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Simple and efficient generation of aryl radicals from aryl triflates: synthesis of aryl boronates and aryl iodides at room temperature

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ABSTRACT: Despite the wide use of aryl radicals in organic synthesis, current methods to prepare them from aryl halides, carboxylic acids, boronic acids and diazonium salts suffer from limitations. Aryl triflates, easily obtained from phenols, are promising aryl radical progenitors but remain elusive in this regard. Inspired by single electron transfer process for aryl halides to access aryl radicals, we developed a simple and efficient protocol to convert aryl triflates to aryl radicals. Our success lies in exploiting sodium iodide as the soft electron donor assisted by light. This strategy enables the scalable synthesis of two types of important organic molecules i.e. aryl boronates and aryl iodides in good to high yields, with broad functional group compatibility in a transition metal-free manner at room temperature. This protocol is anticipated to find potential applications in other aryl radical-involved reactions by using aryl triflates as aryl radical precursor.

1. Introduction

Aryl radicals are versatile synthetic intermediates in organic chemistry.¹⁹ In addition, they also play interesting roles in biology, such as in the DNA cleavage process.¹⁰ However, due to their high reactivity, aryl radicals can only be accessed from limited functional groups, including aryl halides,¹¹⁻¹² aryl carboxylic acids,¹³⁻¹⁶ aryl boronic acids,¹⁷⁻²¹ aryl diazonium salts²²⁻²³ as well as their variations.^{3, 24-25} Although these methods have found broad applications, they still suffer from at least one of the following limitations: 1) toxic or expensive reagents, such as tin or silicon reagents, are used for aryl halides; 2) stoichiometric amounts of harsh oxidants or reductants, such as K₂S₂O₈ or Mn(OAc)₂ are used for aryl carboxylic acids or boronic acids, and SmI₂ for aryl halides or aryl diazonium salts; 3) transition metals, such as silver salt, are used for aryl boronic acids and aryl carboxylic acids; 4) energy intensive reagents aryl diazonium salts are used directly (Scheme 1a). Therefore, developing an approach to generate aryl radicals, which can exploit more sustainable precursor without harsh oxidants or reductants and in a transition metal-free manner would be highly desirable.

Aryl triflates are common reactants in coupling reactions, such as the Suzuki and the Stille couplings among many others.²⁶⁻²⁹ Aryl triflates are synthesized from phenols, which can be obtained from abundant and renewable biomass, for instance lignin and coal.^{30-3¹ In this context, aryl triflates as well as other phenol derivatives³²⁻³⁶ carry more advantages towards sustainable chemical synthesis than other aryl compounds. To} the best of our knowledge, despite these benefits, aryl triflates and other phenol derivatives have never been employed to prepare aryl radicals.³⁷⁻³⁸ To fill this gap, herein we described a simple and efficient approach to access aryl radicals from aryl triflates under mild conditions in absence of transition metal-catalyst at room temperature (Scheme 1b). Moreover, to illustrate its synthetic utility, we have demonstrated that this approach allows the efficient and scalable synthesis of two types of organic compounds i.e. aryl boronates and aryl iodides, which represent the two reactants among one of the most important cross-coupling reactions i.e. Suzuki coupling in modern chemical science.

2. Results and discussion

2.1. Research design. In 2008, the Itami group reported a transition-metal-free approach to synthesize biaryls from aryl halides and electron-deficient nitrogen heterocycles promoted by t-BuOK.³⁹ Following this seminal work, Hayashi⁴⁰, Shi⁴¹, Lei⁴² and many others⁴³⁻ ⁵² further extended the scope of electron-deficient arenes to regular arenes by adding catalytic amounts of nitrogen bases or other promoters in presence of t-BuOK or t-BuONa. This type of reaction, via aryl radical addition onto the arenes, is called the "homolytic aromatic substitution".53-54 Recently, Murphy group, Lei group and Jiao group have conducted mechanistic investigations on how aryl radicals were generated in these reactions.⁵⁵⁻⁶² Their studies suggest a singleelectron-transfer process (SET) from the initiators to aryl halides. Following SET, the aryl halide radical anions tend to fragment to produce aryl radicals and

Scheme 1. a): Known methods to generate aryl radicals. b): This work.



halide anions. Usually, these *t*-BuOK-involved reactions require high temperature to induce the SET. In addition to the thermal-driven approaches, photoinduced aryl radical formation methods were also reported at room temperature, known as photo induced electron transfer (PET).⁶³⁻⁶⁷ Inspired by these precedents (Scheme 2a), we hypothesized that an analogous SET could also occur from an appropriate electron donor to aryl triflates to induce the fragmentation and subsequently generate aryl radicals.

Although this hypothesis is conceptually simple, two major challenges remain to overcome in order to realize this SET strategy from aryl halides to aryl triflates. First, above-mentioned methods suitable for aryl halides require *t*-BuOK(or *t*-BuONa) and electron-rich additives (usually strong nucleophiles after deprotonation by *t*-BuOK)⁵⁷, which are incompatible with aryl triflates. These strong nucleophiles would react with aryl triflates to generate phenol salts through additionelimination mechanism⁶⁸ (Scheme 2b, path 1). Second, even when SET occurs, the sulfur atom in aryl triflates as the most electron-deficient site instead of the arene ring would accept the electron and aryl triflates would be eventually reduced to phenol salts instead of the desired aryl radicals⁶⁹⁻⁷⁰ (Scheme 2b, path 2). For

Scheme 2: a): Well studied process to convert aryl halides into aryl radical via SET. b): Challenges for aryl triflates to undergo SET. c): Design strategy for aryl triflates as the radical precursor.



example, Murphy and co-workers have shown that aryl triflates are reduced to phenols in high yields via S-O cleavage with super electron donors as the reductants.⁶⁹ Yus and co-workers have also shown that even in presence of stoichiometric amount of NiCl₂, the major products of aryl triflates under Birch reduction conditions are phenols as well.⁷¹ Jutand and coworkers disclosed that aryl triflates can be mainly reduced to phenols under electro-chemical conditions even in presence of palladium catalyst together with C-O bond cleavage products.⁷² It is noteworthy that transition metal catalysts including Pd and Ni can insert into the C-O bonds in triflates, which would facilitate the reduction of aryl triflates to arenes. Despite the metal catalysts' assistance, under reduced conditions,⁷¹ ⁷² the S-O cleavage still outweighs the C-O cleavage. Thus, it can be predicted that S-O cleavage in aryl triflates to generate phenols under reduced conditions represent a considerable competing reaction with the desired C-O cleavage. Therefore, identifying an appropriate electron donor without reacting in an undesirable way would be crucial for aryl triflates to undergo SET to generate aryl radicals. Considering the unique properties of iodide ion i.e. high reducing ability and weak nucleophilicity to aryl triflates, we hypothesized that simple **sodium iodide**⁷³⁻⁷⁴ would be an applicable electron donor in this regard (Scheme 2c). With all these considerations in mind, we both evaluated the thermal and photo conditions by mixing sodium iodide and aryl triflates in presence of radical trappers.

2.2. Evaluation of thermal vs photo conditions and evidences of the generation of aryl radical. Aryl radicals have been thoroughly investigated in the context of arylation of arenes such as the Gomberg-Bachmann reaction.⁴ Trapped by arenes can be considered as the evidence of aryl radicals' presence.⁵³ Initially, the thermal conditions were examined for SET from sodium iodide (NaI) to *p*-tolyl trifluoromethanesulfonate with benzene as the aryl radical trapper. However, even at 120 °C, the desired compound could not be detected (Scheme 3a). Fortunately, under photo-

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59 60 irradiation, the desired biaryl compound could be observed (Scheme 3b). To obtain further evidence to corroborate the presence of aryl radical, another experiment to trap the aryl radical by Bu₃SnH was conducted (Scheme 3c). It has been measured that hydrogen abstraction rate from Bu₃SnH by aryl radical is close to diffusion limit.⁷⁵ As expected, by using 4acetamidophenyl trifluoromethanesulfonate as the substrate, the desired reducing product can be obtained. In addition, it has been documented that aryl radical can abstract chlorine from CCl₄ to produce aryl chloride.⁷⁶ To further confirm the generation of aryl radical, CCl₄ was added as a co-solvent besides CH₂CN. As depicted in Scheme 3d, aryl chloride was obtained from aryl triflate. Control experiments without NaI of b, c, d in Scheme 3 failed to produce any desired compounds, which indicate the crucial role of NaI in these reactions. These trapping experiments clearly suggest the generation of aryl radical from aryl triflate under photo irradiation by using NaI as the electron donor. Moreover, as a direct evidence of SET, the Stern-Volmer analysis were conducted. p-methyl aryl triflate has a strong absorption at 254 nm and the emission maxima is located at 520 nm. The fluorescence of aryl triflate can be gradually quenched by adding NaI (Fig. 1a). These experiments suggest that under photoirradiation, SET from NaI to aryl triflate occurs to generate aryl radical. Finally, the EPR signal of aryl radical with the spin trap (3,3,5,5-tetramethyl-1-pyrroline Noxide) can be detected under photo conditions but not under thermal conditions in presence of NaI (Fig. 1b). After successfully verifying the generation of the aryl radicals from aryl triflates under such mild conditions, we then decided to exploit the synthetic potentials of this interesting chemistry. By using this method, we wish to report two important applications via aryl radicals as intermediates: synthesis of aryl boronates and aryl iodides as described below.

Scheme 3: Comparison of thermal and photo conditions to promote SET and aryl radical trapping experiments^{*a*}



^aThe products were confirmed by GC/MS analysis.



Figure 1: a: Fluorescence of 4-methylphenyltriflate with various concentration of NaI. The excitation wavelength was selected at 260 nm and the concentration of 4-methylphenyltriflate is 1 μ M. b: The EPR signal of adduct of aryl radical with spin trap (3,3,5,5-tetramethyl-1-pyrroline *N*-oxide) in presence of NaI.

2.3. Synthesis of aryl boronates. Recently, aryl boronic compounds have become very powerful due to the development of the Suzuki coupling among others such as the Petasis reaction and the Chan-Lam coupling.^{26, 77} Classical approaches to synthesize them are by converting aryl halides into aryl metal reagents, which can subsequently react with boronic electrophiles. However, this approach needs stoichiometric amounts of metallic reagents, which are not convenient to handle. In addition, numerous catalytic methods have also been reported, among which is the wellknown Miyaura borylation catalyzed by Pd.⁷⁸⁻⁷⁹ One drawback of this method is the undesired Suzuki coupling between products and the aryl halides in situ. To avoid such by-products and the metal catalysts, various transition-metal-free protocols have been developed.⁸⁰⁻ ⁸⁷ However, these protocols require diazonium inter-

mediates and other sensitive reagents. Earlier in 2016, three groups independently reported mild and simple photo-promoted protocols to convert aryl halides into aryl boronic species.⁸⁸⁻⁹⁰ More recently, Jiao et al. developed an elegant protocol to transform aryl halides into aryl boronic esters using pyridine as the catalyst.⁹¹ Jiao's mechanistic studies supports a radical-radical coupling process via an aryl radical intermediate. By taking advantage of our method to generate aryl radical, we postulated that aryl triflates can be directly transformed into aryl boronates without any transition metals following a mechanistic hypothesis as shown in Scheme 4.

Scheme 4: Proposed strategy to synthesize aryl boronates via aryl triflates as radical precursors with iodide as the electron donor



Table 1: Evaluation of various conditions for aryl borylation

OTf

MeO	MeO $\xrightarrow{nv, B_2(pin)_2}$ $\xrightarrow{MeO} \xrightarrow{B_0}$				
entry	solvent	additives	yield (%) ^{a, b}		
1	CH₃CN	Nal (0.5 eq.)	49		
2	CH₃CN	Nal (0.5 eq.)/TMDAM (0.5 eq.)	58		
3	CH₃CN	Nal (0.5 eq.)/TMDAM (1 eq.)	72 (iso.)		
4	CH₃CN	Nal (0.5 eq.)/DIPEA (1 eq.)	69		
5	CH₃CN	Nal (0.5 eq.)/Py (1 eq.)	21		
6	CH₃CN	Nal (0.5 eq.)/DBU (1 eq.)	43		
7	CH₃CN	TMDAM (1 eq.)	5		
8	CH₃CN	Nal (0.2 eq.)/TMDAM (1 eq.)	41		
9	CH₃CN	Nal (1 eq.)/TMDAM (1 eq.)	40		
10	MeOH	Nal (0.5 eq.)/TMDAM (1 eq.)	17		
11	Acetone	Nal (0.5 eq.)/TMDAM (1 eq.)	25		
12	CH₃CN	Nal (0.5 eq.)/TMDAM (1 eq.)	38 ^c		

^aReaction conditions: 4-methoxyphenyltriflate (o.1 mmol), Nal (o.05 mmol), B₂(pin)₂ (o.2 mmol), solvent (1 mL), at room temperature (ca. 25°C) under Ar atmosphere. ^bIsolated yields. ^cIn air. TMDAM: *N*, *N*, *N*', *N*'-tetramethyldiaminomethane; DIPEA: *N*, *N*-diisopropylethylamine; Py: pyridine; DBU: 1,8diazabicyclo (5.4.0) undec-7-ene.

To begin the study, 4-methoxyphenyltriflate was selected as the model substrate. To our delight, under photo-irradiation, when NaI was added, the desired boronates can be isolated at 49% yield (entry 1, Table 1). In order to generate the ate-complex to facilitate SET, various base additives were evaluated, which are

Scheme 5: Scope of the borylation reaction



^aReaction conditions: aryl trilfate (0.1 mmol), NaI (0.05 mmol), $B_2(pin)_2$ (0.2 mmol), TMDAM (0.1 mmol), CH_3CN (1 mL), at room temperature (ca 25 °C) under Ar atmosphere. ^bIsolated yields.

fortunately beneficial. TMDAM (0.5 equiv) can increase the isolated yield to 58% (entry 2, Table 1) and TMDAM (1 equiv) can increase the isolated yield to 72% (entry 3, Table 1). DIPEA shows a similar impact as TMDAM (69%) (entry 4, Table 1) but different from Jiao's work44, whereas pyridine and DBU would decrease the yields to 21% and 43% respectively (entries 5 and 6, Table 1). As a control experiment, TMDAM alone can only produce a yield of 5% (entry 7, Table 1), suggesting the importance of iodide to this reaction system. Further control experiments show that either less or more NaI in this system would result in harmful effect (41% and 40%) (entries 8 and 9, Table 1). Brief investigation of solvent effect demonstrates that MeOH and acetone are not as efficient as acetonitrile (entries 10 and 11, Table 1). Finally, when the reaction was performed in air instead of argon, the yield dropped to 38% (entry 12, Table 1), which also suggests a radical mechanism. With the optimized conditions established, the scope of this borylation was subsequently explored (Scheme 5). Various substituted boronic esters, including non-substituted (2a), alkyl (2b, **2d**, **2e**), methoxy (**2c**), nitrile (**2f**), ester (**2g**), -CF₃ (**2h**), -Ph (2i), and -Bn (2j) substituted, could be obtained in good yields by using this protocol. It is noticeable that a di-boronic ester can also be produced under our conditions in synthetically useful yield (2k). Furthermore, vinyl boronic ester can be obtained smoothly from vinyl triflate as well (21). This broad functional group compatibility would likely find applications in multi-step synthesis. Besides aryl triflate, aryl mesylate 1

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59 60 can also serve as the reactants albeit with a lower yield (2a). To the best of our knowledge, this approach represents the first method to prepare aryl boronates from phenol derivatives without involving transition metal catalysts.

2.4. Synthesis of aryl iodides. Aryl halides are basic building blocks in organic synthesis. Many wellknown reactions, which are performed on daily basis in every synthetic laboratory all around the world, such as the Suzuki coupling, the Heck coupling and the Buchwald-Hartwig aminations etc., all require aryl halides. Among them, aryl iodides display the highest reactivity and can be operated at mild temperature without special ligands and additives.^{26, 77, 92} Unfortunately, aryl iodides are expensive and less accessible due to the challenge to synthesize them. Therefore, novel methods that can produce aryl iodides from abundant precursors at room temperature with broad functional group compatibility would be highly useful. Considering the remarkable advantages of aryl triflates toward sustainable chemical synthesis, simple and efficient protocols that can transform aryl triflates into aryl iodides would be desirable. To achieve this goal, harsh conditions⁹³⁻⁹⁴ or multi-step synthesis^{79, 95} were usually required. However, a few relatively general metalcatalyzed methods have recently been disclosed. In 2009, the Hayashi group reported a protocol converting vinyl triflates into vinyl halides catalyzed by Ru in presence of Grignard additive.⁹⁶ Although one aryl triflate example was shown, it was only limited to the special 2-naphthyl triflate and the protocol is not applicable to regular aryl triflates. In 2012, the same group reported an updated protocol by using another Ru catalyst as well as increasing the temperature, which could convert regular aryl triflates into aryl halides.⁹⁷ In addition to Hayashi's Ru protocols, in 2010, the Buchwald group developed a Pd-catalyzed approach that can transform aryl (vinyl) triflates into aryl (vinyl) bromides and chlorides, which was later improved to a more friendly version in 2011;98-99 however, aryl iodides cannot be synthesized by the palladium system due to their higher reactivity than that of aryl triflates. It has been well recognized that the rate constant for aryl radical abstracting iodine atom from other iodine source is close to diffusion rate limit, which would be synthetically appropriate to generate aryl iodides. Therefore, we hypothesized that through our method, aryl triflates may be transformed into aryl iodides in presence of elemental I₂ or other iodine sources (Scheme 6a). However, despite this promising hypothesis, some potential challenges can be foreseen (Scheme 6b). First, aryl iodides are more photoreactive than aryl triflates. To synthesize more reactive molecules from less reactive reactants would cause a dilemma. Second, the hydrogen abstraction for phenyl radical from solvent to produce the reducing product

would also be a significant obstacle to ensure a satisfactory yield. Finally, aryl triflates would tend to undergo S-O homolytic cleavage, which would also compete with the desired reaction.

Despite these challenges, to start the study, we selected 2-acetamidophenyltriflate as the model substrate considering its less volatility, using CH₃CN as the solvent and NaI as the iodide source with 0.1 equivalent of I₂ within 24 hrs under argon. To our delight, the desired aryl iodide could be detected in 50% yield (entry 1, Table 2). Encouraged by this result, various base additives were examined. It was found that TMDAM, DIPEA, KF, NaF and CsF all resulted in inferior results (entries 2-6, Table 2). However, when LiF was used, the yield increased to 57% with aryl triflate not completely consumed (entry 7, Table 2). Fortunately, after the reaction time was prolonged to 48 hrs, aryl triflate reacted completely and the desired product could be isolated in 85% yield (entry 8, Table 2). Based on this condition, control experiments were further performed. Entry 9 demonstrated that water (10%) as the co-solvent poses deleterious effect on this reaction. Similarly, 50% acetone in this reaction system also decreased the yield to 46% (entry 10, Table 2). Control experiment in the darkness could not afford any product (entry 11, Table 2). In addition, when the reaction was conducted in air instead of argon, the yield dropped to 50% (entry 12, Table 2). The control experiment without adding I_2 produces a yield of 67% (entry 13, Table 2). Finally, when 2 equivalents of NaI instead of 4 equivalents was employed in this reaction, the yield dropped to 54% (entry 14, Table 2).

Scheme 6: a): Proposed strategy to synthesize aryl iodides from aryl triflates; b): Potential challenges for this strategy to synthesize aryl iodides.



With the optimized conditions identified (Table 3, entry 8), we then turned our attention to the substrate scope investigation. Various aryl triflates with different

substituents can be converted into the desired aryl iodides (Scheme 7). Firstly, the substrates with para substituents were examined. Diverse aryl triflates with electron-withdrawing and electron-donating groups can undergo the reaction smoothly, with the corresponding iodides isolated in modest to good yields (49-61%) (3a-3g). However, when the para substituent is acyl group, the yield dropped to 20% (3h). Subsequently, substrates with substituents at other positions were tested. 3-Fluoro phenyl iodide (3i) and 3trifluoromethylphenyl iodide (3j) can both be obtained in good yields. In addition, different aryl triflates with phenyl substituents can also be converted into aryl iodides smoothly (**3k-3m**). Interestingly, when the aryl triflate bears an iodo substituent, the di-iodo arene compound could be synthesized (3n), which suggests the mildness of our protocol since, in previous transition-metal-catalyzed protocols, the iodo substituent can not be tolerated. In addition, various aniline derived iodides are also accessible by this method (30-3s). Some heterocycles are also compatible with our conditions, with 4-iodoindole (3t) and 4-iodocarbozole (**3u**) being produced in good

Table 2: Evaluation of different conditions for aryl iodination

	OTf	hv, 🖡		
	NHAc addt	ives, solvent, rt	[™] NH.	Ac
entry	solvent	additives	time	yield (%) ^b
1	CH ₃ CN	I ₂ /none	24h	50
2	CH ₃ CN	I2/TMDAM	24h	19
3	CH ₃ CN	I₂/DIPEA	24h	23
4	CH ₃ CN	I2/KF	24h	39
5	CH ₃ CN	I₂/NaF	24h	41
6	CH ₃ CN	I ₂ /CsF	24h	43
7	CH ₃ CN	I₂/LiF	24h	57
8	CH ₃ CN	I ₂ /LiF	48h	85 ^e (iso.)
9	CH ₃ CN/H₂O	I ₂ /LiF	48h	Trace
10	CH ₃ CN/acetone	I₂/LiF	48h	46
11 ^c	CH ₃ CN	I ₂ /LiF	48h	0
12 ^d	CH ₃ CN	I₂/LiF	48h	50
13	CH ₃ CN	LiF	48h	67
14 ^f	CH ₃ CN	I ₂ /LiF	48h	54

^{*a*}Reaction conditions: 2-acetamidophenyl trifluoromethanesulfonate (0.1 mmol), NaI (0.4 mmol), I₂ (0.1 mmol), solvent (1 mL), at rt (ca 25° C) under Ar atmosphere and base additives are all 0.1 mmol (1 equivalent). ^bYields were determined by ¹H-NMR, with 1,3,5trimethoxybenzene as the internal standard. ^cIn the darkness. ^d Under air atmosphere. ^eIsolated yield. ^fOnly 2 equivalents of NaI used instead of 4 equivalents.

Scheme 7: Scope of the substrates for the iodination.



^aReaction conditions: 1 (0.1 mmol), NaI (0.4 mmol), LiF (0.1 mmol), I_2 (0.01 mmol), CH₃CN (1 mL), at rt (ca 25 °C) under Ar atmosphere, reaction time: 48 hrs ^bYields were determined by ¹H-NMR, with 1,3,5-trimethoxybenzene as the internal standard. ^cReaction time: 72 hrs.

yields. Besides the phenyl triflates, naphthyl triflate also undergoes the transformation well (**3v**). Due to the importance of Suzuki coupling, the boron substituent was also examined and 4-iodo phenyl boronic ester (**3w**) could be isolated in 79% yield. The unique structure feature of this compound (**3w**) may find broad applications in polymer chemistry, considering the complementary reactive sites in the compound. More importantly, the successful synthesis of this compound further illustrates the power of our protocol. In order to further evaluate the synthetic utility of our protocol, some complicated substrates were subjected to the standard conditions. It was found that tyrosine-derived triflate could deliver the iodide, on 1

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gram scale, in 81% and 71% yields, respectively. Sterolbased aryl triflate could also be converted into the iodide with good yield (**3y**). This broad functional group compatibility and the scalability would find applications in complex natural product synthesis. In addition to aryl triflates, vinyl triflates could also be converted to the corresponding vinyl iodides in moderate to good yields (**3z**, **3a**). To obtain more insight on this reaction, reactivity comparison of aryl triflates with other phenol derivatives were conducted, which suggested that aryl triflates display the highest reactivity (**3a** in Scheme 7) even though some other phenol derivatives are also reactive (Scheme 8).

Scheme 8. Preliminary investigation of other phenol derivatives' reactivities.



3. Conclusion

In summary, we described a simple and efficient method to convert aryl triflates into aryl radicals under mild conditions. The success of our strategy hinges upon using sodium iodide as the electron donor. Via this strategy, two types of important organic molecules i.e. aryl boronates and aryl iodides have been synthesized readily from aryl triflates with broad functional group tolerance in good to high yields with the scalability in a transition-metal-free manner at room temperature. More significantly, this work serves as an interesting divergent case to synthesize both electrophiles and nucleophiles from the same intermediates. This protocol is anticipated to expand aryl triflates to other reaction systems involving aryl radicals. Further mechanistic studies are undergoing in our laboratory, which will be reported in due course.

ASSOCIATED CONTENT

Supporting Information. 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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