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ARTICLE TYPE

Benzylic-Type Couplings Provide an Important Asymmetric Entry to Functionalized, Non-Racemic Helicenes[†]

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Benzylic-type couplings are key reactions to make non-racemic helicenes. Their simplicity contributes to a short,
10 **efficient, and scalable asymmetric route to functionalized [7]helicenes. It widens the scope and uses of enantiopure helicenes, which are unequivocally needed for new chiroptical-electronic materials. A mechanistic proposal featuring an electrocyclization is based on experiments, X-ray**
15 **crystallography and calculations.**

Helicenes are known for over 100 years, but their importance is growing because of their attractive chiroptical, photophysical, physico-chemical, and electronic properties.[1] Those features are highly desirable
20 for further developments in materials science and in other fields.[2] Today, a real challenge is the convenient preparations of enantiopure, tailor-made, non-racemic helicenes (including the longest ones) from the simplest scalable methods. One of the solutions to those problems is
25 disclosed here in the non-racemic synthesis of a series of [7]helicenes, and a tentative mechanistic rationale of the benzylic couplings.

For nearly five decades, the preferred synthetic method to make racemic helicenes has been the oxidative photo-
30 cyclodehydrogenation.[3] A well-known drawback is the high dilution in solvents (100 mg/L; 10^{-3}M) for producing a modest amount of helicenes in yields averaging 50-60%. To circumvent those issues, some elegant, thermal methods have been reported.[1,2] However, only a few provide short,
35 scalable and general entries to helicene chemistry, but more rarely from non-racemic, stereoselective routes.[4]

Racemic benzylic-type couplings have combined easy functionalization, high yields, cheap reagents and simple equipments for producing [5]helicenes,[5,6] which allowed
40 further applications in nanoscience.[7] All results focussed on racemic, configurationally labile, short helicenes.

This work is distinct from the previous ones because stereoselective benzylic couplings to enantiopure, long helicenes, were never reported by us or by others in
45 helicene chemistry (schemes 1,3). Additionally, functionalization of non-racemic (scheme 3) and racemic

(scheme 4) heptahelicenes are reported, after an optimization of a biphenanthrol synthesis (scheme 2). A direct access to either enantiomers of helicenes **1**
50 (disubstituted) and **2** (monosubstituted), in only three steps from the known bis(triflate) (±), (-) or (+) **6**, is a key feature.[8] Those couplings also prompted us to propose a mechanistic rationale based on calculations (scheme 5) and X-ray crystallography (scheme 1).
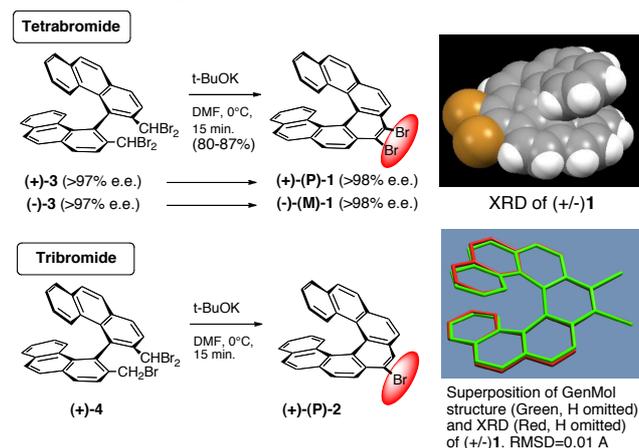

55 **Scheme 1.** Asymmetric benzylic-type couplings in the synthesis of non-racemic [7]helicenes

Toward a non-racemic entry to [7]helicenes, we first efficiently produced (±)-biphenanthrol **5**, as shown in scheme 2. The oxidative coupling of 3-phenanthrol with a
60 molar excess of a $Cu(NO_3)_2/(\pm)1,2$-diphenylethylamine complex under an inert atmosphere yielded (±)**5** in a 77% yield (previously: 20%).[9] For a better convenience, we optimized a catalytic method[8,10] in air with Cu(TMEDA)ClOH (15-20 mol%) to provide (±)**5** in a 90%
65 yield, (>3g, previously 68%[9]). Racemic (±)**5** was easily resolved to (-)**5** (85% e.e.) and to (+)**5** (92% e.e.) on a gram scale.[8,11] The stereochemistry of helicenes was thus set from the start from non-racemic (+)- or (-)-biphenanthrol **5** with a full retention of configuration.
70 Having **5** in hand, a triflation with pyridine in DCM, afforded bis(triflate) **6** (scheme 3) in a racemic (98%yield)

or in a non-racemic form ((-)-94% or (+)-96% yield). From (±)**6**, a Ni-catalyzed methylation produced (±)**7** in a 86% yield (scheme 3).[12] Similarly, non-racemic (+)**7** (85% yield, 97% e.e.) or (-)**7** (79% yield, 85% e.e.) were
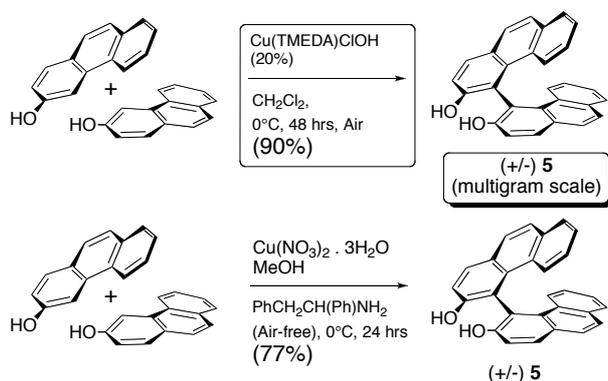

Scheme 2. Efficient synthesis of 3,3'-dihydroxy-4,4' biphenanthryl **5**

obtained with a retention of configuration. A radical tetrabromination of (±)**7** to (±)**3** (85-91% yield) required an excess of NBS. The satisfactory purity allowed to pursue the synthesis of (±)**1**. Under similar conditions, both enantiomers (-)**3** (>95% e.e.) and (+)**3** were also produced with a retention of configuration. A spontaneous ring closure of (±)**3** provided (±)-9,10-dibromo-heptahelicene **1** (80-88% yield) or each enantiomers (M)(-)**1** (>98%e.e.) and (P)(+)**1** (>98%e.e.). Traces of **2** (<4%, HPLC) came from the cyclization of residual tribromide **4** (<4% in **3**, HPLC).
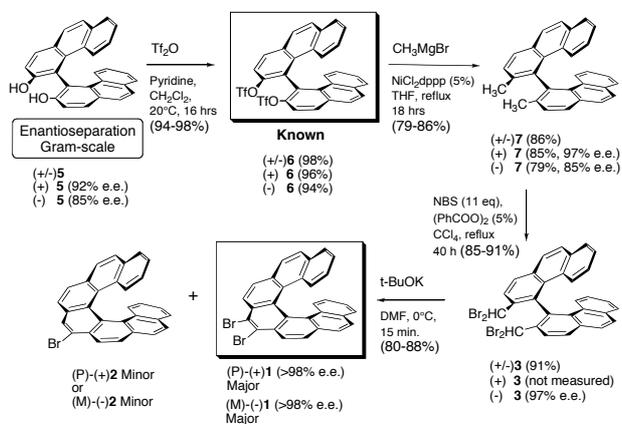
Scheme 3. An efficient entry to non-racemic [7]helicenes via asymmetric benzylic-type couplings

As a preliminary optimization of the benzylic couplings to (±)**1**, a few parameters were examined for the first time: a) bases, b) temperatures, c) solvents, d) addition rates. In short, tBuOK was one of the most practical and efficient bases. However, LiHMDS did not provide a significant coupling in the absence of HMPA, in spite of a higher basicity. Similarly, K$_2$CO$_3$ did not promote a cyclization to **1** in DMF. As for the temperature, incomplete reactions and slow rates were noticed at -35°C with tBuOK in DMF.

The best yields of **1** were thus obtained near 0-3°C. A polar solvent was needed and DMF provided the best results with tBuOK. Less polar solvents such as THF, dioxane or CH$_2$Cl$_2$ were not successful with tBuOK, and a fast addition of tBuOK to the precursor **3** produced a high molar ratio **1/2**.

As a convenience, crude **3** generated a molar ratio **1/2** : 4.2 in a 80% yield. The tribromide **4** accounts for the formation of **2**. If **3** is almost pure (HPLC: 96% of **1**; 4% of **4**), a 87% yield of **1** is then obtained. We next turned our attention to the reactivity of (±)**1** in some metal-catalyzed couplings (scheme 4). A double Sonogashira reaction in triethylamine, with PdCl$_2$(PPh$_3$)$_2$/CuI as catalysts, generated (±)**8** in a 95% yield. Removal of TMS groups from (±)**8** with K$_2$CO$_3$ in MeOH lead quantitatively to (±)**9**. As an innovative one-pot functionalization, a double cyanation with CuCN in moist N-methyl-pyrrolidinone at 180°C directly produced the 9,10-imido-helicene (±)**10** (75% yield).
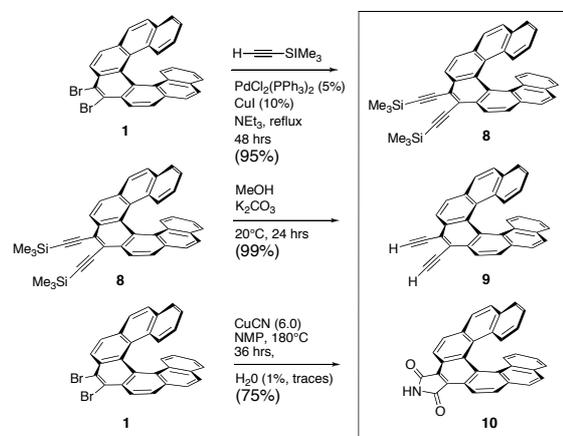
Scheme 4. A new entry to functionalized [7]helicenes

We wanted to understand the coupling mechanism from **11**. A previous thought was a carbenoid coupling coming from α-eliminations of HBr at the benzylic positions. However, it was found unlikely with LiHMDS/HMPA at 0°C from a [5]helicene derivative.[5] For the first time, a hypothetical mechanism is outlined in scheme 5. A long-range benzylic-type elimination from **11** is reasonable, based on numerous reports.[13] It could then lead to trienes **12** and/or **13**, followed by an electrocyclic rearrangement to **14**. As a support of this proposal, another type of electrocyclization was suggested, but in a [5]helicene formation.[14] Finally, an aromatization after a second elimination would generate **15**. The first elimination might be a rate-determing step sensitive to a polar solvent (such as DMF), due to a stabilization of a polarized transition state. To get further insights, preliminary calculations with the GenMol® program were performed.[15] In the [7]helicene series, the relative constraint energy (torsion, angle, steric, electrostatic energy) of each species under study was evaluated (scheme 5). Compounds **11** (52.3 kcal/mol) and **15** (48.7 kcal/mol) were more energetic or comparable
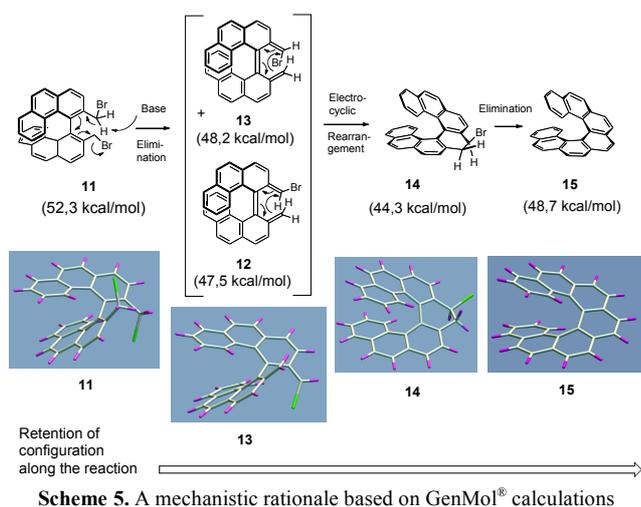
Scheme 5. A mechanistic rationale based on GenMol® calculations

to **12** (47.5 kcal/mol) or to **13** (48.2 kcal/mol). As a consequence, **12** or **13** are thus energetically attainable intermediates. A similar biphenanthryl structure with a bridged double-bond supports the assumption of a thermal stability of **12** or **13**.[16] As for **11**, a positive electrostatic potential at each C-H benzylic-type proton induces a strong benzylic repulsion, combined to a steric strain at both terminal benzene rings. The constraint energy of **14** is less than for **15** because of a staggered conformer at the 9,10-position, causing also less steric repulsion at the terminal rings. As for the π-orbitals overlap of **12** and **13**, a distance of 3.2Å and 3.3Å, respectively, was found between the terminal methylene carbon atoms in the lowest-energy conformers. Even if a distorsion of **12** or **13** for shortening this distance costs in energy, a slight deviation from planarity over many atoms provides a minimal activation energy of the transition states.

Conclusions

For the first time, stereoselective benzylic-type couplings are shown as key reactions in some expeditive, non-racemic (or racemic[17]) routes to functionalized higher helicenes. All intermediates of the three-step sequence to helicenes proceed with a full retention of configuration, which is set from the start. Such efficient and scalable syntheses are rare in the literature for making enantiopure [7]helicenes. Based on X-ray crystallography, experiments, and GenMol® calculations, an electrocyclization mechanism is proposed. Carbenoid couplings are unlikely. This work significantly widens the production and uses of non-racemic helicenes, which are absolutely required for enantiopure chiroptical-electronic materials. It will unequivocally add a contribution to chiroscience, materials and nanoscience, chemical-biology, and supramolecular chemistry. Importantly, the simplicity of this method will encourage a spread use of it within the scientific community.[18]

Acknowledgments

Notes and References

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