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Silica gel supported bis-cinchona alkaloid: a highly efficient chiral ligand for heterogeneous asymmetric dihydroxylation of olefins

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Abstract: Comparable reactivity and enantioselectivity to those in homogeneous solution have been achieved in heterogeneous catalytic asymmetric dihydroxylation (AD) of olefins using a new silica gel supported cinchona alkaloid containing 1,4-bis(9-*O*-quininyl)phthalazine ((QN)$_2$–PHAL). Moreover, the silica supported alkaloid exhibited much greater binding ability for OsO_4 than its homogeneous analogue. © 1997 Elsevier Science Ltd. All rights reserved.

The Sharpless catalytic asymmetric dihydroxylation (AD) of olefins using catalytic amounts of osmium tetroxide in the presence of cinchona alkaloid derivatives, allows access to a wide variety of enantiomerically pure vicinal diols.[1] In particular, the catalytic system based on bis-cinchona alkaloids such as 1,4-bis(9-*O*-dihydroquininyl)phthalazine ((DHQ)$_2$–PHAL) has received a great deal of interest, due to their broad scope of substrates and high enantioselectivities.[2] However, there are limitations to performing the catalytic AD reaction on a large scale due to the toxicity and high cost of osmium tetroxide and the cinchona alkaloid derivatives. To explore the possibility of the repetitive use of both components, several polymer-bound cinchona alkaloid derivatives have been employed.[3] However, most of the polymers require complicated synthetic manipulations and, moreover, their catalytic efficiency remains far from satisfactory. Recently, we have reported the heterogeneous catalytic AD reaction using polymeric bis-cinchona alkaloids, in which the vinyl group of the chiral monomer, (QN)$_2$–PHAL, was utilized as the connecting site to the polymer support.[3g] These polymers exhibited the highest enantioselectivity (99.9% ee for *trans*-stilbene and 99.3% ee for methyl *trans*-cinnamate) in heterogeneous catalytic asymmetric dihydroxylations (AD) of olefins. On the basis of these results, it could be imagined that such heterogenation could provide rigid U-shaped conformation of bis-cinchona alkaloid immobilized on polymer support, which may be crucial to the high ee's.[4]

In continuing our efforts to improve the mechanical and thermal properties of solid supported bis-cinchona alkaloids, we have now immobilized (QN)$_2$–PHAL on silica gel[5] and examined their catalytic efficiency in the catalytic AD reaction resulting the excellent reactivity and enantioselectivity. Here we report our preliminary results.

The silica gel supported bis-cinchona alkaloid **3** was prepared by the reaction of chiral monomer **1** with mercaptopropylsilanized silica gel **2**[6] in the presence of α,α'-azoisobutyronitrile (AIBN) as radical initiator in chloroform (Scheme 1).[7] Chiral monomer **1**, 1,4-bis(9-*O*-quininyl)phthalazine ((QN)$_2$–PHAL) was prepared as reported earlier.[3g] The nitrogen analysis of **3** confirmed 15.9 wt% incorporation of monomeric alkaloid **1**.

The heterogeneous ADs using silica gel supported alkaloid **3** were carried out under standard conditions, in *t*-BuOH/H_2O (1:1) at 10°C using $K_3Fe(CN)_6$–K_2CO_3 (3 equiv.) as secondary oxidant. The results are summarized in Table 1. As shown in Table 1, all reactions using **3** exhibited comparable reaction rates with those of homogeneous analogue (DHQ)$_2$–PHAL and excellent asymmetric

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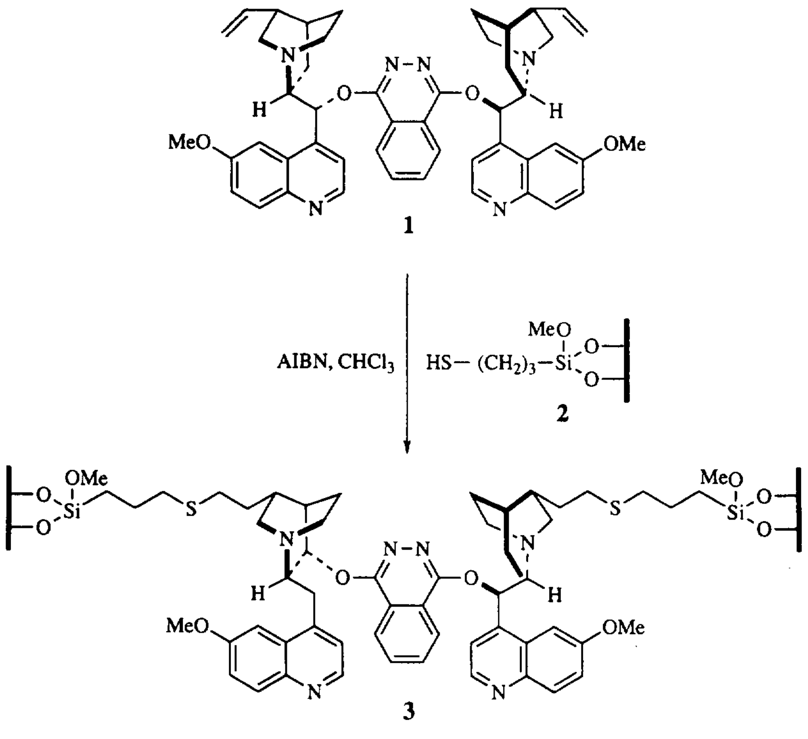

Scheme 1.

induction. The observed results suggest that alkaloid moieties on silica gel remain highly exposed to the reactants and thus substrates can access to the catalytic sites easily. Moreover, alkaloid moieties on silica gel exist in a favorable binding conformation, that is, the binding of substrates to the reaction pocket of OsO_4-bis-cinchona alkaloids may be very effective. Moreover, the silica gel supported alkaloid **3** revealed much greater binding ability for OsO_4 than its homogeneous analogue. Thus, silica gel supported alkaloid–OsO_4 complex could be reused without any significant loss of reactivity and enantioselectivity after simple filtration (entry 5). In the homogeneous solution, the complex formation of alkaloid and OsO_4 is in equilibrium. The binding constant K_{eq} ranges generally from 15 to 30.[3a] Thus, the enantiomeric excess in the homogeneous reaction approaches the maximum value with increasing ligand concentration. For the best results the reaction usually requires excess of expensive alkaloid ligands to osmium. However, in this heterogeneous system, excellent ee has been achieved with only an equimolar amount of ligand to osmium (entry 6).

In conclusion, we have achieved excellent results for the heterogeneous catalytic AD using silica gel supported bis-cinchona alkaloids **3**. Moreover, the silica gel supported ligand–OsO_4 complex exhibited a promising reusebility. Thus, this type of silica gel supported alkaloids will provide a possibility to overcome the intrinsic problems of traditional catalytic AD reactions. In addition, the catalysis occurs on the solid phase, and the catalysts have specific binding sites for OsO_4 and the olefin. Therefore, the catalytic action mode of silica gel supported bis-cinchona alkaloid is very similar with enzymes in terms of general function.[4c]

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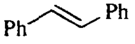
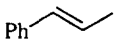
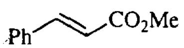
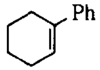
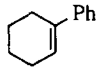
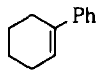
Table 1. Heterogeneous AD of olefins using silica gel supported bis-cinchona alkaloids 3[a]

Entry	Olefin	Reaction time	$[\alpha]_D^{20}$ (c, solvent)	% Yield[b]	% ee[c]	Config[c]
1		25h	-92.12(0.99, EtOH)	88	>99	*S,S*
2		15h	+30.00(1.32, EtOH)	92	96.5	*S,S*
3		20h	+10.19(1.03, $CHCl_3$)	93	95.2	*2R,3S*
4		15h	-18.56(1.11, C_6H_6)	96	96.2	*S,S*
5[d]		21h	-17.77(1.03, C_6H_6)	92	92.1	*S,S*
6[e]		16h	-18.30(1.06, C_6H_6)	95	94.8	*S,S*

[a]The reaction conditions were not optimized: molar ratio of olefin/OsO_4/silica gel supported alkaloid = 1/0.01/0.02; reaction temperature (10°C). [b]Isolated yields by column chromatography. [c]% ee and absolute configurations were determined by comparison of $[\alpha]_D$ with literature value.[8] [d]Reaction was carried out with silica gel supported alkaloid 3 which had been used in entry 4 without further addition of OsO_4. [e]Molar ratio of olefin/OsO_4/silica gel supported alkaloid = 1/0.01/0.01.

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homogeneous analogue, however much more inferior enantioselectivity; Lohray, B. B.; Nandanan, E.; Bhushan, V. *Tetrahedron: Asymmetry* **1996**, *7*, 2805.

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7. **Immobilization of monomer 1 on silica gel**: LiChrosorb SI 60 (Merck, 5 µm, 5.25 g) was treated with 23 ml of (3-mercaptopropyl)trimethoxysilane in 22 ml of anhydrous 1:1 pyridine/toluene. The slurry was heated at 90°C for 24 hours. After filtration the solid was washed (toluene, acetone, diethyl ether, pentane) and dried under vacuum for 1 hr, resulting in 6.05 g of a derivatized silica containing 3.82% S, corresponding to 1.19 mmol of S per g of derivatized silica. This derivatized silica **2** (5.98 g) was suspended in chloroform and refluxed with 1,4-bis(9-*O*-quininyl)phthalazine (2.90 g) and α,α'-azoisobutyronitrile (AIBN, 165 mg), as radical initiator, for 48 hours. Again, after filtration, the solid was exhaustively washed with methanol until the 1,4-bis(9-*O*-quininyl)phthalazine in excess was completely removed and dried under vacuum.
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