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Polysiloxane-bound ligand accelerated catalysis: a modular approach to heterogeneous and homogeneous macromolecular asymmetric dihydroxylation ligands

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Polysiloxane acts as a modular scaffold for macromolecular reagent development. Two separate components were covalently integrated into one material, one constituent provided reagent functionality, the other modulated solubility. In particular cinchona alkaloid based ligands used in the osmium tetroxide catalyzed asymmetric dihydroxylation (AD) reaction were covalently attached to commercially available polysiloxane. To enhance the reactivity of these polymeric ligands, multifunctional reagents were designed to include both the cinchona alkaloid and an alkoxyethylester solubilizing moiety providing random co-polymers. While the mono-functional materials led to heterogeneous conditions, the bi-functional polymers resulted in homogeneous reaction mixtures. Although both reagent types provided diol products with excellent yield and selectivity (>99% ee in nearly quantitative yield) the homogeneous analog has nearly twice the reactivity. Every repeat unit in the heterogeneous material was functionalized along the polysiloxane backbone while approximately half of these sites contained ligand in the homogeneous version. This approach led to macromolecular catalysts with high loadings of ligand and therefore materials with very low equivalent weights. Although these polymers are highly loaded they do maintain reactivity on a par with their free ligand counterpart. Using straightforward purification techniques (*i.e.* precipitation, simple filtration, or ultrafiltration) these polymeric ligands were easily separated from diol product and reused multiple times. Polysiloxane is a viable support for the catalysis of AD reactions and may provide a generally useful backbone for other catalytic systems.

Introduction

The Sharpless asymmetric dihydroxylation (AD) reaction makes use of catalytic osmium tetroxide in the presence of cinchona alkaloid derivatives to oxidize olefins enantioselectively and form a wide variety of vicinal diols.[1–4] Immobilization of cinchona derivatives can enhance the separation of AD reaction products while facilitating the recovery and reuse of the chiral ligand, as well as the toxic metal.[5–8] The isolation of product can in general be simplified by converting the reagent into a macromolecule.[9,10] AD ligands have been engineered onto a variety of macromolecular supports providing heterogeneous[5,11] and homogeneous[6,12–16] reaction conditions. Although the recyclable nature of heterogeneous AD ligands is an advantageous trait, these reagents can suffer from reduced reactivity leading to extended reaction times and lower selectivity.[5,17,18] Desired properties with reactivity comparable to the equivalent free ligand are possible when AD ligands are tethered to supports that provide homogeneous reaction conditions.[6,13,19–21] However, a major drawback to homogeneous macromolecular reagents is the excess of inert material needed to enhance the solubility of the reagent. Current homogeneous macromolecular reagents are thus plagued by low catalyst loadings leading to materials with large equivalent weights making them relatively unattractive, especially in the industrial settings for which they were designed. Eliminating or reducing the inert material in scaffolds for polymeric reagents while maintaining high reactivity and selectivity is the next crucial step in this field.

We thus sought a solution to the drawbacks associated with macromolecular reagent development by applying knowledge gained from our previous work with photorefractive polymers.[22,23] Specifically, we previously developed a modular approach to discover and optimize holographic materials using polysiloxane as a modifiable scaffold. Functionalized olefins were grafted onto commercial poly(methylhydrosiloxane)[24] (PMHS) in mono- and bi-functional formats, by platinum catalyzed hydrosilation.[22,25–28]

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Despite the high solubility of polysiloxane in a wide variety of solvents[28] cinchona alkaloid derivatized polysiloxanes were only sparingly soluble under AD reaction conditions. However, bi-functional polymers, with a second functionality that grants solubility, allowed for the rapid development of soluble polymeric cinchona alkaloid based reagents for the AD reaction. The PMHS support satisfied the criteria for an inexpensive material while maintaining high catalyst loadings giving reagents with relatively low equivalent weights.

Results and discussion

Initial siloxane ligand

To understand the feasibility of polysiloxane as a support for AD ligands a mono-functional cinchona polymer was prepared (Scheme 1). Although, it was conceivable that quinidine itself could be directly hydrosilated to polysiloxane without chemical modification this approach was not successful. Simple modification of hydroquinidine hydrochloride provided a compound that was directly grafted onto polysiloxane. The reaction of hydroquinidine hydrochloride with 10-undecenoyl chloride in the presence of triethylamine provided **1**. Hydrosilation of **1** to PMHS was accomplished using a catalytic amount of dichlorodi(cyclopentadienyl)platinum(II) (Cl_2Ptdcp) with toluene as solvent.[26,27] The hydrosilation reaction could be considered >99% complete when the Si–H bond vanished from a convenient window in the IR spectrum (2160 cm^{-1}).[29] Polymer purification was achieved by an initial toluene–hexanes precipitation, followed by a repetitive reprecipitation procedure using tetrahydrofuran as solvent and hexanes as a precipitant. Disappearance of olefin signals from ^{1}H NMR verified that the polymeric ligand was clean of starting material. Evaporation of residual solvents from the precipitate yielded **2** as a tan solid. Polymer **2** was marginally soluble in acetone and essentially insoluble in hexanes, *tert*-butyl alcohol and methanol; however, **2** was highly soluble in tetrahydrofuran, toluene, $CHCl_3$ and CH_2Cl_2, which allowed for its full characterization.

Ligand **2** was initially screened for AD activity by assaying its ability to convert *trans*-stilbene into hydrobenzoin using stan-

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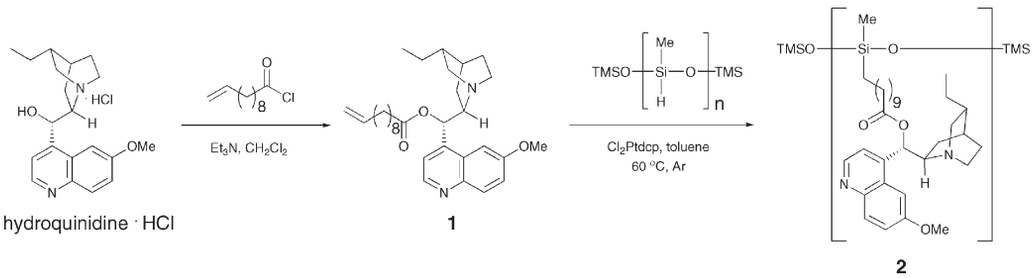


Scheme 1 Cinchona alkaloid attached to polysiloxane.

dard reaction conditions.[5,6] These conditions converted the olefin (1.0 equiv.) to diol product using a mixture of 4-methylmorpholine *N*-oxide (NMO, 1.5 equiv.), tetraethylammonium acetate tetrahydrate (1.0 equiv.), a catalytic amount of OsO_4 (0.01 equiv.) and the polymeric ligand (0.25 equiv.) in an acetone–water (10 : 1, v/v) solvent mixture at 0 °C. Upon complete transformation a simple filtration procedure was used to isolate cleanly the desired product from the insoluble ligand. Analysis of the diol product using optical rotation provided a quick assay for the enantiomeric excess (ee).[30] Under these conditions the preliminary results for **2** were encouraging since the diol product was obtained in 60% yield with 70% ee under 24 h. By comparison, the hydrobenzoin product was obtained in 85% yield and 82% ee using the analogous free ligand under similar AD conditions.[1]

Soluble siloxane ligand

With the precedent established for polysiloxane's ability to function as a scaffold for solid phase reagents, it became a priority to improve and refine the process while determining its scope. The preliminary results for **2** indicated that the reactivity and selectivity were lower than desired for AD reactions. Increasing the solubility of this reagent in acetone should increase reactivity, and varying the steric bulk at the O9 hydroxyl on the cinchona alkaloid is known to improve the stereoselectivity of ligands used in the AD reaction.[31,32] Integrating these aspects into the design of future materials was easy to implement.

Compound **2** was already slightly soluble in acetone; a slight modification of this material made the reagent completely soluble and hence attained the desired increase in reactivity. A search for bi-functional materials with a component that enhanced solubility of the polymer material in acetone–water as well as *tert*-butyl alcohol/water solvent mixtures was carried out.

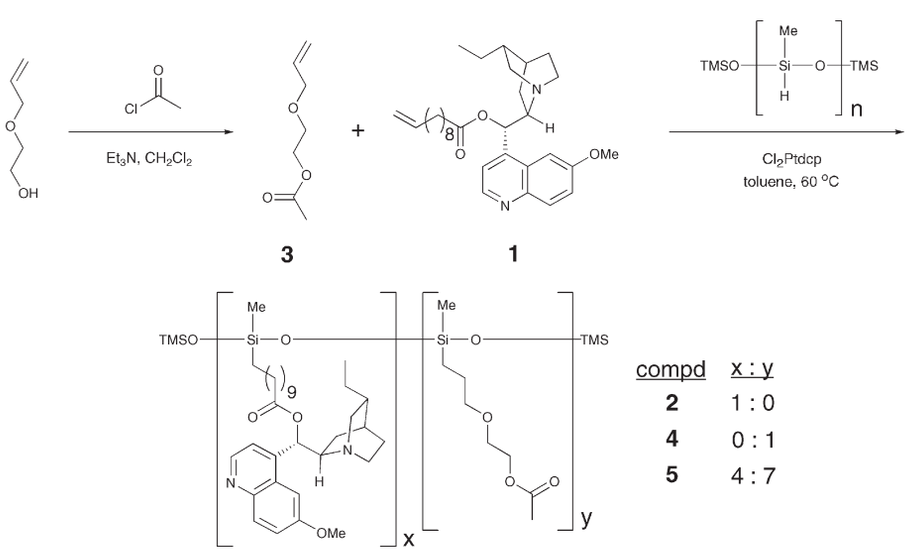
The search for polysiloxane solubilizing moieties began by looking at simple commercially available polyether and ester materials with terminal olefins. Attempts to graft di(ethylene glycol) ethyl ether acrylate to PMHS did not produce the desired polymer product. This occurrence, as well as other cases,[33] indicated that acrylates in general cannot be attached to PMHS by this method. Allyl acetate could be grafted to PMHS, but the resulting polymer was not soluble in acetone.

Ethylene glycol mono-allyl ether was treated with acetyl chloride to provide **3** followed by attachment to polysiloxane (Scheme 2). The resulting polymer **4** was soluble in acetone and *tert*-butyl alcohol. The solublizing group **3** was grafted to polysiloxane in the presence of the cinchona alkaloid derivative **1** in a single synthetic step to provide the bi-functional polymer **5**. The relative ratio of grafted groups in bi-functional material **5** can be determined by comparing the integration of unique signals stemming from each graft type in the ^{1}H NMR spectrum. Furthermore, this ratio can be regulated empirically by modifying the initial olefin concentrations prior to grafting.[22]

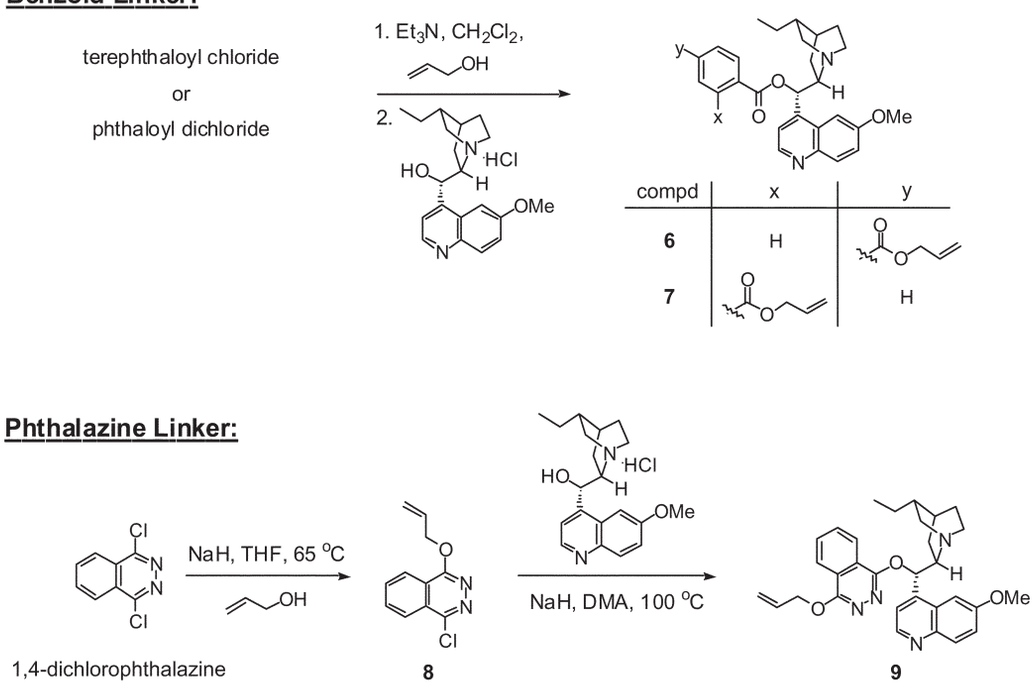
The bi-functional polymer **5** was completely soluble in acetone and *tert*-butyl alcohol providing homogeneous conditions for typical AD reactions. However, the material precipitated when a high concentration of water was added; such a solubility difference allows for simple separation of product from reagent. Ligand **5** gave diol product from *trans*-stilbene with similar yield and selectivity as that provided by **2**; however, this reaction was complete in less than 5 h compared to 24 h as found with compound **2** under identical AD conditions. Once a component capable of increasing the derivatized polysiloxane's solubility and reactivity in typical AD conditions was identified, the issue of selectivity could be addressed.

Array of ligands

To improve the stereoselectivity of these materials a limited search for attachable cinchona alkaloid derivatives with steric linkers covalently bound at the O9 hydroxyl was initiated (Scheme 3). Addition of aromatic substituents to the O9 position of the cinchona alkaloid has led to increased enantioselectivity in AD reactions.[31,32] Initially, two isomeric phthalic acid moieties were integrated into the O9 position to provide **6** and **7** containing terminal olefins. Changing the regio-chemistry from a 1,4-terephthalic acid to the 1,2-phthalic acid derivatized linker probed the polymer chain's influence on the selectivity. The larger phthalazine linker was also incorporated into



Scheme 2 Modular approach towards soluble siloxane ligand.



Scheme 3 Modified cinchona alkaloid ligands with increased steric bulk on the O9 hydroxyl.

the O9 position in a two-step chemical process to provide **9**. The steric phthalazine linker may have an enhanced effect on the stereochemical outcome of diols produced when these solid phase ligands are used to dihydroxylate olefins.

Once compounds **6**, **7** and **9** were prepared they were individually attached to PMHS, using the standard conditions already described, to provide mono-functional materials **10**, **12** and **14** accordingly (Fig. 1). Furthermore, the ligands **6**, **7** and **9** were separately grafted together with **3** to provide bi-functional materials **11**, **13**, and **15**, respectively. As before, the bi-functional materials **11**, **13** and **15** were soluble under common AD conditions, whereas mono-functional polymers **10**, **12** and **14** were not.

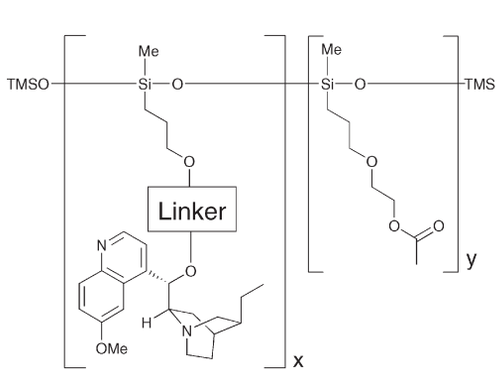
The new class of ligands **10–14** (0.25 equiv.) was individually tested for their ability to dihydroxylate *trans*-stilbene (1.0 equiv.) using OsO_4 (0.01 equiv.), NMO (1.5 equiv.) and tetraethylammonium acetate tetrahydrate (1.0 equiv.) in an acetone/water (10 : 1, v/v) solvent mixture at 0 °C (Table 1). The modified materials have improved reactivity and selectivity compared to the initial ligands **2** and **5**. The second generation of polysiloxane materials were capable of converting *trans*-stilbene to hydrobenzoin in as short as 2 h with >80% isolated yield and >80% ee. However, after an initial increase in selectivity and yield (entry 1) each subsequent modification of the steric linker (*i.e.* ligands **12** and **14**) reflected essentially no benefit. Furthermore, the reactivity difference decreased between heterogeneous and homogeneous materials. For example, insoluble ligand **10** required only 30 additional minutes to convert all starting material to product compared to its soluble counterpart **11** under identical conditions.

Limited concentration of OsO_4

To understand the performance of polysiloxane bound AD ligands better, the dependence of OsO_4 concentration relative to heterogeneous ligand **10** and homogeneous ligand **11** was investigated (Table 2). The soluble ligands showed dramatically improved reactivity over the insoluble ligands when a limited concentration of OsO_4 was used. For example, complete conversion to diol product using 0.1 mol% OsO_4 required 46 h with the heterogeneous ligand **10** (entry 1) compared to 29 h for the homogeneous ligand **11** (entry 4) under matching conditions.

Bis-cinchona alkaloid ligands

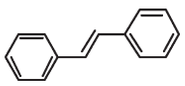
A slight modification of the synthesis Sharpless used to prepare $(DHQD)_2PHAL$[3,34] was applied to make a dimeric cinchona ligand with a terminal olefin capable of attachment to polysiloxane (Scheme 4). Exchange of one chlorine atom for quinidine on 1,4-dichlorophthalazine to provide **16** occurred *via* nucleophilic aromatic substitution at slightly elevated temperature. Hydroquinidine was then covalently linked to **16** by displacement of the second chloride on the phthalazine heterocycle at a higher temperature yielding **17**. Compound **17** can be attached to polysiloxane using the standard conditions to provide both mono- and bi-functional polymers. The



compd	Linker	x:y
10		1:0
11		5:7
12		1:0
13		3:2
14		1:0
15		13:10

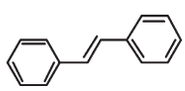
Fig. 1 Modified cinchona alkaloid ligands attached to polysiloxane.

Table 1 Dihydroxylation reactions using polysiloxane ligands[a]

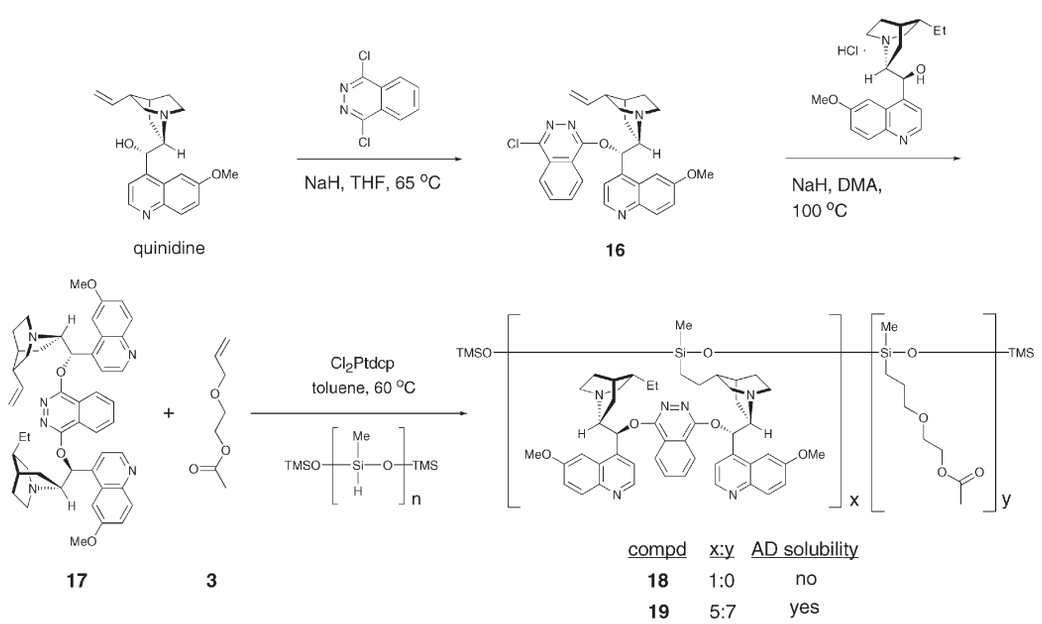
Entry	Ligand	Olefin	OsO_4 (mol%)	Amount of ligand[b] (mol%)	Reaction time/h	Yield[c] (%)	ee[d] (%)
1	**10**		1	25	2.5	85	83
2	**11**		1	25	2.0	77	79
3	**12**		1	25	2.0	72	79
4	**13**		1	25	2.0	83	82
5	**14**		1	25	3.0	86	79

[a] Reaction conditions: NMO (1.5 equiv.) as secondary oxidizer, $Et_4N^+CH_3CO_2^-$ (1.0 equiv.), acetone–water (10 : 1, v/v), 0–4 °C. [b] Amount of ligand used was based on alkaloid incorporation. [c] Isolated yield. [d] Enantiomeric excess was determined by comparing optical rotation with the literature values.[3,30]

Table 2 Dihydroxylation reactions with polysiloxane ligands using limited OsO_4[a]

Entry	Ligand	Olefin	OsO_4 (mol%)	Amount of ligand[b] (mol%)	Reaction time/h	Yield[c] (%)	ee[d] (%)
1	**10**		0.1	25	46	79	69
2	**10**		0.5	25	3.5	85	82
3	**10**		1.0	25	2.5	85	83
4	**11**		0.1	25	29	72	76
5	**11**		0.5	25	3.0	73	85
6	**11**		1.0	25	2.0	77	79

[a] Reaction conditions: NMO (1.5 equiv.) as secondary oxidizer, $Et_4N^+CH_3CO_2^-$ (1.0 equiv.), acetone–water (10 : 1, v/v), 0–4 °C. [b] Amount of ligand used was based on alkaloid incorporation. [c] Isolated yield. [d] Enantiomeric excess was determined by comparing optical rotation with the literature values.[3,30]



Scheme 4 $(DHQD)_2PHAL$ attached to polysiloxane.

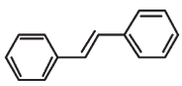
bi-functional polymer **19** led to homogeneous conditions when subjected to common AD solvents while the mono-functional polymer **18** gave heterogeneous conditions. Reagent **19** has a much lower equivalent weight compared to similar homogeneous macromolecular reagents designed for the AD reaction[13] and only about 30% more than the simple free ligand. The siloxane based reagent **19** has an equivalent weight of around 1000 g mol^{-1} compared to >5000 g mol^{-1} for the analogous material designed by Janda and 800 g mol^{-1} for $(DHQD)_2PHAL$. This low equivalent weight is a simple result of the high loading factor possible in PMHS.

The mono-functional heterogeneous ligand **18** was evaluated for its ability to convert *trans*-stilbene to hydrobenzoin (Table 3). This polysiloxane bound dimeric ligand was superior to all previous siloxane materials tried. At first, the material was tested using standard conditions established by Sharpless[5] for two different secondary oxidants.[35,36] Based on superior yield and ee it was rapidly established that the $K_3Fe(CN)_6$ conditions were optimal for this new ligand. Enantioselectivity equivalent to the free ligand $(DHQD)_2PHAL$ was achieved using polymeric ligand **18** and $K_3Fe(CN)_6$ as secondary oxidant.[3] Next, experiments to establish the minimal amount of ligand needed to achieve optimal results were conducted. It was shown that ligand concentrations as low as 5 mol% (based on the number of active sites) produced a desired outcome with 1 mol% OsO_4. By comparison, the commonly used AD-mix β contains 10 mol% of the ligand $(DHQD)_2PHAL$ and 0.2 mol% osmium.[3]

To further evaluate the scope and utility of these materials an array of olefins was dihydroxylated with polysiloxane bound dimeric cinchona alkaloid ligands **18** and **19**. Initially, a variety of olefin substrates based on a styrene core were used to determine the scope of the heterogeneous polysiloxane ligand **18** (Table 4). The majority of substrates were screened using $K_3Fe(CN)_6$ as the optimal secondary oxidant with 5 mol% of ligand based on the alkaloid incorporation to the polymer support. These conditions proved to be very good for oxidizing olefins having multiple substitutions. However, the ligand's performance dropped as the degree of substitution on the alkene was decreased. The data showed that ligand **18** worked best with 1,2-*trans*- and 1,1-disubstituted alkenes followed by styrene and last 1,2-*cis*-disubstituted olefins.

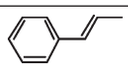
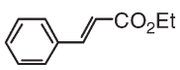
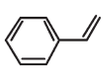
Homogeneous bi-functional ligand **19** was screened under several different conditions for its ability to convert olefin to diol product (Table 5). Low yields of hydrobenzoin product were observed when 25 mol% of ligand was used (entry 1). When a lower concentration of ligand was employed (entries 2–3) the hydrobenzoin yield went up and the ee remained high. The soluble siloxane-bound ligands were quickly separated from diol product by precipitating the crude reaction mixture into an excess of water. The low yields could arise from

Table 3 Dihydroxylation reactions using the heterogeneous ligand **18**

Entry	Olefin	OsO_4 (mol%)	Amount of ligand[a] (mol%)	Secondary oxidant[b]	Reaction time/h	Yield[c] (%)	ee[d] (%)
1		1	25	NMO	3	87	93
2		1	25	$K_3Fe(CN)_6$	24	94	99
3		1	10	$K_3Fe(CN)_6$	24	92	95
4		1	5	$K_3Fe(CN)_6$	24	98	93
5		1	5	NMO	3	85	91

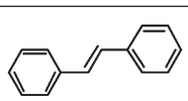
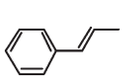
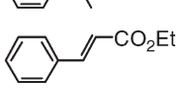
[a]Amount of ligand used was based on alkaloid incorporation. [b]With NMO (1.5 equiv.) acetone–water (10 : 1, v/v) solvent was used at 0–4 °C and with $K_3Fe(CN)_6$ (3.0 equiv.) *tert*-butyl alcohol–water (1 : 1, v/v) solvent was used at 0–4 °C. [c]Isolated yield. [d]Enantiomeric excess was determined by comparing optical rotation with the literature values.[3,30]

Table 4 Scope of heterogeneous ligand **18**

Entry	Olefin	OsO_4 (mol%)	Amount of ligand[a] (mol%)	Secondary oxidant[b]	Reaction time/h	Yield[c] (%)	ee[d] (%)
1		1	5	NMO	2.3	92	84
2		1	5	$K_3Fe(CN)_6$	18	92	92
3		1	5	NMO	2	89	64
4		1	5	$K_3Fe(CN)_6$	2	91	92
5		1	5	$K_3Fe(CN)_6$	24	91	96
6		1	5	$K_3Fe(CN)_6$	18	73	85
7		1	5	$K_3Fe(CN)_6$	8	70	36

[a]Amount of ligand used was based on alkaloid incorporation. [b]With NMO (1.5 equiv.) acetone–water (10 : 1, v/v) solvent was used at 0–4 °C and with $K_3Fe(CN)_6$ (3.0 equiv.) *tert*-butyl alcohol–water (1 : 1, v/v) solvent was used at 0–4 °C. [c]Isolated yield. [d]Enantiomeric excess was determined by comparing optical rotation with the literature values.[3,30,37,38]

Table 5 Dihydroxylation reactions using the homogeneous ligand **19**

Entry	Olefin	OsO_4 (mol%)	Amount of ligand[a] (mol%)	Secondary oxidant[b]	Reaction time/h	Yield[c] (%)	ee[d] (%)
1		1	25	NMO	2.5	65	96
2		1	10	NMO	3.0	71	91
3		1	5	NMO	2.0	84	92
4		1	5	$K_3Fe(CN)_6$	21	88	83
5		1	5	NMO	2.5	91	89
6		1	5	$K_3Fe(CN)_6$	14	93	92
7		1	5	NMO	1	86	76
8		1	5	$K_3Fe(CN)_6$	2	93	90
9		1	5	$K_3Fe(CN)_6$	12.5	90	91

[a]Amount of ligand used was based on alkaloid incorporation. [b]With NMO (1.5 equiv.) acetone–water (10 : 1, v/v) solvent was used at 0–4 °C and with $K_3Fe(CN)_6$ (3.0 equiv.) *tert*-butyl alcohol–water (1 : 1, v/v) solvent was used at 0–4 °C. [c]Isolated yield. [d]Enantiomeric excess was determined by comparing optical rotation with the literature values.[3,30,37]

inclusion of the diol by the precipitated polymer ligand **19** during the workup.[39] Higher yields of diols were observed as product polarity increased, consistent with the assumption of co-precipitation.

While the selectivity and yield remained essentially the same for the two ligands, formation of diol product using the heterogeneous catalyst **18** (Table 4) was in general slower compared to the reaction with homogeneous ligand **19** (Table 5) under identical conditions; in some specific cases the reaction times for **19** were half of what was needed for **18**. Polysiloxane based catalysts **18** and **19** have a broad scope, in the conversion of many substrates nearly quantitatively to a single enantiomer using about 5 mol% catalyst.

Recycling ligands

An important aspect of solid phase reagents is that they can be reused multiple times to decrease waste and reduce the cost of a particular synthetic transformation per mole of reagent. Simple filtration of reactions employing **18** allowed essentially complete recovery of the heterogeneous ligand with partial recovery of OsO_4. When 25 mol% of **18** was used to catalyze the AD of *trans*-stilbene under NMO conditions (Table 3, entry 1) the recovered ligand can be reused to catalyze the identical transformation. Recycled ligand **18** can provide hydrobenzoin product after reacting for 2 days with 88% yield and 94% ee without the addition of more OsO_4. Although 2 days is significantly longer than the initial reaction time of 3 h the product was obtained with comparable quantity and purity. A wide variety of cinchona alkaloid supports also suffer from the general problem of OsO_4 leaching[11,13,40,41] with only limited examples successfully retaining the metal.[42,43] In general, successive trials of recovered macromolecular bound AD ligands require additional OsO_4 to retain high reactivity and selectivity.

To establish the extent these materials can be recycled ligand **18** (0.1 equiv.) was recovered and reused multiple times for dihydroxylation of 1.0 equiv. of *trans*-stilbene (Fig. 2). For each consecutive iteration of the recycled ligand a fresh aliquot of OsO_4 (0.01 equiv.) was added. Using $K_3Fe(CN)_6$ (3.0 equiv.) and *tert*-

butyl alcohol–water (1 : 1, v/v) as the solvent, four iterations of the ligand were made to prepare hydrobenzoin product without any loss of reactivity or selectivity. For example, in the fourth trial only 26 h was needed to reach completion compared to the initial reaction requiring 24 h.

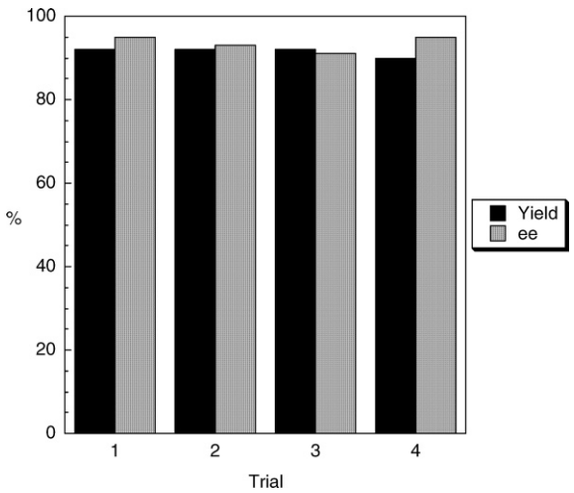


Fig. 2 Recycling heterogeneous ligand **18** using a fresh aliquot of OsO_4 with each iteration and $K_3Fe(CN)_6$ as the secondary oxidant.

When the homogeneous ligand **19** was used for the AD of olefins its recovery and reuse was possible by adding an excess of H_2O (≥4/1, v/v) to the completed reaction. The polymer ligand was insoluble when subjected to a high concentration of H_2O and was selectively precipitated. Filtration of the precipitate allowed for the recovery of the ligand while extraction of the mother-liquor with CH_2Cl_2 provided the diol product. Although this method recovered a significant amount of the ligand (>90%) it unfortunately retained only a fractional amount of OsO_4. When 25 mol% of **19** was used to dihydroxylate *trans*-stilbene under the NMO conditions (Table 5, entry 1) the recovered ligand will not catalyze a second iteration unless additional OsO_4 was added. Using the recovered ligand with fresh substrate and a secondary oxidizer resulted in detection of very little hydrobenzoin product even after a reaction time of 2 weeks. However, when an additional aliquot of OsO_4 (0.01 equiv.) was added the reaction was complete in only 3 h with a nearly identical outcome as the initial trial.

Ultrafiltration

Separation methods ranging from selective precipitation to multi-phasic techniques have been employed to isolate various homogeneous macromolecule reagents from their corresponding products.[44–47] We investigated ultrafiltration as an alternative method to help separate the diol product from the homogeneous macromolecular ligand **19**. A 30 kD centrifugal concentrator compatible with organic solvents was successfully used to isolate diol product from the soluble siloxane catalyst. The apparatus used had a filtering volume capacity of 2 mL that allowed the reactions to be run inside the filtering unit. *trans*-Stilbene was dihydroxylated inside the ultrafiltration device. Initially, the polymer ligand **19** (0.011 mmol) was pre-filtered from an acetone solution to remove the low molecular weight oligomers. Then the dihydroxylation reaction proceeded by adding all necessary components directly into the filtration device. Using the standard conditions for NMO as a secondary oxidant the dihydroxylation of *trans*-stilbene yielded hydrobenzoin in 86% yield and 91% ee in 3 h. The use of the centrifugal concentrator allowed the trivial separation of diol product from ligand in a reasonable amount of time. In a second iteration the apparatus containing filtered ligand was reused to dihydroxylate *trans*-stilbene to provide hydrobenzoin with nearly identical results (87% yield, 94% ee, 3 h). In principle, a larger version of this apparatus could be used to prepare diol product cleanly and efficiently on an industrial scale with reduced waste.

Conclusions

Polysiloxane is a viable support for solid phase synthesis, as well as a useful material for mediating AD reactions. It is inexpensive and simple to modify, allowing for rapid innovations. Unlike typical polymer supports this material allows for high catalyst loadings while maintaining excellent reactivity. Macromolecular reagents with comparatively low equivalent weights (500–1000 g mol^{-1}) are possible with polysiloxane. The performance of the siloxane bound ligands was equivalent to the analogous free reagent, and also maintained the desired macromolecular properties. Heterogeneous and homogeneous ligands were easily separated from product and were reused multiple times. While heterogeneous siloxane ligands have an enhanced affinity towards OsO_4, the homogeneous analogs displayed greater reactivity due to their superior solubility. Expansion of siloxane bound reagents beyond the AD reaction should be particularly interesting for industrial chemical processes.

Experimental

General methods

NMR spectroscopy (^1H and ^{13}C) was recorded on Varian (Mercury 300 MHz, Mercury 400 MHz, or Unity 500 MHz) spectrometers. ^1H NMR spectra were referenced to tetramethylsilane (TMS) at 0.00 ppm. ^{13}C NMR spectra were referenced to 77.0 ppm in chloroform-*d* ($CDCl_3$) and 53.5 ppm in dichloromethane-d_2 (CD_2Cl_2). High-resolution mass spectra (HRMS) were obtained from the University of California at Riverside's mass spectrometry facility in the fast atom bombardment (FAB) or electron impact (EI) mode. Ultraviolet spectroscopy (UV-vis) was recorded on a Perkin-Elmer Lambda 19 UV/vis/NIR spectrophotometer. Infrared (IR) spectra were recorded on a Perkin-Elmer 1420 IR spectrophotometer. Melting points (mp) were obtained on a Mel-Temp melting point apparatus and were recorded uncorrected.

All experiments were carried out under argon in freshly distilled solvents under anhydrous conditions unless otherwise noted. Commercial chemicals were acquired from Sigma–Aldrich with the exception of dichlorodi(cyclopentadienyl)platinum(II) that was obtained from Strem Chemicals, Inc. Commercial chemicals were used as supplied unless otherwise stated. Osmium tetroxide (OsO_4) was stored at −5 °C under an atmosphere of argon. Tetrahydrofuran (THF) was distilled from sodium/benzophenone; toluene and dichloromethane (CH_2Cl_2) were distilled from calcium hydride; triethylamine was distilled from NaOH, and pyridine was distilled from KOH. Preparative column chromatography was performed with silica gel (230–425 mesh) from Fisher Scientific Company. Thin-layer chromatography (TLC) was performed on aluminium backed silica gel 250 μm F_{254} plates from Whatman. Centrifugal filter (2 mL capacity) with a nominal molecular weight limit cellulose membrane was acquired from Millipore (catalogue number UFC4 LTK 25).

Optical rotation measurements were performed on a Perkin-Elmer model 241 polarimeter. The specific rotation was determined using the following formula:

$$[\alpha]_{\lambda}^{t^\circ} = \frac{\alpha}{lc}$$

where [α] = specific rotation, t = temperature in degrees Celsius, λ = wavelength of incident light (for the sodium D lamp, indicated simply by "D", λ = 589 nm, the yellow emission line of hot sodium vapor), α = observed optical rotation in degrees, l = length of sample container in decimeters (its value was 1, *i.e.* 10 cm), c = concentration (grams per milliliter of solution). The optical purity (op) was determined by the following formula:

$$\text{op} = 100\left(\frac{[\alpha]_{\text{observed}}}{[\alpha]_{\text{pure enantiomer}}}\right)$$

The rough equality of op and ee for the reaction was confirmed by Mosher's analysis[48,49] for a few representative diol products.

General hydrosilation procedure

The procedure was adapted from Strohriegl.[26,27] To a two-neck round-bottom flask equipped with condenser, gas inlet, stir bar, and glass stopper was added toluene and poly(methylhydrosiloxane)[24] (PMHS, 0.2–0.3 M, 1 equiv., $\overline{M}_n$ = 9500) under a flow of argon. The olefin(s) (1.1–1.3 equiv.) was then added to the mixture followed by dichlorodi(cyclopentadienyl)platinum(II) (1.0 mg, 0.0025 mmol). The mixture was stirred at elevated temperature (60–65 °C). The reaction progress was monitored using IR spectroscopy. After an initial reaction time of 20 h, an aliquot of the neat reaction solution was evaporated on NaCl plates, and the IR spectrum was recorded to follow the disappearance of the Si–H stretch at 2150 cm^1. Additional dichlorodi(cyclopentadienyl)platinum(II) (*ca*. 1 mg) was added at regular intervals until the IR spectrum of an aliquot showed no residual Si–H stretch. If the reaction was incomplete, then additional dichlorodi(cyclopentadienyl)platinum(II) (*ca.* 1 mg) was added. This cycle was continued at regular time intervals (*ca.* 1 h) until the silicon-hydrogen signal was no longer present in the IR spectrum. In most cases the reactions required little or no additional dichlorodi(cyclopentadienyl)platinum(II) to reach completion. Upon completion, the reaction was cooled to room temperature. Then the reaction solution was added dropwise into an excess of hexanes. Unless otherwise stated this caused the polymeric product to precipitate. The precipitate was collected by centrifuge and decanted. Then the precipitated polymer residue was dissolved in a minimal amount of THF (amount varies on substrate and scale) needed to completely dissolve the crude polymer. This THF solution was precipitated again into an excess of hexanes. The precipitation process was continued until the polymer residue is free of monomers as determined by ^{1}H NMR. Unless otherwise stated, a total of three precipitations were all that was needed for clean product. The residual solvents were removed from the polymer residue under reduced pressure. In most cases the products become a solid foam after solvents were evacuated by vacuum. In the case of bi-functional polymers the ratio was determined by integration of unique signals from ^{1}H NMR.

General asymmetric dihydroxylation procedure

NMO secondary oxidant. The procedure was adapted from Janda.[6] A 10 mL screw-top vial equipped with magnetic stir bar was charged with the polymer catalyst (0.011–0.55 mmol, 0.05–0.25 equiv. based on alkaloid incorporation), 4-methylmorpholine *N*-oxide (39 mg, 0.33 mmol), tetraethylammonium acetate tetrahydrate (57 mg, 0.22 mmol), acetone (3.6 mL), water (0.4 mL) and OsO_4 in *tert*-butyl alcohol (28 μL of OsO_4 2.5 wt% solution, 0.0022 mmol). After stirring the solution for 5 min at 0–4 °C, the olefin (0.22 mmol) was added in one portion. The reaction mixture was stirred vigorously at 0–4 °C until the olefin completely disappeared as judged by TLC. The work-up procedure varied depending if heterogeneous or homogeneous ligands were employed (see work-up).

$K_3Fe(CN)_6$ secondary oxidant. The procedure was adapted from Sharpless.[5] To a 10 mL screw-top vial equipped with magnetic stir bar and wrapped in aluminium foil was charged with the polymer catalyst (0.011–0.55 mmol, 0.05–0.25 equiv. based on alkaloid incorporation), potassium ferricyanide (217 mg, 0.66 mmol), potassium carbonate (91 mg, 0.66 mmol), *tert*-butyl alcohol (2 mL), water (2 mL), and OsO_4 in *tert*-butyl alcohol (28 μL of OsO_4 2.5 wt% solution, 0.0022 mmol). After stirring the solution for 10 min at 0–4 °C, the olefin (0.22 mmol) was added in one portion. The reaction mixture was stirred vigorously at 0–4 °C until the olefin disappeared as judged by TLC. The work-up procedure varied depending if heterogeneous or homogeneous ligands were employed (see work-up).

Centrifugal filter apparatus. To the filtration cup section of a 2 mL capacity centrifugal filter (30,000 nominal molecular weight limit regenerated cellulose membrane, Millipore catalogue number UFC4 LTK 25) equipped with magnetic stir bar was charged with the polymer catalyst **19** (12 mg, 0.011 mmol, 0.1 equiv. based on alkaloid incorporation) and acetone (2 mL). This mixture was stirred at room temperature until the polymeric ligand was completely dissolved (*ca.* 5 min). Then the apparatus was centrifuged to a concentrated volume of *ca.* 30 μL (*ca.*1.0 h). The mother-liquor was discarded since it contained only low molecular weight oligomers. Then the filtration cup was charged with 4-methylmorpholine *N*-oxide (20 mg, 0.165 mmol), tetraethylammonium acetate tetrahydrate (29 mg, 0.11 mmol), acetone (1.8 mL), water (0.2 mL) and OsO_4 in *tert*-butyl alcohol (14 μL of OsO_4 2.5 wt% solution, 0.0011 mmol). After stirring the solution for 5 min at 0–4 °C, *trans*-stilbene (21 mg, 0.11 mmol) was added in one portion. The reaction mixture was stirred vigorously at 0–4 °C until the olefin disappeared as judged by TLC. Then the apparatus was centrifuged to a concentrated volume of *ca.* 30 μL (*ca.*1.0 h). The filter cup was washed with acetone (3 × 2 mL) and centrifuged to a concentrated volume each time. The combined mother-liquors were worked up similar to the heterogeneous description below considering that the polymer ligand was thoroughly removed.

Asymmetric dihydroxylation work-up procedure

Heterogeneous ligands. Once the reaction was complete the vial was centrifuged and the reaction solution decanted leaving behind the heterogeneous ligand ready for reuse without further purification. The mother-liquor was treated with solid sodium metabisulfite (500 mg) for 5 min followed by Na_2SO_4 to remove water. All solids were removed by filtration and washed with CH_2Cl_2 (3 × 10 mL). The combined filtrates were evaporated to dryness giving nearly pure dihydroxylated product. Further purification using silica gel column chromatography was performed when needed.

Homogeneous ligands. To the completed reaction was added H_2O (15 mL) to selectively precipitate the siloxane ligand. This cloudy solution was centrifuged then decanted leaving behind the recycled ligand. No further purification of the ligand was performed. The mother-liquor was extracted using CH_2Cl_2 (3 × 10 mL). The organic layers were combined and stirred over sodium metabisulfite (500 mg) for 15 min followed by Na_2SO_4. All solids were removed by filtration and washed with CH_2Cl_2 (3 × 10 mL). The combined filtrates were evaporated to dryness giving nearly pure dihydroxylated product. Further purification of the dihydroxylated product using silica gel column chromatography was performed when needed.

Undec-10-enoic acid ((2*R*,5*R*)-(+)-5-ethyl-1-azabicyclo[2.2.2]oct-2-yl)(6-methoxyquinolin-4-yl)-(*S*)-methyl ester (1). To a 250 mL two-neck round-bottom flask equipped with stir bar, 100 mL dropping addition funnel, condenser and gas inlet was charged hydroquinidine hydrochloride (3.34 g, 9.2 mmol), CH_2Cl_2 (50 mL) and triethylamine (6.4 mL, 46 mmol) under a flow of argon. A solution of 10-undecenoyl chloride (2.96 mL, 13.8 mmol) in CH_2Cl_2 (10 mL) was prepared in the addition funnel and added dropwise into the stirred reaction solution at 0 °C. The reaction was then brought to room temperature and stirred overnight. Then the reaction mixture was carefully poured into a separatory funnel containing water (100 mL). The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (1 × 50 mL) solution and dried over $MgSO_4$. The solvent was removed using a rotary evaporator to yield a crude yellow oil. Purification *via* flash chromatography using silica as absorbent (acetone–EtOAc, 4 : 1) yielded a light yellow oil (3.8 g, 84%), $[\alpha]_D^{22}$ = 34.4 (*c* 0.53, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, *J* = 7.2 Hz, 3H), 1.22–1.67 (m, 18H), 1.71–1.81 (m, 2H), 2.02 (q, *J* = 6.8 Hz, 2H), 2.38 (t, *J* = 6.4 Hz, 2H), 2.62–2.82 (m, 3H), 2.85–2.94 (m, 1H), 2.28 (q, *J* = 8.4 Hz, 1H), 3.91 (s, 3H), 4.92 (dd, *J* = 10.0, 0.8 Hz, 1H), 4.98 (dd, *J* = 17.2, 2.0 Hz, 1H), 5.74–5.85 (m, 1H), 6.53 (d, *J* = 7.6 Hz, 1H), 7.32–7.36 (m, 1H), 7.37 (d, *J* = 2.4 Hz, 1H), 7.42 (d, *J* = 2.4 Hz, 1H), 8.01 (d, *J* = 9.2 Hz, 1H), 8.73 (d, *J* = 4.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.05, 23.43, 24.90, 25.47, 26.07, 27.20, 28.84, 29.00, 29.08, 29.15, 29.24, 33.73, 34.46, 37.31, 49.87, 50.71, 55.48, 59.01, 73.22, 101.20, 113.95, 118.39, 121.59, 126.84, 131.51, 138.81,

143.75, 144.45, 147.14, 157.50, 172.42. HRMS-EI$^+$ *m*/*z*: found 492.3349; calc. ($C_{31}H_{44}N_2O_3$) 492.3352.

Poly(methylundecanoic acid ((2*R*,5*R*)-5-ethyl-1-azabicyclo[2.2.2]oct-2-yl)(6-methoxyquinolin-4-yl)-(*S*)-methyl ester siloxane) (2). Refer to general hydrosilation procedure. The reaction was run using **1** (2.6 g, 5.2 mmol), PMHS (280 μL, 4.7 mmol), toluene (30 mL) and dichlorodi(cyclopentadienyl)platinum(II) (20 mg, 0.05 mmol) to provide a tan solid (1.1 g, 48%), equiv. wt. 552. ^{1}H NMR (500 MHz, CD_2Cl_2): δ −0.02–0.30 (br s, 3H), 0.44–0.64 (br s, 2H), 0.82–1.01 (br s, 3H), 1.08–1.90 (br m, 24H), 2.25–2.50 (br s, 2H), 2.57–2.81 (br s, 3H), 2.83–3.02 (br s, 1H), 3.16–3.35 (br s, 1H), 3.82–4.13 (br s, 3H), 6.32–6.77 (br s, 1H), 7.18–7.41 (br m, 2H), 7.43–7.62 (br s, 1H), 7.86–8.14 (br s, 1H), 8.54–8.82 (br s, 1H). ^{13}C NMR (125 MHz, CD_2Cl_2): δ −2.40, 12.25, 18.13, 23.59, 25.45, 25.93, 26.64, 27.32, 27.46, 29.70, 29. 81, 29.95, 30.10, 30.15, 34.03, 34.95, 37.70, 50.19, 51.15, 56.33, 60.22, 73.45, 102.28, 119.14, 122.44, 127.73, 132.34, 145.10, 145.30, 148.02, 158.65, 173.21. IR (neat): ν_{Si-O} 1010, $\nu_{C=O}$ 1725, ν_{C-H} 2895 cm^{-1}.

Acetic acid 2-allyloxyethyl ester (3). A 250 mL two-neck round-bottom flask equipped with stir bar, rubber septum, condenser and gas inlet was charged with ethylene glycol monoallyl ether (5.3 mL, 50 mmol), CH_2Cl_2 (85 mL), and triethylamine (13.9 mL, 100 mmol) under a flow of argon. Acetyl chloride (4.3 mL, 60 mmol) was added *via* syringe to the reaction solution at 0 °C in a dropwise fashion. The reaction mixture was warmed to room temperature and stirred overnight. Then the reaction solution was poured slowly into a saturated aqueous solution of $NaHCO_3$ (50 mL). This mixture was extracted with Et_2O (2 × 75 mL). The ether layers were combined, dried over $MgSO_4$, filtered and evaporated under reduced pressure to yield a yellow liquid. Purification *via* simple vacuum distillation provided a colorless liquid (5.2 g, 72%), bp 30–32 °C (1 mm Hg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.09 (s, 3H), 3.62 (t, *J* = 4.8 Hz, 2 H), 4.04 (dt, *J* = 5.6, 1.2 Hz, 2H), 4.23 (t, *J* = 4.8 Hz, 2 H), 5.21 (dd, *J* = 10.0, 1.6 HZ, 1H), 5.30 (dd, *J* = 17.2, 2.0 Hz, 1H), 5.86–5.97 (m, 1H); lit.[50] δ 2.02 (s, 3H), 3.55 (t, 2H), 3.96 (d, 2H), 4.15 (t, 2H), 5.1–6.1 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 63.6, 67.8, 72.1, 117.3, 134.2, 170.8.

Poly(methylacetic acid 2-propoxyethyl ester siloxane) (4). Refer to general hydrosilation procedure. The reaction was run using **3** (1.0 g, 6.9 mmol), PMHS (340 μL, 5.7 mmol), toluene (12 mL) and dichlorodi(cyclopentadienyl)platinum(II) (1 mg, 0.0025 mmol) to provide a colorless oil (860 mg, 74%), equiv. wt. 204. ^{1}H NMR (300 MHz, $CDCl_3$): δ −0.10–0.20 (br s, 3H), 0.44–0.58 (br m, 2H), 1.54–1.68 (br m, 2H), 1.98–2.18 (br s, 3H), 3.36–3.46 (br t, *J* = 6.6 Hz, 2H), 3.56–3.68 (br t, *J* = 4.8 Hz, 2H), 4.16–4.26 (br t, *J* = 4.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −0.3, 13.5, 21.0, 23.1, 63.5, 68.4, 73.7, 170.6. IR (neat): ν_{Si-O} 1120, $\nu_{C=O}$ 1730, ν_{C-H} 2930 cm^{-1}.

Poly(methylundecanoic acid ((2*R*,5*R*)-5-ethyl-1-azabicyclo[2.2.2]oct-2-yl)(6-methoxyquinolin-4-yl)-(*S*)-methyl ester siloxane-*co*-methylacetic acid 2-propoxyethyl ester siloxane) (5). Refer to general hydrosilation procedure. The reaction was run using **1** (245 mg, 0.5 mmol), **3** (72 mg, 0.5 mmol), PMHS (50 μL, 0.83 mmol), toluene (7.5 mL) and dichlorodi(cyclopentadienyl)-platinum(II) (5 mg, 0.013 mmol) to provide a yellow solid (160 mg, 51%). This procedure gave a material with a ratio of 4 : 7 for the cinchona alkaloid to the soluble linker, respectively. The ratio was determined by comparing the integration of a unique ^{1}H NMR signal from the cinchona alkaloid (δ 8.7, 1H) to a unique signal from the soluble linker (δ 2.0, 3H). The ^{1}H NMR integration data is reported relative to four cinchona units, equiv. wt. 909. ^{1}H NMR (300 MHz, $CDCl_3$): δ −0.16–0.21 (br s, 33H), 0.33–0.59 (br s, 22H), 0.76–0.95 (br s, 12H), 1.00–1.77 (br m, 110H), 1.91–2.11 (br s, 21H), 2.24–2.45 (br m, 8H) 2.57–2.81 (br s, 12 H), 2.83–3.02 (br s, 4H), 3.12–3.26 (br s, 4H), 3.28–3.43 (br s, 14H), 3.47–3.64 (br s, 14H), 3.83–4.00 (br s, 12H), 4.04–4.27 (br s, 14H), 6.45–6.76 (br s, 4H), 7.17–7.55 (br m, 12H), 7.88–8.08 (br m, 4H), 8.59–8.80 (br s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −2.65, −0.32, 12.16, 13.57, 18.03, 21.05, 23.15, 23.92, 25.45, 25.92, 26.68, 27.35, 27.49, 29.75, 29.81, 29.95, 30.10, 30.19, 34.03, 35.21, 36.70, 50.19, 50.95, 55.35, 60.02, 63.97, 68.92, 73.07, 74.23, 102.38, 118.34, 122.44, 128.35, 132.54, 145.01, 145.37, 147.82, 159.73, 170.65, 173.12. IR (neat): ν_{Si-O} 1040, $\nu_{C=O}$1735, ν_{C-H} 2910 cm^{-1}.

Terephthalic acid 1-allyl ester 4-[((2*R*,5*R*)-(−)-5-ethyl-1-azabicyclo[2.2.2]oct-2-yl)(6-methoxyquinolin-4-yl)-(*S*)-methyl] ester (6). A 250 mL two-neck round-bottom flask equipped with stir bar, rubber septum, condenser and gas inlet was charged with terephthaloyl chloride (2.03 g, 10 mmol), CH_2Cl_2 (50 mL) and triethylamine (5.6 mL, 40 mmol) under a flow of argon. Allyl alcohol (680 μL, 10 mmol) was added *via* syringe to the reaction solution at 0 °C in a dropwise fashion. After the addition was complete the reaction was stirred for 10 min at room temperature. Then hydroquinidine hydrochloride (3.63 g, 10 mmol) was added in one portion. The rubber septum was exchanged with a glass stopper and the reaction mixture was heated to 35 °C with vigorous stirring. The consumption of hydroquinide hydrochloride was monitored using TLC (SiO_2, acetone–EtOAc, 3 : 1). After 1 h the reaction was cooled to room temperature followed by the slow addition of a saturated aqueous solution of $NaHCO_3$ (100 mL). This mixture was then extracted using CH_2Cl_2 (3 × 50 mL). All organic layers were combined and dried over $MgSO_4$. The solvent was removed using a rotary evaporator to yield a crude white product. Purification *via* flash chromatography with silica as absorbent (acetone–EtOAc, 3 : 1) yielded a white solid (3.4 g, 66%), mp 52–54 °C, $[\alpha]_D^{22} = -76.1$ (*c* 1.08, EtOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90 (t, *J* = 6.5 Hz, 3H), 1.40–1.53 (m, 4H), 1.55–1.64 (m, 2H), 1.75 (s, 1H), 1.91 (t, *J* = 11.5 Hz, 1H), 2.73 (t, *J* = 10.0 Hz, 2H), 2.82 (t, *J* = 12.0 Hz, 1H), 2.93 (t, *J* = 13.0 Hz, 1H), 3.46 (q, *J* = 8.0 Hz, 1H), 3.99 (s, 3H), 4.85 (d, *J* = 4.5 Hz, 2H), 5.30 (d, *J* = 11.0 Hz, 1H), 5.42 (d, *J* = 17.5 Hz, 1H), 5.99–6.09 (m, 1H), 6.79 (d, *J* = 7.0 Hz, 1H), 7.39 (d, *J* = 8.5 Hz, 1H), 7.46 (d, *J* = 4.5 Hz, 1H), 7.54 (s, 1H), 8.04 (d, *J* = 9.0 Hz, 1H), 8.14–8.23 (m, 4H), 8.76 (d, *J* = 4.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.62, 23.37, 25.16, 25.84, 26.89, 37.09, 49.69, 50.58, 55.31, 59.25, 65.77, 74.52, 101.23, 118.49, 118.55, 121.75, 126.94, 129.49, 129.64, 131.71, 131.72, 133.44, 134.25, 143.55, 144.67, 147.34, 157.86, 164.79, 165.10. HRMS-EI$^+$ [M + H]$^+$: found 515.2554; calc. ($C_{31}H_{35}N_2O_5$) 515.2546.

Phthalic acid 1-allyl ester 2-[((2*R*,5*R*)-5-ethyl-1-azabicyclo[2.2.2]oct-2-yl)(6-methoxyquinolin-4-yl)-(*S*)-methyl] ester (7). The synthesis and purification of this compound was analogous to **6**. Combining phthaloyl dichloride (2.03 g, 10 mmol), CH_2Cl_2 (50 mL), triethylamine (5.6 mL, 40 mmol), allyl alcohol (680 μL, 10 mmol), and hydroquinidine hydrochloride (3.63 g, 10 mmol) in the manner indicated above yielded a white solid (3.0 g, 57%), mp 22–24 °C, $[\alpha]_D^{22} = +61.4$ (*c* 1.3, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, *J* = 7.2 Hz, 3H), 1.40–1.65 (m, 6H), 1.77–1.89 (m, 2H), 2.64–2.79 (m, 3H), 2.87–2.94 (m, 1H), 3.38 (q, *J* = 8.8 Hz, 1H), 3.95 (s, 3H), 4.43 (dd, *J* = 12.8, 6.0 Hz, 1H), 4.55 (dd, *J* = 13.2, 5.6 Hz, 1H), 5.10 (d, *J* = 10.4 Hz, 1H), 5.18 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.64–5.75 (m, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 7.38 (dd, *J* = 4.6, 2.8 Hz, 1H), 7.44 (d, *J* = 4.8 Hz, 1H), 7.49 (d, *J* = 2.4 Hz, 1H), 7.53–7.60 (m, 2H), 7.69–7.78 (m, 2H), 8.02 (d, *J* = 9.2 Hz, 1H), 8.76 (d, *J* = 4.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.12, 24.19, 25.56, 26.23, 27.33, 37.47, 49.90, 50.77, 55.58, 59.76, 66.20, 74.75, 101.52, 118.34, 119.06, 121.75, 127.14, 128.44, 129.07, 130.96, 131.20, 131.23, 131.57, 131.61, 131.93, 143.55, 144.61, 147.30, 157.58, 166.29, 166.62. HRMS-FAB$^+$ [M + H]$^+$: found 515.2571; calc. ($C_{31}H_{35}N_2O_5$) 515.2546.

1-Allyloxy-4-chlorophthalazine (8). The procedure was adapted from Sharpless.[3,34] A 250 mL two-neck round-bottom flask equipped with stir bar, rubber septum, condenser and gas inlet was charged with sodium hydride (390 mg, 9.8 mmol, 60% in mineral oil), and THF (30 mL) under a flow of argon. Allyl alcohol (313 μL, 4.6 mmol) was then added in a dropwise fashion to the stirred reaction solution at room temperature. This mixture was stirred for

30 min, then 1,4-dichlorophthalazine (1.0 g, 5.0 mmol) was added in one portion. The rubber septum was replaced with a glass stopper and the reaction was stirred at reflux. The reaction mixture gradually changed colors from a cloudy white, to a yellow then finally brown suspension after addition of 1,4-dichlorophthalazine. The consumption of 1,4-dichlorophthalazine was monitored using TLC (SiO_2, hexanes–EtOAc, 1 : 4). After stirring the reaction at reflux overnight it was cooled to room temperature. Excess NaH was quenched by the slow addition of a water–THF (75 mL, 1 : 1 v/v) mixture to the vigorously stirred reaction at 0 °C. This solution was extracted with CH_2Cl_2 (2 × 75 mL). All organic layers were combined and dried over $MgSO_4$. The solvent was removed using a rotary evaporator to yield a crude yellow solid. Purification *via* flash chromatography with silica as absorbent (EtOAc–hexanes, 3 : 7) yielded a white solid (680 mg, 67%), mp 90–91 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.17 (d, J = 5.6 Hz, 2H), 5.36 (dd, J = 10.4, 1.6 Hz, 1H), 5.53 (dd, J = 17.2, 1.6 Hz, 1H), 6.16–6.28 (m, 1H), 7.88–7.97 (m, 2H), 8.18 (dd, J = 7.2, 1.6 Hz, 1H), 8.25 (dd, J = 6.4, 2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 68.35, 118.46, 121.37, 123.47, 124.95, 127.48, 132.29, 132.67, 132.96, 149.91, 159.69. HRMS-EI$^+$ *m*/*z*: found 220.0415; calc. ($C_{11}H_9N_2OCl$) 220.0403. UV-vis ($CHCl_3$) λ_{max}: 274, 309 nm.

1-Allyloxy-4-[((2*R*,5*R*)-(−)-5-ethyl-1-azabicyclo[2.2.2]oct-2-yl)(6-methoxyquinolin-4-yl)-(*S*)-methoxy]phthalazine (9). The procedure was adapted from Sharpless.[3,34] A 100 mL two-neck round-bottom flask equipped with stir bar, glass stopper, condenser and gas inlet was charged with sodium hydride (330 mg, 8.3 mmol, 60% in mineral oil) and *N*,*N*-dimethylacetamide (20 mL) under a flow of argon. Hydroquinidine hydrochloride (1.4 g, 3.8 mmol) was then added in three equal portions to the stirred reaction solution at room temperature. This mixture was stirred for 30 min at 100 °C over which time the reaction changed in color from a cloudy white to an orange and finally a green suspension. The reaction was cooled to room temperature and **8** (800 mg, 3.6 mmol) was added all at once. The reaction mixture was again stirred at 100 °C. The consumption of hydroquinidine hydrochloride was monitored using TLC (SiO_2, EtOAc–MeOH, 4 : 1). After stirring the reaction at 100 °C overnight it was cooled to room temperature. Excess NaH was quenched by the slow addition of a water–THF (10 mL, 1 : 1 v/v) mixture to the vigorously stirred reaction at 0 °C. Then the solution was diluted with water (50 mL). This solution was extracted with CH_2Cl_2 (2 × 50 mL). The organic layers were combined and washed with water (5 × 75 mL), dried over $MgSO_4$, filtered and evaporated to yield a crude white solid. Purification *via* flash chromatography with silica as absorbent (EtOAc–MeOH, 4 : 1) yielded a white solid (1.5 g, 82%), mp 65–68 °C, $[\alpha]_D^{22} = -189.5$ (*c* 1.2, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, J = 6.8 Hz, 3H), 1.42–1.64 (m, 6H), 1.76 (s, 1H), 2.12 (t, J = 12.0 Hz, 1H), 2.70–2.80 (m, 1H), 2.85 (d, J = 9.6 Hz, 1H), 2.92 (d, J = 8.0 Hz, 2H), 3.49 (q, J = 8.4 Hz, 1H), 3.99 (s, 3H), 4.93–5.07 (m, 2H), 5.27 (d, J = 10.4 Hz, 1H), 5.41 (dd, J = 17.6, 1.2 Hz, 1H), 6.08–6.20 (m, 1H), 7.15 (d, J = 5.6 Hz, 1H), 7.35 (dd, J = 8.8, 2.4 Hz, 1H), 7.47 (d, J = 4.4 Hz, 1H), 7.64 (d, J = 2.4 Hz, 1H), 7.82–7.94 (m, 2H), 7.99 (d, J = 8.8 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H), 8.35 (d, J = 8.0 Hz, 1H), 8.65 (d, J = 4.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.05, 23.13, 25.50, 26.52, 27.39, 37.53, 50.10, 50.93, 55.62, 59.88, 67.61, 76.78, 102.14, 117.58, 118.51, 121.47, 122.21, 122.25, 122.35, 123.32, 126.96, 131.42, 131.82, 131.87, 132.77, 144.39, 144.54, 147.19, 156.19, 157.14, 157.30. HRMS-EI$^+$ *m*/*z*: found 510.2634; calc. ($C_{31}H_{34}N_4O_3$) 510.2631. UV-vis ($CHCl_3$) λ_{max}: 282, 310, 334 nm.

Poly(methylterephthalic acid 1-[((2*R*,5*R*)-5-ethyl-1-azabicyclo[2.2.2]oct-2-yl)(6-methoxyquinolin-4-yl)-(*S*)-methyl] ester 4-propyl ester siloxane) (10). Refer to general hydrosilation procedure. The reaction was run using **6** (272 mg, 0.53 mmol), PMHS (26 µL, 0.44 mmol), toluene (5 mL) and dichlorodi(cyclopentadienyl)platinum(II) (2 mg, 0.005 mmol) to provide a tan solid (190 mg, 75%), equiv. wt. 575. ^{1}H NMR (400 MHz, $CDCl_3$): δ −0.05–0.30 (br s, 3H), 0.52–0.70 (br s, 2H), 0.78–1.00 (br s, 3H), 1.30–1.84 (br m, 6H), 1.88–1.98 (br s, 1H), 2.04–2.26 (br s, 1H), 2.28–2.44 (br s, 2H), 2.86–3.08 (br s, 2H), 3.10–3.20 (br s, 1H), 3.22–3.38 (br s, 1H), 3.44–3.60 (br s, 1H), 3.86–4.02 (br s, 3H), 4.16–4.34 (br s, 2H), 7.28–7.46 (br m, 2H), 7.54–7.72 (br m, 2H), 7.94–8.04 (br m, 1H), 8.06–8.26 (br m, 4H), 8.62–8.74 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −2.82, 11.67, 13.01, 20.98, 22.25, 25.17, 25.83, 26.09, 36.03, 49.06, 49.64, 56.14, 58.29, 67.69, 73.01, 100.69, 117.41, 122.58, 126.02, 129.00, 129.62, 130.73, 131.60, 133.92, 141.78, 144.35, 146.86, 158.46, 164.14, 171.33. IR (neat): ν_{Si-O} 1100, $\nu_{C=O}$ 1720, ν_{C-H} 2945 cm^{-1}.

Poly(methylterephthalic acid 1-[((2*R*, 5*R*)-5-ethyl-1-azabicyclo[2.2.2]oct-2-yl)(6-methoxyquinolin-4-yl)-(*S*)-methyl] ester 4-propyl ester siloxane-*co*-methylacetic acid 2-propoxyethyl ester siloxane) (11). Refer to general hydrosilation procedure. The reaction was run using **6** (875 mg, 1.7 mmol), **3** (187 mg, 1.3 mmol), PMHS (150 µL, 2.5 mmol), toluene (10 mL) and dichlorodi(cyclopentadienyl)platinum(II) (2 mg, 0.005 mmol). The purification was modified after the first precipitation of the toluene reaction mixture into hexanes. Not all of the precipitated material was soluble in THF. Thus the polymer residue was titurated with THF (3 × 10 mL). The insoluble residue was discarded. All THF fractions were combined and evaporated under reduced pressure. The tan oily residue that remained after evaporation was dissolved in a minimal amount of THF (4 mL) and precipitated into an excess of hexanes (8 mL). No further precipitations were needed to reach a pure material. The residual solvents were removed from the polymer residue under reduced pressure to provide a tan solid (370 mg, 38%). This procedure gave a material with a ratio of 5 : 7 for the cinchona alkaloid to the soluble linker, respectively. The ratio was determined by comparing the integration of a unique ^{1}H NMR signal from the cinchona alkaloid (δ 3.9, 3H) to a unique signal from the soluble linker (δ 2.1, 3H). The ^{1}H NMR integration data is reported relative to five cinchona units, equiv. wt. 861. ^{1}H NMR (400 MHz, $CDCl_3$): δ −0.6–0.32 (br s, 36H), 0.42–0.72 (br m, 24H), 0.81–0.98 (br s, 15H), 1.43–1.70 (br m, 49H), 1.72–1.91 (br m, 15H), 1.93–2.12 (br s, 21H), 2.54–3.13 (br m, 20H), 3.31–3.50 (br m, 19H), 3.52–3.66 (br s, 14H), 3.88–4.01 (br s, 15H), 4.08–4.22 (br s, 14H), 4.24–4.36 (br s, 10H), 6.85–7.00 (br s, 5H), 7.32–7.45 (br m, 10H), 7.49–7.62 (br m, 5H), 7.96–8.21 (br m, 25H), 8.64–8.75 (br m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −2.91, −0.63, 11.79, 13.02, 13.25, 20.86, 22.24, 22.88, 23.37, 25.27, 26.01, 26.35, 36.74, 49.48, 50.27, 55.65, 58.85, 63.42, 67.57, 68.28, 73.02, 73.56, 100.88, 117.01, 122.01, 126.45, 129.27, 129.40, 131.43, 133.42, 140.30, 142.74, 144.22, 146.84, 157.92, 164.09, 165.07, 170.59. IR (neat): ν_{Si-O} 1180, $\nu_{C=O}$ 1730, ν_{C-H} 2940 cm^{-1}.

Poly(methylphthalic acid 1-[((2*R*,5*R*)-5-ethyl-1-azabicyclo[2.2.2]oct-2-yl)(6-methoxyquinolin-4-yl)-(*S*)-methyl] ester 2-propyl ester siloxane) (12). Refer to general hydrosilation procedure. The reaction was run using **7** (1.0 g, 1.9 mmol), PMHS (94 µL, 0.44 mmol), toluene (8 mL) and dichlorodi(cyclopentadienyl)platinum(II) (6 mg, 0.015 mmol) to provide a tan solid (500 mg, 55%), equiv. wt. 575. ^{1}H NMR (400 MHz, $CDCl_3$): δ −0.10–0.20 (br s, 3H), 0.32–0.56 (br s, 2H), 0.70–0.86 (br m, 3H), 1.08–1.18 (br m, 2H), 1.24–1.56 (br m, 6H), 1.58–1.78 (br m, 2H), 2.52–2.80 (br s, 3H), 2.82–2.96 (br s, 1H), 3.28–3.40 (br m, 1H), 3.62–3.74 (br m, 2H), 3.78–4.04 (br s, 3H), 6.65–6.85 (br s, 1H), 7.08–7.13 (br d, J = 9.2 Hz, 1H), 7.28–2.34 (br d, J = 4.4 Hz, 1H), 7.42–7.58 (br m, 2H), 7.61–7.68 (br d, J = 7.2 Hz, 1H), 7.76–7.82 (br d, J = 9.2 Hz, 1H), 7.88–7.94 (br d, J = 7.6 Hz, 1H), 7.95–8.03 (br s, 1H), 8.62–8.67 (br d, J = 4.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −2.72, 11.69, 19.88, 24.37, 24.59, 25.32, 25.47, 26.11, 35.53, 49.39, 49.79, 55.23, 57.30, 71.23, 74.50, 100.44, 116.43, 122.57, 125.49, 126.21, 128.75, 128.87, 130.59, 131.06, 131.21, 131.50, 141.18, 144.16, 146.03, 158.09, 165.86, 166.27. IR (neat): ν_{Si-O} 1120, $\nu_{C=O}$ 1730, ν_{C-H} 2945 cm^{-1}.

Poly(methylphthalic acid 1-[((2*R*,5*R*)-5-ethyl-1-azabicyclo[2.2.2]oct-2-yl)(6-methoxyquinolin-4-yl)-(*S*)-methyl] ester 2-propyl ester siloxane-*co*-methylacetic acid 2-propoxyethyl ester siloxane) (13). Refer to general hydrosilation proce-

dure. The reaction was run using **7** (1.75 mg, 3.4 mmol), **3** (353 mg, 2.45 mmol), PMHS (280 μL, 4.68 mmol), toluene (20 mL) and dichlorodi(cyclopentadienyl)platinum(II) (6 mg, 0.015 mmol). The purification was modified after the first precipitation of the toluene reaction mixture into hexanes. Not all of the precipitated material was soluble in THF. Thus the polymer residue was titurated with chloroform (2 × 5 mL). The insoluble residue was discarded. All chloroform fractions were combined and precipitated into an excess of hexanes (15 mL). No further precipitations were needed to reach a pure material. The residual solvents were removed from the polymer residue under reduced pressure to provide a tan solid (940 mg, 52%). This procedure gave a material with a ratio of 3 : 2 for the cinchona alkaloid to the soluble linker, respectively. The ratio was determined by comparing the integration of a unique ^{1}H NMR signal from the cinchona alkaloid (δ 4.0, 3H) to a unique signal from the soluble linker (δ 2.1, 3H). The ^{1}H NMR integration data is reported relative to three cinchona units, equiv. wt. 712. ^{1}H NMR (400 MHz, $CDCl_3$): δ −0.60–0.32 (br s, 15H), 0.39–0.66 (br s, 10H), 0.75–0.98 (br t, J = 7.2 Hz, 9H), 1.12–1.28 (br s, 6H), 1.33–1.94 (br m, 28H), 1.99–2.16 (br s, 6H), 2.67–2.88 (br s, 9H), 2.91–3.06 (br s, 3H), 3.17–3.48 (br m, 7H), 3.51–3.68 (br s, 4H), 3.70–3.82 (br m, 6H), 3.85–4.06 (br s, 9H), 4.11–4.29 (br s, 4H), 6.76–6.95 (br s, 3H), 7.11–7.89 (br m, 21H), 7.93–8.12 (br s, 3H), 8.66–8.82 (br s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −2.72, −0.60, 11.73, 12.99, 20.91, 21.97, 22.93, 24.35, 24.55, 25.29, 25.44, 26.09, 35.51, 49.74, 50.34, 55.20, 57.32, 63.52, 67.61, 68.32, 73.63, 74.47, 100.46, 116.44, 122.56, 125.51, 126.17, 128.16, 128.89, 130.50, 130.95, 131.38, 131.83, 141.20, 144.02, 146.01, 158.11, 165.88, 170.64, 172.50. IR (neat): $\nu_{Si–O}$ 1060, $\nu_{C=O}$ 1730, $\nu_{C–H}$ 2940 cm^{-1}.

Poly(methyl-1-[((2*R*,5*R*)-5-ethyl-1-azabicyclo[2.2.2]oct-2-yl)(6-methoxyquinolin-4-yl)-(*S*)-methoxy]-4-propoxyphthalazine siloxane) (14). Refer to general hydrosilation procedure. The reaction was run using **9** (1.35 g, 2.6 mmol), PMHS (130 μL, 2.16 mmol), toluene (10 mL) and dichlorodi(cyclopentadienyl)-platinum(II) (4 mg, 0.01 mmol) to provide a tan solid (560 mg, 45%), equiv. wt. 571. ^{1}H NMR (400 MHz, $CDCl_3$): δ −0.20–0.20 (br s, 3H), 0.50–0.70 (br s, 2H), 0.75–0.95 (br s, 3H), 1.30–1.65 (br s, 6H), 1.70–1.95 (br m, 3H), 2.05–2.30 (br s, 1H), 2.55–3.05 (br m, 4H), 3.30–3.55 (br s, 1H), 3.85–4.05 (br s, 3H), 4.20–4.50 (br s, 2H), 7.10–7.35 (br m, 2H), 7.40–7.50 (br s, 1H), 7.55–7.70 (br s, 1H), 7.80–8.00 (br m, 3H), 8.05–8.15 (br s, 1H), 8.20–8.35 (br s, 1H), 8.50–8.65 (br m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −2.88, 11.98, 13.21, 22.52, 25.44, 26.50, 26.92, 37.37, 49.99, 50.76, 55.80, 59.07, 59.86, 69.28, 76.48, 102.12, 118.36, 121.95, 122.19, 122.35, 122.74, 123.34, 126.90, 131.73, 132.01, 132.95, 144.38, 144.62 146.99, 155.70, 156.92, 157.60. IR (neat): $\nu_{Si–O}$ 1090, $\nu_{C–H}$ 2950 cm^{-1}. UV-vis ($CHCl_3$) λ_{max}: 290, 311, 334 nm.

Poly(methyl-1-[((2*R*,5*R*)-5-ethyl-1-azabicyclo[2.2.2]oct-2-yl)(6-methoxyquinolin-4-yl)-(*S*)-methoxy]-4-propoxyphthalazinesiloxane-*co*-methylacetic acid 2-propoxyethyl ester siloxane) (15). Refer to general hydrosilation procedure. The reaction was run using **9** (820 mg, 1.6 mmol), **3** (184 mg, 1.3 mmol), PMHS (140 μL, 2.4 mmol), toluene (8 mL) and dichlorodi(cyclopentadienyl)-platinum(II) (3 mg, 0.01 mmol) to provide a tan solid (390 mg, 42%). This procedure gave a material with a ratio of 13 : 10 for the cinchona alkaloid to the soluble linker, respectively. The ratio was determined by comparing the integration of a unique ^{1}H NMR signal from the cinchona alkaloid (δ 3.9, 3H) to a unique signal from the soluble linker (δ 2.0, 3H). The ^{1}H NMR integration data is reported relative to 13 cinchona units, equiv. wt. 728. ^{1}H NMR (500 MHz, $CDCl_3$): δ −0.33–0.22 (br s, 69H), 0.35–0.50 (br s, 20H), 0.53–0.65 (br s, 26H), 0.72–0.93 (br m, 39H), 1.27–1.62 (br s, 98H), 1.67–1.85 (br m, 39H), 1.89–2.05 (br s, 30H), 2.09–2.21 (br s, 13H), 2.61–2.99 (br m, 52H), 3.08–3.59 (br m, 53H), 3.82–4.00 (br s, 39H), 4.02–4.20 (br s, 20H), 4.22–4.44 (br s, 26H), 7.07–7.21 (br s, 13H), 7.23–7.34 (br m, 13H), 7.36–7.47 (br s, 13H), 7.52–8.34 (br m, 78H), 8.52–8.68 (br s, 13H). ^{13}C NMR (125 MHz, CDCl3): δ −3.12, −0.90, 11.57, 11.79, 12.96, 22.32, 22.82, 25.27, 26.32, 26.53, 26.75, 37.28, 49.95, 50.73, 55.65, 58.97, 59.82, 63.52, 68.31, 69.29, 73.66, 76.47, 102.20, 118.55, 121.68, 122.21, 122.37, 122.89, 125.29, 127.05, 131.93, 132.22, 133.15, 144.22, 144.75, 147.34, 156.90, 157.22, 157.89, 170.96. IR (neat): $\nu_{Si–O}$ 1040, $\nu_{C=O}$ 1745, $\nu_{C–H}$ 2940 cm^{-1}.

1-Chloro-4-[(6-methoxyquinolin-4-yl)-((2*R*, 5*R*)-(−)-5-vinyl-1-azabicyclo[2.2.2]oct-2-yl)-(*S*)-methoxy]phthalazine (16). The procedure was adapted from Sharpless.[3,34] A 500 mL two-neck round-bottom flask equipped with stir bar, glass stopper, condenser and gas inlet was charged with sodium hydride (2.0 g, 50 mmol, 60% in mineral oil), and THF (125 mL) under a flow of argon. Quinidine (7.45 g, 23 mmol) was then added in one portion to the stirred reaction solution at room temperature. This mixture was stirred at reflux for 30 min. Then 1,4-dichlorophthalazine (5.0 g, 25 mmol) was added all at once to the reaction cooled to room temperature. This mixture was then stirred at reflux. The reaction mixture gradually changed colors from a cloudy white to a brown suspension after addition of 1,4-dichlorophthalazine. The consumption of quinidine was monitored using TLC (SiO_2, EtOAc–MeOH, 4 : 1). After stirring the reaction at reflux overnight it was cooled to room temperature. Excess NaH was quenched by the slow addition of a water–THF (75 mL, 1 : 1 v/v) mixture to the vigorously stirred reaction at 0 °C. This solution was diluted with water (100 mL) then extracted with CH_2Cl_2 (3 × 100 mL). All organic layers were combined and dried over $MgSO_4$. The solvent was removed using rotary evaporator to yield a crude red oil. Purification *via* flash chromatography with silica as absorbent (EtOAc–MeOH, 9 : 1) yielded a white solid (7.4 g, 66%), mp 94–96 °C, $[\alpha]_D^{22} = -248.7$ (*c* 1.06, EtOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.56–1.70 (m, 2H), 1.89 (s, 1H), 1.97 (s, 1H), 2.17 (t, J = 11.0 Hz, 1H), 2.32 (q, J = 8.0 Hz, 1H), 2.74–2.83 (m, 1H), 2.87–2.94 (m, 1H), 2.95–3.02 (m, 1H), 3.07–3.15 (m, 1H), 3.52 (q, J = 8.5 Hz, 1H), 4.00 (s, 3H), 5.10 (d, J = 17.5 Hz, 1H), 5.13 (d, J = 10.5 Hz, 1H), 6.02–6.12 (m, 1H), 7.31 (d, J = 6.0 Hz, 1H), 7.37 (dd, J = 9.5, 2.5 Hz, 1H), 7.45 (d, J = 4.5 Hz, 1H), 7.63 (d, J = 2.5 Hz, 1H), 7.96–8.01 (m, 3H), 8.17–8.22 (m, 1H), 8.40–8.45 (m, 1H), 8.66 (d, J = 4.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.44, 26.41, 27.65, 39.53, 49.49, 49.88, 55.66, 59.84, 76.17, 101.72, 114.88, 118.35, 121.53, 121.96, 123.26, 125.50, 127.29, 127.87, 131.73, 133.09, 133.41, 140.40, 144.06, 144.78, 147.36, 150.43, 157.95, 159.31. HRMS-FAB$^+$ $[M + H]^+$: found 487.1897; calc. ($C_{28}H_{28}ClN_4O_2$) 487.1901. UV-vis ($CHCl_3$) λ_{max}: 281, 335 nm.

1-[((2*R*,5*R*)-(−)-5-Ethyl-1-azabicyclo[2.2.2]oct-2-yl)(6-methoxyquinolin-4-yl)(*S*)-methoxy]-4-[(6-methoxyquinolin-4-yl)((2*R*, 5*R*)-5-vinyl-1-azabicyclo[2.2.2]oct-2-yl)-(*S*)-methoxy]phthalazine (17). The procedure was adapted from Sharpless.[3,34] A 250 mL two-neck round-bottom flask equipped with stir bar, glass stopper, condenser and gas inlet was charged with sodium hydride (1.3 g, 32 mmol, 60% in mineral oil), and *N*,*N*-dimethylacetamide (70 mL) under a flow of argon. Hydroquinidine hydrochloride (5.3 g, 14.5 mmol) was then added in one portion to the stirred reaction solution at room temperature. This mixture was stirred for 15 min at 100 °C. The reaction was cooled to room temperature and **16** (6.7 g, 13.8 mmol) was added all at once. The reaction was again stirred at 100 °C. The consumption of **16** was monitored using TLC (SiO_2, EtOAc–MeOH, 3 : 2). After stirring the reaction at 100 °C overnight it was cooled to room temperature. Excess NaH was quenched by the slow addition of water (100 mL) to the vigorously stirred reaction at 0 °C. A white precipitate occurred upon the addition of water that was collected using a Buchner funnel. The solid was washed with water (30 mL) and dried under reduced pressure to yield a white solid (9.0 g). This white solid was recrystallized from methanol (75 mL) to yield white crystals (6.4 g, 60%), mp 136–138 °C, $[\alpha]_D^{22} = -257.9$ (*c* 1.7, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80 (t, J = 6.8 Hz, 3H), 1.26 (s, 1H), 1.34–1.46 (m, 4H), 1.48–1.60 (m, 4H), 1.69 (s, 1H), 1.81 (s, 1H), 1.96 (t, J = 12.8 Hz, 1H), 2.08 (t, J = 12.8 Hz, 1H), 2.21 (q, J = 8.4 Hz, 1H), 2.52–2.88 (m, 7H), 2.92–3.00 (m, 1H), 3.41 (q, J = 8.8 Hz, 2H), 3.90 (s, 6H),

4.98 (d, J = 13.6 Hz, 2H), 5.88–6.00 (m, 1H), 6.97 (d, J = 6.4 Hz, 1H), 7.03 (d, J = 5.6 Hz, 1H), 7.32–7.40 (m, 2H), 7.43 (d, J = 4.8 Hz, 1H), 7.45 (d, J = 4.8 Hz, 1H), 7.52–7.59 (m, 2H), 7.89–7.96 (m, 2H), 7.99 (dd, J = 9.0, 2.0 Hz, 2H), 8.30–8.38 (m, 2H), 8.65 (t, J = 4.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.99, 23.36, 23.60, 25.36, 26.34, 26.55, 27.36, 27.80, 37.46 39.71, 49.49, 49.85, 49.96, 50.87, 55.58, 55.61, 60.07, 60.22, 76.05, 76.28, 101.83, 101.93, 114.47, 118.11, 118.37, 121.59, 121.67, 122.22, 122.24, 122.60, 122.85, 127.06, 127.09, 127.16, 127.18, 131.33, 131.90, 131.97, 140.11, 144.43, 144.69, 144.75, 147.14, 156.06, 156.12, 156.18, 157.26, 157.33. HRMS-FAB$^+$ $[M + H]^+$: found 777.4141; calc. ($C_{48}H_{53}N_6O_4$) 777.4128. UV-vis ($CHCl_3$) λ_{max}: 281, 334 nm.

Poly(methylDHQD$_2$PHAL siloxane) (18). Refer to general hydrosilation procedure. The reaction was run using **17** (2.75 g, 3.5 mmol), PMHS (170 µL, 2.9 mmol), toluene (20 mL) and dichlorodi(cyclopentadienyl)platinum(II) (1 mg, 0.0025 mmol). The purification was difficult and required special conditions to separate the polymer product from **17**. After the initial precipitation subsequent precipitations were done by dissolving the crude material in toluene (5 mL) and dripping a drop at a time into hexanes (10 mL). A total of six precipitations from toluene to hexanes were needed for clean material. The residual solvents were removed from the polymer residue under reduced pressure to provide a tan solid (520 mg, 22%), equiv. wt. 837. ^{1}H NMR (500 MHz, $CDCl_3$): δ −0.10–0.20 (br s, 3H), 0.35–0.60 (br s, 2H), 0.72–0.84 (br s, 3H), 1.24–1.58 (br m, 10H), 1.62–1.72 (br s, 2H), 1.90–2.02 (br s, 2H), 2.50–2.86 (br m, 6H), 3.28–3.58 (br s, 8H), 3.76–3.96 (br s, 6H), 6.86–7.04 (br s, 2H), 7.30–7.46 (br m, 4H), 7.48–7.60 (br s, 2H), 7.84–8.06 (br s, 4H), 8.24–8.40 (br s, 2H), 8.54–8.70 (br s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ −1.00, 11.79, 14.56, 22.91, 23.32, 24.84, 25.21, 26.24, 26.43, 27.22, 27.71, 37.38, 39.63, 49.65, 49.94, 50.05, 50.84, 55.55, 55.69, 60.04, 60.25, 76.02, 76.32, 101.73, 102.04, 118.19, 118.56, 121.60, 121.81, 122.22, 122.43, 122.73, 122.88, 126.89, 127.01, 127.22, 127.32, 132.17, 132.30, 140.37, 144.70, 144.87, 144.94, 147.35, 156.29, 156.39, 156.49, 157.61, 157.73. IR (neat): ν_{Si-O} 1050, ν_{C-H} 2930 cm^{-1}. UV-vis ($CHCl_3$) λ_{max}: 281, 336 nm.

Poly(methylDHQD$_2$PHAL siloxane-*co*-methylacetic acid 2-propoxyethyl ester siloxane) (19). Refer to general hydrosilation procedure. The reaction was run using **17** (1.2 g, 1.5 mmol), **3** (165 mg, 1.15 mmol), PMHS (130 µL, 2.2 mmol), toluene (15 mL) and dichlorodi(cyclopentadienyl)platinum(II) (1 mg, 0.005 mmol). The purification was difficult and required special conditions to separate the polymer product from **17**. After the initial precipitation subsequent precipitations were done by dissolving the crude material in toluene (5 mL) and dripping a drop at a time into hexanes (10 mL). A total of six precipitations from toluene to hexanes were needed for clean material. The residual solvents were removed from the polymer residue under reduced pressure to provide a tan solid (250 mg, 22%). This procedure gave a material with a ratio of 5 : 7 for the cinchona alkaloid to the soluble linker, respectively. The ratio was determined by comparing the integration of a unique ^{1}H NMR signal from the cinchona alkaloid (δ 8.6, 2H) to a unique signal from the soluble linker (δ 4.2, 2H). The ^{1}H NMR integration data is reported relative to five cinchona units, equiv. wt. 1123. ^{1}H NMR (500 MHz, $CDCl_3$): δ −0.07–0.26 (br s, 36H), 0.37–0.61 (br s, 24H), 0.71–0.82 (br s, 15H), 1.30–1.81 (br m, 74H), 1.88–2.12 (br m, 31H), 2.55–2.84 (br m, 30H), 3.27–3.52 (br m, 54H), 3.54–3.65 (br s, 14H), 3.78–3.95 (br m, 30H), 4.07–4.23 (br s, 14H), 6.84–7.05 (br s, 10H), 7.26–7.44 (br m, 20H), 7.46–7.61 (br s, 10H), 7.82–8.07 (br m, 20H), 8.23–8.42 (br s, 10H), 8.53–8.70 (br s, 10H). ^{13}C NMR (125 MHz, $CDCl_3$): δ −1.19, −0.94, 11.76, 12.85, 14.53, 20.78, 22.61, 22.74, 23.20, 24.76, 25.18, 26.21, 26.35, 27.16, 27.63, 37.33, 39.62, 49.63, 49.90, 50.01, 50.80, 55.33, 55.54, 59.98, 60.19, 63.56, 68.37, 73.69, 76.25, 76.36, 101.89, 101.97, 118.32, 118.53, 121.82, 121.97, 122.17, 122.42, 122.71, 122.86, 126.98, 127.11, 127.19, 127.28, 132.16, 132.30, 140.35, 144.56, 144.69, 144.90, 147.31, 156.26, 156.38, 156.44, 157.42, 157.65, 170.96. IR (neat): ν_{Si-O} 1050, $\nu_{C=O}$ 1740, ν_{C-H} 2940 cm^{-1}. UV-vis ($CHCl_3$) λ_{max}: 281, 336 nm.

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References

1 S. G. Hentges and K. B. Sharpless, *J. Am. Chem. Soc.*, 1980, **102**, 4263–4265.
2 E. N. Jacobsen, I. Marko, W. S. Mungall, G. Schroeder and K. B. Sharpless, *J. Am. Chem. Soc.*, 1988, **110**, 1968–1970.
3 K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K. S. Jeong, H. L. Kwong, K. Morikawa, Z. M. Wang, D. Xu and X.-L. Zhang, *J. Org. Chem.*, 1992, **57**, 2768–2771.
4 H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483–2547.
5 (*a*) B. M. Kim and K. B. Sharpless, *Tetrahedron Lett.*, 1990, **31**, 3003–3006; (*b*) I. Motorina and C. M. Credden, *Org. Lett.*, 2001, **3**, 2325.
6 H. Han and K. D. Janda, *J. Am. Chem. Soc.*, 1996, **118**, 7632–7633.
7 P. Salvadori, D. Pini, A. Petri and A. Mandoli, *Catalytic Heterogeneous Enantioselective Dihydroxylation and Epoxidation*, Wiley-VCH Verlag, Weinheim, Germany, 2000.
8 T. Frenzel, W. Solodenko and A. Kirschning, *Polymeric Materials in Organic Synthesis and Catalysis*, Wiley-VCH: Weinheim, 2003.
9 N. E. Leadbeater and M. Marco, *Chem. Rev.*, 2002, **102**, 3217–3273.
10 M. Benaglia, A. Puglisi and F. Cozzi, *Chem. Rev.*, 2003, **103**, 3401–3429.
11 C. Bolm and A. Gerlach, *Eur. J. Org. Chem.*, 1998, 21–27.
12 C. Bolm and A. Gerlach, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 741–743.
13 H. Han and K. D. Janda, *Tetrahedron Lett.*, 1997, **38**, 1527–1530.
14 D. J. Gravert and K. D. Janda, *Chem. Rev.*, 1997, **97**, 489–509.
15 P. H. Toy and K. D. Janda, *Acc. Chem. Res.*, 2000, **33**, 546–554.
16 T. J. Dickerson, N. N. Reed, K. D. Janda, *Polymeric Materials in Organic Synthesis and Catalysis*, Wiley-VCH, Weinheim, 2003.
17 B. B. Lohray, E. Nandanan and V. Bhushan, *Tetrahedron Lett.*, 1994, **35**, 6559–6562.
18 A. Petri, D. Pini and P. Salvadori, *Tetrahedron Lett.*, 1995, **36**, 1549–1552.
19 F. Sieber, P. Wentworth Jr. and K. D. Janda, *J. Comb. Chem.*, 1999, **1**, 540–546.
20 F. Sieber, P. Wentworth Jr., J. D. Toker, A. D. Wentworth, W. A. Metz, N. N. Reed and K. D. Janda, *J. Org. Chem.*, 1999, **64**, 5188–5192.
21 T. S. Reger and K. D. Janda, *J. Am. Chem. Soc.*, 2000, **122**, 6929–6934.
22 M. S. Bratcher, M. S. DeClue, A. Grunnet-Jepsen, D. Wright, B. R. Smith, W. E. Moerner and J. S. Siegel, *J. Am. Chem. Soc.*, 1998, **120**, 9680–9681.
23 D. Wright, U. Gubler, W. E. Moerner, M. S. DeClue and J. S. Siegel, *J. Phys. Chem. B*, 2003, **107**, 4732–4737.
24 Commercial poly(methylhydrosiloxane) available through Aldrich with $\overline{M}_n$ = 9500.
25 R. N. Meals, *Pure Appl. Chem.*, 1966, **13**, 141–157.
26 P. Strohriegl, *Makromol. Chem., Rapid Commun.*, 1986, **7**, 771–775.
27 M. Lux, P. Strohriegl and H. Höcker, *Makromol. Chem.*, 1987, **188**, 811–820.
28 S. J. Clarson and J. A. Semlyen, *Siloxane Polymers*, PTR Prentice Hall, NJ, 1993.
29 G. Nestor, M. S. White, G. W. Gray, D. Lacey and K. J. Toyne, *Makromol. Chem.*, 1987, **188**, 2759–2767.
30 The rough equality of optical purity and ee was confirmed by Mosher's analysis.
31 Y. Ogino, H. Chen, E. Manoury, T. Shibata, M. Beller, D. Lubben and K. B. Sharpless, *Tetrahedron Lett.*, 1991, **32**, 5761–5764.
32 W. Amberg, Y. L. Bennani, R. K. Chadha, G. A. Crispino, W. D. Davis, J. Hartung, K. S. Jeong, Y. Ogino, T. Shibata and K. B. Sharpless, *J. Org. Chem.*, 1993, **58**, 844–849.
33 M. S. DeClue, PhD Thesis, University of Califorina – San Diego, CA, 2003.
34 H. C. Kolb, P. G. Andersson, Y. L. Bennani, G. A. Crispino, K. S. Jeong, H. L. Kwong and K. B. Sharpless, *J. Am. Chem. Soc.*, 1993, **115**, 12226–12227.
35 V. Van Rheenen, R. C. Kelly and D. Y. Cha, *Tetrahedron Lett.*, 1976, 1973–1976.
36 M. Minato, K. Yamamoto and J. Tsuji, *J. Org. Chem.*, 1990, **55**, 766–768.
37 P.-O. Norrby, H. Becker and K. B. Sharpless, *J. Am. Chem. Soc.*, 1996, **118**, 35–42.
38 D. R. Boyd, N. D. Sharma, N. I. Bowers, P. A. Goodrich, M. R. Groocock, A. J. Blacker, D. A. Clarke, T. Howard and H. Dalton, *Tetrahedron: Asymmetry*, 1996, **7**, 1559–1562.

39 3,3′,5,5′-Tetramethylstilbene was synthesized and used to confirm the inclusion of apolar diol products using ligand **19**. Tetramethylstilbene has a distinctly different ^{1}H NMR spectrum than the dihydroxylated product 1,2-bis(3,5-dimethylphenyl)ethane-1,2-diol. The ^{1}H NMR spectrum of the crude precipitate from the AD reaction using **19** and tetramethylstilbene revealed nearly complete co-precipitation of product and ligand.
40 P. Salvadori, D. Pini and A. Petri, *J. Am. Chem. Soc.*, 1997, **119**, 6929–6930.
41 C. E. Song, J. W. Yang and H.-J. Ha, *Tetrahedron: Asymmetry*, 1997, **8**, 841–844.
42 S. Nagayama, M. Endo and S. Kobayashi, *J. Org. Chem.*, 1998, **63**, 6094–6095.
43 S. Kobayashi, T. Ishida and R. Akiyama, *Org. Lett.*, 2001, **3**, 2649–2652.
44 D. E. Bergbreiter and C. Li, *Org. Lett.*, 2003, **5**, 2445–2447.
45 D. E. Bergreiter, P. L. Osburn, T. Smith, C. Li and J. D. Frels, *J. Am. Chem. Soc.*, 2003, **125**, 6254–6260.
46 D. E. Berbreiter and J. Li, *Chem. Commun.*, 2004, 42–43.
47 D. E. Bergbreiter and J. Li, *Top. Curr. Chem.*, 2004, in press.
48 J. A. Dale, D. L. Dull and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543–2549.
49 J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, 1973, **95**, 512–519.
50 M. P. Bertrand, J. M. Surzur, M. Boyer and M. L. Mihailovic, *Tetrahedron*, 1979, **35**, 1365–1372.