ORGANIC
LETTERS

2004
Vol. 6, No. 2
169−172

Efficient Heterogeneous Asymmetric Transfer Hydrogenation of Ketones Using Highly Recyclable and Accessible Silica-Immobilized Ru-TsDPEN Catalysts

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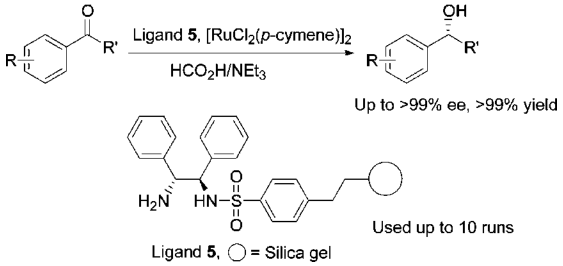
Received October 23, 2003

ABSTRACT



Chiral Ru-TsDPEN [*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine]-derived catalysts were first successfully immobilized onto amorphous silica gel and mesoporous silicas of MCM-41 and SBA-15 by an easily accessible approach. The catalyst immobilized on silica gel demonstrated remarkably high catalytic activities and excellent enantioselectivities (up to >99% ee) for the heterogeneous asymmetric transfer hydrogenation of various ketones. Particularly, the catalyst could be readily recovered and reused in multiple consecutive catalytic runs (up to 10 uses) with the completely maintained enantioselectivity.

Optically active secondary alcohols are currently important intermediates for the construction of many optically and biologically active compounds. One of the most attractive methods to prepare such alcohols is the asymmetric transfer hydrogenation of prochiral ketones due to its high enantioselectivity, high product yield, and operational simplicity. Consequently, many efforts have been devoted to the development of new chiral catalysts and rapid progress has been made,[1] among which the most significant is the discovery of ruthenium(II) complex of (1*S*,2*S*)- or (1*R*,2*R*)-TsDPEN **1**, as reported by Noyori et al.[2]

In recent years, covalent immobilization of chiral catalysts to insoluble supports has created fast-growing interest,[3,4] as it provides an easy separation of the products from the catalysts without tedious experimental workup and enables the efficient recovery of the often expensive or toxic catalysts and potentially allows the adaptation of the immobilized catalysts to continuous flow-type processes. Compared to

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[1] For reviews of asymmetric transfer hydrogenation: (a) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045. (b) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051.

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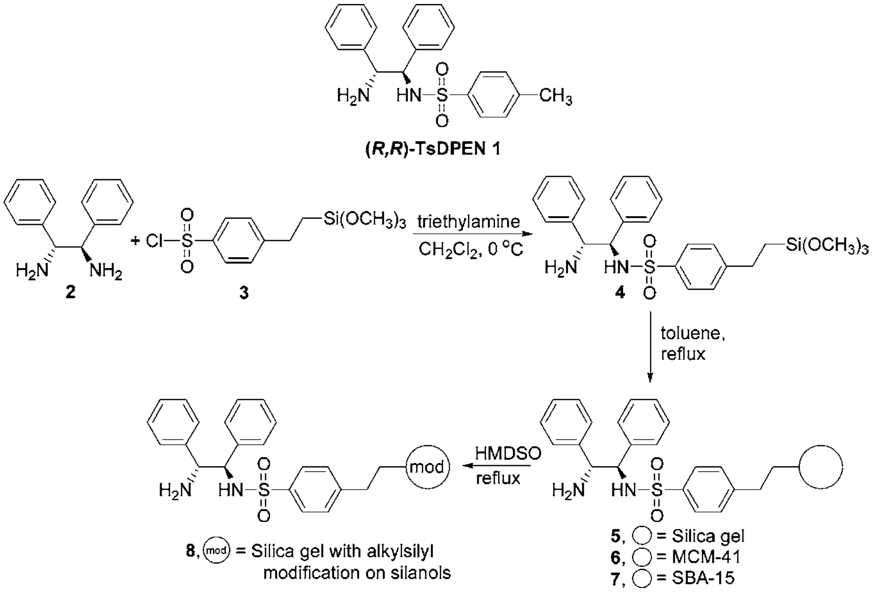
10.1021/ol036065z CCC: $27.50

Scheme 1. Synthesis of the Immobilized Ligands **5**−**8**



organic polymers, inorganic material-immobilized catalysts possess some advantages, though they attract little attention.[4] For example, they prevent the intermolecular aggregations of the active species because of their rigid structures, do not swell or dissolve in organic solvents, and often exhibit superior thermal and mechanical stability under the catalytic conditions. For the asymmetric transfer hydrogenation of ketones, however, examples of immobilized catalysts have been rare so far[5] and even more rare for the immobilization of the catalysts onto inorganic supports.[6,7] Recently, van Leeuwen et al. reported some heterogeneous catalysts, the best of which is the ruthenium(II) complex of (1*R*,2*S*)-*N*-benzyl-norephedrine covalently tethered to silica.[7] However, this heterogeneous catalyst in a continuous flow reactor gave only 90% ee for acetophenone, and the batchwise catalytic reactions with the recovered catalyst gave lower enantioselectivities and very low conversions.

In connection with our recent efforts for developing practical, efficient, and highly recyclable catalytic systems, we have designed and synthesized the novel heterogeneous catalysts by directly grafting a chiral TsDPEN derivative onto the surface of amorphous silica gel and mesoporous silicas of MCM-41 and SBA-15 and provided very successful application for the heterogeneous asymmetric transfer hydrogenation of a series of ketones. Herein, we present our experimental results.

As shown in Scheme 1, TsDPEN-derived ligand **4** was synthesized by reacting (1*R*,2*R*)-1,2-diphenylethylenediamine (DPEN) **2** with commercially available 2-(4-chlorosulfonylphenyl)ethyltrimethoxysilane **3** using triethylamine as a base. The ligand **4** was then anchored onto amorphous silica gel and mesoporous silicas of MCM-41 and SBA-15 by refluxing in toluene for 24 h, affording the organic−inorganic hybrid ligands **5**−**7**. The silanol sites of silica gel of ligand **5** were modified to alkylsilanes by treating **5** with a large excess of hexamethyldisiloxane (HMDSO) at reflux for 18 h to form the ligand **8**. Elemental analysis of **5**−**8** calculated from mass % of N showed that loading ratios of the chiral ligands were 0.15, 0.14, 0.10, and 0.12 mmol/g, respectively. In addition, the pore sizes of **5**−**8** were measured to be 9.0, 1.9, 6.2, and 8.7 nm, respectively.

The heterogeneous asymmetric transfer hydrogenation was studied using acetophenone as the model substrate with the catalysts Ru-**5**−Ru-**8** generated in situ by reacting the corresponding ligands with $[RuCl_2(p\text{-cymene})]_2$ and triethylamine in CH_2Cl_2 at 28 °C for 1 h, wherein the generated active species would be similar to that in the homogeneous system.[2c] Reductions were then performed using a solution of acetophenone in formic acid−triethylamine azeotrope containing Ru-**5**−Ru-**8** under various conditions to give the chiral 1-phenyl ethanol, whose optical purities and yields were determined by GC and listed in Table 1. The reduction with Ru-**5** displayed remarkably high catalytic activity (>99% yield after 6 h) and excellent enantioselectivity (97% ee), which were as good as the results from the nonimmo-

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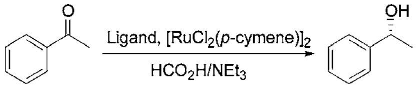
Table 1. Immobilized Ruthenium(II) Complexes Ru-***n***-Catalyzed Asymmetric Transfer Hydrogenation of Acetophenone[a]



entry	ligand	s/c	temp (°C)	run	time (h)	conversion (%)[b]	ee (%)[c]
1	**5**	100	40	1	6	>99	97
2	**5**	100	40	2	8	>99	97
3	**5**	100	40	3	9	97	97
4	**5**	100	40	4	22	99	97
5	**5**	100	40	5	44	94	97
6	**1**	100	40	1	5.5	>99	97
7	**4**	100	40	1	5.5	>99	97
8	**6**	100	40	1	8	99	96
9	**6**	100	40	2	24	99	96
10	**6**	100	40	3	88	44	96
11	**7**	100	40	1	8	>99	97
12	**7**	100	40	2	11	99	97
13	**7**	100	40	3	24	92	97
14	**7**	100	40	4	72	45	96
15	**8**	100	40	1	9	98	96
16	**8**	100	40	2	60	5	
17	**5**	100	28	1	9	99	98
18	**5**	100	28	2	13	98	98
19	**5**	100	28	3	77	87	98
20	**5**	100	50	1	2	99	97
21	**5**	100	50	2	5	>99	97
22	**5**	100	50	3	14	>99	96
23	**5**	100	50	4	47	78	96
24[d]	**5**	200	40	1	12	>99	97
25[d]	**5**	200	40	2	20	99	97
26[d]	**5**	200	40	3	43	96	97
27[d]	**5**	200	40	4	63	29	97
28[e]	**5**	500	40	1	26	>99	97
29[e]	**5**	500	40	2	30	86	97
30[e]	**5**	500	40	3	84	56	97
31[f]	**5**	1000	40	1	50	92	97
32[f]	**5**	1000	40	2	90	10	96

[a] Reactions were carried out using 0.4 mmol of acetophenone in 0.2 mL of formic acid−triethylamine azeotrope with Ru:ligand = 1:1.7. [b] Based on GC analysis. [c] Determined by GC with a CP-Chirasil-DEX CB column (25 m × 0.32 mm), and the configuration *R* was determined by the optical rotation value. [d] Performed with 0.8 mmol of acetophenone in 0.4 mL of formic acid−triethylamine azeotrope. [e] Performed with 2.0 mmol of acetophenone in 0.4 mL of formic acid−triethylamine azeotrope. [f] Performed with 4.0 mmol of acetophenone in 0.6 mL of formic acid−triethylamine azeotrope.

bilized homogeneous catalysts Ru-**1** and Ru-**4** (entries 1, 6, and 7). Moreover, this heterogeneous catalyst could be readily recovered by centrifugation and could completely maintain the high enantioselectivity even for the fifth use with slight loss of activity (entries 1−5). The leaching of Ru metal might be one of the main reasons for decreasing catalytic activity since 30−40% of ruthenium lost from the catalyst after five uses. Moreover, the color of the catalyst changed from yellow to red in the recycling routine and further addition of [RuCl$_2$(*p*-cymene)]$_2$ into the catalytic system could not regain the reactivity, which showed that decomposition or deactivation of the active species would occur irreversibly in the recycling routine.

Catalysts Ru-**6**−Ru-**8** prepared from the more expensive or complex ligands **6**−**8**, respectively, afforded the worse recovery results, although in the first reaction they gave nearly the same enantioselectivities and catalytic activities as Ru-**5** (entries 8−16). It appears that the very cheap amorphous silica gel without modification worked as the best support for Ru-TsDPEN-catalyzed transfer hydrogenation of ketone in our experimental scope, probably because of its comparably large pore size and thus better accessibility for substrates and reactants. Therefore, the successive investigations were focused on Ru-**5** to search for the optimum conditions for the transfer hydrogenation by changing the reaction temperature and substrate/catalyst ratios (s/c, in moles). As indicated in entries 17−23, when the temperature was lowered to 28 °C, the reduction gave slightly enhanced enantioselectivity (98% ee) and slightly decreased catalytic activity (>99% yield after 9 h), while in the homogeneous catalytic system, a much longer reaction time of 20 h was needed.[2b] On the contrary, as the temperature was increased to 50 °C, the catalytic activity increased and the enantioselectivities decreased slightly in the third and fourth runs. However, the recovery performance of the catalyst was badly affected at both temperatures. Reductions with higher s/c ratios (200:1 or 500:1) gave the chiral alcohol with the same result in 97% ee and in quantitative yield after prolonged reaction times, but the recovered catalyst performed poorly upon recycling (entries 24−30). Reduction could also be effective even with much higher s/c ratios (1000:1), in which the enantioselectivity was maintained at 97% ee along with 92% yield in the first run, but the yield decreased greatly in the second run (entries 31 and 32).

Moreover, a series of aromatic ketones **9**−**18** were chosen for the transfer hydrogenation with the amorphous silica gel-immobilized catalyst Ru-**5** under the optimum conditions (40 °C, s/c = 100:1). The results are summarized in Table 2, which showed that the transfer hydrogenation of all ketones achieved very high catalytic activities (>99% yields after 1.5−16 h) and excellent enatioselectivities comparable to those of the homogeneous catalysis.[2b,f,8] Moreover, the recycling experiments of all ketones performed very well in 4−10 runs with maintained enatioselectivities and high yields. Further inspection of Table 2 revealed more detailed information. For example, reductions of the halogen-substituted acetophenones **9**−**12** demonstrated high catalytic activities (entries 1, 3, 5, and 7), especially the meta- and ortho-fluoro-substituted acetophenones **9** and **10**, for which >99% yields were obtained after just 3−4 h in the first run. Although slightly lowered enantioselectivities of 93−94% ee were obtained, almost the same results were observed in the homogeneous catalytic systems with much longer reaction times (entries 1−9).[2b,8] Particularly notable was that for the fluorine-substituted acetophenones **9** and **10**, the recovered catalyst could still give a high yield without any loss of enantioselectivity even in the 10th run of the reductions

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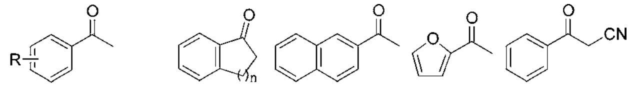
Table 2. Immobilized Ruthenium(II) Complex Ru-**5**-Catalyzed Asymmetric Transfer Hydrogenation of Ketones[a]



9; R = *m*-F; **10**: R = *o*-F; **11**: R = *o*-Cl; **12**: R = *o*-Br; **13**: R = *m*-OCH$_3$

14: n = 1; **15**: n = 2

16

17

18

entry	ketone	run	time (h)	conversion (%)[b]	ee (%)[c,d]
1	**9**	1−6	3−9	>99	94
2	**9**	7−10	8−23	95−97	94
3	**10**	1−6	4−9	>99	93
4	**10**	7−10	10−23	95−97	93
5	**11**	1−5	5−10	99	94
6	**11**	6	28	98	94
7	**12**	1−3	7−15	>99	93
8	**12**	4	22	97	93
9	**12**	5	48	89	94
10	**13**	1−3	8−10	>99	96
11	**13**	4−5	12−23	97−98	96
12	**13**	6	47	87	96
13	**14**	1−5	12−35	96−99	>99[e]
14	**14**	6	42	69	99[e]
15	**15**	1−2	16−19	>99	>99[e]
16	**15**	3−4	21−24	95−96	>99[e]
17	**15**	5	41	84	>99[e]
18	**16**	1−6	10−32	98−99	95−96[f]
19	**16**	7	47	76	95[f]
20	**17**	1−7	5−23	>99	95−96
21	**17**	8	47	87	96
22	**18**	1−5	1.5−3.5	>99[g]	97[f]
23	**18**	6	16	>99[g]	96[f]

[a] Reactions were carried out at 40 °C using 0.4 mmol of acetophenone in 0.2 mL of formic acid−triethylamine azeotrope with Ru:ligand:ketone = 1:1.7:100. [b] Based on GC analysis. [c] Determined by GC with a CP-Chirasil-DEX CB column (25 m × 0.32 mm) unless noted. [d] Configurations of the products were all determined to be *R* by the optical rotation values. [e] Determined by HPLC on Chiralcel OB column. [f] Determined by HPLC on Chiralcel OJ column. [g] Isolated yield.

(entries 1−4). For 3′-methoxy-acetophenone **13** with an electron-donating group, high catalytic activity, excellent enantioselectivity and good recovery performance were also obtained (entries 10−12), while in the homogeneous catalytic system at 28 °C, a much longer reaction time of 50 h was needed for high conversion.[2b] Asymmetric reductions of 1-indanone **14** and 1-teralone **15** with the rigid structures were best effected to give (*R*)-1-indanol and (*R*)-1-teralol in extremely high enantioselectivities of >99% ee and in good catalytic activities, as in the fourth or fifth run 95−96% yields were still observed (entries 13−17). Furthermore, 2′-acetonaphthone **16** and 2-furyl methyl ketone **17** could be reduced to the chiral alcohols in excellent enantioselectivities of 95−96% ee and in quantitative yields within 5 or 10 h, respectively. The recycling reactions of these substrates with the recovered catalyst performed very well, and the reactions were run 7−8 times with maintained enantioselectivities and high yields (entries 18−21). Asymmetric reduction of 2-cyanoacetophenone **18** demonstrated excellent enantioselectivity of 97% ee and such high catalytic activity that the quantitative yield was obtained just after 1.5 h. In addition, the recycling reactions also performed well, as 1−5 runs all gave high catalytic activities and maintained ee values; in the sixth run quantitative yield and 96% ee were still obtained with a prolonged reaction time (entries 22 and 23). Moreover, the product could be readily reduced with BH$_3$/S(CH$_3$)$_2$ in THF to give optically active 1-phenyl-3-amino-1-propanol, which is a key intermediate for the synthesis of fluoxetine, a very important antidepressant.[2f,9] In addition, we tried to expand the substrates to the aliphatic ketones, but the experimental results were undesired. For example, reductions of benzylacetone just gave 21% ee, although high yields and 4 reaction runs could be achieved.

In summary, we have developed and optimized a practical, efficient, and highly recyclable heterogeneous catalyst Ru-**5** through immobilization of Ru-TsDPEN onto a very cheap amorphous silica gel by an easily accessible approach for the first time. This catalytic system primarily demonstrated remarkably high catalytic activities (>99% yields for all tested ketones after 1.5−16 h) and excellent enantioselectivities (up to >99% ee) for the asymmetric transfer hydrogenation of various aromatic ketones, which were better or as good as the results obtained from homogeneous catalysis. The particular feature of this system was that the catalyst could be readily recovered and reused in multiple consecutive catalytic runs (up to 10 uses without recharging of Ru!) with completely maintained high enantioselectivity, which is beneficial for possible industrial application. This catalytic system could be the best one to date for the heterogeneous asymmetric transfer hydrogenation of ketones. Among the tested 11 ketone substrates, **9** and **10** showed the highest reusability (10 runs), **14** and **15** gave the highest enantioselectivities (>99% ee), **18** gave a very useful product in the highest catalytic activity and in the excellent enantioselectivity of 97% ee, and all examples gave 95−99% yields within 4−10 runs.

Acknowledgment. We are grateful for the financial support of the Natural Science Foundation of China (NSFC Nos. 29925205, 30271488, 20021001, 203900501). We thank Prof. Jinggen Deng for the valuable suggestions.

Supporting Information Available: Experimental procedure for the synthesis and characterization of (*R*,*R*)-**4** and ligands **5**−**8**, determination of leaching of Ru metal in catalyst Ru-**5**, and analytical data for obtained chiral aromatic alcohols. This material is available free of charge via the Internet at http://pubs.acs.org.

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