



ChemComm

Rapid Approach to Cationic Organic Triflates Based on Flash Electrolysis in Flow

Journal:	<i>ChemComm</i>
Manuscript ID	CC-COM-04-2022-002344.R1
Article Type:	Communication

SCHOLARONE™
Manuscripts

COMMUNICATION

Rapid Approach to Cationic Organic Triflates Based on Flash Electrolysis in Flow

Masahiro Takumi,^a Hodaka Sakae,^a Daiki Shibasaki^a and Aiichiro Nagaki^{*ab}

Received 00th April 2022,
Accepted 00th April 2022

DOI: 10.1039/x0xx00000x

Flash (extremely fast) electrochemical generation of unstable arylbis(arythio)sulfonium triflates [ArS(ArSSAr)]⁺ [OTf]⁻ that are unsuitable for accumulation in batch process was achieved within 10 sec in a divided-type flow electrochemical reactor, enabling one-flow access to vinyl triflates, short-lived oxocarbenium triflates and glycosyl triflates.

Organic trifluoromethanesulfonate (triflate, [OTf]⁻) species are widely utilized in organic synthesis.¹ They serve as highly reactive cationic intermediates due to the outstanding nucleofugal property of triflate and play a crucial role in the construction of diverse molecular skeletons.² Traditionally, they are generated in the presence of nucleophiles by the treatment of precursors with chemical activators such as metal triflates,³ triflic acid (TfOH)⁴ and triflic anhydride (Tf₂O)⁵ and immediately trapped to suppress the decomposition.

On the other hand, electrochemical oxidation is a powerful and straightforward method for generating reactive cationic intermediates.⁶ This technique, involving forced electron removal between the anode and substrate, uses electrons as a mild and traceless activator, enabling irreversible generation. Among them, the cation pool method that involves the generation and accumulation of the organic cations in the absence of nucleophiles have been widely studied due to its flexibility and versatility of nucleophiles.⁷ However, the applicability of this method is strongly influenced by the stability of generated cations, and long electrolysis time caused by a small surface-to-volume ratio of the electrodes in batch reactors resulted in the decomposition of the cation. In fact, to the best of our knowledge, detailed studies on cationic organic triflate intermediates in the cation pool method have been limited to those on glycosyl triflates.⁸ Moreover, although the indirect strategy that allows rapid generation of organic cations mediated by anodically generated reactive species have been

developed by Yoshida's group,⁹ this strategy must use accumulable mediators with counter anions [BF₄]⁻ or [B(C₆F₅)₄]⁻.

To overcome this challenge, we have recently focused on the combined reactor¹⁰ of flow chemistry and electrochemistry and developed a divided-type flow electrochemical reactor that can perform flash electrolysis.¹¹ This enables flash generation of short-lived carbocations and subsequent reactions with nucleophiles before the decomposition of the cations. On the basis of these backgrounds, we report herein proof-of-principle study on the flash electrochemical generation of highly unstable arylbis(arythio)sulfonium triflates within 10 sec in the flow electrochemical reactor, allowing rapid access to various organic triflates including vinyl triflates, oxocarbenium triflates and glycosyl triflates.

Initially, we examined the electrochemical generation and accumulation of a [ArS(ArSSAr)]⁺ [OTf]⁻ (Ar = *p*-FC₆H₄) using a batch electrochemical reactor according to the cation pool method (Table 1 (a)). Yoshida et al. reported that [ArS(ArSSAr)]⁺ [BF₄]⁻ was accumulable in solution at -78 °C and reacted with aromatic nucleophiles to give arylthiolated products in excellent yields.¹² Diaryldisulfide ArSSAr (Ar = *p*-FC₆H₄) **1** in CH₂Cl₂ was anodically oxidized until 0.67 F/mol of electricity was consumed using Bu₄NOTf as a supporting electrolyte; 0.67 F/mol is the theoretical amount of electricity required to convert ArSSAr to [ArS(ArSSAr)]⁺ (Scheme S1). After electrolysis, a CH₂Cl₂ solution of 1,3,5-trimethoxybenzene **2** was added and the mixture was stirred for 10 min, followed by treatment with triethylamine to give arylthiolated products **3** and **4**. Trials under cryogenic conditions at -78 °C and -50 °C yielded unsatisfactory results (Table 1, entries 1 and 2). Moreover, when the electrolysis temperature was increased to 0 °C, a significant decrease in the yield was observed (Table 1, entry 3). These results suggest that [ArS(ArSSAr)]⁺ [OTf]⁻ is highly unstable and unsuitable for accumulation in a batch process that requires prolonged electrolysis in contrast to [ArS(ArSSAr)]⁺ [BF₄]⁻ and [ArS(ArSSAr)]⁺ [B(C₆F₅)₄]⁻ (Table S1, entries 4-7).

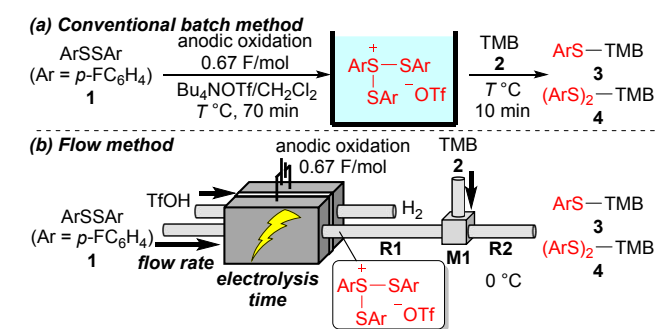
Subsequently, we investigated the flash generation of [ArS(ArSSAr)]⁺ [OTf]⁻, followed by the reaction with **2** using a flow electrochemical reactor system (Table 1 (b)).

^a Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Kyoto, 615-8510, Japan.

^b Current address: Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo, 060-0810, Japan.

E-mail: nagaki@sci.hokudai.ac.jp

† Electronic Supplementary Information (ESI) available: See DOI: 10.1039/x0xx00000x

Table 1 Electrochemical generation and reaction of $[\text{ArS}(\text{ArSSAr})]^+ [\text{OTf}]^-$ 

entry	method	temperature <i>T</i> [°C]	flow rate [mL/min]	electrolysis time	yield of 3 [%] ^a	yield of 4 [%] ^a
1	batch	-78	-	70 min	61	0
2	batch	-50	-	70 min	58	2
3	batch	0	-	70 min	44	3
4	flow	0	0.6	42 sec	59	5
5	flow	0	1.0	25 sec	84	4
6	flow	0	2.0	13 sec	91	3
7	flow	0	3.0	8 sec	96	1

Batch conditions: H-type divided cell, **1** (0.50 mmol), current = 8 mA, electrolysis time = ca. 70 min, **2** (2.5 mmol). Flow conditions: **1** (0.05 M in Bu₄NOTf/CH₂Cl₂, 0.10 mmol), TfOH (0.05 M in Bu₄NOTf/CH₂Cl₂), **2** (0.34 M in CH₂Cl₂, 5 eq. for [ArS(ArSSAr)]⁺ [OTf]⁻), residence time in R1 = 12 sec, residence time in R2 = 8 sec, see ESI for more detailed conditions. ^a Determined by GC analysis. TMB = 1,3,5-trimethoxybenzene.

The flow electrochemical reactor system consists of a divided-type flow electrochemical reactor and microreactors (see ESI[†] for details). For the flow system, a solution of **1** in Bu₄NOTf/CH₂Cl₂ was introduced by syringe pumping into the anodic chamber equipped with a carbon felt anode. A solution of TfOH in Bu₄NOTf/CH₂Cl₂ was introduced into the cathodic chamber, which was equipped with a platinum plate cathode as an electrolysis promoter. Constant-current electrolysis was performed at 0 °C, and [ArS(ArSSAr)]⁺ [OTf]⁻ was generated in the anodic compartment and quickly transferred to a microtube reactor (R1). The resulting solution was then mixed with solution of **2** in a micromixer (M1) to give products **3** and **4**. The flow rate was varied to evaluate the effect of flash generation. The initial trial with a flow rate of 0.6 mL/min gave a moderate yield, even at 0 °C (Table 1, entry 4). As the flow rate was gradually increased to 3.0 mL/min, a significant increase in yield was observed (Table 1, entries 5–7). It is noteworthy that an almost quantitative yield was obtained at 3.0 mL/min, when the electrolysis was completed in 8 sec. These results clearly show that flash electrolysis in the flow reactor was effective for using highly unstable [ArS(ArSSAr)]⁺ [OTf]⁻. In addition, [ArS(ArSSAr)]⁺ [BF₄]⁻ and [B(C₆F₅)₄]⁻ were successfully generated with the same flow setup by changing the supporting electrolytes, as shown in Figure 1. Comparing the yields between 0.6 and 3.0 mL/min, [ArS(ArSSAr)]⁺ [OTf]⁻ was more unstable than [ArS(ArSSAr)]⁺ [BF₄]⁻. When Bu₄NB(C₆F₅)₄ was used as a supporting electrolyte, although almost no significant yield improvement was observed, [ArS(ArSSAr)]⁺ with bulky weakly coordinating anions could be used in subsequent reactions quickly under the mild condition.

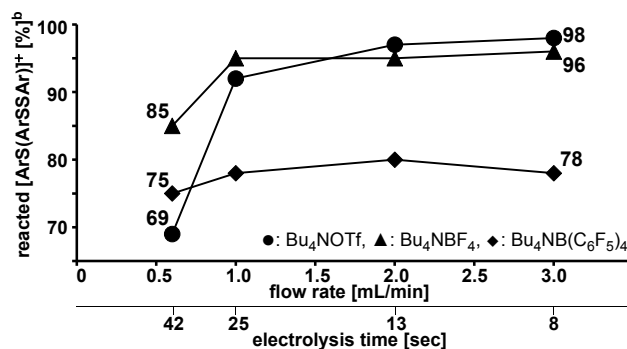
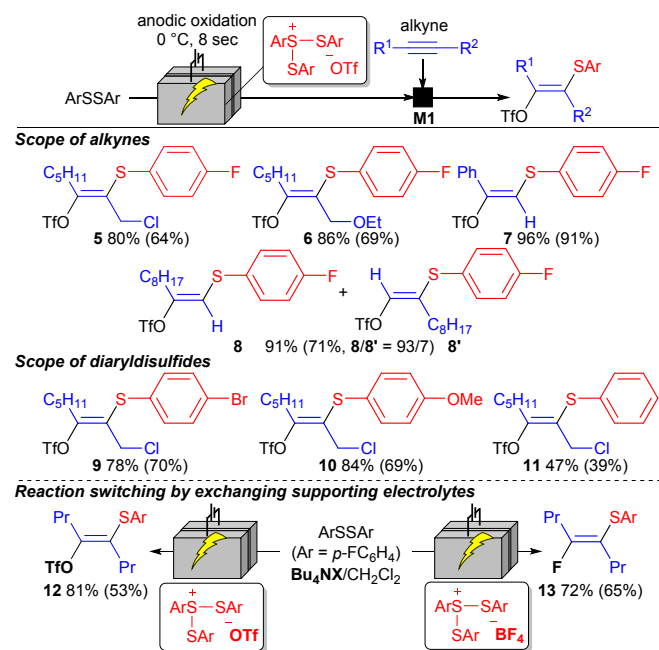


Fig. 1 Effect of supporting electrolyte and electrolysis time for generation and reaction of $[\text{ArS}(\text{ArSSAr})]^+$ by flow electrochemical reactor system. ^a Conditions: **1** (0.05 M in Bu₄NX (X = OTf, BF₄ or B(C₆F₅)₄)/CH₂Cl₂, 0.10 mmol), TfOH (0.05 M in Bu₄NOTf/CH₂Cl₂), **2** (0.34 M in CH₂Cl₂, 5 eq. for [ArS(ArSSAr)]⁺) See ESI for more detailed conditions. ^b Reacted [ArS(ArSSAr)]⁺ was calculated from the yields of product **3** and **4**.

We then focused on the reaction of this cation with alkynes. Electrochemically generated [ArS(ArSSAr)]⁺ [BF₄]⁻ (Ar = *p*-FC₆H₄) is known as an efficient thiofluorinating reagent for alkynes to synthesize vinyl triflates.¹³ In this reaction, [BF₄]⁻ serves as a fluoride donor. Thus, we hypothesized that the reaction of [ArS(ArSSAr)]⁺ [OTf]⁻ with alkynes could provide vinyl triflates. To confirm the hypothesis, the preliminary experiment of reaction of [ArS(ArSSAr)]⁺ [OTf]⁻ with 1-chloro-2-octyne was conducted to obtain the desired product **5** in good yield (Scheme 1, see Table S3).



Scheme 1 Reactions of anodically generated $[\text{ArS}(\text{ArSSAr})]^+ [\text{OTf}]^-$ with alkynes. Reactions were performed on a 0.07–0.34 mmol scale based on the alkyne. See ESI for each condition. Yields are determined by ¹H NMR, and the numbers in parentheses are the yields of the isolated compound.

With the standard condition in hand, the scope was investigated (Scheme 1). Various unsymmetrical alkynes were converted to the corresponding vinyl triflates **6–8** in good to excellent yields. The E-selectivity of the products indicates that

the formation of an episulfonium ion intermediate and subsequent anti-addition of $[\text{OTf}]^-$ proceeded as previously reported.^{13,14} Notably, the reaction with the unsymmetrical alkynes showed the high regioselectivity, presumably because the selective nucleophilic attack of $[\text{OTf}]^-$ occurred at the position where a more stable cation was generated. Next, scope of diaryldisulfides was explored; *p*-bromo and *p*-methoxy diaryldisulfide gave the desired products **9** and **10** in good yields. When diphenyldisulfide was used, the yield of **11** was relatively low because of the oligomerization of the cation. In addition, it is possible to switch the product between the vinyl triflate **12** and the vinyl fluoride **13** by exchanging supporting electrolyte, demonstrating the applicability of this methodology to various alkyne difunctionalization.

Having confirmed that $[\text{ArS}(\text{ArSSAr})]^+ [\text{OTf}]^-$ serves as an useful building block, we used this intermediate as an activator for thioacetals. Electrooxidatively generated $[\text{ArS}(\text{ArSSAr})]^+ [\text{OTf}]^-$ is known to serve as a chemical activator for thioacetals,⁹ dithioacetals,¹⁵ and *N,S*-acetals,¹⁶ resulting in the corresponding carbocations. Consequently, we designed an integrated flow electrochemical reactor system, as shown in Figure 2 (a), to generate oxocarbenium triflate. Thus, the electrochemical generation of $[\text{ArS}(\text{ArSSAr})]^+ [\text{OTf}]^-$ was carried out in flow, and a CH_2Cl_2 solution of thioacetal **14** was mixed in **M1** to generate oxocarbenium triflate, which was reacted with enol silyl ether in **M2** to give the coupling product **15**. The reactions were performed at various temperatures and residence times in **R2** (t^{R2}) to evaluate the stability of oxocarbenium triflate. The yields of **15** were plotted against temperature and t^{R2} as a map with colored data points (Figure 2 (b)). The map indicates that the yields depend significantly on the residence time in **R2** and the temperature. At -75°C , a significant amount of **14** was recovered in a short residence time (e.g., 0.37 and 1.3 s). However, an increase in t^{R2} resulted in an increase in the conversion of **14**, giving **15** in 93% yield at a t^{R2} of 5.2 s. However, a further increase in t^{R2} caused a decrease in yield because of the decomposition of **15**, suggesting the high instability of the cation. At -50°C , faster increases and decreases in yield were observed, suggesting faster generation and degradation of the intermediate. At longer residence times in **R2**, oligomerized byproducts were detected by ESI-MS, indicating a β -elimination of the generated cation and an addition reaction with the remaining one (Figure S5). In contrast, the reaction at -25°C or higher resulted in significantly lower yields, indicating the quick decomposition of almost all cations. Similar evaluations were then conducted at -50°C by changing the supporting electrolyte (Figure 2 (c)). The results have implications regarding the relative reactivity of sulfonium ions and the stability of oxocarbenium ions. $[\text{ArS}(\text{ArSSAr})]^+ [\text{OTf}]^-$ activated thioacetal faster than $[\text{ArS}(\text{ArSSAr})]^+ [\text{BF}_4]^-$, and the resulting oxocarbenium ion decomposed more quickly. In addition, the oxocarbenium ion of $[\text{B}(\text{C}_6\text{F}_5)_4]^-$ resulted in significantly lower yields even at -50°C , indicating its extreme instability.

To further expand the synthetic utility of this method, we investigated the glycosylation reactions. The use of Bu_4NOTf as

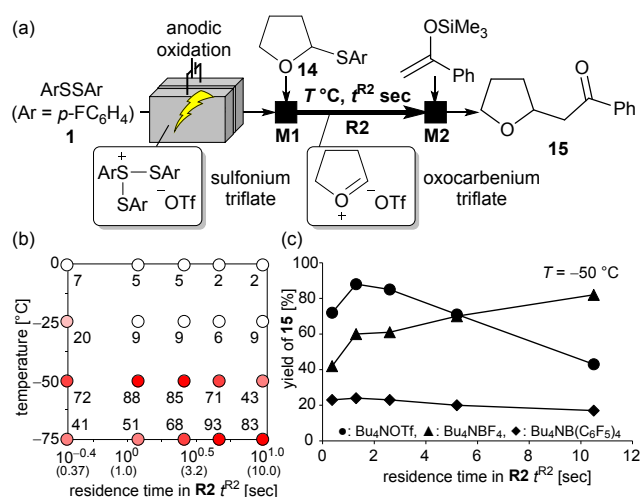
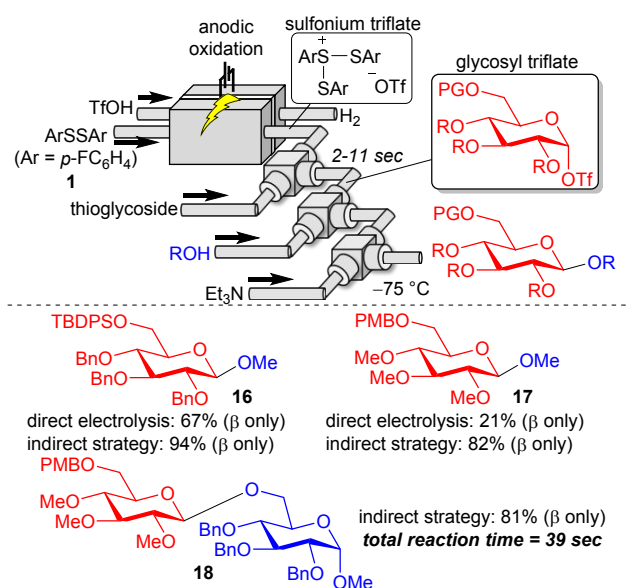


Fig. 2 (a) Sequential generation of $[\text{ArS}(\text{ArSSAr})]^+ [\text{OTf}]^-$ and oxocarbenium triflate using an integrated flow electrochemical reactor system. (b) Effect of temperature and residence time in **R2** on the yields of **15**. (c) Stability comparison of oxocarbenium ions at -50°C . Reactions were performed on a 0.05–0.07 mmol scale based on **14**. See ESI for more detailed conditions.

a supporting electrolyte enables the generation and accumulation of a glycosyl triflate through the direct electrochemical oxidation of thioglycosides.⁸ Under these conditions, although simple protecting groups such as methyl, acetyl, and benzyl groups were mainly used as protecting groups for glycosyl donors, some useful protecting groups, such as silyl protecting groups and oxidatively labile PMB (*p*-methoxybenzyl), did not survive.¹⁷ We assumed that present non-oxidative activation strategy would be effective in suppressing deprotection of these protecting groups. Before applying this strategy, we examined the direct flash electrolysis approach. The generation of glycosyl triflates by direct anodic oxidation of thioglycosides bearing TBDPS or PMB group in flow, and the subsequent glycosylation with MeOH gave unsatisfactory yields (Scheme 2, **16** and **17**, direct electrolysis). When indirect strategy was applied, the desired products were obtained in good to excellent yields, clearly demonstrating that the strategy was effective (Scheme 2, indirect strategy). Finally, a sequence of electrochemical generation of $[\text{ArS}(\text{ArSSAr})]^+ [\text{OTf}]^-$, indirect generation of glycosyl triflate bearing a PMB group followed by reaction with a carbohydrate acceptor, and quenching with Et_3N was successfully performed in the integrated flow system to afford the desired disaccharide **18** in 81% yield. Notably, the series of reactions from anodic oxidation to Et_3N quenching required only 40 sec, enabling rapid synthesis that was impossible in batch.

In conclusion, we have developed a powerful method for utilizing highly unstable organic triflate intermediates by using flow electrochemical reactor system. The key to the success is the achievement of the flash generation of highly reactive $[\text{ArS}(\text{ArSSAr})]^+ [\text{OTf}]^-$ by extremely fast electrolysis in flow. This enabled direct use of the intermediate not only as an efficient thiotriflating reagent for alkynes, but also a mediator for sequential generation of a short-lived oxocarbenium triflate and glycosyl triflates bearing oxidatively labile protecting

groups. These reactions could probably be applied to gram-scale production using the set-up reported in the previous reports.¹¹ It is expected that the present methodology contributes to the deepening not only organic triflate chemistry but also organic cation chemistry.



Scheme 2 Rapid glycosylation via sequential generation of $[\text{ArS}(\text{ArSSAr})]^+ [\text{OTf}]^-$ and glycosyl triflate in an integrated flow electrochemical reactor system. Reactions were performed on a 0.05–0.15 mmol scale based on the thioglycoside. PG = protecting group. TBDPS = *tert*-butyldiphenylsilyl, PMB = *p*-methoxybenzyl. See ESI for detailed conditions.

This work was supported by JSPS KAKENHI (JP15H05849, JP17K06910, JP19K22186, JP20KK0121, JP21H01936, and JP21H05080), AMED (JP20ak0101090 and JP21ak0101156), CREST (JPMJCR18R1), JST A-step program (18067420), New Energy and Industrial Technology Development Organization (NEDO), the Japan Keirin Autorace Foundation, and the Ogasawara Foundation.

Conflicts of interest

There are no conflicts to declare.

References

- (a) R. D. Howells and J. D. McCown, *Chem. Rev.*, 1977, **77**, 69–92; (b) P. J. Stang, M. Hanack and L. R. Subramanian, *Synthesis*, 1982, **1982**, 85–126; (c) K. Ritter, *Synthesis*, 1993, **1993**, 735–762; (d) B. Dhakal, L. Bohe and D. Crich, *J. Org. Chem.*, 2017, **82**, 9263–9269.
- (a) D. Crich, *Acc. Chem. Res.*, 2010, **43**, 1144–1153; (b) R. R. Naredla and D. A. Klumpp, *Chem. Rev.*, 2013, **113**, 6905–6948; (c) C. S. Bennett and M. C. Galan, *Chem. Rev.*, 2018, **118**, 7931–7985.
- S. Kobayashi, M. Sugiura, H. Kitagawa and W. W. L. Lam, *Chem. Rev.*, 2002, **102**, 2227–2302.
- (a) T. Akiyama and K. Mori, *Chem. Rev.*, 2015, **115**, 9277–9306; (b) Y. B. Chen, P. C. Qian and L. W. Ye, *Chem. Soc. Rev.*, 2020, **49**, 8897–8909.
- (a) T. Yanagi, K. Nogi and H. Yorimitsu, *Tetrahedron Lett.*, 2018, **59**, 2951–2959; (b) Z. Tashrifi, M. Mohammadi-

Khanaposhtani, B. Larijani and M. Mahdavi, *ChemistrySelect*, 2021, **6**, 5320–5328.

- For selected reviews on electrochemical synthesis, see: (a) M. Yan, Y. Kawamata and P. S. Baran, *Chem. Rev.*, 2017, **117**, 13230–13319; (b) A. Wiebe, T. Gieshoff, S. Möhle, E. Rodrigo, M. Zirbes and S. R. Waldvogel, *Angew. Chem. Int. Ed.*, 2018, **57**, 5594–5619; (c) Y. Yuan and A. Lei, *Acc. Chem. Res.*, 2019, **52**, 3309–3324; (d) C. Zhu, N. W. J. Ang, T. H. Meyer, Y. Qiu and L. Ackermann, *ACS Cent. Sci.*, 2021, **7**, 415–431; (e) S. H. Shi, Y. Liang and N. Jiao, *Chem. Rev.*, 2021, **121**, 485–505.
- (a) J. Yoshida, K. Kataoka, R. Horcajada and A. Nagaki, *Chem. Rev.*, 2008, **108**, 2265–2299; (b) J. Yoshida, A. Shimizu and R. Hayashi, *Chem. Rev.*, 2018, **118**, 4702–4730.
- T. Nokami, A. Shibuya, H. Tsuyama, S. Suga, A. A. Bowers, D. Crich and J. Yoshida, *J. Am. Chem. Soc.*, 2007, **129**, 10922–10928.
- (a) S. Suga, K. Matsumoto, K. Ueoka and J. Yoshida, *J. Am. Chem. Soc.*, 2006, **128**, 7710–7711; (b) K. Saito, K. Ueoka, K. Matsumoto, S. Suga, T. Nokami and J. Yoshida, *Angew. Chem. Int. Ed.*, 2011, **50**, 5153–5156.
- For selected reviews on flow electrochemical reactors, see: (a) M. Atobe, H. Tateno and Y. Matsumura, *Chem. Rev.*, 2018, **118**, 4541–4572; (b) D. Pletcher, R. A. Green and R. C. D. Brown, *Chem. Rev.*, 2018, **118**, 4573–4591; (c) K. Mitsudo, Y. Kurimoto, K. Yoshioka and S. Suga, *Chem. Rev.*, 2018, **118**, 5985–5999; (d) T. Noël, Y. Cao and G. Laudadio, *Acc. Chem. Res.*, 2019, **52**, 2858–2869; (e) N. Tanbouza, T. Ollever and K. Lam, *iScience*, 2020, **23**, 10172. For selected reports, also see: (f) S. Suga, M. Okajima, K. Fujiwara and J. Yoshida, *J. Am. Chem. Soc.*, 2001, **123**, 7941–7942; (g) D. Horii, T. Fuchigami and M. Atobe, *J. Am. Chem. Soc.*, 2007, **129**, 11692–11693; (h) R. A. Green, R. C. D. Brown and D. Pletcher, *Org. Process Res. Dev.*, 2015, **19**, 1424–1427; (i) A. Folguez-Amador, K. Philipps, S. Guilbaud, J. Poelakker and T. Wirth, *Angew. Chem. Int. Ed.*, 2017, **56**, 15446–15450; (j) C. Gütz, A. Stenglein and S. R. Waldvogel, *Org. Process Res. Dev.*, 2017, **21**, 771–778; (k) D. Wang, P. Wang, S. Wang, Y. H. Chen, H. Zhang and A. Lei, *Nat. Commun.*, 2019, **20**, 2796–2803; (l) G. Laudadio, D. L. Browne, E. Barmopoulos, C. Schotten, L. Struik, S. Govaerts and T. Noël, *J. Am. Chem. Soc.*, 2019, **141**, 5664–5668; (m) Y. Mo, Z. Lu, G. Rughoobur, P. Patil, N. Gershenfeld, A. I. Akinwande, S. L. Buchwald and K. F. Jensen, *Science*, 2020, **368**, 1352–1357; (n) E. Sato, M. Fujii, H. Tanaka, K. Mitsudo, M. Kondo, S. Takizawa, H. Sasai, T. Washio, K. Ishikawa and S. Suga, *J. Org. Chem.*, 2021, **86**, 16035–16044; (o) X. Zhong, M. A. Hoque, M. D. Graaf, K. C. Harper, F. Wang, J. D. Genders and S. S. Stahl, *Org. Proc. Res. Dev.*, 2021, **25**, 2601–2607; (p) Y. Naito, M. Kondo, Y. Nakamura, N. Shida, K. Ishikawa, T. Washio, S. Takizawa and M. Atobe, *Chem. Commun.*, 2022, **58**, 3893–3896.
- (a) M. Takumi, H. Sakaue and A. Nagaki, *Angew. Chem. Int. Ed.*, 2022, **61**, e202116177; (b) M. Takumi and A. Nagaki, *Front. Chem. Eng.*, 2022, **4**, 862766.
- K. Matsumoto, Y. Kozuki, Y. Ashikari, S. Suga, S. Kashimura and J. Yoshida, *Tetrahedron Lett.*, 2012, **53**, 1916–1919.
- S. Fujie, K. Matsumoto, S. Suga and J. Yoshida, *Chem. Lett.*, 2009, **38**, 1186–1187.
- (a) W. A. Smit, R. Caple and I. P. Smoliakova, *Chem. Rev.*, 1994, **94**, 2359–2382; (b) D. J. Fox, D. House and S. Warren, *Angew. Chem. Int. Ed.*, 2002, **41**, 2462–2482.
- A. Shimizu, K. Takeda, S. Mishima, K. Saito, S. Kim, T. Nokami and J. Yoshida, *Bull. Chem. Soc. Jpn.*, 2016, **89**, 61–66.
- K. Mitsudo, J. Yamamoto, T. Akagi, A. Yamashita, M. Haisa, K. Yoshioka, H. Mandai, K. Ueoka, C. Hempel, J. Yoshida and S. Suga, *Beilstein J. Org. Chem.*, 2018, **14**, 1192–1202.
- T. Nokami, H. Tsuyama, A. Shibuya, T. Nakatsutsumi and J. Yoshida, *Chem. Lett.*, 2008, **37**, 942–943.