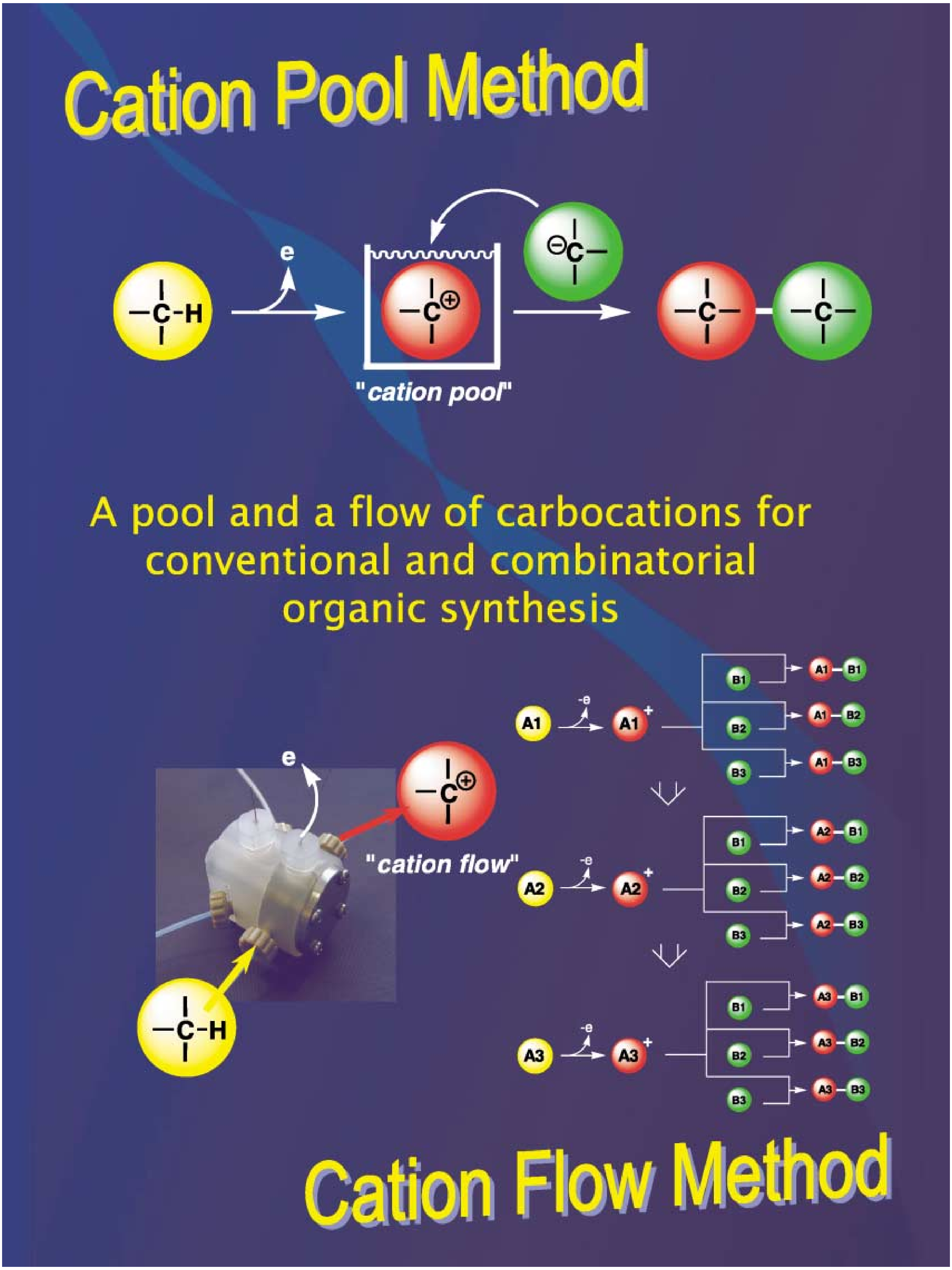


Cation Pool Method

A pool and a flow of carbocations for conventional and combinatorial organic synthesis

Cation Flow Method

Basic Concepts of “Cation Pool” and “Cation Flow” Methods and Their Applications in Conventional and Combinatorial Organic Synthesis

Jun-ichi Yoshida* and Seiji Suga[a]

Abstract: Carbocations have been generally considered to be relatively unstable and transient species. But the “cation pool” method enables the easy accumulation of carbocations in conventional reaction media such as dichloromethane. In the “cation pool” method, carbocations are generated by low-temperature electrochemical oxidation and accumulated in a solution. In the next step, the carbocations thus produced are allowed to react with various nucleophiles. Combinatorial parallel synthesis based upon the “cation pool” method has also been developed. The applicability of the “cation pool” method depends upon the stability of the cation that is accumulated. This problem can be overcome by the “cation flow” method. In the “cation flow” method, carbocations are generated in a microflow electrochemical system. Short residence times and efficient temperature control of the microflow system are advantageous. Combinatorial sequential synthesis has been achieved based on the “cation flow” method.

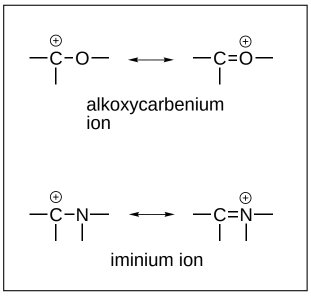
Keywords: carbocations · combinatorial chemistry · electrochemistry · microreactors · oxidation

Introduction

Carbocations are positively charged carbon-centered reactive intermediates.[1] In the pioneering works by Meerwein, Ingold, Whitmore, and other chemists, carbocations were found to play key roles in various organic reactions, although they were considered to be relatively unstable and transient species.

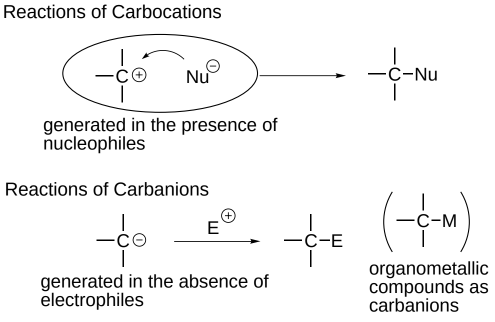
Olah’s extensive work in 1960s, however, revealed that carbocations can be long-lived species in superacid media.[2] Various carbocations were generated and accumulated in superacid, and they were characterized by spectroscopic methods. The proof of the existence of carbocations was an epoch-making discovery in organic chemistry. However, the nature of carbocations in conventional reaction media, which are used for organic synthesis, has not been fully clarified as yet.

Carbocations are important reactive intermediates in organic synthesis. Quite a few reactions involving carbocations, especially those stabilized by neighboring heteroatoms such as oxygen (alkoxycarbenium ion) and nitrogen (iminium ion), have been developed so far (Scheme 1). It is noteworthy that other names, such as oxocarbenium ion[3] and carboxonium ion,[4] have been used for oxygen-stabilized carbocations. Reactions of such heteroatom-stabilized carbocations have witnessed a steady increase in modern organic synthesis.



Scheme 1. Carbocations stabilized by neighboring heteroatoms.

From a viewpoint of synthesizing compounds by using carbocations, it is noteworthy that the manner in which we carry out the reactions of carbocations is different from that for carbanions (Scheme 2). Usually, carbanions are generated



Scheme 2. The reaction mode of carbocations and that of carbanions.

---

[a] Prof. J. Yoshida, Dr. S. Suga
Department of Synthetic Chemistry & Biological Chemistry
Graduate School of Engineering
Kyoto University, Kyoto 606-8501 (Japan)
Fax: (+81) 75-753-5911
E-mail: yoshida@sbchem.kyoto-u.ac.jp

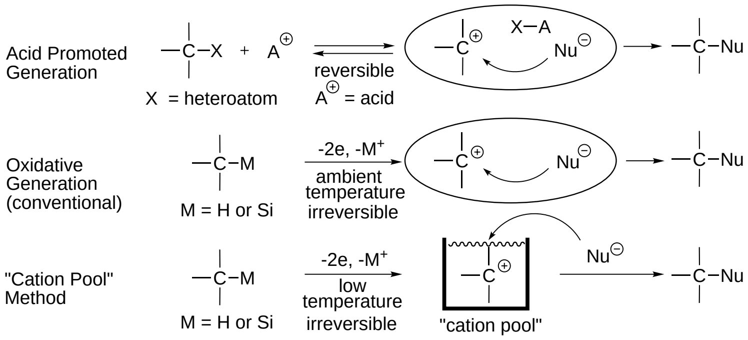
0947-6539/02/0812-2651 $ 20.00+.50/0

and accumulated in a solution in the absence of electrophiles. After the generation process, such as deprotonation or a halogen–metal exchange reaction, is completed, an electrophile is added to the solution of the thus generated carbanion to achieve the desired transformation. In contrast, carbocations are usually generated in the presence of nucleophiles. This is probably because carbocations are considered to be relatively unstable and transient in conventional reaction media and should be trapped by nucleophiles immediately after the generation in situ. Therefore, reactions of carbocations suffer from the limitation of the variation of nucleophiles. This comparison is, however, probably not fair, because we usually regard organometallic compounds as carbanions. Organometallic compounds have carbon–metal covalent bonds, although the magnitude of the ionic character depends on the nature of the metal and substituents on the carbon. In contrast, we do not regard an organic molecule having a leaving group bound to the carbon by a covalent bond as a carbocation. We only regard "real" ionic species as carbocations. Apart from such arguments, development of a new method that enables the generation of carbocations in the absence of nucleophiles is strongly needed for expanding the scope of the chemistry of carbocations in organic synthesis.

Recently it has been demonstrated that heteroatom-stabilized carbocations can be generated in the absence of nucleophiles in normal reaction media by using the "cation pool"[5] and the "cation flow"[6] methods, although their applications to alkyl cations have not been explored as yet. These methods enable easy manipulation of carbocations just like stable compounds. The objective of this paper is to provide a brief outline of these methods with an emphasis on their principles.

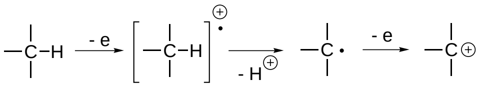
Conventional Methods for the Generation of Carbocations

Before discussing the concepts of "cation pool" and "cation flow" methods, let us touch briefly on the generation methods of carbocations. In principle there are two methods, that is, acid promoted reaction and oxidative reaction, to generate carbocations for preparative purposes (Scheme 3). Acid promoted reactions are the most commonly used for the generation of carbocations. In this method, a proton or a Lewis acid is used to activate a leaving group, and then the heterolysis of the bond between the carbon and the leaving group occurs to generate the carbocation. Because these steps are reversible, several species often exist in the solution as an equilibrium mixture. Then, a nucleophile, which is usually present in the solution, attacks the carbocation to give the final product. However, there is still the question of the existence of carbocations as intermediates in the conventional reaction media such as dichloromethane, which is commonly used for preparative reactions. Sometimes only a covalent species (a complex with an acid) is involved in the reaction, and such an intermediate undergoes a S_N2 type displacement to give the final product.



Scheme 3. Methods for the generation and reactions of carbocations.

Another method is oxidative generation (Scheme 4). The first electron transfer generates the radical cation species. The elimination of a proton gives the carbon radical that is further oxidized to give the carbocation. These steps are essentially irreversible. Then a nucleophile attacks the carbocation to give the product. By virtue of irreversibility, the oxidative generation could serve as a good method for studying the chemistry of carbocations. However, the oxidative generation of carbocations is also usually carried out in the presence of nucleophiles because of the instability of carbocations. In this case the concentration of carbocations should be low, and therefore, it is difficult to detect carbocations intermediates spectroscopically.



Scheme 4. Oxidative generation of carbocations.

"Cation Pool" Method

In the "cation pool" method, carbocations are generated and accumulated in relatively high concentration by electrochemical oxidation. The electrolysis is carried out at low temperature such as −70 °C in order to avoid decomposition of carbocations. It was considered to be difficult to carry out preparative electrolyses at such low temperature probably because of the high viscosity of the solution, which in turn disfavors the movement of ions to carry the electricity. By choosing an appropriate solvent and a supporting electrolyte, however, the electrolysis at such low temperature can be accomplished to generate and accumulate carbocations. A divided cell having a sintered glass separator is used in order to avoid the electrochemical reduction of anodically generated carbocations (vide infra; Figure 1). Tetrabutylammoni-

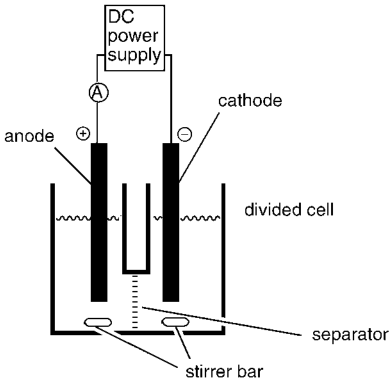


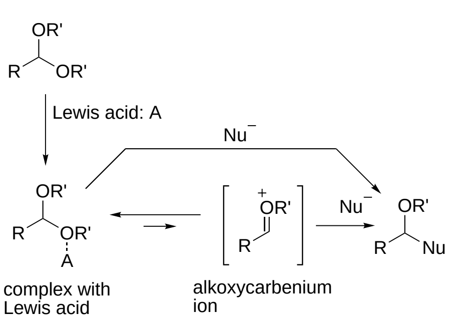
Figure 1. The electrochemical cell for the "cation pool" method.

um tetrafluoroborate is usually used as supporting electrolyte, and dichloromethane is suitable as solvent because of low viscosity at low temperature. TfOH (trifluoromethanesulfonic acid) is added in the cathodic chamber to facilitate the reduction of protons in the cathodic process.

In the next step, carbocations are allowed to react with nucleophiles. In principle, any kind of nucleophiles can be used, because the nucleopile is absent during the course of the generation. This is true for carbon nucleophiles, which are easily oxidized and often cannot be used for in situ oxidation. In the next section, the "cation pool" method is illustrated for the generation of alkoxycarbenium ions and their reactions with nucleophiles.

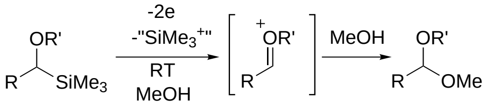
Alkoxycarbenium Ion Pool

Alkoxycarbenium ions are carbenium ions stabilized by an alkoxy substituent. Alkoxycarbenium ions are important reactive intermediates in modern organic synthesis.[7] For example, they are often generated from the corresponding acetals by treatment with Lewis acids and allowed to react with carbon nucleophiles (Scheme 5). Thus, these reactions serve as efficient methods for carbon–carbon bond formation.



Scheme 5. Lewis acid promoted reactions of acetals.

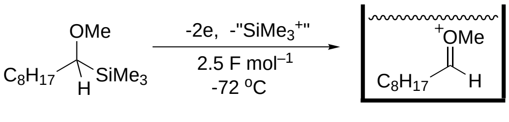
The mechanism of the Lewis acid promoted reaction of acetals has been investigated extensively. Denmark revealed the presence of Lewis acid–acetal complexes in NMR studies but never detected alkoxycarbenium ions. The absence of alkoxycarbenium ions in spectra, however, does not necessarily rule out their intermediacy in the reactions with nucleophiles.[8] Therefore, it has been imperative to accomplish the reactions of spectroscopically characterized, nonstabilized alkoxycarbenium ions with carbon nucleophiles.[9] The "cation pool" method makes it possible and opens a new aspect of the chemistry of alkoxycarbenium ions. As precursors of alkoxycarbenium ions in the "cation pool" method, ethers should be of the first choice. The oxidation potentials of ethers, however, are very positive, and therefore, it is rather difficult to oxidize ethers selectively under usual conditions.[10] The regioselectivity is another problem. Usually a mixture of two regioisomers is obtained because two regioisomeric alkoxycarbenium ions are generated. The concept of electroauxiliary[11] is quite powerful to solve these problems. The pre-introduction of a silyl group[12] as an electroauxiliary decreases the oxidation potential of dialkyl ethers by virtue of orbital interaction. The interaction of the nonbonding p orbital (lone pair) of the oxygen with the C–Si σ orbital raises the HOMO level, which in turn favors the electron transfer. As a matter of fact, it has been already demonstrated that the anodic oxidation of an α-silyl ether takes place smoothly in methanol (Scheme 6).[13] Selective cleavage of the C–Si bond occurs, and the methoxy group is introduced on the carbon to which the silyl group has been attached.



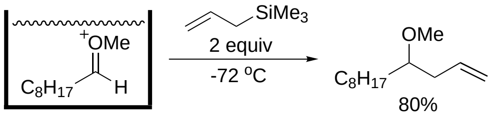
Scheme 6. Electrochemical oxidation of α-silyl ethers in methanol.

Thus, α-silyl ethers serve as suitable precursors of alkoxycarbenium ions in the "cation pool" method (Scheme 7). The low-temperature electrochemical oxidation of the α-silyl ether gives a solution of alkoxycarbenium ion, which exhibits a ^{1}H NMR signal at $\delta = 9.55$ ppm for a methine proton, and a ^{13}C NMR signal at $\delta = 231.0$ ppm due to a methine carbon.[5b] These chemical shifts are consistent with those of an alkoxycarbenium ion generated in superacid reported by Olah and Forsyth, respectively,[14] and suggest the presence of a strong positive charge at the carbon.

The alkoxycarbenium ion pool reacts with allyltrimethylsilane as a carbon nucleophile to give the corresponding allylated product (80%, Scheme 8). The success of this nucleophilic reaction also indicates the presence of the alkoxycarbenium ion in relatively high concentration in the solution.



Scheme 7. "Cation pool" method using low-temperature electrolysis.



Scheme 8. The reaction of an alkoxycarbenium ion pool with allyltrimethylsilane.

The thermal stability of the alkoxycarbenium ion is interesting. When the electrolysis is complete, the cation pool is allowed to warm to a second temperature. After being kept there for 30 min, the cation is then allowed to react with allyltrimethylsilane. The yield of the allylated product is plotted against the temperature. It can be seen from Figure 2 that the alkoxycarbenium ion is stable at temperatures lower than approximately −50 °C. Above this temperature, the yield of the allylated product decreases significantly, and this indicates that the alkoxycarbenium ion decomposed above −50 °C.

The alkoxycarbenium ions generated by the “cation pool” method react smoothly with various carbon nucleophiles such as substituted allylsilanes and enol silyl ethers to give the corresponding coupling products in good yields. It should be noted that the reactions of alkoxycarbenium ion pools with such nucleophiles are much faster than the Lewis acid promoted reactions of acetals with similar nucleophiles. A higher concentration of the cationic species in the “cation pool” method seems to be responsible.

The diastereoselectivity of the reactions with enol silyl ethers is worth noting. For example, the reaction with the enol silyl ether derived from cyclohexanone gives a mixture of two diastereomers, and the selectivity is somewhat lower than that reported for the Lewis acid promoted reaction of the acetal,[15] although the reason is not clear at present.

Ketene silyl acetals and enol acetates also serve as effective carbon nucleophiles. More interesting is the observation that 1,3-dicarbonyl compounds, which are much weaker as nucleophiles, are also effective, although five equivalents of the 1,3-dicarbonyl compound are usually employed. Scheme 9 summarizes the carbon nucleophiles, which have been applied to the “cation pool” method.

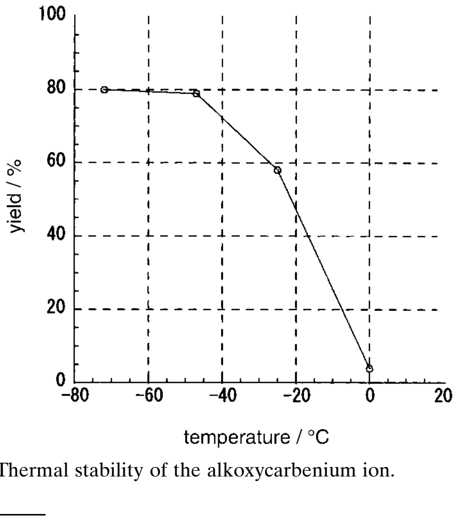
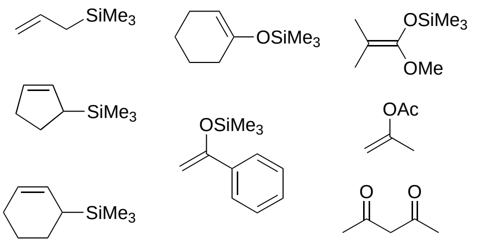


Figure 2. Thermal stability of the alkoxycarbenium ion.

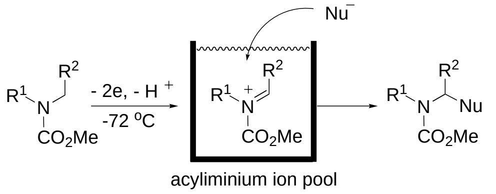


Scheme 9. Nucleophiles used for the reactions of alkoxycarbenium ion pools.

N-Acyliminium Ion Pool

N-Acyliminium ions are also important intermediates in organic synthesis, especially the synthesis of various nitrogen-containing natural and unnatural products of biological interest.[16] *N*-Acyliminium ions also act as carbocations toward various nucleophiles including carbon nucleophiles.

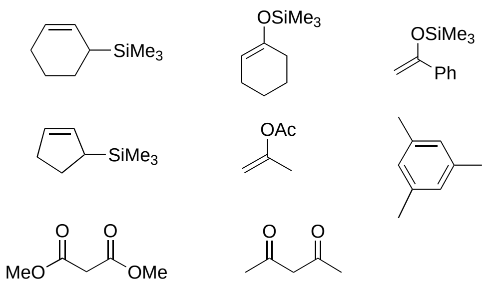
The “cation pool” method can also be applied to the generation of *N*-acylimium ions (Scheme 10), and carbamates are suitable precursors because extensive work has been done on the electrochemical oxidation of carbamates to generate *N*-acyliminium ions, which are trapped in situ usually by methanol used as solvent.[17] The low-temperature electrolysis of a carbamate derived from pyrrolidine gives the corresponding *N*-acyliminium ion as a single species, which is indicated by NMR analysis (^{1}H NMR: $\delta = 9.38$ ppm due the methine proton; ^{13}C NMR: $\delta = 193.36$ ppm due to the methine carbon).[5a] These chemical shifts indicate that there is a strong positive charge at the carbon and that there is formation of the *N*-acyliminium ion as an ionic species.[18] The addition of allyltrimethylsilane to the solution of this cation affords the allylated product in good yield.



Scheme 10. Generation and reaction of the *N*-acyliminium ion by using the “cation pool” method.

The *N*-acyliminium ion can also be characterized by FTIR spectroscopy. The starting carbamate exhibits an absorption at 1694 cm^{-1} due to the carbonyl stretching, while the *N*-acyliminium ion generated by the “cation pool” method exhibits an absorption at 1814 cm^{-1}. The higher wavenumber of the cation is consistent with the existence 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.

The “cation pool” method is generally applicable to various carbon nucleophiles. Allylsilanes, enol silyl ethers, enol acetates, 1,3-dicarbonyl compounds, and aromatic compounds are effective as carbon nucleophiles, and the corresponding



Scheme 11. Nucleophiles used for the reactions of *N*-acyliminium ion pools.

C–C bond formation products are obtained directly (Scheme 11).

The use of organometallics of higher basicity such as organolithium compounds gives rise to the formation of a complex mixture, probably because of a β-elimination reaction. Therefore, organolithium compounds are not suitable as nucleophiles for the *N*-acyliminium ion. In contrast, the reactions with Grignard reagents having alkyl, allyl, and aryl groups take place smoothly.[5c]

Other organometallic compounds such as organozinc and organoaluminum reagents are also effective as carbon nucleophiles. The low basicity of such reagents, which might suppress the competing elimination process, seems to be responsible for the success of the reactions.

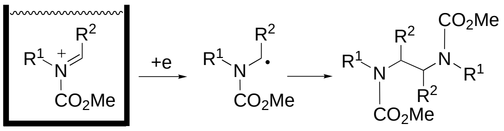
It is noteworthy that the "cation pool" method can be applied to parallel combinatorial synthesis.[19] Combinatorial chemistry has emerged as a concept for creating a multiplicity of molecules to discover compounds having desired activity or function, and parallel synthesis serves as an effective approach to realizing this concept. Required for successful combinatorial synthesis are reactions of high generality to couple any desired combination of molecules we want. The "cation pool" method seems to be suitable for this purpose, because carbocations generated by this method are usually so highly reactive as to couple with a wide range of nucleophiles. The general principle of the parallel synthesis based on the "cation pool" method is shown in Figure 3. A solution of a cation generated by low-temperature electrolysis is divided into several portions. To each portion, different nucleophiles are added to obtain different combinations of C–C bond formation products. This approach has been successfully applied for the parallel synthesis by using a *N*-acyliminium ion pool.[5a]

The procedure can be easily automated by a robotic synthesizer equipped with automated syringes and low-temperature reaction vessels. The yields of the products are essentially the same as those obtained by one-pot reactions with manual operation. The parallel synthesis based on the "cation pool" method opens up a new aspect of automated solution-phase combinatorial synthesis.[20]

Reduction of a "Cation Pool"

Armed with an understanding of the basic principles of the "cation pool" method, we are now in a position to apply it to achieve new transformations otherwise difficult to perform. Let us briefly touch on the reduction of a "cation pool".[5d] It is well recognized that one electron reduction of a carbocation generates a carbon radical.[21] Although such a relationship has been well established, this chemistry has been rather limited to analytical studies with highly stabilized carbocations.[22] The "cation pool" method serves as a method for realizing this chemistry in a preparative fashion.

N-Acyliminium ions generated by low-temperature electrolysis are easily reduced electrochemically to produce the corresponding homocoupling product (Scheme 12).[23] A mechanism involving one electron reduction to carbon radicals has been proposed.



Scheme 12. Reductive homocoupling of a "cation pool".

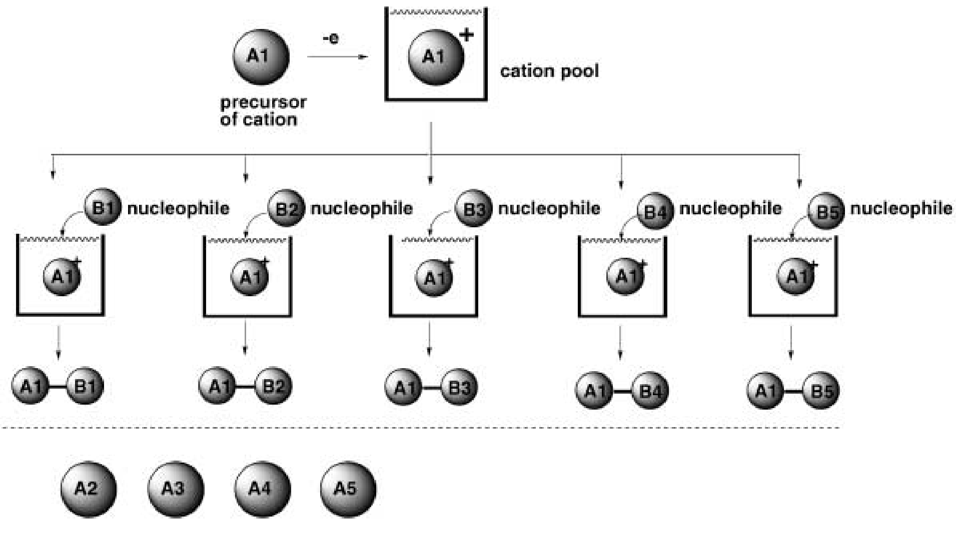
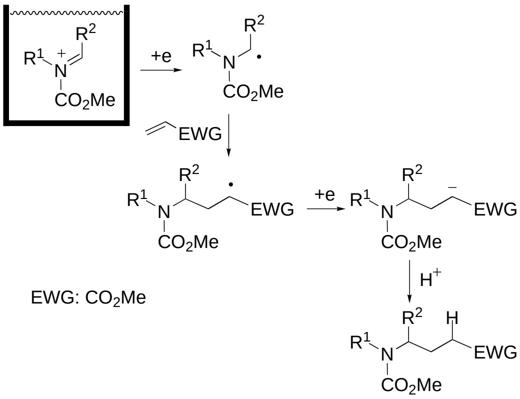


Figure 3. Parallel combinatorial synthesis based upon the "cation pool" method.

The reduction in the presence of radical accepting alkenes, such as methyl acrylate, is more interesting (Scheme 13). The radical adds to the alkene,[24] and the resulting radical is further reduced to give the carbanion, which is trapped by a proton to give the final product.



Scheme 13. Reductive coupling of a “cation pool” with an activated alkene.

Reduction of a “cation pool” provides a new strategy for the radical-mediated carbon–carbon bond formation, and this strategy opens new opportunities to manipulate reactive carbon species by using redox processes in organic synthesis.

“Cation Flow” Method

As described in the previous sections, the “cation pool” method enables easy manipulation of carbocation intermediates to achieve reactions with various nucleophiles, but its applicability strongly depends on the stability of the carbocation that is generated and accumulated. In order to solve this problem, a “cation flow” method using a microflow electrochemical system has been developed.[6]

Microflow reactors have received significant interest in terms of the downsizing of chemistry.[25] Although microflow reactors have been mainly utilized in chemical analysis (µTAS: micro total analysis system, Lab-on-a-Chip),[26] they are now expected to make an innovative and revolutionary change in chemical synthesis.[27, 28] Several advantages of microflow reactors that stem from the high surface-to-volume ratio should be noted. Highly effective heat transfer enables precise temperature control, and high efficiency of mass transfer facilitates heterogeneous reactions on the surface. Short residence times in microflow reactors may also be advantageous from a viewpoint of the manipulation of highly reactive intermediates such as carbocations.

In the “cation flow” system, a carbocation is generated continuously by low-temperature electrolysis by using an electrochemical microflow reactor (Figure 4). A schematic diagram of the “cation flow” system is shown in Figure 5. The reaction of a *N*-acyliminium ion with allyltrimethylsilane is performed as a representative reaction. A solution of a precursor (carbamate) is introduced into the anodic chamber equipped with a carbon felt anode made of carbon fibers ($\phi = 10\,\mu m$). A solution of the supporting electrolyte and TfOH as a proton source is introduced into the cathodic chamber equipped with a platinum wire cathode.

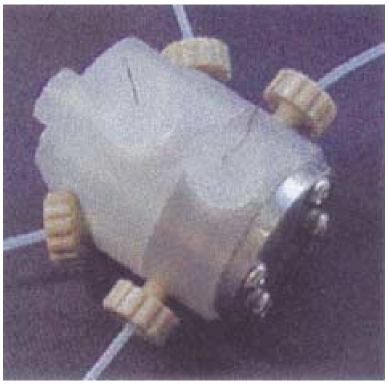


Figure 4. An electrochemical microflow reactor for the “cation flow” method.

The generation of the cation can be 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 *N*-acyliminium ion is monitored with the absorption at 1814 cm^{-1}, which increased with the increase in the electric current.

Thus, the cationic intermediate generated by low-temperature electrolysis is immediately transferred to a vessel, in which a nucleophilic reaction with allyltrimethylsilane takes place to give a final coupling product. The reactions with other carbon nucleophiles also take place smoothly to give the oxidative C–C bond formation products, and they provide a useful method for the synthesis of nitrogen-containing organic molecules.

More outstanding is that the “cation flow” method enables the continuous sequential combinatorial synthesis[29] by simple flow switching as shown in Figure 6. In the first step, the

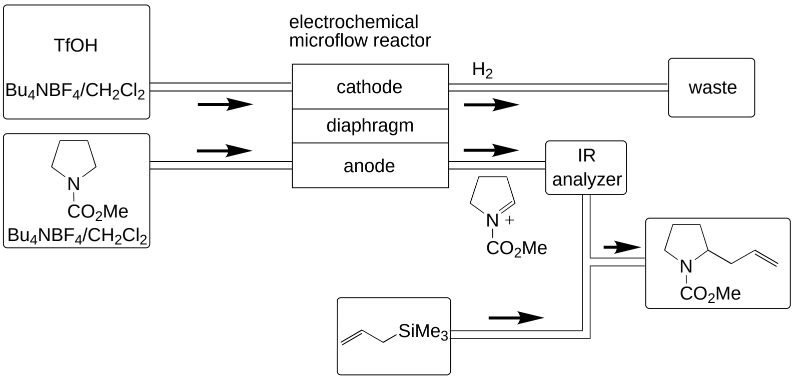


Figure 5. Schematic diagram of the “cation flow” system.

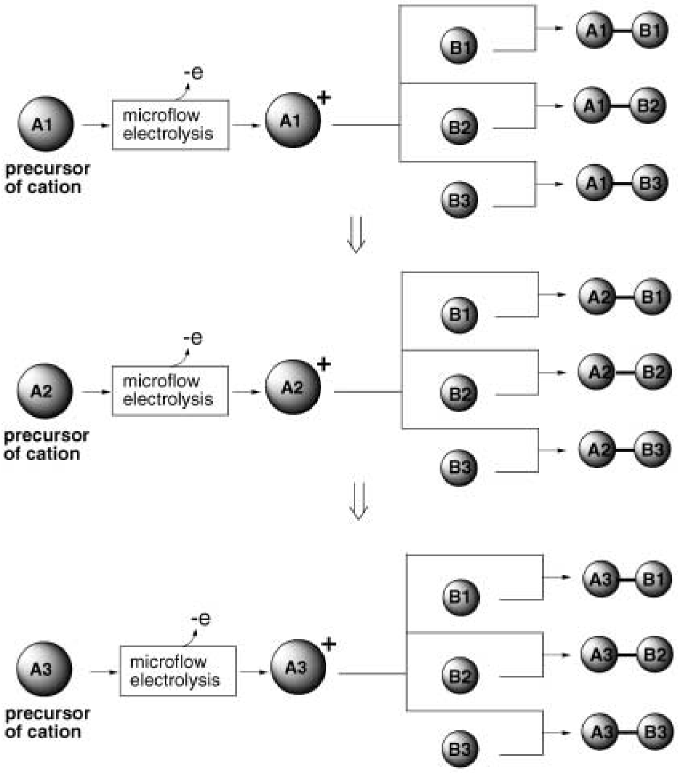


Figure 6. Continuous sequential combinatorial synthesis using the “cation flow” system.

“cation flow” generated from **A1** is allowed to react with nucleophile **B1**. Then, the “cation flow” is allowed to react with nucleophile **B2**. In the third step, the “cation flow” is allowed to react with nucleophile **B3**. Then, the precursor of the cation is switched to **A2**, and the “cation flow” generated from **A2** is allowed to react with nucleophiles **B1**, **B2**, and **B3** sequentially. Then, the precursor of the cation is switched to **A3**, and the “cation flow” generated from **A3** is allowed to react with nucleophiles **B1**, **B2**, and **B3** sequentially. Although parallel syntheses enjoy versatile applications in combinatorial chemistry, the present continuous sequential method opens up a new intriguing aspect of combinatorial synthesis.

Future Outlook

The “cation pool” and “cation flow” methods demonstrated here open up a new aspect of the chemistry based upon carbocations, which have been considered to be difficult to manipulate in normal reaction media. These methods enable the generation of carbocations in the absence of nucleophiles, spectroscopic characterization, and reactions with a variety of carbon nucleophiles to achieve direct carbon–carbon bond formation. The successful applications to alkoxycarbenium ions and *N*-acyliminium ions speak well for their potentiality in conventional and combinatorial organic synthesis. Future work aimed at improving the efficiency of these methods and expanding the scope of the substrates and reaction patterns will hopefully enable manipulation of “carbocations” just like conventional reagents in organic synthesis.

Acknowledgements

This work is supported by Grants-in-Aid for Scientific Research and Special Coordination Funds for Promoting Science and Technology from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

---

[1] For example, *Stable Carbocation Chemistry* (Eds.: G. K. S. Prakash, P. v. R. Schleyer), Wiley Interscience, New York, **1997**.

[2] a) G. A. Olah, *Angew. Chem.* **1995**, *107*, 1519; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1393; b) G. A. Olah, *J. Org. Chem.* **2001**, *66*, 5943.

[3] J. A. C. Romero, S. A. Tabacco, K. A. Woerpel, *J. Am. Chem. Soc.* **2000**, *122*, 168.

[4] a) H. Mayr, G. Gorath *J. Am. Chem. Soc.* **1995**, *117*, 7862; b) L. A. B. Moraes, M. A. Mendes, R. Sparrapan, M. N. Eberlin, *J. Am. Soc. Mass Spectrom.* **2001**, *12*, 14.

[5] a) J. Yoshida, S. Suga, S. Suzuki, N. Kinomura, A. Yamamoto, K. Fujiwara, *J. Am. Chem. Soc.* **1999**, *121*, 9546; b) S. Suga, S. Suzuki, A. Yamamoto, J. Yoshida, *J. Am. Chem. Soc.* **2000**, *122*, 10244; c) S. Suga, M. Okajima, J. Yoshida, *Tetrahedron Lett.* **2001**, *42*, 2173; d) S. Suga, S. Suzuki, J. Yoshida, *J. Am. Chem. Soc.* **2002**, *124*, 30.

[6] S. Suga, M. Okajima, K. Fujiwara, J. Yoshida, *J. Am. Chem. Soc.* **2001**, *123*, 7941.

[7] For example: M. Santelli, J.-M. Pons, *Lewis Acids and Selectivity in Organic Synthesis*, CRC Press, Boca Raton, **1995**, Chapter 4.

[8] S. E. Denmark, T. M. Willson in *Selectivities in Lewis Acid Promoted Reactions* (Ed.: D. Schinzer), Kluwer Academic, Dordrecht, **1989**, p. 247.

[9] Highly stabilized alkoxycarbenium ions are well characterized spectroscopically: Benzylic alkoxycarbenium ions: a) M. Rabinovitz, D. Bruck, *Tetrahedron Lett.* **1971**, 245; b) T. L. Amyes, W. P. Jencks, *J. Am. Chem. Soc.* **1989**, *111*, 7888; c) V. Jagannadham, T. L. Amyes, J. P. Richard, *J. Am. Chem. Soc.* **1993**, *115*, 8465; d) H. Mayr, G. Gorath, *J. Am. Chem. Soc.* **1995**, *117*, 7862. Di- and trialkoxycarbenium ions: e) B. G. Ramsey, R. W. Taft, *J. Am. Chem. Soc.* **1966**, *88*, 3058; f) S. Steenken, J. Buschek, R. A. McClelland, *J. Am. Chem. Soc.* **1986**, *108*, 2808; g) R. A. McClelland, S. Steenken, *J. Am. Chem. Soc.* **1988**, *110*, 5860; h) S. Steenken, R. A. McClelland, *J. Am. Chem. Soc.* **1989**, *111*, 4967. 1-Benzopyrylium ion: i) R. Doodeman, F. P. J. T. Rutjes, H. Hiemstra, *Tetrahedron Lett.* **2000**, *41*, 5979.

[10] For example: T. Shono in *The Chemistry of Ethers*, *Crown Ethers*, *Hydroxyl Groups and Their Sulfur Analogues*, *Part 1* (Ed.: S. Patai), Wiley, Chichester, **1980**, Chapter 8.

[11] a) J. Yoshida, K. Nishiwaki, *J. Chem. Soc. Dalton Trans.* **1998**, 2589; b) J. Yoshida, M. Sugawara, M. Tatsumi, N. Kise, *J. Org. Chem.* **1998**, *63*, 5950; c) J. Yoshida, M. Watanabe, H. Toshioka, M. Imagawa, S. Suga, *Chem. Lett.* **1998**, 1011; d) M. Sugawara, K. Mori, J. Yoshida, *Electrochim. Acta* **1997**, *42*, 1995; e) J. Yoshida, Y. Ishichi, S. Isoe, *J. Am. Chem. Soc.* **1992**, *114*, 7594.

[12] a) J. Yoshida, T. Maekawa, T. Murata, S. Matsunaga, S. Isoe, *J. Am. Chem. Soc.* **1990**, *112*, 1962; b) J. Yoshida, S. Suga, K. Fuke, M. Watanabe, *Chem. Lett.* **1999**, 251.

[13] a) J. Yoshida, T. Murata, S. Isoe, *J. Organomet. Chem.* **1988**, *345*, C23; b) J. Yoshida, S. Matsunaga, T. Murata, S. Isoe, *Tetrahedron* **1991**, *47*, 615.

[14] a) G. A. Olah, J. M. Bollinger, *J. Am. Chem. Soc.* **1967**, *89*, 2993; b) G. A. Olah, J. Sommer, *J. Am. Chem. Soc.* **1968**, *90*, 4323; c) D. A. Forsyth, V. M. Osterman, J. R. DeMember, *J. Am. Chem. Soc.* **1985**, *107*, 818.

[15] a) T. Mukaiyama, M. Hayashi, *Chem. Lett.* **1974**, 15; b) A. Hosomi, M. Endo, H. Sakurai, *Chem. Lett.* **1976**, 941; c) S. Murata, M. Suzuki, R. Noyori, *J. Am. Chem. Soc.* **1980**, *102*, 3248; d) S. E. Demmark, N. G. Almstead, *J. Am. Chem. Soc.* **1991**, *113*, 8089.

[16] a) W. N. Speckamp, H. Hiemstra, *Tetrahedron* **1985**, *41*, 4367; b) H. Hiemstra, W. N. Speckamp in *Comprehensive Organic Synthesis*, *Vol. 2* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, p. 1047; c) H. E. Zaugg, *Synthesis* **1984**, 85; d) H. E. Zaugg, *Synthesis* **1984**, 181; e) W. N. Speckamp, M. J. Moolenaar, *Tetrahedron* **2000**, *56*, 3817.

[17] a) T. Shono, H. Hamaguchi, Y. Matsumura, *J. Am. Chem. Soc.* **1975**, *97*, 4264; b) T. Shono, Y. Matsumura, K. Tsubata, *Org. Synth.* **1985**, *63*, 206. The oxidative α-methoxylation of amides has also been reported: c) S. Ross, D. Finkelstein, R. C. Peterson, *J. Am. Chem. Soc.* **1966**, *88*, 4657; d) K. Nyberg, R. Servin, *Acta Chem. Scand. Ser. B* **1976**, *30*, 640; e) K. D. Moeller, *Tetrahedron* **2000**, *56*, 9527.

[18] a) Y. Yamamoto, T. Nakada, H. Nemoto, *J. Am. Chem. Soc.* **1992**, *114*, 121; b) Y. Kodama, M. Okumura, N. Yanabu, T. Taguchi, *Tetrahedron Lett.* **1996**, *37*, 1061; c) H. Mayr, A. R. Ofial, E.-U. Würthwein, N. C. Aust, *J. Am. Chem. Soc.* **1997**, *119*, 12727; d) A. K. Bose, G. Spiegelman, M. S. Manhas, *Tetrahedron Lett.* **1971**, 3167.

[19] For example, a) S. Borman, *Chem. Eng. News* **1996**, *February 12*, 28; b) L. A. Thompson, J. A. Ellman, *Chem. Rev.* **1996**, *96*, 555; c) S. Borman, *Chem. Eng. News* **1997**, *February 24*, 43; d) S. Borman, *Chem. Eng. News* **1999**, *March 3*, 33; e) R. Dagani, *Chem. Eng. News* **1999**, *March 3*, 51, and references therein.

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

[21] a) J. B. Conant, A. W. Sloan, *J. Am. Chem. Soc.* **1923**, *45*, 2466; b) J. B. Conant, L. F. Small, B. S. Taylor, *J. Am. Chem. Soc.* **1925**, *47*, 1959; c) J. B. Conant, B. F. Chow, *J. Am. Chem. Soc.* **1933**, *55*, 3752; d) H. Volz, W. Lotsch, *Tetrahedron Lett.* **1969**, 2275; e) K. Okamoto, K. Komatsu, O. Murai, O. Sakaguchi, *Tetrahedron Lett.* **1972**, 4989.

[22] For example, E. M. Arnett, K. E. Molter, E. C. Marchot, W. H. Donovan, P. Smith, *J. Am. Chem. Soc.* **1987**, *109*, 3788.

[23] Although the reductive coupling of the *N*-acyliminium ion was unknown, the reductive coupling of the iminium ion was reported in the literature. a) C. P. Andrieux, J. M. Savéant, *Bull. Soc. Chim. Fr.* **1968**, 4671; b) C. P. Andrieux, J. M. Savéant, *J. Electroanal. Chem.* **1970**, *26*, 223; c) C. P. Andrieux, J. M. Savéant, *J. Electroanal. Chem.* **1970**, *28*, 446; d) J. B. Kerr, P. E. Iversen, *Acta. Chem. Scand. Ser. B* **1978**, *32*, 405.

[24] For example: a) B. Giese, *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, Pergamon, Oxford, **1986**; b) D. P. Curran in *Comprehensive Organic Synthesis*, *Vol. 4* (Eds.: B. M. Trost, I. Fleming, M. F. Semmelhack), Pergamon, Oxford, **1991**, p. 715; c) H. Fischer, L. Radom, *Angew. Chem.* **2001**, *113*, 1380; *Angew. Chem. Int. Ed.* **2001**, *40*, 1340.

[25] a) *Microreaction Technology* (Ed.: W. Ehrfeld), Springer, Berlin, **1998**; b) W. Ehrfeld, V. Hessel, H. Löwe, *Microreactor*, Wiley-VCH, Weinheim, **2000**; c) *Microsystem Technology in Chemistry and Life Sciences* (Eds.: A. Manz, H. Becker), Springer, Berlin, **1999**; d) T. Zech, D. Hönicke, *Erdoel Erdgas Kohle* **1998**, *114*, 578; e) K. Schubert, *CHEMTECH* **1998**, *27*, 124.

[26] a) D. J. Harrison, K. Fluri, K. Seiler, Z. Fan, C. S. Effenhauser, A. Manz, *Science* **1993**, *261*, 895; b) M. Freemantle, *Chem. Eng. News* **1999**, *February 22*, 27; c) P. Fletcher, S. Haswell, *Chem. Br.* **1999**, *November*, 38; d) I. M. Hsing, R. Srinivasan, M. P. Harold, K. F. Jensen, M. A. Schmidt, *Chem. Eng. Sci.* **2000**, *55*, 3.

[27] Reviews on the applications of microreactors in organic synthesis: for example, a) S. H. DeWitt, *Curr. Opin. Chem. Biol.* **1999**, *3*, 350; b) H. Okamoto, *J. Syn. Org. Chem. Jpn.* **1999**, *57*, 805; c) T. Sugawara, *Pharmacia* **2000**, *36*, 34; d) S. J. Haswell, R. J. Middleton, B. O'Sullivan, V. Skelton, P. Watts, P. Styring, *Chem. Commun.* **2001**, 391.

[28] a) H. Salimi-Moosavi, T. Tang, D. J. Harrison, *J. Am. Chem. Soc.* **1997**, *119*, 8716; b) R. D. Chambers, R. C. H. Spink, *Chem. Commun.* **1999**, 883; c) H. Löwe, W. Ehrfeld, *Electrochim. Acta* **1999**, *44*, 3679; d) P. J. A. Kenis, R. F. Ismagilov, S. Takayama, G. M. Whitesides, S. Li, H. S. White, *Acc. Chem. Res.* **2000**, *33*, 841; e) G. M. Greenway, S. J. Haswell, D. O. Morgan, V. Skelton, P. Styring, *Sens. Actuators B* **2000**, *63*, 153; f) K. Jähnisch, M. Baerns, V. Hessel, W. Ehrfeld, V. Haverkamp, H. Löwe, Ch. Wille, A. Guber, *J. Fluorine Chem.* **2000**, *105*, 117.

[29] Combinatorial chemistry using microreactors: for example, a) S. M. Senkan, S. Ozturk, *Angew. Chem.* **1999**, *111*, 867; *Angew. Chem. Int. Ed.* **1999**, *38*, 791; b) S. M. Senkan, *Angew. Chem.* **2001**, *113*, 322; *Angew. Chem. Int. Ed.* **2001**, *40*, 312.