was performed using Drysyn® heating blocks. In the cases where silver salts were used, the resulting solutions were filtered using syringe filters PTFE (0.2 µm, 13 mm diameter) from Camlab. Analytical thin-layer chromatography was performed on glassplates pre-coated with silica gel (Silica Gel 60 F_{254}; Merck). Plates were visualised using UV light (λ = 254 nm) and then stained with either aqueous ceric ammonium molybdate (CAM), aqueous basic potassium permanganate ($KMnO_4$) or anisaldehyde and developed upon heating. Flash chromatography was performed using silica gel [Apollo Scientific 60 (40–63 µm), Sigma Aldrich (Davisil®grade 636, pore size 60 Å, 35–60 mesh), Merck 60 Å or VWR (40–63 µm)]. Pressure was applied at the column head via a flow of nitrogen with the solvent system used in parentheses. Nuclear magnetic resonance spectra were acquired in deuterated solvents at room temperature on Bruker: AVIIIHD 400 nanobay, AVIIIHD 500, AVII 500, AVII 500 with cryoprobe spectrometers. Chemical shifts (δ) are reported in ppm from the residual solvent. Coupling constants (*J*) are quoted in hertz (Hz) and are recorded to the nearest 0.1 Hz. Resonances are described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), doublet of doublets (dd), doublet of doublets of doublets (ddd), doublet of triplets (dt), multiplet (m) and broad (br). Labels Hb and Ha refer to diastereotopic protons attached to the same carbon and impart no stereochemical information. Assignments were made with the assistance of gCOSY, DEPT-Q, gHSQC and gHMBC NMR spectra. Low-resolution (LRMS) and high-resolution (HRMS) mass spectral analyses were acquired by electrospray ionisation (ESI), electron impact (EI), field ionisation (FI). Low resolution ESI were recorded using an Agilent 6120 quadrupol LC/MS. High-resolution accurate ESI were recorded using a Thermo Exactive 1.1 SP5 Benchtop orbitrap MS and EI/FI on a Waters GTC temperature programmed solid probe inlet within the department of chemistry, University of Oxford. Infrared spectroscopy (IR) measurements (neat, thin film) were carried out using a Bruker Tensor 27 FT-IR with internal calibration in the range of 4000–600 cm^{-1}. Absorption maxima are reported as wavenumbers (cm^{-1}). Optical rotations were recorded using a Schmidt Haensch Unipol L 2000 Polarimeter. Chiral HPLC separations were achieved using an Agilent 1260 Infinity series normal phase HPLC unit and HP Chemstation software. Chiralpak® columns (250 × 4.6 mm), fitted with matching Chiralpak® Guard Cartridges (10 × 4 mm), were used as specified. Solvents used were of HPLC grade (Fisher Scientific, Sigma Alrich or Rathburn). All eluent systems were isocratic.

6,10-Dioxaspiro[4.5]decan-2-ones 6 and 7; General Procedure

In a flame-dried flask under an argon atmosphere, Cp_2ZrHCl (3.0 equiv) was added to a solution of the appropriate alkene (3.5 equiv) in CH_2Cl_2 (0.5 mL), and the mixture was vigorously stirred until a clear yellow solution was obtained (20–40 min). Simultaneously, in another flask under an inert atmosphere, CuCl (0.20 equiv) and ligand *(R)*-**B** (0.22 equiv) were covered with Et_2O (2.2 mL), and the mixture was stirred for 1 h at r.t. AgOTf (0.20 equiv) was added to the freshly prepared Cu/ligand-containing solution and the mixture was stirred for an additional 1 h. The resulting catalyst mixture was taken up by syringe and injected through a filter into the flask containing the freshly prepared alkylzirconocene species, and this flask was then cooled to 0 °C. After 10 min, the solid cyclopent-4-ene-1,3-dione monoacetal **3** (1.0 equiv) was added in one portion by quickly tipping the solid into the black solution. TMSCl (5.0 equiv) was then added dropwise, and the mixture was stirred overnight then allowed to warm slowly to r.t. The mixture was diluted with Et_2O (2 mL) and the reaction was quenched with 1 M aq NH_4Cl (3 mL). The mixture was partitioned and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic extracts were combined, washed with sat. aq $NaHCO_3$ (30 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography to give the enantioenriched products. Additional details are provided in the Supporting Information.

(4*S*)-8,8-Dimethyl-4-(4-phenylbutyl)-6,10-dioxaspiro[4.5]decan-2-one (6a)

Prepared by the general procedure from but-3-en-1-ylbenzene and 8,8-dimethyl-6,10-dioxaspiro[4.5]dec-3-en-2-one (**3a**), and purified by flash chromatography (silica gel, 5–10% Et_2O–pentane) to give a clear oil; yield: 60.5 mg (48%; 87% ee).

HPLC: Chiralpak IC; hexane–*i*-PrOH (95:5); 1.0 mL/min, λ = 210 nm; t_R = 11.8 min (major enantiomer), t_R = 15.6 min (minor enantiomer); 87% ee.

IR (ATR): 2931, 2858, 1748, 1466, 1396, 1285, 1186, 1118, 1055, 1017, 979, 747, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.23–7.17 (m, 2 H), 7.13–7.08 (m, 3 H), 3.46–3.34 (m, 4 H), 2.89 (d, *J* = 18.2 Hz, 1 H), 2.62–2.50 (m, 2 H), 2.41 (dd, *J* = 17.7, 8.0 Hz, 1 H), 2.27–2.19 (m, 2 H), 2.02 (dd, *J* = 18.2, 10.7 Hz, 1 H), 1.86–1.77 (m, 1 H), 1.66–1.53 (m, 2 H), 1.42–1.23 (m, 3 H), 1.10 (s, 3 H), 0.70 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 213.7, 142.7, 128.5, 128.4, 125.8, 104.3, 73.1, 71.5, 46.1, 44.3, 43.2, 36.0, 31.8, 30.4, 27.9, 27.5, 22.8, 22.2.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{29}O_3$: 317.21112; found: 317.21117.

$[\alpha]^{25}_{589}$ = +67.9 (*c* = 1.0 in $CHCl_3$, 87% ee).

(4*S*)-8,8-Diphenyl-4-(4-phenylbutyl)-6,10-dioxaspiro[4.5]decan-2-one (7a)

Prepared by the general procedure from but-3-en-1-ylbenzene and 8,8-diphenyl-6,10-dioxaspiro[4.5]dec-3-en-2-one (**3b**), and purified by flash chromatography (silica gel, 10–20% Et_2O–pentane) to give a clear oil; yield: 107.8 mg (61%; 92% ee).

HPLC: Chiralpak IA; hexane–*i*-PrOH (90:10); 1.0 mL/min, λ = 210 nm; t_R = 7.6 min (major enantiomer), t_R = 13.4 min (minor enantiomer); 92% ee.

IR (ATR): 3026, 2933, 1749, 1400, 1279, 1132, 1044, 751, 699 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 8.0 Hz, 2 H), 7.37 (d, *J* = 7.5 Hz, 2 H), 7.35–7.19 (m, 7 H), 7.18 (d, *J* = 7.6 Hz, 2 H), 7.11 (d, *J* = 7.6 Hz, 2 H), 4.67–4.60 (m, 2 H), 4.36 (d, *J* = 12.0 Hz, 1 H), 4.24 (d, *J* = 12.0 Hz, 1 H), 3.13 (d, *J* = 18.0 Hz, 1 H), 2.60–2.48 (m, 3 H), 2.43 (d, *J* = 18.0 Hz, 1 H), 2.35–2.26 (m, 1 H), 2.15 (dd, *J* = 18.1, 11.0 Hz, 1 H), 1.70–1.59 (m, 1 H), 1.55 (app. quint, 2 H), 1.36–1.13 (m, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 213.2, 143.7, 143.4, 142.8, 128.8, 128.7, 128.5, 128.4, 128.2, 127.1, 126.5, 126.5, 125.7, 104.8, 70.9, 68.9, 46.0, 45.0, 44.8, 43.4, 35.8, 31.8, 27.7, 27.5.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{30}H_{32}NaO_3$: 463.22437; found: 463.22410.

$[\alpha]^{25}_{589}$ = +50.4 (*c* = 1.1 in $CHCl_3$, 92% ee).

(4*S*)-8,8-Diphenyl-4-(2-phenylethyl)-6,10-dioxaspiro[4.5]decan-2-one (7b)

Prepared by the general procedure from styrene and 8,8-diphenyl-6,10-dioxaspiro[4.5]dec-3-en-2-one (**3b**), and purified by flash chromatography (silica gel, 10–20% Et_2O–pentane) to give a white oil; yield: 64.0 mg (36%; 95% ee).

HPLC: Chiralpak IA; hexane–*i*-PrOH (90:10); 1.0 mL/min, λ = 210 nm; t_R = 7.8 min (major enantiomer), t_R = 16.5 min (minor enantiomer); 95% ee.

IR (ATR): 3026, 2924, 1749, 1602, 1496, 1448, 1400, 1279, 1188, 1132, 1032, 970, 753, 699 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 8.7 Hz, 2 H), 7.42–7.20 (m, 9 H), 7.15 (d, *J* = 8.4 Hz, 2 H), 7.12 (d, *J* = 7.6 Hz, 2 H), 4.66 (ddd, *J* = 12.2, 3.0, 2.7 Hz, 2 H), 4.38 (d, *J* = 11.9 Hz, 1 H), 4.28 (d, *J* = 12.2 Hz, 1 H), 3.17 (d, *J* = 17.9 Hz, 1 H), 2.63–2.50 (m, 3 H), 2.47 (d, *J* = 18.0 Hz, 1 H), 2.43–2.35 (m, 1 H), 2.22 (dd, *J* = 17.8, 10.9 Hz, 1 H), 2.07–1.98 (m, 1 H), 1.68–1.58 (m, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 213.0, 143.7, 143.4, 142.1, 128.9, 128.7, 128.4, 128.4, 128.3, 127.1, 126.6, 126.5, 125.9, 104.9, 70.9, 68.9, 45.2, 45.0, 44.9, 43.4, 33.9, 29.1.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{28}H_{28}NaO_3$: 435.19307; found: 435.19317.

$[\alpha]^{25}_{589}$ = +65.6 (*c* = 1.0 in $CHCl_3$, 95% ee).

(4*S*)-4-Hexyl-8,8-diphenyl-6,10-dioxaspiro[4.5]decan-2-one (7c)

Prepared by the general procedure from hex-1-ene and 8,8-diphenyl-6,10-dioxaspiro[4.5]dec-3-en-2-one (**3b**), and purified by flash chromatography (silica gel, 10–20% Et_2O–pentane) to give a yellow oil; yield: 98.9 mg (63%; 89% ee).

HPLC: Chiralpak IA; hexane–*i*-PrOH (90:10); 1.0 mL/min, λ = 210 nm; t_R = 5.9 min (major enantiomer), t_R = 10.6 min (minor enantiomer); 89% ee.

IR (ATR): 2926, 2856, 2360, 1750, 1496, 1464, 1399, 1280, 1188, 1129, 1035, 771, 699, 642 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 7.9 Hz, 2 H), 7.37–7.20 (m, 6 H), 7.10 (d, *J* = 7.2 Hz, 2 H), 4.64–4.57 (m, 2 H), 4.34 (d, *J* = 12.0 Hz, 1 H), 4.22 (d, *J* = 12.0 Hz, 1 H), 3.09 (d, *J* = 17.9 Hz, 1 H), 2.52 (dd, *J* = 17.9, 8.0 Hz, 1 H), 2.42 (d, *J* = 18.2 Hz, 1 H), 2.34–2.25 (m, 1 H), 2.13 (dd, *J* = 17.9, 10.7 Hz, 1 H), 1.63–1.51 (m, 1 H), 1.35–1.07 (m, 9 H), 0.89 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 213.4, 143.8, 143.5, 128.8, 128.7, 128.2, 127.1, 126.6, 126.5, 104.9, 70.9, 69.0, 46.0, 45.0, 44.9, 43.4, 31.8, 29.6, 28.0, 27.8, 22.8, 14.2.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{33}O_3$: 393.24242; found: 393.24238.

$[\alpha]^{25}_{589}$ = +89.0 (*c* = 1.4 in $CHCl_3$, 89% ee).

(4*S*)-4-(6-Chlorohexyl)-8,8-diphenyl-6,10-dioxaspiro[4.5]decan-2-one (7d)

Prepared by the general procedure from 6-chlorohex-1-ene and 8,8-diphenyl-6,10-dioxaspiro[4.5]dec-3-en-2-one (**3b**), and purified by flash chromatography (silica gel, 10–20% Et_2O–pentane) to give a white oil; yield: 96.2 mg (56%; 91% ee).

HPLC: Chiralpak IA; hexane–*i*-PrOH (90:10); 1.0 mL/min, λ = 210 nm; t_R = 8.1 min (major enantiomer), t_R = 16.5 min (minor enantiomer); 91% ee.

IR (ATR): 2931, 2859, 1769, 1727, 1275, 1130, 699 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 7.3 Hz, 2 H), 7.38–7.21 (m, 6 H), 7.10 (d, *J* = 7.3 Hz, 2 H), 4.66–4.58 (m, 2 H), 4.35 (d, *J* = 11.6 Hz, 1 H), 4.22 (d, *J* = 11.6 Hz, 1 H), 3.52 (t, *J* = 6.8 Hz, 2 H), 3.12 (d, *J* = 17.7 Hz, 1 H), 2.51 (dd, *J* = 17.9, 8.3 Hz, 1 H), 2.42 (d, *J* = 18.1 Hz, 1 H), 2.33–2.25 (m, 1 H), 2.14 (dd, *J* = 17.6, 11.1 Hz, 1 H), 1.78–1.70 (app. quint, 2 H), 1.64–1.53 (m, 1 H), 1.39–1.08 (m, 7 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 213.1, 143.7, 143.3, 128.8, 128.7, 128.2, 127.1, 126.5, 126.4, 104.8, 70.9, 68.9, 46.0, 45.2, 44.9, 44.8, 43.4, 32.7, 29.1, 27.8, 27.6, 26.7.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{26}H_{31}ClNaO_3$: 449.18539; found: 449.18561.

$[\alpha]^{25}_{589}$ = +66.5 (*c* = 0.9 in $CHCl_3$, 91% ee).

(4*S*)-8,8-Diphenyl-4-[3-(trimethylsilyl)propyl]-6,10-dioxaspiro[4.5]decan-2-one (7e)

Prepared by the general procedure from allyl(trimethyl)silane and 8,8-diphenyl-6,10-dioxaspiro[4.5]dec-3-en-2-one (**3b**), and purified by flash chromatography (silica gel, 10–20% Et_2O–pentane) to give a clear oil; yield: 65.5 mg (39%; 92% ee).

HPLC: Chiralpak IA; hexane–*i*-PrOH (90:10); 1.0 mL/min, λ = 210 nm; t_R = 5.0 min (major enantiomer), t_R = 7.3 min (minor enantiomer); 92% ee.

IR (ATR): 2951, 2870, 1749, 1259, 1130, 835, 752, 697 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 7.6 Hz, 2 H), 7.37–7.21 (m, 6 H), 7.09 (d, *J* = 7.8 Hz, 2 H), 4.64–4.55 (m, 2 H), 4.34 (d, *J* = 12.6 Hz, 1 H), 4.21 (d, *J* = 12.6 Hz, 1 H), 3.08 (d, *J* = 17.6 Hz, 1 H), 2.52 (dd, *J* = 18.1, 8.1 Hz, 1 H), 2.42 (d, *J* = 18.1 Hz, 1 H), 2.38–2.27 (m, 1 H), 2.14 (dd, *J* = 17.8, 10.4 Hz, 1 H), 1.63–1.54 (m, 1 H), 1.35–1.20 (m, 2 H), 1.20–1.08 (m, 1 H), 0.48–0.35 (m, 2 H), –0.06 (s, 9 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 231.4, 143.9, 143.5, 128.8, 128.7, 127.1, 126.6, 126.5, 104.9, 70.9, 69.0, 45.6, 44.9, 44.8, 43.3, 31.5, 22.5, 16.8, –1.5.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{26}H_{34}NaO_3Si$: 445.21694; found: 445.21689.

$[\alpha]^{25}_{589}$ = +144.3 (*c* = 1.2 in $CHCl_3$, 92% ee).

(4*S*)-4-[4-(Benzyloxy)butyl]-8,8-diphenyl-6,10-dioxaspiro[4.5]decan-2-one (7f)

Prepared by the general procedure from [(but-3-en-1-yloxy)methyl]benzene and 8,8-diphenyl-6,10-dioxaspiro[4.5]dec-3-en-2-one (**3b**), and purified by flash chromatography (silica gel, 10–20% Et_2O–pentane) to give a yellow oil; yield: 130.3 mg (69%; 89% ee).

HPLC: Chiralpak IA; hexane–*i*-PrOH (90:10); 1.0 mL/min, λ = 210 nm; t_R = 9.9 min (major enantiomer), t_R = 16.0 min (minor enantiomer); 89% ee.

IR (ATR): 2929, 2862, 1748, 1496, 1448, 1278, 1188, 1131, 1049, 752, 699, 642 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 7.5 Hz, 2 H), 7.40–7.18 (m, 11 H), 7.09 (d, *J* = 7.5 Hz, 2 H), 4.64–4.57 (m, 2 H), 4.49 (s, 2 H), 4.33 (d, *J* = 11.8 Hz, 1 H), 4.20 (d, *J* = 12.5 Hz, 1 H), 3.38 (t, *J* = 6.8 Hz, 2 H), 3.10 (d, *J* = 17.9 Hz, 1 H), 2.51 (dd, *J* = 17.9, 8.0 Hz, 1 H), 2.41 (d, *J* = 17.9 Hz, 1 H), 2.34–2.24 (m, 1 H), 2.13 (dd, *J* = 17.3, 10.5 Hz, 1 H), 1.63–1.49 (m, 3 H), 1.34–1.12 (m, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 213.2, 143.7, 143.4, 138.8, 128.8, 128.7, 128.5, 128.3, 127.8, 127.7, 127.1, 126.6, 104.8, 73.0, 71.0, 70.3, 68.9, 46.1, 45.0, 44.8, 43.4, 30.1, 27.6, 24.7.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{35}O_4$: 471.25299; found: 471.25290.

$[\alpha]^{25}_{589}$ = +58.3 (*c* = 1.1 in $CHCl_3$, 89% ee).

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379928.

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