O-nitroso aldol synthesis: Catalytic enantioselective route to \(\alpha\)-aminooxy carbonyl compounds via enamine intermediate

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The approach using pyrrolidine enamine as substrate has been studied for this synthesis, and an important catalyst structural feature has been developed. After survey of pyrrolidine-based Brønsted acid catalyst, tetrazole catalyst (3f) was found to be optimal in synthesis of aminooxy carbonyl compounds in high yields, with complete enantioselectivity not only for aldehydes but also for ketones.

Regio- and stereoselective replacement of hydrogen by oxygen results in a rapid increase of molecular complexity (1–6). We recently described the catalytic enantioselective synthesis of \(\alpha\)-hydroxy carbonyl compounds from ketone enolates (7). This method depends heavily on the new nitroso aldol synthesis (Eq. 1 and refs. 8 and 9), and by choosing the right catalyst, nitroso-benzene can function as an oxy electrophile for the enantioselective introduction of oxygen to \(\alpha\)-position at carbonyl derivatives. The silver 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) catalyst has been developed further into a highly reactive complex to generate \(\alpha\)-aminooxy ketone with excellent regio- and enantioselectivity (Eq. 2).

In 1972, Lewis et al. (10) reported the reaction of nitrosobenzene with 1-morpholin-1-ylcyclohexene followed by simple hydrolysis to give the hydroxyamino ketone as the major product. Surprisingly, however, we found that the similar reaction of nitrosobenzene with 1-pyrrolidin-1-ylcyclohexene followed by treatment with acetic acid gave rise to the aminooxy ketone almost exclusively (Eq. 3). The observed discrepancies may originate from the structural difference of enamines (11–18). We describe herein careful experiments on nitrosobenzene with pyrrolidine.

More recently MacMillan and coworkers (19), Zhong (20), and Hayashi et al. (21) independently reported the enantioselective nitroso aldol synthesis of nitrosobenzene and simple aldehydes using proline catalyst (Eq. 4). In fact, a series of recent reports of organic catalysts have shown that natural amino acid proline has been used to activate ketones and aldehyde as nucleophilic enamine intermediates for various reactions (22–25). We also reported a diamine-protonic acid catalyst (26, 27) and pyrrolidine-base tetrazole catalyst (28, 29) for asymmetric direct aldol reaction with high catalyst turnover. Herein we report that the tetrazole catalyst gave the aminooxy carbonyl compound in high yields with complete enantioselectivity not only for aldehydes but also for ketones (Eq. 5 and refs. 30 and 31).

Experimental Procedures

Preparation of L-Pyrrolidine-2-yl-1H- tetrazole (3f) (Scheme 1 and refs. 32 and 33). The ammonium hydrogen carbonate (1.26 eq) was added to the stirred solution of carbobenzyloxy-L-proline (1 eq), pyridine, and Boc\(_2\)O (1.30 eq) in MeCN and stirred for 20 h. The solvent was removed, and the residue was diluted with ethyl acetate, washed with water, extracted with ethyl acetate, dried

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over MgSO₄, and evaporated in vacuo to afford N-Benzoylcarbonyl-L-prolinamide as colorless crystals. ¹H NMR (CDCl₃, 400 MHz) δ 7.36 (m, 5H, Ar-H), 6.71 (s, 1H, NH), 5.81 (s, 1H, NH), 5.20 (d, 1H, J = 12 Hz, OCH₃), 5.15 (d, 1H, J = 12 Hz, OCH₃), 4.32 (m, 1H, NCH), 3.53 (m, 2H, NCH₂), 1.91–2.33 (m, 4H, CH₂CH₂).

The phosphorus oxychloride in dichloromethane was added over 10 min to the solution of N-Benzoylcarbonyl-L-prolinamide in dry pyridine at approximately −5 to −10°C under N₂. The mixture was stirred at approximately −5 to −10°C for 1 h, and then it was poured on ice and extracted with saturated cupric sulfate solution and saturated sodium chloride solution, dried over MgSO₄, and evaporated in vacuo to afford N-Benzoylcarbonyl-L-proline nitrile as a pale-yellow oil. ¹H NMR (CDCl₃, 400 MHz) δ 87.96 (d, 2H, J = 7.2 Hz, Ar-H), 7.90 (t, 1H, J = 7.2 Hz, Ar-H), 7.77 (t, 2H, J = 8.0 Hz, Ar-H), 4.80 (s, 1H), 3.28–3.36 (m, 2H), 2.34–2.52 (m, 1H), 2.04–2.20 (m, 3H).

The mixture of N-Benzoylcarbonyl-L-prolinamide (1 eq), sodium azide (1.04 eq), ammonium chloride (1.1 eq), and dry dimethylformamide was stirred at −90–95°C under N₂ for 6 h. The mixture was poured onto ice, acidified to pH 2 with dilute HCl, and extracted with CHCl₃. The CHCl₃ layer was washed with water and saturated sodium chloride, dried over Na₂SO₄, and evaporated in vacuo to afford crude material. This crude material was purified with silica gel chromatography to pure N-Benzoylcarbonylpyrrolidin-2-yl-1H-tetrazole. ¹H NMR (CDCl₃, 400 MHz) δ 87.37 (s, 5H), 5.20 (m, 3H), 3.55 (m, 2H), 2.06–2.34 (m, 4H).

N-Benzoylcarbonyl pyrrolidin-2-yl-1H-tetrazole and 10% palladium on charcoal in acetic acid/water (9:1) was stirred under H₂ at room temperature (rt) for 4 h. The mixture was filtered through Celite, and the filtrate was evaporated in vacuo to afford crude 1-pyrrolidin-2-yl-1H-tetrazole, which was recrystallized from acetic acid and diethyl ether. (α)D ≈ −8.5⁰ (c = 0.63, MeOH); ¹H NMR (CD₃OD, 400 MHz) δ 8.42 (m, 2H), 3.33 (m, 2H), 2.39 (m, 1H), 2.02–2.41 (m, 3H); ¹³C NMR (CD₃OD, 100 MHz) δ 81.93, 62.1, 46.6, 31.1, 24.8.

General Procedure for the O-Nitroso Aldol Reaction of Ketone to Nitrosobenzene Using L-Pyrrolidine-Based Tetrazole Catalyst (3f). To an rt solution of pyrrolidine-based tetrazole catalyst (10 mol %) in acetonitrile (1 ml) was added nitrosobenzene (1 eq, 0.5 mmol) in one portion and stirred at rt for 10 min. To this green, heterogeneous solution then was added aldehyde (3 eq, 1.5 mmol) in one portion. The resulting mixture was stirred at this temperature until the nitrosobenzene was consumed completely (~15–30 min), as determined by TLC (hexane/ethyl acetate = 2:1). Then, the reaction was transferred to a methanol suspension of NaBH₄ at 0°C. After 20 min, the reaction mixture then was poured into a saturated NH₄Cl solution. The aqueous layer was extracted with diethyl ether (20 ml, three times). The combined organic extracts were dried over Na₂SO₄ with cooling and concentrates under reduced pressure after filtration. The residual crude product was chromatographed on a column filled with silica gel using a mixture of ethyl acetate and hexane as the eluant to give the product.

General Procedure for the Synthesis of 3-Phenyl-propane-1,2-diol (9f). The solution of 2-N-phenyl aminoxy-3-phenylpropan-1-ol 8f (1 eq) MeOH (1 ml) was added to a methanol suspension of CuSO₄ (0.3 mmol) at 0°C and stirred at this temperature for 3 h. The reaction mixture was quenched by cooled brine (20 ml), and the aqueous layer was extracted with ethyl acetate (10 ml, three times). The combined organic extracts were washed with brine, dried over Na₂SO₄ with cooling, and concentrated under reduced pressure after filtration. The residual crude product was chromatographed on a silica gel using a mixture of ethyl acetate and hexane as the eluant to give the product.

Determination of Absolute Configuration 5a. Basic data of x-ray structure are provided in Data Set 1 and Figs. 4–7, which are published as supporting information on the PNAS web site. The reduction to diol for determination of absolute configuration was also attempted by using cyclohexanone under the 5 mol % of 3f as follows: after the nitroso aldol reaction, the treatment of CuSO₄ in MeOH to afford α-hydroxy ketone, followed by reduction with NaBH₄ in MeOH or the reduction with NaBH₄ in MeOH for transformation of aminoxy alcohol, followed by N—O cleavage using Adam’s catalyst. Unfortunately, however, the reaction product remained as a mixture of ethanol and hexane as the eluant to give the product.
both cases could not provide enough pure trans-1,2-cyclohexanediol to compare with absolute configuration in the literature.

Results and Discussion

Reaction of nitrosobenzene with pyrrolidine enamine in benzene at 0°C generated a new intermediate 1, which was converted to the second intermediate 2 by the exposure of acetic acid. The intermediate 2 was able to be transformed to the aminooxy ketone after usual work-up (Fig. 1). Various solvents and temperature combination were examined for this transformation, and DMSO emerged as the most suitable solvent to afford aminooxy ketone without production of azoxy dimer by-product. 1H NMR study in DMSO-d6 revealed a downfield shift of enamine olefin proton (J/H11005 3.9 Hz) from /H9254 4.1 to 4.4 ppm, one proton broad singlet at /H9254 8.2 ppm due to the aminooxy N\text{H}, and one proton triplet (J/H11005 4.5 Hz) at pyrrolidine /H9251 position at /H9254 4.3 ppm, which indicate the formation of the intermediate 1. After treatment with acetic acid, complete conversion to a single new species is observed. This species is assigned as the iminium salt 2 (34, 35) based on the significant downfield shift from 4.3 to 4.9 ppm. Table 1. Catalyst survey of O-nitroso aldol reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol %)</th>
<th>Time</th>
<th>Yield, %*</th>
<th>5a/6a/7a</th>
<th>ee of 5a, %‡ (Conf.)§</th>
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<tbody>
<tr>
<td>1</td>
<td>3a (5)</td>
<td>1 day</td>
<td>&lt;1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3b (5)</td>
<td>1 day</td>
<td>&lt;1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3c (5)</td>
<td>1 day</td>
<td>&lt;1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3d (5)</td>
<td>1 h 4</td>
<td>&gt;99/-/1-</td>
<td>37 (S)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3e (5)</td>
<td>1 h 3</td>
<td>98/-/2/-</td>
<td>&gt;99 (R)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3f (5)</td>
<td>1 h 4</td>
<td>&gt;99/-/1-</td>
<td>&gt;99 (R)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>3f (2)</td>
<td>1 h 4</td>
<td>94/-/1-</td>
<td>&gt;99 (R)</td>
<td></td>
</tr>
</tbody>
</table>

Reactions were conducted with a catalytic amount of 3, 1.0 eq of nitrosobenzene, and 3 eq of cyclohexanone (4a) in DMSO at room temperature.
*Isolated yield.
†Determined by yield of each isolated isomer.
‡Determined by HPLC and Chiralpak ad (see supporting information).
§Determined after conversion to the corresponding diol (see Supporting Text).

Table 2. Scope of O-nitroso aldol reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>4 Yield, %*</th>
<th>5/7† ee of 5, %‡ (Conf.)§</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>4a 94</td>
<td>&gt;99/-/1- &gt;99 (R)</td>
</tr>
<tr>
<td>2</td>
<td>4b 87</td>
<td>&gt;99/-/1- &gt;99</td>
</tr>
<tr>
<td>3</td>
<td>4c 97</td>
<td>&gt;99/-/1- 99</td>
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<td>4</td>
<td>4d 95</td>
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</tr>
<tr>
<td>5</td>
<td>4e 75</td>
<td>72/28 &gt;99</td>
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<tr>
<td>6</td>
<td>4f 67</td>
<td>&gt;99/-/1- 98 (R)</td>
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<tr>
<td>7</td>
<td>4g 65</td>
<td>&gt;99/-/1- 98</td>
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<tr>
<td>8</td>
<td>4h 69</td>
<td>&gt;99/-/1- 98</td>
</tr>
</tbody>
</table>

Reactions were conducted with 5 mol % of 3f, 1.0 eq of nitrosobenzene, and 3 eq of 4 in DMSO at rt.
*Isolated yield.
†Determined by yield of each isolated isomer.
‡Determined by HPLC (Supporting Text).
§Determined after conversion to the corresponding diol (Supporting Text).
¶Reaction was conducted with 20 mol % of 3f in DMSO at rt.
††Reaction was conducted with 20 mol % of 3f in MeCN at rt.
‡‡Reaction was conducted with 10 mol % of 3f in MeCN at rt.
***Reaction was conducted with 20 mol % of 3f in MeCN at rt.

[Figure 1: Reaction of nitrosobenzene with pyrrolidine enamine in benzene at 0°C generated a new intermediate 1, which was converted to the second intermediate 2 by the exposure of acetic acid. The intermediate 2 was able to be transformed to the aminooxy ketone after usual work-up. Various solvents and temperature combination were examined for this transformation, and DMSO emerged as the most suitable solvent to afford aminooxy ketone without production of azoxy dimer by-product. 1H NMR study in DMSO-d6 revealed a downfield shift of enamine olefin proton (J/H11005 3.9 Hz) from /H9254 4.1 to 4.4 ppm, one proton broad singlet at /H9254 8.2 ppm due to the aminooxy N\text{H}, and one proton triplet (J/H11005 4.5 Hz) at pyrrolidine /H9251 position at /H9254 4.3 ppm, which indicate the formation of the intermediate 1. After treatment with acetic acid, complete conversion to a single new species is observed. This species is assigned as the iminium salt 2 (34, 35) based on the significant downfield shift from 4.3 to 4.9 ppm.]
5.3 ppm (α-proton of iminium group) and disappearance of the 84.4 ppm triplet. After work-up, the iminium salt 2 can be hydrolyzed to α-aminoxy ketone (detailed spectral data are provided in Supporting Text, which is published as supporting information on the PNAS web site).

This information, together with the reported proline-catalyzed reactions of nitrosobenzene with aldehydes, prompted us to test the possible enantioselective O-nitroso aldol synthesis of cyclohexanone by using pyrrolidine-based Brønsted acid catalysts (26–29, 36–43). The results with various catalysts are summarized in Table 1 and Eq. 6 (44). The several kinds of substituted pyrrolidine-trifluoroacetic acid (3a–3e) were unable to catalyze nitroso aldol process after 1 day at rt. The diamine-protonic acid catalyst (3d) afforded O-adduct with S configuration but did not provide catalyst turnover. The proline (3e) and pyrrolidine-based tetrazole (3f) afforded a promising level of regioselectivity and enantioselectivity with R configuration for the O-nitroso aldol adduct. The tetrazole catalyst especially was shown to be more attractive from the higher reactivity. The difference of reactivity is clearly demonstrated by the following comparison experiments taking advantage of the complete enantioselectivity for aminoxy ketone (Eq. 7): under the 3 mol % l-pyrrolidine-based tetrazole and d-proline as a mixed catalyst, the O-nitroso aldon product was isolated in 81% yield, with 32% ee mainly from the tetrazole catalyst (R/S = 66:34).

The scope of the O-nitroso aldol reaction was investigated further by using other ketones and aldehydes (Table 2 and Eq. 8). Optimal results were obtained with 5 mol % of l-pyrrolidine-tetrazole (3f) in the reaction of nitrosobenzene with an excess of cyclohexanone (5a: 94%, >99% ee). The other substituted cyclohexanones (4b, 4c, and 4d) also reacted smoothly in the presence of 3f (5 mol %) to afford O-adducts 5 in 87–97% yield and in >99% ee. When the acyclic ketone (4e) and aldehydes (4f–4h) were used, the enantioselectivities were still maintained in excellent level, but yields of O-nitroso aldol products were moderate due to production of N-adduct (7e) and azoxy dimer by-product. The use of 10–20 mol % catalyst, however, afforded a 67–75% yield.

The absolute configuration of α-aminoxy compounds was determined by the x-ray structure of the product provided by the reaction of p-bromo nitrosobenzene and cyclohexanone (Fig. 2) and reduction to the corresponding diols derived from hydrocinnamaldehyde (Eq. 9; ref. 45) (see Experimental Procedures). This observation indicated the similar transition-state-proposed models for the proline-catalyzed aldol reaction. The most stable enamine conformer derived from ketone or aldehyde can be assigned as shown in Fig. 3 (46–50). Taking into consideration the basic properties of enamine or nitroso compound as both nucleophilic and electrophilic functions (51–53), the reaction of nitrosobenzene may proceed from the same side of tetrazole (or carboxylic acid) by either direct activation of nitrosobenzene by acidic proton (10a) or an indirect route via amine-nitrosobenzene complexation followed by rearrangement (10a*).

Conclusions

The O-nitroso aldol synthesis has been developed by using pyrrolidine-tetrazole catalyst not only for aldehydes but also ketones. With the appropriate Brønsted acidity in tetrazole catalyst, both high ees and reactivity were realized in catalytic reaction. Identification of clean and regioselective transformation of O-nitroso aldol adducts furnished from pyrrolidine enamine gave the essential information to achieve a catalytic enantioselective route by using chiral amine catalyst. We believe that this O-nitroso aldol synthesis offers an entry into pyrrolidine-based organic catalysis and delivers valuable information about the relationship between small amines and nitroso compounds.

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