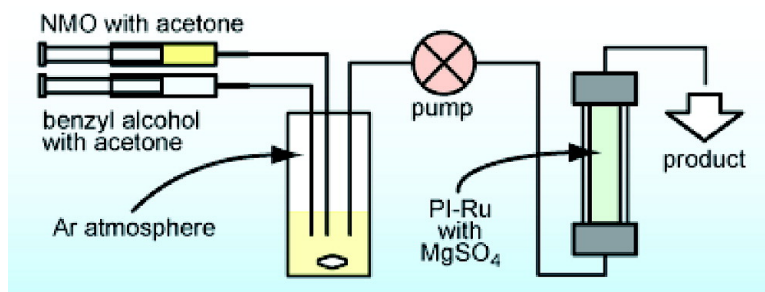Article

Highly Active, Immobilized Ruthenium Catalysts for Oxidation of Alcohols to Aldehydes and Ketones. Preparation and Use in Both Batch and Flow Systems

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Highly Active, Immobilized Ruthenium Catalysts for Oxidation of Alcohols to Aldehydes and Ketones. Preparation and Use in Both Batch and Flow Systems

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Abstract: A novel, highly active immobilized ruthenium catalyst, which can be successfully used in oxidation of alcohols to aldehydes and ketones, has been developed. In contrast to most immobilized catalysts, the Ru catalyst has activity that is higher than that of the original nonimmobilized catalyst. In a batch system, the Ru catalyst was recovered and reused several times without loss of activity. The catalyst was also applied to a flow system, in which excellent conversions and yields were demonstrated. No leaching of Ru was observed in both cases.
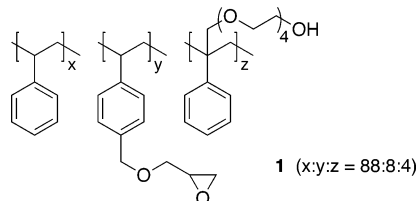
Introduction

Immobilized catalysts are of interest primarily for two reasons. First, they are crucial for achieving environmentally benign chemical synthesis,[1] the catalysts are readily recovered and reused, and total waste is decreased. Second, immobilized catalysts play a key role for combinatorial library generation,[1d,2] synthetic procedures are simplified using immobilized catalysts, and their application to automation is facile. However, many immobilized catalysts have been developed, but many of them are less active than the original nonimmobilized catalysts.[1] Moreover, few examples are known for immobilized catalysts that have high activity and can be used in both batch and flow systems.[3] In this paper, we describe novel immobilized ruthenium catalysts, which have high activity for the oxidation of alcohols to aldehydes and ketones in both batch and flow systems.

Results and Discussion

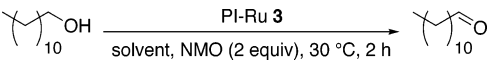Oxidation of alcohols to aldehydes and ketones is one of the most important transformations in organic synthesis.[4] While several metal-based oxidizing reagents have been developed, in many cases, stoichiometric amounts of metal oxidants, and thus large amounts of metal containing wastes, are needed. In this aspect, oxidation of alcohols using a catalytic amount of a metal reagent is very attractive.[5] Although several successful examples of catalytic oxidation of alcohols have been developed,[6] highly active immobilized catalysts that can be used in both batch and flow systems are limited.[7]

1 (x:y:z = 88:8:4)

Recently, we have developed novel immobilization methods for metal catalysts, microencapsulation and polymer incarcerated methods, which are based on electronic interactions between

(1) (a) Gladysz, J. A. *Chem. Rev.* **2002**, *102*, 3215. (b) McNamara, C. A.; Dixon, M. J.; Bradley, M. *Chem. Rev.* **2002**, *102*, 3275. (c) *Polymeric Materials in Organic Synthesis and Catalysis*; Buchmeiser, M. R., Ed.; Wiley-VCH: Weinheim, Germany, 2003. (d) Kobayashi, S.; Akiyama, R. *Chem. Commun.* **2003**, 449. (e) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 1998.
(2) (a) Lee, A.; Ley, S. V. *Org. Biomol. Chem.* **2003**, *1*, 3263. (b) Dolle, R. E. *J. Comb. Chem.* **2004**, *6*, 623.
(3) Reviews: (a) Jas, G.; Kirschning, A. *Chem.—Eur. J.* **2003**, *9*, 5708. (b) Kirschning, A.; Monenschein, H.; Wittenberg, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 650. See also: (c) Kirschning, A.; Altwicker, C.; Dräger, G.; Harders, J.; Hoffmann, N.; Hoffmann, U.; Schönfeld, H.; Solodenko, W.; Kunz, U. *Angew. Chem., Int. Ed.* **2001**, *40*, 3995. (d) Solodenko, W.; Wen, H.; Leue, S.; Stuhlmann, F.; Sourkouni-Argirusi, G.; Jas, G.; Schönfeld, H.; Kunz, I. U.; Kirschning, A. *Eur. J. Org. Chem.* **2004**, 3601.
(4) (a) Hill, C. L. In *Advances in Oxygenated Processes*; Baumstark, A. L., Ed.; JAI Press: London, 1988; Vol. 1, p 1. (b) Hundlucky, M. *Oxidations in Organic Chemistry*; ACS Monograph Series; American Chemical Society: Washington, DC, 1990.
(5) (a) Sheldon, R.; Kochi, J. K. *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press: New York, 1981. (b) Madin, A. In *Comprehensive Organic Chemistry*; Trost, B. M., Fleming, I., Ley, S. V., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 7, p 251. (c) Parshall, G. W.; Ittel, S. D. *Homogeneous Catalysis*, 2nd ed.; John Wiley & Sons: New York, 1992.
(6) Review: Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815.
(7) Review: (a) Mallat, T.; Baiker, A. *Chem. Rev.* **2004**, *104*, 3037. See also: (b) Yamaguchi, K.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2000**, *122*, 7144. (c) Yamaguchi, K.; Mizuno, N. *Chem.—Eur. J.* **2003**, *9*, 4353. (d) Langer, P. *J. Prakt. Chem.* **2000**, *342*, 728. (e) Bleloch, A.; Johnson, F. G.; Ley, S. V.; Price, A. J.; Shephard, D. S.; Thomas, A. W. *Chem. Commun.* **1999**, 1907. (f) Mori, K.; Hara, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2003**, *125*, 11460. (g) Motokura, K.; Nishimura, D.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2004**, *126*, 5662. (h) Zhang, Y.; Fei, J.; Yu, Y.; Zheng, X. *Catal. Commun.* **2004**, *5*, 643 and references cited therein. While molecular oxygen is regarded as an environmentally friendly oxidant, applications are sometimes limited due to safety reasons. In addition, the use of molecular oxygen in combinatorial flow systems is rare.

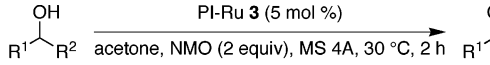**Table 1.** Effect of Solvents and Additives

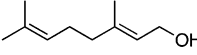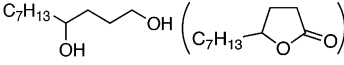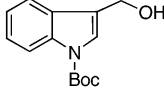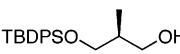|			Yield[a]/% [leaching[b] (%)]		
entry	PI–Ru (mol %)	solvent	first	second	third
1	15	toluene	33 [nd]	28 [nd]	19 [nd]
2	15	THF	31 [nd]	27 [2.4]	31 [nd]
3	15	DMF	57 [6.8]	50 [nd]	48 [nd]
4	15	CH_3CN	41 [nd]	48 [nd]	42 [nd]
5	15	CH_2Cl_2	48 [nd]	45 [nd]	56 [nd]
6	15	acetone	61 [nd]	70 [nd]	73 [nd]
7	5	acetone	64 [nd]	72 [nd]	65 [nd]
8[c]	5	acetone	quant [nd]	96 [nd]	92 [nd]

[a] Yields were determined by GC analysis. [b] Leachings were measured by XRF analysis; nd = not detected. [c] 500 mg/mmol of MS 4A was used.

metals and benzene rings of polystyrene derivatives and are successful in immobilizing highly active catalysts.[8] We decided to use these methods for immobilization and chose dichlorotris-(triphenylphosphine)ruthenium ($RuCl_2(PPh_3)_3$) as a starting catalyst[9] because we thought that the three PPh_3 groups of $RuCl_2(PPh_3)_3$ would be eliminated during immobilization[8a] to create a more Lewis acidic, less hindered active catalyst. Epoxide-containing copolymer (**1**) was dissolved in tetrahydro-furan (THF) at room temperature, and $RuCl_2(PPh_3)_3$ was added to this solution. Hexane was then added to form microcap-sules,[1d,10] which were filtered, washed, and dried. The micro-capsules were next heated at 120 °C for 3.5 h to afford polymer incarcerated Ru (PI–Ru (**2**)). PI–Ru (**2**) was preliminarily oxidized using 5 equiv of *N*-methylmorpholine-*N*-oxide (NMO) in acetone/2-propanol (1/9) at room temperature for 12 h before being subjected to oxidation reactions.[11]

PI–Ru (**3**) thus prepared was initially examined in the oxidation of dodecanol using NMO as a co-oxidant in a batch system (Table 1). Several solvents were tested, and it was found that the oxidation proceeded smoothly in acetone to afford dodecanol in good yield using 15 mol % of PI–Ru at 30 °C for 2 h (entry 6). The catalyst was recovered quantitatively by simple filtration and reused three times without loss of activity. In addition, no leaching of Ru was detected by fluorescence X-ray (XRF) analysis. When the catalyst loading was reduced to 5 mol %, similar results were obtained. Finally, the yield was dramatically improved by adding molecular sieves (MS) 4A (entry 8). Molecular sieves would remove water that is generated during the oxidation and would prevent deactivation of the catalyst as well as further oxidation of the aldehyde to the corresponding carboxylic acid.

Under the optimized conditions, several alcohols were oxidized, and the results are summarized in Table 2. Primary and secondary, aliphatic and aromatic, and even allylic alcohols were oxidized smoothly in the presence of PI–Ru (**3**) to afford the corresponding carbonyl compounds in high yields (entries 1–7). It should be noted that the yields were better than those using the parent metal source, $RuCl_2(PPh_3)_3$. Heterocyclic
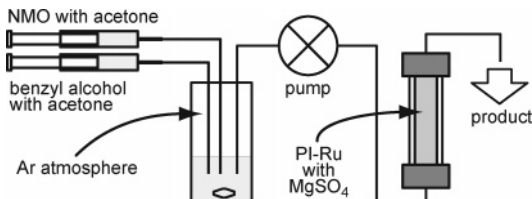
(8) (a) Akiyama, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 3412. (b) Okamoto, K.; Akiyama, R.; Kobayashi, S. *J. Org. Chem.* **2004**, *69*, 2871.
(9) Sharpless, K. B.; Akashi, K.; Oshima, K. *Tetrahedron Lett.* **1976**, *17*, 2503. See also: (b) Naota, T.; Takaya, H.; Murahashi, S.-I. *Chem. Rev.* **1998**, *98*, 2599.
(10) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1998**, *120*, 2985.
(11) Details are shown in the Experimental Section (Supporting Information).

Table 2. PI−Ru Catalyzed Oxidation of Various Substrates[a]

entry	substrate	yield[b] (%)
1	*n*-dodecanol	quant (84%)[c]
2	cyclohexanol	94
3	benzyl alcohol	99
4	*sec*-phenetyl alcohol	93
5[e]	3-phenyl-1-propanol	80
6		95
7	cinnamyl alcohol	85
8		79[f]
9		86[d,g]
10	2-thiophenemethanol	98
11[c]		77[d] [81% ee][i]
12[h]		66[d] [91% ee][i]
13		84[d] [97% ee][i]

[a] 500 mg/mmol of MS 4A was used. The leaching of Ru to the reaction mixture was measured by XRF and ICP analyses. No peaks for Ru were detected in all entries (<0.5 ppm). [b] Yields were determined by GC analysis. [c] $RuCl_2(PPh_3)_3$ (5 mol %) was used instead of PI−Ru. [d] Isolated yield.[e] The reaction was performed for 0.5 h. [f] The product is shown in parentheses. [g] 86% yield using PI−Ru (1 mol %) for 4 h; 89% yield using PI−Ru (0.5 mol %) for 15 h. [h] TPAP (5 mol %) in acetonitrile was used instead of PI−Ru. [i] Enantiomeric excess of the product was determined by chiral HPLC analysis.

alcohols also worked well (entries 9 and 10), and a 1,4-dihydroxy compound gave the corresponding lactone directly (entry 8). For optically active aldehydes having a stereogenic center at the 2-position, it is well-known that partial racemization occurs during oxidation and that a racemic aldehyde is formed in many cases. Indeed, when optically pure alcohol **4** (>99% ee) was oxidized using $RuCl_2(PPh)_3$, the corresponding aldehyde **5** was obtained in 77% yield with 81% ee. While a somewhat better result was obtained using tetra-*n*-propylammonium per-ruthenate (TPAP)[12] (66% yield, 91% ee), PI−Ru (**3**) was excellent so that the desired aldehyde was obtained in 84% yield with almost no racemization (97% ee). We assume that the polymer serves to reduce the basicity of the reaction mixture to prevent the partial racemization of the aldehyde.

PI−Ru was then applied to a flow system. Flow systems are now very important not only in industries but also in high-throughput organic synthesis related to combinatorial library generation.[3] Whereas many immobilized catalysts have been developed, those that can be applied to flow systems are limited. Our flow system was set up as shown in Scheme 1. PI−Ru and $MgSO_4$[13] were placed into a column, and an acetone solution of an alcohol and NMO was passed through the column. Under

(12) Review: Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

Table 3. PI–Ru Catalyzed Oxidation Reaction Using Flow System

$$\text{PhCH}_2\text{OH} \xrightarrow[\text{rt}]{\text{flow system}} \text{PhCHO}$$

time (h)[b]	0–1.05	1.05–2.10	2.10–3.15	3.15–4.20	4.20–5.25	5.25–6.30	6.30–7.35	7.35–8.40
conversion (%)[c]	>99	>99	>99	>99	99	98	96	94
yield (%)[c]	94	92	87	>99	95	88	89	92

[a] 1.99 mg/mL of benzyl alcohol and 6.94 mg/mL of NMO acetone solution were passed through a column containing 40.3 mg of PI–Ru (loading level is 0.312 mmol/g) with MgSO$_4$. Flow rate was 0.08 mL/min. [c] Conversion and yield was calculated based on the total starting material as an average of 1.05 h.

Scheme 1
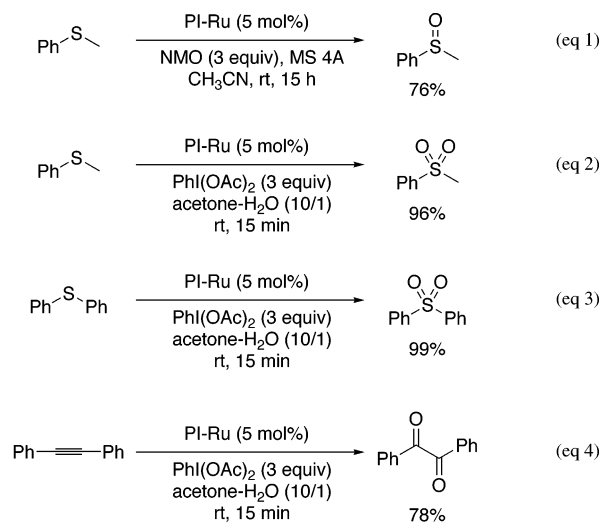

Table 4. Elemental Analysis of PI–Ru

	Ru (mmol/g)[a] [equiv]	Cl (mmol/g) [equiv]	P (mmol/g) [equiv]
microcapsules before cross-linking	0.29 [1.0]	0.64 [2.2]	0.31 [1.1]
PI–Ru (**2**)	0.31 [1.0]	0.66 [2.1]	0.14 [0.5]
PI–Ru (**3**)	0.29 [1.0]	0.66 [2.3]	0.08 [0.3]

[a] Observed by XRF analysis.

the conditions shown in the scheme, the substrate mixture came in contact with the catalyst in the column for approximately 20 min. After passing through the column, the alcohol was converted to the aldehyde almost quantitatively (Table 3).[14] It is noted that high conversions and yields were kept even after 8 h continuous flow,[15] and that no leaching of Ru was observed.[11] Applications to a large-scale synthesis as well as combinatorial chemistry using this flow system are underway.[16]

For the use of PI–Ru in other oxidation reactions, we have briefly examined the oxidation of sulfides and an acetylene derivative (eqs 1–4). In the presence of PI–Ru (5 mol %) and MS 4A, thioanisole was treated with NMO in acetonitrile at room temperature for 15 h to afford methyl phenyl sulfoxide in 76% yield (eq 1). On the other hand, methyl phenyl sulfone was obtained in high yield using (diacetoxyiodo)benzene (PhI-(OAc)$_2$) as a co-oxidant. Thus, thioanisole was treated with PhI-(OAc)$_2$ in the presence of PI–Ru (5 mol %) in acetone/water (10/1) at room temperature for 15 min to afford methyl phenyl

sulfone in 96% yield (eq 2).[17] Diphenyl sulfide gave diphenyl sulfone in 99% yield under the same reaction conditions (eq 3). The system was also used for the oxidation of diphenyl-acetylene, and benzyl was obtained in good yield under mild reaction conditions (eq 4). It is noted that, in all cases, the Ru catalyst was recovered by simple filtration and reused without loss of activity. Moreover, no leaching of Ru was observed in all cases.

At this stage, we have information on the structure of PI–Ru. In our initial plan, the three PPh$_3$ groups of RuCl$_2$(PPh$_3$)$_3$ would be eliminated during immobilization to create a more active catalyst. For the activity of the newly created immobilized catalyst (RI–Ru (**3**)), higher activity of PI–Ru (**3**) compared with that of RuCl$_2$(PPh$_3$)$_3$ was demonstrated in several cases. Elemental analyses of PI–Ru (**3**) support our working hypothesis (Table 4). We analyzed a Ru catalyst just after micro-encapsulation (before cross-linking), PI–Ru before activation (PI–Ru (**2**)), and PI–Ru after activation (PI–Ru (**3**)). In all cases, the same levels of Ru loadings were observed, and 2 equiv of chlorine to Ru was detected. More importantly, almost all of the PPh$_3$ was removed during the preparation of PI–Ru (**3**). Analyses by EXAFS also support this structure, but more experiments are needed to further clarify the precise structure of PI–Ru.

Conclusion

We have developed a novel, highly active immobilized ruthenium catalyst, which can be successfully used in oxidation

(13) We tested MS 4A and MgSO$_4$ in both batch and flow systems, and MS 4A was better for the batch system, while MgSO$_4$ was better for the flow system. Although the precise reason is not clear at this stage, the rate difference of the absorption of water may explain the results.
(14) After the column, the solution was passed through a short silica gel pad to afford the almost pure aldehyde (>98%). See Experimental Section (Supporting Information).
(15) We did not continue the flow system experiment after 8.40 h due to an experimental reason.
(16) While polymer-supported perruthenate was used for oxidation of alcohols in a batch system, its catalytic activity was lower than that of PI–Ru. See: (a) Hinzen, B.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1907. On the other hand, stoichiometric use of an immobilized co-oxidant for oxidation of alcohols in both batch and flow systems was reported. (b) Brünjes, M.; Sourkouni-Argirusi, G.; Kirschning, A. *Adv. Synth. Catal.* **2003**, *345*, 635. See also ref 3.

(17) Greater than 99% yield using PI–Ru (1 mol %) for 2 h; 95% yield using PI–Ru (0.5 mol %) for 15 h.

of alcohols to aldehydes and ketones. In contrast to most immobilized catalysts, the Ru catalyst has activity that is higher than that of the original nonimmobilized catalyst. In a batch system, the Ru catalyst was recovered and reused several times without loss of activity. The catalyst was also applied to a flow system, in which excellent conversions and yields were demonstrated. No leaching of Ru was observed in both cases. Further investigations to develop other reactions using PI−Ru as well as to clarify the precise structure of the PI−Ru catalyst are now in progress.

Supporting Information Available: Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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