

Communication

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# The Stabilized Cation Pool Method. Metal- and Oxidant-Free Benzylic C–H/Aromatic C–H Cross-Coupling

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Supporting Information Placeholder

**ABSTRACT:** Electrochemical oxidation of toluene derivatives in the presence of a sulfilimine gave benzylaminosulfonium ions as stabilized benzyl cation pools, which reacted with subsequently added aromatic nucleophiles to give the corresponding cross-coupling products. The transformation serves as a powerful metal- and chemical-oxidant-free method for benzylic C–H/aromatic C–H cross-coupling. The method has been successfully applied to synthesis of TP27, an inhibitor of PTPase

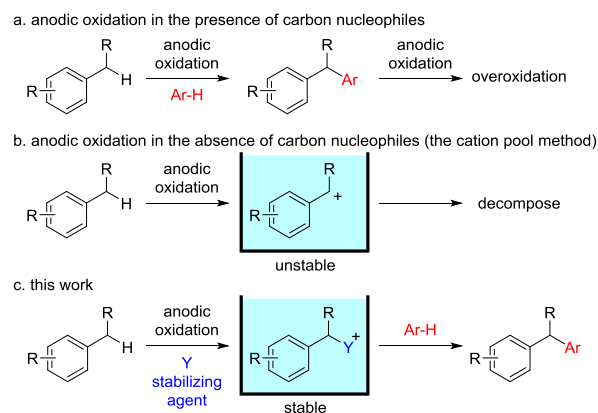
Organic cations, such as carbenium ions, and onium ions are widely used as reactive intermediates in organic synthesis. Although organic anions such as organolithium and –magnesium compounds are usually generated in the absence of electrophiles by virtue of stabilization by the metal counter anion, organic cations are often generated in the presence of nucleophiles.<sup>1</sup> This is because organic cations are often unstable and transient, although they can exist as stable species in super acidic media.<sup>2</sup> This situation, however, limits the utility of organic cations in chemical synthesis. To solve the problem we developed the cation pool method<sup>3</sup> in which organic cations are electrochemically generated and accumulated in solutions in the absence of nucleophiles at low temperatures. Reactions with subsequently added nucleophiles give desired products. However, the cation pool method cannot be applied to highly unstable cations which decompose during the course of the electrolysis, even at low temperatures. To expand the scope of the cation pool method, we have developed the stabilized cation pool method in which organic cations stabilized by suitable stabilizing agents are electrochemically generated and accumulated in solution. In the next step, the reactions with subsequently added nucleophiles give desired products. In this paper we showcase the stabilized cation pool method, *i.e.* the generation and reactions of stabilized benzylic cations to achieve benzylic C–H/aromatic C–H cross-coupling.

C–H/C–H cross-coupling reactions<sup>4</sup> serve as atom-<sup>5</sup> and step-economical<sup>6</sup> methods for carbon-carbon bond formation because prefunctionalization of two carbon sites are not required. In particular, C<sub>sp3</sub>–H/aromatic C–H cross-coupling is useful for connecting an aliphatic part and an aromatic part in synthesis of complex organic molecules. Three methods have been developed so far: 1) transition metal catalyzed activation of C<sub>sp3</sub>–H bonds at  $\alpha$  or  $\beta$  position of carbonyl group,<sup>7</sup> 2) Minisci-type reactions which involve the generation of radical species by abstraction of a hy-

drogen atom to achieve alkylation of pyridine derivatives,<sup>8</sup> and 3) Friedel-Crafts-type reactions which involves carbocations generated by oxidation of benzylic C–H bonds or C–H bonds adjacent to a heteroatom.<sup>9</sup> However, such methods inevitably suffer from the problem of overreaction.

Electrochemical oxidation serves as a powerful method for generating reactive cationic species via C–H bond cleavage.<sup>10</sup> Although C<sub>sp3</sub>–H/C<sub>sp3</sub>–H cross-coupling reactions have been successfully achieved by electrochemical oxidation,<sup>11</sup> C<sub>sp3</sub>–H/aromatic C–H cross-coupling suffers from inevitable overoxidation because cross-coupling products, alkylated aromatics usually have lower oxidation potentials than starting materials (Scheme 1a). The cation pool method does not suffer from the problem of overoxidation. However, the method cannot be applied to benzylic cations which are usually too unstable to be accumulated in solution even at low temperatures (Scheme 1b).

## Scheme 1. Three Approaches to Electrochemical Benzylic C–H/ Aromatic C–H Cross-Coupling

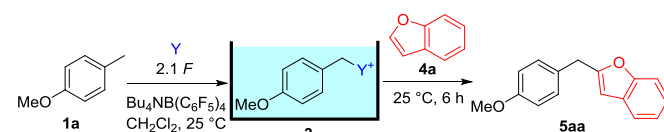








On the basis of these backgrounds, we envisaged that benzylic C–H/aromatic C–H cross-coupling can be achieved by the electrochemical generation and accumulation of stabilized benzylic cation followed by their reactions with subsequently added aromatic nucleophiles (Scheme 1c). Choice of the stabilizing agent Y is crucial for the success of the transformation. The requirements for Y are as follows: 1) Y has higher oxidation potential than those of toluene derivatives to enable selective electrochemical

oxidation to generate benzyl cations. 2) Y does not have a proton. In this case the reaction of the benzyl cation with Y gives a cationic intermediate, and the strong electron-withdrawing effect of the positive charge avoids overoxidation. 3) Y has sufficient nucleophilicity to stabilize benzyl cations and also has sufficient leaving ability for the nucleophilic substitution reaction with aromatic nucleophiles.

We first screened stabilizing agents Y (Table 1). Thus, 4-methoxytoluene (**1a**) was electrochemically oxidized in the presence of various Y in dichloromethane to generate stabilized benzyl cations (**3**).  $\text{Bu}_4\text{NB}(\text{C}_6\text{F}_5)_4$  was used as a supporting electrolyte to prevent undesired nucleophilic attack of the counter anion on the benzylic carbon. After the electrolysis at 25 °C, benzofuran (**4a**) was added to the resulting solution at the same temperature.

**Table 1. Screening of Stabilizing Agents**

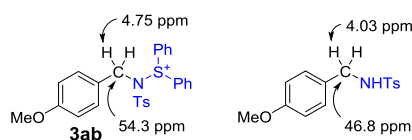


entry	Y	yield	entry	Y	yield	entry	Y	yield
1	none	N.D.	4		N.D.	6		25% (68%) <sup>a)</sup>
2		N.D.	5		N.D.	7		77%
3		N.D.						

4-Methoxytoluene (**1a**, 0.1 mmol) was electrochemically oxidized in the presence of 1.0 mmol of Y in a 0.1 M solution of the  $\text{Bu}_4\text{NB}(\text{C}_6\text{F}_5)_4$  in  $\text{CH}_2\text{Cl}_2$  at 25 °C. After 2.1 F of electricity was applied, the resulting solution was treated with benzofuran (**4a**, 0.5 mmol) at 25 °C. Yields are isolated yields of **5aa** based on **1a** used. a) After the electrolysis, reaction was carried out for 66 h.

When no Y was used, the desired cross-coupling product **5aa** was not obtained at all, indicating that the benzyl cation itself is too unstable to be accumulated under the conditions (entry 1). When pyridine was used as Y,<sup>12</sup> a mixture of benzylpyridinium derivative and phenylpyridinium derivative was observed after the electrolysis (entry 2). The formation of the latter intermediate can be explained in terms of strong nucleophilicity of pyridine, which leads to the reaction with the radical cation of 4-methoxytoluene before proton elimination occurred at the benzylic position. In addition, the benzylpyridinium intermediate did not react with **4a** to give **5aa**. Thus, 1-mesylimidazole, which has lower nucleophilicity than pyridine was used as Y (entry 3).<sup>13</sup> Although the corresponding benzylimidazolium intermediate was observed after the electrolysis, it did not react with **4a**. When dimethyl sulfoxide (DMSO) and diphenylsulfoxide (DPSO) were used as Y (entries 4 and 5),<sup>14</sup> cross-coupling product **5aa** was not obtained.

However, the nitrogen analogue of DMSO, dimethylsulfilimine **2a** was found to be effective as Y (entry 6). The benzylaminosulfonium ion was observed after the electrolysis, and its reaction with **4a** gave desired cross-coupling product **5aa** in 25% yield.<sup>15</sup> Elongation of the reaction time for the coupling with **4a** gave **5aa** in 68% yield. Moreover, when diphenylsulfilimine **2b** was used as Y, **5aa** was obtained in 77% without elongation of the reaction time (entry 7). The benzylaminosulfonium ion **3ab** was successfully characterized by <sup>1</sup>H and <sup>13</sup>C NMR analyses and mass spectroscopy (Figure 1).



**Figure 1.** NMR data of *p*-methoxybenzyl(tosyl)aminosulfonium ion **3ab** and those of *p*-methoxybenzyl(tosyl)amine<sup>16</sup>

Notably, the oxidation potential (decomposition potential) of **2b** ( $E_d = 2.01$  V vs. SCE) is higher than that of **1a** (1.38 V), indicating **1a** can be selectively oxidized in the presence of **2b** (Table S1). The oxidation potential of benzofuran **4a** (1.49 V) is close to that of **1a**, and this means that selective oxidation of **1a** in the presence of **4a** is difficult.

The reactivity of 4-methoxybenzylaminosulfonium ion **3ab** was compared with that of 4-methoxybenzyl bromide, because a similar transformation might be achieved by radical bromination of toluene derivatives followed by the Friedel-Crafts type reactions of benzyl bromides with aromatic compounds. When 4-methoxybenzyl bromide was allowed to react with benzofuran (**4a**) under similar conditions the desired cross-coupling product was not obtained at all and 4-methoxybenzyl bromide was recovered in 85% yield. The result indicates that benzylaminosulfonium ion **3ab** is much more reactive than the corresponding benzyl bromide.

The electrochemical reactions were usually carried out with 10 equivalents of **2b** to generate **3ab** efficiently. This seems to be disadvantageous from a view point of synthesis. However, **2b** was recovered in 100% after the reaction with **4a**, and therefore, **2b** can be recycled and used for the next reaction.

The present one-pot transformation is applicable to other toluene derivatives bearing various functional groups as shown in Table 2. 4-Methoxy toluene derivatives having bromo, iodo, and ester carbonyl groups at 3-position were successfully coupled with benzofuran (**4a**) (entries 2–4). The reaction of **1e**, which has two benzylic positions, is interesting. The methyl group *para* to the methoxy group selectively reacted (entry 5). Secondary benzylic C–H can also be used for the transformation (entries 6–9). The successful reactions with ethylbenzene derivatives (**1h** and **1i**) indicate that the transformation does not suffer from  $\beta$ -hydrogen elimination. Notably, diphenylmethane (**1j**), which could not be used for the cation pool method, was successfully used for the present transformation (entry 10).<sup>3c</sup> Moreover, stabilized dicationic species could be generated by four-electron oxidation of ditolyl ether (**1k**) and the subsequent reaction with **4a** gave the desired product in a reasonable yield (entry 11).

Next, we examined reactions of benzylaminosulfonium ion **3ab** with various nucleophiles (Table 3). Several heterocyclic compounds such as benzofuran, indole, and benzothiophene gave the corresponding cross-coupling products (entries 1–3). Anisole and phenol reacted with **3ab** at *para* position selectively (entries 4 and 5). *p*-Cresol reacted at *ortho* position (entry 6). 1-Methoxynaphthalene also gave the corresponding cross-coupling product (entry 7). Not only the aromatic nucleophiles but also other carbon nucleophiles such as acetylacetone, ketene silyl acetal, allyltrimethylsilane, and trimethylsilylacetylene can be used for the transformation (entries 8–11).

Table 2. Scope of Benzylic Substrates

entry	substrate	T (°C)	t (h)	product	yield (%)
1		25	6		77%
2		35	22		83% <sup>a)</sup>
3		35	68		88%
4		35	30		76% <sup>a)</sup>
5		25	22		74%
6		25	24		76% <sup>a)</sup>
7		25	24		68% <sup>a)</sup>
8		25	17		64% <sup>a,b)</sup>
9		35	19		61% <sup>a,c)</sup>
10		25	6		63%
11		35	40		51% <sup>a,d)</sup>

Benzylic substrate **1** (0.1 mmol) was electrochemically oxidized in the presence of 1.0 mmol of **2b** in a 0.1 M solution of  $\text{Bu}_4\text{NB}(\text{C}_6\text{F}_5)_4$  in  $\text{CH}_2\text{Cl}_2$  at 25 °C. After 2.1 *F* of electricity was applied, the resulting solution was treated with benzofuran (**4a**, 0.5 mmol). Yields are isolated yields of the products based on **1** used. a) Benzofuran (1.0 mmol) was used. b) 3.0 *F* of electricity was applied at 0 °C. c) 2.5 *F* of electricity was applied. d) 4.1 *F* of electricity was applied.

Table 3. Scope of Nucleophiles

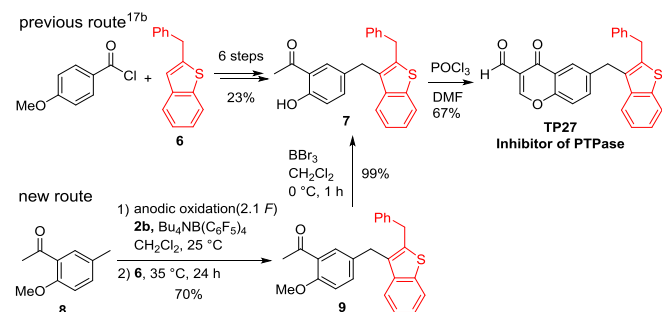
entry	T (°C)	t (h)	Nu	product	yield (%)
1	25	6			77%
2	25	6			75%
3	25	6			56%
4	25	7			65%
5	25	6			77%
6	25	6			84%
7	25	6			82%
8	25	6			88%
9	25	6			67%
10	50	6			81%
11	25	17			55%

4-Methoxytoluene (**1a**, 0.1 mmol) was electrochemically oxidized in the presence of 1.0 mmol of **2b** in a 0.1 M solution of  $\text{Bu}_4\text{NB}(\text{C}_6\text{F}_5)_4$  in  $\text{CH}_2\text{Cl}_2$  at 25 °C. After 2.1 *F* of electricity was applied, the resulting solution was treated with the nucleophile (0.5 mmol). Yields are isolated yields of the products based on **1a** used.

To demonstrate the usefulness of the method, we synthesized a precursor of TP27, an inhibitor of PTPases<sup>17</sup>. In the previous synthesis by Cho, the precursor **7** was prepared from 4-methoxybenzoyl chloride and benzothiophene derivative **6** in 6 steps in 23% yield. On the other hand, we synthesized **7** starting from readily available **6** and **8** in 2 steps in 69% yield. The anodic oxidation **8** in the presence of **2b** followed by the reaction with **6**

gave cross-coupling product **9** in 70% yield. The subsequent demethylation gave **7** in 99% yield.

## Scheme 2. Synthesis of TP27



In conclusion, we developed the stabilized cation pool method using sulfilimines as stabilizing agents, and the method was successfully applied to metal- and chemical-oxidant-free benzylic C–H/aromatic C–H cross-coupling. These findings open new possibilities of cationic reactions and the electrochemical method in organic synthesis.

## ASSOCIATED CONTENT

### Supporting Information

Experimental procedures and spectroscopic data of compounds data (PDF). 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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