The Stabilized Cation Pool Method: Metal- and Oxidant-Free Benzylic C−H/Aromatic C−H Cross-Coupling

Ryutaro Hayashi, Akihiro Shimizu, and Jun-ichi Yoshida*

Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Nishikyo-ku, Kyoto 615-8510, Japan

S *Supporting Information*

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 counteranion, organic cations are often generated in the presence of nucleophiles.[1] This is done because organic cations are often unstable and transient, although they can exist as stable species in superacidic media.[2] This situation, however, limits the utility of organic cations in chemical synthesis. To solve this problem, we developed the cation pool method,[3] 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 the desired products. However, the cation pool method cannot be applied to highly unstable cations that 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 the desired products. In this paper we showcase the stabilized cation pool method by the generation and reaction of stabilized benzyl cations to achieve benzylic C−H/aromatic C−H cross-coupling.

C−H/C−H cross-coupling reactions[4] serve as atom-[5] and step-economical[6] methods for carbon−carbon bond formation because prefunctionalization of two carbon sites is not required. In particular, C_{sp^3}−H/aromatic C−H cross-coupling is useful for connecting an aliphatic part and an aromatic part in syntheses of complex organic molecules. Three methods have been developed to date: (1) transition-metal-catalyzed activation of C_{sp^3}−H bonds α or β to a carbonyl group,[7] (2) Minisci-type reactions involving the generation of radical

species by abstraction of a hydrogen atom to achieve alkylation of pyridine derivatives,[8] and (3) Friedel−Crafts-type reactions involving carbocations generated by oxidation of benzylic C−H bonds or C−H bonds adjacent to a heteroatom.[9] However, such methods inevitably suffer from the problem of over-reaction.

Electrochemical oxidation serves as a powerful method for generating reactive cationic species via C−H bond cleavage.[10] Although C_{sp^3}−H/C_{sp^3}−H cross-coupling reactions have been successfully achieved by electrochemical oxidation,[11] C_{sp^3}−H/ aromatic C−H cross-coupling suffers from inevitable over-oxidation because the cross-coupling products, alkylated aromatics, usually have lower oxidation potentials than the starting materials (Scheme 1a). The cation pool method does

Scheme 1. Three Approaches to Electrochemical Benzylic C−H/Aromatic C−H Cross-Coupling
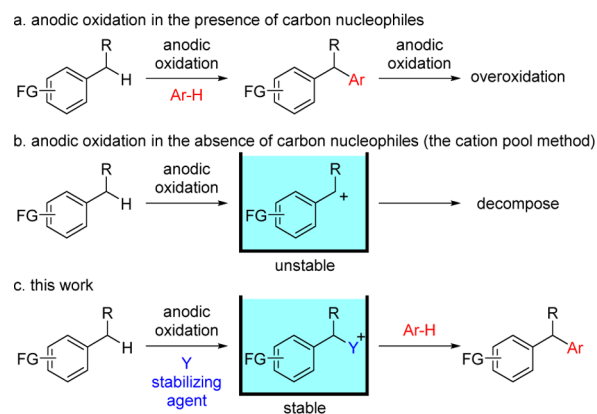
not suffer from the problem of overoxidation. However, the method cannot be applied to benzylic cations, which are usually too unstable to be accumulated in solution even at low temperatures (Scheme 1b).

On the basis of this background, we envisaged that benzylic C−H/aromatic C−H cross-coupling could be achieved by the electrochemical generation and accumulation of stabilized benzyl cations followed by their reactions with subsequently added aromatic nucleophiles (Scheme 1c). The choice of the stabilizing agent Y is crucial for the success of the transformation. The requirements for Y are as follows: (1) Y must

have a higher oxidation potential than the toluene derivatives to enable selective electrochemical oxidation to generate benzyl cations. (2) Y cannot 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 must have sufficient nucleophilicity to stabilize benzyl cations and also have sufficient leaving ability for the nucleophilic substitution reaction with aromatic nucleophiles.

We first screened stabilizing agents Y (Table 1). 4-Methoxytoluene (**1a**) was electrochemically oxidized in the

Table 1. Screening of Stabilizing Agents[a]

entry	Y	yield	entry	Y	yield	entry	Y	yield
1	none	N.D.	4	DMSO	N.D.	6	**2a**	25% (68%)[b]
2	pyridine	N.D.	5	DPSO	N.D.	7	**2b**	77%
3	N,N-Ms	N.D.						

[a]**1a** (0.1 mmol) was electrochemically oxidized in the presence of 1.0 mmol of Y in a 0.1 M solution of $Bu_4NB(C_6F_5)_4$ in CH_2Cl_2 at 25 °C. After 2.1F of electricity was applied, the resulting solution was treated with **4a** (0.5 mmol) at 25 °C. Yields are isolated yields of **5aa** based on **1a** used. [b]After the electrolysis, the reaction was carried out for 66 h.

presence of various Y in dichloromethane to generate stabilized benzyl cations **3**. $Bu_4NB(C_6F_5)_4$ was used as a supporting electrolyte to prevent undesired nucleophilic attack of the counteranion on the benzylic carbon. After the electrolysis at 25 °C, benzofuran (**4a**) was added to the resulting solution at the same temperature.

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,[12] a mixture of benzylpyridinium and phenylpyridinium derivatives was observed after the electrolysis (entry 2). The formation of the latter intermediate can be explained in terms of the strong nucleophilicity of pyridine, which led to the reaction with the radical cation of 4-methoxytoluene before proton elimination at the benzylic position could occur. 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).[13] Although the corresponding benzylimidazolium intermediate was observed after the electrolysis, it did not react with **4a**. When dimethyl sulfoxide (DMSO) and diphenyl sulfoxide (DPSO) were used as Y (entries 4 and 5),[14] cross-coupling product **5aa** was not obtained.

However, a 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 the desired cross-coupling product **5aa** in 25% yield.[15] 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 ^{1}H and ^{13}C NMR analyses and mass spectroscopy (Figure 1).
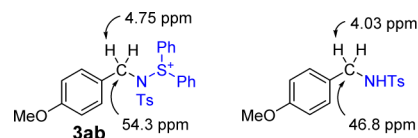

Figure 1. NMR data for *p*-methoxybenzyl(tosyl)aminosulfonium ion **3ab** and *p*-methoxybenzyl(tosyl)amine[16]
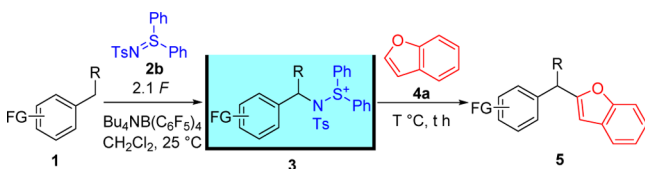
Notably, the oxidation potential (decomposition potential) of **2b** (E_d = 2.01 V vs SCE) is higher than that of **1a** (1.38 V), indicating that **1a** can be selectively oxidized in the presence of **2b** (Table S1). The oxidation potential of **4a** (1.49 V) is close to that of **1a**, which means 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 Friedel–Crafts-type reactions of benzyl bromides with aromatic compounds. When 4-methoxybenzyl bromide was allowed to react with **4a** under similar conditions, the desired cross-coupling product was not obtained at all, and 4-methoxybenzyl bromide was recovered in 85% yield. This result indicates that benzylaminosulfonium ion **3ab** is much more reactive than the corresponding benzyl bromide.

The electrochemical reactions were usually carried out with 10 equiv of **2b** to generate **3ab** efficiently. This seems to be disadvantageous from the viewpoint of synthesis. However, **2b** was recovered in 100% yield 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-Methoxytoluene derivatives having bromo, iodo, and ester carbonyl groups at the 3-position were successfully coupled with **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 bonds 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 β-hydrogen elimination. Notably, diphenylmethane (**1j**), which could not be used for the cation pool method, was successfully used for the present transformation (entry 10).[3c] Moreover, stabilized dications 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 the 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 the para position selectively (entries 4 and 5). *p*-Cresol reacted at the ortho position (entry 6). 1-Methoxynaphthalene also gave the corresponding cross-coupling product (entry 7). Not only aromatic nucleophiles but also other carbon nucleophiles such as acetylacetone, ketene silyl acetal, allyltrimethylsilane, and
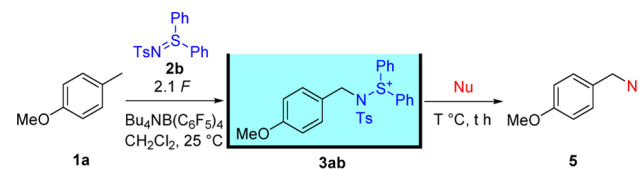
Table 2. Scope of Benzylic Substrates[a]

entry	substrate	T (°C)	t (h)	product	yield (%)
1	1a	25	6	5aa	77%
2	1b	35	22	5ba	83%[b]
3	1c	35	68	5ca	88%
4	1d	35	30	5da	76%[b]
5	1e	25	22	5ea	74%
6	1f	25	24	5fa	76%[b]
7	1g	25	24	5ga	68%[b]
8	1h	25	17	5ha	64%[b,c]
9	1i	35	19	5ia	61%[b,d]
10	1j	25	6	5ja	63%
11	1k	35	40	5ka	51%[b,e]

[a]1 (0.1 mmol) was electrochemically oxidized in the presence of 1.0 mmol of 2b in a 0.1 M solution of $Bu_4NB(C_6F_5)_4$ in CH_2Cl_2 at 25 °C. After 2.1F of electricity was applied, the resulting solution was treated with 4a (0.5 mmol). Yields are isolated yields of the products based on 1 used. [b]Benzofuran (1.0 mmol) was used. [c]3.0F of electricity was applied at 0 °C. [d]2.5F of electricity was applied. [e]4.1F of electricity was applied.

trimethylsilylacetylene can be used for the transformation (entries 8−11).

To demonstrate the usefulness of the method, we synthesized a precursor of TP27, an inhibitor of PTPases (Scheme 2). In the previous synthesis by Cho,[17] the precursor

Table 3. Scope of Nucleophiles[a]

entry	T (°C)	t (h)	Nu	product	yield (%)
1	25	6	4a	5aa	77%
2	25	6	4b	5ab	75%
3	25	6	4c	5ac	56%
4	25	7	4d	5ad	65%
5	25	6	4e	5ae	77%
6	25	6	4f	5af	84%
7	25	6	4g	5ag	82%
8	25	6	4h	5ah	88%
9	25	6	4i	5ai	67%
10	50	6	4j	5aj	81%
11	25	17	4k	5ak	55%

[a]1a (0.1 mmol) was electrochemically oxidized in the presence of 1.0 mmol of 2b in a 0.1 M solution of $Bu_4NB(C_6F_5)_4$ in CH_2Cl_2 at 25 °C. After 2.1F 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.

7 was prepared from 4-methoxybenzoyl chloride and benzothiophene derivative 6 in six steps in 23% yield. On the other hand, we synthesized 7 starting from readily available 6 and 8 in two steps in 69% yield. Anodic oxidation of 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.

In conclusion, we have developed the stabilized cation pool method using sulfilimines as stabilizing agents, and the method was successfully applied to metal- and chemical-oxidant-free

Scheme 2. Synthesis of TP27
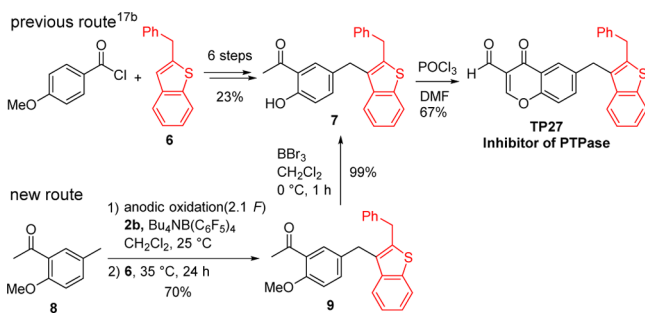
benzylic C−H/aromatic C−H cross-coupling. These findings open new possibilities for cationic reactions and the electrochemical method in organic synthesis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b05273.

> Experimental procedures and spectroscopic data of compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*yoshida@sbchem.kyoto-u.ac.jp

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

■ REFERENCES

(1) Yoshida, J.; Suga, S. *Chem. - Eur. J.* **2002**, *8*, 2650.

(2) (a) Olah, G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1393. (b) Olah, G. *J. Org. Chem.* **2001**, *66*, 5943.

(3) (a) Yoshida, J.; Suga, S.; Suzuki, S.; Kinomura, N.; Yamamoto, A.; Fujiwara, K. *J. Am. Chem. Soc.* **1999**, *121*, 9546. (b) Suga, S.; Suzuki, S.; Yamamoto, A.; Yoshida, J. *J. Am. Chem. Soc.* **2000**, *122*, 10244. (c) Okajima, M.; Soga, K.; Nokami, T.; Suga, S.; Yoshida, J. *Org. Lett.* **2006**, *8*, 5005. (d) Kim, S.; Hayashi, K.; Kitano, Y.; Tada, M.; Chiba, K. *Org. Lett.* **2002**, *4*, 3735. (e) Kim, S.; Shoji, T.; Kitano, Y.; Chiba, K. *Chem. Commun.* **2013**, *49*, 6525.

(4) (a) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (b) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780. (c) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (d) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74. (e) Sun, C.-L.; Shi, Z.-J. *Chem. Rev.* **2014**, *114*, 9219. (f) Liu, C.; Yuan, J.; Gao, M.; Tang, S.; Li, W.; Shi, R.; Lei, A. *Chem. Rev.* **2015**, *115*, 12138. (g) Narayan, R.; Matcha, K.; Antonchick, A. P. *Chem. - Eur. J.* **2015**, *21*, 14678. (h) Schubert, M.; Franzmann, P.; von Leupoldt, A. W.; Koszinowski, K.; Heinze, K.; Waldvogel, S. R. *Angew. Chem., Int. Ed.* **2016**, *55*, 1156.

(5) Trost, B. M. *Science* **1991**, *254*, 1471.

(6) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40.

(7) (a) Moon, Y.; Kwon, D.; Hong, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 11333. (b) Yip, K.-T.; Nimje, R. Y.; Leskinen, M. V.; Pihko, P. M. *Chem. - Eur. J.* **2012**, *18*, 12590.

(8) (a) Zhang, Y.; Feng, J.; Li, C.-J. *J. Am. Chem. Soc.* **2008**, *130*, 2900. (b) Antonchick, A. P.; Burgmann, L. *Angew. Chem., Int. Ed.* **2013**, *52*, 3267.

(9) (a) Li, Y.-Z.; Li, B.-J.; Lu, X.-Y.; Lin, S.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3817. (b) Huo, C.; Yuan, Y.; Wu, M.; Jia, X.; Wang, X.; Chen, F.; Tang, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 13544.

(10) (a) Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527. (b) Sperry, J. B.; Wright, D. L. *Chem. Soc. Rev.* **2006**, *35*, 605. (c) Yoshida, J.; Kataoka, K.; Horcajada, R.; Nagaki, A. *Chem. Rev.* **2008**, *108*, 2265. (d) Yoshida, J.; Shimizu, A.; Ashikari, Y.; Morofuji, T.; Hayashi, R.; Nokami, T.; Nagaki, A. *Bull. Chem. Soc. Jpn.* **2015**, *88*, 763.

(11) Examples of C−C bond formation by electrochemical C−H bond activation: (a) Yoshida, K.; Fueno, T. *J. Org. Chem.* **1972**, *37*, 4145. (b) Bidan, G.; Genies, M. *Tetrahedron* **1981**, *37*, 2297. (c) Ho, X.-H.; Mho, S.; Kang, H.; Jang, H.-Y. *Eur. J. Org. Chem.* **2010**, 4436. (d) Morofuji, T.; Shimizu, A.; Yoshida, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 7259. (e) Shoji, T.; Kim, S.; Yamamoto, K.; Kawai, T.; Okada, Y.; Chiba, K. *Org. Lett.* **2014**, *16*, 6404. (f) Elsler, B.; Schollmeyer, D.; Dyballa, K. M.; Franke, R.; Waldvogel, S. R. *Angew. Chem., Int. Ed.* **2014**, *53*, 5210. (g) Arai, T.; Tateno, H.; Nakabayashi, K.; Kashiwagi, T.; Atobe, M. *Chem. Commun.* **2015**, *51*, 4891.

(12) Morofuji, T.; Shimizu, A.; Yoshida, J. *J. Am. Chem. Soc.* **2013**, *135*, 5000.

(13) Morofuji, T.; Shimizu, A.; Yoshida, J. *J. Am. Chem. Soc.* **2014**, *136*, 4496.

(14) (a) Ashikari, Y.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2011**, *133*, 11840. (b) Ashikari, Y.; Nokami, T.; Yoshida, J. *Org. Lett.* **2012**, *14*, 938.

(15) Gu, Y.; Tian, S.-K. *Synlett* **2013**, *24*, 1170.

(16) NMR data for *p*-methoxybenzyl(tosyl)amine: Das, B. G.; Ghorai, P. *Chem. Commun.* **2012**, *48*, 8276.

(17) (a) Shim, Y. S.; Kim, K. C.; Lee, K. A.; Shrestha, S.; Lee, K.-H.; Kim, C. K.; Cho, H. *Bioorg. Med. Chem.* **2005**, *13*, 1325. (b) Shrestha, S.; Hwang, S. Y.; Lee, K.-H.; Cho, H.-J. *Bull. Korean Chem. Soc.* **2005**, *26*, 1138.