

Asymmetric Catalysis

**A Facile and Rapid Route to Highly Enantiopure 1,2-Diols by Novel Catalytic Asymmetric α -Aminooxylation of Aldehydes*****Guofu Zhong**

Enantioselective routes to optically active 1,2-diols are of considerable interest since this structural moiety is widely found in biologically active natural products and synthetic pharmaceuticals.^[1] A number of methods for their synthesis have been developed and, among them, the Sharpless asymmetric dihydroxylation of olefins is most often

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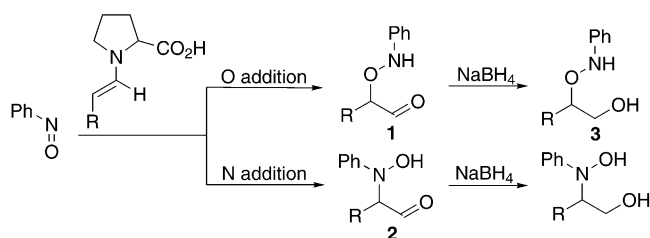
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used.^[1c,2] Another potential route to chiral 1,2-diols is the asymmetric α -hydroxylation of aldehydes and subsequent reduction. However, a direct chemical method for the α -hydroxylation of aldehydes has not been reported.^[3] This is because of the facile aldol reactions that occur during enolate formation. The only example leading to α -hydroxyaldehydes in high enantiomeric purity is shown by the oxidation of preformed enolates from aldehydes derivatized with chiral auxiliaries.^[4] For these reasons, the development of new methodologies for the direct catalytic enantioselective α -hydroxylation of aldehydes has become an intriguing target in organic synthesis. Recent studies in enamine chemistry in which chiral amines were employed to mimic enzymatic catalysis^[5] have led to the utilization of aldehydes as donors to form C–C bonds (for example, in aldol,^[6] Mannich,^[7] Michael,^[8] and Diels–Alder^[9] reactions) and C–N bonds (in Michael-like amination^[10]). In contrast to the classic preformed enolates, these reactions are believed to proceed through the direct in situ production of enamines from aldehydes, in a similar way to natural enzymes.^[11] These findings prompted us to investigate whether the amine catalysts could be applied to the formation of a C–O bond in the asymmetric α -aminoxylation of aldehydes.

Herein, we report the first direct catalytic enantioselective α -aminoxylation of aldehydes by using enantiopure proline as the catalyst and nitrosobenzene as the oxygen source. This method provides a simple, yet efficient, route to chiral 1,2-diol precursors (O addition products in Scheme 1) in a one-pot sequence with excellent enantioselectivities (*ee* values from 94 to 99 %) and good yields (54–86 %).

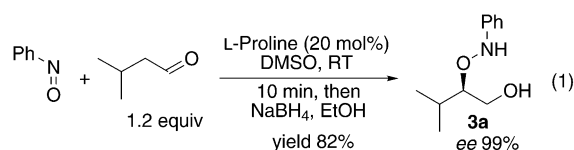


Scheme 1. Possible nucleophilic addition of the enamine intermediate on the nitroso double bond.

On the basis of previous results, we suspected that the highly reactive enamine intermediates formed between aldehydes and proline might serve as nucleophiles and add stereoselectively to the nitroso functional group, either on the oxygen atom or the nitrogen atom. Nucleophilic O attacks of the enamines on the nitroso double bond might give the α -aminoxy product **1**. While nucleophilic N attacks would afford the α -N-hydroxyamino product **2**. It was anticipated that this organocatalysis might provide a solution to the synthetic challenge if nucleophilic attacks could be directed to the oxygen side of the nitroso compounds.

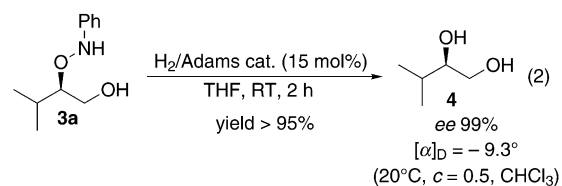
We initially tested the reaction using isovaleraldehyde as the donor. The superior reactivity of nitrosobenzene over the aldehyde itself as the acceptor meant that the concurrent self-aldolization^[6a,b] of the aldehyde was remarkably minimized. Only a small excess of the aldehyde (1.2 equiv) was required to accomplish the reaction. Initial experiments were con-

ducted with the reaction of isovaleraldehyde (1.2 equiv), nitrosobenzene (1.0 equiv), and L-proline (20 mol %) in DMSO under fast stirring. To our delight, this reaction was completed in just 10 min. The reaction course can be easily monitored by observation of its color change from green to orange. The isolation and characterization of the main product by flash column chromatography over silica gel showed that an O-regioselective addition product **1** (Scheme 1; R = isopropyl) was formed, but the yield of the isolated product was not satisfying (less than 50 %). The N-selective product **2** (R = isopropyl) was not found. This O-selective attack of the in situ generated enamine on the nitroso group clearly differs from that found in N-selective “nitroso-aldol reactions”^[12] using preformed ketone enolates in the absence of catalysts, where the reactions give exclusively N-addition products, namely, α -N-hydroxyamino products. However, it is similar to that in the O-selective reactions of the preformed ketone enolates with catalysts.^[13] Since longer reaction times caused a decrease in yield, we suspected that the poor yield obtained by flash chromatography might be a consequence of the labile properties of the product on silica gel as a result of the co-existence of both aldehyde and amine functions. We next tried in situ conversion of the intermediate **1** into the more stable 2-aminoxy alcohol **3a** (Scheme 1; R = isopropyl) by reduction with sodium borohydride in the mixed solvent of DMSO and ethanol. The corresponding product **3a** was then isolated in good yield (82 %, one pot in two steps) and with excellent enantioselectivity by column chromatography on silica gel [Eq. (1), the



99 % *ee* of the product **3a** was determined by chiral-phase HPLC on a chiralcel AD column using hexane/isopropanol]. In addition to DMSO, a solvent screening with DMF, THF, diethyl ether, 1,4-dioxane, EtOH, CH₂Cl₂, CHCl₃, and EtOAc was performed under the same reaction conditions. It was found that DMSO afforded the best reaction rate, yield, and enantioselectivity than any other solvent. Accordingly, DMSO was utilized as the solvent in all subsequent studies.

The stereochemistry of this transformation was determined by conversion of 2-aminoxy alcohol **3a** into 1,2-diol **4**, the absolute configuration and optical rotation of which are known.^[1b,c] Catalytic hydrogenation of the alcohol **3a** over platinum dioxide (Adams catalyst with 83 % Pt) in THF cleaved cleanly the O–N bond of **3a** to furnish diol **4** with a yield greater than 95 %. The absolute configuration of the diol **4** was assigned *R* [Eq. (2)] from optical rotation measure-



ments. It should be noted that the removal of the phenylamino group from the O–N bond did not result in any loss in optical purity.

Encouraged by these initial results, we further explored the scope of these novel transformations with a series of aliphatic aldehydes under the same reaction conditions. In every case, the reaction proceeded rapidly. Typically it was done in 10 to 20 minutes. After in situ reduction with NaBH₄, the reactions afforded O-regioselective products **3b–3h** with excellent enantioselectivities (94–99% *ee*) in good overall yields (54–86%; Table 1). The racemic analogues required to establish the HPLC conditions were made by using racemic proline.

Table 1: Direct catalytic enantioselective α -aminoxylation of aldehydes.

Aldehyde	Product	Yield ^[a] [%]	<i>ee</i> ^[b] [%]
	3a	82	99
	3b	60	97
	3c	71	99
	3d	75	99
	3e	86	99
	3f	73	99
	3g	54	99
	3h	61	94

[a] Yields of isolated products. [b] The *ee* values were determined by chiral-phase HPLC using Chiracel AD column. Boc = *tert*-butoxycarbonyl.

The observed enantioselectivity of the catalytic α -aminoxylation of aldehydes can be rationalized by invoking an enamine mechanism operating through a chair transition state where the *Si* face of an *E* enamine formed from the aldehyde and L-proline approaches the less-hindered oxygen atom of nitrosobenzene to provide a chiral α -aminoxyaldehyde with *R* configuration (Figure 1). This mechanism is completely in accord with the previously proposed models for proline-catalyzed aldol reactions.^[6c,14]

In summary, we have discovered the first direct catalytic enantioselective α -aminoxylation of aldehydes which provides a facile route to enantiopure α -aminoxyaldehyde intermediates. This novel reaction proceeds rapidly and is typically completed in 10–20 minutes in the presence of 20% equivalents of the proline catalyst. Since proline is commercially available in both enantiopure forms, a one-pot sequence—catalytic α -aminoxylation of aldehydes followed by in situ reduction with NaBH₄—affords *R*- or *S*-

configured 1,2-diol units (the secondary alcohol “protected” by an O-amino group) with excellent enantioselectivities and in good yields which are important building blocks in natural product synthesis.^[1c] The operational procedure is very simple and generally involves mixing and stirring the reaction components together at ambient temperature. The reaction does not require anhydrous or oxygen-free conditions. The process is ideally suited for industrial-scale preparation because of its wide scope and excellent enantioselectivity. The nitroso group has been found to be a good oxygen source for the formation of C–O bonds.^[15] Studies addressing the mechanism and the synthetic scope of this new asymmetric transformation are ongoing.

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