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Cationic Three-component Coupling Involving an Optically Active Enamine Derivative. From Time Integration to Space Integration of Reactions

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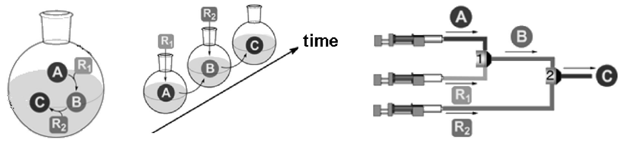
Three-component coupling of an *N*-acyliminium cation pool, an optically active 2-*t*-butyloxazole derivative, and a carbon nucleophile such as allyltrimethylsilane was effectively achieved by a rapid one-pot method at −78 °C and a flow microreactor method at 0 °C.

Integration of chemical reactions enhances the power and speed of organic synthesis. Conventional step-by-step synthesis has been molting into integrated synthesis which combines multiple components in a single operation in one-pot or in one-flow. Recently, extensive efforts have been devoted to integration of reactions,[1] which can be classified into three types (Figure 1): (a) *time and space integration*, where all reaction components are mixed at once to perform a sequence of reactions in one-pot (domino, tandem, or cascade reactions),[2] (b) *time integration*, where a sequence of reactions is conducted in one-pot by adding components at intervals (one-pot sequential synthesis),[3] and (c) *space integration*, where a sequence of reactions is conducted in one flow by adding components at different places (flow synthesis),[4] We have been interested in *time integration* and *space integration* using reactive intermediates for fast chemical synthesis, because these integration methods are more flexible as far as choice of reagents is concerned due to stepwise addition of components. Herein, we describe one example of this approach.



(a) (b) (c)

Figure 1. Classification of reaction integration: (a) *time and space integration*, (b) *time integration*, and (c) *space integration*.

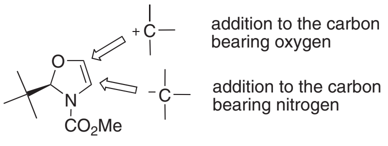


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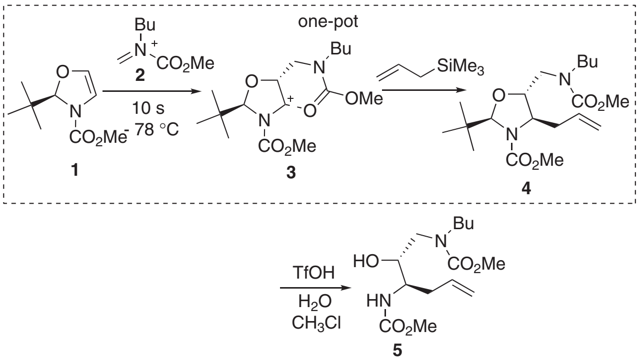
Figure 2. Cationic three-component coupling using 2-*t*-butyl-3-methoxycarbonyloxazole (**1**).



Scheme 1. Cationic three-component coupling of compound **1**, cation pool of **2**, and allyltrimethylsilane based on *time integration* followed by hydrolysis.

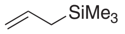
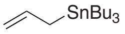
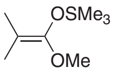
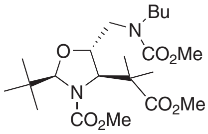
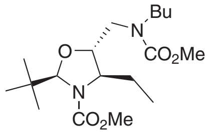
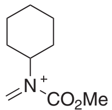
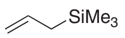
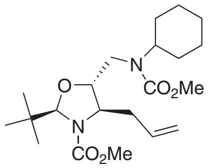
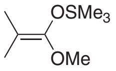
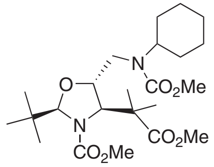
The present work stems from our earlier studies[5] on three-component coupling based on the cation pool method.[6] The addition of a cation pool to an electron-rich olefin generates a new cation pool, which is reacted with a carbanion equivalent. This transformation is the umpolung of the anionic three-component coupling.[7] In this paper we focus on 2-*t*-butyl-3-methoxycarbonyloxazole (**1**) (Figure 2) developed by Seebach[8] as a versatile electron-rich olefin because the optically active form of **1** can be easily synthesized.[9] There are two possibilities for the addition of a cation to the carbon–carbon double bond: addition to the carbon-bearing oxygen or the carbon-bearing nitrogen. Generally, the electrophilic addition to the carbon-bearing oxygen is suggested to be more feasible than that to the carbon-bearing nitrogen,[8c] a cation should add to the carbon-bearing oxygen. Thus, highly regioselective reactions would be expected via a sequential addition of a cation component followed by a trapping of a carbanion equivalent.

First, we studied the three-component coupling based on *time integration* (one-pot sequential method) (Scheme 1). Thus, **1** was reacted with *N*-acyliminium ion **2**, which was generated by the cation pool method.[10] After stirring for 10 s at −78 °C to generate **3**,[11] allyltrimethylsilane was added. Quenching with triethylamine gave **4** as a single diastereomer in 54% yield (Scheme 1 and Table 1).[12]

As was expected, the regiochemistry of **4** indicates that cation **2** added to the carbon-bearing oxygen to generate a new carbocation adjacent to nitrogen selectively. The stereochemistry of **4** and very high diastereoselectivity indicate that cation **3** existed as a cyclic form,[5a] although the details have not yet been established at present. Compound **4** could be easily hydrolyzed with a catalytic amount of TfOH to give **5** in 81% yield (Scheme 1). The present transformation can be applied to other *N*-acyliminium ion pools and carbon nucleophiles as shown in Table 1.

Because the addition of **2** to **1** seems to be very fast (<10 s) and prolonged reaction time did not increase the yield, we

Table 1. Cationic three-component coupling of **1**, a pooled cation, and a nucleophile based on *time integration*[a]

Cation pool	Nucleophile	Product	Yield/%[b]
2		4	54[c]
		4	47[c]
		 6	63
	Et$_3$Al	 7	45
 8		 9	73
		 10	80

[a]The ractions were usually carried out with a cation precursor (0.25 mmol), **1** (0.17 mmol), and nucleophiles (0.8 mmol). [b]Isolated yield based on **1**. [c]GC yield.

examined the *space integration* using a microflow system, which enables the transformation in much shorter period. Recently, we proposed the concept of flash chemistry[13] for carrying out extremely fast reactions in organic synthesis using flow microreactor systems or microreactors.[14] Flow microreactor systems have been expected to make a revolutionary change in chemical synthesis, because they exhibit numerous advantages stemming from small size and high surface-to-volume ratio of microstructures. In particular, the length of time that the solution remains inside the reactor—the residence time—can be greatly reduced by adjusting the length of microchannels and flow speed. This feature of flow microreactor systems is extremely useful in controlling reactive intermediates: short-lived reactive intermediates can be transferred to another location to be used in the subsequent reaction before they decompose.[15]

Thus, a flow microreactor system consisting of two micromixers (**M1** and **M2**) and two microtube reactors (**R1** and **R2**) was constructed (Figure 3), and the reaction was carried out at 0 °C (Table 2). Mixing of **1** with cation **2** in **M1** led to generation of cation **3** in **R1** (residence time $t^{\mathrm{R}} = 0.48$ s). In **M2**, **3** reacted with allyltrimethylsilane to give product **4** in 79% yield, which was significantly higher than that obtained with *time integration*. Another important point is that the transformation could be accomplished at 0 °C, which is much higher than that required for the macrobatch reaction (−78 °C). Presumably extremely fast mixing in **M1** and the precise residence time control in **R1** seem to be responsible. Extremely fast heat transfer may also play some role. At lower temperatures the yield was lower presumably because the reaction was not complete within 0.48 s. However, the reaction was fast at 0 °C because the highest yield was obtained with $t^{\mathrm{R}} = 0.16$ s. Further decrease in t^{R} resulted in a decrease in the yield.

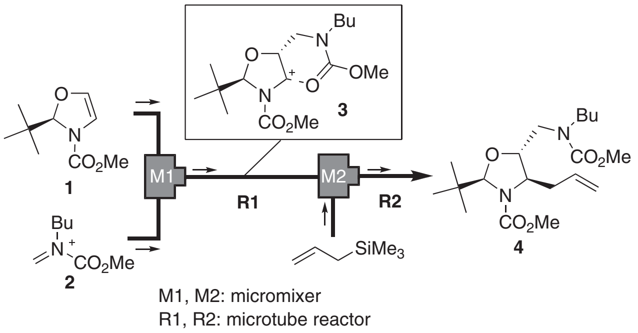
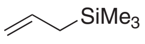
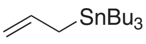
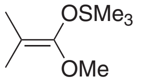


Figure 3. *Space integration* of cationic three-component coupling.

Table 2. Cationic three-component coupling of **1**, **2**, and carbon nucleophiles based on *space integration*[a]

Nucleophile	Product	Temperature /°C	Residence time in **R1**/s	Yield/%
	4	−78	0.48	46
		−48	0.48	53
		−28	0.48	70
		0	0.48	79
		0	0.16	82
		0	0.04	53
	4	0	0.48	70
	6	0	0.48	89

[a]The reactions were usually carried out with a solution of **2**/CH_2Cl_2 (0.05 M), a solution of **1**/CH_2Cl_2 (0.33 M), and a solution of a nucleophile/CH_2Cl_2 (0.28 M).

Other nucleophiles are also effective for this transformation. The reaction with allyltributylstannane gave **4** and that with a ketene silyl acetal gave **6** in good yields.

In conclusion, we found that three-component coupling of optically active 2-*t*-butyl-3-methoxycarbonyloxazole (**1**), an *N*-acyliminium cation pool, and a carbon nucleophile took place regio- and diastereoselectively. The use of a flow microreactor system gave rise to significant improvement of the yield. The method serves as a useful method for synthesis of diamino alcohols in optically active forms. It is also worth noting that the present observations open a new aspect of multicomponent coupling[16] based on space integration using flow microreactor systems. Further work is in progress to explore a wide range of applications of reaction integration.

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