

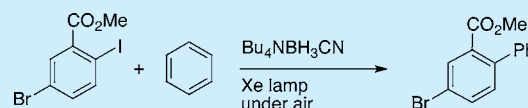
Cyanoborohydride-Promoted Radical Arylation of Benzene

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Supporting Information

ABSTRACT: Radical biaryl coupling of iodoarenes and benzene can be effectively promoted by tetrabutylammonium cyanoborohydride with air under photoirradiation conditions using a Xe lamp. The utility of this methodology is highlighted by its functional group tolerance and chemoselectivity.



Homolytic aromatic substitution (HAS) reactions by an aryl radical are one of the most straightforward methods for the construction of biaryl motifs.^{1–4} Recent research in this area includes base-promoted HAS (BHAS) reactions; for example, in 2008, Itami reported that biaryl coupling of electron-deficient nitrogen heterocycles and haloarenes was promoted by KO-*t*-Bu.⁵ Kwong and Lei,⁶ Shi,⁷ and Shirakawa and Hayashi⁸ all independently expanded this benzene-arylation chemistry by using a strong base and a bidentate ligand.^{9,10} Curran and Studer have reported BHAS reactions using PhNHNH₂ as an initiator with KO-*t*-Bu.¹¹ Rossi demonstrated that BHAS reactions could proceed under photoirradiation conditions at ambient temperature.¹² More recently, Zheng and Guo reported that TMEDA-catalyzed radical arylation of benzene under photoirradiation conditions with high tolerance of functional groups.¹³ Recently, we reported radical C–C bond-forming reactions using borohydride reagents as chain mediators.^{14,15} In this paper, we report that cyanoborohydride promotes the synthesis of biaryl compounds from iodoarenes and benzene under aerobic photoirradiation conditions. This reaction proceeds in a chemoselective fashion for bromo- and iodo-substituted arenes.

4-Iodoanisole (**1a**) was chosen as a model substrate for the initial study (Table 1). When a benzene solution of **1a** was

irradiated with a 500 W Xe lamp in a Pyrex tube for 24 h under air, the desired 4-methoxy-1-phenylbenzene (**2a**) was obtained in 38% yield together with 2% yield of anisole (**3a**) (Table 1, entry 1). For comparison, we also examined radical arylation of benzene under degassed conditions by freeze–pump–thaw cycles, which gave the arylation product **2a** (38%) and an increased amount of reduced product **3a** (16%) (Table 1, entry 2).¹⁶ Under aerobic conditions, the addition of 0.75 and 1 equiv of Bu₄NBH₃CN increased the yield of **2a** to 55 and 78%, respectively (Table 1, entries 3 and 4). However, further increases of the amount of Bu₄NBH₃CN, such as 2 equiv, resulted in an increase in the formation of reduced product anisole (**3a**), compared to the desired arylation product (Table 1, entry 5).¹⁷

With the optimized conditions of entry 4 in hand, we next examined the substrate scope for aromatic arylation and the results are given in Table 2. 4-Iodotoluene (**1b**), ethyl 4-iodobenzoate (**1c**), ethyl 2-(4-iodophenyl)acetate (**1d**), 4-iodoacetophenone (**1e**), 1-fluoro-4-iodobenzene (**1f**), and 4-trifluoromethyl-1-iodobenzene (**1g**) were converted to the corresponding biaryls **2b**, **2c**, **2d**, **2e**, **2f**, and **2g** in 70, 68%, 53%, 55%, 67%, and 48%, respectively (Table 2, entries 2–7). The reactions of 3-iodoanisole (**1h**), ethyl 3-iodobenzoate (**1i**), 2-iodoanisole (**1j**), 2-iodotoluene (**1k**), and ethyl-2-iodobenzoate (**1l**) were also successful (Table 2, entries 8–12). Both 1- and 2-iodonaphthalene (**1m** and **1n**) worked well to give 1-phenylnaphthalene (**2m**) and 2-phenylnaphthalene (**2n**) in 57 and 82% yields, respectively (Table 2, entries 13 and 14). We performed the reactions by reacting aryl iodides **1a** with toluene. As expected, reactions of **1a** with toluene afforded regioisomeric mixtures favoring the *ortho* products (Table 2, entry 15).¹⁸

Shirakawa and Hayashi have reported that under controlled conditions the HAS reaction of 1-bromo-4-iodobenzene (**1p**) with NaO-*t*-Bu and catalytic amount of Ph-phen (4,7-diphenyl-1,10-phenanthroline) takes place chemoselectively at the aryl-iodine bond to give 4-bromobiphenyl (**2p**).⁸ In contrast, KO-*t*-Bu-promoted HAS reaction of benzene with either 1-chloro- (**1o**) or 1-bromo-4-iodobenzene (**1p**) afforded only 1,4-

Table 1. Optimization of Arylation Reaction Conditions

1a (0.5 mmol)			
entry	Bu ₄ NBH ₃ CN (equiv)	2a ^a (%)	3a ^a (%)
1	0	38	2
2 ^b	0	38	16
3	0.75	55	7
4	1	78 ^c	9
5	2	38	41

^aGC yield. ^bReaction was performed under degassed conditions by freeze–pump–thaw cycles. ^cIsolated yield after silica gel column chromatography.

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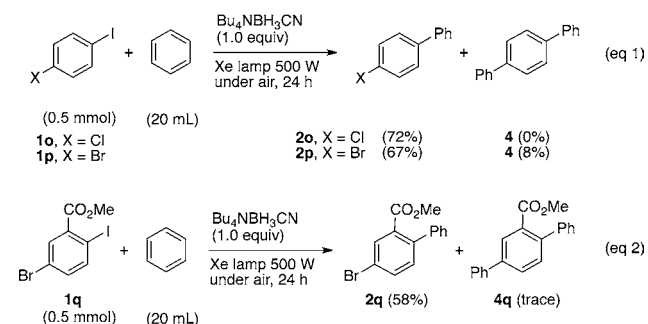
Table 2. Arylation of Benzene with Various Aryl Iodides

$\text{R}-\text{C}_6\text{H}_4\text{I} + \text{C}_6\text{H}_6 \xrightarrow[\text{Xe lamp 500 W under air, 24 h}]{\text{Bu}_4\text{NBH}_3\text{CN (1.0 equiv)}} \text{R}-\text{C}_6\text{H}_4\text{Ph}$			
entry	1	2	yield in 2 ^a
1			2a 78%
2			2b 70%
3			2c 68%
4 ^b			2d 53%
5			2e 55%
6			2f 67%
7			2g 48%
8			2h 79%
9			2i 62%
10			2j 50%
11			2k 47%
12 ^c			2l 70%
13			2m 57%
14			2n 82%
15 ^d			2a' 39% ^e

^aIsolated yield based on **1**. ^b**1d** was recovered in 20% yield. ^cBorohydride was added in two portions (0.5 + 0.5 equiv). ^dToluene was used instead of benzene. ^eRegioisomeric mixture with an *o*:*m*:*p* ratio 62:24:14 was isolated.

diphenylbenzene (**4**).^{6,7,11,12,10b,f,g} To gain insight into the chemoselectivity of the present method, we tested the arylation of benzene with the bihaloarenes **1o** and **1p** using cyanoborohydride (Scheme 1, eq 1). Under our standard reaction conditions, a chemoselective reaction took place at the aryl–iodine bond but not at the aryl–bromine or aryl–chlorine

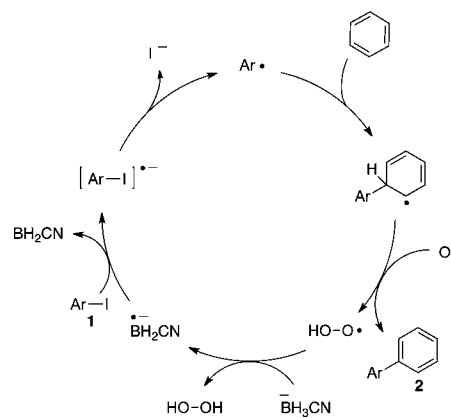
Scheme 1. Reaction of 1-Halo-4-iodobenzenes



bond. Since 8% of terphenyl (**4**) was formed in the reaction of 1-bromo-4-iodobenzene, we examined the experiment with **1o** and stopped the reaction at low conversion. After 3 h, 38% conversion was achieved but at this stage no terphenyl was obtained. This result suggests that the formation of terphenyl is via the further reaction of the initially formed **2p** but not via the formation of the biaryl radical anion, which was suggested by Kwong and Lei.⁶ Similarly, the reaction of methyl 5-bromo-2-iodobenzoate (**1q**) gave the bromo biaryl **2q** (Scheme 1, eq 2). The carbon–bromine bonds present in the biaryl products can be subsequently converted to carbon–carbon bonds by cross-coupling reactions such as Suzuki–Miyaura and Sonogashira reactions.¹⁹

A potential mechanism, mediated by oxygen and cyanoborohydride, is shown in Scheme 2. Photoirradiation of aryl iodide

Scheme 2. Possible Mechanism



leads to generation of an aryl radical.^{2,20} The aryl radical adds to benzene to form cyclohexadienyl radical, which reacts with oxygen to give biaryl product and hydroperoxy radical.^{2,3a,21} The resulting hydroperoxy radical could abstract hydrogen from cyanoborohydride to give the cyanoborane radical anion. Subsequent reaction with aryl iodide through single-electron transfer would give the corresponding radical anion that fragments to aryl radical and iodide ion, thus completing the radical chain reaction.

In summary, we have found that cyanoborohydride can promote arylation of benzene under aerobic conditions. Using this protocol, both aryl iodides bearing an electron-donating or -withdrawing group can be accommodated. The reaction takes place chemoselectively at the aryl–iodine bond in preference to either an aryl–bromine or aryl–chlorine bond. These mild reaction conditions are unusual for base-promoted HAS reactions and provide considerable synthetic flexibility, as

illustrated by the subsequent conversion of C–Br bonds into C–C bonds via cross-coupling reactions following the cyanoborohydride-promoted arylation reaction.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and spectroscopic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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- (19) See the Supporting Information.
- (20) It should be noted that no further reaction was observed when the light was turned off (Supporting Information), which suggested that this arylation reaction has poor chain propagation.
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