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On the Origin of Diastereoselectivity in [2 + 2 + 2] Cycloisomerization of Chiral Triynes: Controlling Helicity of Helicene-like Compounds by Thermodynamic Factors

Petr Sehnal,[†,‡] Zuzana Krausová,[†,‡] Filip Teplý,[†] Irena G. Stará,*[,†,‡] Ivo Starý,*[,†,‡] Lubomír Rulíšek,*[,†,‡] David Šaman,[†] and Ivana Císařová[§]

Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo nám. 2, 166 10 Prague 6, Czech Republic, and Department of Inorganic Chemistry, Charles University, Albertov 2030, 128 40 Prague 2, Czech Republic

stara@uochb.cas.cz; stary@uochb.cas.cz; rulisek@uochb.cas.cz

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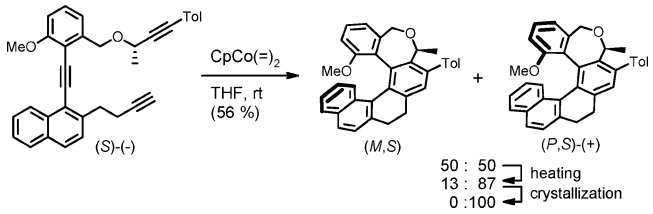

Diastereoselective Co^{I}-mediated [2 + 2 + 2] cycloisomerization of CH_3O-substituted optically pure aromatic triynes to obtain nonracemic functionalized helicene-like compounds (comprising a penta-, hexa-, and heptacyclic helical scaffold) was studied. The stereochemical outcome of the reaction at 140 °C using $CpCo(CO)_2$ was controlled by thermodynamic factors yielding diastereomeric ratios up to 91:9. Using $CpCo(ethylene)_2$ at room temperature, a kinetic control took place leading to the loss of stereoselectivity. Barriers to epimerization for selected helicene-like compounds were measured indicating their lower configurational stability in comparison to the parent carbohelicenes. Free energy differences between corresponding pairs of diastereomers (calculated at the DFT B3LYP/TZV+P level) were in excellent agreement with the experimental data and allowed for the prediction of the stereochemical outcome of the reaction. An optically pure hexacyclic helicene-like alcohol was prepared on a multigram scale. Its X-ray structure confirmed the previous helicity assignments being based on $^1H-^1H$ correlations in ROESY ^1H NMR spectra.

Introduction

Asymmetric synthesis of helicenes[1] and their congeners is envisioned to be the most straightforward and efficient route to single enantiomers of these attractive, helically chiral compounds. Various concepts have emerged[2] demonstrating basic principles rather than generally useful methodologies. However, some of them might be identified as highly promising because remarkable progress in obtaining nonracemic helicenes has already been achieved. Carreño and Urbano successfully developed an asymmetric version of the Diels−Alder approach (originally invented by Katz as a nonstereoselective process)[3] providing helicene quinones with excellent optical purities.[4] A remarkable stereocontrol in the synthesis of [5]helicenes was achieved by Karikomi, who used a completely diastereoselective

[†] IOCB Prague.

[‡] Center for Biomolecules and Complex Molecular Systems (supported by the Ministry of Education, Youth, and Sports of the Czech Republic).

[§] Charles University.

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aromatic oxy-Cope rearrangement as a key step.[5] An original approach was published by Genet, who took advantage of chirality transfer from an enantiopure tether to a flexible [5]-helicene backbone under thermal conditions, making it configurationally locked.[6] Nozaki described a stereospecific synthesis of hetero[7]helicenes via Pd-catalyzed N- or O-arylation of axially chiral substrates derived from optically pure 4,4′-biphenanthryl-3,3′-diol.[7] Very recently, Tanaka has demonstrated enatioselective Rh-catalyzed [2 + 2 + 2] cyclotrimerization of triynes in the synthesis of helicene-like compounds.[8] In addition to that, the past decade has witnessed other attempts at asymmetric synthesis of helicenes, but stereocontrol observed has been moderate rather than high as published by Rajca,[9] Tanaka,[10] Pérez and Guitián,[11] and our laboratory.[12] In spite of the above-mentioned achievements, practical asymmetric synthesis of helical aromatics has so far remained a challenging task.

Recently, we have contributed to solving this problem by synthesizing nonracemic [7]helicene-like scaffolds using diastereoselective [2 + 2 + 2] cycloisomerization of centrally chiral aromatic triynes.[13] Herein, we report the utilization of this methodology in the synthesis of functionalized penta-, hexa-, and heptacyclic aromatics in a nonracemic form. We also provide a detailed view of the origin of diastereoselectivity of the cyclization.

Methods

Quantum Chemical Calculations. All density functional theory (DFT) calculations reported in the study were carried out using Turbomole 5.7 program.[14] The PBE and B3LYP functionals[15,16] have been used throughout. The calculations were expedited by expanding the Coulomb integrals in an auxiliary basis set, the resolution-of-identity (RI) approximation.[17,18] All of the geometry optimizations were carried out using the RI-PBE method and 6-31G-(d) basis set,[19] whereas the single-point energies were recomputed in larger basis set TZV+P (triple-ζ valence with one polarization function on each atom),[20] using the B3LYP method. To account for solvation effects, the conductor-like screening model (COSMO) method[21,22] was used with the dielectric constant corresponding to acetonitrile ($\epsilon_r = 36.6$). Gibbs free energy was then calculated as the sum of these contributions (eq 1)

$$G = E_{el} + G_{solv} + E_{ZPE} - RT \ln(q_{trans}q_{rot}q_{vib}) \quad (1)$$

where E_{el} is the in vacuo energy of the system (at B3LYP/TZV+P level, using the geometry optimized at the RI-PBE/6-31G(d) level as described above), G_{solv} is the solvation free energy (at the RI-PBE/6-31G(d) level), E_{ZPE} is the zero-point energy, and $-RT \ln q_{trans}q_{rot}q_{vib}$) accounts for the entropic terms and the thermal correction to the enthalpy (obtained from a frequency calculation with the same method and software as for the geometry optimizations at RI-PBE/6-31G(d) level, 298 K and 1 atm pressure, using an ideal-gas approximation).[23] The free energy calculated according to eq 1 is a good approximation to ΔG in diluted solution.

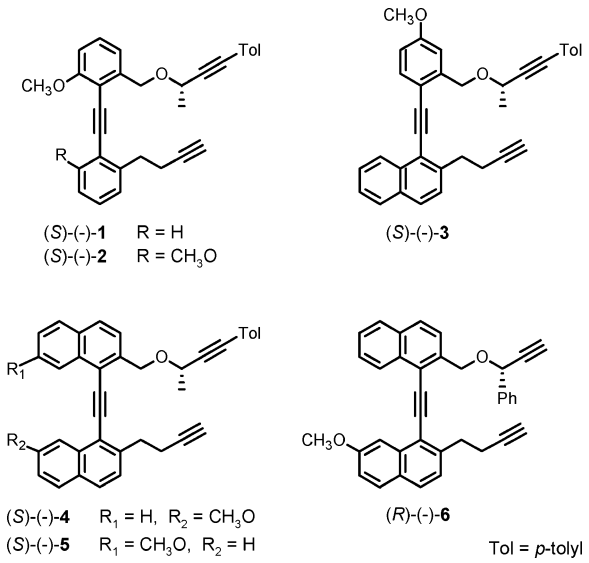

FIGURE 1. Model triynes for diastereoselective [2 + 2 + 2] cycloisomerization.

Results and Discussion

Synthesis of optically pure aromatic triynes (*S*)-(−)-**1**−**5** and (*R*)-(−)-**6** (Figure 1) containing an asymmetric carbon atom of known absolute configuration was accomplished[24] using the general methodology we published previously.[25]

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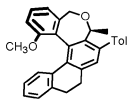
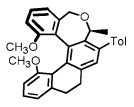
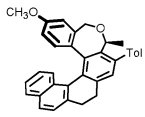
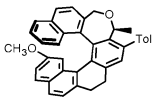
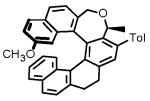
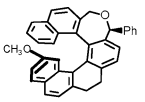
Diastereoselective [2 + 2 + 2] Cycloisomerization of Chiral Triynes 1−6. Triynes (*S*)-(−)-**1**−**5** and (*R*)-(−)-**6** bearing methoxy group(s) were subjected to [2 + 2 + 2] cycloisomerization under uniform reaction conditions using $CpCo(CO)_2$ with PPh_3 at 140 °C and visible light irradiation (Table 1). The presence of a chiral center was proposed to control the stereochemical outcome of the reaction giving rise to (*M*) or (*P*) helix predominantly.[26] In agreement with such an expectation, triyne (*S*)-(−-**1** provided the pentacyclic product (*P*,*S*)-(+)-**7** with high diastereoselectivity (Table 1, entry 1). Practically identical results were obtained with an analogous triyne (*S*)-(−)-**2**, which afforded the major dimethoxy derivative (*P*,*S*)-(+)-**8** (Table 1, entry 2). Moreover, triyne (*S*)-(−)-**3** was cycloisomerized to hexacyclic (*P*,*S*)-(+)-**9** with the same stereochemical outcome (Table 1, entry 3). Triynes (*S*)-(−)-**4** and (*S*)-(−)-**5**, differing only in the position of the methoxy group, provided heptacyclic (*P*,*S*)-(+)-**10** and (*P*,*S*)-(+)-**11**, respectively, with slightly lower distereoselectivity than in the previous runs (Table 1, entries 4 and 5). Thus, regardless of the helical backbone length and the methoxy group position, (*S*) configuration at the asymmetric center induced (*P*) helicity of the product. For the sake of increased diastereoselectivity, the methyl group at the chiral carbon was replaced with a more bulky phenyl one. However, cyclization of (*R*)-(−)-**6**[27]provided (*M*,*S*)-(−)-**12** with reversed diastereoselectivity (Table 1, cf. entry 4 and 6).

Synthesis of Optically Pure Alcohol (*P*,*S*)-(+)-25. As [2 + 2 + 2] cycloisomerization of the model functionalized triynes exhibited a good and predictable stereochemical outcome, we embarked upon a practical use of this reaction to prepare optically pure helical alcohol (*P*,*S*)-(+)-**25** on a gram scale (Scheme 1). The convergent synthesis started from commercially available *o*-vanillin **13** that was, upon transformation to nonaflate **14**, ethynylated with (triisopropylsilyl)acetylene under Pd^{II} catalysis. The presence of two ortho substituents did not hamper the coupling reaction, which led smoothly to **15**. The triisopropylsilyl protecting group was chosen to survive basic conditions in the following steps. To attach a chiral moiety, the aldehyde group in **15** was reduced with diisobutylaluminum hydride to afford benzylic alcohol **16**, which was further reacted with phosphorus tribromide providing benzylic bromide **17**.

Afterward, **17** was treated with a sodium salt of (*S*)-(−)-**18** (ref 25) to accomplish the synthesis of ether (*S*)-(−)-**19**, leaving the triisopropylsilyl group untouched. To assemble a triyne scaffold, (*S*)-(−)-**19** was desilylated with tetrabutylammonium fluoride and the resulting alkyne (*S*)-(−)-**20** was coupled with naphthyl iodide **21** (ref 28) under Pd^0/Cu^I catalysis to provide (*S*)-(−)-**22**. Deprotecting a pendant acetylene unit with tetrabutylammonium fluoride, the triyne (*S*)-(−)-**23** was obtained which could undergo the key [2 + 2 + 2] cyclization step. Under Co^I catalysis, the helical products (*P*,*S*)-(+)- and (*M*,*S*)-**24** were obtained in a 87:13 ratio and in a good preparative yield. Although diastereoselectivity of the cyclization was lower than required, a single crystallization of the mixture led to the optically pure (*P*,*S*)-(+)-**24**.

TABLE 1. Diastereoselective [2 + 2 + 2] Cycloisomerization

entry	educt	cond.[a] (°C, h)	products[b,c]	yield (%)[d]
1	(*S*)-(-)-**1**	A 140°, 4	 (*M*,*S*)-**7** : (*P*,*S*)-**7** = 10 : 90 ([α]$_D$ +170, c 0.20, CH_2Cl_2)	56
2	(*S*)-(-)-**2**	A 140°, 4	 (*M*,*S*)-**8** : (*P*,*S*)-**8** = 9 : 91 ([α]$_D$ +231, c 0.004, CH_2Cl_2)[f]	89 (59)[e]
3	(*S*)-(-)-**3**	A[g] 120°, 36	 (*M*,*S*)-**9** : (*P*,*S*)-**9** = 10 : 90 ([α]$_D$ +204, c 0.27, CH_2Cl_2)	50
4	(*S*)-(-)-**4**	A 140°, 3	 (*M*,*S*)-**10** : (*P*,*S*)-**10** = 17 : 83 ([α]$_D$ +297, c 0.10, CH_2Cl_2)	58
5	(*S*)-(-)-**5**	A 140°, 3	 (*M*,*S*)-**11** : (*P*,*S*)-**11** = 27 : 73 ([α]$_D$ +136, c 0.08, CH_2Cl_2)	72
6	(*R*)-(-)-**6**	A 140°, 1	 (*M*,*S*)-**12** : (*P*,*S*)-**12** = 84 : 16[h] ([α]$_D$ -257, c 0.34, CH_2Cl_2)	95

[a] A: $CpCo(CO)_2$ (1.0 equiv), PPh_3 (2.0 equiv), decane, irradiated with a halogen lamp unless noted otherwise. [b] The optical rotations were measured for the diastereomer ratios indicated unless noted otherwise. [c] The ratios of diastereomers were inferred from ^{1}H NMR spectra unless noted otherwise. [d] Isolated yield of a mixture of both diastereomers. [e] The yield of pure (*P*,*S*)-(+) diastereomer after crystallization of the mixture of diastereomers. [f] Optical rotation of pure (*P*,*S*)-(+) diastereomer. [g] In dioxane. [h] The ratio of diastereomers was determined by HPLC on a Chiralcel OD-H column.

The helicity assignment of (*P*,*S*)-(+)-**24** stems from a ROESY ^{1}H NMR spectrum[13b] where a decisive through-space interaction between proximal 3-H and 2′,6′-H of the 4-tolyl group (ca. 2.3 Å) was monitored. In contrast, such an interaction could not be observed in (*M*,*S*)-**24** possessing the opposite helicity and,

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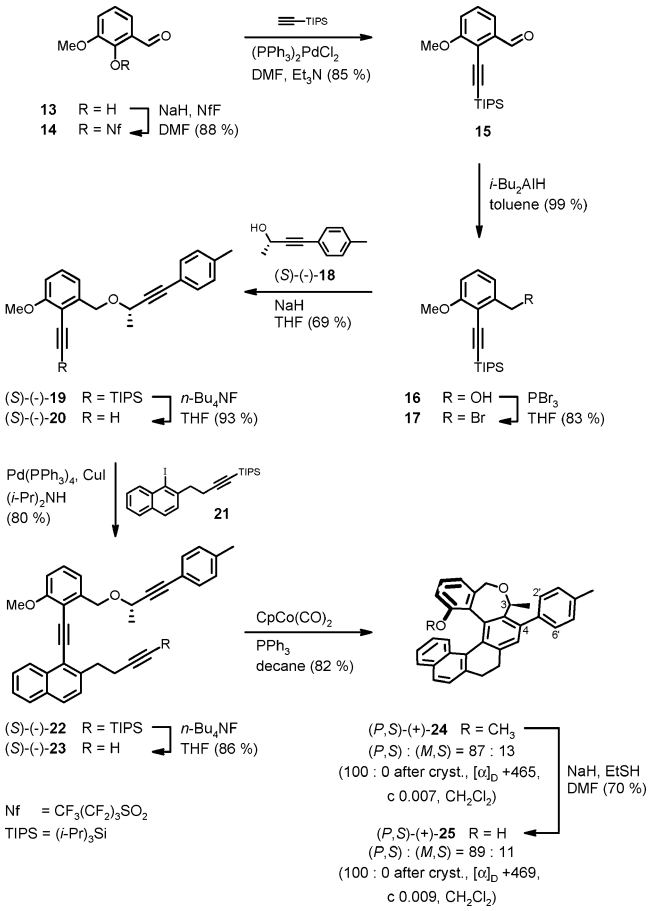
(26) Helicity assignments are based on considering distances between relevant protons and observed ^{1}H−^{1}H correlations in ROESY ^{1}H NMR spectra. Such an approach is described in ref 13b and exemplified here by a structure analysis of (*P*,*S*)-(+)-**24**.

(27) Although the sense of absolute configuration at the chiral center was conserved, the CIP notation denotes it contrariwise.

(28) Stará, I. G.; Kollárovič, A.; Teplý, F.; Starý, I.; Šaman, D.; Fiedler, P. *Collect. Czech. Chem. Commun.* **2000**, *65*, 577.

SCHEME 1. Synthesis of Optically Pure Helical Alcohol (*P*,*S*)-(+)-25



accordingly, having a significantly larger distance between the above-mentioned protons (ca. 4.6 Å). Furthermore, the 3-CH_3 signal of (*P*,*S*)-(+)-**24** lies at 0.67 ppm while for diastereomer (*M*,*S*)-**24** at 0.92 ppm. It corresponds to a helicity−chemical shift relation observed recently in ^{1}H NMR spectra of a series of analogous heptacyclic helicene-like compounds.[13b] In that case, the CH_3 groups were found to resonate within a 0.54−0.62 ppm interval for (*P*)-helices and within a 1.58−1.67 ppm interval for (*M*)-helices.

To accomplish the preparation of alcohol (*P*,*S*)-(+)-**25**, the final demethylation step was examined. The use of boron tribromide resulted in the formation of a complex mixture of products. However, the treatment of (*P*,*S*)-(+)-**24** with sodium ethanethiolate at 130 °C led exclusively to the removal of the methyl group leaving the benzylic moiety untouched, and therefore, (*P*,*S*)-(+)-**25** was isolated in good yield. It should be noted that, starting from diastereomerically pure (*P*,*S*)-(+)-**24**, partial epimerization took place obtaining (*P*,*S*)-(+)- and (*M*,*S*)-**25** in a 89:11 ratio. Similar to the above-mentioned purification of (*P*,*S*)-(+)-**24**, a single crystallization provided the optically pure product (*P*,*S*)-(+)-**25**. As suitable crystals for an X-ray analysis were grown,[29] the structure could be ultimately confirmed as being in full accordance with that inferred from

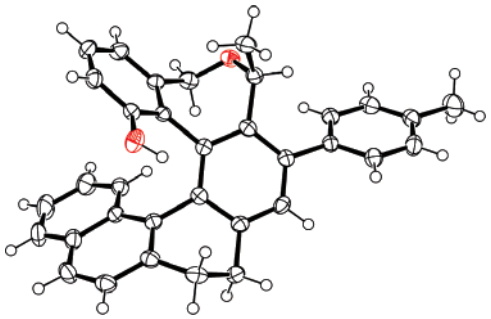


FIGURE 2. Single-crystal molecular structure of (*P*,*S*)-(+)-**25**.

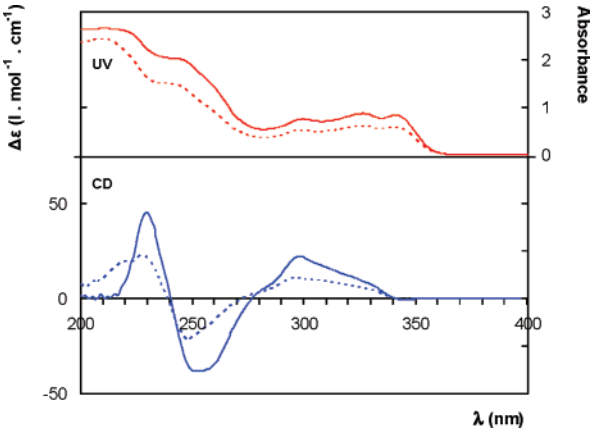


FIGURE 3. UV absorption spectrum (top, ordinate on the right, red) and CD spectrum (bottom, ordinate on the left, blue) of a 1.0×10^{-3} M solution of (*P*,*S*)-(+)-**24** (solid line) and (*P*,*S*)-(+)-**25** (dashed line) in CH_3CN.

^{1}H NMR spectra (Figure 2). In addition, CD spectra of (*P*,*S*)-(+)-**24** and (*P*,*S*)-(+)-**25** were measured (Figure 3). Throughout the whole synthetic scheme, isolated yields ranged from good to excellent ones and all steps were performed on a multigram scale.

Thermodynamic versus Kinetic Control. Despite the fact that a successful synthesis of optically pure (*P*,*S*)-(+)-**25** was developed, we decided to strive for higher diastereoselectivity in the key [2 + 2 + 2] cycloisomerization step. Provided the cyclization of (*S*)-(−)-**23** proceeds at a lower temperature, a better stereochemical outcome might be expected. Using Jonas catalyst CpCo(ethylene)$_2$,[30] which exhibits generally higher reactivity than CpCo(CO)$_2$, the practically instantaneous cyclization of (*S*)-(−)-**23** took place at room temperature. To our surprise, the reaction yielded (*P*,*S*)-(+)- and (*M*,*S*)-**24** in an equimolar ratio (Scheme 2). In order to verify such an unexpected result, the structurally related triyne (*S*)-(−)-**26**[13b] was cyclized under the same reaction conditions to provide (*P*,*S*)-(+)- and (*M*,*S*)-**27** in a nearly equimolar ratio (44 : 56).[31] Thus, diastereoselectivity was practically lost by lowering the reaction temperature.

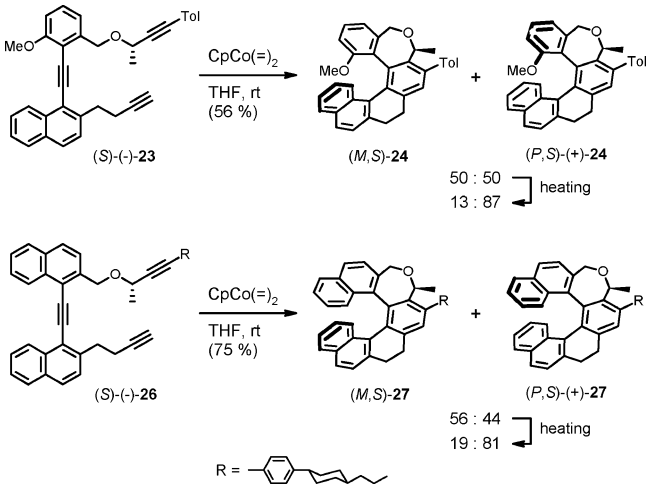
This behavior raised a rather fundamental question whether [2 + 2 + 2] cycloisomerization of chiral triynes (*S*)-(−)-**1**−**5**, (*R*)-(−)-**6**, (*S*)-(−)-**23**, and (*S*)-(−)-**26** is controlled by kinetic

(29) CCDC-625112 contains the supplementary crystallographic data for (*P*,*S*)-(+)-**25**. These data can be obtained free of charge from Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_reguest/cif or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223) 336033; e-mail: deposit@ccdc.cam.ac.uk.

(30) (a) Cammack, J. K.; Jalisatgi, S.; Matzger, A. J.; Negrón, A.; Vollhardt, K. P. C. *J. Org. Chem.* **1996**, *61*, 4798. (b) Jonas, K.; Deffense, E.; Habermann, D. *Angew. Chem. Int. Ed.* **1983**, *22*, 716; *Angew. Chem. Suppl.* **1983**, 1005.

(31) It should be noted that utilizing CpCo(CO)$_2$ at 140 °C resulted in a preferential formation of (*P*,*S*)-(+)-**27** (ref. 13b).

SCHEME 2. [2 + 2 + 2] Cycloisomerization of Chiral Triynes (*S*)-(−)-23 and 26 and Epimerization of the Helical Products 24 and 27 under Thermal Conditions



or thermodynamic factors. Hence, having in hand two helical products **24** and **27**, each of them in the form of two distinct diastereomeric mixtures, their configurational stability was examined under the cyclization reaction conditions (140 °C, decane, 6 h). While the initial ratios of (*P*,*S*)/(*M*,*S*) = 87:13 (for **24**) and 81:19 (for **27**) did not change over the course of time, the initial ratios of (*P*,*S*)/(*M*,*S*) = 50:50 (for **24**) and 44:56 (for **27**) converged to the values of about 87:13 (for **24**) and 81:19 (for **27**). Obviously, both **24** and **27** undergo thermal epimerization process during the $CpCo(CO)_2$-mediated cyclization of the corresponding triynes at 140 °C in such a way that the stereochemical outcome of the reactions reflects the thermodynamic stability of the diastereomeric products. On the other hand, the kinetic control apparently operates under the $CpCo(ethylene)_2$ catalysis at room temperature.[32] Such observations indicate, moreover, that diastereoselective cyclizations of triynes (*S*)-(−)-**1**−**5** and (*R*)-(−)-**6** (Table 1) at elevated temperature proceeds under thermodynamic control.

Barriers to Epimerization. To characterize the dynamic behavior of the helicene-like compounds **24** and **27** in detail, their barriers to epimerization $\Delta G^{\ddagger}$ were measured. A purely conformational process under the thermal conditions was considered, leading to a mutual interconversion of the (*P*) and (*M*) helices while conserving the (*S*) absolute configuration at the asymmetric carbon atom (eq 2).

$$(M,S) \underset{k_{P\rightarrow M}}{\overset{k_{M\rightarrow P}}{\rightleftharpoons}} (P,S) \qquad (2)$$

Such a reversible monomolecular reaction can be described by the first-order kinetic equation in an integrated form (eq 3) considering the equilibrium conditions at the same time (eq 4). Here, $k_{M\rightarrow P}$ and $k_{P\rightarrow M}$ are rate constants (s^{-1}) for the (*M*)→(*P*) and (*P*)→(*M*) helix interconversions, (*M*,*S*) represents a current concentration (%) of (*M*,*S*) diastereomer, $(M,S)_{eq}$ represents its equilibrium concentration (%), $(M,S)_0$ represents its initial concentration (%), and *t* is time (s).

$$(M,S) = (M,S)_{eq} + [(M,S)_0 - (M,S)_{eq}] \exp(-(k_{M\rightarrow P} + k_{P\rightarrow M})t) \qquad (3)$$

$$\frac{k_{M\rightarrow P}}{k_{P\rightarrow M}} = \frac{100 - (M,S)_{eq}}{(M,S)_{eq}} \qquad (4)$$

$$\Delta G^{\ddagger} = RT \ln\left(\frac{k_B T}{h k_{exp}}\right) \qquad (5)$$

By heating the mixtures of (*M*,*S*) and (*P*,*S*) diastereomers of **24** (initially 50:50, at 87 °C in heptane) and **27** (initially 56:44, at 131 °C in decane) and monitoring continuously the diastereomer ratios by HPLC (on a Chiralcel OD-H column), the kinetic data could be acquired. After applying exponential regression to the plotted time-dependent concentration of the (*M*,*S*) diastereomer, the $(M,S)_{eq}$ concentration and the sum of the rate constants ($k_{M\rightarrow P} + k_{P\rightarrow M}$) could be read. Using these figures and eqs 4 and 5, the barriers to epimerization were calculated along with other kinetic data (Table 2).

Thus, configurational stabilities of the helicene-like products were found to be lower than originally expected. This is more obvious from a comparison of the barrier to epimerization of hexacyclic (*P*,*S*)-(+)-**24** (27.7 kcal/mol) and heptacyclic (*P*,*S*)-(+)-**27** (31.9 kcal/mol) with the barriers to racemization of parent fully aromatic hexahelicene (36.2 kcal/mol)[33] and heptahelicene (41.7 kcal/mol),[33a] respectively. It indicates that the incorporation of more flexible dihydrobenzene and dihydrooxepine rings results in a higher conformational flexibility of the helical scaffold and, therefore, in lowering the barrier to epimerization. Note that even the presence of the 1-methoxy group in (*P*,*S*)-(+)-**24** does not lead to its considerably higher configurational stability as it is known from 1-substituted helicenes.[34]

Quantum Chemical Calculations. Apparently, thermodynamic factors may control the stereochemical outcome of the studied triyne [2 + 2 + 2] cycloisomerization. To gain a deeper insight into diastereoselectivity of the reaction, the differences in Gibbs free energies between the (*M*,*S*) and (*P*,*S*) diastereomers of helicene-like compounds **7**−**12**, **24**, and **27**−**31**[13b] were calculated at the DFT B3LYP/TZV+P level. The results are summarized in Table 3 and compared with the experimental values (Figure 4).

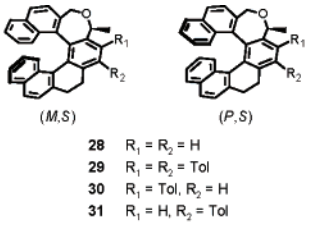
A remarkable agreement between the experimental and computed (*M*,*S*) vs (*P*,*S*) diastereomer ratios of helicene-like compounds **7**−**12**, **24**, and **27**−**31** was found. The mean absolute deviation (MAD) between the computed and experimental values has been calculated as $MAD(\Delta G_{calc} - \Delta G_{exp}) = 0.63$ kcal/mol. Therefore, the stereochemical outcome of chiral triyne [2 + 2 + 2] cycloisomerization at higher temperature might be fully predicted on the basis of thermodynamic stabilities of the (*M*,*S*) and (*P*,*S*) diastereomeric pairs.

On the Origin of Diastereoselectivity. To address the origin of diastereoselectivity in [2 + 2 + 2] cycloisomerization of chiral triynes, the possible rationale for that can be clarified on the example of the helicene-like compounds **28** and **29** (Figure 5). The difference in free energy content between (*M*,*S*) and

(32) Diastereomerically pure (*P*,*S*)-(+)-**24** and **27** were found to be configurationally stable at room temperature.

(33) (a) Martin, R. H.; Marchant, M. J. *Tetrahedron* **1974**, *30*, 347. (b) Martin, R. H.; Marchant, M. J. *Tetrahedron Lett.* **1972**, *35*, 3707.

(34) (a) Janke, R. H.; Haufe, G.; Würthwein, E.-U.; Borkent, J. H. *J. Am. Chem. Soc.* **1996**, *118*, 6031. (b) Scherübl, H.; Fritzsche, U.; Mannschreck, A. *Chem. Ber.* **1984**, *117*, 336. (c) Borkent, J. H.; Laarhoven, W. H. *Tetrahedron* **1978**, *34*, 2565.



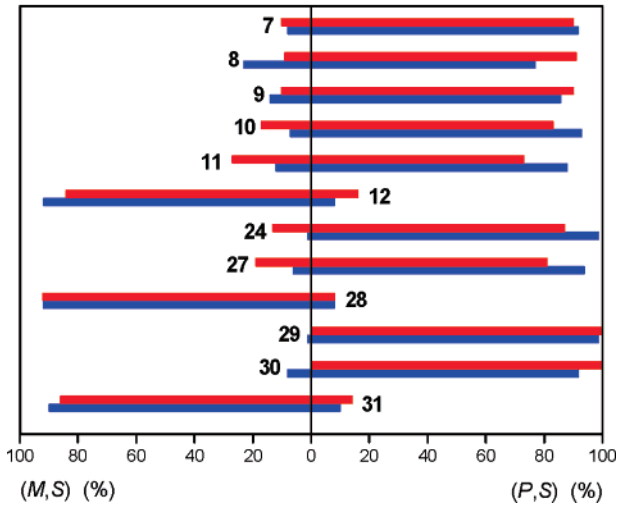


FIGURE 4. (*M*,*S*) to (*P*,*S*) diastereoisomer ratios of helical products **7**−**12**, **24**, and **27**−**31** (red bars, experimental results; blue bars, computed).

TABLE 2. Kinetic Data for 24 and 27

	24	**27**
T (K)	360.0	403.8
solvent	heptane	decane
$k_{M\rightarrow P}$ (s^{-1})	6.96×10^{-4}	1.98×10^{-4}
$k_{P\rightarrow M}$ (s^{-1})	1.07×10^{-4}	4.63×10^{-5}
$\Delta G^{\ddagger}_{M\rightarrow P}$ (kcal/mol)	26.4	30.7
$\Delta G^{\ddagger}_{P\rightarrow M}$ (kcal/mol)	27.7	31.9
$t_{1/2}$ (min) for (*M*,*S*)	16.6	58.3
$t_{1/2}$ (min) for (*P*,*S*)	108.0	249.5

TABLE 3. Calculated Differences in Gibbs Free Energies (in kcal/mol) between the (*M*,*S*) and (*P*,*S*) Pairs of Diastereomers

compd	ΔG_{calc} [a,b]	(*M*,*S*)/(*P*,*S*)$_{calc}$ [b]	(*M*,*S*)/(*P*,*S*)$_{exp}$ [c]	$\Delta G_{calc} - \Delta G_{exp}$ [d]
7	2.04	8:92	10:90	−0.23
8	1.00	23:77	9:91	0.91
9	1.48	14:86	10:90	0.33
10	2.16	7:93	17:83	−0.86
11	1.65	12:88	27:73	−0.83
12	−3.02	98:2	84:16	1.65
24	1.38	16:84	13:87	0.18
27	2.20	6:94	19:81	−1.00
28	−1.99	92:8	92:8	−0.02
29	4.18	1:99	0:100	
30	2.05	8:92	0:100	
31	−1.78	90:10	86:14	0.29

[a] The positive value indicates the higher stability of (*P*,*S*) diastereomer. [b] Calculated at the B3LYP/TZV+P//RI-PBE/6-31G* level. [c] The stereochemical outcome of $CpCo(CO)_2$ mediated [2 + 2 + 2] cycloisomerization at 140 °C. [d] Mean absolute deviation (MAD) = 0.63 kcal/mol.

(*P*,*S*) diastereomers is given by competing steric interactions of (1*S*)-CH_3 with either a naphthalene unit fused to the dihydrooxepine ring or a substituent at C-19. The inspection of molecular models shows that an (*M*) helical arrangement brings (1*S*)-CH_3 and the substituent at C-19 to a steric interaction and, vice versa, a (*P*) helical arrangement leads to a steric interaction of (1*S*)-CH_3 with the naphthalene unit. If the substituent at C-19 is small (e.g., hydrogen), then the interaction between it and (1*S*)-CH_3 is favored and, accordingly, (*M*,*S*) diastereomer is more populated as evidenced by a ratio of (*M*,*S*)-**28**/(*P*,*S*)-**28** = 92 : 8. In contrast, if the substituent at C-19 is larger (e.g., the tolyl group), then its interaction with (1*S*)-CH_3 is disfavored and (*P*,*S*) diastereomer prevails as manifested by a ratio of (*M*,*S*)-**29**/(*P*,*S*)-**29** = 0 : 100.

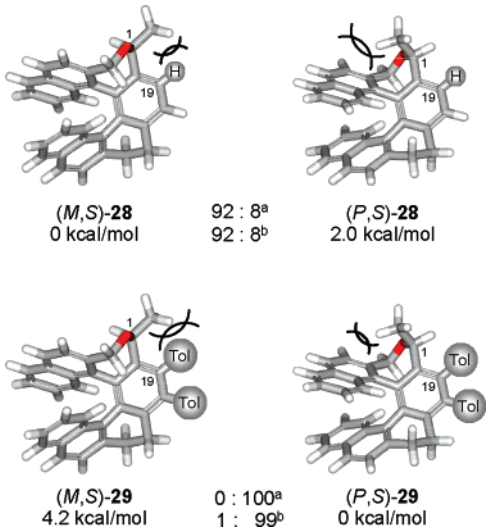


FIGURE 5. Steric repulsion in compounds **28** and **29** between 1-CH_3 and a substituent at C-19 (H, tolyl) or the proximal naphthalene moiety ([a]experimental, [b]calculated; relative energies computed by DFT B3LYP/TZV+P method).

Conclusions

In summary, most attention was paid to $CpCo(CO)_2$-catalyzed diastereoselective [2 + 2 + 2] cycloisomerization of CH_3O-substituted optically pure triynes to provide nonracemic functionalized helicene-like compounds. Performing the cyclization of *p*-tolyl-substituted triynes at 140 °C, diastereomer ratios ranged from 27:73 to 9:91. The (*S*) configuration at the asymmetric center of triynes induced predominantly (*P*) helicity of the products regardless of the CH_3O group position and the helical backbone size. By contrast, cyclization of triyne without the *p*-tolyl group displayed reversed diastereoselectivity. Performing $CpCo(ethylene)_2$ mediated [2 + 2 + 2] cycloisomerization of chiral triynes at room temperature, no or marginal diastereoselectivity was observed. Kinetic studies revealed that (*M*,*S*) and (*P*,*S*) diastereomers of the helicene-like compounds with a hexacyclic or heptacyclic backbone underwent thermal equilibration, which led finally to the same ratios of (*M*,*S*) and (*P*,*S*) diastereomers as those monitored in the corresponding [2 + 2 + 2] cycloisomerizations at elevated temperature. Barriers to epimerization were measured for both diastereomers of selected compounds and found to be lower than those for parent helicenes due to a higher flexibility of the not fully aromatic helicene-like skeletons. It clearly indicated that diastereoselectivity of [2 + 2 + 2] cycloisomerization of chiral triynes at 140 °C was controlled by thermodynamic factors whereas kinetic factors operated at room temperature. Computing the differences in free energies between the (*M*,*S*) and (*P*,*S*) pairs

of diastereomers at the DFT B3LYP/TZV+P level, an excellent agreement was found between theory and experiment. Accordingly, the stereochemical outcome of diastereoselective [2 + 2 + 2] cycloisomerization of chiral triynes at elevated temperature might be predicted on the theoretical basis. Stemming from these findings, the preparation of optically pure helicene-like alcohol (*P*,*S*)-(+)-**25** was accomplished on a multigram scale. Finally, the X-ray structure of it confirmed the previous helicity assignments based on ^{1}H-^{1}H correlations in ROESY ^{1}H NMR spectra. Work is presently being done to utilize (*P*,*S*)-(+)-**25** in enantioselective catalysis.

Experimental

2-Formyl-6-methoxyphenyl 1,1,2,2,3,3,4,4,4-Nonafluorobutane-1-sulfonate (14). A 250 mL flask was charged with NaH (80% suspension in mineral oil, 2.56 g, 85.40 mmol, 1.30 equiv) and put under argon. Dry petroleum ether (10 mL) was added, and after the mixture was stirred for 2 min, the liquid was removed via syringe. DMF (23 mL) was added, and the stirred suspension was cooled to 0 °C. A solution of **13** (10.00 g, 65.7 mmol) in DMF (44 mL) was added dropwise, and the reaction mixture was stirred at room temperature for 90 min. After the mixture was cooled again to 0 °C, nonaflate fluoride (24.56 g, 81.3 mmol, 1.24 equiv) was added, and the reaction mixture was stirred at room temperature for 18 h. The solvent was removed in vacuo (60 °C, 20 mbar), and the crude product was chromatographed on silica gel (petroleum ether−ether−acetone 80:10:10) to provide **14** (26.46 g, 93%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.92 (3 H, s), 7.28 (1 H, dd, J = 8.2, 1.7 Hz), 7.42 (1 H, ddd, J = 8.2, 7.8, 0.8 Hz), 7.48 (1 H, dd, J = 7.8, 1.7 Hz), 10.22 (1 H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ 56.5 (q), 118.7 (d), 120.9 (d), 129.1 (d), 129.5 (s), 139.5 (s), 151.7 (s), 186.7 (d). IR (CCl_4): 3081 vw, 3018 w, 2844 w, 1707 vs, 1682 w, 1609 w, 1583 s, 1481 s, 1459 m, 1439 s (sh), 1432 vs, 1393 m, 1353 s, 1313 s, 1285 vs, 1242 vvs, 1227 vs, 1208 vs, 1202 vs, 1147 vs, 1077 s, 1070 s, 1032 m, 1010 m, 912 m, 720 m, 594 m, 570 m, 530 m, 510 m. EI MS: 434 ($M^{+\bullet}$, 24), 151 (100), 136 (12), 108 (16), 93 (18). HR EI MS: calcd for $C_{12}H_7O_5F_9S$ 433.9871, found 433.9868.

3-Methoxy-2-{[tris(1-methylethyl)silyl]ethynyl}benzaldehyde (15). A Teflon autoclave was charged with $PdCl_2(PPh_3)_2$ (1.16 g, 1.65 mmol, 5 mol %) and put under argon. Via septum and syringe, a solution of **14** (14.60 g, 33.60 mmol) in DMF (44 mL), (triisopropylsilyl)acetylene (7.36 g, 40.30 mmol, 1.20 equiv), and triethylamine (17.42 g, 172 mmol, 5.12 equiv) were added, and the autoclave was heated to 90 °C for 2 h. Solvents were removed in vacuo, and the crude product was chromatographed on silica gel (petroleum ether−ether−acetone 95:5:0 to 80:10:10) to provide **15** (19.45 g, 90%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.12−1.18 (21 H, m), 3.91 (3 H, s), 7.10 (1 H, dd, J = 8.2, 1.1 Hz), 7.37 (1 H, dt, J = 8.1, 8.1, 1.0 Hz), 7.51 (1 H, dd, J = 7.8, 1.1 Hz), 10.62 (1H, d, J = 1.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.3 (d), 18.65 (q), 56.3 (q), 97.7 (s), 104.2 (s), 115.8 (d), 116.9 (s), 118.6 (d), 129.2 (d), 137.5 (s), 161.5 (s), 192.1 (d). IR (CCl_4): 3069 w, 3006 m, 2866 vs, 2840 s (sh), 2826 m (sh), 2740 w, 2154 s, 1704 vs, 1678 m, 1593 s, 1573 s, 1472 vs, 1465 vs (sh), 1452 s (sh), 1438 s, 1384 s, 1367 w, 1296 s, 1270 vs, 1244 vs, 1207 m, 1185 m, 1151 w, 1080 s, 1071 s, 997 s, 912 s, 883 s, 835 s, 735 m, 680 vs, 660 s, 619 m, 545 w, 498 m, 463 m. FAB MS: 317 ([M + H]$^+$), 273, 249, 231, 217, 203, 181. HR FAB MS: calcd for $C_{19}H_{29}O_2Si$ 317.1937, found 317.1904.

(3-Methoxy-2-{[tris(1-methylethyl)silyl]ethynyl}phenyl)methanol (16). A 750 mL flask was charged with **15** (23.60 g, 74.56 mmol) and put under argon. Toluene (250 mL) was added, and the resulting solution was cooled to −78 °C. Via syringe, a diisobutylaluminium hydride solution (1.5 M in toluene, 52.2 mL, 78.30 mmol, 1.05 equiv) was added dropwise. The reaction mixture was stirred at −78 °C for 1 h. A saturated NaCl solution (200 mL) was added to decompose unreacted hydride, and the resulting mixture was extracted with dichloromethane (4 × 200 mL). The organic phase was dried over anhydrous Na_2SO_4, and the solvents were removed in vacuo. Chromatography of the crude product on silica gel (petroleum ether−ether−acetone 80:10:10) provided **16** (23.15 g, 97%) as a crystalline solid. Mp: 36−39 °C (petroleum ether−ether−acetone). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.12−1.17 (21 H, m), 2.33 (1 H, m), 3.87 (3 H, s), 4.82 (2 H, bd, J = 5.6 Hz), 6.82 (1 H, dd, J = 8.3, 0.6 Hz), 7.01 (1 H, ddt, J = 7.7, 1.0, 0.7, 0.7 Hz), 7.27 (1 H, dd, J = 8.3, 7.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.3 (d), 18.7 (q), 56.0 (q), 64.3 (t), 100.4 (s), 100.9 (s), 110.1 (d), 110.9 (s), 119.3 (d), 129.5 (d), 145.0 (s), 161.2 (s). IR (CCl_4): 3638 w, 3620 w, 3574 w, 3490 vw (br), 3070 w, 3028 w (sh), 3004 w, 2866 vs, 2839 m, 2150 s, 1597 w, 1577 s, 1473 vs, 1462 s, 1438 m, 1388 m, 1384 m, 1367 w, 1341 w, 1298 m, 1274 vs, 1252 w (sh), 1210 m, 1193 w, 1183 w (sh), 1152 vw, 1085 s, 1072 m (sh), 1041 s, 1018 s, 997 m, 920 w, 900 w, 883 s, 839 s, 722 m, 678 s, 662 s, 619 w, 582 w, 546 w, 498 w, 464 w. EI MS: 318 ($M^{+\bullet}$, 35), 275 (47), 260 (5), 245 (94), 233 (100), 217 (26), 205 (95), 189 (30), 173 (19), 161 (10), 149 (33), 129 (32), 115 (73), 102 (43), 91 (26), 75 (39), 61 (55), 43 (78). HR EI MS: calcd for $C_{19}H_{30}O_2Si$ 318.2015, found 318.2005.

{[2-(Bromomethyl)-6-methoxyphenyl]ethynyl}[tris(1-methylethyl)]silane (17). A 250 mL flask was charged with **16** (13.48 g, 42.32 mmol) and put under argon. THF (80 mL) was added, and the resulting solution was cooled to 0 °C. Phosphorus tribromide (12.60 g, 46.54 mmol, 1.10 equiv) was added dropwise, and the reaction mixture was stirred at 0 °C for 1 h. Solvent was removed in vacuo, and the crude product was chromatographed on silica gel (petroleum ether−ether−acetone 80:10:10) to provide **17** (15.68 g, 97%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.12−1.22 (21 H, m), 3.86 (3 H, s), 4.68 (2 H, s), 6.81 (1 H, dd, J = 8.4, 1.0 Hz), 7.02 (1 H, dd, J = 7.7, 1.0 Hz), 7.23 (1 H, dd, J = 8.4, 7.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.4 (d), 18.7 (q), 31.8 (t), 56.0 (q), 99.5 (s), 101.9 (s), 110.8 (d), 113.0 (s), 121.7 (d), 129.3 (d), 141.2 (s), 161.2 (s). IR (CCl_4): 3070 w, 3038 w (sh), 3005 m, 2866 vs, 2839 s, 2155 s, 1595 m, 1575 vs, 1473 vs, 1462 vs (sh), 1438 s, 1384 m, 1367 w, 1300 vs, 1275 vs, 1223 s, 1206 s, 1188 w, 1152 w, 1084 vs, 1071 vs, 1018 m, 997 s, 920 m, 883 vs, 835 s, 722 s, 677 vs, 660 vs, 624 s, 613 m (sh), 547 m, 512 w, 496 m, 463 m. EI MS: 380/382 ($M^{+\bullet}$, 8), 337/339 (17), 307/309 (8), 295 (8), 267 (8), 187 (8), 173 (8), 149 (15), 129 (8), 115 (14), 71 (8), 57 (17), 43 (100). HR EI MS: calcd for $C_{19}H_{29}OSi\ ^{81}Br$ 382.1151, found 382.1144; calcd for $C_{19}H_{29}OSi\ ^{79}Br$ 380.1171, found 380.1157.

{[2-Methoxy-6-({[(1*S*)-1-methyl-3-(4-methylphenyl)prop-2-yn-1-yl]oxy}methyl)phenyl]ethynyl}[tris(1-methylethyl)]silane (19). A 250 mL three-neck flask was charged with NaH (80% suspension in mineral oil, 517 mg, 17.20 mmol, 1.21 equiv) and put under argon. Dry petroleum ether (10 mL) was added, and after the mixture was stirred for 2 min, the liquid was removed via syringe. THF (8 mL) was added, and the stirred suspension was cooled to 0 °C. A solution of (*S*)-(−)-**18** (2.73 g, 17.00 mmol, 1.20 equiv) in THF (50 mL) was added dropwise. The reaction mixture was stirred at room temperature for 1 h and then warmed to 40 °C until all NaH dissolved. A solution of **17** (5.42 g, 14.20 mmol) in THF (50 mL) was added and the reaction was heated to 60 °C for 8 h. Solvent was removed in vacuo, and the crude product was chromatographed on silica gel (petroleum ether−ether 100:0 to 98:2) to provide (*S*)-(−)-**19** (4.86 g, 74%) as an oil. Optical rotation: $[\alpha]^{22}_D$ −93 (*c* 0.006, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.07−1.16 (21 H, m), 1.58 (3 H, d, J = 6.6 Hz), 2.34 (3 H, s), 3.85 (3 H, s), 4.51 (1 H, q, J = 6.6 Hz), 4.82 (1 H, d, J = 13.3 Hz), 4.91 (1 H, d, J = 13.3 Hz), 6.78 (1 H, dd, J = 8.2, 0.9 Hz), 7.10 (2 H, m), 7.14 (1 H, dq, J = 7.9, 0.9, 0.9, 0.9 Hz), 7.27 (1 H, t, J = 8.1 Hz), 7.31 (2 H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.4 (d), 18.7 (q), 21.4 (q), 22.3 (q), 56.0 (q), 65.8 (d), 68.8 (t), 85.2 (s), 88.3 (s), 100.1 (s), 100.6 (s), 109.6 (d), 111.2 (s), 119.1 (d), 119.8 (s), 128.9 (d), 129.1 (d), 131.7 (d), 138.2 (s), 142.5 (s),

160.9 (s). IR (CCl_4): 3071 w, 3052 w, 3031 w, 2987 m, 2866 vs, 2838 m, 2228 w, 2153 m, 1597 w, 1579 m, 1511 s, 1473 vs, 1462 s, 1438 s, 1408 w, 1384 m, 1371 m, 1328 s, 1313 m, 1275 vs, 1209 m, 1184 w, 1152 w (sh), 1116 s, 1106 s, 1087 s, 1063 vs, 1031 m, 1019 m, 996 m, 919 m, 883 s, 839 s, 818 s, 730 w, 723 w (sh), 709 w, 677 s, 663 s, 648 m (sh), 621 w, 546 w, 522 w, 498 w, 463 w. EI MS: 417 ($[M - CH(CH_3)_2]^+$, 8), 390 (3), 373 (4), 289 (10), 259 (6), 239 (4), 227 (5), 185 (13), 157 (9), 143 (100), 128 (27), 115 (17), 59 (14). HR EI MS: calcd for $C_{27}H_{33}O_2Si$ [M − $CH(CH_3)_2$] 417.2250, found 417.2254.

2-Ethynyl-1-methoxy-3-({[(1*S*)-1-methyl-3-(4-methylphenyl)-prop-2-yn-1-yl]oxy}methyl)benzene (20). A 250 mL flask was charged with (*S*)-(−)-**19** (13.10 g, 28.43 mmol) and put under argon. THF (125 mL) was added, and the resulting solution was treated with a tetrabutylammonium fluoride solution (1.072 M in THF, 32 mL, 34.30 mmol, 1.21 equiv). The reaction mixture was stirred at room temperature for 40 min. Solvent was removed in vacuo, and the crude product was chromatographed on silica gel (petroleum ether−ether 95:5) to provide (*S*)-(−)-**20** (7.91 g, 91%) as a crystalline solid. Mp: 80−82 °C (petroleum ether−ether). Optical rotation: $[\alpha]^{22}_D$ −125 (*c* 0.012, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.57 (3 H, d, J = 6.6 Hz), 2.34 (3 H, s), 3.53 (1 H, s), 3.90 (3 H, s), 4.50 (1 H, q, J = 6.6 Hz), 4.79 (1 H, d, J = 12.8 Hz), 4.97 (1 H, d, J = 12.8 Hz), 6.83 (1 H, dd, J = 8.3, 1.0 Hz), 7.11 (2 H, m), 7.16 (1 H, dq, J = 7.8, 0.9, 0.9, 0.9 Hz), 7.32 (1 H, t, J = 8.0 Hz), 7.33 (2 H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.4 (q), 22.2 (q), 56.0 (q), 65.7 (d), 68.6 (t), 77.5 (s), 85.3 (s), 86.1 (d), 88.4 (s), 109.5 (d), 109.8 (s), 119.8 (s), 120.0 (d), 129.0 (d), 129.7 (d), 131.6 (d), 138.3 (s), 142.8 (s), 160.8 (s). IR (CCl_4): 3316 s, 3085 w, 3072 w, 3053 w, 3030 m, 2838 s, 2227 w, 2188 vw, 2106 w, 1598 m, 1581 s, 1510 vs, 1473 vs, 1460 vs, 1438 s, 1408 w, 1328 vs, 1312 s, 1300 s, 1277 vs, 1258 s (sh), 1210 w, 1184 w, 1152 w (sh), 1115 vs, 1100 vs, 1088 vs, 1063 vs, 1022 m, 835 m, 709 m, 647 s, 606 s, 461 w, 408 m. EI MS: 303 ($[M - H]^+$, 11), 289 (53), 276 (14), 261 (63), 245 (22), 229 (16), 213 (12), 173 (16), 143 (40), 129 (62), 115 (100). HR EI MS: calcd for $C_{21}H_{19}O_2$ [M − H] 303.1385, found 303.1387.

[4-(1-{[2-Methoxy-6-({[(1*S*)-1-methyl-3-(4-methylphenyl)-prop-2-yn-1-yl]oxy}methyl)phenyl]ethynyl}naphthalen-2-yl)but-1-yn-1-yl][tris(1-methylethyl)]silane (22). A 750 mL flask was charged with **21** (13.10 g, 28.31 mmol, 1.09 equiv), $Pd(PPh_3)_4$ (1.62 g, 1.41 mmol, 5 mol %), and CuI (495 mg, 2.60 mmol, 10 mol %) and put under argon. A solution of (*S*)-(−)-**20** (7.91 g, 25.98 mmol) in diisopropylamine (360 mL) was added, and the reaction was stirred at room temperature for 5 min and then heated at 80 °C for 60 min. Solvent was removed in vacuo, and the crude product was chromatographed on silica gel (petroleum ether−ether 95:5) to provide (*S*)-(−)-**22** (11.99 g, 72%) as an oil. Optical rotation: $[\alpha]^{22}_D$ −97 (*c* 0.002, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.95−1.04 (21 H, m), 1.61 (3 H, d, J = 6.5 Hz), 2.29 (3 H, s), 2.77 (2 H, t, J = 7.2 Hz), 3.32 (2 H, t, J = 7.2 Hz), 4.00 (3 H, s), 4.57 (1 H, q, J = 6.5 Hz), 5.02 (1 H, d, J = 12.8 Hz), 5.18 (1 H, d, J = 12.8 Hz), 6.89 (1 H, dd, J = 8.4, 1.0 Hz), 6.98 (2 H, m), 7.24 (1 H, dd, J = 7.7, 1.0 Hz), 7.24 (2 H, m), 7.34 (1 H, dd, J = 8.4, 7.7 Hz), 7.42 (1 H, ddd, J = 8.1, 6.8, 1.3 Hz), 7.47 (1 H, d, J = 8.4 Hz), 7.48 (1 H, ddd, J = 8.5, 6.8, 1.5 Hz), 7.72 (1 H, bd, J = 8.4 Hz), 7.80 (1 H, ddt, J = 8.1, 1.5, 0.6, 0.6 Hz), 8.60 (1 H, ddt, J = 8.5, 1.3, 0.8, 0.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.3 (d), 18.6 (q), 21.1 (t), 21.4 (q), 22.3 (q), 34.7 (t), 56.0 (q), 65.5 (d), 69.0 (t), 80.9 (s), 85.5 (s), 88.3 (s), 92.7 (s), 95.3 (s), 108.5 (s), 109.5 (d), 111.6 (s), 119.6 (s), 119.80 (s), 119.82 (d), 125.6 (d), 126.5 (d), 126.7 (d), 127.82 (d), 127.84 (d), 128.0 (d), 128.9 (d), 129.2 (d), 131.6 (d), 132.0 (s), 133.6 (s), 138.2 (s), 141.4 (s), 141.5 (s), 160.6 (s). IR (CCl_4): 3088 w (sh), 3056 m, 3031 m, 2990 s (sh), 2865 vs, 2839 s, 2227 w, 2200 vw, 2169 s, 1620 w, 1596 w, 1577 m, 1568 w (sh), 1510 s, 1472 vs, 1463 vs, 1438 s, 1388 m, 1383 m, 1371 m, 1328 s, 1314 m, 1302 m, 1272 vs, 1257 m (sh), 1240 w (sh), 1185 w, 1117 s, 1100 s, 1088 vs, 1063 vs, 1025 m, 996 m, 952 w, 919 m, 884 s, 865 w, 835 w, 708 w, 677 s, 660 s, 628 m, 617 m, 456 w, 405 w. EI MS: 638 ($M^{+\bullet}$, 8), 595 (6), 429 (23), 321 (11), 289 (8), 239 (7), 173 (13), 159 (21), 149 (26), 143 (100), 128 (42), 115 (50), 73 (36), 59 (42). HR EI MS: calcd for $C_{44}H_{50}O_2Si$ 638.3580, found 638.3595.

2-But-3-yn-1-yl-1-{[2-methoxy-6-({[(1*S*)-1-methyl-3-(4-methylphenyl)prop-2-yn-1-yl]oxy}methyl)phenyl]ethynyl}-naphthalene (23). A 250 mL three-neck flask was charged with a solution of (*S*)-(−)-**22** (11.99 g, 18.80 mmol) in THF (160 mL) under argon. A tetrabutylammonium fluoride solution (1.072 M in THF, 21 mL, 22.50 mmol, 1.20 equiv) was added, and the reaction mixture was stirred at room temperature for 1 h. Solvent was removed in vacuo, and the crude product was chromatographed on silica gel (petroleum ether−ether−acetone 90:10:0 to 80:10:10). The obtained product was triturated with petroleum ether (3 × 150 mL) to provide (*S*)-(−)-**23** (7.80 g, 86%) as an amorphous solid. Optical rotation: $[\alpha]^{22}_D$ −134 (*c* 0.005, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.61 (3 H, d, J = 6.6 Hz), 1.98 (1 H, t, J = 2.6 Hz), 2.29 (3 H, s), 2.69 (2 H, dt, J = 7.7, 7.7, 2.6 Hz), 3.34 (2 H, t, J = 7.7 Hz), 4.00 (3 H, s), 4.59 (1 H, q, J = 6.6 Hz), 5.04 (2 H, d, J = 12.7 Hz), 5.19 (2 H, d, J = 12.7 Hz), 6.90 (1 H, dd, J = 8.3, 1.1 Hz), 6.98 (2 H, m), 7.23 (1 H, dd, J = 7.7, 1.1 Hz), 7.23 (2 H, m), 7.35 (1 H, dd, J = 8.3, 7.7 Hz), 7.41 (1 H, d, J = 8.4 Hz), 7.43 (1 H, ddd, J = 8.1, 6.8, 1.3 Hz), 7.49 (1 H, ddd, J = 8.3, 6.8, 1.4 Hz), 7.75 (1 H, bd, J = 8.4 Hz), 7.80 (1 H, ddt, J = 8.1, 1.4, 0.6, 0.6 Hz), 8.61 (1 H, ddt, J = 8.3, 1.3, 0.8, 0.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.6 (t), 21.4 (q), 22.3 (q), 34.6 (t), 56.0 (q), 65.6 (d), 68.8 (d), 69.0 (t), 84.3 (s), 85.5 (s), 88.4 (s), 92.9 (s), 95.2 (s), 109.5 (d), 111.4 (s), 119.6 (s), 119.8 (d), 120.0 (s), 125.8 (d), 126.5 (d), 126.9 (d), 127.4 (d), 127.9 (d), 128.2 (d), 128.9 (d), 129.3 (d), 131.6 (d), 132.0 (s), 133.7 (s), 138.2 (s), 141.2 (s), 141.5 (s), 160.6 (s). IR (CCl_4): 3313 s, 3294 w, 3088 w (sh), 3056 m, 3031 w, 2838 m, 2227 w, 2205 vw (sh), 2119 w, 1620 w, 1596 w, 1578 m, 1569 w, 1510 s, 1473 vs, 1459 m, 1438 m, 1430 m (sh), 1407 vw, 1389 w, 1371 m, 1313 w, 1300 w (sh), 1272 vs, 1186 w, 1116 s, 1105 s (sh), 1099 s (sh), 1087 s, 1063 vs, 1026 m, 865 w, 836 w, 722 w, 708 w, 635 s, 522 w, 457 w, 442 w. EI MS: 482 ($M^{+\bullet}$, 2), 467 (8), 439 (20), 429 (25), 407 (9), 323 (15), 279 (21), 252 (24), 239 (45), 226 (25), 191 (25), 171 (30), 143 (59), 128 (100), 115 (38), 91 (35), 55 (27), 43 (93). HR EI MS: calcd for $C_{35}H_{30}O_2$ 482.2246, found 482.2251.

(*P*,3*S*)-14-Methoxy-3-methyl-4-(4-methylphenyl)-1,3,6,7-tetrahydrobenzo[*c*]benzo[5,6]phenanthro[4,3-*e*]oxepine (24). (*S*)-(−)-**23** (3.10 g, 6.43 mmol), PPh_3 (1.35 g, 5.13 mmol, 80 mol %), and $CpCo(CO)_2$ (340 μL, 2.57 mmol, 40 mol %) were subjected to general cyclization procedure A in decane (280 mL). Eluent: petroleum ether−ether 100:0 to 93:7. Yield: 2.59 g (82%, (*M*,*S*)-**24**/(*P*,*S*)-**24** = 13:87). Crystallization from boiling heptane (800 mL) provided pure (*P*,*S*)-**24** (1.97 g, 63%) as a white solid. Mp: 303−304 °C. Optical rotation: $[\alpha]^{22}_D$ +465 (*c* 0.007, CH_2Cl_2) for pure (*P*,*S*)-**24**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.67 (3 H, d, J = 7.1 Hz), 2.43 (3 H, s), 2.72 (3 H, s), 2.77 (1 H, dddd, J = 15.7, 14.5, 4.5, 1.4 Hz), 2.88−2.95 (2 H, m), 3.04 (1 H, dt, J = 15.0, 15.0, 1.3 Hz), 4.72 (1 H, d, J = 11.4 Hz), 5.00 (1 H, d, J = 11.4 Hz), 5.32 (1 H, q, J = 7.1 Hz), 6.09 (1 H, dd, J = 7.8, 1.6 Hz), 6.73 (1 H, ddd, J = 8.5, 6.7, 1.5 Hz), 6.92 (1 H, t, J = 7.6 Hz), 6.95 (1 H, dd, J = 7.4, 1.6 Hz), 7.03 (1 H, ddd, J = 8.1, 6.7, 1.3 Hz), 7.20 (1 H, bdq, J = 8.5, 0.9, 0.9, 0.9 Hz), 7.27 (2 H, m), 7.38 (2 H, m), 7.38 (1 H, d, J = 1.2 Hz), 7.46 (1 H, d, J = 8.1 Hz), 7.54 (1 H, dd, J = 8.1, 1.5 Hz), 7.60 (1 H, bd, J = 8.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.2 (q), 22.4 (q), 30.6 (t), 30.7 (t), 54.4 (q), 67.9 (t), 72.4 (d), 110.2 (d), 121.4 (d), 123.5 (d), 123.9 (d), 125.8 (d), 125.9 (d), 126.7 (d), 126.9 (d), 128.7 (s), 129.0 (d), 129.10 (d), 129.13 (d), 130.0 (d), 130.1 (s), 132.3 (s), 133.2 (s), 133.3 (s), 134.1 (s), 135.6 (s), 136.6 (s), 137.9 (s), 138.0 (s), 138.9 (s), 140.1 (s), 141.5 (s), 154.7 (s). IR (CCl_4): 3050 w, 3024 w, 2835 m, 1620 vw, 1594 w, 1587 w, 1580 w (sh), 1568 vw (sh), 1514 m, 1475 s, 1436 m, 1368 m, 1340 w, 1317 w, 1300 w, 1272 vs, 1260 s, 1214 w, 1185 w, 1111 w (sh), 1097 s, 1085 s, 1075 m (sh), 1061 w, 1023 w, 863 w, 844 w, 821 vs, 728 w, 701 w, 529

w. EI MS: 482 ($M^{+\bullet}$, 100), 467 (44), 439 (35), 424 (7), 149 (7), 95 (12), 83 (13), 69 (16), 57 (32), 43 (20). HR EI MS: calcd for $C_{35}H_{30}O_2$ 482.2246, found 482.2239. Cyclization with CpCo(ethylene)$_2$: (*S*)-(−)-**23** (50 mg, 0.104 mmol) and $CpCo(C_2H_4)_2$ (27 mg, 0.150 mmol, 1.45 equiv) were subjected to general cyclization procedure B in THF (4 mL). Eluent: petroleum ether−ether 92:8. Yield 28 mg (56%, (*M*,*S*)-**24**/(*P*,*S*)-**24** = 50:50, diastereomers not separated).

(*P*,3*S*)-3-Methyl-4-(4-methylphenyl)-1,3,6,7-tetrahydrobenzo[*c*]benzo[5,6]phenanthro[4,3-*e*]oxepin-14-ol (25). A 250 mL three-neck flask was charged with NaH (80% suspension in mineral oil, 3.13 g, 104 mmol, 20.00 equiv) and put under argon. Dry petroleum ether (25 mL) was added, and after the mixture was stirred for 2 min, the liquid was removed via syringe. DMF (25 mL) was added, and the stirred suspension was cooled to 0 °C. Ethanethiol (7.5 mL, 101 mmol, 19.40 equiv) was added dropwise, and the reaction mixture was stirred at 0 °C until all NaH dissolved. A solution of **24** (2.51 g, 5.21 mmol) in DMF (200 mL) was added, and the reaction was heated to 130 °C for 15 h. The reaction mixture was diluted with water (250 mL), acidified with concd HCl to pH 1, and extracted with dichloromethane (3 × 300 mL). The organic phase was dried over anhydrous Na_2SO_4, and the solvents were removed in vacuo. Chromatography of the crude product on silica gel (petroleum ether-acetone 95:5 to 80:20) provided an equilibrium mixture of (*P*,*S*)-**25** and (*M*,*S*)-**25** (2.16 g, 89%, (*M*,*S*)/(*P*,*S*) = 11:89). 1.11 g of this mixture was crystallized twice from heptane-toluene-ethanol to provide pure (*P*,*S*)-(+)-**25** (791 mg, 72%) as a white crystalline solid. Mp: 278−280 °C (heptane−*n*-propanol) for pure (*P*,*S*)-(+)-25. Optical rotation: $[\alpha]^{22}_D$ +469 (*c* 0.009, CH_2Cl_2) for pure (*P*,*S*)-(+)-**25**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.63 (3 H, d, J = 7.1 Hz), 2.44 (3 H, s), 2.80 (1 H, dddd, J = 14.6, 10.7, 8.6, 1.2 Hz), 2.92−3.02 (1 H, m), 2.92−3.02 (2 H, m), 4.29 (1 H, s), 4.73 (1 H, d, J = 11.4 Hz), 5.00 (1 H, d, J = 11.4 Hz), 5.30 (1 H, q, J = 7.1 Hz), 6.18 (1 H, dd, J = 8.0, 1.3 Hz), 6.81 (1 H, ddd, J = 8.4, 6.8, 1.4 Hz), 6.87 (1 H, dd, J = 8.0, 7.4 Hz), 6.94 (1 H, dd, J = 7.4, 1.3 Hz), 7.09 (1 H, ddd, J = 8.1, 6.8, 1.2 Hz), 7.26 (1 H, dq, J = 8.4, 1.0, 1.0, 1.0 Hz), 7.29 (2 H, m), 7.37 (2 H, m), 7.45 (1 H, d, J = 1.2 Hz), 7.47 (1 H, d, J = 8.2 Hz), 7.60 (1 H, bdd, J = 8.1, 1.4 Hz), 7.74 (1 H, bd, J = 8.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.3 (q), 22.2 (q), 30.5 (t), 30.7 (t), 68.1 (t), 72.3 (d), 116.1 (d), 121.7 (d), 124.0 (d), 124.5 (d), 125.6 (d), 126.2 (d), 127.2 (d), 127.8 (s), 128.8 (d), 128.9 (s), 129.1 (d, 2 × C), 129.6 (d), 129.7 (d), 130.4 (s), 132.1 (s), 132.4 (s), 132.6 (s), 136.7 (s), 137.0 (s), 137.6 (s), 138.4 (s), 138.6 (s), 141.3 (s), 142.8 (s), 151.6 (s). IR (CCl_4): 3604 w, 3558 m, 1612 w, 1595 w, 1588 w, 1578 w, 1514 m, 1465 s, 1438 m, 1369 m, 1181 m, 1090 s, 1073 m, 822 vs, 730 m, 701 w. EI MS: 468 ($M^{+\bullet}$, 46), 453 (18), 425 (15), 279 (18), 167 (40), 149 (96), 129 (17), 113 (20), 97 (29), 83 (40), 71 (64), 57 (100), 43 (87). HR EI MS: calcd for $C_{34}H_{28}O_2$ 468.2089, found 468.2076.

General Cyclization Procedure A. A Schlenk flask was charged with the starting triyne and triphenylphosphine (2.00 equiv or 80 mol %) and put under argon. The degassed solvent was added via syringe and the reaction mixture was warmed to 140 °C. $CpCo(CO)_2$ (1.00 equiv or 40 mol %) was added via Hamilton syringe, and the reaction mixture was heated to 140 °C with concomitant irradiation with a halogen lamp for 1−36 h. The solvent was removed in vacuo (80 °C, 20 mbar), and the crude product was chromatographed on silica gel to provide an equilibrium mixture of (*P*,*S*) and (*M*,*S*) diastereoisomers of the respective cyclized product.

General Cyclization Procedure B. A Schlenk flask was charged with a solution of the starting triyne in THF under argon. A solution of $CpCo(C_2H_4)_2$ (typically 150 mol %) in THF was added and the reaction mixture was stirred at room temperature for 15 min. The solvent was removed in vacuo, and the crude product was chromatographed on silica gel to provide a mixture of (*P*,*S*) and (*M*,*S*) diastereoisomers of the respective cyclized product.

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Supporting Information Available: General experimental data for compounds **7**−**12** and **27**, crystallographic data for (*P*,*S*)-(+)-**25**, kinetic and thermodynamic data for epimerization of **24** and **27**, ^{1}H NMR spectra for the new compounds **7**−**12**, **14**−**17**, **19**, **20**, and **22**−**25**, CIF file for (*P*,*S*)-(+)-**25**, and *xyz* geometries and molecular energies for **7**−**12**, **24**, and **27**−**31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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