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Heterogeneous asymmetric catalytic aminohydroxylation promoted by a bis-Cinchona alkaloid derivative supported onto an insoluble organic polymeric matrix

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Abstract

By using a bis(quinidinyl)phthalazine derivative linked to an insoluble organic polymer, 87% e.e. was obtained in the osmium-mediated catalytic heterogeneous asymmetric aminohydroxylation of isopropyl *trans*-cinnamate. The recycling of the polymeric ligand–osmium complex was also investigated.

In recent years, catalytic asymmetric aminohydroxylation (AA) joined the toolkit of effective carbon–carbon double bond enantioselective oxidation procedures. In fact, remarkable results in the AA of several alkenes have been attained in the homogeneous phase by Sharpless et al., by employing a mixture of $K_2OsO_2(OH)_4$, a Cinchona alkaloid derivative and various nitrogen sources.[1] Given the importance of the β-aminohydroxyl group as a structural motif of many chiral biologically active substances, some of which are of pharmaceutical relevance, and in view of larger scale applications, the improvement of AA by the use of heterogenized catalytic systems appears to be of great interest.[2] To date, only one example of heterogeneous AA with an organic polymer supported quinine derivative has been reported by Nandanan et al.[3] They prepared highly crosslinked copolymers between ethylene glycol dimethacrylate (90 mol%) and a bis(quininyl)pyridazine derivative (10 mol%) and used it as an insoluble ligand in AA of various olefins. Employing Chloramine-T as the nitrogen source, yields in the 52–65% range and enantiomeric excess values of 34–54% were obtained.[3] Furthermore, an attempt to recycle the alkaloid–osmium complex failed and few details were reported on the possibility of reuse of the ligand alone.

In this paper we report our preliminary findings in the heterogeneous AA of isopropyl *trans*-cinnamate, by using the copolymer **P1** containing a bis(quinidinyl)phthalazine derivative, previously employed with success in the heterogeneous asymmetric dihydroxylation of alkenes.[4]

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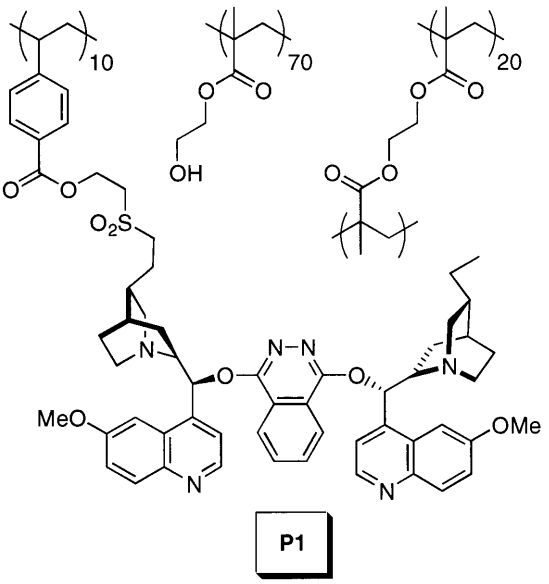
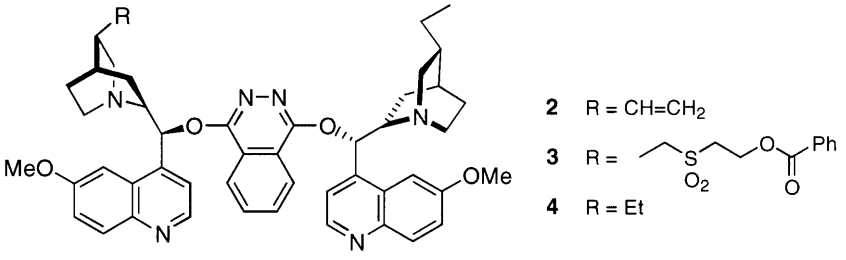
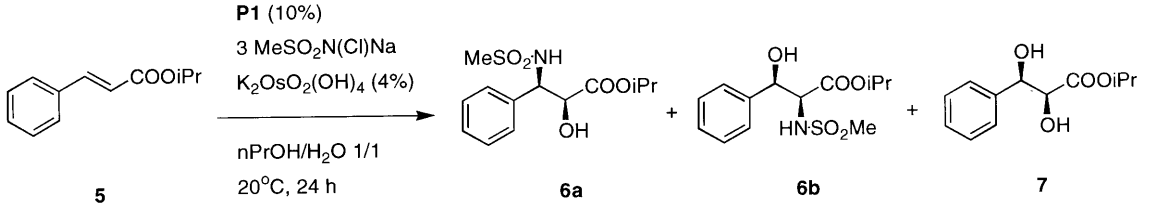


P1 (0.42 mmol alkaloid/g by elemental analysis) was prepared by known methods[4] from the intermediate **2**,[5] and the soluble model **3** was also synthesized for comparative purposes; Sharpless' ligand **4** was commercially available.



The catalytic AA runs of isopropyl cinnamate **5**, as a model substrate, were conducted under the recommended conditions for the homogeneous phase.[1a] In a typical procedure, to copolymer **P1** (0.10 mmol of chiral alkaloid units) suspended in nPrOH/H_2O = 1/1 (15 ml), *N*-chloromethanesulfonamide sodium salt (Chloramine-M, 3 equiv.), **5** (1 mmol) and $K_2OsO_2(OH)_4$ (0.04 mmol) were added in that order (Scheme 1). The reaction was monitored by TLC and HPLC with chiral stationary phase, determining at the same time conversion, chemoselectivity, regioselectivity and e.e. values, on the crude material.



Scheme 1. Asymmetric aminohydroxylation of isopropyl *trans*-cinnamate

The results obtained with the unmodified phthalazine ligand **4**, the soluble model **3** and the polymeric material **P1**, are summarized in the Table 1.

Table 1
Asymmetric aminohydroxylation of isopropyl *trans*-cinnamate in the homogeneous and heterogeneous phase

Entry	Ligand	Conversion %[a] **6a**+**6b**+**7**	Chemoselectivity %[a] (**6a**+**6b**)/(**6a**+**6b**+**7**)	Regioselectivity %[a] **6a**/(**6a**+**6b**)[b]	Ee %[a] (2*S*,3*R*)-**6a**
1	**4**	93	96	96	96
2	**3**	96	92	92	95
3	**P1**	98	94	91	87
4[c]	**P1**	73	91	89	83
5[c]	**P1**	58	84	89	81
6[d]	**P1**	59	79	88	78

[a] By HPLC (Daicel Chiralpack AD, 1.0 ml/min hexane/2-propanol = 70/30), after calibration with standard solutions.

[b] Configuration of the prevailing enantiomer of **6a**, by comparison of its HPLC retention time and optical rotatory power with that of an authentic sample (Ref. 1a). Configuration of prevailing enantiomer of **6b** not determined.

[c] Recycling run without addition of $K_2OsO_2(OH)_4$.

[d] Recycling run with addition of 10 mol% of initial amount of $K_2OsO_2(OH)_4$.

As far as soluble ligands are concerned, the model compound **3** was completely equivalent to Sharpless' ligand **4** (entries 1 and 2), demonstrating that the linker side arm does not affect activity or selectivity of the catalytic system. Moreover, the insoluble material **P1** afforded in a first run (entry 3) values of activity, regio- and chemoselectivity comparable to those obtained in homogeneous phase (entry 2). Even if a modest lowering of enantioselectivity was observed with respect to the soluble ligands, the e.e. value recorded with **P1** (87%, entry 3) is significantly higher than those previously reported with the comparable systems by Nandanan et al.[3] Although at present the reason of such an improvement is not clear, it is worth noting that **P1** features a minor crosslinking degree and the presence of pendant hydroxyethyl groups, which probably increase the compatibility of the polymer backbone with the reaction medium.

The possibility of recycling the **P1**–osmium complex was also briefly examined. After recovering by filtration and washing (H_2O and *n*PrOH), the insoluble material was directly used in two successive runs without adding any osmium salt (entries 4 and 5). While the regioselectivity did not change appreciably and only a slight decrease of chemo- and enantioselectivity was observed, the activity was significantly reduced during the recycles. Because this could be a consequence of metal leaching, the addition of 10% of the initial osmium loading was investigated (entry 6). However, while the added osmium salt prevented a further worsening of the catalyst performances (compare entries 5 and 6), a complete restoring of the initial activity could not be achieved.

In conclusion, the possibility of carrying out the effective asymmetric aminohydroxylation of a cinnamate ester with an organic polymer-supported alkaloid derivative **P1** has been demonstrated. Activity, chemo- and regioselectivity values equivalent to those obtained with soluble ligands have been achieved, together with a moderate reduction of enantioselectivity. Nonetheless, e.e. values of synthetic interest could be obtained in the course of few recycle runs of the insoluble ligand–osmium complex.[6]

Further studies are in progress in order to optimize the enantioselectivity in the AA reaction and to improve the recycle effectiveness of the catalytic system.

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5. Prepared by a published procedure, with modifications: Lohray, B. B.; Nandanan, E.; Bhushan, V. *Tetrahedron Lett.* **1994**, *35*, 6559.
6. One could argue that the catalysis with **P1** takes place in the homogeneous phase because of the ligand leaching under the reaction conditions. In this respect it is interesting to note that the solutions obtained by filtering the aged suspensions of the polymeric alkaloid alone in the pure solvent, or in the presence of Chloramine-M, contained only minute amounts of the ligand (less than 0.5% of the total supported alkaloid, by UV analysis). Accordingly, after the addition of the lacking reagents to these filtrates, the AA reaction proceeded with regio- and enantioselectivity values (66–69% and 23–34%, respectively) much lower than those obtained in the presence of **P1**. Furthermore, after **P1** had been filtered off at 55% conversion in an AA test run, a substantial worsening of the selectivity was observed (76% regioselectivity and 34% enantioselectivity after the filtration).