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Direct Arylation of Alkenes with Aryl Iodides/Bromides through an Organocatalytic Radical Process

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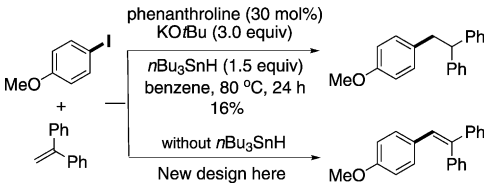
Dedicated to Professor Christian Bruneau on the occasion of his 60th birthday

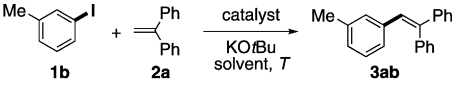
Radical addition into a carbon–carbon double bond is a fundamental and important process in radical chemistry.[1] The intramolecular radical addition to a C=C bond is regarded as an efficient tool for cyclization and has been widely developed and applied into organic synthesis.[2] In general, aryl radicals can be generated through many methods to process the radical addition.[3–5] For example, diazo compounds[4] and diaroyl peroxides[5] are efficient precursors to initiate the homolytic cleavage of Ar–X to generate aryl radicals. Recently, Itami and co-workers reported a KO*t*Bu-promoted coupling of electron-deficient nitrogen heterocycles with aryl iodides.[6] Later, we and other groups reported additional examples of transition-metal-free couplings of arenes with aryl halides, which were promoted by KO*t*Bu together with a catalytic amount of phenanthroline derivatives or DMEDA (*N*,*N*′-dimethylethane-1,2-diamine).[7] Such a reported process is now identified as a new radical pathway. To confirm the radical intermediate in our previous investigation, we carried out the addition of 4-iodoanisole (**1a**) towards 1,1-diphenylethylene (**2a**) in the presence of nBu$_3$SnH and an alkene hydroarylation product was observed albeit in a low yield (Scheme 1).[7a] We envision that, in the absence of the hydrogen source, such aryl radicals might undergo an addition to a C=C bond followed by hydrogen elimination to carry out the arylation of olefins.

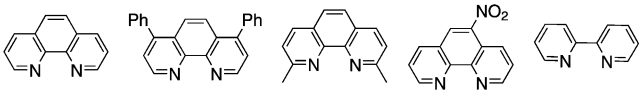
With this idea in mind, 1,1-diphenylethylene (**2a**) was selected as the substrate. The arylation of **2a** was obtained under suitable conditions in the presence of KO*t*Bu and various dinitrogen compounds (Table 1). After screening several catalysts, we found that bathophenanthroline (bathophen)



Scheme 1. Our previous observation and design of a radical arylation of alkenes with aryl halides.

Table 1. A radical arylation of 1,1-diphenylethylene with 3-iodotoluene under different reaction conditions.[a]





Entry	Catalyst	Solvent	T [°C]	Yield[b] [%]
1	phen	benzene	110	63
2	neo	benzene	110	51
3	NO_2-phen	benzene	110	18
4	bipy	benzene	110	5
5	DMEDA	benzene	110	18
6	bathophen	benzene	110	95 (90)[g]
7[c]	bathophen	benzene	110	71
8[d]	bathophen	benzene	110	45
9[e]	bathophen	benzene	110	58
10	bathophen	benzene	100	65
11[f]	bathophen	benzene	110	73
12	–	benzene	110	0
13	bathophen	mesitylene	110	55
14	bathophen	DMF	110	16
15	bathophen	dioxane	110	82
16	bathophen	diglyme	110	61

[a] The reactions were carried out in the scale of 0.5 mmol of **1b** in the presence of a catalyst (0.3 equiv), **2a** (3.0 equiv) and KO*t*Bu (3.0 equiv) in benzene (1 mL) in sealed Schlenk tubes for 36 h. [b] The yields of the product **3ab** were determined by GC. [c] Catalyst (0.2 equiv) was added. [d] Compound **2a** (2.0 equiv) was added. [e] Benzene (2 mL) was added. [f] Reaction time was 24 h. [g] Isolated product yield.

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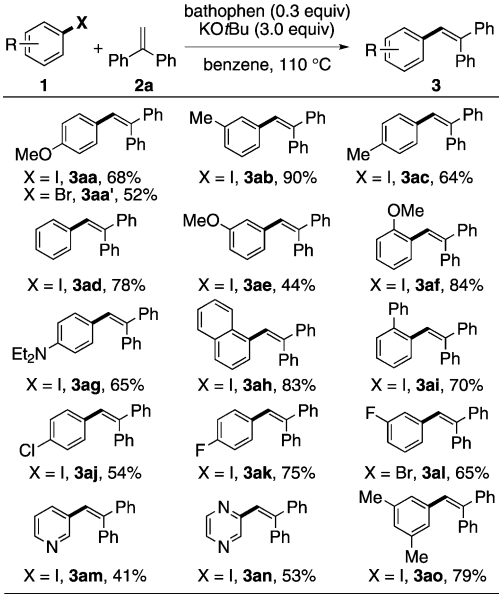
exhibits the best catalytic ability (Table 1, entries 1–6). In the presence of bathophen (30 mol%) and KO*t*Bu (3.0 equiv), such an arylation between 3-iodotoluene (**1b**) and **2a** takes place at 110°C and the product **3ab** is obtained in 90% yield (Table 1, entry 6). The reaction has the same outcome as the Mizoroki–Heck cross-coupling,[8] however, it proceeds through an organocatalytic radical process in the absence of any additional transition-metal catalysts. Although the previous studies indicated that the arylation of aryl halides with benzene ran smoothly at 80–100°C,[7] benzene is found as the best solvent in this report (see Table 1, entry 6 and entries 13–16), with only a trace amount of biaryl as the byproduct. This result indicates that the arylation of olefination is highly preferred. It is noteworthy that when lowering the amount of **2a**, or diluting the reaction mixture, the yields of **3ab** diminish and the amount of the competitive phenylation byproduct increases (Table 1, entries 8 and 9). Lowering the amount of bathophen or temperature or shortening the reaction time leads to an incomplete conversion (Table 1, entry 7, 10, and 11). Moreover, the absence of bathophen terminates the reaction (Table 1, entry 12).

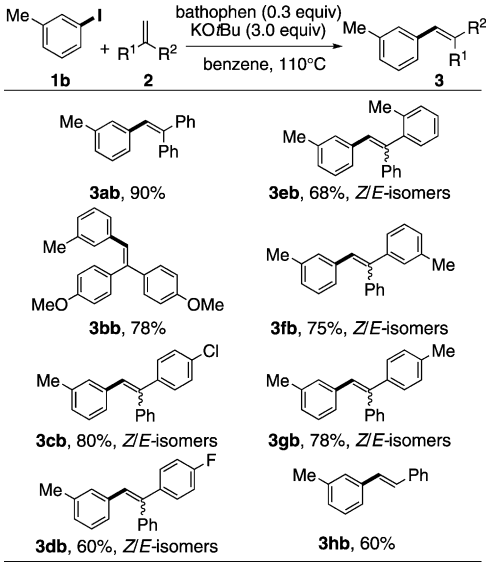
Various aryl halides were further investigated (Scheme 2). *Para*-electron-donating substitutents gave the products in moderate yields (compounds **3aa**, **3ac**, and **3ag**), whereas the *meta*-methoxy substituent shows the worst reactivity (compound **3ae**). *o*-Iodoanisole exhibits an exceptional reactivity and the desired product **3af** is isolated in 84% yield. The *meta*-methyl substituent (**3ab**) promotes the efficiency a great deal, however, this cannot be well explained at this stage. Other substitutents, for example, naphthyl (**3ah**), phenyl (**3ai**), and less reactive halides (such as Cl and F, compounds **3aj**, **3ak**, and **3al**) are well tolerated, offering the potential for further orthogonal functionalizations.[9] Heterocyclic iodides are also suitable, albeit with slightly lower efficacy (compounds **3am** and **3an**). Notably, aryl bromides with either electron-donating or electron-withdrawing groups, for example, 4-bromoanisole and 1-bromo-3-fluorobenzene (compounds **3aa**, X = Br, and **3al**), are suitable; however, the relatively low efficacy may arise from the lower reactivity of C–Br bond.

Other alkene derivatives were surveyed (Scheme 3). The presence of different substituents on aryl group does not affect the efficiency significantly and the desired products **3** are obtained in good to excellent yields (**3ab**–**3gb**). However, different geminal aryl substituents induce a mixture of two stereoisomers, which cannot be separated by chromatography due to their similar polarities (**3cb**–**3gb**). The electronic and steric effects influence the ratio of two isomers (see Scheme 3, compounds **3eb** to **3fb** and **3gb**). Similarly, the compatibility of OMe, Cl, and F provides the potential for further functionalization (Scheme 3, **3bb**–**3db**).[8–10] Notably, styrene is also a good substrate and only the *trans* isomer (**3hb**) is obtained in 60% yield, which shows the same selectivity as the traditional Mizoroki–Heck reaction.[8b] Unfortunately, aliphatic alkenes are not suitable for this transformation.

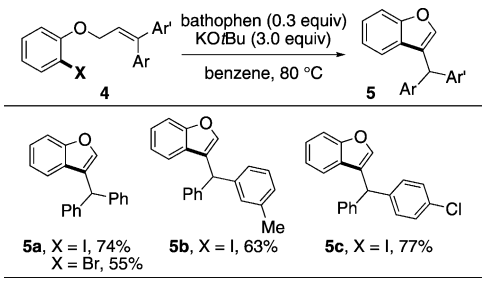
We further explored the intramolecular radical cyclization to construct heterocycles. Starting from easily available *ortho*-iodophenyl allyl ether **4**, the 3-substituted benzofurans **5** are produced in good yields (Scheme 4). During this transformation, a C=C migration takes place to produce thermo-



Scheme 2. Direct arylation of **2a** with various aryl halides. The reactions were carried out in the scale of 0.5 mmol of **1** in the presence of catalyst (0.3 equiv), **2a** (3.0 equiv) and KO*t*Bu (3.0 equiv) in benzene (1 mL) in sealed Schlenk tubes for 36 h. All the yields are those of the isolated products.



Scheme 3. Direct arylation of various alkenes with **1b**. The reactions were carried out in the scale of 0.5 mmol of **1b** in the presence of catalyst (0.3 equiv), **2** (3.0 equiv) and KO*t*Bu (3.0 equiv) in benzene (1 mL) in sealed Schlenk tubes for 36 h. All the yields are those of the isolated products. For **3eb**, **3fb**, **3cb**, **3gb**, and **3db**, the yield is a total of two isomers and the exact ratio of two isomers could not be determined because the two isomers are unknown compounds and their separation is difficult. For **3hb**, 10 equiv of styrene was added in this reaction.

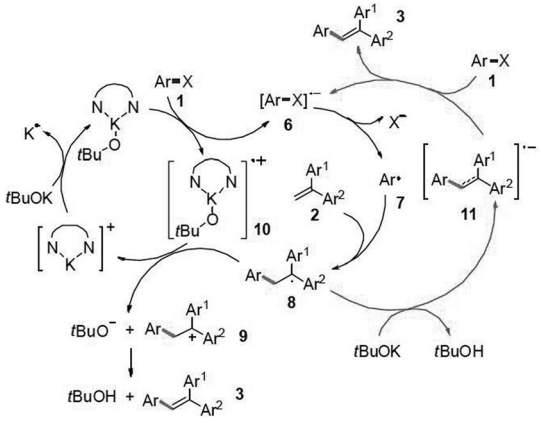


Scheme 4. Intramolecular radical coupling and synthesis of 3-substituted benzofurans. The reactions were carried out in the scale of 0.5 mmol of **4** in the presence of catalyst (0.3 equiv) and KO*t*Bu (3.0 equiv) in benzene (3 mL) in sealed Schlenk tubes at 80 °C for 15 h. All the yields are those of the isolated products.

dynamically stable benzofuran derivatives. Moreover, from the corresponding bromo derivatives, the desired benzofuran **5a** is also produced, albeit in a lower yield. This reaction offers a simple method to construct benzofuran structural units from commercially available 2-halophenols and allyl alcohols. As we know, in traditional Pd^0 chemistry, the benzylic and allylic C–O bonds are easily cleaved for various transformations.[11] The herein reported method offers a complementary pathway to traditional Pd^0 chemistry.

A possible mechanism is proposed as Scheme 5. The complex of KO*t*Bu with dinitrogen ligands is considered to be a radical precursor. After the single electron transfer (SET) to ArX, a radical anion **6** is generated that further undergoes a dehalogenation to generate an aryl radical **7** to initiate the radical process. Aryl radical **7** adds to 1,1-diarylethylene **2** to produce a new radical **8**, which is stabilized by aryl groups. From radical **8**, two possible pathways are presented. One pathway is another SET to form benzyl cation, followed by deprotonation with the assistance of tBuO$^-$. The other pathway is a deprotonation occurs first on radical **8** in the presence of base to generate another radical anion **11**, followed by a SET with ArX to produce the product **3** and the radical anion **6** to process the radical chain.[12]

In summary, we have reported an unprecedented radical arylation of polysubstituted alkenes with aryl halides promoted by KO*t*Bu and bathophenanthroline. This transformation prefers the polysubstituted olefins, which offers a complementary process to traditional Mizoroki–Heck reactions. With this development, 3-substituted benzofurans are constructed from easily available chemicals. Further understanding of this process and its applications in organic synthesis are underway.



Scheme 5. Possible mechanism of this radical process.

Experimental Section

General procedure for direct arylation of alkenes: Catalysts, alkenes (if solid) and aryl bromides/iodides (if solid, 0.5 mmol) were added into Schlenk tubes. KO*t*Bu was added into Schlenk tubes in glove box. Aryl bromides/iodides (if liquid, 0.5 mmol) and alkenes (if liquid) were added into tubes by syringe. The solvent benzene was added by syringe. The tubes were degassed and refilled with N_2. The mixture was stirred under N_2 atmosphere in sealed Schlenk tubes at the corresponding temperature. The reaction was cooled down to room temperature. The mixture was filtered through a short plug of silica gel and washed with copious amounts of ethyl acetate. The combined organic phase was concentrated under vacuum. The product was purified through flash column chromatography on 200–300 mesh silica gel with petroleum ether/ethyl acetate as eluent with a suitable ratio according to the TLC experiments.

General procedure for intramolecular annulation: Catalysts and substrates (if solid, 0.5 mmol) were added into Schlenk tubes. KO*t*Bu was added into Schlenk tubes in glove box. The substrates (if liquid, 0.5 mmol) were added into Schlenk tubes by syringe. The solvent benzene was added by syringe. The tubes were degassed and refilled with N_2. The mixture was stirred under N_2 atmosphere in sealed Schlenk tubes at 80 °C for 15 h. The reaction was cooled down to room temperature. The mixture was filtered through a short plug of silica gel and washed with copious amounts of ethyl acetate. The combined organic phase was concentrated under vacuum. The product was purified through flash column chromatography on 200–300 mesh silica gel with petroleum ether/ethyl acetate as eluent with a suitable ratio according to the TLC experiments.

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Keywords: alkenes · benzofuran · C–C addition · organocatalysis · radicals

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