

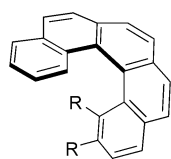
Recent Developments in the Synthesis of Helicene-Like Molecules

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Keywords:

arenes · asymmetric synthesis · helical structures · helicenes · synthetic methods

For many years [*n*]helicenes, nonplanar *ortho*-fused aromatic compounds that exhibit helical chirality, were regarded as little more than an academic curiosity.^[1] More recently, helicene chemistry has grown from the stage of a descriptive field of aesthetic and curious

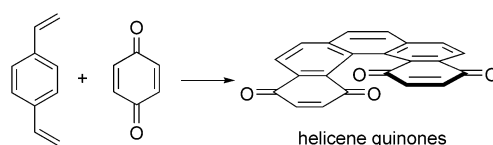
[*n*]helicenes

molecules to an important field of research owing to the extraordinary optical and electronic properties of these compounds,^[2] closely associated to their inherent chirality. Though useful, the classical synthesis of helicenes based on the oxidative photocyclization of stilbene-type precursors^[3] has been hampered by fundamental drawbacks from evolving into a really convenient method for preparing these molecules. This has led to the development of several new methodologies during the last decade which provide useful alternatives for the synthesis of this type of helical skeleton. Among them, the pioneering work of Katz and Liu^[4] led to the production of racemic helicene bisquinones through a Diels–Alder approach (Scheme 1),^[5] supplemented by an efficient procedure for effecting the required resolutions.^[6] Despite remarkable progress in helicene chemistry, the task of developing new, short, and efficient strategies to racemic and enan-

tiopure helicenes which fulfill criteria of atom economy remains a challenge.

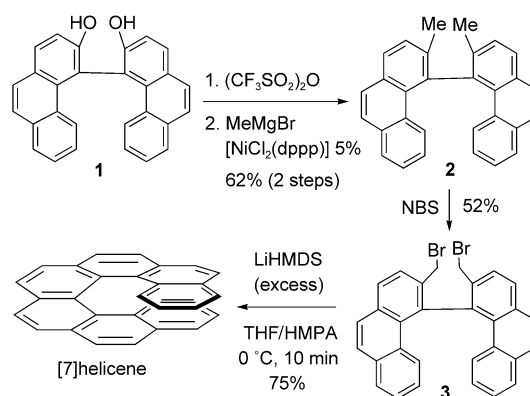
For example, the first nonphotochemical preparation of [7]helicene, which was the first carbocyclic helicene to be synthesized by dehydrophotocyclization,^[7] was not described until 1999 when Gingras and Dubois^[8] reported a five-step approach using a “carbenoid coupling” strategy (Scheme 2). Biphenanthrol **1**, obtained by oxidative Cu-promoted coupling of 3-phenanthrol, was treated with triflic anhydride followed by addition of MeMgBr in the presence of a nickel catalyst to afford derivative **2** in 62% yield. After bromination of **2** and “carbenoid coupling” of dibromide **3** with excess LiHMDS, [7]helicene was obtained in 75% yield.

A related strategy was presented in 2000 by Rajca and co-workers^[9] for the synthesis of a novel oligothiophene **4** (Scheme 3), in which the thiophene rings are cross-conjugated and annelated into a helix. The synthetic route consisted of two iterations using 3,4-dibromothiophene and compound **6** as the functionalized starting modules. In each iteration,

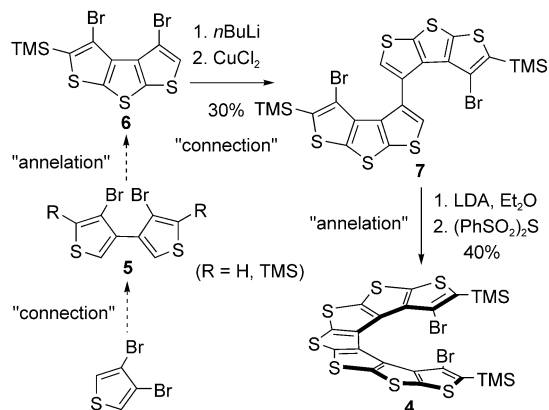


helicene quinones

Scheme 1. Simple nonphotochemical route to helicene quinones by Katz and Liu.



Scheme 2. First nonphotochemical synthesis of [7]helicene by a “carbenoid coupling” strategy. dppp = 1,3-bis(diphenylphosphanyl)propane, NBS = *N*-bromosuccinimide, LiHMDS = lithium hexamethyldisilazide, HMPA = hexamethyl phosphoramide.



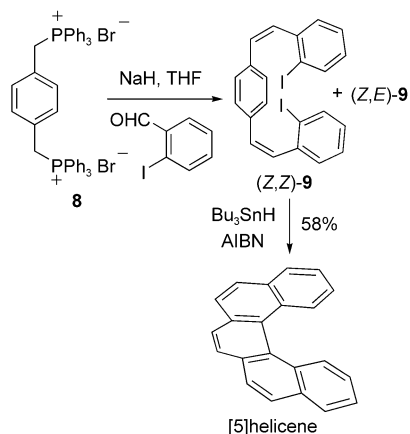
Scheme 3. Iterative (“connection”–“annelation”) synthesis of racemic carbon–sulfur helicene **4**. TMS = trimethylsilyl, LDA = lithium diisopropylamide.

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the modules were connected by means of a single Li/Br exchange followed by oxidative coupling with CuCl_2 , and then “annellated” through the LDA-mediated dilithiation of the unprotected α positions of the thiophene rings in **5** and **7** and further reaction with bis(phenylsulfonyl)sulfide.

A new route to [5]helicenes, based on a tin-mediated, non-reducing tandem radical cyclization of (*Z,Z*)-1,4-bis(2-iodostyryl)-benzene derivatives was recently described by Harrowven et al.^[10]

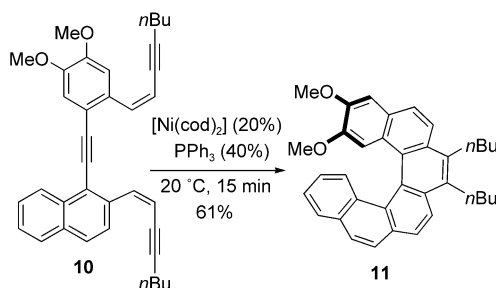
The bisphosphonium salt **8** (Scheme 4), obtained from the corresponding dibromide, was subjected to a Wittig reaction with *o*-iodobenzaldehyde to give compound (*Z,Z*)-**9**, together with the *E,Z* isomer. After separation and treatment of **9** with tributyltin hydride under



Scheme 4. [5]Helicene by tandem radical cyclization of (*Z,Z*)-1,4-bis(2-iodostyryl)benzene (**9**). AIBN = azobisisobutyronitrile.

standard radical-forming conditions, [5]helicene was obtained in 58% yield. This short and easy protocol provided different substituted [5]helicenes with yields ranging from 35 to 58%.

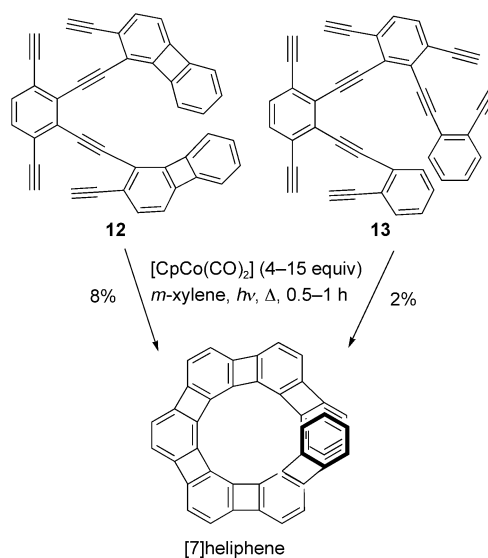
An important breakthrough in the field was reported in 2002 by Stará, Starý, and co-workers,^[11] in an innovative approach to helicenes that exploited atom-economic isomerization of aromatic *cis,cis* dienetrynes under transition-metal catalysis (Scheme 5). Thus, the nickel(0)-catalyzed [2+2+2] cycloisomerization of derivative **10** afforded substituted [6]helicene **11** in 61% yield, after formation of three new cycles in



Scheme 5. Nickel(0)-catalyzed [2+2+2] cycloisomerization of aromatic *cis,cis*-dienetryne **10**. cod = cycloocta-1,5-diene.

one step under very mild conditions. The scope of this efficient procedure was clearly demonstrated with the synthesis of different substituted [5], [6], and [7]helicenes with yields ranging from 60 to 83%.

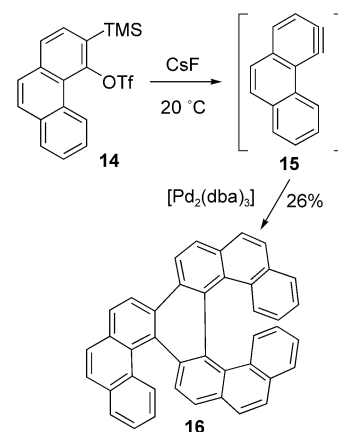
An impressive demonstration of the ability of transition-metal catalysis to build up helical frameworks is the recently described total synthesis of angular [*n*]phenylenes, comprised of *n* alternating benzene units fused with *n*−1 cyclobutadiene rings, the first helical phenylenes, called heliphenes by the authors Vollhardt et al.^[12] A first approach to [7]heliphene (Scheme 6) was effected by a cobalt-catalyzed double cycloisomerization of hexayne intermediate **12** in 8% yield through the one-step formation of six new cycles.^[12a] In an even more convergent approach, the nonayne precursor **13** was submitted



Scheme 6. Cobalt-catalyzed double and triple cycloisomerizations of aromatic hexayne **12** and nonayne **13**.

to an unprecedented cobalt-catalyzed triple cycloisomerization protocol to afford [7]heliphene in only 2% yield, but forming nine rings in one step, including all six of the component cyclobutadienes.^[12b] Such methodology proved to be suitable for the preparation of [6], [7], [8], and [9]heliphenes. Surprisingly, none of these helical molecules could be resolved into their enantiomers, showing much lower barriers to racemization than those of the corresponding helicenes.^[13]

A new palladium-catalyzed cyclotrimerization of arynes developed by Guitián and co-workers was very recently applied to the synthesis of **16** in 26% yield (Scheme 7), the first double heli-



Scheme 7. Palladium-catalyzed cyclotrimerization of aryne **15**. dba = dibenzylideneacetone.

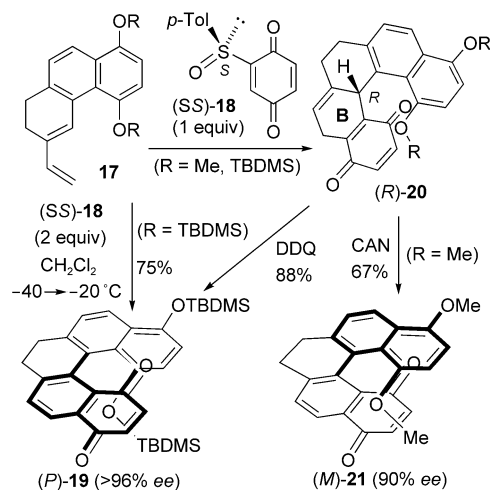
cene formed by a pentahelicene and a heptahelicene with two rings in common.^[14]

Another major challenge in the chemistry of helicenes is the efficient preparation of the individual enantiomers with high enantioselectivity. Most of the asymmetric approaches reported to date were based on the resolutions of the racemic derivatives. Although several enantio- or diastereoselective syntheses have been described, only moderate asymmetric inductions have been achieved, except in a few cases.

To extend the range of applications of functionalized helicenes, there is still a need for general, efficient, and versatile enantiose-

lective approaches to both *M* and *P* helimers.

In this context, Carreño et al. described the first enantioselective synthesis of 7,8-dihydro[5]helicene quinones and bisquinones based on a three-step one-pot domino process (Scheme 8).^[15] Thus, the reaction of vinyl 3,4-dihydrophenan-



Scheme 8. Domino process for the enantiodivergent synthesis of 7,8-dihydro[5]helicene quinones (*P*)-**19** and (*M*)-**21**. TBDMS = *tert*-butyldimethylsilyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, CAN = cerium ammonium nitrate.

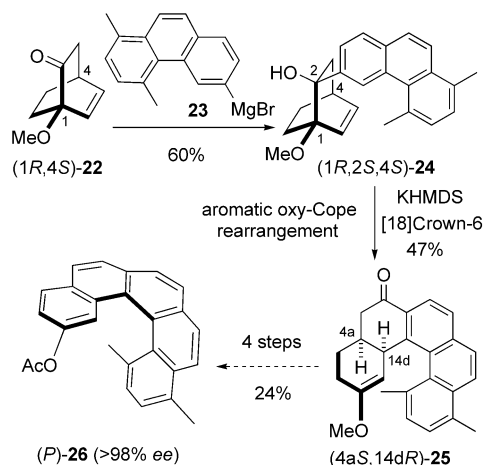
threne **17** (*R* = TBDMS) with 2 equivalents of enantiopure (*SS*)-2-(*p*-tolylsulfinyl)-1,4-benzoquinone (**18**) led, under very mild conditions, to 7,8-dihydro[5]helicene quinone (*P*)-**19** in 75% yield, through a domino process comprising a Diels–Alder reaction and the elimination of the sulfoxide, followed by aromatization of the B ring of intermediate **20** (*R* = TBDMS) effected by excess quinone. Helicene **19** was obtained in optically pure form ($[\alpha]_D^{20} = +3700$ ($c = 0.015$, CHCl_3)) with the absolute configuration *P*.

The versatility of this methodology was probed, after isolation of the cycloaddition/sulfoxide-elimination product (*R*)-**20** (*R* = Me, TBDMS), with the enantiodivergent synthesis of either *P* or *M* helimers from such common intermediates by simply selecting the aromatizing reagent.^[16] The aromatization of the B ring of **20** (*R* = TBDMS) with DDQ gave helicene (*P*)-**19** in 67% yield with

96% *ee*, whereas helicene (*M*)-**21** was obtained in 88% yield with 90% *ee* ($[\alpha]_D^{20} = -3030$ ($c = 0.003$, CHCl_3)) when the aromatization of **20** (*R* = Me) was effected with CAN.

In another asymmetric approach to helical conjugated molecules, Karikomi and co-workers developed a practical method for the synthesis of chiral [5]helicenes using an aromatic oxy-Cope rearrangement strategy (Scheme 9).^[17] The chiral bicyclo[2.2.2]ketone (*1R,4S*)-**22**, obtained by enzymatic resolution, reacted with the Grignard reagent **23** to give (*1R,2S,4S*)-**24** as the major product. Aromatic oxy-Cope rearrangement afforded pentacyclic fused-ring derivative (*4aS,14dR*)-**25** in 47% yield. [5]Helicene (*P*)-**26** was obtained from **25** in 24% yield and in enantiomerically pure form ($[\alpha]_D^{20} = +1243$ ($c = 0.015$, CHCl_3)) in four steps (reduction, hydrolysis and dehydration, enol-acetylation, and aromatization). The same procedure was followed to synthesize the enantiomer (*M*)-**26** from (*1S,4R*)-**22**.

In summary, these recent protocols constitute a significant advancement of synthetic methodology that allows straightforward access to helicene-like molecules. The development of efficient asymmetric approaches should lead to further applications of chiral nonracemic helicenes, both in asymmetric synthesis and catalysis and in materials science.

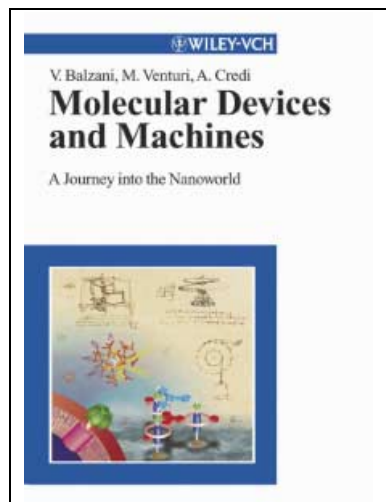


Scheme 9. Synthesis of chiral [5]helicene (*P*)-**26** with an aromatic oxy-Cope rearrangement as the key step.

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