Novel Catalysis in Internal Nanocavity of Polyamine Dendrimer for Intramolecular Michael Reaction

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ABSTRACT

We found a novel catalysis of dendrimers derived from the internal nanocavity of the alkylated poly(propylene imine) (PPI) dendrimers, which showed a high catalytic efficiency for the intramolecular Michael reaction of (*E*)-9-nitro3-nonen-2-one. The kinetic studies revealed that the substrate was stabilized in the reactive conformation within the sterically confined nanocavity of the PPI dendrimer.

Keywords: Dendrimer, Nanocavity, Organocatalyst

1 INTRODACTION

Dendrimers have received considerable attention as promising nanomaterials in various research areas[1] because of the following characteristics: 1) tunable chemical and physical properties by changing core, branch, and peripheral units, and 2) internal nanocavities which can encapsulate organic molecules,[2a] metal complexes,[2b,c] and metal nanoparticles.[2d,e] In the field of catalysis, dendrimers allow precise design of catalytically active species and reaction environments within the internal nanocavities, exhibiting unique activities and selectivities. To date, various dendrimers have been reported to show positive dendritic effects on catalysis,[3a-g] such as site-isolation of active species,[3a] locally high concentrations of substrates,[3b,c] or catalytically active species,[3d] polar/non-polar reaction environments,[3e] and catalytic pump effects.[3f] However, the catalysis due to the steric effect of the confined nanocavities of dendrimers has been rarely investigated.[4]

Herein, we investigated the intramolecular Michael reaction of (*E*)-9-nitro3-nonen-2-one using the alkylated poly(propylene imine) (PPI) dendrimers as tertiary amine catalysts and found a novel dendritic effect of the internal nanocavity of PPI dendrimers.[5,6] The PPI dendrimers accommodated the substrate in a reactive conformation for the intramolecular cyclization within the nanocavity, with the result that the intramolecular Michael reaction proceeded smoothly (Figure 1).

2 EXPERIMENT

General: The third generation PPI dendrimer (G_3-NH_2) and polyethyleneimine (polyethyleneimine 10000, Mw = 10000) were purchased from SyMO-Chem B.V. (The Netherland) and Junsei Chemical Co., Ltd, respectively. Other chemicals

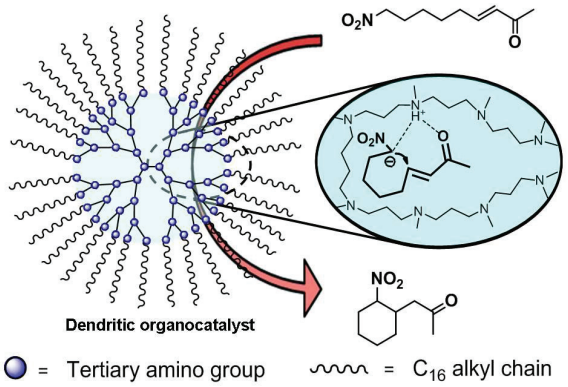


Figure 1. Intramolecular Michael reaction using the alkylated PPI dendrimer as an tertiary amine catalyst.

were commercially obtained from Wako Pure Chemicals, Tokyo Kasei Co., and Sigma-Aldrich Inc., and used after appropriate purification. ^{1}H NMR and ^{13}C{^{1}H}-NMR spectra were recorded on a JEOL GSX-270 or JNM-ESC400 spectrometer. Chemical shifts (δ) were reported in ppm downfield from tetramethylsilane. Infrared spectra were obtained using a JASCO FTIR-410 spectrometer. Gas chromatography (GC-FID) was carried out on a Shimazu GC-1700 equipped with a fused silica capillary column (Inert Cap 17, ID 0.25 mm × L 30 m × df 0.25 μm). Dynamic light scattering (DLS) was measured using a HORIBA LB-500.

Synthesis and characterization of PPI dendrimers modified with C_{16} alkyl chain (Gx-C_{16}, x = 3, 4, and 5): Alkylated PPI dendrimers were synthesized according to the reported procedure.[3e,7] Third- to fifth-generation NH_2-terminated PPI dendrimers G_x-NH_2 (x = 3, 4, and 5, denoting the generation number of the dendrimer) were treated with palmitoyl chloride to afford alkylated PPI dendrimers, G_x-C_{16} (Figure 2). DLS measurement of G_x-C_{16} in toluene and their molecular modeling revealed that G_x-C_{16} were unimolecular micelles with average diameters of 6.0 ± 0.9, 6.9 ± 1.0, and 8.0 ± 1.5 nm, respectively (Figure 3). Based on the molecular modeling, G_5-C_{16} posseses the PPI unit of diameter of ca. 4 nm and a few nanometers of internal cavity (Scheme 1). The concentration of tertiary amino

groups in the internal nanocavity of G_5-C_{16} was calculated as 3.3 mol·dm^{-3}.

Synthesis of polyethyleneimine modified with C_{16} alkyl chain (PEI-C_{16}): To a THF solution (100 mL) of polyethyleneimine (0.50 g, 3.15, 3.15, and 2.7 mmol for primary, secondary, and tertiary amine, respectively) and triethylamine (3.07 g, 30.4 mmol) was added palmitoyl chloride dropwise (2.42 g, 8.8 mmol) at 303 K for 5 min. The mixture was stirred at 313 K for 48 h, then concentrated under reduced pressure. The residue was washed with 1 M NaOH aqueous solution (3 x 200 mL) and water (5 x 200 mL), and dried under vaccum for 24 h to give PEI-C_{16} as a yellowish solid (1.48 g) (Figure 2). The product was identified by comparison of ^{1}H and ^{13}C{^{1}H} NMR spectra with reported data.[8]

Intramolecular Michael reaction of (*E*)-9-nitro-3-nonen-2-one (1) by G_x-C_{16}: To a toluene solution (2 mL) of G_x-C_{16} (30 μmol of tertiary N atom) was added **1** (0.2 mmol) under Ar atmosphere at 343 K, and the mixture was stirred. After the reaction, the reaction mixture was concentrated under the reduced pressure and analyzed by ^{1}H NMR using naphthalene as an internal standard in $CDCl_3$ to determine the conversion,

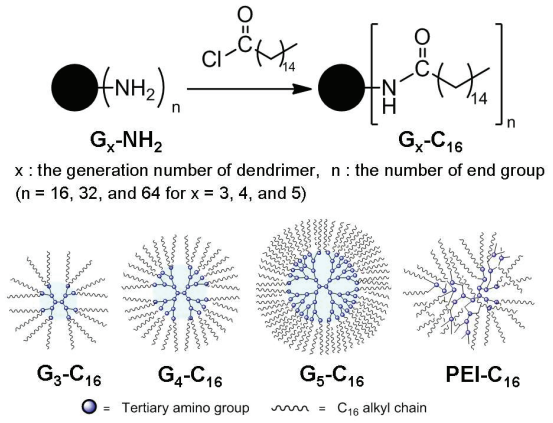


Figure 2. Schematic structures of G_x-C_{16} dendrimers and polyethyleneimine modified with palmitoyl chloride (PEI-C_{16}).

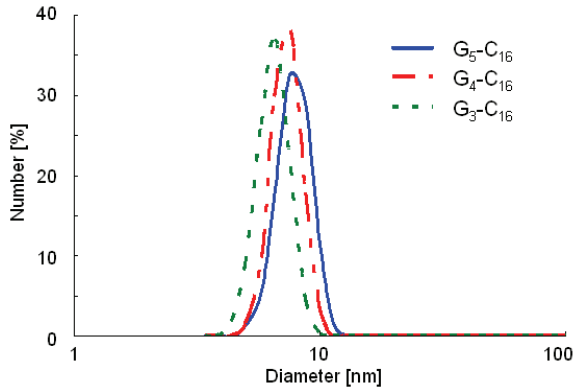
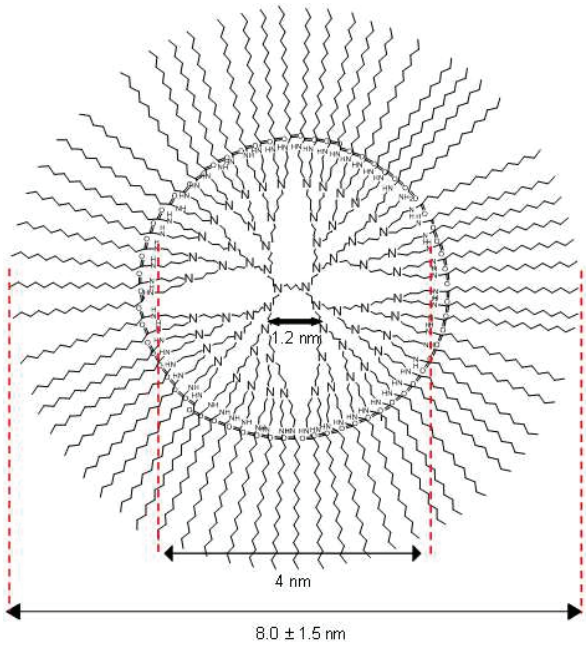
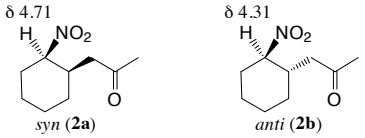


Figure 3. The size distributions of G_x-C_{16} in toluene by DLS measurement.



Scheme 1. Structure of G_5-C_{16} dendrimer

and the yields. The diastereoselectivity of the product 1-(2-nitrocyclohexyl)propan-2-one (**2**) was determined from the area ratio of proton signals of δ4.71 for **2a** and δ4.31 **2b** as shown below (Scheme 2).



Scheme 2. *syn*- and *anti*-(1-Nitrocyclohexyl)propan-2-one (**2**)

Intermolecular Michael reaction of 1-nitropropane and methyl vinyl ketone catalyzed by G_x-C_{16}: To a toluene solution (2 mL) of G_x-C_{16} (30 μmol of tertiary N atom) was added 1-nitropropane (**3**) (0.2 mmol) and methyl vinyl ketone (**4**) (0.5 mmol) under Ar atmosphere at 343 K. The mixture was stirred for 24 h, and then analyzed by GC using an internal standard technique.

3 RESULTS and DISCUSSION

The intramolecular Michael reaction of **1** to **2** was examined using G_x-C_{16} as a catalyst (Table 1). G_5-C_{16} (pK_a = 10.35)[9] catalyzed the intramolecular Michael reaction of **1** quantitatively in 2 h (entry 3). Interestingly, the catalytic activity of G_x-C_{16} increased as the generation of the dendrimer increased (entries 2, 5 and 6). Triethylamine (TEA, pK_a = 10.7),[10] which corresponds to the amine component of the nanocavity of G_5-C_{16}, did not promote this reaction (entry 12). Other low-molecular-weight amines such as *N*,*N*,*N*',*N*'-tetramethyl-1,3-propanediamine (TMPDA, pK_a = 10.5),[10] *N*,*N*- dimethyl-4-aminopyridine

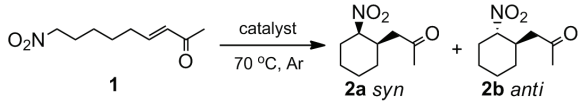
(DMAP, pK_a = 9.2),[10] and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, pK_a = 18.7)[10] showed lower catalytic activities than G_5-C_{16} (entry 1 vs entries 7, 9, and 11). Even a solvent amount of TEA, with higher amine concentration than the nanocavity of G_5-C_{16}(7.2 and 3.3mol·dm^{-3}, respectively), gave a low yield of **2** (entry 13). The initial reaction rates for the intramolecular Michael reaction of **1** in the presence of G_5-C_{16} and in a TEA solvent were 0.56 and 0.046 μmol·s^{-1}, respectively; the catalytic activity of G_5-C_{16} was 12 times greater than that of TEA. When using the polyethyleneimine modified with C_{16} alkyl chains (PEI-C_{16}, Figure 2) as an irregularly branched polyamine catalyst without internal nanocavity, the intramolecular Michael reaction did not proceed efficiently (entry 14).

In the intramolecular Michael reaction of **1**, a diastereomeric mixture of **2a** and **2b** with a *syn:anti* ratio of 45:55 was obtained (entries 1 and 8). In the case of G_5-C_{16}, isomerization of **2a** to the thermodynamically stable *anti* isomer **2b** did not occur to a significant extent until complete conversion of **1** had taken place (entries 1–4). On the other hand, when using DMAP, the isomerization reaction proceeded simultaneously with the intramolecular Michael reaction (entries 8–10).

The intramolecular Michael reaction generally occurs via nucleophilic attack of a carbanion generated by deprotonation of a donor part to a distant acceptor part and subsequent protonation of the corresponding enolate intermediate.[11] Noting the positive generation effect observed for G_x-C_{16} and the low catalytic activity of PEI-C_{16}, it was suggested that the efficient intramolecular Michael reaction using G_5-C_{16} proceeds through substrate orientation within the sterically confined nanocavity consisting of regularly arranged tertiary amino groups of G_5-C_{16} (Figure 4); the encapsulated substrate **1** is deprotonated by the tertiary amino group to form the corresponding carbanion species (**1a**) together with a quaternary ammonium cation. Next, the acceptor part of **1a** is oriented toward the distant donor part of **1a** by a sterically confined nanocavity consisting of the core and branch units of G_5-C_{16}. This conformation allows an electrostatic interaction between the quaternary ammonium cation of the nanocavity and the carbonyl group of **1a**,[12] resulting in facile nucleophilic attack of the donor part of **1a** to form a cyclized enolate intermediate. Subsequent protonation of the enolate intermediate furnishes the product **2**. The sluggish isomerization of **2a** to **2b** during the intramolecular Michael reaction may be due to the preferential accommodation of **1** over **2** into the nanocavity of G_5-C_{16}. After complete conversion of **1**, the isomerization of **2a** to **2b** occurs.

To support this suggested substrate orientation in the intramolecular Michael reaction, the preliminary kinetic studies of the intramolecular Michael reaction of **1** were carried out using G_5-C_{16}, TEA and PEI-C_{16} (Table 2). The activation entropies $\Delta S^{\ddagger}$ of G_5-C_{16}, TEA and PEI-C_{16} were –266, –249, and –243 J·K^{-1}·mol^{-1}, respectively. The smaller $\Delta H^{\ddagger}$ value of G_5-C_{16} confirms that the transition state for cyclization is more restricted by steric effects when this catalyst is used compared to the case of TEA and PEI-C_{16}.[13] G_5-C_{16}, TEA and PEI-C_{16}, respectively, showing that the nanocavity of G_5-C_{16} lowered the barrier for intramolecular nucleophilic attack by stabilizing the transition state. The activation energy E_a of G_5-C_{16} (20.0 kJ·mol^{-1}) was much lower than that of TEA and PEI-C_{16} (31.7 and 33.3 kJ·mol^{-1}, respectively).

Table 1. Intramolecular Michael reaction of **1** using various amine catalysts[a]



Entry	catalyst	time	conv. (%)[b]	yield (%)[b]	*syn:anti*
1	G_5-C_{16}	15 min	69	68	43:57
2	G_5-C_{16}	1 h	85	84	44:56
3	G_5-C_{16}	2 h	99	98 (89[c])	43:27
4	G_5-C_{16}	24 h	99	98	25:75
5	G_4-C_{16}	1 h	72	70	42:58
6	G_3-C_{16}	1 h	62	60	41:59
7	DBU	15 min	60	58	20:80
8	DMAP	5 min	13	12	44:56
9	DMAP	15 min	30	29	34:66
10	DMAP	8 h	99	98	10:90
11	TMPDA	1 h	7	3	-
12	TEA	1 h	N. R.	-	-
13	TEA[d]	1 h	17	15	43:57
14	PEI-C_{16}	1 h	13	12	41:59

[a] Reaction conditions: **1** (0.2 mmol), catalyst (tertiary N atom: 30 μmol), toluene (2 mL). [b] Determined by ^{1}H NMR using an internal standard technique. [c] Isolated yield. [d] TEA (2 mL) was used instead of toluene.

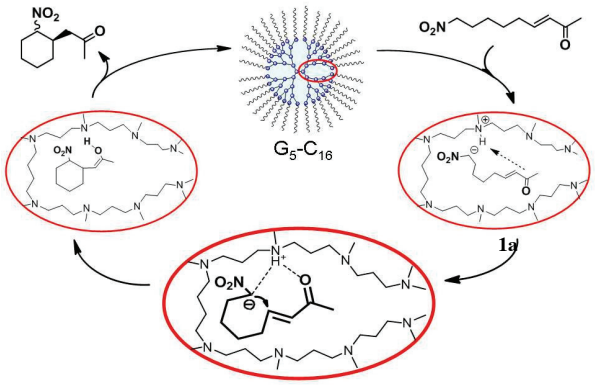


Figure 4. Proposed reaction mechanism.

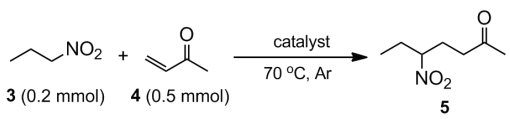
Table 2. Activation parameters of G_5-C_{16}, PEI-C_{16}, and TEA solvent for the intramolecular Michael reaction of **1**

catalyst	$\Delta S^{\ddagger}$[a] [JK^{-1}mol^{-1}]	$\Delta H^{\ddagger}$[b] [kJmol^{-1}]	$\Delta G^{\ddagger}$[c] [kJmol^{-1}]	E_a[d] [kJmol^{-1}]
G_5-C_{16}	-266	16.4	107	20.0
PEI-C_{16}	-243	30.6	115	31.7
TEA	-249	29.0	114	31.0

[a] Activation entropy. [b] Activation enthalpy. [c] Activation free energy. [d] Activation energy

The catalytic activities of G_x-C_{16} and other amines were examined in the *intermolecular* Michael reaction of **3** and **4** to 5-nitroheptan-2-one (**5**) (Table 3).[14] The catalytic activities of G_5-C_{16} and a solvent amount of TEA were almost the same

Table 3. Intermolecular Michael reaction of **3** and **4** to **5**[a]



3 (0.2 mmol) **4** (0.5 mmol) **5**

entry	catalyst	conv. of **3** (%)[b]	yield of **5** (%)[b]
1	G_5-C_{16}	47	45
2[c]	G_5-C_{16}	85	70
3	G_4-C_{16}	25	24
4	G_3-C_{16}	14	12
5	TMPDA	8	6
6	TEA	4	3
7	TEA[d]	45	43
8	PEI-C_{16}	24	22

[a] Reaction conditions: **3** (0.2 mmol), **4** (0.5 mmol), catalyst (tertiary N atom : 30 μmol), toluene (2 mL), 24 h. [b] Determined by GC using an internal standard technique. [c] 48 h. 1-(5-Ethyl-2-hydroxy-2-methyl-5-nitrocyclohexyl)ethanone was obtained in 13 % yield by consecutive reaction of **5** (see ref [14]). [d] TEA (2 mL) was used instead of toluene.

in terms of yield (entry 1 vs entry 7) and initial reaction rate (1.43 and 1.58 $\mu mol \cdot s^{-1}$ for G_5-C_{16} and TEA, respectively), which was in sharp contrast to the results obtained for the intramolecular Michael reaction of **1** (Table 1, entry 2 vs entry 13). Further, the difference of the catalytic activity between G_5-C_{16} and PEI-C_{16} was smaller in the intermolecular Michael reaction than that in the intramolecular Michael reaction (Table 1, entry 3 vs entry 14, and Table 3, entry 1 vs entry 8). These remarkably different results between *intramolecular* Michael reaction and *intermolecular* one support the occurrence of specific substrate orientation for intramolecular cyclization of **1** within the internal nanocavity of G_5-C_{16}.

4 CONCLUSION

The alkylated PPI dendrimer G_5-C_{16} acted as an organocatalyst and showed a novel dendritic effect in the intramolecular Michael reaction based on substrate orientation within its internal nanocavity. The sterically confined nanocavity consisting of regularly arranged amino groups of G_5-C_{16} could accommodate the substrate in a reactive conformation for intramolecular cyclization. We believe that such substrate orientation within the internal nanocavities of dendrimers may be applicable not only to the intramolecular Michael reaction but also to other cyclization reactions.

REFERENCES

1 (a) *Dendrimers and Other Dendritic Polymers*, ed. by J. M. J. Fréchet, D. A. Tomalia, Wiley & Sons, New York, 2001. (b) D. Astruc, E. Boisselier, C. Ornelas, *Chem. Rev*. **2010**, *110,* 1857.

2 (a) S. H. Medina , M E. H. El–Sayed, *Chem. Rev*. **2009**, *109,* 3141. (b) S.-H. Hwang, C. D. Shreiner, C. N. Moorefield, G. R. Newkome, *New J. Chem*. **2007**, *31*, 1192. (c) K. Yamamoto, T. Imaoka, *Bull. Chem. Soc. Jpn*. **2006**, *79*, 511. (d) V. S. Myers, M. G. Weir, E. V. Carino, D. F. Yancey, S. Pande, R. M. Crooks, *Chem. Sci*. **2011**, *2*, 1632. (e) D. Astruc, D. Ornelas, J. Ruiz, *Acc. Chem. Res*. **2008**, *41*, 841.

3 (a) C. Muller, L. J. Ackerman, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. V. Leeuwen, *J. Am. Chem. Soc*. **2004**, *126*, 14960. (b) B. Helms, C. O. Liang, C. J. Hawker, J. M. J. Fréchet, *Macromolecules* **2005**, *38*, 5411. (c) A. K. Diallo, E. Boisselier, L. Liang, J. Ruiz, D. Astruc, *Chem. Eur. J*. **2010**, *16*, 11832. (d) T. Imaoka, Y. Kawana, M. Tsuji, K. Yamamoto, *Chem. Eur. J*. **2010**, *16*, 11003. (e) T. Mizugaki, C. E. Hetrick, M. Murata, K. Ebitani, M. D. Amiridis, K. Kaneda, *Chem. Lett*. **2005**, *34*, 420. (f) M. E. Piotti, Jr., F. Rivera, R. Bond, C. J. Hawker, J. M. J. Fréchet, *J. Am. Chem. Soc*. **1999**, *121*, 9471. (g) A recent review of positive dendritic effect; B. Helms, J. M. J. Fréchet, *Adv. Synth. Catal*. **2006**, *348*, 1125.

4 (a) A. R. Chianese, A. Mo, D. Datta, *Organometallics* **2009**, *28*, 465. (b) M. Ooe, M. Murata, T. Mizugaki, K. Ebitani, K. Kaneda, *J. Am. Chem. Soc*. **2004**, *126*, 1604. (c) P. Bhyrappa, J. K. Young, J. S. Moore, K. S. Suslick, *J. Am. Chem. Soc*. **1996**, *118*, 5708.

5 Recent reports on Michael reaction using metallodendrimer catalysts: (a) M. Q. Slagt, S.–E. Stiriba, H. Kautz, R. J. M. K. Gebbink, H. Frey, G. van Koten, *Organometallics* **2004,** *23,* 1525. (b) H. P. Dijkstra, M. Q. Slagt, A. McDonald, C. A. Kruithof, R. Kreiter, A. M. Mills, M. Lutz, A. L. Spek, W. Klopper, G. P. M. van Klink, G. van Koten, *Eur. J. Inorg. Chem*. **2003**, 830. (c) T. Sekiguti, Y. Iizuka, S. Takizawa, D. Jayaprakash, T. Arai, H. Sasai, *Org. Lett*. **2003**, *5*, 2647. (d) T. Arai, T. Sekiguti, Y. Iizuka, S. Takizawa, S. Sakamoto, K. Yamaguchi, H. Sasai, *Tetrahedron: Asymmetry* **2002**, *13*, 2083. (e) V. Maraval, R. Laurent, A.-M. Caminade, J.-P. Majoral, *Organometallics* **2000**, *19,* 4025.

6 Recent reports on Michael reaction using dendritic organocatalysts: (a) C.–M. Lo, H.–F. Chow, *J. Org. Chem*. **2009**, *74*, 5181. (b) L. Tuchman–Shukrona, M. Portnoy, *Adv. Synth. Catal*. **2009**, *351*, 541. (c) G. Lv, R. Jin, W. Mai, L. Gao, *Tetrahedron*: *Asymmetry*, **2008**, *19*, 2568. (d) E. Bellis, G. Kokotos, *J. Mol. Cat. A*: *Chem*. **2005**, *241*, 166. (e) A. Sarkar, P. Ilankumaran, P. Kisanga, J. G. Verkade, *Adv. Synth. Catal*. **2004**, *346*, 1093.

7 (a) A. P. H. J. Schenning, C. Elissen-Roman, J.–W. Weener, M. W. P. L. Baars, S. J. van der Gaast, E. W. Meijer, *J. Am. Chem. Soc*. **1998**, *120,* 8199. (b) E. M. M. de Brabander-van den Berg, E. W. Meijer, *Angew. Chem., Int. Ed. Engl*. **1993**, *32*, 1308.

8 C. Aymonier, U. Schlotterbeck, L. Antonietti, P. Zacharias, R. Thomann, J. C. Tiller, S. Mecking, *Chem. Commun*. **2002**, 3018.

9 G. J. M. Koper, M. H. P. van Genderen, C. Elissen-Román, M. W. P. L. Baars, E. W. Meijer, M. Borkovec, *J. Am. Chem. Soc*. **1997**, *119*, 6512.

10 E.-I. Room, A. Kutt. I. Kaljurand, I. Koppel, I. Leito, T. A. Koppel, M. Mishima, K. Goto, Y. Miyahara, *Chem. Eur. J*. **2007**, *13*, 7631.

11 R. D. Daniel, M. R. Masjedizadeh, O. Wallquist, J. I. Mcloughlin, *Organic Reactions,* Wiley, New York, **1995**, *47*, 315.

12 M. A. Ramirez, J. M. Padron, J. M. Palazon, V. S. Martin, *J. Org. Chem*. **1999**, *62*, 4584.

13 B. D. Stubbert, T. J. Marks, *J. Am. Chem. Soc,* **2007**, *129*, 6149.

14 K. Motokura, S. Tanaka, M. Tada, Y. Iwasawa, *Chem. Eur. J*. **2009**, *15*, 10871.