Direct Asymmetric N-Specific Reaction of Nitrosobenzene with Aldehydes Catalyzed by a Chiral Primary Amine-Based Organocatalyst

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ABSTRACT Nitroso compounds have two reactive nitrogen and oxygen atoms. It is interesting and important to perform a nitrogen or oxygen selective reaction with interesting substrates. These atom specific reactions are crucial to specifically synthesis of specific compounds. An enantioselective *N*-specific reaction of nitrosobenzene with unmodified aldehydes was successfully achieved catalyzed first by a variety of primary amine-based organocatalysts with higher yield and enantioselectivity. The bulkier substituted groups of the organocatalyst and two hydrogen bonds from the organocatalyst and the oxygen atom of nitrosobenzene make the reaction preferentially *N*-specific and predominantly afford *R* products. *Chirality 23:527–533, 2011.* © 2011 Wiley-Liss, Inc.

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INTRODUCTION

Atom-specific reaction is very interesting and important for a compound including variable reactive atoms to prepare distinct product from each other. Nitroso compounds are such interesting compounds, they have different highly reactive N and O atoms toward nucleophiles (for reviews, see: Refs. 1-7) and are frequently used to prepare nitrogen- or oxygen-containing molecules. Therefore, various catalytic asymmetric reactions of nitroso compounds such as aminoxylation,⁸⁻²³ hydroxyamination,²⁴⁻²⁷ and nitroso Diels-Alder reactions^{28,29} have recently been developed, which exploited their unique properties. Because of the high reactivity of the nitroso compounds, regioselective control of either the nitrogen or oxygen to preferentially react with the nucleophile, i.e., atom-specific reaction, is a challenge of fundamental importance. Investigations of the reaction of nitrosobenzene with a silvl or metal enolate have revealed that the O versus N selectivity is dependent on the nature of the enolate and the presence or absence of a Lewis acid catalyst.³⁰⁻³³ Momiyama and Yamamoto reported that preformed enamines reacted with nitrosobenzene in the presence of the chiral glycolic acid to preferentially give O-nitroso aldol product, but to result in the N-nitroso product in the presence of the chiral TADDOL (Fig. 1).³⁴

Organocatalytic asymmetric reactions are current interesting centers because they are metal-free, environmentally friendly, and easily handled. Therefore, organocatalyzed reactions of nitrosobenzene in the presence of L-proline and the similar organocatalysts have also been actively investigated and gave α -oxygenated carbonyl compounds as the major products.^{8–23} In comparison with this *O*-specific reaction, the organocatalytic *N*-specific adducts were rarely been disclosed. Recently, three research groups of Gong and coworkers,²⁴ Maruoka and coworkers,²⁵ and Palomo et al.²⁷ successively reported direct nitroso-aldol reactions of carbonyl compounds that occurred preferentially at the nitrogen of nitrosobenzene with high enantioselectivity. Their used orga-

nocatalysts were all based on secondary amines, the derivatives of L-Proline and its similar synthetic molecules. When compared with proline, primary amine-based enantioenriched amino acids are more common in natural chiral amine pools, and many natural enzymes in cells are based its catalytic groups on primary amine amino acids, such as L-Lys locates in the active center of the aldolase,³⁵⁻³⁹ whereas L-proline has rarely been reported to appear as an active component of the active center of an enzyme. A more abundant chiral primary than secondary amine pool will conveniently furnish more different and efficient primary amine organocatalysts. Furthermore, primary amine organocatalysts will be greatly beneficial to reasonably clarify the mechanism of abundant primaryamine-based natural enzymatic reactions. Undoubtedly, chiral primary amine organocatalysts will introduce new contents to amine-catalyzed nitroso aldol reactions. To the best of our knowledge, there has not been any report on N-specific reaction of nitroso compounds with aldehydes to give α -hydroxyaminated aldehydes catalyzed by an enantioenriched primary amine-based organocatalyst to date. This situation makes it more challenging and interesting to develop a successful primary amine organocatalyst to promote the preferentially Nselective Aldol reaction of nitrosobenzene with aldehydes.

Not long ago, our group reported that the direct highly asymmetric aldol reactions could be catalyzed by an efficient

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Fig. 1. The O- or N-selective reaction of nitrosobenzene.

primary organocatalyst system formed by a primary amine organocatalyst, which was readily derived from natural primary amino acids, and an efficient cocatalyst DNP (2,4-dinitrophenol).^{40,41} We presumed that the primary amine organocatalysts **1a–g** (Scheme 1) with an additional cocatalyst DNP or others might also successfully catalyze the reaction of unmodified aldehydes with nitrosobenzene to preferentially result in *N*-specific aldol products. Herein, we present this direct asymmetric α -hydroxyamination of aldehydes, which was first and successfully catalyzed by a primary amine organocatalyst.

EXPERIMENTAL General Methods

All reagents were commercial products. The reactions were monitored by thin layer chromatography (TLC). The column and preparative TLC purification were carried out using silica gel. Melting points were measured on X-4 melting point apparatus without correction. Optical rotations were recorded on a polarimeter. ¹H NMR spectra were recorded on 200 MHz and 400 MHz spectrometers. The chemical shifts were reported in ppm with TMS as an internal standard. Data were reported as follows: chemical shift, multiplicity (s = single, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz). ¹³C NMR spectra were recorded on 400 MHz. HRMS were measured with ESI mass spectrometer. IR spectra were obtained by FT-IR. The *ee* value determination was carried out using HPLC with chiral OJ-H, AS-H, or AD-H column. For NMR Spectra and HPLC conditions and spectra, see the supporting information of this work

General Procedure for Preparation of Aminoalcohols (3a–e)

The freshly prepared Grignard reagent RMgBr 60 ml (2.5 M, 150 mmol) in ether was cooled to 0° C under an argon atmosphere, and 15 mmol hydrochloride of methyl ester of amino acid **5** was added in 10



Scheme 1. Synthesis of organocatalysts.

portions (addition of too much methyl ester hydrochloride in one portion would make the reaction too violent on account of the rapid reaction of HCl with PhMgBr). The reaction was then naturally warmed to room temperature and allowed to stir overnight. When the reaction was completed checked by TLC, the mixture was slowly poured into 60 ml stirring ice water, then 2 ml (0.25 mmol) concentrated HCl was added. The mixture was stirred for an hour, filtered, and washed thrice with water to afford a yellow residue. The yellow residue was introduced with NaOH (55 ml, 0.25 mmol), stirred for another 30 min, and then extracted thrice with ether. The ether layers were combined, concentrated in vacuo, and recrystallized from ethyl acetate or purified by preparative column to yield the amino alcohols **3a–e**.

(S)-Diphenyl phenylalanol (3a). White solid; Yield 53%; m.p. 145–146°C; $[\alpha]_{D}^{2D} = -73$ (*c* 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.59–7.66 (dd, J = 8.4 Hz, J = 8.0 Hz, 4H), 7.28–7.35 (m, 6H), 7.17–7.25 (m, 5H), 4.16–4.20 (dd, J = 2.6 Hz, J = 10.6 Hz, 1H), 2.62–2.66 (dd, J = 2.0 Hz, J = 14.0 Hz, 1H), 2.41–2.47 (dd, J = 10.8 Hz, J = 13.6 Hz, 1H).

(S)-Diphenyl leucinol (3b). White solid; Yield 51%; m.p. $121-123^{\circ}$ C; $[\alpha]_{D}^{20} = -96$ (*c* 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.60–7.62 (d, *J* = 7.6 Hz, 2H), 7.47–7.48 (d, *J* = 7.2 Hz, 2H), 7.14–7.33 (m, 6H), 3.97–3.99 (dd, *J* = 2.0 Hz, *J* = 10.0 Hz, 2H), 1.55–1.62 (m, 1H), 1.21–1.30 (m, 2H), 0.89–0.90 (d, *J* = 6.4 Hz, 3H), 0.86–0.87 (d, *J* = 6.8 Hz, 3H).

(S)-Diethyl phenylalaninol (3c).. Colorless oil; Yield 63%; $[\alpha]_{D}^{20} = -28$ (*c* 1.0, CHCl₃); FT-IR 3389, 3026, 2966, 2936, 2881, 1600, 1494, 1457, 1378, 1032, 951, 753, 700 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.35–7.17 (m, 5H), 3.00–2.94 (dd, *J* = 3.2 Hz, *J* = 12.4 Hz, 2H), 2.37–2.24 (app t, *J* = 12.5 Hz, 1H), 1.73–1.41 (m, 4H), 1.00–0.92 (2× t, *J* = 7.3 Hz, 6H); ¹³C NMR (50 MHz, CDCl₃) δ 140.1, 129.1, 126.3, 74.4, 57.3, 38.1, 27.9, 26.6, 7.7. HRMS calcd. for (C₁₃H₂₁NO + H)⁺ 208.1696, found 208.1691.

(S)-Di-3,5-bis(trifluoromethyl)phenyl-phenylalaninol (3d). Colorless oil; Yield 54%; $[\alpha]_D^{20} = -50$ (*c* 1.0, CHCl₃); FT-IR 3398, 3092, 2932, 2873, 2461, 1949, 1712, 1623, 1463, 1369, 1284, 1169, 1128, 900, 844, 707 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 8.12 (s, 2H), 8.04 (s, 2H), 7.80 (s, 2H), 7.39–7.13 (m, 5H), 5.03 (s, 1H), 4.23 (t, J = 6.7 Hz, 1H), 2.48–2.45 (d, J = 6.7 Hz, 2H), 1.26–1.17 (br, 2H); ¹³C NMR (50 MHz, CDCl₃) δ 148.4, 145.5, 137.7, 132.5 (q, ${}^2J_{c,f} = 13.5$ Hz), 132.7 (q, ${}^2J_{c,f} = 13.5$ Hz), 129.1, 129.0, 127.2, 126.0 (q, ${}^3J_{c,f} = 2.5$ Hz), 125.7 (q, ${}^3J_{c,f} = 2.5$ Hz), 121.8, 121.6, 120.5, 120.4, 76.4, 58.1, 36.6. HRMS calcd. for ($C_{25}H_{17}F_{12}NO + H$)⁺ 576.1191, found 576.1180.

(R)-Diphenyl phenylalanol (3e). White solid; Yield 53%; m.p. 125–127°C; $[\alpha]_{20}^{D} = +68$ (*c* 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.59–7.66 (dd, J = 8.4 Hz, J = 8.0 Hz, 4H), 7.28–7.35 (m, 6H), 7.17–7.25 (m, 5H), 4.16–4.20 (dd, J = 2.6 Hz, J = 10.6 Hz, 1H), 2.62–2.66 (dd, J = 2.0 Hz, J = 14.0 Hz, 1H), 2.41–2.47 (dd, J = 10.8 Hz, J = 13.6 Hz, 1H).

General Procedure for Preparation of Catalysts (1a-f)

CICOOⁱBu (5.1 mmol, 0.67 ml) was slowly introduced dropwise into a mixture of 5.1 mmol Boc-protected amino acid **4** and 0.56 ml NMM (5.1 mmol) in 25 ml dry THF under an argon atmosphere at -15° C. Five minutes later, the amino alcohol **3** in THF (10 ml) was added dropwise into the mixture. After stirring for 30 min at the same temperature, the reaction was warmed to room temperature and continued stirring until it finished. THF was evaporated in vacuo, and the residue was redissolved with CH₂Cl₂, washed successively with dilute HCl, water, 10% NaHCO₃,

water and a little brine, dried with anhydrous Na₂SO₄, and condensed in vacuo to give the residue. The residue was recrystallized from ethyl acetate and petroleum ether to give a crystal or solid. The solid was redissolved with CH₂Cl₂ and cooled to 0°C, then 2 ml TFA in CH₂Cl₂ (TFA/ CH₂Cl₂ = 1:1) was added dropwise. The mixture was stirred for 1–2 h until the reaction finished checked by TLC, and then condensed to dryness in vacuo. The residue was redissolved with CH₂Cl₂ and NH₃·H₂O was added to adjust the solution pH to 10.0 or so. The organic layer was separated, and the aqueous layer was re-extracted thrice with CH₂Cl₂. Then the combined organic layers were washed with a little brine, dried with anhydrous Na₂SO₄, condensed to dryness in vacuo, and recrystallized from ethyl acetate and petroleum ether to give the catalyst **1a–g**. The configuration was assigned by comparison of the retention time of the major isomer in HPLC with reported values and by comparison of the sign of the optical rotation with the reported value.^{24–27}

(S,S)-2-Amino-N-(1-hydroxy-1,1,3-triphenylpropan-2-yl)-4-methyl-

pentanamide (1a). White solid; Yield 41%; m.p. $167-168^{\circ}$ C; $[\alpha]_{20}^{20} = -30$ (*c* 1.0, DMSO); ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.76–7.78 (d, *J* = 9.6 Hz, 1H), 7.59–7.51 (d, *J* = 7.6 Hz, 2H), 7.30–7.34 (t, *J* = 7.6 Hz, 2H), 7.03–7.18 (m, 8H), 6.19 (s, 1H), 5.05–5.09 (t, *J* = 9.6 Hz, *J* = 8.0 Hz, 1H), 2.74–2.78 (dd, *J* = 19.4 Hz, *J* = 5.6 Hz, *J* = 8.4 Hz, 1H), 2.57–2.70 (m, 2H), 1.26 (br, 1H), 1.15–1.22 (m, 1H), 0.79–0.86 (m, 1H), 0.65–0.69 (m, 1H), 0.62–0.64 (d, *J* = 7.2 Hz, 3H), 0.59–0.60 (d, *J* = 5.6 Hz, 3H).

(S,S)-2-Amino-N-(1-hydroxy-4-methyl-1,1-diphenylpentan-2-yl)-4-methylpentan-amide (1b). White solid; Yield 54%; m.p. 180–182°C; $[\alpha]_D^{20} = -44$ (*c* 1.0, DMSO); ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.54–7.56 (q, *J* = 7.8 Hz, *J* = 8.0 Hz, 4H), 7.40–7.43 (d, *J* = 8.8 Hz, 1H), 7.13–7.35 (m, 5H), 4.78–4.84 (t, *J* = 9.6 Hz, 1H), 1.75–3.18 (dd, *J* = 4.2 Hz, *J* = 10.2 Hz, 1H), 1.56–1.63 (m, 1H), 1.44–1.49 (m, 1H), 1.21–1.33 (m, 4H), 0.97–0.98 (d, *J* = 6.8 Hz, 3H), 0.85–0.86 (d, *J* = 6.4 Hz, 3H), 0.84–0.85 (d, *J* = 6.4 Hz, 3H), 0.80–0.82 (d, *J* = 6.8 Hz, 3H).

(S,S)-2-Amino-N-(1,1-bis(3,5-bis(trifluoromethyl)phenyl)-1-hydroxy-3phenylpropan-2-yl)-4-methylpentanamide (1c). White solid; Yield 42%; m.p. 169–171°C; $[\alpha]_D^{20} = -75$ (*c* 1.0, CHCl₃); FT-IR 3315, 3094, 2960, 2874, 1711, 1643, 1527, 1369, 1280, 1172, 1135, 900, 843, 707, 682 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 8.17–7.82 (m, 6H), 7.35–6.99 (m, 5H), 4.42–4.32 (m, 1H), 3.39–3.27 (dd, *J* = 11.2 Hz, *J* = 14.2 Hz, 1H), 3.28–3.21 (dd, *J* = 4 Hz, *J* = 9.6 Hz, 1H), 2.71–2.63 (app t, *J* = 4 Hz, 1H), 1.32–1.17 (m, 3H), 1.14–1.08 (br, 1H), 0.73–0.69 (2× d, *J* = 6.4 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 178.5, 148.5, 146.5, 138.4, 132.1, 131.7, 129.0, 128.8, 127.0, 126.2, 125.9, 124.5, 121.7, 121.2, 79.0, 83.9, 53.1, 43,5, 33.3, 24.6, 22.8, 21.2; HRMS calcd. for (C₃₁H₂₈F₁₂N₂O₂ + H)⁺ 689.2032, found 689.2037.

(S,S)-2-Amino-N-(1-hydroxy-1,1,3-triphenylpropan-2-yl)-3-methylbutanamide (1d). White solid; Yield 58%; m.p. 160–162°C; $[\alpha]_D^{20} = -89$ (*c* 1.0, CHCl₃); FT-IR 3326, 3027, 2958, 2927, 2869, 1952, 1710, 1638, 1525, 1448, 1365, 1170, 1063, 750, 700 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.71–7.55 (m, 5H), 7.38–7.06 (m, 10H), 6.29 (br, 1H), 4.76–4.65 (m, 1H), 3.23–3.11 (dd, *J* = 11.2 Hz, *J* = 14.2 Hz, 1H), 2.96 (d, *J* = 4 Hz, 1H), 2.87–2.78 (dd, *J* = 2.8 Hz, *J* = 14.2 Hz, 1H), 1.97–1.87 (m, 1H), 0.92 (br, 1H), 0.67–0.63 (d, *J* = 7 Hz, 3H), 0.19–0.16 (d, *J* = 7 Hz, 3H); ¹³C NMR (50 MHz, CDCl₃) δ 175.6, 146.6, 145.2, 139.7, 129.1, 128.3, 128.0, 126.7, 126.5, 126.3, 125.8, 125.6, 80.2, 61.9, 60.0, 34.1, 30.3, 19.4, 15.2; HRMS calcd. for (C₂₆H₃₀N₂O₂ + H)⁺ 403.2380, found 403.2375.

(S,S)-2-Amino-N-(1-hydroxy-4-methyl-1,1-diphenylpentan-2-yl)-3methylbutanamide (1e). White solid; Yield 51%; m.p. 177–178°C; $[\alpha]_D^{20} = -49 \ (c \ 1.0, \ DMSO);$ ¹H NMR (400 MHz, $DMSO-d_6$) δ 7.64–7.66 (d, $J = 9.6 \ Hz, 1H$), 7.46–7.50 (t, $J = 8.0 \ Hz, J = 8.4 \ Hz, 4H$), 7.02–7.27 (m, 5H), 5.92 (s, 1H), 4.90–4.96 (t, $J = 10.2 \ Hz, 1H$), 2.68–2.69 (d, J =4.4 Hz, 1H), 1.64–1.68 (m, 1H), 1.45–1.51 (m, 4H), 0.76–0.78 (d, J =7.2 Hz, 3H), 0.72–0.73 (d, $J = 6.0 \ Hz, 3H$).

(S,S)-2-Amino-N-(3-ethyl-3-hydroxy-1-phenylpentan-2-yl)-3-methylbutanamide (1f). White solid; Yield 65%; m.p. $106-107^{\circ}$ C; $[\alpha]_D^{20} = -73$ (*c* 1.0, CHCl₃); FT-IR 3335, 3027, 2962, 2931, 2878, 1644, 1521, 1457, 1383, 1135, 1033, 731, 698 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.23 (d, J = 8.8 Hz, 1H),7.29–7.11 (m, 4H), 4.16–4.14 (m,1H), 3.10–3.00 (m, 2H), 2.78–2.65 (dd, J = 11.8 Hz, J = 14 Hz, 1H), 2.18–2.02 (m, 1H), 1.76–1.42 (m, 4H), 1.08–1.01 (br, 2H), 1.00–0.90 (2× t, J = 7.4 Hz, 6H), 0.80–0.77 (d, J = 7 Hz, 3H), 0.36–0.33 (d, J = 6.8 Hz, 3H); ¹³C NMR (50 MHz, CDCl₃) δ 175.3, 139.1, 129.1, 128.4, 126.3, 76.6, 60.1, 56.9, 35.0, 30.1, 28.5, 27.7, 19.6, 15.4, 7.9, 7.6; HRMS calcd. for (C₁₈H₃₀N₂O₂ + H)⁺ 307.2380, found 307.2385.

(S,R)-2-Amino-N-(1-hydroxy-1,1,3-triphenylpropan-2-yl)-4-methylpentanamide (1g). White solid; Yield 45%; m.p. $162-163^{\circ}$ C; $[\alpha]_D^{20} = +49 (c \ 1.0, CHCl_3)$; FT-IR 3349, 3061, 2956, 2932, 2868, 1648, 1551, 1495, 1451, 1170, 1163, 747, 700 cm⁻¹; ¹H NMR (200 MHz, CDCl_3) δ 7.67–7.01 (m, 15H), 4.90–4.79 (m, 1H), 3.16–2.99 (m, 2H), 2.89–2.81 (dd, J = 3 Hz, J = 14.2 Hz, 1H), 1.43–1.22 (m, 4H), 0.9–0.86 (m, 1H), 0.83–0.80 (d, J = 6.2 Hz, 2H), 0.76–0.73 (d, J = 6.2 Hz, 2H); ¹³C NMR (100 MHz, DMSO- d_6) δ 175.8, 146.4, 145.0, 139.2, 129.2, 128.4, 128.3, 128.0, 126.8, 126.6, 126.3, 125.7,125.6, 80.8, 60.0, 53.2, 43.5, 34.7, 24.6, 23.1, 21.4; HRMS calcd. for (C₂₇H₃₂N₂O₂ + H)⁺ 417.2537, found 417.2538.

(S,S)-2-Amino-N-(1-hydroxy-4-methyl-1,1-diphenylpentan-2yl)propanamide (1h). White solid; Yield 53%; m.p. 165–167°C; $[\alpha]_D^{20}$ = -22 (*c* 1.0, CHCl₃); FT-IR 3306, 3027, 2956, 2930, 2871,1963, 1645, 1525, 1448, 1366, 1139, 1060, 750, 702 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.57–7.52 (m, 3H), 7.39–7.09 (m, 7H), 4.91–4.81 (m, 1H), 3.29–3.19 (dd, *J* = 6.8 Hz, *J* = 13.8 Hz, 1H), 1.70–1.57 (m, 2H), 1.29–1.17 (m, 1H), 0.99–0.95 (d, *J* = 6.8 Hz, 6H), 0.87–0.84 (d, *J* = 6.4 Hz, 3H); ¹³C NMR (50 MHz, CDCl₃) δ 175.9, 145.9, 145.0, 128.2, 127.9, 126.8, 126.6, 125.7, 125.6, 81.1, 54.9, 50.7, 38.7, 25.1, 23.9, 21.6, 21.2; HRMS calcd. for (C₂₁H₂₈N₂O₂ + Na)⁺ 363.2043, found 363.2048.

(S,S)-2-Amino-N-(1-hydroxy-1,1,3-triphenylpropan-2-yl)-3-phenylpropanamide (1i). White solid; Yield 46%; m.p. $172-173^{\circ}$ C; $[\alpha]_D^{20} = -125 \ (c \ 1.0, \ CHCl_3)$; FT-IR 3312, 3026, 2923, 2856,1952, 1647, 1531, 1446, 1349, 1164, 1060, 750, 697 cm⁻¹; ¹H NMR (200 MHz, CDCl_3) δ 7.70–7.57 (m, 5H), 7.40–7.07 (m, 13H), 6.70–6.95 (m, 2H), 5.61 (br, 1H), 4.82–4.73 (t, *J* = 8.6 Hz, 1H), 3.35–3.28 (m, 1H), 3.19–3.07 (m, 1H), 2.90–2.78 (m, 2H), 1.82–1.70 (m, 1H), 1.00 (br, 2H); ¹³C NMR (50 MHz, CDCl_3) δ 175.2, 146.2, 145.0, 139.3, 137.8, 129.2, 129.0, 128.6, 128.4, 128.3, 128.0, 126.8, 126.7, 126.3, 125.8, 125.6, 80.5, 60.3, 56.3, 40.2, 34.8; HRMS calcd. for (C₃₀H₃₀N₂O₂ + Na)⁺ 473.2199, found 473.2185.

(S,S)-2-amino-N-(1-hydroxy-4-methyl-1,1-diphenylpentan-2-yl)-3-phenylpropanamide (1j). White solid; Yield 48%; m.p. 152–153°C; $[\alpha]_D^{20} = -42 \ (c \ 1.0, CHCl_3)$; FT-IR 3318, 3026, 2953, 2926, 2868, 1950, 1644, 1515, 1448, 1366, 1164, 1062, 746, 700 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.57–7.47 (m, 5H), 7.36–7.06 (m, 10H), 4.92–4.81 (m, 1H), 3.36–3.30 (m, 1H), 3.03–2.94 (m, 1H), 2.31–2.20 (m, 1H), 1.72–1.51 (m, 2H), 1.30–1.17 (m, 2H), 0.99–0.96 (d, J = 6.6 Hz, 3H), 0.86–0.83 (d, J = 6.4 Hz, 3H); ¹³C NMR (50 MHz, CDCl₃) δ 174.5, 145.9, 144.9, 137.8, 129.1, 129.1, 128.6, 128.3, 128.2, 128.0, 127.9, 126.8, 126.7, 126.6, 125.8, 125.7, 125.6, 81.1, 56.4, 54.9, 40.6, 38.6, 25.1, 23.9, 21.6; HRMS calcd. for (C₂₇H₃₂N₂O₂ + Na)⁺ 439.2356, found 439.2343.

General Procedure for the Hydroxyamination of Aldehydes with Nitrosobenzene

The solid of catalyst 1 (0.2 mmol, 20 mol %) was added to a solution of the aldehyde (3.0 mmol, 3.0 equiv) in CH_2Cl_2 (1.0 ml) at $-20^{\circ}C$. A solution of nitrosobenzene (1.0 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 ml) was then added dropwise to the reaction mixture, and the resulting mixture was stirred at $-20^{\circ}C$ for 3–5 days. EtOH (2.0 ml) and NaBH₄ (4.0 mmol) were successively added at the same temperature. After 30 min, the reaction was quenched with saturated brine (2.0 ml), extracted with CH_2Cl_2 (3× 2.0 ml), dried over anhydrous Na₂SO₄, and concentrated under a reduced pressure. The residue was purified over silica gel by the flash column chromatography to afford the hydroxyamination adducts. The enantiomeric excess was determined by chiral HPLC.

(R)-2-(N-Phenylhydroxyamino)propanol (6a). Pale yellow oil; Yield 49%; $[\alpha]_D^{20} = -12.8 \ (c \ 1.0, CHCl_3)$, Ref. 27 $[\alpha]_D^{24} = 8.0 \ (c \ 1.0, CHCl_3)$; ¹H NMR (200 MHz, CD₃OD) δ 7.26–7.08 (m, 4H), 6.90–6.82 (app t, J = 7.2 Hz, 1H), 3.84–3.65 (m, 2H), 3.58–3.53 (m, 1H), 1.02–0.98 (d, J = 6.2 Hz, 3H). ee = 51%, determined by chiral HPLC. The enantiomeric excess was determined by HPLC with an AD-H column (hexane/ethanol = 90/10), 1.0 ml/min; t = 9.2 min (major), t = 13.4 min (minor).

(R)-2-(N-Phenylhydroxyamino)propanol (6b). Pale yellow oil; Yield 51%; $[\alpha]_D^{20} = -3.2$ (*c* 1.0, CHCl₃), Ref. 27 $[\alpha]_D^{25} = -2.5$ (*c* 1.0, CH₂Cl₂); ¹H NMR (200 MHz, CD₃OD) δ 7.24–7.07 (m, 4H), 6.86–6.77 (app t, J = 7.2 Hz, 1H), 3.77–3.56 (m, 2H), 3.52–3.29 (m, 1H), 1.70–1.55 (m, 2H), 0.97–0.89 (t, J = 7.4 Hz, 3H). *ee* = 54%, determined by chiral HPLC. The enantiomeric excess was determined by HPLC with an AD-H column (hexane/ethanol = 90/10), 1.0 ml/min; t = 7.9 min (major), t = 10.4 min (minor).

(R)-2-(Hydroxy(phenyl)amino)pentan-1-ol (6c). Pale yellow oil; Yield 54%; $[\alpha]_{20}^{20} = -12.4$ (*c* 1.0, CHCl₃), Ref. 25 $[\alpha]_{24}^{24} = 8.6$ (*c* 0.9, CHCl₃); ¹H NMR (200 MHz, CD₃OD) δ 7.25–7.06 (m, 4H), 6.86–6.78 (app t, J = 7.0 Hz, 1H), 3.74–3.55 (m, 3H), 1.48–1.30 (m, 4H), 0.96–0.89 (t, J = 7.2 Hz, 3H). *ee* = 60%, determined by chiral HPLC. The enantiomeric excess was determined by HPLC with an AD-H column (hexane/ethanol = 95/5), 1.0 ml/min; t = 10.4 min (major), t = 13.2 min (minor).

(R)-2-(N-Phenylhydroxyamino)-3-methylbutanol (6d). Pale yellow oil; Yield 63%; $[\alpha]_D^{20} = -6.4$ (*c* 1.0, CHCl₃), Ref. 25 $[\alpha]_D^{20} = 11.6$ (*c* 1.0, CHCl₃); ¹H NMR (200 MHz, CD₃OD) δ 7.22–7.15 (app t, J = 7.0 Hz, 2H), 7.07–7.03 (d, J = 7.6 Hz, 2H), 6.81–6.74 (app t, J = 7.1 Hz, 1H), 3.80–3.76 (m, 2H), 3.28–3.18 (m, 2H), 2.20–2.09 (m, 1H), 1.05–1.00 (2× d, J = 6.8 Hz, 6H). *ee* = 65%, determined by chiral HPLC. The enantiomeric excess was determined by HPLC with an OJ-H column (hexane/ethanol = 96/4), 1.0 ml/min; t = 12.7 min (major), t = 18.0 min (minor).

(R)-2-(N-Phenylhydroxyamino)-3-phenylpropanol (6e). Pale yellow oil; Yield 60%; $[\alpha]_D^{20} = +27$ (*c* 1.0, CHCl₃), Ref. 25 $[\alpha]_D^{20} = -99.3$ (*c* 0.8, CHCl₃); ¹H NMR (200 MHz, CD₃OD) δ 7.27–7.08 (m, 9H), 6.85 (app t, *J* = 7.3 Hz, 1H), 3.83–3.73 (m, 3H), 2.91–2.82 (dd, *J* = 5.0 Hz, *J* = 14.0 Hz, 1H), 2.79–2.75 (dd, *J* = 7.8 Hz, *J* = 13.8 Hz, 1H). *ee* = 61%, determined by chiral HPLC. The enantiomeric excess was determined by HPLC with an AD-H column (hexane/ethanol = 90/10), 1.0 ml/min; *t* = 9.6 min (major), *t* = 13.5 min (minor).

(R)-3-(4-tert-butylphenyl)-2-(hydroxy(phenyl)amino)propan-1-ol (6f). Pale yellow oil; Yield 70%; $[\alpha]_D^{20} = +16$ (*c* 1.0, CHCl₃); FT-IR 3320, 3058, 2960, 2868, 1708, 1596, 1488, 1362, 1221, 1026, 832, 760, 695, 568 cm⁻¹; ¹H NMR (200 MHz, CD₃OD) & 7.26–7.01 (m, 8H), 6.89–6.81 (app t, *J* = 7.6 Hz, 1H), 3.87–3.75 (m, 2H), 3.53–3.42 (dd, *J* = 7.1 Hz, 1H), 2.87–2.78 (dd, *J* = 4.8 Hz, *J* = 13.8 Hz, 2H), 2.74–2.63 (dd, *J* = 7.7 Hz, *J* = 14.2 Hz, 2H), 1.28 (s, 9H); ¹³C NMR (50 MHz, CD₃OD): & 154.1, 149.8, 138.0, 129.8, 129.6, 126.2, 121.7, 117.2, 71.0, 62.2, 35.1, 33.1, 31.9, 31.8. HRMS calcd. for (C₁₉H₂₅NO₂ + H)⁺: 300.1958, found 300.1962. *ee* = 37%, determined by chiral HPLC. The enantiomeric excess was determined by HPLC with an AD-H column (hexane/ethanol = 90/10), 1.0 ml/min; *t* = 6.8 min (major), *t* = 8.0 min (minor).

(R)-2-(Hydroxy-phenyl-amino)-2-methyl-butan-1-ol (6g). Colorless oil; Yield 68%; $[\alpha]_D^{20} = -5.8$ (*c* 1.0, CHCl₃); ¹H-NMR (200 MHz, CDCl₃) δ 7.26–7.09 (m, 5H), 3.69 (d, *J* = 11.4 Hz, 1H), 3.53 (d, *J* = 11.4 Hz, 1H), 1.79–1.68 (m, 1H), 1.30–1.16 (m, 1H), 0.94 (s, 3H), 0.81 (t, *J* = 7.5Hz, 3H); Ref. 26. *ee* = 31%, determined by chiral HPLC. The enantiomeric excess was determined by HPLC with an AD-H column (hexane/ ethanol = 95/5), 1.0 ml/min; *t* = 12.7 min (major), *t* = 15.2 min (minor).

(R)-2-(Hydroxy-phenyl-amino)-2-methyl-pentan-1-ol (6h). Colorless oil; Yield 73%; $[\alpha]_D^{20} = -8$ (*c* 1.0, CHCl₃); ¹H-NMR (200 MHz, CDCl₃) δ 7.26–7.11 (m, 5H), 3.67 (d, *J* = 11.4 Hz, 1H), 3.57 (d, *J* = 11.4 Hz, 1H), 1.67–1.60 (m, 1H), 1.29–1.11 (m, 4H), 0.95 (s, 3H), 0.82 (t, *J* = 6.8 Hz, 3H); Ref. 24. *ee* = 35%, determined by chiral HPLC. The enantio-

 TABLE 1. Solvent screening in the hydroxyamination reaction of 3-methylbutanal with nitrosobenzene^a



Entry	Solvent	Time (day)	Yield (%) ^b	ee (%) ^c
1	CH ₂ Cl ₂	3	62	65
2	THF	4	ND^d	ND^d
3	CHCl ₃	3	56	33
4	$(CH_2)_2Cl_2$	3	60	41
5	EtOAc	4	45	27
6	EtOH	2	24	21
7	TBME	5	35	45
8	DMF	5	12	15
9	PhCH ₃	4	55	37
10	DMB	4	58	43
11	CH ₂ Cl ₂ /MeOH (9:1)	2	$62^{\rm e}$	51
$12^{\rm f}$	CH_2Cl_2	2	56	36
13^{g}	CH_2Cl_2	1	58	21

^aReactions were conducted with 3.0 equiv 3-methylbutanal, 0.2 equiv catalyst, and 1.0 equiv nitrosobenzene at -20° C.

^bIsolated yield.

^cDetermined by chiral HPLC analysis (Chiralcel OJ-H). The configuration was assigned by comparison of the retention time of the major isomer in HPLC with reported values and by comparison of the sign of the optical rotation with the reported value.^{24–27}

^dNot determined.

^eA little *O*-nitroso aldol product was observed.

^fThe reaction was carried out at 0°C.

^gThe reaction was carried out at room temperature.

meric excess was determined by HPLC with an AS-H column (hexane/i-PrOH = 98/2), 1.0 ml/min; t = 16.1 min (minor), t = 17.3 min (major).

RESULTS AND DISCUSSION

The seven organocatalysts **1a–g** were readily prepared by using the routine mixed anhydride method to combine the Boc-protected amino acids **4** with the amino alcohols **3a–e** from natural amino primary amino acids, and successively remove the Boc group with TFA (Scheme 1).^{40,41} When L-phenylalanine was replaced by D-phenylalanine, **1g**, the diastereomeric isomer of **1a**, was afforded.

In initial experiments, a model reaction of 3-methylbutanal and nitrosobenzene was investigated by using 20 mol % organocatalyst **1a** in a variety of solvents at -20° C without any additive (Table 1, entries 1–11).* As expected, *N*-specific nitroso-aldol adduct, which was then reduced in situ into amino alcohol with NaBH₄, was fortunately obtained as the only product. The results showed that dichloromethane was the optimal solvent that exclusively gave the *N*-selective product with the highest yield and enantioselectivity (Table 1, entry 1). A portion of MeOH in DCM accelerated the reaction but decreased in its enantioselectivity and generated a little *O*-selective aminoxylated side product (Table 1, entry 11). The other solvents were found to be less satisfactory in terms of the chemical yield, reaction rate and enantioselectivity. Accordingly, CH₂Cl₂ was selected to be the optimal sol-

^{*}Because nitrosobenzene is very reactive and unstable, we used threefold aldehyde to nitrobenzene to make the reaction complete more quickly and get higher yield in agreement with the reported procedures.²⁴⁻²⁷ The selfaldol reaction of the aldehyde was not observed in this reaction.

TABLE 2. Catalysts screening in the hydroxyamination reaction of 3-methylbutanal with nitrosobenzene^a



Entry	Catalyst	Additive (20%)	Time (day)	Yield (%) ^b	ee (%) ^c
1	1a	_	3	62	65 (R)
2	1b	_	2	45	41 (R)
3	1c	-	8 h	58	12 (R)
4	1d	_	3	51	61 (R)
5	1e	_	3	47	62 (R)
6	1f	_	3	34	61 (R)
$7^{\rm d}$	1f	_	1	42	3 (R)
8	1g	_	4	35	32 (R)
9	1ĥ	-	2	37	38 (R)
10	1i	_	3	48	60 (R)
11	1j	_	3	41	32 (R)
$12^{\rm e}$	1a	_	3.5	46	56 (R)
13 ^f	1a	_	3	60	55 (R)
14^{g}	1a	_	2	58	59 (R)
15	1a	DNP	1	64	11 (R)
16	1a	Phenol	2.5	56	51 (R)
17	1a	Et ₃ N	3	15	27(R)
18	1a	4 Å MS	4	13	61 (R)

^aReactions were conducted with 3.0 equiv 3-methylbutanal, 0.2 equiv catalyst, and 1.0 equiv nitrosobenzene at -20° C.

^DIsolated yield.

^cDetermined by chiral HPLC analysis (Chiralcel OJ-H). The configuration was assigned by comparison of the retention time of the major isomer in HPLC with reported values and by comparison of the sign of the optical rotation with the reported value.^{24–27}

^dThe catalyst is in the form of hydrochloride.

^eThe reaction was carried out in the presence of 15 mol % catalyst.

^tThe reaction was carried out in the presence of 25 mol % equiv catalyst.

^gThe reaction was carried out in the presence of 30 mol % catalyst.

vent. Raising temperature did not lead to a higher yield but lowered the enantioselectivity (Table 1, entries 12 and 13).

The effects of the catalyst loading and additive on the catalytic efficiency of **1a** were then tested (Table 2, entries 9– 16). Changing the loading of the catalyst had no significant improvement in enantioselectivity but only accelerated the reaction (Table 2, entries 9-11). We wished to find some effective additive to raise the enantioselectivity and yield. Unexpectedly, however, DNP sharply reduced the enantioselectivity although it significantly accelerated the reaction (Table 2, entry 12). Similarly, the lower acidity phenol slightly decreased the enantiomeric excess (Table 2, entry 13). A basic additive triethylamine was also observed but it also sharply reduced the enantioselectivity (Table 2, entry 14). Although 4 Å molecular sieves as another additive were tested, it only made the reaction very slow with no increase in the enantioselectivity (Table 2, entries 15).²⁷ DNP itself can not catalyze this reaction. As we know, an acid will quicken the formation of enamine from an amine group with carbonyl group of the aldehyde or ketone. We speculate that DNP might serve an acid to make the enamine quick formation from the organocalyst with the aldehyde. This quick enamine might contribute to the accelerated reaction. With regard to the decreased *ee* value, it is very unclear here in combination with the behavior of the basic and molecular sieves additives.

We then investigated the effects of these different catalysts on the reaction. As showed in Table 2, **1a**, **1d**, **1e**, **1f**, and **1i** showed higher enantioselectivity ($\geq 60\%$) than other catalysts (Table 2, entries 1, 4, 5, and 6). **1c**, which had a stronger acidic hydroxyl and bulky diaryl groups, gave the fastest reaction with a very low enantioselectivity (Table 2, entry 3). In comparison with **1a**, **1g** which is the diastereomeric isomer of **1a** with a D-Phe instead of L-Phe only lowered the enantioselectivity with no influence on the configuration of the product (Table 2, entries 1 and 8). In terms of yield and enantioselectivity, **1a** could be considered as the optimal catalyst.

With the optimized reaction conditions in hand, the scope of this reaction for various aldehydes with nitrosobenzene was next investigated, and the results are shown in Table 3. Generally, all the reactions proceeded smoothly and gave the *N*-specific product β -amino alcohols. And it is noteworthy that no O-selective aminoxylated product was detected. This result indicated that this primary amine-based organocatalyst is efficient to the atom specific reaction. As shown in Table 3, a bulkier group in β -carbon is helpful to afford higher yields and enantioselctivity (Table 3, entry 1–5), and β methyl butyraldehyde afforded the highest 65% enantioselectivity and higher yield. An exceptional case was 3-(4-tertbutylphenyl)propanal, it resulted in a low enantioselectivity but a higher 70% yield. Maybe the great steric hindrance is disadvantageous to the enantioselctivity, however, the α branched aldehydes achieved lowered enantioselectivity with higher yields. Among the series aldehydes, 3-methylbutanal got the highest 65% enantioselectivity while (Table 3, entry 4) while 2-methylvaleraldehyde harvested the highest 73% vield (Table 3, entry 8).

TABLE 3. Enantioselective hydroxyamination reaction of various aldehydes with nitrosobenzene catalyzed by 1a^a



Entry	Aldehyde	Time (day)	Yield (%) ^b	ee (%) ^c
1	<u> </u>	5	49	51 (R)
2	СНО	5	51	54 (R)
3	СНО	4	54	60 (R)
4	СНО	3	62	65 (R)
5	СНО	4	60	61 (<i>R</i>)
cd	СНО	2	70	37 (R)
o d	t-Bu	4	68	31 (<i>R</i>)
7 ⁻ 8 ^d	СНО	3	73	35 (R)

^aReactions were conducted with 3.0 equiv aldehyde, 0.2 equiv catalyst, and 1.0 equiv nitrosobenzene at -20° C.

^bIsolated yield.

^cDetermined by chiral HPLC analysis. The configuration was assigned by comparison of the retention time of the major isomer in HPLC with reported value and by comparison of the sign of the optical rotation with the reported value.^{24–27}

^dThe reaction was carried out at 0°C.



Fig. 2. The proposed transition state.

It is supposed that the nitrogen is activated by two hydrogen-bonds formed with the oxygen of the nitrosobenzene and the hydrogen atoms from both the amide and hydroxy groups of the organocatalyst (Fig. 2). The steric effect of the organocatalyst and the two pairs of lone electrons of oxygen atom of the nitrosobenzene make the catalyst itself preferentially select the O-atom to form the two hydrogen bonds and thus facilitate the enamine to N-specifically and nucelophilically attack to nitrosobenzene. On account of the bulky isobutyl and phenyl groups of the catalyst shielding the Si face of the *E*-enamine which was formed by the primary amine of the catalyst with aldehydes, this activation to the nitroso group would admit the same group mainly accept the nucleophilic attack of the electronically enriched E-enamine from its Re face. Therefore, the N-selective nitroso-aldol product with *R*-configuration was predominantly afforded.²⁴ The result is in accordance with the previous description.^{24–27}

CONCLUSIONS

In summary, we have described a successful direct asymmetric hydroxyamination reaction of unmodified aldehydes with nitrosobenzene which is firstly catalyzed by a primary amine-based organocatalyst to date. The organocatalysts could be readily synthesized starting from naturally occurred primary amino acids. The acidic additives could markedly accelerate the reaction but sharply decrease in the enantioselectivity. A basic additive did not raise the enantioselectivity and the yield. In spite of the two reactive nitrogen and oxygen atoms in nitrosobenzene, the reaction is N-specific. The bulkier substituents of the organocatalyst and two hydrogen bonds formed between the organocatalyst and nitrosobenze make the reaction preferentially nitrogen selective. To aldehydes, a bulkier group in the chain is advantageous to higher yield. However, a bulkier β -carbon substituted group can raise the enantioselectivity, whereas α -branched aldehydes normally achieved lowered enantioselectivity.

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