Aryl–aryl coupling *via* directed lithiation and oxidation†

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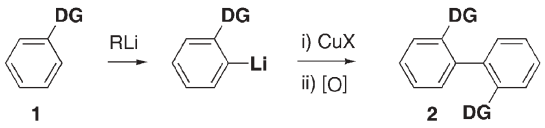
Aryl lithium reagents formed by directed lithiation reactions undergo transmetallation with copper(I) salts to form organocuprates, which may be efficiently oxidized to yield *ortho*-substituted biaryls.

The formation of biaryl bonds is one of the most important processes in organic chemistry due to the appearance of this motif in numerous natural products, pharmaceuticals, agrochemicals, dyes and chiral catalysts and as such remains an area of intensive research.[1] The oxidation of aromatic organocuprates is known to give biaryls.[2] Such cuprates have been formed by a halogen–metal exchange between an aryl halide and an alkyl lithium[2c] or magnesium reagent,[2d] followed by transmetallation with a copper(I) salt. The disadvantage of these methods is the requirement for a halogen atom to be present on the aromatic nucleus, which increases the number of steps required in a synthetic sequence. Furthermore, halogen–metal exchange can be slow for electron rich substrates.[3] An organolithium species, formed by a directed lithiation reaction[4] with **1**, could also be used in this context to yield a substituted biaryl (**2**) without the need for a halogen atom to be present on the aromatic nucleus (Scheme 1) and would be applicable to electron rich compounds.

We began by investigating the *ortho*-lithiation of anisole and were pleased to find that the organolithium generated by this method underwent an efficient transmetallation when treated with copper(I) bromide-dimethyl sulfide complex to give an organocuprate which could be oxidized to the dimer **2a** in good yield (Table 1).

The choice of oxidant is critical to the success of this sequence. It has recently been reported that dinitroamide **3** is effective in the oxidation of organocuprates derived from Grignard reagents, allowing facile separation of products from oxidant derived by-products by an aqueous acid wash during work-up.[2c] It was pleasing to discover that **3** was equally successful when used in this system. The reaction is not limited to the use of the methoxy directing group: alkoxy ethers (**1c**), sulfonamides (**1d**), carboxylates[5] (**1e**) and heterocycles (**1f**) also proved effective.



Scheme 1 General reaction sequence. DG = directing group.

† Electronic supplementary information (ESI) available: analytical and spectroscopic data for all new compounds. See http://www.rsc.org/suppdata/cc/b5/b501939g/

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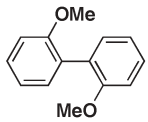
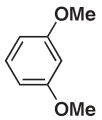
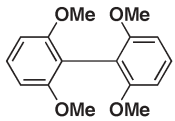
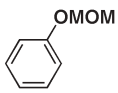
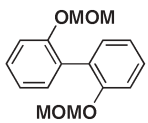
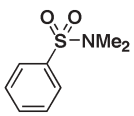
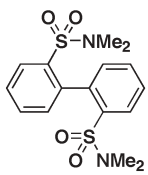
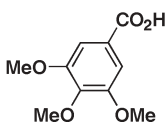
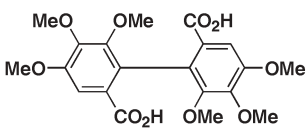
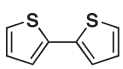
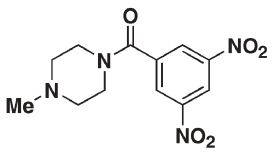
Table 1 Intermolecular biaryl bond formation

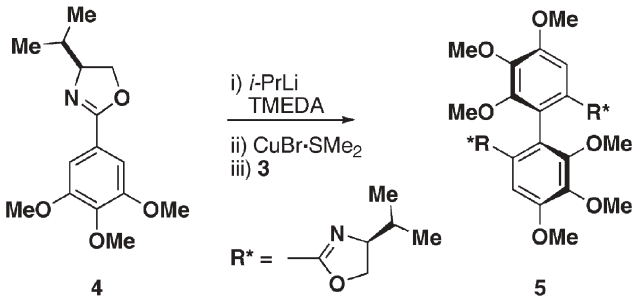
Entry	Substrate (**1**)	Product (**2**)	Yield
a			75%[a]
b			52%[a]
c			79%[b]
d			59%[c]
e			60%[d]
f			54%[e]

[a] Lithiation conditions: *n*-BuLi (1.2 equiv.), TMEDA (1.2 equiv.), Et_2O, RT. [b] *t*-BuLi (1.1 equiv.), Et_2O, 0 °C. [c] *n*-BuLi (1.1 equiv.), Et_2O, −70 °C to 0 °C. [d] LiTMP (4 equiv.), THF, −78 °C to 0 °C. [e] *n*-BuLi (1.1 equiv.), THF −20 °C to RT.

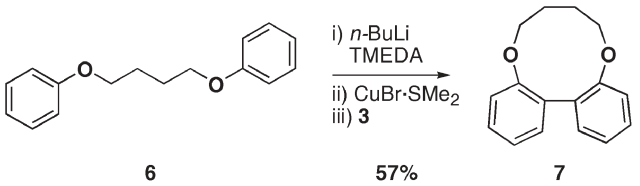


3

The applicability of the reaction to the formation of tetra-*ortho*-substituted biaryls (**2b** and **2e**) encouraged us to employ a chiral directing group in the hope of performing diastereoselective biaryl bond formation. An enantiopure, valinol-derived oxazoline[6]



Scheme 2 Diastereoselective biaryl bond formation.



Scheme 3 Intramolecular biaryl bond formation to give the 10-membered medium ring product **7**.

proved to be the most effective in this role,[7] leading to the formation of a single diastereomer (d.r. > 50:1) of the desired biaryl (*M*)-**5** in 38% yield[8] (Scheme 2).[9]

Interestingly it has been found that an Ullmann coupling on the 2-bromo derivative of **4** gives (*P*)-**5**.[10] It has been shown that (*P*)-**5** is the thermodynamically favoured diastereoisomer under the Ullmann reaction conditions.[10b] (*M*)-**5** appears to be the kinetically favoured product under the low temperature conditions of our organocuprate oxidation reaction. Our complementary procedure allows both enantiomers of diphenic acid **2e** to be prepared using the same enantiomer of the oxazoline auxiliary derived from natural valine.[11]

Intramolecular reactions are also possible, for example, performing a double lithiation on **6**, followed by intramolecular cuprate formation and oxidation gives **7** which contains a biaryl bond within a 10-membered ring (Scheme 3).

In conclusion, organocuprates formed by an *ortho*-lithiation–transmetallation sequence may be oxidized efficiently to yield biaryls. The reaction is effective when used in both an inter- and an intramolecular sense and high diastereoselectivity can be achieved using a valinol-derived oxazoline to direct the lithiation. The process allows for an efficient synthesis of biaryls which should prove useful in the synthesis of pharmaceuticals and natural products.‡

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Notes and references

‡ *Representative procedure: n*-BuLi (1.2 mmol, 0.49 mL of 2.4 M solution in hexanes) was added to a stirred solution of anisole (1 mmol, 0.11 mL) and TMEDA (1.2 mmol, 0.18 mL) in Et_2O (4 mL) under argon at ambient temperature. After 2 h a solution of $CuBr{\cdot}SMe_2$ (0.5 mmol, 0.103 g) and LiBr (1 mmol, 0.173 g) in THF (1 mL) was added *via* cannula followed by a solution of oxidant **3** (2.5 mmol, 0.735 g) in THF (4 mL). The reaction mixture was then filtered through a pad of silica, the solvent removed under reduced pressure and the residue purified by flash column chromatography.

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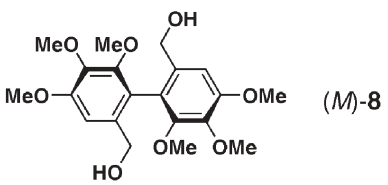
7 The use of enantiopure secondary amides gave poor diastereocontrol.
8 Although several attempts were made at improving the yield of this reaction (20–38%) the only other compound that could be isolated was starting material (30%). (*P*)-**5** was not observed in the crude reaction mixture.
9 

(*M*)-**8**
The configuration about the biaryl axis was determined by ring opening of the oxazoline (TFA, H_2O), acetylation (Ac_2O, pyridine) and reduction ($LiAlH_4$) to give the corresponding diol (*M*)-**8** (adapted from: T. D. Nelson and A. I. Meyers, *J. Org. Chem.*, 1994, **59**, 2577) $[\alpha]_D^{25} = -67.5$ (*c* = 0.2, $CHCl_3$) (lit., $[\alpha]_D^{22} = -43.2$ (*c* = 1.98, $CHCl_3$), A. M. Warshawsky and A. I. Meyers, *J. Am. Chem. Soc.*, 1990, **112**, 8090).
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