

# Computational Elucidation of the Origins of Reactivity and Selectivity in Non-Aldol Aldol Rearrangements of Cyclic Epoxides

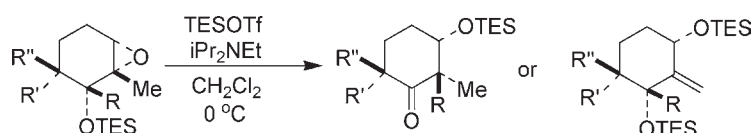
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Received April 29, 2011

## ABSTRACT

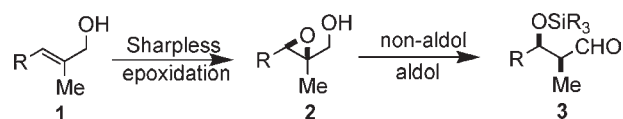


The non-aldol aldol reaction of the isomeric epoxy silyl ethers is controlled by the conformation of the transition states leading to an internal hydride shift. One isomer rearranges to the  $\beta$ -silyloxy ketone whereas the other isomer gives a  $\beta$ -elimination product. Theoretical calculations show that the substrates with substituents that favor the formation of the chairlike transition state rearrange normally while those that do not undergo elimination instead.

Lewis acid induced rearrangements are useful synthetic tools that provide access to unique and highly functionalized systems. The non-aldol aldol rearrangement is a semipinacol rearrangement of epoxy alcohols that generates silyl-protected aldol products in high yields.<sup>1,2</sup> Reactions of optically active epoxy alcohols, **2**, derived from the Sharpless asymmetric epoxidations<sup>3</sup> of the allyl alcohols, **1**, with a silyl triflate induce a 1,2-hydride shift followed by formation of the silyl protected

aldols, **3**, in excellent yields and enantioselectivities (Scheme 1). The process has been implemented in the total syntheses of several polyketide natural products, including auripyrones A and B.<sup>4</sup>

Scheme 1



Recently, the non-aldol aldol rearrangement was extended to cyclic systems to prepare silyloxycycloalkanones from the corresponding 2,3-epoxy-cycloalkanols.<sup>5</sup>

This strategy is expected to succeed as long as an antiperiplanar CH is available to migrate upon epoxide opening in such conformationally constrained ring systems. However, in the course of our application of this cyclic non-aldol aldol rearrangement to the total

(1) For an excellent review of semi-pinacol rearrangements, see: Snape, T. J. *Chem. Soc. Rev.* **2007**, *36*, 1823.

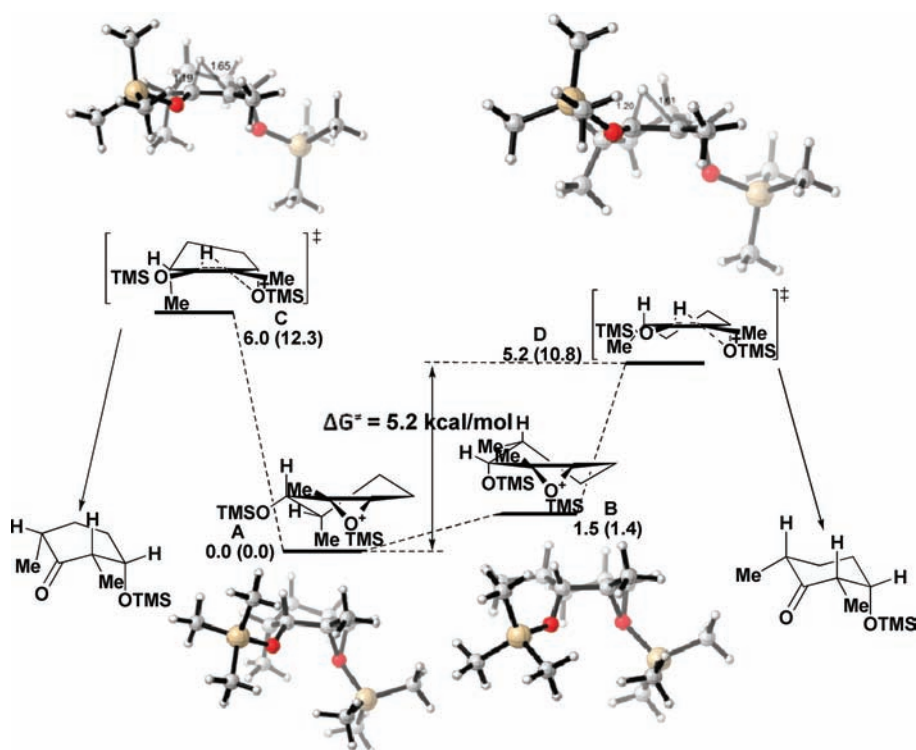
(2) (a) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1993**, *115*, 12208. (b) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1995**, *117*, 7379. (c) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1997**, *119*, 12150. (d) Jung, M. E.; Marquez, R. *Tetrahedron Lett.* **1999**, *40*, 3129. (e) Jung, M. E.; Lee, W. S.; Sun, D. *Org. Lett.* **1999**, *1*, 307. (f) Jung, M. E.; Sun, D. *Tetrahedron Lett.* **1999**, *40*, 8343. (g) Jung, M. E.; van den Heuvel, A. *Tetrahedron Lett.* **2002**, *43*, 8169. (h) Jung, M. E.; Hoffmann, B.; Rausch, B.; Contreras, J.-M. *Org. Lett.* **2003**, *5*, 3159. (i) Jung, M. E.; van den Heuvel, A.; Leach, A. G.; Houk, K. N. *Org. Lett.* **2003**, *5*, 3375. (j) Jung, M. E.; van den Heuvel, A. *Org. Lett.* **2003**, *5*, 4705.

(3) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(4) (a) Jung, M. E.; Marquez, R. *Org. Lett.* **2000**, *2*, 1669. (b) Jung, M. E.; Lee, C. P. *Tetrahedron Lett.* **2000**, *41*, 9719. (c) Jung, M. E.; Lee, C. P. *Org. Lett.* **2001**, *3*, 333. (d) Jung, M. E.; Yoo, D. *Org. Lett.* **2007**, *9*, 3543. (e) Mitton-Fry, M. J.; Cullen, A. J.; Sammakia, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 1066. (f) Jung, M. E.; Zhang, T. *Org. Lett.* **2008**, *10*, 137. (g) Jung, M. E.; Yoo, D. *Tetrahedron Lett.* **2008**, *49*, 816. (h) Jung, M. E.; Salehi-Rad, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 8766. (i) Jung, M. E.; Chaumontet, M.; Salehi-Rad, R. *Org. Lett.* **2010**, *12*, 2872.

(5) Jung, M. E.; Allen, D. A. *Org. Lett.* **2008**, *10*, 2039. See also: Jung, M. E.; Allen, D. A. *Org. Lett.* **2009**, *11*, 757.

(6) (a) Stratmann, K.; Moore, R. E.; Bonjouklian, R.; Deeter, J. B.; Patterson, G. M. L.; Shaffer, S.; Smith, C. D.; Smitka, T. A. *J. Am. Chem. Soc.* **1994**, *116*, 9935. (b) Smith, C. D.; Zilfou, J. T.; Stratmann, K.; Patterson, G. M. L.; Moore, R. E. *Mol. Pharmacol.* **1995**, *47*, 241.



**Figure 1.** B3LYP optimized geometries of **4a** (A and B) and transition structures (C and D) for the non-aldol aldol rearrangement. Values below each structure are relative energies in kcal/mol. Values enclosed in parentheses are relative single-point energies calculated by the M06-2X method in kcal/mol.

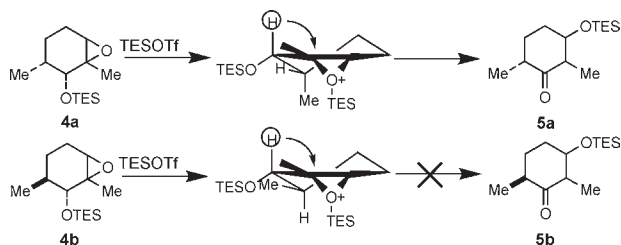
synthesis of *N*-methylwelwitindolinone C isothiocyanate,<sup>6</sup> we have found that the facility of the reaction is a sensitive function of substitution and that the conformation of the transition states is different from that of substrates.<sup>7</sup> We provide computational evidence that stereoelectronic effects and a combination of ground state destabilization and transition state stabilization control the non-aldol processes in these systems and competition between rearrangement and elimination reactions.

As shown in Scheme 2, one of the two diastereomers of a 6-methyl-2,3-epoxycyclohexyl silyl ether, **4a**, leads to the non-aldol aldol rearrangement in good yield, while the

Scheme 2, the requisite antiperiplanar arrangement of the migrating hydrogen is apparent in both reactants. The axial methyl in the preferred conformer of **4a** might have been expected to disfavor the reaction. In fact, the opposite is true.

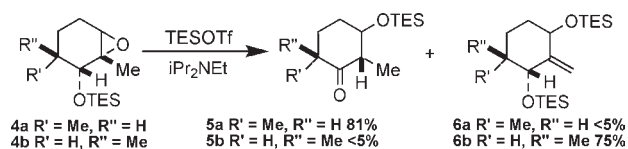
Reaction of epoxide **4a** with TESOTf and Hunig's base gave the non-aldol aldol product **5a**.<sup>7</sup> Surprisingly, however, treatment of the 6-methyl diastereomer **4b** did not afford the expected **5b**, despite the hydride positioned antiperiplanar to the epoxide at 161° in the crystal structure of the alcohol **4b**. Rather, the exocyclic olefin **6b**, the product of elimination, was isolated (Scheme 3).<sup>7</sup>

#### Scheme 2



other diastereomer, **4b**, undergoes mostly elimination and decomposition. This result is surprising, since, as shown in

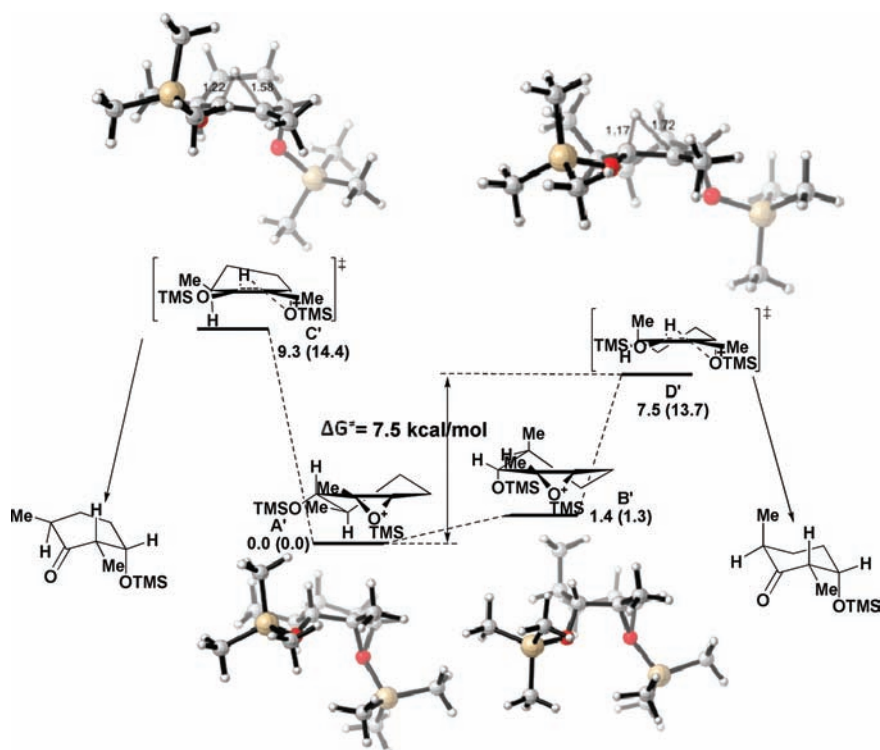
#### Scheme 3



Computational investigations provide the explanation of these perplexing results.<sup>8</sup> B3LYP/6-31G(d) calculations

(7) Allen, D. A. Ph.D. thesis, University of California, Los Angeles, CA, 2010.

(8) Frisch, M. J. et al. *Gaussian 03*, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.



**Figure 2.** B3LYP optimized geometries of **4b** (**A'** and **B'**) and transition structures (**C'** and **D'**) for the non-aldol aldol rearrangement. Values below each structure are relative energies in kcal/mol. Values enclosed in parentheses are relative single-point energies calculated by M06–2X method in kcal/mol. **A'** is 1.4 kcal/mol more stable than **A** (Figure 1) or 0.9 kcal/mol at the M06-2X level.

on the silylated epoxides and transition states for the rearrangements were carried out for each case. The full systems were computed, except that a TMS was substituted for each TES group.

The computed structures of silylated epoxides are shown in Figures 1 and 2, and the computed relative energies are shown below each structure. The full energetics for these reactions are given in the Supporting Information. Each stereoisomer involves two possible half-chair conformers, **A**  $\rightleftharpoons$  **B** (Figure 1) and **A'**  $\rightleftharpoons$  **B'** (Figure 2) that are in rapid equilibrium. The ring opening of the epoxide is accompanied by a hydride shift. As shown in Figure 1, **4a** has two possible half-chair conformers **A** and **B**. **A** leads to the half-boat TS **C** that leads to the boat conformer of the product, while conformer **B** proceeds via the half-chair TS **D** to give the chair conformer of the product. The preferred rearrangement pathway involves a conformation flip of **A** to **B** and then to transition state **D** with the overall activation energy of 5.2 kcal/mol, via a Curtin–Hammett process. Transition state **C** and the boat conformer of the product are both disfavored due to torsional strain; both experience eclipsing interactions. By contrast, the half-chair **D** and corresponding product are more nearly staggered.

In Figure 2, the structures for the isomeric reactant, **4b**, are shown. The equatorial methyl of **A'** causes the silylated epoxide, **A'**, to be 1.4 kcal/mol lower in energy than **A**. The preferred transition state **D** with an equatorial methyl

group (Figure 1) is more stable than **D'** formed by **4b** by 0.9 kcal/mol (Figure 2). Consequently, the rearrangement of the cis isomer **4a** to give the non-aldol aldol product has an activation energy of only 5.2 kcal/mol, while the trans isomer **4b** has a higher activation energy of 7.5 kcal/mol (see Supporting Information: Figure S1). Compound **4b** will undergo the rearrangement almost 100 times more slowly than **4a**. Experimentally, **4b** gives the alternative intermolecular elimination product **6b**, rather than the non-aldol aldol product **5b**. Single-point calculations with M06-2X using B3LYP-optimized geometries leads to 5–6 kcal/mol higher activation energies, but the energy difference calculated for **4a** and **4b** by the M06-2X method is 2.9 kcal/mol, similar to the B3LYP result of 2.3 kcal/mol.

The exploration of these results is essentially the same as the Fürst–Plattner rule<sup>9</sup> for nucleophilic ring-opening of epoxides. Torsional effects favor formation of the trans-diaxial product. In the case of **4a**, transition states **C** and **D** both lead to trans-diaxial epoxide opening, but **D** leads to the preferred chair product, while **C** leads to the twist boat product which is torsionally destabilized. With **4b**, the preference for **D'** over **C'** follows the same pattern.

In order to investigate the competing elimination reaction, trimethylamine was used instead of Hunig's base to

(9) Fürst, A.; Plattner, P. A. *Helv. Chim. Acta* **1949**, *32*, 275.

model the reaction pathway. The most stable elimination transition states of the two diastereomers **4a** and **4b** are located, and the computed energetics for the elimination reactions are compared to the non-aldol aldol transition states (see Supporting Information: Figures S2–S4). The elimination barriers of 7.4 and 6.5 kcal/mol (13.6 and 12.5 kcal/mol by M06-2X) are similar and are in between the non-aldol barriers of **4a** and **4b**.

The stereoisomer **4a** has a higher activation energy (7.4 kcal/mol) for the elimination reaction than the barrier of the non-aldol aldol pathway (5.2 kcal/mol) (see Supporting Information: Figure S3). This is consistent with the experimental observation that **4a** will undergo the desired non-aldol aldol reaction instead of the elimination reaction. M06-2X results give a similar prediction, with the elimination barrier 2.8 kcal/mol above the non-aldol aldol barrier.

However, the elimination pathway of the isomeric reactant **4b**, which proceeds via TS **M'** to give the elimination product, has an activation energy of 6.5 kcal/mol, lower than that for the non-aldol aldol pathway, which has a higher barrier of 7.5 kcal/mol (see Supporting Information: Figure S4). Again, M06-2X also predicts the elimination to be favored, by 1.2 kcal/mol.

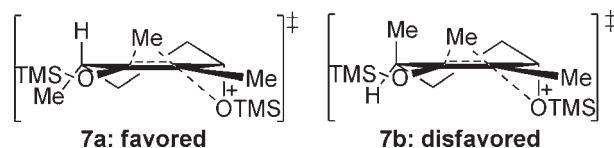
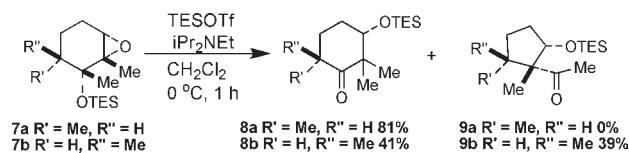
The substituent effects on the migration of an alkyl group were also investigated. Treatment of epoxide **7a**<sup>10</sup> with TESOTf afforded the expected rearranged product **8a** (Scheme 4).<sup>7</sup> However, exposure of the epoxide with the equatorial methyl group **7b** to TESOTf gave a 1:1 mixture of the methyl migration product **8b** and the product of the ring contraction **9b**, via ring-carbon migration.<sup>7</sup>

As shown in Figure 3, the transition state model for the non-aldol aldol rearrangement of **7a** has an equatorial methyl group which is favored, whereas the TS model of **7b** which is disfavored has an axial methyl group in the half-chair structure.

These findings confirm the hypothesis that diastereomeric 5- and 6-substituted 2,3-epoxycyclohexyl silyl ether

(10) Safaryn, J. E.; Chiarello, J.; Chen, K. M.; Jollie, M. M. *Tetrahedron*. **1986**, *42*, 2635.

#### Scheme 4



**Figure 3.** Half-chair transition state models for the non-aldol aldol rearrangement of **7a** and **7b**.

substrates that can access the favored half-chair TS rearrange normally, while those which have disfavored axial substituents in the TS undergo other reaction processes instead. Further studies of this ‘remote control’ and application of these findings to the total synthesis of *N*-methyl-welwitindolinones will be reported in due course.

**Acknowledgment.** This work was supported by the National Science Foundation (CHE 0614591) and National Institute of General Medical Sciences, National Institute of Health (GM36700). Computations were performed on the National Science Foundation Terascale Computing System at the National Center for Supercomputing Applications (NCSA), on the California NanoSystems Institute clusters and UCLA cluster.

**Supporting Information Available.** Optimized geometries and energies of all computed species and full authorship of ref 8. This material is available free of charge via the Internet at <http://pubs.acs.org>.