DOI: 10.1002/chem.200600725

Direct Catalytic Enantioselective α-Aminomethylation of Aldehydes

Ismail Ibrahem, Gui-Ling Zhao, and Armando Córdova*[a]

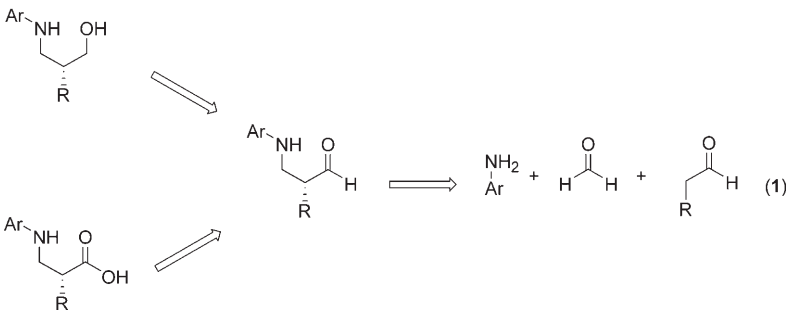
Abstract: The direct catalytic asymmetric α-aminomethylation of aldehydes is presented. The chiral amine and amino acid catalyzed reactions between unmodified aldehydes and a formaldehyde-derived imine precursor were fast and proceeded with high chemo- and enantioselectivities. The corresponding dibenzyl-protected γ-amino alcohols were isolated in high yields with up to 98% *ee* after in situ reduction. The reaction is a novel entry to valuable β^2-amino acid derivatives.

Keywords: alpha-aminomethylation · aldehydes · amino acids · asymmetric catalysis · diarylprolinol

Introduction

The classical Mannich reaction,[1] in which an aminomethyl group is introduced in the α-position to a carbonyl compound, is an important reaction in organic chemistry.[2] The resulting Mannich bases are of particular interest due to their biological activity, use as synthetic building blocks, and precursors of valuable pharmaceutical γ-amino alcohols.[2] In this context, a few elegant diasteroselective α-aminomethylation reactions have been developed.[3,4]

The development of catalytic asymmetric Mannich-type reactions has received increased attention in recent years.[5] These reactions are used for the synthesis of valuable chiral nitrogen-containing compounds, such as amino acid derivatives, β-lactams, and amino alcohols.[5–11] Direct catalytic Mannich-type reactions between ketones and preformed imines are catalyzed by organometallic complexes[7] with high enantioselectivity. Moreover, organocatalytic direct asymmetric Mannich-type reactions have been developed that are catalyzed by Brønsted acids,[8] chincona alkaloids,[9] and amino acids and their derivatives.[10] Recently, the direct catalytic asymmetric α-aminomethyaltion of ketones was reported.[11] However, developing a direct catalytic enantioselective α-aminomethylation of aldehydes is more challenging.[12] This reaction is highly interesting, as it is a direct entry to β-amino aldehydes, which can be converted to important β^2-amino acid derivatives and γ-amino alcohols [Eq. (1)].



However, proline does not catalyze the direct one-pot three-component α-aminomethylation of aldehydes and the desired products are not formed.[11b] Enders and Shibasaki have utilized aminomethyl ethers,[4,7a] which are useful equivalents of iminium ions, in stereoselective asymmetric α-aminomethylation reactions with ketones. Inspired by these reports and our experience in organocatalysis,[13] we envisioned a plausible novel chiral amine-catalyzed direct catalytic asymmetric α-aminomethylation reaction between aldehydes and aminomethyl ethers [Eq. (2)].

Herein, we report the direct catalytic enantioselective α-aminomethylation reactions between aldehydes and a dibenzylamine-derived aminomethyl ether, which furnished the

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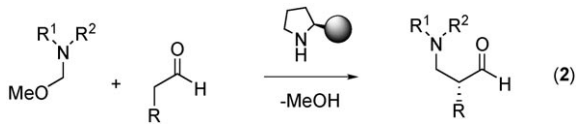
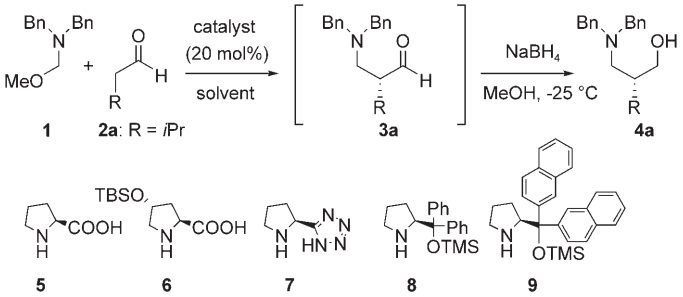


corresponding γ-amino alcohols in high yields with up to 98% *ee* after in situ reduction. The enantioselectivity of the protected diaryprolinol-catalyzed reactions was significantly improved by the addition of lithium halide salts.

Results and Discussion

In initial experiments, we screened proline **5**, proline derivatives **6**[14]–**7**[10o,15], and chiral pyrrolidines **8**–**9**[16] for their ability to catalyze the reaction between dibenzyl amine-derived aminomethyl ether **1**[4a] and isovaleraldehyde **2a** under different reaction conditions. A few of them are shown in Table 1.

Table 1. Catalysts screened.[a]

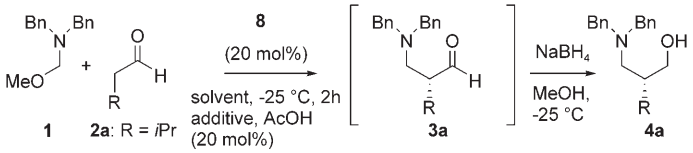


Entry	Catalyst	Solvent	T [°C]	t [h]	Conv. [%][b]	*ee* [%][c]
1	**5**	DMF	−20	16	>95	65[d]
2	**5**	DMF	4	2	>95	51[d]
3	**6**	DMF	−20	16	>95	55[d]
4	**7**	DMSO	23	2	>95	18[d]
5	**8**	$CHCl_3$	4	4	46	68
6	**8**	CH_3CN	4	4	>95[e]	66[e]
7	**8**	DMF	−25	2	80[e]	78[e]
8	**9**	$CHCl_3$	4	3	>95[e]	50[e]

[a] Aldehyde **2a** (1 mmol) was added at the temperature shown in the table to a vial charged with the catalyst (20 mol%) in solvent (1 mL). Next, the aminomethyl ether **1** (0.5 mmol) was added. After stirring for the time shown in the table, MeOH (2 mL) was added, the temperature was set to −25°C, and then the β-amino aldehyde **3a** was reduced in situ to amino alcohol **4a**, which was isolated by silica-gel column chromatography. [b] Conversion was determined by NMR spectroscopic analyses. [c] Determined by chiral-phase HPLC analysis of **4a**. [d] Enantiomeric excess of *ent*-**4a**. [e] Acetic acid added (20 mol%).

To our delight, all the chiral amines catalyzed the formation of the corresponding α-aminomethylated aldehyde **3a** in high conversion (>95%), which was reduced in situ to the more stable alcohol **4a**.[17] All reactions were highly chemoselective and traces of elimination products were only detected after full conversion had occurred. Proline **5** and diphenylprolinol **8** catalyzed the asymmetric α-aminomethylation reaction with the highest enantioselectivity. For instance, (*S*)-proline and chiral pyrrolidine **8** catalyzed the formation of *ent*-**4a** with 65% *ee* and **4a** with 78% *ee*, respectively (entries 1 and 7). Moreover, catalysts **5**–**7** furnished the opposite enantiomer, *ent*-**3a**, as opposed to protected chiral prolinols **8** and **9**. The efficiency and enantioselectivity of the protected diarylprolinol-catalyzed enantioselective reactions were significantly improved by the addition of an organic acid (20 mol%). We found that acetic acid gave the best results with respect to conversion and enantioselectivity of the reaction. The addition of achiral alkali cations has been shown by Adolfsson and co-workers to increase the enantioselectivity of small peptide catalyzed asymmetric transformations.[18] Thus, we decided to investigate the possibility of using this positive additive effect on the chiral pyrrolidine **8**-catalyzed asymmetric α-aminomethyaltion reaction (Table 2).

Table 2. Screen of different additives.[a]



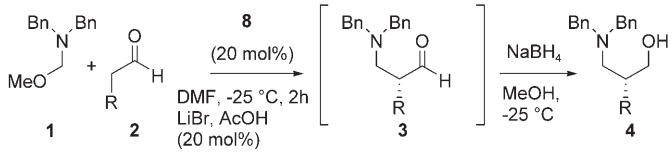
Entry	Additive	Solvent	Conv. [%][b]	*ee* [%][c]
1	none	DMF	80	78
2	NaCl	DMF	>95	72
3	LiCl	DMF	>95	90
4	LiBr	DMF	>95	96
5	LiI	DMF	>95	88
6	$LiClO_4$	DMF	96	74
7	LiOAc	DMF	>95	75
8	NH_4Cl	DMF	90	66
9	LiBr	CH_3CN	>95	75
10	LiBr	NMP	96	58
11	LiBr	*i*PrOH	68	58
12	LiBr	$CHCl_3$	86	37

[a] The additive (1 mmol) was added to a vial containing the solvent (1 mL) and the mixture was stirred for 5 min. Next, the catalyst and the aldehyde **2a** (1 mmol) were added and the reaction temperature decreased to −25°C. The aminomethyl ether **1** (0.5 mmol) was added and the reaction was vigorously stirred for 2 h followed by addition of MeOH (2 mL). The β-amino aldehyde **3a** was reduced in situ to amino alcohol **4a**, which was isolated by silica-gel column chromatography. [b] Conversion was determined by NMR spectroscopic analyses. [c] Determined by chiral-phase HPLC analysis of **4a**.

We found that the addition of salts increased the rate of the reactions. Notably, lithium halide salts significantly increased the enantioselectivity in the following order: LiBr > LiCl > LiI. For instance, complete conversion was achieved within 2 h by the addition of LiBr (2 equiv) and the optical purity of **4a** produced increased from 78 to 96% *ee*. This positive effect is plausibly due to the higher Lewis acidity of the lithium halide salts as compared to $LiClO_4$ and LiOAc, which did not increase the enantioselectivity of the reaction. In addition, lithium with its higher Lewis acidity was the cation of choice, as NaCl did not improve the enantioselectivity of the reaction. Moreover, the highest enantioselectivi-

ty for the solvents tested was achieved in DMF, which suggests that the solubility of the lithium halide salts may be important. With these results in hand, we decided to investigate the chiral pyrrolidine **8**-catalyzed reaction between dibenzylaminomethyl ether **1** and different aldehydes **2** in the presence of LiBr (Table 3).

Table 3. Chiral diphenyl prolinol **8**-catalyzed direct asymmetric α-aminomethylation of aldehydes **2**.[a]



Entry	R	Product	Yield [%][b]	*ee* [%][c]
1	*i*Pr	**4a**	80	96
2	Me	**4b**	82	98
3	$PhCH_2$	**4c**	79	98
4	*n*-pent	**4d**	81	91
5		**4e**	78	92
6	$TBSOCH_2$	**4f**	75	95

[a] LiBr (1 mmol) was added to a vial containing DMF (1 mL) and the mixture was stirred until it became homogeneous. Next, the catalyst and the aldehyde **2** (1 mmol) were added and the reaction temperature decreased to −25 °C. The aminomethyl ether **1** (0.5 mmol) was added and the reaction was vigorously stirred for 2 h followed by addition of MeOH (2 mL). The β-amino aldehyde **3** was reduced in situ to amino alcohol **4**, which was isolated by silica-gel column chromatography. [b] Isolated yield of pure amino alcohol **4**. [c] Determined by chiral-phase HPLC analysis. TBS = *tert*-butyldimethyl silyl.

The direct catalytic asymmetric α-aminomethylation reactions were fast, highly chemo- and enantioselective, and the corresponding amino alcohol products **4** were isolated in high yields with up to 98% *ee*. In most cases, the amino alcohols were furnished with >90% *ee*. For instance, the catalytic asymmetric α-aminomethylations of aldehydes **2b** and **2c** with **1** gave the corresponding amino alcohols **4b** and **4c** after one-pot reduction with $NaBH_4$ in 82 and 79% yields with 98% *ee*, respectively.

To establish the absolute configuration of the amino alcohols **4** and demonstrate the synthetic utility of the novel reaction, amino alcohol **4b** was deprotected to amino alcohol **10**, which was directly converted to Boc-protected amino alcohol **11** in 95% yield (Scheme 1). Subsequent oxidation gave the corresponding naturally-occurring Boc-protected (*R*)-3-amino-2-methyl-propanoic acid **12** in high yield as established by optical rotation and comparison to the literature ($[\alpha]_D = -17.5$ ($c = 1.0$ in MeOH), lit.[19] $[\alpha]_D = -18.4$ ($c = 2.0$ in MeOH)). Thus, the direct catalytic asymmetric α-aminomethylation of aldehydes is an efficient direct entry for the synthesis of β^2-amino acids, which are present in natural products and used as building blocks in important β-peptide foldamers.[19–20]

Moreover, the β^2-amino acid synthesis established that protected (*S*)-diarylprolinols **8** and **9** furnished (*R*)-aminoaldehydes **3** and that (*S*)-proline and its derivatives **6** and **7** furnished the opposite (*S*)-enantiomers *ent*-**3**. Based on these results we propose transition-state **I** to account for the stereochemical outcome for the protected diarylprolinol-catalyzed, highly enantioselective reactions (Figure 1). In accordance, the *Re*-face of the chiral enamine is approached by the aminomethyl ether **1** via a plausible six-membered transition state. The proton from the acetic acid or lithium cation possibly stabilizes the proposed transition-state **I** by activation of the methoxy leaving group of **1**. Transition-state **II** is plausibly less-favored due to repulsion between the lithium cation and the iminium ion.

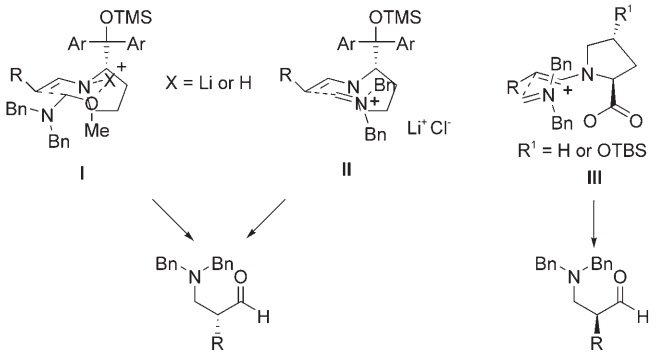
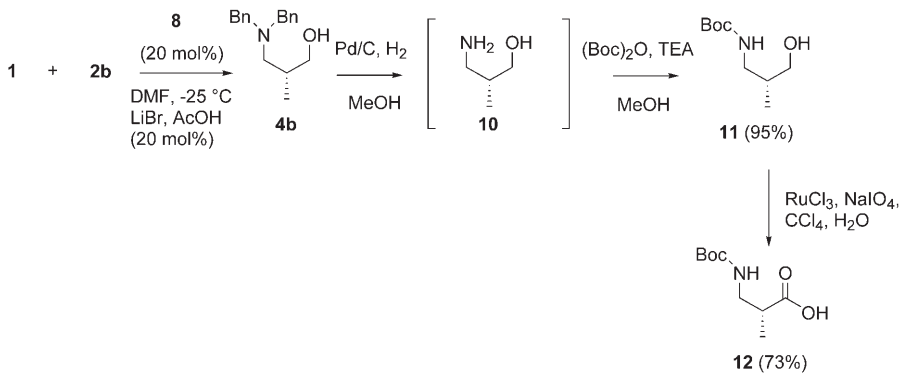


Figure 1. Proposed transition-state models evoked to account for the enantioselectivity of the (*S*)-diarylprolinol **8** and **9**, (*S*)-proline, and **6**-catalyzed reactions.

In the case of the (*S*)-proline- and **6**-catalyzed α-aminomethylation reaction, the plausible ionic transition state **III** is proposed to account for the stereochemical outcome of the reaction (Figure 1). Thus, the *Si*-face of the chiral enamine is approached by the in situ generated iminium ion which forms an ionic intermediate with the carboxylate



Scheme 1. Asymmetric synthesis of Boc-protected (*R*)-3-amino-2-methyl-propanoic acid **12**.

group of the amino acid catalyst. Hence, the chiral pyrrolidine and proline-catalyzed α-aminomethylation reaction plausibly occurs via completely different transition states.

Conclusion

We report the direct catalytic asymmetric α-aminomethylation of aldehydes. The simple amino acid and chiral pyrrolidine-catalyzed reactions are highly chemo- and enantioselective. The diarylprolinol-catalyzed reactions furnished the corresponding dibenzyl protected γ-amino alcohols in high yields with up to 98% *ee* after in situ reduction. In this case, the enantioselectivity was increased by the presence of achiral lithium halide salts. Notably, the α-aminomethylation reaction is a novel entry for the asymmetric synthesis of β^2-amino acids. Moreover, the α-aminomethylation reaction shows that imine equivalents with a readily removable protective group can be used in organocatalytic Mannich-type reactions. Further elaboration of this transformation, density functional studies, and its synthetic applications to natural product synthesis are ongoing.

Experimental Section

General: Chemicals and solvents were either purchased puriss p.A. from commercial suppliers or purified by standard techniques. Amino methyl ether **1** was synthesized according to literature procedures.[21] For TLC, silica gel plates Merck 60 F_{254} were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (25 g), $Ce(SO_4)_2{\cdot}H_2O$ (10 g), conc. H_2SO_4 (60 mL), and H_2O (940 mL) followed by heating or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. H_2SO_4 (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating. Flash chromatography was performed by using silica gel Merck 60 (particle size 0.040–0.063 mm), ^1H and ^{13}C NMR spectra were recorded on Varian AS 400. Chemical shifts are given in δ relative to TMS, and the coupling constants J are given in Hz. The spectra were recorded in $CDCl_3$ at room temperature, and TMS served as internal standard ($\delta = 0$ ppm) for ^1H NMR. $CDCl_3$ was used as internal standard ($\delta = 77.0$ ppm) for ^{13}C NMR. HPLC was carried out by using a Waters 2690 Millennium with photodiode array detector. Optical rotations were recorded on a Perkin–Elemer 241 Polarimeter ($\lambda =$ 589 nm, 1 dm cell). High-resolution mass spectra were recorded on an IonSpec FTMS mass spectrometer with a DHB-matrix and a Bruker MicrOTOF spectrometer.

Typical experimental procedure for the catalyst screen: The catalyst (20 mol%), followed by aldehyde **2a** (1 mmol) was added to a vial containing the solvent (1 mL) at room temperature. Next, the reaction temperature was set to the value shown in Table 1 and the aminomethyl ether **1** (0.5 mmol) was added. After vigorously stirring for the time shown in the table, MeOH (2 mL) was added and the β-amino aldehyde **3a** was reduced in situ with excess $NaBH_4$ (10 mmol) to amino alcohol **4a** at −25 °C. Next, the reaction temperature was increased to 0 °C. After 5 min of stirring, the solution was poured into a mixture of aqueous NH_4Cl (4 mL) and Et_2O (20 mL) at 0 °C. Excess Na_2SO_4 was added to the stirred aqueous mixture and after the solution had become clear, the drying agent was removed by filtration. The solvent was then removed under reduced pressure followed by purification of the crude product mixture by silica-gel column chromatography (toluene/EtOAc 2:1) to afford γ-amino alcohol **4a** as a clear oil. The *ee* of **4a** was determined by chiral-phase HPLC analysis.

Typical experimental procedure for the additive screen: The additive (1 mmol) was added to a vial containing DMF (1 mL) and the mixture was stirred at room temperature for 5 min. Next, the catalyst **8** was added followed by the addition of aldehyde **2a** (1 mmol) at room temperature. The reaction temperature was decreased to −25 °C and the aminomethyl ether **1** (0.5 mmol) was added. After 2 h of vigorously stirring, MeOH (2 mL) was added and the β-amino aldehyde **3a** was reduced in situ with excess $NaBH_4$ (10 mmol) to amino alcohol **4a** at −25 °C. The reaction temperature was then increased to 0 °C. After 5 min of stirring, the solution was poured into a mixture of aqueous NH_4Cl (4 mL) and Et_2O (20 mL) at 0 °C. Excess Na_2SO_4 was added to the stirred aqueous mixture and after the solution had become clear, the drying agent was removed by filtration. Next, the solvent was removed under reduced pressure followed by purification of the crude product mixture by silica-gel column chromatography (toluene/EtOAc 2:1) to afford γ-amino alcohol **4a** as a clear oil. The *ee* of **4a** was determined by chiral-phase HPLC analysis.

Typical experimental procedure: (see Table 3, entry 1) To a vial containing DMF (1 mL) was added LiBr (1 mmol) and the mixture was stirred at room temperature until it had become homogeneous. Next, the catalyst **8** (20 mol%) and acetic acid (20 mol%) were added followed by the addition of aldehyde **2a** (1 mmol) at room temperature. The reaction temperature was decreased to −25 °C and the aminomethyl ether **1** (0.5 mmol) was added. After 2 h of vigorously stirring, MeOH (2 mL) was added and the β-amino aldehyde **3a** was reduced in situ with excess $NaBH_4$ (10 mmol) to amino alcohol **4a** at −25 °C. The reaction temperature was then increased to 0 °C. After 5 min of stirring, the solution was poured into a mixture of aqueous NH_4Cl (4 mL) and Et_2O (20 mL) at 0 °C. Excess Na_2SO_4 was added to the stirred aqueous mixture, and after the solution had become clear, the drying agent was removed by filtration. Next, the solvent was removed under reduced pressure followed by purification of the crude product mixture by silica-gel column chromatography (toluene/EtOAc 2:1) to afford γ-amino alcohol **4a** in 80% yield as a clear oil. The *ee* of **4a** was 96% as determined by chiral-phase HPLC analysis.

*Compound (2*R*)-**4a***: ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 0.80$ (d, $J = 6.8$ Hz, 3H), 0.85 (d, $J = 6.8$ Hz, 3H), 1.48 (m, 1H), 1.90 (m, 1H), 2.48 (m, 1H), 2.69 (m, 1H), 3.15 (d, $J = 13.1$ Hz, 2H), 3.34 (m, 1H), 3.72 (m, 1H), 4.02 (d, $J = 13.1$ Hz, 2H), 5.38 (br s, 1H), 7.28–7.37 ppm (m, 10H); ^{13}C NMR (100 MHz): $\delta = 20.0$, 20.4, 28.8, 42.0, 57.9, 59.3 (2C), 67.2, 127.6, 128.7, 129.6, 138.0 ppm; HPLC (Daicel Chiralpak OD-H, isohexanes/*i*PrOH 97:3, flow rate: 0.5 mL min^{-1}, $\lambda = 257$ nm): major isomer: $t_R = 19.31$ min, minor isomer: $t_R = 23.52$ min; $[\alpha]_D = -58.5$ ($c = 1.0$ in $CHCl_3$); MALDI-TOF MS: calcd for $C_{20}H_{27}NO$: 320.1990 $[M+Na]^+$; found: 320.1991.

Typical experimental procedure for chiral pyrrolidine 8-catalyzed direct α-aminomethylation of aldehydes: LiBr (1 mmol) was added to a vial containing DMF (1 mL) and the mixture was stirred at room temperature until it became homogeneous. Next, the catalyst **8** (20 mol%) and acetic acid (20 mol%) were added followed by the addition of aldehyde **2** (1 mmol) at room temperature. The reaction temperature was decreased to −25 °C and the aminomethyl ether **1** (0.5 mmol) was added. After 2 h of vigorously stirring, MeOH (2 mL) was added and the β-amino aldehyde **3** reduced in situ with excess $NaBH_4$ (10 mmol) to amino alcohol **4** at −25 °C. The reaction temperature was then increased to 0 °C. After 5 min of stirring, the solution was poured into a mixture of aqueous NH_4Cl (4 mL) and Et_2O (20 mL) at 0 °C. Excess Na_2SO_4 was added to the stirred aqueous mixture, and after the solution had become clear, the drying agent was removed by filtration. Next, the solvent was removed under reduced pressure followed by purification of the crude product mixture by silica-gel column chromatography (toluene/EtOAc mixtures) to afford γ-amino alcohol **4** as a clear oil. The *ee* of **4** was determined by chiral-phase HPLC analysis.

*Compound (2*R*)-**4b***: ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 0.71$ (d, $J = 6.7$ Hz, 3H), 2.27 (m, 1H), 2.40 (m, 1H), 2.55 (m, 1H), 3.16 (d, $J = 13.2$ Hz, 2H), 3.26 (m, 1H), 3.61 (m, 1H), 4.02 (d, $J = 13.2$ Hz, 2H), 5.49 (br s, 1H), 7.30–7.40 ppm (m, 10H); ^{13}C NMR (100 MHz): $\delta = 15.2$, 31.7, 59.2 (2C), 61.6, 70.7, 127.5, 128.7, 129.4, 138.2 ppm; HPLC (Daicel Chiralpak OD-H, isohexanes/*i*PrOH 99:1, flow rate: 0.5 mL min^{-1}, $\lambda = 257$ nm): major

isomer: $t_R = 36.70$ min, minor isomer: $t_R = 43.30$ min; $[\alpha]_D = -46.4$ ($c = 1.0$ in $CHCl_3$); HRMS (ESI): *m/z*: calcd for $C_{18}H_{24}NO$: 270.1852 $[M+H]^+$; found: 270.1846.

*Compound (2*R*)-**4c***: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 2.29$–2.39 (m, 3H), 2.46 (m, 1H), 2.58 (m, 1H), 3.15 (d, $J = 13.1$ Hz, 2H), 3.31 (m, 1H), 3.68 (m, 1H), 3.94 (d, $J = 13.1$ Hz, 2H), 5.38 (brs, 1H), 7.18–7.34 ppm (m, 15H); ^{13}C NMR (100 MHz): $\delta = 36.7$, 38.7, 59.1, 59.2, 68.6, 59.2 (2C), 68.6, 127.6, 128.6, 128.7, 129.1, 129.5, 138.0, 140.1 ppm; HPLC (Daicel Chiralpak OD-H, isohexanes/*i*PrOH 97:3, flow rate: 0.5 mL min^{-1}, $\lambda = 257$ nm): major isomer: $t_R = 38.21$ min, minor isomer: $t_R = 58.42$ min; $[\alpha]_D = -51.2$ ($c = 1.0$ in $CHCl_3$). HRMS (ESI): *m/z*: calcd for $C_{24}H_{28}NO$: 346.2165 $[M+H]^+$; found: 346.2169.

*Compound (2*R*)-**4d***: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.89$ (t, $J = 7.2$ Hz, 3H), 1.02 (m, 2H), 1.22–1.32 (m, 6H), 2.05 (m, 1H), 2.45 (m, 1H), 2.55 (m, 1H), 3.15 (d, $J = 13.1$ Hz, 2H), 3.25 (m, 1H), 3.70 (m, 1H), 4.04 (d, $J = 13.1$ Hz, 2H), 5.66 (brs, 1H), 7.26–7.40 ppm (m, 10H); ^{13}C NMR (100 MHz): $\delta = 14.2$, 22.7, 27.1, 30.1, 32.2, 36.6, 59.2 (2C), 60.4, 69.2, 127.6, 128.7, 129.5, 138.1 ppm; HPLC (Daicel Chiralpak OD-H, isohexanes/*i*PrOH 97:3, flow rate: 0.5 mL min^{-1}, $\lambda = 257$ nm): major isomer: $t_R = 18.14$ min, minor isomer: $t_R = 20.10$ min; $[\alpha]_D = -56.4$ ($c = 1.0$ in $CHCl_3$). HRMS (ESI): *m/z*: calcd for $C_{22}H_{32}NO$: 326.2478 $[M+H]^+$; found: 326.2484.

*Compound (2*R*)-**4e***: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.83$ (m, 2H), 2.17 (m, 1H), 2.49 (m, 1H), 2.57 (m, 1H), 3.18 (d, $J = 13.1$ Hz, 2H), 3.28 (m, 1H), 3.70 (m, 1H), 4.02 (d, $J = 13.1$ Hz, 2H), 5.00 (m, 2H), 5.36 (brs, 1H), 5.74 (m, 1H), 7.28–7.40 ppm (m, 10H); ^{13}C NMR (100 MHz): $\delta =$ 34.6, 36.5, 59.3 (2C), 59.5, 68.6, 116.6, 127.6, 128.8, 129.5, 136.3, 138.1 ppm; HPLC (Daicel Chiralpak OD-H, isohexanes/*i*PrOH 97:3, flow rate: 0.5 mL min^{-1}, $\lambda = 257$ nm): major isomer: $t_R = 22.43$ min, minor isomer: $t_R = 31.71$ min; $[\alpha]_D = -52.0$ ($c = 1.0$ in $CHCl_3$). HRMS (ESI): calcd for $C_{20}H_{26}NO$: 296.2009 $[M+H]^+$; found: *m/z*: 296.2019.

*Compound (2*R*)-**4f***: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.00$ (s, 6H), 0.84 (s, 9H), 2.19–2.24 (m, 1H), 2.43 (dd, $J = 12.4$, 4.4 Hz, 1H), 2.57 (dd, $J =$ 12.4, 10.4 Hz, 1H), 3.26 (d, $J = 13.2$ Hz, 2H), 3.38 (dd, $J = 10.4$, 6.8 Hz, 1H), 3.45–3.55 (m, 2H), 3.69 (dd, $J = 10.4$, 4.4 Hz, 1H), 3.87 (d, $J =$ 13.2 Hz, 2H), 4.68 (brs, 1H), 7.25–7.33 ppm (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -5.4$, 18.3, 26.0, 39.8, 55.5, 59.1 (2C), 64.1, 66.5, 127.4, 128.6, 129.3, 138.4 ppm; $[\alpha]_D = -31.5$ ($c = 1.0$ in $CHCl_3$); the alcohol **4f** was acetylated and the *ee* was determined by HPLC (Daicel Chiralpak OD-H, isohexanes/*i*PrOH 99:1, flow rate: 0.5 mL min^{-1}, $\lambda =$ 257 nm): major isomer: $t_R = 14.03$ min; minor isomer: $t_R = 15.71$ min. HRMS (ESI): *m/z*: calcd for $C_{22}H_{32}NO_2Si$: 370.2196 $[M+H]^+$; found: 370.2205.

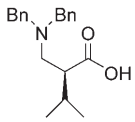
(*R*)-3-[(*tert*-Butoxycarbonyl)amino]-2-methylpropan-1-ol (11):[19] β-Amino alchol **4b** (2 mmol) in MeOH (10.0 mL) was treated with a catalytic amount of Pd/C. After 17 h of hydrogenolysis (90 MPa), the catalyst was filtered off by using Celite and the solvent concentrated to 4 mL. The γ-amino alcohol **10** was Boc-protected by addition of triethylamine (400 μL) and di-*tert*-butyldicarbonate (0.54 g, 2.5 mmol). After 1 h of stirring, the solvent was removed under reduced pressure, the residue was dissolved in CH_2Cl_2 and the solution was washed twice with $KHSO_4$ (1 M) and once with brine. The organic layer was dried with Na_2SO_4, filtered, and concentrated. The crude amino alcohol **11** was purified by silica-gel column chromatography (toluene/EtOAc 2:1) to give **11** as a clear viscous oil (95% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.83$ (d, $J = 7.0$ Hz, 3H), 1.40 (s, 9H), 1.72 (m, 1H), 3.01 (m, 1H), 3.19 (m, 1H), 3.31 (m, 1H), 3.54 (m, 1H), 5.05 ppm (brs, 1H); ^{13}C NMR (100 MHz): $\delta = 14.6$, 28.5, 36.4, 42.8, 64.6, 79.7, 157.6 ppm; $[\alpha]_D = -17.1$ ($c = 1.0$ in $CHCl_3$).[19]

(*R*)-3-[(*tert*-Butoxycarbonyl)amino]-2-methylpropanoic acid (12):[19] $RuCl_3$ hydrate (0.03 mmol) was added to a solution of alcohol (*R*)-**11** (1.2 mmol), sodium periodate (3.5 mmol), CCl_4 (2.5 mL), CH_3CN (2.5 mL), and H_2O (3.8 mL), and the mixture was stirred at room temperature for 1 h. After this time, the mixture was diluted with CH_2Cl_2 (10 mL) and then filtered through Celite. The filtrated solution was basified with K_2CO_3 (2 M) solution, and the water layer was washed with ether. The aqueous layer was acidified with $KHSO_4$ (1 M) at 0 °C and extracted with CH_2Cl_2. The combined organic extracts were dried with Na_2SO_4. The drying agent was removed by filtration and the solvent was removed under reduced pressure followed by purification of the crude product **12** by silica-gel column chromatography (pentane/EtOAc 1:5) to afford β^2-amino acid **12** as a solid (73% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.20$ (d, $J = 7.0$ Hz, 3H), 1.42 (s, 9H), 1.81 (m, H), 3.01 (m, 1H), 3.20 (m, 1H), 3.31 (m, 1H), 5.05 ppm (brs, 1H); ^{13}C NMR (100 MHz): $\delta = 14.8$, 28.6, 40.2, 42.9, 79.8, 156.3, 181.0 ppm; $[\alpha]_D = -17.5$ ($c = 1.0$ in MeOH), lit.[19] $[\alpha]_D = -18.4$ ($c = 2.0$ in MeOH).

(*S*)-Proline-catalyzed synthesis of *ent*-3a: (*S*)-Proline (20 mol%) followed by aldehyde **2a** (1 mmol) was added to a vial containing the solvent (1 mL) at −20 °C. Next, the aminomethyl ether **1** (0.5 mmol) was added. After vigorously stirring for 5 h, the reaction was quenched by extraction with aqueous NH_4Cl solution (4 mL) and Et_2O (3×20 mL). The organic phase was then dried with Na_2SO_4. The drying agent was removed by filtration and the solvent was removed under reduced pressure followed by purification of the crude product *ent*-**3a** by silica-gel column chromatography (pentane/EtOAc 10:1) to afford β-amino aldehyde **3a** as a clear oil (66% yield, 54% *ee*).

*Compound ent-**3a***: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.84$ (d, $J = 6.8$ Hz, 3H), 0.92 (d, $J = 6.8$ Hz, 3H), 1.81–1.86 (m, 1H), 2.33–2.38 (m, 1H), 2.52 (dd, $J = 12.8$, 4.4 Hz, 1H), 2.90 (dd, $J = 12.8$, 11.2 Hz, 1H), 3.25 (d, $J =$ 13.6 Hz, 2H), 3.80 (d, $J = 13.6$ Hz, 2H), 7.22–7.34 (m, 10H), 9.32 ppm (d, $J = 4.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.3$, 20.5, 27.6, 51.6, 56.4, 58.6, 127.2, 128.4, 129.2, 139.1, 205.4 ppm; $[\alpha]_D^{25} = +25.0$ ($c = 1.0$ in $CHCl_3$); the *ee* was determined by HPLC on Daicel Chiralpak ODH with isohexanes/*i*PrOH (99:1) as the eluent: major isomer: $t_R = 12.94$ min, minor isomer: $t_R = 14.66$ min; HRMS (ESI): *m/z*: calcd for $C_{20}H_{26}NO$: 296.2009 $[M+H]^+$; found: 296.2006.

(2*S*)-*N*,*N*-Dibenzyl-2-aminomethyl-3-methylbutanoic acid: KH_2PO_4 (0.48 mmol), 2-methyl-2-butene (1.9 mmol), and $NaClO_2$ (0.95 mmol) were added to a stirred solution of amino aldehyde *ent*-**3a** (0.24 mmol), synthesized by (*S*)-proline catalysis, in *t*BuOH/H_2O (5:1, 3.0 mL). The mixture was stirred for 17 h and turned from yellow to colorless. The reaction mixture was then concentrated under reduced pressure, extracted with EtOAc, and washed with H_2O and brine. The organic extracts were dried with Na_2SO_4. The drying agent was removed by filtration and the solvent was removed under reduced pressure followed by purification of the crude product by silica-gel column chromatography (toluene/EtOAc 2:1) to afford the corresponding 2-aminomethyl-3-methylbutanoic acid as a clear oil (72% yield). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.86$ (d, $J =$ 6.9 Hz, 3H), 0.94 (d, $J = 6.9$ Hz, 3H), 2.34–2.37 (m, 1H), 2.48 (m, 1H), 2.61 (dd, $J = 12.3$, 4.5 Hz, 1H), 2.92 (t, $J = 12.3$ Hz, 1H), 3.50 (d, $J =$ 13.5 Hz, 2H), 3.95 (d, $J = 13.5$ Hz, 2H), 7.19–7.37 (m, 10H), 11.62 ppm (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.6$, 20.2, 27.4, 45.8. 50.9, 57.8, 128.3, 128.9, 129.7, 135.3, 175.8 ; $[\alpha]_D^{25} = +26.3$ ($c = 1.0$ in $CHCl_3$). HRMS (ESI): *m/z*: calcd for $C_{20}H_{26}NO_2$: 312.1958 $[M+H]^+$; found: 312.1956.



Acknowledgements

We gratefully acknowledge the Swedish National Research council and Carl-Trygger Foundation for financial support. We thank Prof. Dr. H. Adolfsson, Prof. J-E. Bäckvall, and Dr. A. Zaitsev for valuable discussions.

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Received: May 24, 2006
Published online: October 13, 2006

