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Origin of Stereoselectivity in the Imidazolidinone-Catalyzed Reductions of Cyclic α,β-Unsaturated Ketones

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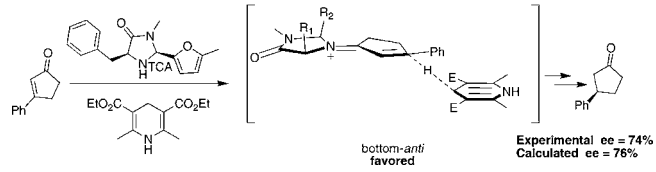
ABSTRACT



The organocatalytic transfer hydrogenation reactions of 3-phenyl-2-cyclopentenone with imidazolidinone catalysts are evaluated using the hybrid density functional (B3LYP/6-31G(d)) theory. The origin of the preference for the (*E*) iminium transition state is determined, and the stereoselectivity of hydride transfer is investigated.

Organocatalyzed asymmetric transfer hydrogenations have been successfully employed in reduction of C═O, C═N, and C═C containing organic compounds using Hantzsch[1] esters as the hydride source.[2] Recently, the groups of MacMillan[3] and List[4] reported the reduction of α,β-unsaturated cyclic ketones using the valine ester phosphate salts and the imidazolidinone salts as catalysts.

The furyl imidazolidinone catalyst **3**, a catalyst that previously enabled Diels−Alder reactions with cyclic enones,[5] gave excellent yields, 57−96%, with moderate enantiocontrol, 74−91%, in hydrogenations of a variety of β-substituted α,β-unsaturated cyclic enones (Figure 1). The amine catalysts **1** and **2**, which were previously shown to be efficient in hydrogenations of aldehydes,[6] yielded poor results, 0% and 5% yields, respectively, and exhibited low or no enantiocontrol with α,β-unsaturated cyclic ketones. The enantioselectivity was explained by the condensation of the enone **4** with **3** to form the (*E*) iminium ion intermediate rather than the (*Z*) intermediate (Scheme 1). Subsequent hydride attack by the Hantzsch ester **5** from the less hindered *si* ("bottom") face leads to the observed major product.

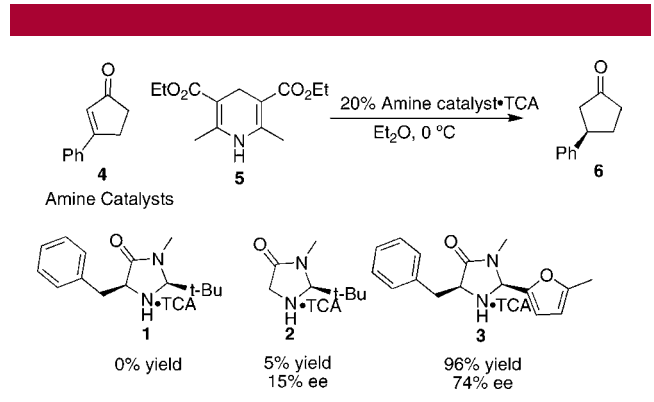


Figure 1. Experimental results from the reaction of 3-phenyl-2-cyclopentenone with imidazolidinone catalysts and Hantzsch ester **5**.[4]

(1) Hantzsch, A. *Justus Liebigs Ann. Chem.* **1882**, *215*, 1.
(2) (a) You, S. *Chem. Asian J.* **2007**, *2*, 820. (b) Adolfsson, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 3340. (c) Ouellet, S. G.; Walji, A. M.; MacMillan, D. W. C. *Acc. Chem. Res.* **2007**, *40*, 1327.
(3) Tuttle, J. B.; Ouellet, S. G.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 12662.
(4) Martin, N. J. A.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368.
(5) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458.
(6) Yang, J. W.; Fonseca, M. T. H.; Vignola, N.; List, B. *Angew. Chem., Int. Ed.* **2004**, *44*, 108. Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32.

10.1021/ol901586t CCC: $40.75
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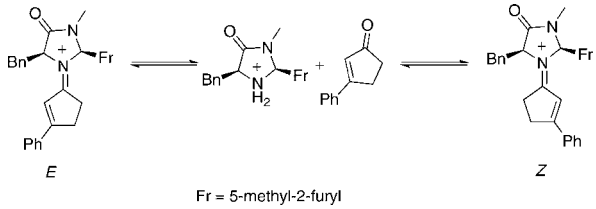
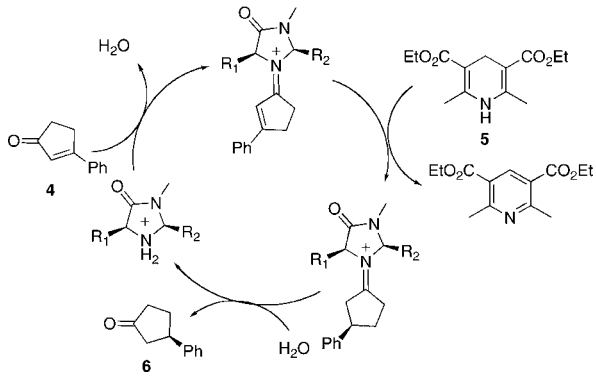
Scheme 1



We have undertaken a detailed DFT study to provide a more quantitative explanation of observed enantioselectivity. Quantum mechanical calculations were carried out with density functional theory, B3LYP,[7] with the 6-31G(d)[8] basis set, implemented in Gaussian 03,[9] which our group has shown to be effective in explaining stereoselectivities of various organic reactions.[10]

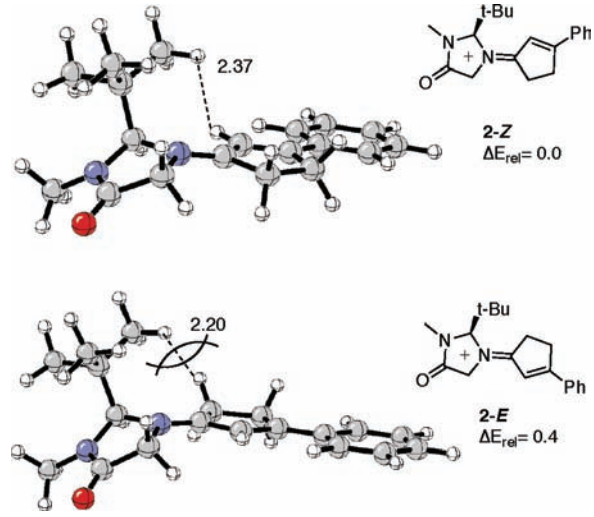
Scheme 2



Organocatalyzed hydrogenation proceeds as shown in Scheme 2 by reversible formation of iminium ion intermediates, hydride transfer from Hantzsch's ester to the highly reactive iminum intermediate, and hydrolysis.

Condensation between 3-phenyl-2-cyclopentenone and **2** leads to the reversible formation of **2-*E*** and **2-*Z*** iminium intermediates. Calculations show a 0.4 kcal/mol preference for **2-*Z***, which avoids a steric repulsion between the methylene group of the cyclopentenone ring and the *t*-butyl group of the catalyst (Scheme 3). A shorter distance, 2.20 Å, is observed between the *t*-butyl group and the methylene of the substrate's ring in the **2-*E*** iminium intermediate.[11] While only one (*E*) and one (*Z*) iminium conformer were found from **2**, several are expected to be formed from **3**.[12] A large number of possible conformers from furyl rotation about the $C_\alpha-C_{furyl}$ bond and phenyl rotation about the $C_\alpha-C_{phenyl}$ bond were considered in the search for iminium ion intermediates formed from **3** (Figure 2). The eclipsed −120°, rather than staggered 180° conformer, was found as noted earlier.[10c,12]

Scheme 3



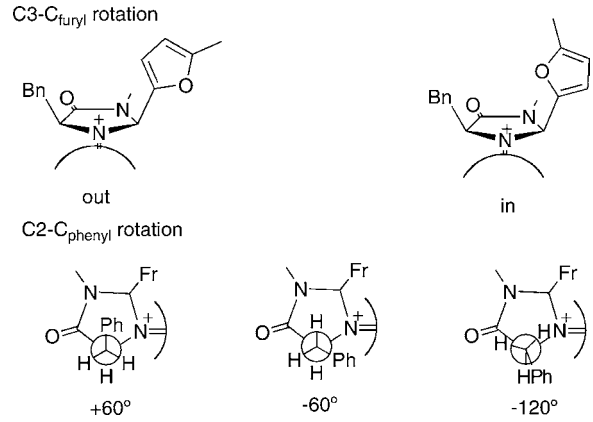


Figure 2. Iminium conformers of **3-*E*** and **3-*Z*** iminium intermediates.

Both (*E*) and (*Z*) iminium ions prefer the staggered conformations, **3-*E*-f**, **3-*E*-b**, **3-*Z*-f**, and **3-*Z*-b** as shown in Table 1. These four conformers account for 86% of the total at 25 °C and 84% at 0 °C. The (*in*, −60°) conformations

(7) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B.* **1988**, *37*, 785.

(8) (a) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971**, *54*, 724. (b) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257. (c) Hariharan, P. C.; Pople, J. A. *Theor. Chem. Acta* **1973**, *28*, 213.

(9) Frisch, M. J. *Gaussian 03*, revision C.02; Gaussian, Inc.: Wallingford CT, 2004 (For full reference, see Supporting Information).

(10) See, for example: (a) Um, J. M.; Houk, K. N.; Phillips, A. J. *Org. Lett.* **2008**, *10*, 3769. (b) Iafe, R.; Houk, K. N. *Org. Lett.* **2006**, *8* (16), 3469. (c) Gordillo, R.; Carter, J.; Houk, K. N. *Adv. Synth. Catal.* **2004**, *346*, 1175.

(11) The X-ray structures of the iminium ion intermediate derived from cinnamaldehyde and **2** are available. (a) Groselj, U.; Badine, D. M.; Schweizer, W. B.; Beck, A. K.; Seebach, D. *Helv. Chim. Acta* **2008**, *91*, 1999. (b) Schweizer, W. B.; Ebert, M.; Seebach, D. K. *Helv. Chim. Acta* **2009**, *92*, 1.

(12) For a detailed DFT study on conformers with **3** and cinnamaldehyde. Gordillo, R.; Houk, K. N. *J. Am. Chem. Soc.* **2006**, *128*, 3543.

Table 1. Conformers of **3-*E*** and **3-*Z*** Iminium Ion Intemediates Formed from Amine **3** and Enone **4**[a]

iminium ion	conformer	E_{rel} (kcal/mol)	% at 25 °C	% at 0 °C
3-*E*	**3-*E*-a**	2.1	1.0	1.3
	3-*E*-b	1.0	8.8	9.4
	3-*E*-c	1.7	2.7	3.2
	3-*E*-d	3.3	0.2	0.2
	3-*E*-e	1.0	7.9	8.6
	3-*E*-f	0.0	52.7	48.8
3-*Z*	**3-*Z*-a**	2.8	0.2	0.3
	3-*Z*-b	1.1	6.3	7.0
	3-*Z*-c	2.1	1.5	1.9
	3-*Z*-d	3.7	0.1	0.1
	3-*Z*-e	2.3	0.6	0.9
	3-*Z*-f	0.5	18.1	18.4

[a] Gas phase percentages of each structure are given at 25 and 0 °C.

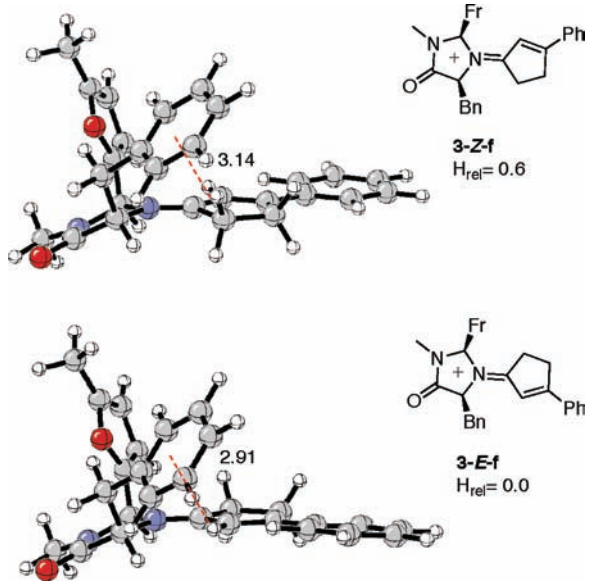


Figure 3. Iminium intermediates via **3**. Relative enthalpies of formation are in kcal/mol. Bond distances are in Å.

3-*E*-f and **3-*Z*-f** are found to be the most stable conformers. This conformational preference is hypothesized to be stabilized by a weak CH···O attractive interaction between the furyl oxygen and the CH_2 of the benzyl group and by a CH···π interaction[13] between the electron-rich phenyl group and the α-methylene of the iminium, with CH−π distances of 3.14 and 2.91 Å (Figure 3). The highest-energy iminium ions, **3-*E*-d** and **3-*Z*-d**, have the furyl oxygen and the phenyl ring facing each other causing an electrostatic repulsion between the oxygen and the phenyl ring leading to a destabilization of up to 3.7 kcal/mol. A Boltzmann distribution calculation using all conformers listed in Table 1 revealed a **3*E*:3*Z*** ratio

(13) *The CH/π Interaction: Evidence, Nature, and Consequences*; Nishio, M., Umezawa, H. Y., Eds.; Wiley-VCH: New York, 1998.

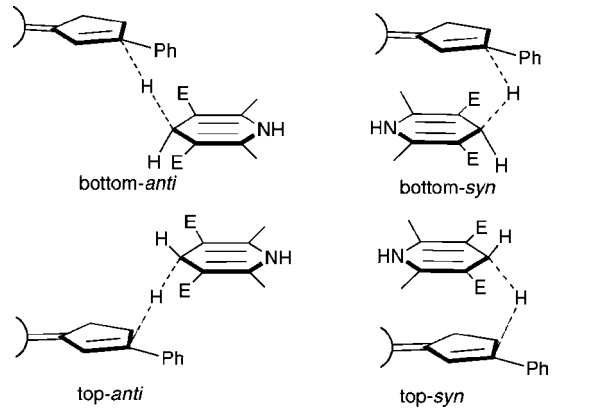


Figure 4. Proposed hydride attack transition structures.

of 78:22 in the gas phase,[14] consistent with the higher, 74% ee, enantioselectivity observed by MacMillan et al. using amine **3**.

Four possible modes of attack by Hantzsch ester **5** on the iminium ion intermediates were considered (Figure 4).[15] In all the transition structures, steric effects dominate the mode of hydride attack. Hydride transfer on the iminium derived from **2** is energetically favored when **5** attacks *anti* from the less hindered ("bottom") face (entries 1 and 5 in Table 2). The low energy implies that both pathways are accessible. Hydride attack on the more hindered top face of the (*Z*) intermediate, entry 8, is only 0.1 kcal/mol higher in energy than attack on the bottom face, entry 5. The accessibility of the top face is achieved by attacking *anti* to the iminium ion and thus avoiding steric hindrance with the *t*-butyl group. The (top-*syn*) attack, entries 3 and 7, is the most energetically disfavored due to the close proximity of **5** to the *tert*-butyl group.

Table 2. Hydride Attack Transition Structures on **2-*E*** and **2-*Z***

entry	iminium ion	transition state	E_{rel} (kcal/mol)	% at 0 °C	product
1	**2-*E***	bottom-*anti*	0.0	38.6	*R*
2		bottom-*syn*	1.6	1.9	*R*
3		top-*syn*	5.1	0.0	*S*
4		top-*anti*	0.8	8.4	*S*
5	**2-*Z***	bottom-*anti*	0.2	27.4	*S*
6		bottom-*syn*	3.7	0.0	*S*
7		top-*syn*	6.0	0.0	*R*
8		top-*anti*	0.3	23.7	*R*

The low activation energy difference between the bottom and top face attacks will lead to the relatively equal

(14) Single-point calculations on iminium ion intermediates at the B3LYP/6-311++G(d,p) revealed similar *E*/*Z* ratio of 62:38. A similar ratio, 66:34, was calculated for the iminium ions formed from the reaction from **3** and 3-methyl-2-cyclopentenone at the B3LYP/6-31G(d) level.

(15) Wu, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 2226.

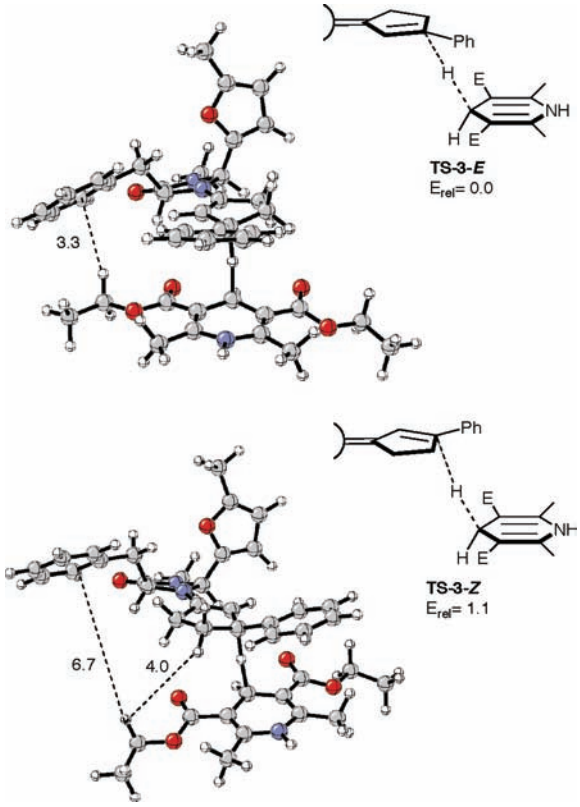


Figure 5. Hydride attack transition structures by **5** into **3-*E*** and **3-*Z***. Relative activation energies are in kcal/mol.

populations of both *R* and *S* products. Low enantioselectivity, 15% ee, is found experimentally. Due to the expense of calculations, only the lowest energy mode of attack (bottom-*anti*) was considered for transition state searching with **3-*E*** and **3-Z**.

Hantzsch ester (bottom-*anti*) attack on the (*E*) iminium, **TS-3-*E***, is found to be favored by 1.1 kcal/mol over the attack on the (*Z*) iminium, **TS-3-*Z*** (Figure 5).[16] The energy difference between the two iminium ions, **3-*E*-f** and **3-*Z*-f**, increased upon hydride attack from 0.5 to 1.1 kcal/mol. The small difference in activation energies suggests that both pathways are accessible and will yield both *R* and *S* products. However, the 1.1 kcal/mol preference for hydrogenation through the (*E*) iminium ion intermediate will yield an *S*:*R* of 76% ee at 0 °C, in agreement with experimental data, 74% ee.

DFT calculations explain the stereoselectivity in hydrogenation of α,*β*-unsaturated cyclic ketones via MacMillan's imidazolidinone catalysts. Only one face of each iminium intermediate is accessible to attack by the hydride donor. The transition state for attack on the (*E*) iminium is formed, in part, due to the inherently greater stability of the (*E*) iminium. Current efforts are underway to design a more enantioselective imidazolidinone catalyst.

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Supporting Information Available: Cartesian coordinates and energies of all reported structures and full reference of 9. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Calculated hydride attack transition state structures for the reaction with 3-methyl-2-cyclopentenone imininium intermediate and Hantzsch ester **5** revealed a 0.8 kcal/mol reference for hydride attack on the (*E*) iminium ion. This result is consistent with experimental data which show a preference for the *S* product derived upon hydride attack by the *t*-butyl-substituted Hantzsch ester into the (*E*) iminium ion.