

Synthesis of Biaryls via Intermolecular Radical Addition of Heteroaryl and Aryl Bromides onto Arenes

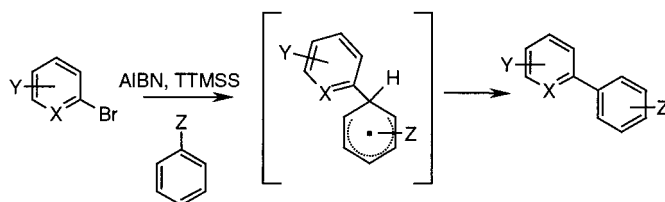
Valentín Martínez-Barrasa, Aránzazu García de Viedma, Carolina Burgos,^{*,†} and Julio Alvarez-Builla^{*}

Departamento de Química Orgánica, Universidad de Alcalá,
28871 Alcalá de Henares, Madrid, Spain

jalvarez@quimor.alcala.es

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ABSTRACT



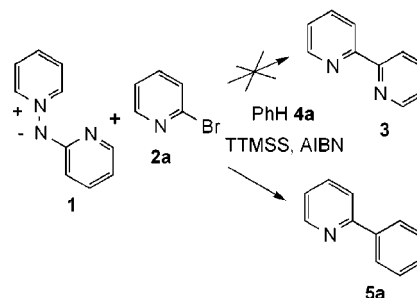
Tris(trimethylsilyl)silane (TTMSS) and azobisisobutyronitrile (AIBN) promoted the easy intermolecular arylation of aryl and heteroaryl bromides under thermal conditions via a radical pathway.

Biaryls and their homologues, such as oligo- and polyaryls, are an important class of organic compounds, represented in several areas including natural products, polymers, advanced materials, and molecules of pharmacological interest.¹ A number of methods for the preparation of these systems from monoaryl precursors have been developed. Catalytic cross-coupling reactions are, perhaps, the most attractive methods, and biaryl compounds have been prepared by a number of different procedures such as Stille, Suzuki, or Negishi couplings.^{1,2} As a continuation of our interest in this kind of compounds,³ we planned to study alternative methods for their preparation that avoided the traditional coupling reactions. Additional methods reported in the literature for the preparation of biaryls include some examples of the arylation of arenes via a radical mechanism under photochemical conditions.^{4–6} Intramolecular radical arylations under reductive radical conditions, using tri-*n*-butyltin hydride in the presence of azobisisobutyronitrile (Bu₃SnH/AIBN), are known.^{7,8} Recently, Motherwell and co-

workers⁶ have developed a method for the synthesis of biaryls involving an intramolecular radical *ipso* substitution that avoided the use of organotin hydrides. However, corresponding intermolecular processes have not been reported to date, although intermolecular alkylations of aromatic systems by alkylmercury compounds and alkyl halides were reported by Russell and co-workers,^{10,11} also performed under photochemical conditions.

In the course of our studies on the reactivity of pyridinium *N*-aminides **1** (Scheme 1),^{12,13} we attempted to arylate ylide **1** with the radical derived from the heteroaryl bromide **2a**

Scheme 1



[†] E-mail: carolina.burgos@uah.es.

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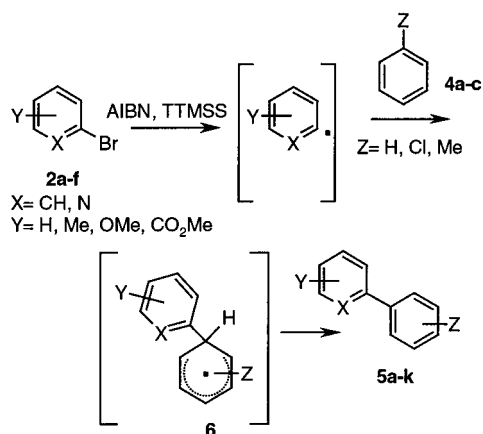
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to obtain the biaryl derivative **3**. To our surprise, product **3** was not observed, but the unexpected reaction of the radical derived from the heteroaryl bromide **2a** with benzene, **4a**, which was used as solvent, did occur to give the biaryl **5a**. We then decided to investigate the process, and herein we report our preliminary findings concerning the extension of this reaction to the arylation of aryl and heteroaryl bromides, under thermal conditions, by using tris(trimethylsilyl)silane (TTMSS) and AIBN.

When a solution of TTMSS and AIBN in benzene was added to a solution of 2-bromopyridine, **2a**, in benzene, **4a**, at 80 °C, 2-phenylpyridine, **5a**, was formed (23% yield). The formation of biaryl derivative **5a** (Scheme 2) was rationalized

Scheme 2



through the formation of an aryl radical, generated from the bromoaryl derivative, which is reluctant to propagate the chain by hydrogen abstraction. This aryl radical then undergoes addition to an arene to generate a new cyclohexadienyl radical, **6**. The ultimate fate of **6** is, usually, rearomatization to generate a substituted arene, **5**, although the mechanism by which the oxidation step takes place is not yet well understood and has been the subject of debate in the literature.^{14,15}

Full equivalents of AIBN and TTMSS were required in this reaction, as reported previously in Bu₃SnH/AIBN-mediated cyclizations,¹⁶ suggesting that the cyclohexadienyl

radical **6** might be oxidized by the initiator or an initiator-derived radical.¹⁷ Moreover, Bowman and co-workers⁷ advanced a further hypothesis for aromatic alkylations involving alkyl halides in the presence of Bu₃SnH and AIBN. These authors proposed a mechanism related to an SRN1-type reaction, in which the adduct radical undergoes deprotonation to give a radical anion, which in turn transfers an electron to the alkyl halide, to achieve aromaticity. This situation could suggest that Bu₃SnH can also serve as a proton acceptor in these processes. This hypothesis is supported by the fact that organic bases such as DABCO (1,4-diazabicyclo[2.2.2]octane) could also promote this substitution reaction.^{10,11}

To investigate the scope and efficiency of the process, a number of parameters were modified and the results are shown in Table 1. The best yields were obtained by slow

Table 1. Compounds **5** Obtained

Entry	Aryl Bromide	Solvent	Product	Yield ^a (%)	Ratio o:m:p	Method
1				41		A
2				10		B
3				7		C
4	2a	4a	5a	7		D
5		4a		74		A
6		4a		55		A
7	2a			84	13:0:1	A
8	2a			61	2:1:1	A
9		4a		51		A
10		4a		50		A
11		4a		52		A

^a Yields refer to isolated pure product. All the products were identified by spectroscopic and literature data. Method A: TTMSS (2 equiv), AIBN (2 equiv), the corresponding aryl bromide **2** (1 equiv) in the solvent **4** (5 mL) added to 10 mL of the corresponding solvent **4**, 80 °C, 24 h. Method B: TTMSS (0.1 equiv), AIBN (0.1 equiv), aryl bromide **2** (1 equiv) in the solvent **4** (5 mL) added to 10 mL of the solvent **4**, 80 °C, 24 h. Method C: TTMSS (0.1 equiv), AIBN (0.1 equiv), DABCO (4 equiv), aryl bromide **2** (1 equiv) in the solvent **4** (5 mL) added to 10 mL of the solvent **4**, 80 °C, 24 h. Method D: Bu₃SnH (2 equiv), AIBN (2 equiv), aryl bromide **2** (1 equiv) in the solvent **4** (5 mL) added to 10 mL of the solvent **4**, 80 °C, 24 h.

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addition (8 h) of a solution of TTMSS (2 equiv), AIBN (2 equiv), and aryl halide **2** (1 equiv) in 5 mL of benzene, over an additional 10 mL of benzene, **4a**, at 80 °C (Entry 1, Method A). The reaction did not go to completion when only catalytic amounts of AIBN and TTMSS were employed (Entry 2, Method B), even along with a stoichiometric amount of DABCO (Entry 3, Method C). Similar negative results were obtained by replacing TTMSS with Bu₃SnH (Entry 4, Method D).¹⁸

In a similar manner, 3-bromopyridine, **2b**, and 4-bromopyridine, **2c**, reacted with benzene, **4a**, to afford biaryl derivatives **5b,c** (Entries 5 and 6). Attempts to extend the scope of the process were carried out using chlorobenzene, **4b**, or toluene, **4c**, as the aromatic solvents (Entries 7 and 8). The reactions took place smoothly to give an o:m:p mixture of coupled products. The regioisomeric distribution of the products on using chlorobenzene, **4b**, as solvent differs from that observed in other free-radical phenylations of aryl compounds.¹⁹ In general, the regioselectivity depends on the electrophilicity or nucleophilicity of both, the radical, and the substrate as well as on polar effects and orbital control. On the other hand, the philicity of aryl radicals is a controversial subject and there has been considerable debate regarding the nature of aryl radicals and whether they could be nucleophilic,²⁰ electrophilic,^{21,22} or relatively neutral^{7,23,24} species. Moreover, although chlorobenzene, **4b**, could be considered as an electron-poor substrate, the mesomeric π -donor character of the Cl substituent must be taken into consideration. In contrast, the isomeric distribution, o:m:p, observed on using toluene, **4c**, is in agreement with the regioselectivity reported for other radical phenylations.¹⁹

On the assumption that aryl and heteroaryl radicals should react in a similar manner, given that the unpaired electron would be in an orbital orthogonal to the aromatic π -system (π -excessive or π -deficient) and thus have little or no effect on the reactivity of such species,²⁵ we carried out additional experiments using 4-methylphenyl, 4-methoxyphenyl, and

4-methoxycarbonylphenyl bromides (**2d–f**, respectively) (Entries 9–11) and obtained essentially the same results.

In conclusion, we report a simple method for the synthesis of biaryl compounds, based on the intermolecular radical addition of aryl- or heteroaryl radicals onto aromatic solvents. This process takes place under reductive radical conditions (TTMSS, AIBN), and it is noteworthy that radical addition takes place prior to hydrogen abstraction from TTMSS. This methodology should be complementary to the preparation of biaryl compounds by organometallic-based aryl cross-coupling methods and is currently being extended to the synthesis of other related systems.

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Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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