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A Strategy for Generating Aryl Radicals from Arylborates by Using Organic Photoredox Catalysis: Photo-Meerwein Type Arylations of Electron-Deficient Alkenes

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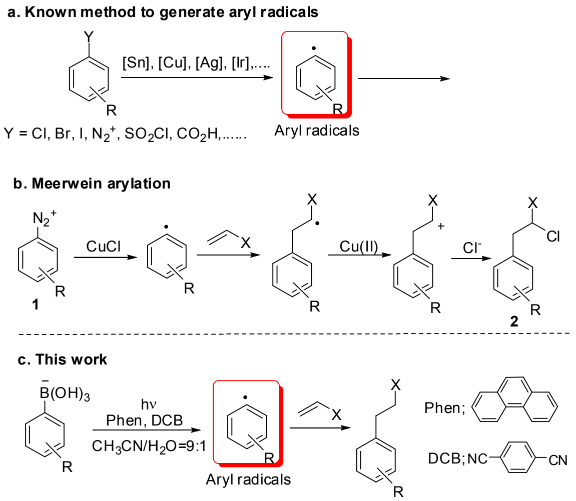
Photoinduced reactions of arylboronic acids with electron deficient alkenes under mild organic photoredox catalysis conditions lead to formation of Meerwein arylation type adducts via generation of aryl radicals. Direct evidence for generation of aryl radicals in these photoreactions comes from the observation of TEMPO trapping.

Aryl radicals are useful reactive intermediates in reactions that introduce aryl groups.[1] Generation of aryl radicals typically requires the use of both stoichiometric amounts of toxic metals and/or sensitive substrates, such as aryl halides and aryl diazonium salts, as well as harsh reaction conditions (Scheme 1a).[2-7] In particular, methodology for C–C bond formation by addition of aryl radicals to alkenes is limited to Meerwein arylations using aryl diazonium salts **1** and CuCl (Scheme 1b).[8,9] In this process, an aryl diazonium salt is reduced by Cu(I) to generate an aryl radical, which adds to an electron-deficient alkene giving a radical that is then oxidized by Cu(II) to produce a corresponding cation that serves as the precursor of the adduct **2**. Although this reaction leads to C–C bond formation, diazonium salts bearing sensitive substituents can't be used as substrates and they are often dangerously explosive and toxic. Therefore, the development of a new approach to generate aryl radicals from stable precursors without the use of metals and under mild conditions is a desirable goal.

Recently, we described a general method for generating alkyl radicals from aliphatic carboxylates that involves decarboxylation of carboxy radicals produced using light and organic photoredox catalysts such as phenanthrene (Phen) and 1,4-dicyanobenzene (DCB).[10,11] In addition, we observed that the generated alkyl radicals react with a variety of reagents to form products in high yields. Although this photoinduced decarboxylative radical generation protocol has synthetic advantages, it can't be employed to generate aryl radicals from benzoates under similar photoredox catalysis conditions. This finding encouraged us to conduct a screen to uncover suitable substrates for the generation of aryl radicals using the photoredox procedure. In this effort, we found that arylboronic acids and arylborates, which are stable, commercially available substances frequently used in Suzuki-Miyaura coupling reactions[12], are useful substrates for photochemical aryl radical generation (Scheme 1c). The results of the investigation that led to the development of a new method both for generating aryl radicals from aryl-boronic acids and -borates as part of C–C bond forming addition reactions with alkenes are described below.



Scheme 1. Generating aryl radicals and Meerwein arylation.

In the initial phase of this study, we explored the photoredox promoted reaction of phenylboronic acid **3a** with acrylonitrile **4a**. This effort, in which the effects of **4a** concentration, and the nature of photocatalyst, solvent and base were assessed (Table S1–S3 (ESI)), demonstrated that adduct **5aa** formation occurs optimally when a room temperature aqueous acetonitrile solution (CH_3CN/H_2O=9:1 (v/v)) containing **3a** (20 mM), 5 equiv. of **4a** (100 mM), 1 equiv. of NaOH (20 mM), phenanthrene (Phen, 50 mol%, 10 mM), and 1,4-dicyanobenzene (DCB, 50 mol%, 10 mM) under argon is irradiated (100 W high-pressure mercury lamp, Pyrex vessels (λ > 280 nm), 15 × 180 mm) for 6 h. This process generates adduct **5aa** in 78% yield (Entry 1, Table 1) along with almost

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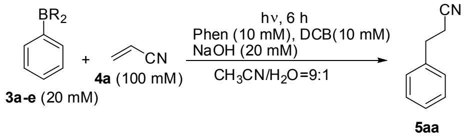
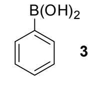
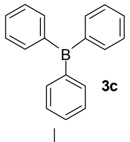
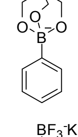
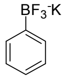
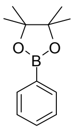
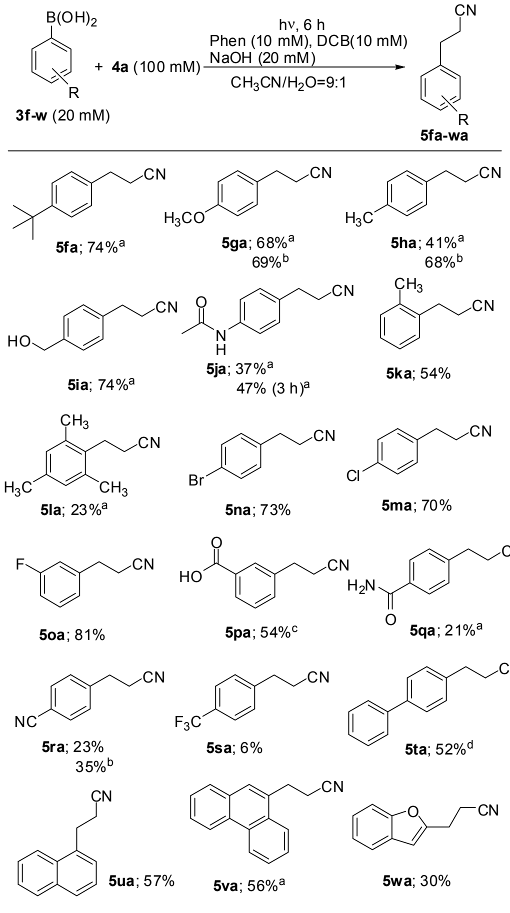
Table 1. Photo-Meerwein type arylation of **3** with **4a**[a]



Entry	3	Yield of **5aa**/%	Entry	3	Yield of **5aa**/%
1	 **3a**	78	5	 **3c**	43
2[b]	**3a**	64	6[d]	 **3d**	48
3[c]	**3a**	43	7[d]	 **3e**	11
4	 **3b**	73			

[a]Photoreactions of $CH_3CN/H_2O=9:1$ containing **3** (20 mM), **4a** (100 mM), Phen (10 mM), and DCB (10 mM) for 6 h at room temperature under an Ar atmosphere. [b][Phen]=5 mM, [DCB]=5 mM, irradiation time 12 h. [c][**3a**]=5 mM, [**4a**]=25 mM, [Phen]=2 mM, [DCA]=2 mM, 28 W blue LED, and irradiation time 12 h. [d]In the absence of NaOH.

Table 2. Arylbonic acid scope of photoreaction with **4a**



[a]$CH_3CN/H_2O=7:3$. [b]The corresponding ArBpin was used as a reactant. [c]$CH_3CN/H_2O=7:3$, [NaOH]=40 mM. [d]$CH_3CN/H_2O=7:3$ at 50 °C.

quantitatively recovered Phen and DCB. Photoreactions using lower concentrations of Phen (5 mM) and DCB (5 mM) and employing longer irradiation times (12 h) were found to produce **5aa** in only moderate yield (64%, Entry 2). Blue LED (28 W) derived visible light induced reaction of **3a** (5 mM) with 5 equiv. of **4a** (25 mM) using Phen (2 mM) and 9,10-dicyanoanthracene (DCA, 2 mM) for 12 h also led to formation of **5aa** in a slightly decreased yield (43%, Entry 3). In the absence of light, NaOH, Phen or DCB, or both Phen and DCB, **5aa** is not generated. These observations indicate that both a photoredox catalytic system and the borate, formed by reaction of **3a** with NaOH, are essential for the reaction to take place. Finally, an examination of reactions of borates such as **3b–e**, which can potentially serve as phenyl radical precursors, under the same photochemical conditions showed that **5aa** is produced. Specifically, we observed that photoreactions of PhBpin **3b** and triphenylborane **3c** with **4a** in the presence of 1 equiv. of NaOH (Entries 4 and 5), as well as those of borates **3d** and **3e** in the absence of NaOH (Entries 6,7) take place to form **5aa** in lower yields.

In an effort aimed at elucidating the boronic acid scope of the new process, photoreactions of variously substituted arylboronic acids **3f–w** with **4a** were investigated (Table 2). In cases of arylboronic acids **3f–j**,**l**,**p**,**q**,**t**,**v**, $CH_3CN/H_2O=7:3$ instead of $CH_3CN/H_2O=9:1$ solution was used, and reaction of **3t** required heating at 50 °C because of the low solubility of this substrate. When the corresponding ArBpin substrates are used in the place of arylboronic acids **3g**,**h**,**r**, yields of the respective adducts **5ga** and **5ha**,**ra** are higher, a likely result of the increased solubilities of the Bpin derivatives. The photoreactions of arylboronic acids **3f–i** bearing electron-donating groups at *para*-position react efficiently to yield the corresponding adducts **5fa–ia** in high yields. An exception to this trend is the reaction of **3j**, which forms **5ja** in a low yield because of the occurrence of a secondary photoreaction of photoproduct **5ja**. The yield of **5ja** can be enhanced by carrying out the reaction for a shorter time (3 h). Reactions of sterically hindered *ortho*-methylaetd arylboronic acids **3k**,**l** take place to form the respective adducts **5ka**,**la** in lower yields, whereas the halogenated arylboronic acids **3n–o** undergo efficient photoredox catalyzed reactions generating the corresponding adducts **5na–oa** in high yields. Moreover, photoreaction of **3p** bearing unprotected carboxylic acid group in the presence of 2 equiv. of NaOH undergoes this reaction to yield adduct **5pa** in a moderate yield. In contrast to the high efficiencies of arylation reactions with electron-donating group substituted systems, those of *para*-electron-withdrawing group ($CONH_2$, CN, and CF_3) substituted arylboronic acids, **3q–s** occur in significantly decreased yields. This is likely a consequence of the lower rates of addition of electron-deficient aryl radicals to electron-deficient alkenes, which competes with reduction of the aryl radicals by hydrogen atom transfer from CH_3CN (see below). In fact, in the case of **3p**, reduction product (benzoic acid) was obtained in 15% yield along with adduct **5pa**. Biphenyl-, naphthyl-, phenanthyl- and benzofuryl-boronic acids **3t–w** were found to participate in moderately yielding photoreactions that produce the respective adducts **5ta–wa**, while *N*-Boc-2-pyrrolyl- and 2-furyl-boronic acids are not substrates for this process. The combined results show that a variety of arylboronic acids participate in C–C bond forming, photoredox catalyzed addition reactions with **4a** in yields that

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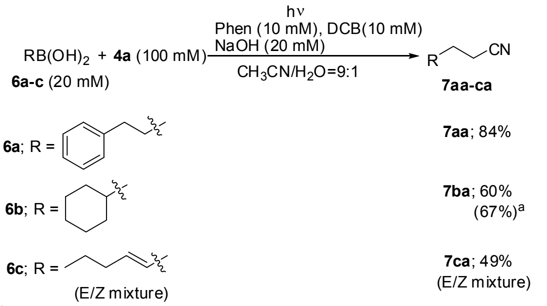


^{a}[biphenyl]=10 mM, [DCN]=10 mM, [**4a**]=20 mM.

Scheme 2. Photoreactions of alkyl- and alkenyl-boronic acids **6** with **4a**

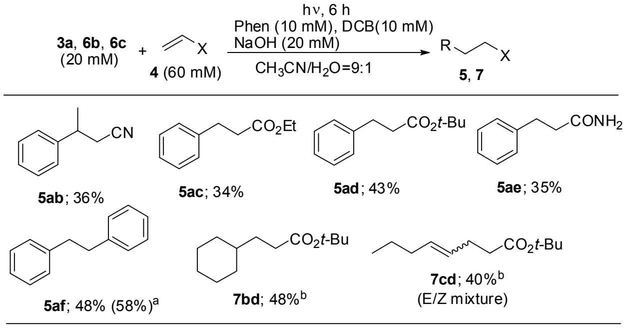
depend on the electronic nature of arene ring substituents.

The reactivity of alkyl- and alkenyl-boronic acids **6a–c** with **4a** under the photoredox catalyzed conditions was examined. The results show that these reactions take place to form the corresponding adducts **7aa–ca** in moderate to high yields (Scheme 2). The photoreaction of cyclohexylboronic acid **6b** with 1 equiv. of **4a** (20 mM) using biphenyl (10 mM) and 1,4-dicyanonaphthalene (DCN, 10 mM) in place of Phen and DCB occurs in a slightly higher yield (67%).

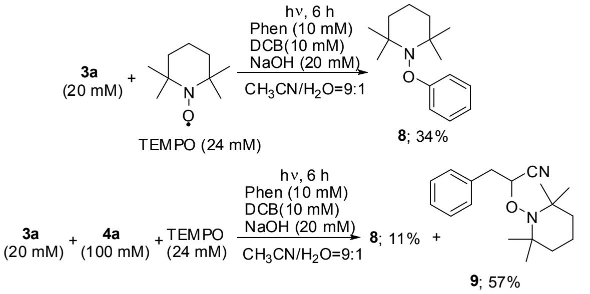
To determine the alkene scope of the process, we explored reactions of **3a** using 3 equiv. of the alkenes, crotononitrile **4b**, ethyl acrylate **4c**, *t*-butyl acrylate **4d**, acrylamide **4e**, and styrene **4f** under the same conditions. All of these photoredox promoted reactions lead to low yielding formation of the corresponding adducts **5ab–af** along with oligomeric materials (Table 3). In the case of styrene, a higher yield of adduct **5af** formation occurs when 5 equiv. of styrene is used. Finally, photoreactions of the alkyl- and alkenyl-boronic acid **6b**,**c** with 1 equiv. of *t*-butyl acrylate **4d** produce adducts **7bd**,**cd** in only moderate yields.

To gain information about the participation of aryl radicals as intermediates in the mechanistic pathway for the photoredox catalyzed addition reaction, TEMPO radical trapping was performed (Scheme 3). Reaction of **3a** in the absence of **4a** and presence of 1.2 equiv. of TEMPO under the optimal conditions described above was found to produce the *O*-phenyl-TEMPO coupling product **8** (34%). Also, reaction in the presence of **4a** and TEMPO generates products arising from TEMPO trapping of both the initially formed phenyl radical trapping (**8**) and the radical generated by addition of the phenyl radical to **4a** (**9**) in 11% and 57% respective yields. These results clearly indicate that aryl radicals are generated from arylboronic acids under the photoredox catalysis conditions and also that these radicals undergo radical addition to alkenes.

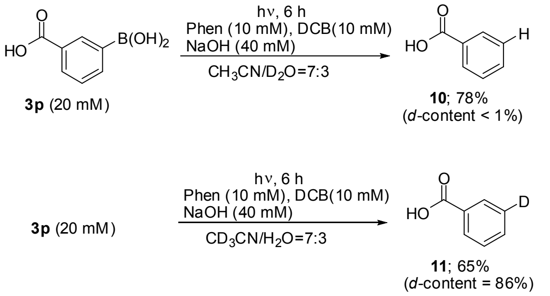
Table 3. Scope of alkene **4** in the photoreaction of **3a, 6b**, and **6c**



^{a}[**4f**]=100 mM. ^{b}[**4d**]=20 mM



Scheme 3. TEMPO trapping of radicals in the photoreaction of **3a**



Scheme 4. Deuterium labeling study of the photoreaction of **3p** in D$_2$O/CH$_3$CN and H$_2$O/CD$_3$CN

Additional mechanistic insight into this process comes from the results of deuterium labeling experiments. Specifically, we observed that irradiation of solutions of **3p**, Phen, DCB and 2 equiv. of NaOH in CH$_3$CN/D$_2$O=7:3 results in the generation of benzoic acid **10** containing less than 1% of deuterium (Scheme 5). In contrast, this process carried out in CD$_3$CN/H$_2$O=7:3 solution results in formation of *m*–deuteriobenzoic acid **11** with an approximately 86% *d*-content (Scheme 4). These findings indicate that, in the absence of an electron deficient alkene, the aryl radical intermediate abstracts a hydrogen atom from CH$_3$CN to form a reduced product.

Based on the results emanating from this study, it is possible to suggest that the photoredox catalyzed reactions take place via the mechanistic pathway depicted in Scheme 5. In this route, photoinduced electron transfer takes place between the excited state of Phen (Phen*), generated by direct light absorption, and DCB to form the radical cation of Phen and the radical anion of DCB. The radical cation of Phen then oxidizes the arylborate, formed by the reaction of **3** with NaOH. This step is thermodynamically favorable because the oxidation potential of a borates (tetraphenylborate +0.22 V *vs.* SCE in CH$_3$CN)[13] should be lower than that of Phen (+1.50 V *vs.* SCE in CH$_3$CN).[14] The homolysis of B-Ar bond of ArB(OH)$_3$ radical **12** smoothly takes place.[15,16] The aryl radical produced in this manner then adds to the electron-deficient alkene **4** to form radical that subsequently participates in back electron transfer with the radical anion of DCB to form a carbanion, which undergoes protonation to yield adduct **5**. The quantum yield of

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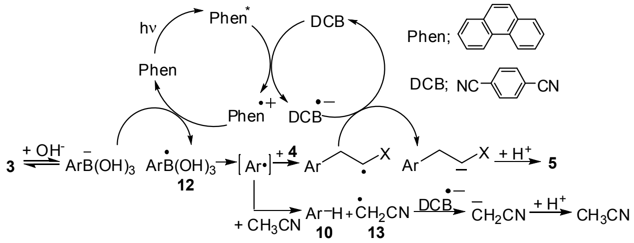

Scheme 5. A plausible mechanism in the photoreaction of **3** and **4**.

this photoinduced radical addition of **3a** to **4a** is about 0.2. In contrast to the analogous photoreaction of alkyl carboxylic acids that take place via decarboxylation to produce alkyl radicals, reactions of the arylborates require the use of 5 rather 1 equiv. of an alkene. The difference is a likely consequence of the higher reactivity of aryl radicals, which can abstract a hydrogen atom from CH_3CN to produce a reduced product **10**. The back transfer from the radical anion of DCB to the resulting cyanomethyl radical **13** generates cyanomethyl anion followed by the protonation to reproduce CH_3CN as reported by us.[17] Thus, the competitive radical reduction and addition processes are existed in the photoreaction, and the high rate of the radical addition to alkene requires the high concentration (100 mM) of alkene. Unfortunately, the use of a high alkene concentration (> 100 mM) makes oligomerization more efficient, and requires the high concentrations of photocatalyst for preventing oligomerization.[18]

In conclusion, the results of this effort show that aryl-boronic acids and -borates undergo photoredox catalyzed addition reactions with electron deficient alkenes via a pathway involving the intermediacy of aryl radicals. The process represents a new type of Meerwein arylation, in which stable arylboronic acids serve as substrates. Also, the process takes place using alkyl- and alkenyl-boronic acids. A variety of aryl-boronic acids and borates, and alkenes are acceptable substrates for this photoreaction. The process represents a new synthetic method for introducing aryl groups. Further investigations of the applicability of this methodology in synthetic organic chemistry are underway.

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Conflicts of interest

There are no conflicts to declare.

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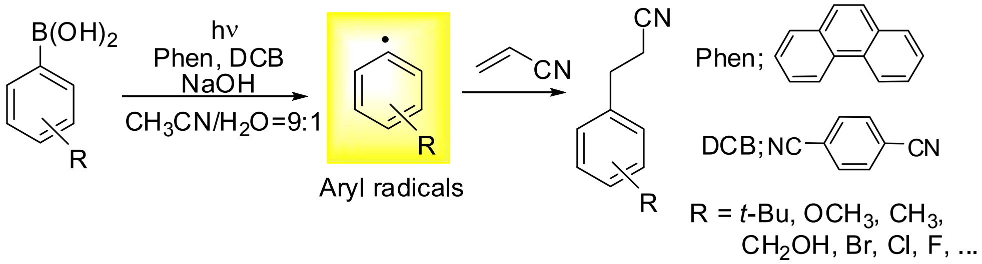

Generation of a variety of aryl radicals from arylboronic acids by using metal-free photoredox catalysis under mild conditions