Polymer-Supported Catalytic Asymmetric Sharpless Dihydroxylations of Olefins

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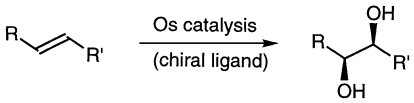
The need for catalyst systems for the asymmetric dihydroxylation of olefins (AD) that combine the positive characteristics of the original homogeneous osmium catalysts with the ease of separation of heterogeneous catalysts led to the introduction of polymer-supported alkaloid ligands. Two major strategies for ligand recovery will be discussed here: (a) Attachment of the alkaloids to a *solid* support, such as an organic polymer or silica gel. After catalysis the ligands can easily be recycled by simple filtration. (b) The alkaloids are anchored to a polymeric unit which allows catalysis to be performed under *homogeneous* conditions. After the reaction is complete, the ligand is isolated by precipitation upon addition of solvent followed by filtration. Recent results of investigations of both strategies will be presented.

Introduction

Cinchona alkaloid catalyzed asymmetric Sharpless dihydroxylation (AD)[1] has emerged as one of the most general methods for the enantioselective functionalization of olefins. Since its discovery in 1988,[2] the alkaloid ligands and cooxidant/solvent systems have been optimized so that now almost all classes of olefins can be dihydroxylated with excellent enantioselectivity.[3]

Due to the high cost of both the alkaloid-derived ligands and the metal, methods for facile and efficient catalyst recovery are of major interest. This aspect is particularly important in large-scale applications. Various concepts have been applied to address this problem.[4] The most successful alkaloid-derived ligands have been immobilized by attaching them on solid organic polymers or inorganic supports. In principle, this eased the separation of the ligands after the AD, but many positive aspects of the original homogeneous catalyst system, such as the high activity and



Carsten Bolm, born in 1960, studied chemistry in Braunschweig (Germany) and at the University of Wisconsin, Madison (USA). He completed his doctorate with Prof. M. T. Reetz in Marburg (Germany) on chiral catalysts for enantioselective C−C coupling. After a postdoctoral stay with Prof. K. B. Sharpless at the Massachusetts Institute of Technology, Boston (USA), he worked with Prof. B. Giese in Basel (Switzerland), to obtain his habilitation on enantioselective catalysis with chiral ligand−metal complexes. In 1993 he became Professor of Organic Chemistry at the University of Marburg (Germany). Since 1996 he has been a chair of Organic Chemistry at the RWTH Aachen (Germany). His awards include the Heinz-Maier-Leibnitz prize, the ADUC-Jahrespreis for habilitands, the annual prize for Chemistry of the Akademie der Wissenschaften zu Göttingen, and the Otto-Klung prize.

Arne Gerlach, born in 1970, studied chemistry at the Freie Universität Berlin (Germany). In 1995 he finished his Diploma after having carried out research at Degussa AG, Hanau, under the guidance of Prof. J. Mulzer and Prof. K. Drauz. Subsequently, he joint the research group of Prof. C. Bolm at the University of Marburg. Presently, he is completing his doctorate at the RWTH Aachen (Germany).

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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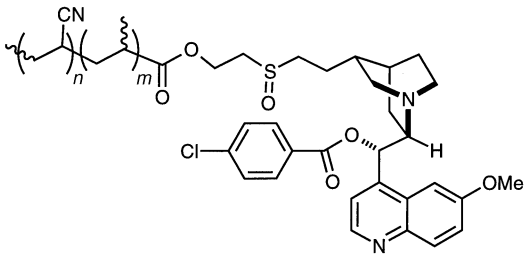
enantioselectivity, were diminished. Significant optimization was required to develop heterogeneous AD catalysts giving diols with high enantiomeric excess (*ee*). Alternatively, *soluble* supported ligands have been prepared. When they are applied, most characteristics of the homogeneous AD remain, and products with very high enantiomeric excesses can be obtained. After the reaction, these ligands are then easily recovered by precipitation followed by filtration.

All approaches described above allow a more or less efficient recovery of the ligands, and thus, important practical applications can be foreseen. This short, but comprehensive review summarizes in detail the current state of the art.

Organic Copolymers

The very first use of polymer-bound cinchona alkaloid derivatives in the catalytic asymmetric dihydroxylation of olefins has already been reported in 1990 by Kim and Sharpless.[5][6] Besides other polyacrylonitriles, they synthesized insoluble polymer **1** by radical copolymerization of a 9-(*p*-chlorobenzoyl)quinidine acrylate with acrylonitrile and tested it in the AD of *trans*-stilbene.

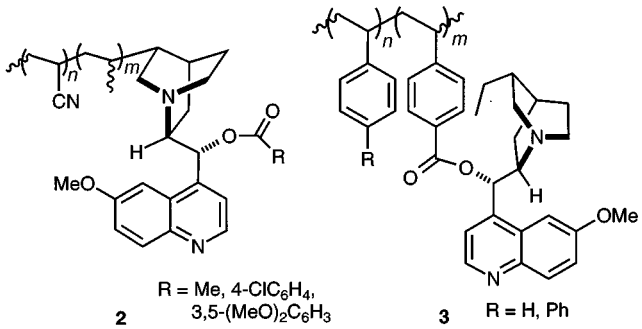


1

With *N*-methyl morpholine *N*-oxide (NMO)[7] as secondary oxidant in acetone/water (10:1, v/v) good to excellent enantioselectivies (85−93% *ee*) and reasonable reaction rates (2−3 d) were observed. The asymmetric induction varied slightly depending on the batches of the polymer. Even after completion of the reaction the activity of the OsO_4−polymer complex was preserved, thus allowing repetetive use of the complex with only moderate loss of reactivity and enantioselectivity.

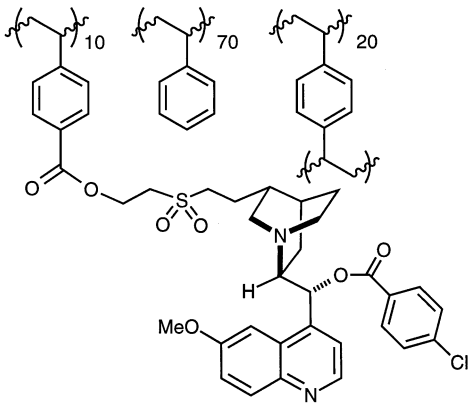
Almost at the same time, Salvadori and coworkers[8] developed the related polyacrylonitrile-supported 9-*O*-acylquinine derivatives **2**. In these compounds the alkaloids are directly bound to the polymer chain without a spacer. Under the same reaction conditions used by Sharpless various optically active diols were obtained in good chemical yields but with significantly lower enantiomeric excesses (6−46% *ee*).

Polystyrene-supported 9-*O*-acylquinidine derivatives **3** were introduced by Lohray et al.[9] Among all the polymers examined, the one with 10% dihydroquinidine loaded on the polystyrene backbone proved to be the most effective for the AD of *trans*-stilbene, furnishing hydrobenzoin with 85% *ee*. An increase in the amount of immobilized alkaloid led to a significantly reduced rate and lowered the enantiomeric excess of the diol. Use of recycled polymer gave less product with decreased enantioselectivity. The catalyst efficiency with recycled polymer could be regained by the addition of 0.1 mol% of osmium. Interestingly, if the reaction was carried out with the homopolymer of dihydroquinidine 4-vinylbenzoate (**3** with $n = 0$, $m = 1$) nearly racemic hydrobenzoin was formed in only 20% chemical yield after 2−3 d. Later, the use of this homopolymer was reinvestigated by Song et al.,[10] and in sharp contrast to the previous observations,[9] they found that it exhibited excellent enantioselectivity (ee_{max} = 93% for *trans*-stilbene and 91% *ee* for *trans*-methyl cinnamate) with $K_3[Fe(CN)_6]$ as secondary oxidant. The asymmetric induction was slightly improved by using crosslinked polystyrene-supported 9-(*p*-chlorobenzoyl)quinine **4**.[11]



2 R = Me, 4-ClC_6H_4, 3,5-$(MeO)_2C_6H_3$

3 R = H, Ph



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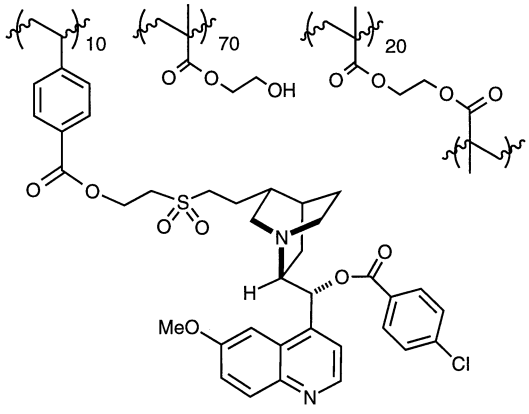

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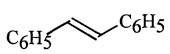
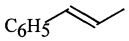
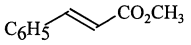
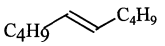
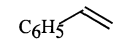
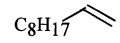
In **4** a spacer group between the quinine derivative and the polymer backbone was introduced to let the quinuclidinic moiety of the ligand, which is responsible for the OsO_4 complexation, unaffected by the steric hindrance of the polymeric chain. AD of *trans*-stilbene using this copolymer and NMO as secondary oxidant gave the product with good stereoselectivity (87% *ee*). In contrast, with $K_3[Fe(CN)_6]$ as oxidant in *t*-BuOH/water (1:1, v/v) no diol was formed. In this polar protic solvent system the copolymer probably collapses, thus preventing substrate penetration. This effect was overcome by the use of copolymer **5**, which bears hydroxyl groups in the polymer backbone.[12] Although **5** is insoluble, it swells very well in polar protic solvents. The AD of several olefins, terminal and internal, was investigated with either NMO or potassium ferricyanide as secondary oxidants. In general, the reaction proceeded with high enantioselectivity (up to 95% *ee*), and in many cases the results were comparable to those obtained with 9-(*p*-chlorobenzoyl)quinine itself. Compared to NMO, higher enantiomeric excesses were obtained with potassium ferricyanide, as was also found in the homogeneous AD reactions, indicating that the low-enantioselective "second cycle" could thus be avoided.[13] Major results are summarized in Table 1.

Table 1. Enantioselectivities in the AD using **5**

No.	Olefin	*ee* [%]	
		$K_3[Fe(CN)_6]$	NMO
1		95	90
2		81	60
3		80	60
4		75	13
5		65	40
6		50	14

Polymer-supported 3,6-bis-(9-*O*-dihydrochininyl)pyridazine [$(DHQ)_2PYDZ$] (**6**) was prepared by Lohray et al.[14] It has a large pore size and its hydrophilic properties allow the AD of *trans*-stilbene to proceed at 20°C when using $K_3[Fe(CN)_6]$ as secondary oxidant, giving the product with 98% *ee* within 20 h. In comparison, the corresponding free DHQD-pyridazine ligand gives the diol with >99% *ee*.[15]

In the continuous effort to further improve the asymmetric induction in the AD, Salvadori et al. introduced the first polymer-bound 1,4-bis-(9-*O*-dihydrochinidinyl)-phthalazine [$(DHQD)_2PHAL$] (**7**).[16][17] In the homogeneous case the PHAL ligands provided the best enantioselectivity for five out of six classes of olefins. With potassium ferricyanide as secondary oxidant, 0.5−1 mol% of osmium tetroxide and 10−25 mol% of immobilized PHAL **7**, the highest enantiomeric excesses so far, in the AD using organic polymers, have been achieved (Table 2).[16][17]

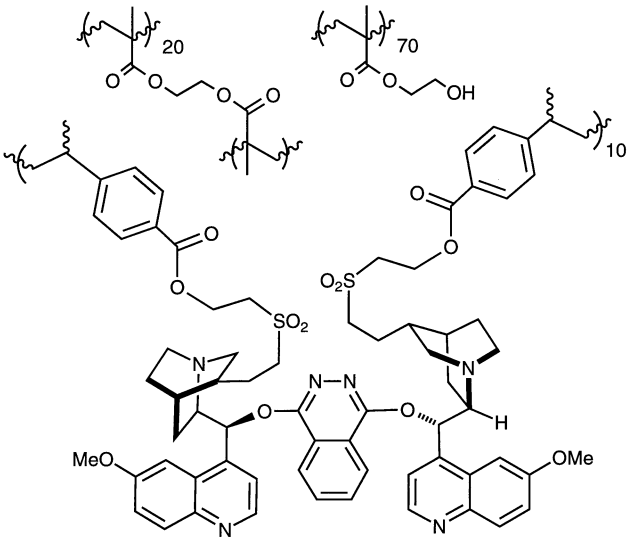


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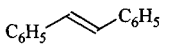
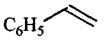
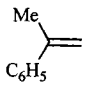
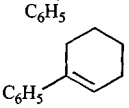
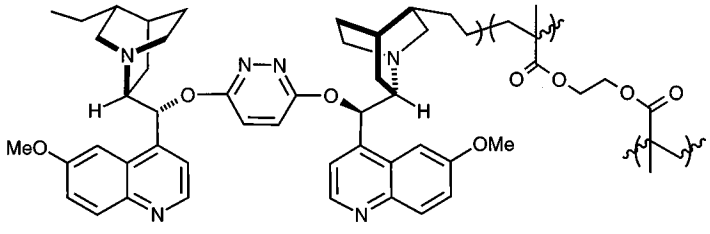
Table 2. Enantioselectivities in the AD using **7**

No.	Olefin	*ee* [%][a]
1		>99 (>99)
2		91 (97)
3		94 (94)
4		97 (99)

[a] The *ee* values of products which were obtained from catalysis with non-polymer-attached $(DHQD)_2PHAL$ ligand are given in parentheses.



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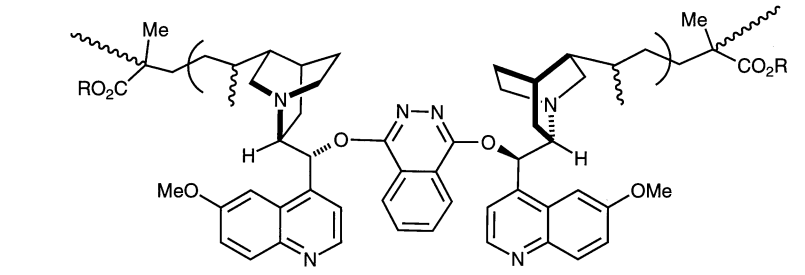
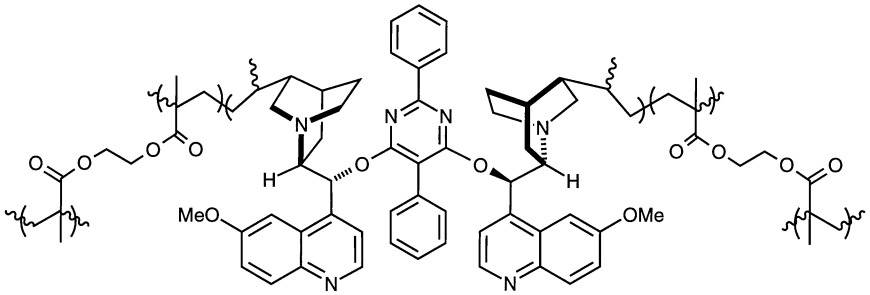
The insoluble polymeric chiral ligand is quantitatively recovered by filtration. Because of the significant loss of metal during this separation, 0.2 mol% of osmium tetroxide have to be added to restore the original reactivity.[17] The swollen, polar polyhydroxyl methacrylic backbone provides highly accessible reaction sites. This fact was revealed by comparing the reaction rates of the AD of styrene using either polymer **5** or the unbounded 4-chlorobenzoate of quinidine.

Recently, Song et al.[18] reported the synthesis of the new polymer-supported PHAL ligands **8**. The AD of *trans*-stilbene and *trans*-cinnamate using **8** (R = Me) proceeded with exceedingly high enantioselectivity (>99% *ee* for both olefins).



8 R = CH_3, CH_2CH_2OH



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A similar PHAL ligand exhibiting high asymmetric induction (>98% *ee* for *trans*-stilbene) had previously been mentioned by Salvadori et al.[16] Their UV spectrophotometric analysis of the polymer washings after prolonged extraction time (up to 7 days) still showed a significant absorption maximum belonging to the chiral monomer. From this they concluded that the PHAL monomer was not completely bound to the polymer matrix, but that it was only absorbed to some extent in the swollen polymer.

The homogeneous AD of terminal monosubstituted olefins is best performed with 4,6-bis-(9-*O*-dihydrochininyl)pyrimidine (PYR) ligands. Recently, a polymer-bound version of such ligands was introduced.[19] Using **9** in the AD of 1-decene, 64% *ee* was achieved. 3,3-Dimethyl-1-butene and vinylcyclohexane gave 76 and 67% *ee*, respectively. Compared to catalysis with non-supported ligands, however, these *ee*-values are lower by about 10%.

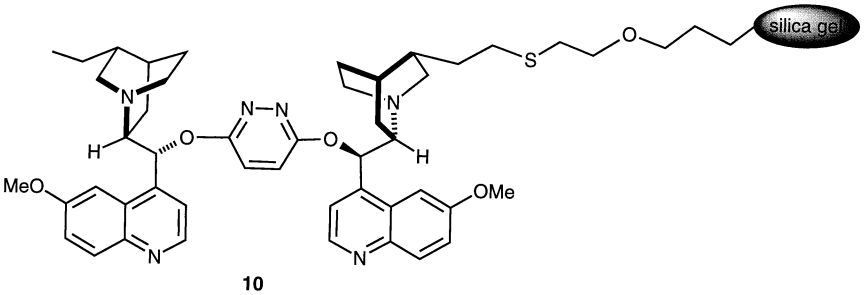
Silica Gel

As a more practical approach to the heterogeneous catalytic AD reaction for large-scale synthesis, Lohray et al. immobilized 3,6-bis-(9-*O*-dihydrochininyl)pyridazine on silica gel.[20] This inorganic support should have superior mechanical and thermal properties compared to organic counterparts. Furthermore, the cinchona alkaloid derivatives were expected be located on the surface of the silica, therefore completely exposed to the reactants. Compared to catalysis with organic polymers, where the ligand may be encapsulated in the less rigid polymer matrix, this fact could lead to an enhanced enantioselectivity.

First attempts along these lines, however, remained unsatisfactory. Thus, silica gel-supported pyridazine **10** exhibited significantly reduced enantioselectivity. *trans*-Stilbene and styrene were dihydroxylated with only 80 and 56% *ee,* respectively, using potassium ferricyanide as secondary oxidant.[20] These values were even lower than those previously reported for ADs with the purely organic polyacrylate-bound pyridazine ligand.[14]

More successful were ADs with the silica gel-supported $(DHQ)_2PHAL$ ligand **11**, which was recently described by Song et al.[21] Aromatic 1,2-di- and trisubstituted olefins were dihydroxylated with the same enantioselectivity as the free homogeneous phthalazine from Sharpless. Reuse of filtrated **11** without addition of osmium tetroxide, however, led to an about 40% prolonged reaction time and decreased enantioselectivity (tested in the AD of 1-phenylcyclohexene). Both observations can be explained by a significant loss of metal during catalyst recovery.

The polymeric second generation pyridazine (PYDZ) and phthalazine (PHAL) ligands reviewed so far were bound to the polymer backbone (with or without spacer group) via the olefinic double bond of the cinchona alkaloids. We introduced a different approach.[22] In ligands **12** and **13** the chirality-bearing part of the molecule is connected to the inorganic support through the nitrogen-containing heterocycles. By this attachment negative steric interactions be-



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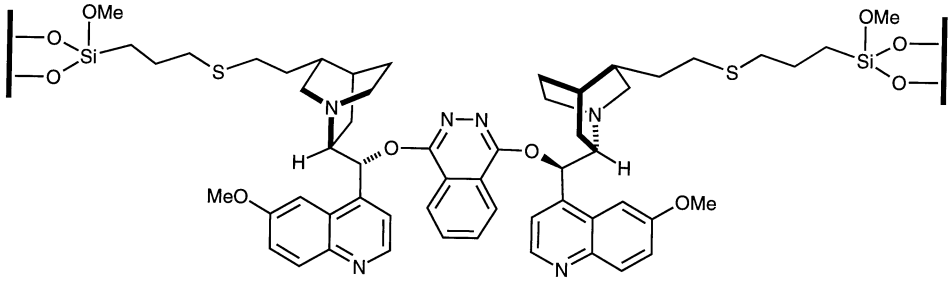

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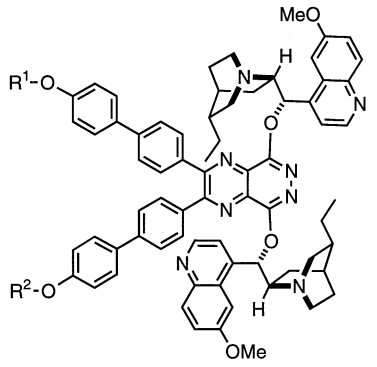
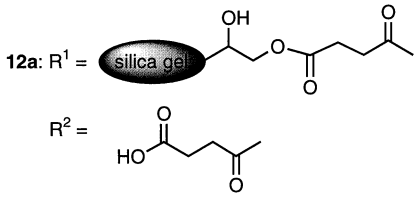
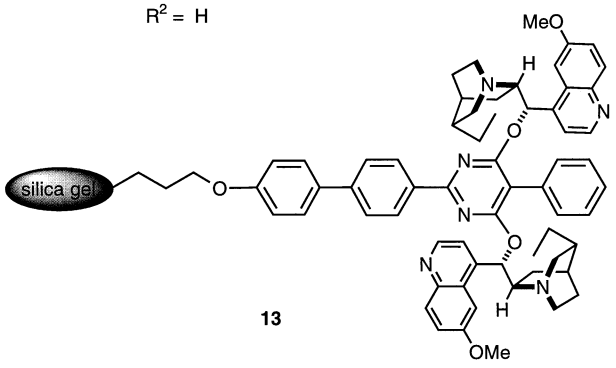


12 a, b



R^2 = H



13

tween the polymer backbone and the quinuclidinic moiety, responsible for osmium complexation, are minimized. Therefore ligands of this type were expected to give highly favorable results in AD reactions.

Supporting this concept, it was found that ester-bound DPP ligand **12a** exhibited a very high asymmetric induction in the AD of styrene (97% *ee*).[22] In order to test the efficiency of the catalyst recovery, reactions with recycled ligand were performed. It was found that after four consecutive runs the enantioselectivity slightly dropped (to 94% *ee*). Because this decrease in *ee* was believed to be due to a loss of ligand via ester hydrolysis under the standard aqueous basic (pH 12.2) AD reaction conditions with potassium ferricyanide as oxidant, aryl ether-bound DPP ligand **12b** was synthesized. As expected, **12b** also provided products with exceedingly high enantiomeric excesses (*trans*-stilbene: 99% *ee*; styrene: 98% *ee*). Now, a significant reduction of the *ee* value using recycled ligand was not observed anymore.

A summary of results with various silica gel-supported alkaloid ligands is given in Table 3.

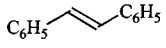
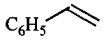
For the AD of terminal aliphatic olefins, supported PYR ether **13** was introduced. With **13** the corresponding diol of 1-decene was obtained with 84% *ee*, which is only slightly lower than the result of the reaction under homogeneous conditions (89% *ee*).[22]

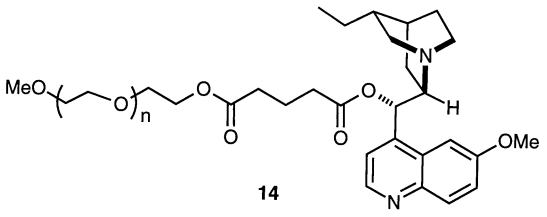
Although these silica gel-supported DPP ligands are easily recovered, their consecutive use still requires the addition of ca. 1 mol% of osmium after each run to avoid a decrease in chemical yield and enantioselectivity. Further studies are directed towards isolation procedures which reduce this metal loss during catalyst recovery.

Polyethylene Glycol

Catalyst modification by polyethylene glycol (PEG) has been known for a long time.[23][24][25][26] Already in the sev-

Table 3. Comparison between various silica-bound ligands in the AD

No.	Olefin	Ligand	Yield [%]	*ee* [%]
1		**10**	96	80
2		**11**	88	>99
3		**12b**	77	>99
4		**10**	92	56
5		**12b**	93	97
6		**12b**	94	98



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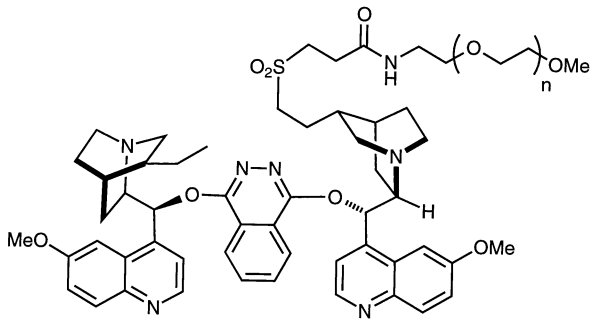
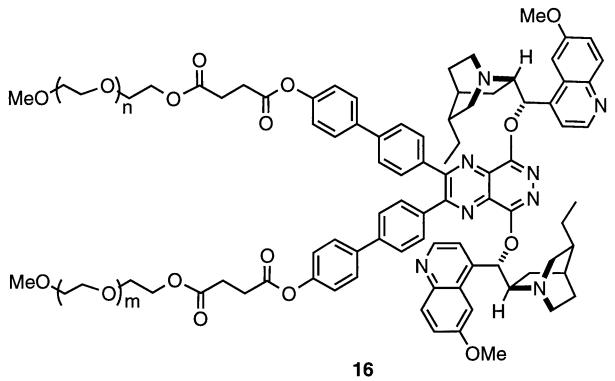


15

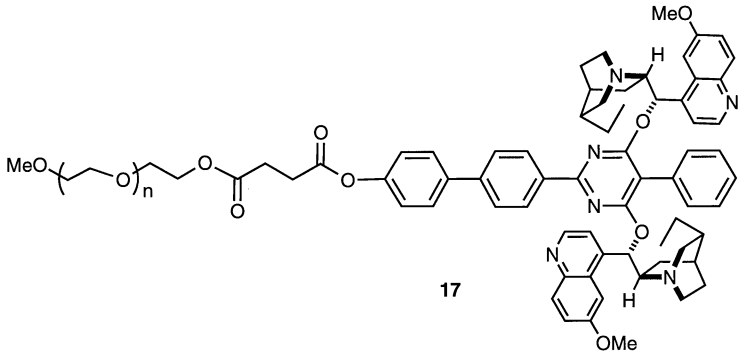
enties, Bayer and Schurig reported the use of a number of soluble polymer-attached hydrogenation catalysts, including PEG-functionalized ones, which could be separated from the reaction mixture by precipitation or membrane filtration.[24][25][26] For the AD, Han and Janda introduced PEG-modified ligands in 1996.[27] Alkaloids bound to polyethylene glycol monomethyl ethers (MeO-PEG; MW 5000), such as dihydroquinidine **14**, are completely soluble under the usual AD reaction conditions using NMO as oxidant and acetone/water (v/v = 1:1) as solvent. Due to this property, positive effects such as the strong "ligand-acceleration",[28] which were observed in the original homogeneous Sharpless system remain unaffected.

MeO-PEG-modified ligand **14** can be considered as a member of the first generation of AD ligands, and it is therefore not surprising that the AD of selected olefins gave products with only unsatisfactory *ee* values (e. g. *trans*-stilbene 88% *ee*, styrene 60% *ee*). After the reaction, the PEG-bound cinchona alkaloid can be recovered almost quantitatively (>98%) by precipitation upon addition of dialkyl ethers followed by filtration. Repetitive use of the ligand was possible without significant loss of enantioslectivity when osmium tetroxide was added after each run.

With the desire to further improve this method, MeO-PEG-modified phthalazine **15**[29] was tested in the AD using potassium ferricyanide as secondary oxidant. For



16



17

trans-stilbene, *trans*-methyl styrene, styrene and *trans*-5-decene the corresponding diols were now obtained with very high enantiomeric excesses (>96% *ee*). As an extension of this work, **15** has recently been used in the AD of polymer-bound substrates.[30]

The first polymer-supported diphenylpyrazinopyridazine (DPP) and pyrimidine (PYR) derived ligands (**16** and **17**) were introduced by Bolm and Gerlach.[31] Pyridazine **16** exhibits exceedingly high asymmetric induction in the AD of *trans*-stilbene (99% *ee*), styrene (98% *ee*) and 2-methylstyrene (95% *ee*). Reaction of 1-decene and 3,3-dimethyl-1-butene using pyrimidine **17** provided the corresponding diols with 87% and 90% *ee*, respectively. These *ee*-values are the highest ones for aliphatic terminal monosubstituted olefins using polymer bound alkaloid ligands.

Ligand recovery and sequential catalyst use was tested in the AD of styrene with pyridazine **16**. After constant *ee*-values in the first 4 runs a slight decrease of the enantioselectivity was observed (run 1−4: 98% *ee*; run 5: 97% *ee*; run 6: 96% *ee*). This effect was explained by a loss of alkaloid due to minor ester hydrolysis under the basic reaction conditions using $K_3Fe(CN)_6/K_2CO_3$. Changing the MeO−PEG-attachment from an ester- to an ether linker solved this problem and the significant reduction in the enantioselectivity with recycled ligand was not observed anymore.[32]

Conclusion

The osmium-catalyzed asymmetric dihydroxylation of olefins developed by Sharpless et al. during the last decade has become a highly mature method for the synthesis of optically active diols. For ligand recovery various successful protocols based on the properties associated with the applied polymeric supports have been introduced. Which of those will be most applicable in large-scale use is not obvious yet. This decision will also be influenced by the extent to which osmium can be recycled when a particular polymeric support is used. Intensive research will also undoubtedly offer solutions to this problem.

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