Organic Reactions Using Electrooxidatively Generated Cationic Intermediates

Ryutaro Hayashi

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Preface

The studies presented in this thesis have been carried out under the direction of Professor Jun-ichi Yoshida at the Department of Synthetic Chemistry and Biological Chemistry of Kyoto University during 2012-2018. The studies are concerned with development of new electrochemical reactions.

The author would like to express his sincerest gratitude to Professor Jun-ichi Yoshida for his kind guidance and valuable discussions throughout this work. The author appreciates the circumstance to investigate in the field of the chemistry. The author is greatly indebted to Dr. Akihiro Shimizu for his constant advice and valuable discussions during the course of this work. The author deeply appreciates to Dr. Aiichiro Nagaki and Dr. Heejin Kim for their kind guidance and encouragement. The author is also thankful to Associate Professor Toshiki Nokami of Tottori University and Dr. Keisuke Asano for their helpful advice.

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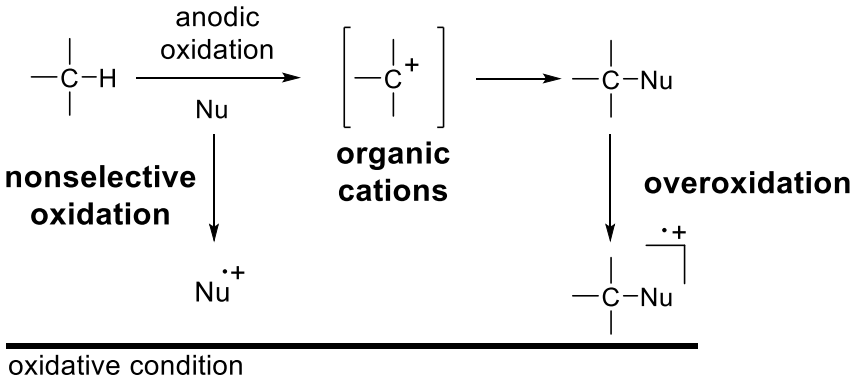
Contents

General Introduction

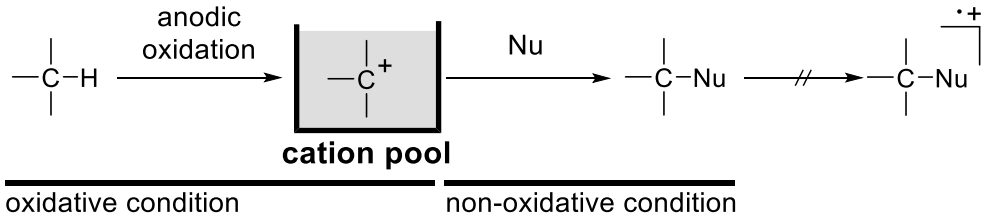
Organic compounds exist in our lives as components of food, medicine, cloth, and plastic. Synthesis of organic compounds which have various properties contributes to our lives. However, the synthesis of organic compounds often requires multi-step processes and are time-consuming and costly. Therefore, the development of more efficient methods for synthesizing organic compounds is desired.

Oxidation is one of the fundamental processes in organic chemistry and the electrochemical method[1] serves as a useful and efficient method for oxidation of organic compounds. Electrochemical oxidation enables various reactions by generating organic cations via the cleavage of C−H or C−S bond under mild conditions. Conventionally, starting materials are oxidized in the presence of nucleophiles because organic cations are usually unstable. However, nonselective oxidation of nucleophiles and/or overoxidation often takes place (Scheme 1).



Scheme 1: Electrochemical Oxidation in the Presence of Nucleophiles.

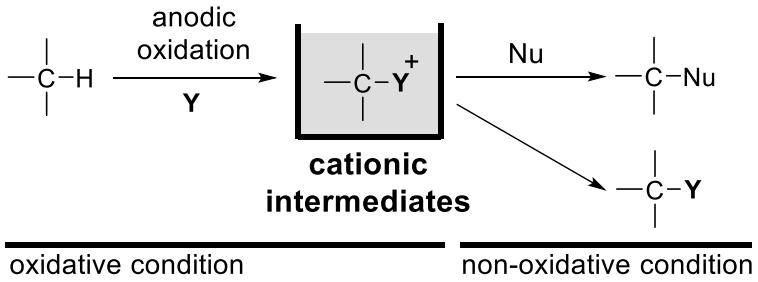
To solve the problem Yoshida and coworkers developed the cation pool method in which organic cations are electrochemically generated and accumulated in solutions in the absence of nucleophiles at low temperatures (Scheme 2).[2] Reactions with subsequently added nucleophiles give desired products. However, the cation pool method cannot be applied to highly unstable cations which decompose during the course of the electrolysis, even at low temperatures.



Scheme 2: Electrochemical Oxidation in the Absence of Nucleophies (Cation Pool Method).

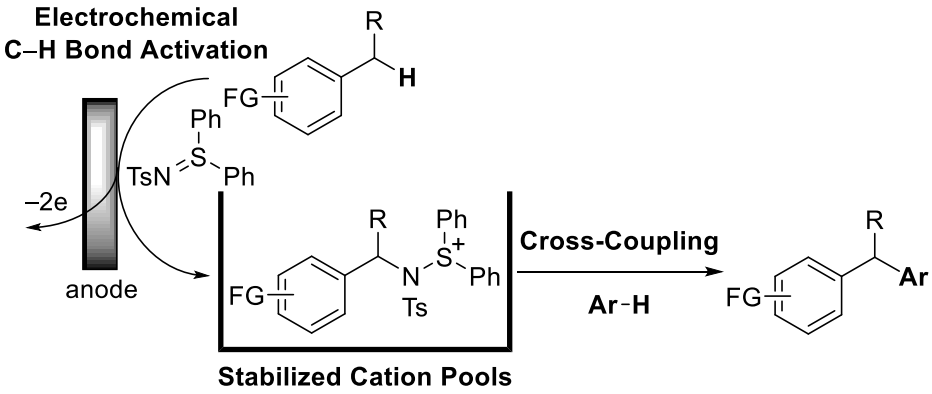
On the basis of these backgrounds, this thesis describes a new type of cation pool method, in which organic cations stabilized by appropriate nucleophiles Y, are electrochemically generated and accumulated in solution (Scheme 3). In the next step, the reactions with subsequently added nucleophiles give the desired products. Choice of nucleophile Y is crucial for the success of the transformation. The requirements for Y are as follows: 1) Y has

higher oxidation potential than starting materials to enable selective electrochemical oxidation to generate organic cations. 2) Y reacts with the organic cations to give the corresponding cationic intermediate which can be accumulated. 3) The cationic intermediate can undergo various transformations.



Scheme 3: Electrochemical Oxidation in the Presence of Appropriate Nucleophiles and Subsequent Transformations.

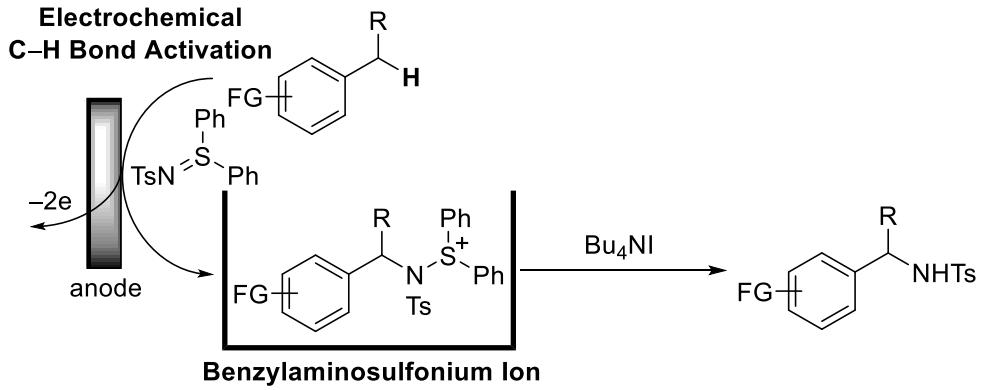
Chapter 1 describes benzylic C−H/aromatic C−H cross-coupling by using stabilized cation pool method. Benzyl cations need to be generated in the presence of nucleophiles because they are unstable and cannot be accumulated even by the conventional cation pool method.[3] This chapter describes the stabilized benzyl cation pool method in which benzyl cations are electrochemically generated in the presence of sulfilimine to accumulate benzylaminosulfonium ions as stabilized cation pools. Benzylaminosulfonium ions react with aromatic nucleophiles as benzyl cation equivalent to generate the corresponding diarylmethane. In principle, sulfilimines can be recovered after the transformation. To demonstrate the power of the method, PTPase inhibitor was synthesized.[4]



Scheme 4: Electrochemical Benzylic C−H/Aromatic C−H Cross-Coupling by Usnig Stabilized Cation Pool Method.

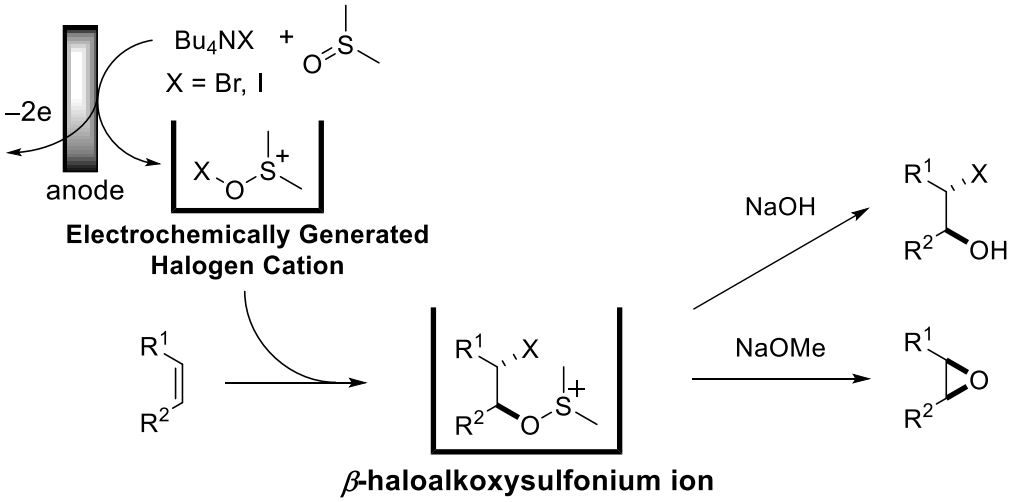
Chapter 2 describes benzylic C−H amination via benzylaminosulfonium ions. Although many C−H amination reactions have been reported so far, excess amounts of carbon substrates are often required.[5] This chapter deals with a new method for C−H amination of benzylic substrates involving benzylaminosulfonium ions, which are

generated by the same method described in chapter 1 (Scheme 5). The use of tetrabutylammonium iodide as a nucleophile leads to selective cleavage of the N−S bond to give the corresponding benzylamines. The method has broad applicability because the sulfilimine has higher oxidation potential that those of common toluene derivatives.



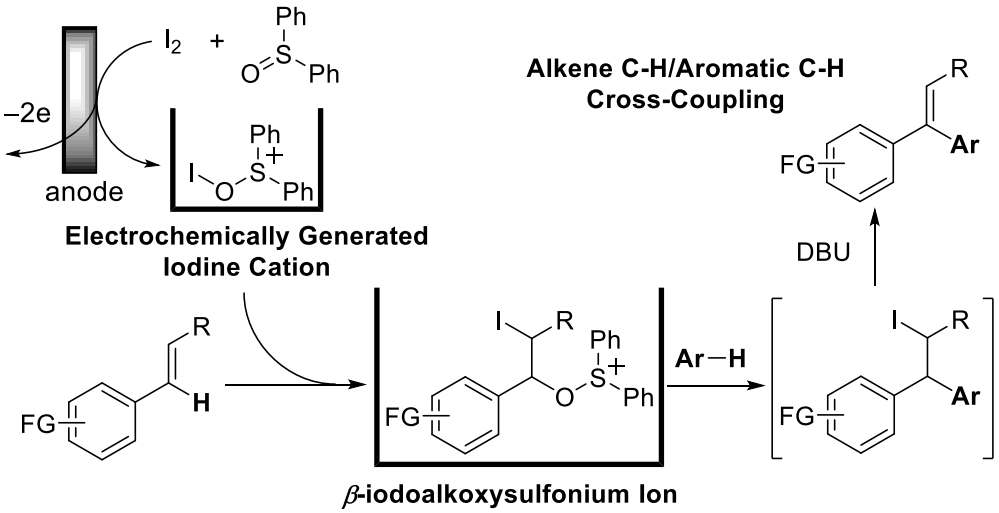
Scheme 5: Electrochemical Benzylic C−H Amination.

Chapter 3 describes synthesis of halohydrins and epoxides via electrochemically generated *β*-haloalkoxysulfonium ions. Although halogen cations are unstable even at low temperatures, halogen cations stabilized by dimethyl sulfoxide (DMSO) can be accumulated in solution.[6] These cations react with alkenes to give *β*-haloalkoxysulfonium ions, which can be transformed to *α*-carbonyl compounds by the treatment with base. This chapter deals with synthesis of halohydrins or epoxides from *β*-haloalkoxysulfonium ions (Scheme 6). The treatment of *β*-haloalkoxysulfonium ions with sodium hydroxide gives the corresponding halohydrins, whereas the treatment with sodium methoxide gives epoxides.



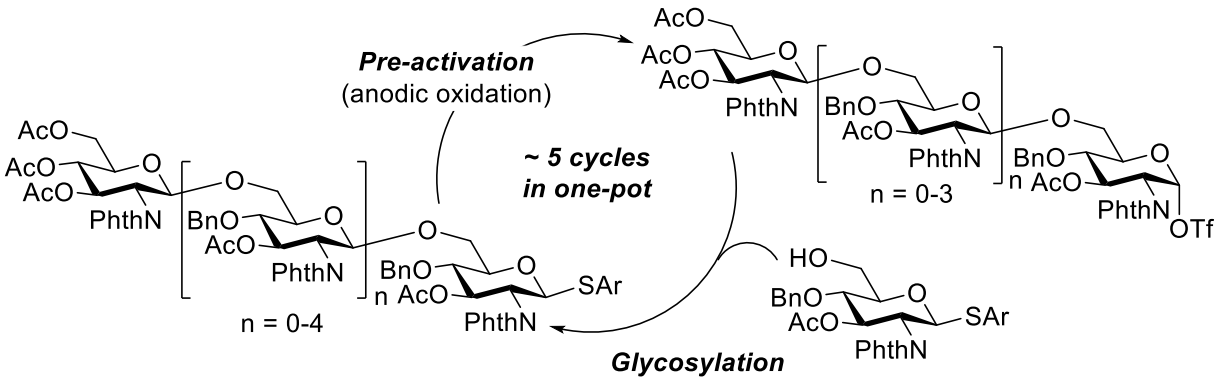
Scheme 6: Synthesis of Halohydrins and Epoxides via Electrochemically Generated *β*-Haloalkoxysulfonium Ions

Chapter 4 describes alkenyl C−H/Aromatic C−H cross-coupling via electrochemically generated *β*-iodoalkoxysulfonium ions. Although *β*-haloalkoxysulfonium ions are useful for alkene difunctionalization as shown in chapter 3, only oxygen functional groups derived from DMSO can be introduced. In this chapter, *β*-iodoalkoxysulfonium ions generated from styrene derivatives reacts with aromatic nucleophiles as benzyl cation equivalents (Scheme 7). In this case diphenyl sulfoxide serves as a better leaving group than DMSO. In addition, subsequent treatment with DBU in one-pot gives the corresponding diarylethylenes to achieve formal alkenyl C−H/Aromatic C−H cross-coupling.



Scheme 7: Alkenyl C−H/Aromatic C−H Cross-Coupling via Electrochemically Generated *β*-Iodoalkoxysulfonium Ions.

Chapter 5 describes synthesis of oligosaccharide via electrochemically generated glycosyl triflate. Although glycosyl cations, which can be generated by electrochemical oxidation of thioglycosides, are unstable, glycosyl cations stabilized by triflate anions (glycosyl triflates) can be accumulated.[7] Glycosyl triflates react with glycosyl acceptors such as other thioglycosides with free OH groups to give disaccharides. On the basis of this method, oligosaccharides can be synthesized by iterative electrochemical glycosylation (Scheme 8). Synthesis of a hexasaccharide was achieved by using the method in one-pot.



Scheme 8: Iterative Synthesis of Oligosaccharides Based on the Activation of a Thioglycoside Donor in the Absence of a Glycosyl Acceptor.

Reference

(1) (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. (e) Horn, E. J.; Rosen, B. R.; Baran, P. S. *ACS Cent. Sci.* **2016**, *2*, 302.

(2) (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.

(3) (a) Hoormann, D.; Kubon, C.; Jorissen, J.; Kroner, L.; Putter, H. *J. Electroanal. Chem.* **2001**, *507*, 215. (b) Horcajada, R.; Okajima, M.; Suga, S.; Yoshida, J. *Chem. Commun.* **2005**, 1303. (c) Tajima, T.; Fuchigami, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 4760. (d) Ashikari, Y.: Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2011**, *133*, 11840. (e) Ashikari, Y.; Nokami, T.; Yoshida, J. *Org. Lett.* **2012**, *14*, 938. (f) Morofuji, T.: Shimizu, A.; Yoshida, J. *J. Am. Chem. Soc.* **2014**, *136*, 4496.

(4) (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. *Bull. Korean Chem. Soc.* **2005**, *26*, 1138.

(5) (a) Fan, R.; Li, W.; Pu, D.; Zhang, L. *Org. Lett.* **2009**, *11*, 1425. b) Baba, H.; Togo, H. *Tetrahedron Lett.* **2010**, *51*, 2063. c) Ramesh, D.; Ramulu, U.; Mukkanti, K.; Venkateswarlu, Y.; *Tetrahedron. Lett.* **2012**, *53*, 2904. d) Buslov, I.; Hu, X. *Adv. Synth. Catal.* **2014**, *356*, 3325.

(6) Ashikari, Y.; Shimizu, A.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2013**, *135*, 16070.

(7) Nokami, T.; Shibuya, A.; Tsuyama, H.; Suga, S.; Bowers, A. A.; David, C.; Yoshida, J. *J. Am. Chem. Soc.* **2007**, *129*, 10922.

Chapter 1

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

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.

Introduction

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.[1] This is because organic cations are often unstable and transient, although they can exist as stable species in super acidic media.[2] This situation, however, limits the utility of organic cations in chemical synthesis. To solve the problem Yoshida and coworkers 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 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, the stabilized cation pool method in which organic cations stabilized by suitable stabilizing agents are electrochemically generated and accumulated in solution have been developed. In the next step, the reactions with subsequently added nucleophiles give desired products. In this chapter the stabilized cation pool method, *i.e.* the generation and reactions of stabilized benzylcations to achieve benzylic C−H/aromatic C−H cross-coupling is described.

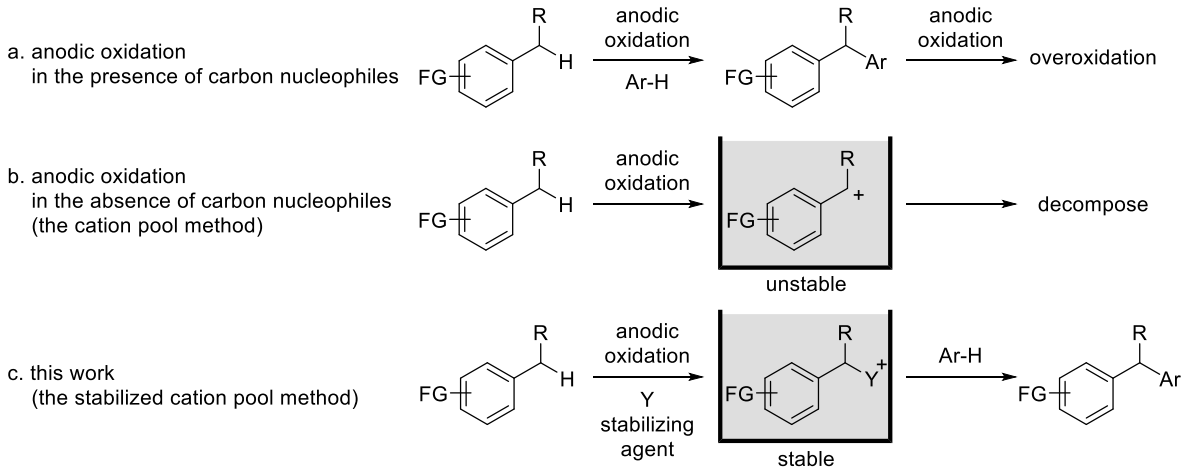
C−H/C−H cross-coupling reactions[4] serve as atom-[5] and step-economical[6] methods for carbon-carbon bond formation because prefunctionalization of two carbon sites are not required. In particular, C_{sp3}−H/aromatic C−H cross-coupling is useful for connecting an aliphatic part and an aromatic part in synthesis of complex organic molecules. The following three methods have been developed so far: 1) transition metal catalyzed activation of C_{sp3}−H bonds at α or β position of carbonyl group,[7] 2) Minisci-type reactions which involve the generation of radical species by abstraction of a hydrogen atom to achieve alkylation of pyridine derivatives,[8] 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.[9] 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.[10] Although some C−H/C−H cross-coupling reactions have been successfully achieved by electrochemical oxidation,[11] C_{sp3}−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 without additional stabilizing groups because they are usually too unstable to be accumulated in solution even at low temperatures (Scheme 1b).

On the basis of these backgrounds, this chapter shows benzylic C−H/aromatic C−H cross-coupling can be achieved by the electrochemical generation and accumulation of stabilized benzyl 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.

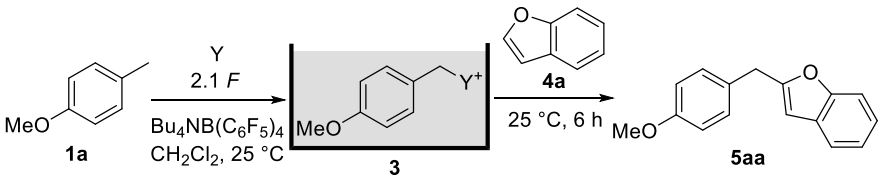
Scheme 1. Three Approaches to Electrochemical Benzylic C−H/ Aromatic C−H Cross-Coupling.



Results and Discussions

Table 1 shows screening of stabilizing agents Y (Table 1). 4-Methoxytoluene (**1a**) was electrochemically oxidized in the 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 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	DMSO	N.D.	6	**2a**	25% (68%)[a]
2		N.D.						
3		N.D.	5	DPSO	N.D.	7	**2b**	77%

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 $Bu_4NB(C_6F_5)_4$ in CH_2Cl_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. Isolated yield based on **1a** used is shown. 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,[12] a mixture of benzylpyridinium derivative and phenylpyridinium derivative was observed after the electrolysis (entry 2) (See Chapter 2 for the details). 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 benzylpyridnium 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 desired cross-coupling product **5aa** in 25% yield.[15] Elongation of the reaction time led to the fromation of **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).

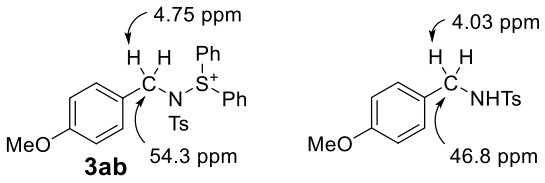


Figure 1. NMR data of *p*-methoxybenzyl(tosyl)aminosulfonium ion **3ab** and those of *p*-methoxybenzyl(tosyl)amine.[16]

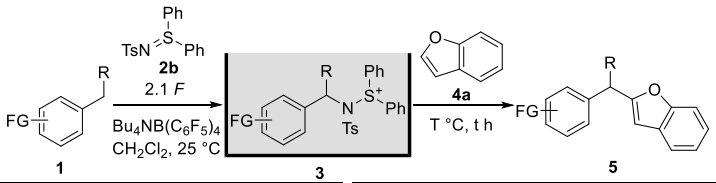
Notably, the oxidation potential (decomposition potential) of **2b** (E_d = 2.01 V vs. SCE) is higher than that of **1a** (1.38 V), indicating **1a** can be selectively oxidized in the presence of **2b** (see experimental section). The oxidation potential of benzofuran **4a** (1.49 V) is close to that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

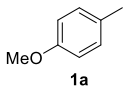
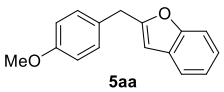
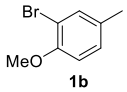
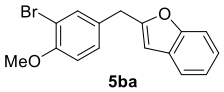
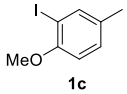
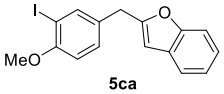
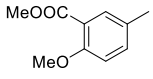
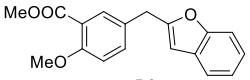
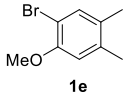
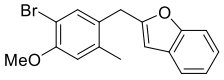
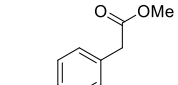
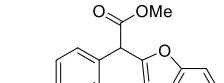
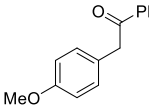
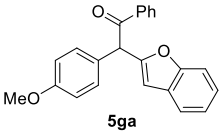
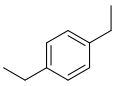
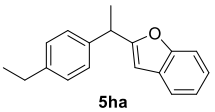
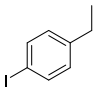
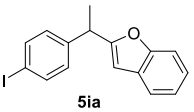
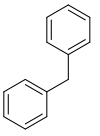
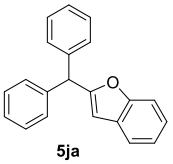
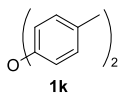
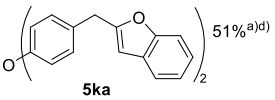
The reactivity of 4-methoxybenzylaminosulfonium ion **3ab** was compared with that of 4-methoxybenzyl bromide, because a similar transformation might be achieved by radical bromination of toluene derivatives followed by the Friedel-Crafts type reactions of benzyl bromides with aromatic compounds. When 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 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).

Table 2. Scope of Benzylic Substrates.



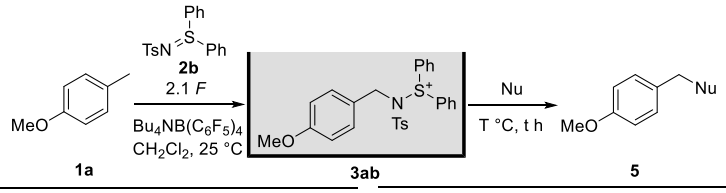
entry	substrate	T (°C)	t (h)	product	yield (%)
1	 **1a**	25	6	 **5aa**	77%
2	 **1b**	35	22	 **5ba**	83%[a]
3	 **1c**	35	68	 **5ca**	88%
4	 **1d**	35	30	 **5da**	76%[a]
5	 **1e**	25	22	 **5ea**	74%
6	 **1f**	25	24	 **5fa**	76%[a]
7	 **1g**	25	24	 **5ga**	68%[a]
8	 **1h**	25	17	 **5ha**	64%[a)b)]
9	 **1i**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

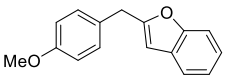
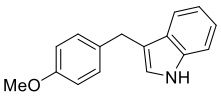
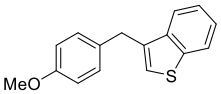
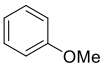
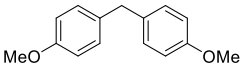
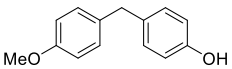
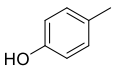
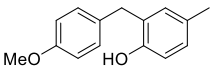
Benzylic substrate **1** (0.1 mmol) was electrochemically oxidized in the presence of 1.0 mmol of **2b** in a 0.1 M solution of $Bu_4NB(C_6F_5)_4$ in CH_2Cl_2 at 25 °C. After 2.1 *F* of electricity was applied, the resulting solution was treated with benzofuran (**4a**, 0.5 mmol). Isolated yield based on **1** used is shown. 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.

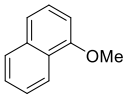
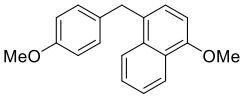
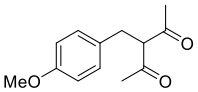
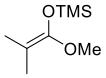
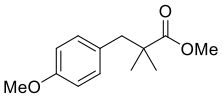
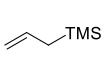
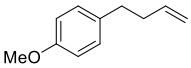
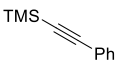
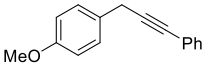
Next, reactions of benzylaminosulfonium ion **3ab** with various nucleophiles (Table 3) were examined. Several heterocyclic compounds such as benzofuran, indole, and benzothiophene gave the corresponding cross-coupling

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 3. Scope of Nucleophiles.



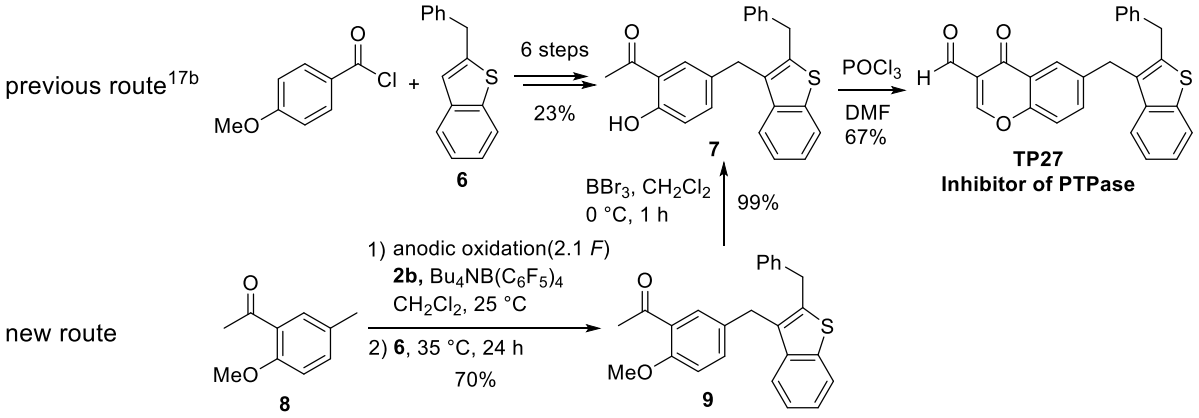
entry	T (°C)	t (h)	Nu	product	yield (%)
1	25	6	 **4a**	 **5aa**	77%
2	25	6	 **4b**	 **5ab**	75%
3	25	6	 **4c**	 **5ac**	56%
4	25	7	 **4d**	 **5ad**	65%
5	25	6	 **4e**	 **5ae**	77%
6	25	6	 **4f**	 **5af**	84%

entry	T (°C)	t (h)	Nu	product	yield (%)
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%

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 $Bu_4NB(C_6F_5)_4$ in CH_2Cl_2 at 25 °C. After 2.1 *F* of electricity was applied, the resulting solution was treated with the nucleophile (0.5 mmol). Isolated yield based on **1a** used is shown.

To demonstrate the usefulness of the method, a precursor of TP27, an inhibitor of PTPases was synthesized.[17] 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, starting from readily available **6** and **8**, the precursor **7** was synthesized 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, and the subsequent demethylation gave **7** in 99% yield.

Scheme 2. Synthesis of TP27.



Conclusion

The stabilized cation pool method using sulfilimines as stabilizing agents was developed, 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.

Experimental Section

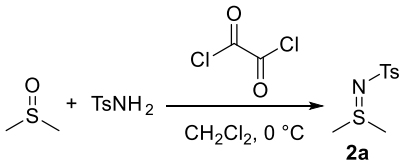
General

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian MERCURY plus-400 (^{1}H 400 MHz, ^{13}C 100 MHz) spectrometer with tetramethylsilane as an internal standard unless otherwise noted. Mass spectra were obtained on a JEOL EXACTIVE (ESI and APCI) mass spectrometer and a JEOL JMS-SX102A mass spectrometer (EI). GC analysis was performed on a SHIMADZU GC-2014 gas chromatograph equipped with a flame ionization detector using a fused silica capillary column (column, CBP1; 0.22 mm x 25 m). Merck precoated silica gel F254 plates (thickness 0.25 mm) were used for thin-layer chromatography (TLC) analysis. Flash chromatography was carried out using Kanto Chem. Co., Silica Gel N (spherical, neutral, 40−100 μm). Preparative gel permeation chromatography (GPC) was performed on a Japan Analytical Industry LC-918. All reactions were carried out under argon atmosphere unless otherwise noted. Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification.

The anodic oxidation was carried out using an H-type divided cell (4G glass filter) equipped with an anode made of carbon strings (Nippon Carbon GF-20-P21E, ca. 160 mg for 0.20 mmol scale, dried at 300 °C/1 mmHg for 3 h before use) and a platinum plate cathode (10 mm x 10 mm). Dichloromethane was washed with water, distilled from P_2O_5, redistilled from dried K_2CO_3 to remove a trace amount of acid, and stored over molecular sieves 4A. $NaB(C_6F_5)_4$ was provided from Nippon Shokubai Co. as a precursor of $Bu_4NB(C_6F_5)_4$. $Bu_4NB(C_6F_5)_4$ was synthesized according to the reported literature[18].

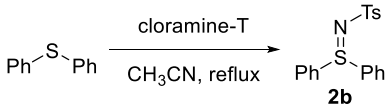
Synthesis of Sulfilimines

Synthesis of *S,S*-Dimethyl-*N*-(4-methylphenylsulfonyl)sulfilimine (2a)[19]



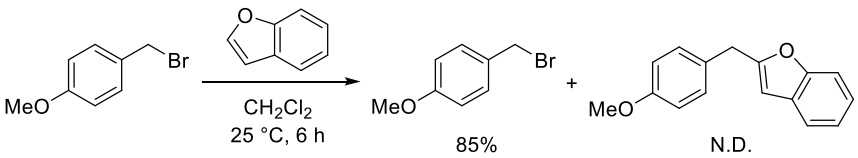
To a round-bottom flask were added DMSO (5 mL, 70 mmol), *p*-toluenesulfonamide (1.7 g, 10 mmol), and CH_2Cl_2 (40 mL). A solution of oxalyl chloride (1.9 mL, 22 mmol) in CH_2Cl_2 (5 mL) was added dropwise at 0 °C over 3 min. After being stirred at 0 °C for 2 h, Et_3N (8.5 mL) was added to the mixture. The mixture was washed with 1 M NaOH aq, H_2O, and brine, dried over Na_2SO_4, and concentrated in vacuum. The residue was purified by recrystallization from CH_2Cl_2 to give ***S,S*-dimethyl-*N*-(4-methylphenylsulfonyl)sulfilimine (2a)** in 76% yield (1.76 g, 7.6 mmol). TLC R_f 0.08 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H), 2.69 (s, 6H), 7.25 (d, *J* = 7.9 Hz, 2H), 7.78 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 36.0, 126.2, 129.3, 141.2, 141.8; HRMS (ESI) calcd for $C_9H_{13}NO_2S_2$ ($M+H^+$): 232.0460, found: 232.0457.

Synthesis of *S,S*-Diphenyl-*N*-(4-methylphenylsulfonyl)sulfilimine 2b[20]



To a round-bottom flask were added phenyl sulfide (13 mL, 80 mmol), cloramine-T (trihydrate, 25 g, 110 mmol), and CH_3CN (200 mL). The mixture was refluxed for 3 h. CH_2Cl_2 (300 mL) was added to the solution and the precipitate was removed by filtration. The filtrate was concentrated under vacuum and the residue was purified by recrystallization from EtOAc and hexane to give ***S,S*-diphenyl-*N*-(4-methylphenylsulfonyl)sulfilimine (2b)** in 66% yield (19 g, 53 mmol). TLC R_f 0.36 (hexane/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 3H), 7.14 (d, *J* = 7.9 Hz, 2H), 7.42−7.48 (m, 4H), 7.48−7.53 (m, 2H), 7.60−7.64 (m, 4H), 7.75 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 126.3, 127.2, 129.1, 129.8, 132.2, 136.6, 141.4, 141.6 ; HRMS (ESI) calcd for $C_{19}H_{18}NO_2S_2$ ($M+H^+$): 356.0773, found: 356.0766.

Reaction of 4-Methoxybenzyl Bromide with Benzofuran

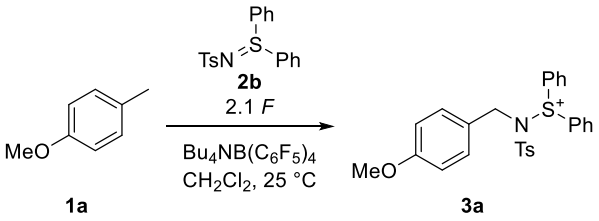


To a round-bottom flask were added 4-methoxybenzyl bromide (19.5 mg, 0.097 mmol), benzofuran (55 μL, 0.51 mmol), and CH_2Cl_2 (10 mL). The mixture was stirred at 25 °C for 6 h. The solvent was removed under reduced pressure. The GC analysis using hexadecane as an internal standard indicated that

2-(4-methoxybenzyl)-benzofuran was not produced and that 4-methoxybenzyl bromide was recovered in 85% yield.

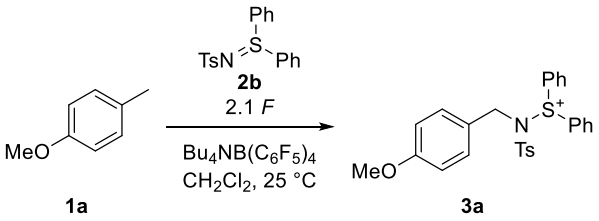
Generation and Observation of *p*-Methoxybenzylaminosulfonium Ion (3a)

Observation of 3a by NMR Spectroscopy



In the anodic chamber were placed 4-methoxytoluene (**1a**) (24.4 mg, 0.200 mmol), *S*,*S*-diphenyl-*N*-(4-methylbenzenesulfonyl)sulfilimine (**2b**) (353 mg, 0.994 mmol), and 0.1 M $Bu_4NB(C_6F_5)_4/CH_2Cl_2$ (10 mL). In the cathodic chamber were placed TfOH (60 μL, 0.68 mmol) and 0.1 M $Bu_4NB(C_6F_5)_4/CH_2Cl_2$ (10 mL). The constant current electrolysis (8.0 mA) was carried out at 25 °C with magnetic stirring until 2.1 *F* of electricity was consumed. The solution in the anodic chamber was collected and the solvent was removed under reduced pressure. The crude product was dissolved in $CDCl_3$ and dried over molecular sieves 4A. The solution was analyzed by NMR spectroscopy. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 3.73 (s, 3H), 4.75 (s, 2H), 6.68 (d, *J* = 8.8 Hz, 2H), 6.78 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.3 Hz, 2H), 7.50−7.54 (m, 4H), 7.62−7.65 (m, 4H), 7.82 (t, *J* = 7.5 Hz, 2H).

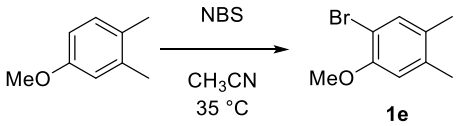
Observation of 3a by Mass Spectroscopy



In the anodic chamber were placed 4-methoxytoluene (**1a**) (23.6 mg, 0.193 mmol), *S*,*S*-diphenyl-*N*-(4-methylbenzenesulfonyl)sulfilimine (**2b**) (348 mg, 0.980 mmol), and 0.1 M $Bu_4NB(C_6F_5)_4/CH_2Cl_2$ (10 mL). In the cathodic chamber were placed TfOH (60 μL, 0.68 mmol) and 0.1 M $Bu_4NB(C_6F_5)_4/CH_2Cl_2$ (10 mL). The constant current electrolysis (8.0 mA) was carried out at 25 °C with magnetic stirring until 2.1 *F* of electricity was consumed. The solution in the anodic chamber was collected and about half the amount of the solvent was removed under reduced pressure. The reaction mixture was analyzed by ESI-MS. HRMS (ESI) calcd for $C_{27}H_{26}NO_3S_2$ (M^+): 476.1349, found: 476.1359.

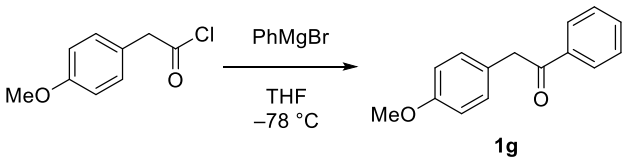
Reactions of 3 with Benzofuran

Preparation of 1-Bromo-2-methoxy-4,5-dimethylbenzene (1e)[21]



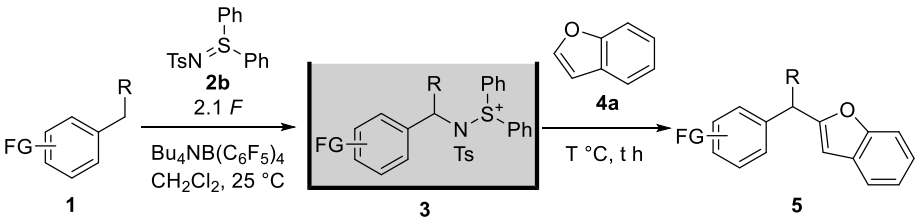
To a round-bottom flask were added 1,2-dimethylanisole (1.4 mL, 10 mmol) and CH_3CN (50 mL). After addition of *N*-bromosuccinimide (1.95 g, 10.9 mmol), the mixture was stirred at 35 °C for 20 h. The solvent was removed under reduced pressure. The residue was dissolved in hexane and the precipitate was separated by filtration. The filtrate was concentrated in vacuum and the residue was purified by recrystallization from hexane to give **1-bromo-2-methoxy-4,5-dimethylbenzene (1e)** in 45% yield (968 mg, 4.5 mmol). TLC R_f 0.62 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (s, 3H), 2.22 (s, 3H), 3.86 (s, 3H), 6.69 (s, 1H), 7.28 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6, 19.9, 56.3, 107.8, 113.4, 130.0, 133.8, 136.9, 153.6; HRMS (EI) calcd for $C_9H_{11}BrO$ (M^+): 213.9988, found: 213.9985.

Preparation of 2-(4-Methoxyphenyl)-1-phenylethanone (1g)[22]



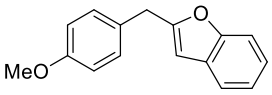
To a round-bottom flask were added 4-methoxyphenylacetyl chloride (4.6 mL, 30 mmol) and THF (20 mL). Phenylmagnesium bromide (1.0 M in THF, 30 mL, 30 mmol) was added dropwise at −78 °C. After being stirred at room temperature for 17 h, the mixture was diluted with EtOAc, washed with H_2O, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography (hexane/EtOAc 5/1) and recrystallized from hexane/EtOAc to give **2-(4-methoxyphenyl)-1-phenylethanone (1g)** in 16% yield (1.1 g, 4.8 mmol). TLC R_f 0.33 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 4.22 (s, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 7.18 (d, *J* = 8.8 Hz, 2H), 7.45 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.55 (tt, *J* = 1.6, 7.2 Hz, 1H), 8.01 (d, *J* = 7.2 Hz, 2H); The ^{1}H NMR spectrum is in agreement with that in the literature.[23]

Typical procedure for the generation of benzylaminosulfonium ions and their reactions with benzofuran



In the anodic chamber were placed benzylic substrate **1** (0.10 mmol), *S*,*S*-diphenyl-*N*-(4-methylbenzenesulfonyl)sulfilimine (**2b**) (355 mg, 1.00 mmol), and 0.1 M $Bu_4NB(C_6F_5)_4/CH_2Cl_2$ (10 mL). In the cathodic chamber were placed TfOH (30 μL, 0.68 mmol) and 0.1 M $Bu_4NB(C_6F_5)_4/CH_2Cl_2$ (10

mL). The constant current electrolysis (4.0 mA) was carried out at 25 °C with magnetic stirring until 2.1 *F* of electricity was consumed. Benzofuran (**4a**) (54 μL, 0.50 mmol) was added to the anodic chamber, and the resulting mixture was stirred T °C for t h (Tables 2 and 3). The solution in the anodic chamber was collected and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography and GPC to obtain the coupling product **5**.

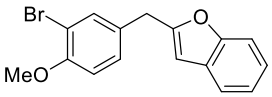


5aa

2-(4-methoxybenzyl)benzofuran (5aa).

Electrochemical oxidation (2.1 *F*) of 4-methoxytoluene (**1a**) (12.5 mg, 0.102 mmol) in the presence of **2b** (355 mg, 1.00 mmol), and the treatment with benzofuran followed by flash chromatography (hexane/EtOAc 100:0 to 50:1 to Et_2O) and GPC gave the title compound (18.9 mg, 0.079 mmol, 77%). TLC R_f 0.50 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 4.05 (s, 2H), 6.34 (s, 1H), 6.87 (d, *J* = 6.8 Hz, 2H), 7.15−7.24 (m, 4H), 7.38−7.42 (m, 1H), 7.44−7.48 (m, 1H); The ^{1}H NMR spectrum is in agreement with that in the literature.[24]

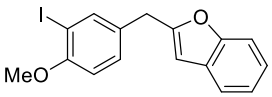
***S,S*-diphenyl-*N*-(4-methylbenzenesulfonyl)sulfilimine (2b)** was recovered in 100% yield (354 mg, 1.00 mmol) by flash chromatography followed by GPC.



5ba

2-(3-bromo-4-methoxybenzyl)benzofuran (5ba).

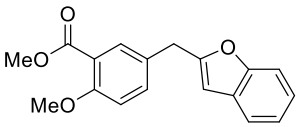
Electrochemical oxidation (2.1 *F*) of 3-bromo-4-methoxytoluene (**1b**) (18.6 mg, 0.092 mmol) and the treatment with benzofuran[25] followed by flash chromatography (hexane/EtOAc 100:0 to 50:1) gave the title compound (28.0 mg, 0.077 mmol, 88%). TLC R_f 0.45 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 3H), 4.02 (s, 2H), 6.38 (s, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 7.14−7.24 (m, 3H), 7.37−7.42 (m, 1H), 7.45−7.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.7, 56.3, 103.4, 110.9, 111.7, 112.0, 120.4, 122.6, 123.5, 128.7, 128.8, 130.8, 133.6, 154.8, 155.0, 157.3; HRMS (EI) calcd for $C_{16}H_{13}BrO_2$ (M^+): 316.0099, found: 316.0096.



5ca

2-(3-iodo-4-methoxybenzyl)benzofuran (5ca).

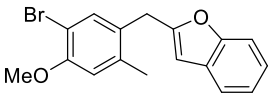
Electrochemical oxidation (2.1 *F*) of 3-iodo-4-methoxytoluene (**1c**) (21.7 mg, 0.088 mmol) and the treatment with benzofuran[25] followed by flash chromatography (hexane/EtOAc 100:0 to 50:1) gave the title compound (28.0 mg, 0.077 mmol, 88%). TLC R_f 0.44 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3H), 4.00 (s, 2H), 6.37 (s, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 7.15−7.26 (m, 3H), 7.38−7.42 (m, 1H), 7.46−7.50 (m, 1H), 7.72 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.5, 56.4, 86.0, 103.4, 110.87, 110.92, 120.4, 122.6, 123.5, 128.7, 129.9, 131.3, 139.7, 154.9, 157.0, 157.4; HRMS (ESI) calcd for $C_{16}H_{14}IO_2$ ($M+H^+$): 365.0033, found: 365.0030.



5da

2-[4-methoxy-3-(methoxycarbonyl)benzyl]benzofuran (5da).

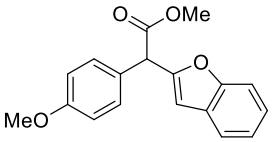
Electrochemical oxidation (2.1 *F*) of 4-methoxy-3-(methoxycarbonyl)toluene (**1d**) (18.0 mg, 0.100 mmol) and the treatment with benzofuran[25] followed by flash chromatography (hexane/EtOAc 100:0 to 10:1) and GPC gave the title compound (23.1 mg, 0.078 mmol, 78%). TLC R_f 0.19 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3 H), 3.89 (s, 3 H), 4.06 (s, 2 H), 6.36 (s, 1H), 6.94 (d, *J* = 8.8 Hz, 1H), 7.15−7.24 (m, 2H), 7.38−7.43 (m, 2H), 7.45−7.49 (m, 1H), 7.75 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.9, 52.0, 56.1, 103.4, 110.9, 112.3, 120.0, 120.4, 122.5, 123.5, 128.7, 128.9, 132.0, 133.9, 154.9, 157.5, 158.0, 166.5; HRMS (ESI) calcd for $C_{18}H_{17}O_4$ ($M+H^+$): 297.1121, found: 297.1112.



5ea

2-[(5-bromo-4-methoxy-2-methylphenyl)methyl]benzofuran (5ea).

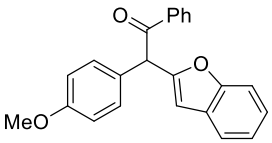
Electrochemical oxidation (2.1 *F*) of 5-bromo-4-methoxy-2-methyltoluene (**1e**) (21.5 mg, 0.100 mmol) and the treatment with benzofuran[25] followed by flash chromatography (hexane/EtOAc 100:0 to 20:1) and GPC gave the title compound (24.4 mg, 0.074 mmol, 74%). TLC R_f 0.55 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3H), 3.88 (s, 3H), 4.00 (s, 2H), 6.24 (s, 1H), 6.74 (s, 1H), 7.14−7.24 (m, 2H), 7.38−7.47 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6, 31.7, 56.2, 103.3, 108.4, 110.9, 114.0, 120.4, 122.5, 123.4, 128.7, 128.9, 134.2, 137.2, 154.6, 154.8, 157.0; HRMS (EI) calcd for $C_{16}H_{13}BrO_2$ (M^+): 330.0250, found: 330.0256.



5fa

2-[(methoxycarbonyl)-(4-methoxyphenyl)methyl]benzofuran (5fa).

Electrochemical oxidation (2.1 *F*) of (methoxycarbonyl)-(4-methoxyphenyl) methane (**1f**) (17.9 mg, 0.099 mmol) and the treatment with benzofuran[25] followed by flash chromatography (hexane/EtOAc 100:0 to 20:1) and GPC gave the title compound (22.4 mg, 0.074 mmol, 76%). TLC R_f 0.45 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 3.80 (s, 3 H), 5.09 (s, 1H), 6.56 (s, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.16−7.26 (m, 2H), 7.36 (d, *J* = 8.8 Hz, 2H), 7.40−7.44 (m, 1H), 7.47−7.51 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 50.8, 52.7, 55.3, 105.0, 111.1, 114.2, 120.9, 122.7, 124.0, 127.4, 128.2, 129.7, 154.95, 154.97, 159.4, 170.8; HRMS (ESI) calcd for $C_{18}H_{16}O_4Na$ ($M+Na^+$): 319.0941, found: 319.0940.

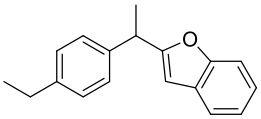


5ga

2-[(4-methoxyphenyl)-(phenylcarbonyl)methyl]benzofuran (5ga).

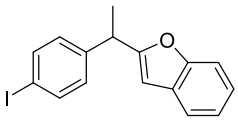
Electrochemical oxidation (2.1 *F*) of (4-methoxyphenyl)-(phenylcarbonyl) methane (**1g**) (22.3 mg, 0.099 mmol) and the treatment with benzofuran[25] followed by flash chromatography (hexane/EtOAc 100:0 to 50:1 to 20:1) and GPC gave the title compound (23.2 mg, 0.068 mmol, 68%). TLC R_f 0.38 (hexane/EtOAc 5:1); ^{1}H

NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 6.09 (s, 1H), 6.47 (s, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.14−7.26 (m, 2H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.38−7.48 (m, 4H), 7.53 (t, *J* = 7.5 Hz, 1H) 8.03 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.9, 55.2, 105.9, 111.1, 114.4, 120.8, 122.6, 123.9, 127.6, 128.4, 128.7, 128.9, 130.2, 133.3, 136.1, 155.0, 156.1, 159.3, 195.4; HRMS (ESI) calcd for $C_{23}H_{19}O_3$ ($M+H^+$): 343.1329, found: 343.1325.


5ha

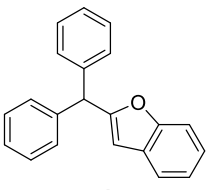
2-[1-(4-ethylphenyl)ethyl]benzofuran (5ha).

Electrochemical oxidation (3.0 *F*) of *p*-diethylbenzene (**1h**) (13.1 mg, 0.098 mmol) at 0 °C and the treatment with benzofuran[25] followed by flash chromatography (hexane/EtOAc 100:0 to 100:1) and GPC gave the title compound (15.6 mg, 0.062 mmol, 64%). TLC R_f 0.59 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7.4 Hz, 3H), 1.68 (d, *J* = 7.0 Hz, 3H), 2.63 (q, *J* = 7.4 Hz, 2H), 4.22 (q, *J* = 7.5 Hz, 1H), 6.42 (s, 1H), 7.12−7.22 (m, 6H), 7.36−7.40 (m, 1H), 7.46−7.50 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 20.4, 28.4, 39.2, 101.9, 110.9, 120.4, 122.4, 123.3, 127.4, 128.0, 128.6, 140.5, 142.6, 154.8, 162.4; HRMS (APCI) calcd for $C_{18}H_{19}O$ ($M+H^+$): 251.1430, found: 251.1421.


5ia

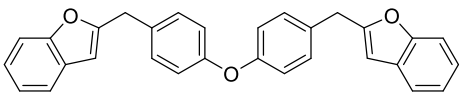
2-[1-(4-iodophenyl)ethyl]benzofuran (5ia).

Electrochemical oxidation (2.5 *F*) of 1-ethyl-4-iodobenzene (**1i**) (46.1 mg, 0.199 mmol) and the treatment with benzofuran[25] followed by flash chromatography (hexane/EtOAc 100:0 to 50:1) and GPC gave the title compound (42.3 mg, 0.121 mmol, 61%). TLC R_f 0.21 (hexane/EtOAc 50:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66 (d, *J* = 7.4 Hz, 3H), 4.19 (q, *J* = 7.0 Hz, 1H), 6.43 (s, 1H), 7.03 (d, *J* = 8.4 Hz, 2H), 7.15−7.23 (m, 2H), 7.36−7.39 (m, 1H), 7.47−7.51 (m, 1H), 7.63 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 39.2, 92.0, 102.3, 111.0, 120.5, 122.5, 123.6, 128.4, 129.5, 137.6, 143.0, 154.8, 161.2; HRMS (EI) calcd for $C_{16}H_{13}IO$ (M^+): 348.0006, found: 348.0007.


5ja

2-diphenylmethylbenzofuran (5ja).

Electrochemical oxidation (2.1 *F*) of diphenylmethane (**1j**) (15.7 mg, 0.093 mmol) and the treatment with benzofuran followed by flash chromatography (hexane/EtOAc 100:0 to 50:1) and GPC gave the title compound (23.8 mg, 0.059 mmol, 63%). TLC R_f 0.70 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.58 (s, 1H), 6.27 (s, 1H), 7.15−7.35 (m, 12H), 7.39−7.42 (m, 1H), 7.45−7.47 (m, 1H). The ^{1}H NMR spectrum is in agreement with that in the literature.[26]

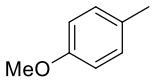
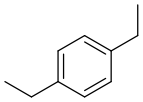
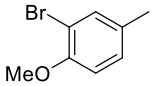
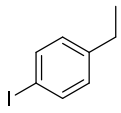
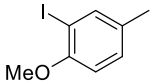
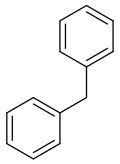
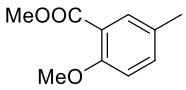
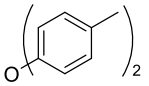
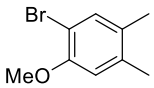
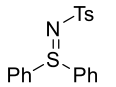
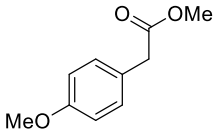
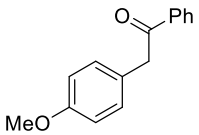
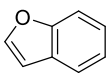


5ka

Bis[4-(2-benzofurylmethyl)phenyl]ether (5ka).

Electrochemical oxidation (4.1 *F*) of di-*p*-tolylether (**1k**) (20.7 mg, 0.104 mmol) and the treatment with benzofuran[25] followed by flash chromatography (hexane/EtOAc 100:0 to 50:1) and GPC gave the title compound (23.0 mg, 0.053 mmol, 51%). TLC R_f 0.56 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.08 (s, 4H), 6.38 (s, 2H), 6.96 (d, *J* = 8.3 Hz, 4H), 7.15−7.28 (m, 8H), 7.39−7.43 (m, 2H), 7.46−7.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.2, 103.3, 110.9, 118.9, 120.4, 122.5, 123.4, 128.7, 130.2, 132.0, 154.9, 156.0, 157.8; HRMS (EI) calcd for $C_{30}H_{22}O_3$ (M^+): 430.1563, found: 430.1561.

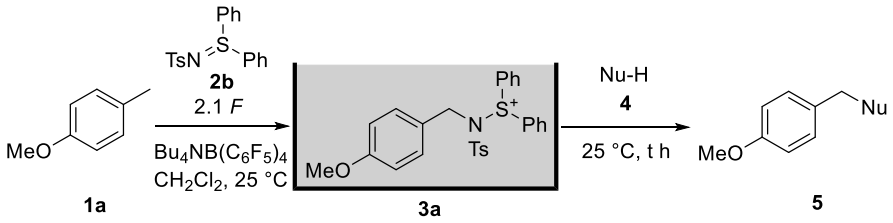
Oxidation Potentials

substrate	decomposition potential (V)	substrate	decompositon potential (V)
 **1a**	1.38[12]	 **1h**	1.75
 **1b**	1.59	 **1i**	1.82
 **1c**	1.52	 **1j**	1.91[3c]
 **1d**	1.61	 **1k**	1.50
 **1e**	1.49	 **2b**	2.01
 **1f**	1.54		
 **1g**	1.47	 **4a**	1.49

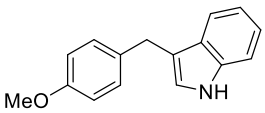
Rotating-disk electrode (RDE) voltammetry was carried out using BAS 600C and BAS RRDE-3 rotating disk electrodes. Measurements were carried out in 0.1 M $LiClO_4/CH_3CN$ using a glassy carbon disk working electrode, a platinum wire counter electrode, and an SCE reference electrode with sweep rate of 10 mVs^{-1} at 3000 rpm at room temperatue. The substrate concentration was 10.0 mM.

Reactions of 3a with Nucleophiles

Typical procedure for the generation of benzylaminosulfonium ions and their reactions with nucleophiles



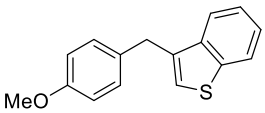
In the anodic chamber were placed 4-methoxytoluene (**1**) (12.2 mg, 0.10 mmol), *S*,*S*-diphenyl-*N*-(4-methylbenzenesulfonyl)sulfilimine (**2b**) (355 mg, 1.00 mmol), and 0.1 M $Bu_4NB(C_6F_5)_4/CH_2Cl_2$ (10 mL). In the cathodic chamber were placed TfOH (30 μL, 0.68 mmol) and 0.1 M $Bu_4NB(C_6F_5)_4/CH_2Cl_2$ (10 mL). The constant current electrolysis (4.0 mA) was carried out at 25 °C with magnetic stirring until 2.1 *F* of electricity was consumed. Nucleophile **4** (0.50 mmol) was added to the anodic chamber, and the resulting mixture was stirred T °C for t h. The solution in the anodic chamber was collected and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography and GPC to obtain the coupling product **5**.



5ab

3-(4-methoxybenzyl)indole (5ab).

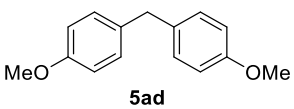
Electrochemical oxidation (2.1 *F*) of 4-methoxytoluene (11.7 mg, 0.096 mmol) and the treatment with indole (**4b**) followed by flash chromatography (hexane/EtOAc 100:0 to 5:1) and GPC gave the title compound (17.1 mg, 0.072 mmol, 75%). TLC R_f 0.27 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 4.06 (s, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.88−6.91 (m, 1H), 7.07 (ddd, *J* = 1.2, 7.6, 8.4 Hz, 1H), 7.15−7.22 (m, 3H), 7.35 (td, *J* = 0.8, 8.0 Hz, 1H), 7.49−7.53 (m, 1H), 7.93 (br, 1H). The ^{1}H NMR spectrum is in agreement with that in the literature.[27]



5ac

3-(4-methoxybenzyl)benzo[*b*]thiophene (5ac).

Electrochemical oxidation (2.1 *F*) of 4-methoxytoluene (11.8 mg, 0.097 mmol) and the treatment with benzo[*b*]thiophene (**4c**) followed by flash chromatography (hexane/EtOAc 100:0 to 50:1) and GPC gave the title compound (13.9 mg, 0.054 mmol, 56%). TLC R_f 0.60 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 4.13 (s, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 6.98 (s, 1H), 7.18 (d, *J* = 8.8 Hz, 2H), 7.32−7.35 (m, 2H), 7.68−7.71 (m, 1H), 7.84−7.87 (m, 1H). The ^{1}H NMR spectrum is in agreement with that in the literature.[28]

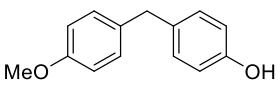


5ad

di(4-methoxyphenyl)methane (5ad).

Electrochemical oxidation (2.1 *F*) of 4-methoxytoluene (11.6 mg, 0.095 mmol) and the treatment with anisole (**4d**) followed by flash chromatography (hexane/EtOAc

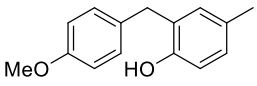
100:0 to 20:1) and GPC gave the title compound (14.2 mg, 0.062 mmol, 65%). TLC R_f 0.57 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 6H), 3.86 (s, 4H), 6.82 (d, *J* = 8.4 Hz, 4H), 7.09 (d, *J* = 8.4 Hz, 4H). The ^{1}H NMR spectrum is in agreement with that in the literature.[29]



5ae

4-(4-methoxybenzyl)phenol (5ae).

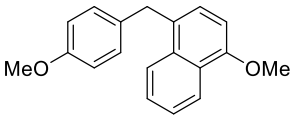
Electrochemical oxidation (2.1 *F*) of 4-methoxytoluene (11.0 mg, 0.090 mmol) and the treatment with phenol (**4e**) followed by flash chromatography (hexane/EtOAc 100:0 to 5:1) gave the title compound (14.8 mg, 0.069 mmol, 77%). TLC R_f 0.60 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 3.85 (s, 2H), 4.82 (br, 1H), 6.74 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H). The ^{1}H NMR spectrum is in agreement with that in the literature.[30,31]



5af

2-(4-methoxybenzyl)-4-methylphenol (5af).

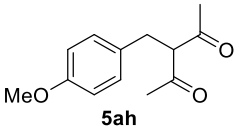
Electrochemical oxidation (2.1 *F*) of 4-methoxytoluene (11.5 mg, 0.094 mmol) and the treatment with *p*-cresol (**4f**) followed by flash chromatography (hexane/EtOAc 100:0 to 10:1) and GPC gave the title compound (18.0 mg, 0.079 mmol, 84%). TLC R_f 0.27 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 3.78 (s, 3H), 3.89 (s, 2H), 4.56 (br, 1H), 6.68 (d, *J* = 8.3 Hz, 1H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.84−6.92 (m, 2H), 7.14 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 35.6, 55.2, 114.1, 115.6, 126.9, 128.1, 129.6, 130.1, 131.4, 131.8, 151.5, 158.1; HRMS (EI) calcd for $C_{15}H_{16}O_2$ (M^+): 228.1150, found: 228.1150.



5ag

1-methoxy-4-(4-methoxybenzyl)naphthalene (5ag).

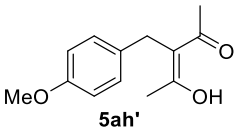
Electrochemical oxidation (2.1 *F*) of 4-methoxytoluene (11.6 mg, 0.095 mmol) and the treatment with 1-methoxynaphthalene (**4g**) followed by flash chromatography (hexane/EtOAc 100:0 to 50:1) and GPC gave the title compound (21.8 mg, 0.078 mmol, 82%). TLC R_f 0.47 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 3.98 (s, 3H), 4.30 (s, 2H), 6.74 (d, *J* = 7.6 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 1H), 7.42−7.47 (m, 2H), 7.87−7.94 (m, 1H), 8.26−8.32 (m, 1H). The ^{1}H NMR spectrum is in agreement with that in the literature.[32]



5ah

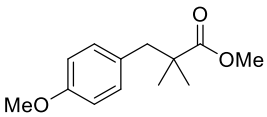
3-(4-methoxybenzyl)-2,4-pentanedione (5ah).

Electrochemical oxidation (2.1 *F*) of 4-methoxytoluene (11.5 mg, 0.094 mmol) and the treatment with 2,4-pentanedione (**4h**) followed by flash chromatography (hexane/EtOAc 100:0 to 50:1 to 5:1) gave the title compound (18.3 mg, 0.083 mmol, 88%, 2:3 mixture of **5ah** and **5ah'**). TLC R_f 0.26 (hexane/EtOAc 5:1); ^{1}H NMR (400



5ah'

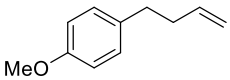
MHz, $CDCl_3$) **5ah** δ 2.08 (s, 6H), 3.09 (d, *J* = 7.4 Hz, 2H), 3.78 (s, 3H), 3.97 (t, *J* = 7.5 Hz, 1H) 6.80−6.87 (m, 2H), 7.04−7.10 (m, 2H); **5ah** δ 2.12 (s, 6H), 3.59 (s, 2H), 3.79 (s, 3H), 6.80−6.87 (m, 2H), 7.04−7.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 29.7, 32.0, 33.5, 55.2, 55.3, 70.2, 108.6, 114.0, 114.1, 128.3, 129.6, 129.9, 131.5, 158.1, 158.4, 191.9, 203.7; HRMS (EI) calcd for $C_{13}H_{16}O_3$ ($M+Na^+$): 243.0992, found: 243.0991.



5ai

methyl 3-(4-methoxyphenyl)-2,2-dimethylpropanoate (5ai).

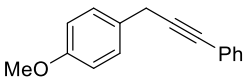
Electrochemical oxidation (2.1 *F*) of 4-methoxytoluene (11.8 mg, 0.097 mmol) and the treatment with methyl trimethylsilyl dimethylketene acetal (**4i**) followed by flash chromatography (hexane/EtOAc 100:0 to 50:1 to 20:1) and GPC gave the title compound (14.4 mg, 0.065 mmol, 67%). TLC R_f 0.42 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 6H), 2.79 (s, 2H), 3.65 (s, 3H), 3.78 (s, 3H), 6.80 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 8.4 Hz, 2H). The ^{1}H NMR spectrum is in agreement with that in the literature.[33]



5aj

4-(4-methoxyphenyl)-1-butene (5aj).

Electrochemical oxidation (2.1 *F*) of 4-methoxytoluene (11.4 mg, 0.093 mmol) and the treatment with allyltrimethylsilane (**4j**)[34] followed by flash chromatography (hexane/EtOAc 100:0 to 50:1) gave the title compound (12.2 mg, 0.075 mmol, 81%). TLC R_f 0.64 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30−2.38 (m, 2H), 2.65 (t, *J* = 7.2 Hz, 2H), 3.79 (s, 3H), 4.90−5.07 (m, 2H), 6.80 (tdd, *J* = 7.6, 12.8, 16.8 Hz, 1H), 6.83 (d, *J* = 8.8 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H); The ^{1}H NMR spectrum is in agreement with that in the literature.[35]



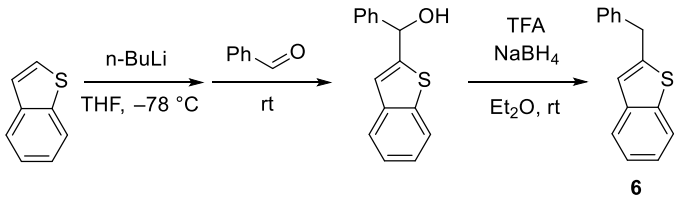
5ak

3-(4-methoxyphenyl)-1-phenylpropyne (5ak).

Electrochemical oxidation (2.1 *F*) of 4-methoxytoluene (10.7 mg, 0.088 mmol) and the treatment with 1-phenyl-2-(trimethylsilyl)acetylene (**4k**) followed by flash chromatography (hexane/EtOAc 100:0 to 50:1) and GPC gave the title compound (10.7 mg, 0.048 mmol, 55%). TLC R_f 0.45 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 2H), 3.81 (s, 3H), 6.88 (d, *J* = 8.4 Hz, 2H), 7.27−7.30 (m, 2H), 7.33 (d, *J* = 8.8 Hz, 2H), 7.42−7.46 (m, 2H). The ^{1}H NMR spectrum is in agreement with that in the literature.[36]

Synthesis of an Inhibitor of PTPase

Preparation of 2-Benzylbenzo[*b*]thiophene 6[17b]

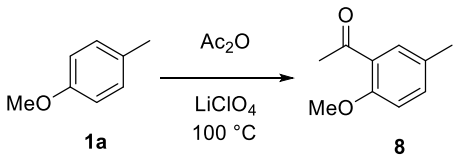


6

To a round-bottom flask were added benzo[*b*]thiophene (3.72 g, 27.9 mmol) and THF (100 mL). *n*-BuLi (2.5 M in hexane, 12 mL, 30 mmol) was added dropwise at −78 °C. After being stirred at −78 °C for 1 h, benzaldehyde (3.2 mL, 32 mmol) was added to the mixture. After stirring at room temperature for 30 min, the mixture was diluted with Et_2O, washed with sat. NH_4Cl, H_2O and brine, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by recrystallization from hexane/Et_2O to give **benzo[*b*]thiophen-2-yl-phenylmethanol** in 74% yield (4.96 g, 20.6 mmol). TLC R_f 0.21 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (d, *J* = 4.4 Hz, 1H), 6.12 (d, *J* = 4.4 Hz, 1H), 7.12 (t, *J* = 0.8 Hz, 1H), 7.25−7.41 (m, 5H), 7.47−7.51 (m, 2H), 7.66−7.70 (m, 1H), 7.75−7.79 (m, 1H). The ^{1}H NMR spectrum is in agreement with that in the literature.[37]

To a round-bottom flask were added benzo[*b*]thiophen-2-yl-phenylmethanol (2.01 g, 8.36 mmol), $NaBH_4$ and Et_2O (150 mL). To the mixture was added CF_3COOH (12 mL, 16 mmol) dropwise, and the mixture was stirred at room temperature for 6 h. To the mixture was added 10 wt% *aq*NaOH (150 mL), and the mixture was stirred at room temperature for 30 min. The mixture was washed with H_2O and brine, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography (hexane) to give **2-benzylbenzo[*b*]thiophene (6)** in 80% yield (1.50 g, 6.69 mmol). TLC R_f 0.72 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (s, 2H), 6.99−7.01 (m, 1H), 7.22−7.36 (m, 7 H), 7.64−7.67 (m, 1H), 7.71−7.75 (m, 1H). The ^{1}H NMR spectrum is in agreement with that in the literature.[38]

Preparation of 3-Acetyl-4-methoxytoluene (8)[39]

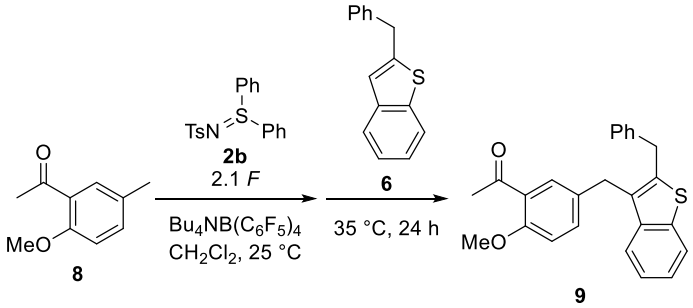


1a **8**

To a round-bottom flask were added $LiClO_4$ (2.11 g, 19.8 mmol) and Ac_2O (1 mL, 10.6 mmol). To the mixture was added 4-methoxytoluene (1.25 mL, 9.92 mmol) dropwise at 100 °C, and the mixture was stirred at 100 °C for 3 h. Then, the mixture was diluted with CH_2Cl_2, washed with sat. $NaHCO_3$ and H_2O, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by GPC to give **3-acetyl-4-methoxytoluene (8)** in 77% yield (1.12 g, 7.43 mmol). TLC R_f 0.33 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H), 2.61 (s, 3H), 3.88 (s, 3H), 6.86 (d, *J* = 8.4 Hz, 1H), 7.26 (dd, *J* = 1.8, 8.4 Hz, 1H),

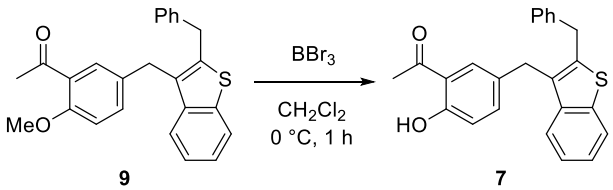
7.53 (d, J = 2.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 31.8, 55.5, 111.5, 127.8, 129.8, 130.6, 134.1, 156.9, 200.1; HRMS (ESI) calcd for $C_{10}H_{12}O_2$ ($M+H^+$): 165.0910, found: 165.0907.

Synthesis of 2-Benzyl-3-(3-acetyl-4-methoxybenzyl)benzo[*b*]thiophene (9)



In the anodic chamber were placed 3-acetyl-4-methoxytoluene (**8**) (15.4 mg, 0.094 mmol), *S*,*S*-diphenyl-*N*-(4-methylbenzenesulfonyl)sulfilimine (**2b**) (351 mg, 0.99 mmol), and 0.1 M $Bu_4NB(C_6F_5)_4/CH_2Cl_2$ (10 mL). In the cathodic chamber were placed TfOH (30 μL, 0.68 mmol) and 0.1 M $Bu_4NB(C_6F_5)_4/CH_2Cl_2$ (10 mL). The constant current electrolysis (4.0 mA) was carried out at 25 °C with magnetic stirring until 2.1 F of electricity was consumed. The solution in the anodic chamber was transferred to a 100 mL round-bottom flask under argon atmosphere. 2-Benzylbenzo[*b*]thiophene (**6**) (219 mg) was added to the solution, and the resulting mixtures were stirred at 35 °C for 24 h. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography (hexane/EtOAc 100:0 to 10:1) and GPC to obtain **2-benzyl-3-(3-acetyl-4-methoxybenzyl)benzo[*b*]thiophene (9)** in 70% yield (25.5 mg, 0.066 mmol). TLC R_f 0.32 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.56 (s, 3H), 3.83 (s, 3H), 4.17 (s, 2H), 4.22 (s, 2H), 6.77 (d, J = 8.8 Hz, 1H), 7.07 (dd, J = 2.6, 8.8 Hz, 1H), 7.19−7.30 (m, 7H), 7.49−7.54 (m, 1H), 7.61 (d, J = 2.6 Hz, 1H), 7.71−7.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.0, 31.7, 34.4, 55.4, 111.7, 121.8, 122.1, 123.7, 123.9, 126.5, 127.9, 128.46, 128.50, 129.7, 129.8, 131.5, 132.9, 138.8, 139.3, 140.00, 140.04, 157.3, 199.6; HRMS (EI) calcd for $C_{25}H_{23}O_2S$ ($M+H^+$): 387.1413, found: 387.1407.

Synthesis of 2-Benzyl-3-(3-acetyl-4-hydroxybenzyl)benzo[*b*]thiophene (7)[17b]



To a round-bottom flask were added 2-benzyl-3-(3-acetyl-4-methoxybenzyl)benzo[*b*]thiophene (**9**) (56.2 mg, 0.145 mmol) and CH_2Cl_2 (2 mL). BBr_3 (1.0 M in CH_2Cl_2, 0.60 mL) was added at 0 °C. After being stirred at 0 °C for 1 h, H_2O (5 mL) was added to the mixture. After being stirred at room temperature for 30 min, the mixture was washed with H_2O, dried over Na_2SO_4. The solvent was removed under reduced pressure to give **2-benzyl-3-(3-acetyl-4-hydroxybenzyl)benzo[*b*]thiophene (7)** in 99% yield (53.4 mg, 0.143 mmol). TLC R_f 0.42 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H), 4.18 (s, 2H), 4.23 (s, 2H), 6.84 (d, J = 8.3 Hz,

1H), 7.18−7.32 (m, 8H), 7.35 (d, J = 1.8 Hz, 1H), 7.50−7.54 (m, 1H), 7.77−7.80 (m, 1H), 12.10 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.5, 31.1, 34.5, 118.4, 119.4, 121.7, 122.3, 123.9, 124.1, 126.6, 128.5, 128.6, 129.5, 129.66, 129.74, 136.4, 138.9, 139.3, 139.9, 140.1, 160.7, 204.4; HRMS (EI) calcd for $C_{24}H_{21}O_2S$ ($M+H^+$): 373.1257, found: 373.1251.

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 oxidation of C−H bonds: (a) Yoshida, K.; Fueno, T. *J. Org. Chem.* **1972**, *37*, 4145. (b) Ho, X.-H.; Mho, S.; Kang, H.; Jang, H.-Y. *Eur. J. Org. Chem.* **2010**, 4436. (c) Morofuji, T.; Shimizu, A.; Yoshida, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 7259. (d) Shoji, T.; Kim, S.; Yamamoto, K.; Kawai, T.; Okada, Y.; Chiba, K. *Org. Lett.* **2014**, *16*, 6404. (e) Elsler, B.; Schollmeyer, D.; Dyballa, K. M.; Franke, R.; Waldvogel, S. R. *Angew. Chem., Int. Ed.* **2014**, *53*, 5210. (f) 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 of *p*-methoxybenzyl(tosyl)amine: Ghorai, P.; Das, B. G. *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. *Bull. Korean Chem. Soc.* **2005**, *26*, 1138.

(18) Saito, K.; Ueoka, K.; Matsumoto, K.; Suga, S.; Nokami, T.; Yoshida, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 5153.

(19) Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 4537.

(20) Marzinzik, A. L.; Sharpless, K. B. *J. Org. Chem.* **2001**, *66*, 594.

(21) Murigi, F. N.; Nichol, G. S.; Mash, E. A. *J. Org. Chem.* **2010**, *75*, 1293.

(22) Schneider, M. R.; Angerer, E.; Schonenberger, H.; Michel, R. T.; Fortmeyer, H. P. *J. Med. Chem.* **1982**, *25*, 1070.

(23) Yu, J.-W.; Mao, S.; Wang, Y.-Q. *Tetrahedron Lett.* **2015**, *56*, 1575.

(24) Zhou, L.; Shi, Y.; Xian, Q.; Liu, Y.; Ye, F.; Zhang, Y.; Wang, J. *Org. Lett.* **2011**, *13*, 968.

(25) After electrolysis, the solution in the anodic chamber was transferred to a 100 mL round-bottom flask under argon atmosphere.

(26) Xian, T.; Dong, X.; Zhou, L. *Org. Biomol. Chem.* **2013**, *11*, 1490.

(27) Chu, X.-Q.; Jiang, R.; Fang, Y.; Gu, Z.-Y.; Meng, H.; Wang, S.-Y.; Ji, S.-J. *Tetrahedron Lett.* **2013**, *69*, 1166.

(28) Kupracz, L.; Kirschning, A. *J. Flow. Chem.* **2012**, *3*, 11.

(29) Maity, P.; Shacklady-McAtee, D. M.; Yap, G. P. A.; Sirianni, E. R.; Watson, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 280.

(30) Chem, D.; Xu, C.; Deng, J.; Jiang, C.; Wen, X.; Kong, L.; Zhang, J.; Sun, H. *Tetrahedron* **2014**, *70*, 1975.

(31) Bartoli, G.; Dalpozzo, R.; Nino, A. D.; Maiuolo, L.; Nardi, M.; Procopio, A.; Tagarelli, A. *Eur. J. Org. Chem.* **2004**, 2176.

(32) Marjan, J.; Vrazic, D. *Org. Biomol. Chem.* **2013**, *11*, 1978.

(33) Nishimoto, Y.; Yasuda, M.; Baba, A. *Org. Lett.* **2007**, *9*, 4931.

(34) After electrolysis, the solution in the anodic chamber was transferred to a 100 mL round-bottom flask, the solvent was removed and 1,2-dichloromethane (5 mL) was added as solvent.

(35) Li, Y.; Hu, Y.-Y.; Zhang, S.-L. *Chem. Commun.* **2013**, *49*, 10635.

(36) Meyer, V. J.; Niggemann, M. *Chem. Eur. J.* **2012**, *18*, 4687.

(37) Kuriyama, M.; Ishiyama, N.; Shimazawa, R.; Onomura, O. *Tetrahedron* **2010**, *66*, 6814.

(38) Lapointe, D.; Fagnou, K. *Org. Lett.* **2009**, *11*, 4160.

(39) Bartoli, G.; Bosco, M.; Marcantoni, E.; Massaccesi, M.; Rinaldi, S.; Sambri, L. *Tetrahedron Lett.* **2002**, *43*, 6331.

Chapter 2

Metal-Free Benzylic C–H Amination via Electrochemically Generated Benzylaminosulfonium Ions

Abstract

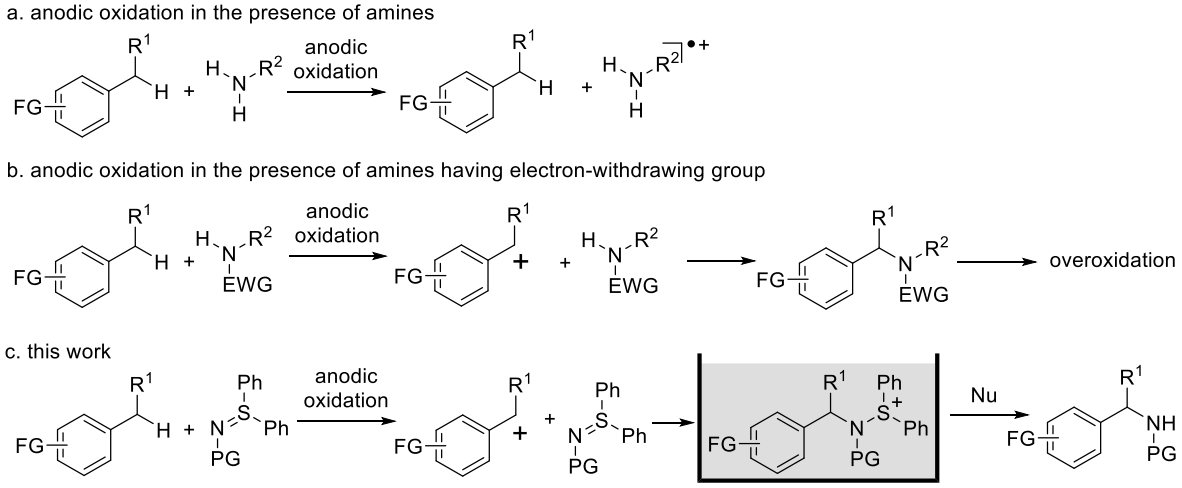
Electrochemical oxidation of toluene derivatives in the presence of *N*-tosyldiphenylsulfilimine gave the corresponding benzylaminosulfonium ions, which were treated with tetrabutylammonium iodide under non-electrolytic conditions to give *N*-tosylbenzylamines. The transformation serves as a metal- and chemical-oxidant-free method for benzylic C–H amination. Because of high oxidation potential of *N*-tosyldiphenylsulfilimine the present method can be applied to synthesis of various benzylamines from toluene derivatives bearing various functional groups.

Introduction

C–H amination[1] serves as a step-economical[2] method for C–N bond formation because prefunctionalization of carbon substrates is not required. In particular, developing a new method for intermolecular $C_{sp}{}^3$–H amination is interesting, because low reactivity of $C_{sp}{}^3$–H bonds makes its functionalization more difficult than that of other C–H bonds.[3] Also, selective intermolecular C–H functionalization is generally difficult from viewpoints of chemo- and regiochemistry. While several transition-metal-catalyzed intermolecular $C_{sp}{}^3$–H amination reactions have been reported,[4] transition-metal-free methods should be preferred from an environmental point of view.[1e,5] However, in many cases, an excess amount of a carbon substrate is necessary to suppress overreaction. Although there are some reports aimed at solving such a problem,[6] the development of a more versatile method is still desired, in particular, for benzylic C–H amination.

Electrochemical oxidation serves as a powerful method for generating reactive cationic species via benzylic C–H bond cleavage.[7,8] However, electrochemical benzylic C–H amination often suffers from undesired oxidation of nitrogen nucleophiles, which have usually lower oxidation potentials than those of carbon substrates (Scheme 1a). The use of amines bearing an electron-withdrawing group would lead to selective oxidation of carbon substrates, but oxidation of the amination products (overoxidation) is unavoidable because the products have similar oxidation potentials to those of carbon substrates (Scheme 1b). The use of acetonitrile as a nucleophile/solvent leads to effective introduction of a nitrogen atom on the carbon, but the products obtained after hydrolysis are acetoamide derivatives which are rather difficult to transform into other nitrogen-containing compounds in comparison with amines and other protected amines.[9]

Scheme 1. Electrochemical Benzylic C–H Amination.



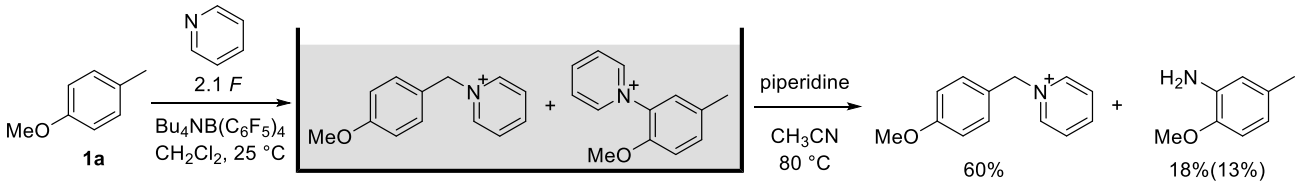
Recently, Yoshida and Waldvogel have reported, independently, electrochemical aromatic and benzylic C–H functionalization using nitrogen nucleophiles such as pyridine,[10a,e] *N*-mesylimidazole,[10b] pyrimidine,[10c] oxazoline,[10d] and sulfilimine.[10f] In these reactions, starting carbon substrates are electrochemically oxidized in the presence of nitrogen nucleophiles to generate and accumulate electrooxidatively inactive cationic intermediates. After the electrolysis, the cationic intermediates are transformed into desired products by chemical reactions under

non-oxidative conditions. Because of the intermediacy of the cationic species, overoxidation is completely suppressed. Therefore, the use of excess amounts of carbon substrates is not necessary for the transformation. On the basis of these backgrounds, electrochemical benzylic C–H amination without using excess amounts of carbon substrates was achieved using a similar methodology.

Results and Discussions

First, benzylic C–H amination using pyridine was examined because aromatic C–H amination using pyridine have been previously reported (Scheme 2).[10a] When 4-methoxytoluene (**1a**) was electrochemically oxidized in the presence of pyridine, a mixture of the benzylpyridinium derivative and the phenylpyridinium derivative were obtained, indicating that selective benzylic C–H transformation using pyridine is difficult. Moreover, the benzylpyridinium derivative did not react with piperidine to give the desired benzylamine. The result indicates that pyridine is not a suitable nitrogen nucleophile for benzylic C–H amination.

Scheme 2. Benzylic C–H amination using pyridine. Yields determined by NMR are shown. The yield in the parenthesis was determined by GC.

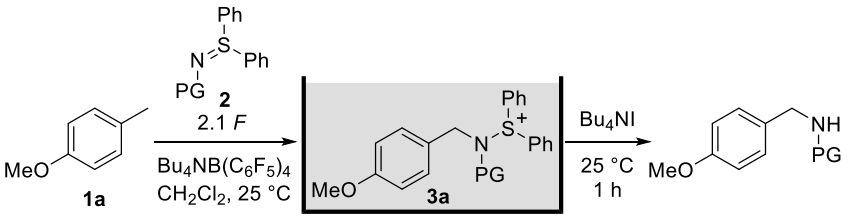


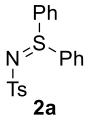
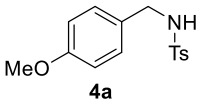
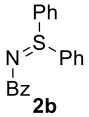
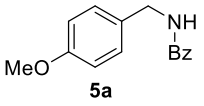
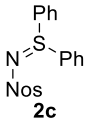
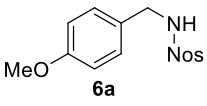
Then benzylic C–H amination using a sulfilimine bearing tosyl (Ts) group (**2a**) was examined. As described in chapter 1, the electrochemical oxidation of benzylic substrates gives *N*-tosylbenzylaminosulfonium ions which reacted as benzyl cation equivalent with carbon nucleophiles via C–N bond cleavage.[10f] This chapter shows that under suitable conditions *N*-tosylbenzylaminosulfonium ions can be transformed into the corresponding benzylamine via N–S bond cleavage without cleaving the C–N bond (Scheme 1c). Bu_4NI was chosen as a nucleophile because N–S bond in sulfilimines is known to be reductively cleaved by I^-.[11] In fact, the *N*-tosylbenzylaminosulfonium ion **3a**, which was generated by the electrochemical oxidation of **1a** in the presence of **2a**, was successfully converted into the corresponding benzylamine **4a** and diphenyl sulfide by the treatment with Bu_4NI (Table 1, entry 1). In addition, unchanged **2a** was also recovered (See Experimental Section for the details). Notably, benzylic C–H amination of **1a** was successfully achieved without using an excess amount of **1a**. Also, the fact that the oxidation potential of **4a** (decomposition potential: 1.49 V vs SCE) is close to that of **1a** (1.38 V) indicates that the direct oxidation of **1a** to **4a** should suffer from overoxidation. Thus, the present two step transformation via the cationic intermediate is advantageous.

Next, the effect of the substituent on the nitrogen atom was examined because it should affect the oxidation potential and nucleophilicity of sulfilimines (Table 1). A sulfilimine having benzoyl (Bz) group **2b** also gave the corresponding benzylamine **5a** in 81% yield (entry 2). However, the sulfilimine having 4-nitrobenzenesulfonyl (Nos) group **2c** gave the corresponding benzylamine **6a** in only 1% (entry 3). This is probably because of low

nucleophilicity of **2c**, which is expected from its high oxidation potential (2.15 V). Hereafter **2a** was used as a nitrogen source because the oxidation potential of **2a** (2.01 V), is higher than that of **2b** (1.82 V), which enables selective oxidation of wider range of toluene derivatives. In addition, several methods for deprotection of tosyl group have been reported.[12]

Table 1. Benzylic C–H amination using sulfilimines.

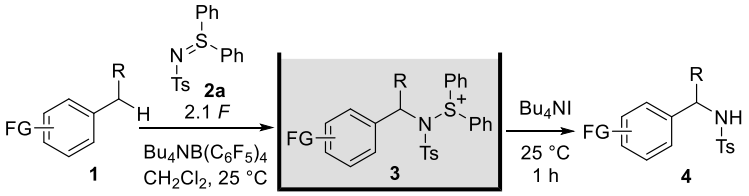


entry	sulfilimine	oxidation potential(V vs SCE)[a]	product	yield
1	 **2a**	2.01	 **4a**	79%
2	 **2b**	1.82	 **5a**	81%
3	 **2c**	2.15	 **6a**	1%

1a (0.1 mmol) was electrochemically oxidized in the presence of 1.0 mmol of **2** in a 0.1 M solution of $Bu_4NB(C_6F_5)_4$ in CH_2Cl_2 at 25 °C. After 2.1 *F* of electricity was applied, the resulting solution was treated with Bu_4NI (0.5 mmol) at 25 °C. Isolated yield of the products based on the amount of **1a** used is shown. a) Decomposition potential (V vs SCE).

The present two-step one-pot transformation is applicable to various toluene derivatives whose oxidation potentials are 1.38–1.94 V because of high oxidation potential of **2a** (Table 2). Toluene (**1b**), xylenes, and toluene derivatives having *tert*-butyl, aryl, acetoxy, *N*-phthaloyl (PhthN), and halogen groups at 4-position gave the corresponding *N*-tosylbenzylamines (entries 1–12). It is noteworthy that the substrate having two benzylic C–H bonds gave the monoaminated product selectively (entries 2, 3, 4, and 6). 4-Methoxytoluene derivatives having bromo, ketone carbonyl, ester carbonyl, and nitro groups at 3-position were successfully transformed to the corresponding *N*-tosylbenzylamines (entries 14–17). Toluene derivatives having secondary benzylic C–H bonds can also be transformed to the corresponding *N*-tosylbenzylamines. Ethylbenzene (**1r**) gave *N*-tosyl-1-phenylethylamine (entry 18). The benzylic C–H bonds at α-position of ketone and ester carbonyl groups were also successfully transformed to the coresponidng α-amino ketone and α-amino ester (entries 19 and 20). Moreover, heteroaromatic compounds such as 2-methylthiophene derivative **1u** was successfully aminated (entry 21).

Table 2. Benzylic C–H amination of various toluene derivatives.



entry	substrate	oxidation potential[a] (V vs SCE)	product	yield
1	**1b**	1.94	**4b**	38%
2	**1c**	1.84	**4c**	66%
3	**1d**	1.85	**4d**	53%
4	**1e**	1.85	**4e**	84%
5	**1f**	1.79	**4f**	73%
6	**1g**	1.50	**4g**	62%
7	**1h**	1.82	**4h**	85%[b]
8	**1i**	1.81	**4i**	48%
9	**1j**	1.93	**4j**	69%
10	**1k**	1.94	**4k**	31%
11	**1l**	1.89	**4l**	74%
12	**1m**	1.79	**4m**	81%
13	**1a**	1.38	**4a**	79%
14	**1n**	1.59	**4n**	86%[b]
15	**1o**	1.58	**4o**	76%
16	**1p**	1.62	**4p**	66%
17	**1q**	1.77	**4q**	90%
18	**1r**	1.94	**4r**	69%[c]
19	**1s**	1.50	**4s**	76%
20	**1t**	1.54	**4t**	76%
21	**1u**	1.75	**4u**	41%

1 (0.1 mmol) was electrochemically oxidized in the presence of **2a** (1.0 mmol) in a 0.1 M solution of $Bu_4NB(C_6F_5)_4$ in CH_2Cl_2 at 25 °C. After 2.1 *F* of electricity was applied, the resulting solution was treated with Bu_4NI (0.5 mmol) at 25 °C. Isolated yields of the products based on the amount of **1** used are shown. (a) Decomposition potential (V vs SCE). (b) **1** (0.2 mmol) was used. (c) 3.0 *F* of electricity was applied.

Conclusion

In conclusion, a two-step one-pot metal- and chemical-oxidant-free method for benzylic C–H amination via electrochemically generated *N*-tosylbenzylaminosulfonium ions have been developed without using excess amounts of carbon substrates. The method is applicable to various functionalized toluene derivatives by virtue of the high oxidation potential and sufficient nucleophilicity of the *N*-tosylsulfilimine.

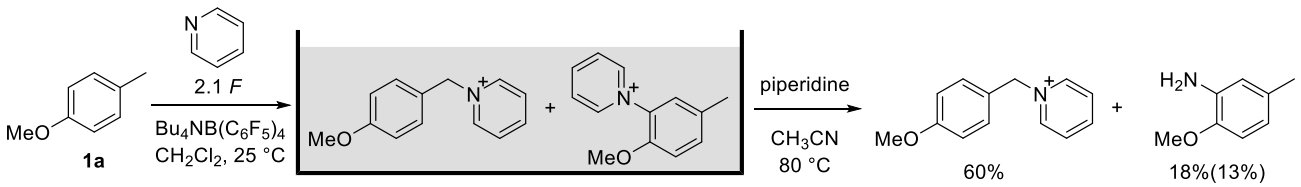
Experimental Section

General

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian MERCURY plus-400 (^{1}H 400 MHz, ^{13}C 100 MHz) spectrometer with tetramethylsilane as an internal standard unless otherwise noted. Mass spectra were obtained on a JEOL EXACTIVE (ESI and APCI) mass spectrometer and a JEOL JMS-SX102A mass spectrometer (EI). GC analysis was performed on a SHIMADZU GC-2014 gas chromatograph equipped with a flame ionization detector using a fused silica capillary column (column, CBP1; 0.22 mm x 25 m). Merck precoated silica gel F254 plates (thickness 0.25 mm) were used for thin-layer chromatography (TLC) analysis. Flash chromatography was carried out using Kanto Chem. Co., Silica Gel N (spherical, neutral, 40−100 μm). Preparative gel permeation chromatography (GPC) was performed on a Japan Analytical Industry LC-918. All reactions were carried out under argon atmosphere unless otherwise noted. Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification.

The anodic oxidation was carried out using an H-type divided cell (4G glass filter) equipped with an anode made of carbon strings (Nippon Carbon GF-20-P21E, ca. 160 mg for 0.20 mmol scale, dried at 300 °C/1 mmHg for 3 h before use) and a platinum plate cathode (10 mm x 10 mm). Dichloromethane was washed with water, distilled from P_2O_5, redistilled from dried K_2CO_3 to remove a trace amount of acid, and stored over molecular sieves 4A. $NaB(C_6F_5)_4$ was provided from Nippon Shokubai Co. as a precursor of $Bu_4NB(C_6F_5)_4$. $Bu_4NB(C_6F_5)_4$, **1o**, and **2a** were synthesized according to the reported literature.[10f]

Benzylic C–H amination using pyridine[10a]



In the anodic chamber were placed 4-methoxytoluene **1a** (12.2 mg, 0.100 mmol), pyridine (80 μL, 0.988 mmol), and 0.1 M $Bu_4NB(C_6F_5)_4/CH_2Cl_2$ (10 mL). In the cathodic chamber were placed TfOH (30 μL, 0.68 mmol) and 0.1 M $Bu_4NB(C_6F_5)_4/CH_2Cl_2$ (10 mL). The constant current electrolysis (4.0 mA) was carried out at 25 °C with magnetic stirring until 2.1 *F* of electricity was consumed. After the electrolysis, the reaction mixture was

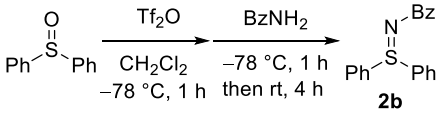
transferred to a round-bottom flask. After removal of the solvent under reduced pressure, piperidine (100 μL) and CH_3CN (10 mL) were added to the reaction mixture. The resulting mixture was stirred at 80 °C for 12 hours. The solvent was removed under reduced pressure. The NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard indicated that 4-methoxybenzylpyridinium ion and 2-methoxy-5-methylaniline were obtained in 60% and 18% yield, respectively. Then, the residue was filtered through a short column (2 x 4 cm) of silica gel to remove $Bu_4NB(C_6F_5)_4$ by using Et_2O as an eluent. The GC analysis using hexadecane as an internal standard indicated that 2-methoxy-5-methylaniline was obtained in 13% yield.

4-methoxybenzylpyridinium ion: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 5.53 (s, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 7.21 (d, *J* = 8.8 Hz, 2H), 7.96 (t, *J* = 7.0 Hz, 2H), 8.44−8.50 (m, 3H).

2-methoxy-5-methylaniline: TLC R_f 0.52 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.22 (s, 3H), 3.82 (s, 3H), 6.50−6.56 (m, 2H), 6.68 (d, *J* = 8.0 Hz, 2H); The ^{1}H NMR spectrum is in agreement with that in the literature.[13]

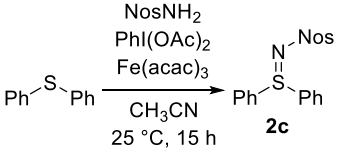
Synthesis of sulfilimines

Synthesis of *S*,*S*-diphenyl-*N*-benzoylsulfilimine (2b)[14]



To a round-bottom flask were added diphenylsulfoxide (10 g, 50 mmol), and CH_2Cl_2 (100 mL). Triflic anhydride (9.3 mL, 55 mmol) was added dropwise at −78 °C. After being stirred at −78 °C for 1 h, benzamide (14 g, 100 mmol) was added to the mixture. The solution was stirred for 1 h at −78 °C, and then was stirred for 4 h at room temperature. The mixture was washed with sat $NaHCO_3$ aq, dried over Na_2SO_4, and concentrated in vacuum. The residue was purified by recrystallization from EtOAc and hexane to give ***S*,*S*-diphenyl-*N*-benzoylsulfilimine (2b)** in 47% yield (7.13 g, 23.3 mmol). TLC R_f 0.16 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (t, *J* = 7.4 Hz, 2H), 7.43−7.52 (m, 7H), 7.81−7.86 (m, 4H), 8.24−8.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.76, 127.80, 128.9, 129.8, 130.8, 131.8, 136.37, 136.44, 176.5; HRMS (ESI) calcd for $C_{19}H_{16}NOS$ ($M+H^+$): 306.0947, found: 306.0938.

Synthesis of *S*,*S*-diphenyl-*N*-(4-nitrophenylsulfonyl)sulfilimine (2c)[15]

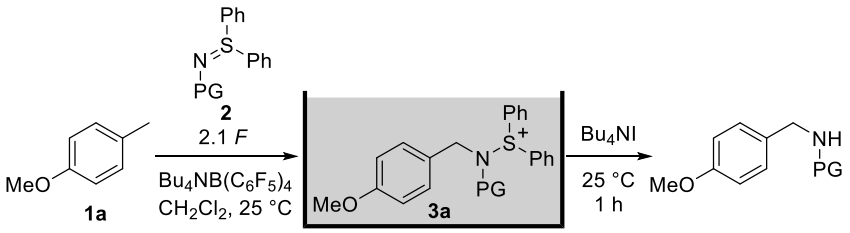


To a round-bottom flask were added diphenyl sulfide (3.3 mL, 20 mmol), 4-nitrobenzenesulfonamide (6.1 g, 30 mmol), $PhI(OAc)_2$ (12 g, 37 mmol), $Fe(acac)_3$ (1.1 g, 3.1 mmol), and CH_3CN (150 mL). The mixture was stirred at 25 °C for 15 h. The mixture was diluted with $CHCl_3$, washed with NaOH aq, H_2O, and, brine, dried over Na_2SO_4, and concentrated in vacuum. The residue was purified by recrystallization from EtOAc and hexane to give

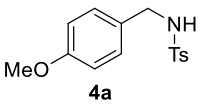
***S*,*S*-diphenyl-*N*-(4-nitrophenylsulfonyl)sulfilimine (2c)** in 60% yield (4.6 g, 12 mmol). TLC R_f 0.36 (hexane/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.2 Hz, 2H), 7.54 (d, *J* = 7.2 Hz, 2H), 7.64 (d, *J* = 7.2 Hz, 4H), 8.02 (d, *J* = 8.8 Hz, 2H), 8.19 (d, *J* = 8.8 Hz, 2H); The ^{1}H NMR spectrum is in agreement with that in the literature.[16]

Benzylic C–H amination using sulfilimines

Typical procedure for the generation of benzylaminosulfonium ions and their reactions with Bu_4NI



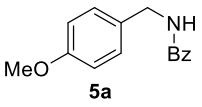
In the anodic chamber were placed 4-methoxytoluene (**1a**) (12.2 mg, 0.10 mmol), sulfilimine **2** (1.00 mmol), and 0.1 M $Bu_4NB(C_6F_5)_4/CH_2Cl_2$ (10 mL). In the cathodic chamber were placed TfOH (30 μL, 0.68 mmol) and 0.1 M $Bu_4NB(C_6F_5)_4/CH_2Cl_2$ (10 mL). The constant current electrolysis (4.0 mA) was carried out at 25 °C with magnetic stirring until 2.1 *F* of electricity was consumed. 0.5 M Bu_4NI/CH_2Cl_2 (1 mL, 0.50 mmol) was added to both the anodic and the cathodic chambers, and the resulting solutions were stirred 25 °C for 1 h. The solution in the anodic chamber was collected and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography and GPC to obtain the benzylamine.



4a

***N*-[(4-methoxyphenyl)methyl]-4-methylbenzenesulfonamide (4a)**

Electrochemical oxidation (2.1 *F*) of 4-methoxytoluene (12.8 mg, 0.105 mmol) in the presence of **2a** (351 mg, 0.989 mmol) and the subsequent treatment with Bu_4NI followed by flash chromatography (hexane/EtOAc 100:0, then 20:1, and then 10:3) gave the title compound (24.2 mg, 0.083 mmol, 79%). TLC R_f 0.35 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 3.78 (s, 3H), 4.05 (d, *J* = 6.0 Hz, 2H), 4.50–4.60 (m, 1H), 6.80 (d, *J* = 8.8 Hz, 2H), 7.11 (d, *J* = 8.8 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.76 (d, *J* = 8.4 Hz, 2H); The ^{1}H NMR spectrum is in agreement with that in the literature.[17]

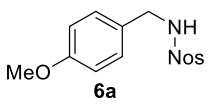


5a

***N*-[(4-methoxyphenyl)methyl]-benzamide (5a)**

Electrochemical oxidation (2.1 *F*) of 4-methoxytoluene (12.1 mg, 0.099 mmol) in the presence of **2b** (307 mg, 1.01 mmol), and the subsequent treatment with Bu_4NI followed by flash chromatography (hexane/EtOAc 100:0, then 10:3) gave the title compound (19.4 mg, 0.080 mmol, 81%). TLC R_f 0.29 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 4.57 (d, *J* = 6.8 Hz, 2H), 6.41 (br, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.41 (t, *J* = 8.0 Hz, 2H), 7.49 (t, *J* = 8.8 Hz, 1H), 7.78 (d, *J* = 6.8 Hz, 2H); The

^{1}H NMR spectrum is in agreement with that in the literature.[18]



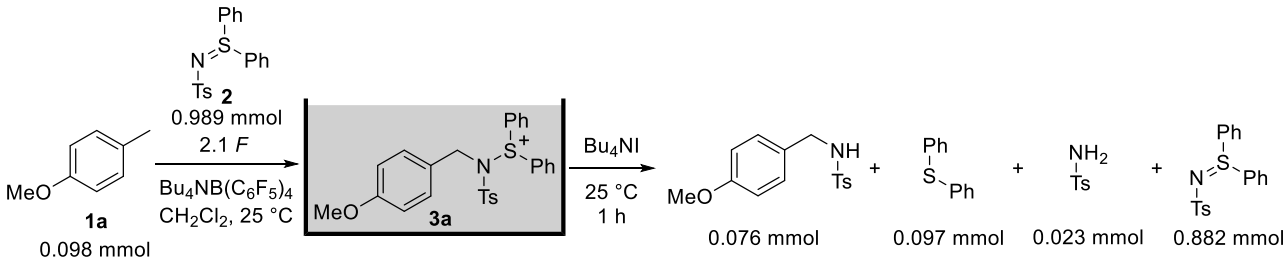
6a

***N*-[(4-methoxyphenyl)methyl]-4-nitrobenzenesulfonamide (6a)**

Electrochemical oxidation (2.1 *F*) of 4-methoxytoluene (11.8 mg, 0.097 mmol) in the presence of **2c** (392 mg, 1.02 mmol) and the subsequent treatment with Bu_4NI followed by flash chromatography (hexane/EtOAc 100:0, then 10:3) and GPC gave the title compound (0.2 mg, 0.0006 mmol, 1%). TLC R_f 0.38 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 4.16 (d, *J* = 5.2 Hz, 2H), 4.89 (br, 1H), 6.78 (d, *J* = 8.8 Hz, 2H), 7.08 (d, *J* = 8.3 Hz, 2H), 7.99 (d, *J* = 8.8 Hz, 2H), 8.31 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.9, 55.3, 114.2, 124.3, 127.4, 128.3, 129.3, 146.1, 150.0, 159.6; HRMS (ESI) calcd for $C_{14}H_{13}N_2O_5S$ ($M-H^+$): 321.0551, found: 321.0546.

Isolation of byproducts

The reaction of **1a** was conducted to determine the amount of diphenylsulfide, tosylamide, and unused **2a**.



In the anodic chamber were placed 4-methoxytoluene (**1a**) (11.9 mg, 0.098 mmol), *S*,*S*-diphenyl-*N*-(4-methylbenzenesulfonyl)sulfilimine (**2a**) (351 mg, 0.989 mmol), and 0.1 M $Bu_4NB(C_6F_5)_4/CH_2Cl_2$ (10 mL). In the cathodic chamber were placed TfOH (30 μL, 0.68 mmol) and 0.1 M $Bu_4NB(C_6F_5)_4/CH_2Cl_2$ (10 mL). The constant current electrolysis (4.0 mA) was carried out at 25 °C with magnetic stirring until 2.1 *F* of electricity was consumed. 0.5 M Bu_4NI/CH_2Cl_2 (1 mL, 0.50 mmol) was added to both the anodic and the cathodic chambers, and the resulting solutions were stirred 25 °C for 1 h. The solution in the anodic chamber was collected and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (hexane/EtOAc 100:0, then 20:1, then 10:3, then 2:1) obtain ***N*-[(4-methoxyphenyl)methyl]-4-methylbenzenesulfonamide (4a)** in 78% yield (22.0 mg, 0.076 mmol).

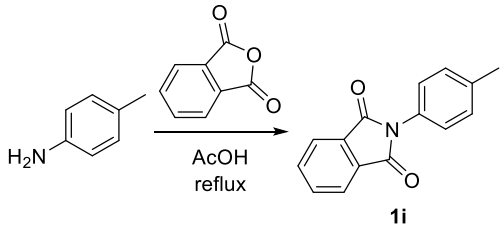
Diphenylsulfide generated by both the reaction of **3a** with Bu_4NI and the reaction of **2a** with Bu_4NI was obtained (18.1 mg, 0.097 mmol) by flash chromatography. TLC R_f 0.78 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.40 (m, 10H); The ^{1}H NMR spectrum is in agreement with that in the literature.[13]

Tosylamide generated by reaction of **2a** with Bu_4NI was obtained (4.0 mg, 0.023 mmol) by flash chromatography followed by GPC. TLC R_f 0.19 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 4.92 (br, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.81 (d, *J* = 8.0 Hz, 2H); The ^{1}H NMR spectrum is in agreement with that in the literature.[13]

***S*,*S*-diphenyl-*N*-(4-methylbenzenesulfonyl)sulfilimine (2a)** was recovered (313 mg, 0.882 mmol) by flash chromatography followed by GPC.

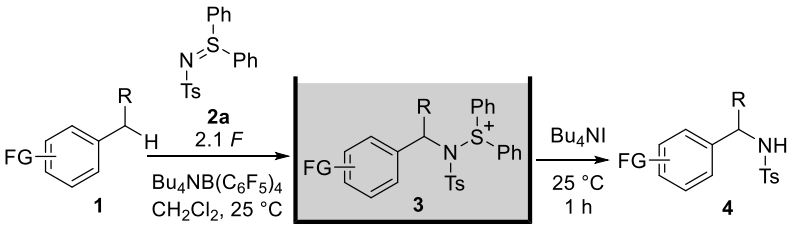
Benzylic C–H amination of various toluene derivatives

Preparation of 4-phthalimidotoluene (1i)[19]

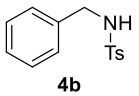


To a round-bottom flask were added *p*-toluidine (1.0 g, 9.3 mmol), phthalic anhydride (1.4 g, 9.3 mmol), and AcOH (20 mL). The mixture was refluxed for 3 h, and the precipitate was collected by filtration. The precipitate was purified by recrystallization from EtOAc and hexane to give **4-phthalimidotoluene (1i)** in 74% yield (1.6 g, 6.8 mmol). TLC R_f 0.48 (hexane/EtOAc 10:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 7.31 (s, 4H), 7.76–7.81 (m, 2H), 7.93–7.98 (m, 2H); The ^{1}H NMR spectrum is in agreement with that in the literature.[20]

Typical procedure for the generation of benzylaminosulfonium ions and their reactions with Bu_4NI



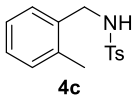
In the anodic chamber were placed toluene derivatives **1** (0.100 mmol), *S*,*S*-diphenyl-*N*-(4-methylbenzenesulfonyl)sulfilimine (**2a**) (355 mg, 1.00 mmol), and 0.1 M $Bu_4NB(C_6F_5)_4/CH_2Cl_2$ (10 mL). In the cathodic chamber were placed TfOH (30 μL, 0.68 mmol) and 0.1 M $Bu_4NB(C_6F_5)_4/CH_2Cl_2$ (10 mL). The constant current electrolysis (4.0 mA) was carried out at 25 °C with magnetic stirring until 2.1 *F* of electricity was consumed. 0.5 M Bu_4NI/CH_2Cl_2 (1 mL, 0.50 mmol) was added to both the anodic and the cathodic chambers, and the resulting solutions were stirred 25 °C for 1 h. The solution in the anodic chamber was collected and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography and GPC to obtain the benzylamine **4**.



4b

***N*-benzyl-4-methylbenzenesulfonamide (4b)**

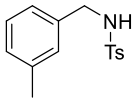
Electrochemical oxidation (2.1 *F*) of toluene (11.8 mg, 0.128 mmol) in the presence of **2a** (363 mg, 1.02 mmol) and the subsequent treatment with Bu_4NI followed by flash chromatography (hexane/EtOAc 10:3) and GPC gave the title compound (13.4 mg, 0.049 mmol, 38%). TLC R_f 0.24 (hexane/EtOAc 10:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 4.13 (d, *J* = 6.4 Hz, 2H), 4.60 (t, *J* = 6.0 Hz, 1H), 7.18–7.21 (m, 2H), 7.25–7.29 (m, 3H), 7.29–7.33 (m, 2H), 7.77 (d, *J* = 8.4 Hz, 2H); The ^{1}H NMR spectrum is in agreement with that in the literature.[21]



4c

***N*-[(2-methylphenyl)methyl]-4-methylbenzenesulfonamide (4c)**

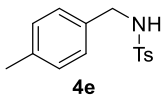
Electrochemical oxidation (2.1 *F*) of *o*-xylene (21.8 mg, 0.206 mmol) in the presence of **2a** (713 mg, 2.01 mmol) and the subsequent treatment with Bu_4NI followed by flash chromatography (hexane/EtOAc 100:0, then 10:3) gave the title compound (37.7 mg, 0.137 mmol, 66%). TLC R_f 0.52 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 2.43 (s, 3H), 4.08 (d, *J* = 5.6 Hz, 2H), 4.60 (t, *J* = 5.6 Hz, 1H), 7.08–7.14 (m, 3H), 7.18–7.21 (m, 1H), 7.30 (d, *J* = 7.6 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 2H); The ^{1}H NMR spectrum is in agreement with that in the literature.[21]



4d

***N*-[(3-methylphenyl)methyl]-4-methylbenzenesulfonamide (4d)**

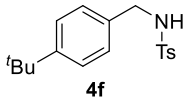
Electrochemical oxidation (2.1 *F*) of *m*-xylene (21.1 mg, 0.199 mmol) in the presence of **2a** (716 mg, 2.02 mmol) and the subsequent treatment with Bu_4NI followed by flash chromatography (hexane/EtOAc 100:0, then 10:3) gave the title compound (37.7 mg, 0.137 mmol, 66%). TLC R_f 0.57 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 3H), 2.44 (s, 3H), 4.08 (d, *J* = 6.4 Hz, 2H), 4.66 (br, 1H), 6.95–7.00 (m, 2H), 7.06 (d, *J* = 7.6 Hz, 1H), 7.16 (t, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 7.6 Hz, 2H), 7.76 (d, *J* = 8.0 Hz, 2H); The ^{1}H NMR spectrum is in agreement with that in the literature.[22]



4e

***N*-[(4-methylphenyl)methyl]-4-methylbenzenesulfonamide (4e)**

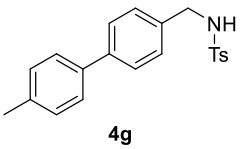
Electrochemical oxidation (2.1 *F*) of *p*-xylene (20.2 mg, 0.190 mmol) in the presence of **2a** (704 mg, 1.98 mmol) and the subsequent treatment with Bu_4NI followed by flash chromatography (hexane/EtOAc 100:0, then 10:3) gave the title compound (44.2 mg, 0.160 mmol, 84%). TLC R_f 0.58 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H), 2.43 (s, 3H), 4.06 (d, *J* = 6.0 Hz, 2H), 4.78 (t, *J* = 8.0 Hz, 1H), 7.07 (s, 4H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 2H); The ^{1}H NMR spectrum is in agreement with that in the literature.[21]



4f

***N*-[(4-*tert*-butylphenyl)methyl]-4-methylbenzenesulfonamide (4f)**

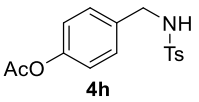
Electrochemical oxidation (2.1 *F*) of 4-*tert*-butyltoluene (13.5 mg, 0.091 mmol) in the presence of **2a** (356 mg, 1.00 mmol) and the subsequent treatment with Bu_4NI followed by flash chromatography (hexane/EtOAc 100:0, then 10:3) gave the title compound (21.2 mg, 0.067 mmol, 73%). TLC R_f 0.61 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 9H), 2.42 (s, 3H), 4.08 (d, *J* = 6.1 Hz, 2H), 4.77 (br, 1H), 7.11 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 4H), 7.74 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 31.2, 34.4, 46.9, 125.5, 127.1, 127.6, 129.6, 133.1, 136.8, 143.3, 150.9; HRMS (ESI) calcd for $C_{18}H_{23}NO_2SNa$ ($M+Na^+$): 340.1342, found: 340.1333.



4g

***N*-[(4'-methylbiphenyl-4-yl)methyl]-4-methylbenzenesulfonamide (4g)**

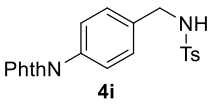
Electrochemical oxidation (2.1 *F*) of 4,4'-dimethylbiphenyl (19.0 mg, 0.104 mmol) in the presence of **2a** (355 mg, 1.00 mmol) and the subsequent treatment with Bu_4NI followed by flash chromatography (hexane/EtOAc 100:0, then 10:3) gave the title compound (22.6 mg, 0.064 mmol, 62%). TLC R_f 0.26 (hexane/EtOAc 10:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H), 2.44 (s, 3H), 4.16 (d, *J* = 6.1 Hz, 2H), 4.58 (t, *J* = 6.2 Hz, 1H), 7.22–7.28 (m, 4H), 7.32 (d, *J* = 7.9 Hz, 2H), 7.44 (d, *J* = 7.9 Hz, 2H), 7.49 (d, *J* = 7.9 Hz, 2H), 7.78 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 21.5, 46.9, 126.8, 127.07, 127.13, 128.2, 129.5, 129.7, 134.9, 136.8, 137.2, 137.5, 140.7, 143.4; HRMS (ESI) calcd for $C_{21}H_{21}NO_2SNa$ ($M+Na^+$): 374.1185, found: 374.1182.



4h

***N*-[(4-acetoxyphenyl)methyl]-4-methylbenzenesulfonamide (4h)**

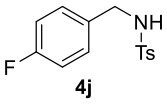
Electrochemical oxidation (2.1 *F*) of 4-acetoxytoluene (13.5 mg, 0.091 mmol) in the presence of **2a** (357 mg, 1.00 mmol) and the subsequent treatment with Bu_4NI followed by flash chromatography (hexane/EtOAc 100:0, then 10:3) gave the title compound (21.2 mg, 0.067 mmol, 73%). TLC R_f 0.61 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 3H), 2.42 (s, 3H), 4.08 (d, *J* = 6.1 Hz, 2H), 5.01 (br, 1H), 6.97 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 7.9 Hz, 2H), 7.73 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 21.5, 46.5, 121.7, 127.0, 128.9, 129.7, 133.9, 136.7, 143.5, 150.1, 169.4; HRMS (ESI) calcd for $C_{16}H_{17}NO_4SNa$ ($M+Na^+$): 342.0770, found: 342.0767.



4i

***N*-[(4-phthalimidophenyl)methyl]-4-methylbenzenesulfonamide (4i)**

Electrochemical oxidation (2.1 *F*) of 4-phthalimidotoluene (28.7 mg, 0.121 mmol) in the presence of **2a** (354 mg, 1.00 mmol) and the subseqeunt treatment with Bu_4NI gave the crude product. The NMR analysis indicated that the title compound was obtained (0.096 mmol, 79%). The crude product was purified by flash chromatography and GPC to obtain the title compound (23.4 mg, 0.048 mmol, 48%). TLC R_f 0.19 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 4.20 (d, *J* = 6.6 Hz, 2H), 4.68 (t, *J* = 6.6 Hz, 1H), 7.31–7.39 (m, 6H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.79–7.82 (m, 2H), 7.93–7.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 46.8, 123.8, 126.8, 127.2, 128.6, 129.8, 131.4, 131.7, 134.5, 136.2, 136.8, 143.7, 167.1; HRMS (ESI) calcd for $C_{22}H_{18}N_2O_4SNa$ ($M+Na^+$): 429.0879, found: 429.0871.

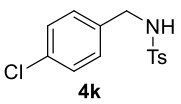


4j

***N*-[(4-fluorophenyl)methyl]-4-methylbenzenesulfonamide (4j)**

Electrochemical oxidation (2.1 *F*) of 4-fluorotoluene (22.0 mg, 0.200 mmol) in the presence of **2a** (356 mg, 1.00 mmol) and the subsequent treatment with Bu_4NI followed by flash chromatography (hexane/EtOAc 10:3) gave the title compound (38.8 mg, 0.139 mmol, 69%). TLC R_f 0.27 (hexane/EtOAc 10:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s,

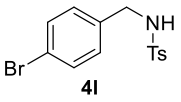
3H), 4.10 (d, *J* = 6.4 Hz, 2H), 4.60 (t, *J* = 6.0 Hz, 1H), 6.96 (t, *J* = 8.8 Hz, 2H), 7.18 (dd, *J* = 5.6, 8.8 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 2H); The ^{1}H NMR spectrum is in agreement with that in the literature.[23]



4k

***N*-[(4-chlorophenyl)methyl]-4-methylbenzenesulfonamide (4k)**

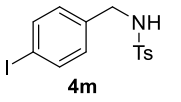
Electrochemical oxidation (2.1 *F*) of 4-chlorotoluene (11.6 mg, 0.091 mmol) in the presence of **2a** (355 mg, 1.00 mmol) and the subsequent treatment with Bu_4NI followed by flash chromatography (hexane/EtOAc 10:3) and GPC gave the title compound (8.5 mg, 0.029 mmol, 31%). TLC R_f 0.50 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 4.10 (d, *J* = 6.0 Hz, 2H), 4.65 (t, *J* = 6.0 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.22–7.28 (m, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.74 (d, *J* = 8.4 Hz, 2H); The ^{1}H NMR spectrum is in agreement with that in the literature.[23]



4l

***N*-[(4-bromophenyl)methyl]-4-methylbenzenesulfonamide (4l)**

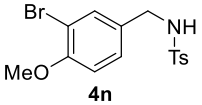
Electrochemical oxidation (2.1 *F*) of 4-bromotoluene (14.9 mg, 0.087 mmol) in the presence of **2a** (355 mg, 1.00 mmol) and the subsequent treatment with Bu_4NI followed by flash chromatography (hexane/EtOAc 100:0, then 10:3) gave the title compound (21.8 mg, 0.064 mmol, 74%). TLC R_f 0.50 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 4.08 (d, *J* = 6.4 Hz, 2H), 4.82 (t, *J* = 6.0 Hz, 1H), 7.07 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.73 (d, *J* = 8.4 Hz, 2H); The ^{1}H NMR spectrum is in agreement with that in the literature.[21]



4m

***N*-[(4-iodophenyl)methyl]-4-methylbenzenesulfonamide (4m)**

Electrochemical oxidation (2.1 *F*) of 4-iodotoluene (31.1 mg, 0.143 mmol) in the presence of **2a** (352 mg, 0.992 mmol) and the subsequent treatment with Bu_4NI followed by flash chromatography (hexane/EtOAc 2:1) gave the title compound (44.7 mg, 0.115 mmol, 81%). TLC R_f 0.50 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 4.05 (d, *J* = 6.4 Hz, 2H), 4.99 (t, *J* = 6.0 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 2H); The ^{1}H NMR spectrum is in agreement with that in the literature.[24]

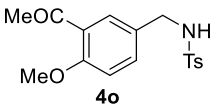


4n

***N*-[(3-bromo-4-methoxyphenyl)methyl]-4-methylbenzenesulfonamide (4n)**

Electrochemical oxidation (2.1 *F*) of 3-bromo-4-methoxytoluene (38.1 mg, 0.190 mmol) in the presence of **2a** (353 mg, 0.994 mmol) and the subsequent treatment with Bu_4NI followed by flash chromatography (hexane/EtOAc 5:1) gave the title compound (60.6 mg, 0.164 mmol, 86%). TLC R_f 0.38 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 3.85 (s, 3H), 4.03 (d, *J* = 6.6 Hz, 2H), 4.87 (t, *J* = 6.1 Hz, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 7.12 (dd, *J* = 2.2, 8.3 Hz, 1H), 7.25–7.32 (m, 3H), 7.72 (d, *J* = 8.4 Hz,

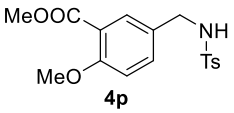
2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 46.0, 56.2, 111.5, 111.7, 127.0, 128.1, 129.7, 129.8, 132.8, 136.7, 143.6, 155.3; HRMS (ESI) calcd for $C_{15}H_{16}BrNO_3SNa$ ($M+Na^+$): 391.9926, found: 391.9926.



4o

***N*-[(3-acetyl-4-methoxyphenyl)methyl]-4-methylbenzenesulfonamide (4o)**

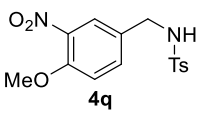
Electrochemical oxidation (2.1 *F*) of 3-acetyl-4-methoxytoluene (15.0 mg, 0.091 mmol) in the presence of **2a** (353 mg, 0.994 mmol) and the subsequent treatment with Bu_4NI followed by flash chromatography (hexane/EtOAc 2:1) and GPC gave the title compound (23.1 mg, 0.069 mmol, 76%). TLC R_f 0.19 (hexane/EtOAc 10:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 2.57 (s, 3H), 3.90 (s, 3H), 4.07 (d, *J* = 6.2 Hz, 2H), 4.58 (t, *J* = 6.1 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 2H), 7.41 (dd, *J* = 2.6, 8.4 Hz, 1H), 7.47 (d, *J* = 2.2 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 31.7, 46.4, 55.6, 112.0, 127.1, 127.8, 128.5, 129.7, 129.8, 133.4, 136.8, 143.5, 158.5, 199.4; HRMS (ESI) calcd for $C_{17}H_{19}NO_4SNa$ ($M+Na^+$): 356.0927, found: 356.0916.



4p

***N*-[(3-methoxycarbonyl-4-methoxyphenyl)methyl]-4-methylbenzenesulfonamide (4p)**

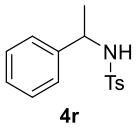
Electrochemical oxidation (2.1 *F*) of 3-methoxycarbonyl-4-methoxytoluene (18.0 mg, 0.100 mmol) in the presence of **2a** (358 mg, 1.01 mmol) and the subsequent treatment with Bu_4NI followed by flash chromatography (hexane/EtOAc 2:1) and GPC gave the title compound (23.0 mg, 0.066 mmol, 66%). TLC R_f 0.28 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 4.08 (d, *J* = 6.1 Hz, 2H), 4.64 (t, *J* = 6.1 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 2H), 7.35 (dd, *J* = 2.2, 8.8 Hz, 1H), 7.58 (d, *J* = 2.2 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 46.4, 52.1, 56.1, 112.3, 119.9, 127.2, 127.9, 129.8, 131.2, 133.2, 136.7, 143.6, 158.8, 166.2; HRMS (ESI) calcd for $C_{17}H_{19}NO_5SNa$ ($M+Na^+$): 372.0876, found: 372.0866.



4q

***N*-[(3-nitro-4-methoxyphenyl)methyl]-4-methylbenzenesulfonamide (4q)**

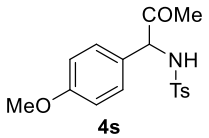
Electrochemical oxidation (2.1 *F*) of 3-nitro-4-methoxytoluene (18.0 mg, 0.108 mmol) in the presence of **2a** (355 mg, 1.00 mmol) and the subsequent treatment with Bu_4NI followed by flash chromatography (hexane/EtOAc 10:3) and GPC gave the title compound (32.6 mg, 0.097 mmol, 90%). TLC R_f 0.03 (hexane/EtOAc 10:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 3.94 (s, 3H), 4.13 (d, *J* = 6.1 Hz, 2H), 4.78 (t, *J* = 6.1 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 2H), 7.48 (dd, *J* = 2.2, 8.8 Hz, 1H), 7.58 (d, *J* = 2.2 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 45.8, 56.6, 113.8, 125.0, 127.0, 129.0, 129.8, 133.8, 136.6, 139.1, 143.8, 152.4; HRMS (ESI) calcd for $C_{15}H_{16}N_2O_5SNa$ ($M+Na^+$): 359.0672, found: 359.0664.



4r

***N*-1-phenylethyl-4-methylbenzenesulfonamide (4r)**

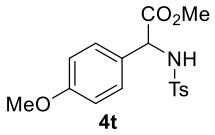
Electrochemical oxidation (3.0 *F*) of ethylbenzene (10.3 mg, 0.097 mmol) in the presence of **2a** (350 mg, 0.986 mmol) and the subsequent treatment with Bu_4NI followed by flash chromatography (hexane/EtOAc 5:1) gave the title compound (18.4 mg, 0.069 mmol, 69%). TLC R_f 0.21 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (d, *J* = 6.8 Hz, 3H), 2.38 (s, 3H), 4.46 (quin, *J* = 6.8 Hz, 2H), 4.77–4.95 (br, 1H), 7.08–7.12 (m, 2H), 7.15–7.22 (m, 5H), 7.62 (d, *J* = 8.4 Hz, 2H); The ^{1}H NMR spectrum is in agreement with that in the literature.[24]



4s

***N*-[acetyl-(4-methoxyphenyl)methyl]-4-methylbenzenesulfonamide (4s)**

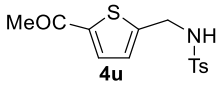
Electrochemical oxidation (2.1 *F*) of acetyl-(4-methoxyphenyl)methane (15.7 mg, 0.096 mmol) in the presence of **2a** (352 mg, 0.992 mmol) and the subsequent treatment with Bu_4NI followed by flash chromatography (hexane/EtOAc 10:3) gave the title compound (24.4 mg, 0.073 mmol, 76%). TLC R_f 0.32 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98 (s, 3H), 2.35 (s, 3H), 3.76 (s, 3H), 4.98 (d, *J* = 5.2 Hz, 2H), 6.03 (d, *J* = 5.2 Hz, 2H), 6.73 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H); The ^{1}H NMR spectrum is in agreement with that in the literature.[25]



4t

***N*-[(methoxycarbonyl)(4-methoxyphenyl)methyl]-4-methylbenzenesulfonamide (4t)**

Electrochemical oxidation (2.1 *F*) of (methoxycarbonyl)(4-methoxyphenyl) -methane (18.6 mg, 0.103 mmol) in the presence of **2a** (363 mg, 1.02 mmol) and the subsequent treatment with Bu_4NI followed by flash chromatography (hexane/EtOAc 2:1) gave the title compound (27.4 mg, 0.078 mmol, 76%). TLC R_f 0.28 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H), 3.57 (s, 3H), 3.77 (s, 3H), 5.00 (d, *J* = 7.5 Hz, 2H), 5.59 (d, *J* = 7.5 Hz, 1H), 6.77 (d, *J* = 8.8 Hz, 2H), 7.12 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 7.9 Hz, 2H), 7.61 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 52.9, 55.3, 58.7, 114.2, 127.17, 127.26, 128.4, 129.4, 137.0, 143.4, 159.8, 170.7; HRMS (ESI) calcd for $C_{17}H_{19}NO_5SNa$ ($M+Na^+$): 372.0876, found: 372.0866.



4u

***N*-[(5-acetylthiophen-2-yl)methyl]-4-methylbenzenesulfonamide (4u)**

Electrochemical oxidation (2.1 *F*) of (5-acetylthiophen-2-yl)methane (13.5 mg, 0.096 mmol) in the presence of **2a** (358 mg, 1.01 mmol) and the subsequent treatment with Bu_4NI gave the crude product. The NMR analysis indicated that the title compound was obtained (0.060 mmol, 62%). The crude product was purified by flash chromatography and GPC to obtain the title compound (12.3 mg, 0.040 mmol, 41%). TLC R_f 0.22 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 2.50 (s, 3H), 4.34 (d, *J* = 5.3 Hz, 2H), 4.85 (br, 1H), 6.93 (d, *J* = 4.0 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 4.4 Hz, 1H), 7.75 (d, *J* = 7.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 26.6, 42.4,

127.0, 127.2, 129.8, 132.4, 136.6, 144.0, 144.2, 148.3, 190.4; HRMS (ESI) calcd for $C_{14}H_{15}NO_3S_2Na$ ($M+Na^+$): 332.0386, found: 332.0379.

References

(1) Reviews: (a) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (b) Collet, F.; Dodd, R. H.; Dauban, P. *Chem. Commun.* **2009**, 5061. (c) Che, C.-M.; Lo, V. K.-Y.; Zhou, C.-Y.; Huang, J.-S. *Chem. Soc. Rev.* **2011**, *40*, 1950. (d) Gephart, R. T.; Warren, T. H. *Organometallics* **2012**, *31*, 7728. (e) Samanta, R.; Matcha, K.; Antonchick, A. P. *Eur. J. Org. Chem.* **2013**, 5769. (f) Louillat, M.-L.; Patureau, F. W. *Chem. Soc. Rev.* **2014**, *43*, 901. (g) Shin, K.; Kim, H.; Chang, S. *Acc. Chem. Res.* **2015**, *48*, 1040.

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

(3) Narayan, R.; Matcha, K.; Antonchick, A. P. *Chem. Eur. J.* **2015**, *21*, 14678.

(4) Recent examples of metal-catalyzed C–H amination: (a) Yu, X.-Q.; Huang, J.-S.; Zhou, X.-G.; Che, C.-M. *Org. Lett.* **2000**, *2*, 2233. (b) Ni, Z.; Zhang, Q.; Xiong, T.; Zheng, Y.; Li, Y.; Zhang, H.; Zhang, J.; Liu, Q. *Angew. Chem. Int. Ed.* **2012**, *51*, 1244. (c) Zhang, Y.; Feng, B.; Zhu, C. *Org. Biomol. Chem.* **2012**, *10*, 9137. (d) Liu, Y.; Guan, X.; Wong, E. L.-M.; Liu, P.; Huang, J.-S.; Che, C.-M. *J. Am. Chem. Soc.* **2013**, *135*, 7194. (e) Tang, C.; Zou, M.; Liu, J.; Wen, X.; Sun, X.; Zhang, Y.; Jiao, N. *Chem. Eur. J.* **2016**, *22*, 11165.

(5) Recent examples of metal-free C–H amination: (a) Fan, R.; Li, W.; Pu, D.; Zhang, L. *Org. Lett.* **2009**, *11*, 1425. (b) Baba, H.; Togo, H. *Tetrahedron Lett.* **2010**, *51*, 2063. (c) Ramesh, D.; Ramulu, U.; Mukkanti, K.; Venkateswarlu, Y. *Tetrahedron. Lett.* **2012**, *53*, 2904. (d) Buslov, I.; Hu, X. *Adv. Synth. Catal.* **2014**, *356*, 3325.

(6) (a) Borah, A. J.; Phukan, P. *Chem. Commun.* **2012**, *48*, 5491. (b) Liu, J.; Zhang, H.; Yi, H.; Liu, C.; Lei, A. *Sci. China Chem.* **2015**, *58*, 1323. (c) Pandey, G.; Laha, R. *Angew. Chem. Int. Ed.* **2015**, *54*, 14875. (d) Wang, Y.-Y.; Sun, M.-H.; Zeng, N.-N.; Chen, J.; Zhou, L. *Synlett* **2016**, *27*, 1438.

(7) (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.

(8) Examples of electrochemical benzylic C–H transformation: (a) Hoormann, D.; Kubon, C.; Jörissen, J.; Kröner, L.; Pütter, H. *J. Electroanal. Chem.* **2001**, *507*, 215. (b) Tajima, T.; Fuchigami, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 4760. (c) Okajima, M.; Soga, K.; Nokami, T.; Suga, S.; Yoshida, J. *Org. Lett.* **2006**, *8*, 5005. (d) Ashikari, Y.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2011**, *133*, 11840. (e) Ashikari, Y.; Nokami, T.; Yoshida, J.*Org. Lett.* **2012**, *14*, 938.

(9) (a) Eberson, L.: Nyberg, K. *Tetrahedron Lett.* **1966**, *7*, 2389. (b) Parker, V. D.; Burgert, B. E. *Tetrahedron Lett.* **1968**, *9*, 2411. (c) Eberson, L.; Olofsson, B. *Acta Chem. Scand.* **1969**, *23*, 2355.

(10) (a) Morofuji, T.; Shimizu, A.; Yoshida, J. *J. Am. Chem. Soc.* **2013**, *135*, 5000. (b) Morofuji, T.; Shimizu, A.; Yoshida, J. *J. Am. Chem. Soc.* **2014**, *136*, 4496. (c) Morofuji, T.; Shimizu, A.; Yoshida, J. *Chem. Eur. J.* **2015**, *21*, 3211. (d) Morofuji, T.; Shimizu, A.; Yoshida, J. *J. Am. Chem. Soc.* **2015**, *137*, 9816. (e) Herold, S.; Mohle, S.; Zirbes, M.; Richter, F.; Nefzger, H.; Waldvogel, S. R. *Eur. J. Org. Chem.* **2016**, 1274. (f) Hayashi, R.; Shimizu, A.; Yoshida, J. *J. Am. Chem. Soc.* **2016**, *138*, 8400.

(11) (a) Young, P. R.; McMahon, P. E. *J. Am. Chem. Soc.* **1985**, *107*, 7572. b) Young, P. R.; Huang, H. C. *J. Am. Chem. Soc*. **1987**, *109*, 1810.

(12) Examples of deprotection of tosyl group: (a) Maia, H. L. S.; Medeiros, M. J.; Montenegro, M. I.; Court, D.; Pletcher, D. *J. Electroanal. Chem.* **1984**, *164*, 347. (b) Roemmele, R. C.; Rapoport, H. *J. Org. Chem*. **1988**, *53*, 2367. c) Ankner, T.; Hilmersson, G. *Org. Lett.* **2009**, *11*, 503.

(13) SDBSWeb : http://sdbs.db.aist.go.jp (National Institute of Advanced Industrial Science and Technology, August 25, 2016)

(14) Kirsch, P.; Lenges, M.; Kuhne, D.; Wanczek, K.-P. *Eur. J. Org. Chem*. **2005**, 797.

(15) Mancheno, O. G.; Bolm, C. *Org. Lett.* **2006**, *8*, 2349.

(16) Okamura, H.; Bolm, C. *Org. Lett.* **2004**, *6*, 1305.

(17) Das, B. G.; Ghorai, P. *Chem. Commun.* **2012**, *48*, 8276.

(18) Schneider, A. E.; Manolikakes, G. *Synlett* **2013**, *24*, 2057.

(19) Capitosti, S. M.; Hansen, T. P.; Brown, M. L. *Bioorg. Med. Chem.* **2004**, *12*, 327.

(20) Sawant, D. N.; Wagh, Y. S.; Bhatte, K. D.; Bhanage, B. M. *Eur. J. Org. Chem.* **2011**, *6*719.

(21) Muther, K.; Mohr, J.; Oestreich, M. *Organometallics* **2013**, *32*, 6643.

(22) Cui, X.; Shi, F.; Tse, M. K.; Gordes, D.; Thurow, K.; Beller, M.; Deng, Y. *Adv. Synth. Catal.* **2009**, *351*, 2949.

(23) Sreedhar, B.; Reddy, P. S.; Reddy, M. A.; Neelima, B.; Arundhathi, R. *Tetranhedron Lett.* **2007**, *48*, 8174.

(24) Borah, A. J.; Phukan, P. *Chem. Commun.* **2012**, *48*, 5491.

(25) Baumann, T.; Bachle, M.; Brase, S. *Org. Lett.* **2006**, *8*, 3797.

Chapter 3

Switching the Reaction Pathways of Electrochemically Generated β-Haloalkoxysulfonium Ions – Synthesis of Halohydrins and Epoxides

Abstract

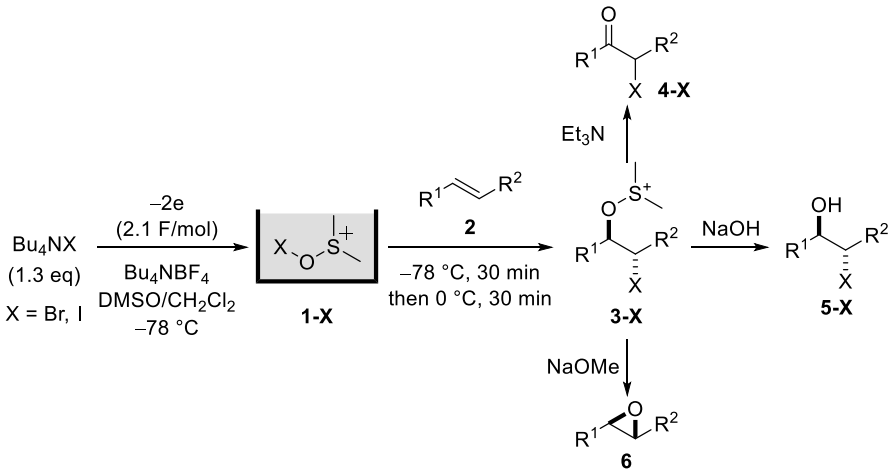
β-Haloalkoxysulfonium ions generated by the reaction of electrogenerated bromine and iodine cations stabilized by dimethyl sulfoxide (DMSO) reacted with sodium hydroxide and sodium methoxide to give the corresponding halohydrins and epoxides, respectively, whereas the treatment with triethylamine gave *α*-halocarbonyl compounds.

Introduction

Alkene difunctionalization via three-membered ring halonium ion intermediates[1] is an important transformation in organic synthesis. Although the halonium ion such as bromonium or iodonium are usually generated by the reaction of alkenes with Br_2 and I_2,[2] the most straightforward method is the reactions of alkenes with halogen cations such as Br^+ and I^+. I^+ cation-pool exists as reported by Filimonov et al.[3] However, the solvent is conc. sulfuric acid and not compatible with most organic compounds.

The electrochemical oxidation[4] is a powerful method to generate and accumulate highly reactive cationic species in the solution (the "cation pool" method).[5] Although halogen cations are too unstable to accumulate in the solution as "cation pools", halogen cations stabilized by appropriate stabilizing agents that coordinate the cations can be accumulated in the solution. For example, "I^+" cation stabilized by acetonitrile (CH_3CN)[6] and that stabilized by trimethyl orthoformate (TMOF)[7] were reported in the literature. Recently, Yoshida and coworkers reported that dimethyl sulfoxide (DMSO) effectively stabilizes halogen cations (Scheme 1).[8]

Scheme 1. Synthesis of Halohydrins and Epoxides via the *β*-Haloalkoxysulfonium Ions Generated by the Reaction of Alkenes with DMSO-stabilized Halogen Cations.

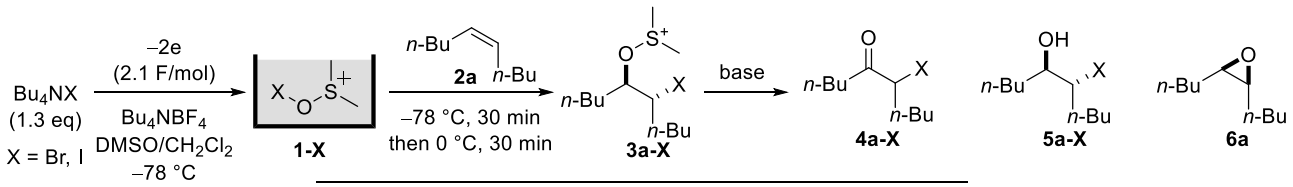


The pools of the stabilized halogen cations enable alkene difunctionalization. Yoshida and coworkers previously reported that the reaction of alkenes with DMSO-stabilized halogen cations such as Br^+ and I^+ gave *β*-haloalkoxysulfonium ions and subsequent treatment with triethylamine gave *α*-halocarbonyl compounds via Swern−Moffatt type oxidation.[9] Recently reaction integration[10] has received significant research interest because it enhances the power and speed of organic syntheses, and this is an example of integration of an electrochemical reaction and a chemical reaction using a reactive intermediate. This chapter shows that the reaction pathways of *β*-haloalkoxysulfonium ions can be switched to give different products by changing the base, expanding the utility of the present method. The treatment of *β*-haloalkoxysulfonium ions with sodium hydroxide gave the corresponding halohydrins, while the treatment with sodium methoxide gave epoxides (Scheme 1).

Results and Discussion

First the reactions of *β*-bromoalkoxysulfonium ion **3a-Br** generated by the reaction of (*Z*)-5-decene (**2a**) with Br^+/DMSO (**1-Br**)[8] (Scheme 1, X = Br) was examined. Bu_4NBr in DMSO/CH_2Cl_2 (1:9 v/v) was electrochemically oxidized at −78 °C in a divided cell using Bu_4NBF_4 as a supporting electrolyte. After 2.1 F/mol of electricity was applied, **2a** was added to the solution, and the mixture was stirred at 0 °C to give **3a-Br**, which was characterized by NMR spectroscopy. The treatment of **3a-Br** with triethylamine gave *α*-bromoketone **4a-Br** in 83% yield. However, the treatment of **3a-Br** with NaOH gave bromohydrin **5a-Br** in 89% yield as shown in Table 1. These phenomena can be explained as follows: Due to the steric repulsion, triethylamine cannot attack the sulfur atom of **3a-Br** and acts as base to abstract a proton attached to the carbon adjacent to the sulfur. The carbanion part of the resulting sulfur ylide abstracts a proton attached to the carbon adjacent to the oxygen to give α-bromoketone **4a-Br** by the Swern−Moffatt type oxidation mechanism.[9] On the other hand, the hydroxide ion attacks the sulfur atom of **3a-Br** to cleave the S−O bond to give the alkoxide ion, which is protonated by water to give bromohydrin **5a-Br** (Scheme 2). The stereochemistry determined by NMR indicates that the addition of Br^+ and DMSO across the C−C double bond is anti-selective, which is consistent with the results reported previously.

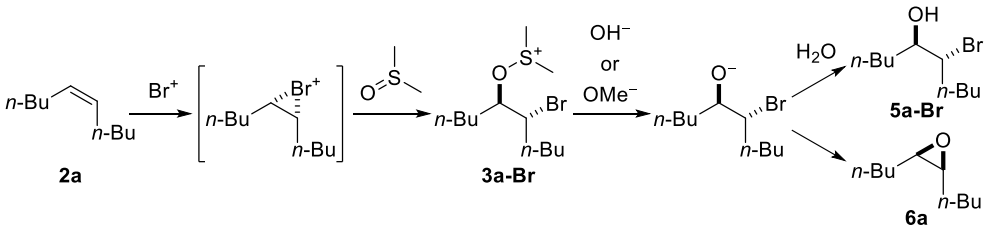
Table 1. Reaction of **3a-X** (X = Br, I) with Bases.



	% yield of product					
	X = Br			X = I		
base	**4a-Br**	**5a-Br**	**6a**	**4a-I**	**5a-I**	**6a**
Et_3N/CH_2Cl_2	83	N.D.	N.D.	85	N.D.	1
$NaOH/H_2O$	N.D.	89	2	N.D.	84	1
NaOMe/MeOH	N.D.	N.D.	95	N.D.	N.D.	96

The electrolysis was carried out using 1.3 equiv of Bu_4NBr or Bu_4NI (based on the alkene which was added after electrolysis) with 2.1 F/mol of electricity based on Bu_4NBr or Bu_4NI. GC yield based on **2a** is shown.

Scheme 2. Proposed Reaction Mechanisms for the Syntheses of Bromohydrin **5a-Br** and Epoxide **6a**.

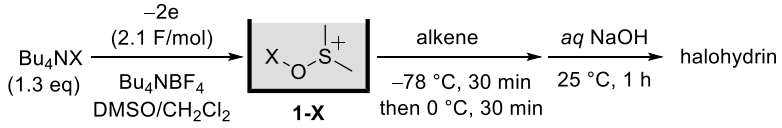


The treatment of **3a-Br** with NaOMe gave a different product, epoxide **6a** in 95% yield. In this case, the methoxide ion attacks the sulfur atom to cleave the S−O bond to give the alkoxide ion, but it attacks the carbon atom bearing bromine to give epoxide **6a** (Scheme 2). Presumably, protonation of the alkoxide ion with MeOH is slower than the intramolecular nucleophilic attack. The stereochemistry determined by NMR[11] is consistent with a mechanism involving the back-side attack of the alkoxide ion to form epoxide **6a**.

Next the reactions of *β*-iodoalkoxysulfonium ion **3a-I** generated by the reaction of (*Z*)-5-decene (**2a**) with I^+/DMSO (**1-I**) pool (Scheme 1, X = I) was examined. Bu_4NI in DMSO/CH_2Cl_2 (1:19 v/v) was electrochemically oxidized at −78 °C in a divided cell using Bu_4NBF_4 as a supporting electrolyte until 2.1 F/mol of electricity was applied. After addition of **2a** to the solution, the mixture was stirred at 0 °C to give **3a-I**, which was characterized by NMR spectroscopy. The treatment of **3a-I** with triethylamine gave *α*-iodoketone **4a-I** in 85% yield as reported previously. However, the treatment of **3a-I** with NaOH and NaOMe gave iodohydrin **5a-I** in 84% yield and epoxide **6a** in 96% yield, respectively (Table 1). The stereochemistry determined by NMR indicated that the addition of I^+ and DMSO across the C−C double bond was anti-selective as anticipated.

The present method was successfully applied to the synthesis of halohydrins and epoxides from various alkenes. The reactions of alkenes with **1-X** followed by the treatment with NaOH gave the corresponding halohydrins as shown in Table 2. The reactions of *E* and *Z* isomers of 1-phenyl-1-propene (**2d**) with **1-Br** gave **5d-Br** and **5d'-Br**, respectively (entries 7 and 9), indicating the anti addition of Br^+ and DMSO across the C−C double bond. The reaction with **1-I** also gave the anti-addition products (entries 8 and 10). Therefore, the reaction is stereospecific, and the stereochemistry is consistent with the proposed reaction mechanisms (Scheme 2). The addition of Br^+ or I^+ and DMSO to unsymmetrically substituted olefins **2c** and **2d** is regioselective giving the corresponding bromohydrins as a single regioisomer (entries 5-10). Regioselectivity of the product can be explained by the stability of carbocations (benzyl > secondary > primary). In the case of terminal alkene **2c**, Br and I were introduced to a primary carbon, whereas OH was introduced to a secondary carbon. In the case of styrene derivative **2d**, Br and I were introduced to a secondary carbon, whereas OH was introduced to the benzyl carbon. DMSO seems to attack the more positively charged carbon of the three-membered ring bromonium ion or iodonium ion.

Table 2. Synthesis of Halohydrins by the Reaction of **1-X** with Alkenes followed by the Treatment with NaOH.



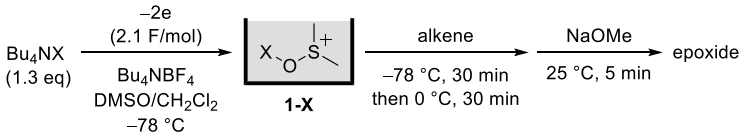
entry	alkene		product		yield(%)
1	*n*-Bu, *n*-Bu	**2a**	OH, X, *n*-Bu, *n*-Bu	**5a-Br**	87
2				**5a-I**	84[a]
3		**2b**	OH, X	**5b-Br**	74 (*cis*:*trans*=21:79)
4	(*E*:*Z* = 28:72)			**5b-I**	94 (*cis*:*trans*=29:71)

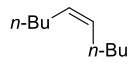
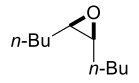
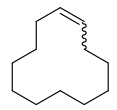
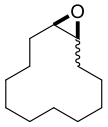
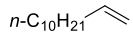
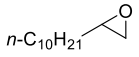
entry	alkene		product		yield(%)
5	*n*-$C_{10}H_{21}$	**2c**	OH, X, *n*-$C_{10}H_{21}$	**5c-Br**	57
6				**5c-I**	53
7	Ph	**(*E*)-2d**	OH, Ph, X	**5d-Br**	73
8				**5d-I**	35
9	Ph	**(*Z*)-2d**	OH, X, Ph	**5d'-Br**	75
10				**5d'-I**	51

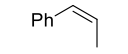
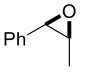
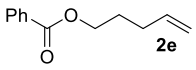
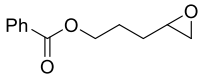
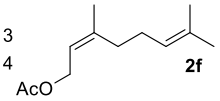
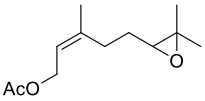
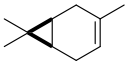
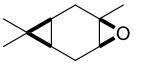
The electrolysis of Bu_4NBr and Bu_4NI was carried out using 1.3 equiv of Bu_4NX (based on **2** which was added after the electrolysis) with 2.1 F/mol of electricity based on Bu_4NX. Isolated yield based on **2** used is shown. b) Yield was determined by GC.

The reaction of **1-X** with alkenes followed by the treatment with NaOMe gave the corresponding epoxides as shown in Table 3. Alkenes having an alkoxycarbonyl group gave the corresponding epoxides in moderate yields (entries 11-14). Diene **2f** reacted with **1-Br** and **1-I** to give monoepoxide **6f** in moderate yields (entries 13 and 14). Interestingly, **2g** reacted with **1-Br** to give **6g** but not with **1-I** (entries 15 and 16). Higher stability of **1-I** than **1-Br** may cause the difference in the reactivity. The facial selectivity of the reaction is the opposite to that of the epoxidation using conventional reagents such as *m*-chloroperoxybenzoic acid (mCPBA) which epoxidizes alkenes from less hindered face.[12] In this reaction, Br^+ adds to the C−C double bond of **2g** from less hindered face to form the corresponding three-membered ring bromonium ion intermediate. DMSO attacks the bromonium ion from the more hindered face to form the corresponding *β*-haloalkoxysulfonium ion. The treatment of *β*-haloalkoxysulfonium ion with NaOMe cleaves the O−S bond to generate the alkoxide ion, which attacks the carbon atom bearing bromine to give epoxide **6g**. Therefore, the epoxidation takes place from the more hindered face.

Table 3. Synthesis of Epoxides by the Reaction of **1-X** with Alkenes followed by the Treatment with NaOMe.



entry	alkene	product	X	yield(%)
1	 **2a**	 **6a**	Br	95[a]
2			I	96[a]
3	 **2b** (*E*:*Z* = 28:72)	 **6b**	Br	68 (*cis*:*trans* = 74:26)
4			I	89 (*cis*:*trans* = 74:26)
5	 **2c**	 **6c**	Br	73[a]
6			I	86[a]
7	 **(*E*)-2d**	 **6d**	Br	53
8			I	38[b]

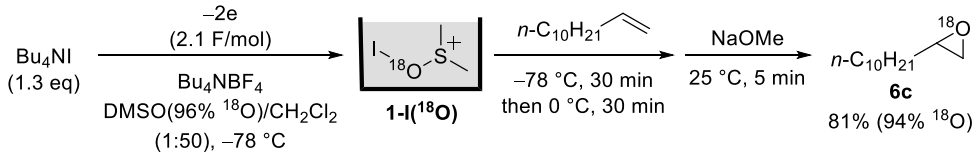
entry	alkene	product	X	yield(%)
9	 **(*Z*)-2d**	 **6d'**	Br	60
10			I	67[b]
11	 **2e**	 **6e**	Br	52[c]
12			I	57[c]
13	 **2f**	 **6f**	Br	49[c]
14			I	47[c]
15	 **2g**	 **6g**	Br	69
16			I	0

The electrolysis was carried out using 1.3 equiv of Bu_4NBr or Bu_4NI (based on **2** which was added after electrolysis) with 2.1 F/mol of electricity based on Bu_4NBr or Bu_4NI. Isolated yield based on **2** used is shown.
a) Yield was determined by GC. b) 2.0 equiv of Bu_4NI was used. c) Reacted with 2.5 equiv of NaOMe for 2 h.

Reaction mechanism

To confirm the mechanism shown in Scheme 2, the experiment using DMSO (96% ^{18}O)/CH_2Cl_2 (1:50 v/v) was carried out. As shown in Scheme 3, epoxide **6c** containing ^{18}O (94% ^{18}O) was obtained in 81% yield, indicating that the oxygen atom in the product was derived from the oxygen atom of DMSO. Because ^{18}O-DMSO can be easily synthesized from $H_2{}^{18}O$, the present transformation serves as a convenient method for synthesizing ^{18}O labeled epoxides, which can be used for various mechanistic and biological studies.[13]

Scheme 3. Mechanistic Study Using ^{18}O-DMSO.



Conclusion

In conclusion, the reaction pathways of *β*-haloalkoxysulfonium ions generated by the reaction of electrogenerated bromine and iodine cations stabilized by dimethyl sulfoxide (DMSO) can be switched by changing the nature of the base. The present transformation serves as stereospecific way to halohydrins and epoxides from alkenes. The method is also useful for synthesizing ^{18}O-labeled epoxides.

Experimental Session

General

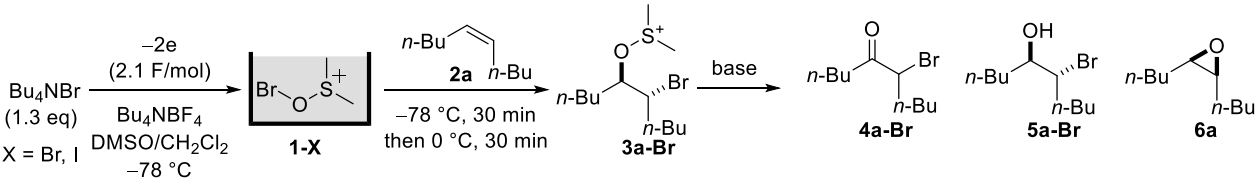
^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian MERCURY plus-400 (^{1}H 400 MHz, ^{13}C 100 MHz), or JEOL ECA-600P spectrometer (^{1}H 600 MHz, ^{13}C 150 MHz) spectrometer with tetramethylsilane as an internal standard unless otherwise noted. Mass spectra were obtained on a JEOL EXACTIVE (ESI and APCI) mass spectrometer and a JEOL JMS-SX102A mass spectrometer (EI). GC analysis was performed on a SHIMADZU GC-2014 gas chromatograph equipped with a flame ionization detector using a fused silica capillary column (column, CBP1; 0.22 mm x 25 m). Merck precoated silica gel F254 plates (thickness 0.25 mm) were used for thin-layer chromatography (TLC) analysis. Flash chromatography was carried out using Kanto Chem. Co., Silica Gel N (spherical, neutral, 40−100 μm). All reactions were carried out under argon atmosphere unless otherwise noted. Dimethyl sulfoxide (DMSO) and triethylamine were dried over molecular sieves 4A before use. Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification.

The anodic oxidation was carried out using an H-type divided cell (4G glass filter) equipped with an anode made of carbon strings (Nippon Carbon GF-20-P21E, ca. 160 mg for 0.20 mmol scale, dried at 300 °C/1 mmHg for 3 h before use) and a platinum plate cathode (10 mm x 10 mm). Dichloromethane was washed with water, distilled from P_2O_5, redistilled from dried K_2CO_3 to remove a trace amount of acid, and stored over molecular sieves 4A.

Reaction of 3a-X (X = Br, I) with Bases

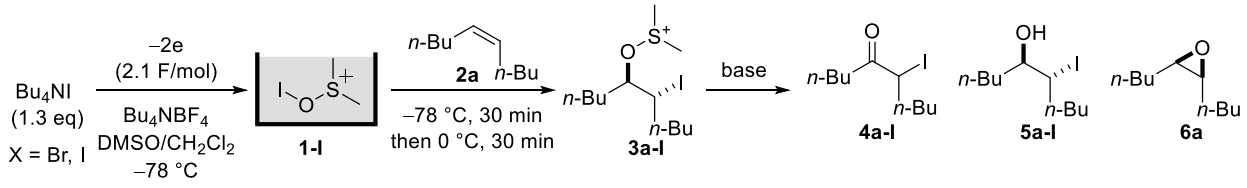
Generation of **1-Br** and **1-I** was conducted in a similar manner to a procedure from ref. 8.

Typical Procedure for Generation of 1-Br and 3a-Br and Reaction of 3a-Br with Bases



In the anodic chamber were placed Bu_4NBr (80.7 mg, 0.251 mmol), Bu_4NBF_4 (100 mg, 0.3 mmol), DMSO (1 mL), and 0.3 M Bu_4NBF_4/CH_2Cl_2 (9 mL). In the cathodic chamber were placed TfOH (60 μL, 0.68 mmol) and 0.3 M Bu_4NBF_4/CH_2Cl_2 (10 mL). The constant current electrolysis (8.0 mA) was carried out at −78 °C with magnetic stirring until 2.1 F mol^{-1} of electricity was consumed. To the anodic chamber was added a solution of (*Z*)-5-decene (**2a**) (27.7 mg, 0.197 mmol) in CH_2Cl_2 (0.5 mL), and to the cathodic chamber 0.5 mL of CH_2Cl_2 was added at −78 °C. The solution was stirred for 30 min at −78 °C, and then was stirred for 30 min at 0 °C. Et_3N (100 μL) was added to both the anodic and the cathodic chambers, and the resulting mixture was warmed to 25 °C and was stirred for 1 h. The solution in the anodic chamber was collected and the solvent was removed under reduced pressure. The residue was filtered through a short column (2 x 4 cm) of silica gel to remove Bu_4NBF_4 by using hexane/EtOAc (1:1) as an eluent. The GC analysis using hexadecane as an internal standard indicated that **6-bromodecan-5-one** (**4a-Br**) was obtained in 83% yield (38.6 mg, 0.164 mmol). The ^{1}H NMR data was reported previously[1]. Addition of NaOH (2.5 M in H_2O, 0.16 mL) instead of Et_3N gave **(5*R**,6*R**)-6-bromodecan-5-ol** (**5a-Br**) in 89% yield (0.174 mmol). TLC R_f 0.19 (hexane/EtOAc 20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.2 Hz, 6 H), 1.25−1.61 (m, 10 H), 1.84 (d, *J* = 8.0 Hz, 1 H), 1.86−2.00 (m, 2 H), 3.20−3.57 (m, 1 H), 4.07 (ddd, *J* = 3.2, 5.2, 8.4 Hz, 1 H); The ^{1}H NMR spectrum is in agreement with that of an authentic sample synthesized using NBS according to the literature[14] (*vide infra*). Addition of NaOMe (5.0 M in MeOH, 0.2 mL) instead of Et_3N gave **(5*R**,6*S**)-5,6-epoxydecane** (**6a**) in 95% yield (0.187 mmol). TLC R_f 0.83 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.2 Hz, 6 H), 1.37−1.55 (m, 12 H), 2.88−2.94 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.6, 27.5, 28.3, 57.2; HRMS (APCI) calcd for $C_{10}H_{21}O$ ($M+H^+$): 157.1587, found: 157.1587. Stereochemistry was determined by comparison of the ^{1}H NMR spectrum with that in the literature.[11]

Typical Procedure for Generation of 1-I and 3a-I and Reaction of 3a-I with Bases



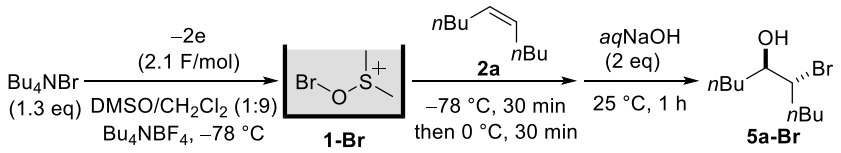
In the anodic chamber were placed Bu_4NI (91.6 mg, 0.248 mmol), Bu_4NBF_4 (102 mg, 0.3 mmol), DMSO (1 mL), and 0.3 M Bu_4NBF_4/CH_2Cl_2 (9 mL). In the cathodic chamber were placed TfOH (60 μL, 0.68 mmol) and 0.3 M Bu_4NBF_4/CH_2Cl_2 (10 mL). The constant current electrolysis (8.0 mA) was carried out at −78 °C with magnetic stirring until 2.1 F mol^{-1} of electricity was consumed. To the anodic chamber was added a solution of (*Z*)-5-decene (**2a**) (28.7 mg, 0.205 mmol) in CH_2Cl_2 (0.5 mL), and to the cathodic chamber was added 0.5 mL of CH_2Cl_2 at −78 °C. The solution was stirred for 30 min at −78 °C, and then was stirred for 30 min at 0 °C. Et_3N (100 μL) was added to both the anodic and the cathodic chambers, and the resulting mixture was warmed to 25 °C and was

stirred for 1 h. The solution in the anodic chamber was collected and the solvent was removed under reduced pressure. The residue was filtered through a short column (2 x 4 cm) of silica gel to remove Bu_4NBF_4 by using hexane/EtOAc (1:1 v/v) as an eluent. The GC analysis using hexadecane as an internal standard indicated that **6-iododecan-5-one** (**4a-I**) was obtained in 85% yield (49.2 mg, 0.174 mmol). The ^{1}H NMR data was reported previously.[1] Addition of NaOH (2.5 M in H_2O, 0.16 mL) instead of Et_3N gave **(5*R**,6*R**)-6-iododecan-5-ol** (**5a-I**) in 84% yield (0.169 mmol). TLC R_f 0.19 (hexane/EtOAc 20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.2 Hz, 6 H), 1.25−1.61 (m, 10 H), 1.84 (d, *J* = 8.0 Hz, 1 H), 1.86−2.00 (m, 2 H), 3.20−3.57 (m, 1 H), 4.07 (ddd, *J* = 3.2, 5.2, 8.4 Hz, 1 H); The ^{1}H NMR spectrum is in agreement with that of an authentic sample synthesized using I_2 and H_2O_2 according to the literature[15] (*vide infra*). Addition of NaOMe (5.0 M in MeOH, 0.2 mL) instead of Et_3N gave **(5*R**,6*S**)-5,6-epoxydecane** (**6a**) in 96% yield (0.191 mmol). TLC R_f 0.83 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.2 Hz, 6 H), 1.37−1.55 (m, 12 H), 2.88−2.94 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.6, 27.5, 28.3, 57.2; HRMS (APCI) calcd for $C_{10}H_{21}O$ ($M+H^+$): 157.1587, found: 157.1587. Stereochemistry was determined by comparison of the ^{1}H NMR spectrum with that in the literature[11].

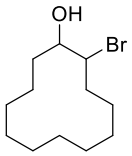
Synthesis of Halohydrins

Generation of **1-Br** and **1-I** was conducted in a similar manner to a procedure from ref. 1.

Typical Procedure for Generation of 1-Br and Synthesis of Bromohydrins

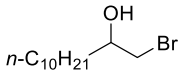


In the anodic chamber were placed Bu_4NBr (81.0 mg, 0.252 mmol), Bu_4NBF_4 (101 mg, 0.3 mmol), DMSO (1 mL), and 0.3 M Bu_4NBF_4/CH_2Cl_2 (9 mL). In the cathodic chamber were placed TfOH (60 μL, 0.68 mmol) and 0.3 M Bu_4NBF_4/CH_2Cl_2 (10 mL). The constant current electrolysis (8.0 mA) was carried out at −78 °C with magnetic stirring until 2.1 F mol^{-1} of electricity was consumed. To the anodic chamber was added a solution of (*Z*)-5-decene (**2a**) (27.0 mg, 0.193 mmol) in CH_2Cl_2 (0.5 mL), and to the cathodic chamber 0.5 mL of CH_2Cl_2 was added at −78 °C. The solution was stirred for 30 min at −78 °C, and then was stirred for 30 min at 0 °C. NaOH (2.5 M in H_2O, 0.16 mL) was added to both the anodic and the cathodic chambers, and the resulting mixture was warmed to 25 °C and was stirred for 1 h. The solution in the anodic chamber was collected and the solvent was removed under reduced pressure. The residue was filtered through a short column (2 x 4 cm) of silica gel to remove Bu_4NBF_4 by using hexane/EtOAc (1:1) as an eluent. After removal of the solvent under reduced pressure, the crude product was purified by flash chromatography (hexane/EtOAc 20:1) to obtain **(5*R**,6*R**)-6-bromodecan-5-ol** (**5a-Br**) in 87% yield (40.0 mg, 0.169 mmol). TLC R_f 0.19 (hexane/EtOAc 20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.2 Hz, 6 H), 1.25−1.61 (m, 10 H), 1.84 (d, *J* = 8.0 Hz, 1 H), 1.86−2.00 (m, 2 H), 3.20−3.57 (m, 1 H), 4.07 (ddd, *J* = 3.2, 5.2, 8.4 Hz, 1 H); The ^{1}H NMR spectrum is in agreement with that of an authentic sample synthesized using NBS according to the literature[14] (*vide infra*).



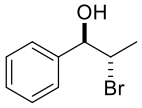
5b-Br

2-bromocyclododecan-1-ol (5b-Br). Electrochemical oxidation (2.1 F mol^{-1}) of Bu_4NBr (82 mg, 0.25 mmol), subsequent addition of the solution of cyclododecene (**2b**) (*Z*/*E* = 72:28, 31.6 mg, 0.190 mmol) in CH_2Cl_2 (0.5 mL), and the treatment with NaOH followed by flash chromatography (hexane/EtOAc 20:1) gave the title compound as mixture of the diastereomers (37.3 mg, 0.142mmol, 74%, *trans:cis* = 79:21). TLC R_f 0.42 and 0.48 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24−1.82 (m, 18 H), 1.85−1.96 (m, 1 H), 2.01−2.16 (m, 2 H), 2.23 (d, *J* = 5.2 Hz, 1 H), 3.80 (td, *J* = 5.2, 12.0 Hz, trans 1 H), 3.90 (br, cis 1 H), 4.32−4.41 (m, 1 H); The ^{1}H NMR spectrum is in agreement with that in the literature.[16]



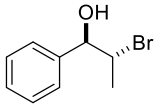
5c-Br

1-bromododecan-2-ol (5c-Br). Electrochemical oxidation (2.1 F mol^{-1}) of Bu_4NBr (81 mg, 0.25 mmol), subsequent addition of the solution of 1-dodecene (**2c**) (32.5 mg, 0.193 mmol) in CH_2Cl_2 (0.5 mL), and the treatment with NaOH followed by flash chromatography (hexane/EtOAc 100:0 to 50:1) gave the title compound (29.3 mg, 0.110 mmol, 57%). TLC R_f 0.48 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.8 Hz, 3 H), 1.23−1.61 (m, 20 H), 2.10−2.14 (m, 1 H), 3.39 (dd, *J* = 7.2, 10.4 Hz, 1 H), 3.55 (dd, *J* = 2.8, 10.4 Hz, 1 H), 3.74−3.82 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 25.6, 29.3, 29.47, 29.48, 29.54, 29.6, 31.9, 35.1, 40.7, 71.1; HRMS (EI) calcd for $C_{12}H_{24}OBr$ ($M-H^+$): 263.1016, found: 263.1013. The ^{1}H NMR spectrum is in agreement with that in the literature.[17]



5d-Br

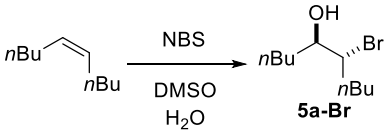
(1*R,2*S**)-2-bromo-1-phenyl-1-propanol** (**5d-Br**)**.** Electrochemical oxidation (2.1 F mol^{-1}) of Bu_4NBr (81.2 mg, 0.252 mmol), subsequent addition of the solution of (*E*)-*β*-methylstylene (**(*E*)-2d**) (22.8 mg, 0.193 mmol) in CH_2Cl_2 (0.5 mL), and the treatment with NaOH followed by flash chromatography (hexane/EtOAc 100:0 to 20:1) gave the title compound (30.2 mg, 0.140 mmol, 73%). TLC R_f 0.33 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (d, *J* = 6.8 Hz, 3 H), 2.51 (m, 1 H), 4.43 (dq, *J* = 3.6, 6.8 Hz, 1 H), 5.01 (t, *J* = 3.6 Hz, 1 H), 7.27–7.40 (m, 5 H). The ^{1}H NMR spectrum is in agreement with that in the literature.[8]



5d'-Br

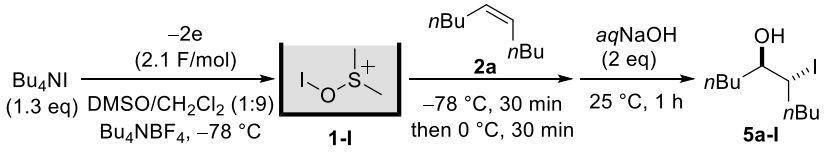
(1*R,2*R**)-2-bromo-1-phenyl-1-propanol** (**5d'-Br**)**.** Electrochemical oxidation (2.1 F mol^{-1}) of Bu_4NBr (81.9 mg, 0.254 mmol), subsequent addition of the solution of (*Z*)-*β*-methylstylene (**(*Z*)-2d**) (23.5 mg, 0.199 mmol) in CH_2Cl_2 (0.5 mL), and the treatment with NaOH followed by flash chromatography (hexane/EtOAc 100:0 to 20:1) gave the title compound (32.2 mg, 0.150 mmol, 75%). TLC R_f 0.38 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57 (d, *J* = 6.8 Hz, 3 H), 2.77 (m, 1 H), 4.34 (dq, *J* = 6.8, 7.6 Hz, 1 H), 4.62 (dd, *J* = 3.6, 7.6 Hz, 1 H), 7.30–7.40 (m, 5 H). The ^{1}H NMR spectrum is in agreement with that in the literature.[8]

Synthesis of (5*R,6*R**)-6-bromodecan-5-ol (5a-Br)**

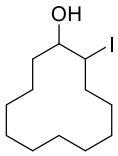


To a round-bottom flask were added NBS (640 mg, 3.59 mmol), (*Z*)-5-decene (417 mg, 2.97 mmol), DMSO (10 mL), and H_2O (0.1 mL). The mixture was stirred for 4 h. After addition of NBS (600 mg, 3.37 mmol), the mixture was stirred at room temperature for 1 d. The solution was diluted with EtOAc (30 mL), washed with sat aq $NaHCO_3$ (10 mL x 2), H_2O (10 mL x 2), and brine (10 mL) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by flash chromatography (hexane/EtOAc 100:0 to 20:1) to obtain **(5*R**,6*R**)-6-bromodecan-5-ol** (**5a-Br**) in 60% yield (420 mg, 1.77 mmol). TLC R_f 0.19 (hexane/EtOAc 20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.2 Hz, 6 H), 1.25−1.61 (m, 10 H), 1.84 (d, *J* = 8.0 Hz, 1 H), 1.86−2.00 (m, 2 H), 3.20−3.57 (m, 1 H), 4.07 (ddd, *J* = 3.2, 5.2, 8.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 14.0, 22.1, 22.6, 27.8, 30.0, 35.48, 35.52, 65.5, 73.8; HRMS (EI) calcd for $C_{10}H_{20}OBr$ ($M-H^+$): 235.0703, found: 235.0702.

Typical Procedure for the Generation of 1-I and the Synthesis of Iodohydrins

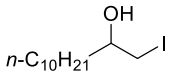


In the anodic chamber were placed Bu_4NI (93 mg, 0.25 mmol), Bu_4NBF_4 (980 mg, 3.0 mmol), DMSO (1 mL), and CH_2Cl_2 (9 mL). In the cathodic chamber were placed TfOH (60 μL, 0.68 mmol) and 0.3 M Bu_4NBF_4/CH_2Cl_2 (10 mL). The constant current electrolysis (8.0 mA) was carried out at −78 °C with magnetic stirring until 2.1 F mol^{-1} of electricity was consumed. To the anodic chamber was added a solution of (*Z*)-5-decene (**2a**) (27.0 mg, 0.193 mmol) in CH_2Cl_2 (0.5 mL), and to the cathodic chamber was added 0.5 mL of CH_2Cl_2 at −78 °C. The solution was stirred for 30 min at −78 °C, and then was stirred for 30 min at 0 °C. NaOH (2.5 M in H_2O, 0.16 mL) was added to both the anodic and the cathodic chambers, and the resulting mixture was warmed to 25 °C and was stirred for 1 h. The solution in the anodic chamber was collected and the solvent was removed under reduced pressure. Then, the residue was filtered through a short column (2 x 4 cm) of silica gel to remove Bu_4NBF_4 by using hexane/EtOAc (1:1 v/v) as an eluent. The GC analysis using hexadecane as an internal standard indicated that **(5*R**,6*R**)-6-iododecan-5-ol** (**5a-I**) was obtained in 84% yield (0.169 mmol). TLC R_f 0.56 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.2 Hz, 6 H), 1.25–1.46 (m, 6 H), 1.47–1.60 (m, 4 H), 1.62 (d, *J* = 8.4 Hz, 1 H), 1.78–1.88 (m, 1 H), 1.98–2.09 (m, 1 H), 2.85–2.90 (m, 1 H), 4.19 (ddd, *J* = 2.8, 4.8, 9.2 Hz, 1 H); The ^{1}H NMR spectrum is in agreement with that of an authentic sample synthesized using I_2 and H_2O_2 according to the literature[15] (*vide infra*).



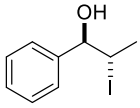
5b-I

2-iodocyclododecan-1-ol (5b-I). Electrochemical oxidation (2.1 F mol^{-1}) of Bu_4NI (90.8mg, 0.246 mmol), subsequent addition of the solution of cyclododecene (**2b**) (*Z*/*E* = 72:28, 31.4 mg, 0.189 mmol) in CH_2Cl_2 (0.5 mL), and the treatment with NaOH followed by flash chromatography (hexane/EtOAc 20:1) gave the title compound (55.0 mg, 0.177 mmol, 94%, *trans:cis* = 71:29). TLC R_f 0.42 and 0.50 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20−1.80 (m, 18 H), 1.91−2.08 (m, 3 H), 3.39 (m, trans 1 H), 4.51 (dt, *J* = 6.0, 6.0 Hz, 1 H); The ^{1}H NMR spectrum is in agreement with that of an authentic sample synthesized using I_2 and H_2O_2 according to the literature[15] (*vide infra*).



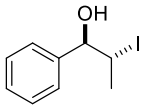
5c-I

1-iodododecan-2-ol (5c-I). Electrochemical oxidation (2.1 F mol^{-1}) of Bu_4NI (93 mg, 0.25 mmol), subsequent addition of the solution of 1-dodecene (**2c**) (33.9 mg, 0.201 mmol) in CH_2Cl_2 (0.5 mL), and the treatment with NaOH followed by flash chromatography (hexane/EtOAc 10:1) gave the title compound (33.0 mg, 0.106 mmol, 53%). TLC R_f 0.26 (hexane/EtOAc 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.8 Hz, 3 H), 1.10−1.50 (m, 16 H), 1.52−1.58 (m, 2 H), 1.98 (d, *J* = 5.2 Hz, 1 H), 3.23 (dd, *J* = 6.8, 10.0 Hz, 1 H), 3.40 (dd, *J* = 3.6, 10.4 Hz, 1 H), 3.45−3.60 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 16.9, 22.7, 25.6, 29.3, 29.43, 29.47, 29.53, 29.6, 31.9, 36.6, 71.0; HRMS (EI) calcd for $C_{12}H_{25}OBr$ (M^+): 312.0951, found: 312.0958. The ^{1}H NMR spectrum is in agreement with that in the literature.[18]



5d-I

(1*R,2*S**)-2-iodo-1-phenyl-1-propanol** (**5d-I**)**.** Electrochemical oxidation (2.1 F mol^{-1}) of Bu_4NI (87.4 mg, 0.236 mmol), subsequent addition of the solution of (*E*)-*β*-methylstylene (**(*E*)-2d'**) (21.8 mg, 0.185 mmol) in CH_2Cl_2 (0.5 mL), and the treatment with NaOH followed by flash chromatography (hexane/EtOAc 100:0 to 50:1) gave the title compound (16.9 mg, 0.064 mmol, 35%). TLC R_f 0.35 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.74 (d, *J* = 6.8 Hz, 3 H), 2.37(s, 1 H), 4.52 (dq, *J* = 3.6, 7.2 Hz, 1 H), 4.96 (t, *J* = 3.6 Hz, 1 H), 7.29−7.40 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 35.9, 78.5, 126.4, 128.0, 128.4, 139.7; HRMS (EI) calcd for $C_9H_{11}OI$ (M^+): 261.9855, found: 261.9860. Stereochemistry was determined by comparison of the ^{1}H NMR spectrum with that in the literature.[19]

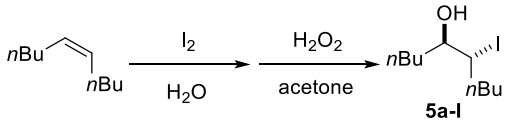


5d'-I

(1*R,2*R**)-2-iodo-1-phenyl-1-propanol** (**5d'-I**)**.** Electrochemical oxidation (2.1 F mol^{-1}) of Bu_4NI (93.1 mg, 0.252 mmol), subsequent addition of the solution of (*Z*)-*β*-methylstylene (**(*Z*)-2d**) (22.4 mg, 0.190 mmol) in CH_2Cl_2 (0.5 mL), and the treatment with NaOH followed by flash chromatography (hexane/EtOAc 10:1) gave the title compound (27.0 mg, 0.098 mmol, 51%). TLC R_f 0.13 (hexane/EtOAc 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81 (d, *J* = 6.8 Hz, 3 H), 2.51 (d, *J* = 4.0 Hz, 1 H), 4.39−4.47 (m, 2 H), 7.31−7.41 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4, 39.1, 79.6, 126.3, 128.4, 128.6, 139.9; HRMS (EI) calcd for

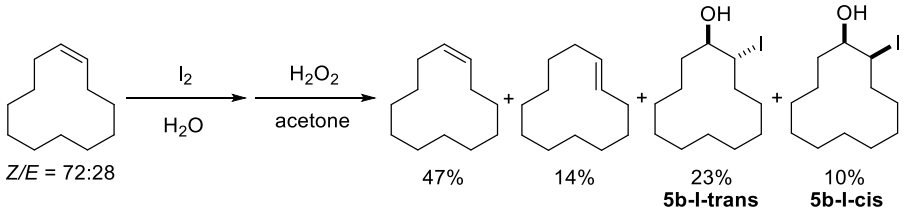
$C_9H_{11}OI$ (M^+): 261.9855, found: 261.9856. Stereochemistry was determined by comparison of the ^1H NMR spectrum with that in the literature.[19]

Synthesis of (5*R,6*R**)-6-iododecan-5-ol (5a-I)**



To a round-bottom flask were added iodine (1.07 g, 4.22 mmol), (*Z*)-5-decene (271 mg, 1.94 mmol), H_2O (10 mL) were stirred. After 30 min, acetone (10 mL), H_2O_2 (31% in H_2O, 400 μL, 3.64 mmol) were added and the mixture was stirred at room temperature. After 3 days, the solution was extracted with CH_2Cl_2 (20 mL x 3) and was dried over Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by flash chromatography (hexane/EtOAc 100:0 to 20:1) to obtain **(5*R**,6*R**)-6-iododecan-5-ol** (**5a-I**) in 91% yield (500 mg, 1.76 mmol). TLC R_f 0.56 (hexane/EtOAc 5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.2 Hz, 6 H), 1.25–1.46 (m, 6 H), 1.47–1.60 (m, 4 H), 1.62 (d, *J* = 8.4 Hz, 1 H), 1.78–1.88 (m, 1 H), 1.98–2.09 (m, 1 H), 2.85–2.90 (m, 1 H), 4.19 (ddd, *J* = 2.8, 4.8, 9.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 14.0, 22.0, 22.6, 27.7, 32.0, 37.4, 37.7, 50.5, 74.1; HRMS (ESI) calcd for $C_{10}H_{21}OICl$ ($M+Cl^-$): 319.0331, found: 319.0331.

Synthesis of 2-Iodocyclododecan-1-ol (5b-I)



To a round-bottom flask were added iodine (550 mg, 2.16 mmol), cyclododecene (*Z*/*E* = 72:28, 174 mg, 1.05 mmol), and H_2O (5 mL). The mixture was stirred for 30 min at room temperature. After addition of acetone (5 mL) and H_2O_2 (31% in H_2O, 200 μL, 1.82 mmol), the mixture was stirred at room temperature for 3 d. The solution was extracted with CH_2Cl_2 (20 mL x 3) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was obtained. The NMR analysis indicated that (*Z*)- and (*E*)-cyclododecenes were recovered in 47%, 14% yield, respectively and that (1S*,2S*)-2-iodocyclododecan-1-ol and (1S*,2R*)-2-iodocyclododecan-1-ol were obtained in 23%, and 10% yield, respectively. (1*S**,2*S**)-2-iodocyclododecan-1-ol and (1*S**,2*R**)-2-iodocyclododecan-1-ol were isolated by using column chromatography.

(1*R,2*R**)-2-iodocyclododecan-1-ol (5b-I-trans)**: TLC R_f 0.57 (hexane/EtOAc 5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 1.20−1.80 (m, 18 H), 1.88 (d, *J* = 6.4 Hz, 1 H), 1.91−2.01 (m, 1 H), 2.08−2.18 (m, 1 H), 3.39 (m, 1 H), 4.52 (dt, *J* = 6.0, 6.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 23.0, 23.3, 23.4, 23.8, 23.9, 24.0, 24.4, 32.1, 34.9, 47.3, 70.8; HRMS (ESI) calcd for $C_{12}H_{23}IONa^+$ ($M+Na^+$): 333.0686, found: 333.0685.

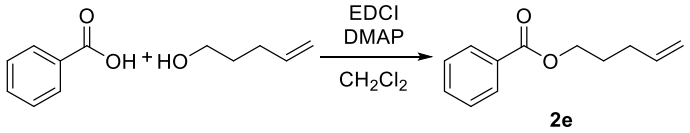
(1*R,2*S**)-2-iodocyclododecan-1-ol (5b-I-cis)**: TLC R_f 0.45 (hexane/EtOAc 5:1); ^1H NMR (600 MHz, $CDCl_3$, 50 °C) δ 1.25−1.56 (m, 17 H), 1.71−1.80 (m, 1 H), 1.88 (s, br, 1 H), 2.02 (dt, *J* = 7.2, 7.2 Hz, 2 H), 3.59 (s, br, 1 H), 4.50 (t, *J* = 7.2 Hz, 1 H); ^{13}C NMR (150 MHz, pyridine–d5, 100 °C) δ 22.8, 22.9, 24.91, 24.98, 25.01, 25.4, 25.9,

32.5, 33.8, 45.5, 73.5; HRMS (ESI) calcd for $C_{12}H_{23}OICl^-$ (M+Cl^-): 345.0488, found: 345.0490.

Synthesis of Epoxides

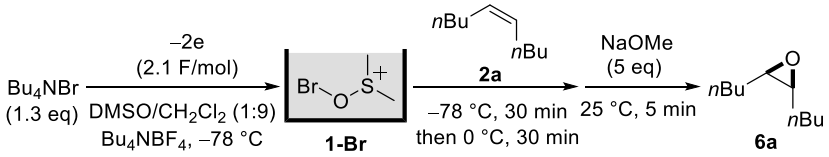
Generation of **1-Br** and **1-I** was conducted in a similar manner to a procedure from ref. 8.

Preparation of 4-Pentenyl Benzoate



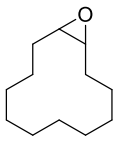
To a round-bottom flask were added 4-pentenol (430 mg, 5.0 mmol), benzoic acid (630 mg, 5.2 mmol), EDCI (1.15 g, 6.0 mmol), DMAP (120 mg, 0.98 mmol), and CH_2Cl_2 (15 mL). The mixture was stirred at room temperature for 2 d. After addition of water, the solution was extracted with CH_2Cl_2 (20 mL x 3). The solvent was removed under reduced pressure, and the residue was purified through a short column (2 x 4 cm) of silica gel by using hexane/EtOAc (1:1) as an eluent. After removal of the solvent under reduced pressure, the crude product was further purified by flash chromatography (hexane/EtOAc 20:1) to obtain **4-pentenyl benzoate (2e)** in 96% yield (910 mg, 4.78 mmol). TLC R_f 0.59 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88 (tt, *J* = 6.4, 7.6 Hz, 2 H), 2.23 (td, *J* = 6.8, 8.0 Hz, 2 H), 4.34 (t, *J* = 6.4 Hz, 2 H), 5.02 (dd, *J* = 2.0, 10.0 Hz, 1 H), 5.08 (dd, *J* = 2.0, 16.8 Hz, 1 H), 5.86 (tdd, *J* = 6.4, 10.4, 17.2 Hz, 1 H), 7.44 (t, *J* = 7.2 Hz, 2 H), 7.56 (t, *J* = 7.6 Hz, 1 H), 8.05 (d, *J* = 7.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.9, 30.2, 64.3, 115.4, 128.3, 129.5, 130.4, 132.8, 137.5, 166.6; HRMS (EI) calcd for $C_{12}H_{14}O_2Ma$ (M+Na^+): 213.0886, found: 213.0883. The ^{1}H NMR spectrum is in agreement with that in the literature.[20]

Typical Procedure for the Generation of 1-Br and the Synthesis of Epoxides

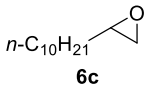


In the anodic chamber were placed Bu_4NBr (80.6 mg, 0.250 mmol), Bu_4NBF_4 (97 mg, 0.29 mmol), DMSO (1 mL), and 0.3 M Bu_4NBF_4/CH_2Cl_2 (9 mL). In the cathodic chamber were placed TfOH (60 μL, 0.68 mmol) and 0.3 M Bu_4NBF_4/CH_2Cl_2 (10 mL). The constant current electrolysis (8.0 mA) was carried out at −78 °C with magnetic stirring until 2.1 F mol^{-1} of electricity was consumed. To the anodic chamber was added a solution of (*Z*)-5-decene (**2a**) (27.7 mg, 0.197 mmol) in CH_2Cl_2 (0.5 mL), and to the cathodic chamber 0.5 mL of CH_2Cl_2 was added at −78 °C. The solution was stirred for 30 min at −78 °C, and then was stirred for 30 min at 0 °C. Then NaOMe (5.0 M in MeOH, 0.2 mL) was added to both the anodic and the cathodic chambers, and the resulting mixture was warmed to 25 °C and was stirred for 5 min. The solution in the anodic chamber was filtered through a short column (2 x 4 cm) of silica gel to remove Bu_4NBF_4 by using Et_2O as an eluent. The GC analysis using hexadecane as an internal standard indicated that **(5*R**,6*S**)-5,6-epoxydecane** (**6a**) was obtained in 95% yield (0.187 mmol). TLC R_f 0.83 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.2 Hz, 6 H), 1.37−1.55 (m, 12 H), 2.88−2.94

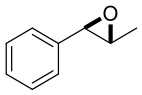
(m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.6, 27.5, 28.3, 57.2; HRMS (APCI) calcd for $C_{10}H_{21}O$ ($M+H^+$): 157.1587, found: 157.1587. Stereochemistry was determined by comparison of the ^{1}H NMR spectrum with that in the literature.[11]


6b

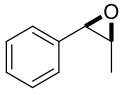
1,2-epoxycyclododecane (6b). Electrochemical oxidation (2.1 F mol^{-1}) of Bu_4NBr (81.7 mg, 0.254 mmol), subsequent addition of the solution of cyclododecene (**2b**) (*Z*/*E* = 72:28, 32.7 mg, 0.196 mmol) in CH_2Cl_2 (0.5 mL), and treatment with NaOMe followed by flash chromatography (hexane) gave the title compound (22.3 mg, 0.134 mmol, 68%, *cis:trans* = 74:26). TLC R_f 0.54 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20−1.61 (m, 20 H), 1.70−1.87 (m, cis 2 H), 2.15−2.23 (m, trans 2 H), 2.71 (m, trans 2 H), 2.90 (td, *J* = 1.6, 10.0 Hz, cis 2 H). The ^{1}H NMR spectrum is in agreement with the literature.[21]


6c

1,2-epoxydodecane (6c). Electrochemical oxidation (2.1 F mol^{-1}) of Bu_4NBr (80.5 mg, 0.250 mmol), subsequent addition of the solution of 1-dodecene (**2c**) (31.8 mg, 0.189 mmol) in CH_2Cl_2 (0.5 mL), and treatment with NaOMe gave the title compound (0.138 mmol, 73%). The yield was determined by GC analysis using hexadecane as internal standard. TLC R_f 0.63 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.8 Hz, 3 H), 1.20−1.38 (m, 14 H), 1.40−1.56 (m, 4 H), 2.46 (dd, *J* = 2.8, 4.8 Hz, 1 H), 2.75 (dd, *J* = 3.6, 4.0 Hz, 1 H), 2.88−2.94 (m, 1 H). The ^{1}H NMR spectrum is in agreement with the literature.[22]

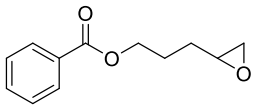

6d

(1*R,2*R**)-1-phenyl-1,2-epoxypropane** (**6d**)**.** Electrochemical oxidation (2.1 F mol^{-1}) of Bu_4NBr (82.4 mg, 0.256 mmol), subsequent addition of the solution of (*E*)-*β*-methylstylene (**(*E*)-2d**) (22.9 mg, 0.194 mmol) in CH_2Cl_2 (0.5 mL), and treatment with NaOMe followed by flash chromatography[23] (hexane) gave the title compound (13.7 mg, 0.102 mmol, 53%). TLC R_f 0.58 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (d, *J* = 5.2 Hz, 3 H), 3.04 (dq, *J* = 2.0, 5.2 Hz, 1 H), 3.58 (d, *J* = 1.6 Hz, 2 H), 7.24−7.39 (m, 5 H). The ^{1}H NMR spectrum is in agreement with the literature.[24]


6d'

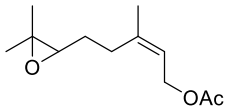
(1*R,2*S**)-1-phenyl-1,2-epoxypropane** (**6d'**)**.** Electrochemical oxidation (2.1 F mol^{-1}) of Bu_4NBr (81.7 mg, 0.254 mmol), subsequent addition of the solution of (*Z*)-*β*-methylstylene (**(*Z*)-2d**) (22.9 mg, 0.194 mmol) in CH_2Cl_2 (0.5 mL), and treatment with NaOMe followed by flash chromatography[23] (hexane) gave the title compound (15.7 mg, 0.117 mmol, 60%). TLC R_f 0.56 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (d, *J* = 5.6 Hz, 3 H), 3.34 (dq, *J* = 4.4, 5.2 Hz, 1 H), 4.07 (d, *J* = 4.4 Hz, 1 H) 7.26−7.40 (m, 5 H). The ^{1}H NMR spectrum is in agreement with the

literature.[24]



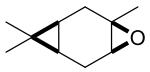
6e

4,5-epoxypentenyl benzoate (6e). Electrochemical oxidation (2.1 F mol^{-1}) of Bu_4NBr (81.6 mg, 0.253 mmol), subsequent addition of the solution of 4-pentenyl benzoate (**2f**) (37.2 mg, 0.196 mmol) in CH_2Cl_2 (0.5 mL), and treatment with NaOMe followed by flash chromatography[23] (hexane/EtOAc 100:0 to 20:1) gave the title compound (21.0 mg, 0.102 mmol, 52%). TLC R_f 0.29 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62−1.82 (m, 2 H), 1.88−2.04 (m, 2 H), 2.52 (dd, *J* = 2.8, 5.2 Hz, 1 H), 2.78 (dd, *J* = 4.0, 5.2 Hz, 1 H), 2.98−3.02 (m, 1 H), 4.38 (dt, *J* = 2.4, 6.4 Hz, 2 H), 7.44 (t, *J* = 8.0 Hz, 2 H), 7.56 (t, *J* = 7.6 Hz, 1 H), 8.04 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 29.1, 47.0, 51.7, 64.4, 128.3, 129.5, 130.2, 132.9, 166.5; HRMS (ESI) calcd for $C_7H_7O_2$ ($M-H^+$): 207.1016, found: 207.1012. The ^{1}H NMR spectrum is in agreement with the literature.[25]



6f

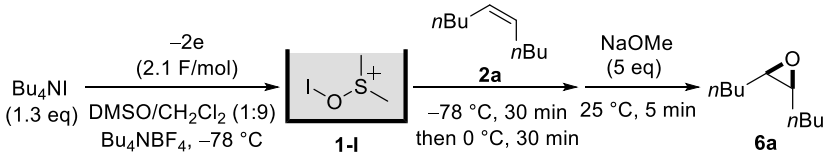
6,7-epoxyneryl acetate (6f). Electrochemical oxidation (2.1 F mol^{-1}) of Bu_4NBr (80.7 mg, 0.251 mmol), subsequent addition of the solution of neryl acetate (**2f**) (357.3 mg, 0.190 mmol) in CH_2Cl_2 (0.5 mL), and treatment with NaOMe followed by flash chromatography[23] (hexane/EtOAc 100:0 to 50:1) gave the title compound (19.7 mg, 0.093 mmol, 49%). TLC R_f 0.30 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 3 H), 1.31 (s, 3 H), 1.56−1.71 (m, 2 H), 1.79 (s, 3 H), 2.05 (s, 3 H) 2.23−2.29 (m, 2 H), 2.71 (t, *J* = 6.0 Hz, 1 H), 4.59 (d, *J* = 7.6 Hz, 2 H), 5.41 (t, *J* = 7.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 21.0, 23.4, 24.8, 27.5, 28.8, 58.4, 60.8, 63.7, 119.7, 141.7, 171.0; HRMS (ESI) calcd for $C_{12}H_{20}O_3Na$ ($M+Na^+$): 235.1305, found: 235,1299. The ^{1}H NMR spectrum is in agreement with the literature.[26]



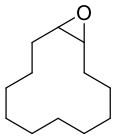
6g

(1*S*,3*R*,4*S*,6*R*)-3,4-epoxycarane (6g). Electrochemical oxidation (2.1 F mol^{-1}) of Bu_4NBr (80.4 mg, 0.250 mmol), subsequent addition of the solution of (+)-3-carene (**2g**) (26.1 mg, 0.192 mmol) in CH_2Cl_2 (0.5 mL), and treatment with NaOMe followed by flash chromatography[23] (hexane) gave the title compound. (20.1 mg, 0.132 mmol, 69%). TLC R_f 0.50 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.52 (dt, *J* = 2.0, 9.2 Hz, 1 H), 0.57 (dt, *J* = 2.0, 9.2 Hz, 1 H), 0.92 (s, 3 H), 0.96 (s, 3 H), 1.30 (s, 3 H), 1.78 (d, *J* = 15.6 Hz, 2 H), 2.06 (dd, *J* = 9.2, 16.4 Hz, 1 H) 2.28 (ddd, *J* = 5.6, 9.2, 16.4 Hz, 1 H) 2.88 (d, 5.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7, 17.3, 17.5, 18.3, 19.4, 23.9, 24.7, 29.1, 55.9, 58.2; HRMS (ESI) calcd for $C_{10}H_{17}O$ ($M+H^+$): 153.1274, found: 153.1270. Stereochemistry was determined by comparison of the ^{1}H NMR spectrum with that in the literature.[27]

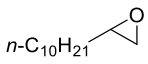
Typical Procedure for the Generation of 1-I and the Synthesis of Epoxides



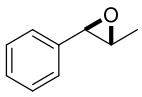
In the anodic chamber were placed Bu_4NI (91.7 mg, 0.248 mmol), Bu_4NBF_4 (102 mg, 0.3 mmol), DMSO (1 mL), and 0.3 M Bu_4NBF_4/CH_2Cl_2 (9 mL). In the cathodic chamber were placed TfOH (60 μL, 0.68 mmol) and 0.3 M Bu_4NBF_4/CH_2Cl_2 (10 mL). The constant current electrolysis (8.0 mA) was carried out at −78 °C with magnetic stirring until 2.1 F mol^{-1} of electricity was consumed. To the anodic chamber was added a solution of (*Z*)-5-decene (**2a**) (27.9 mg, 0.199 mmol) in CH_2Cl_2 (0.5 mL), and to the cathodic chamber 0.5 mL of CH_2Cl_2 was added at −78 °C. The solution was stirred for 30 min at −78 °C, and then was stirred for 30 min at 0 °C. Then NaOMe (5.0 M in MeOH, 0.2 mL) was added to both the anodic and the cathodic chambers, and the resulting mixture was warmed to 25 °C and was stirred for 5 min. The solution in the anodic chamber was filtered through a short column (2 x 4 cm) of silica gel to remove Bu_4NBF_4 by using Et_2O as an eluent. The GC analysis using hexadecane as an internal standard indicated that **(5*R**,6*S**)-5,6-epoxydecane** (**6a**) was obtained in 96% yield (0.191 mmol). TLC R_f 0.83 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.2 Hz, 6 H), 1.37−1.55 (m, 12 H), 2.88−2.94 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ14.0, 22.6, 27.5, 28.3, 57.2; HRMS (APCI) calcd for $C_{10}H_{21}O$ ($M+H^+$): 157.1587, found: 157.1587. Stereochemistry was determined by comparison of the ^{1}H NMR spectrum with that in the literature.[11]


6b

1,2-epoxycyclododecane (6b). Electrochemical oxidation (2.1 F mol^{-1}) of Bu_4NI (92.5 mg, 0.250 mmol), subsequent addition of the solution of cyclododecene (**2b**) (*Z*/*E* = 72:28, 33.3 mg, 0.200 mmol) in CH_2Cl_2 (0.5 mL), and treatment with NaOMe followed by flash chromatography (hexane/EtOAc 50:1) gave the title compound (32.6 mg, 0.179 mmol, 89%, *cis:trans* = 74:26). TLC R_f 0.54 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20−1.61 (m, 20 H), 1.70−1.87 (m, cis 2 H), 2.15−2.23 (m, trans 2 H), 2.71 (m, trans 2 H), 2.90 (td, *J* = 1.6, 10.0 Hz, cis 2 H). The ^{1}H NMR spectrum is in agreement with the literature.[21]

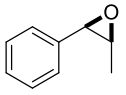

6c

1,2-epoxydodecane (6c). Electrochemical oxidation (2.1 F mol^{-1}) of Bu_4NI (91.5 mg, 0.248 mmol), subsequent addition of the solution of 1-dodecene (**2c**) (31.8 mg, 0.189 mmol) in CH_2Cl_2 (0.5 mL), and treatment with NaOMe gave the title compound(0.162 mmol, 86%, The yield was determined by GC analysis using hexadecane as internal standard. TLC R_f 0.63 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.8 Hz, 3 H), 1.20−1.38 (m, 14 H), 1.40−1.56 (m, 4 H), 2.46 (dd, *J* = 2.8, 4.8 Hz, 1 H), 2.75 (dd, *J* = 3.6, 4.0 Hz, 1 H), 2.88−2.94 (m, 1 H). The ^{1}H NMR spectrum is in agreement with the literature.[22]



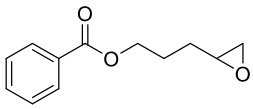
6d

(1*R,2*R**)-1-phenyl-1,2-epoxypropane** (**6d**)**.** Electrochemical oxidation (2.1 F mol^{-1}) of Bu_4NI (148 mg, 0.401 mmol), subsequent addition of the solution of (*E*)-*β*-methylstylene (**(*E*)-2d**) (22.8 mg, 0.193 mmol) in CH_2Cl_2 (0.5 mL), and treatment with NaOMe followed by flash chromatography[23] (hexane) gave the title compound (10.0 mg, 0.074 mmol, 38%). TLC R_f 0.58 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (d, *J* = 5.2 Hz, 3 H), 3.04 (dq, *J* = 2.0, 5.2 Hz, 1 H), 3.58 (d, *J* = 1.6 Hz, 2 H), 7.24−7.39 (m, 5 H); The ^{1}H NMR spectrum is in agreement with the literature.[24]



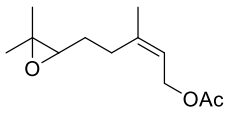
6d'

(1*R,2*S**)-1-phenyl-1,2-epoxypropane** (**6d'**)**.** Electrochemical oxidation (2.1 F mol^{-1}) of Bu_4NI (149 mg, 0.403 mmol), subsequent addition of the solution of (*Z*)-*β*-methylstylene (**(*Z*)-2d**) (23.6mg, 0.200 mmol) in CH_2Cl_2 (0.5 mL), and treatment with NaOMe followed by flash chromatography[23] (hexane) gave the title compound (134 mg, 0.134 mmol, 67%). TLC R_f 0.56 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (d, *J* = 5.6 Hz, 3 H), 3.34 (dq, *J* = 4.4, 5.2 Hz, 1 H), 4.07 (d, *J* = 4.4 Hz, 1 H) 7.26−7.40 (m, 5 H). The ^{1}H NMR spectrum is in agreement with the literature.[24]



6e

4,5-epoxypentenyl benzoate (6e). Electrochemical oxidation (2.1 F mol^{-1}) of Bu_4NI (91.0 mg, 0.246 mmol), subsequent addition of the solution of 4-penteneyl benzoate (**2f**) (39.0 mg, 0.205 mmol) in CH_2Cl_2 (0.5 mL), and treatment with NaOMe followed by flash chromatography[23] (hexane/EtOAc 100:0 to 20:1) gave the title compound (24.0 mg, 0.116 mmol, 57%). TLC R_f 0.29 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62−1.82 (m, 2 H), 1.88−2.04 (m, 2 H), 2.52 (dd, *J* = 2.8, 5.2 Hz, 1 H), 2.78 (dd, *J* = 4.0, 5.2 Hz, 1 H), 2.98−3.02 (m, 1 H), 4.38 (dt, *J* = 2.4, 6.4 Hz, 2 H), 7.44 (t, *J* = 8.0 Hz, 2 H), 7.56 (t, *J* = 7.6 Hz, 1 H), 8.04 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 29.1, 47.0, 51.7, 64.4, 128.3, 129.5, 130.2, 132.9, 166.5; HRMS (ESI) calcd for $C_7H_7O_2$ ($M+H^+$): 207.1016, found: 207.1012. The ^{1}H NMR spectrum is in agreement with the literature.[25]

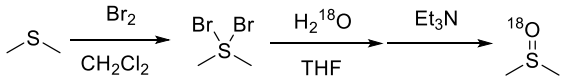


6f

6,7-epoxyneryl acetate (6f). Electrochemical oxidation (2.1 F mol^{-1}) of Bu_4NI (92.8 mg, 0.251 mmol), subsequent addition of the solution of neryl acetate (**2f**) (35.6 mg, 0.182 mmol) in CH_2Cl_2 (0.5 mL), and treatment with NaOMe followed by flash chromatography[23] (hexane/EtOAc 100:0 to 20:1) gave the title compound (18.2 mg, 0.086 mmol, 47%). TLC R_f 0.30 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 3 H), 1.31 (s, 3 H), 1.56−1.71 (m, 2 H), 1.79 (s, 3 H), 2.05 (s, 3 H) 2.23−2.29 (m, 2 H), 2.71 (t, *J* = 6.0 Hz, 1 H), 4.59 (d, *J* = 7.6 Hz, 2 H), 5.41 (t, *J* = 7.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 21.0, 23.4, 24.8, 27.5, 28.8, 58.4, 60.8, 63.7, 119.7, 141.7, 171.0; HRMS (ESI) calcd for $C_{12}H_{20}O_3Na$ ($M+Na^+$): 235.1305, found: 235,1299. The ^{1}H NMR spectrum is in agreement with the literature.[26]

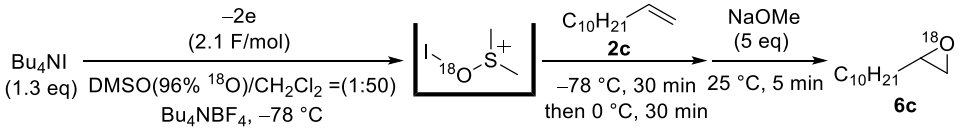
Synthesis of ^{18}O-Labelled Epoxide

Synthesis of ^{18}O-Labelled DMSO[13]



To a round-bottom flask were added dimethylsulfide (2.6 mL, 33 mmol) and CH_2Cl_2 (10 mL). Bromine (1.8 mL, 33 mmol) was added dropwise to the solution at 0 °C over 30 min. The mixture was stirred at 0 °C for 30 min to precipitate a yellow solid material. The solid material was purified by removing the solution phase by syringe and by washing the solid material with dry CH_2Cl_2 under Ar atmosphere. THF (10 mL) was added, and then $H_2{}^{18}O$ (242 mg, 12.1 mmol) was added dropwise at 0 °C over 5 min. After stirring at 0 °C for 1 h, Et_3N (6.4 mL) was added to the mixture. The precipitate of triethylamine hydrobromide was separated by filtration and was washed twice with CH_2Cl_2. The combined yellow filtrate and washings were evaporated under reduced pressure to remove the solvents. The residue was purified by flash chromatography (hexane/EtOAc 1:1 to 0:100 to EtOAc/MeOH 10:1). After distillation using Kugelrohr (20 mmHg, 80 °C), **^{18}O-labelled DMSO** was obtained in 34% yield (332 mg, 4.14 mmol). TLC R_f 0.05 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.62 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.5; HRMS (ESI) calcd for $C_4H_{12}{}^{18}O_2S$ ($2M+H^+$): 161.0436, found: 161.0433.

Synthesis of ^{18}O-Labelled Epoxide 6c



In the anodic chamber were placed Bu_4NI (91.8 mg, 0.248 mmol), DMSO (96% ^{18}O, 0.2 mL), and 0.3 M Bu_4NBF_4/CH_2Cl_2 (10 mL). In the cathodic chamber were placed TfOH (60 μL, 0.68 mmol) and 0.3 M Bu_4NBF_4/CH_2Cl_2 (10 mL). The constant current electrolysis (8.0 mA) was carried out at −78 °C with magnetic stirring until 2.1 F mol^{-1} of electricity was consumed. To the anodic chamber was added a solution of 1-dodecene (**2c**) (32.5 mg, 0.193 mmol) in CH_2Cl_2 (0.5 mL), and to the cathodic chamber was added 0.5 mL of CH_2Cl_2 at −78 °C. The solution was stirred for 30 min at −78 °C, and then was stirred for 30 min at 0 °C. NaOMe (5.0 M in MeOH, 0.2 mL) was added to both the anodic and cathodic chambers, and the resulting mixture was warmed to 25 °C and was stirred for 5 min. The solution in the anodic chamber was filtered through a short column (2 x 4 cm) of silica gel to remove Bu_4NBF_4 by using Et_2O as an eluent. After removal of the solvent under reduced pressure the crude product was purified by flash chromatography[9] (hexane) to obtain **^{18}O-labelled 1,2-epoxydodecane** (**6c**) in 81% yield (29.0 mg, 0.155 mmol). TLC R_f 0.67 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 6 H), 1.22–1.56 (m, 18 H), 2.46 (dd, J = 2.8, 5.2 Hz, 1 H), 2.74 (dd, J = 4.0, 5.2 Hz, 1 H), 2.88–2.93 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 26.0, 29.3, 29.4, 29.54, 29.57, 31.9, 32.5, 47.1, 52.4; HRMS (APCI) calcd for $C_{12}H_{25}{}^{18}O$ ($M+H^+$): 187.1942, found: 187.1940.

References

(1) Olah, G. A.; Laali, K. K.; Wang, Q.; Prakash G. K. S. Onium ions, Wiley, New York, 1998; Chapter 6, pp 246.

(2) Rodriguez, J.; Dulcère, J.-P. *Synthesis* **1993,** 1177.

(3) Chaikovski, V. K.; Kharlova, T. S.; Filimonov, V. D.; Saryucheva, T. A. *Synthesis* **1999,** 748.

(4) (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) Kirste, A.; Elsler, B.; Schnakenburg, G.; Waldvogel, S. R. *J. Am. Chem. Soc.* **2012,** *134,* 3571. (e) Finney, E. E.; Ogawa, K. A.; Boydston, A. J. *J. Am. Chem. Soc.* **2012,** *134,* 12374. (f) Sumi, K.; Saitoh, T.; Natsui, K.; Yamamoto, T.; Atobe, M.; Einaga, Y.; Nishiyama, S. *Angew. Chem., Int. Ed.* **2012,** *51,* 5443. (g) Morofuji, T.; Shimizu, A.; Yoshida, J. *J. Am. Chem. Soc.* **2013,** *135,* 5000. (h) Yamaguchi, Y.; Okada, Y.; Chiba, K. *J. Org. Chem.* **2013,** *78,* 2626.

(5) (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) Yoshida, J.; Suga, S. *Chem. -Eur. J.* **2002,** *8,* 2650. (d) Suzuki, S.; Matsumoto, K.; Kawamura, K.; Suga, S.; Yoshida, J. *Org. Lett.* **2004,** *6,* 3755. (e) Suga, S.; Matsumoto, K.; Ueoka, K.; Yoshida, J. *J. Am. Chem. Soc.* **2006,** *128,* 7710. (f) Matsumoto, K.; Sanada, T.; Shimazaki, H.; Shimada, K.; Hagiwara, S.; Fujie, S.; Ashikari, Y.; Suga, S.; Kashimura, S.; Yoshida, J. *Asian J. Org. Chem.* **2013,** *2,* 325.

(6) (a) Miller, L. L.; Kujawa, E. P.; Campbell, C. B. *J. Am. Chem. Soc.* **1970,** *92,* 2821. (b) Miller, L. L.; Watkins, B. F. *J. Am. Chem. Soc.* **1976,** *98,* 1515. (c) Midorikawa, K.; Suga, S.; Yoshida, J. *Chem. Commun.* **2006,** 3794.

(7) Shono, T.; Matsumura, Y.; Katoh, S.; Ikeda, K.; Kamada, T. *Tetrahedron Lett.* **1989,** *30,* 1649.

(8) Ashikari, Y.; Shimizu, A.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2013,** *135,* 16070.

(9) (a) Kornblum, N.; Powers, J. W.; Anderson, G. J.; Jones, W. J.; Larson, H. O.; Levand, O.; Weaver, W. M. *J. Am. Chem. Soc.* **1957,** *79,* 6562. (b) Mancuso, A. J.; Swern, D. *Synthesis* **1981,** 165. (c) Phan, T. B.; Nolte, C.; Kobayashi, S.; Ofial, A. R.; Mayr, H. *J. Am. Chem. Soc.* **2009,** *131,* 11392. (d) Ashikari, Y.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2011,** *133,* 11840. (e) Ashikari, Y.; Nokami, T.; Yoshida, J. *Org. Biomol. Chem.* **2013,** *11,* 3322.

(10) (a) Schmidt, B. *Pure Appl. Chem.* **2006,** *78,* 469. (b) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006,** *441,* 861. (c) Yoshida, J.; Saito, K.; Nokami, T.; Nagaki, A. *Synlett* **2011,** 1189. (d) Suga, S.; Yamada, D.; Yoshida, J. *Chem. Lett.* **2010,** *39,* 404.

(11) Brimeyer, M.; Mehrota, A.; Quici, S.; Nigam, A.; Regen, S. L. *J. Org. Chem.* **1980,** *45,* 4254.

(12) (a) Gianini, M.; von Zelewsky, A. *Synthesis* **1996,** 702. (b) The similar facial selectivity was observed. Majetich, G.; Shimkus, J.; Li, Y. *Tetrahedron Lett.* **2010,** *51,* 6830.

(13) Fenselau, A. M.; Moffatt, J. G. *J. Am. Chem. Soc.* **1966,** *88,* 1762.

(14) Van Ende, D.; Krief, A. *Tetrahedron Lett.* **1975**, *31*, 2709.

(15) Sumrell, G.; Wyman, B. M.; Howell, R. G.; Harvey, M. C. *Can. J. Chem.* **1964**, *42*, 2710.

(16) Haufe, G.; Muhlstadt, M. *Monatsh. Chem.* **1976**, *107*, 653.

(17) Macharla, A. K.; Nappunni, R. C.; Nama, N. *Tetrahedron Lett.* **2012**, *53*, 1401.

(18) Kuroboshi, M.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1799.

(19) Schmid, G. H.; Gordon, J. W. *J. Org. Chem.* **1983**, *48*, 4010.

(20) Wang, X.; Ye, Y.; Zhang, S.; Feng, J.; Xu, Y.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 16410.

(21) Terent'ev, A. O.; Boyarinova, K. A.; Nikishin, G. I. *Russ. J. Gen. Chem.* **2008**, *78*, 592.

(22) McPake, C. B.; Murray, C. B.; Sandford, G. *Tetrahedron Lett.* **2009**, *50*, 1674.

(23) Flash chromatography was carried out on a silica gel (Fuji Silysia Chemical Ltd., CHROMATOREX FL100DX, spherical, pH = 8.7, 100 μm)

(24) Koya, S.; Nishioka, Y.; Mizoguchi, H.; Uchiba, T.; Katsuki, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 8243.

(25) Wu, Y.; Shen, X.; Yang, Y.; Hu, Q.; Huang, J. *J. Org. Chem.* **2004**, *69*, 3857.

(26) Fillion, E.; Beingessner, R. L. *J. Org. Chem.* **2003**, *68*, 9485.

(27) Cimarelli, C.; Fratoni, D.; Palmieri, G. *Tetrahedron Asymmetry* **2011**, *22*, 603.

Chapter 4

Metal- and Oxidant-Free Alkenyl C−H/Aromatic C−H Cross-Coupling Using Electrogenerated Iodosulfonium Ions

Abstract

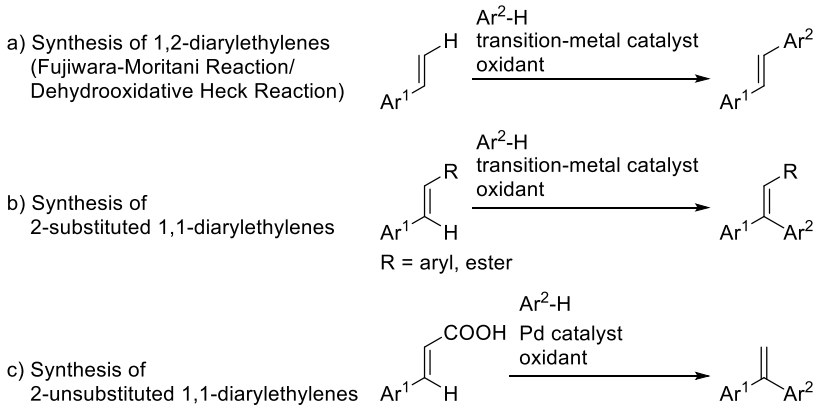
A three-step transformation consisting of (1) addition of electrochemically generated iodosulfonium ions to vinylarenes to give (1-aryl-2-iodoethoxy)sulfonium ions, (2) nucleophilic substitution by subsequently added aromatic compounds to give 1,1-diaryl-2-iodoethane, and (3) elimination of HI with a base to give 1,1-diarylethenes was developed. The transformation serves as a powerful metal- and chemical-oxidant-free method for alkenyl C−H/aromatic C−H cross-coupling.

Introduction

C−H/C−H cross-coupling serves a powerful method for making C−C bonds and they are synthetically useful from viewpoints of atom-[1] and step-economy.[2] In particular, alkenyl C−H/aromatic C−H cross-coupling is useful for the introduction of alkenyl groups to aromatic compounds. Fujiwara-Moritani reaction is an early example of metal-catalyzed alkenyl C−H/aromatic C−H cross-coupling.[3] Later, dehydrogenative Heck reaction was developed.[4] However, in many cases 1,2-diarylethylenes are obtained as major products from vinylarenes (Scheme 1a).

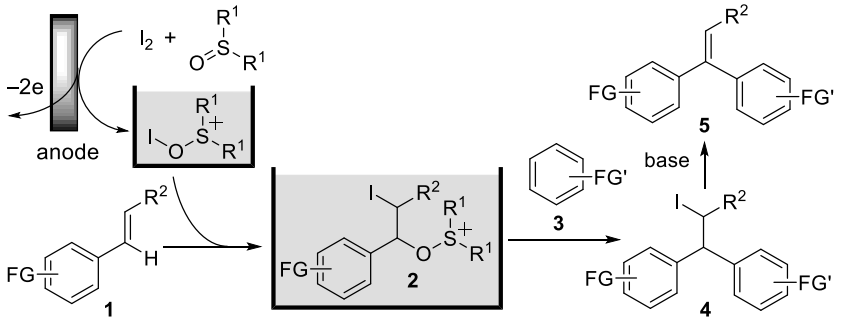
The method for synthesis of 1,1-diarylethylenes has been highly desired because the 1,1-diarylethylene moieties are contained in many biologically active compounds.[5] 1,1-Diarylethylenes having aryl or ester group at 2-position were synthesized by metal-catalyzed alkenyl C−H/aromatic C−H cross-coupling of vinylarenes with aromatic compounds (Scheme 1b).[6] However, the synthesis of 2-unsubstituted 1,1-diarylethylenes is limited to decarboxylative cross-coupling of cinnamic acid derivatives and arenes (Scheme 1c)[7] and cross-coupling of indolizine derivatives and vinylarenes.[8] Therefore, the development of more versatile methods of alkenyl C−H/aromatic C−H cross-coupling to make 1,1-diarylethylenes still remains a challenge.

Scheme 1. Synthesis of Diarylethylenes.



Electrochemical oxidation serves as a powerful method for generating reactive cationic species under mild conditions without metal catalysts.[9] Various electrochemical C−H bond transformations including C−H/C−H cross-coupling have been developed using the reactive cationic species.[10] Chapter 1 described the stabilized cation pool method, in which organic cations are electrochemically generated and accumulated in solutions in the presence of stabilizing agents.[11] In this case electrooxidatively generated benzyl cations are stabilized by sulfilimines. This chapter shows another aspect of the stabilized cation pool method. As described in chapter 3 iodosulfonium ions electrooxidatively generated from I_2 and sulfoxides react with vinylarenes **1** to give β-iodoalkoxysulfonium ions **2** (Scheme 2).[12] If ions **2** reacts as stabilized benzyl cations with aromatic compounds **3**, the resulting 1,1-diaryl-2-iodoethanes **4** can be easily transformed to 1,1-diarylethylene **5** by treatment with a base. Thus, alkenyl C−H/aromatic C−H cross-coupling can be achieved. The concept works, and this chapter describes metal- and oxidant-free alkenyl C−H/aromatic C−H cross-coupling using electrogenerated iodosulfonium ions.

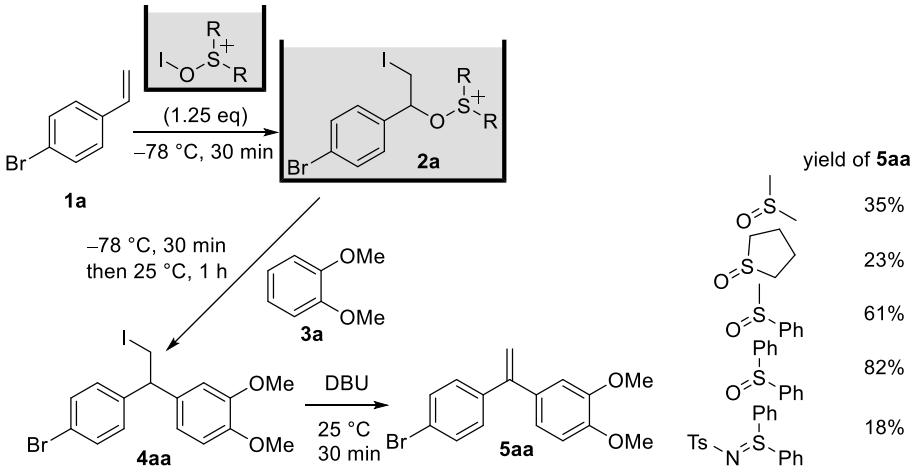
Scheme 2. Alkenyl C−H/Aromatic C−H Cross-Coupling via *β*-Iodoalkoxysulfonium Ions.



Results and Discussion

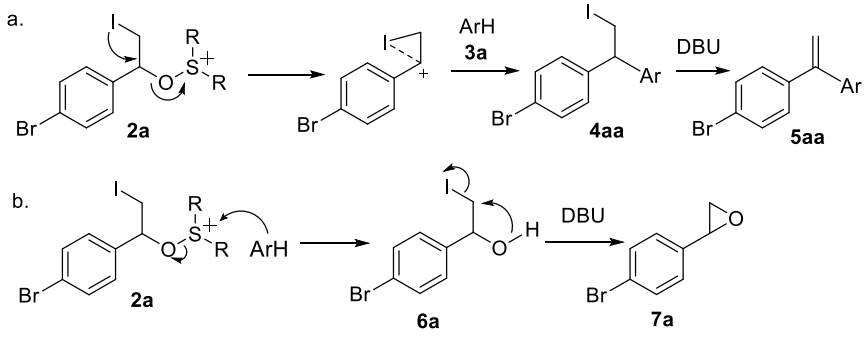
Scheme 3 shows screening of sulfoxides. Iodine was electrochemically oxidized in the presence of various sulfoxides in dichloromethane to generate the corresponding iodosulfonium ions. After the electrolysis was complete, 4-bromostyrene (**1a**) was added to the anodic solution to generate *β*-iodoalkoxysulfonium ion **2a**. The reaction of **2a** with 1,2-dimethoxybenzene (**3a**) gave **4aa** presumably via benzylic cation stabilized by intramolecular participation of iodine, indicating that the solution of **2a** serves as a stabilized cation pool for aromatic compounds. The subsequent reaction with DBU[13] gave 1,1-diarylethylene **5aa** (Scheme 4a). When DMSO was used as sulfoxide, **5aa** was obtained in 35% yield. In this case, the corresponding epoxide **7a** was also obtained in 13% yield probably because **3a** attacked the sulfur atom of **2a** to give **6a**, which underwent cyclization by the action of DBU to give **7a** (Scheme 4b).[14,15] To suppress the epoxide formation, sulfoxides having bulky substituents were examined. The yield of **5aa** decreased to 23% when tetramethylene sulfoxide was used, whereas the yield increased to 61% when methyl phenyl sulfoxide was used. Diphenyl sulfoxide was the more effective to give **5aa** in 82% yield. On the other hand, the use of sulfilimine[11] gave **5aa** in only 18% yield. Therefore, hereafter diphenyl sulfoxide was used.

Scheme 3. Screening of Sulfoxides.



Iodine (0.5 mmol) was electrochemically oxidized in the presence of 2.0 mmol of sulfoxide or sulfilimine in a 0.3 M solution of Bu_4NBF_4 in CH_2Cl_2 at −78 °C. After 3.0 *F* of electricity was applied, **1a** (0.4 mmol) was added. The resulting solution was treated with **2a** (2.0 mmol) and DBU (2.0 mmol). Isolated yields based on the amount of **1a** used are shown.

Scheme 4. A Plausible Mechanism.



β-Iodoalkoxysulfonium ion **2a** derived from **1a** and diphenyl sulfoxide was successfully characterized by mass spectroscopy and ^{1}H and ^{13}C NMR analyses (See experimental section for details). Significant lower chemical shift of the benzylic proton of **2a** compared with that of **6a** is remarkable (Figure 1). Variable-temperature ^{1}H NMR analysis revealed that **2a** is stable at the temperatures lower than −20 °C (Figure S2). Notably, 1,1-diaryl-2-iodoethane **4aa** was isolated in 85% yield when DBU was not added.

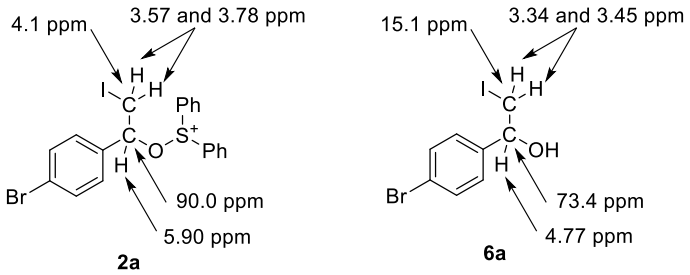
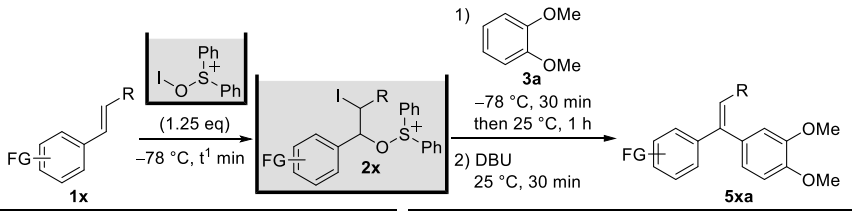


Figure 1. ^{1}H and ^{13}C NMR chemical shifts of **2a** and 1-(4-bromophenyl)-2-iodoethanol.[16]

The present one-pot transformation is applicable to other vinylarenes bearing various functional groups as shown in Table 1. Styrene (**1b**) and styrenes having methyl, ester, and bromo groups on the phenyl ring gave the corresponding 1,1-diarylethyrenes (entries 1–6). Stereoselectivity is interesting. The reaction of (*Z*)-**1g** with **3a** gave (*Z*)-**5ga** as major product and (*E*)-**5ga** as minor product, while that of (*E*)-**1g** with **3a** gave (*E*)-**5ga** as a sole product. The present reaction can be applied to cyclic alkenes. Indene (**1h**), a 5-membered ring alkene, gave the corresponding 1,1-diarylethylene **5ha** via *trans*-**4ha**,[17] while 1,2-dihydronaphthalene (**1i**), a 6-membered ring alkene, gave the alkene **5ia'** instead of the corresponding diarylethylene via *trans*-**4ia**. The elimination of HI from **4ha** seemed to give **5ha'**, because the proton attached to the carbon bearing the dimethoxyphenyl group is *cis* to the iodine. However, rapid isomerization might take place to give **5ha**.[18] In the case of **4ia**, no isomerization took place and **5ia'** was obtained as a sole product (Scheme 5). The reaction of **1j** with two equivalents of iododiphenylsulfonium ion and **3a** gave the double arylated alkene **5ja**.

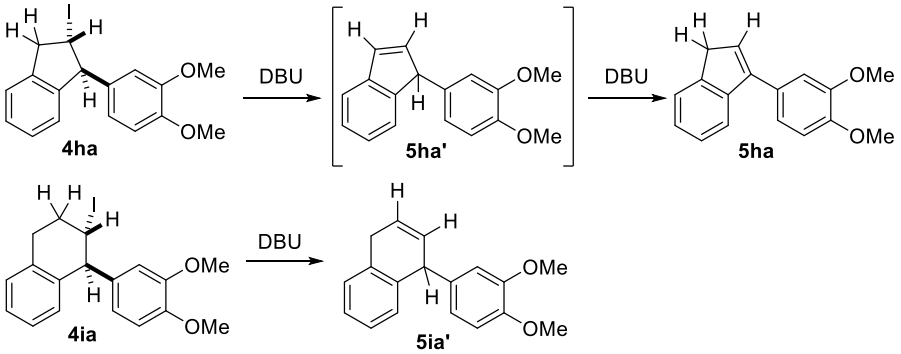
Table 1. Scope of Vinylarene Substrates.



entry	substrate	t^1 (min)	product	yield
1	**1a**	30	**5aa**	82%
2	**1b**	30	**5ba**	74%[a]
3	**1c**	30	**5ca**	64%
4	**1d**	90	**5da**	81%
5	**1e**	30	**5ea**	70%
6	**1f**	30	**5fa**	67%
7	(*Z*)-**1g**	90	**5ga**	70% (*E*/*Z* = 28:72))
8	(*E*)-**1g**	90	**5ga**	77% (*E* isomer only)
9	**1h**	30	**5ha**	51%[b]
10	**1i**	30	**5ia'**	80%[c]
11	**1j**	30	**5ja**	53%[d]

I_2 (0.5 mmol) was electrochemically oxidized in the presence of 2.0 mmol of diphenylsulfoxide in a 0.3 M solution of Bu_4NBF_4 in CH_2Cl_2 at −78 °C. After 3.0 *F* of electricity was applied, **1** (0.4 mmol) was added to the resulting solution, followed by the treatment with **3a** (2.0 mmol) and DBU (2.0 mmol). Isolated yield based on **1** used is shown. a) Yield was determined by GC. b) After the addition of DBU, the mixture was stirred at 35 °C for 3 h. c) 10 equiv of DBU was used, and the mixture was stirred for 68 h. d) **1j** (0.2 mmol) was used.

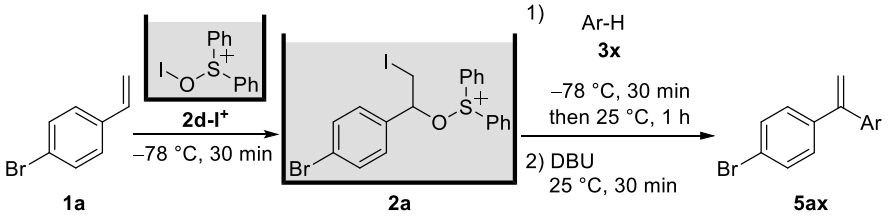
Scheme 5. Proposed Mechanism of the Elimination in the Reaction of Cyclic Alkenes.

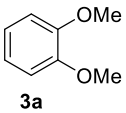
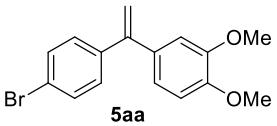
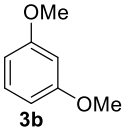
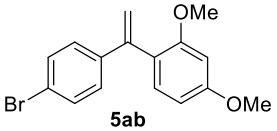
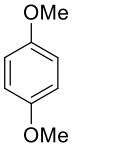
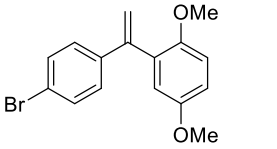
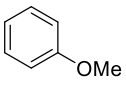
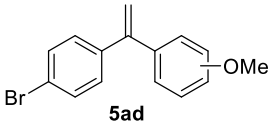
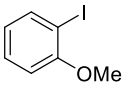
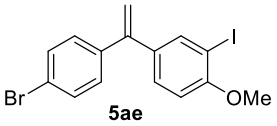


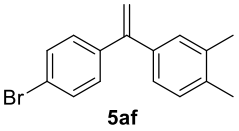
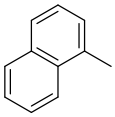
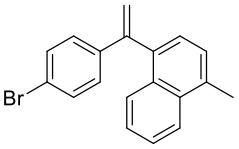
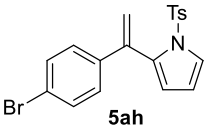
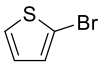
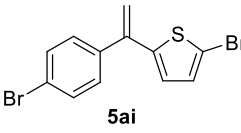
Next, the reactions of *β*-iodoalkoxysulfonium ion **2a** with various aromatic nucleophiles were examined (Table 2). 1,2-Dimethoxybenzene (**3a**) and 1,4-dimethoxybenzene (**3c**) gave **5aa** and **5ac** in good yield, while

1,3-dimethoxybenzene (**3b**) gave **5ab** in poor yield. Anisole (**3d**) gave the 1,1-diarylethylene as a mixture of two isomers, while 2-iodoanisole (**3e**) gave **5ae** as a single isomer. Xylene (**3f**) and 1-methylnaphthalene (**3g**) gave the corresponding 1,1-diarylethylene. Heterocyclic compounds such as *N*-tosyl pyrrole (**3h**) and bromothiophene (**3i**) gave the corresponding 1,1-diarylethylene.

Table 2. Scope of Aromatic Nucleophile.



entry	Ar-H	product	yield
1	 **3a**	 **5aa**	82%
2	 **3b**	 **5ab**	32%
3	 **3c**	 **5ac**	61%
4	 **3d**	 **5ad**	70% *o*:*p* = 11:89
5	 **3e**	 **5ae**	69%

entry	Ar-H	product	yield
6	 **3f**	 **5af**	74%[a]
7	 **3g**	 **5ag**	80%
8	 **3h**	 **5ah**	62%
9	 **3i**	 **5ai**	64%

I_2 (0.5 mmol) was electrochemically oxidized in the presence of 2.0 mmol of diphenylsulfoxide in a 0.3 M solution of Bu_4NBF_4 in CH_2Cl_2 at −78 °C. After 3.0 *F* of electricity was applied, **1a** (0.4 mmol) was added to the resulting solution, followed by the treatment with **3** (2.0 mmol) and DBU (2.0 mmol). Isolated yield based on **1a** used is shown. a) After the addition of **3f** (5 mL), the mixture was stirred at −20 °C for 42 h then at 25 °C for 1 h.

Conclusion

In conclusion, metal-free alkenyl C−H/aromatic C−H cross-coupling using iododiphenylsulfonium ion which can be easily generated from commercially available I_2 and diphenyl sulfoxide using the electrochemical method have been developed. The present one-pot transformation enables the access to various 1,1-diarylethylenes which serve as useful building blocks in organic synthesis.

Experimental Section

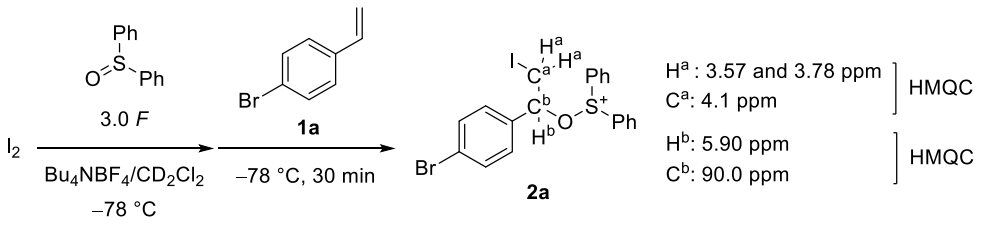
General

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian MERCURY plus-400 (^{1}H 400 MHz, ^{13}C 100 MHz) spectrometer with tetramethylsilane as an internal standard unless otherwise noted. Mass spectra were obtained on a JEOL EXACTIVE (ESI and APCI) mass spectrometer and a JEOL JMS-SX102A mass spectrometer (EI). GC analysis was performed on a SHIMADZU GC-2014 gas chromatograph equipped with a flame ionization detector using a fused silica capillary column (column, CBP1; 0.22 mm x 25 m). Merck precoated silica gel F254 plates (thickness 0.25 mm) were used for thin-layer chromatography (TLC) analysis. Flash chromatography was carried out using Kanto Chem. Co., Silica Gel N (spherical, neutral, 40−100 μm). Preparative gel permeation chromatography (GPC) was performed on a Japan Analytical Industry LC-918. All reactions were carried out under argon atmosphere unless otherwise noted. Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. **1j**[11a] and *S*,*S*-Dimethyl-*N*-(4-methylphenylsulfonyl)sulfilimine[19] were synthesized according to the reported literature.

The anodic oxidation was carried out using an H-type divided cell (4G glass filter) equipped with an anode made of carbon strings (Nippon Carbon GF-20-P21E, ca. 160 mg for 0.20 mmol scale, dried at 300 °C/1 mmHg for 3 h before use) and a platinum plate cathode (10 mm x 10 mm). Dichloromethane was washed with water, distilled from P_2O_5, redistilled from dried K_2CO_3 to remove a trace amount of acid, and stored over molecular sieves 4A.

Generation and Observation of *β*-Iodoalkoxysulfonium Ion

Observation of 2a by NMR Spectroscopy



In the anodic chamber were placed iodine (32.4 mg, 0.128 mmol), Bu_4NBF_4 (490 mg), diphenylsulfoxide (204 mg, 1.01 mmol), and CD_2Cl_2 (6.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (40 μL), Bu_4NBF_4 (500 mg), and CD_2Cl_2 (6.0 mL). The constant current electrolysis (4.0 mA) was carried out at −78 °C with magnetic stirring until 3.0 *F* of electricity was consumed. To the anodic chamber was added a solution of 4-bromostyrene (**1a**) (37.3 mg, 0.204 mmol) in CD_2Cl_2 (0.5 mL), and to the cathodic chamber 0.5 mL of CD_2Cl_2 was added at −78 °C. The solution was stirred for 30 min at −78 °C. The reaction mixture of the anodic chamber (0.6 mL) was transferred to a 5 mm ϕ NMR tube with septum cap under argon atmosphere at −78 °C. Chemical shifts are reported using methylene signals of CD_2Cl_2 at δ 5.32 as an internal standard. Selected signals for **2a** at −78 °C: ^{1}H NMR (500 MHz, CD_2Cl_2) δ 3.57 (dd, J = 5.2, 11.2 Hz, 1H), 3.78 (dd, J = 8.9, 11.4 Hz, 1H), 5.90 (dd, J = 5.2, 8.8 Hz, 1H); ^{13}C NMR (500 MHz, CD_2Cl_2) δ 4.1, 90.0. HMQC was observed as shown above.

^{1}H NMR spectra of the reaction mixture were also measured at various temperatures as shown in Figure S2. **2a** seemed to react with F^- derived from BF_4^- to give 1-(4-bromophenyl)-1-fluoro-2-iodoethane **(S1)** at the temperatures higher than 0 °C.[20] Selected signals for **S1** at 25 °C: ^{1}H NMR (500 MHz, CD_2Cl_2) δ 3.47−3.54 (m, 2H), 5.51 (ddd, *J* = 6.0, 6.0, 45.8 Hz, 1H). Although isolation of **S1** was failed, fluorinated styrene **S2** was obtained as shown below.

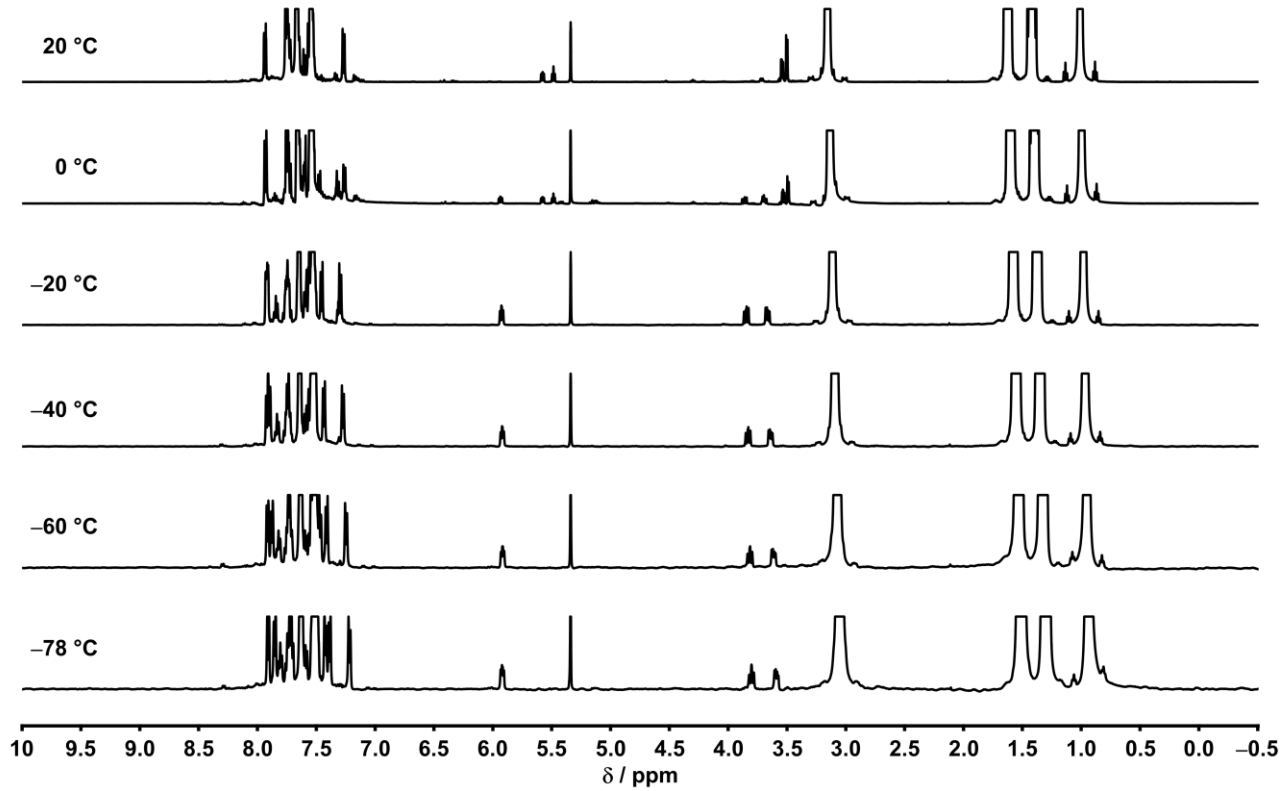
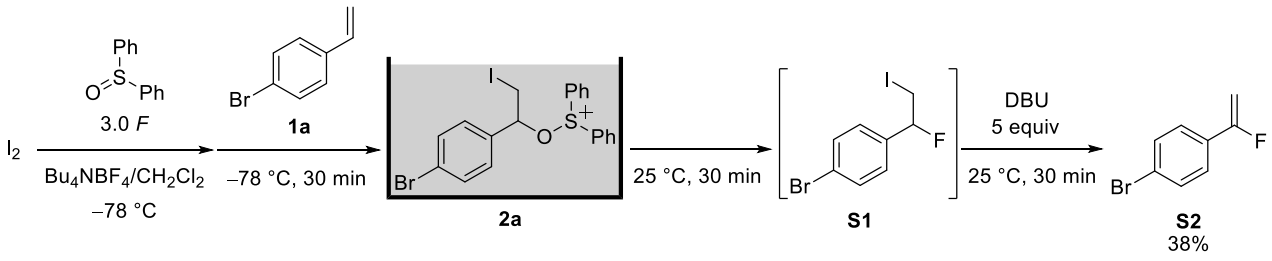


Figure S1. ^{1}H-NMR spectra of *β*-iodoalkoxysulfonium ion **2a** at various temperatures.

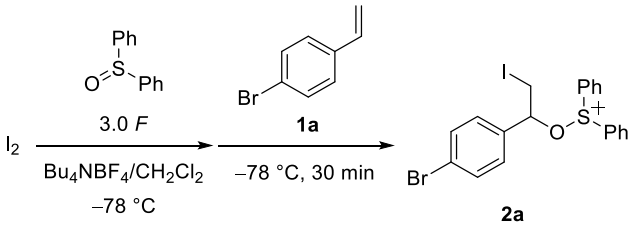
Decomposition of 2a



In the anodic chamber were placed iodine (61.9 mg, 0.244 mmol), diphenylsulfoxide (410 mg, 1.01 mmol), and 0.3 M Bu_4NBF_4/CH_2Cl_2 (10.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (80 μL), 0.3 M Bu_4NBF_4/CH_2Cl_2 (10.0 mL). The constant current electrolysis (8.0 mA) was carried out at −78 °C with magnetic stirring until 3.0 *F* of electricity was consumed. To the anodic chamber was added a solution of 4-bromostyrene (**1a**) (72.4 mg, 0.396 mmol) in CH_2Cl_2 (0.5 mL), and to the cathodic chamber 0.5 mL of CH_2Cl_2 was added at −78 °C. The solution was stirred for 30 min at −78 °C, and then was stirred for 1 h at 25 °C. Then

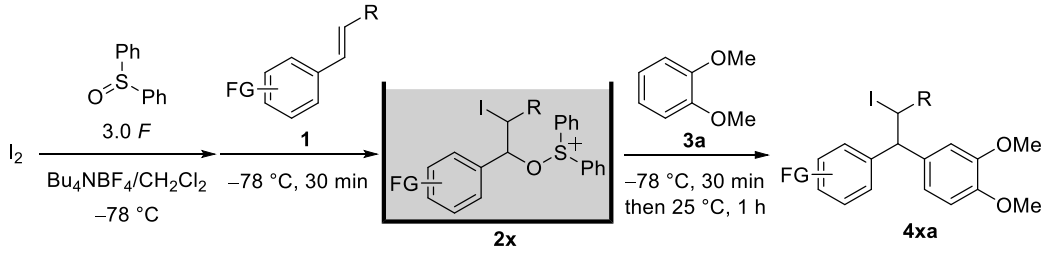
DBU (300 μL) was added to both the anodic and cathodic chambers, and the resulting mixture was stirred for additional 30 min. The solution in the anodic chambers was collected and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (hexane) and GPC to obtain 1-(4-bromophenyl)-1-fluoroethylene (**S2**) in 38% yield (30.4 mg 0.151 mmol). TLC R_f 0.74 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.88 (dd, J = 3.5, 17.6 Hz, 1H), 5.03 (dd, J = 3.5, 49.2 Hz, 1H), 7.41 (d, J = 8.3 Hz, 2H), 7.50 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 90.2 (d, $J_{C–F}$ = 21.8 Hz), 123.5, 126.1 (d, $J_{C–F}$ = 6.7 Hz), 130.9 (d, $J_{C–F}$ = 30.2 Hz), 131.6 (d, $J_{C–F}$ = 2.0 Hz), 162.0 (d, $J_{C–F}$ = 248.3 Hz); HRMS (ACPI) calcd for C_8H_6BrF ($M^{+\cdot}$): 199.9631, found: 199.9635.

Observation of 2a by Mass Spectroscopy



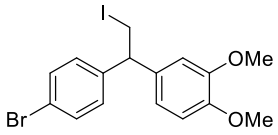
In the anodic chamber were placed iodine (267 mg, 1.25 mmol), diphenylsulfoxide (2.07 g, 10.2 mmol), and 0.3 M Bu_4NBF_4/CH_2Cl_2 (10.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (400 μL), 0.3 M Bu_4NBF_4/CH_2Cl_2 (10.0 mL). The constant current electrolysis (8.0 mA) was carried out at −78 °C with magnetic stirring until 3.0 F of electricity was consumed. To the anodic chamber was added a solution of 4-bromostyrene (**1a**) (378 mg, 2.06 mmol) in CH_2Cl_2 (0.5 mL), and to the cathodic chamber 0.5 mL of CH_2Cl_2 was added at −78 °C. The solution was stirred for 30 min at −78 °C. The reaction mixture was analyzed by CSI-MS at −10 °C. HRMS (CSI) calcd for $C_{20}H_{17}BrIOS$ (M^+): 510.9223, found: 510.9230.

Synthesis of 1,1-Diaryl-2-iodoethanes



In the anodic chamber were placed iodine (63.4 mg, 0.25 mmol), diphenylsulfoxide (404 mg, 1.00 mmol), and 0.3 M Bu_4NBF_4/CH_2Cl_2 (10.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (80 μL), 0.3 M Bu_4NBF_4/CH_2Cl_2 (10.0 mL). The constant current electrolysis (8.0 mA) was carried out at −78 °C with magnetic stirring until 3.0 F of electricity was consumed. To the anodic chamber was added a solution of styrene substrates **1** (0.40 mmol) in CH_2Cl_2 (0.5 mL), and to the cathodic chamber 0.5 mL of CH_2Cl_2 was added at −78 °C. After the solution was stirred for 30 min at −78 °C, to the anodic chamber was added a solution of 1,2-dimethoxybenzene (**3a**) (254 μL, 2.00 mmol) in CH_2Cl_2 (0.5 mL), and to the cathodic chamber 0.5 mL of CH_2Cl_2 was added at −78 °C.

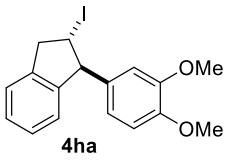
The solution was stirred for 30 min at −78 °C, and then was stirred for 1 h at 25 °C. The solution in the anodic chambers was collected and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography and GPC to obtain the product **4xa**.



4aa

1-(4-bromophenyl)-1-(3,4-dimethoxyphenyl)-2-iodoethane (**4aa**)

Electrochemical oxidation (3.0 *F*) of iodine (64.2 mg, 0.253 mmol), subsequent addition of the solution of 4-bromostyrene (**1a**) (75.0 mg, 0.410 mmol) in CH_2Cl_2 (0.5 mL), the solution of 1,2-dimethoxybenzene (**3a**) (260 μL, 2.05 mmol) in CH_2Cl_2 (0.5 mL), followed by flash chromatography (hexane/EtOAc 100:0, then 20:1) and GPC gave the title compound (149 mg, 0.348 mmol, 85%). TLC R_f 0.26 (hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (dd, *J* = 2.2, 8.3 Hz, 1H), 3.84 (s, 3H), 3.86 (s, 3H), 4.24 (t, *J* = 7.9 Hz, 1H), 6.67 (d, *J* = 2.2 Hz, 1H), 6.75 (dd, *J* = 6.1, 8.3 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 7.44 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.0, 53.0, 55.76, 55.81, 111.0, 111.1, 119.3, 120.7, 129.3, 131.6, 134.4, 141.4, 148.0, 148.9; HRMS (ACPI) calcd for $C_{16}H_{16}BrIO_2$ (M^+): 445.9373, found: 445.9364.

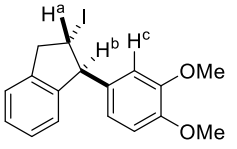


4ha

1-(3,4-dimethoxyphenyl)-2-iodo-1,2-dihydroindene (4ha)

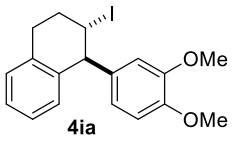
Electrochemical oxidation (3.0 *F*) of iodine (63.6 mg, 0.251 mmol), subsequent addition of the solution of indene (**1h**) (45.4 mg, 0.390 mmol) in CH_2Cl_2 (0.5 mL), the solution of 1,2-dimethoxybenzene (**3a**) (250 μL, 1.97 mmol) in CH_2Cl_2 (0.5 mL), followed by flash chromatography (hexane/EtOAc 100:0, then 20:1) and GPC gave the title compound (90.9 mg, 0.239 mmol, 61%). TLC R_f 0.37 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.49 (dd, *J* = 9.2, 15.8 Hz, 1H), 3.60 (dd, *J* = 7.0, 16.2 Hz, 1H), 3.83 (s, 3H), 3.88 (s, 3H), 4.28 (dt, *J* = 7.0, 8.8 Hz, 1H), 4.53 (d, *J* = 8.8 Hz, 1H), 6.70 (d, *J* = 2.2 Hz, 1H), 6.76 (dd, *J* = 1.8, 7.9 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 6.95 (d, *J* = 7.5 Hz, 1H), 7.14−7.28 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.8, 44.7, 55.8, 55.9, 62.7, 111.1, 111.3, 120.8, 123.6, 124.6, 127.19, 127.24 133.4, 142.4, 144.4, 148.2, 149.1; HRMS (ACPI) calcd for $C_{17}H_{17}IO_2$ ($M^{+\cdot}$): 380.0268, found: 380.0253.

NOESY analysis



H^a: 4.28 ppm
H^b: 4.53 ppm — The crosspeak was not observed.
H^c: 6.70 ppm — The crosspeak was observed.

The absence of the crosspeak between H^a and H^b indicates trans addition of iodine and **3a**.

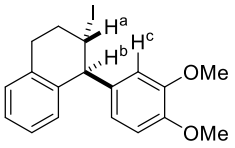


4ia

1-(3,4-dimethoxyphenyl)-2-iodo-1,2,3,4-tetrahydronapthalene (4i)

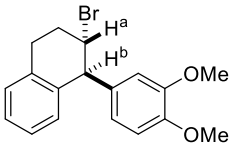
Electrochemical oxidation (3.0 *F*) of iodine (63.6 mg, 0.251 mmol), subsequent addition of the solution of 1,2-dihydronaphthalene (**1i**) (49.5 mg, 0.380 mmol) in CH_2Cl_2 (0.5 mL), the solution of 1,2-dimethoxybenzene (**3a**) (250 μL, 1.97 mmol) in CH_2Cl_2 (0.5 mL), followed by flash chromatography (hexane/EtOAc 100:0, then 20:1) and GPC gave the title compound (95.1 mg, 0.241 mmol, 63%). TLC R_f 0.36 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14−2.31 (m, 2H), 2.90−3.10 (m, 2H), 3.81 (s, 3H), 3.84 (s, 3H), 4.52 (d, *J* = 6.1 Hz, 1H), 4.67 (ddd, *J* = 4.7, 6.2, 7.5 Hz, 1H), 6.53 (dd, *J* = 1.8, 8.4 Hz, 1H), 6.60 (d, *J* = 2.2 Hz, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 6.85 (d, *J* = 7.9 Hz, 1H), 7.04−7.10 (m, 1H), 7.14−7.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.2, 31.1, 36.2, 55.5, 55.7, 55.8, 110.7, 111.9, 121.3, 126.1, 126.5, 128.6, 130.5, 134.9, 136.2, 137.8, 147.7, 148.7; HRMS (ACPI) calcd for $C_{18}H_{19}IO_2$ ($M^{+\cdot}$): 394.0424, found: 394.0411.

NOESY analysis



H^a: 4.67 ppm
H^b: 4.52 ppm — The crosspeak was not observed.
H^c: 6.60 ppm — The crosspeak was observed.

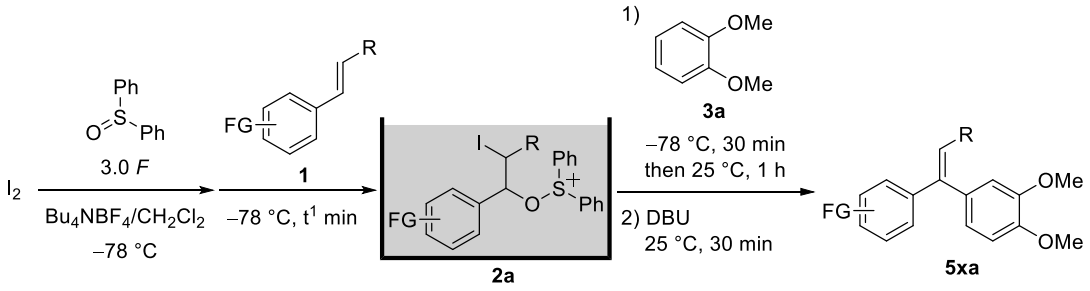
The absence of the crosspeak between H^a and H^b indicates trans addition of iodine and **3a**. In this case, the coupling constant between H^a and H^b (*J* = 6.1 Hz) is consistent with that of *trans*-1-(3,4-dimethoxyphenyl)-2-bromo-1,2,3,4-tetrahydronapthalene (*J* = 5.69 Hz) prepared by $Sm(OTf)_3$ promoted addition of Br (NBS) and 1,2-dimethoxybenzene to 1,2-dihydronaphthane.[21]



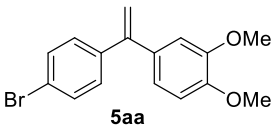
H^a: 4.64–4.50 ppm (m)
H^b: 4.44 ppm (d, *J* = 5.69 Hz)

Reaction of 2a with 1,2-Dimethoxybenzene

Typical procedure for the generation of *β*-iodoalkoxysulfonium ions and their reaction with 1,2-dimethoxybenzene

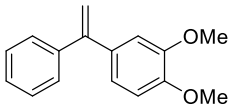


In the anodic chamber were placed iodine (63.4 mg, 0.25 mmol), diphenylsulfoxide (404 mg, 1.00 mmol), and 0.3 M Bu_4NBF_4/CH_2Cl_2 (10.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (80 μL), 0.3 M Bu_4NBF_4/CH_2Cl_2 (10.0 mL). The constant current electrolysis (8.0 mA) was carried out at −78 °C with magnetic stirring until 3.0 *F* of electricity was consumed. To the anodic chamber was added a solution of styrene substrates **1** (0.40 mmol) in CH_2Cl_2 (0.5 mL), and to the cathodic chamber 0.5 mL of CH_2Cl_2 was added at −78 °C. After the solution was stirred for 30 min at −78 °C, to the anodic chamber was added a solution of 1,2-dimethoxybenzene (**3a**) (254 μL, 2.00 mmol) in CH_2Cl_2 (0.5 mL), and to the cathodic chamber 0.5 mL of CH_2Cl_2 was added at −78 °C. The solution was stirred for 30 min at −78 °C, and then was stirred for 1 h at 25 °C. Then DBU (300 μL) was added to both the anodic and cathodic chambers, and the resulting mixture was stirred for additional 30 min. The solution in the anodic chambers was collected and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography and GPC to obtain the coupling product **5xa**.



1-(4-bromophenyl)-1-(3,4-dimethoxyphenyl)ethylene (5aa).

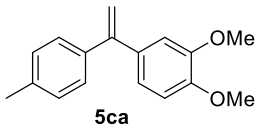
Electrochemical oxidation (3.0 *F*) of iodine (63.2 mg, 0.249 mmol), subsequent addition of the solution of 4-bromostyrene (**1a**) (70.6 mg, 0.386 mmol) in CH_2Cl_2 (0.5 mL), the solution of 1,2-dimethoxybenzene (**3a**) (260 μL, 2.05 mmol) in CH_2Cl_2 (0.5 mL), and DBU (300 μL) followed by flash chromatography (hexane/EtOAc 100:0, then 10:1) and GPC gave the title compound (101 mg, 0.316 mmol, 82%). TLC R_f 0.32 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H), 3.90 (s, 3H), 5.37 (d, *J* = 0.9 Hz, 1H), 5.41 (d, *J* = 0.9 Hz, 1H), 6.81−6.87 (m, 3H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.88, 55.90, 110.7, 111.2, 113.6, 129.9, 131.2, 133.7, 140.6, 148.6, 148.7, 149.0; HRMS (ACPI) calcd for $C_{16}H_{16}BrO_2$ ($M+H^+$): 319.0328, found: 319.0321.



5ba

1-(3,4-dimethoxyphenyl)-1-phenylethylene (5ba).

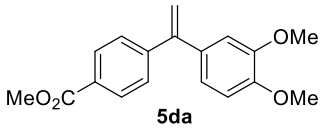
Electrochemical oxidation (3.0 *F*) of iodine (62.9 mg, 0.248 mmol), subsequent addition of the solution of styrene (**1b**) (40.6 mg, 0.388 mmol) in CH_2Cl_2 (0.5 mL), the solution of 1,2-dimethoxybenzene (**3a**) (260 μL, 2.05 mmol) in CH_2Cl_2 (0.5 mL), and DBU (300 μL) gave the title compound (37.4 mg, 95%). The yield was determined by GC analysis using hexadecane as internal standard. TLC R_f 0.44 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 3.88 (s, 3H), 5.36 (d, *J* = 0.9 Hz, 1H), 5.40 (d, *J* = 1.3 Hz, 1H), 6.67 (d, *J* = 8.8 Hz, 1H), 6.80−6.90 (m, 2H), 7.29−7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.76, 55.80, 110.6, 111.3, 113.1, 120.8, 127.6, 128.0, 128.2, 134.2, 141.5, 148.4, 148.7, 149.6; HRMS (ACPI) calcd for $C_{16}H_{17}O_2$ ($M+H^+$): 241.1223, found: 241.1213.



5ca

1-(3,4-dimethoxyphenyl)-1-(4-methylphenyl)ethylene (5ca).

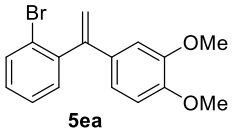
Electrochemical oxidation (3.0 *F*) of iodine (54.2 mg, 0.214 mmol), subsequent addition of the solution of 4-methylstyrene (**1c**) (47.7 mg, 0.403 mmol) in CH_2Cl_2 (0.5 mL), the solution of 1,2-dimethoxybenzene (**3a**) (260 μL, 2.05 mmol) in CH_2Cl_2 (0.5 mL), and DBU (300 μL) followed by flash chromatography (hexane/EtOAc 20:1) and GPC gave the title compound (65.0 mg, 0.256 mmol, 64%). TLC R_f 0.35 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 3.84 (s, 3H), 3.90 (s, 3H), 5.36 (s, 2H), 6.83 (d, *J* = 8.3 Hz, 1H), 6.87−6.91 (m, 2H), 7.14 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 55.78, 55.81, 110.6. 111.4, 112.4, 120.8, 128.1, 128.7, 134.4, 137.4, 138.6, 148.4, 148.7, 149.5; HRMS (ACPI) calcd for $C_{17}H_{19}O_2$ ($M+H^+$): 255.1380, found: 255.1370.



5da

1-(3,4-dimethoxyphenyl)-1-(4-methoxycarbonylphenyl)ethylene (5da).

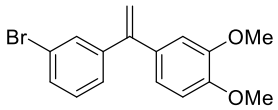
Electrochemical oxidation (3.0 *F*) of iodine (62.5 mg, 0.246 mmol), subsequent addition of the solution of 4-methoxycarbonylstyrene (**1d**) (64.1 mg, 0.395 mmol) in CH_2Cl_2 (0.5 mL), the solution of 1,2-dimethoxybenzene (**3a**) (260 μL, 2.05 mmol) in CH_2Cl_2 (0.5 mL), and DBU (300 μL) followed by flash chromatography (hexane/EtOAc 100:0, then 20:1, then 10:1) and GPC gave the title compound (95.8 mg, 0.321 mmol, 81%). TLC R_f 0.16 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 5.45 (d, *J* = 0.9 Hz, 1H), 5.40 (d, *J* = 0.9 Hz, 1H), 6.82−6.88 (m, 3H), 7.42 (d, *J* = 8.4 Hz, 2H), 8.01 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.9, 55.70, 55.75, 110.6, 111.1, 114.6, 120.7, 128.1, 129.2, 129.3, 133.4, 146.1, 148.5, 148.8, 148.9, 166.7; HRMS (ACPI) calcd for $C_{18}H_{19}O_4$ ($M+H^+$): 299.1278, found: 299.1267.



5ea

1-(2-bromophenyl)-1-(3,4-dimethoxyphenyl)ethylene (5ea).

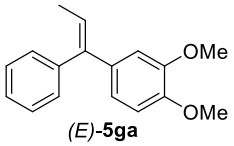
Electrochemical oxidation (3.0 *F*) of iodine (63.9 mg, 0.252 mmol), subsequent addition of the solution of 2-bromostyrene (**1e**) (73.9 mg, 0.404 mmol) in CH_2Cl_2 (0.5 mL), the solution of 1,2-dimethoxybenzene (**3a**) (260 μL, 2.05 mmol) in CH_2Cl_2 (0.5 mL), and DBU (300 μL) followed by flash chromatography (hexane/EtOAc 20:1) and GPC gave the title compound (86.0 mg, 0.269 mmol, 67%). TLC R_f 0.26 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 3.87 (s, 3H), 5.17 (d, *J* = 0.9 Hz, 1H), 5.75 (d, *J* = 0.9 Hz, 1H), 6.69 (dd, *J* = 1.7, 8.4 Hz, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 6.90 (d, *J* = 0.9 Hz, 1H), 7.20 (ddd, *J* = 2.2, 7.0, 8.1 Hz, 1H), 7.29−7.37 (m, 2H), 7.59 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.74, 55.75, 109.4, 110.6, 114.2, 119.5, 123.2, 127.2, 128.8, 131.4, 132.4, 132.8, 142.7, 148.4, 148.7, 148.8; HRMS (ACPI) calcd for $C_{16}H_{16}BrO_2$ ($M+H^+$): 319.0328, found: 319.0320.



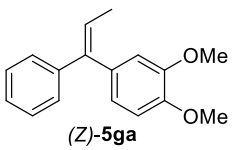
5fa

1-(3-bromophenyl)-1-(3,4-dimethoxyphenyl)ethylene (5fa).

Electrochemical oxidation (3.0 *F*) of iodine (63.8 mg, 0.252 mmol), subsequent addition of the solution of 3-bromostyrene (**1f**) (73.3 mg, 0.400 mmol) in CH_2Cl_2 (0.5 mL), the solution of 1,2-dimethoxybenzene (**3a**) (260 μL, 2.05 mmol) in CH_2Cl_2 (0.5 mL), and DBU (300 μL) followed by flash chromatography (hexane/EtOAc 20:1) and GPC gave the title compound (90.0 mg, 0.282 mmol, 70%). TLC R_f 0.26 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 3.90 (s, 3H), 5.38 (d, *J* = 0.9 Hz, 1H), 5.43 (d, *J* = 1.3 Hz, 1H), 6.83−6.86 (m, 3H), 7.20 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.25−7.28 (m, 1H), 7.43−7.47 (m, 1H), 7.51 (dd, *J* = 2.2, 2.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.8, 110.8, 111.2, 114.1, 120.8, 122.3, 126.9, 129.6, 130.6, 131.2, 133.5, 143.8, 148.4, 148.6, 149.0; HRMS (ACPI) calcd for $C_{16}H_{16}BrO_2$ ($M+H^+$): 319.0328, found: 319.0321.



(E)-**5ga**



(Z)-**5ga**

(*E*)-1-(4-bromophenyl)-1-(3,4-dimethoxyphenyl)-1-propene ((*E*)-5ga) and (*Z*)-1-(4-bromophenyl)-1-(3,4-dimethoxyphenyl)-1-propene ((*Z*)-5ga).

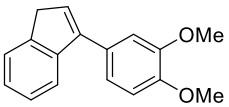
Electrochemical oxidation (3.0 *F*) of iodine (62.5 mg, 0.246 mmol), subsequent addition of the solution of (*Z*)-*β*-methylstyrene ((*Z*)-**1g**) (45.0 mg, 0.380 mmol) in CH_2Cl_2 (0.5 mL), the solution of 1,2-dimethoxybenzene (**3a**) (254 μL, 2.00 mmol) in CH_2Cl_2 (0.5 mL), and DBU (300 μL) followed by flash chromatography (hexane/EtOAc 100:0, then 20:1) and GPC gave the title compound (67.3 mg, 0.265 mmol, 70%, *E*/*Z* = 28:72).

Electrochemical oxidation (3.0 *F*) of iodine (65.9 mg, 0.260 mmol), subsequent addition of the solution of (*E*)-*β*-methylstyrene ((*E*)-**1g**) (46.3 mg, 0.392 mmol) in CH_2Cl_2 (0.5 mL), the solution of 1,2-dimethoxybenzene (**3a**) (260 μL, 2.05 mmol)

in CH_2Cl_2 (0.5 mL), and DBU (300 μL) followed by flash chromatography (hexane/EtOAc 100:0, then 10:1) and GPC gave the title compound (76.9 mg, 0.302 mmol, 77%, *E* isomer only).

(*E*)-5ga TLC R_f 0.42 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75 (d, *J* = 7.0 Hz, 3H), 3.81 (s, 3H), 3.86 (s, 3H), 6.10 (q, *J* = 7.0 Hz, 1H), 6.69 (dd, *J* = 2.2, 8.4 Hz, 1H), 6.75 (d, *J* = 8.3 Hz, 1H), 6.80 (d, *J* = 2.2 Hz, 1H), 7.17−7.20 (m, 2H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 55.67, 55.75, 110.3, 110.6, 119.8, 122.6, 126.7, 128.0, 129.9, 136.0, 140.0, 142.0, 148.0, 148.4; HRMS (ACPI) calcd for $C_{17}H_{19}O_2$ ($M+H^+$): 255.1380, found: 255.1372.

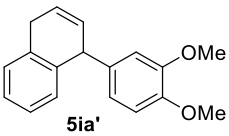
(*Z*)-5ga TLC R_f 0.42 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.78 (d, *J* = 7.0 Hz, 3H), 3.81 (s, 3H), 3.90 (s, 3H), 6.14 (q, *J* = 7.0 Hz, 1H), 6.68 (d, *J* = 1.7 Hz, 1H), 6.75 (dd, *J* = 1.7, 7.9 Hz, 1H), 6.88 (d, *J* = 7.9 Hz, 1H), 7.17−7.31 (m, 5H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.7, 55.78, 55.81, 110.7, 113.1, 122.4, 123.8, 126.7, 127.1, 128.0, 132.5, 142.1, 142.9, 147.8, 148.6; HRMS (ACPI) calcd for $C_{17}H_{19}O_2$ ($M+H^+$): 255.1380, found: 255.1372.



5ha

3-(3,4-dimethoxyphenyl)indene (5ha).

Electrochemical oxidation (3.0 *F*) of iodine (61.7 mg, 0.243 mmol), subsequent addition of the solution of indene (**1h**) (46.2 mg, 0.397 mmol) in CH_2Cl_2 (0.5 mL), the solution of 1,2-dimethoxybenzene (**3a**) (260 μL, 2.05 mmol) in CH_2Cl_2 (0.5 mL), and DBU (300 μL) followed by flash chromatography (hexane/EtOAc 100:0, then 10:1) and GPC gave the title compound (51.3 mg, 0.203 mmol, 51%). TLC R_f 0.42 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.50 (d, *J* = 2.2 Hz, 2H), 3.93 (s, 6H), 6.53 (t, *J* = 2.2 Hz, 1H), 6.95 (d, *J* = 8.3 Hz, 1H), 7.12 (d, *J* = 2.2 Hz, 1H), 7.17 (dd, *J* = 1.7, 7.9 Hz, 1H), 7.25 (t, *J* = 7.4 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.53 (d, *J* = 7.0 Hz, 1H), 7.59 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.0, 55.91, 55.93, 111.0, 111.3, 120.0, 120.2, 124.1, 124.8, 126.1, 129.0, 130.0, 144.0, 144.78, 144.82, 148.6, 148.9; HRMS (ACPI) calcd for $C_{17}H_{17}O_2$ ($M+H^+$): 253.1223, found: 253.1215.

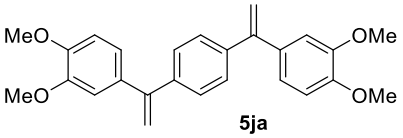


5ia'

1,4-dihydro-1-phenylnaphthalene (5ia').

Electrochemical oxidation (3.0 *F*) of iodine (64.4 mg, 0.254 mmol), subsequent addition of the solution of 1,2-dihydronaphthalene (**1i**) (51.6 mg, 0.396 mmol) in CH_2Cl_2 (0.5 mL), the solution of 1,2-dimethoxybenzene (**3a**) (260 μL, 2.05 mmol) in CH_2Cl_2 (0.5 mL), and DBU (600 μL) followed by flash chromatography (hexane/EtOAc 100:0, then 20:1) and GPC gave the title compound (85.0 mg,

0.319 mmol, 80%). TLC R_f 0.44 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.45 (d, *J* = 21.5 Hz, 1H), 3.56 (d, *J* = 22.0 Hz, 1H), 3.80 (s, 3H), 3.83 (s, 3H), 4.55 (d, *J* = 4.8 Hz, 1H), 5.91−5.96 (m, 1H), 5.98−6.04 (m, 1H), 6.67 (d, *J* = 2.2 Hz, 1H), 6.72 (dd, *J* = 1.8, 8.4 Hz, 1H), 6.78 (d, *J* = 7.9 Hz, 1H), 7.01 (d, *J* = 7.5 Hz, 1H), 7.08−7.19 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.8, 45.4, 55.75, 55.82, 111.1, 111.5, 120.3, 123.6, 126.0, 126.1, 128.2, 129.2, 129.7, 133.4, 137.7, 138.8, 147.5, 149.0; HRMS (ACPI) calcd for $C_{18}H_{19}O_2$ ($M+H^+$): 267.1380, found: 267.1374.



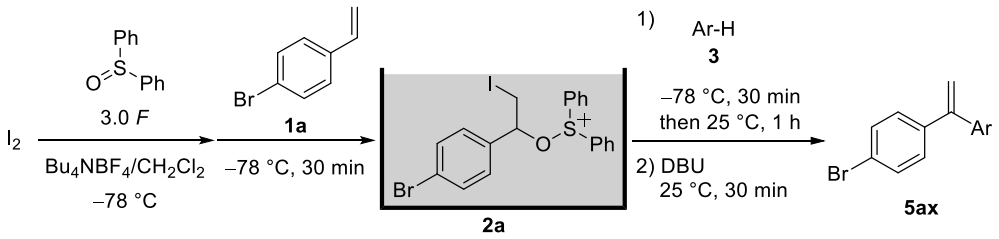
5ja

1,4-bis-[1-(3,4-dimethoxyphenyl)ethenyl]benzene (5ja).

Electrochemical oxidation (3.0 *F*) of iodine (64.2 mg, 0.253 mmol), subsequent addition of the solution of 1,4-diethenylstyrene (**1j**) (26.4 mg, 0.203 mmol) in CH_2Cl_2 (0.5 mL), the solution of 1,2-dimethoxybenzene (**3a**) (260 μL, 2.05 mmol) in CH_2Cl_2 (0.5 mL), and DBU (300 μL) followed by flash chromatography (hexane/EtOAc 5:1) and GPC gave the title compound (43 mg, 0.107 mmol, 53%). TLC R_f 0.10 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 6H), 3.91 (s, 6H), 5.41 (d, *J* = 1.3 Hz, 2H), 5.44 (d, *J* = 1.3 Hz, 2H), 6.84 (d, *J* = 7.9 Hz, 2H), 6.90−6.94 (m, 4H), 7.33 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.8, 110.7, 111.5, 113.2, 120.9, 128.0, 134.2, 140.8, 148.5, 148.8, 149.3; HRMS (ACPI) calcd for $C_{26}H_{27}O_4$ ($M+H^+$): 403.1904, found: 403.1896.

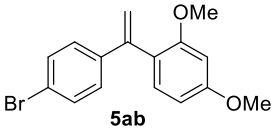
Reactions of 2a with Nucleophiles

Typical procedure for the generation of *β*-iodoalkoxysulfonium ions and their reactions with nucleophiles.



In the anodic chamber were placed iodine (63.4 mg, 0.25 mmol), diphenylsulfoxide (**2d**) (404 mg, 1.00 mmol), and 0.3 M Bu_4NBF_4/CH_2Cl_2 (10.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (80 μL), 0.3 M Bu_4NBF_4/CH_2Cl_2 (10.0 mL). The constant current electrolysis (8.0 mA) was carried out at −78 °C with magnetic stirring until 3.0 *F* of electricity was consumed. To the anodic chamber was added a solution of 4-bromostyrene (**1a**) (73.2 mg, 0.40 mmol) in CH_2Cl_2 (0.5 mL), and to the cathodic chamber 0.5 mL of CH_2Cl_2 was

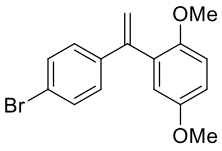
added at −78 °C. After the solution was stirred for 30 min at −78 °C, to the anodic chamber was added a solution of nucleophile **3** (2.00 mmol) in CH_2Cl_2 (0.5 mL), and to the cathodic chamber 0.5 mL of CH_2Cl_2 was added at −78 °C. The solution was stirred for 30 min at −78 °C, and then was stirred for 1 h at 25 °C. Then DBU (300 μL) was added to both the anodic and cathodic chambers, and the resulting mixture was stirred for additional 30 min. The solution in the anodic chambers was collected and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography and GPC to obtain the coupling product **5ax**.



5ab

1-(4-bromophenyl)-1-(2,4-dimethoxyphenyl)ethylene (5ab).

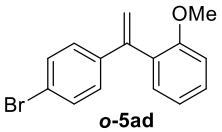
Electrochemical oxidation (3.0 *F*) of iodine (61.9 mg, 0.244 mmol), subsequent addition of the solution of 4-bromostyrene (**1a**) (72.9 mg, 0.398 mmol) in CH_2Cl_2 (0.5 mL), the solution of 1,3-dimethoxybenzene (**3b**) (260 mg, 2.02 mmol) in CH_2Cl_2 (0.5 mL), and DBU (300 μL) followed by flash chromatography (hexane/EtOAc 100:0, then 20:1) and GPC gave the title compound (41.4 mg, 0.130 mmol, 32%). TLC R_f 0.61 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60 (s, 3H), 3.84 (s, 3H), 5.30 (d, *J* = 1.3 Hz, 1H), 5.63 (d, *J* = 1.3 Hz, 1H), 6.47 (d, *J* = 2.6 Hz, 1H), 6.51 (dd, *J* = 2.6, 4.3 Hz, 1H), 7.12−7.17 (m, 3H), 7.38 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.37, 55.47, 98.9, 104.2, 115.5, 121.1, 123.1, 128.0, 131.0, 131.6, 140.5, 145.8, 158.0, 160.8; HRMS (ACPI) calcd for $C_{16}H_{16}BrO_2$ ($M+H^+$): 319.0328, found: 319.0321.



5ac

1-(4-bromophenyl)-1-(2,5-dimethoxyphenyl)ethylene (5ac).

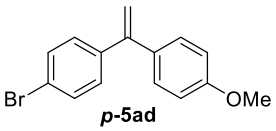
Electrochemical oxidation (3.0 *F*) of iodine (63.8 mg, 0.252 mmol), subsequent addition of the solution of 4-bromostyrene (**1a**) (74.1 mg, 0.405 mmol) in CH_2Cl_2 (0.5 mL), the solution of 1,4-dimethoxybenzene (**3c**) (276.6 mg, 2.00 mmol) in CH_2Cl_2 (0.5 mL), and DBU (300 μL) followed by flash chromatography (hexane/EtOAc 100:0, then 20:1) and GPC gave the title compound (79.0 mg, 0.247 mmol, 61%). TLC R_f 0.50 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.58 (s, 3H), 3.79 (s, 3H), 5.34 (d, *J* = 1.3 Hz, 1H), 5.69 (d, *J* = 1.3 Hz, 1H), 6.81 (d, *J* = 3.5 Hz, 1H), 6.83−6.88 (m, 2H), 7.16 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 56.2, 112.5, 113.5, 115.9, 117.0, 121.2, 128.0, 131.0, 131.4, 140.0, 145.9, 151.1, 153.5; HRMS (ACPI) calcd for $C_{16}H_{16}BrO_2$ ($M+H^+$): 319.0328, found: 319.0320.



***o*-5ad**

1-(4-bromophenyl)-1-(2-methoxyphenyl)ethylene (*o*-5ad) and
1-(4-bromophenyl)-1-(4-methoxyphenyl)ethylene (*p*-5ad).

Electrochemical oxidation (3.0 *F*) of iodine (61.7 mg, 0.243 mmol), subsequent addition of the solution of 4-bromostyrene (**1a**) (71.6 mg, 0.391 mmol) in CH_2Cl_2 (0.5 mL), the solution of anisole (**3d**) (220 μL, 2.04 mmol) in CH_2Cl_2 (0.5 mL), and DBU

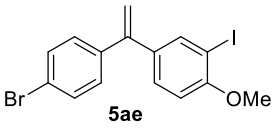


***p*-5ad**

(300 μL) followed by flash chromatography (hexane/EtOAc 100:0, then 10:1) and GPC gave the title compound (79.4 mg, 0.274 mmol, 70%).

***o*-5ad** TLC R_f 0.61 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (s, 3H), 5.33 (d, *J* = 1.3 Hz, 1H), 5.70 (d, *J* = 1.3 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.99 (t, *J* = 7.4 Hz, 1H), 7.15 (d, *J* = 8.8 Hz, 2H), 7.34 (t, *J* = 7.9 Hz, 1H), 7.38 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 111.1, 115.9, 120.6, 121.2, 128.0, 129.2, 130.4, 131.0, 131.1, 140.0, 146.1, 156.9; HRMS (ACPI) calcd for $C_{15}H_{14}BrO$ ($M+H^+$): 289.0223, found: 289.0214.

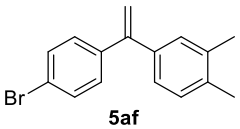
***p*-5ad** TLC R_f 0.61 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 5.34 (d, *J* = 0.9 Hz, 1H), 5.40 (d, *J* = 1.3 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 7.21 (d, *J* = 8.3 Hz, 2H), 7.22 (d, *J* = 9.2 Hz, 2H), 7.45 (d, *J* = 8.3 Hz, 2H); The ^{1}H NMR spectrum is in agreement with that in the literature.[22]



5ae

1-(4-bromophenyl)-1-(3-iodo-4-methoxyphenyl)ethylene (5ae).

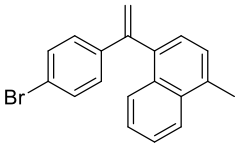
Electrochemical oxidation (3.0 *F*) of iodine (64.2 mg, 0.253 mmol), subsequent addition of the solution of 4-bromostyrene (**1a**) (70.7 mg, 0.386 mmol) in CH_2Cl_2 (0.5 mL), the solution of 2-iodoanisole (**3e**) (260 μL, 2.00 mmol) in CH_2Cl_2 (0.5 mL), and DBU (300 μL) followed by flash chromatography (hexane/EtOAc 100:0, then 20:1) and GPC gave the title compound (110 mg, 0.265 mmol, 69%). TLC R_f 0.58 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H), 5.37 (d, *J* = 0.9 Hz, 1H), 5.39 (d, *J* = 0.9 Hz, 1H), 6.77 (d, *J* = 8.8 Hz, 1H), 7.19 (d, *J* = 8.8 Hz, 2H), 7.23 (dd, *J* = 2.2, 8.8 Hz, 1H), 7.46 (d, *J* = 8.8 Hz, 2H), 7.75 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.4, 85.8, 110.3, 114.3, 121.9, 129.3, 129.8, 131.3, 135.4, 138.9, 140.0, 147.1, 157.8; HRMS (ACPI) calcd for $C_{15}H_{13}BrIO$ ($M+H^+$): 414.9189, found: 414.9178.



5af

1-(4-bromophenyl)-1-(3,4-dimethylphenyl)ethylene (5af).

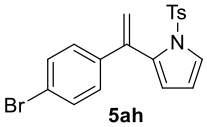
Electrochemical oxidation (3.0 *F*) of iodine (63.4 mg, 0.250 mmol), subsequent addition of the solution of 4-bromostyrene (**1a**) (72.0 mg, 0.393 mmol) in CH_2Cl_2 (0.5 mL), xylene (**3f**) (5 mL), and DBU (300 μL) followed by flash chromatography (hexane) and GPC gave the title compound (84.0 mg, 0.292 mmol, 74%). TLC R_f 0.80 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 3H), 2.26 (s, 3H), 5.36 (d, *J* = 0.9 Hz, 1H), 5.41 (d, *J* = 1.3 Hz, 1H), 7.03 (dd, *J* = 1.8, 7.5 Hz, 1H), 7.06−7.10 (m, 2H), 7.20 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 19.8, 113.9, 121.6, 125.6, 129.3, 129.5, 129.9, 131.2, 136.36, 136.41, 138.5, 140.7, 149.0; HRMS (ACPI) calcd for $C_{16}H_{16}Br$ ($M+H^+$): 287.0430, found: 287.0423.



5ag

1-(4-bromophenyl)-1-(4-methyl-1-naphthyl)ethylene (5ag).

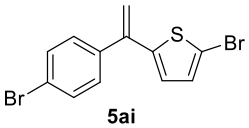
Electrochemical oxidation (3.0 *F*) of iodine (61.9 mg, 0.244 mmol), subsequent addition of the solution of 4-bromostyrene (**1a**) (72.9 mg, 0.398 mmol) in CH_2Cl_2 (0.5 mL), the solution of 1-methylnaphthalene (**3g**) (280 μL, 2.01 mmol) in CH_2Cl_2 (0.5 mL), and DBU (300 μL) followed by flash chromatography (hexane) and GPC gave the title compound (100 mg, 0.309 mmol, 80%). TLC R_f 0.76 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70 (s, 3H), 5.37 (d, *J* = 0.9 Hz, 1H), 5.91 (d, *J* = 1.3 Hz, 1H), 7.14 (d, *J* = 8.8 Hz, 2H), 7.28−7.34 (m, 5H), 7.44 (ddd, *J* = 1.3, 6.2, 8.4 Hz, 1H), 7.70 (d, *J* = 8.3 Hz, 1H) 7.99 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 116.6, 121.7, 124.3, 125.60, 125.61, 126.2, 127.0, 128.2, 131.4, 131.6, 134.4, 137.4, 140.1, 147.4; HRMS (ACPI) calcd for $C_{19}H_{16}Br$ ($M+H^+$): 323.0430, found: 323.0424.



5ah

1-(4-bromophenyl)-1-[N-(4-methylbenzenesulfonyl)-2-pyrrolyl]ethylene (5ah).

Electrochemical oxidation (3.0 *F*) of iodine (64.2 mg, 0.253 mmol), subsequent addition of the solution of 4-bromostyrene (**1a**) (71.5 mg, 0.391 mmol) in CH_2Cl_2 (0.5 mL), the solution of N-tosyl pyrrole (**3h**) (443 mg, 2.00 mmol) in CH_2Cl_2 (0.5 mL), and DBU (300 μL) followed by flash chromatography (hexane/EtOAc 100:0, then 10:1) and GPC gave the title compound (96.8 mg, 0.241 mmol, 62%). TLC R_f 0.44 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 5.29 (d, *J* = 1.3 Hz, 1H), 5.68 (d, *J* = 1.3 Hz, 1H), 6.23 (dd, *J* = 1.8, 3.1 Hz, 1H), 6.31 (dd, *J* = 3.0, 3.5 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 7.11 (d, *J* = 7.9 Hz, 2H), 7.21 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.40 (dd, *J* = 1.8, 3.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 111.7, 116.6, 119.2, 121.7, 123.9, 126.7, 128.1, 129.4, 130.9, 134.0, 135.6, 139.0, 139.4, 144.5; HRMS (ACPI) calcd for $C_{19}H_{17}BrNO_2S$ ($M+H^+$): 402.0158, found: 402.0149.



5ai

1-(4-bromophenyl)-1-(5-bromo-2-thienyl)ethylene (5ai).

Electrochemical oxidation (3.0 *F*) of iodine (64.8 mg, 0.256 mmol), subsequent addition of the solution of 4-bromostyrene (**1a**) (71.2 mg, 0.389 mmol) in CH_2Cl_2 (0.5 mL), the solution of 2-bromothiophene (**3i**) (190 μL, 1.99 mmol) in CH_2Cl_2 (0.5 mL), and DBU (300 μL) followed by flash chromatography (hexane) and GPC gave the title compound (86.0 mg, 0.250 mmol, 64%). TLC R_f 0.77 (hexane/EtOAc 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.22 (s, 1H), 5.50 (s, 1H), 6.62 (d, *J* = 4.0 Hz, 1H), 6.93 (d, *J* = 3.5 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.1, 114.3, 122.4, 126.7, 129.9, 130.2, 131.4, 139.0, 141.6, 145.5; HRMS (ACPI) calcd for $C_{12}H_9Br_2S$ ($M+H^+$): 342.8786, found: 342.8778.

References

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

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

(3) (a) Moritani, I.; Fujiwara, Y. *Tetrahedron. Lett.* **1967**, *12*, 1119. (b) Fujiwara, Y.; Moritani, I.; Danno, S.; Asano, R.; Teranishi, S. *J. Am. Chem. Soc.* **1969**, *91*, 7166.

(4) (a) Bras, J. L.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170. (b) Liu, C.; Yuan, J.; Gao, M.; Tang, S.; Li, W.; Shi, R.; Lei, A. *Chem. Rev.* **2015**, *115*, 12138. (c) Bag, S.; Maiti, D. *Synthesis.* **2016**, *48*, 804.

(5) (a) Boehm, M. F.; Zhang, L.; Badea, B. A.; White, S. K.; Mais, D. E.; Berger, E.; Suto, C. M.; Goldman, M. E.; Heyman, R. A. *J. Med. Chem.* **1994**, *37*, 2930. (b) Silverstri, M. A.; Nagarajan, M.; Clercq, E. D.; Pannecouque, C.; Cushman, M. *J. Med. Chem.* **2004**, *47*, 3149. (c) Hamze, A.; Giraud, A.; Messaoudi, S.; Provot, O.; Peyrat, J.-F.; Bignon, J.; Liu, J.-D.; Wdzieczak-Bakala, J.; Thoret, S.; Dubois, J.; Brion, J.-D.; Alami, M. *ChemMedChem*, **2009**, *4*, 1912. (d) Ruchelman, A. L.; Man, H.-W.; Chen, R.; Liu, W.; Lu, L.; Cedzik, D.; Zhang, L.; Leisten, J.; Collette, A.; Narla, R. K.; Raymon, H. K.; Muller, G. W. *Bioorg. Med. Chem.* **2011**, *19*, 6356. (e) Renko, D.; Provot, O.; Rasolofonjatovo, E.; Bignon, J.; Rodrigo, J.; Dubois, J.; Brion, J.-D.; Hamze, A.; Alami, M. *Eur. J. Med. Chem.* **2015**, *90*, 834.

(6) (a) Tsuji, J.; Nagashima, H. *Tetrahedron* **1984**, *14*, 2699. (b) Dams, M.; Vos, D. E. D.; Celen, S.; Jacobs, P. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 3512. (c) Jones, R. C.; Galezowski, M.; O'Shea, D. F. *J. Org. Chem.* **2013**, *78*, 8044.

(7) Agasti, S.; Dey, A.; Maiti, D. *Chem. Commun.* **2016**, *52*, 12191.

(8) Yang, Y.; Cheng, K.; Zhang, Y. *Org. Lett.* **2009**, *11*, 5606.

(9) (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. (e) Horn, E. J.; Rosen, B. R.; Baran, P. S. *ACS Cent. Sci.* **2016**, *2*, 302. (f) Yoshida, J.; Shimizu, A.; Hayashi, R. *Chem. Rev.* in press.

(10) Examples of C−C bond formation by electrochemical C−H bond functionalization: (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) Aiso, H.; Kochi, T.; Mutsutani, H.; Tanabe, T.; Nishiyama, S.; Kakiuchi, F. *J. Org. Chem.* **2012**, *77*, 7718. (f) Shoji, T.; Kim, S.; Yamamoto, K.; Kawai, T.; Okada, Y.; Chiba, K. *Org. Lett.* **2014**, *16*, 6404. (g) Elsler, B.; Schollmeyer, D.; Dyballa, K. M.; Franke, R.; Waldvogel, S. R. *Angew. Chem., Int. Ed.* **2014**, *53*, 5210. (h) Arai, T.; Tateno, H.; Nakabayashi, K.; Kashiwagi, T.; Atobe, M. *Chem. Commun*. **2015**, *51*, 4891. (i) Tang, S.; Gao, X.; Lei, A. *Chem. Commun.* **2017**, *53*, 3354.

(11) (a) Hayashi, R.; Shimizu, A.; Yoshida, J. *J. Am. Chem. Soc.* **2016**, *138*, 8400. (b) Hayashi, R.; Shimizu, A.; Song, Y.; Ashikari, Y.; Nokami, T.; Yoshida, J. *Chem. Eur. J.* **2017**, *23*, 61.

(12) (a) Ashikari, Y.; Shimizu, A.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2013**, *135*, 16070. (b) Shimizu, A.; Hayashi, R.; Ashikari, Y.; Nokami, T.; Yoshida, J. *Beilstein J. Org. Chem.* **2015**, *11*, 242.

(13) (a) Yoshino, H.; Matsubara, S.; Oshima, K.; Matsumoto, K.; Hagiwara, R.; Ito, Y. *J. Fluorine Chem.* **2004**, *125*, 455. (b) Yoshino, H.; Matsubara, S.; Oshima, K.; Matsumoto, K.; Hagiwara, R.; Ito, Y. *J. Fluorine Chem.* **2005**, *126*, 121.

(14) Examples of the reactions of aromatic nucleophiles with activated sulfoxide; (a) Akhtar, S. R.; Crivello, J. V.; Lee, J. L. *J. Am. Chem. Soc.* **1990**, *55*, 4222. (b) Becht, J.-M.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* **2003**, *68*, 5758. (c) Liu, G.; Mori, S.; Wang, X.; Noritake, S.; Tokunaga, E.; Shibata, N. *New. J. Chem.* **2012**, *36*, 1769.

(15) Examples of the transformation of iodohydrins by DBU; (a) Anand, N.; Kapoor, M.; Koul, S.; Taneja, S. C.; Sharma, R. L.; Qazi, G. N. *Tetrahedron Asymmetry* **2004**, *15*, 3131. (b) Eugenia, M.; Carrera, I.; Seoane, G. A.; Brovetto, M. *Tetrahedron Lett.* **2014**, *55*, 853. (c) Valiullina, Z. R.; Akhmet'yanova, V. A.; Ivanova, N. A.; Erastov, A. S.; Meshcheryakova, E. S.; Miftakhov, M. S. *Russ. J. Org. Chem.* **2015**, *51*, 1524.

(16) Agrawal, M. K.; Adimurthy, S.; Ganguly, B.; Ghosh, P. K. *Tetrahedron* **2009**, *65*, 2791.

(17) The *anti*-addition of I-$OS^{+}Ph_2$ to the carbon-carbon double bond seems to take place via an iodonium ion intermediate(ref. 12a). In the next step, the S_N1-like elimination of $O{=}SPh_2$ gives the benzylic cation stabilized by intramolecular participation of iodine, and the aromatic ring seems to attack the benzylic carbon from the back-side of the iodine to give *trans*-**4ha** (Scheme 4a).

(18) Rosocha, G.; Batey, R. A. *Tetrahedron* **2013**, *69*, 8758.

(19) Ludwiczak, M.; Bayda, M.; Dutkiewicz, M.; Frackowiak, D.; Majchrzak, M.; Marciniak, B.; Marciniec, B. *Organometallics* **2016**, *35*, 2454.

(20) Fujie, S.; Matumoto, K.; Suga, S.; Yoshida, J. *Chem. Lett.* **2009**, *38*, 1186.

(21) Hajra, S.; Maji, B.; Bar, S. *Org. Lett.* **2007**, *9*, 2783.

(22) Rao, M. L. N.; Jadhav, D. N.; Venkatesh, V. *Eur. J. Org. Chem.* **2009**, 4300.

Chapter 5

Automated Solution-Phase Synthesis of Oligosaccharides Using Electrochemically Generated Glycosyl Triflates

Abstract

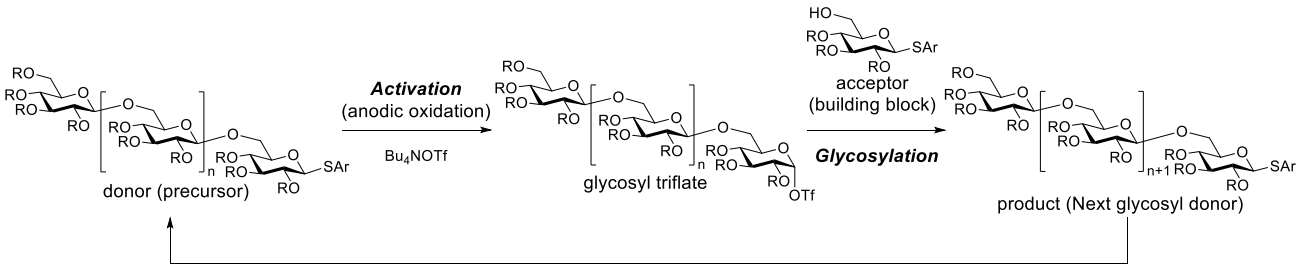
A new iterative one-pot sequential method for the solution-phase synthesis of oligosaccharides has been devised on the basis of the electrochemical oxidation of a propagating thioglycoside terminus to generate the corresponding triflate, followed by the reaction with a thioglycoside building block having a free hydroxyl group. A practical automated synthesizer was developed for the method and was effectively used for assembling up to six thioglycoside building blocks to synthesize partial structures of poly-β-D-(1−6)-N-acetylglucosamine.

Introduction

Iterative assembly of small molecules through the integration of reactions[1] in one-pot is a powerful method to construct large structures efficiently. Oligosaccharide syntheses in both solid-phase and solution-phase are good examples which require iterative assembly of carbohydrate building blocks.[2] Although oligosaccharide synthesis in solid-phase is advantageous from a viewpoint of purification,[3] it often suffers from disadvantages of limited scale, the high price of solid supports, low reactivity in the resin-bound media, and difficulties in the analysis of intermediates.

A one-pot sequential solution-phase method has already been used to synthesize oligosaccharides. However, at least two orthogonal activation protocols are necessary for the success of the method because a glycosyl donor (precursor of reactive intermediate) is usually activated in the presence of a glycosyl acceptor (building block).[4] A method consisting of activation of a precursor in the absence of a building block followed by the addition of a building block is beneficial because only one activation protocol is necessary.[5] Based on such a method, glycosylations can be easily repeated in a one-pot sequential manner to obtain oligosaccharides (Scheme 1).[6]

Scheme 1. Iterative Synthesis of Oligosaccharides Based on the Activation of a Thioglycoside Donor in the Absence of a Glycosyl Acceptor.



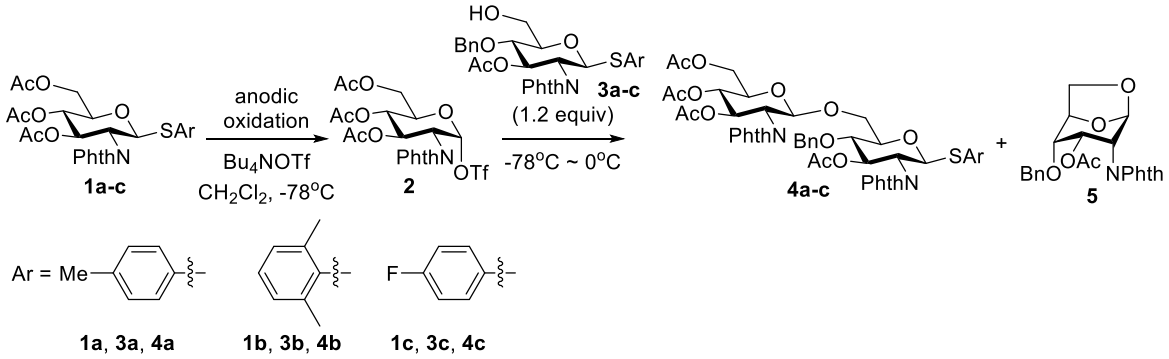
An electrochemical method,[7] for generation and accumulation of glycosyl triflates, which serve as useful intermediates for chemical glycosylation has been developed.[8] The electrochemical method avoids the use of strong activators and formation of byproducts derived from such activators. On the basis of these advantages, this chapter describes the development of an automated protocol for synthesis of oligosaccharides based on the electrochemical method. To demonstrate the utility of the protocol, automated synthesis of partial structures of poly-β-D-(1-6)-N-acetylglucosamine (PNAG),[9] which is the major component of the biofilm formed by pathogens, was accomplished.[10]

Results and Discussion

First, the anomeric ArS group of a building block (Table 1) was optimized. Glycosyl triflate **2** was electrochemically generated from arylthioglycoside **1a** as a precursor according to the previous report (See experimental session). The reaction with building block **3a**, which has the same aryl substituent on sulfur gave the corresponding disaccharide **4a** in 84% yield in addition to 1,6-anhydrosugar **5** in 13% yield (entry 1). To prevent the formation of 1,6-anhydrosugar **5**, which was obtained by the intramolecular glycosylation of **3a**,[11] the reaction

of **3b**, which has a bulky aryl group was examined (entry 2).[12] Although the yield of 1,6-anhydrosugar **5** slightly decreased from 13% to 8%, the yield of desired disaccharide **4b** also decreased. However, the use of building block **3c**, which has an electron-withdrawing fluorine atom on the phenyl ring resulted in the formation of the corresponding disaccharide **4c** in 84% yield. 1,6-Anhydrosugar **5** was produced only in a trace amount (entry 3). The anomeric leaving group of precursors also affected yields of disaccharides (entries 4 and 5). The combination of building block **3c** with precursor **1c** gave the best result (**4c**: 92% yield). Therefore, the following oligoglucosamine syntheses were carried out using thioglycosides having the 4-FC_6H_4- group on sulfur.

Table 1. Optimization of the Anomeric Leaving Group of a Building Block.

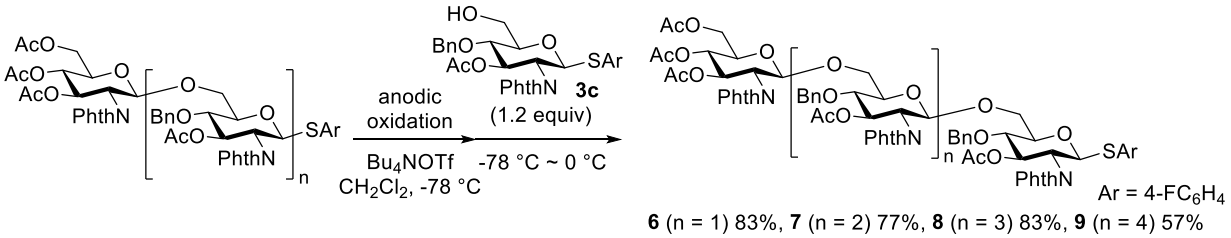


precursor	building block (E_{ox})[a]	product yields[b]
1a	**3a** (1.54 V)	**4a** 84%/**5** 13%
1a	**3b** (1.50 V)	**4b** 76%/**5** 8%
1a	**3c** (1.67 V)	**4c** 84%/**5** trace
1b	**3b** (1.50 V)	**4b** 76%/**5** trace
1c	**3c** (1.67 V)	**4c** 92%/**5** -[c]

a) Decomposition potential (V vs SCE) b) NMR yields based on 1,1,2,2-tetrachloroethane as an internal standard. c) **5** was not detected by ^{1}H NMR.

With the optimized building block in hand, the manual synthesis of oligosaccharides in a one-pot sequential way up to the hexasaccharide **9** (n = 4) was performed as shown in Scheme 2. Thioglycoside precursors were converted to the corresponding glycosyl triflates, and the subsequent glycosylations with 1.2 equiv of building block **3c** were performed to obtain oligoglucosamines **6**–**9** (n = 1–4). Although oxidation potentials of oligoglucosamines were around 1.7 V vs. SCE, which are slightly higher than that of thioglycoside **1**, the length of the oligoglucosamines did not affect the current efficiency of the electrochemical oxidation and chemical yields of oligosaccharides except for hexasaccharide **9**.[13] Prompted by this result, an automated synthesizer have been developed in order to carry out the assembly of the building block automatically.

Scheme 2. Stepwise Synthesis of Oligoglucosamines.



6 (n = 1) 83%, **7** (n = 2) 77%, **8** (n = 3) 83%, **9** (n = 4) 57%

An automated synthesizer for oligosaccharide synthesis was developed by assembling commercially available devices such as a syringe pump, a DC power supply, a temperature controlling system, a magnetic stirrer, an electrochemical reaction system equipped with a divided electrolysis cell, and system controller (Figure 1). The system controller,[14] which is connected to a DC power supply, a syringe pump, and a chiller, controls the schedule of the electrochemical oxidation (1.0 F/mol, –80 °C, 40 min) and the addition of a building block (CH_2Cl_2 solution, 1.0 equiv, 1 min). It takes 20 min to change the temperature of the cooling bath from –80 °C to –60 °C or vice versa (rate of temperature change = ±1 °C/min). The reaction with a building block was carried out at –60 °C for 30 min.

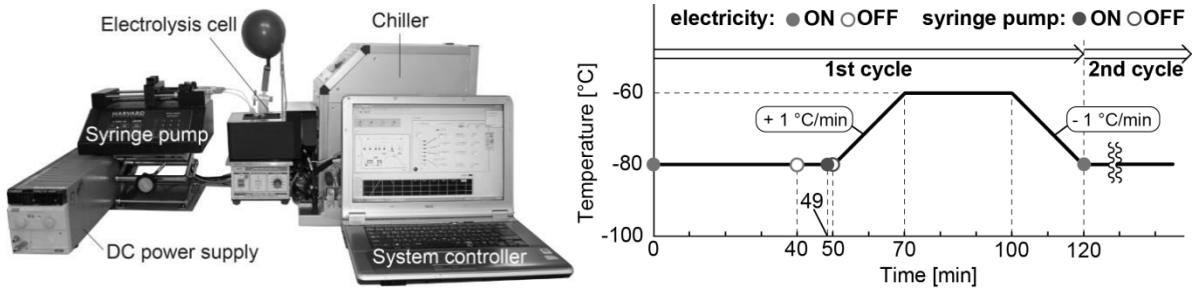
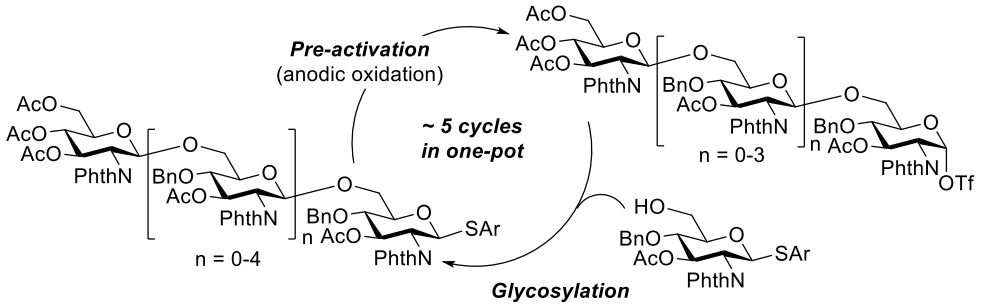


Figure 1. The automated synthesizer for oligosaccharide synthesis and the schedule of the automated process.

As shown in Table 2 several oligoglucosamines could be successfully synthesized using the automated synthesizer. One of the benefits of the solution-phase synthesis is that the reactions in each cycle can be monitored by thin layer chromatography (TLC) and/or mass spectrometry (MS) analyses. Indeed, the corresponding molecular ions of oligoglucosamines were observed in every cycle by analyzing the reaction mixture with MALDI-TOF MS (See Experimental Session). Further optimization of the reaction conditions showed that glycosylation at slightly higher temperature (–50 °C) afforded the corresponding oligoglucosamines **6**–**9** in better yields, and average yields were improved by around 10%. Although the targeted oligoglucosamines were contaminated with byproducts such as 1,6-anhydrosugar **5** and shorter oligoglucosamines, such byproducts were easily separated by preparative recycling gel permeation chromatography (PR-GPC). Thus, partial structures of PNAG could be easily prepared. Repeating the cycle many times, in principle, leads to the synthesis of PNAG of higher molecular weight.

Table 2. Automated Iterative Synthesis of Oligoglucosamines.



cycles	oligosaccharide	yields[a] (average yields per cycle) condition A[b]	condition B[c]
2	**6** (n = 1)	50% (71%)	69% (82%)
3	**7** (n = 2)	34% (70%)	52% (81%)
4	**8** (n = 3)	17% (64%)	31% (75%)
5	**9** (n = 4)	9% (62%)	15% (68%)

a) Isolated yield. b) Condition A (glycosylation temp: −60 °C, changing rate: ±1 °C/min). c) Condition B (glycosylation temp: −50 °C, changing rate: ±2 °C/min).

Conclusion

In summary, an iterative method for one-pot solution-phase synthesis of oligosaccharides based on the electrochemical method has been developed. A simple automated synthesizer equipped with an electrolysis cell, a DC power supply, a syringe pump, a cooling system, and a system controller is useful for practical synthesis of oligoglucosamines up to the hexasaccharide. The automated synthesizer is applicable to preparation of other oligosaccharides, because the electrochemical method can activate various types of thioglycosides as precursors of glycosyl triflates.

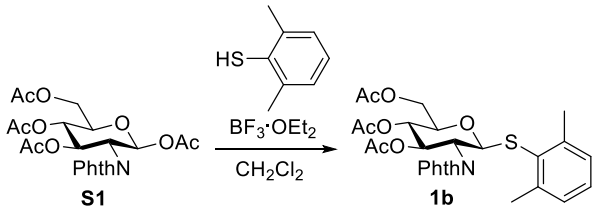
Experimental Session

General

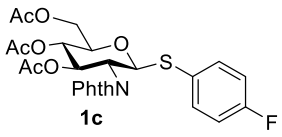
^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian MERCURY plus-400 (^{1}H 400 MHz, ^{13}C 100 MHz) spectrometer and JEOL ECA-600P (^{1}H 600 MHz, ^{13}C 150 MHz) spectrometer with tetramethylsilane as an internal standard unless otherwise noted. 1,1,2,2-Tetrachloroethane was used as an internal standard for NMR yield (^{1}H NMR, 5.95 ppm, 2 H). Mass spectra were obtained on a JEOL EXACTIVE (ESI and APCI) mass spectrometer, a JEOL JMS-SX102A mass spectrometer (EI), and Thermo Scientific Exactive spectrometer (ESI-TOF MS). Merck precoated silica gel F254 plates (thickness 0.25 mm) were used for thin-layer chromatography (TLC) analysis. Flash chromatography was carried out using Kanto Chem. Co., Silica Gel N (spherical, neutral, 40−100 μm). Preparative gel permeation chromatography (GPC) was performed on a Japan Analytical Industry LC-918. Rotating-disk electrode voltammetry was carried out using BAS 700c analyzer and RRDE-3 rotating ring disk electrode. Measurements were carried out in 0.1 M Bu_4NOTf/CH_2Cl_2 using a glassy carbon disk working electrode,

a platinum wire counter electrode, and an SCE reference electrode with sweep rate of 10 mV/s at 3000 r.p.m. Optical rotation was recorded on JASCO DIP-1000 digital polarimeter in chloroform. All reactions were carried out under argon atmosphere unless otherwise noted. Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. Dichloromethane was washed with water, distilled from P_2O_5, redistilled from dried K_2CO_3 to remove a trace amount of acid, and stored over molecular sieves 4A, and Bu_4NOTf was dried over P_2O_5 under vacuum. Starting material **S1**,[15] glycosyl donor **1a**,[16] and glycosyl acceptors **3a**[8d] were prepared according to the reported procedures.

Preparation of building blocks



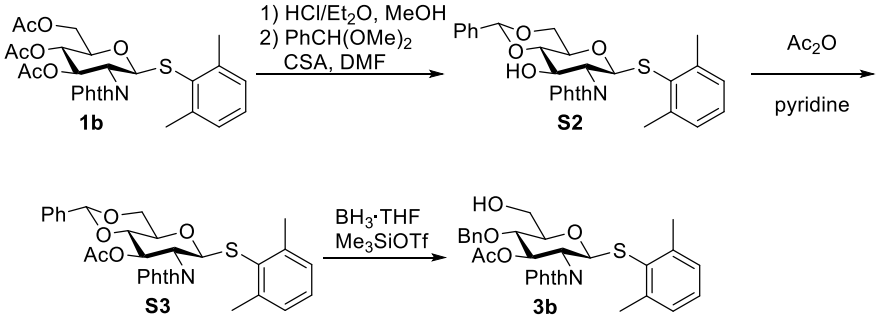
To a stirred solution of **S1** (12.8 g, 26.8 mmol) and 2,6-dimetylthiophenol (5.0 g, 36.2 mmol) in CH_2Cl_2 (50 mL) at 0 °C, $BF_3{\cdot}OEt_2$ (6.8 mL, 53.6 mmol) was added. After the mixture was stirred for another hour at rt, the reaction was quenched by $NaHCO_3$ aq. The solution was then concentrated and purified by recrystallization to give **2,6-Dimethylphenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (1b)** as white solid in 79% yield (11.8 g, 21 mmol). TLC R_f 0.45 (hexane/EtOAc 1:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.91−7.86 (m, 2 H), 7.78−7.75 (m, 2 H), 7.10 (pseudo-t, *J* = 6.8 Hz, 1 H), 7.02 (d, *J* = 7.6 Hz, 2 H), 5.83 (pseudo-t, *J* = 10.3 Hz, 1 H, H-3), 5.40 (d, *J* = 10.3 Hz, 1 H, H-1), 5.15 (pseudo-t, *J* = 10.3 Hz, 1 H, H-4), 4.48 (pseudo-t, *J* = 10.3 Hz, 1 H, H-2), 4.21 (dd, *J* = 11.7, 5.5 Hz, 1 H, H-6), 4.07 (dd, *J* = 12.4, 2.7 Hz, 1 H, H-6'), 3.70 (ddd, *J* = 10.3, 5.5, 2.0 Hz, 1 H, H-5), 2.35 (s, 6 H), 2.03 (s, 3 H), 2.01 (s, 3 H), 1.86 (s, 3 H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 170.6, 170.1, 169.5, 167.8, 167.1, 144.2, 134.5, 134.3, 131.6, 131.2, 129.7, 129.2, 128.2, 123.8, 123.5, 84.8 (C-1), 75.3 (C-5), 71.4 (C-3), 69.1 (C-4), 62.3 (C-6), 54.3 (C-2), 22.1, 20.63, 20.60, 20.4; HRMS (ESI) *m/z* calcd for $C_{28}H_{33}N_2O_9S$ $[M+NH_4]^+$, 573.1901; found, 573.1888.

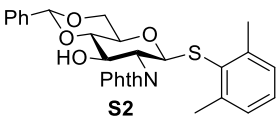


4-Fluorophenyl-3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (1c)

To a stirred solution of **S1** (4.8 g, 10.1 mmol) and 4-fluorothiolphenol (1.67 g, 13 mmol) in CH_2Cl_2 (20 mL) at 0 °C, $BF_3{\cdot}OEt_2$ (2.5 mL, 20 mmol) was added. After the mixture was stirred at room temperature (rt) for another 1 h, the reaction was quenched by $NaHCO_3$ aq. The solution was then concentrated and purified by recrystallization to give the title compound as white solid in 79% yield (4.3 g, 7.9 mmol). TLC R_f 0.55 (hexane/EtOAc 1:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.89−7.88 (m, 2 H), 7.79−7.77 (m,

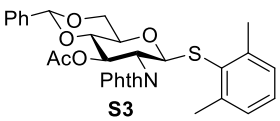
2 H), 7.43 (dd, *J* = 8.9, 5.5 Hz, 2 H), 6.99 (psuedo-t, *J* = 8.9 Hz, 1 H), 5.77 (dd, *J* = 10.3, 8.9 Hz, 1 H, H-3), 5.63 (d, *J* = 10.3 Hz, 1 H, H-1), 5.11 (psuedo-t, *J* = 10.3 Hz, 1 H, H-4), 4.29 (pseudo-t, *J* = 10.3 Hz, 1 H, H-2), 4.28 (d, *J* = 12.4 Hz, 1 H, H-6), 4.20 (dd, *J* = 12.4, 2.0 Hz, 1 H, H-6'), 3.89 (ddd, *J* = 10.3, 4.8, 2.0 Hz, 1 H, H-5), 2.11 (s, 3 H), 2.03 (s, 3 H), 1.84 (s, 3 H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 170.6, 170.1, 169.4, 167.8, 166.9, 163.2 (d, *J* = 247.0 Hz), 136.4 (d, *J* = 8.6 Hz), 134.5, 134.4, 131.5, 131.1, 125.3 (d, *J* = 2.9 Hz), 116.0 (d, *J* = 21.5 Hz), 82.8 (C-1), 75.9 (C-5), 71.5 (C-3), 68.5 (C-4), 62.1 (C-6), 53.5 (C-2), 20.7, 20.6, 20.4. HRMS (ESI) *m/z* calcd for $C_{26}H_{28}FN_2O_9S$ $[M+NH_4]^+$, 563.1494; found, 563.1469.





2,6-Dimethylphenyl-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (S2)

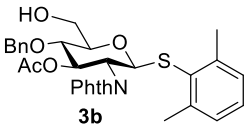
1b (11.8 g, 21.8 mmol) was dissolved in MeOH (50 mL) and treated with 1.0 M HCl/Et_2O solution (27.3 mL, 27.3 mmol) at rt for 7 h, and then most of solvent was removed. The solution of the mixture, benzaldehyde dimethyl acetal (9.8 mL, 65 mmol), CSA (510 mg, 2.2 mmol), and DMF (50 mL) was stirred overnight at rt, until TLC showed the reaction was complete. The reaction was quenched with saturated $NaHCO_3$ aq, and the mixture was diluted with EtOAc, washed with H_2O and brain, dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was purified by flash column chromatography to give the title compound as a white solid in 75% yield. TLC R_f 0.25 (hexane/EtOAc 5:2); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.92−7.85 (m, 2 H), 7.76−7.74 (m, 2 H), 7.48−7.45 (m, 2 H), 7.36−7.34 (m, 3 H), 7.10 (pseudo-t, *J* = 8.2 Hz, 1 H), 7.03 (d, *J* = 7.5 Hz, 2 H), 5.56 (s, 1 H), 5.34 (d, *J* = 10.3 Hz, 1 H, H-1), 4.68 (pseudo-t, *J* = 9.7 Hz, 1 H, H-3), 4.41 (pseudo-t, *J* = 11.0 Hz, 1 H, H-2), 4.24 (dd, *J* = 10.3, 3.4 Hz, 1 H, H-6), 3.76 (pseudo-t, *J* = 10.3 Hz, 1 H, H-6'), 3.64 (pseudo-t, *J* = 8.9 Hz, 1 H, H-4), 3.51–3.46 (m, 1 H, H-5), 2.56 (bs, 1 H), 2.34 (s, 6 H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 168.3, 167.7, 144.0, 136.9, 134.4, 134.3, 131.8, 131.5, 130.2, 129.7, 129.3, 129.2, 129.0, 128.4, 128.2, 126.3, 123.9, 123.2, 101.9, 85.9 (C-1), 82.0 (C-4), 69.8 (C-5), 69.4 (C-3), 68.5 (C-6), 56.1 (C-2), 22.2; HRMS (ESI) *m/z* calcd for $C_{29}H_{28}N_2O_6S$ $[M+H]^+$, 519.1632; found, 519.1622.



S3

2,6-Dimethylphenyl-3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (S3)

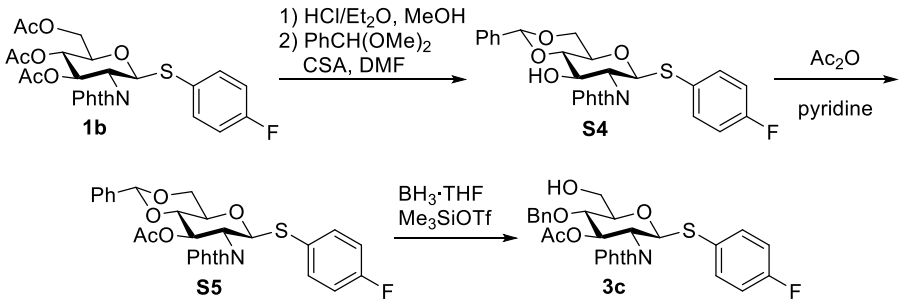
The mixture of **S2** (8.5 g, 16.4 mmol), DMAP (37 mg, 0.30 mmol) in pyridine (50 ml) was stirred at 0 °C, then Ac_2O (30 mL, 30 mmol) was added, and reaction was stirred overnight at rt. The reaction mixture was diluted with EtOAc, washed with H_2O and brine, and dried over anhydrous Na_2SO_4. The solution was then concentrated and purified by flash column chromatography to give the title compound as a white solid (4.0 g, 7.1 mmol). TLC R_f 0.35 (hexane/EtOAc 5:2); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.90−7.87 (m, 2 H), 7.78−7.74 (m, 2 H), 7.44−7.42 (m, 2 H), 7.36−7.33 (m, 3 H), 7.10 (pseudo-t, *J* = 6.9 Hz, 1 H), 7.03 (d, *J* = 6.9 Hz, 2 H), 5.93 (pseudo-t, *J* = 9.6 Hz, 1 H, H-3), 5.53 (s, 1 H), 5.51 (d, *J* = 10.3 Hz, 1 H, H-1), 4.47 (pseudo-t, *J* = 10.3 Hz, 1 H, H-2), 4.29 (dd, *J* = 10.3, 4.8 Hz, 1 H, H-6), 3.81 (pseudo-t, *J* = 9.6 Hz, 1 H, H-4), 3.78 (pseudo-t, *J* = 10.3 Hz, 1 H, H-6'), 3.61 (td, *J* = 9.6, 4.8 Hz, 1 H, H-5), 2.33 (s, 6 H), 1.90 (s, 3 H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 170.2, 167.8, 167.4, 144.0, 136.9, 134.5, 134.2, 131.8, 131.2, 129.9, 129.3, 129.1, 128.3, 128.2, 126.3, 123.7, 123.6, 101.6, 85.3 (C-1), 79.1 (C-4), 70.5 (C-3), 69.9 (C-5), 68.5 (C-6), 54.9 (C-2), 22.2, 20.6; HRMS (ESI) *m/z* calcd for $C_{31}H_{30}NO_7S$ $[M+H]^+$, 560.1737; found, 560.1725.

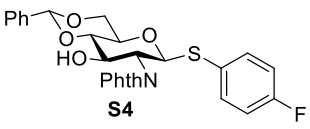


3b

2,6-Dimethylphenyl-3-*O*-acetyl-4-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (3b)

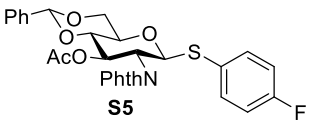
To a stirred solution of **S3** (2.0 g, 3.6 mmol) in BH_3·THF (9.0 mL) at 0 °C, TMSOTf (0.90 mL) was added dropwise. After the mixture was stirred at 0 °C for 2 hours, the reaction was quenched by methanol (1.0 mL) and triethylamine (2.0 mL). The solution was then concentrated and purified by flash column chromatography and recrystallization to give the title compound as white solid in 55% yield (1.1 g, 2.0 mmol). TLC R_f 0.55 (hexane/EtOAc 1:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.88−7.86 (m, 2 H), 7.77−7.74 (m, 2 H), 7.34−7.24 (m, 5 H), 7.09 (dd, *J* = 8.3, 6.9 Hz, 1 H), 7.03 (d, *J* = 7.6 Hz, 2 H), 5.83 (psuedo-t, *J* = 8.9 Hz, 1 H, H-3), 5.47 (d, *J* = 10.3 Hz, 1 H, H-1), 4.66 (d, *J* = 11.7 Hz, 1 H), 4.63 (d, *J* = 11.0 Hz, 1 H), 4.36 (pseudo-t, *J* = 10.3 Hz, 1 H, H-2), 3.83 (dd, *J* = 11.6, 2.0 Hz, 1 H, H-6), 3.78 (pseudo-t, *J* = 9.6 Hz, 1 H, H-4), 3.71 (dd, *J* = 11.7, 3.5 Hz, 1 H, H-6'), 3.49 (ddd, *J* = 9.7, 4.1, 2.8 Hz, 1 H, H-5), 2.36 (s, 6 H), 1.78 (s, 3 H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 170.1, 167.8, 167.5, 143.9, 137.7, 134.4, 134.2, 131.8, 131.2, 129.8, 129.2, 128.5, 128.3, 128.0, 127.8, 123.56, 123.54, 84.3 (C-1), 78.8 (C-5), 76.2 (C-4), 74.6, 73.8 (C-3), 62.0 (C-6), 55.0 (C-2), 22.2, 20.6; HRMS (ESI) *m/z* calcd for $C_{31}H_{31}NO_7SCl$ $[M+Cl]^-$, 596.1504; found, 596.1478.





4-Fluorophenyl-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (S4)

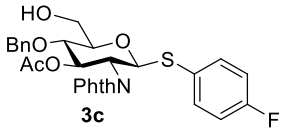
1b (29.7 g, 54.4 mmol) was dissolved in MeOH (100 mL) and treated with HCl/Et_2O solution (60 mL, 60 mmol) for 12 h at rt, then most of solvent was removed. The solution of the mixture, benzaldehyde dimethyl acetal (25.4 mL, 163 mmol) and CSA (1.25 g, 5.4 mmol) was stirred at rt, until TLC analysis showed the reaction was complete. The reaction was quenched with saturated $NaHCO_3$ aq, and the mixture was diluted with EtOAc, washed with H_2O and brain, dried over anhydrous Na_2SO_4, and concentrated in vacuum. The residue was purified by flash column chromatography to give the title compound as a white solid (20 g, 39.4 mmol). TLC R_f 0.20 (hexane/EtOAc 5:2); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.89 (d, *J* = 5.5 Hz, 2 H), 7.84 (d, *J* = 5.5 Hz, 1 H), 7.48−7.44 (m, 2 H), 7.39 (dd, *J* = 8.9, 5.5 Hz, 2 H), 7.36−7.34 (m, 3 H), 6.99−6.95 (m, 2 H), 5.57 (d, *J* = 10.3 Hz, 1 H, H-1), 5.54 (s, 1 H), 4.58 (td, *J* = 9.7, 4.1 Hz, 1 H, H-3), 4.37 (dd, *J* = 10.3, 4.8 Hz, 1 H, H-6), 4.25 (pseudo-t, *J* = 10.3 Hz, 1 H, H-2), 3.78 (pseudo-t, *J* = 10.3 Hz, 1 H, H-6'), 3.65 (td, *J* = 9.7, 4.8 Hz, 1 H, H-5), 3.53 (pseudo-t, *J* = 9.7 Hz, 1 H, H-4), 2.65 (bs, 1 H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 168.2, 167.5, 163.0 (d, J = 248.5 Hz), 136.8, 135.8 (d, *J* = 8.6 Hz), 134.2, 131.54, 131.45, 129.3, 128.3, 126.3, 126.2, 123.8, 123.3, 116.0 (d, *J* = 21.5 Hz), 101.9, 84.1 (C-1), 81.7 (C-4), 70.3 (C-5), 69.6 (C-3), 68.4 (C-6), 55.5 (C-2); HRMS (ESI) *m/z* calcd for $C_{27}H_{26}FN_2O_6S$ $[M+NH_4]^+$, 525.1490; found, 525.1469.



4-Fluorophenyl-3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (S5)

The mixture of **S4** (5.0 g, 9.9 mmol), DMAP (24 mg, 0.20 mmol) in pyridine (30 mL) was stirred at 0 °C, then Ac_2O (20 mL) was added, and stirred overnight at rt. The reaction mixture was diluted with EtOAc, washed with H_2O and brine, and dried over anhydrous Na_2SO_4. The solution was then concentrated and purified by recrystallization to give the title compound as a white solid (4.8 g, 8.7 mmol, 88% yield). TLC R_f 0.25 (hexane/EtOAc 5:2); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.90−7.87

(m, 2 H), 7.78−7.75 (m, 2 H), 7.45−7.43 (m, 2 H), 7.41−7.39 (m, 2 H), 7.36−7.34 (m, 3 H), 7.01−6.97 (m, 2 H), 5.87 (pseudo-t, *J* = 8.9 Hz, 1 H, H-3), 5.73 (d, *J* = 10.3 Hz, 1 H, H-1), 5.52 (s, 1 H), 4.42 (dd, *J* = 8.9, 3.4 Hz, 1 H, H-6), 4.29 (pseudo-t, *J* = 9.7 Hz, 1 H, H-2), 3.82 (pseudo-t, *J* = 9.6 Hz, 1 H, H-5), 3.78 (td, *J* = 9.6, 4.1 Hz, 1 H, H-6'), 3.71 (pseudo-t, *J* = 8.9 Hz, 1 H, H-4), 1.87 (s, 3 H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 170.2, 167.9, 167.2, 163.2 (d, *J* = 247.0 Hz), 136.8, 136.2 (d, *J* = 8.6 Hz), 134.5, 134.3, 131.6, 131.1, 129.2, 128.2, 126.2, 125.5 (d, *J* = 2.9 Hz), 123.8, 123.6, 116.1 (d, *J* = 21.5 Hz), 101.7, 83.7 (C-1), 78.9 (C-4), 70.55 (C-5), 70.52 (C-3), 68.5 (C-6), 54.2 (C-2), 20.5; HRMS (ESI) *m/z* calcd for $C_{29}H_{28}FN_2O_7S$ $[M+NH_4]^+$, 567.1596; found, 567.1574.

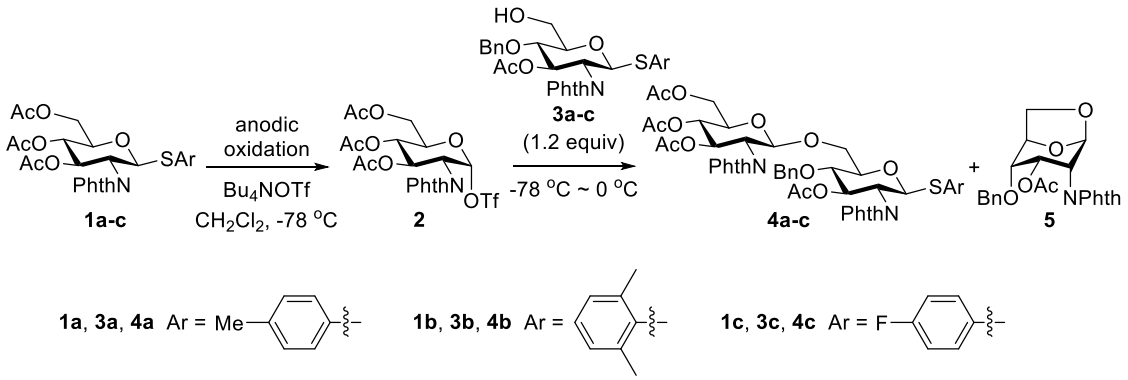


3c

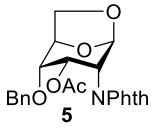
4-Fluorophenyl-3-*O*-acetyl-4-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (3c)

To a stirred solution of **S5** (5.3 g, 9.6 mmol) in BH_3·THF (24.0 mL) at 0 °C, TMSOTf (2.4 mL) was added dropwise. After the mixture was stirred at 0 °C for 2 hours, the reaction was quenched by methanol (1.0 mL) and triethylamine (2.0 mL). The solution was then concentrated and purified by flash column chromatography and recrystallization to give the title compound as white solid in 56% yield (3.0 g, 5.4 mmol). TLC R_f 0.15 (hexane/EtOAc 5:2); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.88−7.85 (m, 2 H), 7.77−7.74 (m, 2 H), 7.40−7.37 (m, 2 H), 7.33−7.31 (m, 2 H), 7.29−7.24 (m, 3 H), 7.00−6.96 (m, 2 H), 5.78 (psuedo-t, *J* = 8.9 Hz, 1 H, H-3), 5.70 (d, *J* = 10.3 Hz, 1 H, H-1), 4.67 (d, *J* = 11.0 Hz, 1 H), 4.63 (d, *J* = 11.0 Hz, 1 H), 4.19 (pseudo-t, *J* = 10.3 Hz, 1 H, H-2), 3.95 (ddd, *J* = 11.6, 4.8, 2.0 Hz, 1 H, H-6), 3.80–3.76 (m, 1 H, H-6'), 3.75 (pseudo-t, *J* = 8.9 Hz, 1 H, H-4), 3.64 (ddd, *J* = 9.7, 4.1, 2.8 Hz, 1 H, H-5), 1.89 (s, 1 H), 1.76 (s, 3 H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 170.1, 167.8, 167.3, 163.1 (d, *J* = 247.0 Hz), 137.6, 135.9 (d, *J* = 8.6 Hz), 134.5, 134.2, 131.6, 131.1, 128.5, 127.9, 127.7, 125.9 (d, *J* = 2.9 Hz), 123.7, 123.6, 116.2 (d, *J* = 21.6 Hz), 83.0 (C-1), 79.4 (C-5), 75.9 (C-4), 74.7, 73.9 (C-3), 61.7 (C-6), 54.1 (C-2), 20.5; HRMS (ESI) *m/z* calcd for $C_{29}H_{30}FN_2O_7S$ $[M+NH_4]^+$, 570.1786; found, 570.1762.

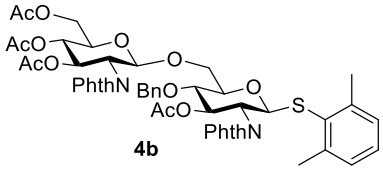
Optimization of manual synthesis of disaccharide



The anodic oxidation was carried out in an H-type divided cell (4G glass filter) equipped with a carbon felt anode (Nippon Carbon JF-20-P7, ca. 180 mg, dried at 350 °C/1 mmHg before use) and a platinum plate cathode (10 mm×20 mm). In the anodic chamber were placed a thioglycoside **1a** (54.2 mg, 0.100 mmol) and 0.1 M Bu_4NOTf in CH_2Cl_2 (5.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (13 μL, 0.15 mmol) and 0.1 M Bu_4NOTf in CH_2Cl_2 (5.0 mL). The constant current electrolysis (4.0 mA) was carried out at −78 °C with magnetic stirring until 1.0 F/mol of electricity was consumed. Glycosyl acceptor **3a** (65.7 mg, 0.120 mmol) dissolved in CH_2Cl_2 (1.0 mL) was added under an argon atmosphere at −78 °C, and the reaction mixture was stirred for additional 30 min at −78 °C and then the temperature was raised to −60 °C and kept for 30 min. Et_3N (500 μL) was added and the mixture was filtered through a short column (2×3 cm) of silica gel to remove Bu_4NOTf. The removal of the solvent under reduced pressure afforded disaccharide **4a**[8d] in 84% NMR yield (0.084 mmol based on the internal standard) together with anhydrosugar **5** in 11% NMR yield (0.013 mmol).



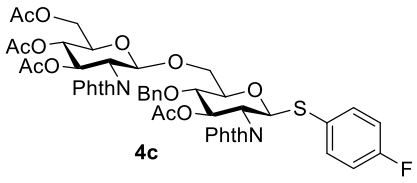
1,6-Anhydro-3-*O*-acetyl-4-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranose (5) TLC R_f 0.45 (hexane/EtOAc 1:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.87−7.84 (m, 2 H), 7.74−7.71 (m, 2 H), 7.36−7.28 (m, 5 H) , 5.62 (s, 1 H, H-1), 5.55 (dd, *J* = 9.6, 7.6 Hz, 1 H, H-3), 4.70 (d, *J* = 5.5 Hz, 1 H, H-5), 4.67 (d, *J* = 11.8 Hz, 1 H), 4.62 (d, *J* = 12.4 Hz, 1 H), 4.13 (d, *J* = 8.9 Hz, 1 H, H-2), 3.80 (dd, *J* = 7.6, 5.5 Hz, 1 H, H-6), 3.77 (d, *J* = 7.6 Hz, 1 H, H-6'), 3.61 (d, *J* = 7.6 Hz, 1 H, H-4), 1.89 (s, 3 H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 170.3, 167.6, 137.5, 134.2, 131.6, 128.5, 128.0, 127.8, 123.5, 101.8 (C-1), 81.7 (C-4), 76.3 (C-5), 71.8, 70.8 (C-3), 67.8 (C-6), 56.1 (C-2), 20.7; HRMS (ESI) *m/z* calcd for $C_{23}H_{21}NO_7Na$ $[M+Na]^+$, 446.1210; found, 446.1208.



2,6-Dimethylphenyl-3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→6)-3-*O*-acetyl-4-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-gluco-pyranoside (4b).

Preparation of glycosyl triflate **2** from thioglycoside **1a** (54.3 mg,

0.100 mmol) and its reaction with glycosyl acceptor **3b** (70.7 mg, 0.126 mmol) afforded the title compound in 76% NMR yield (0.076 mmol based on the internal standard) together with anhydrosugar **5** in 8% NMR yield (0.0079 mmol based on the internal standard). The crude mixture was purified by silica gel chromatography (59 mg, 0.060 mmol, 60% isolated yield). TLC R_f 0.40 (hexane/EtOAc 1:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.87−7.81 (m, 2 H), 7.81−7.75 (m, 2 H), 7.74−7.71 (m, 2 H), 7.66−7.63 (m, 2 H), 7.20−7.18 (m, 3 H), 7.11 (pseudo-t, *J* = 7.6 Hz, 1 H), 7.03 (d, *J* = 7.6 Hz, 2 H), 6.97−6.95 (m, 2 H), 5.71 (pseudo-t, *J* = 9.7 Hz, 1 H), 5.69 (dd, *J* = 10.3, 8.9 Hz, 1 H), 5.44 (d, *J* = 8.2 Hz, 1 H), 5.37 (d, *J* = 11.0 Hz, 1 H), 5.12 (pseudo-t, *J* = 9.6 Hz, 1 H), 4.38 (dd, *J* = 10.3, 8.3 Hz, 1 H), 4.33 (d, *J* = 11.7 Hz, 1 H), 4.289 (pseudo-t, *J* = 10.3 Hz, 1 H), 4.286 (d, *J* = 11.7 Hz, 1 H), 4.19 (dd, *J* = 12.4, 2.8 Hz, 1 H), 4.16 (dd, *J* = 12.4, 4.8 Hz, 1 H), 4.93 (dd, *J* = 11.0, 1.4 Hz, 1 H), 3.83−3.79 (m, 2 H), 3.64 (pseudo-t, *J* = 9.6 Hz, 1 H), 3.51 (ddd, *J* = 9.7, 4.9, 2.0 Hz, 1 H), 2.33 (s, 6 H), 2.15 (s, 3 H), 2.05 (s, 3 H), 1.87 (s, 3 H), 1.69 (s, 3 H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 170.8, 170.2, 170.0, 169.4, 167.7, 167.3, 144.4, 137.4, 134.2, 134.0, 131.7, 131.2, 129.9, 129.1, 128.3, 128.1, 127.7, 127.4, 123.6, 123.4, 97.9, 84.3, 77.6, 76.8, 74.4, 73.7, 71.8, 70.9, 68.9, 68.3, 62.2, 54.7, 54.5, 22.1, 20.8, 20.6, 20.4; HRMS (ESI) *m/z* calcd for $C_{51}H_{54}N_3O_{16}S$ $[M+NH_4]^+$, 996.3219; found, 996.3206.



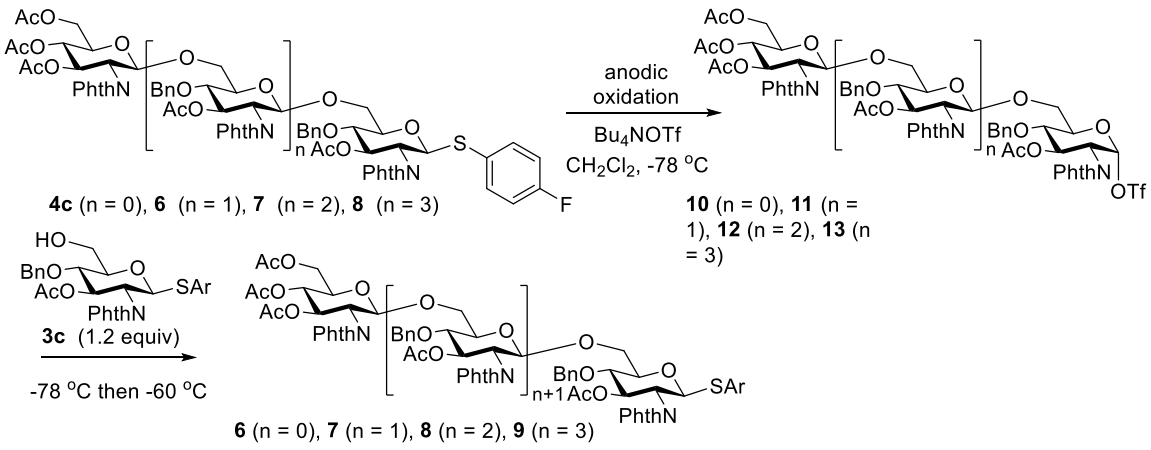
4c

4-Fluorophenyl-3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→6)-3-*O*-acetyl-4-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (4c)

Preparation of glycosyl triflate **2** from thioglycoside **1c** (218 mg, 0.40 mmol) and its reaction with glycosyl acceptor **3c** (265 mg, 0.48 mmol) afforded the title compound in 92% NMR yield (0.367 mmol based on the internal standard). The crude mixture was purified by silica gel chromatography (351 mg, 0.362 mmol, 91% isolated yield). TLC R_f 0.45 (hexane/EtOAc 1:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.85−7.81 (m, 2 H), 7.78−7.76 (m, 2 H), 7.74−7.72 (m, 2 H), 7.65−7.62 (m, 2 H), 7.37−7.34 (m, 2 H), 7.24−7.21 (m, 3 H), 7.05−7.01 (m, 4 H), 5.78 (dd, *J* = 10.9, 8.9 Hz, 1 H), 5.66 (pseudo-t, *J* = 10.3 Hz, 1 H), 5.55 (d, *J* = 10.3 Hz, 1 H), 5.53 (d, *J* = 8.9 Hz, 1 H), 5.21 (pseudo-t, *J* = 8.9 Hz, 1 H), 4.40 (dd, *J* = 11.0, 8.9 Hz, 1 H), 4.38–4.31 (m, 3 H), 4.20 (dd, *J* = 12.4, 2.0 Hz, 1 H), 4.10 (dd, *J* = 11.0, 1.4 Hz, 1 H), 4.03 (pseudo-t, *J* = 10.3

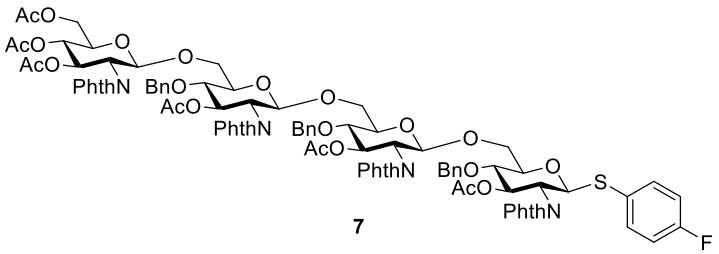
Hz, 1 H), 3.81−3.77 (m, 2 H), 3.68 (ddd, *J* = 10.3, 5.8, 2.1 Hz, 1 H), 3.46 (pseudo-t, *J* = 9.6 Hz, 1 H), 2.10 (s, 3 H), 2.05 (s, 3 H), 1.89 (s, 3 H), 1.65 (s, 3 H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 170.7, 170.1, 169.8, 169.4, 167.7, 167.1, 163.0 (d, *J* = 247.0 Hz), 137.3, 135.9 (d, *J* = 7.2 Hz), 134.3, 134.2, 134.1, 131.6, 131.2, 131.0, 128.3, 127.7, 127.4, 125.4, 123.6, 123.4, 115.9 (d, *J* = 21.5 Hz), 98.0, 81.9, 78.2, 76.4, 74.4, 73.7, 71.9, 70.7, 68.8, 68.1, 61.9, 54.4, 53.7, 20.7, 20.5, 20.4, 20.3; HRMS (ESI) *m/z* calcd for $C_{49}H_{49}FN_3O_{16}S$ $[M+NH_4]^+$, 986.2812; found, 986.2815.

Manual synthesis of oligosaccharides



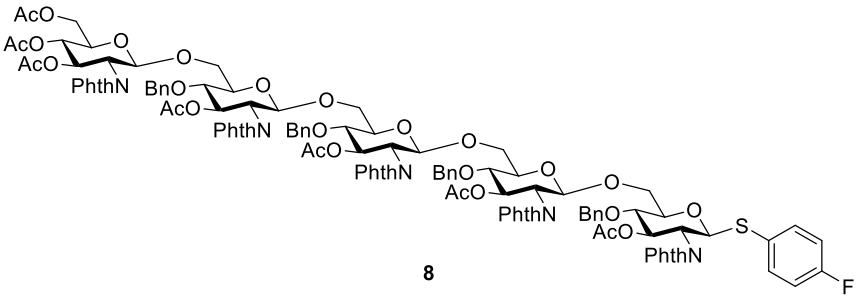
The anodic oxidation was carried out in an H-type divided cell (4G glass filter) equipped with a carbon felt anode (Nippon Carbon JF-20-P7, ca. 350 mg, dried at 350 °C/1 mmHg before use) and a platinum plate cathode (20 mm×20 mm). In the anodic chamber were placed a disaccharide **4c** (287 mg, 0.296 mmol) and 0.1 M Bu_4NOTf in CH_2Cl_2 (10.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (50 μL, 0.57 mmol) and 0.1 M Bu_4NOTf in CH_2Cl_2 (10.0 mL). The constant current electrolysis (6.0 mA) was carried out at −78 °C with magnetic stirring until 1.0 F/mol of electricity was consumed. Glycosyl acceptor **3c** (196 mg, 0.355 mmol) dissolved in CH_2Cl_2 (2.0 mL) was added under an argon atmosphere at −78 °C, and the reaction mixture was stirred for additional 30 min at −78 °C and then the temperature was raised to −60 °C and kept for 30 min. Et_3N (1.0 mL) was added and the mixture was filtered through a short column (2×3 cm) of silica gel to remove Bu_4NOTf. The removal of the solvent under reduced pressure afforded **4-Fluorophenyl-3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→6)-3-*O*-acetyl-4-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→6)-3-*O*-acetyl-4-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (6)** in 83% isolated yield (342 mg, 0.246 mmol). The crude product was purified by silica gel chromatography. TLC R_f 0.25 (hexane/EtOAc

1:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.85−7.69 (m, 10 H), 7.58 (bs, 2 H), 7.36 (dd, *J* = 9.1, 5.4 Hz, 2 H), 7.28−7.19 (m, 6 H), 7.10 (d, *J* = 7.6 Hz, 2 H), 7.04 (pseudo-t, *J* = 8.9 Hz, 2 H), 6.99 (dd, *J* = 7.6, 2.0 Hz, 2 H), 5.81 (dd, *J* = 10.3, 8.9 Hz, 1 H), 5.69 (dd, *J* = 11.0, 8.9 Hz, 1 H), 5.62 (dd, *J* = 10.3, 8.9 Hz, 1 H), 5.59 (d, *J* = 8.2 Hz, 1 H), 5.50 (d, *J* = 10.3 Hz, 1 H), 5.44 (d, *J* = 8.9 Hz, 1 H), 5.18 (pseudo-t, *J* = 9.6 Hz, 1 H), 4.42 (dd, *J* = 10.3, 8.9 Hz, 1 H), 4.41 (d, *J* = 11.7 Hz, 1 H), 4.38−4.33 (m, 2 H), 4.22−4.17 (m, 3 H), 4.14 (dd, *J* = 11.0, 1.4 Hz, 1 H), 4.09 (dd, *J* = 10.3, 2.0 Hz, 1 H), 3.97 (pseudo-t, *J* = 10.3 Hz, 1 H), 3.92–3.87 (m, 2 H), 3.69–3.66 (m, 2 H), 3.60 (pseudo-t, *J* = 9.7 Hz, 1 H), 3.54 (ddd, *J* = 10.3, 4.1, 2.0 Hz, 1 H), 3.40 (pseudo-t, *J* = 9.6 Hz, 1 H), 2.08 (s, 3 H), 2.00 (s, 3 H), 1.86 (s, 3 H), 1.74 (s, 3 H), 1.59 (s, 3 H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 170.7, 170.1, 169.8, 169.4, 167.9, 167.7, 167.4, 167.1, 163.1 (d, *J* = 247.0 Hz), 137.5, 137.4, 136.2 (d, *J* = 8.6 Hz), 134.3, 134.0, 131.6, 131.2, 131.1, 128.3, 128.2, 127.8, 127.6, 127.5, 127.3, 125.3 (d, *J* = 2.9 Hz), 123.6, 123.44, 123.35, 116.0 (d, *J* = 21.5 Hz), 98.0, 97.6, 81.8, 78.0, 76.9, 76.4, 74.7, 74.5, 74.4, 73.7, 73.0, 71.9, 70.7, 68.8, 67.8, 67.5, 61.9, 54.9, 54.5, 53.6, 20.7, 20.5, 20.41, 20.37, 20.25; HRMS (ESI) *m/z* calcd for $C_{72}H_{70}FN_4O_{23}S$ $[M+NH_4]^+$, 1409.4130; found, 1409.4139.



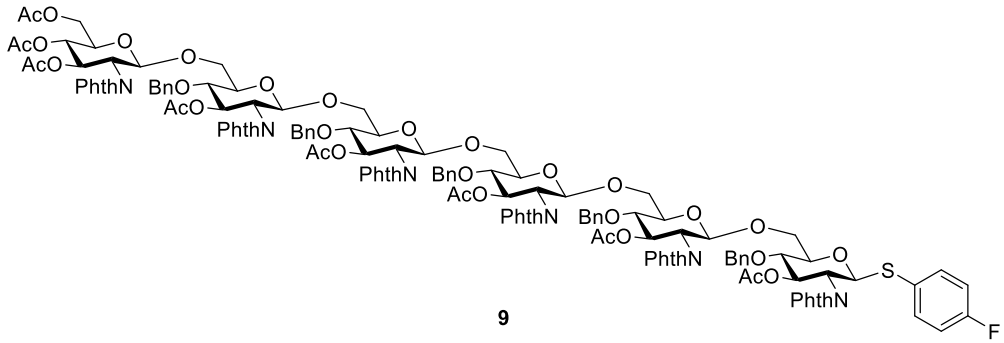
7

Preparation of glycosyl triflate from trisaccharide **6** (279 mg, 0.20 mmol) and its reaction with glycosyl acceptor **3c** (144 mg, 0.26 mmol) followed by flash chromatography gave **4-Fluorophenyl-3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-gluco-pyranosyl-(1→6)-3-*O*-acetyl-4-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→6)-3-*O*-acetyl-4-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→6)-3-*O*-acetyl-4-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (7)** in 77% yield (281 mg, 0.155 mmol). TLC R_f 0.50 (hexane/EtOAc 1:2); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.84−7.56 (m, 16 H), 7.36−7.33 (m, 2 H), 7.27−7.16 (m, 9 H), 7.08−7.03 (m, 6 H), 6.98−7.96 (m, 2 H), 5.82 (dd, *J* = 11.0, 8.9 Hz, 1 H), 5.67 (pseudo-t, *J* = 8.9 Hz, 1 H), 5.65 (pseudo-t, *J* = 8.3 Hz, 1 H), 5.58 (d, *J* = 8.3 Hz, 1 H), 5.51 (d, *J* = 8.2 Hz, 1 H), 5.47 (d, *J* = 11.0 Hz, 1 H), 5.42 (d, *J* = 8.2 Hz, 1 H), 5.41 (d, *J* = 8.2 Hz, 1 H), 5.19 (pseudo-t, *J* = 8.9 Hz, 1 H), 4.46 (d, *J* = 11.7 Hz, 1 H), 4.42 (dd, *J* = 10.3, 8.3 Hz, 1 H), 4.40 (d, *J* = 11.7 Hz, 1 H), 4.36−4.32 (m, 4 H), 4.20−4.13 (m, 4 H), 4.10−4.05 (m, 2 H), 4.02 (dd, *J* = 11.0, 1.4 Hz, 1 H), 3.92 (pseudo-t, *J* = 10.1 Hz, 1 H), 3.84 (ddd, *J* = 10.3, 4.1, 2.0 Hz, 1 H), 3.82 (dd, *J* = 11.0, 5.5 Hz, 1 H), 3.70 (dd, *J* = 11.0, 4.8 Hz, 1 H), 3.69−3.65 (m, 2 H), 3.55−3.48 (m, 3 H), 3.45 (pseudo-t, *J* = 9.7 Hz, 1 H), 3.35 (pseudo-t, *J* = 9.6 Hz, 1 H), 2.09 (s, 3 H), 2.01 (s, 3 H), 1.86 (s, 3 H), 1.69 (s, 6 H), 1.57 (s, 3 H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 170.7, 170.1, 170.02, 169.95, 169.9, 169.5, 167.9, 167.8, 167.4, 167.1, 163.2 (d, *J* = 247.0 Hz), 137.7, 137.6, 137.5, 136.6 (d, *J* = 7.2 Hz), 134.4, 134.1, 131.7, 131.5, 131.2, 131.1, 128.33, 128.25, 127.8, 127.7, 127.6, 127.5, 127.3, 124.9, 123.6, 123.5, 123.4, 116.0 (d, *J* = 21.5 Hz), 98.2, 97.44, 97.38, 81.3, 78.0, 76.4, 74.51, 74.46, 74.4, 73.8, 73.02, 72.97, 71.9, 70.7, 68.9, 68.1, 67.2, 67.1, 61.9, 55.0, 54.5, 53.6, 20.8, 20.6, 20.4, 20.3; HRMS (ESI) *m/z* calcd for $C_{95}H_{91}FN_5O_{30}S$ $[M+NH_4]^+$, 1832.5448; found, 1832.5455.



8

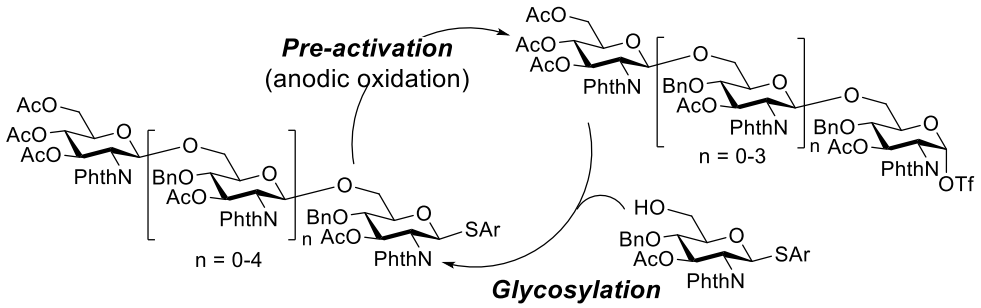
Preparation of glycosyl triflate from tetrasaccharide **7** (283 mg, 0.156 mmol) and its reaction with glycosyl acceptor **3c** (103 mg, 0.187 mmol) followed by flash chromatography and GPC gave **4-Fluorophenyl-3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→6)-3-*O*-acetyl-4-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→6)-3-*O*-acetyl-4-*O*-benzyl-2-deoxy-2-phthalimido-β-D-gluco-pyranosyl-(1→6)-3-*O*-acetyl-4-*O*-benzyl-2-deoxy-2-phthalimido-β-D-gluco-pyranosyl-(1→6)-3-*O*-acetyl-4-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (8)** in 83% NMR yield (291 mg, 0.130 mmol). TLC R_f 0.45. (hexane/EtOAc 1:2); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.84−7.53 (m, 20 H), 7.33−7.31 (m, 4 H), 7.25−7.15 (m, 12 H), 7.09−7.07 (m, 4 H), 7.05−7.02 (m, 4 H), 6.98−6.96 (m, 2 H), 5.82 (dd, *J* = 11.0, 9.7 Hz, 1 H), 5.68 (dd, *J* = 11.0, 8.9 Hz, 1 H), 5.65 (d, *J* = 11.0 Hz, 1 H), 5.63 (d, *J* = 10.3 Hz, 1 H), 5.56 (pseudo-t, *J* = 10.3 Hz, 1 H), 5.50 (d, *J* = 8.2 Hz, 1 H), 5.44 (d, *J* = 11.0 Hz, 1 H), 5.43 (d, *J* = 8.3 Hz, 1 H), 5.39 (d, *J* = 8.2 Hz, 1 H), 5.38 (d, *J* = 8.3 Hz, 1 H), 5.21 (pseudo-t, *J* = 8.9 Hz, 1 H), 4.50 (d, *J* = 11.0 Hz, 1 H), 4.43 (dd, *J* = 11.0, 8.3 Hz, 1 H), 4.42−4.31 (m, 8 H), 4.25 (d, *J* = 11.7 Hz, 1 H), 4.22−4.03 (m, 5 H), 3.95 (d, *J* = 9.6 Hz, 1 H), 3.90 (pseudo-t, *J* = 10.3 Hz, 1 H), 3.84 (ddd, *J* = 10.3, 4.1, 2.8 Hz, 1 H), 3.79−3.75 (m, 2 H), 3.66 (dd, *J* = 11.0, 4.9 Hz, 1 H), 3.64−3.60 (m, 2 H), 3.55−3.41 (m, 5 H), 3.32 (pseudo-t, *J* = 9.7 Hz, 1 H), 2.09 (s, 3 H), 2.00 (s, 3 H), 1.84 (s, 3 H), 1.68 (s, 3 H), 1.66 (s, 3 H), 1.63 (s, 3 H), 1.54 (s, 3 H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 170.7, 170.1, 170.0, 169.9, 169.8, 169.4, 167.9, 167.7, 167.4, 167.0, 163.1 (d, *J* = 247.0 Hz), 137.7, 137.62, 137.56, 137.5, 136.4 (d, *J* = 8.6 Hz), 134.4, 134.3, 134.0, 131.6, 131.4, 131.2, 131.0, 128.28, 128.26, 128.24, 128.20, 127.7, 127.60, 127.56, 127.5, 127.4, 127.3, 124.8, 123.6, 123.5, 123.4, 123.3, 115.9 (d, *J* = 21.5 Hz), 98.2, 97.51, 97.48, 97.3, 81.2, 77.9, 76.4, 74.7, 74.44, 74.37, 74.3, 73.8, 73.0, 72.9, 72.8, 71.9, 70.7, 68.9, 68.2, 67.3, 67.1, 66.8, 61.8, 54.92, 54.85, 54.5, 53.5, 20.7, 20.5, 20.4, 20.3, 20.2; HRMS (ESI) *m/z* calcd for $C_{118}H_{112}FN_6O_{37}S$ $[M+NH_4]^+$, 2256.6800; found, 2256.6825.

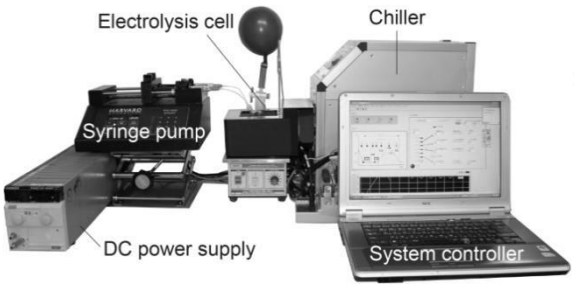


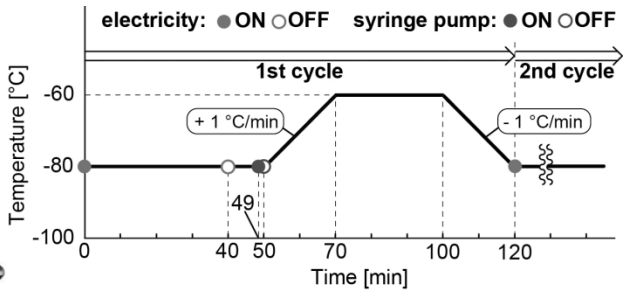
9

Preparation of glycosyl triflate from pentasaccharide **8** (141 mg, 0.063 mmol) and its reaction with glycosyl acceptor **3c** (42 mg, 0.075 mmol) followed by GPC gave **4-Fluorophenyl-3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→6)-3-*O*-acetyl-4-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→6)-3-*O*-acetyl-4-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→6)-3-*O*-acetyl-4-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→6)-3-*O*-acetyl-4-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→6)-3-*O*-acetyl-4-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (9)** in 57% (96 mg, 0.036 mmol). TLC R_f 0.40 (hexane/EtOAc 1:2); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.82−7.55 (m, 24 H), 7.31−7.28 (m, 2 H), 7.25−7.15 (m, 15 H), 7.10−7.00 (m, 10 H), 6.98−6.97 (m, 2 H), 5.81 (dd, *J* = 10.7, 8.9 Hz, 1 H), 5.67 (dd, *J* = 10.6, 8.9 Hz, 1 H), 5.64−5.60 (m, 3 H), 5.55 (dd, *J* = 10.3, 8.9 Hz, 1 H), 5.50 (d, *J* = 8.2 Hz, 1 H), 5.43 (d, *J* = 10.3 Hz, 1 H), 5.375 (d, *J* = 8.3 Hz, 1 H), 5.365 (d, *J* = 8.2 Hz, 1 H), 5.36 (d, *J* = 8.3 Hz, 1 H), 5.34 (d, *J* = 8.2 Hz, 1 H), 5.20 (dd, *J* = 10.0, 9.2 Hz, 1 H), 4.52 (d, *J* = 11.7 Hz, 1 H), 4.45−4.40 (m, 4 H), 4.36−4.30 (m, 4 H), 4.27 (d, *J* = 11.7 Hz, 1 H), 4.25 (d, *J* = 11.6 Hz, 1 H), 4.20−4.07 (m, 8 H), 4.04 (d, *J* = 10.3 Hz, 1 H), 4.01 (dd, *J* = 11.0, 1.7 Hz, 1 H), 3.94 (d, *J* = 10.3 Hz, 1 H), 3.91 (d, *J* = 10.0 Hz, 1 H), 3.88 (pseudo-t, *J* = 4.3 Hz, 1 H), 3.81 (ddd, *J* = 10.3, 4.4, 2.4 Hz, 1 H), 3.78 (dd, *J* = 11.3, 5.1 Hz, 1 H), 3.72 (dd, *J* = 11.0, 4.5 Hz, 1 H), 3.66 (dd, *J* = 11.3, 4.4 Hz, 1 H), 3.62−3.50 (m, 5 H), 3.45−3.39 (m, 4 H), 3.28 (pseudo-t, *J* = 9.7 Hz, 1 H), 2.09 (s, 3 H), 1.99 (s, 3 H), 1.85 (s, 3 H), 1.69 (s, 3 H), 1.64 (s, 3 H), 1.63 (s, 3 H), 1.61 (s, 3 H), 1.54 (s, 3 H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 170.5, 169.93, 169.85, 167.7, 169.7, 169.3, 167.8, 167.6, 167.3, 166.9, 163.0 (d, *J* = 247.0 Hz), 137.7, 137.6, 137.5, 137.3, 136.3 (d, *J* = 8.6 Hz), 134.3, 134.2, 134.0, 131.5, 131.3, 131.0, 130.9, 128.2, 128.1, 127.6, 127.5, 127.4, 127.3, 127.2, 127.0, 124.8, 123.5, 123.3, 115.8 (d, *J* = 21.5 Hz), 98.1, 97.5, 97.3, 81.2, 77.8, 76.2, 74.5, 74.4, 74.33, 74.26, 74.1, 73.7, 72.9, 72.8, 72.7, 71.8, 70.6, 68.7, 68.1, 67.2, 67.1, 66.9, 66.7, 61.7, 54.8, 54.4, 53.4, 20.6, 20.4, 20.3, 20.2, 20.1; HRMS (ESI) *m/z* calcd for $C_{141}H_{133}FN_7O_{44}S$ $[M+NH_4]^+$, 2679.8118; found, 2679.8180.

Automated synthesis of hexasaccharides

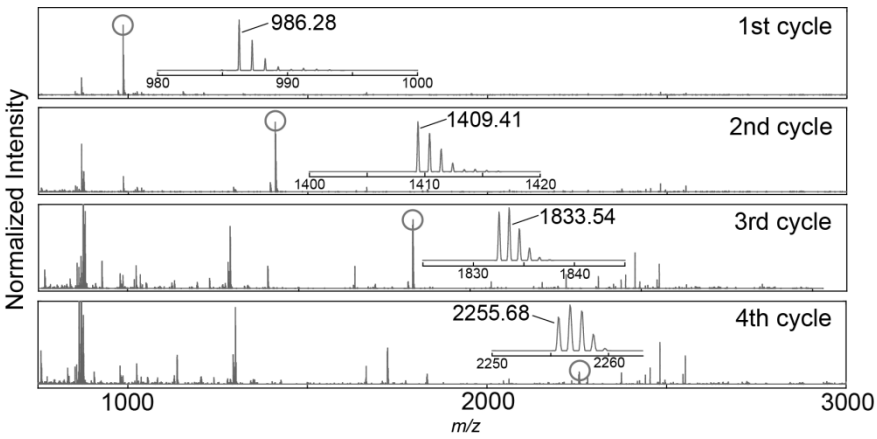






The automated synthesizer is consist of the commercially available instruments such as the chiller with a cooling bath (UCR-150, Techno Sigma), the power suppy for constant current electrolysis (PMC 350-0.2 A, KIKUSUI), the syringe pump (PHD 2000 infusion, Harvard apparatus), and the system controller (LabVIEW, National Instruments). The automated synthesis of hexasaccharide **9** was carried out in an H-type divided cell (4G glass filter) equipped with a carbon felt anode (Nippon Carbon JF-20-P7, ca. 350 mg, dried at 350 °C/1 mmHg before use) and a platinum plate cathode (20 mm×20 mm). In the anodic chamber were placed a glycosyl donor **1c** (81.8 mg, 0.15 mmol) and 0.1 M Bu_4NOTf in CH_2Cl_2 (16.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (160 μL, 1.8 mmol) and 0.1 M Bu_4NOTf in CH_2Cl_2 (16.0 mL). The constant current electrolysis (6.0 mA) was carried out at −80 °C with magnetic stirring until 1.0 F/mol of electricity was consumed. After the electrolysis, glycosyl acceptor **3c** (439 mg, 0.80 mmol) dissolved in CH_2Cl_2 (5.3 mL) was subsequently added by the syringe pump (1.0 mL for one cycle) under an argon atmosphere at −78 °C, and then the temperature was raised to −50 °C and kept for 30 min. The reaction temperature was cooled down to −80 °C and the next cycle starts automatically. After the 5th cycle, Et_3N (0.2 mL) was added and the mixture was filtered through a short column (4×3 cm) of silica gel to remove Bu_4NOTf. The removal of the solvent under reduced pressure afforded a mixture of oligosaccharides. The crude product was purified by silica gel chromatography and GPC with $CHCl_3$ as an eluent and hexasaccharide **9** was obtained in 15% yield (59.8 mg, 0.022 mmol).

MALDI-TOF-MS analysis of oligosaccharide intermediates



cycle	intermediate	$[M+NH_4]^+$ (calc/obs)	cycle	intermediate	$[M+NH_4]^+$ (calc/obs)
1st	disaccharide **4c**	986.28/986.28	3rd	tetrasaccharide **7**	1833.55/1833.54
2nd	trisaccharide **6**	1409.41/1409.41	4th	pentasaccharide **8**	2255.68/2255.68

References.

(1) (a) Ho, T.-K. *Tactics of Organic Synthesis*; Wiley: New York, 1994. (b) Feuerbacher, N.; Vögtle, F. *Top. Curr. Chem.* **1998**, *197*, 1. (c) Nokami, T.; Ohata, K.; Inoue, M.; Tsuyama, H.; Shibuya, A.; Soga, K.; Okajima, M.; Suga, S.; Yoshida, J. *J. Am. Chem. Soc.* **2008**, *130*, 10864. (d) Wang, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 5240. (e) Suga, S.; Yamada, D.; Yoshida, J. *Chem. Lett.* **2010**, *39*, 404. (f) Yoshida, J.; Saito, K.; Nokami, T.; Nagaki, A. *Synlett.* **2011**, 1189.

(2) (a) Seeberger, P. H.; Haase, W.-C. *Chem. Rev.* **2000**, *100*, 4349. (b) Seeberger, P. H. *Chem. Commun.* **2003**, 1115. (c) Seeberger, P. H. *Chem. Soc. Rev.* **2008**, *37*, 19. (d) Boltje, T. J.; Kim, J.-H.; Park, J.; Boons, G.-J. *Nat. Chem.* **2010**, *2*, 552. (e) Hsu, C.-H.; Hung, S.-C.; Wu, C.-Y.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2011**, *50*, 11872.

(3) (a) Plante, O. J.; Palmacci, E. R.; Seeberger, P. H. *Science* **2001**, *291*, 1523. (b) Werz, D. B.; Castagner, B.; Seeberger, P. H. *J. Am. Chem. Soc.* **2007**, *129*, 2770. (c) Walvoort, M. T. C.; Van den Elst, H.; Plante, O. J.; Kröck, L.; Seeberger, P. H.; Overkleeft, H. S.; Van der Marel, G. A.; Codée, J. D. C. *Angew. Chem., Int. Ed.* **2012**, *51*, 4393. (d) Ganesh, N. V.; Fujikawa, K.; Tan, Y. H.; Stine, K. J.; Demchenko, A. V. *Org. Lett.* **2012**, *14*, 3036. (e) Kröck, L.; Esposito, D.; Castagner, B.; Wang, C-C.; Bindschädler, P.; Seeberger, P. H. *Chem. Sci.* **2012**, *3*, 1617.

(4) (a) Zhang, Z.; Ollmann, I. R.; Ye, X.-S.; Wischnat, R.; Baasov, T. Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734. (b) Tanaka, H.; Adachi, M.; Tsukamoto, H.; Ikeda, T.; Yamada, H.; Takahashi, T. *Org. Lett.* **2002**, *4*, 4213. (c) Tanaka, H.; Matoba, N.; Tsukamoto, H.; Takimoto, H.; Yamada, H.; Takahashi, T. *Synlett* **2005**, 824.

(5) (a) Yamago, S.; Yamada, T.; Hara, O.; Ito, Y.; Yoshida, J. *Org. Lett.* **2001**, *3*, 3867. (b) Yamago, S.; Yamada, T.; Maruyama, T.; Yoshida, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2145. (c) Yamada, T.; Kinjyo, S.; Yoshida, J.; Yamago, S. *Chem. Lett.* **2005**, *34*, 1556. (d) Yamada, T.; Takemura, K.; Yoshida, J.; Yamago, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 7575.

(6) (a) Huang, X.; Huang, L.; Wang, H. Ye, X.-S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5221. (b) van den Bos, L. J.; Boltje, T. J.; Provoost, T.; Mazurek, J.; Overkleeft, H. S.; Van der Marel, G. A. *Tetrahedron Lett.* **2007**, *48*, 2697.

(7) For the electrochemical method in organic synthesis, see: (a) Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527. (b) Lund, H. *J. Electrochem. Soc.* **2002**, *149*, S21. (c) Sperry, J. B.; Wright, D. L. *Chem. Soc. Rev.* **2006**, *35*, 605. (d) Yoshida, J.; Kataoka, K.; Horcajada, R.; Nagaki, A. *Chem. Rev.* **2008**, *108*, 2265. (e) Waldvogel, S. R.; Elsler, B. *Electrochim. Acta* **2012**, *82*, 434.

(8) (a) Nokami, T.; Shibuya, A.; Tsuyama, H.; Suga, S.; Bowers, A. A.; Crich, D.; Yoshida, J. *J. Am. Chem. Soc.* **2007**, *129*, 10922. (b) Nokami, T.; Tsuyama, H.; Shibuya, A.; Nakatsutsumi, T.; Yoshida, J. *Chem. Lett.* **2008**, *37*, 942. (c) Nokami, T.; Shibuya, A.; Manabe, S.; Ito, Y.; Yoshida, J. *Chem. Eur. J.* **2009**, *15*, 2252. (d) Nokami, T.; Nozaki, Y.; Saigusa, Y.; Shibuya, A.; Manabe, S.; Ito, Y.; Yoshida, J. *Org. Lett.* **2011**, *13*, 1544. (e) Nokami, T.; Shibuya, A.; Saigusa, Y.; Manabe, S.; Ito, Y.; Yoshida, J. *Beilstein J. Org. Chem.* **2012**, *6*, 456. (f) Nokami, T.; Saito, K.; Yoshida, J. *Carbohydr. Res.* **2012**, *363*, 1.

(9) Chemical syntheses of PNAG see: (a) Melean, L. G.; Love, K. R.; Seeberger, P. H. *Carbohydr. Res.* **2002**, *337*, 1893. (b) Yang, F.; He, H.; Du, Y. *Tetrahedron Lett.* **2002**, *43*, 7561. (c) Gening, M. L.; Titov, D. V.; Grachev, A. A.; Gerbst, A. G.; Yudina, O. N.; Shashkov, A. S.; Chizhov, A. O.; Tsvetkov, E.; Nifantiev, N. E. *Eur. J. Org.*

Chem. **2010**, 2465. (d) Fekete, A.; Borbás, A.; Gyémánt, G.; Kandra, L.; Fazekas, E.; Ramasubbu, N.; Antus, S. *Carbohydr. Res.* **2011**, *346*, 1445.

(10) Biological studies of PNAG see: (a) Wang, X.; Preston III, J. F.; Romeo, T. *J. Bacteriol.* **2004**, *186*, 2724. (b) Sloan, G. P.; Love, C. F.; Sukumar, N.; Mishra, M.; Deora, R. *J. Bacteriol.* **2007**, *189*, 8270. (c) Izano, E. A.; Sadovskaya, I.; Vinogradov, E.; Mulks, M. H.; Velliyagounder, K.; Ragunath, C.; Kher, W. B.; Ramasubbu, N.; Jabbouri, S.; Perry, M. B.; Kaplan, J. B. *Microbial Pathogenesis* **2007**, *43*, 1; (d) Gening, M. L.; Maira-Litrán, T.; Kropec, A.; Skurnik, D.; Grout, M.; Tsvetkov, Y. E.; Nifantiev, N. E.; Pier, G. B. *Infect. Immun.* **2010**, *78*, 764.

(11) Glycosyl triflates work as thiophilic reagents which can activate thioglycoside building block to form 1,6-anhydrosugar.

(12) Li, Z.; Gildersleeve, J. C. *J. Am. Chem. Soc.* **2006**, *128*, 11612.

(13) Reactivity of glycosyl triflates of pentasaccharide might be low, because starting pentasaccharide **8** was consumed after the electrolysis.

(14) The system controller is a Windows PC equipped with the original program which was written in LabVIEW (National Instrument Corporation) to control instruments.

(15) Landström, J.; Bergström, M.; Hamark, C.; Ohlson, S.; Widmalm, G. *Org. Biomol. Chem.* **2012**, 10, 3019.

(16) Das, S. K.; Roy, J.; Reddy, K. A.; Abbineni, C. *Carbohydr. Res.* **2003**, *338*, 2237.

List of Publications

1. The Stabilized Cation Pool Method. Metal- and Oxidant-Free Benzylic C−H/Aromatic C−H Cross-Coupling
   Hayashi, R.; Shimizu, A.; Yoshida, J. *J. Am. Chem. Soc.* **2016**, *138*, 8400-8403.
   (Chapter 1)

2. Metal-Free Benzylic C–H Amination via Electrochemically Generated Benzylaminosulfonium Ions
   Hayashi, R.; Shimizu, A.; Song, Y.; Ashikari, Y.; Nokami, T.; Yoshida, J. *Chem. Eur. J.* **2017**, *23*, 61-64.
   (Chapter 2)

3. Switching the Reaction Pathways of Electrochemically Generated β-Haloalkoxysulfonium Ions – Synthesis of Halohydrins and Epoxides
   Shimizu, A.; Hayashi, R.; Ashikari, Y.; Nokami, T.; Yoshida, J. *Beilstein J. Org. Chem.* **2015**, *11*, 242-248.
   (Chapter 3)

4. Metal- and Oxidant-Free Alkenyl C−H/Aromatic C−H Cross-Coupling Using Electrogenerated Iodosulfonium Ions
   Hayashi, R.; Shimizu, A.; Davies, J.; Willis, C.; Yoshida, J. in preraration.
   (Chapter 4)

5. Automated Solution-Phase Synthesis of Oligosaccharides via Iterative Electrochemical Assembly of Thioglycosides
   Nokami, T.; Hayashi,R.; Saigusa, Y.; Shimizu, A.; Liu, C.-Y.; Mong, K.-K. T.; Yoshida, J. *Org. Lett.* **2013**, *15*, 4520-4523.
   (Chapter 5)

Other Publications

1. Automated Electrochemical Assembly of the Protected Potential TMG-chitotriomycin Precursor Based on Rational Optimization of the Carbohydrate Building Block.
   Nokami, T.; Isoda, Y.; Sasaki, N.; Takaiso, A.; Hayase, S.; Itoh, T.; Shimizu, A.; Hayashi, R.; Yoshida, J. *Org. Lett.* **2015**, *17*, 1525-1528.

2. Reaction Integration Using Electrogenerated Cationic Intermediates.
   Yoshida, J.; Shimizu, A.; Ashikari, Y.; Morofuji, T.; Hayashi, R.; Nokami, T.; Nagaki, A. *Bull. Chem. Soc. Jpn.* **2015**, *88*, 763-775.

3. Electrogenerated Cationic Reactive Intermediates: The Pool Method and Further Advances.
   Yoshida, J.; Shimizu, A.; Hayashi, R. *Chem. Rev.* accepted.