Synthesis of Carbohelicenes and Derivatives
by "Carbenoid Couplings"
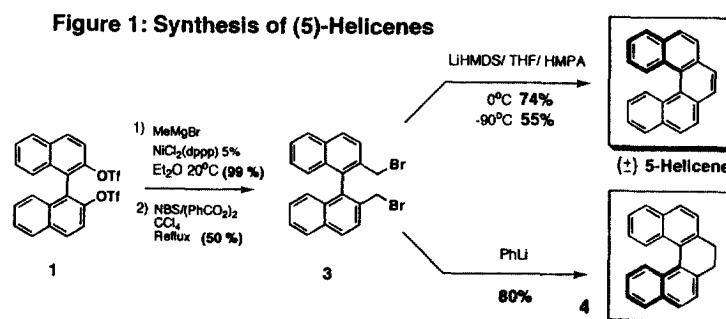
Marc Gingras* and Fabien Dubois

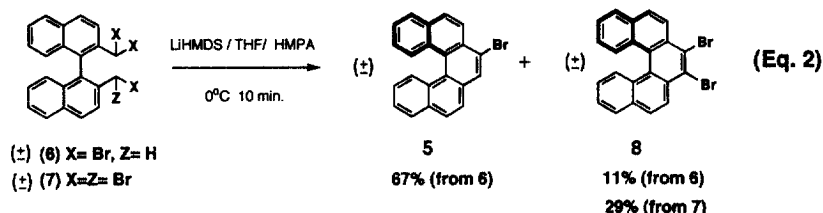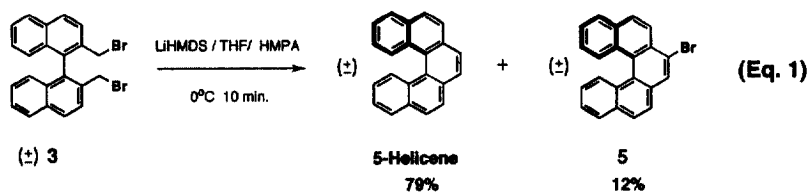Received 15 November 1998; accepted 14 December 1998

Organic Chemistry Division, Laboratory of Supramolecular Chemistry and Catalysis,
Faculty of Sciences, Université Libre de Bruxelles, C.P. 160-06,
50 Ave. F. D. Roosevelt, 1050 Brussels, Belgium

Abstract: Short synthetic sequences to carbohelicenes have been achieved under thermal conditions, without using photochemistry and high dilution. Couplings of aromatic bis(bromomethyl) moieties, in the presence of an excess of LiHMDS, are key reactions in the final ring closures to carbohelicenes. These optimized, quick and efficient reactions occur at 0°C within 10 min. and often provide [5]-helicene, [5]-helicene derivatives and [7]-helicene in ~75% yield. Preliminary data questioned the formation of carbenoid anions and carbenes in the so called "carbenoid couplings". © 1999 Elsevier Science Ltd. All rights reserved.

In recent years, helicene chemistry has grown up from the stage of a descriptive field of aesthetic and curious molecules to an important field of research in material sciences (polymers, conductors, liquid crystals, etc.),[1] as chiral ligands in asymmetric catalysis[2] and as possible helicoidal building blocs in supramolecular chemistry. For instance, a breakthrough was achieved in 1990 with the nice production of helicene bisquinones, which opened up new avenues in material sciences.[3] A few thermal preparations of [5]-helicenes and higher analogs were known but the synthetic sequences were often less convenient.[1,4] Because of this renewed popularity of helicenes, there is an urgent need for simple syntheses. It prompted us to improve or develop short synthetic routes to carbohelicenes, without using photochemistry and high dilution techniques (10^{-3} M is frequent).

We previously participated in these new challenges by promoting the couplings of brominated benzylic-type substrates as some key reactions for the efficient and quick assembly of polyaromatic systems, such as [5]-helicene and phenanthrene (Figure 1).[5]

Figure 1: Synthesis of (5)-Helicenes

$$(\pm)\ \mathbf{3} \xrightarrow[\text{0°C 10 min.}]{\text{LiHMDS / THF/ HMPA}} (\pm)\ \text{5-Helicene} \quad + \quad (\pm)\ \mathbf{5} \qquad \textbf{(Eq. 1)}$$

5-Helicene
79%

5
12%

$$(\pm)\ (\mathbf{6})\ X=Br,\ Z=H \quad (\pm)\ (\mathbf{7})\ X=Z=Br \xrightarrow[\text{0°C 10 min.}]{\text{LiHMDS / THF/ HMPA}} (\pm)\ \mathbf{5} \quad + \quad (\pm)\ \mathbf{8} \qquad \textbf{(Eq. 2)}$$

(±) (6) X= Br, Z= H
(±) (7) X=Z= Br

5
67% (from 6)

8
11% (from 6)
29% (from 7)

We have brought back a methodology left aside for many years in organic chemistry, while changing the reaction conditions in order to improve its usefulness in helicene chemistry.For instance, tetrabenzophenanthrene was formed in an optimized 37% yield,[6] under Kharash's conditions with KNH_2 in liquid NH_3.[7] On the other hand, "carbenoid couplings" of propargyl bromides and LiHMDS/HMPA were used as a high yielding route to cyclic enediynes.[8] It is now the purpose of this work to further elaborate on the syntheses of [7]-, [5]-helicene and derivatives. Additionally, we will report one of the scarce thermal preparation of a [7]-carbohelicene.[9] An enantioselective route to 7,8-dihydro-[5]-helicene **4** will also be discussed because this compound is configurationally stable at 20°C, in contrast to [5]-helicene (Figure 1).

We already used dibromide (±) **3** as a key intermediate, for successfully testing "carbenoid couplings" to (±) [5]-helicene.[5] This last polyaromatic compound was conveniently produced in a 74-79% yield within 10 min. at 0°C.[5] Equation 1 and Table 1 describe the optimization of the procedure to [5]-helicene. The conditions used by Jones and Huber were tried,[8] but some dibromide (±) **3** remained unreacted and (±) [5]-helicene was only produced in a 38% yield (Entry 1). A large excess of base generated the helicene in a 55% yield (Entry 2). If LiHMDS was slowly added to the dibromide (±) **3** at 20°C, (±) 7-bromo-[5]-helicene **5** was formed (33 % yield) along with (±) [5]-helicene (53 % yield, Entry 3). However, [5]-helicene was cleanly produced in a 74 % yield at 20°C from a fast injection of LiHMDS (a few seconds) to the dibromide solution (Entry 4). An exothermic reaction took place with a bright yellow color. In Entries 5 and 6, we tested a reversed addition by a slow injection of dibromide (±) **3** to an excess of base, while controlling the exotherm at ~3°C (ice bath).

Table 1: Conditions for carbenoid couplings of dibromide **3** to (5)-helicenes

Entry No	Addition	T (°C)	Base[e]	(5)-helicene (%)	7-Bromo-(5)-helicene (%)
1	Slow[a]	-90	2.2	38[c]	undetermined
2	Slow[a]	-90	12	55[c]	undetermined
3	Slow[a]	20	17	53[c]	33[c]
4	Fast[a]	20	17	74[c]	27[c]
5	Slow[b]	0	17	71[c]	undetermined
6	Slow[b]	0	10	79[c]	12[c]
7	Slow[b]	-40	10	73[d]	10[d]
8	Slow[b]	-78 ·	10	43[d]	18[d]

(a): Addition of the base to dibromide **3**
(b): Addition of dibromide **3** to the base
(c): Isolated yields
(d): Estimated yields by ^1H NMR of the crude products
(e): Molar ratio of LiHMDS to dibromide **3**;
    Molar ratio LiHMDS/HMPA = 1.0

(±) 9   Carbene   **(Eq. 3)**
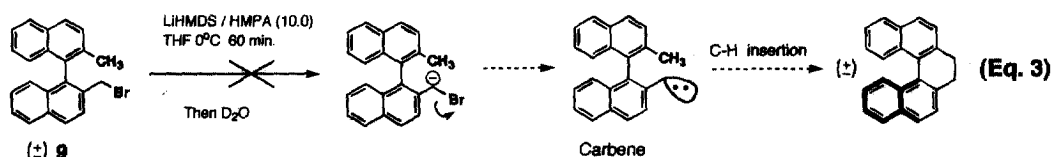
Good yields were consistently reproduced (74-79%), the reaction being clean and almost instantaneous. Below -40°C (Entries 7 and 8), an incomplete consumption of the dibromide (±) 3 and lower yields of (±) [5]-helicene were observed. In short, we found the best conditions to be an excess of base, at 0-3°C for about 10 min. (ice bath used to control the exotherm).In Equation 2, several brominated binaphthyl derivatives were tested for making functionalized (±) [5]-helicenes. Under our best conditions, tribromide (±) 6 generated a mixture of (±) 7-bromo-[5]-helicene 5 (67% yield)[10] and (±) 7,8-dibromo-[5]-helicene 8 (11% yield) in a 78% overall yield. Finally, the easily accessible (±) tetrabromide 7[11] produced (±) 7,8-dibromo-[5]-helicene 8 in 29% yield (unoptimized).

Some mechanistic insights have been delineated. The proposed mechanism by Jones stated the formation of carbenoid anions at low temperature, followed by an intramolecular S_N2 reaction and elimination of HBr.[8] An increase of the temperature at 20°C would logically generate carbenes, even if some arguments about the stabilizing effects of LiBr have been put forward.[8] In our intramolecular model study, it seemed improbable that free carbenes have been involved at 0-20°C (Eq. 3). Treatment of monobromide 9,[10] in the presence of a 10-fold excess of LiHMDS at 3°C for >60 min. and quenching with D$_2$O, did not indicate a significant reaction or any incorporation of deuterium. Moreover, >90% of the starting material was recovered (repeated twice). These facts argued against the generation of carbenoid anions. Additionally, carbene formation and intramolecular C-H insertion in our model compound 9 were not clearly observed. Further studies are required to delineate the exact mechanism of these benzylic-type couplings. In the meantime, the expression "carbenoid coupling" described by Jones only serve to illustrate an equivalent synthetic transformation.

The configurationally stable (M)-(-)- 7,8-dihydro-[5]-helicene 4 was quickly prepared in a three-step sequence (Figure 1). Enantioenriched dibromide (R)-(+)-3 (58% e.e.) treated with PhLi gave (M)-(-)- 4 in 80 % yield (55% e.e.).[12] A 95% retention of the configuration was found. Enantioselective conversion of (R)-(-)-2 to (R)-(+)-3 had already been described (>95% e.e.) and 2,2'-dimethyl-1,1' binaphthyl 2 was selectively produced from (R)-(-) bis triflate 1 (99% yield, 95% e.e.).

Figure 2: Synthesis of (7)-Helicene by Carbenoid Coupling
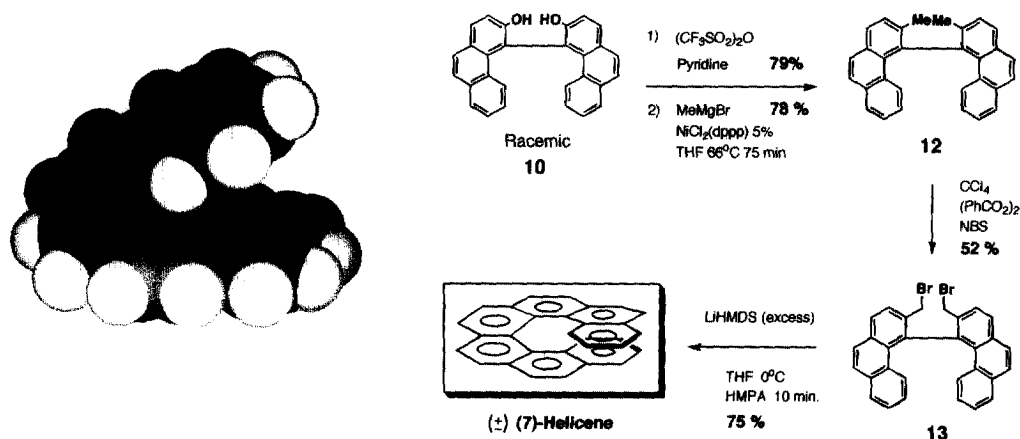
The route to (±) [5]-helicene and derivatives served as a model study to the carbenoid couplings leading to (±) [7]-helicene. Figure 2 describes a simple five-step synthesis of (±) [7]-helicene from 3-phenanthrol.[13] The oxidative Cu-coupling of 3-phenanthrol to (±) 3,3'-dihydroxy-4,4'-biphenanthryl 1 0, under oxygen-free

conditions, was achieved in a 77% yield.[14] Compound 10 was treated with $(CF_3SO)_2O$ in pyridine to produce (±) bis-triflate 11 in a 79% yield.[15] We again applied the methodology of Snieckus with MeMgBr and 5% $NiCl_2(dppp)$ as a catalyst.[16] A slow reaction occurred at 20°C but a significant polar by-product was formed. Heating in refluxing THF solved the kinetic problems and a 78% yield of (±) 12 was obtained. A double Wohl-Ziegler bromination with NBS afforded dibromide (±) 13 in a 52% yield, with a contamination by a tribromide by-product. Compound 13 was easily purified by a filtration over SiO_2 and recrystallization. A carbenoid coupling, in our best conditions, afforded a reproducible 75-80 % yield of (±) [7]-helicene within 10 min. at 0°C (repeated three times). A persistent bright yellow color seemed indicative of a successful coupling. Because (±) 10 had already been produced as a single enantiomer for making some catalysts,[15] this route might possibly lead to enantiopure [7]-helicene (to be verified).

In summary, we have contributed to an important new field by showing useful, simple and short synthetic sequences to [5]-helicene and brominated derivatives, without using photochemistry and high dilution. Optimized coupling conditions to [5]-helicene were shown. Some preliminary mechanistic insights argued against the generation of carbanions and carbenes. The first thermal method to the synthesis of [7]-helicene was demonstrated. Our contribution could widen some future applications of helicenes in material sciences, as asymmetric ligands, in exotic polymers or as chiral building blocs.

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