

Osmium-catalyzed asymmetric dihydroxylation of olefins in ionic liquids The effect of the chiral ligand structure on recyclability

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Abstract

Effective osmium-catalyzed asymmetric dihydroxylation was observed with 1,4-bis(9-*O*-diquininyl)phthalazine, (DQ)₂PHAL, as the chiral ligand in the ionic liquid, 1-*n*-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF₆]. It was shown that the ligand undergoes dihydroxylation during the reaction, affording a more polar ligand which remains in the ionic liquid phase, when the latter is extracted with diethyl ether, thus facilitating catalyst recycling. In contrast, when 1,4-bis(9-*O*-dihydroquininyl)phthalazine, (DHQ)₂PHAL, which cannot undergo dihydroxylation, was used as the chiral ligand, the catalyst was extracted into the organic layer.

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1. Introduction

Osmium-catalyzed asymmetric dihydroxylation (ADH) of olefins constitutes an effective method for the synthesis of chiral diols [1]. However, the high cost of the osmium and the chiral ligands, and the toxicity issues associated with osmium, seriously impede its widespread industrial application. Consequently, immobilization of the catalysts on, e.g. organic polymers, silica gel and layered double hydroxides (LDH) has been extensively investigated [2–5]. However, several chemical steps are often involved in anchoring the chiral ligand to the surface, rendering it recyclable but even more expensive. Recently, room-temperature ionic liquids (RTILs) have received increasing attention as non-volatile solvents for a variety of catalytic processes [6,7]. In principle, this can also form the basis for efficient recycling of the catalyst, e.g. by extracting the product into a separate phase with an organic solvent or supercritical carbon dioxide, and recycling the RTIL phase containing the (homogeneous) catalyst. Obviously for this concept to work the catalyst must remain completely in the RTIL phase and not be extracted into the second phase.

The osmium-catalyzed dihydroxylation of olefins, in the absence of chiral ligands, in RTILs was reported by Yao [8] and Yanada and Takemoto [9]. More recently, two groups [10,11] reported the asymmetric dihydroxylation of olefins in RTILs. This prompted us to report our results which focus on the recyclability of the catalyst in these systems, a condition sine qua non for industrial viability.

2. Experimental

2.1. Materials

The chiral ligands (DQ)₂PHAL [12] and [bmim][PF₆] [13] were synthesized according to literature procedures. (DHQ)₂PHAL, NMO and *trans*-stilbene were purchased from Aldrich.

2.2. Asymmetric dihydroxylation of *trans*-stilbene in [bmim][PF₆]

In a 25 ml flask, 15 mg (0.02 mmol) of (DHQ)₂PHAL or (DQ)₂PHAL was dissolved in 6 ml of solvent [bmim][PF₆]/H₂O/acetone (1:2:3 v/v), and 7.2 mg (0.02 mmol)

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$K_2OsO_2(OH)_2$ and 176 mg (1.3 mmol) of NMO were added after 5 min. Subsequently, 180 mg (1 mmol) of *trans*-stilbene was added and the mixture stirred at room temperature for 24 h. Following evaporation of all the volatiles (acetone, H_2O and *N*-methylmorpholine), the solution was extracted with 3×15 ml diethyl ether. The ionic liquid phase was recycled to the next run. The ether phase was evaporated and the crude product thus obtained was purified by flash silica gel column chromatography (EtOAc/hexane = 4:1). The enantiomeric purity (% ee) of the product was determined by comparison of the specific rotation with the literature value [12].

In a recycling experiment, 2 ml of H_2O , 3 ml of acetone, and 176 mg of *N*-methylmorpholine-*N*-oxide (NMO) were added to the ionic liquid layer from the above experiment. After stirring for 5 min, *trans*-stilbene (180 mg, 1 mmol) was added and the solution stirred for a further 24 h and worked up as described above.

2.3. Determination of the distribution of chiral ligands between [bmim][PF₆] and diethyl ether

15.6 mg of (DQ)₂PHAL or (DHQ)₂PHAL was dissolved in 1 ml of [bmim][PF₆] and the solution extracted with 3×15 ml diethyl ether. The combined ether layers were evaporated and the residue dissolved in 25 ml methanol. Similarly, the [bmim][PF₆] layer was diluted to 25 ml with methanol. The relative amounts of the chiral ligands present in the ionic liquid and ether phases were determined by HPLC on a 250 mm \times 4.6 mm Hypersil BDS C₁₈5u column fitted with a UV detector at 270 nm (mobile phase methanol, $r = 1$ ml/min).

Similarly, relative amounts of the oxidized products of the (DQ)₂PHAL ligand present in the ionic liquid and ether phases were determined by HPLC using MeOH/ H_2O (9:1) as the mobile phase and $r = 1.2$ ml/min. The retention times

Table 1
Asymmetric dihydroxylation of *trans*-stilbene, with (DHQ)₂PHAL as chiral ligand^a

Recycle	Yield (%)	ee (%)
1	67	81
2	72	75
3	57	56
4	No reaction	

^a Substrate/catalyst molar ratio = 50; NMO as oxidant, [bmim][PF₆]/ H_2O /acetone (1:2:3 v/v) as solvent, 24 h at room temperature.

of (DQ)₂PHAL, (DOHQ)₂PHAL and (D2OHQ)₂PHAL (see Fig. 2 for structures) were 11.83, 8.64 and 6.64 min, respectively.

3. Results and discussion

As our model reaction, we selected the asymmetric dihydroxylation of *trans*-stilbene using $K_2OsO_2(OH)_2$ (2 mol%), in combination with (DQ)₂PHAL or (DHQ)₂PHAL as the chiral ligand and *N*-methylmorpholine oxide (NMO) as the primary oxidant, in [bmim][PF₆]/ H_2O /acetone (1:2:3 v/v) as solvent (Fig. 1).

When the reaction was complete, volatiles were evaporated on a rotary evaporator and the product(s) was/were extracted into diethyl ether. The ionic liquid layer was recycled with a fresh batch of *trans*-stilbene and NMO. As shown in Table 1, when (DHQ)₂PHAL was used as the chiral ligand, the ee of the product decreased with each recycle and after recycling three times no reaction was observed. Analysis of the organic phase by TLC showed that it contained (DHQ)₂PHAL. Hence, the decrease in activity observed after each recycle is a result of the catalyst being abstracted into the organic phase. The accompanying decrease in enantioselectivity is a result of partial extraction of the chiral ligand

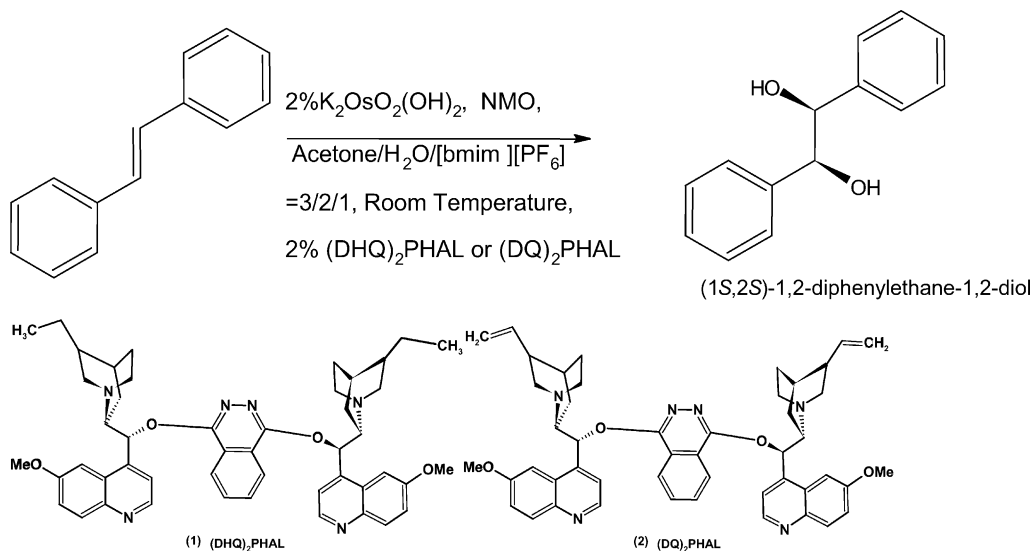


Fig. 1. Osmium-catalyzed asymmetric dihydroxylation of *trans*-stilbene in an ionic liquid.

Table 2
Asymmetric dihydroxylation of *trans*-stilbene with (DQ)₂PHAL as chiral ligand^a

Recycle	S/C ^b	Reaction times (h)	Yield (%)	ee (%)
1	50	24	65.7	85.3
2	50	24	65.0	67.7
3	81	48	64.3	72.0
4	50	48	64.6	50.6
5	50	48	69.0	22.9

^a See Section 2 for details.

^b S/C = substrate/catalyst molar ratio.

into the ether phase, leaving chiral ligand-free osmium in the ionic liquid phase.

In contrast, when (DQ)₂PHAL was used as the chiral ligand the ionic liquid phase could be recycled four times without significant loss of activity, albeit with decreasing enantioselectivity. The latter can be attributed to the fact that not all of the (DQ)₂PHAL ligand is hydroxylated (see Table 2, reaction mixture) and the unreacted (DQ)₂PHAL is extracted into the ether phase. Similarly, there is a slight decrease in activity, owing to partial extraction of the catalyst into the organic phase, but substantially less than that observed with (DHQ)₂PHAL.

A plausible explanation for this difference is that the double bonds present in the (DQ)₂PHAL ligand undergo dihydroxylation to produce the dihydroxylated and tetrahydroxylated analogues (see Fig. 2). The latter, being more polar, are not extracted from the ionic liquid by the diethyl ether. This was confirmed by determining the distribution of the various ligands between the ionic liquid and diethyl ether using HPLC (see Section 2 for details).

As shown in Table 3, 75% of the (DHQ)₂PHAL was extracted into the ether phase, compared with 26% for (DQ)₂PHAL. However, when the solution of (DQ)₂PHAL was pretreated with osmium and NMO, under the conditions of the dihydroxylation, no (DQ)₂PHAL was present in the ether phase following extraction. The ionic liquid phase was shown to contain the dihydroxylated and tetrahydroxylated

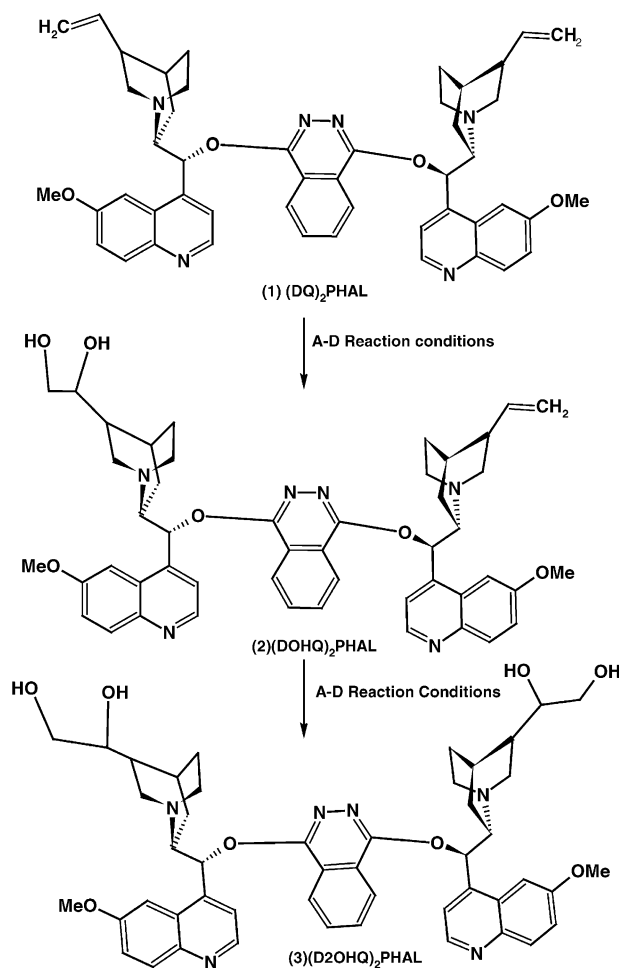


Fig. 2. Transformation of (DQ)₂PHAL to more polar chiral ligand under asymmetric dihydroxylation (ADH) conditions.

ligands and no (DQ)₂PHAL was present. Apparently, in the presence of MeOH/H₂O (the mobile phase) the free ligand is generated from the corresponding osmium complex.

Similarly, when the dihydroxylation reaction mixtures were subjected to ether extraction 80% of the (DHQ)₂PHAL

Table 3
Distribution of (DHQ)₂PHAL or (DQ)₂PHAL and its hydroxylated derivatives between Et₂O and [bmim][PF₆]

Chiral ligand	Distribution (%) of chiral ligand					
	No pretreatment ^a		Pretreatment ^b		Reaction mixture ^c	
	[bmim][PF ₆]	Et ₂ O	[bmim][PF ₆]	Et ₂ O	[bmim][PF ₆]	Et ₂ O
(DHQ) ₂ PHAL	25.3	74.7			20.1	79.9
(DQ) ₂ PHAL	74.7	25.9	n.d.*	n.d.*	73.0	26.9
(DOHQ) ₂ PHAL			98.2	1.78	99.3	0.75
(D2OHQ) ₂ PHAL			98.4	1.62	99.4	0.6

^a 15.6 mg (DHQ)₂PHAL or (DQ)₂PHAL dissolved in 1 ml [bmim][PF₆] and extracted with 15 × 3 ml Et₂O.

^b 15.6 mg (DQ)₂PHAL dissolved in 6 ml mixture of [bmim][PF₆]/H₂O/acetone = 1:2:3, oxidized under the ADH reaction condition (7.2 mg K₂OsO₂(OH)₂ (0.02 mmol), NMO 17.6 mg (0.13 mmol) RT, 24 h.

^c 180 mg *trans*-stilbene in [bmim][PF₆]/H₂O/acetone = 1:2:3, 15.6 mg (DHQ)₂PHAL or (DQ)₂PHAL, 7.2 mg (0.02 mmol) K₂OsO₂(OH)₂, NMO 176 mg (1.3 mmol) RT, 24 h.

* Not determined.

was present in the ether phase. When (DQ)₂PHAL was used as the ligand, the distribution of unreacted (DQ)₂PHAL in [bmim][PF₆] was 73% and the ether phase contained 27% similar to the distribution observed in the absence of the reaction components. Hence, we conclude that the (1*S*,2*S*)-1,2-diphenylethane-1,2-diol product had no effect on the distribution. In contrast, the dihydroxylated and tetrahydroxylated derivatives were almost entirely in the ionic liquid phase.

4. Conclusions

The suitability of using an ionic liquid for recycling of the catalyst in osmium-catalyzed dihydroxylations of olefins is largely dependent on the relative solubilities of the chiral ligand in the ionic liquid and the organic solvent used for product removal (diethyl ether). During the course of the dihydroxylation the unsaturated ligand (DQ)₂PHAL undergoes dihydroxylation to produce hydroxylated derivatives which are much more polar and difficult to extract from the ionic liquid. Hence, recycling is feasible with this ligand, in contrast to (DHQ)₂PHAL. Indeed, tuning the polarity of the (chiral) ligand is presumably of crucial importance in the design of effective recyclable catalytic systems in ionic liquid media.

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