Asymmetric Dihydroxylation with Recoverable Cinchona Alkaloid Derivatives: A Warning Note and an Improved, Insoluble Polymer-Bound Ligand Architecture

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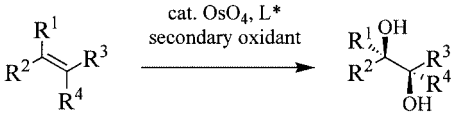
The nature of catalytic asymmetric dihydroxylation (AD), in particular the problem of ligand leaching from insoluble polymer-bound (IPB) *Cinchona* alkaloid derivatives, has been investigated. An upper limit to the amount of dissolved ligand, and methods for its evaluation, which assure a basically heterogeneous character of the observed AD reaction, are presented. A new copolymer architecture, which meets the established stability requirements and allows the highly enantioselective (87–99% *ee*) IPB-AD of representative alkene substrates, is also described.

Introduction

Osmium-mediated asymmetric dihydroxylation (AD) in the presence of soluble 10,11-dihydroquinine (DHQ) or 10,11-dihydroqinidine (DHQD) derivatives (Sharpless AD, Scheme 1) is one of the most powerful methods for the catalytic enantioselective oxidation of organic compounds as it allows the preparation of highly enantio-enriched 1,2-diols from a variety of alkene substrates.[1]



Scheme 1. Sharpless AD.

However, given the relatively high cost of the alkaloid ligands and of the osmium compounds the development of the homogeneous AD reaction has been accompanied, from the beginning, by the investigation of immobilized variants[2,3] in an attempt to improve the economic convenience by making possible an easier recovery of the catalytic system, or at least of the chiral auxiliary.[4]

The systematic modification of the support structure and linking technique has led to a variety of immobilized alkaloid derivatives, prototypical examples of which are shown in Figure 1.[5] These include insoluble organic polymers (e.g. **1**),[6] inorganic materials (e.g. **2**),[7] and soluble polymer-bound (SPB,e.g. **3** and **4**)[7c,8] or linear polymeric ligands.[9] In some cases patents have also been filed claiming the use of SPB or silica gel-supported *Cinchona* derivatives.[10]

While soluble systems like **3** and **4** operate in the homogeneous phase and the chiral auxiliary can be recovered after precipitation with a poor solvent, the truly insoluble ligands such as **1** and **2** benefit from a simplified separation (by filtration or centrifugation), in the case of the best materials at no apparent cost in terms of activity or stereoselectivity.

Unfortunately, this long-term quest for the optimal supported ligand (i.e. the one that combines easy preparation with catalytic performances comparable to those of the parent, unmodified alkaloid derivative) has been punctuated with occasional pitfalls. Indeed, as suggested by us and later demonstrated by Sherrington and coworkers,[6e,11] attempts to incorporate the chiral ligand into insoluble matrices by direct copolymerization of the double bonds of quinine or quinidine derivatives with ethylene glycol dimethacry-late,[6d,6h,6j] resulted in insoluble materials that were likely to contain no covalently bound alkaloid. Under these circumstances, the supposed heterogeneous catalyst precursor appeared to be just a reservoir of soluble ligand species physically trapped in the polymer network, which nonetheless were able to leach appreciably into solution. This conclusion prompted Sherrington's group to question the real heterogeneous nature of the catalysis at work and to recommend the inclusion of proper checks and controls in any study dealing with supported catalytic systems.

In a critical re-examination of the whole field of immobilized ligands for the AD reaction, it occurred to us that the same kind of problems could arise for most of the supported alkaloid derivatives reported to date, because of a fundamental instability under the common AD conditions. Indeed, while initial studies employed *N*-methylmorpholine

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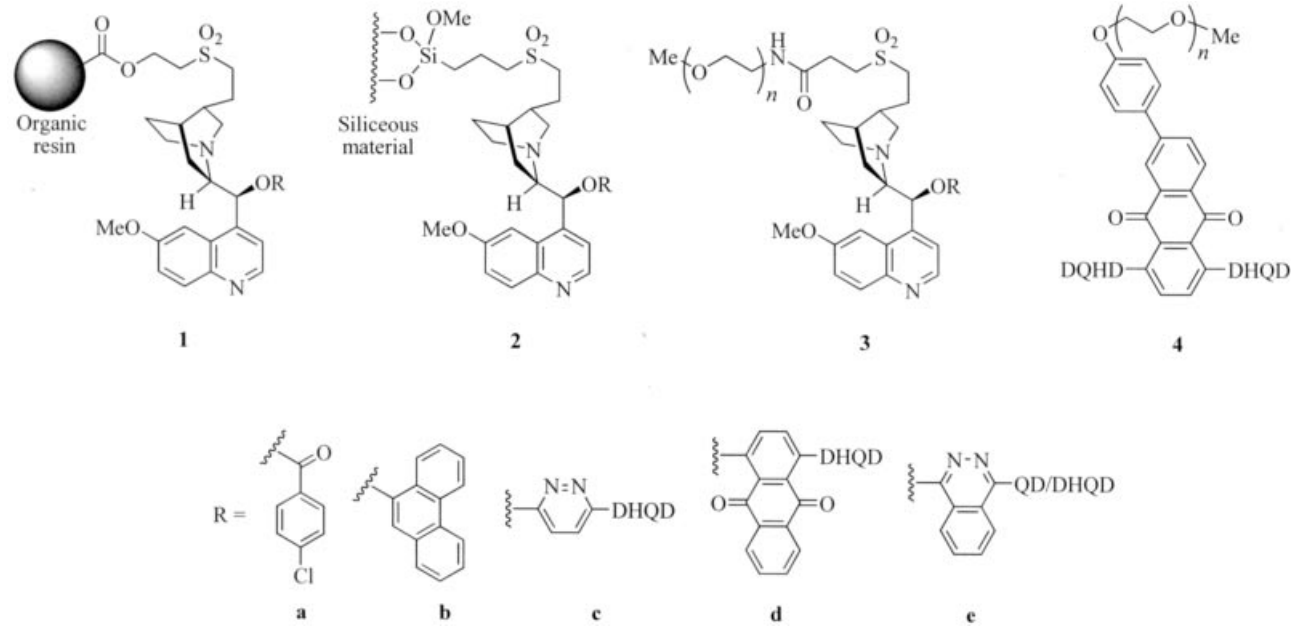


Figure 1. Typical supports and linker groups for immobilized alkaloid ligands used in the AD reaction (QD = 9-*O*-quinidinyl; DHQD = 10,11-dihydro-9-*O*-quinidinyl).

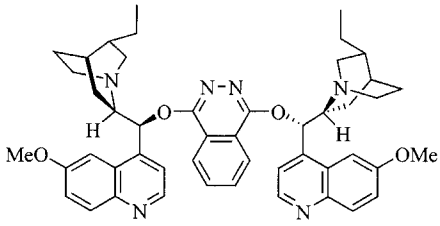
N-oxide (NMO) as the stoichiometric oxidant, the better yields and *ee* values attained with potassium ferricyanide in a *t*BuOH/H_2O solvent mixture (1:1) prompted subsequent work to be done mostly with this oxidant system, which has to be used in a strongly alkaline medium (pH 10.3–12.2).[1a] If the typical structures of supported AD ligands are considered (Figure 1), it becomes clear that, with few exceptions,[7c,8e,8g] base-sensitive structural motifs are usually present in the spacer linking the alkaloid unit to the support, e.g. ester, β-acyloxy- or β-alkoxysulfoxide or sulfone, siloxane and β-sulfonylcarbonyl. Because all these functional groups are likely or known to undergo hydrolysis under relatively mild alkaline conditions,[12,13] some ligand detachment from the support can therefore be anticipated. Unfortunately, even if the possible occurrence of this problem has occasionally been mentioned before,[6a,7b,7f,8d] this aspect seems to have been largely overlooked to date, in spite of its evident relevance to recycling effectiveness and product contamination for both SPB and IPB derivatives. Moreover, an additional caveat for the latter kind of materials is the possible existence of a significant contribution to the catalysis by the dissolved alkaloid. Accordingly, not only the practical convenience of the recoverable ligand can be impaired, but in the case of IPB materials the assumed heterogeneous nature of the catalytic system may also be under question.

In this paper we wish to report our observations on the effect of small amounts of soluble dihydroquinidine phthalazine ether derivative **5** on the AD reaction. We discuss the significance of the results in connection with previous work with analogous IPB alkaloid derivatives. An acceptable upper limit for the leaching of the supported ligand is estimated, and we also present a new polymeric material for which a basically heterogeneous type of catalysis can be demonstrated.

Results and Discussion

AD at Reduced Alkaloid Concentrations

One of the striking features of the use of *Cinchona* alkaloid derivatives in the AD reaction is the induction of a strong *ligand acceleration effect* (LAE).[14] Thus, a higher dihydroxylation rate is found in the presence of the chiral ligand L* than with osmium tetroxide alone. Thanks to the faster reaction with the alkene substrate of [OsO_4L*] relative to free osmium tetroxide, the most favorable consequence of this effect is the attainment of high *ee* values also under conditions where OsO_4 is largely in the uncomplexed form. In fact, the competition between the enantioselective path (involving [OsO_4L*]) and the racemic one (due to OsO_4) leads to a saturation profile when the *ee* values obtained in AD runs are plotted against the chiral ligand amount, at constant osmium concentration.[15] While this behavior normally prompts the use of an excess of the chiral ligand with respect to the osmium compound in standard AD reactions, the recommended L*/Os ratio is largely dependent on the ligand structure, with optimal values (10–60 for first-generation derivatives, 2–5 for dimeric systems like **5**)[1a] that reflect the remarkably higher effectiveness in AD of last-generation ligands.



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For the phthalazine ether **5**, the catalytic efficiency is further witnessed by the observation by Sharpless and coworkers that even with an L*/Os ratio as low as 1/20 the AD of stilbene still proceeds to afford the diol product having 96% *ee*.[14,16] Although stilbene is arguably one of the best substrates for the AD reaction, this result clearly indicates that the dihydroxylation reaction may be funneled to a large extent through the enantioselective path in spite of a much reduced chiral ligand concentration. In order to gain a clearer picture of the possible effect of minor amounts of leached alkaloid, and in view of the frequent incorporation of the phthalazine unit (or other related second-generation dimeric derivatives) into supported AD ligands, at the onset of this work it therefore became interesting to evaluate the dependence of the enantioselectivity extent on the **5**/Os ratio for two widely employed substrates, styrene and 1-phenylcyclohexene, in greater detail. Therefore AD runs were carried out under otherwise standard conditions, but with decreasing ligand loadings, to afford the data summarized in Figure 2.

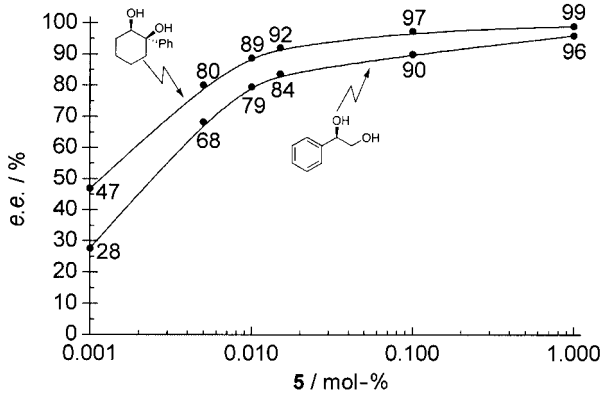


Figure 2. *ee* values in the AD of styrene and 1-phenylcyclohexene with different amounts (in mol-% vs. the olefin) of the ligand **5** (conditions: 0.35 mol-% OsO_4, 3 equiv. $K_3Fe(CN)_6$, 3 equiv. K_2CO_3, *t*BuOH/H_2O = 1:1, 0 °C).

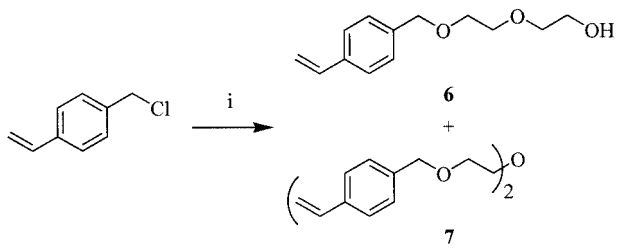
From these results it is evident that the anticipated relationship between enantioselectivity and ligand amount was observed, with the occurrence of a relatively flat plateau in the experimental curves whose practical consequence is the lack of a dramatic drop in the enantioselectivity before the amount of the alkaloid derivative is lowered by almost two orders of magnitude with respect to the usual AD conditions.[17] Because the attainment of remarkable *ee* values with only a minute concentration of the ligand **5** is not limited to stilbene, but can also be achieved for a range of alkene substrates, these results appear to be a serious warning against the possible catalytic implications of minor amounts of dissolved alkaloid species.

Indeed, as typical heterogeneous AD runs have been carried out with 1–2 mol-% of the supported phthalazine derivative with respect to the alkene, it may be calculated that the leaching of 5–10% of the immobilized alkaloid would afford a concentration in solution falling in the flat region of the *ee*/ligand loading graphs. Under these conditions, the dissolved ligand alone could account for the formation of diol products with *ee* values close to 5–10% of those obtained in standard homogeneous AD runs, thus jeopardizing the interpretation of the catalysis runs' outcome. In particular, the sole attainment of a high enantioselectivity, even in the case of a few (5–10) successful recycles, cannot be taken as a proof of heterogeneity.

On the basis of these considerations, and taking into account that a leaching of around 10% is not unrealistic, at least for silica-gel-supported ligands,[18] a specific investigation of the stability of typical IPB materials under AD conditions was therefore performed. At the same time, the design of a new architecture for a phthalazine derivative linked to a cross-linked organic copolymer was undertaken. Somewhat arbitrarily, at this stage the aim was to assure a leaching of the supported alkaloid at around the 0.5% level, which would correspond to an amount of ligand released into solution in the range where the most evident inflection in the *ee* values takes place (Figure 2). Under these conditions it was expected that a discrimination between the heterogeneous and the homogeneous contribution to the catalysis could be more easily made.

Preparation of the New Materials

In order to improve the hydrolytic stability of the IPB ligand, the material architecture was fundamentally modified with respect to the precedents reported so far, paying attention to avoid any obvious base-sensitive structural motif. Discarding the possibility of using a methacrylate-type backbone because of the facile side-group saponification, a polystyrene-based material was selected. However, because of the intrinsic incompatibility of this kind of support with the protic AD reaction medium,[6b] the introduction of suitable hydrophilic chains appeared necessary. For this reason **6** and **7** were synthesized (Scheme 2), respectively as the achiral comonomer and cross-linker for the material to be developed.[19] The use of the latter type of cross-linker as a



Scheme 2. Reagents and conditions: i) NaH, excess diethylene glycol; yields 80% (**6**) and 13% (**7**).

replacement for divinylbenzene has been demonstrated to improve the swelling of styrene copolymers in polar solvents.[19b]

The initial attempts at the synthesis of the alkaloid-bearing monomer focused on the carbon or oxygen functionalization of the quinidine C10–C11 double bond of the corresponding phthalazine ether derivative. Although this approach appeared attractive as a mean to introduce a robust spacer group in the alkaloid structure, all the efforts were unfortunately plagued by synthetic drawbacks.[20]

For these reasons the linker group had to be introduced by resorting to the well-established radical addition of thiols to the alkaloid C=C bond. However, in order to avoid potential fragmentation paths permitted by the proximity of functional groups, the commonly employed β-mercaptoethanol was replaced in this study by 6-mercaptohexanol.[7e] Starting with the easily accessible symmetric phthalazine ether **8**, the derivative **9** was therefore prepared and smoothly converted into the mono- and distyryl monomers **10** and **11**, respectively, by a Williamson reaction with two equivalents of *p*-chloromethylstyrene (Scheme 3). The radical copolymerization of **6**, **7**, and **10** (or **11**) with varying monomer ratios (Table 1) was carried out in solution or suspension, and afforded cross-linked insoluble materials whose thioether groups were oxidized to avoid any interference when used in the AD catalysis (Scheme 4).[21,22]

After exhaustive extraction with THF and ethanol to remove the soluble components, the materials **12** and **13a**,**b** were characterized by spectroscopic means (IR) and elemental analysis. Regardless of the polymerization conditions, the chiral ligand loading that resulted from the nitrogen content appeared to coincide with the composition of the monomer feed, thus demonstrating that a rather uniform incorporation of the alkaloid unit had taken place (Table 1).

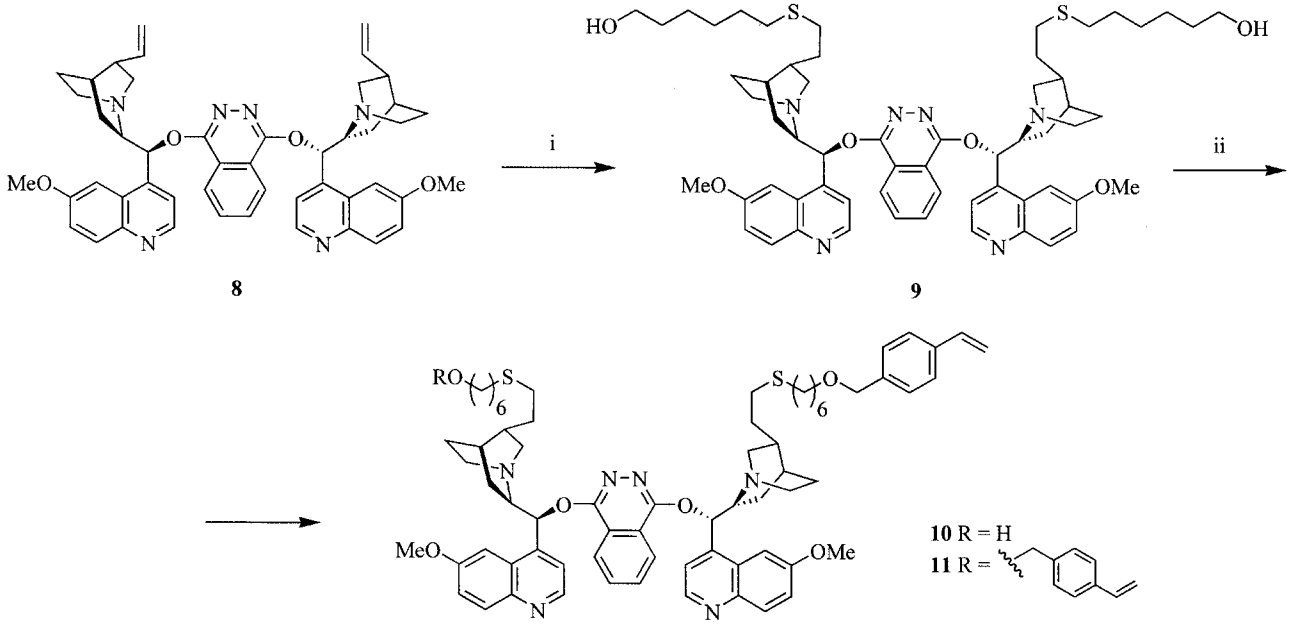
Table 1. Polymerization conditions and characterization for the materials **12** and **13**.

Monomers molar ratio **6**/**7**/chiral monomer[a]	Polymerization conditions (solvent)	Material	Alkaloid content [mmol g^{-1}][b]
93:2:5 (**10**)	solution (chlorobenzene)	**12**	0.16 (0.18)
85:10:5 (**11**)	solution (toluene)	**13a**	0.17 (0.17)
85:10:5 (**11**)	suspension (chlorobenzene/H_2O)	**13b**	0.17 (0.17)

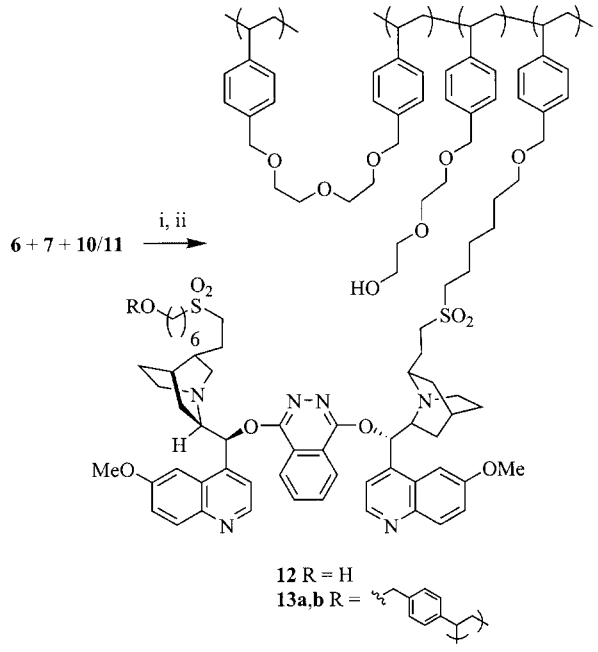
[a] The chiral monomer employed is given in parentheses. [b] Determined by nitrogen elemental analysis. The expected values, based on feed composition, are given in parentheses.

Leaching Studies

In view of its adequate sensitivity in the micromolar range, UV spectroscopy was selected as the analytical tool to assess the extent of ligand dissolution in an alkaline medium. These controls were performed for both the newly prepared materials **12** and **13a**,**b** and two known phthalazine derivatives anchored either to a cross-linked methacrylate matrix (**1e**)[6k] or to silica gel (**2e**).[7d] Because of the strong spectroscopic interference by the AD terminal oxidant [$K_3Fe(CN)_6$], these leaching experiments could not be carried out under normal dihydroxylation conditions. Instead, samples of the supported alkaloids were vigorously stirred for 18 h with a mixture of *t*BuOH/H_2O (1:1), K_2CO_3, and K_2SO_4, with the amount of the latter calculated to provide the same ionic strength as the ferricyanide oxidant in real AD runs. After filtration through a glass



Scheme 3. Reagents and conditions: i) $HO(CH_2)_6SH$, AIBN, $CHCl_3$, 90%; ii) NaH, DMF then 2 equiv. 4-chloromethylstyrene; yields 23% (**10**) and 61% (**11**).



Scheme 4. Reagents and conditions: i) solvent, AIBN, Δ; ii) cat. OsO_4, NMO, THF/*t*BuOH.

frit, the dissolved alkaloid was quantified from the absorbances at 254 and 353 nm. The results of these leaching tests under simulated AD conditions are collected in Table 2 and compared with data from control runs at neutral pH, in which the supported ligands were stirred with the solvents alone.

Table 2. Results of leaching experiments with the supported phthalazine ligands.

Material	*t*BuOH/H_2O		Simulated AD	
	Leaching [%][a]	Leached amount [mol-%][b]	Leaching [%][a]	Leached amount [mol-%][b]
1e	1.9	0.048	12	0.30
2e	0.50	0.013	8.1	0.20
12	0.20	0.005	0.76	0.018
13a	0.20	0.005	0.48	0.012
13b	0.29	0.007	0.58	0.015

[a] Dissolved alkaloid with respect to the total supported ligand. [b] Dissolved ligand to alkene ratio, calculated for a heterogeneous AD run with 2.5 mol-% of supported ligand.

In spite of the extensive purification by continuous extraction, all the materials examined appeared to leach to some extent, even in the neutral *t*BuOH/H_2O mixture, an observation that suggests the presence of minor amounts of residual chiral derivative physically trapped in the insoluble matrix or sub-micron particles that are not retained on the frit.[23] Remarkably, the behavior of the diverse supported ligands diverged, however, when exposure to a strongly alkaline medium was examined. Indeed, both the methacrylate copolymer **1e**, previously reported by us,[6k] and the silica-gel material **2e**, prepared according to the procedure of Song and co-workers for the analogous quinine derivative,[7d] appeared to undergo a dramatic increase in the extent of ligand detachment under simulated AD conditions (8–12%), as confirmed also by elemental analysis of the recovered insoluble materials. On the contrary, a leaching below 0.5–0.8% of the total immobilized alkaloid was observed for all the new derivatives **12** and **13a**,**b**, substantially fulfilling the planned stability requirements. In fact, even in AD runs employing as much as 2.5 mol-% of the supported phthalazine derivative with respect to the alkene, a limiting dissolved alkaloid concentration of less than 0.02 mol-% vs. the olefin substrate could be estimated from these results (Table 2), a value that approaches the rapidly decreasing region of the *ee*/ligand concentration curves (Figure 2).[24]

AD Runs and Catalytic Activity in the Filtrate

Because the leaching experiments described so far could not fully reproduce the actual AD conditions, and in order to tackle the critical issue of the homogeneous contribution to the catalysis directly, some control dihydroxylation runs with styrene were initially performed. With this aim the supported ligands **1e**, **2e**, **12**, or **13a**,**b** (2.3–2.5 mol-%) were stirred for 12–18 h at 0–20 °C with a mixture of K_2CO_3 and $K_3Fe(CN)_6$ in *t*BuOH/H_2O, in the usual ratios for the AD reaction. After filtration, OsO_4 (0.35 mol-%) and styrene were added to the filtrate at 0 °C whilst monitoring the reaction progress and the enantioselectivity by HPLC.[25] As expected on the basis of the observed leaching under simulated AD conditions, the dihydroxylation in the filtrate afforded a nonracemic diol product. However, while in the case of **1e** and **2e***ee* values as high as 90–93% were obtained, a significantly reduced enantioselectivity (72–78% *ee*) was observed in the filtrate from the new materials **12** and **13a**,**b**. Interestingly, all these results are only slightly lower than predicted from the leaching data under simulated AD conditions for the different materials (Table 2) and the dependence of the enantioselectivity on the alkaloid concentration (Figure 2). In fact, given the large *ee* variations, especially at the low concentration end of the graph, the latter relationship could be used as a convenient probe to assess the ligand leaching under AD-like conditions. For instance, when the *ee* values obtained in the control experiments were converted into the amount of dissolved alkaloid by means of Figure 2, a leaching degree of 4–20% for **1e** and **2e** and 0.3–0.4% for **12** and **13a**,**b** was obtained. Besides demonstrating the suitability of the UV method for a quick estimation of the leaching, these data confirm that the new copolymer architecture of **12** and **13a**,**b** is effective in improving ligand stability of more than one order of magnitude in comparison with the precedent materials **1e** and **2e**.

Having put an upper limit to the *ee* of the diol obtained through the homogeneous AD reaction caused by the dissolved ligand, the dihydroxylation of styrene in the presence of the polymeric materials **12** and **13a**,**b** was studied next. To compensate for the occurrence of inaccessible alkaloid

units the reactions were carried out with 2.3–2.5 mol-% of supported ligands under the conditions described above; the results are summarized in Table 3. As can be seen from these data, **12** and **13a**,**b** provide comparable asymmetric induction extents with *ee* values (86–87%, Table 3, entries 1–3) definitely higher than those found in the AD runs in the corresponding filtrates, that therefore could not be ascribed to the homogeneous AD reaction (vide infra). As far as the catalytic activity is concerned, the copolymer **12** (Table 3, entry 3) is more effective than **13a**,**b** (Table 3, entries 1 and 2), which suggests that the better swelling permitted by the lower cross-linking density has a deeper impact on the catalytic properties than the nature of the solvent and the polymerization technique. In view of the faster dihydroxylation with **12**, only this material was used in further catalysis experiments, which were initially devoted to the evaluation of the extensive recycling of the supported ligand (Figure 3).

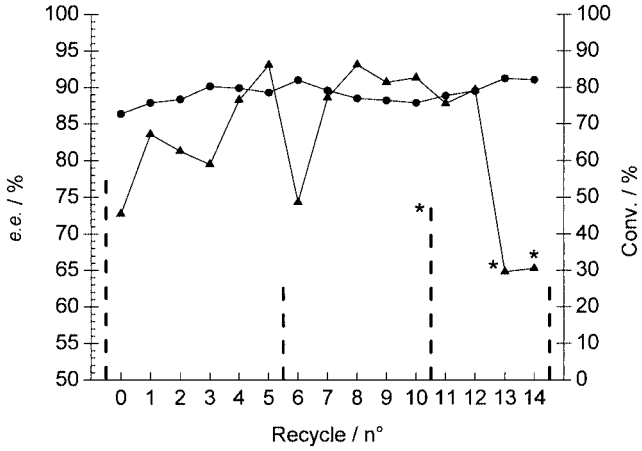
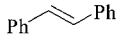
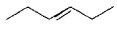
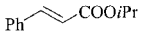


Figure 3. Conversion at 1.5 h (▲) and *ee* values (●) in the recycles of **12** in the AD of styrene (*ee*'s in the filtrate are indicated as broken lines; in the runs marked with an asterisk only 0.1–0.15 mol-% OsO_4 was added, see text).

Table 3. Results in the heterogeneous AD of selected alkenes with the supported ligands **12** and **13a**,**b**.

Entry	Material	Recycle	Substrate	OsO_4 [mol-%]	*T* [°C]	*t* [h]	Conversion [%][a]	*ee* [%][b]
1	**13a**	0		0.35	0	22	88	87 (96)
2	**13b**	0		0.35	0	22	76	86
3	**12**	0		0.35	0	16	100	87
4	**12**	13		0.10	0	22	100	91
5	**12**	15		0.35	0	16	100	87 (94)
6	**12**	16		0.35	0	22	100	99 (99.8)
7	**12**	17		0.35	0	20	100	94 (97)[c]
8	**12**	18		0.35	25	30	95	98 (97)[d]
9	**12**	19		0.35	0	44	96	97 (99)

[a] By HPLC or GLC. [b] By HPLC (entries 1–6, 8, 9) or GLC (entry 7) with chiral stationary phases. The absolute configuration of the products followed the Sharpless rule. *ee* values under standard homogeneous AD conditions in parentheses (ref.[1a]). [c] Literature value for *trans*-5-decene. [d] Literature value for ethyl cinnamate.

With this aim **12**, recovered by filtration from the initial reaction mixture (Table 3, entry 4), was thoroughly washed to restore the initial conditions and used in further styrene AD runs. In these experiments 0.35 mol-% of OsO_4 was added in each of the early 12 recycles, while in the last two a reduced osmium amount (0.1 mol-%) was employed.[26] With this procedure, *ee* values falling in the 87–91% range were obtained in all cases. Moreover, the catalytic activity was also maintained along the recycles, with some fluctuations in the reaction progress at 1.5 h that, however, did not preclude a complete substrate conversion after 16 h. In this respect it is interesting to note that the enantioselectivity and conversion trends approximately mirror each other, which suggests that some differences in the osmium concentration (and hence in the ligand to metal ratio) may arise between the consecutive runs. In the initial 12 recycles, where the same amount of OsO_4 was added each time, this could be a consequence of variable metal retention by the polymeric ligand, although alternative explanations (e.g. stirring-related effects) cannot be discounted at present. To monitor the alkaloid leaching along the lifetime of the supported ligand **12**, the catalytic activity in the filtrate was also checked by the procedure described above, after 5, 10, and 14 recycles. The results of these experiments, included in Figure 3 as broken lines, indicate that the AD due to the leaching from recovered **12** proceeds with a much reduced enantioselectivity with respect to the initial check with the fresh material, hence proving a corresponding reduction of the dissolved ligand concentration. For instance, the 63–65% *ee* values obtained in the second and fourth control runs can be translated, with the aid of Figure 2, into a lower than 0.2% leaching degree. Even when the OsO_4 added to the filtrate was reduced to 0.15 mol-% (thereby improving the ligand to metal ratio in solution, third control run, Figure 3), the enantioselectivity still remained well below 80% *ee* Remarkably, the conversion of the alkene substrate at 1.5 h for the AD runs in the presence of **12** and with 0.35% OsO_4 (recycles 0–12, Figure 3) was generally comparable or higher than observed in the control experiments (50–71%), thus demonstrating that under the heterogeneous conditions most of the added osmium is actually present in a catalytically active form. Finally, after 19 recycles of the same sample of **12** (vide infra) a run in the filtrate with 1-phenylcyclohexene was also carried out; under these conditions the corresponding diol was obtained in 81% *ee* which, from Figure 2, is once again consistent with an alkaloid leaching of around 0.2%. From the trend of the *ee* values in the filtrate it may therefore be concluded that, instead of

causing a progressive weakening of the ligand binding to the support, the mechanical and chemical stress put on **12** along its successive uses appear just to produce the initial release of loosely retained (physically entrapped?) alkaloid species followed by a substantial chemical stability of the material and a leaching close to the 1‰ level. As a consequence, the effective recovery and recycling of the heterogenized ligand is possible, and the crude diol product is contaminated by vanishingly low amounts of the alkaloid derivative (<0.05% by weight, on the basis of the data discussed above and NMR or UV spectroscopic checks), thereby allowing, in most cases, its direct recrystallization or use in further synthetic steps.

More importantly, after a few consecutive runs with styrene the gap between the enantioselectivity recorded in the presence of the new polymeric ligand and that in the filtrate appeared to be increased to 25% *ee*, strongly supporting the notion of a basically heterogeneous type of catalysis in the former situation. As anticipated, an analogous comparison for 1-phenylcyclohexene led to a similar conclusion (81% *ee* in the filtrate, 97% *ee* in the presence of **12**, see Table 3, entry 9).[27]

In this respect, strikingly different results were obtained with the known materials **1e** and **2e**, for which the *ee* values achieved in the AD of styrene in the filtrate (90–93%, vide supra) were coincidental, within the experimental uncertainties, with those observed in the presence of the supported ligand (90–91% *ee*).[6k,18] Although it is presently difficult to predict the relative importance of the two processes during actual AD runs, it is clear that under these circumstances a prominent homogeneous contribution to the catalysis cannot be discounted for **1e** and **2e**, and, indeed, it is likely to accompany the purported heterogeneous AD. Accordingly, the interpretation of the results of catalysis experiments should be made with care in these cases, which serves as a further warning of the danger of taking indirect evidence (such as the successful achievement of a few recycle runs, even with high and almost unchanged *ee* values) as proof of a basically heterogeneous reaction.

As a final topic, the AD of selected alkenes was evaluated, using the material recovered from the styrene dihydroxylation recycles (Table 3, entries 5–9). For all the substrates examined, which are representative of the main olefin-substitution patterns for which the phthalazine derivatives are known to be effective, the results confirmed that the ligand **12** can deliver uniformly high activity and enantioselectivity levels. Irrespective of the alkene structure, and even though no $MeSO_2NH_2$ was added to accelerate the reaction,[1] almost quantitative yields of the diol products were obtained in 16–44 h, with *ee* values similar to, or only slightly lower than, those reported with the soluble ligand **5**. Although a moderate reduction of the dihydroxylation rate was observed with respect to the optimized homogeneous conditions, the catalytic efficiency shown by **12** demonstrates therefore that most of the chiral ligand units in the material are easily accessible to the reagents, probably thanks to the effective swelling in the reaction solvent due to the hydrophilic diethylene glycol side-chains.

Perspectives for the Further Development of Recovery Strategies for AD Ligands

Because the development of recoverable chiral ligands for catalysts is generally aimed at improving known enantioselective systems, the success in terms of catalyst economy has been commonly measured against the original homogeneous procedure making use of the unmodified catalyst, typically under *ee* optimized conditions. However, given the frequent drop in the catalytic activity and enantioselectivity encountered with many of the engineered catalysts, this comparison is not necessarily the most meaningful one. For instance, a 2–5% reduction in the *ee*'s with respect to the use of **5** under standard (1 mol-%) conditions has been commonly reported for the AD of styrene and phenylcyclohexene upon adopting different recovery strategies for the phthalazine derivatives,[4,5] a result that, on the basis of the findings of this work, can in fact be attained in the homogeneous process using just 0.1 mol-% of the soluble ligand **5** (Figure 2).[28] As enantioselectivity is normally of primary concern in judging an asymmetric catalytic procedure, in these cases the ligand-depleted conditions appear therefore as a more correct comparison term. Clearly, the "equivalent soluble ligand loading" in the previous reasoning (i.e. the amount of **5** in the standard Sharpless procedure sufficient to afford the same *ee* as with a particular modified system) is directly dependent on the performances attained with the engineered catalyst (with possible significant substrate-dependence); consequently, the development of recoverable systems with the same, or possibly better,[4n] stereoselectivity as **5** at equal ligand loading appears to be an obvious goal in order to reduce the initial handicap with respect to the original AD protocol. The ability to recycle the chiral auxiliary up to an overall product-to-ligand ratio significantly higher than for the equivalent AD reaction with **5** is a second main point that has to be considered in order to claim practical advantages by any particular recovery approach. Taking into account the additional synthetic and economic issues often involved in the modification of the ligand (e.g. SPB or IPB approach, use of functionalized alkaloid derivatives) or of the reaction conditions (e.g. use of ionic-liquid solvents),[4e,4k,4m,4n] this aim could be probably achieved for the strategies reported so far, by scoring (upon recycling) an average alkaloid loading in the 0.01 mol-% range. To date this ambitious goal seems to have been substantially unattained. Even in the case of the material **12** of this work that (including AD runs and control experiments) was used 25 times, the final ligand-to-product ratio just approached the 0.1 mol-% value. In fact, thanks to the sustained performances of **12** further runs could be probably carried out, therefore improving somewhat the overall ligand economy; nonetheless the achievement of an order-of-magnitude-larger number of recycles appears unlikely because of the occurrence of mechanical stability problems. In general, it may be hence concluded that, from the point of view of the use of the alkaloid derivative, no decisive advantage seems demonstrable for the presently available recovery strategies for AD ligands. On

the other hand, when the aspects of diol product purity and downstream handling simplification are taken into account, we feel that low-leaching IPB materials, such as **12**, already possess the potential for improving the process economics in a real scenario.

In summary, to be practically useful the development of new approaches for the simplified recovery of AD alkaloid derivatives appears to require the achievement of a high catalytic efficiency (activity, enantioselectivity), together with the demonstration of a sufficient number of successful recycles. Hopefully, any future discussion about the convenience of newly developed recovery methods will include the punctual evaluation of often neglected aspects, such as ligand loading, recovery effectiveness, and overall economy in the use of the chiral auxiliary, that should be critically presented in comparison with competent conditions for the original catalytic system. From this point of view, the alkaloid leaching should be routinely assessed as it represents an obvious problem irrespective of the specific recovery approach. Finally, in the case of the AD reaction, more than elsewhere, the direct evaluation of the relevance of the dissolved ligand for the catalysis is another crucial duty when working with IPB alkaloid derivatives, in order to exclude the accidental occurrence of "Trojan horses"[29] of the kind evidenced in this study, and therefore the fundamentally erroneous interpretation of the nature of the catalytic process.

Conclusions

Stimulated by the lack of any evidence about the nature of the catalysis for the heterogenized *Cinchona* alkaloid derivatives reported to date, in this work the problem of ligand leaching in the asymmetric dihydroxylation of alkenes with IPB phthalazine ligands and the $K_3Fe(CN)_6/K_2CO_3$ oxidant system was addressed.

By combining the determination of the relationship between chiral-ligand concentration and enantioselectivity in the AD of two common substrates with the UV evaluation of the dissolved ligand and control runs in the filtrate, it was found that for two typical IPB materials reported in the literature (**1e** and **2e**) a 4–20% leaching degree and a significant homogeneous process take place, thus casting serious doubts on the assumed heterogeneous nature of the observed catalysis. Although hardly predictable at present (because of the strong dependence of the catalytic effectiveness on the actual chiral ligand structure), due to the omission of proper control experiments the occurrence of the same problem cannot be excluded for other heterogenized ligands described so far.

In general, for the IPB derivatives of the phthalazine class, an upper limit to the ligand leaching was set at around 0.5% in order to rule out a prominent homogeneous contribution to the catalytic process. These requirements appear to be fulfilled by the newly designed materials **12** and **13a**,**b**, which allow, for the first time, the satisfactory demonstration of a basically heterogeneous AD reaction in the ferricyanide-based process. In this regard it is worth noting that, albeit conceptually annoying, the occurrence to some extent of a homogeneous enantioselective process seems inevitable for the reaction under study given the intrinsic high effectiveness of the phthalazine ligands and the intimate nature of any IPB material: For instance, *ee* values in the 30–50% range would still be expected in the control runs of the kind adopted in this work, even in the event of a leaching as low as 0.5‰.

From a practical point of view, *ee* values in the range 87–99% were obtained in the AD of differently substituted alkene substrates in the presence of **12** and **13a**,**b** in the course of 20 successive recycles.

Experimental Section

General Remarks: All reactions involving sensitive compounds were carried out under dry nitrogen, in flame-dried glassware with magnetic stirring. When necessary, the solvents were refluxed with the proper drying agent and distilled before use under nitrogen or at reduced pressure. Commercially available compounds were purchased from Aldrich and used as received without further purification. The supported ligands **1e** and **2e** were prepared as described previously;[6k,7d] the alkaloid content was found to be 0.42 and 0.18 mmol g^{-1}, respectively, by elemental analysis. The phthalazine ether **8** was prepared in 94% yield by a literature procedure.[4k,7f,30] UV/Vis spectra were recorded on a Perkin–Elmer Lambda-9 UV/Vis-NIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were registered as $CDCl_3$ solutions, on a Varian Gemini 200, and are reported in ppm relative to TMS (^{1}H) or to the solvent (^{13}C; $CDCl_3$ at δ = 77.0 ppm). TLC analyses were carried out with Merk 60 F_{254} plates (0.2 mm) and chromatographic purifications with Macherey–Nagel flash-grade silica gel (230–400 mesh). Melting points (uncorrected) were measured with a Reichert hot-stage apparatus. Optical rotations were measured as solutions in 1 dm cells at the sodium D line, using a Jasco DIP360 polarimeter. IR spectra were recorded neat or as KBr disks, using a Perkin–Elmer 1600 Series FT-IR. Ion-spray mass spectra were recorded as methanol solutions on a Perkin–Elmer-Sciex Api III spectrometer. Exact masses were determined with a Bruker Daltonics microTOF LC spectrometer. For chiral GC analysis a Cyclodex-B column (30 m) was used. HPLC analyses were carried out on a Jasco PU-980 chromatograph, equipped with a UV-975 detector. Elemental analyses were performed at the microanalytical laboratory of the Dipartimento di Farmacia, Università di Pisa.

Preparation of the Comonomer 6 and Cross-Linker 7: A 250-mL, two-necked flask, equipped with a dropping funnel, was charged with di(ethylene glycol) (15.0 mL, 160 mmol) and a few drops of nitrobenzene. While cooling at 0 °C, NaH (50% in mineral oil, 2.4 g, 50 mmol) was added in small portions. When the gas evolution had ceased (15 min), chloromethylstyrene (4.5 mL, 32 mmol) was added dropwise and the resulting suspension was stirred at room temperature until disappearance (GC) of the starting chloromethylstyrene (18 h). After cooling in an ice bath, the resulting suspension was cautiously treated with 50 mL of H_2O and extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with H_2O (2 × 50 mL) and dried with Na_2SO_4. The solvent was removed under reduced pressure and the residue was submitted to flash chromatography (pet. ether/EtOAc, from 90:10 to 30:70) to give 5.70 g (80%) of the comonomer **6** and 0.69 g (13%) of the cross-linker **7**. The structures of the products **6** and **7**

were confirmed by comparison of the IS-MS, ^1H and ^{13}C NMR spectra with those reported in the literature.[19]

Preparation of the Chiral Monomers 10 and 11

Preparation of 9: Compound **8** (6.40 g, 8.3 mmol), 6-mercaptohexanol (9.8 mL, 70 mmol), and AIBN (0.68 g, 4.1 mmol) were dissolved in 50 mL of degassed $CHCl_3$ in a 50-mL, two-necked flask equipped with a dropping funnel, and the solution was heated at reflux for 34 h, with the intermediate addition of a further amount of AIBN (0.15 g, 0.91 mmol). After cooling to room temperature, the solution was diluted with 100 mL of $CHCl_3$ and treated with 200 mL of 25% HCl. The acid layer was extracted with $CHCl_3$ (4×100 mL) and then made alkaline by the cautious addition of 30% NaOH. The resulting white organic suspension was extracted with CH_2Cl_2 (6×100 mL) and the combined organic phases washed with brine (2×100 mL), dried with Na_2SO_4, and concentrated. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH/EtN_3, 90:10:0.1) to give **9** as a solid foam (yield 90%). R_f= 0.60 (CH_2Cl_2/MeOH/EtN_3, 90:10:0.5).$[\alpha]_D^{30}$ = –160.2 (*c* = 1.33, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.1–2.0 (m, 34 H), 2.0–2.2 (m, 2 H), 2.2–2.6 (m, 6 H), 2.6–3.2 (m, 8 H), 3.3–3.5 (m, 2 H), 3.56 (t, *J* = 6.6 Hz, 4 H), 3.92 (s, 6 H), 7.09 (d, *J* = 6.0 Hz, 2 H), 7.3–7.5 (m, 4 H), 7.56 (d, *J* = 2.2 Hz, 2 H), 7.9–8.1 (m, 4 H), 8.3–8.4 (m, 2 H), 8.62 (d, *J* = 4.4 Hz, 2 H) ppm. ^{13}C NMR (50.2 MHz, $CDCl_3$): δ = 23.0, 25.3, 26.5, 27.1, 28.5, 29.9, 32.1, 32.6, 34.8, 49.9, 50.6, 55.6, 60.0, 62.3, 62.4, 76.5, 102.1, 118.4, 121.8, 122.4, 122.8, 127.2, 131.4, 132.4, 144.5, 144.8, 147.2, 156.3, 157.7 ppm. HRMS (ESI): calcd. for $C_{60}H_{79}N_6O_6S_2$ *m*/*z* = 1043.5497 $[M + H]^+$; found 1043.5503; calcd. for $C_{60}H_{78}N_6NaO_6S_2$ *m*/*z* = 1065.5316 $[M + Na]^+$; found 1065.5327.

Preparation of 10 and 11: A 250-mL, two-necked flask was charged with **9** (4.0 g, 3.8 mmol) and 15 mL of dry DMF. While cooling the solution to 0 °C, NaH (50% in mineral oil, 0.44 g, 9.2 mmol) was added in small portions under vigorous stirring. When the gas evolution had ceased (30 min), a few drops of nitrobenzene were introduced followed by chloromethylstyrene (1.1 mL, 7.7 mmol). After stirring in the dark at room temperature for 72 h, the resulting suspension was cooled to 0 °C, H_2O (20 mL) was cautiously added, and the mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were washed with H_2O (4×10 mL) and dried with Na_2SO_4. The solvent was removed under reduced pressure and the residue was submitted to flash chromatography on silica gel (CH_2Cl_2/MeOH/EtN_3, from 98:2:0.1 to 95:5:0.1) to give **10** (yield 23%) and **11** (yield 61%) as viscous, pale-yellow oils. The sensitive monomers were characterized by NMR spectroscopy and ESI mass spectrometry and immediately employed in the polymerization runs.

10: R_f = 0.25 (CH_2Cl_2/MeOH/EtN_3, 95:5:0.1). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.1–1.8 (m, 33 H), 1.8–2.1 (m, 2 H), 2.2–2.5 (m, 6 H), 2.5–2.9 (m, 8 H), 3.2–3.4 (m, 4 H), 3.49 (t, *J* = 6.6 Hz, 2 H), 3.82 (s, 3 H), 3.83 (s, 3 H), 4.40 (s, 2 H), 5.14 (d, *J* = 10.6 Hz, 1 H), 5.65 (d, *J* = 17.6 Hz, 1 H), 6.62 (dd, *J* = 17.6, 10.9 Hz, 1 H), 6.9–7.0 (m, 2 H), 7.2–7.4 (m, 8 H), 7.4–7.5 (m, 2 H), 7.8–8.0 (m, 4 H), 8.2–8.3 (m, 2 H), 8.5–8.6 (m, 2 H) ppm. ^{13}C NMR (50.2 MHz. $CDCl_3$): δ = 22.7, 23.2, 25.3, 25.8, 26.5, 27.1, 28.5, 28.7, 29.4, 29.5, 29.6, 30.0, 32.1, 32.2, 32.5, 32.6, 34.7, 34.8, 49.8, 49.9, 50.6, 50.7, 55.7, 59.9, 60.0, 62.5, 70.3, 72.6, 76.5, 102.0, 102.2, 113.7, 118.2, 118.6, 121.7, 121.9, 122.4, 122.8, 126.2, 127.1, 127.2, 127.8, 131.5, 131.6, 132.4, 136.6, 136.9, 138.3, 144.6, 144.7, 144.8, 147.2, 147.3, 156.3, 156.4, 157.6, 157.7 ppm. HRMS (ESI): calcd. for $C_{69}H_{87}N_6O_6S_2$ *m*/*z* = 1159.6123 $[M + H]^+$; found 1159.6150.

11: R_f = 0.32. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.1–1.8 (m, 32 H), 1.9–2.1 (m, 2 H), 2.1–2.5 (m, 6 H), 2.5–2.8 (m, 8 H), 3.2–3.4 (m, 6 H), 3.89 (s, 6 H), 4.47 (s, 4 H), 5.14 (d, *J* = 11.0 Hz, 2 H), 5.65 (d, *J* = 17.6 Hz, 2 H), 6.63 (dd, *J* = 17.6, 10.6 Hz, 2 H), 6.94 (d, *J* = 5.6 Hz, 2 H), 7.2–7.4 (m, 12 H), 7.43 (d, *J* = 2.6 Hz, 2 H), 7.8–8.1 (m, 4 H), 8.2–8.3 (m, 2 H), 8.55 (d, *J* = 4.4 Hz, 2 H) ppm. ^{13}C NMR (50.2 MHz. $CDCl_3$): δ = 22.9, 25.9, 26.5, 27.1, 28.7, 29.6, 29.7, 30.0, 32.2, 32.5, 34.7, 50.0, 50.7, 55.7, 60.0, 70.3, 72.6, 76.5, 102.1, 113.7, 118.3, 121.8, 122.5, 122.9, 126.2, 127.2, 127.8, 131.6, 132.4, 136.6, 136.9, 138.3, 144.7, 147.4, 156.4, 157.7 ppm. HRMS (ESI): calcd. for $C_{78}H_{95}N_6O_6S_2$ *m*/*z* = 1275.6749 $[M + H]^+$; found 1275.6800.

Preparation of the Supported Ligands 12, 13a, and 13b

Solution Polymerization (12 and 13a): A polymerization vial with a Teflon stopcock was charged with the chiral monomer **10** or **11** (0.5 mmol, 5 mol-%), the comonomer **6** (85–93 mol-%), the cross-linker **7** (2–10 mol-%), AIBN (1% wt/wt with respect to the monomer), and 5 mL of chlorobenzene or toluene (for the exact molar ratio see Table 1). After degassing by three freeze-pump cycles, the vial was closed and immersed in an oil bath heated at 88 °C; gelation occurred within about 90 min. After 24 h, the heating was interrupted and the resulting mass was transferred with acetone into a cellulose thimble and continuously extracted in a Soxhlet device with THF and EtOH. The UV spectra of the final washings were virtually flat ($A < 0.01$, 2 cm cell) in the region where monomer **10** absorbs (230–350 nm). After drying under vacuum, the polymeric materials were obtained in 77–81% yield as light-yellow powders, which were subjected to the following oxidation step.

Suspension Polymerization (13b):[31] A polymerization reactor was charged with poly(vinyl alcohol) (M_w = 31 000–50 000, 0.67 g), NaCl (2.50 g), and H_2O (HPLC grade, 100 mL) and the resulting solution was stirred and degassed by heating at 85 °C and bubbling N_2 for 30 min. A solution of the chiral monomer **11** (0.5 g, 0.39 mmol, 5 mol-%), comonomer **6** (1.47 g, 6.6 mmol, 85 mol-%), cross-linker **7** (0.26 g, 0.78 mmol, 10 mol-%), and AIBN(40 mg,1% wt/wt with respect to the monomer) in 5 mL of degassed chlorobenzene was added to the vigorously stirred (450 rpm) aqueous solution; the formation of solid beads was observed in 60 min. After 20 h the suspension was cooled and the polymer beads were collected by filtration through a coarse glass frit. The insoluble polymeric material was thoroughly washed with boiling water, MeOH, THF, CH_2Cl_2, Et_2O, and *n*-hexane and then continuously extracted in a Soxhlet device with THF and EtOH, until disappearance of the chiral ligand absorption in the washings (UV check). After drying under vacuum, 1.6 g (70% yield) of the copolymer was obtained as hard, yellow-orange beads, which were subjected to the following oxidation step.

Oxidation of the Sulfide Groups: A suspension of the polymeric ligand in *t*BuOH/THF (1:4, 7 mL g^{-1} of polymer), containing NMO·H_2O (2.5 equiv. vs. the theoretical sulfur content) and OsO_4 (0.02 equiv. vs. the theoretical sulfur content) was magnetically stirred at room temperature for 48 h. After filtration, the resulting brown solid was continuously extracted in a Soxhlet device with THF and then EtOH, until the UV spectrum of the washings had $A < 0.01$ (2 cm cell) in the 230–350 nm region. ffacuum drying afforded the supported ligand in nearly quantitative yields, as a dark-orange material. For **12**: Elem. anal. C 68.43, H 7.64, N 1.37, S 1.95. For **13a**: Elem. anal. C 78.94, H 7.59, N 1.40, S 1.68. For **13b**: Elem. anal. C 68.42, H 7.47, N 1.40, S 2.05. The IR spectra of **12**, **13a**, and **13b** all show the same features. IR (KBr): $\tilde{\nu}$ 3440, 2922, 2856, 1906, 1802, 1656, 1615, 1500, 1344, 1094, 802 cm^{-1}.

Leaching Measurements for 1e, 2e, 12, 13a, and 13b

In the Solvent Mixture: A centrifuge tube equipped with a magnetic stirring bar was charged with a known amount of the supported

ligand (50–150 mg, corresponding to 25 μmol of alkaloid derivative), H_2O (5 mL), *t*BuOH (5 mL), and K_2SO_4 (1.04 g) and the resulting suspension was vigorously stirred (500 rpm) for 20 h at room temp. The insoluble material was filtered through a glass frit and washed with H_2O (4 × 5 mL) and EtOH (3 × 5 mL); the clear filtrates were collected in a volumetric flask. After addition of 37% HCl (0.3 mL) and dilution to 50 mL with H_2O, the absorbance values at 254 and 353 nm were measured in a 2 cm quartz cell against a blank solution containing H_2O, *t*BuOH, and K_2SO_4.

Under Simulated AD Conditions: The same procedure as described above was followed, with the exception that the initial mixture also contained K_2CO_3 (0.42 g) and a larger amount of 37% HCl (3.0 mL) was cautiously added to the filtrate before dilution, in order to neutralize the carbonate and to avoid poor reproducibility in the spectral shape.

AD of Styrene and 1-Phenylcyclohexene With Reduced Amounts of the Soluble Ligand 5: The reactions were carried out on a 1-mmol scale under standard Sharpless conditions for the $K_3Fe(CN)_6$/K_2CO_3 oxidant system,[1a] adding OsO_4 as a 1.53×10^{-2} M solution in MeCN (0.23 mL, 0.35 mol-%) and the commercial ligand **5** as a 4.01×10^{-3} M solution in *t*BuOH (2.5 μL–2.5 mL, for the exact molar ratios see Figure 2). No $MeSO_2NH_2$ was employed. Samples taken at time intervals from the 500 rpm stirred mixture were analyzed by chiral HPLC as described previously,[6k] determining the conversion of the alkene and the *ee* of the diol. After 24 h the product was isolated by standard work-up and characterized by NMR spectroscopy and chiral HPLC.

Heterogeneous Catalytic AD of Olefins With the Supported Ligands 12, 13a, and 13b. General Procedure: A Schlenk tube equipped with a lateral glass frit was charged with $K_2Fe(CN)_6$ (0.99 g, 3 mmol), K_2CO_3 (0.42 g, 3 mmol), H_2O (5 mL), *t*BuOH (5 mL), OsO_4 (0.23 mL of a 1.53×10^{-2} M solution in MeCN, 0.35 mol-%), and the polymeric ligand **12**, **13a**, or **13b** (ca. 150 mg, 2.3–2.5 mol-% of supported alkaloid). After stirring for 10 min at room temp., 1 mmol of olefin was introduced at 0 °C (25 °C in the case of isopropyl cinnamate) and the suspension was stirred at the indicated temperature whilst following the reaction progress and enantioselectivity by chiral HPLC. At the end of the reaction (14–44 h) the mixture was filtered through the frit and the insoluble material was washed with water (3 × 5 mL). The diol product was isolated from the filtrate by standard work-up and characterized by NMR spectroscopy and chiral HPLC as described elsewhere.[6g] The enantiomers of hexane-3,4-diol were separated with a Lipodex A GLC column (Macherey–Nagel, 50 m × 0.25 mm, 95 °C, 28 psi He): (*S*,*S*)-enantiomer, t_R = 14.0 min; (*R*,*R*)-enantiomer, t_R = 14.3 min. After briefly drying under vacuum, the recovered supported ligand could be used in further AD runs, by adding the solvent mixture, the inorganic salts, and the initial OsO_4 amount to the Schlenk tube.

Determination of Catalytic Activity in the Filtrate from 12, 13a, and 13b: A centrifuge tube equipped with a magnetic stirring bar was charged with a known amount of the supported ligand **12**, **13a**, or **13b** (ca. 150 mg, corresponding to 2.3–2.5 mol-% of alkaloid derivative), H_2O (5 mL), *t*BuOH (5 mL), $K_3Fe(CN)_6$ (0.99 g, 3 mmol), and K_2CO_3 (0.42 g, 3 mmol) and the resulting suspension was vigorously stirred (500 rpm) for 12–18 h at room temp. After filtration through a glass frit, OsO_4 (0.10–0.23 mL of 1.53×10^{-2} M solution in MeCN, 0.15–0.35 mol-%) was added to the filtrate and the solution was stirred for 10 min at room temp. The alkene substrate (1 mmol) was then added at 0 °C whilst monitoring the reaction progress and enantioselectivity by chiral HPLC.

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[21] Even if it has been shown that substrates containing thioether groups can be dihydroxylated without affecting the sulfur moiety, previous work in this group indicated that the omission of the oxidation step causes a retardation of AD when the supported ligands are employed in catalysis. The presence of sulfone groups in **12** and **13** is assumed by analogy with solution-phase behavior: W. Priebe, G. Grynkiewicz, *Tetrahedron Lett.* **1991**, *32*, 7353–7356.

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[24] While the extensive dissolution for the former materials **1e** and **2e** under simulated AD conditions may be explained as a consequence of base-promoted cleavage of ester, β-oxysulfone, or siloxane groups, a slight increase in the alkaline leaching with respect to the neutral *t*BuOH/H_2O solvent system was also observed in the case of the modified architecture of **12** and **13a**,**b**. At present, however, the complex nature of the triphasic system under investigation makes it difficult to ascertain if this behavior is related to a slow base-induced fragmentation of the covalent linker or to the intrinsic heterogeneity of the polymeric materials, that could lead to a medium-dependent release of minor amounts of trapped monomers and soluble oligomers into solution.

[25] In other control experiments OsO_4 was also added during the stirring stage, or the mixture of an actual styrene AD run was filtered at partial conversion, followed by the monitoring of the reaction progress in the filtrate. The results obtained with these experimental arrangements were similar to those observed in Os-free leaching studies, excluding any major osmium-related effect in the ligand dissolution process. To avoid possible uncertainties caused by OsO_4 volatilization, the procedure discussed in the text was preferentially used in this work.

[26] In response to a referee's comment, it must be noted that because the focus of this study was on the recycling of the chiral ligand, no detailed investigation was carried out to asses the extent of metal leaching or to optimize the recovery of osmium compounds. Nonetheless, after extensive washing with water (required to remove the abundant precipitate of inorganic salts) a very low catalytic activity in the AD reaction was obtained for the recovered polymeric material, thereby suggesting a substantial metal loss. This conclusion is in agreement with previous observations.[8e]

[27] Effectively, because the achievement of a certain level of enantioselectivity is dependent on both the ligand and the osmium concentration, it could be speculated that the higher *ee* values obtained in the supposed heterogeneous runs are a consequence of the trapping of most of the osmium by the polymeric ligand in a catalytically inactive form. This would leave a small residual amount of active metal species in solution, for which the tiny amount of leached alkaloid could prove sufficient in promoting a highly stereoselective homogeneous process. This hypothesis can, however, be discarded in view of the kinetic data presented. In particular, the dihydroxylation rate in the presence of **12** appears to be not lower than in the control experiments, thus demonstrating that the concentration of cat-

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