# $Organo catalysts\ immobilised\ onto\ gold\ nanoparticles:\ application\ in\ the\ asymmetric\ reduction\ of\ imines\ with\ trichlorosilane^{\dagger}$

Andrei V. Malkov,\*‡ Marek Figlus, Graeme Cooke,\* Stuart T. Caldwell, Gouher Rabani, Mark R. Prestly and Pavel Kočovský\*

Received 28th November 2008, Accepted 6th February 2009 First published as an Advance Article on the web 25th March 2009 DOI: 10.1039/b821391g

Gold nanoparticles functionalised with a valine-derived formamide have been developed as effective homogenous catalysts for the asymmetric reduction of ketimine **1** with trichlorosilane ( $\leq$ 84% ee) in toluene. This methodology both simplifies the recovery of the catalyst and its separation from the product, as the nanoparticles can be readily removed and subsequently recycled by precipitation from the reaction mixture.

# Introduction

Organocatalysts, small organic molecules capable of promoting enantioselective reactions, are rapidly gaining ground as viable alternatives to their organometallic and bio-catalytic counterparts.<sup>1</sup> However, typical organocatalytic procedures developed to date generally require a relatively high catalyst loading, which creates problems in product isolation. To overcome the separation difficulties, some of the successful organocatalysts have been immobilised onto polymers.<sup>2</sup> Most of these systems have utilised commercially available polymers (*e.g.*, polystyrenes); however, this approach often produces catalysts that exhibit lower activity and selectivity than the parent systems, presumably due to the impaired accessibility of the catalytic site, problems associated with polymer swelling, and/or the background reaction catalysed by the polymer itself.

Catalyst-functionalised nanoparticles<sup>3</sup> offer an attractive alternative for the development of new supported catalysts.<sup>4</sup> In particular, the ability to functionalise monolayer-protected nanoparticles *via* place-exchange reactions allows the synthesis of soluble systems, whereby both the number and accessibility of the catalyst molecules attached to the surface can be conveniently controlled.<sup>5</sup> Furthermore, the catalyst molecules immobilised onto nanoparticles are located on the surface, which is in contrast with polymer-supported catalysts, where a number of catalyst molecules will be encapsulated inside the polymer.

The asymmetric reduction of prochiral ketimines (Scheme 1), is one of the key reactions in synthetic organic chemistry that provides precious building blocks for the fine-chemical industry.<sup>6</sup> The organocatalytic<sup>1</sup> version is currently characterized by two fundamentally different approaches: (i) hydrosilylation with trichlorosilane, catalysed by chiral Lewis-bases, which activate the nucleophilic hydride donor (Scheme 1),<sup>7,8</sup> and (ii) reduction with Hantzsch dihydropyridine, catalysed by chiral



Scheme 1 The asymmetric reduction of an imine with trichlorosilane.

Brønsted acids, which activate the electrophilic recipient (*i.e.*, the imine).<sup>9</sup>

During the last few years, Kočovský, Malkov and co-workers have developed Lewis-basic organocatalysts for the reduction of imines with Cl<sub>3</sub>SiH.<sup>7</sup> In particular, the formamides **3a**,**b**<sup>7b-d,10</sup> based on the N-methyl valine scaffold (Scheme 1), proved to be most effective (Table 1, entries 1 and 2). The workup and isolation procedures were then simplified by appending a fluorous tag  $(e.g. 3c)^{7d}$  or by anchoring the catalyst to an insoluble polymer (e.g. 3d)<sup>7e</sup> (entries 3 and 4). However, the increased cost of the former and reduced efficiency in the latter methodology has hampered the further development of these systems. Herein, we report on the immobilisation of a Lewis-basic amino acid-derived formamide onto the monolayer-protected gold nanoparticles and the application of this system as a catalyst for the asymmetric reduction of ketimines with Cl<sub>3</sub>SiH. It was anticipated that the solubility of these systems in organic solvents would restore the benefits of working in a homogeneous solution, whilst the relatively easy recovery of the inorganic support material would reduce the cost implications.

## **Results and discussion**

## Synthesis

The synthesis of the catalyst-functionalised nanoparticles (Scheme 2) commenced with the phenolic derivative  $4.^{7d,e}$  Esterification with lipoic acid, using standard carbodiimide protocol,

WestCHEM, Department of Chemistry, Joseph Black Building, University of Glasgow, Glasgow, UK G12 8QQ. E-mail: A.Malkov@lboro.ac.uk, graemec@chem.gla.ac.uk, pavelk@chem.gla.ac.uk

<sup>†</sup> Electronic supplementary information (ESI) available: TEM images of 6a and 7a. See DOI: 10.1039/b821391g

<sup>‡</sup> Current address: Department of Chemistry, Loughborough University, Loughborough, UK LE11 3TU

entry	run	catalyst	yield <sup>b</sup> (%)	ee <sup>c</sup> , <sup>d</sup> (%)
1	_	3a <sup>e</sup>	85	91 <sup>k</sup>
2		3b/	95	94 <sup>k</sup>
3		3c <sup>e</sup>	90	91 <sup>k</sup>
4		$3d^{e,g}$	81	82 <sup>k</sup>
5		3e <sup>e</sup>	90	91
6		5 <sup>e</sup>	80	89
7		<b>6a</b> <sup>h</sup>	51	
8	1	$7a^{h}$	90	84
9	2	7a	92	82
10	3	7a	92	80
11	4	7a	89	68
12		$\mathbf{7b}^{i}$	88	70
13		15 <sup>j</sup>	86	79

<sup>*a*</sup> The reaction was carried out at 0.2 mmol scale with 2.0 equiv of Cl<sub>3</sub>SiH in toluene at 20 °C overnight unless stated otherwise. <sup>*b*</sup> Isolated yield. <sup>*c*</sup> Determined by chiral HPLC. <sup>*d*</sup> The absolute configuration of the product was (*S*)-(-)-**2** as shown by the optical rotation and by HPLC *via* comparison with an authentic sample. <sup>*c*</sup> 10 mol%. <sup>*f*</sup> 5 mol%. <sup>*g*</sup> Chloroform was used as solvent instead of toluene. <sup>*h*</sup> 100 mg. <sup>*i*</sup> 79 mg. <sup>*j*</sup> 20 mol%. <sup>*k*</sup> Ref. 7b–e.



Scheme 2 Organocatalyst immobilisation on gold nanoparticles *via* a lipoic acid linker.

afforded ester **5** (80%). In parallel, gold nanoparticles **6a** and **6b** were prepared from HAuCl<sub>4</sub>·3H<sub>2</sub>O *via* reduction with NaBH<sub>4</sub>, carried out in the presence of butane-thiol or octane-thiol and tetraoctylammonium bromide as a phase-transfer catalyst, in a toluene–water two-phase system.<sup>11,12</sup> The resulting ~2 nm nanoparticles **6a** and **6b** were then isolated by precipitation with absolute ethanol, followed by filtration.<sup>11</sup> The subsequent place-exchange reactions between the latter nanoparticles **7a** and **7b**, respectively, which were isolated again by precipitation with ethanol. The <sup>1</sup>H NMR spectra of **7a** and **7b** displayed broad resonances for valine-derived catalytic moiety and in particular revealed the presence of broad signals for the formamide protons

(~8.14 ppm). FT- IR spectroscopy confirmed the ester and amide carbonyls (at 1755 and 1655 cm<sup>-1</sup>). <sup>1</sup>H NMR spectroscopy was used to estimate the degree of catalyst loading on the butyl and octyl protected nanoparticles. Based upon the integration of the formamide proton (CON*H*) and the terminal methyl groups (C*H*<sub>3</sub>) of the butyl and octyl chains (in **7a** and **7b**), we estimate the average ratio to be approximately  $1 : \ge 20$  (CONH : CH<sub>3</sub>), suggesting a low loading of the catalyst. Nanoparticles **7a** and **7b** exhibited good solubility in non-polar solvents (*e.g.*, CH<sub>2</sub>Cl<sub>2</sub> and toluene) but proved to be poorly soluble in more polar solvents (*e.g.*, CH<sub>3</sub>OH).

Since the linker unit between the catalyst and the support often affects the activity quite dramatically, we prepared another nanoparticle-immobilized catalyst 15 for comparison (Scheme 3). Here, an undecanethiol unit was used to link the catalytic moiety via an ether link, to the gold nanoparticle. Ether links have proved to be an excellent choice in our previous work (3c,d).<sup>7d,e</sup> Compound 10 was prepared from 11-bromoundecan-1-ol 9 and phenolic derivative 8 via a Mitsunobu reaction. The nitro group of compound 10 was then reduced to an amino group to yield 11. Compound 11 was reacted with a BOC-protected N-(Me)-Val derivative to afford 12, which was deprotected and converted into the formamide derivative 13. The bromide in 13 was replaced by a thiol group upon reaction with  $(Me_3Si)_2S^{13}$  and Bu<sub>4</sub>NF in THF at 0 °C for 2 h. The resulting thiol 14 (90%) was immobilized by an exchange reaction with the butanethiolprotected gold nanoparticles 6a to produce nanoparticles 15. Following integration of the broad <sup>1</sup>H NMR resonances for the formamide protons (CONH) and the terminal methyl groups



Scheme 3 Organocatalyst immobilisation on gold nanoparticles *via* a thiol linker.

Table 1

and 15<sup>4</sup>

 $(CH_3)$  of the butyl chains, we estimate the average ratio to be approximately 1 : 10 (CONH : CH<sub>3</sub>), suggesting a higher catalyst loading compared to **7a**.

#### Catalyst screening

The screening of the new catalyst candidates in the reduction of imine 1, our bench-mark substrate,<sup>7</sup> was carried out under the conditions previously optimized for the non-supported catalysts 3a,b.7a-d Thus, Cl<sub>3</sub>SiH (0.40 mmol) was added to a solution of 1 (0.20 mmol) and 7a (100 mg) in dry toluene at 0 °C and the mixture was stirred at room temperature overnight under an argon atmosphere. After the reaction was complete, toluene was evaporated and the residue was treated with methanol. The resulting mixture was centrifuged, allowing the separation of the solid catalyst from the product, which remained in the solution. The methanolic solution was evaporated and the residue was worked-up with aqueous NaHCO<sub>3</sub> as previously described,<sup>7</sup> to afford amine (S)-(-)-2 (84% ee; Table 1, entry 8). The octanethiolcoated nanoparticles 7b exhibited lower enantio-selectivity (70% ee, entry 12), whereas 15 behaved in a similar manner as 7a (79%) ee, entry 13).14

The convenient recovery of 7a allowed us to probe the recyclability of this system (entries 9-11), with the recovered catalyst being re-used without further purification. While the 2nd and 3rd run gave essentially the same results as the fresh catalyst (compare entry 8 with 9 and 10), considerable deterioration of enantioselectivity was observed in the 4th run, although the isolated yield remained practically unchanged (entry 11). Control experiments showed that acetate 3e and the free lipoic acid ester 5 catalysed the reduction very effectively (91 and 89% ee, entries 5 and 6). Interestingly, the butanethiol-protected nanoparticles **6a**, lacking the organocatalyic moiety, were also found to catalyse the reduction although at a lower rate, reflected in a reduced conversion. Naturally, the resulting amine 2 was racemic (entry 7). The latter result suggests that the significant deterioration of enantioselectivity in the 4th run (entry 11) may stem from partial desorption of the immobilised organocatalyst from the nanoparticle, and its gradual removal during the repeated workup, so that the background reaction, catalysed by the stripped nanoparticles, becomes competitive. Aggregation of the nanoparticles15 may also be regarded as a contributing factor, as a decreased solubility of the nanoparticles was observed after the 3rd run, thereby shifting the clearly homogeneous system (1st run) to nearly heterogeneous (4th run).

### Conclusions

In conclusion, we have synthesised gold nanoparticles **7a,b** and **15** functionalised with a valine-derived formamide and demonstrated their propensity to catalyse the asymmetric reduction of imine **1** with  $Cl_3SiH$  at room temperature in the environmetally benign toluene as solvent. The highest level of catalytic activity and enantioselectivity ( $\leq 84\%$  ee) was attained with **7a**. This result can be extrapolated to a number of derivatives of imine **1**, since we have previously demonstrated little variation of the yield and enantioselectivity as a function of the substitution pattern in the imine structure for catalysts **3a–d**.<sup>7</sup> This new homogenous methodology simplifies the recovery of the catalyst and its

separation from the product, as the nanoparticles can be readily removed from the reaction mixture by precipitation and re-used. Hence, this work may be viewed as a proof of concept, which can be further extended to other, less expensive nanoparticle systems, such as those based on Fe.<sup>16</sup>

#### **Experimental section**

#### **General Methods**

Melting points were determined on a Kofler block and are uncorrected. Optical rotations were recorded in CHCl<sub>3</sub> at 25 °C unless otherwise indicated, with an error of  $\leq \pm 0.1$ . The  $[\alpha]D$  values are given in 10<sup>-1</sup>deg cm<sup>3</sup> g<sup>-1</sup>. The NMR spectra were recorded as CDCl<sub>3</sub> solutions,  $^1\mathrm{H}$  at 400 MHz and  $^{13}\mathrm{C}$  at 100.6 MHz, with chloroform-d1 (& 7.26, 1H; & 77.0, 13C) 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 KBr discs or for a thin film 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. All reactions were performed under an atmosphere of dry, oxygen-free nitrogen in oven-dried glassware, twice evacuated and filled with inert gas. Solvents and solutions were transferred by syringe-septum and cannula techniques. All solvents for the reactions were of reagent grade and were dried and distilled under nitrogen immediately before use as follows: toluene from sodium/benzophenone, dichloromethane from calcium hydride, triethylamine from calcium hydride. Petroleum ether refers to the fraction boiling in the range of 60-80°C. 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 behaviour. The chiral HPLC methods were calibrated with the corresponding racemates.

Synthesis of 5. Phenolic derivative 4<sup>7e</sup> (200 mg, 0.72 mmol) and 4-(dimethylamino)-pyridine (DMAP, 28 mg, 0.23 mmol) were consecutively added to a solution of (3-dimethylaminopropyl)-3ethylcarbodiimide hydrochloride (EDCI; 344 mg, 1.79 mmol) and (±)-lipoic acid (296 mg, 1.43 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and the reaction mixture was stirred at 25 °C for 20 h. The mixture was then diluted with ethyl acetate (30 mL) and washed consecutively with water  $(2 \times 40 \text{ mL})$ , 0.5M HCl (40 mL), saturated NaHCO<sub>3</sub>  $(2 \times 40 \text{ mL})$ , water (40 mL), and brine (40 mL) and dried over MgSO<sub>4</sub>, filtered and evaporated. The residue (357 mg) was purified by chromatography on a column of silica gel (25 g) eluting with a mixture of CH<sub>2</sub>Cl<sub>2</sub> and MeOH (100:1), to afford pure formamide (-)-5 (280 mg, 80%) as a yellow oil:  $R_f = 0.44$  and 0.26 (two spots; CH<sub>2</sub>Cl<sub>2</sub>-MeOH, 49 : 1); [α]<sub>D</sub> -89.20 (c 0.65, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 Hz, CDCl<sub>3</sub>, a mixture of rotamers in ca. 4: 1 ratio; the signals for the minor rotamer are marked with an \*)  $\delta 0.91$  (d, J = 6.6 Hz, 3H), 1.03 (d, J = 6.5 Hz, 3H), 1.48–1.64 (m, 2H), 1.66–1.77 (m, 2H), 1.78-1.85 (m, 2H), 1.88-1.96 (m, 1H), 2.10 (s, 6H), 2.36-2.51 (m, 2H), 2.60 (t, J = 7.5 Hz, 2H), 2.91 (s, 0.37H\*), 2.99 (s, 2.63H \* 3.09-3.22 (m, 2H), 3.50 (d, J = 10.4 Hz, 0.14H\*), 3.54-3.62 (m, 1H), 4.39 (d, J = 11.3, 0.89H), 7.23 (s, 0.31 H\*), 7.27 (s, 1.63H), 7.99 (s, br. 0.11H\*), 8.13 (s, 0.89H), 8.19 (s, 0.77H), 8.22 (s, 0.18H\*); <sup>13</sup>C NMR  $\delta$  16.49 (CH<sub>3</sub>), 18.53 (CH<sub>3</sub>), 19.52 (CH<sub>3</sub>), 24.81 (CH<sub>2</sub>), 25.20 (CH), 28.85 (CH<sub>2</sub>), 31.60 (CH<sub>3</sub>), 33.74 (CH<sub>2</sub>), 34.59 (CH<sub>2</sub>), 38.42 (CH<sub>2</sub>), 40.21 (CH<sub>2</sub>), 56.26 (CH), 63.26 (CH), 119.83 (CH), 130.74 (C), 135.10 (C), 144.52 (C), 163.98 (CHO), 167.06 (CO), 171.26 (CO); IR (KBr) v 3434, 2926, 1753, 1656, 1556, 1485, 1411, 1372, 1187 1124 cm<sup>-1</sup>; MS (FAB) *m/z* (%) 467 ([MH]<sup>++</sup>, 14), 278 (22), 189 (16), 1432 (94), 115 (100), 88 (30), 79 (23); HRMS (FAB) 467.2043 (C<sub>23</sub>H<sub>35</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub> requires 467.2038).

Synthesis of gold nanoparticles 6a. A solution of hydrogen tetrachloroaurate hydrate HAuCl<sub>4</sub>·3H<sub>2</sub>O (2.0 g, ~49% Au metal basis, 5.0 mmol) in deionised water (150 mL) was added to a stirred solution of tetraoctyl ammonium bromide (6.80 g, 12.44 mmol, 2.5 equiv) in toluene (480 mL). The mixture was stirred for 10 min, the organic layer was separated and butanethiol (132 µL, 1.24 mmol, 0.25 equiv) was added. The solution was stirred for 10 min and then a solution of NaBH<sub>4</sub> (1.88 g, 49.8 mmol, 10 eq.) in deionised water (150 ml) was added over ~10 s.12 The resulting black solution was stirred at room temperature for 3.5 h after which time the layers were separated and the toluene layer was concentrated to near dryness under vacuum. Ethanol (70 mL) was then added and the precipitate was isolated by gravity filtration, and then washed with ethanol (300 mL) and acetone (450 mL) to afford nanoparticles **6a** as a black powder (1.07 g): <sup>1</sup>H NMR (400 Hz, CDCl<sub>3</sub>) δ 0.95 (broad signal), 1.27 (broad signal), 1.54 (broad signal), 1.68 (broad signal), 3.38 (broad signal).

Synthesis of gold nanoparticles 6b. Synthesised on a 1.0 g scale from HAuCl<sub>4</sub>·3H<sub>2</sub>O (1.0 g, 2.5 mmol) in an identical manner to that shown above but using octanethiol (91 mg, 0.62 mmol) instead of butanethiol. <sup>1</sup>H NMR (400 Hz, CDCl<sub>3</sub>)  $\delta$  0.88 (broad signal), 1.27 (broad signal), 1.55 (broad signal), 1.66 (broad signal), 3.37 (broad signal).

Synthesis of gold nanoparticles 7a. Disulfide (–)-5 (538 mg, 1.15 mmol) was added to a solution of butylthiolate-stabilised gold nanoparticles 6a (538 mg, 0.63 mmol) in toluene (70 mL) and the resulting solution was stirred at room temperature for 3 days. The solution was then concentrated under vacuum and EtOH (50 mL) was added. The resulting precipitate was filtered by gravity filtration and washed with EtOH (150 mL) and acetone (150 mL) to furnish nanoparticles 7a (493 mg) as a black powder: <sup>1</sup>H NMR (400 Hz, CDCl<sub>3</sub>)  $\delta$  0.89 (broad signal), 1.55 (broad signal), 2.97 (broad signal), 3.54 (broad signal), 4.33 (broad signal), 8.14 (broad signal); IR (KBr) v 3446, 2954, 2923, 2869, 1757, 1655, 1560, 1456, 1416, 1375, 1261, 1210, 1094 cm<sup>-1</sup>. Anal. found: C, 7.14; H, 1.15. The filtrate was concentrated under vacuum and then passed quickly through a plug of silica gel, eluting with a CH<sub>2</sub>Cl<sub>2</sub>–Me<sub>2</sub>CO mixture (3 : 1) to give unreacted lipoic ester 5 (371 mg).

Synthesis of gold nanoparticles 7b. Disulfide (-)-5 (59 mg, 0.13 mmol) was added to a solution of octylthiolate-stabilised gold nanoparticles **6b** (100 mg, 0.10 mmol) in DCM (20 mL) and the resulting solution was stirred at room temperature for 2 days. The solution was then concentrated under vacuum and EtOH (50 mL) was added. The resulting precipitate was filtered by gravity filtration and washed with EtOH (100 mL) and acetone (100 mL) to furnish nanoparticles **7b** (88 mg) as a black powder: <sup>1</sup>H NMR (400 Hz, CDCl<sub>3</sub>)  $\delta$  0.93 (broad signal), 1.12 (s), 1.61 (broad signal), 1.79 (broad signal), 2.10 (s), 2.42–2.51 (m), 2.60 (t,

J = 7.6 Hz), 2.97 (s), 4.33 (d, J = 10.3 Hz), 8.00 (broad signal), 8.13 (broad signal); IR (KBr) v 3440, 2951, 2927, 2869, 1760, 1649, 1560, 1460, 1418, 1375, 1266, 1211, 1094 cm<sup>-1</sup>.

Synthesis of 10. Triphenylphosphine (1.96 g, 7.47 mmol), 11-bromo-1-undecanol (1.86 g, 7.40 mmol), and 97% diethyl azodicarboxylate (1.17 mL, 7.46 mmol) were added consecutively to a stirred solution of 2,6-dimethyl-4-nitrophenol 8 (1.0 g, 5.98 mmol) in THF (14 mL) at 0 °C. The resulting mixture was stirred at 25 °C for 18 h and the solvent was then evaporated. The residue (6.12 g) was purified by chromatography on a column of silica gel (80 g) eluting with a mixture of petroleum ether and  $CH_2Cl_2$  (4 : 1), to give 10 (1.96 g, 82%) as a yellowish oil:  $R_{\ell}$  = 0.42 (petroleum ether–CH<sub>2</sub>Cl<sub>2</sub>, 4 : 1); <sup>1</sup>H NMR (400 Hz, CDCl<sub>3</sub>)  $\delta$ 1.30-1.56 (m, 14H), 1.82 (pent, J = 6.6 Hz, 2H), overlapped with 1.85 (pent, J = 6.9 Hz, 2H), 2.34 (s, 6H), 3.41 (t, 2H, J = 6.8 Hz), 3.81 (t, J = 6.6 Hz, 2H), 7.91 (s, 2H); <sup>13</sup>C NMR  $\delta$  16.60 (CH<sub>3</sub>), 26.00 (CH<sub>2</sub>), 28.13 (CH<sub>2</sub>), 28.73 (CH<sub>2</sub>), 29.38 (CH<sub>2</sub>), 29.43 (CH<sub>2</sub>), 29.50 (CH<sub>2</sub>), 30.32 (CH<sub>2</sub>), 32.79 (CH<sub>2</sub>), 34.06 (CH<sub>2</sub>), 72.75 (CH<sub>2</sub>), 124.19 (CH), 132.32 (C), 143.28 (C), 161.66 (C); MS (EI) m/z (%) 401 and 399 (M<sup>++</sup>, 14), 167 (100), 137 (33), 97 (30), 55 (62); HRMS (EI) 399.1415 (C<sub>19</sub>H<sub>30</sub>BrNO<sub>3</sub> requires 399.1409).

Synthesis of 11. Tin(II) chloride dihydrate (4.50 g, 19.94 mmol) was added to a solution of the nitro ether 10 (2.00 g, 5.00 mmol) in EtOH (25 mL) and the resulting solution was stirred at 40 °C for 25 h. The mixture was then cooled and a saturated aqueous solution of NaHCO<sub>3</sub> (80 mL) was added to reach pH 10. The product was extracted with ether  $(3 \times 150 \text{ mL})$  and the organic phase was dried over MgSO<sub>4</sub>. The filtrate was concentrated to ~250 mL and aqueous 1M HCl (20 mL) was added. The mixture was stirred for 10 min, the precipitated white solid was collected by filtration and washed with ether  $(3 \times 100 \text{ mL})$ . Drying in the air afforded the aniline salt 11 (1.05 g, 52%) as a white powder: mp 188–192 °C (dec); <sup>1</sup>H NMR (400 Hz, CDCl<sub>3</sub>) δ 1.30–1.52(m, 14H), 1.78 (pent, J = 6.7, Hz 2H), 1.85 (pent, J = 7.3 Hz, 2H), 2.27 (s, 6H), 3.41 (t, J = 6.9 Hz, 2H), 3.71 (t, J = 6.5 Hz, 2H), 7.16 (s, 2H), 10.33 (br s, 2.65H); <sup>13</sup>C NMR δ 16.26 (CH<sub>3</sub>), 26.08 (CH<sub>2</sub>), 28.16 (CH<sub>2</sub>), 28.74 (CH<sub>2</sub>), 29.40 (CH<sub>2</sub>), 29.45 (CH<sub>2</sub>), 29.48 (CH<sub>2</sub>), 29.51 (CH<sub>2</sub>), 30.31 (CH<sub>2</sub>), 32.83 (CH<sub>2</sub>), 34.02 (CH<sub>2</sub>), 72.56 (CH<sub>2</sub>), 123.12 (CH), 124.50 (C), 133.23 (C), 156.55 (C); MS (CI) m/z 372 and 370 (M<sup>+</sup>, 100), 369 (22), 290 (13), 138 (78), 137 (21), 69 (48); HRMS (CI) 370.1752 (C<sub>19</sub>H<sub>33</sub>BrNO<sub>3</sub> requires 370.1746).

Synthesis of 12. The aniline hydrochloride 11 (1.00 g, 2.46 mmol) was added to a stirred mixture of CH<sub>2</sub>Cl<sub>2</sub> (50 mL), H<sub>2</sub>O (10 mL), and sat. NaHCO<sub>3</sub> (10 mL) and the stirring was continued for 10 min. The organic phase was separated, dried over MgSO<sub>4</sub>, and concentrated to ~10 mL by evaporation, to furnish solution A. To a stirred solution of (S)-BOC-Nmethyl-valine (0.69 g, 2.98 mmol) in CH2Cl2 (7 mL) were successively added at 0 °C: solution A, triethylamine (0.46 mL, 3.30 mmol), 1-hydroxy-benzotriazole (HOBt; 0.46 g, 3.41 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI; 0.61 g, 3.19 mmol). The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 22 h. The mixture was then diluted with ethyl acetate (100 mL) and washed successively with water (60 mL), cold 0.5M HCl ( $2 \times 55$  mL), saturated NaHCO<sub>3</sub> ( $2 \times 55$  mL), and brine (55 mL) and dried over MgSO<sub>4</sub> and evaporated. The residue (0.95 g) was purified by chromatography on a column of silica gel (100 g) eluting with a mixture of petroleum ether and ethyl acetate (12:1), to afford pure amide (S)-(-)-12 (741 mg, 51%) as a pale orange oil:  $R_{f} = 0.52$ (petroleum ether–ethyl acetate, 8 : 1);  $[\alpha]_D$  –55.0 (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 Hz, CDCl<sub>3</sub>)  $\delta$  0.90 (d, J = 6.6 Hz, 3H), 1.00 (d, J = 6.4 Hz, 3H), 1.48 (s, 9H), as a part of 1.25–1.52 (m, 23H), 1.77 (pent, J = 7.3 Hz, 2H), 1.85 (pent, J = 7.3 Hz, 2H), 2.24 (s, 6H), 2.30-2.40 (m, 1H), 2.82 (s, 3H), 3.40 (t, J = 6.9 Hz, 2H), 3.69(t, J = 6.6 Hz, 2H), 4.09 (d, J = 11.0 Hz, 1H), 7.16 (s, 2H), 8.03(br s, 0.74 H); <sup>13</sup>C NMR δ 16.36 (CH<sub>3</sub>), 18.55 (CH<sub>3</sub>), 19.84 (CH<sub>3</sub>), 25.88 (CH), 26.12 (CH<sub>2</sub>), 28.14 (CH<sub>2</sub>), 28.34 (CH<sub>3</sub>), 28.73 (CH<sub>2</sub>), 29.38 (CH<sub>2</sub>), 29.45 (CH<sub>2</sub>), 29.52 (CH<sub>2</sub>), 30.34 (CH<sub>2</sub>), 32.80 (CH<sub>2</sub>), 34.08 (CH<sub>2</sub>), 65.85 (CH), 72.45 (CH<sub>2</sub>), 80.54 (C), 120.04 (CH), 131.46 (C), 133.28 (C), 152.49 (C), 157.33 (CO), 168.56 (CO); MS (EI) m/z (%) 584 and 582 (M<sup>++</sup>, 8), 368 (37), 157 (52), 129 (95), 86 (100), 57 (48); HRMS (EI) 582.3038 (C<sub>30</sub>H<sub>51</sub>BrN<sub>2</sub>O<sub>4</sub> requires 582.3032).

Synthesis of 13. Trifluoroacetic acid (13.5 mL) was added dropwise to a solution of the BOC derivative 12 (1.54 g, 2.64 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) at 0 °C and the stirring was continued at the same temperature for 1 h. The acid was removed under reduced pressure and the residue was co-evaporated with toluene (2  $\times$ 20 mL) to afford a TFA salt of the deprotected amine as a brownish oil, which was used in the following step without further purification. The crude ammonium salt was dissolved in formic acid (15.2 mL) and the resulting solution was cooled to 0 °C. Acetic anhydride (11.5 mL) was then added dropwise and the mixture was allowed to stir at room temperature for 15 h. The volatiles were then evaporated and the residue (1.42 g) was purified by chromatography on a column of silica gel (140 g) eluting with a mixture of CH<sub>2</sub>Cl<sub>2</sub> and MeOH (70 : 1), to afford formamide (S)-(-)-13 (1.19 g; 88%) as a yellow oil:  $R_f = 0.42$  and 0.30 (two spots; CH<sub>2</sub>Cl<sub>2</sub>-MeOH, 70:1); [α]<sub>D</sub> -78.0 (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 Hz, CDCl<sub>3</sub> a mixture of rotamers in *ca*. 4 : 1 ratio; the signals for the minor rotamer are marked with an \*)  $\delta 0.90$  (d, J = 6.6 Hz, 3H), 1.03 (d, J = 6.3 Hz, 3H), 1.29–1.47 (m, 14H), 1.76 (pent, J =7.2 Hz, 2H), 1.84 (pent, J = 7.1 Hz, 2H), 2.22 (s, 6H), 2.38–2.51 (m, 1H), 2.91 (s, 0.47H\*), 3.00 (s, 2.49H), 3.40 (t, J = 6.9 Hz, 2H), 3.55 (d, J = 10.6 Hz, 0.18H\*), 3.68 (t, J = 6.5 Hz, 2H), 4.42 (d, J = 11.2 Hz, 0.82H), 7.14 (s, 0.32H\*), 7.18 (s, 1.64H), 8.13 (s, 0.82H), 8.22 (s, 0.77H), 8.25 (s, 0.22H\*), 8.34 (s, 0.17H\*); <sup>13</sup>C NMR δ 16.32 (CH<sub>3</sub>), 18.56 (CH<sub>3</sub>), 19.48 (CH<sub>3</sub>), 25.32 (CH), 26.09 (CH<sub>2</sub>), 28.11 (CH<sub>2</sub>), 28.70 (CH<sub>2</sub>), 29.35 (CH<sub>2</sub>), 29.42 (CH<sub>2</sub>), 29.49 (CH<sub>2</sub>), 30.31 (CH<sub>2</sub>), 31.53 (CH<sub>3</sub>), 32.77 (CH<sub>2</sub>), 34.05 (CH<sub>2</sub>), 62.86 (CH), 72.40 (CH<sub>2</sub>), 120.27 (CH), 131.43 (C), 132.90 (C), 152.70 (C), 163.85 (CO), 167.02 (CO); MS (EI) m/z (%) 512 and 510 (M<sup>++</sup>, 22), 369 (36), 114 (100), 86 (25), 55 (12); HRMS (EI) 510.2455 (C<sub>26</sub>H<sub>43</sub>BrN<sub>2</sub>O<sub>3</sub> requires 510.2457).

Synthesis of 14. Tetrabutyl-ammonium fluoride (TBAF, 1M soln in THF; 1.22 mL, 1.22 mmol) was slowly added to a solution of formamide (*S*)-(–)-13 (571 mg, 1.12 mmol) and hexamethyldisilathiane (0.28 mL, 1.35 mmol) in THF (6 mL) at 0 °C and the mixture was stirred at this temperature for 100 min. Sat. NH<sub>4</sub>Cl (35 mL) was added and the stirring was continued for an additional 5 min. The mixture was then extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 100 mL) and the organic extract was dried, and evaporated. The residue (623 mg) was purified by chromatography on a column

of silica gel (70 g) eluting with a mixture of CH<sub>2</sub>Cl<sub>2</sub> and MeOH (70 : 1), to afford pure formamide (S)-(-)-14 (461 mg, 90%) as a yellowish oil:  $R_f = 0.42$  and 0.30 (two spots; CH<sub>2</sub>Cl<sub>2</sub>-MeOH, 70 : 1); [α]<sub>D</sub> -77.0 (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 Hz, CDCl<sub>3</sub>; a mixture of rotamers in ca. 4 : 1 ratio; the signals for the minor rotamer are marked with an \*)  $\delta$  0.91 (d, J = 6.6 Hz, 3H), 1.04 (d, J = 6.5 Hz, 3H), 1.29–1.41 (m, 13H), 1.44–1.51 (m, 2H), 1.61 (pent, J = 7.2 Hz, 2H), 1.77 (pent, J = 7.3 Hz, 2H), 2.24 (s, 4.94H),2.25 (s, 0.75H\*) 2.39–2.48 (m, 1H), 2.52 (q, J = 7.5 Hz, 2H), 2.93 (s,  $0.53H^*$ ), 2.98 (s, 2.48H), 3.46 (d, J = 10.3 Hz,  $0.13H^*$ ), 3.53 (t, J = 6.6 Hz, 0.11 H), 3.69 (t, J = 6.6 Hz, 1.90 H), 4.35 (d, J =11.3 Hz, 0.85H), 7.14 (s, 0.24H\*), 7.16 (s, 1.64H), 7.88 (s, 0.82H), 8.14 (s, 0.83H), 8.22 (s, 0.11H\*); <sup>13</sup>C NMR δ 16.35 (CH<sub>3</sub>), 18.53 (CH<sub>3</sub>), 19.56 (CH<sub>3</sub>), 24.66 (CH<sub>2</sub>), 25.14 (CH), 26.13 (CH<sub>2</sub>), 28.36 (CH<sub>2</sub>), 29.05 (CH<sub>2</sub>), 29.47 (CH<sub>2</sub>), 29.50 (CH<sub>2</sub>), 29.52 (CH<sub>2</sub>), 29.55 (CH<sub>2</sub>), 30.35 (CH<sub>2</sub>), 31.55 (CH<sub>3</sub>), 34.04 (CH<sub>2</sub>), 63.10 (CH), 72.48 (CH<sub>2</sub>), 120.25 (CH), 131.54 (C), 132.84 (C), 152.77 (C), 163.94 (CO), 166.91 (CO); IR (KBr) v 3433, 2962, 2925, 2853, 1656, 1612, 1552, 1485, 1409, 1261, 1215, 1069, 1024, 802; MS (EI) m/z (%) 464 (M<sup>++</sup>, 48), 323 (83), 142 (58), 114 (100), 86 (25), 55 (12); HRMS (EI) 464.3076 (C<sub>26</sub>H<sub>44</sub>N<sub>2</sub>O<sub>3</sub>S requires 464.3073).

Synthesis of gold nanoparticles 15. Thiol (-)-14 (6.7 mL of a ~60 mg/mL solution in CH<sub>2</sub>Cl<sub>2</sub>, ~0.87 mmol) was added to a solution of butylthiolate-stabilized gold nanoparticles 6a (400 mg) in  $CH_2Cl_2$  (60 mL) (~2 : 1 14 : butanethiol mol ratio) and the resulting solution was stirred at room temperature overnight. The solution was concentrated under vacuum to near dryness and petroleum ether (70 mL) was added. The resulting solid was isolated by filtration and washed with petroleum ether (300 mL) to give the functionalised nanoparticles 15 (521 mg) as a black powder, soluble in most solvents except petroleum ether: <sup>1</sup>H NMR (400 Hz, CDCl<sub>3</sub>) δ 0.92 (broad signal), 1.03 (broad signal), 1.28 (broad signal), 1.60 (broad signal), 2.00 (broad signal), 2.24 (broad signal), 2.44 (broad signal), 2.97 (broad signal), 3.06 (broad signal), 3.51 (broad signal), 4.51 (broad signal), 7.00 (broad signal), 8.14 (broad signal), 8.29 (broad signal); IR (KBr) v 3465, 3286, 2921, 2851, 1655, 1611, 1551, 1484, 1409, 1214, 1062. Anal. found: C, 24.97; H, 3.40; N, 2.15.

General Procedure for the Asymmetric Reduction of Imine 1 Catalysed by 7a,b. The imine 1 (50 mg, 0.22 mmol) was added to a suspension of catalyst 7a (100 mg) or 7b (79 mg) in toluene (1.5 mL), followed by the addition of trichlorosilane (50  $\mu$ L) at 0 °C and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was treated with methanol (25 mL) to form a dispersion, which was centrifuged. The black solid was separated from the solution and dispersed again in MeOH (25 mL). Repeated centrifugation of the latter dispersion afforded a regenerated catalyst,17 which was dried under high vacuum prior to the next use. Methanolic solutions were combined, the solvent was evaporated, and the residue was dissolved in chloroform (30 mL), followed by washing with NaHCO<sub>3</sub> (10 mL). The aqueous phase was additionally extracted with chloroform (30 mL) and the combined organic extracts were dried over MgSO<sub>4</sub> and the solvent was evaporated. The crude product was purified by chromatography on a column of silica gel (10 g) eluting with a mixture of petroleum ether and ethyl acetate (15:1), to give pure amine 2. The results are summarized in the Table 1.

#### 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. We thank Colin How and Jim Gallagher for help with the electron microscopy studies.

## Notes and references

- 1 (a) Asymmetric Organocatalysts ed. A. Berkessel and H. Gröger, Wiley-VCH, Weinheim, 2005; (b) J. Seayad and B. List, Org. Biomol. Chem., 2005, 3, 719; (c) Enantioselective Organocatalysis, ed. P. I. Dalko, Wiley-VCH, 2007.
- 2 (a) For recent examples, see, e.g.: C. A. McNamara, M. J. Dixon and M. Bradley, *Chem. Rev.*, 2002, **102**, 3275; (b) M. Heitbaum, F. Glorius and I. Escher, *Angew. Chem., Int. Ed.*, 2006, **45**, 4732; (c) F. Cozzi, *Adv. Synth. Catal.*, 2006, **348**, 1367.
- 3 Nanoparticles and Catalysis, ed. D. Astruc, Wiley-VCH, Weinheim, 2008.
- 4 For a recent example of chiral organocatalytic nanoparticles see: S. Luo, X. Zheng and J.-P. Cheng, *Chem. Commun.*, 2008, 5719.
- 5 A. C. Templeton, M. J. Hostetler, E. K. Warmoth, S. W. Chen, C. M. Hartshorn, V. M. Krishnamurthy, M. D. E. Forbes and R. W. Murray, J. Am. Chem. Soc., 1998, 120, 4845.
- 6 (a) For reviews on the reduction of imines, see: Asymmetric Synthesis, ed. J. D. Morrison, Academic, New York, 1983, vol. 2; (b) R. Noyori, Asymmetric Catalysis in Organic Synthesis, Wiley and Sons, New York, 1994; (c) I. Ojima, Catalytic Asymmetric Synthesis, J. Wiley, and Sons, New York, 2nd edn, 2000; (d) B. R. James, Catal. Today, 1997, 37, 209; (e) S. Kobayashi and H. Ishitani, Chem. Rev., 1999, 99, 1069; (f) B. T. Cho, Tetrahedron, 2006, 62, 7621; (g) For an overview of metal-catalysed reductions, seeJ. S. M. Samec, J.-E. Bäckvall, P. G. Andersson and P. Brandt, Chem. Soc. Rev., 2006, 35, 237; (h) For enzymatic approaches to chiral amines via reduction, see, e.g. C. J. Dunsmore, R. Carr, T. Fleming and N. J. Turner, J. Am. Chem. Soc., 2006, 128, 2224 and refs cited therein.
- 7 (a) A. V. Malkov, A. Mariani, K. N. MacDougall and P. Kočovský, Org. Lett., 2004, 6, 2253; (b) A. V. Malkov, S. Stončius, K. N. MacDougall, A. Mariani, G. D. McGeoch and P. Kočovský, Tetrahedron, 2006, 62, 264; (c) A. V. Malkov, S. Stončius and P. Kočovský, Angew. Chem., Int. Ed., 2007, 46, 3722; (d) A. V. Malkov, M. Figlus, S. Stončius and P. Kočovský, J. Org. Chem., 2007, 72, 1315; (e) A. V. Malkov, M. Figlus and P. Kočovský, J. Org. Chem., 2008, 73, 3985.

- 8 (a) F. Iwasaki, O. Onomura, K. Mishima, T. Kanematsu, T. Mak and Y. Matsumura, *Tetrahedron Lett.*, 2001, **42**, 2525; (b) O. Onomura, Y. Kouchi, F. Iwasaki and Y. Matsumura, *Tetrahedron Lett.*, 2006, **47**, 3751; (c) Z. Wang, X. Ye, S. Wei, P. Wu, A. Zhang and J. Sun, Org. Lett., 2006, **8**, 999; (d) Z. Wang, M. Cheng, P. Wu, S. Wei and J. Sun, Org. Lett., 2006, **8**, 3045; (e) Z. Wang, S. Wei, C. Wang and J. Sun, *Org. Lett.*, 2006, **8**, 3045; (e) Z. Wang, S. Wei, C. Wang and J. Sun, *Tetrahedron: Asymmetry*, 2007, **18**, 705; (f) D. Pei, Z. Wang, S. Wei, Y. Zhang and J. Sun, Org. Lett., 2006, **8**, 5913; (g) C. Wang, X. Wu, L. Zhou and J. Sun, Chem. Eur. J., 2008, **14**, 8789; (h) D. Pei, Y. Zhang, S. Wei, M. Wang and J. Sun, Adv. Synth. Catal., 2008, **350**, 619; (i) H. Zheng, J. Deng, W. Lin and X. Zhang, Tetrahedron Lett., 2007, **48**, 7934; (j) H.-J. Zheng, W. B. Chen, Z.-J. Wu, J.-G. Deng, W.-Q. Lin, W.-C. Yuan and X.-M. Zhang, Chem. Eur. J., 2008, **14**, 9864; (k) S. Guizzetti, M. Benaglia, F. Cozzi, S. Rossi and G. Celentano, Chirality, 2009, **21**, 233.
- 9 (a) M. Rueping, E. Sugiono, C. Azap, T. Theissmann and M. Bolte, Org. Lett., 2005, 7, 3781; (b) M. Rueping, A. P. Antonchick and T. Theissmann, Angew. Chem. Int. Ed., 2006, 45, 3683; (c) M. Rueping, A. P. Antonchick and T. Theissmann, Angew. Chem., Int. Ed., 2006, 45, 6751; (d) M. Rueping and A. P. Antonchick, Angew. Chem., Int. Ed., 2007, 46, 4562; (e) S. Hoffman, A. M. Seayad and B. List, Angew. Chem., Int. Ed., 2005, 44, 7424; (f) S. Hoffmann, M. Nicoletti and B. List, J. Am. Chem. Soc., 2006, 128, 13074; (g) J. Zhou and B. List, J. Am. Chem. Soc., 2007, 129, 7498; (h) R. I. Storer, D. E. Carrera, Y. Ni and D. W. C. MacMillan, J. Am. Chem. Soc., 2006, 128, 84; (i) S. G. Ouellet, A. M. Walji and D. W. C. MacMillan, Acc. Chem. Res., 2007, 40, 1327; (j) T. Marcelli, P. Hammar and F. Himo, Chem. Eur. J., 2008, 14, 8562.
- 10 Catalysts 3a,b are now commercially available as Kenamide and Sigamide.
- 11 (a) For the method, see: M. Brust, M. Walker, D. Bethel, D. J. Schiffrin and R. J. Whyman, J. Chem. Soc., Chem. Commun., 1994, 801; (b) M. J. Hostetler, J. E. Wingate, C.-J. Zhong, J. E. Harris, R. W. Vachet, M. R. Clark, J. D. Londono, S. J. Green, J. J. Stokes, G. D. Wignall, G. L. Glish, M. D. Porter, N. D. Evans and R. W. Murray, Langmuir, 1998, 14, 17.
- 12 The speed of addition of the solution of  $NaBH_4$  ( $\leq 10$  s) proved to be crucial for obtaining reproducible results.
- 13 For the method, see: J. Zhu, A. Kell and M. S. Workentin, *Org. Lett.*, 2006, **8**, 4993.
- 14 An analogue of **15** with a 1,3-propane-spacer (instead of the 1,11undecane) proved ineffective as a catalyst.
- 15 B. S. Lee, S. K. Namgoong and S. Lee, *Tetrahedron Lett.*, 2005, 46, 4501.
- 16 C. Ó. Dálaigh, S. A. Corr, Y. Gun'ko and S. J. Connon, Angew. Chem. Int. Ed., 2007, 46, 4329.
- 17 Catalyst 7b was recovered only in 32% and was not used again.