Enantioselective Synthesis of 1,12-Disubstituted [4]Helicenes
Thierry Hartung, Rafael Machleid, Martin Simon, Christopher Golz, and Manuel Alcarazo*

Abstract: A highly enantioselective synthesis of 1,12-disubstituted [4]carbohelicenes is reported. The key step for the developed synthetic route is a Au-catalyzed intramolecular alkyne hydroarylation, which is achieved with good to excellent regio- and enantioselectivity by employing TADDOL-derived (TADDOL = a,a,a,a-tetraaryl-1,3-dioxolane-4,5-dimethanol) α-cationic phosphonites as ancillary ligands. Moreover, an appropriate design of the substrate makes the assembly of [4]helicenes of different substitution patterns possible, thus demonstrating the synthetic utility of the method. The absolute stereochemistry of the newly prepared structures was determined by X-ray crystallography and characterization of their photophysical properties is also reported.

Carbohelicenes are screw-shaped molecules formally derived from the ortho-condensation of benzene rings. Even though no stereogenic centers are present in their structures, the twisted geometry imposed by their connectivity makes them chiral. The energetic barrier for the interconversion between the two enantiomeric forms is strongly dependent on the number of ortho-fused benzene units. The first member of the carbohelicene family with a helicoidal structure is [4]helicene, which is configurationally unstable under ambient conditions. [5]Helicene can be resolved, but the low activation energy of racemization (ΔG°‡ = 24.1 kcal mol⁻¹) does not hamper the slow interconversion of the enantiomers. Hence, the racemization of these structures is typically complete after a couple of days at room temperature. The first configurationally stable member of the helicene family is [6]helicene. Racemization of [6]helicene only occurs after intensive heating (ΔG°‡ = 36.2 kcal mol⁻¹; t½(rac) = 48 min at 205 °C), making this scaffold the first carbohelicene intrinsically useful for the design of thermally stable chiral architectures.

Nevertheless, the absolute configuration of low-order [4] and [5]helicenes can be fixed either by installation of appropriate substituents at one or both termini of their fjord region, or by embedment of the helicene moiety into a more extended π-conjugated scaffold. As an illustrative example, on the incorporation of a methyl substituent in the 1-position of [5]helicene, the enantiomerization barrier increases up to ΔG°‡ = 39.1 kcal mol⁻¹, making 1-(methyl)-[5]helicene even more reluctant to racemize than [6]helicene. The situation is analogous for [4]helicenes, but these structures require positions 1- and 12- to be simultaneously substituted to freeze the racemization process (Figure 1).

Despite the impressive development already achieved in the synthesis of helicenes and the number of applications that configurationally stable low-order helicenes have found in diverse areas such as asymmetric catalysis, or the design of molecular machines, highly enantioselective syntheses of [5]carbohelicene derivatives are scarce. To the best of our knowledge, no enantioselective route is available for the preparation of 1,12-disubstituted[4]helicenes.

Being aware of the potential offered by Au-catalyzed hydroarylation reactions for the assembly of conveniently designed alkyne into polyarenes, we conceived the enantioselective synthesis of 1,12-disubstituted [4]helicenes from substrates of general formulae A or B (Figure 2).
TADDOL-derived α-cationic phosphonites recently developed in our laboratory were chosen as ancillary ligands for the preparation of the necessary Au precatalysts 2 because of their high modularity, which allows easy tuning of the chiral pocket around the Au atom; and their cationic character, ultimately responsible for the enhanced activity of the actual catalytic species if compared with other Au catalysts of similar structure but derived from neutral ligands.[15]

We began our investigation by synthesizing dialkyne 3a, which was obtained by Suzuki coupling between known bistriol 4 and boronic acid 5a (Scheme 1a).[17] Subsequently, a complete array of Au precatalysts 2a–g were screened for the successive double hydroarylation required to transform the model substrate into [4]helicene 1a. Our initial explorative conditions were set up as follows: catalyst loading of 10 mol%, fluorobenzene as solvent, and a working temperature of –20°C. All reactions were allowed to proceed for 96 hours or until total consumption of the starting material.

The performance of catalysts 2a–c, all containing an acetonide backbone, was modest in terms of regio- and enantioselectivity (Table 1, Entries 1–3). Interestingly, replacement of the acetonide motif by methoxy groups, such as in Au complexes 2d,e, improved the performance of the catalysts.[18] Specifically, catalyst 2e, which contains four p-(CF3)Ph substituents, was able to promote the desired double cyclization towards [4]helicene 1a with excellent enantio- (> 97% ee) and regioselectivity (1a:9:198:2) (Table 1, Entry 5). The catalytic system suffers, however, from low reactivity, and reaction times of up to four days were necessary.

In an attempt to solve this issue, the imidazolium moiety in ligand 2e was exchanged by more-electron-withdrawing 1,2,3-triazolium units, and the already optimal chiral environment around the Au atom was maintained. Both resulting catalysts, 2f and 2g, were able to match, or even slightly overtake, the already outstanding regio- and enantioselectivities of 2e (Table 1, Entries 6 and 7), and by employing 2g the reaction times were shortened to only two days. No product derived from the 5-exo-dig cyclization of the substrate was observed in any of these experiments. A final solvent screening indicated that 2g does not require the employment of fluorobenzene to maintain excellent levels of enantioinduction; highly competitive results were also obtained working in dichloromethane (Table 1, Entry 8).[15c] Finally, crystals of precatalyst 2g were obtained, and its molecular connectivity was confirmed by X-ray diffraction (see Scheme 1c and the Supporting Information).

**Table 1**: Screening of chiral Au-phosphonite complexes in the hydroarylation of mono- and diynes towards [4]helicenes.

| Entry | Au catalyst | Substrate | Yield [%] | 1a | 1b (ee [%]) |
|-------|-------------|-----------|-----------|----|-------------|
| 1     | 2a          | 3a        | 50        | 75.25 | 1a (36)    |
| 2     | 2b          | 3a        | 13        | 50.50 | 1a (30)    |
| 3     | 2c          | 3a        | 91        | 94.6 | 1a (8)     |
| 4     | 2d          | 3a        | 52        | 68.32 | 1a (28)    |
| 5     | 2e          | 3a        | 94        | 98.2 | 1a (97)    |
| 6     | 2f          | 3a        | 97        | 99.1 | 1a (98)    |
| 7     | 2g          | 3a        | 98        | 98.2 | 1a (99)    |
| 8     | 2g          | 3a        | 95        | 96.4 | 1a (98)    |
| 9     | 2g          | 3b        | 94        | 97.3 | 1b (97)    |
| 10    | 2g          | 3c        | 84        | 93.7 | 1c (89)    |
| 11    | 2g          | 3d        | 4         | >99.1 | 1d (95)    |
| 12    | 2g          | 8a        | 57        | 98.2 | 1e (88)    |
| 13    | 2g          | 8b        | 65        | 94.6 | 1e (97)    |

[a] Reaction conditions: 3a–d (0.02 mmol), catalysts 2a–g, 10 mol%, AgSbF6 10 mol%, FC6H5 (0.05 mmol), –20°C, 96 h. Yields are of the isolated mixtures; regioisomer ratios were determined by 1H NMR spectroscopy and ee values by chiral HPLC. [b] CH2Cl2 was used as solvent (0.05 mmol). [c] Reaction carried out at 0°C. [d] Catalyst loading of 5 mol%.

Scheme 1. Synthesis of [4]helicene precursors and structures of the catalysts tested. Reagents and conditions: a) Pd2(dba)3 (5 mol%), SPPhos (10 mol%), Cs2CO3 (4 equiv), THF/H2O (10:1), 80°C, 24 h, 3a, 62%; 3b, 67%; 3c, 65%; 3d, 89%; b) 19 (9 mol%), AgSbF6 (9 mol%), DCM, 7a, 87%; 7b, 42%, both from 6 (two steps); c) TFSO (1.5 equiv), pyridine (4.0 equiv), and then 5a or 5c, Pd2(dba)3 (5 mol%), SPPhos (10 mol%), Cs2CO3 (2 equiv), THF/H2O (10:1), 80°C, 24 h, 8a, 60%; 8b, 25% (two steps). X-ray structure of 2g. H atoms, co-crystallized solvents and SbF6 anions are removed for clarity. Aren moieties are drawn as reduced sticks, ellipsoids drawn at 50% probability level.[19]
By using the conditions already optimized, the respective cyclization reactions of diynes 3h,i to 1b,c took place with high levels of regio- and enantioselectivity (Table 1, Entries 9 and 10). Interestingly, the more reactive nature of 3c, decorated with terminal p-anisyl substituents allowed a reduction of the catalyst loading to only 5 mol % without significant erosion of the yield. On the other hand, the cyclization of diyne 3d, bearing strong electron-withdrawing CF3 substituents proved to be difficult and only traces of the desired [4]helicene 1d was obtained under the standard reaction conditions, although with outstanding ee (4 % yield of isolated product, 95 % ee). The mono-cyclized intermediate is the main species present in the mixture (Table 1, Entry 11).

The hydroarylation of substrates 8a and 8b towards non C2-symmetrically substituted 1e proceeded in both cases with acceptable yields. The same major enantiomer was obtained from both reactions, albeit the enantioselectivity of the cyclization is slightly eroded when using 8a as the substrate (Table 1, Entries 12 and 13). Considering that only one hydroarylation event is required to obtain 1e from these substrates, it is not surprising that only 5 mol % of precatalyst 2g is required for the reactions to conclude in 48 h. The X-ray structure of substrate 8a and precursor 7a are depicted in the Supporting Information.

Encouraged by these results, and seeking to further explore the viability of our cycloisomerization protocol towards other [4]helicene structures, additional alkyne precursors were evaluated. Thus, phenanthrene derivatives 18a–j were prepared following a multistep route, which is described in detail in Scheme 2.

For substrates 13a,b, containing a terminal alkyne, the cycloisomerization proceeded successfully in the presence of catalytic amounts of PtCl2,[19] neither PtCl2 or Ph3P–AuCl/AgSbF6 were able to satisfactorily promote the hydroarylation step for internal alkyne 14c,d. Only the employment of Au precatalyst 19, containing a strong N-acceptor N-arylpyridino phosphine as an ancillary ligand, induced the formation of 15c,d in synthetically practical yields.[20]

For substrates 18a–c (R2 = Me), the performance of 2g (5 mol %) is mediocre in terms of regio- and enantioselectivity (Table 2, Entries 1–3), and significant amounts of undesired benzo[ghi]tetraphenes 21a–c were obtained as side products. Interestingly, complete control over the enantioselectivity (97–99 % ee) is achieved by formal exchange of the methyl groups at position R2 by phenyl groups (substrates 18d–f), however, the regioselectivity of the cyclization for these substrates is still far from ideal (Table 2, Entries 4–6). Note that 8a,b only differs from 18d–f in a remote benzanulation, but this seems to be crucial to effectively direct the hydroarylation to the inner position of the phenanthrene (Table 1, Entries 11–12).

Similarly, alkyne 18g,h only differs from 18a,b in a phenyl substituent from the outer rim of the phenanthrene; however, for these structures the cyclization is again selectively directed to the desired position affording 20g,h with high regioselectivity (Table 2, Entries 7–8). The best results of the series were obtained for substrates 18i,j (R1 = Ph, R2 = OMe), which were transformed into 20i,j with excellent regio- and enantioselectivities. Further scrutiny is ongoing to fully understand the effect of remote substitutions on the hydroarylation site, but it seems to be consistent that catalyst 2g promotes higher enantioselectivities for π-extended structures.[21]

The connectivity of parent [4]helicene 1a was unambiguously confirmed by X-ray crystallography employing a racemic single crystal (Figure 3). In this compound the vertical distance between the overlapping C1 and C7 carbon atoms is 3.243(1) Å, which is basically identical to the value in [6]helicene (3.215 Å). On the other hand, the torsion angles along the inner rim in 1a (from C1 to C7, ϕ = 20.3, 27.6, 27.6, 20.3°) vary significantly if compared with those in [6]helicene (ϕ = 11.2, 30.1, 31.0, 15.2°), in particular for rings A and D. This difference is likely to be caused by the higher tolerance towards geometrical distortion of the one-point-connected phenyl groups.[22] To examine the chiral stability of the [4]helicenes prepared, enantioenriched 1a (98 % ee) was heated at 180°C in 1,2-dichlorobenzene for 24 h and later monitored by chiral
Table 2: Scope of the Au-catalyzed hydroarylation of 18a–j towards [4]helicenes. 

| Entry | Substrate | Yield [%] | 20:21 | 20 (ee [%]) |
|-------|-----------|-----------|-------|------------|
| 1     | 18a       | 95        | 63:37 | 20a (60)   |
| 2     | 18b       | 43        | 42:58 | 20b (75)   |
| 3     | 18c       | 85        | 44:56 | 20c (70)   |
| 4     | 18d       | 93        | 69:31 | 20d (97)   |
| 5     | 18e       | 93        | 54:46 | 20e (99)   |
| 6     | 18f       | 75        | 38:62 | 20f (98)   |
| 7     | 18g       | 87        | 90:10 | 20g (67)   |
| 8     | 18h       | 93        | 98:2  | 20h (79)   |
| 9     | 18i       | 93        | 99:1  | 20i (92)   |
| 10    | 18j       | 94        | 95:5  | 20j (90)   |

[a] Reaction conditions: 18a–j (0.02 mmol), catalyst 2g, 5 mol %, AgSbF6 10 mol %, CH2Cl2 (0.05 M), −20°C, 96 h. Yields are of the isolated 20:21 mixtures; regioisomer ratios were determined by 1H NMR spectroscopy and ee values by chiral HPLC.

Figure 3. X-ray structure of rac-1a (left) and 20j (right). H atoms are removed for clarity and ellipsoids drawn at 50% probability level.

The absorption and fluorescence spectra of the [4]helicenes synthesized can be found in the Supporting Information. Interestingly, compounds 1a–e display blue fluorescence, with the emission maximum being located at 438–440 nm. The emission bands for 20a–j, architectures characterized by only one benzannulation of the parent [4]helicene, are slightly blue-shifted and appear at 426–433 nm.

In summary, we report herein the first highly enantioselective synthesis of 1,12-disubstituted [4]carbohelicenes, achieved through the Au-catalyzed intramolecular hydroarylation of appropriate alkyne and employing a TADDOL-derived α-cationic phosphinite as an ancillary ligand. Single-crystal X-ray analysis unambiguously determined the connectivity of the new structures obtained and established their absolute configuration. Ongoing work in our laboratory is focused on the further optimization of the catalytic system developed towards the enantioselective synthesis of higher-order carbohelicenes and other polyhelic scaffolds.

Acknowledgements

Financial support from the Deutsche Forschungsgemeinschaft (AL 1348/8-1, INST 186/1237-1 and INST 186/1324-1) is gratefully acknowledged.

Conflict of interest

The authors declare no conflict of interest.

Keywords: [4]helicenes · asymmetric catalysis · Au catalysis · enantioselective synthesis · ligand design

How to cite: Angew. Chem. Int. Ed. 2020, 59, 5660–5664
Angew. Chem. 2020, 132, 5709–5713

[1] a) Y. Shen, C.-F. Chen, Chem. Rev. 2012, 112, 1463–1535; b) M. Gingras, Chem. Soc. Rev. 2013, 42, 968–1006; c) M. Gingras, G. Félix, R. Peresutti, Chem. Soc. Rev. 2013, 42, 1007–1050; d) M. Gingras, Chem. Soc. Rev. 2013, 42, 1051–1095; e) C.-F. Chen, Y. Shen, Helicene Chemistry, From Synthesis to Applications, Springer, Berlin, 2017.
For diastereoselective syntheses, see:

a) M. C. Carreño, S. García-Cerrada, A. Urbano, Angew. Chem. Int. Ed. 2001, 123, 7929–7930;
b) Y. Ogawa, T. Ueno, M. Karikomi, K. Seki, H. Haga, T. Uyehara, Tetrahedron Lett. 2002, 43, 7827–7832;
c) Y. Ogawa, M. Toyama, M. Karikomi, K. Seki, H. Haga, T. Uyehara, Tetrahedron Lett. 2003, 44, 2167–2170;
d) M. C. Carreño, S. García-Cerrada, A. Urbano, Chem. Eur. J. 2003, 9, 4118–4131;
e) M. Šámal, S. Chercheja, J. Rybčík, J. V. Chocholoušová, J. Vacek, L. Bednárová, D. Šaman, I. G. Starý, I. Starý, J. Am. Chem. Soc. 2015, 137, 8469–8474;
f) A. Urbano, A. M. del Hoyo, A. Martínez-Carrión, M. C. Carreño, Org. Lett. 2019, 21, 4623–4627.

For diastereoselective syntheses, see:

a) M. C. Carreño, S. García-Cerrada, M. J. Sanz-Cuesta, Angew. Chem. Commun. 2001, 1452–1453;
b) M. C. Carreño, A. Enríquez, S. García-Cerrada, M. J. Sanz-Cuesta, A. Urbano, F. Maesras, A. Nonell-Canals, Chem. Eur. J. 2008, 14, 603–620;
c) A. Latorre, A. Urbano, M. C. Carreño, Chem. Commun. 2011, 47, 8103–8105.

Manuscript received: December 11, 2019
Accepted manuscript online: January 21, 2020
Version of record online: February 20, 2020