Heterohelicenes

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A General Approach to Optically Pure [5]-, [6]-, and [7]Heterohelicenes**

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The lack of a general method for the effective synthesis of nonracemic helicenes[1] and their analogues has been a major hurdle that has limited a wider exploitation of these helically chiral aromatic systems in enantioselective catalysis, molecular recognition, self-assembly, surface science, chiral materials, and other branches of science.[2] Ideally, a practical asymmetric synthesis would be independent of both the length of the helical backbone and the presence of functional groups. Since the pioneering studies by Martin et al.[3a] and Katz et al.,[3b] who successfully used diastereoselective photodehydrocyclization of stilbene-type precursors, various concepts of the asymmetric synthesis of helicenes have been explored[4] but no general procedure for obtaining optically pure helicenes or their analogues with a wide structural diversity has yet been reported.

Recently, we demonstrated diastereoselective [2+2+2] cycloisomerization of centrally chiral triynes to receive nonracemic helicene-like compounds with incorporated dihydrooxepine or dihydroazepine ring(s).[5] This promising approach, however, has not yet reached the merit of being general and practical.[6] Herein, we present fundamental progress in this endeavor to receive optically pure and functionalized [5]-, [6]-, and [7]heterohelicenes by means of asymmetric synthesis.

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With the aim of keeping the molecular shape of the helicene analogues as close as possible to that of the parent helicenes, such as **1** (Figure 1), we proposed embedding two

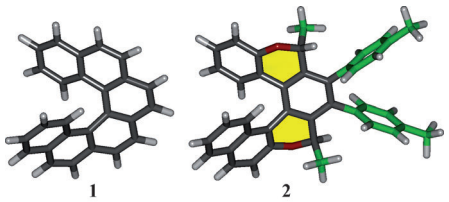


Figure 1. The molecular shape of the prototypical (*M*)-[6]helicene **1** and its proposed (*M*,*R*,*R*)-2*H*-pyran analogue **2** (the 2*H*-pyran rings: yellow; additional substituents: green).

2*H*-pyran rings in a helical scaffold comprising two stereogenic centers as in **2**. Such helical systems could be synthesized by [2+2+2] cycloisomerization of the corresponding triynes. If there is a significant energy difference (>2.7 kcal mol^{-1}) between the diastereomers of the opposite helicity and they are stereolabile at a given temperature, asymmetric transformation of the first kind[7] might control the stereochemical outcome of the entire cyclization process to reach up to d.r. $=>99:<1$.[8]

To verify this assumption, two diastereomeric pairs of the simplest pentacyclic models (*M*,*R*,*R*)/(*P*,*R*,*R*)-**3** and (*M*,*R*,*R*)/(*P*,*R*,*R*)-**4** were first investigated computationally (Figure 2). Using density functional theory (DFT), their equilibrium energies and barriers to interconversion were calculated. (*P*,*R*,*R*)-**3** was found to be only about 0.2 kcal mol^{-1} more stable than (*M*,*R*,*R*)-**3**.[9] In sharp contrast, the energy difference between the tolyl-substituted diastereomers (*M*,*R*,*R*)- and (*P*,*R*,*R*)-**4** was remarkable: 9.2 kcal mol^{-1} in favor of the diastereomer with the (*M*) helicity. The system obviously adopts a deep-minimum conformation with the CH_3 groups at the stereogenic centers in the pseudo axial position (moving out of the plane of the central benzene ring). Such an arrangement evidently prevents an unfavorable allylic-like 1,3-strain[10] arising otherwise from the interaction between the CH_3 groups at the stereogenic centers occupying the pseudo equatorial position and the tolyl groups at the central benzene ring (both lying in the same plane) of the diastereomeric (*P*,*R*,*R*)-**4**. Accordingly, (*M*,*R*,*R*)-**4** should exist as a sole diastereomer (detectable within the HPLC or NMR limits) in the thermodynamic equilibrium regardless of the barrier to helicity inversion, which was calculated to be 11.9 or

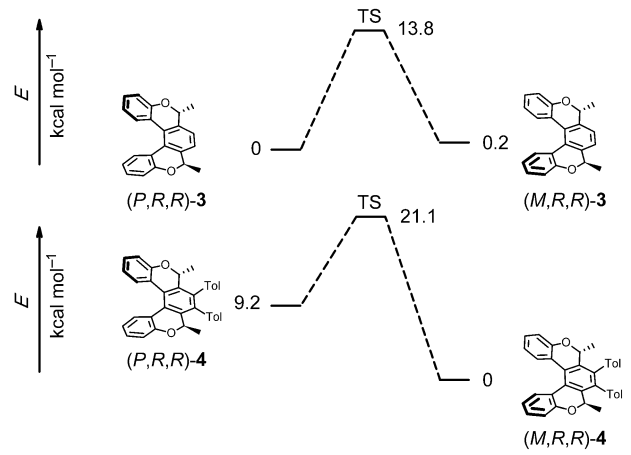
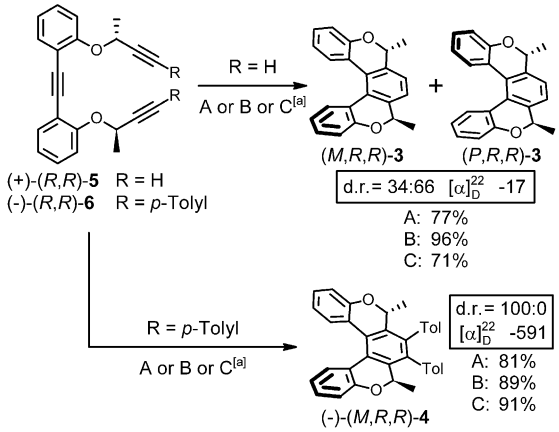


Figure 2. The relative equilibrium free energies and barriers to epimerization of (*M*,*R*,*R*)/(*P*,*R*,*R*)-**3** and (*M*,*R*,*R*)/(*P*,*R*,*R*)-**4**. These values were calculated by DFT (B3LYP/cc-pVTZ), and the transition states TS were localized by the QST3 method (Gaussian 09).

21.1 kcal mol^{-1} (13.6 or 13.8 kcal mol^{-1} for **3**). We hypothesized that such a stereocontrol might operate in the higher and functionalized derivatives as well.

In accord with the theoretical calculations, the stereochemical outcome of [2+2+2] cycloisomerization of the centrally chiral triyne (*R*,*R*)-**5**[11] with terminal alkyne units was unsatisfactory, as a 34:66 mixture of (*M*,*R*,*R*)- and (*P*,*R*,*R*)-**3** was formed regardless of the reaction conditions used (Scheme 1). As predicted, the presence of the tolyl groups at the tethered alkyne units had a dramatic effect on the stereochemical outcome of the reaction: The cyclization of the chiral triyne (*R*,*R*)-**6** afforded exclusively the helicene



Scheme 1. Structure optimization for diastereoselective [2+2+2] cycloisomerization. [a] A: [CpCo(CO)$_2$] (20 mol%), PPh$_3$ (40 mol%), irradiated by a halogen lamp, decane, 140°C, 1 h; B: [CpCo(CO)(fum)] (20 mol%), 1-butyl-2,3-dimethylimidazolium tetrafluoroborate (25 μL mL^{-1} of the reaction solution), microwave reactor, THF, 180°C, 20 min; C: [Ni(cod)$_2$] (20 mol%), PPh$_3$ (40 mol%), THF, room temperature, 30 min. fum = dimethylfumarate. Yields of isolated product after column chromatography are given. The diastereomeric ratios were determined by ^{1}H NMR spectroscopy (the stereochemical outcomes were independent of the cyclization procedure used). $[\alpha]_D^{22}$ values were determined in chloroform (c = 0.28–0.40).

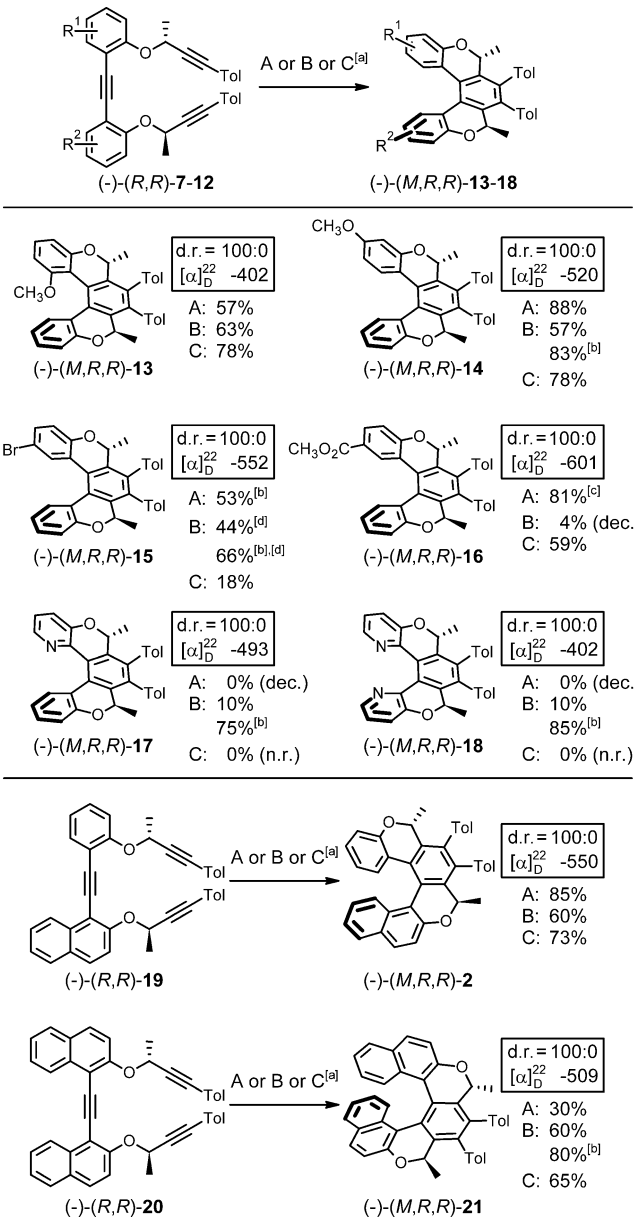
(*M*,*R*,*R*)-**4**[11] in a high yield. Note that the opposite helicity (*M*) prevailed in this case.

Encouraged by this observation, we focused on exploring the scope and limitations of this diastereoselective cycloisomerization. Therefore, the chiral triynes (*R*,*R*)-**7**–**12**, **19**, and **20**[11] with tolyl-terminated alkyne units were cyclized to the corresponding heterohelicenes with an excellent 100:0 diastereoselectivity in favor of the (*M*,*R*,*R*) stereoisomers of **2**, **13**–**18**, and **21** (Scheme 2). The stereochemical outcome of all of these reactions was sensitive to neither the reaction conditions used nor the presence of different substituents (CH_3O, Br, and CO_2CH_3 in the different positions) nor heterocyclic subunit(s), namely pyridine. Regardless of the length of the helical scaffold, this method allowed for the construction of [5]-, [6]-, and [7]heterohelicenes in optically pure form. Mostly good to high preparative yields were obtained under at least one of the reaction conditions screened: A) [CpCo(CO)$_2$]/PPh$_3$ with simultaneous visible light irradiation; B) [CpCo(CO)(fum)][12] (fum = dimethylfumarate) in combination with microwave irradiation; and C) [Ni(cod)$_2$]/PPh$_3$. The bromo derivative (*M*,*R*,*R*)-**15** was obtained in only moderate yield (a two-step chromatographic purification was necessary) and the cyclization of both the pyridine-derived triynes required a stoichiometric amount of the [CpCo(CO)(fum)] complex to afford the helical pyridohelicenes (*M*,*R*,*R*)-**17** and (*M*,*R*,*R*)-**18** (no other cyclization conditions were effective).

The helicity of the key cyclized product (*M*,*R*,*R*)-**4** could not be unequivocally assigned by measuring NOE in the ^{1}H NMR spectra, and we did not obtain suitable crystals for a single-crystal analysis. However, the theoretical calculations predicted its *M* helicity convincingly in the case of an *R* configuration at stereogenic centers (see Figure 2). That result was further supported by comparing the observed and calculated electronic CD spectra and the chemical shifts of (*M*,*R*,*R*)-**4** in the ^{1}H and ^{13}C NMR spectra, which were juxtaposed with the calculated parameters of the synthetically inaccessible (*P*,*R*,*R*)-**4** (for details and the experimental CD spectra of (*M*,*R*,*R*)-**3**/(*P*,*R*,*R*)-**3**, (*M*,*R*,*R*)-**4**, (*M*,*R*,*R*)-**2**, and (*M*,*R*,*R*)-**21**; see the Supporting Information).

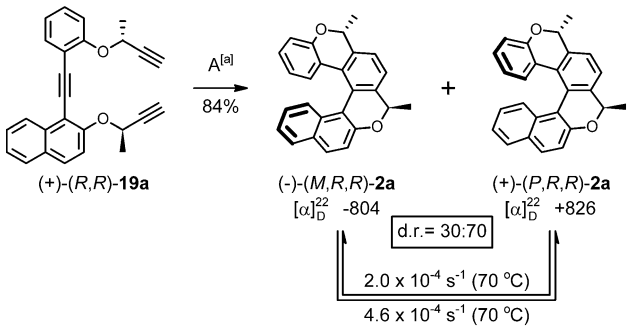
The helicity of the cyclized products (*M*,*R*,*R*)/(*P*,*R*,*R*)-**3** was assigned by measuring the NOE in the ^{1}H NMR spectra. Furthermore, we found a good agreement between the observed and calculated chemical shifts in the ^{1}H and ^{13}C NMR spectra of the distinguishable diastereomers (*M*,*R*,*R*)- versus (*P*,*R*,*R*)-**3** (for details, see the Supporting Information).

The dynamic equilibrium between (*M*,*R*,*R*)- and (*P*,*R*,*R*)-**3** allowed the determination of the corresponding barriers to epimerization by the temperature-dependent ^{1}H NMR measurements. In accord with the theoretical calculations (Figure 2), we determined the experimental barrier to be 13.0 kcal mol^{-1} for the (*P*,*R*,*R*)-**3**→(*M*,*R*,*R*)-**3** process and 12.8 kcal mol^{-1} for the (*M*,*R*,*R*)-**3**→(*P*,*R*,*R*)-**3** backward conversion (the diastereomers differed in Gibbs energy by about 0.2 kcal mol^{-1}). A single-crystal analysis of the minor diastereomer (*M*,*R*,*R*)-**3**, which crystallized preferentially from the 34:66 equilibrium mixture of (*M*,*R*,*R*)- and (*P*,*R*,*R*)-**3**, was performed (for details, see the Supporting Information).[13]



Scheme 2. Diastereoselective [2+2+2] cycloisomerization. [a] A: $[CpCo(CO)_2]$ (20 mol%), PPh_3 (40 mol%), irradiated by a halogen lamp, decane, 140°C, 1–3 h; B: [CpCo(CO)(fum)] (20 mol%), 1-butyl-2,3-dimethylimidazolium tetrafluoroborate (5–25 μL mL^{-1} of the reaction solution), microwave reactor, THF, 180°C, 20 min; C: $[Ni(cod)_2]$ (20 mol%), PPh_3 (40 mol%), THF, room temperature, 2–24 h. Yields of isolated product after column chromatography are given. The diastereomeric ratios were determined by ^{1}H NMR spectroscopy (the stereochemical outcomes were independent of the cyclization procedure used). $[\alpha]_D^{22}$ values were determined in chloroform or dichloromethane (c = 0.086–0.54). [b] A stoichiometric amount of the Co catalyst was used. [c] Heated in a microwave reactor at 140°C in THF. [d] PPh_3 was added (40 mol% or 2.0 equiv).

In the case of the [5]helicene analogues (*M*,*R*,*R*)-**4**, **13**–**18**, the observed diastereoselectivity is apparently defined by the post-cyclization equilibration between the (*M*,*R*,*R*) and (*P*,*R*,*R*) diastereomers (under thermodynamic stereocontrol) owing to the low barriers to the epimerization of the products (see below).[8] On the other hand, the competition/cooperation of kinetic versus thermodynamic stereocontrol in the diastereoselective cycloisomerization of (−)-(*R*,*R*)-**19**, **20** becomes intuitively more important, as the [6]- and [7]helicene analogues (*M*,*R*,*R*)-**2**, **21** that are formed are expected to be configurationally more stable. We also cyclized the non-tolylated triyne (*R*,*R*)-**19a** to a 30:70 equilibrium mixture of (*M*,*R*,*R*)- and (*P*,*R*,*R*)-**2a** (Scheme 3).[14] The observed diastereoselectivity was practically the same as for the aforementioned (*M*,*R*,*R*)/(*P*,*R*,*R*)-**3**. The (*M*,*R*,*R*) and (*P*,*R*,*R*) diastereomers **2a** were separated by flash chromatography on a silica gel that allowed for a determination of the barriers to epimerization: 26.0 kcal mol^{-1} for the (*P*,*R*,*R*)-**2a**→(*M*,*R*,*R*)-**2a** process and 25.4 kcal mol^{-1} for the (*M*,*R*,*R*)-**2a**→(*P*,*R*,*R*)-**2a** backward conversion (the diastereomers differed in Gibbs energy by about 0.6 kcal mol^{-1}). Importantly, these barriers to epimerization are significantly lower than the barrier to the racemization of the parent [6]helicene (36.2 kcal mol^{-1}).[15] As the half-life of (*M*,*R*,*R*)- and (*P*,*R*,*R*)-**2a** to interconvert at 170°C is in the range of seconds or fractions of seconds,[16] a reaction period of 10 min is sufficient to complete the post-cyclization equilibration of the diastereomers **2a** (under thermodynamic stereocontrol).



Scheme 3. The synthesis and thermal epimerization of (*M*,*R*,*R*)- and (*P*,*R*,*R*)-**2a**. [a] A: [CpCo(CO)(fum)] (50 mol%), 1-butyl-2,3-dimethylimidazolium tetrafluoroborate (25 μL mL^{-1} of the reaction solution), microwave reactor, THF, 170°C, 10 min. The yield after flash chromatography is given. The diastereomeric ratios in the thermal equilibrium or during the thermal epimerization of the separated diastereomers (at 70°C in 1,2-dichloroethane) were determined by HPLC on a Phenomenex Gemini-NX C-18 column (250×4.6 mm, 5 μm, methanol). $[\alpha]_D^{22}$ values were determined in chloroform (c = 0.27–0.31).

The presence of the tolyl groups at the central benzene ring is expected to cause the energy profile of the (*M*,*R*,*R*)-**2**⇄(*P*,*R*,*R*)-**2** epimerization to be highly asymmetric (in contrast to that of **2a**) owing to the occurrence of the allylic-like 1,3-strain. However, the barrier to the (*P*,*R*,*R*)-**2**→(*M*,*R*,*R*)-**2** conformational change should be comparable to those of the (*M*,*R*,*R*)-**2a**⇄(*P*,*R*,*R*)-**2a** process (around 25–26 kcal mol^{-1}). Such a barrier will result in a slow post-cyclization equilibration at room temperature as the half-life of the less stable diastereomer (*P*,*R*,*R*)-**2** at 25°C will be in the range of day(s). Intriguingly, the Ni^0-catalyzed cycloisomerization of (*R*,*R*)-**19** at this temperature after 16 h provides solely the more stable diastereomer (*M*,*R*,*R*)-**2** (condition C, Scheme 2). Presumably, kinetic stereocontrol in favor of the

thermodynamically more stable diastereomer operates in this case.[8] However, thermodynamic stereocontrol (operating in the post-cyclization equilibration) dominates in the Co^I-mediated cycloisomerization of (*R*,*R*)-**19** at high temperatures (conditions A, B: 140 °C for 1 h or 180 °C for 20 min; Scheme 2). Similarly, kinetic stereocontrol (at low temperature) as well as thermodynamic stereocontrol (at high temperature) are consonant in the diastereoselective cycloisomerization of (*R*,*R*)-**20** to provide the configurationally more stable [7]helicene analogue (*M*,*R*,*R*)-**21** as a sole product (conditions A, B, C, Scheme 2).

In summary, a general method for the preparation of optically pure [5]-, [6]-, and [7]heterohelicenes has been developed for the first time. The diastereoselective [2+2+2] cycloisomerization of centrally chiral triynes in the presence of Co^I or Ni^0 complexes plays a key role in the formation of helical scaffolds with two 2*H*-pyran rings. The major advantages of this methodology are that 1) excellent diastereoselectivity is guaranteed (d.r. uniformly 100:0); 2) the stereochemical outcome of the cyclization is highly tolerant to the structural diversity of the products; 3) the synthesized 2*H*-pyran hetero[5]helicenes exist as single helices even at higher temperature (in contrast to the parent [5]helicene that racemizes at room temperature); 4) the helicity of the products can be easily predicted computationally; and 5) both enantiomers of but-3-yn-2-ol (a key chiral building block) are commercially available. The 2*H*-pyran-modified helicenes might widely be applied to enantioselective catalysis, for example, as was recently described by Carbery et al.[2c] Further studies in this regard are underway in our laboratory.

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[1] For recent reviews, see: a) Y. Shen, C.-F. Chen, *Chem. Rev.* **2012**, *112*, 1463 – 1535; b) I. G. Stará, I. Starý in *Science of Synthesis Vol. 45b* (Eds.: J. S. Siegel, Y. Tobe), Thieme, Stuttgart, **2010**, pp. 885 – 953; c) I. Starý, I. G. Stará in *Strained Hydrocarbons* (Ed.: H. Dodziuk), Wiley-VCH, Weinheim, **2009**, pp. 166 – 176; d) A. Rajca, M. Miyasaka in *Functional Organic Materials* (Eds.: T. J. J. Müller, U. H. F. Bunz), Wiley-VCH, Weinheim, **2007**, pp. 547 – 581; e) A. Urbano, *Angew. Chem.* **2003**, *115*, 4116 – 4119; *Angew. Chem. Int. Ed.* **2003**, *42*, 3986 – 3989.

[2] Remarkable applications of helicenes have already been reported, but the limited number of examples does not correspond to the utilization potential of these helical aromatics. For their very recent use in enantioselective catalysis, see: a) Z. Krausová, P. Sehnal, B. P. Bondzic, S. Chercheja, P. Eilbracht, I. G. Stará, D. Šaman, I. Starý, *Eur. J. Org. Chem.* **2011**, 3849 – 3857; b) J. Chen, B. Captain, N. Takenaka, *Org. Lett.* **2011**, *13*, 1654 – 1657; c) M. R. Crittall, H. S. Rzepa, D. R. Carbery, *Org. Lett.* **2011**, *13*, 1250 – 1253; in molecular recognition: d) K. Shinohara, Y. Sannohe, S. Kaieda, K. Tanaka, H. Osuga, H. Tahara, Y. Xu, T. Kawase, T. Bando, H. Sugiyama, *J. Am. Chem. Soc.* **2010**, *132*, 3778 – 3782; in self-assembly: e) M. A. Shcherbina, X. Zeng, T. Tadjiev, G. Ungar, S. H. Eichhorn, K. E. S. Phillips, T. J. Katz, *Angew. Chem.* **2009**, *121*, 7977 – 7980; *Angew. Chem. Int. Ed.* **2009**, *48*, 7837 – 7840; in surface science: f) P. Rahe, M. Nimmrich, A. Greuling, J. Schütte, I. G. Stará, J. Rybáček, G. Huerta-Angeles, I. Starý, M. Rohlfing, A. Kühnle, *J. Phys. Chem. C* **2010**, *114*, 1547 – 1552; in chiral materials: g) L. Norel, M. Rudolph, N. Vanthuyne, J. A. G. Williams, C. Lescop, C. Roussel, J. Autschbach, J. Crassous, R. Réau, *Angew. Chem.* **2010**, *122*, 103 – 106; *Angew. Chem. Int. Ed.* **2010**, *49*, 99 – 102; in other branches of science: h) L. Adriaenssens, L. Severa, D. Koval, I. Císařová, M. Martínez Belmonte, E. C. Escudero-Adán, P. Novotná, P. Sázelová, J. Vávra, R. Pohl, D. Šaman, M. Urbanová, V. Kašička, F. Teplý, *Chem. Sci.* **2011**, *2*, 2314 – 2320.

[3] a) J. Vanest, R. H. Martin, *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 113; b) T. J. Katz, A. Sudhakar, M. F. Teasley, A. M. Gilbert, W. E. Geiger, M. P. Robben, M. Wuensch, M. D. Ward, *J. Am. Chem. Soc.* **1993**, *115*, 3182 – 3198.

[4] a) Y. Sawada, S. Furumi, A. Takai, M. Takeuchi, K. Noguchi, K. Tanaka, *J. Am. Chem. Soc.* **2012**, *134*, 4080 – 4083, and references therein; b) T. Shibata, T. Uchiyama, Y. Yoshinami, S. Takayasu, K. Tsuchikama, K. Endo, *Chem. Commun.* **2012**, *48*, 1311 – 1313; c) A. Latorre, A. Urbano, M. C. Carreño, *Chem. Commun.* **2009**, 6652 – 6654, and references therein; d) K. Tanaka, N. Fukawa, T. Suda, K. Noguchi, *Angew. Chem.* **2009**, *121*, 5578 – 5581; *Angew. Chem. Int. Ed.* **2009**, *48*, 5470 – 5473; e) A. Grandbois, S. K. Collins, *Chem. Eur. J.* **2008**, *14*, 9323 – 9329; f) J. Caeiro, D. Peña, A. Cobas, D. Pérez, E. Guitián, *Adv. Synth. Catal.* **2006**, *348*, 2466 – 2474; g) M. Miyasaka, A. Rajca, M. Pink, S. Rajca, *J. Am. Chem. Soc.* **2005**, *127*, 13806 – 13807; h) K. Nakano, Y. Hidehira, K. Takahashi, T. Hiyama, K. Nozaki, *Angew. Chem.* **2005**, *117*, 7298 – 7300; *Angew. Chem. Int. Ed.* **2005**, *44*, 7136 – 7138; i) R. El Abed, B. Ben Hassine, J. P. Genêt, M. Gorsane, J. Madec, L. Ricard, A. Marinetti, *Synthesis* **2004**, 2513 – 2516; j) F. Teplý, I. G. Stará, I. Starý, A. Kollárovič, D. Šaman, P. Fiedler, Š. Vyskočil, *J. Org. Chem.* **2003**, *68*, 5193 – 5197; k) Y. Ogawa, M. Toyama, M. Karikomi, K. Seki, K. Haga, T. Uyehara, *Tetrahedron Lett.* **2003**, *44*, 2167 – 2170; l) I. G. Stará, I. Starý, A. Kollárovič, F. Teplý, Š. Vyskočil, D. Šaman, *Tetrahedron Lett.* **1999**, *40*, 1993 – 1996; m) K. Tanaka, H. Suzuki, H. Osuga, *J. Org. Chem.* **1997**, *62*, 4465 – 4470.

[5] a) P. Sehnal, I. G. Stará, D. Šaman, M. Tichý, J. Míšek, J. Cvačka, L. Rulíšek, J. Chocholoušová, J. Vacek, G. Goryl, M. Szymonski, I. Císařová, I. Starý, *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 13169 – 13174; b) P. Sehnal, Z. Krausová, F. Teplý, I. G. Stará, I. Starý, L. Rulíšek, D. Šaman, I. Císařová, *J. Org. Chem.* **2008**, *73*, 2074 – 2082; c) I. G. Stará, Z. Alexandrová, F. Teplý, P. Sehnal, I. Starý, D. Šaman, M. Buděšínský, J. Cvačka, *Org. Lett.* **2005**, *7*, 2547 – 2550.

[6] The diastereomer ratios obtained were typically about 90:10, and some of the individual diastereomers (separated by crystallization) were not configurationally stable at elevated temperature (see Ref. [5b]). These studies indicated that the stereochemical outcome of the diastereoselective [2+2+2] cycloisomerization at higher temperature was directed by thermodynamic rather than kinetic factors.

[7] C. Wolf in *Dynamic Stereochemistry of Chiral Compounds*, RSC Publishing, Cambridge, **2008**, pp. 334 – 337.

[8] In principle, both kinetic stereocontrol (operating in the irreversible cyclization) and thermodynamic stereocontrol (operating in the post-cyclization thermal equilibration of the products) can lead to the same ratio of diastereomers. At a proper temperature, the post-cyclization equilibration can be fast enough to rewrite the outcome of the primary kinetic stereocontrol.

[9] The methyl groups at the stereogenic centers in the non-tolylated **3** can occupy either the pseudo equatorial position as in (*P*,*R*,*R*)-**3** or pseudo axial position as in (*M*,*R*,*R*)-**3** (not

encompassing any 1,3-diaxial interaction). There is a preference for (*P*,*R*,*R*)-**3** over (*M*,*R*,*R*)-**3** (66:34 as found experimentally).
[10] The introduction of the tolyl group into the central benzene ring creates an equivalent of a *Z*-configured double bond, where a strong allylic-like 1,3-interaction between the tolyl group and the methyl group on the neighboring benzylic-type stereogenic center can take place; for the demonstration of such an effect and discussion on the allylic 1,3-strain, see: a) D. A. Evans, C. J. Dinsmore, *Tetrahedron Lett.* **1993**, *34*, 6029 – 6032; b) R. W. Hoffmann, *Chem. Rev.* **1989**, *89*, 1841 – 1860.
[11] The chiral triynes (*R*,*R*)-**5**–**12**, **19**, **19a**, and **20** were prepared from (*S*)-but-3-yn-2-ol (both enantiomers are commercially available) employing the Mitsunobu and Sonogashira reactions as the key operations (for details, see Supporting Information).
[12] A. Geny, N. Agenet, L. Iannazzo, M. Malacria, C. Aubert, V. Gandon, *Angew. Chem.* **2009**, *121*, 1842 – 1845; *Angew. Chem. Int. Ed.* **2009**, *48*, 1810 – 1813.
[13] CCDC 851844 ((*M*,*R*,*R*)-**3**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[14] This experiment was inspired by a referee's comments.
[15] R. H. Martin, M. J. Marchant, *Tetrahedron Lett.* **1972**, *13*, 3707 – 3708.
[16] The half-life $t_{1/2}$ of (*M*,*R*,*R*)/(*P*,*R*,*R*)-**2a** to reach 50% of the epimerization equilibrium at a reaction temperature of 170°C is about 0.2 s (estimated by using the two-point form of the Arrhenius equation).

