

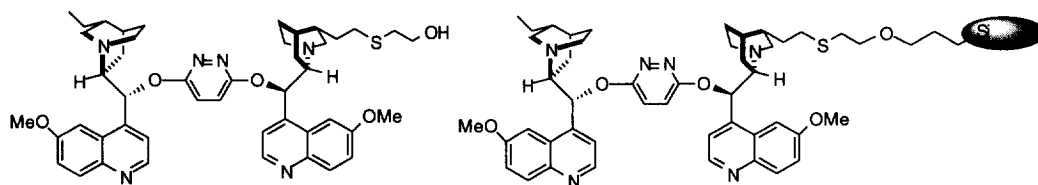
Catalytic Asymmetric Dihydroxylation of Alkenes Using Silica Gel Supported Cinchona Alkaloid#

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Abstract: Immobilization of 3,6-bis(9-*O*-dihydroquinyl)pyridazine and 3,6-bis(9-*O*-dihydroquinidyl) pyridazine on silica gel support has been reported. The use of immobilized auxiliary has lead to comparable rate with that of the homogeneous catalytic AD of alkenes, however with lower *ee*. Copyright © 1996 Elsevier Science Ltd

In recent years, several reports have appeared dealing with efficient osmium tetroxide catalyzed asymmetric dihydroxylation (AD) of alkenes using polymer supported cinchona alkaloids as chiral controllers.¹⁻³ All the heterogeneous catalytic AD reactions suffer from one or more drawbacks such as low reactivity, poor enantioselectivity, longer reaction time and poor yield. Recently, we have reported a



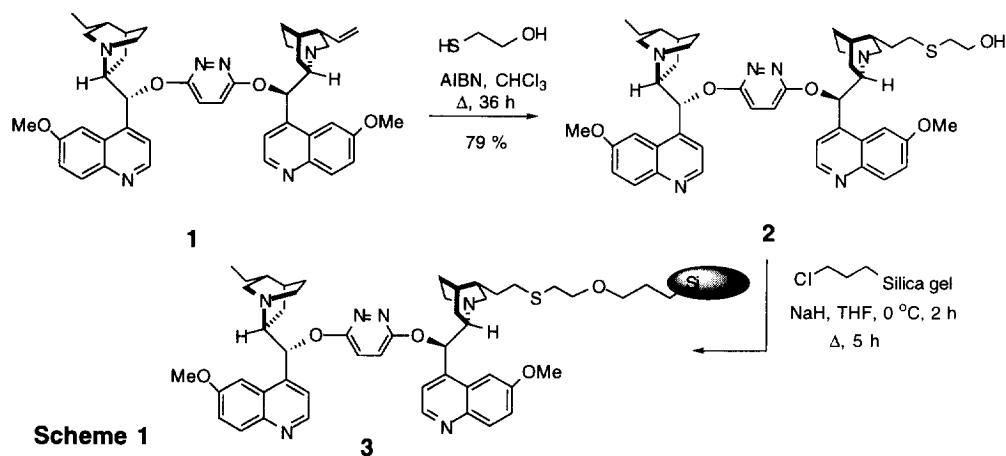
DHQ2-PY-monomer-2

DHQ2-PY-Silica gel Polymer-3

catalytic heterogeneous AD reaction immobilizing 3,6-(bis-9-*O*-dihydroquinyl) and 3,6-(bis-9-*O*-dihydroquinidyl) pyridazine on an ethylene glycol dimethacrylate backbone as the chiral auxiliary which compares favourably with homogeneous catalytic reactions.⁴ More recently, Salvadori *et.al.*^{2e} and Song and co-workers^{2f} have achieved good *ee* for certain aliphatic alkenes using polymer supported bis-(9-*O*-dihydroquinidyl) phthalazine. Thus, a steady improvement in the *ee* of diols from heterogeneous AD reactions

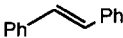

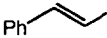



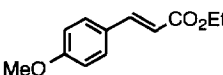
have been observed. As a more practical approach to the heterogeneous catalytic AD reactions for large scale synthesis, we envisioned the possible immobilization of the chiral auxiliary on an inorganic support such as clay, zeolite or silica gel due to their superior mechanical and thermal properties compared to organic polymer supported heterogeneous catalysts. We report here the successful grafting of the chiral cinchona alkaloid derivatives on a silica gel support which allows the chiral ligand to remain exposed for catalytic AD reactions.

The 6-(9-*O*-dihydroquinyl)-3-(9-*O*-quinyl)pyridazine was prepared as reported earlier⁴ and was reacted with thioethanol in the presence of azobisisobutyronitrile (AIBN) in chloroform to furnish bisdihydroquinyl pyridazine derivative **2**, in 79% yield.⁵ The chiral monomer **2** was then immobilized on silica gel using chloropropyl functionalized silica gel (2.5% chloride content, obtained from Aldrich) (Scheme 1).⁶ The amount of chiral monomer immobilized on silica gel was determined by combustion analysis by measuring the percentage of nitrogen.



This showed the presence of 2.1% chiral auxiliary immobilized on silica support. The advantage of using chiral auxiliary on silica gel support over the organic polymers is the better availability of active site and superior reaction rate and thus shorter reaction time. These properties may be attributed to the binding of chiral auxiliary on the silica surface which therefore remains exposed to the reactants unlike in the case of organic polymers in which chiral auxiliary may be encapsulated in the polymer matrix.¹⁻³ Table 1 shows the yield and enantiomeric excesses of various diols obtained by catalytic AD reaction of alkenes using silica gel supported chiral auxiliary **3**.⁷ All the reactions were performed in *t*-BuOH-H₂O (1 : 1) using K₃Fe(CN)₆-K₂CO₃ as co-oxidant at ca 20 °C. As expected, the rate of reaction, yield and the reaction time were comparable to that of the homogeneous reaction (Table 1), however, *ees* of the diols were surprisingly lower especially in the case of aliphatic mono- and disubstituted alkenes. Even aryl substituted alkenes showed inferior *ees* compared to the homogeneous case (Table 1, column 7) or on the organic polymer bound quinine derivative (Table 1, column 6).⁴ Reuse of silica gel bound auxiliary indicate some leaching of OsO₄ and ca 10% addition of OsO₄ became desirable to achieve the required rate. With the present information it is difficult to ascertain the actual cause of inferior selectivity, however, the following reasons may be assigned

Table 1 : Comparison of *ees* of the diols obtained in the AD reaction using (DHQ)2-PY-Silica gelPolymer 3, (DHQ)2-PY-Polymer and (DHQ)2-PY^a

S.No.	Alkene	Reaction time (h)	Yield (%)	Polymer-3	$[\alpha]_D^{25}$ ^b	(DHQ)2-PY- Poly ⁴	(DHQ)2-PY ⁸
1.		24	96	80	-73.6 (1.0) ^c	96	99.5
2.		15	92	56	+36.7(2.5) ^d	95	97
3.		15	86	64	+19.36(1.3) ^c	87	-
4.		15	90	52	+2.1 (2.9) ^c	86	-
5.		15	80	14	-2.6 (0.6) ^e	45	93
6.		15	83	22	-0.1 (2.4) ^d	-	-
7.		36	69	97	5.3 (0.23) ^d	-	96

(a) Enantiomeric excesses (%) of the diols were determined either by comparison of the specific rotation with the authentic samples and / or by the methods reported in the reference 4. The configuration of the diol follows the mechanistic mnemonics (b) The value in parentheses indicates concentration (c) in ethanol (d) in chloroform (e) in water.

with *caution*, namely the chiral auxiliary available for the AD reaction is perhaps very small due to highly insoluble nature of the polymer and therefore binding of the substrate to the reaction pocket⁹ may not be effective. Presently, we are investigating the possibilities of suitable modification of the silica surface which might be playing a crucial role resulting in lower *ees* of the diols. Modification of the silica surface may also lead to better availability of the chiral controller in organic phase which might improve the *ees*.

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5. **Preparation of monomer 2:** 3-Dihydroquinyl-6-quinyl pyridazine (2 g, 2.75 mmol) was added to a solution of 2-mercaptoethanol (234 mg, 210 μ L, 3 mmol) and AIBN (50 mg, 0.03 mmol) in CHCl₃ (6 ml) under argon. The reaction mixture was refluxed for 36 h. The pale yellow solution was cooled to room temperature and extracted with chloroform (3 x 15 ml), washed with brine (15 ml) dried (Na₂SO₄) and concentrated under reduced pressure to give a pale yellow solid which was purified by flash chromatography on silica gel (CHCl₃ : MeOH, 10 : 1), to furnish 1.75 g (79%) of **2** as a colourless solid, m.p. 172 °C, IR: (KBr) ν_{max} 3417, 1621 cm⁻¹, ¹H NMR : (200 MHz, CDCl₃) δ 8.67 (d, *J* = 3.8 Hz, 2 H), 8.0 (d, *J* = 9.61 Hz, 2 H), 7.6 - 7.3 (m, 6 H), 7.0 (s, 2 H), 6.75 (d, *J* = 5.8 Hz, 2 H), 3.91 (s, 6 H), 3.7 (t, *J* = 5.7 Hz, 2 H), 3.5 - 2.9 (m, 7 H), 2.68 (t, *J* = 4.5 Hz, 2 H), 2.6-2.2 (m, 5 H), 1.9-1.15 (m, 17 H), 0.85 (t, *J* = 5.8 Hz, 3 H); ¹³C NMR (50 MHz, CDCl₃) δ 160.5, 157.6, 146.9, 144.1, 131.0, 121.8, 121.3, 118.4, 101.6, 76.2, 60.4, 59.8, 59.3, 58.0, 57.7, 55.5, 42.6, 41.1, 36.9, 34.7, 34.4, 34.2, 29.6, 27.8, 27.3, 25.0, 22.8, 11.7. MS (*m/z*, relative intensity) 805 (M+1, 0.5 %), [α]_D²⁵ = + 116.2° (c, 1.0, EtOH)
6. **Immobilization of monomer 2 on silica gel support:** The monomer **2** (1.61 g, 2 mmol) was dissolved in dry THF (10 ml) under argon at ca. 0 °C and NaH (0.12 g, 5 mmol) was added and allowed to stir for 2 h at 0 °C. The chlorofunctionalized silica gel (2.5 % chloride content, 2.84 g) was added and stirred for additional 2 h at 0 °C. The reaction mixture was then refluxed for further 5 h and cooled to room temperature, quenched with crushed ice, filtered, washed several times with water, methanol and ether and dried over P₂O₅.
7. The actual chiral auxiliary in the reaction may be the corresponding sulfone derivative of **3** which is generated *in situ* by the oxidation of **3**.
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