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Regiochemical Reversals in Nitrosobenzene Reactions with Carbonyl Compounds: α -Aminooxyketone versus α -Hydroxyaminoketone Products

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Abstract

The Lewis acid-catalyzed reaction of nitrosobenzene with a ketone can produce an α -aminooxyketones or an α -hydroxyaminoketone, with reaction regiochemistry switching from the latter to the former, dependent upon the addition of Lewis acid or sterically-hindered solvent. While the latter (C-N bond formation) is easily explained by attack of the enolate α -carbon at N, the former (C-O bond formation) has been an enigma, with few proposed explanations, and none which explain simultaneously formation of both products and all the regiochemical reversals.

Herein, the regiochemistry reversal is proposed to occur via (1) nucleophile formation governed by Hard and Soft Acids and Bases (HSAB) theory, (2) a nucleophilic attack by the enolate O at N, followed by (3) a [2,3]-sigmatropic rearrangement. This mechanistic pathway and HSAB considerations account for formation of both products and explain the three reported regiochemistry reversals, which are observed upon the introduction of (A) Lewis acid catalyst, (B) AcOH, or (C) solvent bulkiness.

Keywords

2,3-Sigmatropic rearrangement; Enolate chemistry; HSAB theory; Regiochemical reversal

Introduction

Introducing an aminooxy group at the alpha position of a carbonyl compound or an enamine is of interest in both chemistry and medicine, because the resulting C-O-NHR linkage is an essential building block in numerous important natural products and pharmaceuticals.^[1] Condensation of a carbonyl compound and a nitroso derivative in the presence of a Lewis acid catalyst offers a particularly simple route to such important aminooxyketones.^[2]

In this transformation, a silyl or tin enolate **1** typically reacts with nitrosobenzene **2** in the presence of a Lewis acid catalyst to afford the aminooxyketone **3** (eq 1). A variety of enol ethers **1** (Z = SiMe₃, SnMe₃, SnBu₃) and Lewis acid catalysts (LAX = Me₃SiOTf, Et₃SiOTf, *t*-BuMe₂SiOTf, Me₃SiNTf₂, TiCl₄) have been used.^[2-5] The yields in eq 1 are for cyclohexanone enolates; the Lewis acid used with SiMe₃ enolate^[2] is Et₃SiOTf, while (R)-TolBINAP:AgOTf is used^[3] with SnMe₃ and SnBu₃ enolates. A direct comparison of yields for these enol ethers is not possible, because yields for all three reacting with one LAX have not been reported. However, we find the yields for reactions of silyl enol ethers to be always lower than those from reactions of trimethyl and tributyl tin enolates with nitrosobenzene; also, reactions of

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Z = SiMe₃ (44 %), SnBu₃ (92 %), SnMe₃ (95 %)

trimethyl tin enolates give slightly higher yields than tributyl tin enolates. This synthetically useful reaction was one of the first Lewis acid-catalyzed, nucleophilic addition reactions with N=O bonds, which display a high selectivity for carbon-oxygen bond formation.^[2,4,5]

At least two mechanisms (eqs 2 and 3), either individually or in combination,^[2,4] have been proposed for this formation of α -aminooxyketone **3**; both include nucleophilic attack at oxygen, which is typically regarded in organic chemistry as rare and occurring only under strongly driving conditions.^[6] These proposed^[2,4] mechanisms involve Lewis acid catalyzed attack by the enolate nucleophile at oxygen of either the complexed nitrosobenzene monomer (eq 2) or dimer (eq 3).

The unusual nucleophilic attack at oxygen (eq 2) was difficult to justify, and no rationale was provided.^[2,4] Compound **3** formation was also proposed^[2] via a nitrosobenzene dimer (eq 3), which was generated in situ in the presence of a Lewis acid. It was reasoned^[2,7] that Lewis acid coordination at one oxygen of the nitrosobenzene dimer, might withdraw electron density sufficiently to facilitate nucleophilic attack by the enolate **1** at oxygen at the other end of the dimer (eq 3).^[4] Some previous arguments concluded^[8] that ancillary evidence refuted this mode of activation, as follows: (I) Nucleophilic attack by enolate **1** upon the oxygen atom of nitrosobenzene **2** would require a significant partial positive charge on the oxygen in **2**, but Lewis acid complexation would not generate sufficient partial positive charge.^[9] (II) Even if one accepts both nitrosobenzene dimer and its coordination with a Lewis acid, this still does not rule out the monomer as the kinetically active species in the reaction pathway (eq 2).^[8] (III) The simultaneous occurrence^[2,7] of both mechanisms cannot be excluded, because nitrosobenzene **2** is reported to exist in both monomer and dimer forms in the presence of Lewis acids.^[2,7] (IV) The exact timing and ordering of the above proposed complexation and alkylation steps are uncertain.^[2] Thus, the nucleophilic

attack at oxygen shown in either eq 2 or 3 is contested, and a less controversial mechanism for this reaction is desirable.

An alternative perspective on the reaction in eq 1 (C-O bond formation) is to view it as a modification of the similar C-N bond formation shown in eq 4, which predominates under slightly different reaction conditions.

Using identical reaction conditions except without using Lewis acid,^[2] provides α-Hydroxyaminoketone **4**, which originates^[2] from nitrosobenzene monomer **2** via a straightforward mechanism^[4] (eq 5, Z = SiMe₃, SnMe₃, or SnBu₃) and provides different regiochemistry (eqs 4 vs 1).

A strong mechanism for eq 1 will explain not only the regiochemistry of eq 5, but also its reversal caused by changing reaction conditions. Three reported ways to reverse regiochemistry in eq 5, from C-N to C-O bond formation, provide clues to the reaction mechanism; the following review of these regiochemistry determinants will facilitate its mechanistic analysis.

Results and Discussion

At least three determinants each effect a regiochemistry reversal in this reaction: (A) Lewis acid addition,^[3,4,10,11] (B) AcOH addition,^[12-14] and (C) using a sterically hindered solvent.^[8,15] These regiochemistry reversals upon changing conditions, have reportedly baffled researchers^[8,12] and a different rationale was given for each observation.^[2,4,8,12] However, one general mechanistic analysis, which simultaneously accommodates multiple observations, is stronger and more desirable than a group of unrelated explanations. Thus, a single mechanism for all the C-O bond-forming reactions, and how it accommodates the reported regiochemical reversals, is provided below. Four critical influences at points A – D in the reaction with Lewis acid (eq 6) differentiate this proposed mechanism from previous ones, and explain all the regiochemical reversals. Critical points in the mechanism are: (A) Correctly identifying the site of complexation or protonation in Ph-N=O (**2b**). (B) Using Hard and Soft Acids and Bases (HSAB) theory, in order to determine whether N of Ph-N=O (**2** or **2b**) is attacked by carbon or oxygen of the enolate (**1**). (C) LAX catalyst regeneration provides the O-anion (**6a**). (D) A [2,3]-sigmatropic rearrangement transforms the O-anion (**6a**) into the resonance-stabilized N-anion (**7**).

A. Site of activating complexation or protonation in Ph-N=O

A previous explanation for C-O bond formation and aminooxy products **3** was that Lewis acid coordination or protonation at one oxygen of the nitrosobenzene dimer withdraws sufficient electron density, to enable nucleophilic attack by enolate **1** at the opposite oxygen (eq 3).^[4] In order to explore the plausibility of this explanation, calculations^[16] were carried out at the 6-31G* level on nitrosobenzene dimer, with and without a proton complexed to oxygen. The calculated charges on oxygen in these molecules are given in Table 1 below. The results predict that protonation at one oxygen of the dimer does reduce the negative charge on the opposite oxygen (from -0.607 to -0.345), but not sufficiently to generate a positive charge on the opposite oxygen.

Attack at oxygen in **2b**, the N-complexed monomer of **2** (eq 2), was proposed^[17a-c] based on prior^[17d] computational predictions favoring protonation at nitrogen. The preferred site of protonation in Ph-N=O **2** has alternately been reported to be at O atom to give protonated nitrosobenzene (2c) or at the N atom to give 2d (Figure 1).^[17a-17c] Reports favoring protonation at N generally cite references traceable to an early study by Hehre, Pople, et al.^[17d] However, close examination of that early report^[17d] reveals the clear statement "...protonation at oxygen is favored." Our results agree with that early report,^[17d] predicting oxygen-protonated **2** to be 4.69 kcal/mol more stable than nitrogen-protonated **2**.

It was also desirable to explore the effects of Lewis acid complexation at oxygen upon the molecular characteristics of monomer Ph-N=O **2**. This was done by molecular orbital calculations^[16] at the 6-31G* level on nitrosobenzene **2** with and without cations H⁺, Me₃Si⁺, and Cl₃Ti⁺ complexed to oxygen of **2**; this estimates the change in charge upon oxygen and nitrogen and the change in N=O bond order, due to complexation. The resulting computational data are shown in Table 2, along with the experimental regioselectivities as % yields of C-amination (C-N bond formation),^[2,12] which correspond to nucleophilic attack by the enolate carbon at nitrogen versus nucleophilic attack by the enolate oxygen at nitrogen (O-N bond formation, followed by rearrangement) to form ultimately a new C-O bond.

In Table 2, all cationic complexations at oxygen of **2** are predicted to (1) increase the positive charge at nitrogen, (2) increase the negative charge at oxygen, and (3) decrease the N=O bond order. Curiously, the calculations did not always show an increase in positive charge at nitrogen upon complexation at oxygen, but the nitrogen-oxygen charge difference was always predicted to increase. Our computational results agree generally with the data from experimental studies of the effect of complexation upon regiochemistry.

B. Hard and Soft Acids and Bases (HSAB) theory

HSAB^[18] theory can explain the regiochemistry of this reaction. HSAB predicts that hard acids (or electrophiles) generally react faster and form stronger bonds with hard bases (or nucleophiles), and that soft acids (or electrophiles) generally react faster and form stronger bonds with soft bases (or nucleophiles), if all other factors are equal. In order to apply this concept to the reactions in eqs 1 and 4, it is necessary to identify hard and soft characteristics of reactants **1** and **2**. Enolate **1** has three resonance structures **1a**, **1b**, and **1c** as shown in Figure 2. In two resonance structures, the bond between oxygen and Z is broken, which affords a negative charge on oxygen and carbon in **1b** and **1c** respectively.

Resonance structure **1a** is the greater resonance contributor in this reaction, but **1b** and **1c** are significant, pertinent to this reaction, and help explain the reactivity of the system and its rationale, while the more stable enol resonance structure **1b** has a partial negative charge on oxygen of the enolate. The keto resonance structure **1c** bears a negative charge on the carbonyl α carbon. A shorthand combination of resonance structures **1b** and **1c** can be drawn as **1d**, in which the enolate negative charge is distributed between oxygen and the α -carbon. Hard and soft ends of structure **1d** are identified in structure **1e**, with more (larger) negative charge on the “hard” oxygen and less (smaller) on the “soft” α -carbon. A simple perspective is that the greater negative charge on the highly electronegative oxygen of **1** (represented most clearly in resonance structure **1b**) makes oxygen the hard end of the enolate, and more prone to react with a hard acid (such as nitrosobenzene complexed to a Lewis acid). Conversely, the smaller negative charge on the less electronegative α -carbon of **1** (represented most clearly in resonance structure **1c**) makes carbon the soft end, which favors reacting with a soft acid (such as free nitrosobenzene).

The simple resonance structure analysis for charge distribution of enolate **1** agrees with the results of 6-31G* calculations on Me₃Si-O-CH=CH₂ as a model. The results support assignment of the enolate hard and soft ends based on computed charge densities. Atomic charges of O, carbonyl C, and α -C of the model were calculated to be -0.740, 0.217, and -0.476, respectively. These values predict oxygen to be the hard end of the enolate, and carbon to be the soft end of the enolate, respectively (Figure 2, structure 2e).

In **2**, N=O is polarized to put more π electron density on O and a partial positive charge on N (Table 2), due to the greater electronegativity of oxygen, similarly to a carbonyl.^[6] Thus, nitrogen is always the more electrophilic site and the soft end in **2** (Table 2), but the N=O bond is less polarized without a Lewis acid.

1. Soft-soft interaction: Formation of α -hydroxyaminoketones such as **4**—

HSAB theory explains the α -carbon (soft end) of enol **1** attacking the nitrogen atom (soft end) of N=O (eq 7). In the absence of a Lewis acid, nitrogen of nitrosobenzene **2** behaves as a soft acid and reacts with the soft end of enolate **1**. The α -carbon, which has a smaller partial negative charge, is more prone to react with **2** at nitrogen, via a soft-soft interaction; this is easily visualized as forming the bond between carbon of resonance structure **1c** and nitrogen of nitrosobenzene **2**, producing intermediate **5**, which is converted to α -hydroxyaminoketone **4** upon workup (eq 7).

a. Effect of using a Lewis acid catalyst: In contrast to the C-N bond-forming reaction (eq 4), adding a Lewis acid catalyst to complex with Ph-N=O produces only the aminooxyketone **3** (eq 1), in which a C-O bond is formed.^[3,4,10,11] A reasonable mechanism (eq 6) for the reaction of compound **1** with **2** in the presence of a Lewis acid is similar to that without one (eq 7). Complexing a Lewis acid to the Ph-N=O oxygen in **2** increases both the N=O π bond polarization, as well as the magnitude of the difference between the partial positive charge on N versus on O (Table 2); therefore, O-complexation makes N more susceptible to nucleophilic attack, analogously to carbonyl protonation.^[6] Following the principles of HSAB, complexation at O increases the δ^+ charge at N and converts **2** from a soft acid to a hard acid. This reverses the regiochemistry of the Ph-N=O reaction with enolate **1** (eq 7); the hard electrophilic nitrogen of **2** now reacts with the hard (oxygen) end of enolate **1** (eq 6). Therefore, enolate **1**, with a greater partial negative charge on oxygen than on carbon, can be visualized as reacting through resonance structure **1b** via a hard-hard interaction; a bond forms between oxygen of **1d** and nitrogen of nitrosobenzene **2** to afford intermediate **6** (eq 6), which rearranges further.

The relatively simple mechanism (eq 9) depicts the hydrogen bonding needed to activate Ph-N=O mildly.

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Initially, these reversals were termed “surprising”^[12] with no explanation for the selectivity offered.^[8] Since that time, the selectivity leading to C-O bond formation in eq 10 has been attributed to multiple simultaneous, extended hydrogen bondings in the transition state structure^[12b] and the stability of an eight-membered ring transition state.^[12b,12c] However, the regiochemistry reversal is easily and simply explained by HSAB, analogously to that caused by Lewis acid addition (eqs 2 and 1). The regiochemistry reversal caused by acetic acid addition (eqs 10 versus 8) is similar to the reversal caused by Lewis acid addition (eqs 1 versus 4), and the reason is analogous. The mechanistic steps in the enamine system, shown below (eq 11) are analogous to those of the enolate system (eq 6).

(i) MeOH forms a hydrogen bond with O of Ph-N=O **2**, activating it sufficiently to react as a soft acid and forming a C-N bond (eq 9). (ii) Acetic acid is a sufficiently strong H⁺ donor to protonate O of Ph-N=O (Table 2) and change nitrosobenzene **2** into a hard acid (eq 11). (iii) Protonated **2** favors nucleophilic attack by enamine **10** from its hard end; nitrogen of the pyrrolidine moiety in **10** attacks protonated nitrosobenzene at nitrogen to afford intermediate **13**. (iv) Deprotonation by AcO⁻ is analogous to LAX catalyst regeneration. (v) [2,3]-Sigmatropic rearrangement gives resonance-stabilized intermediate **14**, which rearranges to intermediate **15**, followed by aqueous workup to give the *O*-alkylated product **11** (eq 11).

A similar proline-catalyzed reaction^[9a] also shows the same regiochemical reversal. In this case, an internal carboxylic acid functionality is the acid source. Another study^[12c] using an asymmetric proline catalyst gives >99 %ee with a variety of aldehydes and carboxylic acids; yields of the *O*-alkylated product were increased by using more acidic carboxylic acids, lower temperatures, and less polar solvents. These determinants for increasing %ee, lower reaction temperature, and less polar solvent are in accord with the pericyclic reaction in eq 11.^[12c] The nonpericyclic reaction, which gives the *N*-alkylated product, generally yields lower %ee values and yields, and requires higher reaction temperatures and more polar solvents, as expected.^[12c]

c. Solvent effects: Using 10 mol% of the Lewis acid 2:1 silver(I)triflate:BINAP complex in ethylene glycol diethyl ether solvent (eq 12), the reaction of tin enolate **16** with **2** gives α-hydroxyamino product **9** (C-N bond formation) with high enantioselectivity. The chirality of (AgOTf)₂:(*R*)-BINAP (Figure 3) induces chirality in the reaction products. In contrast, the same reaction in THF solvent yields the aminooxy product **11** (C-O bond formation) with little enantioselectivity (eq 13).^[15] The two reactions are run under identical conditions, except the solvent is changed from EtOCH₂CH₂OEt. No explanation for this reversal in

regioselectivity upon changing solvent has been reported,^[8] but a combination of HSAB and steric effects explains this reversal.

The 2:1 silver(I) triflate:BINAP complex gives^[8] predominantly C-N bond formation yielding **9** in bidentate ethylene glycol diethyl ether solvent, but predominantly C-O bond formation yielding compound **11** in the more polar^[19] THF solvent. These solvents differ in at least three ways considered below: (1) polarity, (2) steric effects, (3) and the number of complexing heteroatoms in each molecule.

The X-ray crystal structure of the 2:1 catalyst complex used in these reactions shows each phosphorous of BINAP coordinated to a separate Ag^I center; one metal center bears two triflates and the other two water molecules.^[8] This solid phase X-ray structure may offer little insight into the structure of the complex in solution, functioning as a catalyst. However, the structure suggests that the BINAP catalyst induces chirality in the reaction by Ag complexing to both or either of the heteroatoms, as well as the solvent; it is reported that the exact identities of all donors complexed to Ag in this compound are not certain.^[8]

Nevertheless, solvent interaction with the BINAP catalyst in this reaction is confirmed by data in Table 3; switching solvent from ethylene glycol diethyl ether to THF reduces the reaction %ee from 99 to 9 and reverses its regiochemistry.^[15] Both observations are simultaneously explained by the mechanism proposed earlier as follows: (1) The nitrosyl oxygen of nitrosobenzene **2**^[8] associates with the silver (I) triflate:BINAP Lewis acid, as suggested by the X-ray data. This induces the enantioselectivity in the reaction. (2) The solvent oxygen(s) is (are) also in association with Ag of the BINAP catalyst, as suggested by the X-ray data. (3) The solvent with lower steric requirements (THF) permits attack at N of **2** by the more sterically hindered oxygen end (OSnBu₃) of the enolate, followed by a [2,3]-sigmatropic rearrangement; this is analogous to the reactions with Lewis acid or AcOH. These three analogous reactions have the same regiochemistry, because complexation with O of Ph-N=O converts Ph-N=O into a strong (HSAB) acid, which reacts with the strong (HSAB) base (O) end of the enolate. The steric effects are small enough so that HSAB effects predominate. (4) The polar bidentate ethylene glycol diethyl ether solvent is more sterically demanding than THF, but its oxygens still associate with Ag. Ordinarily HSAB would cause attack by O at N of Ph-N=O, but the more sterically demanding solvent (EtOCH₂CH₂OEt) hinders nucleophilic attack by the bulkier end (O bearing SnBu₃) of enolate **16**; therefore, this reaction proceeds by attack at N of Ph-N=O by the less sterically hindered carbon end of the enolate to form a new C-N bond producing **9** (eq 12). In this case, steric effects outweigh the influences of HSAB.

Solvent polarity was also proposed^[8,15] to influence regioselectivity; this hypothesis can be tested by examining the reaction selectivities versus characteristics of the reaction solvents (Table 3). DMF, 1,2-dimethoxyethane, and 1,2-diethoxyethane have dielectric constants^[19] of 36.70, 7.20, and 5.60 respectively, while THF and Et₂O have values of 7.58, and 4.2 respectively, as shown in Table 3. The former trio of solvents produce more C-N bond

formation due to attack by the enolate carbon, than the latter pair, with regioselectivities 94, 92, 96, 5, and 73% respectively.^[15] THF has the least selectivity for the N product, although other solvents have higher or lower dielectric constants^[19]; this indicates little influence of dielectric constant upon selectivity. A similar analysis can be made with dipole moments^[19] of the four solvents DMF, 1,2-dimethoxyethane, THF, and Et₂O, which are 3.24, 1.71, 1.75, and 1.15 D respectively (Table 3). Therefore, there is little correlation by using only the solvent characteristics versus the reaction selectivities.

The %ee data in Table 3 correlate best with the solvents by grouping the data according to the number of heteroatoms in each solvent; data in Table 3 is partitioned in this manner to reveal the trends. Within each group, the %ee increases as dielectric constant and steric requirements increase, and as the dipole moment decrease. Clearly the major considerations here, is solvent steric effects.

C. LAX catalyst use and regeneration

When a Lewis acid catalyst or AcOH is used in this reaction, it is regenerated. The presence of either produces two changes: (1) complexation with O of Ph-N=O changes the site of nucleophilic attack upon Ph-N=O, and (2) upon regeneration, the cation loss leaves a negative charge on O in **6**. This provides intermediate **6a** (eq 6) or **13a** (eq 11) respectively; these intermediates are capable of undergoing a [2,3]-sigmatropic rearrangement to produce resonance-stabilized anions **7** and **14**, respectively. Thus, adding either causes a regiochemistry reversal, for similar reasons and by similar mechanisms.

D. [2,3]-Sigmatropic rearrangement

The O-anions **6a** and **13a** can gain resonance stability via [2,3]-sigmatropic rearrangements to produce anions **7** and **14**, respectively. Precedents for such reactions are discussed below.

1. Analogous [3,3]-sigmatropic reaction—A pericyclic process similar to the [2,3]-sigmatropic rearrangements described above has been documented in the analogous [3,3]-sigmatropic rearrangement (eq. 14).^[20] This reaction similarly delivers oxygen to the alpha position.

2. Categorization of [2,3]-sigmatropic rearrangement—At least five categories of [2,3]-sigmatropic rearrangement have been reported: ylide (terminal anion),^[21] ylide (terminal cation),^[22] carbene,^[23] cation,^[21e-g,24] and anion.^[25] Examples of these are shown in Scheme 1 below. The [2,3]-sigmatropic rearrangement in the mechanism herein is an anion type rearrangement, because the negative charge initially on O is transferred to N during the rearrangement (eq 12 or 10).

Conclusions

Three pairs of enol ether reactions with Ph-N=O document similar product regiochemistry reversals, with no previous satisfactory explanation or single mechanism reported, which would bring consistency to the group. This manuscript proposes simple and reasonable reaction mechanisms for the formation of α -aminooxyketones and of α -

hydroxyaminoketones, from enol ethers with nitrosobenzene (1) in the presence and absence of Lewis acid, (2) upon switching from proton donor AcOH to MeOH, and (3) upon increasing solvent bulkiness.

The mechanism proposed for C-N bond formation providing α -hydroxyaminoketones is straightforward. Key considerations in the mechanism leading to the more complicated C-O bond forming reaction to give α -aminoxyketones are (1) Lewis acid complexation at O of nitrosobenzene to produce significant positive charge at nitrogen, (2) HSAB-governed attack by enolate or enamine at the nitrogen of nitrosobenzene, (3) catalyst regeneration, and (4) [2,3]-sigmatropic rearrangement.

Experimental Section

Methods

An ab initio method at HF level with a 6-31G* basis set was used to obtain the calculated data. Minimum energy geometries were calculated for each molecule, with full geometry optimization.^[16]

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Figure 1.
Structures of protonated nitrosobenzene

Figure 2.

Resonance structures of enolate 1 with hard and soft ends labeled.

Figure 3.
Simple drawing of the 2:1 complex of silver(I)triflate:(*R*)-BINAP solid, based on its reported^[15] X-ray crystal structure determination.

Scheme 1.

Heavy atom skeletons showing the five known types of [2,3]-sigmatropic rearrangement.

Table 1

Calculated Mulliken charges on atoms in nitrosobenzene dimer, protonated and not protonated.

	H	O	N	N	O
dimer		-0.607	0.125	0.125	-0.607
dimer-H ⁺	0.508	-0.527	-0.113	0.274	-0.345

Table 2

Yields for reaction of **1** with and computational data for Ph-N=O, with and without complexation to Lewis Acids Cl₃Ti⁺, Me₃Si⁺, and H⁺

Complexing cation	% yield		Mulliken atomic charge			N=O bond order
	C-N bond	C-O bond	N	O	Δ	
none	100	0	0.025	-0.334	0.36	1.923
H ⁺	48	52	0.004	-0.481	0.49	1.229
Cl ₃ Ti ⁺	29	71	0.061	-0.658	0.72	1.374
Me ₃ Si ⁺	14	86	0.060	-0.540	0.60	1.500

Table 3

Regioselectivity toward C-N bond formation in the reaction (eqs 12 & 13) catalyzed by (AgOTf)₂:(R)-BINAP (2:1) in different solvents.

solvent	dipole moment ^[19]	dielectric constant ^[19]	regioselectivity % of α - hydroxyaminoketone ^[15]	%ee ^[15]
DMF	3.24	36.70	94	5
1,2-dimethoxyethane	1.71	7.20	92	40
1,2-diethoxyethane		5.60	96	>99
THF	1.75	7.58	5	9
Et ₂ O	1.15	4.20	73	90