

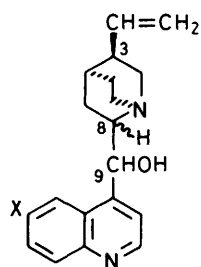
Michael Additions Catalysed by Cinchona Alkaloids Bound *via* their Vinyl Groups to Preformed Crosslinked Polymers

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Cinchona alkaloids have been satisfactorily bound *via* their vinyl groups to crosslinked polymers containing thiol residues. The products have been used to catalyse one or more of the following Michael additions: the additions of (1) thio-*p*-cresol, (2) *p*-chlorothiophenol, and (3) thiobenzoic acid to cyclohex-2-en-1-one, and (4) of toluene- α -thiol to 2-nitrostyrene. The steric course of reactions (1)–(3) is dominated by the configurations of C-8 and C-9 in the alkaloids, but the nature of the C-3 group does have an effect and this probably explains why the optical yields obtained using the polymer-supported catalysts were lower than those obtained using the free alkaloids. The optical yields obtained in reaction (4), though small, did not follow this pattern. The polymers afforded higher optical yields than the free alkaloids and, in one case, the predominant enantiomer was of opposite configuration.

One of the most attractive types of asymmetric synthesis is that in which chiral products are generated from achiral substrates under the influence of chiral catalysts.¹ Polymer-supported versions of such catalysts are especially attractive.² They are not only easily removed from the reaction product, but it may also be possible to re-use them, thereby making it economic to synthesize complex catalysts in order to achieve high enantiomeric excesses.

To assess the effect of binding chiral catalysts to polymer supports we have bound cinchonidine (1), cinchonine (2), quinine (3), and quinidine (4) to crosslinked polystyrenes *via* their vinyl groups, and compared their catalytic properties in Michael reactions with those of the unbound alkaloids. We now report the results.

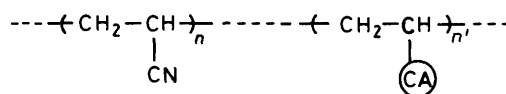


Configuration at

Alkaloid	C-8	C-9	X
Cinchonidine (1)	S	R	H
Cinchonine (2)	R	S	H
Quinine (3)	S	R	OMe
Quinidine (4)	R	S	OMe

Cinchona alkaloids have been bound to crosslinked polystyrenes before *via* the quinuclidine nitrogen atom^{3,4} or the 9-hydroxy group,⁵ but these methods of attachment destroy the β -hydroxy amine system which is so important for obtaining significant asymmetric synthesis. Linear polymeric catalysts (5) retaining the β -hydroxy amine system have been prepared by copolymerising the alkaloids with acrylonitrile.^{6–9} It is clearly

of interest to compare the activity of these soluble catalysts with that of ours.

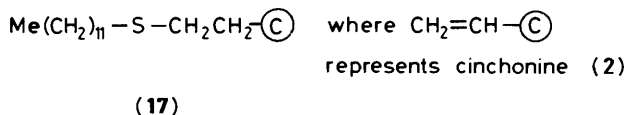
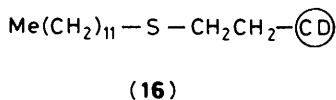
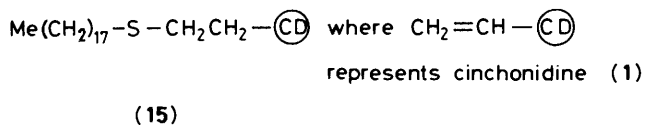
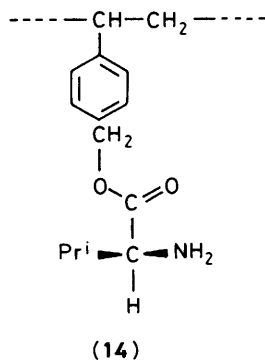
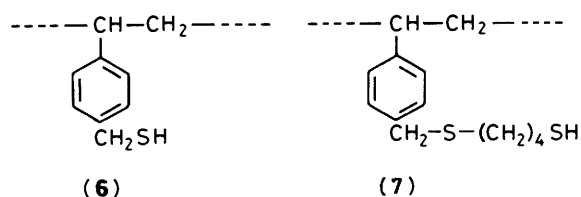


Where $\text{CH}_2=\text{CH}-\text{CA}$ represents a cinchona alkaloid
 (5)

Preparation of Catalysts.—The catalysts were prepared by allowing the vinyl groups of the alkaloids to react with the polymer-supported thiols (6) and (7). Polymers with thiol residues (6) were prepared by successively treating chloromethylated crosslinked polystyrenes with thiourea and then sodium hydroxide.¹⁰ Some polymer-supported catalysts are more effective if the reactive moiety is bound to the polymer *via* a 'spacer group'.¹¹ Accordingly, polymers containing thiol residues (7) were prepared by treating chloromethylated crosslinked polystyrene with butane-1,4-dithiol and base under phase transfer conditions.¹² The addition reactions were carried out in chloroform and were initiated using azobisisobutyronitrile (AIBN).¹³ At the end of the reaction period any unchanged thiol groups were 'capped' by the base-catalysed addition of methyl vinyl ketone or cyclohex-2-en-1-one, and the catalysts were freed of any unbound alkaloid by prolonged Soxhlet extraction. The preparations and capacities of the various polymeric catalysts (8)–(13) are summarised in Table 1.

A further catalyst investigated was polymer-supported valine (14). This was prepared by treating chloromethylated crosslinked polystyrene with *t*-BOC-valine under phase transfer conditions,¹⁴ followed by removal of the *N*-protecting group.¹⁵

Catalysis of Michael Reactions.—The free cinchona alkaloids and the various polymer-supported catalysts were used to catalyse one or more of the Michael additions (1)–(4), which involve three different types of sulphur nucleophile. The reactions were generally carried out by treating equimolar amounts of the substrates in toluene at 20 °C under nitrogen



with a 5 mol % of the various catalysts. The free alkaloids and polymer-supported catalysts were all catalytically active and gave optically active products.

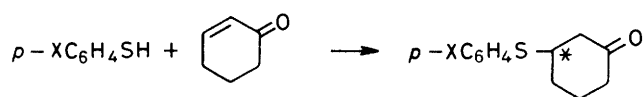
Catalysis of reactions 1 and 2. The results are summarised in Table 2. The following points should be noted.

(i) Neither reaction occurred in the presence of unfunctionalised polystyrene.*

(ii) As expected,¹⁶ cinchonine (2) and quinidine (4) gave predominantly one enantiomer whilst cinchonidine (1) and quinine (3) gave predominantly the other enantiomer. The optical yields obtained in reaction (1) with quinine (3) and in reaction (2) with cinchonidine (1) agree well with those reported in the literature.^{16,17}

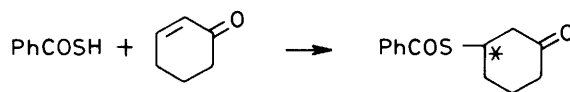
(iii) Although the predominant enantiomer obtained with each polymer-supported alkaloid was the same as that obtained with the corresponding free alkaloid, the optical yields were always less. In reaction (1) the best results were obtained with catalysts (9) and (8) which gave a 45% optical yield of the (–)-isomer and 28% optical yield of the (+)-isomer, respectively. In reaction (2) the optical yields with the same catalysts were 26% of the (–)-isomer and 9% of the (+)-isomer, respectively.

(iv) Catalysts (12) and (13) which incorporate the 'spacer arm'

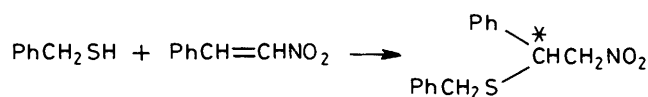


Reaction (1), X = Me

Reaction (2), X = Cl



Reaction (3)



Reaction (4)

gave lower optical yields in reaction (1) than the corresponding catalysts (8) and (9).

(v) To obtain a better model for the polymer-supported catalysts than the free alkaloid, octadecanethiol was treated with cinchonidine (1) to give compound (15).¹³ When the latter was used as a catalyst in reactions (1) and (2) the optical yields obtained were very similar to those obtained using catalyst (8).

(vi) Catalyst (9), recovered from reactions (1) and (2), was re-used three times in reaction (1). The chemical and optical yields obtained on each occasion were not significantly different from those obtained when the catalyst was first used. Further evidence for the stability of the catalyst was obtained by treating it with *p*-thiocresol in toluene for 48 h at 20 °C. The catalyst was then filtered off. The filtrate had no significant catalytic activity whilst that of the polymer was unchanged.

(vii) Although the polymer-supported valine (14) was catalytically active the optical yield of the (–)-isomer in reaction (1) was only 1%.

Catalysis of reaction (3). The results, summarised in Table 2, generally support the points (ii)–(v) and (vii) presented above. However, in this case the reaction proceeded significantly in the absence of any added catalyst and this is probably the main reason why the optical yields obtained with cinchonidine (1) and cinchonine (2) in toluene were lower than those reported in the literature for the same reactions carried out in benzene.¹⁸ The polymer-supported catalysts (8) and (12) were successfully recycled once.

Catalysis of reaction (4). The results are summarised in Table 3. The following points should be noted.

(i) This reaction proceeded slowly in the presence of unfunctionalised polystyrene.

(ii) Cinchonidine (1) and cinchonine (2) both gave the (+)-enantiomer in optical yields of 5 and 7%, respectively, in good agreement with the literature.¹⁹

(iii) The polymer-supported catalysts (8) and (9) gave the (+)-enantiomer in an optical yield of 12% and the (–)-enantiomer in an optical yield of 15%, respectively. These results differ considerably from those obtained by Kobayashi using linear polymers (5) prepared from cinchonidine (1) and from cinchonine (2) [both of which gave the (+)-enantiomer in 12% optical yields^{7,9}], and those using the model compounds (16) and (17), prepared from cinchonidine (1) and cinchonine (2),

* In earlier work reaction (1) was found to proceed slowly in the absence of any added catalyst. Presumably this was due to traces of impurities.⁴

Table 1. Structures and capacities of catalysts derived from cinchona alkaloids.

Catalyst	Prepared from ^a			Capacity (mmol per g)
	Thiol ^b	Alkaloid	Capping group ^c	
(8)	(6)	Cinchonidine (1)	CH	0.40
(9)	(6)	Cinchonine (2)	MVK	0.65
(10)	(6)	Quinine (3)	MVK	0.46
(11)	(6)	Quinidine (4)	MVK	0.20
(12)	(7)	Cinchonidine (1)	MVK	0.31
(13)	(7)	Cinchonine (2)	MVK	0.33

^a See Experimental section for a typical preparation. ^b Polymer-supported thiols (6) and (7) had capacities of 1.19 and 0.68 mmol per g respectively. ^c CH = cyclohex-2-enone; MVK = methyl vinyl ketone.

Table 2. Reactions of thiophenols with cyclohex-2-enone in the presence of various catalysts^a

Catalyst	Reaction (1)				Reaction (2)			
	Reaction time (h)	Chemical yield (%)	Optical yield (%)	Config. of major product	Reaction time (h)	Chemical yield (%)	Optical yield (%)	Config. of major product
Polystyrene	168	0	0		168	0	0	
(1)	72	61	61	R	120	70	36 ^b	R
(2)	72	69	71	S	120	67	54	S
(3)	72	68	44 ^c	R				
(4)	72	78	48	S				
(8)	48	92	28	R	120	99	9	R
(9)	24	81	45 ^d	S	120	98	26	S
(10)	48	84	18	R				
(11)	48	70	26	S				
(12)	72	80	25	R				
(13)	48	83	8	S				
(14)	240	65	1	S				
(15)	168	74	28	R	168	90	10	R

^a See Experimental section for details of experimental procedures and optical rotations of optically pure materials of known configuration. ^b Lit.,¹⁶ 35% e.e. of *R*-isomer. ^c Lit.,¹⁷ 46% e.e. of *R*-isomer. ^d Reactions carried out with 5 ml, 10 ml, and 15 ml of solvent all gave the same optical yield.

Table 3. Reactions of thiobenzoic acid with cyclohex-2-enone [reaction (3)] and toluene- α -thiol with ω -nitrostyrene [reaction (4)] in the presence of various catalysts.^a

Catalyst	Reaction (3)				Reaction (4)			
	Reaction time (h)	Chemical yield (%)	Optical yield (%)	Config. of major product	Reaction time (h)	Chemical yield (%)	Optical yield (%)	Sign of rotation of major product ^b
Polystyrene	168	44			148	9		
(1)	168	88	36	R	96	70	5 ^c	+
(2)	168	75	43	S	96	80	7 ^d	+
(8)	120	86	17 ^e	R	168	100	12	+
(9)	96	74	18	S	168	99	15	-
(12)	148	95	6 ^f	R				
(13)	148	95	6	S				
(14)	240	75	2	S				
(15)	148	87	19	R	17		4 ^{g,h}	+

^a See Experimental section for details of experimental procedures and optical rotations of optically pure materials. ^b Absolute configuration unknown. ^c Lit.,¹⁹ +4°. ^d Lit.,¹⁹ +10°. ^e Optical yield 16% with recycled catalyst. ^f Optical yield 7% with recycled catalyst. ^g Lit.,^{9,13} value with catalyst (16). ^h Lit.,^{9,13} value with catalyst (17) is a 12% optical yield of the (+)-enantiomer.

which again both gave the (+)-enantiomer, in this case in optical yields of 4 and 12%, respectively.^{9,13}

Conclusions.—Cinchona alkaloids can be satisfactorily attached *via* their vinyl groups to polymer-supported thiols (6) and (7). The products serve as catalysts for one or more of the reactions (1)–(4) and are sufficiently stable under the reaction

conditions that, in some cases at least, they can be recycled successfully.

The steric course of reactions (1), (2), and (3) is dominated by the stereochemistry at C-8 and C-9 in the alkaloids^{13,16} with the result that the polymer-supported catalysts (8)–(13) afford the same optical isomers as the corresponding free alkaloids, albeit in lower optical yields. The group at C-3 of the alkaloids

affects the magnitude of the optical yields.¹³ This is probably the main reason for the lower optical yields obtained with catalysts (8)—(13), since the optical yields obtained with the model compound (15) were very similar to those obtained with the corresponding polymer-supported catalyst (8). This demonstrates the importance of using good model compounds when investigating apparent 'polymer effects'. The catalysts (12) and (13) which incorporated the 'spacer arm' surprisingly gave lower optical yields than catalysts (8) and (9). It is not clear why. Polymer-supported valine (14) gave very poor optical yields and this illustrates the importance of the β -hydroxy amine system of the cinchona alkaloids in asymmetric synthesis.

In reaction (4) the steric course is not dominated by the stereochemistry at C-8 and C-9 in the alkaloids, but is very sensitive to the nature of the group at C-3.¹³ The results obtained with our polymer-supported catalysts differed considerably from those obtained with model compounds (16) and (17)¹³ or the more polar polymer-supported catalysts (5).⁹ In particular, polymer-supported catalyst (9) is the only one so far studied which affords predominantly the (–)-enantiomer from reaction (4). This latter result suggests that in some cases polymer-supported chiral catalysts may not only prove to be practically superior to conventional catalysts, but they may also afford significantly different optical yields.

Experimental

Experimental notes are as given previously.⁴

Preparation of Polymer-supported Thiol (6):—Chloromethylation²⁰ of 1% crosslinked polystyrene beads gave a product containing, by elemental analysis, Cl = 4.47% corresponding to 1.26 mmol of chloromethyl groups per g. This was successively treated with thiourea then aqueous sodium hydroxide.¹⁰ The product had S = 3.82% corresponding to 1.19 mmol of residues of (6) per g. The i.r. spectrum showed no band at 1265 cm⁻¹, indicating that all the chloromethyl groups had reacted.

Preparation of Polymer-supported Thiol (7):—Chloromethylation²⁰ of 1% crosslinked polystyrene beads gave a product containing Cl = 6.44%, corresponding to 1.81 mmol of chloromethyl groups per g. This product (6.44 g, 11.65 mmol) was treated with butane-1,4-dithiol and base under 'three phase' conditions as described before,¹² using a chloromethyl group–base–dithiol mol ratio of 0.13:1.00:2.45. The product (7.13 g) had Cl = 0.70% and S = 6.79%. Hence the final product contained 1.41 mmol of chloromethyl groups and 15.13 mmol of sulphur, corresponding to the product having 1.48 mmol of sulphur for each chloromethyl group that reacted, i.e. 64% of the butane-1,4-dithiol that reacted became 'singly bound'. This corresponds to the presence of 1.36 mmol of residues of (7) per g.

Preparation of Polymer-supported Catalysts (8) to (13):—The following is typical of the preparations summarised in Table 1.

Catalyst (9): A mixture of polymer-supported thiol (6) (12.000 g), cinchonine (2) (11.75 g), AIBN (180 mg), and chloroform (200 ml) was vigorously stirred and heated under reflux under nitrogen for 5 days. Further portions of AIBN were added after 24, 40, and 96 h. At the end of the reaction period the polymer was filtered off and washed successively with portions (2 × 50 ml) of chloroform, methylene dichloride, and ether. The polymer was then suspended in chloroform (70 ml) and treated for 48 h with methyl vinyl ketone (0.60 g) and piperidine (0.10 g) at 20 °C under nitrogen. The polymer was again filtered off and washed as before. To remove all the unbound alkaloid the polymer was Soxhlet extracted with toluene for 1 week. The solvent was changed daily. Evaporation of the final portion of toluene left a residue (2 mg) of oily material which was shown by

¹H n.m.r. spectroscopy to contain no alkaloid. The final weight of dried polymer was 14.821 g. The weight increase (2.821 g) corresponds to an alkaloid content of 9.60 mmol, equivalent to 0.65 mmol per g and a reaction yield of 67%.

Preparation of Polymer-supported Valine (14):—The above chloromethylated polystyrene (9.36 g, 11.8 mmol of chloromethyl groups) was treated with the potassium salt of *N*-t-BOC-L-valine and 18-crown-6 in dimethylformamide as described by Roeske and Gesellchen.¹⁴ The product (10.05 g) had Cl = 0% and the lack of chloromethyl groups was confirmed by i.r. spectroscopy. The *N*-protecting group was removed using trifluoroacetic acid in methylene dichloride.¹⁵ Assuming quantitative coupling and deprotection the product (8.84 g) contained 1.33 mmol of valine per g.

Preparation of Compound (15):—Cinchonidine (1) and octadecanethiol were allowed to react in the presence of AIBN using the general procedure given by Kobayashi *et al.*¹³ This gave compound (15) (76% yield), m.p. 120–121 °C (from chloroform–methanol), $[\alpha]_D^{18} - 70.38^\circ$ (*c* 0.14 in toluene) (Found: C, 76.5; H, 10.5; N, 4.95. Calc. for C₃₇H₆₀N₂OS: C, 76.50; H, 10.41; N, 4.82%). The ¹H n.m.r. spectrum was very similar to that of cinchonidine (1) but it lacked the signals due to vinyl protons and had signals due to the aliphatic chain.

Procedure for Reaction (1):—The following is typical of those summarised in Table 2.

Reaction (1) catalysed by catalyst (9): A mixture of toluene-*p*-thiol (319 mg, 2.57 mmol), cyclohex-2-enone (247 mg, 2.57 mmol), and catalyst (9) (198 mg, 0.13 mmol) in toluene (5 ml) was stirred at 20 °C under nitrogen for 24 h. The polymer was then filtered off and the filtrate diluted with toluene (10 ml). The toluene solution was washed successively with 2*M*-hydrochloric acid (2 × 8 ml), 2*M*-aqueous potassium hydroxide (2 × 8 ml), and brine (2 × 8 ml) and then dried (MgSO₄). Evaporation of the solvent and any excess cyclohex-2-enone left the product as an oil (452 mg, 80%)¹⁷ with ν_{\max} (liquid film) 1715 cm⁻¹ and a ¹H n.m.r. spectrum identical with that of an authentic sample. The product had $[\alpha]_{578}^{20} - 33.2^\circ$ (*c* 2.13 in benzene) {lit.¹⁷ for optically pure *R*-isomer: $[\alpha]_{578}^{21} + 70^\circ$ (*c* 2.0 in benzene)} corresponding to an optical yield of 47%.

A duplicate experiment gave the adduct in 82% yield with $[\alpha]_{578}^{20} - 31.4^\circ$ (*c* 2.20 in benzene) corresponding to an optical yield of 45%.

Experiments on the Re-useability and Stability of Catalyst (9):—Recovered catalyst (9) [from reactions (1) and (2)] was washed with toluene on a filter, dried, and then re-used on three successive occasions. The chemical and optical yields obtained in reaction (1) were respectively 65 and 46%, 75 and 41%, and 80 and 43%.

An experiment similar to reaction (1) was carried out using catalyst (9) but the cyclohex-2-enone was omitted. After 48 h the polymer was filtered off. Cyclohex-2-enone was added to the filtrate and after 48 h the yield of adduct was 7%, but it was optically inactive. The recovered polymer was used in a fresh reaction (1). After 48 h the chemical and optical yields were 85 and 42%, respectively.

Procedure for Reaction (2):—The examples of reaction (2) summarised in Table 2 were carried out using the same procedure as that described above for reaction (1). The products were solids, m.p. 55–60 °C (lit.¹⁷ 60–61 °C) with ν_{\max} (liquid film) 1715 cm⁻¹ and ¹H n.m.r. spectra identical with those of authentic samples. The $[\alpha]_{578}^{18}$ values were measured for solutions in carbon tetrachloride. Optical yields were calculated using $[\alpha]_{578}^{21} = 88.6^\circ$ (*c* 1.0 in carbon tetrachloride).¹⁶ All

experiments were carried out in duplicate. Chemical yields varied by $\pm 8\%$ but optical yields varied by only $\pm 1\%$.

Procedure for Reaction (3).—The examples of reaction (3) summarised in Table 3 were carried out using the same procedure as that described above for reaction (1). The products were solids, m.p. 70–77 °C with ν_{\max} (KBr disc) 1 652 and 1 711 cm^{-1} and ^1H n.m.r. spectra identical with those of authentic samples. The $[\alpha]_{578}^{18}$ values were measured for solutions in carbon tetrachloride. Optical yields were calculated using $[\alpha]_{578}^{\text{corr temp.} + 61.8^\circ}$ (c not given, carbon tetrachloride) for the pure *R*-isomer.¹⁸ All experiments were carried out in duplicate and gave yields which were within the limits noted above.

Procedure for Reaction (4).—The examples of reaction (4) summarised in Table 3 were carried out using the same procedure as that described above for reaction (1). The products were oils with ^1H n.m.r. spectra identical with those of authentic samples. The $[\alpha]_{\text{D}}^{20}$ values were measured for solutions in toluene. Optical yields were calculated using $[\alpha]_{\text{D}}^{25 202^\circ}$ (c 2–3 in toluene).⁷ All experiments were carried out in duplicate; the yields were within the limits noted above.

Acknowledgements

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