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# New organocatalysts for the asymmetric reduction of imines with trichlorosilane

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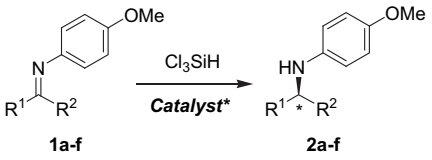
ABSTRACT

Asymmetric reduction of prochiral ketimines **1a**–**f** with trichlorosilane can be catalyzed by the Lewis-basic formamides (*S*)-**4a**,**b**, derived from *N*-methyl valine, with ≤91% enantioselectivity and low catalyst loading (≤5 mol %) at room temperature in toluene.



## 1. Introduction

Enantioselective reduction of prochiral ketimines, such as **1**, represents an attractive route to enantiomerically enriched (or pure) amines **2** (Scheme 1), many of which serve as building blocks for the pharmaceutical and fine chemicals industry. In addition to the transition metal-catalyzed reduction[1–4] and hydrogenation,[5] a new organocatalytic methodology is emerging, which utilizes trichlorosilane as a stoichiometric reagent, activated by a Lewis-basic catalyst,[6,7] typically a formamide derived from an amino acid.[8–10] As part of these efforts, we have recently synthesized formamides **3a**–**g** (Chart 1) from *N*-methyl valine, whose carboxyl was converted into an amide moiety with a primary aromatic amine.[11,12] The latter features proved to be the key to high enantioselectivity.[11] Herein, we report on two new amides of this series, namely **4a**,**b**, with a bulky aromatic system.




1a-f 2a-f

**Scheme 1.** Asymmetric reduction of ketimines. For $R^1$ and $R^2$, see Table 1.

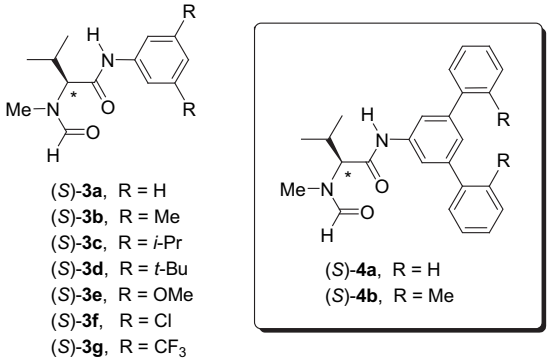



**Chart 1.**

## 2. Results and discussion

In the past few years we have developed a series of Lewis-basic organocatalysts **3a**–**g** for the asymmetric reduction of imines with

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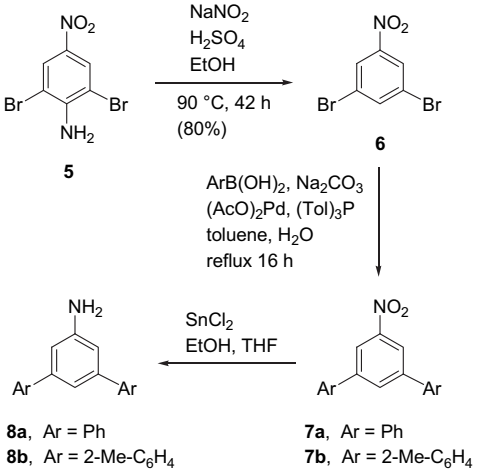
$Cl_3SiH$. These catalysts are characterized by the *N*-methyl formamide group and the aromatic amide moiety with an increasing steric bulk (R=H, Me, *i*-Pr, and *t*-Bu); the highest enantioselectivities were attained with the 3,5-di-*tert*-butyl derivative **3d** (Sigamide).[11c,d,f,g] Since the increased steric bulk proved to be beneficial to the catalyst efficiency, we embarked on the synthesis of the 3,5-diaryl analogues **4a**,**b**. Here, the steric bulk was expected to be increased, especially in the case of the 3,5-di-(*o*-tolyl) derivative **4b**, where the peripheral tolyl moieties are likely to be orientated perpendicularly to the central phenyl.

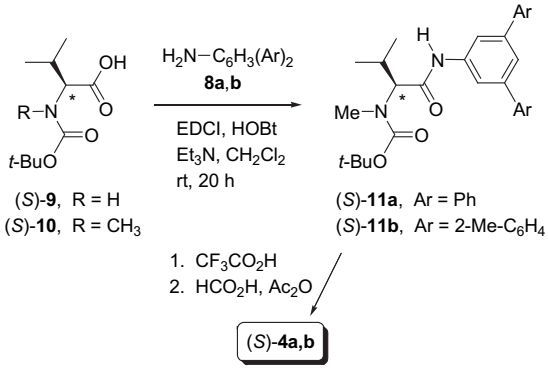
## 2.1. Catalyst synthesis

The aromatic amines **8a**,**b**, required for the preparation of amides **4a**,**b**, were synthesized as follows (Scheme 2). Diazotation of the commercially available 2,6-dibromo-4-nitroaniline (**5**), followed by reduction with ethanol, afforded 3,5-dinitrobenzene (**6**; 80%),[13] which was then submitted to the Suzuki–Miyaura coupling with the respective, commercially available aryl boronic acids. The coupling reaction was carried out in the presence of $(AcO)_2Pd$ as precatalyst and tri(*o*-tolyl)phosphine as ligand under standard conditions[14] to afford the 3,5-diaryl derivatives **7a**[14] (69%) and **7b** (80%). Reduction of the latter nitro derivatives with $SnCl_2$ proceeded uneventfully[15] and furnished amines **8a** (93%) and **8b** (92%), respectively.[16]




**Scheme 2.** Synthesis of 3,5-diarylanilines.

In the end game, the Boc-protected valine **9** was methylated with MeI in the presence of NaH[17] and the resulting *N*-methyl valine **10**[11] was converted into amides **11a** (56%) and **11b** (47%) by using the carbodiimide method.[11] Standard Boc-deprotection with $CF_3CO_2H$, followed by formylation with the mixed anhydride of formic and acetic acid,[11] afforded formamides **4a** (69%) and **4b** (96%), respectively (Scheme 3).




**Scheme 3.** Synthesis of the formamide catalysts; EDCI=1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride.

## 2.2. Catalytic reduction of ketimines

The scope of the reduction was demonstrated previously by us for **3a**–**g** as catalysts and a broad range of imines.[11] Therefore, the reduction was now carried out with a limited set of imines derived from acetophenone and its congeners (Scheme 1 and Table 1), where the steric bulk, the electronics of the aromatic moiety, and the

**Table 1**
Reduction of ketimines **1a**–**f** with trichlorosilane to give amines **2a**–**f**, catalyzed by the *N*-methyl valine-derived formamides (*S*)-**3d** and (*S*)-**4a**,**b**[a]

| Entry | Catalyst | R | Imine **1** | $R^1$ | $R^2$ | Amine **2** | Yield[b] (%) | **2**,[c] %ee[d] |
|---|---|---|---|---|---|---|---|---|
| 1 | **3d** | *t*-Bu | **1a** | Ph | Me | **2a** | 95 | 94[e] |
| 2 | **3d** | *t*-Bu | **1b** | 4-$CF_3C_6H_4$ | Me | **2b** | 92 | 92[e] |
| 3 | **3d** | *t*-Bu | **1c** | 4-$MeOC_6H_4$ | Me | **2c** | 91 | 91[e] |
| 4 | **3d** | *t*-Bu | **1d** | 2-Naphthyl | Me | **2d** | 93 | 92[e] |
| 5 | **3d** | *t*-Bu | **1e** | Thiophen-2-yl | Me | **2e** | 77 | 89 |
| 6 | **3d** | *t*-Bu | **1f** | Ph | $CH_2CO_2Et$ | **2f** | 98[f] | 89[g] |
| 7 | **4a** | H | **1a** | Ph | Me | **2a** | 92 | 73[e] |
| 8 | **4a** | H | **1b** | 4-$CF_3C_6H_4$ | Me | **2b** | 83 | 91[e] |
| 9 | **4a** | H | **1c** | 4-$MeOC_6H_4$ | Me | **2c** | 91 | 85[e] |
| 10 | **4a** | H | **1d** | 2-Naphthyl | Me | **2d** | 94 | 91[e] |
| 11 | **4a** | H | **1e** | Thiophen-2-yl | Me | **2e** | 95 | 61 |
| 12 | **4a** | H | **1f** | Ph | $CH_2CO_2Et$ | **2f** | 88[f] | 54[g] |
| 13 | **4b** | Me | **1a** | Ph | Me | **2a** | 98 | 90[e] |
| 14 | **4b** | Me | **1b** | 4-$CF_3C_6H_4$ | Me | **2b** | 66 | 83[e] |
| 15 | **4b** | Me | **1c** | 4-$MeOC_6H_4$ | Me | **2c** | 75 | 86[e] |
| 16 | **4b** | Me | **1d** | 2-Naphthyl | Me | **2d** | 94 | 89[e] |
| 17 | **4b** | Me | **1e** | Thiophen-2-yl | Me | **2e** | 87 | 78 |
| 18 | **4b** | Me | **1f** | Ph | $CH_2CO_2Et$ | **2f** | 71[f] | 37[g] |

[a] The reaction was carried out at 0.2 mmol scale with 2.0 equiv of $Cl_3SiH$ at 18 °C for 16 h in toluene with 5 mol % of the catalyst unless stated otherwise.
[b] Isolated yield.
[c] The absolute configuration of the amines was established by comparison of their optical rotation (measured in $CHCl_3$) with the literature data (see Experimental) and/or by comparison of their HPLC behavior with that of authentic samples.[11] Amines **2a**–**d** and **2f** were (*S*)-configured; the configuration of **2e** is assumed to be (*S*) in analogy with the rest of the series and our previous experiments.
[d] Determined by chiral HPLC.
[e] Ref. 11c.
[f] The reaction was carried out for 48 h in the presence of acetic acid (1 equiv) to facilitate the enamine–imine equilibration.[11f]
[g] Ref. 11f.

functionality in $R^2$ were varied (**1a**–**d** and **1f**);[11,18] one representative example of the heteroaromatic realm (**1e**) was also included. The reductions proceeded uneventfully and afforded the corresponding amines in high yields and good to high enantioselectivities with both catalysts **4a** (Table 1; entries 7–12) and **4b** (entries 13–18). The efficiency of the new catalysts turned out to be comparable with that of Sigamide **3d** (Table 1, entries 1–6),[11c,f,g] which however still remains the champion catalyst.

## 3. Conclusions

We have prepared two new valine-derived organocatalysts **4a**,**b** with a bulky aromatic amide moiety. The latter Lewis bases catalyzed the reduction of ketimines **1a**–**f** with $Cl_3SiH$ to afford the corresponding amines (*S*)-**2a**–**f** in high yields and with ≤91% ee. These results are comparable to those previously reported by us (for **3d**)[11] and by other groups[8–10] and are complementary to those obtained by the reduction employing Hantzsch dihydropyridine as a reducing agent, catalyzed by chiral Brønsted acids.[7]

## 4. Experimental

### 4.1. General Methods

Melting points were determined on a Kofler block and are uncorrected. The NMR spectra were recorded for $CDCl_3$ solutions, $^1H$ at 400 MHz and $^{13}C$ at 100.6 MHz with chloroform-$d_1$ ($\delta$ 7.26, $^1H$; $\delta$ 77.0, $^{13}C$) or TMS as internal standard unless otherwise indicated. Various 2D-techniques and DEPT experiments were used to establish the structures and to assign the signals. The IR spectra were recorded for a thin film of $CHCl_3$ solutions between NaCl plates. The mass spectra (EI and/or CI) were measured on a dual sector mass spectrometer using direct inlet and the lowest temperature enabling evaporation. Some reactions, when needed, were performed under an atmosphere of dry, oxygen-free argon in oven-dried glassware twice evacuated and filled with the argon. Solvents and solutions were transferred by syringe–septum technique. Solvents for the reactions were of reagent grade and were dried as follows: benzene was distilled from sodium and stored under argon; THF, toluene, and dichloromethane were obtained from Pure-Solv™ Solvent Purification System (Innovative Technology). *p*-Anisidine was distilled prior to use. Petroleum ether (PE) refers to the fraction boiling in the range of 40–60 °C, AcOEt refers to ethyl acetate, MeOH refers to methanol, AcOH refers to acetic acid, and TsOH refers to *p*-toluenesulfonic acid. Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. The identity of the products prepared by different methods was checked by comparison of their NMR, IR, and MS data and by the TLC behavior. The chiral HPLC methods were calibrated with the corresponding racemates. Imines **1a**–**f** were prepared from *p*-anisidine and the corresponding ketones.[11,18] For the chiral HPLC traces of the reduction products, see our recent paper.[11g] The *N*-methyl formamide **10** was prepared by methylation of Boc-valine **9** using our standard procedure ($CH_3I$, NaH, THF).[11b]

*4.1.1. Formamide (S)-(−)-**4a**.* Trifluoroacetic acid (1.5 mL) was added dropwise, under argon, to a solution of the Boc-protected derivative **11a** (114 mg, 0.225 mmol) in $CH_2Cl_2$ (1.5 mL) at 0 °C and the reaction mixture was stirred at this temperature for 1 h. The solvent was then removed in vacuo and the residue was co-evaporated with toluene (3×20 mL) to afford the TFA salt of the deprotected amine. The crude amine was dissolved in formic acid (0.75 mL) and the resulting solution was cooled to 0 °C. Acetic anhydride (0.38 mL) was added dropwise and the reaction mixture was allowed to stir at room temperature overnight. The mixture was then evaporated and the residue was co-evaporated with toluene (3×20 mL). The crude product was purified by chromatography on a column of silica gel (10 g) with a mixture of petroleum ether and ethyl acetate (100:0 to 50:50) to afford the formamide derivative **4a** (60 mg, 69%) as a white solid: mp 143–146 °C (petroleum ether/acetone); $[\alpha]_D$ −123.7 (*c* 1.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$, a mixture of rotamers in ratio ca. 10:1, the minor one is marked *) $\delta$ 8.31 (br s, 1H), 8.29* (s, 0.1H), 8.18 (s, 1H), 7.77 (d, *J*=1.6 Hz, 2H), 7.77* (d, *J*=1.5 Hz 0.2H), 7.63–7.65 (m, 4.4H), 7.56 (t, *J*=1.6 Hz, 1H), 7.43–7.47 (m, 4.4H), 7.35–7.39 (m, 2.2H), 4.45 (d, *J*=11.3 Hz, 1H), 3.56* (d, *J*=10.3 Hz, 0.1H), 3.02 (s, 3H), 2.97* (s, 0.3H), 2.51 (d sept, *J*=11.4, 6.6 Hz, 1.1H), 1.09 (d, *J*=6.5 Hz, 3H), 0.94 (d, *J*=6.6 Hz, 3H); $^{13}C$ NMR (only major rotamer is given) $\delta$ 167.6 (C), 164.1 (CH), 142.7 (2×C), 140.7 (2×C), 138.7 (C), 128.9 (4×CH), 127.7 (2×CH), 127.3 (4×CH), 122.2 (CH), 117.7 (2×CH), 63.1 (CH), 31.7 ($CH_3$), 25.5 (CH), 19.6 ($CH_3$), 18.7 ($CH_3$); IR $\nu$ 3289, 3034, 2965, 1657, 1599, 1561, 1496, 1462, 1427, 1388, 1218 $cm^{-1}$; MS (EI) *m*/*z* (%) 386 ($M^{+\bullet}$, 25), 245 (20), 142 (45), 114 (100), 86 (25); HRMS (EI) 386.1996 ($C_{25}H_{26}O_2N_2$ requires 386.1994).

*4.1.2. Formamide (S)-(−)-**4b**.* Trifluoroacetic acid (2.0 mL) was added dropwise, under argon, to a solution of the Boc-protected derivative **11b** (174 mg, 0.36 mmol) in $CH_2Cl_2$ (2.0 mL) at 0 °C and the reaction mixture was stirred at this temperature for 1 h. The solvent was then removed in vacuo and the residue was co-evaporated with toluene (3×20 mL) to afford the TFA salt of the deprotected amine. The crude amine was dissolved in formic acid (1.0 mL) and the resulting solution was cooled to 0 °C. Acetic anhydride (0.5 mL) was added dropwise and the reaction mixture was allowed to stir at room temperature overnight. The mixture was then evaporated and the residue was co-evaporated with toluene (3×20 mL). The crude product was purified by chromatography on a column of silica gel (10 g) with a mixture of petroleum ether and ethyl acetate (100:0 to 50:50) to afford the formamide derivative **4b** (143 mg, 96%) as a white solid: mp 178–182 °C (petroleum ether/acetone); $[\alpha]_D$ −126.6 (*c* 1.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$, a mixture of rotamers in ratio ca. 10:1, the minor one is marked *) $\delta$ 8.49 (br s, 1H), 8.37* (br s, 0.1H), 8.30* (s, 0.1H), 8.15 (s, 1H), 7.50 (d, *J*=1.3 Hz, 2H), 7.22–7.28 (m, 8.8H), 7.08* (s, 0.1H), 7.06 (s, 1H), 4.46 (d, *J*=11.3 Hz, 1H), 3.60* (d, *J*=10.4 Hz, 0.1H), 3.01 (s, 3H), 2.91* (s, 0.3H), 2.48 (d sept, *J*=11.4, 6.5 Hz, 1.1H), 2.33 (s, 6.6H), 1.07 (d, *J*=6.4 Hz, 3H), 0.92 (d, *J*=6.6 Hz, 3H); $^{13}C$ NMR (only major rotamer is given) $\delta$ 167.3 (C), 164.1 (CH), 142.5 (2×C), 141.2 (2×C), 137.3 (C), 135.4 (2×C), 130.4 (2×CH), 129.8 (2×CH), 127.5 (2×CH), 126.4 (CH), 125.8 (2×CH), 119.4 (2×CH), 63.2 (CH), 31.7 ($CH_3$), 25.4 (CH), 20.6 (2×$CH_3$), 19.6 ($CH_3$), 18.6 ($CH_3$); IR $\nu$ 3269, 3024, 2963, 1654, 1612, 1563, 1489, 1430, 1385, 1220 $cm^{-1}$; MS (EI) *m*/*z* (%) 414 ($M^{+\bullet}$, 30), 273 (15), 142 (60), 114 (100), 86 (20), 55 (5); HRMS (EI) 414.2302 ($C_{27}H_{30}O_2N_2$ requires 414.2307).

*4.1.3. 3,5-Dibromonitrobenzene[13] (**6**).* Solid sodium nitrite (3.76 g, 54.1 mmol, 3.2 equiv) was added as rapidly as foaming would permit to a stirred, boiling (90 °C) solution of 2,6-dibromo-4-nitroaniline (**5**) (5.0 g, 16.9 mmol, 1.0 equiv) and concentrated sulfuric acid (7.5 mL) in ethanol (75 mL). The reaction mixture was stirred at 90 °C for 42 h. Then, the mixture was allowed to cool, poured onto ice, and the precipitate was isolated by filtration and thoroughly washed with cold water. The 3,5-dibromonitrobenzene was dissolved in boiling ethanol, filtered while hot and left to crystallize, affording **6** (3.77 g, 80%) as a brown crystalline solid: $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.32 (d, *J*=1.7 Hz, 2H), 8.00 (t, *J*=1.7 Hz, 1H) in accordance with the literature.[13]

*4.1.4. 3,5-Diphenylnitrobenzene (**7a**).* An aqueous solution of $Na_2CO_3$ (2 M, 0.6 mL; purged with argon for 1 h) was added to a solution of 3,5-dibromonitrobenzene (**6**) (700 mg, 2.5 mmol, 1.0 equiv), phenyl boronic acid (670 mg, 5.5 mmol, 2.2 equiv), tri(*o*-tolyl)phosphine

(68 mg, 0.23 mmol, 9 mol %), and palladium(II) acetate (28 mg, 0.13 mmol, 5 mol %) in degassed toluene (18 mL) and the reaction mixture was heated to reflux overnight. The mixture was then cooled to room temperature and an aqueous solution of NaOH (1 M, 70 mL) was added. The phases were separated and the aqueous phase was extracted with AcOEt (3×20 mL). The combined organic phase was dried over $Na_2SO_4$ and concentrated in vacuo. The product was purified by chromatography on a column of silica gel (20 g) with a mixture of petroleum ether and ethyl acetate (100:0 to 98:2) to afford **7a** (477 mg, 69%) as a white solid: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.42 (d, $J$=1.6 Hz, 2H), 8.12 (t, $J$=3.2, 1.6 Hz, 1H), 7.68–7.70 (m, 4H), 7.51–7.54 (m, 4H), 7.44–7.48 (m, 2H) in accordance with the literature.[14]

*4.1.5. 3,5-Di-(2′-tolyl)nitrobenzene (**7b**).* An aqueous solution of $Na_2CO_3$ (4 M, 1.8 mL; purged with argon for 1 h) was added to a solution of 3,5-dibromonitrobenzene (**6**) (300 mg, 1.07 mmol, 1.0 equiv), *o*-tolyl boronic acid (640 mg, 4.7 mmol, 4.4 equiv), tri(*o*-tolyl)phosphine (30 mg, 0.1 mmol, 9 mol %), and palladium(II) acetate (12 mg, 0.05 mmol, 5 mol %) in degassed toluene (8 mL) and the reaction mixture was refluxed overnight. The mixture was then cooled to room temperature and an aqueous solution of NaOH (1 M, 30 mL) was added. The phases were separated and the aqueous phase was extracted with AcOEt (3×20 mL). The combined organic phase was dried over $Na_2SO_4$ and concentrated in vacuo. The product was purified by chromatography on a column of silica gel (10 g) with a mixture of petroleum ether and ethyl acetate (100:0 to 98:2) to afford **7b** (260 mg, 80%) as a white solid: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.19 (d, $J$=1.5 Hz, 2H), 7.64 (t, $J$=1.5 Hz, 1H), 7.27–7.34 (m, 8H), 2.33 (s, 6H); $^{13}$C NMR $\delta$ 148.1 (C), 143.3 (2×C), 139.4 (2×C), 136.2 (CH), 135.2 (2×C), 130.8 (2×CH), 129.8 (2×CH), 128.4 (2×CH), 126.3 (2×CH), 122.5 (2×CH), 20.5 (2×$CH_3$); IR $\nu$ 3065, 3021, 2955, 2925, 2871, 1535, 1494, 1457, 1350, 1098, 907, 765, 749, 702 cm$^{-1}$; MS (EI) $m/z$ (%) 303 ($M^{+\bullet}$, 100), 242 (30), 241 (20), 165 (20), 115 (18), 83 (36); HRMS (EI) 303.1262 ($C_{20}H_{17}O_2N$ requires 303.1259).

*4.1.6. 3,5-Diphenylaniline (**8a**).* Anhydrous tin(II) chloride (698 mg, 3.6 mmol, 5 equiv) was slowly added to a solution of the nitrobenzene derivative **7a** (200 mg, 0.73 mmol, 1 equiv) in a mixture of ethanol (2 mL) and THF (2 mL) while stirring under air and the stirring continued at room temperature for 24 h. The solvent was then removed in vacuo and an aqueous solution of NaOH (1 M, 40 mL) was added and the mixture was stirred at room temperature for 2 h. The product was extracted into ether (3×15 mL) and the organic phase was dried over $Na_2SO_4$ and evaporated in vacuo to afford amine **8a** (167 mg, 93%) as an off-white solid, which was used in the next step without purification: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.61–7.63 (m, 4H), 7.42–7.46 (m, 4H), 7.34–7.38 (m, 2H), 7.22 (t, $J$=1.5 Hz, 1H), 6.91 (d, $J$=1.5 Hz, 2H), 3.87 (br s, 2H) in accordance with the literature.[14,19]

*4.1.7. 3,5-Di-(2′-tolyl)aniline (**8b**).* Anhydrous tin(II) chloride (812 mg, 4.28 mmol, 5 equiv) was slowly added to a solution of the nitrobenzene derivative **7b** (260 mg, 0.86 mmol, 1 equiv) in a mixture of ethanol (2.5 mL) and THF (2.5 mL) while stirring under air and the stirring continued at room temperature for 24 h. The solvent was then removed in vacuo and an aqueous solution of NaOH (1 M, 50 mL) was added and the mixture was stirred at room temperature for 2 h. The product was extracted into ether (3×15 mL) and the organic phase was dried over $Na_2SO_4$ and evaporated in vacuo to afford amine **8b** (217 mg, 92%) as an off-white solid, which was used in the next step without purification: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.22–7.29 (m, 8H), 6.69 (t, $J$=1.5 Hz, 1H), 6.63 (d, $J$=1.5 Hz, 2H), 3.76 (br s, 2H), 2.33 (s, 6H); $^{13}$C NMR $\delta$ 145.9 (C), 142.8 (2×C), 142.1 (2×C), 135.4 (2×C), 130.3 (2×CH), 129.7 (2×CH), 127.2 (2×CH), 125.7 (2×CH), 121.0 (CH), 114.6 (2×CH), 20.6 (2×$CH_3$); IR $\nu$ 3665, 3377, 3213, 3015, 2954, 2923, 1616, 1596, 1493, 1458, 1419, 1354, 1216 cm$^{-1}$; MS (EI) $m/z$ (%) 273 ($M^{+\bullet}$, 100), 272 (30), 257 (10), 182 (25), 180 (15), 115 (10); HRMS (EI) 273.1519 ($C_{20}H_{19}N$ requires 273.1517).

*4.1.8. Amide (S)-(−)-**11a**.* 1-Hydroxybenzotriazole (HOBt; 76 mg, 0.56 mmol, 1.3 equiv) and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDCI; 108 mg, 0.56 mmol, 1.3 equiv) were added to a solution of *N*-methyl-*N*-Boc-valine **10** (100 mg, 0.43 mmol, 1.0 equiv), triethylamine (91 μL, 66 mg, 0.65 mmol, 1.5 equiv), and amine **8a** (128 mg, 0.52 mmol, 1.2 equiv) in $CH_2Cl_2$ (5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 20 h. The mixture was then diluted with ethyl acetate (10 mL) and washed successively with water (20 mL), cold aqueous 0.5 M HCl (10 mL), a saturated $NaHCO_3$ solution (20 mL), brine (20 mL), and then dried over $Na_2SO_4$ and evaporated in vacuo. The crude product was purified by chromatography on a column of silica gel (10 g) with a mixture of petroleum ether and ethyl acetate (100:0 to 80:20) to afford amide **11a** (111 mg, 56%) as a white foam: $[\alpha]_D$ −68.5 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.50 (br s, 1H), 7.77 (s, 2H), 7.62–7.65 (m, 4H), 7.48 (t, $J$=1.5 Hz, 1H), 7.43–7.47 (m, 4H), 7.35–7.39 (m, 2H), 4.17 (d, $J$=11.3 Hz, 1H), 2.86 (s, 3H), 2.41 (d sept, $J$=11.3, 6.5 Hz, 1H), 1.59 (s, 9H), 1.05 (d, $J$=6.5 Hz, 3H), 0.94 (d, $J$=6.6 Hz, 3H); $^{13}$C NMR $\delta$ 168.1 (C), 156.6 (C), 141.5 (2×C), 139.7 (2×C), 137.9 (C), 127.3 (4×CH), 126.6 (2×CH), 126.2 (4×CH), 120.8 (CH), 116.3 (2×CH), 79.8 (C), 65.0 (CH), 29.5 ($CH_3$), 27.4 (3×$CH_3$), 24.9 (CH), 18.9 ($CH_3$), 17.6 ($CH_3$); IR $\nu$ 3317, 2969, 2931, 1690, 1657, 1599, 1560, 1153 cm$^{-1}$; MS (EI) $m/z$ (%) 458 ($M^{+\bullet}$, 20), 245 (72), 130 (100), 86 (72), 57 (46); HRMS (EI) 458.2571 ($C_{29}H_{34}O_3N_2$ requires 458.2569).

*4.1.9. Amide (S)-(−)-**11b**.* 1-Hydroxybenzotriazole (HOBt; 120 mg, 0.87 mmol, 1.3 equiv) and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDCI; 170 mg, 0.87 mmol, 1.3 equiv) were added to a solution of *N*-methyl-*N*-Boc-valine **10** (154 mg, 0.67 mmol, 1.0 equiv), triethylamine (140 μL, 103 mg, 1.0 mmol, 1.5 equiv), and amine **8b** (220 mg, 0.80 mmol, 1.2 equiv) in $CH_2Cl_2$ (7.5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 20 h. The mixture was then diluted with ethyl acetate (10 mL) and washed successively with water (20 mL), cold aqueous 0.5 M HCl (10 mL), a saturated $NaHCO_3$ solution (20 mL), and brine (20 mL) and then dried over $Na_2SO_4$ and evaporated in vacuo. The crude product was purified by chromatography on a column of silica gel (10 g) with a mixture of petroleum ether and ethyl acetate (100:0 to 80:20) to afford amide **11b** (153 mg, 47%) as a white foam: $[\alpha]_D$ −84.2 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.44 (br s, 1H), 7.48 (s, 2H), 7.22–7.48 (m, 8H), 7.04 (s, 1H), 4.14 (d, $J$=10.5 Hz, 1H), 2.85 (s, 3H), 2.38 (d sept, $J$=11.4, 6.5 Hz, 1H), 2.33 (s, 6H), 1.48 (s, 9H), 1.03 (d, $J$=6.4 Hz, 3H), 0.92 (d, $J$=6.6 Hz, 3H); $^{13}$C NMR $\delta$ 169.0 (C), 157.5 (C), 142.5 (2×C), 141.3 (2×C), 137.6 (C), 135.4 (2×C), 130.4 (2×CH), 129.8 (2×CH), 127.4 (2×CH), 126.1 (CH), 125.8 (2×CH), 119.2 (2×CH), 80.8 (C), 28.4 (3×$CH_3$), 26.0 (CH), 20.6 (2×$CH_3$), 20.0 ($CH_3$), 18.6 ($CH_3$); IR $\nu$ 3322, 2969, 1661, 1609, 1557, 1420, 1366, 1217 cm$^{-1}$; MS (EI) $m/z$ (%) 487 ($M^{+\bullet}$, 15), 273 (60), 186 (15), 130 (100), 86 (65), 57 (28); HRMS (EI) 486.2880 ($C_{31}H_{38}O_3N_2$ requires 486.2882).

## 4.2. General procedure for enantioselective reduction of imines

Trichlorosilane (40 μL, 0.4 mmol, 2 equiv) was added dropwise to a cooled solution (0 °C) of the imine (0.2 mmol, 1 equiv), catalyst (0.01 mmol, 5 mol %) in anhydrous toluene (2 mL) under an argon atmosphere and the reaction mixture was allowed to stir at room temperature for 24 h (unless otherwise stated). Then the reaction mixture was diluted with ethyl acetate (5 mL), quenched with a saturated $NaHCO_3$ solution (20 mL), and the layers were separated. The aqueous layer was extracted with AcOEt (2×5 mL) and

the combined organic phase was washed with water (2×15 mL), brine (5 mL), dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by flash chromatography on a silica gel column (25 mL) with a petroleum ether/ethyl acetate mixture (98:2 to 85:15). The yields and enantioselectivities are given in Table 1. The absolute configuration of the amines was established by comparison of their optical rotation (measured in $CHCl_3$) with the literature data and/or by comparison of their HPLC behavior with that of authentic samples; all are known compounds.[11]

*4.2.1. Amines **2a**–**f**[11].* Amine **2a**:[11a–c,g] 7.34–7.41 (m, 4H), 7.24–7.28 (m, 1H), 6.71–6.75 (m, 2H), 6.49–6.53 (m, 2H), 4.45 (q, *J*=6.7 Hz, 1H), 3.82 (br s, 1H), 3.73 (s, 3H), 1.53 (d, *J*=6.7 Hz, 3H); HPLC analysis (Chiralpak IB, hexane/propan-2-ol (99:1), 0.75 mL/min, $t_R$ (minor)=15.6 min, $t_R$ (major)=16.7 min).

Amine **2b**:[11a–c,g] 7.58 (d, *J*=8.2 Hz, 2H), 7.49 (d, *J*=8.2 Hz, 2H), 6.68–6.72 (m, 2H), 6.42–6.46 (m, 2H), 4.46 (q, *J*=6.7 Hz, 1H), 3.79 (br s, 1H), 3.70 (s, 3H), 1.51 (d, *J*=6.7 Hz, 3H); HPLC analysis (Chiralpak IB, hexane/propan-2-ol (95:5), 0.90 mL/min, $t_R$ (minor)=11.8 min, $t_R$ (major)=13.6 min).

Amine **2c**:[11a–c,g] 7.26–7.30 (m, 2H), 6.84–6.88 (m, 2H), 6.68–6.72 (m, 2H), 6.46–6.50 (m, 2H), 4.38 (q, *J*=6.7 Hz, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 1.5483 (d, *J*=6.7 Hz, 3H); HPLC analysis (Chiralpak IB, hexane/propan-2-ol (98:1), 0.60 mL/min, $t_R$ (minor)=21.7 min, $t_R$ (major)=22.9 min).

Amine **2d**:[11a–c,g] 7.794–7.83 (m, 4H), 7.51 (dd, *J*=8.6, 1.4 Hz, 1H), 7.41–7.48 (m, 2H), 6.66–6.70 (m, 2H), 6.50–6.54 (m, 2H), 4.57 (q, *J*=6.7 Hz, 1H), 3.68 (s, 3H), 1.58 (d, *J*=6.7 Hz, 3H); HPLC analysis (Chiralpak IB, hexane/propan-2-ol (99:1), 0.75 mL/min, $t_R$ (minor)=24.4 min, $t_R$ (major)=26.7 min).

Amine **2e**:[11g] 7.14 (dd, *J*=4.9, 1.4 Hz, 1H), 6.97 (ddd, *J*=3.5, 1.2, 0.9 Hz, 1H), 6.94 (dd, *J*=4.9, 3.5 Hz, 1H), 6.74–6.78 (m, 2H), 6.58–6.62 (m, 2H), 4.74 (q, *J*=6.6 Hz, 1H), 3.73 (s, 3H), 3.73 (br s, 1H), 1.61 (d, *J*=6.6 Hz, 3H); HPLC analysis (Chiralpak IB, hexane/propan-2-ol (99:1), 0.75 mL/min, $t_R$ (minor)=19.4 min, $t_R$ (major)=21.0 min).

Amine **2f**:[11f] 7.36–7.38 (m, 2H), 7.30–7.34 (m, 2H), 7.22–7.26 (m, 1H), 6.68–6.72 (m, 2H), 6.50–6.54 (m, 2H), 4.75 (t, *J*=6.7 Hz, 1H), 4.34 (br s, 1H), 3.73 (s, 3H), 4.11 (qd, *J*=7.1, 1.4 Hz, 2H), 3.69 (s, 3H), 2.77–2.79 (m, 2H), 1.19 (t, *J*=7.1 Hz, 3H); HPLC analysis (Chiralpak IB, hexane/propan-2-ol (99:1), 0.75 mL/min, $t_R$ (minor)=10.3 min, $t_R$ (major)=11.2 min).

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## Supplementary data

$^1H$ and $^{13}C$ NMR spectra for key compounds. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.08.048.

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