

A new bifunctional catalyst for tandem Heck–asymmetric dihydroxylation of olefins†

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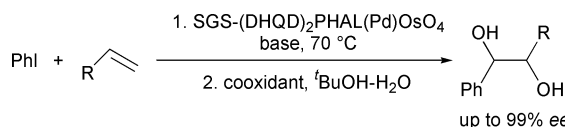
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A new bifunctional catalyst consisting of active palladium and osmium species anchored on silica gel through a mercaptopropyl spacer and a cinchona alkaloid respectively has been prepared for the first time and used in the heterogeneous tandem Heck–asymmetric dihydroxylation of olefins to afford diols with excellent yields and enantiomeric excesses (ee's) in presence of *N*-methylmorpholine *N*-oxide or $K_3Fe(CN)_6$ as cooxidants.

Improving the efficiency of organic processes in terms of conservation of energy, lowering the process time and inventory of equipment and minimizing the use of chemicals and production of waste is a major goal in synthetic chemistry. Performing multistep synthesis in one pot, prevalent in biosystems, is an attractive strategy to achieve this goal.¹ Significant progress using a combination of two catalysts for effecting tandem reactions has been achieved.² The recent design of a single matrix bifunctional catalyst comprising a BINOL–BINAP copolymer for the tandem asymmetric diethylzinc addition and hydrogenation of acetyl benzaldehydes marks a new era in bifunctional catalysis.³ Chiral vicinal diol units are often observed as key structures of natural products and also used in the synthesis of chloramphenicol (broad spectrum antibiotic), diltiazem (calcium channel blocker), taxol side chain, macrocyclic antitumor drugs and β -lactams. Sharpless asymmetric dihydroxylation of olefins offers one of the most efficient methods for the preparation of chiral diols.⁴ Heterogenisation of the chiral ligands on various polymers⁵ and silica gel⁶ is undertaken in order to effect the easy recovery and reuse of ligand in asymmetric dihydroxylation. Besides this, osmium complexed to the ligand, which constitutes a major portion, is recovered. Recently osmium has been immobilized on various supports based on microencapsulation⁷ and ion-exchange techniques⁸ to achieve complete recovery of metal. We have devised a new bifunctional catalyst anchored on a single matrix to execute tandem Heck–asymmetric dihydroxylation reactions for the synthesis of chiral diols. We report a synthesis of a new bifunctional catalyst covalently anchored on silica, comprising Pd–thiol and Os–cinchona alkaloid complexes, to perform Heck vinylation of aryl halides to obtain the desired prochiral olefin *in situ* for the asymmetric dihydroxylation to afford chiral diols successfully in a single pot (Scheme 1) for the first time in an effort to eliminate upstream unit operation otherwise necessary for the Heck reaction.

The synthesis of the bifunctional catalyst is effected as described in Scheme 2. The silica gel support contains silanol (SiOH) groups on the surface, which could be suitably derivatised to anchor a chiral catalyst.⁶ The external surface of

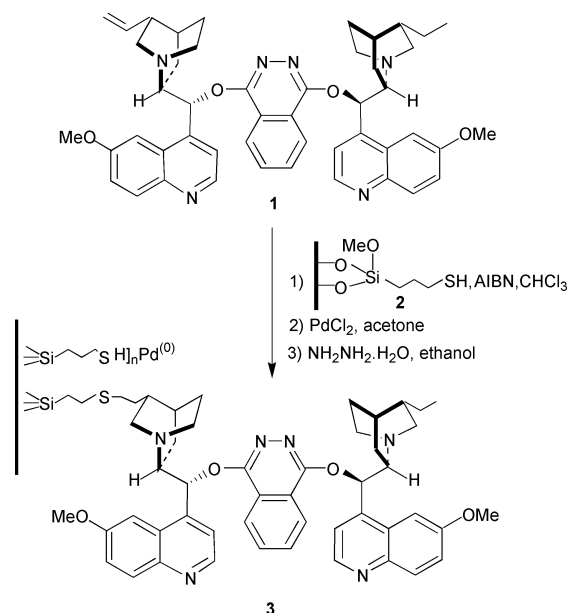


Scheme 1 Tandem Heck–asymmetric dihydroxylation catalyzed by a bifunctional catalyst.

† Electronic supplementary information (ESI) available: TEM image of **3**, experimental procedures, characterization data of products and heterogeneity tests. See <http://www.rsc.org/suppdata/cc/b1/b110681n/>


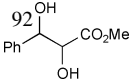
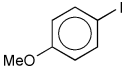

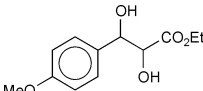
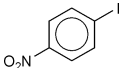

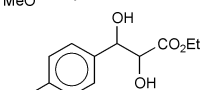


silica gel was treated with 3-mercaptopropyl trimethoxysilane to yield a material with mercaptopropyl tethers.^{6b} The silica gel anchored bis-cinchona alkaloid was prepared by the reaction of 4-(9-*O*-dihydroquinidiny)-1-(9-*O*-quinidiny)phthalazine **1**^{5b} with **2** in the presence of AIBN as the radical initiator in chloroform. The elemental analysis confirms the incorporation of 15.34 wt.% of monomeric alkaloid **1** based on nitrogen, and the presence of excess sulfur to indicate part of the thiol is unaffected in this process of anchoring. This is further substantiated by the IR spectra which shows the vibration at 2575 cm^{-1} assigned to the SH group. The SGS-(DHQD)₂PHAL containing SH groups was treated with PdCl₂ in acetone under reflux for 24 h. The resulting dark yellow powder was stirred with hydrazine hydrate and ethanol at room temperature for 4 h to give **3**. The formation of palladium nano particles upon reduction of thiol–palladium chloride complex with hydrazine hydrate is observed by UV, in which the absorption maxima at 280 nm, a characteristic band for Pd(II) disappeared. The transmission electron microscopy (TEM) image shows a high and homogeneous dispersion of palladium metal particles, with a particle size distribution centered at around 10–15 nm diameter.

In an effort to understand the scope and application of the bifunctional catalyst, we tested a tandem Heck–asymmetric dihydroxylation reaction on a variety of substrates (Table 1). Various disubstituted olefins were prepared *in situ* by Heck reaction⁹ and subsequently subjected to asymmetric dihydroxylation in a single pot. In the Heck reaction, the *trans*-olefins are formed exclusively. The heterogeneous dihydroxylation of olefins using **3**·OsO₄ was performed in *t*-BuOH–H₂O using NMO or $K_3Fe(CN)_6$ as cooxidants.⁴ All these reactions using **3**·OsO₄ recorded comparable reaction rates and marginally improved ee's over the homogeneous and heterogeneous dihydroxylation reactions using NMO oxidant.^{4–6} When the



Scheme 2 Synthesis of bifunctional catalyst (**3**·OsO₄).

Table 1 Tandem Heck–asymmetric dihydroxylation of olefins using heterogeneous bifunctional catalyst **3**-OsO₄

Entry	Aryl iodide	Olefin	Product	Cooxidant			
				NMO		K ₃ Fe(CN) ₆	
				Yield (%)	ee (%)	Yield (%)	ee (%)
1	PhI			90	93	99	
2				94	93	96	99
3				92	88	95	98 ^b
4	PhI			90	99	92	99
5 ^c				67	99	65	99
6 ^d				89	99	91	99

^a Catalyst **3** (50 mg, 0.01 mmol) and OsO₄ (0.01 mmol) in acetonitrile (5 ml) were stirred for 10 min and aryl iodide (1 mmol), olefin (1 mmol) and base (1–2 mmol) were added and stirred at 70 °C for 8 h (16 h for entry 2). At this stage, the heating was stopped and solvent was removed under vacuum. A cooxidant in t-BuOH–H₂O was added and stirred at room temperature for 12–24 h. Ee was determined by HPLC analysis using chiral columns. ^b One equivalent of CH₃SO₂NH₂ was used. ^c Reaction was carried out using recovered catalyst from entry 4 without further addition of OsO₄. ^d Reaction was carried out using recovered catalyst from entry 4 with addition of 0.3 mol% OsO₄.

recovered catalyst was reused as such without further addition of palladium or osmium, identical activity was observed for the Heck reaction. The palladium is found strongly bound to the thiol groups throughout the reaction; the thiols seem to stabilize and hold nanoparticles of Pd(0) and Pd(II) during the redox process of the Heck reaction. However, a drop in activity and consistent ee is noticed in dihydroxylation reaction (entry 5). The loss of activity for dihydroxylation with used catalyst is attributed to the leaching of the osmium into solution in the preceding cycle during the reaction. However, when the recovered catalyst from the fresh cycle is reused after replenishing with 0.3 mol% OsO₄, the activity in dihydroxylation reaction is restored (entry 6).

The use of bifunctional catalyst in place of a mixture of two homogeneous catalysts simplifies the catalyst recovery and purification of the products. Apart from this, excellent ee's are achieved with 1:1 ratio of ligand to osmium in contrast to the homogeneous reaction wherein excess of expensive chiral ligand to osmium is usually required.⁴ These results provide evidence that the binding ability of the present heterogeneous catalyst is greater than the homogeneous analogue.⁶ Secondly, the total mass of the heterogeneous catalyst is low, when two catalytic functions are created on a single matrix. Because of steric effects caused by the cinchona alkaloid, the process of anchoring left many of the SH groups intact. The use of such SH groups for the immobilization of palladium reduces the total mass of the bifunctional catalyst, when compared with the two heterogeneous catalysts made independently with cinchona alkaloid and Pd. Most importantly the byproduct, Et₃N·HI formed in the Heck reaction induces higher ee's in dihydroxylation reaction using NMO oxidant over the reported homogeneous and heterogeneous osmium catalysts.^{4–6} The improved ee's are ascribed to the Et₃N·HI salt that hastened the hydrolysis of osmate ester to give higher ee's. Finally, the bifunctional catalyst is tested for Heck and dihydroxylation reactions independently and identical activity is observed when compared to their analogues of heterogeneous Pd and Os catalysts with identical percentage of loading. This result indicates that there is no interaction between Pd and Os.

In summary, we have shown that a new bifunctional heterogeneous catalyst is highly efficient in the tandem Heck–

asymmetric dihydroxylation of olefins to afford the diols with high yields and ee's. Reduction of unit operations allows advancement of process design in terms of conservation of energy and lowering the process time and inventory of equipment. The simple procedure, easy recovery and reusable catalytic systems are expected to contribute to the development of benign chemical processes and products.

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