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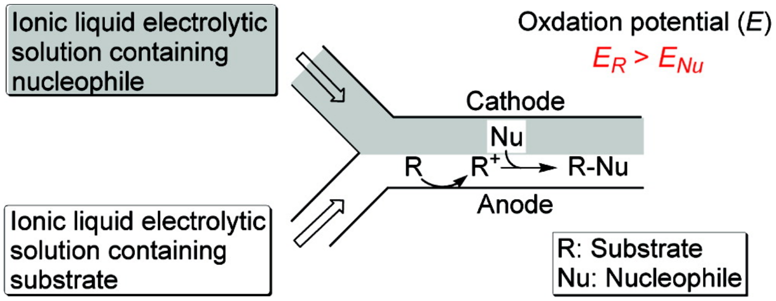

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A New Approach to Anodic Substitution Reaction Using Parallel Laminar Flow in a Micro-Flow Reactor

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Nucleophilic reactions between chemically and electrochemically generated carbocations from organic substrates and nucleophiles are one of the most important reactions in organic syntheses.[1] Since carbocations are usually unstable intermediates, the oxidative generation of carbocations often has to be conducted in the presence of nucleophiles. However, in general, the oxidation potentials of nucleophiles are lower than that of organic substrates, and therefore the presence of nucleophiles would prevent oxidation of organic substrates.[2] In this regard, Yoshida and co-workers have recently developed a “cation pool” method that involves generation and accumulation of highly reactive carbocations by very low-temperature electrolysis.[3] Although this method enables the manipulation of carbocation intermediates to achieve direct oxidative C−C bond formation, its applicability strongly depends on the stability of the carbocation that is accumulated.

On the other hand, micro-flow reactors enable the precise control of reactive intermediates and thereby facilitate highly selective reactions that are difficult to achieve in conventional reactors[4] because micro-flow reactors have several advantages, such as large specific interfacial area (liquid−liquid or liquid−solid), short molecular diffusion distance, and short residence time in reactors.[5] Such advantages would favorably affect heterogeneous processes, and therefore the application of micro-flow system to heterogeneous processes, particularly electrosynthetic processes, has received much attention.[6] Yoshida et al. have successfully demonstrated that *N*-acyliminium cations are generated by a micro-flow electrochemical system under very low temperature and are immediately transferred to a vessel in which a nucleophilic reaction took place to give final coupling products in high selectivity.[7]

On the other hand, the channel of micro-flow reactor is small enough to ensure that the flow is stable and laminar. As shown in Figure 1, when two solutions are introduced through the two inlets (named inlets 1 and 2 in Figure 1), a stable liquid−liquid interface can be formed, and mass transfer between input streams occurs only via diffusion. Hence substrates would be oxidized dominantly to generate carbocations, while oxidation of nucleophiles would be avoided when the opposing sidewalls of the channel are the anode and cathode, and substrate and nucleophile solutions are introduced through inlet 1 (anode side inlet) and inlet 2 (cathode side inlet), respectively. Consequently, the carbocations generated at anode would rapidly diffuse to the bulk electrolytic solution and react with nucleophiles to afford desired products. Thus, this system would enable nucleophilic reactions to overcome the restraints such as the oxidation potential of nucleophiles and the stability of carbocations.

In this paper, we wish to report our results indicating that this concept works. We chose anodic substitution reaction of *N*-(methoxycarbonyl)pyrrolidine **1** (oxidation potential $E_{ox} = 1.91$ V vs Ag/AgCl) with allyltrimethylsilane **2** (oxidation potential $E_{ox} =$ 1.75 V vs Ag/AgCl) as a model reaction (Scheme 1).[8]

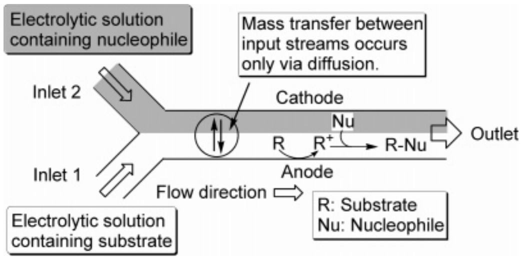


Figure 1. Schematic representation of parallel laminar flow in the micro-flow reactor. The illustrated model reaction is anodic substitution reaction in this reactor.

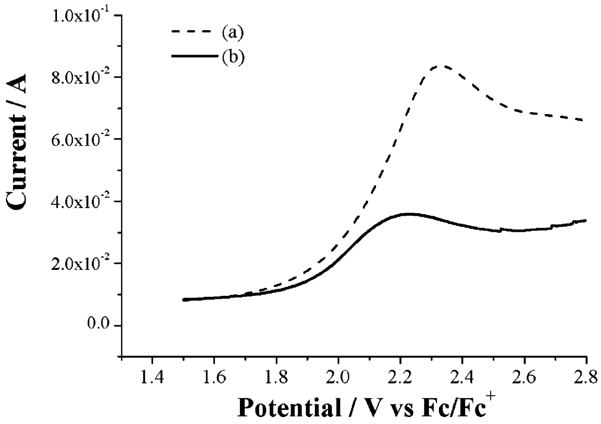
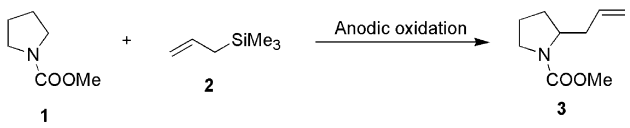


Figure 2. Linear sweep voltammograms for oxidation of **2** in 0.1 M *n*-Bu_4NBF_4/acetonitrile recorded in the micro-flow reactor at 20 °C. Ag wire as a reference electrode was externally placed downstream near the outlet of the micro-flow reactor. Scan rate was 0.5 V s^{-1}. (a) The electrolytic solution containing **2** (0.05 M) was introduced through inlet 1 at a flow rate of 0.2 mL min^{-1}. (b) The electrolytic solution with **2** (0.05 M) was introduced through inlet 2, and the electrolytic solution without **2** was introduced through inlet 1 at a flow rate of 0.1 mL min^{-1} each.

Scheme 1. Anodic Substitution Reaction of **1** with **2**



First, we measured linear sweep voltammograms for oxidation of nucleophile **2** in 0.1 M *n*-Bu_4NBF_4/acetonitrile in the micro-flow reactor. As shown in Figure 2a, oxidation peak of **2** could be observed clearly at 2.3 V vs Fc/Fc^+ when an electrolytic stream containing **2** only entered through inlet 1. On the other hand, the peak current was decreased appreciably when an electrolytic solution with **2** was introduced through inlet 2, and a solution without **2** was introduced through inlet 1, as shown in Figure 2b. These results indicate that the use of parallel laminar flow did prevent **2** from reaching the anode when it was introduced through inlet 2.

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Table 1. Anodic Substitution Reaction of **1** with **2** Using Parallel Laminar Flow Mode[a]

entry	electrolytic solution	conversion of **1** (%)[b]	yield of **3** (%)[c]
1	0.1 M *n*-Bu_4NBF_4/acetonitrile	73	0.6
2	0.1 M *n*-Bu_4NBF_4/TFE	58	59
3	[emim][BF_4]	61	62
4	[emim][TFSI]	66	73
5	[deme][TFSI]	54	91

[a] The flow rates of two electrolytic solutions containing **1** and **2**, respectively, were fixed at 0.1 mL min^{-1} each. Current density was 3 mA cm^{-2}. The reaction temperature was at 20 °C. [b] Determined by GC. [c] Yield based on the amount of consumed starting material.

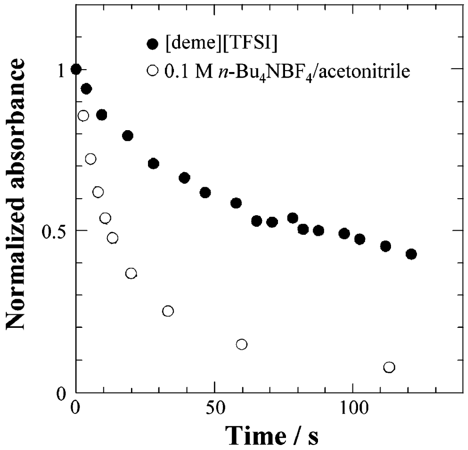

Figure 3. Time changes in absorbance at 1815 cm^{-1} of carbocation intermediate observed after electrolysis of substrate **1** (0.1 M) in 0.1 M *n*-Bu_4NBF_4/acetonitrile (○) and [deme][TFSI] (●), respectively, at 24 °C.

We then carried out a preparative scale experiment of the anodic substitution reaction of substrate **1** (0.01 M) with nucleophile **2** (0.1 M). Substrate **1** (E_{ox} = 1.91 V vs Ag/AgCl) is less easily oxidized than nucleophile **2** (E_{ox} = 1.75 V vs Ag/AgCl). When an acetonitrile electrolytic solution containing both **1** and **2** was introduced through inlet 1 at a flow rate of 0.2 mL min^{-1}, both the yield and the percent conversion of **1** were low (36% conversion, 6% yield). In this case, probably **2** was oxidized preferentially. On the other hand, as shown in entry 1 of Table 1, the use of parallel laminar flow mode resulted in an improvement of the conversion of **1**. In this demonstration, because the electrolytic solutions containing **1** and **2** were introduced through inlets 1 and 2, respectively, **1** should be oxidized dominantly. However, a low yield problem still remained. This was ascribed to decomposition of the anodically generated carbocation in the acetonitrile electrolytic solution decomposed before trapping by **2** at ambient temperature. To overcome this problem, the reaction was carried out in 2,2,2-trifluoroethanol (TFE), which is known as a stabilizing solvent for carbocations.[9] As a result, conversion yield of **3** was increased dramatically (entry 2). Moreover, it should be noted that the yield of **3** was further improved when ionic liquids such as 1-ethyl-3-methylimidazolium tetrafluoroborate [emim][BF_4], 1-ethyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide [emim][TFSI], and *N*,*N*-diethyl-*N*-methyl-*N*-(2-methoxyethyl)ammonium bis(trifluoromethanesulfonyl)imide [deme][TFSI] were used as reaction media (entries 3−5). These results apparently suggest that ionic liquids have an excellent stabilizing ability for the carbocation, and therefore the carbocation generated from **1** could react with **2** before its decomposition.

To evaluate the stability of the carbocation intermediate generated from **1** in electrolytic media used, we finally measured in situ FT-IRA (Fourier transform infrared reflection absorption) spectra of the carbocation in 0.1 M *n*-Bu_4NBF_4/acetonitrile and [deme][TFSI], respectively.[10] After 20 s of an applied potential (2.4 V vs Fc/Fc^+), a new IR signal appeared at 1815 cm^{-1} (see Supporting Information). The band at 1815 cm^{-1} is consistent with the band reported in the literature (1814 cm^{-1}).[7a] Figure 3 shows the change of normalized absorbance of IR signal at 1815 cm^{-1} after stopping the potential application. In 0.1 M *n*-Bu_4NBF_4/acetonitrile electrolytic solution, absorbance of the carbocation decreased dramatically. In contrast, in [deme][TFSI], the absorbance of the carbocation decayed very slowly even at ambient temperature (24 °C). From these results, it is confirmed that ionic liquid has an excellent stabilizing ability for the carbocation.

In conclusion, we have developed a novel electrosynthetic system for anodic substitution reaction using a micro-flow reactor. This system enables nucleophilic reactions to overcome the restraints such as the oxidation potential of nucleophiles and the stability of carbocations by the combined use of ionic liquids as reaction media and the parallel laminar flow in the reactor. We expect that this new methodology will make a significant contribution not only to carbocation chemistry but also to chemistry using highly reactive intermediates. The scope, limitations, and the further applications of this new methodology are currently under investigation.

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Supporting Information Available: Experimental procedures, analysis protocols, and IR spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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