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Enantioselective Cobalt-Catalyzed [6+2] Cycloadditions of Cycloheptatriene with Alkynes

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Abstract: The enantioselective cobalt-catalyzed [6+2] cycloadditions of cycloheptatriene **1** with alkynes **2** is reported. Chiral phosphoramidites based on 3,3′-disubstituted (*R*)-BINOL appeared to be efficient ligands, affording the corresponding cycloadducts with good yields and up to 92% *ee*. A vibrational circular dichroism study afforded the absolute configuration of new chiral (+)-(1*S*,6*R*)-7-phenyl[4.2.1]bicyclononatriene **3a** and (−)-(1*S*,6*R*)-7-trimethylsilyl-[4.2.1]bicyclononatriene **3c**.

Keywords: cobalt; cycloaddition reactions; enantioselective catalysis; phosphoramidites; vibrational circular dichroism

Introduction

Enantioselective [4+2] cycloaddition reactions are among the most powerful tools for the synthesis of natural products. Metal- or Lewis acid-catalyzed processes afford direct and versatile entries to six-membered rings with the stereocontrolled formation of up to four stereocenters, including quaternary carbons.[1] In contrast such major results have not been achieved for the creation of medium-sized rings through higher order cycloadditions.[2–11] For instance, to the best of our knowledge, the enantioselective [6+2] cycloaddition remains to be designed. Iron-, ruthenium-, molybdenum-, and titanium-assisted [6+2] cycloadditions have been reported,[3–6] but the reactions of triene-chromium complexes with alkynes or alkenes[8–11] have been by far the most studied and developed method. Despite noteworthy achievements, this methodology suffers from some limitations. In particular, it is restricted to internal alkynes, with terminal alkynes 2:1 alkyne-triene adducts are obtained.[9] Furthermore, the design of an enantioselective version, with the introduction of chiral external ligands, remains tricky. Indeed even in catalytic versions, the active catalyst is prone to be a phosphine-free "$CrCO_x$" species.[10] As a matter of fact only diastereoselective reactions with chiral triene-chromium complexes, alkenes or alkynes have been disclosed to date.[10e,11]

Recently, we reported the first cobalt-catalyzed [6+2] cycloaddition.[3] The catalytic system (CoI_2/ligand/Zn/ZnI_2) is not only compatible with a broad range of organic functions, but also, in contrast to the Cr-based methodology, it is smooth enough to perform the selective addition of terminal alkynes with trienes. Considering that ligands such as phosphines dramatically increase the rate of the reaction, we took advantage of this versatile catalytic system to design an enantioselective [6+2] cycloaddition. Herein, we report the preliminary results of this study.

Results and Discussion

We chose cycloheptatriene **1** and phenylacetylene **2a** as model substrates, and proceeded to a screening of chiral phosphorus-based ligands (Figure 1). Considering that dppe [1,2-bis(diphenylphosphino)ethane] was an efficient ligand for that process, affording the cycloadducts in 75% chemical yield, we first tested some classical related chiral diphosphines. Disappointingly, (*S*,*S*)-Chiraphos or (*S*,*S*)-Et-Duphos afforded the desired adducts with 34% and 63% enantiomeric excess (*ee*), respectively, but in only 10–20% yields. A fair yield of 60% was finally reached with (*R*,*R*)-NORPHOS, but with no *ee*. The reactivity of the cobalt catalyst system was considerably reduced

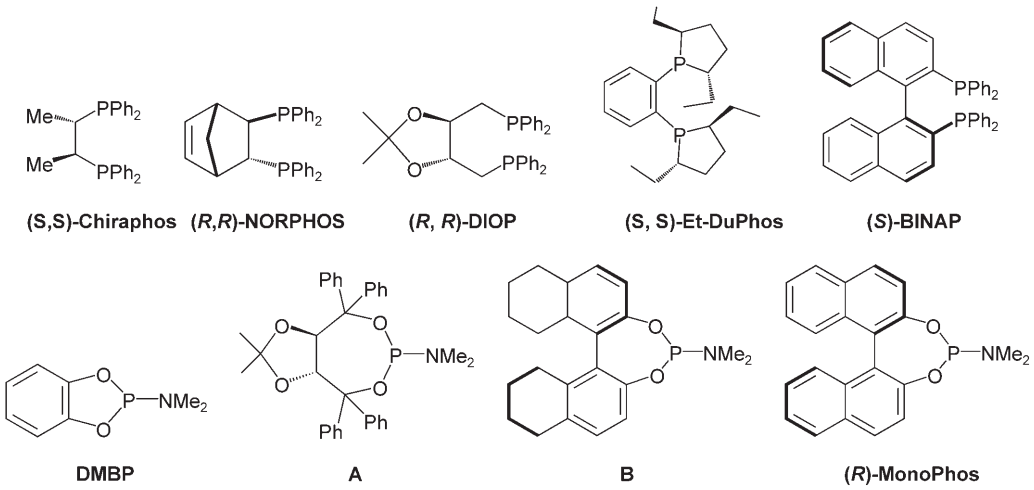


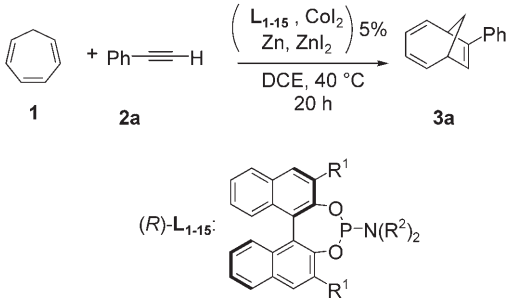
Figure 1. Some chiral bidentate phosphines and monodentate phosphoramidites.

when increasing the chain length between the two phosphorus atoms: the popular ligands (*S*)-BINAP or (*R*,*R*)-DIOP afforded no conversion.

These results led us to consider chiral monodentate ligands. We chose to focus on P-ligands containing heteroatom-phosphorus bonds. These ligands are easy to prepare, highly tunable, and generally stable towards air.[12] As we had already observed that 2-dimethylamino-1,3,2-benzodioxaphosphole (DMBP) was a suitable ligand for our catalytic system,[3a] we decided to test some representative chiral phosphoramidites (Figure 1).[13] The (*R*,*R*)-TADDOL-based ligand **A** afforded the cycloadduct **3a** in 10% yield and with low enantioselectivity (26%). On the other hand, (*R*)-MonoPhos $\mathbf{L_1}$ stood out, providing both a good yield (76%) and a significant *ee* (63%). In the case of the (*R*)-8*H*-BINOL-based **B**, the cycloadduct was obtained in excellent chemical yield (88%) but with a lower enantioselectivity (50%).

Then, having identified (*R*)-BINOL-based phosphoramidites as promising candidates, and taking advantage of the modular structure of these ligands we tuned the structure of $\mathbf{L_1}$.[14] As shown in Table 1, the product **3a** was generally obtained in good to excellent isolated yields. Concerning the enantioselectivity, the variation of the amino group led only to slight improvements with *ee*s up to 75% (entries 1–8). As a matter of fact, there is no obvious correlation between $N(R^2)_2$ groups and enantioselectivity. Importantly, no match/mismatch effect was observed with chiral amino groups, the absolute configuration being controlled by the chiral (*R*)-BINOL backbone (entries 7 and 8). In contrast, *ee*s were very sensitive to substitutions in the 3 and 3′ positions of the BINOL moiety ($R^1 \neq H$). Depending on R^1, a dramatic variation of the enantioselectivity was observed. The most spectacular effects were observed with aryl substituents, the absolute configuration of the major enantio-

Table 1. Tuning of the chiral phosphoramidite ligands.



Entry[a]	L	$N(R^2)_2$	R^1	Product	*ee* [%][b] (yield [%])[c]
1	$\mathbf{L_1}$	NMe_2	H	(−)-**3a**	63 (76)
2	$\mathbf{L_2}$	NEt_2	H	(−)-**3a**	58 (80)
3	$\mathbf{L_3}$	$N(i\text{-}Pr)_2$	H	(−)-**3a**	51 (70)
4	$\mathbf{L_4}$	$N(CH_2)_4$	H	(−)-**3a**	40 (76)
5	$\mathbf{L_5}$	$N(CH_2)_5$	H	(−)-**3a**	59 (72)
6	$\mathbf{L_6}$	NPh_2	H	(−)-**3a**	75 (91)
7	$\mathbf{L_7}$		H	(−)-**3a**	70 (81)
8	$\mathbf{L_8}$		H	(−)-**3a**	70 (61)
9	$\mathbf{L_9}$	NEt_2	Me	(−)-**3a**	21 (88)
10	$\mathbf{L_{10}}$	NMe_2	Ph	(+)-**3a**	84 (91)
11	$\mathbf{L_{11}}$	NEt_2	Ph	(+)-**3a**	49 (99)
12	$\mathbf{L_{12}}$	NMe_2	3,5-Me_2 (C_6H_3)	(+)-**3a**	86 (93)
13	$\mathbf{L_{13}}$	NMe_2	3,5-$(F_3C)_2$ (C_6H_3)	-	- (0)
14	$\mathbf{L_{14}}$	NMe_2	2-Ph(C_6H_4)	(+)-**3a**	51 (94)
15	$\mathbf{L_{15}}$	NMe_2	1-naphthyl	(+)-**3a**	90 (93)

[a] Triene/alkyne/CoI_2/Ligand/Zn/ZnI_2 in a 1.2/1.0/0.05/0.10/0.15/0.10 molar ratio.

[b] The *ee* was determined by chiral HPLC on Chiracel OD-H.

[c] Yields after purification.

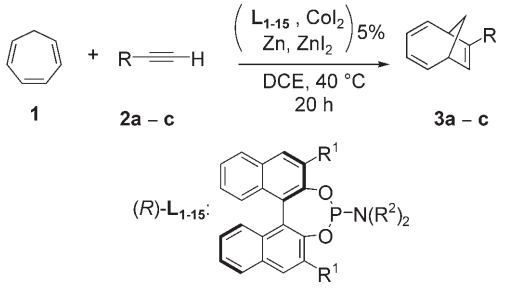
mer being reversed in comparison with $R^1 = H$, Me (entries 10–15). With these latter substituents, good *ee*s were obtained, and finally 90% *ee* was reached with $\mathbf{L_{15}}$ as ligand (R^1 = 1-naphthyl, entry 15).

This "inversion of asymmetric induction", which is observed when introducing aryl groups as R^1 substituents, may be partially attributed to π-stacking interactions between substituents of the ligands and phenylacetylene **2a**. However the contribution of steric factors to this effect is not negligible. Indeed a similar trend was observed with hex-1-yne as reactant: the configuration of the major enantiomer of **3b** (which features no aryl, but an *n*-butyl substituent) was also dependent on R^1 groups of the chiral BINOL backbone of the ligand (entries 1–4, Table 2). Interestingly, **3b** was obtained with lower *ee*s (up to 47% only), whereas compound **3c**, with a bulkier trimethylsilyl group, can be synthesized with a good yield and 92% *ee* (with ligand $\mathbf{L_{11}}$, entry 9 in Table 2). Note that, in that case, the substitutions in 3 and 3′ positions of the BINOL moiety of the ligand (R^1 groups) appeared to be particularly critical: when $R^1 = H$, no enantioselectivity was observed. Only aryl substituents afforded good *ee*s ranging from 74 to 92%.

We determined the absolute configuration of these new chiral molecules by means of vibrational circular dichroism.[15] Compounds **3a** and **3c** are rather rigid, such that their VCD spectrum can be easily predicted by DFT calculations [(b3pw91, 6-311++G(d,p)], see Supporting Information). As shown in Figure 2 the calculated VCD and IR spectra are in excellent agreement with the experimental ones. Note that in several places in the spectra intense bands in the VCD are only weak in the IR and *vice versa*. This behavior is very well reproduced by the calculations, which provides a high level of confidence for the assignment of the absolute configuration. Since the experimental and calculated VCD spectra have opposite signs and the calculations were performed for the (1*R*,6*S*) enantiomers of **3a** and **3c** we could unambiguously attribute the absolute configuration of **3a**, which is the (+)-(1*S*,6*R*)-7-phenyl[4.2.1]bicyclononatriene, and **3c**, which is the (−)-(1*S*,6*R*)-7-trimethyl-silyl[4.2.1]bicyclononatriene.

It has to be noted that trienes **3** can be involved in further transformations. In particular, the diene and alkene moieties can be easily differentiated: cycloadducts **3a,b** reacted cleanly with *m*-CPBA to afford *exo*-epoxides **4a,b** with excellent chemo- and diastereoselectivity (Scheme 1). In addition compound **3c** should benefit from the versatile reactivity of vinylsilanes. Thus (−)-**3c** reacted with *N*-iodosuccinimide to afford the vinyl iodide (−)-**5** (Scheme 1). The enantiospecificity of the reaction was demonstrated by chiral HPLC analysis, **5** being obtained with unchanged *ee* (92%). Compound **5** is a potential versatile precursor for various highly enantioenriched compounds through lithiation or cross-coupling methodologies. As a general statement, compounds **3** are valuable synthons, for instance, for the synthesis of biologically active compounds that feature a bicyclo[4.2.1]nonanoid pattern, such as mediterranneol derivatives.[16]

Table 2. Cycloaddition of cycloheptatriene with other alkynes.



Entry[a]	L	$N(R^2)_2$	R^1	R	Product	*ee* [%] (yield [%])[b]
1	$\mathbf{L_1}$	NMe_2	H	*n*-Bu	(+)-**3b**	45[c] (11)
2	$\mathbf{L_{10}}$	NMe_2	Ph	*n*-Bu	(−)-**3b**	30[c] (90)
3	$\mathbf{L_{11}}$	NEt_2	Ph	*n*-Bu	(−)-**3b**	21[c] (88)
4	$\mathbf{1_{15}}$	NMe_2	1-naphthyl	*n*-Bu	(−)-**3b**	47[c] (89)
5	$\mathbf{L_1}$	NMe_2	H	Me_3Si	-	0 (33)
6	$\mathbf{L_4}$	$N(CH_2)_4$	H	Me_3Si	-	0 (33)
7	$\mathbf{L_9}$	NEt_2	Me	Me_3Si	(−)-**3c**	53[d] (72)
8	$\mathbf{L_{10}}$	NMe_2	Ph	Me_3Si	(−)-**3c**	83[d] (82)
9	$\mathbf{L_{11}}$	NEt_2	Ph	Me_3Si	(−)-**3c**	92[d] (86)
10	$\mathbf{L_{12}}$	NMe_2	3,5-Me_2 (C_6H_3)	Me_3Si	(−)-**3c**	86[d] (61)
11	$\mathbf{L_{14}}$	NMe_2	2-Ph- (C_6H_4)	Me_3Si	(−)-**3c**	74[d] (64)
12	$\mathbf{L_{15}}$	NMe_2	1-naphthyl	Me_3Si	(−)-**3c**	85[d] (75)

[a] Triene/alkyne/CoI_2/ligand/Zn/ZnI_2 in a 1.2/1.0/0.05/0.10/0.15/0.10 molar ratio.
[b] Yields after purification.
[c] The *ee* was determined by chiral HPLC on Chiralpak AD after transformation into epoxide **4b**.
[d] The *ee* was determined by chiral HPLC on Chiralpak AD-RH.

Conclusions

In conclusion, 3,3′-disubstituted BINOL-based chiral phophoramidites are efficient ligands for the cobalt-catalyzed enantioselective [6+2]cycloaddition of cycloheptatriene with alkynes. Development of diaste-

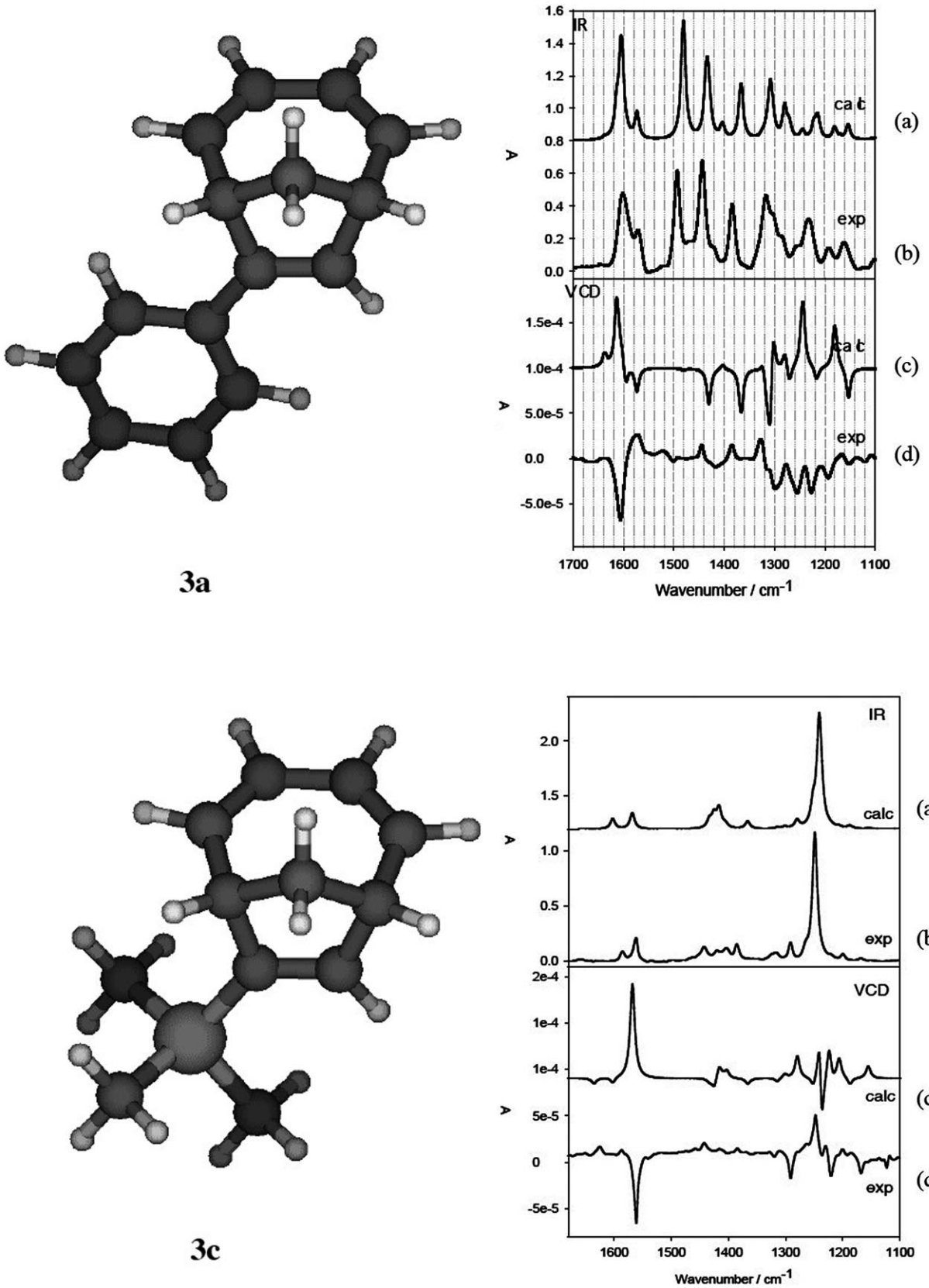
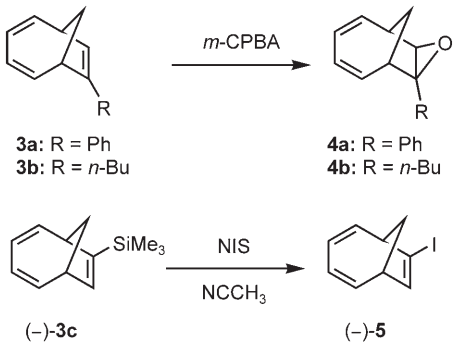


Figure 2. *Above*: calculated structure, IR (a) and VCD spectra (c) of (1*R*,6*S*)-**3a** and corresponding experimental spectra (b and d) of (+)-**3a.** *Below:* calculated structure, IR (a) and VCD spectra (b) of (1*R*,6*S*)-**3c** and corresponding experimental spectra (b and d) of (−)-**3c**. All the calculated spectra were shifted for clarity.



Scheme 1. Stereoselective transformation of compounds **3a,b,c**.

reoselective transformations of the resulting [6+2] adducts for original strategies in natural products synthesis, as well as enhancement of the enantioselectivities through the screening of new families of chiral ligands, are underway in our laboratory.

Experimental Section

General Remarks

All reactions were carried out under a dry nitrogen atmosphere. Cycloheptatriene **1** was freshly distillated before use. Zinc(II) iodide, cobalt(II) iodide, zinc powder, alkynes **2a–c**, 1,2-dichloroethane (DCE), *m*-CPBA, *N*-iodosuccinimide were purchased, stored under nitrogen and used as received. Ligands $\mathbf{L_{1–15}}$ were synthesized from enantiopure BINOL according to known methods.[14] ^{1}H NMR spectra were recorded on a Bruker Avance (200 MHz) spectrometer and are reported in ppm from $CDCl_3$ as internal standard (7.26 ppm). ^{13}C NMR spectra were recorded at 50 MHz on the same spectrometer and are reported in ppm from $CDCl_3$ as internal standard (77.0 ppm).

IR and VCD Measurements

Infrared (IR) and vibrational circular dichroism (VCD) spectra were recorded on a Bruker PMA 50 accessory coupled to a Tensor 27 Fourier transform infrared spectrometer. A photoelastic modulator (Hinds PEM 90) set at l/4 retardation was used to modulate the handedness of the circular polarized light. Demodulation was performed by a lock-in amplifier (SR830 DSP). An optical low-pass filter ($< 1800\ cm^{-1}$) put before the photoelastic modulator was used to enhance the signal/noise ratio. Spectra of the neat samples were recorded at room temperature with a resolution of $8\ cm^{-1}$ in a cell equipped with CaF_2 windows and a 50 mm Teflon spacer. The VCD spectrum of the racemic mixture (reference) measured under identical conditions was subtracted from the raw VCD spectrum of the enantioenriched sample. For both sample and reference 15,000 scans were averaged. The empty cell served as reference for the IR spectra. The spectra are presented without smoothing or further data processing.

DFT Calculations

Density functional theory (DFT) calculations were performed with Gaussian03[17] using the b3pw91 functional with a 6–311++G(d,p) basis set. Prior to the calculation of the VCD and IR spectra a complete geometry optimization was performed. Vibrational frequencies were scaled by a factor of 0.97. IR absorption and VCD spectra were constructed from calculated dipole and rotational strengths assuming Lorentzian band shape with a half-width at half-maximum of $8\ cm^{-1}$.

General Procedure for the Enantioselective Co(I)-Catalyzed [6+2] Cycloaddition

Under a nitrogen atmosphere, ligand (0.10 equiv. when monodentate, or 0.05 equiv. when bidentate) was added to a solution of CoI_2 (13 mg; 0.042 mmol; 0.05 equiv.) in 1,2-dichloroethane (1 mL). The mixture was stirred 10 min. and powdered zinc (8.3 mg; 0.127 mmol; 0.15 equiv.) was added. Then, a solution of 1,3,5-cycloheptatriene (93 mg; 1 mmol; 1.20 equivs.) in 1,2-dichloroethane (1 mL), a solution of **2a–c** (1 equiv.) in 1,2-dichloroethane (1 mL) and zinc iodide (27 mg; 0.085 mol; 0.10 equiv.) were added successively. The resulting mixture was heated at 40 °C for 20 h. After cooling to room temperature, the reaction was quenched with petroleum ether (5 mL). The reaction mixture was filtered through celite® and removal of solvent followed by column chromatography on silica gel (petroleum ether) gave compound **3a–c**. Analytical data, in particular NMR spectra, are in agreement with those of known racemic compounds.[3a]

3a: Following the above general procedure with ligand (*R*)-$\mathbf{L_{15}}$, **3a** was obtained as a colorless oil; yield: 110.8 mg (93 %). R_f 0.40 (petroleum ether). HPLC: t_R (1*R*,6*S*)-**3a** 13.45 min (5 %); t_R (1*S*,6*R*)-**3a** 14.59 min (95 %) (Chiralcel OD-H, hexane, 1 mL min^{-1}); $[\alpha]_D^{20}$: +78.2 (*c* 0.44, CH_2Cl_2).

3b: Following the above general procedure with ligand (*R*)-$\mathbf{L_{15}}$, **3b** was obtained as a colorless oil; yield: 94.1 mg (89 %). R_f 0.75 (petroleum ether). The enantiomeric excess (47 %) was determined after transformation into epoxide **4b** (see below); $[\alpha]_D^{20}$: −8.9 (*c* 1.16, $CHCl_3$).

3c: Following the above general procedure with ligand (*R*)-$\mathbf{L_{11}}$, **3c** was obtained as a colorless oil; yield: 85.3 mg (83 %); R_f 0.80 (petroleum ether); HPLC: t_R (1*R*,6*S*)-**3c** 9.08 min (4 %); t_R (1*S*,6*R*)-**3c** 10.87 min (96 %) (Chiralpak AD-RH, 70/30 EtOH/water, 0.5 mL min^{-1}); $[\alpha]_D^{20}$: −12.3 (*c* 1.60, $CHCl_3$).

Epoxides 4a and b

At 0 °C, a solution of *m*-CPBA (121.1 mg; 0.702 mmol; 1.3 equivs.) in chloroform (2 mL) was added to a mixture of cycloadduct **3a,b** (1.0 equiv.) and $NaHCO_3$ (59.0 mg; 0.702 mmol; 1.3 equivs.) in chloroform (6 mL). The mixture was stirred for 10 min at 0 °C and the reaction was quenched with 1 M NaOH (2 mL). The mixture was stirred for 15 min at 0 °C and the two phases were separated. The organic phase was washed with 1 M NaOH (2 mL), with brine (2× 3 mL), and dried over Na_2SO_4. Removal of solvent gave compounds **4a** and **b**.

4a: Following the above general procedure with **3a** (410 mg; 2.11 mmol; 1.0 equiv.), $NaHCO_3$ (231 mg; 2.75 mmol; 1.3 equivs.) and *m*-CPBA (474 mg; 2.75 mmol;

1.3 equivs.), **4a** was obtained as a colorless oil; yield: 331 mg (75%); R_f 0.58 (petroleum ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.41–7.27 (m, 5H), 6.03–5.70 (m, 4H), 3.73 (s, 1H), 3.22 (t, J=7.2 Hz, 1H), 3.11 (t, J=6.7 Hz, 1H), 2.38–2.25 (m, 1H), 1.60 (d, J=12.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=135.7, 134.6, 132.4, 128.2, 128.1, 126.9, 125.6, 70.1, 65.3, 41.6, 40.0, 25.4.

4b: Following the above general procedure with enantioenriched cycloadduct **3b** (94.1 mg; 0.540 mmol; 1.0 equiv.), $NaHCO_3$ (59.0 mg; 0.702 mmol; 1.3 equivs.) and *m*-CPBA (121.1 mg; 0.702 mmol; 1.3 equivs.), **4b** was obtained as a colorless oil; yield: 99.4 mg (97%); R_f 0.71 (petroleum ether); HPLC: t_R (−)-**4b** 6.84 min (26.6%); t_R (+)-**4b** 7.93 min (73.4%) (Chiralpak AD-H, hexane, 1 mL.min^{-1}); $[\alpha]_D^{20}$: +8.57 (*c* 0.70, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ=6.03–5.73 (m, 4H), 3.19 (s, 1H), 2.93 (t, J=6.4 Hz, 1H), 2.80 (t, J=7.0 Hz, 1H), 2.16–2.06 (m, 2H), 1.57–1.30 (m, 5H), 1.41 (d, J=12 Hz, 1H), 0.89 (t, J=6.9 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=134.72, 132.79, 126.60, 125.52, 70.47, 64.69, 40.90, 39.69, 28.66, 27.60, 24.82, 22.85, 13.98; HR-MS (ESI-MS) [M−H$^+$]: m/z=191.1430 calcd. for $C_{13}H_{18}O$: 191.1430.

Vinyl Iodide 5

At 0°C and under nitrogen atmosphere, *N*-iodosuccinimide (1.429 g; 6.35 mmol; 1.7 equivs.) was added to a solution of enantioenriched **3c** (710 mg; 3.74 mmol; 1 equiv., *ee* 91%) in freshly distilled acetonitrile. The reaction mixture was stirred in the dark at 0°C. After 3 h, the reaction was quenched with a 20% aqueous solution of $Na_2S_2O_3$. The two phases were separated and the aqueous phase was extracted with pentane (2×10 mL). The acetonitrile phase was also extracted with pentane (4×30 mL). The combined pentane solutions were dried over Na_2SO_4. Careful removal of solvent afforded compound **5** as an orange oil; yield: 680.9 mg (75%); R_f 0.70 (petroleum ether); HPLC: t_R (−)-**5** 20.33 min (3–4%); t_R (+)-**5** 23.02 min (96–97%) (Chiralpak AD-RH, 60/40 EtOH/water, 0.5 mL.min^{-1}); $[\alpha]_D^{20}$: −71.2 (*c* 1.86, pentane); IR (CCl_4, NaCl): ν=3021, 2974, 2934, 2860, 2802, 1575, 1383, 1350, 1120, 845 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ=6.20–5.87 (m, 4H), 5.67 (d, J=2.8 Hz, 1H), 3.31 (t, J=6.8 Hz, 1H), 3.00 (td, J=6.8, 2.8 Hz, 1H), 2.29–2.17 (dt, J=11.4, 6.8 Hz, 1H), 1.40 (d, J=11.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=137.45, 137.36, 134.49, 125.81, 124.89, 84.44, 52.50, 45.31, 30.86; MS (ESI-MS) [M−H$^+$]: m/z=245 calcd. for C_9H_9I: 245.

Supporting Information

NMR spectra and chiral HPLC analyses of enantioenriched compounds. VCD studies: xyz coordinates found for compounds **3a,c**.

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