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Direct proline catalyzed asymmetric α-aminooxylation of aldehydes

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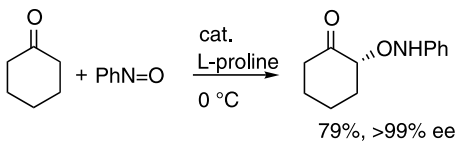
Abstract—The direct catalytic enantioselective α-aminooxylation of aldehydes has been developed using nitrosobenzene as the oxygen source and L-proline as catalyst, affording versatile α-aminooxylated aldehydes in high yield with excellent enantioselectivities.

Optically active α-hydroxyaldehydes are important intermediates in organic synthesis. Because of this utility, many methods have been developed for their preparation,[1] for instance, transformation from chiral natural sources such as amino acids,[2] sugars,[3] and chiral α-hydroxy acids.[4] Diastereoselective reactions such as nucleophilic addition to chiral glyoxal derivatives,[5] or alkylation of chiral hydrazones,[1] are other useful synthetic methods. Asymmetric hydrocyanation,[6] and enzymatic resolution[7] have also been employed as a key step for their synthesis. Most of these preparations, however, require multiple manipulations and there is no direct method, nor catalytic asymmetric method for their synthesis from the corresponding aldehyde.

On the other hand, proline[8] has been found to be an excellent asymmetric catalyst of the aldol reaction[9] and Mannich reaction,[10] and for α-amination of carbonyl compounds.[11] Recently, Momiyama and Yamamoto have reported an excellent catalytic asymmetric nitroso-aldol reaction, in which the tin enolate of a ketone reacts with nitrosobenzene in the presence of a catalytic amount of BINAP–AgOTf complex, affording an α-aminooxy ketone in high enantioselectivity, which is easily converted into the corresponding α-hydroxy ketone.[12] Inspired by the notion that nitrosobenzene could act as an electrophilic aminooxylating reagent, we examined the reaction between a ketone and nitrosobenzene in the presence of proline, and have discovered the direct, L-proline catalyzed, asymmetric α-aminooxylation of ketones (Scheme 1).[13] As an extension of this methodology to the synthesis of the much more versatile α-aminooxy- and α-hydroxy-aldehydes, we have developed the direct catalytic enantioselective α-aminooxylation of aldehydes using nitrosobenzene as an oxidant and proline as catalyst, which is reported in this communication.[14]

The reaction of propanal and nitrosobenzene was selected as a model and the effect of solvent was examined with the results summarized in Table 1. As the α-aminooxy aldehyde product is rather labile, isolation and characterization was performed after conversion to the corresponding α-aminooxy alcohol by treatment of the reaction mixture with $NaBH_4$. Though the α-aminooxylation reaction is readily accomplished with very high enantioselectivity in most of the solvents employed, the solvent effect is found to be rather different from that of the α-aminooxylation of ketones: While polarized solvents such as DMF, DMSO, CH_3NO_2, NMP,[15] and CH_3CN are all suitable for the α-aminooxylation of ketones,[13] CH_3CN is superior in the reaction of aldehyde, which proceeds at −20°C,



Scheme 1. Direct asymmetric α-aminooxylation of cyclohexanone.

Keywords: organocatalyst; asymmetric reaction; catalytic reaction; proline; α-aminooxylation.
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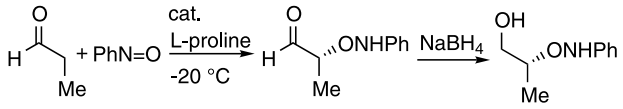
Table 1. Solvent effect of α-aminooxylation of propanal[a]



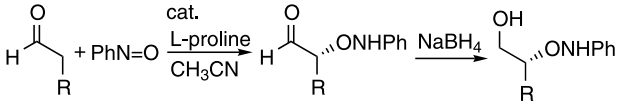
Entry	Solvent	Yield (%)[b]	ee (%)[c]
1	THF	18	99
2	NMP	34	98
3	CH_3NO_2	43	98
4	$CHCl_3$	43	98
5	DMF	49	98
6	CH_2Cl_2	63	98
7	CH_3CN	Quant.	98

[a] Reaction conditions: propanal:nitrosobenzene:L-proline = 3:1:0.3, reaction time: 24 h, reaction temperature: −20°C.
[b] Isolated yield of the alcohol (two steps).
[c] Determined by chiral HPLC.

affording the α-aminooxylated aldehyde quantitatively in 98% ee.[16] In this reaction, no α-hydroxyamino aldehyde was formed at all, while α-hydroxyamino ketones are major products in the reaction of nitrosobenzene with a variety of alkali metal or tin enolates of ketones.[17]

Next, reaction temperature was investigated with the results summarized in Table 2 (entries 1 and 2). The yield decreases to 80%, while the excellent enantioselectivity is maintained when the reaction is conducted at higher temperature (0°C), because of side reactions

Table 2. Proline-catalyzed direct asymmetric α-aminooxylation of aldehydes[a]



Entry	R	Temp. (°C)	Yield (%)[b]	ee (%)[c]
1	Me	−20	Quant.	98
2	Me	0	80	98
3[d]	Me	−20	Quant.	98
4[e]	Me	−20	81	98
5	Et	−20	87	99
6	Et	0	64	98
7	*n*-Pr	−20	81	95
8	*n*-Pr	0	71	95
9	*i*-Pr	−20	77	97
10	*i*-Pr	0	77	97
11	Ph	−20	62	99
12	Ph	0	44	99
13	CH_2Ph	−20	70	99
14	CH_2Ph	0	53	99

[a] Unless otherwise noted, reactions were conducted with 30% mol of L-proline, 1.0 equiv. of nitrosobenzene, and 3.0 equiv. of aldehyde in CH_3CN for 24 h at the temperature indicated.
[b] Isolated yield of alcohol (two steps).
[c] Determined by chiral HPLC.
[d] Reaction was conducted with 10% mol of catalyst.
[e] Reaction was conducted with 5% mol of catalyst.

such as the homo-dimerization of nitrosobenzene, which proceed at 0°C (vide infra). The self-aldol reaction of propanal is another side reaction, which is known to proceed at 4°C.[18]

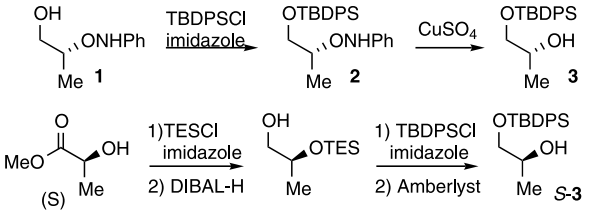
The catalyst loading can be reduced to 5 mol% without loss of enantioselectivity, and while still giving a synthetically useful yield (entry 4).

For the synthesis of α-aminooxy ketones, syringe pump addition of nitrosobenzene to the ketone in the presence of proline is a key for obtaining the high yield in order to suppress both dimerization of nitrosobenzene and α,α′-di-aminooxylation.[13] On the other hand, such slow addition is not necessary in the reaction of aldehydes. That is, because of the higher reactivity of aldehydes compared to that of ketones, α-aminooxylation of aldehydes proceeds at a lower temperature (−20°C) than that of ketones (0°C), and at this lower temperature dimerization of nitrosobenzene to form azoxybenzene does not proceed.

As the best reaction conditions had been established, the generality of the reaction was examined with the results summarized in Table 2. Not only propanal, but also linear chain aldehydes such as *n*-butanal and *n*-pentanal react with nitrosobenzene, affording α-aminooxy aldehydes in good yield with excellent enantioselectivity. Branched aldehydes such as 3-methylbutanal are also suitable substrates, successfully converted to the α-aminooxylated product in good yield with excellent enantioselectivity. Aldehydes containing an aromatic moiety such as 3-phenylpropanal and phenylacetaldehyde were successfully employed in this reaction, affording the α-aminooxylated compounds in moderate yield and excellent enantioselectivity. With regard to the temperature effect, the same influence on yield and enantioselectivity as for propanal was observed with all the aldehydes examined except for 3-methylbutanal: Better yield and the same enantioselectivity are obtained when the reaction is carried out at −20°C compared with that at 0°C.

The absolute configuration of the 2-anilinooxypropanal product was determined as follows: 2-Anilinooxypropanol **1** was converted into *tert*-butyldiphenylsilyl (TBDPS) ether **2** by treatment with TBDPSCl and imidazole. The transformation of the anilinooxy moiety into an hydroxy group can be successfully carried out by treatment with a catalytic amount of copper sulfate under the conditions developed by Yamamoto,[12] affording alcohol **3**. The absolute stereochemistry of alcohol **3** was unambiguously determined to be (*R*), based on HPLC analysis[19] and comparison of the optical rotation with that of authentic (*S*)-**3** prepared from (*S*)-methyl lactate as shown in Scheme 2.

The following transition state model (Fig. 1), which is the same as that proposed for the α-aminooxylation of ketones,[13] and similar to that proposed for the aldol reaction[9] and the α-amination of aldehydes[11a] by List, explains the absolute stereochemistry of the α-



Scheme 2. The determination of the absolute configuration of **1**.

aminooxylated aldehydes, though two reaction mechanisms have been proposed for the nitroso-aldol reaction of ketones, one proceeding via a nitrosobenzene-monomer, the other a nitrosobenzene-dimer.[17]

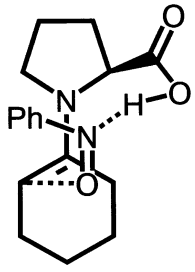


Figure 1. The transition state model.

In summary, the direct α-aminooxylation of aldehydes has been realized in excellent enantioselectivity by using nitrosobenzene as oxidant and L-proline as catalyst. The success of this process lies in the low temperature used (−20°C), at which side-reactions such as the dimerization of nitrosobenzene and aldol reactions can be suppressed. Because of the easy conversion of the α-aminooxy moiety to an α-hydroxy group, the present method is synthetically useful for the preparation of α-hydroxy aldehydes, which are versatile chiral intermediates in natural product synthesis.[20]

Acknowledgements

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19. HPLC conditions: Chiral OD-H column, *i*-PrOH:hexane 1:40, 0.5 mL/min, retention time: 11.5 min (*R*-isomer) and 12.7 min (*S*-isomer). Racemic (±)-**3** was prepared from hydroxyacetone by the two steps: (1) TBDPSCl, imidazole, (2) $NaBH_4$.

20. Typical experimental procedure is as follows (Table 2, entry 1): To a CH_3CN solution (3 mL) of propanal (108 μL, 1.5 mmol) and nitrosobenzene (53.5 mg, 0.5 mmol) was added L-proline (17.3 mg, 0.15 mmol, 0.3 equiv.) at −20°C. After stirring the reaction mixture for 24 h at that temperature, MeOH (1 mL) and $NaBH_4$ (94.5 mg, 2.5 mmol) were added to the reaction mixture, which was stirred for 10 minutes at that temperature. After addition of the phosphate buffer, the organic materials were extracted with AcOEt three times and the combined organic phase was dried over Na_2SO_4. Purification by column chromatography with silica gel (AcOEt/hexane = 1/10–1/3) afforded aminooxy aldehyde (83.5 mg, 0.5 mmol) quantitatively.