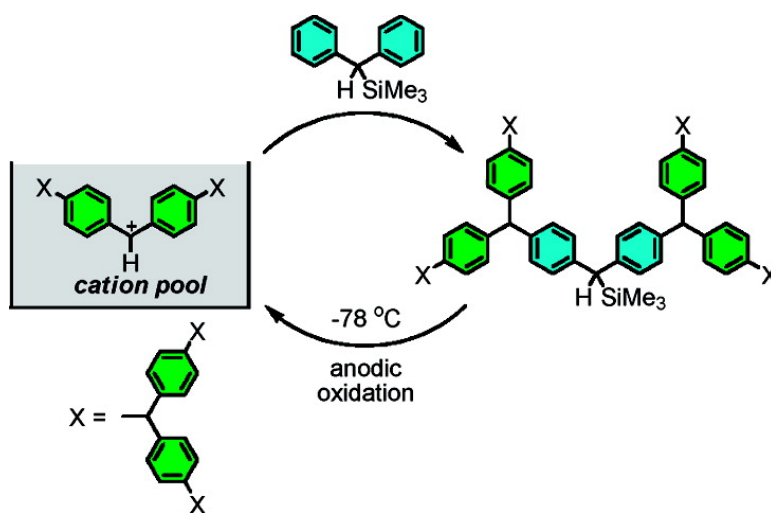


Iterative Molecular Assembly Based on the Cation-Pool Method. Convergent Synthesis of Dendritic Molecules

Toshiki Nokami, Kousuke Ohata, Masafumi Inoue, Hiroaki Tsuyama, Akito Shibuya, Kazuya Soga, Masayuki Okajima, Seiji Suga, and Jun-ichi Yoshida

J. Am. Chem. Soc., **2008**, 130 (33), 10864-10865 • DOI: 10.1021/ja803487q • Publication Date (Web): 29 July 2008

Downloaded from <http://pubs.acs.org> on February 8, 2009



More About This Article

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

- Supporting Information
- 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](#)

Iterative Molecular Assembly Based on the Cation-Pool Method. Convergent Synthesis of Dendritic Molecules

Toshiki Nokami, Kousuke Ohata, Masafumi Inoue, Hiroaki Tsuyama, Akito Shibuya, Kazuya Soga, Masayuki Okajima, Seiji Suga, and Jun-ichi Yoshida*

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

Received May 9, 2008; E-mail: yoshida@sbchem.kyoto-u.ac.jp

Iterative processes that are based on multiple use of the same reaction sequence serve as powerful methods for construction of relatively large structurally well-defined organic molecules.¹ Various iterative processes have been developed, and they are widely utilized in the synthesis of organic compounds. To achieve such processes, a method involving generation and accumulation of a highly reactive species (activation) followed by the coupling reaction with a building block, which is equipped with a potential active site for the generation of the reactive species in the next sequence, is quite effective (Figure 1).

The cation-pool method² that involves generation and accumulation of highly reactive organic cations using anodic oxidation³ in the absence of a nucleophile seems to be suitable for the present purpose. Recently we have reported that diarylcarbenium ions **2**⁴ can be generated and accumulated by low-temperature anodic oxidation of diarylmethanes **1** (Scheme 1a).⁵

Based on this finding, the following working hypothesis came to mind. If diarylcarbenium ion **2** reacts with two benzene rings of diphenylmethane derivative **3** in a Friedel–Crafts manner (Scheme 1b), the resulting extended diarylmethane **4** could be used as a precursor of the next activation–coupling sequence (Scheme 1c). Consequently, multiple use of this sequence leads to convergent synthesis⁶ of dendritic molecules⁷ (Scheme 1). This concept works, and we report herein the results of our proof-of-principle study on iterative molecular assembly using the cation-pool method.

Although the anodic oxidation of diphenylmethane led to the formation of a complex mixture, the reactions of substituted diphenylmethanes **1** (Ar = *p*-FC₆H₄, *p*-CH₃C₆H₄, *p*-CH₃OC₆H₄, *p*-ClC₆H₄, etc.) gave rise to effective formation of the corresponding diarylcarbenium ion pools.³ We chose to use di(*p*-fluorophenyl)methane **1a** (Ar = *p*-FC₆H₄) as a starting material because the conversion to diarylcarbenium ion **2a** is very efficient among the examined (Scheme 2). The resulting **2a** was allowed to react with diphenylmethane **3a** (X = H), but the expected 1:2 adduct **4a** (Ar = *p*-FC₆H₄, X = H) was not produced. Instead, the 1:1 adduct **7** was obtained in very low yield (11%).

To solve this problem, a silyl-substituted diphenylmethane, **3b** (X = SiMe₃), was used because the introduction of a silyl group at the benzylic position increases the HOMO level of the benzene ring to increase its reactivity.⁸ Also if the outer-sphere electron transfer takes place, the C–Si bond in the resulting radical cation is readily cleaved.⁹ However, Mayr, Fukuzumi, and co-workers reported that the outer-sphere electron transfer is definitely excluded for the reaction of diarylcarbenium ions with nucleophiles.¹⁰ In fact, the reaction of **3b** (X = SiMe₃) with **2a** proceeded without cleavage of the C–Si bond to give desired **4b** (Ar = *p*-FC₆H₄, X = SiMe₃) [G-1, the first generation] in 79% yield.¹¹

There is another merit in the use of a silyl group. For the oxidation of **4b** to generate diarylcarbenium ion **5** in the next

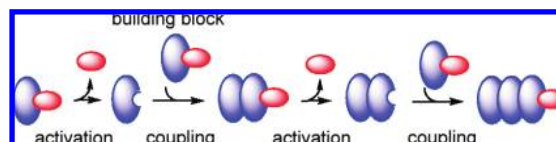
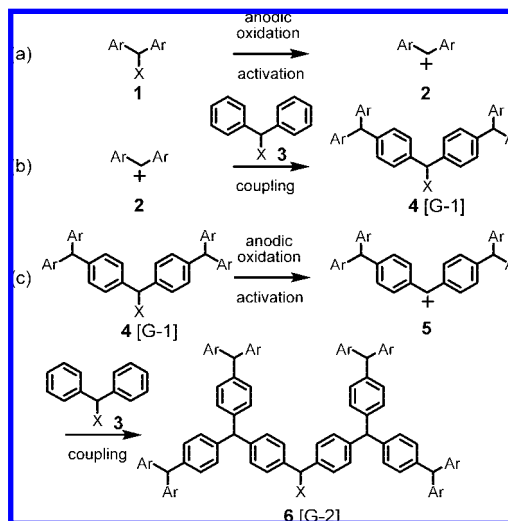
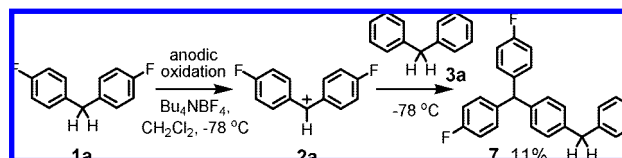


Figure 1. Iterative process based on activation–coupling sequence.

Scheme 1



Scheme 2



sequence, the silyl group works as an electroauxiliary,¹² which activates the molecule toward oxidation and controls the reaction pathway. In fact, the oxidation potential of **4b** (1.25 V) was found to be much less positive than those of **1a** (1.77 V) and **3a** (1.81 V). The anodic oxidation of **4b** took place smoothly, and the C–Si bond was cleaved selectively¹³ without affecting other C–H bonds at benzylic positions. The resulting **5** (Ar = *p*-FC₆H₄) was allowed to react with **3b** (X = SiMe₃) to give **6** (Ar = *p*-FC₆H₄, X = SiMe₃) [G-2, the second generation] in 75% yield.¹⁴

The anodic oxidation of **6** was accomplished in a similar manner. The resulting solution of diarylcarbenium ion **8** exhibited a single set of ¹H NMR signals at –78 °C (Figure 2). A signal at 9.87 ppm (singlet) is assigned to the proton adjacent to the cationic carbon (H^a). The solution also exhibited a ¹³C NMR signal at 193.7 ppm

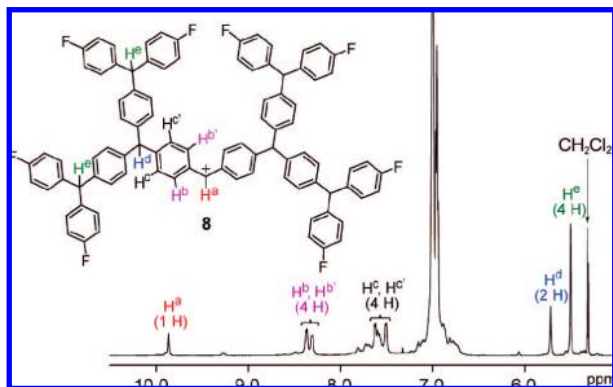


Figure 2. ^1H NMR spectrum of dendritic diarylcarbenium ion **8**.

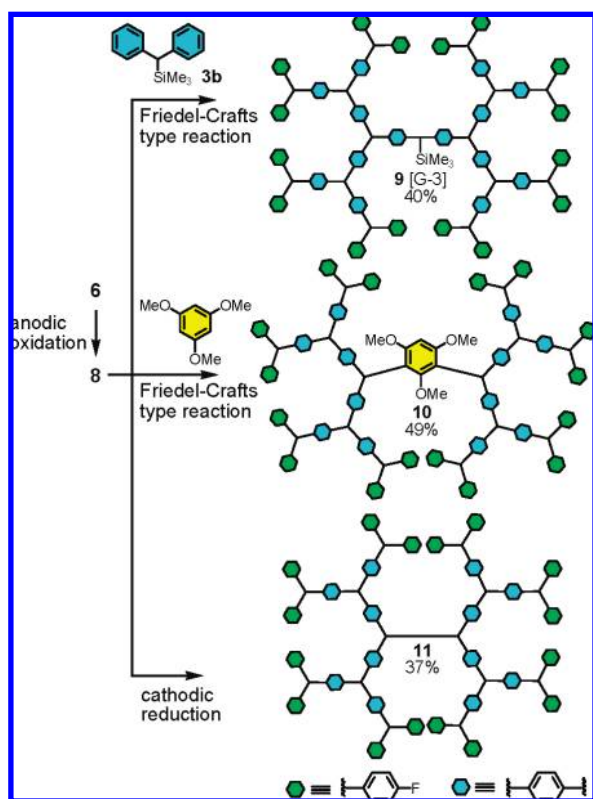


Figure 3. Dendritic molecules synthesized from cation **8**.

from the cationic carbon. These chemical shifts are very similar to those of **2a** (^1H NMR: 9.90 ppm, ^{13}C NMR: 192.6 ppm) and **5** (^1H NMR: 9.92 ppm, ^{13}C NMR: 194.4 ppm).

Dendritic diarylcarbenium ion **8** has sufficient reactivity for further transformation. In Figure 3, the reaction with **3b** proceeded to give **9** [G-3, the third generation] (40%, FAB-MS: m/z calcd for $\text{C}_{198}\text{H}_{144}\text{F}_{16}\text{Si}$: 2853.0764, found: 2853.0782), which can be utilized for the next sequence. The Friedel–Crafts type reaction with 1,3,5-trimethoxybenzene gave the disubstituted product **10** in 49% yield (FAB-MS: m/z calcd for $\text{C}_{191}\text{H}_{136}\text{O}_3\text{F}_{16}$: 2781.0234, found: 2781.0198), suggesting that dendritic molecules having various core structures can be synthesized in a similar manner. Cation **8** is also useful as a precursor for free radical reactions.¹⁵ For example, cathodic reduction gave homocoupling product **11**, although the

yield was not optimized (37%, FAB-MS: m/z calcd for $\text{C}_{182}\text{H}_{126}\text{F}_{16}$: 2614.9604, found: 2614.9590).

In summary, we have developed a new iterative and convergent method for making dendritic molecules based on the cation–pool method. The silyl-substituted diphenylmethane serves as a useful building block. Development of new building blocks and applications to synthesis of dendrimers that have various cores and functional groups exhibiting a variety of functions¹⁶ are under way in our laboratory.

Acknowledgment. This work was partially supported by the Grant-in-Aid for Scientific Research. The authors thank Dr. Keiko Kuwata of Kyoto University for MS analysis and Dr. Tetsuaki Fujiwara of Kyoto University for fruitful discussions.

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

References

- (1) (a) Ho, T.-K. *Tactics of Organic Synthesis*; Wiley: New York, 1994. (b) Feuerbacher, N.; Vögtle, F. *Top. Curr. Chem.* **1998**, *197*, 1.
- (2) (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) Yoshida, J.; Suga, S. *Chem.–Eur. J.* **2002**, *8*, 2650. (d) Suga, S.; Watanabe, M.; Yoshida, J. *J. Am. Chem. Soc.* **2002**, *124*, 14824. (e) Suga, S.; Nishida, T.; Yamada, D.; Nagaki, A.; Yoshida, J. *J. Am. Chem. Soc.* **2004**, *126*, 14338. (f) Okajima, M.; Suga, S.; Itami, K.; Yoshida, J. *J. Am. Chem. Soc.* **2005**, *127*, 6930. (g) Maruyama, T.; Suga, S.; Yoshida, J. *J. Am. Chem. Soc.* **2005**, *127*, 7324. (h) Suga, S.; Matsumoto, K.; Ueoka, K.; Yoshida, J. *J. Am. Chem. Soc.* **2006**, *128*, 7710.
- (3) (a) Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527. (b) Sperry, J. B.; Wright, D. L. *Chem. Soc. Rev.* **2006**, *35*, 605.
- (4) (a) Minegishi, S.; Loos, R.; Kobayashi, S.; Mayr, H. *J. Am. Chem. Soc.* **2005**, *127*, 2641. (b) Denekamp, C.; Sandlers, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 2093. and references cited therein.
- (5) Okajima, M.; Soga, K.; Nokami, T.; Suga, S.; Yoshida, J. *Org. Lett.* **2006**, *8*, 5005.
- (6) Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638.
- (7) (a) Grayson, S. M.; Fréchet, J. M. J. *Chem. Rev.* **2001**, *101*, 3819. (b) *Dendrimers and Dendrons: Concepts, Synthesis, Application*; Newkome, G. R., Moorefield, C. N., Vögtle, F., Eds.; Wiley-VHC: Weinheim, 2001. (c) Newkome, G. R.; Moorefield, C. N. *Dendrimers*. In *Comprehensive Supramolecular Chemistry*; Lehn, J.-M., Ed.; Pergamon: New York, 1996; Vol. 10, pp 777–832.
- (8) (a) Traylor, T. G.; Hanstein, W.; Berwin, H. J.; Clinton, N. A.; Brown, R. S. *J. Am. Chem. Soc.* **1971**, *93*, 5715. (b) Giordan, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6544. (c) Bock, H. *Angew. Chem., Int. Ed.* **1989**, *28*, 1627.
- (9) (a) Yoshida, J.; Murata, T.; Ise, S. *Tetrahedron Lett.* **1986**, *27*, 3373. (b) Koizumi, T.; Fuchigami, T.; Nonaka, T. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 219. (c) Porter, J. M.; Xuan, X.; Blackman, B.; Hsu, D.; Fry, A. J. *Tetrahedron Lett.* **1997**, *38*, 7147. (d) Maruyama, T.; Mizuno, Y.; Shimizu, I.; Suga, S.; Yoshida, J. *J. Am. Chem. Soc.* **2007**, *129*, 1902. and references cited therein.
- (10) Ofial, A. R.; Ohkubo, K.; Fukuzumi, S.; Lucius, R.; Mayr, H. *J. Am. Chem. Soc.* **2003**, *125*, 10906.
- (11) Friedel–Crafts reactions of benzylsilanes have been reported. Georgakilas, V.; Perdikomatis, G. P.; Triantafyllou, A. S.; Siskos, M. G.; Zarkadis, A. K. *Tetrahedron* **2002**, *58*, 2441.
- (12) Yoshida, J.; Nishiwaki, K. *J. Chem. Soc., Dalton Trans.* **1998**, 2589.
- (13) (a) Baciocchi, E.; Del Giacco, T.; Elisei, F.; Ioele, M. *J. Org. Chem.* **1995**, *60*, 7974. (b) Cermenati, L.; Freccero, M.; Venturello, P.; Albini, A. *J. Am. Chem. Soc.* **1995**, *117*, 7869. (c) Fukuzumi, S.; Fujita, M.; Noura, S.; Ohkubo, K.; Suenobu, T.; Araki, Y.; Ito, O. *J. Phys. Chem. A* **2001**, *105*, 1857. (d) Fukuzumi, S.; Satoh, N.; Okamoto, T.; Yasui, K.; Suenobu, T.; Seko, Y.; Fujitsuka, M.; Ito, O. *J. Am. Chem. Soc.* **2001**, *123*, 7756. (e) Dockery, K. P.; Dinnocenzo, J. P.; Farid, S.; Goodman, J. L.; Gould, I. R.; Todd, W. P. *J. Am. Chem. Soc.* **1997**, *119*, 1876.
- (14) Various 1 → 2 C-branched dendrimers have already been synthesized as a precursor of polyradicals. (a) Rajca, A.; Janicki, S. *J. Org. Chem.* **1994**, *59*, 7099. (b) Rajca, A. *Chem. Rev.* **1994**, *94*, 871. and references therein.
- (15) (a) Suga, S.; Suzuki, S.; Yoshida, J. *J. Am. Chem. Soc.* **2002**, *124*, 30. (b) Suga, S.; Suzuki, S.; Maruyama, T.; Yoshida, J. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1545.
- (16) (a) Boas, U.; Heegaard, P. M. H. *Chem. Soc. Rev.* **2004**, *33*, 43. (b) Lee, C. C.; MacKay, J. A.; Fréchet, J. M. J.; Szoka, F. C. *Nat. Biotechnol.* **2005**, *23*, 1517. (c) Grimsdale, A. C.; Müllen, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 5592. (d) Lo, S.-C.; Burn, P. L. *Chem. Rev.* **2007**, *107*, 1097.

JA803487Q