Pergamon

Tetrahedron Letters 44 (2003) 8177–8181

TETRAHEDRON
LETTERS

Electronic effects of icosahedral carboranes: mechanistic alteration in solvolysis of α-(*o*-carboranyl)benzyl tosylates by electronic effect of substituents

Yoshiyuki Taoda[a] and Yasuyuki Endo[b,*]

[a]*Graduate School of Pharmaceutical Sciences, University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan*
[b]*Faculty of Pharmaceutical Sciences, Tohoku Pharmaceutical University, 4-4-1, Komatsushima, Aoba-ku, Sendai 981-8558, Japan*

Received 22 July 2003; revised 14 August 2003; accepted 22 August 2003

Abstract—Solvolysis of α-(*o*- and *m*-carboranyl)benzyl toluene-*p*-sulfonates bearing a range of substituents at the 3- or 4-position of the benzyl group has been investigated. The rates of hydrolysis of *m*-carboranyl derivatives increased linearly with increasing electron-releasing character of the substituent group ($\rho = -5.37$ correlated to σ^+), which indicates that the hydrolysis proceeds through a typical S_N1 process. In contrast, the hydrolysis rates of the *o*-carboranyl derivatives with a wide range of electron-withdrawing substituents did not show significant change, but suddenly began to show a linear increase with increasing electron-releasing character of the substituents ($\rho = -5.91$ correlated to σ^+). Moreover, the optical purity of the retentive hydrolysis of the *o*-carboranyl derivatives rapidly declined with increasing electron-donating effects of the substituents. This indicates that the mechanism of the hydrolysis changes from the retentive mechanism to an S_N1 mechanism.

Icosahedral *closo* carboranes have been described as three-dimensional aromatic systems, and the implications for electronic interaction with substituents have been of particular interest since the first synthesis of these compounds.[1] The icosahedral carboranes behave as strongly electron-withdrawing groups in the sequence *ortho*≫*meta*>*para* towards substituents at a carbon atom.[2] In our kinetic investigations, we found that the order of the rates of acetolysis of α-(*o*-, *m*- and *p*-carboranyl)benzyl tosylates (**1a**, **2a** and **3**)[3] was consistent with the electron-withdrawing effects of the icosahedral carboranes.[4] However, the hydrolysis of **1a**, bearing what is thought to be the most electron-withdrawing group among the carboranes, was significantly accelerated compared with those of **2a** and **3**.[4] Furthermore, in the hydrolysis of (+)-**1a**, the reaction afforded the *retentive* product, with an enantiomeric purity of 71%, whereas the products formed from (+)-**2a** and (+)-**3** were racemic.[4] We suggested a mechanism involving interaction between the oxygen atom of the nucleophile and the 3-position boron atom in the *o*-carborane cage to explain the characteristic reaction of **1a**. Recently, we have reported the results of the solvolysis of α-(*o*-, *m*- and *p*-carboranyl)benzyl tosylates substituted at the second carbon atom with a phenyl group bearing a range of substituents (**4**, **5** and **6**).[5] In the hydrolysis of **5** and **6**, the rates linearly increased with increasing electron-donating power of the substituent Y.[5] In contrast, the hydrolysis rate of **4** linearly decreased with increasing electron-donating power of the substituent Y.[5] These results indicate that the interaction between the B(3) atom of the *o*-carborane cage and the nucleophile controls this particular reaction. In this paper, we present the results of a kinetic and stereochemical investigation of α-(*o*- (**1**) and *m*-carboranyl)benzyl toluene-*p*-sulfonates (**2**) bearing a range of substituents, which directly affect the reaction center, at the 3- or 4-position of the benzyl group.

To evaluate the electronic effects of substituents at the benzyl group, we designed α-(*o*- and *m*-carboranyl)benzyl tosylates bearing a range of electron-releasing or -withdrawing substituents at the 3- or 4-position of the benzyl group (**1** and **2**), as shown in Figure 1. α-(*o*-Carboranyl)benzyl tosylates (**1a**–**k**) were prepared by the reaction of *o*-carborane and 3- or 4-substituted benzaldehydes in the presence of tetra-

---

Keywords: carboranes; electronic effects; kinetics; neighboring group effects.

* Corresponding author. Tel.: +81 22 234 4181; fax: +81 22 275 2013; e-mail: yendo@tohoku-pharm.ac.jp

doi:10.1016/j.tetlet.2003.08.119

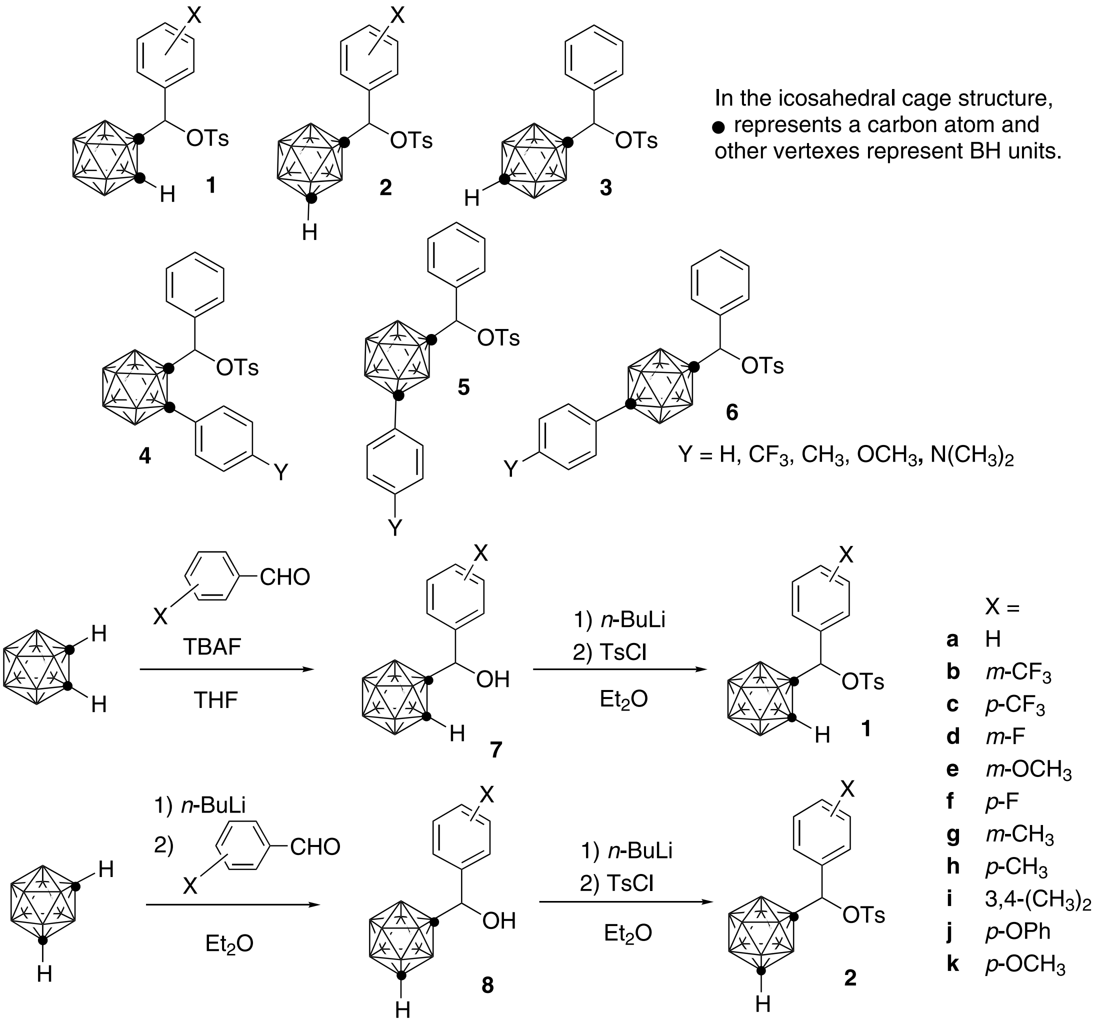


Figure 1.

butylammonium fluoride (TBAF),[6] followed by reaction with *p*-toluenesulfonyl chloride. α-(*m*-Carboranyl)benzyl tosylates (**2a**–**h**) were prepared by reaction of the lithiate of *m*-carborane and 3- or 4-substituted benzaldehydes,[7] followed by reaction with *p*-toluenesulfonyl chloride.

The kinetic experiments on the acetolysis of the α-(carboranyl)benzyl tosylates (**1** and **2**) in CD_3COOD at 105.0°C were performed by NMR measurement of the decrease of starting materials.[8] The acetolysis of **1** and **2** quantitatively gave the corresponding acetates. The rate constants for the acetolysis are summarized in Table 1. Figure 2 shows a clear linear relation between the substituent electronic effect, represented by the Brown σ^+ value,[9] and the relative rate (k_X/k_H). The slopes of the lines correspond to the anticipated increase with increasing electron-releasing power of the substituent in each of the *o*- and *m*-carboranyl series. The ρ values of **1** and **2** were −4.37 and −4.58, respectively. The large negative ρ values indicate that the substituents of the benzyl group directly affect the stability of the intermediate benzyl cation.

Kinetic experiments on the hydrolysis of the α-(carboranyl)benzyl tosylates (**1** and **2**) in 70% dioxane-d_8–D_2O at 67.9°C for **1**, and at 95.4°C for **2**, were also per-

Table 1. Pseudo-first-order rate constants (k_1 s^{-1}) for the acetolysis of **1** and **2** in CD_3COOD at 105.0°C

	R	k_1 (s^{-1})	k_X/k_H
1b	*m*-CF_3	Slow	
1c	*p*-CF_3	Slow	
1d	*m*-F	2.20×10^{-6}	0.044
1e	*m*-OCH_3	5.33×10^{-5}	1.07
1a	H	4.96×10^{-5}	1.00
1f	*p*-F	1.34×10^{-4}	2.70
1g	*m*-CH_3	2.11×10^{-4}	4.25
1h	*p*-CH_3	1.71×10^{-3}	34.48
2b	*m*-CF_3	Slow	
2c	*p*-CF_3	Slow	
2d	*m*-F	3.36×10^{-6}	0.039
2e	*m*-OCH_3	7.95×10^{-5}	0.93
2a	H	8.59×10^{-5}	1.00
2f	*p*-F	2.77×10^{-4}	3.22
2g	*m*-CH_3	2.32×10^{-4}	2.70
2h	*p*-CH_3	4.02×10^{-3}	46.80

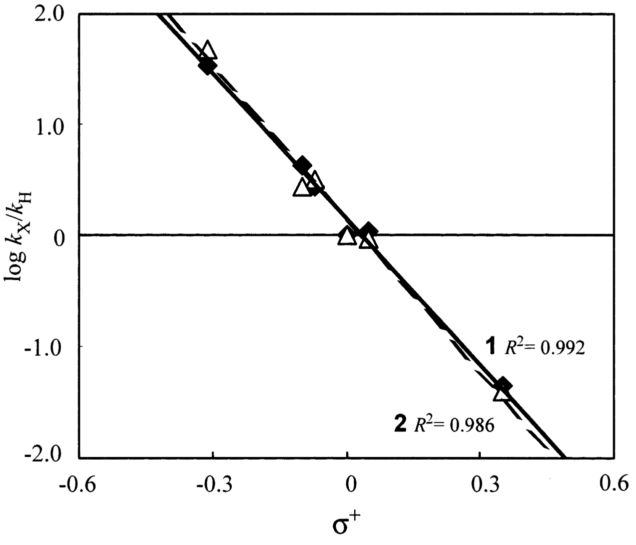


Figure 2. Hammett plot of kl_X/k_H against σ^+ for the acetolysis of **1** and **2**.

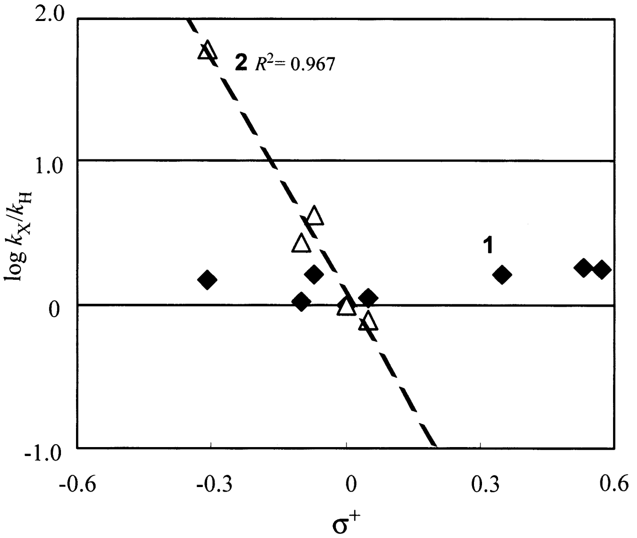


Figure 3. Hammett plot of k_X/k_H against σ^+ for the hydrolysis of **1** and **2** in 70% dioxane-d_8–D_2O at 67.9°C and **2** in 70% dioxane-d_8–D_2O at 95.4°C

formed by NMR measurement of the decrease of the starting materials.[8] The hydrolysis of **1** and **2** quantitatively gave the corresponding alcohol. The rate constants for the hydrolysis are summarized in Table 2. Figure 3 shows a plot of the rate constants against Brown σ^+ values.[9] A linear relationship were obtained in the case of **2**, as in the case of the acetolysis. The ρ value of **2** was −5.37. However, the rate constants of *o*-carboranyl series **1a**–**h** did not correlate to the σ^+ values, and were almost constant, in contrast with those in the case of hydrolysis of **2**. The results indicate that the substituents of the benzyl group do not affect the reaction center and the mechanism of hydrolysis of **1** is distinct from that of **2**. Surprisingly, however, the rates of hydrolysis of **1** with strong electron-donating substituents (**1j**: *p*-OPh, **1k**: *p*-OMe) were too fast to be measured in 70% dioxane-d_8–D_2O. To examine the seeming discrepancy, we performed the hydrolysis of **1** under different conditions, 90% dioxane-d_8–D_2O at 67.9°C. The rate constants for the hydrolysis of **1** in 90% dioxane-d_8–D_2O are summarized in Table 3. Figure 4 shows a plot of the rate constants against the Brown σ^+ values. The rates of the *o*-carboranyl derivatives with a range of electron-withdrawing substituents did not show significant change, but suddenly began to increase linearly with increasing electron-releasing character of the substituents ($\rho = -5.91$ correlated to σ^+).

Table 2. Pseudo-first-order rate constants (k_1 s^{-1}) for the hydrolysis of **1** in 70% dioxane-d_8–D_2O at 67.9°C and **2** in 70% dioxane-d_8–D_2O at 95.4°C

	R	k_1 (s^{-1})	k_X/k_H
1b	*m*-CF_3	4.86×10^{-4}	1.75
1c	*p*-CF_3	4.99×10^{-4}	1.80
1d	*m*-F	4.55×10^{-4}	1.64
1e	*m*-OCH_3	3.12×10^{-4}	1.13
1a	H	2.77×10^{-4}	1.00
1f	*p*-F	4.43×10^{-4}	1.60
1g	*m*-CH_3	2.89×10^{-4}	1.05
1h	*p*-CH_3	4.17×10^{-4}	1.51
2b	*m*-CF_3	Slow	
2c	*p*-CF_3	Slow	
2d	*m*-F	1.48×10^{-6}	0.028
2e	*m*-OCH_3	4.24×10^{-5}	0.79
2a	H	5.37×10^{-5}	1.00
2f	*p*-F	2.24×10^{-4}	4.17
2g	*m*-CH_3	1.46×10^{-4}	2.72
2h	*p*-CH_3	3.31×10^{-3}	61.78

Stereochemically, the hydrolysis of **1a** affords the *retentive* product with an enantiomeric purity of 71% in 70% dioxane–H_2O at 70°C.[4] Optically active α-(carboranyl)benzyl tosylates were prepared from the corresponding alcohols, which were obtained by optical resolution of the racemic alcohols (**1c**, **1h**, **1j** and **1k**) as (−)-camphonic acid esters, followed by alkaline hydrolysis.[4] The optical purity of the optically active α-(carboranyl)benzyl derivatives was determined by ^1H NMR measurement in the presence of a chiral shift reagent: tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III). Hydrolysis of (+)-*S*-

Table 3. Pseudo-first-order rate constants (k_1 s^{-1}) for the hydrolysis of **1** in 90% dioxane-d_8–D_2O at 67.9°C

	R	k_1 (s^{-1})	k_X/k_H
1b	*m*-CF_3	2.95×10^{-5}	0.72
1c	*p*-CF_3	2.89×10^{-5}	0.70
1d	*m*-F	3.48×10^{-5}	0.85
1e	*m*-OCH_3	3.56×10^{-5}	0.87
1a	H	4.11×10^{-5}	1.00
1f	*p*-F	8.22×10^{-5}	2.00
1g	*m*-CH_3	4.26×10^{-5}	1.04
1h	*p*-CH_3	6.42×10^{-5}	1.56
1i	3,4-$(CH_3)_2$	6.24×10^{-5}	1.52
1j	*p*-OPh	3.76×10^{-4}	9.16
1k	*p*-OCH_3	1.03×10^{-2}	250.6

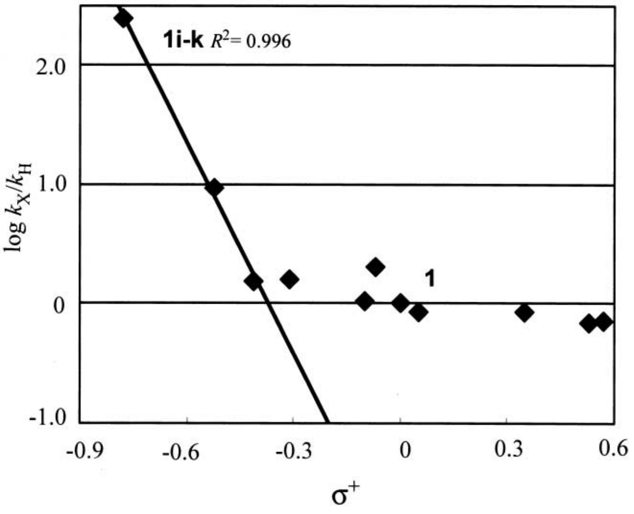
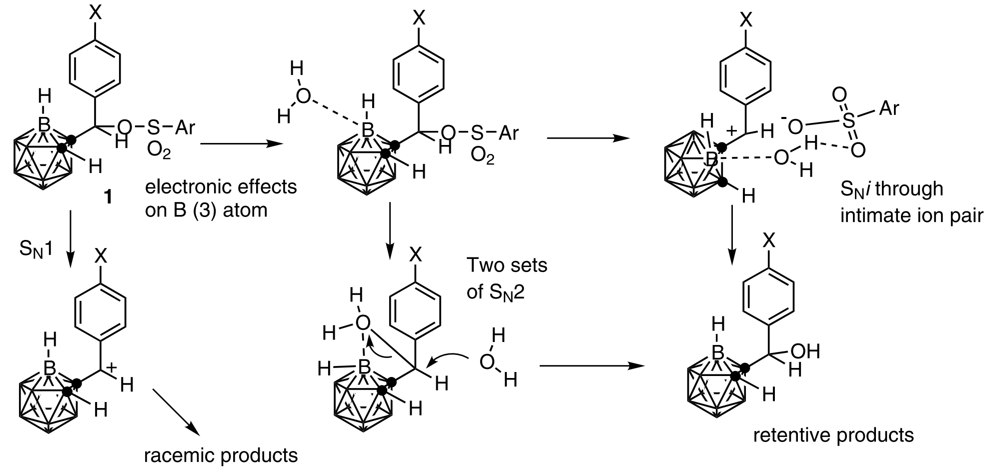


Figure 4. Hammett plot of k_X/k_H against σ^+ for the hydrolysis of **1** in 90% dioxane-d_8–D_2O at 67.9°C.

1c with an electron-withdrawing substituent in 70% dioxane–H_2O afforded (+)-*S*-**6** in 71% ee, which was the same as in the case of the hydrolysis of **1a**. However, the enantiomeric purity was reduced to 24% in the hydrolysis of (+)-*S*-**1g** with an electron-donating substituent. In the hydrolysis of **1a**, **1c**, **1g**, **1j** and **1k** in 90% dioxane–H_2O at 70°C, the enantiomeric purity decreased in the order of **1b**: *p*-CF_3 (75%)>**1a**: H (61%)>**1g**: *p*-CH_3 (33%)>**1j**: *p*-OPh (3%)>**1k**: *p*-OCH_3 (2%), with decreasing σ^+ values of the substituents.

In previous kinetic and stereochemical investigations, we have demonstrated that the acetolysis of **1a**, **2a** and **3a** and the hydrolysis of **2a** and **3a** proceed through typical S_N1 processes.[4] In the present study, the large negative ρ values in the acetolysis of **1** and **2** and the hydrolysis of **2** directly demonstrate involvement of a positive charge at the benzylic carbon in the reaction pathway. In contrast, the rate constants of the hydrolysis of **1** do not correlate to σ^+ values, and were almost constant for a range of substituents from weak electron-releasing to electron-withdrawing (**1a**–**h**), both in 70% and 90% dioxane-d_8–D_2O. The results clearly indicated that positive charge at the benzylic carbon is not involved in the hydrolysis of **1a**–**h**. On the other hand, we have reported that the electron deficiency of the 3-position boron atom of the *o*-carborane cage and the character of the nucleophile determine the rate of this reaction, by means of a kinetic investigation of **4**–**6**.[4] The interaction between the oxygen atom of the nucleophile and the most electron-deficient 3-position boron atom in the *o*-carborane cage accounts for the characteristic reaction of α-(*o*-carboranyl)benzyl tosylates, because the interaction is expected to occur in the first step of deboronation of *o*-carborane to the *nido*-7,8-$C_2B_9H_{12}$- by strong nucleophiles such as alkoxides,[10] aliphatic amines[11] and fluoride ion.[12] Nucleophilicity of acetic acid is too weak to interact with the 3-position boron atom. Scheme 1 outlines two possible mechanisms, which involve the interaction between the oxygen atom of a nucleophile and the 3-position boron atom in the carborane cage, as the first step in the hydrolysis of **1**. One of the mechanisms is an intermolecular S_Ni mechanism, in which the substrate is attacked from the front side of the leaving group by the nucleophile interacting with the 3-position boron atom. However, most S_Ni mechanisms involve an ionic character, such as C^+ and O^-. Therefore, the mechanism may not be consistent with the present kinetic results. The other mechanism involves two sets of S_N2 processes. The first intermediate is generated via an intramolecular S_N2. This intermediate is attacked by another nucleophile, and elimination occurs to give the retentive product. In this mechanism, a positive charge does not develop at the benzylic carbon in the reaction pathway. This set of two S_N2 processes seems to be a plausible mechanism for the hydrolysis of **1**, although the nature of the boron-nucleophile intermediate is still unclear.

We also found an alteration of the reaction mechanism depending on the electronic effects of the substituents on the benzyl group. From the viewpoint of direct stabilization of the benzyl cation in an S_N1 process, it



Scheme 1.

seems reasonable to consider that hydrolysis of **1j** and **1k**, each with a highly electron-donating substituent at the benzyl group, proceeds through an S_N1 process. The hydrolysis of **1** with substituents in the range from weak electron-releasing to electron-withdrawing proceeds through the retentive mechanism, because the substituents destabilize the benzyl cation. In this case, the S_N1 process makes little contribution. However, the S_N1 process becomes predominant in the hydrolysis of substrates with a highly electron-donating substituent. The stereochemical results of the hydrolysis of some optically active α-(carboranyl)benzyl tosylates are consistent with such a mechanistic alteration.

References

1. For review, see: Bregradze, V. I. *Chem. Rev.* **1992**, *92*, 209–223.
2. (a) Hawthorne, M. F.; Berry, T. E.; Wegner, P. A. *J. Am. Chem. Soc.* **1965**, *87*, 4746–4750; (b) Zakharkin, L. I.; Kalinin, V. N.; Rys, E. G. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1974**, 2632–2635.
3. In this paper, *o*-carboranyl and *m*-carboranyl represent 1,2-dicarba-*closo*-dodecaboran-1-yl and 1,7-dicarba-*closo*-dodecaboran-1-yl, respectively, by the common practice.
4. Endo, Y.; Sawabe, T.; Taoda, Y. *J. Am. Chem. Soc.* **2000**, *122*, 180–181.
5. Endo, Y.; Taoda, Y. *Tetrahedron Lett.* **2001**, *42*, 6327–6331.
6. Nakamura, H.; Aoyagi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 1167–1171.
7. Maurer, J. L.; Berchier, F.; Serino, A. J.; Knobeler, C. B.; Hawthorne, M. F. *J. Org. Chem.* **1990**, *55*, 838–843.
8. The appropriate solvent (dioxane-d_8 in D_2O 70:30 v/v or acetic acid-d_4) was added to the tosylate (5.0 mg) and 1,4-dimethoxybenzene (1.5 mg, internal standard) in a 5 mm diameter NMR tube. The tube was sealed, inserted into a JEOL JMN-A500 spectrometer (500 MHz), and warmed to the desired temperature. ^{1}H NMR spectra were recorded at intervals. Decrease of the starting materials followed good first-order kinetics ($R^2=0.99$). The temperature in the NMR probe were corrected by the measurement and calibration of the chemical shifts of ethylene glycol. Van Geet, A. L. *Anal. Chem.* **1968**, *40*, 2227–2229; Marino, D. F.; Wolff, F.; Ingle, J. D., Jr. *Anal. Chem.* **1979**, *51*, 2050–2051.
9. March, J. *Advanced Organic Chemistry*, 4th Ed.; John Wiley: New York, 1992; pp. 278–286.
10. (a) Wiesboeck, R. A.; Hawthorne, M. F. *J. Am. Chem. Soc.* **1964**, *86*, 1642–1643; (b) Hawthorne, M. F.; Wegner, P. A.; Stafford, R. C. *Inorg. Chem.* **1965**, *4*, 1675.
11. Hawthorne, M. F.; Young, D. C.; Garrett, P. M.; Owen, D. A.; Schwerin, S. G.; Tebbe, F. N.; Wegner, P. A. *J. Am. Chem. Soc.* **1968**, *90*, 862–868.
12. Tomita, H.; Luu, H.; Onak, T. *Inorg. Chem.* **1991**, *30*, 812–815.