Helical Structures

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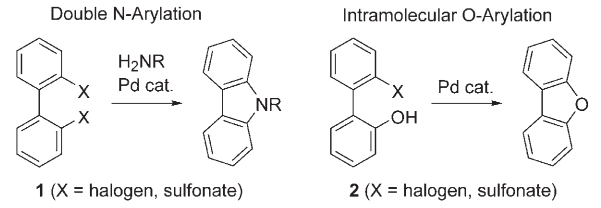
Stereospecific Synthesis of Hetero[7]helicenes by Pd-Catalyzed Double *N*-Arylation and Intramolecular *O*-Arylation**

*Koji Nakano, Yuko Hidehira, Keita Takahashi, Tamejiro Hiyama, and Kyoko Nozaki**

Helicenes consist of *ortho*-annulated aromatic and/or heteroaromatic rings endowed with a helical chirality.[1] Enantiopure helicenes can be isolated because of their stable and rigid helical conformation; furthermore, some of them form aggregates to give helical supramolecular architectures potentially applicable to nonlinear optics, electrooptic switches, and circularly polarized luminescent materials.[2] To expand the application of helicene molecules as functional materials, it is important to develop an efficient synthetic strategy for the production of helicenes with a variety of frameworks and substituents in enantiopure form. The classical methodology to synthesize helicenes is an oxidative photocyclization of stilbene-type precursors.[3] Several non-photochemical synthetic methods have been reported,[4] which have been applied to the syntheses of enantioenriched helicenes.[4a,f,5] Among these previous examples of helicene synthesis, however, only a few demonstrate the synthesis of azahelicenes with pyrrole rings or oxahelicenes with furan rings in spite of their potential to alter molecular properties,[5g,6,7] which prompted us to develop a new synthetic route that would produce aza- and oxahelicenes.

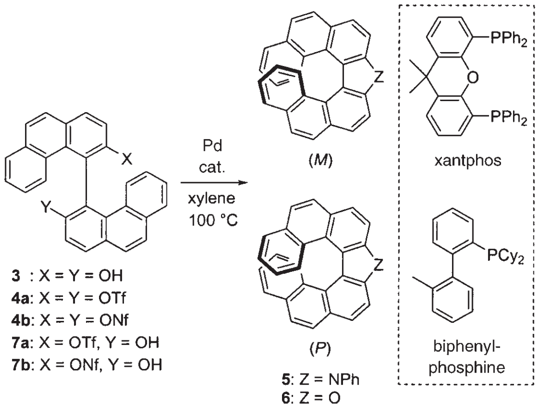
The key reactions in the heterohelicene syntheses are shown in Scheme 1. Carbazole derivatives can be prepared by the double N-arylation of primary amines with dihalobiphenyls or biphenylylene disulfonate **1**, as we reported recently.[8] The intramolecular O-arylation of 2′-hydroxybiphenyl-2-yl halides or sulfonates **2** is anticipated to give dibenzofuran, which we refer to as the palladium-catalyzed intermolecular diaryl ether synthesis.[9] These reactions of biphenyls were applied to biphenanthryls to form an efficient synthetic route to hetero[7]helicenes.



Scheme 1. Key reactions for the synthesis of heterohelicenes.

The target aza[7]helicene *rac*-**5** was obtained in 64% yield by the reaction of aniline with racemic 4,4′-biphenanthryl-3,3′-ylene ditriflate (*rac*-**4a**), which was prepared from racemic 4,4′-biphenanthryl-3,3′-diol (*rac*-**3**; Table 1, run 1). Oxa[7]helicene *rac*-**6** was produced as a by-product (10% yield) through the intramolecular O-arylation of 3′-hydroxy-4,4′-biphenanthryl-3-yl triflate (*rac*-**7a**), which was formed by

Table 1: Syntheses of aza[7]helicene and oxa[7]helicene.



Run	Substrate	Conditions[a]	*t* [h]	Product	Yield [%]
1	*rac*-**4a**	A	141	*rac*-**5**	64[b]
2	*rac*-**4b**	A	123	*rac*-**5**	88
3	(*S*)-**4b**	B	123	(*P*)-**5**	94 (>99% *ee*) $[\alpha]_D^{22} = +2310$ (c=0.10, $CHCl_3$)
4	*rac*-**7a**	C	18	*rac*-**6**	45[c]
5	*rac*-**7b**	C	96	*rac*-**6**	62
6	(*S*)-**7b**	C	96	(*P*)-**6**	60 (20% *ee*)
7	(*S*)-**7b**	D	13	(*P*)-**6**	49 (94% *ee*) $[\alpha]_D^{23} = +1430$ (c=0.10, $CHCl_3$)

[a] Reaction conditions: A: H_2NPh (1.2 equiv), $[Pd_2(dba)_3]\cdot CHCl_3$ (5 mol%), xantphos (10 mol%), K_3PO_4 (2.8 equiv); B: H_2NPh (1.2 equiv), $[Pd_2(dba)_3]\cdot CHCl_3$ (10 mol%), xantphos (20 mol%), K_3PO_4 (2.8 equiv); C: $[Pd_2(dba)_3]\cdot CHCl_3$ (5 mol%), biphenylphosphine (20 mol%), K_3PO_4 (2.0 equiv); D: $[Pd_2(dba)_3]\cdot CHCl_3$ (10 mol%), biphenylphosphine (40 mol%), K_3PO_4 (2.0 equiv). [b] A 10% yield of *rac*-**6** as a by-product was obtained. [c] Consumption of the substrate was confirmed by TLC; the major by-product was diol *rac*-**3**. Cy = cyclohexyl, dba = dibenzylideneacetone.

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[*] Dr. K. Nakano, Y. Hidehira, Prof. Dr. K. Nozaki
Department of Chemistry and Biotechnology
Graduate School of Engineering
The University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656 (Japan)
Fax: (+81) 3-5841-7261
E-mail: nozaki@chembio.t.u-tokyo.ac.jp

K. Takahashi, Prof. Dr. T. Hiyama
Department of Material Chemistry
Graduate School of Engineering
Kyoto University
Nishikyo-ku, Kyoto 615-8510 (Japan)

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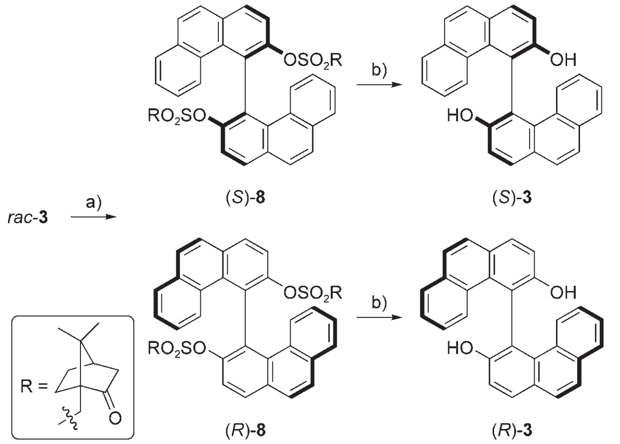
the partial hydrolysis of *rac*-**4a**. The hydrolysis of the sulfonate functionality was successfully avoided by using a nonaflate (Nf) group instead of a triflate (Tf).[10] Thus, the yield was elevated to 88% (run 2) under the optimized reaction conditions (*rac*-**4b** with aniline (1.2 equiv), [$Pd_2(dba)_3$] (5 mol%), xantphos (10 mol%), K_3PO_4 (2.8 equiv), xylene, 100°C, 123 h).

The optical resolution of *rac*-**3**[11] was investigated for the preparation of optically active heterohelicenes (Scheme 2).



Scheme 2. Optical resolution of *rac*-**3**. a) RSO_2Cl (3.0 equiv), 4-(*N*,*N*-dimethylamino)pyridine (5.0 mol%), Et_3N, DMF, 0°C→RT, 15 h, separation by column chromatography on silica gel ((*S*)-**8**: 49% yield; (*R*)-**8**: 47% yield); b) THF, MeOH, aq. NaOH (5.0 M), reflux, 15 h ((*S*)-**3** and (*R*)-**3**: 95% yield; (*S*)-**3**: >99% *ee*; (*R*)-**3**: >99% *ee*). DMF = dimethylformamide.

The esterification of *rac*-**3** with the commercially available (1*S*)-10-camphorsulfonyl chloride gave diastereomers of disulfonate **8**, which were readily separated by column chromatography on silica gel. Hydrolysis of the obtained two single diastereomers gave (*S*)-**3** and (*R*)-**3** in enantiopure form.

A single enantiomer of **5** was readily prepared from (*S*)-**4b** by a stereospecific double N-arylation reaction; transformation of (*S*)-**4b** (>99% *ee*) gave (*P*)-**5** in 94% yield with >99% *ee* (Table 1, run 3). The absolute configuration of (*P*)-**5** was confirmed by its optical rotation ($[\alpha]_D^{22} = +2310$ ($c = 0.10$, $CHCl_3$)) and CD spectrum,[12] both of which are similar to those of the known dextrorotatory (*P*)-heterohelicenes.[5g,6a,13] Thus, the absolute configuration of (*S*)-**4b** is maintained under the reaction conditions (100°C, 123 h) in contrast to the O-arylation of (*S*)-**7b** (see below).

Oxa[7]helicene **6** was successfully synthesized through intramolecular O-arylation. The reaction of triflate *rac*-**7a** or nonaflate *rac*-**7b** using a palladium catalyst gave the desired *rac*-**6** in yields of 45 or 62%, respectively (runs 4 and 5). Unlike the double N-arylation of (*S*)-**4b** (run 3), however, the reaction of optically active (*S*)-**7b** (>99% *ee*) gave (*P*)-**6** (20% *ee*) with significant loss of enantiomeric excess (run 6; 100°C, 96 h). Racemization was suppressed effectively by shortening the reaction time (13 h) to afford (*P*)-**6** in 49% yield with high enantiopurity (94% *ee*; $[\alpha]_D^{23} = +1430$ ($c = 0.10$, $CHCl_3$); run 7). It should be noted that racemization of (*P*)-**6** takes place under the reaction conditions: treatment of optically active (*P*)-**6** (92% *ee*) in toluene at 100°C for 88 h resulted in partial racemization (42% *ee*). In contrast, none of (*S*)-**7b** (98% *ee*), (*R*)-**4b** (>99% *ee*), and (*M*)-**5** (97% *ee*) underwent racemization in toluene at 100°C. These results indicate that the stereospecific intramolecular O-arylation of (*S*)-**7b** gives (*P*)-**6** without any significant loss of enantiopurity, and the racemization takes place after the formation of (*P*)-**6**. The lower tolerance of **6** to racemization relative to **5** may be attributed to the differences in their structure. Indeed, the single-crystal X-ray analyses suggested that **6** has a less-distorted structure than **5** (Figure 1), thus indicating that the terminal two rings in **6** have weaker steric repulsions which should lead to a lower racemization barrier.[14,15]

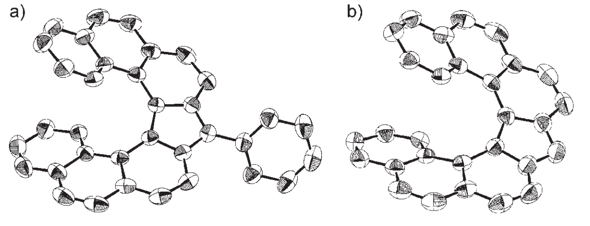
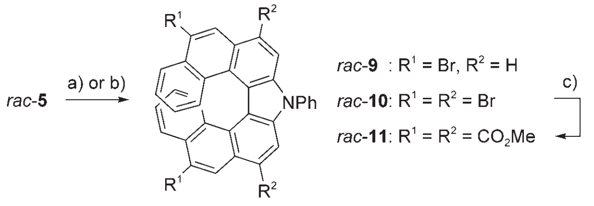


Figure 1. ORTEP drawings of a) **5** and b) **6**, with thermal ellipsoids shown at the 50% probability level. All hydrogen atoms and the $CHCl_3$ molecule are omitted for clarity.

The introduction of substituents into aza[7]helicene was investigated toward the development of hetero[7]helicenes as functional materials. Regioselective bromination was successfully achieved by the treatment of *rac*-**5** with two and four equivalents of NBS to yield di- and tetrabromoaza[7]helicenes *rac*-**9** and *rac*-**10**, respectively (Scheme 3).[16] The substituted positions were determined by single-crystal X-ray analyses.[17] These brominated aza[7]helicenes should be useful intermediates for further functionalizations; for example, *rac*-**10** was converted into tetraester *rac*-**11** in 44% yield (Scheme 3).



Scheme 3. Functionalization of *rac*-**5**. a) NBS (2.0 equiv), SiO_2 (2.0 g mmol^{-1} NBS), CH_2Cl_2, RT, 31 h (*rac*-**9**: 61% yield; b) NBS (4.0 equiv), SiO_2 (2.0 g mmol^{-1} NBS), CH_2Cl_2, RT, 43 h (*rac*-**10**: 84% yield); c) *t*BuLi (8.4 equiv), THF, −78°C, 4 h, then $ClCO_2Me$ (8.4 equiv), −78°C→RT, 13 h, (*rac*-**11**: 44% yield). NBS = *N*-bromosuccinimide.

In conclusion, we have reported an efficient strategy for the synthesis of aza- and oxa[7]helicenes **5** and **6** from the same precursor, 4,4′-biphenanthryl-3,3′-diol (**3**); highly enantioenriched **5** and **6** were successfully obtained in good yields. In addition, tetrabromoaza[7]helicene **10** was produced by the regioselective bromination of **5**. Aggregates of the aza[7]helicenes, which are potentially attractive new materials, could be synthesized by further functionalization of **10**, with the introduction, for example, of long alkyl chains.[2]

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[17] ORTEP drawings and the X-ray crystallographic data of **9** and **10** are given in the Supporting Information; CCDC-280430–280433 (**5**·$CHCl_3$, **6**, **9**, and **10**·$CHCl_3$, respectively) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.