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Visible-Light Photoredox in Homolytic Aromatic Substitution: Direct Arylation of Arenes with Aryl Halides

Yannan Cheng, Xiangyong Gu, and Pixu Li*

Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering, and Materials Science, Soochow University, 199 RenAi Road, Suzhou, Jiangsu 215123, China

lipixu@suda.edu.cn

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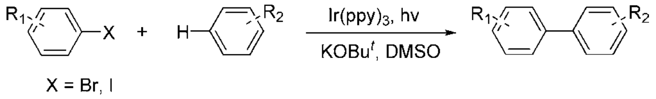
ABSTRACT



Direct arylation of unactivated arenes or heteroarenes with aryl halides could be carried out in the presence of potassium *tert*-butoxide and dimethyl sulfoxide under visible-light irradiation. Ir(ppy)$_3$ was found to be an effective photoredox catalyst for this reaction. The reactions of aryl iodides occurred at room temperature. Elevated temperature was required for aryl bromides. Homolytic aromatic substitution was proposed to be the operative reaction pathway.

Biaryl compounds are of great importance in the areas of pharmaceuticals, materials, and catalysis.[1] The common strategy to construct biaryl structures is transition-metal-catalyzed cross-coupling.[2] The recent breakthrough in the construction of biphenyl derivatives was mediated by strong bases without the involvement of transition metals.[3] Homolytic aromatic substitution (HAS)[4] was proposed to be the operating pathway.[5]

The visible-light photoredox catalysis using ruthenium/iridium polybipyridyl complexes as the sensitizers has been successfully applied in organic synthesis recently. The ability to utilize visible light as the driving force for chemical transformation has attracted the attention of many researchers.[6] Aryl halides were believed to be substrates not suitable for the visible-light photoredox chemistry because of their high redox potentials. However, two recent reports involving unactivated organohalides in visible-light-mediated reactions changed the view on these substrates in visible-light photoredox chemistry.[7] In both reports, the authors proposed a common aryl halide radical anion and an aryl radical as the key intermediates for aryl halide substrates. The construction of aryl–aryl bond under visible-light photoredox conditions has been achieved by using aryldiazonium salts[8] and diaryliodonium salts[9] as the radical precursors. In continuation of our interest in radical addition to aromatic rings,[10] we proposed a visible-light photoredox HAS pathway for the formation of biaryl compounds from aryl halides (Scheme 1). In the proposed mechanism, aryl halide radical anion was

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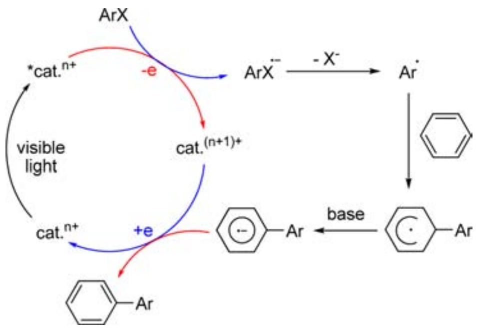
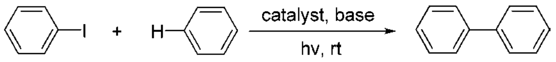
generated through SET from the visible-light excited photoredox catalyst, followed by the formation of an aryl radical via the dissociation of C−X bond to give up a halogen anion. The aryl radical then reacted with arene to form biaryl radical. In the presence of a strong base, the resulting biaryl radical was deprotonated to give biaryl radical anion. The highly reductive biaryl radical anion then transferred an electron to the oxidized photoredox catalyst to afford the biaryl product and fulfilled the catalytic cycle.

Scheme 1. Proposed Mechanism of Photoredox Homolytic Aromatic Substitution



To validate our proposal of the visible-light photoredox HAS of aryl halides with arenes, we started the investigation of the reaction between iodobenzene and benzene hoping to find mild HAS reaction conditions for the formation of biphenyl. The first set of the reaction conditions was iodobenzene (0.5 mmol) in benzene (3 mL, 67 equiv) with Ru(bpy)$_3$Cl$_2$·6H$_2$O (0.5 mol %) as the catalyst and KOBu^t (2 equiv) as the base. After irradiation under a 14 W compact fluorescent light for 24 h, only a trace amount of the desired biphenyl was observed (Table 1, entry 1). Because neither the catalyst nor base dissolved well in benzene, DMF and DMSO were added as cosolvents (entries 2 and 3). DMF did not affect the reaction, but the addition of DMSO provided the biphenyl in 6% yield. To our delight, the yield was improved to 74% by switching to Ir(ppy)$_3$ and increasing the base to 3 equiv (entry 4). DMSO seemed to be critical to the reaction. The reaction was almost shut down without DMSO or changing to DMF or MeCN (entries 5−7). The yields dropped to 34% and 0%, respectively, when the base was changed to NaOBu^t or LiOBu^t, indicating that the cation had significant impact on the reaction (entries 8 and 9). Similarly, using KOH gave 37% yield while using NaOH did not afford any biphenyl product (entries 10 and 11). No reaction occurred when organic bases, DIEA or Bu$_3$N, were used (entries 12 and 13). The amount of DMSO used in the reaction was also examined. Less DMSO (0.25 mL) gave a much lower 31% yield (entry 14), and more DMSO (1 mL) did not improve the yield either (entry 15). It is postulated that the combination of KOBu^t and DMSO, known as a superbase, might be involved in the deprotonation of biphenyl radical step in our proposed mechanism. When the system was degassed using freeze−pump−thaw procedure, the yield of biphenyl was increased to 85% (entry 16), suggesting that the reaction might be very sensitive to dioxygen. When the reaction was carried out without the photoredox catalyst, background reaction was observed. Biphenyl was formed in 20% yield after 24 h (entry 17). A similar result was reported very recently by Rossi and co-workers.[11] They achieved a much faster reaction in a photochemical reactor cooled with water using a strong light source (two HPI-T 400 W lamps) without photoredox catalyst under otherwise surprisingly similar conditions to ours. Rossi's and our results suggested that Ir(ppy)$_3$ effectively acted as a catalyst in the reaction. Iridium catalyst probably lowered the energy barrier of the radical initiation step. With the help of the catalyst, our reaction could be done using regular lab glassware under a household CFL lamp instead of a special photoreactor. Compared to the recent transition-metal free biaryl formation reactions that required high temperature,[3] our reaction occurred at room temperature probably due to the same reason. A reaction with 40 mol % of phenylpyridine instead of the Ir catalyst afforded biphenyl in 22% (entry 18). The yield was very close to that of the background reaction (entry 17). This result showed that the reaction was not a metal-free biaryl formation reaction catalyzed by the ligand. A control reaction done in the dark afforded only trace amount of biphenyl, indicating that the reaction was indeed a photochemical reaction (entry 19).

Table 1. Optimization of Reaction Conditions[a]



1 2a 3a

entry	catalyst	base	additive	yield[b] (%)
1	Ru(bpy)$_3$Cl$_2$	KOBu$^{t\,c}$		trace
2	Ru(bpy)$_3$Cl$_2$	KOBu$^{t\,c}$	DMF	trace
3	Ru(bpy)$_3$Cl$_2$	KOBu$^{t\,c}$	DMSO	6
4	Ir(ppy)$_3$	KOBu^t	DMSO	74
5	Ir(ppy)$_3$	KOBu^t	DMF	NR
6	Ir(ppy)$_3$	KOBu^t	MeCN	7
7	Ir(ppy)$_3$	KOBu^t		NR
8	Ir(ppy)$_3$	NaOBu^t	DMSO	34
9	Ir(ppy)$_3$	LiOBu^t	DMSO	NR
10	Ir(ppy)$_3$	KOH	DMSO	37
11	Ir(ppy)$_3$	NaOH	DMSO	NR
12	Ir(ppy)$_3$	DIEA	DMSO	NR
13	Ir(ppy)$_3$	Bu$_3$N	DMSO	NR
14	Ir(ppy)$_3$	KOBu^t	DMSO (0.25 mL)	31
15	Ir(ppy)$_3$	KOBu^t	DMSO (1 mL)	70
16	Ir(ppy)$_3$	KOBu^t	DMSO	85[d]
17		KOBu^t	DMSO	20
18	ppy[e]	KOBu^t	DMSO	22
19	Ir(ppy)$_3$	KOBu^t	DMSO	trace[f]

[a] Reaction conditions: iodobenzene (0.5 mmol), catalyst (0.5 mol %), base (3 equiv), additive (0.5 mL), and benzene (3 mL, 67 equiv), irradiated under a 14 W CFL at rt. [b] GC yield. [c] Base (2 equiv). [d] Freeze−thaw degassed. [e] 40 mol % of phenylpyridine. [f] Reaction was carried out in the dark.

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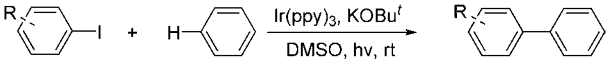
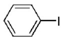
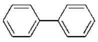
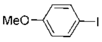
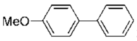
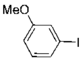
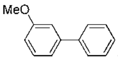
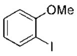
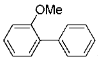
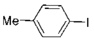
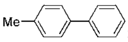
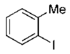
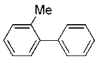
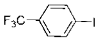
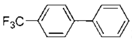
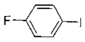
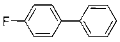
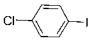
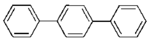
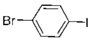
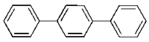
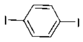
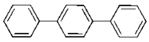
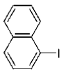
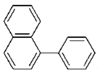
We then turned our attention to the investigation of the application of different aryl iodides in the visible-light photoredox HAS reaction with benzene. The results are summarized in Table 2. The aryl iodides bearing electron-donating groups worked well under the standard reaction conditions with benzene (entries 2–6). Steric effect seemed to have some impact on the reaction. The yields of the *ortho*-substituted aryl iodides were lower than the *para*-substituted ones (entries 2 and 4, entries 5 and 6). 1-Iodo-4-(trifluoromethyl)benzene gave the corresponding biphenyl in 67% yield (entry 7). However, methyl 4-iodobenzoate and 4′-iodoacetophenone did not provide any desired biphenyl products. 1,4-Haloiodobenzenes behaved differently. *p*-Fluoroiodobenzene afforded the *p*-fluorobiphenyl in 62% yield (entry 8). Other 1,4-Haloiodobenzenes provided *p*-terphenyl as the major product (entry 9–11), suggesting the reaction went through an intramolecular electron-transfer HAS mechanism.[3c,5] The reaction of 1-iodonaphthalene and benzene afforded the corresponding biaryl compound **3n** in 71% yield (entry 12).

Table 2. Visible-Light HAS Reactions of Aryl Iodide with Benzene[a]

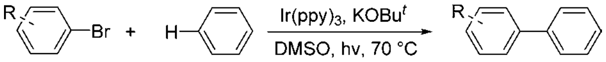


1 **2a** **3**

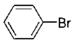
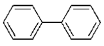
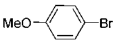
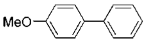
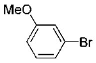
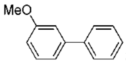
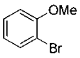
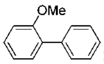
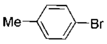
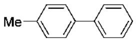
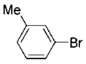
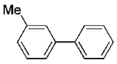
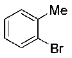
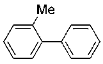
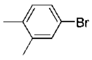
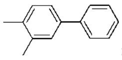
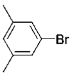
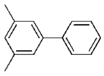
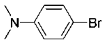
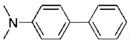
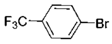
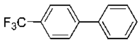
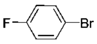
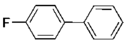
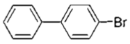
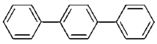
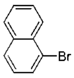
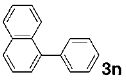
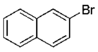
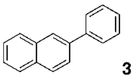
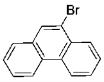
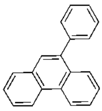
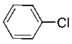
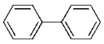
entry	aryl iodide	product	yield (%)[b]
1		 **3a**	85
2		 **3b**	76
3		 **3c**	89
4		 **3d**	62
5		 **3e**	72
6		 **3g**	65
7		 **3k**	67
8		 **3l**	62
9		 **3m**	61[c]
10		 **3m**	48[d]
11		 **3m**	46[e]
12		 **3n**	71

[a] Reaction conditions: aryl iodide **1** (0.5 mmol), KOBu^t (3 equiv), Ir(ppy)$_3$ (0.5 mol %), DMSO (0.5 mL), and benzene (3 mL, 67 equiv), irradiated under 14 W CFL at rt for 24 h. [b] Isolated yield. [c] 4% biphenyl formed by GC. [d] 5% biphenyl formed by GC. [e] 14% biphenyl formed by GC.

Table 3. Visible-Light HAS Reactions of Aryl Bromide with Benzene[a]



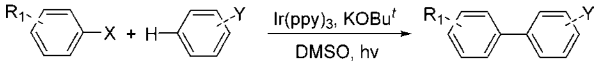
4 **2a** **3**

entry	aryl bromide	product	yield (%)[b]
1		 **3a**	79
2		 **3b**	80
3		 **3c**	45[c]
4		 **3d**	77
5		 **3e**	73
6		 **3f**	72
7		 **3g**	50
8		 **3h**	70
9		 **3i**	58
10		 **3j**	45[e]
11		 **3k**	40[d]
12		 **3l**	73[d]
13		 **3m**	72
14		 **3n**	51[c]
15		 **3o**	61
16		 **3p**	40[c]
17		 **3a**	35[fg]

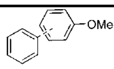
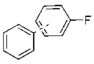
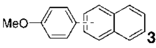
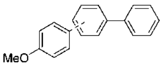
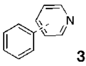
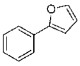
[a] Reaction conditions: aryl bromide **4** (0.5 mmol), KOBu^t (3 equiv), Ir(ppy)$_3$ (2.5 mol %), DMSO (0.83 mL), and benzene (5 mL, 112 equiv), irradiated under 14 W CFL at 70 °C for 36 h. [b] Isolated yield. [c] The reaction was carried out at room temperature. [d] The reaction was carried out at 35 °C. [e] The reaction temperature was 80 °C. [f] The reaction was carried out at 90 °C. [g] GC yield.

Compared to iodobenzenes, bromobenzenes would be more desirable substrates because they are usually more accessible and less expensive. The visible-light-promoted direct arylation reaction would find more synthetic applications if aryl bromides could be used. Therefore, we investigated the reaction of aryl bromide. Bromobenzene did not react under the standard conditions probably due to the fact that the C–Br bond is more difficult to reduce than a C–I bond. Nonetheless, satisfactory yield was

Table 4. Visible-Light HAS Reactions of Aryl Halides with Arenes[a]



3

entry	aryl halide	product	yield / ratio[b]
1	X = I	 **3q**	55% (o/m/p = 6.5/1.3/1)
2	X = Br		79% (o/m/p = 4.2/1.4/1)
3	X = I	 **3r**	83% (o/m/p = 2.8/1/2.21)
4	X = Br		62% (o/m/p = 3.8/1/4.2)[c]
5	X = Br	 **3s**	75% (α/β = 3.4/1)
6	X = Br	 **3t**	50% (o/m = 1.7/1)
7	X = I	 **3u**	80% (o/m/p = 3.5/1.1/1)
8	X = I	 **3v**	49%
9	X = Br		50%

[a] Reaction conditions: aryl iodide (0.5 mmol), KOBu^t (3 equiv), Ir(ppy)$_3$ (0.5 mol %), DMSO (0.5 mL), and arene (100 equiv), irradiated under 14 W CFL at rt for 24 h; or aryl bromide (0.5 mmol), KOBu^t (3 equiv), Ir(ppy)$_3$ (2.5 mol %), DMSO (0.83 mL), and arene (100 equiv) under 14 W CFL at 80 °C for 24 h. [b] Isolated yield. Isomeric ratios were determined by NMR. [c] The reaction was carried out at 70 °C.

obtained when the reaction temperature was elevated to 70 °C (Table 3, entry 1). Ir(ppy)$_3$ (2.5 mol %), DMSO (0.83 mL), and benzene (5 mL, 112 equiv) were identified to be the optimized conditions for the direct arylation of bromobenzene at 0.5 mmol scale. A scope survey of aryl bromides was conducted. In general, aryl bromides afforded similar results as those of aryl iodides (Table 3). For disubstituted bromobenzenes, 3,5-dimethylbromobenzene and 3,4-dimethylbromobenzene afforded the desired biphenyl products in 70% and 58% yields, respectively (entries 8 and 9). 2,6-Dimethylbromobenzene did not give any biphenyl product. This suggested that steric effects might have some impact either on the radical formation step or on the radical addition step. In several cases of aryl bromides with more labile C–Br bonds, the reaction temperature had to be lowered to get better yields. This was probably due to the radical intermediates being more reactive at high temperature and proceeding via a different reaction pathway. For 3-bromoanisole, only 14% yield was obtained at 70 °C. The yield of the product was increased to 45% at room temperature (entry 3). The reactions of 1-bromonaphthalene (entry 14) and 9-bromophenanthrene (entry 16) occurred at room temperature as well. The optimal reaction temperature was 35 °C for 1-bromo-4-fluorobenzene and 1-bromo-4-(trifluoromethyl)benzene (entries 11 and 12). Chlorobenzene was also tested. A higher reaction temperature was required for it to react. Biphenyl was formed in 35% yield at 90 °C (entry 17).

The visible-light-promoted HAS was not limited to the arylation of benzene. Several arenes were used as the substrates to demonstrate the applicability of the reaction (Table 4). Both anisole and fluorobenzene underwent HAS with iodobenzene and bromobenzene to afford the corresponding products as a mixture of regioisomers (entries 1–4). The different isomeric ratios in the products are probably due to the different reaction temperatures. *Ortho*-substituted products as the major products indicated that the reaction went through a radical pathway. Other arenes such as naphthalene and biphenyl were tested and gave direct arylation products as well (entries 5 and 6). Heteroatom containing arenes, such as electron-deficient pyridine and electron-rich furan, were able to react with aryl halides under the visible-light irradation conditions too (entries 7–9).

In summary, we have developed a mild visible-light-promoted homolytic aromatic substitution reaction. In this reaction, aryl iodides and bromides were activated under visible-light irradiation in a superbasic media. The resulting aryl radicals reacted with arenes intermolecularly to afford biphenyl derivatives.

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Supporting Information Available. Experimental procedures and ^{1}H and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.