2,2′,6-Tribromobiphenyl via Transition-Metal-Free ARYNE Coupling: A Valuable Tool in the Synthesis of Biphenyls

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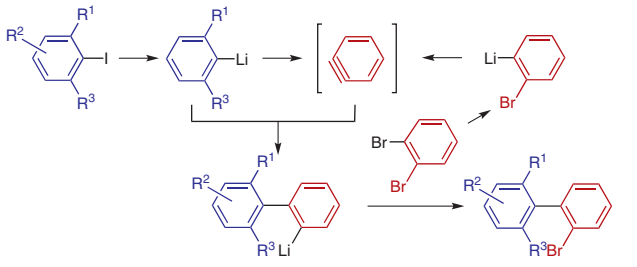
Abstract: We report a high yielding synthesis of 2,2′,6-tribromobiphenyl (TBBP) via aryne coupling, and we discuss the fundamental influence of the reaction conditions.

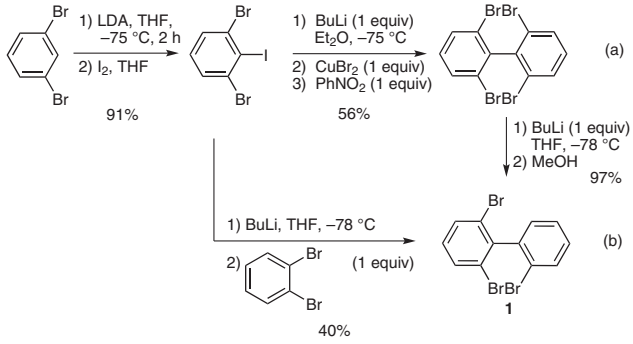
Key words: arynes, biaryls, lithiation, metalation, cross-coupling

As part of our work dealing with the synthesis of new atropisomeric biaryl ligands,[1–3] we recently devised a powerful hetero- and homo-transition-metal-free coupling[4,5] between polyhalogenated aryls towards *ortho*,*ortho′*-dibromobiphenyls. This reaction proceeds via a highly reactive transient aryne species, resulting from a subtle interplay of several organometallic intermediates and allows the selective formation of the expected biaryls in high yields,[4] that is, without formation of polycoupling products (Scheme 1). These polyhalogenated biaryls were found to be valuable precursors for the synthesis of a variety of biaryl-based phosphine ligands.[3]

In this context, 2,2′,6-tribromobiphenyl (TBBP, **1**) appeared as the most promising building block and turned out to be a suitable toolbox for the synthesis of several biphenyls. Indeed, it can be readily functionalized by means of regioselective bromine/lithium permutations[6,7] followed by trapping with a suitable electrophile.[3,8] We described its preparation for the first time via a low-temperature modification of the classical Ullmann coupling[9] of 1,3-dibromo-2-iodobenzene to give 2,2′,6,6′-tetra-bromobiphenyl followed by subsequent debromination using halogen–metal exchange and hydrolysis. Thus, TBBP was obtained in an overall yield of 49% (Scheme 2, a).[10] Alexakis and co-workers recently optimized the preparation of 2,2′,6,6′-tetrabromobiphenyl avoiding the use of nitrobenzene, which is very difficult to separate from the product, via a one-pot procedure using benzoquinone or chloranil as a coupling agent.[11] However, the yield of this multistep synthesis remained still low and we investigated the possibility to access TBBP by direct cross-coupling. Transition-metal-catalyzed coupling reactions were shown not to be suitable for this purpose because of the marked lack of selectivity. However, by applying transition-metal-free ‘aryne coupling’ between 1,3-dibromo-2-iodobenzene and 1,2-dibromobenzene using butyllithium as a base at –78 °C, TBBP was obtained in a low yield of 40% (Scheme 2, b).



Scheme 1 Aryne coupling as key reaction towards biaryl ligands



Scheme 2 Synthesis of 2,2′,6-tribromobiphenyl TBBP (**1**)

Due to the fact that TBBP is a suitable starting material for the preparation of various biphenyl derivatives and in particular atropisomeric biphenyl ligands, we continued to look for an improved access.[8,10,12–14] We report now on its multigram synthesis in almost quantitative yield by means of a carefully optimized protocol.

We focused on the use of alkyllithium reagents, carrying out the reaction using *tert*-butyllithium as a base at different temperatures. When the reaction was performed at –78 °C on a 50 mmol scale, only 32% of TBBP (**1**) was isolated, but surprisingly, 2,2″,6,6″-tetrabromo-2′-iodo-1,1′:3′,1″-terphenyl (**2**; 12%) was also formed as shown in Scheme 3. A chlorinated analogue has been described.[15]

The formation of the uncommon substituted terphenyl **2** as a side product can be explained by a mechanism where

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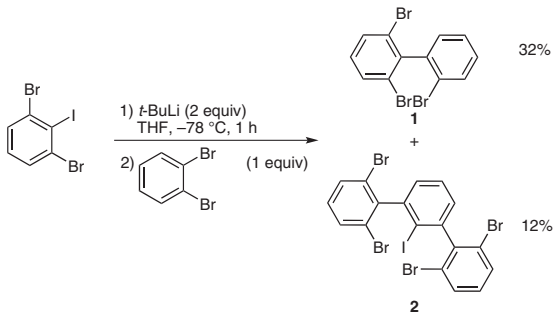
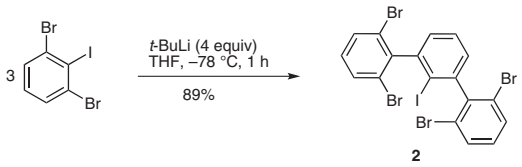


Scheme 3 Formation of terphenyl **2** during the aryne coupling

three equivalents of 1,3-dibromo-2-iodobenzene and four equivalents of *tert*-butyllithium are required (Scheme 4). This hypothesis was confirmed by the fact that under these modified conditions the terphenyl **2** was the only product to be formed and could be isolated in 89% yield (Scheme 5).



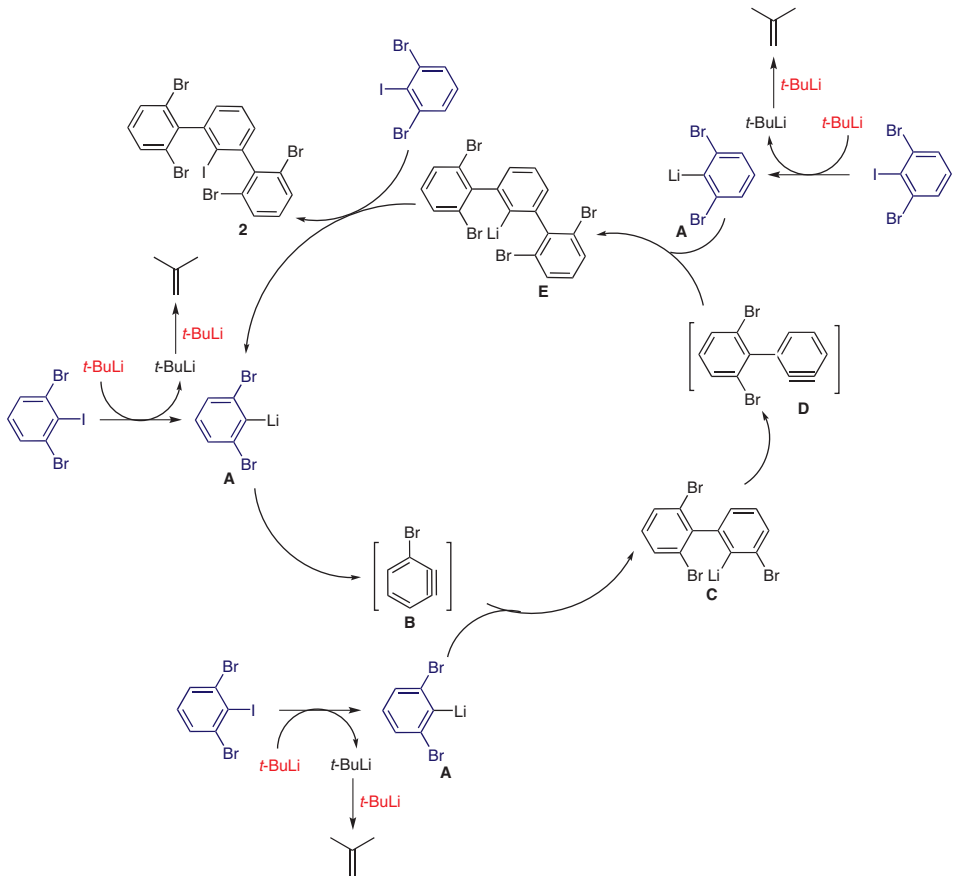
Scheme 5 Synthesis of terphenyl **2**

In contrast to the desired hetero aryl/aryl coupling of 1,3-dibromophenyllithium and benzyne (Scheme 1), 1,3-dibromophenyllithium **A** decomposes to a 3-bromo-substituted benzyne **B**, which undergoes the aryne coupling with an other equivalent of 1,3-dibromophenyllithium **A**.

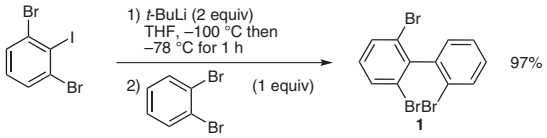
The sequence continues with the formation of a new aryne species **D** derived from the resulting biaryl lithium **C**. Finally, after a third coupling with **A** and a last I–Li exchange between the starting material and intermediate **E**, 2,2″,6,6″-tetrabromo-2′-iodo-1,1′:3′,1″-terphenyl (**2**) is obtained (Scheme 4).

This observation highlighted the sensitivity of the aryne coupling. The nature of the alkyllithium, which promotes the reaction, is crucial. Simply by replacing *n*-butyllithium by the more basic *tert*-butyllithium, the reaction profile was modified and the outcome of the reaction was deeply affected. Finally, when the addition of *tert*-butyllithium was performed at –100 °C, TBBP was obtained in a yield of 97% (Scheme 6).[8] Nevertheless, the addition of *tert*-butyllithium has to be performed very slowly (approx 15 mL/h) and carefully in order to avoid the formation of **2** as a minor side product. Under these conditions, the reaction is perfectly reproducible even on multigram scale (50 mmol) and affords TBBP with an excellent degree of purity. The replacement of butyllithium by isopropylmagnesium chloride was completely unsuccessful as no coupling product was observed, probably due to the lower basicity of the Grignard reagent.

Presently, the use of 2,2′,6-tribromobiphenyl to obtain enantiomerically pure phosphine ligands is under investigation and will be reported in due course.



Scheme 4 Proposed mechanism for the formation of 2,2″,6,6″-tetrabromo-2′-iodo-1,1′:3′,1″-terphenyl (**2**)



Scheme 6 Up-to-date access to TBBP (**1**)

1,3-Dibromo-2-iodobenzene

At –78 °C, 1,3-dibromobenzene (47.2 g, 24.2 mL, 200 mmol, 1 equiv) was added dropwise to a 0.5 M solution of LDA (200 mmol, 1 equiv) in THF (400 mL). After 2 h, a solution of iodine (50.8 g, 200 mmol, 1 equiv) in THF (200 mL) was added, and the reaction mixture was then allowed to reach 25 °C. The solvent was evaporated and the residue was taken up in Et_2O. The organic layer was washed with a sat. solution of Na_2SO_3 (3 × 100 mL), dried, and evaporated. Crystallization from EtOH afforded 1,3-dibromo-2-iodobenzene (60.6 g, 167 mmol, 84%) as colorless platelets; mp 95–97 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 8.0 Hz, 2 H), 6.99 (t, 1 H, *J* = 7.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 131.3, 131.0, 130.3, 109.4. Anal. Calcd (%) for $C_6H_3Br_2I$ (361.8): C, 19.92; H, 0.84. Found (%): C, 19.97; H, 0.80.

2,2′,6-Tribromobiphenyl (1)

At –100 °C, 1.7 M *t*-BuLi (75.9 mmol, 2 equiv) in pentane (44.6 mL) was slowly added over the course of 3 h to a solution of 1,3-dibromo-2-iodobenzene (13.7 g, 37.9 mmol, 1 equiv) in THF (160 mL). After 1 h, 1,2-dibromobenzene (8.94 g, 4.57 mL, 37.9 mmol) was added dropwise and the reaction mixture was then allowed to reach 25 °C. After 15 h, distilled H_2O (150 mL) was added, followed by extraction with EtOAc (3 × 150 mL). The combined organic layers were dried, filtered, and evaporated. The residue was purified by flash chromatography which afforded 2,2′,6-tribromobiphenyl (**1**; 12.9 g, 33 mmol, 97%) as a colorless solid; mp 95–97 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 8.1 Hz, 1 H), 7.64 (dd, *J* = 8.1, 0.7 Hz, 2 H), 7.42 (tt, *J* = 7.5, 0.9 Hz, 1 H), 7.29 (ddt, *J* = 7.8, 1.8, 0.7 Hz, 1 H), 7.18 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.12 (dd, *J* = 8.1, 0.7 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.2, 141.9, 132.6, 131.4, 130.6, 130.3, 129.8, 127.4, 124.4, 123.3. Anal. Calcd (%) for $C_{12}H_7Br_3$ (390.7): C, 36.8; H, 1,81. Found (%): C, 36.82, H, 1.66.

2,2″,6,6″-Tetrabromo-2′-iodo-1,1′:3′,1″-terphenyl (2)

At –78 °C, 1.7 M *t*-BuLi (26.7 mmol, 4 equiv) in pentane (15.7 mL) was rapidly added to a solution of 1,3-dibromo-2-iodobenzene (20.0 mmol, 7.24 g, 3 equiv) in THF (100 mL). Then the reaction mixture was allowed to reach 25 °C over the course of 12 h. Distilled H_2O was added, followed by extraction with EtOAc. The combined organic layers were dried, filtered, and evaporated. Purification by column chromatography on silica gel using cyclohexane–EtOAc (19:1) as the eluent afforded 2,2″,6,6″-tetrabromo-2′-iodo-1,1′:3′,1″-terphenyl (**2**; 3.98 g, 89%) as a colorless solid; mp 219–221 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 8.0 Hz, 4 H), 7.49 (t, *J* = 7.6 Hz, 1 H), 7.10 (d, *J* = 7.6 Hz, 2 H), 7.05 (t, *J* = 8.0 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.2 (2 C), 145.4 (2 C), 131.7 (4 C), 130.4 (2 C), 129.1 (2 C), 128.8, 124.9 (4 C), 104.9. MS(EI): *m/z* (%) = 671 (59) [M^+], 590 (83) [M^+ – Br], 464 (14) [M^+ – Br – I], 385 (8) [M^+ – 2 Br – I], 306 (39) [M^+ – 3 Br – I], 224 (100) [M^+ – 4 Br – I]. Anal. Calcd (%) for $C_{18}H_9Br_4I$ (671.78): C, 32.18; H, 1.35. Found: C, 32.10; H, 1.59%.

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