Cross-aldol reactions of ketones catalyzed by leucinol: a mechanistic investigation

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Cross-Aldol Reaction of Isatin with Acetone Catalyzed by Leucinol: A Mechanistic Investigation

Mikhail A. Kabeshov,*a,b Ondřej Kysilka,c Lubomír Rulíšek,d Yury V. Suleimanove, Marco Bella,f Andrei V. Malkov,*a and Pavel Kočovský*d,g

Dedicated to Professor Gilbert Stork on the occasion of his 94th birthday and in appreciation of his pioneering work in the area of enamines.

Abstract: Comprehensive mechanistic studies of the enantioselective aldol reaction between isatin (1a) and acetone, catalyzed by L-leucinol (3a), unraveled that isatine, apart from being a substrate, also plays an active catalytic role. Conversion of the intermediate oxazolidine 4 into the reactive syn-enamine 6, catalyzed by isatin, was identified as the rate determining step by both the calculations (ΔG° = 26.1 kcal mol⁻¹ for the analogous L-alaninol, 3b) and the kinetic isotope effect (kH/kD = 2.7 observed for the reaction using d₄-acetone). The subsequent reaction of the syn-enamine 6 with isatin produces (S)-2a (calculated ΔG° = 11.6 kcal mol⁻¹). The calculations suggest that the overall stereochemistry is controlled by two key events: (1) the isatin-catalyzed formation of the syn-enamine 6, which is thermodynamically favored over its anti-rotamer 7 by 2.3 kcal mol⁻¹; and (2) the high preference of the syn-enamine 6 to produce (S)-2a on reaction with isatin (1a) rather than its enantiomer (ΔΔG° = 2.6 kcal mol⁻¹).

Introduction

Proline and related secondary amines have enjoyed a widespread use as chiral organocatalysts in aldol and other reactions, which proceed via enamine intermediates.[1-5] By contrast, primary amines have only been utilized occasionally,[6] presumably owing to their tendency to form stable imines rather than enamines. Furthermore, in contrast to the successful reactions between an aldehyde and a ketone, the catalytic ketone-ketone cross-aldol reactions are rare.[1,2,7] Part of the problem here, aside from the competing self- and cross-coupling, is that the corresponding aldol products tend to be less stable than their precursors, so that the equilibrium is often shifted toward the starting materials.[8] Hence, to attain good conversions and high selectivity, one of the partners has to be more electrophilic and preferably non-enolizable, whereas the other counterpart should readily produce enols and consequently enamines, all in a catalytic manifold.

Isatin (1a), a non-enolizable activated ketone, has been the focus of numerous catalytic studies.[9,10] In our preliminary paper,[9] we have reported on an asymmetric synthesis of both enantiomers of convolutamydine A (2b)[11] from 4,6-dibromoisatin 1b and acetone (a symmetrical, enolizable ketone). Rather surprisingly, leucinol (3a) and valinol, i.e., vicinal amino alcohols with a primary amino group at the chiral center, were identified as the most efficient catalysts (Scheme 1), by far superior to proline and its congeners.[9]

Computational studies, carried by Houk, Barbas, List, and Armstrong and Rzepa[3a,3b,12] for the proline-based catalytic system, recently unveiled the origins of the enantio- and diastereoselectivity in the aldol reaction catalyzed by primary amino acids.[13] However, the mechanistic picture of a synthetically more challenging ketone-ketone aldol reaction and in particular, the surprisingly high efficiency of primary amino alcohols as catalysts, remain unclear.[13] Herein,
we provide a mechanistic insight into this catalytic process based on quantum chemistry calculations and kinetic studies.

Results and Discussion

The aldol reaction of isatin (1a) with acetone (30 equivs), carried out in CH₂Cl₂ with 0.1% of water, proceeded readily at room temperature (−18 °C) over 36 h in the presence of 20 mol% of L-leucinol (3a), giving rise to the aldol product (S)-(-)2a (87% isolated yield, 94% ee).[9] The latter reaction was found to be first-order in 1a and the key importance of the NH₂ and OH groups has been demonstrated.[9] The reaction can also be catalyzed by BuNH₂ or Et₂NH, whereas Et₂N was found to be inert, suggesting an enamine intermediate. Furthermore, N-methylleucinol failed to catalyze the reaction at an appreciable rate, demonstrating the key importance of the primary amino group. On the other hand, the methyl ether of leucinol and O-trimethylsilyleucinol turned out to catalyze the reaction but more slowly and far less selectively than leucinol (both reached <50% conversion over 36 h at RT, with 50% ee). The observed linear correlation between the enantioptureity of leucinol and that of the aldol product 2a (after full conversion) shows that only one molecule of the catalyst is likely to be involved in the stereo-discriminating step.[9] In the presence of water, the methylleucinol failed to catalyze the reaction but more slowly and far less selectively than leucinol (both reached <50% conversion over 36 h at RT, with 50% ee). The observed linear correlation between the enantioptureity of leucinol and that of the aldol product 2a (after full conversion) shows that only one molecule of the catalyst is likely to be involved in the stereo-discriminating step.[9] Monitoring a mixture of acetone and leucinol in CDCl₃ by NMR spectroscopy revealed a gradual conversion of leucinol into oxazolidine 4 (Scheme 2), reaching completion within 2 h at 37 °C. No other species could be detected but the existence of intermediates 5-7 in the equilibrium can be envisioned (in concentrations below the NMR detection threshold). Interestingly, isatin 1a (added to a mixture of leucinol and acetone in CDCl₃) was found to catalyze the formation of 4, reaching completion within 10 min at room temperature. On the other hand, the isolated oxazolidine 4 proved to be unstable in the absence of excess acetone, as its solution in wet CDCl₃ slowly decomposed back to acetone and leucinol, presumably via enamine 6/7 and/or imine 5 (ca 50% conversion at room temperature within 24 h).

![Scheme 2](image)

Scheme 2. Relative stability of reactive intermediates. R = i-PrCH₂ (3a) in the NMR study, R = Me (3b) in the calculations. [a] Calculated by using the (ωB97xd/cc-PVTZ+SMD)/(ωB97xd/cc-PVVDZ+SMD) method.

Similar equilibria, involving analogous oxazolidinones derived from proline, i.e., from an amino acid (with a secondary amino group) rather than from an amino alcohol, have been observed before.[3,14,16] These intermediates, to whose side the equilibrium is heavily shifted at the expense of the desired reactive enamines, have actually been shown to act as catalysts.[25,16b,c] Recently, Gschwind detected the enamine intermediate in the proline-catalyzed self-aldolization of propionaldehyde and demonstrated its formation from the corresponding oxazolidinone by detailed NMR studies.[17] In her seminal papers,[17] she also stated that enamines were only detected for aldehydes (though at low concentrations) but not for ketones, where the equilibrium is almost entirely shifted toward oxazolidinones due to the Thorpe-Ingold effect of the geminal alkyls.[17,18] In a subsequent paper, published after our preliminary communication[9] and while this work was in progress, Gschwind demonstrated the formation of an oxazolidine intermediate (congener of 4) from prolinol and propionaldehyde.[19]

Oxazolidine 4 has now been found to catalyze the aldol reaction of 1a with acetone in CHCl₃ at 37 °C as efficiently as leucinol, with the same rate constant (at 20 mol% catalyst loading).[20] This observation is in full agreement with the Gschwind NMR study,[17] in which she showed that the proline-derived oxazolidinone generates the reactive enamine, confirming an earlier mechanism formulated by Seebach and Eschenmoser[24] and Vilarrasa[16] according to which oxazolidinones should serve as reactive intermediates rather than "parasitic" species.

To rationalize the experimental observations and obtain complementary information, the latter aldol reaction was studied in silico by using the Gaussian 09 software (see the Experimental part for details).[21] Here, for convenience, L-leucinol (3a, R = i-PrCH₂) was replaced by L-alaninol (3b, R = Me). Aiming at the quantitative accuracy of the computed data, a number of modern DFT functionals[22] have been compared with the “golden standard” coupled cluster CCSD(T) ab initio method. We expected that coupling the CCSD(T) method with presumably one of the most accurate solvation method, COSMO-RS,[23] should yield the quantitatively accurate data for the equilibrium between the species 4–7 in solution, i.e., in the process that we consider as the representative model capturing most of the essential changes of electronic structure studied here.

The results are summarized in Table 1, from which it can be con·cluded that the best correlation between the benchmark CCSD(T)/def2-QZVP+COSMO-RS[23] values and the tested DFT functionals was obtained for the ωB97xd/cc-PVTZ method in combination with SMD[24] solvation model (Table 1). In line with the studies by Clark and Tsogoeva,[23e] performing the geometry optimization with the ωB97xd/cc-PVVDZ method turned out to afford a better correlation with the CCSD(T) data than that attained by using the B3LYP/6-31g(d,p) method (compare methods A and D, Table 1). Therefore, (ωB97xd/cc-PVTZ + SMD)/(ωB97xd/cc-PVVDZ + SMD) was employed as the method of choice for further calculations.

The computational study of the equilibrium mixture of the species 4–7 (R = Me) arising from acetone and the catalyst revealed the energies of the individual molecules (Scheme 2). Here, oxazolidine 4 was identified as the most stable product, being, most likely, the catalyst resting state, whereas imine 5 is predicted to be less stable by 5.1 kcal mol⁻¹. Most significantly,
the syn-enamine 6 was found to be preferred over the anti-rotamer 7 by 2.3 kcal mol\(^{-1}\), which stands in stark contrast to the proline-derived enamines.\[2,3,12,17\] Note that this scenario is systematically predicted by all the methods using the larger 6-311++g(2d,p) and cc-pVTZ basis sets (see Table 1 and Supporting Information).

Further calculations were performed to find the most plausible reaction pathway from oxazolidine 4 to the reactive enamine intermediates 6/7. No energetically accessible transition state could be located for direct transformation as a single elementary step. When a molecule of water was introduced into the system, transition states 8 and 9 (Scheme 3, upper part) were found for the conversion of oxazolidine 4 into enamines 6 and 7, respectively; here, 8 is lower in energy than 9 by 0.4 kcal mol\(^{-1}\) (30.7 kcal mol\(^{-1}\) vs 31.1 kcal mol\(^{-1}\)), respectively.\[25\]

Since isatin (1a) was experimentally found to catalyze the conversion of the amino alcohol 3 into oxazolidine 4 (vide supra), it is tempting to assume that 1a may also catalyze other interconversions between the intermediates 4–7. In support of this hypothesis, transition states 10 and 11 involving isatin (1a) were located for the reactions 4 → 6 and 4 → 7 (Scheme 3, bottom part). Note that in both instances isatin acts as a bidentate proton donor/acceptor, where the N−H group offers its proton for promoting the cleavage of the C−O bond of the oxazolidine, whereas its amidic carbonyl acts as a base in the abstraction of a proton from the methyl to generate the enamine structure. TS\(^{5}\) 10, giving rise to the syn-enamine 6, was found to be by 0.4 kcal mol\(^{-1}\) higher in energy than its counterpart TS\(^{5}\) 11 generating the anti-enamine 7, which represents quite the opposite preference (though rather marginal) compared to the water-mediated reaction.\[26\] Importantly, both barriers of the isatin-catalyzed reactions (TS\(^{5}\) 10 and TS\(^{5}\) 11), are by more than 4 kcal mol\(^{-1}\) lower than those for the water-catalyzed reactions, i.e., than TS\(^{5}\) 8 and TS\(^{5}\) 9 (26.5 and 26.1 kcal mol\(^{-1}\) vs 30.7 and 31.1 kcal mol\(^{-1}\), respectively; Scheme 3). Based on these results, it can be concluded that the formation of enamines 6/7 is catalyzed by the starting material of the reaction, i.e., by isatin (1a). The anti-enamine 7 is slightly kinetically favored over its syn-enamine 6 (by 0.4 kcal mol\(^{-1}\)) but is thermodynamically less stable (by 2.3 kcal mol\(^{-1}\)). Therefore, under equilibrium conditions, the reaction can be predicted to proceed mainly via the syn-enamine 6.

### Table 1. Gibbs free energies of the 4-7 formation (Scheme 2; R = Me) in solution computed by methods A-D\[a\][H] \[\text{species} \quad \text{A} \quad \text{B} \quad \text{C} \quad \text{D}\]
<table>
<thead>
<tr>
<th></th>
<th>A</th>
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<th>C</th>
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<tr>
<td>4</td>
<td>2.1</td>
<td>7.9 (6.2)</td>
<td>0.3 (-1.0)</td>
<td>1.6</td>
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<tr>
<td>5</td>
<td>7.2</td>
<td>7.6 (5.5)</td>
<td>5.7 (3.3)</td>
<td>7.4</td>
</tr>
<tr>
<td>6</td>
<td>10.5</td>
<td>12.6 (8.4)</td>
<td>8.5 (4.4)</td>
<td>12.4</td>
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<tr>
<td>7</td>
<td>12.8</td>
<td>14.9 (10.4)</td>
<td>11.0 (6.5)</td>
<td>14.7</td>
</tr>
</tbody>
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[a] The energies are given in kcal mol\(^{-1}\); the values in columns A–C were calculated using the SMD solvation model (values in parenthesis were calculated using the CPCM/UAKS solvation model). [b] Methods: A, uB97x-d/cc-pVTZ//uB97x-d/cc-pVDZ; B, B3LYP/6-311++g(2d,p)/B3LYP/6-31g(d,p); C, M06-2X/cc-pVTZ/B3LYP/6-31g(d,p); D, CSDT[T]lelZ/QZV/ + COSMO-RS/B3LYP/6-31g(d,p).

Scheme 3. Formation of the syn- and anti-enamines 6 and 7 via 8 - 11. The computed values were obtained at the (ωB97xd/cc-pVTZ + SMD)((ωB97xd/cc-pVTZ + SMD) level of theory.

Computational investigation of the aldol step (1a + 6/7 → 2a) indicates that syn-enamine 6 should produce (S)-2a, since the pathway toward its enantiomer would require overcoming an activation barrier that is higher by 10.6 kcal mol\(^{-1}\) (Scheme 4, left part, and Figure 1). By contrast, anti-enamine 7 (disfavored thermodynamically, vide supra) would predominantly produce (R)-2a, as the corresponding transition state is preferred by 2.4 kcal mol\(^{-1}\) over that generating (S)-2a (Scheme 4, right part; Figure 1). In other words, the syn-enamine 6 should produce mainly (S)-2a (via the transition state 12), whereas its anti-rotamer 7 would predominantly afford (R)-2a (via the transition state 13).

The barrier for the syn-anti enamine interconversion via the transition state 14 was found to be relatively low (9.7 kcal mol\(^{-1}\) for the 6 → 7 transformation and 7.4 kcal mol\(^{-1}\) for the 7 → 6 transformation; Scheme 3 and Figure 1). As that barrier is considerably lower than the activation energy of the aldol step (compare 7.4 kcal mol\(^{-1}\) and 9.7 kcal mol\(^{-1}\) vs 11.9 kcal mol\(^{-1}\) and 11.6 kcal mol\(^{-1}\); Scheme 4), the thermodynamic equilibrium between 6 and 7 should settle quickly in favor of 6, and the system can be viewed as obeying the Curtin-Hammett principle (Figure 1).\[27\] Accordingly, the ΔΔG° for the aldol step is 2.6 kcal
mol$^{-1}$ [(11.9 – 11.6) + (10.7 – 8.4) = 2.6 kcal mol$^{-1}$]; Scheme 4 and Figure 1] in favor of (S)-2a, consistent with the experiment.

This analysis can also account for the experimentally observed initial formation of a nearly racemic product, apparently resulting from a different catalytic process, possibly using free leucinol.[28] Before the Curtin-Hammett equilibrium is attained, the concentration of enamine 7 can be higher (note that 7 is kinetically slightly preferred over 6; Scheme 4), which results in more (R)-2a being produced via the transition state 13 (Scheme 4). As soon as all the leucinol is consumed by conversion into oxazolidine 4, the reaction follows the scenario shown in Scheme 4 and (S)-2a is produced almost exclusively.

A moderate primary kinetic isotope effect (KIE)[29] ($k_H/k_D = 2.7$) was observed for the reaction of isatin (1a) with $d_6$-acetone, catalyzed by L-leucinol, implying that the enamine formation can be the rate determining step.[30] This is consistent with the DFT calculations (Figure 1), showing that the activation energy of the enamine formation is the highest point on the computed reaction pathway (26.1 vs 18.1 and 20.0 kcal mol$^{-1}$; Figure 1).[31] Hence, both the calculations and the KIE suggest that the rate-limiting step in this case precedes the aldol step. This is understandable as 1a is a highly activated electrophile, so that the aldol step can become faster than the enamine formation.[32,33]

The aldol reaction mechanism. R = Me. Computed values were obtained at the (ωB97xd/cc-PVTZ + SMD)/(ωB97xd/cc-PVDZ + SMD) level of theory.

Figure 1. The calculated reaction pathway for the formation of 2a from 4 (Scheme 3 and 4; R = Me). The preferred pathway is marked bold.
Importantly, the barrier for the enamine 6/7 isomerization (TS\(^{\ddagger}\) 14; Figure 1) is lower than the TS\(^{\ddagger}\) 12 of the aldol step. Hence, in agreement with the Curtin-Hammett principle, the system thus produces (S)-2a with high enantioselectivity. As isatin (1a) catalyzes the rate-determining formation of enamine 6/7, the reaction should be 1st order in isatin, which is in agreement with the experiment. Notably, Figure 1 clearly shows that the reaction is “up-hill”, i.e., that the final aldol product 2a is higher in energy than oxazolidine 4 (and consequently higher than the starting isatin 1a). Under the equilibrium conditions, the reaction is obviously driven to completion by a large excess of acetone as one of the starting materials.

Conclusions

In conclusion, L-leucinol (3a), a primary amino alcohol, has been shown to serve as an efficient, enantioselective organocatalyst for the cross-aldol reaction of isatin 1a (an activated, non-enolizable ketone) with acetone (an enolizable, less electrophilic ketone). The reaction proceeds at room temperature with a trace of water in CH\(_2\)Cl\(_2\) as an optimal solvent, at 10-20 mol% catalyst loading (Scheme 1). Mechanistic and computational studies unraveled the initial formation of oxazolidine 4 that has been identified as the catalyst resting state; its formation turned out to be dramatically accelerated by the starting isatin, so that in its presence practically all of the leucinol is converted into 4 within 10-15 min (Scheme 2). Conversion of the latter oxazolidine into the reactive syn-enamine 6, also catalyzed by isatin (acting as a bidentate hydrogen-bond donor/acceptor), is rate determining as demonstrated by both the calculations (Δ\(G\) = 26.1 kcal mol\(^{-1}\) for the analogous L-alaninol 3b, R = Me) and the isotope effect (k\(_{i/d}\) = 2.7 observed for the reaction using d\(_{0}\)-acetone). The calculated barrier of 26.1 kcal/mol compares well with the experimental reaction half life of 210 min (R = i-Bu; for more details see Isotope Effect Experiment below) that corresponds to 23.2 kcal mol\(^{-1}\), estimated by Eyring equation. We expect that the calculated barrier would be further lowered by ~1 kcal mol\(^{-1}\) if tunneling corrections were taken into consideration.\(^{[34]}\)

Therefore, the agreement between the experimental and computed “absolute” activation energies is within 2 kcal/mol which provides further evidence for the presented reaction mechanism. According to the calculations, the syn-enamine 6 is thermodynamically favored over its anti-rotamer 7 by 2.3 kcal mol\(^{-1}\) (Scheme 3 and Figure 1). The subsequent aldol reaction of 6 with isatin via TS\(^{\ddagger}\) 12 (the pathway marked bold in Scheme 4 and Figure 1) produces (S)-2a (calculated Δ\(G\) = 11.6 kcal mol\(^{-1}\)) which is kinetically favored over the formation of its enantiomer (calculated ΔΔ\(G\) = 10.6 kcal mol\(^{-1}\)). The overall stereochemical outcome of this aldol reaction is thus determined by the Curtin-Hammett scenario with the equilibrium between syn- and anti-enamines 6 and 7 settled relatively quickly due to the low energy of the corresponding TS\(^{\ddagger}\) 14 (Figure 1). The preferential formation of the syn-enamine 6 is noteworthy as it stands in sharp contrast to the well-established anti-enamine generation from proline\(^{[9,12,17]}\) and could thus be regarded as a characteristic feature of primary amino alcohols. Equally notable is the catalytic role of isatin (1a) in the formation of oxazolidine 4 and enamine 6, so that it can be regarded as both the starting material and co-catalyst.

The difference in the calculated activation energies for the (R)- and (S)-channels suggest >99% ee in favor of (S)-2a, whereas only 94% ee was observed experimentally. This discrepancy can be ascribed to the early stages of the reaction, which were shown to be much less enantioselective, presumably due to a different mechanism operating before the Curtin-Hammett equilibrium is established.

In summary, this study suggests that the overall stereochemistry of the aldol reaction of isatin with acetone is controlled by two key events: (1) the isatin-catalyzed formation of the syn-enamine 6; and (2) the high preference of the syn-enamine 6 to produce (S)-2a on reaction with isatin (1a).

Experimental Section

Computational details

Geometries of all structures (minima and saddle points) were optimized at the B3LYP/6-31G(d,p) and wb97xd/cc-pVDZ levels in vacuum or in a solvent (using the SMD solvation model); subsequent vibrational frequency calculations were performed at the same level for all calculated structures. All transition states thus found possess exactly one negative Hessian eigenvalue, while all other stationary points were confirmed to be genuine minima on the potential energy surface (PES). Intrinsic reaction coordinate (IRC) analysis was performed to unambiguously assign located transition states for all the potential reaction pathways. Electronic energies were obtained by performing single point calculations at the wb97xd/cc-pVTZ level (unless stated otherwise) in solvent or in vacuum. Enthalpies are reported as sums of Δ\(E\), zero point vibrational energy (ZPVE) corrections, and thermal corrections at 298 K. Gibbs energies were calculated as Δ\(G\) = Δ\(H\) - TΔ\(S\) at 298 K where enthalpies and entropies were obtained by using standard statistical mechanical formulae for the ideal gas, rigid rotor, and harmonic oscillator approximations following the normal-mode analysis in vacuum. The benchmark reaction energies and Gibbs energies were obtained using CCSD(T)/def2-QZVP\(^{[23a]}\) calculations and Turbomole software\(^{[23a]}\) in combination with Klamt’s conductor-like screening model for realistic solvation (COSMO-RS)\(^{[23b]}\). COSMO-RS calculations were carried out using cosmotherm software and the recommended protocol: BP86/def-TZVP geometry optimizations in vacuo and in ideal conductor (ε = 1) followed by the COSMO-RS calculations in the target solvent (CH\(_2\)Cl\(_2\)). A correction of (1.9-2.1) kcal mol\(^{-1}\) (corresponding to the difference between the concentration of the ideal gas at 298K and 1 atm and its 1 mol l\(^{-1}\) concentration; Δ\(n\) is the change in number of moles in the reaction) has been applied in order that the computed values refer to 1 mol l\(^{-1}\) standard state.

Isotope Effect Experiment

Isatin 1a (16 mg, 0.11 mmol) was added in one portion to a solution of L-leucinol (2.5 mg, 0.02 mmol), H\(_2\)O (3.8 mg, 0.22 mmol), and acetone (0.25 mL) in dichloromethane-d\(_8\) (1 mL) at room temperature, the reaction mixture was transferred into an NMR tube, and monitored by \(^{1}H\) NMR spectroscopy at 24 °C. Linear relationship was found between ln[c(isatin)/c(isatin)] and the reaction time, indicating the first order of the reaction. The reaction half-life was found to be 210 min. In a parallel experiment, isatin 1a (16 mg, 0.11 mmol) was added in one portion to a solution of L-leucinol (2.5 mg, 0.02 mmol), H\(_2\)O (3.8 mg, 0.22 mmol), and...
aceton-δ, (0.25 mL) in dichloromethane-δ2 (1 mL) at room temperature, the reaction mixture was transferred into an NMR tube, and monitored by 1H NMR spectroscopy at 24 °C. Linear relationship was found again between log[(isatin)/c(inalde)] and the reaction time, indicating the first order of the reaction. The reaction half-life was found to be 570 min. Comparison of the two experiments gives KIE = t1/2(reaction 2) / t1/2(reactio 1) = 2.7. Conversion graphs with linear regression analyses are provided in SI.

Acknowledgements

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Keywords: organocatalysis • self-catalysis • computational studies • enamines • isatins • oxazolidines


As a rule, the ketone-ketone aldol reactions proceed only to low conversions. A remedy is to continuously remove the product from the equilibrium, as in the classical example of dimerization of acetone using barium hydroxide in a Soxhlet extractor (which, however, cannot be used in our case): J. B. Conant, N. Tuttle, Org. Synth. 1941, Coll. Vol. 1, 199.


For other aldol reactions of isatin, including the synthesis of Convolutamydine A, see the ref section in [9] and the following: (b) Q. Guo, M. Banushali, C.-G. Zhao, Angew. Chem. Inter. Ed. 2010, 49, 5460-5464; (c) A. Suresh, N. Molleti, R. Panem, V. K. Singh, Tetrahedron Lett. 2011, 52, 4080-4083; (d) Y. Liu, P. Gao, W. Wang, G. Sun, Z. Ge, R. Li, Synlett 2012, 23, 1031-1034; (e) H. Liu, H. Wu, Z. Luo, J. Shen, G. Kang, B. Liu, Z. Wan, J. Jiang, Chem. Eur. J., 2012, 18, 11899-11903; (f) S. Wei, B. Schmid, F. M. Macaev, S. N. Curlat, A. Luo, J. Shen, G. Kang, B. Liu, Z. Tang, L. F. Cun, L. Z. Gong, Sun, Z. Ge, R. Li, Synlett 2013, 4, 352-356; (g) N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka, Angew. Chem. Int. Ed. 2013, 52, 1793-1803. For stabilization of the proline-derived enamines via hydrogen bonding between the carboxyl group and the solvent, allowing their detection by NMR spectroscopy. On the other hand, protic solvents, such as MeOH, can provide hydrogen-bonding stabilization of isoxazolidinones and, as a result of this, the enamine concentration drops below the NMR detection.\(^\text{17}\)


Aprotic solvents, such as MeCN, DMSO, and DMF were found to stabilize the proline-derived enamines via hydrogen bonding between the carboxyl group and the solvent, allowing their detection by NMR spectroscopy. On the other hand, protic solvents, such as MeOH, can provide hydrogen-bonding stabilization of isoxazolidinones and, as a result of this, the enamine concentration drops below the NMR detection.\(^\text{17}\)

Autocatalysis by the product 2a was ruled out by a control experiment, carried out in the presence of \((S)\)-\(-2a\) (20 mol%), added at the onset of the reaction. The latter additive neither catalyzed the reaction nor it altered the enantiomeric ratio of the gradually produced 2a when \(-\text{leucinol} was also added to the mixture.\(^\text{20}\) On the other hand, autocatalysis by the product has been observed before, e.g. in the related Mannich reaction: M. Mauksch, S. B. Tsogoeva, I. M. Martyanova, S. Wei, Angew. Chem. Inter. Ed. 2007, 46, 393-396; Angew. Chem. 2007, 119, 397-400.


For a discussion of the syn/anti-enamines and detailed investigation of the aldol reaction, see refs [14,17,19].

These differences, i.e., 0.4 kcal mol\(^{-1}\) in each instance, are rather marginal. Therefore, one has to be rather careful to make definite conclusions.


[30] The KIE can, in principle, also originate from the formation of the corresponding enolate or enol (rather than enamine). However, the enolate itself could hardly be expected to react with >90% enantioselectivity, even if a loose coordination to the chiral catalyst as simple as leucinol were considered. On the other hand, this mechanism may contribute to the low enantioselectivity observed in the early stages of the reaction. Apparently, the enolate mechanism can only be effective with multifunctional catalysts, such as chiral thioureas.¹⁰b,c

[31] In a reciprocal experiment, i.e., in the L-leucinol-catalyzed reaction of isatin (1a) with non-labeled acetone, carried out in the presence of D₂O (1 equiv), a KIE (k_H/k_D = 1.5) was also observed. This effect can be attributed to an H/D exchange of the N-H of isatin (note that hydrogen bonding involving the N-H is featured in the TS¹⁰/¹¹ as shown in Scheme 3).

[32] Another example of the rate limiting step preceding the C-C bond formation in the aldol reaction can be drawn from the aldol reaction in the Hajos-Parish experiment (catalyzed by proline), where the enamine formation is an intermolecular process, whereas the subsequent aldol C-C bond formation is intramolecular (and therefore entropically favorable): H. Zhu, F. R. Clemente, K. N. Houk, M. P. Meyer, J. Am. Chem. Soc. 2009, 131, 1632-1633.

[33] Both experimental and computational results show that this aldol reaction is an example of the general base catalysis; for an excellent discussion, see: A. Ault, J. Chem. Ed. 2007, 84, 30-39.

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