Radical-Cation Reactions

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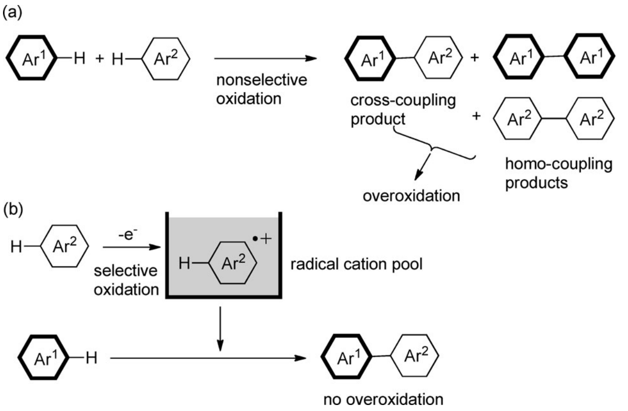
Metal- and Chemical-Oxidant-Free C–H/C–H Cross-Coupling of Aromatic Compounds: The Use of Radical-Cation Pools**

*Tatsuya Morofuji, Akihiro Shimizu, and Jun-ichi Yoshida**

The direct oxidative C–H/C–H cross-coupling, also known as the dehydrogenative cross-coupling,[1] of unactivated aromatic compounds has fascinated many chemists because it does not require prefunctionalization of starting aromatic compounds and it serves as a straightforward, atom-,[2] and step-economical[3] method for connecting two aromatic rings by a single C–C bond.[4,5] In 2007, a metal-catalyzed C–C cross-coupling reaction involving two C–H activations and employing a stoichiometric amount of oxidant was achieved [4a–d] and, since then, the method has been studied extensively.[4e–n] In 2008, a metal-free biaryl compound synthesis that uses a stoichiometric amount of an organoiodine(III) oxidant was developed.[5] A new synthetic method that enables metal- and chemical-oxidant-free C–H/C–H cross-coupling of two aromatic compounds is needed. Electrochemical oxidation[6,7] serves as an efficient method that does not use metal catalysts and chemical oxidants for activating aromatic compounds. In fact, the subjection of a mixture of two unactivated aromatic compounds to electrochemical oxidation can give the cross-coupling products, although yields are usually low.[8] Recently, Waldvogel and co-workers reported a selective electrochemical phenol–arene cross-coupling reaction using boron-doped diamond electrodes.[9] This method, however, cannot be applied to aromatic compounds that do not have a hydroxy group because the phenoxyl radical intermediate plays a crucial role.

In general, the oxidative C–H/C–H cross-coupling of two aromatic compounds suffers from the formation of homo-coupling products derived from the nonselective oxidation of the starting materials (Scheme 1 a). Based on statistics, the yield of the cross-coupling product will be, at most, moderate because of the formation of products derived from homo-coupling. Overoxidation is also unavoidable because the biaryl products have lower oxidation potentials than those of the corresponding starting materials owing to the extended π conjugation of the biaryl products (see below). Therefore, the development of methods for direct anodic cross-coupling is very challenging.



Scheme 1. Oxidative C–H/C–H cross-coupling of aromatic compounds. a) A conventional approach. b) An approach based on the "radical-cation pool" method.

To avoid nonselective oxidation of starting materials and the oxidation of products we have developed a method using "radical-cation pools" (Scheme 1 b). Thus, an aromatic compound is allowed to react with a radical cation of another aromatic compound, a species, which is generated and accumulated by low-temperature electrolysis. In 1999, we developed the cation-pool method, which involves generation and accumulation of an unstable organic cation in the absence of a nucleophile by low-temperature electrochemical oxidation and a subsequent reaction of the cation with a nucleophile under nonelectrolytic conditions. The method has been successfully applied to *N*-acyliminium ions,[10] alkoxycarbenium ions,[11] and diarylcarbenium ions.[12] The present radical-cation-pool method has been developed by analogy with the cation-pool method. This new method serves as a powerful and selective method for synthesizing unsymmetrical biaryl compounds from unactivated electron-rich aromatic compounds in a straightforward and efficient way.

First, we chose to use pentamethylbenzene (**1**) as a substrate because of simplicity of product selectivity (see Table 1). As a coupling partner, we chose to use naphthalene (**2**) because oxidation of **2** to give the corresponding radical cation **3** is known in the literature.[5a,8a,b,13] The electrochemical oxidation of **2** (0.44 mmol) was carried out in a 0.1 M solution of $Bu_4NB(C_6F_5)_4$ in CH_2Cl_2 in a H-type divided cell equipped with a graphite felt anode and a platinum plate cathode at −78 °C in the absence of **1**. After 0.20 mF of electricity was consumed, **1** (0.10 mmol) was added. The reaction mixture was stirred at −78 °C for 3 hours. The desired cross-coupling product **4** was obtained in 33 % yield

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[*] T. Morofuji, Dr. A. Shimizu, Prof. J. Yoshida
Department of Synthetic Chemistry and Biological Chemistry
Graduate School of Engineering, Kyoto University
Nishikyo-ku, Kyoto 615-8510 (Japan)
E-mail: yoshida@sbchem.kyoto-u.ac.jp

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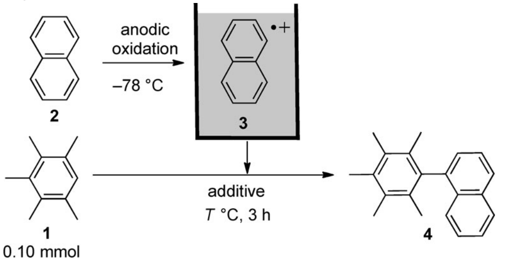
Table 1: Optimization of the reaction conditions.



Entry	*T* [°C]	Additive	Yield of **4** [%][a]	Recovered **1** [%][a]
1	−40	–	11	40
2	−78	–	33	55
3	−90	–	27	52
4[b]	−90	THF	46	32
5[c]	−90	diethyl ether	66	25
6[d]	−90	DME	73	23
7[d,e]	−90	DME	91	–

[a] Yields were determined by GC analysis using hexadecane as an internal standard. [b] Tetrahydrofuran (THF; 0.5 mL) was added. [c] Diethyl ether (0.5 mL) was added. [d] 1,2-Dimethoxyethane (DME; 0.5 mL) was added. [e] The reactions were carried out using **2** (0.66 mmol) with 0.30 mF of electricity.

(Table 1, entry 2). Four moles of **2** is necessary to produce one mole of **4** because **3** is accumulated as a complex with **2** (the radical cation of the naphthalene dimer)[13a] and **4** is produced by the reaction of **1** and **3** followed by one-electron oxidation, wherein the radical-cation naphthalene dimer is the oxidant.

To optimize the reaction conditions the reactions were carried out at a variety of temperatures for the second step. When the second step was carried out at −40 °C (Table 1, entry 1) the yield of **4** was lower than when the step was carried out at −78 °C (Table 1, entry 2) presumably because the decomposition of **3** was competing with the cross-coupling reaction. The reaction at −90 °C (Table 1, entry 3) also gave a lower yield, presumably because of precipitation of **3** at this temperature. To solve this solubility problem, we examined the effect of additives that may enhance the solubility of **3** at low temperatures (Table 1, entries 4–6), and found that 1,2-dimethoxyethane (DME) was quite effective (Table 1, entry 6). Moreover, the use of 0.3 mF of electricity and 0.66 mmol of **2** improved the yield of **4** to 91 % (Table 1, entry 7). It should be noted that the present method does not suffer from oxidation of the products, although the oxidation potential of **4** (1.48 V versus SCE in a 0.1 M solution of $Bu_4NB(C_6F_5)_4$ in CH_2Cl_2) is lower than those of **1** (1.57 V) and **2** (1.60 V).

The regioselectivity of the reaction is notable, because only the 1-substituted naphthalene derivative **4** was obtained. The corresponding 2-substituted product was not detected. This is consistent with the high regioselectivity reported for the reaction of naphthalene radical cations with other nucleophiles such as CN^- and $CH_3CO_2^-$.[13c] Spin density analysis using the DFT calculation also suggests that reaction at the 1-position is favored (Figure 1 a).

Under the optimized reaction conditions, the reaction of several aromatic compounds were examined (Table 2). The reaction of radical cation **3** with pentamethylbenzene (**1**) gave

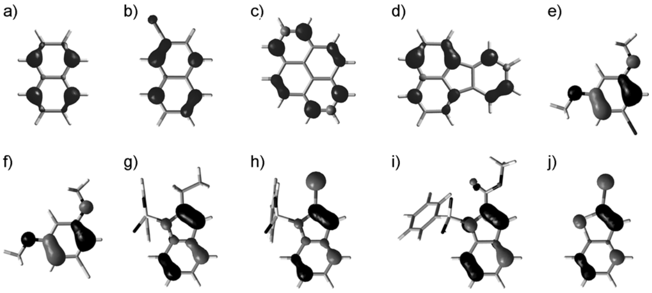
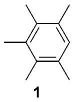
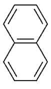
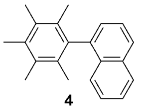
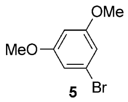
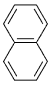
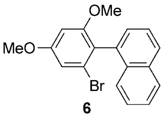
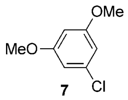
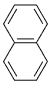
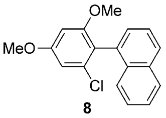
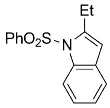
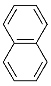
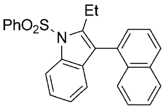
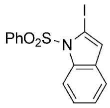
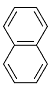
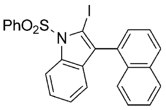
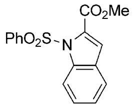
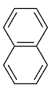
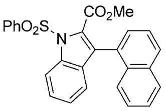
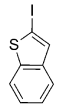
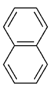
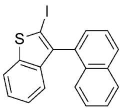
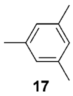
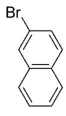
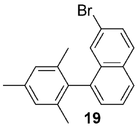
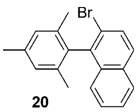
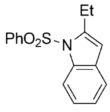
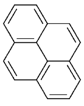
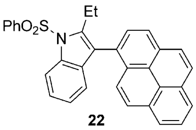
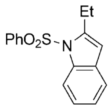
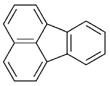
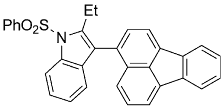


Figure 1. Spin densities of radical cations and HOMOs of nucleophilic aromatic coupling partners obtained by DFT calculations (B3LYP/6-31G*). a–d) Spin densities of radical cations of **2**, **18**, **21**, and **23**, respectively. e–j) HOMO of **5**, **7**, **9**, **11**, **13**, and **15**, respectively (the 3-21G* basis set was used for iodine-containing compounds **11** and **15**).

the cross-coupling product **4** in 87 % yield upon isolation (Table 2, entry 1). Electron-rich benzenes such as **5** and **7** reacted with **3** to give the corresponding cross-coupling products in good yields (Table 2, entries 2 and 3). The regioselectivity observed for **5** and **7** was excellent, in that other isomers were not detected. The HOMO coefficients obtained by DFT calculations are consistent with the observed regioselectivity (Figure 1 e and f). Heteroaromatic compounds, such as indoles **9** and **11**, also gave the corresponding cross-coupling products in good yields (Table 2, entries 4 and 5), although the reactivity of electron-deficient indole **13** was low (Table 2, entry 6). The energy of the HOMO of **13** was lower than that of other substrates; this finding is consistent with the lower reactivity of **13** (see the Supporting Information for details). Benzothiophene **15** was also effective in this reaction (Table 2, entry 7). The regioselectivity of these reactions was also consistent with the HOMO coefficients obtained by DFT calculations (Figure 1 g–j). Notably, iodine-containing compounds **12** and **16** were obtained in very good yields. Usually the oxidative coupling of iodine-containing compounds under electrophilic conditions leads to proto-deiodination[14] and only molybdenum pentachloride is capable of mediating an oxidative coupling of iodoarenes without loss of the iodine substituent.[15]

The present method could also be applied to other radical cations. The reaction of 2-bromonaphthalene (**18**) is interesting: the radical-cation pool derived from **18** was generated in an effective manner by anodic oxidation and the subsequent coupling reaction took place preferentially on the benzene ring not bearing the bromine atom to give **19**. The product derived from C−C bond formation at the position *ortho* to the bromine atom (**20**) was also obtained as a minor product. The regioselectivity is consistent with the spin density values obtained by DFT calculations (Figure 1 b). The anodic oxidation of pyrene (**21**), and fluoranthene (**23**) gave the corresponding radical-cation pools, which reacted with **9** to give the corresponding cross-coupling products in good yields with high regioselectivity, a result, which is consistent with the DFT calculations (Figure 1 c and d). It should be noted that the cheaper electrolyte, Bu_4NPF_6, could be used in these reactions.

Table 2: C−H/C−H cross-coupling of aromatic compounds.[a]

Entry	Ar^1H	Ar^2H	Product	Yield [%][b]
1	 **1**	 **2**	 **4**	87
2[c]	 **5**	 **2**	 **6**	73
3	 **7**	 **2**	 **8**	67
4	 **9**	 **2**	 **10**	92
5	 **11**	 **2**	 **12**	86
6[d,e]	 **13**	 **2**	 **14**	36
7[f]	 **15**	 **2**	 **16**	84
8[g]	 **17**	 **18**	 **19**  **20**	84 (**19**/**20**=1.7:1)
9[d,h,i]	 **9**	 **21**	 **22**	71
10[d,h,i]	 **9**	 **23**	 **24**	70

[a] The radical-cation pool was generated with 0.66 mmol of Ar^1H using 3.0 mF of electricity in a 0.1 M solution of $Bu_4NB(C_6F_5)_4$ in CH_2Cl_2 (10 mL) at −78 °C; then, 0.10 mmol of Ar^2H and DME (0.5 mL) were added at −90 °C and the reaction mixture was stirred at −90 °C for 3 h. [b] Yields of isolated product based on Ar^2H. [c] 5.5 mmol of Ar^1H and 5.0 mF of electricity were used. [d] 8.8 mmol of Ar^1H and 8.0 mF of electricity were used. [e] Additional stirring of the reaction mixture at −30 °C for 5 h. [f] Additional stirring of the reaction mixture at −20 °C for 2 h. [g] 0.1 mL of DME was used. [h] Bu_4NPF_6 was used instead of $Bu_4NB(C_6F_5)_4$. [i] 0.05 mmol of Ar^2H was used and the mixture was stirred at −40 °C for 3 h and then at −15 °C for 1.5 h.

Notably, the regioselectivity of the cross-coupling is generally very high and is predictable based on the spin density of the radical cation and the HOMO coefficients of the nucleophilic aromatic partner obtained by DFT calculations. The high regioselectivity of this method contrasts with the lower regioselectivity of homolytic aromatic substitutions that are used for biaryl compound synthesis.[16] This difference in regioselectivity is probably due to the different reactivity of the reactive intermediates: in homolytic aromatic substitutions, a highly reactive σ radical (aryl radical) reacts with the arene, whereas in the approach herein, a less reactive π radical (aryl radical cation) reacts with the arene. Notably, halogen-substituted aromatic compounds are effective as both substrates (Table 2, entries 2, 3, 5, and 7) and precursors of a radical cation (Table 2, entry 8) and the halogen functionality in the cross-coupling products can be used for further transformations, such as halogen/metal exchange and transition metal catalyzed coupling reactions. Therefore, we anticipate that this new method will form the basis of a wide range of synthetic strategies for making organic compounds containing aromatic rings.

In conclusion, we have developed an efficient method for the C−H/C−H cross-coupling of two unactivated aromatic compounds using "radical-cation pools". Because this method consists of two sequential steps, namely the generation and accumulation of a radical cation of an aromatic compounds under oxidative conditions and then the coupling of the radical cation with another aromatic substrate under nonoxidative conditions, nonselective oxidation of the starting materials and oxidation of the products are avoided. Thus, the method serves as a selective technique for effecting a C−H/C−H cross-coupling of aromatic compounds. The absence of metal complexes and chemical oxidants in the reaction conditions is also advantageous. Exploration of the full range of reactivity of various aromatic compounds and radical-cation pools, and applications to the synthesis of biaryl and heterobiaryl compounds with interesting functions and biological activity is currently in progress.

Experimental Section

General procedure for oxidative cross-coupling: The anodic oxidation was carried out using a H-type divided cell (4G glass filter) equipped with a carbon felt anode (Nippon Carbon JF-20-P7, ca. 160 mg, dried at 300 °C/1 mmHg for 4 h before use) and a platinum plate cathode (10 mm × 10 mm). In the anodic chamber was placed a solution of an aromatic compound (0.66 mmol) in a 0.1M solution of $Bu_4NB(C_6F_5)_4$ in CH_2Cl_2 (10.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (150 μL) and a 0.1M solution of $Bu_4NB(C_6F_5)_4$ in CH_2Cl_2 (10.0 mL). The constant current electrolysis (8.0 mA) was carried out at −78 °C with magnetic stirring of the reaction mixture for 60 min. An aromatic substrate (0.10 mmol) and 1,2-dimethoxyethane (0.5 mL) were added to the anodic chamber at −90 °C. The resulting mixture was stirred at −90 °C for 3 h. Then, Et_3N (0.2 mL) was added and the resulting mixture was warmed to room temperature. After removal of the solvent under reduced pressure, the residue was quickly filtered through a short column (2 × 4 cm) of silica gel to remove electrolyte using *n*-hexane/

EtOAc. The solvent was removed from the filtrate under reduced pressure, and the crude product was purified with flash chromatography on silica gel or GPC to obtain the cross-coupling product.

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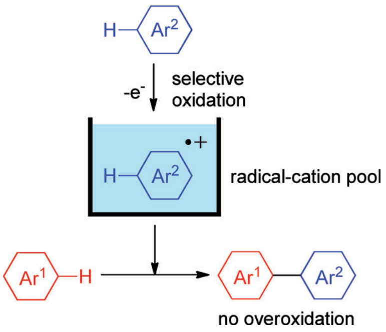
Communications

Radical-Cation Reactions

T. Morofuji, A. Shimizu,
J. Yoshida* ______ ■■■■–■■■■

Metal- and Chemical-Oxidant-Free C–H/C–H Cross-Coupling of Aromatic Compounds: The Use of Radical-Cation Pools



Pool and couple: A method for oxidative C–H/C–H cross-coupling has been developed using “radical-cation pools”. Aromatic compounds react with aryl radical cations, which are generated and accumulated by low-temperature electrolysis (see scheme). This method avoids both the nonselective oxidation of substrates and oxidation of products and effects the C–H/C–H cross-coupling of aromatic compounds without metal complexes and chemical oxidants.