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Enantioselective Synthesis of 1,12-Disubstituted [4]Helicenes

Thierry Hartung, Rafael Machleid, Martin Simon, Christopher Golz and Manuel Alcarazo *[a]

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

Carbohelicenes are screw-shaped molecules formally derived from the ortho-condensation of benzene rings.[1] Even though no stereogenic centers are present in their structures, the twisted geometry imposed by their connectivity makes them chiral, being the energetic barrier for the interconversion between the two enantiomeric forms strongly dependent on the number of ortho-fused benzene units. The first member of the carbohelicene family showing an helicoidally structure is [4]helicene, which is configurationally unstable under ambient conditions.[2] [5]helicene can be resolved, but its still low activation energy of racemization ($\Delta G^{\ddagger}$ = 24.1 kcal/mol) 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.[3] The first configurationally stable member of the helicene family is [6]helicene. Its racemization only occurs after intensive heating ($\Delta G^{\ddagger}$ = 36.2 kcal/mol; $t_{1/2}$(rac) = 48 min. at 205 °C), making this scaffold the first one among carbohelicenes intrinsically useful to design thermally stable chiral architectures. [4]

Notwithstanding, 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.[5] As illustrative example, on incorporating just a methyl substituent in position 1- of [5]helicene, the enantiomerization barrier increases up to $\Delta G^{\ddagger}$ = 39.1 kcal/mol, making 1-(methyl)[5]helicene even more reluctant to racemize than [6]helicene.[6] The situation is analogue for [4]helicenes, but these structures require positions 1- and 12- to be simultaneously substituted in order to freeze the racemization process (Figure 1). [7]

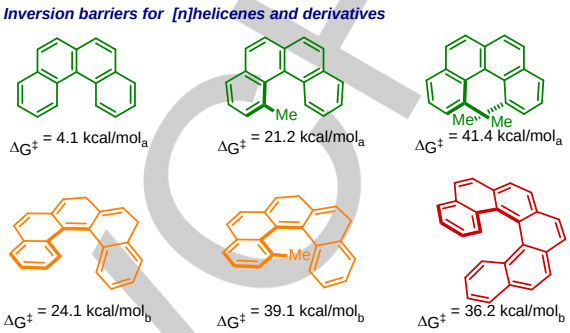

Figure 1. Inversion barriers for [4]-, [5]- and [6]helicenes and their Me-substituted derivatives; [a] Calculated values at the B3LYP/6-31G(d) level of theory; [b] Experimental values.

In spite of the impressive development already achieved in the synthesis of helicenes,[1] and the number of applications that configurationally stable low order helicenes have found in diverse areas such as asymmetric catalysis,[8] chiral recognition,[9] or the design of molecular machines,[10] highly enantioselective syntheses of [5]carbohelicene derivatives are scarce;[11, 12] and to the best of our knowledge, no enantioselective route is available for the preparation of 1,12-disubstituted[4]helicenes.[13]

Being aware of the potential offered by Au-catalysed hydroarylation reactions for the assembly of conveniently designed alkynes into polyarenes;[14] we conceived the enantiomeric synthesis of 1,12-disubstituted [4]helicenes from substrates of general formulae **A** or **B** (Figure 2).

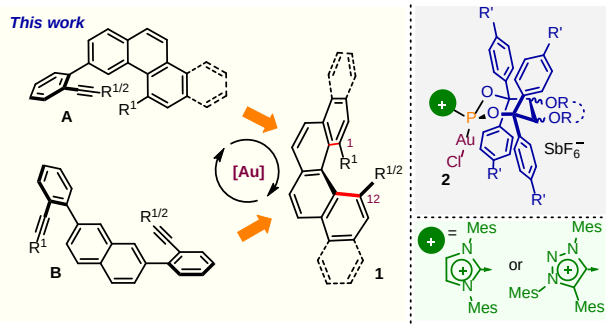

Figure 2. Synthetic approaches to the enantioselective synthesis of 1,12-disubstituted [4]helicenes.

TADDOL-derived monodentate α-cationic phosphonites recently developed in our laboratory were chosen as ancillary ligands for the preparation of the necessary Au-precatalysts **2** due to their high modularity, which allows the easy tuning of the chiral pocket around the Au atom; and their cationic character, ultimately responsible for the enhanced activity of the actual

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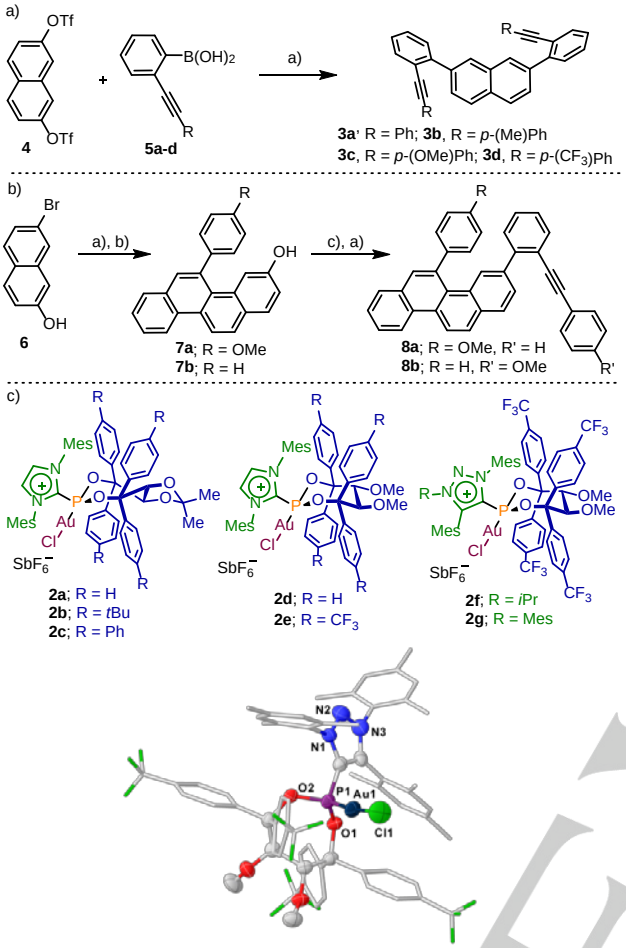
catalytic species if compared with other Au-catalysts of similar structure but derived from neutral ligands.[15]

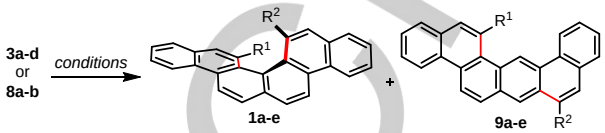


Scheme 1. Synthesis of [4]helicene precursors and structures of the catalysts tested. Reagents and conditions: (a) $Pd_2(dba)_3$ (5 mol%), SPhos (10 mol%), Cs_2CO_3 (4 equiv.), THF/H_2O (10:1), 80°C, 24h, **3a**, 62%; **3b**, 67%; **3c**, 65%; **3d**, 89%;(b) **19** (9 mol%), $AgSbF_6$ (9 mol%), DCM, **7a**, 87%; **7b**, 42%, both from **6** (two steps); (c) Tf_2O (1.5 equiv.), pyridine, and then **5a** or **5c**, $Pd_2(dba)_3$ (5 mol%), SPhos (10 mol%), Cs_2CO_3 (2 equiv.), THF/H_2O (10:1), 80°C, 24h, **8a**, 60%; **8b**, 25% (two steps). X-ray structure of **2g**, H atoms, co-crystalized solvents and SbF_6 anions are removed for clarity. Arene moieties are drawn as reduced sticks, ellipsoids drawn at 50% probability level.[16]

We began our investigation by synthesizing dialkyne **3a**, which was obtained by Suzuki coupling between known bistriflate **4** and boronic acid **5a** (Scheme 1a).[17] Subsequently, a complete array of Au precatalysts **2a-g** were screened on the successive double hydroarylation required to transform that model substrate into [4]helicene **1a**. Our initial explorative conditions were set up as follows: catalyst load 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 catalysts' performance.[18] Specifically, catalyst **2e**, which additionally contain four *p*-(CF_3)Ph substituents, was able to promote the desired double cyclisation towards [4]helicene **1a** with excellent enantio- (97 % ee) and regioselectivites (**1a**:**9a**; 98:2) (Table 1, Entry 5). The catalytic system suffers however from low reactivity, and reaction times of up to four days were necessary.

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



Entry	Au cat	Subst.	Yield (%)	**1**:**9**	**1** (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[b]	**2g**	**3a**	98	98:2	**1a** (99)
8[b,c]	**2g**	**3a**	95	96:4	**1a** (98)
9[b]	**2g**	**3b**	94	97:3	**1b** (97)
10[b,d]	**2g**	**3c**	84	93:7	**1c** (89)
11[b,c]	**2g**	**3d**	4	>99:1	**1d** (95)
12[b,d]	**2g**	**8a**	57	98:2	**1e** (88)
13[b,d]	**2g**	**8b**	65	94:6	**1e** (97)

[a]Reaction conditions: **3a-d** (0.02 mmol), catalysts **2a-g**, 10 mol%, $AgSbF_6$ 10 mol%, FC_6H_5 (0.05 M), -20 °C, 96 h. Yields are of the isolated **1**:**9** mixtures; regioisomer ratios were determined by ^{1}H NMR and ee values by chiral HPLC. [b]CH_2Cl_2 was used as solvent (0.05 M), 48h.. [c]Reaction carried out at 0 °C. [d]Catalyst loading of 5 mol%.

In an attempt to solve this issue, the imidazolium moiety in ligand **2e** was exchanged by more electron withdrawing 1,2,3-triazolium units, but keeping the already optimal chiral environment around the Au atom. 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), but importantly employing **2g** 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).[15a] Finally, crystals of precatalyst **2g** were obtained, and its molecular connectivity was confirmed by X-ray diffraction (See Scheme 1c and the Supporting Information).

Using the conditions already optimized, the respective cyclizations of diynes **3b-c** into **1b-c** took similarly 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 load to only 5 mol% without significant erosion of the yield. On

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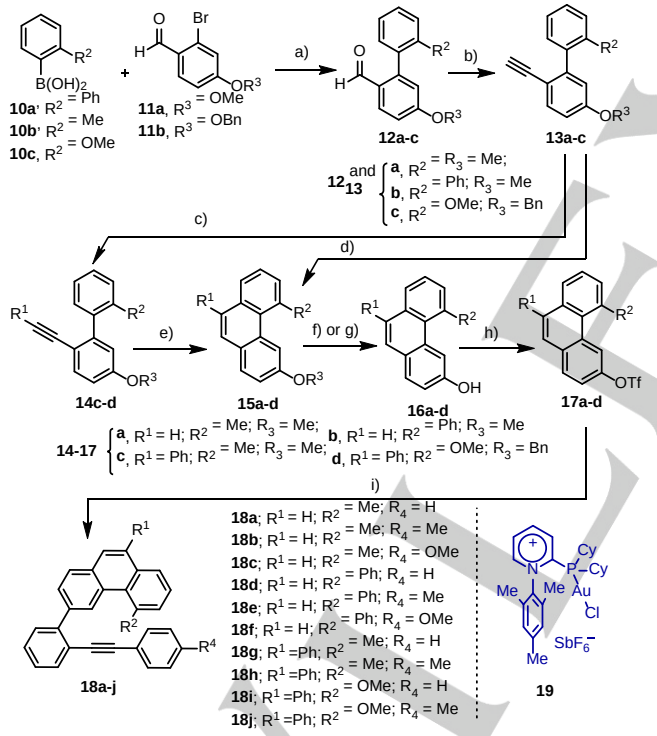
the other hand, the cyclization of diyne **3d**, bearing strong electron withdrawing CF_3-substituents proved to be difficult and only traces of the desired [4]helicene **1d** was obtained under standard reaction conditions, although with outstanding ee (4% isolated yield, 95% ee). The mono-cycled intermediate is the main species present in the mixture (Table 1, Entry11).

The hydroarylation of substrates **8a** and **8b** towards non C_2-symmetrically substituted **1e** proceeded in both cases with acceptable yields. The same major enantiomer was obtained from both reactions, albeit the enantioselectivity of the cyclisation is slightly eroded when using **8a** as 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 48h. 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.

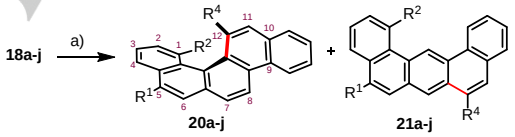


Scheme 2. Synthesis of non-symmetric [4]helicene precursors. Reagents and conditions: a) $Pd(AcO)_2$ (3 mol%), SPhos, (3 mol%), K_3PO_4 (2.0 equiv.), toluene:dioxane (10:1), **12a**, 92%, **12b**, 91%, **12c**, 87%; b) Ohira-Bestmann reagent (3.0 equiv.), K_2CO_3 (3.0 equiv.), MeOH, **13a**, 95%, **13b**, 99%, **13c**, 87%; c) PhI (1.0 equiv.), CuI (3 mol%), $PdCl_2(PPh_3)_2$ (2 mol%), Et_3N (5 mL), **14c**, 89%, **14d**, 71%; d) $PtCl_2$ (10 mol %), toluene, 85°C, **15a**, 60%; **15b**, 89%; e) **19** (10 mol%), $AgSbF_6$ (10 mol%), DCM, **15c**, 73%; **15d**, not isolated; f) BBr_3, DCM, **16a**, 99%; **16b**, 85%; **16c**, 73%; g) BCl_3 (2 equiv.), C_6HMe_5 (3 equiv.),**16d**, 67% (two steps); h) Tf_2O (1.2 equiv.), Et_3N, **17a**, 79%; **17b**, 75%; **17c**, 98%, **17d**, 95%; i) **5a-c**, $Pd_2(dba)_3$ (5 mol%), SPhos (10 mol%), Cs_2CO_3 (2 equiv.), THF/H_2O (10:1), 80°C, 24h, **18a**, 89%; **18b**, 92%; **18c**, 68%; **18d**, 51%; **18e**, 43%; **18f**, 38%; **18g**, 67%; **18h**, 75%; **18i**, 62%; **18j**, 81%.

Key for the success of this synthetic plan was the effective preparation of phenanthrene intermediates **15a-d** by intramolecular hydroarylation of the corresponding alkynes. While for substrates **13a-b**, containing a terminal alkyne, the cycloisomerization proceeded successfully in the presence of catalytic amounts of $PtCl_2$,[19] neither $PtCl_2$ or $Ph_3PAuCl/AgSbF_6$ were able to satisfactorily promote the hydroarylation step for internal alkynes **14c-d**. Only the employment of Au precatalyst **19**, containing a strongly π-acceptor *N*-arylpyridinio phosphine as ancillary ligand, induced the formation of **15c-d** in synthetically practical yields. [20]

For substrates **18a-c** (R^2 = 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[m]tetraphenes **21a-c** were obtained as side products. Interestingly, complete control over the enantioselectivity (97-99% ee) is achieved by formal exchange of the Me- groups at position R^2 by Ph- ones (substrates **18d-f**); however, the regioselectivity of the cyclisation for these substrates is still far from ideal (Table 2, Entries 4-6). Note that **8a,b** only differ from **18d-f** in a remote benzannulation, but this seems to be crucial to effectively direct the hydroarylation to the inner position of the phenanthrene (Table 1, Entries 11-12).

Table 2. Scope of the Au-catalized hydroarylation of **18a-j** towards [4]helicenes[a]



Entry	Subst.	Yield (%)	**20**:**21**	**20** (ee %)
1	**18a**	93	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)

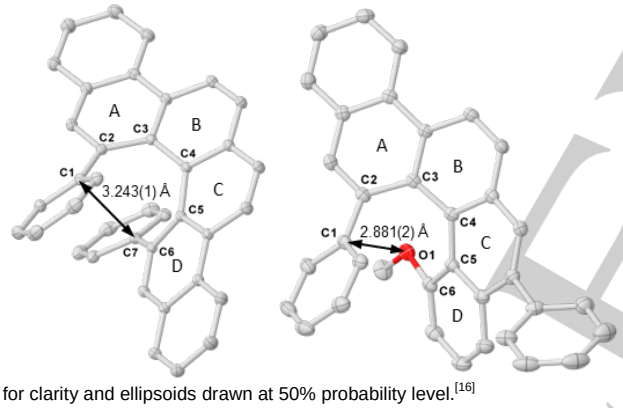
[a]Reaction conditions: **18a-j** (0.02 mmol), catalyst **2g**, 5 mol%, $AgSbF_6$ 10 mol%, CH_2Cl_2 (0.05 M), -20 °C, 48 h. Yields are of the isolated **20**:**21** mixtures; regioisomer ratios were determined by ^{1}H NMR and ee values by chiral HPLC.

Similarly, alkynes **18g-h** only differentiate from **18a-b** in a phenyl substituent from the outer rim of the phenanthrene; however, for these structures the cyclisation 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** (R^1 = Ph, R^2 = OMe), which were transformed into **20i-j** with excellent regio- and

enantioselectivities. Further scrutiny is ongoing to fully understand effect of remote substitutions on the hydroarylation site, but it seems to be a constant that catalyst **2g** promotes higher enantioselectivites for π-extended structures.[15]

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 (3.215Å). 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 to those in [6]helicene (φ = 11.2, 30.1, 31.0, 15.2°), in particular for rings A and D. This is likely to be caused by the higher tolerance to geometrical distortion of the one point connected phenyl groups.[21] To examine the chiral stability of the [4]helicenes prepared, enantioenriched **1a** (98% ee) was heated at 180 °C in 1,2-dichlorobenzene for 24h and later monitored by chiral HPLC. No erosion of the ee was observed, highlighting the configurational stability of 1,12-disubstituted [4]helicenes.

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.[16]



The absolute configuration of the newly prepared helicenes was determined to be *P*- from the X-ray analyses of single crystals of **20i** and **20j** (See Figure 3 and the Supplementary Information).[22] For **20i**, both the Flack and Hooft parameters (0.01(4) and 0.04(3), respectively) unambiguously support this assignment. For **20j** identical conclusion can be reached (0.01(12) and 0.09(5) for the Flack and Hooft parameters respectively). The higher estimated standard deviation for the last case is attributed to lower data redundancy for this measurement. Importantly, both independent results point to the same absolute configuration. Additionally, the circular dichroism spectra for [4]helicenes **1a-e** are shown in Figure 4. Comparison of these EDC spectra with that reported by Yamaguchi for a 1,12-dimethyl substituted [4]helicene further confirms the assignment of the helicity made by crystallographic techniques.[23]

The absorption and fluorescence spectra of the [4]helicenes synthesized can be found in the Supplementary 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.

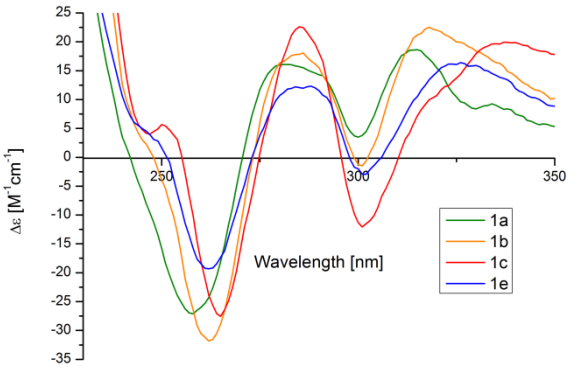


Figure 4. Circular dichroism spectra of **1a-c** and **1e** in dichloromethane.

In summary, we report herein the first highly enantioselective synthesis of 1,12-disubstituted [4]carbohelicenes, which is achieved through the Au-catalyzed intramolecular hydroarylation of appropriate alkynes, employing a TADDOL-derived α-cationic phosphinite as 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 polyhelical scaffolds.

Acknowledgements

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Keywords: [4]helicenes • Enantioselective synthesis• Asymmetric catalysis • Au catalysis • Ligand design

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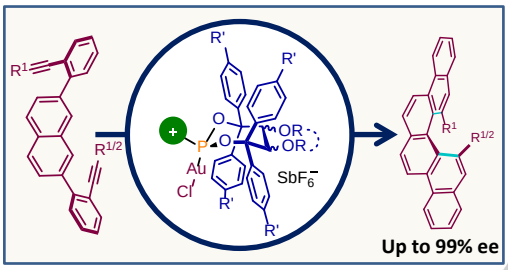
Minimalistic helicenes. The use of chiral Au-catalyst bearing an α-cationic TADDOL-derived phosphonite as ancillary ligand allows the enantioselective assembling of one of the smallest helical polyarene architectures that can be conceived: 1,12-disubstituted [4]helicenes.



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