Organocatalysts immobilised onto gold nanoparticles: application in the asymmetric reduction of imines with trichlorosilane†

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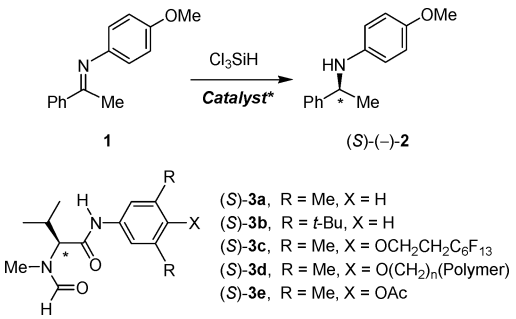
Gold nanoparticles functionalised with a valine-derived formamide have been developed as effective homogenous catalysts for the asymmetric reduction of ketimine **1** with trichlorosilane (≤84% ee) in toluene. This methodology both simplifies the recovery of the catalyst and its separation from the product, 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.[1] 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.[2] 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[3] offer an attractive alternative for the development of new supported catalysts.[4] 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.[5] 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 moieties 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.[6] The organocatalytic[1] 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),[7,8] and (ii) reduction with Hantzsch dihydropyridine, catalysed by chiral Brønsted acids, which activate the electrophilic recipient (*i.e.*, the imine).[9]



Scheme 1 The asymmetric reduction of an imine with trichlorosilane.

During the last few years, Kočovský, Malkov and co-workers have developed Lewis-basic organocatalysts for the reduction of imines with Cl_3SiH.[7] In particular, the formamides **3a**,**b**[7b–d,10] 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**)[7e] (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_3SiH. 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,

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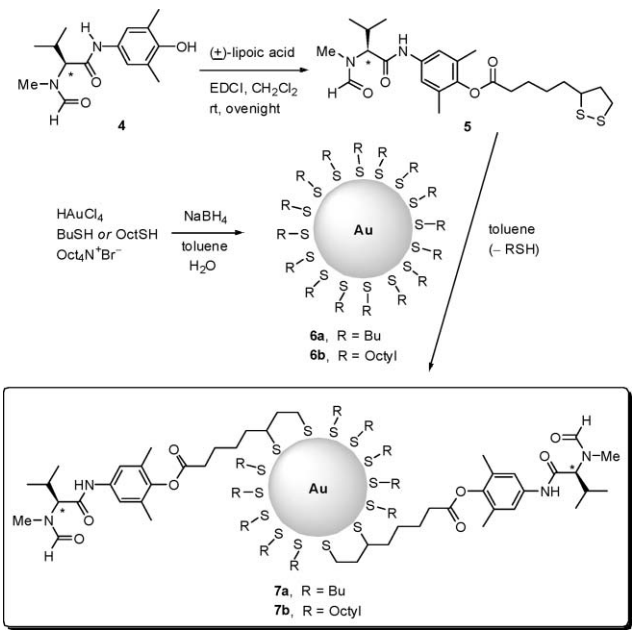
Table 1 Reduction of imine **1** with trichlorosilane, catalysed by **3**, **5–7**, and **15**[a]

entry	run	catalyst	yield[b](%)	ee[c],[d] (%)
1	—	**3a**[e]	85	91[k]
2	—	**3b**[f]	95	94[k]
3	—	**3c**[e]	90	91[k]
4	—	**3d**[e,g]	81	82[k]
5	—	**3e**[e]	90	91
6	—	**5**[e]	80	89
7	—	**6a**[h]	51	—
8	1	**7a**[h]	90	84
9	2	**7a**	92	82
10	3	**7a**	92	80
11	4	**7a**	89	68
12	—	**7b**[i]	88	70
13	—	**15**[j]	86	79

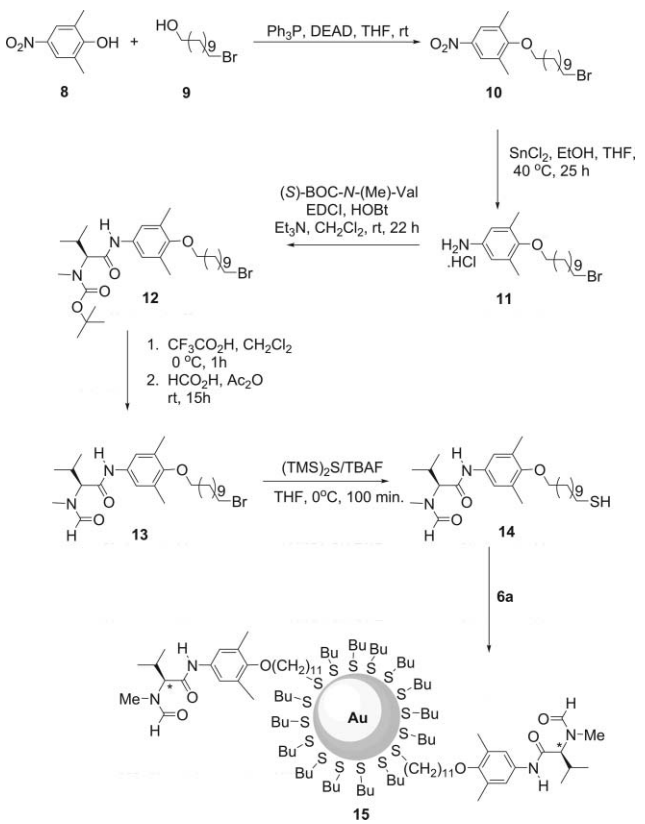
[a] The reaction was carried out at 0.2 mmol scale with 2.0 equiv of Cl_3SiH in toluene at 20 °C overnight unless stated otherwise. [b] Isolated yield. [c] Determined by chiral HPLC. [d] The absolute configuration of the product was (*S*)-(−)-**2** as shown by the optical rotation and by HPLC *via* comparison with an authentic sample. [e] 10 mol%. [f] 5 mol%. [g] Chloroform was used as solvent instead of toluene. [h] 100 mg. [i] 79 mg. [j] 20 mol%. [k] 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 $HAuCl_4 \cdot 3H_2O$ *via* reduction with $NaBH_4$, 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.[11,12] The resulting ~2 nm nanoparticles **6a** and **6b** were then isolated by precipitation with absolute ethanol, followed by filtration.[11] The subsequent place-exchange reactions between the latter nanoparticles and the lipoic ester **5** afforded the catalyst-functionalised nanoparticles **7a** and **7b**, respectively, which were isolated again by precipitation with ethanol. The ^{1}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^{-1}). ^{1}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*$_3$) of the butyl and octyl chains (in **7a** and **7b**), we estimate the average ratio to be approximately 1 : ≥20 (CONH : CH_3), suggesting a low loading of the catalyst. Nanoparticles **7a** and **7b** exhibited good solubility in non-polar solvents (*e.g.*, CH_2Cl_2 and toluene) but proved to be poorly soluble in more polar solvents (*e.g.*, CH_3OH).

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**).[7d,e] 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_4NF in THF at 0 °C for 2 h. The resulting thiol **14** (90%) was immobilized by an exchange reaction with the butanethiol-protected gold nanoparticles **6a** to produce nanoparticles **15**. Following integration of the broad ^{1}H NMR resonances for the formamide protons (CON*H*) and the terminal methyl groups



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

(CH_3) of the butyl chains, we estimate the average ratio to be approximately 1 : 10 ($CONH : CH_3$), 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,[7] was carried out under the conditions previously optimized for the non-supported catalysts **3a**,**b**.[7a–d] Thus, Cl_3SiH (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 $NaHCO_3$ as previously described,[7] to afford amine (*S*)-(−)-**2** (84% ee; Table 1, entry 8). The octanethiol-coated 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 nanoparticles[15] 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 (≤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 enantioselectivty as a function of the substitution pattern in the imine structure for catalysts **3a–d**.[7] 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.[16]

Experimental section

General Methods

Melting points were determined on a Kofler block and are uncorrected. Optical rotations were recorded in $CHCl_3$ at 25 °C unless otherwise indicated, with an error of ≤±0.1. The [α]D values are given in 10^{-1}deg cm^3 g^{-1}. The NMR spectra were recorded as $CDCl_3$ solutions, ^1H at 400 MHz and ^{13}C at 100.6 MHz, with chloroform-*d*1 (δ 7.26, 1H; δ 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**[7e] (200 mg, 0.72 mmol) and 4-(dimethylamino)-pyridine (DMAP, 28 mg, 0.23 mmol) were consecutively added to a solution of (3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI; 344 mg, 1.79 mmol) and (±)-lipoic acid (296 mg, 1.43 mmol) in CH_2Cl_2 (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 × 40 mL), 0.5M HCl (40 mL), saturated $NaHCO_3$ (2 × 40 mL), water (40 mL), and brine (40 mL) and dried over $MgSO_4$, 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_2Cl_2 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_2Cl_2–MeOH, 49 : 1); $[\alpha]_D$ −89.20 (*c* 0.65, $CHCl_3$); ^1H NMR (400 Hz, $CDCl_3$, a mixture of rotamers in *ca.* 4 : 1 ratio; the signals for the minor rotamer are marked with an *) δ 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*); ^{13}C NMR δ 16.49 (CH_3), 18.53 (CH_3), 19.52 (CH_3), 24.81 (CH_2), 25.20 (CH), 28.85 (CH_2), 31.60 (CH_3), 33.74 (CH_2), 34.59 (CH_2), 38.42 (CH_2), 40.21 (CH_2), 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) ν 3434, 2926, 1753, 1656, 1556, 1485, 1411, 1372, 1187 1124 cm^{-1}; MS (FAB) *m/z* (%) 467 ([MH]$^{\bullet+}$, 14), 278 (22), 189 (16), 1432 (94), 115 (100), 88 (30), 79 (23); HRMS (FAB) 467.2043 ($C_{23}H_{35}N_2O_4S_2$ requires 467.2038).

Synthesis of gold nanoparticles 6a. A solution of hydrogen tetrachloroaurate hydrate $HAuCl_4 \cdot 3H_2O$ (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 $NaBH_4$ (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): ^{1}H NMR (400 Hz, $CDCl_3$) 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 $HAuCl_4 \cdot 3H_2O$ (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. ^{1}H NMR (400 Hz, $CDCl_3$) δ 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: ^{1}H NMR (400 Hz, $CDCl_3$) δ 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) ν 3446, 2954, 2923, 2869, 1757, 1655, 1560, 1456, 1416, 1375, 1261, 1210, 1094 cm^{-1}. 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_2Cl_2–Me_2CO 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: ^{1}H NMR (400 Hz, $CDCl_3$) δ 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) ν 3440, 2951, 2927, 2869, 1760, 1649, 1560, 1460, 1418, 1375, 1266, 1211, 1094 cm^{-1}.

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_f = 0.42 (petroleum ether–CH_2Cl_2, 4 : 1); ^{1}H NMR (400 Hz, $CDCl_3$) δ 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); ^{13}C NMR δ 16.60 (CH_3), 26.00 (CH_2), 28.13 (CH_2), 28.73 (CH_2), 29.38 (CH_2), 29.43 (CH_2), 29.50 (CH_2), 30.32 (CH_2), 32.79 (CH_2), 34.06 (CH_2), 72.75 (CH_2), 124.19 (CH), 132.32 (C), 143.28 (C), 161.66 (C); MS (EI) *m/z* (%) 401 and 399 (M$^{\bullet+}$, 14), 167 (100), 137 (33), 97 (30), 55 (62); HRMS (EI) 399.1415 ($C_{19}H_{30}BrNO_3$ 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 $NaHCO_3$ (80 mL) was added to reach pH 10. The product was extracted with ether (3 × 150 mL) and the organic phase was dried over $MgSO_4$. 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 × 100 mL). Drying in the air afforded the aniline salt **11** (1.05 g, 52%) as a white powder: mp 188–192 °C (dec); ^{1}H NMR (400 Hz, $CDCl_3$) 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); ^{13}C NMR δ 16.26 (CH_3), 26.08 (CH_2), 28.16 (CH_2), 28.74 (CH_2), 29.40 (CH_2), 29.45 (CH_2), 29.48 (CH_2), 29.51 (CH_2), 30.31 (CH_2), 32.83 (CH_2), 34.02 (CH_2), 72.56 (CH_2), 123.12 (CH), 124.50 (C), 133.23 (C), 156.55 (C); MS (CI) *m/z* 372 and 370 (M$^+$, 100), 369 (22), 290 (13), 138 (78), 137 (21), 69 (48); HRMS (CI) 370.1752 ($C_{19}H_{33}BrNO_3$ requires 370.1746).

Synthesis of 12. The aniline hydrochloride **11** (1.00 g, 2.46 mmol) was added to a stirred mixture of CH_2Cl_2 (50 mL), H_2O (10 mL), and sat. $NaHCO_3$ (10 mL) and the stirring was continued for 10 min. The organic phase was separated, dried over $MgSO_4$, and concentrated to ~10 mL by evaporation, to furnish solution A. To a stirred solution of (*S*)–BOC-*N*-methyl-valine (0.69 g, 2.98 mmol) in CH_2Cl_2 (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 × 55 mL), saturated $NaHCO_3$ (2 × 55 mL), and brine (55 mL) and dried over $MgSO_4$ 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, $CHCl_3$); ^{1}H NMR (400 Hz, $CDCl_3$) δ 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); ^{13}C NMR δ 16.36 (CH_3), 18.55 (CH_3), 19.84 (CH_3), 25.88 (CH), 26.12 (CH_2), 28.14 (CH_2), 28.34 (CH_3), 28.73 (CH_2), 29.38 (CH_2), 29.45 (CH_2), 29.52 (CH_2), 30.34 (CH_2), 32.80 (CH_2), 34.08 (CH_2), 65.85 (CH), 72.45 (CH_2), 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 ($M^{\bullet+}$, 8), 368 (37), 157 (52), 129 (95), 86 (100), 57 (48); HRMS (EI) 582.3038 ($C_{30}H_{51}BrN_2O_4$ 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_2Cl_2 (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 × 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_2Cl_2 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_2Cl_2–MeOH, 70 : 1); $[\alpha]_D$ −78.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 Hz, $CDCl_3$ a mixture of rotamers in *ca.* 4 : 1 ratio; the signals for the minor rotamer are marked with an *) δ 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*); ^{13}C NMR δ 16.32 (CH_3), 18.56 (CH_3), 19.48 (CH_3), 25.32 (CH), 26.09 (CH_2), 28.11 (CH_2), 28.70 (CH_2), 29.35 (CH_2), 29.42 (CH_2), 29.49 (CH_2), 30.31 (CH_2), 31.53 (CH_3), 32.77 (CH_2), 34.05 (CH_2), 62.86 (CH), 72.40 (CH_2), 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 ($M^{\bullet+}$, 22), 369 (36), 114 (100), 86 (25), 55 (12); HRMS (EI) 510.2455 ($C_{26}H_{43}BrN_2O_3$ 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_4Cl (35 mL) was added and the stirring was continued for an additional 5 min. The mixture was then extracted with CH_2Cl_2 (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_2Cl_2 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_2Cl_2–MeOH, 70 : 1); $[\alpha]_D$ −77.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 Hz, $CDCl_3$; a mixture of rotamers in *ca.* 4 : 1 ratio; the signals for the minor rotamer are marked with an *) δ 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, 0.11H), 3.69 (t, $J = 6.6$ Hz, 1.90H), 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*); ^{13}C NMR δ 16.35 (CH_3), 18.53 (CH_3), 19.56 (CH_3), 24.66 (CH_2), 25.14 (CH), 26.13 (CH_2), 28.36 (CH_2), 29.05 (CH_2), 29.47 (CH_2), 29.50 (CH_2), 29.52 (CH_2), 29.55 (CH_2), 30.35 (CH_2), 31.55 (CH_3), 34.04 (CH_2), 63.10 (CH), 72.48 (CH_2), 120.25 (CH), 131.54 (C), 132.84 (C), 152.77 (C), 163.94 (CO), 166.91 (CO); IR (KBr) ν 3433, 2962, 2925, 2853, 1656, 1612, 1552, 1485, 1409, 1261, 1215, 1069, 1024, 802; MS (EI) *m*/*z* (%) 464 ($M^{\bullet+}$, 48), 323 (83), 142 (58), 114 (100), 86 (25), 55 (12); HRMS (EI) 464.3076 ($C_{26}H_{44}N_2O_3S$ requires 464.3073).

Synthesis of gold nanoparticles 15. Thiol (–)-**14** (6.7 mL of a ~60 mg/mL solution in CH_2Cl_2, ~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: ^{1}H NMR (400 Hz, $CDCl_3$) 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) ν 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 μL) 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 $NaHCO_3$ (10 mL). The aqueous phase was additionally extracted with chloroform (30 mL) and the combined organic extracts were dried over $MgSO_4$ 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.

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