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# Isotope Effects Reveal an Alternative Mechanism for 'Iminium-Ion' Catalysis

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### Isotope Effects Reveal an Alternative Mechanism for 'Iminium-Ion' Catalysis

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ABSTRACT: A novel mechanism for the epoxidation of enals with hydrogen peroxide catalyzed by diarylprolinol silyl ether supported by experimental <sup>13</sup>C kinetic isotope effects (KIEs) and density functional theory calculations is presented. Normal <sup>13</sup>C KIEs, measured on both the carbonyland  $\beta$ -carbon atoms of the enal, suggest participation of both carbon atoms in the rate-determining step. Calculations show that the widely accepted iminium-ion mechanism does not account for this experimental observation. A *syn*-S<sub>N</sub>2' substitution mechanism, that avoids formation of a discrete iminium-ion intermediate, emerges as the most likely mechanism based on agreement between experimental and predicted KIEs.

Enantioselective  $\beta$ -functionalization of  $\alpha$ ,  $\beta$ -unsaturated aldehydes (enals, 1) using chiral primary or secondary amines 3 is an important branch of asymmetric organocatalysis known as iminium-ion catalysis.<sup>1,2</sup> This mode of catalysis is also referred to as 'LUMO-lowering catalysis' since formation of a transient iminium-ion via condensation of 1 and 3 lowers the energy of the LUMO and facilitates nucleophilic attack at the β-carbon atom (Scheme 1).<sup>3</sup> Typical catalysts for this transformation are neutral amines, amine salts, or neutral amines with an acid additive.<sup>1,2,4</sup> The iminium-ion intermediate has been isolated and characterized in a number of reactions employing amine salt catalysts.5 However, the intermediacy of the iminiumion has not been established in reactions conducted with neutral amines as catalyst.<sup>6</sup> Recent observations by Hayashi et al. show that the presence versus absence of an acid cocatalyst can trigger different reaction pathways under otherwise identical conditions.7 The results presented in this communication provide the first experimental evidence for an alternative mechanism in β-functionalization reactions catalyzed by neutral amine catalysts.



Scheme 1. Organocatalytic reactions of enals facilitated via iminium-ion catalysis

In 2005, the enantioselective epoxidation of enals 1 catalyzed by a diarylprolinol silyl ether catalyst 3a with hydrogen peroxide 2a (as an oxidation agent) was developed (Scheme 2).8 The epoxidation reaction, performed in the absence of acid co-catalyst or amine salts, was proposed to proceed via transient formation of an iminium-ion intermediate 8 followed by attack of 2a on the activated  $\beta$ carbon (Scheme 2, outer catalytic cycle). The  $\alpha$ -carbon of the resulting enamine intermediate  $9^{\circ}H^{+}$  functions as a nucleophile to effect the ring closure and provide productiminium-ion species 10. Subsequent hydrolysis regenerates **3a** and delivers the epoxy aldehyde product **5**. Kinetic studies revealed that the reaction is autocatalytic when performed in a biphasic dichloromethane-water mixture.9 This observation was rationalized as being a result of the peroxyhydrate of the epoxy aldehyde 2a' functioning as a 'phase-transfer' nucleophile in the rate-determining βfunctionalization step.



**Scheme 2.** Conflicting mechanisms for the organocatalytic epoxidation of enals catalyzed by secondary amine

Computational studies by Santos suggest that the role of hydrogen peroxide **2a** is as a co-catalyst in multiple steps involved in iminium-ion formation.<sup>10</sup> Specifically, that **2a** acts as a proton shuttle in the conversion of **6** to **7**, and as a proton source that aids in the loss of hydroxide from **7** to form **8** (Scheme 2, inner catalytic cycle). Additionally, the authors assert the explicit involvement of a hydroxide ion to activate **2a** via deprotonation in the  $\beta$ -attack step (inner catalytic cycle, **8** to **9**). Based on the computed free energy profiles, it was proposed that conversion of **6** to **7** is the ratedetermining step (RDS) while conversion of **8** to **9** is the selectivity-determining step.<sup>10</sup>

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To obtain insight into the conflicting mechanistic picture that emerges from these two studies, we decided to investigate this reaction using a combination of experimental <sup>13</sup>C kinetic isotope effects (KIEs) and density functional theory calculations. We report herein, the results from these studies which strongly support a novel mechanism that proceeds via a concerted pathway (Scheme 2, pathway highlighted in green) and renders the key iminium-ion as an off-cycle intermediate in catalysis. We expect this mechanism, proceeding via a *syn*-S<sub>N</sub>2' transition state (TS) involving direct conversion of the carbinolamine intermediate 7 to the  $\beta$ -substituted enamine intermediate 9, to be relevant to other iminium-ion reactions – particularly ones that utilize neutral amines as catalysts.

Experimental KIEs: The reaction of pchlorocinnamaldehyde 1a (1, R = p-ClC<sub>6</sub>H<sub>4</sub>) and hydrogen peroxide 2a catalyzed by 3a was chosen for the determination of experimental <sup>13</sup>C KIEs at natural abundance. Four identical reactions were taken to  $72 \pm 2\%$ ,  $77 \pm 2\%$ ,  $68 \pm 2\%$ , and  $61 \pm 2\%$  conversion (of **1a**) as determined by NMR analysis of the reaction mixture after a reductive workup. The <sup>13</sup>C isotopic composition of reisolated 1a was compared to samples of 1a not subjected to the reaction conditions.<sup>11</sup> From the changes in relative isotopic composition and the fractional conversion, <sup>13</sup>C KIEs were determined in a standard way.12 The experimental KIEs for every position of 1a, as determined from a total of 25 such comparisons, are shown in Figure 1.



Figure 1 Experimental KIEs for the **3a** organocatalyzed epoxidation reaction of **1a**. Numbers in parenthesis represent the 95% confidence range of each experimental KIE as determined from 25 independent measurements.

Qualitative interpretation of experimental KIEs: There is a significant normal KIE (~2.5%) on the carbonyl-carbon (C1) and a smaller, yet non-unity KIE (~1.0%) on the  $\beta$ carbon (C3) of **1a** (Figure 1). All other carbon atoms in the molecule have near-unity KIEs. The qualitative interpretation of these experimental KIEs is that both carbon atoms (C1 and C3) are involved in the first irreversible step for **1a** in the catalytic cycle. This interpretation is *inconsistent* with the Santos mechanism<sup>10</sup> since the proposed RDS (conversion of **6** to **7**) does not involve C1 or C3. The experimental KIEs are also inconsistent with the "classical" iminium-ion mechanism, which involves only C3 in the RDS. In fact, there is no single step in either catalytic cycle that involves simultaneous bonding changes at C1 and C3. Our experimental KIE results cannot be rationalized on the basis of the current understanding of the reaction mechanism. This necessitates an exploration of alternative kinetic scenarios and/or reaction pathways that can account for the KIE measurements.

Computational methods: We modeled the reaction of 1a and 2a catalyzed by 3a (total 84 atoms) at the B3LYP/6-31G\* level of theory as implemented by Gaussian 09.13,14 Transition state (TS) structures were located for each step of the catalytic cycle in order to generate a free energy profile for the title reaction (see SI). A systematic conformational search was performed by varying the orientation of the chiral moiety of the catalyst, the pucker of the pyrrolidine ring, and the orientation of the peroxide for each of the TSs presented in the manuscript.<sup>15</sup> The predicted <sup>13</sup>C KIEs were derived from the scaled vibrational frequencies using the program ISOEFF98.<sup>16,17</sup> An infinite parabola tunneling correction was applied to all predicted KIEs.18 To evaluate the relative energetics of competing pathways, single point energies for the relevant TSs were obtained using B3LYP-D3(BJ)/6-311++G\*\* SMD (water).<sup>19</sup> The computed free energy barriers ( $\Delta G^{\ddagger}$ ) presented in the manuscript are extrapolated Gibbs free energies obtained by adding the free energy correction from the B3LYP/6-31G\* optimization to the high-level single point energy calculation. The  $\Delta G^{\ddagger}$ values in the manuscript were further evaluated using single point energy calculations performed using a total of 10 DFT methods<sup>20</sup> with both an SMD and PCM<sup>21</sup> solvent model – all methods gave identical trends in the relative  $\Delta G^{\ddagger}$  for the TSs described herein.15





Figure 2. Two possible mechanistic pathways that are qualitatively consistent with experimental  $^{13}C$  KIEs. The atoms highlighted in pink in the intermediates preceding the likely rate-determining step indicate positions where a normal  $^{13}C$  KIE is expected.

Our computational investigation of Scheme 2 revealed that all steps leading up to formation of the carbinolamine 7 along with all steps following formation of the enamine peroxide intermediate 9/9 H<sup>+</sup> are facile,<sup>15</sup> and likely not rate-determining.<sup>22</sup> Based on this finding and the qualitative interpretation of our KIEs, two main possibilities emerge as likely explanations: (*i*) formation of iminium-ion and the

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conjugate addition  $(A_{N'})$  of the nucleophile are co-rate-1 determining steps in the catalytic cycle (Figure 2a). In this 2 scenario, the exact magnitude of the observed <sup>13</sup>C KIEs at 3 the carbonyl- and the  $\beta$ -carbon are a weighted average 4 (based on relative energies) of the predicted KIEs of these 5 two TSs,<sup>23</sup> or (*ii*) formation of iminium-ion and the  $\beta$ -attack 6 occurs in a single irreversible step via an S<sub>N</sub>2' TS resulting 7 in normal KIEs on both the carbonyl- and the  $\beta$ -carbon 8 atoms (Figure 2b). Such a mechanism - that does not involve 9 the 'iminium-ion' intermediate in the 10 functionalization step - is without precedent in the 11 literature.24 12 13 14 15 16

1. Iminium-ion formation and conjugate addition are corate-determining steps: We modeled the step involving conversion of 7 to 8 mediated by a molecule of 2a as suggested by Santos (Figure 3, TS-iminium).<sup>10</sup> Examination of this TS reveals that 2a catalyzes the formation of 8 by protonating the hydroxide leaving group. The peroxide anion formed is stabilized by two CH-O-interactions with the moderately acidic CHs of the catalyst. Next, we identified the TS for the hydroxide mediated conjugate addition of 2a to 8 to form 9 (Figure 3, TS- $A_{N'}$ ). In this TS, deprotonation of **2a** by hydroxide results in an 'early' TS ( $r_{C-0} = 2.49$  Å) for the conjugate addition. All attempts to locate a TS corresponding to attack of 2a without activation by hydroxide (Scheme 2,  $8 \rightarrow 9^{\circ}H^{+}$ ) were unsuccessful suggesting that activation of 2a by deprotonation is a key feature of the  $A_{N'}$  step.



Figure 3. Transition structures for iminium-ion formation and conjugate addition  $(A_{N'})$  steps, as proposed by Santos, calculated for the reaction of 1a and 2a catalyzed by 3a. The free energy barriers are computed relative to intermediate 7. Predicted <sup>13</sup>C KIEs for both transition structures are also shown.

The  $\Delta G^{\ddagger}$  values for **TS-iminium** and **TS-A**<sub>N'</sub> are 7.8 and 19.3 kcal/mol, respectively, with respect to intermediate 7.

The significantly higher barrier for  $TS-A_{N'}$  relative to TSiminium suggests that these are likely not co-ratedetermining steps. Furthermore, if TS-iminium and TS-A<sub>N'</sub> are co-rate-determining, a weighted average of the predicted <sup>13</sup>C KIEs for these TSs (based on their relative energies) should be consistent with experiment. However, the predicted <sup>13</sup>C KIEs at C1 and C3 for both these TSs are lower than the corresponding experimental KIEs (Figure 3) suggesting that neither of these TSs nor any combination of these TSs (regardless of the computed relative energies) can account for the experimental <sup>13</sup>C KIEs. Based on these observations, we can eliminate co-rate-determining TSiminium and  $TS-A_{N'}$  as a viable mechanism for the reaction.

2. Nucleophilic substitution mechanism: We then turned our attention to the mechanism involving direct conversion of 7 to 9 via an S<sub>N</sub>2' transition state (TS-S<sub>N</sub>2', Figure 4). TS- $S_N 2'$  is characterized by a *syn* orientation of the nucleophile (2a) and the leaving group.<sup>25</sup> Additionally, there is a proton transfer event from 2a to 7 that occurs concomitantly with C1-O bond-cleavage and C3-O bond-formation. This proton transfer serves two key purposes: (i) facilitates the loss of hydroxide ion from 7 by making it a better leaving group, and (ii) activates 2a for a concomitant nucleophilic attack on 7.

The magnitude of the predicted <sup>13</sup>C KIE at C1 and C3 for  $TS-S_N2'$  is proportional to C–O bond order at these centers. The higher bond order of the breaking C1–O ( $r_{C1-O} = 2.24$ Å) results in a predicted KIE of 1.019 at C1 while the lower C3–O bond order ( $r_{C3-O} = 2.43$  Å) results in a predicted KIE of 1.008 at C3. Both these predicted values are in excellent agreement with experimental KIEs (Figure 4). Finally, the computed  $\Delta G^{\ddagger}$  for TS-S<sub>N</sub>2' is 15.3 kcal/mol (versus 7); this is 4.0 kcal/mol lower in energy relative to TS- $A_{N'}$  – a result that is consistent across all DFT methods explored.<sup>26</sup> This result, along with the excellent match of experimental and predicted KIEs, lends strong support for this unprecedented nucleophilic substitution mechanism for the βfunctionalization of enals.



Figure 4. Transition structure for the concerted pathway (7 to 9), calculated for the reaction of 1a and 2a catalyzed by 3a is shown. The free energy barrier is computed relative to intermediate 7. Predicted <sup>13</sup>C KIEs for this transition structure are also displayed.

It must be noted that conversion of 7 to 8 via TS-iminium occurs more rapidly than the conversion of 7 to 9 via TS- $S_N2'$ . However, the higher barrier for TS- $A_{N'}$  (relative to TS- $S_N2'$ ) forces 8 to revert to 7 and proceed via TS- $S_N2'$ . The *iminium-ion intermediate 8 is therefore proposed as an offcycle intermediate in the catalytic cycle*. Finally, the reaction selectivity was explored by calculating the *syn*- $S_N2'$ transition structure that delivers the opposite chirality at the  $\beta$ -carbon, TS- $S_N2'$ -ent (not shown) is 1.63 kcal/mol higher in energy that TS- $S_N2'$  – a difference that corresponds to 88% ee at room temperature. This is in reasonable agreement with the 98% ee observed experimentally for this reaction and lends support to TS- $S_N2'$  as the enantioselectivity-determining step.

In conclusion, the widely accepted conjugate addition mechanism, termed as 'iminium catalysis', is not applicable to the epoxidation of enals catalyzed by a neutral amine. An  $S_N 2'$  pathway is identified as the rate- and enantioselectivity determining step of this reaction. We expect this unprecedented mechanism to be applicable to a wide range of aminocatalytic  $\beta$ -functionalization reactions that are currently assumed to proceed via an iminium-ion intermediate.

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**Supporting Information Available:** Experimental procedures, coordinates of all calculated structures and product characterization data. This material is available free of charge via the Internet at <u>http://pubs.acs.org.</u>

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- 20 The 10 methods used are B3LYP-D3(0), B3LYP-D3(BJ), M052x-D3(0), M062x-D3(0), M06L-D3(0), ωB97XD, PBE0-D3(BJ), mPW1K, MN15-L (each with 6-311++G\*\* basis set), and ωB97XD/def2-TZVPP.
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26 The uncorrected  $\Delta G^{\ddagger}$  values for **TS-iminium**, **TS-A**<sub>N'</sub>, and **TS-S**<sub>N</sub>**2'** are 18.3, 29.7, and 25.8 kcal/mol respectively, with respect to the separated starting materials. See Supporting Information for  $\Delta G^{\ddagger}$  values calculated using 19 other DFT methods. See ref. 23a for an important discussion on interpretation of free energy barriers obtained from computational studies.



59 60