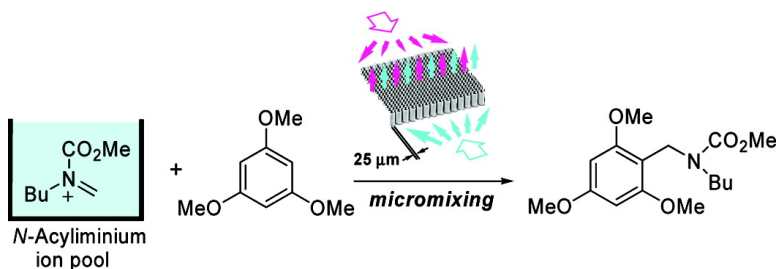


## Control of Extremely Fast Competitive Consecutive Reactions using Micromixing. Selective Friedel–Crafts Aminoalkylation

Aiichiro Nagaki, Manabu Togai, Seiji Suga, Nobuaki Aoki, Kazuhiro Mae, and Jun-ichi Yoshida

*J. Am. Chem. Soc.*, **2005**, 127 (33), 11666-11675 • DOI: 10.1021/ja0527424 • Publication Date (Web): 30 July 2005

Downloaded from <http://pubs.acs.org> on March 25, 2009



### More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 20 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

[View the Full Text HTML](#)

## Control of Extremely Fast Competitive Consecutive Reactions using Micromixing. Selective Friedel–Crafts Aminoalkylation

Aiichiro Nagaki,<sup>†</sup> Manabu Togai,<sup>†</sup> Seiji Suga,<sup>†</sup> Nobuaki Aoki,<sup>‡</sup> Kazuhiro Mae,<sup>‡</sup> and Jun-ichi Yoshida<sup>\*†</sup>

*Contribution from the Department of Synthetic Chemistry and Biological Chemistry and Department of Chemical Engineering, Graduate School of Engineering, Kyoto University, Katsura, Kyoto 615-8510*

Received April 27, 2005 E-mail: yoshida@sbchem.kyoto-u.ac.jp

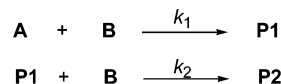
**Abstract:** Friedel–Crafts reactions of aromatic and heteroaromatic compounds with an *N*-acyliminium ion pool were studied. The reaction of 1,3,5-trimethylbenzene in a batch reactor gave rise to the selective formation of a monoalkylation product (69%). Presumably, the second alkylation is slower than the first alkylation because of the protonation of the monoalkylation product that decreases its reactivity. The reaction of 1,3,5-trimethoxybenzene, however, gave rise to the formation of both monoalkylation (37%) and dialkylation (32%) products. Disguised chemical selectivity due to faster reaction than mixing seems to be responsible for the lack of selectivity. The use of micromixing was found to be quite effective to solve this problem to increase the selectivity. The monoalkylation product was obtained in 92% yield together with a small amount of the dialkylation product (4%). The reaction with various aromatic and heteroaromatic compounds revealed that the low mono/dialkylation selectivity was observed only for highly reactive aromatics. In such cases, the use of micromixing was quite effective to improve the selectivity. On the basis of micromixing, the selective sequential dialkylation using two different *N*-acyliminium ions was achieved. CFD simulations using a laminar flow and finite-rate model are consistent with the experimental observations and clearly indicate the importance of mixing.

### Introduction

Chemical reactions are usually achieved by the mixing of two components such as substrate/reagent and substrate/catalyst. Molecules of reaction components come together and collide with each other upon mixing to accomplish the chemical reaction to give products. Although synthetic organic chemists have rather neglected the importance of mixing, the outcomes of chemical reactions are sometimes very sensitive to the way of mixing.

Mixing in a solution phase is defined as a phenomenon that creates homogeneity of all species in the solution. Chemists have tended to believe that such homogeneity is achieved immediately after the addition of one component to the other before the chemical reaction is initiated. This is true if the mixing time is much shorter than the reaction time. In other words, if the reaction is slower than the mixing, the reaction proceeds in a homogeneous solution. However, it is sometimes not the case. Reactions are sometimes faster than mixing, and therefore, the reaction proceeds before the homogeneity of the solution has been established. The use of fast reactions is highly desired in chemical synthesis from a viewpoint of efficiency. Productivity of faster reactions is obviously better than that of slower reactions. In such fast reactions, the way of mixing should strongly affect the outcome of the reaction.

### Scheme 1



Let us focus on a single type of reaction, in which the mixing may affect the product selectivity. The phenomena that two consecutive reactions occur competitively are popular, and it is important to favor the first reaction over the second to synthesize a desired compound efficiently. Product selectivities of such competitive consecutive reactions are intrinsically determined by kinetics. However, if the reaction is faster than mixing, simple kinetics based on the homogeneity of the solution does not work.

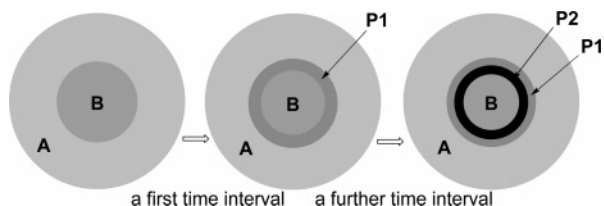
It is known that selectivity of competitive consecutive reactions represented by Scheme 1 is often determined not only by the rate of two reactions but also by the way of mixing.<sup>1</sup> When  $k_1 \gg k_2$  and the stoichiometric ratio of two reaction components is around unity ( $\text{A}:\text{B} = 1:1$ ), the yield of the primary product **P1** should be high. Experiments often contradicted this chemically based prediction. The measured yield of **P1** is sometimes much smaller than that of **P2**. The selectivity is not only determined by classical kinetic principles but also by the way in which the reaction components are mixed.

Rys proposed the concept of disguised chemical selectivities and pointed out the importance of the way of mixing to control

<sup>†</sup> Department of Synthetic Chemistry and Biological Chemistry.

<sup>‡</sup> Department of Chemical Engineering.

(1) For example, Bourne, J. R. in *Handbook of Batch Process Design*; Sharratt, P. N., Ed.; Blackie Academic and Professional: Dordrecht, The Netherlands, 1997; pp 139–152, and references therein.

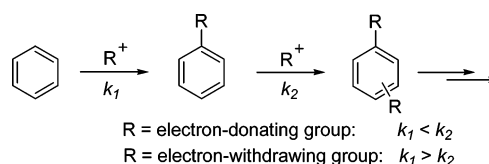


**Figure 1.** Schematic representation of mixing of the determined reaction course for competitive consecutive reactions.

chemical reactions.<sup>2</sup> Rys wrote “If we add a solution of species **B** to a solution of species **A**, eddies of solution **B** in solution **A** are created. As a first approximation, these eddies can be considered as spherical drops with constant mean radius  $R$ . The lifetime of such an eddy can be estimated to be 0.01–1 s. The radius  $R$  depends on the intensity of the turbulence created by mixing and may be controlled, for example, by mechanical stirring. From the theory of turbulence, one can estimate the minimum mean size of such elements of liquid. For the common solvents water, methanol, and ethanol, the mean minimum radius  $R$  of the eddies in optimal turbulence is approximately  $10^{-2}$  to  $10^{-3}$  cm.”<sup>2a</sup> Rys also wrote, “After a first time interval, **A** and **B** will have reacted at the periphery of an eddy to produce the primary product **P1**. In a further time interval, a molecule **B** can react with a further molecule **A** to form **P1**, but only if it succeeds in diffusing through the peripheral zone of **P1** molecules already formed without being trapped there by the substance **P1** in a reaction affording the secondary product **P2**. This succeeds less often, the longer the relaxation time of the diffusion process is in comparison to the relaxation time of the secondary reaction. In the extreme case, a mixing controlled reaction will convert all the **P1** into **P2** before the molecule **B** finds a further molecule **A**. Thus, at the end of the reaction practically only the secondary product **P2** is present, and no primary product **P1** can be detected. In this case, the selectivity  $k_1/k_2$  loses its influence on the product distribution.”<sup>2b</sup>

As described previously, the kinetically based selectivity may be disguised by the mixing problem. This phenomenon may occur often in macroscale batch reactors, where the mixing is not so fast. As a matter of fact, several examples have already been reported in the literature.<sup>3</sup> We envisioned that the problem of disguised chemical selectivity can be solved by extremely fast mixing using a microfabricated device, a micromixer. Microfabricated devices for chemical reactions are generally called microreactors,<sup>4</sup> and they are expected to make a revolutionary change in chemical synthesis<sup>5</sup> from both academic

**Scheme 2**



and industrial viewpoints.<sup>6</sup> The most widely accepted definition of microreactors is “reactors having microstructures for chemical reactions”. According to this definition, microreactors are not necessarily small devices in total size. They can be relatively large as far as they contain microstructures. It is also important to note that microreactors do not necessarily mean reactors for the production of a small quantity of compounds. Microreactors can be applied for industrial scale production.<sup>7</sup>

With the advancement of microfabrication technology to make various kinds of microreactors including micromixers and microheat exchangers, the development of new synthetic methodologies based upon the inherent features that exist at the micrometer scale is strongly needed. It is generally expected that extremely fast and exothermic reactions can be conducted in a highly controlled manner in microreactors by virtue of the advantages of efficient mixing and heat transfer. In this paper, we focus on the efficient mixing ability of micromixers<sup>8</sup> to solve the problem of disguised selectivity of extremely fast competitive consecutive reactions.<sup>9</sup>

As an example of competitive consecutive reactions, the Friedel–Crafts reaction is very popular in organic chemistry (Scheme 2).<sup>10</sup> In the case where the R group is an electron-

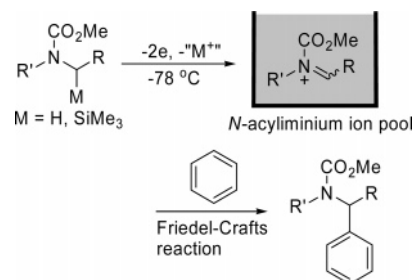
- (2) (a) Rys, P. *Acc. Chem. Res.* **1976**, *10*, 345. (b) Rys, P. *Angew. Chem., Int. Ed. Engl.* **1977**, *12*, 807. In the original papers of Rys **A** is added to **B**, but here we consider the reverse addition (addition of **B** to **A**).
- (3) (a) Agre, C. L.; Dinga, G.; Pflaum, R. *J. Org. Chem.* **1956**, *21*, 561. (b) Stoutland, O.; Helgen, L.; Agre, C. L. *J. Org. Chem.* **1959**, *24*, 818. (c) Tolgyesi, W. S. *Can. J. Chem.* **1965**, *43*, 343. (d) Wood, P. B.; Higginson, W. C. E. *J. Chem. Soc. A* **1966**, 1645. (e) Hanna, S. B.; Hunziker, E.; Saito, T.; Zollinger, H. *Helv. Chim. Acta* **1969**, *52*, 1537. (f) Paul, E. L.; Treybal, R. E. *Am. J. Chem. E.* **1971**, *17*, 718. (g) Ridd, J. H. *Acc. Chem. Res.* **1971**, *4*, 248. (h) Hunziker, E.; Penton, J. R.; Zollinger, H. *Helv. Chim. Acta* **1971**, *54*, 2043. (i) Bourne, J. R.; Rys, P.; Suter, K. *Chem. Eng. Sci.* **1977**, *32*, 711. (j) Bourne, J. R.; Kozicki, F.; *Chem. Eng. Sci.* **1977**, *32*, 1538. (k) Kaminski, R.; Lauk, U.; Skrabal, P.; Zollinger, H. *Helv. Chim. Acta* **1983**, *66*, 2002. (l) Jacobson, A. R.; Makris, A. N.; Sayre, L. M. *J. Org. Chem.* **1987**, *52*, 2592. (m) Paul, E. L.; Mahadevan, H.; Foster, J.; Kennedy, M.; Midler, M. *Chem. Eng. Sci.* **1992**, *47*, 2837.
- (4) (a) Ehrfeld, W. *Microraction Technology*; Springer: Berlin, 1998. (b) Ehrfeld, W.; Hessel, V.; Löwe, H. *Microractors*; Wiley-VCH: Weinheim, 2000. (c) Manz, A.; Becker, H. *Microsystem Technology in Chemistry and Life Sciences*; Springer: Berlin, 1999. (d) Jensen, K. F. *Chem. Eng. Sci.* **2001**, *56*, 293. (e) Hessel, V.; Hardt, S.; Löwe, H. *Chemical Micro Process Engineering*; Wiley-VCH: Weinheim, 2004.

- (5) For organic synthesis (a) Salimi-Moosavi, H.; Tang, T.; Harrison, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 8716. (b) Chambers, R. D.; Spink, R. C. H. *Chem. Commun.* **1999**, 883. (c) de Bellefon, C.; Tanchoux, N.; Caravieilles, S.; Grenouillet, P.; Hessel, V. *Angew. Chem., Int. Ed.* **2000**, *39*, 3442. (d) Suga, S.; Okajima, M.; Fujiwara, K.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 7941. (e) Yoshida, J.; Suga, S. *Chem.—Eur. J.* **2002**, *8*, 2651. (f) Watts, P.; Wiles, C.; Haswell, S. J.; Pombo-Villar, E.; Styring, P. *Chem. Commun.* **2001**, 990. (g) Hisamoto, H.; Saito, T.; Tokeshi, M.; Hibara, A.; Kitamori, T. *Chem. Commun.* **2001**, 2662. (h) Sands, M.; Haswell, S. J.; Kelly, S. M.; Skelton, V.; Morgan, D. O.; Styring, P.; Warrington, B. *Lab Chip* **2001**, *1*, 64. (i) Wiles, C.; Watts, P.; Haswell, S. J.; Pombo-Villar, E. *Lab Chip* **2001**, *1*, 100. (j) Wiles, C.; Watts, P.; Haswell, S. J.; Pombo-Villar, E. *Chem. Commun.* **2002**, 1034. (k) Fukuyama, T.; Shinmen, M.; Nishitani, S.; Sato, M.; Ryu, I. *Org. Lett.* **2002**, *4*, 1691. (l) Ueno, M.; Hisamoto, H.; Kitamori, T.; Kobayashi, S. *Chem. Commun.* **2003**, 936. (m) Garcia-Egido, E.; Spikmans, V.; Wong, S. Y. F.; Warrington, B. H. *Lab Chip* **2003**, *3*, 73. (n) Lai, S. M.; Martin-Aranda, R.; Yeung, K. L. *Chem. Commun.* **2003**, 218. (o) Mikami, K.; Yamanaka, M.; Islam, M. N.; Kudo, K.; Seino, N.; Shinoda, M. *Tetrahedron Lett.* **2003**, *44*, 7545. (p) Kobayashi, J.; Mori, Y.; Okamoto, K.; Akiyama, R.; Ueno, M.; Kitamori, T.; Kobayashi, S. *Science* **2004**, *304*, 1305. (q) Wu, T.; Mei, Y.; Cabral, J. T.; Xu, C.; Beers, K. L. *J. Am. Chem. Soc.* **2004**, *126*, 9980. (r) Nagaki, A.; Kawamura, K.; Suga, S.; Ando, T.; Sawamoto, M.; Yoshida, J. *J. Am. Chem. Soc.* **2004**, *126*, 14702. (s) Horcajada, R.; Okajima, M.; Suga, S.; Yoshida, J. *Chem. Commun.* **2005**, 1303.
- (6) Reviews: for example, (a) DeWitt, S. H. *Curr. Opin. Chem. Biol.* **1999**, *3*, 350. (b) Okamoto, H. *J. Synth. Org. Chem., Jpn.* **1999**, *57*, 805. (c) Sugawara, T. *Pharmacia* **2000**, *36*, 34. (d) Wörz, O.; Jäckel, K. P.; Richter, Th.; Wolf, A. *Chem. Eng. Sci.* **2001**, *56*, 1029. (e) Haswell, S. J.; Middleton, R. J.; O’Sullivan, B.; Skelton, V.; Watts, P.; Styring, P. *Chem. Commun.* **2001**, 391. (f) de Mello, A.; Wootton, R. *Lab Chip* **2002**, *2*, 7N. (g) Fletcher, P. D. I.; Haswell, S. J.; Pombo-Villar, E.; Warrington, B. H.; Watts, P.; Wong, S. Y. F.; Zhang, X. *Tetrahedron* **2002**, *58*, 4735. (h) Jähnisch, K.; Hessel, V.; Lowe, H.; Baerns, M. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 406.
- (7) The use of microreactors toward industrial production: (a) Iwasaki, T.; Yoshida, J. *Macromolecules* **2005**, *38*, 1159. (b) Kawaguchi, T.; Miyata, H.; Ataka, K.; Mae, K.; Yoshida, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 2413.
- (8) For example, (a) Kakuta, M.; Bessoth, F. G.; Manz, A. *Chem. Record* **2001**, *1*, 395. (b) Stroock, A. D.; Dertinger, S. K. W.; Ajdari, A.; Mezias, L.; Stone, H. A.; Whitesides, G. M. *Science* **2002**, *295*, 647. (c) Johnson, T. J.; Ross, D.; Locascio, L. E. *Anal. Chem.* **2002**, *74*, 45. (d) Seong, G. H.; Crooks, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 13360. (e) Song, H.; Tice, J. D.; Ismagilov, R. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 768. (f) Zheng, B.; Roach, L. S.; Ismagilov, R. F. *J. Am. Chem. Soc.* **2003**, *125*, 11170. (g) Song, H.; Ismagilov, R. F. *J. Am. Chem. Soc.* **2003**, *125*, 14613.

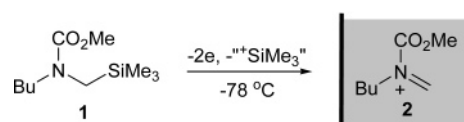
donating group such as an alkyl group (Friedel–Crafts alkylation), it is well-recognized that the primary product is, in principle, more reactive than the starting aromatic compound.<sup>11</sup> Thus, the second reaction takes place more easily than the first reaction. This inevitable problem is usually avoided by the use of a large excess amount of a starting aromatic compound (sometimes an aromatic compound is used as a solvent). Selective monoalkylation using 1 equiv of an aromatic compound has remained one of the most challenging problems in organic synthesis for many years. If the R group is an electron-withdrawing group such as an acyl group (Friedel–Crafts acylation), the primary product is less reactive than the parent aromatic compound. In this case, the second reaction is slower than the first reaction, and therefore, it is possible to stop the reaction to obtain the primary product selectively. Even if the R group is an electron-withdrawing group, the second reaction may sometimes take place in a significant extent because of the problem of disguised chemical selectivity owing to slow mixing.<sup>3</sup> In this case, extremely fast micromixing has a chance to improve product selectivity.

In the Friedel–Crafts reactions, carbocations<sup>12</sup> are used as reagents, which are usually generated in situ by Lewis acid promoted reactions of their precursors such as alkyl halides and acyl halides. In such cases, however, the generation process is reversible, and the equilibrium usually lies to the precursor. Recently, we have developed the cation pool method that involves irreversible oxidative generation and accumulation of carbocations in the absence of nucleophiles at low temperature.<sup>5e,13</sup> For example, *N*-acyliminium ion pools can be easily generated by anodic oxidation<sup>14</sup> of either corresponding carbamates or carbamates having a silyl group as an electroauxiliary<sup>15</sup> and accumulated in a solution at low temperature (Scheme 3). We envisioned that the use of *N*-acyliminium ion pools in Friedel–Crafts reactions would serve as a good probe to test the problem of disguised chemical selectivity and the effectiveness of extremely fast micromixing.

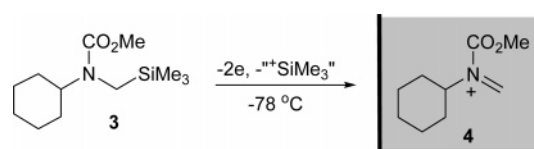
Scheme 3



Scheme 4



Scheme 5



Thus, we have examined the Friedel–Crafts reactions of aromatic compounds with *N*-acyliminium ion pools and found that disguised chemical selectivity was observed in some cases and that this problem was solved by the micromixing.<sup>16</sup>

## Results and Discussion

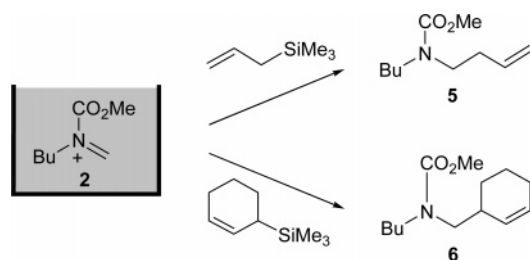
**Generation of *N*-Acyliminium Ion Pools.** We chose to study *N*-acyliminium ion 2 that does not have a substituent at the iminium carbon as shown in Scheme 4 because less sterically demanding *N*-acyliminium ions seem to be suitable for the study of monoalkylation/polyalkylation selectivity. *N*-Acyliminium ion 2 was generated by the anodic oxidation of carbamate 1 having a silyl group as an electroauxiliary in  $\text{Bu}_4\text{NBF}_4/\text{CH}_2\text{Cl}_2$  and accumulated in a solution in the absence of a nucleophile. The formation of 2 as a single species was indicated by NMR (<sup>1</sup>H NMR: 8.56 and 8.83 ppm due the methylene protons, <sup>13</sup>C NMR: 177.0 ppm due to the methylene carbon).

*N*-Acyliminium ion 4 was also generated from precursor 3 in a similar fashion as shown in Scheme 5.

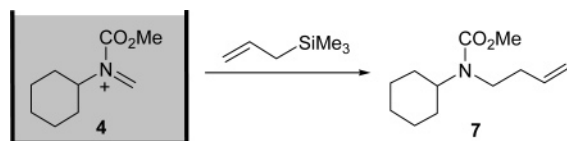
**Reactivity of *N*-Acyliminium Ion Pools (2) and (4) with Allyltrimethylsilane.** Although we have already developed the chemistry of *N*-acyliminium ions having a substituent on the iminium carbon, the reactivity of *N*-acyliminium ions that do not have a substituent at the iminium carbon is not well-known.

- (9) It is reported that the product distribution of two competitive reactions is influenced by the effectiveness of micromixing: (a) Ehrfeld, W.; Golbig, K.; Hessel, V.; Löwe, H.; Richter, T. *Ind. Eng. Chem. Res.* **1999**, *38*, 1075. (b) Suga, S.; Nagaki, A.; Tsutsui, Y.; Yoshida, J. *Org. Lett.* **2003**, *5*, 945. (c) Yoshida, J.; Nagaki, A.; Iwasaki, T.; Suga, S. *Chem. Eng. Technol.* **2005**, *28*, 259. (d) Hessel, V.; Hofmann, C.; Löwe, H.; Meudt, A.; Scherer, S.; Schönfeld, F.; Werner, B. *Org. Process Res. Dev.* **2004**, *8*, 511.
- (10) (a) Olah, G. A.; Spear, R. J.; Messina, G.; Westerman, P. W. *J. Am. Chem. Soc.* **1975**, *97*, 4051. (b) Olah, G. A. *J. Am. Chem. Soc.* **1965**, *87*, 1103. (c) Olah, G. A.; Schlosberg, R. H.; Porter, R. D.; Mo, Y. K.; Kelly, D. P.; Mateescu, G. D. *J. Am. Chem. Soc.* **1972**, *94*, 2034. (d) Effenberger, F. *Acc. Chem. Res.* **1989**, *22*, 27. (e) Olah, G. A. *Acc. Chem. Res.* **1971**, *4*, 2040.
- (11) For example, Bruckner, R. *Advanced Organic Chemistry: Reaction Mechanism*; Harcourt/Academic Press: San Diego, 2002.
- (12) For example, (a) Prakash, G. K. S.; Schleyer, P. v. R. *Stable Carbocation Chemistry*; Wiley: New York, 1997. (b) Olah, G. A.; Laali, K. K.; Wang, Q.; Prakash, G. K. S. *Onium Ions*; Wiley: New York, 1998.
- (13) (a) Yoshida, J.; Suga, S.; Suzuki, S.; Kinomura, N.; Yamamoto, A.; Fujiwara, K. *J. Am. Chem. Soc.* **1999**, *121*, 9546. (b) Suga, S.; Suzuki, S.; Yamamoto, A.; Yoshida, J. *J. Am. Chem. Soc.* **2000**, *122*, 10244. (c) Suga, S.; Okajima, M.; Yoshida, J. *Tetrahedron Lett.* **2001**, *42*, 2173. (d) Suga, S.; Okajima, M.; Fujiwara, K.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 7941. (e) Suga, S.; Suzuki, S.; Yoshida, J. *J. Am. Chem. Soc.* **2002**, *124*, 30. (f) Yoshida, J.; Suga, S. *Chem.—Eur. J.* **2002**, *8*, 2650. (g) Suga, S.; Watanabe, M.; Yoshida, J. *J. Am. Chem. Soc.* **2002**, *124*, 14824. (h) Suga, S.; Kageyama, Y.; Babu, G.; Itami, K.; Yoshida, J. *Org. Lett.* **2004**, *6*, 2709. (i) Szuki, S.; Matsumoto, K.; Kawamura, K.; Suga, S.; Yoshida, J. *Org. Lett.* **2004**, *6*, 3755. (j) Suga, S.; Suzuki, S.; Maruyama, T.; Yoshida, J. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1545. (k) Suga, S.; Nishida, T.; Yamada, D.; Nagaki, A.; Yoshida, J. *J. Am. Chem. Soc.* **2004**, *126*, 14338.
- (14) (a) Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172. (b) Shono, T.; Matsumura, Y.; Tsubata, K. *Tetrahedron Lett.* **1981**, *22*, 2411. (c) Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527. (d) Kim, S.; Hayashi, K.; Kitano, Y.; Tada, M.; Chiba, K. *Org. Lett.* **2002**, *4*, 3735. (e) Wanyoike, G. N.; Onomura, O.; Maki, T.; Matsumura, Y. *Org. Lett.* **2002**, *4*, 1875.
- (15) (a) Yoshida, J.; Nishiwaki, K. *J. Chem. Soc., Dalton Trans.* **1998**, 2589. (b) Yoshida, J.; Sugawara, M.; Tatsumi, M.; Kise, N. *J. Org. Chem.* **1998**, *63*, 5950. (c) Yoshida, J.; Watanabe, M.; Toshioka, H.; Imagawa, M.; Suga, S. *Chem. Lett.* **1998**, 1011. (d) Sugawara, M.; Mori, K.; Yoshida, J. *Electrochim. Acta* **1997**, *42*, 1995. (e) Yoshida, J.; Ishichi, Y.; Isoe, S. *J. Am. Chem. Soc.* **1992**, *114*, 7594. (f) Yoshida, J.; Maekawa, T.; Murata, T.; Matsunaga, S.; Isoe, S. *J. Am. Chem. Soc.* **1990**, *112*, 1962. (g) Yoshida, J.; Isoe, S. *Tetrahedron Lett.* **1987**, *28*, 6621. (h) Sun, H.; Moeller, K. D. *Org. Lett.* **2002**, *4*, 1547. (i) Kamada, T.; Oku, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1105. Photochemical reactions: (j) Xu, W.; Zhang, X. M.; Mariano, P. S. *J. Am. Chem. Soc.* **1991**, *113*, 8863. (k) Gutenberger, G.; Steckhan, E.; Blechert, S. *Angew. Chem., Int. Ed.* **1998**, *37*, 660. Chemical reactions: (l) Narasaka, K. *Pure Appl. Chem.* **1997**, *69*, 601. (m) Pandey, G.; Sahoo, A. K.; Gadre, S. R.; Bagul, T. D.; Phalgune, U. D. *J. Org. Chem.* **1999**, *64*, 4990. (n) Sun, H.; Moeller, K. D. *Org. Lett.* **2003**, *5*, 3189.
- (16) Preliminary results have been reported: Suga, S.; Nagaki, A.; Yoshida, J. *Chem. Commun.* **2003**, 354.

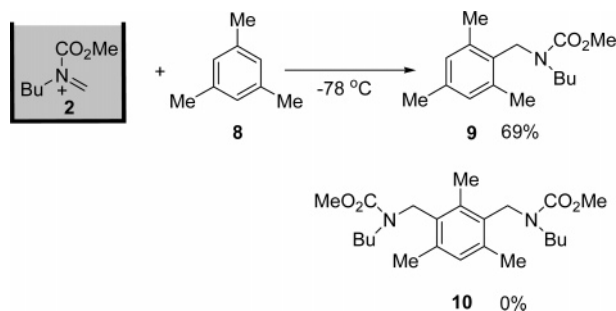
Scheme 6



Scheme 7



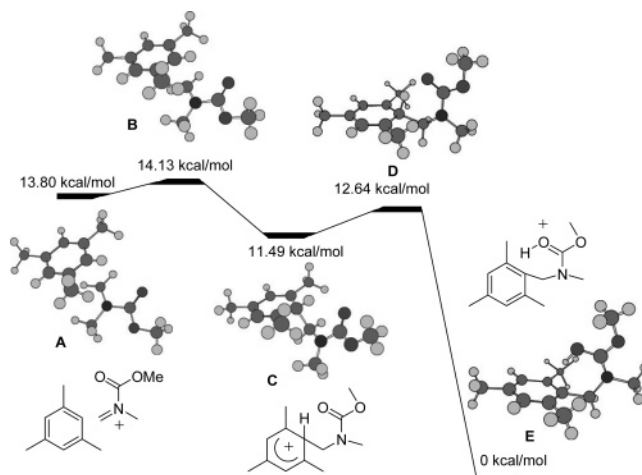
Scheme 8



Thus, we first examined the reaction of **2** with simple carbon nucleophiles. The reaction of **2** with allyltrimethylsilane took place spontaneously at  $-78\text{ }^{\circ}\text{C}$  to give the corresponding allylated product (**5**) in 72% yield as shown in Scheme 6, indicating that **2** is a highly reactive species. *N*-Acyliminium ion **2** also reacted with 3-trimethylsilylcyclohexene to give the corresponding C–C bond formation product (**6**) in 72% yield (Scheme 6). We also examined the reaction of *N*-acyliminium ion pool (**4**) with allyltrimethylsilane. The corresponding allylated product (**7**) was obtained in 57% yield, indicating that **4** is also a highly reactive species (Scheme 7).

***N*-Acyliminium Ion Pool (**2**) with 1,3,5-Trimethylbenzene (**8**) using a Macroscale Batch Reactor.** In the study of the monoalkylation/polyalkylation selectivity of Friedel–Crafts reaction, we first examined the reaction of 1,3,5-trimethylbenzene (**8**) as an aromatic compound because it is highly reactive and has three separate positions for the attack of an electrophile. Because the yield of **2** from **1** is estimated as ca. 80% based on the reactions with various nucleophiles, hereafter 1.2 equiv of **1** was used when 1.0 equiv of **2** was needed for the Friedel–Crafts reaction. The yields of the products are based on the amount of the aromatic compounds used.

The reaction in a conventional macroscale batch reactor with magnetic stirring, which is usually used for laboratory organic synthesis, was examined. The addition of **2** (generated from 1.2 equiv of **1**) to a stirred solution of **8** in dichloromethane resulted in the selective formation of monoalkylation product **9** (69% yield) (Scheme 8). The dialkylation product **10** was not detected. It is well-known that the monoalkylation product is more reactive than the parent compound because alkyl groups are electron-donating. Therefore, it is generally difficult to stop the reaction at the monoalkylation stage. The experimental result,



**Figure 2.** Energy diagram of the reaction of the *N*-methoxycarbonyl-*N*-methyliminium ion with 1,3,5-trimethylbenzene.

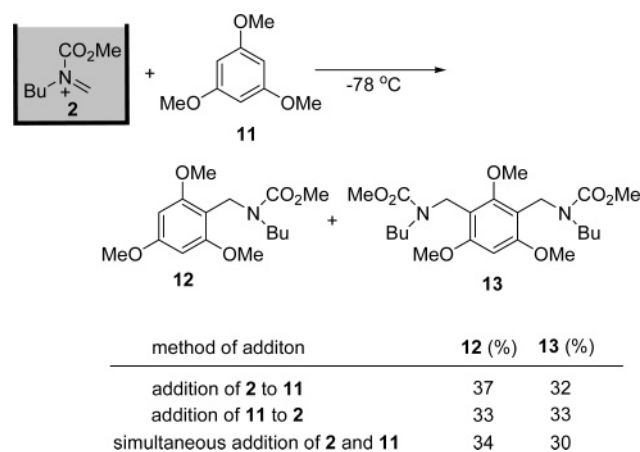
however, contradicted with the expectation. The selective monoalkylation can be explained as follows: Friedel–Crafts reaction of **8** with **2** generates a proton, which protonates the monoalkylation product **9**. The protonated carbamate group should be strongly electron-withdrawing. Therefore, the protonated form of **9** is considered to be less reactive than **8**. Thus, the second alkylation is slower than the first alkylation. This is consistent with the selective formation of the monoalkylation product **9**.

**NMR Studies.** To get the evidence for the protonation of **9**, <sup>13</sup>C NMR studies were carried out. The neutral form of **9** exhibited the signal due to the carbonyl carbon at 155.0 and 155.4 ppm (two rotamers). The addition of HBF<sub>4</sub>OMe<sub>2</sub> caused a downfield shift of the signal (157.5 and 157.7 ppm). This is consistent with the protonation at the carbonyl oxygen, which made the carbonyl carbon more electron-deficient. The <sup>13</sup>C NMR spectrum of the product solution obtained by the reaction of **2** and **8** exhibited the signal at 157.6 and 157.8 ppm. These observations strongly suggest that the protonated form of **9** was produced by the reaction of **2** and **8**.

**DFT Calculations.** To obtain deeper insight into the mechanism of the present reaction, DFT calculations (B3LYP/6-31G-(d)) were carried out for a model system (*N*-methoxycarbonyl-*N*-methyliminium ion with 1,3,5-trimethylbenzene) shown in Figure 2 in the gas phase. The calculations indicate that complex **A**, which is formed prior to the reaction, is converted into the Wheland complex **C** through transition state **B**. In the next step, complex **C** is converted to **E** through transition state **D**, where the proton on the benzene ring is transferred to the carbonyl oxygen atom. Therefore, **E** is the protonated form of the final product. This is consistent with the speculation described previously. The present reaction is exothermic (ca. 14 kcal/mol), and the activation energy is very small (ca. 0.3 kcal/mol). These data obtained by the calculations indicate that the present reaction is very fast.

**Reaction of *N*-Acyliminium Ion Pool (**2**) with 1,3,5-Trimethoxybenzene (**11**) using a Batch Reactor.** The results obtained with *N*-acyliminium ion (**2**) and trimethylbenzene (**8**) indicate that the first alkylation is faster than the second alkylation and that the disguised chemical selectivity was not observed. Thus, we examined the reactions of **2** with more reactive aromatic compounds.

Scheme 9



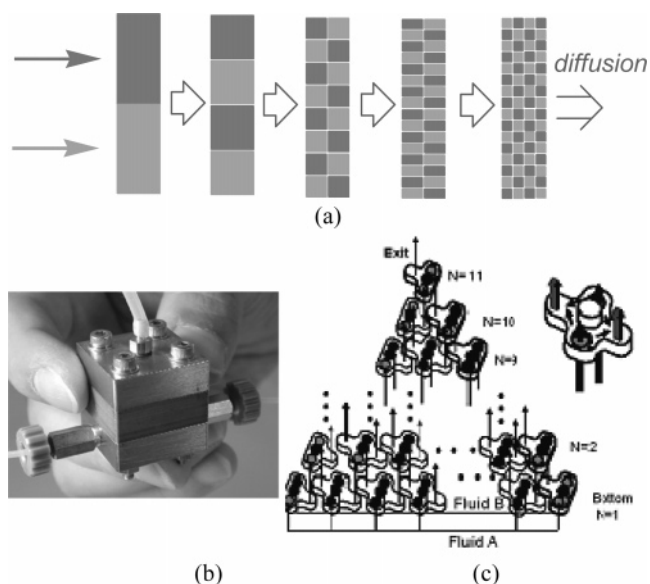
Since alkoxy groups are more electron-donating than alkyl groups, we chose to study 1,3,5-trimethoxybenzene (**11**) as an aromatic compound. The addition of **2** (generated from 1.2 equiv of **1**) to a stirred solution of **11** in dichloromethane in a macroscale batch reactor resulted in the formation of an essentially 1:1 mixture of monoalkylation product **12**<sup>17</sup> and dialkylation product **13** (Scheme 9) after quenching by the triethylamine.<sup>18</sup> The reverse addition gave essentially the same result. The simultaneous addition of a solution of **2** and that of **11** to a batch reactor also gave a similar result. These observations contrast sharply with the case of 1,3,5-trimethylbenzene. Since the monoalkylation product **12** should be protonated to deactivate the aromatic ring, the second alkylation should be slower than the first alkylation. Therefore, the selectivity observed here is considered to be disguised chemical selectivity, which is ascribed to faster reaction than mixing.

**Reaction of *N*-Acyliminium Ion Pool (2) with 1,3,5-Trimethoxybenzene (11) using a Micromixer.** Thus, we examined the reaction using a micromixer to solve the problem of disguised chemical selectivity. There are several principles of micromixers such as injection of many small substreams of one component in a main stream of another component, decrease of diffusion path perpendicular to the flow direction, manifold splitting and recombination, and periodic injection of small fluid segments.

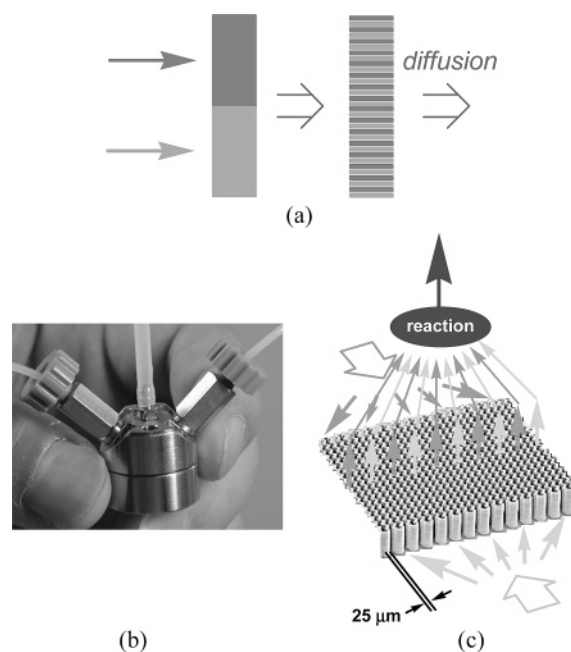
In the present study, we examined three different types of micromixers. The first one is a T-shaped tube mixer, and its diameter is 500  $\mu\text{m}$ . The second one, a Yamatake YM-1 mixer developed by Mae, is a splitting and recombination type micromixer. A multilamination type mixer, IMM (Institut für Mikrotechnik Mainz GmbH) single mixer, was also examined.

In the YM-1 micromixer (Figure 3), two fluids to be mixed were introduced into a segment and combined. Then, the mixture was split into two streams, which were introduced into the next segment.

In the IMM mixer, the fluids to be mixed are introduced into the mixing element as two counter-flows, and the fluids stream into an interdigital channel (25  $\mu\text{m}$ ) configuration (Figure 4). In the next stage, a periodical flow configuration consisting of the lamellae of the two fluids is generated by means of the slit-



**Figure 3.** Splitting and recombination type micromixer (YM-1): (a) principle, (b) outside, and (c) schematic diagram of mixing element.



**Figure 4.** Multilamination type micromixer (IMM single mixer, channel width = 25  $\mu\text{m}$ ): (a) principle, (b) outside, and (c) schematic diagram of mixing element.

shaped interdigital channel. Then, the lamellated flow leaves the device perpendicular to the direction of the feed flows.

The reaction of the *N*-acyliminium ion **2** with aromatic compound **11** using these micromixers was carried out as follows. The solutions of **2** (produced from 1.2 equiv of **1**) and **11** were introduced to the mixer by a syringe pumping technique (flow rate: 5.0 mL/min) at  $-78\text{ }^\circ\text{C}$ , and the product solution that left from the device was immediately quenched with triethylamine to avoid further reactions.<sup>18</sup>

When the T-shaped mixer was used, the selectivity was essentially the same as the batch reactor (Scheme 10). The use of the YM-1 mixer increased the selectivity, but still a significant amount of dialkylation product **13** was formed. We found, however, that the monoalkylation product **12** was obtained in excellent selectivity when the IMM micromixer was used. The

(17)  $\alpha$ -Amidoalkylation: Zaugg, H. E.; Martin, W. B. *Org. React.* **1965**, *14*, 52.

(18) The separate reaction of **2** with triethylamine gave rather inactive species that did not give the allylated product upon treatment with allyltrimethylsilane, although the details are not clear at present. Triethylamine might also suppress the acid-promoted decomposition of the product.

Scheme 10

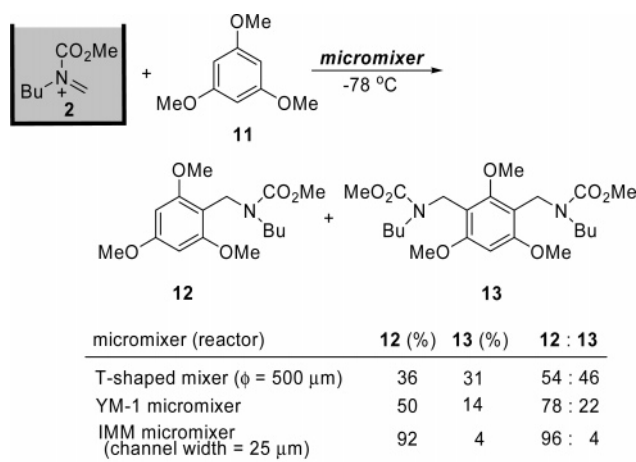


Table 1. Temperature Effect of the Reaction of 2 with 11

temperature ( $^{\circ}\text{C}$ )	reactor	conversion of 11 (%)	12 (%)	13 (%)
-78	micromixer <sup>a</sup>	91	92	4
	batch reactor <sup>b</sup>	75	37	32
-47	micromixer <sup>a</sup>	92	84	15
	batch reactor <sup>b</sup>	86	7	22
-27	micromixer <sup>a</sup>	85	70	19
	batch reactor <sup>b</sup>	99	1	7
0	micromixer <sup>a</sup>	93	30	15
	batch reactor <sup>b</sup>	quantitative	0	1

<sup>a</sup> IMM single mixer was used. <sup>b</sup> A 50 mL flask was used.

Table 2. Effect of Flow Rate of the Reaction of 2 with 11 using the IMM Micromixer

flow rate (mL/min) <sup>a</sup>	12 (%)	13 (%)
1	14	19
3	52	14
5	92	4

<sup>a</sup> A solution of **11** (0.417 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL,  $-78^{\circ}\text{C}$ ) and a cation pool (**2**, 10 mL,  $-78^{\circ}\text{C}$ ) generated from **1** (0.500 mmol) was simultaneously introduced to the micromixer using syringe pumps.

amount of dialkylation product **13** was very small (**12**:**13** = 96:4, total yield 96%).

The reaction temperature was also found to be an important factor governing the selectivity (Table 1). In the case of the IMM micromixer, the selectivity decreased dramatically with the increase of the temperature. A similar tendency was also observed for a batch reactor. Another important point is that the total yield of **12** and **13** also decreased with the increase of the temperature, although the conversion remained very high. Such an effect is much larger for the macroscale batch reactor. Presumably, the products decomposed under the reaction conditions at higher temperatures. In the case of the micromixer, better temperature control was achieved by virtue of high surface-to-volume ratio of the microstructure. In the case of the batch reactor, however, the temperature control was less effective, and therefore, significant amounts of the products decomposed at higher temperatures.

Flow rate is also a very important factor that governs the selectivity of the present reaction. With flow rates of 5 mL/min, the best result was obtained among those examined. Decreasing the flow rate caused a decrease of the yield and selectivity as shown Table 2. The mixing efficiency seems to be strongly dependent on the flow rate. As a matter of fact,

Table 3. Reaction of 2 and 11 in Various Molar Ratios using IMM Micromixer<sup>a</sup>

1 (precursor of 2, equiv)	12 (%)	13 (%)
1.0	66	2
1.2	92	4
1.5	92	5
2.0	71	19
2.5	62	30

<sup>a</sup> A solution of **11** (0.417 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL,  $-78^{\circ}\text{C}$ ) and a cation pool (**2**, 10 mL,  $-78^{\circ}\text{C}$ ) generated from **1** (0.500 mmol) was simultaneously introduced to the micromixer using syringe pumps.

IMM reported that the mixing efficiency strongly depends on the flow rate and decreases with a decrease in the flow rate.<sup>9a</sup>

We also examined the effect of the ratio of the two reaction components (**2** and **11**) on the selectivity using the IMM micromixer. As shown in Table 3, the use of 1.2 equiv of precursor **1** gave the best results. The use of 2.0 and 2.5 equiv of **1** resulted in the formation of a significant amount of **13**. Surplus **2** further reacted with **12** to give **13**.

It should be noted that the use of 2.5 equiv of **1** (more than 2 equiv of **2**) did not give the dialkylation product **13** selectively. This observation seems to indicate that the reaction of monoalkylation product **12** (protonated **12**) with *N*-acyliminium ion **2** is slower than the reaction of the parent aromatic compound **11** with **2**.

**Reaction of *N*-Acyliminium Ion Pool (2) with Various Aromatic and Heteroaromatic Compounds.** The Friedel–Crafts reactions of other aromatic compounds with **2** were examined, and the results are summarized in Table 4.

For less reactive aromatic compounds, such as toluene, *p*-xylene, and 1,3,5-trimethylbenzene, the monoalkylation products were selectively obtained even in a macroscale batch reactor. The protonation at the carbonyl oxygen, which decelerates the second alkylation as described in the previous section, seems to be responsible.


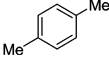
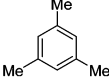


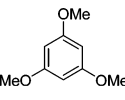



The dramatic effect of micromixing is generally observed for the alkylation of highly reactive aromatic compounds, such as methoxybenzene, 1,2-dimethoxybenzene, and 1,3,5-trimethoxybenzene. The selectivity observed for a macroscale batch reactor seems to be the disguised chemical selectivity. The use of the micromixer solved the problem, and the monoalkylation product was obtained in high selectivity.

The outcome of the reaction with heteroaromatic compounds was also affected by the way of mixing. The reaction of **2** with thiophene with the micromixer took place smoothly to give the monoalkylation product exclusively, while the reaction in the macroscale batch reactor gave a significant amount of dialkylation product. A similar tendency was also observed for the reaction of furan and *N*-methylpyrrole. These results indicate that the reactions of **2** with these heteroaromatic compounds also suffer from the problem of the disguised chemical selectivity in the macroscale batch reactor and that such problem can be solved by micromixing.

It should be noted here that highly nucleophilic aromatic and heteroaromatic compounds suffer from the disguised chemical selectivity. The nucleophilicity parameters reported by Mayr<sup>19</sup>

(19) (a) Mayr, H.; Patz, M. *Angew. Chem., Int. Ed.* **1994**, *33*, 938. (b) Gotta, M. F.; Mayr, H. *J. Org. Chem.* **1998**, *63*, 9769. (c) Mayr, H.; Bug, T.; Gotta, M. F.; Hering, N.; Irrgang, B.; Janker, B.; Kempf, B.; Loos, R.; Ofial, A. R.; Remennikov, G.; Schimmel, H. *J. Am. Chem. Soc.* **2001**, *123*, 9500. (d) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66.

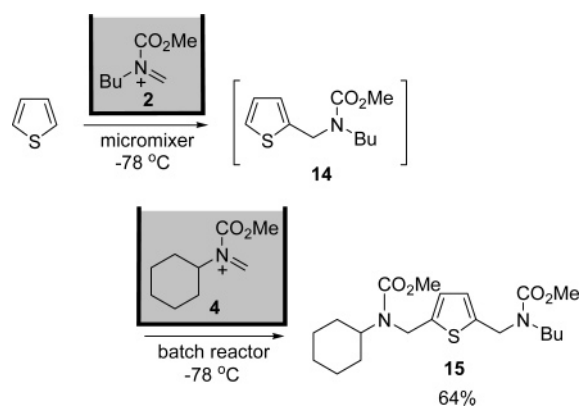
**Table 4.** Reaction of *N*-Acyliminium Ion Pool (**2**) with Various Aromatic and Heteroaromatic Compounds<sup>a</sup>

aromatic compound	nucleophilicity parameter, $N^b$	method	temperature (°C)	% yield of monoalkylation product	% yield of dialkylation product
	-4.47	batch	0	62 <sup>c</sup>	0
	-4.18	batch	0	67 <sup>d</sup>	0
		batch	-78	69	0
	-1.18	batch	-78	24	31
		micro-mixing	-78	26	0
		batch	-78	13	14
		micro-mixing	-78	34	0
	3.40	batch	-78	37	32
		micro-mixing	-78	92	4
	-0.40	batch	-78	14	27
		micro-mixing	-78	84	0
	1.45	batch	-78	11	5
		micro-mixing	-78	39	trace
	6.18	batch	-78	33 <sup>e</sup>	28
		micro-mixing	-78	60 <sup>f</sup>	6

<sup>a</sup> The reactions were usually carried out with **2**, which was generated from 0.50 mmol of **1** and 0.42 mmol of an aromatic compound. <sup>b</sup> Nucleophilicity parameters reported by Mayr.<sup>19</sup> <sup>c</sup> A mixture of two- and four-substituted products. <sup>d</sup> The yield was determined by <sup>1</sup>H NMR using an internal standard. <sup>e</sup> A mixture of two- and three-substituted products (76:24). <sup>f</sup> A mixture of two- and three-substituted products (72:28).

serve as good indicators. Compounds having a nucleophilicity number ( $N$ ) higher than ca.  $-1$  suffer from the problem of disguised selectivity. In such cases, the micromixing serves as a solution to the problem.

**Sequential Dialkylation with Two Different *N*-Acyliminium Ion Pools.** To demonstrate the synthetic utility of the selective Friedel–Crafts monoalkylation using a micromixer, the sequential alkylation with two different alkylating agents

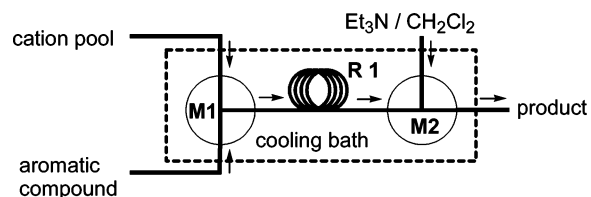
**Scheme 11**

was examined. The first alkylation was carried out with *N*-acyliminium ion **2** using the IMM micromixer to obtain the monoalkylation product **14**, which was directly subjected to the second alkylation with a different *N*-acyliminium ion **4** in a batch reactor to obtain dialkylation product **15** in 64% yield (Scheme 11). Therefore, the present method serves as a simple and straightforward method for the selective introduction of two different alkyl groups on an aromatic ring.

**Estimation of Relative Rates of the First Alkylation and Second Alkylation.** In the previous sections, we assumed that the second alkylation was slower than the first alkylation because the carbamate group in the monoalkylation product should be protonated to deactivate the aromatic ring. To confirm this assumption, we carried out the following experiments using a microflow system shown in Figure 5.

A solution of an aromatic compound and the cation pool **2** (generated from two equivalents of the precursor **1**) was mixed with a YM-1 micromixer at  $-78$  °C (flow rate: 8 mL/min), and the resulting mixture was introduced to a microtube reactor (diameter: 1.0 mm and length: 1.0 cm). Triethylamine was introduced through the second micromixer (YM-1) (flow rate: 8 mL/min) to quench the reaction. The results are summarized in Table 5.

The reaction of 1,3,5-trimethoxybenzene (**11**) was completed within the residence time of 0.03 s. Monoalkylation product **12** was obtained in 78% yield together with dialkylation product **13** (19%). The reaction of monoalkylation product **12**, which was synthesized and isolated in a separate experiment, with **2**

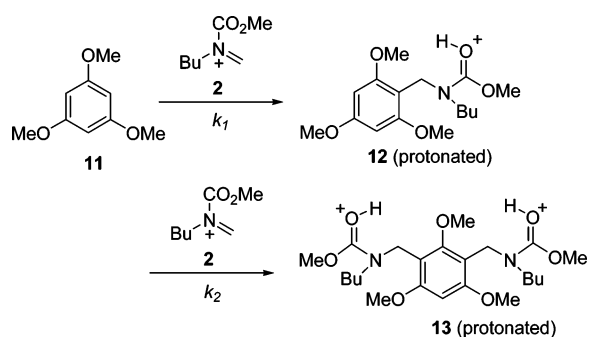
**Figure 5.** Microflow system for the estimation of relative rates of the reaction of aromatic compounds with the cation pool.**Table 5.** Relative Rates of the Reactions of **11** and **12** with **2**<sup>a</sup>

aromatic compound	residence time (s)	monoalkylation product <b>12</b> (%)	dialkylation product <b>13</b> (%)
<b>11</b>	0.03	78	19
<b>12</b> (isolated)	0.03	9	56
<b>12</b> (without isolation, protonated)	0.03	56	6
<b>12</b> (without isolation, protonated)	0.30	18	56

<sup>a</sup> A microsystem consisting of two micromixers (**M1** and **M2**) and a tube reactor (**R1**) was used (Figure 5).



Scheme 12

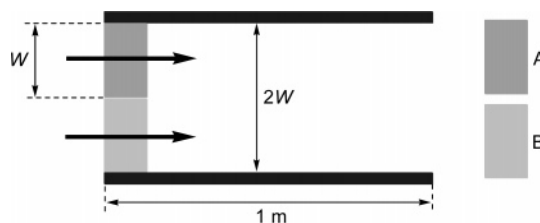


also proceeded smoothly. The reaction rate seems to be comparable to that of **11** because most of **12** was consumed within the residence time of 0.03 s. This observation indicates that the reactivity of unprotonated monoalkylation product **12** is similar to **11**. The reaction of a solution of **12**, which was generated by the reaction of **11** with **2** using micromixing in a separate experiment, was found to be much slower. A significant amount of **12** remained unchanged within the residence time of 0.03 s. With a longer residence time (0.30 s), a significant amount of **12** was consumed to give the dialkylation product **13**. As discussed in the previous section, the monoalkylation product **12** seems to be protonated during the course of its formation to decrease its reactivity because of the electron-withdrawing effect of the protonated carbamate group (Scheme 12). These experiments using the microflow system revealed that the reaction of protonated **12**, which should be formed by the reaction of **11**, is much slower than the reaction of **11**.

The present observations clearly indicated that the second alkylation is much slower than the first alkylation, presumably because of the protonation of the first alkylation product. Therefore, the selectivity observed for the macroscale batch reactor contradicted the prediction based on the normal kinetics and could be the disguised chemical selectivity. The selectivity observed with an IMM micromixer seems to be consistent with the kinetics.

**CFD Simulation of Competitive Consecutive Reaction using Micromixing.** To obtain a deeper understanding of the present dramatic effect of micromixing on the selectivity of the Friedel–Crafts alkylation, it is necessary to analyze how mixing can influence the selectivity of chemical reactions. Thus, we carried out CFD (computational fluid dynamics) simulation using FLUENT. The calculation was performed using a laminar flow and finite-rate model in the package.<sup>20</sup>

Let us consider the competitive consecutive isothermal reaction, described in Scheme 1 with  $k_1 = 10^4$ ,  $10^5$ , and  $10^6$  L/(mol s), whereby 0.01 mol/L solutions of **A** and **B** are fed to a micromixer at a constant rate. As to the shape and size of a micromixer, three models shown in Figure 6 were used for simulation. In mixers a–c, **A** and **B** are introduced as laminar flow, the widths ( $w$ ) of which are 100, 25, and 2.5  $\mu\text{m}$ , respectively. The flow rate is 0.1 m/s, and the length of the reactor is 1 m. We also simulated ideal mixing where **A** and **B** are mixed completely immediately after they are introduced to the mixer. The assumptions of the reactant fluids used in CFD simulations are as follows: physical properties of two reactant fluids are the same, that is, the density is  $1.317 \times 10^3$  kg/m<sup>3</sup>,



**Figure 6.** Models of micromixer for CFD simulation. Mixer (a):  $W = 100 \mu\text{m}$ . Mixer (b):  $W = 25 \mu\text{m}$ . Mixer (c):  $W = 2.5 \mu\text{m}$ . The product yields and distribution were calculated when the reaction is complete. Results are summarized in Tables 6–8.

**Table 6.** Product Yields and Distribution Obtained by CFD Simulation ( $k_1 = 10^4$  L/(mol s) and  $k_2 = 10^2$  L/(mol s))

mixer	lamination width ( $\mu\text{m}$ )	P1 (% yield)	P2 (%yield)	P1:P2
ideal mixing		94.6	2.7	97:3
a	100	60.6	19.7	75:25
b	25	89.6	4.5	95:5
c	2.5	94.7	2.6	97:3

**Table 7.** Product Yields and Distribution Obtained by CFD Simulation ( $k_1 = 10^5$  L/(mol s) and  $k_2 = 10^3$  L/(mol s))

mixer	lamination width ( $\mu\text{m}$ )	P1 (% yield)	P2 (%yield)	P1:P2
ideal mixing		94.6	2.7	97:3
a	100	31.1	34.4	47:53
b	25	67.8	15.9	55:45
c	2.5	94.5	2.7	97:3

**Table 8.** Product Yields and Distribution Obtained by CFD Simulation ( $k_1 = 10^6$  L/(mol s) and  $k_2 = 10^4$  L/(mol s))

mixer	lamination width ( $\mu\text{m}$ )	P1 (% yield)	P2 (%yield)	P1:P2
ideal mixing		94.6	2.7	97:3
a	100	14.5	42.7	25:75
b	25	36.1	31.9	53:47
c	2.5	90.5	4.7	95:5

the molecular diffusion coefficient is  $10^{-9}$  m<sup>2</sup>/s, and the viscosity is 0.00119 Pa s; the initial concentrations of the two reactants are 0.01 mol/L.

Before investigation of the lamination width effect, the effect of the relative rate of two reactions ( $k_1/k_2$ ) was examined for ideal mixing. In the case of  $k_1/k_2 = 100$ , **P1:P2** was calculated to be 97:3, whereas in the case of  $k_1/k_2 = 10$ , **P1:P2** = 87:13. The former value is closer to the experimental observation for the present Friedel–Crafts alkylation. Therefore, hereafter, the simulations were carried out for the case of  $k_1/k_2 = 100$ . The results are summarized in Tables 6–8.

As shown in Table 6, when  $k_1 = 10^4$  L/(mol s), the use of a micromixer of 100  $\mu\text{m}$  lamination width results in the formation of **P1** in ca. 60% yield and **P2** in ca. 20% yield. A decrease of the lamination width causes the increase of the yield of **P1** with the expense of the yield of **P2**. These results indicate that the selectivity increases with the decrease of the lamination width.

The increase of the absolute values of  $k_1$  and  $k_2$  causes dramatic changes of the selectivity of the reaction in mixer a. When  $k_1 = 10^5$  L/(mol s), **P1** and **P2** formed in almost equal amounts (Table 7). When  $k_1 = 10^6$  L/(mol s), the yield of **P2** was much larger than that of **P1** (**P1:P2** = 25:75), even if  $k_1$  is much larger than  $k_2$  ( $k_1/k_2 = 100$ ) (Table 8). Presumably, the reaction time and mixing time are comparable, and the selectivity seems to be disguised. The decrease of the lamination width gave rise to a remarkable increase of the selectivity favoring

(20) Aoki, N.; Hasebe, S.; Mae, K. *Chem. Eng. J.* **2004**, *101*, 323.

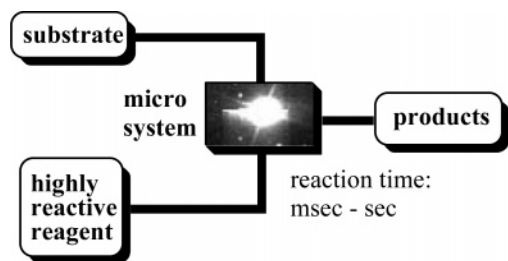


Figure 7. Concept of flash chemistry.

the formation of **P1**. Even if  $k_1 = 10^6$  L/(mol s), **P1** is formed in high selectivity (**P1:P2** = 95:5) in mixer *c* of 2.5  $\mu$ m lamination width. The effect of the increase of  $k_1$  and  $k_2$  obtained by the simulation is consistent with the experimental observation that the effect of micromixing is significant only for the reaction with highly reactive aromatic compounds, for which  $k_1$  and  $k_2$  are expected to be very large (Table 4).

The simulation data described in Tables 6–8 clearly show the dramatic effect of the lamination width on the selectivity of the reaction. Although the micromixer having a 25  $\mu$ m channel width was used for the experiments, the simulation suggests that the lamination width of 2.5  $\mu$ m is necessary to realize the observed selectivity. In the IMM micromixer, the outlet channel is narrowed immediately after the multilamination configuration has been established. This may cause a decrease of the effective lamination width. Anyway, the present results of simulation are, at least qualitatively, consistent with the experimental observations and clearly indicate the importance of micromixing for the improvement of the selectivity of competitive consecutive reactions.

## Conclusions

The present study nicely illustrates that the phenomenon of disguised chemical selectivity is observed for extremely fast competitive consecutive reactions such as Friedel–Crafts reactions of highly reactive aromatic compounds with *N*-acyliminium ion pools. The present study also speaks well for the potentiality of micromixing to effect extremely fast chemical transformations that are difficult to perform in a controlled manner using macroscale batch reactors. Micromixing can provide a solution to the problem of disguised chemical selectivity that complicates the reactions using more conventional chemical methods.

In conventional organic synthesis, rather slow reactions have been used because fast reactions are difficult to control. Reaction times usually range from minutes to hours. To achieve synthesis in a highly time efficient manner, however, the use of much faster reactions in a highly controlled way is strongly needed (reaction time ranges from milliseconds to seconds). Microsystems are expected to serve as powerful tools for conducting extremely fast reactions in a highly controlled manner to effect flash chemistry, where a substrate and a highly reactive reagent are allowed to react to give a desired product quickly (Figure 7).

## Experimental Procedures

***N*-Methoxycarbonyl-*N*-(trimethylsilylmethyl)butylamine (1).** To a suspension of sodium hydride (60 wt % dispersion in mineral oil, 7.91 g, 197 mmol) in DMF (200 mL), *N*-(methoxycarbonyl)butylamine (21.6 g, 165 mmol) was added at 0 °C. The mixture was stirred for

120 min at 60 °C, and iodo(trimethylsilyl)methane (42.6 g, 199 mmol) was added at 0 °C. The reaction mixture was stirred for 14.5 h at 60 °C and poured into water (300 mL). The organic phase was separated, and the aqueous phase was extracted with ether (300 mL  $\times$  3). The combined organic phase was dried over  $\text{Na}_2\text{SO}_4$ , and the solvent was removed to give the crude product. After purification with flash chromatography (hexane/ethyl acetate 10:1), the product was further purified by distillation (120 °C, 20 mmHg) to obtain the title compound (36.0 g, 76%): GC  $t_R$  6.92 min (OV-17; 0.25 mm  $\times$  25 m; oven temperature, 100 °C; rate of temperature increase, 10 °C/min); TLC  $R_f$  0.54 (hexane/ethyl acetate 5:1);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.03 (s, 9H), 0.90 (t, 3H,  $J = 7.2$  Hz), 1.16–1.36 (m, 2H), 1.39–1.55 (m, 2H), 2.68 (s) and 2.72 (s) (total 2H, two rotamers), 3.06–3.26 (m, 2H), 3.64 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  -1.8 and -1.6, 13.7, 19.8, 29.4 and 29.8, 37.9 and 38.6, 48.7 and 49.3, 51.9 and 52.3, 156.6; IR (neat): 2957, 1701, 1473, 1225  $\text{cm}^{-1}$ ; LRMS (EI)  $m/z$  217 ( $\text{M}^+$ ), 202 ( $\text{M}^+ - \text{CH}_3$ ), 186 ( $\text{M}^+ - \text{OMe}$ ), 158 ( $\text{M}^+ - \text{CO}_2\text{Me}$ ); HRMS (EI) calcd for  $\text{C}_{10}\text{H}_{23}\text{NO}_2\text{Si}$  ( $\text{M}^+$ ): 217.1498, found: 217.1501.

**Generation of Iminium Cation Pool. Typical Procedure.** The anodic oxidation was carried out in an H-type divided cell (4G glass filter) equipped with a carbon felt anode (Nippon Carbon JF-20-P7, ca. 320 mg, dried at 250 °C/L mmHg for 1 h before use) and a platinum plate cathode (60 mm  $\times$  30 mm). In the anodic chamber was placed a solution of **1** (610.3 mg, 2.81 mmol) in 0.3 M  $\text{Bu}_4\text{NBF}_4/\text{CH}_2\text{Cl}_2$  (56.0 mL). In the cathodic chamber were placed 0.3 M  $\text{Bu}_4\text{NBF}_4/\text{CH}_2\text{Cl}_2$  (56.0 mL) and trifluoromethanesulfonic acid (1.05 g, 7.00 mmol). The constant current electrolysis (30 mA) was carried out at -78 °C with magnetic stirring until 2.5 F/mol of electricity was consumed.

**General Procedure of the Reaction in a Macroscale Batch Reactor.** To a solution of an aromatic compound (0.417 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL, cooled at -78 °C) was added a cation pool **2** (10 mL, cooled at -78 °C) generated from **1** (0.500 mmol) by a syringe pump (flow rate, 5.0 mL/min). Immediately after mixing, the reaction was quenched by  $\text{Et}_3\text{N}$  (1 mL) at the same temperature. The solvent was removed under reduced pressure, and the residue was quickly filtered through a short column (10 cm) of silica gel to remove  $\text{Bu}_4\text{NBF}_4$ . The silica gel was washed with ether (300 mL). The combined solution was concentrated to give a crude product, which was purified by flash chromatography.

**General Procedure of Micromixing.** A solution of nucleophile (0.417 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL, cooled at -78 °C) and a cation pool **2** (10 mL, cooled at -78 °C) generated from **1** (0.500 mmol) were simultaneously introduced to the micromixer, which was dipped in a coolant at -78 °C, using syringe pumps (flow rate is 5.0 mL/min). Then, the reaction mixture coming out from the outlet of the micromixer was collected with a round-bottomed flask and immediately quenched by  $\text{Et}_3\text{N}$  (1 mL) at -78 °C. The solvent was removed under reduced pressure, and the residue was quickly filtered through a short column (10 cm) of silica gel to remove  $\text{Bu}_4\text{NBF}_4$ . The silica gel was washed with ether (300 mL). The combined solution was concentrated to give a crude product, which was purified by flash chromatography.

**1-(*N*-Butyl-*N*-methoxycarbonylaminomethyl)-2,4,6-trimethoxybenzene (12) and 1,3-Bis(*N*-butyl-*N*-methoxy-carbonylaminomethyl)-2,4,6-trimethoxybenzene (13).** The title compounds were synthesized by the reaction of a cation pool **2** (10 mL) generated from **1** (0.500 mmol) with 1,3,5-trimethoxybenzene **11** (70.1 mg, 0.416 mmol) by micromixing (IMM single mixer, -78 °C). Yields were determined by GC. **12**: 92% yield (GC  $t_R$  11.7 min, OV-1; 0.80 mm  $\times$  1 m; oven temperature, 100 °C; rate of temperature increase, 10 °C/min). TLC  $R_f$  0.49 (hexane/ethyl acetate 1:1);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.84 (t, 3H,  $J = 7.2$  Hz), 1.11–1.30 (m, 2H), 1.35–1.48 (m, 2H), 2.93–3.08 (m, 2H), 3.63–3.80 (m, 9H), 3.81 (s, 3H), 4.45–4.58 (m, 2H), 6.10 (s, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  13.8, 19.9, 29.5 and 30.1, 37.7 and 37.8, 44.2 and 44.7, 52.1, 55.2, 55.5, 90.1, 105.8, 156.8, 156.0, 160.8; IR (neat) 2957, 1697, 1608, 1498, 1151  $\text{cm}^{-1}$ ; LRMS (EI)  $m/z$  311 ( $\text{M}^+$ ), 280 ( $\text{M}^+ - \text{OMe}$ ), 252 ( $\text{M}^+ - \text{CO}_2\text{Me}$ ),

181 ( $M^+ - \text{NBuCO}_2\text{Me}$ ); HRMS (EI) calcd for  $\text{C}_{16}\text{H}_{25}\text{NO}_5$  ( $M^+$ ): 311.1733, found: 311.1733. **13**: 4% yield (GC  $R$  16.7 min, column, OV-1; 0.80 mm  $\times$  1 m; oven temperature, 100 °C; rate of temperature increase, 10 °C/min). TLC  $R_f$  0.37 (hexane/ethyl acetate 1:1):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.81 (t, 6H,  $J = 7.2$  Hz), 1.09–1.28 (m, 4H), 1.29–1.43 (m, 4H), 2.86–3.07 (m, 4H), 3.59–3.79 (m, 9H), 3.80 (s, 6H), 4.50 (s) and 4.55 (s) (total 4H, two rotamers), 6.23 (s, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  14.0, 20.2, 29.8 and 30.3, 38.8, 44.5 and 45.1, 52.6, 55.8, 62.6, 91.3, 111.2, 157.1, 160.0; IR (neat) 2957, 1698, 1609, 1152  $\text{cm}^{-1}$ ; LRMS (EI)  $m/z$  454 ( $M^+$ ), 423 ( $M^+ - \text{OMe}$ ), 395 ( $M^+ - \text{CO}_2\text{Me}$ ); HRMS (EI) calcd for  $\text{C}_{23}\text{H}_{38}\text{N}_2\text{O}_7$  ( $M^+$ ): 454.2679, found: 454.2682.

**Estimation of Relative Rates of the First Alkylation and Second Alkylation using the Microsystem.** A microsystem consisting of two micromixers (**M1** and **M2**) and a tube reactor (**R1**) was used. The whole system was cooled in a dry ice bath at  $-78$  °C. For **M1**, where the cation pool and an aromatic compound were mixed, a splitting and recombination type micromixer, Yamatake YM-1 was used. Thus, a solution of **2** (0.05 M) generated from **1** and that of an aromatic compound (0.03 M) were introduced to **M1** by the syringe pumping technique (flow rate: 8.0 mL/min) at  $-78$  °C. Then, the reaction mixture was introduced to a tube reactor (**R1**) ( $\phi = 1.0$  mm,  $X$  cm). In

the final stage,  $\text{Et}_3\text{N}$  (8 mL/min) was introduced through **M2** to quench the reaction. For **M2**, Yamatake YM-1 was used.

**DFT Calculations.** The DFT calculations were carried out at the B3LYP/6-31G(d) level using the Gaussian 2003W, Revision-B.05.<sup>21</sup> Geometries were fully optimized. All the optimized structures were local minima according to the vibration analysis. The transition state was verified to have exactly one negative eigenvalue. A negative eigenvalue was animated using Gaussian View 3.0 and proved to be the transition state for formation of the expected bond.

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

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

JA0527424

(21) Pople, J. A. et al. *Gaussian 03*, Revision B.05; Gaussian, Inc.: Pittsburgh, PA, 2003.