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# Facial Selectivity and Stereospecificity in the (4 + 3) Cycloaddition of Epoxy Enol Silanes

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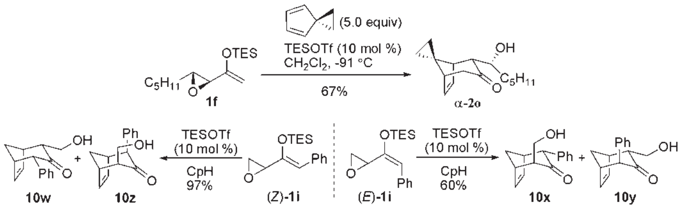
## ABSTRACT



**The scope of the (4 + 3) cycloaddition using epoxy enol silanes has been examined. Unhindered and nucleophilic dienes react to give the highest yields, but hindered dienes give rise to higher diastereoselectivities. Notably, the cycloaddition shows facial selectivity and stereospecificity for the stereochemistry of the epoxy enol silane.**

The (4 + 3) cycloaddition of allyl cations and dienes is an efficient entry into the synthesis of seven-membered rings.[1] Recent research in this field seeks to develop mild and chemoselective methods to assemble and generate the oxyallyl cation for maximum functional group compatibility, for applications in intramolecular cycloadditions, and in late stages of the syntheses of complex natural products.[2] Polyfunctionalized oxyallyl cations that can engage in cycloaddition are also desirable to furnish more sophisticated cycloadducts with a greater potential for synthesis.

Recently we reported on the development and optimization of an intermolecular (4 + 3) cycloaddition which employed epoxy enol silanes as the dienophile.[3] This cycloaddition afforded hydroxymethylenated bicyclo[3.2.1]-octenones under mild reaction conditions and in good yields (Table 1, entry 1). We have found that TES-enol ether **1a**, instead of the previously reported TMS-derivative,[4] reacted at low temperatures with a significant improvement in cycloaddition efficiency. Herein we report on the scope of this reaction and have delineated aspects of the mechanism that could account for the yields and diastereoselectivities. Notably, this (4 + 3) cycloaddition was found to be both facial selective and stereospecific with respect to the epoxy enol silane.

We have observed that silyl triflates were able to promote the cycloaddition through epoxide activation

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(1) Reviews of (4 + 3) cycloadditions: (a) Harmata, M. *Chem. Commun.* **2010**, *46*, 8904–8922. (b) Battiste, M. A.; Pelphrey, P. M.; Wright, D. L. *Chem.—Eur. J.* **2006**, *12*, 3438–3447. (c) Harmata, M. *Adv. Synth. Catal.* **2006**, *348*, 2297–2306. (d) Hartung, I. V.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 1934–1947. (e) Harmata, M.; Rashatasakhon, P. *Tetrahedron* **2003**, *59*, 2371–2395. (f) Harmata, M. *Acc. Chem. Res.* **2001**, *34*, 595–605. (g) Cha, J. K.; Oh, J. *Curr. Org. Chem.* **1998**, *2*, 217–232. (h) Rigby, J. H; Pigge, F. C. *Org. React.* **1997**, *51*, 351–478. (i) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1–19.

(2) Representative recent work on (4 + 3) cycloadditions: (a) Antoline, J. E.; Hsung, R. P.; Huang, J.; Song, Z.; Li, G. *Org. Lett.* **2007**, *9*, 1275–1278. (b) Pascual, M. V.; Proemmel, S.; Beil, W.; Warchow, R.; Hoffmann, H. M. R. *Org. Lett.* **2004**, *6*, 4155–4158. (c) Föhlisch, B.; Flogaus, R.; Henle, G. H.; Sendelbach, S.; Henkel, S. *Eur. J. Org. Chem.* **2006**, 2160–2173. (d) Harmata, M.; Wacharasindhu, S. *Org. Lett.* **2005**, *7*, 2563–2565. (e) Prié, G.; Prévost, N.; Twin, H.; Fernandes, S. A.; Hayes, J. F.; Shipman, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 6517–6519. (f) Trillo, B.; Lopez, F.; Gulias, M.; Castedo, L.; Mascarenas, J. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 951–954. (g) Xiong, H.; Hsung, R. P.; Berry, C. R.; Rameshkumar, C. *J. Am. Chem. Soc.* **2001**, *123*, 7174–7175. (h) Fujita, M.; Oshima, M.; Okuno, S.; Sugimura, T.; Okuyama, T. *Org. Lett.* **2006**, *8*, 4113–4116.

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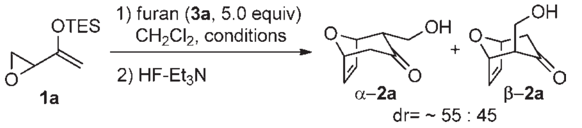
(4) Ohno, M.; Mori, K.; Hattori, T.; Eguchi, S. *J. Org. Chem.* **1990**, *55*, 6086–6091.

10.1021/ol102897d

**Table 1.** Reaction Conditions for Cycloaddition of **1a** and Furan



| entry | acids | *t* (°C) | yield of **2a** |
|---|---|---|---|
| 1 | TESOTf (10 mol %) | −91 | 75% |
| 2 | TESOTf (100 mol %) | −91 | 75% |
| 3[a] | TMSOTf (10 mol %) | −94 | 70% |
| 4 | TBSOTf (20 mol %) | −91 | 58% |
| 5 | TfOH (10 mol %) | −91 | 57%[b] |
| 6 | $Tf_2NH$ (10 mol %) | −91 | 36%[b] |
| 7 | $Tf_2NH$ (100 mol %) | −91 | 59% |
| 8 | TFA (100 mol %) | −78 | 21%[c] |

[a] Reference 3. [b] Result improved from ref 3. [c] Not all of **1a** is consumed.

**Scheme 1.** Proposed Catalytic Cycle

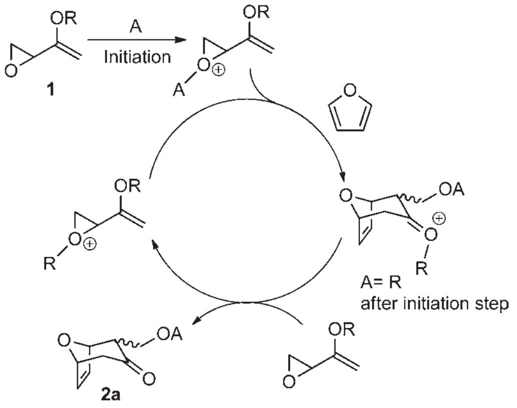
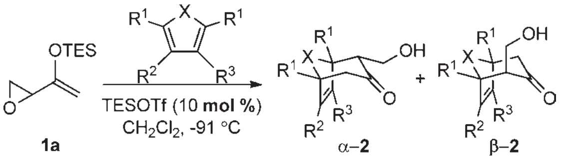


**Table 2.** (4 + 3) Cycloaddition of **1a** with Various Dienes



| entry | diene[a] | X | $R^1$ | $R^2$ | $R^3$ | yield | α-**2**:*β*-**2** |
|---|---|---|---|---|---|---|---|
| 1[b] | **3a** | O | H | H | H | **2a**, 75% | 55:45 |
| 2[c] | **3b** | O | Me | H | H | **2b**, 32%[d] | 66:34 |
| 3 | **3c** | O | H | Me | H | **2c**, 70% | 50:50[e] |
| 4 | **3d** | O | H | Me | Me | **2d**, 73% | 45:55 |
| 5 | **4a** | $CH_2$ | H | H | H | **2e**, 76% | 55:45 |
| 6 | **4b** | $C(CH_2)_2$ | H | H | H | **2f**, 47% | 77:23 |
| 7 | **4c** | $(CH_2)_2$ | H | H | H | **2g**, 22% | 43:57 |

[a] 5 equiv used. [b] Reference 3. [c] Yield improved from ref 3. [d] **5a** (31%) also obtained. [e] 2:1 mixture of regioisomers, total of 4 diastereomeric products.

(Table 1, entries 1−3), initially yielding silylated **2a** (Scheme 1, A = TES) as expected from the proposed catalytic cycle (Scheme 1). Because an aqueous workup resulted in varying degrees of desilylation, all product mixtures were treated with $HF-Et_3N$ to induce complete desilylation for consistency. The bulkier TBSOTf was able to initiate the reaction, but more catalyst was needed for complete reaction. Strong Brønsted acids also activated the epoxide for cycloaddition, even though protonation of the silyl enol ether could be a competing pathway (Table 1, entries 5−7). However, weaker acids such as TFA could not mediate the reaction effectively even in stoichiometric amounts (Table 1, entry 8).

A screening of dienes (Table 2) showed that a range of structural types participate in this cycloaddition. The highest cycloaddition yields were obtained with unhindered dienes of good nucleophilicity (Table 2, entries 1, 3−5). Substituents at or proximate to the site of carbon−carbon bond formation hindered cycloaddition, resulting in lower yields compared with the reactions of their corresponding unsubstituted parent dienes (Table 2, entry 1 vs 2; entry 5 vs 6, 7). Dienes having substituents farther from the site of bond formation (e.g., **3c** and **3d**) underwent cycloaddition with good yields (Table 2, entries 2, 3), but the reaction with the unsymmetrical furan **3c** was not very regioselective (2:1). Electron-deficient dienes such as 3,4-dibromofuran were not reactive (< 15% yields), while diphenylfulvene and 2,3-dimethylbutadiene predominantly underwent polymerization under the reaction conditions. The overall diastereoselectivity (α-**2**:*β*-**2**) of this cycloaddition with **1a** as the dienophile was not high, although a preference for *endo* cycloaddition[5] to give α-**2f** was observed in the reaction with the hindered spirocyclopentadiene, **4b**.

A systematic study on the scope of the epoxy enol silanes **1** was undertaken next, and the results are shown in Tables 3 and 4.[6] With enol silanes bearing sterically more hindered silyl groups (**1b**−**d**), the cycloaddition with furan (**3a**) or cyclopentadiene (**4a**) required more than 10 mol % TESOTf for complete reaction. According to the catalytic cycle (Scheme 1), after the initiating step, the silyl group of the enol ether ultimately propagates the reaction, and it may be that bulky silyl groups are not as effective in activating the epoxides in subsequent rounds. Although low diastereoselectivities were observed with unhindered dienes (Table 3, entries 3−7, 9), the cycloadditions with the bulky TBDPS-substituted enol ether **1d** showed a dramatic range in the mode of cycloaddition. A preference for the *exo*-cycloadducts *β*-**2** could be seen in the reactions of **1d** with furans **3a** and **3d** (Table 3, entries 7−8), but with the hindered spirocyclopentadiene **4b**, the *endo*-cycload-

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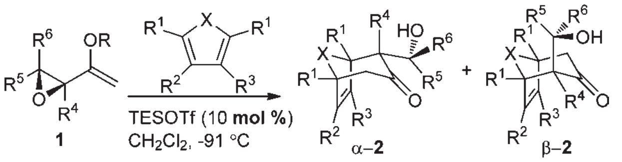
(5) *Endo* refers to a syn relationship between the diene and the oxygen in the dienophile, whereas Hoffmann used the term "compact" to describe this cycloaddition mode: Hoffmann, H. M. R. *Angew. Chem., Int. Ed.* **1973**, *12*, 819–835.

(6) The structures of all cycloadducts were determined by 2-D NMR and NOE correlations about the rigid bicyclic system; see the Supporting Information.

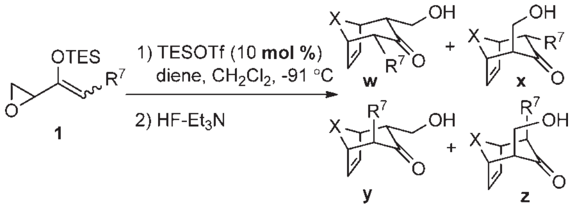
**Table 3.** (4 + 3) Cycloaddition of Epoxy Enol Silanes **1a**−**1g**



| entry | enol silane **1** | diene[a] | yield of **2** | α-**2**:*β*-**2** |
|---|---|---|---|---|
| 1[b] | **1a** (R = TES; $R^4$, $R^5$, $R^6$ = H) | **3a** | **2a**, 75% | 55:45 |
| 2 | **1a** | **4a** | **2e**, 76% | 55:45 |
| 3[c] | **1b** (R = TBS; $R^4$, $R^5$, $R^6$ = H) | **3a** | **2a**, 38% | 65:35 |
| 4[c] | **1b** | **4a** | **2e**, 56% | 52:48 |
| 5[c] | **1c** (R = TIPS; $R^4$, $R^5$, $R^6$ = H) | **3a** | **2a**, 60% | 60:40 |
| 6[c] | **1c** | **4a** | **2e**, 60% | 58:42 |
| 7[c] | **1d** (R = TBDPS; $R^4$, $R^5$, $R^6$ = H) | **3a** | **2a**, 59% | 35:65 |
| 8[c,d] | **1d** | **3d** | **2d**, 43% | 30:70 |
| 9[c] | **1d** | **4a** | **2e**, 55% | 55:45 |
| 10[c,d] | **1d** | **4b** | **2f**, 46% | α-**2f** only |
| 11 | **1e** (R = TES; $R^4$ = Me, $R^5$, $R^6$ = H) | **3a** | **2h**, 57% | 72:28 |
| 12 | **1e** | **3b** | **2j**, 27%[e] | 75:25 |
| 13 | **1e** | **4a** | **2i**, 56% | 45:55 |
| 14 | **1e** | **4b** | NR | -- |
| 15 | **1f** (R = TES; $R^4$, $R^6$ = H, $R^5$ = $C_5H_{11}$) | **3a** | **2k**, 56%[f] | 65:35[g] |
| 16 | **1f** | **3b** | **2m**, 25% | 68:32 |
| 17[d] | **1f** | **3d** | **2n**, 56% | 35:65 |
| 18 | **1f** | **4a** | **2l**, 80% | 51:49 |
| 19 | **1f** | **4b** | **2o**, 67%[h] | α-**2o** only |
| 20 | **1g** (R = TES; $R^4$, $R^5$ = H, $R^6$ = $C_5H_{11}$) | **3a** | **2p**, 27% | 47:53 |
| 21 | **1g** | **4a** | **2q**, 51% | 40:60 |
| 22[d] | **1g** | **3d** | **2r**, 35% | 22:78 |

[a] 5 equiv of diene used. [b] Reference 3. [c] Reaction completed using a total of 20 mol % TESOTf. [d] *t* = −78 °C. [e] **5b** (14%) also obtained. [f] **6a** (24%) also obtained. [g] *endo*/*exo* ratio = 50:50, taking into account that **6a** resulted from an *exo* attack. [h] **6b** (7%) also obtained.

**Table 4.** (4 + 3) Cycloaddition of Epoxy Enol Silanes **1h**−**1i**



| entry | enol silane 1 | diene[a] | yield | dr |
|---|---|---|---|---|
| 1 | (*Z*)-**1h** ($R^7$ = Me) | **3a** | 82% | **7w**:**7x**:**7y** = 45:45:10 |
| 2 | (*Z*)-**1h** | **4a** | 57% | **8w**:**8z** = 50:50 |
| 3 | (*Z*)-**1i** ($R^7$ = Ph) | **3a** | 66%[b,c] | **9w**:**9x** = 25:75 |
| 4 | (*Z*)-**1i** | **4a** | 97% | **10w**:**10z** = 45:55 |
| 5 | (*E*)-**1i** ($R^7$ = Ph) | **3a** | 14%[d] | **9y** only |
| 6 | (*E*)-**1i** | **4a** | 60% | **10x**:**10y** = 28:72 |

[a] 5 equiv used. [b] Yield improved from ref 3. [c] **5c** (26%) also obtained. [d] **5c** (31%) also obtained.

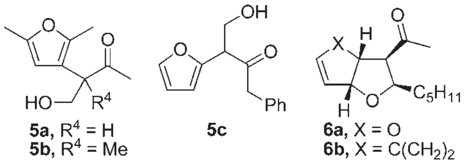


**Figure 1.** (4 + 3) Cycloaddition Side Products **5a**−**c**, **6a**−**b**.

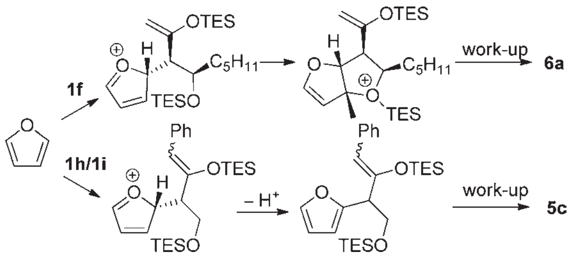
duct α-**2f** was obtained exclusively (Table 3, entry 10). This example demonstrates that it is possible to modify and increase the diastereoselectivities of the cycloadditions by the use of **1** bearing silyl groups with varying steric demands.

Epoxides with substituents at the site of carbon−carbon bond formation (e.g., **1e**, $R^4$ = Me) would be expected to favor C−O cleavage to yield a more substituted and stabilized oxyallyl cation species; on the other hand, this electrophile would also be more hindered. In the event, **1e** underwent cycloaddition with unhindered dienes in slightly diminished yields (Table 3, entries 11, 13), and with a hindered furan such as 2,5-dimethylfuran (**3b**) in significantly lower yield along with rearomatized product **5b** (Table 3, entry 12), revealing the deleterious effects of steric hindrance toward cycloaddition. In the extreme case, no reaction was observed between **1f** and hindered spirocyclopentadiene **4b** (Table 3, entry 14).

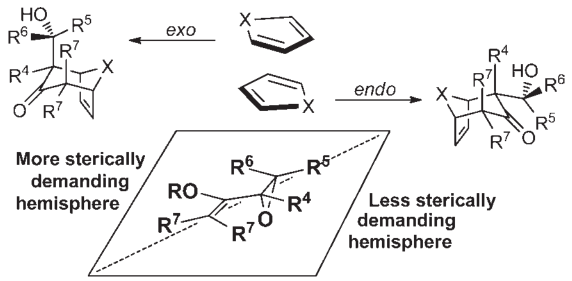
A *trans*- or *cis*-substituent ($R^5$, $R^6 \neq$ H) on the distal carbon of **1f** and **1g**, respectively, would not be able to stabilize the electrophilic species compared to its parent epoxide **1a** but could impose steric demands resulting in different yields and stereodiscrimination in the cycloaddition. Cycloaddition of **1f** ($R^5$ = $C_5H_{11}$) bearing a substituent on a *trans*-epoxide with various dienes resulted in moderate to good yields of cycloadducts (Table 3, entries 15−19). The decreased yield in the cycloaddition of **1f** with furan was due to the formation of a bisfuran side product **6a** (Figure 1, Scheme 2) from the quenching of the cationic intermediate by silyl ether addition, a Class C product as defined by Hoffmann.[1i] Significantly, in the reaction of **1f** and spirocyclopentadiene **4b**, only one *endo* diastereomeric cycloadduct α-**2o** was obtained (Table 3, entry 19). The cycloaddition of **1g** with various dienes proceeded with generally lower yields than in the case of **1f**, showing that a *cis*-substituent in the epoxide is sterically more demanding in the cycloaddition than a *trans*-substituent (Table 3, entries 20−22). The observation of only two diastereomers, instead of four, from the cycloadditions of **1f** and **1g** indicates that the cycloaddition proceeded with facial selectivity with respect to the dienophiles. This infers that there is significant epoxide character in the transition state of the cycloaddition.

Epoxides substituted at the enol silane ($R^7 \neq$ H) would be expected to yield electronically more stabilized but sterically more demanding electrophilic intermediates. The reactions of (*Z*)-**1h** and (*Z*)-**1i** produced good to excellent yields of cycloadducts (Table 4, entries 1−4). The (*E*)-enol ether **1i** was sterically more demanding as a dienophile, as can be seen from the decreased yields of

**Scheme 2.** Formation of Type C Products



**Scheme 3.** Proposed Stereochemical Model



cycloadducts and the concomitant formation of a significant amount of **5c** (Figure 1, Scheme 2), resulting from termination by rearomatization.

The observation of **8w,z** and **10w,z** from the cycloaddition reactions of (*Z*)-**1h**[7] and (*Z*)-**1i** respectively with cyclopentadiene (**4a**) clearly indicated that both *endo* and *exo* cycloaddition modes were operative (Table 4, entries 2, 4). Notably, the reactions of (*Z*)-**1i** and (*E*)-**1i** generated complementary pairs of diastereomeric cycloadducts (Table 4, entries 4, 6), which infers that the reaction is stereospecific with respect to the geometry of the enol silane.

The corresponding cycloadditions of (*Z*)-**1h** and (*Z*)-**1i** with furan yielded cycloadducts **7w** and **9w** from *endo* cycloaddition (Table 4, entries 1, 3), while diastereomers **7x** and **9x** could be understood as having been derived from an initial *exo* attack at the epoxides of (*Z*)-**1h** and (*Z*)-**1i**, followed by the enol ether reacting from the opposite face after bond rotation, to set $R^7$ at the pseudoequatorial positions.[8] This explanation is consistent with the known preference of furan to undergo cycloaddition in an asynchronous manner[9] and with the structures of products **5a**−**c** and **6a** from interrupted cycloaddition, which show that bond formation with furan first occurred at the epoxide in the dienophile.

Summing up the observations of these experiments, the (4 + 3) cycloadditions of epoxy enol silanes occur with good to excellent yields provided that the dienes are sufficiently electron-rich and unencumbered. The stereochemical outcome could be explained by a reactant-like transition state which resembles **1** adopting the conformation as shown (Scheme 3)[10] and the diene approaching the dienophile *anti* with respect to the epoxide via both *endo* and *exo* cycloaddition modes. Based on our empirical observations, the eastern hemisphere of **1** (Scheme 3) appears to be the less sterically demanding end. The sterically more hindered end of the diene having an oxygen with its lone pairs when X = O for **3a**, or the cyclopropyl moiety when X = $C(CH_2)_2$ for **4b**, orients to cycloadd via the *endo* mode (Table 3, entry 19). When the steric demands of the western hemisphere of the dienophile is exacerbated by the use of R = TBDPS, the preference for *endo* cycloaddition is further increased to the point of being exclusive (Table 3, entry 10). On the other hand, when the steric demands of the diene increase at furan substituents $R^2$ and $R^3$ as found in **3d**, *exo*-cycloaddition becomes favored (Table 3, entries 8, 17, 22). When both the diene and dienophile are sterically encumbered, cycloaddition does not proceed (Table 3, entry 14).

In conclusion, the examination of the scope of the (4 + 3) cycloaddition of epoxy enol silanes revealed that the reaction proceeded with facial selectivity and stereospecificity with respect to the epoxy enol silane, indicating that the transition state is reactant-like and has significant epoxide and alkene character. Unhindered and nucleophilic dienes react to give the best yields, and the steric factors of the diene and the dienophile could be manipulated to increase the diastereoselectivity of the cycloaddition. A model to account for the stereochemical outcomes has been proposed. Our studies are ongoing to further delineate the mechanistic pathway through both experimental and computational work.[11]

**Acknowledgment.** This work was supported by the University of Hong Kong Strategic Research Theme on Drugs, and by the Research Grants Council of Hong Kong SAR (GRF HKU 7017/06P, 7015/10P). B.L. thanks the HKU Department of Chemistry for conference support.

**Supporting Information Available.** Experimental procedures, full characterization, $^1H$, $^{13}C$ NMR spectra for **1a**−**i**, **2a**−**r**, **5a**−**c**, **6a,b**, **7w**−**y**, **8w,z**, **9w**−**y**, **10w**−**z**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[7] (*E*)-**1h** could not be obtained in pure form for use in cycloaddition.

[8] The loss of the original oxyallyl cation stereochemistry has been observed and explained previously; see: Rawson, D. I.; Carpenter, B. K.; Hoffmann, H. M. R. *J. Am. Chem. Soc.* **1979**, *101*, 1786–1793.

[9] Fernández, I.; Cossío, F. P.; de Cózar, A.; Lledós, A.; Mascareñas, J. L. *Chem.—Eur. J.* **2010**, *16*, 12147–12157.

[10] While detailed transition state calculations remain to be done, the shown conformation of **1** is rationalized by $\pi$−$\sigma^*$ alignment and minimization of *A*-strain when $R^4$ = H.

[11] (a) Lohse, A. G.; Krenske, E. H.; Antoline, J. E.; Houk, K. N.; Hsung, R. P. *Org. Lett.* **2010**, *12*, 5506–5509. (b) Krenske, E. H.; Houk, K. N.; Harmata, M. *Org. Lett.* **2010**, *12*, 444–447. (c) Krenske, E. H.; Houk, K. N.; Lohse, A. G.; Antoline, J. E.; Hsung, R. P. *Chem. Sci.* **2010**, *1*, 387–392.