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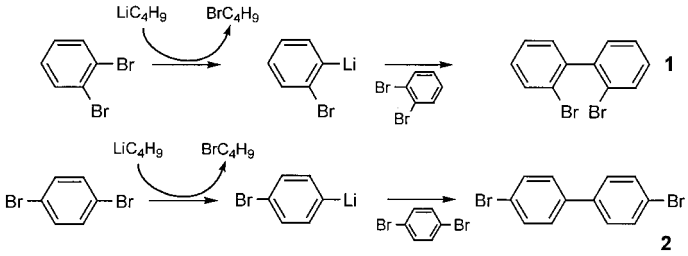
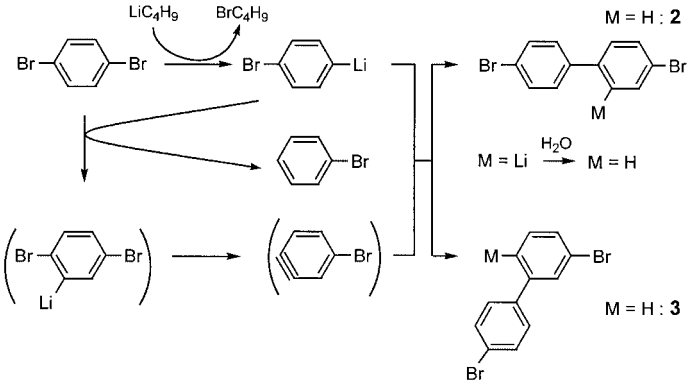
The "Aryne" Route to Biaryls Featuring Uncommon Substituent Patterns**

Frédéric Leroux and Manfred Schlosser*

In 1957, Gilman and Gaj[1] disclosed a facile preparation of 2,2′-dibromobiphenyl (**1**) in 21% yield by treatment of 1,2-dibromobenzene with half a molar equivalent of butyllithium (Scheme 1). In support of the surmised condensation process between dibromobenzene and a phenyllithium intermediate derived from it by halogen–metal permutation, they analogously converted 1,4-dibromobenzene into 4,4′-dibromobiphenyl (**2**; 18%).[1] Effective aryl–aryl coupling in general requires the participation of transition elements. When Lau and co-workers[2] succeeded in raising the yield of 2,2′-dibromobiphenyl to 81% by a careful optimization of the reaction conditions, the condensation hypothesis had to be abandoned. It was tempting to base an alternative mechanism on the intermediacy of 1,2-didehydrobenzene (1,3-cyclohexadien-5-yne, the so-called "benzyne"). However, if such a species were really involved, 1,4-dibromobenzene would have to give rise not only to **2**, as reported,[1] but also to its 3,4′-isomer **3**. As revealed by gas chromatographic analysis, the isomers **2** (M = H; 41%) and **3**[3] (M = H; 21%) were indeed formed concomitantly with bromobenzene (14%; Scheme 2). These findings are in agreement with a metalation, elimination, addition sequence featuring 4-bromophenyllithium, 2,5-dibromophenyllithium, and 4-bromo-1,2-didehydrobenzene as transient entities.



Scheme 1. Reported[1] reaction of 1,2- and 1,4-dibromobenzene with butyllithium to form **1** or **2**, respectively.



Scheme 2. Postulated mechanism of the coupling of 1,4-dibrombenzene with butyllithium to account for the formation of a mixture of **2** and **3**.

The ensuing work developed in three stages. The first objective was to provide evidence for the suspected aryne intermediate in the 1,2-dibromobenzene transformation. Once the essential details of this reaction are understood, one should be able to make use of this knowledge to construct first symmetrical and eventually unsymmetrical biaryls. According to our hypothesis, the final step in the formation of **1** should be bromine abstraction from 1,2-dibromobenzene by the 2′-bromo-2-biphenylyllithium species resulting from the combination of 2-bromophenyllithium with 1,2-didehydrobenzene (Scheme 3). If the starting material were replaced with 1-bromo-2-iodobenzene, iodine transfer would have to occur. In fact, treatment of this dihalo compound with half a

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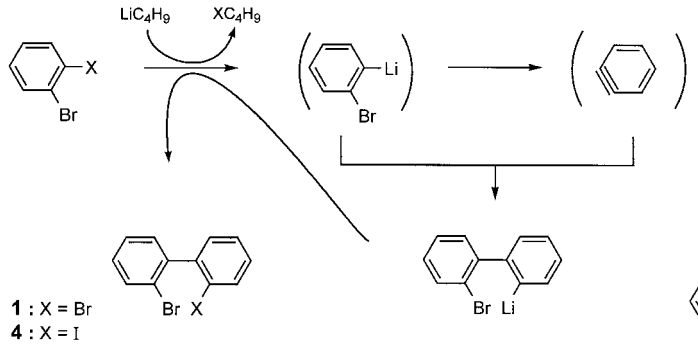
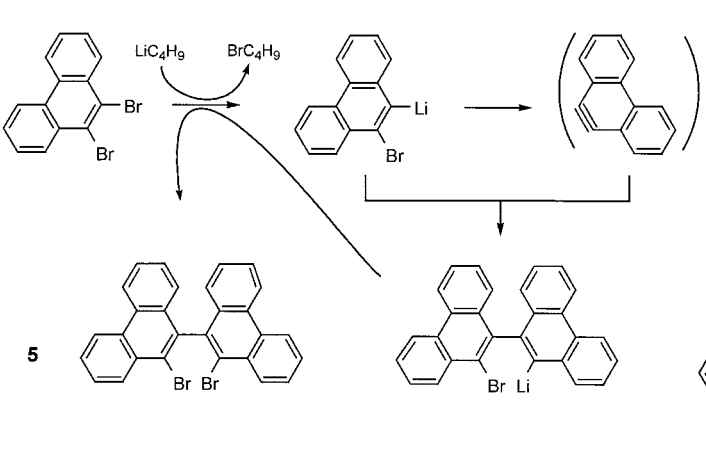


Scheme 3. Reaction of 1,2-dibrombenzene or 1-bromo-2-iodobenzene with butyllithium to form **1** or **4**, respectively.

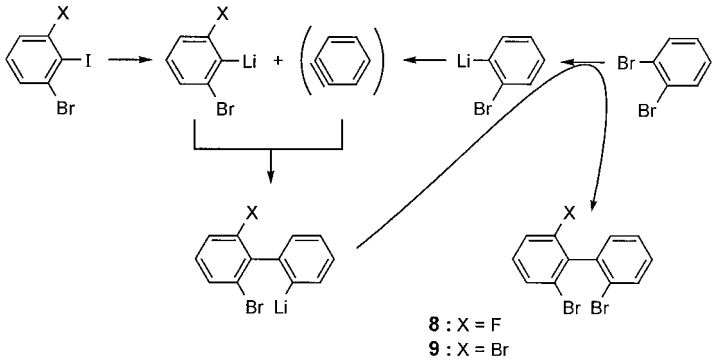
molar equivalent of butyllithium afforded 2-bromo-2′-iodobiphenyl[4] (**4**; X = I, Scheme 3) in 81 % yield.

To demonstrate the general applicability of the new aryl–aryl linking mode, 9,10-dibromophenanthrene[5] was converted into 10,10′-dibromo-9,9′-bisphenanthryl[6] (**5**; 63 %), 1-bromo-3-fluoro-2-iodobenzene[7] into 2-bromo-3′,6-difluoro-2′-iodobiphenyl[8] (**6**; 64 %), and 1-bromo-3-chloro-2-iodobenzene[9] into 2-bromo-3′,6-dichloro-2′-iodobiphenyl (**7**; 62 %; Scheme 4). The crucial steps in all these reactions were, first the nucleophilic addition of the organolithium precursor to the transient aryne species released from it by β-elimination of a lithium halide and, second, stabilization of the resulting 2-biaryl lithium intermediate by in situ transfer of bromine or iodine from the starting material.

This aryl–aryl coupling method can be modified by generating the aryne from a thermally labile 2-haloaryllithium species in the presence of a more stable aryllithium compound which will then act as the trapping reagent. For example, when a solution of 2-bromo-6-fluorophenyllithium was treated with one equivalent of 1,2-dibromobenzene at −75 °C, 2,2′-dibromo-6-fluorobiphenyl[10] (**8**; Scheme 5, X = F) was obtained in 79 % yield. The 2-bromophenyllithium



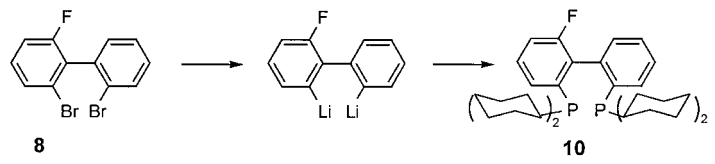
Scheme 4. Formation of the biaryls **5**, **6**, and **7**.



Scheme 5. Trapping of the labile haloaryllithium intermediates by more stable aryl lithium compounds.

species formed by halogen–metal permutation from 1,2-dibromobenzene is labile at temperatures above −125 °C, did not survive the experimental conditions but instantaneously released benzyne, which was trapped by the thermally less sensitive aryllithium component. A similar reaction between the labile 2,6-dibromophenyllithium (made from 1,3-dibromo-2-iodobenzene[7]) and 1,2-dibromobenzene gave 2,2′,6-tribromobiphenyl[11] (**9**) in 43 % yield.

Biaryl species carrying three or four *ortho*-substituents can be resolved into antipodal atropisomers. Therefore, our results provide mechanistic insight and at the same time provide an entry to axially dissymmetric bisphosphanes and other ligands for enantioselective catalysis. 6′-Fluoro-1,1′-biphenylene-2,2′-bis(dicyclohexylphosphane)[12] (**10**) was prepared in 66 % yield by consecutive treatment of 2,2′-dibromo-6-fluorobiphenyl (**8**) with butyllithium and chlorodicyclohexylphosphane (Scheme 6). Its ^{13}C NMR DEPT spectrum



Scheme 6. Formation of the biaryl atropisomeric **10**.

([D$_8$]toluene, 25 °C) showed signals arising from the cyclohexyl methine units as four different doublets ($J_{C,P} \approx 17$ Hz), thus exhibiting stereotopicity. This signal pattern did not change noticeably when the sample was heated to 125 °C. Thus, the barrier to torsional isomerization must exceed 22 kcal mol^{-1} and may well fall in the range of 25–30 kcal mol^{-1} if one bases the estimate on the findings of Jendralla et al.[13] with 6,6′-difluoro-2,2′-biphenylenebis(diphenylphosphane), the planarization of which is hampered

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by two P–F interactions. The bisphosphane **10** should racemize at ambient temperature only slowly, if at all.

A related approach to the synthesis of asymmetric biaryls is presently pursued by Buchwald and co-workers.[14–16] These authors isolated 2′-substituted 2-biphenylylphosphanes in 18–58% yield after having heated a solution of 1-bromo-2-chlorobenzene in tetrahydrofuran under reflux in the presence of magnesium turnings and an *ortho*-substituted Grignard reagent (such as 2-tolylmagnesium bromide, 2-anisylmagnesium bromide, or 2-(dimethylamino)phenylmagnesium chloride), before quenching the mixture with chlorodi-*tert*-butylphosphane or chlorodicyclohexylphosphane.

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[4] **4**: colorless needles (from ethanol); m.p. 88.5–89 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.94$ (d, $J = 7.9$ Hz, 1H), 7.66 (d, $J = 8.0$ Hz, 1H), 7.39 (dt, $J = 12.8$, 7.5 Hz, 2H), 7.2 (m, 3H), 7.08 ppm (dt, $J = 7.6$, 1.4 Hz, 1H); elemental analysis (%) calcd for $C_{12}H_8BrI$ (359.00): C 40.15, H 2.25; found C 40.13, H 2.29.

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[6] **5**: colorless needles (from ethanol); m.p. 344–348 °C (dec.); ^{1}H NMR ([D_6]DMSO, 400 MHz): $\delta = 9.10$ (d, $J = 8.2$ Hz, 2H), 9.05 (d, $J = 8.5$ Hz, 2H), 8.46 (d, $J = 8.0$ Hz, 2H), 7.91 (sym m, 4H), 7.77 (t, $J = 7.9$ Hz, 2H), 7.46 (t, $J = 7.6$ Hz, 2H), 7.13 ppm (d, $J = 8.1$ Hz, 2H); elemental analysis (%) calcd for $C_{28}H_{16}Br_2$ (512.24): C 65.65, H 3.15; found C 65.59, H 3.37.

[7] a) 1-Bromo-3-fluoro-2-iodobenzene: Diisopropylamine (14 mL, 10 g, 0.10 mol) and 1-bromo-3-fluorobenzene (11 mL, 18 g, 0.10 mol) were consecutively added to a solution of butyllithium (0.10 mol) in tetrahydrofuran (150 mL) and hexanes (50 mL) in a methanol/dry-ice bath. After 2 h at −75 °C iodine (25 g, 0.1 mmol) in THF (50 mL) was added, the solvents were evaporated and the residue dissolved in diethyl ether (100 mL). After washing with a 10% aqueous solution of sodium thiosulfate (2 × 50 mL), the organic layer was dried. Upon distillation, a colorless oil was collected; b.p. 108–109 °C (10 Torr); $n_D^{20} = 1.6354$; yield: 24 g (78%); elemental analysis (%) calcd for C_6H_3BrFI (300.89): C 23.95, H 1.00; found C 24.07, H 1.08. b) 1-Bromo-3-chloro-2-iodobenzene**:** Analogously to ref. [7a], the synthesis was carried out from 1-bromo-3-chlorobenzene (12 mL, 19 g, 0.10 mol); colorless needles; m.p. 75–76 °C (from ethanol); yield: 27 g (86%); elemental analysis (%) calcd for C_6H_3BrClI (317.35): C 22.71, H 0.95; found C 22.82, H 0.93. c) 1,3-Dibromo-2-iodobenzene: The synthesis was carried out analogously to ref. [7a] from 1,3-dibromobenzene (12 mL, 24 g, 0.10 mol); colorless platelets; m.p. 99–100 °C (from ethanol); yield: 33 g (91%); elemental analysis (%) calcd for $C_6H_3Br_2I$ (361.80): C 19.92, H 0.84; found C 19.97, H 0.80.

[8] **6**: colorless needles (from ethanol); m.p. 100–101 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.50$ (td, $J = 8.1$, 0.9 Hz, 1H), 7.39 (dt, $J = 7.9$, 5.2 Hz, 1H), 7.28 (dt, $J = 8.2$, 5.7 Hz, 1H), 7.14 (dt, $J = 8.6$, 1.1 Hz, 1H), 7.10 (dt, $J = 8.0$, 1.5 Hz, 1H), 7.02 ppm (dd, $J = 7.5$, 1.1 Hz, 1H); elemental analysis (%) calcd $C_{12}H_6BrF_2I$ (394.98): C 36.49, H 1.53; found C 36.50, H 1.29.

[9] **7**: colorless needles (from ethanol); m.p. 136–138 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.57$ (dd, $J = 8.0$, 0.7 Hz, 1H), 7.52 (dd, $J = 8.1$, 1.6 Hz, 1H), 7.48 (dd, $J = 8.0$, 0.8 Hz, 1H), 7.41 (t, $J = 7.9$ Hz, 1H), 7.25 (t, $J = 8.2$ Hz, 1H), 7.06 ppm (dd, $J = 7.5$, 1.2 Hz, 1H); elemental analysis (%) calcd for $C_{12}H_6BrCl_2I$ (427.89): C 33.68, H 1.41; found C 33.80, H 1.27.

[10] **8**: colorless needles (from ethanol); m.p. 68–70 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.70$ (dd, $J = 8.0$, 1.2 Hz, 1H), 7.48 (td, $J = 7.9$, 1.0 Hz, 1H), 7.40 (dt, $J = 7.8$, 1.3 Hz, 1H), 7.3 (m, 3H), 7.13 ppm (dt, $J = 8.6$, 1.1 Hz, 1H); elemental analysis (%) calcd for $C_{12}H_7Br_2F$ (329.99): C 43.68, H 2.14; found C 44.00, H 2.10.

[11] **9**: colorless needles (from ethanol); m.p. 95–97 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.69$ (d, $J = 8.1$ Hz, 1H), 7.64 (dd, $J = 8.1$, 0.7 Hz, 2H), 7.42 (tt, $J = 7.5$, 0.9 Hz, 1H), 7.29 (ddt, $J = 7.8$, 1.8, 0.7 Hz, 1H), 7.18 (dd, $J = 7.6$, 1.6 Hz, 1H), 7.12 ppm (dd, $J = 8.1$, 0.7 Hz, 1H); elemental analysis (%) calcd for $C_{12}H_7Br_3$ (390.90): C 36.87, H 1.81; found C 36.82, H 1.66.

[12] **10**: colorless needles (from ethyl acetate/hexanes (1:5)); m.p. 184–186 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.5$ (m, 1H), 7.3 (m, 4H), 7.1 (m, 1H), 1.7 (m, 24H), 1.2 ppm (m, 20H); ^{13}C NMR ([D_8]toluene, 101 MHz): $\delta = 162.7$ (d, $J = 10.6$ Hz), 160.2 (d, $J = 10.4$ Hz), 143.8 (d, $J = 5.2$ Hz), 143.8 (d, $J = 5.0$ Hz), 139.6 (d, $J = 22.4$ Hz), 137.1 (d, $J = 19.6$ Hz), 133.6 (d, $J = 5.2$ Hz), 133.4 (s), 133.1 (s), 128.5 (d, $J = 22.4$ Hz), 128.2 (d, $J = 12.2$ Hz), 115.9 (d, $J = 23.6$ Hz), 37.8 (d, $J = 18.4$ Hz), 36.8 (d, $J = 17.2$ Hz), 34.6 (d, $J = 16.6$ Hz), 34.4 (d, $J = 16.8$ Hz), 31 (m), 30.9 (d, $J = 14.2$ Hz), 30.5 (d, $J = 9.3$ Hz), 30.4 (d, $J = 8.4$ Hz), 28 (m), 27.4 ppm (s); elemental analysis (%) calcd for $C_{36}H_{51}FP_2$ (564.75): C 76.56, H 9.10; found C 76.43, H 9.04.

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