Dendron-anchored organocatalysts: the asymmetric reduction of imines with trichlorosilane, catalysed by an amino acid-derived formamide appended to a dendron†

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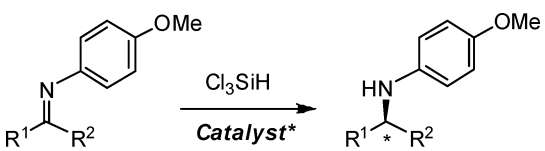
Received 12th August 2009, Accepted 25th September 2009
First published as an Advance Article on the web 27th October 2009
DOI: 10.1039/b916601g

Asymmetric reduction of ketimines **1a–f** with trichlorosilane can be catalysed by the Lewis-basic *N*-methylvaline-derived formamide anchored to a soluble dendron (**11c**) with good enantioselectivity (≤94% ee) and low catalyst loading (typically 5 mol%) at room temperature in toluene. This protocol represents an improvement and simplification of the isolation procedure and recovery of the catalyst.

Introduction

There is an impressive portfolio of protocols for the enantioselective transition metal-catalysed reduction of imines **1**,[1] which include hydrogenation,[2] transfer hydrogenation[3] and hydrosilylation,[4] *etc*.[5] On the other hand, the organocatalytic realm is currently confined to the reduction with Hantzsch dihydropyridine catalysed by chiral Brønsted acids,[6] and hydrosilylation with Cl_3SiH catalysed by chiral Lewis bases (Scheme 1).[7–9] In the last few years Malkov, Kočovský and co-workers have developed a library of Lewis-basic formamides derived from natural amino acids, and those originating from *N*-methyl valine, such as **3–5** (Fig. 1), proved to be particularly efficient (≤97% ee).[7] In order to improve the practicality of the isolation procedure, these catalysts were then modified by appending a fluorous ponytail (**7**),[7c] a solid resin (**8**),[7e] a gold nanoparticle (**9**)[7i] and a soluble polymer (**10**).[7j] Herein, we report on an alternative approach, namely anchoring the catalyst to a dendron.



Scheme 1 Asymmetric reduction of selected ketimines. For structures **a–f** see Table 1.

Dendron- and dendrimer-anchored catalysts provide an attractive architecture for performing a range of catalytic reactions.[10] In particular, the unique structural characteristics of these systems offer advantages over traditional polymeric supports in terms of providing: (i) a well-defined monodisperse structure; (ii) the ability to tune the accessibility and microenvironment of the catalyst by either attaching it to the terminal functionality, or by isolating it within the dendrimer core; and (iii) the ability to augment the rate and/or the selectivity of the reaction *via* the so-called "dendrimer effect".[11] Unsurprisingly, these features have more recently inspired the development of dendrimer/dendron-based catalysts for enantioselective transformations.[12]

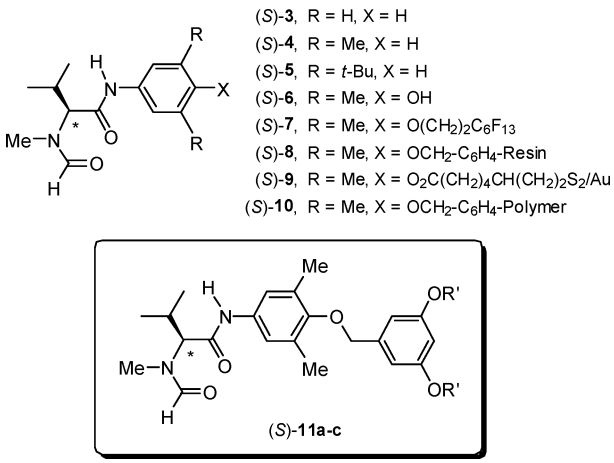


Fig. 1 Catalysts for the asymmetric reduction of imines. For R′ see Scheme 2.

Results and discussion

Synthesis

Dendrons with an appended catalytic moiety were synthesized according to Scheme 2. 3,5-Dibenzyloxy benzyl alcohol **12a**[13] and the phenolic derivative (*S*)-(–)**6**[7e] underwent the Mitsunobu reaction with di-(4-chlorobenzyl)-azodicarboxylate (DCAD) and triphenylphosphine (rt, 67 h) to afford the first-generation dendron **11a** (17%). Similarly, the reaction of benzyl alcohol **12b**[13] with phenol (*S*)-(–)**6**[7e] (rt, 48 h) furnished the second-generation

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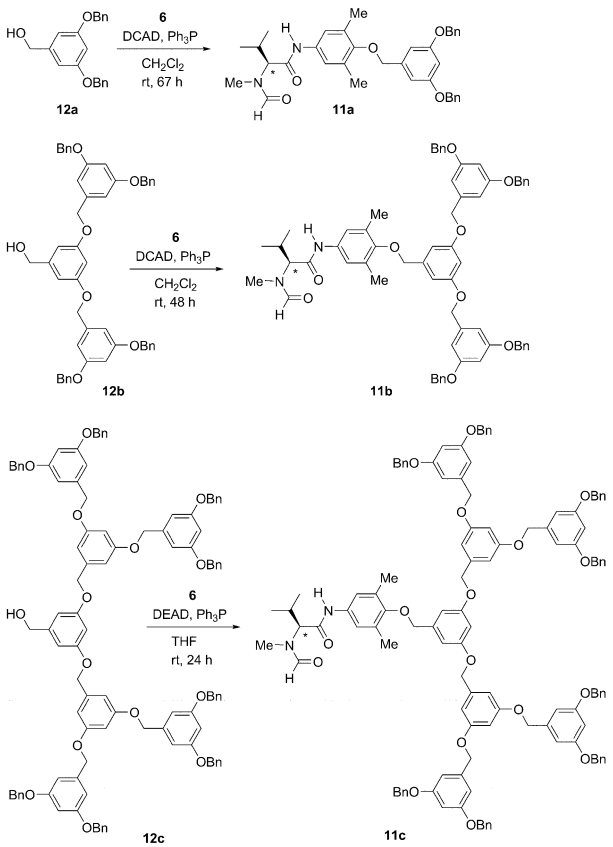
† Electronic supplementary information (ESI) available: General methods, and ^{1}H and ^{13}C NMR spectra of the dendron-anchored catalysts **11a–c**. See DOI: 10.1039/b916601g



Scheme 2 Synthesis of dendron-anchored catalysts **11a–c**.

dendron **11b** (23%), and the benzyl alcohol **12c**[13] (using diethyl azodicarboxylate DEAD) produced the third-generation dendron **11c** (26%; rt, 24 h).

Catalyst screening

The reduction of a substantial portfolio of imines, catalysed by **3–5** and **7–10**, was investigated by us earlier.[7] Since relatively little variation was observed as a function of the imine structure, the present study was confined to a selected set of representative examples of aromatic imines **1a–f** (Scheme 1 and Table 1). The reduction of imine **1a** proceeded uneventfully in the presence of each of the three dendron-supported catalysts **11a–c** (Table 1, entries 1–3) and, when complete, as indicated by TLC, the mixture was added dropwise to vigorously stirred methanol, which was expected to precipitate the catalyst. However, in the case of the first-generation catalyst (**11a**), this operation was unsuccessful as no precipitation was observed, leaving a homogeneous solution. Aqueous workup of the latter solution, followed by evaporation and classical chromatography of the residue, afforded amine **2a** (89% ee; entry 1). With the second-generation catalyst (**11b**), the addition of the organic phase to methanol resulted in the formation of a biphasic system with white droplets of the catalyst (at the bottom) surrounded by a "milky" solution, which was separated and centrifuged. This process removed *ca.* 60% of the catalyst. The supernatant was worked up and evaporated, and the product **2a** was purified by chromatography. The precipitation procedure applied to the reaction catalysed by the third-generation catalyst (**11c**) was more successful: *ca.* 90% of the catalyst was recovered from the mixture by centrifugation so that the product (**2a**) thus obtained (after the aqueous workup) was contaminated with only ≤1% of the catalyst (as revealed by HPLC) and was purified by chromatography.

These experiments demonstrated that only the third-generation catalyst **11c** offered the advantages expected for a dendron. Therefore, this catalyst was employed to establish the scope of this method using our standard set of model imines **1b–f** (Table 1, entries 4–9). The yields and enantioselectivities proved to be similar to those obtained with homogeneous, non-supported catalysts, reaching a maximum of 94% ee for imine **1e** (entry 8). For comparison, Sigamide **5**,[7c,g] one of the most successful catalysts for this transformation known to date,[7,8] produced amine **2e** in 96% ee.[7d] Little variation was observed as a function of the substitution pattern. As with Sigamide,[7c,d,f] toluene was identified as the solvent-of-choice for the dendron-supported catalysts, whereas the less environmentally friendly dichloromethane proved to be inferior (compare entries 5 and 6).

When the regenerated catalyst **11c** (10 mol%) was reused for the reduction of imine **1a**, the corresponding amine **2a** was obtained in the same yield as with the fresh catalysts (90%) but the enantioselectivity dropped to 81% ee (compare with 89% ee, Table 1, entry 3).

Table 1 Reduction of ketimines **1a–f** with trichlorosilane, catalysed by the valine-derived *N*-methyl formamides anchored to dendrons (*S*)-**11a–c**[a]

	Catalyst (mol%)	**1a–f**	R^1	R^2	Yield (%)[b]	**2** ee (%)[c]
1	**11a** (10)	**1a**	Ph	Me	88	89
2	**11b** (10)	**1a**	Ph	Me	90	87
3	**11c** (10)	**1a**	Ph	Me	89	89
4	**11c** (5)	**1b**	4-CF_3Ph	Me	81	91
5	**11c** (5)[d]	**1c**	2-Naphth	Me	68	85
6	**11c** (5)[e]	**1c**	2-Naphth	Me	23	70
7	**11c** (5)	**1d**	4-MeOPh	Me	78	79
8	**11c** (5)	**1e**	Ph	CH_2Cl	69	94
9	**11c** (5)	**1f**[f]	Ph	CH_2CO_2Et	89	82

[a] The reaction was carried out at a 0.2 mmol scale with 2.0 equiv. of Cl_3SiH in toluene. Trichlorosilane was added at 0 °C, and the mixture was allowed to warm up to room temperature and stirred for 16 h. [b] Yields of isolated products. [c] The absolute configuration of the resulting amines was found to be (*S*)-**2** by comparison of their optical rotation and their HPLC behaviour with those of the authentic samples (ref. 7). [d] Trichlorosilane was added at room temperature instead of 0 °C as **1c** was not soluble in toluene at 0 °C. [e] The reaction was carried out in CH_2Cl_2. [f] Ref. 14.

Conclusions

In conclusion, three generations of dendron-supported *N*-methylvaline derivatives **11a–c** were prepared as organocatalysts for the enantioselective reduction of imines **1a–f** with trichlorosilane, a convenient, non-expensive reducing agent. Application of the third-generation catalyst **11c** resulted in a substantial simplification of the isolation procedure, as most of the catalyst (≥90%) can be removed by precipitation and centrifugation.[15] Toluene was again identified as the reaction medium-of-choice and the enantioselectivities (≤94% ee) mirrored those attained with Sigamide (**5**)[7] and its congeners.

Experimental

Imines **1a–f** and amines **2a–f** are known compounds, previously prepared in this laboratory;[7] synthesis of the phenolic derivative **6** was reported by us recently.[7c,e] Dendrons **12a–c** were prepared using the previously reported methodology.[13]

Formamide (*S*)-(−)-11a

Di-(4-chlorobenzyl)-azodicarboxylate (DCAD) (436 mg, 1.19 mmol, 1.2 equiv.) was added to a solution of phenol (*S*)-**6**[7c,e] (305 mg, 1.09 mmol, 1.1 equiv.), alcohol **12a**[13] (319 mg, 0.99 mmol) and triphenylphosphine (313 mg, 1.19 mmol, 1.2 equiv.) in dry CH_2Cl_2 (10 ml). The mixture was stirred at room temperature for 67 h, after which time the resulting precipitate was filtered off and washed with CH_2Cl_2 (10 mL). The combined organic fractions were concentrated under vacuum and purified by chromatography on a column of silica gel (70 g) with a petroleum ether–ethyl acetate mixture (1 : 1) to afford pure formamide (*S*)-(−)-**11a** (96 mg, 17%) as a viscous colourless oil: R_f 0.38/0.25 (petroleum ether–ethyl acetate, 1 : 1); $[\alpha]_D$ −58.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, a mixture of amide rotamers in *ca.* 4 : 1 ratio; only the data for the major rotamer are given) δ 0.93 (d, J = 6.6 Hz, 3H), 1.07 (d, J = 6.5 Hz, 3H), 2.26 (s, 6H), 2.41–2.54 (m, 1H), 3.02 (s, 3H), 4.47 (d, J = 11.2 Hz, 1H), 4.59 (s, 2H), 5.06 (s, 4H), 6.61 (t, J = 2.2 Hz, 1H), 6.74 (d, J = 2.2 Hz, 2H), 7.24 (s, 2H), 7.31–7.45 (m, 10H), 8.15 (s, 1H), 8.38 (s, 1H); ^{13}C NMR δ 16.44 (CH_3), 18.55 (CH_3), 19.45 (CH_3), 25.37 (CH), 31.53 (CH_3), 62.86 (CH), 70.03 (CH_2), 73.90 (CH_2), 101.48 (CH), 106.55 (CH), 122.37 (CH), 127.46 (CH), 127.93 (CH), 128.51 (CH), 131.58 (C), 133.34 (C), 136.73 (C), 139.83 (C), 152.28 (C), 160.01 (C), 163.87 (CHO), 167.11 (CO); IR (film) ν 3317, 2964, 2929, 1656, 1596 cm^{-1}; MS (FAB) *m*/*z* (%) 581 ([M + H]$^+$, 10), 303 (20), 142 (100), 92 (65); HRMS 580.3017 [$C_{36}H_{41}O_5N_2$ requires (M + H)$^+$].

Formamide (*S*)-(−)-11b

Di-(4-chlorobenzyl)-azodicarboxylate (DCAD) (60 mg, 0.15 mmol) was added to a solution of phenol (*S*)-**6**[7c,e] (43 mg, 0.15 mmol), alcohol **12b**[13] (108 mg, 0.14 mmol) and triphenylphosphine (41 mg, 0.15 mmol) in dry CH_2Cl_2 (3 ml). The mixture was stirred at room temperature for 48 h, after which time the resulting precipitate was filtered off and washed with CH_2Cl_2 (10 mL). The combined organic fractions were concentrated under vacuum and purified by chromatography on a column of silica gel (30 g) with a petroleum ether–ethyl acetate mixture (1 : 1) to afford pure formamide (*S*)-(−)-**11b** (33 mg, 23%) as a viscous colourless oil: R_f 0.40/0.23 (petroleum ether–ethyl acetate, 1 : 1); $[\alpha]_D$ −47.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, a mixture of amide rotamers in *ca.* 4 : 1 ratio; only the data for the major rotamer are given) δ 0.93 (d, J = 6.6 Hz, 3H), 1.07 (d, J = 6.5 Hz, 3H), 2.28 (s, 6H), 2.44–2.53 (m, 1H), 3.01 (s, 3H), 4.42 (d, J = 11.2 Hz, 1H), 4.70 (s, 2H), 5.00 (s, 4H), 5.04 (s, 8H), 6.59 (s, 3H), 6.71 (s, 4H), 6.73 (s, 2H) 7.23 (s, 2H), 7.33–7.44 (m, 20H), 8.15 (s, 1H), 8.18 (s, 1H); ^{13}C NMR δ 16.47 (CH_3), 18.51 (CH_3), 19.50 (CH_3), 25.24 (CH), 31.53 (CH_3), 62.99 (CH), 69.95 (CH_2), 70.04 (CH_2), 73.90 (CH_2), 101.50 (CH), 106.32 (CH), 106.54 (CH), 120.36 (CH), 127.52 (CH), 127.96 (CH), 128.55 (CH), 131.63 (C), 133.32 (C), 136.69 (C), 139.19 (C), 139.87 (C), 152.31 (C), 159.93 (C), 160.10 (C), 163.93 (CHO), 167.01 (CO); IR (film) ν 3315, 3032, 2928, 1656, 1595 cm^{-1}; *m*/*z* (FAB) 1006 [(M + H)$^+$, 2%], 531 (95), 303 (30), 219 (100); HRMS 1005.4672 [$C_{64}H_{65}O_9N_2$ requires (M + H)$^+$ 1005.4690].

Formamide (*S*)-(−)-11c

Diethyl azodicarboxylate (DEAD) (0.13 mL, 0.81 mmol) was added to a solution of phenol (*S*)-**6**[7c,e] (151 mg, 0.54 mmol), alcohol **12c**[13] (1.04 g, 0.65 mmol) and triphenylphosphine (212 mg, 0.81 mmol) in dry THF (10 mL). The mixture was stirred at room temperature for 24 h, after which time the solution was concentrated under vacuum. The residue was purified by chromatography on a column of silica gel (130 g) with a petroleum ether–ethyl acetate mixture (2 : 3) to afford a crude product, which was further purified by washing with MeOH (2 × 40 mL) and then ether (2 × 40 mL). Drying of the residue afforded pure formamide (*S*)-(−)-**11c** (263 mg, 26%) as a solid foam: R_f 0.49/0.37 (petroleum ether–ethyl acetate, 2 : 3); $[\alpha]_D$ 24.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, a mixture of amide rotamers in *ca.* 4 : 1 ratio; only the data for the major rotamer are given) δ 0.91 (d, J = 6.6 Hz, 3H), 1.04 (d, J = 6.4 Hz, 3H), 2.25 (s, 6H), 2.41–2.50 (m, 1H), 2.96 (s, 3H), 4.32 (d, J = 11.2 Hz, 1H), 4.67 (s, 2H), 4.96 (s, 8H), 4.97 (s, 4H), 5.01 (s, 16H), 6.53 (t, J = 2.2 Hz, 2H), 6.56 (t, J = 2.2 Hz, 4H), 6.59 (t, J = 2.2 Hz, 1H), 6.66 (d, J = 2.2 Hz, 12H), 6.72 (d, J = 2.2 Hz, 2H), 7.18 (s, 2H), 7.27–7.41 (m, 40H), 7.82 (s, 1H), 8.12 (s, 1H); ^{13}C NMR δ 16.47 (CH_3), 18.49 (CH_3), 19.49 (CH_3), 25.18 (CH), 31.49 (CH_3), 63.00 (CH), 69.90 (CH_2), 70.00 (CH_2), 73.87 (CH_2), 101.37 (CH), 101.50 (CH), 106.30 (CH), 106.39 (CH), 106.54 (CH), 120.34 (CH), 127.50 (CH), 127.93 (CH), 128.51 (CH), 131.62 (C), 133.28 (C), 136.68 (C), 139.13 (C), 139.91 (C), 152.30 (C), 159.99 (C), 160.10 (C), 163.92 (CHO), 166.96 (CO); IR (film) ν 3312, 3032, 2930, 2873, 1658, 1594 cm^{-1}; MS (FAB) *m*/*z* 1855 [(M + H)$^+$, 8%), 846 (10), 606 (13), 423 (45), 303 (100)]; HRMS 1853.8033 [$C_{120}H_{113}O_{17}N_2$ requires (M + H)$^+$ 1853.8039].

General procedure for the asymmetric reduction of 1a catalysed by 11a,b

Trichlorosilane (50 μL) was added to a solution of imine **1a** (0.22 mmol) and catalyst **11a** or **11b** (10 mol%) in toluene (1.5 mL) at 0 °C, and the mixture was stirred at room temperature overnight. Chloroform (30 mL) was then added and the solution was washed with aqueous saturated $NaHCO_3$ (10 mL). The aqueous phase was extracted with chloroform (30 mL) and the combined organic solutions were dried over $MgSO_4$. Chloroform was partially

evaporated, silica gel (1 g) was added to the residue, and the rest of the solvent was evaporated to dryness. The latter silica gel-adsorbed mixture was loaded onto a column of dry silica gel (15 g) and eluted with a mixture of petroleum ether and ethyl acetate (24 : 1 or 9 : 1) to afford pure amine **2a**. For yields and enantioselectivity, see Table 1.

General Procedure for the Asymmetric Reduction of 1a–f Catalysed by 11c

Trichlorosilane (50 μL) was added to a solution of imine **1** (0.22 mmol) and catalyst **11c** (0.022 mmol) in toluene (1.5 mL) at 0 °C and the mixture was stirred at room temperature overnight. The mixture was then poured into rapidly stirred methanol (50 mL), the resulting cloudy mixture was centrifuged, and the clear supernatant was evaporated. The residue was treated with chloroform (30 mL) and the resulting solution was washed with aqueous saturated $NaHCO_3$ (10 mL). The aqueous phase was extracted with chloroform (30 mL), and the combined organic solutions were dried over $MgSO_4$ and evaporated. The crude product was purified by chromatography on a column of silica gel (10 g) using a mixture of petroleum ether and ethyl acetate (15 : 1) to give the pure amine **2** (89%). For yields and enantioselectivity, see Table 1. The amines thus obtained were identical to the authentic samples prepared earlier by us.[7]

Acknowledgements

This work was supported by the EPSRC (grant Nos. GR/S87294/01 and EP/E018211/1), the Royal Society of Edinburgh, and AstraZeneca. We thank the University of Glasgow for a graduate fellowship to M.F. A.S thanks TUBITAK (105S353) and TUBA-GEBIP for financial support.

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