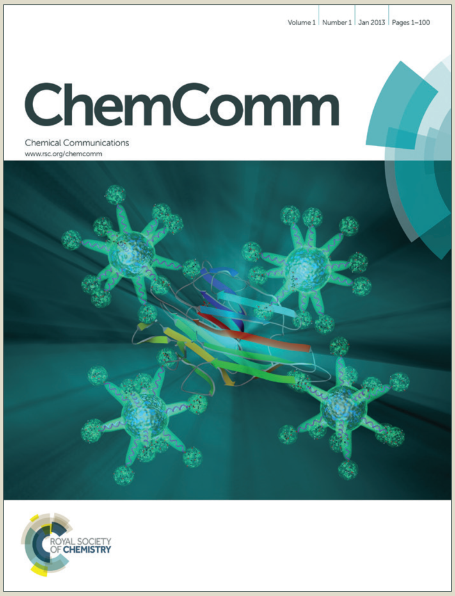
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α-Alkylation of a norbornene-derived tricyclic ketone: are steric factors really in control?

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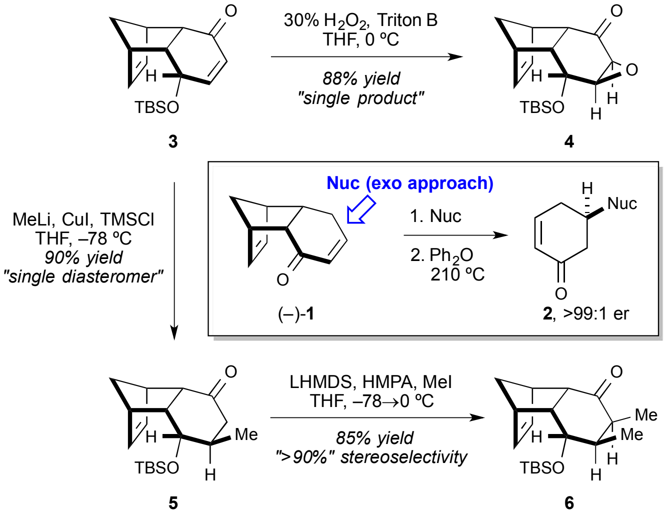
Density functional theory (DFT) has been used to investigate the α-alkylation of a chiral tricyclic ketone. These calculations reveal that torsional strain and a strong conformational preference, rather than steric influences, are responsible for the high levels of observed stereoselectivity and suggest a way by which alternative stereoisomers could be accessed.

Over the last 20 years, the Ogasawara–Takano laboratories,[1] along with important contributions from others,[2] have shown that tricyclic enones like **1** can function as a chiral synthon of cyclohex-2,5-dienone.[3] In this strategy the bicyclo[2.2.1]heptene ring system serves as an effective auxiliary for controlling the stereochemical outcome of a number of diversification reactions. Subsequent retro Diels–Alder reaction removes the auxiliary and provides an enantio-enriched cyclohexenone intermediate (e.g., **1**→**2**, Scheme 1).

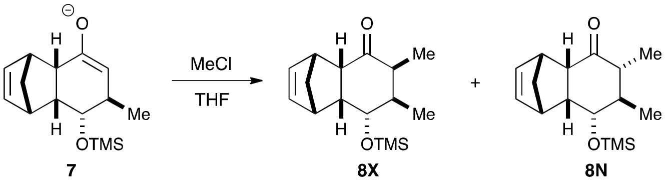
The high level of diastereoselectivity afforded by these building blocks is typically rationalized by effective blocking of the "endo" face of the enone by the auxiliary, leaving the "exo" face available for nucleophilic attack.§ This is exemplified by the formation of oxirane **4** as a "single product" during the nucleophilic epoxidation of **3**.[4] Similarly, Mehta and co-workers have demonstrated that a conjugate addition/α-alkylation sequence can be used to deliver two methyl groups to the exo face of ketone **3**.[5,6] This example is interesting as the auxiliary and the existing methyl group present in ketone **5** could exert opposing steric influences on the approach of the electrophile. Remarkably, these contradictory steric influences are not detrimental and ketone **6** can be formed with ">90%" stereoselectivity.[5]

We became interested in this result as part of a total synthesis project in our laboratory and began to wonder if the stereoselectivity observed during the alkylation of **5** was due solely to the steric effects of the auxiliary (i.e., through-space interactions). Herein, we present a computational investigation of the transformation leading to ketone **6** and suggest a means by which the dominant influences might be used for other accessing other diastereomers.



Scheme 1.

The model transformation used in the present study is shown in Scheme 2. The structures of enolate **7** and the alkylation transition states leading to exo product **8X** and endo product **8N** were considered. DFT calculations were performed at the M06-2X[7] level using the 6–31+G(d)[8] basis set. In order to account for solvation effects, the SMD solvation model[9] for THF was employed during geometry optimizations (see ESI for more details).[10] A few minor changes were made to simplify the calculations. First, the TBS ether present in **5** was changed to a TMS ether. Second, the MeI used by Mehta and co-workers was replaced with MeCl during the transition state analysis.[11] Because the original authors included HMPA during the reaction, enolate **7** was modelled as the free anion.



Scheme 2. The model reaction considered in this study.

The present study began by considering the conformational preference of enolate **7** (Figure 1a). It was reasoned that the bicyclo[2.2.1]heptene ring system would impart a good deal of rigidity to the system, but it was not clear if the TMS ether would occupy a pseudoaxial or pseudoequitorial position (**7A** or **7B**, respectively). Conformer **7A** was found to be about 5.5 kcal/mol higher in energy than **7B**. In the higher energy conformer, the bicyclic auxiliary must swing outward in order to accommodate the large axial silyl ether (Figure 1b). This was demonstrated by measuring the distance between the enolate α-carbon and the proximal alkene carbon of the auxiliary (dashed lines in Figure 1b).

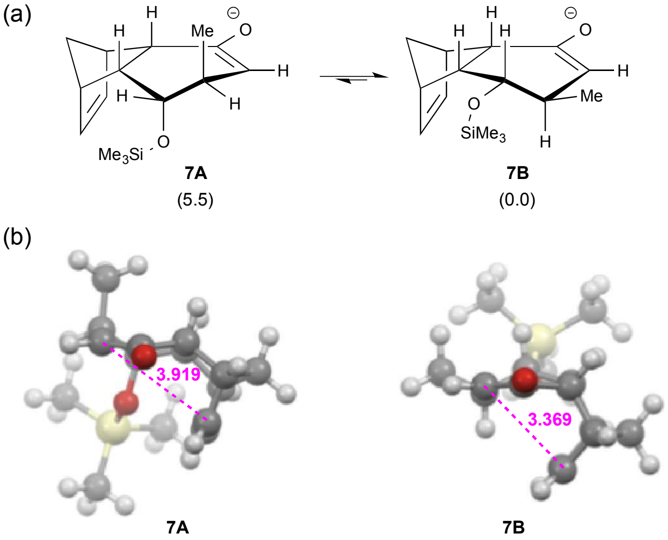


Figure 1. (a) The two enolate conformers considered. Values in parenthesis are relative energies (kcal/mol) calculated by M06-2X. (b) End view of the calculated structures down the enolate C–O bond. Distance measurements (in Å) are represented by dashed lines.

A qualitative assessment of the steric environment of the two enolates was made by examining the space filling model of the two conformers (Figure S1 and S2).† In conformer **7A**, both the methyl group and the silyl ether are in an axial position. This results in similar steric environments for both the endo and exo faces of the enolate. Interestingly, for conformer **7B**, the steric environment of the exo face was not as open as expected. This is due to partial blocking of the exo face by the alkyl groups of the silyl ether. Although the auxiliary did block a majority of the endo face, the coverage of the α-carbon was not complete and there appeared to be sufficient room for a small electrophile such as MeI.

The energy difference between conformers **7A** and **7B** is such that the equilibrium greatly favours **7B** in solution.[12] Nevertheless, transition structures were calculated for the endo and exo approach of MeCl to both conformers (**7A** and **7B**). The resulting structures and their energies (relative to **7B**) are presented in Figure 2. Gratifyingly, exo transition state **TS7BX** was found to be the lowest in energy. Also, the energy difference between **TS7BN** and **TS7BX** ($\Delta\Delta G^{\ddagger}$ = 2.1 kcal/mol) corresponds quite well with the high level of stereoselectivity observed by Mehta.[5,12] Although the two transition states leading from conformer **7A** were higher in energy than the others, it was interesting to see that endo transition state **TS7AN** is lower in energy than exo transition stare **TS7AX**.

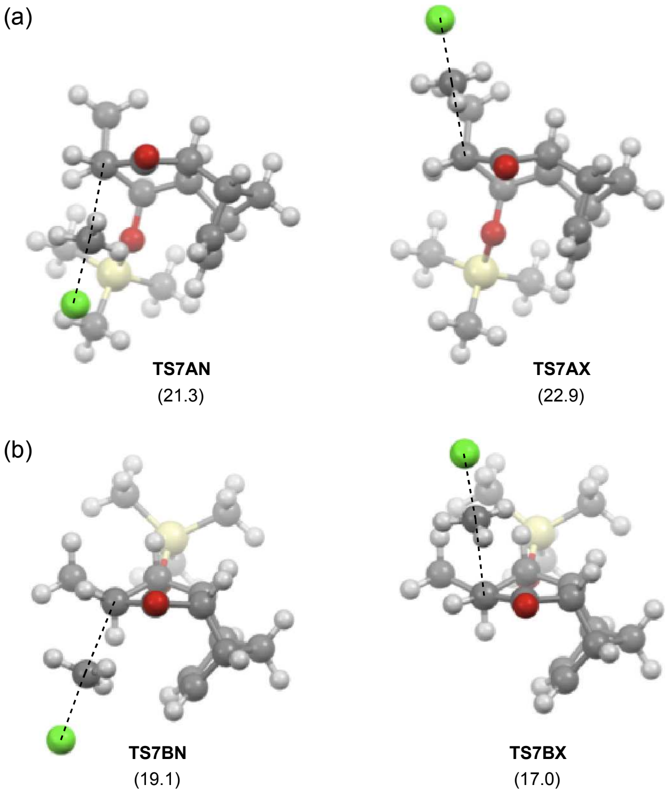


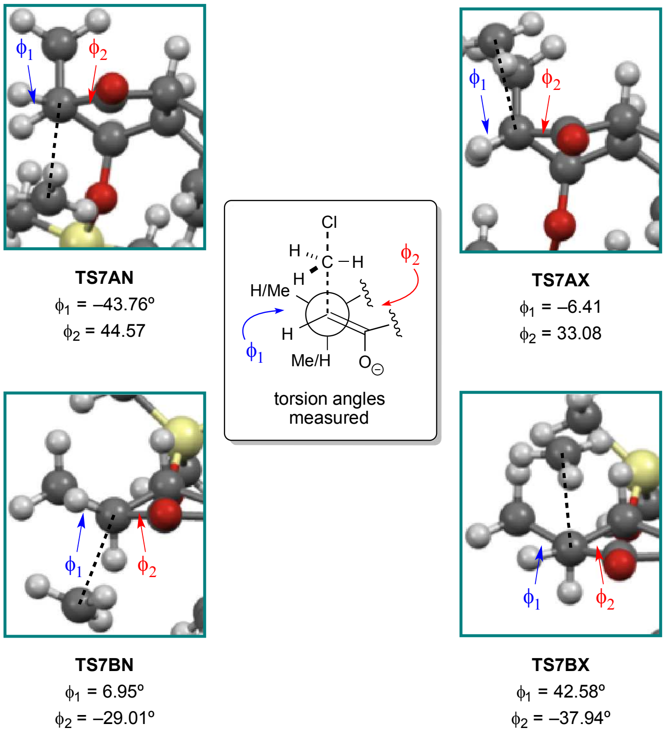
Figure 2. Calculated transition structures for the alkylation of enolate **7**. Values in parenthesis are energies (kcal/mol) relative to conformer **7B**. (a) Endo and exo approach of MeCl to conformer **7A**. (b) Endo and exo approach of MeCl to conformer **7A**. Dashed lines represent the reaction coordinate.

In order to assess the steric contribution to the energy differences observed in the calculated transition structures, we looked for potential H–H interactions between the electrophilic CH_3 group and the tricyclic enolate (Figure S3 and S4).† For **TS7BN**, three H–H interactions (2.183, 2.211, and 2.270 Å) were found to be shorter than the sum of the van der Waals radii.[13] With **TS7BX**, though, there are only two close H–H interactions (2.305 and 2.262 Å). **TS7BX** also has two H–H interactions (2.438 and 2.496 Å) that are slightly longer than the sum of the van der Waals radii. In contrast, with **TS7BN** all of the other H–H distances are longer than 2.6 Å. It should also be mentioned that there is an H–O interaction that is shorter in **TS7BX** than in **TS7BN** (2.374 and 2.478 Å, respectively). Altogether, it is difficult to conclude that one of these transition states is significantly more sterically crowded than the other.

Interestingly, the approach of MeCl in both **TS7AX** and **TS7AN** appears to be even less crowded. With **TS7AX**, the shortest measured H–H distances from the approaching CH_3 group are 2.351 and 2.404 Å. In **TS7AN**, all H–H distances are greater than 2.4 Å. By this measure, it would appear that the endo transition state leading from conformer **7A** is actually *less* sterically crowded than the exo transition state.

In the absence of a clear steric bias in any of the calculated transition structures, we looked for another explanation for the observed energy differences. Houk and co-works have advanced a “torsional steering” model to explain the stereoselectivity observed when a reagent approaches a π-system. Over the years, this model has been applied to several different types of reactions with great success,[14] though it can break down in cases with severe steric strain.[15] Previous work in our laboratory has shown that torsional steering can effectively override steric effects and cause a small electrophile, like MeI, to enter from a seemingly more hindered trajectory.[16]

Examination of the torsion angles contained in the four transition structures revealed some significant differences (Figure 3). Two measurements were made. The first (ϕ_1) was the torsion angle of the pseudoequitorial enolate H atom and the vicinal pseudoequitorial group (either an H or CH_3). The second (ϕ_2) measurement was one of the torsion angles of the six membered ring. From these measurements it is clear that both **TS7BX** and **TS7AN** lead to a staggered arrangement of the relevant atoms, whereas **TS7BN** and **TS7AX** lead to an eclipsed arrangement. This is most clearly seen in the ϕ_1 measurements. It is also worth mentioning that **TS7AX**, the highest energy transition state, is the only one with an eclipsing interaction between the entering CH_3 group and the vicinal methyl group on the six membered ring.



TS7AN
ϕ_1 = –43.76°
ϕ_2 = 44.57

TS7AX
ϕ_1 = –6.41
ϕ_2 = 33.08

TS7BN
ϕ_1 = 6.95°
ϕ_2 = –29.01°

TS7BX
ϕ_1 = 42.58°
ϕ_2 = –37.94°

Figure 3. Torsion angle measurements of the four transition structures. Dashed lines represent the reaction coordinate.

Another curious observation came when comparing the torsion angles of **TS7AN** (ϕ_1: –43.76°, ϕ_2: 44.56°) and **TS7BX** (ϕ_1: 42.58°, ϕ_2: –37.94°). This data suggests that the higher energy transition state (**TS7AN**) actually experiences somewhat smaller torsional strain than the lower energy transition state (**TS7BX**). The situation becomes even more puzzling when the aforementioned through-space measurements are included, as **TS7AN** appears to also be less sterically crowded than **TS7BX** (compare Figures S3 and S4). The reason for this apparent dichotomy becomes clear when the energies for all of the relevant species are plotted together (Figure 4). When this is done it becomes apparent that **TS7BX** does indeed represent the low energy pathway to product. However, it is interesting to note that the $\Delta G^{\ddagger}$ (15.8 kcal/mol) between **7A** and its endo pathway (**TS7AN**) is actually smaller than the $\Delta G^{\ddagger}$ (17.0 kcal/mol) between **7B** and its exo pathway (**TS7BX**). This suggests that the observed exo selectivity is actually due to a combination of torsional steering in the alkylation transition state and the energetic preference for conformer **7B**.

Our finding that the conformational preference of enolate **7** has a role in the overall stereoselectivity has important implications with respect to future reaction and methodology development. According to the Curtin–Hammett principle,[17] if one were to change the system such that the energies of conformers **7A** and **7B** are brought closer together, but keep the $\Delta G^{\ddagger}$'s the same, then alkylation on the same face as the bicyclic auxiliary may be possible. Although this may be difficult to do with enolate **7**, derivatives of **7** with different substitution patterns may give rise to an energy profile that favors endo approach of an electrophile. In turn, this would allow access to diastereomers not currently available from Ogasawara–Takano-type ketones.[18]

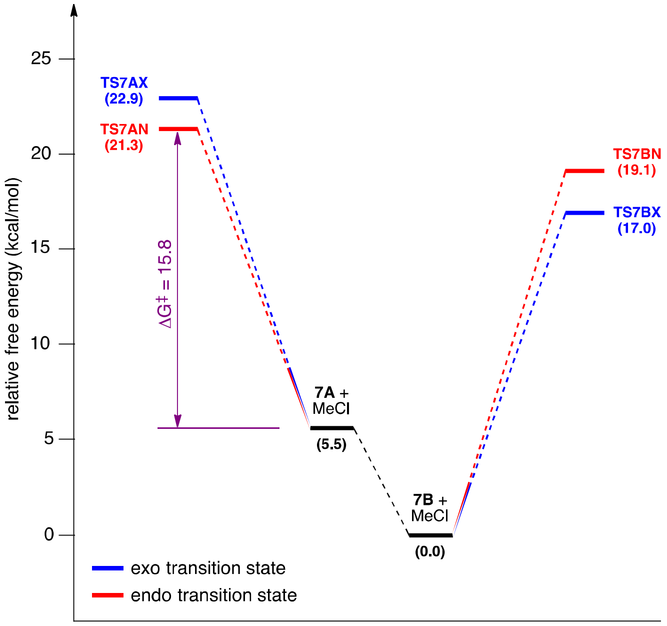


Figure 4. Relative free energy plot for all computed structures.

In conclusion, the computational results presented here refute the notion that steric interactions with the bicyclic auxiliary govern the stereoselectivity observed during the alkylation of ketone **5**.[19] Instead, the observed exo selectivity is due to a combination of torsional steering in the transition state and a significant energetic preference for one enolate conformer over the other. Work is underway to design a system that would take advantage of the Curtin-Hammett kinetics uncovered in this study. These efforts work will be reported in due course.

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† See supporting information.

§ In this manuscript, the terms "endo" and "exo" are being used to describe the face of the enone or enolate relative to the bicyclic auxiliary. The endo face (concave) is on the same side of the six membered ring as the auxiliary. The exo face (convex) is on the opposite side of the six membered ring as the auxiliary.

Electronic Supplementary Information (ESI) available: computational details, extra figures, and optimized geometries and energies of all computed species. See DOI: 10.1039/c000000x/

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18 Unpublished computational results from our lab suggest that it is possible to alter the relative energies of the relevant transition states and conformers in some analogues so that the alternative isomer is produced. Experimental verification will be reported in due course.

19 Performing calculations on the epoxidation of enone **4** is complicated by the protic environment and the need to properly account for protonation state and solvation (see: A. Capobianco, A. Russo, A. Lattanzi, A. Peluso, *Adv. Synth. Catal.* 2012, **354**, 2789; and P.-L. Lv, R.-X. Zhu, D.-J. Zhang, C.-G. Duan, and C.-B. Liu, *J. Phys. Chem. A*, 2012, **116**, 1251). However, preliminary investigations in our lab indicate that an endo approach of the nucleophile appears to be sterically accessible.