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Soluble Polymer-Supported Organocatalysts: Asymmetric Reduction of Imines with Trichlorosilane Catalyzed by an Amino Acid Derived Formamide Anchored to a Soluble Polymer

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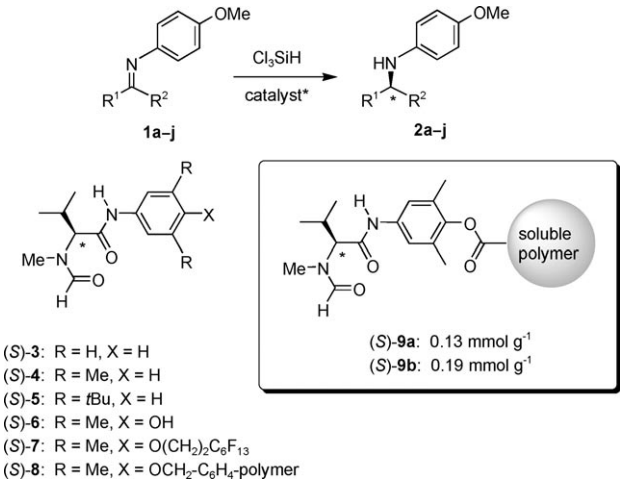
Dedicated to Professor Tomáš Hudlický on the occasion of his 60th birthday

In the development of an efficient catalytic process, facile separation of the product from the catalyst is one of the key technological elements. In organocatalysis, where both the product and the catalyst are small organic molecules, chromatography often represents the only option. Here, immobilization of the catalyst may provide an elegant solution to the problem.[1]

Asymmetric reduction of prochiral imines **1** is one of the key reactions in synthetic organic chemistry (Scheme 1).[2] Its organocatalytic version[3] is characterized by two fundamentally different approaches: 1) hydrosilylation with Cl_3SiH, catalyzed by chiral Lewis-bases,[4–9] and 2) reduction with Hantzsch dihydropyridine, catalyzed by chiral Brønsted acids.[10]

In the past few years, we have developed the amino acid-based formamides **3**–**5** (Scheme 1) as chiral Lewis-basic organocatalysts for the reduction of imines **1** ($\leq$97% *ee*; 1–5 mol% loading).[4] The practicality was then improved by tagging the catalyst to a fluorous ponytail (**7**)[5] and by its anchoring to a polymer support (**8**).[6,11] Catalyst **7**, working in a homogeneous solution, mirrored the enantioselectivities of **3**–**5** and the products were separated from the catalyst by filtration through a pad of fluorous silica.[5] The solid-supported catalysts **8** were separated even more easily via mechanical filtration.[6] However, the latter reactions were heterogeneous and that had a negative impact on the enantioselectivities, which reached $\leq$82% *ee*, that is, about 10–15% *ee* below those of the homogeneous system.[6]



(*S*)-**3**: R = H, X = H
(*S*)-**4**: R = Me, X = H
(*S*)-**5**: R = *t*Bu, X = H
(*S*)-**6**: R = Me, X = OH
(*S*)-**7**: R = Me, X = $O(CH_2)_2C_6F_{13}$
(*S*)-**8**: R = Me, X = OCH_2-C_6H_4-polymer

Scheme 1. Catalysts for asymmetric reduction of imines; for **a**–**j**, see Table 1.

We reasoned that anchoring the catalyst to a soluble polymeric support might serve as a remedy to the problems associated with the heterogeneous systems. Recovery and recycling of the soluble supported catalysts would then rely on the switch of solubility induced either by changing the solvent polarity (e.g., for PEG support) or the temperature (for thermomorphic support).[1b,f,g] Traditionally, PEG polymers are precipitated by non-polar solvents, which may also lead to co-precipitation of the polar products, thereby affecting the overall efficiency of the process. Herein, we report

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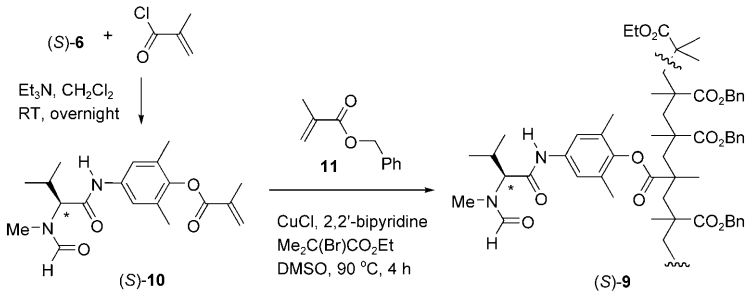
on development of a novel polymeric platform for catalyst immobilization, featuring inverted solubility pattern: the catalyst soluble in a non-polar and insoluble in a polar medium.

In our previous work, the solid-supported catalysts **8** were prepared by constructing an ether link between the phenolic group in **6** and a suitable group on the polymer, namely P-C_6H_4-CH_2Cl or P-C_6H_4-CH_2OH, using the Williamson and Mitsunobu conditions, respectively.[6] In the present study, we have adopted a different strategy, which aimed at the preparation of the anchored catalyst by copolymerization of methacrylates **10** and **11** (Scheme 2).



Scheme 2. Synthesis of the supported catalyst.

Treatment of the phenolic derivative **6**[6] with methacryloyl chloride afforded the monomer **10** (83%), which was copolymerized with benzyl methacrylate **11** using atom transfer radical polymerization (ATRP) methodology,[12] namely by heating a mixture of **10** and **11** (1:99 to 10:90) in the presence of CuCl (1 mol% with respect to **11**), 2,2′-bipyridine (3 mol%), and ethyl 2-bromo-isobutyrate (1 mol%) in DMSO at 90°C for 4 h. The resulting copolymer **9** was precipitated by pouring the cooled mixture into an excess of MeOH.

In the initial polymerizations, the amount of **10** in the mixture was varied in the range of 1, 5, and 10 mol% with respect to **11**, whereas the amount of CuCl was kept constant (1 mol%). Co-polymerization of **10** (1 mol%) with **11** produced **9a** in 46% yield, which contained 0.13 mmol g^{-1} of the active moiety, as revealed by elemental analysis. However, when the amount of **10** in the initial mixture was increased to 5 mol%, the polymerization afforded the copolymer in only 9% yield and a further decrease (to 4%) was observed with 10 mol% of **10**. Clearly, **10** had a negative effect on the activity of the catalyst. Therefore, in the subsequent experiments, the amount of CuCl was increased to match that of **10**, which proved to have a beneficial effect. In a scaled-up, optimized experiment, carried out with a 5:95 mixture of **10** and **11** in the presence of CuCl (5 mol%), 2,2′-bipyridine (15 mol%), and ethyl 2-bromo-isobutyrate (1 mol%), copolymer **9b** (0.19 mmol g^{-1}) was obtained in 48% yield. Further increase in the content of **10** in the mixture did not lead to any significant increase in its incorporation, showing that the copolymerization reached its saturation point. The average molecular weight (M_n) of copolymers **9a** and **9b** was ~7800 and 6000 g mol^{-1}, respectively, as revealed by gel permeation chromatography (GPC). Their poly-dispersity index (PDI) varied from 1.35 (**9a**) to 1.18 (**9b**), indicating a fairly narrow distribution of molecular masses for the polymers.

The reactivity of our immobilized catalysts in the reduction of imines was investigated by using the same reaction conditions as those employed for **3**–**7** (1 equiv of imine, 2 equiv of Cl_3SiH, and catalyst **9** at room temperature). Reduction of imine **1a** in toluene (an optimized solvent for homogeneous conditions[4,5]), catalyzed by **9a**, afforded amine (*S*)-**2a** in 85% *ee* (Table 1, entry 3). Catalyst **9b**, with the higher content of the active component, turned out to be an optimum in terms of its preparation and performance, since high conversions and enantioselectivities were attained (86–88% *ee*; entries 4–6) even with gradually decreasing catalyst loading (from 7 to 1 mol%). The practicality of the protocol was demonstrated by more than 25-fold scale-up experiment (entry 7). Significantly, enantioselectivity of the supported catalyst **9b** remained at the same level as that observed for its monomeric congeners **4** and **6** (entries 1 and 2). When the reaction was complete, as indicated by TLC, the reaction mixture (in toluene) was poured into an excess of a vigorously stirred MeOH, resulting in the precipitation of $\geq$95% of the catalyst, which was then filtered off.[13]

The scope of the homogeneous catalysts **3**–**5** has been shown by us to be quite broad, spanning from a range of aromatic to heteroaromatic and to some aliphatic substrates, while tolerating various functionalities.[4,5] Therefore, only a small set of imines, namely **1b**–**j**, was explored in the present study (Table 1). In agreement with the previous observations, high enantioselectivities were attained for imines derived from aromatic ketones **1b**–**d** with both electron-withdrawing and electron-donating groups (entries 8–10). Imine **1e** with the β-thiophene nucleus (entry 11) exhibited lower enantioselectivity, consistent with the general behavior of aromatic heterocycles.[4,5] By contrast, the presence of heteroatoms in the alkyl part (**1f**,**g**) did not have any adverse effect (entries 12 and 13), reaching the maximum of 91% *ee*. The cyclopropyl and cyclobutyl derivatives **1h**,**i** still exhibited acceptable enantioselectivities (entries 14 and 15), whereas a larger decrease was observed for the bulkier cyclohexyl derivative **1j** (entry 16).

The solid-supported, insoluble catalysts **8** retained their activity when re-used;[6] in fact, we have observed an increase in selectivity in the second run by ~5% *ee*, which was maintained in the subsequent runs; this behavior was attributed to a "conditioning" effect.[6] By contrast, the soluble catalyst **9b** (Table 2) exhibited the same activity in runs 1–5; hence, no "conditioning" was taking place here, which is apparently confined to the heterogeneous protocol.

In conclusion, a new soluble polymeric platform for immobilization of organocatalysts has been developed, which may, a priori, be applied to a wide variety of other catalytic systems. The asymmetric reduction of imines **1a**–**j** with

Table 1. Reduction of ketimines **1a–j** with trichlorosilane, catalyzed by the valine-derived *N*-methyl formamides (*S*)-**9a/b**.[a]

Entry	Catalyst (mol%)	Imine	R^1	R^2	Catalyst recovery [%]	Yield [%][b]	*ee*[d] **2**[c] [%]
1	**4** (10)[e]	**1a**	Ph	Me	–	85	91
2	**6** (10)[e]	**1a**	Ph	Me	–	94	86
3	**9a** (20)	**1a**	Ph	Me	99	90	85
4	**9b** (7)	**1a**	Ph	Me	99	90	86
5	**9b** (3)	**1a**	Ph	Me	98	90	86
6	**9b** (1)	**1a**	Ph	Me	99	90	88
7	**9b** (1)[f]	**1a**	Ph	Me	98	90	88
8	**9b** (7)	**1b**	2-naphthyl	Me	90	88	86
9	**9b** (7)	**1c**	4-CF_3-C_6H_4	Me	92	75	86
10	**9b** (7)	**1d**	4-MeO-C_6H_4	Me	85	87	82
11	**9b** (7)	**1e**	thiophen-2-yl	Me	96	78	65
12	**9b** (7)	**1f**	Ph	CH_2Cl	94	70	91
13	**9b** (7)	**1g**	Ph	CH_2CO_2Et	99	77	81
14	**9b** (7)	**1h**	Ph	*c*-Pr	99	71	73
15	**9b** (7)	**1i**	Ph	*c*-Bu	99	81	75
16	**9b** (7)	**1j**	Ph	*c*-Hex	98	85	55

[a] The reaction was carried out at 0.2 mmol scale with 2.0 equiv of Cl_3SiH at 25 °C for 16 h. [b] Isolated yield. [c] The absolute configuration was established from the optical rotation by comparison with the literature data (see Experimental Section) and by HPLC via comparison with authentic samples; the resulting amines **2a–j** were *S* configured. [d] Determined by chiral HPLC. [e] Ref. [6]. [f] The reaction was carried out at 5 mmol scale.

Table 2. Asymmetric reduction of imine **1a** with Cl_3SiH catalyzed by the reused **9b** (20 mol%) in toluene.[a]

Run	Catalyst recovery [%]	Yield [%][b]	*ee*[c] (*S*)-**2a** [%]
1	99	86	86
2	95	87	86
3	94	90	84
4	93	90	86
5	95	90	86

[a] For the conditions, see Table 1. [b] Isolated yield. [c] Determined by chiral HPLC.

Cl_3SiH, promoted by this new catalyst **9b**, proceeds readily at room temperature. This protocol simplifies the catalyst recovery and produces chiral amines **2a–j** in high yields and with good enantioselectivity ($\leq$91% *ee*) at 1–7 mol% catalyst loading, which is unprecedented in the realm of supported organocatalysts. The catalyst can be recovered almost quantitatively and re-used at least five times without loss of activity, which demonstrates its suitability for multiple and parallel use. The main advantage of the present system **9b** over our previous solid-supported catalysts **8** can be seen in the homogeneous conditions that led to the increase of enantioselectivity (by $\leq$10% *ee*). Furthermore, **9b** with its polymethacrylate backbone, is superior to other soluble polymeric systems, based, for example, on ethylene glycol,[14] in that it works in a non-polar solvent (toluene), can be easily precipitated by a polar solvent (methanol) and reused, and allows a higher concentration of the catalytic moiety in the polymer. The narrow range of the molecular weight of **9b** undoubtedly contributes to the overall behavior of this catalyst.

Experimental Section

Catalyst 9b: Copper(I) chloride (80 mg, 0.82 mmol), 2,2′-bipyridine (384 mg, 2.46 mmol), benzyl methacrylate **11** (2.70 mL, 16 mmol), and ethyl 2-bromoisobutyrate (24 μL, 0.16 mmol) were successively added to a solution of **10** (282 mg, 0.82 mmol) in DMSO (7 mL) and the mixture was stirred under nitrogen for 5 min. This heterogeneous mixture was then degassed by freeze–pump–thaw and stirred under nitrogen at 90 °C for 3 h. The mixture was then cooled to room temperature and poured into a vigorously stirred MeOH (1 L). The precipitated polymer was isolated by filtration, washed with MeOH (300 mL), dissolved in DMSO (7 mL), and the solution was poured into a vigorously stirred MeOH (1000 mL) again. The precipitate was isolated by filtration, washed with MeOH (300 mL), and dried under high vacuum to afford a crude product as a greenish powder (3.19 g). The latter powder was dissolved in CH_2Cl_2 (100 mL) and vigorously stirred with deionized water (100 mL) for 30 min. The organic layer was separated, dried, and evaporated and the residue was dissolved in $CHCl_3$ (7 mL) and the solution was poured into a vigorously stirred MeOH (1 L). The precipitated polymer was isolated by filtration, washed with MeOH (300 mL), and dried under high vacuum to furnish **9b** (2.48 g, 48%) as a white powder. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 0.72 (brs), 0.91 (brs), 1.07 (brs), 1.18 (brm), 1.31 (brm), 1.60 (brm), 1.78 (brs), 1.88–2.04 (brsignal), 2.48 (brm), 2.98 (brs), 3.44 (brm), 4.00 (brm), 4.35 (brd), 4.88 (brd), 5.09 (brm), 5.15 (brm), 7.08 (brm), 7.28 (brs), 7.47 (brm), 8.00 (brs), 8.14 ppm (brs); IR (KBr): ν = 3437, 3064, 3032, 2959, 1728, 1487, 1482, 1455, 1388, 1367, 1262, 1142, 751, 697 cm^{-1}; GPC: M_n = 6000 g mol^{-1}, M_w = 7134 g mol^{-1}, PDI = 1.19; elemental analysis (%) found: C 73.78, H 6.88, N 0.53, this corresponds to 0.19 mmol g^{-1} loading.

Procedure for a large scale asymmetric reduction of 1a catalyzed by 9b: Cl_3SiH (1.15 mL, 10 mmol) was added to a solution of imine **1a** (1.15 g, 5.10 mmol) and the supported catalyst **9b** (253 mg; containing 0.62% of N, which corresponds to 1 mol% loading) in toluene (46 mL) at 0 °C and the mixture was stirred at room temperature overnight. The mixture was then poured into a rapidly stirred MeOH (900 mL), and the precipitated polymer was separated by filtration, washed with MeOH (200 mL), and dried in a vacuum to afford the regenerated catalyst **9b** (249 mg, 98%). The methanolic filtrate, containing the amine and inorganic impurities, was evaporated and the residue was dissolved in CH_2Cl_2 (200 mL) and the resulting solution was washed with aqueous saturated $NaHCO_3$ (100 mL). The aqueous phase was extracted with CH_2Cl_2 (200 mL) and the combined organic solutions were dried over $MgSO_4$. Evaporation of the solvent furnished amine **2a** in ~95% purity as a brownish oil (1.05 g, 90%, 88% *ee*).

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