Clean osmium-catalyzed asymmetric dihydroxylation of olefins in ionic liquids and supercritical CO_2 product recovery†

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The combination of ionic liquids (ILs) as solvents in the asymmetric Sharpless dihydroxylation (AD) with the use of *sc*CO_2 in the separation process allows a very simple, efficient, clean and robust system for the reuse of the AD catalytic system, which also does not need the use of organic solvents either for the reaction or for the separation of products and allows the isolation of the diol, in high yield and enantiomeric excess and basically without contamination with osmium.

Osmium-catalyzed asymmetric dihydroxylation (AD) of olefins is one of the most reliable methods for the preparation of chiral vicinal diols, which act as intermediaries in the syntheses of many biologically active substances. The obstacles to its large-scale application in the pharmaceutical and fine chemicals industries remain the osmium catalyst's high cost, toxicity and potential product contamination. To address this problem, several groups have investigated the possibility of immobilizing the osmium catalyst by microencapsulation,[1] anchoring it to porous resins,[2] or by ion exchange on various solid supports.[3] However, none of these methods proved successful to recover and reuse the catalyst for a larger number of cycles, and to prevent catalyst leaching. Recently, a novel way to immobilize the osmium and chiral ligand catalyst system was achieved by using ionic liquids (ILs) as co-solvents to the traditional reaction solvent, consisting of *t*-BuOH/water and acetone/water.[4]

Herein we report on extended research of catalyst immobilization in ionic liquids only, without any other reaction solvents, by combining it with supercritical CO_2 extraction, in order to enhance product quality, minimize osmium catalyst loss and make its reuse possible. The combination of supercritical CO_2 (*sc*CO_2) with ionic liquids (ILs) as an alternative reaction medium has recently become an intensive focus of research.[5] In fact, the remarkable properties of both solvents can bring numerous advantages to chemical processes. Due to their ionic nature and negligible vapour pressure, ionic liquids exhibit no appreciable solubility in *sc*CO_2; at the same time, *sc*CO_2 is remarkably soluble in most ionic liquids, and can be used to extract numerous organic substances from them without any IL contamination in the final product.[6] As it is possible to achieve homogeneous catalysis, with high selectivity and atom efficiency, by immobilising the catalyst in an IL, the extraction of the product with supercritical CO_2 that follows introduces, in principle, easy product recovery and catalyst recycle.

Provided that the AD reaction proceeds efficiently in ILs, the application of this concept requires that *sc*CO_2 will be selective towards the reaction products, and that it will not extract the catalyst. The solvent power of *sc*CO_2 is easily tuneable, because it depends essentially on its density, which varies rapidly with pressure and temperature. The strategy in this work was to try and use *sc*CO_2 at the lowest possible density where it can still dissolve to some extent the reaction products, but does not carry any catalyst out of the ionic liquid solution. In these high selectivity conditions, the lower solubility of the product in *sc*CO_2 can be compensated by extracting with higher amounts of the supercritical solvent.

The AD reaction was performed with the substrates 1-hexene and styrene, using the catalytic system consisting of $(DHQD)_2PHAL$ (1.0 mol%) and $K_2OsO_2(OH)_4$ (0.5 mol%) and the co-oxidants $K_3Fe(CN)_6$ and *N*-methylmorpholine oxide (NMO). Under these conditions, a range of ILs based on the methylimidazolium [mim], dimethylimidazolium [bdmim][7] and tetraalkyldimethylguanidinium [dmg][8] cations were screened. From those ILs, $[C_4mim]NTf_2$, $[C_8mim]BF_4$, $[bdmim]PF_6$, $[bdmim]BF_4$ and $[bdmim]NTf_2$ allowed the formation of the diol in high yields (87–98%) and enantiomeric excesses (e.e.) (90–97%), using NMO as the co-oxidant.‡ Similar results were also obtained for other olefins and using the ligands $(DHQD)_2PYR$, $(DHQD)_2PHAL$, $(DHQD)_2AQN$ and $(DHQ)_2PHAL$.‡ It is also important to mention that in previously reported methods using NMO as co-oxidant,[4,9] it was always necessary to add the olefin slowly in order to achieve high e.e. In contrast, in this work, with the above-mentioned ILs as reaction media, high e.e. were observed by adding the olefin at once. This advantage is due to the low solubility of the olefin in the ILs, since we observed the formation of a second phase of the olefin, which slowly disappears during the reaction.

Optimised results obtained for several representative olefins in the selected ILs $[C_4mim]NTf_2$ and $[bdmim]NTf_2$ are presented in Table 1.‡ They clearly show yields and e.e. which are better, or similar to those reported using the optimised solvent systems consisting of organic solvent/water[9] or ILs as a co-solvent.[4]

The use of NMO in opposition to $K_3Fe(CN)_6$ is advantageous for the removal of the reaction products from the IL, since NMO can be extracted from the IL phase using a non-aqueous solvent. In the case of $K_3Fe(CN)_6$, further extraction of the IL with water is required, which implies additional leaching of the osmium catalyst.[4] The reuse of the IL and the catalytic system was tested for 1-hexene using the above optimised conditions for

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† Electronic supplementary information (ESI) available: results of the AD reaction using different ILs, co-oxidants, ligands and substrates, schematic diagram of the apparatus used in *sc*CO_2 extraction, general experimental information and spectral data of initial and reused room temperature ionic liquid. See http://www.rsc.org/suppdata/cc/b4/b411325j/

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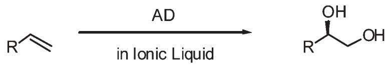
Table 1 Asymmetric dihydroxylation of olefins using ionic liquids as reaction media[a]



Ionic liquid	Styrene yield (ee)	α-methylstyrene yield (ee)	1-hexene yield (ee)	1-methylcyclohexene yield (ee)	*trans*-stilbene yield (ee)	*trans*-5-decene yield (ee)
[C$_4$mim]NTf$_2$	92 (93)	92 (89)	96 (97)	99 (98)	97 (67)	94 (99)
[bdmim]NTf$_2$	92 (98)	94 (89)	93 (95)	92 (93)	94 (85)	89 (98)

[a] Reaction conditions: (0.5 mmol), $K_2OsO_2(OH)_4$ (0.5 mol%), $(DHQD)_2PHAL$ (1.0 mol%), NMO (1 mol equiv.), IL (1.0 mL), rt, 24 h.

[C$_4$mim]NTf$_2$ and [bdmim]NTf$_2$. After each cycle, the reaction mixture was extracted with diethyl ether. We observed that this system is extremely robust ([C$_4$mim]NTf$_2$: run 1, yield = 98%, e.e. = 96%; run 14, yield = 92%, e.e. = 92%; [bdmim]NTf$_2$: run 1, yield = 94%, e.e. = 93%; run 13, yield = 93%, e.e. = 92%; run 14, yield = 88%, e.e. = 87%) and after new addition of the catalyst and ligand in run 15, the reaction restored again the high profile for the maximum of sixteen runs tested ([C$_4$mim]NTf$_2$: yield = 97%, e.e. = 97%; [bdmim]NTf$_2$: yield = 94%, e.e. = 94%).‡ However, the osmium content in the crude ethereal phase of each cycle has been found in the range of 1–2% of the initial amount of osmium catalyst, which would lead to some contamination of the product stream.

The concept of *sc*CO$_2$ extraction was tested for 1-hexene as a substrate model, using the same experimental conditions described above. After the reaction was finished, the reaction mixture was transferred to the *sc*CO$_2$ extraction apparatus, consisting of screw injector pump, high-pressure cell and a cold trap.‡ When two volumes of screw injector pump filled with CO$_2$ were passed through the system (120 cm^3; 1.72 mol of CO$_2$), the extraction was considered finished. The ethanol samples were collected, and divided into two equal parts. One was used for the determination of the osmium content by ICP and the other was used for the isolation of the 1,2-(*R*)-hexanediol and for the e.e. determination.

The initial round of *sc*CO$_2$ extraction experiments was performed in [bdmim]BF$_4$ at 40 °C and four different pressures (100, 120, 140 and 200 bar). The results indicate that lowering the pressure of CO$_2$ has a dramatic effect on the osmium content of the extracts. While 24.22% initial osmium content in the cell was extracted at 200 bar, only 0.34% (close to the detection limit of the analytical method) was measured at 100 bar.

A second round of experiments was then performed, at 100 bar, with four additional ionic liquids ([C$_8$mim]BF$_4$, [C$_{10}$mim]BF$_4$, [bdmim]NTf$_2$, and [C$_4$mim]NTf$_2$). For all five ILs, the amounts of osmium catalyst extracted were very small, up to a maximum of 0.69% of the initial osmium content of the cell. For [C$_4$mim]NTf$_2$ and [C$_{10}$mim]BF$_4$, high yields and e.e. were obtained, together with low osmium content.‡ Hence they were used in the third round of experiments, where successive reaction–extraction cycles were performed with the same ionic liquid + osmium catalyst mixture. In each new cycle, the substrate and co-oxidant were added to the IL phase, that remains in the cell after *sc*CO$_2$ extraction.

The succession was stopped only when the accumulation of the salt NMO rendered the solution too viscous for the reaction to take place within a feasible time interval. Still, after washing the mixture with water and diethyl ether, the reaction medium can be restored,‡ and its reuse can be resumed.

Table 2 Mass and yield of 1,2-hexanediol extracted, enantiomeric excess and osmium content for recycling experiments on osmium catalyst, immobilized in ionic liquid [C$_4$mim]NTf$_2$

Run	Extract [mg][a]	Yield [%][a]	ee [%]	Os content [%][b]
1	230 (37)	74 (12)	94	0.28
2	255 (23)	82 (7)	93	0.21
3	258 (17)	83 (5)	95	0.30
4	266 (6)	86 (2)	95	0.30
5	272	88	96	0.34
6	252	81	91	0.30
7	235	76	92	0.38
8	205 (14)	66 (5)	87	0.30
9	174	56	80	0.40

[a] The results in brackets represent the product mass and extraction yield, after the second volume of screw injector was introduced. [b] The osmium content in the extract for all runs is in the range of the detection limit of the method used (ICP).

The results of recycling experiments on osmium catalyst immobilized in [C$_4$mim]NTf$_2$ are presented in Table 2.

For some extraction cycles (runs 1, 2, 3, 4 and 8 in Table 2), the sample was also collected at the point when the first volume of screw injector pump filled with CO$_2$ (60 cm^3, 0.86 mol of CO$_2$) was passed through the system, in order to check how much of the product is extracted with this quantity of *sc*CO$_2$. The results suggest that most of the product is recovered with the first 60 cm^3 of CO$_2$ (CO$_2$/product molar ratio ∼400).‡

The product is obtained in high yield (above 80% until run 6) and enantiomeric excess (above 90% until run 8), with the lowest reported catalyst leaching.[4]

In summary, performing dihydroxylation in ILs provides a very efficient, simple and robust method for the immobilisation of the catalytic system in the AD reaction and when combined with an *sc*CO$_2$ extraction system allows a cleaner process with high product quality, as well as easy product recovery.

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Notes and references

‡ See more details in electronic supporting information.

1 T. Ishida, R. Akiyama and S. Kobayashi, *Adv. Synth. Catal.*, 2003, **345**, 576.

2 B. M. Choundary, K. Jyothi, S. Madhi and M. L. Kantam, *Adv. Synth. Catal.*, 2003, **345**, 1190; J. W. Yang, H. Han, E. J. Roh, S. Lee and C. E. Song, *Org. Lett.*, 2002, **4**, 4685.

3 B. M. Choundary, N. S. Chowdari, M. L. Kantam and K. V. Raghavan, *J. Am. Chem. Soc.*, 2001, **123**, 9220.

4 L. C. Branco and C. A. M. Afonso, *J. Org. Chem.*, 2004, **69**, 4381; R. Jiang, Y. Kuang, X. Sun and S. Zhang, *Tetrahedron: Asymmetry*, 2004, **15**, 743; C. E. Song, D. Jung, E. J. Roh, S. Lee and D. Y. Chi, *Chem. Commun.*, 2002, 3038; L. C. Branco and C. A. M. Afonso, *Chem. Commun.*, 2002, 3036.

5 R. A. Brown, P. Pollet, E. McKoon, C. A. Eckert, C. L. Liotta and P. G. Jessop, *J. Am. Chem. Soc.*, 2001, **123**, 1254; F. Liu, M. B. Abrams, R. T. Baker and W. Tumas, *Chem. Commun.*, 2001, 433; M. F. Sellin, P. B. Webb and D. J. Cole-Hamilton, *Chem. Commun.*, 2001, 781; A. Bösmann, B. Franciò, E. Janssen, M. Solinas, W. Leitner and P. Wasserscheid, *Angew. Chem., Int. Ed.*, 2001, **40**, 2679; P. B. Webb, M. F. Sellin, T. E. Kunene, S. Williamson, A. M. Z. Slawin and D. J. Cole-Hamilton, *J. Am. Chem. Soc.*, 2003, **125**, 15577; P. G. Jessop, *J. Synth. Org. Chem. Jpn.*, 2003, **61**, 484; V. Najdanovic-Visak, A. Serbanovic, J. M. S. S. Esperança, H. J. R. Guedes, L. P. N. Rebelo and M. Nunes da Ponte, *Chem. Phys. Chem.*, 2003, **4**, 520; P. Lozano, T. de Diego, D. Carrie, M. Vaultier and J. L. Iborra, *Chem. Commun.*, 2002, 692; S. V. Dzyuba and R. A. Bartsch, *Angew. Chem., Int. Ed.*, 2003, **42**, 148; D. J. Cole-Hamilton, *Science*, 2003, **299**, 1702.

6 L. A. Blanchard, D. Hancu, E. J. Beckman and J. F. Brennecke, *Nature*, 1999, **399**, 28; L. A. Gu, Z. Blanchard and J. F. Brennecke, *J. Phys. Chem. B*, 2001, **105**, 2437; C. Cadena, J. L. Anthony, J. K. Shah, T. I. Morow, J. F. Brennecke and E. J. Maginn, *J. Am. Chem. Soc.*, 2004, **126**, 5300.

7 J. Duppont, R. F. Souza and P. A. Z. Suarez, *Chem. Rev.*, 2002, **102**, 3667; P. Wasserscheid and W. Keim, *Angew. Chem., Int. Ed.*, 2000, **39**, 3772; T. Welton, *Chem. Rev.*, 1999, **99**, 2071; J. D. Holbrey and K. R. Seddon, *Clean Prod. Process.*, 1999, **1**, 223; L. C. Branco, J. N. Rosa, J. J. M. Ramos and C. A. M. Afonso, *Chem. Eur. J.*, 2002, **8**, 3671.

8 N. M. M. Mateus, L. C. Branco, N. M. T. Lourenço and C. A. M. Afonso, *Green Chem.*, 2003, **5**, 347.

9 R. A. Johnson and K. B. Sharpless, in *Catalytic Asymmetric Synthesis*, 2nd edn.; Ojima, I., Ed.; VCH: Weinheim, 2000; p. 357; H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483.