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Organocatalyzed asymmetric α-hydroxyamination of α-branched aldehydes: asymmetric synthesis of optically active N-protected α,α-disubstituted amino aldehydes and amino alcohols

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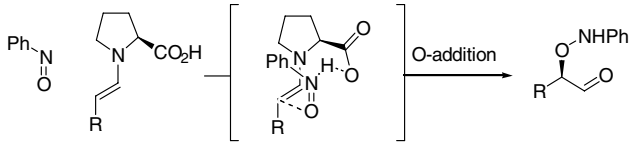
Abstract—Enantioselective direct α-hydroxyamination and α-aminoxylation of α-branched aldehydes using a proline-derived tetrazole catalyst is described herein. α-Hydroxyamination adducts with up to 90% ee were obtained by the reaction of nitrosobenzene with unactivated α-branched aldehydes under mild reaction conditions.

The class of compound with quaternary carbons bearing nitrogen displays a wide variety of attractive properties. In addition to many natural alkaloids such as lepadiformine, daphniphylline and (−)-adaline,[1] they include chiral α,α-dialkylated amino acids, which are not only useful molecular building blocks for the synthesis of peptides with specific properties,[2] but also have powerful biologically activities.[3] Optically active α,α-disubstituted amino aldehydes have also been used in many synthetic applications.[4] The asymmetric synthesis of quaternary nitrogen-bearing centres is therefore an important synthetic goal.

Organocatalytic asymmetric reactions have been extensively investigated in recent years and have been given numerous impressive results.[5] Among them, proline-catalyzed reaction has been exploited to reveal useful new avenues for the aldol, Mannich, Machel, α-amination and α-aminoxylation.[5b,6] In particular, the α-aminoxylation reaction has received attention in many research groups because the corresponding α-hydroxyaldehydes and ketones are important intermediate in organic synthesis.[7] Very recently, we have also applied this α-aminoxylation reaction to the synthesis of a natural product.[8] In due course we had interest in α-branched aldehydes, which could react with nitrosobenzene to give α-aminoxy or α-hydroxyamino products that are precursors to quaternary α-amino acid. Herein we wish to report an enantioselective direct α-hydroxyamination of α-branched aldehydes using a proline-derived tetrazole catalyst.[9,10] This transformation yields N-protected α,α-disubstituted amino aldehyde with up to a 90% ee and good yield.

On the basis of previous reported studies, we were prompted to consider the α-hydroxyamination of α-branched aldehydes with nitrosobenzene. In the reaction of non-α-branched aldehyde and nitrosobenzene in the presence of L-proline, exclusively the α-aminoxy product was given as the major product. In the proposed transition state,[11] the (*E*)-*anti* enamine formed between an aldehyde and proline attacks the oxygen of nitrosobenzene, adopting its phenyl group in a pseudo-axial position and *anti* with respect to the carbonyl group of proline (Scheme 1). However, we suspected that the enamine intermediate formed between an α-methyl aldehyde and proline might attack nitrogen of nitrosobenzene



Scheme 1.

Keywords: Hydroxyamination; Aminoxylation; Asymmetric catalysis; Organocatalysis.
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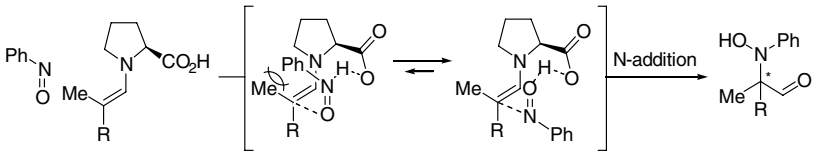
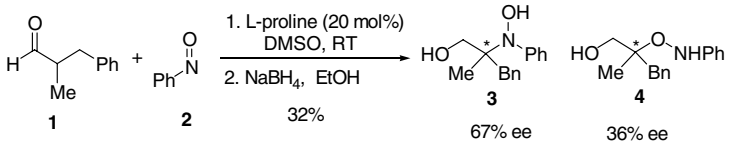


Scheme 2.



Scheme 3.

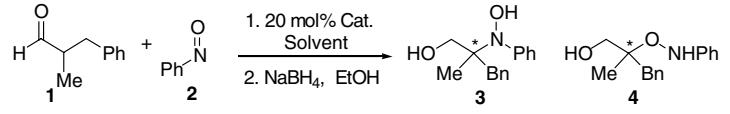
giving an α-hydroxyamino product due to the steric repulsion between the α-methyl group of enanmine and the phenyl group of nitrosobenzene (Scheme 2). It was anticipated that this reaction might provide a simple synthetic methodology to access optically active α,α-disubstituted amino aldehydes and alcohols if nucleophilic attack could be directed to the nitrogen of nitrosobenzene as we anticipated.

To test our assumption, we initially examined the reaction to 2-methyl-3-phenylpropionaldehyde **1** (2 equiv) with nitrosobenzene **2** (1 equiv) using a catalytic amount of L-proline (20 mol %) in DMSO at room temperature. The reaction proceeded to furnish the corresponding α-hydroxyamino product as we anticipated, though the yield and the selectivity between *N*-adduct and *O*-adduct were not as desired (Scheme 3).

Encouraged by this result, we investigated other organocatalysts for the α-hydroxyamination reaction to 2-methyl-3-phenylpropionaldehyde **1** with nitrosobenzene **2** to improve both reactivity and enantioselectivity (Table 1). *trans*-4-*tert*-Butyldimethylsiloxy-L-proline (**5b**),[12] which is a highly active catalyst in the α-aminoxylation reaction of non-α-branched aldehydes, showed similar results with L-proline in this reaction. However, in the presence of tetrazole catalyst (**5c**)[13] the reaction proceeded fast to give the corresponding α-hydroxyamino product. The best results were obtained in DMF giving 81% ee of α-hydroxyamino product and a 96% isolated yield after subsequent reduction with $NaBH_4$, albeit having no regioselectivity. Tetrazole catalyst (**5d**)[14] having *trans*-4-*tert*-butyldimethylsiloxy group might be expected to be superior to tetrazole catalyst (**5c**) in stereoselectivity due to an increased solubility, but did not show any advantage in this reaction.

The scope of this reaction for various α-branched aldehydes using tetrazole catalyst (**5c**) was next investigated (Table 2).[15] For α-methyl aldehydes, the reaction proceeded to generate α-hydroxyamino and α-aminoxy adducts in a high yields (up to 98%) and with high enantioselcetivities of up to 90% ee for α-hydroxyamino adduct (entries 1–7). Even 2-methylbutyraldehyde gave the α-hydroxyamino product in 70% ee (entry 8). However, α-ethyl aldehydes reacted with nitrosobenzene to

Table 1. Enantioselective α-N-hydroxyamination and α-aminoxylation of 2-methyl-3-phenylpropionaldehyde with nitrosobenzene



Entry	Catalyst	Solvent	Temperature (°C)	Time (h)	Yield[a] (%)	**3**/**4**[b]	ee of **3**[c] (%)	ee of **4**[c] (%)
1	**5a**	DMSO	25	24	32	1.5/1	67	36
2	**5b**	DMSO	25	24	24	1/1	66	22
3	**5c**	DMSO	25	4	97	1/1	70	41
4	**5d**	DMSO	25	4	74	1/1	73	29
5	**5c**	DMF	25	3	96	1/1	81	37
6	**5d**	DMF	25	3	93	1/1	83	31

[a] Yield of isolated product.
[b] Determined by ^1H NMR analysis.
[c] Determined by chiral HPLC analysis (Chiralcel AD-H).

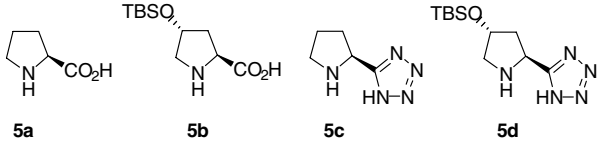
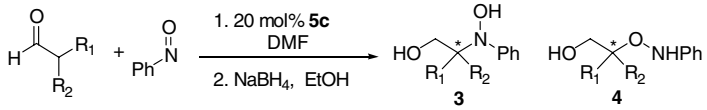
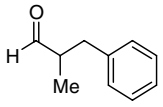
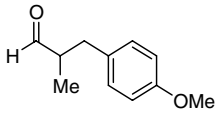
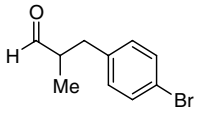
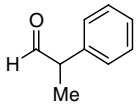
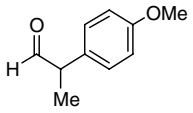
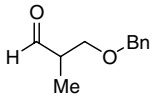
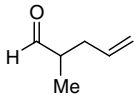
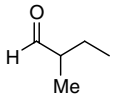
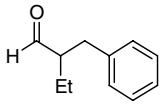
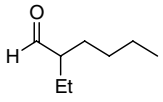


Table 2. Enantioselective α-N-hydroxyamination and α-aminoxylation of α-branched aldehydes with nitrosobenzene and catalyzed by **5c**



Entry	Aldehyde	Temperature (°C)	Time (h)	Yield[a] (%)	**3**/**4**[b]	ee of **3**[c] (%)	ee of **4**[c] (%)
1		25	3	96	1/1	81	37
2		0	8	75	1.7/1	90[d]	35
3		0	3	98	1.4/1	86	45
4		25	24	83	20/1	64[d]	—[e]
5		25	24	65	10/1	45	—[e]
6		0	4	89	0.8/1	79	5
7		25	3	91	0.7/1	62	27
8		25	12	76	1.7/1	70	8[d]
9		25	6	67	1.3/1	25[d]	11[d]
10		25	12	55	0.6/1	5	2

[a] Yield of isolated product.
[b] Determined by ^{1}H NMR analysis.
[c] Determined by chiral HPLC analysis (Chiralcel AD-H).
[d] Determined by chiral HPLC analysis (Chiralcel OD-H).
[e] Not determined.

give moderate yields and low enantioselectivities (entries 9 and 10). The stereoselectivity between *N*-adduct and *O*-adduct has been surprisingly increased in the case of α-methyl-α-aryl substituted aldehydes (entries 4 and 5). 2-Phenylpropionaldehyde reacted with nitrosobenzene in high yield with a stereoselective ratio of 20:1 in favour of the α-hydroxyamino adduct.

In summary, we have described the enantioselective direct α-hydroxyamination of α-branched aldehydes

with nitrosobenzene using a proline-derived tetrazole catalyst in a good yield with a moderate to high enantioselectivity. Although regioselectivity is moderate in α-methyl-α-aliphatic substituted aldehydes, this method provides a direct access to optically active α,α-disubstituted amino aldehydes and amino alcohols, which are precursors to quaternary α-amino acids. Further studies into the mechanism and catalytic regio- and enantioselective variants of this reaction are now in progress and will be presented in due course.

Acknowledgements

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14. Tetrazole catalyst (**5d**) was synthesized starting from *trans*-4-*tert*-butyldimethylsiloxy-L-proline using the same procedure with the synthesis of tetrazole catalyst (**5c**). Mp 262–263 °C; $[\alpha]_D^{27}$ +11.39 (*c* 0.50, CH_3OH); IR (KBr) 3223, 2985, 2793, 2363, 1415; ^1H NMR (200 MHz, CD_3OD) 5.23 (dd, $J = 6.8$, 10.6 Hz, 1H), 4.88 (br s, 1H), 3.66 (dd, $J = 4.0$, 12.2 Hz, 1H), 3.36 (d, $J = 12.2$ Hz, 1H), 2.42–2.66 (m, 2H), 0.96 (s, 9H), 0.19 (s, 6H); ^{13}C NMR (50 MHz, CD_3OD) 157.2, 70.7, 53.2, 52.7, 39.3, 24.3, 16.9, −7.0, −6.7; HRMS (M+Na) calcd for $C_{11}H_{23}N_5NaO_2Si^+$ 292.1566, found 292.1570.
15. In a typical experiment: To a solution of 2-methyl-3-phenylpropionaldehyde **1** (296 mg, 2.0 mmol) and (*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole **5c** (28 mg, 0.2 mmol) in DMF (2 mL) was added a solution of nitrosobenzene **2** (107 mg, 1.0 mmol) in DMF (1 mL) by a syringe pump over 1 h at room temperature. After additional stirring for 2 h at room temperature, the reaction mixture was diluted with EtOH (5 mL), the solution was cooled to 0 °C and excess $NaBH_4$ was added. After 20 min, the reaction was treated with saturated aqueous $NaHCO_3$, extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude residue was purified by flash column chromatography (10% EtOAc/hexane) to afford products **3** and **4** (257 mg, 96%). The regioselectivity of the product was determined by ^1H NMR spectra. The enantiomeric excess of products **3** and **4** was measured by HPLC analysis after separation of isomer using column chromatography. *2-(Hydroxy-phenyl-amino)-2-methyl-3-phenyl-propan-1-ol* (**3**): White powder; mp 123–125 °C; $[\alpha]_D^{28}$ +4.40 (*c* 1.00, CH_3OH); IR (KBr) 3345, 2957, 2935, 1597, 1487, 1452, 1031 ^1H NMR (200 MHz, $CDCl_3$) 7.21–7.40 (m, 10H), 3.56 (d, $J = 6.2$ Hz, 2H), 3.27 (d, $J = 12.6$ Hz, 1H), 2.53 (d, $J = 12.6$ Hz, 1H), 0.95 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) 149.0, 137.8, 130.8, 127.9, 127.8, 126.2, 125.4, 125.0, 66.3, 65.2, 38.7, 17.7; HRMS (M+Na) calcd for $C_{16}H_{19}NNaO_2^+$ 280.1313, found 280.1309; HPLC (Chiralcel AD-H, 4.0% EtOH/hexanes,

1 mL/min); $t_{minor} = 29.5$ min, $t_{major} = 32.3$ min, 80% ee; *2-Methyl-3-phenyl-2-(N-phenyl-aminooxy)-propan-1-ol* (**4**): Colourless oil; $[\alpha]_D^{28}$ +8.09 (*c* 1.00, $CHCl_3$); IR (KBr) 3406, 3263, 2945, 1600, 1494, 1454, 1043 ^{1}H NMR (200 MHz, $CDCl_3$) 6.98–7.41 (m, 10H), 3.77 (d, $J = 11.8$ Hz, 1H), 3.65 (d, $J = 11.8$ Hz, 1H), 3.14 (d, $J = 13.2$ Hz, 1H), 3.01 (d, $J = 13.2$ Hz, 1H), 1.24 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) 149.0, 137.3, 130.8, 129.1, 128.3, 126.6, 122.4, 114.9, 83.4, 67.2, 41.5, 19.4; HRMS (M+Na) calcd for $C_{16}H_{19}NNaO_2^+$ 280.1313, found 280.1307; HPLC (Chiralcel AD-H, 4.0% EtOH/hexanes, 1 mL/min); $t_{minor} = 45.7$ min, $t_{major} = 48.9$ min, 42% ee.