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Synthesis of Hindered Biaryls via Aryne Addition and *in Situ* Dimerization

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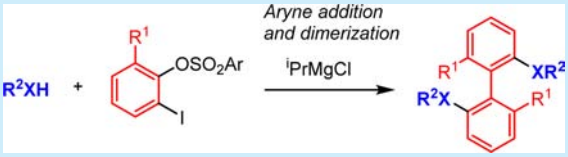
Supporting Information

ABSTRACT: Benzynes generated under Knochel conditions from 2-iodophenylsulfonates and ^{i}PrMgCl smoothly add to thiol, selenol, and amine nucleophiles. Treatment of the resulting aryl Grignard intermediate with a copper salt and an organic oxidant then affords symmetrical biaryls in good yield. 3-Substituted arynes undergo regioselective addition, enabling synthesis of atropisomeric biaryls with chelating S, Se, or N groups in the 2,2′ positions.



Biaryls containing 2,2′-heteroatomic functionality are important structures in pharmaceuticals, materials, and catalysis. Applications in the latter area are especially prominent, with tetra-*ortho*-substituted biaryls playing a fundamental role in the development of asymmetric synthesis as chiral atropisomeric ligands.[1] A major driver in this area has been the exceptionally effective synthesis of BINOL (**1**), through oxidative homodimerization of 2-naphthol.[2] Known for over a century, this reaction is key to the synthesis of many 1,1′-bi-2-naphthol derivatives through subsequent resolution and functional group interconversion chemistry (Figure 1).[1a] Oxidative homodimerization in the benzene series, by contrast, is far more challenging due to the formation of regioisomers and oxidation byproducts.[3] As a result, these biaryls are usually synthesized through stepwise coupling procedures; e.g., for the N-series, metal-mediated dimerization of an *ortho*-halo-nitrobenzene, followed by reduction and N-functionalization, would be a typical approach.[4] Recent work in the C−H activation field has shown promise in demonstrating homodimerization at the *ortho*-position of suitably activated arenes, but is currently limited to a restricted set of directing groups.[5]

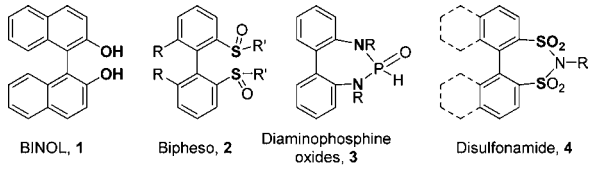
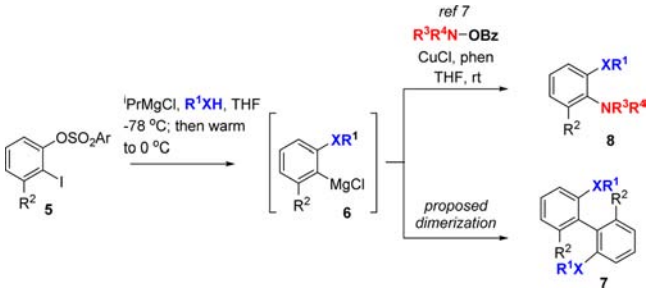


Figure 1. Representative examples of 2,2′-heteroatom substituted 1,1′-biaryl scaffolds[6]

Recent work from our group on heteroatom addition to arynes suggested an alternative approach to these valuable compounds.[7] We demonstrated that *ortho*-substituted aryl Grignards (**6**), generated under Knochel conditions from 2-iodoarylsulfonates (**5**) and an S, N, or Se nucleophile,[8] can react with electrophilic N or S sources to access 1,2-difunctionalized arenes (**8**) (Scheme 1). In the course of developing this latter step, we observed

Scheme 1. Proposed Aryne Route to Biaryls



significant homocoupling of **6** to give the biaryl **7** under some catalyst systems. If this process could be optimized, it would provide a straightforward approach to a variety of 2, 2′-S-, N-, or Se- substituted biaryls. The proposed transformation would complement existing aryne methods for biaryl synthesis which use aryl organometallics as the nucleophile, followed by trapping with an electrophilic heteroatom source.[9]

We began by investigating the addition of magnesium *p*-methoxybenzenethiolate (generated in situ from the corresponding thiol) to benzyne, followed by a screen of oxidative coupling conditions (Table 1). Initial attempts used catalytic or stoichiometric copper salts in the presence of molecular oxygen as the terminal oxidant (entries 1−6, Table 1). Encouragingly, these conditions did afford the desired product **7a**, but in low to moderate yields accompanied by significant amounts of phenolic byproduct. The use of other transition metal catalysts such as $FeCl_3$ in the presence of oxygen, or 1,2-DCE, as the oxidant was unsuccessful (entries 7 and 8, Table 1).[10] Likewise, metal-free methods[11] using organic oxidants such as TEMPO or quinone derivatives were ineffective in the reaction, producing protonated **6a** as the main product after workup. Copper-mediated coupling in the presence of organic oxidants,[12] however, gave good yields of the desired biaryl (entries 12−16), with CuBr·SMe_2 and

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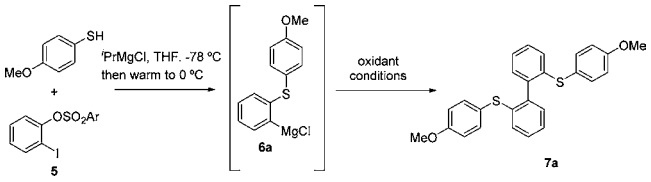
Table 1. Oxidative Dimerization Screen[a]



entry	catalyst (mol %)	oxidant (equiv)	yield (%)[b]
1	$CuCl_2$ (5)	O_2	32
2	CuCN·2LiCl (100)	O_2	traces
3	CuCN·2LiCl (10)	O_2	25
4	$CuCl_2$ (100)	O_2	10
5	CuCN·2LiCl (50)	O_2	45
6	$CuBr{\cdot}SMe_2$ (100)	O_2	36
7	$FeCl_3$ (5)/bipy (10)	O_2	traces
8	$FeCl_3$ (10)	1,2-DCE (3)	traces
9	–	TEMPO (1)	0
10	–	DPQ (1)	traces
11	CuCl (50)	TEMPO (1)	traces
12	CuCl (50)	DPQ (1)	57[c]
13	CuCl (50)	nitrobenzene (1)	60
14	$CuBr{\cdot}SMe_2$ (50)	DPQ (1)	72[c]
15	$CuBr{\cdot}SMe_2$ (50)	1,3-DNB (1)	70
16	CuCN·2LiCl (50)	DPQ (1)	42

[a]Reactions were carried out using 0.5 mmol of *p*-methoxybenzenethiol, 0.6 mmol of benzyne precursor **5**, and 1.1 mmol of ^{i}PrMgCl. [b]NMR yields. [c]Isolated yields. DPQ = 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone. 1,2-DCE = 1,2-dichloroethane. 1,3-DNB = 1,3-dinitrobenzene. Bipy = bipyridyl.

3,3′,5,5′-tetra-*tert*-butyldiphenoquinone[13] or 1,3-dinitrobenzene being optimal (entries 14 and 15, 72% and 70% yield respectively).

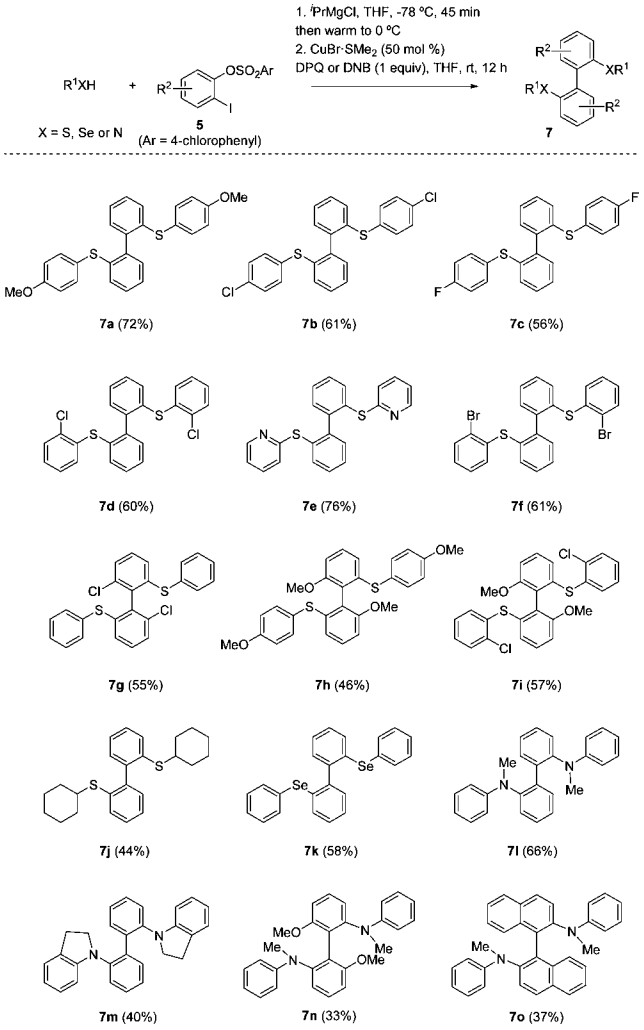
Substrate scope studies established excellent versatility for thiophenols, with a range of electron-donating (OMe) and electron-withdrawing (F, Cl, pyridyl) groups being well tolerated in the reaction (Scheme 2). Pleasingly, we could access atropisomeric biaryls using 3-substituted arynes via regioselective addition of thiolate to the distal position of the strained triple bond (compounds **7g**, **7h**, and **7i**). Alkyl thiols were not generally effective in the reaction, but we could successfully synthesize the cyclohexyl derivative **7j** in moderate yield.

The reaction was also productive in the Se- and N-series, affording the biaryls **7k**–**7o** from addition of phenylselenide and aniline derivatives, respectively. As observed previously,[7] yields in the N-series were lower than those for the analogous thiolate addition, due to the lower nucleophilicity and higher steric demand of anilides compared to thiols.

The stability of aryl halide functionality to the magnesiation conditions (e.g., **7d**, **7f**, and **7g**) suggested that intermediate Grignard **6** could be exploited in alternative reaction pathways. Intramolecular cyclization of **6d** derived from aryne addition to 2-halo-thiophenol using Kumada-type coupling would produce dibenzothiophene (DBTP) derivatives, a widely applied scaffold in medicinal and organic materials chemistry. A short optimization study (see Supporting Information) established that Ni(II) catalysis was effective for this transformation,[14] giving the DBTP derivatives **9a**–**c** in a two-step procedure, starting from the halo-thiophenols (Scheme 3).

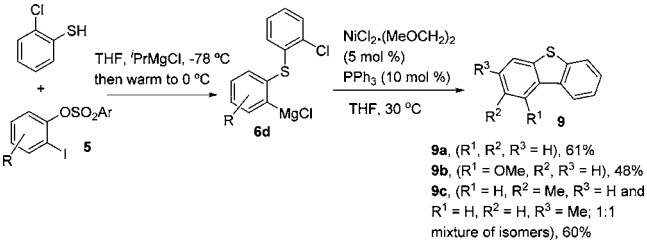
To conclude, we have reported an effective synthesis of hindered biaryls using a benzyne dimerization procedure. The process offers a modular approach to heteroatom-containing,

Scheme 2. Substrate Scope[a]



[a]DPQ used for **7a**, **7e**, and **7h**. DNB used for **7b**, **7c**, **7d**, **7f**, **7g**, **7i**, **7j**, **7k**, **7l**, **7m**, **7n**, and **7o**.

Scheme 3. Dibenzothiophene Synthesis



9a, (R^1, R^2, R^3 = H), 61%
9b, (R^1 = OMe, R^2, R^3 = H), 48%
9c, (R^1 = H, R^2 = Me, R^3 = H and R^1 = H, R^2 = H, R^3 = Me; 1:1 mixture of isomers), 60%

atropisomeric, biaryl scaffolds that are extensively employed in transition metal catalysis. The versatility of the aryl Grignard intermediate in the reaction is further exemplified through intramolecular Kumada-type coupling to access dibenzothiophenes.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds is available in the Supporting Information. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01115.

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Notes

The authors declare no competing financial interest.

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