Solid-Phase Synthesis of Homogeneous Ruthenium Catalysts on Silica for the Continuous Asymmetric Transfer Hydrogenation Reaction

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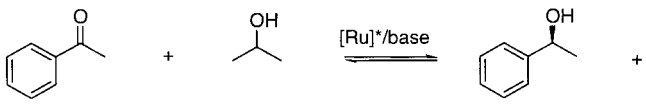
Abstract: The solid-phase synthesis of new asymmetric transfer hydrogenation catalysts as well as the use of these silica supported systems in batch and flow reactors is reported. The ruthenium complex of NH-benzyl-(1*R*,2*S*)-(−)-norephedrine covalently tethered to silica showed a high activity and enantioselectivity in the reduction of acetophenone. In three consecutive batchwise catalytic runs, we obtained *ee* values of 88%. In a continuous flow reactor, a very constant catalytic activity was observed; no catalyst deactivation occurred over a period of one week. This has been ascribed to successful site isolation. Using optimized conditions in this flow reactor, the *ee* was as high as 90% at 95% conversion. The supported catalysts generally show the same trend in catalyst performance as in solution. The viability of our approach was further shown in one example, the ruthenium(II) complex of (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol, for which an enantiomeric excess of 58% was observed, which is nearly three times higher than its homogeneous analogue.

Keywords: asymmetric catalysis · hydrogen transfer · immobilization · ruthenium · solid-phase synthesis

Introduction

Chiral alcohols form an important class of intermediates for the pharmaceutical, agrochemical, flavor, and fragrance industry. The enantioselective synthesis of chiral secondary alcohols by catalytic reduction of the corresponding ketone is therefore an important transformation in organic synthesis.[1] One of the most attractive methods for this reaction is asymmetric transfer hydrogenation since it can give a high product yield with high enantiomeric excess at relatively mild conditions [Eq. (1)].



(1)

Much effort has been devoted to the development of new chiral catalysts and rapid progress has been made in this area.[2] Insight into the mechanism is increasing rapidly and the rational design of catalysts has led to several efficient systems.[3] The best catalysts reported so far are ruthenium(II) complexes with chiral diamine and amino alcohol ligands.[4] In our previous studies, the ruthenium complex of NH-benzyl-(1*R*,2*S*)-(−)-norephedrine proved to be an excellent catalyst for the reduction of acetophenone, showing up to 95% *ee* at high conversions.[5]

The utilization of *immobilized* catalysts in the asymmetric transfer hydrogenation reaction can provide a significant improvement over the homogeneous process. It enables the long-term use of expensive catalyst and provides a clean and straightforward separation of the product. More importantly, the transfer hydrogenation reaction in isopropanol benefits from a continuous process as it requires a low substrate concentration to obtain high enantioselectivity. Hence, the space-time-yield can be increased by using a continuous flow reactor. Examples of immobilized asymmetric transfer hydrogenation catalysts, however, are still rare.[6] A few interesting approaches were recently reported that concern the anchoring of transfer hydrogenation catalysts onto *organic* supports.[7] Although high *ee* values were obtained, the applicability of these immobilized systems is limited due to swelling of the support which results in low activity and poor recyclability. The immobilization onto *inorganic* supports could thus improve the catalyst performance. To the best of our knowledge, only two examples have been reported in literature to date concerning a silica-immobilized asymmetric

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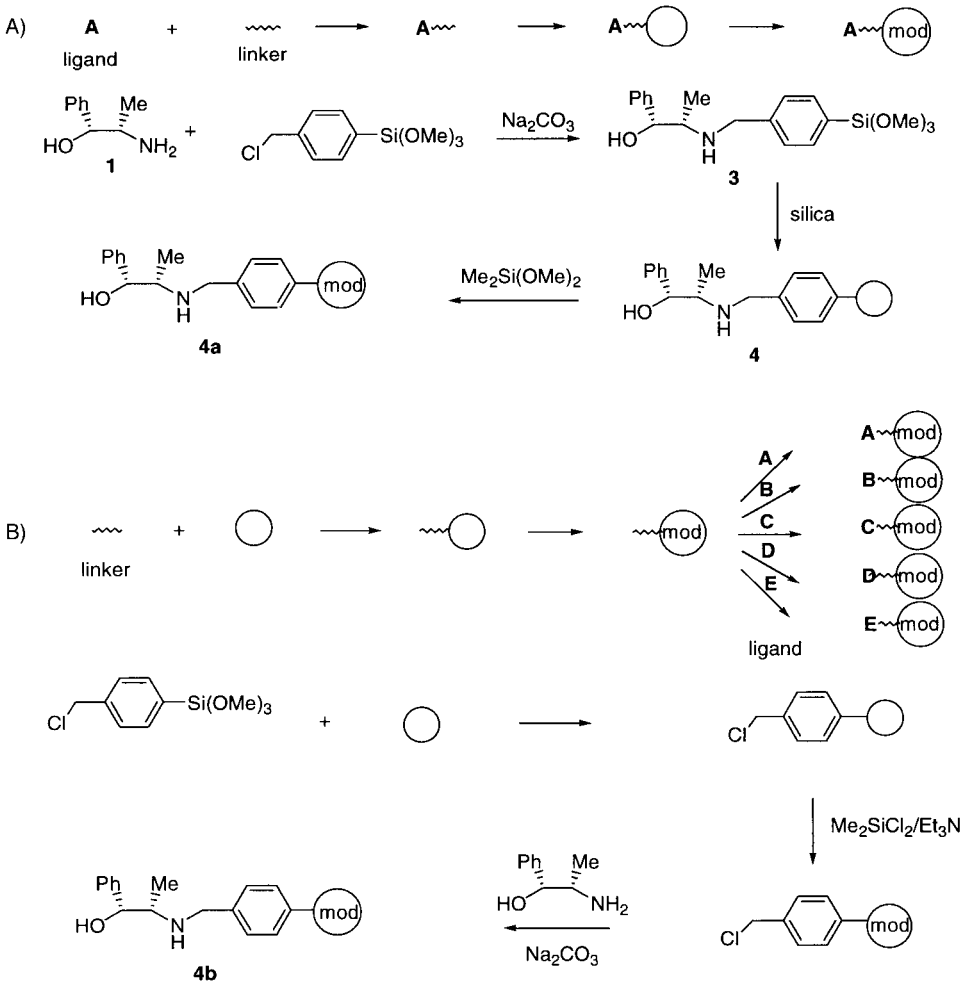
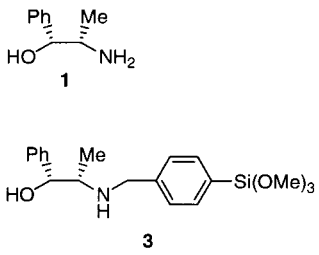
transfer hydrogenation catalyst. Lemaire et al. reported a catalyst "noncovalently" linked to the silica support that showed a good initial performance in a continuous flow reactor.[8] This system suffered from deactivation of the catalyst due to catalyst destruction or leaching of catalytically active material. A covalently anchored catalyst based on a rhodium complex of gamma-silylated amines was reported by Moreau et al.[9] This system was found to be extremely slow and *ee* values ranged between 25 and 80%. The recovery or recycling of this catalyst was not reported. Herein, we report the synthesis of asymmetric transfer hydrogenation catalysts on silica and the use of these systems in batch and flow reactors. Furthermore, we recognized that one of our synthetic strategies towards immobilized transfer hydrogenation catalysts could be applied expeditiously in the solid-phase synthesis of novel transfer hydrogenation catalysts. This is shown by the synthesis and subsequent testing of a small series of new asymmetric transfer hydrogenation catalysts on silica. We will show that silica is a valuable support for solid-phase synthesis, catalysis and catalyst recycling.

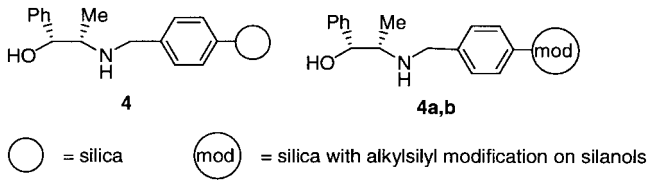


Scheme 1. Synthetic approaches to silica-immobilized amino alcohol ligands. A) Ligand synthesis followed by immobilization. B) Solid-phase synthesis of amino alcohol ligands.

Results and Discussion

Ligand immobilization: The novel ligand NH-3-(trimethoxysilyl)benzyl-(1*R*,2*S*)-norephedrine (**3**) was synthesized by N-alkylation of (1*R*,2*S*)-norephedrine (**1**) by *p*-(chloromethyl)phenyl-trimethoxysilane using Na_2CO_3 as a base (Scheme 1 A). This ligand is the trialkoxy-functionalized analogue of the *N*-benzylated norephedrine ligand **2** that gave high *ee* values in homogeneously catalyzed reactions in our previous studies.[5] Ru(**3**) in solution also gave high *ee* values at a high conversion (vide infra). Ligand **3** was immobilized on silica by refluxing a suspension of silica and **3** in toluene for 18 h, followed by several washes with toluene to obtain **4**. The support was modified by reacting **4** with a large excess of dimethyldimethoxysilane to form **4a**. As a result, the silanol sites of the silica support are transformed into alkylsilane sites.





Alternatively, the solid-phase synthesis route was also investigated (Scheme 1 B). In this method, the silica support was first functionalized with *p*-benzyl chloride sites. In the next step, the silanol sites are modified to alkylsilanes with an excess of dichlorodimethylsilane in the presence of triethylamine. The ligand synthesis of **4b** is then completed by coupling the amino alcohol to the *p*-benzyl chloride sites.

Catalytic experiments were performed with ruthenium amino alcohol complexes freshly prepared in situ using [{$RuCl_2(\eta^6$-*p*-cymene}] as the Ru^{II} precursor.

Catalyst studies: The catalytic performance of the silica-immobilized systems was initially examined in batch experiments using suspensions that contain 400 mg silica loaded with 0.06 mmol NH-3-(trimethoxysilyl)benzyl-(1*R*,2*S*)-norephedrine and 0.006 mmol (*p*-cymene)ruthenium(II) chloride dimer in dry propan-2-ol (10 mL) containing *t*BuOK (0.01 mmol) and acetophenone (1 mmol).[10] The ruthenium-catalyzed asymmetric transfer hydrogenation of acetophenone (Table 1, entry 3) resulted in *ee* values up to 88% at 95% conversion.

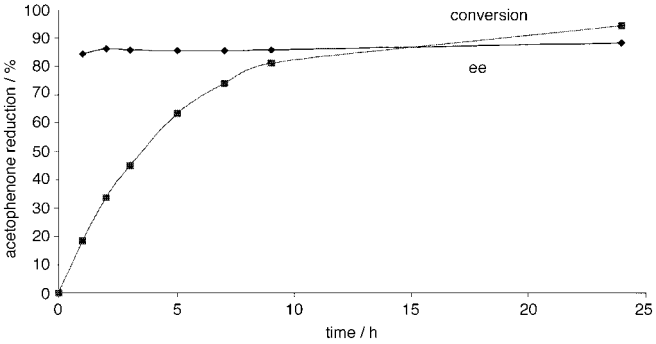


Figure 1. Evolution of the asymmetric transfer hydrogenation of acetophenone catalyzed by Ru(**4**) (for more details, see Experimental Section).

Table 1. Results from the hydrogen transfer reduction of acetophenone in a batch slurry reaction.[a]

Entry	Catalyst {cycle}	Conversion[b] [%]	*ee* alcohol[c] [%]	Ru-leaching[d] [%]
1[e]	Ru(**2**)	88[f]	95	
2	Ru(**3**) homogeneous	81	93	
3	Ru(**4**)	95[g]	88	
4	Ru(silica)	0.2	0	
5	Ru(**1**)/silica	4	91	
6	Ru(**4**) {1}	38	88	6
7	Ru(**4**) {2}	33	88	3
8	Ru(**4**) {3}	27	88	2
9	Ru(**4a**) {1}	25	88	7
10	Ru(**4a**) {2}	27	88	1
11	Ru(**4a**) {3}	20	87	<1
12	Ru(**4b**) {1}	51	85	11
13	Ru(**4b**) {2}	43	86	6
14	Ru(**4b**) {3}	34	92	3

[a] The reaction was carried out with 6×10^{-6} mol [{$RuCl_2$(*p*-cymene)}$_2$] and 400 mg silica, containing 6×10^{-5} mol ligand at room temperature in isopropanol (10 mL) containing acetophenone (0.1M) and *t*BuOK (0.01M). [b] Conversions after 2 h, determined by means of GLC analysis. [c] Determined by means of GLC analysis using a chiral cycloSil-B column. [d] Determined by means of atomic emission spectroscopy, percentage of the total amount of Ru charged. [e] Data taken from ref. [5]. [f] Conversion after 1 h. [g] Conversion after 24 h.

The catalyst is remarkably fast; a conversion of 20% was obtained after 1 h, which is only two to three times slower than the homogeneous analogue under the same conditions. Monitoring the reaction showed that the reaction rate is initially almost independent of the substrate concentration (Figure 1). At higher conversions, the rate becomes dependent of the substrate concentration, which was also observed for the homogeneously catalyzed analogue.[5]

A blank reaction, in the absence of amino alcohol ligand, was performed to investigate the effect of the inorganic support on the catalytic reaction. On mixing [{$RuCl_2(\eta^6$-*p*-cymene)}] and silica without any ligand, the Ru^{II} precursor adsorbs on the silica, which was concluded from the color change of the silica from white to orange. The reactivity of these Ru species, however, is negligible (Table 1, entry 4). The influence of acidic silanol sites of the support on the catalysis was further investigated by comparing the result of Ru(**4**) with that of Ru(**4a**). It was found that these sites do not influence the stereoselectivity of the catalytic reaction (Table 1, entries 6 and 9).[11] This again shows that the reaction is not catalyzed by unligated Ru^{II} species that are adsorbed or ionically bonded to the silica. The catalytic activity was found to be somewhat lower for Ru(**4a**) than for Ru(**4**). We ascribe this to the partial poisoning of the immobilized amino alcohol sites during the premodification procedure.[12] Using alternatively prepared Ru(**4b**), this is effectively circumvented since the amino alcohol ligand is introduced after the modification procedure. We did indeed find that the activity of Ru(**4b**) is higher than that of Ru(**4a**) (Table 1, entries 9 and 12). Conversion after two hours increases from 25% for Ru(**4a**) to 51% for Ru(**4b**). More importantly, Ru(**4b**) was also more active than the catalyst anchored on unmodified silica Ru(**4**). The results indicate that nonmodified silica does affect the catalyst by adsorbing part of the Ru^{II}, hence the formation of catalytically active sites is disturbed. This is effectively suppressed by premodification of the silica with alkylsilane groups by method B (see Scheme 1B).

To show the importance of the benzyl chloride linker in tethering the amino alcohol to the surface, a catalytic experiment was performed by using a mixture of **1**, [{$RuCl_2(\eta^6$-*p*-cymene}], and silica. After thorough washing of the reaction mixture, it showed poor catalytic activity (Table 1, entry 5). It was concluded from this experiment that immobilization is not effective without benzyl chloride linker.[8, 13]

Catalyst recovery: Recovery of the catalyst was investigated by performing subsequent batchwise experiments (Table 1). In three consecutive catalytic runs, the enantioselectivity remained the same (88%) or was even increased (from 85 to 92%). Atomic emission spectroscopy studies showed that ruthenium leached from the catalyst system more in the first catalytic runs (5 to 10%) than in subsequent runs (1 or 2%).

The catalyst showed a very constant, steady performance within a catalytic run up to high conversions (Figure 1). A small decrease in catalyst activity was found in successive runs. This is probably due to the slow decomposition of catalyst caused by the recycling routine, since color changes (from purple-red to orange-yellow) were observed upon addition of a fresh batch of reaction mixture. This can also account for the observed ruthenium leaching.[14]

The performance of Ru(**4b**) in a continuous flow reactor was investigated in order to obtain a more robust system for

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the asymmetric reduction of ketones with an immediate and straightforward separation of the product from the catalyst. For this reason, a small column equipped with a glass-filter was charged with freshly prepared Ru(**4b**) (1 g catalyst that contains 10–20 mg ruthenium precursor). A homogeneous isopropanol solution containing 0.01 M potassium *tert*-butoxide (*t*BuOK) and 0.1 M acetophenone was allowed to pass through the catalyst bed. The catalyst performance was measured at flow rates in the range of 120–1400 $\mu L\,h^{-1}$ (Figure 2 and Table 2).

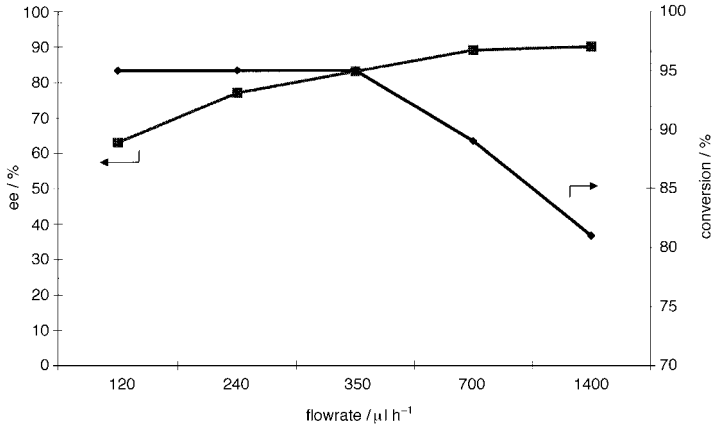


Figure 2. Dependency of *ee* and conversion on the flow rate in a continuous flow reactor for the hydrogen transfer reduction of acetophenone (see Experimental Section).

Table 2. Results from the hydrogen transfer reduction of acetophenone in a flow reactor[a]

Entry	Flow rate [$\mu L\,h^{-1}$]	Conversion[b] [%]	*ee* alcohol[c] [%]	Ru-leaching[d] [%]
1	120	95	63	n.d.
2	240	95	77	n.d.
3	350	95	83	n.d.
4	700	90	89	< 1
5	1400	81	90	< 1
6[e]	1400	95	89	< 1
7[f]	1400	95	89	< 1
8[g]	**1400**	**95**	**90**	< **1**
9[h]	1400	53	88	< 1
10[i]	1400	29	88	< 1

[a] The reactions were carried out at room temperature using silica (1 g), containing ~0.35 mmol ligand and [{$RuCl_2$(*p*-cymene)}$_2$] (0.0143 mmol) and an eluent of isopropanol, containing *t*BuOK (0.01 M) and acetophenone (0.1 M). [b] Conversions are average numbers of 2–11 h continuous product stream, determined every 30 or 60 min by means of GLC analysis. [c] Average numbers of 2–11 h stabilized product stream determined by means of GLC analysis using a chiral cycloSil-B column. [d] Determined by means of atomic emission spectroscopy, percentage of the total amount of Ru per h. n.d. = not determined. [e] [{$RuCl_2$(*p*-cymene)}$_2$] charging = 0.0324 mmol. [f] As entry 6, but c[*t*BuOK] = 0.005 M. [g] As entry 6, but in the absence of *t*BuOK. [h] As entry 8, but [acetophenone] = 0.4 M. [i] As entry 8, but [acetophenone] = 0.8 M.

As expected, catalyst performance is strongly dependent on the flow rate. At a flow rate of 120 $\mu L\,h^{-1}$, the observed *ee* of the product is 63% at 95% conversion, whereas at flow rates higher than 700 $\mu L\,h^{-1}$, the product is formed in 89% *ee*. At a lower flow rate and hence a longer residence time of the product, equilibration becomes significant. This results in a decreased *ee*, because the reverse reaction is faster for the product formed in enantiomeric excess in the reduction reaction.[15] Under the reaction conditions used, the catalyst performed best at a flow rate of 700 $\mu L\,h^{-1}$ (89% *ee* at 90% conversion).

The influence of the base concentration was found to be small. Lowering the amount of *t*BuOK in the substrate mixture to 0.005 M did not change catalyst performance (Table 2, entry 7). In the complete absence of base, it was found that the catalyst performed optimally, with 90% *ee* at 95% conversion (Table 2, entry 8). The results clearly show, in accordance with Noyori's work on ruthenium diamine catalysts,[16] that the base is required only for the formation of the active transfer hydrogenation complex. This feature is particularly interesting in the use of our continuous flow system since the chiral product is obtained immediately, free from base and catalyst.

The influence of the substrate concentration on *ee* was investigated using acetophenone concentrations ranging from 0.1 to 0.8 M (Table 2, entries 6, 9, and 10). The enantioselectivity remained unchanged in this range (89 ± 1%) and the conversion at an acetophenone concentration of 0.8 M is still 29%. Application of the immobilized catalyst in a continuous set-up resulted in interestingly high space-time-yields. Depending on the acetophenone concentration, the space-time-yield was between 15 (Table 2, entry 8) and 39 $g\,L^{-1}\,h^{-1}$ (Table 2, entry 10), whereas for the homogeneous analogue it was estimated at 5.7 $g\,L^{-1}\,h^{-1}$.[15, 17]

The immobilized ruthenium catalyst applied in the continuous flow system is remarkably stable. In order to study the difference in stability, we performed several experiments to compare the flow system with the homogeneously catalyzed reaction. At an acetophenone concentration of 0.1 M, the homogeneous system Ru(**2**) was deactivated after 95% conversion of the first batch of substrate (Figure 3). In a second experiment at a higher concentration (0.8 M), we observed complete catalyst deactivation at 33% conversion. Catalyst deactivation occurred typically after a reaction time of 20 h.

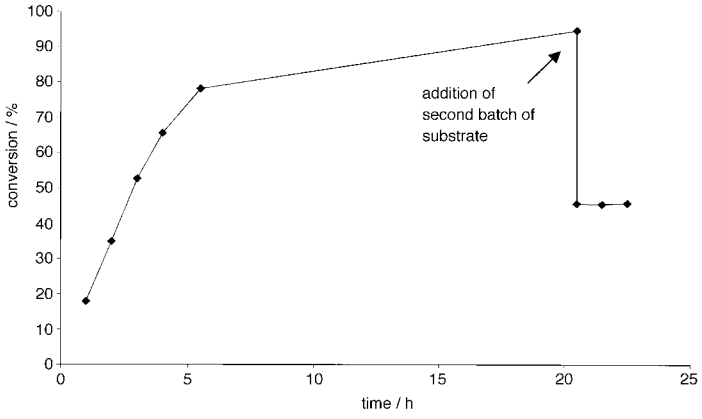


Figure 3. Catalyst performance of Ru(**2**) in the homogeneous hydrogen transfer reduction of two subsequent batches of acetophenone (The reaction was carried out at 20 °C using [{$RuCl_2$(*p*-cymene)}$_2$] (0.01225 mmol), **2** (0.0313 mmol), *t*BuOK (0.075 mmol), and acetophenone (5 mmol) in propan-2-ol (50 mL).

In the continuous flow reactor, the catalyst is surprisingly more stable; both conversion and enantioselectivity remained the same for days (Figure 4). The reaction was monitored at

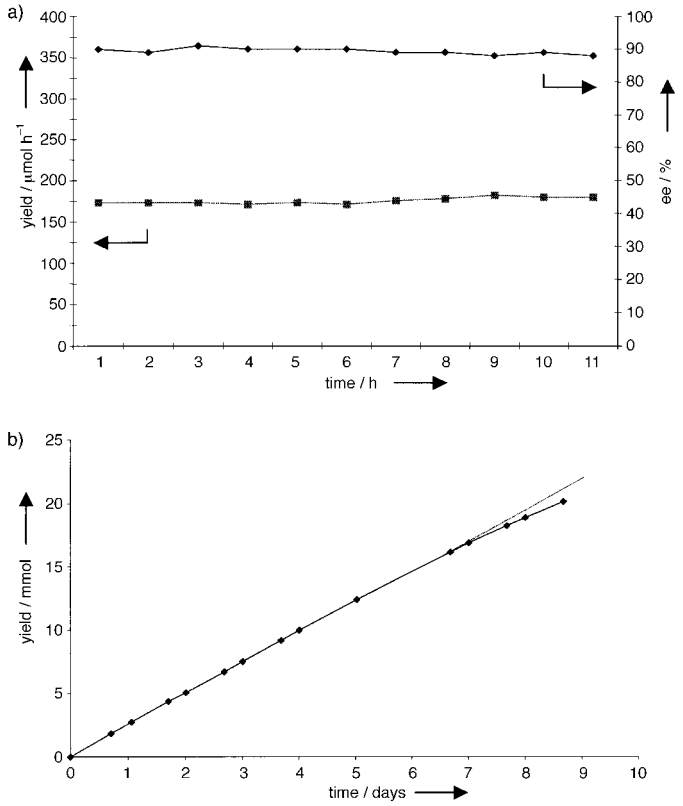
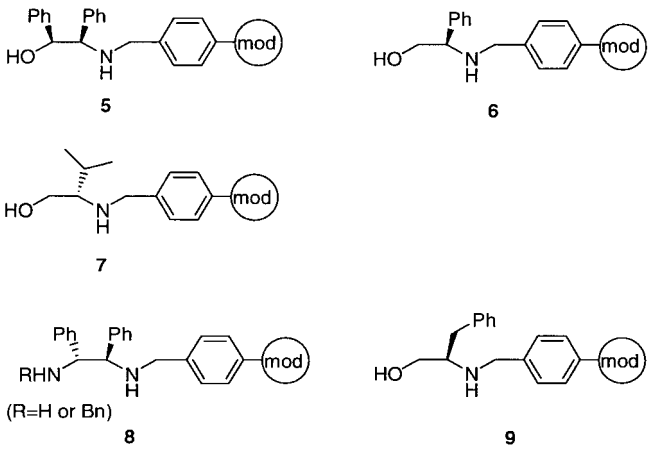


Figure 4. Catalyst performance of Ru(**4b**) in a continuous flow reactor for the hydrogen transfer reduction of acetophenone. a) Detailed monitoring of the product yield per hour and enantiomeric excess of the product flow. b) Study of the long-term catalyst stability (see Experimental Section).

one hour intervals over a period of 11 h and the product yield was found to be stable with a constant enantiomeric excess of 90% (Figure 4a). To study catalyst stability, the reaction was monitored over a longer period (Figure 4b). A small decrease in activity of the catalyst was observed only after one week. Within seven days, no notable changes were observed in both product yield and enantioselectivity of the catalyst; the catalyst was still active after three weeks of continuous use. The chiral product was obtained free from polluting base and ruthenium, which was substantiated by atomic emission spectroscopy (AES) experiments (leaching was less than 1% of the ruthenium charged during 3–11 h of catalysis). The remarkable difference in catalyst stability between Ru(**2**) in solution and the silica-immobilized analogue is suggested to be an effect of *site isolation*.[18–20] Clear evidence, supporting the view that the polymer matrix maintains the isolation of active catalytic sites has been reported in the reduction of olefins using polymer-anchored titanocene catalysts.[21] Also, in the enantioselective hydrogenation using immobilized rhodium and iridium catalysts, site isolation was shown to play an important role:[22] the catalytic sites were prevented from irreversible clustering towards catalytically inactive species. In the enantioselective reduction of 3-oxobutanoate using [RuCl((*S*)-binap)(arene)]Cl (binap = 2,2′bis(diphenylphosphanyl)-1,1′-binaphthyl), the formation of ruthenium trimers was reported to cause complete catalyst deactivation.[23, 24] Since the Ru(**2**)-catalyzed reduction proceeds under comparable conditions, we suggest that ruthenium clustering is also responsible for the observed catalyst deactivation in our case. The difference in catalyst stability between Ru(**2**) and the immobilized analogue is therefore likely to be a results of effective site isolation.

Catalyst screening: Although some excellent catalysts for the transfer hydrogenation of acetophenone have been reported, there is still a challenge to find selective catalysts for functionalized substrates of industrial interest. Solid-phase synthesis and rapid screening techniques[25] are being applied increasingly to speed up the search for novel catalysts.[26] Silica has not been reported as a support for solid phase synthesis of homogeneous catalysts thus far, whereas inorganic materials already have proven to be very useful in libraries of heterogeneous catalysis and in combinatorial material science.[27]

Solid-phase synthesis strategy B (Scheme 1), which proved to be a viable procedure for the preparation of Ru(**4b**), facilitates the development of series of potentially interesting silica immobilized catalysts. This is demonstrated by the straightforward synthesis (and screening) of a small series of immobilized chiral ruthenium complexes **5**–**9**. The immobi-



lized NH-benzylated ligands were derived from five different amino alcohols: (1*R*,2*S*)-norephedrine (**4b**), (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol (**5**), (*R*)-(−)-2-amino-2-phenylethanol (**6**), (*S*)-(+)-2-amino-3-methyl-1-butanol (**7**), (*R*)-(+)-2-amino-3-phenyl-1-propanol (**9**); and a diamine: (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine (**8**). These systems were (simultaneously) prepared in separate vials and applied in combination with ruthenium in the transfer hydrogenation of acetophenone in a batchwise process.

All ruthenium amino alcohol complexes showed good activity and significant enantioselectivity in the transfer-hydrogenation of acetophenone, whereas diamine **8** induced hardly any *ee* (Table 3). Surprisingly, catalyst Ru(**5**), with 58% *ee*, was far more selective than the homogeneous analogue for which an *ee* of 20% had been reported.[5, 28] We suggest that higher catalyst stability due to immobilization can give rise to

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Table 3. Results from the screening of catalysts Ru(**4b**) to Ru(**9**) in the hydrogen transfer reduction of acetophenone in a batch slurry reactor[a]

Entry {cycle}	Catalyst	Conversion[b] [%]	*ee* alcohol[c] [%]	Configuration
1 {1}	Ru(**4b**)	51	85	*R*
2 {2}	Ru(**4b**)	43	86	*R*
3 {1}	Ru(**5**)	9	58	*S*
4 {2}	Ru(**5**)	5	49	*S*
5 {1}	Ru(**6**)	48	27	*R*
6 {2}	Ru(**6**)	30	27	*R*
7 {1}	Ru(**7**)	49	32	*S*
8 {2}	Ru(**7**)	73	29	*S*
9 {1}	Ru(**8**)	8	5	*R*
10 {2}	Ru(**8**)	0	–	–
11 {1}	Ru(**9**)	83	13	*R*
12 {2}	Ru(**9**)	52	19	*R*

[a] The reaction was carried out with $[\{RuCl_2(p\text{-cymene})\}_2]$ (4×10^{-6} mol) and silica (250 mg), containing $\sim 3.5 \times 10^{-5}$ mol ligand at room temperature in isopropanol (10 mL) containing acetophenone (0.1M) and *t*BuOK (0.01M). [b] Conversions after 2 h, determined by means of GLC analysis. [c] Determined by means of GLC analysis using a chiral cycloSil-B column

improved catalyst selectivity, especially for complexes that are intrinsically less stable due to steric restrictions. The other catalysts performed as expected, based on previous detailed studies on substituent effects of homogeneous systems.[3] All Ru^{II} amino alcohol catalysts could be used in a second catalyst run and generally showed approximately the same *ee* values (Table 3) at lower conversions.

Conclusion

We have shown that silica is a valuable support for enantioselective transfer hydrogenation catalysts. Owing to the properties (chemical and physical) of the support, the immobilized catalysts are only slightly less active than the homogeneous analogue. The silica surface was found to influence catalyst efficiency, because it adsorbs inactive ruthenium species. This was effectively suppressed by modifying the silica with alkylsilane groups.

The silica-immobilized ruthenium complex of NH-3-(trimethoxysilyl)benzyl-(1*R*,2*S*)-norephedrine complex showed a good performance in successive runs in the asymmetric transfer hydrogenation of acetophenone. An even better performance was found for this catalyst in a continuous flow reactor. Under optimized conditions, this process converts a constant flow of acetophenone into phenylethanol in 95% yield and 90% *ee*. The performance of this system is virtually unaltered for one week, showing no significant ruthenium leaching. The high stability of this system is in contrast with that of the homogeneous analogue. In this respect, effective site isolation due to the immobilization of the ruthenium catalyst was found to be of great importance.

The flow system is potentially interesting for applications in the synthesis of fine chemicals; the facile and immediate separation of the catalyst from the product, which is obtained free from polluting ruthenium and base, is more convenient than conventional separation methods. It also requires much smaller equipment than the homogeneous analogue since the reaction is concentration-restricted.

The solid-phase synthesis strategy, in which the amino alcohol ligand is introduced in the final step of the synthesis, enables the unique integration of a rapid catalyst synthesis method with the application of these systems in subsequent batch reactions or a continuous flow reactor. Any successful "hit" in the screening experiment can subsequently be tested in a continuous flow reactor on a range of different substrates. In view of the rapid development in combinatorial approaches in catalysis, we believe that the strategy to use silica supports for solid-phase synthesis in combination with catalyst immobilization is very promising.

Experimental Section

General information: All reactions and manipulations were routinely performed under an argon or nitrogen atmosphere using standard Schlenk techniques. Acetonitrile, propan-2-ol, methanol, and triethylamine were distilled from CaH_2, THF and toluene were distilled from Na prior to use. Acetophenone was degassed and stored over molecular sieves. All other reagents and chemicals were reagent grade and were used as received from commercial suppliers. Column chromatography was performed by using silica 60, 70–230 mesh ASTM (Merck). ^{1}HNMR spectra were recorded on a Varian AMX 300 spectrometer and ^{13}CNMR spectra were recorded on a Varian Inova 500 spectrometer. Chemical shifts are in ppm relative to tetramethylsilane (TMS). Mass spectra were recorded on a JEOL JMS SX/SX102A four section mass spectrometer, coupled to a JEOL MS-MP7000 data system. Microanalyses (C, H, N) were performed on an Elementar-Vario EL apparatus (Foss Electric). Gas chromatography was performed by using a Carlo Erba GC Vega 2 instrument, 25 m column: CycloSil-B (chiral) and a Carlo Erba HRGC Mega 2 instrument, 25 m column: BPX6635 (SGE) (nonchiral).

Synthesis of NH-3-(trimethoxysilyl)benzyl-(1*R*,2*S*)-norephedrine (3): At 0 °C, *p*-(chloromethyl)phenyltrimethoxysilane (448 mg, 1.85 mmol) was added to a suspension of norephedrine (250 mg, 1.65 mmol) and Na_2CO_3 (192 mg, 1.85 mmol) in acetonitrile (20 mL). The white turbid suspension was slowly heated and stirred for 18 h at 60 °C. The reaction mixture was filtered over a pad of Celite and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (silica 60, eluent: ethyl acetate) and obtained as a colorless oil.(The ligand was stored under an inert atmosphere at −20 °C). Yield 19% (113 mg); ^{1}HNMR (300 MHz, $CDCl_3$): $\delta = 7.63-7.34$ (ab, $^3J = 8.1$ Hz, 4H; ArH), 7.29–7.24 (m, 5H; ArH), 4.80 (d, $^3J = 3.9$ Hz, 1H; C*H*OH), 3.89 (s, 2H; CH_2), 3.61 (s, 9H; OCH_3), 2.99 (dq, $^3J = 3.9$ Hz, $^3J = 2.7$ Hz, 1H; C*H*NH), 0.85 (d, $^3J = 6.6$ Hz, 3H; CH_3); ^{13}CNMR (500 MHz, $CDCl_3$): $\delta = 142.85$ (*C*-CH_2), 141.34 (*C*-CHOH), 135.20 (SiC-*C*H), 128.24 (SiC), 128.20 (CHOH-C-*C*H), 127.82 (CHOH-C-CH-*C*H), 127.23 (CH-*C*H-CH), 126.23 (CH_2-C-*C*H), 73.26 (CHOH), 57.89 (*C*H-CH_3), 51.34 (CH_2), 51.00 (OCH_3), 14.86 (CH_3); HRMS (FAB): calcd for $C_{19}H_{28}O_4NSi$: 362.1787; found 362.1787; elemental analysis (%) for $C_{19}H_{27}O_4NSi$: calcd: C 63.13, H 7.53, N 3.87; found: C 62.83, H 7.11, N 3.73.

Immobilization procedures: 4: Degassed and predried silica gel 60 (1 g) was slurried in a solution of NH-3-(trimethoxysilyl)benzyl-(1*R*,2*S*)-norephedrine (**3**) (50 mg, 0.14 mmol) in toluene (20 mL). The suspension was stirred for 18 h at 100 °C. The silica was washed with toluene (3 × 5 mL) and dried under reduced pressure.

4a: Dimethyldimethoxysilane (1 mL) was added to a suspension of **4** (500 mg) in toluene (10 mL). The suspension was stirred for 18 h at 100 °C and the silica was washed with toluene (3 × 5 mL) and dried under reduced pressure.

4b: Degassed silica 60 (4 g) was suspended in a solution of *p*-(chloromethyl)phenyltrimethoxysilane (350 mg, 1.42 mmol) in toluene (20 mL). After the slurry was stirred for 2.5 h at 80 °C, the toluene was removed under vacuum and the silica was subsequently washed with toluene (3 × 5 mL). Then toluene (30 mL) and triethylamine (10 mL) were added

followed by the dropwise addition of dichlorodimethylsilane (5 mL). A white precipitate formed immediately. After the reaction mixture was stirred for 18 h at room temperature, the crude product was collected on a filter and subsequently washed with THF (3×10 mL), MeOH (3×10 mL), and THF (3×10 mL), and finally dried under reduced pressure.
The above described benzyl chloride functionalized silica (2 g) was suspended in a mixture of norephedrine (200 mg, 1.32 mmol) and triethylamine (2 mL) in acetonitrile (30 mL). The slurry was stirred for 18 h at 70 °C. After the liquids were removed from the reaction mixture under vacuum, **4b** was washed with MeOH (2×10 mL) and THF (2×10 mL). Compound **4b** was dried under reduced pressure and was stored at -20 °C under an inert atmosphere.

Catalysis procedure: In a typical catalysis experiment, a suspension of (*p*-cymene)ruthenium(II) chloride dimer (3.5 mg, 0.006 mmol) and silica (400 mg) that contains NH-3-(trimethoxysilyl)benzyl-(1*R*,2*S*)-norephedrine (0.06 mmol) in dry propan-2-ol (7 mL) was heated at 60 °C for 30 min. After the deep red reaction mixture had been cooled to 0 °C, 0.1 M *t*BuOK in propan-2-ol (3 mL) and acetophenone (0.1 mL) were added. The resulting purple-red suspension was stirred for 2 h at room temperature. The liquids were subsequently removed from the catalyst by means of a syringe. Then propan-2-ol (9 mL), 0.1 M *t*BuOK (1 mL), and acetophenone (0.1 mL) were added to the catalyst. Catalytic reactions were typically run for 2 h and recycled twice.

Continuous flow reactor: A mixture of [{$RuCl_2(\eta^6$-*p*-cymene}] (20 mg, 0.033 mmol) and **4b** (1 g, containing $\sim$0.35 mmol NH-benzylated ligand) were slurried in propan-2-ol (20 mL) and heated at 60 °C for 30 min. After the resulting red mixture had been cooled down to 0 °C, 0.1 M *t*BuOK in propan-2-ol (4 mL) and acetophenone (0.3 mL) were added. The resulting purple-red mixture was stirred at room temperature until a deep red silica in a light-yellow solution was obtained (ca. 20 min). The flow reactor (diameter of 0.7 cm) was loaded with the reaction mixture by using a glass elbow (forming a catalyst bed that is $\sim$1.5 cm high). The catalyst bed was allowed to settle and the reaction mixture on top was gently forced through the bed with a small over-pressure of argon or nitrogen. A fresh reaction mixture of propan-2-ol (50 mL) containing acetophenone (0.1 M) and *t*BuOK (0.01 M) was allowed to pass through the catalyst bed. Samples were taken every 30 or 60 min and analyzed by GC. Experiments were started when product streams were stabilized after the initiation period (ca. 1 h). The flow rate of the reactor was adjusted with the over-pressure of argon or nitrogen. Overnight standing was applied by the maintenance of a very small argon overpressure and a low flow rate.

Catalyst screening: The series of catalysts in the screening experiment were synthesized in a procedure similar to that of **4b**. Compounds **5**–**9** were prepared on stirring slurries of *p*-benzyl chloride on silica (250 mg), amino alcohol or diamine (25 mg), triethylamine (250 μL) in acetonitrile (5 mL) for 18 h at 60 °C. After removal of the solvent, all samples were successively washed with: methanol (2×4 mL), THF (2×4 mL), and propan-2-ol (4 mL). The samples were charged with [{$RuCl_2(\eta^6$-*p*-cymene}] (2.5 mg, 4×10^{-6} mol) and propan-2-ol (8 mL), and stirred for 30 min at 60 °C. After the mixture had been cooled to room temperature, a mixture containing *t*BuOK (0.1 M; 0.1 mL) and acetophenone (1 mL) was added. All reactions were sampled after 2 h and fresh substrate solutions were added after removal of the liquid layer.

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