Magnitudes and Chemical Consequences of R2N+-C-H-O=C Hydrogen Bonding

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Abstract: The magnitude of the stabilizing interaction between an aliphatic C-H bond attached to an ammonium nitrogen and a carbonyl oxygen was evaluated by ab initio calculations at the MP2/6-311+ +G** level of theory. Attractive R2N+-C-H-O=C interactions play an important role in supramolecular recognition and various types of stereoselective catalysis. Our calculations show that R2N+-C-H-O=C is the strongest hydrogen bond of the C-H-O type known to date. Such hydrogen bonds remain as stabilizing interactions even in water for amide acceptors.

Introduction

In the past decade a growing interest in unusual hydrogen bonding patterns emerged in the fields of structural chemistry and biology. The role of C-H...O hydrogen bonds in conformational analysis, protein structure and crystal packing, molecular recognition processes, the stabilization of inclusion complexes, and in the stability and possibly even in the activity of biological macromolecules has been well documented. The geometries of C-H...O interactions in crystal structures have been analyzed in detail. Calculated interaction energies for different combinations of donors and acceptors in vacuum range from 0.5 to 3.8 kcal/mol, values which are approximately half the interaction energies calculated for normal nonionic O-H...O hydrogen bonds (3-8 kcal/mol). The ability of the C-H group to donate hydrogen bonds increases with the larger s character of the hybridization of the C-H bond orbital and with the number and strength of electron-withdrawing groups on carbon. The electron-withdrawing ability and positive charge of ammonium ion led to high computed interaction energies in the gas phase of around 9 kcal/mol for the complex H3N+-CH3...O=C.

Recently, interaction energies of 88.1 kcal/mol in the gas phase were calculated for the ion pair N-methylpyridinium cation/dimethyl phosphate anion, a model system for the binding of pyridinium derivatives to DNA. This strong Coulombic attraction energy drops to ~19.7 kcal/mol in CHCl3 and becomes repulsive in H2O (+4.2 kcal/mol) for the gas-phase geometry.

We have shown that attractive interactions between tri-methylammonium cation and an ester carbonyl substituent of a reacting enolate direct the stereoselective outcome of the Merck process used for the synthesis of arylopionic acid nonsteroidal anti-inflammatory drugs (NSAIDS). Sanders and co-workers recently showed that attractive interactions between tri-methylammonium cation and an ester carbonyl substituent of a reacting enolate direct the stereoselective outcome of the Merck process used for the synthesis of arylopionic acid nonsteroidal anti-inflammatory drugs (NSAIDS). Sanders and co-workers

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of electron-deficient olefins by hydroxamic acids.\textsuperscript{23} Purely synthetic $C_2$-symmetric quaternary ammonium\textsuperscript{26} and quaternary hydrazonium\textsuperscript{27} salts were shown to be highly efficient in the same kind of alkylation and Michael addition reactions. Finally, cinchona alkaloid derivatives, as well as other synthetic tertiary amines, have been successfully employed as chiral modifiers in the enantioselective hydrogenation of ethyl pyruvate catalyzed by platinum,\textsuperscript{28} in the enantioselective dihydroxylation of olefins by osmium tetroxide,\textsuperscript{29} and in the enantioselective (up to the record $87\%$ ee) fluorination of trimethylsilyl enolates and $\beta$-cyano-esters in acetonitrile ($\epsilon = 36.7$).\textsuperscript{30} In these last three cases, ammonium cations have been postulated as the reactive species, and although they are not tetraalkylammonium ions, it is possible that $^{14}N$–$CH_2\cdots O=C$ hydrogen bonds are also important.

Although relatively nonspecific electrostatic interactions are frequently invoked for all these processes, they all possess one common feature: the formation of a relatively strong hydrogen-bonded complex between a tetraalkylammonium cation and one or more carbonyl groups of esters or amides, or the oxygen of an enolate.

We have investigated quantum mechanically the strength of these interactions in different model systems that mimic the interactions in cation–neutral carbonyl complexes and ion pairs. We selected trimethylammonium cation as a model to assess both $^{14}N$–$H$ and $^{14}N$–$C$–$H$ hydrogen bond donor groups. Methyl acetate, methyl acetate enolate, and dimethylformamide were chosen as the hydrogen bond acceptors. We report the geometries and interaction energies of the $[^4N\cdots C\cdots H\cdots O=\cdot C]$, $[^4N\cdots H\cdots O=\cdot C]$, and $[^4N\cdots C\cdots H\cdots O=\cdot C\cdots C]$ hydrogen bonds present in $[\text{Me}_3\text{NH}\cdot\text{MeCOOMe}]^+$, $[\text{Me}_2\text{NH}\cdot\text{HCONMe}_2]^+$, and $[\text{Me}_2\text{NH}\cdot\text{CH}_2\text{COOMe}]^+$.

**Computational Methodology**

Hydrogen-bonded complexes between trimethylammonium cation and methyl acetate, methyl acetate enolate, and dimethylformamide were first optimized at the restricted Hartree–Fock (RHF) level of theory and fully characterized as minima by frequency analysis. Subsequent geometry optimizations were performed at the correlated second-order Moller–Plesset (MP2) level starting from the RHF geometries. The $6-311++G^{**}$ basis set, including polarization and diffuse functions on all hydrogen atoms, was used throughout this study. The reported values of binding energies include zero-point energy corrections based on the RHF vibrational frequencies, scaled by a factor of 0.89.

The effect of the polarity of different solvents on the MP2 binding energies was studied by using the Polarizable Continuum Model (PCM) of Tomasi et al.\textsuperscript{11} with dielectric constants of 80.1 ($\text{H}_2\text{O}$), 33.0 ($\text{MeOH}$), 7.52 (THF), 4.81 ($\text{CHCl}_3$), and 2.38 (toluene). Solvation calculations consisted of single points at the MP2/6-311++$G^{**}$ level of theory on

![Figure 1. Ammonium recognition displayed by a dynamic combinatorial library.](image)
the MP2 gas-phase optimized geometries. While these calculations are still approximate because they do not include explicit solvent molecules, they do provide reasonable estimates of the effect of solvent polarity on the binding energies of the complexes. We expect a change in the geometry of the complexes upon solvation, but the size of the system and the general difficulties of convergence of the geometry optimizations involving the PCM method preclude a full optimization in solution at the MP2 level. The reported values include corrections for the basis set superposition error (BSSE) determined in the gas phase at the MP2/6-311++G** level, through the counterpoise method of Boys and Bernardi. All calculations were carried out with the Gaussian 98 program.

Electrostatic potential surfaces were created with SPARTAN. The electrostatic potential for each structure was mapped onto a total electron density surface contour at 0.08 e/au.

Results and Discussion

Different hydrogen-bonded complexes of Me$_3$+NH with dimethylformamide or methyl acetate were constructed and preoptimized at the RHF/6-311++G** level of theory. Those structures that corresponded to minima on the RHF/6-311++G** potential energy surface were fully optimized at the correlated level MP2/6-311++G**, giving rise to the final geometries 8, 9, 10, and 11 shown in Figure 3. Similarly, the

**(34) SPARTAN SGI V5.0.3 OpenGL, 1997; Wavefunction, Inc.: 18401 Von Karman Ave., suite 370, Irvine, CA 92612.
complexes between the alkoxide oxygen of methyl acetate enolate and the NH or CH protons of Me$_3$NH were preoptimized. MP2/6-311++G** optimization gave the structures 7 and 12 shown in Figure 3. Figure 3 shows the final MP2 optimized complexes in order of decreasing stability on the left, and their corresponding electrostatic potential surfaces on the right. In 7, the plane containing the enolate is parallel to one of the tetrahedral faces of the trimethylammonium cation. Each N$^+$–C–H hydrogen interacts simultaneously with two of the three partially negative atoms (enolate O$^-$, CH$_2$, and OMe) with H⋯O distances ranging from 2.015 to 2.945 Å. Five out of the six total interactions are shorter than 2.7 Å, which corresponds to the sum of the van der Waals radii of an oxygen atom (1.5 Å) and a carbon-bonded hydrogen (1.2 Å). The BSSE corrected, gas-phase MP2/6-311++G** interaction energy (Table 1) is −95.1 kcal/mol. This interaction energy is reduced to −22.2 kcal/mol in CHCl$_3$, and to −40.9 kcal/mol in toluene, the most common solvents used in phase transfer catalysis, and becomes positive in water, which suggests that the stability of this ionic pair is dominated by electrostatic terms.

Corey et al. provided a specific example of this type of interaction. They studied the X-ray crystal structures of cinchonidinium p-nitrophenoxide salts and formulated a model that explains the highly enantioselective alkylation of $\beta,\gamma$-unsaturated ester enolates. They proposed that the efficient transfer of stereochemical information between the ammonium salt and the

![Figure 3](image)

**Figure 3.** Computed complexes of trimethylammonium cation. Binding energies in the gas phase (kcal/mol) and electrostatic potentials are shown for each complex.

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* The values in square brackets correspond to the interaction energies calculated by subtracting the energies of the separately optimized and zero-point corrected donor and acceptor molecules, from the energy of the optimized and zero-point energy corrected complex [MP2/6-311++G** + ZPE(RHF)]. The other values correspond to BSSE corrected interaction energies.
enolate is possible because the quaternary ammonium structure has a well-defined geometry in which the negative oxygen of the aryloxy counterion is in close contact (O⋯N+ = 3.46 Å) with the least sterically hindered tetrahedral face of N+.

They assumed that the enolate oxygen forms an intimate ion pair with the cation in the same way as p-nitrophenoxoide and developed a model that explains the enantioselectivity in which the plane of the enolate double bond is perpendicular to the plane defined by the three N+−C−H hydrogen-bonding hydrogens. The tert-buty1 group of the enolate is in close van der Waals contact with the N-9-anthracenylmethyl substituent exposing the si face to electrophilic attack. Our results suggest that it is the combination of three N+−C−H interactions with the π face of the enolate that is strong enough in organic solvents to be responsible for the tight association of the reacting enolate and the ammonium catalyst. Furthermore, the optimized structure, 7, of the complex [Me3NH−CH2COOMe] shown in Figure 3 provides the most stabilized ion pair arrangement, in which one face of the enolate is parallel to one of the four tetrahedral faces of the N+ cation, with shorter hydrogen bond distances. The ion pair 7 in Figure 3 is the only minimum on the MP2 potential energy surface, regardless of the starting structure preoptimized at the HF/6-311++G** level. Ion pair 7 is approximately 4.3 kcal/mol more stable in the gas phase than an optimized ion pair arrangement in which only the enolate oxygen interacts with the N+−C−H bonds (single point at the MP2 level on a fully optimized HF geometry that resembles that of structure 10). Upon solvation this energy difference decreases to 3.0 kcal/mol in toluene and to 2.6 kcal/mol in water. The results reported here suggest an alternative model that also explains the enantioselectivity observed based on the preferred arrangement of the enolate and the cation in the highly organized transition state. In this model, the ion pair arrangement resembles that of structure 7 (Figure 3), but now the phenyl substituent of the enamine is π-stacked with the N-9-anthracenylmethyl substituent, exposing the si face to electrophilic attack. Figure 4 shows the electrostatic potential of a model of the enolate derived from tert-buty1 glycinate-benzophenone Schiff base approaching a portion of the ammonium catalyst 6 (Figure 2). The three C−H bonds α to the quaternary N are parallel to each other, and the three hydrogens (blue in the electrostatic potential plot) define a plane. The deep blue of the N+−C−H hydrogens corresponds to the most positive electrostatic potential on the catalyst and complements well the negatively charged positions (in red) of the reacting enolate. This arrangement also allows π stacking between the electron-rich phenyl ring of the enolate and the electron-deficient anthracenyl unit of the catalyst.

When trimethylammonium interacts with neutral hydrogen bond acceptors (8, 9, 10, and 11 in Figure 3), the interaction energy in the gas phase drops significantly but is still substantial. Dimethylformamide is a better hydrogen bond acceptor, and this is reflected in the larger interaction energies of 8 and 10 with respect to 9 and 11, respectively.

The gas-phase stabilization energy calculated for 11, −12.9 kcal/mol, is in excellent agreement with experimental values of −12.1 ± 1.2 kcal/mol for the hydrogen-bonded complex between tetramethylammonium and methyl acetate. Pulsed high-pressure mass spectrometry was also used to evaluate the binding energies between (CH3)2N+ and amide groups such as dimethylacetamide and methyl acrylyglycinate, and showed that they bind even more strongly (18−20 kcal/mol), in agreement with the calculated value for complex 10 (18.1 kcal/mol).36

We observe a strong complementarity between the positive electrostatic potential on the N−H and C−H bonds of trimethylammonium (represented by the deep blue color), and the negative electrostatic potential (bright red) on the OCOCH3 fragment of methyl acetate enolate of 7, and on the carbonyl oxygen of dimethylformamide in 8 and 10 and methyl acetate in 9 and 11 (Figure 3). Similar intensity of blue on the N+−H and the N+−C−H bonds indicates areas of comparable electrostatic potential.

There is an increase of C−H bond length from 1.090 Å in trimethylammonium to 1.098, 1.096, and 1.095 Å upon formation of complex 7. Elongation of N−H bonds was also observed, from 1.024 Å in trimethylammonium to 1.057 and 1.045 Å in complexes 8 and 9, respectively, although no changes in C−H bond length were observed for complexes 10 and 11. Finally, the enol O−H bond length increased from 0.963 in the isolated enol to 1.004 Å in the hydrogen-bonded complex 12. These observations correlate with the following order of hydrogen bond strength: [N+−C−H⋯O=O=C] < [N+−H⋯O=O=C] < [N⋯HO=O=C].

Several generalizations can be made: (1) The stabilization of the complexes 10 and 11 in the gas phase that involve three N+−CH3⋯O=O=C hydrogen bonds is two-thirds of the stabilization of complexes 8 and 9, respectively, that involve one strong N+−H⋯O=O=C hydrogen bond and two longer and weaker N+−CH3⋯O=O=C hydrogen bonds. The stabilization of the complexes 10 and 11 in solvent is half of the stabilization of complexes 8 and 9, respectively, regardless of the polarity of the solvent. These results suggest that any process that allows these N+−CH3⋯O=O=C interactions to occur in concert will be highly stabilized, even in organic solvents of moderate to low polarity (THF, CHCl3, toluene).

(2) Three +N−CH3⋯O=O=C hydrogen bonds are more effective in stabilizing the resulting hydrogen-bonded complexes (7, 9, and 11) than the strong [N+−H⋯O] hydrogen bond present in structure 12, where trimethylamine is hydrogen bonded to methyl acetate enol in the gas phase. Although these N+−CH3⋯O=O=C interactions in 836

Figure 4. New model proposed for the enantioselective alkylation of tert-buty1 glycinate-benzophenone Schiff base catalyzed by cinchonidinium salt.
O=C hydrogen bonds are completely suppressed in water and MeOH, they remain as competitive stabilizing interactions in common organic solvents such as THF.

(3) The hydrogen-bonding interactions involving the amide carbonyl as the hydrogen bond acceptor (structures 8 and 10) are not completely suppressed in water. This observation suggests that [N+—C—H•••O] interactions involving aspartate or glutamate residues or even the amide backbones of proteins could control the recognition of quaternary ammonium haptens by catalytic antibodies, and therefore be responsible for catalysis by stabilizing the cationic transition states that are mimicked by ammonium haptens. Antibody 14D9, for example, was elicited toward a piperidinium derivative that mimics the rate-limiting transition state in the pH-dependent hydrolysis of ketals37 and epoxides,38 as well as the transition state for the enantioselective protonation of enol ethers.39 The aspartate or glutamate residues present in the active site of 14D9 proved to be the major factor in the catalytic activity.40

Figure 5 shows a model, 13, for the interaction between the N+—C—H•••O bonds of the trimethylammonium catalyst and the ester carbonyl substituent of (S)-methyl lactate, as they interact in the transition state, 14, of the enol—keto tautomerization step. This determines the diastereoselectivity of the Merck process for the addition of chiral alcohols to ketenes.12 This model was constructed from the original transition state (calculated at B3LYP/6-31G*) shown below in Figure 5 by deleting the phenylmethyl ketene enolate and substituting the methyl and OH groups of the (S)-methyl lactate by hydrogen atoms. Only the coordinates of these newly added hydrogens were allowed to optimized at the MP2 level while the rest of the structure remained frozen, to give 13. Two [N+—C—H•••O=C] hydrogen bonds are present with H•••O distances of about 2.2–2.3 Å and

C–H–O angles of 150–152°, similar to those in the fully optimized complex 11 with H⋯O distances around 2.3 Å and C–H–O angles of 142–143°. Nevertheless, the stabilization energy decreases to about 50% in the gas phase, underlining the synergistic effect of these interactions that seems to be more important than their directionality. These hydrogen bonds, responsible for facial control of the proton delivery to the enolate carbon, are worth 1.6 kcal/mol in toluene, the solvent used in the experiments.

Conclusions

In the gas phase the stabilization of complexes involving three [N⁺–C–H⋯O=C] hydrogen bonds is two-thirds of the stabilization involving one [N⁺–H⋯O=C] hydrogen bond. Upon solvation, the stabilization of complexes containing [N⁺–C–H–O=C] hydrogen bonds is only one-half the stabilization from one [N⁺–H⋯O=C] hydrogen bond, regardless the polarity of the solvent. Furthermore, the [N⁺–C–H⋯O=C] interaction is the strongest hydrogen bond of the type C–H⋯O known to date for an amide carbonyl acceptor (10 in Figure 3). Stabilization energies are comparable to the complex between trimethylamine and an enol in the usual range of solvent polarities. The fact that they remain as stabilizing interactions in water could have implications for biological phenomena such as the recognition of the quaternary ammonium, acetylcholine, by its receptor during the transmission of nerve impulses.41–43

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The Direct Catalytic Asymmetric Three-Component Mannich Reaction

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The Mannich reaction is enormously useful for the construction of nitrogenous molecules. In this transformation, three components, a ketone, an aldehyde, and an amine, react to form a \( \beta \)-amino-ketone. The increasing popularity of the Mannich reaction has been fueled by the ubiquitous nature of nitrogen in drugs and natural products as well as by the potential of this multicomponent reaction to generate diversity. Both direct variants with preformed ketone donors and indirect variants utilizing preformed enolate equivalents have been described. In addition, the imine intermediate may be preformed or its amine and aldehyde precursors used directly (eq 1).

Only a handful of catalytic asymmetric Mannich reactions have been reported, and all but one of these are direct. Here we report direct proline-catalyzed highly enantioselective three-component Mannich reactions.

Few reports concerning asymmetric Mannich reactions exist. Catalytic methods have been introduced only very recently by the groups of Tomioka, Kobayashi, Sodeoka, Lectka, and Shibasaki. Noncatalytic enantioselective methods include the addition of chiral preformed enamines to imines. Our interest in testing whether chiral amines or amino acids would also catalyze the Mannich reaction is based on these reports. Kobayashi’s elegant work on three-component Mannich reactions, the pioneering lessons we have learned from aldolase antibody 38C2, and our own finding that proline catalyzes the direct asymmetric aldol reaction. According to our mechanistic hypothesis, proline reacts with ketones to form a chiral enamine. We reasoned that (a) the nucleophilic addition of the proline enamine would be faster to an imine than to an aldehyde and (b) that imine formation with a primary amine would be faster than concurrent aldolization. Consequently, a Mannich reaction catalyzed by proline or another chiral amine can be performed as a three-component reaction utilizing an aldehyde, a ketone, and a primary amine.

We found that after stirring proline (35 mol %), \( p \)-nitrobenzaldehyde (1 eq), and \( p \)-anisidine (1.1 eq) in acetone/DMSO (1:4) for 12h, the corresponding Mannich product 1 was formed in 50% yield and 94% ee (eq 2).

The aldol addition and condensation products were observed as side products in this reaction. Similarly, if 2-naphthaldehyde was used, \( \beta \)-amino-ketone 2 was obtained in excellent enantioselectivity (96% ee), albeit in modest yield (35%) (Table 1, entry 2). Both \( \alpha \)-substituted and \( \alpha \)-unsubstituted aldehydes gave the corresponding \( \beta \)-amino ketones in good to excellent yields and with ee’s of up to 93% (Table 1, entries 3–6). Moreover, the reactions with \( \alpha \)-unsubstituted aldehydes were performed in pure acetone, and after completion, proline could be recovered from the reaction mixture in almost quantitative yield by filtration. These reactions can also be performed in chloroform containing 20 vol % of acetone (Table 1, entry 3).

The PMP (p-methoxyphenyl) amine protecting group has been chosen because it can readily be removed under oxidative conditions (Scheme 1), although other anilines can be used. Furthermore, we found that ketones other than acetone furnish the desired Mannich products in excellent yields and enantioselectivities. Most importantly, hydroxyacetone is an efficient and selective donor. For example, in the reaction with isovaleraldehyde, \( \text{syn} \)-amino alcohol 9 was formed within 12 h as the only detectable regioisomer in good ee (65%) and dr (17:1).

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(Scheme 1). The relative and absolute configuration was determined from the X-ray structure of cyclic derivative 10a and via conversion to enantiomerically pure N-(BOC)-D-valinol (11), respectively. The Mannich reactions with hydroxyacetone complement the Sharpless asymmetric aminohydroxylation (AA) for the construction of chiral nonracemic Vic-amino alcohols.

Currently we speculate that this reaction follows an enamine mechanism and involves either a boatlike transition state A or chairlike transition state B. Both transition states include a (Z)-imine, which has been implicated earlier in related reactions with boron enolates. The geometry of the enamines from substituted ketones (X ≠ H) is (E) in A and (Z) in B. These transition states readily explain the observed si-facial enantioselectivity. The opposite selectivity has previously been observed in proline-catalyzed aldol reactions. The additional nitrogen substituent of the imine may destabilize the corresponding chairlike transition state of the aldol reaction.

In summary, we have shown the first examples of the proline-catalyzed asymmetric three-component Mannich reaction. Important features of this new transformation are the following: (1) The reactions typically display high enantioselectivity (up to 99% ee) and yield. (2) The inexpensive catalyst proline is available in both enantiomeric forms and can be recovered from the reaction mixture via filtration. (3) The PMP group can be readily removed after further transformations. (4) Aliphatic unbranched aldehydes can be utilized in this process. (5) The reactions do not require preformed enolate equivalents or preformed imine equivalents. Further studies will aim to shed light on the mechanism and scope of this reaction and on further applications of proline and other chiral amines in important carbon–carbon bond-forming reactions.

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Supporting Information Available: Experimental procedures, characterization of new compounds, determination of absolute configurations, and X-ray structural analysis of oxazolidine 10a (print/PDF). This material is available free of charge via the Internet at http://pubs.acs.org. See any current masthead page for ordering information and Web access instructions.

JA001923X

In all these reactions, we used the ketone component in excess. However, Mannich reactions in which all three components are used stoichiometrically have been reported. See ref 4.

(11) The following products were obtained via the reaction:

(12) In all these reactions, we used the ketone component in excess. However, Mannich reactions in which all three components are used stoichiometrically have been reported. See ref 4.


The Direct and Enantioselective Organocatalytic α-Oxidation of Aldehydes

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Abundant among natural isolates and highly versatile as a functional intermediate, the α-oxycarbonyl synthon remains an important structural target for the development of new enantioselective technologies. At the present time, however, catalytic oxidation approaches to this asymmetric motif have relied exclusively upon the use of preformed enolates or enolate equivalents.1 As part of a program aimed at developing broadly useful organic catalysts for asymmetric synthesis,2 we recently reported the first direct proline-catalyzed cross-aldol reaction of aldehydes (eq 1).3 In this communication we advance this enamine catalysis concept to describe a highly enantioselective protocol for the α-oxidation of aldehydes. To our knowledge, this study represents the first example of a direct catalytic α-carbonyl oxidation that can be accomplished with high levels of asymmetric induction.

Yamamoto and co-workers recently disclosed a conceptually novel approach to the enantioselective oxidation of tin enolates using nitrosobenzene4 as an electrophilic source of oxygen in the presence of various BINAP-AgX catalysts.5 On the basis of these studies, as well as the recent elegant work by List,6 we were prompted to consider the direct, proline-catalyzed α-oxyamination of aldehydes with nitrosobenzene (eq 2).7 While Yamamoto has shown that uncatalyzed reactions of silyl ketene acetals with nitrosobenzene lead exclusively to N-selective nucleophilic addition,8 we hypothesized that the enhanced Brønsted basicity of the nitrogen atom should partition the addition toward the desired, O-addition manifold. Direct formation of highly versatile aldehyde products without preactivation via an enol derivative is attractive from operational, atom-9 and step-economy standpoints. Moreover, the facile conversion to terminal 1,2-diols represents an alternative and practical solution to the long-standing question of asymmetric terminal olefin dihydroxylation.10

Table 1. Effect of Solvent on the Asymmetric α-Oxyamination

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<td>7</td>
<td>CH3CN</td>
<td>67</td>
<td>96</td>
</tr>
<tr>
<td>8</td>
<td>PhH</td>
<td>67</td>
<td>97</td>
</tr>
<tr>
<td>9</td>
<td>CHCl3</td>
<td>78</td>
<td>96</td>
</tr>
</tbody>
</table>

*a Isolated yield at arbitrary 15-min time point. The α-oxaldehyde product was found to be oligomeric in solution. Yields were calculated after conversion to the corresponding primary alcohol. b Enantiomeric excess determined by chiral HPLC analysis (Chiralcel AD).

The effect of catalyst loading on reaction efficiency was next evaluated (Table 2). Remarkably, catalyst loadings as low as 0.5 mol % can be utilized without significant loss in enantiocontrol (entry 5, 94% ee). In terms of operational convenience, the use of 2 mol % L-proline ensures high levels of reaction efficiency and enantioselectivity while maintaining expedient reaction times (entry 3, 2 mol % L-proline, 88% yield, 97% ee, 2 h).

Table 2. Effect of Catalyst Loading on Organocatalyzed Oxidation

<table>
<thead>
<tr>
<th>entry</th>
<th>mol % L-proline</th>
<th>time</th>
<th>% yield</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>20 min</td>
<td>88</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>45 min</td>
<td>86</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>1 h</td>
<td>88</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>8 h</td>
<td>83</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>0.5</td>
<td>18 h</td>
<td>68</td>
<td>94</td>
</tr>
</tbody>
</table>

*a Yields based upon isolation of the corresponding primary alcohol. b Determined by chiral HPLC analysis (Chiralcel AD).

Experiments that probe the scope of the aldehyde substrate are summarized in Table 3. Considerable variation in the steric demand of the aldehyde component (R = Me, Bu, t-Pr, and Ph, entries 1–3

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and 6) is possible without loss in efficiency or enantiocontrol (60–88% yield, 97–99% ee). Notably, these mild reaction conditions allow the use of electron-rich π-systems which are typically prone to oxidative degradation. For example, enamine oxidation to access enantio-enriched to oxidative degradation. For example, enamine oxidation to access excellent enantioselectivity (eq 3). Furthermore, a convenient one-borohydride provides 1,2-amino alcohols in high yield and with oxyamination product with dibenzylamine and sodium triacetoxytypical of aldehydes. For example, treatment of the unpurified most conveniently isolated as the corresponding primary alcohols. Allow the use of electron-rich (88% yield, 97–99% ee). Notably, these mild reaction conditions conducting in an aerobic atmosphere with wet solvents.

**Table 3. Enantioselective α-Oxamination: Substrate Scope**

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>Product</th>
<th>% yield</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>O=NPh</td>
<td>88</td>
<td>97%</td>
</tr>
<tr>
<td>2</td>
<td>n-Bu</td>
<td>O=NPh</td>
<td>79</td>
<td>98%</td>
</tr>
<tr>
<td>3</td>
<td>i-Pr</td>
<td>O=NPh</td>
<td>85</td>
<td>99%</td>
</tr>
<tr>
<td>4</td>
<td>CH₂CH=CH₂</td>
<td>OTIPS</td>
<td>80</td>
<td>99%</td>
</tr>
<tr>
<td>5</td>
<td>CH₃Ph</td>
<td>O=NPh</td>
<td>95</td>
<td>97%</td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>O=NPh</td>
<td>60</td>
<td>99%</td>
</tr>
<tr>
<td>7</td>
<td>(CH₂)₂OTIPS</td>
<td>OTIPS</td>
<td>76</td>
<td>98%</td>
</tr>
<tr>
<td>8</td>
<td>CH₂(3'-N-methyl-indole)</td>
<td>O=NPh</td>
<td>83%</td>
<td>98%</td>
</tr>
</tbody>
</table>

*Yields based upon isolation of the corresponding primary alcohol.

Using 2 mol % L-proline.

Using 10 mol % L-proline.

Yields based upon isolation of the corresponding primary alcohol.

Enantiomeric excess determined by chiral HPLC analysis (Chiracel AD).

Using 2 mol % t-proline.

Using 10 mol % t-proline.

Yield determined by NMR analysis.

In summary, we have described the first direct, enantioselective α-oxamination of aldehydes. Further efforts to evaluate the scope of this and related processes are underway. A full account of these studies will be forthcoming.

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**Supporting Information Available:** Experimental procedures, structural proofs, and spectral data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

**References**


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