

Direct Oxidative Carbon–Carbon Bond Formation Using the “Cation Pool” Method. 1. Generation of Iminium Cation Pools and Their Reaction with Carbon Nucleophiles

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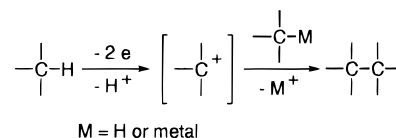
Abstract: We have developed a method that involves the generation of a “cation pool” using low-temperature electrolysis, and then its reaction with nucleophiles under non-oxidative conditions. This one-pot method solves problems associated with conventional oxidative generation of cations and their in situ reaction with nucleophiles, and provides an efficient method for direct oxidative carbon–carbon bond formation. As an example of this method, generation of cation pools from carbamates by low-temperature electrolysis ($-72\text{ }^{\circ}\text{C}$) and their reactions with carbon nucleophiles such as allylsilanes, enol silyl ethers, and enol acetates were examined and the desired products were obtained in good yields. Aromatic compounds and 1,3-dicarbonyl compounds can also be utilized as carbon nucleophiles. The present method was also applied to combinatorial parallel synthesis using a robotic synthesizer.

The oxidative deprotonation of organic compounds to generate carbocations¹ followed by their reactions with carbon nucleophiles is one of the most straightforward approaches to carbon–carbon bond formation (Scheme 1). This transformation contrasts with the transformations starting from compounds having a leaving group (Scheme 2), and serves as an efficient method for carbon–carbon bond formation.

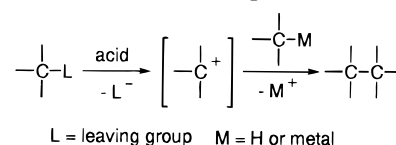
This type of transformation is, however, generally rather difficult to achieve for the following reasons. Extensive studies have been carried out for the generation of carbocations from C–H compounds using superacids.² For synthetic purposes, however, milder reaction conditions which are compatible with various functional groups are needed. To this end, electrochemical and chemical reactions have been developed.³ In these cases the oxidative generation of a carbocation often needs to be carried out in the presence of a nucleophile, because the carbocations generated are generally not stable to the reaction conditions used. Nucleophiles, especially carbon nucleophiles, are, however, often easily oxidized during the course of oxidative generation of the carbocation, although electrochemical or chemical oxidative cyanations have been achieved in the presence of the cyanide ion.⁴

To avoid these problems, the two-step transformation shown in Scheme 3 is usually used to achieve an oxidative carbon–

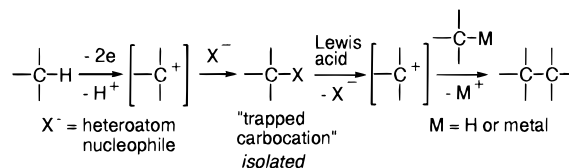
Scheme 1. Oxidative Generation of a Carbocation and Its Reaction with a Carbon Nucleophile in Situ



Scheme 2. Non-Oxidative Generation of a Carbocation and Its Reaction with a Carbon Nucleophile in Situ



Scheme 3. Two-Step Procedure for Carbon–Carbon Bond Formation Involving Temporary Trapping of an Oxidatively Generated Carbocation



carbon bond formation.³ In the first step, the carbocation is generated in the presence of an excess amount of a heteroatom nucleophile (X^-) of high oxidation potential such as methanol. The nucleophile immediately traps the carbocation intermediate. The “trapped carbocation” is separated and then is used for the regeneration of the carbocation under non-oxidative conditions. Thus, the treatment of the “trapped carbocation” with a Lewis acid in the presence of a carbon nucleophile gives the desired carbon–carbon bond formation product.

This two-step procedure is tedious in comparison with the direct reaction shown in Scheme 1. Therefore, we searched for

(1) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Ley, S., Eds.; Pergamon Press: Oxford, 1991; Vol. 7 (Oxidation).

(2) For example: (a) Olah, G. A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1393–1405. (b) *Stable Carbocation Chemistry*; Prakash, G. K. S., Schleyer, P. v. R., Eds.; Wiley-Interscience: New York, 1997.

(3) For an electrochemical example, see: (a) Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172–1176. (b) Shono, T. *Tetrahedron* **1984**, *40*, 811–850. (c) Malmberg, M.; Nyberg, K. *Acta Chem. Scand., Ser. B* **1979**, *33*, 69–72. (d) Mori, M.; Kagechika, K.; Sasai, H.; Shibasaki, M. *Tetrahedron* **1991**, *47*, 531–540. (e) Li, W.; Moeller, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 10106–10112. (f) Danielmeier, K.; Schierle, K.; Steckhan, E. *Tetrahedron* **1996**, *52*, 9743–9754. For an example using Ru catalyzed oxidation, see: Naota, T.; Nakato, T.; Murahashi, S. *Tetrahedron Lett.* **1990**, *31*, 7475–7478.

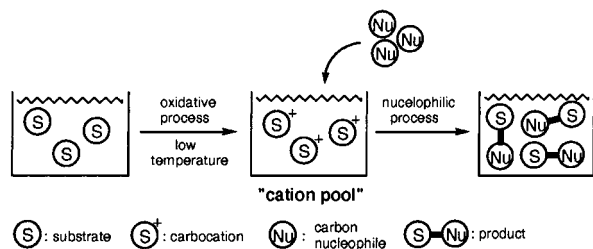


Figure 1. "Cation pool" method for oxidative carbon–carbon bond formation.

a general method for the direct reaction of oxidatively generated carbocation intermediates with carbon nucleophiles to achieve the carbon–carbon bond formation, and found that a "cation pool" method is quite effective for this type of transformation (Figure 1). In the "cation pool" method, carbocations are generated and accumulated in relatively high concentration by electrochemical oxidation at low temperature. In the next step, the carbocations are allowed to react with nucleophiles. This one-pot method has an advantage over conventional processes because nucleophiles that might be otherwise oxidized during an in situ process can be used without any difficulty. In addition, there is no need for temporary trapping of the carbocation intermediate, isolation of the "trapped carbocation", or a Lewis acid promoted regeneration of the carbocation.

We report herein the principle of the "cation pool" method and its application to the oxidative carbon–carbon bond forming reactions of nitrogen-containing compounds. The usefulness of this tool for both conventional and combinatorial organic syntheses is examined.

Results and Discussions

We chose carbamates as precursors of cations because oxidation of the carbon adjacent to the nitrogen atom to generate the corresponding iminium cation is well-established as a biomimetic type oxidation and enjoys various applications in organic synthesis.^{5,6} As carbon nucleophiles, we first examined allylsilanes because their reactions with carbocations are also well-established.⁷ The reaction of *N*-(methoxycarbonyl)pyrrolidine (**1**) with allyltrimethylsilane (**2**) is representative (Scheme 4). Compound **1** (oxidation potential $E_{\text{ox}} = 1.91$ V vs Ag/AgCl in 0.1 M Bu₄NClO₄/CH₂Cl₂) is less easily oxidized than compound **2** ($E_{\text{ox}} = 1.75$ V). As a matter of fact, the oxidation of a mixture of **1** and 2 equiv of **2** under electrolytic conditions (divided cell at room temperature) gave rise to the formation

Scheme 4. The Oxidative Carbon–Carbon Bond Formation of *N*-(Methoxycarbonyl)pyrrolidine (**1**) with Allyltrimethylsilane (**2**)

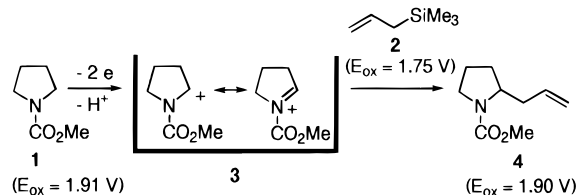


Table 1. Effect of the Temperature on the Electrolysis of **1**^a

| temp (°C) | conversion (%) | yield ^b (%) |
|-----------|----------------|------------------------|
| −72 | 100 | 82 |
| −47 | 100 | 78 |
| −25 | 84 | 31 |
| 0 | 77 | 10 |
| 20 | 61 | 5 |

^a After the electrolysis (2.5 F/mol based on **1**), the "cation pool" of **3** thus generated was allowed to react with **2** (2 equiv). ^b Determined by GC analysis.

of the desired product **4** in only 7% yield. Probably **2** was oxidized preferentially because 75% of **1** was recovered unchanged. The oxidation potential of the product **4** ($E_{\text{ox}} = 1.90$ V) was very close to that of **1** implying that overoxidation of **4** would also be a problem for this reaction, although the overoxidized products were not detected. It is also noteworthy that the electrochemical oxidation of **1** in the absence of **2** at room temperature followed by the addition of **2** gave a complex mixture, probably because iminium cation **3** decomposed during the electrolysis (vide infra).

The "cation pool" method solved these problems. The electrochemical oxidation of **1**⁸ was carried out in CH₂Cl₂ using a graphite felt anode at −72 °C in the absence of **2**. At this temperature, the iminium cation **3** was accumulated without decomposition. Although the conventional electrolysis is usually carried out at much higher temperature because the conductivity of the solution generally decreases with decrease of the temperature, the tuning of the electrolysis conditions such as the concentrations of the substrate and the electrolyte, and additives (see the Supporting Information) enabled us to perform the preparative electrolysis at such a low temperature. After the electrolysis was completed, **2** (2 equiv) was added to the newly generated "iminium cation pool" containing **3** to obtain the desired carbon–carbon bond formation product **4** in 82% yield (method A). The yield of **4** decreased dramatically with the increase of temperature of the electrolysis (Table 1), indicating that the reaction temperature was essential for the accumulation of the cation. It was difficult to suppress the decomposition of **3** at temperatures higher than ca. −50 °C. In addition to the yield the conversion of **1** also decreased with increasing electrolysis temperature. Presumably, the decomposition product derived from **3** was also oxidized to consume the electricity, although the decomposition product was not identified. The choice of the supporting electrolyte was also important for the low-temperature electrolysis to generate the "cation pool". The use of Bu₄NBF₄ as the supporting electrolyte gave the highest

(4) As an exception, direct introduction of CN[−] has been achieved because the oxidation potential of CN[−] is relatively high. It is also noteworthy that the CN group is strongly electron-withdrawing so that the oxidation potential of the product is expected to be much higher than the starting material. Electrochemical cyanation: (a) Chiba, T.; Tanaka, Y. *J. Org. Chem.*, **1977**, *42*, 2973–2977. Chemical oxidative cyanation: (b) Chen, C.-K.; Hortmann, A. G.; Marzabadi, M. R. *J. Am. Chem. Soc.* **1988**, *110*, 4829–4831. Some amines having very low oxidation potentials, such as dimethylmesidine, could exceptionally be substrates for the electrooxidative C–C bond formation: (c) Renaud, R. N.; Bérubé, D.; Stephens, C. J. *Can. J. Chem.* **1983**, *61*, 1379–1382.

(5) Electrochemical α -oxidation of amine derivatives: (a) Shono, T. *Electroorganic Chemistry as a New Tool in Organic Synthesis*; Springer-Verlag: Berlin, 1984. Transition metal promoted α -oxidation of amine derivatives: (b) Murahashi, S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2443–2465.

(6) Reviews for the synthetic utility of acyliminium cation, see: (a) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367–4416. (b) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I. Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 1047–1082. (c) Zaugg, H. E. *Synthesis* **1984**, 85–110. (d) Zaugg, H. E. *Synthesis* **1984**, 181–212.

(7) For example: (a) Sakurai, H. *Pure Appl. Chem.* **1982**, *54*, 1–22. (b) Chan, T. H.; Fleming, I. *Synthesis* **1979**, 761–786.

(8) The conventional electrochemical oxidation of carbamates using methanol as a nucleophile has been developed: (a) Shono, T.; Hamaguchi, H.; Matsumura, Y. *J. Am. Chem. Soc.* **1975**, *97*, 4264–4268. (b) Shono, T.; Matsumura, Y.; Tsubata, K. *Org. Synth.* **1985**, *63*, 206–213. The oxidative α -methoxylation of amides has also been reported: (c) Ross, S. D.; Finkelstein, M.; Peterson, R. C. *J. Am. Chem. Soc.* **1966**, *80*, 4657–4660. (d) Nyberg, K.; Servin, R. *Acta Chem. Scand., Ser. B* **1976**, *30*, 640–642.

Table 2. Thermal Stability of the "Cation Pool" of **3** after the Electrolysis^a

| temp (°C) | conversion (%) | yield ^b (%) |
|-----------|----------------|------------------------|
| -72 | 100 | 82 |
| -47 | 100 | 80 |
| -25 | 100 | 83 |
| 0 | 100 | 81 |
| 20 | 100 | 76 |

^a After the electrolysis (2.5 F/mol based on **1**), the "cation pool" of **3** thus generated was kept at the designated temperature for 0.5 h and then was allowed to react with **2** (2 equiv). ^b Determined by GC analysis.

Table 3. Direct Carbon–Carbon Bond Formation of Carbamates with Allylsilanes, Enol Silyl Ethers, and Related Compounds Using the "Cation Pool" Method^a

| precursor of the cation | carbon nucleophile | product | manual yield (%) ^c | robotic synthesizer yield (%) ^{c,d} |
|-------------------------|--------------------|---------|-------------------------------|--|
| | | | 82 | 84 |
| | | | 84 | 93 |
| | | | 87 | 94 |
| | | | 84 | 49 |
| | | | 68 | — |
| | | | 88 | 72 |
| | | | 64 | — |
| | | | 78 | — |

^a After the electrolysis (2.5 F/mol based on the carbamates) at -72 °C, the carbon nucleophile (2 equiv) was added at the same temperature to the "cation pool" thus generated, and then the reaction mixture was stirred for 30–120 min to give the product (method A). ^b A carbon nucleophile was added to the "cation pool" at -28 °C. ^c Determined by GC analysis. ^d The reaction using a robotic synthesizer was carried out at 0 °C. The dash means that the reaction was not tried.

yield of **4** among the electrolytes examined (PF_6^- (48%), OTf^- (59%), and ClO_4^- (5%)). The stability of **3** and its reactivity toward **2** were also dependent upon the nature of the counteranion derived from the supporting electrolyte.⁹

The thermal stability of the "cation pool" was also studied. Thus, the electrolysis of **1** was carried out at -72 °C (ca. 3.5 h). After the electrolysis was completed, the "cation pool" was allowed to warm to a second temperature. After being kept there for 0.5 h, the carbocation was then allowed to react with **2** at the same temperature. As shown in Table 2, the "cation pool" of **3** is rather stable at temperatures lower than 0 °C. This observation contrasts sharply with the temperature effect of the

(9) For the effect of the counteranion on reactivity, see: Yamaguchi, R.; Hatano, B.; Nakayasu, T.; Kozima, S. *Tetrahedron Lett.* **1997**, 38, 403–406.

Table 4. Direct Carbon–Carbon Bond Formation of Carbamate **1** with Aromatic Compounds and 1,3-Dicarbonyl Compounds Using the "Cation Pool" Method

| aromatic and 1,3-dicarbonyl compound | method of addition ^a | temperature | product | yield (%) ^b |
|--------------------------------------|---------------------------------|-------------|---------|------------------------|
| | B | -72 °C | | 53 |
| | C | 0 °C | | 72 |
| | B | -72 °C | | 57 |
| | | | | 19 |
| | B | -72 °C | | 65 |
| | | | | 9 |
| | C | 0 °C | | 46 |
| | C | 0 °C | | 71 |

^a Method B: After the electrolysis (2.5 F/mol based on **1**) at -72 °C, the "cation pool" thus generated and a solution of an aromatic compound (1 equiv) were added simultaneously to an empty reaction flask cooled at -72 °C. The reaction was completed immediately. Method C: To the "cation pool" thus generated was added an excess amount of an aromatic compound or a 1,3-dicarbonyl compound, and the mixture was stirred at 0 °C for 24 h. ^b Isolated yields.

electrolysis shown in Table 1. There seems to be significant difference between the stability of **3** during the electrolysis and that after the electrolysis, although the mechanistic details have not been clarified as yet.

It is important to know the nature of the "cation pools" generated by the low-temperature electrolysis. Are they ionic compounds or covalent compounds? To gain insight into this point, the "cation pool" generated by low-temperature electrolysis of **1** in CD_2Cl_2 was analyzed by NMR spectroscopy.¹⁰ ¹H NMR spectroscopy exhibited a single set of signals at 2.45, 3.54, 4.09, 4.45, and 9.38 ppm at 0 °C. These signals did not

(10) NMR study of iminium cations have been reported: (a) Yamamoto, Y.; Nakada, T.; Nemoto, H. *J. Am. Chem. Soc.* **1992**, 114, 121–125. (b) Kodama, Y.; Okumura, M.; Yanabu, N.; Taguchi, T. *Tetrahedron Lett.* **1996**, 37, 1061–1064. (c) Mayr, H.; Ofial, A. R.; Würthwein, E.-U.; Aust, N. C. *J. Am. Chem. Soc.* **1997**, 119, 12727–12733 and references therein. It has been reported that the covalent structure exhibits the signal at 7.9 ppm in ¹H NMR spectroscopy: (d) Bose, A. K.; Spiegelman, G.; Manhas, M. S. *Tetrahedron Lett.* **1971**, 3167–3170.

change significantly when the temperature was decreased to -80 °C, indicating that a single species was generated by the low-temperature electrolysis. The chemical shifts of the signals were consistent with the structure of the iminium cation. The chemical shift of the methine proton at 9.38 ppm indicated that this species was an iminium cation and not a covalently bonded intermediate. In ^{13}C NMR spectroscopy the “cation pool” exhibited a single signal at 193.36 ppm at 0 °C due to the methine carbon. This value also suggests the presence of a strong positive charge at the carbon, again supporting the formation of the “cation pool” as a solution of a single ionic species. Currently it is difficult to distinguish whether the iminium cation is a free ion or an ion pair.

The generality of the “cation pool” method was demonstrated by the results shown in Table 3. The reaction of the “cation pool” of **3** generated from **1** with other allylsilanes such as 2-cyclopentenyltrimethylsilane and 2-cyclohexenyltrimethylsilane took place smoothly indicating the effectiveness of substituted allylsilanes as nucleophiles. The reaction with other carbon nucleophiles such as enol silyl ethers and enol acetates also proceeded smoothly to give the corresponding carbon–carbon bond formation products. The “cation pools” of other iminium ions were also generated from carbamates derived from piperidine and diethylamine, and they were effective for the carbon–carbon bond formation.

Aromatic compounds and 1,3-dicarbonyl compounds (Table 4) can also be utilized as carbon nucleophiles. In the case of aromatic compounds with high reactivity such as 1,3,5-trimethoxybenzene, a solution of the cation and a solution of a nucleophile (1 equiv) were added simultaneously to an empty reaction vessel (method B) to avoid undesired side reactions such as polyalkylation. In the case of less reactive aromatic compounds such as 1,3,5-trimethylbenzene, a solution of the cation was added to an aromatic compound (excess amount) and the mixture was stirred at 0 °C for 24 h (method C). For the reaction with 1,3-dicarbonyl compounds such as dimethyl malonate and acetylacetone (2,4-pentanedione), method C was employed.

In addition to using the “cation pool” method for conventional organic synthesis, it was also applied to solution-phase combinatorial parallel synthesis.¹¹ The opportunities for variation in the source of “cation pools” and nucleophiles in this work enabled the direct synthesis of a variety of coupling products. Thus, the substrate was subjected to low-temperature electrolysis to generate the “cation pool” which was then divided into several portions as shown in Figure 2. The portions were each allowed to react with different nucleophiles to give the corresponding coupling products. To demonstrate the feasibility of this concept, the “cation pool” of **3** generated from **1** was delivered to several reaction vessels cooled at 0 °C using a robotic synthesizer. To each vessel was added a different nucleophile to accomplish

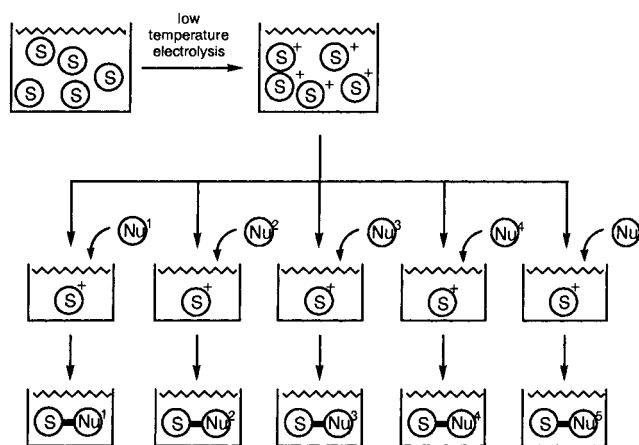


Figure 2. Combinatorial parallel synthesis based on the “cation pool” method.

the carbon–carbon bond formation. The yields of the products were essentially the same as those obtained by the one-pot reactions with manual operation as shown in Table 3. The present results demonstrate the potentiality of the parallel synthesis based on the “cation pool” method and open a new aspect of automated solution-phase combinatorial synthesis.¹²

Conclusion

The “cation pool” method described in this paper provides a new, efficient procedure for direct oxidative carbon–carbon bond formation. This methodology, which involves first the generation of a cation pool using low-temperature electrolysis and second a reaction of the cation pool with nucleophiles under non-oxidative conditions, solved problems associated with conventional oxidative generation of cations and their in situ reactions with nucleophiles. The present method can also be applied to solution-phase combinatorial parallel synthesis using a robotic synthesizer. This concept will hopefully make significant contributions to carbocation chemistry and open a new aspect of organic synthesis using carbocations.

Acknowledgment. This research was supported by a Grant-in-Aid for Scientific Research from Monbusho. We thank Tecan Japan Ltd. for giving us opportunities to use a robotic synthesizer.

Supporting Information Available: Experimental details including conditions for electrolysis and spectroscopic data of the products (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(11) For example: (a) Borman, S. *Chem. Eng. News* **1996** (February 12), 28–73. (b) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, 96, 555–600. (c) Borman, S. *Chem. Eng. News* **1997** (February 24), 43–62. (d) Borman, S. *Chem. Eng. News* **1999** (March 3), 33–48. (e) Dagani, R. *Chem. Eng. News* **1999** (March 3) 51–60 and references therein.

(12) For example: (a) Booth, R. J.; Hodges, J. C. *Acc. Chem. Res.* **1999**, 32, 18–26. (b) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, 97, 489–509. (c) Studer, A.; Hadida, S.; Ferritto, R.; Kim, S.-Y.; Jeger, P.; Wipf, P.; Curran, D. P. *Science* **1997**, 275, 823–826. (d) Cheng, S.; Commer, D. D.; Williams, J. P. Myers, P. L.; Boger, D. L. *J. Am. Chem. Soc.* **1996**, 118, 2567–2573 and references therein.