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Osmium tetroxide–$(QN)_2$PHAL in an ionic liquid: a highly efficient and recyclable catalyst system for asymmetric dihydroxylation of olefins

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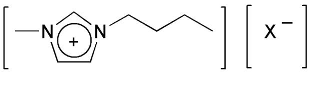
Received (in Cambridge, UK) 14th October 2002, Accepted 30th October 2002
First published as an Advance Article on the web 15th November 2002

In Os-catalysed asymmetric dihydroxylation using NMO as a co-oxidant, the combination of an ionic liquid and the new bis-cinchona alkaloid 2 generated *in situ* from $(QN)_2$PHAL during reaction provided a simple and practical approach to the recycling of both catalytic components (osmium tetroxide and chiral ligand).

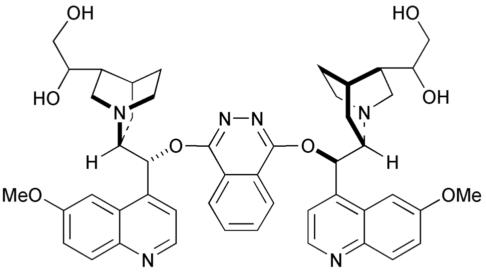
The Os-catalysed asymmetric dihydroxylation (AD) of olefins provides one of the most elegant methods for the synthesis of chiral vicinal diols.[1] Although the AD reaction offers a number of processes that could be applied to the synthesis of chiral drugs, natural products, fine chemicals, *etc*., the high cost of osmium and chiral ligands as well as the high toxicity and volatility of the osmium component has made their large-scale industrial application difficult. In order to explore the possibility of the repetitive use of both catalytic components, several attempts to immobilise this catalytic system have been made.[2–4] Early attempts to immobilise OsO_4 on solid-supported alkaloid ligands failed due to severe osmium leaching.[2] Recently, Kobayashi reported that microencapsulated OsO_4 in a polymer matrix can be used as a recyclable osmium catalyst.[3] However, high loading (5 mol%) of osmium was required in a typical dihydroxylation reaction. Very recently, another approach to immobilise $K_2OsO_4{\cdot}2H_2O$ has been achieved by using an ion-exchange technique on various solid supports.[4] Although recycling experiments using 1 mol% of this type of immobilised osmium catalysts have been successfully performed for five cycles, the amount of catalyst required is much higher than that needed in homogeneous AD reactions. In homogeneous cases, 0.2 mol% of osmium is enough to complete most reactions.

For catalyst recycling, a new approach has recently been adopted in a number of catalytic reactions involving the use of room temperature ionic liquids, in particular, consisting of 1,3-dialkylimidazolium cations and their counter anions.[5] In these solvents, catalysts having polar or ionic character can be immobilised and thus the ionic solutions containing the catalyst can be easily separated from reagents and products. During our on going research[6] using room temperature ionic liquids to immobilise transition metal-based catalysts, we have found that the combination of an ionic liquid **1** (1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6], **1a**) and 1-butyl-3-methylimidazolium hexafluoroantimonate ([bmim][SbF_6], **1b**),[7] and a new bis-cinchona alkaloid **2** provided a simple and practical approach to the recycling of both catalytic components (osmium tetroxide and the chiral ligand **2**). During our work, two papers[8] on immobilisation of OsO_4 involving an ionic liquid have quite recently been published for non-asymmetric dihydroxylation. This prompted us to report our preliminary results here.



[bmim][X] (**1**); X = PF_6 (**1a**)
SbF_6 (**1b**)

To investigate the effect of an ionic liquid on catalysis as well as recyclability of catalytic components, the AD reactions of *trans*-stilbene and methyl *trans*-cinnamate were initially carried out with the well-known ligand, 1,4-bis(9-*O*-dihydroquininyl-)phthalazine [$(DHQ)_2$PHAL], under the standard Upjohn conditions[9] (*N*-methylmorpholine-*N*-oxide (NMO) as a co-oxidant) in the presence of the ionic liquid **1a** at 20 °C. As shown in entries 1, 3, 8 and 9 in Table 1, the results obtained in the presence of the ionic liquid were quite comparable to those without an ionic liquid. Especially, when olefin was added in one portion, the reaction proceeded very fast, and thus, AD reactions of *trans*-stilbene and methyl *trans*-cinnamate in the presence of the ionic liquid **1** were completed within 20 min (entry 1 in Table 1) and 4 h (entry 8 in Table 1), respectively. Moreover, overoxidation of the product diols, a fairly common side reaction in the Upjohn dihydroxylation, was not observed in the presence of the ionic liquid **1**. Encouraged by this result, we next performed the following catalyst recycling experiment



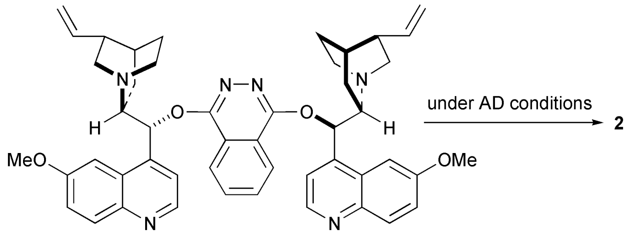
2

Table 1 Asymmetric dihydroxylation of olefins in the presence of the ionic liquid **1**[a]

Entry	Ligand	Olefin	Ionic liquid	Yield (%)	ee[b] (%)	Abs. config.
1[c]	$(DHQ)_2$PHAL	*trans*-Stilbene	**1a**	95	85	*S,S*
2[d]	$(DHQ)_2$PHAL	*trans*-Stilbene	**1a**	45	n.d.	*S,S*
3	$(DHQ)_2$PHAL	*trans*-Stilbene	**1a**	94	97	*S,S*
4	$(QN)_2$PHAL	*trans*-Stilbene	**1b**	92	94	*S,S*
5	$(QN)_2$PHAL	*trans*-Stilbene	**1a**	95	97	*S,S*
6	$(QN)_2$PHAL	Styrene	**1a**	89	72	*S*
7	$(QN)_2$PHAL	β-Methyl-*trans*-styrene	**1a**	92	90	*S,S*
8[e]	$(DHQ)_2$PHAL	Methyl *trans*-cinnamate	**1a**	96	91	2*R*,3*S*
9	$(DHQ)_2$PHAL	Methyl *trans*-cinnamate	**1a**	96	95	2*R*,3*S*
10	$(QN)_2$PHAL	Methyl *trans*-cinnamate	**1a**	96	94	2*R*,3*S*
11	$(QN)_2$PHAL	Methyl *p*-methoxy-*trans*-cinnamate	**1a**	93	96	2*R*,3*S*
12	$(QN)_2$PHAL	α-Methylstyrene	**1a**	98	63	*S*

[a] Unless indicated otherwise, all reactions were carried out on a 1 mmol reaction scale of olefin using 1 mol% of OsO_4, 2.5 mol% of chiral ligand, 1.5 mmol of NMO and 2 mmol of the ionic liquid **1** in acetone–H_2O (v/v = 10 : 1, 10 mL) at 20 °C. Olefins were added for 12 h. [b] Determined by chiral HPLC. [c] Olefin was added in one portion. Reaction time was 20 min. [d] Reaction was carried out with the recovered ionic liquid phase obtained from the reaction in entry 1 without further addition of OsO_4 and $(DHQ)_2$PHAL. [e] Olefin was added in one portion. Reaction time was 4 h.

DOI: 10.1039/b210104c



$(QN)_2PHAL$

Scheme 1

(entry 2 in Table 1): After completion of the reaction, all the volatiles were removed under reduced pressure and the chiral diols produced were extracted with pre-cooled (0 °C) diethyl ether from the residue. The remained ionic liquid phase was then subjected without any addition of osmium and ligand to the next run with a new batch of the olefin and NMO. However, further re-use of the recovered ionic liquid phase resulted in a dramatic decrease in the yield (45% after 24 h) of the product due to severe leaching of both osmium and $(DHQ)_2PHAL$ during the extraction with ether (entry 2 in Table 1). Leaching of the catalytic components during the extraction can be ascribed to some solubility of $(DHQ)_2PHAL$ in ether. Since the complex formation of OsO_4 and an alkaloid ligand is expected to be reversible, the lowering of the concentration of chiral ligand in the ionic liquid phase might result in more leaching of OsO_4 from the ionic liquid phase. Therefore, it is reasonable to assume that the use of an alkaloid ligand, which can be strongly immobilised in an ionic liquid, can minimise Os leaching during the extraction of the product. To prove our assumption, we used 1,4-bis(9-*O*-quininyl)phthalazine [$(QN)_2PHAL$] as the ligand. $(QN)_2PHAL$ will be converted to the alkaloid **2** bearing highly polar residues (four hydroxy groups) during AD reactions of olefins (Scheme 1). $(QN)_2PHAL$ is more economically preparable by the reaction of quinine and 1,4-dichlorophathalazine than the conventional $(DHQ)_2PHAL$.[10]

The use of $(QN)_2PHAL$ instead of $(DHQ)_2PHAL$ afforded the same yields and ees (entries 4–7 and 10–12 in Table 1) and, moreover, resulted in drastic improvement in recyclability of both catalytic components.† The recovered ionic liquid phase containing osmium and **2** could be recycled several times, even in the recycle experiments using 0.1 mol% of OsO_4 (Table 2). In the case of the recycle experiments using 0.1 mol% of OsO_4, the total turnover number (TON) was 2370 (entry 2 in Table 2). To the best of our knowledge, this is the highest TON value ever reported under Upjohn conditions. It should also be noted here that separate experiments with pure **2**[11] gave the same results. However, a gradual decrease in catalytic activity and enantioselectivity over successive reactions was observed and thus upon re-use the reaction time became longer. The loss of activity can be ascribed to osmium leaching and/or deactivation. However, during the extraction of diol with Et_2O, no leaching of the chiral ligand was observed.

Table 2 AD reactions of *trans*-stilbene in the ionic liquid **1a** using OsO_4–**2** as recyclable and reusable catalyst

Entry	%Yield (%ee)				
	Run 1	Run 2	Run 3	Run 4	Run 5
1†[a]	92 (98)	88 (96)	91 (94)	70 (94)	50 (94)
2[b]	90 (98)	89 (92)	58 (89)	—	—

[a] Recycle experiments were carried out on a 3 mmol reaction scale of olefin using 1 mol% of OsO_4, 5 mol% of $(QN)_2PHAL$, 4.5 mmol of NMO and 3 mL of the ionic liquid **1a** in acetone–H_2O (v/v = 10 : 1, 30 mL) at 20 °C. Olefin was added by a syringe pump for 12 h.†. [b] Recycle experiments were carried out on a 3 mmol reaction scale of olefin using 0.1 mol% of OsO_4 and 5 mol% of $(QN)_2PHAL$, 4.5 mmol of NMO and 0.3 mL of the ionic liquid **1a** in acetone–H_2O (v/v = 10 : 1, 30 mL) at 20 °C. Olefin was added by a syringe for 12 h.

In summary, this work demonstrates that the combination of an ionic liquid and a new bis-cinchona alkaloid **2** generated *in situ* from $(QN)_2PHAL$ during AD reaction provides a simple and practical approach to the immobilisation of both catalytic components (osmium and the alkaloid ligand) for AD reactions. This present method requires neither any additional modification of ligand nor high loading of osmium. Moreover, $(QN)_2PHAL$ is more economically preparable than the conventional AD ligands such as $(DHQ)_2PHAL$ [1,4-bis(9-*O*-dihydroquininyl)phthalazine]. Thus, we hope that the method described here might open up new perspectives for immobilisation of catalyst for AD reactions. Further optimisation of the recyclability of the both catalytic components is currently underway.

This research was supported by a grant (NRL-program) from Ministry of Science and Technology in Korea.

Notes and references

† *Typical procedure of asymmetric dihydroxylation of olefins using OsO_4-$(QN)_2PHAL$ and ionic liquid*: A 50 mL flask was charged with acetone-H_2O (10 : 1, v/v, 30 mL), [bmim][PF_6] (**1a**, 3 mL), OsO_4 (0.72 mL of 1 wt% of aqueous solution, 0.03 mmol) and $(QN)_2PHAL$ (116.2 mg, 0.15 mmol). After stirring for 10 min, *N*-methylmorpholine-*N*-oxide (NMO, 527.2 mg, 4.5 mmol) was added. *trans*-Stilbene (540.4 mg, 3 mmol) was then added by a syringe pump for 12 h and the reaction mixture was stirred at 20 °C for 20 min. All the volatiles were then removed under reduced pressure and the ionic liquid layer extracted with pre-cooled (0 °C) Et_2O (3 × 30 mL). The combined ether extracts were concentrated to dryness and the crude product was purified by flash column chromatography on silica (EtOAc/hexane 1 : 2) to give 592 mg (92%) of pure 1,2-diphenyl-1,2-ethanediol as a white solid.

Recycling and re-use of OsO_4–ligand–ionic liquid: To the ionic liquid layer recovered from the above experiment was added acetone–H_2O (10 : 1, v/v, 30 mL) and NMO (527.2 mg, 4.5 mmol). *trans*-Stilbene (540.4 mg, 3 mmol) was then added by a syringe pump for 12 h and the reaction mixture was stirred at 20 °C. Similar work-up and purification gave 567 mg (88%) of pure 1,2-diphenyl-1,2-ethanediol. The reaction was repeated for four times. The results were listed in Table 2.

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