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“Cation Flow” Method: A New Approach to Conventional and Combinatorial Organic Syntheses Using Electrochemical Microflow Systems

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Microflow reactors[1] have received significant interest in the stream of downsizing of chemistry,[2] and they are expected to make an innovative and revolutionary change for chemical synthesis.[3] In addition to the safety and environmental benefits of dealing with smaller quantities of material, microflow reactors have several advantages[4] over conventional systems stemming from the high surface-to-volume ratio; for example, precise temperature control and high efficiency of heterogeneous mass transfer. Short residence times in reactors may also be advantageous from a viewpoint of the control of highly reactive intermediates. The advantages of microflow reactors of easy modulation[5] and the possibility of combining reactors in parallel promising a quick means for scale-up[6] also warrant comment.

Recently we have developed a “cation pool” method that involves generation and accumulation of highly reactive carbocations by low-temperature electrolysis.[7] This method enables the manipulation of carbocation intermediates to achieve direct oxidative C−C bond formation, but its applicability strongly depends on the stability of the carbocation that is accumulated. We envisioned that the application of microflow systems expands the scope of this methodology because of high efficiency of the temperature control and short residence time.

In this paper we report direct electrooxidative C−C bond formation using a low-temperature electrochemical microflow system.[8] This system generates carbocation continuously as “cation flow”. The “cation flow” method is expected to enable the manipulation of unstable carbocations and opens a new aspect of chemical synthesis using carbocation intermediates.[9]

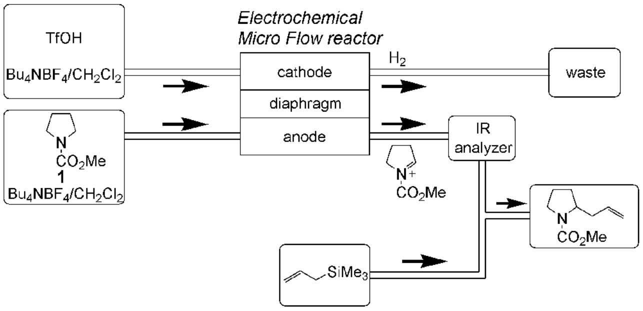

Figure 1. Schematic diagram of “cation flow” system.

To prove the principle of the “cation flow” method, we chose carbamates as precursors of cations because their chemistry is well established in the “cation pool” method. We developed the electrochemical microflow reactor composed of diflone and stainless steel bodies by a mechanical manufacturing technique (Figure 1). The two-compartment cell was divided by a diaphragm of PTFE membrane. A typical reaction procedure is as follows. A 0.05 M solution of methyl pyrrolidinecarboxylate (**1**) containing supporting electrolyte (Bu$_4$NBF$_4$, 0.3 M) in dichloromethane was introduced with cooling (−72 °C) by syringe pumping (flow rate is 2.1 mL/h) to the anodic chamber equipped with a carbon felt anode (7 mm × 7 mm × 5 mm) made of carbon fibers (ϕ 10 μm). A solution of the supporting electrolyte and trifluoromethanesulfonic acid (TfOH) as a proton source was introduced to the cathodic chamber equipped with a platinum wire cathode. The cationic intermediate generated by low-temperature electrolysis (14 mA) of **1** was immediately transferred to a vessel in which a nucleophilic reaction took place to give the final coupling product.

It is important to construct a monitoring device for the flow system. FTIR spectroscopy was applied for the online monitoring of the cationic intermediate. The starting material **1** exhibited an absorption at 1694 cm^{-1} due to the carbonyl stretching, while the acyliminium cation generated by the “cation pool” method[7a] from **1** exhibited an absorption at 1814 cm^{-1}. The higher wavenumber of the cation is consistent with the formation of a positive charge at the nitrogen adjacent to the carbonyl carbon. The shift to higher wavenumber is also supported by DFT (density functional theory) calculations,[10] which indicate that wavenumbers for C═O vibration of model compounds $(CH_3)_2N(CO_2CH_3)$ and $CH_3N^+({=}CH_2)CO_2CH_3$ are 1734 and 1856 cm^{-1}, respectively.

Thus, the “cation flow” system was monitored by the FTIR spectrometer (ATR method) equipped with a low-temperature flow cell attached to the outlet of the electrochemical microflow reactor. The formation of the acyliminium cation was indicated by the absorption at 1814 cm^{-1}, which increased with the increase of the electric current (Figure 2). The current of 14 mA was applied in the following preparative reactions, because FTIR monitoring indicated that it was sufficient for the generation of the acyliminium cation.

The present “cation flow” system can be applied to the direct oxidative C−C bond formation with various carbon nucleophiles.[11,12] Thus, the stream of the cation generated from **1** was allowed to react with various carbon nucleophiles such as allylsilanes and enol ethers to obtain the corresponding C−C bond

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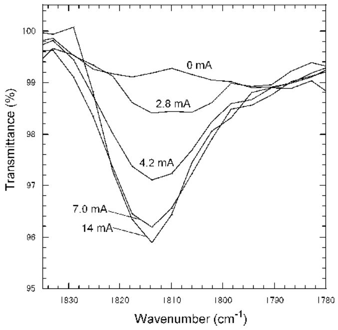
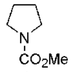
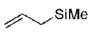
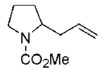
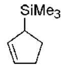
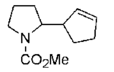
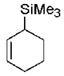
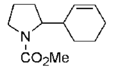
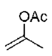
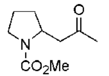
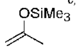
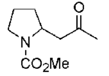
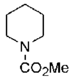
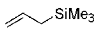
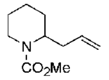
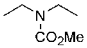
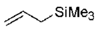
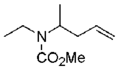
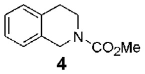
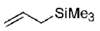
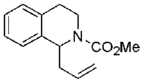
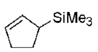
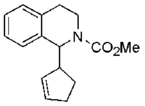


Figure 2. FTIR spectra of the "cation flow".

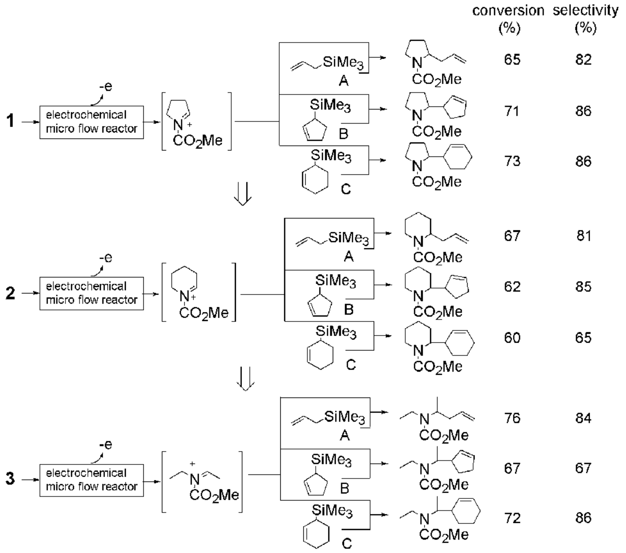
Table 1. Direct Electrooxidative C−C Bond Formation of Carbamates Using "Cation Flow" System[a]

substrate	nucleophile	product	conversion (%)	selectivity (%)[b]
 **1**			69	91
			69	100
			67	99
	 [c]		64	66
	 [c, d]		61	72
 **2**			60	93
 **3**			55	98
 **4**			49	67
			49	67

[a] The nucleophilic reactions were usually carried out with a carbamate (0.4 mmol) and a carbon nucleophile (0.8 mmol) at −72 °C. [b] Yield based on consumed starting material. [c] The nucleophilic reactions were caried out at −28 °C. [d] 2.3 mmol of the enol silyl ether was used.

formation products (Table 1). The "cation flow" method can also be applicable to other carbamates (**2**-**4**) as cation precursors.

Scheme 1. Continuous Sequential Combinatorial Synthesis Using "Cation Flow" System



Another outstanding feature of the "cation flow" system is that continuous sequential combinatorial synthesis[13] can be accomplished by simple flow switching. The results of preliminary experiments are shown in Scheme 1. In the first step, the "cation flow" generated from **1** was allowed to react with nucleophile **A**. Then, the "cation flow" was allowed to react with nucleophile **B**. In the third step, the "cation flow" was allowed to react with nucleophile **C**. Then, the precursor of the cation was switched to **2**, and the "cation flow" generated from **2** was allowed to react with nucleophiles **A**, **B**, and **C** sequentially. Then the precursor of the cation was switched to **3**, and the "cation flow" generated from **3** was allowed to react with nucleophiles **A**, **B**, and **C** sequentially. Although parallel syntheses enjoy versatile applications in combinatorial chemistry, the present continuous sequential method opens a new intriguing aspect of combinatorial synthesis. Further downsizing of the reactor together with the development of related techniques will hopefully lead to a new dimension of combinatorial synthesis.

The results shown here demonstrate that electrochemical microflow systems open a new aspect of the chemistry using carbocations. Further work aimed at establishing the scope of the "cation flow" system and its applications to conventional and combinatorial organic syntheses are currently in progress.

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Supporting Information Available: Experimental procedures and analytical and spectroscopic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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