Origins of the Enantio- and N/O Selectivity in the Primary-Amine-Catalyzed Hydroxyamination of 1,3-Dicarbonyl Compounds with In-Situ-Formed Nitrosocarbonyl Compounds: A Theoretical Study

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Abstract: Chemoselective control over N/O selectivity is an intriguing issue in nitroso chemistry. Recently, we reported an unprecedented asymmetric α-amination reaction of β-ketocarbonyl compounds that proceeded through the catalytic coupling of enamine carbonyl groups with in-situ-generated carbonyl nitroso moieties. This process was facilitated by a simple chiral primary and tertiary diamine that was derived from tert-leucine. This reaction featured high chemoselectivity and excellent enantioselectivity for a broad range of substrates. Herein, a computational study was performed to elucidate the origins of the enantioselectivity and N/O regioselectivity. We found that a bidentate hydrogen-bonding interaction between the tertiary N*-H and nitrosocarbonyl groups accounted for the high N selectivity, whilst the enantioselectivity was determined by Si-facial attack on the (E)- and (Z)-enamines in a Curtin–Hammett-type manner. The bidentate hydrogen-bonding interaction with the nitrosocarbonyl moieties reinforced the facial selectivity in this process.

Keywords: computational chemistry · enamines · enantioselectivity · hydroxyamination · reaction mechanisms

Introduction

The N-selective asymmetric nitroso aldol reaction is a straightforward route for the synthesis of chiral α-amino carbonyl compounds.[1] Previous studies have mainly focused on the reaction of carbonyl compounds with stable nitroso-benzene derivatives and both α-aminoxylation and hydroxyamination reactions have been realized with different catalytic systems.[2] However, the application of these systems is highly limited, owing to the difficulty of N-aryl bond cleavage. Recently, the direct α-coupling of carbonyl compounds to carbonyl-nitroso groups, which are generated in situ from N-hydroxy carbamates under oxidative conditions, has emerged as a new strategy for α-amination reactions.[3] Read de Alaniz and co-workers reported the copper-catalyzed racemic N-nitroso aldol and asymmetric O-nitroso aldol reactions of β-ketoesters by using O2 as an oxidant,[3a,b] whilst Maruoka and co-workers realized chiral secondary-amino-catalyzed asymmetric N-nitroso aldol reactions by using benzyl peroxide/2,2,6,6-tetramethylpiperidine-Oxyl (BPO-TEMPO) or MnO2 as the oxidant.[3c,d] Yamamoto and co-workers also reported asymmetric O- and N-selective nitroso aldol reactions by using chiral Lewis acids or chiral secondary amines as catalysts.[3e,f] As part of our ongoing efforts towards the development of chiral primary-amine-type organocatalysts,[4] we were very pleased to find that tert-leucine-derived chiral primary–tertiary diamines, such as compound 1, could catalyze the α-amination of β-ketocarbonyl compounds under aerobic oxidation conditions with high regioselectivity and enantioselectivity.[5]

Chemoselective control over N/O selection is an intriguing issue in nitroso chemistry (Scheme 1). In related reactions of nitrosobenzene, Momiyama and Yamamoto found that an alcohol group promoted C–N bond formation, whereas organic acids that contained a carboxylic acid group facilitated C–O bond formation.[5a] DFT calculations revealed that the switch in regiochemistry originated from multiple hydrogen bonds in the transition states.[5b] Nelson et al. employed hard/soft acids and bases to explain the reversal in the regiochemistry of Lewis-acid-catalyzed reactions of nitrosobenzene.[5c]
In aminocatalytic N-nitroso aldol reactions with nitroso-benzene, hydrogen-bonding interactions between the nitroso O atom—either mono-[2u] or bidentate [2t] interactions—and the catalyst moiety are generally proposed to account for the observed N selectivity. [2w] Cheong and Houk studied proline-catalyzed nitroso aldol reactions and revealed that the key reason for the regioselectivity was the difference in basicity of the N and O atoms; that is, nitrogen atoms formed hydrogen-bonding interactions with the catalyst more easily, owing to their higher basicity. [8,9] In addition, good N selectivity has also been obtained with diphenylprolinol-type aminocatalysts, in which steric effects are believed to steer the selectivity (Scheme 1).

With the advent of procedures for the in situ oxidation of N-hydroxycarbamates, carbonyl-nitroso chemistry has demonstrated its versatility in a number of transformations. In this regard, both O- and N-nitroso aldol reactions have been reported with good chemo- and enantioselectivity. In particular, the use of chiral amine catalysts has been found to promote stereoselective N-nitroso aldol reactions with aldehydes and β-ketocarbonyl compounds. [3c,f,5] The origin of the N-selectivity in these aminocatalytic systems is quite intriguing, as previous efforts with chiral Lewis acid complexes have all led to O-selective processes and the addition of (chiral) ligands has been found to enhance the O selectivity or even reverse the original N selectivity. [3b] In the latter cases, a steric model has been proposed to account for the O selectivity. [3b] Based on our own efforts towards developing primary-amine-catalyzed N-nitroso aldol reactions with aerobically generated nitrosocarbonyl compounds, [5] we endeavored to probe the origins of this N selectivity, as well as of the enantioselectivity, by using density functional theory. A bidentate hydrogen-bonding interaction with the nitroso-carbonyl group was found to govern the chemo- and stereoselectivity (Scheme 2). Herein, we report these mechanistic details.

Results and Discussion

Experimental Studies

Catalytic Cycle

Recently, we reported that a tert-leucine-derived chiral primary amine could catalyze the α-amination of β-ketocarbonyl compounds through the CuI-mediated aerobic oxidation of N-hydroxycarbamate. [5] The reactions occurred smoothly under aerobic conditions to give the amination adducts with excellent enantioselectivities (Scheme 3). Both β-
ketoesters and 1,3-diketones were tolerated under the reaction conditions. An enamine catalytic cycle has been proposed for the reaction. In this mechanism, the first step is the generation of an enamine intermediate from the catalyst and the β-ketocarbonyl compound, followed by α-amination with an in-situ-formed nitroso compound to give an imine intermediate; then, the imine undergoes hydrolysis to regenerate the catalyst and release the product (Scheme 4). In this process, it was found that the challenging issue of catalytic turnover with enamine carbonyl compounds could be addressed by judicious choice of acidic additives; in this case, triflic acid (TfOH) and meta-nitrobenzoic acid were identified as the optimal acidic additives, consistent with the known effects of acids in aminocatalysis, as well as with our previous studies on primary amine catalysis. [4a] Control experiments and stoichiometric reactions with preformed enamine esters provided direct evidence for the proposed
cycle (Scheme 5). As shown in Scheme 5, the addition of weak acid meta-nitrobenzoic acid not only facilitated the catalytic turnover, but also enhanced the chemoselectivity.

Scheme 4. Proposed catalytic cycle.

Scheme 5. a) Acidic additive effect; b) stoichiometric reactions.

Enamine Geometry

To account for the stereoinduction, we first considered the geometry of the enamine. Pleasingly, we obtained single crystals of the enamine intermediate in its active protonated state. The X-ray crystal structure of the enamine clearly indicated that the (Z)-enamine was stabilized by an intramolecular N-H-O hydrogen bond. NMR analysis of preformed enamine 5 in CDCl3 also showed that it adopted a Z configuration, consistent with the solid-state structure. On this basis, it is readily conceivable that a H-bonding network that involves the protonated tertiary amine moiety and the N-H moiety in the (Z)-enamine could stereoselectively guide the approach of an electrophile, such as nitroso-carbonyl (Scheme 3), thereby accounting for the experimentally observed high chemo- and stereoselectivity. The observed acidic additive effect is in line with this hypothesis.

In both the catalytic and stoichiometric experiments (Scheme 5), the combination of TfOH and meta-nitrobenzoic acid led to much improved chemoselectivity, thus showing the critical role of enhanced acidity, likely of the protonated tertiary amine, for inducing stereocontrol. These mechanistic insights set the basis for our further theoretical studies.

Role of Copper

The primary role of CuI in this reaction is likely to mediate the aerobic oxidation of N-hydroxycarbamates, as in many similar aerobic oxidation processes. Although the direct involvement of copper ions in inducing stereocontrol cannot be completely ruled out, experimental evidence—as well as previous observations—suggest that it is unlikely: 1) chiral copper catalysis only promote O-nitroso aldol processes, whereas this current procedure is highly N-selective; 2) no reaction was observed when preformed enamine 5 was treated with CuCl alone, thereby further highlighting the critical role of H-bonding interactions of the acidic additives in channeling the reaction (Scheme 5a); 3) a higher loading of CuCl led to severe deterioration of both the enantioselectivity and chemoselectivity for a sluggish ethyl ketone substrate, likely through a non-selective copper-mediated enol process (Scheme 6). In this instance, decreasing the loading of CuCl from 10% to 5% led to a dramatic improvement in chemo- and enantioselectivity. Thus, for these reasons, we did not consider CuCl in our subsequent computational studies of the regio- and enantiocontrol.

Scheme 6. The effect of CuCl.

Theoretical Analysis of the Chemo- and Stereocontrol

Computational Methods

Quantum mechanical calculations were performed by using density functional theory with the Gaussian 09 program package. The recently developed M06-2X functional and the 6-31G(d) basis set were used for the geometry optimizations and vibrational calculations because Houk and co-workers found good agreement between predicted and experimental data in primary-amine-catalyzed aldol reactions with the M06-2X functional. Each geometry was confirmed as either a minimum (no imaginary frequency) or transition state (one imaginary frequency) by calculating the harmonic vibrational frequencies. The SMD continuum salvation model with MeCN as the solvent were used in the
single-point energy calculations at the M06-2X/6–31+G-(d,p) level with gas-phase-optimized structures.

1. Geometry of the Enamine Intermediates

First we investigated the possible geometries of the enamine intermediates, which are critical determinants of both the regio- and enantioselectivity of this reaction. In the solid-state structure of protonated enamine 5, the TfO− anion is weakly hydrogen-bonded to the protonated amine. We expected that the hydrogen bonds would be largely weakened in polar solvents, such as MeCN, and that its influence on the enamine geometry—although it can’t be neglected—would be minimal. Therefore, the triflate anion was omitted from our calculations, owing to a balance of computation cost and accuracy. When necessary, the possible impact of the anion was pursued separately.

The structures of the enamine intermediates were explored by considering both the possible E/Z configurations and their trans/cis orientations (Scheme 7). Our computations showed that Zs-trans-1 was the most stable enamine isomer (Figure 1), in good agreement with the crystal structure (Figure 2). Three factors contribute to this result: 1) an intramolecular H-bonding interaction between the enamine N atom and the protonated N+−H group helps to stabilize the enamine conformation, a feature that is ubiquitously shared by all of the low-energy conformers, as well as by similar diamine catalysis;[2h,j,k] 2) a H-bonding interaction between the enamine N−H atom and the carbonyl O atom stabilizes the Z configuration. In comparison, the corresponding E conformation (E-s-trans-1) is 1.83 kcal mol−1 higher in energy, owing to the lack of this hydrogen bond. In these instances, H-bonding with the carbonyl O atom is 3.0 kcal mol−1 more energetically favorable than with the ester O atom (Zs-trans-1 vs Zs-trans-2 and Zs-cis-1 vs Zs-cis-2); 3) the s-trans geometry is largely favored over the s-cis geometry because it avoids the steric repulsion between the tert-butyl group on the catalyst and the methyl group on the substrate.

Owing to our omission of TfO− in the calculations, we observed a stronger hydrogen-bonding network with the ester moiety and, as a result, Zs-trans-3 was slightly favored over Zs-trans-1 by 0.3 kcal mol−1. However, this unexpected hydrogen-bonding network caused severe distortion of the enamine geometries, and it even outweighed the energy gain owing to the multiple-hydrogen-bonding network (Zs-cis-3 vs Zs-cis-1). When the triflate anion was incorporated, Zs-trans-3 quickly equilibrated to afford the standard (Z)-enamine structure. A similar effect could be expected if this conformer interacted with a reacting electrophile through H-bonding interactions. Hence, we focused on Zs-trans-1 enamine in our calculations on stereoselectivity.

2. Origin of the N Regioselectivity

Based on our experimental observations, we expected that H-bonding interactions with the nitroso carbonyl moiety played a key role in the stereoselectivity.[20] Accordingly, H-bonding interactions of the O (I) or N atoms (III) with the nitroso moiety may lead to N and O selectivity, respectively. In the reaction of nitrosobenzene, the basicity of the N/O atoms, as well as the acidity of the H-bond donor (from the catalyst), were found to dictate the H-bonding interactions with the N/O atoms and consequently the chemoselectivity.[21] Unlike nitrosobenzene, nitrosocarbonyl compounds have a bidentate H-bonding mode, in which the carbonyl group can also cooperatively contribute to the H-bonding interactions (Scheme 8, II). Bearing these factors in mind, we studied the C–N bond and C–O bond-forming transi-
The transition states with the lowest free energies are shown in Figure 3. **TS-NR1**, in which the N\(^{\text{+}}\)-H moiety hydrogen bonds to Cbz-NO in a bidentate manner, is the lowest in energy, thereby leading to a N-selective adduct. Furthermore, a C-H-π interaction between the α-methyl group of the enamine and the benzyl group of the electrophile is also formed; AIM analysis of this structure confirmed the existence of this weak bonding interaction (\(\rho = 0.009, \Delta^2\rho = 0.027\)), which further enhanced the stability of this transition state. N-selective transition state **TS-NR2**, which contained a monodentate H-bond, was also located. **TS-NR2** was disfavored by 2.7 kcal/mol \(^1\) compared to **TS-NR1**, thus highlighting the critical impact of bidentate H-bonding with the nitroso carbonyl group. Notably, all of the bonds around the newly formed C–N bond in these two transition states were staggered, thereby fulfilling Seebach's topological rule.\(^{[10]}\) The O-selective production pathway was also probed by considering N-H-N and N bond interactions (Scheme 8, IV), and we successfully reached two transition states, **TS-OR1** and **TS-OR2**, which showed minimum energy barriers for O-selective production. In both of these transition states, monodentate H-bonding with a N atom directed the approach of the nitroso moiety (Figure 3b). In addition, a bidentate hydrogen-bonding mode with N and O atoms was also considered (Scheme 8, IV); however, such a bidentate mode could not be reached and extensive optimization invariably led to a mono-binding structure as the energy minimum, thus suggesting that the four-membered hydrogen-bonding ring was highly unstable. In all cases, the most stable O-selective **TS-OR1** was 2.8 kcal/mol \(^1\) higher in energy than N-selective **TS-NR1**.

Based on these calculations, we concluded that the reaction would mainly give the hydroxyamination product (N/O ratio > 99:1), consistent with our experimental results.

3. **Origin of the Enantioselectivity**

Next, we investigated the origin of the enantioselectivity in this amination reaction. N-selective transition state **TS-NR1** was also enantioselective, thereby giving the \(R\)-adduct, which was the major experimentally obtained enantiomer. Reaction pathways for the minor \(S\) product were probed by DFT calculations (Figure 4). \(S\)-facial attack on **Zs-trans-1**, **Zs-cis-1**, and **Es-trans-1** (with an ethyl ester), the three lowest-energy enamine intermediates (Figure 4, II, III, and IV, respectively), all led to the minor \(S\) products. Pleasingly, we successfully located the transition states for these three \(S\)-selective modes. For comparison, **TS-NR1** was also listed. As shown in Figure 4, **TS-NS1**, which represented \(S\)-facial attack on the most stable enamine, **Zs-trans-1**, the nitroso moiety was H-bonded to the enamine N–H group in an ene-like structure. The tertiary amine N\(^{\text{+}}\)-H participated in a H-bonding interaction with the ester moiety. As such, the substituents around the newly formed C–N bond adopted an eclipsed structure (\(\phi_{\text{C–N–O}} = 29.9^\circ\)); thus, the free energy of **TS-NS1** was 14.3 kcal/mol \(^1\) higher than that of **TS-NR1**, which indicated that the minor \(S\) product could not be formed through this pathway. A much higher energy structure was also found for \(S\)-facial attack on enamine **Zs-cis-1** (Figure 4, II), which was possibly caused by the instability of the enamine structure. Finally, \(S\)-facial attack on enamine **Es-trans-1** (Figure 4, III) appeared to be a plausible pathway for the \(S\)-selective adduct, the free energy was 4.9 kcal mol\(^{-1}\) higher than that of **TS-NR1**, which corresponded to >99% ee. In this transition state, the bidentate H-bonding interaction between the tertiary amine N\(^{\text{+}}\)-H and nitroso-carbonyl moieties was restored. Taken together, these results indicate that the enantioselectivity was mainly deter-

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**Scheme 8.** Possible hydrogen-bonding modes with the nitrosocarbonyl group.

**Figure 3.** N/O-selective transition states for nitrosocarbonyl compounds. \(\Delta H\) values are given in parentheses (in kcal mol\(^{-1}\)).
mined by electrophilic attack on coexisting enamine geometric isomers as a result of reinforced facial selection by bidentate H-bonding interactions with the nitrosocarbonyl group. Notably, \( E\text{-}s\text{-}t r a n s\text{-}V \) (with the ethyl ester) was only 0.8 kcal mol\(^{-1}\) higher in energy than \( Z\text{-}s\text{-}t r a n s\text{-}V \) (see the Supporting Information) and the two isomers were mutually inter-convertible, which constituted Curtin–Hammett-type enantioselective control.\(^{[18]}\)

**Conclusion**

In summary, we have uncovered the origins of the region and enantioselectivity in the asymmetric enamine-based \( \alpha \)-amination reaction of nitrosocarbonyl compounds. The \( Z\text{-}s\text{-}t r a n s \) configuration was found to be the dominant enamine geometry. A bidentate hydrogen-bonding interaction between the tertiary N\(^+\)–H and nitrosocarbonyl groups was found to play a key role by differentiating between N and O addition, as well as by reinforcing the facial selection of the enamine attack. Owing to the versatility of nitrosocarbonyl chemistry, this chelation model is also relevant for similar reactions in which bidentate complexation with nitroso-carbonyl compounds through H-bonding or metal-coordination interactions can be applied.

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