

Heterogeneous asymmetric aminohydroxylation of alkenes using a silica gel-supported bis-cinchona alkaloid

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Received (in Cambridge, UK) 7th September 1998, Accepted 5th October 1998

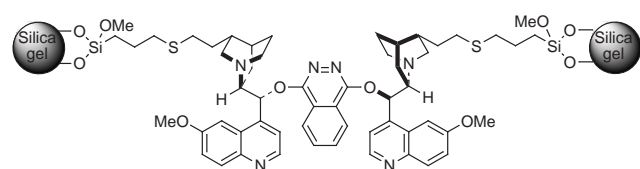
Excellent enantioselectivities of up to >99% ee have been achieved in the heterogeneous asymmetric aminohydroxylation of *trans*-cinnamate derivatives using silica gel-supported (QN)₂PHAL [SGS-(QN)₂PHAL **1**]; the dark brown 1-Os complex, recovered by simple filtration after reaction, could be reused without any loss of enantioselectivity.

Highly efficient methods for osmium-catalyzed asymmetric aminohydroxylation (AA) of alkenes in the presence of (DHQ)₂PHAL or (DHQD)₂PHAL ligands have been discovered recently by Sharpless and co-workers.¹ Initially, the catalytic AA reaction exploited TsNCINa (Chloramine-T) as the oxidant/nitrogen source.^{1a,b} Subsequently, with the development of new procedures which utilize carbamates^{1d} and amide-derived oxidants,^{1e} the substrate scope and selectivity has been greatly improved. The resulting chiral β-amino alcohol group is an important structural element in many biologically active molecules as well as the starting point in the design of many chiral ligands.

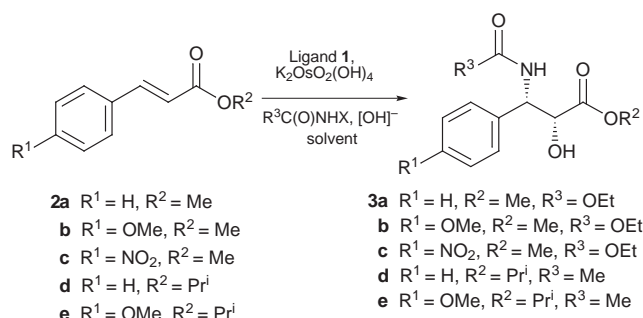
Recently, we prepared silica gel-supported (QN)₂PHAL [SGS-(QN)₂PHAL **1**],² which with OsO₄ yielded excellent

(DHQ)₂PHAL. No trace amounts of osmium could be found in all filtrates examined. These results encouraged us to examine the efficiency of **1** in the heterogeneous AA reactions. We report here our preliminary findings.

The heterogeneous AA reactions of *trans*-cinnamate derivatives using **1** were carried out either with EtOCONH₂/Bu^tOCl/NaOH^{1d} or AcNHBr/LiOH^{1e} as the oxidant/nitrogen source under the same reaction conditions adopted for the analogous homogeneous process (Scheme 1). The results are summarized in Table 1. The data show that all reactions examined using **1** exhibited excellent enantioselectivities. Generally, the amide-based AA reactions (Table 1, entries 4 and 6) gave higher yields and ees (>99% ee) than those employing the carbamate-based chemistry (entries 1–3). In particular, the AA reactions at 4 °C with amide as oxidant gave similar chemical yields (71–76%) and ees (>99% ee) to those obtained in homogeneous AA reactions.^{1e} It is noteworthy that when these reactions were carried out at room temperature, the chemical yields were significantly decreased (*ca.* 30–40% yield), whereas the ees were maintained. The reactions always stopped after *ca.* 50% conversion, and the pH of the mixture at the end of the reactions was about 5–6. It is probable that Hoffmann rearrangement³ of the *N*-bromoacetamide is a significant concurrent reaction at this temperature.



enantioselectivities in asymmetric dihydroxylation of alkenes (>99% ee for *trans*-stilbene). Moreover the catalytic system, the SGS-(QN)₂PHAL **1**-osmium complex, could be reused after simple filtration without any significant loss of enantioselectivity. UV analysis of the filtrate of the simple mixture of ligand **1** and OsO₄ in Bu^tOH–H₂O (1:1) in several molar ratios (1:1, 2:1, 4:1 *etc.*) showed that the binding affinity of **1** to OsO₄ is much greater than that of the homogeneous analogue



Scheme 1

Table 1 Heterogeneous catalytic AA reaction using SGS-(QN)₂PHAL **1**^a

Entry	Substrate	Oxidant	Solvent	t/h	Yield (%) ^b	Ee (%) ^c	Configuration ^c
1	2a	EtOCONCINa	Pr ⁱ OH–H ₂ O	12	40	88	2 <i>R</i> ,3 <i>S</i>
2	2b	EtOCONCINa	Pr ⁱ OH–H ₂ O	12	43	92	2 <i>R</i> ,3 <i>S</i>
3	2c	EtOCONCINa	CH ₃ CN–H ₂ O	12	52	92	2 <i>R</i> ,3 <i>S</i>
4	2d	AcNHBrLi	Bu ^t OH–H ₂ O	7	71	>99	2 <i>R</i> ,3 <i>S</i>
5 ^d	2d	AcNHBrLi	Bu ^t OH–H ₂ O	7	30	>99	2 <i>R</i> ,3 <i>S</i>
6	2e	AcNHBrLi	Bu ^t OH–H ₂ O	9	76	>99	2 <i>R</i> ,3 <i>S</i>
7 ^d	2e	AcNHBrLi	Bu ^t OH–H ₂ O	9	32	>99	2 <i>R</i> ,3 <i>S</i>
8 ^e	2e	AcNHBrLi	Bu ^t OH–H ₂ O	7	81	>99	2 <i>R</i> ,3 <i>S</i>

^a In all cases 4 mol% K₂OsO₂(OH)₄ and 5 mol% ligand were used. The reactions in entries 1–3 were carried out at 10 °C under the same reaction conditions as those reported in ref. 1(d). The reactions in entries 4–7 were carried out at 4 °C under the same reaction conditions as those reported in ref. 1(e).

^b Isolated yields by column chromatography. ^c The ees and absolute configuration were determined by chiral HPLC analysis.[†] ^d Reaction was carried out with **1**-Os complex recovered from the reaction in entries 4 and 6 respectively without further addition of K₂OsO₂(OH)₄. ^e Reaction was carried out with **1**-Os complex recovered from the reaction in entry 6 with the addition of small amounts of K₂OsO₂(OH)₄ (2 mol%).

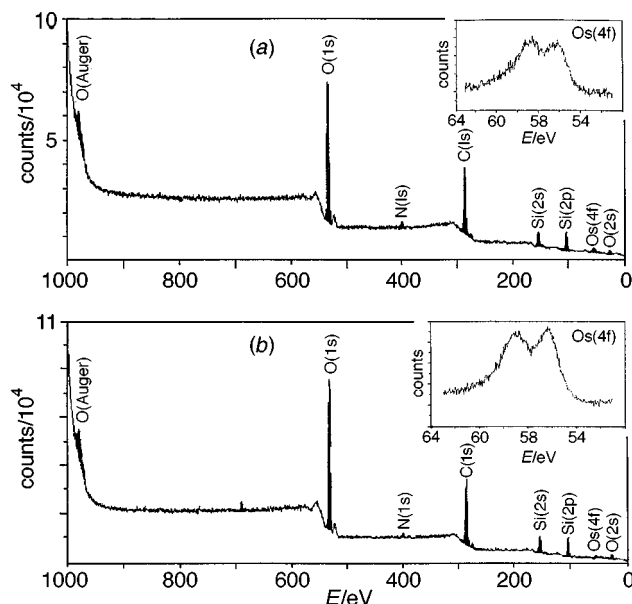


Fig. 1 XPS-spectra of the **1**-Os complex recovered after reaction, entry 4 (a) and entry 6 (b).

The efficiency with which the catalyst can be recycled has also been examined. The dark brown-coloured **1**-Os complex was recovered by simple filtration after each reaction (entries 4 and 6), which is not possible in a homogeneous process. XPS (X-Ray Photoelectron Spectroscopy)-analysis (Fig. 1) of the samples shows clearly that these recovered complexes contain osmium. However, the recovery yields were not high enough (<50%). The rest of the osmium was obviously lost to the mother liquor. The AA reactions were repeated with these samples without further addition of osmate salt. As shown in entries 5 and 7, the required amino alcohols **3d,e** were obtained in 30 and 32% yield with >99% ee, respectively. Moreover, the addition of small amounts of osmium to the recovered catalyst regenerated completely the reaction conditions (entry 8). These results indicate the viability of the repetitive use of osmium and

the chiral ligand, which is a current intrinsic limitation of catalytic AA and AD reactions.

In conclusion, we have achieved excellent ees for the heterogeneous catalytic AA of alkenes using a silica gel-supported bis-cinchona alkaloid **1**. Moreover, the recovered dark brown-coloured **1**-Os complex can be reused without any loss of enantioselectivity. We have also determined the Os content of this complex by XPS analysis. Further studies are currently in progress to increase the product yield, and the recovery of both the chiral ligand and the osmium.

This research was supported by a grant (MOST 2N17410) from the Ministry of Science and Technology in Korea.

Notes and references

† Determination of enantiomeric excesses: For **3a**: Chiralcel AD, PrⁱOH–hexane (10:90), 0.7 ml min^{−1}; 25.0 min (2*R*,3*S*), 29.6 min (2*S*,3*R*). For **3b**: Chiralcel AD, PrⁱOH–hexane (10:90), 0.7 ml min^{−1}; 36.1 min (2*R*,3*S*), 54.0 min (2*S*,3*R*). For **3c**: Chiralcel AD, PrⁱOH–hexane (10:90), 1 ml min^{−1}; 26.9 min (2*R*,3*S*), 43.2 min (2*S*,3*R*). For **3d**: Chiralcel AD, PrⁱOH–hexane (20:80), 1 ml min^{−1}; 6.9 min (2*R*,3*S*), 10.9 min (2*S*,3*R*). For **3e**: Chiralcel AD, PrⁱOH–hexane (20:80), 1 ml min^{−1}; 9.6 min (2*R*,3*S*), 16.7 min (2*S*,3*R*).

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- (a) C. E. Song, J. W. Yang and H. J. Ha, *Tetrahedron: Asymmetry*, 1997, **8**, 841; (b) For the preparation of chiral monomer, C. E. Song, J. W. Yang, H. J. Ha and S. G. Lee, *Tetrahedron: Asymmetry*, 1996, **7**, 645; (c) SGS-(QN)₂PHAL **1** was prepared as reported in ref. 2(a) using silica gel Merck-60 (230–400 mesh) instead of Li Chrosorb SI 60 (Merck, 5 mm). The content of alkaloid in **1** was determined by nitrogen analysis (0.21 mmol of alkaloid per gram).
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Communication 8/06959J