Bipolar Electrochemical Fluorination of Triphenylmethane and Bis(phenylthio)diphenylmethane Derivatives in a U-shaped Cell

Naoki SHIDA,a,§ Elena VILLANI,a,§ Mokurai SANUKI,a Kazuhiro MIYAMOTO,a Akihiro GOTOU,b Tomohiro ISOGAI,b,§ Akiyoshi YAMAUCHI,b Toshio FUCHIGAMI,a,§ Ikuyoshi TOMITA,a,§ and Shinsuke INAGIa,c,*,§

a Department of Chemical Science and Engineering, School of Materials and Chemical Technology, Tokyo Institute of Technology, 4259 Nagatsuta-cho, Midori-ku, Yokohama 226-8502, Japan
b Daikin Industries Ltd., 1-1 Nishi-Hitotsuya, Settsu, Osaka 566-8585, Japan
c PRESTO, Japan Science and Technology Agency (JST), 4-1-8 Honcho, Kawaguchi, Saitama 332-0012, Japan

* Corresponding author: inagi@cap.mac.titech.ac.jp

© The Author(s) 2021. Published by ECSJ. This is an open access article distributed under the terms of the Creative Commons Attribution Non-Commercial Share Alike 4.0 License (CC BY-NC-SA, http://creativecommons.org/licenses/by-nc-sa/4.0/), which permits non-commercial reuse, distribution, and reproduction in any medium by share-alike, provided the original work is properly cited. For permission for commercial reuse, please email to the corresponding author. [DOI: 10.5796/electrochemistry.21-00074].

This is the final version of an authors’ manuscript, submitted by the author(s) and accepted for publication after peer review and technical editing by the Editorial Board of The Electrochemical Society of Japan. This manuscript may contain minor errors or incomplete designs that do not affect the judgment for publication. It is the responsibility of the authors to correct any errors in the Just Accepted manuscript during galley proof review.

§ ECSJ Active Member
S. Inagi orcid.org/0000-0002-9867-1210
Bipolar Electrochemical Fluorination of Triphenylmethane and Bis(phenylthio)diphenylmethane Derivatives in a U-shaped Cell

Naoki Shida, Elena Villani, Mokurai Sanuki, Kazuhiro Miyamoto, Akihiro Gotou, Tomohiro Isogai, Akiyoshi Yamauchi, Toshio Fuchigami, Ikuyoshi Tomita, Shinsuke Inagi

a. Department of Chemical Science and Engineering, School of Materials and Chemical Technology, Tokyo Institute of Technology, 4259 Nagatsuta-cho, Midori-ku, Yokohama 226-8502, Japan

b. Daikin Industries Ltd., 1-1 Nishi-Hitotsuya, Settsu, Osaka 566-8585, Japan.

c. PRESTO, Japan Science and Technology Agency (JST), 4-1-8 Honcho, Kawaguchi, Saitama 332-0012, Japan

*Corresponding Author: inagi@cap.mac.titech.ac.jp

§. ECSJ Active Member
Abstract

Electrochemical fluorination of triphenylmethane derivatives and bis(phenylthio)diphenylmethane derivatives by using a split bipolar electrode is described. The reaction conditions for the fluorination of triphenylmethane were further optimized from the previous report to obtain the desired product in quantitative yields. Fluorination reaction cleanly proceeded under a wide range of voltage applied between the driving electrodes, from 25 to 100 V. Use of lower voltage is preferable in terms of energy efficiency, whereas higher voltage shortened the reaction time. The optimized conditions were applicable to the fluorination of other triphenylmethane derivatives and bis(phenylthio)diphenylmethane derivatives to give the corresponding fluorinated products.

Keywords: Electrosynthesis, Bipolar Electrochemistry, Anodic Fluorination, Organic Electrochemistry
Fluorine-containing organic molecules are an important class of chemicals in medicinal and agricultural chemistry.\textsuperscript{1–3} The introduction of fluorine atom often improves the efficacy of medicines and agrochemicals, thus the methodology for the selective partial fluorination is still an important challenge in organic chemistry. A variety of methodologies have been proposed to introduce fluorine atoms into organic molecules by using fluorinating reagents\textsuperscript{4–6} often in combination with transition metal catalysts.\textsuperscript{5–8} Electrochemical partial fluorination is also a highly potent methodology.\textsuperscript{9} Most electrochemical fluorinations are achieved by an umpolung strategy using oxidation of a target substrate on an anode, followed by the nucleophilic attack of fluoride ions derived from ionic liquid of HF-amine complex\textsuperscript{10} or other fluorine sources.\textsuperscript{11,12} Electrochemical fluorination is an environmentally friendly and safe method since neither harsh reaction conditions nor equimolar of oxidants are required. However, one inevitable drawback of the electrolysis is the use of a high concentration of supporting electrolytes (> 0.1 M), which results in a large amount of chemical waste as well as the additional steps for purification.

Recently, our group has reported the electrochemical partial fluorination of organic compounds based on bipolar electrochemistry.\textsuperscript{13} A bipolar electrode (BPE) is a wireless electrode embedded in between a pair of driving electrodes, and is driven by the influence of an external electric field.\textsuperscript{14–16} According to the principle that a lower concentration of supporting salts is preferred for the efficient formation of an electric field, we have reported the electrochemical fluorination of triphenylmethane (1a) with only 5 mM of cesium fluoride (CsF) used both as a supporting electrolyte and a fluorine
Herein, we report the quantitative fluorination of 1a under the further optimized reaction conditions, and its application to the reaction of triphenylmethane derivatives. We also successfully expanded the scope of this system to fluorination of bis(phenylthio)diphenylmethane derivatives.

In the previous study, we reported the bipolar electrochemical fluorination of 5 mM of 1a in 5 mM CsF/0.6 M poly(ethylene glycol) (PEG, $M_n$~600)/acetonitrile (MeCN) electrolyte under the application of 100 V between the driving electrodes, where PEG was used to solubilize CsF. A pair of platinum (Pt) plates were used for driving electrodes in a U-shaped cell (Figs. 1a and S1 in the Supporting Information). Another pair of Pt plates were interconnected by wires with an ammeter to form a split BPE (s-BPE) configuration, so that the current flowing between BPE-anode and BPE-cathode can be monitored.

Figs. S2 and S3 show the experimentally measured IR-drop and the computationally simulated electric field using COMSOL Multiphysics, respectively, in the U-shaped cell. The steep IR-drop was observed around the edge of the shielding wall, which enables the efficient application of an electric field to the s-BPE. Since the s-BPE has an equipotential, an interfacial potential difference between the s-BPE and the solution (anodic and cathodic overpotentials, $\eta_a$ and $\eta_c$, respectively), can be the driving forces for electrochemical reactions (Fig. 1b). We recently developed an analytical tool for visualizing an electrode potential on BPEs using luminol/H$_2$O$_2$-based electrogenerated chemiluminescence (ECL). The ECL emission derived from an electrochemical oxidation of luminol
can visualize that a certain potential range is generated on a part of BPEs during its operation. For the U-shaped cell we observed a relatively uniform anodic potential on a s-BPE anode as estimated by the IR-drop measurement and COMSOL simulation above. This result corroborates that target oxidation reaction can take place on almost whole BPE anode in the U-shaped s-BPE system in this study.

(Figure 1)

With the above proof that the s-BPE works as expected, we first revisited the optimization of the reaction conditions. The anodic fluorination of 1a was conducted with the s-BPE with the electrolyte containing 5 mM CsF, 30 mM PEG (Mn~600) in a MeCN solution until the charge passed through s-BPE reached 4 F/mol (Table 1). In Entry 1, the anodic fluorination under a still condition proceeded to give the corresponding fluorinated product, trityl fluoride 2a, in a low yield (14%). The electrolysis under stirring improved the yield of the fluorinated product, due to the enhanced mass transfer in the reaction mixture (Table 1, Entry 2). The yield was moderate since the amount of the fluorine source used was equimolar to that of the substrate. Then, the effect of concentration of 1a was examined. The decrease of concentration of 1a to 2 mM, which corresponds to 0.4 eq of CsF, resulted in giving the desired product in 94% yield (Table 1, Entry 3). When a lower concentration (1 mM) of the substrate was employed, the yield decreased (Table 1, Entry 4), presumably due to the lower chance for the substrate to react at the electrode surface. As a control experiment, the electrolysis was also conducted in the absence of the s-BPE for the same period of time to that in the presence of the s-BPE, resulting in the lower yields of the product in each entry (Table S1).
We next performed the anodic fluorination of 1a under the application of lower voltages. As reported in our previous paper,\textsuperscript{13} we observed sufficient potential difference for proceeding the redox reactions (ca. 3.5 V estimated by voltammetry) even when lower DC voltages were applied between the driving electrodes (Table S2). To our delight, the fluorinated product was obtained in a quantitative yield even down to 25 V, while the time period required for the reaction became longer at the lower voltage, due to the slower reaction kinetics on the electrodes (Table 2). Even so, the lower voltage is advantageous in terms of energy consumption and reaction selectivity avoiding overreactions; thus, the optimized conditions should be determined based on the balance of these factors. In this study, we set 100 V as a standard condition to complete the reaction in a shorter time period.

In addition to triphenylmethane substrate, its phenylthio derivative, trityl phenyl sulfide (3) was examined for the anodic fluorination to give fluorodesulfurization product 2a (Scheme 1). A phenylthio group works as an electroauxiliary to reduce the oxidation potential of triphenylmethane and as well as a good leaving group. 5 mM of 2a resulted in 29 % of the product yield, while the yield of the fluorinated product was significantly improved up to 86 % by lowering the concentration of 3 to 2 mM. Relatively lower product yield is presumably due to the redox shuttling of the eliminated phenylthio moiety in the undivided U-shaped cell.
With the optimal conditions in hand, we then performed the anodic fluorination of triphenylmethane derivatives 1b–1e having various para-substituents on one aryl ring (Table 3). 1b–1e were prepared according to the reported procedure.21 1b–1e were successfully fluorinated in moderate yields. The lower yields compared to 1a was attributed to the higher oxidation potential of all these compounds as evidenced by the cyclic voltammetry measurement (Fig. S4), which indicates the lower stability of the resulting cationic intermediates.

We next envisioned the anodic fluorination of diphenylmethane derivatives. The first attempt of C-H fluorination of diphenylmethane gave no desired product under any conditions examined, presumably due to its high oxidation potential and low stability of its cationic intermediates. Thus, we turned our attention to use bis(phenylthio)diphenylmethane derivatives 4a–4d, bearing the phenylthio electroauxiliary (Table 4), which were prepared according to the reported procedure.22 Non-substituted substrate 4a successfully gave mono-fluorinated product 5a in 81 % yield (Table 4, Entry 1). The fluorination also proceeded under the application of lower voltage (75 and 50 V), although the yield of 5a decreased (Table 4, Entries 2 and 3). Cl- and F-substituted compounds 4b and 4c gave mono-fluorinated product 5b and 5c, respectively, with slightly lower yields (Table 4, Entries 4 and 5). In contrast, methoxy-substituted substrate 4d preferably gave difluorinated product 6d while mono-fluorinated product 5d was not detected (Table 4, Entry 6). Substrate 4d, which possesses electron-
donating methoxy groups in its structure, showed a lower oxidation potential compared to 4a–4c (Fig. S5), and thus the second fluorination proceeded successfully. Considering the mass balance of the product, mono-fluorinated 5d might be once produced. However, due to the electron-donating methoxyphenyl groups, it seems to be unstable to easily release the fluoride ion and the PhS moiety, resulting in the formation of diarylketone during work-up process.

(Table 4)

In conclusion, we have demonstrated the electrochemical fluorination of triphenylmethane derivatives and bis(diphenylthio)diphenylmethane derivatives with using s-BPE in the U-shaped cell. The improved reaction conditions enabled quantitative fluorination of triphenylmethane 1a, and the fluorination reaction proceeded with a wide range of applied voltage (25 to 100 V). The anodic fluorination of triphenylmethane derivatives and bis(diphenylthio)diarylmethane derivatives having a variety of substituents were also successfully demonstrated. This study indicates the possibility of the bipolar electrochemical process as an environmentally benign methodology for the production of fluorine-containing fine chemicals.

Acknowledgments

This work was supported by Kakenhi Grant-in-Aids (JP17H03095, JP19F19769 and JP20H02796) from the Japan Society for the Promotion of Science (JSPS) and PRESTO (No. JPMJPR18T3) of the Japan Science and Technology Agency (JST).
References

1. S. Purser, P. R. Moore, S. Swallow, and V. Gouverneur, *Chem. Soc. Rev.*, **37**, 320 (2008).

2. Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Acení, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.*, **116**, 422 (2016).

3. T. Fujiwara and D. O’Hagan, *J. Fluorine Chem.*, **167**, 16 (2014).

4. C. Ni, M. Hu, and J. Hu, *Chem. Rev.*, **115**, 765 (2015).

5. T. Liang, C. N. Neumann, and T. Ritter, *Angew. Chem. Int. Ed.*, **52**, 8214 (2013).

6. P. A. Champagne, J. Desroches, J. D. Hamel, M. Vandamme, and J. F. Paquin, *Chem. Rev.*, **115**, 9073 (2015).

7. C. Hollingworth and V. Gouverneur, *Chem. Commun.*, **48**, 2929 (2012).

8. M. G. Campbell and T. Ritter, *Chem. Rev.*, **115**, 612 (2015).

9. T. Fuchigami and S. Inagi, *Acc. Chem. Res.*, **53**, 322 (2020).

10. T. Fuchigami and S. Inagi, *Chem. Commun.*, **47**, 10211 (2011).

11. T. Sawamura, K. Takahashi, S. Inagi, and T. Fuchigami, *Angew. Chem. Int. Ed.*, **51**, 4413 (2012).

12. M. Balandeh, A. Rios, N. Allison, S. Shirazi, A. Gomez, L. Rambaran, T. Holloway, and S. Sadeghi, *ChemElectroChem*, **5**, 3353 (2018).

13. K. Miyamoto, H. Nishiyama, I. Tomita, and S. Inagi, *ChemElectroChem*, **6**, 97 (2019).

14. G. Loget, D. Zigah, L. Bouffier, N. Sojic, and A. Kuhn, *Acc. Chem. Res.*, **46**, 2513 (2013).

15. S. E. Fosdick, K. N. Knust, K. Scida, and R. M. Crooks, *Angew. Chem. Int. Ed.*, **52**, 10438 (2013).
16. N. Shida, Y. Zhou, and S. Inagi, *Acc. Chem. Res.*, **52**, 2598 (2019).

17. S. Inagi, Y. Ishiguro, M. Atobe, and T. Fuchigami, *Angew. Chem. Int. Ed.*, **49**, 10136 (2010).

18. Y. Ishiguro, S. Inagi, and T. Fuchigami, *Langmuir*, **27**, 7158 (2011).

19. S. Inagi, Y. Ishiguro, N. Shida, and T. Fuchigami, *J. Electrochem. Soc.*, **159**, G146 (2012).

20. E. Villani and S. Inagi, *Anal. Chem.*, **93**, 8152 (2021).

21. H. S. P. Rao and A. V. B. Rao, *Beilstein J. Org. Chem.*, **12**, 496 (2016).

22. T. Yoshiyama and T. Fuchigami, *Chem. Lett.*, **21**, 1995 (1992).
Figure 1. (a) Schematic illustration of a U-shaped cell equipped with Pt driving electrodes and s-BPE (Pt plates connected with an ammeter). (b) An expected potential profile on the BPE surfaces for the U-shaped configuration; \( \eta_a \) and \( \eta_c \) symbols indicate the anodic and cathodic overpotential, respectively.
Table 1. Bipolar electrochemical fluorination with different concentration of 1a

| Entry | Concentration of 1a [mM] | Reaction time [min] | Charge [F/mol]^a | Yield of 2a [%]^b |
|-------|--------------------------|---------------------|------------------|------------------|
| 1^c   | 5                        | 230                 | 3.8              | 14               |
| 2     | 5                        | 200                 | 3.8              | 46               |
| 3     | 2                        | 60                  | 4.3              | 94               |
| 4     | 1                        | 30                  | 4.6              | 37               |

^a) Charge passed through the s-BPE. ^b) ^19^F NMR yield. ^c) Without stirring.
Table 2. Bipolar electrochemical fluorination of 1a under the application of various voltages

![Chemical structure](image)

| Entry | Driving voltage [V] | Reaction time [min] | Charge [F/mol] \(a\) | Yield of 2a [%] \(b\) |
|-------|----------------------|----------------------|-----------------------|-----------------------|
| 1     | 100                  | 60                   | 4.3                   | 94                    |
| 2     | 75                   | 65                   | 4.3                   | > 99                  |
| 3     | 50                   | 120                  | 4.1                   | > 99                  |
| 4     | 25                   | 340                  | 4.3                   | > 99                  |

\(a\) Charge passed through the s-BPE. \(b\) \(^{19}\)F NMR yield.
**Scheme 1.** Bipolar electrochemical fluorination of trityl phenyl sulfide 3

\[
\text{3} \xrightarrow{-e, -1/2 \text{ PhSSPh}, +F^-} \text{2a}
\]

- 5 mM CsF/30 mM PEG (M_w ~ 600)/MeCN
- r.t., 4 F/mol, Pt s-BPE
- 100 V Pt driving electrodes

5 mM: 29% yield
2 mM: 86% yield
Table 3. Bipolar electrochemical fluorination of triphenylmethane derivatives

![Chemical structures and reaction scheme](image-url)

| Entry | X (substrate) | Reaction time [min] | Charge [F/mol] | Yield [%] (product) |
|-------|---------------|---------------------|----------------|-------------------|
| 1     | Br (1b)       | 64                  | 4.2            | 48 (2b)           |
| 2     | Cl (1c)       | 58                  | 4.1            | 60 (2c)           |
| 3     | F (1d)        | 58                  | 4.1            | 59 (2d)           |
| 4     | CF₃ (1e)      | 60                  | 3.8            | 58 (2e)           |

a) Charge passed through the s-BPE. b) ¹⁹F NMR yield.
Table 4. Bipolar electrochemical fluorination of bis(phenylthio)diphenylmethane derivatives

![Chemical structure diagram: Y-Ph-SPh-Y, 4a-4d (2 mM) reacting with \( n \) electrons and \( n/2 \) PhSSPh to form 5a-5d and 6a-6d.]

| Entry | Y (substrate) | Driving Voltage [V] | Reaction time [min] | Charge [F/mol]a | Yield [%]b |
|-------|---------------|---------------------|---------------------|----------------|-----------|
| 1     | H (4a)        | 100                 | 45                  | 3.9            | 81 (5a)   |
| 2     | H (4a)        | 75                  | 63                  | 4.1            | 67 (5a)   |
| 3     | H (4a)        | 50                  | 100                 | 4.0            | 57 (5a)   |
| 4     | Cl (4b)       | 100                 | 50                  | 4.0            | 45 (5b)   |
| 5     | F (4c)        | 100                 | 50                  | 4.2            | 35 (5c)   |
| 6     | OMe (4d)      | 100                 | 45                  | 4.0            | – (5d)    |

a) Charge passed through the s-BPE. b) \(^{19}\)F NMR yield.

5 mM CsF/30 mM PEG (M<sub>n</sub>~600)/MeCN r.t., 4 F/mol, Pt s-BPE 100 V Pt driving electrodes Y = H, Cl, F, OMe
Graphical Abstract