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# Mechanism of the Regio- and Diastereoselective Ring Expansion Reaction Using Trimethylsilyldiazomethane

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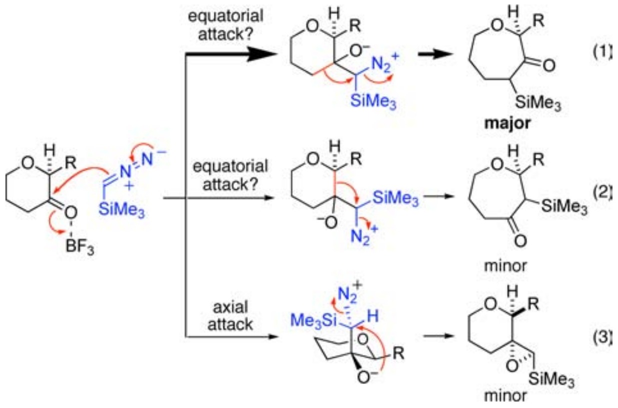
## ABSTRACT

**An equatorial attack of TMS-diazomethane was determined to be the first step of the $BF_3$-promoted ring expansion reaction of six-membered ketones using TMS-diazomethane. The migration reaction occurred in a conformation in which the carbonyl oxygen and the TMS group were antiperiplanar to predominantly afford *trans*-seven-membered ketones.**

TMS-diazomethane is one of the most common reagents for homologation reactions used to construct medium-sized rings.[1,2] The ring expansion reaction using TMS-diazomethane is usually regioselective because a less substituted carbon migrates more readily than a more substituted carbon. Double-expansion reactions to produce larger-sized rings are suppressed because the initial products are less-reactive silylketones. These features make this reaction attractive and feasible in many situations[3] with the aid of Lewis acids such as $BF_3$,[4] trialkyl aluminums,[5] and scandium salts.[6,7]

In our synthetic studies of natural polycyclic ethers, we often use the ring expansion reaction with TMS-diazomethane for the construction of seven-membered ether rings.[7b,8] As shown in Scheme 1, the major product is

**Scheme 1.** Ring Expansion Reaction of a Tetrahydropyran-3-one with TMS-Diazomethane



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[1] For a recent review of TMS-diazomethane, see: Shioiri, T.; Aoyama, T. Trimethylsilyldiazomethane. (First updated by Snowden, T.) In *Reagents for Silicon-Mediated Organic Synthesis*; Fuchs, P. L., Ed.; Handbook of Reagents for Organic Synthesis; John Wiley & Sons Ltd.: United Kingdom, 2011; pp 590−598.

[2] For a review of the ring expansion reaction to seven-membered rings, see: Kantorowski, E. J.; Kurth, M. J. *Tetrahedron* **2000**, *56*, 4317–4353.

[3] For recent applications of the ring expansion reaction using TMS-diazomethane, see: (a) Saito, T.; Nakata, T. *Org. Lett.* **2009**, *11*, 113–116. (b) Hennig, R.; Metz, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1157–1159. (c) Pazos, G.; Pérez, M.; Gándara, Z.; Gómez, G.; Fall, Y. *Tetrahedron Lett.* **2009**, *50*, 5285–5287. (d) Furuta, H.; Hasegawa, Y.; Mori, Y. *Org. Lett.* **2009**, *11*, 4382–4385. (e) Sletten, E. M.; Nakamura, H.; Jewett, J. C.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2010**, *132*, 11799–11805. (f) Macías, F. A.; Carrera, C.; Chinchilla, N.; Fronczek, F. R.; Galindo, J. C. G. *Tetrahedron* **2010**, *66*, 4125–4132. (g) Furuta, H.; Hasegawa, Y.; Hase, M.; Mori, Y. *Chem.—Eur. J.* **2010**, *16*, 7586–7595.

[4] (a) Hashimoto, N.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1980**, *21*, 4619–4622. (b) Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1982**, *30*, 119–124.

[5] (a) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *J. Org. Chem.* **1994**, *59*, 4725–4726. (b) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *Synthesis* **1994**, 1283–1290.

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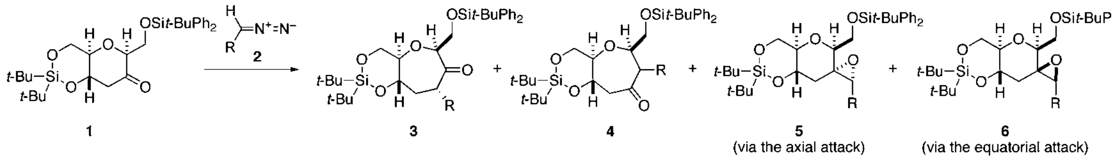
**Table 1.** Ring Expansion Reaction of Ketone **1** with Various Silyldiazomethanes



| entry | diazomethane | | conditions | 3 yield (%) | | 4 yield (%) | | 5 yield (%) | | 6 yield (%) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **2a** | R = H | MeOH, rt, 45 min | **3a** | 0 | **4a** | 49 | **5a** | 1[a] | **6a** | 4[a] |
| 2[b] | **2b** | R = $SiMe_3$ | $BF_3\cdot OEt_2$, MS 4 Å, $CH_2Cl_2$, −80 °C, 50 min, then PPTS, $CH_2Cl_2$/MeOH | **3a**[c] | 75 | **4a**[c] | 6 | **5b** | 13[d] | **6b** | 1[d] |
| 3 | **2c** | R = $SiMe_2Ph$ | $BF_3\cdot OEt_2$, MS 4 Å, $CH_2Cl_2$, −80 °C, 3 h, then PPTS, $CH_2Cl_2$/MeOH | **3a**[c] | 79 | **4a**[c] | 2 | **5c** | 5 | **6c** | 0 |
| 4 | **2d** | R = Si(O*i*-Pr)$_2$Me | $BF_3\cdot OEt_2$, MS 4 Å, $CH_2Cl_2$, −80 °C, 1 h | **3d** | 57 | **4d** | 6 | **5d** | 0 | **6d** | 1 |

[a] Spiro-epoxides **5a** and **6a** were isolated as a mixture. [b] The yield of the major product was previously reported in ref 8b. Complete byproduct yields, however, are newly reported. [c] In entries 2 and 3, desilylated seven-membered ketone **3a** and **4a** (R = H) were isolated after PPTS treatment. [d] Spiro-epoxides **5b** and **6b** were isolated as a mixture.

always (1) a seven-membered ketone that is generated by migration of the less-hindered secondary carbon. Small amounts of (2) a regioisomeric seven-membered ketone, which is generated by migration of the sterically hindered carbon, and (3) a spiro-epoxide formed by 3-*exo* cyclization are also produced as byproducts.

With regard to the mechanism of the ring expansion reaction, both the Seto[9] and Cushman[10] groups proposed that axial attack of TMS-diazomethane on six-membered ketones is the first step in the ring expansion reaction. The fact that only a small amount of epoxide arising from the axial attack of TMS-diazomethane (3) was isolated in our previous study,[8c] however, suggests that the major isomer results from an equatorial attack on the ketone (1).

In addition, we are confident that seven-membered ketones are generated from the equatorial attack of TMS-diazomethane for the following reasons. First, in general, $BF_3$-promoted nucleophilic addition reactions of carbon nucleophiles with six-membered ketones provide equatorial adducts.[11] Second, diazomethane approaches from the equatorial side of ketones in the ring expansion reaction without a Lewis acid.[12] Therefore, we report here a combined experimental and computational study of the ring expansion reaction with silylated diazomethanes to gain insight into the stereochemical course of the reaction.

We selected the six-membered ketone **1** as a substrate because its conformation is fixed as in the case of *trans*-decalone. The first reaction was conducted with diazomethane **2a** in methanol in the absence of a Lewis acid (Table 1, entry 1). Ketone **4a** was obtained as a major product generated by the migration of an electron-rich bond according to the general trend of migration aptitude, as well as a small amount of the mixture of spiro-epoxides **5a** and **6a** in a 28:72 ratio.[12a] Ring expansion with TMS-diazomethane **2b** in the presence of $BF_3\cdot OEt_2$ gave ketone **3a** as a major product in 75% yield (entry 2).[8b] Careful analysis of the byproducts led to the isolation of the regioisomeric ketone **4a** and two diastereomeric epoxides **5b** and **6b** in 6%, 13%, and 1%, respectively. The major α-epoxide **5b** came from the axial attack of TMS-diazomethane **2b**, and the TMS group was located at the less hindered side of the molecule.[8c] We next examined reactions with a bulky silyldiazomethane **2c** to increase the ratio of the equatorial attack (entry 3). The yield of the seven-membered ketones **3a** was slightly increased, and the α-epoxide **5c** was obviously decreased, as expected. In the reaction with bulkier diazomethane **2d**, silylketones **3d** and **4d** were isolated following column chromatography (entry 4). The configuration of the major ketone **3d** was

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(6) Dabrowski, J. A.; Moebius, D. C.; Wommack, A. J.; Kornahrens, A. F.; Kingsbury, J. S. *Org. Lett.* **2010**, *12*, 3598–3601.

(7) The migratory aptitude of ring expansion reactions using diazomethanes varies depending on Lewis acids. For example: (a) Müller, E.; Lürken, W.; Bauer, M. *Tetrahedron Lett.* **1962**, *3*, 775–778. (b) Mori, Y.; Yaegashi, K.; Furukawa, H. *Tetrahedron* **1997**, *53*, 12917–12932. (c) Kreuzer, T.; Metz, P. *Eur. J. Org. Chem.* **2008**, 572–579.

(8) (a) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1997**, *119*, 4557–4558. (b) Mori, Y.; Hayashi, H. *Tetrahedron* **2002**, *58*, 1789–1797. (c) Mori, Y.; Nogami, K.; Hayashi, H.; Noyori, R. *J. Org. Chem.* **2003**, *68*, 9050–9060. (d) Sakai, T.; Sugimoto, A.; Mori, Y. *Org. Lett.* **2011**, *13*, 5850–5853.

(9) Seto, H.; Fujioka, S.; Koshino, H.; Hayasaka, H.; Shimizu, T.; Yoshida, S.; Watanabe, T. *Tetrahedron Lett.* **1999**, *40*, 2359–2362.

(10) Wang, Z.; Yang, D.; Mohanakrishnan, A. K.; Fanwick, P. E.; Nampoothiri, P.; Hamel, E.; Cushman, M. *J. Med. Chem.* **2000**, *43*, 2419–2429.

(11) (a) Trost, B. M.; Bonk, P. J. *J. Am. Chem. Soc.* **1985**, *107*, 1778–1781. (b) Jenkins, T. J.; Burnell, D. J. *J. Org. Chem.* **1994**, *59*, 1485–1491. (c) Crane, S. N.; Jenkins, T. J.; Burnell, D. J. *J. Org. Chem.* **1997**, *62*, 8722–8729.

(12) (a) Carlson, R. G.; Behn, N. S. *J. Org. Chem.* **1968**, *33*, 2069–2073. (b) Jones, B.; Price, P. *J. Chem. Soc. D: Chem. Commun.* **1969**, 1478–1479.

(13) Unfortunately, the stereochemistry of the regioisomer **4d** could not be determined unambiguously (see Supporting Information).

determined to be trans based on the NOE results (Figure 1).[13] We detected no α-epoxide and only a trace amount of *β*-epoxide **6d**. These results indicated that an exclusive equatorial attack of **2d** on ketone **1** occurred to generate the ring expansion products **3d** and **4d**.[14]

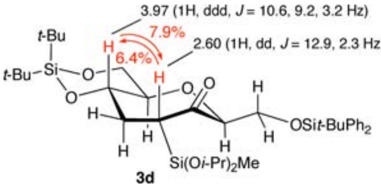
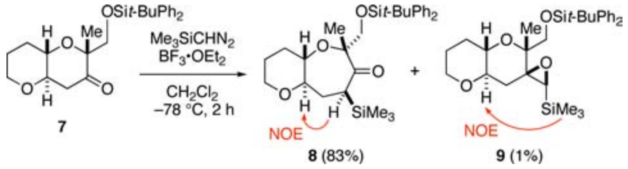


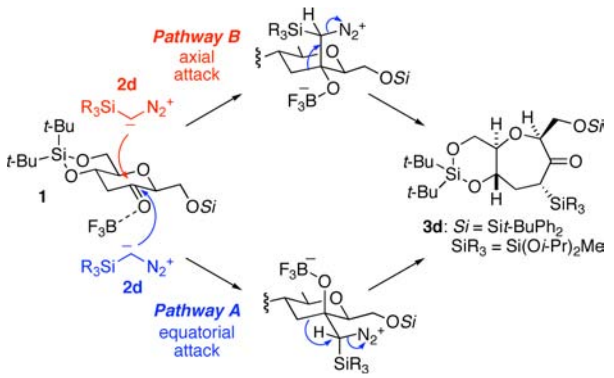
**Figure 1.** Difference NOE correlation of **3d**.

**Scheme 2.** Ring Expansion Reaction of **7** with TMS-Diazomethane **2b**



We also attempted a ring expansion reaction of ketone **7**, which has an axial methyl next to the carbonyl group (Scheme 2). The major product was *trans*-silylketone **8**, similar to entry 4 of Table 1, and only a trace amount of spiro-epoxide **9** was detected. This finding supports the preferential equatorial attack of TMS-diazomethane **2b** on the ketone **7**.

**Scheme 3.** Two Possible Pathways to Silylketone **3d**



There are two possible pathways for the formation of the trans diastereomer **3d**, as shown in Scheme 3. In pathway A, silyldiazomethane **2d** approaches from the equatorial side, and the silyl group is oriented antiperiplanar to the carbonyl group after addition. In pathway B, silyldiazomethane **2d** attacks from the axial side and the silyl group aligns antiperiplanar to the tertiary carbon.

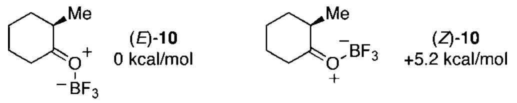


**Figure 2.** ZPVE-corrected energy difference between (*E*)-**10** and (*Z*)-**10** calculated at the B3LYP/6-31G+(d,p) level of theory.

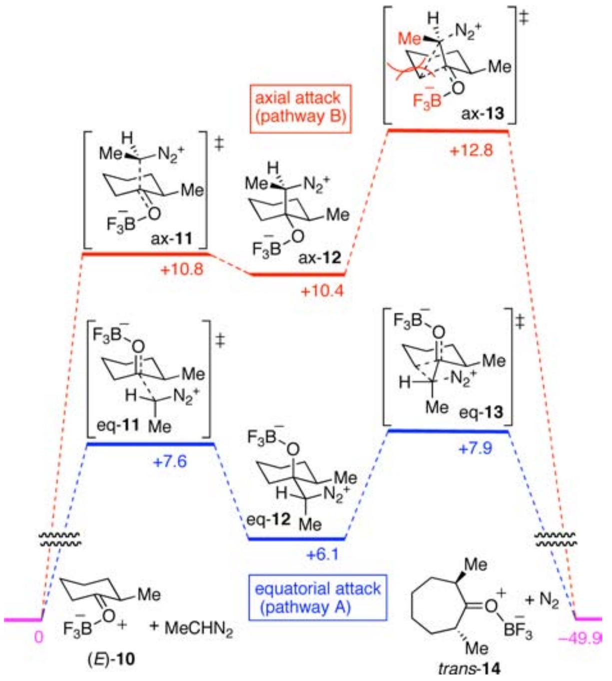


**Figure 3.** Relative energy profiles of the ring expansion reaction of 2-methylcyclohexanone with diazoethane promoted by $BF_3$. The ZPVE-correlated enegies calculated at the B3LYP/6-31G+(d,p) level of theory. The conformational search of *trans*-**14** was not performed in detail. The indicated value (−49.9 kcal/mol) is one of the possible stable conformations.

Based on our experimental results, the stereochemical mechanism should be pathway A initiated by the equatorial attack. Seto et al., however, previously proposed a contrasting mechanism whereby TMS-diazomethane attacks a ketone to avoid the steric repulsion between the silyl group and the branched substituent.[9] We therefore attempted to analyze the two reaction pathways using a computational method.

The calculation was performed using GAMESS[15] at the B3LYP/6-31G+(d,p) level of theory. To simplify the

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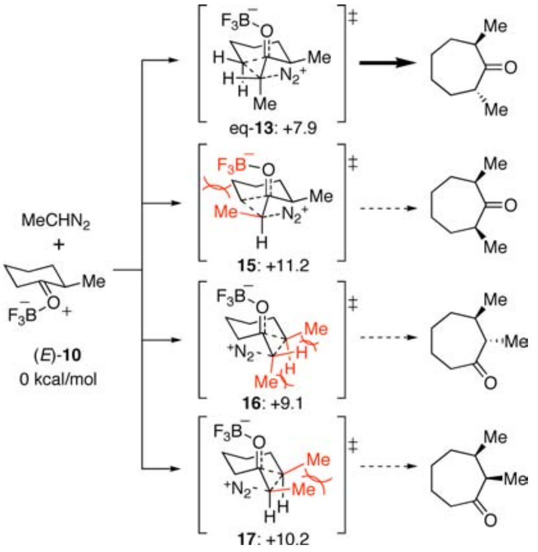
(14) For stereochemical mechanism of spiro-epoxide formation in the ring expansion reaction of 1,6-anhydro-2-hexosuloses using TMS-diazomethane, see: Kawai, T.; Isobe, M.; Peters, S. C. *Aust. J. Chem.* **1995**, *48*, 115–131.

(15) Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. J.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347–1363.

**Scheme 4.** Relative Energy of Transition States toward Four Different Isomers via an Equatorial Attack[a]



[a] The ZPVE-correlated energy (kcal/mol) calculated at the B3LYP/6-31G+(d,p) level of theory.

calculation, diazoethane and 2-methylcyclohexanone were used as model compounds for silyldiazomethane **2** and ketone **1**, respectively. There are two possible geometries of $BF_3$-coordinated 2-methylcyclohexanone **10** (Figure 2). The calculated energy of (*E*)-**10** was lower than that of (*Z*)-**10** by 5.2 kcal/mol. We then performed the following calculations of energy profiles for the ring expansion reaction on the assumption that $BF_3$ is opposite from the methyl group.

The energy profiles calculated for mixed complexes are shown in Figure 3. The energies of pathway A were lower than those of pathway B in both stages of addition and migration. The maximum energy difference was estimated to be 4.9 kcal/mol at the transition state of the migration (**13**). This higher energy transition state ax-**13** can be explained by the repulsion between $BF_3$ and the methyl group of diazoethane.

We next compared the geometry of the migration transition states leading to four possible seven-membered ketones to account for the high regio- and diastereoselectivity. As shown in Scheme 4, eq-**13** had the lowest energy among the four isomers. The energy of transition state **15** was calculated to be more destabilizing by 3.3 kcal/mol compared to that of eq-**13** due to the steric repulsion between $BF_3$ and the methyl group of diazoethane. The regioisomeric transition states **16** and **17** also had higher energies. This is due to the steric interaction between the methyl and hydrogen or the two methyls. Thus, these calculation data indicated that *trans*-2,7-dimethylcycloheptanone is formed as a major product via pathway A where diazoethane attacks from the equatorial side of the carbonyl group.

In conclusion, we described a detailed stereochemical mechanism of the $BF_3$-promoted ring expansion reaction of six-membered ketones with TMS-diazomethane based on experimental and computational methods. The reaction is initiated by the equatorial addition of TMS-diazomethane to a ketone via a transition state in which the bulky silyl group orients antiperiplanar to the carbonyl oxygen, and migration of the less substituted carbon generates a *trans*-seven-membered ketone with high regio- and diastereoselectivity.

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**Supporting Information Available.** Experimental procedures, spectroscopic data, and copies of $^1H$ and $^{13}C$ NMR spectra of all new compounds. Cartesian coordinates and energies of the optimized geometries; Cartesian coordinates, energies, and imaginary frequencies of the transition states. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.