Asymmetric dihydroxylation with silica-anchored alkaloids

Carsten Bolm,* Astrid Maischak and Arne Gerlach

Institut für Organische Chemie, RWTH Aachen, Professor-Pirlet-Strasse 1, D-52056 Aachen, Germany

Diols with excellent enantiomeric excesses are obtained from unfunctionalised alkenes in high yields by osmium-catalysed dihydroxylations using silica-bound pyrimidine and pyrazinopyridazine ligands.

The Sharpless asymmetric dihydroxylation (AD) is an efficient catalytic method for the enantioselective oxidation of unfunctionalised alkenes.[1] Since its discovery in 1988[2] the catalyst system has been continuously optimised,[3] so that now almost any alkene can be transformed to the corresponding diol with high enantioselectivity. In order to ease the recovery of the ligands after the catalysis, the use of various polymer-supported cinchona alkaloids has been studied.[4–7] Most of the insoluble ligands are easily handled but suffer from disadvantages, such as longer reaction times and lower enantioselectivity. Recently, we[6] and others[7] introduced soluble polymer-supported alkaloids with MeO-PEG tethers which gave catalysts with similar reactivity and enantioselectivity as those reported for the original Sharpless system. Ligand recovery was easily accomplished by addition of ethereal solvents to the reaction mixture followed by filtration of the precipitated alkaloid. In our approach,[6] the MeO-PEG attachment was designed such that negative steric interactions between the polymer backbone and the alkaloid moiety were minimised. We now report on the anchoring of this type of specifically modified cinchona alkaloid on insoluble inorganic carriers based on silica. In contrast to organic polymers, this kind of heterogeneous support offers a variety of possible applications due to its mechanical and thermal stability.

The polysiloxane-anchored bis(9-*O*-dihydroquinidinyl)pyrazinopyridazine **1** and bis(9-*O*-dihydroquinidinyl)pyrimidine **2** were synthesised from the corresponding phenols (R^1, R^2 = H)[6] and commercial functionalised silica† using standard acylation or nucleophilic substitution reactions.

The catalysed asymmetric dihydroxylations of representative alkenes were performed under standard reaction conditions in $Bu^tOH–H_2O$ (1 : 1) using $K_3[Fe(CN)_6]–K_2CO_3$ as oxidant, 0.5–1 mol% of $K_2OsO_2(OH)_4$ and 2 mol% of immobilised ligand. Mechanical stirring was applied in order to avoid silica deterioration. The most significant results are summarised in Table 1.

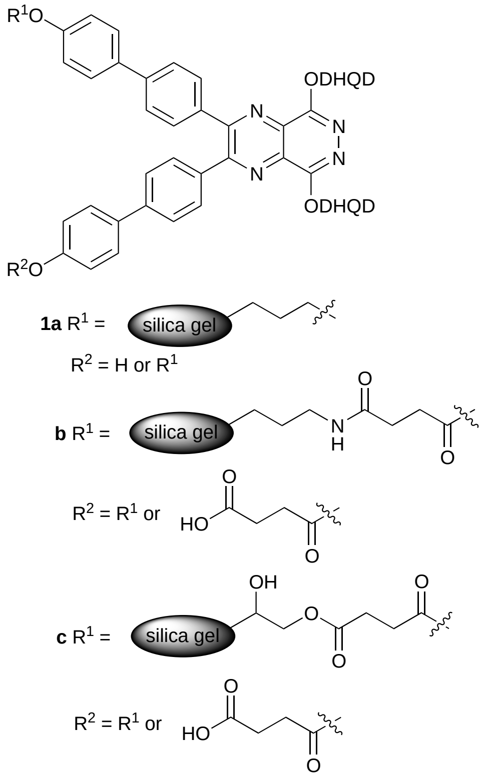
Table 1 Enantioselectivities in the AD of various alkenes[a]

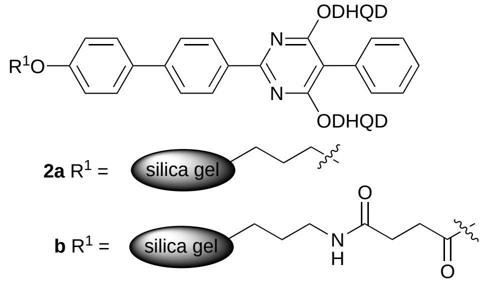
Entry	Alkene	Ligand	Yield (%)	Ee (%)[b]	Configuration
1	*trans*-PhCH=CHPh	**1a**	77	99 (99)	(*R*,*R*)
2	$PhCH=CH_2$	**1a**	93	98 (99)	(*R*)
3	$PhCH=CH_2$	**1b**	93	90	(*R*)
4	$PhCH=CH_2$	**1c**	92	97	(*R*)
5	$C_8H_{17}CH=CH_2$	**2a**	51	84 (89)	(*R*)
6	$C_8H_{17}CH=CH_2$	**2b**	53	61	(*R*)
7	$Bu^tCH=CH_2$	**2b**	62	70 (92)	(*R*)

[a] AD experiments as per typical protocol (see text). [b] Determined either by comparison of the specific rotation with the authentic samples or by HPLC using a chiral stationary phase [refs. 3(*a*), 4(*f*), 6]. The ee values of products which were obtained from catalyses with non-polymer supported DHQD ligands [ref. 3(*b*)] are given in parentheses.

In the AD of styrene and stilbene, exceedingly high enantioselectivities were achieved with heterogeneous silica-anchored ligands **1a** and **1c** having ether and ester linkers, respectively. A slightly lower asymmetric induction was observed when amido linked **1b** was applied (Table 1, entry 3). Presumably, residual amino groups on the silica surface or the amido linker itself have a negative influence, giving diols with reduced enantiomeric excess. Support of this hypothesis was gained in AD experiments performed with alkaloid-free amino functionalized silica gel. The rapid formation of racemic diol revealed the high catalytic activity of the support.

Under homogeneous conditions pyrimidine ligands are most suitable for the enantioselective dihydroxylation of aliphatic, terminal alkenes. Therefore, AD reactions of dec-1-ene were performed with silica-supported pyrimidines **2a** and **2b** (Table 1, entries 5 and 6). Catalyses with both ligands afforded the





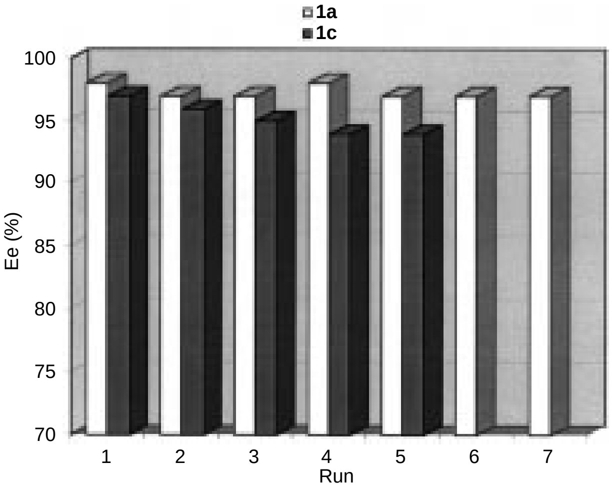


Fig. 1 Enantioselectivities in consecutive AD reactions of styrene using silica-supported alkaloids **1a** and **1c**

corresponding diols in moderate yield with enantiomeric excesses of 84 and 61%, respectively. The former value compares well to the one obtained with the original homogeneous Sharpless system (89% ee).

In order to examine the stability of the catalyst and the possibility of ligand recovery, **1a** and **1c** were used in consecutive AD reactions of styrene. As shown in Fig. 1, silica-supported alkaloid **1a** was used seven times without significant loss of enantioselectivity. The enantiomeric excess of the diol stayed in the range of 97–98%, and the chemical yields were excellent. In contrast, in AD reactions with silica-attached **1c** the efficiency of the catalysis decreased with each run. Presumably, parts of the alkaloid were lost in each recycling process due to a minor ester hydrolysis under the basic reaction conditions. In order to ensure the presence of sufficient amounts of osmium in the reaction mixture, 0.5–1 mol% of $K_2OsO_2(OH)_4$ was added before each run in the experiments described above. Without this addition, a considerable decrease in activity was observed, indicating metal leaching during catalyst recovery. For example, in consecutive AD reactions of styrene in the presence of **1a** *without* the addition of osmium, the diol yield dropped from 93% in the first run to 50 and 34% yield in the second and third run, respectively. Even under these very unfavourable conditions, and despite the metal loss, the catalysis still benefits from the phenomenon of 'ligand acceleration'[8] and gives the products with high enantiomeric excess (run 1: 98% ee; run 2: 98% ee; run 3: 95% ee).

The results of this investigation can be summarised as follows. (i) The enantioselectivities in these heterogeneous AD reactions are excellent, and diols with up to 99% ee are formed. (ii) The new silica-bound alkaloids can be quantitatively recovered by simple filtration. (iii) Recycled ligands give catalysts which perform several times without loss of activity and enantioselectivity. (iv) Consecutive use of the immobilised ligands in AD reactions is possible but requires the addition of small quantities of osmium after each run. If no metal is added the enantioselectivity remains high but the catalyst activity is reduced.

This research was supported in part by grants from the BMBF and the Fonds der Chemischen Industrie.

Footnotes and References

* E-mail: carsten.bolm@rwth-aachen.de

† The chloropropyl functionalised silica (2.5% chloride content) was obtained from Aldrich. Propylamino (0.19 mmol g^{-1}) and diol functionalised (0.35 mmol g^{-1}) polysiloxanes were purchased from Schuller. A double attachment of **1** onto the silica surface *via* the two phenolic hydroxy groups cannot be excluded.

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Received in Cambridge, UK, 10th September 1997; 7/06605H