Highly enantioselective L-thiaproline catalyzed α-aminoxylation of aldehydes in aqueous media†

Pei Juan Chua, Bin Tan and Guofu Zhong*

Received 15th October 2008, Accepted 28th January 2009
First published as an Advance Article on the web 13th February 2009
DOI: 10.1039/b817950f

Highly enantioselective L-thiaproline catalyzed α-aminoxylation of aldehydes in the presence of water and tetrabutylammonium bromide followed by *in situ* reduction to afford the respective α-aminoxy alcohols has been developed in good to high yields (74–88%) and excellent enantioselectivities (93–>99%).

Introduction

The presence of optically active α-hydroxycarbonyl moieties such as 1,2-diols in many biologically active natural products motivated research into finding new routes to provide better stereocontrol for these synthetically useful synthons.[1] Asymmetric α-hydroxylation of enolates[2] and the Sharpless asymmetric dihydroxylation of olefins[3] are some methods to synthesize these compounds. The year 2000 saw a renaissance of organocatalysis, and since then organocatalysis has emerged as a extremely useful tool for the preparation of enantiomerically pure compounds.[4] Operational simplicity, availability and the non-toxicity of the organic catalysts compared to the corresponding transition-metal species, as well as the high efficiencies and selectivities attained in many organocatalytic transformations made this methodology very attractive for the formation of enantiomerically pure compounds.

In 2003 Zhong,[5] MacMillan[6] and Hayashi[7] and co-workers independently reported the direct proline-catalyzed α-aminoxylation of aldehydes with nitrosobenzene and the usefulness of this reaction was demonstrated in the synthesis of several biologically active compounds.[8] Though the scope of the above-mentioned reaction has been quickly extended to that of ketones[9] after the first report, there was little development in new organocatalysts[10] or environmentally friendly reaction protocols.[11]

Conventional chemical synthesis usually focused on improving yield and selectivity, with little regard to a chemical's impact on the environment. Recently, increasing demand for innovative and imaginative synthetic methodologies to improve efficiency and sustainability such as simplicity, atom economy, reduced chemical wastage and energy usage, safety, and environmental friendliness prompted much research in this area.[12] To date, α-aminoxylation is usually carried out in organic solvents such as acetonitrile,[7,13] chloroform,[6] dichloromethane,[14] dimethylformamide[15] and dimethylsulfoxide.[5,16] The use of such solvents contributes to the organic waste and it is essential to develop more environmentally friendly protocols.

Water, no doubt, is the most inexpensive and environmentally benign solvent. Since Breslow reported that the use of water instead of organic solvents could significantly increase the rate of the Diels–Alder reaction[17] considerable attention has been directed towards the development of organic reactions in water. To date, all of the most useful organic reactions have at least a reaction protocol that involves water as a solvent.[18] Although Blackmond raised some doubts about the environmental friendliness and efficiency of water in organocatalysis,[19] we cannot dismiss some of the advantages that accompanies the use of water as a solvent: acceleration of reaction rates and enhancement of reaction selectivities; elimination of tedious protection–deprotection processes for certain acidic-hydrogen containing functional groups and the recycling of water-soluble catalysts after separation from water-insoluble organic products.

Results and discussion

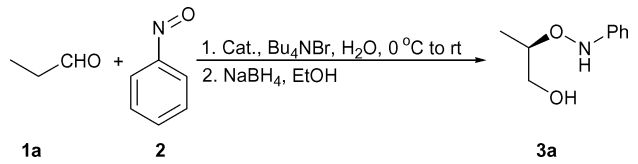
To probe the feasibility of the α-aminoxylation of aldehydes in aqueous media using a phase-transfer catalyst, we first performed α-aminoxylation of propanal to nitrosobenzene in the presence of L-proline **I**, tetrabutylammonium bromide and water at 0 °C and then warmed to room temperature. To our disappointment the yield obtained in this initial reaction was rather low, despite the high enantioselectivity achieved. This prompted us to screen more catalysts **II–VI** (Table 1, entries 2–6). Among all the catalysts investigated, only L-thiaproline **VI** gave a higher yield than **I**. Although **VI** needed a longer reaction time and gave a slightly lower enantioselectivity than **I**, we believed that higher enantioselectivity could be achieved with the optimization of reaction conditions. This is the first instance where L-thiaproline **VI** was used as a catalyst in an α-aminoxylation. The use of **VI** will potentially reduce much hassle for stereoselective reactions as it is commercially available.

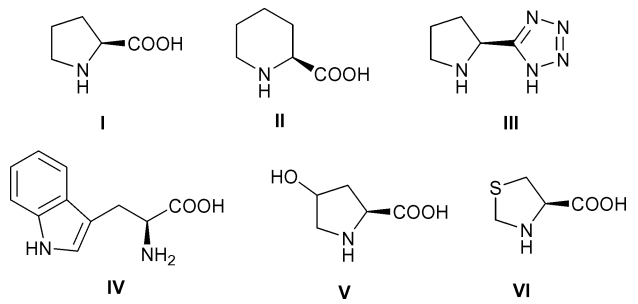
For optimisation of the reaction conditions, we first investigated the effect of catalyst loading on the reaction (Table 2, entries 1–3). Highest yield and enantioselectivity were obtained when 20 mol% of catalyst was used. The results of the reaction

Division of Chemistry & Biological Chemistry, School of Physical & Mathematical Sciences, Nanyang Technological University, 21 Nanyang Link, Singapore, 637371, Singapore. E-mail: guofu@ntu.edu.sg; Fax: +65 6791 1961; Tel: +65 6316 8761

† Electronic supplementary information (ESI) available: General information, general experimental procedure, and experimental data and spectra for compounds **3a**–**k**. See DOI: 10.1039/b817950f

Table 1 Catalyst screening[a]





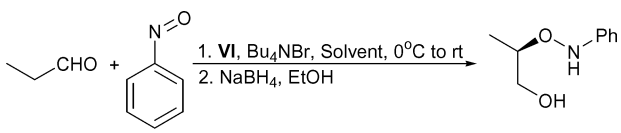
Entry	Catalyst	Time	Yield[b] (%)	ee[c] (%)
1	**I**	1 h	64	96
2	**II**	6 h	39	43
3	**III**	20 min	62	96
4	**IV**	30 min	14	23
5	**V**	30 min	65	82
6	**VI**	1 h 40 min	75	93

[a] Conditions: Nitrosobenzene (0.3 mmol), propanal (3 equiv.), catalyst (30 mol%), tetrabutylammonium bromide (2 equiv.) and water (0.10 mL) was added at 0 °C and then warmed to rt (23 °C) unless otherwise stated. [b] Isolated yields. [c] Determined by chiral phase HPLC.

did not improve under neat conditions (Table 2, entry 4). Screenings of various organic solvents revealed that chloroform and dimethyl sulfoxide, preferred solvents for many α-aminoxylation reactions, were not the best solvents when **VI** was employed as catalyst (Table 2, entries 5–6). Although acetonitrile gave comparable enantioselectivity, its lower yield and longer reaction time made water the preferred choice of solvent for this reaction (Table 2, entry 7). We discovered that 0.10 mL of water is the optimum amount of water added to the system to attain the highest yield and enantioselectivity (Table 2, entries 8–10). Both the yield and enantioselectivity dropped when the amount of phase transfer catalyst was reduced (Table 2, entries 11–12). A similar trend was also observed with decreasing amounts of propanal (Table 2, entries 13–14).

With the optimal reaction conditions established, we probed the scope of the reaction for a variety of aldehydes. The results are summarized in Table 3. In the cases investigated, the α-aminoxy alcohols were obtained in good to high yields (74–88%) and excellent enantioselectivities (93–99%). The L-thiaproline α-aminoxylation reaction between nitrosobenzene and propanal was completed in 2 h with good yield (84%) and excellent enantioselectivity (96%) (Table 3, entry 1). Not only propanal, but linear chain aldehydes such as *n*-butanal, *n*-pentanal and *n*-hexanal react with nitrosobenzene, affording α-aminoxy alcohols in good yield with excellent enantioselectivities (Table 3, entries 2–4). Branched aldehydes such as 3-methylbutanal are also suitable substrates as it was successfully converted to the α-aminoxy alcohols in good yield with excellent enantioselectivity (Table 3, entry 5). Aldehydes containing an aromatic moiety such as phenylacetaldehyde and 3-phenylpropanal were successfully employed in this reaction (Table 3, entries 6 and 7). It is interesting to note that the reaction time for phenylacetylaldehyde was significantly reduced. This may be due to the activating effect of the benzene ring in the α-position of the phenylacetylaldehyde. The introduction of a terminal double bond on the aldehyde did not drastically affect the yield and enantioselevitvity of the reaction (Table 3, entry 8). The reaction also proceeded smoothly with protecting groups such as benzyl ethers and *tert*-butoxycarbonyl carbamates to

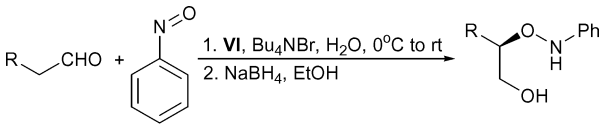
Table 2 Optimisation of reaction conditions[a]



Entry	Solvent	Vol. of solvent	Time	Yield[b] (%)	ee[c] (%)
1[d]	H_2O	0.10 mL	2 h 10 min	78	93
2	H_2O	0.10 mL	2 h	84	96
3[e]	H_2O	0.10 mL	1 h 40 min	75	93
4	—	0.10 mL	1 h 15 min	62	94
5	$CHCl_3$	0.10 mL	1 h 50 min	60	92
6	DMSO	0.10 mL	2 h 15 min	68	90
7	CH_3CN	0.10 mL	3 h 50 min	73	97
8	H_2O	0.05 mL	2 h 20 min	56	93
9	H_2O	0.20 mL	2 h 10 min	67	96
10	H_2O	0.30 mL	1 h 45 min	58	93
11[f]	H_2O	0.10 mL	1 h 55 min	62	94
12[g]	H_2O	0.10 mL	1 h 45 min	62	95
13[h]	H_2O	0.10 mL	2 h 15 min	52	90
14[i]	H_2O	0.10 mL	2 h 25 min	54	92

[a] Conditions: Nitrosobenzene (0.3 mmol), propanal (3 equiv.), catalyst (20 mol%), tetrabutylammonium bromide (2 equiv.) and water (0.10 mL) was added at 0 °C and stirred at rt (23 °C) unless otherwise stated. [b] Isolated yields. [c] Determined by chiral phase HPLC. [d] 10 mol% of **VI**. [e] 30 mol% of **VI**. [f] No Bu_4NBr added. [g] 1 equiv. Bu_4NBr added. [h] 1 equiv. propanal added. [i] 2 equiv. propanal added.

Table 3 The generality of reaction of α-aminoxylation in the presence of water[a]



1a-k 2 3a-k

Entry	R		Time	Yield[b] (%)	ee[c] (%)
1	Me	**3a**	2 h	84	96
2	Et	**3b**	2 h 10 min	75	98
3	Pr	**3c**	2 h 20 min	79	97
4	Bu	**3d**	2 h 35 min	74	96
5	*i*-Pr	**3e**	2 h 10 min	76	97
6	Ph	**3f**	20 min	78	93
7	$PhCH_2$	**3g**	2 h 30 min	77	> 99
8	CH_2=$CHCH_2$	**3h**	1 h	88	96
9	$BnOCH_2CH_2$	**3i**	2 h 20 min	86	97
10	$BocNHCH_2$	**3j**	2 h 30 min	79	93
11[d]	Me	**3k**	2 h 20 min	83	97

[a] Conditions: Nitrosobenzene (0.3 mmol), propanal (3 equiv.), catalyst (20 mol%), tetrabutylammonium bromide (2 equiv.) and water (0.10 mL) was added at 0 °C and stirred at rt (23 °C) unless otherwise stated. [b] Isolated yields. [c] Determined by chiral phase HPLC. [d] Nitrosotoluene was used instead of nitrosobenzene.

afford the α-aminoxy alcohols in good yield with excellent enantioselectivities (Table 3, entries 9–10). The scope of nitroso compounds was briefly tested by replacing nitrosobenzene with nitrosotoluene. When nitrosotoluene was treated with propanal under the optimised conditions, the corresponding α-aminoxy alcohols were obtained in 83% yield with an enantioselecitivity of 97%, which is consistent with the results of nitrosobenzene.

Conclusions

In conclusion, L-thiaproline was used to catalyze α-aminoxylation of aldehydes in aqueous media in the presence of a phase-transfer catalyst to afford the respective α-aminoxy alcohols in good to high yields (74–88%) and excellent enantioselectivities (93–>99%). This reaction protocol may find potential use for industrial-scale preparation due to its simple operation, wide scope, excellent enantioselectivities and environmental friendliness. Further investigation on the application of L-thioproline in asymmetric catalysis is in progress.

Experimental

General experimental procedure for the α-aminoxylation of aldehydes to nitrosobenzene in aqueous media

Water (0.10 mL) and tetrabutylammonium bromide (193.4 mg, 0.6 mmol) was added to a 5 mL drum vial containing nitrosobenzene (**2**, 32.1 mg, 0.3 mmol), corresponding aldehydes (**1**, 0.9 mmol) and a magnetic stirring bar. After stirring for 5 min at 0 °C, L-thiaproline (8 mg, 0.06 mmol) was added. The reaction was first stirred at this temperature for about 10 min and then at room temperature until the green solution turned yellow which indicated complete consumption of the nitrosobenzene. As the α-aminoxy aldehyde product is rather labile, isolation and characterization was performed after conversion to the corresponding α-aminoxy alcohol **3** by treatment of the reaction mixture with $NaBH_4$. The excess $NaBH_4$ was quenched by the addition of water. The reaction mixture was then extracted with CH_2Cl_2 (3 × 30 ml). The combined organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. The crude oil was purified by flash column chromatography (hexane/EtOAc = 9/1–7/3) yielding pure α-aminoxy alcohols **3**.

(*R*)-2-(*N*-Phenylaminoxy)propan-1-ol (3a). α-Aminoxy alcohol **3a** was prepared according to the general procedure from propanal (0.07 mL, 0.9 mmol) to provide the title compound as a pale yellow liquid (42.3 mg, 84% yield) after flash column chromatography on silica gel (hexane/EtOAc = 9/1–7/3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.25 (2H, m), 7.04–6.96 (3H, m), 4.16–4.08 (1H, m), 3.80–3.70 (2H, m), 2.56 (1H, brs), 1.25 (3H, d, J = 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.5, 129.0, 122.4, 114.7, 80.0, 66.5, 15.4. HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 90/10, flow rate 1 mL min^{-1}, λ = 230 nm), t_R (minor) = 10.6 min, t_R (major) = 12.1 min; 96% ee. $[\alpha]_D^{25}$ = +2.9 (c = 1.0, $CHCl_3$).

(*R*)-2-(*N*-Phenylaminoxy)butan-1-ol (3b). α-Aminoxy alcohol **3b** was prepared according to the general procedure from butanal (0.08 mL, 0.9 mmol) to provide the title compound as a pale yellow liquid (40.9 mg, 75% yield) after flash column chromatography on silica gel (hexane/EtOAc = 9/1–7/3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.25 (2H, m), 7.07–6.96 (2H, m), 3.91–3.74 (3H, m), 2.67 (1H, brs), 1.78–1.53 (2H, m), 1.01 (3H, t, J = 7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.4, 129.0, 122.4, 114.8, 85.3, 64.9, 22.9, 10.1. HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 90/10, flow rate 1 mL min^{-1}, λ = 230 nm), t_R (minor) = 10.2 min, t_R (major) = 11.6 min; 98% ee. $[\alpha]_D^{25}$ = +36.0 (c = 1.0, $CHCl_3$).

(*R*)-2-(*N*-Phenylaminoxy)pentan-1-ol (3c). α-Aminoxy alcohol **3c** was prepared according to the general procedure from pentanal (0.10 mL, 0.9 mmol) to provide the title compound as a pale yellow liquid (46.0 mg, 79% yield) after flash column chromatography on silica gel (hexane/EtOAc = 9/1–7/3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.15 (3H, m), 6.98–6.94 (2H, m),

3.94–3.91 (1H, m), 3.85–3.82 (1H, m), 3.75–3.71 (1H, m), 2.93 (1H, brs), 1.67–1.61 (1H, m), 1.54–1.33 (3H, m), 0.97–0.89 (3H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ148.4, 129.0, 122.3, 114.7, 83.7, 65.1, 32.0, 19.0, 14.2. HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 90/10, flow rate 1 mL min^{-1}, $\lambda = 230$ nm), t_R (minor) = 10.0 min, t_R (major) = 11.4 min; 97% ee. $[\alpha]_D^{25} = +28.6$ ($c = 1.0$, $CHCl_3$).

(*R*)-2-(*N*-Phenylaminoxy)hexan-1-ol (3d). α-Aminoxy alcohol **3d** was prepared according to the general procedure from hexanal (0.11 mL, 0.9 mmol) to provide the title compound as a pale yellow liquid (46.4 mg, 74% yield) after flash column chromatography on silica gel (hexane/EtOAc = 9/1–7/3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.26 (2H, m), 7.06–6.96 (3H, m), 3.98–3.92 (1H, m), 3.87–3.84 (1H, m), 3.79–3.72 (1H, m), 2.68 (1H, brs), 1.69–1.50 (1H, m), 1.47–1.30 (4H, m), 0.92 (3H, t, $J = 7.1$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ148.4, 129.0, 122.5, 114.9, 84.0, 65.4, 29.6, 27.9, 22.0, 14.0. HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 90/10, flow rate 1 mL min^{-1}, $\lambda = 230$ nm), t_R (minor) = 9.5 min, t_R (major) = 11.4 min; 96% ee. $[\alpha]_D^{25} = +22.5$ ($c = 1.2$, $CHCl_3$).

(*R*)-3-Methyl-2-(*N*-phenylaminoxy)butan-1-ol (3e). α-Aminoxy alcohol **3e** was prepared according to the general procedure from 3-methylbutanal (0.10 mL, 0.9 mmol) to provide the title compound as a pale yellow liquid (44.8 mg, 76% yield) after flash column chromatography on silica gel (hexane/EtOAc = 9/1–7/3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.26 (2H, m), 7.03–6.99 (3H, m), 3.88–3.87 (2H, m), 3.76–3.74 (1H, m), 2.07–1.99 (1H, m), 1.05 (3H, d, $J = 6.9$ Hz), 1.01 (3H, d, $J = 6.9$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.3, 129.0, 122.5, 115.0, 88.6, 63.6, 28.7, 18.7, 18.6. HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 90/10, flow rate 1 mL min^{-1}, $\lambda = 230$ nm), t_R (minor) = 9.0 min, t_R (major) = 10.1min; 97% ee. $[\alpha]_D^{22} = +33.4$ ($c = 1.0$, $CHCl_3$).

(*R*)-2-Phenyl-2-(*N*-phenylaminoxy)ethanol (3f). α-Aminoxy alcohol **3f** was prepared according to the general procedure from 2-phenylacetaldehyde (0.11 mL, 0.9 mmol) to provide the title compound as a pale yellow liquid (53.5 mg, 78% yield) after flash column chromatography on silica gel (hexane/ether = 9/1–7/3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.31 (5H, m), 7.28–7.20 (2H, m), 6.99–6.94 (3H, m), 5.00 (1H, dd, $J = 3.5$, 8.1 Hz), 3.99–3.92 (1H, m), 3.83–3.78 (1H, m), 2.58 (1H, brs). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.9, 137.7, 129.0, 128.7, 128.5, 127.0, 122.5, 115.0, 86.4, 66.4. HPLC: Chiralpak OD-H (hexane/*i*-PrOH, 95/5, flow rate 1 mL min^{-1}, $\lambda = 230$ nm), t_R (major) = 25.8 min, t_R (minor) = 30.2 min; 93% ee. $[\alpha]_D^{24} = -85.5$ ($c = 1.1$, $CHCl_3$).

(*R*)-3-Phenyl-2-(*N*-phenylaminoxy)propan-1-ol (3g). α-Aminoxy alcohol **3g** was prepared according to the general procedure from 3-phenylpropanal (0.12 mL, 0.9 mmol) to provide the title compound as a pale yellow liquid (55.9 mg, 77% yield) after flash column chromatography on silica gel (hexane/ether = 9/1–7/3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.18 (6H, m), 7.08 (1H, brs), 6.94 (1H, t, $J = 7.3$ Hz), 6.82 (2H, d, $J = 8.0$ Hz), 4.16–4.10 (1H, m), 3.85 (1H, d, $J = 11.8$ Hz), 3.04 (1H, dd, $J = 6.8$, 13.7 Hz), 2.84 (1H, dd, $J = 7.0$, 13.7 Hz), 2.62 (1H, brs). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.3, 137.8, 129.4, 128.9, 128.5, 126.4, 122.3, 114.6, 85.0, 64.1, 36.4. HPLC: Chiralpak OD-H (hexane/*i*-PrOH, 91/9, flow rate 1 mL min^{-1}, $\lambda = 230$ nm), t_R (major) = 57.9 min, t_R (minor) = 62.4 min; >99% ee. $[\alpha]_D^{22} = +55.2$ ($c = 1.3$, $CHCl_3$).

(*R*)-2-(*N*-Phenylaminoxy)pent-4-en-1-ol (3h). α-Aminoxy alcohol **3h** was prepared according to the general procedure from 4-pentenal (0.09 mL, 0.9 mmol) to provide the title compound as a pale yellow liquid (51.0 mg, 88% yield) after flash column chromatography on silica gel (hexane/EtOAc = 9/1–7/3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.26 (2H, m), 7.06–6.96 (3H, m), 5.93–5.82 (1H, m), 5.18–5.11 (2H, m), 4.05–4.00 (1H, m), 3.87–3.75 (2H, m), 2.54–2.32 (3H, m), 1.66 (1H, brs). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.3, 134.0, 129.0, 122.5, 117.8, 114.8, 83.3, 64.6, 34.6. HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 90/10, flow rate 1 mL min^{-1}, $\lambda = 230$ nm), t_R (minor) = 10.5 min, t_R (major) = 12.5 min; 96% ee. $[\alpha]_D^{25} = -22.9$ ($c = 1.0$, $CHCl_3$).

(*R*)-4-(Benzyloxy)-2-(*N*-phenylaminoxy)butan-1-ol (3i). α-Aminoxy alcohol **3i** was prepared according to the general procedure from 4-(benzyloxy)butanal (0.16 mL, 0.9 mmol) to provide the title compound as a pale yellow liquid (73.8 mg, 86% yield) after flash column chromatography on silica gel (hexane/EtOAc = 9/1–7/3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.23 (6H, m), 7.05 (1H, brs), 6.98–6.94 (3H, m), 4.54–4.52 (2H, m), 4.14–4.11 (1H, m), 3.93- 3.87 (1H, m), 3.81–3.77 (1H, m), 3.66 (2H, t, $J = 5.7$ Hz), 2.81 (1H, t, $J = 5.9$ Hz), 2.06–1.89 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.3, 138.0, 129.0, 128.5, 127.8, 122.4, 116.1, 114.8, 81.5, 73.2, 66.7, 64.8, 30.3. HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 91/9, flow rate 1 mL min^{-1}, $\lambda = 230$ nm), t_R (minor) = 18.8 min, t_R (major) = 24.1 min; 97% ee. $[\alpha]_D^{22} = +15.5$ ($c = 1.1$, $CHCl_3$). HRMS (ESI) calcd for $C_{17}H_{21}NO_3$, m/z 288.1600, found 288.1599.

(*R*)-*tert*-Butyl 3-hydroxy-2-(*N*-phenylaminoxy)propylcarbamate (3j). α-Aminoxy alcohol **3j** was prepared according to the general procedure from *tert*-butyl 3-oxopropylcarbamate (0.16 mL, 0.9 mmol) to provide the title compound as a pale yellow liquid (67.2 mg, 79% yield) after flash column chromatography on silica gel (hexane/EtOAc = 9/1–7/3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.24 (3H, m), 6.98–6.94 (2H, m), 5.02 (1H, brs), 3.94–3.92 (1H, m), 3.80 (2H, s), 3.50–3.36 (2H, m), 1.45 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.1, 148.3, 129.0, 122.4, 114.6, 82.4, 80.0, 61.3, 39.6, 28.3. HPLC: Chiralpak OJ-H (hexane/*i*-PrOH, 95/5, flow rate 1 mL min^{-1}, $\lambda = 230$ nm), t_R (minor) = 24.8 min, t_R (major) = 26.6 min; 93% ee. $[\alpha]_D^{22} = -8.2$ ($c = 1.3$, $CHCl_3$). HRMS (ESI) calcd for $C_{14}H_{23}N_2O_4$, m/z 282.1658, found 282.1659.

(*R*)-2-(*p*-Toluidinoxy)propan-1-ol 3k). α-Aminoxy alcohol **3k** was prepared according to the general procedure from propanal (0.07 mL, 0.9 mmol) and nitrosotoluene (36.3 mg, 0.3 mmol) to provide the title compound as a pale yellow liquid (45.0 mg, 83% yield) after flash column chromatography on silica gel (hexane/EtOAc = 9/1–7/3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07 (2H, d, $J = 8.1$ Hz), 6.99 (1H, brs), 6.88 (2H, d, $J = 8.3$ Hz), 4.13–4.07 (1H, m), 3.78–3.68 (2H, m), 2.28 (3H, s), 1.22 (3H, d, $J = 6.5$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ145.8, 132.0, 129.5, 115.3 79.8, 66.6, 20.6, 15.4. HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 90/10, flow rate 1 mL min^{-1}, $\lambda = 230$ nm), t_R (minor) = 10.9 min, t_R (major) = 12.4 min; 97% ee. $[\alpha]_D^{25} =$

+5.5 ($c = 1.5$, $CHCl_3$). HRMS (ESI) calcd for $C_{10}H_{16}NO_2$, m/z 182.1181, found 182.1181.

Acknowledgements

This work is financially supported by grants from the Ministry of Education, Singapore (ARC12/07, no. T206B3225) and the School of Physical and Mathematical Sciences, Nanyang Technological University (URC, RG53/07 and SEP, RG140/06).

Notes and references

1 (*a*) F. A. Davis, and B. C. Chen, *Methods of Organic Chemistry (Houben–Weyl)*, Thieme, Stuttgart, 1995; (*b*) D. Enders and U. Reinhold, *Synlett*, 1994, 792.
2 (*a*) F. A. Davis and B. C. Chen, *Chem. Rev.*, 1992, **92**, 919. and references herein; (*b*) B. B. Lohray and D. Enders, *Helv. Chim. Acta*, 1989, **72**, 980.
3 H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483.
4 (*a*) A. Dondoni and A. Massi, *Angew. Chem., Int. Ed.*, 2008, **47**, 4638; (*b*) S. J. Connon, *Chem. Commun.*, 2008, 2499; (*c*) J. M. M. Verkade, L. J. C. van Hemert, P. J. L. M. Quaedflieg and F. P. J. T. Rutjes, *Chem. Soc. Rev.*, 2008, **37**, 29; (*d*) J. Seayad and B. List, *Org. Biomol. Chem.*, 2005, **3**, 719; (*e*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2004, **43**, 5138.
5 (*a*) G. Zhong, *Angew. Chem., Int. Ed.*, 2003, **42**, 4247; (*b*) M. Lu, D. Zhu, Y. Lu, Y. Hou, B. Tan and G. Zhong, *Angew. Chem., Int. Ed.*, 2008, **47**, 10187; (*c*) D. Zhu, M. Lu, P. J. Chua, B. Tan, F. Wang, X. Yang and G. Zhong, *Org. Lett.*, 2008, **10**, 4585; (*d*) G. Zhong and Y. Yu, *Org. Lett.*, 2004, **6**, 1637; (*e*) G. Zhong, *Chem. Commun.*, 2004, 606; (*f*) X. Zhu, F. Tanaka, Y. Hu, A. Heine, R. Fuller, G. Zhong, A. J. Olson, R. A. Lerner, C. F. Barbas, III and I. A. Wilson, *J. Mol. Biol.*, 2004, **343**, 1269; (*g*) B. Tan, P. J. Chua, Y. Li and G. Zhong, *Org. Lett.*, 2008, **10**, 2437; (*h*) B. Tan, Z. Shi, P. J. Chua and G. Zhong, *Org. Lett.*, 2008, **10**, 3425.
6 S. P. Brown, M. P. Brochu, C. J. Sinz and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2003, **125**, 10808.
7 Y. Hayashi, J. Yamaguchi, K. Hibino and M. Shoji, *Tetrahedron Lett.*, 2003, **44**, 8293.
8 (*a*) S. P. Kotkar, G. S. Suryavansh and A. Sudalai, *Tetrahedron: Asymmetry*, 2007, **18**, 1795; (*b*) S. P. Kotkar, G. S. Suryavanshi and A. Sudalai, *Tetrahedron: Asymmetry*, 2007, **18**, 1738; (*c*) S. P. Kotkar and A. Sudalai, *Tetrahedron Lett.*, 2006, **47**, 6813; (*d*) S. V. Narina and A. Sudalai, *Tetrahedron Lett.*, 2006, **47**, 6799; (*e*) S. G. Kim and T. H. Park, *Tetrahedron Lett.*, 2006, **47**, 6369; (*f*) Sousuke Hara, Kazuishi Makino and Yasumasa Hamada, *Tetrahedron Lett.*, 2006, **47**, 1081; (*g*) I. K. Mangion and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2005, **127**, 3696.
9 (*a*) Y. Hayashi, J. Yamaguchi, T. Sumiya and M. Shoji, *Angew. Chem., Int. Ed.*, 2004, **43**, 1112; (*b*) A. Bøgevig, H. Sundén and H. A. Córdova, *Angew. Chem., Int. Ed.*, 2004, **43**, 1109.
10 (*a*) T. Kano, A. Yamamoto, H. Mii, J. Takai, S. Shirakawa and K. Maruoka, *Chem. Lett.*, 2008, **37**, 250; (*b*) Y. Hayashi, J. Yamaguchi, K. Hibino, T. Sumiya, T. Urushima, M. Shoji, D. Hashizume and H. Koshino, *Adv. Synth. Catal.*, 2004, **346**, 1435; (*c*) H. Sundén, N. Dahlin, I. Ibrahem, H. Adolfsson and A. Córdova, *Tetrahedron Lett.*, 2005, **46**, 3385; (*d*) W. Wang, J. Wang, H. Li and L. Li, *Tetrahedron Lett.*, 2004, **45**, 7235; (*e*) N. Momiyama, H. Torii, S. Saito and H. Yamamoto, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5374.
11 (*a*) D. Font, A. Bastero, S. Sayalero, C. Jimeno and M. A. Pericàs, *Org. Lett.*, 2007, **9**, 1943; (*b*) H.-M. Guo, H.-Y. Niu, M.-X. Xue, Q.-X. Guo, L.-F. Cun, A.-Q. Mi, Y.-Z. Jiang and J.-J. Wang, *Green Chem.*, 2006, **8**, 682.
12 (*a*) M.-K. Zhu, X.-Y. Xu and L.-Z. Gong, *Adv. Synth. Catal.*, 2008, **350**, 1390; (*b*) N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka and C. F. Barbas, III, *J. Am. Chem. Soc.*, 2006, **128**, 734; (*c*) N. Mase, K. Watanabe, H. Yoda, K. Takabe, F. Tanaka and C. F. Barbas, III, *J. Am. Chem. Soc.*, 2006, **128**, 4966; (*d*) D. Gonzalez-Cruz, D. Tejedor, P. de Armas, E. Q. Morales and F. Garcia-Tellado, *Chem. Commun.*, 2006, 2798; (*e*) D. E. White and E. N. Jacobsen, *Tetrahedron: Asymmetry*, 2003, **14**, 3633; (*f*) S. E. Schaus, B. D. Brandes, J. F. Larrow, M. Tokunaga, K. B. Hansen, A. E. Gould, M. E. Furrow and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2002, **124**, 1307; (*g*) A. G. Dossetter, T. F. Jamison and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 1999, **38**, 2398; (*h*) M. Tokunaga, J. F. Larrow, F. Kakuichi and E. N. Jacobsen, *Science*, 1997, **277**, 936.
13 (*a*) A. Córdova, H. Sundén, A. Bøgevig, M. Johansso and F. Himo, *Chem.–Eur. J.*, 2004, **10**, 3673.
14 D. B. Ramachary and I. C. F. Barbas, *Org. Lett.*, 2005, **7**, 1577.
15 S.-G. Kim and T.-H. Park, *Tetrahedron Lett.*, 2006, **47**, 9067.
16 (*a*) S. K. David, M. Shaw and S. V. Ley, *Chem. Commun.*, 2006, 3211; (*b*) H. Sundén, N. Dahlin, I. Ibrahem, H. Adolfsson and A. Córdova, *Tetrahedron Lett.*, 2005, **46**, 3385; (*c*) W. Wang, J. Wang, H. Li and L. Li, *Tetrahedron Lett.*, 2004, **45**, 7235.
17 R. Breslow, *Acc. Chem. Res.*, 2004, **37**, 471.
18 (*a*) C.-J. Li and L. Chen, *Chem. Soc. Rev.*, 2006, **35**, 68; (*b*) L. Chen and C.-J. Li, *Org. Lett.*, 2004, **6**, 3151; (*c*) C. J. Li, *Chem. Rev.*, 1993, **93**, 2023.
19 D. G. Blackmond, A. Armstrong, V. Coombe and A. Wells, *Angew. Chem., Int. Ed.*, 2007, **46**, 3798.