

## Three-Component Coupling Based on the “Cation Pool” Method

Seiji Suga,\* Tomoaki Nishida, Daisuke Yamada, Aiichiro Nagaki, and Jun-ichi Yoshida\*

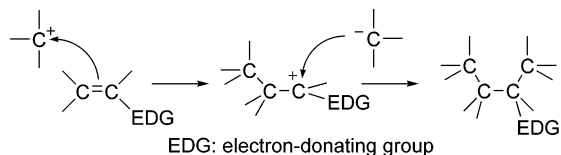
Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Nishikyo-ku, Kyoto 615-8510, Japan

Received July 23, 2004; E-mail: yoshida@sbchem.kyoto-u.ac.jp; suga@sbchem.kyoto-u.ac.jp

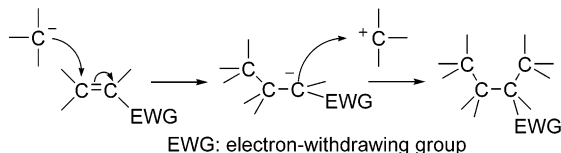
The integration of chemical transformations is one of the central issues in current organic synthesis because of the increasing demand for producing a large number of compounds in highly time-efficient fashion. Multicomponent coupling reactions<sup>1</sup> have received significant research interest in this context, and extensive efforts have been devoted to this field thus far. In tandem or domino reactions,<sup>2</sup> all reaction components are mixed at once, whereas in sequential one-pot reactions,<sup>3</sup> the reaction components are added at intervals.

We have been interested in sequential one-pot multicomponent coupling reactions using highly reactive intermediates. Our approach is based on the “cation pool” method,<sup>4</sup> in which highly reactive carbocations are generated by irreversible oxidative method, accumulated as a solution, and then allowed to react with various nucleophiles in the next step. The “cation pool” method is also suitable for combinatorial synthesis and the production of a large number of compounds in a highly time-efficient fashion.<sup>4a</sup> The basic concept of the present approach is simple, as shown in Scheme 1. The addition of a “cation pool” to an electron-rich carbon–carbon double bond generates a new “cation pool”, which is allowed to react with a carbanion equivalent (carbon nucleophile). This method is one of the most straightforward ways of introducing two different organic groups onto a carbon–carbon double bond.<sup>5</sup> It is interesting to note that this approach is the *umpolung* of the addition of a carbon nucleophile to an electron-deficient carbon–carbon double bond followed by the trapping of the resulting carbanion with a carbon electrophile (Scheme 2).<sup>6</sup>

### Scheme 1

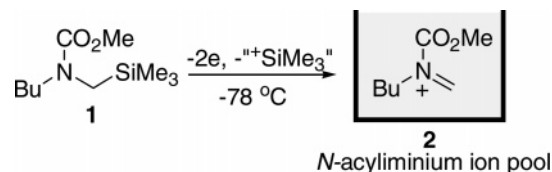


### Scheme 2

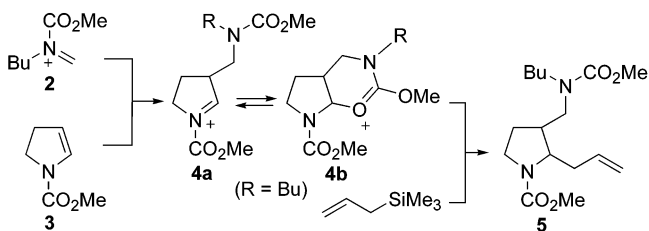


We chose to study the *N*-acyliminium ion **2**, which was generated from **1** by the “cation pool” method at  $-78\text{ }^\circ\text{C}$ , as a cationic component (Scheme 3). Enamine derivative **3**,<sup>7</sup> which was used as an olefinic component, was allowed to react with **2** at  $-78\text{ }^\circ\text{C}$  (Scheme 4). The resulting cation seems to exist in either an acyclic form **4a** ( $R = \text{Bu}$ ) or a cyclic form **4b** ( $R = \text{Bu}$ ) (or an equilibrium mixture of **4a** and **4b**), although the details have not yet been established. After 10 min at  $-78\text{ }^\circ\text{C}$ , allyltrimethylsilane as a carbon nucleophile was added. Consequently, the corresponding three-component coupling product **5** was obtained in 66% yield as a mixture of two diastereomers (84:16).

### Scheme 3



### Scheme 4



Various carbon nucleophiles, such as allylsilanes, allylstannanes, enol silyl ethers, ketene silyl acetals, organoaluminum compounds, and Grignard reagents, were effective as carbon nucleophiles, as depicted in Table 1. As to olefinic components, the six-membered ring enamine **11** was also effective. The present method can also be applied to other *N*-acyliminium ions such as **15**.

The diastereoselectivity of the present reaction is usually high, although it is sensitive to the nature of each component. It was difficult to determine the stereochemistry of dialkyl-substituted nitrogen-containing cyclic compounds by NMR, especially for carbamates because of the existence of rotamers. The stereochemistry of the major isomers of phenyl-substituted compounds (**10** and **14**), however, was determined to be *trans* (see Supporting Information for details). Presumably, the intermediacy of cyclic form **4b** (Figure 1) is responsible for high diastereoselectivity. The attack of a carbon nucleophile from the backside of the carbonyl oxygen, which coordinates to the cationic carbon, leads to the formation of the *trans* isomer.

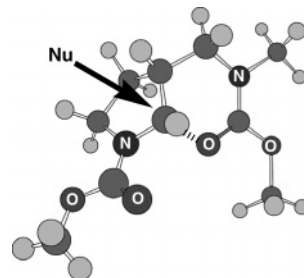


Figure 1. Optimized structure of **4b** ( $R = \text{Me}$ ) obtained by DFT calculations (B3LYP/6-31G(d)).<sup>8</sup>

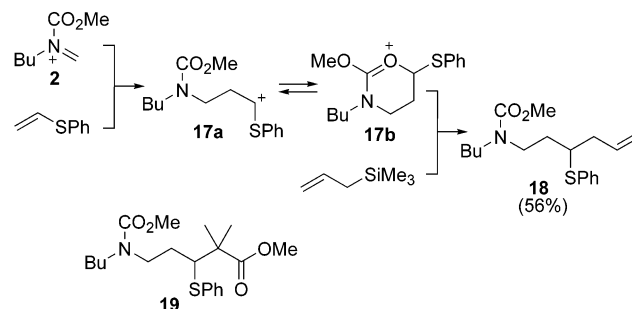
Vinyl sulfides can also be used as olefinic components (Scheme 5). The reaction of the *N*-acyliminium ion **2** with vinyl phenyl sulfide took place smoothly. The trapping of the resulting cation

**Table 1.** Three-Component Coupling Based on the *N*-Acylium Ion Pool<sup>a</sup>

<i>N</i> -acylium ion	olefinic component	carbon nucleophile	product	% yield <sup>b</sup>
				66 (84:16)
2	3			76 (93:7)
2	3			42 (99:1) <sup>c</sup>
2	3			58 (99:1)
2	3			68 (99:1)
2	3	Et <sub>3</sub> Al		61 (89:11)
2	3	PhMgBr		51 (88:12)
2				62 (91:9)
2	11	EtMgBr		71 (61:39)
2	11	PhMgBr		46 (98:2)
	3			70 (91:9)

<sup>a</sup> The reactions were usually carried out with 0.4 mmol precursor of a cation, 0.25 mmol olefinic component, and 0.8 mmol carbon nucleophile. <sup>b</sup> Isolated yields (based on the olefinic components). Diastereomer ratios in parentheses were determined by GC. <sup>c</sup> Although four diastereomers are possible for this case, only two peaks were observed by GC.

(**17a** or **17b**) with allyltrimethylsilane gave three-component coupling product **18** in 56%. The cationic intermediate (**17a** or **17b**)

**Scheme 5**

seemed to be thermally unstable. As a matter of fact, the increase of the reaction temperature resulted in lower yields ( $-48\text{ }^{\circ}\text{C}$ : 41%,  $-27\text{ }^{\circ}\text{C}$ : 39%). Allyltributylstannane and ketene silyl ether were also effective as carbon nucleophiles, and the corresponding coupling products **18** and **19** were obtained in 64 and 75% yields, respectively.

In summary, we have developed a new sequential one-pot three-component coupling reaction that is initiated by the addition of a “cation pool” to a carbon–carbon double bond. The present observations speak well for the potentiality of carbocationic multicomponent coupling reactions in integrated synthesis. Further work is in progress to explore the full range of applicability of the present approach.

**Acknowledgment.** This work was partially supported by the Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture, Japan and Project of Micro-Chemical Technology for Production, Analysis and Measurement Systems of NEDO, Japan.

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

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- Calculations indicated that cyclic **4b** (R = Me) is ca. 16 kcal/mol more stable than acyclic **4a** in gas phase. See Supporting Information for details.

JA0455704