Anomalous Cyclodimerization of 3-Phenyl-3-(phthalimidomethyl)oxetane via Monomer Isomerization and Consecutive Cation Transfer

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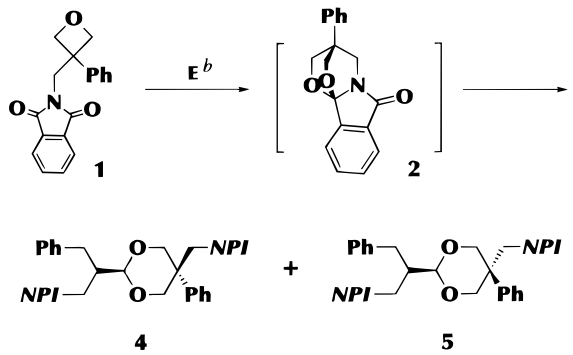
Cyclic ethers can be polymerized cationically. In the propagation, cyclic oxonium ions at growing chain ends are repeatedly opened and regenerated by nucleophilic attack of the ethereal oxygen atom in the monomer. However, intramolecular cyclization could take place, if the oxonium ends suffer "*back-biting*" by any oxygen atom in their own polyether chain or, in a special case, "*end-biting*" by the terminal oxygen atom.[1] Consequently, various types of ring-expanded ethers from a cyclic dimer up to cyclic macromers can be formed accompanying linear polyethers. Such cyclization generally becomes less significant during the cationic processes of oxetane series, because of a great difference in basicity between four-membered cyclic ether and open ones.[1] Therefore, the cationic ring-opening polymerization of oxetane derivatives has been served as a general method for synthesizing variously functionalized polyethers.[2,3] Nevertheless, the formation of cyclic products has been long known, especially at elevated temperatures, and some investigations of the cyclooligomerization of unsubstituted and substituted oxetanes have been made.[4] Therein, cyclic oligoethers from trimer to octamer were detected with the tetramers in the greatest abundance.

During the investigation of the cationic polymerization of oxetanes having a carbonyl-containing substituent, we have more recently found that 3-phenyl-3-(phthalimidomethyl)oxetane (**1**) preferentially undergoes dimerization (Scheme 1). However, the resulting dimers were two geometrical isomers of substituted 1,3-dioxane (**4** and **5**), which were quite different from an eight-membered cyclic ether expected from the well-known "*back-biting*" mechanism. Herein, we wish to report the anomalous cyclodimerization of **1** via monomer isomerization and consecutive cation transfer.

The oxetane **1** was prepared from phenylacetaldehyde as a starting material, according to Scheme 2. The structure of **1** was well characterized by IR and ^{1}H and ^{13}C NMR spectroscopies.[5]

The polymerization of **1** in dichloromethane or chlorobenzene was carried out using trifluoromethanesulfonic acid (TfOH), boron trifluoride etherate (BF_3·OEt_2), trimethylaluminum ($AlMe_3$), or benzylthiolanium hexafluoroantimonate[6] (BnTA), as examples of a Brønsted acid, Lewis acids, or an alkylating agent, respectively. These catalysts showed no polymerizability of **1** at temperatures below 0 °C in dichloromethane, and the

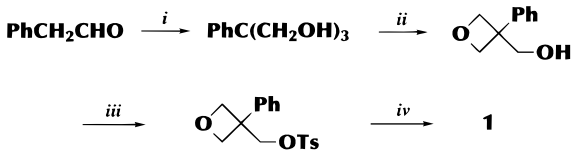
Scheme 1[a]



1 2 4 5

[a] NPI: phthalimido group. [b]Conditions: 5 mol % of catalyst E (BF_3·OEt_2, BnTA, or TfOH), in chlorobenzene, at 130 °C.

Scheme 2. Preparation of 1[a]



[a] (i) 37% Formalin, $Ca(OH)_2$, room temperature to 85 °C, 78 h, yield 37%. (ii) Diethyl carbonate, ethanolic KOH, 100 °C, 5 h, followed by thermal decarboxylation at 200 °C under 20 mmHg, yield 51%. (iii) TsCl, aqueous NaOH−THF, 30 °C, 3 h, yield 94%. (iv) Potassium phthalimide, DMF, 80 °C, 2 h, yield 71%.

monomer remained unreacted. The reaction of **1** using BF_3·OEt_2 at 35 °C for 35 min gave mainly bicyclic acetal (**2**)[7] together with unknown oligomeric products. This isomerization similarly occurred using the other catalysts, and a nearly quantitative conversion into **2** was achieved in the reaction using $AlMe_3$ in chlorobenzene at 130 °C.

Similarly, most of the reactions at this temperature in chlorobenzene produced **2** at a very early stage, but after that the fleeting product was consumed rapidly. As shown in Figure 1, a typical GPC curve of the final reaction mixture seemed to be roughly split into three fractions of unimer, dimer, and higher oligomers. The mass spectrum of the most abundant dimer fraction showed $m/e = 586$ (M^+), suggesting a dimerization of **1** or **2** having a molecular weight of 293. This fraction was collected by preparative TLC and then separated into two pure components **4** and **5** by repeated crystallization.[8] As illustrated in Figure 2, the absolute structure of **4** was established by an X-ray analysis,[9] which unambiguously demonstrated that the largest isopropyl type substituent at the 2-position is in equatorial orientation with the 1,3-dioxane ring in chair conformation. The ^{13}C spectra of **4** and **5** had a strong resemblance, whereas the ^{1}H NMR spectra, especially in coupling pattern, were quite different from each other.[10,11] As can be seen from Figure 3, a long range COSY correlation clearly appeared between *N*-methylene (H13a, b) and *O*-methylene (H4b, H6b) protons in **4**, probably due to a W-type arrangement. The 5-phthalimidomethyl group, therefore, should stay in the axial position not only in the solid but also in solution. In contrast, the spectrum of **5** entirely lacks such a correlation. On the basis of the above results, it may be deduced that **5** is a *cis*/*trans* geometrical isomer of

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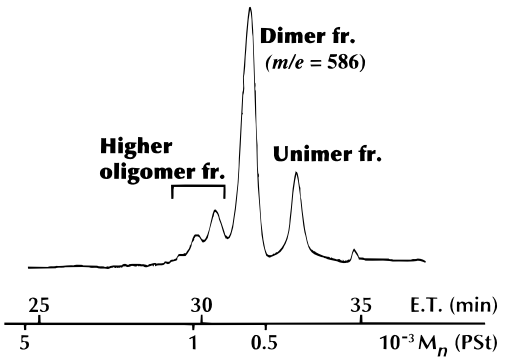


Figure 1. RI-detected GPC chart of the products obtained by the reaction of **1** with BnTA (5 mol %) in chlorobenzene at 130 °C for 24 h: see experiment no. 3 in Table 1.

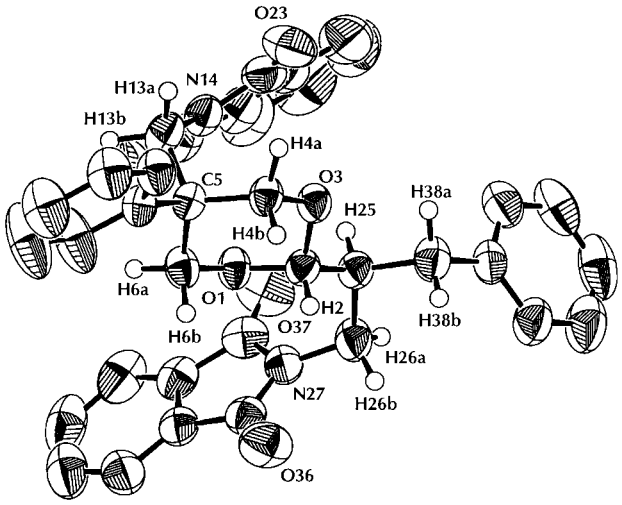


Figure 2. ORTEP view of **4** with 30% probability thermal ellipsoids. The numberings of non-hydrogen atoms are the same as those of the hydrogen atoms to which they are covalently bonded.

4 with respect to the substitution mode at the 5-position. Moreover, we noted the presence of a small doublet having a peculiar pattern $J = 1.96$ Hz at 9.75 ppm in ^{1}H NMR spectra of the reaction mixtures. The signals are characteristic of a CH−CHO unit, indicating that aldehyde **3** was also formed, but attempts to isolate it failed due to its air sensitivity. In GPC, **3** should become the main component in the unimer fraction after disappearance of **1** and **2**.

Products **2**−**5** have been thus identified, but none of the components in the higher oligomer fraction has been characterized yet, except to the extent that they contain phthalimido groups. Thus, the product distributions were estimated from the signal intensities for the aldehydic proton of **3** and each anomeric proton (H2) of **4** and **5** relative to that for the total aromatic protons. The results of the cyclodimerization of **1** at 130 °C are summarized in Table 1.[12] In the designated reaction times, consumption of **2** had been completed. Each catalyst, except for $AlMe_3$, yielded an isomeric mixture of **4** and **5**, with the former predominating, in a maximum yield ranging from approximately 70% to 90%. In addition, a tendency can be seen that the yield of **3** decreased with time while that of higher oligomers increased.

As compared with the known reactions of oxetane derivatives under similar cationic conditions, the new mode of the reaction of **1** seemed quite strange in regard

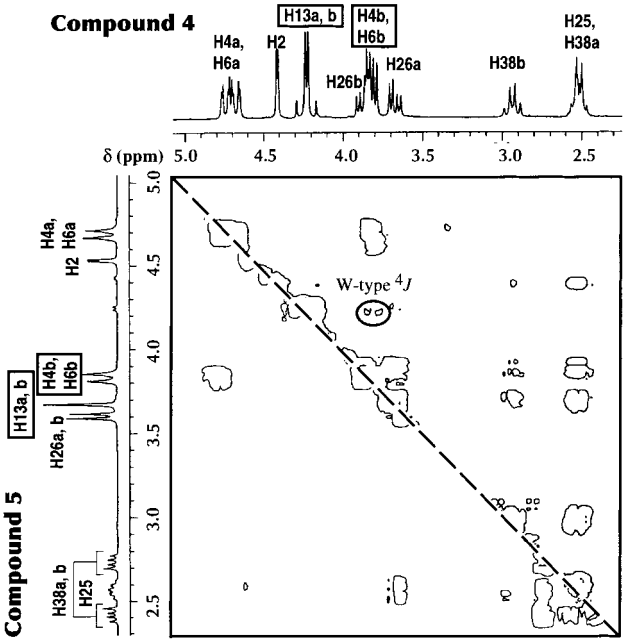


Figure 3. 270-MHz H−H COSY spectra of **4** (upper right) and **5** (lower left) in $CDCl_3$. The numberings of hydrogen atoms are according to those in Figure 2.

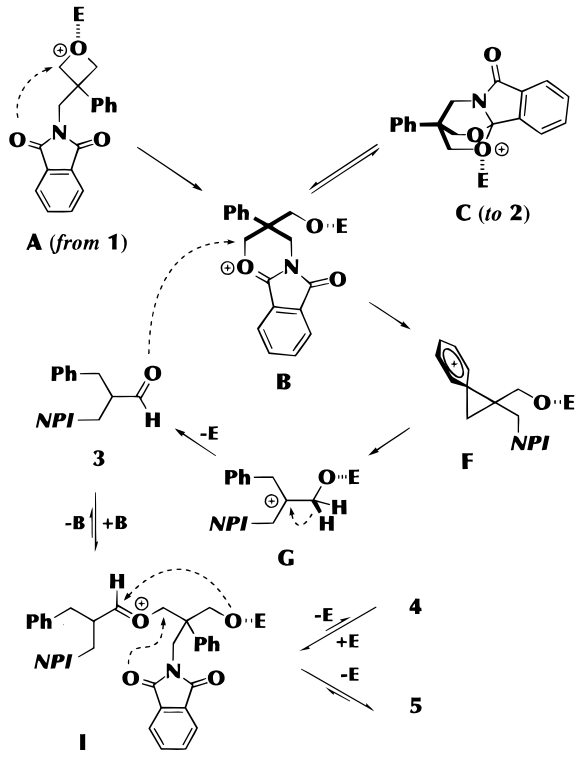
Table 1. Cationic Cyclodimerization of 1[a]

			product distribution, %[b]				
exp no.	catalyst	time, h	**2**	**3**	**4**	**5**	others[c]
1	$AlMe_3$[d]	48	96[e]	0	0	0	0
2	BnTA[f]	6	0	20	49	20	11
3	BnTA[f]	24	0	16	50	21	13
4	BnTA[f]	192	0	10	42	19	29
5	BF_3·OEt_2	132	0	2	60	28	10
6	TfOH	1	0	10	51	27	12
7	TfOH	2	0	13	39	24	24
8	TfOH	3	0	11	33	21	35
9[g]	TfOH	96	0	3	62	25	10

[a] **1**, 0.10 g (0.34 mmol); catalyst concentration, 5 mol %; solvent, chlorobenzene (0.34 mL); temperature, 130 °C; quencher, Et_3N (0.1 mL). [b] Determined by ^{1}H NMR. No unreacted **1** was detected. [c] This part, corresponding to the higher oligomer fraction in GPC, was a complex mixture of unclarified components. [d] **1**, 0.11 g (0.38 mmol); catalyst concentration, 20 mol %; solvent, chlorobenzene (2.0 mL); temperature, 120 °C; quencher, Et_3N (0.1 mL). [e] The remainder was unreacted **1** (4%). [f] Benzylthiolanium hexafluoroantimonate: see ref 6. [g] Starting material, a mixture composed of **4** and **5** in a mole ratio of 43:57.

to the production of **2**−**5**. Among them, **2** is probably produced by the isomerization of **1** in the same way as that proposed for the intramolecular acetalization of cyclic imide-substituted oxetanes.[13] At first, the reaction begins with the coordination of the catalyst E to oxetanyl rather than carbonyl oxygen atom in **1**. Such an oxonium activation mechanism has been previously demonstrated by the ^{1}H NMR induced shift difference in complexing succinimide-substituted oxetane with methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) as a Lewis acid.[13] In the oxonium ion **A**, accessibility between the oxonium α-carbon atom and the suitably disposed carbonyl oxygen atom (relatively 1,6-positioned) renders internal nucleophilic attack preferable. Consequently, neighboring group participation, followed by ring closure in 1,3-oxazin-2-ylium ion **B,** takes place leading to bicyclic oxonium ion **C**. The intervention of **B** is beyond doubt due to evidence that amide-substituted oxetanes can be cationically isomerized to oxazine derivatives.[14]

Scheme 3. Plausible Mechanism for the Cyclodimerization of 1 via Monomer Isomerization and Consecutive Cation Transfer[a]



[a] NPI: phthalimido group.

The other products **3**, **4**, and **5** have, in part, the same isopropyl type carbon skeletons which are absent from the starting **1**. This strongly suggests the reaction involves migration of phenyl group in **1**. The anomalous cyclodimerization of **1**, therefore, may be explained consistently as represented in Scheme 3. Both cations **B** and **C** seem to possess a potentiality to initiate cationic ring-opening polymerization. However, since these unimers carry neophyl type skeletons (shown by heavy lines in structures **B** and **C**) adjacent to positively charged oxygens, the steric hindrance of the electrophilic sites make the intermolecular nucleophilic attack to **1** or **2** difficult. For this reason, polymerization hardly takes place, but the neighboring assistance of the phenyl group brings about self-ring opening of **B**.[15] By a consecutive cation transfer of the resulting phenonium ion **F**, i.e., phenonium rearrangement (**F** to **G**) followed by 1,2-hydride shift (**G** to **3**), **3** is formed. The less hindered carbonyl oxygen atom in **3** is likely to add to **B** much more easily. Finally, the open oxonium dimer **I** cyclizes intramolecularly to afford cyclic dimers **4** and **5** depending on the direction of ring closure. The $n-\pi$ stereoelectronic repulsion in **5** between two oxygen atoms of the 1,3-dioxane ring and the 5-axially standing phenyl group is a tentative explanation of the stereochemical bias of the dioxane isomers. When a mixture composed of **4** and **5** in a mole ratio of 43:57 was similarly treated with TfOH for 96 h at 130 °C in chlorobenzene (experiment no. 9 in Table 1), the product distribution resulted in an increased yield of the former up to 62%. This indicates not only that **4** is a more thermodynamically favorable cycle but also that the interconversion between **4** and **5** passes through an intermediate like **I**. The intervention of **I** is also supported by a further result that **3** was detected in the above reaction mixture, though in a poor yield. There is not enough evidence to explain the formation of the higher oligomers. However, it seems suggestive that the production of this part increased with time at a sacrifice in the yields of **3**, **4**, and **5**, which are reversibly supplied from one another.

In conclusion, we have demonstrated that the cationic polymerization of **1** using a Brønsted acid or Lewis acids at 130 °C in chlorobenzene preferentially gives 1,3-dioxane isomers **4** and **5**, together with small amounts of higher oligomers and aldehyde **3**. The cyclic dimers are formed through a combination of the monomer isomerization of **1** by intramolecular nucleophilic attack and the consecutive cation transfer of the resulting bicyclic acetal **2** to **3**. Thermodynamic preference in the reversible ring closure at the final step brings about the **4**/**5** stereochemical bias with the former predominating. The anomalous cyclodimerization of **1** is attributable primarily to both the bulkiness and the liability to rearrangement of the neophyl type carbon skeleton adjacent to the ionic unimer species generated from **2**.

Supporting Information Available: Experimental text for preparation and characterization for **1**, **2**, **4**, and **5** along with figures showing NMR (270 MHz for ^{1}H nuclei) spectra of these new compounds and tables giving detailed of crystallographic data for **4** (22 pages). Ordering and Internet access information is given on any current masthead page.

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(5) **1**: mp 138.5−139.5 °C ($CHCl_3$−hexane); ^{1}H NMR ($CDCl_3$) δ 4.17 (s-like, 2H, NCH_2), 5.05 (s, 4H, OCH_2), 7.02−7.12 (m, 2H, *o*-H_{Ph}), 7.18−7.38 (m, 3H, *m* and *p*-H_{Ph}), 7.65−7.75, 7.75−7.87 (each m, each 2H, carbonyl *m*- and *o*-H_{Ar}); ^{13}C NMR (67.80 MHz, $CDCl_3$) δ 46.3, 48.8, 80.1, 123.4, 125.9, 127.1, 128.6, 131.7, 134.1, 142.4, 168.6; IR (KBr) 1771, 1718, 1708, 979, 850 cm^{-1}; HRMS found, *m/e* 293.1031 (calcd for $C_{18}H_{15}NO_3$, *m/e* 293.1053). Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.75; H, 5.16; N, 4.75.

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(7) 5,6-Benzo-1-phenyl-8,11,3-dioxazatricyclo[5.2.2.0^{3,7}]undec-5-en-4-one (**2**) was prepared under the conditions of experiment no. 1. The crude product was purified by chromatography (EM Aluminiumoxid 90, ethyl acetate−hexane 1:3) followed by recrystallization from CH_2Cl_2−hexane to give **2** in 43% yield: colorless needles; mp 198.5−199.5 °C; ^{1}H NMR ($CDCl_3$) δ 4.16 (s, 2H, NCH_2), 4.35, 4.63 (each d, J = 8.6 Hz, each 2H, *equatorial* and *axial* OCH_2 with respect to a boat-type 1,3-dioxane ring), 7.23−7.33 (m, 2H, *o*-H_{Ph}), 7.33−7.49 (m, 3H, *m* and *p*-H_{Ph}), 7.51−7.68 (m, 3H, carbonyl *m*- and *p*-H_{Ar}), 7.82 (dd, J_1 = 5.8 Hz, J_2 = 1.8 Hz, 1H, carbonyl *o*-H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 37.8, 48.6, 73.4, 102.0, 122.1, 123.6, 125.4, 128.5, 129.4, 130.9, 132.4, 133.1, 135.5, 139.7, 164.4; IR (KBr) 1703, 1115, 1064−963 cm^{-1}; HRMS found, *m/e* 293.1054 (calcd for $C_{18}H_{15}NO_3$, *m/e* 293.1053). Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.70; H, 5.15; N, 4.78. Found: C, 73.93; H, 5.16; N, 4.82.

(8) To isolate **4** and **5**, the crude products were fractionated by preparative TLC on alumina using ethyl acetate−hexane (1:1 v/v) as an eluent. The dimer fraction [R_f = 0.61, EM TLC aluminum sheets aluminum oxide 60 F_{254} neutral, ethyl acetate−hexane (1:1 v/v)] was carefully separated into front and end halves, which were desorbed using a mixture of MeOH−CH_2Cl_2 (1:1 v/v). Repeated crystallization of the front and end parts from MeOH−CH_2Cl_2−hexane gave pure **4** and **5**, respectively.

(9) Crystal data of **4**: monoclinic, space group *C*2/*c*, $Z = 8$ with a = 32.598(9) Å, b = 11.517(2) Å, c = 19.118(4) Å, V = 5958(2) Å^3, and D_{calc} = 1.308 g cm^{-3}; 9558 measured, 4683 independent reflections, of which 6153 were considered as observed [$I > 3.00\sigma(I)$]. R = 0.048, R_w = 0.056.

(10) *t*-5-Phenyl-*c*-5-phthalimidomethyl-*r*-2-(1-benzyl-2-phthalimidoethyl)-1,3-dioxane (**4**): colorless needles; mp 204−206 °C (MeOH−CH_2Cl_2-hexane); ^{1}H NMR ($CDCl_3$) δ 2.43−2.61 (m, 1H, H25), 2.51, 2.93 (each dd, J_1 = 17.6 Hz, J_2 = 9.2 Hz, each 1H, H38a, b), 3.67, 3.87 (each dd, J_1 = 14.1 Hz, J_2 = 6.6 Hz, each 1H, H26a, b), 3.80, 3.83 (each d, J = 11.6 Hz, each 1H, H4b, H6b), 4.21, 4.25 (each d, J = 14.4 Hz, each 1H, H13a, b), 4.54 (d, J = 2.9 Hz, 1H, H2), 4.67, 4.74 (each dd, J_1 = 11.2 Hz, J_2 = 2.9 Hz, each 1H, H4a, H6a), 6.97−7.27 (m, 10H, H_{Ph}), 7.73−7.80 (m, 8H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 33.5, 37.9, 39.6, 42.2, 44.5, 73.5, 102.0, 123.0, 123.2, 125.2, 125.8, 127.5, 128.2, 128.6, 128.8, 132.0, 132.1, 133.6, 133.7, 139.2, 139.3, 168.2, 168.4; IR (KBr) 1780, 1710, 1140, 1095−1025 cm^{-1}; HRMS found, *m*/*e* 586.2101 (calcd for $C_{36}H_{30}N_2O_6$, *m*/*e* 586.2105). Anal. Calcd for $C_{36}H_{30}N_2O_6$: C, 73.70; H, 5.15; N, 4.78. Found: C, 73.76; H, 5.26; N, 4.67.

(11) *c*-5-Phenyl isomer (**5**): colorless needles; mp 192−193 °C (MeOH−CH_2Cl_2−hexane); ^{1}H NMR ($CDCl_3$) δ 2.40, 2.72 (each dd, J_1 = 13.9 Hz, J_2 = 6.9 Hz, each 1H, H38a, b), 2.50−2.61 (m, 1H, H25), 3.58 (d, J = 7.25 Hz, each 1H, H26a, b), 3.65 (s, 2H, H13a, b), 3.81 (d, J = 11.6 Hz, 2H, H4b, H6b), 4.51 (d, J = 2.3 Hz, 1H, H2), 4.67 (d, J = 11.6 Hz, 2H, H4a, H6a), 6.90−7.37 (m, 10H, H_{Ph}), 7.56−7.84 (m, 8H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 33.5, 37.8, 42.4, 42.9, 43.2, 72.8, 101.5, 122.9, 123.5, 125.6, 126.8, 127.9, 128.1, 128.3, 128.7, 131.7, 132.0, 133.6, 134.2, 139.6, 139.9, 168.4; IR (KBr) 1780, 1710, 1140, 1095−1025 cm^{-1}; HRMS found, *m*/*e* 586.2104 (calcd for $C_{36}H_{30}N_2O_6$, *m*/*e* 586.2105). Anal. Calcd for $C_{36}H_{30}N_2O_6$: C, 73.70; H, 5.15; N, 4.78. Found: C, 73.75; H, 5.19; N, 4.72.

(12) Typically, the reaction of **1** or **2** (0.10 g, 0.34 mmol) with a catalyst (17 μmol) in anhydrous PhCl (0.34 mL) was carried out at 130 °C under dry nitrogen. After the reaction was quenched by adding anhydrous Et_3N (0.1 mL), an aliquot of the reaction mixture was taken out and subjected to ^{1}H NMR and GPC analyses to determine the ratio and molecular weight distribution of the products, respectively.

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