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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 Hantzsch¹ esters as the hydride source.² Recently, the groups of MacMillan³ and List⁴ 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.

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 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

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Supporting Information Available: Cartesian coordinates and energies of all reported structures and full reference of⁹. This material is available free of charge via the Internet at <http://pubs.acs>.

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 iminium 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 was found from **2**, several are expected to be formed from **3**.¹² A large number of possible conformers from furyl rotation about the C_α-C_{furyl} bond and phenyl rotation about the C_α-C_{phenyl} bond were considered in the search for iminium ion intermediates formed from **3** (Figure 3). The eclipsed -120°, rather than staggered 180° conformer, was found as noted earlier.^{10c, 12}

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, **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 CH₂ of the benzyl group and by a CH...π interaction¹³ 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 4). 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 **3E:3Z** ratio of 78:22 in the gas phase¹⁴, 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 5).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.

The low activation energy difference between the bottom and top face attacks will lead to the relatively equal 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 6).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 a *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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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16. Calculated hydride attack transition state structures for the reaction with 3-methyl-2-cyclopentenone iminium 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 shows a preference for the *S* product derived upon hydride attack by the *t*-butyl substituted Hantzsch ester into the *E* iminium ion.

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

C3-C_{furyl} rotation

out

in

C2-C_{phenyl} rotation

+60°

-60°

-120°

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

Figure 4.
Iminium intermediates via **3**. Relative enthalpies of formation are in kcal/mol. Bond distances are in Ångstroms.

Figure 5.
Proposed hydride attack transition structures

Figure 6. Hydride attack transition structures by **5** into **3-E** and **3-Z**. Relative activation energies are in kcal/mol.

Scheme 1.

Scheme 2.

2-Z
 $^2 E_{\text{rel}} = 0.0$

2-E
 $^2 E_{\text{rel}} = 0.4$

Scheme 3.

Table 1

Conformers of **3-E** and **3-Z** iminium ion intermediates formed from amine **3** and enone **4**. Gas phase percentages of each structure are given at 25 °C and 0 °C.

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

Table 2

Hydride attack transition structures on **2-E** and **2-Z**.

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