Room-Temperature Photoinduced Direct C−H-Arylation via Base-Promoted Homolytic Aromatic Substitution
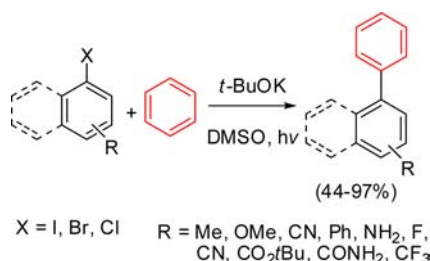
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ABSTRACT

Conceptually different approach toward biaryl syntheses by photoinduced direct C−H arylation of benzene and thiophene in the presence of *t*-BuOK is reported. The reaction proceeds through photo- and base-promoted homolytic aromatic substitution. The *o*-, *m*- and *p*- substituted ArI, as well as the electron-donating and electron-withdrawing nature of the substituents were found be good to excellent substrates. Heteroaryl, ArBr, ArCl and double C−H arylation were successfully achieved.

Biaryl structural motifs are widely available in a variety of natural products, drugs, and ligands for cross coupling reactions catalyzed by transition metals. The synthesis of biaryl has been known for more of a century using different transition metal catalyzes. These reactions typically involve either the coupling of an aryl halide or pseudohalide with an organometallic reagent, or the homocoupling of two aryl halides or two organometallic reagents.[1] Many transition metals have been successfully applied in the direct arylation of arenes by C−H activation.[2] However, these reactions often require a ligand, base and high temperature. New cheap, efficient and noncontaminant methodologies to prepare these motifs are always of great interest.

Over recent years, there have been many reported syntheses of biaryl compounds using homolytic aromatic substitutions (HAS) mediated by Bu₃SnH/AIBN, or (Me₃Si)₃SiH.[3,4] Recently, an attractive alternative to the C−H arylation of arenes using base-promoted HAS reactions has been reported,[5] which avoids the use of stoichiometric amounts of tin or silicon reagents, initiators, or transition metals. In 2008, it was shown that *t*-BuOK caused the addition reaction of ArI and/or ArBr to pyridazine and other electron-poor aromatic rings under elevated temperatures or MW irradiation.[6] Furthermore, the construction of biaryl compounds from unactivated aromatic rings by direct C−H activation using *t*-BuOK and DMEDA or 1,10-phenanthroline as ligands was also reported.[7] Nowadays, these

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methodologies have been successfully extended to different systems by intra[8] and inter[9] approaches.

The proposed base-promoted HAS mechanism is a chain process with radicals and radical anions as intermediates (Scheme 1). The initiation step is an electron transfer (ET) to yield an [ArX]$^{\bullet-}$ radical anion, which then fragments to produce an [Ar]$\bullet$ radical and an X$^-$ ion. The [Ar]$\bullet$ formed is able to couple to ZH moiety to give radical [ArZH]$\bullet$. This radical is deprotonated by the base to generate the [ArZ]$^{\bullet-}$ radical anion, and by an ET from [ArZ]$^{\bullet-}$ to the ArX provides the ArZ product and the [ArX]$^{\bullet-}$ to continue the chain process.[10] The deprotonation step of phenylcyclohexadienyl radical by t-BuO$^-$ was calculated by B3LYP-D/6-31+G* in the presence of a continuum solvent (benzene) and is exothermic ca. -2.75 kcal.mol^{-1}.[11]

Scheme 1. Base-Promoted HAS Mechanism
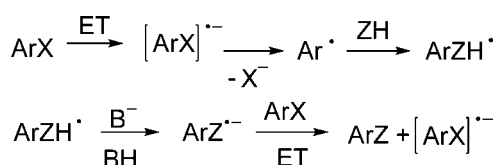
As t-BuOK can form [ArX]$^{\bullet-}$ by ET in photostimulated $S_{RN}1$ reactions,[12] we speculated that the C–H arylation of benzene could be achieved with only t-BuOK and light[13] at room temperature (rt), which would be a very promising approach for clean, efficient, and cheap synthesis of biaryl moieties.

We began this investigation with the reaction of PhI (**1a**) with benzene (**2**), as a model system for the synthesis of biphenyl **3a** (Table 1).

The best result was obtained in the photostimulated reaction of **1a** (1 equiv) with **2** (150 equiv), t-BuOK (3 equiv) and DMSO (13 equiv), which after 1 h gave 90% yield of **3a**

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(11) For a full description, see the Supporting Information.

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(13) Irradiation was conducted in a photochemical reactor equipped with two HPI-T 400 W lamps (cooled with water).

(Table 1, expts. 1–6). Although other bases were also screened, **1a** was recovered quantitatively (Table 1, expts. 7–9). Moreover, the reaction without DMSO, but with MeCN or in the presence of different ligands, did not give **3a** at all (Table 1, expts. 10–14).[14] PhBr (**1b**) only gave 30% yield of **3a** after 8 h of irradiation (Table 1, expt. 15).

We suggest that the formation of Ar$\bullet$ and radical anions are key steps (Scheme 1), which were supported by experiments performed in the presence of the radical scavenger (TEMPO) and a good acceptor electron such as m-dinitrobenzene (m-DNB) which inhibited the reactions (Table 1, expts. 16 and 17). In addition this reaction did not occur in dark conditions (Table 1, expt. 18).

Table 1. Photostimulated Reaction of **1a**–**b** and **2**^{a}

expt	base, additive	time (h)	**3a** (yield %)^b	I$^-$ (%)^c
1^d	t-BuOK, DMSO	3	44	94
2^e	t-BuOK, DMSO	3	76	100
3	t-BuOK, DMSO	3	92	92
4	**t-BuOK, DMSO**	**1**	**90**	**88**
5	t-BuOK, DMSO	0.5	68	77
6	t-BuOK, DMSO	0.25	46	44
7^f	t-BuONa, DMSO	1		<7
8^g	Et$_4$N(OH), DMSO	1		<9
9^g	KOH, DMSO	1		<9
10^g	t-BuOK, none	1		<5
11	t-BuOK, 19 equiv MeCN	1		<9
12	t-BuOK, 0.2 equiv DMEDA	1		<9
13	t-BuOK, 0.3 equiv 1,10-phenanthroline	1	23	33
14	t-BuOK, 0.4 equiv ethylene glycol	1	8	13
15^h	t-BuOK, DMSO	8	30	47
16^g	t-BuOK, DMSO, 0.3 equiv TEMPO	1		7
17^g	t-BuOK, DMSO, 0.3 equiv m-DNB	1		<5
18^{g,i}	t-BuOK, DMSO	1		<5

^{a} The photostimulated reaction was carried out under N$_2$ atmosphere using **1a** (1 equiv, 0.5 mmol), t-BuOK (3 equiv), DMSO (0.5 mL, 13 equiv), and **2** (6.7 mL, 150 equiv) in a sealed tube. ^{b} Yields were determined by GC (internal standard method). ^{c} I$^-$ ions were determined potentiometrically. ^{d} 50 equiv of **2** and 70 equiv of DMSO were used. ^{e} 100 equiv of **2** was used. ^{f} The substrate was recovered in 97% yield. ^{g} The substrate was recovered quantitatively. ^{h} 1 equiv of PhBr (**1b**, 0.25 mmol), 44 equiv of DMSO, and 5 equiv of t-BuOK were used. ^{i} The reaction was carried out under dark conditions.

We next examined the substrate scope for this reaction, and the best results obtained are shown in Table 2.[11] The o-, m- and p- substituted ArI with electron-donating and electron-withdrawing groups were found be good to excellent substrates for the arylation and provided biaryls in 44–97% yields (Table 2, expts. 1–13). However, a prolonged reaction time was necessary for o-substituted ArI (Table 2,

(14) It is proposed that DMSO solvates the t-BuOK and affords the solvent-separated ion pair to act as an electron donor. However, it is worth noting that a larger amount of DMSO gives lower yields due to H-abstraction; see the Supporting Information.

Table 2. Photostimulated Reaction of Substituted ArX with **2**[a]

expt.	aryl halide	Product	3 yield %[b] (yield%)[c] time, X⁻ (%)[d]	expt.	aryl halide	Product	3 yield %[b] (yield%)[c] time, X⁻ (%)[d]
1	Ph—◯—I **1c**	Ph—◯—◯ **3c**	74 (77) 3 h, I⁻ = 90	13	**1o**	**3o**	72[h] 3 h, I⁻ = 94
2	Me—◯—I **1d**	Me—◯—◯ **3d**	91 3 h, I⁻ = 98	14	**1p**	**3p**	86 (81) 2 h, I⁻ = 94
3	**1e** (Me)	**3e** (Me)	83 (79) 3 h, I⁻ = 87	15	**1q**	**3q**	96 (86) 1 h, I⁻ = 97
4	**1f** (Me)	**3f** (Me)	61 5 h, I⁻ = 90	16	Ph—◯—Br **1r**	Ph—◯—◯ **3c**	(79) 3 h, Br⁻ = 92
5	MeO—◯—I **1g**	MeO—◯—◯ **3g**	97 (93) 1.5 h, I⁻ = 94	17[i]	**1s** (Br)	**3o** (Ph)	71 5 h, Br⁻ = 83
6	**1h** (OMe)	**3h** (OMe)	84 (79) 3 h, I⁻ = 94	18[j]	**1t** (Br)	**3t** (Ph)	87 3 h, Br⁻ = 90
7[e]	H₂N—◯—I **1i**	H₂N—◯—◯ **3i**	(44) 5 h, I⁻ = 75	19	**1u** (Br)	**3u** (Ph)	69[k] 8 h, Br⁻ = 95
8	F—◯—I **1j**	F—◯—◯ **3j**	87 (87) 1 h, I⁻ = 92	20[i,l]	**1v** (Br)	**3v** (Ph)	59 5 h, Br⁻ = 78
9	F₃C—◯—I **1k**	F₃C—◯—◯ **3k**	61 (59) 4 h, I⁻ = 82	21[j]	**1w** (Cl)	**3w** (Ph)	63 3 h, Cl⁻ = 80
10[f]	NC—◯—I **1l**	NC—◯—◯ **3l**	85 (75) 2 h, I⁻ = 92	22[m]	**1x** (Cl)	**3o** (Ph)	52 7 h, Cl⁻ = 77
11[f]	ᵗBuO₂C—◯—I **1m**	ᵗBuO₂C—◯—Ph **3m**	67 (38) 4 h, I⁻ = 68				
12[g]	H₂N(O=)C—◯—I **1n**	H₂N(O=)C—◯—◯ **3n**	76 (60) 5 h, I⁻ = 91				

[a] The photostimulated reaction was carried out under N₂ atmosphere using ArX (**1**, 1 equiv, 0.5 mmol), *t*-BuOK (3 equiv), DMSO (0.5 mL, 13 equiv) and **2** (6.7 mL, 150 equiv) in a sealed tube. [b] Yields were determined by GC (internal standard method). [c] Isolated yield. [d] X⁻ ions were determined potentiometrically. [e] The substrate was recovered in 21% yield. [f] 1.2 equiv of *t*-BuOK was used. [g] 6 equiv of *t*-BuOK and 0.8 mL of DMSO were used. [h] Naphthalene was obtained in 16% yield. [i] 0.7 mL of DMSO and 200 equiv of **2** were used and naphthalene was obtained in 10% yield. [j] 1 mL of DMSO was used. [k] Phenanthrene was obtained in 23% yield. [l] 6 equiv of *t*-BuOK was used. [m] 0.7 mL of DMSO was used.

expts. 4 and 6). The photostimulated reaction of 2- (**1p**) and 3-iodopyridine (**1q**) gave excellent yields of the phenyl pyridines **3p** and **3q** (Table 2, expts. 14 and 15).

In contrast, ArBr and ArCl, which have π extended systems, were reactive for C−H arylation. For example, PhBr (**1b**) gave 30% yield of **3a** in 8 h of irradiation (Table 1, expt. 15), whereas 4-bromobiphenyl (**1r**), 1-bromonaphthalene (**1s**), 2-bromonaphthalene (**1t**), 9-bromophenanthrene (**1u**) and 1-chloronaphthalene (**1x**) provided the arylation product in very good yields under mild conditions (Table 2, expts. 16−19 and 22). Finally, 3-bromo-

benzo[*b*]thiophene (**1v**) and 6-chloroquinoline (**1w**), afforded **3v** and **3w** in 59% and 63% yields, respectively.

The behavior of the 1,3- and 1,4-halo-iodobenzenes (**4a−e**) in a photostimulated reaction with **2** was studied (Table 3). For 4-haloiodobenzene (**4a−c**), the arylation product **3c** was obtained in 60−74% yields (Expts. 1−4). Although a similar result was obtained with **4d**, in the case of **4e** the main product was 3-chlorobiphenyl (**1y**) with 71% of isolated yield, with 15% yield of *m*-terphenyl, (**5**) (Expts. 5 and 6). It is remarkable that with these halo-iodobenzenes bromide and chloride were as good

Table 3. Photostimulated Reaction of **4a**–**f** with **2**[a]

| expt.	Substrate	product (yield %)[b]	X⁻ (%)[c]
	X–⟨C₆H₄⟩–I	Ph–⟨C₆H₄⟩–Ph **3c**	
1[d]	**4a**, X = I⁻	54[e]	I⁻ = 83[f]
2[d,g]	**4a**	64	I⁻ = 83[f]
3	**4b**, X = Br⁻	74	I⁻ = 89, Br⁻ = 79
4	**4c**, X = Cl⁻	60	I⁻ = 78, Cl⁻ = 66
	X–⟨C₆H₄⟩–I (meta)	Ph–⟨C₆H₄⟩–Ph (meta) **5**	
5	**4d**, X = Br⁻	80	I⁻ = 82, Br⁻ = 78
6	**4e**, X = Cl⁻	15[h]	I⁻ = 91, Cl⁻ = 18
7	I–⟨C₆H₄⟩–⟨C₆H₄⟩–I **4f**	Ph–⟨C₆H₄⟩–⟨C₆H₄⟩–Ph **6** (61)	I⁻ = 86[f]

[a] The photostimulated reaction was carried out for 1 h under a N₂ atmosphere using haloiodobenzenes (**4**, 1 equiv, 0.5 mmol), t-BuOK (3 equiv), DMSO (0.6 mL), and **2** (9 mL, 200 equiv) in a sealed tube. [b] Yields were determined by GC (internal standard method). [c] X⁻ ions were determined potentiometrically. [d] With 4 equiv of t-BuOK. [e] 21% yield of **1c** and 9% yield of **3a** were obtained. [f] Considering two iodines per mole. [g] Reaction time: 3 h. [h] 3-Chlorobiphenyl (**1y**) was obtained in 71% isolated yield.

leaving groups as iodine, except **4e**. Moreover, 1,4-diiodo-biphenyl (**4f**) reacted with **2** to provide the diarylation product **6** in 61% isolated yield (Expt 7).

Taking into account these results and the mechanisms illustrated in Scheme 1, the radical anion **7** was formed as the intermediate (Scheme 2). This radical anion has two possible ways. One of these is an ET intermolecular to give halobiphenyl **8** (Path A). The other possibility is an ET intramolecular to the C-X bond that after fragmentation gives aryl radical **9**, which finally provides **3c** or **5** (Path B). Indeed, the radical **9** can also be formed by a second ET and fragmentation from **8** (Path C).

To demonstrate if **8** is an intermediate in the formation of **9**, we carried out the reaction at lower conversion.[15] Even at short reaction times (15 min), at which the dihalo-benzene is but partially reacted, only low percentages of monosubstitution product **8** is observable alongside predominant disubstitution. Moreover, when **8** is p-bromobi-phenyl (**1r**) only gives 31% yields of **3c** after 60 min[11] (compare with Table 3, expt. 3, 74% yield). These results suggest that the rate of fragmentation in producing **9** was faster than the intermolecular ET reaction to give **8**, for all the substrates, except **4e**.[16]

The metal-free photoinduced C−H arylation was also effective for thiophene, with the corresponding products

Scheme 2. Competing ET for the Radical Anions
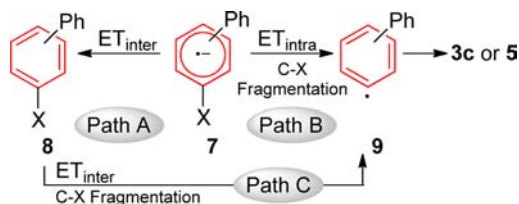
Scheme 3. Photostimulated Reaction of ArX with Thiophene
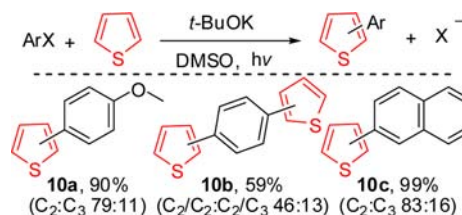
being obtained at excellent yields (Scheme 3). In this case, 4-iodoanisole (**1g**), 4-bromoiodobenzene (**4b**) and 2-bro-monaphthalene (**1t**) were all successful.[17]

In summary, we have developed a conceptually different approach toward the biaryl syntheses metal-free photo-induced direct C−H arylation. Previous known catalysts were not successful. This environmentally friendly methodology effectively promoted the arylation of unactivated arenes, such as benzene and thiophene, using a broad range of aryl and heteroaryl halides, including ArI, ArBr and even ArCl at room temperature. Moreover, double C−H bond arylation was successfully achieved to construct extended π−electron systems. On the basis of our results, a plausible chain mechanism with radicals and radical anions as intermediates for this photoinduced reaction is proposed. This reaction proceeds via photo ET to initiate the formation of an aryl radical. Due to the high reactivity of this a large excess (150 equiv) of benzene (or arene) is required. Further investigations to expand this novel method to a broad number of substrates are underway in our laboratory.

Supporting Information Available. Experimental procedures, sample spectra, and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) The rate of bond fragmentation of radical anions depends on the nature of the halogen and on the spin density on the C-X. It is known that 3-position of the biphenyl has a lower spin density than the 4-position. See: Pierini, A. B.; Vera, M. A. *J. Org. Chem.* **2003**, *68*, 9191.

(17) We tested the feasibility of C−H arylation of thiophene using a known thermal transition-metal-free system. We observed a lower reactivity and similar regioisomeric preference, favoring the C−H coupling at the 2 position of thiophene; see the Supporting Information.