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Computational Analysis of the Stereochemical Outcome in the Imidazolidinone-Catalyzed Enantioselective (4 + 3)-Cycloaddition Reaction

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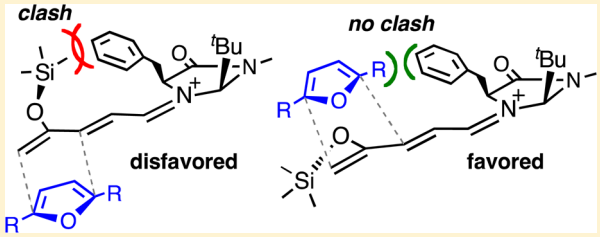
Supporting Information

ABSTRACT: Computations show why the catalytic, asymmetric (4 + 3)-cycloaddition reaction developed in the Harmata laboratories proceeds with facial selectivity opposite to that for models proposed for related catalyzed Diels−Alder reactions. Computations with M06-2X/6-311+G(d,p)//B3LYP/6-31G(d) show that iminium ions derived from MacMillan's chiral 2-*tert*-butyl-5-benzylimidazolidinone and siloxypentadienals undergo (4 + 3)-cycloadditions with furans preferentially on the more crowded face. Conformational reorganization of the benzyl group, to avoid intramolecular interaction with the silyl group, is responsible for differentiating the activation barriers of top- and bottom-face attack.

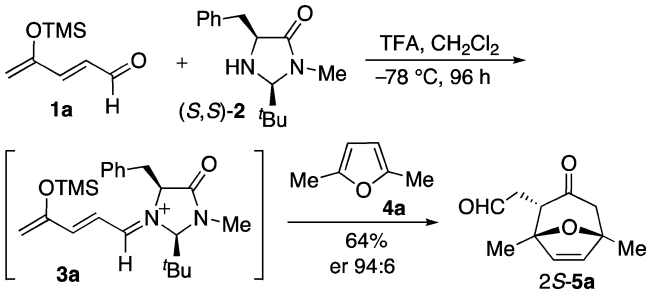


INTRODUCTION

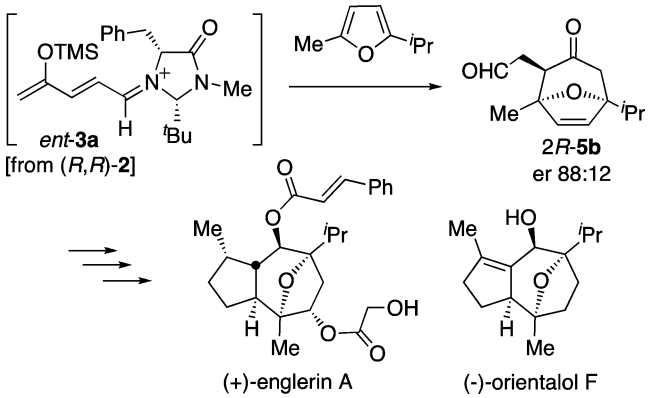
The chemistry of iminium ions derived from chiral secondary amines and unsaturated carbonyl systems constitutes one of the cornerstones of asymmetric organocatalysis and continues to reveal new discoveries regarding mechanism and enantioselectivity.[1] The Harmata laboratory reported the first asymmetric, organocatalytic (4 + 3)-cycloaddition reaction, which utilized a chiral imidazolidinone catalyst.[2] Thus, treatment of **1a** with the MacMillan catalyst[3] (*S*,*S*)-**2** in CH_2Cl_2 and trifluoroacetic acid at −78 °C afforded the cycloadduct **5a** as a single diastereomer in 94:6 er (Scheme 1). The enantiomer ratio was determined by HPLC analysis of a derivative of **5a**, but the absolute configuration was left unassigned at that time.

More recently, Sun, Lin, Xu, and co-workers used our methodology in the synthesis of (+)-englerin A and (−)-orientalol F (Scheme 2).[4,5] Prior to the determination of the absolute configuration of the cycloadduct, both Sun, Lin, Xu, et al.[4] and the Harmata group[2] anticipated that the mechanism of enantioselectivity would resemble the model that MacMillan had earlier proposed for imidazolidinone-catalyzed enantioselective Diels−Alder and Michael reactions onto α,β-unsaturated aldehydes or ketones.[3] The main features of MacMillan's model [i.e., crowding of the *syn* (top) face of the π-system by the benzyl group, favoring addition to the *anti* (bottom) face] were subsequently confirmed theoretically by

Scheme 1. Asymmetric Organocatalytic (4 + 3)-Cycloaddition[2]



Scheme 2. Application of Organocatalytic (4 + 3)-Cycloaddition in Natural Products Synthesis by Sun, Lin, Xu, et al.[4,5]



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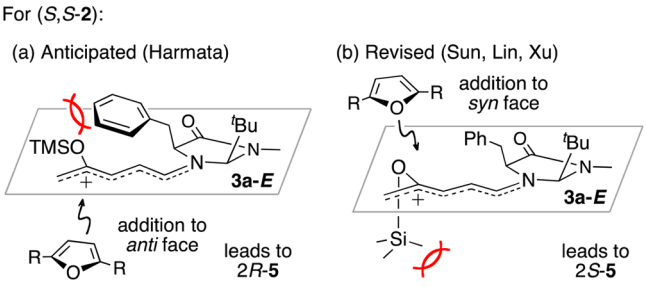
Houk.[6] As applied to the transition state for the (4 + 3)-cycloaddition (Scheme 3a), the benzyl and *t*-butyl groups

Scheme 3. Previously Proposed Mechanisms for the Enantioselective Organocatalytic (4 + 3)-Cycloaddition[2,4,5]



would crowd the *syn* face of the iminium ion **3a-*E***, possibly involving a $\pi-\pi$ interaction between Ph and the dienyliminium moiety. Addition of furan to the less crowded (*anti*) face of **3a-*E*** would lead to 2*R*-**5**. However, Sun et al. later deduced the absolute configuration of the (4 + 3)-cycloadduct by comparing the optical rotations of their synthetic orientalol F, and a synthetic precursor to englerin A, to those of authentic samples. They discovered that the major enantiomer of cycloadduct **5b** obtained using the *R,R* enantiomer of catalyst **2** was 2*R*-**5b**. Thus, in Harmata's cycloaddition (Scheme 1), the major enantiomer of cycloadduct obtained using (*S,S*)-**2** would be 2*S*-**5a**, rather than the anticipated 2*R*-**5a**.[4b,c,5,7] The counter-intuitive conclusion was that the diene reacts at the *syn* face of **3a**, despite the crowding from the benzyl and *t*-butyl groups.[5,8] Sun et al. proposed a revised mechanism (Scheme 3b) in which the silyl group lies out of the iminium plane and blocks the *anti* face of **3a-*E***. Selective addition to the *syn* face would furnish 2*S*-**5**.

Intrigued by this conclusion, and in the attempt to develop catalysts with higher selectivities, we embarked on a computational examination of the process to determine the factors responsible for enantioselectivity.

RESULTS AND DISCUSSION

The imidazolidinone-catalyzed (4 + 3)-cycloadditions of siloxy pentadienals **1** with furans were studied by means of density functional theory (DFT) calculations.[9] The computational procedure comprised geometry optimizations at the B3LYP/6-31G(d) level of theory,[10] followed by single-point energy calculations at the M06-2X/6-311+G(d,p) level[11] and SMD solvation energy computations[12] (B3LYP), from which free energies in dichloromethane were derived.

A conformational analysis of iminium ion **3a** indicated four low-energy isomers (Figure 1). The C=N bond can adopt either the *E* or *Z* configuration. The *E* isomer **3a-*E*(i)** is preferred by 0.2 kcal/mol ($\Delta\Delta G$) over the *Z* isomer **3a-*Z*(i)**. The *E*/*Z* preference is smaller than that of the iminium ion formed from (*S,S*)-**2** and crotonaldehyde (**6**, Figure 1), for which the *E* isomer has been reported[6a] to be 1.3 kcal/mol more stable than the *Z*. In **3a-*E*(i)** and **3a-*Z*(i)**, the bond connecting the benzyl group to the imidazolidinone is staggered, with Ph gauche to hydrogen and the dienyliminium chain. The same benzyl conformation was computed to be favored in **6-*E***[6a] and also was found crystallographically in the iminium ion derived from **2** and cinnamaldehyde.[13] Two other conformers of **3a-*E*** are predicted to be present under the experimental conditions. In **3a-*E*(ii)**, the bond connecting the Bn group to the imidazolidinone ring is close to eclipsed (dihedral PhCCH = 19°), while in **3a-*E*(iii)**, the Ph group is *syn* to the imidazolidinone ring. In this conformation, there is a steric clash between Ph and ^{t}Bu, which may be partially offset by a CH$-\pi$ interaction between Ph and one of the ^{t}Bu hydrogens (2.5 Å). In all conformers of **3a**, the siloxy group lies in the same plane as the conjugated dienyliminium cation,[14] with $SiMe_3$ *syn* to C=CH_2. Thus, the siloxy group does not block one face of the cation any more than the other in iminium ion **3a**.

Transition states for the (4 + 3)-cycloadditions of **3a** with furan were computed (Figure 2). Experimentally, the cycloaddition of **3a** with furan at 0 °C gave the *endo* cycloadduct 2*S*-

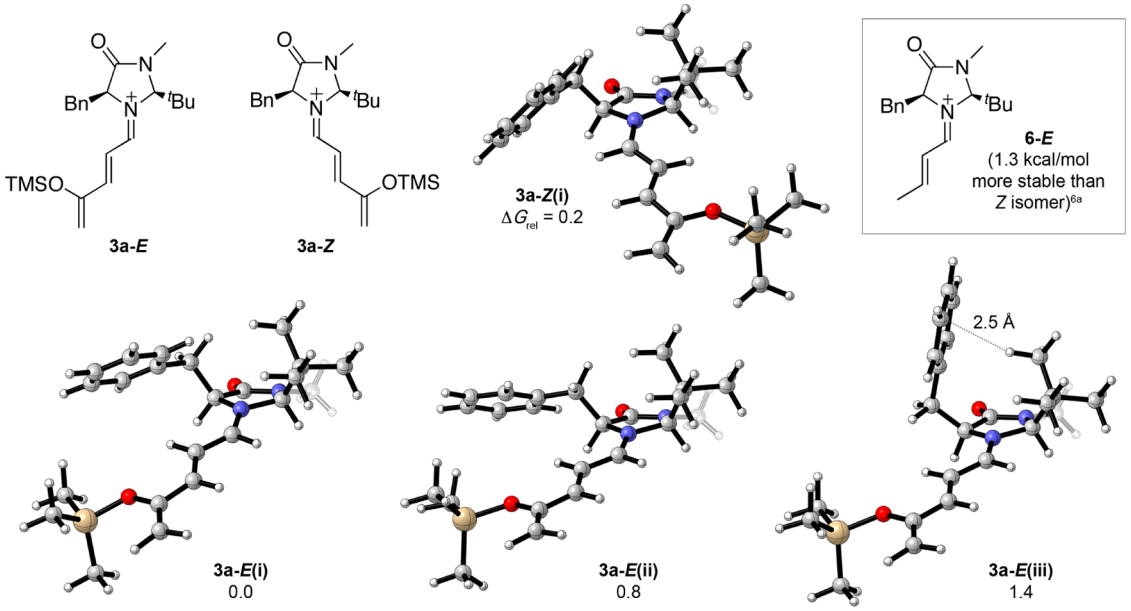


Figure 1. Low-energy conformers of iminium ions **3a-*Z*** and **3a-*E***. ΔG in CH_2Cl_2 (kcal/mol) given at the M06-2X/6-311+G(d,p)//B3LYP/6-31G(d) level of theory.

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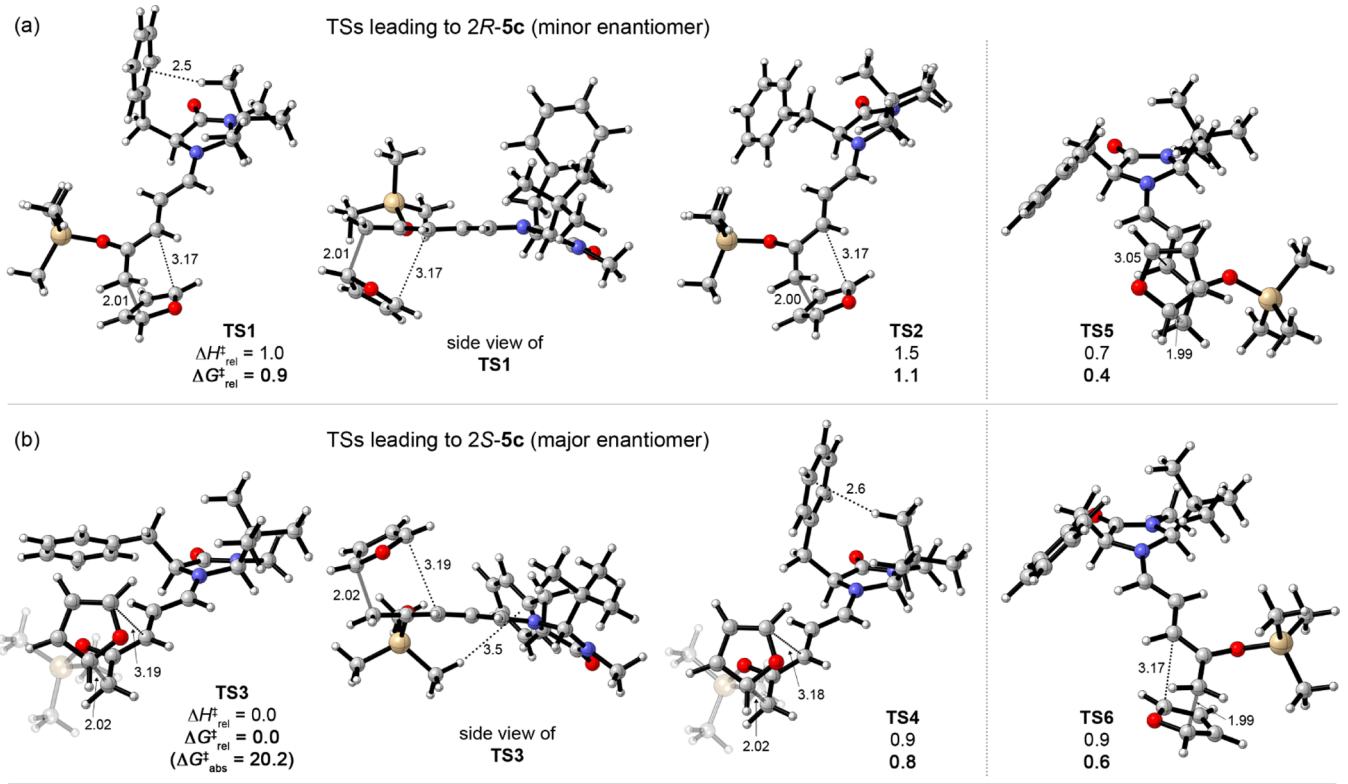

er of 2S-**5c**:
expt[2] 75:25
calcd 66:34 (Curtin–Hammett)
62:38 (non-Curtin–Hammett, from slowly-interconverting *E*/*Z* equilibrium mixture)
78:22 (*E* TSs only)
42:58 (*Z* TSs only)

(c) Distortion/Interaction Analysis

TS	$\Delta\Delta E^{\ddagger}$	$\Delta\Delta E_{dist}$(**3a**)	$\Delta\Delta E_{dist}$(furan)	$\Delta\Delta E_{int}$
TS1	1.2	1.2	0.5	–0.4
TS2	3.2	3.0	0.7	–0.5
TS3	0	0	0	0
TS4	1.2	1.4	0.1	–0.3

Figure 2. Transition states for (4 + 3)-cycloadditions of iminium ion **3a** with furan, leading to (a) 2*R*-**5c** and (b) 2*S*-**5c**. The figure shows top views of all six TSs and side views of **TS1** and **TS3**. All values of $\Delta G^{\ddagger}_{rel}$ are reported relative to **TS3**. (c) Distortion/interaction analysis of the *E* transition states. Distances in Å, energies in kcal/mol.

5c in 75:25 er.[2] Six low-energy *endo* transition states were located (**TS1**–**TS6**). Transition states **TS1**–**TS4** involve the *E* iminium ion, whereas **TS5** and **TS6** involve the *Z* iminium ion. In absolute terms, the *Z* transition states are 0.4–0.6 kcal/mol higher in energy than the lowest-energy *E* transition state (**TS3**). However, the role of the *Z* transition states in determining the enantioselectivity is difficult to ascertain, because the initial ratio of *E* and *Z* iminium ions and their rate of interconversion are not known. Four scenarios can be envisaged, as follows. (i) If the *E* and *Z* iminium ions interconvert rapidly, a Curtin–Hammett situation is established, and all six TSs would contribute to the overall reaction, giving a predicted er of 66:34 (2*S*:2*R*) at 0 °C. (ii) If the *E* and *Z* iminium ions are initially present in their equilibrium ratio (assuming ΔG = 0.2 kcal/mol, this would correspond to *E*/*Z* = 57:43) but the *E*/*Z* interconversion is slow with respect to cycloaddition, then the barriers for the *Z* TSs (**TS5** and **TS6**) must be computed relative to **3a**-*Z*(**i**) rather than to **3a**-*E*(**i**) and the contributions of the various TSs must be weighted according to the initial *E*/*Z* ratio, leading to a predicted er of 62:38. (iii) If the condensation of aldehyde **1a** and imidazolidinone (*S*,*S*)-**2** shows a kinetic selectivity favoring the *E* iminium ion, and *E*/*Z* interconversion is slow, then the contributions of **TS5** and **TS6** would be limited, leading to a predicted er as high as 78:22. (iv) If, on the other hand, the condensation of **1a** with (*S*,*S*)-**2** kinetically favors the *Z* iminium ion, then the contributions of **TS1**–**TS4** would decrease compared to **TS5** and **TS6**, leading to a predicted er of 42:58 in the limiting case of reaction solely involving the *Z* iminium ion. The poor agreement between the latter result and experiment suggests that scenario (iv) does not occur. It is not possible to discriminate between scenarios (i)–(iii), because the predicted ers for these three scenarios are relatively close and are in good agreement with experiment. It appears likely, however, that some involvement of *Z* transition states may occur, and this would slightly reduce the enantioselectivity.[15]

The absolute value of $\Delta G^{\ddagger}$ for addition of furan to **3a**-*E*(**i**) via **TS3** is computed to be 20.2 kcal/mol.[16] We also computed transition states for *exo* addition onto **3a**-*E* (see the Supporting Information). *Exo* addition transition states lie ≥ 3.6 kcal/mol higher in energy than *endo* addition, consistent with the experimental obtention of complete *endo*/*exo* diastereoselectivity.

In **TS1** and **TS2**, furan adds to the *anti* face of **3a**-*E*, leading to the 2*R* enantiomer of cycloadduct. In **TS3** and **TS4**, addition takes place at the *syn* face, giving the 2*S* enantiomer. The cycloaddition is a stepwise process. The TSs for the first bond-forming step, involving bond formation between the iminium terminus and the diene, have "closed" arrangements,[6a] reminiscent of a concerted TS. The interaction between C3 of the iminium ion and furan provides electrostatic stabilization. Similar closed TS geometries have previously been observed in

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DFT calculations on (4 + 3)-cycloadditions involving alkoxy siloxyallyl cations,[17] and in the imidazolidinone-catalyzed additions of pyrroles to α,β-unsaturated aldehydes.[6a]

The selectivity for addition to the *syn* face of **3a**-*E* can be understood through conformational changes within the iminium cation that occur upon interaction with the diene. In favored **TS3**, the diene lies far enough away (≥4 Å) from the Bn and ^{t}Bu groups of the catalyst that it creates no steric clashes with these groups. To accommodate *syn*-face approach by furan, the $SiMe_3$ group deflects downward, out of the iminium plane (see side view in Figure 2). This conformational change can be accommodated without any significant reorganization of the Bn and ^{t}Bu groups on the catalyst. In addition, weak stabilization is derived from a CH−π interaction between the benzyl ring and one of the $SiMe_3$ protons (3.5 Å).[18]

In contrast, addition to the *anti* face of **3a**-*E* requires significant reorganization of the substituents on the imidazolidinone. To accommodate the approach by furan to the *anti* face of **3a**-*E*, the $SiMe_3$ group must rotate toward the *syn* face; however, this leads to steric clashing between $SiMe_3$ and the Bn group. Clashing can be alleviated by rotation of the Bn group into two alternative conformations: either a conformation where Ph clashes with ^{t}Bu (**TS1**, $\Delta\Delta G^{\ddagger}$ = 0.9 kcal/mol) or a conformation in which the π cloud lies close to one of the carbonyl oxygen lone pairs (**TS2**, 1.1 kcal/mol). Compared with **TS1** and **TS2**, the Bn group has undergone much less reorientation in **TS3**.[19] Moreover, in **TS3**, the separation between furan and the Bn and ^{t}Bu groups on the catalyst is ≥4 Å, which is sufficient to allow certain substituents to be incorporated at the furan 2-position without producing clashes. This is consistent with the experimental finding that a Me, Et, or Pr substituent at the furan 2-position did not decrease the enantioselectivity of cycloaddition; only a Ph substituent was found to cause a reduction in enantioselectivity.[2]

The favored TS for addition to the *Z* iminium ion (**TS6**) involves addition to the *syn* face, leading to a cycloadduct having the opposite absolute configuration from that obtained as the experimental major product. However, there are no significant differences between the degrees of steric crowding between the furan and the iminium ion upon addition to the *anti* face compared to the *syn* face, which leads to a very small difference in energies (0.2 kcal/mol) between the two *Z* transition states.

An analysis of the *E* transition-state energies in terms of the distortion energies[20] of the two components (iminium cation and furan) and the interaction between these components is shown in Figure 2c. The distortion/interaction analysis reveals that the activation energies of **TS1**−**TS4** mirror the distortion energies of iminium ion **3a**. Differences in the distortion energy of furan, and in the interaction energy between the reactants, are smaller. The analysis supports the primary role of the iminium conformation in determining the enantioselectivity of cycloaddition. The selectivity is determined not by the blocking effect of the substituents on the imidazolidinone *per se*, but by the conformational reorganization that these groups undergo when the $SiMe_3$ group deflects out of plane to accommodate the diene.[21]

The crucial role of the siloxy group in transmitting chiral information from the catalyst to the bond-forming site is demonstrated by replacement of the $OSiMe_3$ group of **3a** by OH (**3b**, Figure 3).[22] Transition states for (4 + 3)-cycloadditions of OH-substituted iminium ion **3b** with furan, proceeding via attack at the *anti or syn* face, are shown in Figure

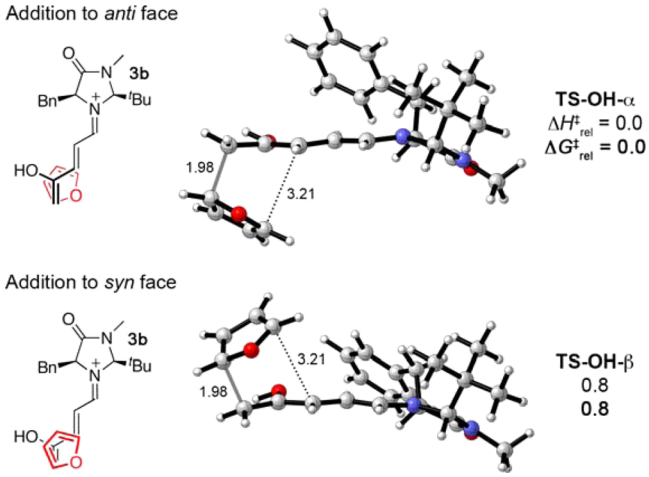

Figure 3. Transition states for (4 + 3)-cycloadditions of OH-substituted iminium ion **3b** with furan. Distances in Å, energies in kcal/mol.

3. In the absence of the bulky $SiMe_3$ group, *anti*-face attack does not require significant reorganization of the Bn group on the catalyst; the Ph ring lies gauche to hydrogen and the dienyliminium chain. The enantioselectivity is now reversed: *anti*-face attack is preferred by 0.8 kcal/mol over *syn*-face attack. The higher energy of the *syn*-face TS is likely due to a slightly higher degree of electrostatic repulsion between the Ph π-cloud and one of the carbonyl lone pairs.

Because the conformation of the siloxy group is important to enantioselectivity, we reasoned that restricting the conformations available to this group, by incorporating a substituent at the iminium terminus, may interfere with selectivity. Transition states for cycloaddition of the methyl-substituted iminium ion **3c** with furan are shown in Figure 4. Five low-energy transition states were located, three of which involve the *E* iminium ion ($\mathbf{TS1_{Me}}$, $\mathbf{TS3_{Me}}$, $\mathbf{TS4_{Me}}$) and two of which involve the *Z* iminium ion ($\mathbf{TS5_{Me}}$, $\mathbf{TS6_{Me}}$). These are analogous to transition states **TS1**,**3**−**6** for the unsubstituted iminium ion (Figure 2). The methyl group causes the O−Si bond to deflect a further 24−44° out of the plane of the π system, relative to the corresponding unsubstituted TSs, thereby moving the $SiMe_3$ group closer to the imidazolidinone. As in the unsubstituted case, addition to both the *E* and the *Z* iminium ions favors *syn* attack, and therefore, the *Z* transition states lower the computed enantioselectivity. The predicted er assuming rapid interconversion of the *E* and *Z* iminium ions is 54:46 (2*S*:2*R*), whereas the er assuming no involvement of the *Z* iminium ion is 76:24. These predictions mirror the experimentally observed decrease in enantioselectivity brought about by incorporation of the methyl substituent on the iminium ion.[2]

■ CONCLUSION

We have identified the origins of enantioselectivity in the imidazolidinone-catalyzed (4 + 3)-cycloaddition reaction. Unlike other additions to imidazolidinone-derived iminium ions,[6,23] the shielding of one face of the iminium ion by the Bn and ^{t}Bu groups on the imidazolidinone is not directly responsible for enantioselectivity in the (4 + 3)-cycloaddition. The site of addition is too remote from the catalyst for these groups to be able to block the approach of the diene. Instead, the $OSiMe_3$ group relays the chiral information. This occurs not at the level of the ground state of the reactive intermediate,[24]

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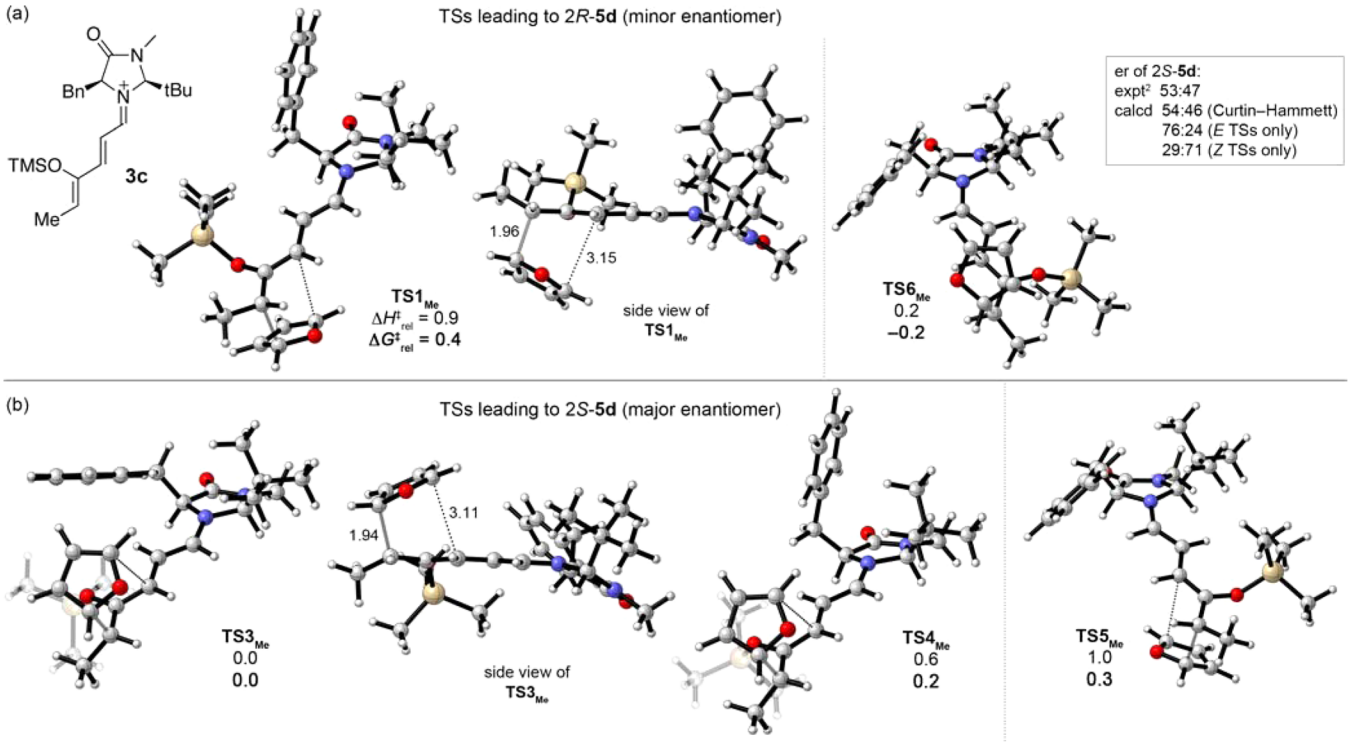
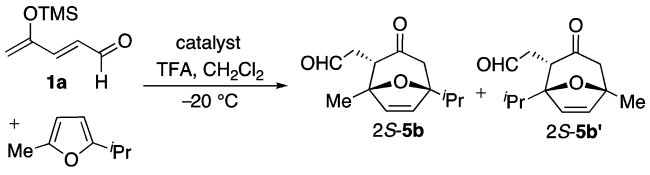


Figure 4. Transition states for (4 + 3)-cycloadditions of methyl-substituted iminium ion **3c** with furan, leading to (a) 2*R*-**5d** and (b) 2*S*-**5d**. The figure shows top views of all five TSs and side views of $\mathbf{TS1}_{Me}$ and $\mathbf{TS3}_{Me}$. All values of $\Delta G^{\ddagger}_{rel}$ are reported relative to $\mathbf{TS3}_{Me}$. Distances in Å, energies in kcal/mol.

but in the transition state. The TS energies are differentiated by the degree of crowding experienced by $SiMe_3$ as it moves out of plane to accommodate the diene. A related mechanism of chirality transfer was proposed by Santos and co-workers for Diels–Alder reactions of α,β-unsaturated *N*-acyloxazolidinones;[25] in that case, chiral information from the auxiliary was transferred to the bond-forming site by interactions between the auxiliary and the achiral Lewis acid catalyst. Imidazolidinone (*S*,*S*)-**2** appears to be a well-engineered first choice of catalyst for the (4 + 3)-cycloaddition. The Bn and ^{t}Bu groups together create a distinct conformational preference that would be lost if either of these groups were changed to a less bulky group. Consistent with this, Sun et al. found[5] that imidazolidinone (*S*,*S*)-**7** (Scheme 4) afforded similar levels of enantioselectivity to (*S*,*S*)-**2** in the (4 + 3)-cycloaddition, while (*S*)-**8** was not an effective catalyst and gave a low yield of product. Building such effects into catalysts designed for enantioselective cycloadditions is an ongoing goal of our research.

Scheme 4. Enantioselectivities Obtained by Sun et al. with Different Imidazolidinone Catalysts in the Organocatalytic Asymmetric (4 + 3)-Cycloaddition[5]



catalyst	(*S*,*S*)-**2**	(*S*,*S*)-**7**	(*S*)-**8**
yield (%)	37	31	<5
dr, 2*S*-**5b**:2*S*-**5b'**	2.7:1	2.7:1	
er, 2*S*-**5b** (%)	88:12	90:10	
er, 2*S*-**5b'** (%)	94:6	94:6	

THEORETICAL CALCULATIONS

Density functional theory calculations were performed using the Gaussian 09 software.[9] Geometries were optimized in the gas phase at the B3LYP/6-31G(d) level of theory.[10] The nature of each stationary point (local minimum or first-order saddle point) was determined from vibrational frequency calculations at this level; the frequency calculations were also used to compute zero-point energies and thermochemical corrections. Errors in computed entropies, introduced by the treatment of low frequency modes as harmonic motions, were minimized by use of Truhlar's approximation,[26] in which all harmonic frequencies below 100 cm^{-1} were raised to exactly 100 cm^{-1} before evaluation of the vibrational component of the thermal contribution to entropy. Solvation energies in dichloromethane were computed from single-point calculations at the B3LYP/6-31G(d) level of theory with the SMD[12] continuum model. Single-point energy computations were performed at the M06-2X/6-311+G(d,p) level of theory[11] in the gas phase on the B3LYP geometries. Free energies in solution (298.15 K, 1 mol/L) were calculated by adding the B3LYP solvation energy, zero-point energy, and thermochemical corrections to the M06-2X single-point energy. Energies are reported in kcal/mol; distances are reported in angstroms.

The effect of solvent on the geometries and energies of conformers of iminium ion **3a** was examined by reoptimizing each conformer in implicit dichloromethane at the B3LYP/6-31G(d) level. Use of solvent-optimized geometries led to prediction of a higher energy for the *Z* isomer compared to the *E* isomer (ΔG_{rel} = 1.5 kcal/mol). A similar comparison was performed using geometries optimized at the

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M06-2X/6-31G(d) level of theory in the gas phase; in this case, the *Z* isomer was less stable again (ΔG_{rel} = 2.1 kcal/mol). Despite these ground-state differences, reoptimization of **TS1**−**TS4** with M06-2X led to only small differences in the relative activation energies of the transition states compared with those in Figure 2; for example, the predicted er (77:23) using M06-2X geometries was almost identical to that obtained using B3LYP geometries (75:25). Further details of methodology and selectivities predicted by different levels of theory are provided in the Supporting Information.

■ ASSOCIATED CONTENT

Supporting Information

Computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(7) Sun, Lin, Xu, et al. utilized the *R*,*R* enantiomer of **2** (refs 3 and 4), whereas we used the *S*,*S* enantiomer (ref 2). Thus, the cycloadducts obtained by Sun, Lin, Xu, et al. have the opposite absolute stereochemistry to ours.

(8) (a) In a recent communication, Grošelj and co-workers reported a related imidazolidinone-catalyzed reaction in which an unexpected reversal of enantioselectivity was brought about by fluorination of one of the substituents on the imidazolidinone. Grošelj, U.; Podlipnik, Č.; Bezenšek, J.; Svete, J.; Stanovnik, B.; Seebach, D. *Helv. Chim. Acta* **2013**, *96*, 1815−1821. (b) Other addition reactions that have shown unexpected facial selectivity include the (4 + 3)-cycloadditions of oxazolidinone-substituted oxyallyls. See: Krenske, E. H.; Houk, K. N.; Lohse, A. G.; Antoline, J. E.; Hsung, R. P. *Chem. Sci.* **2010**, *1*, 387−392. (c) Antoline, J. E.; Krenske, E. H.; Lohse, A. G.; Houk, K. N.; Hsung, R. P. *J. Am. Chem. Soc.* **2011**, *133*, 14443−14451.

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(15) A detailed experimental and theoretical investigation of *E*/*Z* isomerization of iminium ions derived from chiral secondary amines (including imidazolidinones) and α,β-unsaturated aldehydes was reported by Seebach, Gilmour, Ebert, and co-workers. These authors showed that: (i) at equilibrium, solutions of these iminium salts typically contain small percentages of the *Z* isomer, along with the (major) *E* form (e.g., *E*/*Z* = 95:5 for the iminium ion derived from [H**2**]PF_6 and cinnamaldehyde); (ii) in certain cases, the *Z* isomer represents the kinetic product of the condensation of ammonium salt with aldehyde, and thus the *E*/*Z* ratios of iminium ions formed at low conversion may be smaller than the equilibrium *E*/*Z* ratio; and (iii) *E*/*Z* equilibration takes place at ambient temperature in typical solvents. These authors considered a variety of possible *E*/*Z* isomerization mechanisms and discussed the implications of *E*/*Z* equilibria for the stereoselectivity of organocatalytic additions to α,β-unsaturated aldehydes. See: Seebach, D.; Gilmour, R.; Grošelj, U.; Deniau, G.; Sparr, C.; Ebert, M.-O.; Beck, A. K.; McCusker, L. B.; Šišak, D.; Uchimaru, T. *Helv. Chim. Acta* **2010**, *93*, 603−634.

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