

## Helicity control in the synthesis of helicenes and related compounds\*

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**Abstract:** Asymmetric synthesis of helicenes and their congeners has been demonstrated to rely either on enantioselective Ni<sup>0</sup>/PR<sub>3</sub><sup>\*</sup>-catalyzed [2+2+2] cycloisomerization of triynes or on diastereoselective Co<sup>I</sup>-catalyzed [2+2+2] cycloisomerization of chiral triynes. The former approach providing tetrahydrohelicenes in a nonracemic form requires further development as moderate enantioselectivities (up to 54 % ee) have so far been achieved under kinetic control. The latter approach affording helicene-like structures in a diastereomerically enriched form allows for reaching good to excellent diastereoselectivities (up to 100:0) under thermodynamic control.

**Keywords:** helicenes; cycloisomerization; asymmetric synthesis; enantioselective catalysis; diastereoselectivity.

### INTRODUCTION

Helicenes are unique three-dimensional aromatic systems that are inherently chiral, thermally stable, usually well-soluble, and perfectly  $\pi$ -conjugated materials [1]. Actually, they exhibit an attractive molecular structure and, accordingly, promising chemical and physical properties have been demonstrated [2] and others have been foreseen [3]. In spite of that, helicenes were considered to be textbook examples of small helices rather than practically useful entities of most of the five-decade lifetime of helicene chemistry [4]. The main reasons for that were a difficult preparation of helicenes and the absence of a more general synthesis methodology to get individual enantiomers on a preparative scale.

Currently, the renewed interest in helicene chemistry can be witnessed as various original approaches to racemic or nonracemic helicenes and related compounds have emerged. In particular, the revolutionary Diels–Alder approach by Katz can be used for the synthesis of carbo- and heterohelicene quinones, allowing for a racemate resolution via diastereomeric functionalized hydroquinones [5]. However, asymmetric synthesis of helicene derivatives under an efficient stereocontrol would prevent these additional separation steps. It is not surprising that attention to such a challenging problem has recently increased. Stemming from the Katz methodology, Carreño and Urbano developed cleverly its asymmetric version, enabling the enantioselective access to helicene quinones with excellent optical purities [6]. The remarkably high stereocontrol in the synthesis of [5]helicenes was achieved by Karikomi who used the completely diastereoselective aromatic oxy-Cope rearrangement as a key step [7]. A different concept of obtaining nonracemic helicenes was published by Genet who took advantage of chi-

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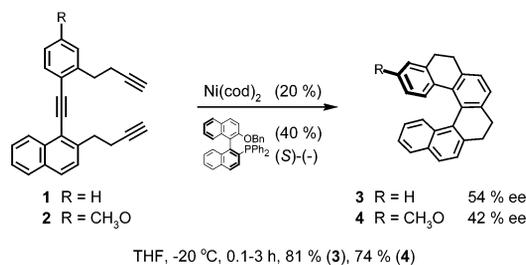
rality transfer from an enantiopure tether to flexible [5]helicene backbone under the thermal conditions, making it configurationally locked [8]. Moreover, other independent synthesis routes to nonracemic helicenes have been explored within the last decade, but the helicity control has been so far less effective. Promising approaches to nonracemic thiaheterohelicenes were published by Rajca, who performed kinetic resolution of a racemic axially chiral intermediate by asymmetric reduction of the ketone group [9a] or, alternatively, he treated the nonracemic axially chiral dilithiated intermediate with a sulfur equivalent to close the thiophene helix [9b]. A diastereoselective biaryl cross-coupling reaction exploiting oxazoline chiral auxiliary is central to asymmetric synthesis of thiaheterohelicenes by Tanaka, achieving a good stereochemical outcome [10]. Regardless of such recent progress and intriguing past achievements [11], the racemate resolution dominates in getting nonracemic helicenes and their derivatives [9a,12].

## RESULTS AND DISCUSSION

Being inspired by an elegance of helicene architecture and stimulated by the unexplored potential of the envisioned use of helicenes, we have devised a novel strategy for the preparation of these compounds. We have recently proven that the intramolecular [2+2+2] cycloisomerization of aromatic triynes under  $\text{Co}^I$  or  $\text{Ni}^0$  catalysis is a feasible concept exhibiting a high degree of synthetic flexibility [13]. Using this methodology, we synthesized various helicene derivatives ranging from penta- to heptacyclic backbones, being partially hydrogenated or fully aromatized, consisting of carbocycles only or incorporating seven-membered heterocycles, and bearing different functional groups at different positions. All of these materials were prepared as racemates.

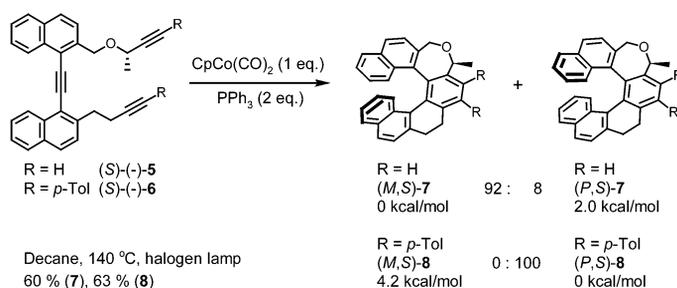
However, the [2+2+2] cycloisomerization reaction should, in principle, allow for a helicity control in the key helix-forming step. Such a goal might be attained, in this case, by performing either enantioselective triyne cyclization catalyzed by chiral metal complexes or diastereoselective cyclization of chiral triynes in the presence of achiral metal complexes.

First, we focused on enantioselective catalysis, which has never been applied to the construction of helicene skeleton before. As we demonstrated previously, the  $\text{Ni}^0/\text{PPh}_3$  catalyst system is very effective in preparing tetrahydrohelicenes via triyne cyclization [13a,b,d]. The use of chiral ligands, obviously phosphines, might result in controlling helicity. Accordingly, we screened numerous phosphorus, nitrogen, and sulfur chiral ligands, but most of them exhibited low reactivity (mostly bisphosphines) or low enantioselectivity. Among them, we identified a class of privileged ligands which have axially chiral biaryl backbone and one coordinating diphenylphosphino group in common. Thus, using Hayashi's MOP ligand or better its benzyl analog [14] we observed moderate enantioselectivities in [2+2+2] cycloisomerization of aromatic triynes **1** and **2** providing tetrahydro[6]helicene **3** [13d] or the 3-methoxyderivative **4** [13a], respectively (Scheme 1). Although these results are promising and demonstrate the feasibility of building a nonracemic helicene backbone via enantioselective cycloisomerization, there is still a long way to go to bring this methodology to practical.



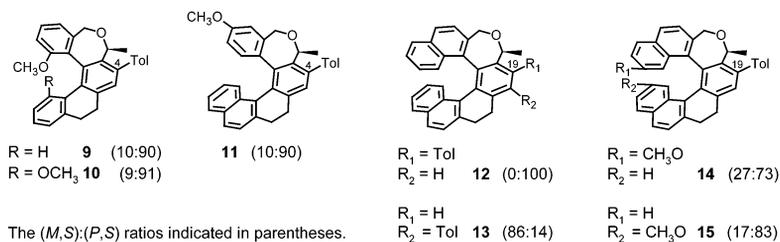
Scheme 1

In parallel, attention has been paid to diastereoselective synthesis of helicene-like compounds. We assumed that a fully aromatic backbone of helicenes might not be essential for utilization of these compounds in some branches of science, providing the helical shape of such helicene derivatives is virtually preserved. Accordingly, we devised nonracemic helicene-like structures whose diastereoselective synthesis relies on a helicity induction by the asymmetric center already present in the triyne molecule (Scheme 2) [15]. We found that [2+2+2] cycloisomerization of chiral triyne (*S*)-**5** mediated by the  $\text{Co}^I/\text{PPh}_3$  system afforded two possible diastereomers (*M,S*)-**7** and (*P,S*)-**7** in a 92:8 ratio. The analogous triyne (*S*)-**6** with two *p*-tolyl groups at the pendant acetylene units provided only (*P,S*)-**8** possessing the opposite helicity. Such a striking stereochemical dichotomy requires explanation. If the reaction proceeds under thermodynamic control, *vide infra*, its stereochemical outcome should reflect the energy contents of the diastereomeric products. Thus, we calculated the relative energies of both pairs (*M,S*)-**7** vs. (*P,S*)-**7** and (*M,S*)-**8** vs. (*P,S*)-**8** in decane at 140 °C using the DFT method (B3LYP/TZV+P), and COSMO solvation model. The calculated free energies clearly indicated a more stable diastereomer from the relevant pair being expected to prevail in the reaction mixture, in excellent agreement with the experimental results.



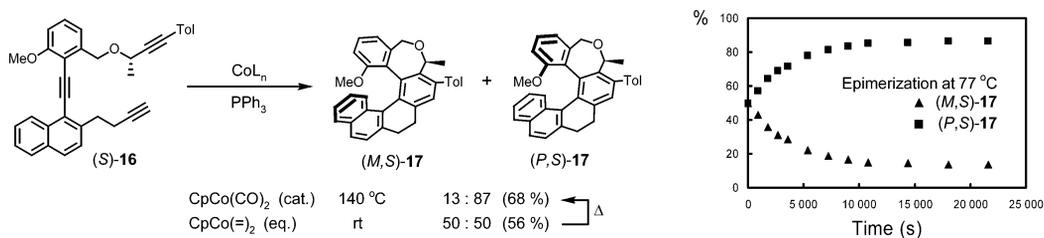
Scheme 2

As it has been clearly shown that the helicity control is possible and diastereoselectivity of the cyclization could be good to excellent, we have decided to explore the scope and limitations of this approach to nonracemic helicene-like compounds. Accordingly, we studied the key [2+2+2] cycloisomerization of a series of chiral triynes in the presence of  $\text{CpCo}(\text{CO})_2/\text{PPh}_3$  in decane at 140 °C to obtain helicene-like compounds **9–15** (Scheme 3). The stereochemical outcome of the reaction was found to be basically invariant to the helicene size and the presence of a functional group attached to the terminal benzene rings. In all cases, the diastereomeric ratio ranged between 73:27 and 100:0. However, the presence of the *p*-tolyl group at C-4 (compounds **9–11**) or C-19 (compounds **12, 14, 15**) effectively controlled the cyclization in favor of (*P*) helix, while its absence at C-19 (compound **13**) resulted in the predominant formation of (*M*) helix.



Scheme 3

The following experiments have shed light on an underlying problem whether the chiral triyne cyclizations proceed under kinetic or thermodynamic control. In the presence of  $\text{CpCo}(\text{CO})_2/\text{PPh}_3$  at  $140\text{ }^\circ\text{C}$ , triyne (*S*)-**16** afforded the major (*P,S*)-**17** along with the minor (*M,S*)-**17** in a 87:13 ratio (Scheme 4). Aiming at better diastereoselectivity, we performed the cyclization at room temperature using the more reactive Jonas catalyst. Surprisingly, we got a 1:1 mixture of both diastereomers (*M,S*)- and (*P,S*)-**17**. More interestingly, when heating this mixture at  $77\text{ }^\circ\text{C}$  we could monitor a diastereomerization process reaching practically the equilibrium within ca. 6 h. The (*M,S*)-**17**:(*P,S*)-**17** ratio after this thermal epimerization was practically the same as obtained from the  $\text{CpCo}(\text{CO})_2$ -catalyzed cyclization at  $140\text{ }^\circ\text{C}$ , *vide supra*. Thus, we can infer that the diastereoselectivity of [2+2+2] cycloisomerizations leading to helicene-like compounds **7–15** is governed by thermodynamic factors.



Scheme 4

## CONCLUSION

We have demonstrated that the asymmetric synthesis of helicenes and their congeners can rely on enantioselective  $\text{Ni}^0/\text{PR}_3^*$ -catalyzed [2+2+2] cycloisomerization of triynes or on diastereoselective  $\text{Co}^I$ -catalyzed [2+2+2] cycloisomerization of chiral triynes. The former approach providing tetrahydrohelicenes requires further development as moderate enantioselectivities (up to 54 % ee) have so far been achieved under kinetic control. The latter approach affording helicene-like structures allows for reaching good to excellent diastereoselectivities (up to 100:0) under thermodynamic control.

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