Synthesis and catalytic activities of (*S*)-1-formylpyrrolidine-2-carboxylic acid derivatives for the enantioselective reductions of both a ketone and a ketimine

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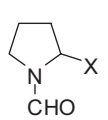
A series of (*S*)-1-formylpyrrolidine-2-carboxylic acid derivatives (**6a**–**t**) have been synthesised and examined as chiral organocatalysts in the asymmetric reduction of both ketone **2** and ketimine **3**. These organic activators afforded good to moderate enantioselectivities in the asymmetric reductions of both the ketone and the ketimine. Among them, organic activator **6h** displayed the best efficiency, affording a 84% yield and 41% ee in the reduction of the ketone and 75% yield and 52% ee in the reduction of the ketimine.

Keywords: organic activators, ketone, ketimine, asymmetric reduction

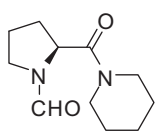
During the past few decades, asymmetric reductions of ketones and imines have emerged as one of the most important fields in organic synthesis. Although a variety of catalytic methods have been used for the enantioselective reductions of both ketones and imines, the transition metal complexes which are commonly used, often require elevated pressures and/or additives to afford high yields and ee values.[1-5] Therefore, attention has been turned to the development of chiral organocatalysts. Organic chiral activators are important in the enantioselective reductions of both ketones and imines by $HSiCl_3$, which is an economical and easy to handle reagent.[6] Matsumura *et al*.[6] reported the first organocatalytic enantioselective reduction method applicable to both ketones and imines. This employed a chiral organic Lewis base (**1a**,**b**) as the catalyst and trichlorosilane ($HSiCl_3$) as the reducing agent. It gave low to moderate enantioselectivities.[6,7] Until now only a few new organic activators for the enantioselective reductions of both ketones and imines have been reported to work well and all the organocatalysts have narrow substrate scope.[8-10] Consequently the search for the efficient organocatalysts for enantioselective reductions of both ketones and imines is still necessary. Herein, we report our studies on the Lewis basic organocatalysts **6a**–**t** (Fig. 1).

Results and discussion

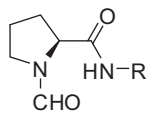
In order to find suitable organic activators for enantioselective reductions of both ketones and ketimines by trichlorosilane, we first prepared a series of (*S*)-1-formylpyrrolidine-2-carboxylic acid derivatives (**6a**–**t**, Fig. 1). The catalysts were examined in the reduction of both *para*-trifluoromethylphenyl methyl ketone **2** and ketimine **3** with $HSiCl_3$ at –20°C for 16 h with dichloromethane as the solvent, affording low to moderate enantioselectivities (Scheme 1). The results are shown in Table 1. It was found that all of the catalysts exhibited better enantioselectivities in the reduction of ketimine **3** than in the reduction of ketone **2** except for catalysts **6a** and **6f** (entries 1 and 6). Organic activator **6h** displayed the best efficacy, affording an 84% yield and 41% ee in the reduction of ketone **2** and 75% yield and 52% ee in the reduction of ketimine **3** (entry 8). Although catalyst **6o** gave an 85% yield and 62% ee for the reduction of ketimine **3**, it showed very



1a: X = CONHPh
1b: X = CONH-1-Naph

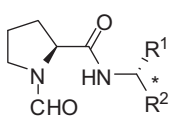


6a

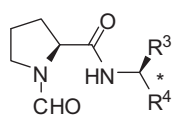


6b-g

6b: R=(2-furyl)CH_2; **6c**: R=4-F$C_6H_4CH_2$;
6d: R=4-Cl$C_6H_4CH_2$; **6e**:R=$C_6H_5CH_2CH_2$;
6f: R=4-$CH_3C_6H_4$; **6g**: R=4-ClC_6H_4.



6h-q



6r-t

6h: R^1=CH_2OAc, R^2=$CH(CH_3)_2$; **6i**: R^1=CH_2OAc, R^2=CH_2OAc;
6j: R^1=CH_2OAc, R^2=CH_3; **6k**: R^1=$COOCH_3$, R^2=CH_3;
6l: R^1=$COOCH_3$, R^2=CH_2COOCH_3;
6m: R^1=$COOCH_3$, R^2=$CH_2CH_2COOCH_3$;
6n: R^1=$COOCH_3$, R^2=Ph; **6o**: R^1=$COOCH_3$, R^2=CH_2Ph;
6p: R^1=$COOCH_3$, R^2=CH_2(4-$CH_3COOC_6H_4$);
6q: R^1=$COOCH_3$, R^2=CH_2(3H- indol-3-yl).

6r: R^3=CH_2OAc, R^4=CH_3;
6s: R^3=$COOCH_3$, R^4=CH_3;
6t: R^3=$COOCH_3$, R^4=CH_2Ph.

Fig. 1 The structures of organic activators **6a–t**.

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Table 1 Asymmetric reduction of ketone **2** and ketimine **3**[a]

Entry	Catalyst	Yield of **4**/%[b]	ee of **4**/%[d]	Yield of **5**/%[c]	ee of **5**/%[d]
1	**6a**	70	39	92	11
2	**6b**	30	7	68	23
3	**6c**	42	0	70	40
4	**6d**	44	0	81	41
5	**6e**	35	0	80	37
6	**6f**	60	45	70	32
7	**6g**	47	5	81	48
8	**6h**	84	41	75	52
9	**6i**	96	28	85	44
10	**6j**	28	13	82	34
11	**6k**	82	1	86	39
12	**6l**	70	5	80	34
13	**6m**	93	5	91	45
14	**6n**	32	25	71	40
15	**6o**	50	7	85	62
16	**6p**	17	9	80	45
17	**6q**	20	3	60	55
18	**6r**	91	8	90	52
19	**6s**	45	23	70	48
20	**6t**	51	37	61	47

[a]Unless specified otherwise, reactions were carried out with 2.0 equiv of $HSiCl_3$ on a 0.2 mmol scale in 1.0 ml of dichloromethane at –20°C for 16 h. [b]Isolated yield based on the ketone **2**. [c]Isolated yield based on the ketimine **3**. [d]The ee values were determined using chiral HPLC.

low enantioselectivity (7% ee) for the reduction of ketone **2**. Moderate enantioselectivities and high reactivities were observed in the reduction of ketimine **3** using organocatalysts **6b**–**e** bearing different R groups, but the enantioselectivities in the reduction of ketone **2** were extremely low (entries 2–5). The existence of an electron donating group on the benzene ring (**6f**) afforded moderate enantioselectivities and reactivities in the reductions of both ketone and ketimine. Although the existence of an electron withdrawing group on benzene ring (**6g**) slightly increased the enantioselectivity and reactivity in the reduction of ketimine, the enantioselectivity for the reduction of ketone decreased rapidly (entries 6–7).

Experimental

Reactions were monitored by thin layer chromatography using silica gel HSGF254 plates. Flash chromatography was performed using silica gel HG/T2354-92. Elemental analyses were carried out with an EA 1112 elemental analyser. Rotations were measured on a Rudolph AuTo Pol IV automatic polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance-300 NMR spectrometer in $CDCl_3$ solution using TMS as an internal reference. MS spectra were recorded on an DECAX-30000 LCQ Deca XP Plus. HPLC analyses were performed on Agilent 1100. Melting points were determined on an XT-4 melting point apparatus and were uncorrected. All chemicals and solvents used were of AR grade.

General procedure of synthesis of **7a**–**b**

Amine (2.4 mmol), 1-hydroxybenzotriazole HOBt (350 mg, 2.4 mmol), *N*, *N*-diisopropylethylamine (DIEA, 700 µl) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) (460 mg, 2.4 mmol) were in turn added to a solution of Boc-*L*-pipecolinic acid (458 mg, 2.0 mmol) in dichloromethane DCM (20 ml) at 0°C. The reaction mixture was stirred at room temperature overnight, and then concentrated under reduced pressure. The resulting mixture was diluted with EtOAc (20 ml). The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (10 ml), aqueous HCl (1.0 N, 10 ml) and brine (10 ml), dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/EtOAc ≈ 2 : 1 or hexane/acetone ≈ 3 : 1) to give **7a**–**b** (Scheme 2).

General procedure of synthesis of **8**

A solution of **7a** (1.0 mmol) in anhydrous THF (5 ml) was cooled to 0°C and added $LiAlH_4$ (190 mg, 5.0 mmol). The mixture was stirred for 0.5 h at 0°C. The reaction mixture was treated with H_2O (190 µl), 15% aqueous NaOH (190 µl), H_2O (570 µl), THF (10.0 ml) and stirred at room temperature for 1 h. The mixture was filtered and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc ≈ 1 : 4 or hexane/acetone ≈ 2 : 1) to give **8**.

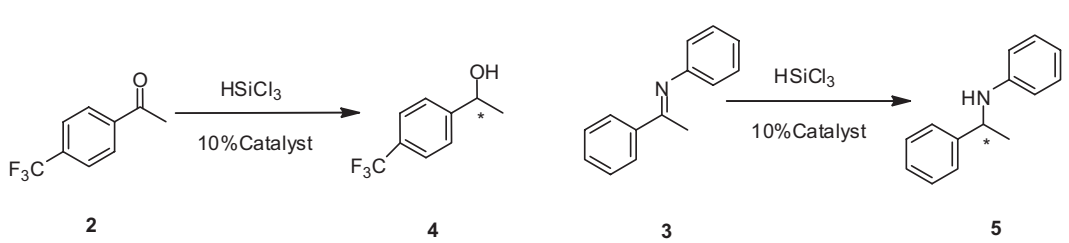
General procedure of synthesis of **9**

A solution of **8** (1.0 mmol) in $CHCl_3$ was treated with acetic anhydride (20.0 mmol) and diethylamine DIEA (1.8 ml, 10.0 mmol). The mixture was refluxed for 5 h and then concentrated under reduced pressure. The product was purified using column chromatography on silica gel (hexane/acetone = 3 : 1) to give **9**.

General procedure of synthesis of **6a**–**t**

9 or **7b** (1.0 mmol) was treated with 20 v% CF_3COOH in DCM (10 ml) and stirred for 1 h, and then concentrated under reduced pressure. The residue was dissolved in formic acid (2.6 ml, 70.0 mmol) and the resulting solution was cooled to 0°C. Acetic anhydride (1.9 ml, 20.0 mmol) was added dropwise and the mixture was allowed to stir at room temperature overnight. After concentration under reduced pressure, the crude product was purified by column chromatography on silica gel (hexane/acetone ≈ 1 : 1 or CH_2Cl_2/CH_3OH ≈ 40 : 1) to afford pure **6a**–**t**.

(S)-2-(piperidine-1-carbonyl)pyrrolidine-1-carbaldehyde (**6a**): Yellow solid (61% yield), m.p. 72–74°C. $[\alpha]_D$ = – 45.1° (*c* 0.130, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ: 8.22 (s, 1H), 4.78 (s, 1H), 3.61–3.44 (m, 6H), 2.17–1.60 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.1, 160.4, 54.0, 46.6, 30.1, 29.3, 25.4, 24.4, 24.3,



Scheme 1 Asymmetric reductions of ketone **2** and ketimine **3**.

23.9, 22.7. MS–ESI (*m/z*): 212.1 ($M^+ + 2$), 211.1 ($M^+ + 1$), 210.2 (M^+), 150.1. Anal. Calcd. for $C_{11}H_{18}N_2O_2$: C, 62.8; H, 8.6; N, 13.3. Found: C, 62.9; H, 8.5; N, 13.2%.

(S)-1-formyl-N-(furan-2-ylmethyl)pyrrolidine-2-carboxamide (**6b**): Colourless liquid (45% yield), $[\alpha]_D = -87.4°$ (*c* 0.123, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ: 8.25 (s, 1 H), 7.33 (m, 2H), 6.28 (t, *J* = 1.4 Hz, 1H), 6.18 (d, *J* = 3.1 Hz, 1H), 4.50–4.36 (m, 3H), 3.58–3.51 (m, 2H), 2.50–1.84 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.2, 162.2, 151.2, 142.0, 110.3, 107.1, 57.8, 46.9, 36.6, 27.1, 24.1. MS–ESI (*m/z*): 224.1 ($M^+ + 2$), 223.2 ($M^+ + 1$), 217.4, 211.2, 204.5, 195.1, 190.2, 174.0. Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.6. Found: C, 59.6; H, 6.2; N, 12.8%.

(S)-N-(4-fluorobenzyl)-1-formylpyrrolidine-2-carboxamide (**6c**): Light yellow solid (55% yield), m.p. 137–139°C. $[\alpha]_D = -73.8°$ (*c* 0.106, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ: 8.25 (s, 1H), 7.44 (s, 1H), 7.28–7.20 (m, 2H), 7.01–6.95 (m, 2H), 4.51–4.35 (m, 3H), 3.59–3.52 (m, 2H), 2.45–1.85 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.4, 162.2, 160.4, 133.9, 129.2, 115.5, 57.8, 46.9, 42.8, 27.3, 24.1. MS–ESI (*m/z*): 251.2 ($M^+ + 1$), 246.5, 235.0, 217.1, 212.2, 204.6. Anal. Calcd. for $C_{13}H_{15}FN_2O_2$: C, 62.4; H, 6.0; N, 11.2. Found: C, 62.6; H, 5.9; N, 11.1%.

(S)-N-(4-chlorobenzyl)-1-formylpyrrolidine-2-carboxamide (**6d**): White solid (51% yield), m.p. 114–116°C. $[\alpha]_D = -66.4°$ (*c* 0.106, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ: 8.27 (s, 1H), 7.42 (s, 1H), 7.33–7.24 (m, 2H), 7.19–7.15 (m, 2H), 4.59–4.36 (m, 3H), 3.60–3.53 (m, 2H), 2.50–1.86 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.3, 162.2, 136.7, 133.0, 128.7, 127.4, 57.9, 46.9, 42.9, 27.0, 24.1. MS–ESI (*m/z*): 267.2 ($M^+ + 1$), 246.3, 239.1, 233.3, 231.1, 211.0, 198.1, 150.4. Anal. Calcd. for $C_{13}H_{15}ClN_2O_2$: C, 58.5; H, 5.7; N, 10.5. Found: C, 58.6; H, 5.5; N, 10.6%.

(S)-1-formyl-N-phenethylpyrrolidine-2-carboxamide (**6e**): Colourless liquid (54% yield), $[\alpha]_D = -75.2°$ (*c* 0.104, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ: 8.21 (s, 1H), 7.34–7.15 (m, 5H), 6.94 (s, 1H), 4.53–4.42 (m, 1H), 3.58–3.43 (m, 4H), 2.86–2.78 (m, 2H), 2.51–1.86 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.4, 162.1, 139.9, 128.7, 128.4, 126.3, 57.8, 46.7, 40.7, 35.5, 26.9, 24.0. MS–ESI (*m/z*): 245.2 ($M^+ - 1$), 235.1, 221.1, 217.1, 200.3, 185.3, 169.2, 157.3. Anal. Calcd. for $C_{14}H_{18}N_2O_2$: C, 68.3; H, 7.4; N, 11.4. Found: C, 68.5; H, 7.2; N, 11.25%.

(S)-1-formyl-N-p-tolylpyrrolidine-2-carboxamide (**6f**): White solid (66% yield), m.p. 150–152°C. $[\alpha]_D = -128.4°$ (*c* 0.102, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ: 9.28 (s, 1H), 8.33 (s, 1H), 7.38 (d, *J* = 8.40 Hz, 2H), 7.07 (d, *J* = 8.13 Hz, 2H), 4.76–4.65 (m, 1H), 3.64–3.56 (m, 2H), 2.62–2.58 (m, 1H), 2.28 (s, 3H), 2.13–1.82 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.9, 162.6, 135.5, 133.6, 129.3, 119.7, 60.3, 47.0, 26.5, 24.1, 20.7. MS–ESI (*m/z*): 233.0 ($M^+ + 1$), 230.2, 212.2, 197.2, 187.2, 174.3. Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.2; H, 6.9; N, 12.1. Found: C, 67.3; H, 6.9; N, 12.1%.

(S)-N-(4-chlorophenyl)-1-formylpyrrolidine-2-carboxamide (**6g**): Colourless liquid (36% yield), $[\alpha]_D = -105.6°$ (*c* 0.10, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ: 9.56 (s, 1H), 8.34 (s, 1H), 7.41 (d, *J* = 8.82 Hz, 2H), 7.18 (d, *J* = 8.82 Hz, 2H), 4.69–4.65 (m, 1H), 3.65–3.60 (m, 2H), 2.56–1.76 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.2, 162.6, 136.7, 129.0, 128.7, 120.8, 58.8, 47.2, 26.8, 24.2. MS–ESI (*m/z*, relative intensity,%): 253.3 ($M^+ + 1$, 29), 251.2 ($M^+ - 1$, 100), 227.0 (10), 223.3, 220.1, 195.3, 167.1. Anal. Calcd. for $C_{12}H_{13}ClN_2O_2$: C, 57.0; H, 5.2; N, 11.1. Found: C, 57.25; H, 5.25; N, 11.0%.

(S)-2-((S)-1-formylpyrrolidine-2-carbonyl-amino)-3-methylbutyl acetate (**6h**): Colourless liquid (27% yield), $[\alpha]_D = -101.5°$ (*c* 0.104, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ: 8.28 (s, 1H), 7.05 (d, *J* = 8.61 Hz, 1H), 4.46 (m, 1H), 4.11 (m, 2H), 4.08 (m, 1H), 3.55 (m, 2H), 2.50–1.81 (m, 8H), 0.89 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.0, 171.1, 163.0, 65.2, 58.8, 54.4, 47.8, 30.3, 27.9, 25.1, 23.8, 21.7, 19.6. MS–ESI (*m/z*): 272.0 ($M^+ + 2$), 271.1 ($M^+ + 1$), 267.3, 242.9, 225.4, 212.1, 211.2, 194.0. Anal. Calcd. for $C_{13}H_{22}N_2O_4$: C, 57.8; H, 8.2; N, 10.4. Found: C, 57.6; H, 8.35; N, 10.4%.

(S)-2-((1-formyl-pyrrolidine-2-carboyl)-amino)-propane-1,3-diyl diacetate (**6i**): Colourless liquid (15% yield), $[\alpha]_D = -63.4°$ (*c* 0.142, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ: 8.29 (s, 1H), 7.44 (d, *J* = 7.80 Hz, 1H), 4.51–4.47 (m, 1H), 4.43–4.36 (m, 1H), 4.24–4.13 (m, 4H), 3.58 (m, 2H), 2.52–2.47 (m, 1H), 2.10 (s, 6H), 2.06–1.86 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.8, 170.2, 162.3, 62.7, 57.8, 47.5, 46.8, 26.8, 24.1, 20.7. MS–ESI (*m/z*, relative intensity,%): 302.1 ($M^+ + 2$, 19), 301.1 ($M^+ + 1$, 100), 279.0 (24), 259.0, 241.1, 216.1, 198.1, 157.8. Anal. Calcd. for $C_{13}H_{20}N_2O_6$: C, 52.0; H, 6.7; N, 9.3. Found: C, 51.8; H, 6.9; N, 9.25%.

(S)-2-((S)-1-formylpyrrolidine-2-carbonyl-amino)propyl acetate (**6j**): Colourless liquid (45% yield), $[\alpha]_D = -85.6°$ (*c* 0.128, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ: 8.29 (s, 1H), 7.09 (d, *J* = 6.78 Hz, 1H), 4.46–4.42 (m, 1H), 4.36–4.27 (m, 1H), 4.21–4.04 (m, 2H), 3.62–3.48 (m, 2H), 2.46–2.16 (m, 1H), 2.07–1.84 (m, 6H), 1.17 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.2, 169.9, 162.2, 66.7, 57.8, 46.9, 44.5, 27.1, 24.1, 20.8, 17.1. MS–ESI (*m/z*, relative intensity,%): 243.1 ($M^+ + 1$), 225.1, 215.1 (20), 201.0, 184.1, 183.1 (100), 165.3, 153.9. Anal. Calcd. for $C_{11}H_{18}N_2O_4$: C, 54.5; H, 7.5; N, 11.6. Found: C, 54.8; H, 7.4; N, 11.6%.

(S)-methyl-2-((S)-1-formylpyrrolidine-2-carbonyl-amino) propanoate (**6k**): Colourless liquid (48% yield), $[\alpha]_D = -97.8°$ (*c* 0.100, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ: 8.30 (s, 1H), 7.40 (s, 1H), 4.62–4.37 (m, 1H), 4.19–4.11 (m, 1H), 3.74 (s, 3H), 3.64–3.50 (m, 2H), 2.38–1.82 (m, 4H), 1.43 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.4, 166.4, 162.0, 59.2, 51.1, 46.8, 45.4, 28.1, 22.7, 17.8. MS–ESI (*m/z*, relative intensity,%): 229.2 ($M^+ + 1$, 100), 228.1 (M^+), 197.2, 183.2, 169.9, 154.1. Anal. Calcd. for $C_{10}H_{16}N_2O_4$: C, 52.6; H, 7.1; N, 12.3. Found: C, 52.5; H, 7.2; N, 12.2%.

(S)-dimethyl-2-((S)-1-formylpyrrolidine-2-carbonyl-amino) succinate (**6l**): White solid (53% yield), m.p. 79–81°C. $[\alpha]_D = -60.2°$ (*c* 0.156, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ: 8.30 (s, 1H), 7.49 (d, *J* = 7.80 Hz, 1H), 4.85 (m, 1H), 4.47 (m, 1H), 3.77 (s, 3H), 3.71 (s, 3H), 6.60 (m, 2H), 2.92 (m, 2H), 2.40–1.82 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.2, 170.9, 170.5, 161.8, 57.8, 52.8, 52.1, 48.7, 46.8, 34.0, 27.8, 24.1. MS–ESI (*m/z*, relative intensity,%): 288.0 ($M^+ + 2$, 14), 287.0 ($M^+ + 1$, 100), 259.0, 255.0 (19), 243.0, 227.0, 183.1, 160.1. Anal. Calcd. for $C_{12}H_{18}N_2O_6$: C, 50.35; H, 6.3; N, 9.8. Found: C, 50.6; H, 6.2; N, 9.7%.

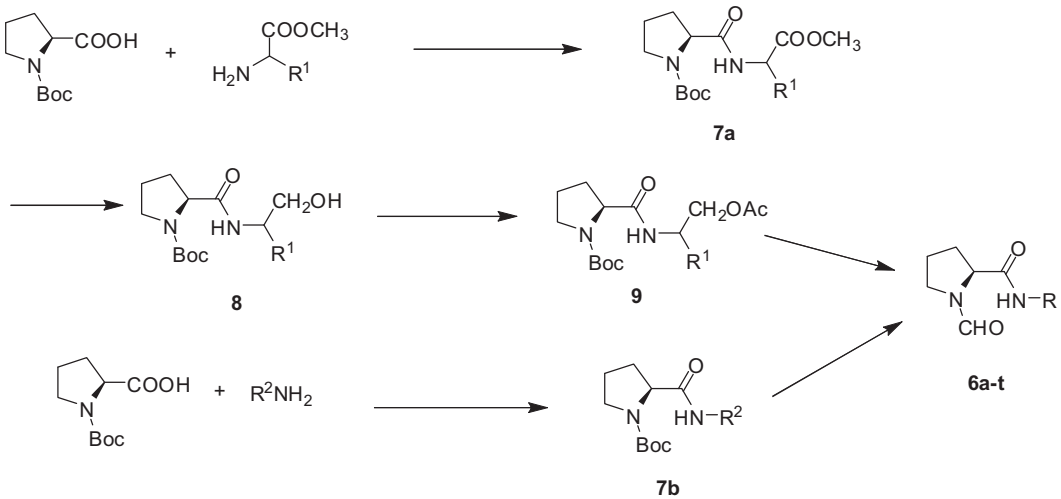
(S)-dimethyl-2-((S)-1-formylpyrrolidine-2-carbonyl-amino) pentanedioate (**6m**): White solid (37% yield), m.p. 69–71°C. $[\alpha]_D = -44.4°$ (*c* 0.120, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ: 8.29 (s, 1H), 7.39 (d, *J* = 7.47 Hz, 1H), 4.55–4.45 (m, 2H), 3.72 (s, 3H), 3.64 (s, 3H), 3.58 (m, 2H), 2.40–1.87 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.0, 171.8, 170.4, 161.9, 57.7, 52.4, 51.9, 51.6, 46.8, 29.7, 27.4, 27.0, 24.1. MS–ESI (*m/z*, relative intensity,%): 302.1 ($M^+ + 2$, 27), 301.1 ($M^+ + 1$, 100), 279.1 (21), 258.4, 242.4 (31), 194.9, 169.0, 150.3. Anal. Calcd. for $C_{13}H_{20}N_2O_6$: C, 52.0; H, 6.7; N, 9.3. Found: C, 52.1; H, 6.6; N, 9.2%.

(S)-methyl-2-((S)-1-formylpyrrolidine-2-carbonyl-amino)-2-phenylacetate (**6n**): White solid (42% yield), m.p. 66–68°C. $[\alpha]_D = +40.1°$ (*c* 0.156, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ: 8.29 (s, 1H), 8.01 (d, *J* = 5.91 Hz, 1H), 7.35 (m, 5H), 5.49 (d, *J* = 6.93 Hz, 1H), 4.63–4.60 (m, 1H), 3.73 (s, 3H), 3.60–3.48 (m, 2H), 2.48–1.86 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.9, 169.8, 162.2, 140.0, 128.9, 128.5, 127.1, 57.7, 56.9, 52.8, 46.9, 27.0, 24.1. MS–ESI (*m/z*, relative intensity,%): 292.0 ($M^+ + 2$, 14), 291.0 ($M^+ + 1$, 100), 259.0 (18), 243.0 (85), 231.0 (38), 183.1 (100), 180.9, 160.1. Anal. Calcd. for $C_{15}H_{18}N_2O_4$: C, 62.1; H, 6.25; N, 9.65. Found: C, 62.3; H, 6.1; N, 9.6%.

(S)-methyl-2-((S)-1-formylpyrrolidine-2-carbonyl-amino)-3-phenylpropanoate (**6o**): Colourless liquid (39% yield), $[\alpha]_D = -37.3°$ (*c* 0.126, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ: 8.10 (s, 1H), 7.31–6.99 (m, 6H), 4.80 (m, 1H), 4.41 (m, 1H), 3.67 (s, 3H), 3.46–2.96 (m, 4H), 2.26–1.76 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.7, 170.2, 162.0, 136.0, 129.3, 129.0, 128.6, 128.2, 126.9, 57.5, 53.3, 52.3, 46.6, 37.8, 27.1, 23.9. MS–ESI (*m/z*, relative intensity,%): 306.0 ($M^+ + 2$, 7), 305.0 ($M^+ + 1$, 42), 289.1, 277.1 (100), 257.3, 227.2 (10), 211.3, 199.3 (17). Anal. Calcd. for $C_{16}H_{20}N_2O_4$: C, 63.1; H, 6.6; N, 9.2. Found: C, 63.3; H, 6.6; N, 9.2%.

(S)-methyl-3-(4-acetoxyphenyl)-2-((S)-1-formylpyrrolidine-2-carbonyl-amino) propanoate (**6p**): Colourless liquid (41% yield), $[\alpha]_D = -37.4°$ (*c* 0.324, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ: 8.13 (s, 1H), 7.75 (s, 1H), 6.93 (m, 2H), 6.72 (m, 2H), 4.78 (m, 1H), 4.45 (m, 1H), 3.73 (m, 3H), 3.50–2.91 (m, 4H), 2.26–1.82 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.8, 172.2, 171.3, 163.1, 156.6, 131.3, 127.8, 116.3, 58.6, 54.5, 53.2, 47.8, 37.9, 28.6, 24.9, 23.1. MS–ESI (*m/z*, relative intensity,%): 364.2 ($M^+ + 2$, 100), 355.1 (10), 333.2 (35), 319.2 (55), 279.9, 227.0, 185.2. Anal. Calcd. for $C_{18}H_{22}N_2O_6$: C, 59.7; H, 6.1; N, 7.7. Found: C, 59.5; H, 6.2; N, 7.6%.

(S)-methyl-2-((S)-1-formylpyrrolidine-2-carbonyl-amino)-3-(1H-indol-2-yl) propanoate (**6q**): Yellow solid (46% yield), m.p. 120–122°C. $[\alpha]_D = -0°$ (*c* 0.156, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ: 10.80 (s, 1H), 8.46 (s, 1H), 7.99 (s, 1H), 7.53 (d, *J* = 7.74 Hz, 1H), 7.35 (m, 1H), 7.21–7.08 (m, 3H), 4.93–4.89 (m, 1H), 4.43 (m, 1H), 3.71 (s, 3H), 3.45–3.26 (m, 4H), 2.35–1.75 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.2, 172.0, 161.8, 136.0, 127.6, 123.7, 121.7, 119.1, 118.4, 111.3, 109.5, 57.6, 53.1, 52.4, 46.6, 31.7, 29.2, 23.9. MS–ESI (*m/z*, relative intensity,%): 345.1 ($M^+ + 2$, 5), 344.1 ($M^+ + 1$, 35), 328.1 (16), 317.1 (24), 316.1 (100), 266.2, 219.0, 196.2. Anal. Calcd. for $C_{18}H_{21}N_3O_4$: C, 63.0; H, 6.2; N, 12.2. Found: C, 62.9; H, 6.2; N, 12.4%.



Scheme 2 The synthesis of **6a–t**.

(R)-2-((S)-1-formylpyrrolidine-2-carbonyl-amino)propyl acetate (**6r**): Colourless liquid (26% yield), $[\alpha]_D = -81.5°$ (*c* 0.120, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ: 8.27 (s, 1H), 7.13 (d, *J* = 6.51 Hz, 1H), 4.48–3.95 (m, 4H), 3.61–3.52 (m,2H), 2.49–2.44 (m, 1H), 2.06 (s, 3H), 2.04–1.86 (m, 3H), 1.18 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.1, 169.8, 162.2, 66.6, 57.8 46.8, 44.4, 26.9, 24.1, 20.8, 17.2. MS–ESI (*m/z*): 243.0 ($M^+ + 1$), 241.9, 215.1, 197.1, 183.1, 181.1, 152.8. Anal. Calcd. for $C_{11}H_{18}N_2O_4$: C, 54.5; H, 7.5; N, 11.6. Found: C, 54.5; H, 7.4; N, 11.7%.

(R)-methyl-2-((S)-1-formylpyrrolidine-2-carbonyl-amino) propanoate (**6s**): Colourless liquid (38% yield), $[\alpha]_D = -83.1°$ (*c* 0.120, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ: 8.32 (s, 1H), 7.41 (d, *J* = 5.91 Hz, 1H), 4.56–4.47 (m, 1H), 4.19–4.13 (m, 1H), 3.73 (s, 3H), 3.61–3.55 (m, 2H), 2.04–1.97 (m, 4H), 1.41 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.6, 170.0, 162.3, 61.3, 57.7, 48.3, 46.8, 27.1, 24.0, 18.0. MS–ESI (*m/z*): 229.2, 227.5 ($M^+ - 1$), 195.5, 181.3, 167.4, 154.1. Anal. Calcd. for $C_{10}H_{16}N_2O_4$: C, 52.6; H, 7.1; N, 12.3. Found: C, 52.5; H, 7.1; N, 12.1%.

(R)-methyl-2-((S)-1-formylpyrrolidine-2-carbonyl-amino)-3-phenylpropanoate (**6t**): Colourless liquid (50% yield), $[\alpha]_D = -54.0°$ (*c* 0.304, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ: 8.21 (s, 1H), 7.28–7.03 (m, 6H), 4.74 (m, 1H), 4.43 (m, 1H), 3.65 (s, 3H), 3.49 (m, 2H), 3.06 (m, 2H), 2.13–1.79 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.7, 170.2, 162.1, 135.9, 129.3, 129.0, 128.7, 128.5, 127.0, 57.6, 53.4, 52.2, 46.7, 37.7, 30.4, 23.9. MS–ESI (*m/z*): 306.0 ($M^+ + 2$, 5), 305.0 ($M^+ + 1$, 44), 289.1, 278.1 (15), 277.1 (100), 257.1, 211.2, 199.3. Anal. Calcd. for $C_{16}H_{20}N_2O_4$: C, 63.1; H, 6.6; N, 9.2. Found: C, 63.3; H, 6.4; N, 9.0%.

General procedure for the catalytic reduction of ketone **2**

Trichlorosilane (40 μl, 0.4 mmol) was added dropwise to a stirred solution of ketone **2** (37.7 mg, 0.20 mmol) and catalyst **6a**–**t** (0.02 mmol) in anhydrous DCM (1.0 ml) at –20°C under an argon atmosphere. The mixture was allowed to stir at the same temperature for 16 h. The reaction was then quenched with a saturated aqueous solution of $NaHCO_3$ (5 ml) and extracted with EtOAc. The combined extracts were dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 7 : 1) to afford pure alcohol **4**. The ee values were determined using established HPLC techniques with chiral stationary phases (Chiral-phase HPLC data: chiral OJ–H column, n-heptane/2-propanol = 97/3, flow rate = 1.0 ml/min, wavelength = 220 nm, t_R = 10.29 min and 11.07 min).

General procedure for the catalytic reduction of ketimine **3**

Trichlorosilane (40 μl, 0.4 mmol) was added dropwise to a stirred solution of ketimine **3** (39.0 mg, 0.20 mmol) and catalyst **6a**–**t** (0.02 mmol) in anhydrous DCM (1.0 ml) at –20°C under an argon atmosphere. The mixture was allowed to stir at the same temperature for 16 h. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (5 ml) and extracted with EtOAc. The combined extracts were dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 60 : 1) to afford pure amine **5**. The ee values were determined using established HPLC techniques with chiral stationary phases (Chiral-phase HPLC data: chiral OD–H column, n-heptane/2-propanol = 99/1, flow rate = 1.0 ml/min, wavelength = 254 nm, t_R = 8.32 min and 9.51 min).

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